

30th June, 2020

The Controller of Patents
The Patent office
Bouddhik Sampada Bhawan
Near Antop Hil Post Office
S.M.Road, Antop Hill
MUMBAI-400 037, India

**Re: Opposition u/s 25(2) of the Patent act – By LOW COST STANDARD
THERAPEUTICS against Indian Patent No. 332280 (Formerly
Application Number No. 201727012821) dated 29/10/2015**
Patentee: GILEAD SCIENCES INC.

Respected Sir,

We submit herewith Post-Grant Opposition under Section 25(2) of the Patent Act, 2005 along with evidence and Form 7.

We crave leave of the Controller to submit additional documents or evidence, if necessary to support any averments in the representation as may be necessitated in the proceeding.

The Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

Lastly, we request the Controller to grant us an opportunity of being heard before the above Opposition is finally decided.

Thanking you,

Yours faithfully,



RAJESHWARI H. IN/PA - 0358
FOR RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

Encl:

- Form 7;
- Opposition; and
- List of documents

C.C.:

K & S PARTNERS
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Sector 47, Gurgaon - 122002, National Capital Region,
India Telephone: 91 (33) 40177100
Email: gurgaon@knspartners.com

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, MUMBAI

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006

AND

IN THE MATTER of Post grant opposition under Section 25(2)

AND

IN THE MATTER of Indian Patent No. 332280

Formerly Indian Patent Application No. 201727012821

IN THE MATTER OF:

LOW COST STANDARD THERAPEUTICS

..... OPPONENT

AND

GILEAD SCIENCES INC

..... PATENTEE

POST-GRANT OPPOSITION BY LOW COST STANDARD THERAPEUTICS

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Dated this 30th day of June, 2020

RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, MUMBAI

FORM 7
THE PATENTS ACT, 1970
(39 OF 1970)
AND
THE PATENTS RULES, 2003
NOTICE OF OPPOSITION
[See Section 25(2) and rule 55A]

We, LOW COST STANDARD THERAPEUTICS, an Indian Company of I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390 001, Gujarat, India, hereby give Notice of opposition to the grant of patent in respect of Indian Patent No. 332280 (Formerly Indian Patent Application No. 201727012821) dated 29/10/2015 made by GILEAD SCIENCES INC. on the grounds:

- (a) Section 25(2)(c): Prior claiming
- (b) Section 25 (2) (b): Lack of novelty
- (c) Section 25(2)(e): Lack of inventive step
- (d) Section 25(2)(f): Invention is not patentable under section 3(d)
- (e) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

(Detailed grounds are set out in the Opposition)

Our address for service in India is:

RAJESHWARI & ASSOCIATES

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Dated this 30th day of June, 2020



RAJESHWARI H. IN/PA – 0358
AGENT FOR THE OPPONENT
OF RAJESHWARI AND ASSOCIATES

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, MUMBAI

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,
MUMBAI**

In the matter of Section 25(2) of the Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of the Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent number 332280 (formerly Application number 201727012821) dated 29/10/2015 in the name of GILEAD SCIENCES INC.

REPRESENTATION BY:

LOW COST STANDARD THERAPEUTICS

..... OPPONENT

AND

GILEAD SCIENCES INC

..... PATENTEE

**STATEMENT OF OPPOSITION UNDER SECTION 25(2)
OF THE PATENTS ACT, 1970**

We, LOW COST STANDARD THERAPEUTICS, an Company formed under the Laws of India, hereby submit as under:

STATEMENT OF CASE OF OPPONENT

1. A Post-grant opposition under Section 25(2) of the Patents Act, 1970, is being submitted by the Opponent, Low Cost Standard Therapeutics, against Indian

Patent No. 332280 (hereinafter referred to as the “impugned patent”) which has been granted in favour of GILEAD SCIENCES INC (hereinafter referred to as the “Applicant/Patentee”).

LOCUS

2. LowCost Standard Therapeutics (hereinafter LOCOST) is a not-for profit organisation having its office at I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390 001, Gujarat, India. LOCOST was established to make essential medicines of quality at reduced costs by eliminating the margins shared with prescribers, distributors and related market costs. LOCOST makes essential medicines for those working with urban and rural poor in India. The goal of LOCOST is to provide good quality medicines at affordable prices for those working in remote areas.
3. Registered as Low-Cost Standard Therapeutics in 1983, it is a public charitable trust that is concerned with public health aspects of medicines: their genesis, costs, clinical trials, licensing, patenting, production, distribution and consumption till it reaches the end users, namely patients. LOCOST is also concerned about the long-term impact of medicines – their use, misuse and overuse, adverse reactions and side effects - and the public regulation of all related issues.
4. LOCOST has its own well-equipped production facility in Vadodara where it produces more than 100 essential and rational medicines. The establishment makes more than 60 essential medicines in 80 formulations (liquids, capsules, tablets).LOC LOCOST is also active in pharmaceutical policy advocacy at regional and national levels. LOCOST products are preferred by many not for profit health institutions across India The sales are directed at institutions and individuals that work on a not-for profit basis or cater to the poorest of people.
5. Manufacturing at LOCOST conforms to the highest standards of production set by the Government of India. LOCOST’s production facilities have Schedule M certification of the Government of India and anytime now it is expected to have

WHO-GMP certification too. LOCOST's management practises ethical business norms that further assure our long-standing clients that no corners are cut on quality standards.

6. LOCOST realizes that mere production of essential medicines is not enough. LOCOST also engages in educating prescribers as well as users. Its education cell focuses on issues related to education and training for rational use of medicines. LOCOST publishes a monthly in Gujarati, namely *Apnu Swasthya*, and other publications for the general public including but not limited to the Gujarati version of classics such as *Where there is no Doctor* and *A Lay Person's Guide to Medicine* (a guide on the use and political economy of medicines).
7. The Opponent is also engaged in the manufacture and sale of various antiviral compounds. Additionally, the Opponent has been conducting research in respect of antiviral compounds. The existence of the impugned patent is against public interest and research in respect of anti-viral compounds. Thus, the Opponent is a person interested having direct and tangible interest in filing the present opposition.

GENERAL BACKGROUND ON REMDESIVIR

8. The Indian Patent No 319927 relates to the anti-viral drug remdesivir (RDV). RDV is generally claimed to be an effective treatment against broad class of "Filoviridae virus infections", particularly for treating Ebola virus, Marburg virus and Cueva virus. The Coronavirus belongs to the same family of filoviridae virus. Originally developed for Ebola treatment, RDV is an investigational broad-spectrum anti-viral drug, which is currently (as of June 2020) undergoing clinical trials, is yet to be approved for the treatment of COVID19. However, it is being used to treat patients as part of compassionate use or clinical trial. Studies have shown that this drug works against SARS and MERS, two other coronaviruses that are more lethal but less contagious.
9. RDV belongs to the nucleoside analogues class of medicines, which was developed at the University of Alabama's (UAB) Antiviral Drug Discovery and

Development Centre (AD3C) with federal government funding[<https://www.statnews.com/2020/03/16/remdesivir-surges-ahead-against-coronavirus/>](Annexed as Annexure 1). The AD3C received about \$37.5 million “U19” grant *to study and develop a treatment for emerging infections like coronaviruses that can trigger SARS, MERS, and remdesivir*(GS) was developed by the researchers at the University after five years of research since 2014.[see<https://www.uab.edu/news/health/item/10307-37-5-million-grant-will-address-research-of-high-priority-infections> (Annexed as Annexure 2) <https://www.trialsitenews.com/university-of-alabama-multi-center-collaboration-help-develop-remdesivir-with-gilead-thanks-to-37-5m-from-nih/>](Annexed as Annexure 3). The grant involves a public-private partnership between academic institutions and Gilead Sciences Inc. [<https://www.bizjournals.com/birmingham/news/2020/03/02/drug-developed-by-uab-nih-researchers-being-used.html>](Annexed as Annexure 4). Hence, the Applicant/Patentee’s claim to have spent billions of dollars is misleading.

10. Despite, being an investigational drug, RDV is being used for the treatment in emergency, severe and critical COVID-19 conditions along with oxygen. RDV is being sold at an exorbitant cost [**\$2340 for five day course of treatment as of June 2020**], the presence of wrongly granted patents for RDV is hindering wide-scale generic production. Hence it is highly important and extremely urgent for the Patent Office to review the grant of patents in light of the prior arts disclosed in opposition and revoke the patent.

ACCESS TO MEDICINES AND STRICT INTERPRETATION OF INDIAN PATENTABILITY STANDARDS

11. The Indian Patents (Amendment) Act, 2005 was passed to bring India into compliance with its obligations under TRIPS [The Agreement on Trade-Related Aspects of Intellectual Property Rights], and introduced a 20-year product patent regime. In 2001, WTO Members adopted a special Ministerial Declaration at the WTO Ministerial Conference in Doha to clarify ambiguities between the need for governments to apply the principles of public health and the terms of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS).

The Doha Declaration on the TRIPS Agreement and Public Health (the Doha Declaration) reaffirmed the right of the WTO members to make use of the flexibilities of the TRIPS Agreement in a manner that is supportive of public health objectives. In this context, patent offices play a very critical role in making use of such flexibilities while determining the patentability of a claim on a pharmaceutical product or process..

12. The Opponent respectfully submits that the obligation to promote access to medicines for all must be upheld and that the Patents Act, 1970 must be interpreted to give effect to this aim. The Doha Declaration should be the underlying value system that informs all patent examinations.
13. Furthermore, the Opponent submits that the Doha Declaration has been incorporated into the Patents Act by Parliament through provisions that protect public health. Patents are given to inventions in exchange for advances in science and technology. Where drug companies are granted patents for only minor improvements of existing drugs, they are at liberty to set the prices of the drugs, and often fix prices well beyond the means of an average person in the developing countries including India. Granting patents for such frivolous applications are thus injurious to both scientific advancement and to public health.
14. In 2005, while amending the Patents Act, 1970, the members of Parliament decided to deny patent protection to multiple patenting of the same substance or proliferation of patents of the same drug and rejected the practice of “evergreening”. In this regard section 3(d) is perhaps the most important provision, which prohibits patents for “a new form of a known substance which does not result in the enhancement of the known efficacy of that substance” or for the mere discovery of a “new use of a known substance”.
15. In this regard, the Supreme Court observed that “ With regard to the genesis of section 3(d), and more particularly the circumstances in which section 3(d) was amended to make it even more constrictive than before, we have no doubt that the “therapeutic efficacy” of a medicine must be judged strictly and narrowly. Our inference that the test of enhanced efficacy in case of chemical

substances, especially medicine, should receive a narrow and strict interpretation is based not only on external factors but there are sufficient internal evidence that leads to the same view. It may be noted that the text added to section 3(d) by the 2005 amendment lays down the condition of “enhancement of the known efficacy”. Further, the explanation requires the derivative to “differ significantly in properties with regard to efficacy”. What is evident, therefore, is that not all advantageous or beneficial properties are relevant, but only such properties that directly relate to efficacy, which in case of medicine, as seen above, is its therapeutic efficacy.” [para 180, *Novartis AG vs Union of India*, (2013)6SCC1]

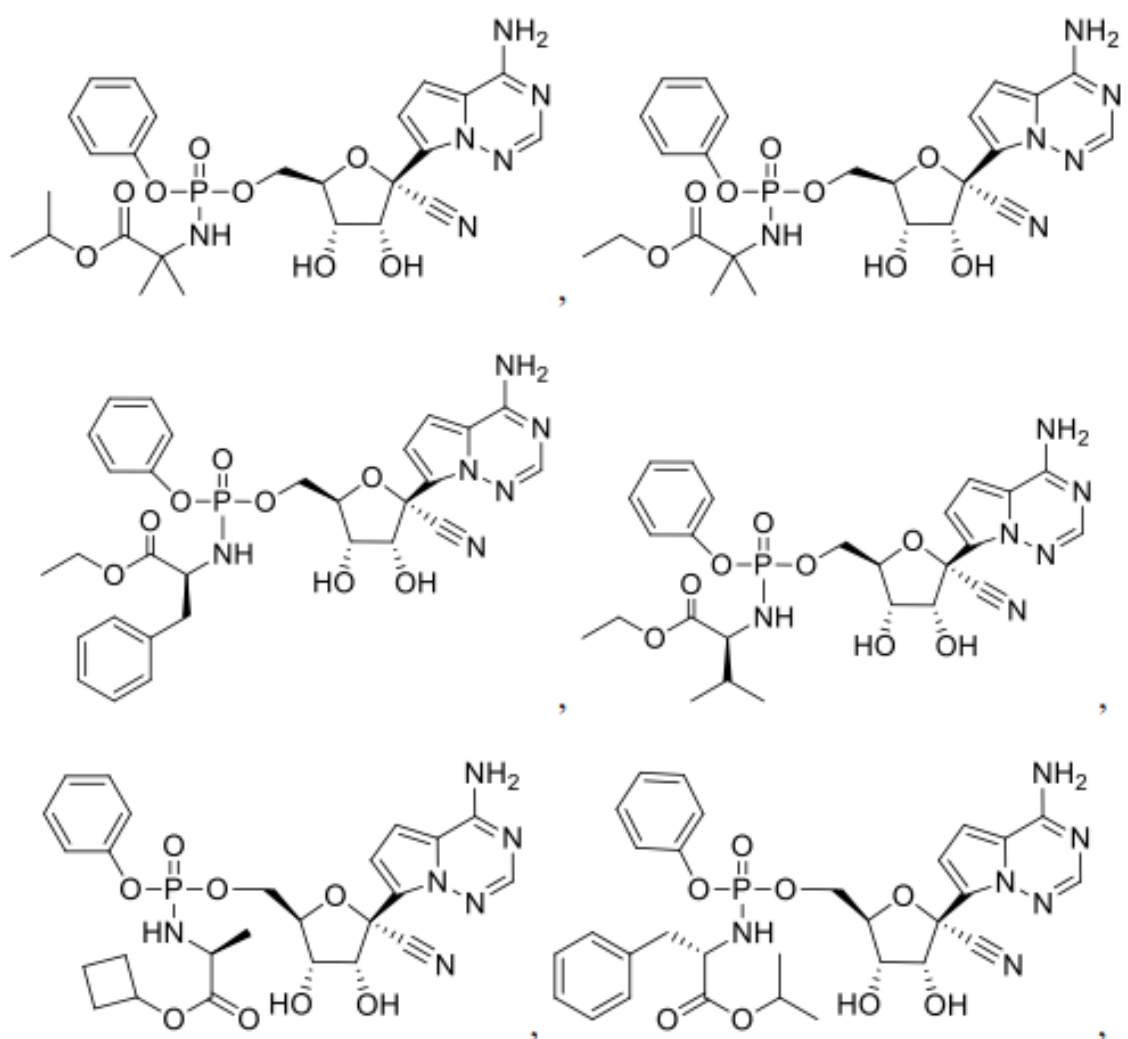
16. Apart from section 3(d), it is also important to implement sections 2(1)(j) and (ja) more diligently and strictly to avoid frivolous and unworthy patent applications from being granted a patent. In this regard, the amended provision for inventive step sets a higher two -step standard for determining the inventive step in a patent application. The applicant has an obligation to prove that the feature of the invention has a technical advance or economic significance and the feature is non-obvious to a person skilled in the art. Thus, it is imperative for the Patent Office to seek scientific evidence for proving inventive step as well as seeking the applicant to disclose the inventive feature of the invention.
17. The Opponent states that the right to health guaranteed under Article 21 of the Constitution of India is of paramount importance and that medicines required for COVID-19 treatment be made available, so that maximum number of people can benefit from the treatment and many lives can be saved. The wrongly granted patents to the Applicant would breach the right to health of a large number of COVID-19 patients languishing in the hospitals unable to access life-saving yet costly medications. It is submitted that the Hon’ble Patent Controller, may examine the Present Application with strict scrutiny, as its decision will have far reaching effect on the availability of affordable access to treatment for COVID-19 and such other infection.
18. The Patentee had filed an Indian Patent Application No. 201727012821 on 11/04/2017. The said application was granted on 18/02/2020 under patent number 332280 (hereinafter referred as the Impugned Patent). The Impugned patent is

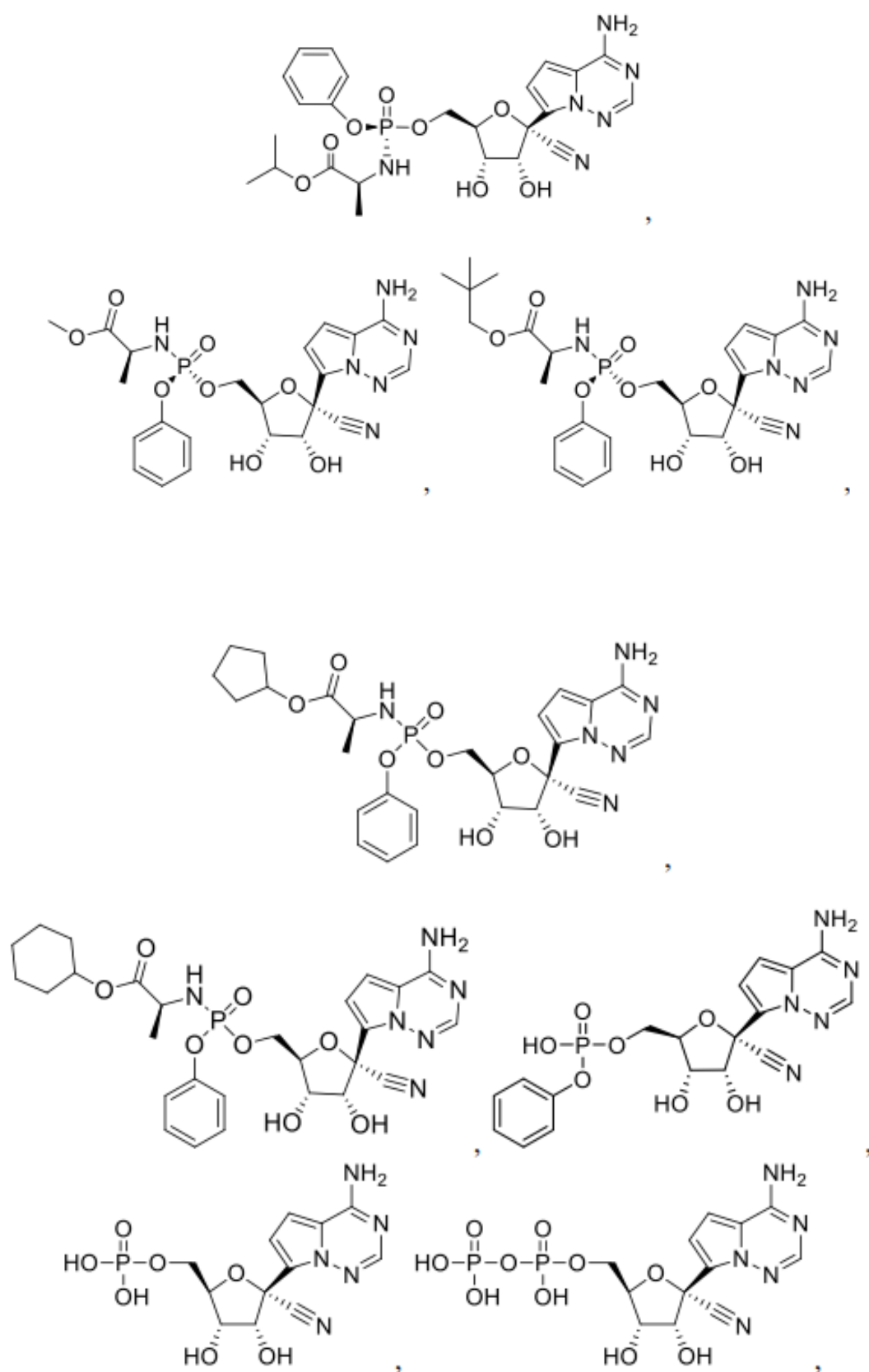
titled as “COMPOUNDS FOR TREATING FILOVIRIDAE INFECTIONS”. The priority date of the impugned patent is 29/10/2014. It appears that the said application was examined by this office and granted as IN’280.

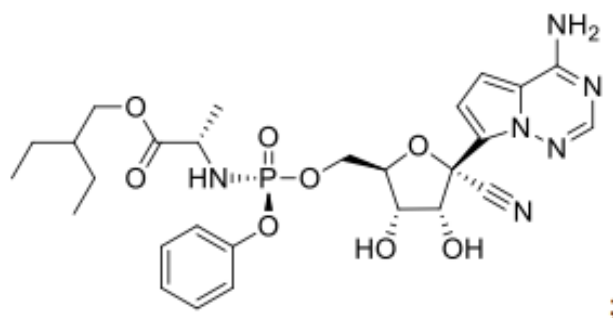
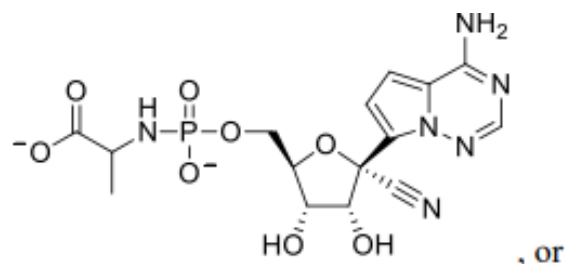
19. The claims currently on record are annexed herewith as **Annexure - 5** and reproduced herein below for ready reference:

Claims:

1. A compound:

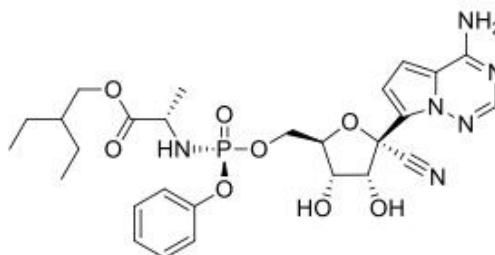






or a pharmaceutically acceptable salt thereof.

2. The compound as claimed in claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in claim 1 or claim 2, or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

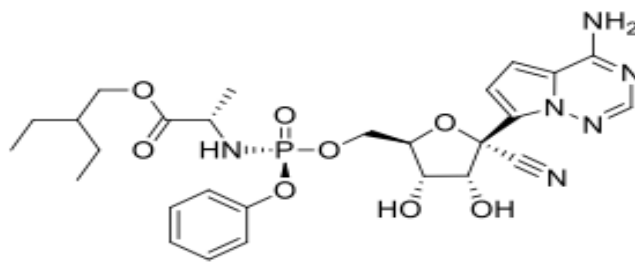
2. The claims of the impugned patent claim various antiviral compounds of which one of the claimed compounds is known by the INN of Remdesivir.

SUMMARY OF GROUNDS FOR OPPOSITION

20. The Opponent is filing this opposition under the following grounds, amongst others, each of which are without prejudice and in the alternative to one another:

- i. Claims 1-3 of the Present patent are not novel as the alleged invention claimed in these claims have been published and are prior claimed before the priority date. Therefore, the Opponent brings this Opposition under Section 25(1)(b)(ii)-
- ii. Claims 1-3 of the Present patent lack inventive step, and therefore fail under Sections 2(1)(j) and 2(1)(ja) of the Patents Act.
- iii. that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document.
- iv. Claims 1-3 of the Present patent do not satisfy the test of Section 3(e) and 3(d) of the Patents Act as the subject matter does not exhibit any synergistic effect.
- v. that the subject of any claim of the complete specification is not an invention within the meaning of this Act.
- vi. The method to arrive at claims 1-3 of the Present patent has not been clearly described in the patent.
- vii. That the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed
- viii. The Opponent brings this opposition under Section 25(1) (h) of the Act viz. that the Patent Applicant has failed to disclose the information required by Section 8 or has furnished information which in any material particular was false to his knowledge.

21. **Disclosure in the impugned patent:** As per the Patentee, the invention relates to methods and compounds for treating Filoviridae virus infections, particularly methods and nucleosides for treating Ebola virus, Marburg virus and Cueva virus. It discloses many compounds including (S) diastereomer Remdesivir.



22. Accordingly, the Opponent submits its opposition by way of representation under Section 25(2) in respect of the said Indian Patent No. **332280** on the following grounds below, which are without prejudice and in the alternative to each other.

- (a) Section 25(2)(c): Prior claiming
- (b) Section 25 (2) (b): Lack of novelty
- (c) Section 25(2)(e): Lack of inventive step
- (d) Section 25(2)(f): Invention is not patentable under section 3(d)
- (e) Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

PRIOR ARTS:

23. The Prior arts relied upon by the Opponent are as below

- D1: US8008264 publication date Aug. 2011
- D2: WO 2009/132135 publication date Oct.2009 (IN 275967)
- D3: WO2012012776 publication date Jan. 2012 (IN319927)
- D4: Cho et al “Synthesis and antiviral activity of a series of 10 -substituted 4-aza-7,9-dideazaadenosine C-nucleosides” Volume 22, Issue 8, 15 April 2012, Pages 2705-2707
- D5: Mehellou et. al. “Aryloxy PhosphoramidateTriesters: a Technology forDelivering Monophosphorylated Nucleosides and Sugarsinto Cells” ChemMedChem 2009, 4, 1779 – 1791

GROUND I: PRIOR CLAIMING UNDER SECTION 25(2)(c)

24. It is submitted that the invention as claimed in the impugned patent as set out in granted claims 1 to 3 liable to be revoked for prior claiming under Section 25(2)(c) of the Act.

PRIOR CLAIMING BY IN 332280 (IN' 280)

25. The claims of the impugned Patent IN 332280 are prior claimed by IN 319927 herein reproduced as IN'927. The IN'927 (formerly 1328/CHENP/2013) was filed on 19.02.2013 and granted on 05.9.2019. It has a PCT application PCT/US2011/045102 that was filed on 22.07.2011. The conditions for prior claiming is fulfilled in IN'927 because:-

- a) IN'927 claims priority date 22.07.2010, which is prior to the priority date of the impugned patent i.e. 29.10.2014.
- b) IN'927 is published after the priority date 29.10.2014 of the impugned patent i.e. published on 03.06.2016 (publication date of the application of IN'927);
- c) IN'927 is an Indian patent emerging from an application filed in India.

It is submitted that IN'927 fulfils all tenets of Section 25(2)(c) as set out hereinabove.

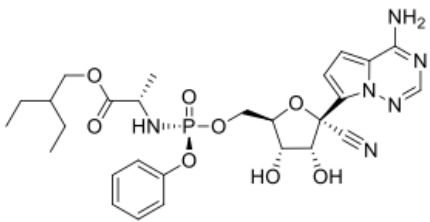
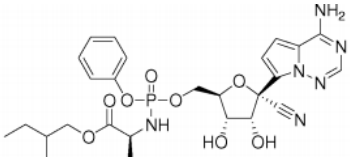
Table 1: PRIOR CLAIMING BY IN '927

Patent Number	Priority data	Publication date
Impugned Patent IN'280	62/072,331US (29.10.2014) 62/105,619 US (20.01.2015)	09.06.2017
Prior art IN '927	61/366,609 US (22.07.2010)	03.06.2016

26. From the table above, it is clear that IN'927 –

- a) Has earlier priority date (22.07.2010) as compared to Impugned Patent IN'280 (whose priority is 29.10.2014)
- b) Has been published after the priority date of impugned patent i.e. published on 03.06.2016 i.e. after 29.10.2014.

Further, a comparison of the claims of the impugned patent with IN'927 (Prior art) it can be clearly seen that Remdesivir which is claimed in the impugned patent is also covered and claimed by Claim 1 of IN' 927as illustrated herebelow.

Impugned Patent (IN'280)	(IN'927) (Prior art)
Claim 1 includes one of the compound  The chemical structure of Remdesivir is shown. It consists of a 2,6-diaminopurine-9-yl group attached to a ribose sugar, which is linked via a phosphonate group to a chiral center. This chiral center is also attached to a phenyl group and a 2,2,4,4-tetramethyl-1,3-dioxane-5-carboxamide group.	A compound that is  or or a pharmaceutically acceptable salt thereof The specification supports that “All mixtures of such enantiomers and <u>diastereomers</u> are within the scope of the present invention” Specification further discloses, thatIn other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The

racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

Specification, further goes on disclosing **Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, reactivities**

For example, the compounds of Formula I-IV may have a chiral phosphorus atom when R⁷ is



and W¹ and W² are different. When at least one of either W or W also has a chiral center, for example with W or W is a nitrogen-linked, chiral, naturally occurring α -amino acid ester, then the compound of Formula I-IV will exist as diastereomers because there are two centers of chirality in the molecule. **All such diastereomers and their uses**

	described herein are encompassed by the instant invention. Mixtures of diastereomers may be separate under high resolution analytical procedures such as electrophoresis, crystallization and/or chromatography. Diastereomeres may have different physical attributes such as, but not limited to, solubility, chemical stabilities and crystallinity

27. In law, a case of prior claiming is made out if it appears that the same compound or substance is being “re-monopolized”. In the present case, it is clear from the above that ‘Remdesivir’ which was claimed in IN ‘297 is being claimed again in the impugned patent.
28. From the above, it is clear that if the compound Remdesivir which is claimed in the impugned patent, is already claimed is granted in a prior art patent.
29. In view of the above, case of prior claiming is fully made out. Hence, the impugned patent ought to be revoked on this ground alone

GROUND 2: LACK OF NOVELTY

30. Section 2(1)(j) of the Patents Act defines an “invention” as “a new product or process involving an inventive step and capable of industrial application” (emphasis added). Section 25 (2)(b)(ii) of the Patents Act allows opposition of a patent if the alleged invention, as claimed in any claim of the complete specification has been published before the priority date of the claim in India or elsewhere, in any other document. Therefore, claims of a patent are to be rejected if a publication dated before the priority date of the patent application in question

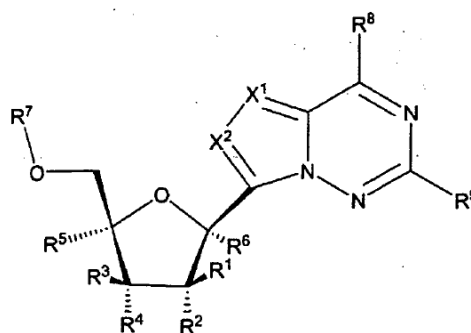
discloses the alleged invention. Whether the prior publication discloses the alleged invention may be determined by comparing the claims of the patent application in question to that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim-

- (i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January, 1912; or
- (ii) in India or elsewhere, in any other document:

Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or sub-section (3) of section 29;

31. Opponent states that the claims of the impugned patent are already claimed and published by WO 2009/132135. The PCT application includes a Markush claim, which claims and covers Remdesivir. WO 2009/132135 discloses generally to compounds with antiviral activity, more particularly nucleosides active against Flaviviridae infections and most particularly to inhibitors of hepatitis C virus RNA-dependent RNA polymerase. It further discloses a general scaffold (page 10: specification). The specification has been reproduced below.

In another aspect, compounds of Formula I are represented by Formula II:



Formula II

or a pharmaceutically acceptable salt, thereof;

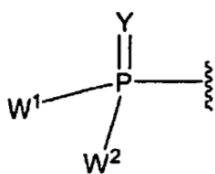
Further, it disclosed the functional groups on the sugar are disclosed as R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and the functional groups on the base are R^8 , R^9 and X^1 and X^2 .

Of the above, R^1 , R^3 , R^5 can be H, R^2 and R^4 can be OR^a wherein R^a can be H (See page 11), Hence R^2 and R^4 can be OH.

R^6 can be CN. [page 11].

R^8 can be NH_2 (R^9 , R^{10} is H) [see page 13] R^9 and X^1 and X^2 can be CH;

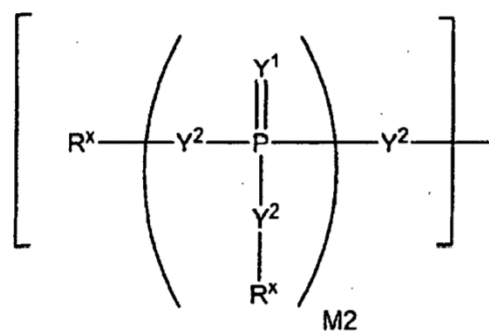
R^7 can be



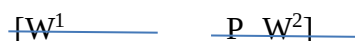
(Page 11)

Y is O (oxygen)

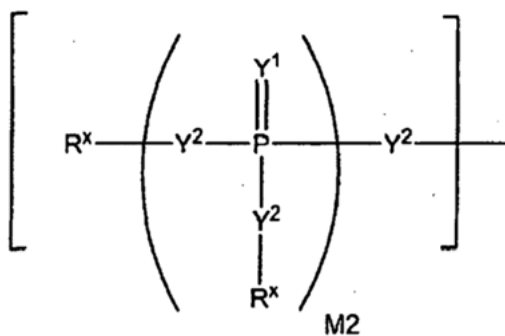
W^1 and W^2 are each, independently, a group of the Formula Ia:



1. Though the template for the formula of W^1 and W^2 are the same, both W^1 and W^2 are independent and functional group substituents can be different for each.
(Page 11)



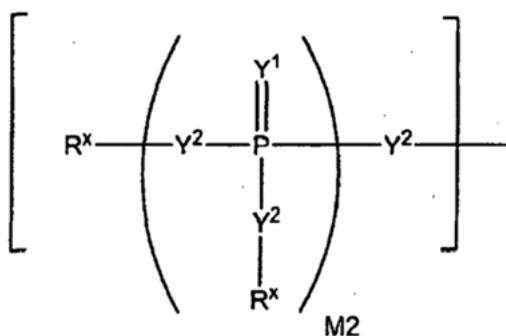
W^1 can be



8

In the above structure Y^2 can be O, M^2 is zero, R^x is independently R^y and R^y is R and R can C_6-C_{20} aryl- that is R^x is C_6H_5 .

W^2 can be

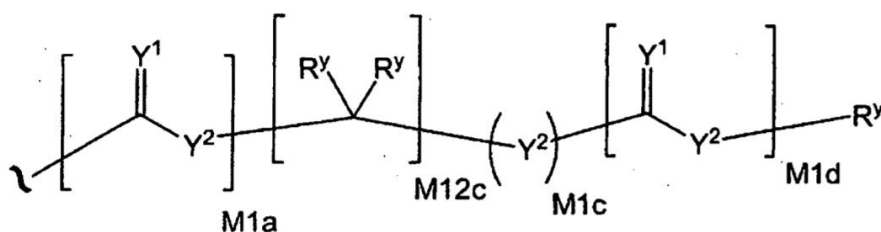


Of the above Y^2 is NR-where R can be H, So Y^2 is NH (page 13);

M^2 is zero

R^x is the formula:

each R^x is independently R^y or the formula:



wherein:

each $M1a$, $M1c$, and $M1d$ is independently 0 or 1;

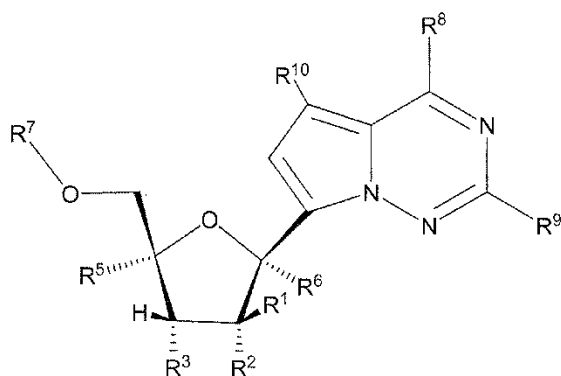
$M1a$ is Zero, $M1c$ is zero, $M12c$ is one (1), $M1d$ is one (1). Each R^y in above formula can be independent.

So (from the left) R^y can be H, R^y can be R and R can be C1-C8 alkyl such as CH_3 methyl; Y^1 is O and Y^2 is O (page 11). R^y can be R and R can be substituted alkyl. At page 37, substituted alkyl (non-hydrogen substituent) R^b substituted butyl-ethyl group-hence R^y can be ethyl substituted butyl or 2-ethyl-1-butyl. Substituting the above embodiments in the Formula II, we get remdesivir

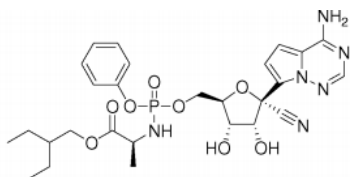
It further discloses that all enantiomers, **diastereomers**, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I, Formula II, or Formula III and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

WO2012012776 discloses methods and compounds for the treatment of infections caused by the Paramyxoviridae virus family. Provided, is a method for treating a

Paramyxoviridae infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



It specifically discloses the compound 9



The specification states that “All mixtures of such enantiomers and diastereomers are within the scope of the present invention”

32. Specification further discloses, that “In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.
33. Specification, further sets out that diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, reactivities

For example, the compounds of Formula I-IV may have a chiral phosphorus atom when R^7 is



and W^1 and W^2 are different. When at least one of either W or W also has a chiral center, for example with W or W is a nitrogen-linked, chiral, naturally occurring α -amino acid ester, then the compound of Formula I-IV will exist as diastereomers because there are two centers of chirality in the molecule. All such diastereomers and their uses described herein are encompassed by the instant invention. Mixtures of diastereomers may be separated under high resolution analytical procedures such as electrophoresis, crystallization and/or chromatography. Diastereomers may have different physical attributes such as, but not limited to, solubility, chemical stabilities and crystallinity.

Thus, a case of lack of novelty is made out and the impugned patent should be revoked on this ground alone.

GROUND 3: LACK OF INVENTIVE STEP

CLAIMS 1 TO 3 ARE OBVIOUS, DO NOT INVOLVE A TECHNICAL ADVANCE, AND LACK INVENTIVE STEP AS DEFINED UNDER SECTION 2(1)(ja) AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(2)(e) OF THE PATENTS ACT

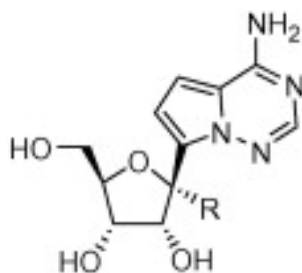
34. Section 2(1) (j) defines an “invention” as “a new product or process involving an inventive step and capable of industrial application.” For an alleged invention to qualify for a patent, it must satisfy the criteria of inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as “a feature of an invention that involves technical advance as compared to the existing knowledge ... and that makes the invention not obvious to a person skilled in the art” Sub-sections (j) and (ja) of Section 2(1) of the Patents Act thus require a Patent Applicant to show that the

feature of the alleged invention involve a technical advance and that it is not obvious to a person skilled in the art (POSITA).

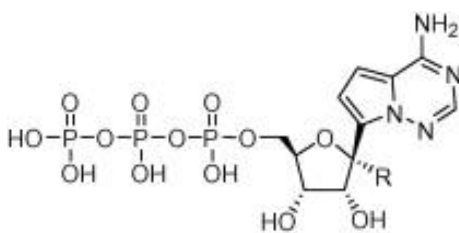
35. Section 25(2)(e) of the Patents Act provides a ground for opposition if the alleged invention is obvious and does not involve an inventive step having regard to matter published, as described in section 25(2)(b) of the Patents Act. The published matter to be considered under this provision includes matter published in India or elsewhere in any document before the priority date of the alleged invention. The Opponent submits that claims 1-3 of the Present patent lack an inventive step and therefore should be rejected.

36. Cho *et. al* discloses a series of 1'-substituted analogs of 4-aza-7,9-dideazaadenosine C-nucleoside were prepared and evaluated for the potential as antiviral agents. These compounds showed a broad range of inhibitory activity against various RNA viruses. In particular, the whole cell potency against HCV when R = CN was attributed to inhibition of HCV NS5B polymerase and intracellular concentration of the corresponding nucleoside triphosphate.

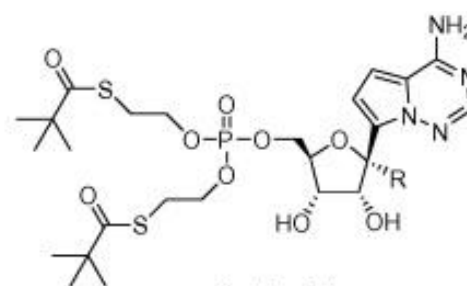
37. It further discloses below compound (3a) and their prodrug 8 (a) and 9(a)



3a R = CN
3b R = CH₃
3c R = vinyl
3d R = ethynyl



8a R = CN
8b R = CH₃
8c R = vinyl
8d R = ethynyl



9a R = CN
9b R = CH₃
9c R = vinyl
9d R = ethynyl

38. It also discloses the synthesized nucleosides **3a–3d** were evaluated in cell-based assays against a panel of RNA viruses. Anti-HCV activity was obtained using a subgenomic replicon. Viruses tested included representatives of *Flaviviridae* (HCV, YFV, DENV-2, WNV), *Orthomyxoviridae* (influenza A), *Paramyxoviridae* (parainfluenza 3), *Picornaviridae* (Coxsackie A), and *Coronaviridae* (SARS-CoV). Antiviral activity (EC_{50}) and cytotoxicity (CC_{50} for host cells in each assay).

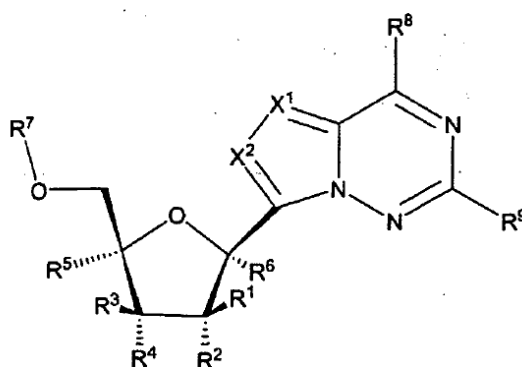
Compound 3a (R = CN) displayed broader spectrum activity (HCV, YFV, DENV-2, Influenza A, Parainfluenza 3 and SARS-CoV.

39. The prodrugs 9a and 9b showed markedly enhanced replicon activity when compared to the parent nucleosides. These monophosphate prodrugs afforded >100-fold higher levels of the TP species than the parent nucleosides.

40. Hence, before the priority date of the impugned patent it was known that GS-441524 (active metabolite of Remdesivir) and its prodrugs have a potent activity for viral RNA dependent RNA polymerases (RdRp)

41. WO 2009/132135 discloses compounds with antiviral activity, more particularly nucleosides active against **Flaviviridae infections** and most particularly to inhibitors of hepatitis C virus RNA-dependent RNA polymerase. it further discloses a general scaffold (page 10: specification). The specification has been reproduced below.

In another aspect, compounds of Formula I are represented by Formula II:



Formula II

or a pharmaceutically acceptable salt, thereof;

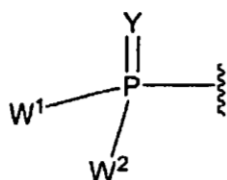
Further, it disclosed the functional groups on the sugar are disclosed as R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and the functional groups on the base are R^8 , R^9 and X^1 and X^2 .

Of the above, R^1 , R^3 , R^5 can be H, R^2 and R^4 can be OR^a wherein R^a can be H (See page 11), Hence R^2 and R^4 can be OH.

R^6 can be CN. [page 11].

R^8 can be NH_2 (R^9 , R^{10} is H) [see page 13] R^9 and X^1 and X^2 can be CH;

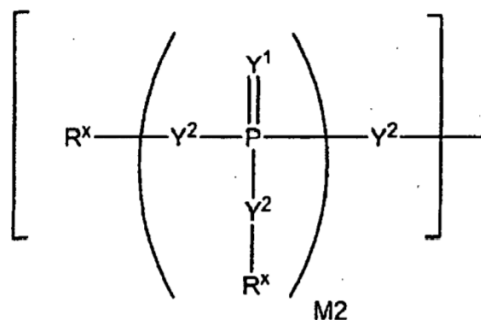
R^7 can be



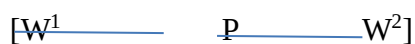
(Page 11)

Y is O (oxygen)

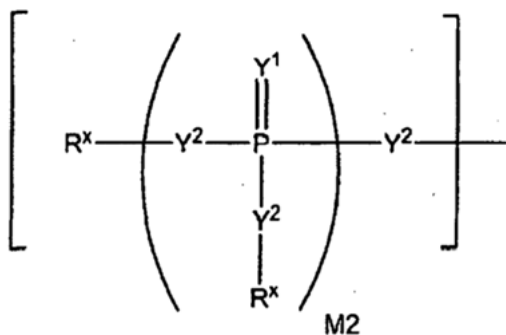
W^1 and W^2 are each, independently, a group of the Formula Ia:



Though the template for the formula of W^1 and W^2 are the same, both W^1 and W^2 are independent and functional group substituents can be different for each. (Page 11)



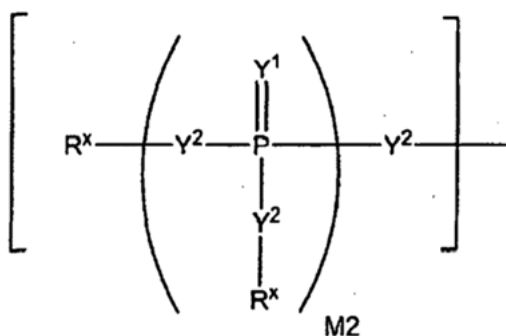
W^1 can be



8

In the above structure Y^2 can be O, M^2 is zero, R^x is independently R^y and R^y is R and R can C_6 - C_{20} aryl- that is R^x is C_6H_5 .

W^2 can be

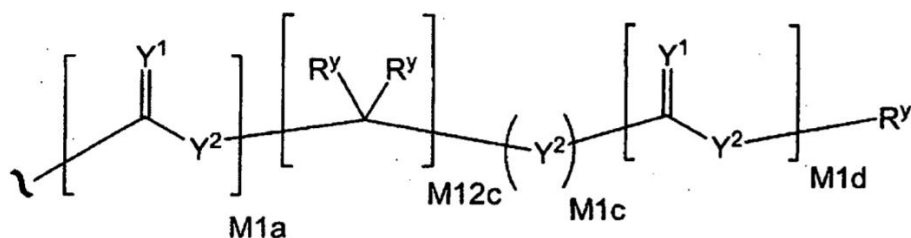


Of the above Y^2 is NR-where R can be H, So Y^2 is NH (page 13);

M^2 is zero

R^x is the formula:

each R^x is independently R^y or the formula:



wherein:

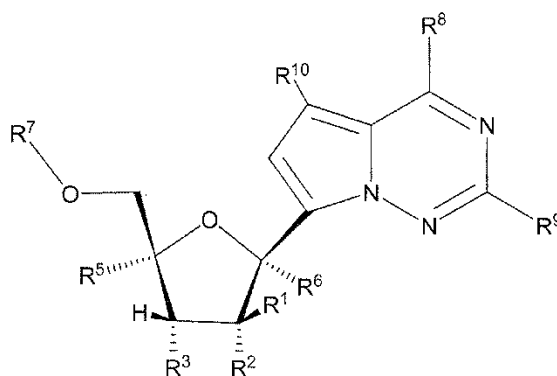
each $M1a$, $M1c$, and $M1d$ is independently 0 or 1;

$M1a$ is Zero, $M1c$ is zero, $M12c$ is one (1), $M1d$ is one (1). Each R^y in above formula can be independent.

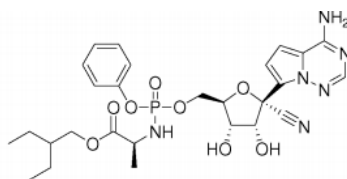
Hence (from the left) R^y can be H, R^y can be R and R can be C1-C8 alkyl such as CH_3 methyl; Y^1 is O and Y^2 is O (page 11). R^y can be R and R can be substituted alkyl. At page 37, substituted alkyl (non-hydrogen substituent) R^b substituted butyl-ethyl group-hence R^y can be ethyl substituted butyl or 2-ethyl-1-butyl.

Substituting the above embodiments in the Formula II, we get remdesivir

42. WO2012012776 discloses methods and compounds for the treatment of infections caused by the Paramyxoviridae virus family. Provided, is a method for treating a Paramyxoviridae infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



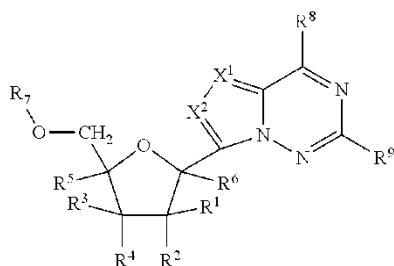
It specifically discloses the compound 9



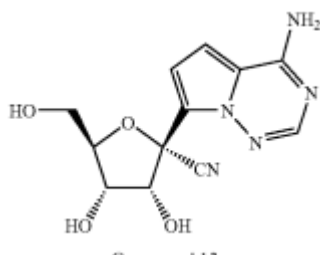
43. US8008624 discloses the invention also comprises compounds that inhibit viral nucleic acid polymerases, particularly HCV RNA-dependent RNA polymerase (RdRp), rather than cellular nucleic acid polymerases. Therefore, the compounds of the instant invention are useful for treating Flaviviridae infections in humans and other animals.

In one aspect, this invention provides a compound of Formula I:

Formula I



or a pharmaceutically acceptable salt, thereof; It specifically discloses compound 13



44. Mehellou et. al. discloses the phosphoramidate triester prodrug approach has been well investigated and established as a viable method for the intracellular delivery of monophosphate nucleoside analogues. This approach has been proven to considerably improve the anti-viral and anticancer profiles of many nucleoside analogues.
45. The phosphoramidate triester prodrug technology has proved effective as a tool for drug discovery, and so far at least four phosphoramidate triester-based drugs are undergoing clinical trials (one anticancer and three antiviral agents).
46. In light of the above documents, it would be obvious for a person skilled in art to arrive at the claimed invention without any ingenuity. The inventive step claims in the alleged patent IN'927 are destroyed as what is claimed as there is reasonable expectation of success embedded in the prior art that motivates a skilled person to arrive at the alleged invention. Additionally, obviousness does not require absolute predictability of success. All that is required is reasonable expectation of success in the matter of pharmaceutical drugs. All the prior art documents annexed hereto provide reasonable predictability of success, and the patent ought not to have been granted.

Thus, a case of lack of obviousness is made out and the impugned patent should be revoked on this ground alone.

GROUND 4: CLAIMS NOT PATENTABLE UNDER SECTION 25(2)(f)

The subject matter of claims is not patentable under Section 3(d) of the Act:

47. It is submitted process and product as claimed in the impugned patent are not patentable under Section 3(d) which states that

Section 3(d) in of Patents Act, 1970

the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known

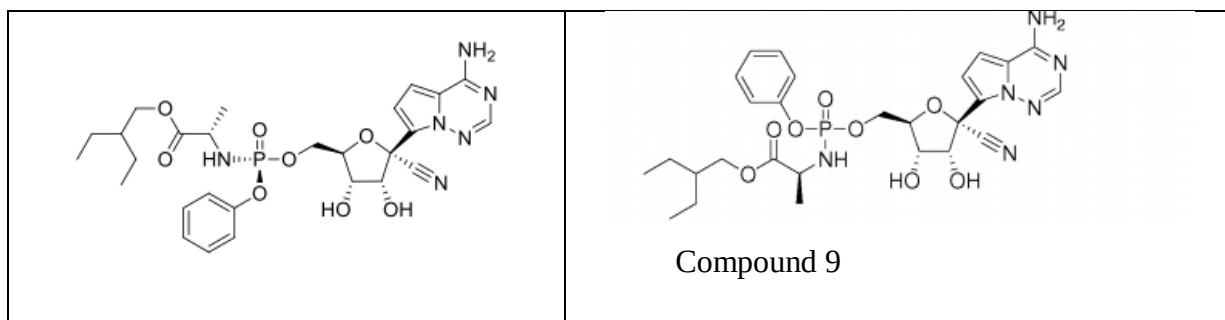
process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.

The Opponent states that the compounds claimed in impugned patent is the new form of the known compound disclosed in WO'135 and WO' 176. The opponent submits that the Patentee has failed to demonstrate any enhancement in the therapeutic efficacy with respect to the known efficacy of the form disclosed in WO'135 and WO' 176. All the process parameters viz, the starting material, solvents, was already known in the art.

The Opponent states that the compounds claimed in impugned patent is the new form of the known compound disclosed in WO'135 and WO'176 which does not result in the enhancement of known efficacy and thus not patentable under section 3 (d). Complete specification of the impugned patent does not provide any comparative data to demonstrate enhancement in the therapeutic efficacy with respect to the known efficacy of form disclosed in WO'135 and WO'176. The Opponent states that the patentee miserably failed to provide data demonstrating enhanced 'therapeutic' efficacy as there is no comparative data disclosed in the impugned patent showing improved efficacy of new form of impugned patent over known form disclosed in WO'135 and WO'176

IN'280 (Impugned Patent)	WO'176 (Prior art)



Thus, the subject matter of impugned patent squarely falls within the purview of Section 3(d) of the Act. Hence the impugned patent should be rejected under section 25(2)(f).

The subject matter of claims of impugned patent is not patentable under Section 3(e) of Act:

48. It is submitted that the formulation as claimed claims 2-3 in the impugned patent are not patentable under Section 3(e) which states that:

a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance.

The opponent submits that the subject matter of Claims 3 of the impugned patent falls under 3(e). The claimed composition in claim 3 does not defined in terms of ratio and concentration of the components which constitute the impugned patent and is thus a mere admixture.. The Patentee has merely used common general knowledge in the art and combined actives with excipients to achieve the desired resultant composition. However, the Patentee has not disclosed any evidence or experimental data in the impugned patent outlining that the claimed composition displays any effect which unexpectedly supersedes the effect produced by the individual components.

In absence of any comparative data highlighting the synergistic effect of the components of the claimed composition of the impugned patent over its individual components, the impugned patent should be rejected under section 3(e) read with section 25(2)(f) of the Act.

CLAIMS NOT PATENTABLE UNDER SECTION 25(2)(g)

49. Claim 1 of the impugned patent pertains to many compounds. However, the patentee discloses the use of the compounds for filoviruses. However, the patentee has not provided any experimental data showing that all the compounds of the impugned patent will be effective against all the diseases caused by filoviruses. The person skilled in the art would have to do the undue experimentation to find out which compound is effective against which disease caused by Filoviruses.
50. Claim 3 of the impugned patent claims a composition of the compound but there is no disclosure of ratio or percentage of individual components of the composition. Further, the impugned specification does not disclose even a single working example of the composition claimed in impugned patent. The ratio/percentage of said components is greatly significant since change in the relative ratios/percentages of said components results varied forms of the active. Absence of this essential technical feature renders the scope of claims of impugned patent indefinite and unclear.
51. In light of above, it is clear that impugned patent does not sufficiently and clearly describe the invention. Therefore, the impugned patent should be rejected.

SECTION 25(1)(H): THE PATENTEE HAS FAILED TO DISCLOSE TO THE CONTROLLER THE INFORMATION REQUIRED UNDER SECTION 8

63. It is submitted that the Patentee has filed huge number of corresponding patents in many countries outside India. However, the Form 3 details submitted by the Patentee do not disclose the details of all these corresponding patents at Indian Patent Office.
64. The opponent submits that the Patentee has purposefully and with malafide intention refrained from disclosing details of all the corresponding patents filed outside India and the prosecution details of same to the Learned Controller and therefore, on this ground alone the patent patents should be rejected.

The opponents crave leave to file further submissions and evidence with respect to this ground.

P R A Y E R

In the facts and circumstances of the case, the Opponent prays as follows:

- i. that the Indian Patent 332280, be revoked under Section 25(2) of the Patents (Amendment) Act, 2005;
- ii. the Opponent may be allowed to file further documents as evidence if necessary to support its averments;
- iii. the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;

Dated this 30th day of June, 2020



RAJESHWARI H.
AGENT FOR THE OPPONENT,
RAJESHWARI AND ASSOCIATE

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, MUMBAI

STAT

ANNEXURE - 1

As the coronavirus spreads, a drug that once raised the world's hopes is given a second shot

By [Andrew Joseph @DrewQJoseph](#)

March 16, 2020

[Reprints](#)

Alex Hogan/STAT

A decade ago, a group of chemists cooked up a compound [they simply called 3a](#) and that, in lab experiments, fought off a number of different viruses. One was a type of coronavirus.

Now, the descendant of that molecule — Gilead Sciences' remdesivir — is being rushed to patients with infections from the novel coronavirus in hopes that it can reduce the intensity and duration of Covid-19 and ease the burden of the pandemic on health systems.

Remdesivir, in the spotlight as scientists and governments scramble to find a treatment for the disease, took a circuitous route to center stage. Born as a general antiviral candidate, researchers threw it at an array of viruses and saw where it stuck. It bounced along from Gilead's labs to academic centers, nudged by both federal taxpayer dollars and support from the company. It kept turning up whiffs of potential in cells and animals infected by other coronaviruses like SARS and MERS, but these bugs weren't causing sustained global crises. For years, Gilead was primarily focused on ushering remdesivir into trials and toward approval for a different kind of infection: Ebola.

But there's nothing like a pandemic to break the emergency glass on all possible options.

Remdesivir is now being tested in five Covid-19 clinical trials that have been set up at breakneck speed. It's been delivered through a compassionate use program to some patients, including the first case in the United States. The first

trial results are expected next month, though some analysts have [already raised concerns](#) about the prospects based on the drips of data emerging from a small number of patients.

Others' hopes are high for the drug. As of now, there are no approved therapies for any coronavirus infection, and remdesivir is the farthest along in the development process of any candidate.

“There’s only one drug right now that we think may have real efficacy,” Bruce Aylward of the World Health Organization said last month. “And that’s remdesivir.”

Support STAT: If you value our coronavirus coverage, please consider making a one-time contribution to support our journalism.

Remdesivir’s odyssey illuminates the complicated trajectory drugs can take as they are forged, refined, scrutinized, and moved into human studies. But its long, meandering path also underscores why drugs need to demonstrate their efficacy in these studies. The drug similarly had lofty expectations as an Ebola treatment, and strong data from animal studies to boot. But in [a landmark trial](#) that compared four experimental therapies and was published last year, two other treatments were shown to dramatically reduce deaths from the infection, while remdesivir faltered, producing less impressive survival benefits.

“Drug discovery and development is usually a very long and tedious process and you could have many failures on the path to an approved product,” Tomas Cihlar, Gilead’s vice president of virology, said in an interview with STAT.

As for remdesivir’s chances in Covid-19, Cihlar said: “It would be wonderful if it works. But it needs to be proven.”



When the patient with the first known U.S. case of Covid-19 was admitted to Providence Regional Medical Center in Everett, Wash., on Jan. 20, he wasn’t

all that sick.

The 35-year-old man had the respiratory infection's most common symptoms of fever and cough, but had no trouble breathing and no evidence of pneumonia — inflammation of the lungs' air sacs. But around that time, his doctors saw a report from China that detailed that some patients there developed more severe symptoms several days into their illnesses.

“That perked our ears to the worsening of this disease,” said George Diaz, the infectious disease section chief at the hospital.

Within a few days, the man — who had visited family in Wuhan, China, where the outbreak is believed to have started, and returned home to Washington Jan. 15 — started experiencing shortness of breath and requiring oxygen. An X-ray revealed pneumonia.

Diaz informed officials at the Centers for Disease Control and Prevention, with whom he had been conferring daily, that the patient was taking a turn for the worse. The CDC suggested trying an experimental drug, and mentioned Gilead's remdesivir.

Hospital officials got in touch with Gilead about providing the drug, and then got the approval from the Food and Drug Administration to treat the patient through a compassionate use program, which allows unapproved drugs to be given under select circumstances outside of clinical trials. Gilead overnighted the drug to the hospital.

“Treatment with intravenous remdesivir was initiated on the evening of day 7, and no adverse events were observed,” the medical team wrote in [a case report](#) in the New England Journal of Medicine. The man started feeling better the following day.

“We were aware that he was the first patient on the planet getting the drug for this infection, so we were super interested to see, hopefully, if he would improve,” Diaz recalled.

The apparent success in one patient does not prove the drug is effective. That is where the large trials that will compare remdesivir to placebos come in.

Remdesivir has been able to advance into clinical studies so quickly for two key reasons. For one, thanks to its use in Ebola, it was known to be generally safe in humans. And two, it had a large body of preclinical evidence — that is, data from studies in cells in lab experiments and in infected animals — that indicated it could temper coronavirus infections. [One study](#) published [just last month](#) by researchers from Gilead and the National Institute of Allergy and Infectious Diseases showed remdesivir inhibited the replication of MERS, a related coronavirus, in infected monkeys.

[Much of this preclinical research](#) has been conducted through collaboration among the National Institutes of Health, academic labs, and Gilead, steered by the Antiviral Drug Discovery and Development Center, or [AD3C](#). The center is an NIH-funded program run out of the University of Alabama at Birmingham that, since 2014, has been on the hunt for new treatments for emerging viruses.

Since drug screens revealed that remdesivir had potential as a coronavirus fighter, it was routed into the arm of AD3C focused on this family, a project led by Mark Denison at Vanderbilt University and Ralph Baric at University of North Carolina. Starting in about 2015 and with the backing of Gilead, they and scientists in their labs have pulled back the curtain on how exactly remdesivir curtails coronaviruses and demonstrated that it can block the viruses from multiplying in infected animals.



Bottles of remdesivir in a hospital for Covid-19 patients in Wuhan, China. *FeatureChina via AP*

The researchers got an additional NIH grant to ready remdesivir for clinical trials, and thought the target could be MERS, which has caused 858 deaths and nearly 2,500 cases, mostly in Saudi Arabia, since it started infecting people in 2012. But even with that focus, they were also thinking about how the drugs they were studying could be used for the next spillover — when a virus jumps from animals to people.

“We’ve always thought that coronaviruses were a family on the move,” said Tim Sheahan, a UNC coronavirus expert.

Even with that expectation, though, the researchers who have toiled away for years on these projects without much fanfare find themselves caught off guard now.

“People like me, people doing basic science, oftentimes the work that we’re doing has no obvious direct translation to improving human health,” Sheahan said. “It’s hard to imagine that the work we’ve done in a lab in North Carolina could be saving people’s lives around the world. It’s incredibly gratifying, but it’s surprising and unusual for someone like me to experience this.”

But if remdesivir had hopes as an Ebola treatment, how can it also work against coronaviruses? Their viral families are so different, “it’s like saying a giraffe versus an elephant,” said Gene Olinger, a former U.S. Army Ebola researcher, who is now the scientific advisor at MRI Global, a nonprofit research organization.

The trick is that remdesivir does not go after the virus directly. Instead, it targets the system the virus uses to replicate itself, hijacking it like you would your office’s copy machine as part of a company-wide prank.

These viruses have a genome that consists of a strand of RNA. To make copies of themselves, they rely on a molecule called a polymerase to string together the individual building blocks of the viral genome. These are like the “letters” that we think of composing DNA.

[Trending Now:](#)

[**Gilead announces long-awaited price for Covid-19 drug remdesivir**](#)

Remdesivir is an “analog,” designed to mimic the appearance of one of the RNA letters, adenosine. It looks so similar that the polymerase can unknowingly pick it up instead of the real adenosine and insert it into the strand of viral genome that’s being constructed, like bringing home [the wrong twin from summer camp](#). Once in place, the analog acts as a cap, preventing any additional pieces from being strung on. This leaves the strand short of the full genome. The virus can’t go on to replicate or infect other cells.

“The polymerase grabs it almost accidentally and uses it in place of adenosine,” said Maria Agostini, a postdoctoral researcher in Denison’s Vanderbilt lab. “The polymerase can kind of get it mixed up sometimes.”

The drug can inhibit coronaviruses as well as Ebola because their polymerases are similar enough that its cloak-and-dagger operation fools them all. (Remdesivir [does not appear](#) to work on other viruses with more unrelated forms of polymerase.)

Like a bad song clears out a dance floor, remdesivir can clear the viral levels in a person, as long as it can interrupt enough replication. The key, researchers say, is that it has to be delivered somewhat early in an infection, as the virus is

still proliferating. In patients who develop severe disease, it's not the virus that's always the main problem. The body's own immune system can react by heading into overdrive and causing secondary complications like organ damage. An antiviral can't head that off once it's begun.

"If you wait to treat someone until they're in the ICU on a ventilator, it's too late, you're not going to do a darn thing," said Richard Whitley, an infectious disease expert at UAB who coordinates the antiviral consortium.



When remdesivir [stumbled in the Ebola trials last year](#), it was a disappointment, Gilead's Cihlar acknowledged. But he argued it refocused the company's attention to other targets for the drug.

They didn't have to wait long.

In December, reports popped up from Wuhan of mysterious pneumonia cases. In early January, word came of a new coronavirus. "At that point, we started getting ready," Cihlar said.

And when Chinese scientists published the virus' genome, Gilead zeroed in on the portion that contained the recipe for the replication machinery — the polymerase. They saw it was nearly identical to the version in SARS — evidence that remdesivir might work against this virus as well. "That was a really strong signal for us," he said.

There are now five clinical trials of remdesivir in Covid-19: two run by Chinese scientists, one looking at severe infections, and one at mild and moderate infections; one sponsored by NIAID; and two sponsored by Gilead in countries around the world with a large number of cases, looking at different disease severities and dosing regimens.

If the drug is successful in trials, most antiviral experts think the drug should primarily be used for patients with more severe symptoms and those who are hospitalized — some 15% to 20% of cases. But observers have also raised a

number of points that could potentially trip up the trials. For one, the process moved so quickly that analysts have wondered if the best doses were chosen. They have also pointed to the fact that one of the Chinese trials includes patients whose symptoms started up to 12 days prior. There are concerns that might be too late.

“The overall trial might not be as spectacular as people think,” Umer Raffat, an analyst at Evercore ISI, said in a presentation last week. But, Raffat added, results from patients who start treatment early might show the drug has efficacy if given soon after symptoms arise.

Another detail that will be scrutinized: Can the drug, which is given intravenously into the bloodstream, reach the cells it needs to clear the respiratory infection?

“We don’t know if the amount of remdesivir that’s going to get into the lungs is enough to get the virus down,” said Andre Kalil, an infectious disease specialist at University of Nebraska Medical Center and an investigator in the NIAID-sponsored trial. “This is part of the reason we’re doing the study.”

Remdesivir may have had a head start, but other efforts are underway to come up with Covid-19 treatments. (These are separate from vaccine projects.) Virologists said they were keeping an eye on a candidate pursued by researchers at Vanderbilt, UNC, and Emory University that, in its various forms, has been identified as [NHC](#), [EIDD-2801](#), and [EIDD-1931](#). The drug company [Regeneron](#), which steered its Ebola antiviral to success in the same trial in which remdesivir stumbled, is working on a treatment, as are other biopharma companies. Some experts have [proposed using antibody-containing blood](#) from survivors of Covid-19 as a therapy.



If remdesivir does succeed in clinical trials, Gilead will only face a new round of questions.

The company has run into a buzzsaw of public and governmental criticism in

the past over the cost of its HIV and hepatitis C antivirals, and any drug approved to treat Covid-19 will certainly face pricing scrutiny. A Gilead spokesperson said the company was not discussing pricing yet.

Health authorities are already stressing the importance of access to therapeutics that do make it to market.

“We cannot have a situation where people who need the drug don’t get it and people who don’t need the drug do,” Mike Ryan, who leads the WHO’s emergency program, said at a briefing this month when asked about the ongoing clinical trials. “We must find ways to ensure we can scale up production of any drugs that prove effective and we can ensure that those drugs are distributed on the basis of need and the basis of benefit.”

We want to hear from you: Are you a health care worker affected by the coronavirus outbreak? Please tell us about your experience.

That points to another challenge Gilead could face with an approval for remdesivir: supply. Even if it was recommended only for people with severe infections who are hospitalized, that could still amount to thousands of patients needing doses, and needing them soon.

On a call with analysts this month, Gilead CEO Daniel O’Day said the company was “engaging our manufacturing and supply chain in the event of success” and said that it was already talking with partners about increasing production of remdesivir. But given that the drug is still in trials, he said, “right now the demand is really unknown.”

That same day, O’Day appeared at the White House with other drug and vaccine makers.

“We’re moving as fast as we can,” O’Day told President Trump as he described remdesivir. “I think everybody around the table is moving as fast as we can.”

Trump had a simple message for O’Day: “Get it done, Daniel. Don’t disappoint us, Daniel.”

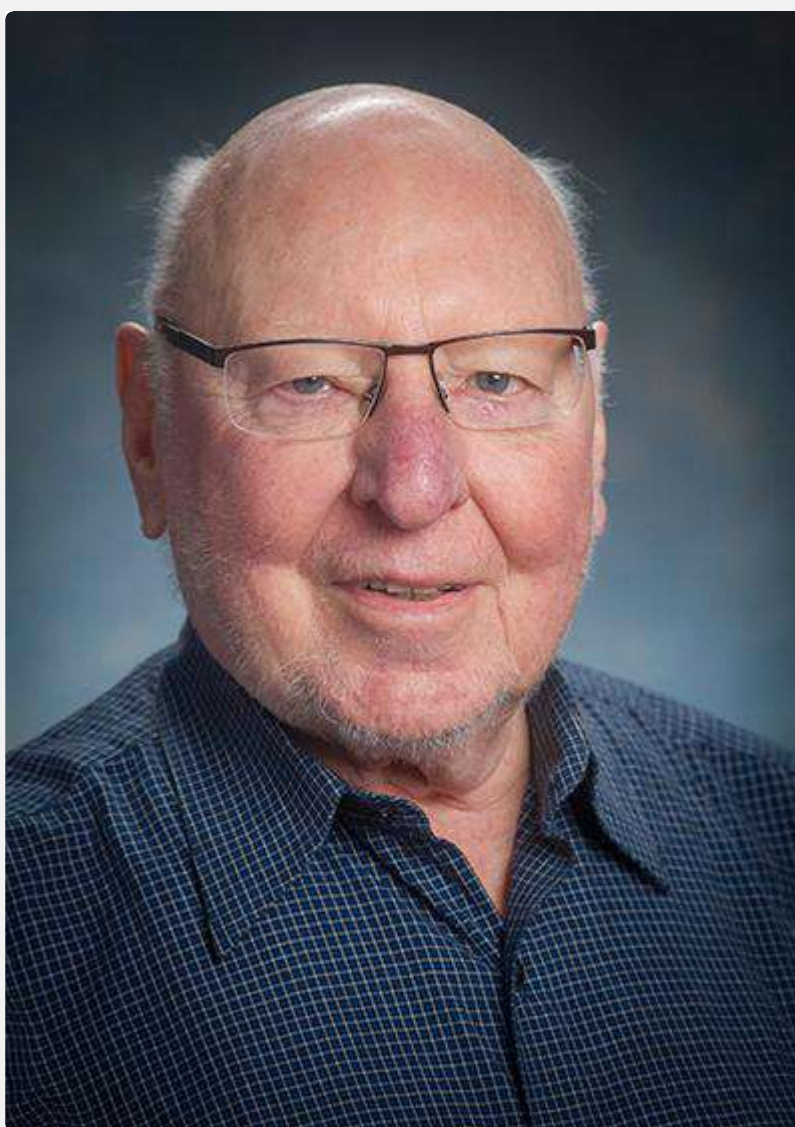
About the Author [Reprints](#)

Health & Medicine

\$37.5 million grant will address research of high-priority infections

by Savannah Koplon

The Antiviral Drug Discovery and Development Center (AD3C) at the University of Alabama at Birmingham has been awarded a five-year, \$37.5 million grant from the National Institute of Allergy and Infectious Diseases Centers of Excellence for Translational Research to study and develop treatment for high-priority infections.



Richard Whitley, M.D.

These infections to be studied include influenza, flaviviruses like dengue, West Nile virus and Zika, coronaviruses that cause SARS and MERS, and

alphaviruses such as Venezuelan equine encephalitis virus and chikungunya.

Led by Richard Whitley, M.D., Distinguished Professor at UAB, AD3C's goals involve developing new small molecule therapeutics for emerging and re-emerging viral infections. Additionally, AD3C provides an infrastructure to accelerate the development of new potential drugs from the lab toward the clinic.

"This grant will help us improve and create new treatment options for these four virus families and ultimately impact the global understanding of these viruses at large," Whitley said. "The viruses of focus within AD3C are of the highest priority to the United States government. We are confident that our future findings will help transform the way we treat patients, unmet medical needs and the safety of millions."

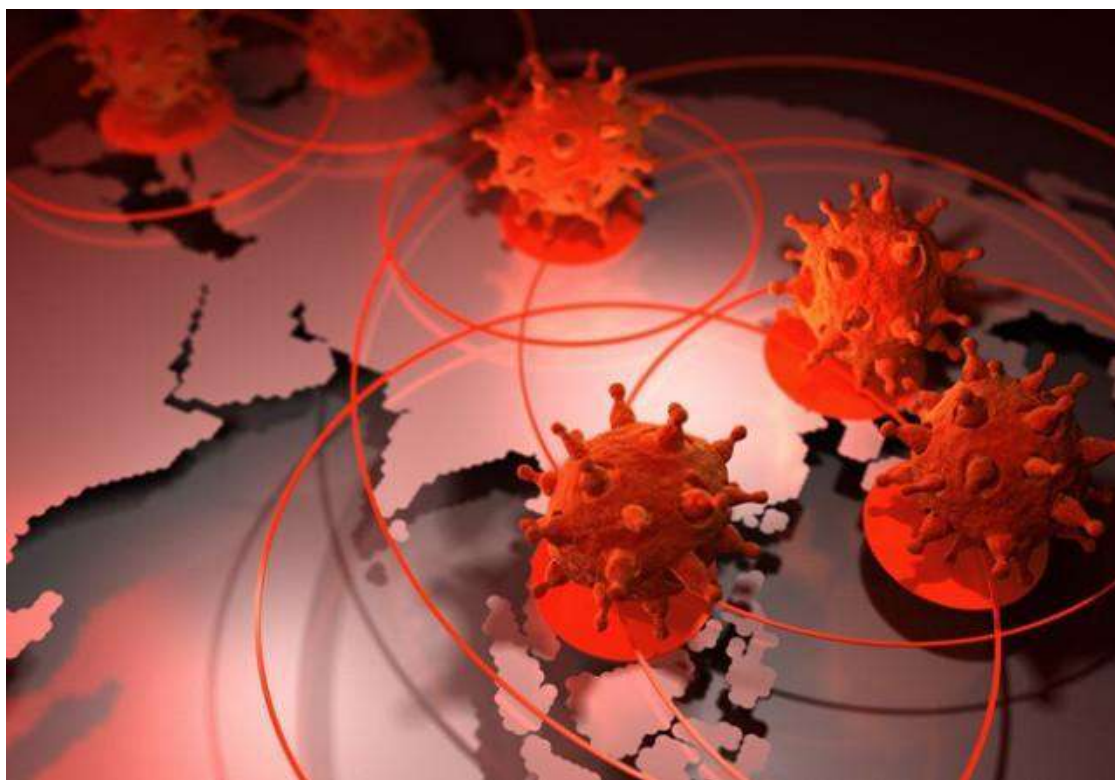
UAB is the lead institution for AD3C, but the team unifies scientists experienced in virology, viral immunology, pathogenesis, medicinal chemistry and translation to human disease from UAB, University of North Carolina, Vanderbilt University, Emory University, Washington University, The University of Texas Medical Branch, Southern Research, and Oregon Health & Science University.

Since its inception, AD3C has already contributed significant data to an IND filed for MERS and two patent applications for compounds with activity against chikungunya, illustrating the success of the collaborative, multi-institutional model.



University of Alabama & Multi-Center Collaboration Help Develop Remdesivir with Gilead Thanks to \$37.5m from NIH

MAR 1, 2020 | 2019-NCOV, CORONAVIRUS, UNIVERSITY OF ALABAMA, VACCINE



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Discovery and Development Center (AD3C) is now being used to treat certain coronavirus patients in China. The drug, known as Remdesivir (Gilead), is the result of a five-year, **\$37.5 million “U19” grant** to study and develop treatment for emerging infections like coronaviruses that can trigger SARS, MERS and now the COVID-19—the latest strain that triggered an outbreak in China. The virus is now spreading around the globe.

The Grant

The U19 grant originated from the **National Institute of Allergy and Infectious Diseases Center of Excellence for Translational Research** to study and development treatment for high-priority emerging infections. The grant supports an intense research effort led by the “Crimson Tide”-based investigative team to uncover drugs for emerging influenza, flaviviruses, (dengue, West Nile virus and Zika), coronaviruses that trigger SARS and MERS, and alphaviruses, such as Venezuelan equine encephalitis virus and chikungunya. The grant supports multi-institutional collaboration to accelerate drug discovery for these emerging infections and represents a public-private partnership between the academic institutions and biotech company Gilead Sciences.

The Drug

Remdesivir was developed to treat the coronavirus causing MERS and found to be have significant activity against the 2019-nCoV strain when the outbreak commenced in Wuhan, China, reports Savannah Koplon writing for UAB News. A preclinical status vaccine, remdesivir demonstrated efficacy against coronaviruses MERS and SARS in cell culture and animal models, reported Ms. Koplon. Physicians in the U.S. generated compassionate plea requests and thereafter Gilead released the drug for use in a selection of patients. Again, the drug has not been through clinical trials as of yet, so it hasn’t been tested for efficacy in human beings.

Principal Investigator Lead

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principal investigator of the U19 grant noted in February, “The release of remdesivir for safety and efficacy studies is a major accomplishment for the AD3C—namely the U19 grant—as it shows significant and swift advance of antiviral drugs to help treat and respond to emerging infectious disease outbreaks on an international scale and importantly, to anticipate the introduction of these infections in the United States.”

UAB Expert Panel on 2019 Coronavirus

For more information about remdesivir and how it can potentially be applied to the coronavirus, watch the Director of Infectious Diseases, [Jeanne Marrazzo, MD](#) at UAB and others discuss the research effort.

The Collaboration

The grant involves an intensive collaboration between UAB and colleagues at Southern Ranch, Vanderbilt University and the University of North Carolina along with Gilead. Responsive, dynamic and working in real time, this team has leveraged public funds (NIH) and contributed to the necessary response to outbreaks, such as what is occurring with 2019-nCoV. Effective research is a collaborative, team-based endeavor and, thus far, this team exhibits a positive and progressive, not to mention seemingly effective model for public-private research models.

Although UAB is the lead institution for AD3C, the team involves experts in their respective fields across virology, viral immunology, pathogenesis, medicinal chemistry and translation to human disease from not only UAB but importantly a network of prominent research centers from University of North Carolina, Vanderbilt University, Emory University, Washington University, The University of Texas Medical Branch, Southern Research, the Emory Institute of Drug Discovery, the University of Colorado, Denver and Oregon Health & Science University.

Lead Research/Investigator

[Professor Richard Whitley](#), MD, Distinguished Professor at UAB

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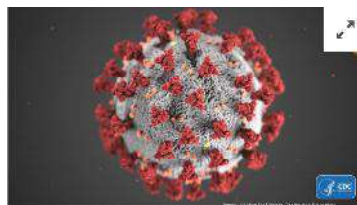
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ANNEXURE - 4

Health Care

Drug developed at UAB in partnership with Gilead Sciences being used to treat coronavirus



A drug developed by research centered at UAB is being used to treat novel coronavirus patients.
CENTERS FOR DISEASE CONTROL AND PREVENTION

RECOMMENDED

CAREER & WORKPLACE

HBJ reveals honorees for 2020 Most Admired CEO Award, inaugural Business Impact Awards



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See full profile >

Mar 2, 2020, 8:00am CST **Updated** Mar 2, 2020, 10:36am CST

A drug developed through research centered at UAB is being used to treat some coronavirus patients in the U.S. and China who have been affected by the outbreak of COVID-19.

Remdesivir, which was developed through research conducted by the Antiviral Drug Discovery and Development Center, was initially developed to treat the coronavirus that causes MERS, [according to UAB](#).

UAB was awarded a \$37.5 million, five-year U19 grant from the National Institute of Allergy and Infectious Diseases Centers of Excellence for Translational Research to study and develop treatment for high-priority emerging infections. The grant involves a public-private partnership between academic institutions and Gilead Sciences Inc. (Nasdaq: GILD)

But remdesivir was found to have significant activity against COVID-19 - the coronavirus strain that started in Wuhan, China, and has since spread to many locations around the globe - with a number of cases in Iran, Italy and South Korea.

Based on the compassionate plea requests of treating physicians in the United States, Gilead Sciences released remdesivir for use in a few patients, although the drug has not yet been tested for safety or efficacy in these diseases.

“The release of remdesivir for safety and efficacy studies is a major accomplishment for the AD3C - namely the U19 grant - as it shows significant and swift advance of antiviral drugs to help treat and respond to emerging infectious disease outbreaks on an international scale and, importantly, to anticipate the introduction of these infections in the United States,” said Dr. Richard Whitley, Distinguished Professor at UAB and principal investigator of the U19 grant.

The drug is one of several examples of the role Birmingham is playing in containing COVID-19 and reducing its impact. As we noted last week, Southern Research is collaborating with Tonix Pharmaceuticals to support the development of a vaccine against the disease.

FORM 2**ANNEXURE - 5**

THE PATENTS ACT, 1970

(39 of 1970)

&

THE PATENTS RULES, 2003

COMPLETE SPECIFICATION

(See section 10, rule 13)

**“METHODS FOR TREATING FILOVIRIDAE VIRUS
INFECTIONS”**

**GILEAD SCIENCES, INC. of 333 Lakeside Drive, Foster
City, CA 94404, U.S.**

The following specification particularly describes the invention and the manner in which it is to be performed.

METHODS FOR TREATING *FILOVIRIDAE* VIRUS INFECTIONS

FIELD OF THE INVENTION

[0001] The invention relates generally to methods and compounds for treating *Filoviridae* virus infections, particularly methods and nucleosides for treating Ebola virus, Marburg virus and Cueva virus.

BACKGROUND OF THE INVENTION

[0002] Filoviruses (*e.g.*, Ebola virus (EBOV) and Marburg virus (MARV)) are among the most lethal and destructive viruses. They cause severe, often fatal viral hemorrhagic fevers in humans and nonhuman primates (*e.g.*, monkeys, gorillas, and chimpanzees). Filoviruses are of particular concern as possible biological weapons since they have the potential for aerosol dissemination and weaponization.

[0003] The incubation period for Filovirus infection ranges from 2 to 21 days. The onset of illness is abrupt and is characterized by high fever, headaches, joint and muscle aches, sore throat, fatigue, diarrhea, vomiting, and stomach pain. A rash, red eyes, hiccups and internal and external bleeding may be seen in some patients. Within one week of becoming infected with the virus, most patients experience chest pains and multiple organ failure, go into shock, and die. Some patients also experience blindness and extensive bleeding before dying.

[0004] Filoviridae are a family of RNA viruses. Two members of the Filoviridae family have been identified: EBOV and MARV. Two key pathogenic types of the Filoviridae family have been identified: Ebolavirus and MARV. There is one identified variant of MARV and five identified species of ebolavirus: Zaire (*i.e.* Ebola virus, EBOV), Sudan, Tai Forest, Bundibugyo, and Reston. The exact origin, locations, and natural habitat of Filoviridae are unknown. However, on the basis of available evidence and the nature of similar viruses, it is postulated that Filoviridae are zoonotic (*i.e.*, animal-borne) and are normally maintained in an animal host that is native to the African continent.

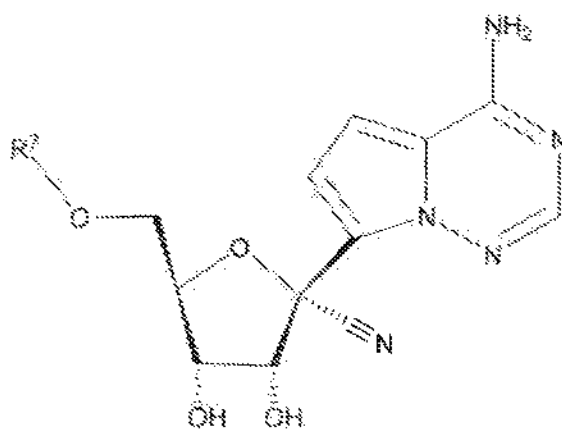
[0005] For more than 30 years, ebolaviruses have been associated with periodic episodes of hemorrhagic fever in Central Africa that produce severe disease in infected patients. Mortality rates in outbreaks have ranged from 50% for the Sudan species of ebolavirus (SEBOV) to up to 90% for the Zaire species of ebolavirus (EBOV, ZEBOV) (Sanchez *et al.*, *Filoviridae: Marburg and Ebola Viruses*, in *Fields Virology* (eds. Knipe, D.M. & Howley, P.M.) 1409-1448 (Lippincott Williams & Wilkins, Philadelphia)). An outbreak late in 2007 caused by an apparently new species of ebolavirus in Uganda resulted in a fatality rate of about 25% (Towner *et al.*, *PLoS Pathog.*, 4:e1000212 (2008)). ZEBOV has also decimated populations of wild apes in this same region of Africa (Walsh *et al.*, *Nature*, 422:611-614 (2003)).

[0006] Prevention and treatment of filovirus infections, including ebolaviruses (i.e. EBOV) presents many challenges. In fact, there are no vaccines or post exposure treatment modalities available for preventing or managing EBOV infections. Patients instead receive supportive therapy, *i.e.*, electrolyte and fluid balancing, oxygen, blood pressure maintenance, and treatment for any secondary infections.

[0007] Thus, there is a need for compositions and methods for treating EBOV infections. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

[0008] Provided, is a method for treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula IV:



Formula IV

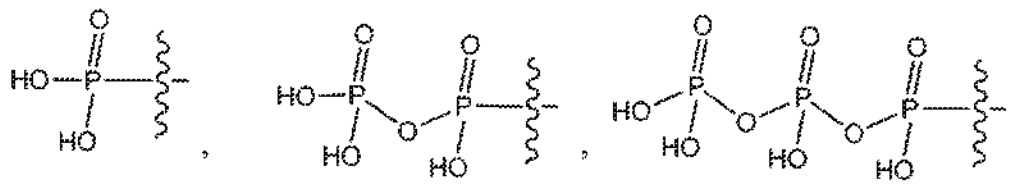
or a pharmaceutically acceptable salt, hydrate or ester, thereof;

wherein,

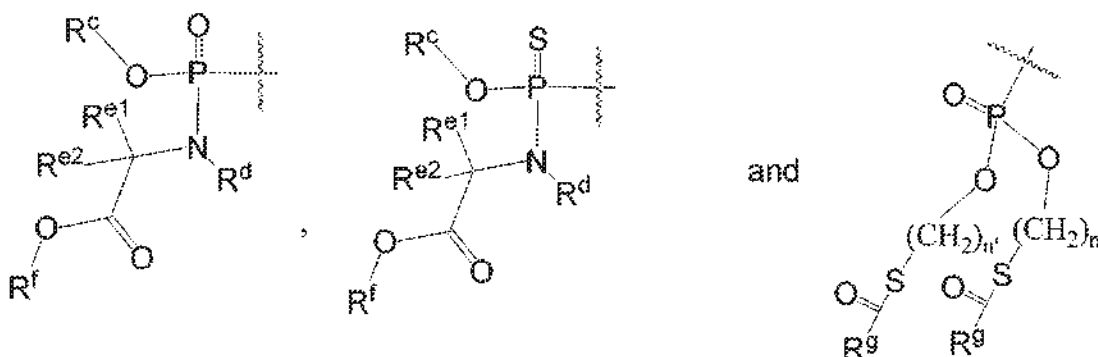
R^7 is selected from the group consisting of

a) H , $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

b)

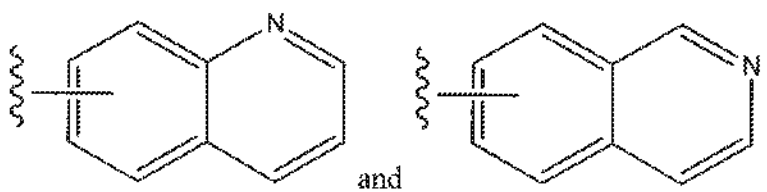


c) a group selected from:



wherein:

R^c is selected from the group of phenyl, 1-naphthyl, 2-naphthyl,



R^d is selected from the group of H or CH_3 ;

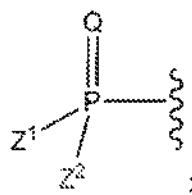
R^{e1} and R^{e2} are each independently selected from the group of H , (C_1-C_6) alkyl or benzyl;

R^f is selected from the group of from H , (C_1-C_8) alkyl, benzyl, (C_3-C_6) cycloalkyl, and $-CH_2-(C_3-C_6)$ cycloalkyl;

R^g is selected from selected from the group of (C_1-C_8) alkyl, $-O-(C_1-C_8)$ alkyl, benzyl, $-O$ -benzyl, $-CH_2-(C_3-C_6)$ cycloalkyl, $-O-CH_2-(C_3-C_6)$ cycloalkyl, and CF_3 ; and

n' is an integer selected from the group of 1, 2, 3, and 4; and

d) a group of the formula:



wherein:

Q is selected from the group of O, S, NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, or $N-NR_2$;

Z^1 and Z^2 , when taken together, are $-Q^1(C(R^y)_2)_3Q^1-$;

wherein

each Q^1 is independently selected from the group of O, S, or NR; and

each R^y is independently selected from the group of H, F,

Cl, Br, I, OH, R, $-C(=Q^2)R$, $-C(=Q^2)OR$, $-$

$C(=Q^2)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, $-SR$, $-S(O)R$, $-$

$S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Q^1)R$, $-$

$OC(=Q^2)OR$, $-OC(=Q^2)(N(R)_2)$, $-SC(=Q^2)R$, $-$

$SC(=Q^2)OR$, $-SC(=Q^2)(N(R)_2)$, $-N(R)C(=Q^2)R$, $-$

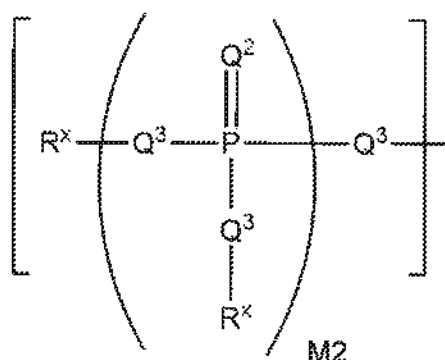
$N(R)C(=Q^2)OR$, $-N(R)C(=Q^2)N(R)_2$, $-SO_2NR_2$,

$-CN$, $-N_3$, $-NO_2$, $-OR$, or Z^3 ; or when taken

together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, or $N-NR_2$; or

Z^1 and Z^2 are each, independently, a group of the Formula Ia:



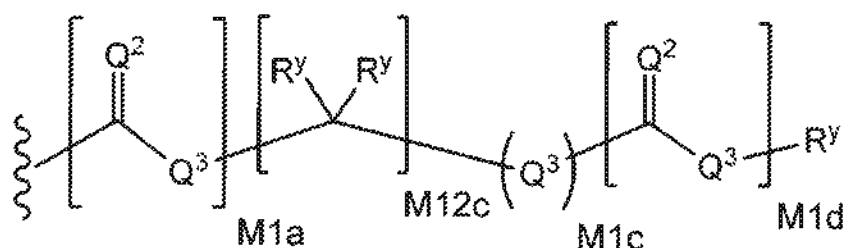
Formula Ia

wherein:

each Q^3 is independently selected from the group of a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

M2 is an integer selected from the group of 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is an integer independently selected from the group of 0 or 1;

M12c is an integer selected from the group of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

Z^3 is Z^4 or Z^5 ;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-SO_2R^y$, or $-SO_2Z^5$;

and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups;

each R^{11} or R^{12} is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,

(C₄-C₈)carbocyclalkyl, (C₆-C₂₀)optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(C_1-C_8)alkyl$ or

(C₆-C₂₀)aryl(C₁-C₈)alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a;

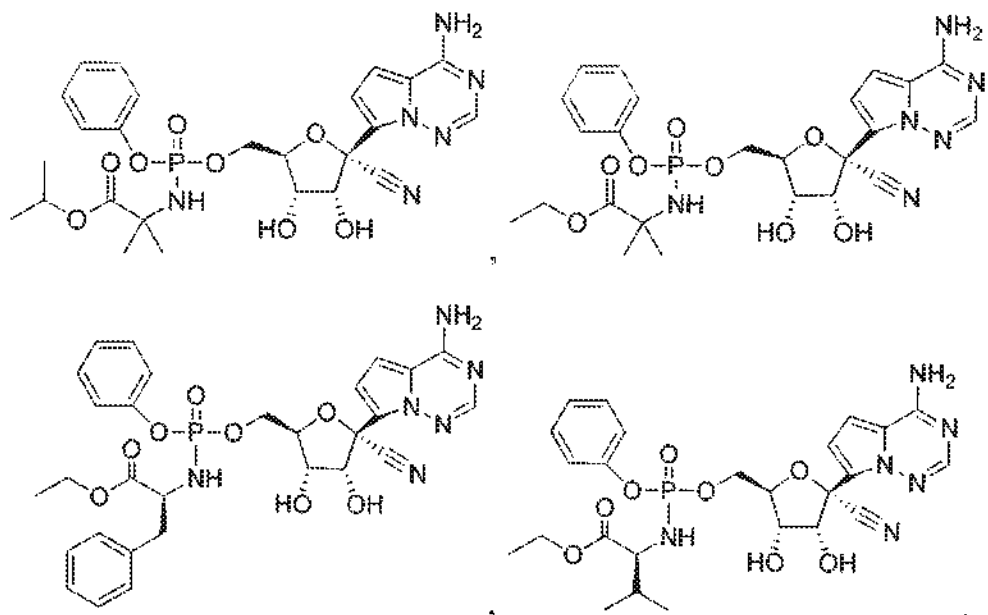
each R^a is independently selected from the group of H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_6-C_{20}) aryl (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, or $-SO_2NR_2$; wherein

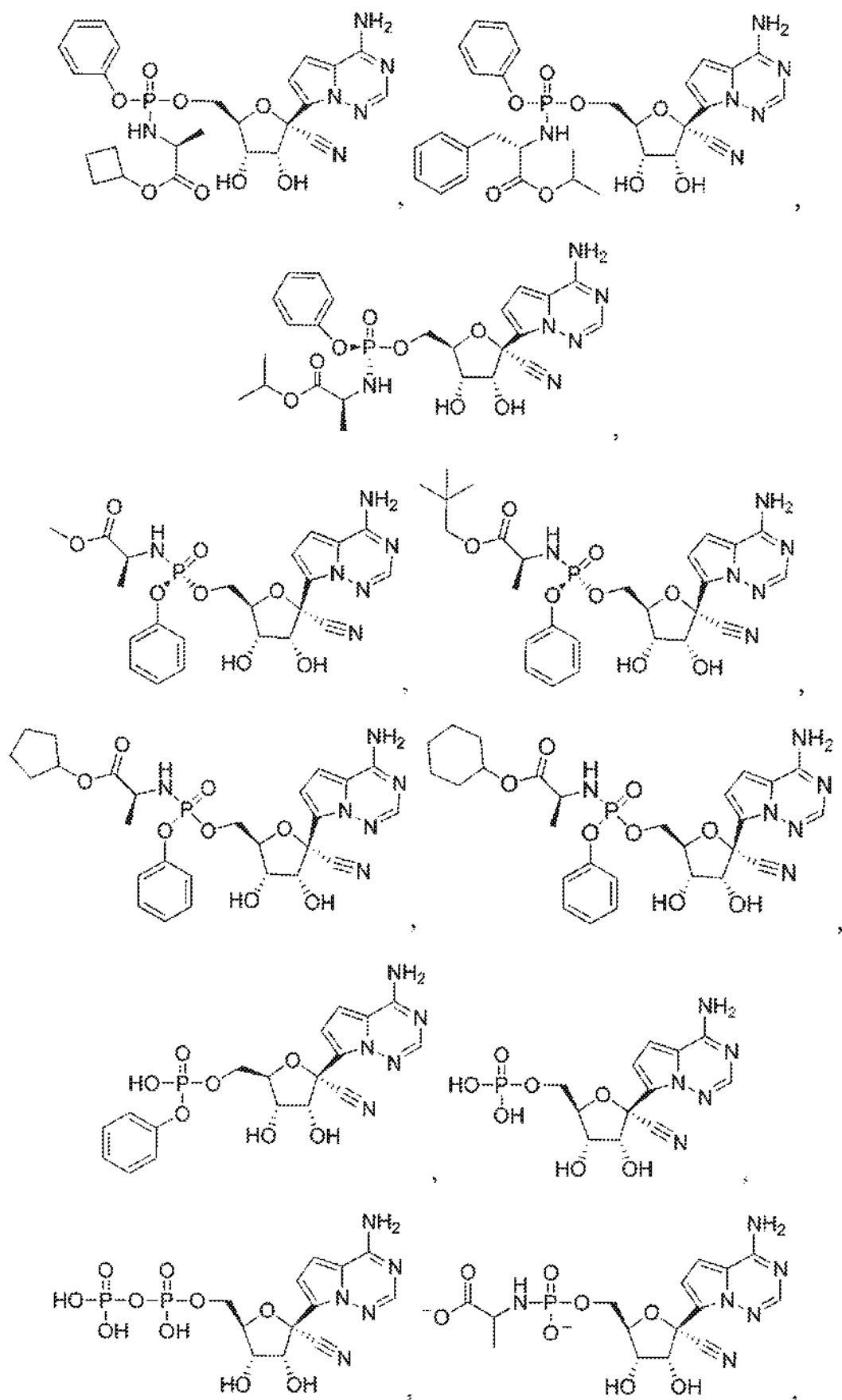
each R is independently selected from the group of H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, (C_6-C_{20}) aryl, (C_6-C_{20}) substituted aryl, (C_2-C_{20}) heterocyclyl, (C_2-C_{20}) substituted heterocyclyl, (C_6-C_{20}) aryl (C_1-C_8) alkyl or substituted (C_6-C_{20}) aryl (C_1-C_8) alkyl;

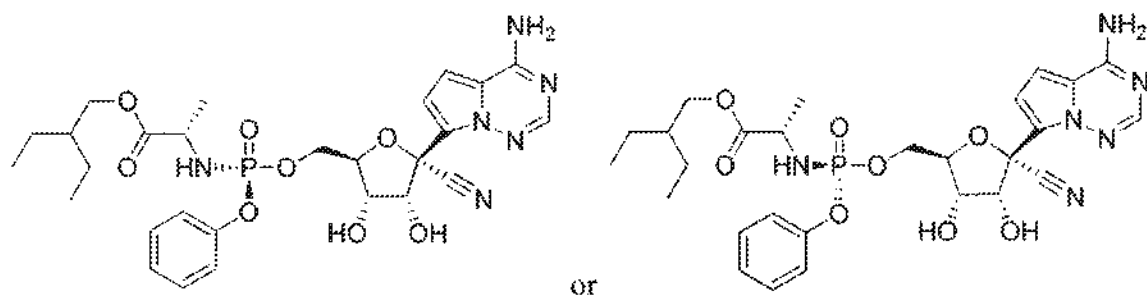
each n is an integer independently selected from the group of 0, 1, or 2; and

wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or (C_6-C_{20}) aryl (C_1-C_8) alkyl of each R^{11} or R^{12} is, independently, optionally substituted with one or more substituents selected from the group of halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with $-O-$, $-S-$ or $-NR^a-$.

[0009] In another embodiment, the present invention provides a compound that is







or a pharmaceutically acceptable salt, hydrate, or ester thereof.

DETAILED DESCRIPTION OF THE INVENTION

I. DEFINITIONS

[0010] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

[0011] When trade names are used herein, applicants intend to independently include the trade name product and the active pharmaceutical ingredient(s) of the trade name product.

[0012] As used herein, "a compound of the invention" or "a compound of Formula IV" means a compound of Formula IV or a pharmaceutically acceptable salt, thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

[0013] "Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkyl), 1 to 8 carbon atoms (*i.e.*, C₁-C₈ alkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl ($\underline{n}$ -Pr, $\underline{n}$ -propyl, -CH₂CH₂CH₃), 2-propyl ($\underline{i}$ -Pr, $\underline{i}$ -propyl, -CH(CH₃)₂), 1-butyl ($\underline{n}$ -Bu, $\underline{n}$ -butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl ($\underline{i}$ -Bu, $\underline{i}$ -butyl, -CH₂CH(CH₃)₂), 2-butyl ($\underline{s}$ -Bu, $\underline{s}$ -butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl ($\underline{t}$ -Bu, $\underline{t}$ -butyl, -C(CH₃)₃), 1-pentyl ($\underline{n}$ -pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl

(-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl (-CH₂)₇CH₃).

[0014] “Alkoxy” means a group having the formula --O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH₃ or -OMe), ethoxy (-OCH₂CH₃ or -OEt), *t*-butoxy (-O-C(CH₃)₃ or -OtBu) and the like.

[0015] “Haloalkyl” is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable haloalkyl groups include, but are not limited to, -CF₃, -CHF₂, -CFH₂, -CH₂CF₃, and the like.

[0016] “Alkenyl” is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp*² double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkenyl), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

[0017] “Alkynyl” is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkyne), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH₂C≡CH), and the like.

[0018] “Alkylene” refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene (-CH₂-), 1,1-ethyl (-CH(CH₃)-), 1,2-ethyl

(-CH₂CH₂-), 1,1-propyl (-CH(CH₂CH₃)-), 1,2-propyl (-CH₂CH(CH₃)-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

[0019] “Alkenylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, an alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

[0020] “Alkynylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH₂C≡C-), and 4-pentynyl (-CH₂CH₂CH₂C≡C-).

[0021] “Amino” refers generally to a nitrogen radical which can be considered a derivative of ammonia, having the formula -N(X)₂, where each “X” is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, etc. The hybridization of the nitrogen is approximately sp³. Nonlimiting types of amino include -NH₂, -N(alkyl)₂, -NH(alkyl), -N(carbocyclyl)₂, -NH(carbocyclyl), -N(heterocyclyl)₂, -NH(heterocyclyl), -N(aryl)₂, -NH(aryl), -N(alkyl)(aryl), -N(alkyl)(heterocyclyl), -N(carbocyclyl)(heterocyclyl), -N(aryl)(heteroaryl), -N(alkyl)(heteroaryl), etc. The term “alkylamino” refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino groups include -NH₂, -NH(CH₃), -N(CH₃)₂, -NH(CH₂CH₃), -N(CH₂CH₃)₂, -NH(phenyl), -N(phenyl)₂, -NH(benzyl), -N(benzyl)₂, etc. Substituted alkylamino refers generally to alkylamino groups, as defined above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes -NH(alkylene-C(O)-OH), -NH(alkylene-C(O)-O-alkyl), -N(alkylene-C(O)-OH)₂, -N(alkylene-C(O)-O-alkyl)₂, etc.

[0022] “Aryl” means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl

groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

[0023] “Arylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 7 to 20 carbon atoms, e.g., the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

[0024] “Arylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 8 to 20 carbon atoms, e.g., the alkenyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

[0025] “Arylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 8 to 20 carbon atoms, e.g., the alkynyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

[0026] The term “substituted” in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, “substituted alkyl”, “substituted alkylene”, “substituted aryl”, “substituted arylalkyl”, “substituted heterocyclyl”, and “substituted carbocyclyl” means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, $-X$, $-R^b$, $-O^+$, $=O$, $-OR^b$, $-SR^b$, $-S^+$, $-NR^b_2$, $-N^+R^b_3$, $=NR^b$, $-CX_3$, $-CN$, $-OCN$, $-SCN$, $-N=C=O$, $-NCS$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-NHC(=O)R^b$, $-OC(=O)R^b$, $-NHC(=O)NR^b_2$, $-S(=O)_2-$, $-S(=O)_2OH$, $-S(=O)_2R^b$, $-OS(=O)_2OR^b$, $-S(=O)_2NR^b_2$, $-S(=O)R^b$, $-OP(=O)(OR^b)_2$, $-P(=O)(OR^b)_2$, $-P(=O)(O^-)_2$.

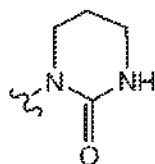
-P(=O)(OH)₂, -P(O)(OR^b)(O⁻), -C(=O)R^b, -C(=O)X, -C(S)R^b, -C(O)OR^b, -C(O)O⁻, -C(S)OR^b, -C(O)SR^b, -C(S)SR^b, -C(O)NR^b₂, -C(S)NR^b₂, -C(=NR^b)NR^b₂, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

[0027] The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

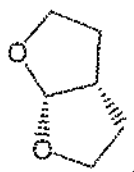
[0028] One skilled in the art will recognize that substituents and other moieties of the compounds of Formula IV should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula IV which have such stability are contemplated as falling within the scope of the present invention.

[0029] "Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., -OCH₃, etc.), an amine (e.g., -NHCH₃, -N(CH₃)₂, etc.), or a thioalkyl group (e.g., -SCH₃). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., -CH₂CH₂-O-CH₃, etc.), an alkyl amine (e.g., -CH₂NHCH₃, -CH₂N(CH₃)₂, etc.), or a thioalkyl ether (e.g., -CH₂-S-CH₃). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., -CH₂CH₂-OH), an aminoalkyl group (e.g., -CH₂NH₂), or an alkyl thiol group (e.g., -CH₂CH₂-SH). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C₁-C₆ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

[0030] "Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings, partially unsaturated rings, and aromatic rings (*i.e.*, heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



[0031] Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, phthalazinyl, naphthyridinyl, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carboliny, phenanthridinyl, acridinyl, pyrimidinyl, phenanthroliny, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazoliny, piperazinyl, indoliny, isoindoliny, quinuclidiny, morpholiny, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, isatinoyl, and bis-tetrahydrofuranyl:



[0032] By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

[0033] By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

[0034] "Heterocyclalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclalkyl radical (*i.e.*, a heterocyclalkyl-alkylene- moiety). Typical heterocyclalkyl groups include, but are not limited to heterocyclalkyl- CH_2 -, 2-(heterocyclalkyl)ethan-1-yl, and the like, wherein the "heterocyclalkyl" portion includes any of the heterocyclalkyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclalkyl group can be attached to the alkyl portion of the heterocyclalkyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclalkyl alkyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms and the heterocyclalkyl moiety is 2 to 14 carbon atoms. Examples of heterocyclalkyls include by way of

example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

[0035] “Heterocyclylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also a sp^2 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkenylene- moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkenyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

[0036] “Heterocyclylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkynylene- moiety). The heterocyclyl portion of the heterocyclyl alkynyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocyclyl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclyl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkynyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocyclyl alkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

[0037] “Heteroaryl” refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of

those aromatic rings listed in the definition of “heterocyclyl”, including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

[0038] “Carbocycle” or “carbocyclyl” refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 7 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl, tetrahydronaphthalene, and decaline.

[0039] “Carbocyclylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein. Typical, but non-limiting, examples of carbocyclylalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

[0040] “Arylheteroalkyl” refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

[0041] “Heteroarylalkyl” refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-purinyl, -CH₂-furanyl, -CH₂-thienyl, -CH₂-benzofuranyl,

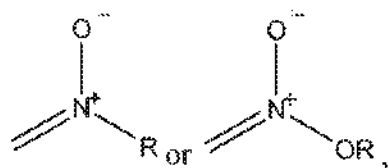
-CH₂-benzothiophenyl, -CH₂-carbazolyl, -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-purinyl, -CH(CH₃)-furanlyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranlyl, -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl, -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl, -CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-pyrazyl, etc.

[0042] The term “optionally substituted” in reference to a particular moiety of the compound of Formula IV (e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by substituents such as those listed under the definition of “substituted”.

[0043] The term “optionally replaced” in reference to a particular moiety of the compound of Formula IV (e.g., the carbon atoms of said (C₁-C₈)alkyl may be optionally replaced by -O-, -S-, or -NR^a-) means that one or more of the methylene groups of the (C₁-C₈)alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., -O-, -S-, or -NR^a-).

[0044] The term “non-terminal carbon atom(s)” in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl moiety -CH₂(C^{*})H₂(C^{*})H₂CH₃ or alkylene moiety -CH₂(C^{*})H₂(C^{*})H₂CH₂- the C^{*} atoms would be considered to be the non-terminal carbon atoms.

[0045] Certain Q and Q¹ alternatives are nitrogen oxides such as ⁺N(O)(R) or ⁺N(O)(OR). These nitrogen oxides, as shown here attached to a carbon atom, can also be represented by charge separated groups such as



respectively, and are intended to be equivalent to the aforementioned representations for the purposes of describing this invention.

[0046] "Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms. Linkers include repeating units of alkyloxy (e.g. polyethyleneoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

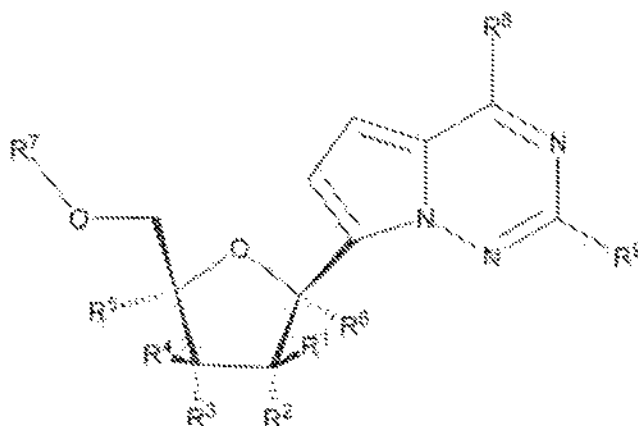
[0047] The terms such as "oxygen-linked", "nitrogen-linked", "carbon-linked", "sulfur-linked", or "phosphorous-linked" mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, a nitrogen-linked amino acid would be bonded through a nitrogen atom of the amino acid rather than through an oxygen or carbon atom of the amino acid.

[0048] In some embodiments of the compounds of Formula IV, one or more of Z^1 or Z^2 are independently a radical of a nitrogen-linked naturally occurring α -amino acid ester. Examples of naturally occurring amino acids include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, selenocysteine, serine, tyrosine, arginine, histidine, ornithine and taurine. The esters of these amino acids comprise any of those described for the substituent R, particularly those in which R is optionally substituted (C_1 - C_8)alkyl.

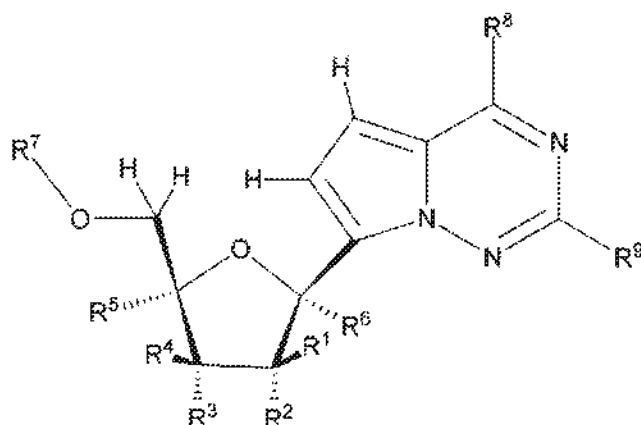
[0049] The term "purine" or "pyrimidine" base comprises, but is not limited to, adenine, N^6 -alkylpurines, N^6 -acylpurines (wherein acyl is $C(O)(\text{alkyl, aryl, alkylaryl, or arylalkyl})$), N^6 -benzylpurine, N^6 -halopurine, N^6 -vinylpurine, N^6 -acetylenic purine, N^6 -acyl purine, N^6 -hydroxyalkyl purine, N^6 -allylaminopurine, N^6 -thioalkyl purine, N^2 -alkylpurines, N^2 -alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, 5-halouracil, including 5-fluorouracil, C^5 -alkylpyrimidines, C^5 -benzylpyrimidines, C^5 -halopyrimidines, C^5 -vinylpyrimidine, C^5 -acetylenic pyrimidine, C^5 -acyl pyrimidine, C^5 -hydroxyalkyl purine, C^5 -amidopyrimidine, C^5 -cyanopyrimidine, C^5 -5-iodopyrimidine, C^6 -iodo-pyrimidine, C^5 -Br-vinyl pyrimidine, C^6 -Br-vinyl pyrimidine, C^5 -nitropyrinidine, C^5 -amino-pyrimidine, N^2 -alkylpurines, N^2 -alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. The purine and pyrimidine bases are linked to the ribose sugar, or analog thereof, through a nitrogen atom of the base. Functional oxygen and nitrogen groups on the base can be protected as necessary or

desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyl dimethylsilyl, and t-butyl diphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

[0050] Unless otherwise specified, the carbon atoms of the compounds of Formula IV are intended to have a valence of four. In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen. For example,



has the same meaning as



[0051] "Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. See also

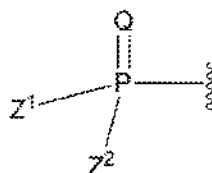
Protective Groups in Organic Chemistry, Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive. "Hydroxy protecting groups" refers to those protecting groups useful for protecting hydroxy groups (-OH).

[0052] Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

[0053] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0054] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0055] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, reactivities and biological properties. For example, the compounds of Formula IV may have a chiral phosphorus atom when R⁷ is



and Z^1 and Z^2 are different. When at least one of either Z^1 or Z^2 also has a chiral center, for example with Z^1 or Z^2 is a nitrogen-linked, chiral, naturally occurring α -amino acid ester, then the compound of Formula IV will exist as diastereomers because there are two centers of chirality in the molecule. All such diastereomers and their uses described herein are encompassed by the instant invention. Mixtures of diastereomers may be separated under high resolution analytical procedures such as electrophoresis, crystallization and/or chromatography. Diastereomers may have different physical attributes such as, but not limited to, solubility, chemical stabilities and crystallinity and may also have different biological properties such as, but not limited to, enzymatic stability, absorption and metabolic stability.

[0056] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0057] The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

[0058] The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

[0059] The term "therapeutically effective amount", as used herein, is the amount of compound of Formula IV present in a composition described herein that is needed to provide a desired level of drug in the secretions and tissues of the airways and lungs, or alternatively, in the bloodstream of a subject to be treated to give an anticipated physiological response or desired biological effect when such a composition is administered by the chosen route of administration. The precise amount will depend upon numerous factors, for example the particular compound of Formula IV, the specific activity of the composition, the delivery device employed, the physical characteristics of the composition, its intended use, as well as patient

considerations such as severity of the disease state, patient cooperation, etc., and can readily be determined by one skilled in the art based upon the information provided herein.

[0060] The term “normal saline” means a water solution containing 0.9% (w/v) NaCl.

[0061] The term “hypertonic saline” means a water solution containing greater than 0.9% (w/v) NaCl. For example, 3% hypertonic saline would contain 3% (w/v) NaCl.

[0062] “Forming a reaction mixture” refers to the process of bringing into contact at least two distinct species such that they mix together and can react. It should be appreciated, however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0063] “Coupling agent” refers to an agent capable of coupling two disparate compounds. Coupling agents can be catalytic or stoichiometric. For example, the coupling agents can be a lithium based coupling agent or a magnesium based coupling agent such as a Grignard reagent. Exemplary coupling agents include, but are not limited to, *n*-BuLi, MgCl₂, *i*PrMgCl, *t*BuMgCl, PhMgCl or combinations thereof.

[0064] “Silane” refers to a silicon containing group having the formula SiR₄, where each R group can be alkyl, alkenyl, cycloalkyl, phenyl, or other silicon containing groups. When the silane is linked to another compound, the silane is referred to as a “silyl” and has the formula -SiR₃.

[0065] “Halo-silane” refers to a silane having at least one halogen group linked to the silicon atom. Representative halo-silanes have the formula Halo-SiR₃, where each R group can be alkyl, alkenyl, cycloalkyl, phenyl, or other silicon containing groups. Specific halo-silanes include Cl-Si(CH₃)₃, and Cl-Si(CH₃)₂CH₂CH₂Si(CH₃)₂-Cl.

[0066] “Non-nucleophilic base” refers to an electron donor, a Lewis base, such as nitrogen bases including triethylamine, diisopropylethyl amine, *N,N*-diethylaniline, pyridine, 2,6-lutidine, 2,4,6-collidine, 4-dimethylaminopyridine, and quinuclidine.

[0067] “Leaving group” refers to groups that maintain the bonding electron pair during heterolytic bond cleavage. For example, a leaving group is readily displaced during a nucleophilic displacement reaction. Suitable leaving groups include, but are not limited to,

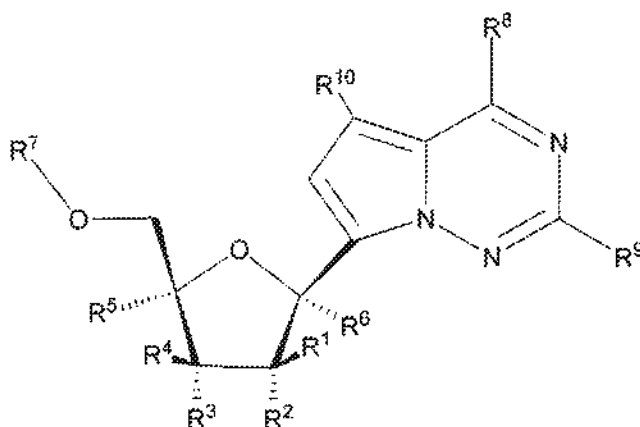
chloride, bromide, mesylate, tosylate, triflate, 4-nitrobenzenesulfonate, 4-chlorobenzenesulfonate, 4-nitrophenoxy, pentafluorophenoxy, etc. One of skill in the art will recognize other leaving groups useful in the present invention.

[0068] “Deprotection agent” refers to any agent capable of removing a protecting group. The deprotection agent will depend on the type of protecting group used. Representative deprotection agents are known in the art and can be found in *Protective Groups in Organic Chemistry*, Peter G. M. Wuts and Theodora W. Greene, 4th Ed., 2006.

II. COMPOUNDS OF THE PRESENT INVENTION

[0069] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention.

[0070] Provided, is a method for treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, hydrate or ester, thereof;

wherein:

each R¹ is H or halogen;

each R^2 , R^3 , R^4 or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl;

wherein

each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, or $-SO_2NR_2$;

each R is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycl, C_2-C_{20} substituted heterocycl, arylalkyl or substituted arylalkyl;

or any two R^2 , R^3 , R^4 or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl (C_1-C_8) alkyl;

wherein

each R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl (C_1-C_8) alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-O-$, $-S-$ or $-NR^a$;

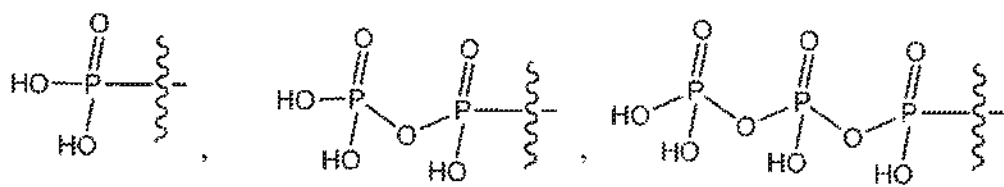
each n is independently 0, 1, or 2;

R^7 is selected from a group consisting of

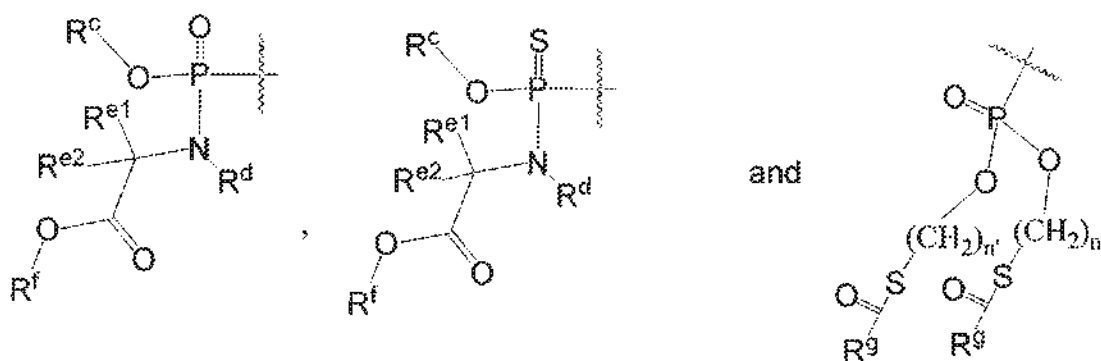
- a) H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$,

wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each R¹¹ or R¹² is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a-, and

b)

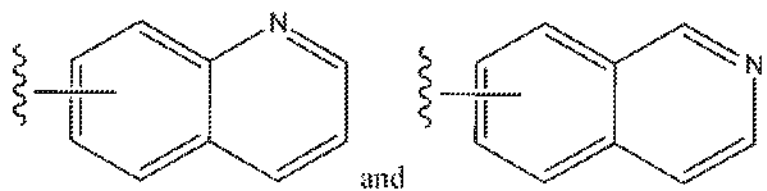


c) a group selected from:



wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,



R^d is H or CH₃;

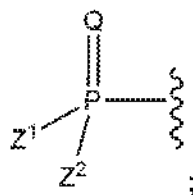
R^{e1} and R^{e2} are each independently H, C₁-C₆ alkyl or benzyl;

R^f is selected from H, C₁-C₈ alkyl, benzyl, C₃-C₆ cycloalkyl, and -CH₂-C₃-C₆ cycloalkyl;

R^g is selected from C₁-C₈ alkyl, -O-C₁-C₈ alkyl, benzyl, -O-benzyl, -CH₂-C₃-C₆ cycloalkyl, -O-CH₂-C₃-C₆ cycloalkyl, and CF₃; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:



wherein

Q is O, S, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), or N–NR₂;

Z¹ and Z², when taken together, are –Q¹(C(R^y)₂)₃Q¹–;

wherein

each Q¹ is independently O, S, or NR; and

each R^y is independently H, F, Cl, Br, I, OH, R, –C(=Q²)R, –C(=Q²)OR, –

C(=Q²)N(R)₂, –N(R)₂, –⁺N(R)₃, –SR, –S(O)R, –S(O)₂R, –S(O)(OR), –

S(O)₂(OR), –OC(=Q¹)R, –OC(=Q²)OR, –OC(=Q²)(N(R)₂), –SC(=Q²)R, –

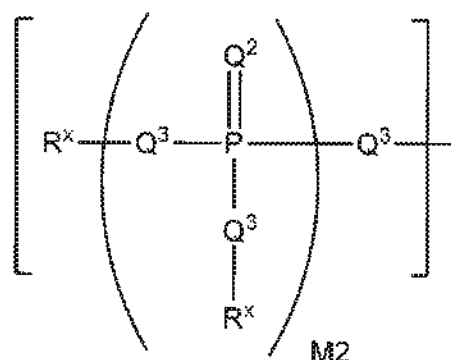
SC(=Q²)OR, –SC(=Q²)(N(R)₂), –N(R)C(=Q²)R, –N(R)C(=Q²)OR, –

N(R)C(=Q²)N(R)₂, –SO₂NR₂, –CN, –N₃, –NO₂, –OR, or Z³; or when

taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q² is independently, O, S, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), or N–NR₂; or

Z¹ and Z² are each, independently, a group of the Formula Ia:



Formula Ia

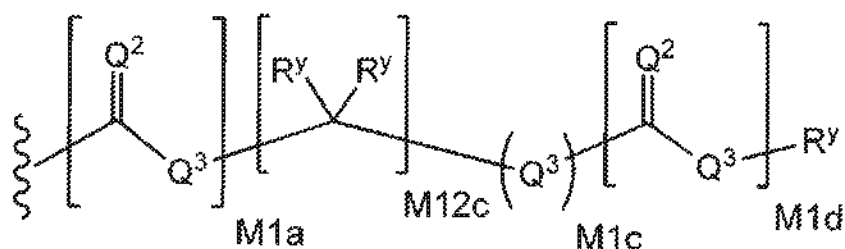
wherein:

each Q³ is independently a bond, O, CR₂, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR),

N–NR₂, S, S–S, S(O), or S(O)₂;

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

Z^3 is Z^4 or Z^5 ;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-SO_2R^y$, or $-SO_2Z^5$; and

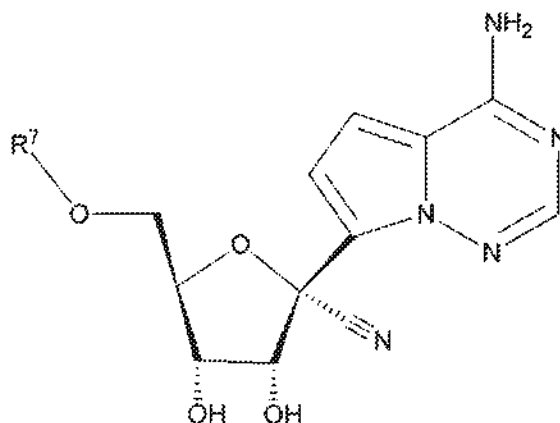
Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups;

each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl(C_1-C_8)alkyl, OR^{11} or SR^{11} ;

each R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} ; and

wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl(C_1-C_8)alkyl of each R^2 , R^3 , R^5 , or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with $-O-$, $-S-$ or $-NR^a$.

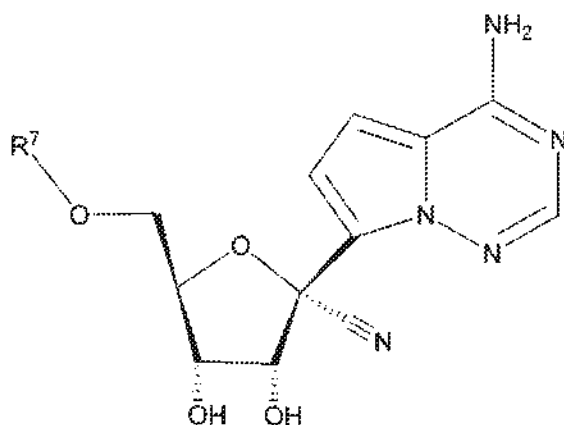
[0071] In another embodiment, provided is a compound of Formula IV:



Formula IV

or a pharmaceutically acceptable salt, hydrate or ester, thereof;
wherein R^7 is as defined above for Formula I.

[0072] Provided, is a method for treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula IV:



Formula IV

or a pharmaceutically acceptable salt or ester, thereof;
wherein:

R^7 is selected from the group of

- a) H , $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$,

wherein

each R^{11} or R^{12} is independently H , (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl (C_1-C_8) alkyl; or R^{11}

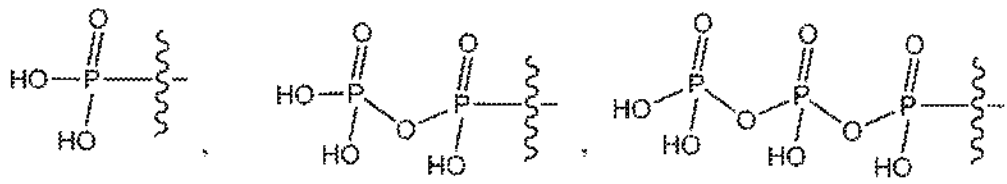
and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$;

each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, $-C(=O)R$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, or $-SO_2NR_2$;

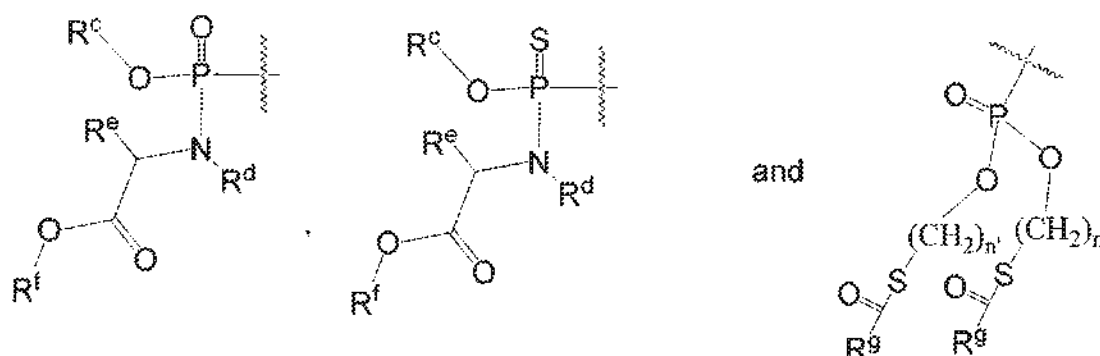
wherein each R is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocyclyl, C_2-C_{20} substituted heterocyclyl, arylalkyl or substituted arylalkyl; and

wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl of each R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with -O-, -S- or $-NR^a$, and

b)

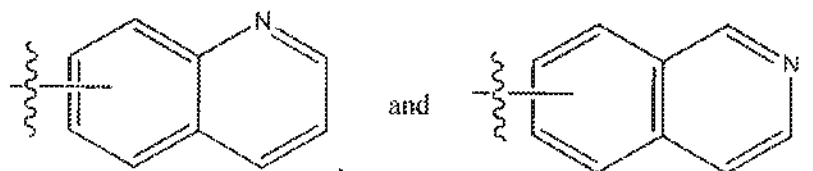


c) a group selected from:



wherein:

R^c is selected from phenyl, 1-naphthyl, 2-naphthyl,



R^d is H or CH_3 ;

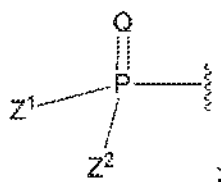
R^e is H or $\text{C}_1\text{-C}_6$ alkyl;

R^f is selected from H, $\text{C}_1\text{-C}_8$ alkyl, benzyl, $\text{C}_3\text{-C}_6$ cycloalkyl, and $-\text{CH}_2\text{-C}_3\text{-C}_6$ cycloalkyl;

R^g is selected from $\text{C}_1\text{-C}_8$ alkyl, $-\text{O-C}_1\text{-C}_8$ alkyl, benzyl, $-\text{O-benzyl}$, $-\text{CH}_2\text{-C}_3\text{-C}_6$ cycloalkyl, $-\text{O-CH}_2\text{-C}_3\text{-C}_6$ cycloalkyl, and CF_3 ; and

n' is selected from 1, 2, 3, and 4; and

d) a group of the formula:



wherein

Q is O, S, NR, $^+\text{N}(\text{O})(\text{R})$, $\text{N}(\text{OR})$, $^+\text{N}(\text{O})(\text{OR})$, or N-NR_2 ;

Z^1 and Z^2 , when taken together, are $-\text{Q}^1(\text{C}(\text{R}^y)_2)_3\text{Q}^1-$;

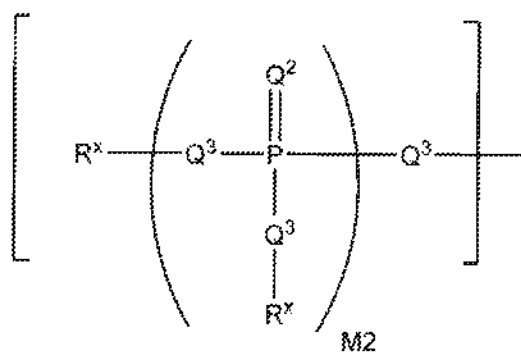
wherein

each Q^1 is independently O, S, or NR; and

each R^y is independently H, F, Cl, Br, I, OH, R, $-\text{C}(=\text{Q}^2)\text{R}$, $-\text{C}(=\text{Q}^2)\text{OR}$, $-\text{C}(=\text{Q}^2)\text{N}(\text{R})_2$, $-\text{N}(\text{R})_2$, $^+\text{N}(\text{R})_3$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})(\text{OR})$, $-\text{S}(\text{O})_2(\text{OR})$, $-\text{OC}(=\text{Q}^1)\text{R}$, $-\text{OC}(=\text{Q}^2)\text{OR}$, $-\text{OC}(=\text{Q}^2)(\text{N}(\text{R})_2)$, $-\text{SC}(=\text{Q}^2)\text{R}$, $-\text{SC}(=\text{Q}^2)\text{OR}$, $-\text{SC}(=\text{Q}^2)(\text{N}(\text{R})_2)$, $-\text{N}(\text{R})\text{C}(=\text{Q}^2)\text{R}$, $-\text{N}(\text{R})\text{C}(=\text{Q}^2)\text{OR}$, $-\text{N}(\text{R})\text{C}(=\text{Q}^2)\text{N}(\text{R})_2$, $-\text{SO}_2\text{NR}_2$, $-\text{CN}$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{OR}$, or Z^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+\text{N}(\text{O})(\text{R})$, $\text{N}(\text{OR})$, $^+\text{N}(\text{O})(\text{OR})$, or N-NR_2 ; or

Z^1 and Z^2 are each, independently, a group of the Formula Ia:



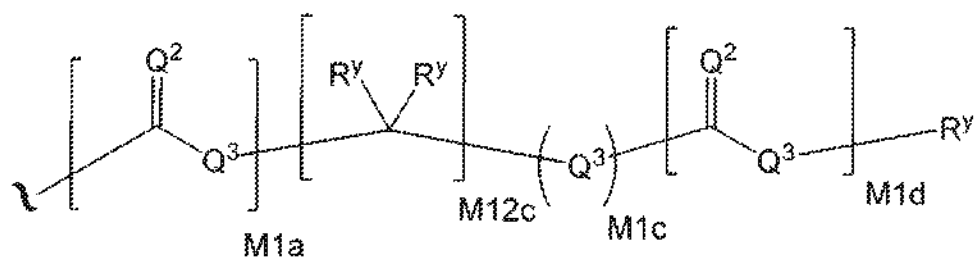
Formula Ia

wherein:

each Q^3 is independently a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

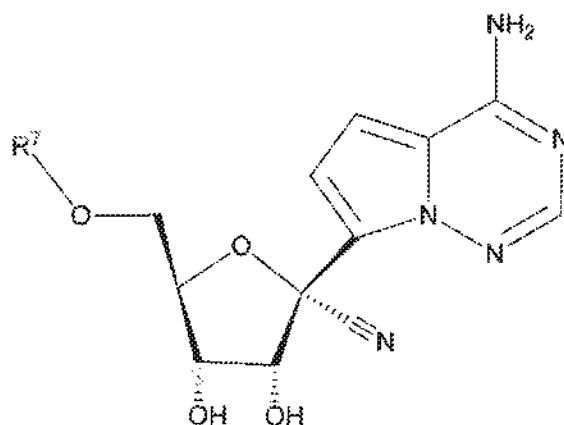
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

Z^3 is Z^4 or Z^5 ;

Z^4 is R, $-C(Q^2)R^y$, $-C(Q^2)Z^5$, $-SO_2R^y$, or $-SO_2Z^5$; and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups.

[0073] Provided, is a method for treating a *Filoviridae* infection in a human in need thereof comprising administering a therapeutically effective amount of a compound of Formula IV:



Formula IV

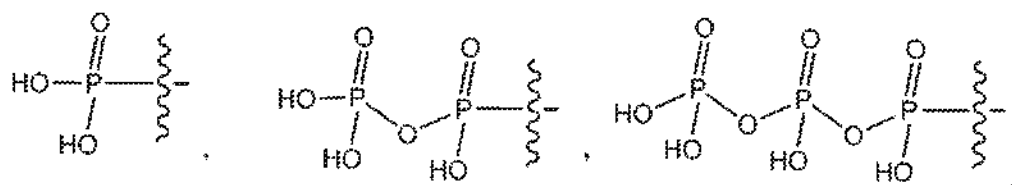
or a pharmaceutically acceptable salt, hydrate or ester, thereof;

wherein,

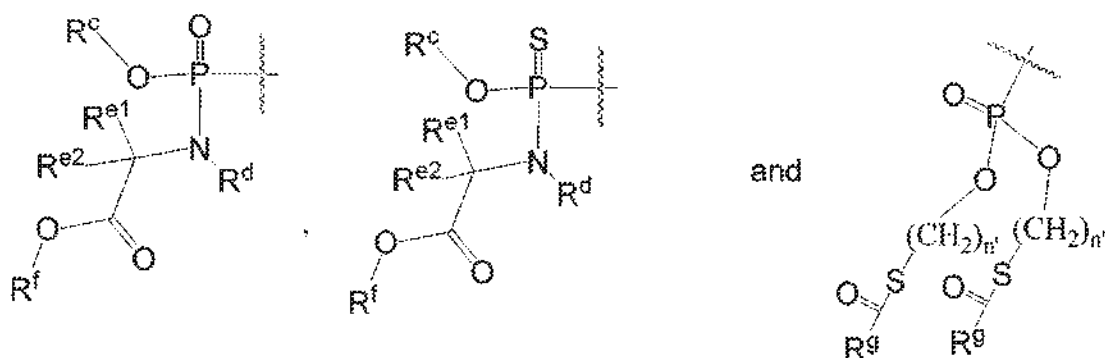
R^7 is selected from the group consisting of

- a) H , $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

b)

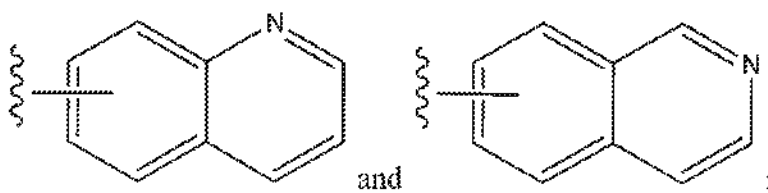


c) a group selected from:



wherein:

R^c is selected from the group of phenyl, 1-naphthyl, 2-naphthyl,



R^d is selected from the group of H or CH_3 ;

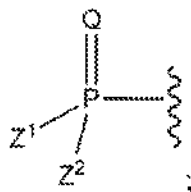
R^{e1} and R^{e2} are each independently selected from the group of H, $(\text{C}_1\text{--C}_6)\text{alkyl}$ or benzyl;

R^f is selected from the group of from H, $(\text{C}_1\text{--C}_8)\text{alkyl}$, benzyl, $(\text{C}_3\text{--C}_6)\text{cycloalkyl}$, and $-\text{CH}_2\text{--}(\text{C}_3\text{--C}_6)\text{cycloalkyl}$;

R^g is selected from selected from the group of $(\text{C}_1\text{--C}_8)\text{alkyl}$, $-\text{O--}(\text{C}_1\text{--C}_8)\text{alkyl}$, benzyl, $-\text{O--benzyl}$, $-\text{CH}_2\text{--}(\text{C}_3\text{--C}_6)\text{cycloalkyl}$, $-\text{O--CH}_2\text{--}(\text{C}_3\text{--C}_6)\text{cycloalkyl}$, and CF_3 ; and

n' is an integer selected from the group of 1, 2, 3, and 4; and

d) a group of the formula:



wherein:

Q is selected from the group of O, S, NR, $^+\text{N}(\text{O})(\text{R})$, $\text{N}(\text{OR})$, $^+\text{N}(\text{O})(\text{OR})$, or N--NR_2 ;

Z^1 and Z^2 , when taken together, are $-\text{Q}^1(\text{C}(\text{R}^y)_2)_3\text{Q}^1-$;

wherein

each Q^1 is independently selected from the group of O, S, or NR; and

each R^y is independently selected from the group of H, F, Cl, Br, I, OH, R, $-\text{C}(=\text{Q}^2)\text{R}$, $-\text{C}(=\text{Q}^2)\text{OR}$, $-\text{C}(=\text{Q}^2)\text{N}(\text{R})_2$, $-\text{N}(\text{R})_2$, $^+\text{N}(\text{R})_3$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})(\text{OR})$, $-\text{S}(\text{O})_2(\text{OR})$, $-\text{OC}(=\text{Q}^1)\text{R}$, $-\text{OC}(=\text{Q}^2)\text{OR}$, $-\text{OC}(=\text{Q}^2)(\text{N}(\text{R})_2)$, $-\text{SC}(=\text{Q}^2)\text{R}$, $-\text{SC}(=\text{Q}^2)\text{OR}$, $-\text{SC}(=\text{Q}^2)(\text{N}(\text{R})_2)$, $-\text{N}(\text{R})\text{C}(=\text{Q}^2)\text{R}$, -

$N(R)C(=Q^2)OR$, $-N(R)C(=Q^2)N(R)_2$, $-SO_2NR_2$,

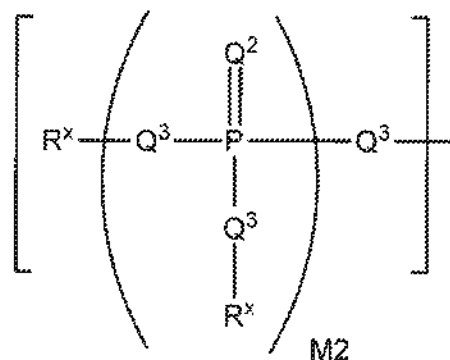
$-CN$, $-N_3$, $-NO_2$, $-OR$, or Z^3 ; or when taken

together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each Q^2 is independently, O, S, NR, $^+N(O)(R)$, $N(OR)$,

$^+N(O)(OR)$, or $N-NR_2$; or

Z^1 and Z^2 are each, independently, a group of the Formula Ia:



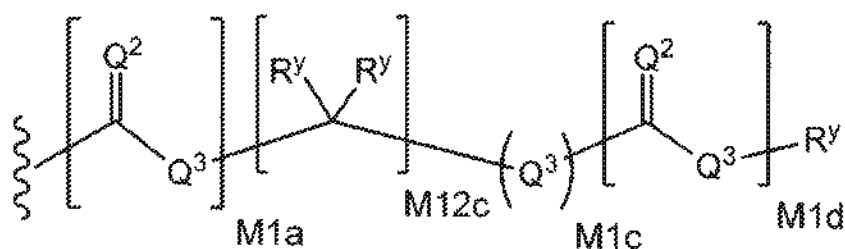
Formula Ia

wherein:

each Q^3 is independently selected from the group of a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

M2 is an integer selected from the group of 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is an integer independently selected from the group of 0 or 1;

M12c is an integer selected from the group of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

Z^3 is Z^4 or Z^5 ;

Z^4 is R, $-C(Q^3)R^y$, $-C(Q^2)Z^5$, $-SO_2R^y$, or $-SO_2Z^5$;

and

Z^5 is a carbocycle or a heterocycle wherein Z^5 is independently substituted with 0 to 3 R^y groups;

each R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, (C_6-C_{20}) optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or (C_6-C_{20}) aryl (C_1-C_8) alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$;

each R^a is independently selected from the group of H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_6-C_{20}) aryl (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, or $-SO_2NR_2$; wherein

each R is independently selected from the group of H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, (C_6-C_{20}) aryl, (C_6-C_{20}) substituted aryl, (C_2-C_{20}) heterocyclyl, (C_2-C_{20}) substituted heterocyclyl, (C_6-C_{20}) aryl (C_1-C_8) alkyl or substituted (C_6-C_{20}) aryl (C_1-C_8) alkyl;

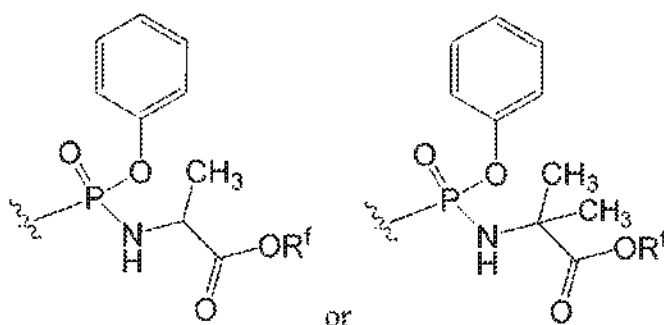
each n is an integer independently selected from the group of 0, 1, or 2; and

wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or (C_6-C_{20}) aryl (C_1-C_8) alkyl of each R^{11} or R^{12} is, independently, optionally substituted with one or more substituents selected from the group of halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with -O-, -S- or $-NR^a$.

[0074] In another embodiment of a compound of Formula IV, R^7 can be H. In another embodiment of a compound of Formula IV, R^7 is selected from the group of a), b), or c) as defined for Formula IV.

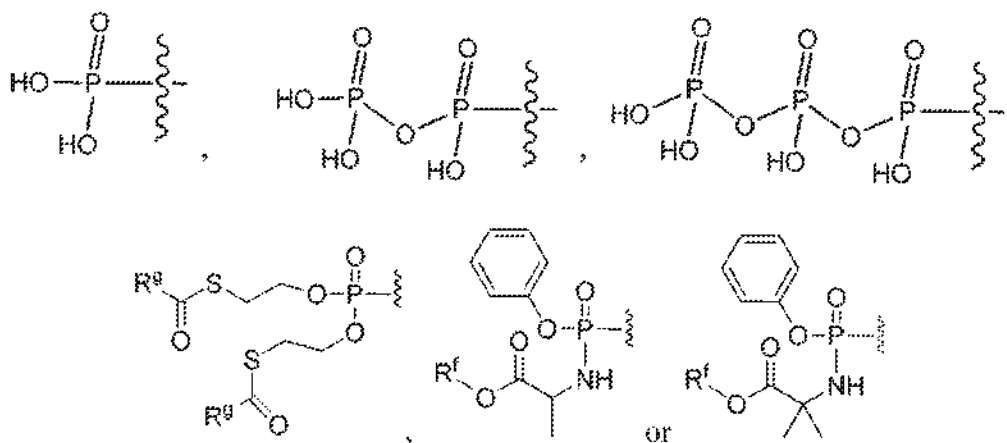
[0075] In some embodiments, R^{e1} and R^{e2} can each independently be selected from the group of H, C_1 - C_6 alkyl or benzyl. In some embodiments, R^{e1} can be H, C_1 - C_6 alkyl or benzyl, and R^{e2} can be H or C_1 - C_6 alkyl. In some embodiments, R^{e1} and R^{e2} can each independently be H or C_1 - C_6 alkyl. In some embodiments, R^{e1} and R^{e2} can each independently be H or benzyl. In some embodiments, R^{e1} can be H, methyl or benzyl, and R^{e2} can be H or methyl. In some embodiments, R^{e1} can be H or methyl, and R^{e2} can be H or methyl. In some embodiments, R^{e1} can be methyl, and R^{e2} can be H or methyl. In some embodiments, R^{e1} can be H or benzyl, and R^{e2} can be H or methyl.

[0076] In another embodiment of a compound of Formula IV, R^7 is



wherein R^f is selected from the group of H, C_1 - C_8 alkyl, benzyl, C_3 - C_6 cycloalkyl, and $-CH_2$ - C_3 - C_6 cycloalkyl. In another embodiment of a compound of Formula IV, R^f is C_1 - C_8 alkyl.

[0077] In another embodiment of a compound of Formula IV, R^7 is

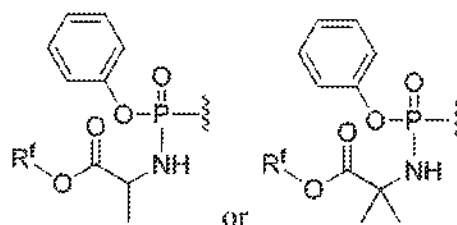


wherein

R^f is selected from the group of H, C_1 - C_8 alkyl, benzyl, C_3 - C_6 cycloalkyl, and $-CH_2$ - C_3 - C_6 cycloalkyl; and

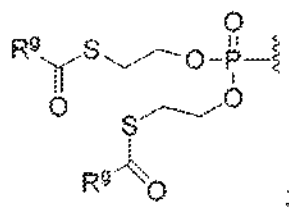
R^2 is selected from the group of C_1 - C_8 alkyl, $-O$ - C_1 - C_8 alkyl, benzyl, $-O$ -benzyl, $-CH_2$ - C_3 - C_6 cycloalkyl, $-O$ - CH_2 - C_3 - C_6 cycloalkyl, and CF_3 .

[0078] In another embodiment of a compound of Formula IV, R^7 is



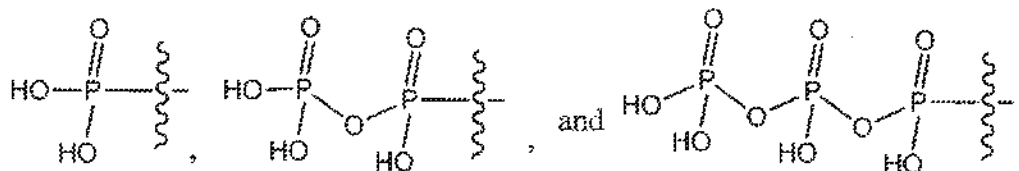
wherein R^f is selected from the group of H, C_1 - C_8 alkyl, benzyl, C_3 - C_6 cycloalkyl, and $-CH_2$ - C_3 - C_6 cycloalkyl. In another embodiment of a compound of Formula IV, R^f is C_1 - C_8 alkyl. In another embodiment of a compound of Formula IV, R^f is C_1 - C_6 alkyl.

[0079] In another embodiment of a compound of Formula IV, R^7 is:

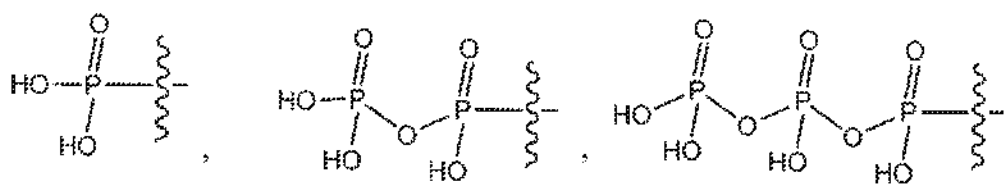


wherein R^f is selected from the group of C_1 - C_8 alkyl, $-O$ - C_1 - C_8 alkyl, benzyl, $-O$ -benzyl, $-CH_2$ - C_3 - C_6 cycloalkyl, $-O$ - CH_2 - C_3 - C_6 cycloalkyl, and CF_3 . In another embodiment of a compound of Formula IV, R^f is C_1 - C_8 alkyl. In another embodiment of a compound of Formula IV, R^f is C_1 - C_6 alkyl.

[0080] In another embodiment of a compound of Formula IV, R^7 is selected from the group of:

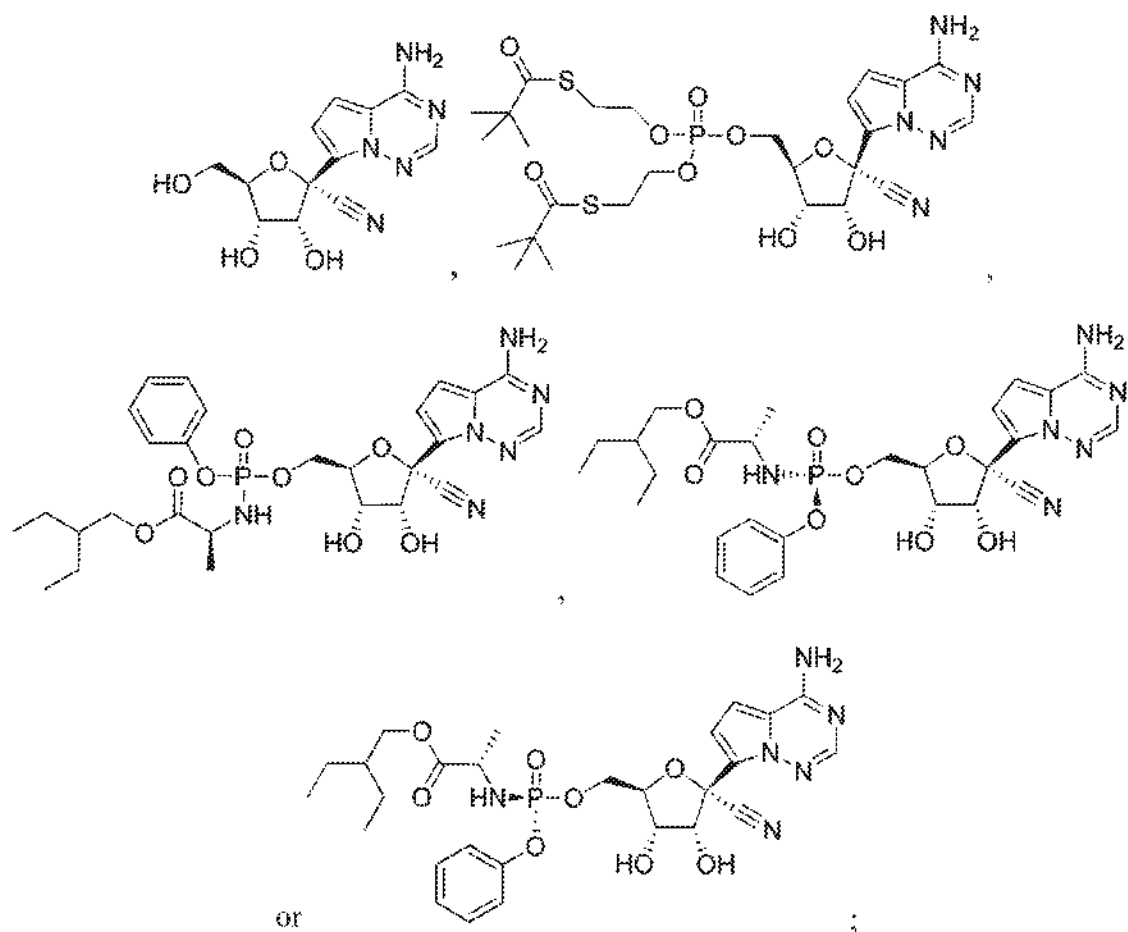


[0081] In another embodiment of a compound of Formula IV, R^7 is



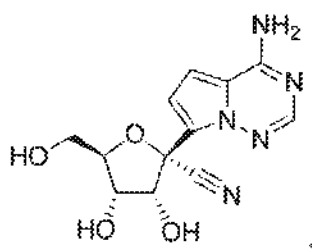
or a pharmaceutically acceptable salt or ester thereof.

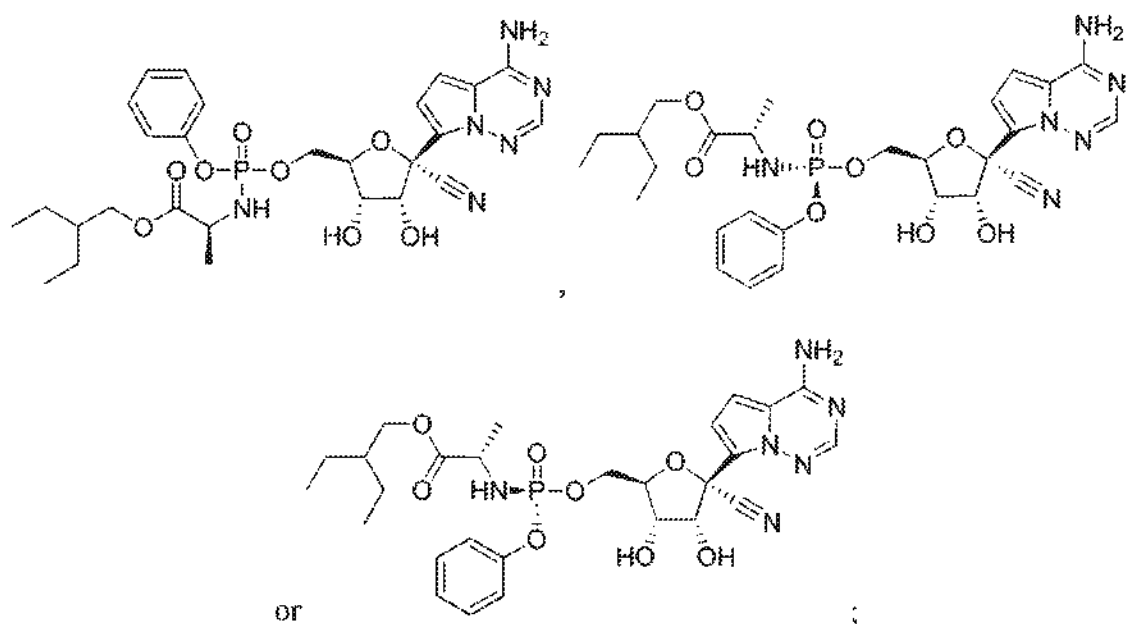
[0083] In another embodiments, provided is a compound of Formula IV that is:



or a pharmaceutically acceptable salt or ester thereof.

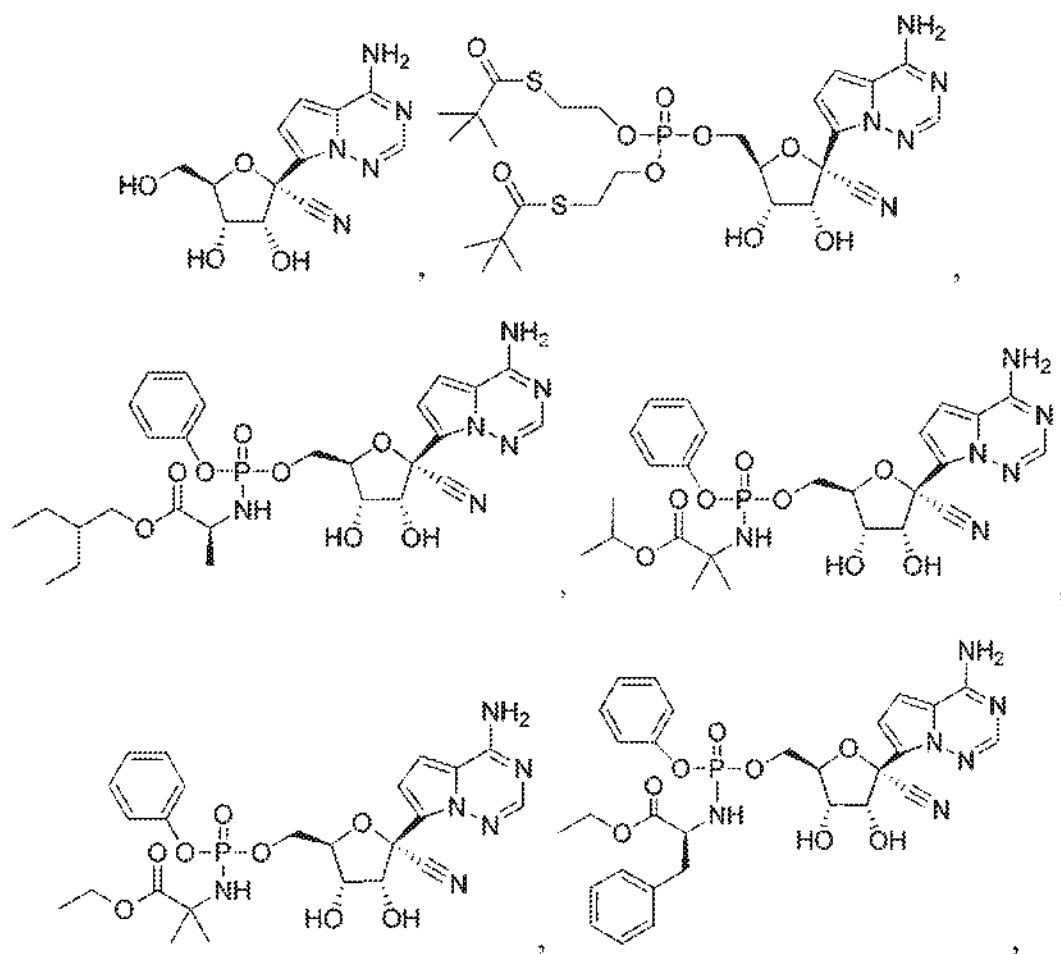
[0084] In another embodiments, provided is a compound of Formula IV that is:

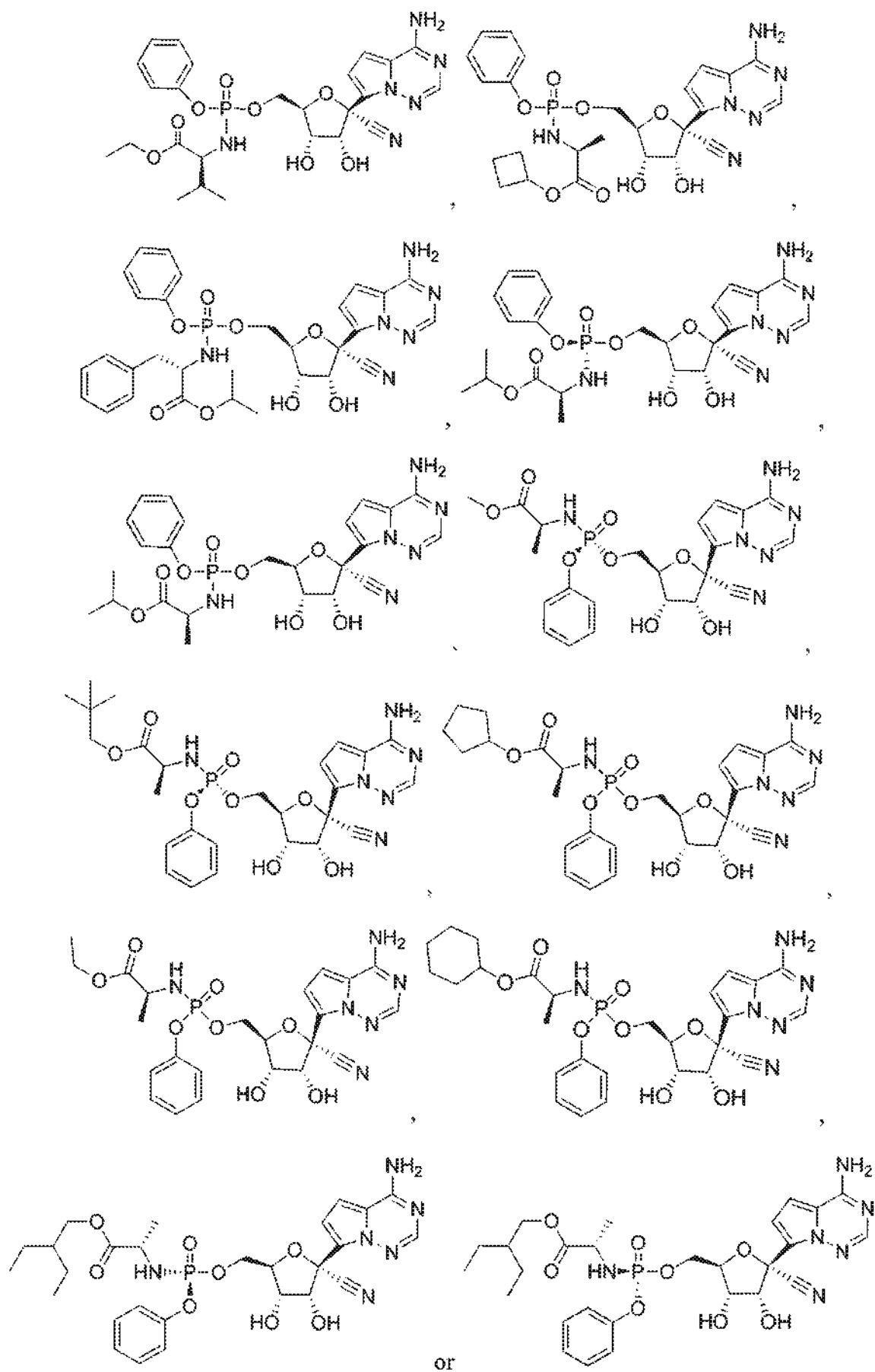




or a pharmaceutically acceptable salt, hydrate, or ester thereof.

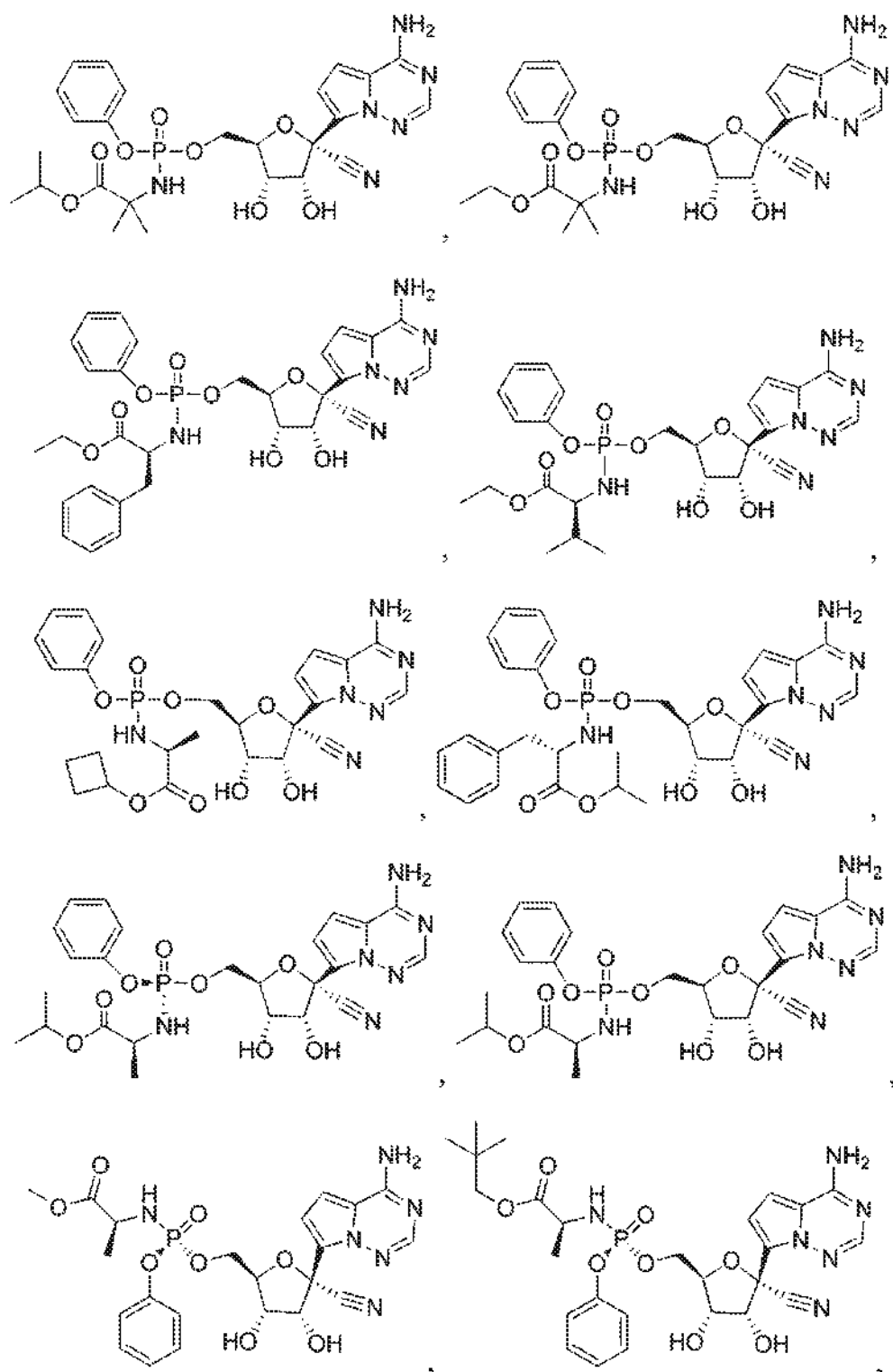
[0085] In another embodiment, provided is a compound of Formula IV that is

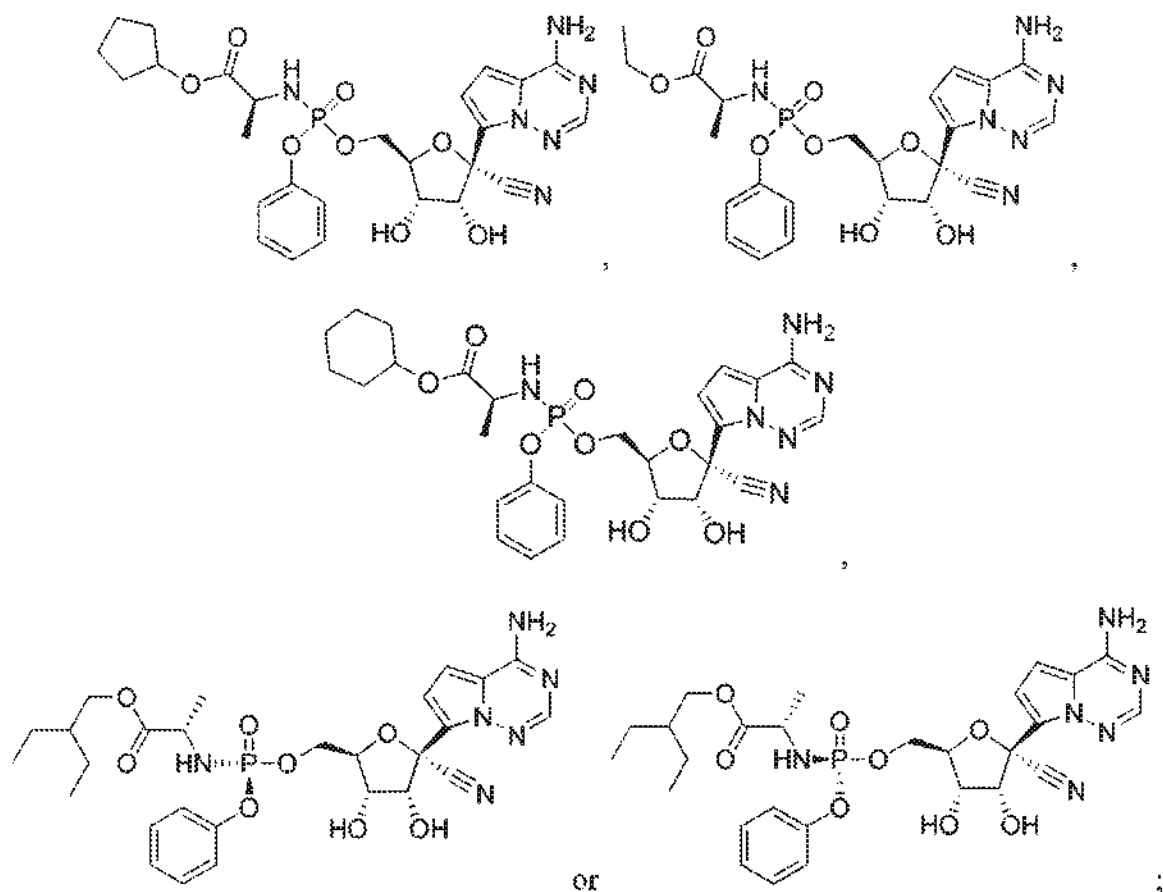




or a pharmaceutically acceptable salt or ester thereof.

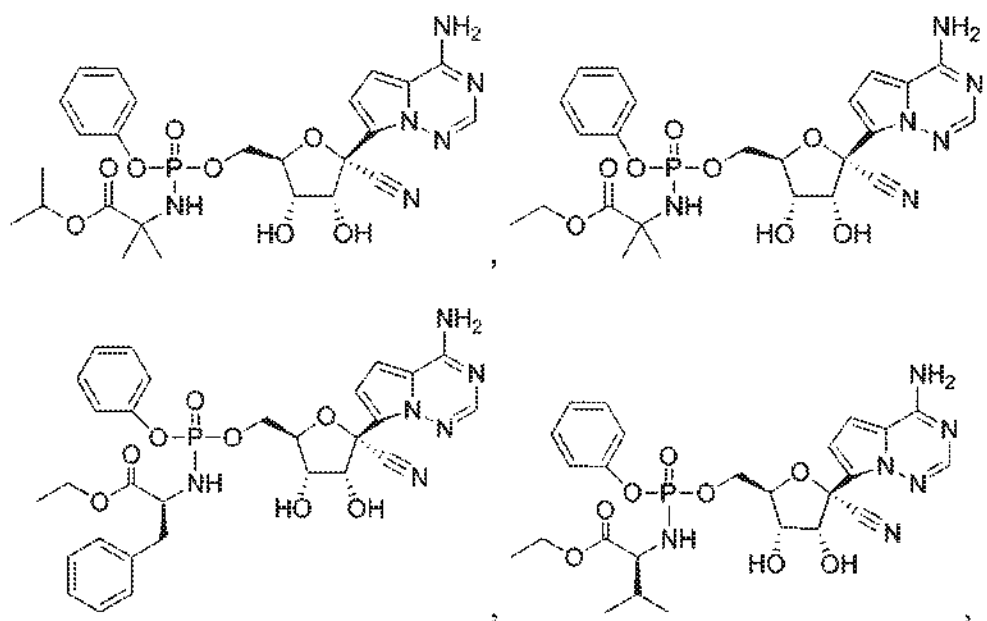
[0086] In another embodiment, the present invention provides a compound that is

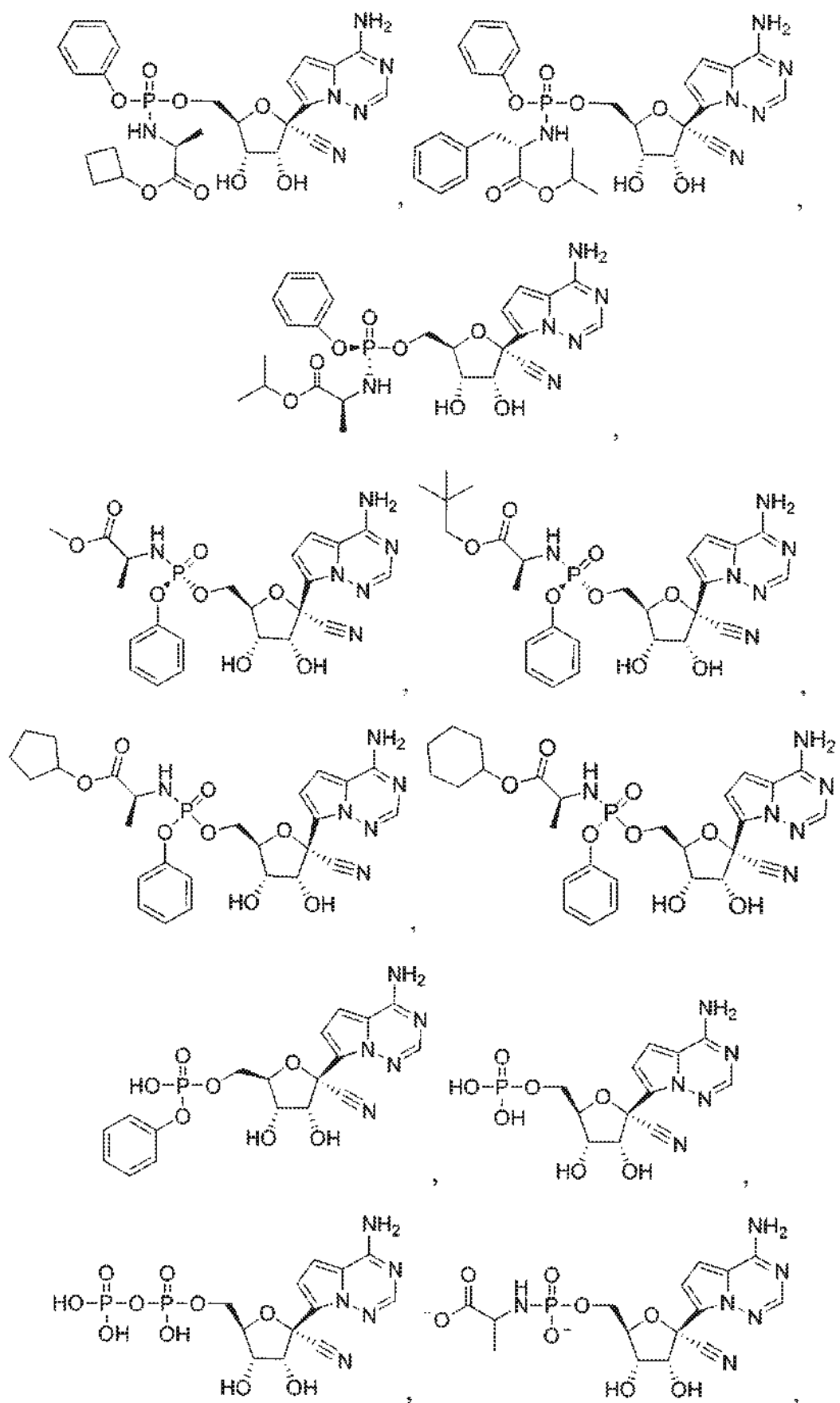


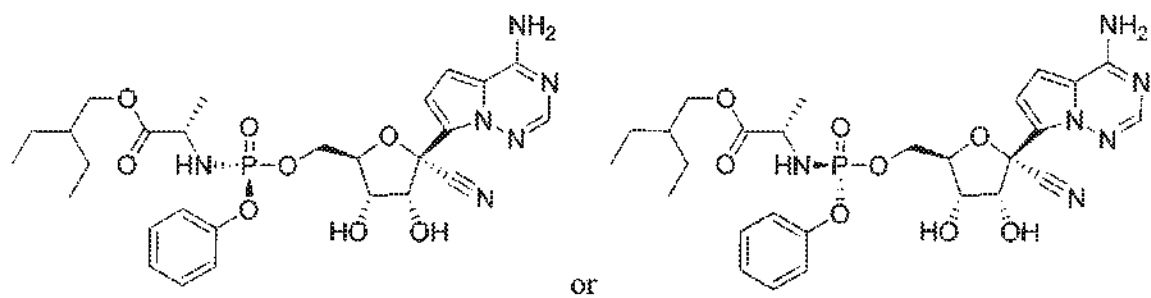


or a pharmaceutically acceptable salt or ester thereof.

[0087] In another embodiment, the present invention provides a compound that is

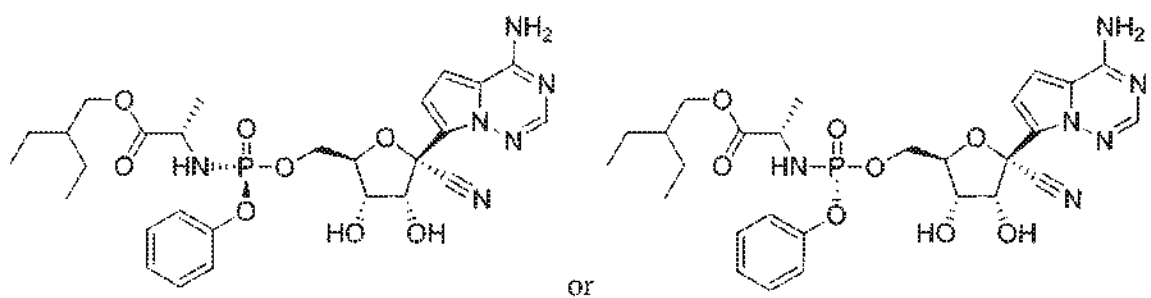






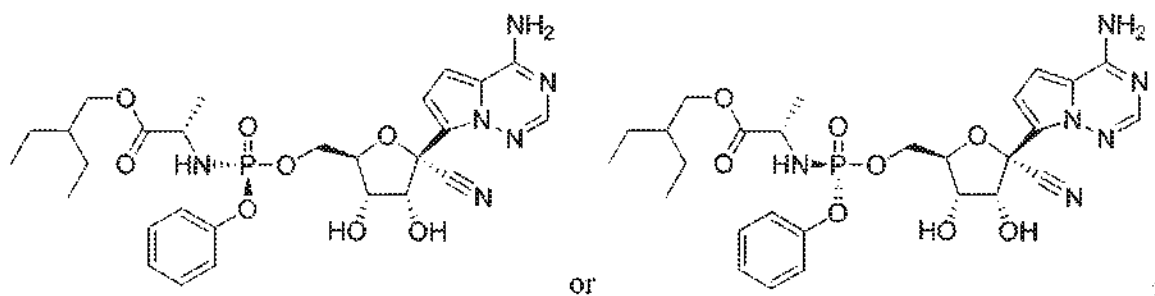
or a pharmaceutically acceptable salt, hydrate, or ester thereof.

[0088] In another embodiment, the present invention provides a compound that is



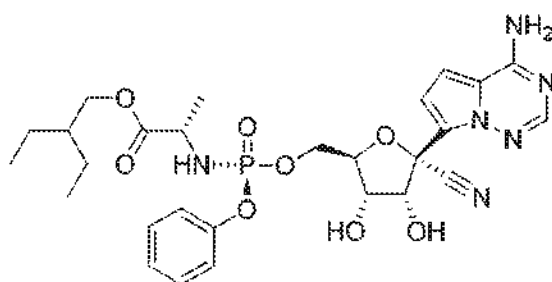
or a pharmaceutically acceptable salt or ester thereof.

[0089] In another embodiment, the present invention provides a compound that is



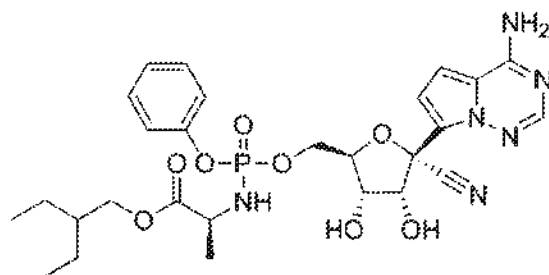
or a pharmaceutically acceptable salt or ester thereof.

[0090] In another embodiment, the present invention provides a compound that is

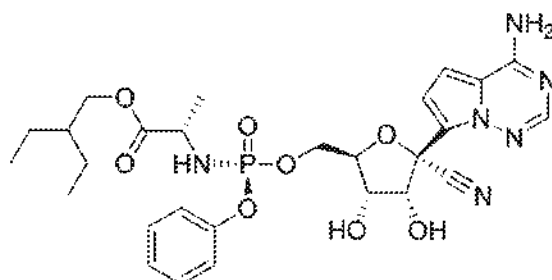


or a pharmaceutically acceptable salt or ester thereof.

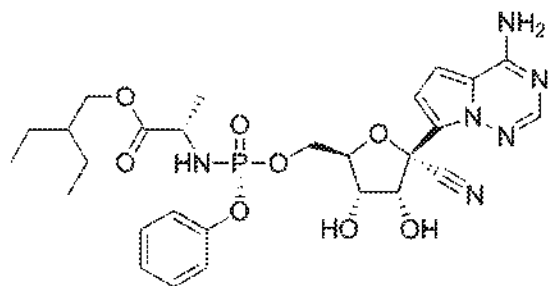
[0091] Names of compounds of the present disclosure are provided using ACD/Name software for naming chemical compounds (Advanced Chemistry Development, Inc., Toronto, Canada). Other compounds or radicals may be named with common names or systematic or non-systematic names. The naming and numbering of the compounds of the disclosure is illustrated with a representative compound of Formula IV:



which is named (2S)-2-ethylbutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate. Other compounds of the present invention include:

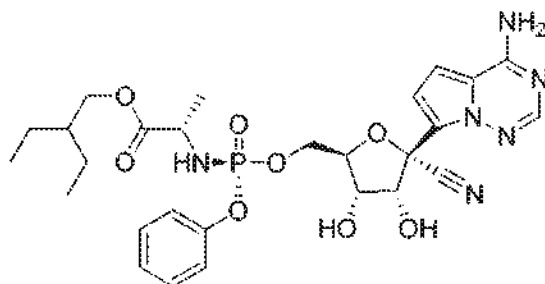


which is named (S)-2-ethylbutyl 2-(((S)-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate, and



which is named (S)-2-ethylbutyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.

(S)-2-ethylbutyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate may also be illustrated as



[0092] Any reference to the compounds of the invention described herein also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+ , Li^+ , K^+ , Ca^{+2} and Mg^{+2}), ammonium and NR_4^+ (wherein R is defined herein). Physiologically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pantoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NR_4^+ .

[0093] A compound of Formula IV and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means

the ability of a crystalline compound to exist in different crystal structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula IV and their pharmaceutically acceptable salts.

[0094] A compound of Formula IV and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula IV and their pharmaceutically acceptable salts.

[0095] For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

[0096] Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

[0097] It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula IV and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

[0098] The compounds of the invention, exemplified by Formula IV may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In

addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

[0099] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (-), or l meaning that the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0100] The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

[0101] Any formula or structure given herein, including Formula IV compounds, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^2H (deuterium, D), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl and ^{125}I . Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^3H , ^{13}C and ^{14}C are incorporated. Such isotopically labeled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[0102] The disclosure also included compounds of Formula IV in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound of Formula IV when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[0103] Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of Formula IV.

[0104] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

[0105] Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R¹", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines, ~~~~~, indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

[0106] Selected substituents comprising the compounds of Formula IV are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R. R can be Z³. Z³ can be Z⁴ and Z⁴ can be R or comprise substituents comprising R^y. Alternatively, Z³ can be Z⁵ which can comprise substituents comprising R^y. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

[0107] By way of example and not limitation, Z³ and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each recursive substituent can independently occur 12 or fewer times in a given embodiment. Even more typically, each recursive substituent can independently occur 3 or fewer times in a given embodiment. For example, Z³ will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more typically, Z³ will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

[0108] Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

[0109] The compounds of the present invention can be prepared by methods known to one of skill in the art. For example, the compounds of the present invention can be prepared according to the methods described in U.S. Patent No. 8,008,264 and U.S. Application Publication No. US 2012/0027752.

A. Metabolites of the Compounds of the Invention

[0110] Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no anti Filoviridae activity of their own.

[0111] Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C. Simply

because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

III. PHARMACEUTICAL FORMULATIONS

[0112] The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10. In some embodiments, the pH of the formulations ranges from about 2 to about 5, but is ordinarily about 3 to about 4. In some embodiments, the pH of the formulations ranges from about 2 to about 10, but is ordinarily about 3.5 to about 8.5.

[0113] While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients, particularly those additional therapeutic ingredients as discussed herein. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0114] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by

uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0115] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

[0116] A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0117] For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

[0118] If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[0119] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0120] Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate. Further emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 80.

[0121] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[0122] Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable

for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0123] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0124] Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). Further non-limiting examples of suspending agents include Captisol® (sulfobutyl ether beta-cyclodextrin, SBE- β -CD). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0125] Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0126] Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0127] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[0128] The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. The sterile injectable preparation may also be a sterile injectable solution or suspension in a parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution isotonic sodium chloride solution, hypertonic sodium chloride solution, and hypotonic sodium chloride solution.

[0129] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μ g of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0130] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

[0131] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0132] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0133] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of *Filoviridae* infections as described below.

[0134] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0135] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0136] The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0137] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0138] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

[0139] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0140] Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

IV. ROUTES OF ADMINISTRATION

[0141] One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

[0142] In the methods of the present invention for the treatment of *Filoviridae* infection, the compounds of the present invention can be administered at any time to a human who may come into contact with humans suffering from *Filoviridae* infection or is already suffering from *Filoviridae* infection. In some embodiments, the compounds of the present invention can be administered prophylactically to humans coming into contact with humans suffering from *Filoviridae* infection. In some embodiments, administration of the compounds of the present invention can be to humans testing positive for *Filoviridae* infection but not yet showing symptoms of *Filoviridae* infection. In some embodiments, administration of the compounds of the present invention can be to humans upon commencement of symptoms of *Filoviridae* infection.

[0143] Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about .01 to about 5 mg/kg body weight per day; most typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

[0144] The effective dose of a compound of the present invention for treating the *Filoviridae* infection can depend on whether the dose is to be used prophylactically or to treat a human already suffering from *Filoviridae* infection. Moreover, the dose can depend on whether the

human suffering from *Filoviridae* infection does not yet show symptoms or is already showing symptoms of *Filoviridae* infection. Larger doses may be necessary for treating humans testing positive for *Filoviridae* infection and for humans showing symptoms of *Filoviridae* infection as compared to humans receiving prophylactic treatment.

[0145] Any suitable period of time for administration of the compounds of the present invention is contemplated. For example, administration can be for from 1 day to 100 days, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, or 90 days. The administration can also be for from 1 week to 15 weeks, including 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 weeks. Longer periods of administration are also contemplated. The time for administration can depend on whether the compound is being administered prophylactically or to treat a human suffering from a *Filoviridae* infection. For example, a prophylactic administration can be for a period of time while the human is in regular contact with other humans suffering from a *Filoviridae* infection, and for a suitable period of time following the last contact with a human suffering from a *Filoviridae* infection. For humans already suffering from a *Filoviridae* infection, the period of administration can be for any length of time necessary to treat the patient and a suitable period of time following a negative test for *Filoviridae* infection to ensure the *Filoviridae* infection does not return.

V. COMBINATION THERAPY

[0146] Compositions of the invention are also used in combination with other active ingredients. For the treatment of *Filoviridae* virus infections, preferably, the other active therapeutic agent is active against *Filoviridae* virus infections, particularly Marburg virus, Ebola virus and Cueva virus infections. Non-limiting examples of these other active therapeutic agents are ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam®), MEDI-557, A-60444, MDT-637, BMS-433771, amiodarone, dronedarone, verapamil, Ebola Convalescent Plasma (ECP), TKM-100201, BCX4430 ((2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol), favipiravir (also known as T-705 or Avigan), T-705 monophosphate, T-705 diphosphate, T-705 triphosphate, FGI-106 (1-N,7-N-bis[3-(dimethylamino)propyl]-3,9-dimethylquinolino[8,7-h]quinolone-1,7-diamine), JK-05, TKM-Ebola, ZMapp, rNAPc2, VRC-EBOADC076-00-VP, OS-2966, MVA-BN filo, brincidofovir, Vaxart adenovirus vector 5-based ebola vaccine, Ad26-ZEBOV, FiloVax vaccine, GOVX-E301, GOVX-E302, ebola virus entry inhibitors (NPC1 inhibitors), and rVSV-EBOV, and mixtures thereof. The compounds and compositions of the present invention may also be used in

combination with phosphoramidate morpholino oligomers (PMOs), which are synthetic antisense oligonucleotide analogs designed to interfere with translational processes by forming base-pair duplexes with specific RNA sequences. Examples of PMOs include AVI-7287, AVI-7288, AVI-7537, AVI-7539, AVI-6002, and AVI-6003. The compounds and compositions of the present invention are also intended for use with general care provided patients with Filoviridae viral infections, including parenteral fluids (including dextrose saline and Ringer's lactate) and nutrition, antibiotic (including metronidazole and cephalosporin antibiotics, such as ceftriaxone and cefuroxime) and/or antifungal prophylaxis, fever and pain medication, antiemetic (such as metoclopramide) and/or antidiarrheal agents, vitamin and mineral supplements (including Vitamin K and zinc sulfate), anti-inflammatory agents (such as ibuprofen), pain medications, and medications for other common diseases in the patient population, such anti-malarial agents (including artemether and artesunate-lumefantrine combination therapy), typhoid (including quinolone antibiotics, such as ciprofloxacin, macrolide antibiotics, such as azithromycin, cephalosporin antibiotics, such as ceftriaxone, or aminopenicillins, such as ampicillin), or shigellosis.

[0147] It is also possible to combine any compound of the invention with one or more additional active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0148] Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

[0149] Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first,

followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

[0150] The combination therapy may provide “synergy” and “synergistic”, i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

[0151] In still yet another embodiment, the present application provides for methods of inhibiting *Filoviridae* polymerase in a cell, comprising: contacting a cell infected with a Filovirus with an effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, whereby *Filoviridae* polymerase is inhibited.

[0152] In still yet another embodiment, the present application provides for methods of inhibiting *Filoviridae* polymerase in a cell, comprising: contacting a cell infected with Filovirus with an effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby *Filoviridae* polymerase is inhibited.

[0153] In still yet another embodiment, the present application provides for methods of inhibiting *Filoviridae* polymerase in a cell, comprising: contacting a cell infected with *Filoviridae* virus with an effective amount of a compound of Formula IV, or a pharmaceutically

acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected

[0154] In still yet another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

[0155] In still yet another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby *Filoviridae* polymerase is inhibited.

[0156] In still yet another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent.

[0157] Also provided is a kit that includes a compound of Formula IV, or a pharmaceutically acceptable salt, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof. In separate embodiments individual kits are provided includes a compound selected from Formula IV herein, as well as each subgroup and embodiment thereof, including individual Compounds 1, 8, 9, 10, 12, 15, 17, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 (Compounds 1-32), or a pharmaceutically acceptable salt, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof. In one aspect, the kit comprises a compound of Formula IV, or a pharmaceutically acceptable salt thereof. Each of the individual kits described herein may comprise a label and/or instructions for use of the compound in the treatment of a disease or condition in a subject (e.g., human) in need thereof. In some embodiments, the disease or condition is a human *Filoviridae* viral infection, including an Ebola viral infection or a Marburg viral infection. In other embodiments, each separate kit may also contain instructions for use of additional medical agents in combination with the compound of Formula IV in the treatment of a disease or condition in a subject (e.g., human) in need thereof. In certain of these embodiments, the disease or condition is a human *Filoviridae* viral infection, including an Ebola viral infection or a Marburg viral infection. In each of the kits herein there is

a further embodiment in which the kit comprises individual dose units of a compound as described herein, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. Examples of individual dosage units may include pills, tablets, capsules, prefilled syringes or syringe cartridges, IV bags, etc., each comprising a therapeutically effective amount of the compound in question, or a pharmaceutically acceptable salt, racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate thereof. In some embodiments, the kit may contain a single dosage unit and in others multiple dosage units are present, such as the number of dosage units required for a specified regimen or period.

[0158] Also provided are articles of manufacture that include a compound of Formula IV, or a pharmaceutically acceptable salt, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof; and a container. In one aspect, the article of manufacture comprises a compound of Formula IV and individual Compounds 1, 8, 9, 10, 12, 15, 17, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, and 32 (Compounds 1-32), or a pharmaceutically acceptable salt thereof, and a container. In separate embodiments, the container of the article of manufacture may be a vial, jar, ampoule, preloaded syringe, blister package, tin, can, bottle, box, or an intravenous bag.

VI. METHODS OF INHIBITION OF A *FILOVIRIDAE* POLYMERASE

[0159] Another aspect of the invention relates to methods of inhibiting the activity of *Filoviridae* polymerase comprising the step of treating a sample suspected of containing *Filoviridae* with a compound or composition of the invention.

[0160] *Filoviridae* that can be treated using the methods of the present invention are single-stranded negative sense RNA viruses that typically infect primates. Filoviruses are able to multiply in virtually all cell types. The Filovirus antigens and virions are found primarily in fibroblasts and interstitium of an infected individual. There are three identified genera of Filoviruses: the Ebola virus (EBOV; five species); the Marburg virus (MARV); and the Cuevavirus, also known as the Lloviu virus (LLOV). The virions (viral particles) are characteristically shaped as long, cylindrical, filamentous particles which may be straight, curved, coiled, or found in a “6” or “U” shaped configuration. They are occasionally branched and the particles vary greatly in length, but the diameter (about 80 nm) is consistent. The filovirus genome comprises seven genes that encode 4 virion structural proteins (VP30, VP35,

nucleoprotein (NP), and a polymerase protein (L-pol)) and 3 membrane-associated proteins (VP40, glycoprotein (GP), and VP24).

[0161] The Ebola virus genus includes five known species: (1) *Bundibugyo ebolavirus*, also known as Bundibugyo virus (BDBV, previously BEBOV); (2) *Reston ebolavirus*, also known as Reston virus or Ebola-Reston (RESTV, previously REBOV); (3) *Sudan ebolavirus*, also known as Sudan virus or Ebola-Sudan (SUDV, previously SEBOV); (4) *Tai Forest ebolavirus*, also known as Tai Forest virus or Ebola-Tai (TAFV, previously CIEBOV); and (5) *Zaire ebolavirus*, also known as Ebola virus or Ebola-Zaire (EBOV, previously ZEBOV).

[0162] The Marburg virus genus includes the species *Marburg marburgvirus*, also known as Marburg virus (MARV) or Ravn virus (RAVV). The Cuevavirus genus includes the species *Lloviu cuevavirus*, also known as the Lloviu virus (LLOV).

[0163] Compositions of the invention may act as inhibitors of *Filoviridae* polymerase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of *Filoviridae* polymerase having a geometry unique to *Filoviridae* polymerase. Compositions binding *Filoviridae* polymerase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of *Filoviridae* polymerase. Accordingly, the invention relates to methods of detecting *Filoviridae* polymerase in a sample suspected of containing *Filoviridae* polymerase comprising the steps of: treating a sample suspected of containing *Filoviridae* polymerase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

[0164] Within the context of the invention, samples suspected of containing *Filoviridae* polymerase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells

synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces *Filoviridae* polymerase, frequently a pathogenic organism such as a *Filoviridae* virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and manmade materials such as cell cultures.

[0165] The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

[0166] If desired, the activity of *Filoviridae* polymerase after application of the composition can be observed by any method including direct and indirect methods of detecting *Filoviridae* polymerase activity. Quantitative, qualitative, and semiquantitative methods of determining *Filoviridae* polymerase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

[0167] Organisms that contain *Filoviridae* polymerase include the *Filoviridae* virus. The compounds of this invention are useful in the treatment or prophylaxis of *Filoviridae* infections in animals or in man.

[0168] However, in screening compounds capable of inhibiting human *Filoviridae* viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

[0169] In another embodiment, the present application provides for methods of treating *Filoviridae* virus infection in a human, comprising: administering to the patient a therapeutically effective amount of a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof. In some embodiments, the *Filoviridae* infection is caused by a *Filoviridae* virus. In some embodiments, the *Filoviridae* infection is caused by an Ebola virus. In some embodiments, the *Filoviridae* infection is caused by *Bundibugyo ebolavirus*, *Reston ebolavirus*, *Sudan ebolavirus*, *Tai Forest ebolavirus*, or *Zaire ebolavirus*. In some embodiments, the *Filoviridae* infection is caused by a *Marburg* virus. In some embodiments, the *Filoviridae* infection is caused by a *Lloviu* virus. In some embodiments, a *Filoviridae* polymerase is inhibited.

[0170] The compounds of the present invention can be used in the treatment of a human already suffering from a *Filoviridae* infection, or can be administered prophylactically to reduce or prevent the chance of a *Filoviridae* infection. *Filoviridae* infections can be characterized by hemorrhagic fever, hematemesis, diarrhea, retrosternal abdominal pain and prostration. The incubation period is around 21 days following contact with a human suffering from *Filoviridae* infection. The outcome of *Filoviridae* infection is typically death.

[0171] Also provided as separate embodiments are a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula IV, or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method of treating a *Filoviridae* infection in a human. Also provided as separate embodiments are a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula IV, or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method of treating an Ebola virus infection in a human. Also provided as separate embodiments are a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula IV, or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method of treating a Marburg virus infection in a human. Within each of the embodiments herein in which the *Filoviridae* infection is an Ebola virus, there are further separate embodiments with them wherein the *Filoviridae* infection is caused, respectively, by *Bundibugyo ebolavirus*, *Reston ebolavirus*, *Sudan ebolavirus*, *Tai Forest ebolavirus*, or *Zaire ebolavirus*. In some embodiments, the *Filoviridae* infection is caused by a Marburg virus. In some embodiments, the *Filoviridae* infection is caused by a Lloviu virus.

[0172] The present invention also provides compounds of each of the Formula herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula (IV), or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in any of the methods of the invention as defined herein.

[0173] Also provided as separate embodiments are the uses of a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula IV, or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in the preparation of a medicament for treating a Filoviridae infection in a human. Also provided as separate embodiments are the uses of a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula IV, or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in the preparation of a medicament for treating an Ebola virus infection in a human. Also provided as separate embodiments are the uses of a compound selected from each of the Formulas herein, as well as each subgroup and embodiment thereof, including a compound selected from the group of Formula IV, or one of the specific compounds of the examples herein, including Compounds 1-32, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in the preparation of a medicament for treating a Marburg virus infection in a human.

VII. SCREENS FOR FILOVIRIDAE POLYMERASE INHIBITORS.

[0174] Compositions of the invention are screened for inhibitory activity against *Filoviridae* polymerase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of *Filoviridae* polymerase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* K_i (inhibitory constants) of less than about 5×10^{-6} M and preferably less than about 1×10^{-7} M are preferred for *in vivo* use.

[0175] Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

VIII. PREPARATION OF COMPOUNDS

EXAMPLES

[0176] Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

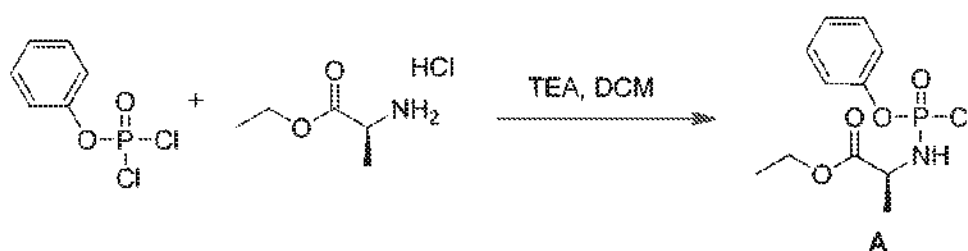
Table 1. List of abbreviations and acronyms.

Abbreviation	Meaning
Ac ₂ O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTCI	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4, 4'-dimethoxytrityl
DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	electrospray ionization
EtOAc	ethyl acetate
HMDS	hexamethyldisilazane
HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH ⁺	mass plus 1
MH ⁻	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
MTBE	tert-butylmethyl ether
NBS	N-bromosuccinimide

Ph	phenyl
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TMSOTf	(trimethylsilyl)trifluoromethylsulfonate
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tic	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
Turbo Grignard	1:1 mixture of isopropylmagnesium chloride and lithium chloride
δ	parts per million down field from tetramethylsilane

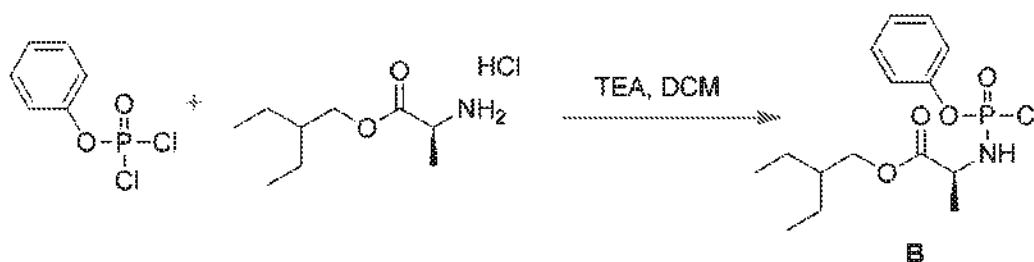
A. Preparation of Compounds

Example 1. (2S)-ethyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate A)



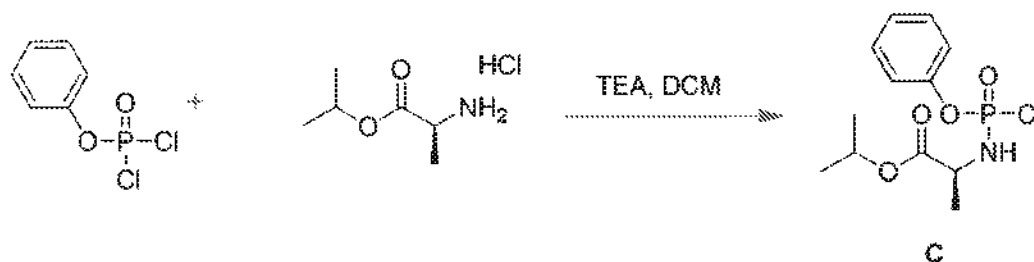
[0177] Ethyl alanine ester hydrochloride salt (1.69 g, 11 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and the mixture stirred with cooling to 0 °C under N_2 (g). Phenyl dichlorophosphate (1.49 mL, 10 mmol) was added followed by dropwise addition of Et_3N over about 10 min. The reaction mixture was then slowly warmed to RT and stirred for about 12 h. Anhydrous Et_2O (50 mL) was added and the mixture stirred for about 30 min. The solid that formed was removed by filtration, and the filtrate concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-50% EtOAc in hexanes to provide intermediate A. ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.27 (m, 5H), 4.27 (m, 3H), 1.52 (m, 3H), 1.32 (m, 3H). ^{31}P NMR (121.4 MHz, CDCl_3) δ 8.2, 7.8.

Example 2. (2S)-2-ethylbutyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate B)



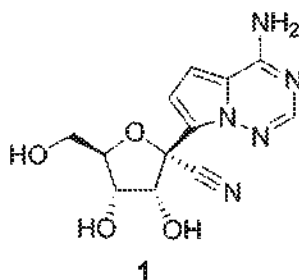
[0178] The 2-ethylbutyl alanine chlorophosphoramidate ester **B** was prepared using the same procedure as chloridate **A** except substituting 2-ethylbutyl alanine ester for ethyl alanine ester. The material is used crude in the next reaction. Treatment with methanol or ethanol forms the displaced product with the requisite LCMS signal.

Example 3. (2S)-isopropyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate C)

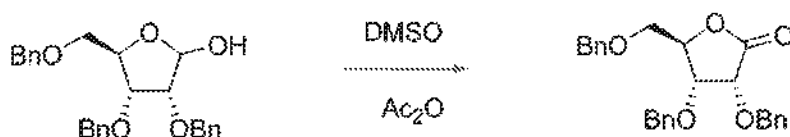


[0179] The isopropyl alanine chlorophosphoramidate ester **C** was prepared using the same procedure as chloridate **A** except substituting isopropyl alanine ester for the ethyl alanine ester. The material is used crude in the next reaction. Treatment with methanol or ethanol forms the displaced product with the requisite LCMS signal.

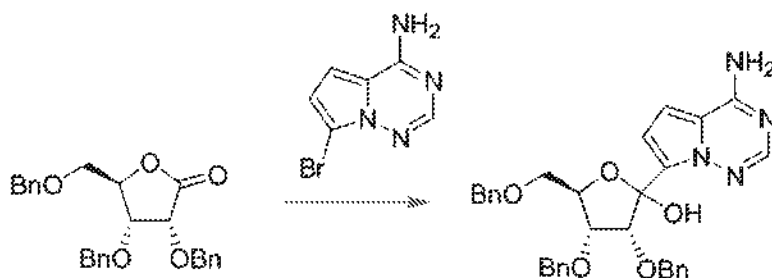
Example 4. (2R, 3R, 4S, 5R)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (Compound 1)



[0180] The preparation of (2R, 3R, 4S, 5R)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile is described below.

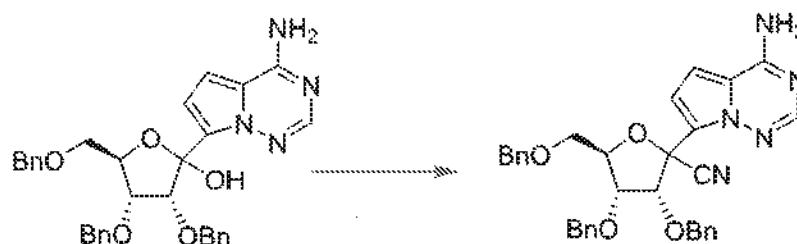


[0181] The commercially available lactol (10 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) under N_2 (g). Ac_2O (20 mL) was added and the resultant reaction mixture stirred at RT for about 48 h. The reaction mixture was poured onto ice H_2O (500 mL) and the mixture stirred for 20 min. The mixture was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were then washed with H_2O (3 x 200 mL). The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and subjected to silica gel chromatography eluting with 25% EtOAc in hexanes to provide the lactone. ^1H NMR (400 MHz, DMSO) δ 7.30-7.34 (m, 13H), 7.19-7.21 (m, 2H), 4.55-4.72 (m, 6H), 4.47 (s, 2H), 4.28 (d, J = 3.9 Hz, 1H), 3.66 (m, 2H). LCMS m/z 436.1 [$M+H_2O$], 435.2 [$M+OH$]- Tr = 2.82 min. HPLC Tr = 4.59 [2-98% ACN in H_2O] over 5 min at 2 mL/min flow.

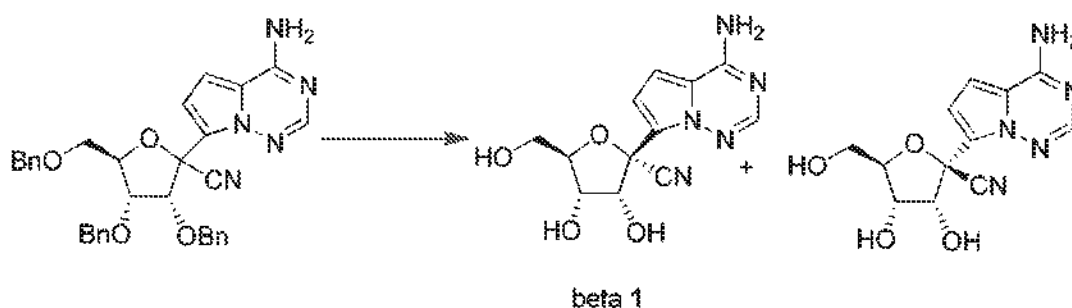


[0182] The bromopyrazole (prepared according to WO2009/132135) (0.5 g, 2.4 mmol) was suspended in anhydrous THF (10 mL) under N_2 (g). The suspension was stirred and $TMSCl$ (0.67 mL, 5.28 mmol) was added. The mixture was stirred for 20 min. at RT and then cooled to about $-78^\circ C$ after which time a solution of $n-BuLi$ (6 mL, 1.6 N in hexanes, 9.6 mmol) was added slowly. The reaction mixture was stirred for 10 min. at about $-78^\circ C$ and then the lactone (1 g, 2.4 mmol) was added *via* syringe. When the reaction was complete as measured by LCMS, $AcOH$ was added to quench the reaction. The mixture was concentrated under reduced pressure and the residue dissolved in a mixture of CH_2Cl_2 and H_2O (100 mL, 1:1). The organic layer was separated and washed with H_2O (50 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica

gel chromatography eluting with 0-50% EtOAc in hexanes to provide the product as a 1:1 mixture of anomers. LCMS m/z 553 [M+H].



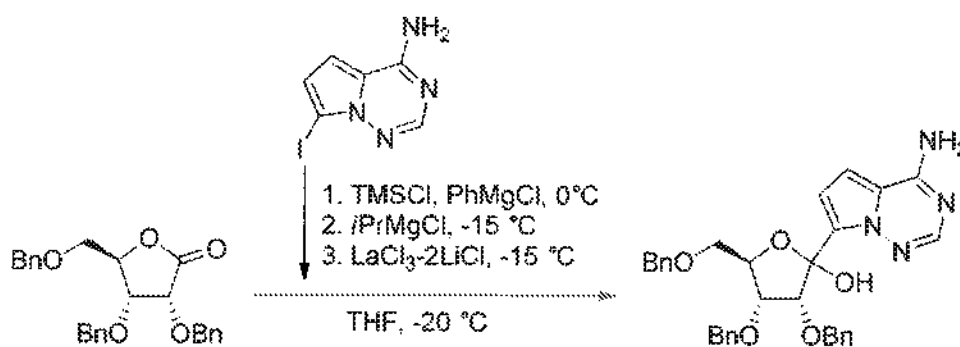
[0183] The hydroxy nucleoside (1.1 g, 2.0 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL) and the solution cooled with stirring to about -78°C under N_2 (g). TMSCN (0.931 mL, 7 mmol) was added and the mixture stirred for a further 10 min. TMSOTf (1.63 mL, 9.0 mmol) was slowly added to the reaction and the mixture stirred for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (120 mL) and aqueous NaHCO_3 (120 mL) was added to quench the reaction. The reaction mixture was stirred for a further 10 min and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (150 mL) and the combined organic extracts dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The residue was dissolved in a minimal amount of CH_2Cl_2 and subjected to silica gel chromatography eluting with a gradient of 0-75% EtOAc and hexanes to provide the tribenzyl cyano nucleoside as a mixture of anomers. ^1H NMR (300 MHz, CD_3CN) δ 7.94 (s, 0.5H), 7.88 (s, 0.5H), 7.29-7.43 (m, 13H), 7.11-7.19 (m, 1H), 6.82-6.88 (m, 1H), 6.70-6.76 (m, 1H), 6.41 (bs, 2H), 5.10 (d, $J = 3.9$ Hz, 0.5H), 4.96 (d, $J = 5.1$ Hz, 0.5H), 4.31-4.85 (m, 7H), 4.09-4.18 (m, 2H), 3.61-3.90 (m, 2H). LCMS m/z 562 [M+H].



[0184] The tribenzyl cyano nucleoside (70 mg, 0.124 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and cooled to about -20°C under N_2 (g). A solution of BCl_3 (1N in CH_2Cl_2 , 0.506 mL, 0.506 mmol) was added and the reaction mixture stirred for 1 h. at -78°C . When the reaction was complete by LC/MS, MeOH was added to quench the reaction. The reaction mixture was allowed to warm to RT and the solvent removed under reduced pressure. The

residue was subjected to C18 reverse phase HPLC, eluting for 5 min with H₂O (0.1 % TFA), followed by a gradient of 0-70% MeCN in H₂O (0.1 % TFA) over 35 min, to elute the α -anomer, and β -anomer 1. (α -anomer) ¹H NMR (300 MHz, D₂O) δ 7.96 (s, 1H), 7.20 (d, J = 4.8 Hz, 1H), 6.91 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 4.4 Hz, 1H), 4.56-4.62 (m, 1H), 4.08-4.14 (m, 1H), 3.90 (dd, J = 12.9, 2.4 Hz, 1H), 3.70 (dd, J = 13.2, 4.5 Hz, 1H). (β -anomer) ¹H NMR (400 MHz, DMSO) δ 7.91 (s, 1H), 7.80-8.00 (br s, 2H), 6.85-6.89 (m, 2H), 6.07 (d, J = 6.0 Hz, 1H), 5.17 (br s, 1H), 4.90 (br s, 1H), 4.63 (t, J = 3.9 Hz, 1H), 4.02-4.06 (m, 1H), 3.94 (br s, 1H), 3.48-3.64 (m, 2H). LCMS m/z 292.2 [M+H], 290.0 [M-H]. T_r = 0.35 min. ¹³C NMR (400 MHz, DMSO), 156.0, 148.3, 124.3, 117.8, 117.0, 111.2, 101.3, 85.8, 79.0, 74.7, 70.5, 61.4. HPLC T_r = 1.32 min

Preparation of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using LaCl₃-2LiCl



[0185] A solution of 7-iodopyrrolo[2,1-f][1,2,4]triazin-4-amine (7.5 g, 28.8 mmol, 1.0 equiv) was prepared in THF (67 mL). The solution was cooled to about 0 °C, and TMSCl (3.3 mL, 30.3 mmol, 1.05 equiv) was added. The reaction mixture was stirred for about 30 min, and then PhMgCl (2 M in THF; 28 mL, 56.8 mmol, 1.97 equiv) was added while maintaining an internal temperature below 5 °C. The reaction mixture was agitated at about 0 °C for about 35 min, and then cooled to about -15 °C. *i*PrMgCl (2 M in THF, 14 mL, 30.2 mmol, 1.05 equiv) was then added while maintaining an internal temperature below about -10 °C. After approximately 15 minutes at about -15 °C, LaCl₃-2LiCl (0.6 M in THF, 50 mL, 14.4 mmol, 0.5 equiv) was added while maintaining an internal temperature below about -15 °C. The reaction mixture was agitated for about 25 min at about -20 °C.

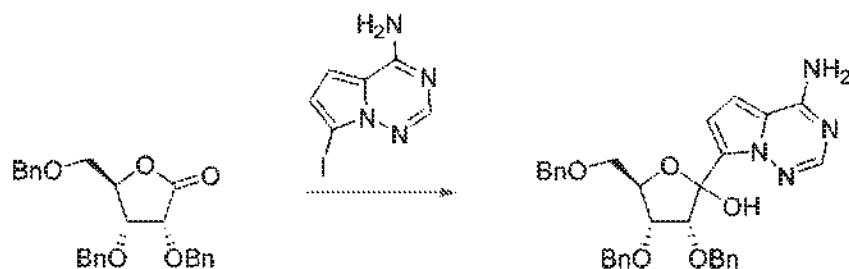
[0186] In a separate flask, a solution of (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2(3H)-one (10.0 g, 23.9 mmol, 0.83 equiv) was prepared in THF (45 mL). The solution was cooled to about -20 °C, and then transferred to the Grignard

solution while maintaining an internal temperature below about -15 °C. The resulting reaction mixture was agitated at about -20 °C for about 30 min.

The reaction was quenched with 2 M HCl (53 mL), and the mixture warmed to about 15 °C. *i*PrOAc (38 mL) was added, and the organic and aqueous phases were separated. The bottom aqueous layer was discharged, and the upper organic layer was washed sequentially with 2.5 wt% NaHCO₃ (53 mL), 2.5 wt% NaHCO₃ (53 mL), and 10 wt% NaCl (53 mL).

[0187] The organic phase was concentrated to about 45 mL, and then diluted with *i*PrOAc (75 mL). The solution was concentrated again to about 45 mL, and then diluted with *i*PrOAc (23 mL). The solution was concentrated to about 45 mL, and then filtered over a pad of Celite. The filtered solution was concentrated to about 26 mL, and then diluted with MTBE (75 mL). After 2h, heptane (23 mL) was slowly added and the slurry was stirred at about 25 °C for about 2 h, and was then cooled to about -5 °C over about 8 h. The solids were isolated by filtration, and the filter cake was washed with MTBE/heptane (4:1, 23 mL). The solids were dried in a vacuum oven at no more than about 35 °C to afford (3R,4R,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol.

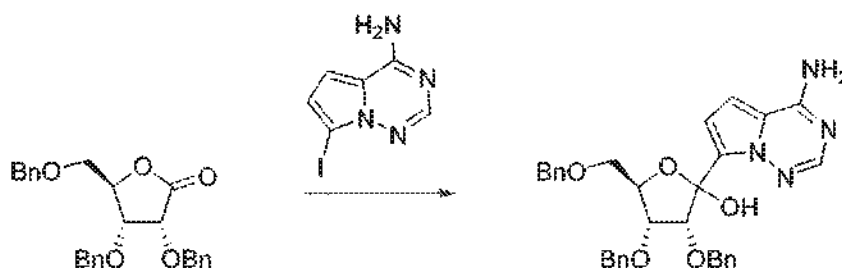
Preparation of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using CeCl₃



[0188] The iodopyrazole (5.02 g, 19.3 mmol) was dissolved in THF (45 g) and the solution was cooled to about 0 °C with stirring. TMSCl (2.04 g, 18.7 mmol) was added, and after about 1 h phenyl magnesium chloride (2.0 M in THF, 19.9 g, 38.2 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propyl magnesium chloride (2.0 M in THF, 9.99 g, 20.5 mmol) was added slowly. After about 30 min, the reaction mixture was transferred to a mixture of anhydrous cerium chloride (4.75 g, 19.3 mmol) in THF (22 g) at about -20 °C. After about 1.5 h a solution of lactone (6.73 g, 16.1 mmol) in THF (22 g) was added slowly, and the resulting reaction mixture was stirred for about 1 h. 2 M HCl (41 g) was added, the mixture was warmed

to about 15 °C, and *iso*-propyl acetate (35 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHCO₃ (2 x 40 g), 10% NaCl (1 x 35 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was charged and the solution was concentrated to about 30 mL volume. *iso*-Propyl acetate (43 g) was charged and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. *tert*-Butylmethyl ether (37 g) was added followed by product seed crystals (10.7 mg). After about 14 h *n*-heptane (10.5 g) was added and the mixture was cooled to about -5 °C and filtered. The solids were washed with *tert*-butylmethyl ether (9 g) at about -5 °C and dried under vacuum at about 34 °C for about 15 h to provide the product.

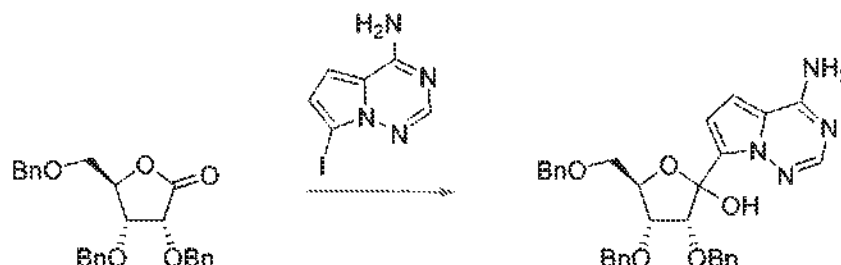
Preparation of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using CeCl₃ and *i*PrMgCl-LiCl



[0189] The iodopyrazole (5.03 g, 19.3 mmol) was dissolved in THF (45 g) and the solution was cooled to about 0 °C with stirring under N₂(g). TMSCl (2.06 g, 19.0 mmol) was added, and after about 1 h phenyl magnesium chloride (2.0 M in THF, 20.23 g, 38.8 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propyl magnesium chloride-lithium chloride complex (2.0 M in THF, 15.37 g, 21.0 mmol) was added slowly. After about 1 h, the reaction mixture was transferred to a mixture of cerium chloride (4.77 g, 19.4 mmol) in THF (22 g) at about -20 °C. After about 1 h a solution of lactone (6.75 g, 16.1 mmol) in THF (23 g) was added slowly, and the resulting reaction mixture was stirred for about 1.5 h. 2 M HCl (40 g) was added, the mixture was warmed to about 15 °C and *iso*-propyl acetate (35 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHCO₃ (2 x 40 g), 10% NaCl (1 x 36 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was added and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. *tert*-Butylmethyl ether (37 g) was added followed by product seed crystals (10.5 mg). After about 14 h *n*-heptane (11 g) was added and the mixture was cooled to about -5 °C and filtered. The solids were washed with

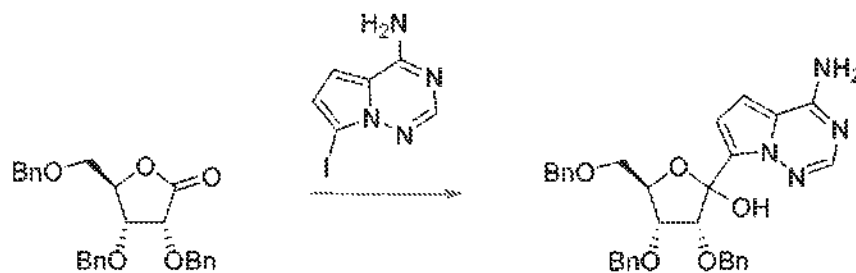
tert-butylmethyl ether (9 g) at about -5 °C and dried under vacuum at about 34 °C for about 15 h to provide the product.

Preparation of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using YCl₃



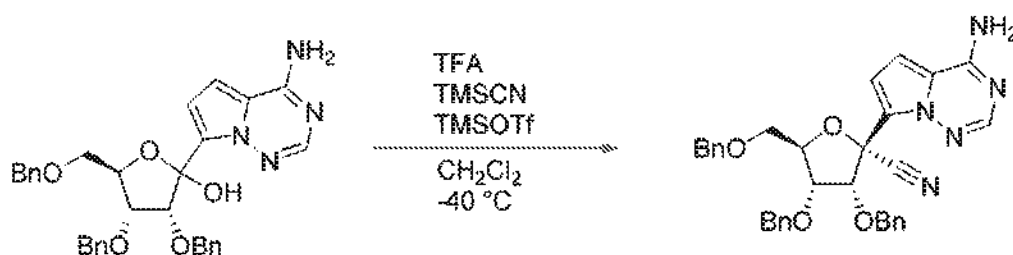
[0190] The iodopyrazole (4.99 g, 19.2 mmol) was dissolved in THF (44 g) and the solution was cooled to about 0 °C with stirring. TMSCl (2.45 mL, 19.4 mmol) was added, and after about 30 min phenyl magnesium chloride (2.0 M in THF, 20.29 g, 39.0 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propyl magnesium chloride (2.0 M in THF, 9.85 g, 20.1 mmol) was added slowly. After about 30 min, the reaction mixture was transferred into a mixture of anhydrous yttrium chloride (3.76 g, 19.3 mmol) and lactone (6.68 g, 16.0 mmol) in THF (24 g) at about -20 °C. After about 2.5 h 2 M HCl (30 g) was added, the mixture was warmed to about 15 °C, and *iso*-propyl acetate (22 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHCO₃ (2 x 40 g), 10% NaCl (1 x 35 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was charged and the solution was concentrated to about 30 mL volume. *iso*-Propyl acetate (45 g) was charged and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. *tert*-Butylmethyl ether (37 g) was added followed by product seed crystals (11.5 mg). After about 1 h *n*-heptane (15 mL) was added and the mixture was cooled to about -5 °C and agitated for about 17 h. The slurry was filtered and the solids were washed with a *tert*-butylmethyl ether (8 g)/*n*-heptane (2 g) mixture precooled to about -5 °C. The resulting solids were dried under vacuum at about 34 °C for about 22 h to afford the product.

Preparation of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol using NdCl_3



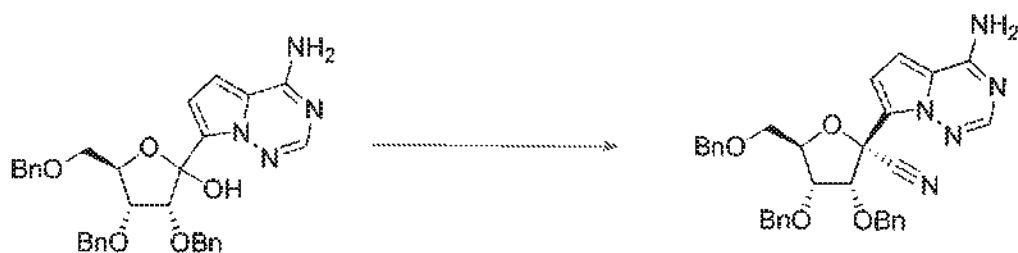
[0191] The iodopyrazole (5.02 g, 19.3 mmol) was dissolved in THF (38 g) and the solution was cooled to about 0 °C with stirring under $\text{N}_2(\text{g})$. TMSCl (2.45 mL, 19.4 mmol) was added, and after about 1 h phenylmagnesium chloride (2.0 M in THF, 19.75 g, 38.0 mmol) was added. The reaction mixture was cooled to about -20 °C and *iso*-propylmagnesium chloride (2.0 M in THF, 9.40 g, 19.2 mmol) was added slowly. After about 1.5 h, the reaction mixture was transferred into a mixture of anhydrous neodymium (III) chloride (4.03 g, 16.1 mmol) and lactone (6.70 g, 16.0 mmol) in THF (22 g) at about -20 °C. After about 1.5 h the reaction mixture was warmed to -10 °C and, after an additional 2 h, 2 M HCl (36 g) was added. The mixture was warmed to about 15 °C and *iso*-propyl acetate (23 g) was added. The layers were separated and the organic layer was washed with 2.5% NaHCO_3 (2 x 44 g), 10% NaCl (1 x 41 g) and concentrated to about 30 mL volume. *iso*-Propyl acetate (44 g) was charged and the solution was concentrated to about 30 mL volume. *iso*-Propyl acetate (45 g) was charged and the solution was concentrated to about 30 mL volume. The solution was filtered and the filtrate was concentrated to about 18 mL volume. *tert*-Butylmethyl ether (37 g) was added followed by product seed crystals (11.9 mg). After about 1 h *n*-heptane (15 mL) was added and the mixture was cooled to about -5 °C and agitated for about 15 h. The slurry was filtered and the solids were washed with a *tert*-butylmethyl ether (8 g)/*n*-heptane (11 g) mixture precooled to about -5 °C. The resulting solids were dried under vacuum at about 34 °C for about 25 h to afford the product.

Preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbonitrile



[0192] To a pre-cooled ($-40\text{ }^{\circ}\text{C}$) solution of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (10.0 grams, 18.1 mmols, 1.0 equiv.) in DCM (100 mL) was charged trifluoroacetic acid (6.19 grams, 54.3 mmols, 3.0 equiv.), followed by a pre-cooled ($-30\text{ }^{\circ}\text{C}$) solution of TMSOTf (24.1 grams, 108.6 mmols, 6.0 equiv.) and TMSCN (10.8 grams, 108.6 mmols, 6.0 equiv.) in DCM (50 mL) while maintaining the internal temperature below about $-25\text{ }^{\circ}\text{C}$. The reaction mixture was agitated at below about $-30\text{ }^{\circ}\text{C}$ for no less than 10 minutes and quenched into a pre-cooled (about $-10\text{ }^{\circ}\text{C}$) solution of 20 wt. % KOH aq. (120 mL). The bi-phasic mixture was warmed to ambient temperature. The organic layer was separated and washed with 10 wt. % NaCl aq. (3 X 50 mL). The organic phase was filtered, concentrated under vacuum to about 50 mL, re-diluted with toluene (200 mL) and concentrated under vacuum to 140 mL at about $50\text{ }^{\circ}\text{C}$. The solution was seeded with (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbonitrile at about $55\text{ }^{\circ}\text{C}$. Agitated at about $55\text{ }^{\circ}\text{C}$ for about an hour and cooled to about $0\text{ }^{\circ}\text{C}$ over about 6 hours. The solids were isolated by filtration and the filter cake was washed with toluene (30 mL). The solids were dried under vacuum at about $50\text{ }^{\circ}\text{C}$.

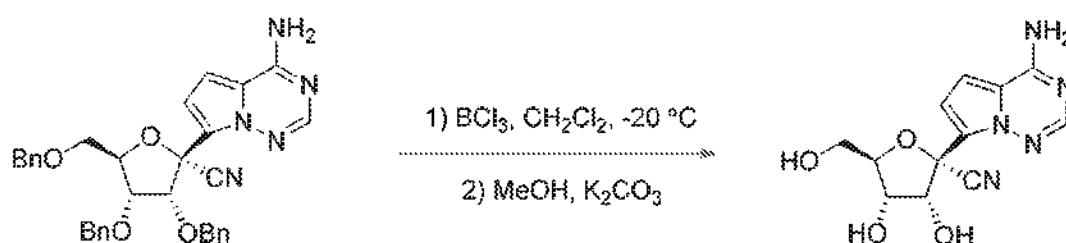
Preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbonitrile via Flow Chemistry



[0193] Solutions of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (23.0 g in 460.07 g of DCM), TMSOTf (55.81 g in 138.07 g of DCM) and TMSCN (25.03 g in 138.10 g of DCM) were sequentially pumped, into a tube reactor at about $-40\text{ }^{\circ}\text{C}$. The reaction mixture was collected in a flask, kept in ice bath, containing 20% KOH aqueous solution (46.91 g KOH and 210 g of water). The layers were separated and the organic phase was sequentially washed with 10%

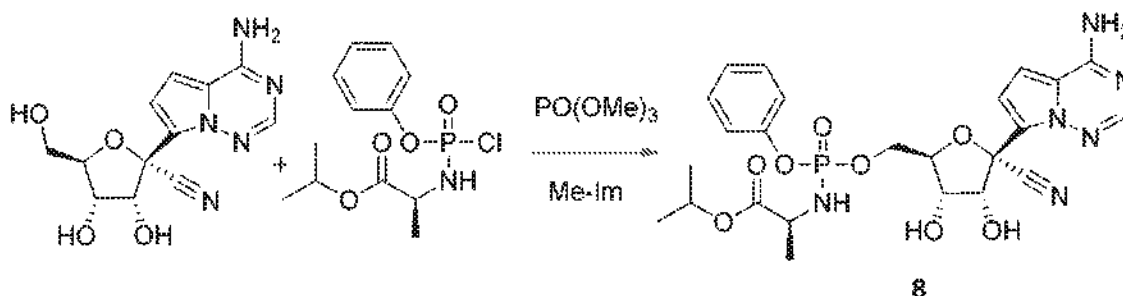
KOH aqueous solution (10 g KOH and 90 mL of water) and with 10% brine (2 x 100 g). The organic phase was concentrated under vacuum to about 4 volumes, isopropyl alcohol was charged (162.89 g) and the mixture was concentrated under vacuum to about 10 volumes. The contents were warmed to about 60 °C, then adjusted to about 0 °C over about 6.5 h and agitated at about 0 °C for about 15.5 h. The resulting slurry was filtered, the solids were rinsed with isopropyl alcohol (61.79 g) and then dried at about 50 °C under reduced pressure overnight to afford the product.

Preparation of (2R, 3R, 4S, 5R)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile



[0194] The tribenzyl cyano nucleoside (48.8 g, 86.9 mmol, 1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (244 mL) and cooled to about -20 °C. A solution of BCl_3 (1M in CH_2Cl_2 , 295 mL, 295 mmol, 3.4 equiv.) was added dropwise, maintaining the internal temperature below about -15 °C. Following addition, the reaction mixture was stirred for 1 h at about -20 °C. MeOH (340 ml) was added dropwise, maintaining the internal temperature below -15 °C. The resulting solution was distilled to about 250 ml, then refilled with about 250 ml MeOH. The resulting solution was again distilled to about 250 ml, then refilled with about 250 ml MeOH, and finally distilled to about 125 ml. Water (125 ml) was added, followed by K_2CO_3 solution (20 wt% in water, 125 ml). The pH was checked, and found to be ~3. K_2CO_3 solution was added (20 wt% in water, 50 ml), and the pH was found to be ~8. The resulting slurry was stirred overnight, then filtered and washed with water (50 ml) and MeOH (50 ml). The wet product cake was dried overnight at about 40 °C overnight. ^1H NMR (300 MHz, D_2O) δ 7.96 (s, 1H), 7.20 (d, J = 4.8 Hz, 1H), 6.91 (d, J = 4.8 Hz, 1H), 4.97 (d, J = 4.4 Hz, 1H), 4.56-4.62 (m, 1H), 4.08-4.14 (m, 1H), 3.90 (dd, J = 12.9, 2.4 Hz, 1H), 3.70 (dd, J = 13.2, 4.5 Hz, 1H).

Example 11. (2S)-isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)-phosphorylamino)propanoate (Compound 8)

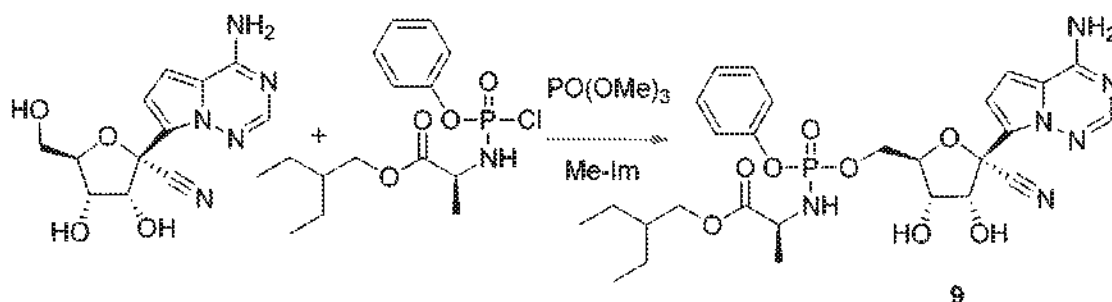


[0195] The nucleoside **1** (45mg, 0.15mmol) was dissolved in anhydrous trimethyl phosphate (0.5 mL) and the solution stirred under N₂ (g) at about 0 °C. Methyl imidazole (36 μ L, 0.45 mmol) was added to the solution. Chlorophosphoramidate **C** (69 mg, 0.225 mmol) was dissolved in anhydrous THF (0.25 mL) and added dropwise to the nucleoside mixture. When the reaction was complete by LCMS, the reaction mixture was diluted with EtOAc and washed with saturated aqueous NaHCO₃ solution, saturated NaCl, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-5% MeOH in CH₂Cl₂ followed by preparative HPLC to give the product. ¹H NMR (300 MHz, CD₃OD) δ 7.95 (m, 1H), 7.31-6.97 (m, 7H), 4.94 (m, 1H), 4.78 (m, 1H), 4.43 (m, 3H), 4.20 (m, 1H), 3.80 (d, 1H), 1.30-1.18 (m, 9H). ³¹P NMR (121.4 MHz, CD₃OD) δ 3.8. LCMS *m/z* 561.0 [M+H], 559.0 [M-H].

Example 12. (2S)-2-ethylbutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (Compound 9)

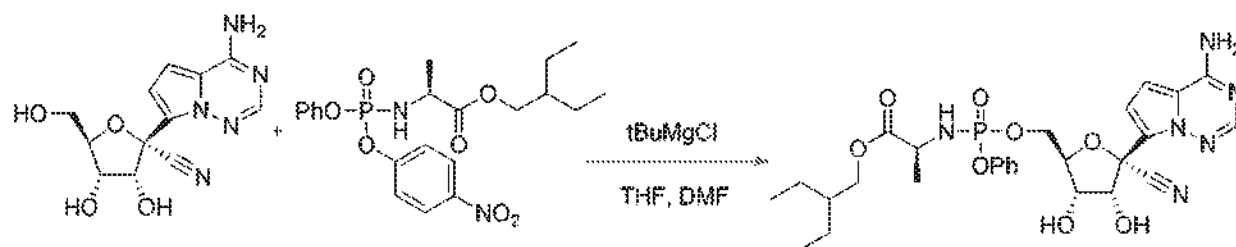
[0196] Compound 9 can be prepared by several methods described below.

Procedure 1

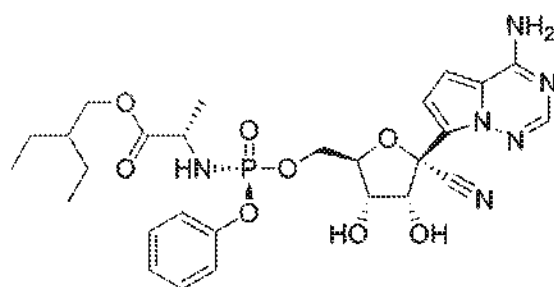


[0197] Prepared from Compound **1** and chloridate **B** according to the same method as for the preparation of compound **8**. ^1H NMR (300 MHz, CD_3OD) δ 7.87 (m, 1H), 7.31-7.16 (m, 5H), 6.92-6.89 (m, 2H), 4.78 (m, 1H), 4.50-3.80 (m, 7H), 1.45-1.24 (m, 8H), 0.95-0.84 (m, 6H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 3.7. LCMS m/z 603.1 $[\text{M}+\text{H}]$, 601.0 $[\text{M}-\text{H}]$.

Procedure 2

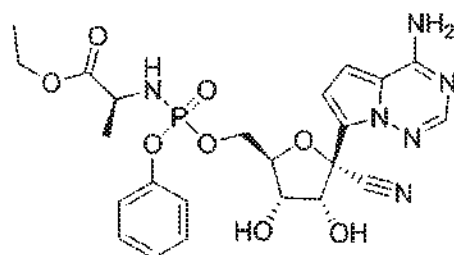


[0198] (2S)-2-ethylbutyl 2-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate. (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (1.08 g, 2.4 mmol) was dissolved in anhydrous DMF (9 mL) and stirred under a nitrogen atmosphere at RT. (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (350 mg, 1.2 mmol) was added to the reaction mixture in one portion. A solution of *t*-butylmagnesium chloride in THF (1M, 1.8 mL, 1.8 mmol) was then added to the reaction dropwise over about 10 minutes. The reaction was stirred for about 2 h, at which point the reaction mixture was diluted with ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 15 mL) followed by saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting oil was purified with silica gel column chromatography (0-10% MeOH in DCM) to afford (2S)-2-ethylbutyl 2-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (311 mg, 43%, 1:0.4 diastereomeric mixture at phosphorus) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.85 (m, 1H), 7.34 – 7.23 (m, 2H), 7.21 – 7.09 (m, 3H), 6.94 – 6.84 (m, 2H), 4.78 (d, J = 5.4 Hz, 1H), 4.46 – 4.33 (m, 2H), 4.33 – 4.24 (m, 1H), 4.18 (m, 1H), 4.05 – 3.80 (m, 3H), 1.52 – 1.39 (m, 1H), 1.38 – 1.20 (m, 7H), 0.85 (m, 6H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.71, 3.65. LCMS m/z 603.1 $[\text{M}+\text{H}]$, 600.9 $[\text{M}-\text{H}]$. HPLC (2–98% MeCN– H_2O gradient with 0.1%



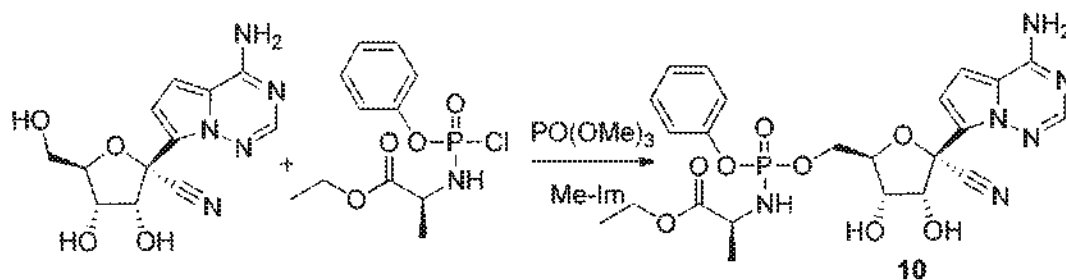
^1H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.36 – 7.28 (m, 3H), 7.23 – 7.14 (m, 3H), 7.08 (d, J = 4.8 Hz, 1H), 4.71 (d, J = 5.3 Hz, 1H), 4.45 – 4.34 (m, 2H), 4.32 – 4.24 (m, 1H), 4.14 (t, J = 5.8 Hz, 1H), 4.08 – 3.94 (m, 2H), 3.93 – 3.85 (m, 1H), 1.47 (sep, J = 6.2 Hz, 1H), 1.38 – 1.26 (m, 7H), 0.87 (t, J = 7.5 Hz, 6H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.73 (s). HPLC (2–98% MeCN– H_2O gradient with 0.1% TFA modifier over 8.5 min, 1.5mL/min, Column: Phenomenex Kinetex C18, 2.6 μm 100 Å, 4.6 x 100 mm) t_R = 5.629 min.

Example 13. (2S)-ethyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (Compound 10)



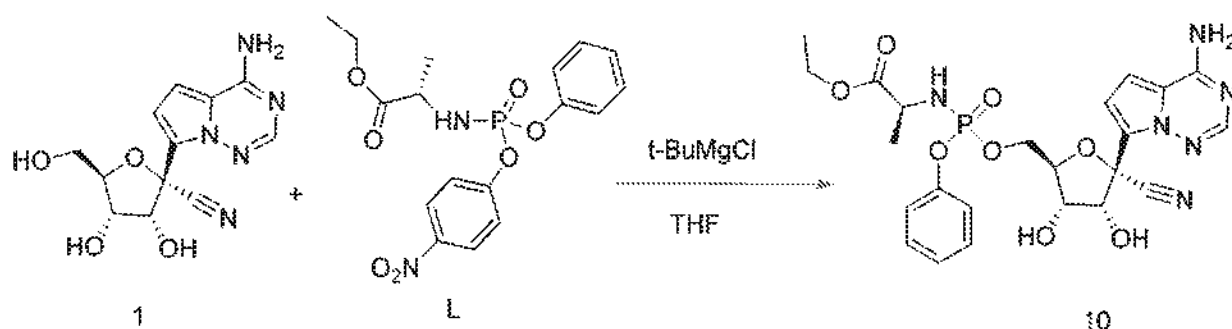
[0202] The preparation of (2S)-ethyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate is described below.

Procedure 1. Preparation via Chloridate A



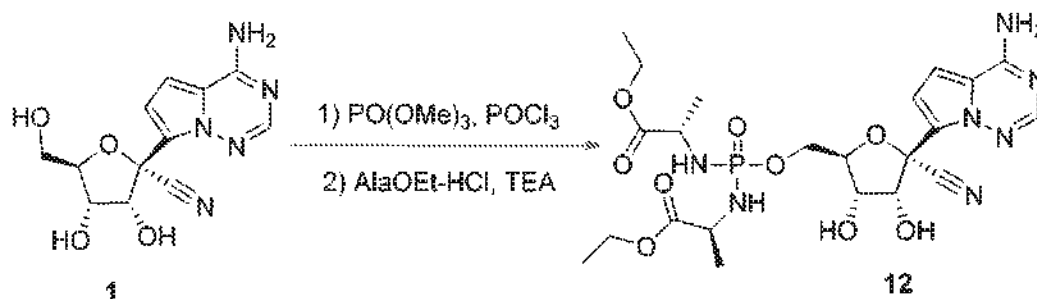
[0203] Prepared from Compound 1 and chloridate A using same method as for the preparation of compound 8. ^1H NMR (300 MHz, CD_3OD) δ 7.95 (m, 1H), 7.32-6.97 (m, 7H), 4.78 (m, 1H), 4.43-4.08 (m, 6H), 3.83 (m, 1H), 1.31-1.18 (m, 6H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 3.7. LCMS m/z 547.0 $[\text{M}+\text{H}]$, 545.0 $[\text{M}-\text{H}]$.

Procedure 2. Preparation via Nitro-Benzene Compound L



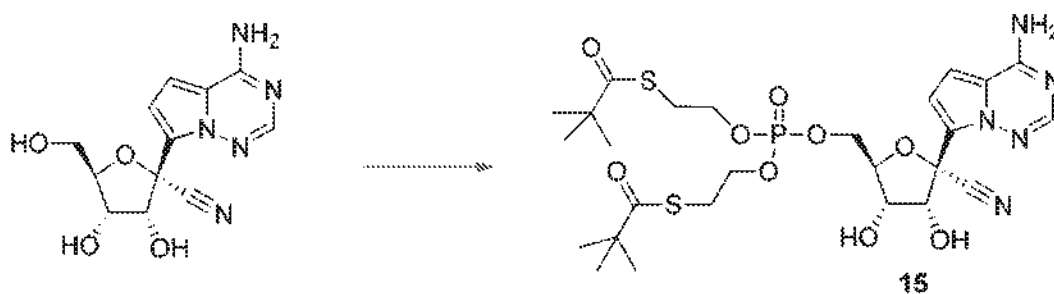
[0204] Compound 1 (50 mg, 0.17 mmol) was dissolved in NMP-THF (1:1 mL) and cooled with ice bath. $t\text{BuMgCl}$ (0.257 mL, 0.257 mmol) was then added over about 5 min. The resulting mixture was allowed to warm to RT and was stirred for about 30 min. Then a solution of compound L (Prepared according to US20120009147, 74.6 mg, 0.189 mmol) in THF (2 mL) was added. After about 30 min, the reaction mixture was purified by HPLC (acetonitrile 10 to 80% in water) to give compound 29 as a yellow solid. The solid was further purified with silica gel chromatography (MeOH 0 to 20% DCM) to afford compound 29. ^1H NMR (400 MHz, CD_3OD) δ 7.76 (d, $J = 6.0$ Hz, 1H), 7.25 – 7.14 (m, 2H), 7.11 – 6.99 (m, 3H), 6.87 – 6.72 (m, 2H), 4.70 (d, $J = 5.4$ Hz, 1H), 4.39 – 4.24 (m, 2H), 4.20 (dddd, $J = 9.7, 7.9, 5.1, 2.8$ Hz, 1H), 4.10 (dt, $J = 12.8, 5.5$ Hz, 1H), 4.06 – 3.91 (m, 2H), 3.72 (ddq, $J = 14.3, 9.3, 7.1$ Hz, 1H), 1.17 (dd, $J = 7.1, 1.0$ Hz, 1H), 1.14 – 1.06 (m, 5H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.73, 3.68. MS $m/z = 547$ ($\text{M}+\text{H}$) $^+$.

Example 15. (2S,2'S)-diethyl 2,2'-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)phosphoryl)bis(azanediyl)dipropionate (Compound 12)



[0205] The nucleoside **1** (14.6 mg, 0.05 mmol) was dissolved in anhydrous trimethyl phosphate (0.5 mL) and stirred under $N_2(g)$ at RT. $POCl_3$ (9.2 μ L, 0.1 mmol) was added and the mixture stirred for about 60 min. Alanine ethyl ester hydrochloride (61 mg, 0.4 mmol) and then Et_3N (70 μ L, 0.5 mmol) was added. The resultant mixture was stirred for about 15 min. and then additional Et_3N (70 μ L, 0.5 mmol) was added to give a solution pH of 9-10. The mixture was stirred for about 2 h. and then diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution followed by saturated aqueous $NaCl$ solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to preparative HPLC (C_{18} column) to yield the product **12**. ^1H NMR (400 MHz, CD_3OD) δ 8.13 (s, 1H), 7.41 (d, $J = 4.8$ Hz, 1H), 7.18 (d, $J = 4.8$ Hz, 1H), 4.78 (d, $J = 5.6$ Hz, 1H), 4.36 (m, 1H), 4.25-4.08 (m, 7H), 3.83 (m, 2H), 1.33-1.23 (m, 12H). ^{31}P NMR (121.4 MHz, CD_3OD) δ 13.8. LCMS m/z 570.0 $[M+H]^+$, 568.0 $[M-H]^-$.

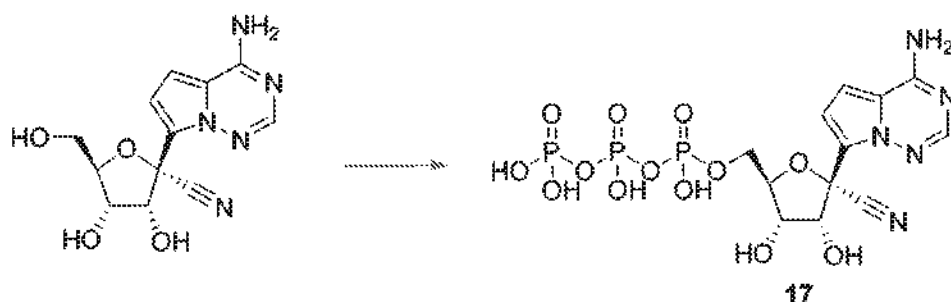
Example 18. S,S'-2,2'-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate) (Compound 15)



[0206] The nucleoside **1** (0.028 g, 0.096 mmol) was dissolved in trimethylphosphate (1 mL). The reaction was stirred under $N_2(g)$ and then treated with 1H-tetrazole (0.021 g, 0.29 mmol).

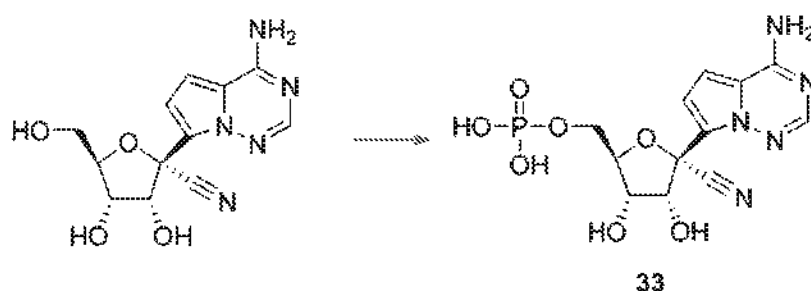
The reaction mixture was cooled to 0 °C and the phosphane (Nucleoside Nucleotides, Nucleic acids; 14; 3-5; 1995; 763 – 766. Lefebvre, Isabelle; Pompon, Alain; Perigaud, Christian; Girardet, Jean-Luc; Gosselin, Gilles; et al.) (87 mg, 0.192 mmol) was added. The reaction was stirred for 2 h. and then quenched with 30% hydrogen peroxide (0.120 mL). The mixture was stirred for 30 min at RT and then treated with saturated aqueous sodium thiosulfate (1 mL). The mixture was stirred for 10 min. and then concentrated under reduced pressure. The residue was subjected to preparative HPLC to isolate the title product **15**. ¹H NMR (300 MHz, CD₃CN) δ 7.98 (s, 1H), 6.92 (d, 1H), 6.81 (d, 1H), 6.44 (bs, 2H), 4.82 (m, 2H), 4.47 (m, 1H), 4.24 (m, 2H), 4.00 (m, 4H), 3.80 (bs, 1H), 3.11 (m, 4H), 1.24 (s, 9H). ³¹P NMR (121.4 MHz, CD₃CN) δ -1.85 (s). LCMS *m/z* 661 [M+H].

Example 20. ((2R, 3S, 4R, 5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound 17)



[0207] Compound **17** was prepared from compound **1** using a similar procedure as previously described (WO2012012776). The product was isolated as the sodium salt. ¹H NMR (400 MHz, D₂O) δ 7.76 (s, 1H), 6.88 (d, *J* = 4.8 Hz, 1H), 6.73 (d, *J* = 4.4 Hz, 1H), 4.86 (d, *J* = 5.2 Hz, 1H), 4.43 (m, 1H), 4.39 (m, 1H), 4.05 (m, 1H), 3.94 (m, 1H). ³¹P NMR (121.4 MHz, D₂O) δ -5.4 (d, 1P), -10.8 (d, 1P), -21.1 (t, 1P). LCMS *m/z* 530 [M-H], 531.9 [M+H] Tr = 0.22 min. HPLC ion exchange Tr=9.95 min.

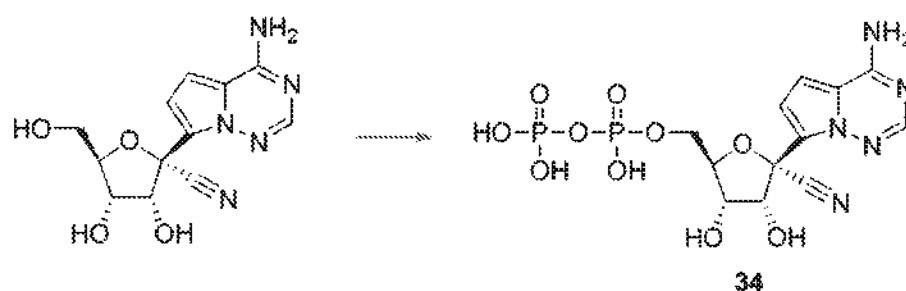
Example 20-a. ((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methyl phosphate (Compound 33)



[0208] A mixture of about 0.05 mmol of compound **1** and about 0.5 mL of trimethylphosphate was sealed in a container for about one to about 48 h. The mixture was cooled to about -10 to about 10 °C and about 0.075 mmol of phosphorus oxychloride is added. After about one to about 24 hours, the reaction was quenched with about 0.5 mL of 1M tetraethylammonium bicarbonate and the desired fractions were isolated by anion exchange chromatography to afford the title compound.

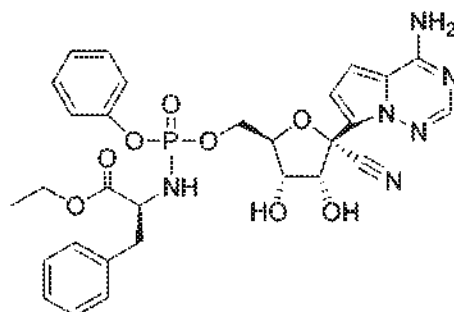
[0209] Compound **33** was prepared as the bis-triethylammonium salt from compound **1** as previously described (WO2011150288). ¹H NMR (400 MHz, D₂O) δ 7.82 (s, 1H), 6.91 – 6.88 (m, 1H), 6.81 – 6.78 (m, 1H), 4.87 – 4.84 (m, 1H), 4.40 – 4.30 (m, 2H), 3.95 – 3.77 (m, 2H), 3.10 – 3.00 (m, 6H), 1.20 – 1.10 (m, 9H). ³¹P NMR (162 MHz, D₂O) δ 2.33. MS *m/z* 371.

Example 20-b. ((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methyl trihydrogen diphosphate (Compound 34)



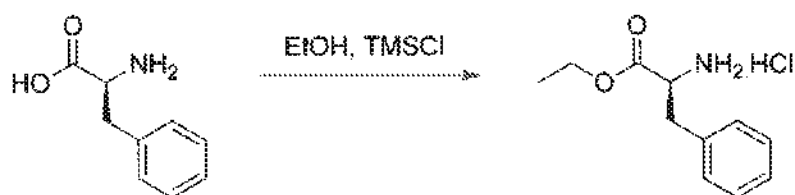
[0210] Compound **34** was prepared as the tri-lithium salt from compound **1** as previously described (WO2002057425). ³¹P NMR (162 MHz, D₂O) δ -5.34 (d), -9.75 (d). MS *m/z* 451.

Example 24. (2S)-ethyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (21)

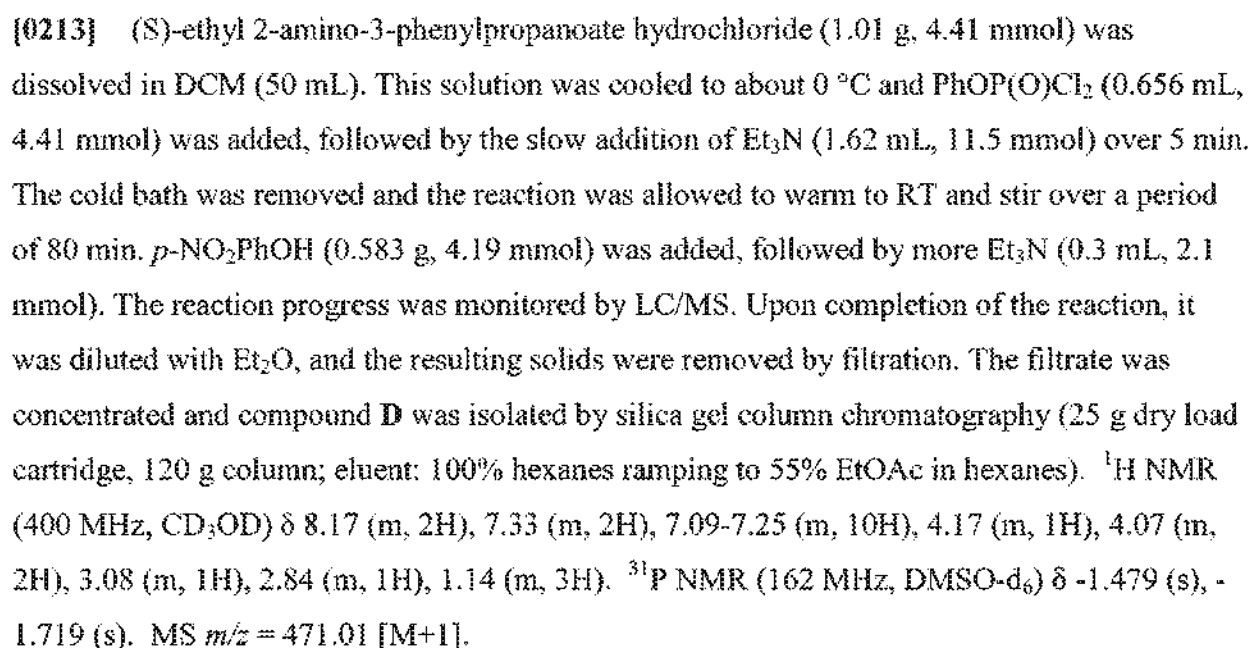


[0211] The preparation of (2S)-ethyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate is described below.

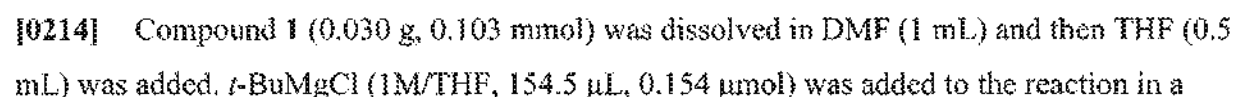
Preparation of (S)-ethyl 2-amino-3-phenylpropanoate hydrochloride.



[0212] L-Phenylalanine (5 g, 30 mmol) was taken up in EtOH (30 mL). TMSCl (6.915 mL, 54 mmol) was added to the reaction at RT. The reaction vessel was fitted with a reflux condenser and the reaction was placed in an 80 °C bath. The reaction was stirred overnight. The next day the reaction was cooled to RT, concentrated under reduced pressure and the resulting residue was taken up in Et₂O. The resulting slurry was filtered and the isolate solids were further washed with Et₂O. The washed solids were placed under high vacuum to yield example (S)-ethyl 2-amino-3-phenylpropanoate hydrochloride. ¹H NMR (400 MHz, DMSO-d₆) δ 8.52 (s, 3H), 7.30 (m, 5H), 4.24 (ABX, *J*_{AX} = 7.8 Hz, *J*_{BX} = 6.2 Hz, 1H), 4.11 (m, 2H), 3.17, 3.05 (ABX, *J*_{AB} = -14 Hz, *J*_{BX} = 5.8 Hz, *J*_{AX} = 7.6 Hz, 2H), 1.09 (t, *J* = 6.8 Hz, 3H).

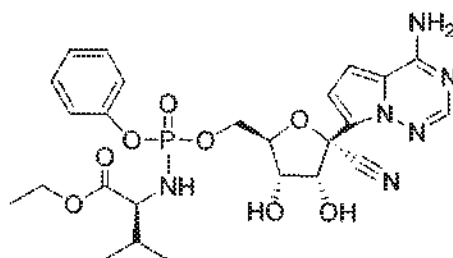


Preparation of (2S)-ethyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound 21)



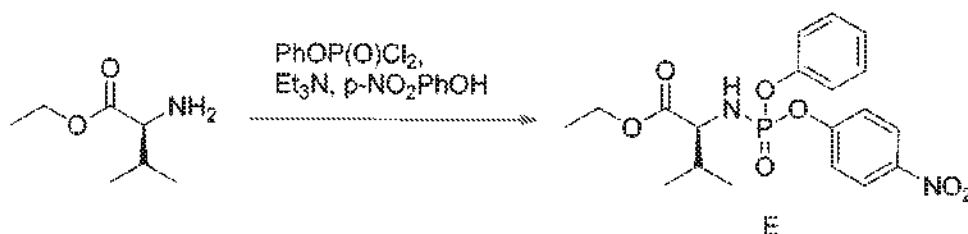
drop-wise manner with vigorous stirring. The resulting white slurry was stirred at RT for about 30 min. A solution of compound **D** (0.058 g, 0.124 mmol) in THF (1 mL) was added in a drop-wise manner to the reaction at RT. The reaction progress was monitored by LC/MS. When the reaction progressed to 50% conversion, the reaction was cooled in an ice bath and quenched with glacial acetic acid (70 μ L). The reaction was concentrated and compound **21** was isolated from the residue by reverse phase HPLC. ^1H NMR (400 MHz, DMSO- d_6) δ 7.91 (d, $J = 4$ Hz, 1H), 7.90 (brs, 2H), 7.09-7.30 (m, 8H), 7.01, (t, $J = 8.2$ Hz, 2H), 6.89 (d, $J = 4.4$ Hz, 1H), 6.82 (t, $J = 4.4$ Hz, 1H), 6.27 (m, 1H), 6.14 (m, 1H), 5.34 (m, 1H), 4.62 (t, $J = 5.6$ Hz, 1H), 4.15 (m, 1H), 3.78-4.01 (m, 6H), 2.92 (m, 1H), 2.78 (m, 1H), 1.04 (m, 3H). ^{31}P NMR (162 MHz, DMSO- d_6) δ 3.69 (s), 3.34 (s). MS $m/z = 623.0$ [M+H].

Example 25. (2S)-ethyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-methylbutanoate (22**)**



[0215] The preparation of (2S)-ethyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-methylbutanoate is described below.

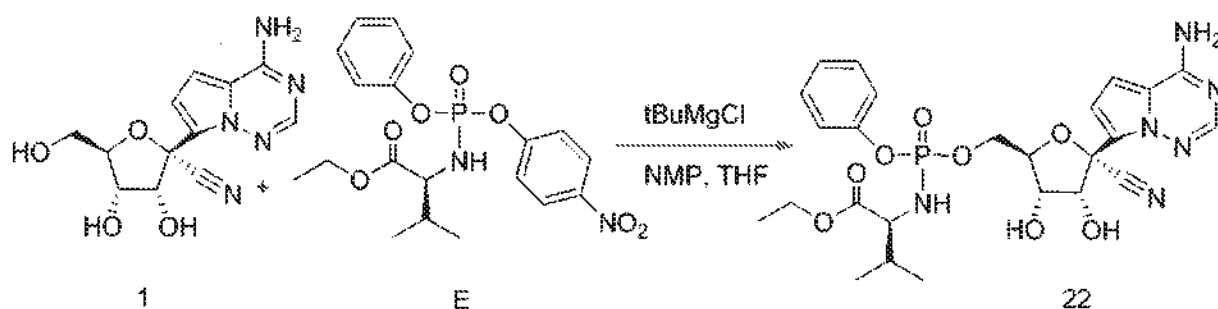
Preparation of (2S)-ethyl 3-methyl-2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino) butanoate (Compound E)



[0216] The (S)-ethyl 2-amino-3-methylbutanoate (0.351 g, 1.932 mmol) was dissolved in DCM (17 mL). This solution was cooled in an ice bath and PhOP(O)Cl₂ (0.287 mL, 1.932 mmol) was added, followed by the slow addition of Et₃N (1.62 mL, 11.4 mmol) over about 5

min. The cold bath was removed and the reaction was allowed to warm to RT and stir over a period of 1 h. *p*-NO₂PhOH (0.255 g, 1.836 mmol) was added, and the reaction progress was monitored by LC/MS. Upon completion of the reaction, the mixture was diluted with Et₂O, and the resulting solids were removed by filtration. The filtrate was concentrated and compound **E** was isolated by silica gel column chromatography (12 g dry load cartridge, 80 g column; eluent: 100% hexanes ramping to 55% EtOAc in hexanes). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (d, *J* = 9.2 Hz, 2H), 7.48 (t, *J* = 9.6 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.20-7.27 (m, 3H), 6.60 (quart, *J* = 11.6 Hz, 1H), 4.01 (m, 2H), 3.61 (m, 1H), 1.93 (m, 1H), 1.11 (m, 3H), 0.79 (m, 6H). ³¹P NMR (162 MHz, DMSO-*d*₆) δ -0.342 (s), -0.578 (s). MS *m/z* = 422.9 [M+H].

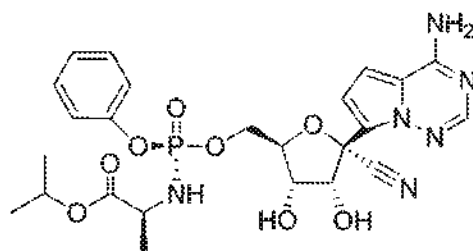
Preparation of (2S)-ethyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-methylbutanoate (Compound 22)



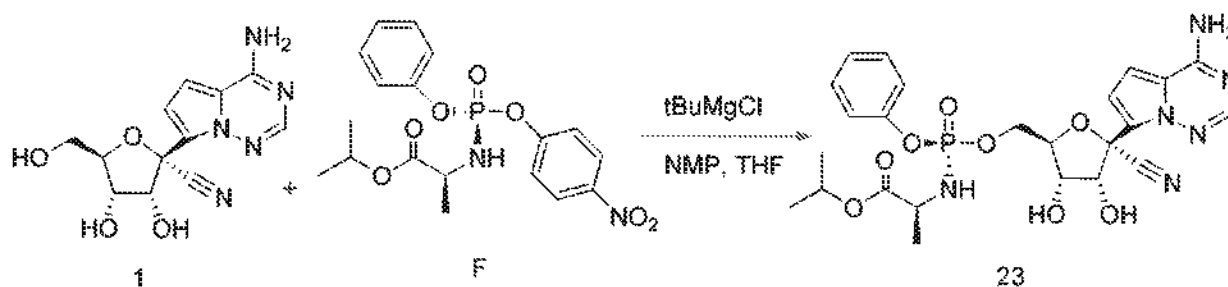
[0217] Compound **1** (0.040 g, 0.137 mmol) was dissolved in NMP (1.5 mL) and then THF (0.25 mL) was added. This solution was cooled in an ice bath and *t*-BuMgCl (1M/THF, 425.7 μL, 0.426 μmol) was added in a drop-wise manner with vigorous stirring. The ice bath was removed and the resulting white slurry was stirred at RT for about 15 min. A solution of compound **E** (0.081 g, 0.192 mmol) in THF (0.5 mL) was added in a drop-wise manner to the reaction at RT. The reaction progress was monitored by LC/MS. When the reaction progressed to 50% conversion, the reaction was cooled in an ice bath and quenched with glacial acetic acid (70 μL). The reaction was concentrated and compound **22** was semi-purified from the residue by reverse phase HPLC. The semi-pure material was further purified by silica gel column chromatography (12 g dry load cartridge, 40 g column; eluent: 100% EtOAc ramping to 10% MeOH in EtOAc) to yield compound **22**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.91 (d, *J* = 1.6 Hz, 1H), 7.88 (brs, 2H), 7.32 (m, 2H), 7.15 (m, 3H), 6.90 (t, *J* = 4.2 Hz, 1H), 6.84 (d, *J* = 4.8 Hz, 1H), 6.26 (dd, *J* = 13.4, 6.2 Hz, 1H), 5.87 (quart, *J* = 11.2 Hz, 1H), 5.35 (m, 1H), 4.64 (m, 1H),

4.25 (m, 2H), 3.93-4.15 (m, 4H), 3.45 (m, 1H), 1.87 (m, 1H), 1.09-1.16 (m, 3H), 0.70-0.83 (m, 6H). ^{31}P NMR (162 MHz, DMSO- d_6) δ 4.59 (s), 4.47 (s). MS m/z = 575.02 [M+H].

Example 26. (S)-isopropyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (23)



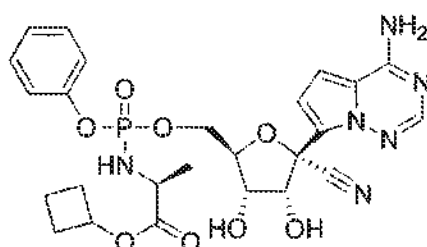
[0218] The preparation of (S)-isopropyl 2-(((R)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.



[0219] Compound **1** (60.0 mg, 206 μmol) was dissolved in NMP (0.28 mL). THF (0.2 mL) was added followed by tert-butyl magnesium chloride (1.0M solution in tetrahydrofuran, 0.309 mL) at RT under an argon atmosphere. After 20 min, a solution of compound **F** (Prepared according to Cho, A. et al *J. Med. Chem.* **2014**, *57*, 1812-1825., 81 mg, 206 μmol) in THF (0.2 mL) was added, and the resulting mixture was warmed to about 50 $^{\circ}\text{C}$. After 3 h, the reaction mixture was allowed to cool to RT and was purified directly by preparatory HPLC (Phenomenex Synergi 4u Hydro-RR 80 $\text{\AA}$ 150 x 30 mm column, 5-100% acetonitrile/water gradient) to afford compound **23**. ^1H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.34 – 7.26 (m, 2H), 7.21 – 7.12 (m, 3H), 6.91 (d, J = 4.6 Hz, 1H), 6.87 (d, J = 4.6 Hz, 1H), 4.92 (sept, J = 6.3 Hz, 1H), 4.80 (d, J = 5.4 Hz, 1H), 4.43 – 4.34 (m, 1H), 4.33 – 4.24 (m, 1H), 4.18 (t, J = 5.6 Hz, 1H), 3.82 (dq, J = 9.7, 7.1 Hz, 2H), 1.27 (dd, J = 7.1, 1.0 Hz, 3H), 1.18 (dd, J = 6.3, 4.8 Hz, 6H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.72 (s). LC/MS: t_R = 1.39 min, MS m/z = 561.11 [M+H]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6 μ XB-C18 100A,

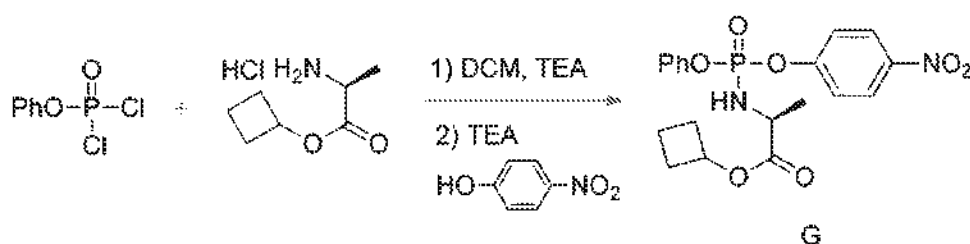
50 x 4.6 mm; Solvents: ACN with 0.1% acetic acid, water with 0.1% acetic acid; Gradient: 0 min-2.0 min 2-100% ACN, 2.0 min-3.05 min 100% ACN, 3.05 min-3.2 min 100%-2% ACN, 3.2 min-3.5 min 2% ACN at 2 μ l/min. HPLC: t_R = 2.523 min; HPLC system: Agilent 1100 series.; Column: Gemini 5 μ C18 110A, 50 x 4.6 mm; Solvents: ACN with 0.1% TFA, Water with 0.1% TFA; Gradient: 0 min-5.0 min 2-98% ACN, 5.0 min-6.0 min 98% ACN at 2 mL/min.

Example 27. (2S)-cyclobutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (24)



[0220] The preparation of (2S)-cyclobutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

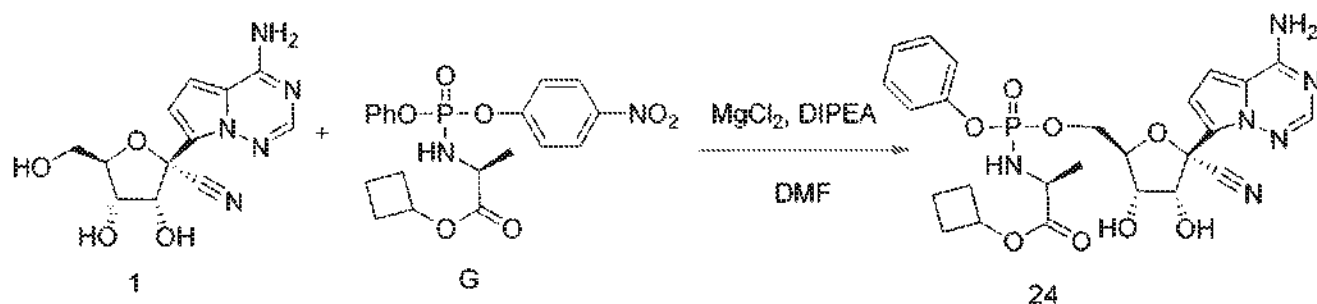
Preparation of (2S)-cyclobutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Compound G)



[0221] Phenyl dichlorophosphate (1.49 mL, 10 mmol) was dissolved in 10 mL of anhydrous DCM and stirred under atmosphere nitrogen in an ice bath. L-Alanine isobutyl ester hydrochloride (0.9 g, 5 mmol) was added in one portion. Triethylamine (765 μ L, 5.5 mmol) was then added dropwise. Reaction stirred for about 1 h. More Triethylamine (765 μ L, 5.5 mmol) was added dropwise and the reaction was stirred for about 45 min. *p*-Nitrophenol (1.25g, 9mmol) was added in one portion and stirred for about 30 min. Triethylamine (765 μ L, 5.5 mmol) was added and the reaction mixture was stirred for about 2 h. Additional *p*-nitrophenol

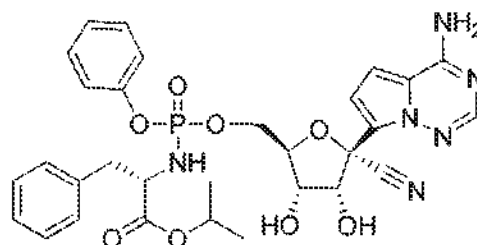
(1.25g, 9 mmol) and triethylamine (765 μ L, 5.5mmol) were then added, and the reaction was stirred for another about 2 h. The reaction mixture was concentrated under reduced pressure. The resulting crude was diluted with EtOAc and washed twice with 5% aqueous citric acid solution, followed with saturated aqueous sodium chloride solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified with silica gel column (0-20-50% EtOAc in hexanes) to give compound G. ^1H NMR (400 MHz, CD_3OD) δ 8.33 – 8.23 (m, 2H), 7.52 – 7.33 (m, 4H), 7.33 – 7.17 (m, 3H), 4.96 – 4.85 (m, 1H), 4.07 – 3.96 (m, 1H), 2.27 (m, 2H), 2.07 – 1.91 (m, 2H), 1.83 – 1.70 (m, 1H), 1.70 – 1.55 (m, 1H), 1.32 (m, 3H). ^{31}P NMR (162 MHz, CD_3OD) δ -1.36, -1.59. MS m/z = 420.9 [M+H].

Preparation (2S)-cyclobutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (Compound 24)



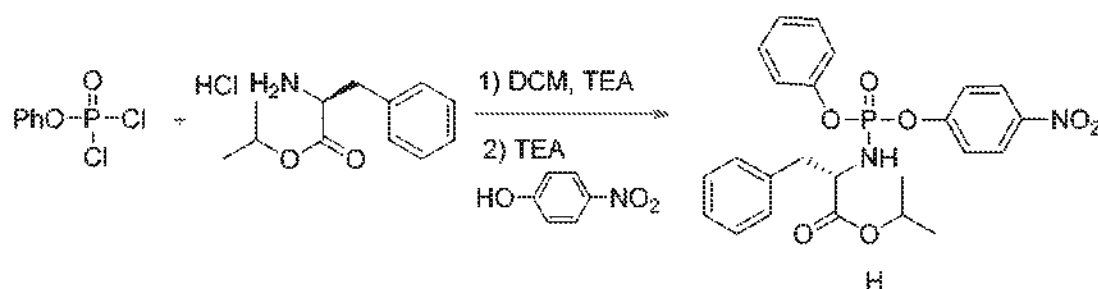
[0222] Compound 1 (58 mg, 0.2 mmol) was mixed with compound G (101 mg, 0.24 mmol) in 2 mL of anhydrous DMF. Magnesium chloride (42 mg, 0.44 mmol) was added in one portion. The reaction mixture was heated to about 50 $^\circ\text{C}$. DIPEA (87 μ L, 0.5 mmol) was added, and the reaction was stirred for about 2 h at about 50 $^\circ\text{C}$. The reaction mixture was cooled to room temperature, was diluted with EtOAc and was washed with 5% aqueous citric acid solution followed by saturated aqueous sodium chloride solution. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified with silica gel column (0-2-5% MeOH in DCM) to afford compound 24. ^1H NMR (400 MHz, Methanol- d_4) δ 7.85 (m, 1H), 7.34 – 7.22 (m, 2H), 7.22 – 7.08 (m, 3H), 6.94 – 6.84 (m, 2H), 4.95 – 4.85 (m, 1H), 4.79 (m, 1H), 4.46 – 4.34 (m, 2H), 4.34 – 4.24 (m, 1H), 4.19 (m, 1H), 3.81 (m, 1H), 2.27 (m, 2H), 2.01 (m, 2H), 1.84 – 1.68 (m, 1H), 1.62 (m, 1H), 1.30 – 1.16 (m, 3H). ^{31}P NMR (162 MHz, cd_3od) δ 3.70, 3.65. MS m/z = 573.0 [M+H].

Example 28. (2S)-isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (25)



[0223] The preparation of (2S)-isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate is described below.

Preparation of (2S)-isopropyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound H)

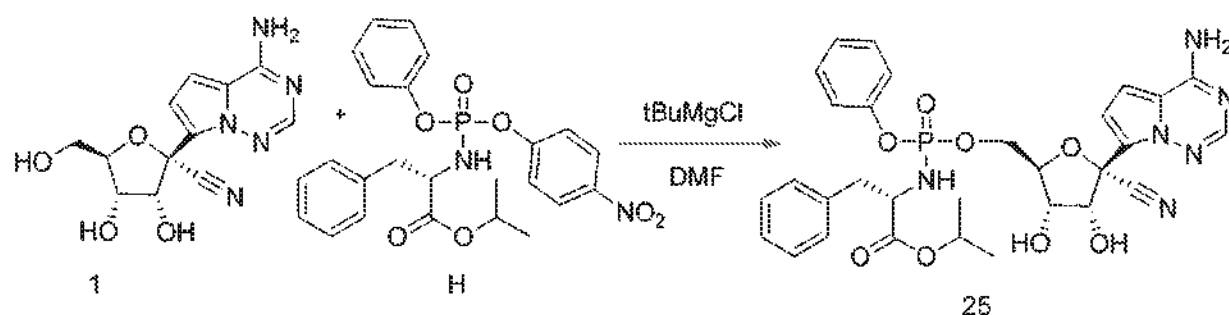


[0224] Phenyl dichlorophosphate (718 μ L, 4.8 mmol) was dissolved in 10 mL of anhydrous DCM and stirred under a nitrogen atmosphere in an ice bath. L-Phenylalanine isopropyl ester hydrochloride (1 g, 4.1 mmol) was added in one portion. Another 10 mL of anhydrous DCM was added. Triethylamine (736 μ L, 5.3 mmol) was added dropwise and the reaction mixture was stirred for about 30 min. More triethylamine (736 μ L, 5.3 mmol) was then added dropwise and the reaction mixture was stirred for 30 min. Additional triethylamine (736 μ L, 5.3 mmol) was then added dropwise and the reaction mixture was stirred for about 15 min. p-Nitrophenol (600 mg, 4.32 mmol) was then added. The ice bath was then removed and the reaction mixture was allowed to warm to room temperature and stirred for about 2 h. More p-nitrophenol (50 mg) and triethylamine (736 μ L, 5.3 mmol) were then added and the reaction mixture was stirred for about 1 h.

[0225] The reaction mixture was then concentrated under reduced pressure, and was diluted with EtOAc and washed twice with 5% aqueous citric acid solution, followed with saturated

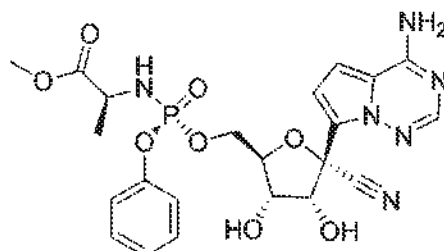
aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and was concentrated under reduced pressure. The crude was purified with silica gel column (0-15% EtOAc in hexanes) to give compound **H**. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (m, 2H), 7.38 – 7.13 (m, 10H), 7.13 – 7.02 (m, 2H), 4.95 (m, 1H), 4.31 (m, 1H), 3.69 (m, 1H), 3.02 (dd, J = 6.1, 1.8 Hz, 2H), 1.21 – 1.08 (m, 6H). ^{31}P NMR (162 MHz, cdcl_3) δ -2.96, -2.98. MS m/z = 485.0 $[\text{M}+\text{H}]$.

Preparation of (2S)-isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-3-phenylpropanoate (Compound 25)

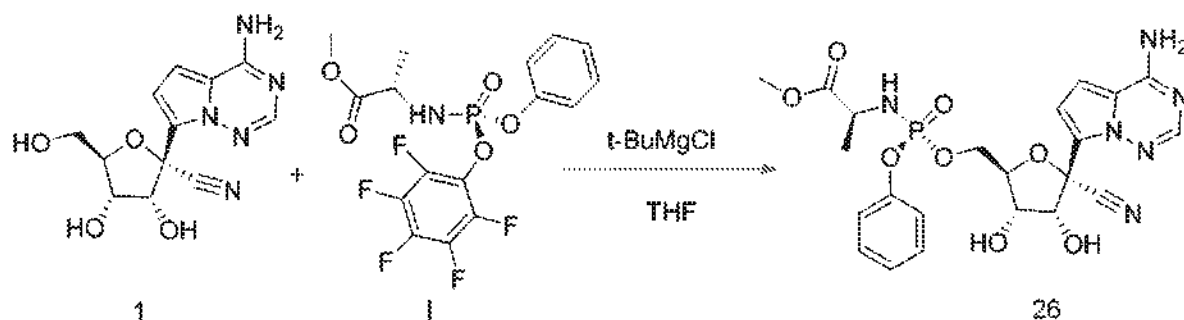


[0226] Compound **1** (58 mg, 0.2 mmol) and compound **H** (116 mg, 0.24 mmol) were mixed and 2 mL of anhydrous DMF was added. The reaction mixture was stirred under a nitrogen atmosphere at room temperature. 1M $t\text{BuMgCl}$ in THF (300 μL , 0.3 mmol) was added dropwise over 3 minutes and the reaction mixture was then stirred for about 16 h. The reaction mixture was diluted with EtOAc and washed with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution and then saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude residue was purified with silica gel column (0-5% MeOH in DCM) to give compound **25**. ^1H NMR (400 MHz, CD_3OD) δ 7.84 (m, 1H), 7.27 – 7.08 (m, 8H), 7.08 – 6.97 (m, 2H), 6.88 (m, 2H), 4.91 – 4.84 (m, 1H), 4.74 (m, 1H), 4.26 (m, 1H), 4.19 – 4.04 (m, 2H), 4.04 – 3.91 (m, 2H), 2.97 (m, 1H), 2.82 (m, 1H), 1.14 (m, 3H), 1.06 (m, 3H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.63, 3.25. MS m/z = 637.0 $[\text{M}+\text{H}]$.

Example 29. (S)-methyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (26)

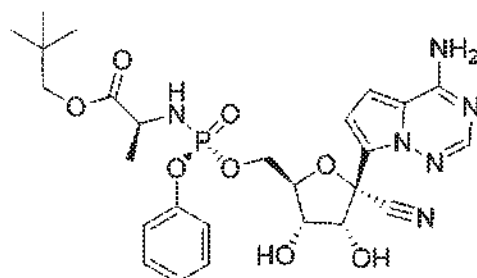


[0227] The preparation of (S)-methyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

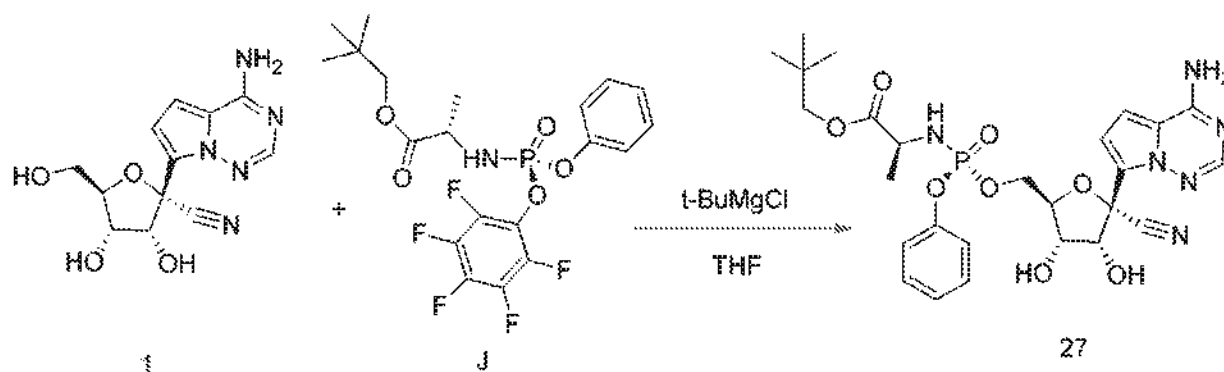


[0228] Compound **1** (100 mg, 0.34 mmol) was dissolved in THF (2 mL) and cooled with an ice water bath. Then 1M *t*-BuMgCl (0.52 mL, 0.77 mmol) was added dropwise slowly. The resulting mixture was stirred for about 30 min at room temperature. Then compound **I** (Prepared according to WO 2012142085, 219 mg, 0.52 mmol) in THF (2 mL) was added over 5 min and the resulting mixture was stirred for about 24 h at room temperature. The reaction mixture was then diluted with EtOAc, cooled under ice-water bath, washed with aq NaHCO₃ (2 mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography (MeOH 0 to 20% in DCM) and prep-HPLC (acetonitrile 10 to 80% in water) to give compound **26**. ¹H NMR (400 MHz, CD₃OD) δ 7.86 (s, 1H), 7.29 (dd, *J* = 8.6, 7.2 Hz, 2H), 7.21 – 7.09 (m, 3H), 6.94 – 6.81 (m, 2H), 4.79 (d, *J* = 5.4 Hz, 1H), 4.38 (ddq, *J* = 10.8, 5.3, 2.7 Hz, 2H), 4.33 – 4.23 (m, 1H), 4.18 (t, *J* = 5.5 Hz, 1H), 3.86 (dq, *J* = 9.9, 7.1 Hz, 1H), 3.62 (s, 3H), 1.27 (dd, *J* = 7.2, 1.1 Hz, 3H). MS *m/z* = 533 (*M*+1)⁺.

Example 30. (S)-neopentyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (27)

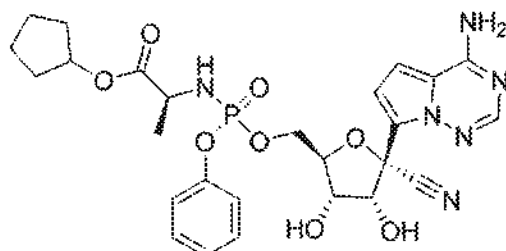


[0229] The preparation of (S)-neopentyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

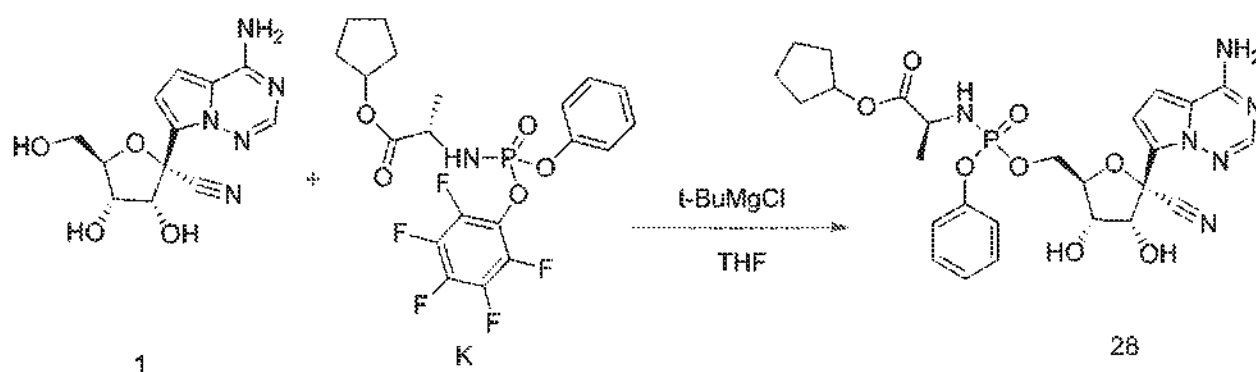


[0230] Compound **1** (100 mg, 0.34 mmol) was dissolved in THF (2 mL) and cooled under ice water bath. Then 1M *t*-BuMgCl (0.52 mL, 0.77 mmol) was added dropwise slowly. The resulting mixture was stirred for about 30 min at room temperature. Then compound **J** (Prepared according to WO2012075140, 248 mg, 0.52 mmol) was added over about 5 min and the resulting mixture was stirred for about 24 h at room temperature, diluted with EtOAc, cooled under ice-water bath, treated with aq NaHCO₃ (2 mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography (MeOH 0 to 20% in DCM) and prep-HPLC (acetonitrile 10 to 80% in water) to give Compound **27**. ¹H NMR (400 MHz, CD₃OD) δ 7.86 (s, 1H), 7.36 – 7.24 (m, 2H), 7.23 – 7.10 (m, 3H), 6.96 – 6.85 (m, 2H), 4.78 (d, *J* = 5.4 Hz, 1H), 4.38 (tdd, *J* = 10.0, 4.9, 2.5 Hz, 2H), 4.32 – 4.24 (m, 1H), 4.17 (t, *J* = 5.6 Hz, 1H), 3.91 (dq, *J* = 9.8, 7.1 Hz, 1H), 3.81 (d, *J* = 10.5 Hz, 1H), 3.69 (d, *J* = 10.5 Hz, 1H), 1.31 (dd, *J* = 7.2, 1.1 Hz, 3H), 0.89 (s, 9H). MS *m/z* = 589 (M+1)⁺.

Example 31. (2S)-cyclopentyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (28)

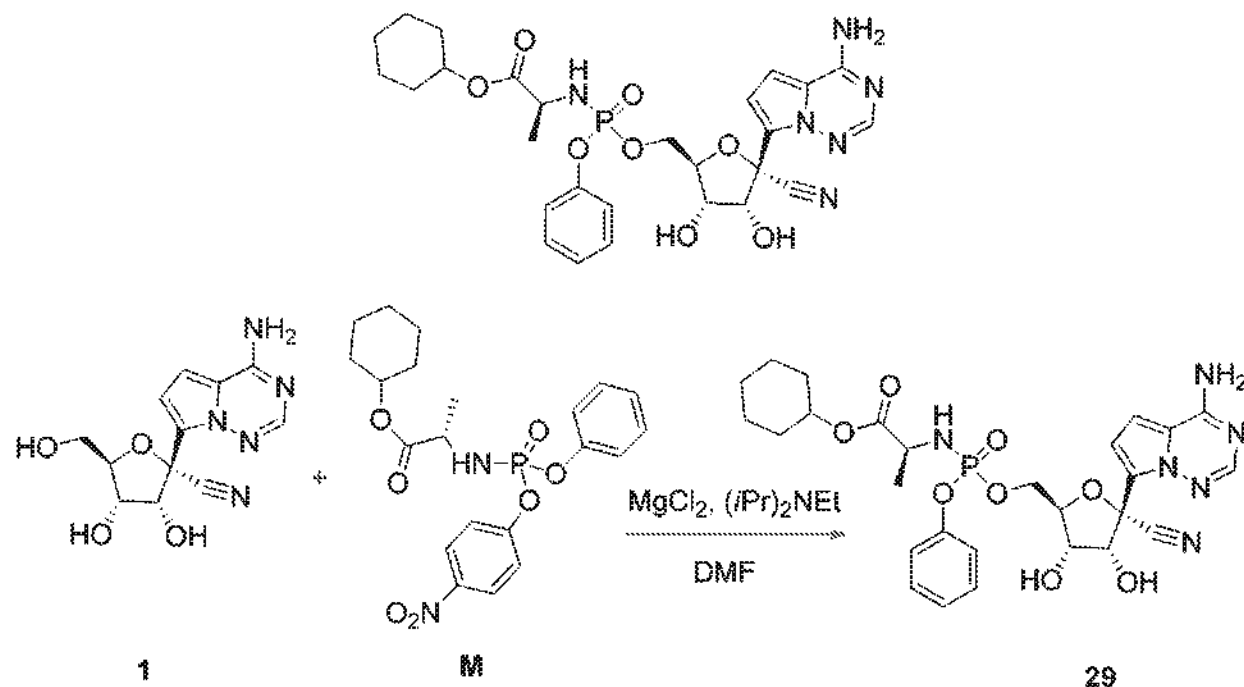


[0231] The preparation of (2S)-cyclopentyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.



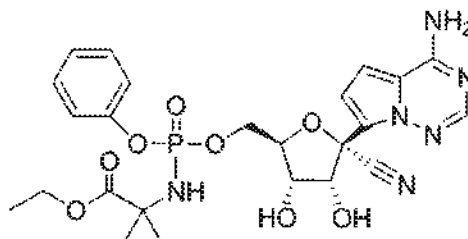
[0232] Compound **1** (100 mg, 0.34 mmol) was dissolved in THF (2 mL) and cooled under ice water bath. Then 1M t-BuMgCl (0.52 mL, 0.77 mmol) was added dropwise slowly. The resulting mixture was stirred for about 30 min at room temperature. Then compound **K** (Prepared according to WO2012075140, 247 mg, 0.52 mmol) in THF (2 mL) was added over about 5 min and the resulting mixture was stirred for about 24 h at room temperature, diluted with EtOAc, cooled under ice-water bath, treated with aq NaHCO₃ (2 mL), washed with brine, dried with sodium sulfate, and concentrated *in vacuo*. The resulting mixture was purified by silica gel column chromatography (MeOH 0 to 20% in DCM) and prep-HPLC (acetonitrile 10 to 80% in water) to give example **28**. ¹H NMR (400 MHz, CD₃OD) δ 7.85 (s, 1H), 7.33 – 7.22 (m, 2H), 7.14 (tdd, *J* = 7.6, 2.1, 1.1 Hz, 3H), 6.95 – 6.87 (m, 2H), 5.13 – 5.00 (m, 1H), 4.78 (d, *J* = 5.4 Hz, 1H), 4.48 – 4.35 (m, 2H), 4.30 (ddd, *J* = 10.6, 5.7, 3.6 Hz, 1H), 4.19 (t, *J* = 5.4 Hz, 1H), 3.78 (dq, *J* = 9.2, 7.1 Hz, 1H), 1.81 (dtd, *J* = 12.5, 5.9, 2.4 Hz, 2H), 1.74 – 1.49 (m, 6H), 1.21 (dd, *J* = 7.1, 1.2 Hz, 3H). MS *m/z* = 587 (*M*+1)⁺.

Example 32. (2S)-cyclohexyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (29)



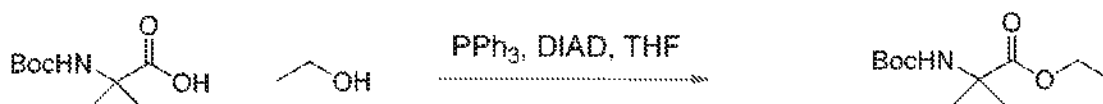
[0233] To a mixture of compound **1** (50 mg, 0.343 mmol), compound **M** (Prepared according to US20130143835, 93 mg, 0.209 mmol), and MgCl_2 (24.5 mg, 0.257 mmol) in DMF (1 mL) was added diisopropylethylamine (0.075 mL, 0.43 mmol) dropwise over about 5 min at about 0 °C. The resulting mixture was stirred at about 50 °C for about 1 h. The reaction mixture was then cooled with an ice-water bath, treated with 1M citric acid (0.5 mL), and was purified directly by prep-HPLC (ACN 0 to 70% in water) to afford compound **29**. ^1H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 7.32 – 7.23 (m, 2H), 7.18 – 7.10 (m, 3H), 6.93 – 6.87 (m, 2H), 4.78 (d, J = 5.4 Hz, 1H), 4.67 (td, J = 8.7, 4.2 Hz, 1H), 4.48 – 4.35 (m, 2H), 4.30 (ddd, J = 10.8, 5.7, 3.7 Hz, 1H), 4.20 (t, J = 5.4 Hz, 1H), 3.88 – 3.71 (m, 1H), 1.83 – 1.63 (m, 4H), 1.58 – 1.46 (m, 1H), 1.46 – 1.24 (m, 5H), 1.24 (s, 3H). ^{31}P NMR (162 MHz, CD_3OD) δ 3.75. MS m/z = 601 ($\text{M}+1$) $^+$.

Example 33. Ethyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (30)



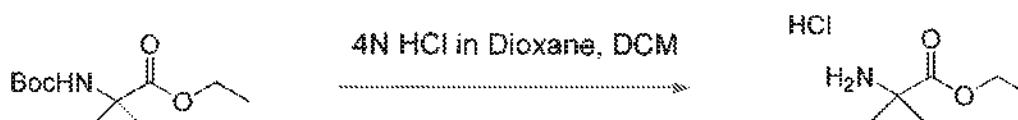
[0234] The preparation of ethyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate is described below.

Preparation of Ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate



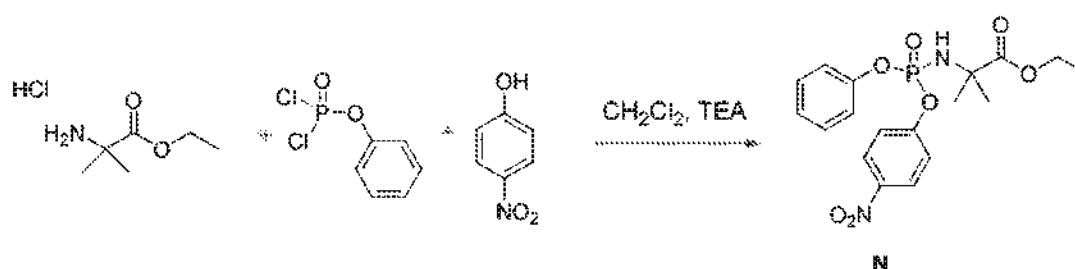
[0235] Take up triphenylphosphine (6.18 g, 25.00 mmol) in THF (30mL). Next charge DIAD (4.92 mL, 25.00 mmol) and stir at room temperature for 10 min. Dissolve 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid (5.08 g, 25.00 mmol) in THF (20 mL) and add to the reaction mixture followed by the addition of ethanol (2.19 mL, 37.49 mmol). Allow the reaction to stir at room temperature for about 1 h. The solvents were removed under reduced pressure and the crude was taken up in 1:1 Et₂O:Hexanes (120 mL). The solid triphenylphosphine oxide was filtered off and the solvent was removed under reduced pressure. The crude was taken up in minimal CH₂Cl₂ and purified by silica gel chromatography 0-50% EtOAc/Hex to afford ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate. ¹H NMR (400 MHz, Chloroform-*d*) δ 4.18 (q, *J* = 7.1 Hz, 2H), 1.49 (s, 6H), 1.43 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H).

Preparation of Ethyl 2-amino-2-methylpropanoate hydrochloride



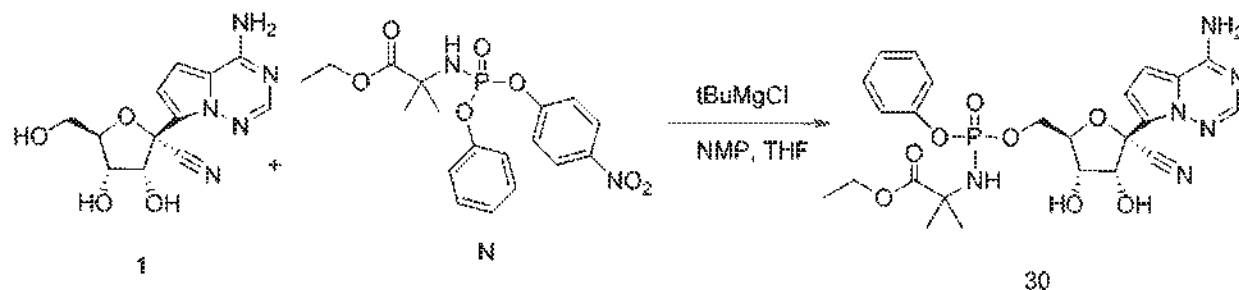
[0236] Take up ethyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate (2.71 g, 11.72 mmol) in CH_2Cl_2 (25 mL) and slowly add 4N HCl in dioxane (25 mmol) and stir at room temperature. At 1h, the reaction was determined to be complete by TLC. The solvents were removed under reduced pressure and the crude was coevaporated with Et_2O two times then placed under high vacuum to afford ethyl 2-amino-2-methylpropanoate hydrochloride. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.70 (s, 3H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.46 (s, 6H), 1.21 (t, $J = 7.1$ Hz, 3H).

Preparation of Ethyl 2-methyl-2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (Compound N)



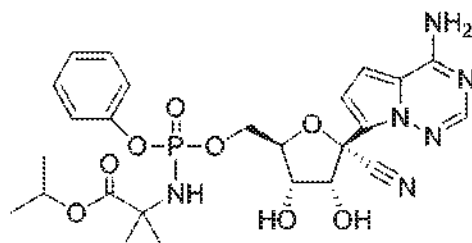
[0237] Take up phenyl dichlorophosphate (0.97mL, 6.50mmol) and ethyl 2-amino-2-methylpropanoate hydrochloride (1.09 g, 6.50 mmol) in CH_2Cl_2 (50 mL). Cool the reaction mixture to about 0°C and slowly add TEA (1.75 mL, 12.45 mmol). Remove the cold bath and allow the reaction mixture to stir at room temperature. After about 2 h, the addition of the amino acid was determined to be complete by ^{31}P NMR. Charge p-nitrophenol (0.860 g, 6.17 mmol) followed by the addition of TEA (0.87 g, 7.69 mmol). Allow the reaction to stir at room temperature. After about 2 h, the reaction was determined to be complete by LCMS. The reaction was diluted with Et_2O and the $\text{TEA}\cdot\text{HCl}$ salts were filtered off. The crude was concentrated and purified by silica gel chromatography (0-50% EtOAc/Hex) to afford compound N. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 – 8.21 (m, 2H), 7.55 – 7.44 (m, 2H), 7.43 – 7.33 (m, 2H), 7.30 – 7.09 (m, 3H), 6.57 (d, $J = 10.1$ Hz, 1H), 3.99 (q, $J = 7.1$ Hz, 2H), 1.39 (s, 6H), 1.08 (t, $J = 7.1$ Hz, 3H). ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ -2.87. LC/MS: $t_R = 1.65$ min, MS $m/z = 408.97$ $[\text{M}+1]$.; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6 μ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Preparation of ethyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxymethyl)phosphoryl)amino)-2-methylpropanoate (Compound 30)



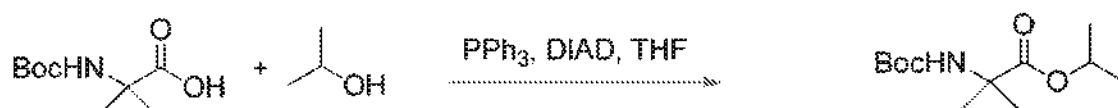
[0238] Take up compound **1** (66 mg, 0.23 mmol) in NMP (2.0 mL). Cool the mixture to about 0 °C and slowly add tBuMgCl (1.0M in THF, 0.34 mL, 0.34 mmol). Allow the reaction to stir at about 0 °C for about 30 min, then add a solution of compound **N** (139mg, 0.34mmol) dissolved in THF (1.0 mL). Remove the cold bath and place the reaction in about 50 °C preheated oil bath. After about 2 h, the reaction was cooled to room temperature and quenched with acetic acid and methanol. The crude was concentrated and purified by reverse phase HPLC without modifier to afford compound **30**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.89 (m, 3H), 7.31 (q, *J* = 8.1 Hz, 2H), 7.22 – 7.05 (m, 3H), 6.87 (d, *J* = 4.5, 1H), 6.80 (d, *J* = 4.5 Hz, 1H), 6.27 (d, *J* = 11.7, 1H), 5.81 (d, *J* = 9.7, 1H), 5.35 (d, *J* = 5.6 Hz, 1H), 4.64 (dt, *J* = 9.0, 5.6 Hz, 1H), 4.24 (m, 2H), 4.11 (m, 1H), 4.04 – 3.90 (m, 3H), 1.39 – 1.23 (m, 6H), 1.10 (t, *J* = 7.1, 3H). ³¹P NMR (162 MHz, DMSO-*d*₆) δ 2.45, 2.41. LC/MS: *t*_R = 1.03 min, MS *m/z* = 561.03 [M+1]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6μ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Example 34. Isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (31)



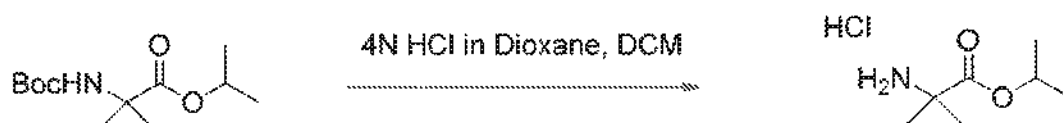
[0239] The preparation of Isopropyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate is described below.

Preparation of Isopropyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate



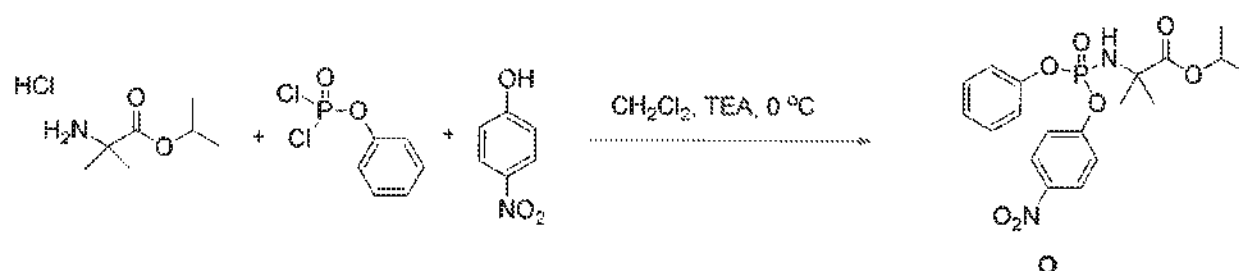
[0240] Take up triphenylphosphine (6.17 g, 25.00 mmol) in THF (30 mL). Next charge DIAD (4.92 mL, 25.00 mmol) and stir at room temperature for about 10 min. Dissolve 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid (5.07 g, 25.00 mmol) dissolved in THF (20 mL) and add to the reaction mixture followed by the addition of isopropanol (1.91 mL, 25.00 mmol). Allow the reaction to stir at room temperature for about 1h. The solvents were removed under reduced pressure and the crude was taken up in 1:1 Et₂O:Hexanes (120 mL). The solid triphenylphosphine oxide was filtered off and the solvent was removed under reduced pressure. The crude was taken up in minimal CH₂Cl₂ and purified by silica gel chromatography (0-50% EtOAc/Hex) to afford isopropyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate. ¹H NMR (400 MHz, Chloroform-*d*) δ 5.03 (p, *J* = 6.2 Hz, 1H), 1.48 (s, 6H), 1.40 (d, *J* = 6.2 Hz, 9H), 1.24 (d, *J* = 6.3 Hz, 6H).

Preparation of Isopropyl 2-amino-2-methylpropanoate hydrochloride



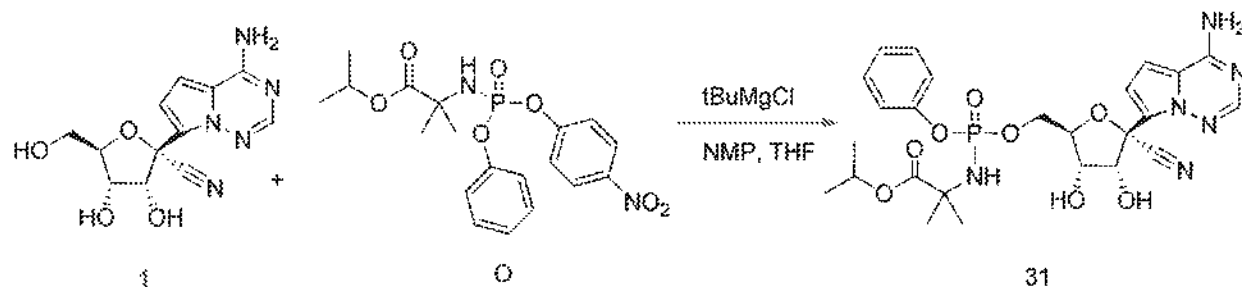
[0241] Take up isopropyl 2-((tert-butoxycarbonyl)amino)-2-methylpropanoate (4.09 g, 16.67 mmol) in CH_2Cl_2 (50 mL) and slowly add 4N HCl in dioxane (50 mmol) and stir at room temperature. At about 1 h, the reaction was determined to be complete by TLC. The solvents were removed under reduced pressure and the crude was coevaporated with Et_2O two times then placed under high vacuum to afford isopropyl 2-amino-2-methylpropanoate hydrochloride. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.61 (s, 3H), 4.96 (p, $J = 6.2$ Hz, 1H), 1.44 (s, 6H), 1.22 (d, $J = 6.2$ Hz, 6H).

Preparation of Isopropyl 2-methyl-2-(((4-nitrophenoxy)(phenoxy)phosphoryl)amino) propanoate (Compound O)



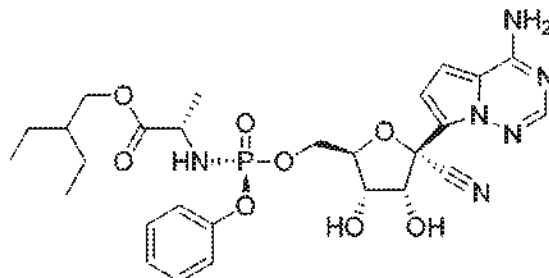
[0242] Take up phenyl dichlorophosphate (0.83 mL, 5.58 mmol) and isopropyl 2-amino-2-methylpropanoate hydrochloride (1.01 g, 5.58 mmol) in CH_2Cl_2 (50 mL). Cool the reaction mixture to $0\text{ }^\circ\text{C}$ and slowly add TEA (1.61 mL, 11.45 mmol). Remove the cold bath and allow the reaction mixture to stir at room temperature. After about 2 h, the addition of the amino acid was determined to be complete by ^{31}P NMR. Charge p-nitrophenol (0.74 g, 5.30 mmol) followed by the addition of TEA (0.81, 5.84 mmol). Allow the reaction to stir at room temperature. After about 2 h, the reaction was determined to be complete by LCMS. The reaction was diluted with Et_2O and the $\text{TEA}\cdot\text{HCl}$ salts were filtered off. The crude was concentrated and purified by silica gel chromatography (0-50% EtOAc/Hex) to afford compound O. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.42 – 8.19 (m, 2H), 7.55 – 7.43 (m, 2H), 7.39 (dd, $J = 8.6, 7.2$ Hz, 2H), 7.30 – 7.12 (m, 3H), 6.53 (d, $J = 10.1$ Hz, 1H), 4.82 (hept, $J = 6.3$ Hz, 1H), 1.38 (s, 6H), 1.09 (d, $J = 6.3$, 6H). ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ -2.84. LC/MS: $t_R = 1.73$ min, MS $m/z = 422.92$ $[\text{M}+1]$; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex $2.6\mu\text{m}$ XB-C18 100A, 50×3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Preparation of Isopropyl 2-((((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)-2-methylpropanoate (Compound 31)



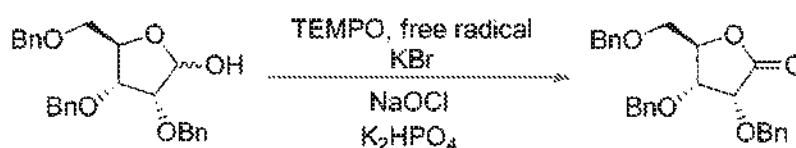
[0243] Take up compound **1** (66 mg, 0.23 mmol) in NMP (2.0 mL). Cool the mixture to about 0 °C and slowly add *t*BuMgCl (1.0M in THF, 0.57mL, 0.57mmol). Allow the reaction to stir at about 0 °C for about 30 min, then add a solution of compound **O** (143 mg, 0.34 mmol) dissolved in THF (1.0 mL). Remove the cold bath and place the reaction in an about 50 °C preheated oil bath. After about 2 h, the reaction was cooled to room temperature and was quenched with acetic acid and methanol. The crude was concentrated and purified by reverse phase HPLC without modifier to afford compound **31**. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (m, 3H), 7.30 (td, *J* = 8.5, 7.0 Hz, 2H), 7.20 – 7.04 (m, 3H), 6.87 (d, *J* = 4.5, 1H), 6.80 (d, *J* = 4.5 Hz, 1H), 6.27 (d, 6.1 Hz, 1H), 5.75 (t, *J* = 9.1 Hz, 1H), 5.34 (d, *J* = 5.7 Hz, 1H), 4.81 (p, *J* = 6.3 Hz, 1H), 4.71 – 4.50 (m, 1H), 4.23 (m, 2H), 4.11 (m, 1H), 4.03 – 3.83 (m, 1H), 1.37 – 1.23 (m, 6H), 1.18 – 1.04 (m, 6H). ³¹P NMR (162 MHz, DMSO) δ 2.47, 2.43. LC/MS: *t*_R = 1.08 min, MS *m/z* = 575.06 [M+1]; LC system: Thermo Accela 1250 UHPLC; MS system: Thermo LCQ Fleet; Column: Kinetex 2.6μ XB-C18 100A, 50 x 3.00 mm; Solvents: Acetonitrile with 0.1% formic acid, Water with 0.1% formic acid; Gradient: 0 min-2.4 min 2-100% ACN, 2.4 min-2.80 min 100% ACN, 2.8 min-2.85 min 100%-2% ACN, 2.85 min-3.0 min 2% ACN at 1.8mL/min.

Example 35. (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (32)



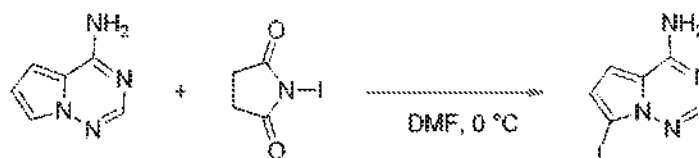
[0244] The preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate is described below.

Preparation of (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2(3H)-one.



[0245] (3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol (15.0 g) was combined with MTBE (60.0 mL), KBr (424.5 mg), aqueous K_2HPO_4 solution (2.5M, 14.3 mL), and TEMPO (56 mg). This mixture was cooled to about 1 °C. Aqueous bleach solution (7.9%wt.) was slowly charged in portions until complete consumption of starting material as indicated through a starch/iodide test. The layers were separated, and the aqueous layer was extracted with MTBE. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to yield the product as a solid.

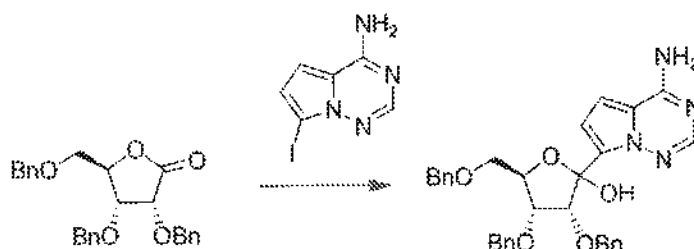
Preparation (4-amino-7-iodopyrrolo[2,1-f][1,2,4]triazine)



[0246] To a cold solution of 4-aminopyrrolo[2,1-f][1,2,4]triazine (10.03 g; 74.8 mmol) in N,N-dimethylformamide (70.27 g), N-iodosuccinimide (17.01 g; 75.6 mmol) was charged in portions, while keeping the contents at about 0 °C. Upon reaction completion (about 3 h at about

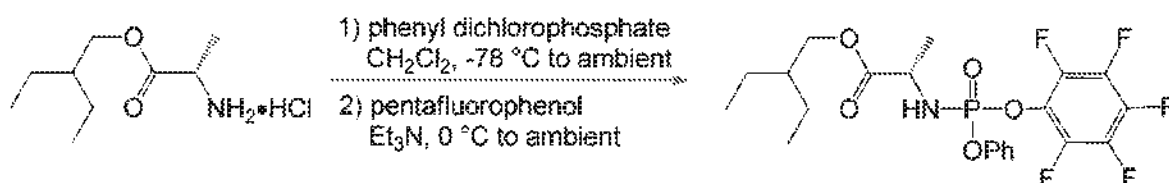
0 °C), the reaction mixture was transferred into a 1 M sodium hydroxide aqueous solution (11 g NaOH and 276 mL water) while keeping the contents at about 20-30 °C. The resulting slurry was agitated at about 22 °C for 1.5 h and then filtered. The solids are rinsed with water (50 mL) and dried at about 50 °C under vacuum to yield 4-amino-7-iodopyrrolo[2,1-f][1,2,4]triazine as a solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.90 (s, 1H), 7.78 (br s, 2H), 6.98 (d, J = 4.4 Hz, 1H), 6.82 (d, J = 4.4 Hz, 1H). ¹³C NMR (101 MHz, DMSO-d₆) δ 155.7, 149.1, 118.8, 118.1, 104.4, 71.9. MS m/z = 260.97 [M+H].

Preparation (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)tetrahydrofuran-2-ol via (4-amino-7-iodopyrrolo[2,1-f][1,2,4]triazine)



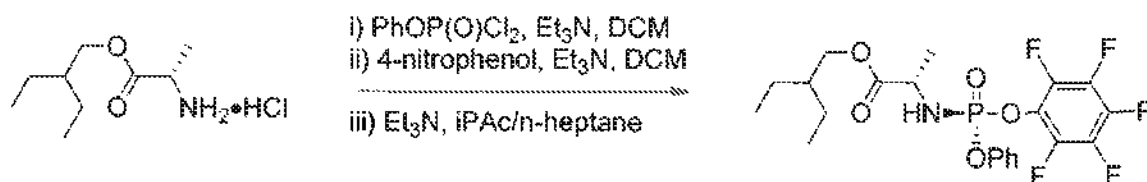
[0247] To a reactor under a nitrogen atmosphere was charged iodobase 2 (81 g) and THF (1.6 L). The resulting solution was cooled to about 5 °C, and TMSCl (68 g) was charged. PhMgCl (345mL, 1.8 M in THF) was then charged slowly while maintaining an internal temperature at about ≤ 5 °C. The reaction mixture was stirred at about 0 °C for 30 min, and then cooled to about -15 °C. *i*PrMgCl- LiCl (311 mL, 1.1 M in THF) was charged slowly while maintaining an internal temperature below about -12 °C. After about 10 minutes of stirring at about -15 °C, the reaction mixture was cooled to about -20 °C, and a solution of lactone 1 (130 g) in THF (400 mL) was charged. The reaction mixture was then agitated at about -20 °C for about 1 h and quenched with AcOH (57 mL). The reaction mixture was warmed to about 0 °C and adjusted to pH 7-8 with aqueous NaHCO₃ (5 wt%, 1300 mL). The reaction mixture was then diluted with EtOAc (1300 mL), and the organic and aqueous layers were separated. The organic layer was washed with 1N HCl (1300 mL), aqueous NaHCO₃ (5 wt%, 1300 mL), and brine (1300 mL), and then dried over anhydrous Na₂SO₄ and concentrated to dryness. Purification by silica gel column chromatography using a gradient consisting of a mixture of MeOH and EtOAc afforded the product.

Preparation ((2S)-2-ethylbutyl 2-(((perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate)
(mixture of *S_p* and *R_p*):



[0248] *L*-Alanine 2-ethylbutyl ester hydrochloride (5.0 g, 23.84 mmol) was combined with methylene chloride (40 mL), cooled to about $-78\text{ }^\circ\text{C}$, and phenyl dichlorophosphate (3.65 mL, 23.84 mmol) was added. Triethylamine (6.6 mL, 47.68 mmol) was added over about 60 min at about $-78\text{ }^\circ\text{C}$ and the resulting mixture was stirred at ambient temperature for 3h. The reaction mixture was cooled to about $0\text{ }^\circ\text{C}$ and pentafluorophenol (4.4 g, 23.84 mmol) was added. Triethylamine (3.3 mL, 23.84 mmol) was added over about 60 min. The mixture was stirred for about 3h at ambient temperature and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with an aqueous sodium carbonate solution several times, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of EtOAc and hexanes (0 to 30%). Product containing fractions were concentrated under reduced pressure to give (2S)-2-ethylbutyl 2-(((perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate as a solid. ^1H NMR (400 MHz, Chloroform- d) δ 7.41 – 7.32 (m, 4H), 7.30 – 7.17 (m, 6H), 4.24 – 4.16 (m, 1H), 4.13 – 4.03 (m, 4H), 4.01 – 3.89 (m, 1H), 1.59 – 1.42 (m, 8H), 1.40 – 1.31 (m, 8H), 0.88 (t, J = 7.5 Hz, 12H). ^{31}P NMR (162 MHz, Chloroform- d) δ -1.52. ^{19}F NMR (377 MHz, Chloroform- d) δ -153.63, -153.93 (m), -160.05 (td, J = 21.9, 3.6 Hz), -162.65 (qd, J = 22.4, 20.5, 4.5 Hz). MS m/z = 496 [M+H].

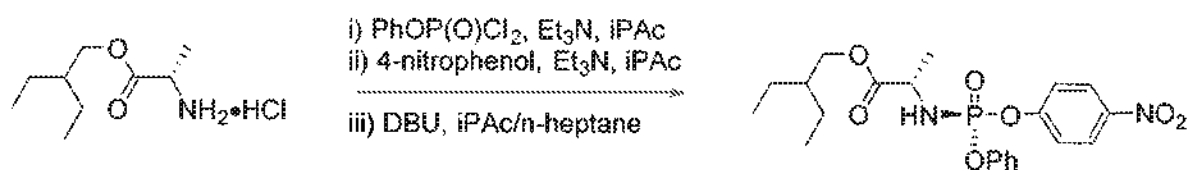
Preparation ((2S)-2-ethylbutyl 2-(((perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate):



L-alanine-2-ethylbutylester hydrochloride (40.10 g, 0.191 mmol) was dissolved in dichloromethane (533 g) and the solution was cooled with stirring to about $-15\text{ }^\circ\text{C}$ under $\text{N}_2(\text{g})$. Phenyl dichlorophosphate (40.32 g, 0.191 mol) was added followed by slow addition of triethylamine (41.58 g, 0.411 mmol) and the reaction mixture was stirred at about $-15\text{ }^\circ\text{C}$ for

about 1.5 h. Pentafluorophenol (35.14 g, 0.191 mol) was added, followed by triethylamine (19.23 g, 0.190 mol) and the reaction mixture was stirred for about 2 h. The reaction mixture was warmed to about 0 °C and 0.5 M HCl (279.19 g) was added. The mixture was warmed to about 22 °C and the organic layer was separated and washed with 5% KHCO₃ aqueous solution (281 g), then water (281 g). An aliquot of the organic layer (453.10 g of the 604.30 g solution) was concentrated to about 120 mL volume, isopropyl acetate (157 g) was added and the solution was concentrated to dryness. The residue was dissolved in isopropyl acetate (158 g). The resulting solution was concentrated to about 120 mL volume and the temperature was adjusted to about 45 °C. n-Heptane (165 g) was added and the mixture was cooled to 22 °C over about 1 h. n-Heptane (167 g) was added and the mixture was cooled to about 0 °C. Triethylamine (2.90 g, 0.0287 mol) was added and the mixture was stirred at 0 °C for about 17 h. The mixture was filtered, the solids were rinsed with n-heptane (145 g) and the solids were dried under vacuum at about 40 °C for about 15 h to provide 2-ethylbutyl ((S)- (pentafluorophenoxy)(phenoxy)phosphoryl)-L-alaninate.

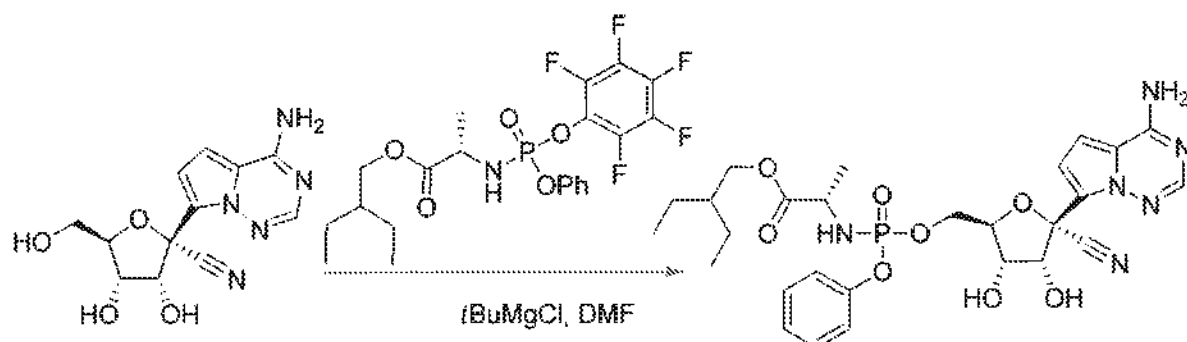
Preparation 2-ethylbutyl ((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)-L-alaninate:



A slurry of L-alanine-2-ethylbutylester hydrochloride (20.08 g, 95.8 mmol) and isopropyl acetate (174 g) was cooled with stirring to about -20 °C. Phenyl dichlorophosphate (20.37 g, 96.5 mmol) was added, followed by slow addition of triethyl amine (20.97 g, 207.2 mmol) and the mixture was stirred at about -20 °C for about 1 h. 4-Nitrophenol (13.23 g, 95.1 mmol) was added, followed by slow addition of triethylamine (10.01 g, 98.8 mmol) and the reaction mixture was stirred for about 1.5 h. The reaction mixture was warmed to about 0 °C and 0.5 M HCl (140 g) was added. The organic layer was separated and washed with 5% Na₂CO₃ (2 x 100 g) and 10% NaCl (2 x 100 g). The organic layer was then concentrated to about 80 mL volume and isopropylacetate (4 g) was added, followed by n-heptane (110 g). Product seed crystals (0.100 g) were added followed by a second portion of n-heptane (110 g) and the mixture was cooled to about 0 °C. 1,8-Diazabicycloundec-7-ene (1.49 g, 9.79 mmol) was added and the mixture was stirred at about 0 °C for about 21 h. The resultant solids were filtered and washed first with n-heptane (61 g) and then with H₂O (2 x 100 g). The solids were stirred with H₂O (200 g) for

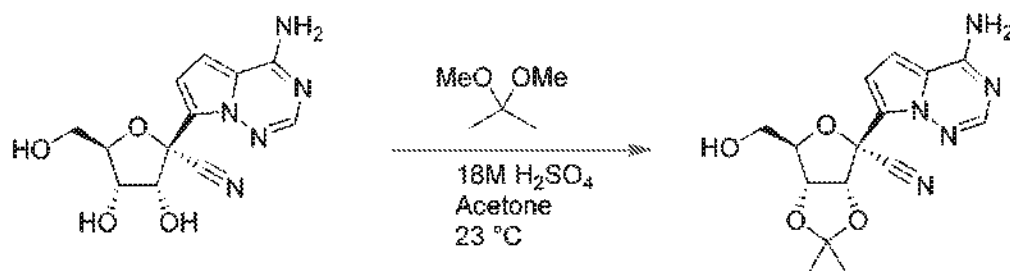
about 1.5 h, filtered, and rinsed with H₂O (3 x 100 g), then n-heptane (61 g). The obtained solids were dried under vacuum at about 40 °C for about 19 h to provide 2-ethylbutyl ((S)-(4-nitrophenoxy)(phenoxy)phosphoryl)-L-alaninate.

Preparation of Title Compound (mixture of *Sp* and *Rp*):



[0249] The nucleoside (29 mg, 0.1 mmol) and the phosphonamide (60 mg, 0.12 mmol) and N,N-dimethylformamide (2 mL) were combined at ambient temperature. *Tert*-Butyl magnesium chloride (1M in THF, 0.15 mL) was slowly added. After about 1h, the reaction was diluted with ethyl acetate, washed with aqueous citric acid solution (5%wt.), aqueous saturated NaHCO₃ solution and saturated brine solution. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of methanol and CH₂Cl₂ (0 to 5%). Product containing fractions were concentrated under reduced pressure to provide the product.

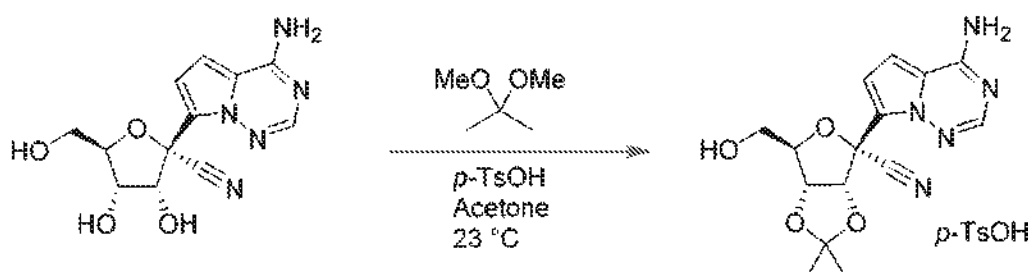
Preparation of (3aR,4R,6R,6aR)-4-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbonitrile:



[0250] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (5.8g, 0.02 mol), 2,2-dimethoxypropane (11.59 mL, 0.09 mol) and acetone (145 mL) at ambient temperature was added sulfuric acid (18M, 1.44 mL). The mixture was warmed to about 45 °C. After about 30 min, the mixture was cooled to ambient temperature and sodium bicarbonate (5.8 g) and water

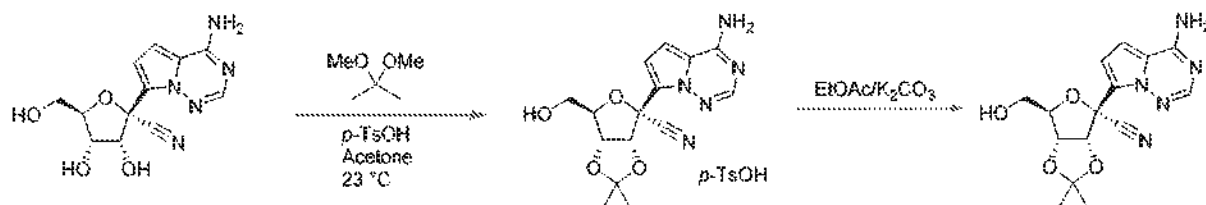
5.8 mL) were added. After 15 min, the mixture was concentrated under reduced pressure. The residue was taken up in ethyl acetate (150 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over sodium sulfate and concentrated under reduced pressure to give crude (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile. ^1H NMR (400 MHz, CD_3OD) δ 7.84 (s, 1H), 6.93 (d, $J = 4.6$ Hz, 1H), 6.89 (d, $J = 4.6$ Hz, 1H), 5.40 (d, $J = 6.7$ Hz, 1H), 5.00 (dd, $J = 6.7, 3.3$ Hz, 1H), 4.48 – 4.40 (m, 1H), 3.81 – 3.72 (m, 2H), 1.71 (s, 3H), 1.40 (s, 3H). MS $m/z = 332.23$ [M+1].

Preparation of (3aR,4R,6R,6aR)-4-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbonitrile TsOH salt:



[0251] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (5.0 g, 17.2 mmol, 1.0 equiv.), 2,2-dimethoxypropane (10.5 mL, 86 mmol, 5.0 equiv.) and acetone (25 mL) at ambient temperature was added *p*-tolylsulfonic acid (3.59 g, 1.1 equiv.). The mixture was stirred at ambient temperature. After about 30 min, isopropyl acetate (25 mL) was added over about one hour. The resulting slurry was filtered and rinsed with 2:1 heptane:isopropyl acetate (25 mL). The product was dried under vacuum at about 40 °C.

Preparation of (3aR,4R,6R,6aR)-4-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbonitrile:

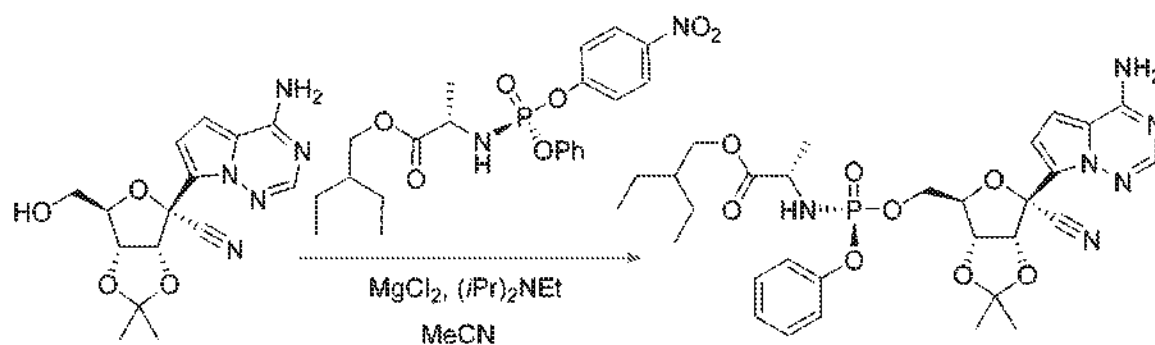


[0252] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (5 g, 17.2 mmol, 1.0 equiv.), 2,2-

dimethoxypropane (10.5 mL, 86 mmol, 5.0 equiv.) and acetone (25 mL) at ambient temperature was added *p*-tolylsulfonic acid (3.59 g, 1.1 equiv.). The mixture was stirred at ambient temperature. After 30 min, isopropyl acetate (25 mL) was added over one hour. The resulting slurry was filtered and rinsed with 2:1 heptane:isopropyl acetate (25 ml). The product was dried under vacuum at 40 °C. The isolated solid was added to a reactor and 5% K₂CO₃ solution (50 ml) and ethyl acetate (50 mL) were added. The layers were separated, and the aqueous layer washed with ethyl acetate (25 ml). The combined organic layers were washed with water (25 ml), then concentrated to ca. 25 ml. The reactor was refilled with isopropyl acetate (25 ml) and concentrated to ca. 25 ml. The reactor was again refilled with isopropyl acetate (25 ml) and concentrated to 25 ml. The resulting solution was seeded, producing a thick slurry. To this was added heptane (25 ml) over one hour. The resulting slurry was filtered and rinsed with 2:1 heptane:isopropyl acetate (25 ml). The product was dried under vacuum at 40 °C. ()

(2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile. ¹H NMR (400 MHz, CD₃OD) δ 7.84 (s, 1H), 6.93 (d, *J* = 4.6 Hz, 1H), 6.89 (d, *J* = 4.6 Hz, 1H), 5.40 (d, *J* = 6.7 Hz, 1H), 5.00 (dd, *J* = 6.7, 3.3 Hz, 1H), 4.48 – 4.40 (m, 1H), 3.81 – 3.72 (m, 2H), 1.71 (s, 3H), 1.40 (s, 3H). MS *m/z* = 332.23 [M+1].

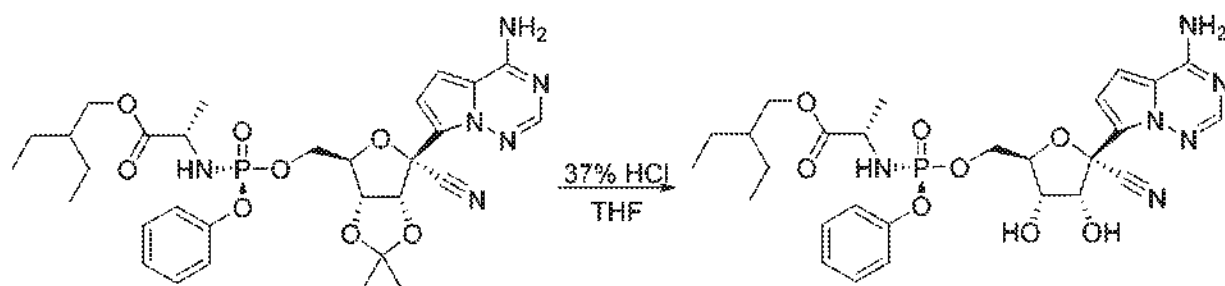
Preparation of (2S)-2-ethylbutyl 2-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate:



[0253] Acetonitrile (100 mL) was combined with (2S)-2-ethylbutyl 2-(((4-nitrophenoxy)(phenoxy)phosphoryl)-amino)propanoate (9.6 g, 21.31 mmol), the substrate alcohol (6.6 g, 0.02 mol),), magnesium chloride (1.9 g, 19.91 mmol) at ambient temperature. The mixture was agitated for about 15 min and *N,N*-diisopropylethylamine (8.67 mL, 49.78 mmol) was added. After about 4h, the reaction was diluted with ethyl acetate (100 mL), cooled to about 0 °C and combined with aqueous citric acid solution (5%wt., 100 mL). The organic

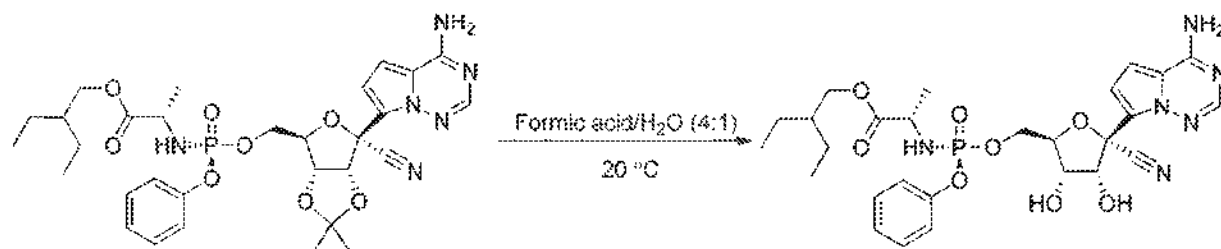
phase was washed with aqueous citric acid solution (5%wt., 100 mL) and aqueous saturated ammonium chloride solution (40 mL), aqueous potassium carbonate solution (10%wt., 2 x 100 mL), and aqueous saturated brine solution (100 mL). The organic phase was dried with sodium sulfate and concentrated under reduced pressure to provide crude product. ^1H NMR (400 MHz, CD_3OD) δ 7.86 (s, 1H), 7.31 – 7.22 (m, 2H), 7.17 – 7.09 (m, 3H), 6.93 – 6.84 (m, 2H), 5.34 (d, J = 6.7 Hz, 1H), 4.98 (dd, J = 6.6, 3.5 Hz, 1H), 4.59 – 4.50 (m, 1H), 4.36 – 4.22 (m, 2H), 4.02 (dd, J = 10.9, 5.7 Hz, 1H), 3.91 (dd, J = 10.9, 5.7 Hz, 1H), 3.83 (dq, J = 9.7, 7.1 Hz, 1H), 1.70 (s, 3H), 1.50 – 1.41 (m, 1H), 1.39 (s, 3H), 1.36 – 1.21 (m, 7H), 0.86 (t, J = 7.4 Hz, 6H). MS m/z = 643.21 $[\text{M}+1]$.

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (Compound 32)



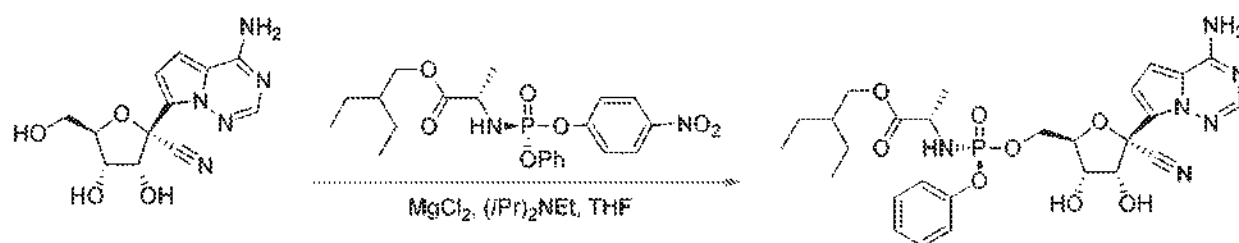
[0254] The crude acetonide (12.85 g) was combined with tetrahydrofuran (50 mL) and concentrated under reduced pressure. The residue was taken up in tetrahydrofuran (100 mL), cooled to about 0 °C and concentrated HCl (20 mL) was slowly added. The mixture was allowed to warm to ambient temperature. After consumption of the starting acetonide as indicated by HPLC analysis, water (100 mL) was added followed by aqueous saturated sodium bicarbonate solution (200 mL). The mixture was extracted with ethyl acetate (100 mL), the organic phase washed with aqueous saturated brine solution (50 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a gradient of methanol and ethyl acetate (0 to 20%). Product containing fractions were concentrated under reduced pressure to provide the product.

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (Compound 32)



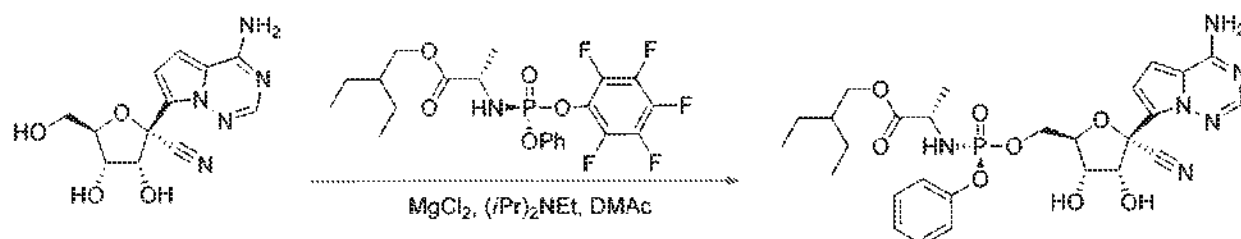
To a vial containing (S)-2-ethylbutyl 2-(((S)-(((3aR,4R,6R,6aR)-6-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-6-cyano-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (30 mg, 0.05 mmol) was added an 80% aqueous formic acid solution (1.5 mL). After 18 h at about 20 °C complete conversion was confirmed by HPLC and LC-MS. MS (m/z) = 603($M+1$)⁺.

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (Compound 32) via Direct Coupling



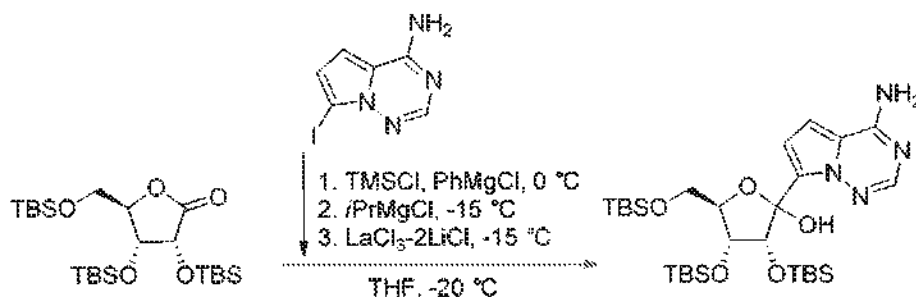
[0255] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (0.5 g, 2 mmol), (S)-2-ethylbutyl 2-(((S)-((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (0.9 g, 2 mmol), and $MgCl_2$ (0.2 g, 2 mmol), was charged N,N-dimethylacetamide (10 mL). The resulting mixture was warmed to about 30 °C with constant stirring. N,N-Diisopropylethylamine (0.7 mL, 4 mmol) was then added slowly, and the reaction mixture was stirred for about 6 h. Water (10 mL) was charged H_2O , followed by 2-MeTHF (10 mL), and the organic and aqueous phases were separated. The aqueous layer was then back-extracted with 2-MeTHF (10 mL). The organic layers were combined, and washed with 10 wt% citric acid solution (10 mL), followed by 10 wt% K_2CO_3

solution (10 mL), and H₂O (10 mL). A small amount of brine was added to resolve emulsions in the water wash before the layers were separated. The organic layer was evaporated to dryness to afford 0.65 g of a foam. *i*PrOAc (2.6 mL) was added then added, and the mixture was warmed to about 40 °C to achieve dissolution. The solution was cooled to about 20 °C, and the mixture was stirred for about 3 days. The solids were isolated by filtration, and the filter cake was washed with a small amount of *i*PrOAc. The solids were dried to afford (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate.



[0256] To a mixture of (2R,3R,4S,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (0.2 g, 0.7 mmol), (S)-2-ethylbutyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate (0.3 g, 0.7 mmol), and MgCl₂ (0.1 g, 1 mmol), was charged N,N-dimethylacetamide (4 mL). The resulting mixture was warmed to about 30 °C with constant stirring. N,N-Diisopropylethylamine (0.3 mL, 2 mmol) was then added slowly, and the reaction mixture was stirred for 5 h. Conversion to the product was confirmed through UPLC analysis.

Preparation of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis((tert-butyl)dimethylsilyl)oxy)-5-(((tert-butyl)dimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol



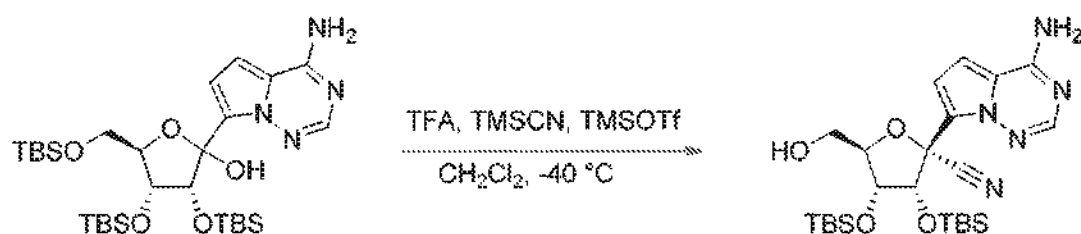
[0257] A solution of 7-iodopyrrolo[2,1-*f*][1,2,4]triazin-4-amine (13.9 g, 53.5 mmol) was prepared in THF (280 mL). The solution was cooled to about 0 °C, and TMSCl (13.6 mL, 107 mmol) was added. The reaction mixture was stirred for about 20 min, and then PhMgCl (2 M in

THF; 53.5 mL, 56.8 mmol) was added while maintaining an internal temperature below about 5 °C. The reaction mixture was agitated at about 0 °C for about 30 min, and then cooled to about -20°C. *i*PrMgCl-LiCl (1.3 M in THF, 43.1 mL, 56 mmol) was then added while maintaining an internal temperature below about -15 °C. The reaction mixture was agitated for about 30 min at about -20 °C.

[0258] In a separate flask, a solution of (3R,4R,5R)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)dihydrofuran-2(3H)-one (25.0 g, 50.9 mmol, 0.83 equiv) was prepared in $\text{LaCl}_3 \cdot 2\text{LiCl}$ (0.6 M in THF, 85 mL, 50.9 mmol). The solution was then transferred to the Grignard solution while maintaining an internal temperature below -20°C. The resulting reaction mixture was agitated at about -20 °C for about 4 h.

[0259] The reaction was quenched with 1 M HCl (140 mL), and the mixture warmed to ambient temperature. EtOAc (140 mL) was added, and the organic and aqueous phases were separated. The water layer was extracted with EtOAc (200 mL). The combined EtOAc layers were extracted sequentially with saturated aqueous NaHCO_3 (2 x 200 mL), water (200 mL), and brine (200 mL). The organic layer was concentrated, and then purified by silica gel chromatography (30% EtOAc/hexane) to afford (3R,4R,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol. ^1H NMR (300 MHz, CDCl_3) δ 8.15 – 7.88 (m, 1H), 7.51 (d, J = 4.8 Hz, 0.5H), 7.02 – 6.92 (m, 0.5H), 6.65 – 6.57 (m, 1H), 5.66 – 5.24 (m, 3H), 4.49 – 3.50 (m, 4H), 0.97 – 0.78 (26H), 0.65 (s, 1.5H), 0.19 – 0.00 (m, 15.5H), -0.22 (s, 1H), -0.55 (s, 1H). . MS m/z = 626 (M+H).

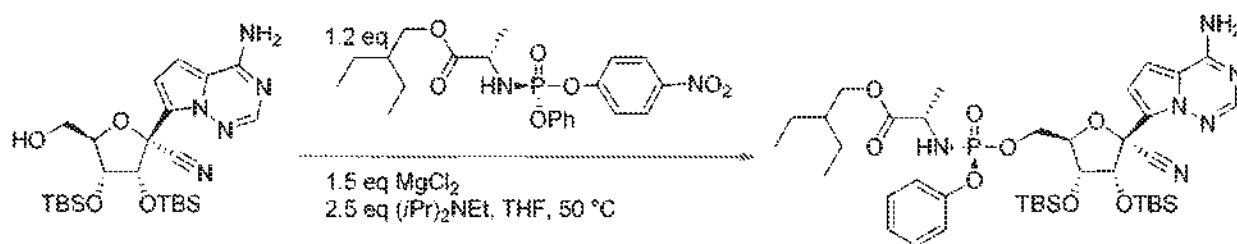
Preparation of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile



[0260] A solution of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol (1.50 g, 2.40 mmol) in CH_2Cl_2 (15 mL) was cooled to about -40 °C. Trifluoroacetic acid (0.555 mL, 7.20

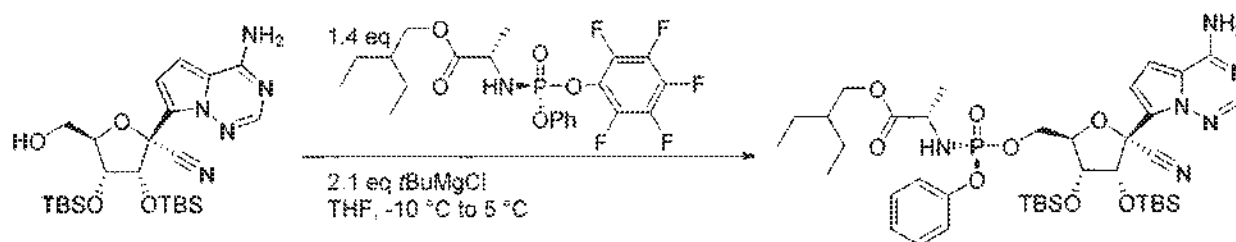
mmol) was added keeping the temperature below -20°C . In a separate flask, trimethylsilyl trifluoromethanesulfonate (2.60 mL, 14.4 mmol) was added to 5 mL of CH_2Cl_2 (5 mL) at about 15°C , followed by trimethylsilyl cyanide (1.92 mL, 14.4 mmol), and the solution was cooled to about -30°C . The cooled solution was added to the solution of (3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-ol while keeping the temperature below -25°C . The reaction mixture was stirred for 15 min at about -30°C . The reaction was quenched with triethylamine (3.34 mL, 24.0 mmol) and the mixture was warmed to about 0°C . Water (50 mL) was added while keeping the temperature below about 20°C . When the addition was complete the mixture was stirred for 15 min at room temperature. The layers were separated and the organic layer was washed sequentially with KOH (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4 , concentrated, and then purified by silica gel chromatography (30% EtOAc / hexane) to afford the product as a 3.8:1 mixture of diastereomers). The mixture was purified further by prep-HPLC (ACN 0 to 95% in water) to afford the product as a single diastereomer. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.14-7.92 (m, 2H), 7.89 (s, 1H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.88 (d, $J = 4.4$ Hz, 1H), 5.27 (d, $J = 4.6$ Hz, 1H), 5.10 (dd, $J = 7.7, 4.6$ Hz, 1H), 4.31 (dd, $J = 4.7, 1.4$ Hz, 1H), 4.12 (ddd, $J = 5.9, 4.1, 1.4$ Hz, 1H), 3.80 – 3.69 (m, 1H), 3.56 (td, $J = 7.8, 3.9$ Hz, 1H), 0.93 (s, 9H), 0.75 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), -0.15 (s, 3H), -0.62 (s, 3H). MS $m/z = 520$ (M+H).

Preparation of (S)-2-ethylbutyl 2-(((S)-(((2R,3R,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-cyanotetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate



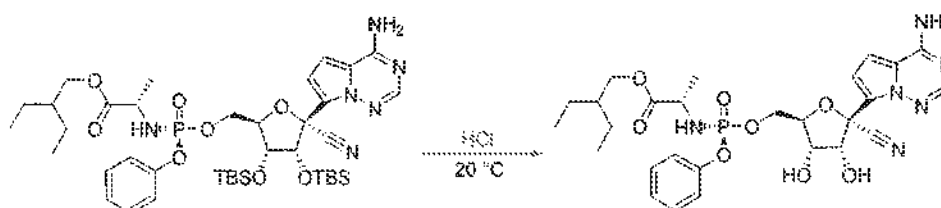
To a mixture of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (16 mg, 0.03 mmol), (S)-2-ethylbutyl 2-(((S)-((4-nitrophenoxy)(phenoxy)phosphoryl)amino)propanoate (17 mg, 0.04 mmol), and MgCl_2 (4 mg, 0.05 mmol), was charged THF (0.3 mL). The resulting mixture was warmed to about 50°C with constant stirring. N,N-Diisopropylethylamine (0.013 mL, 0.08

mmol) was then added, and the reaction mixture was stirred for 21 h. Conversion to the product was confirmed through UPLC and LC-MS analysis. MS m/z = 831 (M+H).



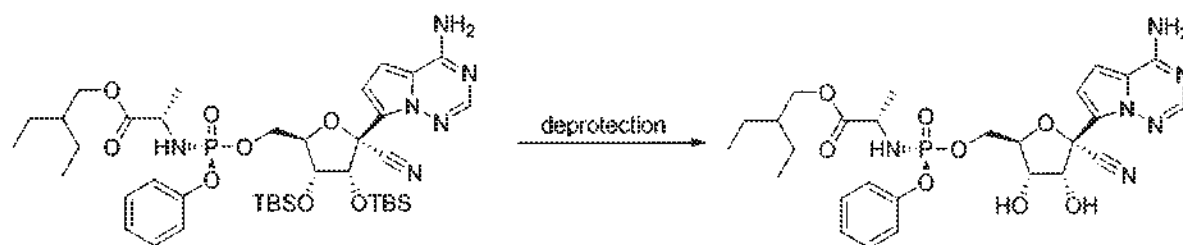
A solution of (2R,3R,4R,5R)-2-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyl dimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (16 mg, 0.03 mmol) in THF (0.3 mL) was cooled to -10 °C. *t*BuMgCl was added dropwise (0.07 mL, 0.07 mmol), followed by a solution of (S)-2-ethylbutyl 2-(((S)-(perfluorophenoxy)(phenoxy)phosphoryl)amino)propanoate (22 mg, 0.04 mmol) in THF (0.15 mL). The reaction mixture was warmed to 5 °C, and stirred for 16 h. The reaction was quenched with MeOH, concentrated, and then purified by silica gel chromatography (EtOAc /hexanes) to afford the product. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 7.38 – 7.29 (m, 2H), 7.25 – 7.21 (m, 2H), 7.21 – 7.13 (m, 1H), 7.11 (d, *J* = 4.6 Hz, 1H), 6.65 (d, *J* = 4.6 Hz, 1H), 5.88 (br s, 2H), 5.35 (d, *J* = 4.4 Hz, 1H), 4.49 – 4.41 (m, 1H), 4.41 – 4.35 (m, 1H), 4.32 – 4.26 (m, 1H), 4.24 (dd, *J* = 4.5, 1.7 Hz, 1H), 4.10 – 3.99 (m, 2H), 3.96 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.80 – 3.72 (m, 1H), 1.48 (h, *J* = 6.2 Hz, 1H), 1.39 – 1.28 (m, 7H), 0.96 (s, 9H), 0.85 (t, *J* = 7.5 Hz, 6H), 0.80 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), -0.13 (s, 3H), -0.56 (s, 3H). ³¹P NMR (162 MHz, CDCl₃) δ 2.74 (s). MS m/z = 831 (M+H).

Preparation of (S)-2-ethylbutyl 2-(((S)-((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate



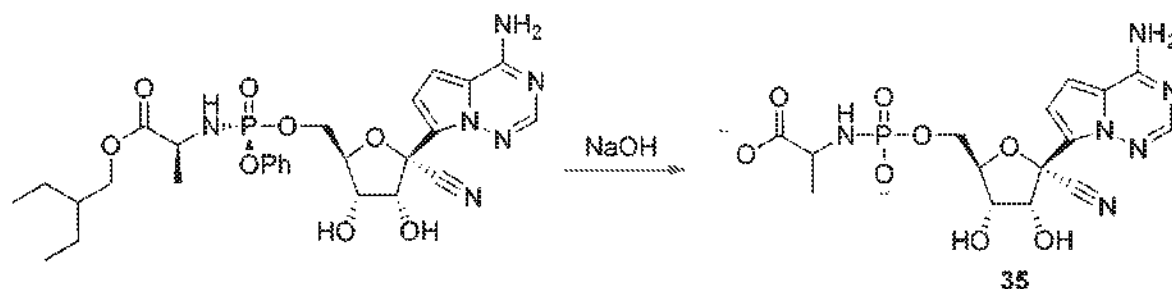
A crude solution of (S)-2-ethylbutyl 2-(((S)-((2R,3R,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyl dimethylsilyl)oxy)-5-cyanotetrahydrofuran-2-

yl)methoxy)(phenoxy)phosphoryl)amino)propanoate was cooled to about 0 °C and conc HCl (0.05 mL, 0.62 mmol) was slowly added. The reaction mixture was stirred for about 72 hours at about 20 °C. Conversion to the product was confirmed through UPLC and LC-MS analysis. MS $m/z = 603$ (M+H).



A solution of (S)-2-ethylbutyl 2-(((S)-(((2R,3R,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3,4-bis((tert-butyldimethylsilyl)oxy)-5-cyanotetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate in a fluoride or acid can deprotect to a solution of (S)-2-ethylbutyl 2-(((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate. Representative fluorides include, but are not limited to TBAF, KF, pyridinium hydrofluoride, triethylammonium hydrofluoride, hydrogen fluoride, hydrochloric acid, toluenesulfonic acid, or any other suitable fluoride source. Representative acids include, but are not limited to those found in Greene, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis*, 4th Ed., John Wiley & Sons: New York, 2006.

Example 35-a. (((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)oxidophosphoryl)alaninate (Compound 35)



[0261] 2-ethylbutyl ((S)-(((2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (130 mg, 0.216 mmol) was dissolved in mixture of acetonitrile (6 mL) and water (2 mL). Aqueous sodium hydroxide solution (2N, 0.5 mL) was added dropwise over 5 min at rt and the reaction

mixture was stirred. After 2 h, the resulting mixture was concentrated under reduced pressure and the residue was purified by HPLC on a C18 column eluting with water to afford the desired product as the bis-sodium salt. ^1H NMR (400 MHz, D_2O) δ 7.79 (s, 1H), 6.86 (d, $J = 4.7$ Hz, 1H), 6.80 (d, $J = 4.7$ Hz, 1H), 4.86 (d, $J = 5.4$ Hz, 1H), 4.40 – 4.34 (m, 1H), 4.30 (dd, $J = 5.3$, 3.0 Hz, 1H), 3.75 (qdd, $J = 11.6$, 4.5, 3.1 Hz, 2H), 3.20 (dq, $J = 8.6$, 7.1 Hz, 1H), 0.86 (d, $J = 7.0$ Hz, 3H). ^{31}P NMR (162 MHz, D_2O) δ 7.30. LCMS m/z 442.95 $[\text{M}+\text{H}]$. HPLC (2–98% MeCN– H_2O gradient with 0.1% TFA modifier over 8.5 min, 1.5mL/min, Column: Phenomenex Kinetex C18, 2.6 μm 100 Å, 4.6 x 100 mm) $t_R = 2.694$ min.

B. Antiviral Activity

[0262] Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

[0263] Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and manmade materials such as cell cultures.

[0264] If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

[0265] The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocols.

Virus	Cell line	Plate format	Cell number	MOI (pfu/cell)	Incubation (Days)	Read out	Values
EBOV (Zaire)	Hela	384	4000	0.5	2	HCS	EC50
EBOV (Zaire)	HFF-1			2		HCS	
EBOV-GFP	Huh-7	96	10000	0.1	4	GFP	
EBOV-GFP	HMVEC-TERT					GFP	
EBOV-LUC	Huh-7					LUC	
MARV-GFP	Huh-7					GFP	
NiV	Hela					CPE	
NiV-GFP	HMVEC-TERT					GFP	
NiV-LUC	HMVEC-TERT					LUC	

EBOV: Ebola virus strain Zaire
 EBOV-GFP: Ebola reporter virus expressing green fluorescent protein
 EBOV-LUC: Ebola reporter virus expressing luciferase
 MARV-GFP: Marburg virus expressing green fluorescent protein
 NiV: Nipah virus
 NiV-GFP: Nipah reporter virus expressing green fluorescent protein
 NiV-LUC: Nipah reporter virus expressing luciferase

HCS: High content imaging (immuno-staining of ebolavirus GP-protein)
 GFP: Green fluorescent protein
 LUC: Luciferase
 CPE: Cytopathic effects measured by cell titer glo (CTG) reagent

Hela: Hela epithelial cell (cervical carcinoma)
 HFF-1: Human foreskin fibroblast
 Huh-7: Hepatocyte
 HMVEC-TERT: Human microvascular endothelial cells immortalized with the telomerase catalytic protein

Example 36. Ebola virus antiviral activity and cytotoxicity assays

[0266] Antiviral activity of Compound 1 and Compound 9 was measured against Ebola virus (EBOV), Marburg virus (MARV) (Table 2), and Nipah virus (NiV) (Table 3) using fully replicating reporter viruses expressing luciferase or green fluorescent protein (GFP) (Uebelhoer, L.S., 2014. AVR; Hoenen, T., 2013. AVR). Further antiviral activity of Compound 1 and Compound 9 was measured against Ebola virus (EBOV), Marburg virus (MARV) (Table 2-a), using fully replicating reporter viruses expressing luciferase or green fluorescent protein (GFP) (Uebelhoer, L.S., 2014. AVR; Hoenen, T., 2013. AVR). All studies were conducted in biosafety level-4 containment (BSL-4) at the Centers for Disease Control and Prevention (CDC). Ebola virus antiviral assays were conducted in primary human microvascular endothelial cells

immortalized with the telomerase catalytic protein (HMVEC-TERT) and in Huh-7 cells (Shao, R., 2004, BBRC). Nipah virus antiviral activity was measured in HMVEC-TERT and Hela cells.

[0267] Antiviral assays were conducted in 96well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence for GFP reporter viruses or after subsequent addition of luciferase substrate for luciferase reporter viruses. For virus yield assays, media from infected cells was removed and a portion was used to quantify viral RNA by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The remaining media was serially diluted and the amount of infectious virus was measured by using the diluted media to infect fresh cell monolayers to determine the tissue culture infectious dose that caused 50% cytopathic effects (TCID₅₀) using Cell TiterGlo reagent (Promega, Madison, WI). For virus cytopathic effect (CPE) assays, viability of infected cells was measure using Cell TiterGlo reagent.

[0268] The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 37. EBOV-GFP HMVEC-TERT cells

[0269] HMVEC-TERT cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded HMVEC-TERT monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and

100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 38. EBOV-GFP Huh-7 cells

[0270] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded Huh-7 monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 39. EBOV-Luc Huh-7 cells

[0271] Huh-7 cells were seeded in 96well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of the EBOV-Luc virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision

plate reader after subsequent addition of luciferase substrate. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 40. MARV-GFP Huh-7 cells

[0272] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded Huh-7 monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of MARV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 41. Ebola Huh-7 (RNA)

[0273] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Huh-7 cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and a portion was used to quantify viral RNA by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by

non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 42. Ebola Huh-7 (Yield)

[0274] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 μ L/well of each dilution was transferred in triplicate onto plates containing preseeded Huh-7 cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of EBOV virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and diluted in 10-fold serial dilutions. The amount of infectious virus was measured by using the diluted media to infect fresh cell monolayers to determine the tissue culture infectious dose that caused 50% cytopathic effects (TCID₅₀) using Cell TiterGlo reagent (Promega, Madison, WI). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 43. Ebola HeLa cells

[0275] The antiviral activity of selected compounds was measured against ebolavirus (EBOV) strain Zaire conducted in biosafety level-4 containment (BSL-4) at the US Army Medical Research Institute for Infectious Disease (USAMRIID). HeLa cells were seeded in 384 well plates at 5000 cells / well. The antiviral activity of each compound was measured in quadruplicate. Eight to ten concentrations of compound were added directly to the cell cultures using the HP300 digital dispenser in 3-fold serial dilution increments 2h prior to infection. The plates were transferred to BSL-4 containment and the appropriate dilution of virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 2 days in a tissue culture incubator. After the incubation, the cells were fixed in formalin solution and virus

replication was measured by quantifying Ebola glycoprotein levels after immunostaining and high content imaging using the Perkin Elmer Opera confocal microscopy instrument. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC_{50} value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 44. Ebola Macrophage cultures

[0276] The antiviral activity of selected compounds was measured against ebolavirus (EBOV) strain Zaire conducted in biosafety level-4 containment (BSL-4) at the US Army Medical Research Institute for Infectious Disease (USAMRIID). Macrophage cultures were isolated from fresh human PBMCs and differentiated in the presence of 5ng/ml GM-CSF and 50uM B-mercaptoethanol. The media was changed every 2 days and cells that adhered to the tissue culture plate after 7 days were removed with 0.5M EDTA in 1x PBS, concentrated by centrifugation at 200 x g for 10 minutes and plated in 384 well assay plates at 40,000 cells / well. The antiviral activity of each compound was measured in quadruplicate. Eight to ten concentrations of compound were added directly to the cell cultures using the HP300 digital dispenser in 3-fold serial dilution increments 2h prior to infection. The plates were transferred to BSL-4 containment and the appropriate dilution of virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 2 days in a tissue culture incubator. After the incubation, the cells were fixed in formalin solution and virus replication was measured by quantifying Ebola glycoprotein levels after immunostaining and high content imaging using the Perkin Elmer Opera confocal microscopy instrument. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC_{50} value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 45. Nipah-GFP HMVEC-TERT cells

[0277] HMVEC-TERT cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto 96 well plates containing preseeded HMVEC-TERT

monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of NIV-GFP virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader by direct fluorescence to measure GFP expression from the reporter virus. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 46. Niv-Luc HMVEC-TERT

[0278] HMVEC-TERT cells were seeded in 96well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of the Niv-Luc virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, virus replication was measured in an Envision plate reader after subsequent addition of luciferase substrate. The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 47. Niv Hela (Yield)

[0279] Hela cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Hela cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of Niv virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells

and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and diluted in 10-fold serial dilutions. The amount of infectious virus was measured by using the diluted media to infect fresh cell monolayers to determine the tissue culture infectious dose that caused 50% cytopathic effects (TCID₅₀) using Cell TiterGlo reagent (Promega, Madison, WI). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Example 48. Niv Hela (RNA)

[0280] Huh-7 cells were seeded in 96 well plates. Eight to ten concentrations of compound were diluted in 3-fold serial dilution increments in media and 100 uL/well of each dilution was transferred in triplicate onto plates containing preseeded Hela cell monolayers. The plates were transferred to BSL-4 containment and the appropriate dilution of Niv virus stock, previously determined by titration and prepared in cell culture media, was added to test plates containing cells and serially diluted compounds. Each plate included three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection, test plates were incubated for 3 to 4 days in a tissue culture incubator. After the incubation, media from infected cells was removed and a portion was used to quantify viral RNA by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The percentage inhibition was calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC₅₀ value for each compound was determined by non-linear regression as the effective concentration of compound that inhibited virus replication by 50%.

Table 2: Ebola and Marburg virus antiviral assays

	EC ₅₀ (nM)							
Assay	Reporter Virus				RNA	Yield	Antigen expression (high content imaging)	
Virus	EBOV-GFP	EVOV-Luc	MARV-GFP	Ebola				
Cell line	HMVEC-TERT	Huh-7	Huh-7	Huh-7	Huh-7		HeLa	Macrophage
Compound 1	771	1492	3126	1726	ND	ND	>20,000	>20,000
Compound 9	121	90	ND	ND	1	1029	290	501
(R)-Diastereomer of Compound 9	62	70	ND	ND	ND	ND		
(S)-Diastereomer of Compound 9 (Compound 32)	40	81	ND	ND	ND	ND		
Compound 10								
Compound 15	630	271	ND	ND	ND	ND		
Compound 21	905							270
Compound 22	ND	ND	ND	ND	ND	ND		
Compound 23	458						1650	243,350
Compound 24								
Compound 25								
Compound 26	283						970, 1180	1180
Compound 27	82						182	
Compound 28	102						975	120
Compound 29								
Compound 30								
Compound 31	11061						>20,000	1230

EBOV-GFP: Ebola virus expressing the GFP reporter gene

EBOV-Luc: Ebola virus expressing the luciferase reporter gene

MARV-GFP: Marburg virus expressing the GFP reporter gene

Ebola: Ebolavirus strain 2014

Table 2-a: Ebola and Marburg virus antiviral assays

	EC ₅₀ (nM)							
Assay	Reporter Virus				RNA	Yield	Antigen expression (high content imaging)	
Virus	EBOV-GFP		EVOV- Luc	MARV- GFP	Ebola			
Cell line	HMVEC- TERT	Huh-7	Huh-7	Huh-7	Huh-7		Hela	Macrophage
Compound 1	771	1492	3126	1726	ND	ND	>20,000	>20,000
Compound 9	121	90	ND	ND	1	1029	290, 270	501, 70
(R)-Diastereomer of Compound 9	62	70	ND	ND	ND	ND	210	112
(S)-Diastereomer of Compound 9 (Compound 32)	40	81	ND	ND	ND	ND	100	87
Compound 10							3200	
Compound 15	630	271	ND	ND	ND	ND	520	591
Compound 21	905, 473							270
Compound 22	ND	ND	ND	ND	ND	ND	11570	
Compound 23	458						1650, 1845	243, 350, 297
Compound 24							785	
Compound 25							6720	
Compound 26	283						970, 1180, 1103	1180, 1290
Compound 27	82						182	
Compound 28	102						975, 682	120
Compound 29							275	
Compound 30	11051						>20000	1230
Compound 31							>20,000, >10000	

EBOV-GFP: Ebola virus expressing the GFP reporter gene

EBOV-Luc: Ebola virus expressing the luciferase reporter gene

MARV-GFP: Marburg virus expressing the GFP reporter gene

Ebola: Ebolavirus strain 2014

Table 3: Nipah and Hendra virus antiviral assays

	EC ₅₀ (nM)			
Assay	Reporter Virus		CPE	Yield
Virus	NiV GFP	NiV Luc	NiV	
Cell line	HMVEC-TERT		Hela	
Compound 1	13420	3500	1484	1000
Compound 9	60	30	ND	ND

NiV GFP: Nipah virus expressing the GFP reporter gene

NiV-Luc: Nipah virus expressing the luciferase reporter gene

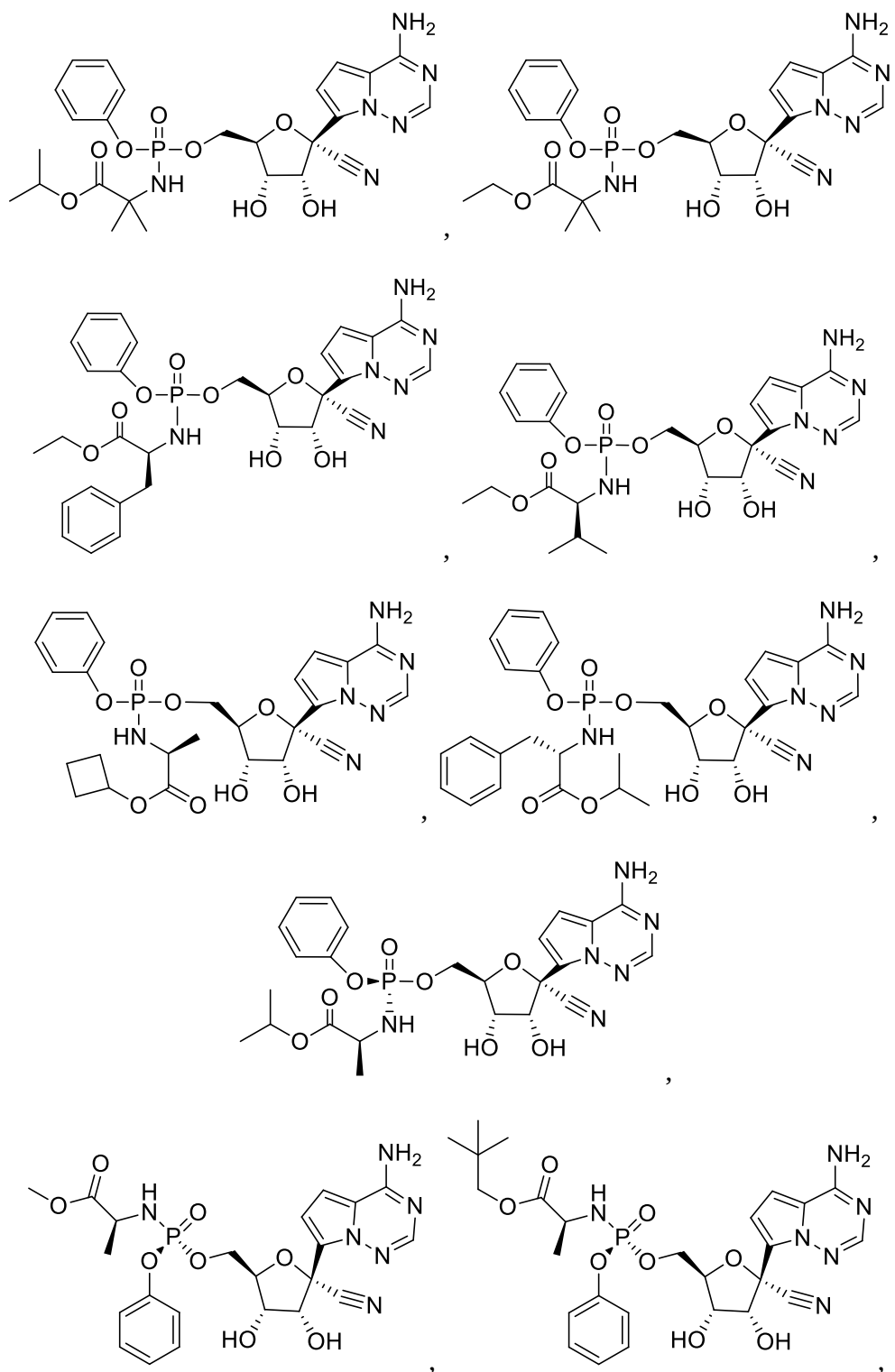
NiV: Nipah virus

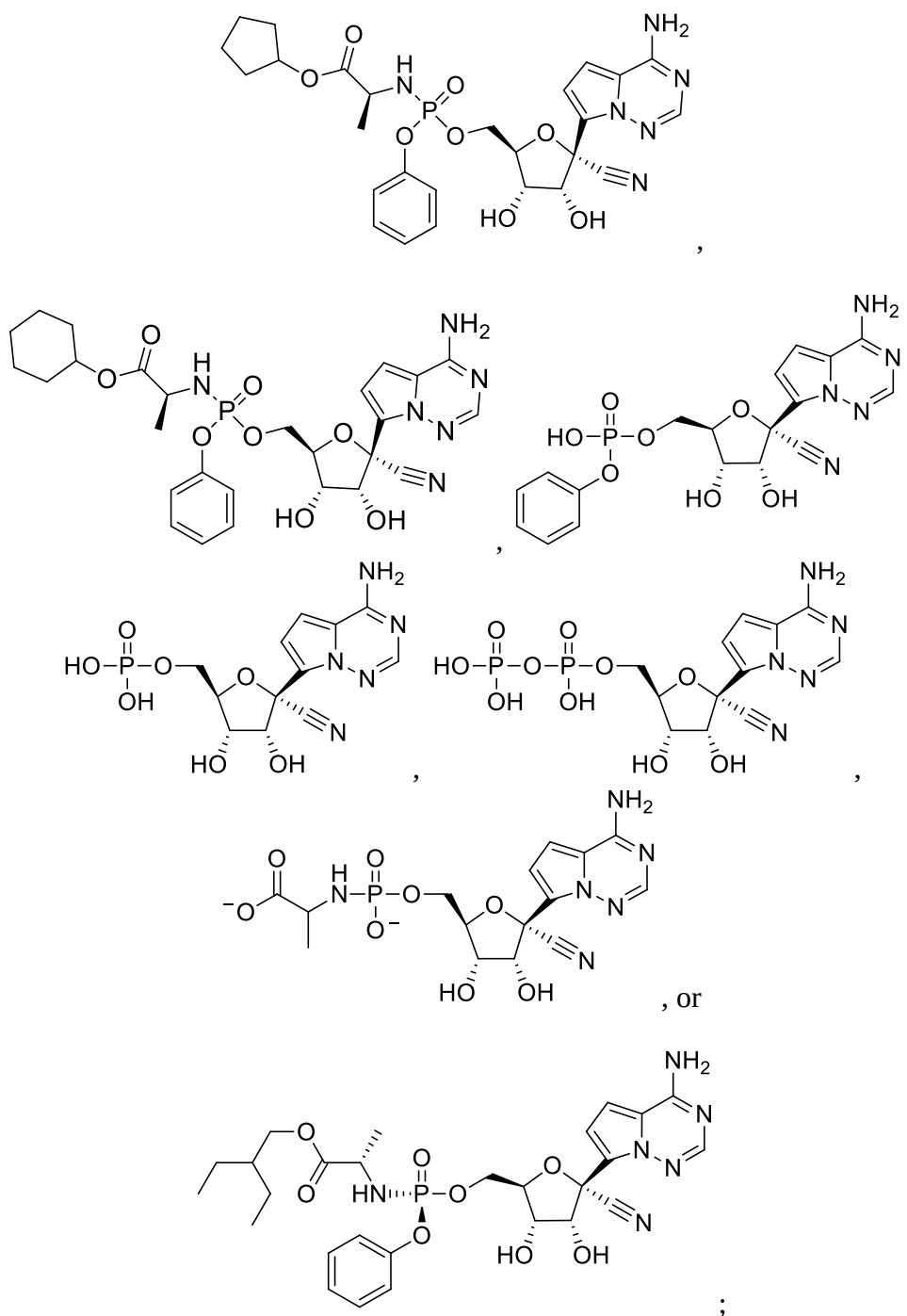
[0281] All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

[0282] The invention has been described with reference to various specific and preferred embodiments and techniques. However, one skilled in the art will understand that many variations and modifications may be made while remaining within the spirit and scope of the invention.

We Claim:

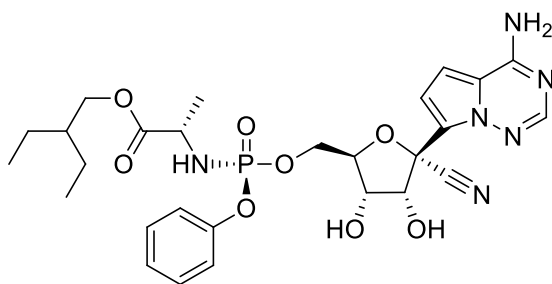
1. A compound:





or a pharmaceutically acceptable salt thereof.

2. The compound as claimed in claim 1, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in claim 1 or claim 2, or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

Dated: 11th Day of April 2017

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(12) **United States Patent**
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(54) **1'-SUBSTITUTED CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT**

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C07H 5/04 (2006.01)

C07H 7/06 (2006.01)

(52) **U.S. Cl.** **514/23**; 536/18.7; 536/29.2; 536/55

(58) **Field of Classification Search** None
See application file for complete search history.

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(57)

ABSTRACT

Provided are pyrrolo[1,2-f][1,2,4]triazinyl, imidazo[1,5-f][1,2,4]triazinyl, imidazo[1,2-f][1,2,4]triazinyl, and [1,2,4]triazolo[4,3-f][1,2,4]triazinyl nucleosides, nucleoside phosphates and prodrugs thereof, wherein the 1' position of the nucleoside sugar is substituted. The compounds, compositions, and methods provided are useful for the treatment of Flaviviridae virus infections, particularly hepatitis C infections.

24 Claims, No Drawings

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1'-SUBSTITUTED CARBA-NUCLEOSIDE
ANALOGS FOR ANTIVIRAL TREATMENT

This application is filed under 35 U.S.C. 111(a) claiming the benefit under 35 U.S.C. 119(e) of U.S. provisional applications 61/047,263 filed Apr. 23, 2008 and 61/139,449 filed Dec. 19, 2008 both of which are herein incorporated by reference in their entireties for all purposes.

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity, more particularly nucleosides active against Flaviviridae infections and most particularly to inhibitors of hepatitis C virus RNA-dependent RNA polymerase.

BACKGROUND OF THE INVENTION

Viruses comprising the Flaviviridae family comprise at least three distinguishable genera including pestiviruses, flaviviruses, and hepaciviruses (Calisher, et al., *J. Gen. Virol.*, 1993, 70, 37-43). While pestiviruses cause many economically important animal diseases such as bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, hog cholera) and border disease of sheep (BDV), their importance in human disease is less well characterized (Moennig, V., et al., *Adv. Vir. Res.* 1992, 48, 53-98). Flaviviruses are responsible for important human diseases such as dengue fever and yellow fever while hepaciviruses cause hepatitis C virus infections in humans. Other important viral infections caused by the Flaviviridae family include West Nile virus (WNV) Japanese encephalitis virus (JEV), tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis, St Louis encephalitis, Omsk hemorrhagic fever virus and Zika virus. Combined, infections from the Flaviviridae virus family cause significant mortality, morbidity and economic losses throughout the world. Therefore, there is a need to develop effective treatments for Flaviviridae virus infections.

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide (Boyer, N. et al. *J. Hepatol.* 32:98-112, 2000) so a significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A. M. and Bacon, B. R., *Scientific American*, October: 80-85, (1999); Gordon, C. P., et al., *J. Med. Chem.* 2005, 48, 1-20; Maradpour, D.; et al., *Nat. Rev. Micro.* 2007, 5(6), 453-463). A number of HCV treatments are reviewed by Bymock et al. in *Antiviral Chemistry & Chemotherapy*, 11:2; 79-95 (2000).

RNA-dependent RNA polymerase (RdRp) is one of the best studied targets for the development of novel HCV therapeutic agents. The NS5B polymerase is a target for inhibitors in early human clinical trials (Sommadosi, J., WO 01/90121 A2, US 2004/0006002 A1). These enzymes have been extensively characterized at the biochemical and structural level, with screening assays for identifying selective inhibitors (De Clercq, E. (2001) *J. Pharmacol. Exp. Ther.* 297:1-10; De Clercq, E. (2001) *J. Clin. Virol.* 22:73-89). Biochemical targets such as NS5B are important in developing HCV therapies since HCV does not replicate in the laboratory and there are difficulties in developing cell-based assays and preclinical animal systems.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), which are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is

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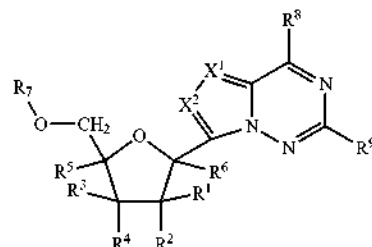
known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* 2002, 62, 507-556) but less than half the patients given this treatment show a persistent benefit. Other patent applications disclosing the use of nucleoside analogs to treat hepatitis C virus include WO 01/32153, WO 01/60315, WO 02/057425, WO 02/057287, WO 02/032920, WO 02/18404, WO 04/046331, WO2008/089105 and WO2008/141079 but additional treatments for HCV infections have not yet become available for patients. Therefore, drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HCV resistance, improved oral bioavailability, greater efficacy, fewer undesirable side effects and extended effective half-life in vivo (De Francesco, R. et al. (2003) *Antiviral Research* 58:1-16) are urgently needed.

Certain ribosides of the nucleobases pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine have been disclosed in *Carbohydrate Research* 2001, 331(1), 77-82; *Nucleosides & Nucleotides* (1996), 15(1-3), 793-807; *Tetrahedron Letters* (1994), 35(30), 5339-42; *Heterocycles* (1992), 34(3), 569-74; *J. Chem. Soc. Perkin Trans. 1* 1985, 3, 621-30; *J. Chem. Soc. Perkin Trans. 1* 1984, 2, 229-38; WO 2000056734; *Organic Letters* (2001), 3(6), 839-842; *J. Chem. Soc. Perkin Trans. 1* 1999, 20, 2929-2936; and *J. Med. Chem.* 1986, 29(11), 2231-5. However, these compounds have not been disclosed as useful for the treatment of HCV. Babu, Y. S., WO2008/089105 and WO2008/141079, discloses ribosides of pyrrolo[1,2-f][1,2,4]triazine nucleobases with antiviral, anti-HCV, and anti-RdRp activity.

SUMMARY OF THE INVENTION

The instant invention provides compounds that inhibit viruses of the Flaviviridae family. The invention also comprises compounds that inhibit viral nucleic acid polymerases, particularly HCV RNA-dependent RNA polymerase (RdRp), rather than cellular nucleic acid polymerases. Therefore, the compounds of the instant invention are useful for treating Flaviviridae infections in humans and other animals.

In one aspect, this invention provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, thereof; wherein:

each R^1 , R^2 , R^3 , R^4 , or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl;

or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

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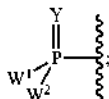
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R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, $(C_1-C_8)alkyl$, $(C_4-C_8)carbocyclalkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$, or $aryl(C_1-C_8)alkyl$ or R^6 and either R^1 or R^2 when taken together are $-O(CO)O-$;

each n is independently 0, 1, or 2;

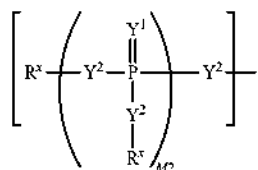
each R^a is independently H , $(C_1-C_8)alkyl$, $(C_1-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $aryl(C_1-C_8)alkyl$, $(C_4-C_8)carbocyclalkyl$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

R^7 is H , $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



each Y or Y^1 is, independently, O , S , NR , $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:



Formula Ia

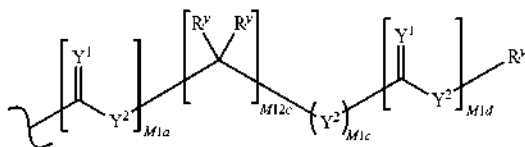
wherein:

each Y^2 is independently a bond, O , CR_2 , NR , $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, $N-NR_2$, S , $S-S$, $S(O)$, or $S(O)_2$;

each Y^3 is independently O , S , or NR ;

M_2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M_{1a} , M_{1c} , and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H , F , Cl , Br , I , OH , R , $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $+N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)N(R)_2$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)N(R)_2$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or

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when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H , $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$, $C_6-C_{20}aryl$, $C_6-C_{20}substituted aryl$, $C_2-C_{20}heterocyclyl$, $C_2-C_{20}substituted heterocyclyl$, $arylalkyl$ or $substituted arylalkyl$;

W^3 is W^4 or W^5 ; W^4 is R , $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

each X^1 or X^2 is independently $C-R^{10}$ or N ;

each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $(C_4-C_8)carbocyclalkyl$, optionally substituted $aryl$, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(C_1-C_8)alkyl$, $aryl(C_1-C_8)alkyl$, OR^{11} or SR^{11} ;

each R^9 or R^{10} is independently H , halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , $-OR^{11}$ or SR^{11} ;

each R^{11} or R^{12} is independently H , $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $(C_4-C_8)carbocyclalkyl$, optionally substituted $aryl$, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(C_1-C_8)alkyl$ or $aryl(C_1-C_8)alkyl$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-O-$, $-S-$ or $-NR^a-$;

wherein each $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$ or $aryl(C_1-C_8)alkyl$ of each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN , N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said $(C_1-C_8)alkyl$ may be optionally replaced with $-O-$, $-S-$ or $-NR^a-$.

In another aspect, the present invention includes compounds of Formula I and pharmaceutically acceptable salts thereof and all racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and amorphous forms thereof.

In another aspect, the present invention provides novel compounds of Formula I with activity against infectious Flaviviridae viruses. Without wishing to be bound by theory, the compounds of the invention may inhibit viral RNA-dependent RNA polymerase and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human virus such as hepatitis C.

In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

In another embodiment, the present application provides for combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of Formula I; or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase I inhibitors,

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cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof; and at least one additional therapeutic agent.

In another embodiment, the present application provides for a method of treating and/or preventing a disease caused by a viral infection wherein the viral infection is caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis virus, St Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhoea virus, Zika virus and Hepatitis C virus, by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof; and at least one additional therapeutic agent.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HCV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination composition or formulation comprising an effective amount of a Formula I compound, and a second compound having anti-HCV properties.

In another aspect, the invention also provides a method of inhibiting HCV, comprising administering to a mammal infected with HCV an amount of a Formula I compound, effective to inhibit the replication of HCV in infected cells in said mammal.

In another aspect, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds of the invention.

In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

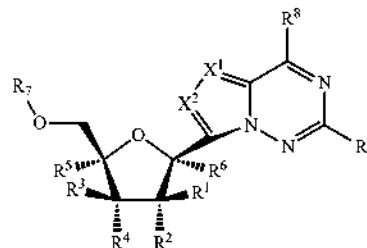
DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention.

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In another aspect, compounds of Formula I are represented by Formula II:

Formula II



or a pharmaceutically acceptable salt, thereof;

wherein:

each R^1, R^2, R^3, R^4 , or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl;

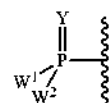
or any two R^1, R^2, R^3, R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl or R^6 and either R^1 or R^2 when taken together are $-O(CO)O-$;

each n is independently 0, 1, or 2;

each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl(C_1-C_8)alkyl, (C_4-C_8) carbocyclylalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

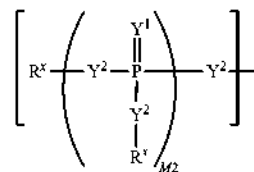
R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



each Y or Y^1 is, independently, O, S, NR, $*N(O)(R)$, $N(OR)$, $*N(O)(OR)$, or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(C(R^v)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:

Formula Ia



wherein:

each Y^2 is independently a bond, O, CR_3 , NR, $*N(O)(R)$, $N(OR)$, $*N(O)(OR)$, $N-NR_2$, S, S-S, $S(O)$, or $S(O)_2$;

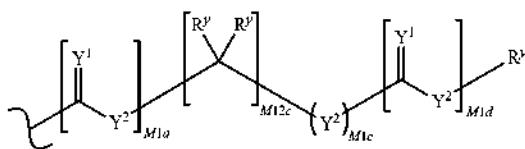
each Y^3 is independently O, S, or NR;

M_2 is 0, 1, or 2;

each R^v is independently R^v or the formula:

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wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R' is independently H, F, Cl, Br, I, OH, R, $-\text{C}(=\text{Y}^1)$, $-\text{C}(=\text{Y}^1)\text{OR}$, $-\text{C}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{N}(\text{R})_2$, $-\text{N}(\text{R})_3$, $-\text{SR}$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})(\text{OR})$, $-\text{S}(\text{O})_2(\text{OR})$, $-\text{OC}(=\text{Y}^1)\text{R}$, $-\text{OC}(=\text{Y}^1)\text{OR}$, $-\text{OC}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{SC}(=\text{Y}^1)\text{R}$, $-\text{SC}(=\text{Y}^1)\text{OR}$, $-\text{SC}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{C}(=\text{Y}^1)\text{R}$, $-\text{N}(\text{R})\text{C}(=\text{Y}^1)\text{OR}$, $-\text{N}(\text{R})\text{C}(=\text{Y}^1)\text{N}(\text{R})_2$, $-\text{SO}_2\text{NR}_2$, $-\text{CN}$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{OR}$, or W^3 ; or when taken together, two R' on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocyclyl, C_2-C_{20} substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W^3 is W^4 or W^5 ; W^4 is R, $-\text{C}(\text{Y}^1)\text{R}'$, $-\text{C}(\text{Y}^1)\text{W}^5$, $-\text{SO}_2\text{R}'$, or $-\text{SO}_2\text{W}^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R' groups;

X^2 is $\text{C}-\text{R}^{10}$ and each X^1 is independently $\text{C}-\text{R}^{10}$ or N; each R^8 is independently halogen, $\text{NR}^{11}\text{R}^{12}$, $\text{N}(\text{R}^{11})\text{OR}^{11}$, $\text{NR}^{11}\text{NR}^{11}\text{R}^{12}$, N_3 , NO , NO_2 , CHO , CN , $-\text{CH}(=\text{NR}^{11})$, $-\text{CH}=\text{NHR}^{11}$, $-\text{CH}=\text{N}(\text{OR}^{11})$, $-\text{CH}(\text{OR}^{11})_2$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{S})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{OR}^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-\text{C}(=\text{O})(\text{C}_1-\text{C}_8)$ alkyl, $-\text{S}(\text{O})_n(\text{C}_1-\text{C}_8)$ alkyl, aryl (C_1-C_8) alkyl, OR^{11} or SR^{11} ;

each R^9 or R^{10} is independently H, halogen, $\text{NR}^{11}\text{R}^{12}$, $\text{N}(\text{R}^{11})\text{OR}^{11}$, $\text{NR}^{11}\text{NR}^{11}\text{R}^{12}$, N_3 , NO , NO_2 , CHO , CN , $-\text{CH}(=\text{NR}^{11})$, $-\text{CH}=\text{NHR}^{11}$, $-\text{CH}=\text{N}(\text{OR}^{11})$, $-\text{CH}(\text{OR}^{11})_2$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{S})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{OR}^{11}$, R^{11} , OR^{11} or SR^{11} ;

each R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-\text{C}(=\text{O})(\text{C}_1-\text{C}_8)$ alkyl, $-\text{S}(\text{O})_n(\text{C}_1-\text{C}_8)$ alkyl or aryl (C_1-C_8) alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^a-$;

wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl of each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN , N_3 , $\text{N}(\text{R}^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^a-$;

In one embodiment of the invention of Formula II, R^1 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^1 is (C_1-C_8) alkyl. In another aspect of this embodiment, R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In a preferred aspect of this embodiment, R^1 is methyl. In another preferred aspect of this embodiment, R^1 is H.

In one embodiment of Formula II, R^2 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN , NO_2 , $\text{S}(\text{O})_n\text{R}^a$, halogen, (C_1-C_8) alkyl, (C_1-C_8) sub-

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stituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, or (C_2-C_8) substituted alkynyl. In another aspect of this embodiment, R^2 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN , SR^a or halogen. In another aspect of this embodiment, R^2 is H, OH, NH_2 , N_3 , CN , or halogen. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In a preferred aspect of this embodiment, R^2 is OH and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^2 is OR^a and R^1 is H. In another preferred aspect of this embodiment, R^2 is OH and R^1 is H. In another preferred aspect of this embodiment, R^2 is F and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^2 is OR^a and R^1 is methyl. In a particularly preferred aspect of this embodiment, R^2 is OH and R^1 is methyl.

In one embodiment of Formula II, R^3 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN , SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In one aspect of this embodiment, R^3 is H or F. In a preferred aspect of this embodiment, R^3 is H. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or halogen and R^1 is H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is H. In another aspect of this embodiment, each R^1 , R^3 and R^5 is H and R^2 is OH.

In one embodiment of Formula II, R^4 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN , SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In a preferred aspect of this embodiment, R^4 is OR^a . In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F, R^3 is H and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a , R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-\text{O}(\text{CO})\text{O}-$, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F, and each R^1 and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a and each R^1 and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-\text{O}(\text{CO})\text{O}-$, and each R^1 and R^3 is H.

In one embodiment of Formula II, R^5 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN , SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or $(\text{C}_2-$

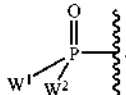
50 In another embodiment of Formula II, R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)R^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl (C_1-C_8) alkyl. In another aspect of this embodiment, R^5 is H, OR^a , $N(R^a)_2$, N_3 , CN , SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^5 is H, N_3 , CN , (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl and R^2 and R^4 are each OR^a . In another aspect of this embodiment, R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this embodiment, R^5 is H, N_3 , CN , methyl, ethenyl

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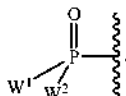
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or ethynyl; R^4 is OR^a and R^3 is H. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^5 is H or N_3 ; R^4 is OR^a ; R^3 is H; and R^2 is OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H and R^2 and R^4 are, independently, OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 are each OH. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 , taken together, are $-O(CO)O-$. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 is H; R^2 and R^4 are independently OR^a and R^5 is N_3 . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H.

In one embodiment of Formula II, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$ or



In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl. In another preferred aspect of this embodiment, R^7 is



In one embodiment of Formula II, X^1 is N or $C-R^{10}$. In another aspect of this embodiment, X^1 is N. In another aspect of this embodiment, X^1 is $C-R^{10}$. In another aspect of this embodiment, X^2 is $C-H$. In another aspect of this embodiment, X^1 is N and X^2 is $C-H$. In another aspect of this embodiment, X^1 is $C-R^{10}$ and X^2 is CH . In another aspect of this embodiment, X^1 is $C-H$ and X^2 is CH . In another aspect of this embodiment, X^1 is CR^{10} and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is CR^{10} ; X^2 is CH ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is CR^{10} ; X^2 is CH ; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN,

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methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is $C-R^{10}$; X^2 is CH ; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; each R^3 and R^5 is H; R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN. In another aspect of this embodiment, X^1 is N and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is N; X^2 is CH ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is N; X^2 is CH ; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is N; X^2 is CH ; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; each R^3 and R^5 is H; R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN.

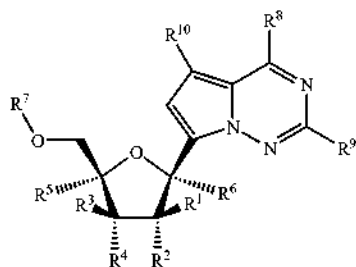
In another embodiment of Formula II, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl(C_1-C_9 alkyl, OR^{11} or SR^{11}). In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 . In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

In another embodiment of Formula II, each R^{10} is, independently, H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} . In another aspect of this embodiment, each R^{10} is H, halogen, CN or optionally substituted heteroaryl.

In another aspect, compounds of Formula I are represented by Formula III:

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Formula III

or a pharmaceutically acceptable salt, thereof;
wherein:

R^1 is H or CH_3 ;

each R^2 , R^3 , R^4 , or R^5 is independently H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_4\text{-C}_8)\text{carbocyclylalkyl}$, $(\text{C}_1\text{-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$, or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$;

or any two R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-\text{O}(\text{CO})\text{O}-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{OR}^{11}$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})(\text{OR}^{11})$, $-\text{S}(\text{O})_2(\text{OR}^{11})$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_4\text{-C}_8)\text{carbocyclylalkyl}$, $(\text{C}_1\text{-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$, or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$ or R^6 and R^2 when taken together are $-\text{O}(\text{CO})\text{O}-$;

wherein each $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$ or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$ of each R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $\text{N}(\text{R}^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said $(\text{C}_1\text{-C}_8)\text{alkyl}$ may be optionally replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^a-$; and

all remaining variables are defined as for Formula I.

In one embodiment of Formula III, R^1 is H.

In one embodiment of Formula III, R^1 is CH_3 .

In one embodiment of Formula III, R^2 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_1\text{-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, or $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$. In another aspect of this embodiment, R^2 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a or halogen. In another aspect of this embodiment, R^2 is H, OH, NH_2 , N_3 , CN, or halogen. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is methyl. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is H. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is methyl. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is H. In a preferred aspect of this embodiment, R^2 is OH and R^1 is methyl. In another preferred aspect of this embodiment, R^2 is OR^a and R^1 is H. In another preferred aspect of this embodiment, R^2 is OH and R^1 is H. In another preferred aspect of this embodiment, R^2 is F. In another preferred aspect of this embodiment, R^2 is OR^a and R^1 is methyl.

In one embodiment of Formula III, R^3 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$. In one aspect of this embodiment, R^3 is H or F. In a preferred aspect of this embodiment, R^3 is H. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or

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halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or halogen and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is H. In another aspect of this embodiment, each R^1 , R^3 and R^5 is H and R^2 is OH.

In one embodiment of Formula III, R^4 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$. In a preferred aspect of this embodiment, R^4 is OR^a . In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F and R^1 is methyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F and R^1 is H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a , R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-\text{O}(\text{CO})\text{O}-$, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-\text{O}(\text{CO})\text{O}-$, R^3 is H and R^1 is H. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a and each R^1 and R^3 is H.

In one embodiment of Formula III, R^5 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$. In another aspect of this embodiment, R^5 is OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{OR}^{11}$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})(\text{OR}^{11})$, $-\text{S}(\text{O})_2(\text{OR}^{11})$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_4\text{-C}_8)\text{carbocyclylalkyl}$, $(\text{C}_1\text{-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$, or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$ and R^5 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$. In another aspect of this embodiment, R^6 is OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{OR}^{11}$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})(\text{OR}^{11})$, $-\text{S}(\text{O})_2(\text{OR}^{11})$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_4\text{-C}_8)\text{carbocyclylalkyl}$, $(\text{C}_1\text{-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$, or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$ and R^6 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$. In another aspect of this embodiment, R^6 is OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, $-\text{C}(=\text{O})\text{R}^{11}$, $-\text{C}(=\text{O})\text{OR}^{11}$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{SR}^{11}$, $-\text{S}(\text{O})\text{R}^{11}$, $-\text{S}(\text{O})_2\text{R}^{11}$, $-\text{S}(\text{O})(\text{OR}^{11})$, $-\text{S}(\text{O})_2(\text{OR}^{11})$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_4\text{-C}_8)\text{carbocyclylalkyl}$, $(\text{C}_1\text{-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$, or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$ and R^6 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$. In another aspect of this embodiment, R^6 is OR^a , N_3 ,

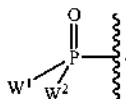
In another embodiment of Formula III, R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl (C_1-C_8) alkyl. In another aspect of this embodiment, R^5 is H, N_3 , CN, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is methyl. In another aspect of this embodiment, R^1 is H and R^2 and R^4 are each OR^a . In another aspect of this embodiment, R^1 is methyl and R^2 and R^4 are each OR^a . In another aspect of this embodiment, R^1 is H; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this embodiment, R^1 is methyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this embodiment, R^5 is H, N_3 , CN, methyl, ethenyl or ethynyl; R^4 is OR^a and R^3 is H. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^5 is H or N_3 ; R^4 is OR^a ; R^3 is H; and R^2 is OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H and R^2 and R^4 are, independently, OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 are each OH. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 , taken together, are $-O(CO)O-$. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 is H; R^2 and R^4 are independently OR^a and R^5 is N_3 . In another aspect of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H; and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is methyl; and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl,

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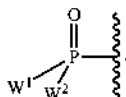
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ethenyl or ethynyl; R^1 is H; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is methyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H.

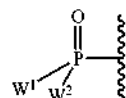
In one embodiment of Formula III, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$ or



In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is H and R^1 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ and R^1 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl and R^1 is H. In another preferred aspect of this embodiment, R^7 is



In another preferred aspect of this embodiment, R^7 is



and R^1 is H.

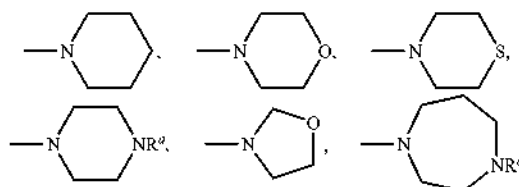
In another embodiment of Formula III, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NHNH^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl (C_1-C_8) alkyl, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is H. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is methyl. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is H. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is methyl. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or

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halogen and R^1 is H. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 . In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is H. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is methyl. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 . In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is H. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is methyl.

In another embodiment of Formula III, each R^{10} is, independently, H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NHNH^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} . In another aspect of this embodiment, R^{10} is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN , methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, each R^{10} is H, halogen, CN or optionally substituted heteroaryl and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN , methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, R^{10} is H and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, each R^3 and R^5 is H; R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN.

In one embodiment of Formulas I-III, R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl (C_1-C_8) alkyl. In another embodiment, R^{11} and R^{12} taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-O-$, $-S-$ or $-NR^a-$. Therefore, by way of example and not limitation, the moiety $-NR^{11}R^{12}$ can be represented by the heterocycles:



and the like.

In another embodiment of Formulas I-III, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl, wherein said (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a . Therefore, by way of example and not limitation, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or

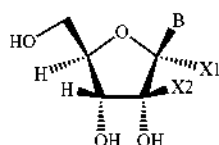
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R¹² could represent moieties such as —CH(NH₂)CH₃, —CH(OH)CH₂CH₃, —CH(NH₂)CH(CH₃)₂, —CH₂CF₃, —(CH₂)₂CH(N₃)CH₃, —(CH₂)₆NH₂ and the like.

In another embodiment of Formula I-III, R², R³, R⁴, R⁵, R⁶, R¹¹ or R¹² is (C₁-C₈)alkyl wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with —O—, —S— or —NR^a—. Therefore, by way of example and not limitation, R², R³, R⁴, R⁵, R⁶, R¹¹ or R¹² could represent moieties such as —CH₂OCH₃, —CH₂OCH₂CH₃, —CH₂OCH(CH₃)₂, —CH₂SCH₃, —(CH₂)₆OCH₃, —(CH₂)₆N(CH₃)₂ and the like.

In still another embodiment, the compounds of Formula I, Formula II, or Formula III are named below in tabular format (Table 6) as compounds of general Formula IV:



Formula IV

wherein X1 and X2, represent substituents attached to the tetrahydrofuranyl ring as defined in Tables 1-2, below; B is a purine defined in Table 4, below; and X3 represents a ring element of the purine base B as described in Table 3, below.

The point of attachment of the core structure ribose is indicated in each of the structures of X1, X2, and B. The point of attachment of the core structure purine is indicated in each of the structures X3. Each structure in Tables 1-4 is represented by an alphanumeric "code". Each structure of a compound of Formula IV can thus be designated in tabular form by combining the "code" representing each structural moiety using the following syntax: X1.X2.X3.B. Thus, for example, X1a.X2c.X3a.B1 represents the following structure:

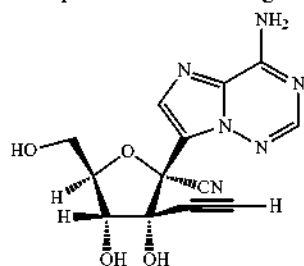


TABLE 1

X1 Structures

Code	Structure
X1a	CN
X1b	CH ₃
X1c	N ₃
X1d	CH ₂ OH

TABLE 2

X2 Structures

Code	Structure
X2a	H
X2b	CH ₃

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TABLE 2-continued

X2 Structures

Code	Structure
X2c	

TABLE 3

X3 Structures

Code	Structure
X3a	—N=
X3b	—CH=
X3c	—CF=

TABLE 4

B Structures

Code	Structure
B1	
B2	
B3	
B4	

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TABLE 6

List of Compounds of Formula IV

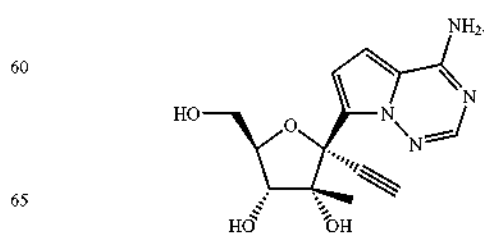
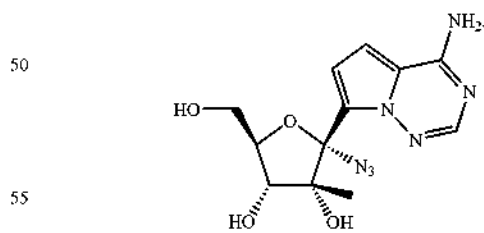
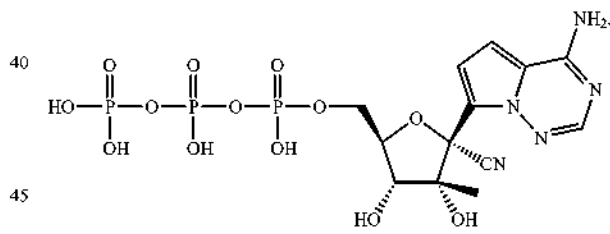
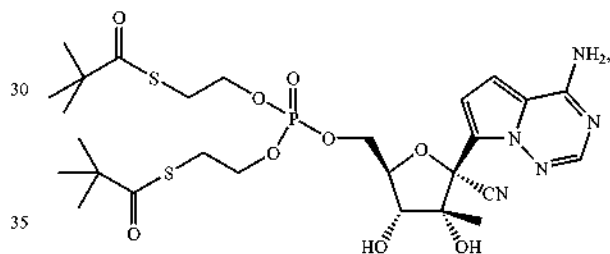
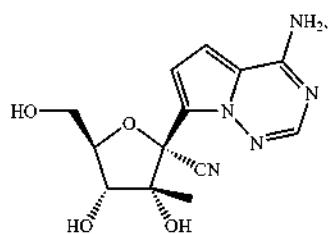
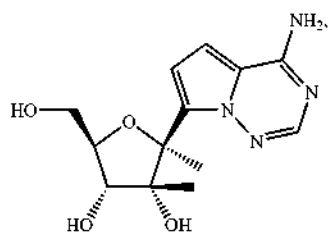
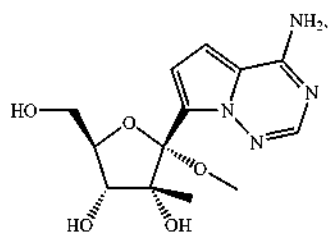
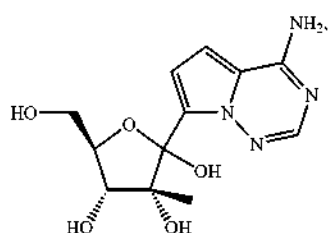
X1a.X2b.X3a.B1, X1a.X2b.X3a.B2, X1a.X2b.X3a.B3, X1a.X2b.X3a.B4, X1a.X2b.X3b.B1, X1a.X2b.X3b.B2, X1a.X2b.X3b.B3, X1a.X2b.X3b.B4, X1a.X2b.X3c.B1, X1a.X2b.X3c.B2, X1a.X2b.X3c.B3, X1a.X2b.X3c.B4, X1a.X2c.X3a.B1, X1a.X2c.X3a.B2, X1a.X2c.X3a.B3, X1a.X2c.X3a.B4, X1a.X2c.X3b.B1, X1a.X2c.X3b.B2, X1a.X2c.X3b.B3, X1a.X2c.X3b.B4, X1a.X2c.X3c.B1, X1a.X2c.X3c.B2, X1a.X2c.X3c.B3, X1a.X2c.X3c.B4, X1b.X2a.X3a.B1, X1b.X2a.X3a.B2, X1b.X2a.X3a.B3, X1b.X2a.X3a.B4, X1b.X2a.X3b.B1, X1b.X2a.X3b.B2, X1b.X2a.X3b.B3, X1b.X2a.X3b.B4, X1b.X2a.X3c.B1, X1b.X2a.X3c.B2, X1b.X2a.X3c.B3, X1b.X2a.X3c.B4, X1b.X2b.X3a.B1, X1b.X2b.X3a.B2, X1b.X2b.X3a.B3, X1b.X2b.X3a.B4, X1b.X2b.X3b.B1, X1b.X2b.X3b.B2, X1b.X2b.X3b.B3, X1b.X2b.X3b.B4, X1b.X2b.X3c.B1, X1b.X2b.X3c.B2, X1b.X2b.X3c.B3, X1b.X2b.X3c.B4, X1b.X2c.X3a.B1, X1b.X2c.X3a.B2, X1b.X2c.X3a.B3, X1b.X2c.X3a.B4, X1b.X2c.X3b.B1, X1b.X2c.X3b.B2, X1b.X2c.X3b.B3, X1b.X2c.X3b.B4, X1b.X2c.X3c.B1, X1b.X2c.X3c.B2, X1b.X2c.X3c.B3, X1b.X2c.X3c.B4, X1c.X2a.X3a.B1, X1c.X2a.X3a.B2, X1c.X2a.X3a.B3, X1c.X2a.X3a.B4, X1c.X2a.X3b.B1, X1c.X2a.X3b.B2, X1c.X2a.X3b.B3, X1c.X2a.X3b.B4, X1c.X2a.X3c.B1, X1c.X2a.X3c.B2, X1c.X2a.X3c.B3, X1c.X2a.X3c.B4, X1c.X2b.X3a.B1, X1c.X2b.X3a.B2, X1c.X2b.X3a.B3, X1c.X2b.X3a.B4, X1c.X2b.X3b.B1, X1c.X2b.X3b.B2, X1c.X2b.X3b.B3, X1c.X2b.X3b.B4, X1c.X2b.X3c.B1, X1c.X2b.X3c.B2, X1c.X2b.X3c.B3, X1c.X2b.X3c.B4, X1c.X2c.X3a.B1, X1c.X2c.X3a.B2, X1c.X2c.X3a.B3, X1c.X2c.X3a.B4, X1c.X2c.X3b.B1, X1c.X2c.X3b.B2, X1c.X2c.X3b.B3, X1c.X2c.X3b.B4, X1c.X2c.X3c.B1, X1c.X2c.X3c.B2, X1c.X2c.X3c.B3, X1c.X2c.X3c.B4, X1d.X2a.X3a.B1, X1d.X2a.X3a.B2, X1d.X2a.X3a.B3, X1d.X2a.X3a.B4, X1d.X2a.X3b.B1, X1d.X2a.X3b.B2, X1d.X2a.X3b.B3, X1d.X2a.X3b.B4, X1d.X2a.X3c.B1, X1d.X2a.X3c.B2, X1d.X2a.X3c.B3, X1d.X2a.X3c.B4.

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In another embodiment, Formulas I-III is a compound
selected from the group consisting of

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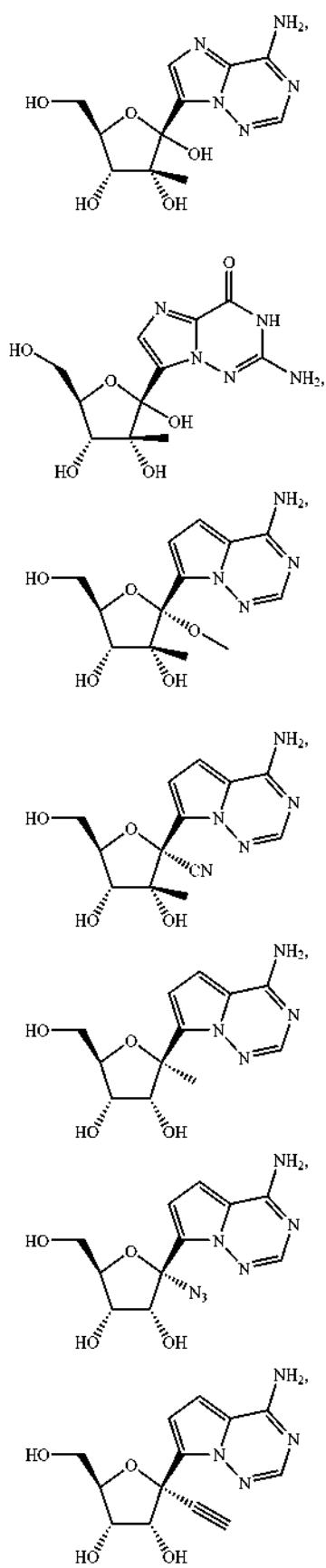


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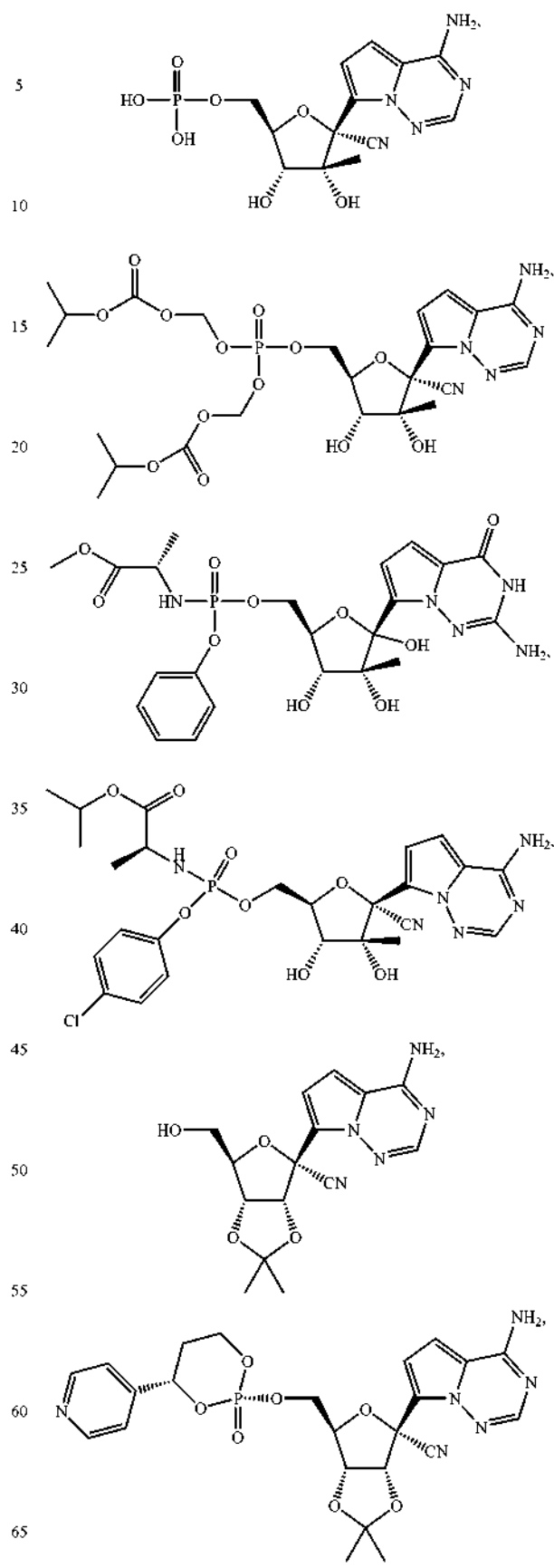
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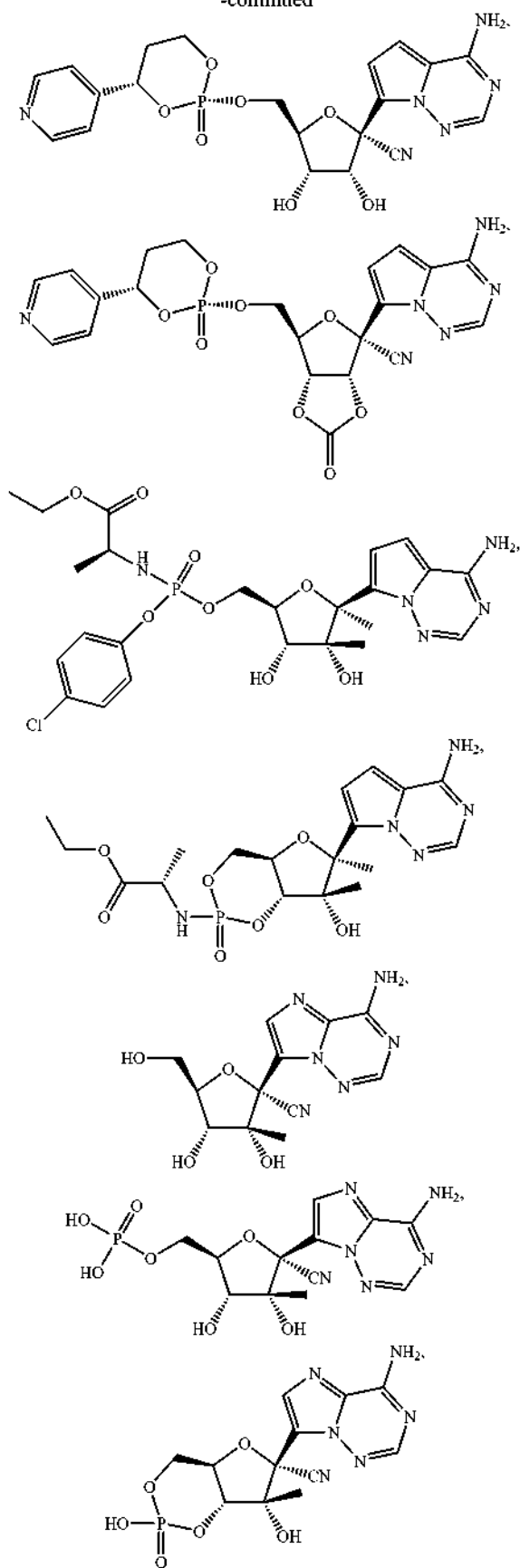
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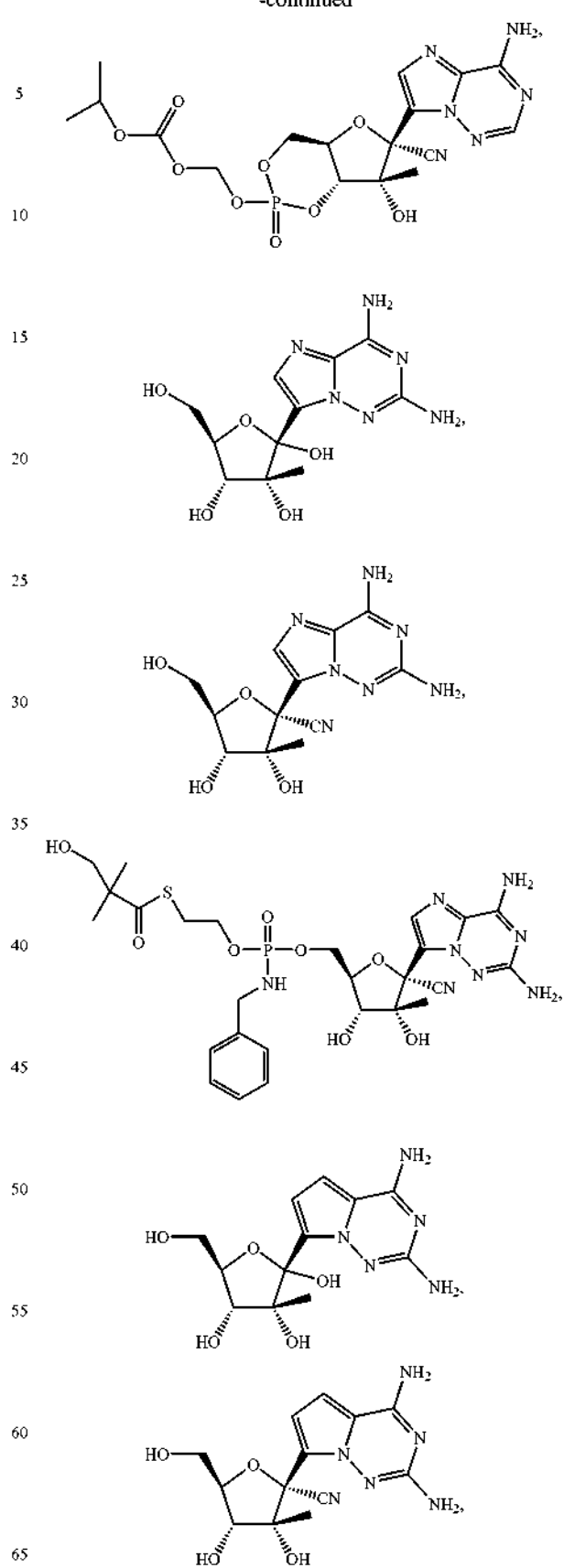
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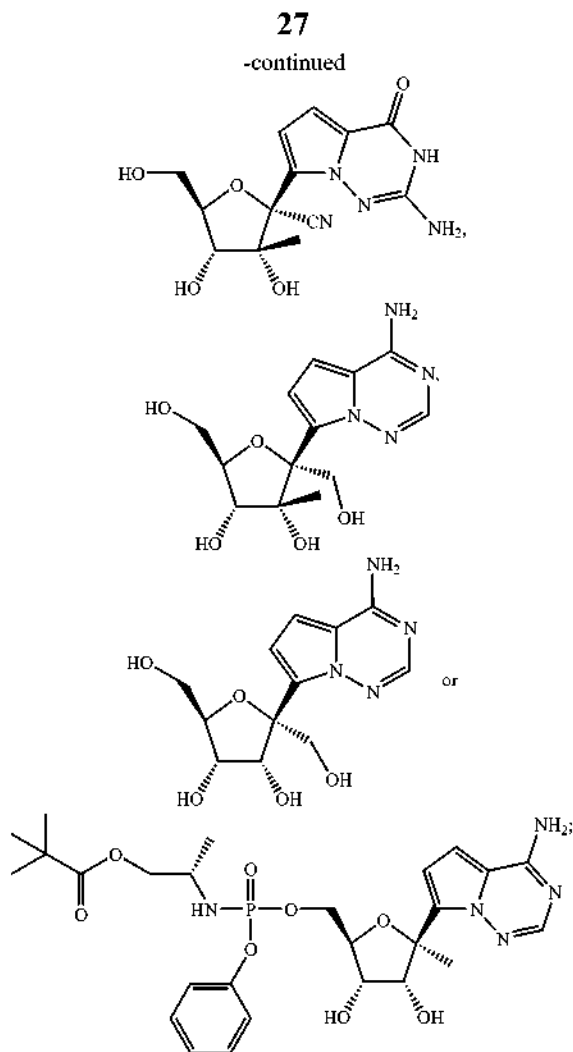
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**26**

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or a pharmaceutically acceptable salt thereof.

Definitions

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

As used herein, "a compound of the invention" or "a compound of Formula I" means a compound of Formula I or a pharmaceutically acceptable salt, thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

"Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkyl), 1 to 8 carbon atoms (i.e., C₁-C₈ alkyl), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, —CH₃), ethyl (Et, —CH₂CH₃), 1-propyl (n-Pr, n-propyl, —CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, —CH(CH₃)CH₂—), 1-butyl (n-Bu, n-butyl, —CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, —CH₂CH(CH₃)CH₂—), 2-butyl (s-Bu, s-butyl, —CH(CH₃)CH₂CH₂—), 2-methyl-2-propyl (t-Bu, t-butyl, —C(CH₃)₃—), 1-pentyl (n-pentyl, —CH₂CH₂CH₂CH₂CH₃), 2-pentyl

(—CH(CH₃)CH₂CH₂CH₃), 3-pentyl (—CH(CH₂CH₃)₂), 2-methyl-2-butyl (—C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (—CH(CH₃)CH(CH₃)CH₂—), 3-methyl-1-butyl (—CH₂CH(CH₃)CH₂CH₃), 2-methyl-1-butyl (—CH₂CH(CH₃)CH₂CH₃), 1-hexyl (—CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (—CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (—CH(CH₂CH₃)CH₂CH₂CH₃), 2-methyl-2-pentyl (—C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (—CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (—CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (—C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (—CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (—C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (—CH(CH₃)C(CH₃)₃), and octyl (—(CH₂)₇CH₃).

"Alkoxy" means a group having the formula —O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (i.e., C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (—O—CH₃ or —OMe), ethoxy (—OCH₂CH₃ or —OEt), t-butoxy (—O—C(CH₃)₃ or —OtBu) and the like.

"Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (i.e., C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (i.e., C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkyl). Examples of suitable haloalkyl groups include, but are not limited to, —CF₃, —CHF₂, —CFH₂, —CH₂CF₃, and the like.

"Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp² double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (i.e., C₂-C₈ alkenyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (—CH=CH₂), allyl (—CH₂CH=CH₂), cyclopentenyl (—C₅H₇), and 5-hexenyl (—CH₂CH₂CH₂CH₂CH=CH₂).

"Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (i.e., C₂-C₈ alkynyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (—C≡CH), propargyl (—CH₂C≡CH), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene (—CH₂—), 1,1-ethyl (—CH(CH₃)—), 1,2-ethyl (—CH₂CH₂—), 1,1-propyl (—CH(CH₂CH₃)—), 1,2-propyl (—CH₂CH(CH₃)—), 1,3-propyl (—CH₂CH₂CH₂—), 1,4-butyl (—CH₂CH₂CH₂CH₂—), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, an alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (—CH=CH—).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene ($-\text{C}\equiv\text{C}-$), propargyl ($-\text{CH}_2\text{C}\equiv\text{C}-$), and 4-pentynyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-$).

"Amino" refers generally to a nitrogen radical which can be considered a derivative of ammonia, having the formula $-\text{N}(\text{X})_2$, where each "X" is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, etc. The hybridization of the nitrogen is approximately sp^3 . Nonlimiting types of amino include $-\text{NH}_2$, $-\text{N}(\text{alkyl})_2$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{carbocyclyl})_2$, $-\text{NH}(\text{carbocyclyl})$, $-\text{N}(\text{heterocyclyl})_2$, $-\text{NH}(\text{heterocyclyl})$, $-\text{N}(\text{aryl})_2$, $-\text{NH}(\text{aryl})$, $-\text{N}(\text{alkyl})(\text{aryl})$, $-\text{N}(\text{alkyl})(\text{heterocyclyl})$, $-\text{N}(\text{carbocyclyl})(\text{heterocyclyl})$, $-\text{N}(\text{aryl})(\text{heterocyclyl})$, $-\text{N}(\text{alkyl})(\text{heteroaryl})$, etc. The term "alkylamino" refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino groups include $-\text{NH}_2$, $-\text{NH}(\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{NH}(\text{phenyl})$, $-\text{N}(\text{phenyl})_2$, $-\text{NH}(\text{benzyl})$, $-\text{N}(\text{benzyl})_2$, etc. Substituted alkylamino refers generally to alkylamino groups, as defined above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes $-\text{NH}(\text{alkylene-C}(\text{O})-\text{OH})$, $-\text{NH}(\text{alkylene-C}(\text{O})-\text{O-alkyl})$, $-\text{N}(\text{alkylene-C}(\text{O})-\text{OH})_2$, $-\text{N}(\text{alkylene-C}(\text{O})-\text{O-alkyl})_2$, etc.

"Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 7 to 20 carbon atoms, e.g., the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 8 to 20 carbon atoms, e.g., the alkenyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 8 to 20 carbon

atoms, e.g., the alkynyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, $-\text{X}$, $-\text{R}^b$, $-\text{O}^-$, $=\text{O}$, $-\text{OR}^b$, $-\text{SR}^b$, $-\text{S}^-$, $-\text{NR}^b_2$, $-\text{N}^+\text{R}^b_3$, $=\text{NR}^b$, $-\text{CX}_3$, $-\text{CN}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{N}=\text{C}=\text{O}$, $-\text{NCS}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$, $-\text{NHC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{NHC}(=\text{O})\text{NR}^b_2$, $-\text{S}(=\text{O})_2-$, $-\text{S}(=\text{O})_2\text{OH}$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^b_2$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{OP}(=\text{O})(\text{OR}^b)_2$, $-\text{P}(=\text{O})(\text{OR}^b)_2$, $-\text{P}(=\text{O})(\text{O}^-)_2$, $-\text{P}(=\text{O})(\text{OH})_2$, $-\text{P}(\text{O})(\text{OR}^b)(\text{O}^-)$, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{X}$, $-\text{C}(\text{S})\text{R}^b$, $-\text{C}(\text{O})\text{OR}^b$, $-\text{C}(\text{O})\text{O}^-$, $-\text{C}(\text{S})\text{OR}^b$, $-\text{C}(\text{O})\text{SR}^b$, $-\text{C}(\text{S})\text{SR}^b$, $-\text{C}(\text{O})\text{NR}^b_2$, $-\text{C}(\text{S})\text{NR}^b_2$, $-\text{C}(=\text{NR}^b)\text{NR}^b_2$, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

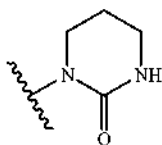
One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-III should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I-III which have such stability are contemplated as falling within the scope of the present invention.

"Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., $-\text{OCH}_3$, etc.), an amine (e.g., $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, etc.), or a thioalkyl group (e.g., $-\text{SCH}_3$). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$, etc.), an alkyl amine (e.g., $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, etc.) or a thioalkyl ether (e.g., $-\text{CH}_2-\text{S}-\text{CH}_3$). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., $-\text{CH}_2\text{CH}_2-\text{OH}$), an aminoalkyl group (e.g., $-\text{CH}_2\text{NH}_2$), or an alkyl thiol group (e.g., $-\text{CH}_2\text{CH}_2-\text{SH}$). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C_1 - C_6 heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

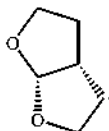
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"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; *Principles of Modern Heterocyclic Chemistry* (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; *The Chemistry of Heterocyclic Compounds, A Series of Monographs* (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (e.g., 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (e.g., O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings, partially unsaturated rings, and aromatic rings (i.e., heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidinonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indoliziny, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinoliziny, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an

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aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (i.e., a heterocyclyl-alkylene-moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl- CH_2 -, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in *Principles of Modern Heterocyclic Chemistry*. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkyl group comprises 3 to 20 carbon atoms, e.g., the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidinylmethyl, pyrazinylmethyl, etc.

"Heterocyclylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^2 carbon atom, but also a sp^3 carbon atom, is replaced with a heterocyclyl radical (i.e., a heterocyclyl-alkenylene-moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in *Principles of Modern Heterocyclic Chemistry*, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkenyl group comprises 4 to 20 carbon atoms, e.g., the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

"Heterocyclylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (i.e., a heterocyclyl-alkynylene-moiety). The heterocyclyl portion of the heterocyclyl alkynyl group includes any of the heterocyclyl

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groups described herein, including those described in *Principles of Modern Heterocyclic Chemistry*, and the alkynyl portion of the heterocyclyl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclyl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkynyl group comprises 4 to 20 carbon atoms, e.g., the alkynyl portion of the heterocyclyl alkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

"Heteroaryl" refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those aromatic rings listed in the definition of "heterocyclyl", including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

"Carbocycle" or "carbocyclyl" refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 7 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4.5], [5.5], [5.6] or [6.6] system, or 9 or 10 ring atoms arranged as a bicyclo [5.6] or [6.6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclic carbocycles includes naphthyl, tetrahydronaphthalene, and decaline.

"Carbocyclalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein. Typical, but non-limiting, examples of carbocyclalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

"Arylheteroalkyl" refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

"Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-purinyl, -CH₂-furanyl, -CH₂-thienyl, -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl, -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-

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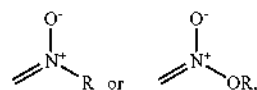
isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-purinyl, -CH(CH₃)-furanyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranyl, -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl, -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl, -CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-pyrazyl, etc.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula I-III (e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by substituents such as those listed under the definition of "substituted".

The term "optionally replaced" in reference to a particular moiety of the compound of Formula I-III (e.g., the carbon atoms of said (C₁-C₈)alkyl may be optionally replaced by -O-, -S-, or -NR²-) means that one or more of the methylene groups of the (C₁-C₈)alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., -O-, -S-, or -NR²-).

The term "non-terminal carbon atom(s)" in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl moiety -CH₂(C*)H₂(C*)H₂CH₃ or alkylene moiety -CH₂(C*)H₂(C*)H₂CH₂- the C* atoms would be considered to be the non-terminal carbon atoms.

Certain Y and Y¹ alternatives are nitrogen oxides such as *N(O)(R) or *N(O)(OR). These nitrogen oxides, as shown here attached to a carbon atom, can also be represented by charge separated groups such as



respectively, and are intended to be equivalent to the aforementioned representations for the purposes of describing this invention.

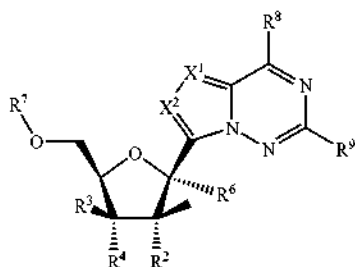
"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms. Linkers include repeating units of alkyloxy (e.g. polyethyleneoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, JeffamineTM); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The terms such as "oxygen-linked", "nitrogen-linked", "carbon-linked", "sulfur-linked", or "phosphorous-linked" mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, a nitrogen-linked amino acid would be bonded through a nitrogen atom of the amino acid rather than through an oxygen or carbon atom of the amino acid.

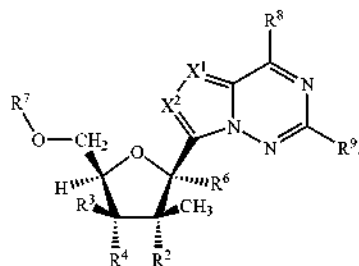
Unless otherwise specified, the carbon atoms of the compounds of Formula I-III are intended to have a valence of four. In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen. For example,

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has the same meaning as



"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991). Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties in vitro and in vivo, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug in vivo. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency in vivo than the parental drug. Protecting groups are removed either in vitro, in the instance of chemical intermediates, or in vivo, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans,

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"Design and Application of Prodrugs" in *Textbook of Drug Design and Development* (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{30}$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^{30}$ where R^{30} is C_1 - C_6 alkyl, C_1 - C_6 substituted alkyl, C_6 - C_{20} aryl or C_6 - C_{20} substituted aryl. The acyloxyalkyl ester was used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also U.S. Pat. Nos. 4,816,570, 4,968,788, 5,663,159 and 5,792,756. In certain compounds of the invention, a prodrug moiety is part of a phosphate group. The acyloxyalkyl ester may be used to deliver phosphoric acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

The phosphate group may be a phosphate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to those comprising a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphoramidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the ortho- or para-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C—O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans.* 12345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.* 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phos-

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phonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, U.S. Pat. No. 6,312,662).

It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I, Formula II, or Formula III and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

A compound of Formula I-III and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I-III and their pharmaceutically acceptable salts.

A compound of Formula I-III and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula I-III and their pharmaceutically acceptable salts.

Selected substituents comprising the compounds of Formula I-III are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R. R can be W^3 . W^3 can be W^4 and W^4 can be R or comprise substituents comprising R^y . One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

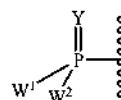
By way of example and not limitation, W^3 and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each recursive substituent can independently occur 12 or fewer times in a given embodiment. Even more typically, each recursive substituent can independently occur 3 or fewer times in a given embodiment. For example, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

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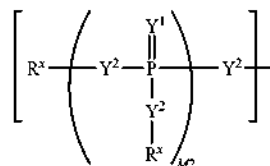
Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

The compounds of the Formula I-III may comprise a phosphate group as R^7 , which may be a prodrug moiety



wherein each Y or Y^1 is, independently, O, S, NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$; W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of Formula Ia:



wherein:

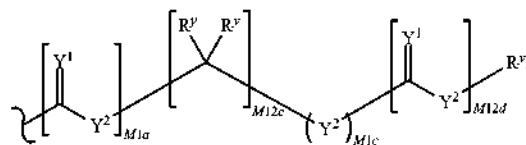
each Y^2 is independently a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

each Y^3 is independently O, S, or NR;

M_2 is 0, 1 or 2;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)$, R , $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)N(R)_2$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)N(R)_2$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, or $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, a protecting group or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R^x is independently R^y , a protecting group, or the formula:



wherein:

M_{1a} , M_{1c} , and M_{1d} are independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R is H, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20}

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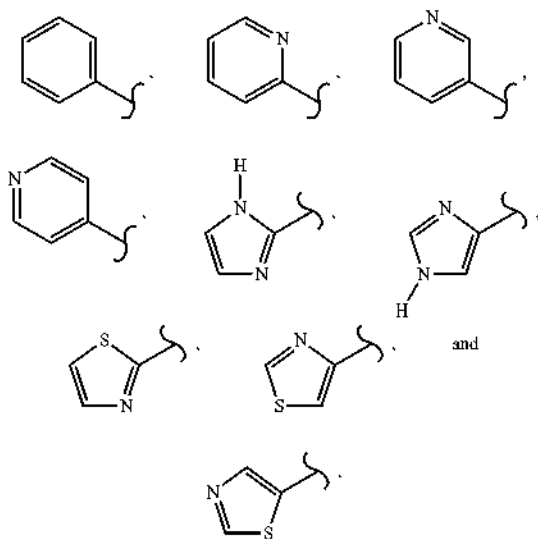
substituted aryl, C₂-C₂₀ heterocycle, C₂-C₂₀ substituted heterocyclyl, arylalkyl, substituted arylalkyl or a protecting group;

W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^1)R^1$, $-C(Y^1)W^5$, $-SO_2R^1$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^1 groups.

W⁵ carbocycles and W⁵ heterocycles may be independently substituted with 0 to 3 R^p groups. W⁵ may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W⁵ may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W⁵ rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

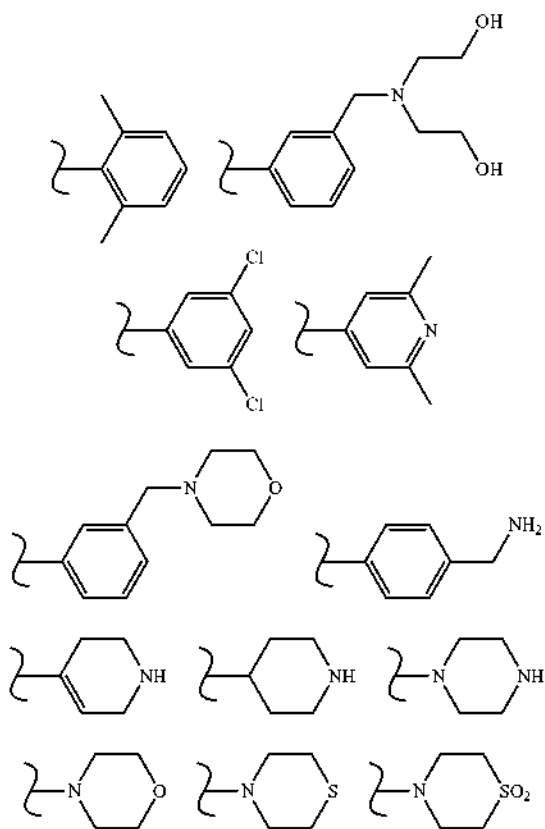
A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

W⁵ heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W⁵ also includes, but is not limited to, examples such as:

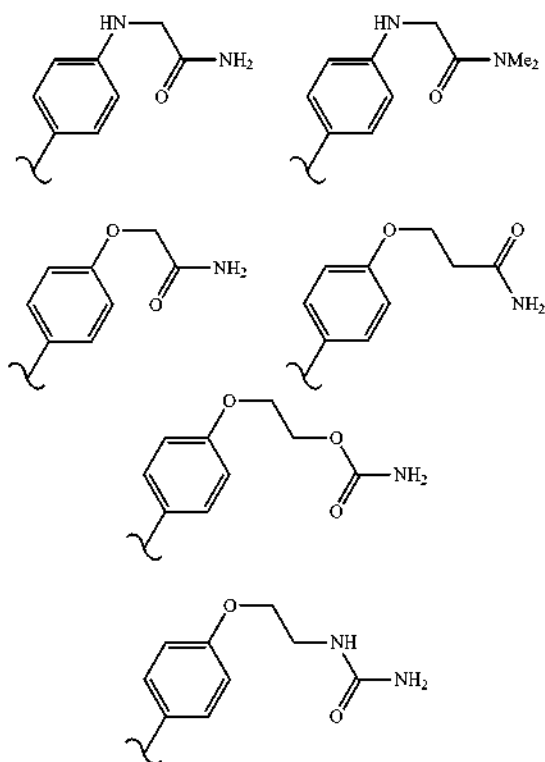


W⁵ carbocycles and heterocycles may be independently substituted with 0 to 3 R groups, as defined above. For example, substituted W⁵ carbocycles include:

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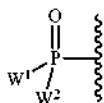
Examples of substituted phenyl carbocycles include:



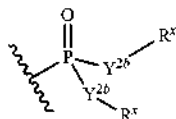
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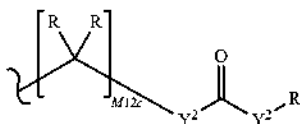
Embodiments of



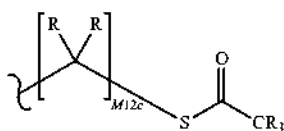
of Formula I-III compounds include substructures such as:



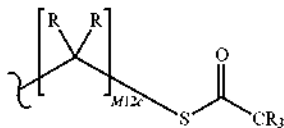
wherein each Y^{2b} is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



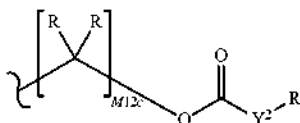
wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S. In another preferred aspect of this embodiment, one $Y^{2b}-R^x$ is $NH(R)$ and the other $Y^{2b}-R^x$ is $O-R^x$ wherein R^x is:



wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



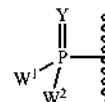
wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



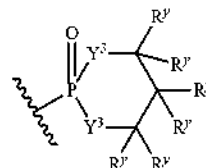
wherein M12c is 1 and Y^2 is a bond, O, or CR_2 .

42

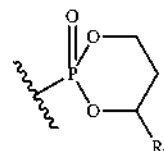
Other embodiments of



of Formulas I-III compounds include substructures such as:

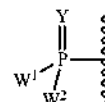


wherein each Y^3 is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^3 is O. In another preferred aspect of this embodiment, the substructure is:

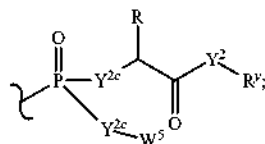


wherein R^y is W^5 as defined herein.

Another embodiment of

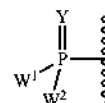


of Formula I-III includes the substructures:



wherein each Y^{2c} is, independently, O, N(R^y) or S.

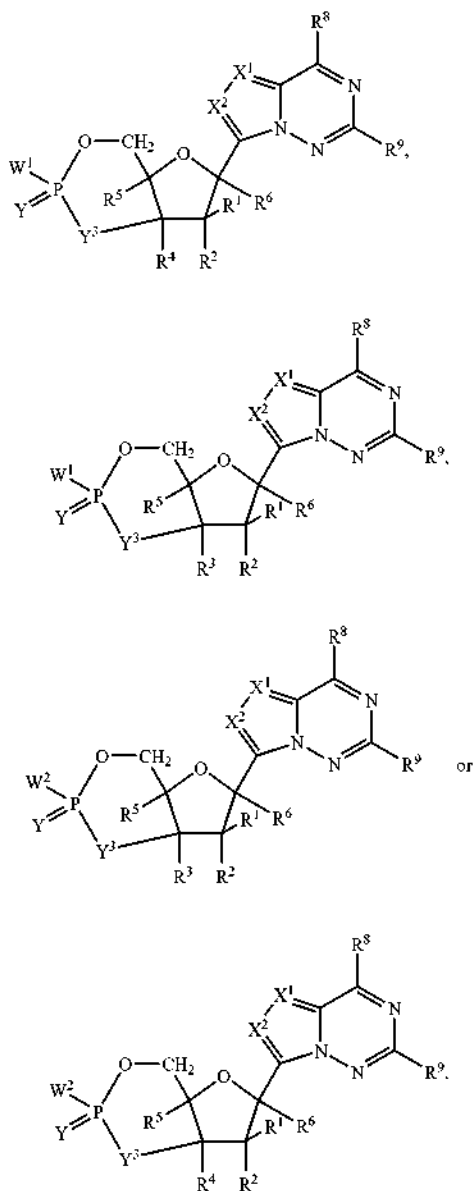
Another embodiment of



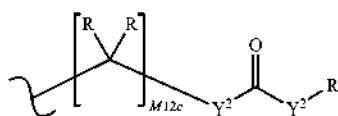
of Formula I-III compounds includes the substructures wherein one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia. Such an embodiment is represented by a compound of Formula Ib selected from:

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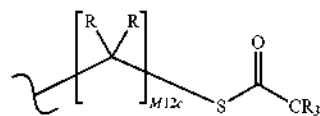
In a preferred aspect of the embodiment of Formula Ib, each Y and Y³ is O. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}—R^x; each Y, Y³ and Y^{2b} is O and R^x is:



wherein M12c is 1, 2 or 3 and each Y² is independently a bond, O, CR₂, or S. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}—R^x; each Y, Y³ and Y^{2b} is O and R^x is:

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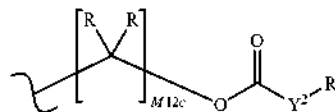
Formula Ib



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wherein M12c is 2. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}—R^x; each Y, Y³ and Y^{2b} is O and R^x is:

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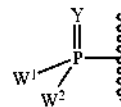
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wherein M12c is 1 and Y² is a bond, O, or CR₂.

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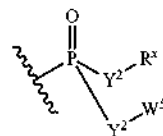
Another embodiment of

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of Formula I-III compounds includes a substructure:

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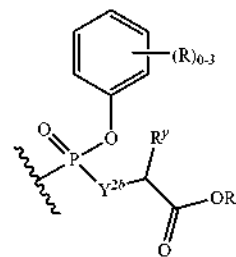


35

wherein W⁵ is a carbocycle such as phenyl or substituted phenyl. In another aspect of this embodiment, the substructure is:

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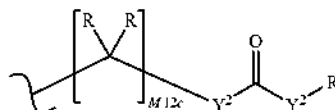


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wherein Y^{2b} is O or N(R) and the phenyl carbocycle is substituted with 0 to 3 R groups. In another aspect of this embodiment of the substructure, R^x is:

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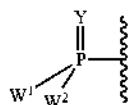
wherein M12c is 1, 2 or 3 and each Y² is independently a bond, O, CR₂, or S.

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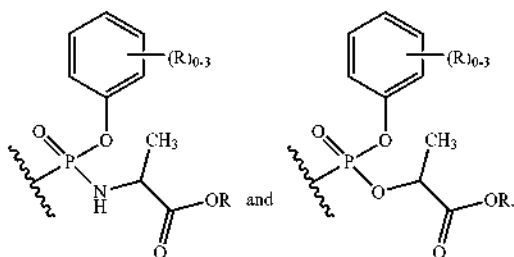
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Another embodiment of

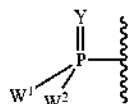


of Formula I-III includes substructures:

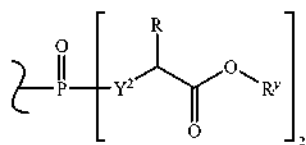


The chiral carbon of the amino acid and lactate moieties may be either the R or S configuration or the racemic mixture.

Another embodiment of



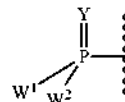
of Formula I-III is substructure



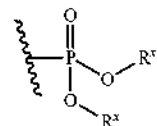
wherein each Y^2 is, independently, $-\text{O}-$ or $-\text{NH}-$. In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl. In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; and R is CH_3 . In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; R is CH_3 ; and each Y^2 is $-\text{NH}-$. In a preferred aspect of this embodiment, W^1 and W^2 are, independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another preferred aspect of this embodiment, W^1 and W^2 are, independently, naturally-occurring 2-hydroxy carboxylic acids or naturally-occurring 2-hydroxy carboxylic acid esters wherein the acid or ester is linked to P through the 2-hydroxy group.

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Another embodiment of

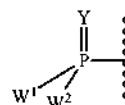


of Formula I, Formula II, or Formula III is substructure:

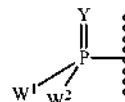


In one preferred aspect of this embodiment, each R^x is, independently, (C_1-C_8) alkyl. In another preferred aspect of this embodiment, each R^x is, independently, C_6-C_{20} aryl or C_6-C_{20} substituted aryl.

Another embodiment of



of Formulas I-III is substructure



wherein W^1 and W^2 are independently selected from one of the formulas in Tables 20.1-20.37 and Table 30.1 below. The variables used in Tables 20.1-20.37 (e.g., W^{23} , R^{21} , etc.) pertain only to Tables 20.1-20.37, unless otherwise indicated.

The variables used in Tables 20.1 to 20.37 have the following definitions:

each R^{21} is independently H or (C_1-C_8) alkyl;
each R^{22} is independently H, R^{21} , R^{23} or R^{24} wherein each R^{24} is independently substituted with 0 to 3 R^{23} ;
each R^{25} is independently R^{23a} , R^{23b} , R^{23c} or R^{23d} , provided that when R^{25} is bound to a heteroatom, then R^{23} is R^{23c} or R^{23d} ;

each R^{23a} is independently F, Cl, Br, I, $-\text{CN}$, N_3 or $-\text{NO}_2$;
each R^{23b} is independently Y^{21} ;

each R^{23c} is independently $-\text{R}^{2x}$, $-\text{N}(\text{R}^{2y})(\text{R}^{2y})$, $-\text{SR}^{2x}$, $-\text{S}(\text{O})\text{R}^{2x}$, $-\text{S}(\text{O})_2\text{R}^{2x}$, $-\text{S}(\text{O})(\text{OR}^{2y})$, $-\text{S}(\text{O})_2(\text{OR}^{2y})$, $-\text{OC}(=\text{Y}^{21})\text{R}^{2x}$, $-\text{OC}(=\text{Y}^{21})\text{OR}^{2x}$, $-\text{OC}(=\text{Y}^{21})(\text{N}(\text{R}^{2x})(\text{R}^{2y}))$, $-\text{SC}(=\text{Y}^{21})\text{R}^{2x}$, $-\text{SC}(=\text{Y}^{21})\text{OR}^{2x}$, $-\text{SC}(=\text{Y}^{21})(\text{N}(\text{R}^{2x})(\text{R}^{2y}))$, $-\text{N}(\text{R}^{2x})\text{C}(=\text{Y}^{21})\text{R}^{2x}$, $-\text{N}(\text{R}^{2x})\text{C}(=\text{Y}^{21})\text{OR}^{2x}$, or $-\text{N}(\text{R}^{2x})\text{C}(=\text{Y}^{21})(\text{N}(\text{R}^{2y})(\text{R}^{2y}))$;

each R^{23d} is independently $-\text{C}(=\text{Y}^{21})\text{R}^{2x}$, $-\text{C}(=\text{Y}^{21})\text{OR}^{2x}$ or $-\text{C}(=\text{Y}^{21})(\text{N}(\text{R}^{2x})(\text{R}^{2y}))$;

each R^{2y} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl, heteroaryl; or two R^{2y} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^{21}-$; and wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^{21}-$;

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each R^{24} is independently (C_1-C_8) alkyl, (C_2-C_8) alkenyl, or (C_2-C_8) alkynyl;

each R^{25} is independently R^{24} wherein each R^{24} is substituted with 0 to 3 R^{23} groups;

each R^{25a} is independently (C_1-C_8) alkylene, (C_2-C_8) alkenylene, or (C_2-C_8) alkynylene any one of which said (C_1-C_8) alkylene, (C_2-C_8) alkenylene, or (C_2-C_8) alkynylene is substituted with 0-3 R^{23} groups;

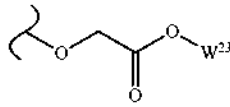
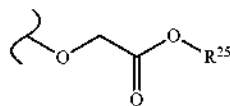
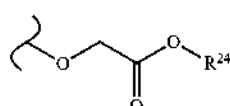
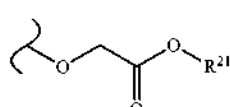
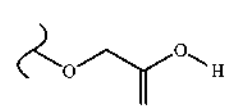
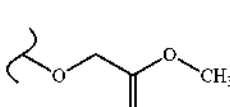
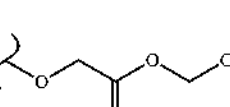
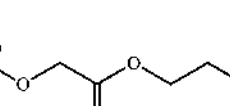
each W^{23} is independently W^{24} or W^{25} ;

each W^{24} is independently R^{25} , $-C(=Y^{21})R^{25}$, $-C(=Y^{21})W^{25}$, $-SO_2R^{25}$, or $-SO_2W^{25}$;

each W^{25} is independently carbocycle or heterocycle wherein W^{25} is independently substituted with 0 to 3 R^{22} groups; and

each Y^{21} is independently O or S.

TABLE 20.1

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TABLE 20.2

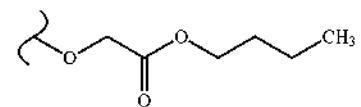
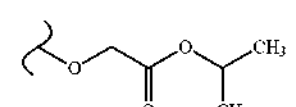
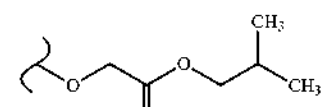
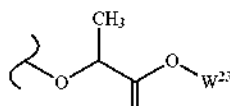
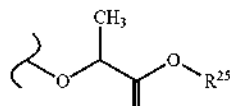
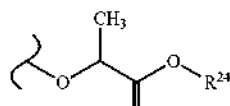
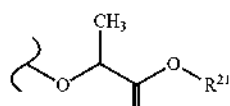
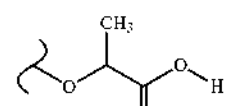
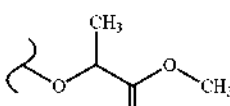
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TABLE 20.3

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TABLE 20.3-continued

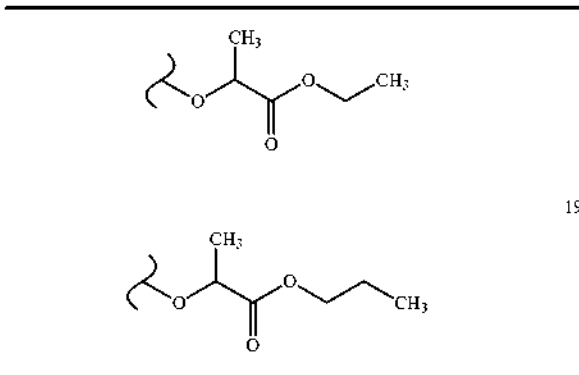


TABLE 20.4

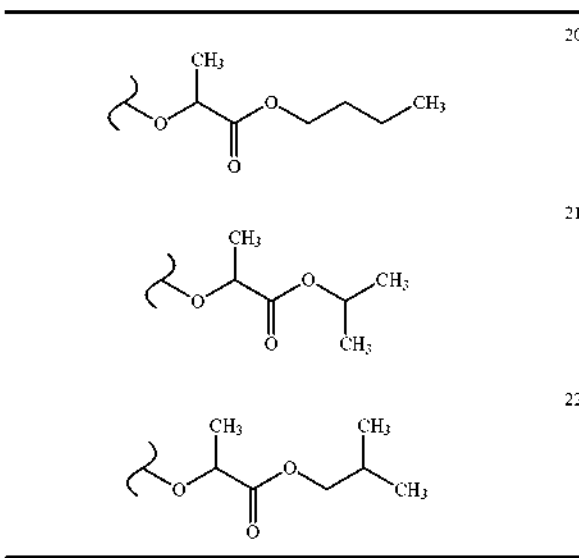
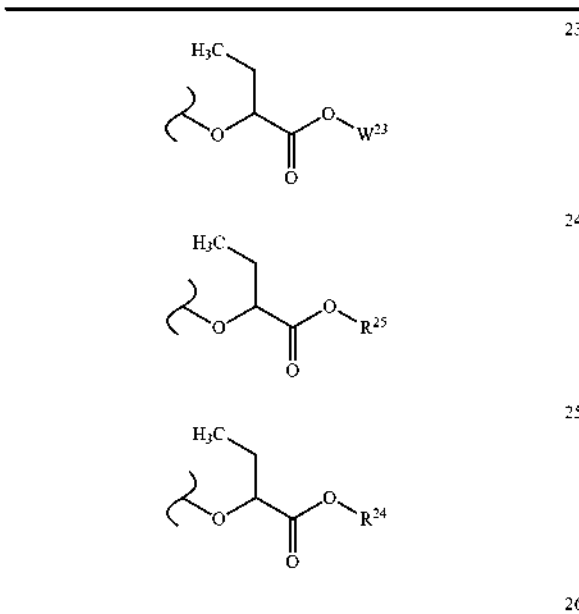


TABLE 20.5



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TABLE 20.5-continued

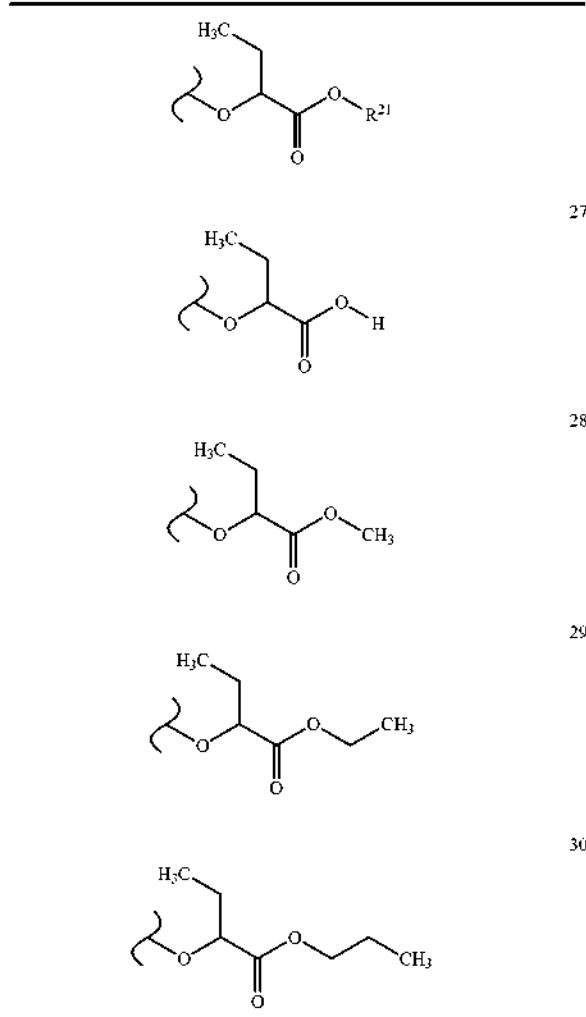
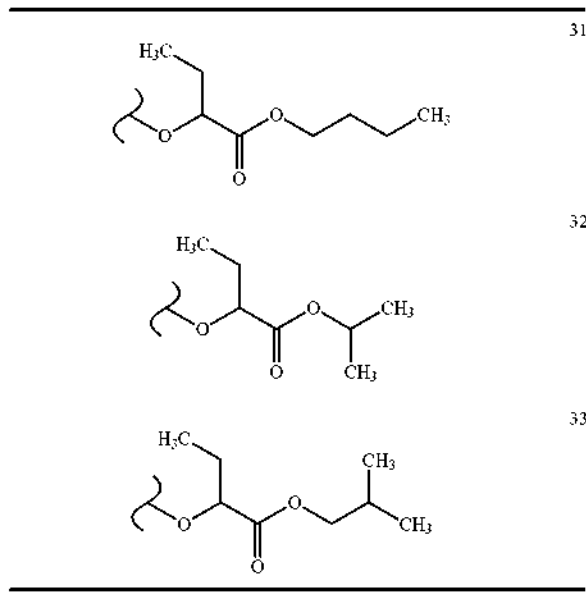


TABLE 20.6



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TABLE 20.7

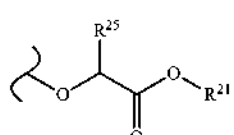
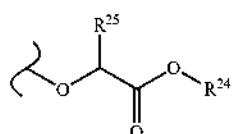
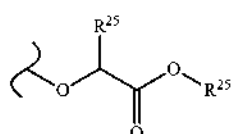
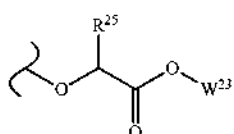
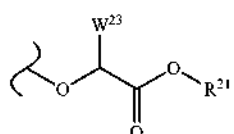
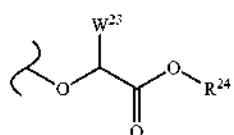
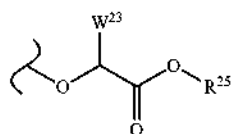
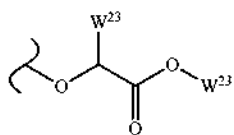


TABLE 20.8

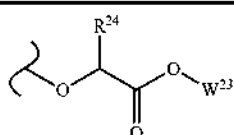
**52**

TABLE 20.8-continued

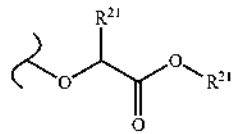
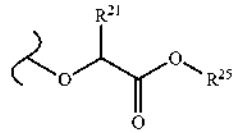
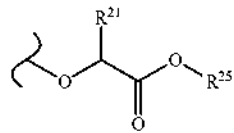
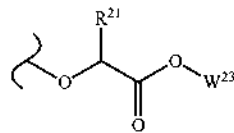
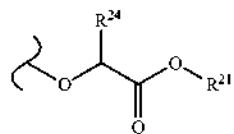
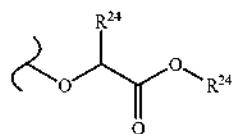
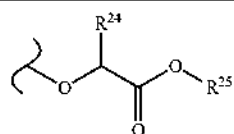
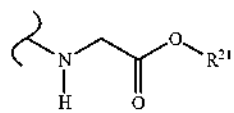
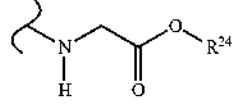
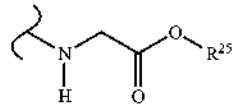
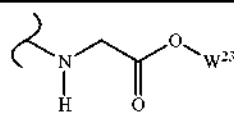


TABLE 20.9



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TABLE 20.9-continued

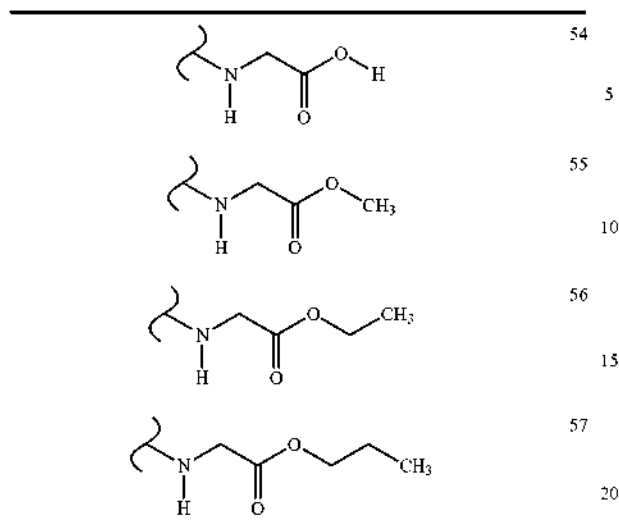


TABLE 20.10

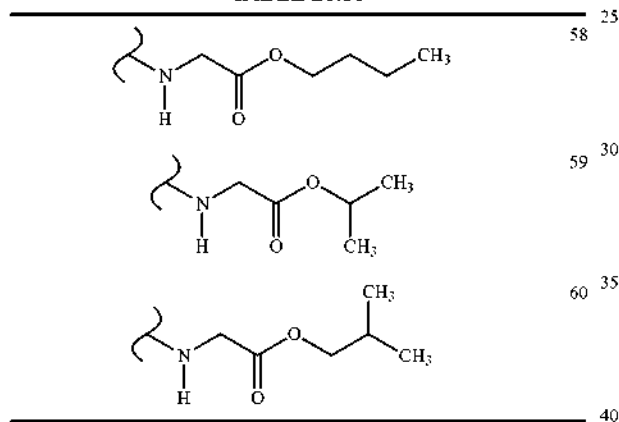
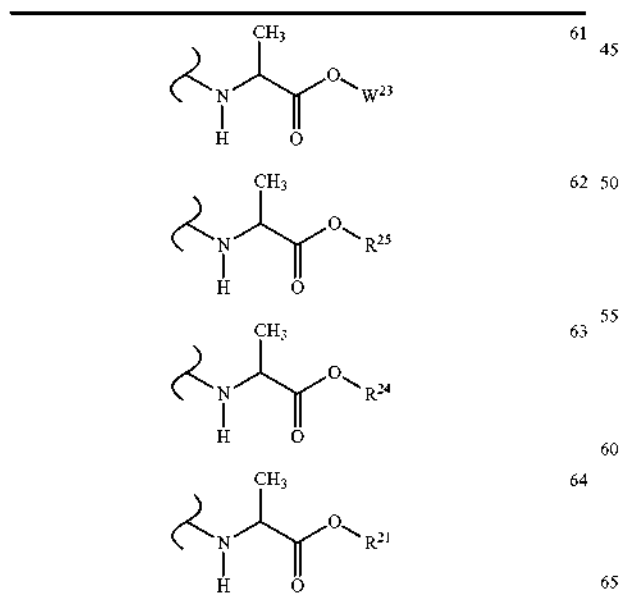


TABLE 20.11



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TABLE 20.11-continued

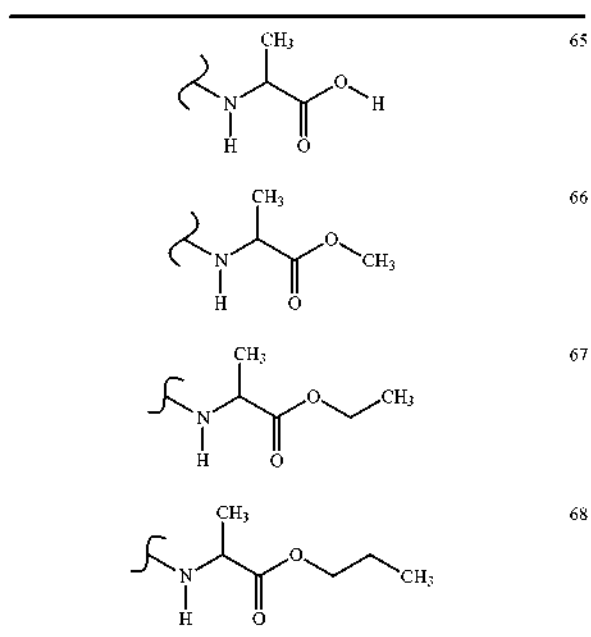


TABLE 20.12

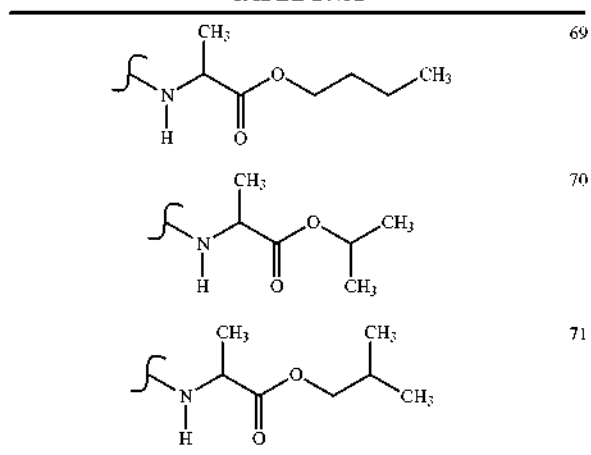
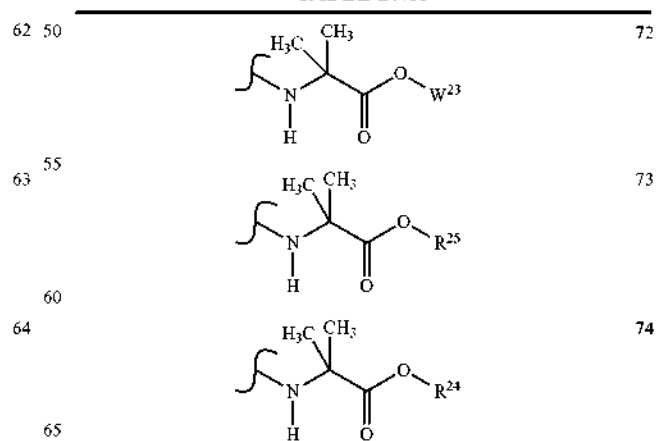


TABLE 20.13



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TABLE 20.13-continued

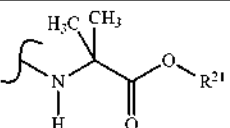
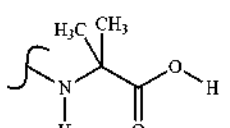
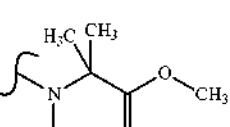
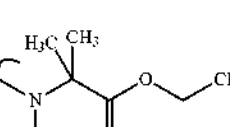
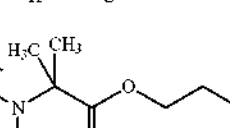
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TABLE 20.14

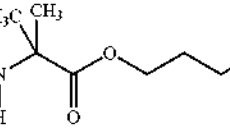
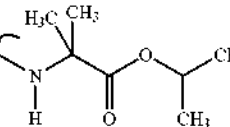
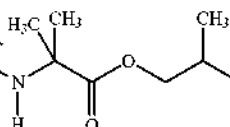
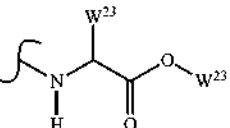
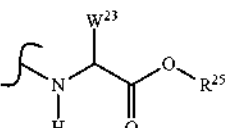
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TABLE 20.15

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TABLE 20.15-continued

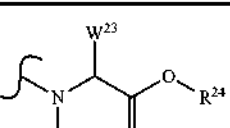
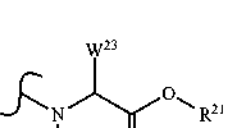
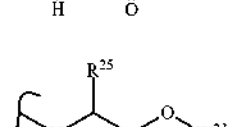
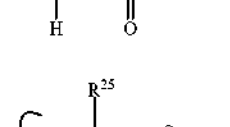
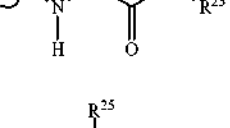
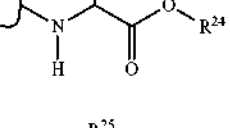
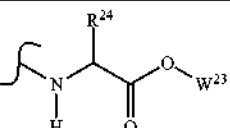
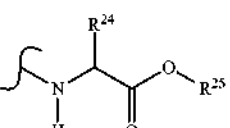
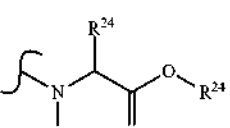
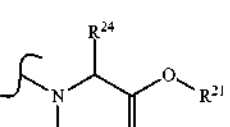
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TABLE 20.16

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TABLE 20.16-continued

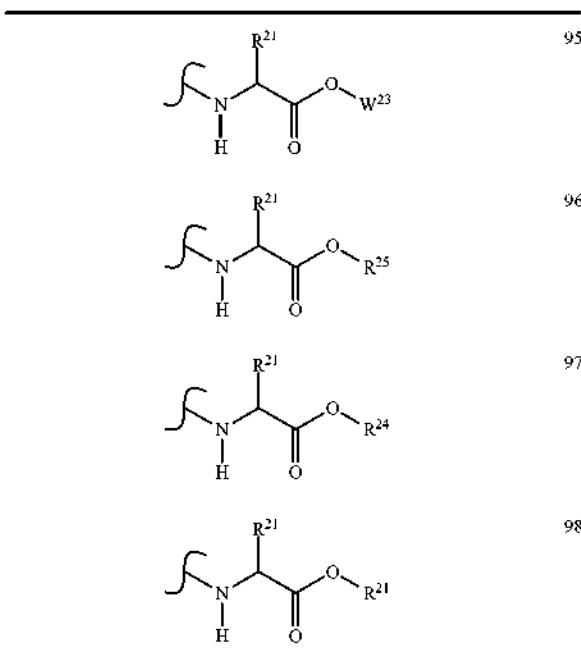
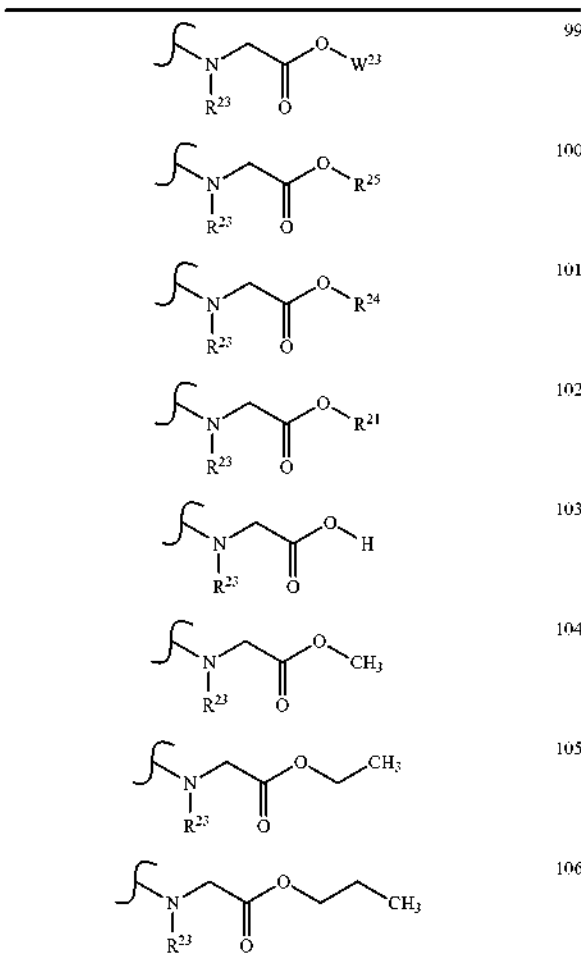


TABLE 20.17



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TABLE 20.18

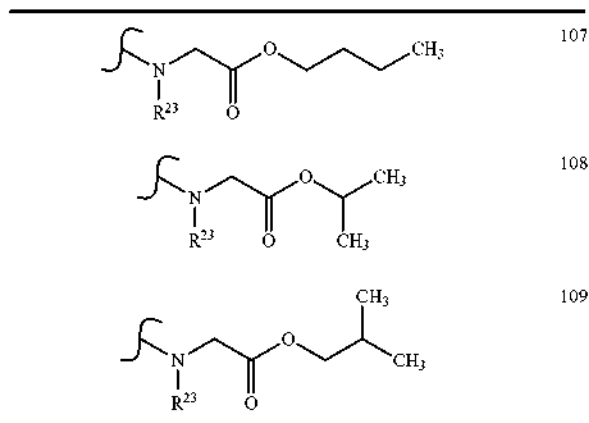
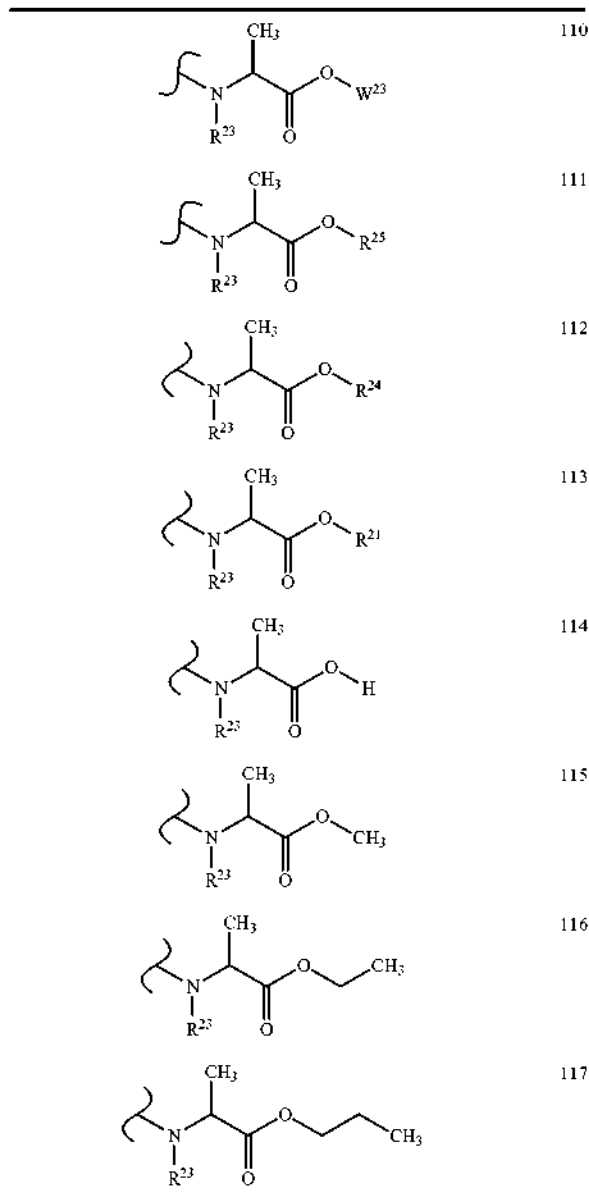


TABLE 20.19



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TABLE 20.20

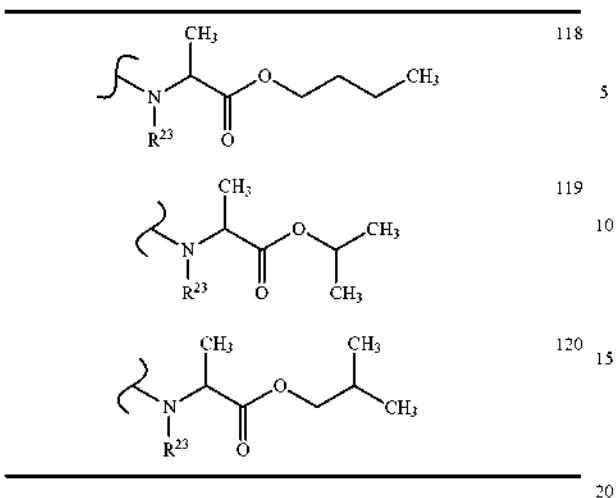
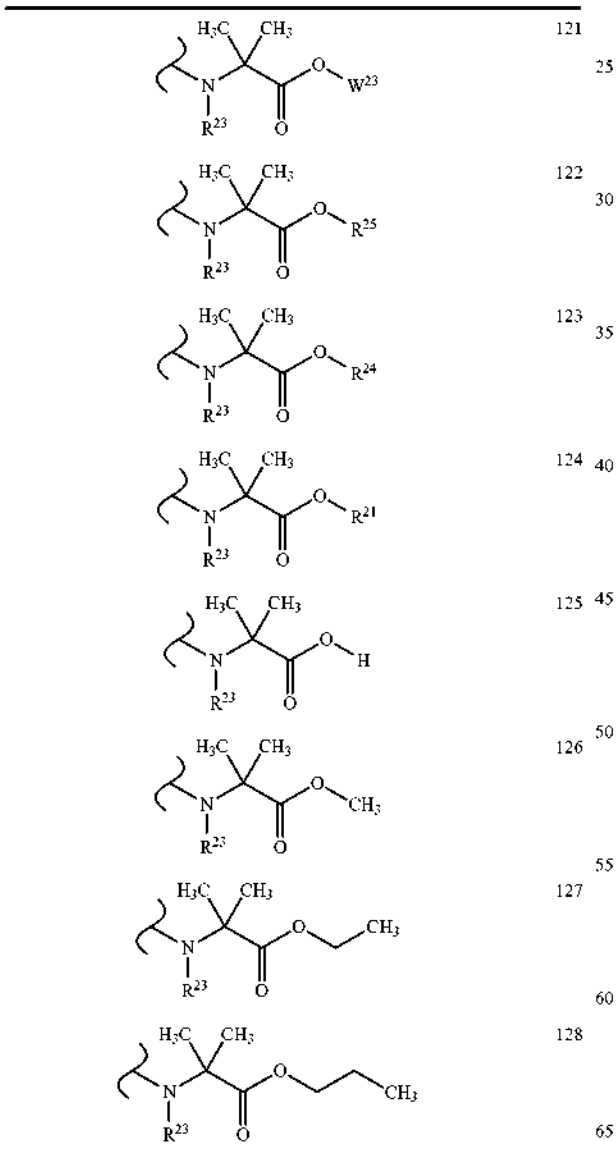


TABLE 20.21



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TABLE 20.22

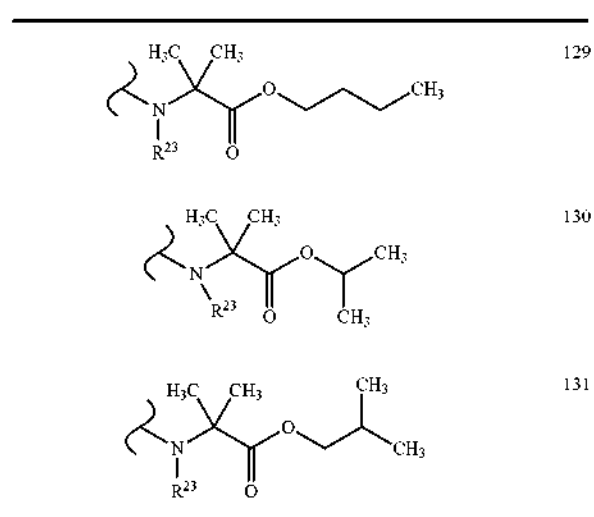
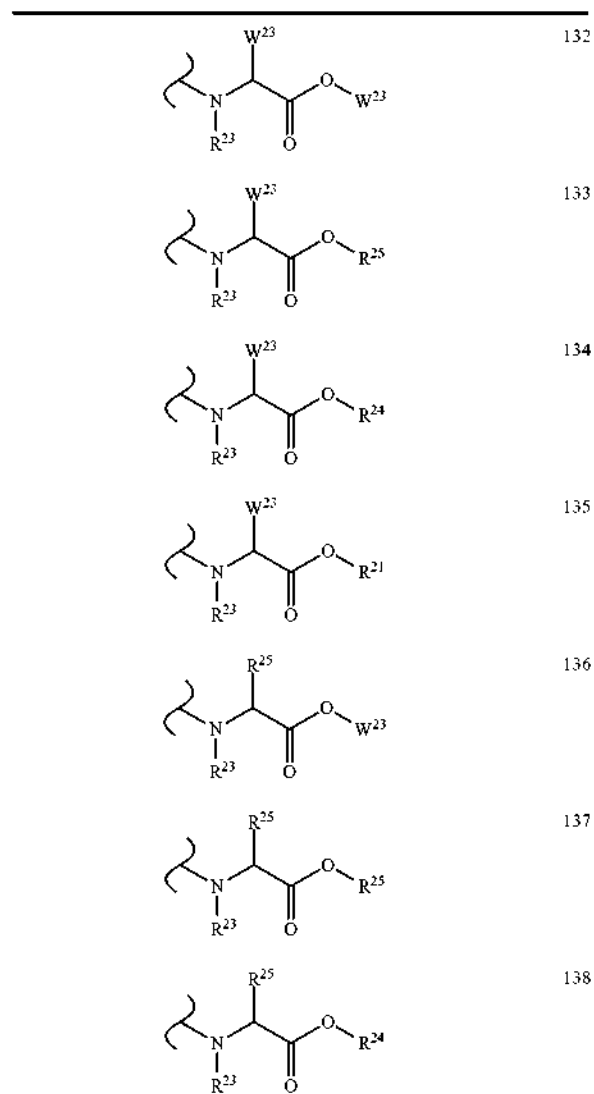


TABLE 20.23



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TABLE 20.23-continued

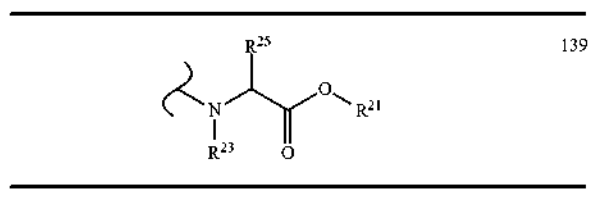


TABLE 20.24

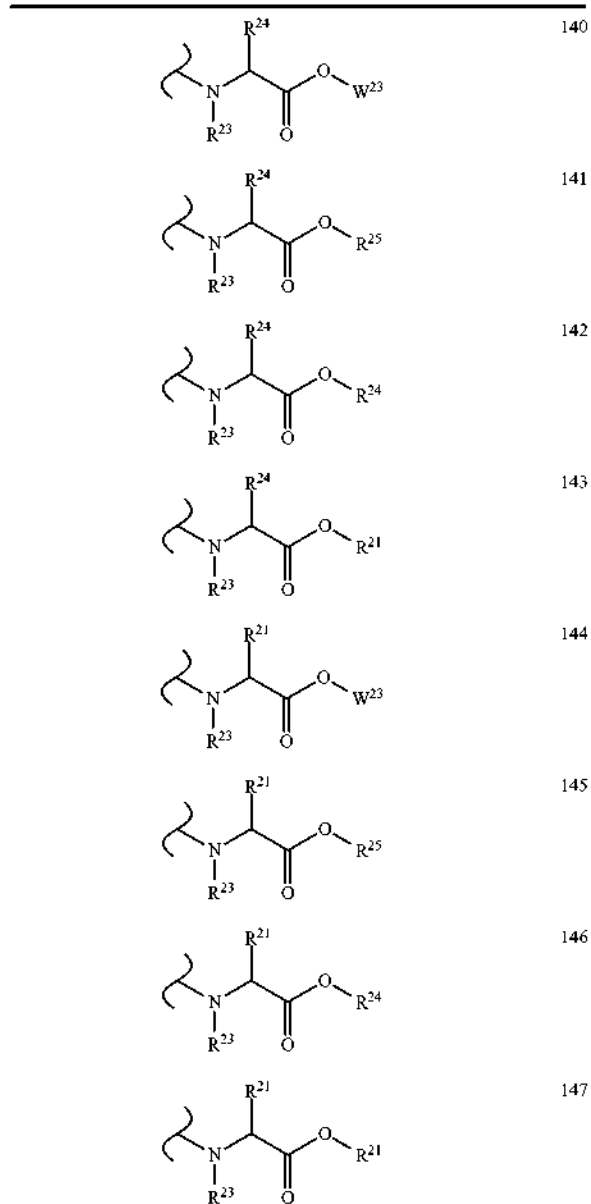


TABLE 20.25

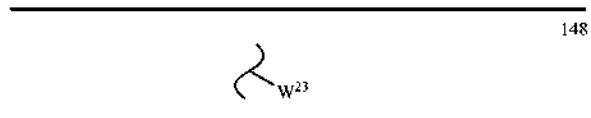
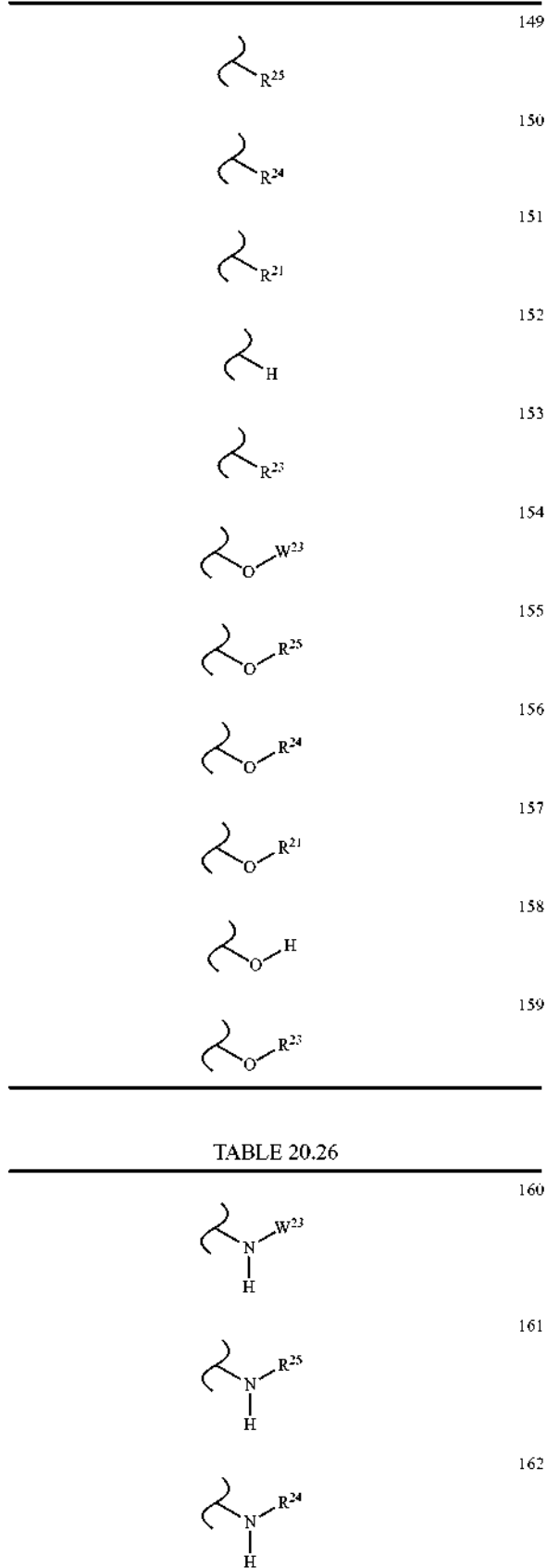
**62**

TABLE 20.25-continued



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TABLE 20.26-continued

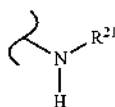
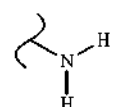
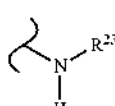
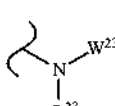
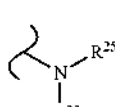
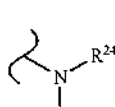
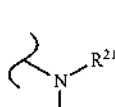
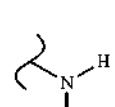
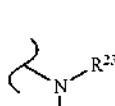
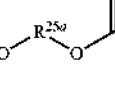
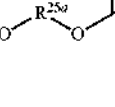
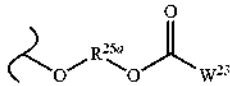
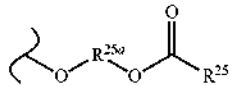
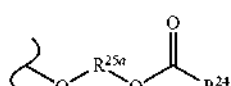
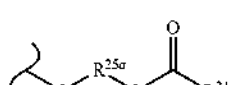
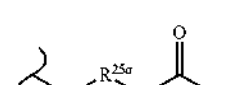
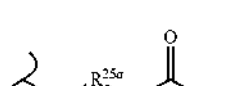
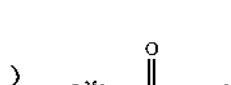
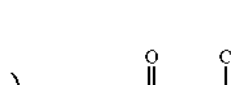
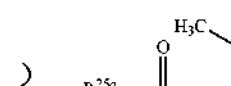
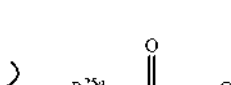
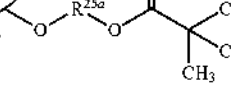
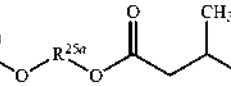
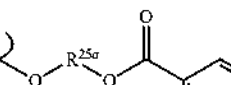
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TABLE 20.27

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TABLE 20.27-continued

	174
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TABLE 20.28	
	180
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TABLE 20.28-continued

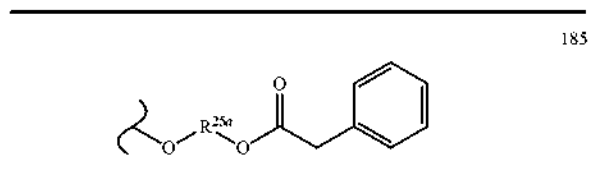


TABLE 20.29

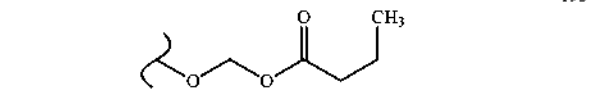
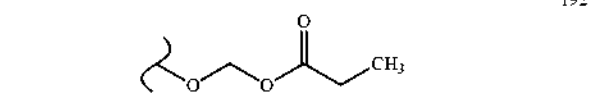
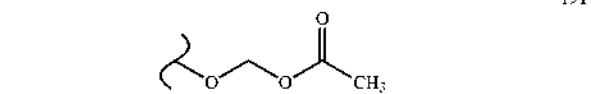
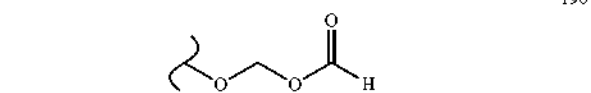
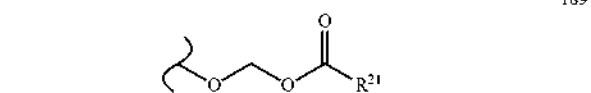
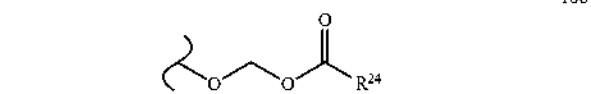
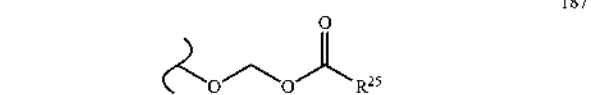
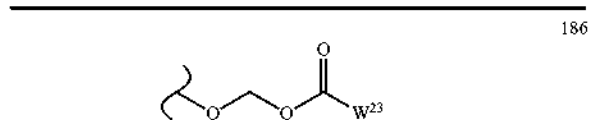


TABLE 20.30

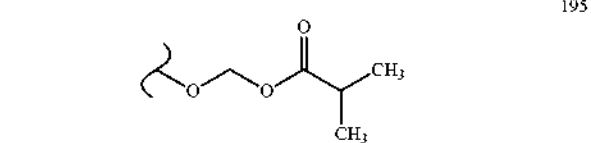
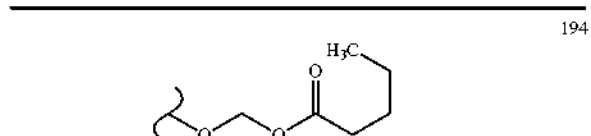
**66**

TABLE 20.30-continued

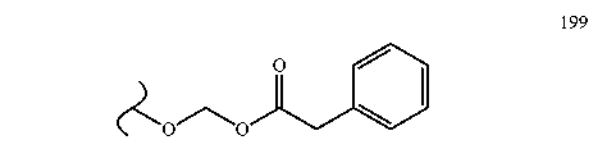
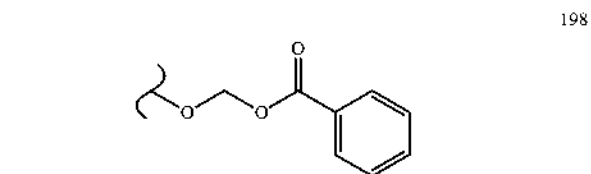
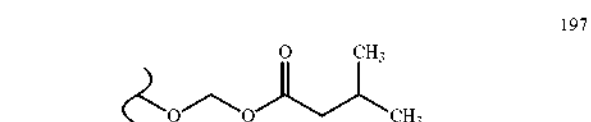
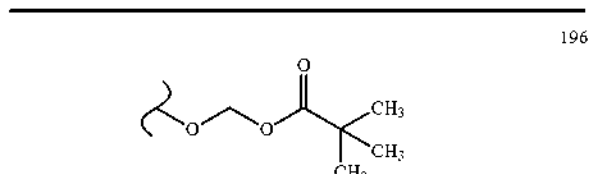
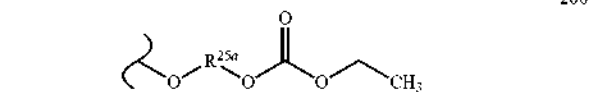
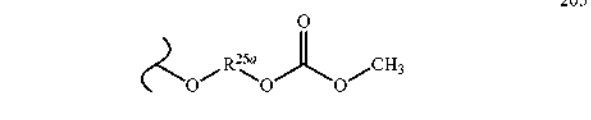
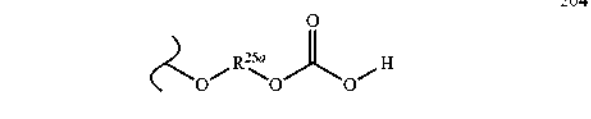
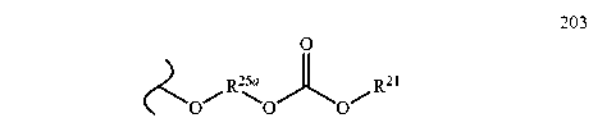
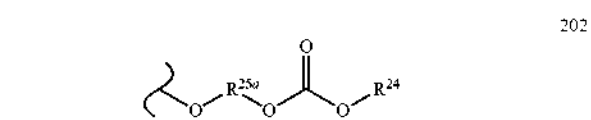
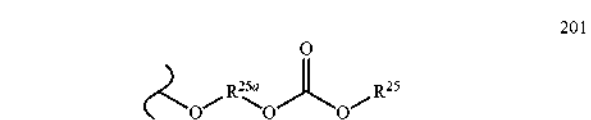
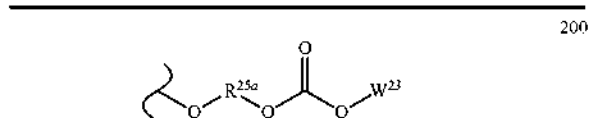


TABLE 20.31



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TABLE 20.31-continued

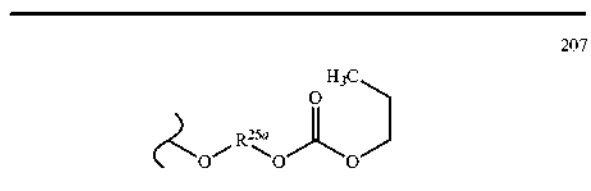


TABLE 20.32

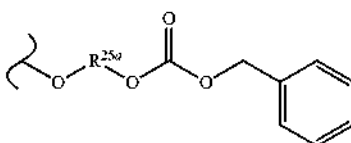
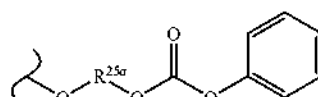
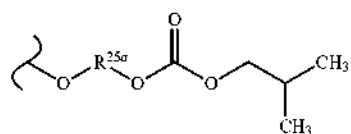
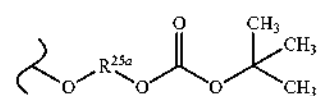
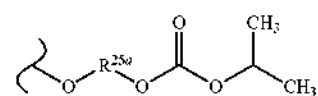
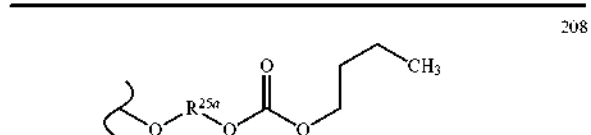
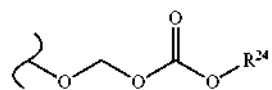
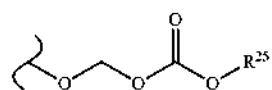
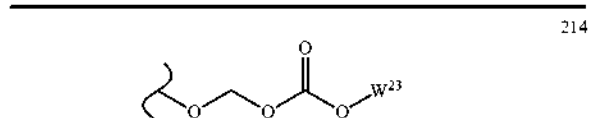


TABLE 20.33



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TABLE 20.33-continued

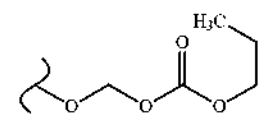
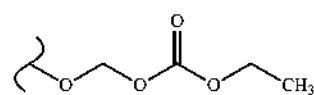
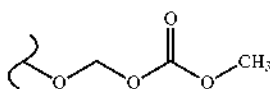
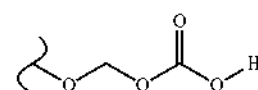
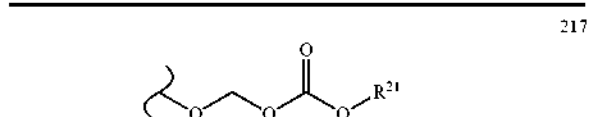
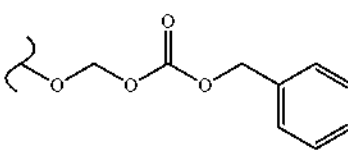
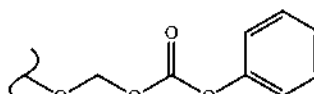
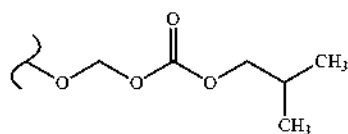
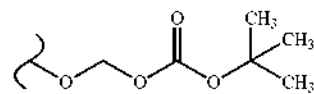
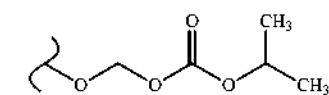
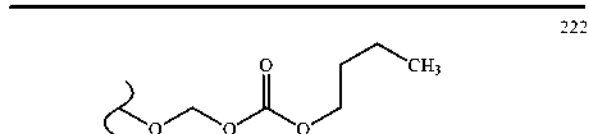


TABLE 20.34



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TABLE 20.35

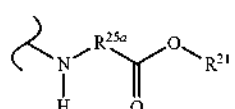
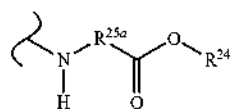
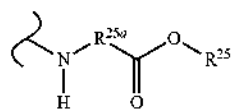
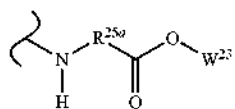
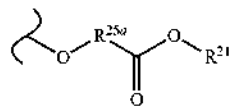
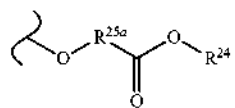
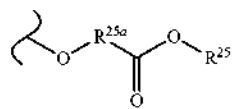
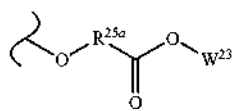
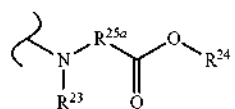
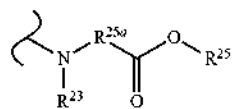
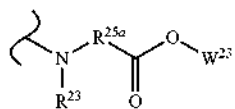


TABLE 20.36



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TABLE 20.36-continued

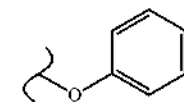
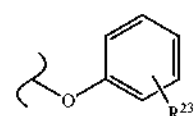
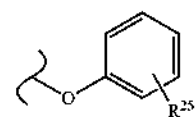
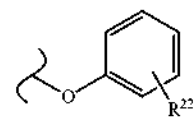
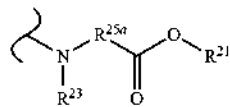
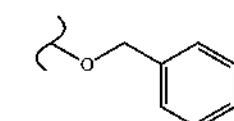
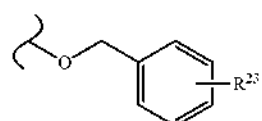
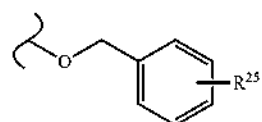
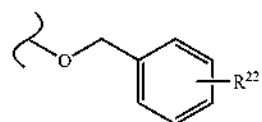


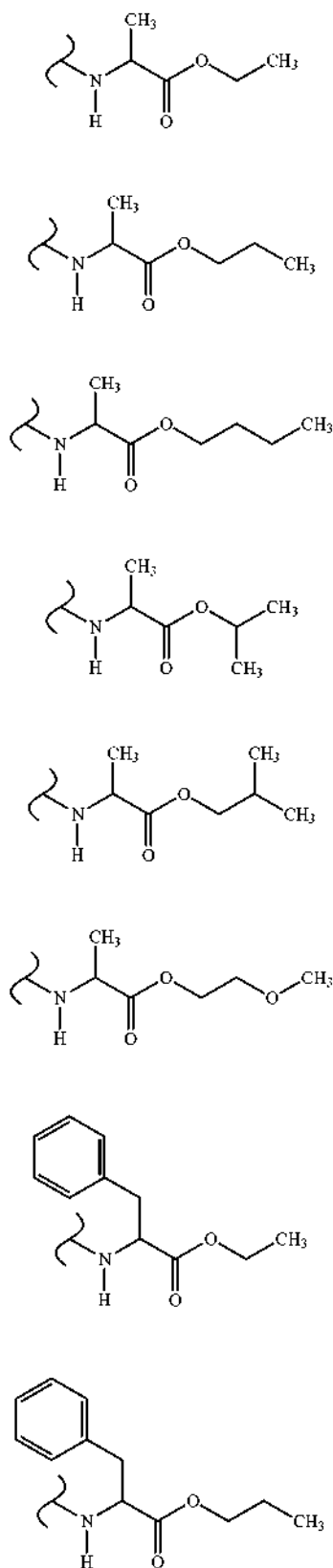
TABLE 20.37



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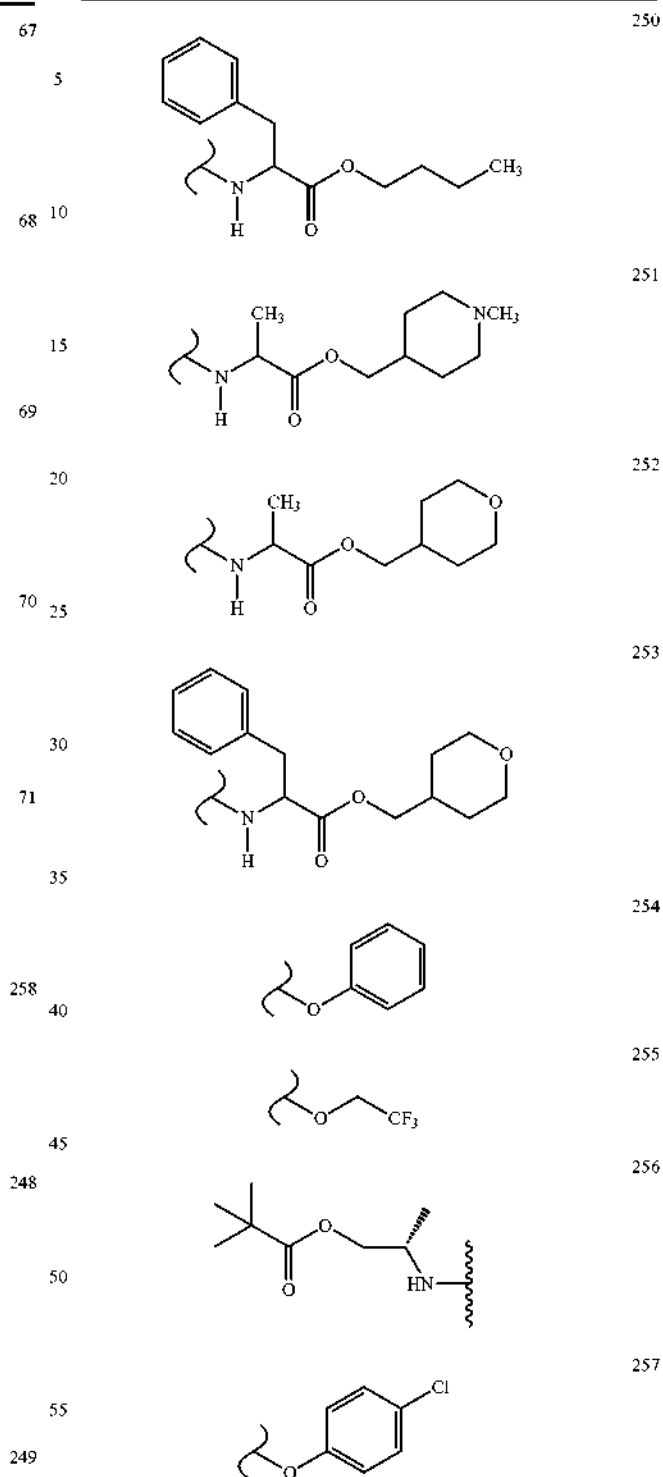
71

TABLE 30.1



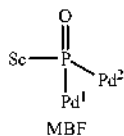
72

TABLE 30.1-continued



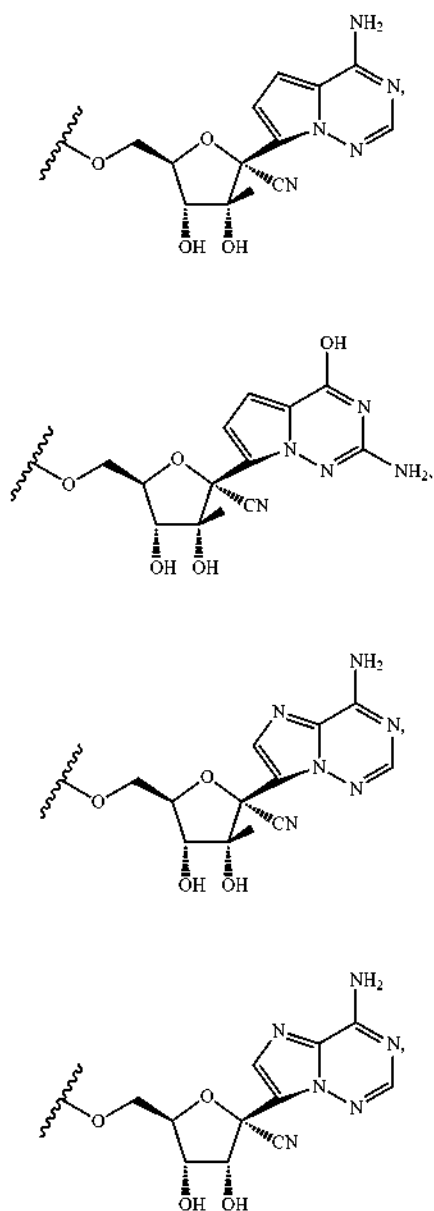
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Each embodiment of MBF is depicted as a substituted nucleus (Sc). Sc is described in formulae A-G of Table 1.1 below, wherein Sc is a generic formula for a compound of Formula I, Formula II, or Formula III and the point of attachment to —P(O)Pd¹Pd² is indicated with a wavy line.

TABLE 1.1



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TABLE 1.1-continued

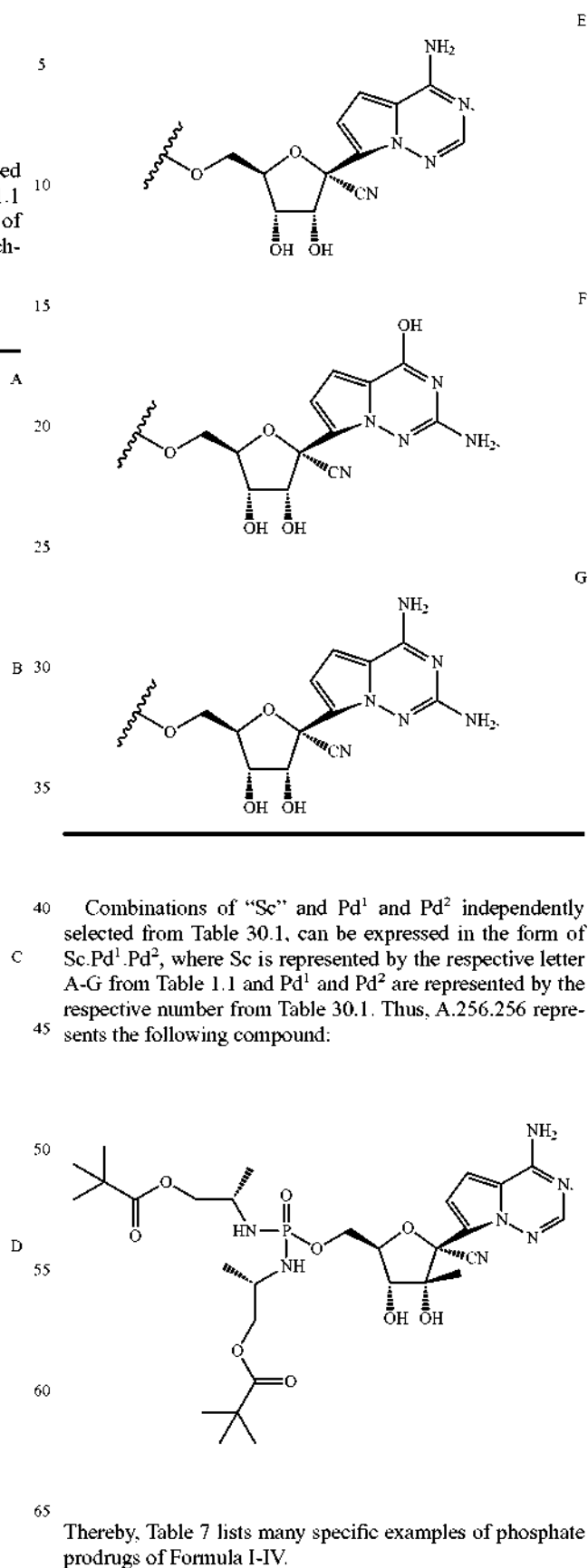
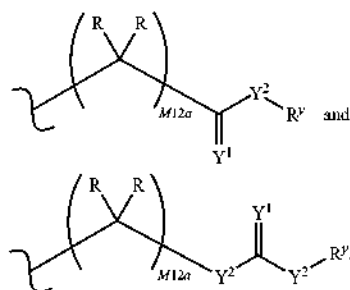


TABLE 7

List of Compounds of MBF

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Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



Any reference to the compounds of the invention described herein also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na⁺, Li⁺, K⁺, Ca⁺² and Mg⁺²), ammonium and NR₄⁺ (wherein R is defined herein). Physiologically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid,

naphthalenesulfonic acid, methanesulfonic acid, p-toluene-sulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pantoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na⁺ and NR₄⁺.

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

The compounds of the invention, exemplified by Formula I-III may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral

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centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds* (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (−) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (−), or l meaning that the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

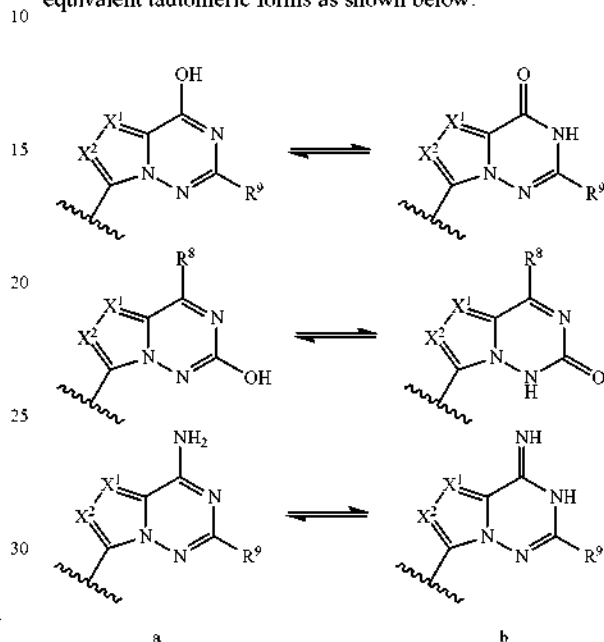
Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R¹", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines, , indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imida-

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zole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

One skilled in the art will recognize that the pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine nucleosides can exist in tautomeric forms. For example, but not by way of limitation, structures (a) and (b) can have equivalent tautomeric forms as shown below:



All possible tautomeric forms of the heterocycles in all of the embodiments disclosed herein are within the scope of the invention.

Methods of Inhibition of HCV Polymerase

Another aspect of the invention relates to methods of inhibiting the activity of HCV polymerase comprising the step of treating a sample suspected of containing HCV with a composition of the invention.

Compositions of the invention may act as inhibitors of HCV polymerase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HCV polymerase having a geometry unique to HCV polymerase. Compositions binding HCV polymerase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HCV polymerase. Accordingly, the invention relates to methods of detecting HCV polymerase in a sample suspected of containing HCV polymerase comprising the steps of: treating a sample suspected of containing HCV polymerase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

Within the context of the invention, samples suspected of containing HCV polymerase include natural or man-made

materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HCV polymerase, frequently a pathogenic organism such as HCV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HCV polymerase after application of the composition can be observed by any method including direct and indirect methods of detecting HCV polymerase activity. Quantitative, qualitative, and semiquantitative methods of determining HCV polymerase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HCV polymerase include the HCV virus. The compounds of this invention are useful in the treatment or prophylaxis of HCV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HCV Polymerase Inhibitors.

Compositions of the invention are screened for inhibitory activity against HCV polymerase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HCV polymerase in vitro and compositions showing inhibitory activity are then screened for activity in vivo. Compositions having in vitro K_i (inhibitory constants) of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for in vivo use.

Useful in vitro screens have been described in detail and will not be elaborated here. However, the examples describe suitable in vitro assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharma-

ceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer.

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It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product

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of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total

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compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 µg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HCV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

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Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about 0.01 to about 5 mg/kg body weight per day; most typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Preferably, the other active therapeutic ingredients or agents are interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

Combinations of the compounds of Formula I-III are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating an infection (e.g., HCV), the compositions of the invention are combined with other active therapeutic agents (such as those described herein).

Suitable active therapeutic agents or ingredients which can be combined with the compounds of Formula I-III can include interferons, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen+actimmune, IFN-omega with DUROS, and albuferon; ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin); NS5a inhibitors, e.g., A-831, A-689 and BMS-790052; NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554,

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GSK625433, and XTL-2125; NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065; alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B; hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451; non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1, 2,4-thiadiazine derivatives, and phenylalanine derivatives; and other drugs for treating HCV, e.g., zidaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, interferon, rebif, locteron, AVI-005, PEG-interferon, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, interferon+actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zidaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease

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inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Combinations of the compounds of Formula I-III and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of Formula I-III may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, e.g., amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir+ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, e.g., capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, e.g., zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir ($\pm$ -FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosaltivudine tidoxil, apricitabine (AVX754), amdoxovir, KP-1461, abacavir+lamivudine, abacavir+lamivudine+zidovudine, zidovudine+lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, e.g., tenofovir, tenofovir disoproxil fumarate+emtricitabine, tenofovir disoproxil fumarate+emtricitabine+efavirenz, and adefovir, 5) a HIV integrase inhibitor, e.g., curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrophostin, derivatives of tyrophostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, e.g., enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, e.g., AMD-070, 8) an entry inhibitor, e.g., SP01A, TNX-355, 9) a gp120 inhibitor, e.g., BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, e.g., immunitin, 10) a CCR5 inhibitor, e.g., aplavivoc, vicrivivoc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, interferon, rebif, locteron, AVI-005, PEG-interferon, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, interferon+actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831, A-689

and BMS-790052, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-34451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating HCV, e.g., zidaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, ogtufanide, PYN-17, KPE02003002, actilon (CPG-1010), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20) RNase H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), amplitgen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

It is also possible to combine any compound of the invention with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or

delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for treating an HCV infection in a patient.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the in vivo metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to

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enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV polymerase inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37° C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed in vivo. The prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

EXAMPLES

Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

TABLE 1

List of abbreviations and acronyms.	
Abbreviation	Meaning
Ac ₂ O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]nonene-5
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undecene-5
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTCI	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4,4'-dimethoxytrityl
DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	electrospray ionization

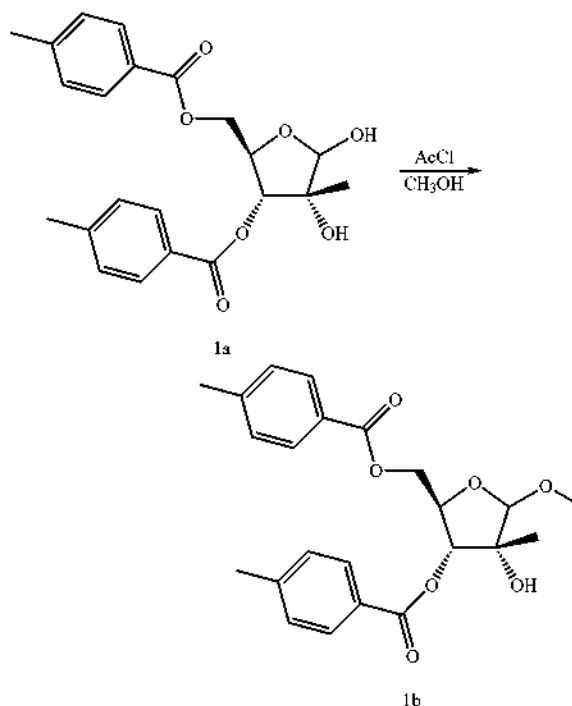
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TABLE 1-continued

List of abbreviations and acronyms.	
Abbreviation	Meaning
HMDS	hexamethyldisilazane
HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperoxybenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH ⁺	mass plus 1
MH ⁻	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromosuccinimide
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyltrimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tlc	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
δ	parts per million down field from tetramethylsilane

Preparation of Compounds

Compound 1a-1f

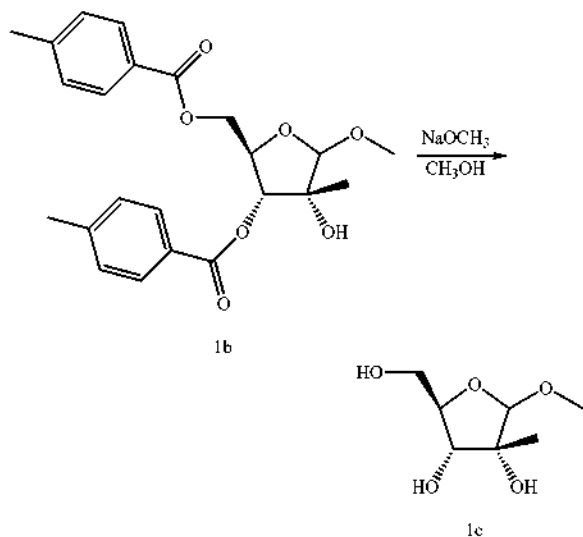


To a solution of 1a (22.0 g, 54.9 mmol, prepared according to the procedures described in *J.O.C.*, 2004, 6257) in methanol (300 mL) was dropwise added acetyl chloride (22 mL) at

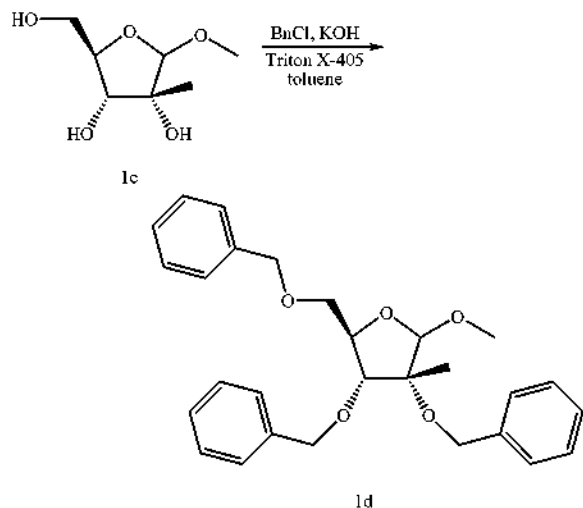
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0° C. using a dropping funnel over a period of 30 min. and then stirred at room temperature for 16 h. The mixture was concentrated, re-dissolved in ethyl acetate (400 mL), washed with ice-cold 2 N NaOH, and concentrated to dryness, affording the crude methyl ether 1b as an oil. MS=437.2 (M+Na⁺).



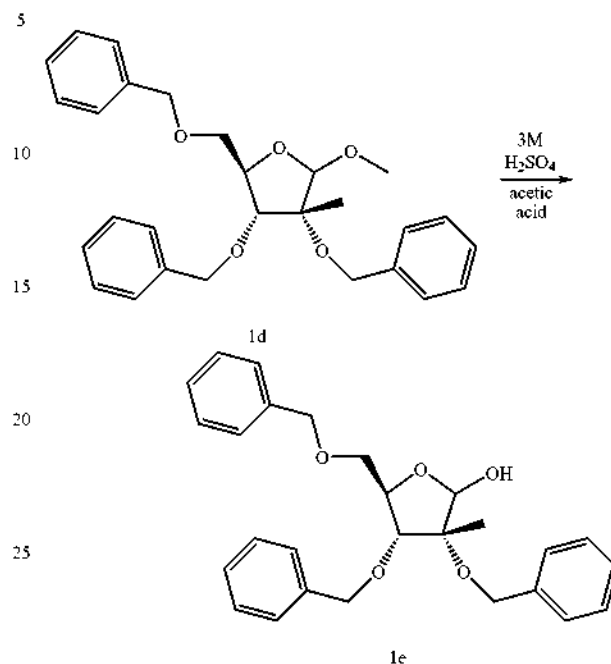
To a solution of 1b (obtained from the previous step) in methanol (300 mL) was added 0.5 M sodium methoxide solution in methanol (20 mL, 10 mmol), and stirred for 16 h at room temperature. The reaction was quenched with 4.0 N HCl solution in dioxane (2.5 mL, 10 mmol). The mixture was then concentrated, affording the crude 1c. MS=201.0 (M+Na⁺).



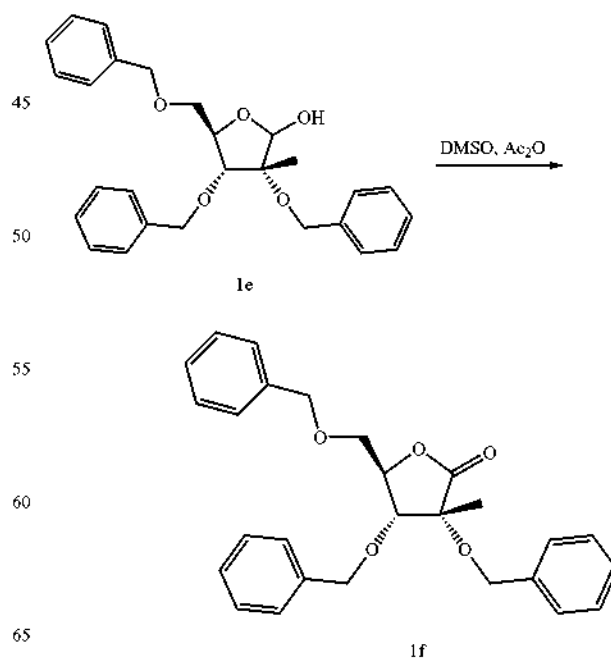
A mixture of 1c (obtained from the previous step), Triton X-405 (70% in water, 6.0 g), 50% KOH (in water, 85 g) in toluene (500 mL) was heated to reflux with a Dean-Stark trap attached. After 1 h collecting ~25 mL of water, benzyl chloride (33 g, 260 mmol) was added and continued to reflux with stirring for 16 h. The mixture was then cooled and partitioned between ethyl acetate (400 mL) and water (300 mL). The organic layer was washed with water (300 mL), and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc/hexanes), affording the methyl ether

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1d as an oil (22.0 g, 89% in three steps). ¹H NMR (300 MHz, CDCl₃): δ 7.3 (m, 15H), 4.5-4.9 (m, 7H), 4.37 (m, 1H), 3.87 (d, 1H), 3.56 (m, 2H), 3.52 (s, 3H), 1.40 (s, 3H).



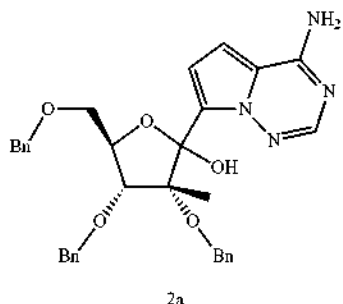
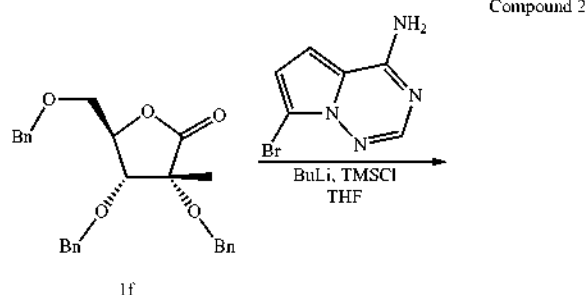
To a solution of 1d (22.0 g, 49.0 mmol) in acetic acid (110 mL) was added ~3 M sulfuric acid (prepared by mixing 4.8 g of concentrated sulfuric acid with 24 mL of water) and stirred at 70° C. for 8 h. The mixture was concentrated to a volume of ~20 mL, and partitioned between ethyl acetate and ice-cold 2N NaOH. The ethyl acetate layer was concentrated, and purified by silica gel column chromatography (~35% EtOAc/hexanes), affording 1e as an oil (17.0 g, 80%). MS=457.2 (M+Na⁺).



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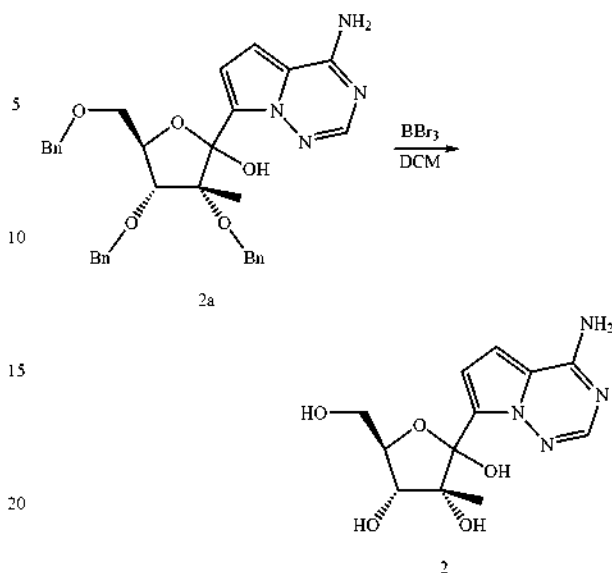
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To a solution of 1e (45 g, 104 mmol) in DMSO (135 mL) was dropwise added acetic anhydride (90 mL, 815 mmol) at room temperature under argon. The mixture was stirred for 16 h at room temperature, and then poured into ice-water (1 L) while stirring. After ice was completely melted (~30 min), ethyl acetate (~500 mL) was added. The organic layer was separated. This extraction process was repeated three times (3×500 mL). The organic extracts were combined and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc/hexanes), affording 1f as an oil (39 g, 88%). ¹H NMR (300 MHz, DMSO-d₆): δ 7.3 (m, 15H), 4.4-4.8 (m, 7H), 4.08 (d, J=7.5 Hz, 1H), 3.75 (dd, J=2.4, 11.4 Hz, 1H), 3.64 (dd, J=5.4, 11.4 Hz, 1H), 1.51 (s, 3H).



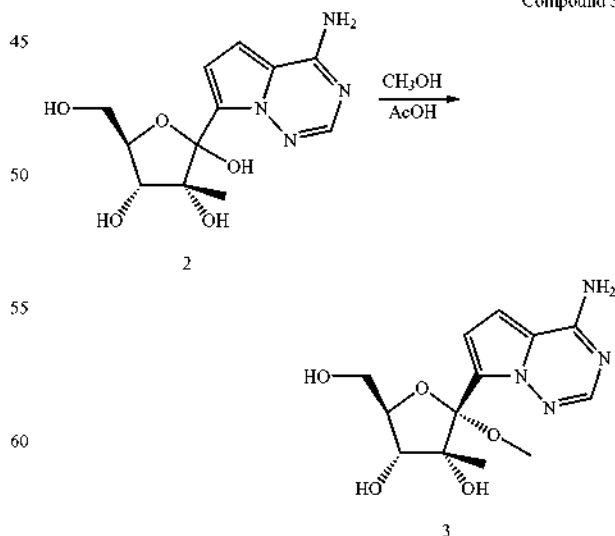
To a dry, argon purged round bottom flask (100 mL) were added 7-bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (234 mg, 1.10 mmol) (prepared according to WO2007056170) and anhydrous THF (1.5 mL). TMSCl (276 μL, 2.2 mmol) was then added and the reaction mixture stirred for 2 h. The flask was placed into a dry ice/acetone bath (~-78° C.) and BuLi (2.5 mL, 4.0 mmol, 1.6M in hexanes) was added dropwise. After 1 h, a solution of 1f (432.5 mg, 1.0 mmol) in THF was cooled to 0° C. and then added to the reaction flask dropwise. After 1 h of stirring at -78° C., the flask was warmed to 0° C. and sat. NH₄Cl (5 mL) was added to quench the reaction. The organics were extracted using EtOAc (3×10 mL) and the combined organic layers were dried using MgSO₄. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (hexanes/EtOAc). 560 mg (99%) of 2a was isolated as a mixture of two anomers. LC/MS=567.2 (M+H⁺). ¹H NMR (300 MHz, CDCl₃): δ 7.85 (m, 1H), 7.27 (m, 15H), 7.01 (m, 1H), 6.51 (m, 1H), 4.66 (m, 8H), 4.40 (m, 2H), 3.79 (m, 3H), 1.62 (s, 2'-CH₃ from the one anomer), 1.18 (s, 2'-CH₃ from the other anomer).

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To a dry, argon purged round bottom flask (50 mL) were added compound 2a (185 mg, 0.33 mmol) and anhydrous dichloromethane (10 mL). The flask was placed into a dry ice/acetone bath (~-78° C.) and the solution stirred for 10 min. BBr₃ (0.25 mL, 0.25 mmol, 1.0 M in DCM) was then added and the reaction continued to stir at -78° C. until complete disappearance of the starting material. After 1 h, a solution of pyridine (2 mL) in MeOH (10 mL) was added and the flask was warmed to room temperature. The solvent was removed under reduced pressure and the crude material was re-dissolved in MeOH. After this process was repeated two more times, the crude material was then dissolved in water and purified using a Gilson Preparatory HPLC system (acetonitrile/H₂O). 49 mg (50%) of Compound 2 was isolated as an isomeric mixture. LC/MS=297.1 (M+H⁺). ¹H NMR (300 MHz, D₂O): δ 7.68 (m, 1H), 6.80 (m, 2H), 4.04 (m, 2H), 3.78 (m, 2H), 3.65 (m, 1H), 1.30 (s, 2'-CH₃), 0.80 (s, 2'-CH₃).

Compound 3

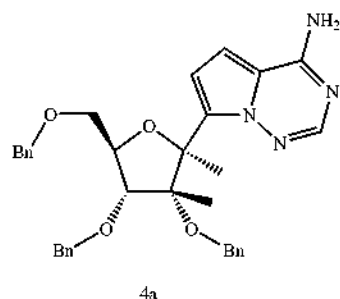
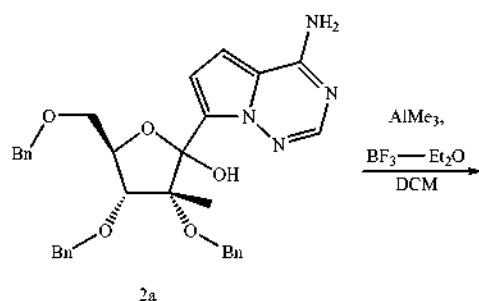


To a dry, argon purged round bottom flask (100 mL) were added Compound 2 (12 mg, 0.04 mmol) (2) and anhydrous

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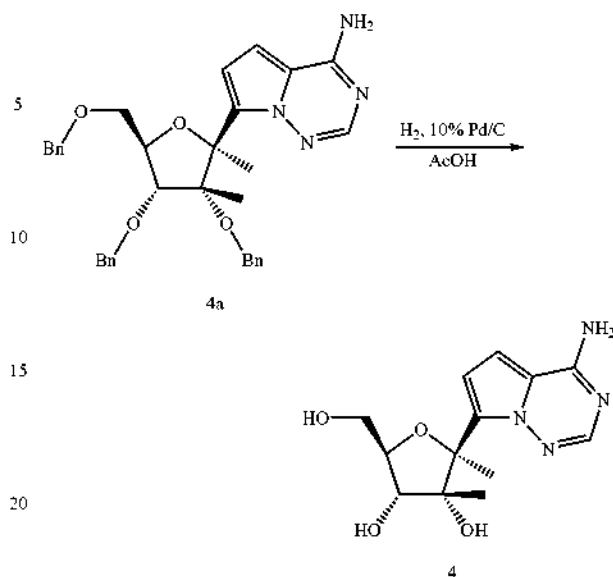
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MeOH (5 mL). Acetic acid (5 mL) was then added and the reaction stirred overnight at room temperature. Saturated NaHCO_3 was added to neutralize the reaction mixture and the crude material was purified using a Gilson Preparatory HPLC system (acetonitrile- H_2O). 2 mg (16%) of the desired material Compound 3 was isolated. LC/MS=311.2 ($\text{M}+\text{H}^+$). ^1H NMR (300 MHz, D_2O): δ 7.71 (s, 1H), 6.78 (s, 2H), 3.98 (m, 1H), 3.83 (dd, 1H), 3.74 (dd, 1H), 3.62 (d, 1H), 2.94 (s, 3H), 0.76 (s, 3H). The other alpha-isomer was also isolated; ^1H NMR (300 MHz, D_2O): δ 7.65 (s, 1H), 6.78 (d, 1H), 6.75 (d, 1H), 4.03 (m, 2H), 3.77 (dd, 1H), 3.59 (d, 1H), 2.95 (s, 3H), 1.31 (s, 3H).



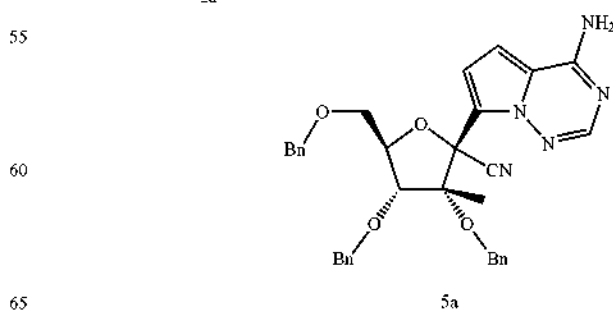
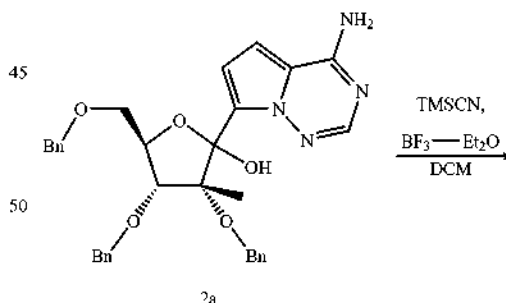
To a dry, argon purged round bottom flask (50 mL) were added compound 2a (220 mg, 0.39 mmol) and anhydrous dichloromethane (10 mL). The flask was placed into a dry ice/acetone bath ($\sim -78^\circ\text{C}$) and the solution stirred for 10 min. $\text{BF}_3\text{--Et}_2\text{O}$ (0.10 mL) was added dropwise and the reaction stirred for 10 min. AlMe_3 (0.58 mL, 1.16 mmol, 2.0 M in toluene) was then added. After a few minutes, the dry ice/acetone bath was removed and the reaction mixture warmed to room temperature over 4 h. A solution of pyridine (2 mL) in MeOH (10 mL) was added and the solvent was removed under reduced pressure. The crude material was purified using flash chromatography (hexanes/ EtOAc). 164 mg (74%) of the desired material 4a was isolated. LC/MS=565.2 ($\text{M}+\text{H}^+$). ^1H NMR (300 MHz, CD_3OD): δ 7.71 (s, 1H), 7.32 (m, 15H), 7.02 (m, 1H), 6.78 (m, 1H), 4.62 (m, 8H), 4.21 (m, 1H), 4.04 (m, 1H), 3.84 (m, 1H), 1.95 (s, 3H), 1.10 (s, 3H).

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To a dry, argon purged round bottom flask (50 mL) were added compound 4a (164 mg, 0.29 mmol) and glacial acetic acid (10 mL). Pd/C (100 mg, 10% by wt.) was then added and the flask was equipped with a balloon containing hydrogen gas. The flask was purged two times to ensure all of the argon had been replaced with hydrogen. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then neutralized using NaHCO_3 and filtered to remove the catalyst. The crude material was purified using a Gilson Preparatory HPLC system (acetonitrile/ H_2O). 6 mg (7%) of the desired material Compound 4 was isolated. LC/MS=295.1 ($\text{M}+\text{H}^+$). ^1H NMR (300 MHz, D_2O): δ 7.66 (s, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 3.93 (m, 1H), 3.76 (m, 3H), 1.63 (s, 3H), 0.76 (s, 3H).

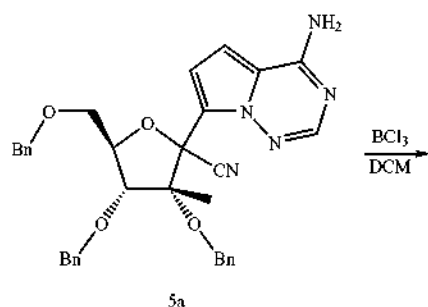
Compound 5



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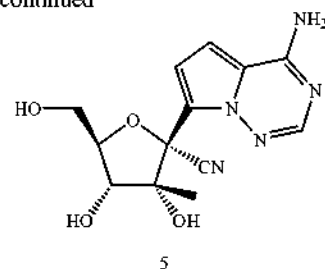
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To a solution of compound 2a (1 g, 1.77 mmol) in CH_2Cl_2 (20 mL) at 0°C , was added TMS-CN (1.4 mL, 10.5 mmol) and $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1 mL, 8.1 mmol). The reaction mixture was stirred at 0°C for 0.5 h, then at room temperature for additional 0.5 h. The reaction was quenched with NaHCO_3 at 0°C , and diluted with $\text{CH}_3\text{CO}_2\text{Et}$. The organic phase was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with $\text{CH}_3\text{CO}_2\text{Et}$ -hexanes (1:1 to 2:1), to give the desired compound 5a (620 mg, 61%) as an isomeric mixture. MS=576.1 ($\text{M}+\text{H}^+$).



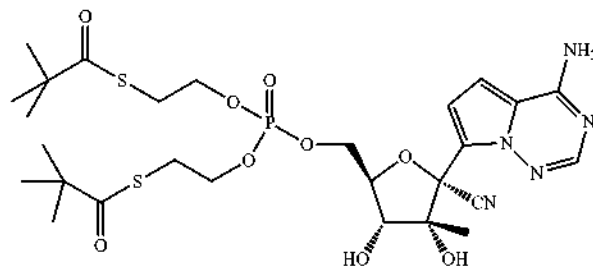
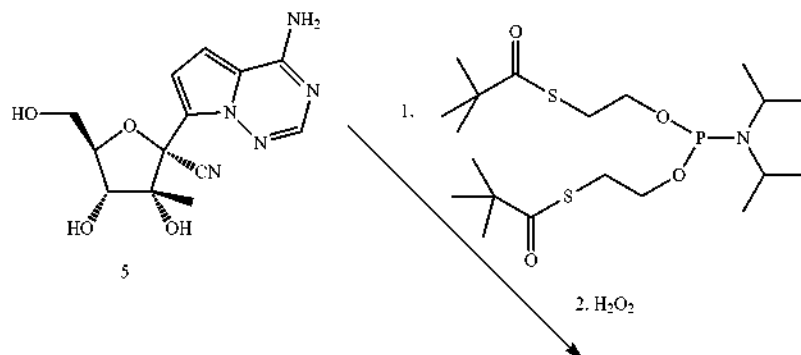
98

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To a solution of compound 5a (150 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) at -78°C , was added BCl_3 (2 mL, 1M in CH_2Cl_2). The reaction mixture was stirred at -78°C for 1 h. The reaction was quenched at -78°C by dropwise addition of TEA (2 mL) and MeOH (5 mL). The mixture was allowed to warm up to room temperature, evaporated, and co-evaporated with MeOH several times. The residue was treated with NaHCO_3 (1 g in 10 mL H_2O), concentrated and purified by HPLC to give the desired product Compound 5 (48 mg, 60%). ^1H NMR (300 MHz, D_2O): δ 7.74 (s, 1H), 6.76 (d, $J=5$ Hz, 1H), 6.73 (d, $J=5$ Hz, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.8 (m, 2H), 0.84 (s, 3H). MS=305.9 ($\text{M}+\text{H}^+$). The other alpha-anomer was also obtained (9 mg, 11%): ^1H NMR (300 MHz, D_2O): δ 7.70 (s, 1H), 6.8 (d, $J=5$ Hz, 1H), 6.7 (d, $J=5$ Hz, 1H), 4.25 (d, $J=9$ Hz, 1H), 4.07 (m, 1H), 3.85 (m, 1H), 3.7 (m, 1H), 1.6 (s, 3H). MS=306.1 ($\text{M}+\text{H}^+$).

Compound 6



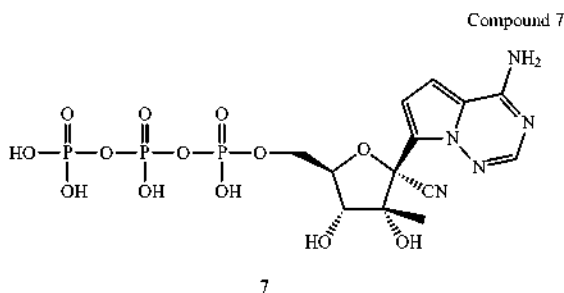
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To a solution of compound 5 (30 mg, 0.098 mmol) and 1H-tetrazole (30 mg, 0.43 mmol) in anhydrous CH₃CN (1 mL) at 0° C. was added 2,2-dimethyl-thiopropionic acid S-(2-{diisopropylamino-[2-(2,2-dimethyl-propionylsulfanyl)-ethoxy]-phosphanyloxy}-ethyl)ester (90 mg, 0.2 mmol) (described in *J. Med. Chem.*, 1995, 3941). The reaction mixture was stirred at 0° C. for 1 h, then H₂O₂ (30%, 80 uL) was added and stirred for 0.5 h at 0° C. The reaction was quenched with sodium thiosulfate (1 M, 1 mL) and NaHCO₃, diluted with CH₃CO₂Et. The organic phase was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by HPLC to give the desired Compound 6 (28 mg, 42%). ¹H NMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 6.85 (d, J=4.5 Hz, 1H), 6.73 (d, J=4.5 Hz, 1H), 6.0 (brs, 2H), 4.6 (m, 1H), 4.4 (m, 2H), 4.1 (m, 4H), 4.0 (d, J=4 Hz, 1H), 3.15 (m, 4H), 1.24 (s, 18H), 0.99 (s, 3H). ³¹P NMR (300 MHz, CDCl₃): δ -1.825. MS=673.9 (M+H⁺), 672.1 (M-H⁻).

General Procedure for Preparation of a Nucleoside Triphosphate:

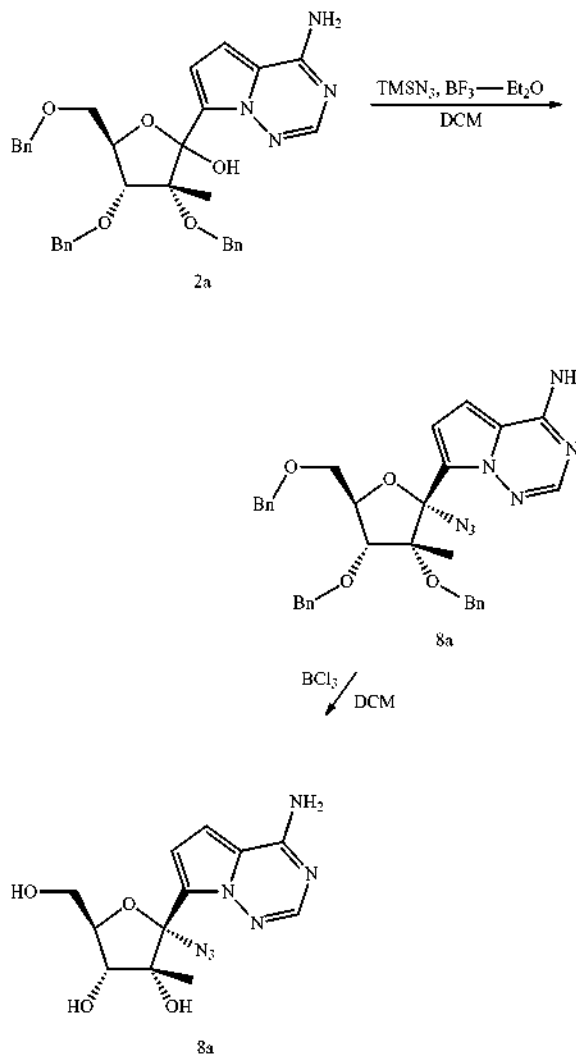
To a pear-shaped flask (5-15 mL) is charged with a nucleoside (~20 mg). Trimethyl phosphate (0.5-1.0 mL) is added. The solution is cooled with ice-water bath. POCl₃ (40-45 mg) is added and stirred at 0° C. until the reaction is complete (1 to 4 h; the reaction progress is monitored by ion-exchange HPLC; analytical samples are prepared by taking ~3 uL of the reaction mixture and diluting it with 1.0 M Et₃NH₂CO₃ (30-50 uL)). A solution of pyrophosphate-Bu₃N (250 mg) and Bu₃N (90-105 mg) in acetonitrile or DMF (1-1.5 mL) is then added. The mixture is stirred at 0° C. for 0.3 to 2.5 h, and then the reaction is quenched with 1.0 M Et₃NH₂CO₃ (~5 mL). The resulting mixture is stirred for additional 0.5-1 h while warming up to room temperature. The mixture is concentrated to dryness, re-dissolved in water (4 mL), and purified by ion exchange HPLC. The fractions containing the desired product is concentrated to dryness, dissolved in water (~5 mL), concentrated to dryness, and again dissolved in water (~5 mL). NaHCO₃ (30-50 mg) is added and concentrated to dryness. The residue is dissolved in water and concentrated to dryness again. This process is repeated 2-5 times. The residue is then subjected to C-18 HPLC purification, affording the desired product as a sodium salt.



Compound 7 was prepared by the general method using Compound 5 as starting material. ¹H NMR (300 MHz, D₂O): δ 7.76 (s, 1H), 6.95 (d, J=4.5 Hz, 1H), 6.8 (d, J=4.5 Hz, 1H), 4.25 (m, 3H), 4.0 (d, J=6 Hz, 1H), 0.92 (s, 3H). ³¹P NMR (300 MHz, D₂O): δ -5.6, -10.7, -21.4. MS=545.8 (M+H⁺), 544.0 (M-H⁻).

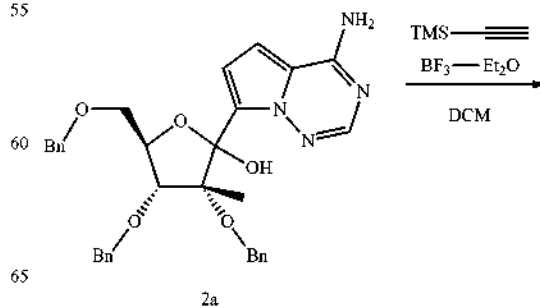
100

Compound 8



Compound 8 may be obtained from 2a in a manner similar to that described in preparation of Compound 5 except using TMSN₃ instead of TMSCN.

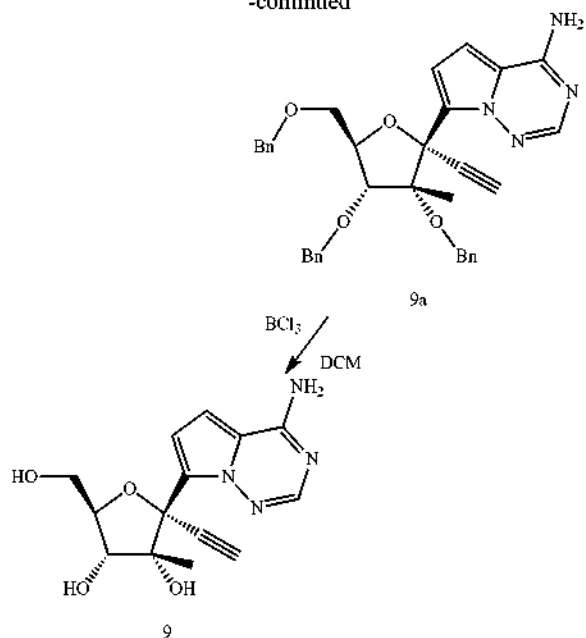
Compound 9



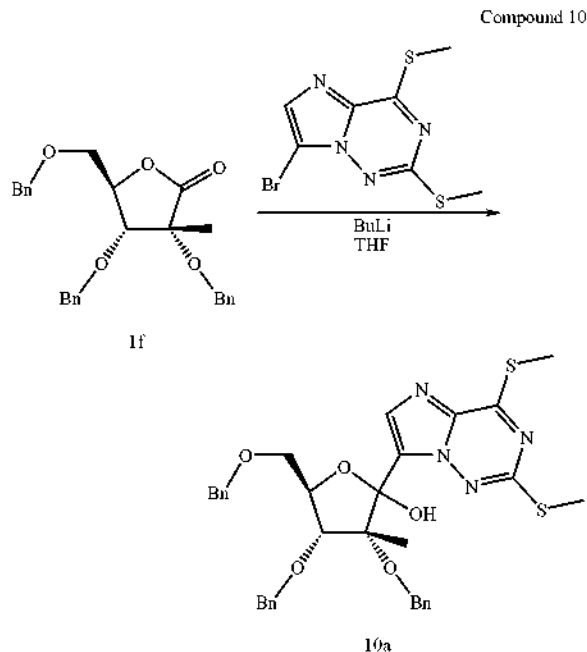
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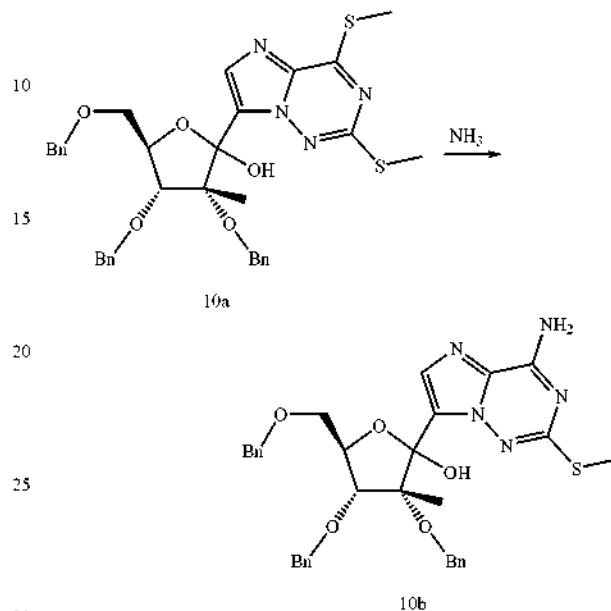
Compound 9 may be obtained from 2a in a manner similar to that described in preparation of Compound 5 except using TMS-acetylene instead of TMSCN.



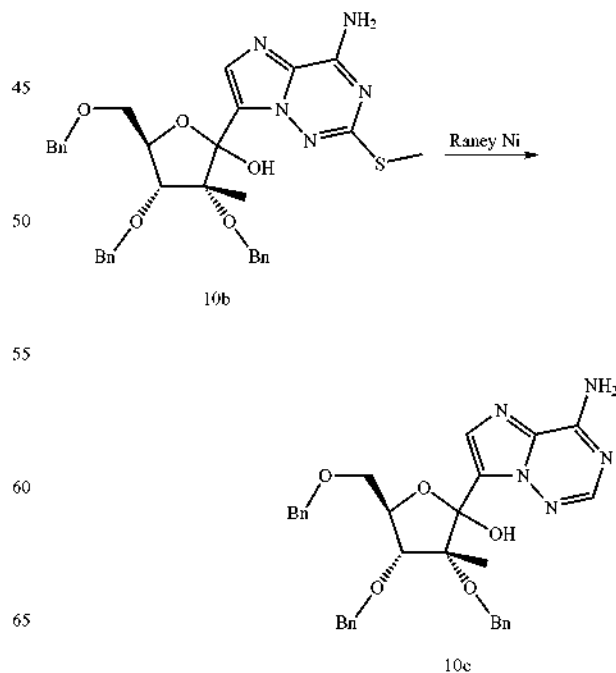
To a suspension of 7-bromo-2,4-bis-methylsulfonyl-imidazo[2,1-f][1,2,4]triazine (prepared according to WO2008116064, 600 mg, 2.06 mmol) in anhydrous THF (6 mL) was dropwise added BuLi (1.6 M in hexanes, 1.75 mL, 2.81 mmol) at -78°C . The suspension became red brown solution after 5 min, and then 1f in THF (0.6 mL) was added dropwise to the mixture. The mixture was then allowed to warm up to room temperature. After 30 min, saturated NH_4Cl was added to quench the reaction. The mixture was diluted

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with ethyl acetate; the organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography ($\sim 40\%$ EtOAc/hexanes), affording 10a as an isomeric mixture (0.77 g, 64%). MS=645.2 ($\text{M}+\text{H}^+$).



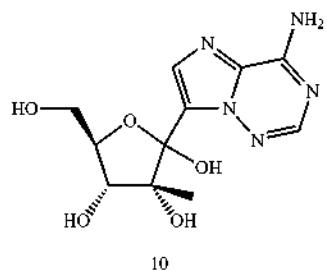
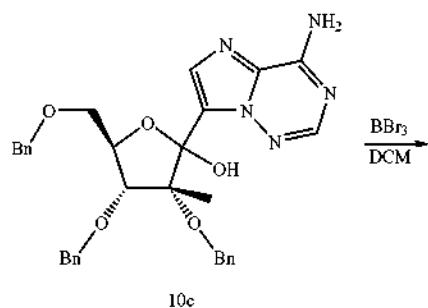
Compound 10a (2.0 g, 3.10 mmol) was transferred to a steel bomb reactor, and cooled at -78°C . Liquid ammonia (~ 20 mL) was collected at -78°C and added to the bomb reactor. The bomb reactor was tightly sealed and warmed up to room temperature. The mixture was then heated at 50°C for 20 h. Complete conversion occurred. After the gas was vented, the residue was purified by silica gel column chromatography (EtOAc/hexanes), affording the product 10b as a pale yellow solid (1.78 g, 94%). MS=614.3 ($\text{M}+\text{H}^+$).



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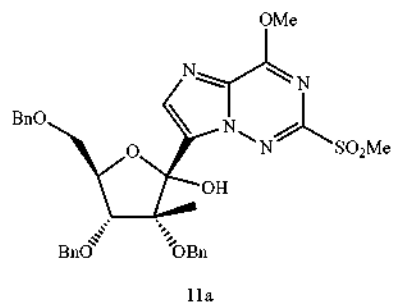
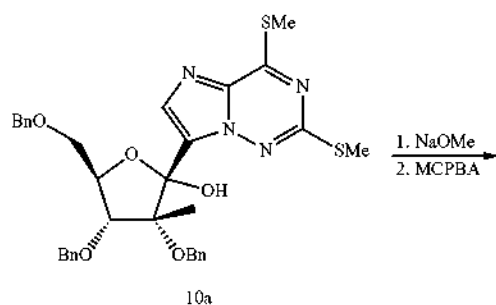
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A solution of 10b (100 mg) in ethanol (about 10 ml) is treated with Raney Ni (about 500 mg) that is neutralized by washing with H₂O. The mixture is then heated to about 35 to about 80° C. until the reaction is complete. The catalyst is removed by filtration and the solution is concentrated in vacuo. The residue is purified by chromatography to give 10c.



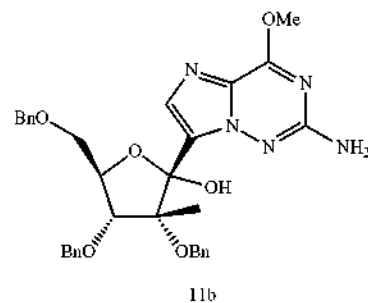
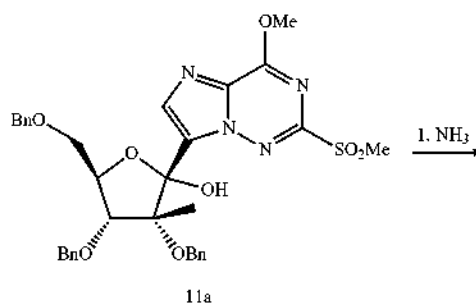
Compound 10c may be treated with BBr₃ in a manner similar to that described in preparation of compound 2 to give Compound 10.

Compound 11

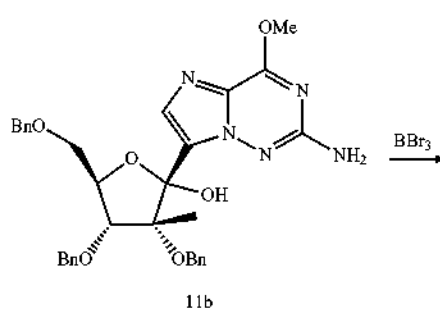


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10a is treated with about one to ten mole equivalents of an alkali metal salt of methanol in a suitable solvent such as dioxane for about one to 48 hours. The mixture may also be heated from about 60 to about 110° C. for about one to 24 hours to complete the reaction. The mixture is neutralized with a strong acid and the intermediate is isolated by extraction and chromatography. The intermediate is dissolved in DCM and treated with about two to about four mole equivalents of MCPBA for about one to about 24 hours. The mixture is treated with saturated NaHCO₃ and the solution is extracted with EtOAc. The organic layer is washed with saturated NaHCO₃ and brine and dried over MgSO₄. The solvent is removed in vacuo and the mixture is purified by chromatography to give 11a.



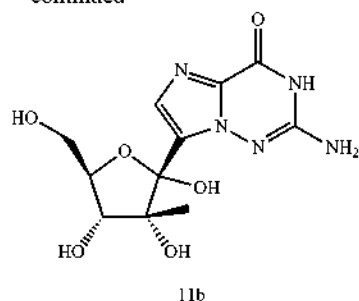
A solution of 11a in a suitable solvent such as methanol or THF is treated with about five to ten mole equivalents of NH₃ in methanol or THF. The reaction is followed by TLC. After about one to 48 hours, the solvent is evaporated and 11b is isolated by chromatography. Alternatively, the mixture of 11a and NH₃ is heated in a sealed glass tube or Parr bomb to about 60 to about 120° C. for about one to about 48 hours and subsequently isolated in the same manner as described.



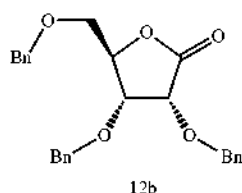
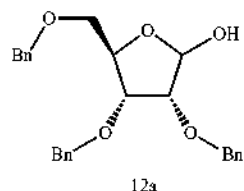
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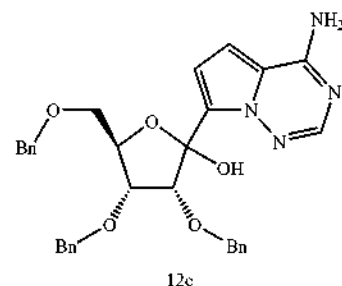
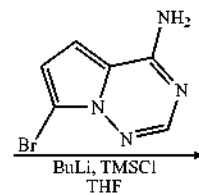
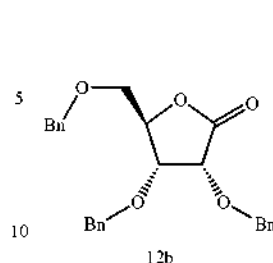


11b in DCM is cooled to about -78°C . and treated with about four to 10 mole equivalents of BBr_3 for about one to about 24 hours. The mixture is treated with about 4:1 MeOH-pyridine and the solution was warmed to room temperature. The solvent is removed in vacuo and the mixture is treated with concentrated NH_4OH followed by removal of solvent ($\times 3$). The mixture is purified by reverse phase HPLC to give 11.

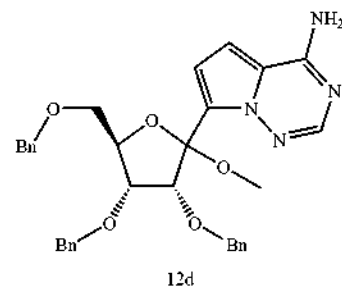
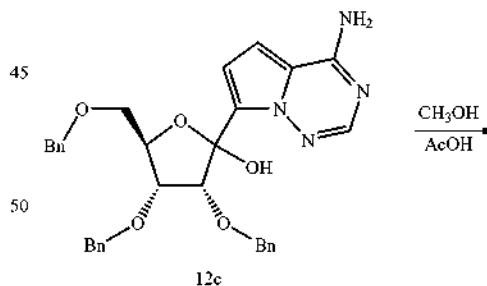


Compound 12a (prepared according to *J. Org. Chem.*, 1961, 26, 4605; 10.0 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) and placed under nitrogen. Acetic anhydride (20 mL) was added, and the mixture was stirred for 48 h at room temperature. When the reaction was complete by LC/MS, it was poured onto 500 mL ice water and stirred for 20 min. The aqueous layer was extracted with ethyl acetate (3×200 mL). The organic extracts were combined and washed with water (3×200 mL). The aqueous layers were discarded and the organic was dried over anhydrous MgSO_4 and evaporated to dryness. The residue was taken up in DCM and loaded onto a silica gel column. The final product 12b was purified by elution with 25% EtOAc/hexanes; 96% yield. $^1\text{H-NMR}$ (CD_3CN): δ 3.63-3.75 (m, 2H), 4.27 (d, 1H), 4.50-4.57 (m, 3H), 4.65 (s, 3H), 4.69-4.80 (m, 2H), 7.25 (d, 2H), 7.39 (m, 13H).

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7-Bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (prepared according to WO2007056170, 0.5 g, 2.4 mmol) was suspended in anhydrous THF (10 mL). Under nitrogen with stirring, TMSCl (0.668 mL, 5.28 mmol) was added and the mixture was stirred for 20 min. at room temperature. The reaction was then cooled to -78°C . and a solution of BuLi (6.0 mL, 1.6 N in hexanes) was added slowly. The reaction was stirred for 10 min. at -78°C . and then the lactone 12b was added via syringe. When the reaction was complete by LC/MS, acetic acid was added to quench. Solvents were removed by rotary evaporation and the residue was taken up in a mixture of 50:50 dichloromethane/water (100 mL). The organic layer was collected and washed with 50 mL additional water, dried over anhydrous MgSO_4 and filtered. Evaporation and purification by column chromatography (0-50% EtOAc:hexanes) provided a 1:1 mixture of anomers 12c; 25% yield. LC/MS (m/z : 553, $\text{M}+\text{H}^+$).

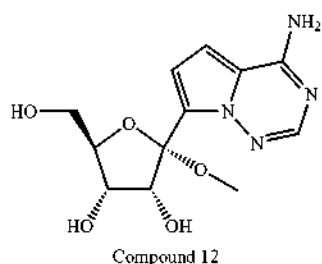
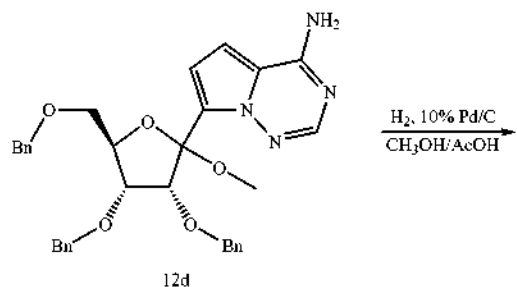


Compound 12c (0.4 g, 0.725 mmol) was stirred in a 1:1 mixture of acetic acid and methanol (10 mL) for 12 h. When

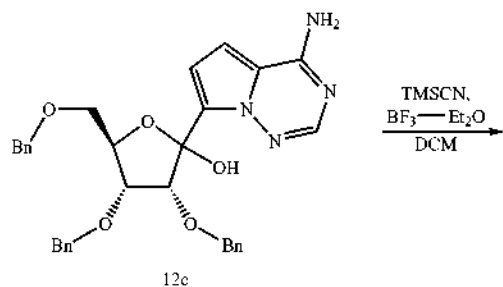
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the reaction was complete by LC/MS, solvents were removed by high vacuum. The residue was taken up in dichloromethane and loaded onto a silica gel column. A mixture of anomers was eluted using a gradient of 0-75% ethyl acetate and hexanes; 51.4% yield of compound 12d. ¹H-NMR (CD₃CN): δ 2.87 (s, 3H), 3.58-3.79 (dd, 2H), 4.11-4.19 (m, 1H), 4.23-4.33 (m, 1H), 4.39-4.42 (m, 1H), 4.49-4.60 (m, 3H), 4.68-4.73 (m, 2H), 6.22 (bs, 2H), 6.72 (d, 2H), 6.79 (d, 1H), 6.84 (d, 1H), 7.17 (m, 2H), 7.39 (m, 13H), 7.84 (s, 1H).



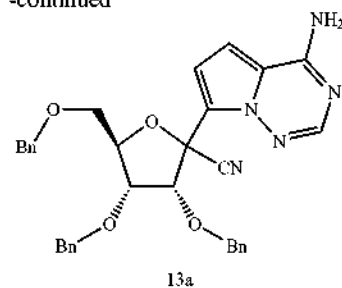
Compound 12d (0.150 g, 0.265 mmol) was dissolved in a 1:1 mixture of methanol and acetic acid (20 mL). 10% Pd/C (150 mg) was added and the reaction was flushed with nitrogen three times. With stirring, hydrogen gas was introduced. The reaction was stirred under hydrogen for 16 h. When the reaction was complete by LC/MS, the catalyst was filtered off and solvents removed under vacuum. The residue was re-dissolved in a mixture of water and TEA (to keep pH at ~10), and both anomers were purified by prep HPLC under neutral conditions; a total of 51% yield. ¹H-NMR of compound 12 (D₂O): δ 3.16 (s, 3H), 3.69-3.84 (dd, 2H), 4.07-4.10 (m, 1H), 4.22-4.24 (m, 1H), 6.74 (d, 1H), 6.78 (d, 1H), 7.70 (s, 1H). ¹H-NMR of the other alpha-anomer (D₂O): δ 2.87 (s, 3H), 3.58-3.84 (dd, 2H), 3.99-4.09 (m, 1H), 4.30-4.38 (m, 1H), 4.49 (d, 1H), 6.75 (d, 1H), 6.82 (d, 1H), 7.69 (s, 1H).



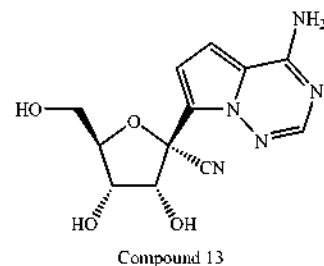
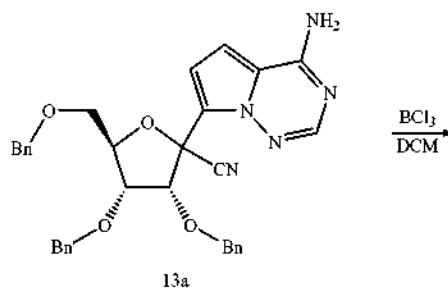
Compound 13

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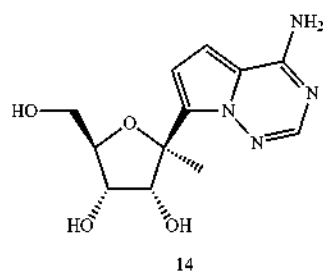
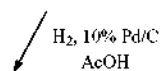
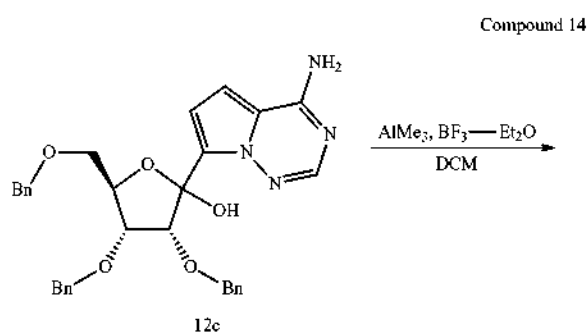
Compound 12c (0.28 g, 0.51 mmol) was dissolved in anhydrous dichloromethane and placed under nitrogen. Trimethylsilyl cyanide (0.35 mL) was added and the mixture was cooled to 0° C. After stirring for 10 min., boron trifluoride etherate (50 ul) was added and the reaction was allowed to warm to room temperature. When the reaction was complete by LC/MS, triethylamine was added to quench and solvents were removed by rotary evaporation. The residue was taken up in dichloromethane and loaded onto a silica gel column. A mixture of anomers was eluted using a gradient of 0-75% ethyl acetate and hexanes; 37% yield of 13a. ¹H-NMR (CD₃CN): δ 3.61-3.90 (m, 2H), 4.09-4.19 (m, 2H), 4.30-4.88 (m, 7H), 4.96 (d, 0.5H), 5.10 (d, 0.5H), 6.41 (bs, 2H), 6.73-6.78 (m, 1H), 6.81-6.88 (m, 1H), 7.17 (m, 2H), 7.39 (m, 13H), 7.86 (s, 0.5H), 7.93 (s, 0.5H).



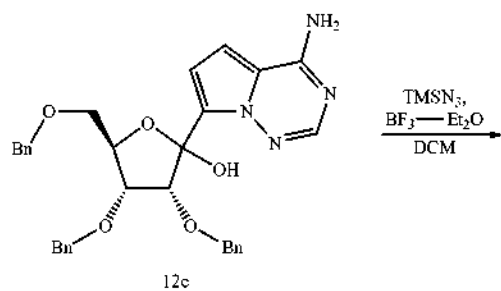
Compound 13a (0.70 mg, 0.124 mmol) was dissolved in anhydrous dichloromethane (2 mL), placed under nitrogen, and cooled to -78° C. A solution of 1 N boron trichloride in dichloromethane (0.506 mL) was added and the reaction stirred for 1 h at -78° C. When the reaction was complete by LC/MS, methanol was added to quench. The reaction was allowed to rise to room temperature and solvents were removed by rotary evaporation. The product anomers were purified by prep-HPLC; a total of 74% yield. ¹H-NMR of Compound 13 (D₂O): δ 3.65-3.75 (dd, 2H), 4.12 (t, 1H), 4.29 (q, 1H), 4.80 (d, 1H), 6.97 (d, 1H), 7.14 (d, 1H), 7.93 (s, 1H). ¹H-NMR of the other alpha-anomer (D₂O): δ 3.72-3.93 (dd, 2H), 4.16-4.19 (m, 1H), 4.60-4.62 (m, 1H), 5.01 (d, 1H), 6.95 (d, 1H), 7.28 (d, 1H), 7.96 (s, 1H).

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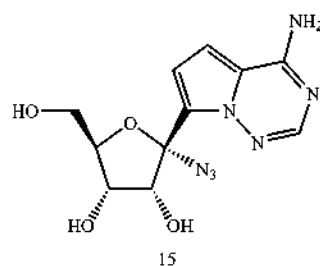
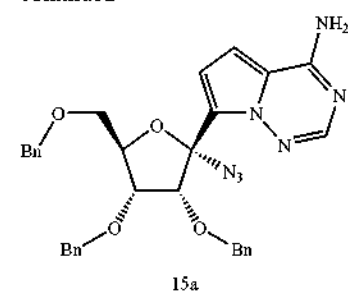


Compound 14 may be obtained from 12c in a manner similar to the method used to synthesize Compound 4.



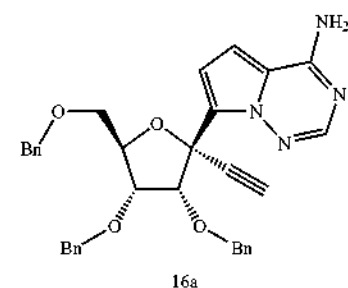
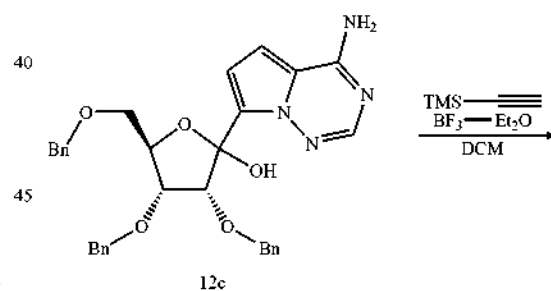
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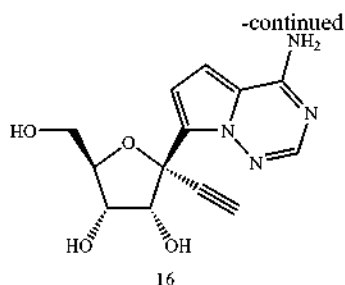
Compound 15 may be obtained from 12c in a manner similar to that described in preparation of Compound 13 except using TMSN₃ instead of TMSCN.

Compound 16



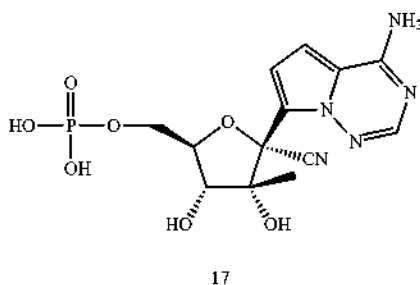
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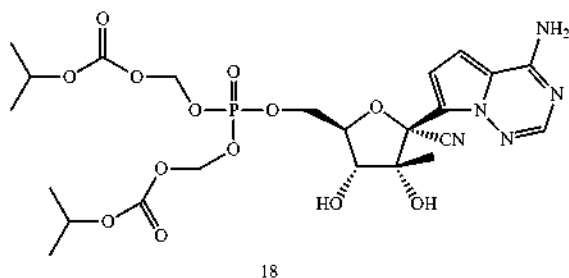
Compound 16 may be obtained from 12c in a manner similar to that described in preparation of Compound 13 except using TMS-acetylene instead of TMSCN.

Compound 17



A mixture of about 0.05 mmol of Compound 5 and about 0.5 mL of trimethylphosphate is sealed in a container for about one to about 48 hours. The mixture is cooled to about -10 to about 10° C. and about 0.075 mmol of phosphorous oxychloride is added. After about one to about 24 hours, the reaction is quenched with about 0.5 mL of 1M tetraethylammonium bicarbonate and the desired fraction are isolated by anion exchange chromatography. The appropriate fractions are then desalted by reverse-phase chromatography to give Compound 17.

Compound 18



Compound 17 (about 1.19 mmol) is dried over phosphorous pentoxide in a vacuum for about overnight. The dried material is suspended in about 4 mL of anhydrous DMF and about 4.92 mmol DIPEA. About 7.34 mmol of iso-propyl chloromethyl carbonate (Antiviral Chemistry & Chemotherapy 8:557 (1997)) is added and the mixture is heated to about 25 to about 60° C. for about 30 min to about 24 hours. Heating is removed for about one to about 48 hours and the reaction filtered. The filtrate is diluted with water, Compound 18 is partitioned into CH₂Cl₂, the organic solution is dried and

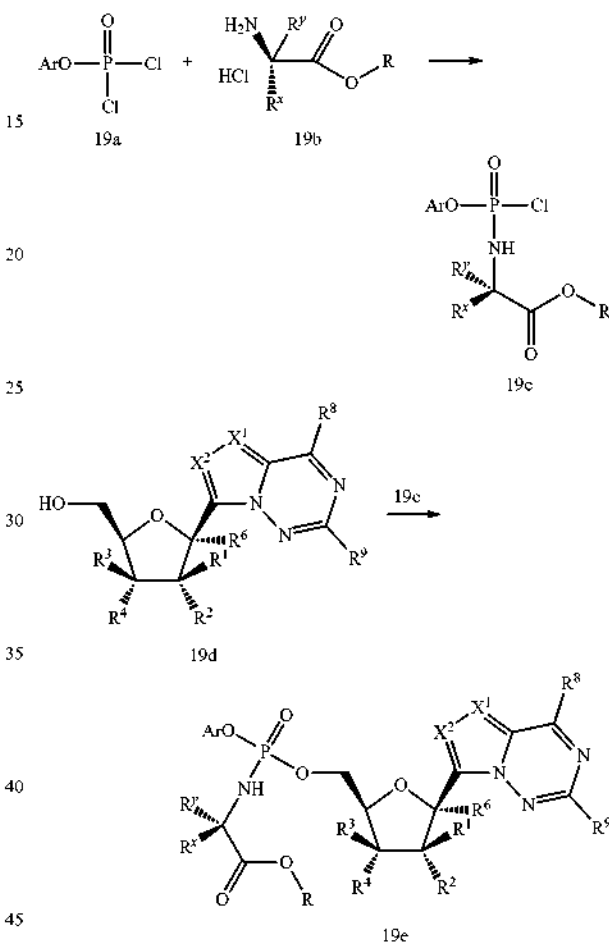
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evaporated, and the residue is purified by reverse-phase HPLC to isolate Compound 18.

Mono Phosphoramidate Prodrugs

Non-limiting examples of mono-phosphoramidate prodrugs comprising the instant invention may be prepared according to general Scheme 1.

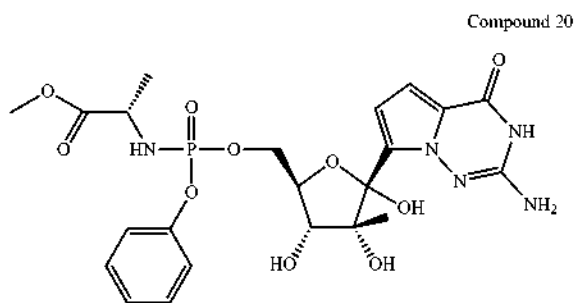
Scheme 1



The general procedure comprises the reaction of an amino acid ester salt 19b, e.g., HCl salt, with an aryl dichlorophosphate 19a in the presence of about two to ten equivalents of a suitable base to give the phosphoramidate 19c. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. Tertiary amines are particularly preferred. Preferably, the product of each step is used directly in the subsequent steps without recrystallization or chromatography. Specific, but non-limiting, examples of 19a, 19b, and 19c can be found in WO 2006/121820 that is hereby incorporated by reference in its entirety. A nucleoside base 19d reacts with the phosphoramidate 19c in the presence of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. The product 19e may be isolated by recrystallization and/or chromatography.

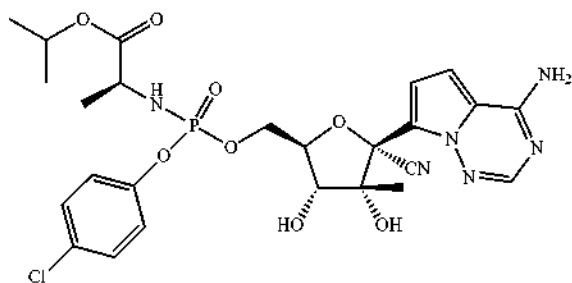
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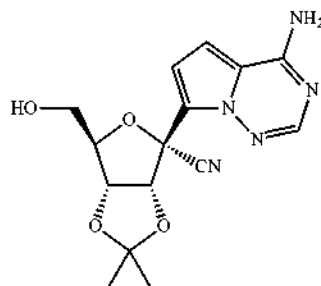
About 3.1 mmol of phenyl methoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* 1993, 36, 1048-1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of Compound 11 and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give Compound 20.

Compound 21



About 3.1 mmol of 4-chlorophenyl 2-propyloxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* 1993, 36, 1048-1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of Compound 5 and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give Compound 21.

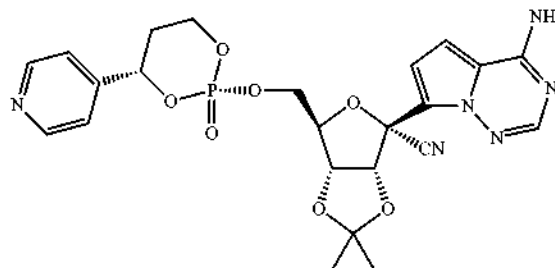
Compound 22



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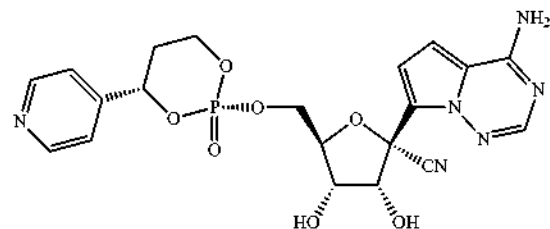
A mixture of about 0.52 mmol of Compound 13 and about 12 mL dry acetone, about 0.7 mL of 2,2-dimethoxypropane and about 1.28 mmol of di-p-nitrophenylphosphoric acid is stirred for about 24 hours to about seven days. The reaction mixture is neutralized with about 20 mL of 0.1 N NaHCO₃ and the acetone is evaporated. The desired material is partitioned into chloroform, the chloroform solution is dried, and the solvent is evaporated. Compound 22 is purified from the residue by conventional means.

Compound 23



A solution of about 0.53 mmol of Compound 22 in about 5 mL of DMF is treated with about 1 mL of a 1 M solution of t-butylmagnesium chloride in THF. After about 30 min to about 5 hours, a solution of about 0.65 mmol of trans-4-[(S)-pyridin-4-yl]-2-(4-nitrophenoxy)-2-oxo-1,3,2-dioxaphosphorinane (Reddy, *Tetrahedron Letters* 2005, 4321-4324) is added and the reaction is stirred for about one to about 24 hours. The solution is concentrated in a vacuum and the residue is purified by chromatography to give Compound 23.

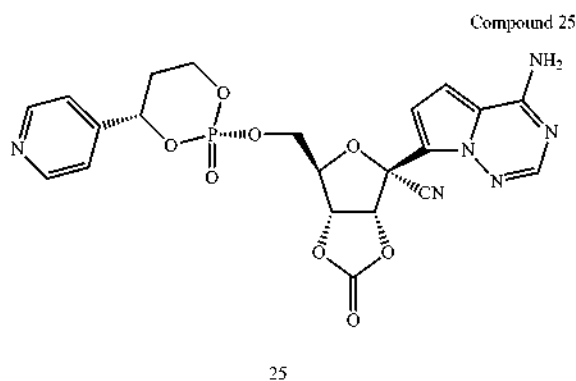
Compound 24



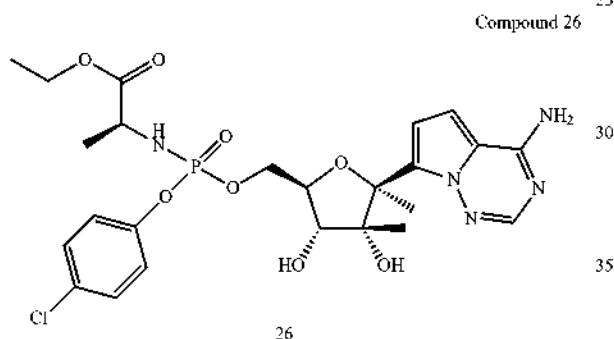
A solution of about 70% aqueous trifluoroacetic acid is cooled to 0° C. and is treated with about 0.32 mmol of Compound 23 for about one to 24 hours. The solution is concentrated and the residue is purified by chromatography to give Compound 24.

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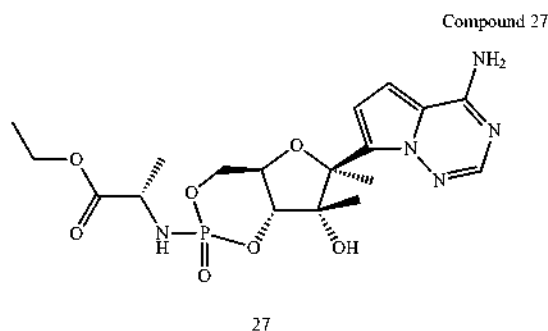
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A solution of about 1.56 mmol of Compound 24 in about 15 mL of THF is treated with about 4.32 mmol of CDI. After about one to about 24 hours, the solvent is evaporated and the residue is purified by chromatography to give Compound 25.



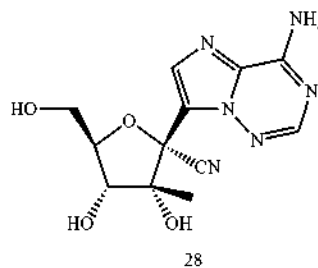
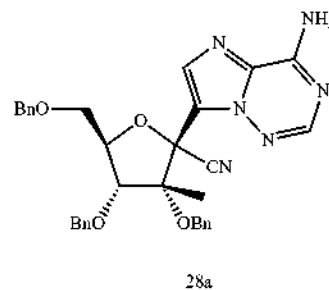
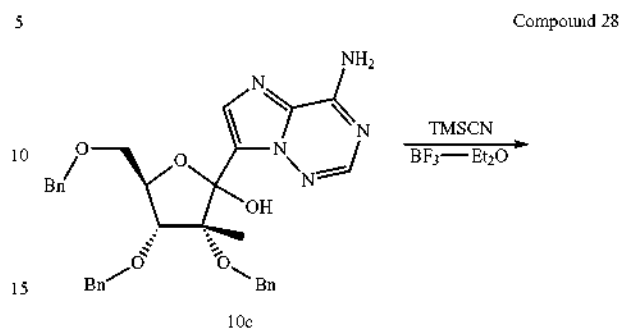
About 3.1 mmol of 4-chlorophenyl 2-ethoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* 1993, 36, 1048-1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of Compound 4 and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give Compound 26.



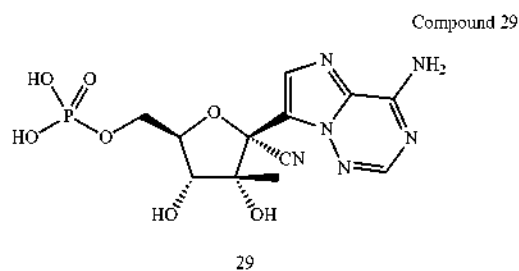
A solution of Compound 26 in DMSO is treated with about 3 mole equivalents of potassium t-butoxide for about 15 min

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to 24 hours. The reaction is quenched with 1N HCl and Compound 27 is isolated by reverse-phase HPLC.



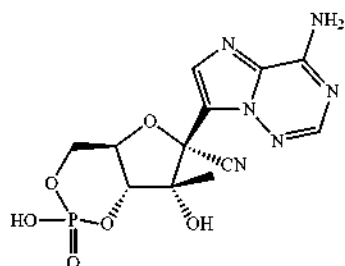
Compound 28 is prepared in the same manner as Compound 5 but using Compound 10c as a starting material.



Compound 29 is prepared in the same manner as Compound 17 using Compound 28 as a starting material.

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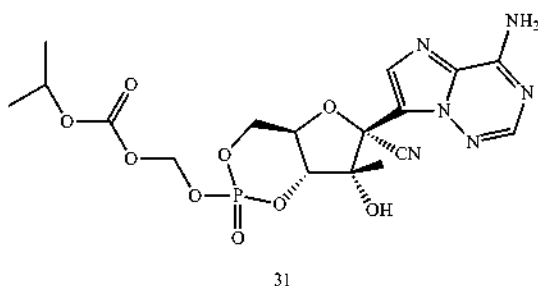
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Compound 30

Compound 30 is prepared by treating Compound 29 with about one to about five equivalents of DCC in pyridine and heating the reaction to reflux for about one to about 24 hours. Compound 30 is isolated by conventional ion exchange and reverse-phase HPLC.

Compound 31

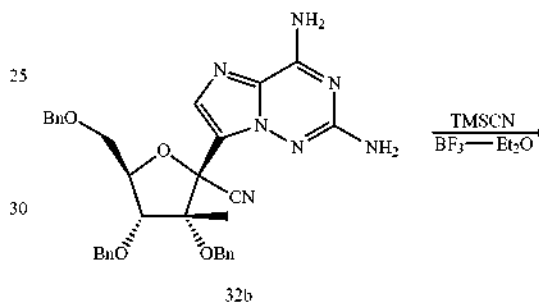


A solution of about 0.4 mmol of Compound 30 in about 10 mL of DMF is treated with about 0.8 mmol of DIPEA and about 0.8 mmol of chloromethyl isopropyl carbonate (WO2007/027248). The reaction is heated to about 25 to about 80° C. for about 15 min to about 24 hours. The solvent is removed under vacuum and the residue is purified by HPLC to give Compound 31.

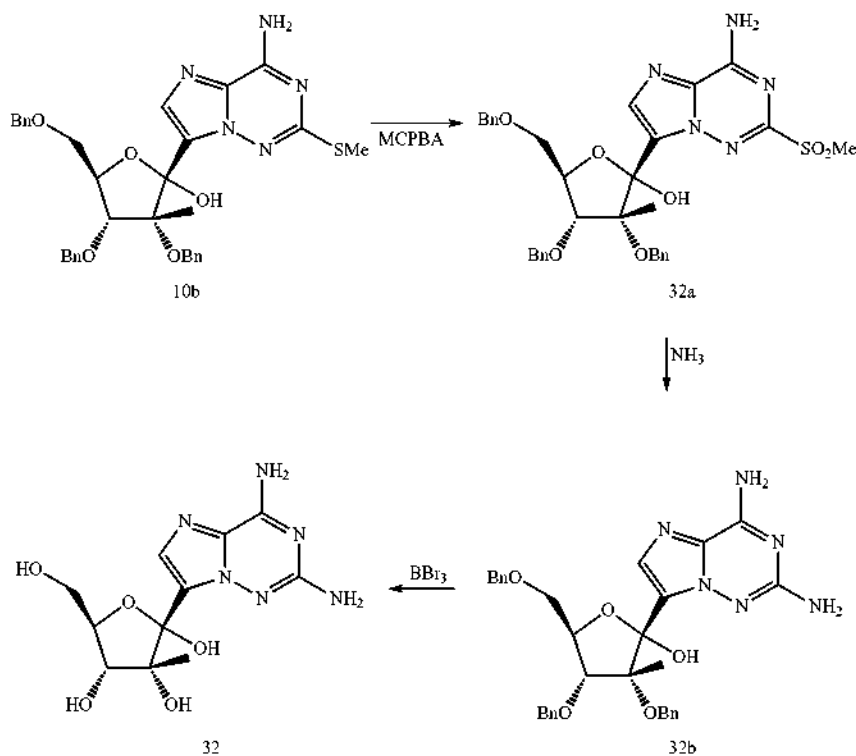
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Compound 10b is dissolved in DCM and treated with about two to about four mole equivalents of MCPBA for about one to about 24 hours. The mixture is treated with saturated NaHCO₃ and the solution is extracted with EtOAc. The organic layer is washed with saturated NaHCO₃ and brine and dried over MgSO₄. The solvent is removed in vacuo and the mixture is purified by chromatography to give 32a. Compound 32a is transferred to a steel bomb reactor, and is cooled at -78° C. Liquid ammonia is collected at -78° C. and is added to the bomb reactor. The bomb reactor is tightly sealed and is warmed up to room temperature. The mixture is heated at about 50° C. for about 24 h. The gas is vented and 32b is isolated by chromatography. Compound 32b is converted to Compound 32 in the same manner as for the conversion of Compound 2a to Compound 2.

Compound 33



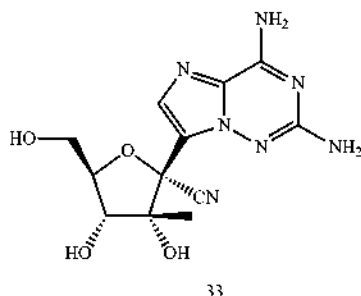
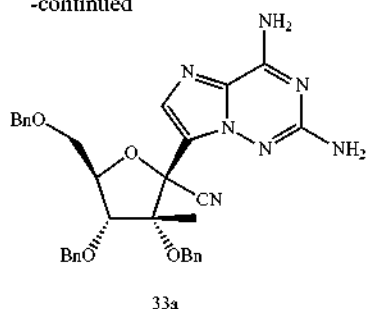
Compound 32



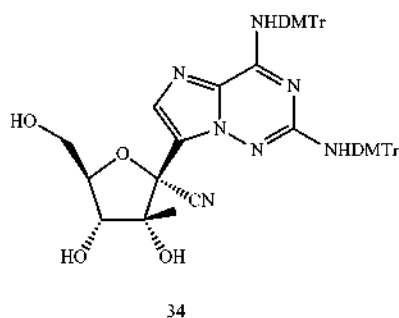
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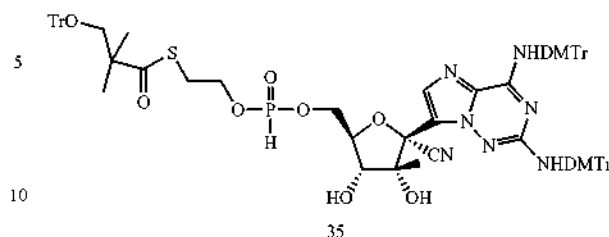
Compound 32b is converted to Compound 33 in the same manner as the conversion of Compound 2a to Compound 5.



Compound 33 (about 0.22 mmol) is dissolved in anhydrous pyridine (about 2 mL) and chlorotrimethylsilane (about 0.17 mL) is added. The mixture is stirred at about 0 to about 25° C. for about one to about 24 hours. Additional chlorotrimethylsilane (about 0.1 mL) is added and the reaction is stirred for about one to about 24 hours. 4,4'-Dimethoxytrityl chloride (about 0.66 mmol) and DMAP (about 0.11 to about 0.22 mmol) is sequentially added. The mixture is stirred for about one to about 24 hours. A solution of TBAF (1.0 M, about 0.22 mL) in THF is added and the reaction is stirred for about one to about 24 hours. The mixture is partitioned between ethyl acetate and water. The ethyl acetate layer is dried and concentrated. The residue is purified chromatography to afford Compound 34 which may be a mixture of mono- and di-dimethoxytritylated compounds.

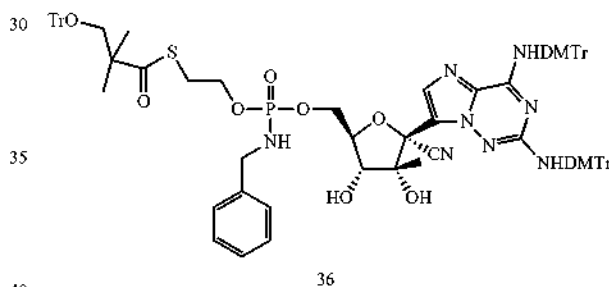
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Compound 35



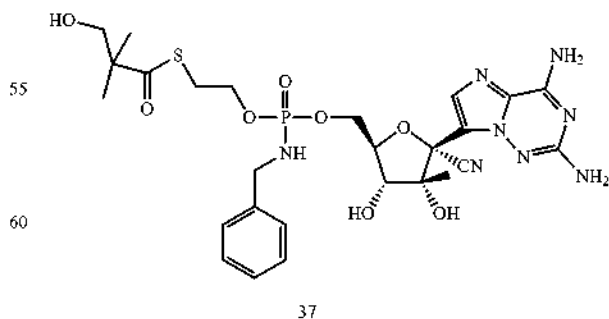
A mixture of about 1.25 mmol of Compound 34 and about 1.9 mmol of triethylammonium 2-(2,2-dimethyl-3-(trityloxy)propanoylthio)ethyl phosphonate (WO2008082601) is dissolved in anhydrous pyridine (about 19 mL). Pivaloyl chloride (about 2.5 mmol) is added dropwise at about -30 to about 0° C. and the solution is stirred at for about 30 min to about 24 hours. The reaction is diluted with methylene chloride and is neutralized with aqueous ammonium chloride (about 0.5M). The methylene chloride phase is evaporated and the residue is dried and is purified by chromatography to give Compound 35 which may be a mixture of mono- and di-dimethoxytritylated compounds.

Compound 36



To a solution of about 0.49 mmol of Compound 35 in anhydrous carbon tetrachloride (about 5 mL) is added dropwise benzylamine (about 2.45 mmol). The reaction mixture is stirred for about one to about 24 hours. The solvent is evaporated and the residue is purified by chromatography to give Compound 36 which may be a mixture of mono- and di-dimethoxytritylated compounds.

Compound 37

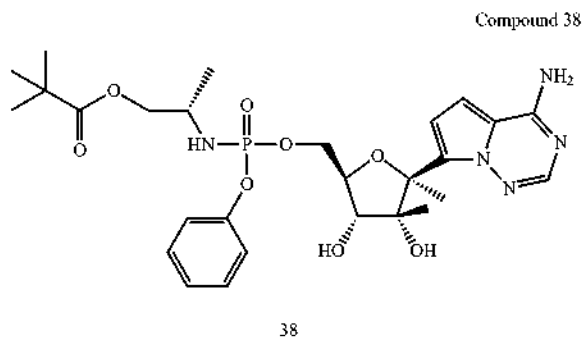


A solution of about 2 mmol of Compound 36 in methylene chloride (about 10 mL) is treated with an aqueous solution of

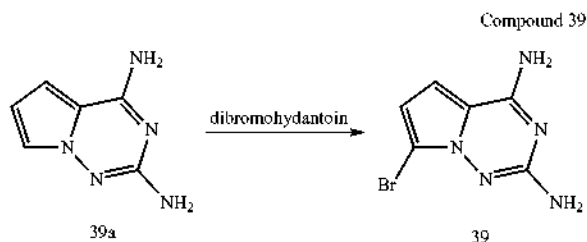
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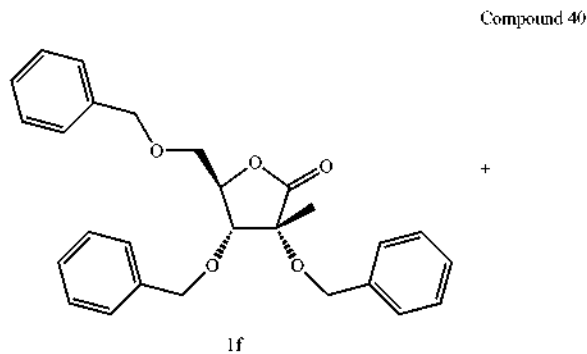
trifluoroacetic acid (90%, about 10 mL). The reaction mixture is stirred at about 25 to about 60° C. for about one to about 24 hours. The reaction mixture is diluted with ethanol, the volatiles are evaporated and the residue is purified by chromatography to give Compound 37.



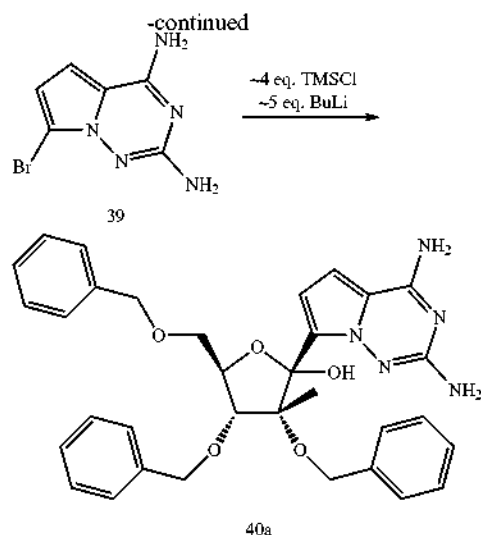
About 90 mM Compound 14 in THF is cooled to about -78° C. and about 2.2 to about 4.4 equivalents of t-butylmagnesium chloride (about 1 M in THF) is added. The mixture is warmed to about 0° C. for about 30 min and is again cooled to about -78° C. A solution of (2S)-2-[(chloro(1-phenoxy)phosphoryl)amino]propyl pivalate (WO2008085508) (1 M in THF, about 2 equivalents) is added dropwise. The cooling is removed and the reaction is stirred for about one to about 24 hours. The reaction is quenched with water and the mixture is extracted with ethyl acetate. The extracts are dried and evaporated and the residue purified by chromatography to give Compound 38.



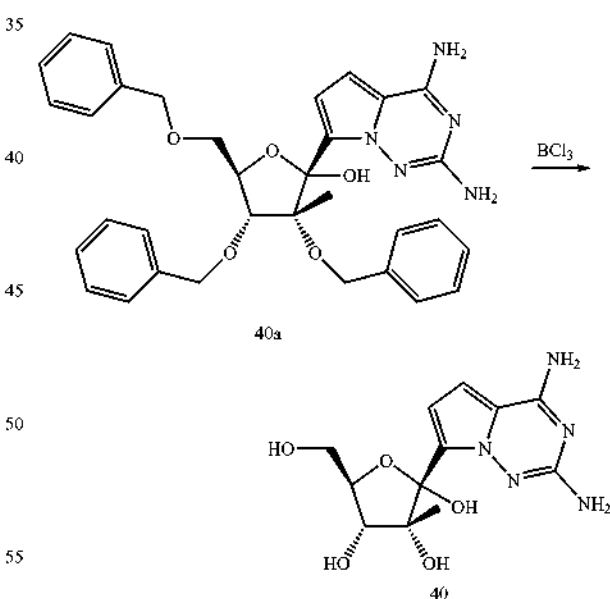
A solution of about one part Compound 39a (Patil, et al.; *Journal of Heterocyclic Chemistry* 1994, 31(4), 781-6) in anhydrous DMF is cooled to about -20° C. and about 0.5 parts of 1,3-diromo-5,5-dimethylhydantoin is added in portions. After about one to about 24 hours, a saturate aqueous sodium bisulfite solution is added and the solids are collected by filtration. The solids are partitioned between ethyl acetate and dilute aqueous sodium carbonate. The organic phase is washed with dilute sodium carbonate then dried and concentrated to give Compound 39.



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A solution of about one part of 39 and about four parts of trimethylsilylchloride in THF is stirred at about 20 to about 60° C. for about 30 min to about six hours. The solution is cooled to about -70 to about -100° C. and a solution of about five parts of butyllithium in hexanes is added. After about 30 min. to about three hours, the reaction is allowed to warm to about 0° C. over about three hours. The reaction is quenched with saturated NaHCO₃ and the mixture is extracted with ether. The ether extracts are washed with brine, dried, and the solvent evaporated to give 40a which may be further purified by chromatography.

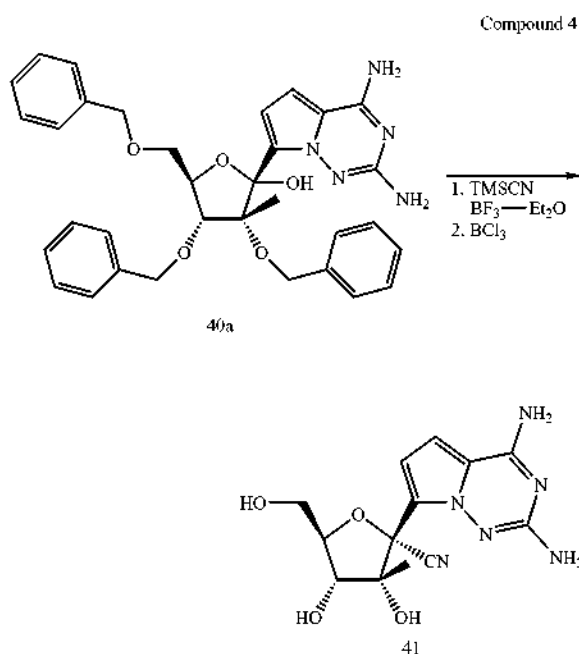


A solution of one part of 40a in dichloromethane is cooled to about -100 to about -70° C. A 1.0 M solution of BCl₃ in dichloromethane (about 10 to 20 parts) is added and the reaction is stirred for about 30 min. to about 3 hours. A mixture of pyridine and methanol (about 1:2) is then added to quench the reaction. The resulting mixture is slowly warmed to room temperature and concentrated. The residue is suspended in about 27% ammonium hydroxide and concentrated. This process is repeated twice. The residue is re-dis-

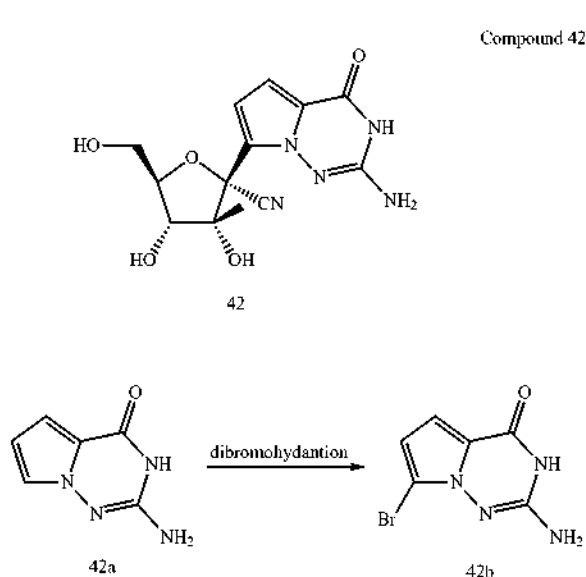
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solved in methanol and concentrated. This process is repeated once. The residue is purified by RP-HPLC to give 40.

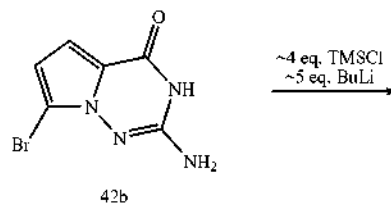
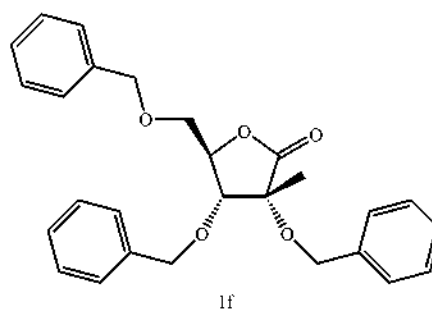


Compound 41 may be prepared from Compound 40a in the same manner as Compound 5 was prepared from Compound 2a.

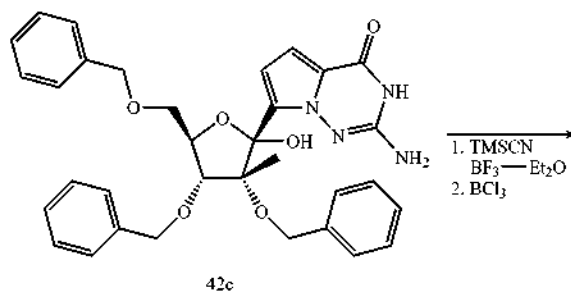


A solution of about one part Compound 42a (Patil, et al.; *Journal of Heterocyclic Chemistry* 1994, 31(4), 781-6) in anhydrous DMF is cooled to about -20° C. and about 0.5 parts of 1,3-diromo-5,5-dimethylhydantoin is added in portions. After about one to about 24 hours, a saturate aqueous sodium bisulfite solution is added and the solids are collected by filtration. The solids are partitioned between ethyl acetate and dilute aqueous sodium carbonate. The organic phase is washed with dilute sodium carbonate then dried and concentrated to give Compound 42b.

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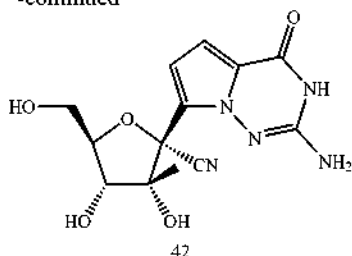
A solution of about one part of 42b and about four parts of trimethylsilylchloride in THF is stirred at about 20 to about 60° C. for about 30 min to about six hours. The solution is cooled to about -70 to about -100° C. and a solution of about five parts of butyllithium in hexanes is added. After about 30 min. to about three hours, the reaction is allowed to warm to about 0° C. over about three hours. The reaction is quenched with saturated NaHCO₃ and the mixture is extracted with ether. The ether extracts are washed with brine, dried, and the solvent evaporated to give 42c which may be further purified by chromatography.



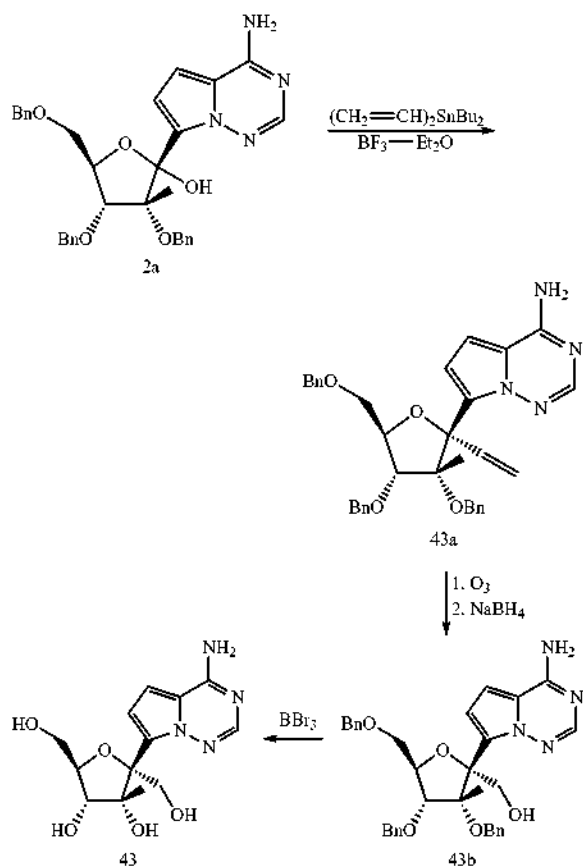
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Compound 42 may be prepared from Compound 42a in the same manner as Compound 5 was prepared from Compound 2a.



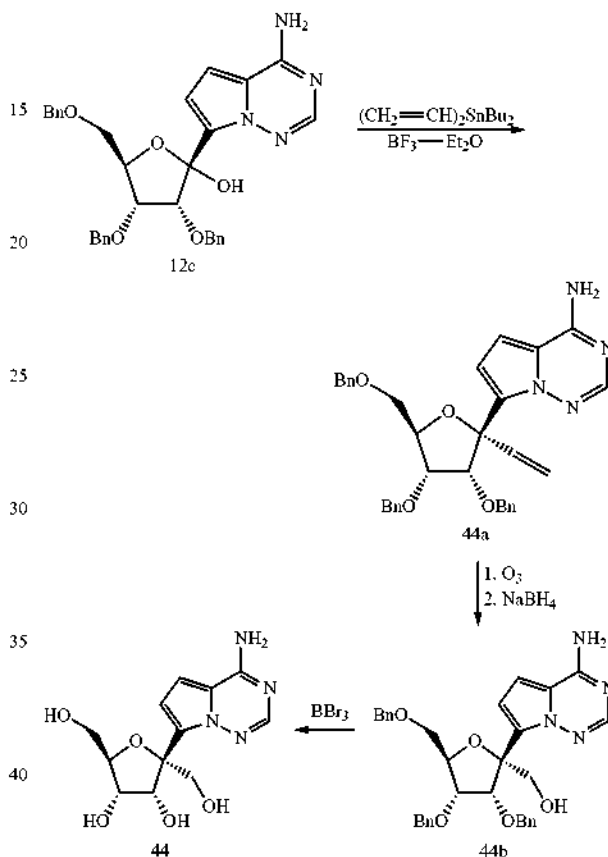
A solution of one part of Compound 2a in CH_2Cl_2 is treated with about two parts of BF_3OEt_2 at about -78°C . under an argon atmosphere and about three parts of $(\text{CH}_2=\text{CH})_2\text{SnBu}_2$. The reaction temperature is gradually raised to rt during about one to four hours. Usual extractive workup followed by purification by chromatography will give Compound 43a. Compound 43a is dissolved in methanol and dichloromethane and cooled to about -78°C . Ozone is bubbled into the stirred solution for about 1.5 hours at -78°C . The solution is then flushed with nitrogen to remove the ozone. Sodium borohydride (about 8 equivalents) is then added in small portions over about 5 minutes at -78°C . Methanol is added and the reaction is slowly warmed to about 0°C . After about 1.5 hours, the reaction is quenched with

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saturated bicarbonate solution and extracted with CH_2Cl_2 . The combined organics are washed with brine, dried, filtered and the solvent is removed in vacuo. The residue is purified by chromatography to give Compound 43b. Compound 43b may be debenzylated in the same manner as Compound 2a to give Compound 43 that may be further purified by chromatography.

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Compound 44



Compound 44 may be obtained in the same manner as Compound 43, starting with Compound 12c.

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocols.

Cell-Based Flavivirus Immunodetection Assay

BHK21 or A549 cells are trypsinized, counted and diluted to 2×10^5 cells/mL in Hams F-12 media (A549 cells) or RPMI-1640 media (BHK21 cells) supplemented with 2% fetal bovine serum (FBS) and 1% penicillin/streptomycin. 2×10^4 cells are dispensed in a clear 96-well tissue culture plates per well and placed at 37°C , 5% CO_2 overnight. On the next day, the cells are infected with viruses at multiplicity of infection (MOI) of 0.3 in the presence of varied concentrations of test compounds for 1 hour at 37°C and 5% CO_2 for another 48 hours. The cells are washed once with PBS and fixed with cold methanol for 10 min. After washing twice with PBS, the fixed cells are blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1 hour at room temperature. The primary antibody solution (4G2) is then added at a concentration of 1:20 to 1:100 in PBS containing 1% FBS and 0.05% Tween-20 for 3 hours. The cells are then washed three times with PBS followed by one hour incubation with horseradish peroxidase (HRP)-conjugated anti-mouse IgG (Sigma, 1:2000 dilution). After washing three times with PBS, 50 microliters of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution (Sigma) is added to each well for two minutes. The reaction is stopped by addition of 0.5 M sulfuric acid. The plates are read at 450 nm absorbance for viral load quantification. After measurement, the cells are washed three times with PBS followed by incubation with propidium iodide for 5 min. The plate is read in a Tecan Safire™ reader (excitation 537 nm, emission 617 nm) for cell number quantification. Dose response curves are plotted from the mean absorbance versus the log of the of the concentration of test compounds. The EC_{50} is calculated by non-linear regression analysis. A positive control such as N-nonyl-deoxyribojirimycin may be used.

Cell-Based Flavivirus Cytopathic Effect Assay

For testing against West Nile virus or Japanese encephalitis virus, BHK21 cells are trypsinized and diluted to a concentration of 4×10^5 cells/mL in RPMI-1640 media supplemented with 2% FBS and 1% penicillin/streptomycin. For testing against dengue virus, Huh7 cells are trypsinized and diluted to a concentration of 4×10^5 cells/mL in DMEM media supplemented with 5% FBS and 1% penicillin/streptomycin. A 50 microliter of cell suspension (2×10^4 cells) is dispensed per well in a 96-well optical bottom PIT polymer-based plates (Nunc). Cells are grown overnight in culture medium at 37°C , 5% CO_2 , and then infected with West Nile virus (e.g. B956 strain) or Japanese encephalitis virus (e.g. Nakayama strain) at $\text{MOI}=0.3$, or with dengue virus (e.g. DEN-2 NGC strain) at $\text{MOI}=1$, in the presence of different concentrations of test compounds. The plates containing the virus and the compounds are further incubated at 37°C , 5% CO_2 for 72 hours. At the end of incubation, 100 microliters of CellTiter-Glo™ reagent is added into each well. Contents are mixed for 2 minutes on an orbital shaker to induce cell lysis. The plates are incubated at room temperature for 10 minutes to stabilize

luminescent signal. Luminescence reading is recorded using a plate reader. A positive control such as N-nonyl-deoxyribojirimycin may be used.

Antiviral Activity in a Mouse Model of Dengue Infection.

Compounds are tested *in vivo* in a mouse model of dengue virus infection (Schul et al. J. Infectious Dis. 2007, 195:665-74). Six to ten week old AG129 mice (B&K Universal Ltd, Hill, UK) are housed in individually ventilated cages. Mice are injected intraperitoneally with 0.4 mL TSV01 dengue virus 2 suspension; Blood samples are taken by retro orbital puncture under isoflurane anaesthesia. Blood samples are collected in tubes containing sodium citrate to a final concentration of 0.4%, and immediately centrifuged for 3 minutes at 6000 g to obtain plasma. Plasma (20 microliters) is diluted in 780 microliters RPMI-1640 medium and snap frozen in liquid nitrogen for plaque assay analysis. The remaining plasma is reserved for cytokine and NS1 protein level determination. Mice develop dengue viremia rising over several days, peaking on day 3 post-infection.

For testing of antiviral activity, a compound of the invention is dissolved in vehicle fluid, e.g. 10% ethanol, 30% PEG 300 and 60% D5W (5% dextrose in water; or 6N HCl (1.5 eq): 1N NaOH (pH adjusted to 3.5): 100 mM citrate buffer pH 3.5 (0.9% v/v: 2.5% v/v: 96.6% v/v). Thirty six 6-10 week old AG129 mice are divided into six groups of six mice each. All mice are infected with dengue virus as described above (day 0). Group 1 is dosed by oral gavage of 200 mL/mouse with 0.2 mg/kg of a compound of the invention twice a day (once early in the morning and once late in the afternoon) for three consecutive days starting on day 0 (first dose just before dengue infection). Groups 2, 3 and 4 are dosed the same way with 1 mg/kg, 5 mg/kg and 25 mg/kg of the compound, respectively. A positive control may be used, such as (2R,3R,4R,5R)-2-(2-amino-6-hydroxy-purin-9-yl)-5-hydroxymethyl-3-methyl-tetrahydro-furan-3,4-diol, dosed by oral gavage of 200 microliters/mouse the same way as the previous groups. A further group is treated with only vehicle fluid.

On day 3 post-infection approximately 100 microliter blood samples (anti-coagulated with sodium citrate) are taken from the mice by retro-orbital puncture under isoflurane anaesthesia. Plasma is obtained from each blood sample by centrifugation and snap frozen in liquid nitrogen for plaque assay analysis. The collected plasma samples are analyzed by plaque assay as described in Schul et al. Cytokines are also analysed as as described by Schul. NS1 protein levels are analysed using a Platelia™ kit (BioRad Laboratories). An anti-viral effect is indicated by a reduction in cytokine levels and/or NS1 protein levels.

Typically, reductions in viremia of about 5-100 fold, more typically 10-60 fold, most typically 20-30 fold, are obtained with 5-50 mg/kg bid dosages of the compounds of the invention.

HCV IC_{50} Determination

Assay Protocol: NS5b polymerase assay (40 μL) was assembled by adding 28 μL polymerase mixture (final concentration: 50 mM Tris-HCl at pH 7.5, 10 mM KCl, 5 mM MgCl_2 , 1 mM DTT, 10 mM EDTA, 4 ng/ μL of RNA template, and 75 nM HCV $\Delta 21$ NS5b polymerase) to assay plates followed by 4 μL of compound dilution. The polymerase and compound were pre-incubated at 35°C for 10 minute before the addition of 8 μL of nucleotide substrate mixture (33P- α -labeled competing nucleotide at K_M and 0.5 mM of the remaining three nucleotides). The assay plates were covered and incubated at 35°C for 90 min. Reactions were then filtered through 96-well DEAE-81 filter plates via vacuum. The filter plates were then washed under vacuum with multiple volumes of 0.125 M NaH_2PO_4 , water, and ethanol to

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remove unincorporated label. Plates were then counted on TopCount to assess the level of product synthesis over background controls. The IC₅₀ value is determined using Prism fitting program.

Preferably, compounds described herein inhibited NS5b polymerase with an IC₅₀'s below 1000 μM, more preferably below 100 μM, and most preferably below 10 μM. For example, compound 17 has an IC₅₀ below 1 μM.

HCV EC₅₀ Determination

Replicon cells were seeded in 96-well plates at a density of 8×10³ cells per well in 100 μL of culture medium, excluding Geneticin. Compound was serially diluted in 100% DMSO and then added to the cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO and a total volume of 200 μL. Plates were incubated at 37° C. for 3 days, after which culture medium was removed and cells were lysed in lysis buffer provided by Promega's luciferase assay system. Following the manufacturer's instruction, 100 μL of luciferase substrate was added to the lysed cells and luciferase activity was measured in a TopCount luminometer. Preferably, compounds described herein have EC₅₀'s below 1000 μM, more preferably below 100 μM, and most preferably below 10 μM.

Representative examples of the activity of the compounds Formula I-III are shown in the Table below wherein A represents an EC₅₀ below 1 μM, B represents an EC₅₀ between 1 and 10 μM, and C represents an EC₅₀ between 10 and 100 μM.

Example No.	EC ₅₀ , μM
2	C
3	C
4	C
5	C
6	A
12	B
13	B

The cytotoxicity of a compound of the invention can be determined using the following general protocol.

Cytotoxicity Cell Culture Assay (Determination of CC₅₀):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate.

Assay Protocol for Determination of CC₅₀:

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 μL media per well) and add various concentrations of the tested compound in triplicate (100 μL/well). Include untreated control.
3. Incubate the cells for 5 days at 37° C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2 mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55° C. for 5 min. Add 50 μL of N-methylphenazonium methasulfate (5 μg/ml) per 6 ml of XTT solution.
5. Remove 100 μL media from each well on the assay plate and add 100 μL of the XTT substrate solution per well. Incubate at 37° C. for 45 to 60 min in a CO₂ incubator.
6. Add 20 μL of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC₅₀ value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

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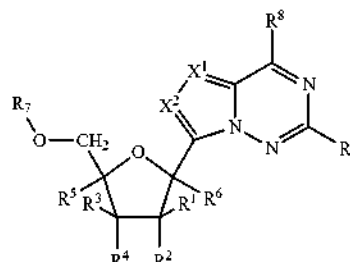
All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, one skilled in the art will understand that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of Formula I:

Formula I



or a pharmaceutically acceptable salt, thereof;

wherein:

each R¹, R², R³, R⁴, or R⁵ is independently H, OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl;

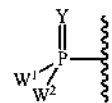
or any two R¹, R², R³, R⁴, or R⁵ on adjacent carbon atoms when taken together are —O(CO)O— or when taken together with the ring carbon atoms to which they are attached form a double bond;

R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl or R⁶ and either R¹ or R² when taken together are —O(CO)O—;

each n is independently 0, 1, or 2;

each R^a is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl(C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), or —SO₂NR¹¹R¹²;

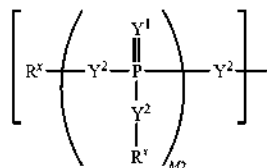
R⁷ is H, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², or



Y is O, S, NR, *N(O)(R), N(OR), *N(O)(OR), or N—NR₂; W¹ and W², when taken together, are —Y³(C(R^v))₂Y³—; or one of W¹ or W² together with either R³ or R⁴ is —Y³— and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:

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Formula Ia

wherein:

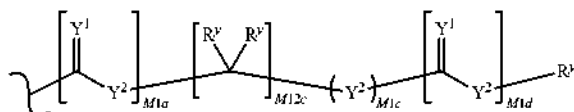
each Y¹ is, independently, O, S, NR, *N(O)(R), N(OR), *N(O)(OR), or N—NR₂;

each Y² is independently a bond, O, CR₂, NR, *N(O)(R), N(OR), *N(O)(OR), N—NR₂, S, S—S, S(O), or S(O)₂;

each Y³ is independently O, S, or NR;

M₂ is 0, 1 or 2;

each R^x is a group of the formula:



wherein:

each M_{1a}, M_{1c}, and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, —CN, —N₃, —NO₂, —OR, —C(=Y¹)R, —C(Y¹)W⁵, —C(=Y¹)

OR, —C(=Y¹)N(R)₂, —N(R)₂, —*N(R)₃, —SR,

—S(O)R, —S(O)₂R, —SO₂W⁵, —S(O)(OR), —S(O)₂(OR), —OC(=Y¹)R, —OC(=Y¹)OR, —OC(=Y¹)(N

(R)₂), —SC(=Y¹)R, —SC(=Y¹)OR, —SC(=Y¹)(N

(R)₂), —N(R)C(=Y¹)R, —N(R)C(=Y¹)OR, —N(R)

C(=Y¹)N(R)₂, —SO₂NR₂, W⁵, (C₁–C₈) alkyl, (C₁–C₈)

substituted alkyl, (C₂–C₈) alkenyl, (C₂–C₈) substituted

alkenyl, (C₂–C₈) alkynyl, (C₂–C₈) substituted alkynyl,

C₆–C₂₀ aryl, C₆–C₂₀ substituted aryl, C₂–C₂₀ heterocyc-

lyl, C₂–C₂₀ substituted heterocyclyl, arylalkyl or sub-

stituted arylalkyl; wherein each alkyl, alkenyl, alkynyl,

aryl, heterocyclyl, or arylalkyl is independently option-

ally substituted with one or more Z groups;

or when taken together, two R^y on the same carbon atom

form a carbocyclic ring of 3 to 7 carbon atoms;

each W⁵ is independently a carbocycle or a heterocycle

optionally substituted with 1 to 3 R^z groups;

each R^z is independently F, Cl, Br, I, OH, —CN, —N₃,

—NO₂, —OR, —C(=Y¹)R, —C(=Y¹)OR,

—C(=Y¹)N(R)₂, —N(R)₂, —*N(R)₃, —SR, —S(O)R,

—S(O)₂R, —S(O)(OR), —S(O)₂(OR), —OC(=Y¹)R,

—OC(=Y¹)OR, —OC(=Y¹)(N(R)₂), —SC(=Y¹)R,

—SC(=Y¹)OR, —SC(=Y¹)(N(R)₂), —N(R)C(=Y¹)

R, —N(R)C(=Y¹)OR, —N(R)C(=Y¹)N(R)₂,

—SO₂NR₂, (C₁–C₈) alkyl, (C₁–C₈) substituted alkyl,

(C₂–C₈) alkenyl, (C₂–C₈) substituted alkenyl, (C₂–C₈)

alkynyl, (C₂–C₈) substituted alkynyl, C₆–C₂₀ aryl,

C₆–C₂₀ substituted aryl, C₂–C₂₀ heterocyclyl, C₂–C₂₀

substituted heterocyclyl, arylalkyl or substituted aryl-

alkyl; wherein each alkyl, alkenyl, alkynyl, aryl, hetero-

cyclyl, or arylalkyl is independently optionally substi-

tuted with one or more Z groups;

each R is independently H, (C₁–C₈) alkyl, (C₁–C₈) substi-

tuted alkyl, (C₂–C₈) alkenyl, (C₂–C₈) substituted alkenyl,

(C₂–C₈) alkynyl, (C₂–C₈) substituted alkynyl, C₆–C₂₀

aryl, C₆–C₂₀ substituted aryl, C₂–C₂₀ heterocyclyl,

C₂–C₂₀ substituted heterocyclyl, arylalkyl or substituted

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arylalkyl; wherein each alkyl, alkenyl, alkynyl, aryl, het-
erocyclyl, or arylalkyl is independently optionally sub-
stituted with one or more Z groups;

each X¹ or X² is independently C—R¹⁰ or N;

each R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹²,

N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹),

—CN=NHNR¹¹, —CN=N(OR¹¹), —CH(OR¹¹)₂,

—C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)

OR¹¹, (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alkynyl,

(C₄–C₈)carbocyclylalkyl, optionally substituted aryl,

optionally substituted heteroaryl, —C(=O)(C₁–C₈)

alkyl, —S(O)_n(C₁–C₈)alkyl, aryl(C₁–C₈)alkyl, OR¹¹ or

SR¹¹; wherein each aryl or heteroaryl is independently

optionally substituted with one or more Z groups;

each R⁹ or R¹⁰ is independently H, halogen, NR¹¹R¹²,

N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN,

—CH(=NR¹¹), —CN=NHNR¹¹, —CN=N(OR¹¹),

—CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹²,

—C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

each R¹¹ or R¹² is independently H, (C₁–C₈)alkyl, (C₂–C₈)

alkenyl, (C₂–C₈)alkynyl, (C₄–C₈)carbocyclylalkyl,

optionally substituted aryl, optionally substituted het-

eroaryl, —C(=O)(C₁–C₈)alkyl, —S(O)_n(C₁–C₈)alkyl

or aryl(C₁–C₈)alkyl; wherein each aryl or heteroaryl is

independently optionally substituted with one or more Z

groups;

or R¹¹ and R¹² taken together with a nitrogen to which they

are both attached form a 3 to 7 membered heterocyclic

ring wherein any one carbon atom of said heterocyclic

ring can optionally be replaced with —O—, —S— or

—NR^a—;

each Z is independently halogen, —O[–], =O, —OR^b,

—SR^b, —S[–], —NR^b₂, —N⁺R^b₃, =NR^b, —CN,

—OCN, —SCN, —N=C=O, —NCS, —NO, —NO₂,

=N₂, —N₃, —NHC(=O)R^b, —OC(=O)R^b, —NHC

(=O)NR^b₂, —S(=O)₂—, —S(=O)₂OH, —S(=O)₂

R^b, —OS(=O)₂OR^b, —S(=O)₂NR^b₂, —S(=O)R^b,

—OP(=O)(OR^b)₂, —P(=O)(OR^b)₂, —P(=O)(O[–])₂,

—P(=O)(OH)₂, —P(O)(OR^b)(O[–]), —C(=O)R^b,

—C(=O)X, —C(S)R^b, —C(O)OR^b, —C(O)O[–],

—C(S)OR^b, —C(O)SR^b, —C(S)SR^b, —C(O)NR^b₂,

—C(S)NR^b₂, —C(=NR^b)NR^b₂, where each R^b is inde-

pendently H, alkyl, aryl, arylalkyl, or heterocycle;

wherein each (C₁–C₈)alkyl, (C₂–C₈)alkenyl, (C₂–C₈)alky-

nyl or aryl(C₁–C₈)alkyl of each R¹, R², R³, R⁴, R⁵, R⁶,

R¹¹ or R¹² is, independently, optionally substituted with

one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and

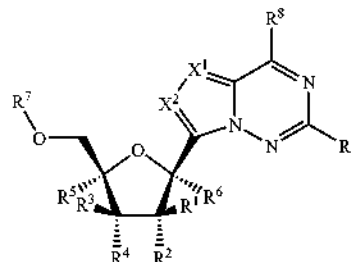
wherein one or more of the non-terminal carbon atoms

of each said (C₁–C₈)alkyl is optionally replaced with

—O—, —S— or —NR^a—.

2. A compound according to claim 1 represented by For-
mula II

Formula II



wherein X² is C—R¹⁰ and each Y and Y¹ is O.

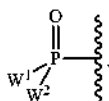
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3. A compound according to claim 2 wherein R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} .

4. A compound according to claim 3 wherein R^9 is H or $NR^{11}R^{12}$.

5. A compound according to claim 4 wherein R^7 is H or



6. A compound according to claim 5 wherein R^6 is OR^a , N_3 , halogen, CN, methyl, hydroxymethyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl.

7. A compound according to claim 6 wherein X^2 is C—H and R^3 and R^5 are each H.

8. A compound according to claim 7 wherein at least one of R^2 or R^4 is OR^a .

9. A compound according to claim 8 wherein X^1 is N or C— R^{10} wherein R^{10} is H, halogen, CN or optionally substituted heteroaryl.

10. A compound according claim 9 wherein R^2 and R^4 are each OR^a .

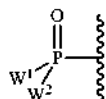
11. A compound according to claim 10 wherein R^2 and R^4 are OH.

12. A compound according to claim 9 wherein R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

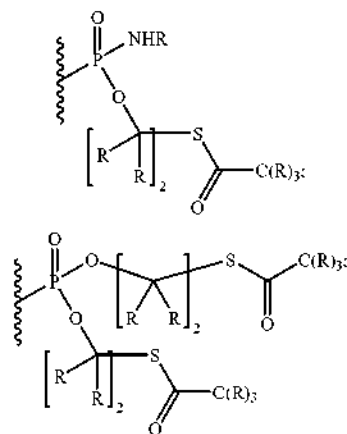
13. A compound according to claim 9 wherein X^1 is N.

14. A compound according to claim 9 wherein X^1 is C—H.

15. A compound according to claim 14 wherein

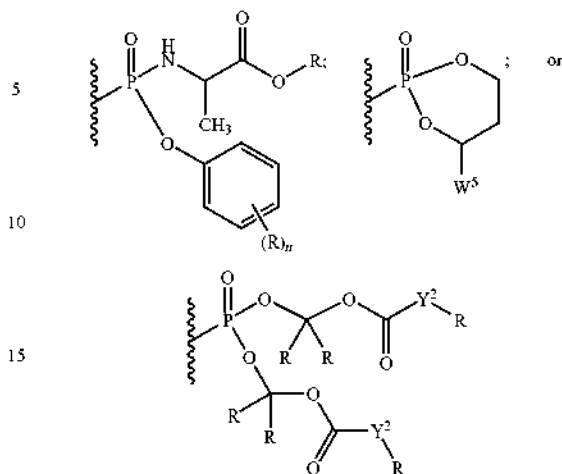


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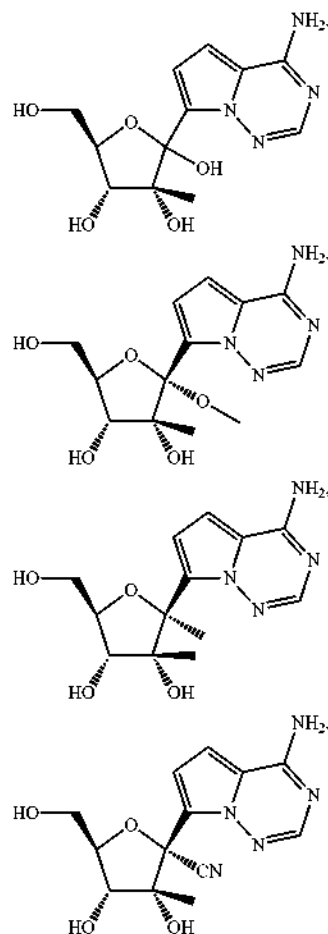


wherein Y^2 is, independently, a bond, O, or CR_2 .

16. A compound according to claim 9 wherein W^1 and W^2 are each, independently, a group of the Formula Ia.

17. A compound according to claim 9 wherein R^7 is H.

18. A compound that is



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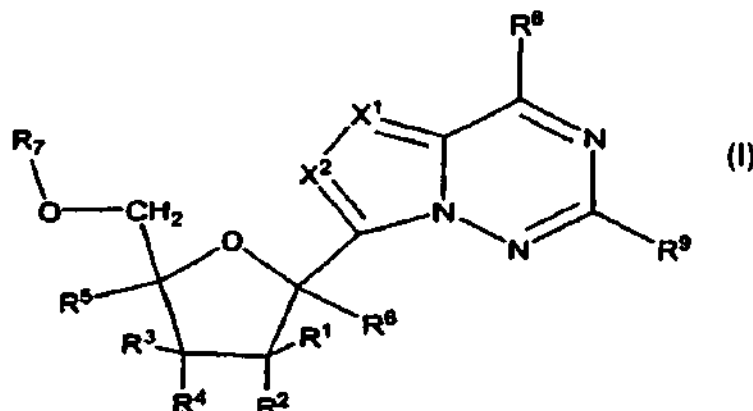
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(54) Title: 1'-SUBSTITUTED CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT



(57) Abstract: Provided are pyrrolo[1,2-f][1,2,4]triazinyl, imidazo[1,5-f][1,2,4]triazinyl, imidazo[1,2-f][1,2,4]triazinyl, and [1,2,4]triazolo[4,3-f][1,2,4]triazinyl nucleosides, nucleoside phosphates and prodrugs thereof, wherein the 1' position of the nucleoside sugar is substituted. The compounds, compositions, and methods provided are useful for the treatment of *Flaviviridae* virus infections, particularly hepatitis C infections. Formula (I), each X¹ or X² is independently C-R¹⁰ or N.

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1'-SUBSTITUTED CARBA-NUCLEOSIDE ANALOGS
FOR ANTIVIRAL TREATMENT

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FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity, more particularly nucleosides active against *Flaviviridae* infections and most particularly to inhibitors of hepatitis C virus RNA-dependent RNA polymerase.

BACKGROUND OF THE INVENTION

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Viruses comprising the *Flaviviridae* family comprise at least three distinguishable genera including *pestiviruses*, *flaviviruses*, and *hepaciviruses* (Calisher, *et al.*, J. Gen. Virol., 1993, 70, 37-43). While *pestiviruses* cause many economically important animal diseases such as bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, hog cholera) and border disease of sheep (BDV), their importance in human disease is less well characterized (Moennig, V., *et al.*, Adv. Vir. Res. 1992, 48, 53-98).

25

Flaviviruses are responsible for important human diseases such as dengue fever and yellow fever while *hepaciviruses* cause hepatitis C virus infections in humans. Other important viral infections caused by the *Flaviviridae* family include West Nile virus (WNV) Japanese encephalitis virus (JEV), tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis, St Louis encephalitis, Omsk hemorrhagic fever virus and Zika virus. Combined, infections from the *Flaviviridae* virus family cause significant

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- 5 mortality, morbidity and economic losses throughout the world. Therefore, there is a need to develop effective treatments for *Flaviviridae* virus infections.

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide (Boyer, N. et al. *J Hepatol.* 32:98-112, 2000) so a significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A.M. and Bacon, B. R., *Scientific American*, Oct.: 80-85, (1999); Gordon, C. P., et al., *J. Med. Chem.* **2005**, 48, 1-20; Maradpour, D.; et al., *Nat. Rev. Micro.* **2007**, 5(6), 453-463). A number of HCV treatments are reviewed by Bymock et al. in *Antiviral Chemistry & Chemotherapy*, 11:2; 79-95 (2000).

- 15 RNA-dependent RNA polymerase (RdRp) is one of the best studied targets for the development of novel HCV therapeutic agents. The NS5B polymerase is a target for inhibitors in early human clinical trials (Sommadosi, J., WO 01/90121 A2, US 2004/0006002 A1). These enzymes have been extensively characterized at the biochemical and structural level, with screening assays for identifying selective inhibitors (De Clercq, E. (2001) *J. Pharmacol. Exp. Ther.* 297:1-10; De Clercq, E. (2001) *J. Clin. Virol.* 22:73-89). Biochemical targets such as NS5B are important in developing HCV therapies since HCV does not replicate in the laboratory and there are difficulties in developing cell-based assays and preclinical animal systems.

- Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), which are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. *Drugs* **2002**, 62, 507-556) but less than half the patients given this treatment show a persistent benefit. Other patent applications disclosing the use of nucleoside analogs to treat hepatitis C virus include WO 01/32153, WO 01/60315, WO 02/057425, WO 02/057287, WO 02/032920, WO 02/18404, WO 04/046331, WO2008/089105 and WO2008/141079 but additional treatments for HCV infections have not yet become available for patients. Therefore, drugs having improved antiviral

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- 5 and pharmacokinetic properties with enhanced activity against development of HCV resistance, improved oral bioavailability, greater efficacy, fewer undesirable side effects and extended effective half-life *in vivo* (De Francesco, R. et al. (2003) *Antiviral Research* 58:1-16) are urgently needed.

Certain ribosides of the nucleobases pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-
10 f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine have been disclosed in *Carbohydrate Research* 2001, 331(1), 77-82; *Nucleosides & Nucleotides* (1996), 15(1-3), 793-807; *Tetrahedron Letters* (1994), 35(30), 5339-42; *Heterocycles* (1992), 34(3), 569-74; *J. Chem. Soc. Perkin Trans. 1* 1985, 3, 621-30; *J. Chem. Soc. Perkin Trans. 1* 1984, 2, 229-38; WO 2000056734; *Organic Letters* (2001),
15 3(6), 839-842; *J. Chem. Soc. Perkin Trans. 1* 1999, 20, 2929-2936; and *J. Med. Chem.* 1986, 29(11), 2231-5. However, these compounds have not been disclosed as useful for the treatment of HCV. Babu, Y. S., WO2008/089105 and WO2008/141079, discloses ribosides of pyrrolo[1,2-f][1,2,4]triazine nucleobases with antiviral, anti-HCV, and anti-RdRp activity.

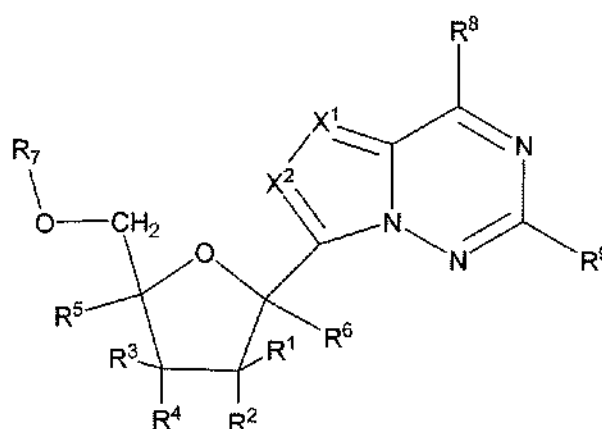
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SUMMARY OF THE INVENTION

The instant invention provides compounds that inhibit viruses of the *Flaviviridae* family. The invention also comprises compounds that inhibit viral nucleic acid
25 polymerases, particularly HCV RNA-dependent RNA polymerase (RdRp), rather than cellular nucleic acid polymerases. Therefore, the compounds of the instant invention are useful for treating *Flaviviridae* infections in humans and other animals.

In one aspect, this invention provides a compound of Formula I:

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Formula I

or a pharmaceutically acceptable salt, thereof;

wherein:

each R^1 , R^2 , R^3 , R^4 , or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 ,

10 $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl;

or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached
15 form a double bond;

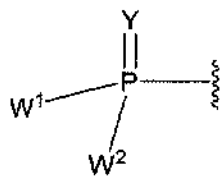
R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted
20 alkynyl, or aryl(C_1-C_8)alkyl or R^6 and either R^1 or R^2 when taken together are $-O(CO)O-$;

each n is independently 0, 1, or 2;

each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl(C_1-C_8)alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;
25

R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or

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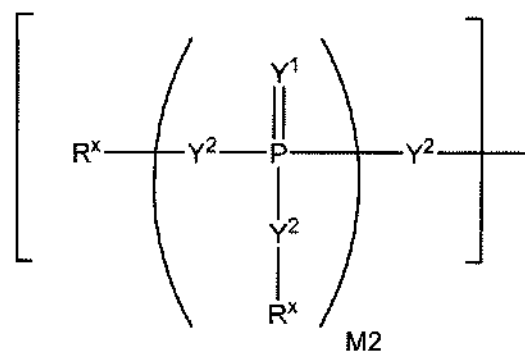


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each Y or Y¹ is, independently, O, S, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), or N-NR₂;

W¹ and W², when taken together, are -Y³(C(R^y)₂)₃Y³-; or one of W¹ or W² together with either R³ or R⁴ is -Y³- and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:

10



Formula Ia

wherein:

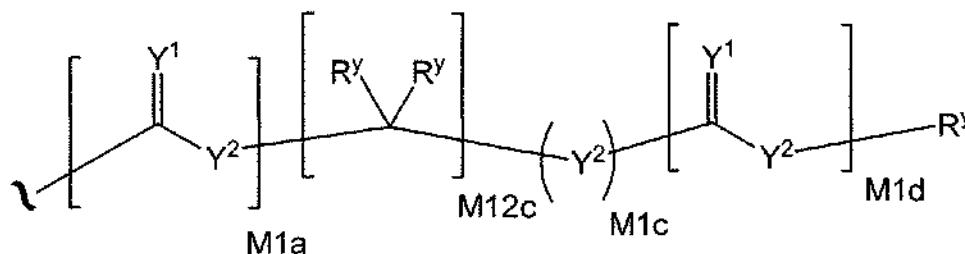
each Y² is independently a bond, O, CR₂, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), N-NR₂, S, S-S, S(O), or S(O)₂;

15

each Y³ is independently O, S, or NR;

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



20

wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

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- 5 each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or when taken together, two R^y on the same carbon atom form a
- 10 carbocyclic ring of 3 to 7 carbon atoms;
- each R is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocyclyl, C_2-C_{20} substituted heterocyclyl, arylalkyl or substituted arylalkyl;
- 15 W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;
- each X^1 or X^2 is independently C- R^{10} or N;
- each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl (C_1-C_8) alkyl, OR^{11} or SR^{11} ;
- 20 each R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} ;
- each R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl (C_1-C_8) alkyl; or R^{11} and R^{12} taken together
- 30 with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$;
- wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl of each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one

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- 5 or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a.

In another aspect, the present invention includes compounds of Formula I and pharmaceutically acceptable salts thereof and all racemates, enantiomers, diastereomers, 10 tautomers, polymorphs, pseudopolymorphs and amorphous forms thereof.

In another aspect, the present invention provides novel compounds of Formula I with activity against infectious *Flaviviridae* viruses. Without wishing to be bound by theory, the compounds of the invention may inhibit viral RNA-dependent RNA polymerase and thus inhibit the replication of the virus. They are useful for treating 15 human patients infected with a human virus such as hepatitis C.

In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

20 In another embodiment, the present application provides for combination pharmaceutical agent comprising:

- a) a first pharmaceutical composition comprising a compound of Formula I; or a pharmaceutically acceptable salt, solvate, or ester thereof; and
- b) a second pharmaceutical composition comprising at least one additional 25 therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides for a method of 30 inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an

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- 5 effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof; and at least one additional therapeutic agent.

In another embodiment, the present application provides for a method of treating and/or preventing a disease caused by a viral infection wherein the viral infection is caused by a virus selected from the group consisting of dengue virus, yellow fever virus,
10 West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis virus, St Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhoea virus, Zika virus and Hepatitis C virus; by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

- 15 In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of treating
20 HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof; and at least one additional therapeutic agent.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HCV infection in an infected animal which comprises
25 administering to, i.e. treating, said animal with a pharmaceutical combination composition or formulation comprising an effective amount of a Formula I compound, and a second compound having anti-HCV properties.

In another aspect, the invention also provides a method of inhibiting HCV, comprising administering to a mammal infected with HCV an amount of a Formula I
30 compound, effective to inhibit the replication of HCV in infected cells in said mammal.

In another aspect, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds of the invention.

In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are

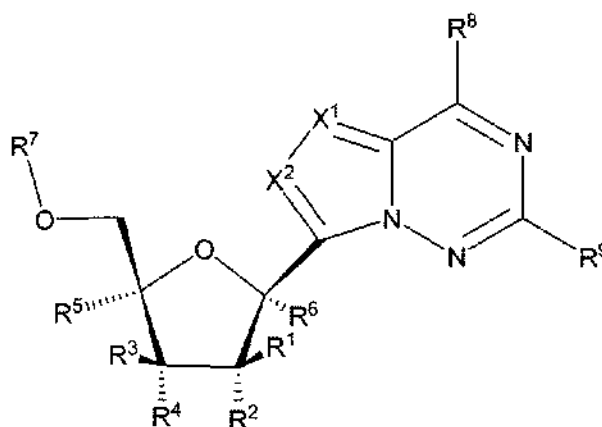
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5 provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention,
 10 examples of which are illustrated in the accompanying description, structures and
 formulas. While the invention will be described in conjunction with the enumerated
 embodiments, it will be understood that they are not intended to limit the invention to
 those embodiments. On the contrary, the invention is intended to cover all alternatives,
 modifications, and equivalents, which may be included within the scope of the present
 15 invention.

In another aspect, compounds of Formula I are represented by Formula II:



Formula II

or a pharmaceutically acceptable salt, thereof;

20 wherein:

each R¹, R², R³, R⁴, or R⁵ is independently H, OR^a, N(R^a)₂, N₃, CN, NO₂,
 S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl,
 (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl,
 or aryl(C₁-C₈)alkyl;

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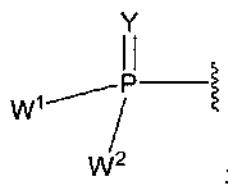
- 5 or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

- R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$,
 10 $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl or R^6 and either R^1 or R^2 when taken together are $-O(CO)O-$;

each n is independently 0, 1, or 2;

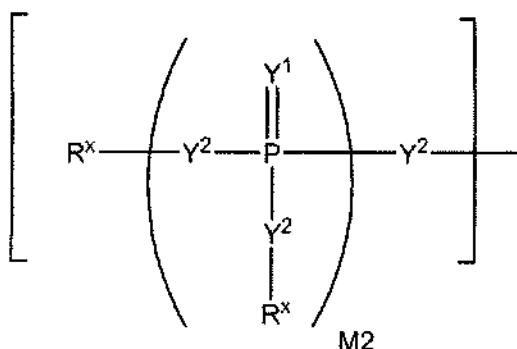
- each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl,
 15 aryl(C_1-C_8)alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



- 20 each Y or Y^1 is, independently, O, S, NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:



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Formula Ia

wherein:

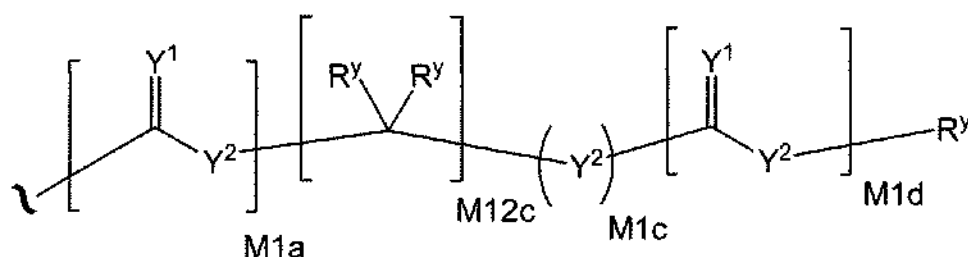
each Y^2 is independently a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

each Y^3 is independently O, S, or NR;

10

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

15

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $^+N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)N(R)_2$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)N(R)_2$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

20

each R is independently H, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

25

W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

X^2 is $C-R^{10}$ and each X^1 is independently $C-R^{10}$ or N;

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- 5 each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $(C_4-C_8)carbocyclalkyl$, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(C_1-C_8)alkyl$, $aryl(C_1-C_8)alkyl$, OR^{11} or SR^{11} ;
- 10 each R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} ;
- each R^{11} or R^{12} is independently H, $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $(C_4-C_8)carbocyclalkyl$, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(C_1-C_8)alkyl$ or $aryl(C_1-C_8)alkyl$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$;
- 15 wherein each $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$ or $aryl(C_1-C_8)alkyl$ of each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN , N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said $(C_1-C_8)alkyl$ may be optionally replaced with -O-, -S- or $-NR^a$.
- 20 In one embodiment of the invention of Formula II, R^1 is $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$ or $(C_2-C_8)alkynyl$. In another aspect of this embodiment, R^1 is $(C_1-C_8)alkyl$. In another aspect of this embodiment, R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In a preferred aspect of this embodiment, R^1 is methyl. In another preferred aspect of this embodiment, R^1 is H.
- 25 In one embodiment of Formula II, R^2 is H, OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, or $(C_2-C_8)substituted alkynyl$. In another aspect of this embodiment, R^2 is H, OR^a , $N(R^a)_2$, N_3 , CN , SR^a or halogen. In another aspect of this embodiment, R^2 is H, OH, NH_2 , N_3 , CN , or halogen. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is H, $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$ or
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- 5 (C₂–C₈)alkynyl. In another aspect of this embodiment, R² is OR^a or F and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In a preferred aspect of this embodiment, R² is OH and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R² is OR^a and R¹ is H. In another preferred aspect of this embodiment, R² is OH and R¹ is H. In another preferred aspect of this embodiment, R² is F and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R² is OR^a and R¹ is methyl. In a particularly preferred aspect of this embodiment, R² is OH and R¹ is methyl.

- In one embodiment of Formula II, R³ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁–C₈)alkyl, (C₂–C₈)alkenyl or (C₂–C₈)alkynyl. In one aspect of this embodiment, R³ is H or F. In a preferred aspect of this embodiment, R³ is H. In another preferred aspect of this embodiment, R³ is H, R² is OR^a or halogen and R¹ is H, (C₁–C₈)alkyl, (C₂–C₈) alkenyl or (C₂–C₈)alkynyl. In another aspect of this embodiment, R³ is H, R² is OR^a or F and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another aspect of this embodiment, R³ is H, R² is OR^a and R¹ is methyl. In another aspect of this embodiment, R³ is H, R² is OH and R¹ is methyl. In another aspect of this embodiment, R³ is H, R² is OR^a or F and R¹ is H. In another aspect of this embodiment, R³ is H, R² is OH and R¹ is H. In another aspect of this embodiment, each R¹, R³ and R⁵ is H and R² is OH.

- In one embodiment of Formula II, R⁴ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁–C₈)alkyl, (C₂–C₈)alkenyl or (C₂–C₈)alkynyl. In a preferred aspect of this embodiment, R⁴ is OR^a. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen and R¹ is H, (C₁–C₈)alkyl, (C₂–C₈) alkenyl or (C₂–C₈)alkynyl. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen and R¹ is H. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen, R³ is H and R¹ is H, (C₁–C₈)alkyl, (C₂–C₈) alkenyl or (C₂–C₈)alkynyl. In another preferred embodiment R⁴ is OR^a, R² is OR^a or F and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or F, R³ is H and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁴ and R² are, independently, OR^a and R¹ is methyl. In another preferred aspect of this embodiment, R⁴ and R² are, independently OR^a, R³ is H and R¹ is

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- 5 methyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. . In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are
- 10 OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F, and each R^1 and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and each R^1 and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$, and each
- 15 R^1 and R^3 is H.

- In one embodiment of Formula II, R^5 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl. In another aspect of this embodiment, R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl,
- 20 (C_4-C_8) carbocyclylalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl and R^5 is H, N_3 , CN, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, or
- 30 (C_2-C_8) substituted alkynyl; R^5 is H, N_3 , CN, methyl, ethenyl or ethynyl; R^4 is OR^a and R^3 is H. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-$

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- 5 $S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^5 is H or N_3 , R^4 is OR^a , R^3 is H, and R^2 is F or OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^5 is H or N_3 , R^4 is OR^a , R^3 is H, R^2 is OR^a and R^1 is methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are H, R^2 and R^4 are, independently, OR^a , and R^1 is methyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, each R^1 , R^3 and R^5 is H, and R^2 and R^4 are, independently, OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are H, R^2 and R^4 are OH, and R^1 is methyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are each H and R^2 and R^4 are OH. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are H, R^2 and R^4 , taken together, are $-O(CO)O-$, and R^1 is methyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are each H and R^2 and R^4 are OH.

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- 5 R^4 , taken together, are $-O(CO)O-$. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^1 and R^3 are each H, R^2 and R^4 are independently OR^a and R^5 is N_3 .
- 10 In one embodiment of Formula II, R^2 and R^4 are each OR^a and at least one of R^1 , R^3 , or R^5 is not H. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^1 is $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$ or $aryl(C_1-C_8)alkyl$. In another embodiment, R^2 and R^4 are each OR^a and R^3 is $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$,
- 15 $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$ or $aryl(C_1-C_8)alkyl$. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^5 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$ or $aryl(C_1-C_8)alkyl$. In another aspect of this embodiment, R^2 and R^4 are each
- 20 OR^a and R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$ or $aryl(C_1-C_8)alkyl$. In another aspect of this embodiment, R^2 and R^4 are both OH and R^6 is OR^a ,
- 25 N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, or $(C_2-C_8)substituted alkynyl$.

- In another embodiment of Formula II, each R^1 and R^2 is H, one of R^3 or R^4 is OR^a
- 30 and the other of R^3 or R^4 is $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, $(C_2-C_8)substituted alkynyl$ or $aryl(C_1-C_8)alkyl$. In another aspect of this embodiment, each R^1 and R^2 is H, one of R^3 or R^4 is OH and the other of R^3 or R^4 is $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$,

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- 5 (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl.

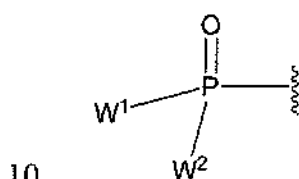
In another embodiment of Formula II, R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl,

- 10 (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl. In another aspect of this embodiment, R⁵ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R⁵ is H, N₃, CN, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R¹ is H,
- 15 methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another aspect of this embodiment, R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl and R² and R⁴ are each OR^a. In another aspect of this embodiment, R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R² and R⁴ are each OR^a; and R³ and R⁵ are each H. In another aspect of this embodiment, R⁵ is H, N₃, CN, methyl, ethenyl or ethynyl; R⁴ is OR^a and R³ is H. In another aspect of this
- 20 embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R⁵ is H or N₃; R⁴ is OR^a; R³ is H; and R² is OR^a. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ and R⁵ are H and R² and R⁴ are, independently, OR^a. In another aspect of this embodiment, R⁶ is OR^a, N₃,
- 25 halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ and R⁵ are H; and R² and R⁴ are each OH. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ and R⁵ are H; and R² and R⁴, taken together, are -O(CO)O-. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen,
- 30 CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ is H; R² and R⁴ are independently OR^a and R⁵ is N₃. In another aspect of this of this embodiment, R⁶ is N₃, halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl. In another aspect of this of this embodiment, R⁶ is N₃, halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl;

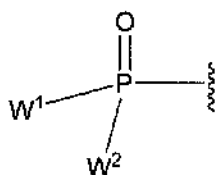
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- 5 and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H.

In one embodiment of Formula II, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$ or



. In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl. In another preferred aspect of this embodiment, R^7 is



- 15 In one embodiment of Formula II, X^1 is N or $C-R^{10}$. In another aspect of this embodiment, X^1 is N. In another aspect of this embodiment, X^1 is $C-R^{10}$. In another aspect of this embodiment, X^2 is C-H. In another aspect of this embodiment, X^1 is N and X^2 is C-H. In another aspect of this embodiment, X^1 is $C-R^{10}$ and X^2 is CH. In another aspect of this embodiment, X^1 is C-H and X^2 is CH. In another aspect of this
- 20 embodiment, X^1 is CR^{10} and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is CR^{10} ; X^2 is CH; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl,
- 25 ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is CR^{10} ; X^2 is CH; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is $C-R^{10}$; X^2 is CH; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; each R^3 and R^5 is H;

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- 5 R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN. In another aspect of this embodiment, X^1 is N and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is N; X^2 is CH; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is N; X^2 is CH; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X^1 is N; X^2 is CH; R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl; each R^3 and R^5 is H; R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN.

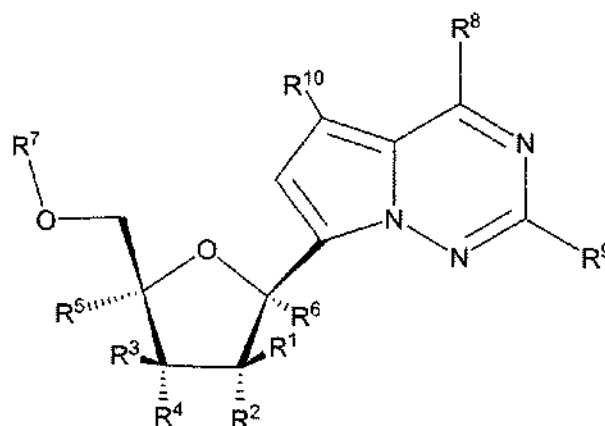
- In another embodiment of Formula II, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl(C_1-C_8)alkyl, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 . In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or

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- 5 ethynyl. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 . In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

- In another embodiment of Formula II, each R^{10} is, independently, H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$,
 10 $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} . In another aspect of this embodiment, each R^{10} is H, halogen, CN or optionally substituted heteroaryl.

In another aspect, compounds of Formula I are represented by Formula III:



Formula III

15

or a pharmaceutically acceptable salt, thereof;

wherein:

R^1 is H or CH_3 ;

- each R^2 , R^3 , R^4 , or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$,
 20 halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl;

- or any two R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached
 25 form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$,

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- 5 $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_4-\text{C}_8)\text{carbocyclalkyl}$, $(\text{C}_1-\text{C}_8)\text{substituted alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_2-\text{C}_8)\text{substituted alkenyl}$, $(\text{C}_2-\text{C}_8)\text{alkynyl}$, $(\text{C}_2-\text{C}_8)\text{substituted alkynyl}$, or aryl $(\text{C}_1-\text{C}_8)\text{alkyl}$ or R^6 and R^2 when taken together are $-\text{O}(\text{CO})\text{O}-$;

wherein each $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_2-\text{C}_8)\text{alkynyl}$ or aryl $(\text{C}_1-\text{C}_8)\text{alkyl}$ of each R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or
 10 more halo, hydroxy, CN, N_3 , $\text{N}(\text{R}^a)_2$ or OR^a ; and wherein one or more of the non-terminal carbon atoms of each said $(\text{C}_1-\text{C}_8)\text{alkyl}$ may be optionally replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^a-$; and

all remaining variables are defined as for Formula I.

In one embodiment of Formula III, R^1 is H.

- 15 In one embodiment of Formula III, R^1 is CH_3 .

In one embodiment of Formula III, R^2 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, NO_2 , $\text{S}(\text{O})_n\text{R}^a$, halogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_1-\text{C}_8)\text{substituted alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$, $(\text{C}_2-\text{C}_8)\text{substituted alkenyl}$, $(\text{C}_2-\text{C}_8)\text{alkynyl}$, or $(\text{C}_2-\text{C}_8)\text{substituted alkynyl}$. In another aspect of this embodiment, R^2 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a or halogen. In another aspect of this
 20 embodiment, R^2 is H, OH, NH_2 , N_3 , CN, or halogen. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is methyl. In another aspect of this embodiment, R^2 is OR^a or halogen and R^1 is H. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is methyl. In another aspect of this embodiment, R^2 is OR^a or F and R^1 is H. In a preferred aspect of this embodiment, R^2 is OH and R^1 is methyl. In another
 25 preferred aspect of this embodiment, R^2 is OR^a and R^1 is H. In another preferred aspect of this embodiment, R^2 is OH and R^1 is H. In another preferred aspect of this embodiment, R^2 is F. In another preferred aspect of this embodiment, R^2 is OR^a and R^1 is methyl.

In one embodiment of Formula III, R^3 is H, OR^a , $\text{N}(\text{R}^a)_2$, N_3 , CN, SR^a , halogen,
 30 $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_2-\text{C}_8)\text{alkenyl}$ or $(\text{C}_2-\text{C}_8)\text{alkynyl}$. In one aspect of this embodiment, R^3 is H or F. In a preferred aspect of this embodiment, R^3 is H. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^3 is H, R^2 is OR^a or halogen and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OR^a or F and R^1 is methyl. In another aspect of this

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- 5 embodiment, R^3 is H, R^2 is OR^a or F and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is methyl. In another aspect of this embodiment, R^3 is H, R^2 is OR^a and R^1 is H. In another aspect of this embodiment, R^3 is H, R^2 is OH and R^1 is H. In another aspect of this embodiment, each R^1 , R^3 and R^5 is H and R^2 is OH.
- 10 In one embodiment of Formula III, R^4 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In a preferred aspect of this embodiment, R^4 is OR^a . In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen and R^1 is H. In another preferred aspect of this embodiment,
- 15 R^4 is OR^a , R^2 is OR^a or halogen, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or halogen, R^3 is H and R^1 is H. In another preferred embodiment R^4 is OR^a , R^2 is OR^a or F and R^1 is methyl. In another preferred embodiment R^4 is OR^a , R^2 is OR^a or F and R^1 is H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a , R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$, R^3 is H and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 , taken together, are $-O(CO)O-$, R^3 is H and R^1 is H. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a and the other of R^4 or R^2 is OH. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, one of R^4 or R^2 is OR^a wherein R^a is not H and the other of R^4 or R^2 is OH, R^3 is H, and R^1 is H. In another preferred aspect of this embodiment, R^4 and R^2 are OH, R^3 is H, and R^1 is methyl. In another preferred aspect of this embodiment, R^4 and R^2 are OH, R^3 is H, and R^1 is H. In another preferred aspect of this embodiment, R^4 is OR^a , R^2 is OR^a or F, and each R^1 and R^3 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently, OR^a and R^1 is H. In another preferred aspect of this embodiment, R^4 and R^2 are, independently OR^a and each R^1 and R^3 is H.
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- 5 In one embodiment of Formula III, R^5 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl,
- 10 (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl and R^5 is H, OR^a , $N(R^a)_2$, N_3 , CN, SR^a , halogen, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl,
- 15 (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl and R^5 is H, N_3 , CN, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen,
- 20 (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, or (C_2-C_8) substituted alkynyl; R^5 is H, N_3 , CN, methyl, ethenyl or ethynyl; R^4 is OR^a and R^3 is H. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl,
- 25 ethynyl, or substituted ethynyl, R^5 is H or N_3 , R^4 is OR^a , R^3 is H, and R^2 is F or OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^5 is H or N_3 , R^4 is OR^a , R^3 is H, R^2 is OR^a and R^1 is methyl. In
- 30 another aspect of this embodiment, R^6 is OR^a , N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are H, R^2 and R^4 are, independently, OR^a , and R^1 is

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- 5 methyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are H, R^2 and R^4 are OH, and R^1 is methyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^1 , R^3 and R^5 are each H and R^2 and R^4 are OH. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^3 and R^5 are H, R^2 and R^4 , taken together, are $-O(CO)O-$, and R^1 is methyl. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^1 , R^3 and R^5 are each H and R^2 and R^4 , taken together, are $-O(CO)O-$. In another aspect of this embodiment, R^6 is OR^a , N_3 , CN , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^1 and R^3 are each H, R^2 and R^4 are independently OR^a and R^5 is N_3 .
- 25 In one embodiment of Formula III, R^2 and R^4 are each OR^a and at least one of R^1 , R^3 , or R^5 is not H. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^1 methyl. In another embodiment, R^2 and R^4 are each OR^a and R^3 is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^5 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^1 and R^3 are each H, R^2 and R^4 are independently OR^a and R^5 is N_3 .
- 30 In one embodiment of Formula III, R^2 and R^4 are each OR^a and at least one of R^1 , R^3 , or R^5 is not H. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^1 methyl. In another embodiment, R^2 and R^4 are each OR^a and R^3 is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^5 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl(C_1-C_8)alkyl. In another aspect of this embodiment, R^2 and R^4 are each OR^a and R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl, R^1 and R^3 are each H, R^2 and R^4 are independently OR^a and R^5 is N_3 .

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- 5 S(O)(OR¹¹), -S(O)₂(OR¹¹), -SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl. In another aspect of this embodiment, R² and R⁴ are both OH and R⁶ is OR^a, N₃, CN, S(O)_nR^a, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -SO₂NR¹¹R¹², halogen,
- 10 (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, or (C₂-C₈)substituted alkynyl.

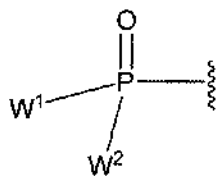
- In another embodiment of Formula III, each R¹ and R² is H, one of R³ or R⁴ is OR^a and the other of R³ or R⁴ is (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-
- 15 C₈)alkyl. In another aspect of this embodiment, each R¹ and R² is H, one of R³ or R⁴ is OR^a and the other of R³ or R⁴ is (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl.

- In another embodiment of Formula III, R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl,
- 20 (C₄-C₈)carbocyclylalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl. In another aspect of this embodiment, R⁵ is H, N₃, CN, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R¹ is H. In another aspect of this embodiment, R¹ is methyl. In another aspect of this embodiment, R¹ is H and R² and R⁴ are each OR^a. In another aspect of this embodiment, R¹ is methyl and R² and R⁴ are each OR^a. In another aspect of this embodiment, R¹ is H; R² and R⁴ are each OR^a; and R³ and R⁵ are each H. In another aspect of this embodiment, R¹ is methyl; R² and R⁴ are each
- 25 OR^a; and R³ and R⁵ are each H. In another aspect of this embodiment, R⁵ is H, N₃, CN, methyl, ethenyl or ethynyl; R⁴ is OR^a and R³ is H. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R⁵ is H or N₃; R⁴ is OR^a; R³ is H; and R² is OR^a. In
- 30

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- 5 another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H and R^2 and R^4 are, independently, OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 are each OH. In another aspect of
- 10 this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 , taken together, are $-O(CO)O-$. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 is H; R^2 and R^4 are independently OR^a and R^5 is N_3 . In another aspect of this
- 15 of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H; and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is methyl; and R^2 and R^4 are each OR^a . In another aspect of this of this
- 20 embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is methyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H.

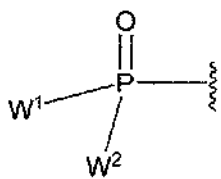
- In one embodiment of Formula III, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$
- 25 or



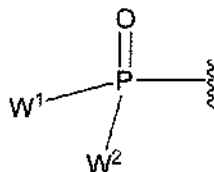
- . In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is H and R^1 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ and R^1 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$
- 30 wherein R^{11} is (C_1-C_8) alkyl. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl and R^1 is H. In another preferred aspect of this embodiment, R^7 is

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In another preferred aspect of this embodiment, R^7 is



and R^1 is H.

- In another embodiment of Formula III, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl (C_1-C_8) alkyl, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is H. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is methyl. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is H. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is methyl. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is H. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 . In another preferred aspect of this embodiment,

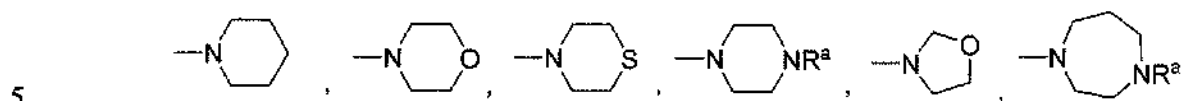
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- 5 R^8 and R^9 are each NH_2 and R^1 is H. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is methyl. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 . In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is H. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is methyl.
- 10 In another embodiment of Formula III, each R^{10} is, independently, H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, -
- 15 $S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, each R^{10} is H, halogen, CN or optionally substituted heteroaryl and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl,
- 20 ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, R^{10} is H and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In
- 25 another aspect of this embodiment, each R^3 and R^5 is H; R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN.

In one embodiment of Formulas I-III, R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or

30 aryl (C_1-C_8) alkyl. In another embodiment, R^{11} and R^{12} taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^a$. Therefore, by way of example and not limitation, the moiety $-NR^{11}R^{12}$ can be represented by the heterocycles:

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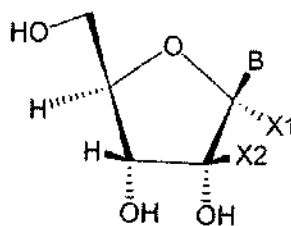
and the like.

In another embodiment of Formulas I-III, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$ or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$, wherein said $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$ or $\text{aryl}(\text{C}_1\text{-C}_8)\text{alkyl}$ are, independently, optionally substituted with one or more halo, hydroxy, CN , N_3 , $\text{N}(\text{R}^a)_2$ or OR^a .

Therefore, by way of example and not limitation, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} could represent moieties such as $-\text{CH}(\text{NH}_2)\text{CH}_3$, $-\text{CH}(\text{OH})\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{NH}_2)\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CF}_3$, $-(\text{CH}_2)_2\text{CH}(\text{N}_3)\text{CH}_3$, $-(\text{CH}_2)_6\text{NH}_2$ and the like.

In another embodiment of Formula I-III, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is $(\text{C}_1\text{-C}_8)\text{alkyl}$ wherein one or more of the non-terminal carbon atoms of each said $(\text{C}_1\text{-C}_8)\text{alkyl}$ may be optionally replaced with $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^a-$. Therefore, by way of example and not limitation, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} could represent moieties such as $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{OCH}(\text{CH}_3)_2$, $-\text{CH}_2\text{SCH}_3$, $-(\text{CH}_2)_6\text{OCH}_3$, $-(\text{CH}_2)_6\text{N}(\text{CH}_3)_2$ and the like.

In still another embodiment, the compounds of Formula I, Formula II, or Formula III are named below in tabular format (Table 6) as compounds of general Formula IV:



Formula IV

wherein X1 and X2 , represent substituents attached to the tetrahydrofuranyl ring as defined in Tables 1-2, below; B is a purine defined in Table 4, below; and X3 represents a ring element of the purine base B as described in Table 3, below.

The point of attachment of the core structure ribose is indicated in each of the structures of X1 , X2 , and B . The point of attachment of the core structure purine is indicated in each of the structures X3 . Each structure in Tables 1-4 is represented by an alphanumeric "code". Each structure of a compound of Formula IV can thus be

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- 5 designated in tabular form by combining the "code" representing each structural moiety using the following syntax: X1.X2.X3.B. Thus, for example, X1a.X2c.X3a.B1 represents the following structure:

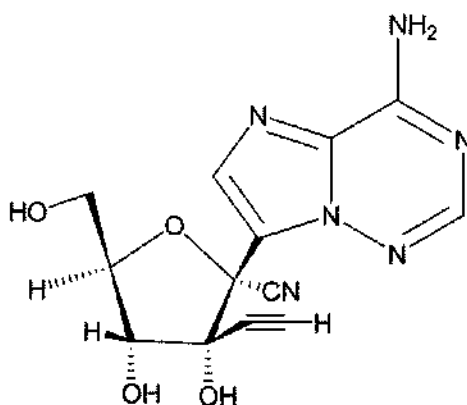


Table 1: X1 Structures

Code	Structure
X1a	CN
X1b	CH ₃
X1c	N ₃
X1d	CH ₂ OH

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Table 2: X2 Structures

Code	Structure
X2a	H
X2b	CH ₃
X2c	

- 15 Table 3: X3 Structures

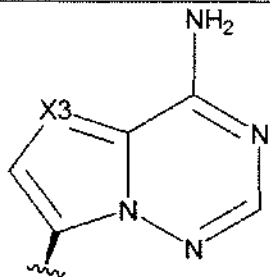
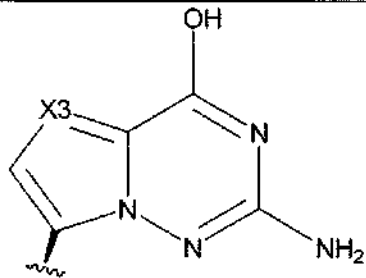
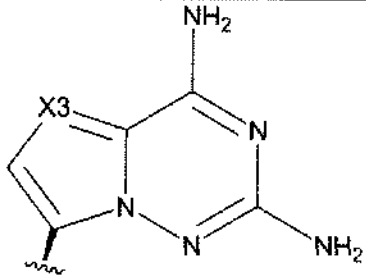
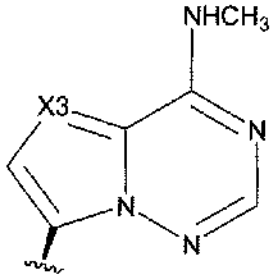
Code	Structure
X3a	-N=

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Code	Structure
X3b	-CH=
X3c	-CF=

Table 4: B Structures

Code	Structure
B1	
B2	
B3	
B4	

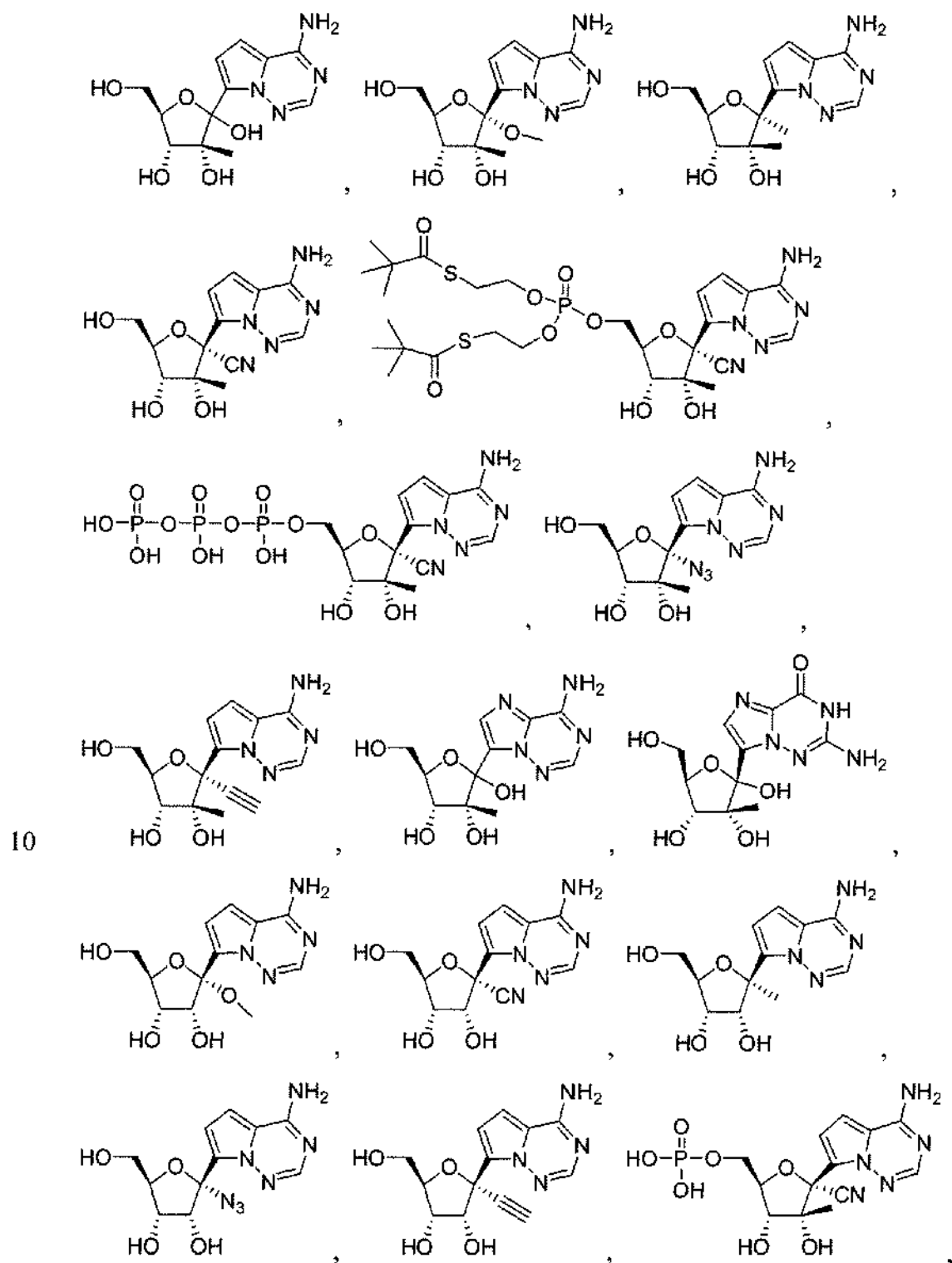
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5 Table 6: List of Compounds of Formula IV

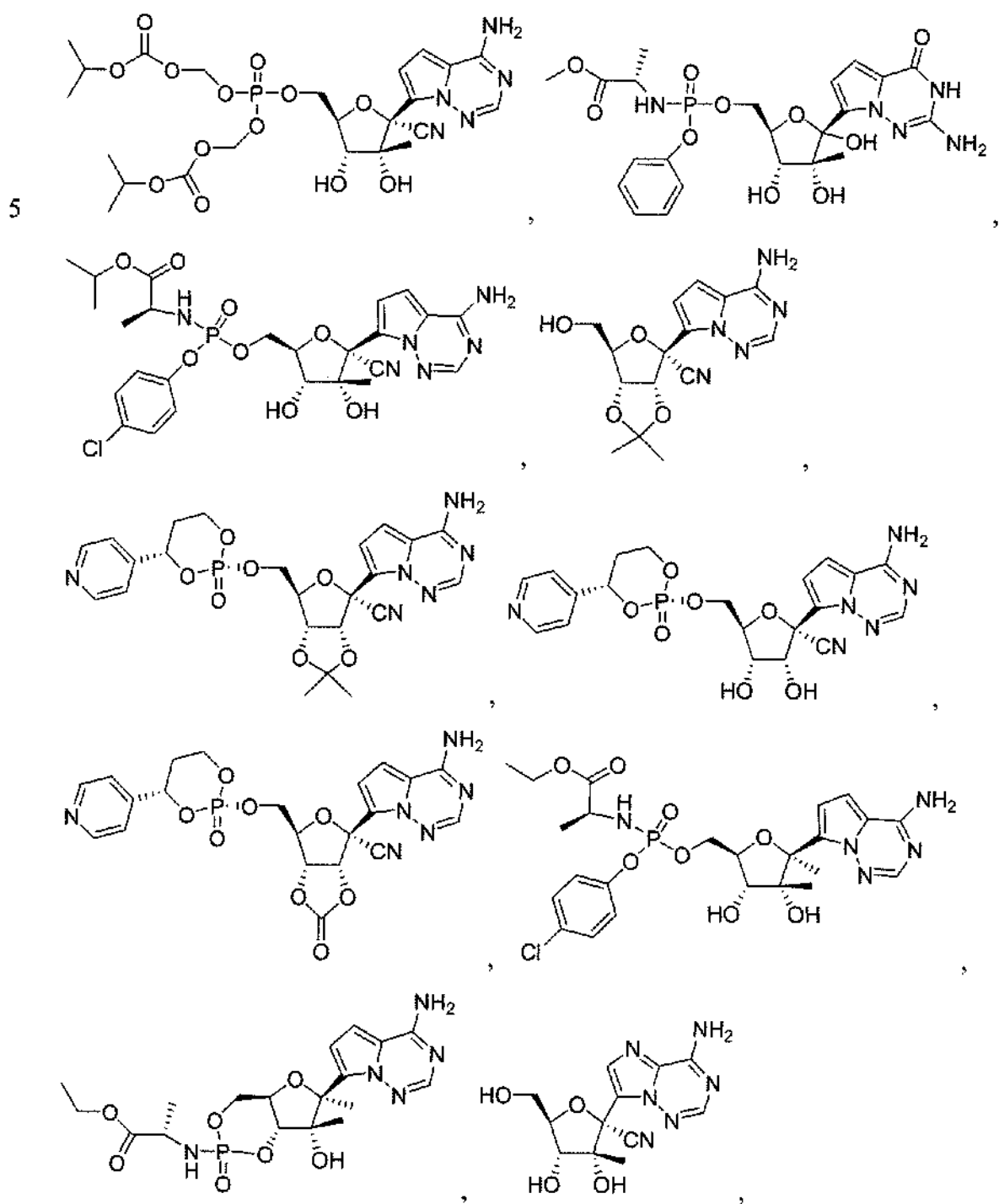
- X1a.X2b.X3a.B1, X1a.X2b.X3a.B2, X1a.X2b.X3a.B3, X1a.X2b.X3a.B4,
 X1a.X2b.X3b.B1, X1a.X2b.X3b.B2, X1a.X2b.X3b.B3, X1a.X2b.X3b.B4,
 X1a.X2b.X3c.B1, X1a.X2b.X3c.B2, X1a.X2b.X3c.B3, X1a.X2b.X3c.B4,
 X1a.X2c.X3a.B1, X1a.X2c.X3a.B2, X1a.X2c.X3a.B3, X1a.X2c.X3a.B4,
 10 X1a.X2c.X3b.B1, X1a.X2c.X3b.B2, X1a.X2c.X3b.B3, X1a.X2c.X3b.B4,
 X1a.X2c.X3c.B1, X1a.X2c.X3c.B2, X1a.X2c.X3c.B3, X1a.X2c.X3c.B4,
 X1b.X2a.X3a.B1, X1b.X2a.X3a.B2, X1b.X2a.X3a.B3, X1b.X2a.X3a.B4,
 X1b.X2a.X3b.B1, X1b.X2a.X3b.B2, X1b.X2a.X3b.B3, X1b.X2a.X3b.B4,
 X1b.X2a.X3c.B1, X1b.X2a.X3c.B2, X1b.X2a.X3c.B3, X1b.X2a.X3c.B4,
 15 X1b.X2b.X3a.B1, X1b.X2b.X3a.B2, X1b.X2b.X3a.B3, X1b.X2b.X3a.B4,
 X1b.X2b.X3b.B1, X1b.X2b.X3b.B2, X1b.X2b.X3b.B3, X1b.X2b.X3b.B4,
 X1b.X2b.X3c.B1, X1b.X2b.X3c.B2, X1b.X2b.X3c.B3, X1b.X2b.X3c.B4,
 X1b.X2c.X3a.B1, X1b.X2c.X3a.B2, X1b.X2c.X3a.B3, X1b.X2c.X3a.B4,
 X1b.X2c.X3b.B1, X1b.X2c.X3b.B2, X1b.X2c.X3b.B3, X1b.X2c.X3b.B4,
 20 X1b.X2c.X3c.B1, X1b.X2c.X3c.B2, X1b.X2c.X3c.B3, X1b.X2c.X3c.B4,
 X1c.X2a.X3a.B1, X1c.X2a.X3a.B2, X1c.X2a.X3a.B3, X1c.X2a.X3a.B4,
 X1c.X2a.X3b.B1, X1c.X2a.X3b.B2, X1c.X2a.X3b.B3, X1c.X2a.X3b.B4,
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 X1c.X2b.X3a.B1, X1c.X2b.X3a.B2, X1c.X2b.X3a.B3, X1c.X2b.X3a.B4,
 25 X1c.X2b.X3b.B1, X1c.X2b.X3b.B2, X1c.X2b.X3b.B3, X1c.X2b.X3b.B4,
 X1c.X2b.X3c.B1, X1c.X2b.X3c.B2, X1c.X2b.X3c.B3, X1c.X2b.X3c.B4,
 X1c.X2c.X3a.B1, X1c.X2c.X3a.B2, X1c.X2c.X3a.B3, X1c.X2c.X3a.B4,
 X1c.X2c.X3b.B1, X1c.X2c.X3b.B2, X1c.X2c.X3b.B3, X1c.X2c.X3b.B4,
 X1c.X2c.X3c.B1, X1c.X2c.X3c.B2, X1c.X2c.X3c.B3, X1c.X2c.X3c.B4,
 30 X1d.X2a.X3a.B1, X1d.X2a.X3a.B2, X1d.X2a.X3a.B3, X1d.X2a.X3a.B4,
 X1d.X2a.X3b.B1, X1d.X2a.X3b.B2, X1d.X2a.X3b.B3, X1d.X2a.X3b.B4,
 X1d.X2a.X3c.B1, X1d.X2a.X3c.B2, X1d.X2a.X3c.B3, X1d.X2a.X3c.B4.

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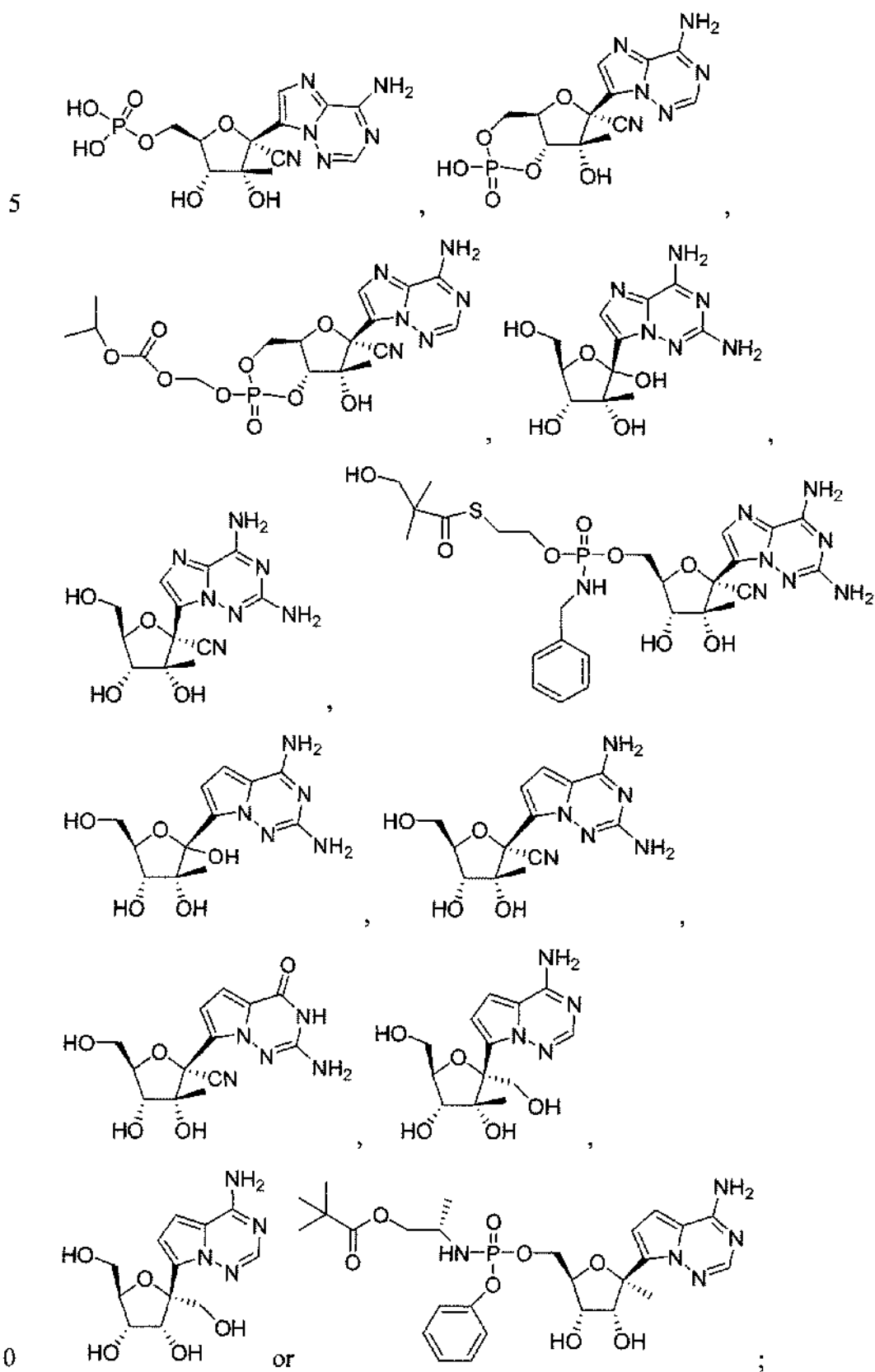
- 5 In another embodiment, Formulas I-III is a compound selected from the group consisting of



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- 5 or a pharmaceutically acceptable salt thereof.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

- 10 When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

As used herein, "a compound of the invention" or "a compound of Formula I" means a compound of Formula I or a pharmaceutically acceptable salt, thereof.

- 15 Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

- "Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkyl), 1 to 8 carbon atoms (*i.e.*, C₁-C₈ alkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)CH₃), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl (-CH₂)₇CH₃).

"Alkoxy" means a group having the formula -O-alkyl, in which an alkyl group,

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5 as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH₃ or -OMe), ethoxy (-OCH₂CH₃ or -OEt), t-butoxy (-O-C(CH₃)₃ or -OtBu) and the like.

10 "Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable haloalkyl groups include, but are not limited to, -CF₃, -CHF₂, -CFH₂, -CH₂CF₃,
15 and the like.

"Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp*² double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkenyl), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkenyl).
20 Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

"Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond.
25 For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkyne), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH₂C≡CH), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon
30 radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene (-CH₂-),

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- 5 1,1-ethyl (-CH(CH₃)-), 1,2-ethyl (-CH₂CH₂-), 1,1-propyl (-CH(CH₂CH₃)-), 1,2-propyl (-CH₂CH(CH₃)-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

“Alkenylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For
10 example, and alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

“Alkynylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two
15 hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH₂C≡C-), and 4-pentynyl (-CH₂CH₂CH₂C≡C-).

“Amino” refers generally to a nitrogen radical which can be considered a derivative
20 of ammonia, having the formula -N(X)₂, where each “X” is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, etc. The hybridization of the nitrogen is approximately sp³. Nonlimiting types of amino include -NH₂, -N(alkyl)₂, -NH(alkyl), -N(carbocyclyl)₂, -NH(carbocyclyl), -N(heterocyclyl)₂, -NH(heterocyclyl), -N(aryl)₂, -NH(aryl), -N(alkyl)(aryl), -
25 N(alkyl)(heterocyclyl), -N(carbocyclyl)(heterocyclyl), -N(aryl)(heteroaryl), -N(alkyl)(heteroaryl), etc. The term “alkylamino” refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino groups include -NH₂, -NH(CH₃), -N(CH₃)₂, -NH(CH₂CH₃), -N(CH₂CH₃)₂, -NH(phenyl), -N(phenyl)₂, -NH(benzyl), -N(benzyl)₂, etc. Substituted alkylamino refers generally to alkylamino groups, as defined
30 above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes -NH(alkylene-C(O)-OH), -NH(alkylene-C(O)-O-alkyl), -N(alkylene-C(O)-OH)₂, -N(alkylene-C(O)-O-alkyl)₂, etc.

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5 “Aryl” means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

10 “Arylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 7 to 20 carbon atoms, e.g., the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

 “Arylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 8 to 20 carbon atoms, e.g., the alkenyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

 “Arylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 8 to 20 carbon atoms, e.g., the alkynyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

30 The term “substituted” in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, “substituted alkyl”, “substituted alkylene”, “substituted aryl”, “substituted arylalkyl”, “substituted heterocyclyl”, and “substituted carbocyclyl” means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently

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- 5 replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R^b, -O⁻, =O, -OR^b, -SR^b, -S⁻, -NR^b₂, -N⁺R^b₃, =NR^b, -CX₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N₂, -N₃, -NHC(=O)R^b, -OC(=O)R^b, -NHC(=O)NR^b₂, -S(=O)₂⁻, -S(=O)₂OH, -S(=O)₂R^b, -OS(=O)₂OR^b, -S(=O)₂NR^b₂, -S(=O)R^b, -OP(=O)(OR^b)₂, -P(=O)(OR^b)₂, -P(=O)(O⁻)₂, -P(=O)(OH)₂, -P(O)(OR^b)(O⁻),
- 10 -C(=O)R^b, -C(=O)X, -C(S)R^b, -C(O)OR^b, -C(O)O⁻, -C(S)OR^b, -C(O)SR^b, -C(S)SR^b, -C(O)NR^b₂, -C(S)NR^b₂, -C(=NR^b)NR^b₂, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is
- 15 used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of

20 spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-III should be selected in order to provide a compound which is

25 sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I-III which have such stability are contemplated as falling within the scope of the present invention.

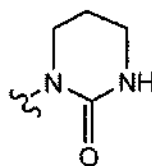
"Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the

30 alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., -OCH₃, etc.), an amine (e.g., -NHCH₃, -N(CH₃)₂, etc.), or a thioalkyl group (e.g., -SCH₃). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are,

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- 5 respectively, an alkyl ether (e.g., $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$, etc.), an alkyl amine (e.g., $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, etc.), or a thioalkyl ether (e.g., $-\text{CH}_2-\text{S}-\text{CH}_3$). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., $-\text{CH}_2\text{CH}_2-\text{OH}$), an aminoalkyl group (e.g., $-\text{CH}_2\text{NH}_2$), or an alkyl thiol group (e.g., $-\text{CH}_2\text{CH}_2-\text{SH}$). A heteroalkyl group can have, for
- 10 example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A $\text{C}_1\text{-C}_6$ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

- “Heterocycle” or “heterocyclyl” as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3,
- 15 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs” (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention “heterocycle” includes a “carbocycle” as defined herein, wherein one or more (e.g. 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (e.g. O, N, or S).
- 20 The terms “heterocycle” or “heterocyclyl” includes saturated rings, partially unsaturated rings, and aromatic rings (i.e., heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:

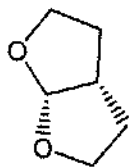


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- Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl,
- 30 isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl,

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- 5 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinoxalinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl,
- 10 phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, piperazinyl, indolyl, isoindolyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolyl, isatinoyl, and bis-tetrahydrofuranyl:



- 15 By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or
- 20 isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.
- 25

- By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2
- 30 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetidedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

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5 “Heterocyclylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkylene- moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl- CH_2 -, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the “heterocyclyl” portion includes any of
10 the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkyl group comprises 3 to 20
15 carbon atoms, *e.g.*, the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolyethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl,
20 morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

 “Heterocyclylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but
25 also a sp^2 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkenylene- moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will
30 also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkenyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

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- 5 “Heterocyclalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocycl radical (*i.e.*, a heterocycl-alkynylene- moiety). The heterocycl portion of the heterocycl alkynyl group includes any of the heterocycl groups described herein, including those described in
- 10 Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocycl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocycl group can be attached to the alkynyl portion of the heterocycl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable.
- 15 The heterocycl alkynyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocycl alkynyl group is 2 to 6 carbon atoms and the heterocycl moiety is 2 to 14 carbon atoms.

“Heteroaryl” refers to an aromatic heterocycl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the

20 aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those aromatic rings listed in the definition of “heterocycl”, including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

- 25 “Carbocycle” or “carbocycl” refers to a saturated (*i.e.*, cycloalkyl), partially unsaturated (*e.g.*, cycloakenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 7 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged
- 30 as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes

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- 5 naphthyl, tetrahydronaphthalene, and decaline.

“Carbocyclalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclalkyl radical as described herein. Typical, but non-limiting, examples of carbocyclalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and
10 cyclohexylmethyl.

“Arylheteroalkyl” refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the
15 resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or
20 exemplified herein.

“Heteroarylalkyl” refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-purinyl, -CH₂-furanyl, -CH₂-thienyl,
25 -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl, -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-purinyl, -CH(CH₃)-furanyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranyl,
30 -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl, -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl, -CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-pyrazyl, etc.

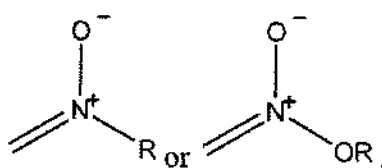
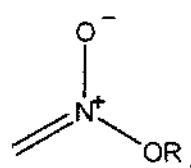
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5 The term “optionally substituted” in reference to a particular moiety of the compound of Formula I-III (e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by substituents such as those listed under the definition of “substituted”.

10 The term “optionally replaced” in reference to a particular moiety of the compound of Formula I-III (e.g., the carbon atoms of said (C₁-C₈)alkyl may be optionally replaced by -O-, -S-, or -NR^a-) means that one or more of the methylene groups of the (C₁-C₈)alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., -O-, -S-, or -NR^a-).

15 The term “non-terminal carbon atom(s)” in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl moiety -CH₂(C^{*})H₂(C^{*})H₂CH₃ or alkylene moiety -CH₂(C^{*})H₂(C^{*})H₂CH₂- the C^{*} atoms would
20 be considered to be the non-terminal carbon atoms.

Certain Y and Y¹ alternatives are nitrogen oxides such as ⁺N(O)(R) or ⁺N(O)(OR). These nitrogen oxides, as shown here attached to a carbon atom, can also be

represented by charge separated groups such as  or ,
25 respectively, and are intended to be equivalent to the aforementioned representations for the purposes of describing this invention.

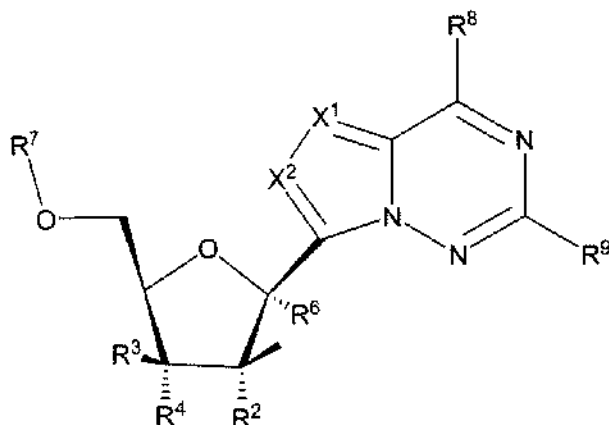
“Linker” or “link” means a chemical moiety comprising a covalent bond or a chain of atoms. Linkers include repeating units of alkyloxy (e.g. polyethyleneoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, JeffamineTM); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and
30 caproamide.

The terms such as “oxygen-linked”, “nitrogen-linked”, “carbon-linked”, “sulfur-linked”, or “phosphorous-linked” mean that if a bond between two moieties can be

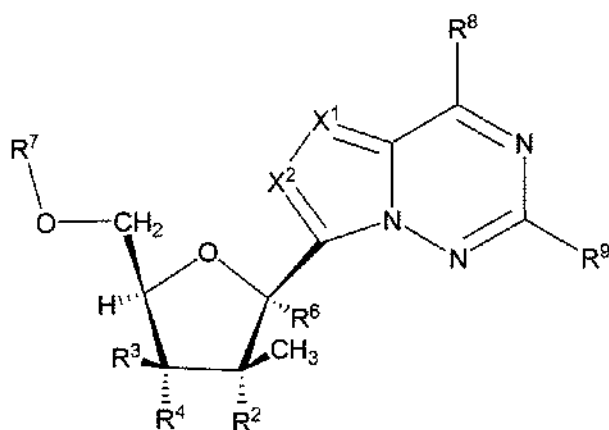
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- 5 formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, a nitrogen-linked amino acid would be bonded through a nitrogen atom of the amino acid rather than through an oxygen or carbon atom of the amino acid.

Unless otherwise specified, the carbon atoms of the compounds of Formula I-III
 10 are intended to have a valence of four. In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen. For example,



has the same meaning as



15

“Protecting group” refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance.

- 20 Chemical protecting groups and strategies for protection/deprotection are well known in

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5 the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides
10 the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized
15 properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be
20 absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more
25 desirable if the products are pharmacologically innocuous.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and Development (1991), P. Krosgaard-
30 Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery,

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5 bioavailability and efficacy.

A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{30}$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^{30}$ where R^{30} is C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_6-C_{20} aryl or
 10 C_6-C_{20} substituted aryl. The acyloxyalkyl ester was used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphate group. The acyloxyalkyl ester may be used to deliver phosphoric acids across cell
 15 membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is
 20 pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

The phosphate group may be a phosphate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to those comprising a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a
 25 phosphoramidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are
 30 reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*- or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C-O bond to generate the phosphoric acid and the quinone methide intermediate.

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- 5 Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an
- 10 ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been
- 15 described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I, Formula II, or Formula III and pharmaceutically acceptable salts thereof are embraced by

20 the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

A compound of Formula I-III and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal

25 structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist

30 due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I-III and their pharmaceutically acceptable salts.

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5 A compound of Formula I-III and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The
10 instant invention comprises all amorphous forms of the compounds of Formula I-III and their pharmaceutically acceptable salts.

 Selected substituents comprising the compounds of Formula I-III are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents,
15 theoretically, a large number of compounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R. R can be W^3 . W^3 can be W^4 and W^4 can be R or comprise substituents comprising R^y . One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties
20 include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

 By way of example and not limitation, W^3 and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 20,
25 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each recursive substituent can independently occur 12 or fewer times in a given embodiment. Even more typically, each recursive substituent can independently occur 3 or fewer times in a given embodiment. For example, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more
30 typically, W^3 will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

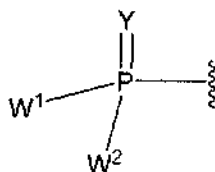
 Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To

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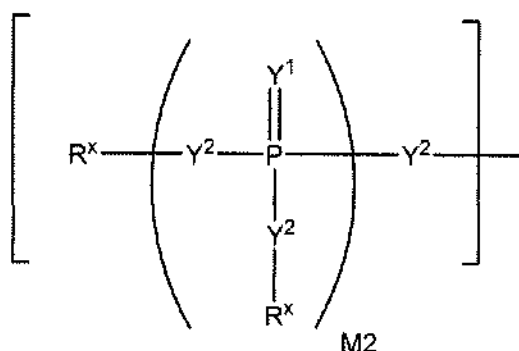
- 5 the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

- 10 The compounds of the Formula I-III may comprise a phosphate group as R^7 ,



- which may be a prodrug moiety wherein each Y or Y^1 is, independently, O, S, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, or N-NR₂; W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of Formula Ia:



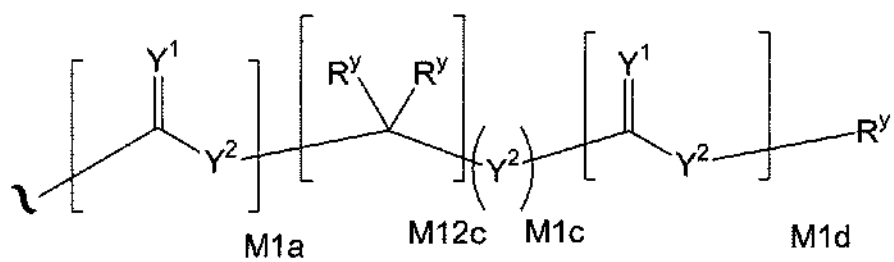
wherein:

- each Y^2 is independently a bond, O, CR₂, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, N-NR₂, S, S-S, S(O), or S(O)₂;
- 20 each Y^3 is independently O, S, or NR;
- M2 is 0, 1 or 2;
- each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-^+N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, or $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$,
- 25

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- 5 $-\text{CN}$, $-\text{N}_3$, $-\text{NO}_2$, $-\text{OR}$, a protecting group or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R^x is independently R^y , a protecting group, or the formula:



wherein:

- 10 M1a, M1c, and M1d are independently 0 or 1;
 M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;
 each R is H, halogen, $(\text{C}_1\text{--}\text{C}_8)$ alkyl, $(\text{C}_1\text{--}\text{C}_8)$ substituted alkyl, $(\text{C}_2\text{--}\text{C}_8)$ alkenyl, $(\text{C}_2\text{--}\text{C}_8)$ substituted alkenyl, $(\text{C}_2\text{--}\text{C}_8)$ alkynyl, $(\text{C}_2\text{--}\text{C}_8)$ substituted alkynyl, $\text{C}_6\text{--}\text{C}_{20}$ aryl, $\text{C}_6\text{--}\text{C}_{20}$ substituted aryl, $\text{C}_2\text{--}\text{C}_{20}$ heterocycle, $\text{C}_2\text{--}\text{C}_{20}$ substituted heterocyclyl, arylalkyl,
 15 substituted arylalkyl or a protecting group;

W^3 is W^4 or W^5 ; W^4 is R, $-\text{C}(\text{Y}^1)\text{R}^y$, $-\text{C}(\text{Y}^1)\text{W}^5$, $-\text{SO}_2\text{R}^y$, or $-\text{SO}_2\text{W}^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups.

- W^5 carbocycles and W^5 heterocycles may be independently substituted with 0 to
 20 3 R^y groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when
 25 containing 6 ring atoms.

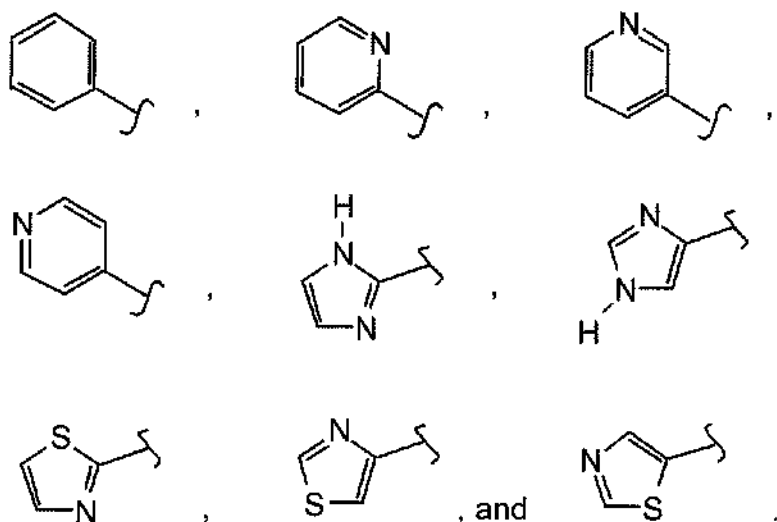
- A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2
 30 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1

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- 5 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 heteroatoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or
 10 other atom by a stable covalent bond.

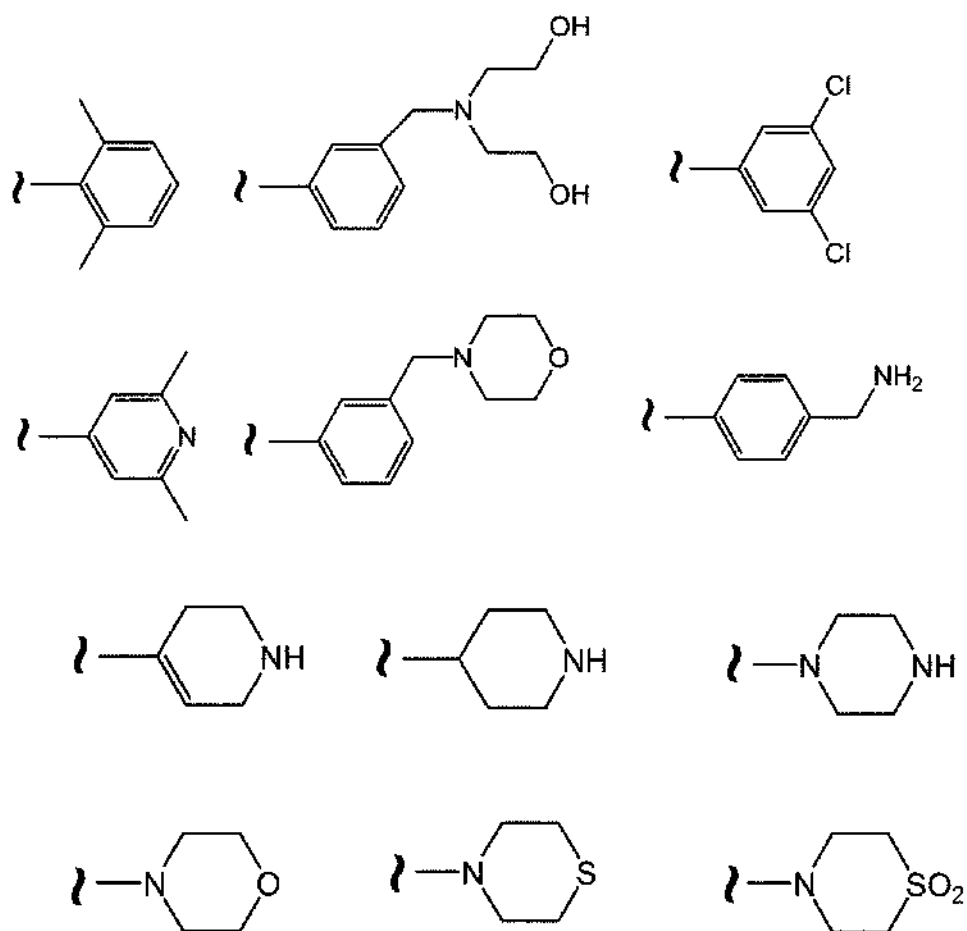
W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:

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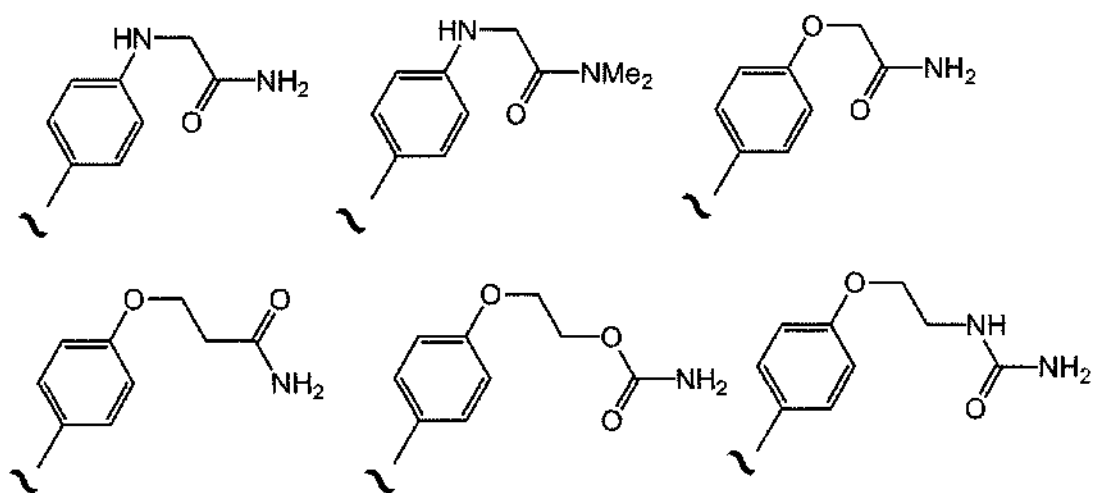
W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R groups, as defined above. For example, substituted W^5 carbocycles include:

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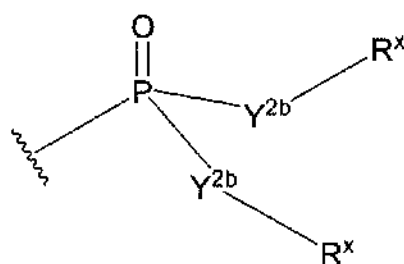
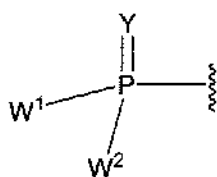
Examples of substituted phenyl carbocycles include:



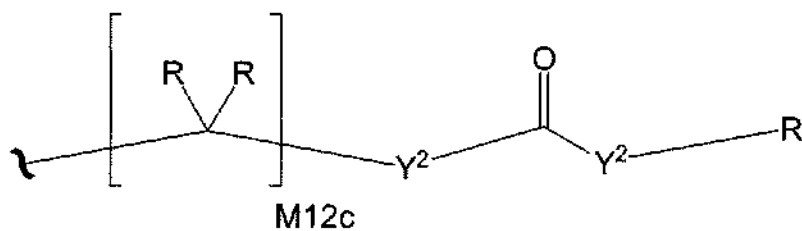
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5 Embodiments of of Formula I-III compounds include substructures such as:

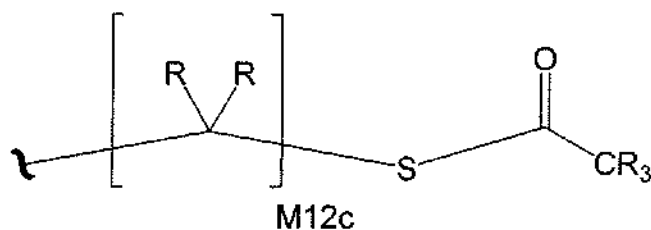


wherein each Y^{2b} is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:

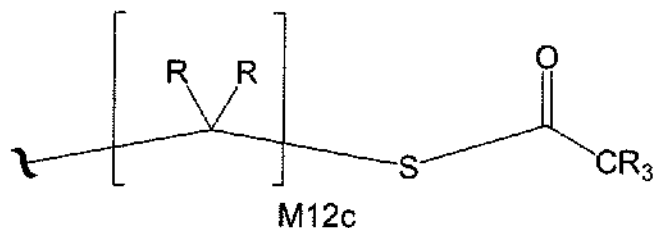


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wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S. In another preferred aspect of this embodiment, one $Y^{2b}-R^x$ is NH(R) and the other $Y^{2b}-R^x$ is O- R^x wherein R^x is:

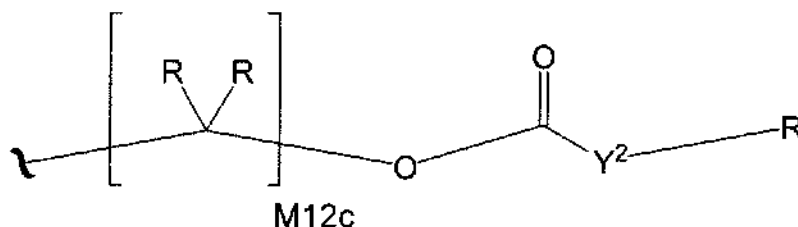


15 wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:

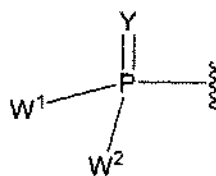


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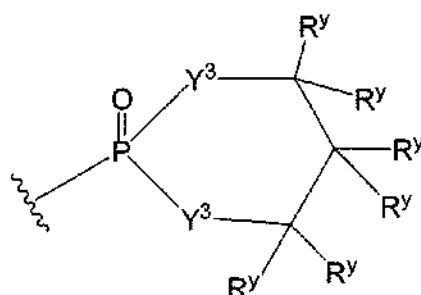
- 5 wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



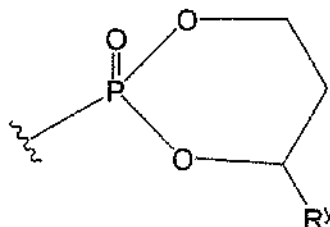
wherein M12c is 1 and Y^2 is a bond, O, or CR_2 .



- 10 Other embodiments of of Formulas I-III compounds include substructures such as:

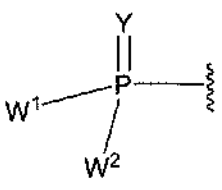


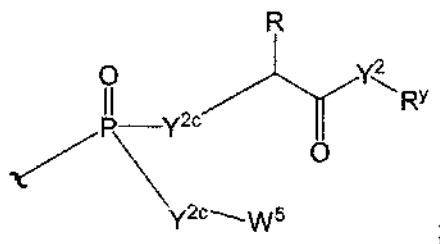
wherein each Y^3 is, independently, O or $N(R)$. In a preferred aspect of this embodiment, each Y^3 is O. In another preferred aspect of this embodiment, the substructure is:



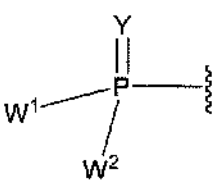
- 15 wherein R^y is W^5 as defined herein.

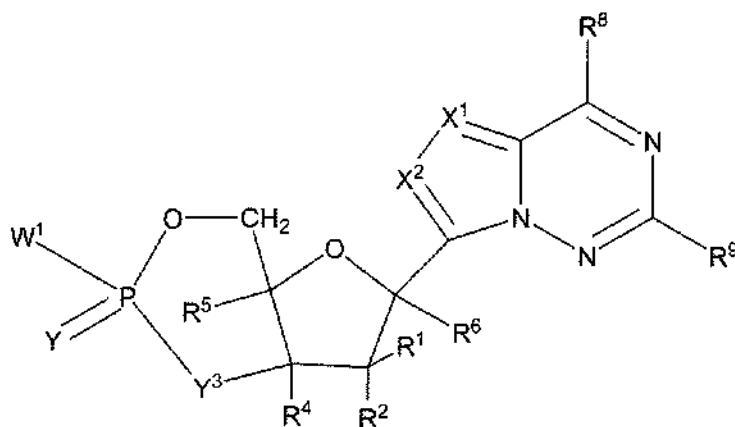
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Another embodiment of  of Formula I-III includes the substructures:



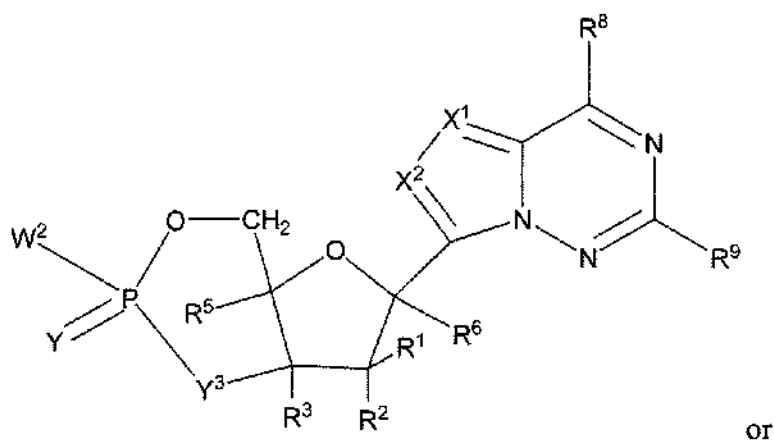
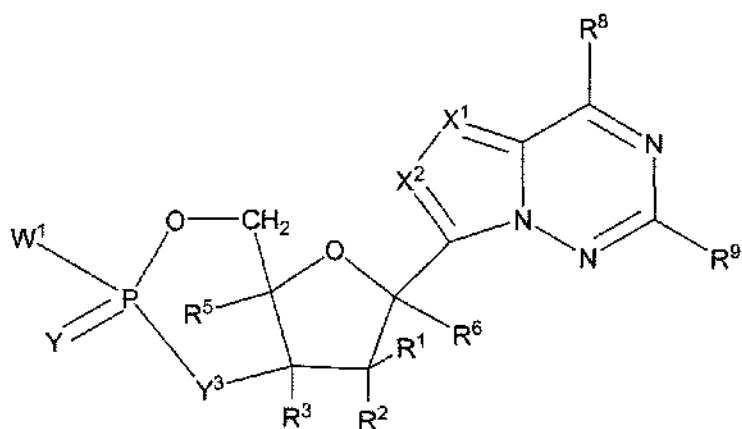
wherein each Y^{2c} is, independently, O, $N(R^y)$ or S.

Another embodiment of  of Formula I-III compounds includes the substructures wherein one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia. Such an embodiment is represented by a compound of Formula Ib selected from:

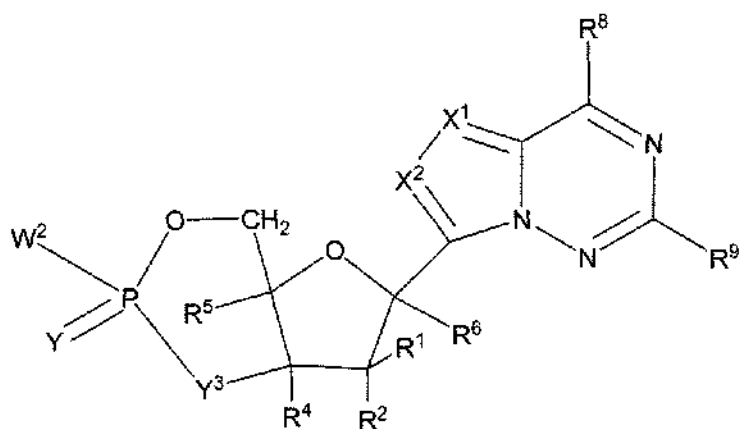


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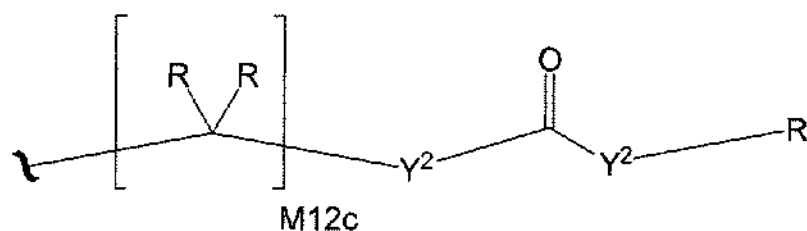
or



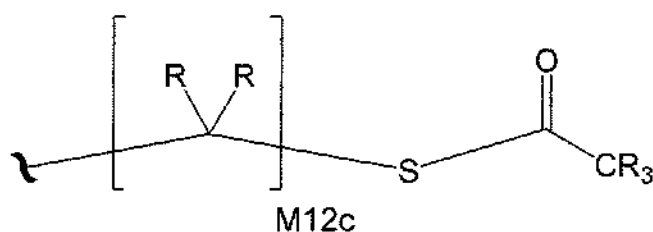
Formula Ib

In a preferred aspect of the embodiment of Formula Ib, each Y and Y³ is O. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:

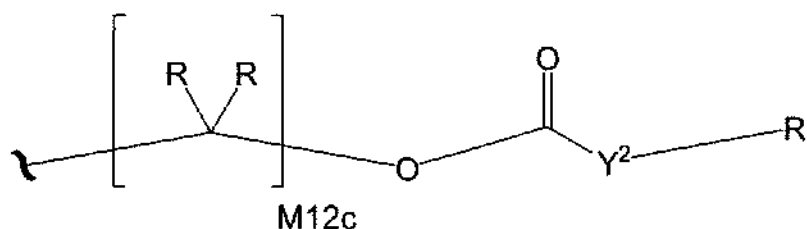
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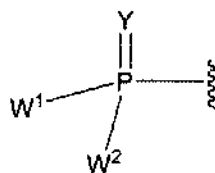
wherein M12c is 1, 2 or 3 and each Y² is independently a bond, O, CR₂, or S. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:

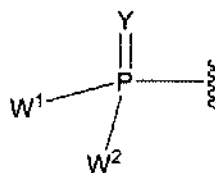


wherein M12c is 2. In another preferred aspect of the embodiment of Formula Ib, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:

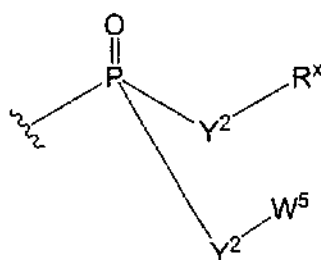


wherein M12c is 1 and Y² is a bond, O, or CR₂.



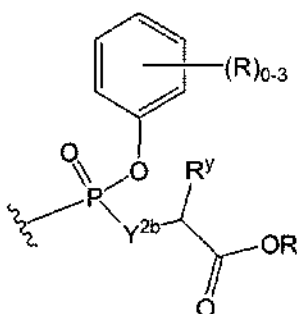
Another embodiment of  of Formula I-III compounds includes a substructure:

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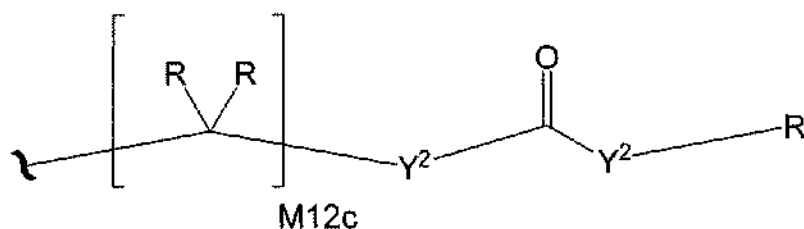
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wherein W^5 is a carbocycle such as phenyl or substituted phenyl. In another aspect of this embodiment, the substructure is:

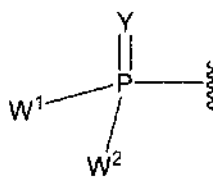


wherein Y^{2b} is O or N(R) and the phenyl carbocycle is substituted with 0 to 3 R groups.

10 In another aspect of this embodiment of the substructure, R^x is:



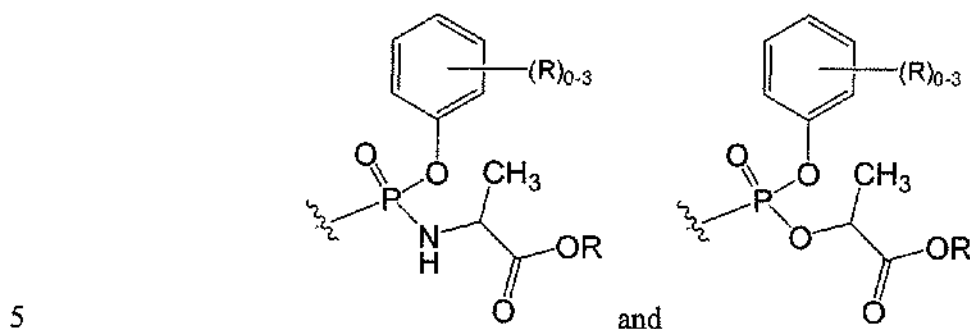
wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S.



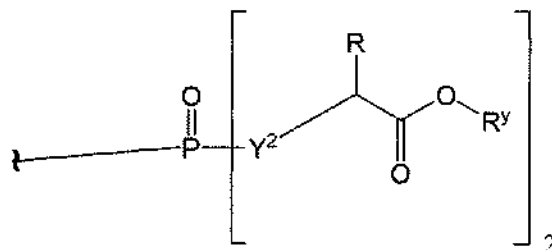
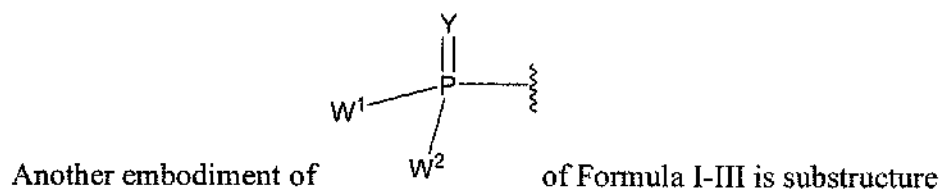
Another embodiment of

of Formula I-III includes substructures:

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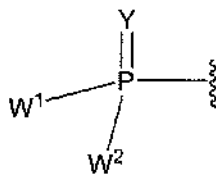
The chiral carbon of the amino acid and lactate moieties may be either the *R* or *S* configuration or the racemic mixture.



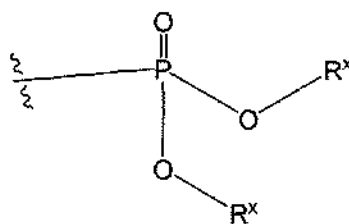
- 10 wherein each Y^2 is, independently, $-O-$ or $-NH-$. In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl. In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; and R is CH_3 .
- 15 In another preferred aspect of this embodiment, R^y is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl; R is CH_3 ; and each Y^2 is $-NH-$. In a preferred aspect of this embodiment, W^1 and W^2 are, independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another preferred aspect of this embodiment, W^1 and W^2
- 20 are, independently, naturally-occurring 2-hydroxy carboxylic acids or naturally-

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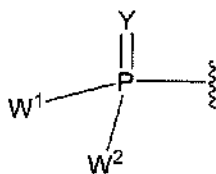
- 5 occurring 2-hydroxy carboxylic acid esters wherein the acid or ester is linked to P through the 2-hydroxy group.



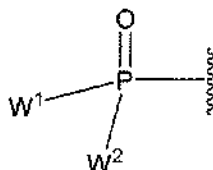
Another embodiment of of Formula I, Formula II, or Formula III is substructure:



- 10 In one preferred aspect of this embodiment, each R^x is, independently, (C_1-C_8) alkyl. In another preferred aspect of this embodiment, each R^x is, independently, C_6-C_{20} aryl or C_6-C_{20} substituted aryl.



Another embodiment of of Formulas I-III is substructure



15

wherein W^1 and W^2 are independently selected from one of the formulas in Tables 20.1-20.37 and Table 30.1 below. The variables used in Tables 20.1-20.37 (e.g., W^{23} , R^{21} , etc.) pertain only to Tables 20.1-20.37, unless otherwise indicated.

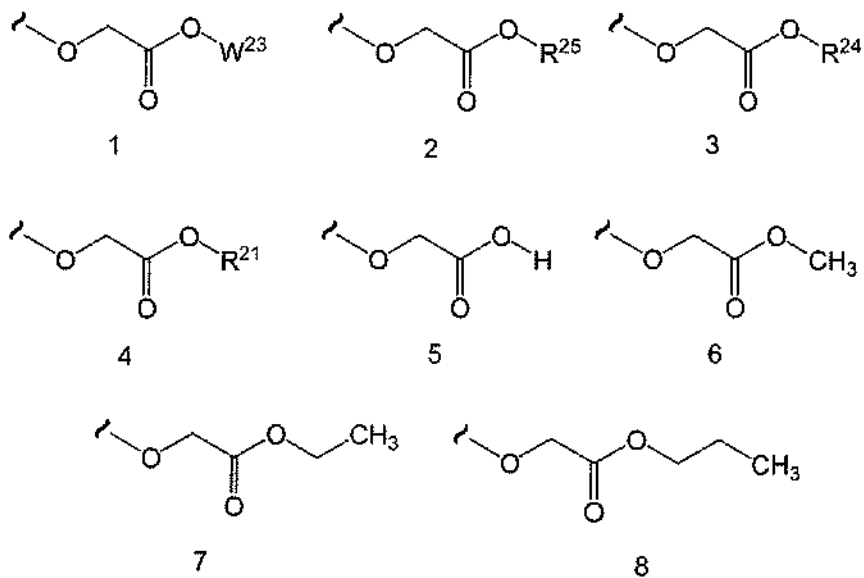
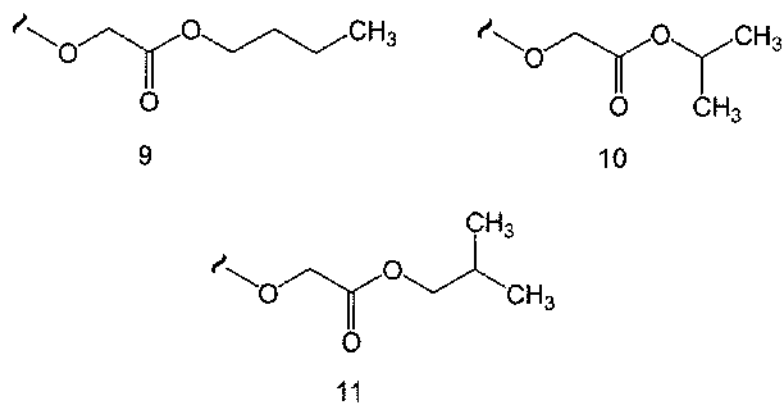
The variables used in Tables 20.1 to 20.37 have the following definitions:

- 20 each R^{21} is independently H or (C_1-C_8) alkyl;

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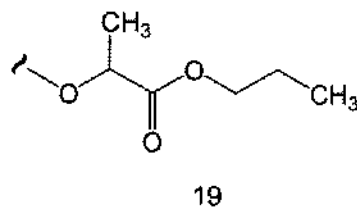
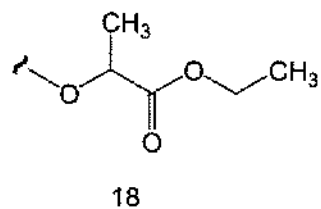
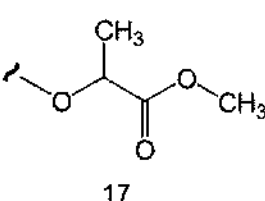
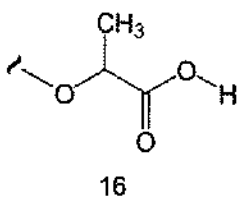
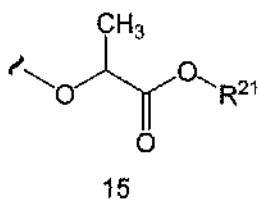
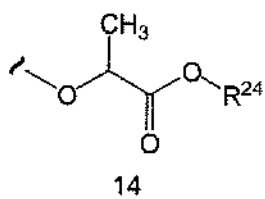
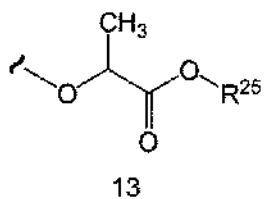
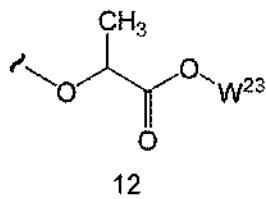
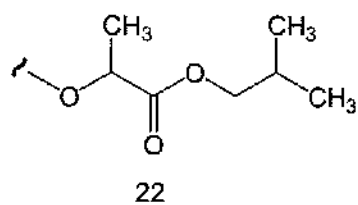
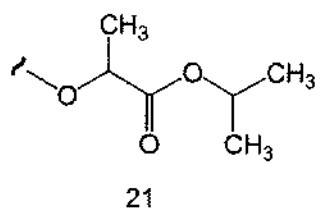
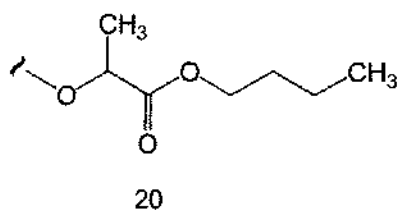
- 5 each R^{22} is independently H, R^{21} , R^{23} or R^{24} wherein each R^{24} is independently substituted with 0 to 3 R^{23} ;
- each R^{23} is independently R^{23a} , R^{23b} , R^{23c} or R^{23d} , provided that when R^{23} is bound to a heteroatom, then R^{23} is R^{23c} or R^{23d} ;
- each R^{23a} is independently F, Cl, Br, I, -CN, N_3 or $-NO_2$;
- 10 each R^{23b} is independently Y^{21} ;
- each R^{23c} is independently $-R^{2x}$, $-N(R^{2x})(R^{2x})$, $-SR^{2x}$, $-S(O)R^{2x}$, $-S(O)_2R^{2x}$, $-S(O)(OR^{2x})$, $-S(O)_2(OR^{2x})$, $-OC(=Y^{21})R^{2x}$, $-OC(=Y^{21})OR^{2x}$, $-OC(=Y^{21})(N(R^{2x})(R^{2x}))$, $-SC(=Y^{21})R^{2x}$, $-SC(=Y^{21})OR^{2x}$, $-SC(=Y^{21})(N(R^{2x})(R^{2x}))$, $-N(R^{2x})C(=Y^{21})R^{2x}$, $-N(R^{2x})C(=Y^{21})OR^{2x}$, or $-N(R^{2x})C(=Y^{21})(N(R^{2x})(R^{2x}))$;
- 15 each R^{23d} is independently $-C(=Y^{21})R^{2x}$, $-C(=Y^{21})OR^{2x}$ or $-C(=Y^{21})(N(R^{2x})(R^{2x}))$;
- each R^{2x} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl, heteroaryl; or two R^{2x} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^{21}-$; and wherein one or
- 20 more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with -O-, -S- or $-NR^{21}-$;
- each R^{24} is independently (C_1-C_8) alkyl, (C_2-C_8) alkenyl, or (C_2-C_8) alkynyl;
- each R^{25} is independently R^{24} wherein each R^{24} is substituted with 0 to 3 R^{23} groups;
- 25 each R^{25a} is independently (C_1-C_8) alkylene, (C_2-C_8) alkenylene, or (C_2-C_8) alkynylene any one of which said (C_1-C_8) alkylene, (C_2-C_8) alkenylene, or (C_2-C_8) alkynylene is substituted with 0-3 R^{23} groups;
- each W^{23} is independently W^{24} or W^{25} ;
- each W^{24} is independently R^{25} , $-C(=Y^{21})R^{25}$, $-C(=Y^{21})W^{25}$, $-SO_2R^{25}$, or $-SO_2W^{25}$;
- 30 each W^{25} is independently carbocycle or heterocycle wherein W^{25} is independently substituted with 0 to 3 R^{22} groups; and
- each Y^{21} is independently O or S.

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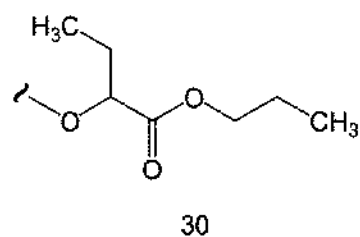
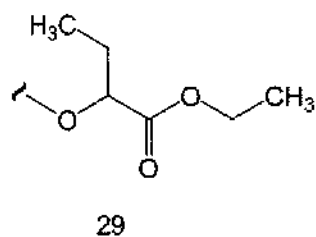
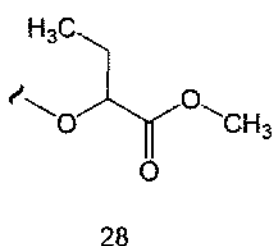
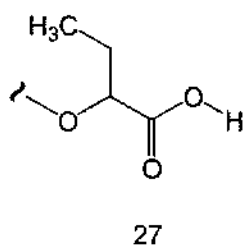
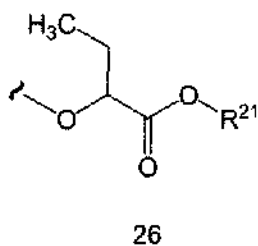
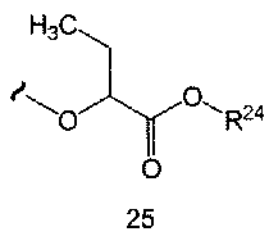
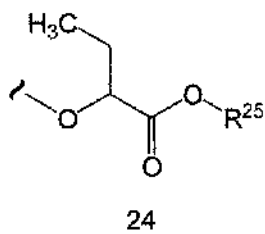
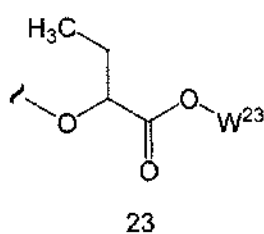
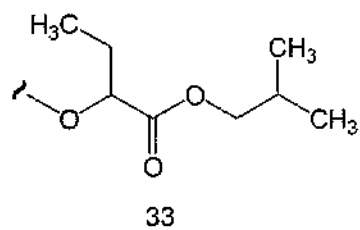
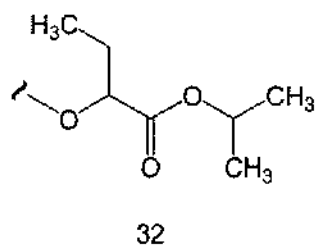
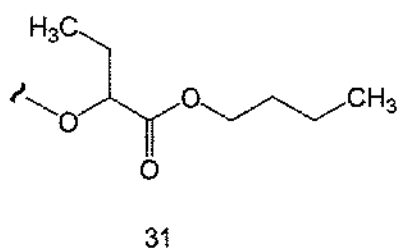
5 Table 20.1Table 20.2

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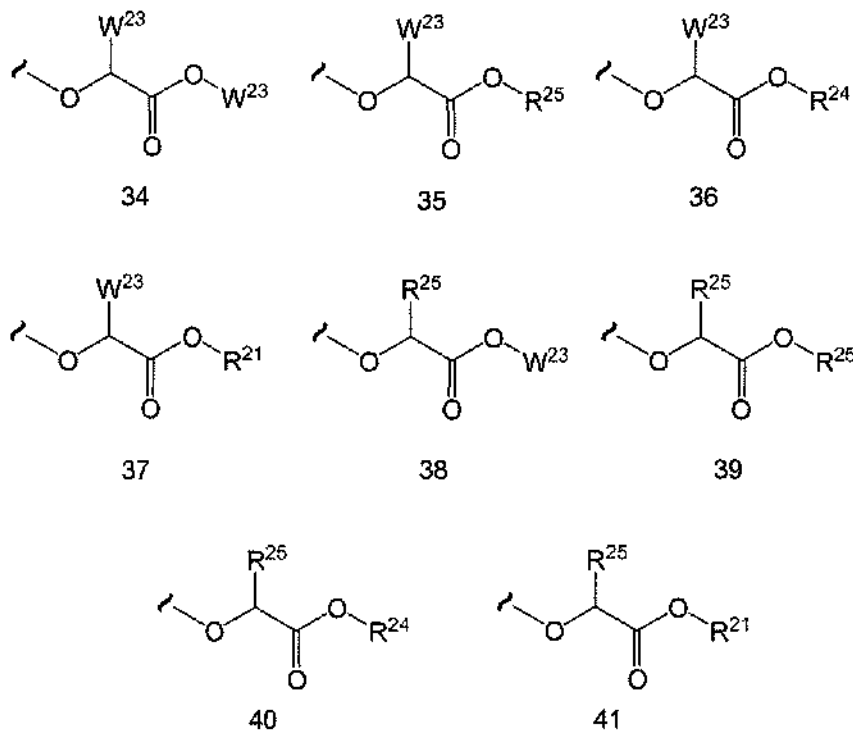
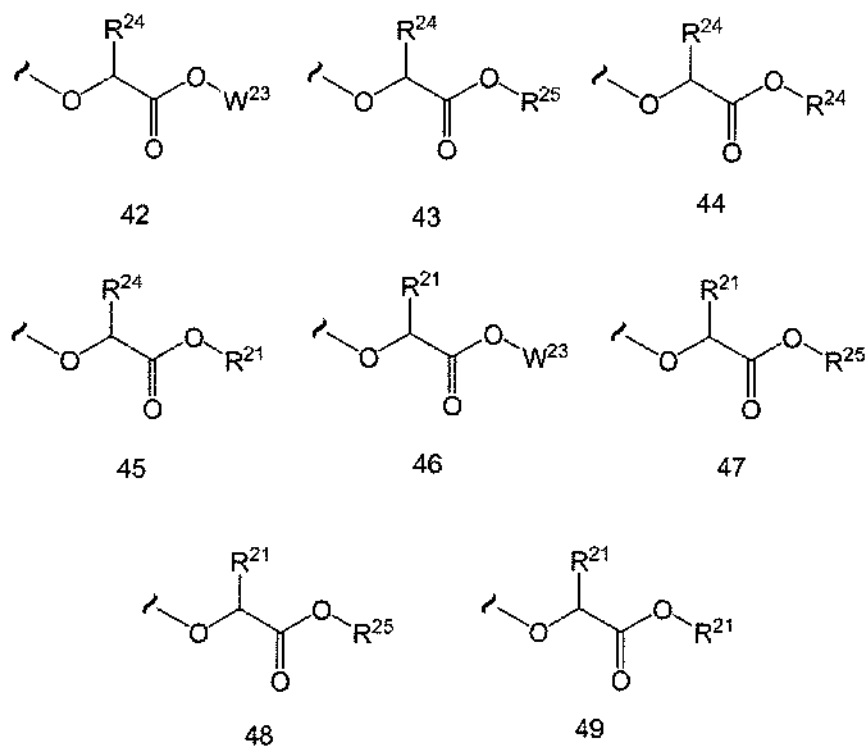
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5 Table 20.3Table 20.4

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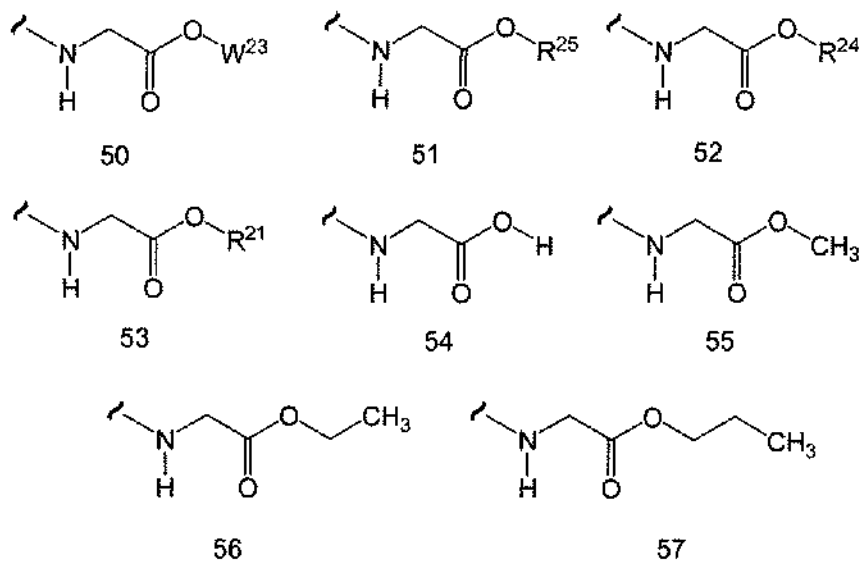
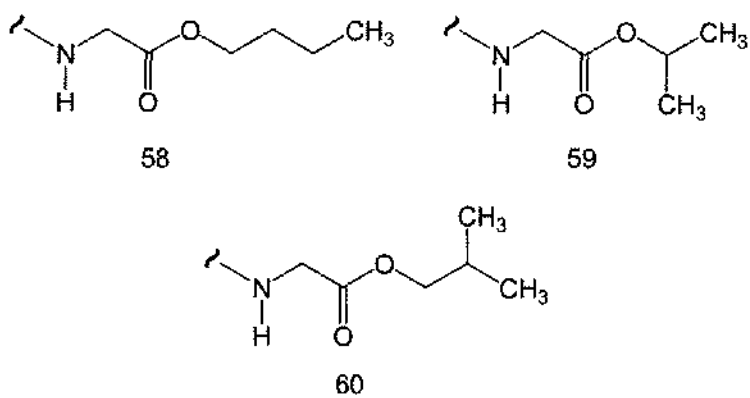
5 Table 20.5Table 20.6

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5 Table 20.7Table 20.8

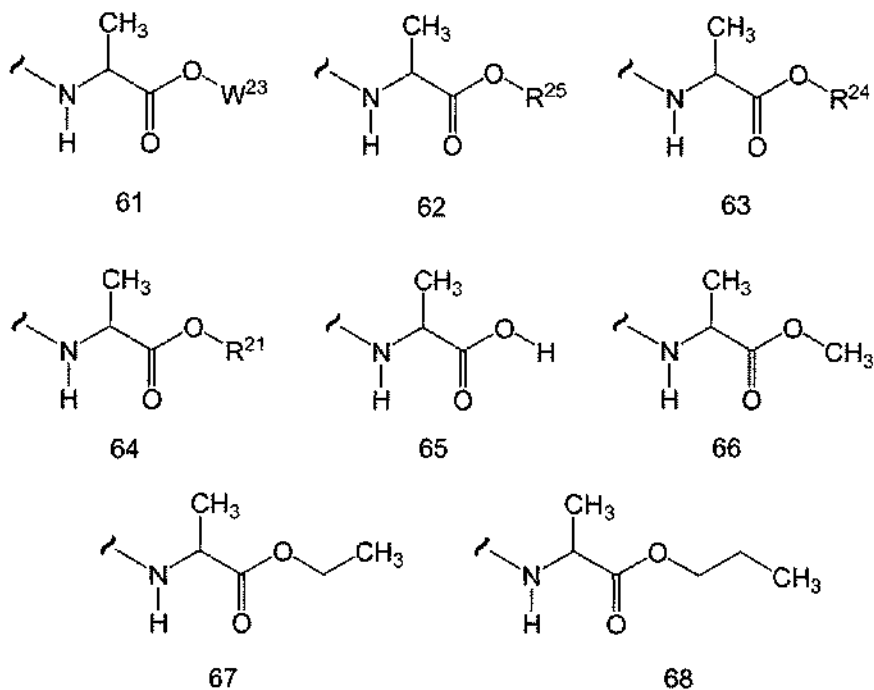
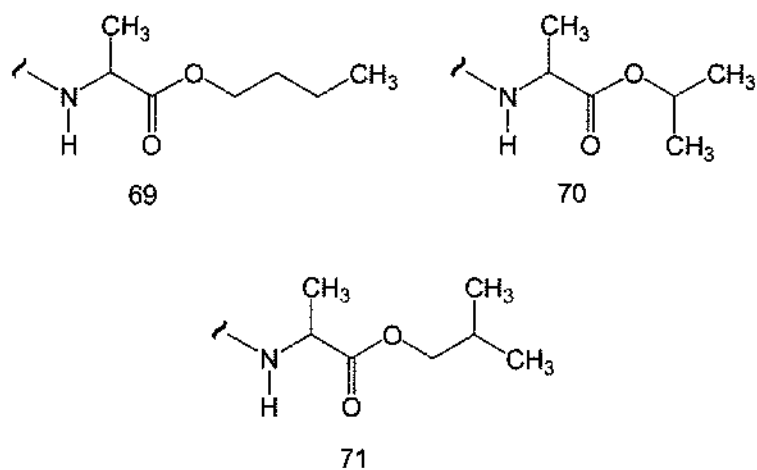
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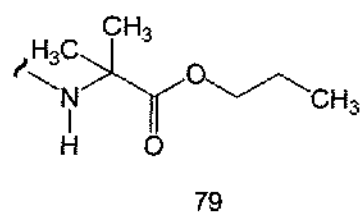
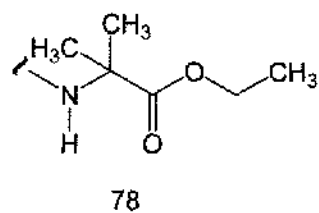
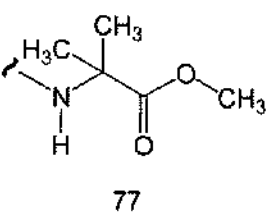
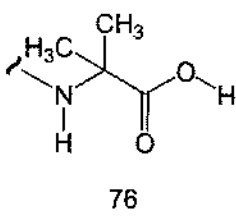
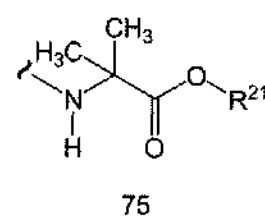
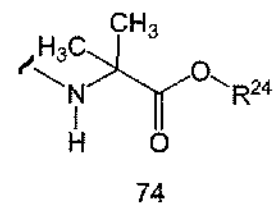
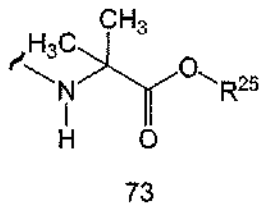
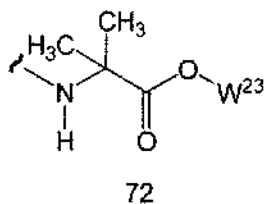
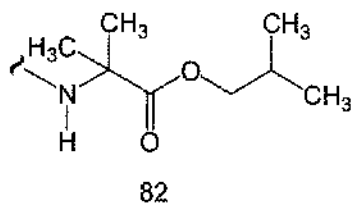
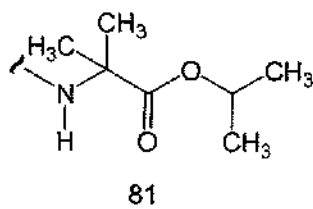
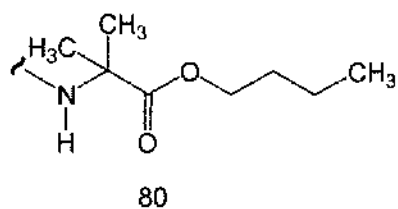
Table 20.9Table 20.10

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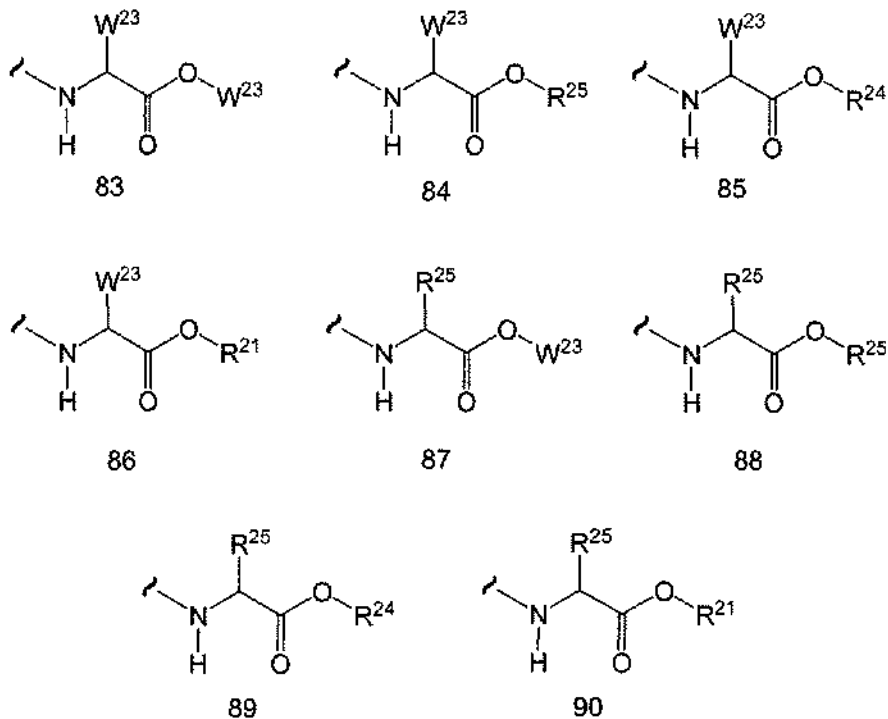
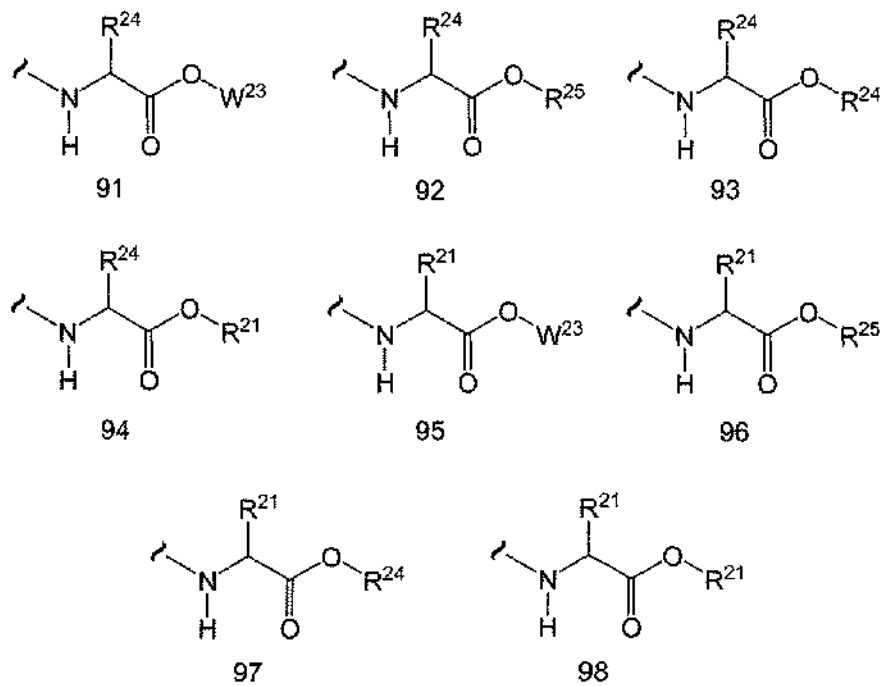
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5 Table 20.11Table 20.12

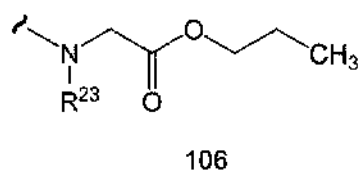
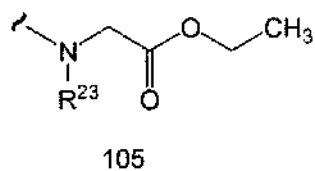
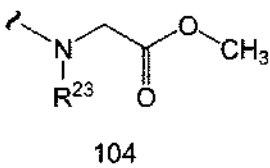
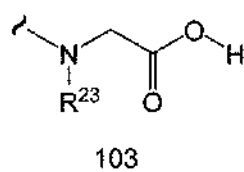
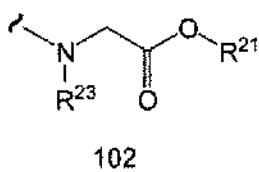
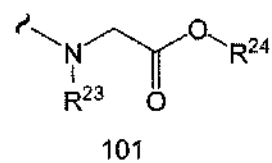
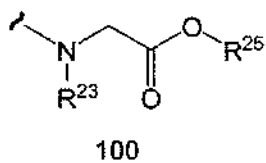
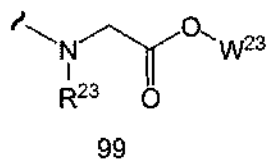
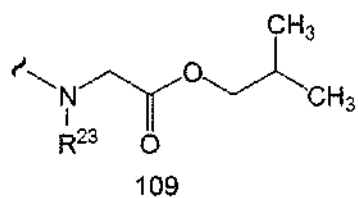
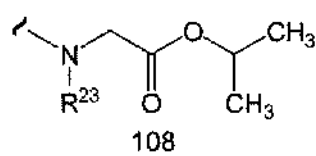
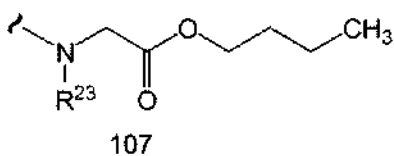
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5 Table 20.13Table 20.14

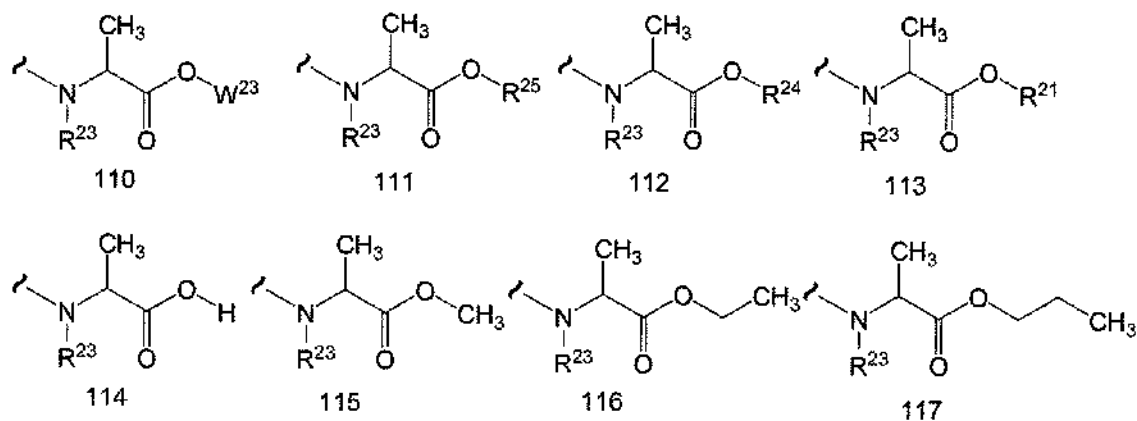
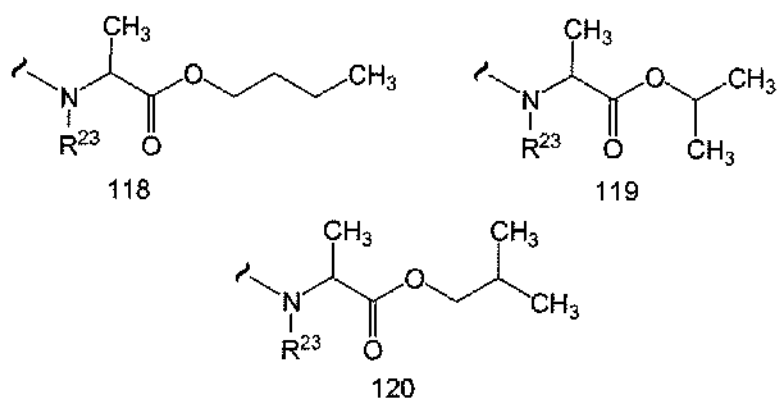
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5 Table 20.15Table 20.16

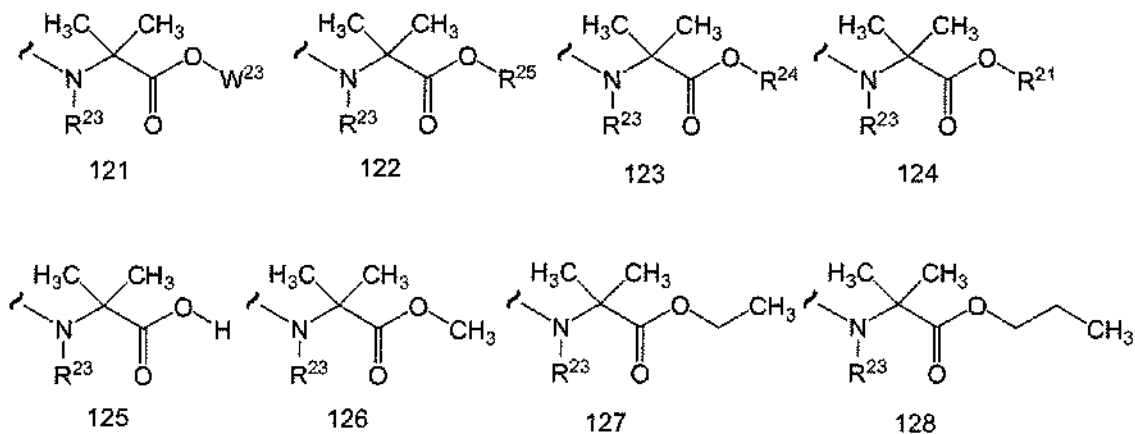
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5 Table 20.17Table 20.18

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5 Table 20.19Table 20.20

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Table 20.21

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Table 20.22

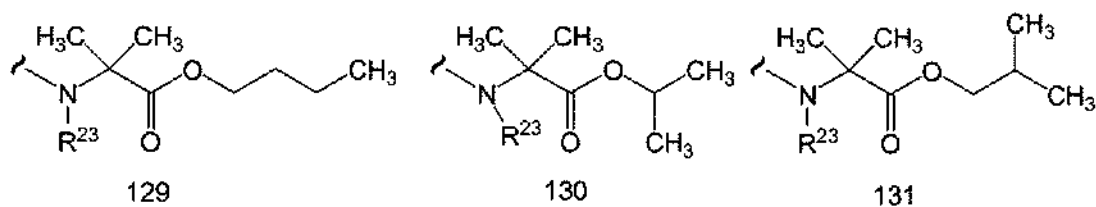
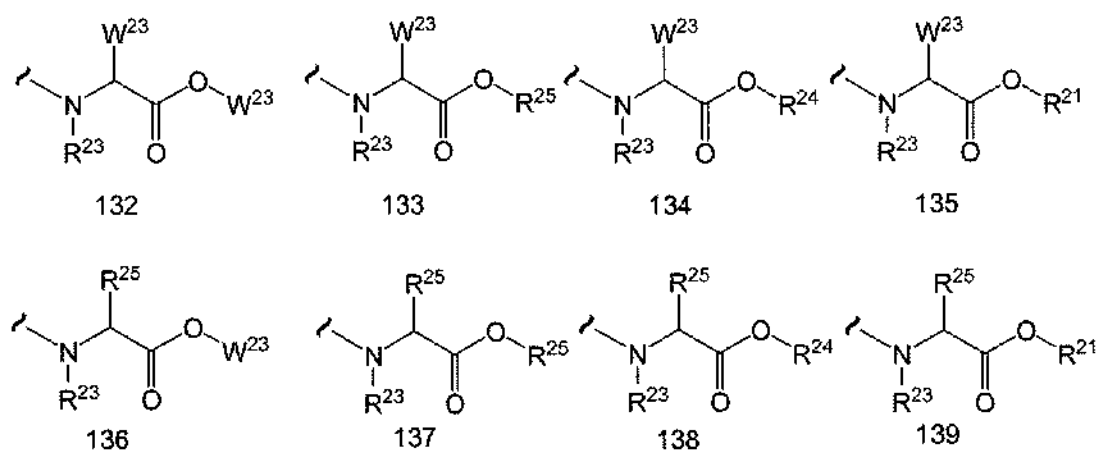
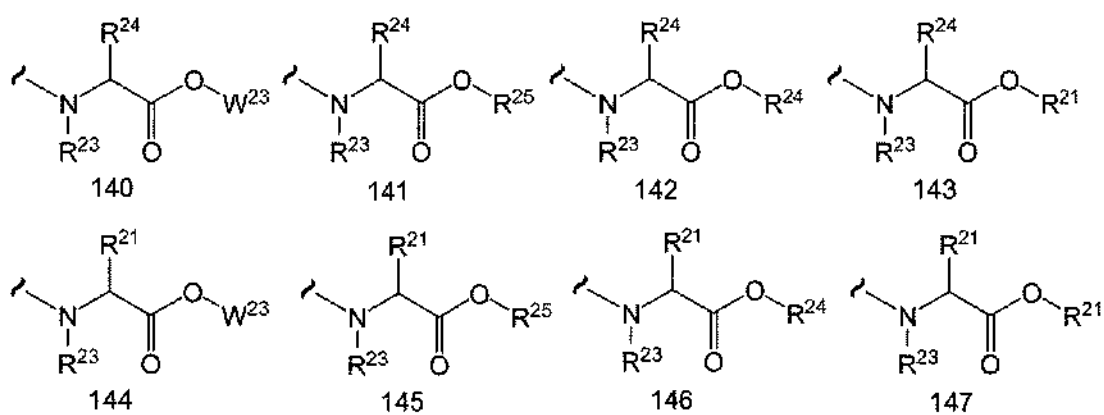


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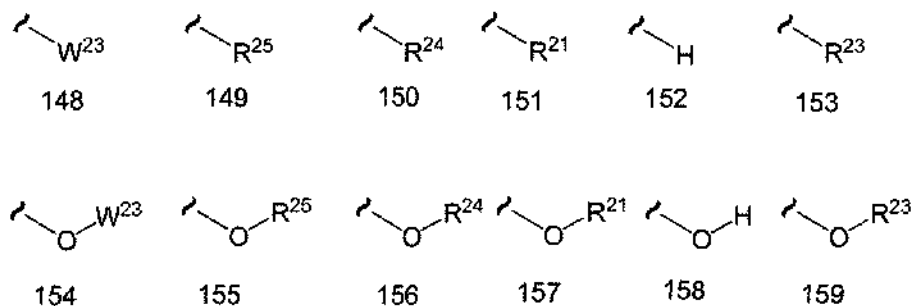
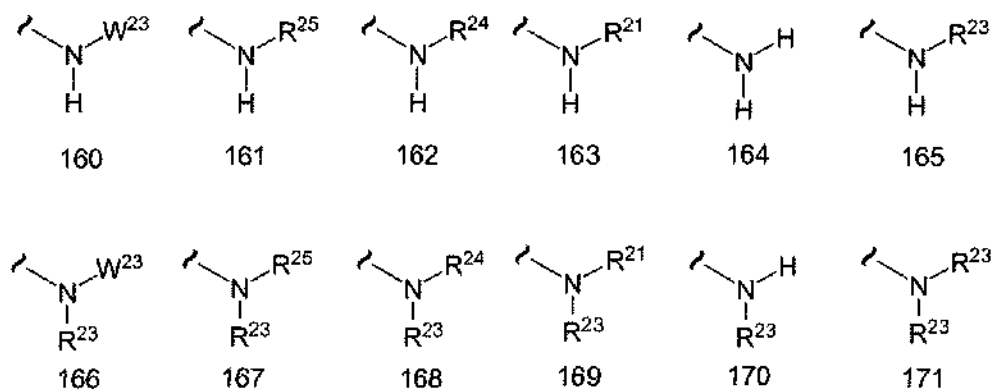


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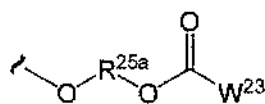


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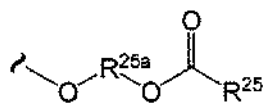
5 Table 20.25Table 20.26

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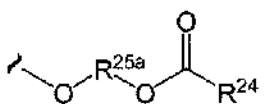
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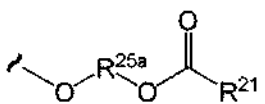
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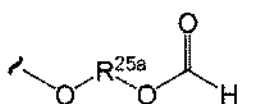
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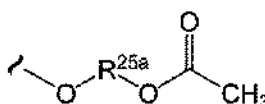
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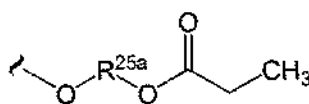
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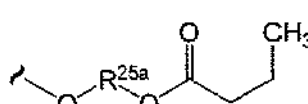
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177



178

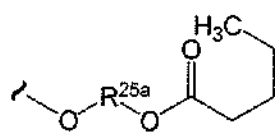


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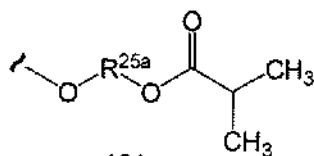
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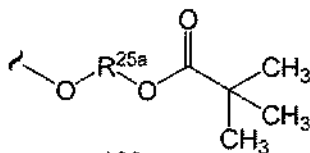
756.PF



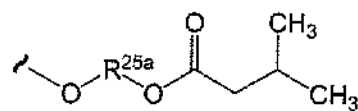
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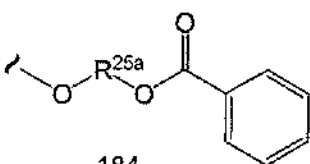
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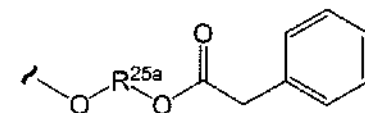
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183



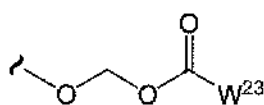
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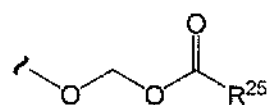
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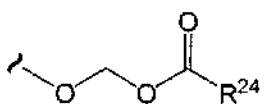
Table 20.29



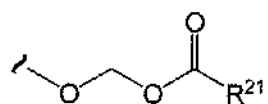
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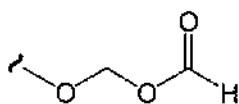
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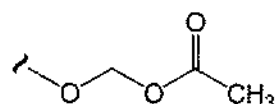
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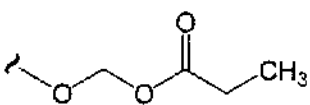
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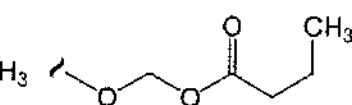
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191



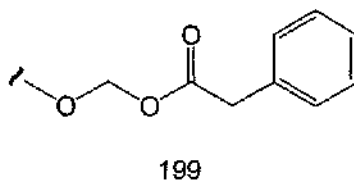
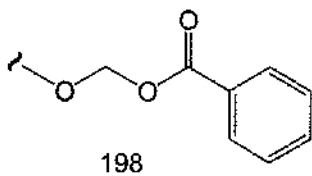
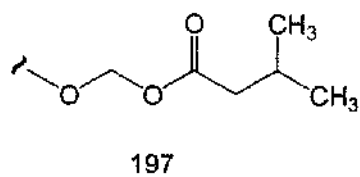
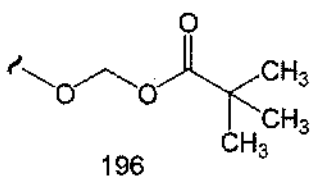
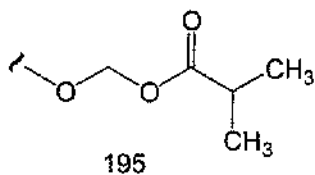
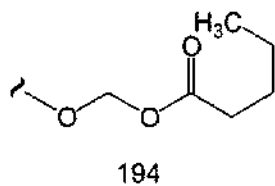
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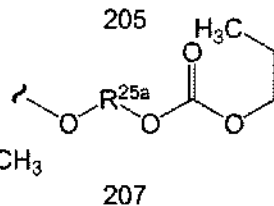
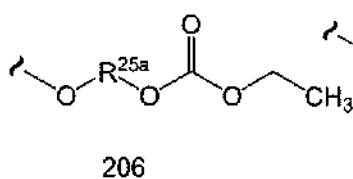
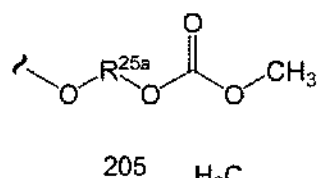
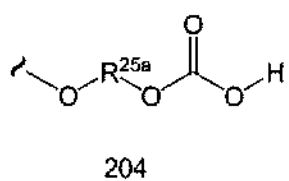
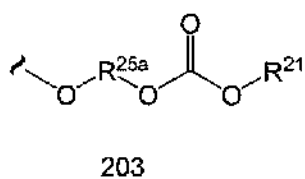
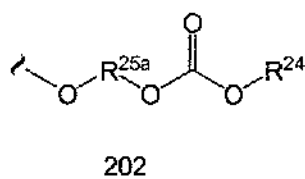
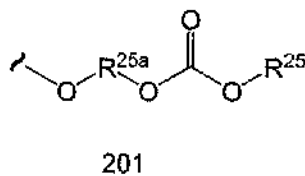
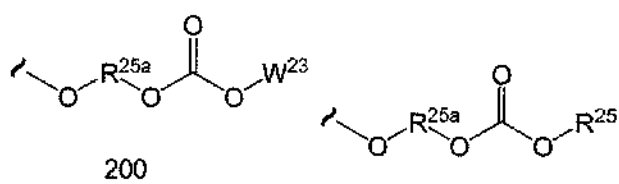
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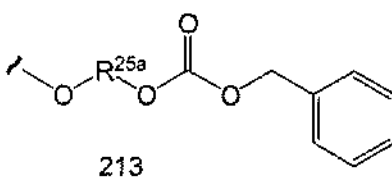
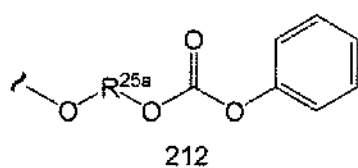
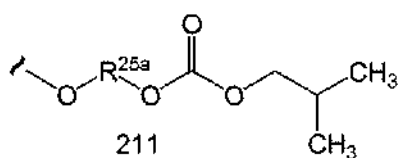
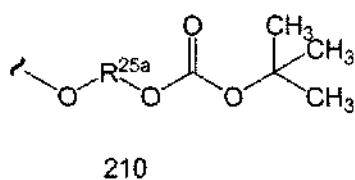
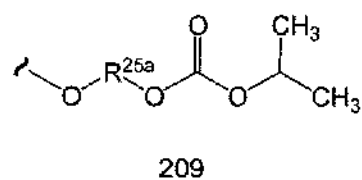
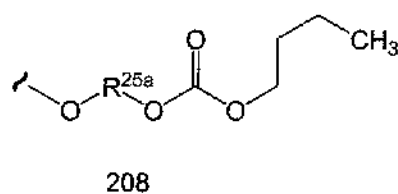
Table 20.30Table 20.31

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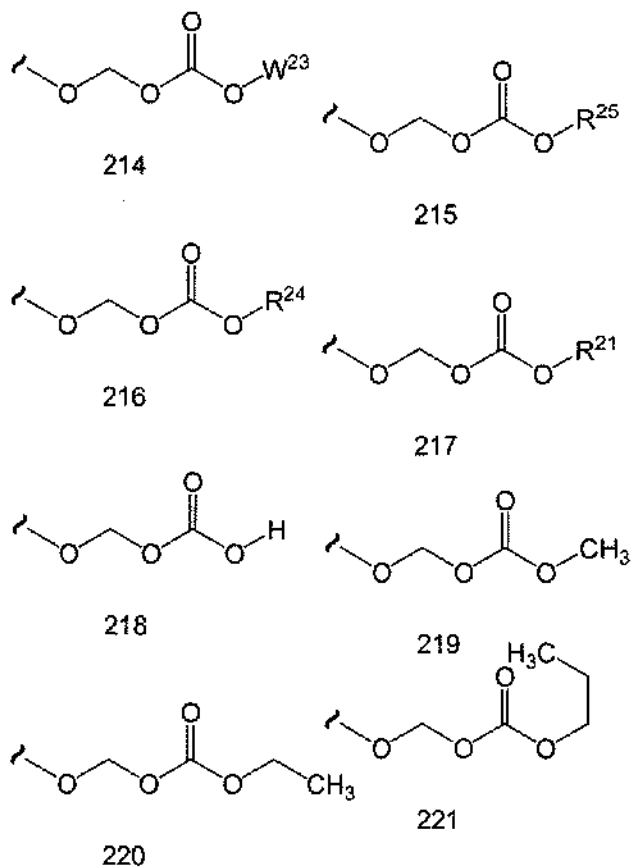


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Table 20.32

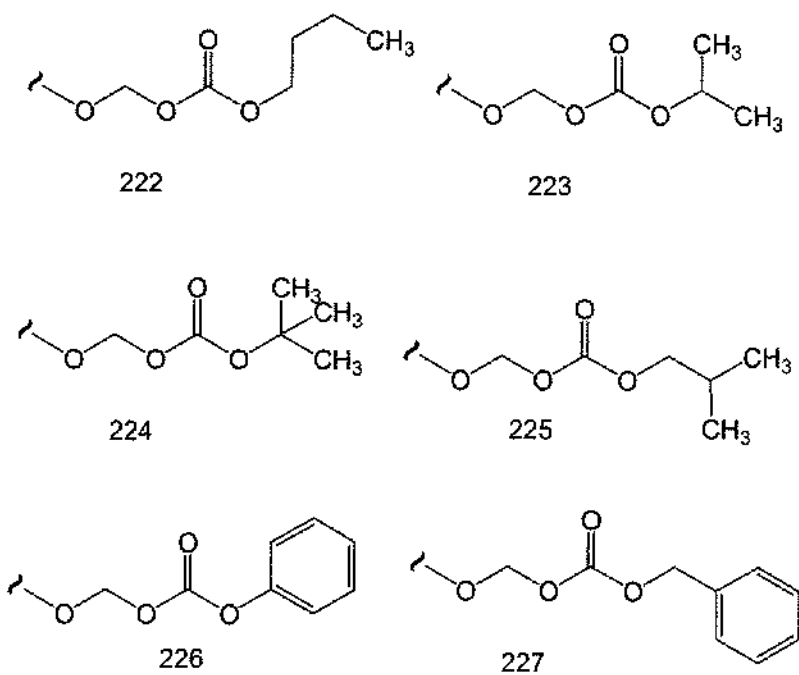
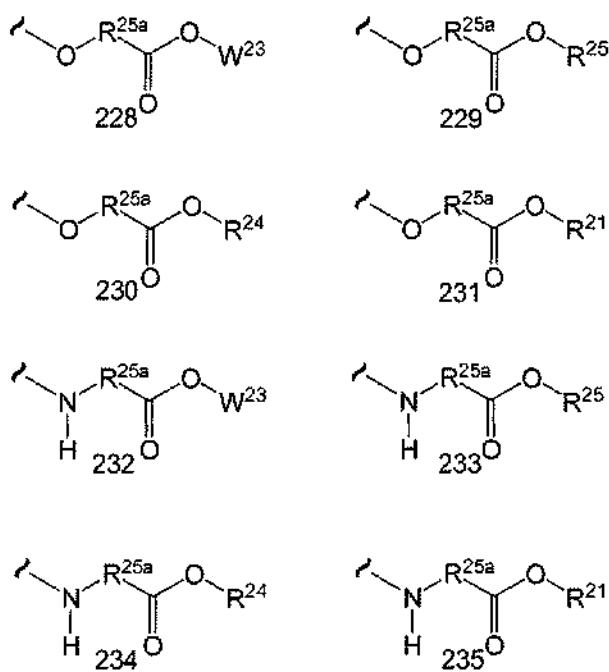


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5 Table 20.33

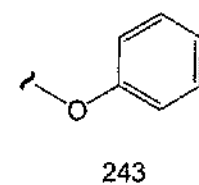
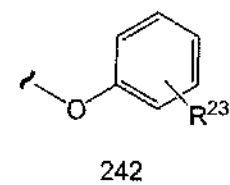
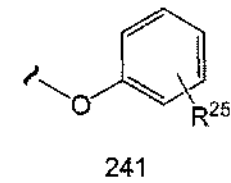
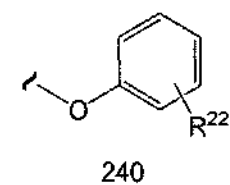
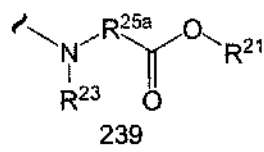
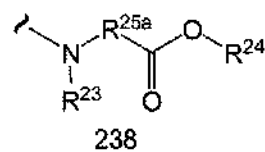
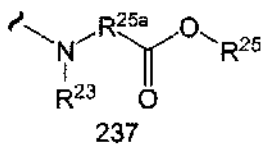
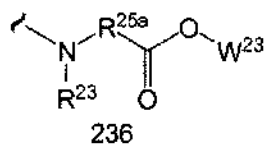
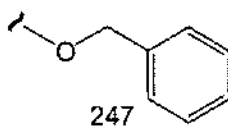
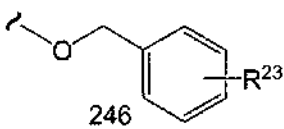
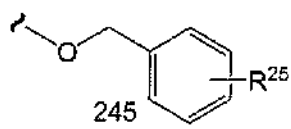
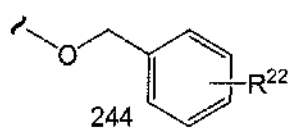
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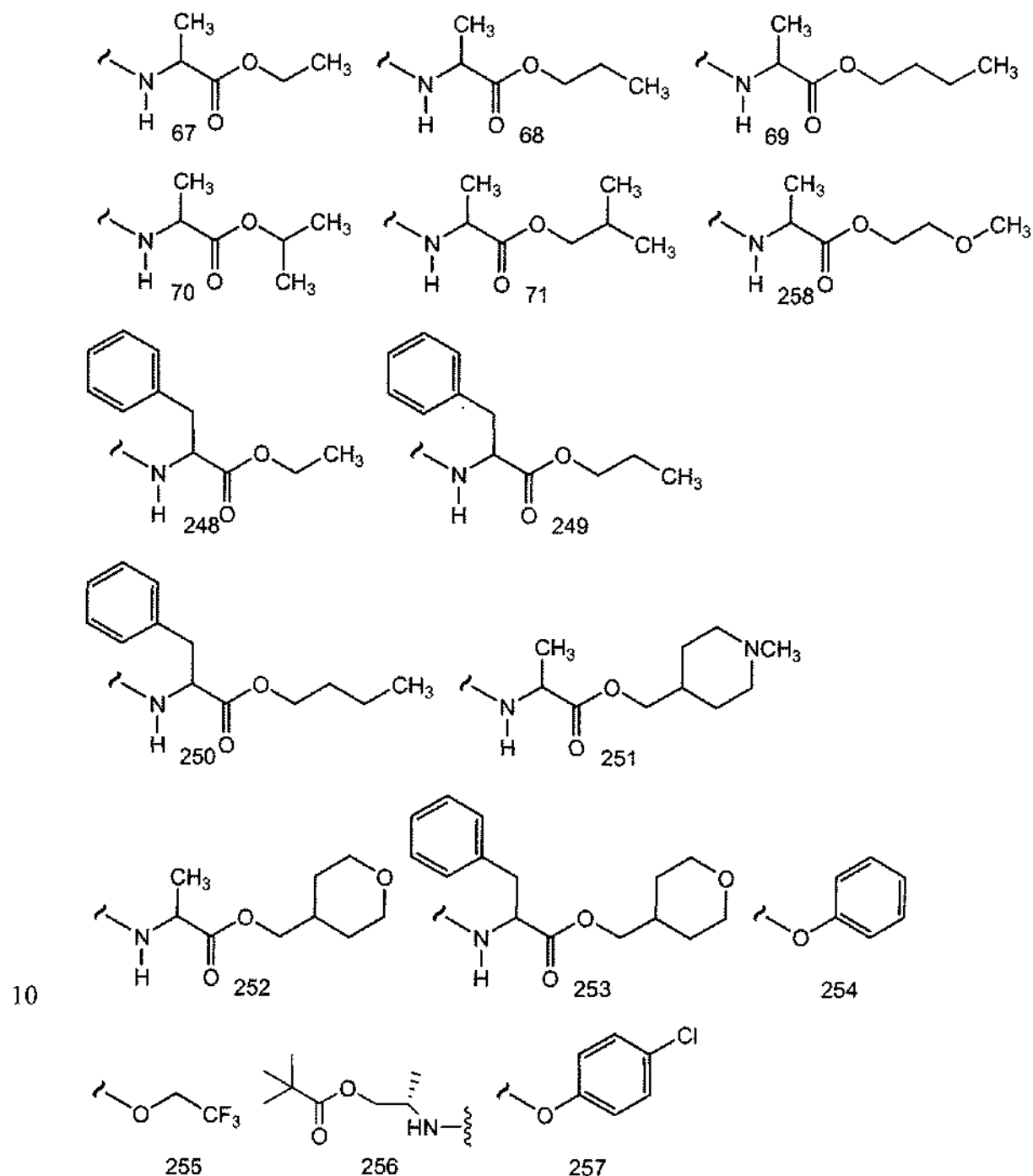
Table 20.34Table 20.35

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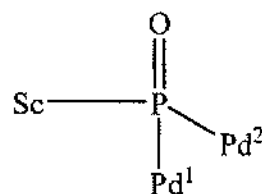
5 Table 20.36Table 20.37

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5 Table 30.1Phosphate Embodiments of Compounds of Formula I-IV

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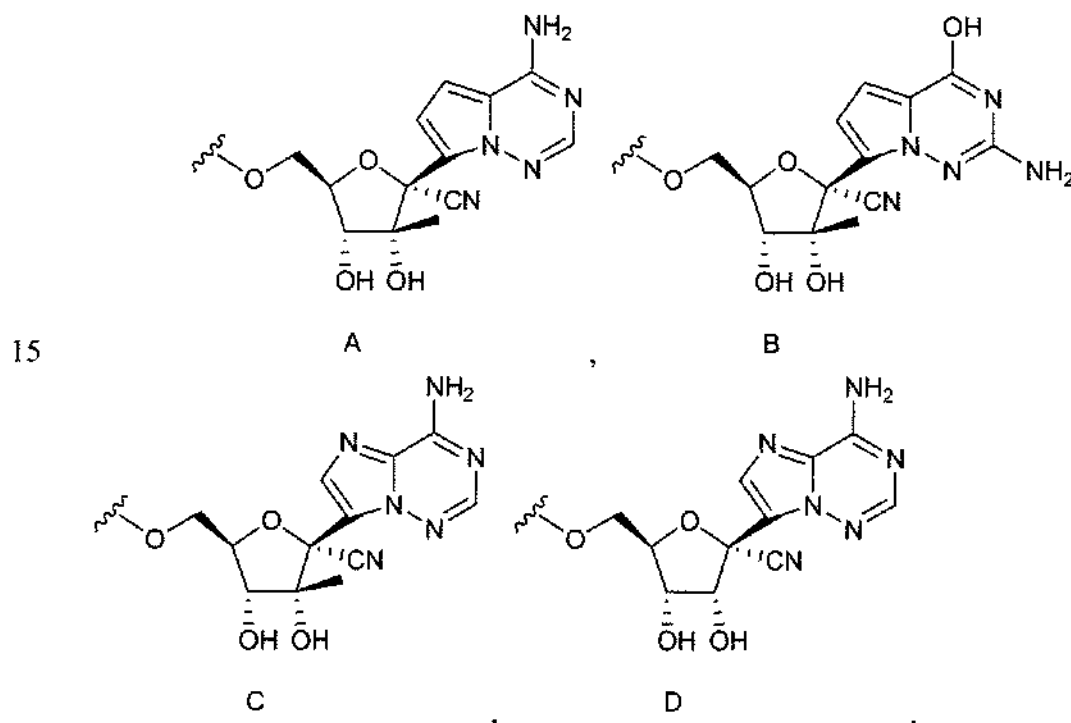
- 5 By way of example and not limitation, the phosphate embodiments of Formula I-IV may be represented by the general formula "MBF":



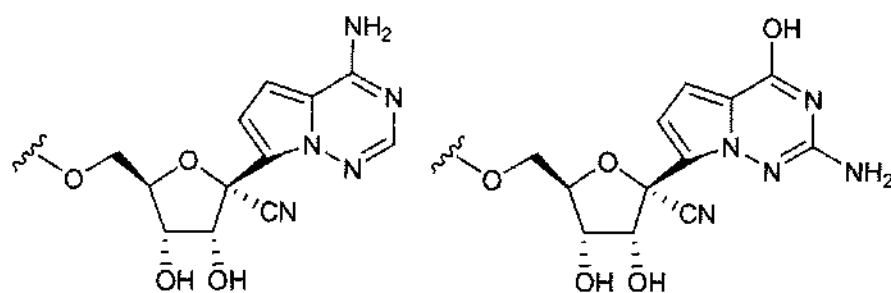
MBF

- Each embodiment of MBF is depicted as a substituted nucleus (Sc). Sc is described in
 10 formulae A-G of Table 1.1 below, wherein Sc is a generic formula for a compound of Formula I, Formula II, or Formula III and the point of attachment to $-P(O)Pd^1Pd^2$ is indicated with a wavy line.

Table 1.1



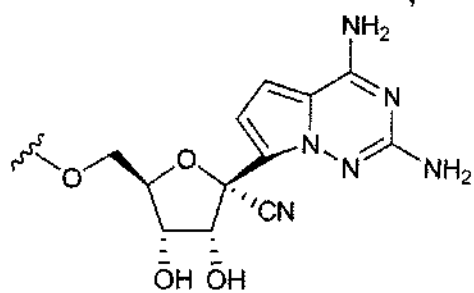
756.PF



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E

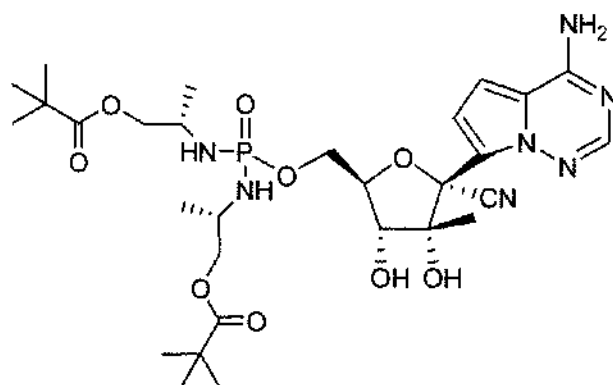
F



G

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- 5 Combinations of "Sc" and Pd¹ and Pd², independently selected from Table 30.1, can be expressed in the form of Sc.Pd¹.Pd², where Sc is represented by the respective letter A-G from Table 1.1 and Pd¹ and Pd² are represented by the respective number from Table 30.1. Thus, A.256.256 represents the following compound:



10

Thereby, Table 7 lists many specific examples of phosphate prodrugs of Formula I-IV.

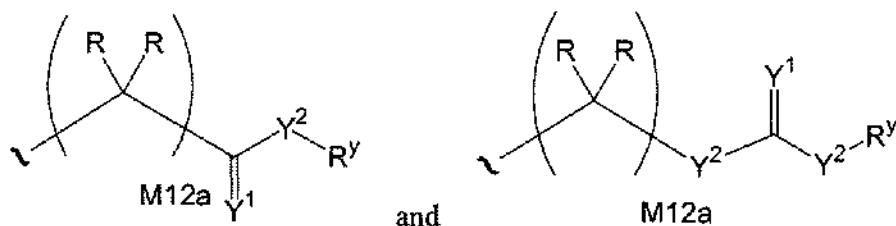
Table 7: List of Compounds of MBF

- A.254.67, A.254.68, A.254.69, A.254.70, A.254.71, A.254.258, A.254.248, A.254.249,
 15 A.254.250, A.254.251, A.254.252, A.254.253, B.254.67, B.254.68, B.254.69, B.254.70,
 B.254.71, B.254.258, B.254.248, B.254.249, B.254.250, B.254.251, B.254.252,
 B.254.253, C.254.67, C.254.68, C.254.69, C.254.70, C.254.71, C.254.258, C.254.248,
 C.254.249, C.254.250, C.254.251, C.254.252, C.254.253, D.254.67, D.254.68, D.254.69,
 D.254.70, D.254.71, D.254.258, D.254.248, D.254.249, D.254.250, D.254.251,
 20 D.254.252, D.254.253, E.254.67, E.254.68, E.254.69, E.254.70, E.254.71, E.254.258,
 E.254.248, E.254.249, E.254.250, E.254.251, E.254.252, E.254.253, F.254.67, F.254.68,
 F.254.69, F.254.70, F.254.71, F.254.258, F.254.248, F.254.249, F.254.250, F.254.251,
 F.254.252, F.254.253, G.254.67, G.254.68, G.254.69, G.254.70, G.254.71, G.254.258,
 G.254.248, G.254.249, G.254.250, G.254.251, G.254.252, G.254.253, A.255.67,
 25 A.255.68, A.255.69, A.255.70, A.255.71, A.255.258, A.255.248, A.255.249, A.255.250,
 A.255.251, A.255.252, A.255.253, B.255.67, B.255.68, B.255.69, B.255.70, B.255.71,
 B.255.258, B.255.248, B.255.249, B.255.250, B.255.251, B.255.252, B.255.253,
 C.255.67, C.255.68, C.255.69, C.255.70, C.255.71, C.255.258, C.255.248, C.255.249,

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- 5 C.255.250, C.255.251, C.255.252, C.255.253, D.255.67, D.255.68, D.255.69, D.255.70, D.255.71, D.255.258, D.255.248, D.255.249, D.255.250, D.255.251, D.255.252, D.255.253, E.255.67, E.255.68, E.255.69, E.255.70, E.255.71, E.255.258, E.255.248, E.255.249, E.255.250, E.255.251, E.255.252, E.255.253, F.255.67, F.255.68, F.255.69, F.255.70, F.255.71, F.255.258, F.255.248, F.255.249, F.255.250, F.255.251, F.255.252, F.255.253, G.255.67, G.255.68, G.255.69, G.255.70, G.255.71, G.255.258, G.255.248, G.255.249, G.255.250, G.255.251, G.255.252, G.255.253, A.67.67, A.68.68, A.69.69, A.70.70, A.71.71, A.258.258, A.248.248, A.249.249, A.250.250, A.251.251, A.252.252, A.253.253, B.67.67, B.68.68, B.69.69, B.70.70, B.71.71, B.258.258, B.248.248, B.249.249, B.250.250, B.251.251, B.252.252, B.253.253, C.67.67, C.68.68, C.69.69, C.70.70, C.71.71, C.258.258, C.248.248, C.249.249, C.250.250, C.251.251, C.252.252, C.253.253, D.67.67, D.68.68, D.69.69, D.70.70, D.71.71, D.258.258, D.248.248, D.249.249, D.250.250, D.251.251, D.252.252, D.253.253, E.67.67, E.68.68, E.69.69, E.70.70, E.71.71, E.258.258, E.248.248, E.249.249, E.250.250, E.251.251, E.252.252, E.253.253, F.67.67, F.68.68, F.69.69, F.70.70, F.71.71, F.258.258, F.248.248, F.249.249, F.250.250, F.251.251, F.252.252, F.253.253, G.67.67, G.68.68, G.69.69, G.70.70, G.71.71, G.258.258, G.248.248, G.249.249, G.250.250, G.251.251, G.252.252, G.253.253, A.256.257, B.256.257, C.256.257, D.256.257, E.256.257, F.256.257, G.256.257, A.256.254, B.256.254, C.256.254, D.256.254, E.256.254, F.256.254, G.256.254, A.256.250, B.256.250, C.256.250, D.256.250, E.256.250, F.256.250, G.256.250, A.256.69, B.256.69, C.256.69, D.256.69, E.256.69, F.256.69, G.256.69, A.256.71, B.256.71, C.256.71, D.256.71, E.256.71, F.256.71, G.256.71, A.256.255, B.256.255, C.256.255, D.256.255, E.256.255, F.256.255, G.256.255.

- Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



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Any reference to the compounds of the invention described herein also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+ , Li^+ , K^+ , Ca^{+2} and Mg^{+2}), ammonium and NR_4^+ (wherein R is defined herein). Physiologically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NR_4^+ .

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

The compounds of the invention, exemplified by Formula I-III may have chiral

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- 5 centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures.
- 10 Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active
- 15 adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The term "chiral" refers to molecules which have the property of non-
20 superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and
25 whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-
30 superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds

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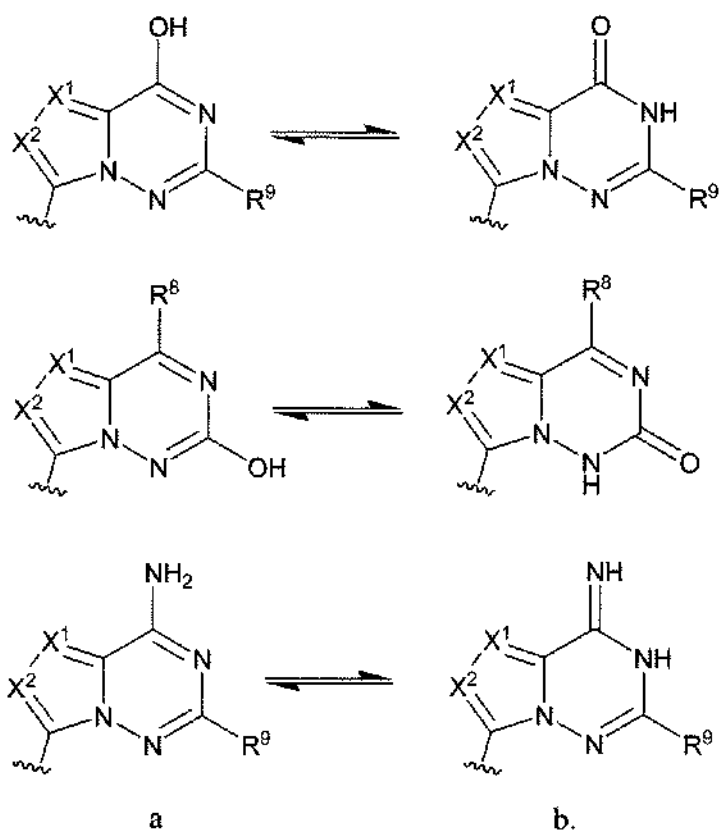
5 exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (-), or l meaning that
10 the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a
15 racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R¹", then it will be understood that the groups may
20 be the same or different, i.e., each group is independently selected. Wavy lines, ~~~~~, indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such
25 forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

One skilled in the art will recognize that the pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-
30 f][1,2,4]triazine nucleosides can exist in tautomeric forms. For example, but not by way of limitation, structures (a) and (b) can have equivalent tautomeric forms as shown below:

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All possible tautomeric forms of the heterocycles in all of the embodiments disclosed herein are within the scope of the invention.

Methods of Inhibition of HCV polymerase

Another aspect of the invention relates to methods of inhibiting the activity of HCV polymerase comprising the step of treating a sample suspected of containing HCV with a composition of the invention.

Compositions of the invention may act as inhibitors of HCV polymerase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HCV polymerase having a geometry unique to HCV polymerase. Compositions binding HCV polymerase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HCV polymerase. Accordingly, the invention relates to methods of detecting HCV

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- 5 polymerase in a sample suspected of containing HCV polymerase comprising the steps of: treating a sample suspected of containing HCV polymerase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

Within the context of the invention, samples suspected of containing HCV polymerase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HCV polymerase, frequently a pathogenic organism such as HCV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of HCV polymerase after application of the composition can be observed by any method including direct and indirect methods of detecting HCV polymerase activity. Quantitative, qualitative, and semiquantitative methods of determining HCV polymerase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HCV polymerase include the HCV virus. The compounds of this invention are useful in the treatment or prophylaxis of HCV infections in animals or in man.

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- 5 However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HCV polymerase Inhibitors.

- 10 Compositions of the invention are screened for inhibitory activity against HCV polymerase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HCV polymerase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* K_i (inhibitory constants)
- 15 of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

- 20 The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set
- 25 forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

- 30 While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally

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- 5 other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be
10 prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately
15 bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or
20 a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable
25 machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide
30 slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6%

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- 5 w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

- If desired, the aqueous phase of the cream base may include, for example, at least
10 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration
15 enhancers include dimethyl sulphoxide and related analogs.

- The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic
20 emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

- 25 Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween[®] 60, Span[®] 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

- The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining
30 and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three

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- 5 being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically
10 acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may
15 be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for
20 manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known
25 techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where
30 the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients

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- 5 include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long
10 chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose
15 or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth
20 above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives.
25 Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis
30 oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as

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- 5 polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile
10 injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-
15 diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in
20 the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active
25 material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μ g of the active ingredient per milliliter of solution in
30 order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and

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- 5 particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a
10 suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is
15 administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or
20 prophylaxis of HCV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-
25 aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example
30 sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-

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- 5 dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

- 10 The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These
15 veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active
20 ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical
25 formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about .01 to about 5 mg/kg body weight per day; most typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult
30 human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated.

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- 5 Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

10

Combination Therapy

- Compositions of the invention are also used in combination with other active ingredients. Preferably, the other active therapeutic ingredients or agents are interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1
15 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

- Combinations of the compounds of Formula I-III are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating an infection (e.g., HCV), the compositions
20 of the invention are combined with other active therapeutic agents (such as those described herein).

- Suitable active therapeutic agents or ingredients which can be combined with the compounds of Formula I-III can include interferons, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus
25 IFN alpha, infigen, rebif, locteron, AVI-005, PEG-infigen, pegylated IFN-beta, oral interferon alpha, feron, reafiron, intermax alpha, r-IFN-beta, infigen + actimmune, IFN-omega with DUROS, and albuferon; ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin); NS5a inhibitors, e.g., A-831, A-689 and BMS-790052; NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656),
30 HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125; NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065; alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B; hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451; non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-

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5 thiadiazine derivatives, and phenylalanine derivatives; and other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

10 In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

According to the present invention, the therapeutic agent used in combination
15 with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside
20 inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b,
25 pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB
30 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI

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- 5 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

- 10 a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and
- b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase,
- 15 HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

- 20 Combinations of the compounds of Formula I-III and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of Formula I-III may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase,
- 25 HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

- 30 More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brexanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-

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- 5 756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.*, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside
- 10 inhibitor of reverse transcriptase, *e.g.*, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir ($\pm$ -FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosaltivudine tidoxil, apricitabine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of
- 15 reverse transcriptase, *e.g.*, tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl
- 20 ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.*, AMD-070, 8) an entry
- 25 inhibitor, *e.g.*, SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 10) a CCR5 inhibitor, *e.g.*, aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus
- 30 IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, *e.g.*, rebetol, copegus, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, *e.g.*, A-831, A-689 and BMS-790052, 14) NS5b polymerase inhibitors, *e.g.*, NM-283, valopicitabine, R1626, PSI-6130

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- 5 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole
 10 derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating HCV, e.g., zidaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic
 15 enhancers, e.g., BAS-100 and SPI452, 20) RNase H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

It is also possible to combine any compound of the invention with one or more
 20 other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active
 25 therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of
 30 the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more

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- 5 other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other
- 10 active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects

15 that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or

20 delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the

25 predicted purely additive effects of the individual compounds of the combination.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically

30 acceptable salt, solvate, and/or ester thereof, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically

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- 5 acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically
10 acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In still yet another embodiment, the present application provides for methods of
15 treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically
20 effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically
25 effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

30 In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for treating an HCV infection in a patient.

Metabolites of the Compounds of the Invention

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5 Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and
10 unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to
15 man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR
20 analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV polymerase inhibitory activity of their own.

25 Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that
30 they cannot be hydrolyzed *in vivo*. The prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Examples

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- 5 Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

Table 1. List of abbreviations and acronyms.

Abbreviation	Meaning
Ac ₂ O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]nonene-5
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undecene-5
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTCI	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4, 4'-dimethoxytrityl
DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	electrospray ionization
HMDS	hexamethyldisilazane

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HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH ⁺	mass plus 1
MH ⁻	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromosuccinimide
rt or r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tlc	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
δ	parts per million down field from tetramethylsilane

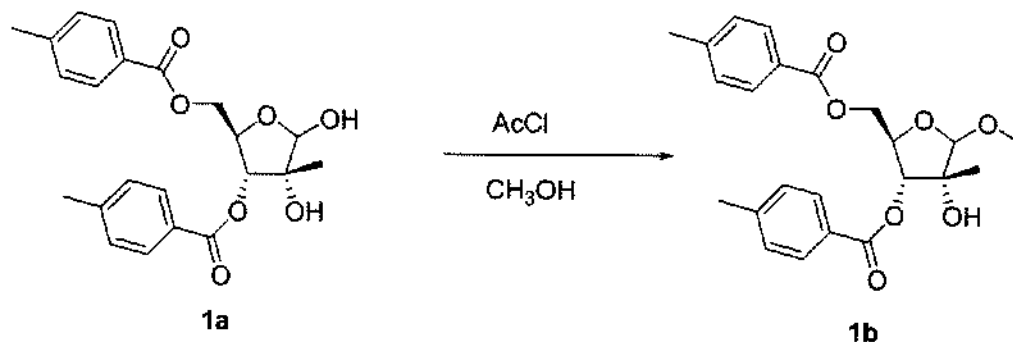
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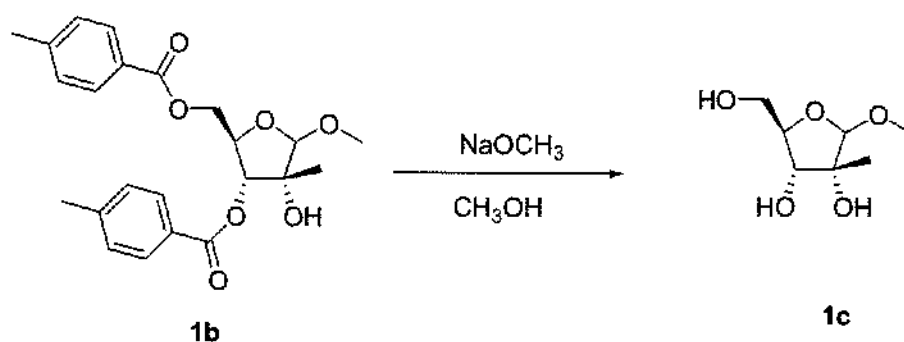
Preparation of Compounds**Compound 1a-1f**

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To a solution of **1a** (22.0 g, 54.9 mmol, prepared according to the procedures described in *J.O.C.*, **2004**, 6257) in methanol (300 mL) was dropwise added acetyl chloride (22 mL) at 0 °C using a dropping funnel over a period of 30 min. and then stirred at room temperature for 16 h. The mixture was concentrated, re-dissolved in ethyl acetate (400 mL), washed with ice-cold 2 N NaOH, and concentrated to dryness, affording the crude methyl ether **1b** as an oil. MS = 437.2 (M + Na⁺).

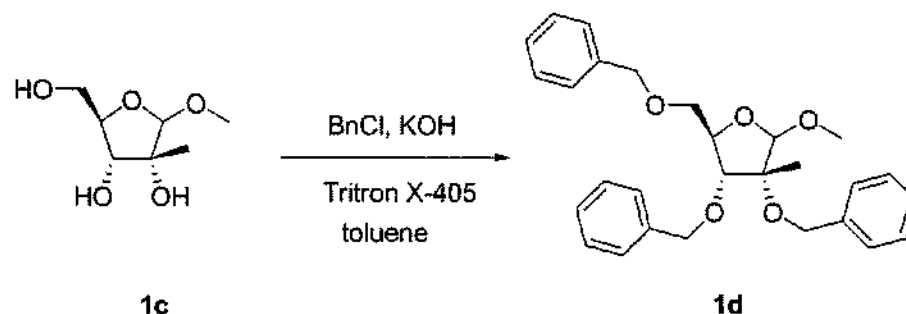
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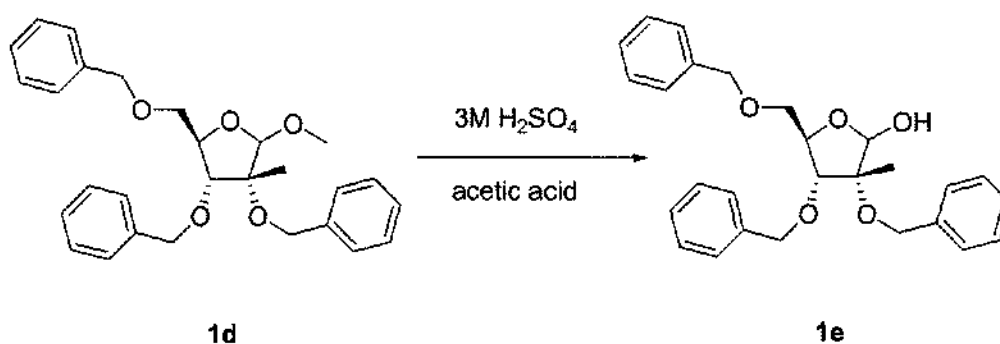
To a solution of **1b** (obtained from the previous step) in methanol (300 mL) was added 0.5 M sodium methoxide solution in methanol (20 mL, 10 mmol), and stirred for 16 h at room temperature. The reaction was quenched with 4.0 N HCl solution in dioxane (2.5 mL, 10 mmol). The mixture was then concentrated, affording the crude **1c**. MS = 201.0 (M + Na⁺).

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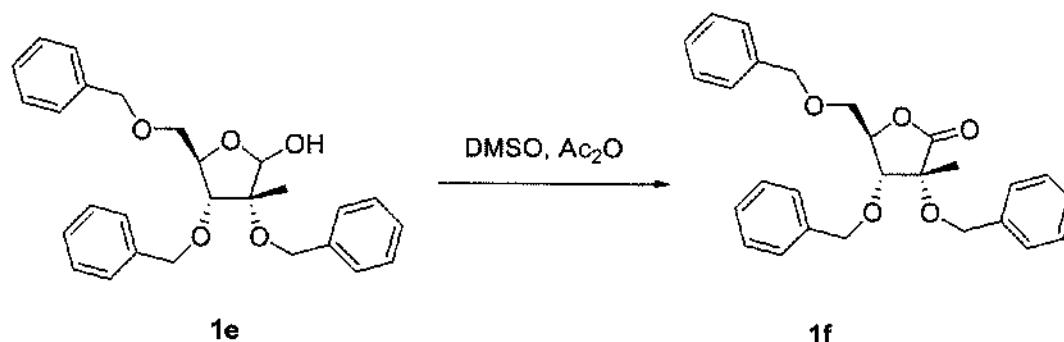
A mixture of **1c** (obtained from the previous step), Triton X-405 (70% in water, 6.0 g), 50% KOH (in water, 85 g) in toluene (500 mL) was heated to reflux with a Dean-Stark trap attached. After 1h collecting ~25 mL of water, benzyl chloride (33 g, 260 mmol) was added and continued to reflux with stirring for 16 h. The mixture was then cooled and partitioned between ethyl acetate (400 mL) and water (300mL). The organic layer was washed with water (300 mL), and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc / hexanes), affording the methyl ether **1d** as an oil (22.0 g, 89% in three steps). ¹H NMR (300 MHz, CDCl₃): δ 7.3 (m, 15H), 4.5 - 4.9 (m, 7H), 4.37 (m, 1H), 3.87 (d, 1H), 3.56 (m, 2H), 3.52 (s, 3H), 1.40 (s, 3H).



To a solution of **1d** (22.0 g, 49.0 mmol) in acetic acid (110 mL) was added ~ 3 M sulfuric acid (prepared by mixing 4.8 g of concentrated sulfuric acid with 24 mL of water) and stirred at 70 °C for 8 h. The mixture was concentrated to a volume of ~20 mL, and partitioned between ethyl acetate and ice-cold 2N NaOH. The ethyl acetate layer was concentrated, and purified by silica gel column chromatography (~35% EtOAc / hexanes), affording **1e** as an oil (17.0 g, 80%). MS = 457.2 (M + Na⁺).

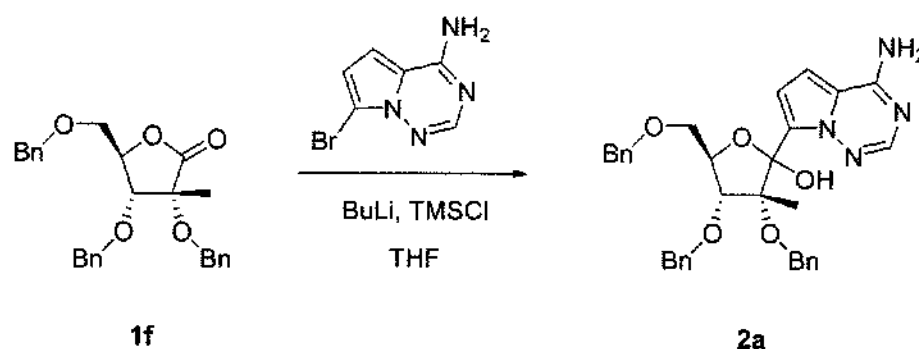
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To a solution of **1e** (45 g, 104 mmol) in DMSO (135 mL) was dropwise added acetic anhydride (90 mL, 815 mmol) at room temperature under argon. The mixture was stirred for 16 h at room temperature, and then poured into ice-water (1 L) while stirring. After ice was completely melted (~30 min), ethyl acetate (~500 mL) was added. The organic layer was separated. This extraction process was repeated three times (3x500 mL). The organic extracts were combined and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc / hexanes), affording **1f** as an oil (39 g, 88%). ¹H NMR (300 MHz, DMSO-d₆): δ 7.3 (m, 15H), 4.4 - 4.8 (m, 7H), 4.08 (d, *J* = 7.5 Hz, 1H), 3.75 (dd, *J* = 2.4, 11.4 Hz, 1H), 3.64 (dd, *J* = 5.4, 11.4 Hz, 1H), 1.51 (s, 3H).

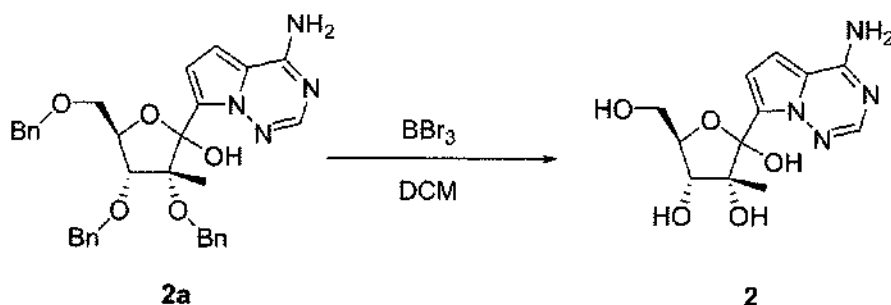
Compound 2



To a dry, argon purged round bottom flask (100 mL) were added 7-bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (234 mg, 1.10 mmol) (prepared according to

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- 5 WO2007056170) and anhydrous THF (1.5 mL). TMSCl (276 μ L, 2.2 mmol) was then added and the reaction mixture stirred for 2 h. The flask was placed into a dry ice/acetone bath (~ -78 $^{\circ}$ C) and BuLi (2.5 mL, 4.0 mmol, 1.6M in hexanes) was added dropwise. After 1h, a solution of **1f** (432.5 mg, 1.0 mmol) in THF was cooled to 0 $^{\circ}$ C and then added to the reaction flask dropwise. After 1 h of stirring at -78 $^{\circ}$ C, the flask
- 10 was warmed to 0 $^{\circ}$ C and sat. NH_4Cl (5 mL) was added to quench the reaction. The organics were extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried using MgSO_4 . The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (hexanes / EtOAc). 560 mg (99 %) of **2a** was isolated as a mixture of two anomers. LC/MS = 567.2 ($\text{M} + \text{H}^+$). ^1H NMR (300
- 15 MHz, CDCl_3): δ 7.85 (m, 1H), 7.27 (m, 15H), 7.01 (m, 1H), 6.51 (m, 1H), 4.66 (m, 8H), 4.40 (m, 2H), 3.79 (m, 3H), 1.62 (s, 2'- CH_3 from the one anomer), 1.18 (s, 2'- CH_3 from the other anomer).



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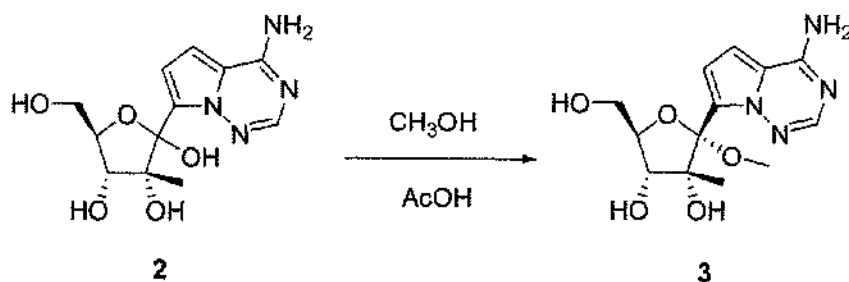
- To a dry, argon purged round bottom flask (50 mL) were added compound **2a** (185 mg, 0.33 mmol) and anhydrous dichloromethane (10 mL). The flask was placed into a dry ice/acetone bath (~ -78 $^{\circ}$ C) and the solution stirred for 10 min. BBr_3 (0.25 mL, 0.25 mmol, 1.0 M in DCM) was then added and the reaction continued to stir at -78 $^{\circ}$ C
- 25 until complete disappearance of the starting material. After 1 h, a solution of pyridine (2 mL) in MeOH (10 mL) was added and the flask was warmed to room temperature. The solvent was removed under reduced pressure and the crude material was re-dissolved in MeOH. After this process was repeated two more times, the crude material was then dissolved in water and purified using a Gilson Preparatory HPLC system (acetonitrile /

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- 5 H₂O). 49 mg (50%) of **Compound 2** was isolated as an isomeric mixture. LC/MS = 297.1 (M + H⁺). ¹H NMR (300 MHz, D₂O): δ 7.68 (m, 1H), 6.80 (m, 2H), 4.04 (m, 2H), 3.78 (m, 2H), 3.65 (m, 1H), 1.30 (s, 2'-CH₃), 0.80 (s, 2'-CH₃).

Compound 3

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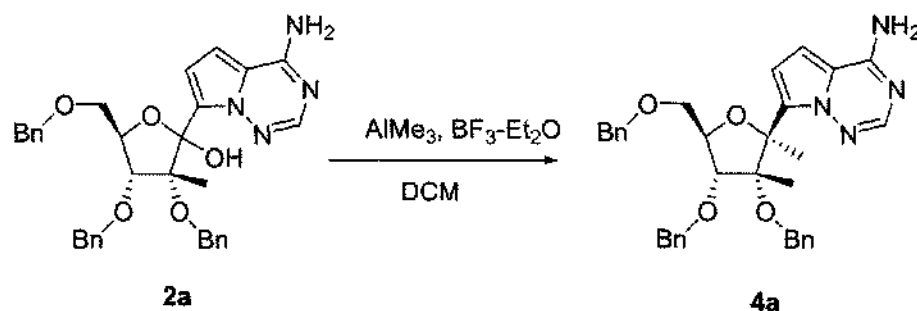


- To a dry, argon purged round bottom flask (100 mL) were added **Compound 2** (12 mg, 0.04 mmol) (**2**) and anhydrous MeOH (5 mL). Acetic acid (5 mL) was then
- 15 added and the reaction stirred overnight at room temperature. Saturated NaHCO₃ was added to neutralize the reaction mixture and the crude material was purified using a Gilson Preparatory HPLC system (acetonitrile-H₂O). 2 mg (16%) of the desired material **Compound 3** was isolated. LC/MS = 311.2 (M + H⁺). ¹H NMR (300 MHz, D₂O): δ 7.71 (s, 1H), 6.78 (s, 2H), 3.98 (m, 1H), 3.83 (dd, 1H), 3.74 (dd, 1H), 3.62 (d, 1H), 2.94 (s,
- 20 3H), 0.76 (s, 3H). The other alpha-isomer was also isolated; ¹H NMR (300 MHz, D₂O): δ 7.65 (s, 1H), 6.78 (d, 1H), 6.75 (d, 1H), 4.03 (m, 2H), 3.77 (dd, 1H), 3.59(d, 1H), 2.95 (s, 3H), 1.31 (s, 3H).

Compound 4

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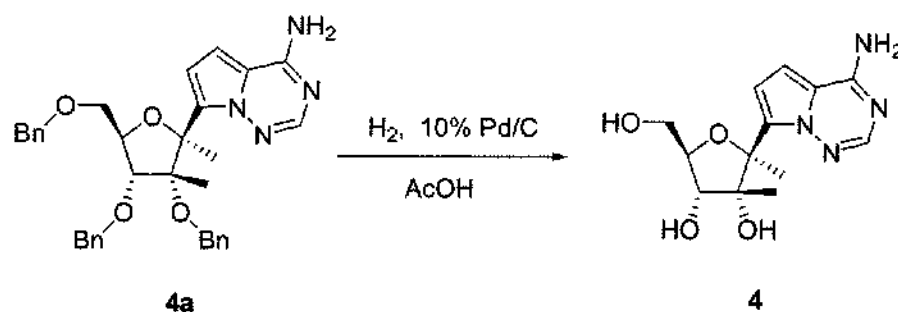
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To a dry, argon purged round bottom flask (50 mL) were added compound **2a** (220 mg, 0.39 mmol) and anhydrous dichloromethane (10 mL). The flask was placed into a dry ice/acetone bath ($\sim -78^\circ\text{C}$) and the solution stirred for 10 min. $\text{BF}_3\text{-Et}_2\text{O}$ (0.10 mL) was added dropwise and the reaction stirred for 10 min. AlMe_3 (0.58 mL, 1.16 mmol, 2.0 M in toluene) was then added. After a few minutes, the dry ice/acetone bath was removed and the reaction mixture warmed to room temperature over 4 h. A solution of pyridine (2 mL) in MeOH (10 mL) was added and the solvent was removed under reduced pressure. The crude material was purified using flash chromatography (hexanes / EtOAc). 164 mg (74 %) of the desired material **4a** was isolated. LC/MS = 565.2 ($\text{M} + \text{H}^+$). ^1H NMR (300 MHz, CD_3OD): δ 7.71 (s, 1H), 7.32 (m, 15H), 7.02 (m, 1H), 6.78 (m, 1H), 4.62 (m, 8H), 4.21 (m, 1H), 4.04 (m, 1H), 3.84 (m, 1H), 1.95 (s, 3H), 1.10 (s, 3H).

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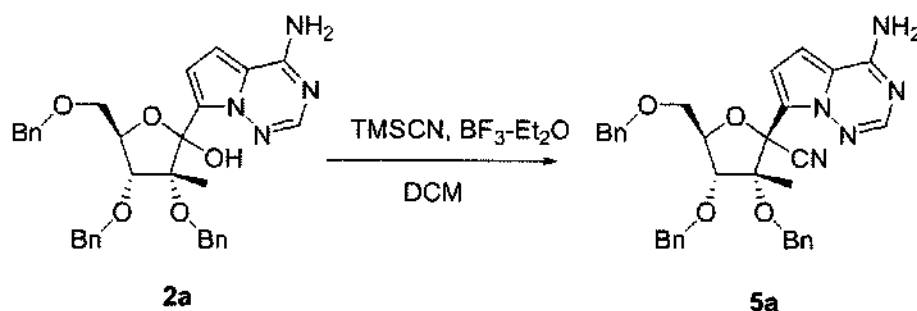
To a dry, argon purged round bottom flask (50 mL) were added compound **4a** (164 mg, 0.29 mmol) and glacial acetic acid (10 mL). Pd/C (100 mg, 10 % by wt.) was

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- 5 then added and the flask was equipped with a balloon containing hydrogen gas. The flask was purged two times to ensure all of the argon had been replaced with hydrogen. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then neutralized using NaHCO_3 and filtered to remove the catalyst. The crude material was purified using a Gilson Preparatory HPLC system (acetonitrile / H_2O). 6
- 10 mg (7 %) of the desired material **Compound 4** was isolated. LC/MS = 295.1 ($\text{M} + \text{H}^+$). ^1H NMR (300 MHz, D_2O): δ 7.66 (s, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 3.93 (m, 1H), 3.76 (m, 3H), 1.63 (s, 3H), 0.76 (s, 3H).

Compound 5

15



- To a solution of compound **2a** (1 g, 1.77 mmol) in CH_2Cl_2 (20 mL) at 0 °C was
- 20 added TMSCN (1.4 mL, 10.5 mmol) and $\text{BF}_3\text{-Et}_2\text{O}$ (1 mL, 8.1 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then at room temperature for additional 0.5 h. The reaction was quenched with NaHCO_3 at 0 °C, and diluted with $\text{CH}_3\text{CO}_2\text{Et}$. The organic phase was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with $\text{CH}_3\text{CO}_2\text{Et}$ -
- 25 hexanes (1:1 to 2:1), to give the desired compound **5a** (620 mg, 61%) as an isomeric mixture. MS = 576.1 ($\text{M} + \text{H}^+$).

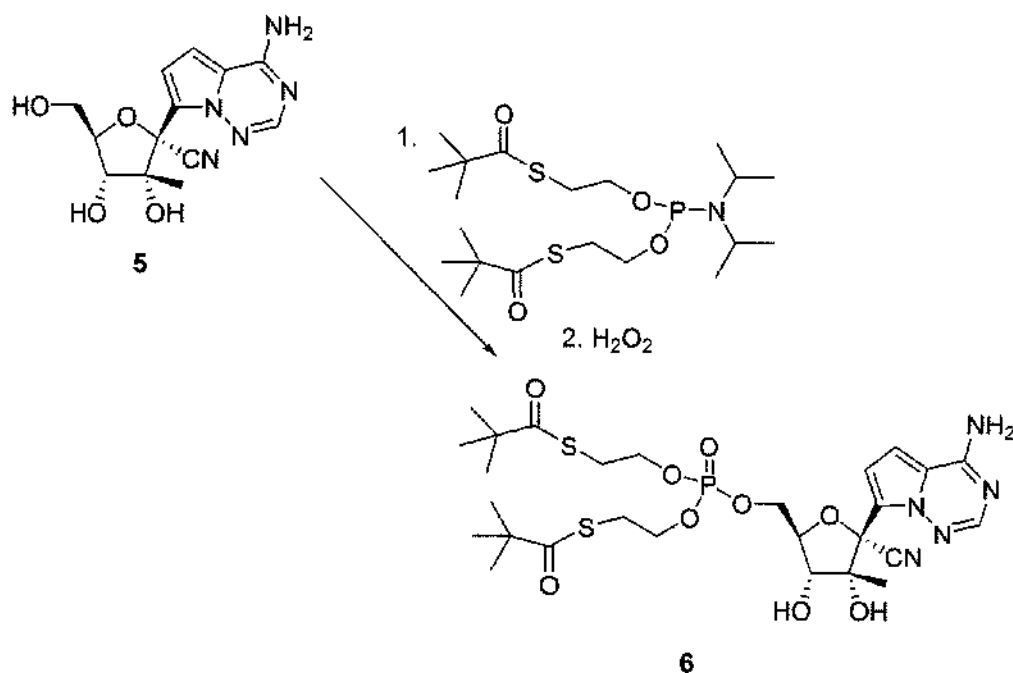
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Compound 6

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To a solution of compound **5** (30 mg, 0.098 mmol) and 1H-tetrazole (30 mg, 0.43 mmol) in anhydrous CH₃CN (1 mL) at 0 °C was added 2,2-dimethyl-thiopropionic acid S-(2-{diisopropylamino-[2-(2,2-dimethyl-propionyl)sulfanyl]-ethoxy}-phosphanyloxy)-ethyl ester (90 mg, 0.2 mmol) (described in *J. Med. Chem.*, **1995**, 3941). The reaction mixture was stirred at 0 °C for 1 h, then H₂O₂ (30%, 80 uL) was added and stirred for 0.5 h at 0 °C. The reaction was quenched with sodium thiosulfate (1 M, 1 mL) and NaHCO₃, diluted with CH₃CO₂Et. The organic phase was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by HPLC to give the desired **Compound 6** (28 mg, 42%). ¹H NMR (300 MHz, CDCl₃): δ 8.04 (s, 1H), 6.85 (d, *J* = 4.5 Hz, 1H), 6.73 (d, *J* = 4.5 Hz, 1H), 6.0 (brs, 2H), 4.6 (m, 1H), 4.4 (m, 2H), 4.1 (m, 4H), 4.0 (d, *J* = 4 Hz, 1H), 3.15 (m, 4H), 1.24 (s, 18H), 0.99 (s, 3H). ³¹P NMR (300 MHz, CDCl₃): δ -1.825. MS = 673.9 (M + H⁺), 672.1 (M - H⁻).

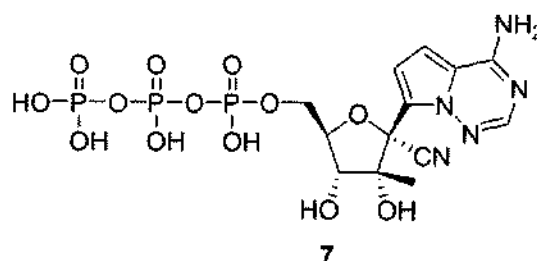
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5 General procedure for preparation of a nucleoside triphosphate:

To a pear-shaped flask (5-15 mL) is charged with a nucleoside (~20 mg). Trimethyl phosphate (0.5-1.0 mL) is added. The solution is cooled with ice-water bath. POCl₃ (40-45 mg) is added and stirred at 0 °C until the reaction is complete (1 to 4 h; the reaction progress is monitored by ion-exchange HPLC; analytical samples are prepared by taking ~3 uL of the reaction mixture and diluting it with 1.0 M Et₃NH₂CO₃ (30-50 uL)). A solution of pyrophosphate-Bu₃N (250 mg) and Bu₃N (90-105 mg) in acetonitrile or DMF (1-1.5 mL) is then added. The mixture is stirred at 0 °C for 0.3 to 2.5 h, and then the reaction is quenched with 1.0 M Et₃NH₂CO₃ (~5 mL). The resulting mixture is stirred for additional 0.5-1 h while warming up to room temperature. The mixture is concentrated to dryness, re-dissolved in water (4 mL), and purified by ion exchange HPLC. The fractions containing the desired product is concentrated to dryness, dissolved in water (~5 mL), concentrated to dryness, and again dissolved in water (~5 mL). NaHCO₃ (30-50 mg) is added and concentrated to dryness. The residue is dissolved in water and concentrated to dryness again. This process is repeated 2-5 times. The residue is then subjected to C-18 HPLC purification, affording the desired product as a sodium salt.

Compound 7



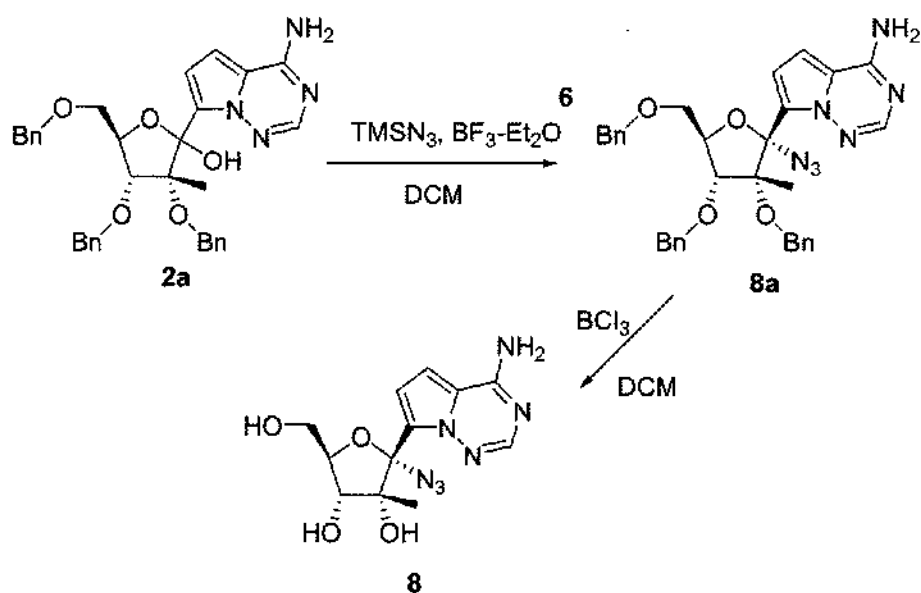
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Compound 7 was prepared by the general method using **Compound 5** as starting material. ¹H NMR (300 MHz, D₂O): δ 7.76 (s, 1H), 6.95 (d, *J* = 4.5 Hz, 1H), 6.8 (d, *J* = 4.5 Hz, 1H), 4.25 (m, 3H), 4.0 (d, *J* = 6 Hz, 1H), 0.92 (s, 3H). ³¹P NMR (300 MHz, D₂O): δ -5.6, -10.7, -21.4. MS = 545.8 (M + H⁺), 544.0 (M - H⁻).

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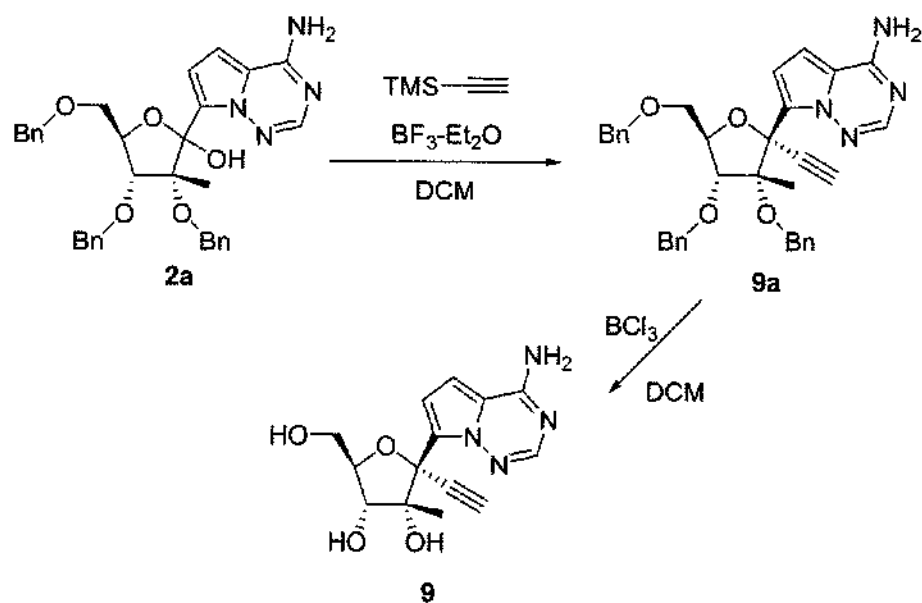
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Compound 8

10 **Compound 8** may be obtained from **2a** in a manner similar to that described in preparation of **Compound 5** except using TMSN_3 instead of TMSCN .

Compound 9

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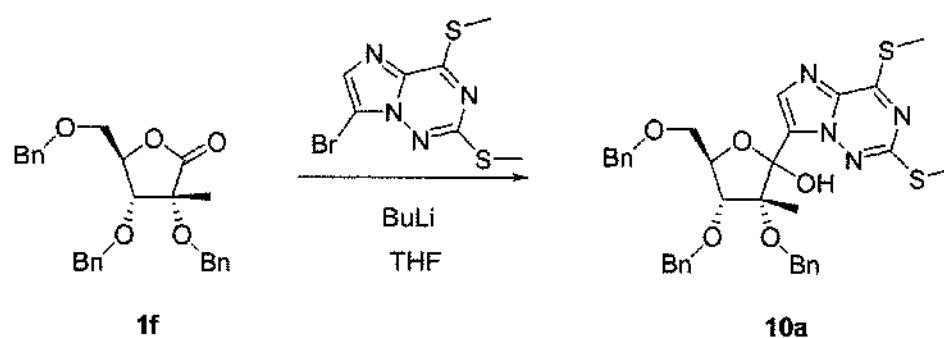


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Compound 9 may be obtained from **2a** in a manner similar to that described in preparation of **Compound 5** except using TMS-acetylene instead of TMSCN.

10

Compound 10

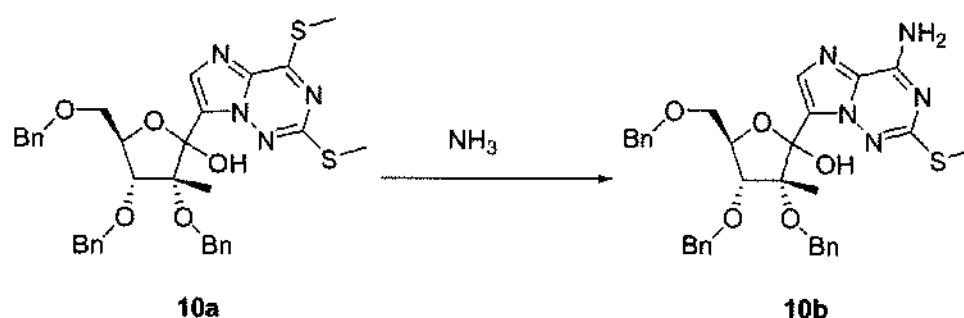


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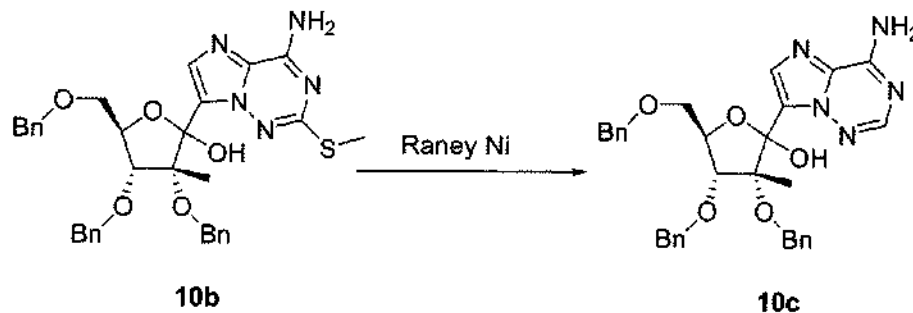
To a suspension of 7-bromo-2,4-bis-methylsulfanyl-imidazo[2,1-f][1,2,4]triazine (prepared according to WO2008116064, 600 mg, 2.06 mmol) in anhydrous THF (6 mL) was dropwise added BuLi (1.6 M in hexanes, 1.75 mL, 2.81 mmol) at -78 °C. The suspension became red brown solution after 5 min, and then **1f** in THF (0.6 mL) was

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- 5 added dropwise to the mixture. The mixture was then allowed to warm up to room temperature. After 30 min, saturated NH_4Cl was added to quench the reaction. The mixture was diluted with ethyl acetate; the organic layer was washed with brine and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (~40% EtOAc / hexanes), affording **10a** as an isomeric mixture (0.77 g, 64%). MS =
- 10 645.2 ($\text{M} + \text{H}^+$).



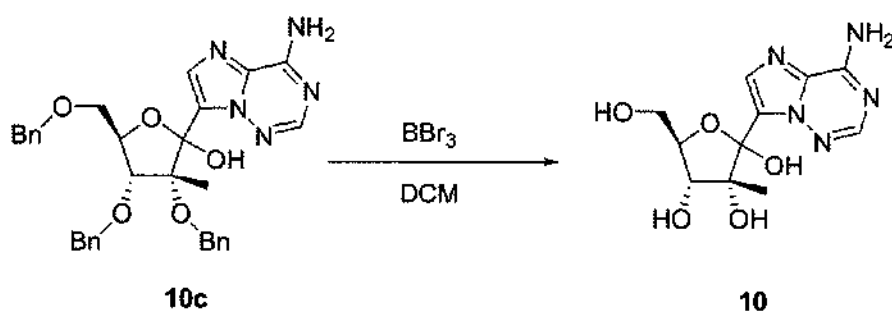
- Compound **10a** (2.0 g, 3.10 mmol) was transferred to a steel bomb reactor, and
- 15 cooled at -78°C . Liquid ammonia (~20 mL) was collected at -78°C and added to the bomb reactor. The bomb reactor was tightly sealed and warmed up to room temperature. The mixture was then heated at 50°C for 20 h. Complete conversion occurred. After the gas was vented, the residue was purified by silica gel column chromatography (EtOAc / hexanes), affording the product **10b** as a pale yellow solid (1.78 g, 94%). MS = 614.3
- 20 ($\text{M} + \text{H}^+$).



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- 5 A solution of **10b** (100 mg) in ethanol (about 10 ml) is treated with Raney Ni (about 500 mg) that is neutralized by washing with H₂O. The mixture is then heated to about 35 to about 80 °C until the reaction is complete. The catalyst is removed by filtration and the solution is concentrated *in vacuo*. The residue is purified by chromatography to give **10c**.

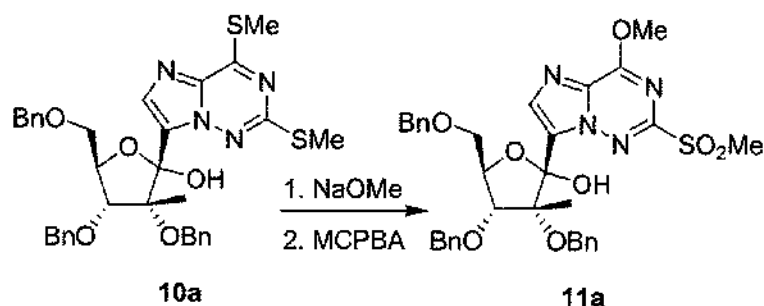
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Compound 10c may be treated with BBr₃ in a manner similar to that described in preparation of compound **2** to give **Compound 10**.

15

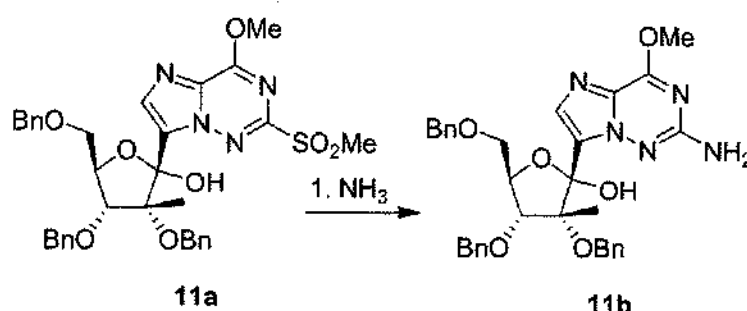
Compound 11



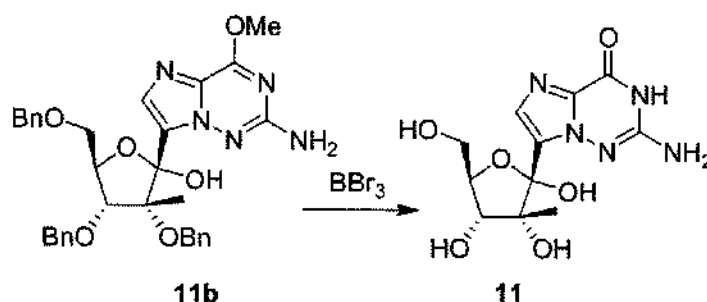
- 20 **10a** is treated with about one to ten mole equivalents of an alkali metal salt of methanol in a suitable solvent such as dioxane for about one to 48 hours. The mixture may also be heated from about 60 to about 110 °C for about one to 24 hours to complete the reaction. The mixture is neutralized with a strong acid and the intermediate is

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- 5 isolated by extraction and chromatography. The intermediate is dissolved in DCM and treated with about two to about four mole equivalents of MCPBA for about one to about 24 hours. The mixture is treated with saturated NaHCO_3 and the solution is extracted with EtOAc. The organic layer is washed with saturated NaHCO_3 and brine and dried over MgSO_4 . The solvent is removed in vacuo and the mixture is purified by
- 10 chromatography to give **11a**.



- A solution of **11a** in a suitable solvent such as methanol or THF is treated with about five to ten mole equivalents of NH_3 in methanol or THF. The reaction is followed by TLC. After about one to 48 hours, the solvent is evaporated and **11b** is isolated by
- 15 chromatography. Alternatively, the mixture of **11a** and NH_3 is heated in a sealed glass tube or Parr bomb to about 60 to about 120 °C for about one to about 48 hours and subsequently isolated in the same manner as described.

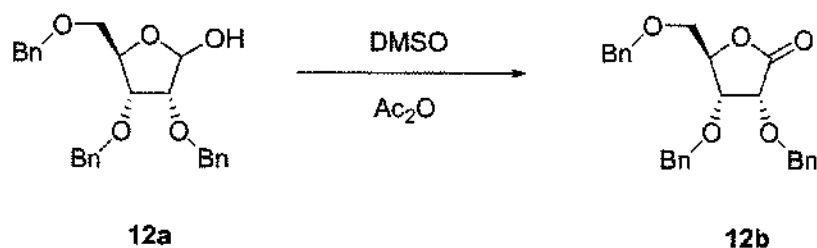


20

11b in DCM is cooled to about -78 °C and treated with about four to 10 mole equivalents of BBr_3 for about one to about 24 hours. The mixture is treated with about 4:1 MeOH-pyridine and the solution was warmed to room temperature. The solvent is

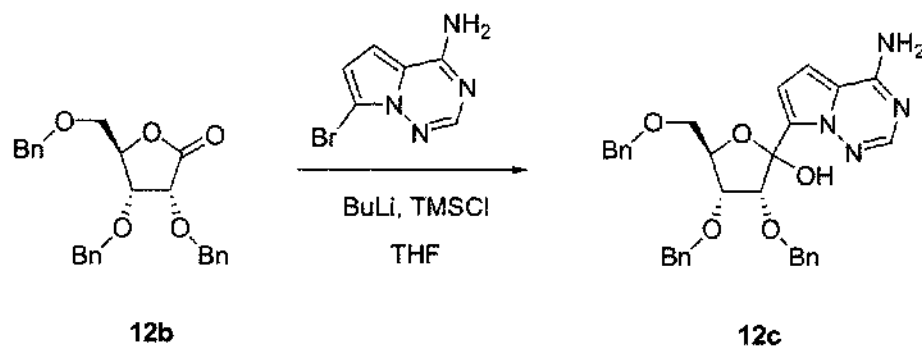
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- 5 removed in vacuo and the mixture is treated with concentrated NH_4OH followed by removal of solvent ($\times 3$). The mixture is purified by reverse phase HPLC to give 11.

Compound 12

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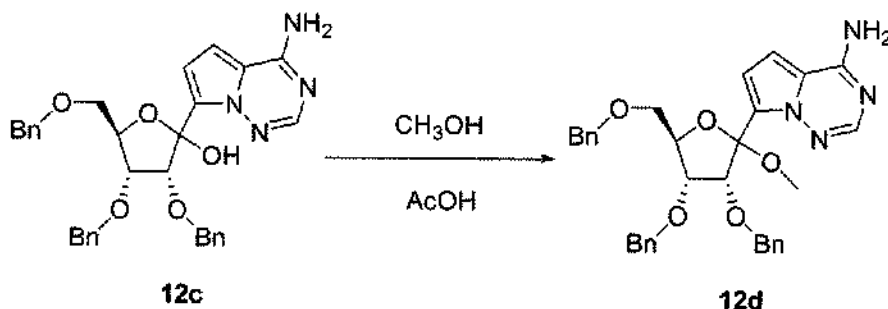
- Compound **12a** (prepared according to *J. Org. Chem.*, **1961**, 26, 4605; 10.0 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) and placed under nitrogen. Acetic anhydride (20 mL) was added, and the mixture was stirred for 48 h at room temperature. When the reaction was complete by LC/MS, it was poured onto 500 mL ice water and stirred for 20 min. The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The organic extracts were combined and washed with water (3 x 200 mL). The aqueous layers were discarded and the organic was dried over anhydrous MgSO_4 and evaporated to dryness. The residue was taken up in DCM and loaded onto a silica gel column. The final product **12b** was purified by elution with 25% EtOAc / hexanes; 96% yield. $^1\text{H-NMR}$ (CD_3CN): δ 3.63-3.75 (m, 2H), 4.27 (d, 1H), 4.50-4.57 (m, 3H), 4.65 (s, 3H), 4.69-4.80 (m, 2H), 7.25 (d, 2H), 7.39 (m, 13H).
- 15
- 20



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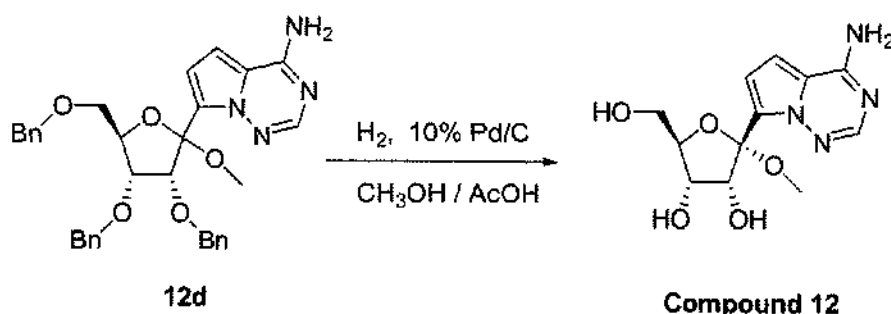
- 5 7-Bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (prepared according to WO2007056170, 0.5 g, 2.4 mmol) was suspended in anhydrous THF (10 mL). Under nitrogen with stirring, TMSCl (0.668 mL, 5.28 mmol) was added and the mixture was stirred for 20 min. at room temperature. The reaction was then cooled to -78 °C and a solution of BuLi (6.0 mL, 1.6 N in hexanes) was added slowly. The reaction was stirred
- 10 for 10 min. at -78 °C and then the lactone **12b** was added via syringe. When the reaction was complete by LC/MS, acetic acid was added to quench. Solvents were removed by rotary evaporation and the residue was taken up in a mixture of 50:50 dichloromethane / water (100 mL). The organic layer was collected and washed with 50 mL additional water, dried over anhydrous MgSO₄ and filtered. Evaporation and purification by
- 15 column chromatography (0 -50% EtOAc: hexanes) provided a 1:1 mixture of anomers **12c**; 25% yield. LC/MS (m/z: 553, M + H⁺).



- 20 Compound **12c** (0.4 g, 0.725 mmol) was stirred in a 1:1 mixture of acetic acid and methanol (10 mL) for 12 h. When the reaction was complete by LC/MS, solvents were removed by high vacuum. The residue was taken up in dichloromethane and loaded onto a silica gel column. A mixture of anomers was eluted using a gradient of 0-75% ethyl acetate and hexanes; 51.4% yield of compound **12d**. ¹H-NMR (CD₃CN):
- 25 δ 2.87 (s, 3H), 3.58-3.79 (dd, 2H), 4.11-4.19 (m, 1H), 4.23-4.33 (m, 1H), 4.39-4.42 (m, 1H), 4.49-4.60 (m, 3H), 4.68-4.73 (m, 2H), 6.22 (bs, 2H), 6.72 (d, 2H), 6.79 (d, 1H), 6.84 (d, 1H), 7.17 (m, 2H), 7.39 (m, 13H), 7.84 (s, 1H).

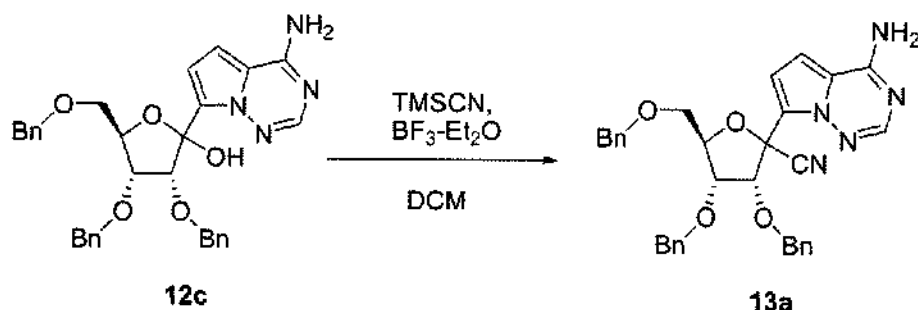
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Compound **12d** (0.150 g, 0.265 mmol) was dissolved in a 1:1 mixture of methanol and acetic acid (20 mL). 10% Pd/C (150 mg) was added and the reaction was flushed with nitrogen three times. With stirring, hydrogen gas was introduced. The reaction was stirred under hydrogen for 16 h. When the reaction was complete by LC/MS, the catalyst was filtered off and solvents removed under vacuum. The residue was re-dissolved in a mixture of water and TEA (to keep pH at ~10), and both anomers were purified by prep HPLC under neutral conditions; a total of 51% yield. ¹H-NMR of **compound 12** (D₂O): δ 3.16 (s, 3H), 3.69-3.84 (dd, 2H), 4.07-4.10 (m, 1H), 4.22-4.24 (m, 1H), 6.74 (d, 1H), 6.78 (d, 1H), 7.70 (s, 1H). ¹H-NMR of the other alpha-anomer (D₂O): δ 2.87 (s, 3H), 3.58-3.84 (dd, 2H), 3.99-4.09 (m 1H), 4.30-4.38 (m, 1H), 4.49 (d, 1H), 6.75 (d, 1H), 6.82 (d, 1H), 7.69 (s, 1H).

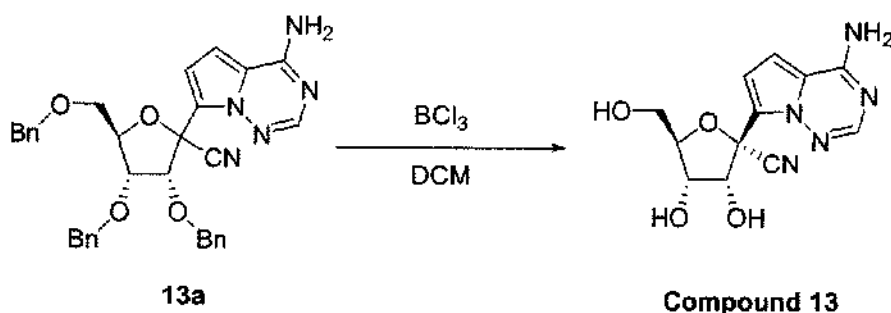
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Compound 13

Compound **12c** (0.28 g, 0.51mmol) was dissolved in anhydrous dichloromethane and placed under nitrogen. Trimethylsilyl cyanide (0.35 mL) was added and the mixture

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- 5 was cooled to 0 °C. After stirring for 10 min., boron trifluoride etherate (50 ul) was added and the reaction was allowed to warm to room temperature. When the reaction was complete by LC/MS, triethylamine was added to quench and solvents were removed by rotary evaporation. The residue was taken up in dichloromethane and loaded onto a silica gel column. A mixture of anomers was eluted using a gradient of 0-75% ethyl
- 10 acetate and hexanes; 37% yield of **13a**. ¹H-NMR (CD₃CN): δ 3.61-3.90 (m, 2H), 4.09-4.19 (m, 2H), 4.30-4.88 (m, 7H), 4.96 (d, 0.5H), 5.10 (d, 0.5H), 6.41 (bs, 2H), 6.73-6.78 (m, 1H), 6.81-6.88 (m, 1H), 7.17 (m, 2H), 7.39 (m, 13H), 7.86 (s, 0.5H), 7.93 (s, 0.5H).

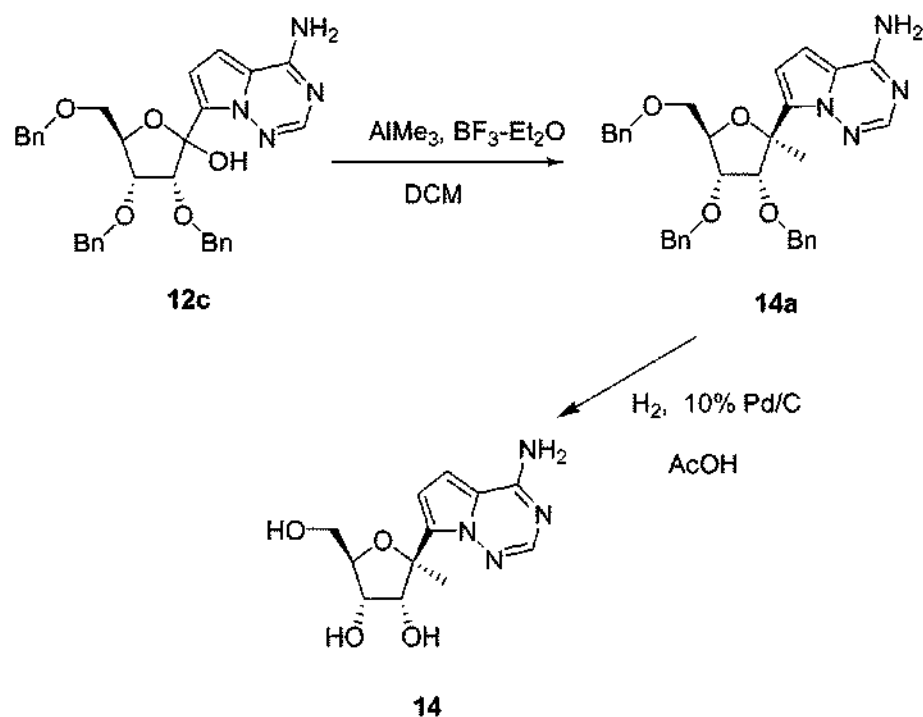


15

- Compound **13a** (0.70 mg, 0.124 mmol) was dissolved in anhydrous dichloromethane (2 ml), placed under nitrogen, and cooled to -78 °C. A solution of 1 N boron trichloride in dichloromethane (0.506 ml) was added and the reaction stirred for 1 h at -78 °C. When the reaction was complete by LC/MS, methanol was added to quench.
- 20 The reaction was allowed to rise to room temperature and solvents were removed by rotary evaporation. The product anomers were purified by prep-HPLC; a total of 74% yield. ¹H-NMR of **Compound 13** (D₂O): δ 3.65-3.75 (dd, 2H), 4.12 (t, 1H), 4.29 (q, 1H), 4.80 (d, 1H), 6.97 (d, 1H), 7.14 (d, 1H), 7.93 (s, 1H). ¹H-NMR of the other alpha-anomer (D₂O): δ 3.72-3.93 (dd, 2H), 4.16-4.19 (m, 1H), 4.60-4.62 (m 1H), 5.01 (d, 1H),
- 25 6.95 (d, 1H), 7.28 (d, 1H) 7.96 (s, 1H).

Compound 14

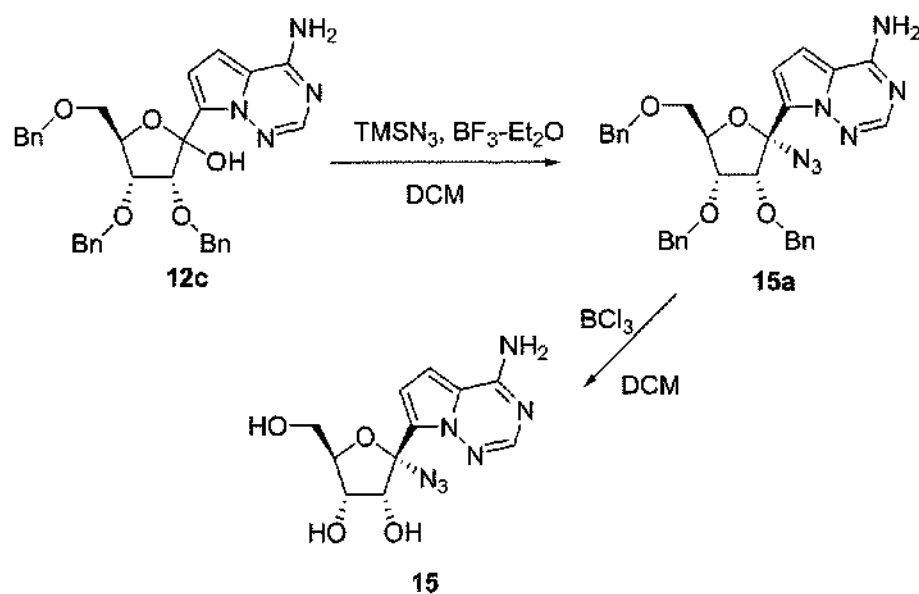
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Compound 14 may be obtained from 12c in a manner similar to the method used to synthesize Compound 4.

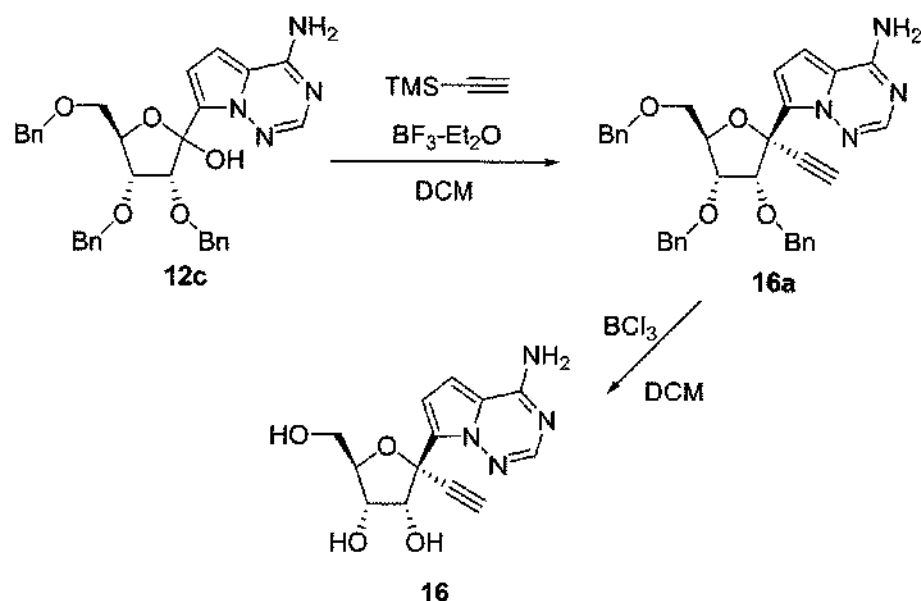
Compound 15



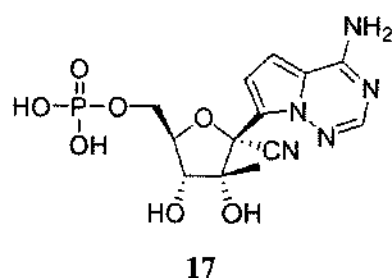
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Compound 15 may be obtained from 12c in a manner similar to that described in preparation of Compound 13 except using TMSN_3 instead of TMSCN .

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5 **Compound 16**

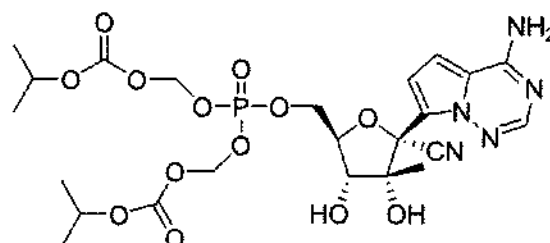
Compound 16 may be obtained from **12c** in a manner similar to that described in preparation of **Compound 13** except using TMS-acetylene instead of TMSCN.

Compound 17

A mixture of about 0.05 mmol of **Compound 5** and about 0.5 mL of trimethylphosphate is sealed in a container for about one to about 48 hours. The mixture is cooled to about -10 to about 10 °C and about 0.075 mmol of phosphorous oxychloride is added. After about one to about 24 hours, the reaction is quenched with about 0.5 mL of 1M tetraethylammonium bicarbonate and the desired fraction are isolated by anion exchange chromatography. The appropriate fractions are then desalted by reverse-phase chromatography to give **Compound 17**.

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Compound 18

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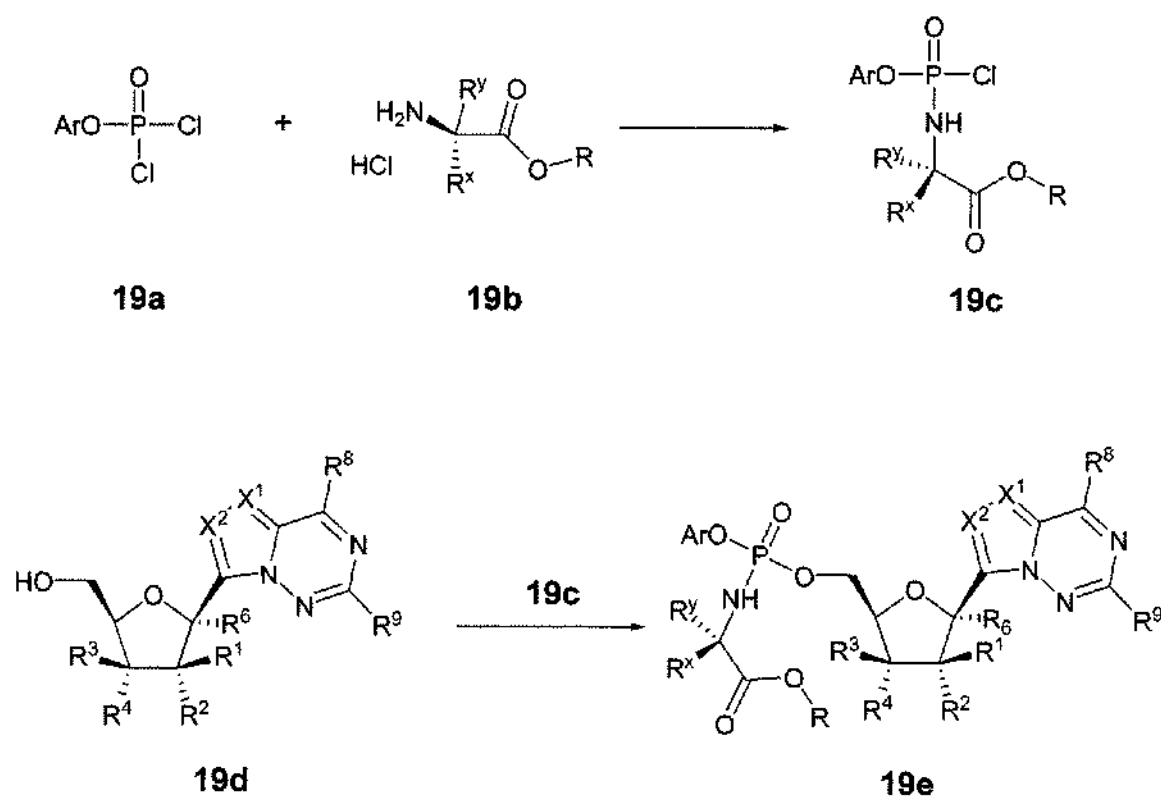
Compound 17 (about 1.19 mmol) is dried over phosphorous pentoxide in a vacuum for about overnight. The dried material is suspended in about 4 mL of anhydrous DMF and about 4.92 mmol DIPEA. About 7.34 mmol of *iso*-propyl chloromethyl carbonate (*Antiviral Chemistry & Chemotherapy* 8:557 (1997)) is added and the mixture is heated to about 25 to about 60 °C for about 30 min to about 24 hours. Heating is removed for about one to about 48 hours and the reaction filtered. The filtrate is diluted with water, **Compound 18** is partitioned into CH₂Cl₂, the organic solution is dried and evaporated, and the residue is purified by reverse-phase HPLC to isolate **Compound 18**.

20 **Mono Phosphoramidate Prodrugs**

Non-limiting examples of mono-phosphoramidate prodrugs comprising the instant invention may be prepared according to general Scheme 1.

25 **Scheme 1**

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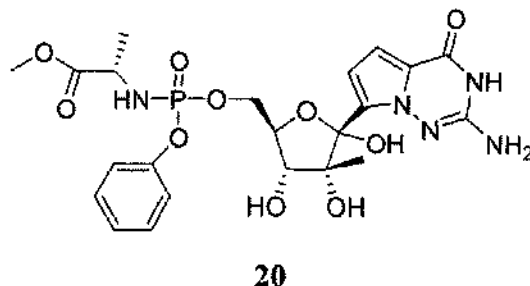


5

The general procedure comprises the reaction of an amino acid ester salt **19b**, e.g., HCl salt, with an aryl dichlorophosphate **19a** in the presence of about two to ten equivalents of a suitable base to give the phosphoramidate **19c**. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. Tertiary amines are particularly preferred. Preferably, the product of each step is used directly in the subsequent steps without recrystallization or chromatography. Specific, but non-limiting, examples of **19a**, **19b**, and **19c** can be found in WO 2006/121820 that is hereby incorporated by reference in its entirety. A nucleoside base **19d** reacts with the phosphoramidate **19c** in the presence of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. The product **19e** may be isolated by recrystallization and/or chromatography.

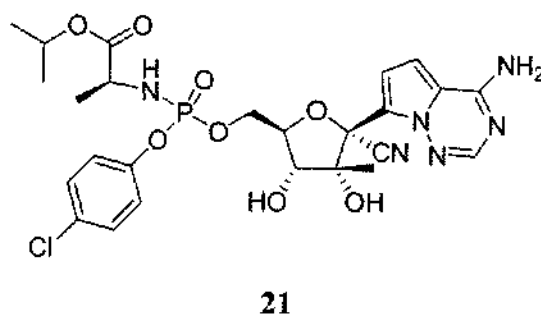
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5 **Compound 20**

About 3.1 mmol of phenyl methoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of **Compound 11** and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give **Compound 20**.

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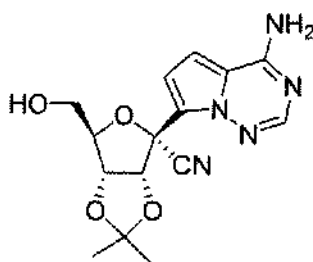
Compound 21

About 3.1 mmol of 4-chlorophenyl 2-propoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of **Compound 5** and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give **Compound 21**.

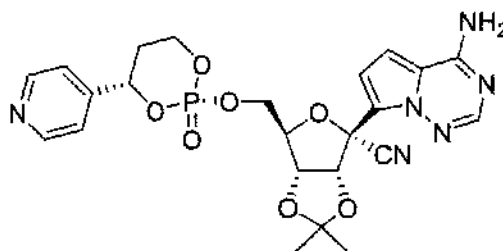
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Compound 22

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**22**

A mixture of about 0.52 mmol of **Compound 13** and about 12 mL dry acetone, about 0.7 mL of 2,2,-dimethoxypropane and about 1.28 mmol of di-*p*-nitrophenylphosphoric acid is stirred for about 24 hours to about seven days. The reaction mixture is neutralized with about 20 mL of 0.1 N NaHCO₃ and the acetone is evaporated. The desired material is partitioned into chloroform, the chloroform solution is dried, and the solvent is evaporated. **Compound 22** is purified from the residue by conventional means.

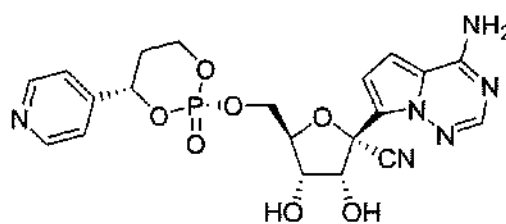
Compound 23**23**

A solution of about 0.53 mmol of **Compound 22** in about 5 mL of DMF is treated with about 1 mL of a 1 M solution of *t*-butylmagnesium chloride in THF. After about 30 min to about 5 hours, a solution of about 0.65 mmol of *trans*-4-[(*S*)-pyridin-4-yl]-2-(4-nitrophenoxy)-2-oxo-1,3,2-dioxaphosphorinane (Reddy, *Tetrahedron Letters* **2005**, 4321-4324) is added and the reaction is stirred for about one to about 24 hours. The solution is concentrated in a vacuum and the residue is purified by chromatography to give **Compound 23**.

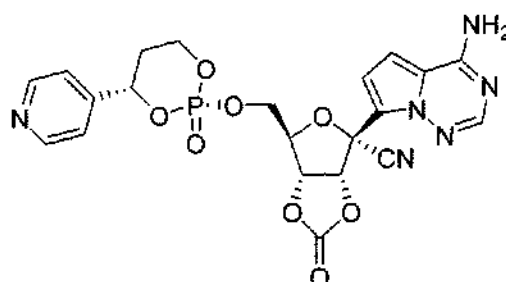
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Compound 24

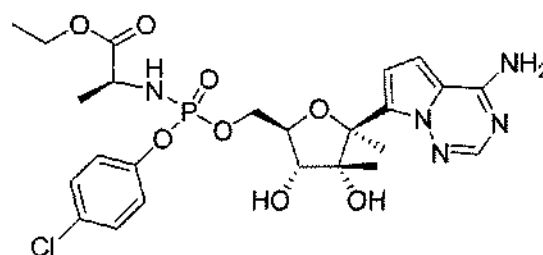
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**24**

A solution of about 70% aqueous trifluoroacetic acid is cooled to 0 °C and is treated with about 0.32 mmol of **Compound 23** for about one to 24 hours. The solution is concentrated and the residue is purified by chromatography to give **Compound 24**.

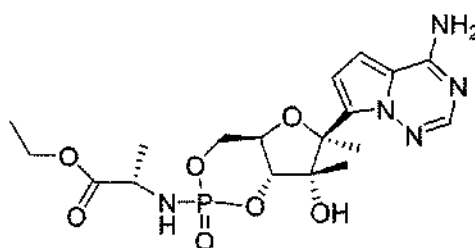
Compound 25**25**

A solution of about 1.56 mmol of **Compound 24** in about 15 mL of THF is treated with about 4.32 mmol of CDI. After about one to about 24 hours, the solvent is evaporated and the residue is purified by chromatography to give **Compound 25**.

Compound 26**26**

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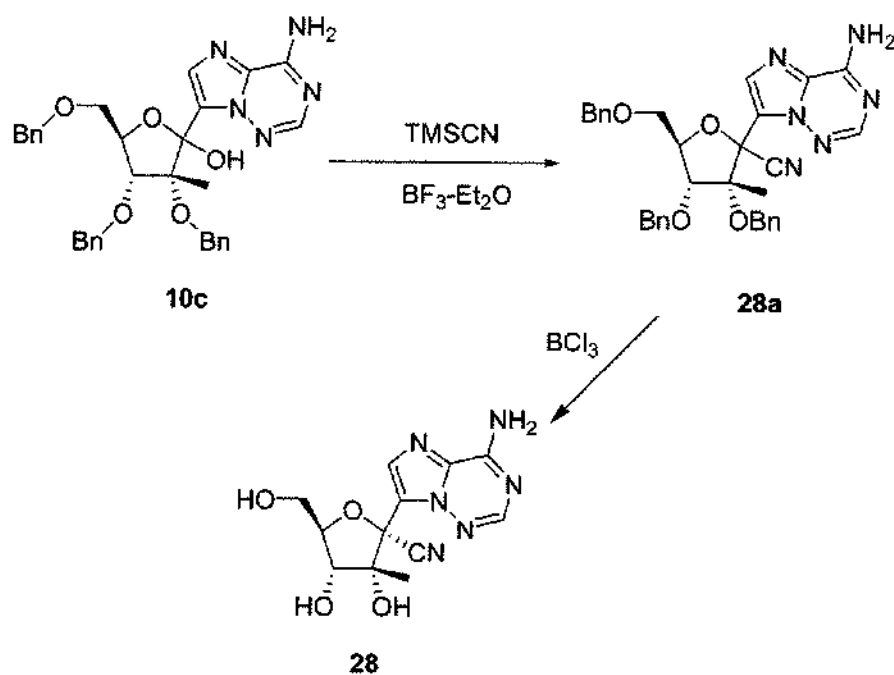
- 5 About 3.1 mmol of 4-chlorophenyl 2-ethoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* **1993**, 36, 1048–1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of **Compound 4** and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by
10 reverse-phase HPLC to give **Compound 26**.

Compound 27**27**

- 15 A solution of **Compound 26** in DMSO is treated with about 3 mole equivalents of potassium *t*-butoxide for about 15 min to 24 hours. The reaction is quenched with 1N HCl and **Compound 27** is isolated by reverse-phase HPLC.

Compound 28

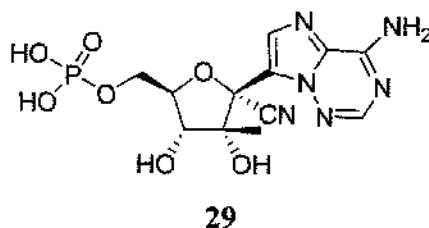
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5

Compound 28 is prepared in the same manner as **Compound 5** but using **Compound 10c** as a starting material.

10 **Compound 29**

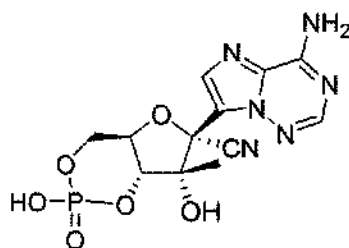


Compound 29 is prepared in the same manner as **Compound 17** using **Compound 28** as a starting material.

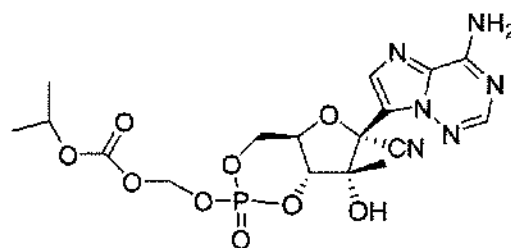
15

Compound 30

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**30**

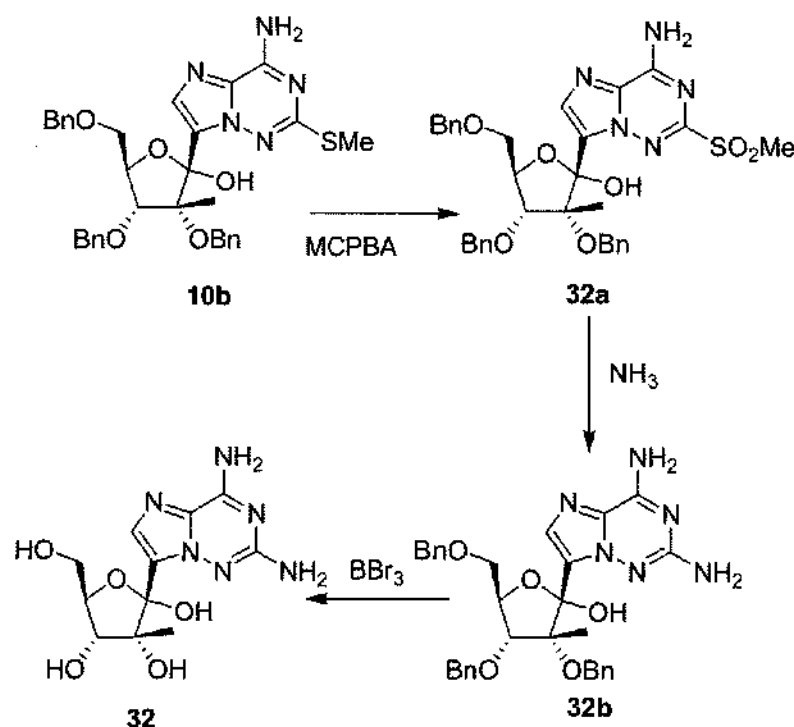
Compound 30 is prepared by treating **Compound 29** with about one to about five equivalents of DCC in pyridine and heating the reaction to reflux for about one to about 24 hours. **Compound 30** is isolated by conventional ion exchange and reverse-phase HPLC.

Compound 31**31**

A solution of about 0.4 mmol of **Compound 30** in about 10 mL of DMF is treated with about 0.8 mmol of DIPEA and about 0.8 mmol of chloromethyl isopropyl carbonate (WO2007/027248). The reaction is heated to about 25 to about 80 °C for about 15 min to about 24 hours. The solvent is removed under vacuum and the residue is purified by HPLC to give **Compound 31**.

Compound 32

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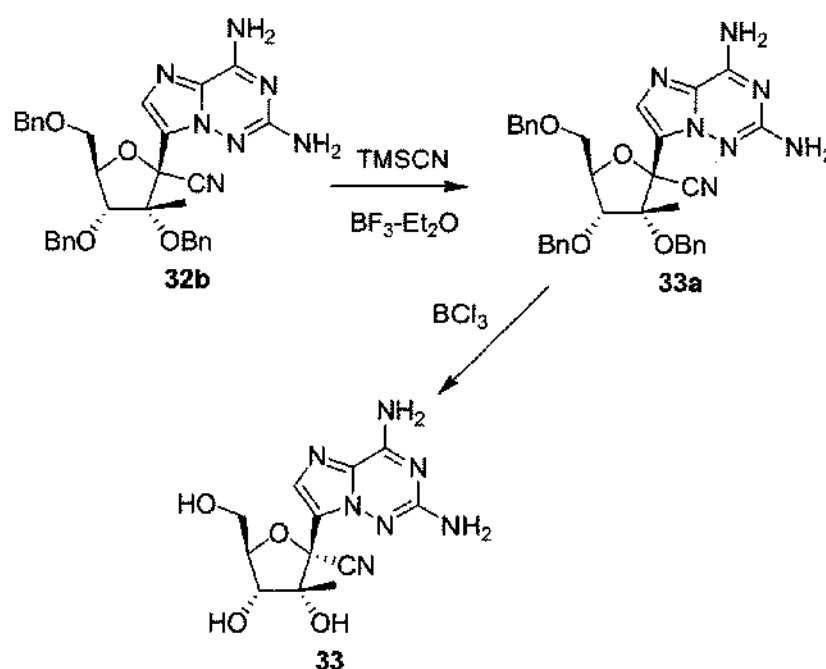
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Compound 10b is dissolved in DCM and treated with about two to about four mole equivalents of MCPBA for about one to about 24 hours. The mixture is treated with saturated NaHCO_3 and the solution is extracted with EtOAc. The organic layer is washed with saturated NaHCO_3 and brine and dried over MgSO_4 . The solvent is removed in vacuo and the mixture is purified by chromatography to give **32a**. **Compound 32a** is transferred to a steel bomb reactor, and is cooled at -78°C . Liquid ammonia is collected at -78°C and is added to the bomb reactor. The bomb reactor is tightly sealed and is warmed up to room temperature. The mixture is heated at about 50°C for about 24 h. The gas is vented and **32b** is isolated by chromatography. **Compound 32b** is converted to **Compound 32** in the same manner as for the conversion of **Compound 2a** to **Compound 2**.

15

Compound 33

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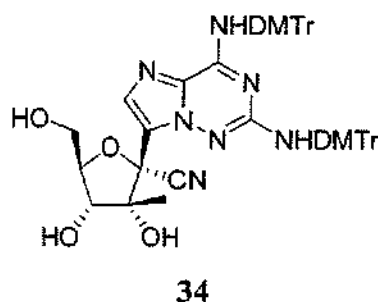


5

Compound 32b is converted to **Compound 33** in the same manner as the conversion of **Compound 2a** to **Compound 5**.

Compound 34

10

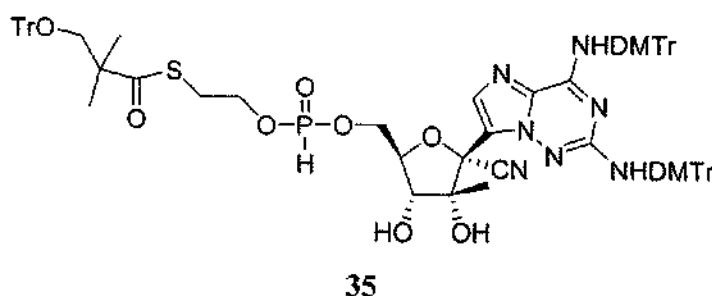


Compound **33** (about 0.22 mmol) is dissolved in anhydrous pyridine (about 2 mL) and chlorotrimethylsilane (about 0.17 mL) is added. The mixture is stirred at about 0 to about 25 °C for about one to about 24 hours. Additional chlorotrimethylsilane (about 0.1 mL) is added and the reaction is stirred for about one to about 24 hours. 4,4'-Dimethoxytrityl chloride (about 0.66 mmol) and DMAP (about 0.11 to about 0.22 mmol) is sequentially added. The mixture is stirred for about one to about 24 hours. A solution of TBAF (1.0 M, about 0.22 mL) in THF is added and the reaction is stirred for about

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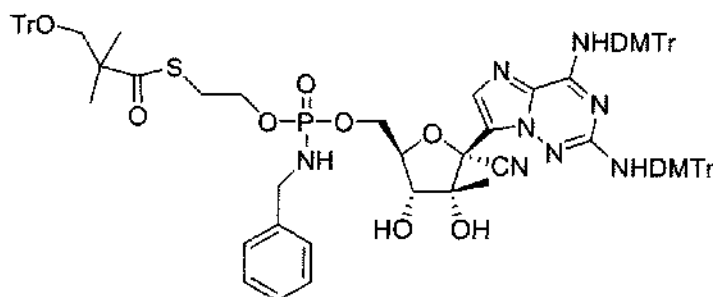
- 5 one to about 24 hours. The mixture is partitioned between ethyl acetate and water. The ethyl acetate layer is dried and concentrated. The residue is purified chromatography to afford **Compound 34** which may be a mixture of mono- and di-dimethoxytritylated compounds.

10 **Compound 35**



- A mixture of about 1.25 mmol of **Compound 34** and about 1.9 mmol of triethylammonium 2-(2,2-dimethyl-3-(trityloxy)propanoylthio)ethyl phosphonate (WO2008082601) is dissolved in anhydrous pyridine (about 19 mL). Pivaloyl chloride (about 2.5 mmol) is added dropwise at about -30 to about 0 °C and the solution is stirred at for about 30 min to about 24 hours. The reaction is diluted with methylene chloride and is neutralized with aqueous ammonium chloride (about 0.5M). The methylene chloride phase is evaporated and the residue is dried and is purified by chromatography to give **Compound 35** which may be a mixture of mono- and di-dimethoxytritylated compounds.

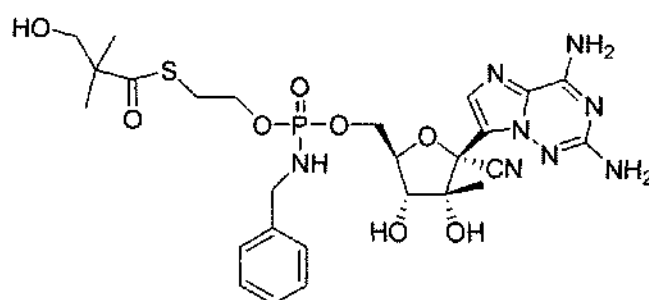
Compound 36



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- 5 To a solution of about 0.49 mmol of **Compound 35** in anhydrous carbon tetrachloride (about 5 mL) is added dropwise benzylamine (about 2.45 mmol). The reaction mixture is stirred for about one to about 24 hours. The solvent is evaporated and the residue is purified by chromatography to give **Compound 36** which may be a mixture of mono- and di-dimethoxytritylated compounds.

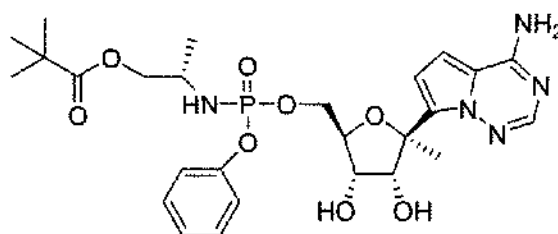
10

Compound 37

37

- 15 A solution of about 2 mmol of **Compound 36** in methylene chloride (about 10 mL) is treated with an aqueous solution of trifluoroacetic acid (90%, about 10 mL). The reaction mixture is stirred at about 25 to about 60 °C for about one to about 24 hours. The reaction mixture is diluted with ethanol, the volatiles are evaporated and the residue is purified by chromatography to give **Compound 37**.

20

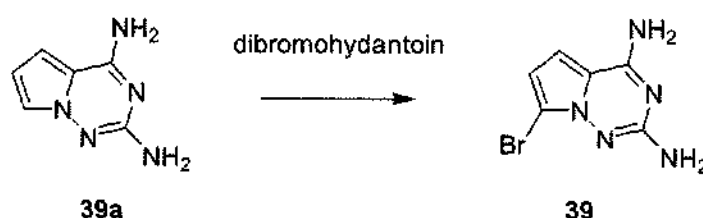
Compound 38

38

- 25 About 90 mM **Compound 14** in THF is cooled to about -78 °C and about 2.2 to about 4.4 equivalents of *t*-butylmagnesium chloride (about 1 M in THF) is added. The

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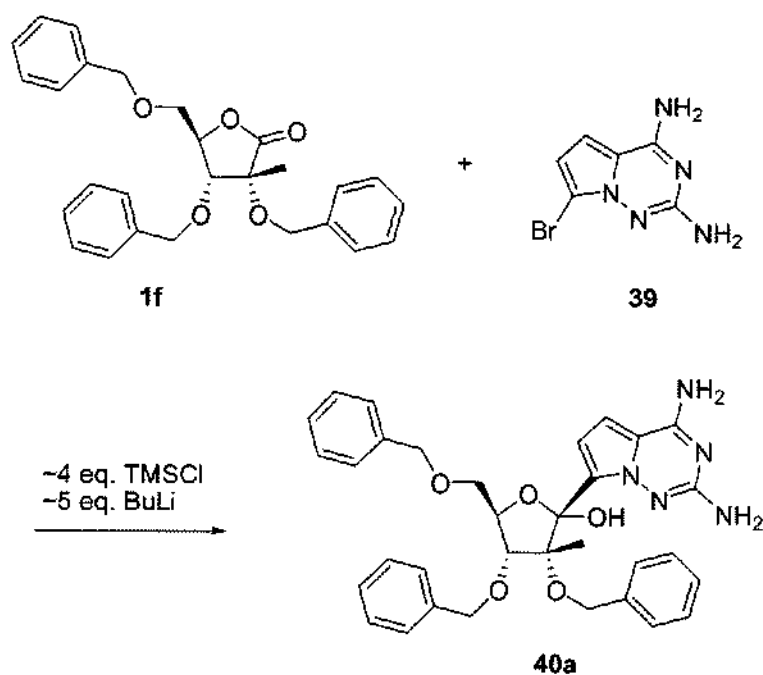
- 5 mixture is warmed to about 0 °C for about 30 min and is again cooled to about -78 °C. A solution of (2*S*)-2-[[chloro(1-phenoxy)phosphoryl]amino}propyl pivaloate (WO2008085508) (1 M in THF, about 2 equivalents) is added dropwise. The cooling is removed and the reaction is stirred for about one to about 24 hours. The reaction is quenched with water and the mixture is extracted with ethyl acetate. The extracts are
10 dried and evaporated and the residue purified by chromatography to give **Compound 38**.

Compound 39

- A solution of about one part **Compound 39a** (Patil, et al. ; *Journal of*
15 *Heterocyclic Chemistry* **1994**, 31(4), 781-6) in anhydrous DMF is cooled to about -20 °C and about 0.5 parts of 1,3-diromo-5,5-dimethylhydantoin is added in portions. After about one to about 24 hours, a saturate aqueous sodium bisulfite solution is added and the solids are collected by filtration. The solids are partitioned between ethyl acetate and dilute aqueous sodium carbonate. The organic phase is washed with dilute sodium
20 carbonate then dried and concentrated to give **Compound 39**.

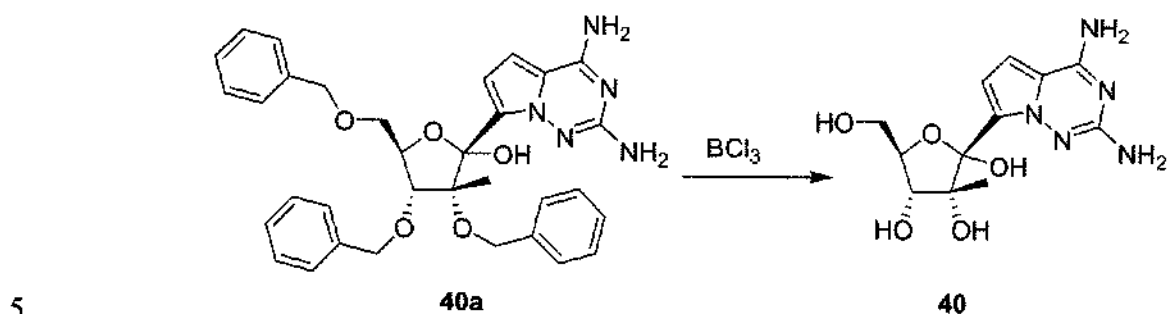
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Compound 40

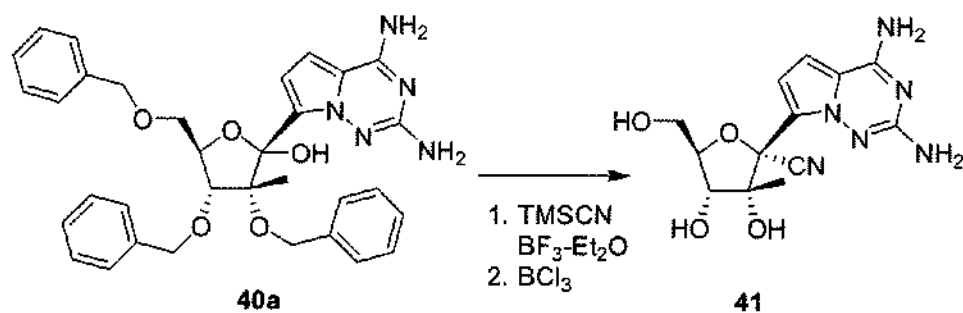
A solution of about one part of **39** and about four parts of trimethylsilylchloride in THF is stirred at about 20 to about 60 °C for about 30 min to about six hours. The solution is cooled to about -70 to about -100 °C and a solution of about five parts of butyllithium in hexanes is added. After about 30 min. to about three hours, the reaction is allowed to warm to about 0 °C over about three hours. The reaction is quenched with saturated NaHCO₃ and the mixture is extracted with ether. The ether extracts are washed with brine, dried, and the solvent evaporated to give **40a** which may be further purified by chromatography.

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A solution of one part of **40a** in dichloromethane is cooled to about -100 to about -70 °C. A 1.0 M solution of BCl_3 in dichloromethane (about 10 to 20 parts) is added and the reaction is stirred for about 30 min. to about 3 hours. A mixture of pyridine and methanol (about 1:2) is then added to quench the reaction. The resulting mixture is slowly warmed to room temperature and concentrated. The residue is suspended in about 27% ammonium hydroxide and concentrated. This process is repeated twice. The residue is re-dissolved in methanol and concentrated. This process is repeated once. The residue is purified by RP-HPLC to give **40**.

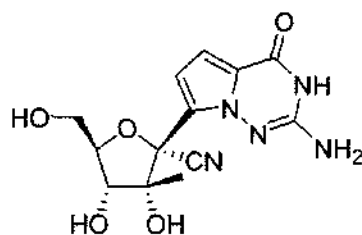
15

Compound 41

20 **Compound 41** may be prepared from **Compound 40a** in the same manner as **Compound 5** was prepared from **Compound 2a**.

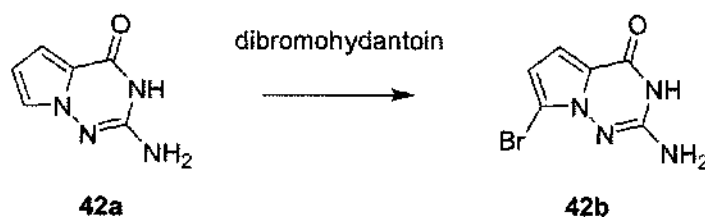
Compound 42

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42

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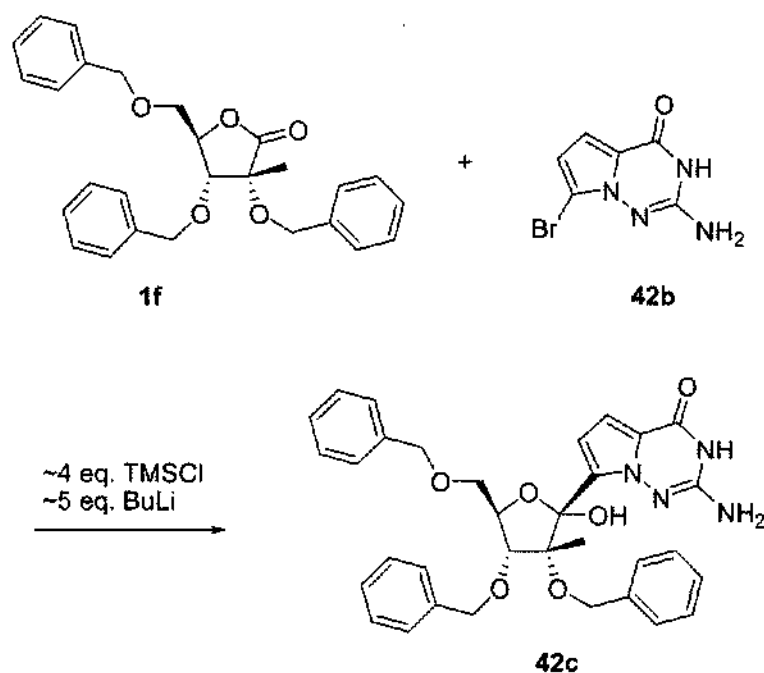


42a

42b

A solution of about one part **Compound 42a** (Patil, et al. ; *Journal of Heterocyclic Chemistry* **1994**, 31(4), 781-6) in anhydrous DMF is cooled to about -20 °C and about 0.5 parts of 1,3-diromo-5,5-dimethylhydantoin is added in portions. After about one to about 24 hours, a saturate aqueous sodium bisulfite solution is added and the solids are collected by filtration. The solids are partitioned between ethyl acetate and dilute aqueous sodium carbonate. The organic phase is washed with dilute sodium carbonate then dried and concentrated to give **Compound 42b**.

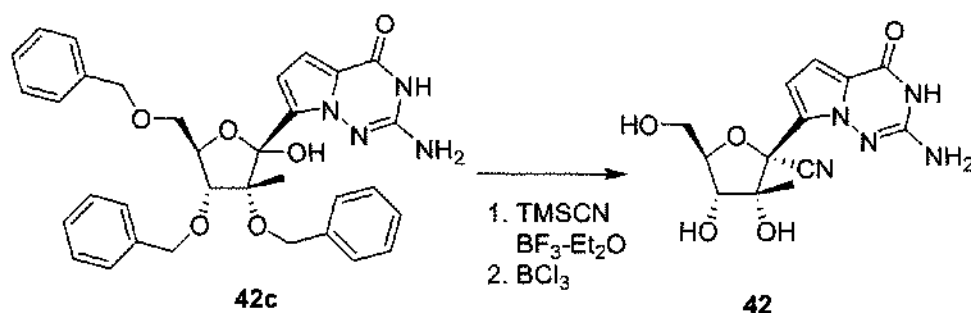
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A solution of about one part of **42b** and about four parts of trimethylsilylchloride in THF is stirred at about 20 to about 60 °C for about 30 min to about six hours. The solution is cooled to about -70 to about -100 °C and a solution of about five parts of butyllithium in hexanes is added. After about 30 min. to about three hours, the reaction is allowed to warm to about 0 °C over about three hours. The reaction is quenched with saturated NaHCO₃ and the mixture is extracted with ether. The ether extracts are washed with brine, dried, and the solvent evaporated to give **42c** which may be further purified by chromatography.

10

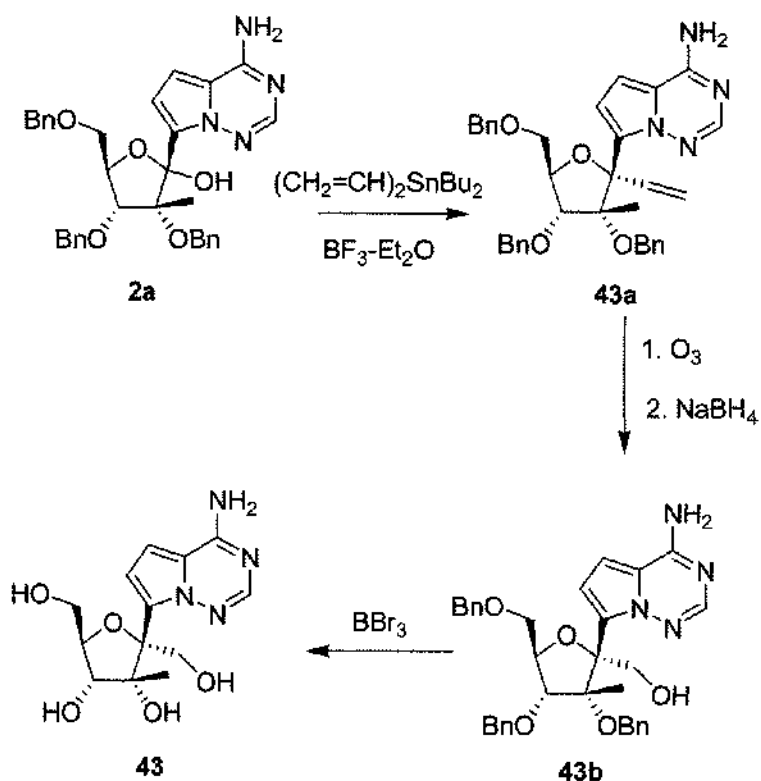


15

Compound 42 may be prepared from **Compound 42a** in the same manner as **Compound 5** was prepared from **Compound 2a**.

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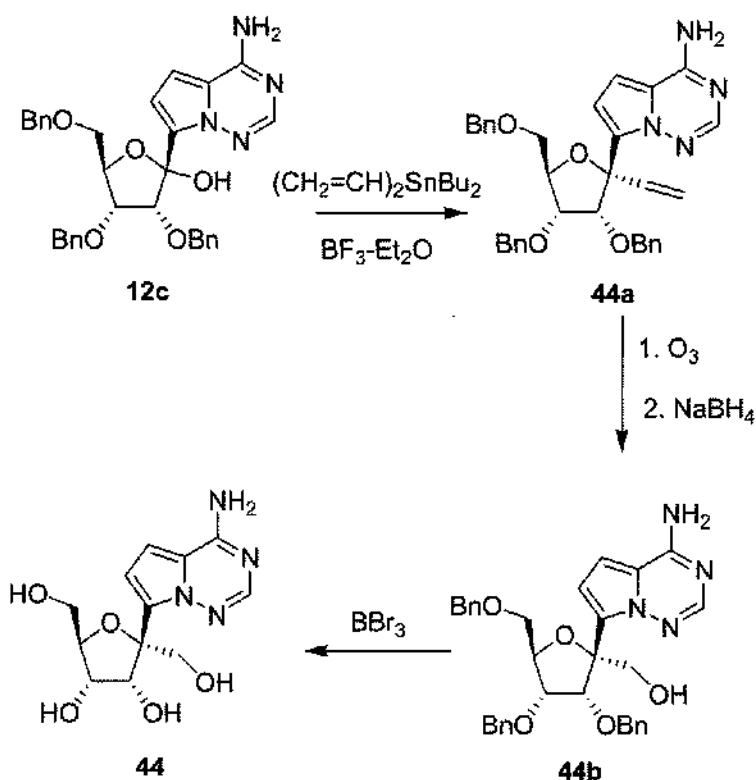
5

Compound 43

- A solution of one part of **Compound 2a** in CH_2Cl_2 is treated with about two parts of BF_3OEt_2 at about -78°C under an argon atmosphere and about three parts of $(\text{CH}_2=\text{CH})_2\text{SnBu}_2$. The reaction temperature is gradually raised to rt during about one to four hours. Usual extractive workup followed by purification by chromatography will give **Compound 43a**. **Compound 43a** is dissolved in methanol and dichloromethane and cooled to about -78°C . Ozone is bubbled into the stirred solution for about 1.5 hours at -78°C . The solution is then flushed with nitrogen to remove the ozone. Sodium borohydride (about 8 equivalents) is then added in small portions over about 5 minutes at -78°C . Methanol is added and the reaction is slowly warmed to about 0°C . After about 1.5 hours, the reaction is quenched with saturated bicarbonate solution and extracted with CH_2Cl_2 . The combined organics are washed with brine, dried, filtered and the solvent is removed in vacuo. The residue is purified by chromatography to give **Compound 43b**. **Compound 43b** may be debenzylated in the same manner as **Compound 2a** to give **Compound 43** that may be further purified by chromatography.

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Compound 44

Compound 44 may be obtained in the same manner as **Compound 43**, starting with **Compound 12c**.

10

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells,

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- 5 particularly recombinant cells synthesizing a desired glycoprotein; and the like.
Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.
- 10 If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the
- 15 physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocols.

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5 Cell-based Flavivirus Immunodetection assay

- BHK21 or A549 cells are trypsinized, counted and diluted to 2×10^5 cells/mL in Hams F-12 media (A549 cells) or RPMI-1640 media (BHK21 cells) supplemented with 2% fetal bovine serum (FBS) and 1% penicillin/streptomycin. 2×10^4 cells are dispensed in a clear 96-well tissue culture plates per well and palced at 37°C , 5% CO_2 overnight.
- 10 On the next day, the cells are infected with viruses at multiplicity of infection (MOI) of 0.3 in the presence of varied concentrations of test compounds for 1 hour at 37°C and 5% CO_2 for another 48 hours. The cells are washed once with PBS and fixed with cold methanol for 10 min. After washing twice with PBS, the fixed cells are blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1 hour at room temperature. The
- 15 primary antibody solution (4G2) is then added at a concentration of 1:20 to 1:100 in PBS containing 1% FBS and 0.05% Tween-20 for 3 hours. The cells are then washed three times with PBS followed by one hour incubation with horseradish peroxidase(HRP)-conjugated anti-mouse IgG (Sigma, 1:2000 dilution). After washing three times with PBS, 50 microliters of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution (Sigma)
- 20 is added to each well for two minutes. The reaction is stopped by addition of 0.5 M sulfuric acid. The plates are read at 450 nm abosorbance for viral load quantification. After measurement, the cells are washed three times with PBS followed by incubation with propidium iodide for 5 min. The plate is read in a Tecan SafireTM reader (excitation 537 nm, emission 617 nm) for cell number quantification. Dose response curves are
- 25 plotted from the mean absorbance versus the log of the of the concentration of test compounds. The EC_{50} is calculated by non-linear regression analysis. A positive control such as N-nonyl-deoxynojirimycin may be used.

Cell-based Flavivirus cytopathic effect assay

- For testing against West Nile virus or Japanese encephalitis virus, BHK21 cells
- 30 are trypsinized and diluted to a concentration of 4×10^5 cells/mL in RPMI-1640 media supplemented with 2% FBS and 1% penicillin/streptomycin. For testing against dengue virus, Huh7 cells are trypsinized and diluted to a concentration of 4×10^5 cells/mL in

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- 5 DMEM media supplemented with 5% FBS and 1% penicillin/streptomycin. A 50 microliter of cell suspension (2×10^4 cells) is dispensed per well in a 96-well optical bottom PIT polymer-based plates (Nunc). Cells are grown overnight in culture medium at 37° C, 5% CO₂, and then infected with West Nile virus (e.g. B956 strain) or Japanese encephalitis virus (e.g. Nakayama strain) at MOI = 0.3, or with dengue virus (e.g. DEN-2
- 10 NGC strain) at MOI = 1, in the presence of different concentrations of test compounds. The plates containing the virus and the compounds are further incubated at 37°C, 5% CO₂ for 72 hours. At the end of incubation, 100 microliters of CellTiter-Glo™ reagent is added into each well. Contents are mixed for 2 minutes on an orbital shaker to induce cell lysis. The plates are incubated at room temperature for 10 minutes to stabilize
- 15 luminescent signal. Luminescence reading is recorded using a plate reader. A positive control such as N-nonyl-deoxynojirimycin may be used.

Antiviral Activity in a Mouse Model of Dengue Infection.

- Compounds are tested *in vivo* in a mouse model of dengue virus infection (Schul *et al.* J. Infectious Dis. 2007; 195:665-74). Six to ten week old AG129 mice (B&K
- 20 Universal Ltd, Hill, UK) are housed in individually ventilated cages. Mice are injected intraperitoneally with 0.4 mL TSV01 dengue virus 2 suspension. Blood samples are taken by retro orbital puncture under isoflurane anaesthesia. Blood samples are collected in tubes containing sodium citrate to a final concentration of 0.4%, and immediately centrifuged for 3 minutes at 6000g to obtain plasma. Plasma (20 microliters) is diluted
 - 25 in 780 microliters RPMI-1640 medium and snap frozen in liquid nitrogen for plaque assay analysis. The remaining plasma is reserved for cytokine and NS1 protein level determination. Mice develop dengue viremia rising over several days, peaking on day 3 post-infection.

- For testing of antiviral activity, a compound of the invention is dissolved in
- 30 vehicle fluid, e.g. 10% ethanol, 30% PEG 300 and 60% D5W (5% dextrose in water; or 6N HCl (1.5 eq):1N NaOH (pH adjusted to 3.5): 100 mM citrate buffer pH 3.5 (0.9% v/v:2.5% v/v: 96.6% v/v). Thirty six 6-10 week old AG129 mice are divided into six

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- 5 groups of six mice each. All mice are infected with dengue virus as described above (day 0). Group 1 is dosed by oral gavage of 200 μ L/mouse with 0.2 mg/kg of a compound of the invention twice a day (once early in the morning and once late in the afternoon) for three consecutive days starting on day 0 (first dose just before dengue infection). Groups 2, 3 and 4 are dosed the same way with 1 mg/kg, 5 mg/kg and 25
- 10 mg/kg of the compound, respectively. A positive control may be used, such as (2R,3R,4R,5R)-2-(2-amino-6-hydroxy-purin-9-yl)-5-hydroxymethyl-3-methyl-tetrahydro-furan-3,4-diol, dosed by oral gavage of 200 microliters/mouse the same way as the previous groups. A further group is treated with only vehicle fluid.

- On day 3 post-infection approximately 100 microliter blood samples (anti-
- 15 coagulated with sodium citrate) are taken from the mice by retro-orbital puncture under isoflurane anaesthesia. Plasma is obtained from each blood sample by centrifugation and snap frozen in liquid nitrogen for plague assay analysis. The collected plasma samples are analyzed by plague assay as described in Schul *et al.* Cytokines are also analysed as as described by Schul. NS1 protein levels are analysed using a PlateliaTM kit (BioRad
- 20 Laboratories). An anti-viral effect is indicated by a reduction in cytokine levels and/or NS1 protein levels.

Typically, reductions in viremia of about 5-100 fold, more typically 10-60 fold, most typically 20-30 fold, are obtained with 5-50 mg/kg bid dosages of the compounds of the invention.

25

HCV IC₅₀ Determination

- Assay Protocol: NS5b polymerase assay (40 μ L) was assembled by adding 28 μ L polymerase mixture (final concentration: 50 mM Tris-HCl at pH 7.5, 10 mM KCL, 5
- 30 mM MgCl₂, 1 mM DTT, 10 mM EDTA, 4 ng/ μ L of RNA template, and 75 nM HCV Δ 21 NS5b polymerase) to assay plates followed by 4 μ L of compound dilution. The polymerase and compound were pre-incubated at 35 °C for 10 minute before the addition

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- 5 of 8 μL of nucleotide substrate mixture (33P- α -labeled competing nucleotide at K_M and 0.5 mM of the remaining three nucleotides). The assay plates were covered and incubated at 35 °C for 90 min. Reactions were then filtered through 96-well DEAE-81 filter plates via vacuum. The filter plates were then washed under vacuum with multiple volumes of 0.125 M NaHPO_4 , water, and ethanol to remove unincorporated label. Plates
10 were then counted on TopCount to assess the level of product synthesis over background controls. The IC_{50} value is determined using Prism fitting program.

Preferably, compounds described herein inhibited NS5b polymerase with an IC_{50} 's below 1000 μM , more preferably below 100 μM , and most preferably below 10 μM . For example, compound 17 has an IC_{50} below 1 μM .

15

HCV EC_{50} Determination

- Replicon cells were seeded in 96-well plates at a density of 8×10^3 cells per well in 100 μL of culture medium, excluding Geneticin. Compound was serially diluted in
20 100% DMSO and then added to the cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO and a total volume of 200 μL . Plates were incubated at 37°C for 3 days, after which culture medium was removed and cells were lysed in lysis buffer provided by Promega's luciferase assay system. Following the manufacturer's instruction, 100 μL of luciferase substrate was added to the lysed cells and luciferase
25 activity was measured in a TopCount luminometer. Preferably, compounds described herein have EC_{50} 's below 1000 μM , more preferably below 100 μM , and most preferably below 10 μM .

- Representative examples of the activity of the compounds Formula I-III are shown in the Table below wherein A represents an EC_{50} below 1 μM , B represents an
30 EC_{50} between 1 and 10 μM , and C represents an EC_{50} between 10 and 100 μM .

Example No.	EC_{50} , μM
2	C

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3	C
4	C
5	C
6	A
12	B
13	B

5

The cytotoxicity of a compound of the invention can be determined using the following general protocol.

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5

Cytotoxicity Cell Culture Assay (Determination of CC50):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate.

Assay protocol for determination of CC50:

- 10 1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 μ l media per well) and add various concentrations of the tested compound in triplicate (100 μ l/well). Include untreated control.
- 15 3. Incubate the cells for 5 days at 37 °C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min. Add 50 μ l of N-methylphenazonium methasulfate (5 μ g/ml) per 6 ml of XTT solution.
- 20 5. Remove 100 μ l media from each well on the assay plate and add 100 μ l of the XTT substrate solution per well. Incubate at 37 °C for 45 to 60 min in a CO₂ incubator.
6. Add 20 μ l of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC50
- 25 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

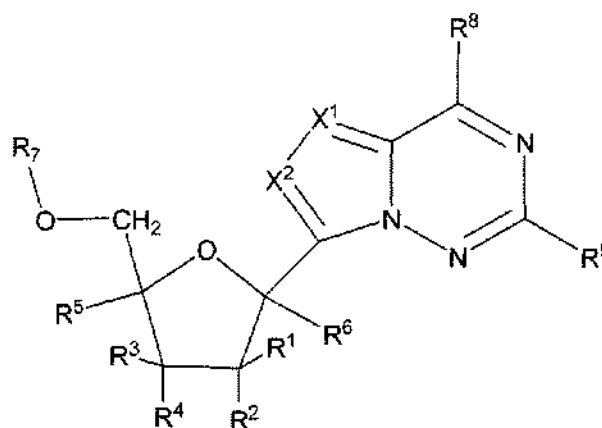
All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

- 30 The invention has been described with reference to various specific and preferred embodiments and techniques. However, one skilled in the art will understand that many variations and modifications may be made while remaining within the spirit and scope of the invention.

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5 What is claimed is

1. A compound of Formula I:



Formula I

10 or a pharmaceutically acceptable salt, thereof;

wherein:

each R^1 , R^2 , R^3 , R^4 , or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl;

or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl or R^6 and either R^1 or R^2 when taken together are $-O(CO)O-$;

25 each n is independently 0, 1, or 2;

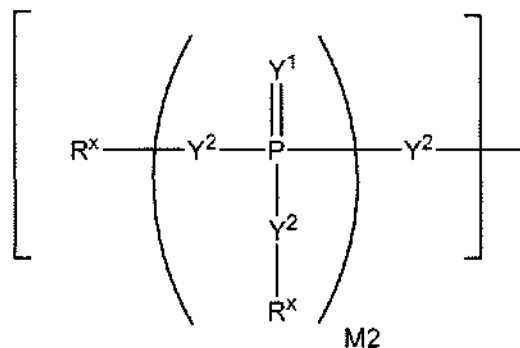
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- 5 each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;
 R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



each Y or Y^1 is, independently, O, S, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$, or N-NR₂;

- W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:
- 15



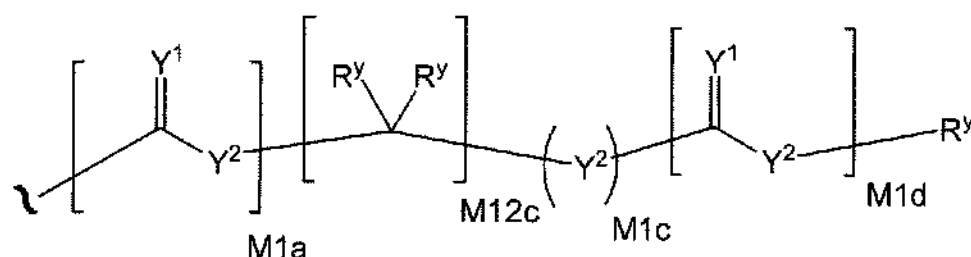
Formula Ia

wherein:

- each Y^2 is independently a bond, O, CR₂, NR, $^+N(O)(R)$, N(OR), $^+N(O)(OR)$,
 20 N-NR₂, S, S-S, S(O), or S(O)₂;
 each Y^3 is independently O, S, or NR;
 M2 is 0, 1 or 2;
 each R^x is independently R^y or the formula:

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5



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, -C(=Y¹)R, -C(=Y¹)OR, -
 10 C(=Y¹)N(R)₂, -N(R)₂, -⁺N(R)₃, -SR, -S(O)R, -S(O)₂R, -S(O)(OR), -S(O)₂(OR), -
 OC(=Y¹)R, -OC(=Y¹)OR, -OC(=Y¹)(N(R)₂), -SC(=Y¹)R, -SC(=Y¹)OR, -
 SC(=Y¹)(N(R)₂), -N(R)C(=Y¹)R, -N(R)C(=Y¹)OR, -N(R)C(=Y¹)N(R)₂, -SO₂NR₂, -CN,
 -N₃, -NO₂, -OR, or W³; or when taken together, two R^y on the same carbon atom form a
 carbocyclic ring of 3 to 7 carbon atoms;

15 each R is independently H, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-
 C₈)alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl,
 C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted
 heterocyclyl, arylalkyl or substituted arylalkyl;

W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)R^y, -C(Y¹)W⁵, -SO₂R^y, or -SO₂W⁵; and W⁵ is a
 20 carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y
 groups;

each X¹ or X² is independently C-R¹⁰ or N;

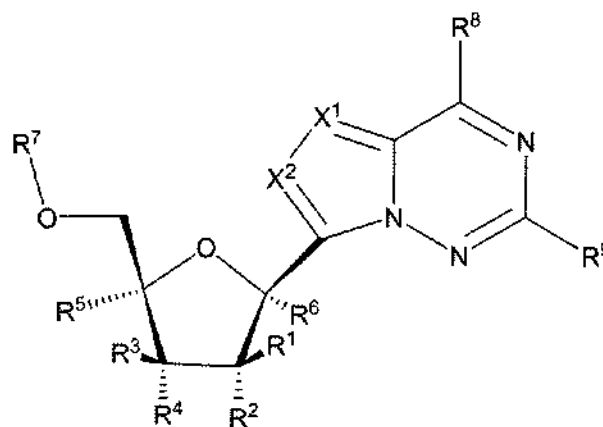
each R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO,
 CN, -CH(=NR¹¹), -CH=NHNR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹²,
 25 -C(=S)NR¹¹R¹², -C(=O)OR¹¹, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
 (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -
 C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, OR¹¹ or SR¹¹;

each R⁹ or R¹⁰ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹²,
 N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NHNR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂,
 30 -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

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- 5 each R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, -
 $C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl (C_1-C_8) alkyl; or R^{11} and R^{12} taken together
 with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring
 wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -
 10 O-, -S- or $-NR^a$;
 wherein each (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl of
 each R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one
 or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more of the non-
 terminal carbon atoms of each said (C_1-C_8) alkyl is optionally replaced with -O-, -S- or -
 15 NR^a .

2. A compound according to claim 1 represented by Formula II



Formula II

20

wherein X^2 is $C-R^{10}$ and each Y and Y^1 is O.

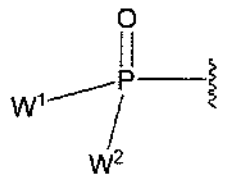
25

3. A compound according to claims 1 or 2 wherein R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} .

4. A compound according any one of claims 1-3 wherein R^9 is H or $NR^{11}R^{12}$.

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- 5 5. A compound according to any one of claims 1-4 wherein R^7 is H or



6. A compound according to any one of claims 1-5 wherein R^6 is OR^a , N_3 , halogen, CN, methyl, hydroxymethyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl.

7. A compound according to any one of claims 1-6 wherein X^2 is C-H and R^3 and R^5 are each H.

8. A compound according to any one of claims 1-7 wherein at least one of R^2 or R^4 is OR^a .

9. A compound according to any one of claims 1-8 wherein X^1 is N or C- R^{10} wherein R^{10} is H, halogen, CN or optionally substituted heteroaryl.

10. A compound according to any one of claims 1-9 wherein R^2 and R^4 are each OR^a .

11. A compound according to any one of claims 1-10 wherein R^2 and R^4 are OH.

12. A compound according to any one of claims 1-11 wherein X^1 is N.

13. A compound according to any one of claims 1-11 wherein X^1 is C-H.

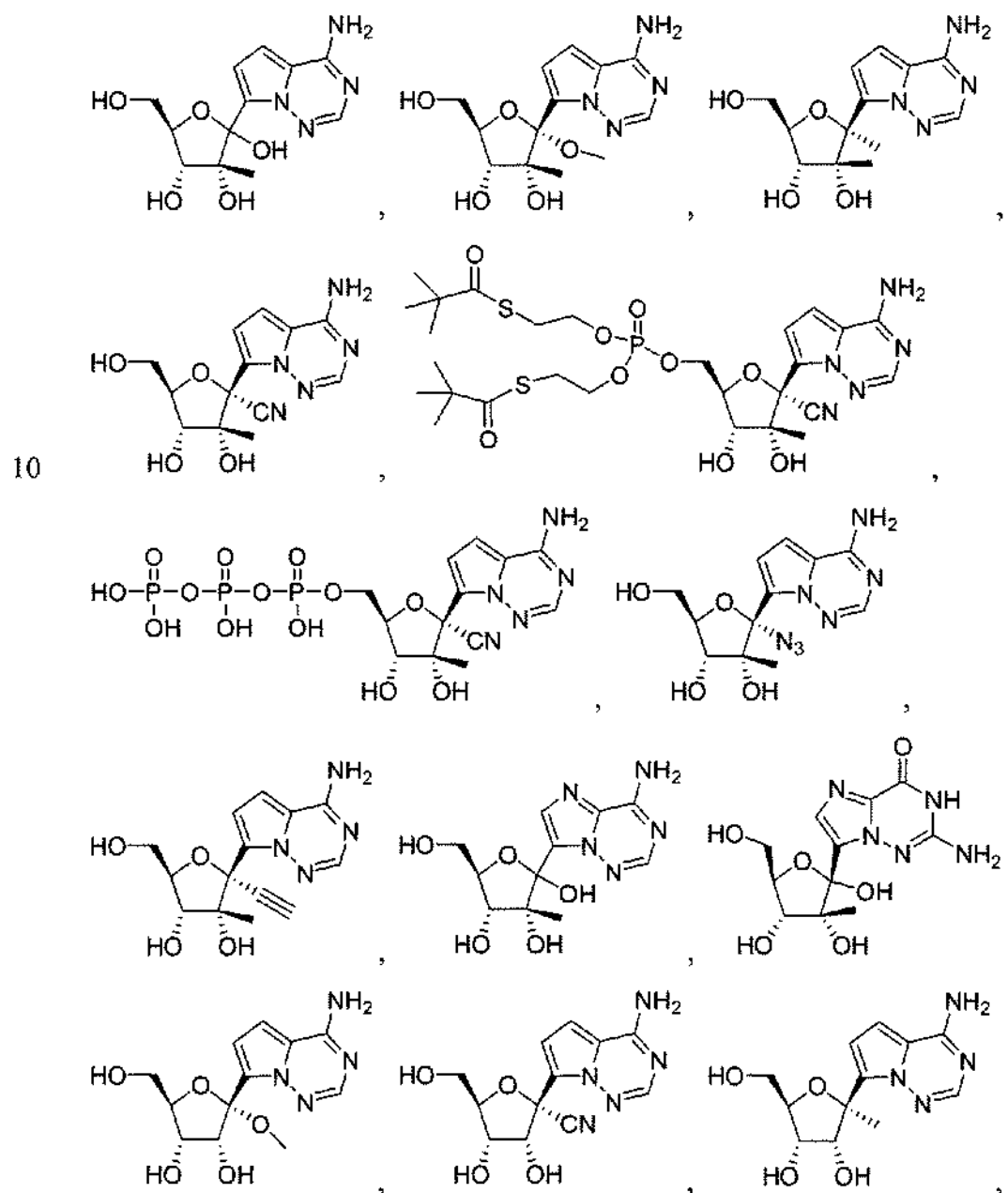
14. A compound according to any one of claims 1-13 wherein R^1 is H, methyl, CH_2OH , CH_2F , ethenyl, or ethynyl.

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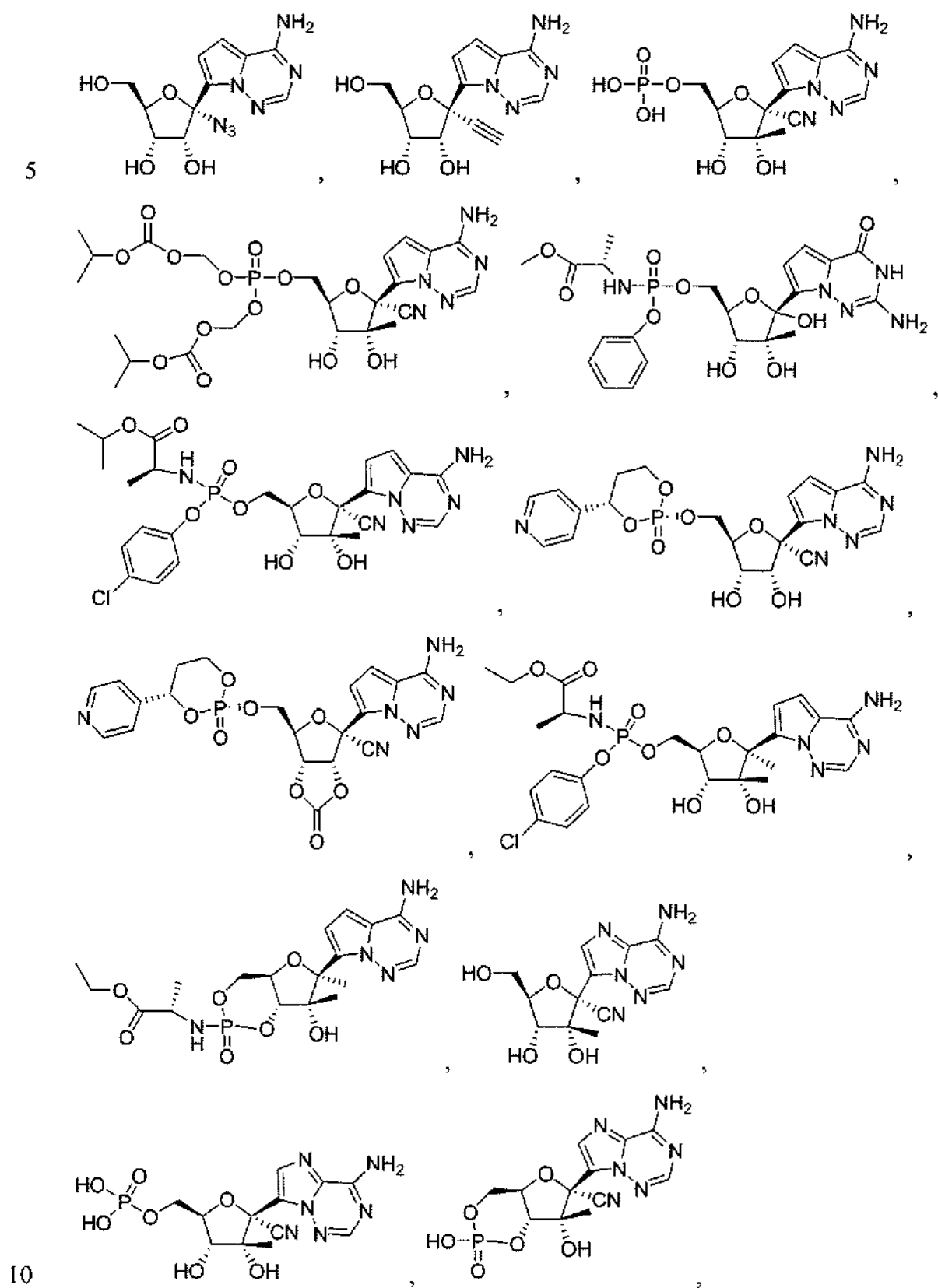
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17. A compound according to any one of claims 1-14 wherein R^7 is H.

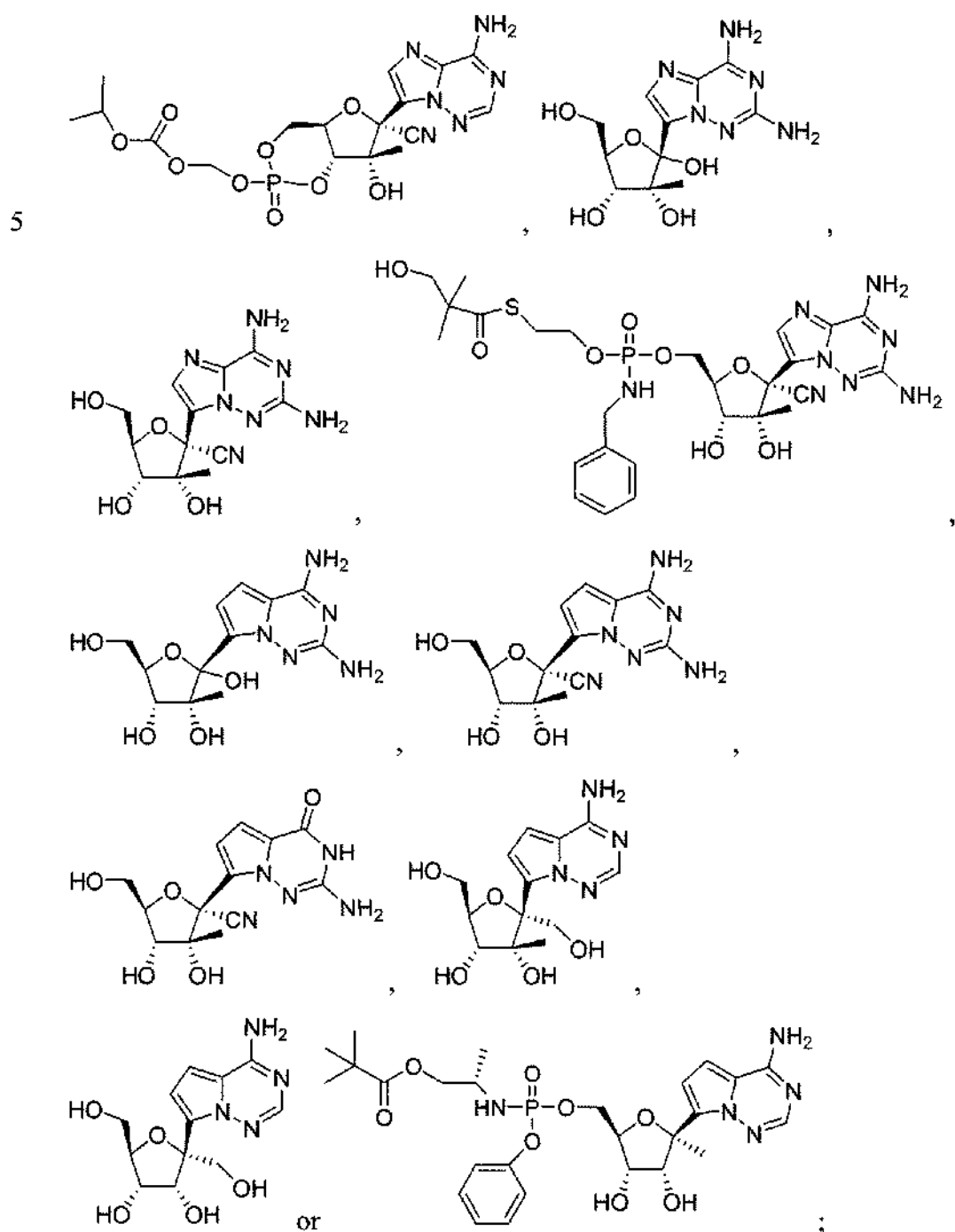
18. A compound according to claim 1 that is



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19. A compound according to any one of claims 1-18 that is in a form of a racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph or amorphous form.

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- 5 20. A pharmaceutical composition comprising a therapeutically effective amount of a compound as in any one of claims 1 to 19 and a pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20 further comprising at least one additional therapeutic agent.

10

22. The pharmaceutical composition of claim 21, wherein said additional therapeutic agent is selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

15

23. A method of inhibiting HCV polymerase comprising the administration to a mammal in need of such treatment a therapeutically effective amount of a compound of any one of claims 1 to 18.

20

24. A method of treating a viral infection caused by a virus of the *Flaviviridae* family comprising the administration to a mammal in need of such treatment a therapeutically effective amount of a compound or pharmaceutical composition of any one of claims 1 to 18.

25

25. The method of claim 23 wherein the viral infection is caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus.

30

26. The method of claim 25 wherein the viral infection is caused by Hepatitis C virus.

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- 5 27. The method of any one of claims 24-26 further comprising administering at least one additional therapeutic agent.

28. The method of claim 27 wherein said at least one additional therapeutic agent is selected from the group consisting of interferons, ribavirin analogs, NS3 protease
10 inhibitors, NS5b polymerase inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

29. A compound as in any one of claims 1 to 18 used in the manufacture of a
15 medicament for treating a viral infection caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus.

20

30. A compound or method as described herein.

International application No

PCT/US2009/041447

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/395 A61K31/41 A61K31/4188 C07H19/23
 A61K31/7052 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/005542 A (GILEAD SCIENCES INC [US]; BOOJAMRA CONSTANTINE G [US]; CHEN JAMES M [U] 10 January 2008 (2008-01-10) the whole document	1-30
Y	WO 02/057287 A (MERCK & CO INC [US]; ISIS PHARMACEUTICALS INC [US]; CARROLL STEVEN S [U] 25 July 2002 (2002-07-25) the whole document	1-30
A	WO 00/56734 A (AVENTIS CROPSOURCE GMBH [DE]) 28 September 2000 (2000-09-28)	1-30
P, Y	WO 2008/141079 A (BIOCRYST PHARM INC [US]; BABU YARLAGADDA S [US]; CHAND POORAN [US]) 20 November 2008 (2008-11-20) the whole document	1-30
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Further documents are listed in the continuation of Box C.



See patent family annex.

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

30 July 2009

Date of mailing of the international search report

07/08/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5618 Patentlaan 2
 NL - 2280 HV Rijswijk
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 Fax: (+31-70) 340-3016

Authorized officer

Klein, Didier

INTERNATIONAL SEARCH REPORT

429

International application No
PCT/US2009/041447

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/041447

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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WO 2008141079	A	20-11-2008	NONE	
WO 2008089105	A	24-07-2008	NONE	

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International Bureau(10) International Publication Number
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C07D 309/10 (2006.01) C07H 19/00 (2006.01)(21) International Application Number:
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(30) Priority Data:
61/366,609 22 July 2010 (22.07.2010) US(71) Applicant (for all designated States except US):
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(72) Inventors; and

(75) Inventors/ Applicants (for US only): MACKMAN, Richard, L. [GB/US]; 360 Ashton Avenue, Millbrae, CA 94030 (US). PARRISH, Jay, P. [US/US]; 720 Bair Island Rd. #106, Redwood City, CA 94063 (US). RAY, Adrian, S. [US/US]; 19 Pilot Circle, Redwood City, CA 94065 (US). THEODORE, Dorothy, Agnes [US/US]; 19487 Vaughn Avenue, Castro Valley, CA 94546 (US).

(74) Agents: VOELK, Eric, K. et al; 333 Lakeside Drive, Foster City, CA 94404 (US).

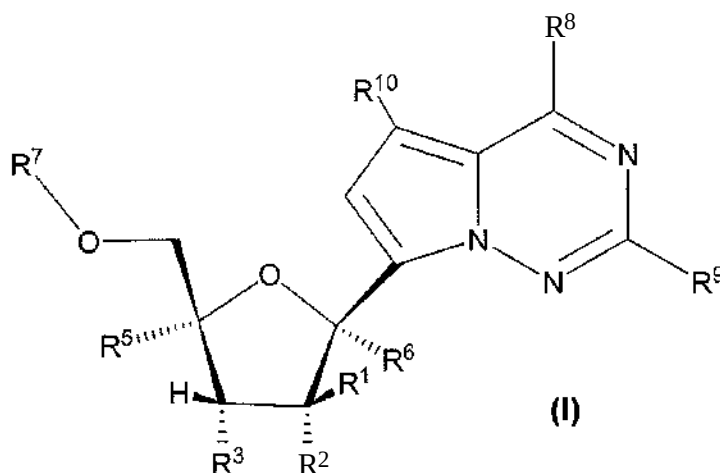
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

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

Published:

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

(54) Title: METHODS AND COMPOUNDS FOR TREATING PARAMYXOVIRIDAE VIRUS INFECTIONS

(57) Abstract: Provided are methods for treating *Paramyxoviridae* virus infections by administering ribosides, riboside phosphates and prodrugs thereof, of Formula (I): wherein the 1' position of the nucleoside sugar is substituted. The compounds, compositions, and methods provided are particularly useful for the treatment of Human parainfluenza and Human respiratory syncytial virus infections.

METHODS AND COMPOUNDS FOR TREATING *PARAMYXOVIRIDAE* VIRUS INFECTIONS

FIELD OF THE INVENTION

5 The invention relates generally to methods and compounds for treating *Paramyxoviridae* virus infections, particularly methods and nucleosides for treating respiratory syncytial virus infections and parainfluenza virus infections.

BACKGROUND OF THE INVENTION

10 Paramyxoviruses of the *Paramyxoviridae* family are negative-sense, single-stranded, RNA viruses that are responsible for many prevalent human and animal diseases. These viruses comprise at least two major subfamilies, *Paramyxovirinae* and *Pneumovirinae*. The subfamily *Paramyxovirina* includes the human parainfluenza viruses (HPIV), measles virus and mumps virus.

15 Although, vaccines are available to prevent measles and mumps infections, these infections caused 745, 00 deaths in 2001 so additional treatments would be desirable for susceptible populations. HPFV are the second most common cause of lower respiratory tract infection in younger children and collectively cause about 75% of the cases of Croup

20 (<http://www.cdc.gov/ncidod/dvrd/revb/respiratory/hpivfeat.htm>). HPIVs can cause repeated infections throughout life including upper respiratory tract illness and even serious lower respiratory tract disease (e.g., pneumonia, bronchitis, and bronchiolitis), the latter being especially of concern among the elderly, and among patients with compromised immune systems (Sable, *Infect. Dis. Clin. North Am.*

25 **1995, 9**, 987-1003). Currently, no vaccines are available to prevent HPIV infections. Therefore there is a need for *mti-Paramyxovirina* therapeutics.

 The subfamily *Pneumovirinae* includes Human respiratory syncytial virus (HRSV). Almost all children will have had an HRSV infection by their second

birthday. HRSV is the major cause of lower respiratory tract infections in infancy and childhood with 0.5% to 2% of those infected requiring hospitalization. The elderly and adults with chronic heart, lung disease or those that are immunosuppressed also have a high risk for developing severe HRSV disease
 5 (http://www.cdc.gov/rsv/index.html). No vaccine to prevent HRSV infection is currently available. The monoclonal antibody palivizumab is available for infants at high risk, e.g., premature infants or those with either cardiac or lung disease, but the cost for general use is often prohibitive. Ribavirin has also been used to treat HRSV infections but has limited efficacy. Therefore, there is a need for anti-
 10 *Pneumovirinae* therapeutics and anti-*Paramyxoviridae* therapeutics in general.

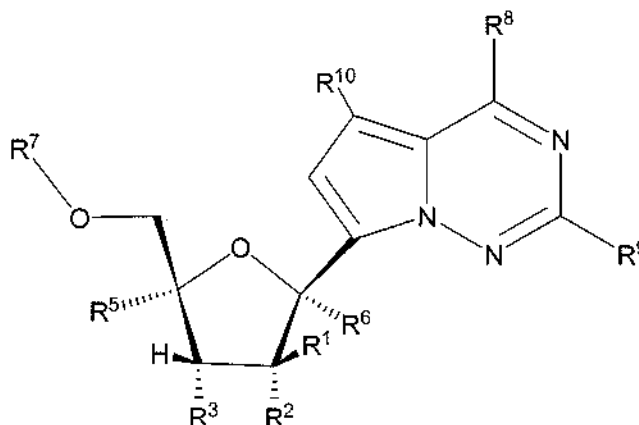
Ribosides of the nucleobases pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine have been disclosed in *Carbohydrate Research* 2001, 331(1), 77-82; *Nucleosides & Nucleotides* (1996), 15(1-3), 793-807; *Tetrahedron Letters*
 15 (1994), 35(30), 5339-42; *Heterocycles* (1992), 34(3), 569-74; *J. Chem. Soc. Perkin Trans. 1* 1985, 3, 621-30; *J. Chem. Soc. Perkin Trans. 1* 1984, 2, 229-38; WO 2000056734; *Organic Letters* (2001), 3(6), 839-842; *J. Chem. Soc. Perkin Trans. 1* 1999, 20, 2929-2936; and *J. Med. Chem.* 1986, 29(11), 2231-5. Ribosides of pyrrolo[1,2-f][1,2,4]triazine nucleobases with antiviral, anti-HCV,
 20 and anti-RdRp activity have been disclosed by Babu (WO2008/089105 and WO2008/141079) and Francom(WO2010/002877).

Butler, et al., WO2009132135, disclose 1' substituted ribosides and prodrugs comprising pyrrolo[1,2-f][1,2,4]triazine nucleobases which have anti-HCV and anti-RdRp activity. However, no methods of treating *Paramyxoviridae*
 25 infections with these compounds have been disclosed.

SUMMARY OF THE INVENTION

Provided are methods and compounds for the treatment of infections caused
 30 by the *Paramyxoviridae* virus family.

Provided, is a method for treating a *Paramyxoviridae* infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

each R^2 , R^3 or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (Ci-Cg)alkyl, $(C_4\text{-}Cg)$ carbocyclalkyl, (Ci-Cg)substituted alkyl, $(C_2\text{-}Cs)$ alkenyl, $(C_2\text{-}Cg)$ substituted alkenyl, $(C_2\text{-}C_8)$ alkynyl or $(C_2\text{-}Cg)$ substituted alkynyl;

or any two R^2 , R^3 or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

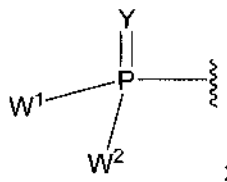
R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, $(C_1\text{-}C_8)$ alkyl, $(C_4\text{-}C_8)$ carbocyclalkyl, (Ci-Cg)substituted alkyl, $(C_2\text{-}Cg)$ alkenyl, $(C_2\text{-}Cg)$ substituted alkenyl, $(C_2\text{-}Cg)$ alkynyl, $(C_2\text{-}C_8)$ substituted alkynyl, or aryl(Ci-Cg)alkyl;

each n is independently 0, 1, or 2;

each R^a is independently H, (Ci-Cg)alkyl, $(C_2\text{-}Cg)$ alkenyl, $(C_2\text{-}Cg)$ alkynyl, aryl(Ci-Cg)alkyl, $(C_4\text{-}C_8)$ carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, -

$C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or

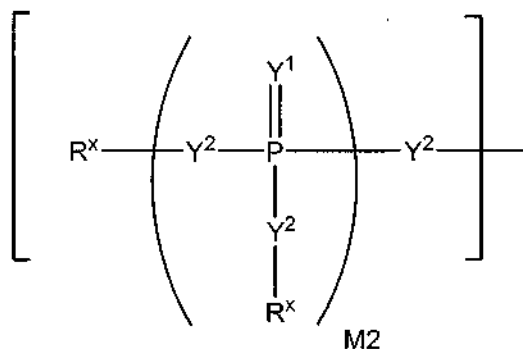


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each Y or Y^1 is, independently, O, S, NR, $+N(0)(R)$, $N(OR)$, $+N(0)(OR)$, or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or

10 W^1 and W^2 are each, independently, a group of the Formula Ia:



Formula Ia

wherein:

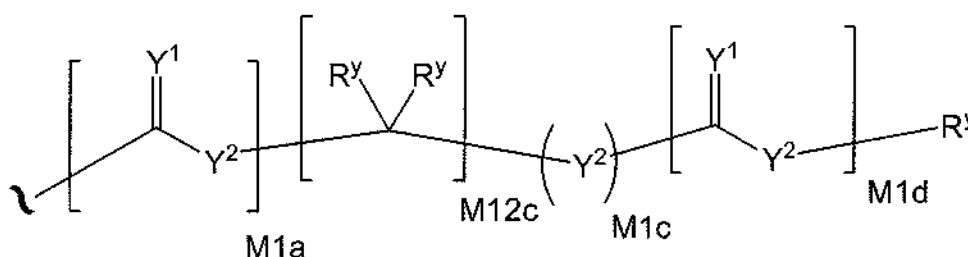
each Y^2 is independently a bond, O, CR_2 , NR, $+N(0)(R)$, $N(OR)$,

15 $+N(0)(OR)$, $N-NR_2$, S, S-S, S(O), or $S(0)_2$;

each Y^3 is independently O, S, or NR;

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

- 5 each R^y is independently H, F, Cl, Br, I, OH, R, -C(=Y¹)R, -C(=Y¹)OR, -C(=Y¹)N(R)₂, -N(R)₂, -N(R)₃, -SR, -S(O)R, -S(O)₂R, -S(O)(OR), -S(O)₂(OR), -OC(=Y¹)R, -OC(=Y¹)OR, -OC(=Y¹)N(R)₂, -SC(=Y¹)R, -SC(=Y¹)OR, -SC(=Y¹)N(R)₂, -N(R)C(=Y¹)R, -N(R)C(=Y¹)OR, -N(R)C(=Y¹)N(R)₂, -S(O)₂NR₂, -CN, -N₃, -NO₂, -OR, or W³; or when taken together, two R^y on the
- 10 same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C₁-C₈) alkyl, (C_i-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

- 15 W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)₃, -C(Y¹)W⁵, -S(O)₂R^y, or -S(O)₂W⁵; and W⁵ is a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

- each R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂,
- 20 -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, (C₁-C₈) alkyl, (C₂-C₈) alkenyl, (C₂-C₈) alkynyl, (C₄-C₈) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈) alkyl, -S(O)_n(C_i-C₈) alkyl, aryl(C₁-C₈) alkyl, OR¹¹ or SR¹¹;

- each R⁹ or R¹⁰ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹,
- 25 NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹,

-CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

each R¹¹ or R¹² is independently H, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclylalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(Ci-C₈)alkyl or aryl(Ci-C₈)alkyl; or R¹¹ and R¹² taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a; and wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(Ci-C₈)alkyl of each R², R³, R⁵, R⁶, R¹¹ or R¹² is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a.

In another embodiment, the method comprises administering a therapeutically effective amount of a racemate, enantiomer, diastereomer, tautomer, polymorph, pseudopolymorph, amorphous form, hydrate or solvate of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof to a mammal in need thereof.

In another embodiment, the method comprises treating a *Paramyxovirina* infection in a mammal in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

In another embodiment, the method comprises treating a parainfluenza, measles or mumps virus infection in a mammal in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

In another embodiment, the method comprises treating a parainfluenza virus infection in a mammal in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

In another embodiment, the method comprises treating a *Pneumovirinae* infection in a mammal in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

5 In another embodiment, the method comprises treating a respiratory syncytial virus infection in a mammal in need thereof by administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or ester thereof.

10 In another embodiment, the method comprises administering a therapeutically effective amount of a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt or ester thereof, in combination with a pharmaceutically acceptable diluent or carrier.

15 In another embodiment, the method comprises administering a therapeutically effective amount of a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt or ester thereof, in combination with at least one additional therapeutic agent.

20 In another embodiment, the method comprises administering a therapeutically effective amount of a combination pharmaceutical agent comprising:

 a) a first pharmaceutical composition comprising a compound of Formula I; or a pharmaceutically acceptable salt, solvate, or ester thereof; and

 b) a second pharmaceutical composition comprising at least one additional therapeutic agent active against infectious *Paramyxoviridae* viruses.

25 In another embodiment, the present application provides for a method of inhibiting a *Paramyxoviridae* RNA-dependent RNA polymerase, comprising contacting a cell infected with a *Paramyxoviridae* virus with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof.

In another embodiment, provided is the use of a compound of Formula I or a pharmaceutically acceptable salt, solvate, and/or ester thereof to treat a viral infection caused by a *Paramyxoviridae* virus.

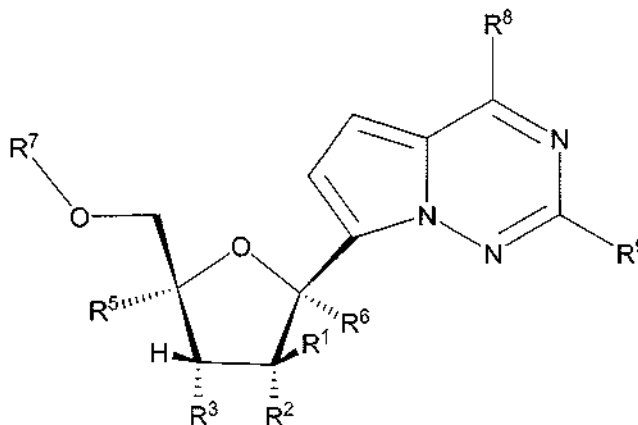
In another aspect, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds of the invention.

In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention.

In another embodiment, provided is a method of treating a *Paramyxoviridae* infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I represented by Formula II:



Formula II

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

5 each R^2 is OR^a or halogen;

each R^3 or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(0)_nR^a$, halogen, (Ci-Cg)alkyl, (C_4-Cg) carbocyclalkyl, (Ci-C8)substituted alkyl, (C_2-Cg) alkenyl, (C_2-Cg) substituted alkenyl, (C_2-Cg) alkynyl or (C_2-Cg) substituted alkynyl;

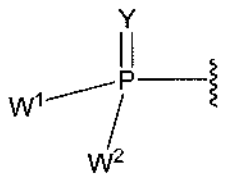
10 or any two R^2 , R^3 or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, $S(0)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (Ci-Cg)substituted alkyl, (C_2-Cg) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-Cg) alkynyl, or (C_2-C_8) substituted alkynyl;

each n is independently 0, 1, or 2;

20 each R^a is independently H, (Ci-Cg)alkyl, (C_2-Cg) alkenyl, (C_2-Cg) alkynyl, aryl(Ci-Cg)alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

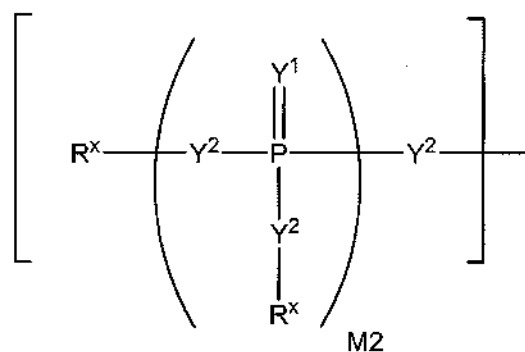
R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



25

each Y or Y^1 is, independently, O, S, NR, $^+N(0)(R)$, $N(OR)$, $^+N(0)(OR)$, or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:



Formula Ia

wherein:

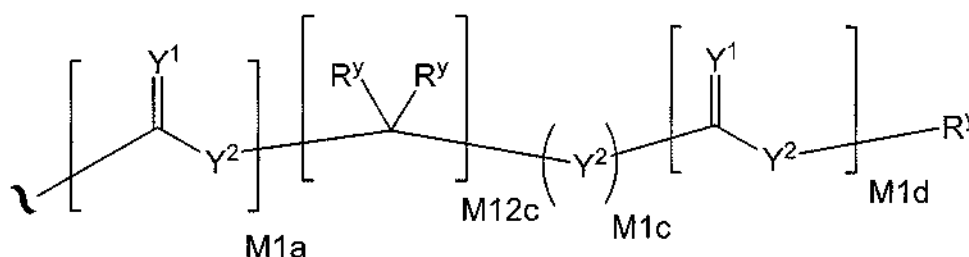
each Y^2 is independently a bond, O, CR_2 , NR, $+N(0)(R)$, $N(OR)$,

$+N(0)(OR)$, $N-NR_2$, S, S-S, $S(O)$, or $S(0)_2$;

each Y^3 is independently O, S, or NR;

M_2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M_{1a} , M_{1c} , and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-N(R)_3$, $-SR$, $-S(0)R$, $-S(0)_2R$, $-S(0)(OR)$, $-S(0)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-S(0)_2NR_2$, $-CN$, $-N_3$, $-N(0)_2$, $-OR$, or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (Ci-C₈) alkyl, (Ci-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

5 W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)R^y, -C(Y¹)W⁵, -SO₂R^y, or -SO₂W⁵; and W⁵ is a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

each R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂,
10 -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(d-C₈)alkyl, -S(O)_n(Ci-C₈)alkyl, aryl(Ci-C₈)alkyl, OR¹¹ or SR¹¹;

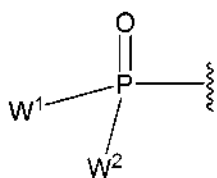
each R⁹ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹²,
15 N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

each R¹¹ or R¹² is independently H, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl;
20 or R¹¹ and R¹² taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a-; and

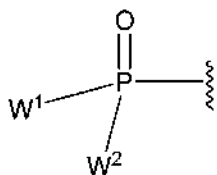
wherein each (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(Ci-C₈)alkyl of each R³, R⁵, R⁶, R¹¹ or R¹² is, independently, optionally substituted
25 with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a-.

In one embodiment of the method of treating a *Paramyxoviridae* infection by administering a compound of Formula II, R¹ of Formula II is H. In another
30 aspect of this embodiment R⁶ of Formula II is N₃, CN, halogen, (Ci-C₈)alkyl,

(C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, or (C₂-C₈)substituted alkynyl. In another aspect of this embodiment, R⁶ of Formula II is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R⁶ of Formula II is CN. In another aspect of this embodiment, R⁶ of Formula II is methyl. In another aspect of this embodiment, R⁵ of Formula II is H. In another aspect of this embodiment, R² of Formula II is OR^a. In another aspect of this embodiment, R² of Formula II is OH. In another aspect of this embodiment, R² of Formula II is F. In another aspect of this embodiment, R³ of Formula II is OR^a. In another aspect of this embodiment, R³ of Formula II is OH, -OC(=O)R¹¹, or -OC(=O)OR¹¹. In another aspect of this embodiment, R³ of Formula II is OH. In another aspect of this embodiment, R⁸ of Formula II is NR¹¹R¹². In another aspect of this embodiment, R⁸ of Formula II is NH₂. In another aspect of this embodiment, R⁸ of Formula II is OR¹¹. In another aspect of this embodiment, R⁸ of Formula II is OH. In another aspect of this embodiment, R⁹ of Formula II is H. In another aspect of this embodiment, R⁹ of Formula II is NR¹¹R¹². In another aspect of this embodiment, R⁹ of Formula II is NH₂. In another aspect of this embodiment, R⁷ of Formula II is H, -C(=O)R¹¹, -C(=O)OR¹¹ or



. In another aspect of this embodiment, R⁷ of Formula II is H. In another aspect of this embodiment, R⁷ of Formula II is

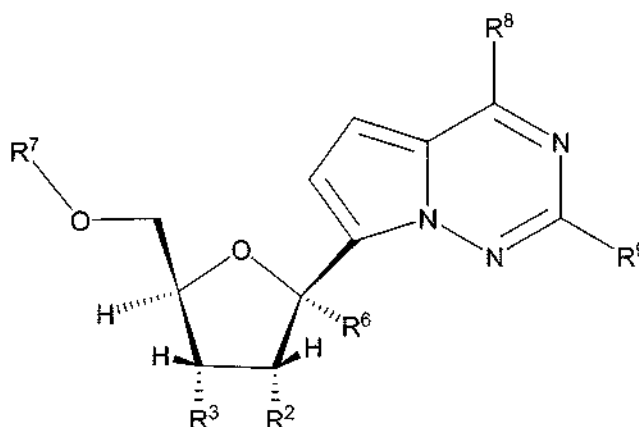


In another embodiment of the method of treating a *Paramyxoviridae* infection comprising administering a compound of Formula II, the *Paramyxoviridae* infection is caused by a *Paramyxovirina* virus. In another aspect of this embodiment, the *Paramyxovirina* virus is a parainfluenza, measles or

mumps virus. In another aspect of this embodiment, the *Paramyxovirina* virus is a *Respirovirus* virus. In another aspect of this embodiment, the *Paramyxovirina* virus is a type 1 or 3 Human parainfluenza virus.

In another embodiment of the method of treating a *Paramyxoviridae* infection comprising administering a compound of Formula II, the *Paramyxoviridae* infection is caused by a *Pneumovirinae* virus. In another aspect of this embodiment, the *Pneumovirinae* virus is a respiratory syncytial virus. In another aspect of this embodiment, the *Pneumovirinae* virus is a Human respiratory syncytial virus.

In another embodiment, provided is a method of treating a *Paramyxoviridae* infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I represented by Formula III:



Formula III

or a pharmaceutically acceptable salt or ester, thereof;
wherein:

each R^2 is OR^a or F;

each R^3 is OR^a ;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, $S(O)_n R^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-S(O)_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_i-C_g) substituted alkyl, (C_2-C_g) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, or (C_2-C_8) substituted alkynyl;

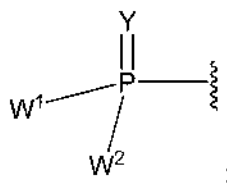
each n is independently 0, 1, or 2;

each R^a is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl(C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, -C(=O)R¹¹, -C(=O)OR¹¹, -

C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(0)R¹¹, -S(0)₂R¹¹, -S(0)(OR¹¹), -S(0)₂(OR¹¹), or

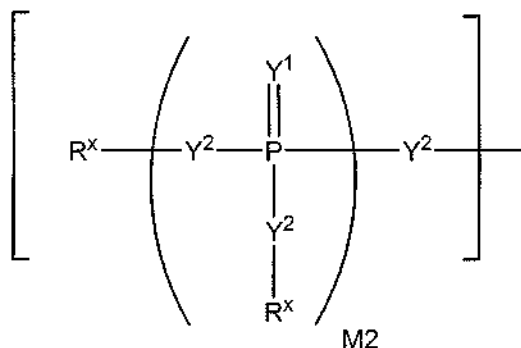
5 -S(0)₂NR¹¹R¹²;

R⁷ is H, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(0)R¹¹, -S(0)₂R¹¹, -S(0)(OR¹¹), -S(0)₂(OR¹¹), -S(0)₂NR¹¹R¹², or



each Y or Y¹ is, independently, O, S, NR, ⁺N(0)(R), N(OR), ⁺N(0)(OR),
10 or N-NR₂;

W¹ and W², when taken together, are -Y³(C(R^y)₂)₃Y³-; or one of W¹ or W² together with either R³ or R⁴ is -Y³- and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:



15 Formula Ia

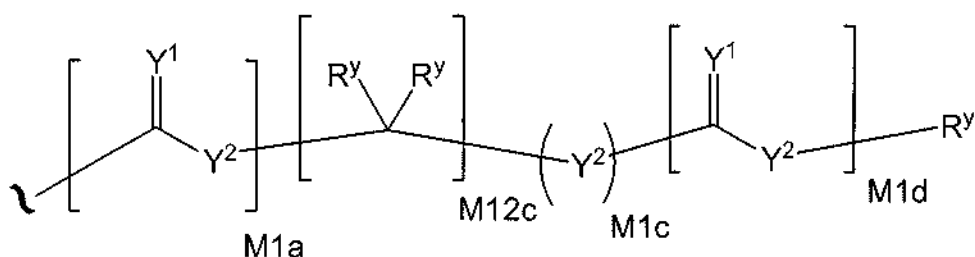
wherein:

each Y² is independently a bond, O, CR₂, NR, ⁺N(0)(R), N(OR), ⁺N(0)(OR), N-NR₂, S, S-S, S(O), or S(0)₂;

each Y³ is independently O, S, or NR;

20 M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

- 5 each R^y is independently H, F, Cl, Br, I, OH, R, $-C^{\wedge}Y^{\wedge}R$, $-C(=Y')OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y')R$, $-OC(=Y')O^{3/4}$, $-OC(=Y')(N(R)_2)$, $-SC(=Y')R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y')R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or when taken together, two R^y on the
- 10 same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (Q-Cg) alkyl, (Ci-C₈) substituted alkyl, (C₂-Cg)alkenyl, (C₂-C₈) substituted alkenyl, (C₂-Cg) alkynyl, (C₂-Cg) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

- 15 W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^{3/4})W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

- each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$,
- 20 $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (Ci-Cg)alkyl, (C₂-C₈)alkenyl, (C₂-Cg)alkynyl, (C₄-Cg)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_n(Ci-C_8)alkyl$, aryl(C₁-C₈)alkyl, OR^{11} or SR^{11} ;

- each R^9 is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$,
- 25 N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$,

$-\text{CH}(\text{OR}^{11})_2$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{S})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{OR}^{11}$, R^{11} , OR^{11} or SR^{11} ;

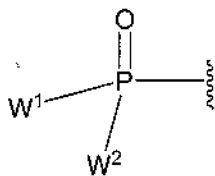
and

each R^{11} or R^{12} is independently H, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_4\text{-C}_8)\text{carbocyclylalkyl}$, optionally substituted aryl, optionally substituted heteroaryl, $-\text{C}(=\text{O})(\text{Ci-C}_8)\text{alkyl}$, $-\text{S}(0), (\text{Ci-C}_8)\text{alkyl}$ or aryl $(\text{Ci-C}_8)\text{alkyl}$; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a; and

wherein each $(\text{Ci-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$ or aryl $(\text{Ci-C}_8)\text{alkyl}$ of each R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said $(\text{Ci-C}_8)\text{alkyl}$ may be optionally replaced with -O-, -S- or -NR^a.

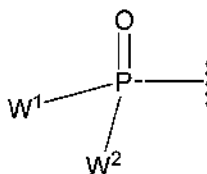
In one embodiment of the method of treating a *Paramyxoviridae* infection comprising administering a compound of Formula III, R^6 of Formula III is N₃, CN, halogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{Ci-C}_8)\text{substituted alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{substituted alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, or $(\text{C}_2\text{-C}_8)\text{substituted alkynyl}$. In another aspect of this embodiment, R^6 of Formula III is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 of Formula III is CN. In another aspect of this embodiment, R^6 of Formula III is methyl. In another aspect of this embodiment, R^2 of Formula III is OR^a. In another aspect of this embodiment, R^2 of Formula III is OH. In another aspect of this embodiment, R^2 of Formula III is F. In another aspect of this embodiment, R^3 of Formula III is OH, $-\text{OC}(=\text{O})\text{R}^{11}$, or $-\text{OC}(=\text{O})\text{OR}^{11}$. In another aspect of this embodiment, R^3 of Formula III is OH. In another aspect of this embodiment, R^8 of Formula III is $\text{NR}^{11}\text{R}^{12}$. In another aspect of this embodiment, R^8 of Formula III is NH₂. In another aspect of this embodiment, R^8 of Formula III is OR¹¹. In another aspect of this embodiment, R^8 of Formula III is OH. In another aspect of this embodiment, R^9 of Formula III is H. In another aspect of this embodiment, R^9 of Formula III is $\text{NR}^{11}\text{R}^{12}$. In another aspect of this embodiment, R^9 of Formula III is NH₂. In

another aspect of this embodiment, R^7 of Formula III is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$ or



. In another aspect of this embodiment, R^7 of Formula III is H.

In another aspect of this embodiment, R^7 of Formula III is



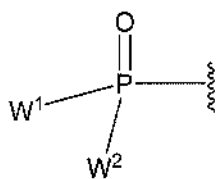
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In another embodiment of the method of treating a *Paramyxoviridae* infection comprising administering a compound of Formula III, R^6 of Formula III is N_3 , CN, halogen, (C_1-C_8) alkyl, (Ci-Cg)substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, or (C_2-C_8) substituted alkynyl and R^8 is NH_2 . In another aspect of this embodiment, R^6 of Formula III is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 of Formula III is CN. In another aspect of this embodiment, R^6 of Formula III is methyl. In another aspect of this embodiment, R^2 of Formula III is OR^a . In another aspect of this embodiment, R^2 of Formula III is OH, $-OC(=O)R^{11}$, or $-OC(=O)OR^{11}$. In another aspect of this embodiment, R^2 of Formula III is OH. In another aspect of this embodiment, R^2 of Formula III is F. In another aspect of this embodiment, R^3 of Formula III is OH, $-OC(=O)R^{11}$, or $-OC(=O)OR^{11}$. In another aspect of this embodiment, R^3 of Formula III is OH. In another aspect of this embodiment, R^9 of Formula III is H. In another aspect of this embodiment, R^9 of Formula III is $NR^{11}R^{12}$. In another aspect of this embodiment, R^9 of Formula III is $N^3/4$. In another aspect of this embodiment, R^7 of Formula III is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$ or

10

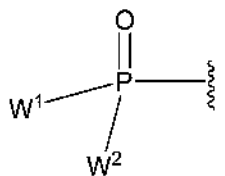
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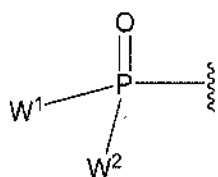
. In another aspect of this embodiment, R^7 of Formula III is H.

In another aspect of this embodiment, R^7 of Formula III is



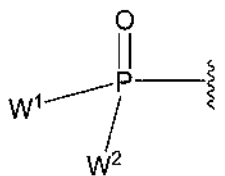
In another embodiment of the method of treating a *Paramyxoviridae*

- 5 infection comprising administering a compound of Formula III, R^6 of Formula III is CN, methyl, ethenyl, or ethynyl, R^8 is $N^{3/4}$, and R^9 is H. In another aspect of this embodiment, R^6 of Formula III is CN. In another aspect of this embodiment, R^6 of Formula III is methyl. In another aspect of this embodiment, R^2 of Formula III is OR^a . In another aspect of this embodiment, R^2 of Formula III is OH, -
- 10 $OC(=O)R^{11}$, or $-OC(=O)OR^{11}$. In another aspect of this embodiment, R^2 of Formula III is OH. In another aspect of this embodiment, R^2 of Formula III is F. In another aspect of this embodiment, R^3 of Formula III is OH, $-OC(=O)R^{11}$, or $-OC(=O)OR^{11}$. In another aspect of this embodiment, R^3 of Formula III is OH. In another aspect of this embodiment, R^7 of Formula III is H, $-C(=O)R^{11}$, -
- 15 $C(=O)OR^{11}$ or



. In another aspect of this embodiment, R^7 of Formula III is H.

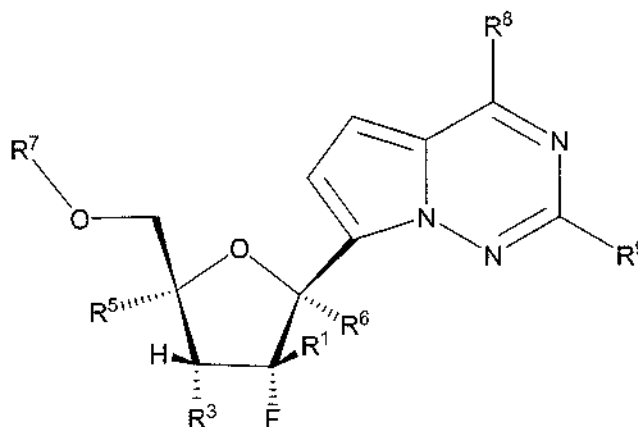
In another aspect of this embodiment, R^7 of Formula III is



In another embodiment of the method of treating a *Paramyxoviridae* infection comprising administering a compound of Formula III, the *Paramyxoviridae* infection is caused by a *Paramyxovirina* virus. In another aspect of this embodiment, the *Paramyxovirina* virus is a parainfluenza, measles or
 5 mumps virus. In another aspect of this embodiment, the *Paramyxovirina* virus is a *Respirovirus* virus. In another aspect of this embodiment, the *Paramyxovirina* virus is a type 1 or 3 Human parainfluenza virus.

In another embodiment of the method of treating a *Paramyxoviridae* infection comprising administering a compound of Formula III, the
 10 *Paramyxoviridae* infection is caused by a *Pneumovirinae* virus. In another aspect of this embodiment, the *Pneumovirinae* virus is a respiratory syncytial virus. In another aspect of this embodiment, the *Pneumovirinae* virus is a Human respiratory syncytial virus.

In one embodiment, provided is a compound of Formula IV:



Formula IV

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

20 each R^3 or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(0)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN , $S(0)_n R^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl,

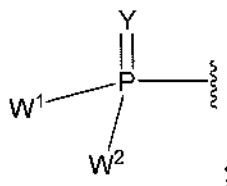
5 (C_2-C_8) alkynyl, or (C_2-C_8) substituted alkynyl;

each n is independently 0, 1, or 2;

each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, or

10 $-SO_2NR^{11}R^{12}$;

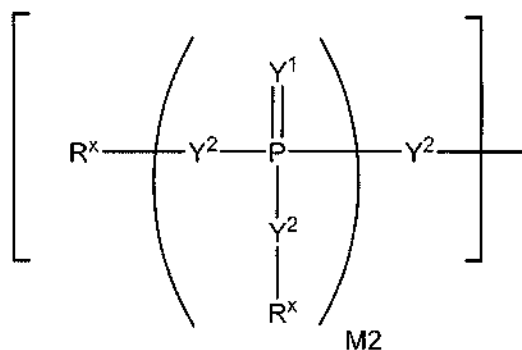
R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(0)R^{11}$, $-S(0)_2R^{11}$, $-S(0)(OR^{11})$, $-S(0)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



each Y or Y^1 is, independently, O, S, NR, $+N(0)(R)$, $N(OR)$, $+N(0)(OR)$,

15 or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:



Formula Ia

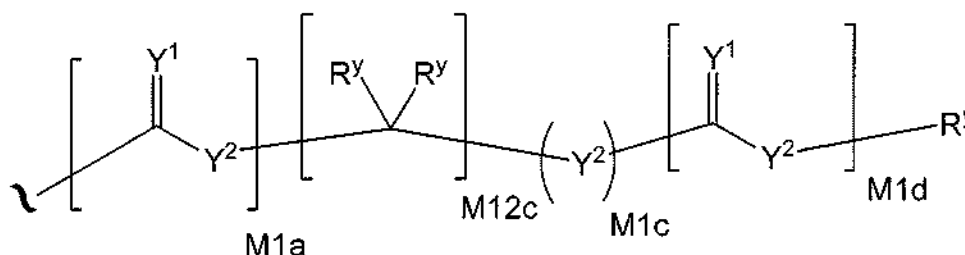
wherein:

each Y^2 is independently a bond, O, CR_2 , NR, $^+N(O)(R)$, $N(OR)$, $^+N(O)(OR)$, $N-NR_2$, S, S-S, $S(O)$, or $S(O)_2$;

each Y^3 is independently O, S, or NR;

M2 is 0, 1 or 2;

5 each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

10 each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $^+N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC^{\wedge}Y^{\wedge}R$, $-OC(=Y')OR$, $-OC(=Y')(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y')OR$, $-SC(=Y')(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y')OR$, $-N(R)C(=Y')N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or when taken together, two R^y on the

15 same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (Ci-C₈) alkyl, (Ci-C_g) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

20 W^3 is W^4 or W^5 ; W^4 is R, $-C(Y')R^y$, $-CCY^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (Ci-C_g)alkyl, (C₂-C₈) alkenyl, (C₂-C₈) alkynyl, (C₄-C₈) carbocyclalkyl, optionally substituted aryl, optionally

substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(0)_n(C_1-C_8)alkyl$, $aryl(C_1-C_8)alkyl$, OR^{11} or SR^{11} ;

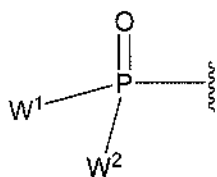
each R^9 is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$,

5 $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11} , OR^{11} or SR^{11} ;

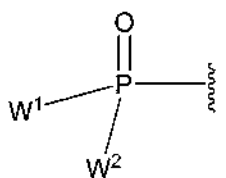
each R^{11} or R^{12} is independently H, **(C₁-C₈)alkyl**, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$, $(C_4-C_8)carbocyclylalkyl$, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(0)_n(C_1-C_8)alkyl$ or **aryl(C₁-C₈)alkyl**; or R^{11} and R^{12} taken together with a nitrogen to which they are both
10 attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a; and

wherein each $(C_1-C_8)alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)alkynyl$ or $aryl(C_1-C_8)alkyl$ of each R^3 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and wherein one or more
15 of the non-terminal carbon atoms of each said $(C_1-C_8)alkyl$ may be optionally replaced with -O-, -S- or -NR^a.

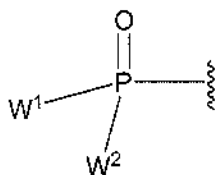
In one embodiment of the compound of Formula IV, R^6 is N_3 , CN, halogen, $(C_1-C_8)alkyl$, $(C_1-C_8)substituted alkyl$, $(C_2-C_8)alkenyl$, $(C_2-C_8)substituted alkenyl$, $(C_2-C_8)alkynyl$, or $(C_2-C_8)substituted alkynyl$. In
20 another aspect of this embodiment, R^6 is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is CN. In another aspect of this embodiment, R^6 is methyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^3 is OH, $-OC(=O)R^{11}$, or $-OC(=O)OR^{11}$. In another aspect of this embodiment, R^3 is OH. In another aspect of this
25 embodiment, R^8 is $NR^{11}R^{12}$. In another aspect of this embodiment, R^8 is NH_2 . In another aspect of this embodiment, R^8 is OR^{11} . In another aspect of this embodiment, R^8 is OH. In another aspect of this embodiment, R^9 is H. In another aspect of this embodiment, R^9 is $NR^{11}R^{12}$. In another aspect of this embodiment, R^9 is NH_2 . In another aspect of this embodiment, R^7 is H, $-C(=O)R^{11}$, -
30 $C(=O)OR^{11}$ or



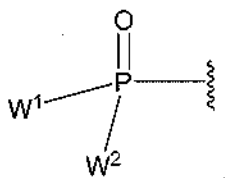
. In another aspect of this embodiment, R^7 is H. In another aspect of this embodiment, R^1 is



- In another embodiment of a compound of Formula IV, R^6 is N_3 , CN, halogen, (C_1-C_8) alkyl, (Ci-Cg)substituted alkyl, (C_2-Cg) alkenyl, (C_2-Cg) substituted alkenyl, (C_2-Cg) alkynyl, or (C_2-Cg) substituted alkynyl and R^8 is NH_2 . In another aspect of this embodiment, R^6 is CN, methyl, ethenyl, or ethynyl. In another aspect of this embodiment, R^6 is CN. In another aspect of this embodiment, R^6 is methyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^3 is OH, $-OC(=O)R^{11}$, or $-OC(=O)OR^{11}$. In another aspect of this embodiment, R^3 is OH. In another aspect of this embodiment, R^9 is H. In another aspect of this embodiment, R^9 is $NR^{11}R^{12}$. In another aspect of this embodiment, R^9 is NH_2 . In another aspect of this embodiment, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$ or

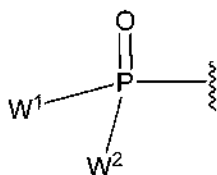


- . In another aspect of this embodiment, R^7 is H. In another aspect of this embodiment, R^7 is

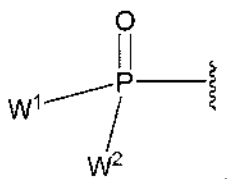


- In another embodiment of the compound of Formula IV, R^6 is CN, methyl, ethenyl, or ethynyl, R^8 is $N\frac{3}{4}$, and R^9 is H. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^6 is CN. In another aspect of this

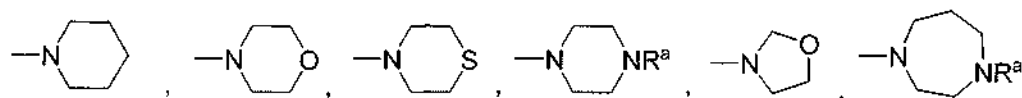
embodiment, R^6 is methyl. In another aspect of this embodiment, R^3 is OH, -OC(=O) R^{11} , or -OC(=O)OR¹¹. In another aspect of this embodiment, R^3 is OH. In another aspect of this embodiment, R^7 is H, -C(=O) R^{11} , -C(=O)OR¹¹ or



. In another aspect of this embodiment, R^7 is H. In another aspect of this embodiment, R^7 is



In another embodiment, provided is a method of treating a *Paramyxoviridae* infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formulas I-IV, wherein R^{11} or R^{12} is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈)alkyl, -S(O)_n(C₁-C₈)alkyl or aryl(d-C₈)alkyl. In another embodiment, R^{11} and R^{12} taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a. Therefore, by way of example and not limitation, the moiety -NR¹¹R¹² can be represented by the heterocycles:



and the like.

In another embodiment, provided is a method of treating a *Paramyxoviridae* infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I-IV, wherein each R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl, wherein said (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-

(C₈)alkynyl or aryl(Ci-Cs)alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a. Therefore, by way of example and not limitation, R³, R⁴, R⁵, R⁶, R¹¹ or R¹² could represent moieties such as -

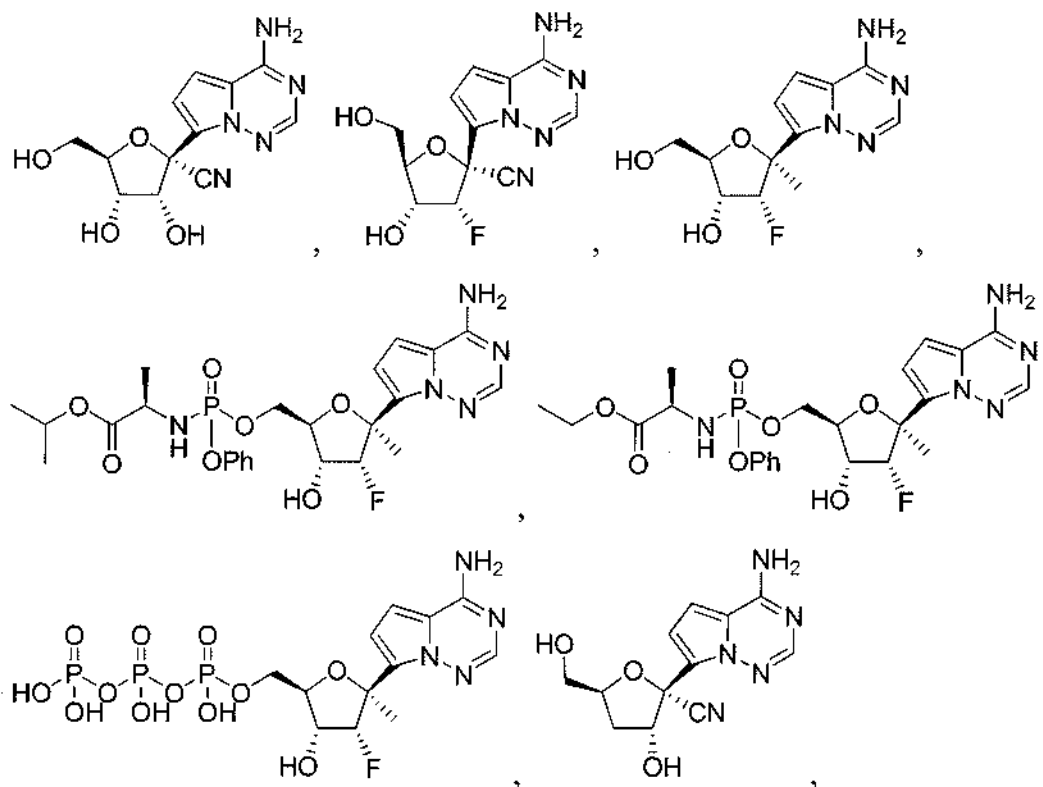
CH(NH₂)CH₃, -CH(OH)CH₂CH₃, -CH(NH₂)CH(CH₃)₂, -CH₂CF₃, -

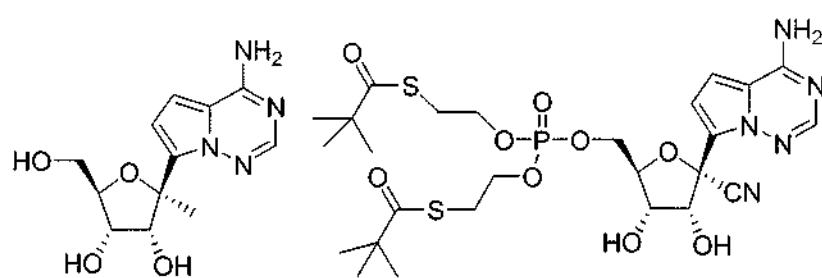
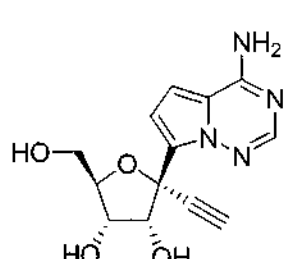
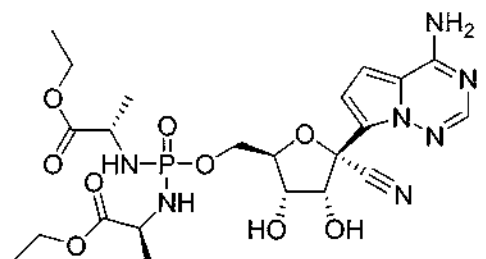
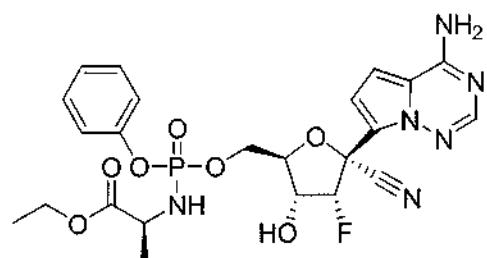
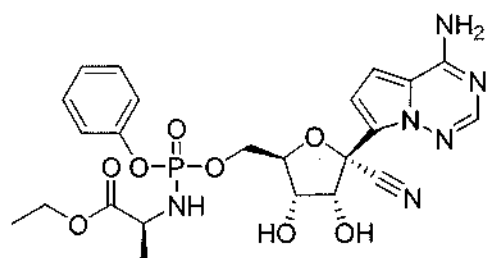
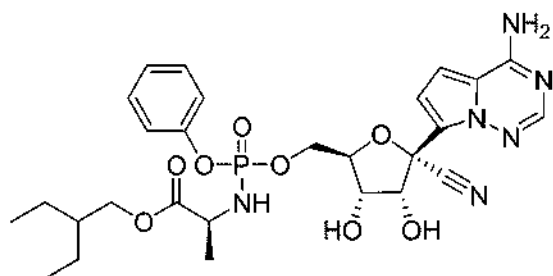
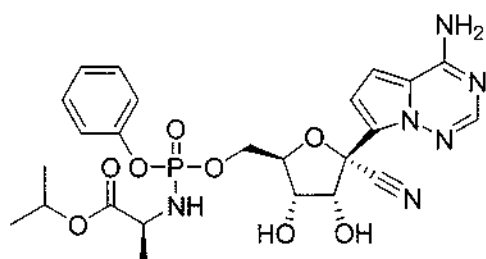
5 (CH₂)₂CH(N₃)CH₃, -(CH₂)₆NH₂ and the like.

In another embodiment, provided is a method of treating a *Paramyxoviridae* infection in a mammal in need thereof comprising administering a therapeutically effective amount of a compound of Formula I-IV, wherein R³, R⁴, R⁵, R⁶, R¹¹ or R¹² is (Ci-C₈)alkyl wherein one or more of the non-terminal

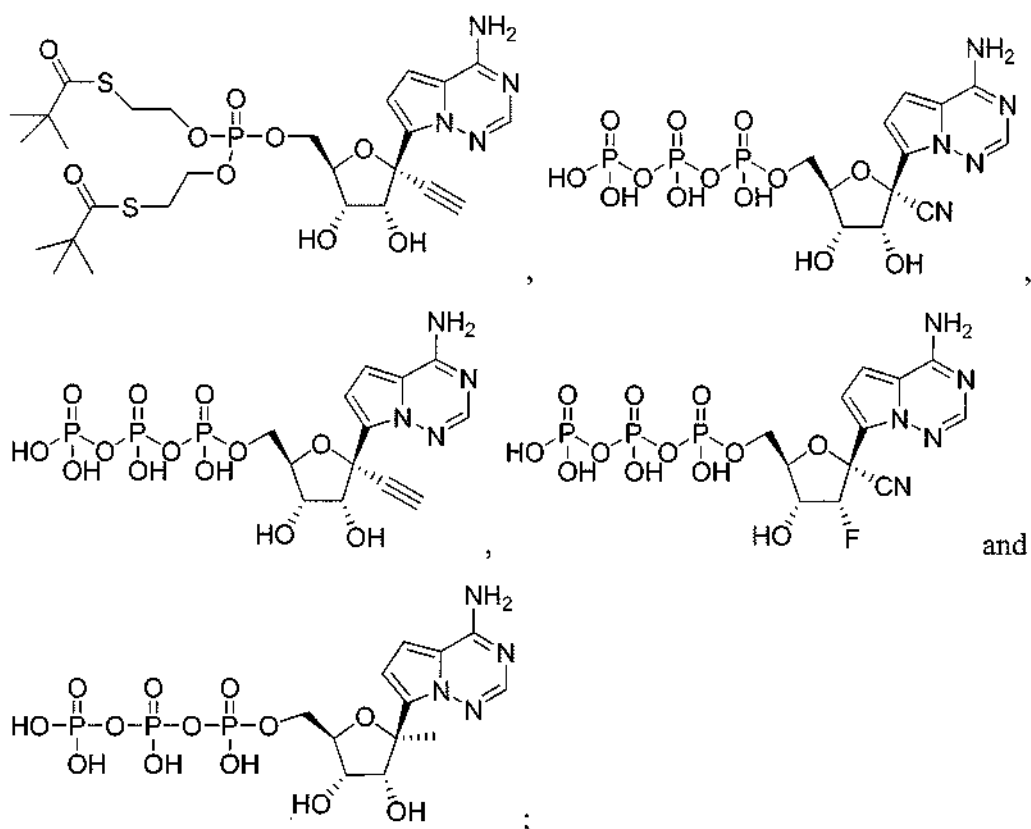
10 carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a-. Therefore, by way of example and not limitation, R³, R⁴, R⁵, R⁶, R¹¹ or R¹² could represent moieties such as -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂OCH(CH₃)₂, -CH₂SCH₃, -(CH₂)₆OCH₃, -(CH₂)₆N(CH₃)₂ and the like.

In another embodiment, provided is a method of treating a
15 *Paramyxoviridae* infection in a sample comprising administering an effective amount of a compound of Formula I selected from the group consisting of:



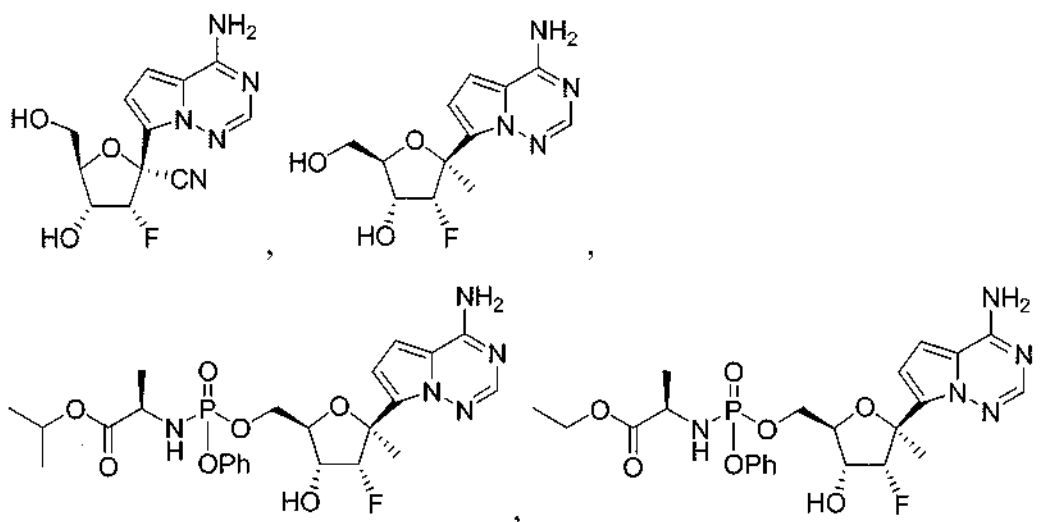


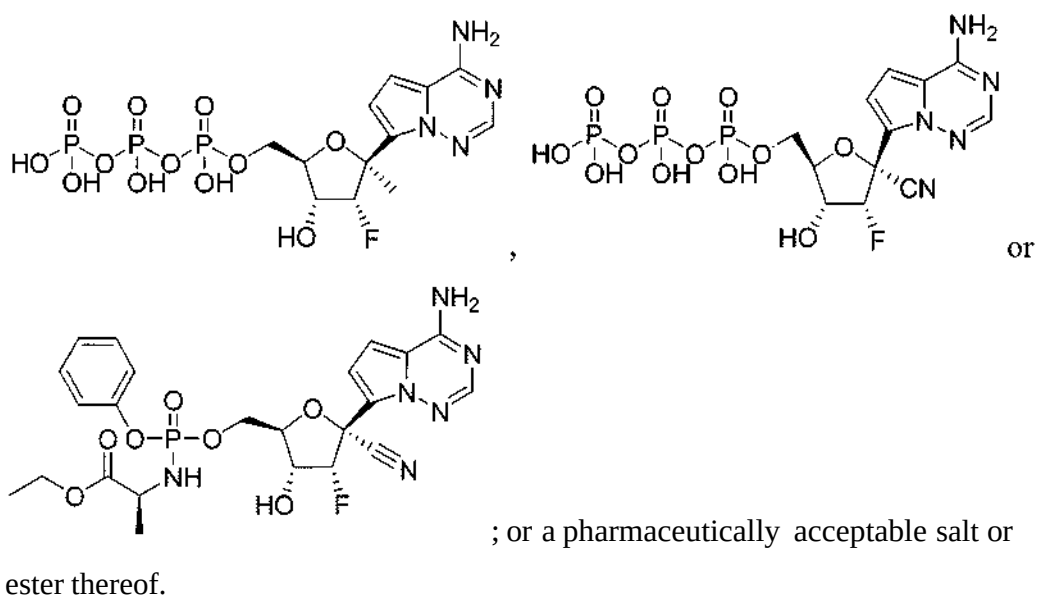
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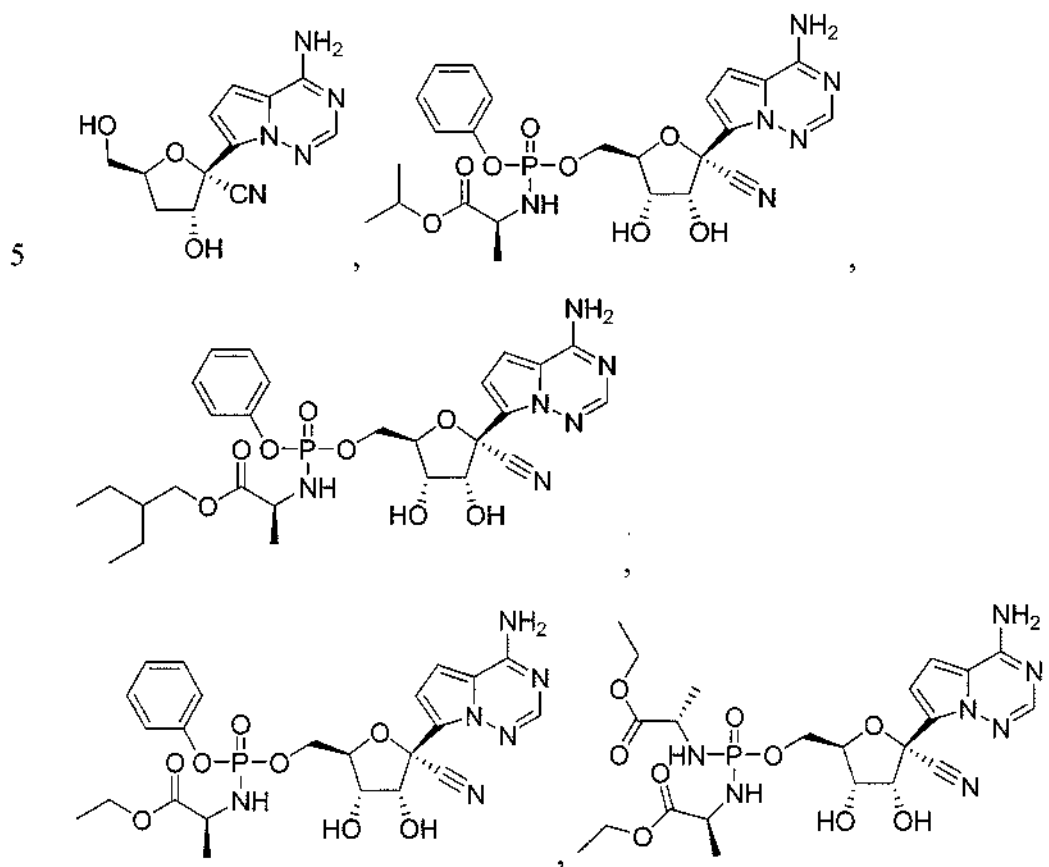
or a pharmaceutically acceptable salt or ester thereof.

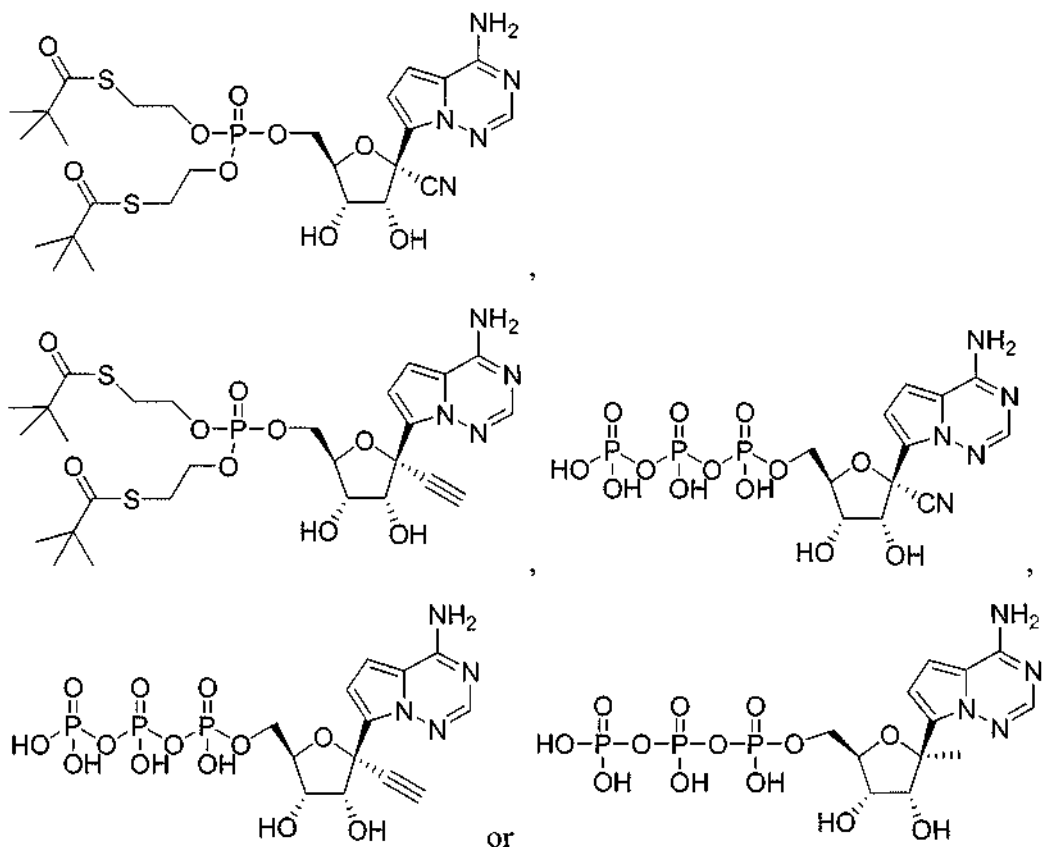
5 In another embodiment, provided is a compound of Formula IV that is





In another embodiment, provided is a compound of Formula I that is





or a pharmaceutically acceptable salt or ester thereof.

5

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

10 When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

As used herein, "a compound of the invention" or "a compound of Formula I" means a compound of Formula I or a pharmaceutically acceptable salt, thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

"Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic

carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkyl), 1 to 8 carbon atoms (*i.e.*, C₁-C₈ alkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃),
 5 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃),
 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl,
 -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH₃)₃), 1-pentyl (n-
 pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl
 (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl
 10 (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl
 (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl
 (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₃)CH(CH₃)(CH₂CH₂CH₃)), 2-methyl-2-
 pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃),
 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-
 15 C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-
 2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl
 (-CH₂)₇CH₃).

"Alkoxy" means a group having the formula -O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom.
 20 The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH₃ or -OMe), ethoxy (-OCH₂CH₃ or -OEt), t-butoxy (-O-C(CH₃)₃ or -OtBu) and the like.

25 "Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ haloalkyl). Examples of suitable haloalkyl groups include, but are
 30 not limited to, -CF₃, -CHF₂, -CFH₂, -CH₂CF₃, and the like.

"Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, sp^2 double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.*, C_2 - C_{20} alkenyl), 2 to 8 carbon atoms (*i.e.*, C_2 - C_8 alkenyl), or 2 to 6 carbon atoms (*i.e.*, C_2 - C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2CH_2CH_2CH_2CH=CH_2$).

"Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.*, C_2 - C_{20} alkynyl), 2 to 8 carbon atoms (*i.e.*, C_2 - C_8 alkyne), or 2 to 6 carbon atoms (*i.e.*, C_2 - C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$), 1,1-ethyl ($-CH(CH_3)-$), 1,2-ethyl ($-CH_2CH_2-$), 1,1-propyl ($-CH(CH_2CH_3)-$), 1,2-propyl ($-CH_2CH(CH_3)-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, an alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene ($-CH=CH-$).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10

carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene ($-G\equiv C-$), propargyl ($-\text{CH}_2\text{C}\equiv\text{C}-$), and 4-pentynyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-$).

"Amino" refers generally to a nitrogen radical which can be considered a derivative of ammonia, having the formula $-\text{N}(\text{X})_2$, where each "X" is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, etc. The hybridization of the nitrogen is approximately sp^3 . Nonlimiting types of amino include $-\text{NH}_2$, $-\text{N}(\text{alkyl})_2$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{carbocyclyl})_2$, $-\text{NH}(\text{carbocyclyl})$, $-\text{N}(\text{heterocyclyl})_2$, $-\text{NH}(\text{heterocyclyl})$, $-\text{N}(\text{aryl})_2$, $-\text{NH}(\text{aryl})$, $-\text{N}(\text{alkyl})(\text{aryl})$, $-\text{N}(\text{alkyl})(\text{heterocyclyl})$, $-\text{N}(\text{carbocyclyl})(\text{heterocyclyl})$, $-\text{N}(\text{aryl})(\text{heteroaryl})$, $-\text{N}(\text{alkyl})(\text{heteroaryl})$, etc. The term "alkylamino" refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino groups include $-\text{NH}_2$, $-\text{NH}(\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{NH}(\text{phenyl})$, $-\text{N}(\text{phenyl})_2$, $-\text{NH}(\text{benzyl})$, $-\text{N}(\text{benzyl})_2$, etc. Substituted alkylamino refers generally to alkylamino groups, as defined above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes $-\text{NH}(\text{alkylene-C}(0)\text{-OH})$, $-\text{NH}(\text{alkylene-C}(0)\text{-O-alkyl})$, $-\text{N}(\text{alkylene-C}(0)\text{-OH})_2$, $-\text{N}(\text{alkylene-C}(0)\text{-O-alkyl})_2$, etc.

"Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can

comprise 7 to 20 carbon atoms, *e.g.*, the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 8 to 20 carbon atoms, *e.g.*, the alkenyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 8 to 20 carbon atoms, *e.g.*, the alkynyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, $-X$, $-R^b$, $-O^-$, $=O$, $-OR^b$, $-SR^b$, $-S^-$, $-NR^b_2$, $-N^+R^b_3$, $=NR^b$, $-CX_3$, $-CN$, $-OCN$, $-SCN$, $-N=O$, $-NCS$, $-NO$, $-NO_2$, $=N_2$, $-N_3$, $-NHC(=O)R^b$, $-OC(=O)R^b$, $-NHC(=O)NR^b_2$, $-S(=O)_2^-$, $-S(=O)_2OH$, $-S(=O)_2R^b$, $-OS(=O)_2OR^b$, $-S(=O)_2NR^b_2$, $-S(=O)R^b$, $-OP(=O)(OR^b)_2$, $-P(=O)(OR^b)_2$, $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, $-P(O)(OR^b)(O^-)$, $-C(=O)R^b$, $-C(=O)X$, $-C(S)R^b$, $-C(O)OR^b$, $-C(O)O^-$, $-C(S)OR^b$, $-C(O)SR^b$, $-C(S)SR^b$, $-C(O)NR^b_2$, $-C(S)NR^b_2$, $-C(=NR^b)NR^b_2$, where each X is independently a halogen: F, Cl, Br, or I; and each

R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups such as arylalkyl, which have two or more moieties
5 capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

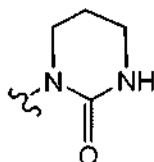
The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed
10 chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-IV should be selected in order to provide a compound
15 which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I-IV which have such stability are contemplated as falling within the scope of the present invention.

"Heteroalkyl" refers to an alkyl group where one or more carbon atoms have
20 been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., -OCH₃, etc.), an amine (e.g., -NHCH₃, -N(CH₃)₂, etc.), or a thioalkyl group (e.g., -SCH₃). If a non-terminal carbon atom of the alkyl group
25 which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., -CH₂CH₂-O-CH₃, etc.), an alkyl amine (e.g., -CH₂NHCH₃, -CH₂N(CH₃)₂, etc.), or a thioalkyl ether (e.g., -CH₂-S-CH₃). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are,
30 respectively, a hydroxyalkyl group (e.g., -CH₂CH₂-OH), an aminoalkyl group (e.g., -CH₂NH₂), or an alkyl thiol group (e.g., -CH₂CH₂-SH). A heteroalkyl group can

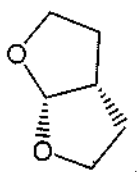
have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C₁-C₆ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more {e.g. 1, 2, 3, or 4} carbon atoms have been replaced with a heteroatom (e.g. O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings, partially unsaturated rings, and aromatic rings (i.e., heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinoliny, isoquinoliny, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, octahydroisoquinoliny, azociny, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl,

- indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl,
- 5 isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolyl, isatinoyl, and bis-tetrahydrofuranyl:



- 10 By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or
- 15 thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl,
- 20 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

- By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole,
- 25 pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-

pyrazolyl, and 1-piperidinyl.

"Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkylene- moiety).

- 5 Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl- CH_2 -, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl
- 10 portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of
- 15 example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolyloethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl,
- 20 pyrimidinylmethyl, pyrazinylmethyl, etc.

- "Heterocyclylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also a sp^2 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkenylene- moiety). The heterocyclyl portion of the heterocyclyl
- 25 alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means
- 30 of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkenyl group comprises 4

to 20 carbon atoms, *e.g.*, the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

"Heterocyclalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkynylene- moiety). The heterocyclyl portion of the heterocyclalkynyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocyclalkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclalkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclalkynyl group comprises 4 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocyclalkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

"Heteroaryl" refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those aromatic rings listed in the definition of "heterocyclyl", including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

"Carbocycle" or "carbocyclyl" refers to a saturated (*i.e.*, cycloalkyl), partially unsaturated (*e.g.*, cycloalkenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 7 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as abicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl,

cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl, tetrahydronaphthalene, and decaline.

5 "Carbocyclylalkyl" refers to to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein. Typical, but non-limiting, examples of carbocyclylalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

10 "Arylheteroalkyl" refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a
15 chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

20 "Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-purinyl, -CH₂-furanyl, -CH₂-thienyl, -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl,
25 -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-purinyl, -CH(CH₃)-furanyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranyl,
30 -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl,

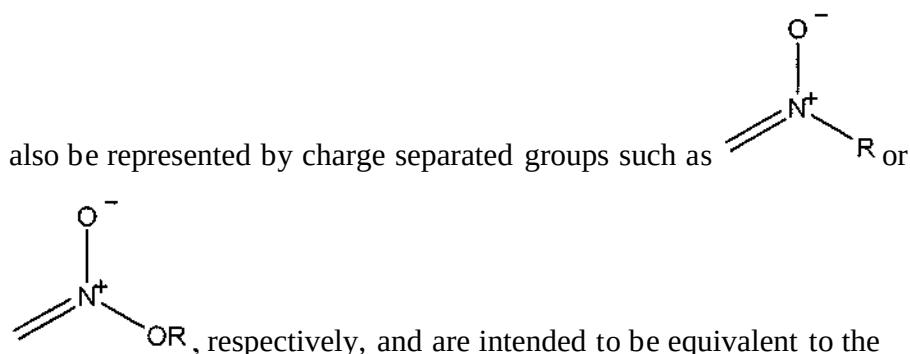
-CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl,
-CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-pyrazyl, etc.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula I-III (e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by substituents such as those listed under the definition of "substituted".

The term "optionally replaced" in reference to a particular moiety of the compound of Formula I-III (e.g., the carbon atoms of said (C₁-C₈)alkyl may be optionally replaced by -O-, -S-, or -NR^a-) means that one or more of the methylene groups of the (C_i-C₈)alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., -O-, -S-, or -NR^a-).

The term "non-terminal carbon atom(s)" in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkynylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl moiety -CH₂(C*)H₂(C*)H₂CH₃ or alkylene moiety -CH₂(C*)H₂(C*)H₂CH₂- the C* atoms would be considered to be the non-terminal carbon atoms.

Certain Y and Y¹ alternatives are nitrogen oxides such as ⁺N(0)(R) or ⁺N(0)(OR). These nitrogen oxides, as shown here attached to a carbon atom, can



aforementioned representations for the purposes of describing this invention.

"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms. Linkers include repeating units of alkyloxy (e.g.

polyethyleneoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

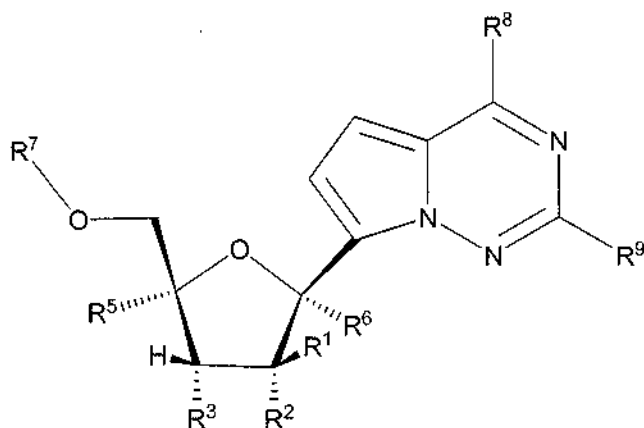
The terms such as "oxygen-linked", "nitrogen-linked", "carbon-linked", "sulfur-linked", or "phosphorous-linked" mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, a nitrogen-linked amino acid would be bonded through a nitrogen atom of the amino acid rather than through an oxygen or carbon atom of the amino acid.

In some embodiments of the compounds of Formula I-IV, one or more of W¹ or W² are independently a radical of a nitrogen-linked naturally occurring amino acid ester. Examples of naturally occurring amino acids include isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, selenocysteine, serine, tyrosine, arginine, histidine, ornithine and taurine. The esters of these amino acids comprise any of those described for the substituent R, particularly those in which R is optionally substituted (C₁-C₈)alkyl.

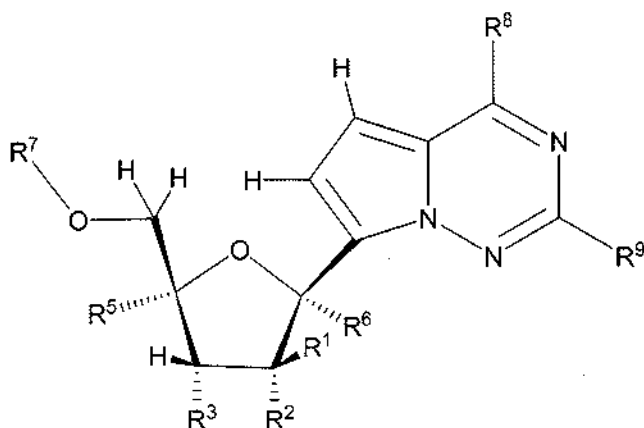
The term "purine" or "pyrimidine" base comprises, but is not limited to, adenine, N⁶-alkylpurines, N⁶-acylpurines (wherein acyl is C(=O)(alkyl, aryl, alkylaryl, or arylalkyl), N⁶-benzylpurine, N⁶-halopurine, N⁶-vinylpurine, N⁶-acetylenic purine, N⁶-acyl purine, N⁶-hydroxyalkyl purine, N⁶-allylaminopurine, N⁶-thioallyl purine, N²-alkylpurines, N²-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, 5-halouracil, including 5-fluorouracil, C⁵-alkylpyrimidines, C⁵-benzylpyrimidines, C⁵-halopyrimidines, C⁵-vinylpyrimidine, C⁵-acetylenic pyrimidine, C⁵-acyl pyrimidine, C⁵-hydroxyalkyl purine, C⁵-amidopyrimidine, C⁵-cyanopyrimidine, C⁵-5-iodopyrimidine, C⁶-iodo-pyrimidine, C⁵-Br-vinyl pyrimidine, C⁶-Br-vinyl pyrimidine, C⁵-nitropyrimidine, C⁵-amino-pyrimidine, N²-alkylpurines, N²-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracil, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine,

adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. The purine and pyrimidine bases of Formula I-III are linked to the ribose sugar, or analog thereof, through a nitrogen atom of the base. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyldimethylsilyl, and t-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

Unless otherwise specified, the carbon atoms of the compounds of Formula I-IV are intended to have a valence of four. In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen. For example,



has the same meaning as



"Protecting group" refers to a moiety of a compound that masks or alters

the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

"Prodrug moiety" means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and

Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{30}$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^{30}$ where R^{30} is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ substituted alkyl, $\text{C}_6\text{-C}_{20}$ aryl or $\text{C}_6\text{-C}_{20}$ substituted aryl. The acyloxyalkyl ester was used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also- US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphate group. The acyloxyalkyl ester may be used to deliver phosphoric acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

The phosphate group may be a phosphate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to those comprising a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphoramidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been

described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-41 15). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho-ov*para-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C-O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans.* 72345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I-IV and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

A compound of Formula I-IV and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the

ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I-III and their pharmaceutically acceptable salts.

A compound of Formula I-IV and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula I-IV and their pharmaceutically acceptable salts.

Selected substituents comprising the compounds of Formula I-IV are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of compounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R . R can be W^3 . W^3 can be W^4 and W^4 can be R or comprise substituents comprising R^y . One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3 and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each recursive substituent can independently occur 12 or fewer times in a given embodiment. Even more

typically, each recursive substituent can independently occur 3 or fewer times in a given embodiment. For example, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

5 Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

10 The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

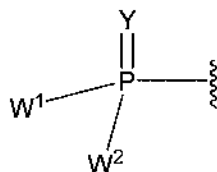
 The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or
15 condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

 The term "therapeutically effective amount", as used herein, is the amount of compound of Formula I-IV present in a composition described herein that is
20 needed to provide a desired level of drug in the secretions and tissues of the airways and lungs, or alternatively, in the bloodstream of a subject to be treated to give an anticipated physiological response or desired biological effect when such a composition is administered by the chosen route of administration. The precise amount will depend upon numerous factors, for example the particular compound
25 of Formula I-IV, the specific activity of the composition, the delivery device employed, the physical characteristics of the composition, its intended use, as well as patient considerations such as severity of the disease state, patient cooperation, etc., and can readily be determined by one skilled in the art based upon the information provided herein.

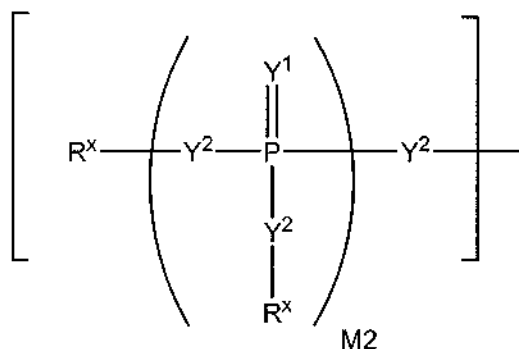
30 The term "normal saline" means a water solution containing 0.9% (w/v) NaCl.

The term "hypertonic saline" means a water solution containing greater than 0.9% (w/v) NaCl. For example, 3% hypertonic saline would contain 3% (w/v) NaCl.

The compounds of the Formula I-IV may comprise a phosphate group as



- 5 R^7 , which may be a prodrug moiety wherein each Y or Y^1 is, independently, O, S, NR, $^+N(0)(R)$, $N(OR)$, $^+N(0)(OR)$, or $N-NR_2$; W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of Formula Ia:



10

wherein:

each Y^2 is independently a bond, O, CR_2 , NR, $^+N(0)(R)$, $N(OR)$, $^+N(0)(OR)$, $N-NR_2$, S, S-S, S(O), or $S(0)_2$;

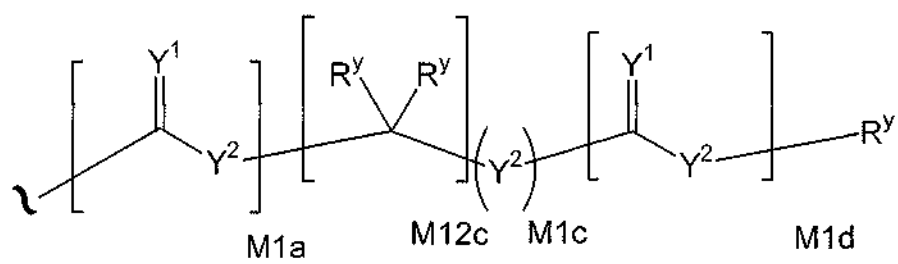
each Y^3 is independently O, S, or NR;

- 15 M2 is 0, 1 or 2;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $^+N(R)_3$, $-SR$, $-S(0)R$, $-S(0)_2R$, $-S(0)(OR)$, $-S(0)_2(OR)$, $-OC^{\wedge}Y^{\wedge}R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, or $-N(R)C(=Y^1)N(R)_2$,

- 20 $-S(0)_2NR_2$, $-CN$, $-N_3$, $-N(0)_2$, $-OR$, a protecting group or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R^x is independently R^y , a protecting group, or the formula:



wherein:

M1a, M1c, and M1d are independently 0 or 1;

5 M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R is H, halogen, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocycle, C₂-C₂₀ substituted heterocyclyl, arylalkyl, substituted arylalkyl or a protecting group;

10 W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)R^y, -C(Y')W⁵, -SO₂R^y, or -SO₂W⁵; and W⁵ is a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups.

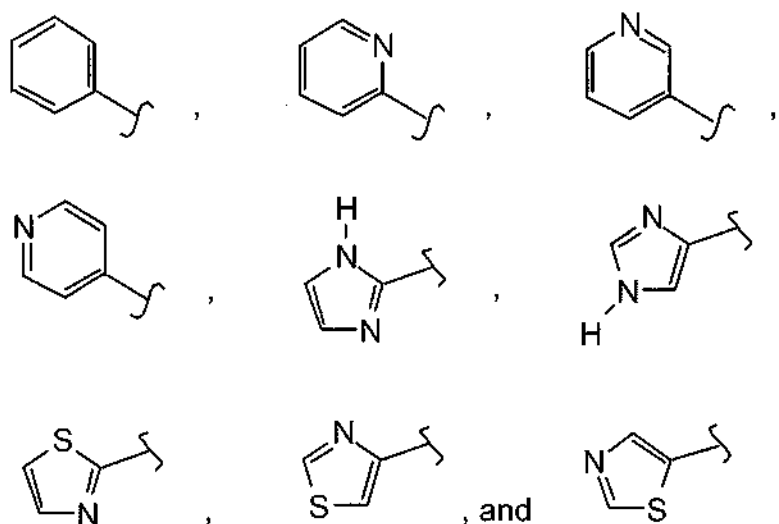
W⁵ carbocycles and W⁵ heterocycles may be independently substituted with 0 to 3 R^y groups. W⁵ may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W⁵ may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W⁵ rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

20 A W⁵ heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W⁵ heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S).
25 W⁵ heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2

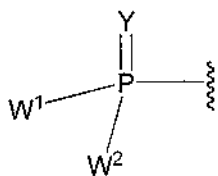
heteroatoms selected from N, O, and S) arranged as abicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W⁵ heterocycle may be bonded to Y² through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

W⁵ heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W⁵ also includes, but is not limited to, examples such as:

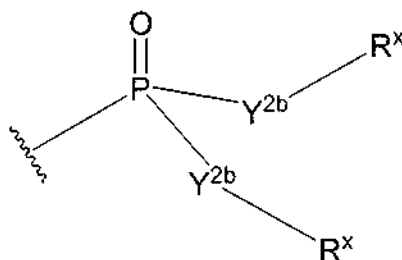
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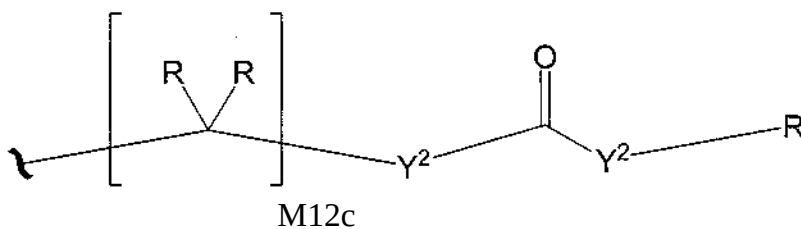
W⁵ carbocycles and heterocycles may be independently substituted with 0 to 3 R groups, as defined above. For example, substituted W⁵ carbocycles include:



Embodiments of of Formula I-IV compounds include substructures such as:

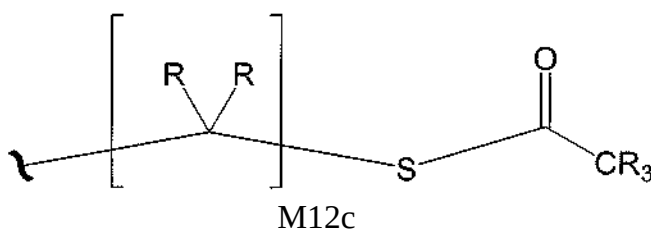


- 5 wherein each Y^{2b} is, independently, O or N(R). In another aspect of this embodiment, each Y^{2b} is O and each R^x is independently:

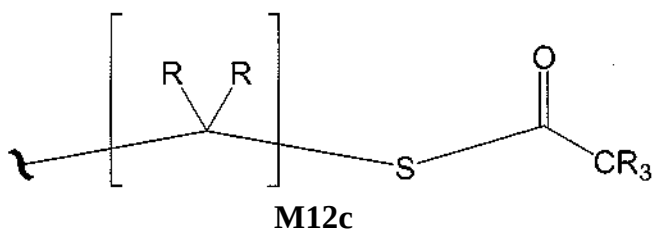


wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S. In another aspect of this embodiment, one $Y^{2b}-R^x$ is NH(R) and the other $Y^{2b}-R^x$ is

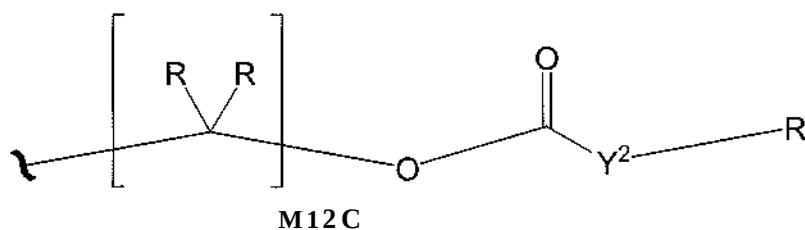
- 10 O- R^x wherein R^x is:



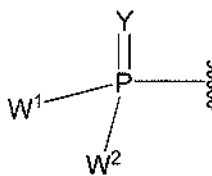
wherein M12c is 2. In another aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



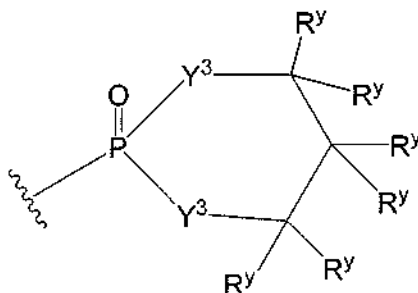
wherein M12c is 2. In another aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



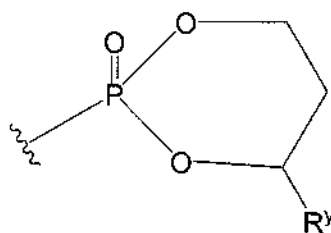
5 wherein M12c is 1 and Y^2 is a bond, O, or CR_2 .



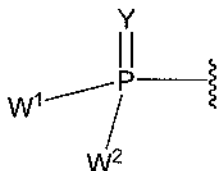
Other embodiments of of Formulas I-IV compounds include substructures such as:



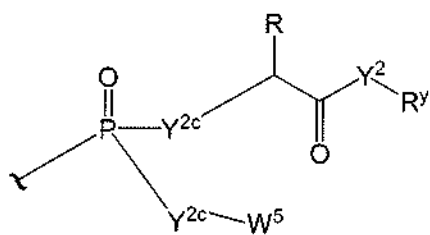
10 wherein each Y^3 is, independently, O or N(R). In another aspect of this embodiment, each Y^3 is O. In another aspect of this embodiment, the substructure is:



wherein R^y is W^5 as defined herein.

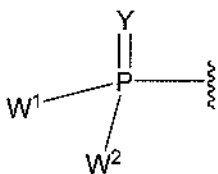


Another embodiment of of Formula I-IV includes the substructures:



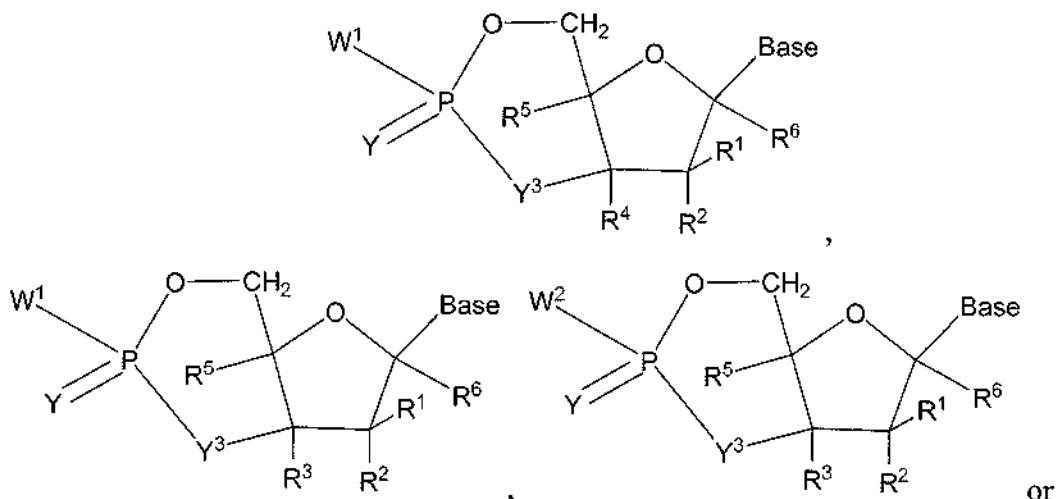
5

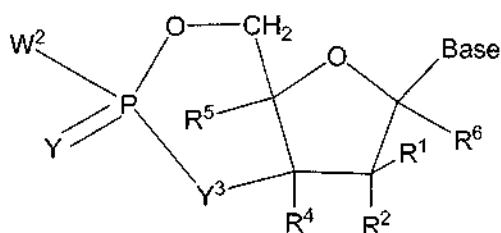
wherein each Y^{2c} is, independently, O, $N(R^y)$ or S.



Another embodiment of of Formula I-IV compounds includes the substructures wherein one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia. Such an embodiment is

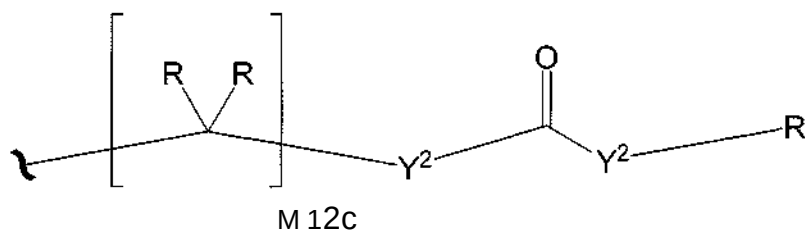
10 represented by a compound of Formula Ib selected from:



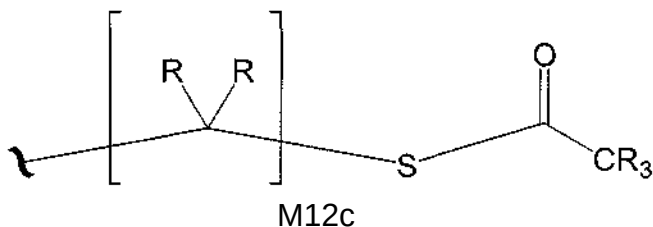


Formula lb

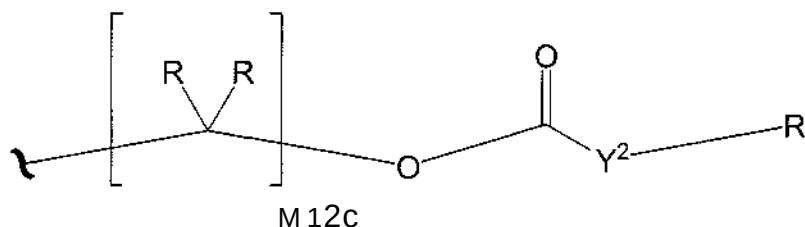
In another aspect of the embodiment of Formula lb, each Y and Y³ is O. In another aspect of the embodiment of Formula lb, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:



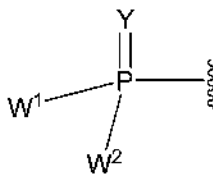
wherein M12c is 1, 2 or 3 and each Y² is independently a bond, O, CR₂, or S. In another aspect of the embodiment of Formula lb, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:



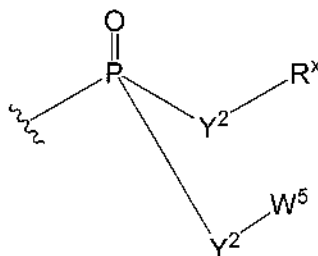
wherein M12c is 2. In another aspect of the embodiment of Formula lb, W¹ or W² is Y^{2b}-R^x; each Y, Y³ and Y^{2b} is O and R^x is:



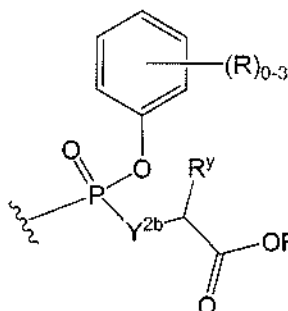
wherein M12c is 1 and Y² is a bond, O, or CR₂.



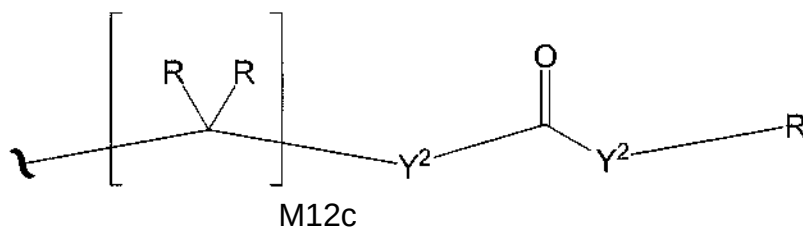
Another embodiment of of Formula I-IV compounds includes a substructure:



- 5 wherein W^5 is a carbocycle such as phenyl or substituted phenyl. In another aspect of this embodiment, the substructure is:

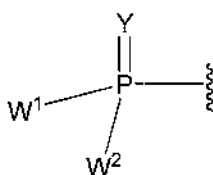


wherein Y^{2b} is O or N(R) and the phenyl carbocycle is substituted with 0 to 3 R groups. In another aspect of this embodiment of the substructure, R^x is:



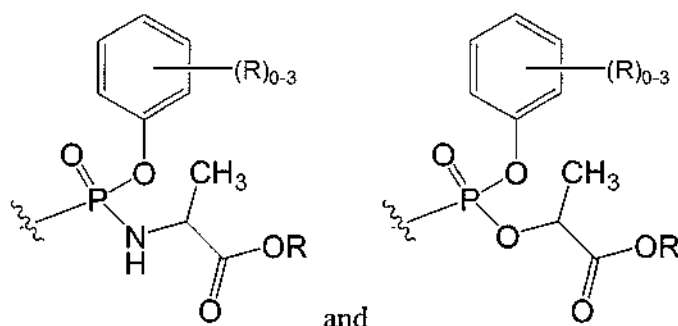
10

wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S.

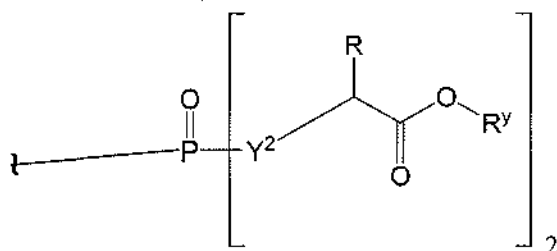
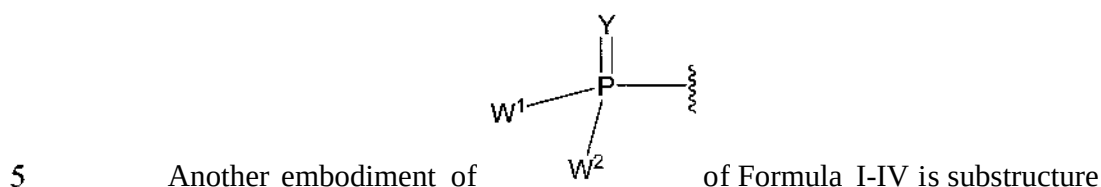


Another embodiment of of Formula I-IV includes

substructures:

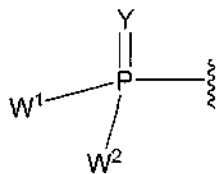


The chiral carbon of the amino acid and lactate moieties may be either the *R* or *S* configuration or the racemic mixture.

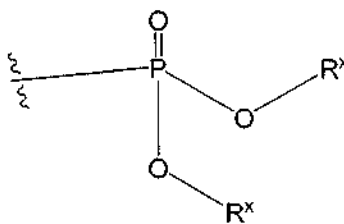


wherein each Y^2 is, independently, -O- or -NH-. In another aspect of this embodiment, R^y is (CrC₈) alkyl, (Ci-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl or (C₂-C₈) substituted alkynyl. In another aspect of this embodiment, R^y is (Ci-C₈) alkyl, (Ci-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl or (C₂-C₈) substituted alkynyl; and R is CH₃. In another aspect of this embodiment, R^y is (Ci-C₈) alkyl, (Ci-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl or (C₂-C₈) substituted alkynyl; R is CH₃; and each Y^2 is -NH-. In another aspect of this embodiment, W^1 and W^2 are, independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another aspect of this embodiment, W^1 and W^2 are, independently, naturally-

occurring 2-hydroxy carboxylic acids or naturally-occurring 2-hydroxy carboxylic acid esters wherein the acid or ester is linked to P through the 2-hydroxy group.

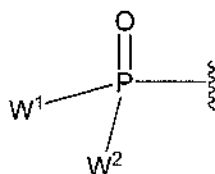


Another embodiment of of Formula I-IV is substructure:

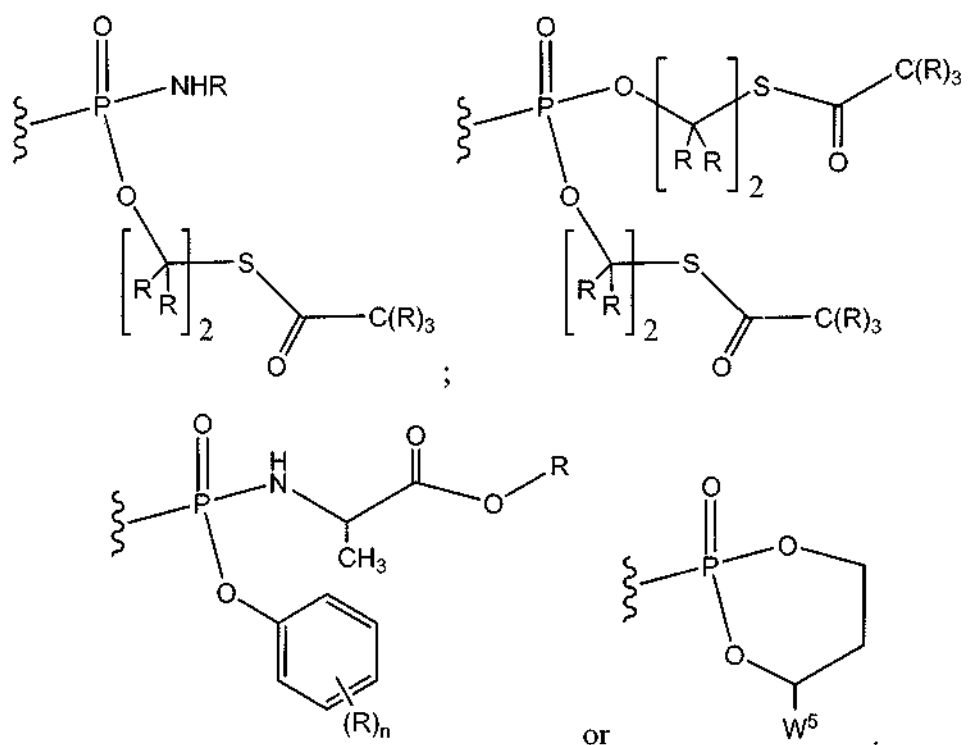


- 5 In one aspect of this embodiment, each R^x is, independently, (C_1-C_8) alkyl. In another aspect of this embodiment, each R^x is, independently, C_6-C_{20} aryl or C_6-C_{20} substituted aryl.

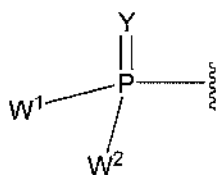
In a preferred embodiment,



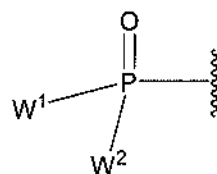
- 10 is selected from



Another embodiment of



of Formulas I-IV is substructure



5

wherein W^1 and W^2 are independently selected from one of the formulas in Tables 20.1-20.37 and Table 30.1 below. The variables used in Tables 20.1-20.37 (e.g., W^{23} , R^{21} , etc.) pertain only to Tables 20.1-20.37, unless otherwise indicated.

The variables used in Tables 20.1 to 20.37 have the following definitions:

10

each R^{21} is independently H or (Ci-Cg)alkyl;

each R^{22} is independently H, R^{21} , R^{23} or R^{24} wherein each R^{24} is independently substituted with 0 to 3 R^{23} ;

- each R^{23} is independently R^{23a} , R^{23b} , R^{23c} or R^{23d} , provided that when R^{23} is bound to a heteroatom, then R^{23} is R^{23c} or R^{23d} ;
- each R^{23a} is independently F, Cl, Br, I, -CN, N_3 or $-NO_2$;
- each R^{23b} is independently Y^{21} ;
- 5 each R^{23c} is independently $-R^{2x}$, $-N(R^{2x})(R^{2x})$, $-SR^{2x}$, $-S(O)R^{2x}$, $-S(O)_2R^{2x}$, $-S(O)(OR^{2x})$, $-S(O)_2(OR^{2x})$, $-OC(=Y^{21})R^{2x}$, $-OC(=Y^{21})OR^{2x}$, $-OC(=Y^{21})(N(R^{2x})(R^{2x}))$, $-SC(=Y^{21})R^{2x}$, $-SC(=Y^{21})OR^{2x}$, $-SC(=Y^{21})(N(R^{2x})(R^{2x}))$, $-N(R^{2x})C(=Y^{21})R^{2x}$, $-N(R^{2x})C(=Y^{21})OR^{2x}$, or $-N(R^{2x})C(=Y^{21})(N(R^{2x})(R^{2x}))$;
- each R^{23d} is independently $-C(=Y^{21})R^{2x}$, $-C(=Y^{21})OR^{2x}$ or $-C(=Y^{21})(N(R^{2x})(R^{2x}))$;
- 10 each R^{2x} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl, heteroaryl; or two R^{2x} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or $-NR^{21-}$; and
- 15 wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with -O-, -S- or $-NR^{21-}$;
- each R^{24} is independently (C_1-C_8) alkyl, (C_2-C_8) alkenyl, or (C_2-C_8) alkynyl;
- each R^{25} is independently R^{24} wherein each R^{24} is substituted with 0 to 3 R^{23} groups;
- 20 each R^{25a} is independently (C_1-C_8) alkylene, (C_2-C_8) alkenylene, or (C_2-C_8) alkynylene any one of which said (C_1-C_8) alkylene, (C_2-C_8) alkenylene, or (C_2-C_8) alkynylene is substituted with 0-3 R^{23} groups;
- each W^{23} is independently W^{24} or W^{25} ;
- each W^{24} is independently R^{25} , $-C(=Y^{21})R^{25}$, $-C(=Y^{21})W^{25}$, $-SO_2R^{25}$, or $-SO_2W^{25}$;
- 25 each W^{25} is independently carbocycle or heterocycle wherein W^{25} is independently substituted with 0 to 3 R^{22} groups; and
- each Y^{21} is independently O or S.

Table 20.1

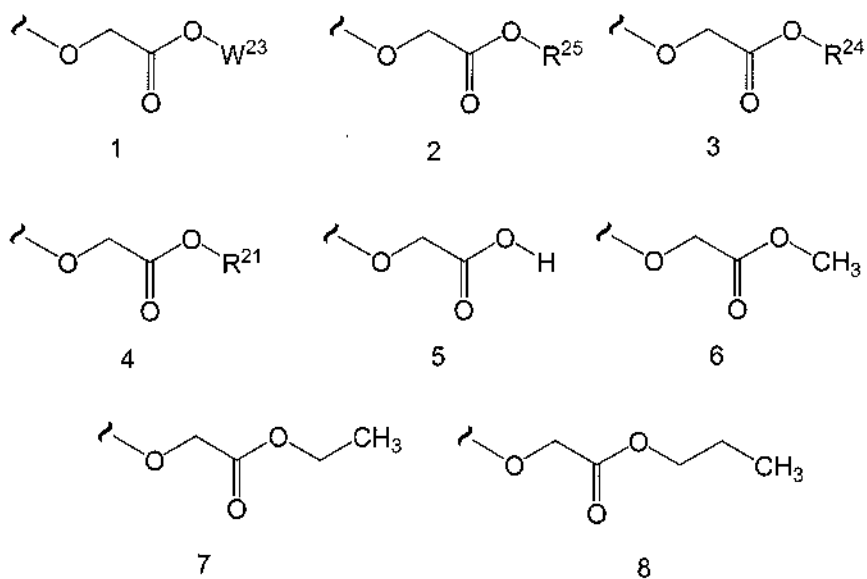


Table 20.2

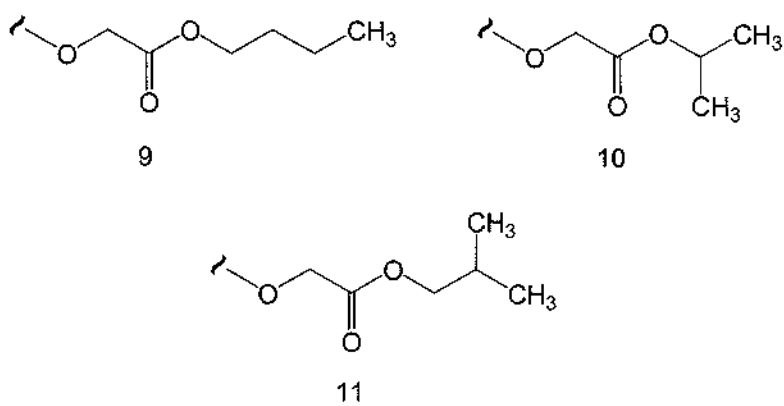


Table 20.3

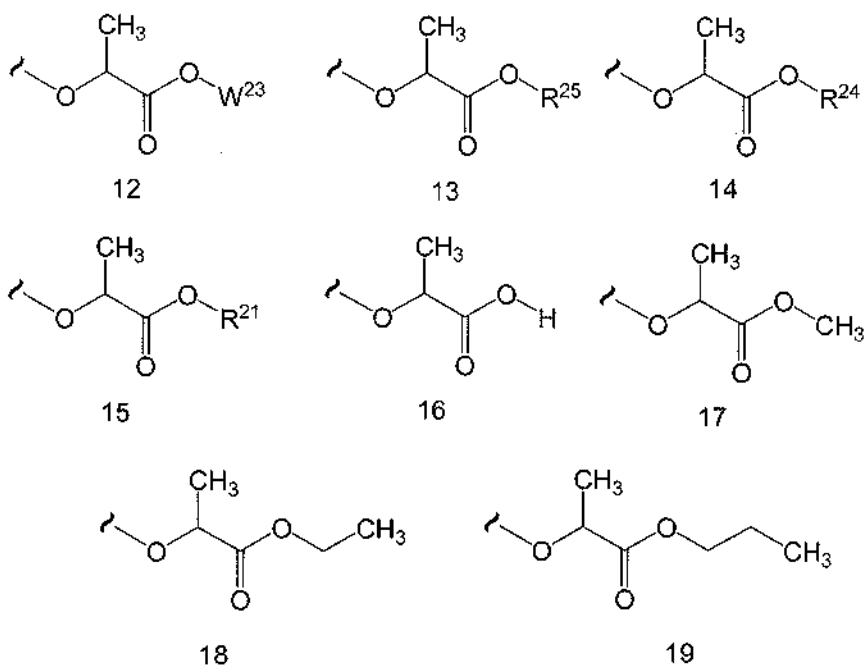


Table 20.4

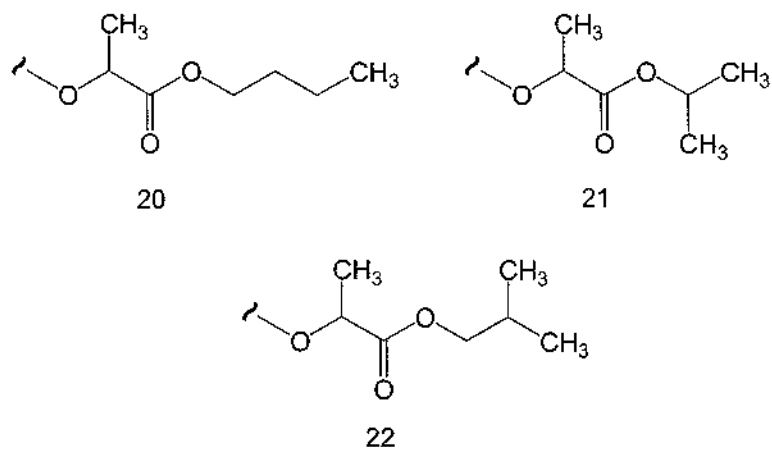


Table 20.5

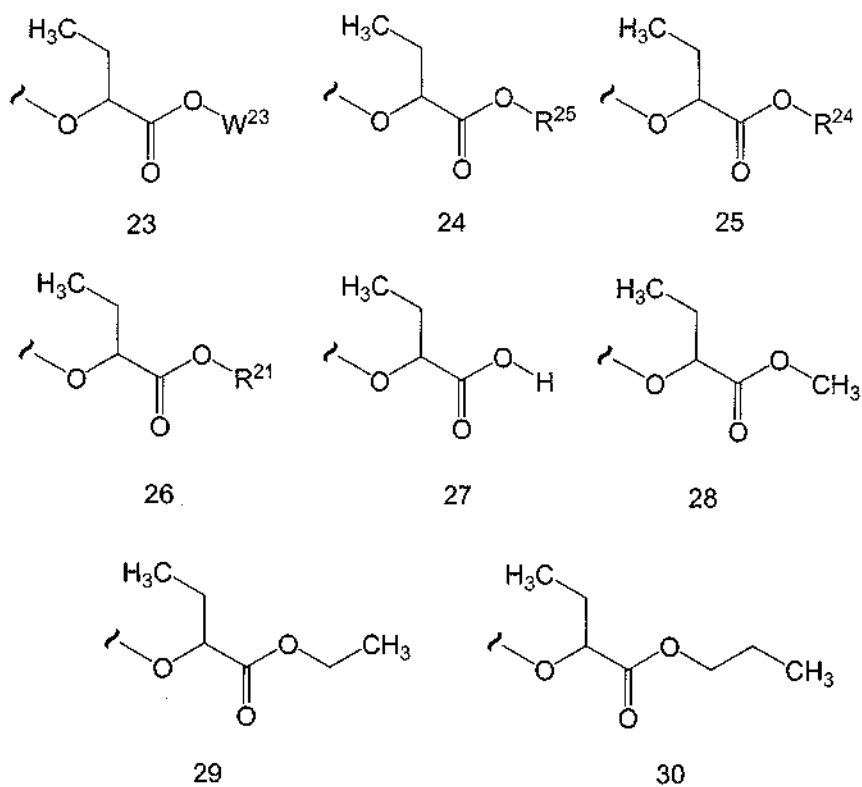


Table 20.6

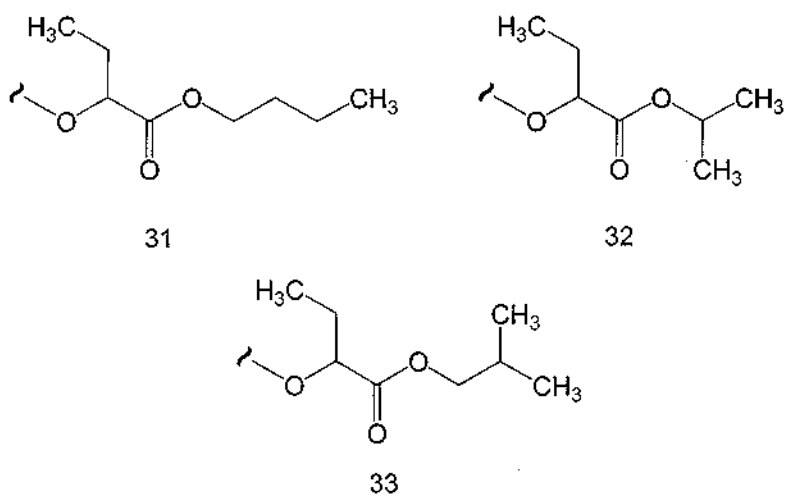


Table 20.7

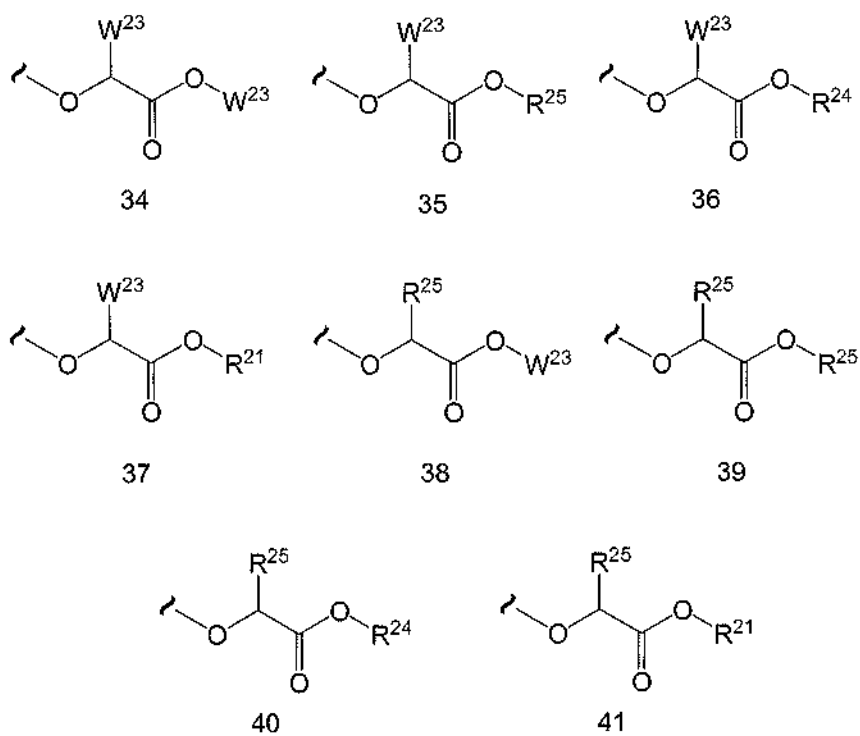


Table 20.8

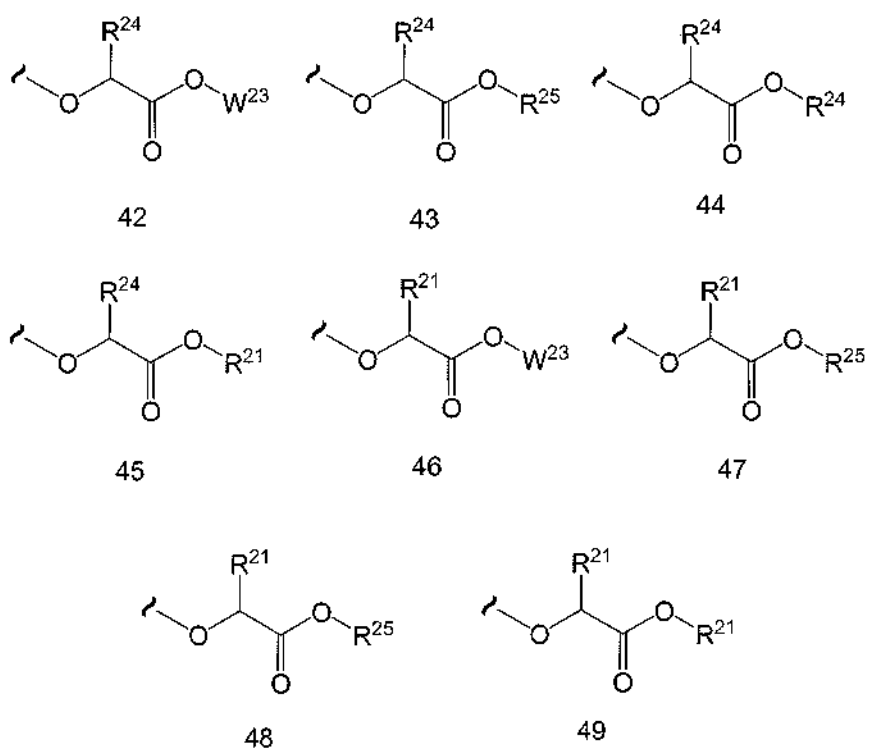
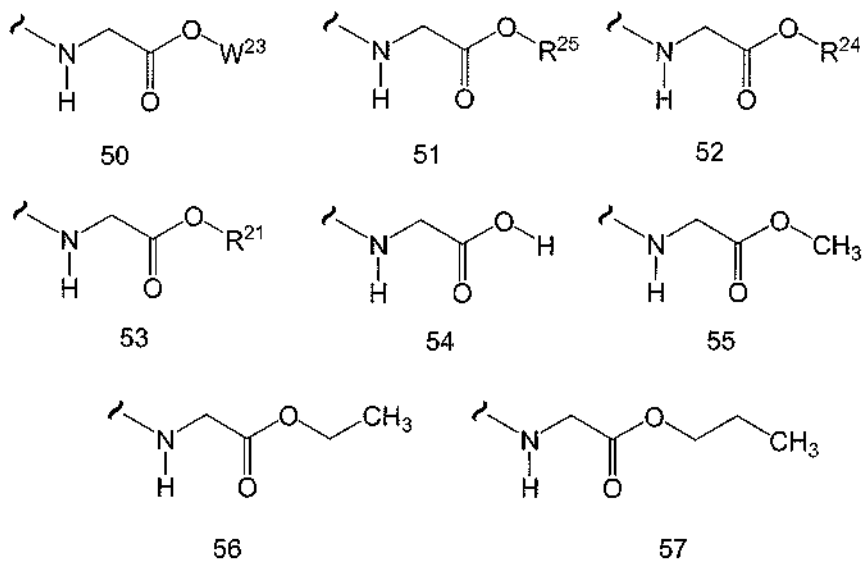


Table 20.9



5 Table 20.10

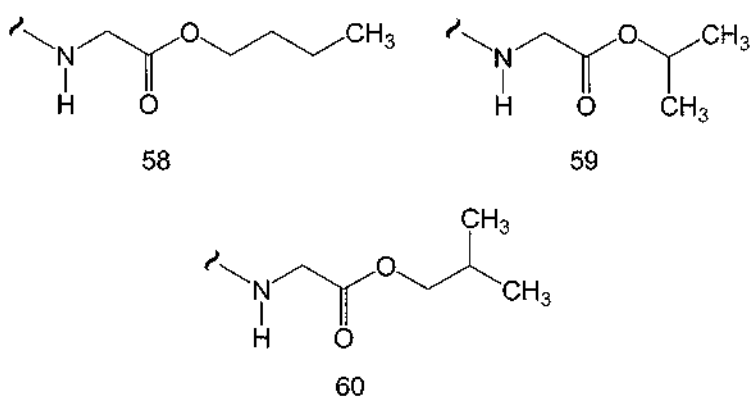


Table 20.11

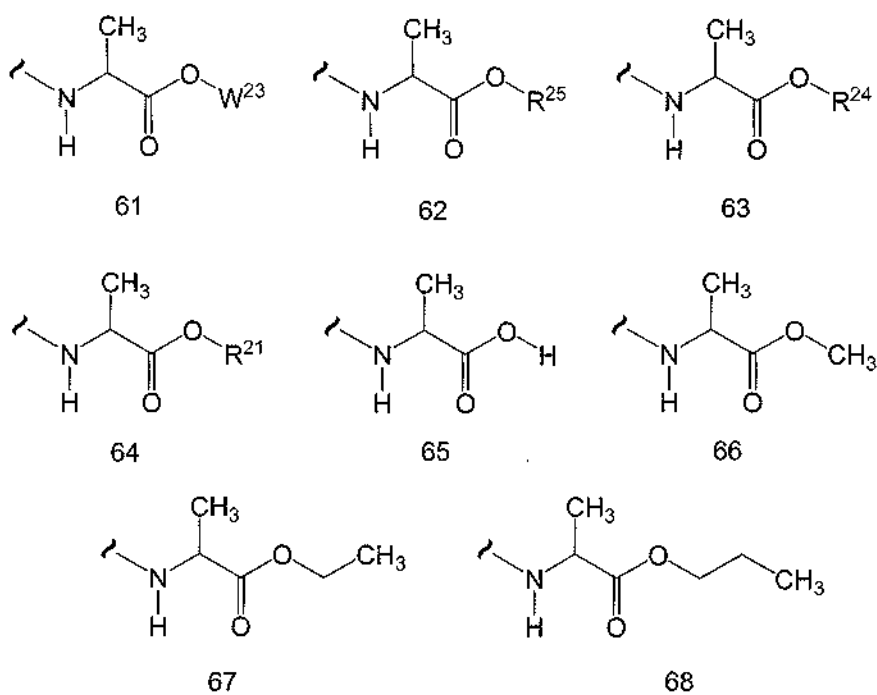


Table 20.12

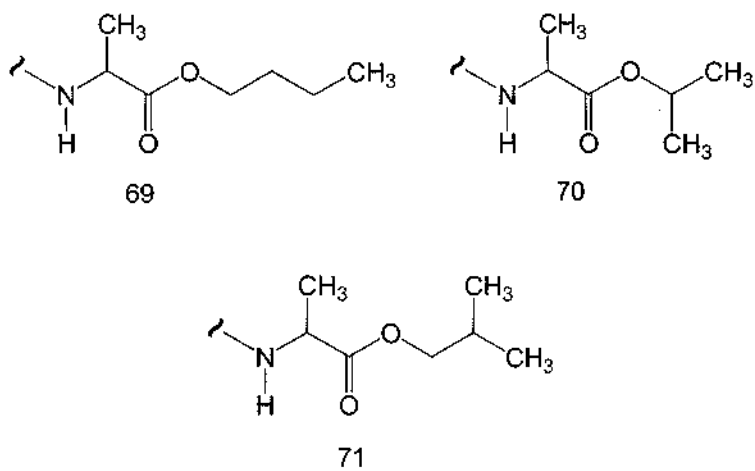


Table 20.13

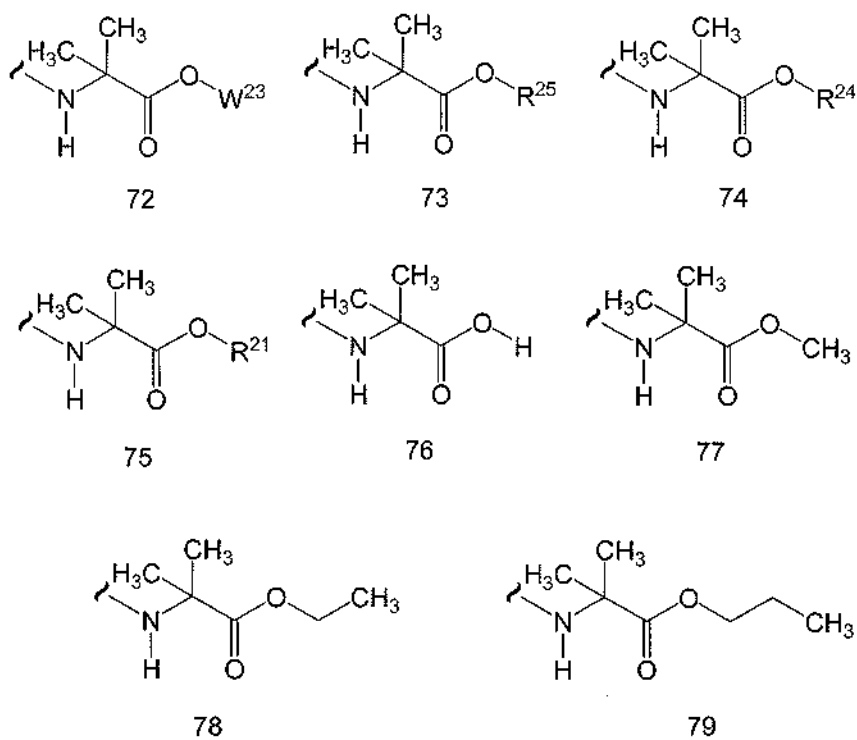


Table 20.14

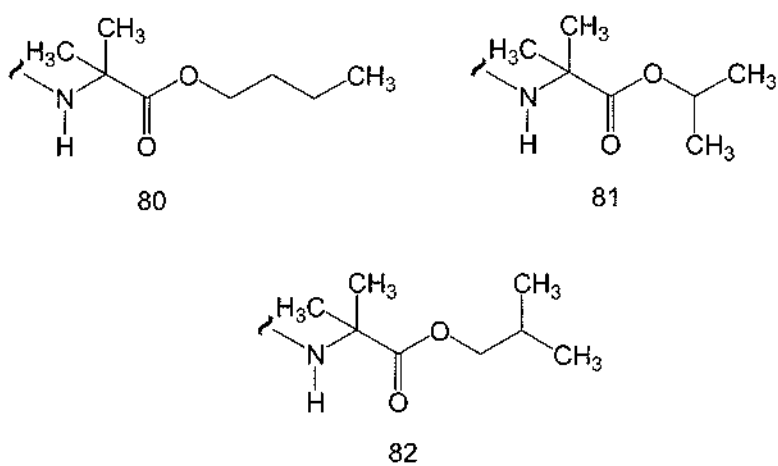


Table 20.15

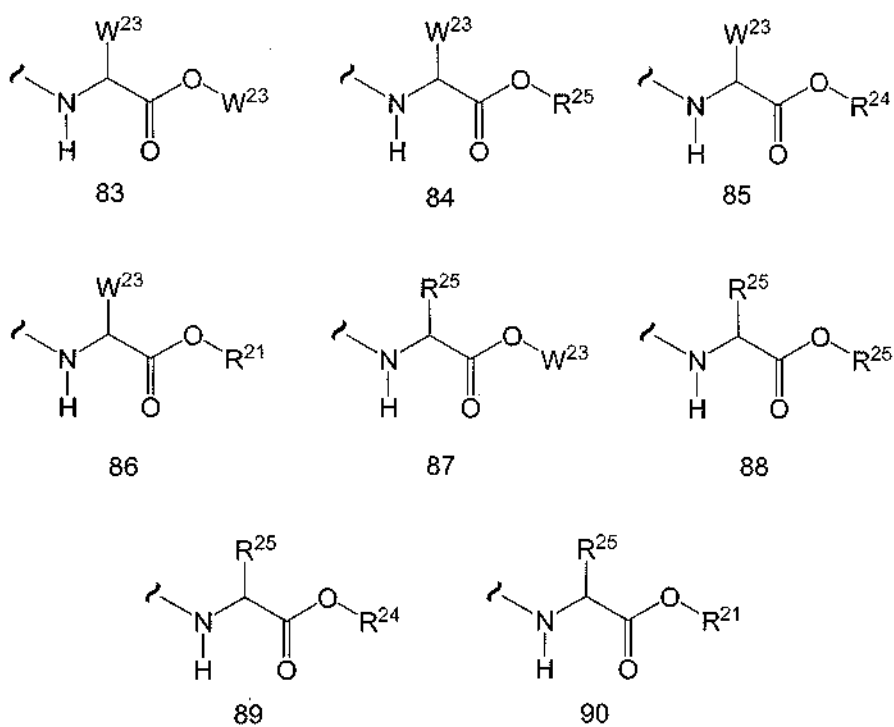


Table 20.16

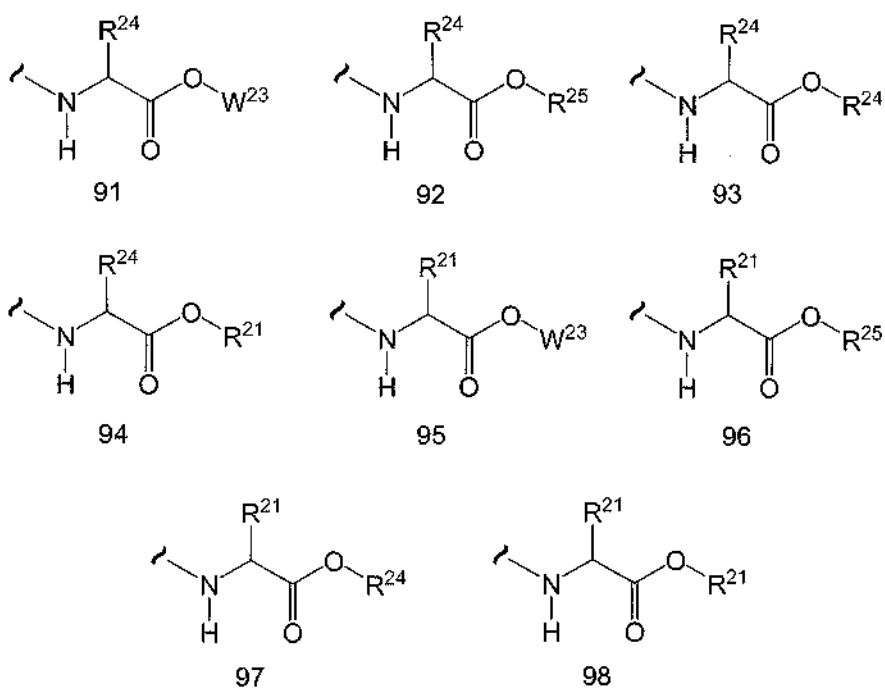


Table 20.17

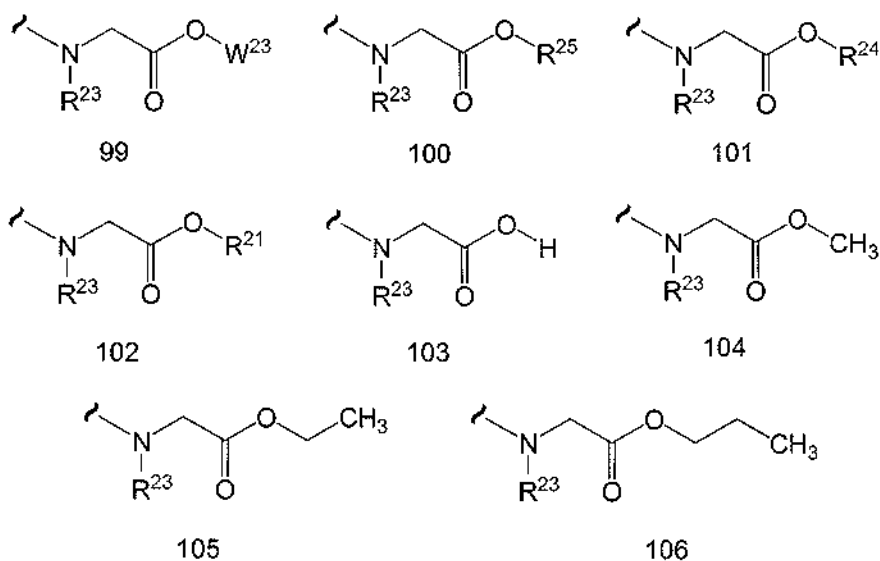
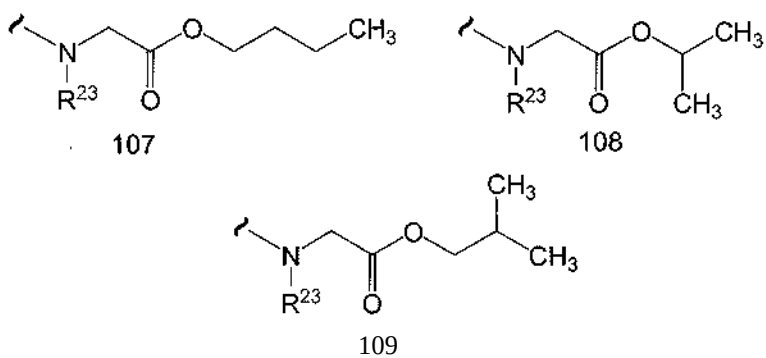


Table 20.18



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Table 20.19

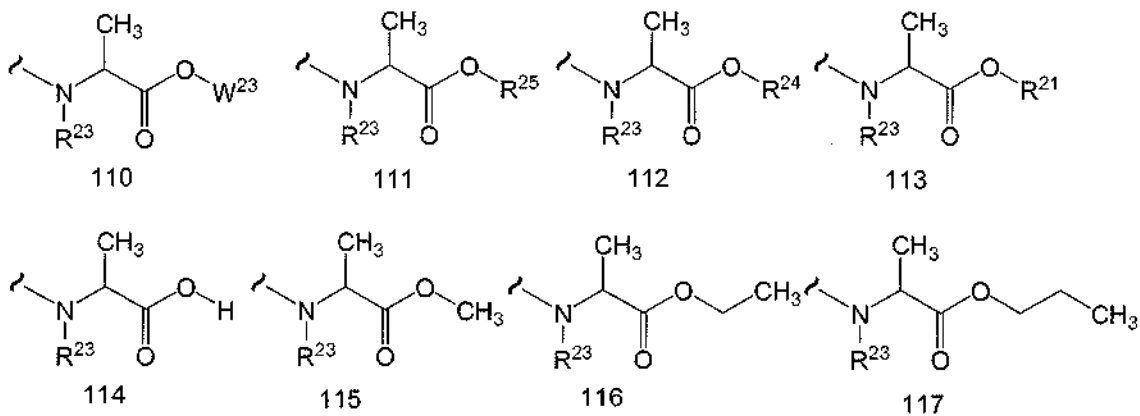
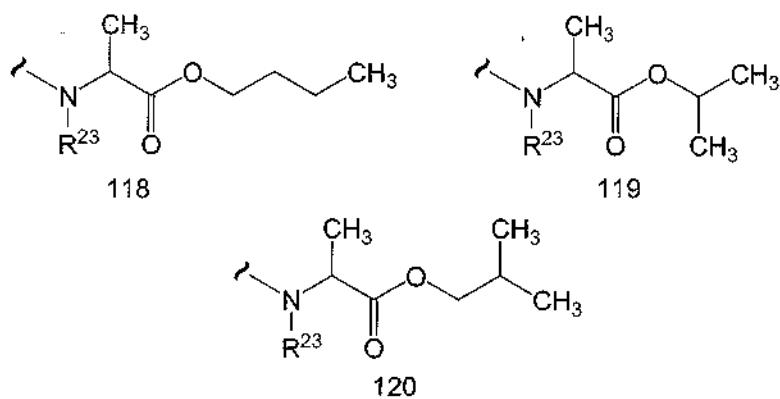


Table 20.20



5 Table 20.21

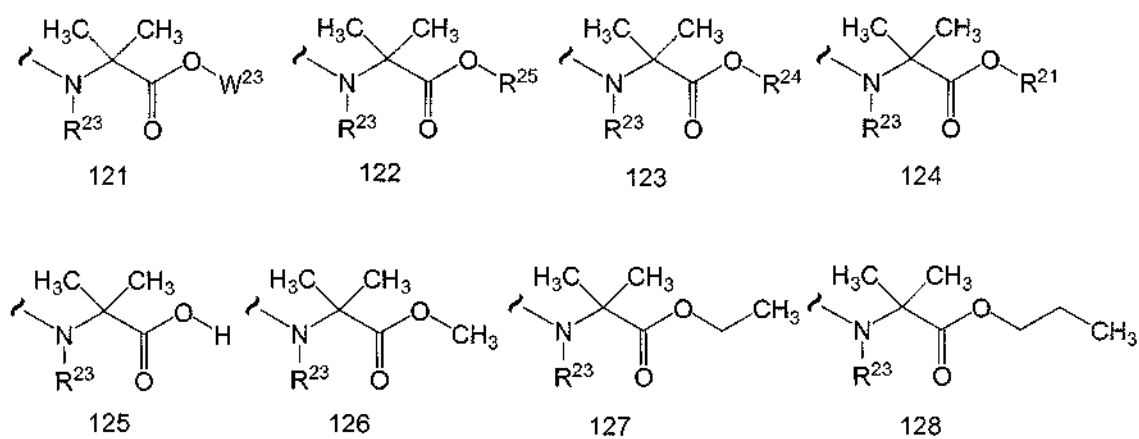


Table 20.22

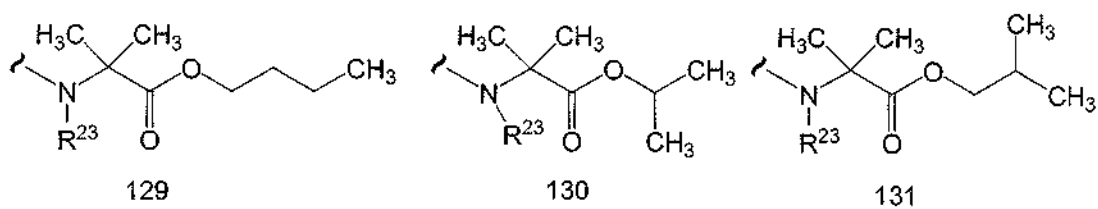
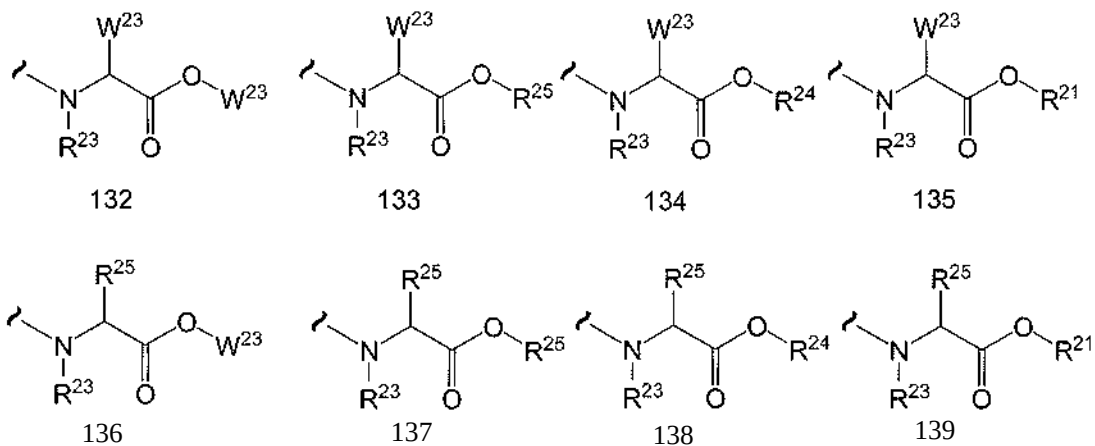


Table 20.23



5 Table 20.24

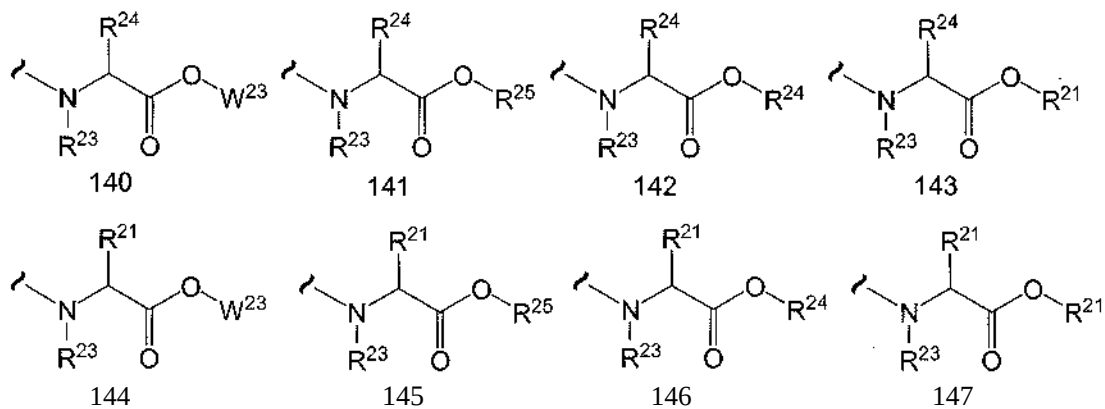
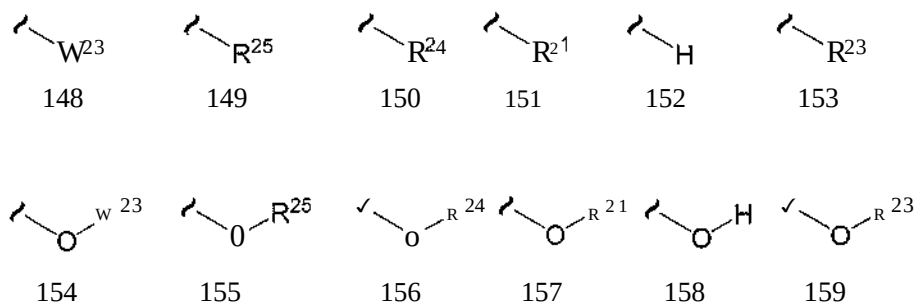


Table 20.25



10

Table 20.26

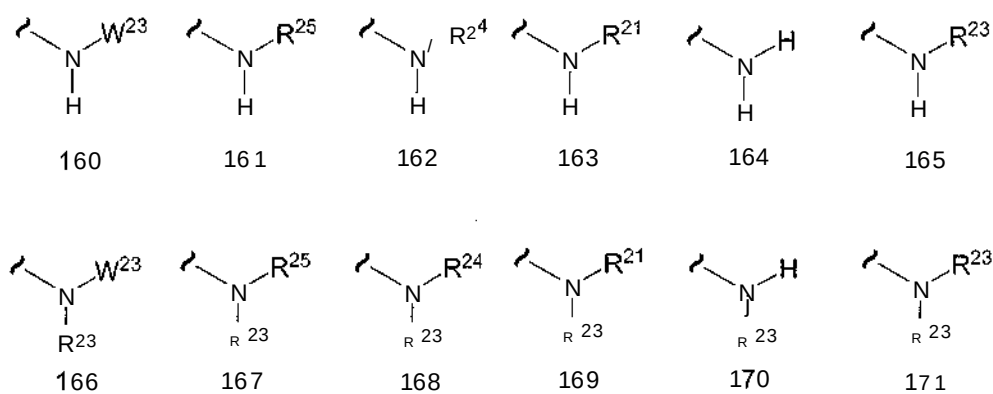
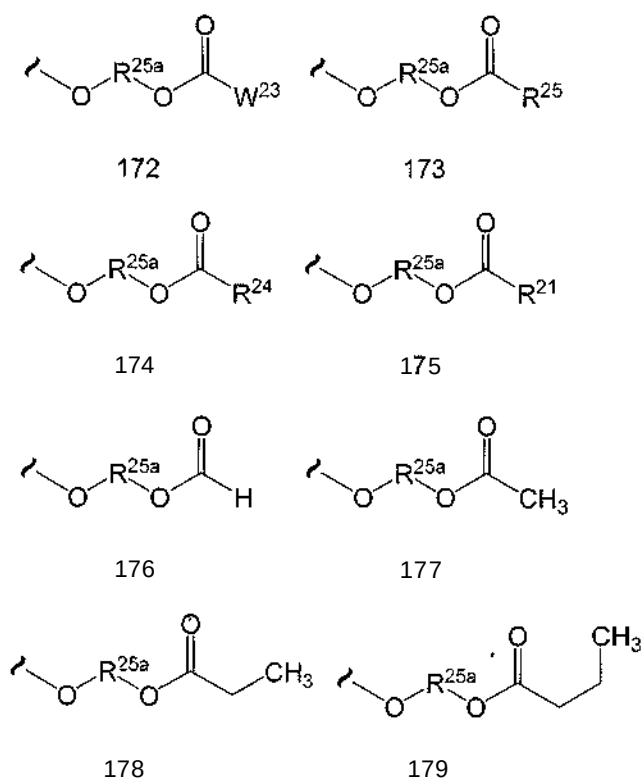


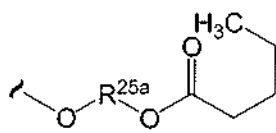
Table 20.27



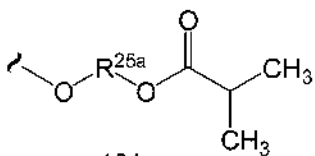
5

10

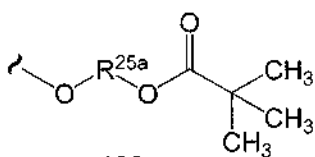
Table 20.28



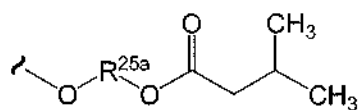
180



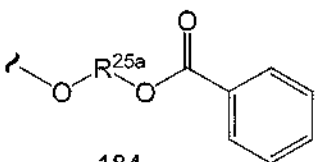
181



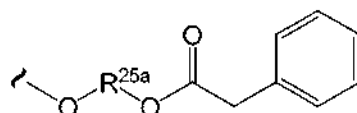
182



183



184



185

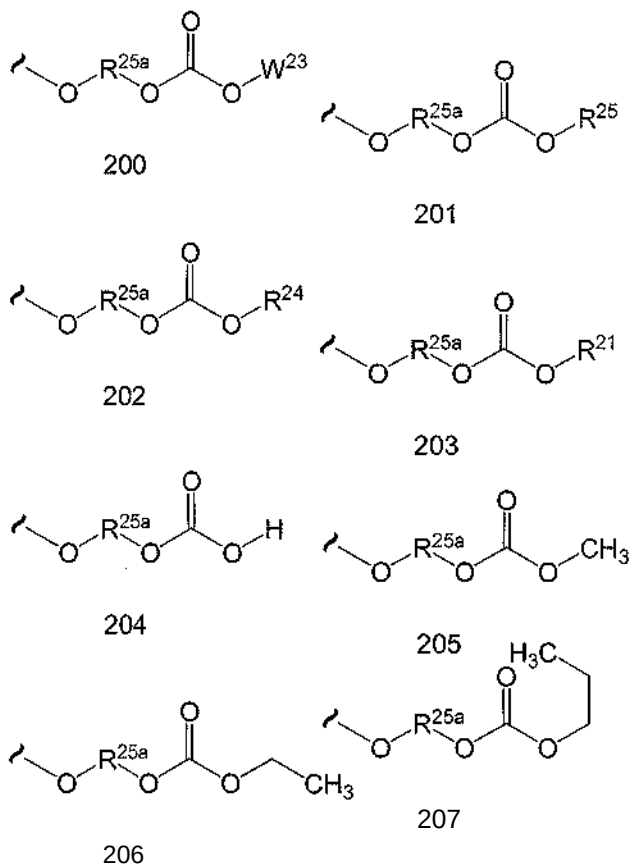
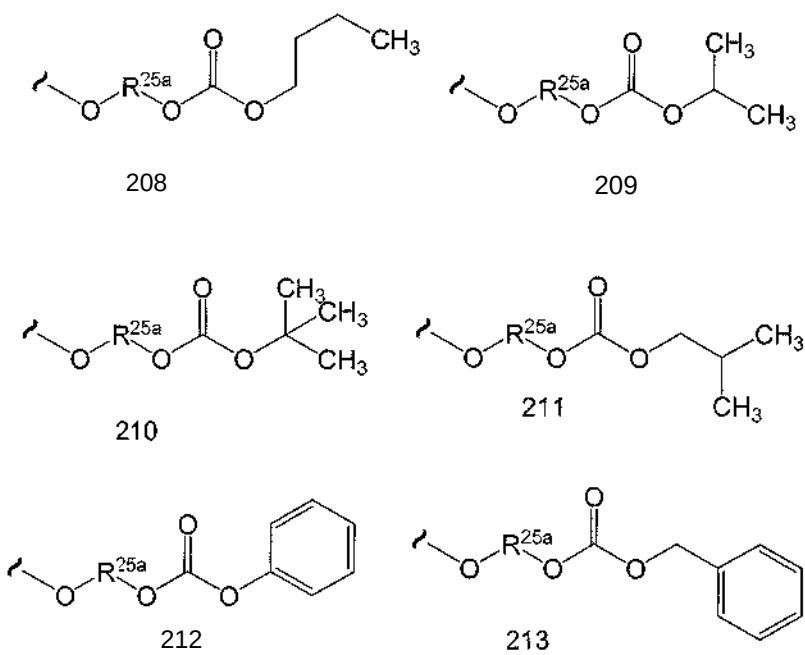
Table 20.31**Table 20.32**

Table 20.33

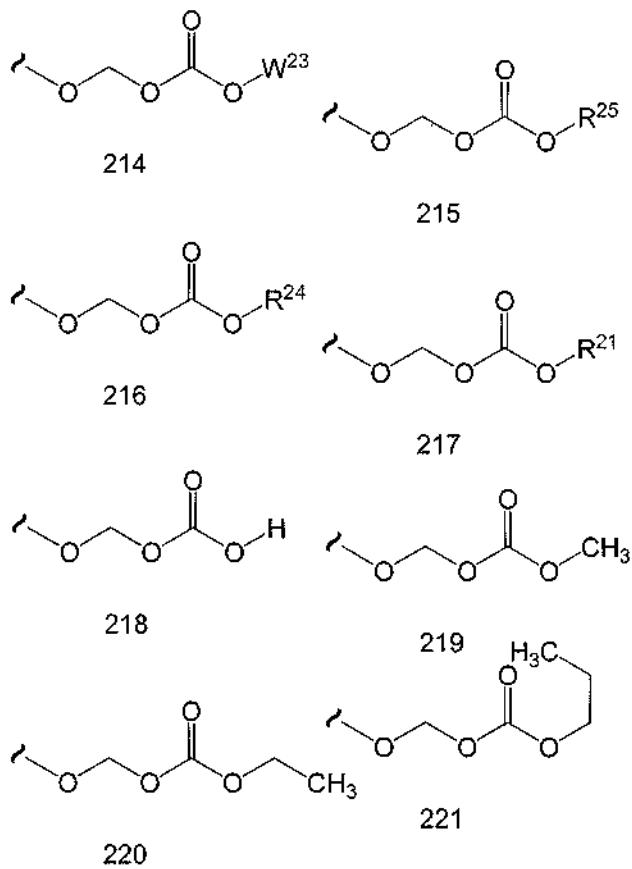


Table 20.34

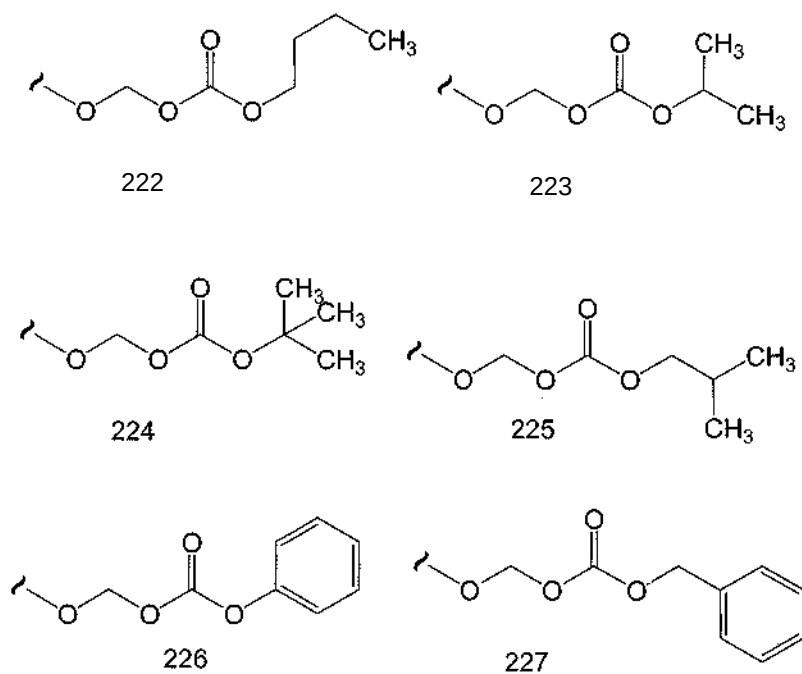


Table 20.35

5

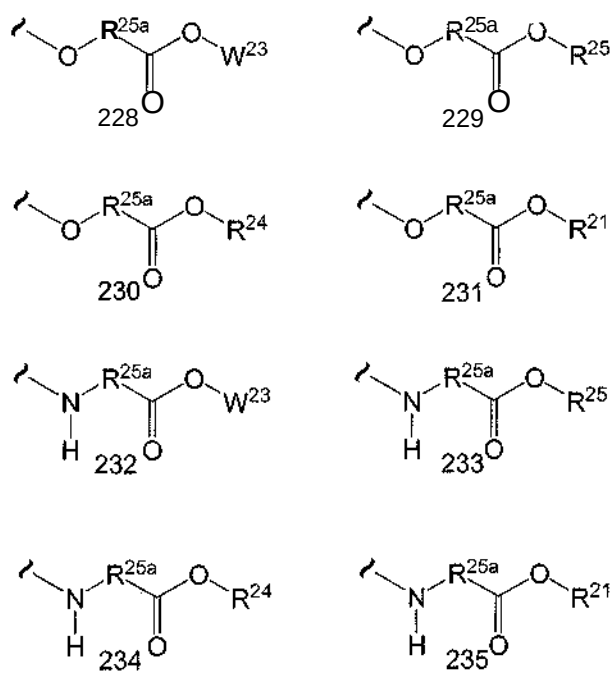


Table 20.36

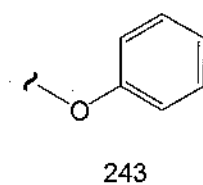
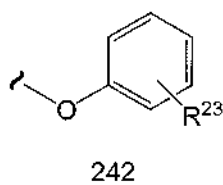
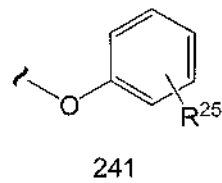
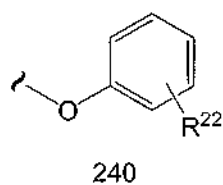
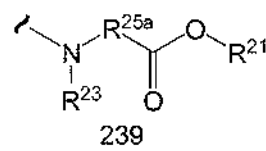
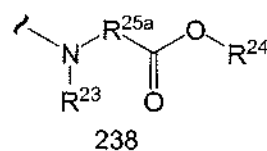
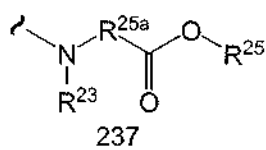
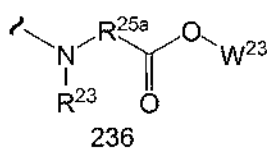


Table 20.37

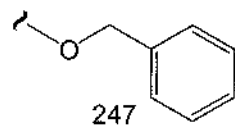
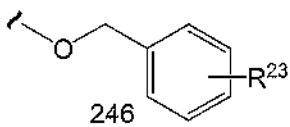
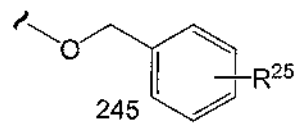
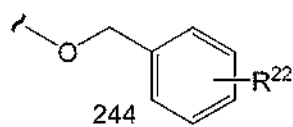
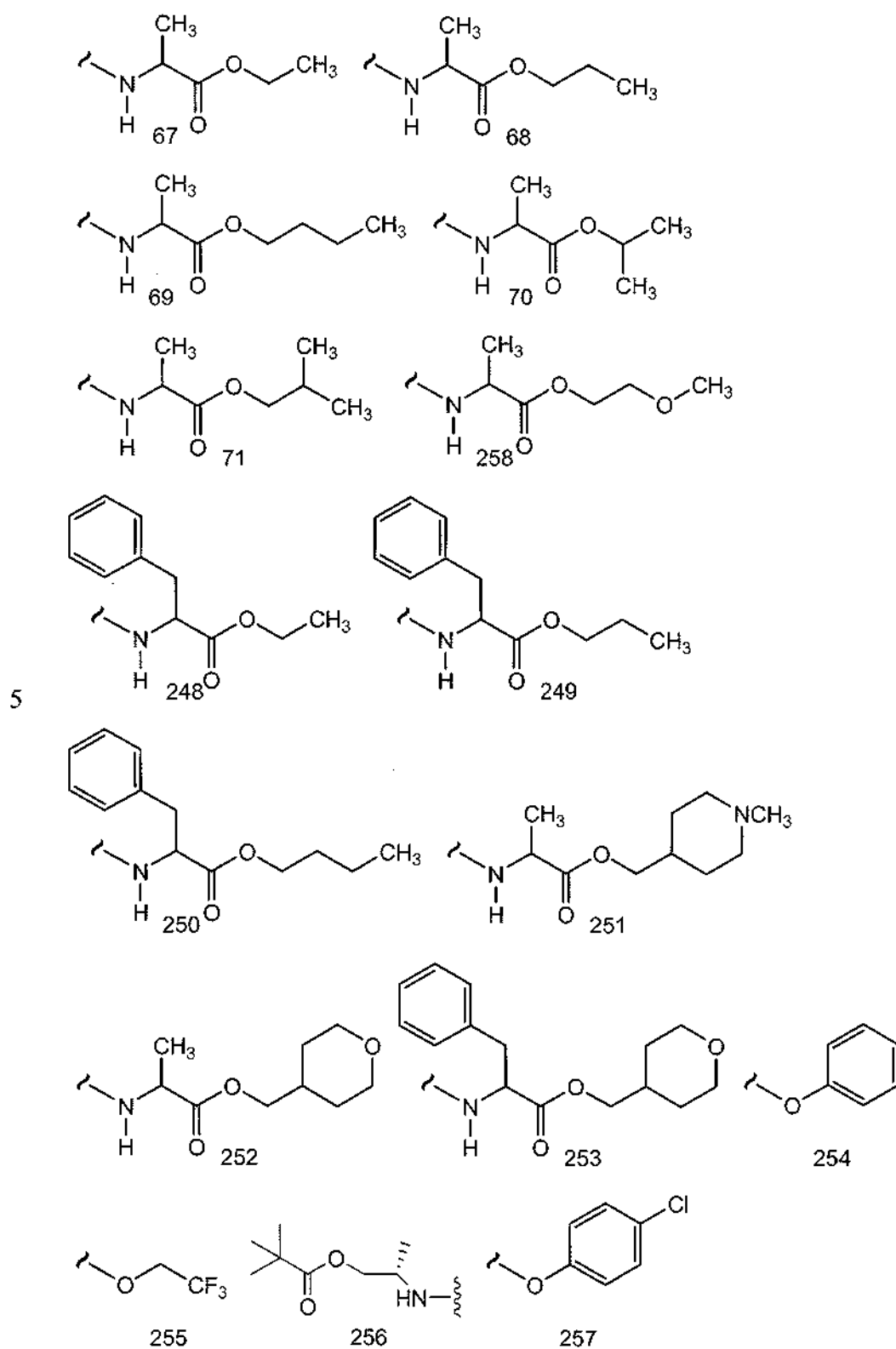
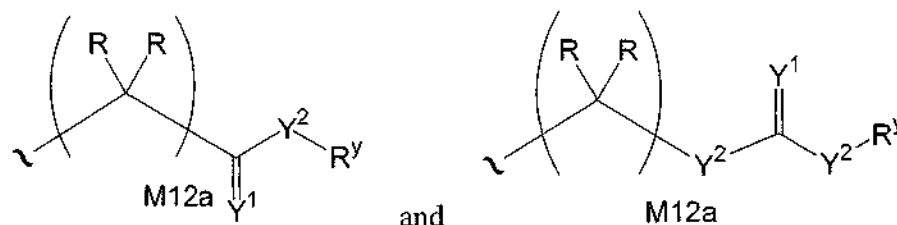


Table 30.1



Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



5

Any reference to the compounds of the invention described herein also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+ , Li^+ , K^+ , Ca^{+2} and Mg^{+2}), ammonium and NR_4^+ (wherein R is defined herein). Physiologically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NR_4^+ .

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

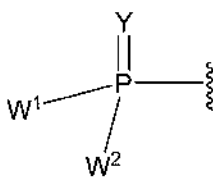
Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

The compounds of the invention, exemplified by Formula I-IV may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

- "Diastereomer" refers to a stereoisomer with two or more centers of
 5 chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, reactivities and biological properties. For example, the compounds of Formula I-IV may have a chiral phosphorus atom when R⁷ is



- and W¹ and W² are different. When at least one of either W¹ or
 10 W² also has a chiral center, for example with W¹ or W² is a nitrogen-linked, chiral, naturally occurring α -amino acid ester, then the compound of Formula I-IV will exist as diastereomers because there are two centers of chirality in the molecule. All such diastereomers and their uses described herein are encompassed by the instant invention. Mixtures of diastereomers may be separate
 15 under high resolution analytical procedures such as electrophoresis, crystallization and/or chromatography. Diastereomers may have different physical attributes such as, but not limited to, solubility, chemical stabilities and crystallinity and may also have different biological properties such as, but not limited to, enzymatic stability, absorption and metabolic stability.

- 20 "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

- Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of
 25 Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the

molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (-), or l meaning that the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R¹", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines, ~~~~~, indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Methods of Inhibition of a *Paramyxoviridae* polymerase

Another aspect of the invention relates to methods of inhibiting the activity of *Paramyxoviridae* polymerase comprising the step of treating a sample suspected of containing *Paramyxoviridae* with a composition of the invention.

Compositions of the invention may act as inhibitors of *Paramyxoviridae* polymerase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of *Paramyxoviridae* polymerase having a geometry unique to *Paramyxoviridae*

polymerase . Compositions binding *Paramyxoviridae* polymerase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes
 5 for the detection of *Paramyxoviridae* polymerase. Accordingly, the invention relates to methods of detecting *Paramyxoviridae* polymerase in a sample suspected of containing *Paramyxoviridae* polymerase comprising the steps of: treating a sample suspected of containing *Paramyxoviridae* polymerase with a composition comprising a compound of the invention bound to a label; and
 10 observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

15 Within the context of the invention, samples suspected of containing *Paramyxoviridae* polymerase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples;
 20 bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces *Paramyxoviridae* polymerase, frequently a pathogenic organism such as a *Paramyxoviridae* virus. Samples can be contained in any medium including water and organic
 25 solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as
 30 described above.

If desired, the activity of *Paramyxoviridae* polymerase after application of

the composition can be observed by any method including direct and indirect methods of detecting *Paramyxoviridae* polymerase activity. Quantitative, qualitative, and semiquantitative methods of determining *Paramyxoviridae* polymerase activity are all contemplated. Typically one of the screening methods
5 described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain *Paramyxoviridae* polymerase include the *Paramyxoviridae* virus. The compounds of this invention are useful in the treatment or prophylaxis of *Paramyxoviridae* infections in animals or in man.

10 However, in screening compounds capable of inhibiting human *Paramyxoviridae* viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for *Paramyxoviridae* polymerase Inhibitors.

15 Compositions of the invention are screened for inhibitory activity against *Paramyxoviridae* polymerase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of *Paramyxoviridae* polymerase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*.

20 Compositions having *in vitro* K_i (inhibitory constants) of less than about 5×10^{-6} M and preferably less than about 1×10^{-7} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

25 The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will

optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

- 5 The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at
10 least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients, particularly those additional therapeutic ingredients as discussed herein. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

15 The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of
20 bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

25 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also
30 be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more

accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a
5 suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the
10 formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active
15 ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more
20 hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl
25 sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably,
30 a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together,

the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example,

inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be
5 coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules
10 where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in
15 admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a
20 condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain
25 one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a
30 mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as

those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

5 Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

10 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or
15 partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may
20 also contain a demulcent, a preservative, a flavoring or a coloring agent.

 The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have
25 been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed
30 oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or

diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μ g of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared

according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of *Paramyxoviridae* infections as described below.

In another aspect, the invention is a novel, efficacious, safe, nonirritating and physiologically compatible inhalable composition comprising a compound of Formula I-IV, or a pharmaceutically acceptable salt thereof, suitable for treating *Paramyxoviridae* infections and potentially associated bronchiolitis. Preferred pharmaceutically acceptable salts are inorganic acid salts including hydrochloride, hydrobromide, sulfate or phosphate salts as they may cause less pulmonary irritation. Preferably, the inhalable formulation is delivered to the endobronchial space in an aerosol comprising particles with a mass median aerodynamic diameter (MMAD) between about 1 and about 5 μm . Preferably, the compound of Formula I-IV is formulated for aerosol delivery using a nebulizer, pressurized metered dose inhaler (pMDI), or dry powder inhaler (DPI).

Non-limiting examples of nebulizers include atomizing, jet, ultrasonic, pressurized, vibrating porous plate, or equivalent nebulizers including those nebulizers utilizing adaptive aerosol delivery technology (Denyer, *J. Aerosol medicine Pulmonary Drug Delivery* 2010, 23 Supp 1, S1-S10). A jet nebulizer utilizes air pressure to break a liquid solution into aerosol droplets. An ultrasonic nebulizer works by a piezoelectric crystal that shears a liquid into small aerosol droplets. A pressurized nebulization system forces solution under pressure through small pores to generate aerosol droplets. A vibrating porous plate device utilizes rapid vibration to shear a stream of liquid into appropriate droplet sizes.

In a preferred embodiment, the formulation for nebulization is delivered to the endobronchial space in an aerosol comprising particles with a MMAD predominantly between about 1 μm and about 5 μm using a nebulizer able to aerosolize the formulation of the compound of Formula I-IV into particles of the required MMAD. To be optimally therapeutically effective and to avoid upper respiratory and systemic side effects, the majority of aerosolized particles should not have a MMAD greater than about 5 μm . If an aerosol contains a large number of particles with a MMAD larger than 5 μm , the particles are deposited in the

upper airways decreasing the amount of drug delivered to the site of inflammation and bronchoconstriction in the lower respiratory tract. If the MMAD of the aerosol is smaller than about $1\text{ }\mu\text{m}$, then the particles have a tendency to remain suspended in the inhaled air and are subsequently exhaled during expiration.

5 When formulated and delivered according to the method of the invention, the aerosol formulation for nebulization delivers a therapeutically efficacious dose of the compound of Formula I-IV to the site of *Paramyxoviridae* infection sufficient to treat the *Paramyxoviridae* infection. The amount of drug administered must be adjusted to reflect the efficiency of the delivery of a
10 therapeutically efficacious dose of the compound of Formula I-IV. In a preferred embodiment, a combination of the aqueous aerosol formulation with the atomizing, jet, pressurized, vibrating porous plate, or ultrasonic nebulizer permits, depending on the nebulizer, about, at least, 20, to about 90%, typically about 70% delivery of the administered dose of the compound of Formula I-IV into the
15 airways. In a preferred embodiment, at least about 30 to about 50% of the active compound is delivered. More preferably, about 70 to about 90% of the active compound is delivered.

 In another embodiment of the instant invention, a compound of Formula I-IV or a pharmaceutically acceptable salt thereof, is delivered as a dry inhalable
20 powder. The compounds of the invention are administered endobronchially as a dry powder formulation to efficacious deliver fine particles of compound into the endobronchial space using dry powder or metered dose inhalers. For delivery by DPI, the compound of Formula I-IV is processed into particles with, predominantly, MMAD between about $1\text{ }\mu\text{m}$ and about $5\text{ }\mu\text{m}$ by milling spray
25 drying, critical fluid processing, or precipitation from solution. Media milling, jet milling and spray-drying devices and procedures capable of producing the particle sizes with a MMAD between about $1\text{ }\mu\text{m}$ and about $5\text{ }\mu\text{m}$ are well know in the art. In one embodiment, excipients are added to the compound of Formula I-IV before processing into particles of the required sizes. In another embodiment, excipients
30 are blended with the particles of the required size to aid in dispersion of the drug particles, for example by using lactose as an excipient.

Particle size determinations are made using devices well known in the art. For example a multi-stage Anderson cascade impactor or other suitable method such as those specifically cited within the US Pharmacopoeia Chapter 601 as characterizing devices for aerosols within metered-dose and dry powder inhalers.

5 In another preferred embodiment, a compound of Formula I-IV is delivered as a dry powder using a device such as a dry powder inhaler or other dry powder dispersion devices. Non-limiting examples of dry powder inhalers and devices include those disclosed in US5,458,135; US5,740,794; US5775320; US5,785,049; US3,906,950; US4,013,075; US4,069,819; US4,995,385; 10 US5,522,385; US4,668,218; US4,667,668; US4,805,811 and US5,388,572. There are two major designs of dry powder inhalers. One design is a metering device in which a reservoir for the drug is placed within the device and the patient adds a dose of the drug into the inhalation chamber. The second design is a factory-metered device in which each individual dose has been manufactured in a separate 15 container. Both systems depend on the formulation of the drug into small particles of MMAD from 1 μm and about 5 μm , and often involve co-formulation with larger excipient particles such as, but not limited to, lactose. Drug powder is placed in the inhalation chamber (either by device metering or by breakage of a factory-metered dosage) and the inspiratory flow of the patient accelerates the 20 powder out of the device and into the oral cavity. Non-laminar flow characteristics of the powder path cause the excipient-drug aggregates to decompose, and the mass of the large excipient particles causes their impaction at the back of the throat, while the smaller drug particles are deposited deep in the lungs. In preferred embodiments, a compound of Formula I-IV, or a 25 pharmaceutically acceptable salt thereof, is delivered as a dry powder using either type of dry powder inhaler as described herein, wherein the MMAD of the dry powder, exclusive of any excipients, is predominantly in the range of 1 μm to about 5 μm .

30 In another preferred embodiment, a compound of Formula I-IV is delivered as a dry powder using a metered dose inhaler. Non-limiting examples of metered dose inhalers and devices include those disclosed in US5,261,538;

US5,544,647; US5,622,163; US4,955,371; US3,565,070; US3,361,306 and
US6,116,234. In preferred embodiments, a compound of Formula I-IV, or a
pharmaceutically acceptable salt thereof, is delivered as a dry powder using a
metered dose inhaler wherein the MMAD of the dry powder, exclusive of any
5 excipients, is predominantly in the range of about 1-5 μm .

Formulations suitable for vaginal administration may be presented as
pessaries, tampons, creams, gels, pastes, foams or spray formulations containing
in addition to the active ingredient such carriers as are known in the art to be
appropriate.

10 Formulations suitable for parenteral administration include aqueous and
non-aqueous sterile injection solutions which may contain anti-oxidants, buffers,
bacteriostats and solutes which render the formulation isotonic with the blood of
the intended recipient; and aqueous and non-aqueous sterile suspensions which
may include suspending agents and thickening agents.

15 The formulations are presented in unit-dose or multi-dose containers, for
example sealed ampoules and vials, and may be stored in a freeze-dried
(lyophilized) condition requiring only the addition of the sterile liquid carrier, for
example water for injection, immediately prior to use. Extemporaneous injection
solutions and suspensions are prepared from sterile powders, granules and tablets
20 of the kind previously described. Preferred unit dosage formulations are those
containing a daily dose or unit daily sub-dose, as herein above recited, or an
appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly
mentioned above the formulations of this invention may include other agents
25 conventional in the art having regard to the type of formulation in question, for
example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least
one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering
30 the composition and may be solid, liquid or gaseous materials which are otherwise
inert or acceptable in the veterinary art and are compatible with the active

ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more
5 compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the
10 condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01
15 to about 10 mg/kg body weight per day; more typically, from about .01 to about 5 mg/kg body weight per day; most typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

20 Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous,
25 intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. For the treatment of *Paramyxoviridae* virus infections, preferably, the other active therapeutic agent is active against *Paramyxoviridae* virus infections, particularly respiratory syncytial virus infections and/or
5 parainfluenza virus infections. Non-limiting examples of these other active therapeutic agents are ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam®), MEDI-557, A-60444, MDT-637, BMS-433771, and mixtures thereof.

Many of the infections of the *Paramyxoviridae* viruses are respiratory
10 infections. Therefore, additional active therapeutics used to treat respiratory symptoms and sequelae of infection may be used in combination with the compounds of Formula I-IV. The additional agents are preferably administered orally or by direct inhalation. For example, other preferred additional therapeutic agents in combination with the compounds of Formula I-IV for the treatment of
15 viral respiratory infections include, but are not limited to, bronchodilators and corticosteroids.

Glucocorticoids, which were first introduced as an asthma therapy in 1950 (Carrier, Journal of Allergy, 21, 282-287, 1950), remain the most potent and consistently effective therapy for this disease, although their mechanism of action
20 is not yet fully understood (Morris, J. Allergy Clin. Immunol., 75 (1 Pt) 1-13, 1985). Unfortunately, oral glucocorticoid therapies are associated with profound undesirable side effects such as truncal obesity, hypertension, glaucoma, glucose intolerance, acceleration of cataract formation, bone mineral loss, and psychological effects, all of which limit their use as long-term therapeutic agents
25 (Goodman and Gilman, 10th edition, 2001). A solution to systemic side effects is to deliver steroid drugs directly to the site of inflammation. Inhaled corticosteroids (ICS) have been developed to mitigate the severe adverse effects of oral steroids. Non-limiting examples of corticosteroids that may be used in combinations with the compounds of Formula I-IV are dexamethasone,
30 dexamethasone sodium phosphate, fluorometholone, fluorometholone acetate, loteprednol, loteprednol etabonate, hydrocortisone, prednisolone, fludrocortisones,

triamcinolone, triamcinolone acetonide, betamethasone, beclomethasone dipropionate, methylprednisolone, fluocinolone, fluocinolone acetonide, flunisolide, fluocortin-21-butyrate, flumethasone, flumetasone pivalate, budesonide, halobetasol propionate, mometasone furoate, fluticasone propionate, ciclesonide; or a pharmaceutically acceptable salts thereof.

Other anti-inflammatory agents working through anti-inflammatory cascade mechanisms are also useful as additional therapeutic agents in combination with the compounds of Formula I-IV for the treatment of viral respiratory infections. Applying "anti-inflammatory signal transduction modulators" (referred to in this text as AISTM), like phosphodiesterase inhibitors (e.g. PDE-4, PDE-5, or PDE-7 specific), transcription factor inhibitors (e.g. blocking NFkB through IKK inhibition), or kinase inhibitors (e.g. blocking P38 MAP, JNK, PI3K, EGFR or Syk) is a logical approach to switching off inflammation as these small molecules target a limited number of common intracellular pathways - those signal transduction pathways that are critical points for the anti-inflammatory therapeutic intervention (see review by P.J. Barnes, 2006). These non-limiting additional therapeutic agents include: 5-(2,4-Difluoro-phenoxy)-1-isobutyl-1H-indazole-6-carboxylic acid (2-dimethylamino-ethyl)-amide (P38 Map kinase inhibitor ARRY-797); 3-Cyclopropylmethoxy-N-(3,5-dichloro-pyridin-4-yl)-4-difluoromethoxy-benzamide (PDE-4 inhibitor Roflumilast); 4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenyl-ethyl]-pyridine (PDE-4 inhibitor CDP-840); N-(3,5-dichloro-4-pyridinyl)-4-(difluoromethoxy)-8-[(methylsulfonyl)amino]-1-dibenzofurancarboxamide (PDE-4 inhibitor Oglemilast); N-(3,5-Dichloro-pyridin-4-yl)-2-[1-(4-fluorobenzyl)-5-hydroxy-1H-indol-3-yl]-2-oxo-acetamide (PDE-4 inhibitor AWD 12-281); 8-Methoxy-2-trifluoromethyl-quinoline-5-carboxylic acid (3,5-dichloro-1-oxy-pyridin-4-yl)-amide (PDE-4 inhibitor Sch 351591); 4-[5-(4-Fluorophenyl)-2-(4-methanesulfonyl-phenyl)-1H-imidazol-4-yl]-pyridine (P38 inhibitor SB-203850); 4-[4-(4-Fluoro-phenyl)-1-(3-phenyl-propyl)-5-pyridin-4-yl]-1H-imidazol-2-yl]-but-3-yn-1-ol (P38 inhibitor RWJ-67657); 4-Cyano-4-(3-cyclopentyloxy-4-methoxy-phenyl)-cyclohexanecarboxylic acid 2-diethylamino-ethyl ester (2-

diethyl-ethyl ester prodrug of Cilomilast, PDE-4 inhibitor); (3-Chloro-4-fluorophenyl)-[7-methoxy-6-(3-morpholin-4-yl-propoxy)-quinazolin-4-yl]-amine (Gefitinib, EGFR inhibitor); and 4-(4-Methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide (Imatinib, EGFR inhibitor).

Combinations comprising inhaled p2-adrenoreceptor agonist bronchodilators such as formoterol, albuterol or salmeterol with the compounds of Formula I-IV are also suitable, but non-limiting, combinations useful for the treatment of respiratory viral infections.

Combinations of inhaled p2-adrenoreceptor agonist bronchodilators such as formoterol or salmeterol with ICS's are also used to treat both the bronchoconstriction and the inflammation (Symbicort® and Advair®, respectively). The combinations comprising these ICS and p2-adrenoreceptor agonist combinations along with the compounds of Formula I-IV are also suitable, but non-limiting, combinations useful for the treatment of respiratory viral infections.

For the treatment or prophylaxis of pulmonary broncho-constriction, anticholinergics are of potential use and, therefore, useful as an additional therapeutic agents in combination with the compounds of Formula I-IV for the treatment of viral respiratory infections. These anticholinergics include, but are not limited to, antagonists of the muscarinic receptor (particularly of the M3 subtype) which have shown therapeutic efficacy in man for the control of cholinergic tone in COPD (Witek, 1999); 1-{4-Hydroxy-1-[3,3,3-tris-(4-fluorophenyl)-propionyl]-pyrrolidine-2-carbonyl}-pyrrolidine-2-carboxylic acid (1-methyl-piperidin-4-ylmethyl)-amide; 3-[3-(2-Diethylamino-acetoxy)-2-phenyl-propionyloxy]-8-isopropyl-8-methyl-8-azonia-bicyclo[3.2.1]octane (Ipratropium-N,N-diethylglycinate); 1-Cyclohexyl-3,4-dihydro-1H-isoquinoline-2-carboxylic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (Solifenacin); 2-Hydroxymethyl-4-methanesulfonyl-2-phenyl-butyric acid 1-aza-bicyclo[2.2.2]oct-3-yl ester (Revatropate); 2-{1-[2-(2,3-Dihydro-benzofuran-5-yl)-ethyl]-pyridin-3-yl}-2,2-diphenyl-acetamide (Darifenacin); 4-Azepan-1-yl-2,2-diphenyl-butyramide

(Buzepide); 7-[3-(2-Diethylamino-acetoxy)-2-phenyl-propionyloxy]-9-ethyl-9-methyl-3-oxa-9-azonia-tricyclo[3.3.1.0^{2,4}]nonane (Oxitropium-N,N-diethylglycinate); 7-[2-(2-Diethylamino-acetoxy)-2,2-di-thiophen-2-yl-acetoxy]-9,9-dimethyl-3-oxa-9-azonia-tricyclo[3.3.1.0^{2,4}]nonane (Tiotropium-N,N-diethylglycinate); Dimethylamino-acetic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-methyl-phenyl ester (Tolterodine-N,N-dimethylglycinate); 3-[4,4-Bis-(4-fluoro-phenyl)-2-oxo-imidazolidin-1-yl]-1-methyl-1-(2-oxo-2-pyridin-2-yl-ethyl)-pyrrolidinium; 1-[1-(3-Fluoro-benzyl)-piperidin-4-yl]-4,4-bis-(4-fluoro-phenyl)-imidazolidin-2-one; 1-Cyclooctyl-3-(3-methoxy-1-aza-bicyclo[2.2.2]oct-3-yl)-1-phenyl-prop-2-yn-1-ol; 3-[2-(2-Diethylamino-acetoxy)-2,2-di-thiophen-2-yl-acetoxy]-1-(3-phenoxy-propyl)-1-azonia-bicyclo[2.2.2]octane (Aclidinium-N,N-diethylglycinate); or (2-Diethylamino-acetoxy)-di-thiophen-2-yl-acetic acid 1-methyl-1-(2-phenoxy-ethyl)-piperidin-4-yl ester.

The compounds of Formula I-IV may also be combined with mucolytic agents to treat both the infection and symptoms of respiratory infections. A non-limiting example of a mucolytic agent is ambroxol. Similarly, the compounds of Formula I-IV may be combined with expectorants to treat both the infection and symptoms of respiratory infections. A non-limiting example of an expectorant is guaifenesin.

Nebulized hypertonic saline is used to improve immediate and long-term clearance of small airways in patients with lung diseases (Kuzik, *J. Pediatrics* 2007, 266). The compounds of Formula I-IV may also be combined with nebulized hypertonic saline particularly when the *Paramyxoviridae* virus infection is complicated with bronchiolitis. The combination of the compounds of Formula I-IV with hypertonic saline may also comprise any of the additional agents discussed above. In a preferred aspect, nebulized about 3% hypertonic saline is used.

It is also possible to combine any compound of the invention with one or more additional active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered

sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential
5 administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the
10 compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within
15 seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed,
20 after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

25 The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered
30 by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be

attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination
5 therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

In still yet another embodiment, the present application provides for
10 methods of inhibiting *Paramyxoviridae* polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, whereby *Paramyxoviridae* polymerase is inhibited.

In still yet another embodiment, the present application provides for
15 methods of inhibiting *Paramyxoviridae* polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby *Paramyxoviridae* polymerase is inhibited.

In still yet another embodiment, the present application provides for
20 methods of inhibiting *Paramyxoviridae* polymerase in a cell, comprising: contacting a cell infected with *Paramyxoviridae* virus with an effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected

In still yet another embodiment, the present application provides for
25 methods of treating *Paramyxoviridae* virus infection in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In still yet another embodiment, the present application provides for
30 methods of treating *Paramyxoviridae* virus infection in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of

Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby *Paramyxoviridae* polymerase is inhibited.

5 In still yet another embodiment, the present application provides for methods of treating *Paramyxoviridae* virus infection in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent.

Metabolites of the Compounds of the Invention

10 Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the
15 invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than
20 about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving
25 in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the
30 compounds of the invention even if they possess no HCV polymerase inhibitory

activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37°C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Examples

Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

Table 1. List of abbreviations and acronyms.

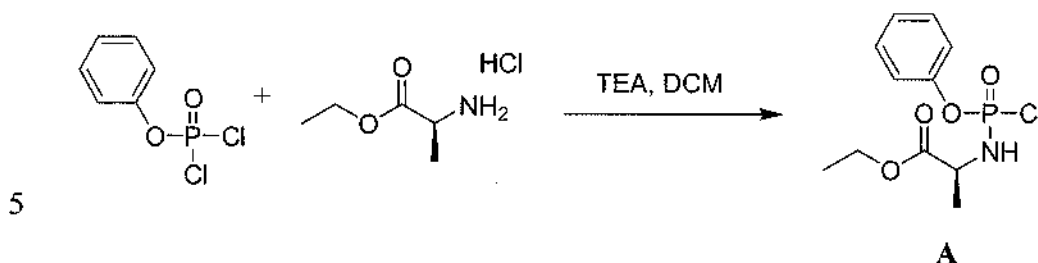
Abbreviation	Meaning
Ac ₂ O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCA	dichloroacetamide

DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMTC1	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4, 4' -dimethoxytrityl
DMF	dimethylform amide
EtOAc	ethyl acetate
ESI	electrospray ionization
HMDS	hexamethyldisilazane
HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH ⁺	mass plus 1
MH ⁻	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromo succinimide
Ph	phenyl
rt or r.t.	room temperature
TBAF	tetrabutyl ammonium fluoride
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane

TMSOTf	(trimethylsilyl)trifluoromethylsulfonate
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyldimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tic	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
Turbo Grignard	1:1 mixture of isopropylmagnesium chloride and lithium chloride
δ	parts per million down field from tetramethylsilane

Preparation of Compounds

(2S)-ethyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate A)



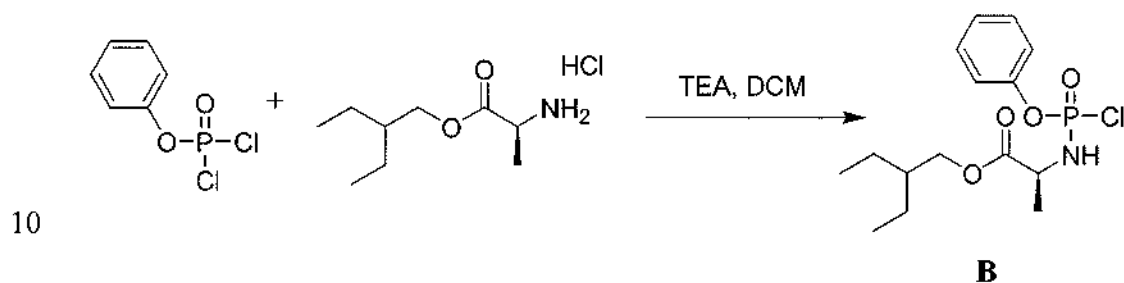
10 Ethyl alanine ester hydrochloride salt (1.69 g, 11 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and the mixture stirred with cooling to 0 °C under $\text{N}_2(\text{g})$. Phenyl dichlorophosphate (1.49 mL, 10 mmol) was added followed by dropwise addition of Et_3N over 10 min. The reaction mixture was then slowly warmed to RT and stirred for 12 h. Anhydrous Et_2O (50 mL) was added and the mixture stirred for 30 min. The solid that formed was removed by filtration, and the filtrate concentrated under reduced pressure. The residue was subjected to

silica gel chromatography eluting with 0-50% EtOAc in hexanes to provide intermediate A (1.13 g, 39%).

¹H NMR (300 MHz, CDCl₃) δ 7.39-7.27 (m, 5H), 4.27 (m, 3H), 1.52 (m, 3H), 1.32 (m, 3H).

5 ³¹P NMR (121.4 MHz, CDCl₃) δ 8.2, 7.8.

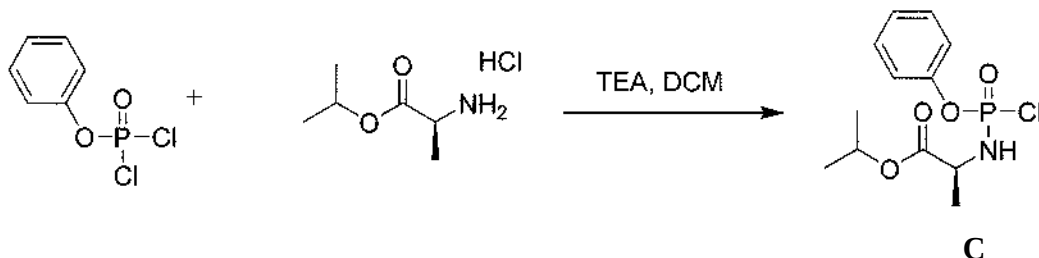
(2S)-2-ethylbutyl 2-(chloro(phenoxy)phosphorylamino)propanoate
(Chloridate B)



The 2-ethylbutyl alanine chlorophosphoramidate ester **B** was prepared using the same procedure as chloridate A except substituting 2-ethylbutyl alanine ester for ethyl alanine ester. The material is used crude in the next reaction.

15 Treatment with methanol or ethanol forms the displaced product with the requisite LCMS signal.

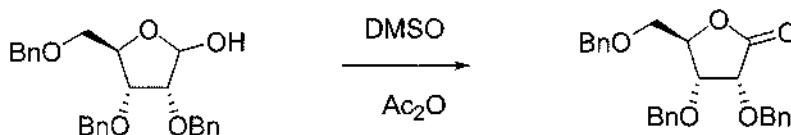
20 **(2S)-isopropyl 2-(chloro(phenoxy)phosphorylamino)propanoate (Chloridate C)**



The isopropyl alanine chlorophosphoramidate ester C was prepared using the same procedure as chloridate A except substituting isopropyl alanine ester for the ethyl alanine ester. The material is used crude in the next reaction. Treatment with methanol or ethanol forms the displaced product with the requisite LCMS

5 signal.

(2R, 3R, 4S, 5R)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3,4-dihydrox-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (Compound 1)



5

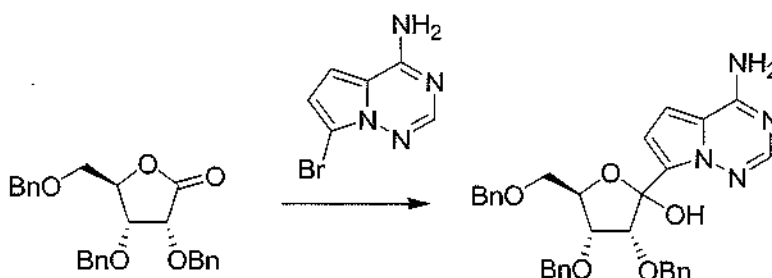
The commercially available lactol (10 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) under N₂(g). Ac₂O (20 mL) was added and the resultant reaction mixture stirred at RT for 48 h. The reaction mixture was poured onto ice H₂O (500 mL) and the mixture stirred for 20 min. The mixture was extracted with EtOAc (3 x 200 mL) and the combined organic extracts were then washed with H₂O (3 x 200 mL). The organic extract was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ and subjected to silica gel chromatography eluting with 25% EtOAc in hexanes to provide the lactone (9.55 g, 96%).

¹H NMR (400 MHz, DMSO) δ 7.30-7.34 (m, 13H), 7.19-7.21 (m, 2H), 4.55-4.72 (m, 6H), 4.47 (s, 2H), 4.28 (d, J = 3.9 Hz, 1H), 3.66 (m, 2H).

LCMS m/z 436.1 [M+H₂O], 435.2 [M+OH]⁻ Tr = 2.82 min

HPLC Tr = 4.59 [2-98% ACN in H₂] over 5 min @ 2ml / min flow.

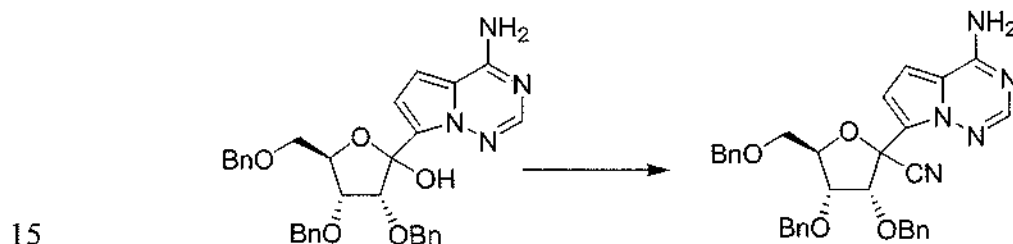
20



The bromopyrazole (prepared according to WO2009/132135) (0.5 g, 2.4 mmol) was suspended in anhydrous THF (10 mL) under N₂(g). The suspension

was stirred and TMSCl (0.67 mL, 5.28 mmol) was added. The mixture was stirred for 20 min. at RT and then cooled to -78 °C after which time a solution of n-BuLi (6 mL, 1.6 N in hexanes, 9.6 mmol) was added slowly. The reaction mixture was stirred for 10 min. at -78 °C and then the lactone (1 g, 2.4 mmol) was added *via* syringe. When the reaction was complete as measured by LCMS, AcOH was added to quench the reaction. The mixture was concentrated under reduced pressure and the residue dissolved in a mixture of CH₂Cl₂ and H₂O (100 mL, 1:1). The organic layer was separated and washed with H₂O (50 mL). The organic layer was then dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-50% EtOAc in hexanes to provide the product as a 1:1 mixture of anomers (345 mg, 26% yield).

LCMS *m/z* 553 [M+H].

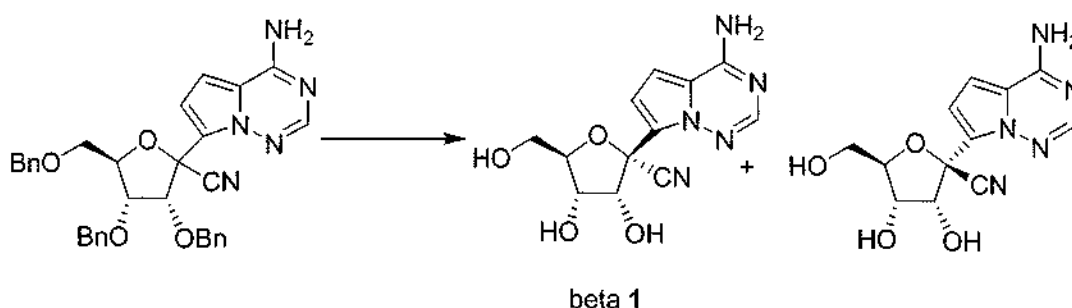


The hydroxy nucleoside (1.1 g, 2.0 mmol) was dissolved in anhydrous CH₂Cl₂ (40 mL) and the solution cooled with stirring to 0 °C under N₂(g). TMSCN (0.931 mL, 7 mmol) was added and the mixture stirred for a further 10 min. TMSOTf (1.63 mL, 9.0 mmol) was slowly added to the reaction and the mixture stirred for 1 h. The reaction mixture was then diluted with CH₂Cl₂ (120 mL) and aqueous NaHCO₃ (120 mL) was added to quench the reaction. The reaction mixture was stirred for a further 10 min and the organic layer separated. The aqueous layer was extracted with CH₂Cl₂ (150 mL) and the combined organic extracts dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was dissolved in a minimal amount of CH₂Cl₂ and subjected to silica gel chromatography eluting with a gradient of 0-75% EtOAc

and hexanes to provide the tribenzyl cyano nucleoside as a mixture of anomers.
(0.9 g, 80%).

¹H NMR (300 MHz, CD₃CN) δ 7.94 (s, 0.5H), 7.88 (s, 0.5H), 7.29-7.43 (m, 13H),
7.11-7.19 (m, 1H), 6.82-6.88 (m, 1H), 6.70-6.76 (m, 1H), 6.41 (bs, 2H), 5.10 (d, J
5 = 3.9 Hz, 0.5H), 4.96 (d, J = 5.1 Hz, 0.5H), 4.31-4.85 (m, 7H), 4.09-4.18 (m, 2H),
3.61-3.90 (m, 2H).
LCMS *m/z* 562 [M+H].

10



The tribenzyl cyano nucleoside (70 mg, 0.124 mmol) was dissolved in
anhydrous CH₂Cl₂ (2 mL) and cooled to -78 °C under N₂(g). A solution of BC1₃
15 (IN in CH₂Cl₂, 0.506 mL, 0.506 mmol) was added and the reaction mixture
stirred for 1 h. at -78 °C. When the reaction was complete by LC/MS, MeOH was
added to quench the reaction. The reaction mixture was allowed to warm to room
RT and the solvent removed under reduced pressure. The residue was subjected to
C18 reverse phase HPLC, eluting for 5 min with H₂O (0.1 % TFA), followed by a
20 gradient of 0-70% MeCN in H₂O (0.1 % TFA) over 35 min, to elute the α-anomer
(20 mg, 37%), and β-anomer 1 (20 mg, 37%).

(α-anomer)

¹H NMR (300 MHz, D₂O) δ 7.96 (s, 1H), 7.20 (d, J = 4.8 Hz, 1H), 6.91 (d, J = 4.8
Hz, 1H), 4.97 (d, J = 4.4 Hz, 1H), 4.56-4.62 (m, 1H), 4.08-4.14 (m, 1H), 3.90 (dd,
25 J = 12.9, 2.4 Hz, 1H), 3.70 (dd, J = 13.2, 4.5 Hz, 1H).

(β-anomer)

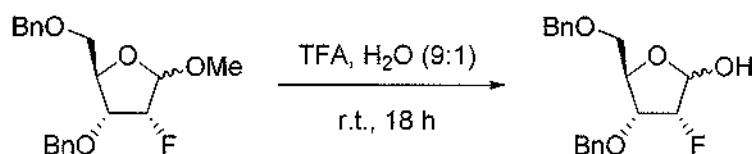
¹H NMR (400 MHz, DMSO) δ 7.91 (s, 1H), 7.80-8.00 (br s, 2H), 6.85-6.89 (m, 2H), 6.07 (d, J = 6.0 Hz, 1H), 5.17 (br s, 1H), 4.90 (br s, 1H), 4.63 (t, J = 3.9 Hz, 1H), 4.02-4.06 (m, 1H), 3.94 (br s, 1H), 3.48-3.64 (m, 2H).

LCMS m/z 292.2 [M+H], 290.0 [M-H]. Tr = 0.35 min.

5 ¹³C NMR (400 MHz, DMSO), 156.0, 148.3, 124.3, 117.8, 117.0, 111.2, 101.3, 85.8, 79.0, 74.7, 70.5, 61.4

HPLC Tr = 1.32 min

10 (2R,3R,4R,5R)-2-(4-aminopyrrolo [1,2-f]1,2,4-triazin-7-yl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (Compound 2)

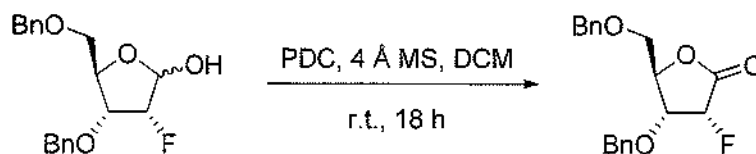


15 **2-Deoxy-2-fluoro-4,5-O-dibenzyl-D-arabinose.** 1-Methoxy-2-deoxy-2-fluoro-4,5-O-dibenzyl-D-arabinose (1.0 g, 2.88 mmol) in TFA (13.5 mL) was treated with H₂O (1.5 mL) and the resultant mixture stirred for 5 h. The mixture was then diluted with EtOAc (100 mL) and treated with saturated NaHCO₃ (50 mL). The organic layer was separated and washed with NaCl (50 mL), dried over
20 anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (80 g SiO₂ Combiflash HP Gold Column) eluting with 0-100% EtOAc in hexanes to afford 2-deoxy-2-fluoro-4,5-O-dibenzyl-D-arabinose (695 mg, 72%) as a white solid: R_f = 0.52 (25% EtOAc in hexanes);

25 ¹H NMR (300 MHz, CDCl₃) δ 7.30 (m, 10H), 5.35 (m, 1H), 4.68-4.29 (m, 7H), 3.70 (d, J = 10.5 Hz, 1H), 3.50 (d, J = 10.5 Hz, 2H).

¹⁹F NMR (282.2 MHz, CDCl₃) δ -207 (m), -211 (m).

LCMS m/z 350 [M+H₂O].



(3*R*, 4*R*, 5*R*)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorodihydrofuran-2(3*H*)-one. 2-Deoxy-2-fluoro-4, 5-0,0-dibenzyl-D-arabinose (4.3 g, 12.8 mmol) was dissolved in $\text{C}_3\text{H}_7\text{Cl}$ (85 mL) was treated with 4 Å MS (10 g) and pyridinium dichromate (14.4 g, 38.3 mmol). The resultant mixture was stirred for 24 h and then filtered through a pad of Celite. The eluant was concentrated under reduced pressure and the residue subjected to silica gel chromatography (120 g SiO_2 HP Gold Combiflash Column) eluting with 0-100% EtOAc in hexanes to afford (3*R*, 4*R*, 5*R*)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorodihydrofuran-2(3*H*)-one as a clear oil (3.5 g, 83%); R_f = 0.25 (25% EtOAc in hexanes).

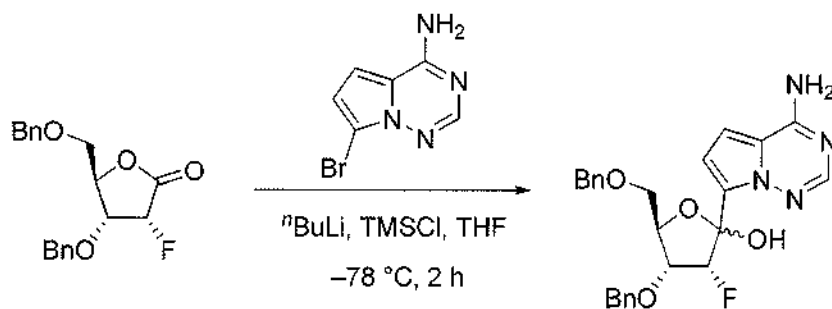
^1H NMR (300 MHz, CDCl_3) δ 7.37 (m, 10H), 5.45 (dd, J = 4.9, 5.7, Hz, 1H), 4.85 (d, J = 11.7 Hz, 1H), 4.52 (m, 4 H), 4.29 (d, J = 5.4 Hz, 1H), 2.08 (dd, J = 15.3, 10.2 Hz, 2H).

^{19}F NMR (282.2 MHz, CDCl_3) δ -216.

LCMS m/z 348 $[\text{M}+\text{H}_2\text{O}]$.

HPLC (6-98% MeCN- H_2O gradient, 0.05% TFA modifier) t_R = 5.29 min.

Phenomenex Synergi 4 m Hydro-RP 80 A, 50 x 4.60 mm, 4 micron; 2 mL/min flow rate



(3*R*, 4*R*, 5*R*)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-ol. 7-Bromopyrrolo [1,2-

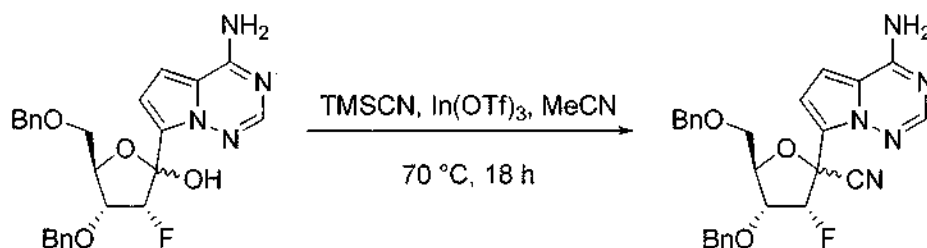
fj[1,2,4]-triazin-4-amine (68 mg, 0.319 mmol) in THF (1.4 mL) was treated with TMSCl (89 μ L, 0.703 mmol) and the mixture stirred for 2 h. The mixture was then cooled to -78 °C and treated with *n*-BuLi (1.0 M in hexanes, 1.09 mL, 1.09 mmol). The solution was stirred for 30 min and then treated with (3*R*, 4*R*, 5*R*)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorodihydrofuran-2(3*H*)-one (106 mg, 0.319 mmol) dropwise in THF (1.4 mL). The resultant mixture was stirred for 30 min and then AcOH (83 μ L, 1.44 mmol) in THF (1.0 mL) was added to quench the reaction. The mixture was warmed to RT and then concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL) and washed with saturated NaCl solution (50 mL). The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (40 g SiO₂ HP Gold Combiflash Column) eluting with 0-100% EtOAc in hexanes followed by a 0-100% gradient of (20% MeOH in EtOAc) in EtOAc to afford (3*R*, 4*R*, 5*i*)-2-(4-aminopyrrolo[1,2-
fj[1,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-ol as a white solid (68 mg, 44%, 60/40 mixture of α/β isomers). *R*_f = 0.32 (EtOAc).

¹H NMR (300 MHz, CDCl₃) δ 8.05 (s, 1H), 7.86 (s, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.26 (m, 10H), 6.95 (m, 1H), 6.71 (m, 1H), 6.08 (m, 1H), 5.34 (m, 1H), 4.65 (m, 6H), 4.71 (m, 2H).

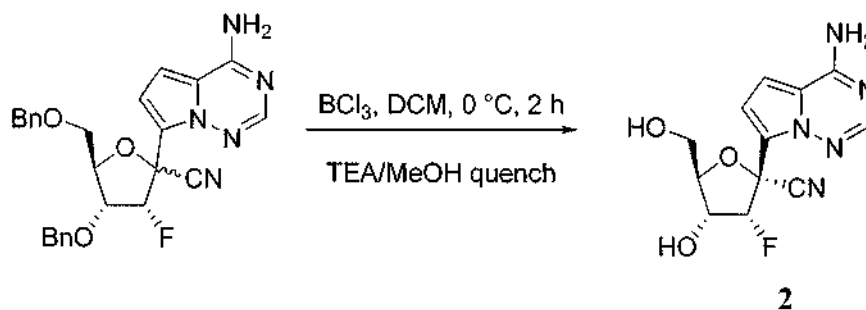
¹⁹F NMR (282.2 MHz, CDCl₃) δ -21.1 (m).

LCMS *m/z* 465 [M+H].

HPLC (6-98% MeCN-H₂O gradient, 0.05% TFA modifier) *t*_R = 4.37 min. (α -isomer), 4.54 min. (β -isomer).



- (3*R*, 4*R*, 5*R*)-2-(4-aminopyrrolo[1,2-*f*][1,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-carbonitrile: (3*R*, 4*R*, 5*i*?) -2-(4-aminopyrrolo[1,2-*f*][1,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxyethyl)-3-fluorotetrahydrofuran-2-ol (195 mg, 0.42 mmol) was dissolved in MeCN (1.4 mL) was treated with TMSCN (336 μ L, 2.52 mmol) and In(OTf)₃ (708 mg, 1.26 mmol). The solution was stirred at 70 °C for 18 h and then cooled to 0 °C. The mixture was treated with saturated NaHCO₃ solution (20 drops) then warmed to RT and diluted with EtOAc (100 mL) and H₂O (50 mL). The organic layer was separated and washed with saturated NaCl solution (50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography (40 g SiO₂ HP Gold Combiflash Column) eluting with 0-100% EtOAc in hexanes to afford (3*R*, 4*R*, 5*i*?) -2-(4-aminopyrrolo[1,2-*f*][1,2,4]triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-carbonitrile as a white solid (110 mg, 55%, 60/40 mixture of α/β isomers). Data for both isomers: R_f = 0.53 (EtOAc).
¹H NMR (300 MHz, CDCl₃) δ 8.01 (s, 1H), 7.94 (s, 1H), 7.30 (m, 10H), 7.00 (d, J = 4.5 Hz, 1H), 6.93 (d, J = 4.8 Hz, 1H), 6.87 (d, J = 5.4 Hz, 1H), 6.70 (d, J = 4.8 Hz, 1H), 5.85 (dd, J = 52, 3.3 Hz, 1H), 5.55 (dd, J = 53, 4.5 Hz, 1H), 4.71 (m, 7H), 3.87 (m, 2H), 3.72 (m, 2H).
¹⁹F NMR (282.2 MHz, CDCl₃) δ -196 (m), -203 (m).
 LCMS m/z 474 [M+H].
 HPLC (6-98% MeCN-H₂O gradient, 0.05% TFA modifier) t_R = 4.98 min.



(2*R*, 3*R*, 4*R*, 5*R*)-2-(4-aminopyrrolo[1,2-*f*]1,2,4-triazin-7-yl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile (2) (3*R*, 4*R*, 5*R*)-2-(4-aminopyrrolo[1,2-*f*]1,2,4-triazin-7-yl)-4-(benzyloxy)-5-(benzyloxymethyl)-3-fluorotetrahydrofuran-2-carbonitrile (110 mg, 0.23 mmol) was dissolved in CH₂Cl₂ (1.5 mL) and cooled to 0 °C. The reaction mixture was treated with BCl₃ (1.0 M in CH₂Cl₂, 766 µL, 0.77 mmol) and stirred for 2 h. The mixture was then cooled to -78 °C and treated with Et₃N (340 µL, 2.44 mmol) followed by MeOH (2 mL) before allowing to warm to RT. The reaction was concentrated under reduced pressure and then co-evaporated with MeOH (3 × 5 mL). The residue was then suspended in H₂O (5 mL) and treated with NaHCO₃ (1 g). The solution was stirred for 10 min and then concentrated under reduced pressure. The residue was filtered and washed with MeOH (3 × 10 mL) on a fritted glass funnel (coarse) and the eluant concentrated under reduced pressure. The residue was subjected to reverse phase HPLC (6-98% MeCN in H₂O gradient with 0.05% TFA modifier) to afford (2*R*, 3*R*, 4*R*, 5*R*)-2-(4-aminopyrrolo[1,2-*f*]1,2,4-triazin-7-yl)-3-fluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-carbonitrile 2 as a white solid (16.8 mg, 25%) and the α-isomer.

Data for the β-isomer: R_f = 0.13 (10% MeOH in EtOAc).

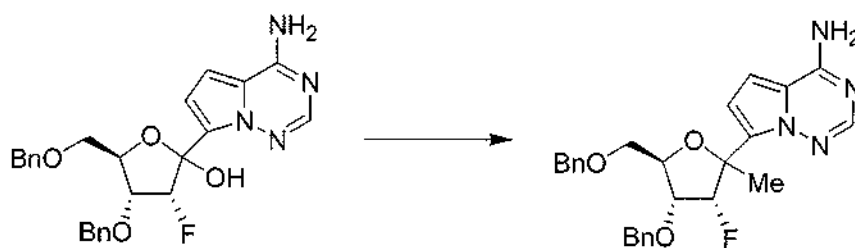
¹H NMR (300 MHz, CD₃OD) δ 8.09 (s, 1H), 7.28 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 5.42 (dd, J = 5.3, 3.3 Hz, 1H), 4.20 (m, 2H), 3.99 (d, J = 3.6 Hz, 1H), 3.77 (d, J = 3.6 Hz, 1H).

¹⁹F NMR (282.2 MHz, CDCl₃) δ -197 (m).

LCMS m/z 294 [M+H].

HPLC (2-98% MeCN-H₂O gradient, 0.05% TFA modifier) t_R = 1.49 min.

(2*R*, 3*R*, 4*R*, 5*S*)-5-(4-aminopyrrolo[1,2-*f*]1,2,4-triazin-7-yl)-4-fluoro-2-(hydroxymethyl)-5-nitrotetrahydrofuran-3-ol (Compound 3)

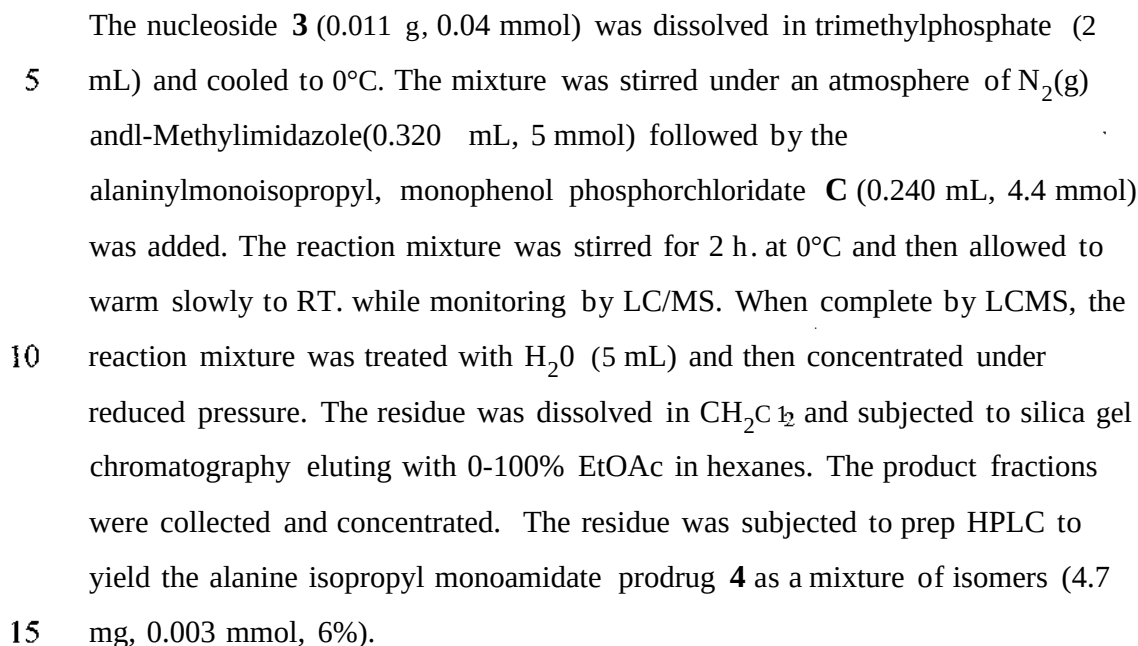


The starting nucleoside (prepared as described in the synthesis of compound 2) (0.355 g, 0.765 mmol) was dissolved in anhydrous THF (35 mL) and cooled to 0°C with stirring under N₂(g). A solution of methyl magnesium chloride (2 mL, 6 mmol) (3N in THF) was added and the resultant mixture stirred overnight. Acetic acid (7 mmol) was added to quench the reaction and then the solvents were removed by rotary under reduced pressure. The residue was re-dissolved in CH₂Cl₂ and the solution subjected to a plug of silica gel to isolate the product (0.355 g) as a crude mixture. LC/MS (m/z : 480, M⁺). The crude material was dissolved in anhydrous CH₂Cl₂ (20 mL) and placed under N₂(g). The solution was stirred and treated with methanesulfonic acid (0.2 mL, 2.74 mmol). The reaction mixture was stirred for 12 h at RT and then quenched by the addition of Et₃N (3.5 mmol). The mixture was concentrated under reduced pressure and the residue subjected to silica gel chromatography to provide the methyl substituted nucleoside (0.174 g, 0.377 mmol, 44% yield) as a 4:1 mixture of beta- and alpha-anomers respectively.

¹H NMR (300 MHz, CD₃CN) major anomer δ 7.87 (s, 1H), 7.27-7.40 (m, 10 H), 6.77 (d, J = 4.5 Hz, 1H), 6.70 (d, J = 4.5 Hz, 1H), 6.23 (br s, 2H), 5.53 (dd, J = 5.3 Hz, 1H), 4.42-4.75 (m, 4H), 4.19-4.26 (m, 1H), 3.65-4.00 (m, 3H), 1.74 (d, J = 3.9 Hz, 3H).

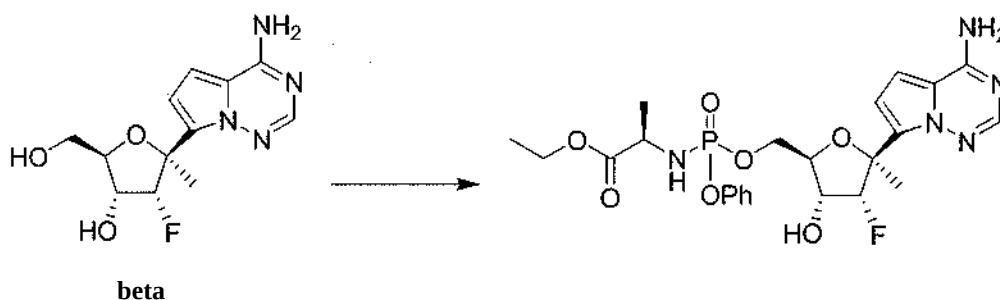
¹⁹F NMR (282.2 MHz, CD₃CN) major anomer δ -207 (m, 1F)

LCMS m/z 463 [M+H].



¹H NMR (300 MHz, CD₃CN) δ 7.87 (s, 1H), 7.17-7.44 (m, 5 H), 6.71-6.83 (m, 2H), 6.14 (br, s, 2H), 5.38 (dd, J = 56, 3.3 Hz, 1H), 4.92-5.01 (m, 1H), 3.86-4.46 (m, 6H), 3.58 (m, 1H), 1.73 (m, 3H), 1.18-1.34 (m, 9H)
LCMS *m/z* 552 [M+H].

(2R)-ethyl 2-((((2R,3R,4R,5S)-5-r4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-4-fluoro-3-hydroxy-5-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (Compound 5)



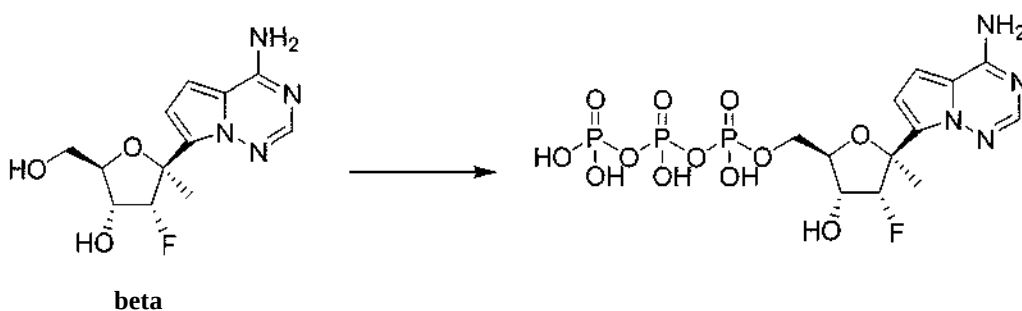
5 The nucleoside **3** (0.026 g, 0.092 mmol) was dissolved in trimethylphosphate (2 mL) and cooled to 0°C. The mixture was stirred under N₂(g) and 1-methylimidazole (0.062 mL, 0.763 mmol) followed by the chloridate A (0.160 g, 0.552 mmol) were added. The reaction mixture was stirred for 2 h. at 0°C and then allowed to warm slowly to RT. 3/4 O (5 mL) was added to quench

10 the reaction and then the mixture concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ and subjected to silica gel chromatography eluting with 0-100% EtOAc in hexanes. The product fractions were collected and concentrated. . Crude product was eluted using 0 to 100 percent EtOAc in hexanes. The crude product was collected and concentrated under reduced

15 pressure. The residue was subjected to prep HPLC to yield **5** (2.0 mg, 4% yield). LCMS m/z 538 [M+H].

((2R, 3R, 4R, 5S)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-4-fluoro-3-hydroxy-5-methyltetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate

20 **(Compound 6)**

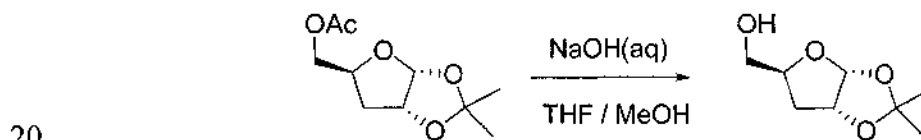


The nucleoside **3** (0.022 g, 0.056 mmol) was dissolved in trimethylphosphate (1 mL) and stirred under N₂(g). Phosphorous oxychloride
 5 (0.067 mL, 0.73 mmol) was added and the mixture stirred for 2 h. Monitoring by analytical ion-exchange column determined the time at which > 80 percent of monophosphate was formed. A solution of tributylamine (0.44 mL, 1.85 mmol) and triethylammonium pyrophosphate (0.327 g, 0.72 mmol) dissolved in anhydrous DMF (1 mL) was added. The reaction mixture was stirred for 20 min
 10 and then quenched by the addition of 1N triethylammonium bicarbonate solution in H₂O (5 mL). The mixture was concentrated under reduced pressure and the residue re-dissolved in H₂O. The solution was subjected to ion exchange chromatography to yield the title product **6** (1.7 mg, 6% yield).

LCMS *m/z* 521 [M-H]. Tr = 0.41

15 HPLC ion exchange TR = 9.40 min

(2R,3R,5S)-2-(4-aminopyrrolon,2-firi,2,4,1triazin-7-yl)-3-hvdroxy-5-(hvdroxymethyl)-tetrahydrofuran-2-carbonitrile (Compound 7)



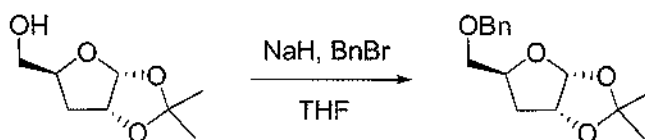
((3aR,5S,6aR)-2,2-dimethyl-tetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methanol

The acetate material (1.2 g, 5.5 mmol) (J. Org. Chem. 1985, 50, 3547, De Bernardo et al) was dissolved in a 1:1 mixture MeOH and THF (10 mL). A 1N

solution of NaOH(aq) (10mL) was added until the pH was 13. The reaction mixture was stirred for 2h and then neutralized to pH 8-9 by the addition of AcOH. The mixture was extracted with EtOAc (10 x 30mL) and the combined organic extracts dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the desired product (866 mg, 90%).

¹H NMR (300 MHz, CDCl₃) δ 5.84 (d, *J* = 3.6 Hz, 1H), 4.78 (t, *J* = 4.5 Hz, 1H), 4.38 (m, 1H), 3.93-3.54 (m, 2H), 2.04-1.84 (m, 2H), 1.52 (s, 3H), 1.33 (s, 3H).

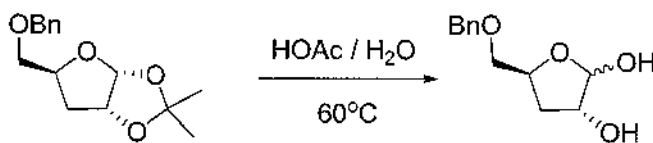
10



(3aR,5S,6aR)-5-(benzyloxymethyl)-2,2-dimethyl-tetrahydrofuro[2,3-

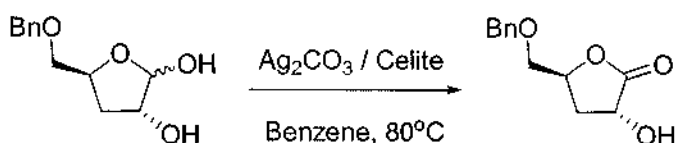
d][1,3]dioxole. Sodium hydride (188 mg, 7.46 mmol) was dissolved in anhydrous THF (5 mL) and stirred under N₂(g) at RT. The alcohol (866 mg, 4.97 mmol) was dissolved in anhydrous THF (3 mL) and then added in portions over 5 min. to the sodium hydride mixture. The resultant mixture was stirred for 20 min. and then benzyl bromide (892 μL, 7.46 mmol) was added. The reaction was stirred for 2 h and then poured onto a mixture of ice cold aqueous NaHCO₃ and EtOAc (30mL). The organic layer was separated and then the aqueous layer re-extracted with EtOAc (30 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-40% EtOAc in hexanes to give the benzyl ether product (912 mg, 69%).

¹H NMR (300 MHz, CDCl₃) δ 7.35-7.27 (m, 5H), 5.86 (d, *J* = 3.6 Hz, 1H), 4.74 (t, *J* = 4.2 Hz, 1H), 4.60 (s, 2H), 4.42 (m, 1H), 3.69-3.53 (m, 2H), 2.10-2.04 (m, 1H), 1.83-1.77 (m, 1H), 1.52 (s, 3H), 1.33 (s, 3H).



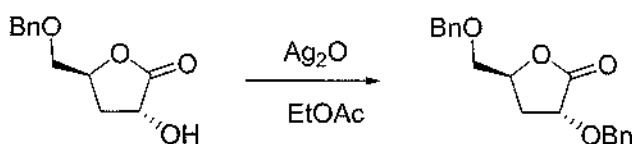
(3R,5S)-5-(benzyloxymethyl)-tetrahydrofuran-2,3-diol. The benzyl ether (910 mg, 3.44 mmol) was dissolved in a 1:1 AcOH and H₂O (20 mL) mixture and stirred at 60°C for 7h. The mixture was concentrated under reduced pressure and the residue subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the diol product (705 mg, 91%).

¹H NMR (300 MHz, CDCl₃) δ 7.36-7.27 (m, 5H), 5.40 (d, *J* = 3.9 Hz, 0.5H), 5.17 (s, 0.5H), 4.67-4.56 (m, 3H), 4.33 (m, 0.5H), 4.24 (d, *J* = 4.8 Hz, 0.5H), 3.71-3.67 (m, 1H), 3.56-3.42 (m, 2H), 2.31-2.22 (m, 1H), 2.08-1.89 (m, 2H).



(3R,5S)-5-(benzyloxymethyl)-3-hydroxy-dihydrofuran-2(3H)-one. The diol (705 mg, 3.14 mmol) was dissolved in benzene (30 mL) and treated with a silver carbonate celite mixture (3.46 g, 6.28 mmol). The resultant mixture was stirred at 80°C under N₂(g) for 2h. The mixture was then cooled to RT, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the lactone product (600 mg, 86%).

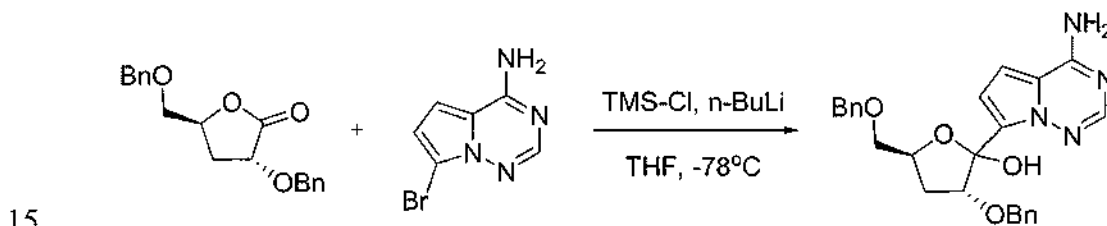
¹H NMR (300 MHz, CDCl₃) δ 7.39-7.27 (m, 5H), 4.75-4.68 (m, 1H), 4.60-4.49 (m, 2H), 3.74-3.54 (m, 2H), 2.61-2.35 (m, 2H), 2.38-2.28 (m, 1H).



(3R, 5S)-3-(benzyloxy)-5-(benzyloxymethyl)-dihydrofuran-2(3H)-one. The lactone (600 mg, 2.7 mmol) was dissolved in EtOAc (30mL) and treated with silver oxide (626 mg, 2.7 mmol) followed by benzyl bromide (387 μ L, 3.24 mmol). The reaction mixture was then stirred at 50°C under N₂(g) for 8h.

- 5 Additional silver oxide (300 mg) was then added and the resultant mixture stirred at 50°C for 16h. Additional benzyl bromide (50 μ L) and silver oxide (150 mg) were added and the mixture stirred for an additional 8h. The reaction mixture was allowed to cool, filtered and then concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-20% EtOAc in
 10 hexanes to give the title product (742 mg, 88%).

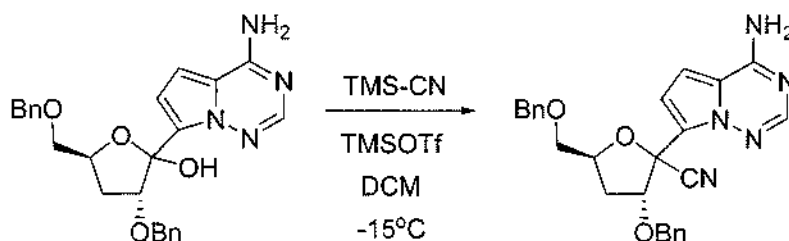
¹H NMR (300 MHz, CDCl₃) δ 7.39-7.27 (m, 10H), 4.99 (d, *J* = 11.4 Hz, 1H), 4.72 (m, 2H), 4.56 (m, 2H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.72-3.51 (m, 2H), 2.42-2.25 (m, 2H).



- (3R,5S)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3-(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-ol.** The 7-bromopyrrolo[1,2-f][1,2,4]triazin-4-amine (607 mg, 2.85 mmol) was dissolved in anhydrous THF (10 mL) and stirred under Ar(g) at RT. TMSCl (1.1 mL, 8.55 mmol) was added dropwise and the mixture stirred for 2h. The reaction was concentrated under reduced pressure and then dried under high vacuum. The residue was suspended in THF (20 mL) and stirred under Ar(g) at -78°C. A 2.5M n-BuLi solution in hexane (2.28 mL, 5.7 mmol) was added dropwise over 10 min. and the resultant
 20 mixture stirred for 60 min. The lactone (742 mg, 2.37 mmol) dissolved in anhydrous THF (7 mL) was added to the above mixture over 20 min. The reaction mixture was stirred for 2 h. and then quenched with AcOH until pH was 5-6. The
 25

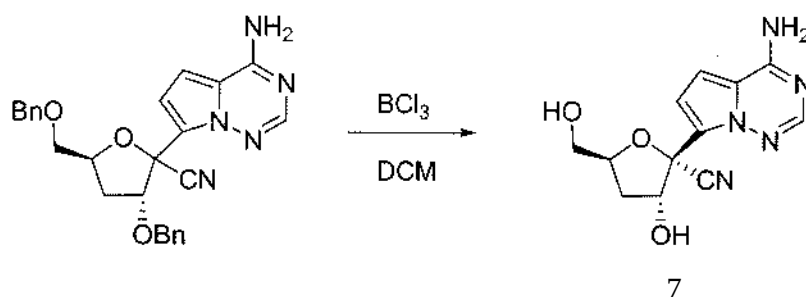
mixture was allowed to warm to RT and then diluted with EtOAc. The solution was washed with saturated NaHCO₃ solution, saturated NaCl, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-80% EtOAc in hexanes to give the title product (250 mg, 24%).

LCMS *m/z* 447.2 [M+H], 445.1 [M-H].



- 10 **(3R,5S)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3-(benzyloxy)-5-(benzyloxymethyl)-tetrahydrofuran-2-carbonitrile.** The alcohol (250 mg, 0.56 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) and stirred under Ar(g) at -15°C. TMSCN (448 μL, 3.36 mmol) was added dropwise and the mixture stirred for 10 min. TMSOTf (466 μL, 2.58 mmol) was added dropwise over 10 min and the resultant mixture stirred for 90 min. at -15°C. Additional TMSCN (224 μL, 3 eq.) and TMSOTf (202 μL, 2 eq.) was added and stirring continued for 5 h.
- 15 Saturated aqueous NaHCO₃ solution was added to quench the reaction and the mixture stirred for 10 min. The organic layer was separated and washed with saturated aqueous NaHCO₃ solution, saturated NaCl solution, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-70% EtOAc in hexanes to give the title product (150 mg, 59%).

LCMS *m/z* 456.3 [M+H], 454.1 [M-H].

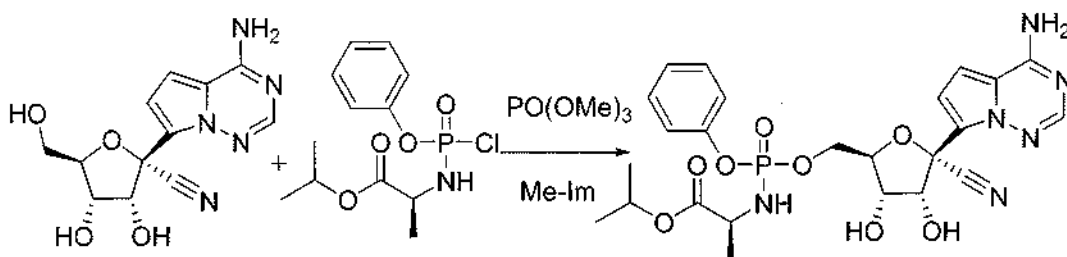


(2R,3R,5S)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-carbonitrile (7). The benzyl ether (150

5 mg, 0.329 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and the mixture stirred under Ar(g) at -20°C . A 1M BCl_3 solution in CH_2Cl_2 (724 μL , 0.724 mmol) was added dropwise and the resultant mixture stirred for 2h. Additional 1M BCl_3 in CH_2Cl_2 (724 μL , 0.724 mmol) was added and stirring continued for 2h. The mixture was then cooled to -78°C and slowly treated with a 2:1 mixture of Et_3N and MeOH (3 mL). The mixture was stirred for 10 min and then treated with MeOH (10 mL). The reaction was allowed to warm to RT and then concentrated under reduced pressure. The residue was dissolved in MeOH and concentrated under reduced pressure. The residue was dissolved in MeOH again and treated with solid NaHCO_3 . The mixture was stirred for 5 min and then the solid removed by filtration. The solution was concentrated under reduced pressure and subjected to preparative HPLC to provide the desired product 7 (10 mg, 11%).

^1H NMR (300 MHz, D_2O) δ 7.71 (s, 1H), 6.75 (d, $J = 4.5$ Hz, 1H), 6.65 (d, $J = 4.8$ Hz, 1H), 4.91 (t, $J = 6.3$ Hz, 1H), 4.57 (m, 1H), 3.67-3.47 (m, 2H), 2.18 (m, 2H). LCMS m/z 276.1 $[\text{M}+\text{H}]$, 274.0 $[\text{M}-\text{H}]$.

(2S)-isopropyl 2-((r(2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phosphorylamino)propanoate (Compound 8)



8

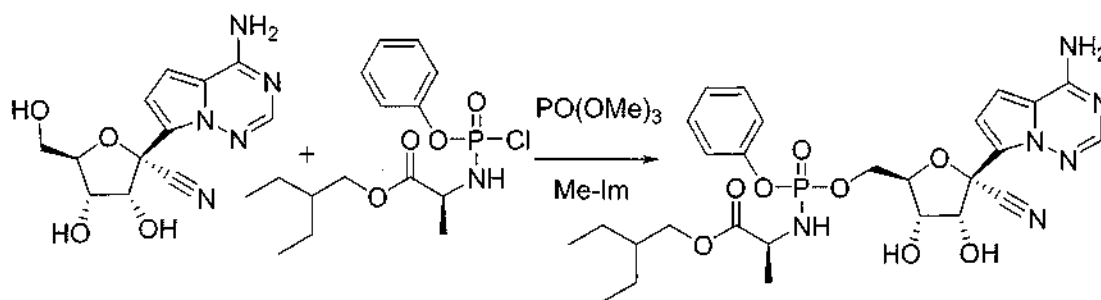
The nucleoside **1** (45mg, 0.15mmol) was dissolved in anhydrous trimethyl phosphate (0.5 mL) and the solution stirred under N₂(g) at 0°C. Methyl imidazole (36 µL, 0.45 mmol) was added to the solution. Chlorophosphoramidate **C** (69 mg, 0.225 mmol) was dissolved in anhydrous THF (0.25 mL) and added dropwise to the nucleoside mixture. When the reaction was complete by LCMS, the reaction mixture was diluted with EtOAc and washed with saturated aqueous NaHCO₃ solution, saturated NaCl, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0-5% MeOH in CH₂Cl₂ followed by preparative HPLC to give the product (20.9 mg, 25%).

¹H NMR (300 MHz, CD₃OD) δ 7.95 (m, 1H), 7.31-6.97 (m, 7H), 4.94 (m, 1H), 4.78 (m, 1H), 4.43 (m, 3H), 4.20 (m, 1H), 3.80 (d, 1H), 1.30-1.18 (m, 9H);

³¹P NMR (121.4 MHz, CD₃OD) δ 3.8.

LCMS *m/z* 561.0 [M+H], 559.0 [M-H].

(2S)-2-ethylbutyl 2-((((2R,3S,4R,5R)-5-(4-aminophenyl)-1,2,4-triazol-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (Compound 9)



9

Prepared from Compound **1** and chloridate **B** according to the same
 5 method as for the preparation of compound **8**.

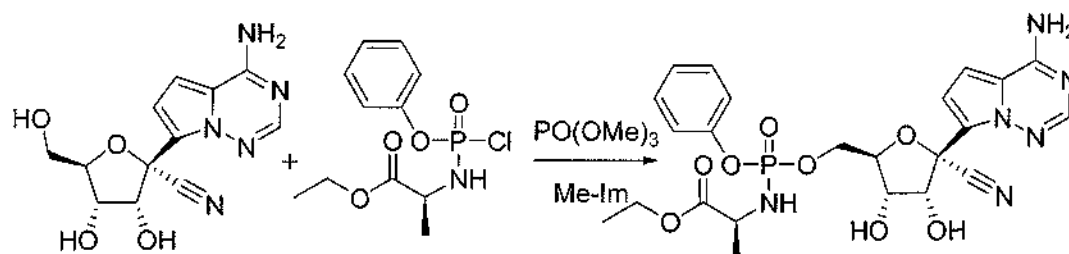
¹H NMR (300 MHz, CD₃OD) δ 7.87 (m, 1H), 7.31-7.16 (m, 5H), 6.92-6.89 (m, 2H), 4.78 (m, 1H), 4.50-3.80 (m, 7H), 1.45-1.24 (m, 8H), 0.95-0.84 (m, 6H).

³¹P NMR (121.4 MHz, CD₃OD) δ 3.7.

LCMS *m/z* 603.1 [M+H], 601.0 [M-H].

10

qSVcthv1 2-(((2R,3S,4R,5R)-5-(4-aminopvriolo[1.2-flK2.4]tria/in-7-vn-5-
cyano-3,4-dihydroxytetrahydrofuran-2-
yl)methoxy)(phenoxy)phosphorylamino)propanoate (Compound 10)



15

10

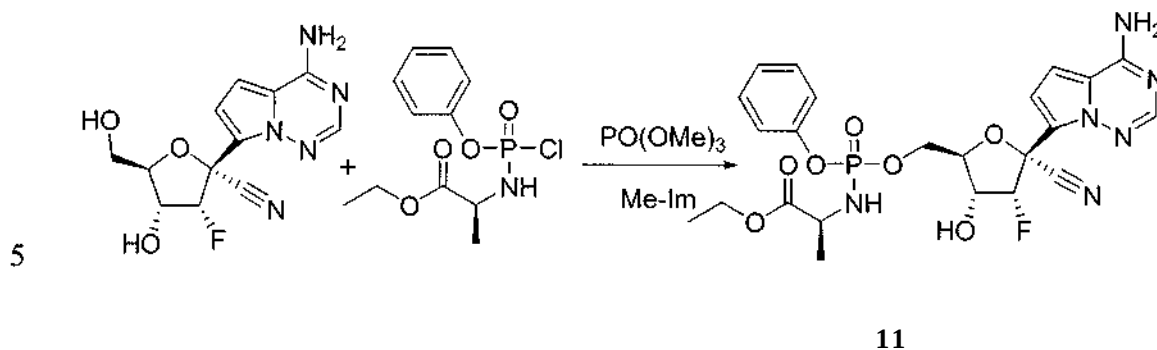
Prepared from Compound **1** and chloridate A using same method as for the
 preparation of compound **8**.

¹H NMR (300 MHz, CD₃OD) δ 7.95 (m, 1H), 7.32-6.97 (m, 7H), 4.78 (m, 1H),
 20 4.43-4.08 (m, 6H), 3.83 (m, 1H), 1.31-1.18 (m, 6H).

³¹P NMR (121.4 MHz, CD₃OD) δ 3.7.

LCMS *m/z* 547.0 [M+H], 545.0 [M-H].

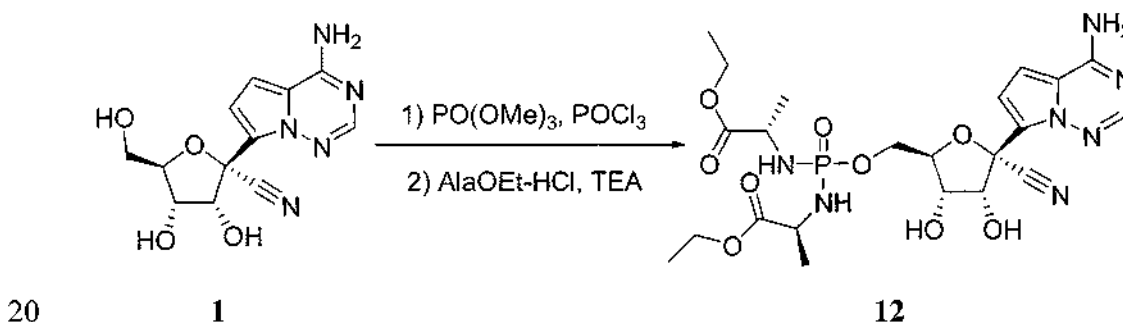
(2S)-ethyl 2-((((2R,3R,4R,5R)-5-(4-aminopyrrolo[1,2-f]1,2,4-triazin-7-yl)-5-cyano-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (Compound 11)



Compound 11 was prepared from Compound 2 and chloridate A using same method as for the preparation of compound 8.

- 10 ¹H NMR (300 MHz, CD₃OD) δ 7.91 (m, 1H), 7.33-7.16 (m, 5H), 6.98-6.90 (m, 2H), 5.59 (m, 1H), 4.50-4.15 (m, 4H), 4.12-3.90 (m, 3H), 1.33-1.18 (m, 6H).
³¹P NMR (121.4 MHz, CD₃OD) δ 3.8.
 LCMS *m/z* 549.0 [M+H], 547.1 [M-H].

- 15 (2S,2'S)-diethyl 2,2'-((((2R,3S,4R,5R)-5-(4-aminopyrrolo[1,2-f]1,2,4-triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)phosphoryl)bis(azanediyldipropionate (Compound 12)



The nucleoside 1 (14.6 mg, 0.05 mmol) was dissolved in anhydrous trimethyl phosphate (0.5 mL) and stirred under N₂(g) at RT. POCl₃ (9.2 μL, 0.1 mmol) was added and the mixture stirred for 60 min. Alanine ethyl ester

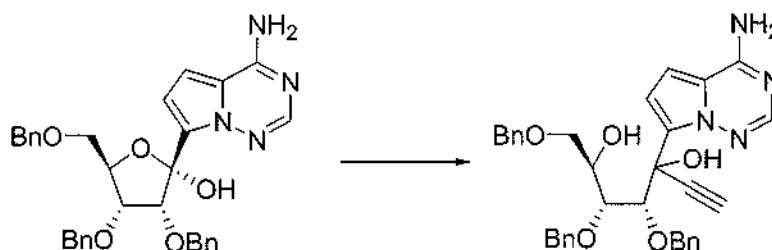
hydrochloride (61 mg, 0.4 mmol) and then Et₃N (70 µL, 0.5 mmol) was added. The resultant mixture was stirred for 15 min. and then additional Et₃N (70 µL, 0.5 mmol) was added to give a solution pH of 9-10. The mixture was stirred for 2 h. and then diluted with EtOAc, washed with saturated aqueous NaHCO₃ solution followed by saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to preparative HPLC (C₁₈ column) to yield the product **12** (5.5 mg, 16%).

¹H NMR (400 MHz, CD₃OD) δ 8.13 (s, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.18 (d, *J* = 4.8 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.36 (m, 1H), 4.25-4.08 (m, 7H), 3.83 (m, 2H), 1.33-1.23 (m, 12H).

³¹P NMR (121.4 MHz, CD₃OD) δ 13.8.

LCMS *m/z* 570.0 [M+H], 568.0 [M-H].

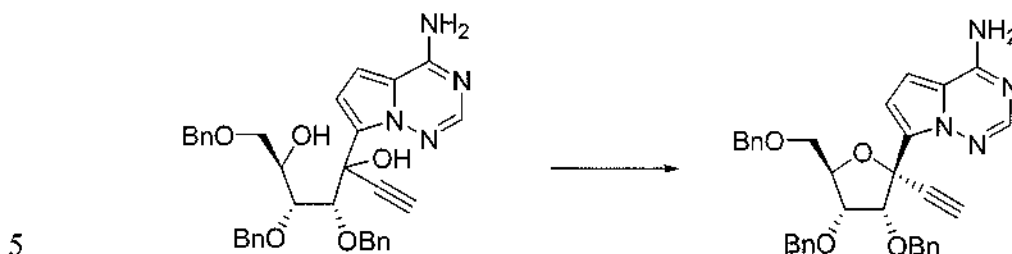
(2S,3R,4S,5R)-2-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-2-ethynyl-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (Compound 13)



The nucleoside alcohol (0.6 g, 1.08 mmol) (prepared as described in Compound **1** synthesis) was dissolved in anhydrous THF (8mL) and placed under N₂(g). The reaction mixture was stirred and cooled to 0°C and then treated with a 0.5N solution of ethynyl magnesium bromide in THF (17.2 mL, 17.2 mmol). The reaction mixture was stirred overnight at RT. AcOH (1.5 mL) was added to quench the reaction. The mixture was concentrated under reduced pressure and the residue redissolved in CH₂Cl₂. The solution subjected to a plug of silica gel

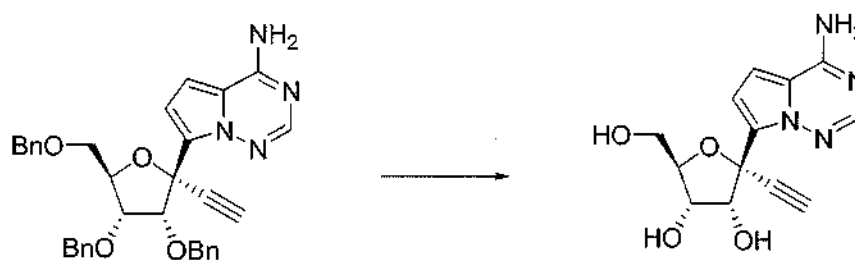
eluting with 0 to 80% EtOAc in Hexanes to provide the title product as a crude mixture.

LCMS m/z 579 [M+H].



The crude ethynyl alcohol (0.624 g, 1.08 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and placed under $\text{N}_2(\text{g})$. The mixture was stirred and sulfonic acid (0.2 mL, 2.74 mmol) was added. The reaction mixture was stirred for 12 h. at RT. When complete by LCMS, Et_3N (0.56 mL) was added to quench the reaction. The reaction was concentrated under reduced pressure and the residue subjected to silica gel chromatography eluting with 0 to 75% EtOAc in Hexanes to yield the ethynyl nucleoside as a mixture of anomers (0.200 g, 33% over 2 steps).

15 LCMS m/z 561 [M+H].



13

The tribenzyl nucleoside (0.650 g, 1.16 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) and cooled to -78°C under $\text{N}_2(\text{g})$. A solution of boron tribromide (1 N in CH_2Cl_2 , 5.5 mL) was added and the reaction mixture stirred for 1 h. at -78°C . A solution of MeOH (10 mL) and pyridine (2 mL) was added to quench the reaction and the mixture was allowed to rise to RT. The mixture was concentrated

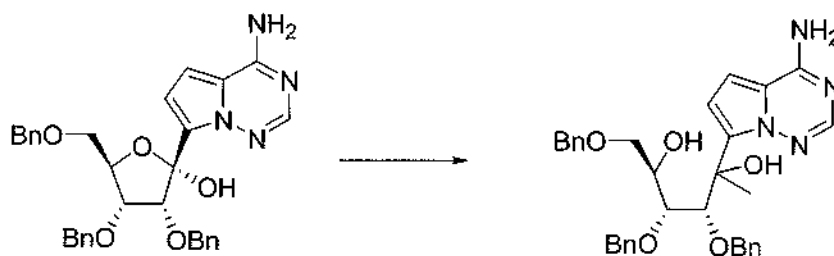
under reduced pressure and subjected to preparative HPLC to provide the α -anomer (20 mg) and β -anomer **13** (110 mg)

(β -anomer) ^1H NMR (300 MHz, DMSO) δ 7.81 (s, 1H), 7.76 (br s, 2H), 6.80-6.85 (m, 2H), 5.11 (d, J = 7.2 Hz, 1H), 4.90 (d, J = 6.0 Hz, 1H), 4.82 (dd, J = 7.2, 4.8 Hz, 1H), 4.62 (t, J = 6.3 Hz, 1H), 3.95-3.99 (m, 1H), 3.85-3.91 (dd, J = 11.4, 5.7 Hz, 1H), 3.61-3.67 (m, 1H), 3.47-3.55 (m, 1H), 3.52 (d, J = 0.9 Hz, 1H).

(α -anomer) ^1H NMR (300 MHz, DMSO) δ 7.80 (s, 1H), 7.59 (bs, 2H), 6.80 (d, J = 4.5 Hz, 1H), 6.54 (d, J = 4.2 Hz, 1H), 5.00 (d, J = 7.2 Hz, 1H), 4.89 (d, J = 4.8 Hz, 1H), 4.74 (t, J = 5.7 Hz, 1H), 4.58 (t, J = 4.5 Hz, 1H), 4.27 (m, 1H), 3.88 (m, 1H), 3.64-3.72 (m, 1H), 3.51-3.59 (m, 1H), 3.48 (d, J = 0.6 Hz, 1H)

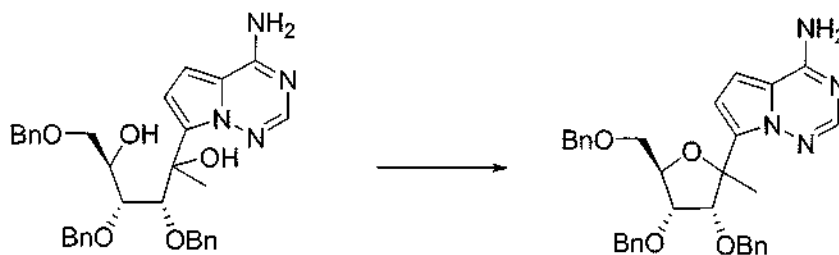
LCMS m/z 291 [M+H].

(2R,3R,4R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-1,3,4-tris(benzyloxy)hexane-2,5-diol (Compound 14)

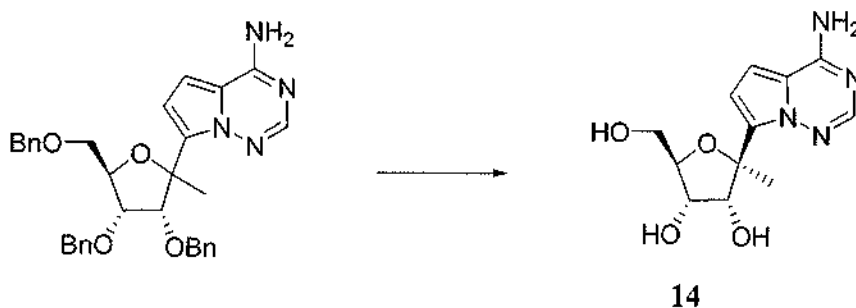


The tribenzyl alcohol from Compound **1** synthesis (0.250 g, 0.453 mmol) was dissolved in anhydrous THF (25 mL) and stirred under N_2 (g). The reaction mixture was cooled to 0°C and then a 3.0 N solution of methyl magnesium chloride in THF (1.2 mL, 3.62 mmol) was added. The reaction mixture was stirred overnight at RT. Acetic acid (1.5 mL) was added to quench the reaction and then the mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 and subjected to a plug of silica gel eluting with 0 to 80% EtOAc in hexanes. The crude product (0.452 g) was then used in the next reaction without further purification.

LCMS m/z 569 [M+H].



The crude methyl nucleoside (0.452 g, 0.796 mmol) was dissolved in
 5 anhydrous CH_2Cl_2 (20 mL) and stirred under $\text{N}_2(\text{g})$. Methanesulfonic acid (0.2 mL, 2.78 mmol) was added and the reaction stirred for 12 hr at RT. Et_3N (0.56 mL) was added to quench the reaction and then the mixture concentrated under reduced pressure. The residue was subjected to silica gel chromatography eluting with 0 to 75% EtOAc in Hexanes to yield the product as a mixture of anomers
 10 (0.20 g, 46% over 2 steps).
 LCMS m/z 551 $[\text{M}+\text{H}]$.



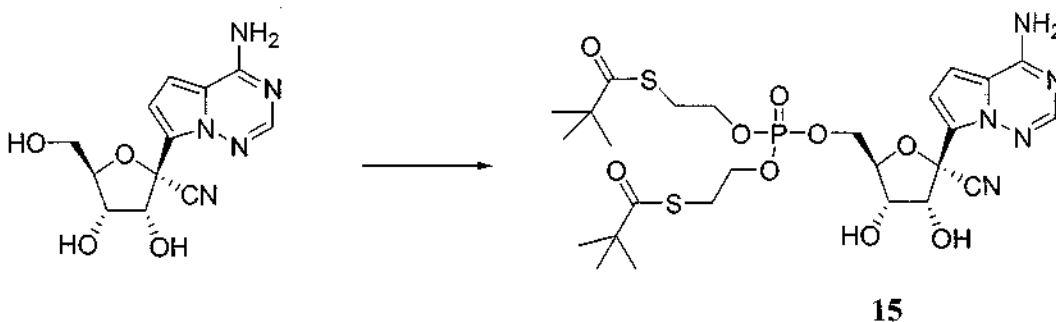
15 The tribenzyl nucleoside (0.20 g, 0.364 mmol) was dissolved in AcOH (30 mL). and charged with Pd/C (Degussa) (400 mg). The stirred mixture was flushed with $\text{N}_2(\text{g})$ three times and then H_2 (g) was introduced, The reaction was stirred under H_2 (g) for 2 h. and then the catalyst removed by filtration. The solution was concentrated under reduced pressure and under the residue was re-dissolved
 20 in H_2O . The solution was subjected to preparative HPLC under neutral conditions to provide the α -anomer and β -anomer **14** in 81% yield.

(α -anomer) ^1H NMR (300 MHz, D_2O) δ 7.81 (s, 1H), 7.22 (d, 1H), 6.75 (d, 1H), 4.47 (d, 1H), 4.25-4.31 (m, 1H), 3.88-4.95 (m, 1H), 3.58-3.86 (dd, 2H), 1.50 (s, 3H).

(β -anomer) ^1H NMR (300 MHz, D_2O) δ 7.91 (s, 1H), 7.26 (d, 1H), 6.90 (d, 1H), 4.61 (d, 1H), 4.00-4.09 (m, 2H), 3.63-3.82 (dd, 2H), 1.67 (s, 3H).

LCMS m/z 281 $[\text{M}+\text{H}]$.

S,S'-2,2'-((((2R,3S,4R,5R)-5-(4-aminopyrroloil,2-flfl,2,4]triazin-7-yl)-S-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,4-diyl) bis(2,2-dimethylpropanethioate) (Compound 15)



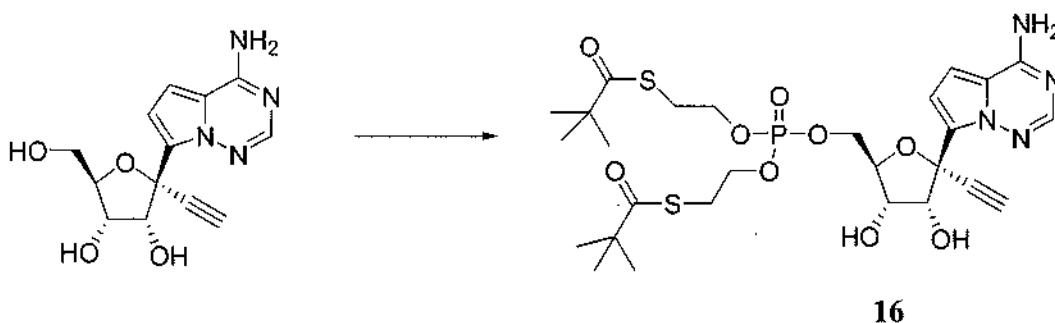
The nucleoside **1** (0.028 g, 0.096 mmol) was dissolved in trimethylphosphate (1 mL). The reaction was stirred under $\text{N}_2(\text{g})$ and then treated with 1H-tetrazole (0.021 g, 0.29 mmol). The reaction mixture was cooled to 0°C and the phosphane (Nucleoside Nucleotides, Nucleic acids; 14; 3-5; 1995; 763 - 766. Lefebvre, Isabelle; Pompon, Alain; Perigaud, Christian; Girardet, Jean-Luc; Gosselin, Gilles; et al.) (87 mg, 0.192 mmol) was added. The reaction was stirred for 2 h. and then quenched with 30% hydrogen peroxide (0.120 mL). The mixture was stirred for 30 min at RT and then treated with saturated aqueous sodium thiosulfate (1 mL). The mixture was stirred for 10 min. and then concentrated under reduced pressure. The residue was subjected to preparative HPLC to isolate the title product **15**.

¹H NMR (300 MHz, CD₃CN) δ 7.98 (s, 1H), 6.92 (d, 1H), 6.81 (d, 1H), 6.44 (bs, 2H), 4.82 (m, 2H), 4.47 (m, 1H), 4.24 (m, 2H), 4.00 (m, 4H), 3.80 (bs, 1H), 3.11 (m, 4H), 1.24 (s, 9H).

³¹P NMR (121.4 MHz, CD₃CN) δ -1.85 (s).

5 LCMS *m/z* 661 [M+H].

S,S'-2,2'-((((2R, 3S, 4R, 5S)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)phosphoryl)bis(oxy)bis(ethane-2,1-diyl) bis(2,2-dimethylpropanethioate) (Compound 16)



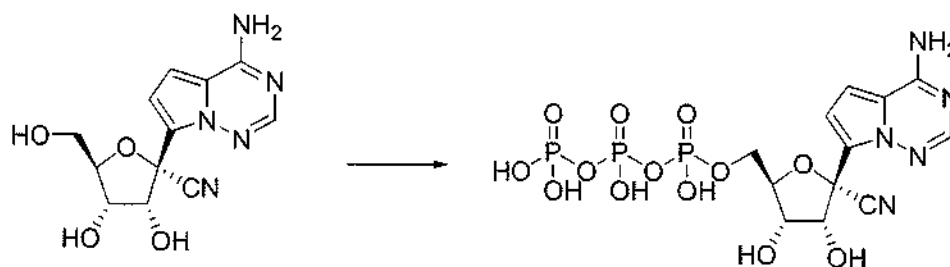
Compound **16** was prepared using the same method as compound **15** except substituting compound **13** as the starting nucleoside.

15 ¹H NMR (300 MHz, CD₃CN) δ 7.91 (s, 1H), 6.86 (d, *J* = 4.8 Hz, 1H), 6.76 (d, *J* = 4.5 Hz, 1H), 6.29 (bs, 2H), 4.69 (t, *J* = 2.7 Hz, 1H), 4.58 (d, *J* = 5.7 Hz, 1H), 4.14-4.33 (m, 5H), 3.99-4.07 (m, 4H), 3.53 (d, *J* = 5.4 Hz, 1H), 3.11 (q, *J* = 5.7 Hz, 4H), 1.22 (s, 18H).

LCMS *m/z* 658.9 [M+]. Tr=2.31

20

(((2R, 3S, 4R, 5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-ethynyl-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound 17)



17

Compound 17 was prepared from compound 1 using a similar procedure to the preparation of compound 6. The product was isolated as the sodium salt.

^1H NMR (400 MHz, D_2O) δ 7.76 (s, 1H), 6.88 (d, $J = 4.8$ Hz, 1H), 6.73 (d, $J = 4.4$ Hz, 1H), 4.86 (d, $J = 5.2$ Hz, 1H), 4.43 (m, 1H), 4.39 (m, 1H), 4.05 (m, 1H), 3.94 (m, 1H)

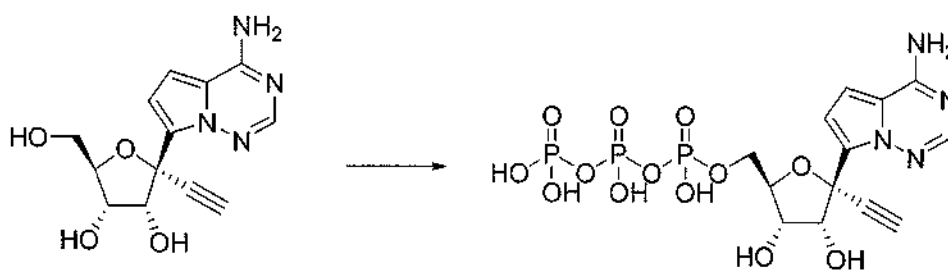
^{31}P NMR (121.4 MHz, D_2O) δ -5.4 (d, IP), -10.8 (d, IP), -21.1 (t, IP).

LCMS m/z 530 [M-H], 531.9 [M+H] Tr = 0.22 min

HPLC ion exchange Tr=9.95 min

((2R, 3S, 4R, 5S)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate

(Compound 18)



18

Compound 18 was prepared from compound 13 using a similar procedure to the preparation of compound 6. The product was isolated as the TEA salt.

¹H NMR (300 MHz, D₂O) δ 7.85 (s, 1H), 7.09 (d, J = 4.6 Hz, 1H), 6.95 (d, J = 4.7 Hz, 1H), 4.23 (m, 2H), 4.08 (m, 2H), 3.06 (q, J = 7.4 Hz, 20H), 1.14 (t, J = 7.3 Hz, 3OH)

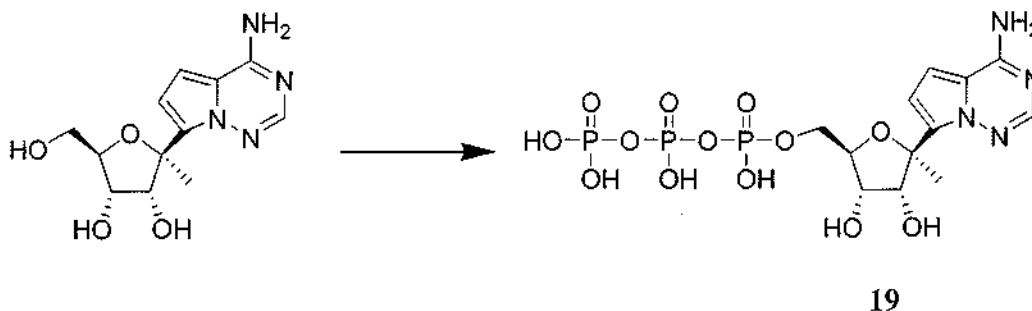
³¹P NMR (121.4 MHz, D₂O) δ -10.8 (d, IP), -11.2 (d, IP), -23.2 (t, IP).

5 LCMS *m/z* 530.8 [M+H], Tr = 0.46

HPLC ion exchange Tr = 9.40 min

((2R, 3S, 4R, 5S)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-3,4-dihydroxy-5-methyltetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate (Compound

10 **19)**



15

Compound **19** was prepared from compound **14** using a similar procedure to the preparation of compound **6**.

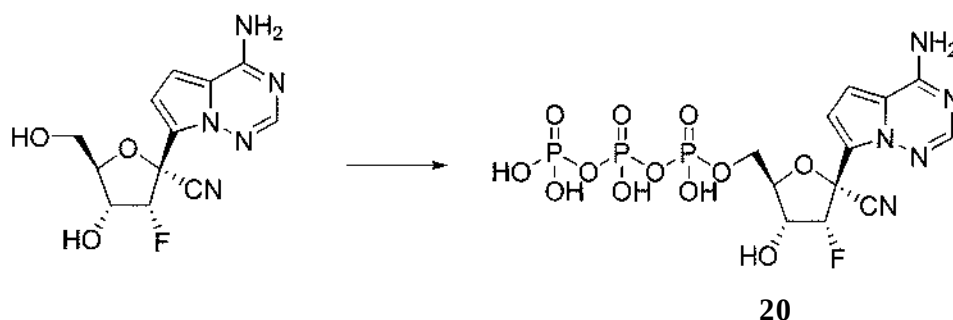
¹H NMR (400 MHz, D₂O) δ 7.78 (s, 1H), 6.98 (m, 1H), 6.84 (m, 1H), 4.45 (m, 1H), 4.04 (m, 4H), 1.54 (s, 3H).

20 ³¹P NMR (161 MHz, D₂O) δ -10.6 (m), -23.0 (m).

LCMS *m/z* 521.0 [M+H].

((2R,3R,4R,5R)-5-(4-aminopyrrolo[1,2-f][1,2,4]triazin-7-yl)-5-cyano-4-fluoro-3-hydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate

25 **(Compound 20)**



Compound **20** was prepared from compound **2** using a similar procedure to the preparation of compound **6**.

¹H NMR (400 MHz, D₂O) δ 7.78 (s, 1H), 6.93 (d, J = 4.4 Hz, 1H), 6.78 (d, J = 4.8 Hz, 1H), 5.45 (dd, J = 5.3, 4.4 Hz, 1H), 4.38-4.50 (m, 2H), 4.13-4.20 (m, 2H).

³¹P NMR (161 MHz, D₂O) δ -5.7 (d, IP), -11.0 (d, IP), -21.5 (t, IP).

LCMS *m/z* 533.9.0 [M+H], 532.0 [M-H] Tr = 1.25 min.

HPLC ion exchange Tr=1 1.0 min

10

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solventWater mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated.

- 5 Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral
10 activity of a compound can be measured using the following general protocols.

Respiratory syncytial virus (RSV) antiviral activity and cytotoxicity assays

Anti-RSV activity

15

Antiviral activity against RSV is determined using an in vitro cytoprotection assay in Hep2 cells. In this assay, compounds inhibiting the virus replication exhibit cytoprotective effect against the virus-induced cell killing that can be quantified using a cell viability reagent. The method used is similar to
20 methods previously described in published literature (Chapman et al., *Antimicrob Agents Chemother.* **2007**, 57(9):3346-53.)

Hep2 cells are obtained from ATCC (Manassas, VI) and maintained in MEM media supplemented with 10% fetal bovine serum and penicillin/streptomycin. Cells are passaged twice a week and kept at subconfluent
25 stage. Commercial stock of RSV strain A2 (Advanced Biotechnologies, Columbia, MD) is titered before compound testing to determine the appropriate dilution of the virus stock that generates desirable cytopathic effect in Hep2 cells.

For antiviral tests, Hep2 cells are seeded into 96-well plates 24 hours before the assay at a density of 3,000 cells/well. On a separate 96well plate,
30 compounds to be tested are serially diluted in cell culture media. Eight

concentrations in 3-fold serial dilution increments are prepared for each tested compound and 100 uL/well of each dilution is transferred in duplicate onto plates with seeded Hep2 cells. Subsequently, appropriate dilution of virus stock previously determined by titration is prepared in cell culture media and 100
5 uL/well is added to test plates containing cells and serially diluted compounds. Each plate includes three wells of infected untreated cells and three wells of uninfected cells that served as 0% and 100% virus inhibition control, respectively. Following the infection with RSV, testing plates are incubated for 4 days in a tissue culture incubator. After the incubation, RSV-induced cytopathic effect is
10 determined using a Cell TiterGlo reagent (Promega, Madison, WI) followed by a luminescence read-out. The percentage inhibition is calculated for each tested concentration relative to the 0% and 100% inhibition controls and the EC50 value for each compound is determined by non-linear regression as a concentration inhibiting the RSV-induced cytopathic effect by 50%. Ribavirin (purchased from
15 Sigma, St. Louis, MO) is used as a positive control for antiviral activity.

Cytotoxicity

Cytotoxicity of tested compounds is determined in uninfected Hep2 cells
20 in parallel with the antiviral activity using the cell viability reagent in a similar fashion as described before for other cell types (Cihlar et al., *Antimicrob Agents Chemother.* **2008**,52(2):655-65.). The same protocol as for the determination of antiviral activity is used for the measurement of compound cytotoxicity except that the cells are not infected with RSV. Instead, fresh cell culture media (100
25 uL/well) without the virus is added to tested plates with cells and prediluted compounds. Cells are then incubated for 4 days followed by a cell viability test using CellTiter Glo reagent and a luminescence read-out. Untreated cell and cells treated with 50 ug/mL puromycin (Sigma, St. Louis, MO) are used as 100% and 0% cell viability control, respectively. The percent of cell viability is calculated
30 for each tested compound concentration relative to the 0% and 100% controls and

the CC50 value is determined by non-linear regression as a compound concentration reducing the cell viability by 50%.

Compound	EC50 / μ M	CC50 / μ M
1	0.48	>100
10	0.18	47
12	6.5	>100
13	34	>100
14	2.7	92
15	0.15	>100
16	3.3	>100

5 RSV RNP Preparation

RSV ribonucleoprotein (RNP) complexes were prepared from a method modified from Mason *et al* (1). HEp-2 cells were plated at a density of 7.1×10^4 cells/cm² in MEM + 10% fetal bovine serum (FBS) and allowed to attach overnight at 37°C (5% CO₂). Following attachment, the cells were infected with RSV A2 (MOI=5) in 35 mL MEM + 2% FBS. At 20 hours post-infection, the media was replaced with MEM + 2% FBS supplemented with 2 μ g/mL actinomycin D and returned to 37°C for one hour. The cells were then washed once with PBS and treated with 35 mL of PBS + 250 μ g/mL lyso-lecithin for one minute, after which all liquid was aspirated. The cells were harvested by scrapping them into 1.2 mL of buffer A [50 mM TRIS acetate (pH 8.0), 100 mM potassium acetate, 1 mM DTT and 2 μ g/mL actinomycin D] and lysed by repeated passage through an 18 gauge needle (10 times). The cell lysate was placed in ice for 10 minutes and then centrifuged at 2400g for 10 minutes at 4°C. The supernatant (S1) was removed and the pellet (P1) was disrupted in 600 μ L of Buffer B [10 mM TRIS acetate (pH 8.0), 100mM potassium acetate and 1.5 mM MgCl₂] supplemented with 1% Triton X-100 by repeated passage through an 18 gauge needle (10 times). The resuspended pellet was placed in ice for 10 minutes and then centrifuged at 2400g for 10 minutes at 4°C. The supernatant (S2) was removed and the pellet (P2) was disrupted in 600 μ L of Buffer B supplemented with 0.5% deoxycholate and 0.1% Tween 40. The resuspended pellet was placed

in ice for 10 minutes and then centrifuged at 2400g for 10 minutes at 4°C. The supernatant (S3) fraction, containing the enriched RSV RNP complexes, was collected and the protein concentration determined by UV absorbance at 280 nm. Aliquoted RSV RNP S3 fractions were stored at -80°C.

5

RSV RNP Assay

Transcription reactions contained 25µg of crude RSV RNP complexes in 30 µL of reaction buffer [50 mM TRIS-acetate (pH 8.0), 120 mM potassium acetate, 5% glycerol, 4.5 mM MgCl₂, 3 mM DTT, 2 mM ethyleneglycol-bis(2-aminoethylether)-tetraacetic acid (EGTA), 50 µg/mL BSA, 2.5 U RNasin (Promega), ATP, GTP, UTP, CTP and 1.5 uCi [α-³²P] NTP (3000 Ci/mmol)]. The radiolabelled nucleotide used in the transcription assay was selected to match the nucleotide analog being evaluated for inhibition of RSV RNP transcription. Cold, competitive NTP was added at a final concentration of one-half its K_m (ATP= 20 µM, GTP= 12.5 µM, UTP= 6 µM and CTP= 2 µM). The three remaining nucleotides were added at a final concentration of 100 µM.

To determine whether nucleotide analogs inhibited RSV RNP transcription, compounds were added using a 6 step serial dilution in 5-fold increments. Following a 90 minute incubation at 30°C, the RNP reactions were stopped with 350 µL of Qiagen RLT lysis buffer and the RNA was purified using a Qiagen RNeasy 96 kit. Purified RNA was denatured in RNA sample loading buffer (Sigma) at 65°C for 10 minutes and run on a 1.2% agarose/MOPS gel containing 2M formaldehyde. The agarose gel was dried and exposed to a Storm phosphorimager screen and developed using a Storm phosphorimager (GE Healthcare). The concentration of compound that reduced total radiolabelled transcripts by 50% (IC₅₀) was calculated by non-linear regression analysis of two replicates.

Reference

- 1) Mason, S., Lawetz, C, Gaudette, Y., Do, F., Scouten, E., Lagace, L., Simoneau, B. and Liuzzi, M. (2004) Polyadenylation-dependent screening

assay for respiratory syncytial virus RNA transcriptase activity and identification of an inhibitor. Nucleic Acids Research, **32**, 4758-4767.

Compound	IC ₅₀ / μ M
6	3.6
17	1.5
18	1.6
19	1.5
20	0.8

5 Description of the Parainfluenza Cytoprotection Assay

The Parainfluenza Cytoprotection assay uses Vero cells and Parainfluenza 3 strain C 243. Briefly virus and cells are mixed in the presence of test compound and incubated for 7 days. The virus is pre-titered such that control wells exhibit 85 to 95% loss of cell viability due to virus replication. Therefore, antiviral effect or cytoprotection is observed when compounds prevent virus replication. Each assay plate contains cell control wells (cells only), virus control wells (cells plus virus), compound toxicity control wells (cells plus compound only), compound colorimetric control wells (compound only), as well as experimental wells (compound plus cells plus virus). Cytoprotection and compound cytotoxicity are assessed by MTS (CellTiter®96 Reagent, Promega, Madison WI) dye reduction. The % reduction in viral cytopathic effects (CPE) is determined and reported; IC₅₀ (concentration inhibiting virus replication by 50%), TC₅₀ (concentration resulting in 50% cell death) and a calculated TI (therapeutic index TC₅₀/IC₅₀) are provided along with a graphical representation of the antiviral activity and compound cytotoxicity when compounds are tested in dose-response. Each assay includes ribavirin as a positive control.

Cell Preparation

Vero cells (Kidney, African green monkey, *Cercopithecus aethiops*) were obtained from the American Type Culture Collection (ATCC, Rockville, Maryland) and are grown in Dulbecco's Modified Eagle's Medium (DMEM)

supplemented with 10% fetal bovine serum (FBS), 2.0 mM L-Glutamine, 100 units/ml Penicillin and 100 ug/ml Streptomycin ("growth medium"). Cells are sub-cultured twice a week at a split ratio of 1:10 using standard cell culture techniques. Total cell number and percent viability determinations are performed using a hemacytometer and trypan blue exclusion. Cell viability must be greater than 95% for the cells to be utilized in the assay. The cells are seeded in 96-well tissue culture plates the day before the assay at a concentration of 1×10^4 cells/well.

10 Virus Preparation

The virus used for this assay is Parainfluenza 3 strain C 243. This virus was obtained from the American Type Culture Collection (ATCC) and was grown in Vero cells for the production of stock virus pools. For each assay, a pre-titered aliquot of virus is removed from the freezer (-80°C) and allowed to thaw slowly to room temperature in a biological safety cabinet. The virus is resuspended and diluted into tissue culture medium such that the amount of virus added to each well is the amount determined to give between 85 to 95% cell killing at 6-7 days post-infection.

20 MTS Staining for Cell Viability

At assay termination (7 days post-infection), the assay plates are stained with the soluble tetrazolium-based dye MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; CellTiter®96 Reagent, Promega) to determine cell viability and quantify compound toxicity.

MTS is metabolized by the mitochondrial enzymes of metabolically active cells to yield a soluble formazan product, allowing the rapid quantitative analysis of cell viability and compound cytotoxicity. This reagent is a stable, single solution that does not require preparation before use. At termination of the assay, 20-25 μL of MTS reagent is added per well and the microtiter plates are then incubated for 4-6 hrs at 37°C, 5% CO_2 to assess cell viability. Adhesive plate sealers are used in place of the lids, the sealed plate is inverted several times to mix the soluble

formazan product and the plate is read spectrophotometrically at 490/650 nm with a Molecular Devices Vmax or SpectraMax Plus plate reader.

Data Analysis

- 5 Using an in-house computer program % Cytopathic Effect (CPE) Reduction, %Cell Viability, IC_{25} , IC_{50} , IC_{95} , TC_{25} , TC_{50} , and TC_{95} and other indices are calculated and the graphical results summary is displayed. Raw data for both antiviral activity and toxicity with a graphical representation of the data are provided in a printout summarizing the individual compound activity. The
- 10 Table below shows the activity of selected compounds against Parainfluenza 3 virus.

Compound	IC_{50} / μM	TC_{50} / μM
1	1.71	>30
14	5.23	>30

- 15 The specific pharmacological and biochemical responses observed in the assays described may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with practice of the present invention.

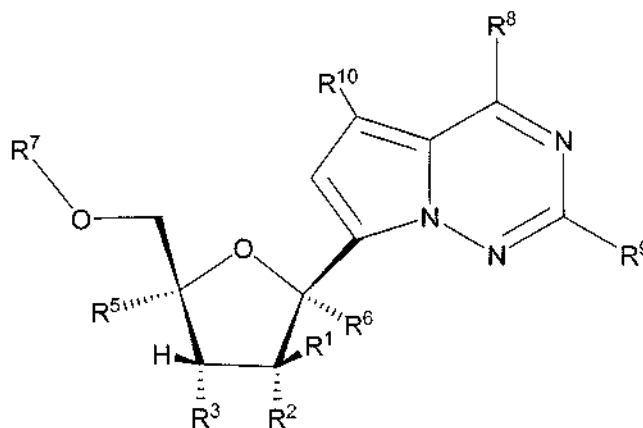
20

 All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

- 25 The invention has been described with reference to various specific and preferred embodiments and techniques. However, one skilled in the art will understand that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is

1. The compound of Formula I for use in treating a *Paramyxoviridae* infection, wherein the compound of Formula I has the structure:



Formula I

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

each R^2 , R^3 or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl;

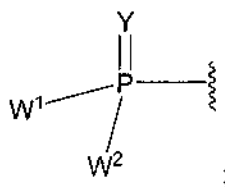
or any two R^2 , R^3 or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, $(d-C_8)$ alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl (C_1-C_8) alkyl;

each n is independently 0, 1, or 2;

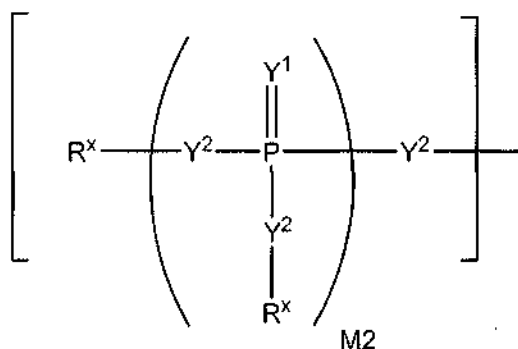
each R^a is independently H, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl(Ci-C₈)alkyl, (C₄-C₈)carbocyclalkyl, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(0)R¹¹, -S(0)₂R¹¹, -S(0)(OR¹¹), -S(0)₂(OR¹¹), or -S(0)₂NR¹¹R¹²;

R⁷ is H, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(0)R¹¹, -S(0)₂R¹¹, -S(0)(OR¹¹), -S(0)₂(OR¹¹), -S(0)₂NR¹¹R¹², or



each Y or Y¹ is, independently, O, S, NR, ⁺N(0)(R), N(OR), ⁺N(0)(OR), or N-NR₂;

W¹ and W², when taken together, are -Y³(C(R^y)₂)₃Y³⁻; or one of W¹ or W² together with either R³ or R⁴ is -Y³⁻ and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:



Formula Ia

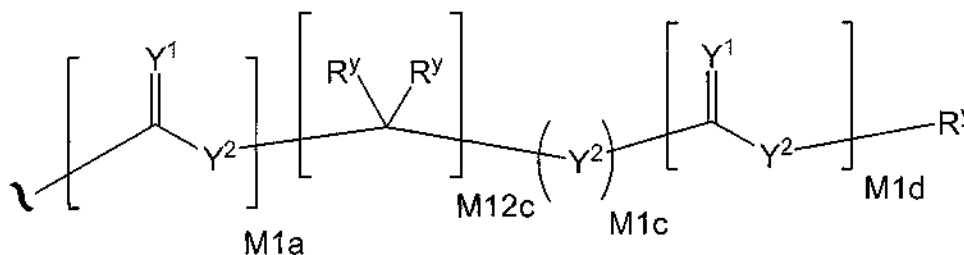
wherein:

each Y² is independently a bond, O, CR₂, NR, ⁺N(0)(R), N(OR), ⁺N(0)(OR), N-NR₂, S, S-S, S(O), or S(0)₂;

each Y³ is independently O, S, or NR;

M2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M1a, M1c, and M1d is independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, -C^YY¹, -C(=Y¹)OR, -C(=Y¹)N(R)₂, -N(R)₂, -N⁺(R)₃, -SR, -S(OR), -S(O)₂R, -S(O)(OR), -S(O)₂(OR), -OC(=Y¹)R, -OC(=Y¹)OR, -OC(=Y¹)(N(R)₂), -SC(=Y¹)R, -SC(=Y¹)OR, -SC(=Y¹)(N(R)₂), -N(R)G(=Y¹)R, -N(R)C(=Y¹)OR, -N(R)C(=Y¹)N(R)₂, -SO₂NR₂, -CN, -N₃, -NO₂, -OR, or W³; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C₁-C₈) alkyl, (C_i-C_g) substituted alkyl, (C₂-C_s) alkenyl, (C₂-C_g) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)R^y, -C(Y¹)W⁵, -SO₂R^y, or -SO₂W⁵; and W⁵ is a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

each R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(-NR¹¹), -CH=NNHR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, (C_i-C₈) alkyl, (C₂-C₈) alkenyl, (C₂-C_g) alkynyl, (C₄-C₈) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(C₁-C₈) alkyl, -S(O)_n(C_i-C₈) alkyl, aryl(C_i-C₈) alkyl, OR¹¹ or SR¹¹;

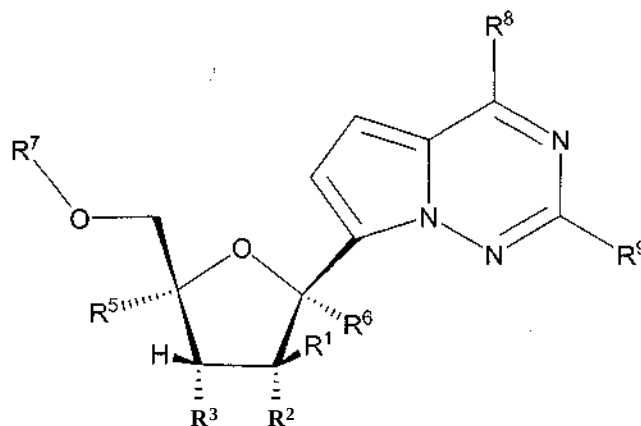
each R⁹ or R¹⁰ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹,

$-\text{CH}=\text{N}(\text{OR}^{11})$, $-\text{CH}(\text{OR}^{11})_2$, $-\text{C}(=\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{S})\text{NR}^{11}\text{R}^{12}$, $-\text{C}(=\text{O})\text{OR}^{11}$, R^{11} , OR^{11} or SR^{11} ; and

each R^{11} or R^{12} is independently H, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-\text{C}(=\text{O})(\text{Ci-C}_8)\text{alkyl}$, $-\text{S}(\text{O})_n(\text{C}_1\text{-C}_8)\text{alkyl}$ or aryl(Q-C₈)alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a-; and

wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each R^2 , R^3 , R^5 , R^6 , R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a-.

2. The compound for use according to claim 1 wherein the compound of Formula I is represented by Formula II:



Formula II

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

each R^2 is OR^a or halogen;

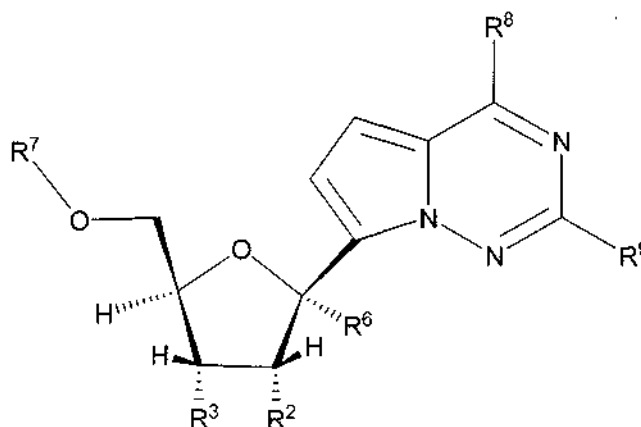
each R^3 or R^5 is independently H, OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (Ci-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (Ci-C₈)substituted alkyl,

(C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl or (C₂-C₈)substituted alkynyl;

or any two R², R³ or R⁵ on adjacent carbon atoms when taken together are -O(CO)O- or when taken together with the ring carbon atoms to which they are attached form a double bond; and

R⁶ is OR^a, N(R^a)₂, N₃, CN, S(O)_nR^a, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -S(O)₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C_i-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, or (C₂-C₈)substituted alkynyl.

3. The compound for use according to claims 1 or 2 wherein the compound of Formula I or II is represented by Formula III:



Formula III

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R² is OR^a or F;

each R³ is OR^a; and

R⁶ is OR^a, N(R^a)₂, N₃, CN, S(O)_nR^a, -C(=O)R¹¹, -C(=O)OR¹¹, -C(=O)NR¹¹R¹², -C(=O)SR¹¹, -S(O)R¹¹, -S(O)₂R¹¹, -S(O)(OR¹¹), -S(O)₂(OR¹¹), -S(O)₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl,

(Ci-C8)substituted alkyl, (C₂-Cs)alkenyl, (C₂-Cg)substituted alkenyl, (C₂-Cg)alkynyl, or (C₂-Cg)substituted alkynyl.

4. The compound for use according to any one of claims 1-3 wherein R⁶ is CN, methyl, ethenyl, or ethynyl.

5. The compound for use according to any one of claims 1-4 wherein R² is OR^a.

6. The compound for use according to any one of claims 1-5 wherein R³ is OH, -OC(=O)R¹¹, or -OC(=O)OR¹¹.

7. The compound for use according to any one of claims 1-6 wherein R⁸ is NR¹¹R¹² or OR¹¹.

8. The compound for use according to any one of claims 1-7 wherein R⁸ is N^{3/4}.

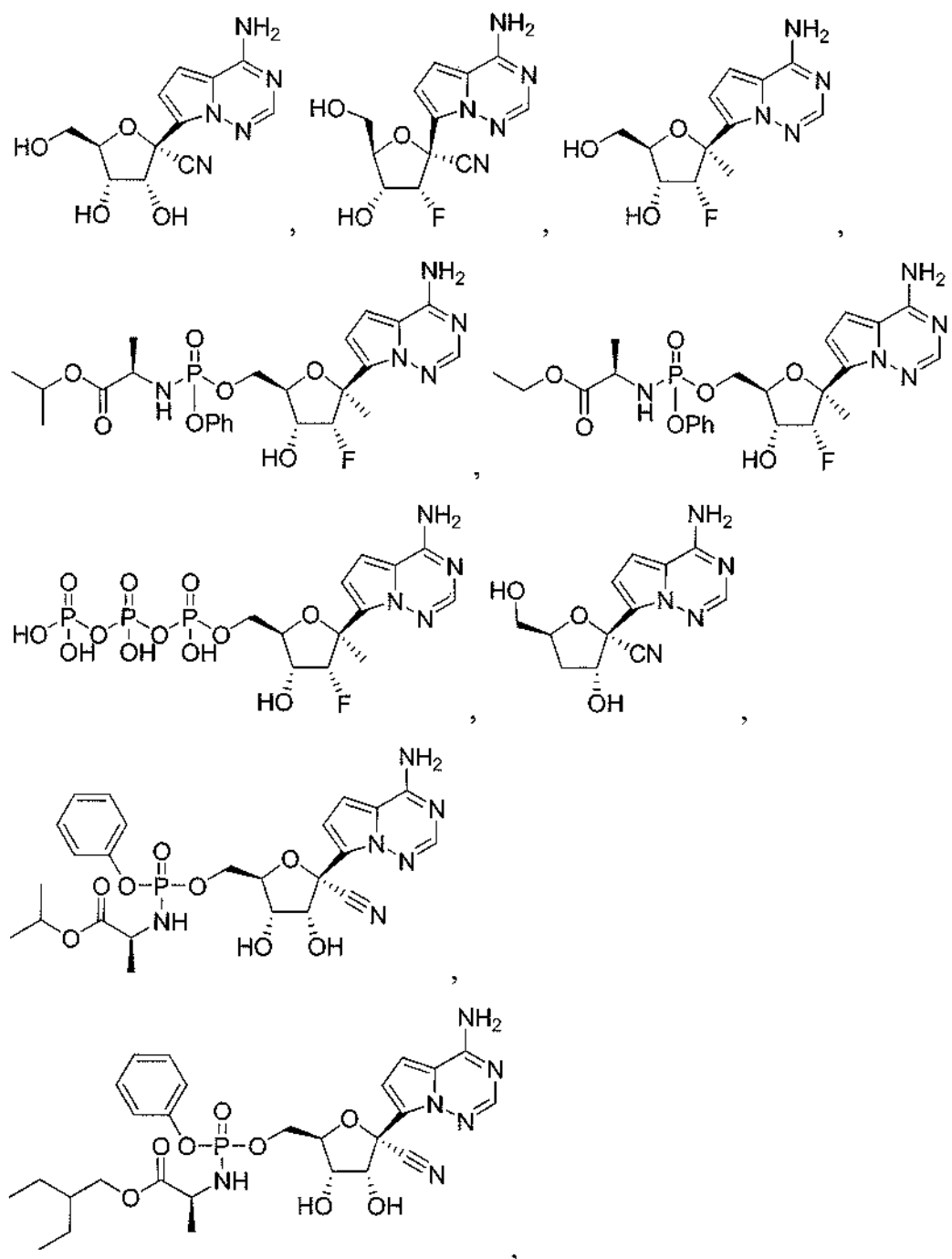
9. The compound for use according to any one of claims 1-7 wherein R⁸ is OH.

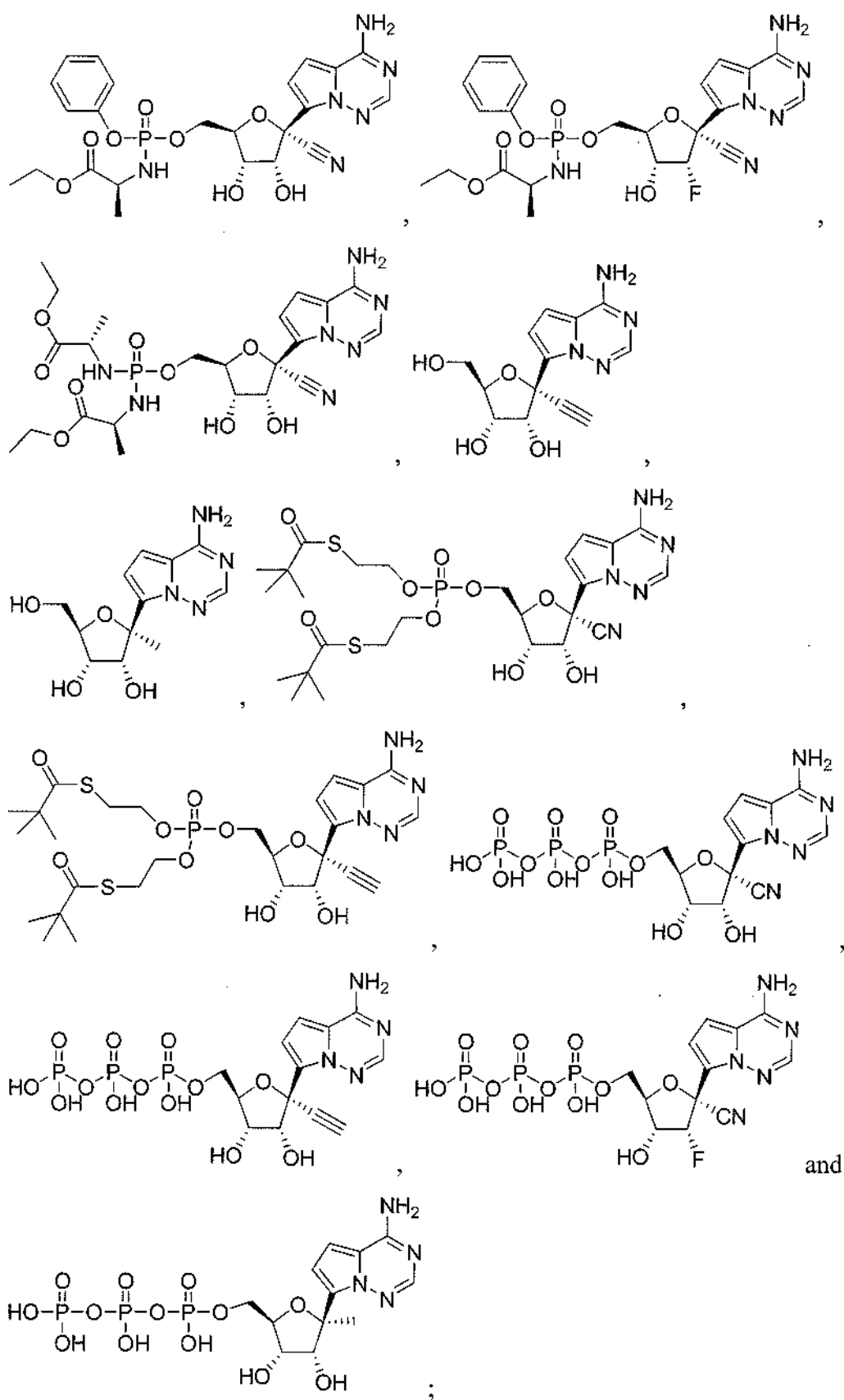
10. The compound for use according to any one of claims 1-9 wherein R⁹ is H.

11. The compound for use according to any one of claims 1-9 wherein R⁹ is NH₂.

12. The compound for use according to any one of claims 1-11 wherein R⁷ is H.

13. The compound for use according to any one of claims 1-3 wherein the compound of Formula I –III is selected from the group consisting of:





or a pharmaceutically acceptable salt or ester thereof.

14. The compound for use according to any one of claims 1-13 further comprising a pharmaceutically acceptable carrier or excipient.

15. The compound for use according to any one of claims 1-14 further comprising administering a therapeutically effective amount of at least one other therapeutic agent or composition thereof selected from the group consisting of a corticosteroid, an anti-inflammatory signal transduction modulator, a β 2-adrenoreceptor agonist bronchodilator, an anticholinergic, a mucolytic agent, hypertonic saline and other drugs for treating *Paramyxoviridae* virus infections; or mixtures thereof.

16. The compound for use according to claim 15 wherein the at least one other therapeutic agent is ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam[®]), MEDI-557, A-60444, MDT-637 or BMS-433771 or mixtures thereof.

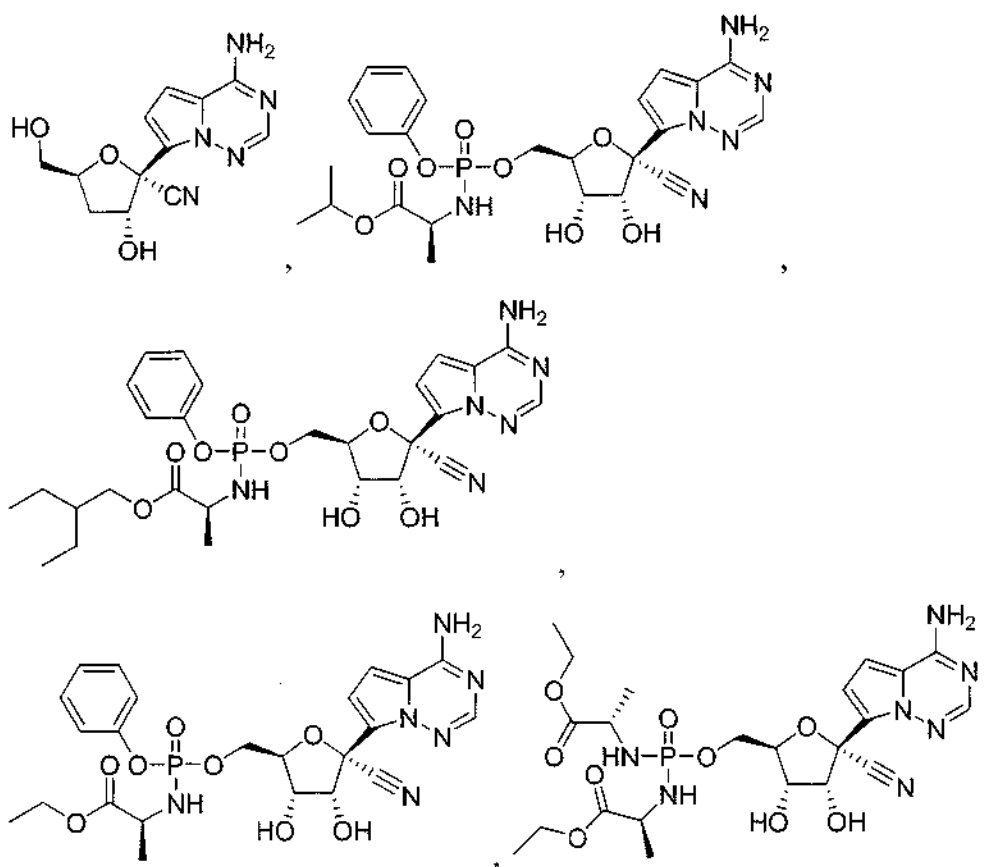
17. The compound for use according to any one of claims 1-16 wherein at least one therapeutic agent or mixtures thereof is administered by inhalation.

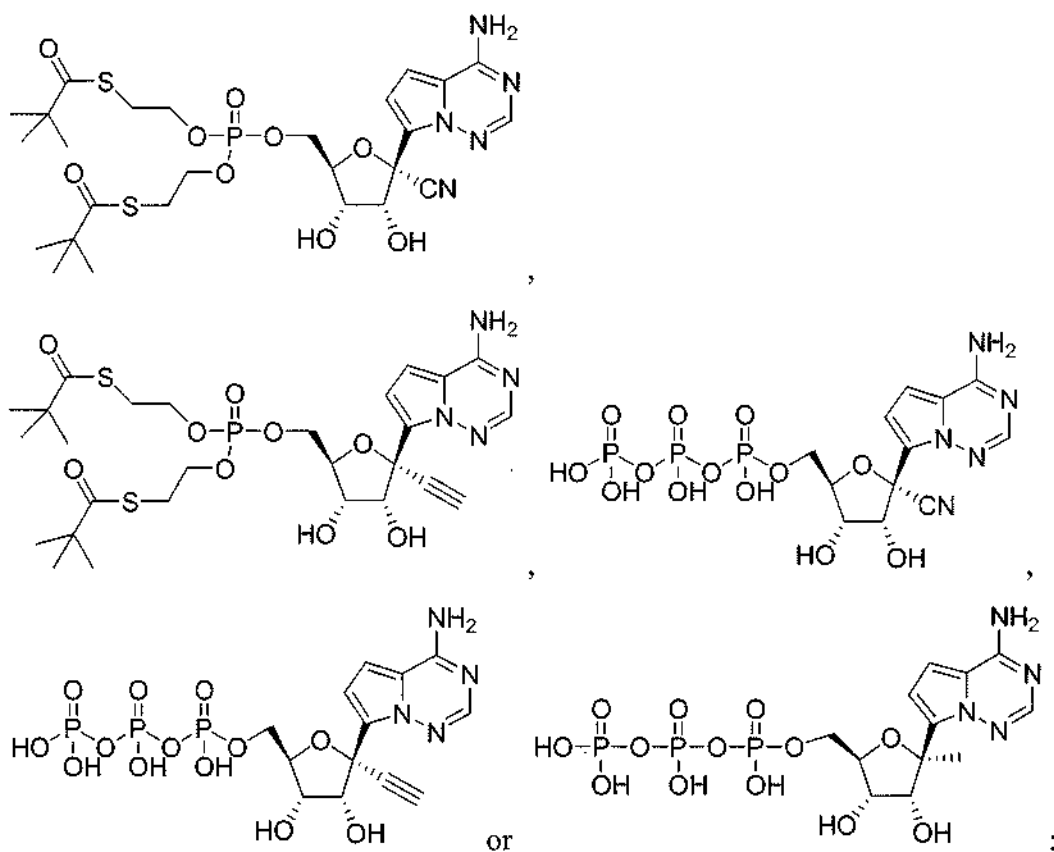
18. The compound for use according to claim 17 wherein at least one therapeutic agent or mixtures thereof is administered by nebulization.

19. The compound for use according to any one of claims 1-18 wherein the *Paramyxoviridae* infection is caused by a *Paramyxovirina* virus.

20. The compound for use according to any one of claims 1-18 wherein the *Paramyxoviridae* infection is caused by a *Respirovirus* virus.

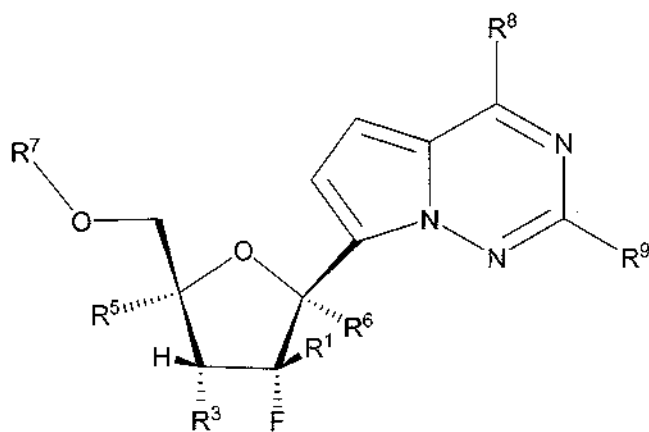
21. The compound for use according to any one of claims 1-18 wherein the *Paramyxoviridae* infection is caused by a type 1 or 3 Human parainfluenza virus.
22. The compound for use according to any one of claims 1-18 wherein the *Paramyxoviridae* infection is caused by a *Pneumovirinae* virus.
23. The compound for use according to any one of claims 1-18 or 22 wherein the *Paramyxoviridae* infection is caused by a Human respiratory syncytial virus.
24. The compound for use according to any one of claims 1-23 wherein a *Paramyxoviridae* polymerase is inhibited.
25. A compound of Formula I that is





or a pharmaceutically acceptable salt or ester thereof.

26. A compound of Formula I represented by Formula IV:



Formula IV

or a pharmaceutically acceptable salt or ester, thereof;

wherein:

each R^1 is H or halogen;

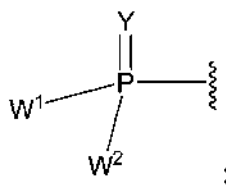
each R^3 or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, halogen, (Ci-Cg)alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl or (C_2-C_8) substituted alkynyl;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN, $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (Ci-C₈)substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, or (C_2-C_8) substituted alkynyl;

each n is independently 0, 1, or 2;

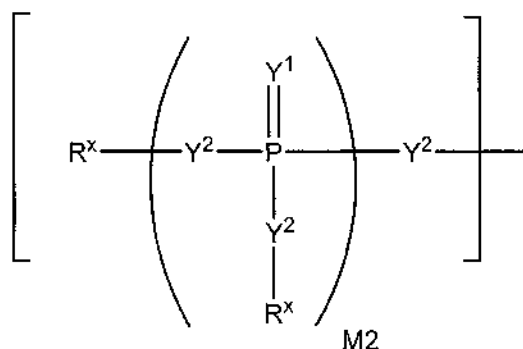
each R^a is independently H, (C_1-C_g) alkyl, (C_2-C_8) alkenyl, (C_2-C_g) alkynyl, aryl(Ci-C₈)alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or



each Y or Y^1 is, independently, O, S, NR, $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, or N-NR₂;

W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:



Formula 1a

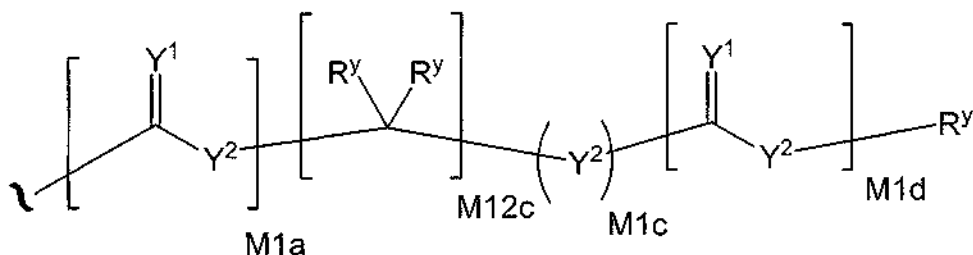
wherein:

each Y^2 is independently a bond, O, CR_2 , NR, $^+N(0)(R)$, $N(OR)$, $^+N(0)(OR)$, $N-NR_2$, S, S-S, $S(O)$, or $S(0)_2$;

each Y^3 is independently O, S, or NR;

M_2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M_{1a} , M_{1c} , and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y')R$, $-C(=Y')OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $^+N(R)_3$, $-SR$, $-S(0)R$, $-S(0)_2R$, $-S(0)(OR)$, $-S(0)_2(OR)$, $-OC(=Y')R$, $-OC(=Y')OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-S(0)_2NR_2$, $-CN$, $-N_3$, $-N(0)_2$, $-OR$, or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted

alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W³ is W⁴ or W⁵; W⁴ is R, -C(Y¹)R^y, -C(Y¹)W⁵, -S(O)₂R^y, or -S(O)₂W⁵; and W⁵ is a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

each R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(Ci-C₈)alkyl, -S(O)_n(Ci-C₈)alkyl, aryl(Ci-C₈)alkyl, OR¹¹ or SR¹¹;

each R⁹ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, -CH(=NR¹¹), -CH=NNHR¹¹, -CH=N(OR¹¹), -CH(OR¹¹)₂, -C(=O)NR¹¹R¹², -C(=S)NR¹¹R¹², -C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

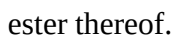
each R¹¹ or R¹² is independently H, (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, -C(=O)(Ci-C₈)alkyl, -S(O)_n(Ci-C₈)alkyl or aryl(Ci-C₈)alkyl; or R¹¹ and R¹² taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S- or -NR^a-; and

wherein each (Ci-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(Ci-C₈)alkyl of each R³, R⁵, R⁶, R¹¹ or R¹² is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (Ci-C₈)alkyl may be optionally replaced with -O-, -S- or -NR^a-.

27. The compound of claim 26 wherein each R¹, R⁵, and R⁷ is H and R³ is OR^a.

28. The compound of claim 26 or 27 wherein R⁶ is CN, methyl, ethenyl, or ethynyl.

30. The compound of claim 26 that is



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32. The composition of claim 31 further comprising administering a therapeutically effective amount of at least one other thereapeutic agent or composition thereof selected from the group consisting of a corticosteroid, an anti-inflammatory signal transduction modulator, a p2-adrenoreceptor agonist bronchodilator, an anticholinergic, a mucolytic agent, hypertonic saline and other drugs for treating *Paramyxoviridae* virus infections; or mixtures thereof.

33. The composition of claim 32 wherein the at least one other thereapeutic agent is ribavirin, palivizumab, motavizumab, RSV-IGIV (RespiGam[®]), MEDI-557, A-60444, MDT-637 or BMS-433771 or mixtures thereof.

International application No

PCT/US2011/045102

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D309/10 C07H19/00
 ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	wo 2010/002877 A2 (BIOTA SCIENT MAN [AU] ; BOEHRINGER INGELHEIM INT [DE] ; FRANCOM PAULA [U] 7 January 2010 (2010-01-07) cited in the applicati on the whole document	1-33
A	wo 2008/141079 AI (BIOCRYST PHARM INC [US] ; BABU YARLAGADDA S [US] ; CHAND POORAN [US]) 20 November 2008 (2008-11-20) cited in the applicati on the whole document	1-33
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Date of the actual completion of the international search

21 October 2011

Date of mailing of the international search report

09/11/2011

Name and mailing address of the ISA/

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 NL - 2280 HV Rijswijk
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/045102

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/045102

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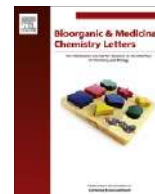
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Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and antiviral activity of a series of 1'-substituted 4-aza-7,9-dideazaadenosine C-nucleosides

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ABSTRACT

A series of 1'-substituted analogs of 4-aza-7,9-dideazaadenosine C-nucleoside were prepared and evaluated for the potential as antiviral agents. These compounds showed a broad range of inhibitory activity against various RNA viruses. In particular, the whole cell potency against HCV when R = CN was attributed to inhibition of HCV NS5B polymerase and intracellular concentration of the corresponding nucleoside triphosphate.

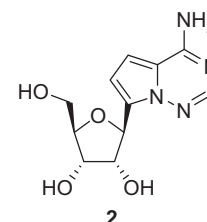
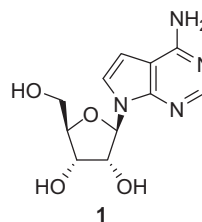
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Structural modification of natural N-nucleosides on either the sugar or the base has led to the discovery of a variety of therapeutic agents, which includes antivirals and anticancer agents. This approach has been continuously employed to further identify agents with improved efficacy and safety over existing drugs, overcome issues associated with drug-resistance, and expand into new therapeutic areas.¹

Among all the conceivable modifications of the sugar moiety, incorporation of a substitution at 1'-position of the N-nucleosides has been rarely exploited in drug discovery.² This is partly due to the chemical instability induced by the 1'-substituent (i.e., ready dissociation of the base and the sugar at lower pH). For example, 1'-C-Me adenosine is rapidly degraded in aqueous solutions at pH < 7.³ However, C-nucleoside, in which the sugar and the base are linked through the C–C bond, should be hydrolytically stable even with a 1'-substituent. Thus, we envisioned that C-nucleoside could be an ideal scaffold to explore various 1'-substituted nucleosides for their therapeutic potential.

As part of an on-going effort to identify new antiviral agents, we were interested in investigating 1'-substituted nucleosides as inhibitors of viral RNA-dependent RNA polymerases. Such nucleoside inhibitors should be converted by intracellular kinases to the triphosphorylated nucleosides, which then function as competitors of the natural nucleoside triphosphates (TP) in RNA synthesis. 7-Deazaadenosine (**1**, Tubercidin) is a naturally occurring, cytotoxic N-nucleoside. It is triphosphorylated inside the cells and then

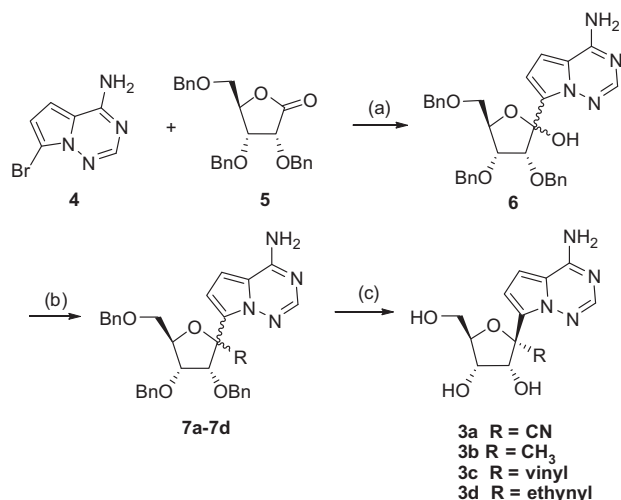
incorporated into RNA by host RNA polymerases, which is believed to be the main mode of action for the observed cytotoxicity.⁴ A C-nucleoside analog of **1**, 4-aza-7,9-dideazaadenosine (**2**) has shown equally potent cytotoxicity to cancer cell lines.⁵ The TP of **2** was also shown to be a substrate of host RNA polymerases and incorporated into RNA (unpublished results). Thus, we chose compound **2** as a template to investigate the effect of the 1'-substituent on antiviral activity and selectivity. Here, we report (1) preparation of a series of novel 1'-substituted analogs of compound **2**, (2) their antiviral activities against a panel of RNA viruses, and (3) correlation of the observed anti-HCV potency with both intrinsic enzyme (HCV NS5B) activity and intracellular level of the corresponding TP.



Compounds **3a–3d** were prepared from a common intermediate **6**, which was obtained from coupling of the bromo heterocycle **4**⁶ with the ribonolactone **5** (Scheme 1).⁷ The resulting hemiketal **6** was reacted with TMSCN and AlMe₃ in the presence of BF₃·Et₂O affording compounds **7a** (R = CN) and **7b** (R = Me), respectively,⁷ while with vinyl magnesium bromide and ethynyl magnesium chloride followed by dehydrative ring closure with methanesulfonic acid providing compounds **7c** (R = vinyl) and **7d** (R = ethynyl), respectively.⁸ These products were obtained as mixtures of the

* Corresponding author.

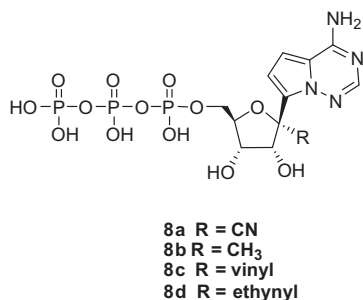
E-mail address: acho@gilead.com (A. Cho).



Scheme 1. Reagents and conditions: (a) 1,1,4,4-tetramethyl-1,4-dichlorodisilylene (1.2 equiv), NaH (2.2 equiv, 60% mineral oil), *n*-BuLi (3.3 equiv), THF, -78°C followed by addition of **5**, 1 h, 60%; (b) TMSCN (4 equiv), $\text{BF}_3\cdot\text{OEt}_2$ (3 equiv), CH_2Cl_2 , -78°C , 5 h, 58% (85:15 β/α) **7a**; AlMe_3 (5 equiv), $\text{BF}_3\cdot\text{OEt}_2$ (4 equiv), CH_2Cl_2 , 0°C , 12 h, 45% (1:1 β/α) **7b**; vinyl magnesium bromide (6 equiv), THF, 0°C to rt, 2 h, and then methanesulfonic acid (cat.), CH_2Cl_2 , rt, 3 h, 85% (1:1 β/α) **7c**; ethynyl magnesium chloride (6 equiv), THF, 0°C to rt, 2 h, and then methanesulfonic acid (cat.), CH_2Cl_2 , rt, 3 h, 65% (2:1 β/α) **7d**; (c) BCl_3 or BBr_3 (4–8 equiv), CH_2Cl_2 , -78°C , 1 h.

two stereoisomers at the 1'-position. Subsequent debenzoylation using BCl_3 provided, after chromatographic separation of the two isomers, the desired nucleosides **3a–3d**.

In addition, the TP derivatives (**8a–8d**) and bis-(SATE) monophosphate prodrugs (**9a–9d**) of these C-nucleosides were also prepared according to published methods.^{9,10}



The synthesized nucleosides **3a–3d** were evaluated in cell-based assays against a panel of RNA viruses.¹¹ Anti-HCV activity was obtained using a subgenomic replicon. Viruses tested included representatives of *Flaviviridae* (HCV, YFV, DENV-2, WNV), *Orthomyxoviridae* (influenza A), *Paramyxoviridae* (parainfluenza 3), *Picornaviridae* (Coxsackie A), and *Coronaviridae* (SARS-CoV). Antiviral activity (EC_{50}) and cytotoxicity (CC_{50} for host cells in each assay) are shown in Table 1. Compound **3a** (R = CN) displayed broader spectrum activity (HCV, YFV, DENV-2, Influenza A, Parainfluenza 3 and SARS-CoV). Compounds **3b** and **3c** showed a reduced potency and a narrower spectrum of antiviral activity, and **3d** no activity. While exhibiting various levels of antiviral activities, these 1'-substituted nucleosides exerted little or no cytotoxicity.

We then investigated to see if the observed antiviral activity was derived from inhibition of viral RNA dependent RNA polymerases (RdRp). Since readily available, the HCV RdRp was used to

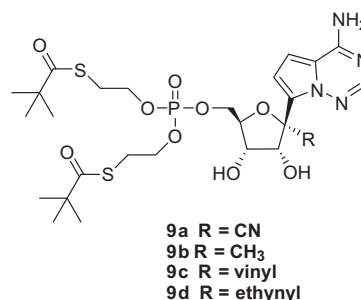
Table 1
Antiviral activity of 1'-substituted 4-aza-7,9-dideazaadenosine C-nucleosides

	$\text{EC}_{50}/\text{CC}_{50}$ (μM)			
	3a	3b	3c	3d
HCV (1b) ^a	4.1/>89	39/>45	>89/>89	>89/>89
YFV	11/>30	ND	ND	ND
DENV-2	9.46/>30	>30/>30	>30/>30	>30/>30
WNV	>30/>30	>30/>30	>30/>30	>30/>30
Influenza A	27.9/>30	>30/>30	>30/>30	>30/>30
Parainfluenza 3	1.71/>30	5.23/>30	>30/>30	>30/>30
SARS-CoV	2.24/>30	>30/>30	14.0/>30	>30/>30
Coxsackie A	>30/>30	>30/>30	>30/>30	>30/>30

^a HCV subgenomic replicon.

determine an enzyme inhibitory activity of TP **8a–8d**. Under the established protocol,¹² the IC_{50} values were obtained (Table 2). These studies revealed a good correlation between the intrinsic enzyme activity and the whole cell HCV potency. For example, compound **3a** showed the most potent anti-HCV activity (EC_{50} of 4.1 μM), and its TP derivative (**8a**) the most potent inhibitory activity against the enzyme (IC_{50} of 5.6 μM).

To gain further insights into the mode of the antiviral activity, bis-(SATE) monophosphate prodrugs were tested in the HCV replicon assay. In addition, intracellular levels of the TPs were measured upon incubation of these prodrugs with replicon cells,¹³ and compared with those from the parent nucleosides. The results are summarized in Table 2. The prodrugs **9a** and **9b** showed markedly enhanced replicon activity when compared to the parent nucleosides. These monophosphate prodrugs afforded >100-fold higher levels of the TP species than the parent nucleosides. Corresponding to the increased potency, an increase in cytotoxicity was also observed for the 4 prepared prodrugs. The selectivity



indices ($\text{CC}_{50}/\text{EC}_{50}$) of **9b**, **9c** and **9d** were less than 10-fold making it difficult to differentiate HCV activity from cellular toxicity. The greater potency and selectivity observed for **9a** (EC_{50} of 0.085 μM and selectivity of 40-fold) likely reflects a combination of the potent enzyme activity and the high intracellular TP concentration (4220 pmol/million cells when cells were incubated with 10 μM of **9a**). Further structural modification to improve the selectivity of **3a** and **9a** is warranted.

In summary, a series of novel 1'-substituted analogs of 4-aza-7,9-dideazaadenosine C-nucleoside were prepared and tested in vitro antiviral assays. These compounds showed a broad range of antiviral activity. In particular, the HCV potency of **3a** and its bis(SATE) prodrug **9a** in the whole cell replicon assay were correlated with the intrinsic enzyme activity and the intracellular levels of the corresponding TP (**8a**), which suggests that the antiviral

Table 2

HCV replicon activity, TP formation of nucleosides and their SATE prodrugs, and inhibition of RdRp by respective TPs

	Nucleoside		SATE prodrug		TP RdRp IC ₅₀ (μM)
	EC ₅₀ /CC ₅₀ (μM)	TP concentration ^a (pmol/million)	EC ₅₀ /CC ₅₀ (μM)	TP concentration ^a (pmol/million)	
3a/9a	4.1/>89	17.6 (8a)	0.085/3.2	4,220 (8a)	5.6 μM (8a)
3b/9b	39/>89	50.8 (8b)	0.078/0.73	ND	20 μM (8b)
3c/9c	>89/>89	2.0 (8c)	3.43/12	440 (8c)	178 μM (8c)
3d/9d	>89/>89	0.66 (8d)	6.01/26	150 (8d)	232 μM (8d)

^a C_{max} of intracellular TP (pmol/million cells) upon incubation of 10 μM of nucleosides or prodrugs in Huh-7 cells for 24 h.¹³

activity is in part derived from inhibition of RdRp. The current work establishes the potential of 1'-substituted nucleosides as antiviral agents.

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- Inhibition of NS5B was studied using GT1b NS5B recombinant protein. All concentrations are final concentration. In a solution containing 50 mM Tris-HCl (pH 7.5), 10 mM KCl, 1 mM DTT, 5 mM MgCl₂, 0.2 unit/μL RNasin (Promega), and 0.01% BSA, 75 nM NS5B was pre-incubated with 4 ng/μL (50 nM) heteropolymer RNA template (sshRNA) at rt for 5 min, followed by the addition and incubation of the inhibitors at RT for 5 min. The reaction was started by addition of a mixture of ATP (3 μM), 0.03 μM ³³-P-labeled ATP (Perkin-Elmer, NEG603H, 3000 Ci/mmol, 3.3 μM), and 500 μM for GTP, CTP, and UTP. After 90 min incubation at 30 °C, the reaction mixture was spotted on DE-81 filter paper and washed with 0.125 M Na₂HPO₄ (3×), distilled water (1×), and reagent ethanol (1×). The filter paper was air-dried and exposed to phosphorimager (Typhoon, GE) and the data was analyzed using ImageQuant software (GE).
- Replicon cells were maintained in Dulbecco's modified Eagle medium containing glutamax supplemented with 10% heat inactivated fetal bovine serum, penicillin-streptomycin, and G418 disulphate salt solution. Cells were transferred to 12-well tissue culture treated plates by trypsonization and grown to confluency (0.88 × 10⁶ cells/well). Cells were treated for 24 h with 10 μM compound. Following 24 h, cells were washed 2 times with 2.0 mL ice cold 0.9% sodium chloride saline. Cells were then scraped into 0.5 mL 70% methanol and frozen overnight to facilitate the extraction of nucleotide metabolites. Extracted cell material in 70% methanol was transferred into tubes and dried. After drying, samples were re-suspended in 1 mM ammonium phosphate pH 8.5. TP levels were quantitated using liquid chromatography coupled to triple quadrupole mass spectrometry by methods similar to those previously reported in Durand-Gasselin, L.; Van Rompay, K. K.; Vela, J. E.; Henne, I. N.; Lee, W. A.; Rhodes, G. R. *Mol. Pharm.* **2009**, *6*, 1145.

Aryloxy Phosphoramidate Triesters: a Technology for Delivering Monophosphorylated Nucleosides and Sugars into Cells

D5

Youcef Mehellou,^[a] Jan Balzarini,^[b] and Christopher McGuigan^{*[a]}

Prodrug technologies aimed at delivering nucleoside monophosphates into cells (protides) have proved to be effective in improving the therapeutic potential of antiviral and anticancer nucleosides. In these cases, the nucleoside monophosphates are delivered into the cell, where they may then be further converted (phosphorylated) to their active species. Herein, we describe one of these technologies developed in our laboratories, known as the phosphoramidate protide method. In this approach, the charges of the phosphate group are fully masked to provide efficient passive cell-membrane penetration. Upon entering the cell, the masking groups are enzymatically cleaved to release the phosphorylated biomolecule. The application of this technology to various therapeutic nucleo-

sides has resulted in improved antiviral and anticancer activities, and in some cases it has transformed inactive nucleosides to active ones. Additionally, the phosphoramidate technology has also been applied to numerous antiviral nucleoside phosphonates, and has resulted in at least three phosphoramidate-based nucleotides progressing to clinical investigations. Furthermore, the phosphoramidate technology has been recently applied to sugars (mainly glucosamine) in order to improve their therapeutic potential. The development of the phosphoramidate technology, mechanism of action and the application of the technology to various monophosphorylated nucleosides and sugars will be reviewed.

Introduction

Synthetic nucleoside mimetics have become an integral part of the therapeutic regimens of patients suffering from viral infections and/or cancers.^[1,2] In most cases, the active species of nucleosides are their 5'-O-triphosphate derivatives, which produce their therapeutic effects as a result of DNA chain termination/polymerase inhibition.^[3,4]

The formation of these 5'-O-triphosphates generally proceeds in three different steps starting from the nucleoside. The inefficiency of these three steps represents a major hurdle for a range of nucleosides. In particular, the first step responsible for the formation of the nucleoside analogue monophosphate is often regarded as the most difficult, and has been shown to be responsible for holding back the full therapeutic potential of certain nucleoside analogues, for example, 2',3'-dideoxy-2',3'-dideoxythymidine (d4T).^[5] Therefore, bypassing this rate-limiting step should improve the therapeutic activities of such compounds. However, because of the charged nature of nucleoside monophosphates under physiological conditions, they show poor cell membrane permeability and are highly susceptible to dephosphorylation; as a result, little therapeutic benefit would be produced following their administration (Figure 1).

Designing a strategy that masks the charges of the nucleoside analogue monophosphates so that they penetrate the membrane and then selectively release the nucleoside analogue monophosphate inside the cell could prove to be useful (Figure 1). The need for such a prodrug approach was previ-

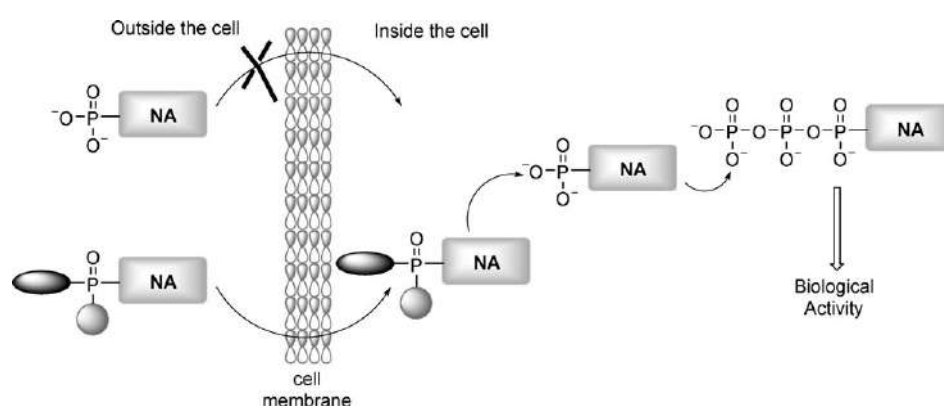


Figure 1. Schematic representation of the pronucleotide (protide) concept (NA: nucleoside analogue).

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ously emphasised in the early 1990s, when a series of nucleotides (phosphonates) were shown to possess interesting antiviral activities.^[6]

Over the last decade or so, numerous pronucleotide strategies using different mechanisms of action have been developed,^[7–9] and have recently been reviewed.^[10] These strategies are based upon either enzymatic and/or chemical intracellular cleavage of the masking groups to release the charged nucleoside monophosphate inside the cell.^[11,12] We have designed and developed a pronucleotide approach, known as the phosphoramidate approach, which is based upon intracellular enzymatic activation of the prodrug to release the nucleoside monophosphate (Figure 2).^[13] The development of the prodrug technology has moved from using simple alkyl groups to block the phosphate charges to more sophisticated structures that

The journey towards aryloxy phosphoramidates triesters

Alkyl and haloalkyl phosphate triesters

The journey towards the current form of phosphoramidates started with simple dialkyl triesters of the antiviral agent araA (1), which showed only moderate biological activity, but did display significantly enhanced stability towards adenosine deaminase.^[15] The application of the same strategy on the anti-neoplastic agent araC (2) also provided reasonable biological activity,^[16] while dialkyl triester derivatives of the anti-HIV (human immunodeficiency virus) agent AZT (3) failed to exert any significant activity in vitro.^[17] This latter result was thought to be due to the stability of the dialkyl esters, as they were considered to be relatively stable, and therefore impeded metabolic conversion into the active 5'-O-triphosphate form of AZT, which is a prerequisite for biological activity.^[17] Various improved haloalkyl masking groups (4) were then used to block the charges of AZT monophosphate. Although some of these haloalkyl derivatives showed some anti-HIV activity, they were still less active than the parent nucleoside, AZT.^[18] In addition, haloalkyl phosphate triesters of 2',3'-di-deoxycytidine (ddC, 5) were found to be devoid of any anti-HIV activity.^[18] Attempts to boost the anti-HIV activity of these haloalkyl phosphate triesters by

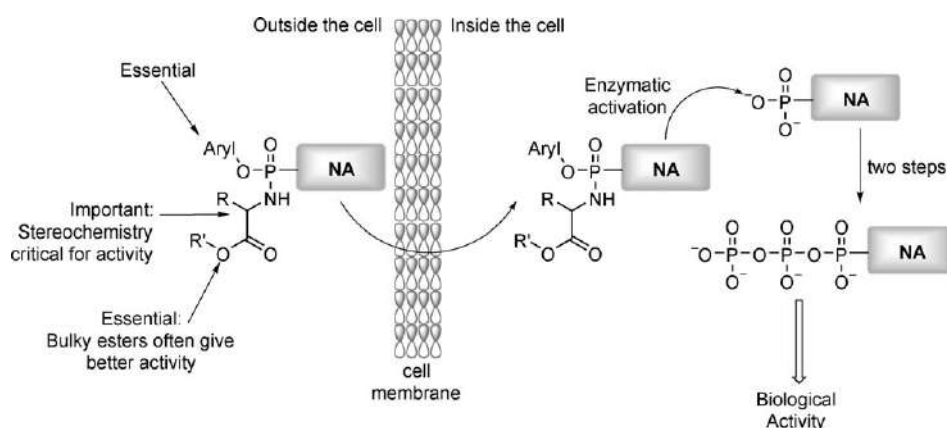
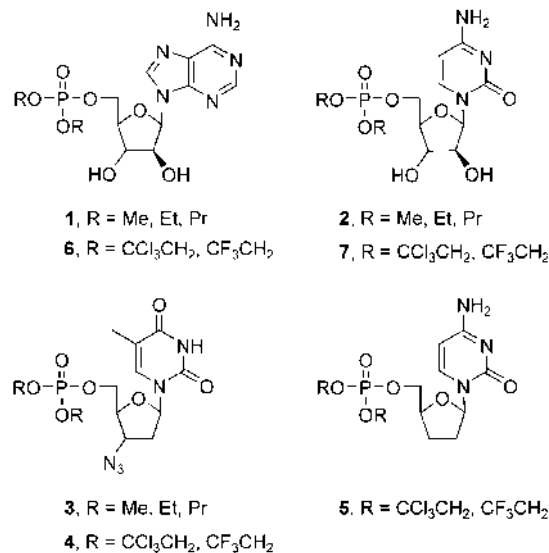


Figure 2. A general representation of how phosphoramidates deliver monophosphates into cells.

may efficiently deliver phosphorylated species into cells. The application of this technology has been shown to improve the activities of various antiviral and anticancer nucleosides as a result of the delivery of their monophosphate derivatives. In fact, several phosphoramidate-based nucleoside analogues have entered clinical trials. In addition, we have recently published the application of the phosphoramidate approach to the antiosteoarthritic carbohydrate-based nutraceutical glucosamine in order to improve its therapeutic potential.^[14]

Extensive work has been carried out to establish the mechanism of action of phosphoramidates and lately there has been a great deal of attention paid towards the identification of the enzymes responsible for the metabolism of phosphoramidates that leads to the release of the phosphorylated species.

In this work, we will summarise a) the development of the phosphoramidate approach, b) the mechanism of action of this technology, c) the results of the application of such a technology to various antiviral and anticancer nucleoside analogues, d) the application of the phosphoramidate prodrug approach to glucosamine, and finally, we will briefly report on some phosphoramidate-based drug candidates undergoing clinical trials, as well as a look at the future of this pronucleotide technology.

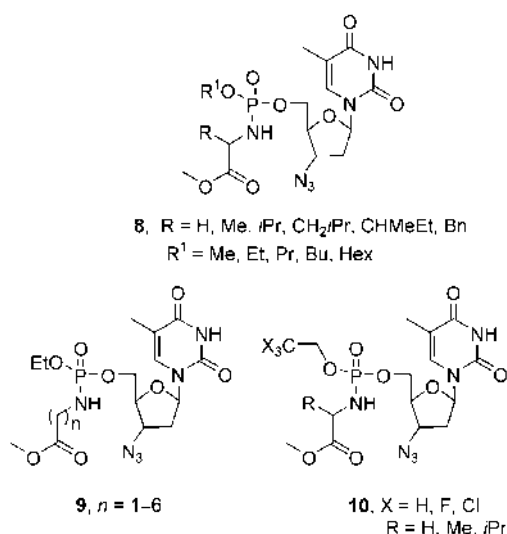


changing the degree or nature of halogenation were generally unsuccessful.^[19] However, haloalkyl triester derivatives of araA (6) and araC (7) did display enhanced biological activities.^[20] Interestingly, the biological activities of araA and araC derivatives correlated to the lipophilicity of the phosphate triester pro-

drugs. Thus, it was concluded that the favourable biological activities of the araA and araC (halo)alkyl derivatives were, in part at least, a result of better membrane permeability rather than intracellular phosphate delivery.^[15, 16, 20]

Alkyloxy phosphoramidates

We originally embarked on designing phosphoramidate-based prodrugs following the concept that HIV protease might cleave a suitable oligopeptide from the phosphate moiety of a blocked nucleotide phosphoramidate.^[21] Initially, simple mono-amino acyl analogues were prepared and evaluated, and showed sufficiently interesting results to pursue in their own right. Thus, a series of simple alkyloxy phosphoramidates of AZT were prepared with a small family of methyl-esterified amino acids (**8**).^[22] Interestingly, alkyloxy phosphoramidates of



AZT (**8**) showed better anti-HIV activity compared to the AZT dialkyl phosphates (**3** and **4**), which was a first example in the development of phosphoramidates. More importantly, the antiviral potential of alkyloxy phosphoramidates was found to correlate to the amino acid side chain; with alanine being most efficacious, and with leucine and, in particular, isoleucine being less active.^[22, 23] In contrast, the length of the alkyl phosphate chain had no significant effect on the biological activity.^[23]

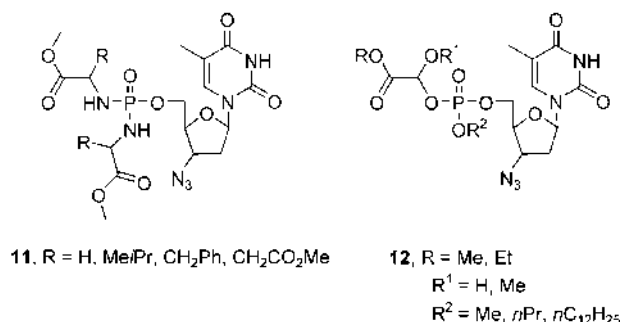
Further studies focussing on the nature of the amino acid were conducted. In one study, α -amino acids were compared to their β and γ derivatives (**9**), and it was found that the parent α system (glycine) provided maximal activity.^[24] Increasing the alkyl spacer length resulted in a significant loss of activity, where changing the length from *n*=2 to *n*=1 leads to > 10-fold decrease in activity.^[24]

Bearing in mind the improvements seen with haloalkyl phosphates compared with their alkyl derivatives, we wondered whether haloalkyl phosphoramidates would also be more potent. Therefore, a small series of haloalkyl phosphoramidates of AZT (**10**) were prepared and examined.^[25] For each of the studied amino acids, glycine, alanine and valine, the alkyl chain

was either ethyl, trifluoroethyl or trichloroethyl. Surprisingly, in contrast to earlier observations, no enhancement in antiviral potency over the haloalkyl compounds was observed, with one striking exception. The trichloroethyl alanine compound (**10**) was active against HIV at 0.08 μ M, 50 times more potent than either the ethyl or the trifluoroethyl analogues. Interestingly, this significant improvement in antiviral activity was only seen with alanine, while no such activity was seen with the glycine and valine systems.^[25] Out of these earlier investigations, alanine emerged as a preferred amino acid, although the mechanistic origins of this preference were at that time unknown. Interestingly, alanine has been the amino acid of choice in many recent examples from a variety of laboratories. Notably, all prodrugs tested to date in the clinic have been alanine derived.

Phosphorodiamidates

The promising activity of alkyl phosphoramidates, particularly those related to alanine, made us wonder whether diamidates would be more efficacious. Thus, several methyl-esterified amino acyl phosphorodiamidates (**11**), as well as non-amino



acyl phosphorodiamidates derived from simple primary and secondary amines, were prepared and tested.^[26] Structure–activity relationships (SAR) indicated a strong preference for amino acids such as phenylalanine.^[26] Hence, a different amino acid SAR emerged for these diamidates as compared to the earlier alkyl phosphoramidates. Interestingly, this preference for aromatic side chains was also seen by other groups for the rather unrelated phosphoramidate diesters.^[12] However, in general diamidates appeared to offer no biological advantage over the amidates, and the chemical yields of the diamidates were significantly lower, and hence they were not further pursued.

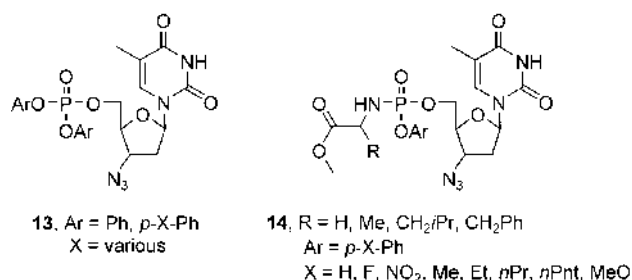
Lactyl-derived systems

In order to establish the importance of the bridging amino acid nitrogen atom to the biological activity of phosphoramidates, we also prepared and evaluated a small family of isosteric O-linked analogues derived from lactic and glycolic acid (**12**).^[27] Overall, this study revealed that lengthening the alkyl phosphate chain (R²) leads to a reduction in potency. Notably, the glycolyl systems (R¹=H) were more active than lactyl

($R^1=Me$) by a factor of ~ 20 , which is in contrast to the earlier work where alanine was preferred over glycine.^[22,23] A brief hydrolytic stability study conducted on compounds **12** revealed the release of polar compounds and traces of AZT in biological media, but not in DMSO/water. Thus, enzyme-mediated activation is a possibility. However, because of the poor anti-HIV activity of such systems, these compounds were not pursued further.

Diaryl phosphates

One of the main breakthroughs in the development of the current form of phosphoramidate triesters came in 1992, when we found aryloxy phosphates and phosphoramidates to be of very high efficacy and in some cases more active than the parent nucleoside.^[28] Using simple phosphorochloridate chemistry, diaryl phosphates of AZT (**13**) were prepared. Inter-



estingly, these diaryl derivatives showed good anti-HIV activity and, for the first time in the development of the phosphoramidate approach, some of the phosphate prodrugs, that is, diaryl derivatives in this case, exerted better activity than the parent nucleoside.^[28] More interestingly, some diaryl derivatives were active in cell lines where the parent nucleoside AZT was inactive.^[28] Initially, the cell line resistant to AZT that we used (T lymphocyte cell line, JM) was considered to be AZT insensitive as a result of poor phosphorylation.^[29] However, it was later found that the poor sensitivity of this cell line towards AZT was due to an AZT efflux pump.^[30] Nevertheless, the conclusion remains valid that the diaryl phosphate was better able to retain activity in the JM cell line, and this may imply a degree of intracellular phosphate delivery. The nitro group was believed to be vital to activity as the parent diphenyl phosphate was ~ 100 -fold less active (C8166 cells). The electron-withdrawing power of the *para*-nitro groups and putative enhancements in the aryl leaving group ability were suggested as the major driving force of this SAR.^[28] Thus, a series of analogues with various electron-withdrawing groups in the *para* position were prepared (**13**).^[31] It soon became very clear that there was a correlation between the electron-withdrawing power of the substituent in the *para* position and the antiviral potency. The nitro- and cyano-substituted compounds were found to be the most potent, the parent phenyl compound showed intermediate activity while the methoxy analogue was the least active, being 500-fold less active than the nitro compound. In order to investigate the effect of the position of the electron-withdrawing nitro group on the aryl moieties, symmetrical bis-*ortho*-nitro and bis-*meta*-nitro analogues were pre-

pared.^[32] Evaluating the activity of these compounds against HIV-1 and HIV-2 revealed that the location of the nitro group had little effect on the activity. However, in this study we were able to assess the activity of the phosphate prodrugs in a true thymidine kinase (TK)-deficient human T cell leukaemia cell line (CEM/TK⁻). The results were quite disappointing as all the diaryl phosphate prodrugs, as well as AZT, failed to show any anti-HIV activity in this cell line. This indicated poor intracellular phosphate delivery, and that the diaryl phosphates were acting largely, if not entirely, as AZT prodrugs and not as AZTMP prodrugs, as intended.^[32] However, the earlier work using JM cells on phosphoramidates^[28] had indicated that aryloxy phosphoramidates may offer a chance for true nucleoside phosphate delivery, and this became the main focus of our work.

Aryloxy phosphoramidates

As a result of the favourable potency boosts seen with *para*-substituted aryls in the diaryl systems, we thus prepared a series of aryloxy phosphoramidates of AZT with various *para* substituents and amino acids (**14**).^[33] These compounds were studied in JM cell lines only to probe potentially implied AZTMP release. From this study, alanine phosphoramidate emerged as strikingly effective compared to other amino acids, for example, leucine, glycine and phenylalanine.^[33] In particular, the phenyl methoxy alaninyl phosphoramidate of AZT was the most potent against HIV ($EC_{50}=0.8\ \mu M$), whilst the parent nucleoside, AZT, showed an EC_{50} value of $\sim 100\ \mu M$ in the same assay. We also observed that there was a marked preference for alanine over leucine (10-fold) and glycine (>100 -fold). Moreover, whilst electron-withdrawing aryl substitution was very effective in the diaryl system,^[31] it was detrimental here. Substitution with a *para*-fluoro group had a slight extraneous effect, but not significantly so, whilst *para*-nitro substitution led to a 100-fold loss of anti-HIV activity.^[34]

In a subsequent report, we studied a selection of AZT phosphoramidates with a wide range of aryl substituents. Interestingly, these compounds were tested in true TK⁺ and TK⁻ cell lines.^[34] However, none of the phosphoramidates retained the high potency (2–4 nM) of AZT in TK competent (TK⁺) human T cell lines (CEM and MT4) against either HIV-1 or HIV-2. However, they retained substantial activity in the TK-deficient cell line CEM/TK⁻, whereas AZT lost all of its activity in this same cell line. This was taken as direct proof of intracellular nucleoside phosphate delivery. Again, alanine emerged as an important component, while the glycine analogue was inactive in all HIV-infected CEM/TK⁻ cultures. In this assay, leucine and phenylalanine were as effective as alanine, although they were less so in CEM/TK⁺ assays. Thus, the parent phenyl methoxy alaninyl phosphoramidate emerged as an important lead which demonstrated efficacy to bypass the nucleoside kinase.^[34]

Application to various antiviral and anticancer nucleosides

We, and others, have applied our aryloxy phosphoramidate approach to many nucleosides with antiviral and anticancer activ-

ities. The results generally varied from one nucleoside to another, and sometimes varied significantly from one phosphoramidate to another for the same nucleoside. Additionally, in some cases, the application of the phosphoramidate approach turns an inactive nucleoside to an active one. Here, we will summarise some of the data obtained from applying the phosphoramidate technology to numerous nucleoside analogues.

4'-Azidouridine

4'-Azidouridine (**15**) is a ribonucleoside that is inactive as an inhibitor of HCV replication,^[35] while the analogous cytosine derivative (4'-azidocytidine) is a well-known potent inhibitor of the virus.^[36] The active species of 4'-azidocytidine was found to be its triphosphate derivative. We hypothesised that 4'-azidouridine was inactive as a result of poor phosphorylation, and consequently applied our phosphoramidate approach to 4'-azidouridine.^[37]

Numerous 4'-azidouridine phosphoramidates (**15a-c**; Table 1) with varying amino acid, aryl and ester groups were

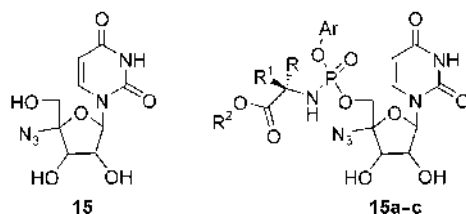


Table 1. Anti-HCV activity of 4'-AzU (**15**) and a series of its phosphoramidate derivatives (**15a-c**).

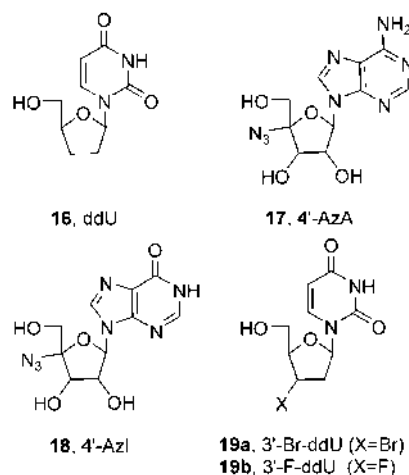
Compd	Ar	Amino acid (R,R')	Ester (R ²)	EC ₅₀ [μM]	CC ₅₀ [μM]
15a	Phenyl	L-Ala	2-Bu	0.63	> 100
15b	Phenyl	L-Ala	Bn	0.61	> 100
15c	Naphthyl	L-Ala	Bn	0.22	> 100
15	–	–	–	> 100	> 100

EC₅₀: 50% effective concentration or compound concentration required to inhibit HCV replication by 50%; CC₅₀: 50% cytotoxic concentration as determined with the MTS dye viability staining method. The HCV replicon assay was performed in the stable replicon cell line 2209-23 derived from Huh-7 cells stably transfected with a bicistronic HCV replicon (genotype 1b) expressing the renilla luciferase reporter gene. Further details of the anti-HCV assay can be found in reference [37].

prepared. Most of the compounds showed improved anti-HCV activity and had no toxicity in the replicon assay (CC₅₀ > 100 μM). Some of the compounds inhibited the replication of HCV at submicromolar concentrations (< 1 μM), while the parent nucleoside was devoid of any activity (EC₅₀ > 100 μM). In terms of SAR, L-alanine phosphoramidates showed better activity than other amino acids such as valine, β-alanine and N-methylglycine. In addition, naphthyl phosphoramidates exhibited improved anti-HCV activity over their phenyl counterparts, most likely due to the better lipophilicity of the naphthyl

derivatives, which enhanced their ability to cross the cell membrane. In one case, the distereoisomers of a phosphoramidate (naphthyl L-alanine benzyl ester) were separated, their absolute stereochemistry determined by molecular modelling and NMR, and subsequently tested. In this case, no significant differences in HCV inhibition were observed for the two distereoisomers (*Rp*, EC₅₀ = 0.39 μM; *Sp*, EC₅₀ = 0.43 μM). The triphosphate derivative of 4'-azidouridine was also synthesised and tested against the HCV polymerase. The data revealed that 4'-azidouridine triphosphate was as potent an inhibitor of HCV polymerase as 4'-azidocytidine triphosphate. This finding, coupled with the success of the phosphoramidate approach to improve the anti-HCV activity of 4'-azidouridine, indicates that these improvements in activity are a direct result of bypassing the first phosphorylation step. This suggested that the inability of 4'-azidouridine to exert any anti-HCV activity was due to poor intracellular phosphorylation to the monophosphate.

As in the case of 4'-azidouridine, the application of our phosphoramidate technology was successful in transforming various inactive nucleosides to active ones, such examples include 2',3'-dideoxyuridine (ddU, **16**),^[38,39] 4'-azidoadenosine (4'-AzA, **17**),^[40] 4'-azidoinosine (4'-AzI, **18**),^[41] and 3'-fluoro- and 3'-bromo derivatives of 2',3'-dideoxyuridine (**19a**, 3'-BrddU; **19b**, 3'-FddU)^[42].



2',3'-Didehydro-2',3'-dideoxythymidine (d4T)

An FDA-approved anti-HIV agent, d4T, exhibits a selective anti-HIV activity in cell culture, and also a reduced toxicity in certain cell types (e.g. bone marrow progenitor cells) compared with other antiretroviral agents such as AZT.^[43–45] The impressive profile of d4T (**20**), as well as the fact that the phosphorylation of d4T to the monophosphate is known to be of low efficiency,^[46] highlighted d4T as an ideal candidate for our phosphoramidate technology. We prepared a family of d4T phosphoramidates and investigated their anti-HIV activity.^[47,48]

Various substituted aryl- and ester-modified d4T phosphoramidates (**20a-e**; Table 2) were prepared and tested against HIV-1 and HIV-2. Generally, d4T phosphoramidates were signifi-

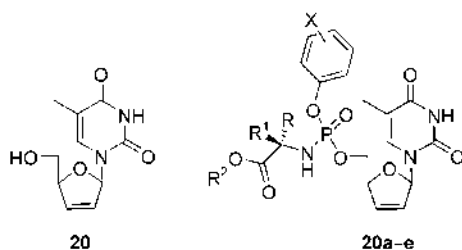


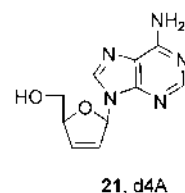
Table 2. Anti-HIV activity of d4T (**20**) and a series of its phosphoramidate derivatives (**20a–e**).

Compd	X	Amino acid (R,R')	Ester (R ²)	EC ₅₀ [μM]			CC ₅₀ [μM]
				HIV-1 CEM(0)	HIV-2 CEM(0)	HIV-2 CEM-TK ⁺	
20a	<i>p</i> -Cl	L-Ala	Me	0.005	0.007	0.006	11
20b	<i>p</i> -Br	L-Ala	Me	0.009	0.016	0.018	17
20c	<i>m</i> -I	L-Ala	Me	0.008	0.007	0.016	25
20d	–	L-Ala	<i>n</i> Pr	0.42	1.1	0.4	≥ 250
20e	–	L-Ala	<i>n</i> Bu	0.50	0.69	0.22	168
20	–	–	–	0.651	0.770	33	267

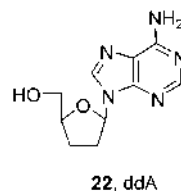
EC₅₀ is the 50% effective compound concentration required to protect CEM cells against the cytopathicity of HIV by 50%. Data are the mean of 2–3 independent experiments. CC₅₀ is the 50% cytostatic compound concentration required to inhibit CEM cell proliferation by 50%. Experimental details can be found in Reference [48].

cantly more active than the parent nucleoside, d4T. In addition, several compounds showed a >10-fold superior selectivity index (SI) compared with d4T.^[48] Although halogen-substituted aryl phosphoramidates of d4T had better lipophilicity profiles compared with other aryl-substituted compounds, no correlation between lipophilicity and anti-HIV activity was observed in this study.^[48] Regarding amino acid variations, it was initially found that L-alanine phosphoramidates of d4T possessed better anti-HIV activity compared with other d4T phosphoramidates with other natural non-L-alanine amino acids.^[47] However, we later observed that L-alanine could be substituted with some unnatural amino acids with no significant loss of anti-HIV activity.^[49] The impressive anti-HIV data obtained with the d4T phosphoramidates led us to investigate the possible ways of improving the aqueous solubility of these agents.^[50] We found that substitution of polyether side chains on the aryl ring resulted in a significant improvement in aqueous solubility. The replacement of the phenol moiety with, for example, a tyrosine substantially increases aqueous solubility, but at the cost of antiviral activity, confirming the importance of maintaining prodrug lipophilicity.

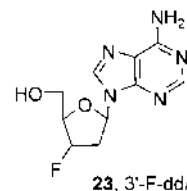
Unlike 4'-AzU, 4'-AzA and ddU, in this case the application of the phosphoramidate approach was successful in significantly improving the antiviral activities of numerous nucleosides that already exert good antiviral activities. Such success was also observed with 2',3'-didehydro-2',3'-dideoxyadenosine (d4A, **21**),^[51] 2',3'-dideoxyadenosine (ddA, **22**)^[51] and 2',3'-dideoxy-3'-fluoroadenosine (3'-F-ddA, **23**)^[52].



21, d4A



22, ddA

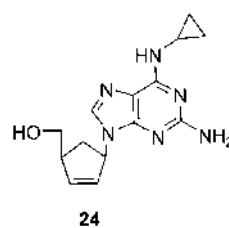


23, 3'-F-ddA

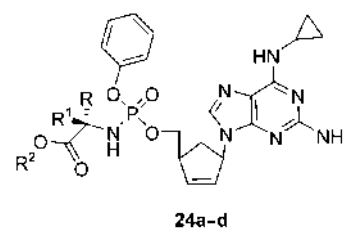
Abacavir

Carbocyclic nucleosides, lacking the labile glycosidic linkage between the heterocycle and sugar moieties, have long been proposed to offer an attractive in vivo stability advantage over the 2',3'-dideoxynucleosides. The first member of this structurally unique family to be approved for clinical use was abacavir (**24**), which is used in the treatment of HIV.^[53–55] This agent is activated via two distinct stages; initially abacavir is metabolised to its monophosphate derivative after which the compound is deaminated by a distinct cytosolic deaminase.^[56,57] The deaminated product, carbovir monophosphate, is then converted to the triphosphate form by two successive phosphorylation processes.^[56] Although abacavir is a relatively potent anti-HIV agent, it is still less potent than numerous other approved anti-HIV drugs such as AZT, 3TC and ddC. Consequently, we wondered whether applying our protide approach would improve the anti-HIV activity of this agent, and whether the micromolar in vitro anti-HBV activity of abacavir could be improved after conversion to its protide form.

We synthesised a wide range of abacavir phosphoramidates (**24a–d**; Table 3) with varying amino acids and esters. These



24



24a–d

compounds were studied for their anti-HIV as well as anti-HBV activities.^[58,59] The parent nucleoside (abacavir) had an EC₅₀ value of ~2.0 μM against both HIV-1 and HIV-2. All of the studied phosphoramidates of abacavir showed significant improvements in antiviral activities. The most potent phosphoramidate was the phenyl L-alanine methyl ester derivative (HIV-1, EC₅₀ = 0.05 μM; HIV-2, EC₅₀ = 0.07 μM). However, this derivative was more toxic in vitro relative to the parent nucleoside (CC₅₀ = 13 μM and 160 μM, respectively).^[59] In terms of anti-HBV activi-

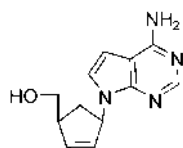
Table 3. Anti-HIV and anti-HBV activities of abacavir (**20**) and a series of its phosphoramidate derivatives (**24 a–d**).

Compd	Amino acid (R,R ¹)	Ester (R ²)	EC ₅₀ [μM]		CC ₅₀ [μM]	EC ₅₀ [μM]	CC ₅₀ [μM]
			HIV-1 CEM	HIV-2 CEM		HBV HepG 2.2.15	HepG2
24 a	L-Ala	Me	0.05	0.05	13	0.55	17
24 b	L-Ala	Et	0.07	0.061	12	0.35	18
24 c	L-Ala	<i>i</i> Pr	0.48	0.85	17	0.33	10
24 d	DiMeGly	Me	0.067	0.064	> 130	0.019	5.5
24	–	–	1.9	3.0	78	5.6	110

EC₅₀: effective concentration required to inhibit HIV or HBV-induced cytopathicity by 50%. CC₅₀: cytostatic concentration required to inhibit HepG2 cell proliferation by 50%. Details of the HIV and HBV assays can be found in Reference [59]. Data are the mean of at least two independent experiments.

ty, the most potent protide is that derived from the unusual achiral amino acid, dimethylglycine, which was ~300-times more potent than abacavir, but again with an increase in cytotoxicity.

We also applied our phosphoramidate approach to carbocyclic 2',3'-dideoxy-2',3'-didehydro-7-deazaadenosine (**25**, 7-deaza-d4A), which is a nucleoside with poor anti-HIV and anti-

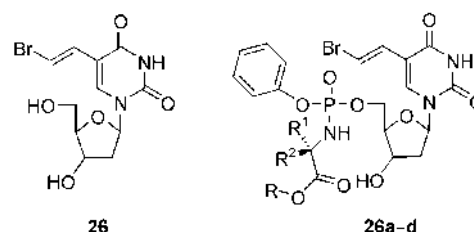
**25**, carbocyclic 7-deaza-d4A

HBV activities (IC₅₀=280 μM and 2 μM, respectively).^[60] The protides of this nucleoside showed significant improvements in both anti-HIV and anti-HBV activities. In regard to anti-HIV activity, the most potent phosphoramidate was the phenyl L-alanine methyl ester derivative (IC₅₀=0.091 μM), offering a 3000-fold boost in po-

tency. This compound also showed potent anti-HBV activity (IC₅₀=0.09 μM), though the phenyl dimethylglycine and phenylalanine methyl ester derivatives were found to be more potent against HBV, with IC₅₀ values of 0.05 μM and 0.055 μM, respectively.^[60]

BVDU

(*E*)-5-(2-Bromovinyl)-2'-deoxyuridine (BVDU, **26**) was among the other antiviral nucleosides to which our phosphoramidate technology was applied. This nucleoside analogue exhibits potent anti-HSV-1 and anti-VZV activity in cell culture.^[61,62]



nia virus (Table 4).^[63] The results showed the phosphoramidates to be less potent than the parent nucleoside against VZV, HSV-1 and HSV-2, although the phenyl benzyl L-alanine derivative of BVDU had an activity comparable to BVDU against HSV-1, and a significantly improved inhibitory activity against HIV-1 TK⁻ than the parent BVDU. In addition, some of the protides were relatively more potent against vaccinia virus compared with BVDU.

To our surprise, NewBiotics reported that some BVDU phosphoramidates possess potent anticancer activities.^[64] Thus, we were interested in studying the cytostatic (antiproliferative) activity of a large series of BVDU phosphoramidates. Our interest was enhanced by the fact that the phenyl L-alanine methoxy phosphoramidate of BVDU (thymectacin) entered clinical trials against colon cancer.^[65] A number of BVDU phosphoramidates were synthesised and tested against various types of cancer cells, such as breast, prostate and bladder cancers.^[66–68]

Table 4. Anti-VZV, Anti-HSV and antivaccinia activities of BVDU (**26**) and a series of its phosphoramidate derivatives (**26 a–d**).

Compd	Amino acid (R,R ¹)	Ester (R ²)	Anti-VZV activity				Anti-HSV and Anti-vaccinia activities					MCC [μm]
			EC ₅₀ [μm]	TK ⁻	VZV (YS)	CC ₅₀ [μm]	EC ₅₀ [μm]	HSV-1 (KOS)	HSV-2 (G)	TK ⁻	HSV-1 (KOS)	
26 a	L-Ala	Me	0.05	0.26	> 50	> 200	0.384	> 48	48	9.6	> 400	
26 b	L-Ala	Bn	0.026	0.025	> 50	81	0.002	> 16	0.348	0.256	80	
26 c	L-Val	Me	11	11	> 200	> 200	1.92	> 240	> 240	32	> 400	
26 d	L-Ala	Me	0.07	0.13	> 20	74	0.015	> 16	16	0.128	400	
26 (BVDU)	–	–	0.003	0.01	96	> 200	0.001	> 80	> 48	0.384	> 400	

EC₅₀: effective concentration required to inhibit virus-induced cytopathicity by 50%. CC₅₀: cytotoxic concentration required to inhibit HEL cell proliferation by 50%. MCC: minimal cytotoxic concentration or compound concentration required to result in a microscopically visible alteration of cell morphology. Further details of the VZV and HSV assays could be found in Reference [63].

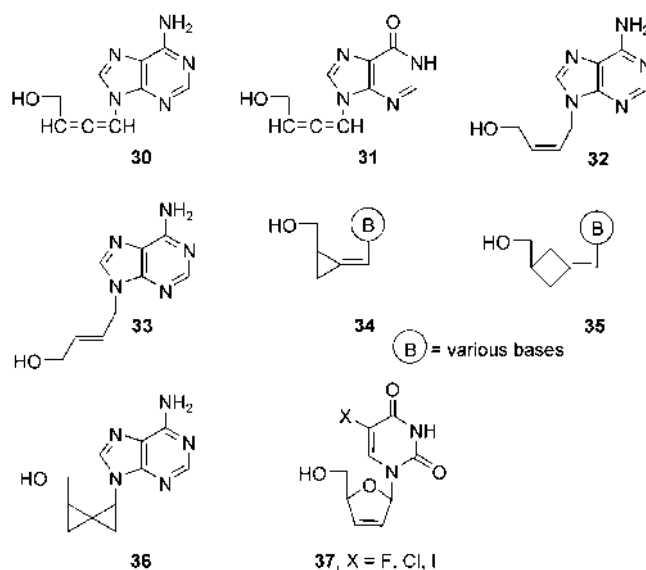
Most of the studied BVDU phosphoramidates exhibited anticancer activities varying from moderate to high (submicromolar) in some cases. One of our compounds, which is the phenyl L-alanine benzyl ester derivative of BVDU, revealed potent cytostatic activity ($IC_{50}=1.4\text{ }\mu\text{M}$) against colon cancer (HT115), and offered a 175-fold improvement in activity over thymectacin against colon cancer cells. The introduction of substitutions at the phenyl ring led to a series of compounds with potent anticancer activities. In particular, the *p*-chlorophenyl L-alanine benzyl ester derivative of BVDU showed activity against breast, colon and prostate cancer cells, with IC_{50} values of 6.2, 3.4 and $2.4\text{ }\mu\text{M}$, respectively. In terms of amino acid variations, the results were favourable. Most of the non-L-alanine compounds retained good activity, and a significant number of them possessed improved anticancer activities over those with L-alanine. In fact, the naphthyl dimethylglycine methyl derivative was found to be most potent against breast cancer MDAMB231 ($IC_{50}=0.32\text{ }\mu\text{M}$), however, its activity was not as potent against a human prostate cancer cell line (PC-3). In addition, the naphthyl L-proline methyl derivative was potent against bladder cancer cells T24 ($IC_{50}=0.4\text{ }\mu\text{M}$), while again such a potent activity was not retained against other types of cancers, including breast and prostate. Thus, it soon became clear that certain phosphoramidate derivatives could be very potent against one cancer cell type, while not necessarily potent against others. The reasons for such differences between cancer types are still unknown, but it may be a result of the levels or types of enzymes present in these cells, which are involved in metabolising phosphoramidates, or it may be related to cell access or efflux.

Application to other nucleosides

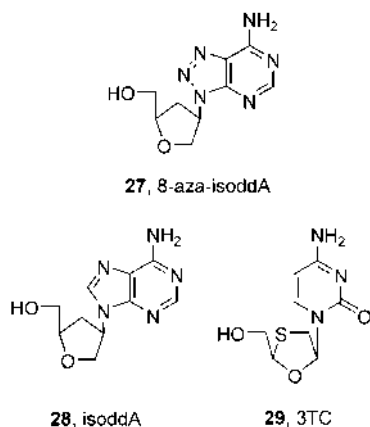
The first application of the aryl phosphoramidate technology to an isonucleoside was reported in 1994 by Franchetti and co-workers.^[69] In fact, they reported the application of the technology to 8-aza-isodda (**27**) and isodda (**28**). The result was a significant boost in the antiviral potency, where the aryl phosphoramidates of 8-aza-isodda (**27**) showed >25-fold increase in antiviral activity, while those of isodda (**28**) displayed a 350–800-fold increase in activity. This was an important study, which demonstrated the power of the aryloxy phosphoramidate approach in greatly improving the biological profiles of weakly active nucleosides. In this study, for example, isodda (**28**) was transformed from $32\text{ }\mu\text{M}$ activity against HIV-2, to 40 nM activity upon phosphoramidate formation. Further studies on these compounds revealed that such improvements in antiviral activity were due to an efficient intracellular phosphate delivery by aryloxy phosphoramidates.^[70]

As a result of the impressive success of phosphoramidates in significantly improving the antiviral activity of isonucleosides, we became interested in applying phosphoramidates to sugar-modified nucleosides. Thus, we applied the approach to 2',3'-dideoxy-3'-thiacytidine (3TC, **29**).^[71] However, the antiviral activity of 3TC phosphoramidates was not as impressive as that seen with the protides of isonucleosides. In fact, the phenyl L-alanine methoxy phosphoramidate derivative of 3TC was less active than the parent nucleoside in deoxycytidine (dCyd) kinase (dCK) expressing HIV-1- and HIV-2-infected cells.^[71] However, conducting the assay in dCK-deficient cells indicated far less of an impact on the potency for the 3TC phosphoramidate than in the parent CEM cells (~20-fold vs. 2000-fold). Interestingly, both compounds were equally effective against hepatitis B virus in hepatoma G2 cells indicating efficient protide activation in these cells but not in CEM cells used for the HIV assay.^[71] This was the first indication that the efficacy of phosphoramidates might be cell-line dependent.

Zemlicka and co-workers used the phosphoramidate approach on various nucleosides, and interestingly they applied such a strategy on nonclassical nucleosides.^[72] Initially, phenyl



methoxy alaninyl phosphoramidates of the anti-HIV agent, adenallene (**30**), and the inactive compound, hypoxallene (**31**) were prepared.^[73] The phosphoramidate derivative of adenallene was shown to exert a 10–20-fold boost in anti-HIV activity. Another study looking at alkenyl adenine nucleosides of structures **32** and **33** revealed some interesting results. In these cases, both (*Z*)-**30** and (*E*)-**31** nucleosides were inactive, whilst the phosphoramidate of **30** was active in the 1–10 μM range



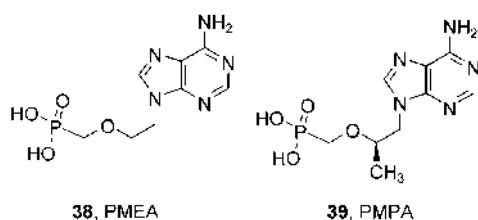
and nontoxic; the isomeric phosphoramidate of **33** remained inactive. The hypoxanthine analogue of **32** was also poorly active.

In a subsequent study, Zemlicka and co-workers investigated the activity of methylenecyclopropane nucleoside (**34**) phosphoramidates in several antiviral assays.^[74–77] In addition to the active *Z*-isomer, the inactive *E*-isomers were also studied. This study led to interesting conclusions in terms of structure–activity relationships. The results revealed that the adenine and 2,6-diaminopurine phosphoramidates were most potent against HIV. Although they were relatively toxic, the SI values of these agents were superior to those of the parent compounds. Notably, these protides were 10-fold more potent against HIV-2 compared with HIV-1.^[77] Strikingly, the phosphoramidates of the inactive (*E*)-isomer were also found to be active. In addition, the phosphoramidates of the (*Z*)-guanine analogues were active against a wide selection of viruses (HCMV, HBV, EBV, and VZV). In these cases, no significant toxicities were noted. The phosphoramidate approach was then applied to cyclobutane **35** and spiropentane **36** nucleosides with varying degrees of success.^[78,79]

To further pursue the kinase bypass approach, we prepared some novel d4T inactive antiviral (i.e. HIV) analogues with 5-halo substituents in place of the 5-methyl group (**37**) and converted them to their phosphoramidates.^[80] Although the parent nucleosides were only weakly active or inactive at >10–50 μM , all the phosphoramidates were active. In particular, the phenyl methoxy alaninyl phosphoramidate of the 5-chloro compound was active at submicromolar concentrations and nontoxic.^[80]

Application to acyclic nucleoside phosphonates

As well as the application to nucleoside analogues, in 2001 we reported the first application of the aryl phosphoramidate technology to nucleoside analogue phosphonates, in particular PMEA (**38**) and (R)PMPA (**39**).^[81] These two nucleoside phos-



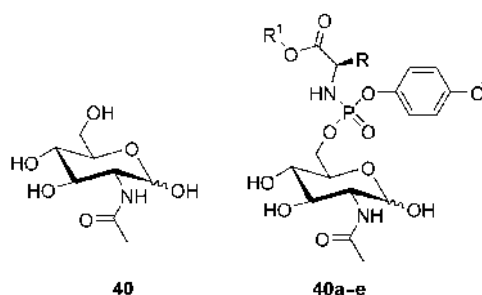
phonate analogues exist in their monophosphonate forms (containing a stable P–C bond). Thus, applying a protide approach to these agents is an attractive possibility. A series of phosphoramidates with substituted phenyl moieties and varying amino acids and esters were prepared and tested against two different HIV-infected cell lines (MT4 and CEM). All the phosphoramidates showed potent activity against HIV-1 and HIV-2 with boosts in activity between 30–100 fold. In our assay, (R)PMPA (tenofovir) was active against HIV-1 at 2.3 μM and HIV-2 at 1.4 μM in MT4 cells, while it was active against HIV-1 and HIV-2 at 3.67 μM in CEM cells. As for the phosphor-

amidates, the majority of them exhibited submicromolar inhibitory activities. In particular, the phenyl L-alanine methyl ester derivative of tenofovir was most potent in MT4 cells (HIV-1, EC_{50} = 0.029 μM ; HIV-2, EC_{50} = 0.026 μM). In CEM cells, the same phosphoramidate derivative was also very potent (HIV-1, EC_{50} = 0.053 μM ; HIV-2, EC_{50} = 0.090 μM). PMEA phosphoramidates were also relatively potent especially the phenyl L-alanine methyl ester. This agent also exhibited inhibitory activity at submicromolar concentrations though it also displayed some toxicity. Most of the other phosphoramidates of both PMEA and (R)PMPA did not possess significant toxicity.

Following our work on PMEA and (R)PMPA in 2001,^[81] there have been some reports in the literature, mainly from Gilead Sciences,^[82–84] on the application of the phosphoramidate technology to acyclic nucleoside phosphonates. Indeed such application has resulted in two very potent anti-HIV drugs, GS-7340 and GS-9131, entering clinical trials, which will be discussed later.

Application to glucosamine

Glucosamine has been used for a long time in the prophylaxis and treatment of osteoarthritis.^[85] Despite the different hypotheses regarding the mechanism of action of glucosamine, the action of the 6-phosphate metabolite on cartilage degradation appears to be a favoured putative mechanism.^[86] Thus, a series of phosphoramidates of *N*-acetyl glucosamine (**40 a–e**; Table 5) were synthesised and tested for antiosteoarthritic activity.^[14]



Although all the phosphoramidates synthesised had the same aryl motif (4-*O*-methoxy phenol), they differed in their amino acid and ester moieties. The assay used for measuring the activity of these compounds was based on the induced GAG (glycosaminoglycan) release. In this assay, glucosamine had some protective activity at 10 mM concentration, though some toxicity was observed. Notably, no protective activity was detected at 1 mM concentration. However, the phosphoramidates of *N*-acetyl glucosamine showed better activity and some of them showed activity at concentrations as low as 0.1 mM with no observed toxicity. Hence, they are approximately ≥ 100 -fold more active than glucosamine in this assay.

Notably, unusual and interesting SARs relative to nucleoside phosphoramidates were observed for the glucosamine protides. In particular, the often favoured L-alanine phosphoramidates showed poor activity, while their D-counterparts were more potent. The reasons for such differences are currently under investigation in our laboratories.

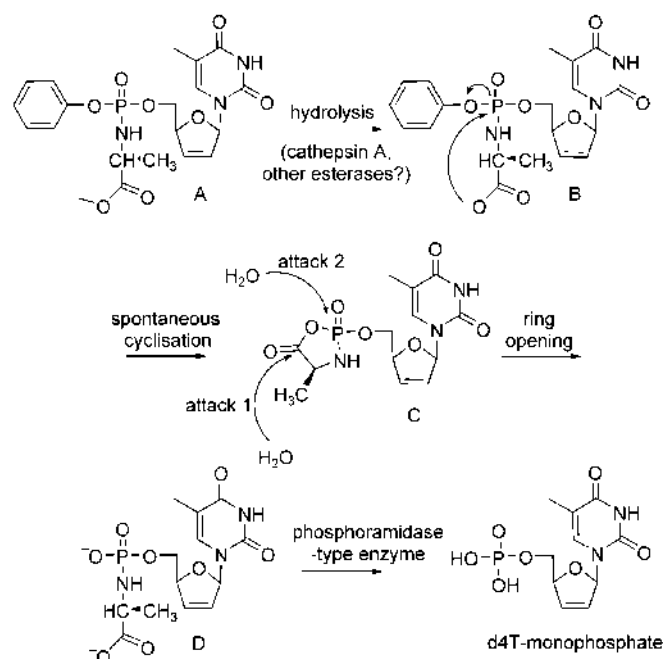
Table 5. Antiosteoarthritic activity of *N*-acetylglucosamine (**40**) and a series of its phosphoramidate derivatives (**40a–e**).^[a]

Compd	Amino acid (R)	Ester (R')	Control GAG fold	GAG fold	Reduction GAG fold ^[b] [%]	MTT ^[b]
40a	Gly	Bn	3.9	4.2	−12.2 (±15.42)	99 (±1.92)
40b	L-Val	Et	3.8	4.4	−21.1 (±25.80)	94 (±3.19)
40c	L-Pro	<i>n</i> Bu	3.8	4.1	−2.2 (±4.44)	104 (±1.2)
40d	L-Ala	Bn	4.5	4.6	−1.9 (±10.19)	89 (±1.29)
40e	D-Ala	Bn	4.2	3.4	24.3 (±16.28)	96 (±2.91)
40	–	–	4.5	4.3	5.4 (±0.41)	107 (±2.03)

[a] Activity measured at 0.1 mM concentration. The average fold increase in GAG release into the culture media in IL-1-treated cultures is calculated using the appropriate control (minus IL-1) for explants cultured in the absence (control GAG fold) and presence (GAG fold) of glucosamine compounds at concentrations ranging from 10 to 0.1 mM; values indicated are the average of these experiments. The percent reduction in GAG-fold was calculated for each experiment as the percent difference observed for each experiment using the following calculation: $\frac{[(\text{control GAG fold}) - (\text{sample GAG fold})]}{(\text{control GAG fold})} \times 100$. The effects of different concentrations of glucosamine compounds on chondrocyte viability were assessed using the MTT assay. The number of experiments carried out varied from one sample to another. Further details on the assay could be found in Reference [14]. [b] Values given in parentheses are the standard error.

Mechanism of action

The activation of aryloxy phosphoramidates to release the monophosphate species is suggested to proceed in four steps: two enzyme-mediated and two spontaneous (Figure 3). The activation process begins with the cleavage of the ester moiety by an esterase-type activity. In an effort to model this in a predictive sense, we exposed various esters to pig liver esterase and followed the progress of the reaction by ³¹P NMR.^[86] Upon

**Figure 3.** Postulated mechanism of phosphoramidate activation.

esterase treatment, the two signals of the starting material, corresponding to the two diastereoisomers of phosphoramidates, disappeared to give a downfield singlet ($\delta_p \sim 8.2$), which was characterised as the amino acyl phosphate monoester. Whilst the rate of cleavage of various esters did not correlate with antiviral activity, we did note that esterase lability was a necessary condition (but not sufficient alone) for high biological potency. Notably, the *tert*-butyl ester was not hydrolysed in this assay, and the *tert*-butyl ester-derived phosphoramidate was the least potent of all tested compounds.^[86] Recently, scientists at Gilead identified cathepsin A as the major enzyme responsible for the cleavage of the ester motif.^[87] This study also looked at the rate of ester hydrolysis, which often correlates with antiviral activity, and the findings of such an investigation were striking. Phosphoramidates containing alanine were hydrolysed quicker than those with branched amino acids. In fact, cathepsin A was unable to hydrolyse phosphoramidates with heavily branched amino acids such as leucine, valine and isoleucine. The reason behind this hydrolysing selectivity remains unclear. Interestingly, another relatively minor enzyme able to hydrolyse phosphoramidates was also detected in this study, but has yet to be identified.

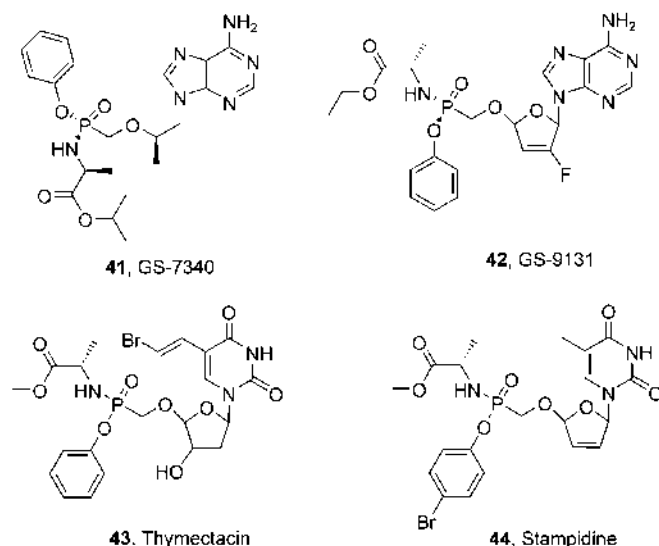
Upon ester hydrolysis, an intracellular displacement of the phenoxy group by the carboxylate anion (B) takes place (Figure 3). This results in the formation of a five-membered ring mixed anhydride (C), with the speed of this process being dependent on the structure of the analogue. Thus, cyclisation of intermediate B of AZT was more difficult than that of d4T.^[88] More interestingly, phosphoramidates with β -alanine only went as far as the ester hydrolysis, as no subsequent metabolites were formed.^[88]

The cyclic anhydride intermediates then undergo hydrolysis, which is not enzyme assisted, to give phosphoalaninate (D). The cleavage of the P–N bond is ruled out at this stage,^[89] hydrolysis can only proceed by either attack on the phosphorous atom or the carbonyl functionality. Often the hydrolysis or methanolysis of mixed carboxylic and phosphoric anhydrides proceeds by attack on the carboxylate moiety (attack 1).^[89] However, in the case of five-membered ring anhydrides, attack on the phosphate group (attack 2) can prevail.^[90,91] Notably, phosphoalaninates of d4T phosphoramidates exhibited an anti-HIV effect comparable to the parent compound, d4T.^[92]

The final activation step of phosphoramidates is the cleavage of the P–N bond of the phosphoalanine intermediate to generate the monophosphate nucleoside analogue. Although this step is believed to be a result of the activity of an intracellular phosphoramidase,^[92,93] direct evidence is still lacking.

Aryloxy phosphoramidates under clinical investigations

At least four different aryloxy triester phosphoramidates have reached clinical evaluation; (**41**, GS-9140; **42**, GS-9131; **43**, thymectacin (NB1011); **44**, stampidine). Apart from thymectacin, which is being developed as an anticancer agent, the other three drugs have been pursued as anti-HIV agents.



GS-7340 and GS-9131

GS-7340 (**41**) and GS-9131 (**42**) are two phosphoramidate triester-based nucleoside analogues that are being developed by Gilead Sciences for the treatment of HIV/AIDS.^[94,95] As well as the potent anti-HIV activities exerted by these agents, they also possessed favourable antiviral drug resistance profiles and low cytotoxicities.^[87,94,95]

GS-7340 (**41**) is a phosphoramidate prodrug of the FDA-approved anti-HIV phosphonate tenofovir (TFV, (R)PMPA). TFV is an acyclic nucleotide analogue of dAMP, and is a potent in vitro and in vivo inhibitor of HIV-1 replication.^[96] TFV is converted to its active species, which acts as a potent inhibitor of HIV-1 reverse transcriptase, following two intracellular phosphorylations by kinases.^[97,100] TFV exhibits low cellular permeability and poor oral bioavailability because a charged phosphate group is inherent in the molecule. Numerous prodrugs have been designed to address these problems; the bis-isopropoxycarbonyloxymethyl ester prodrug of TFV (TDF) has been approved for HIV treatment. Although TDF is well tolerated, infrequent development of resistance and minor long-term toxicities are associated with its use.^[96,101,102] In addition, despite the initial high systemic levels of TFV following TDF administration, the rapid systemic degradation of TDF to TFV, which is charged under physiological conditions, limits its uptake into the target cells.

In order to develop plasma-stable prodrugs of TFV, the Gilead group applied the phosphoramidate approach. Upon optimisation, they identified the phenyl L-alanine isopropyl ester of TFV (GS-7340, **41**) as a good clinical candidate. As well as the improved potency in anti-HIV activity compared to TFV, GS-7340 (**41**) was found to be stable in blood.^[103] Further investigations revealed that 10-fold and 30-fold higher levels of TFV and its phosphorylated metabolites were recorded following incubation of peripheral blood mononuclear cells (PBMC) with GS-7340 (**41**), compared with the incubation with bis-POC TFV and TFV, respectively.^[103] Next, the Gilead group developed a practical large-scale synthesis of GS-7340 (**41**), which also

allowed separation of the distereoisomers.^[104] Interestingly, the group chose the *S*-isomer for development as an HIV inhibitor because it was found to be ~10-fold more potent than the *R*-isomer.^[104] However, Gilead recently discontinued the development of GS-7340 (**41**) as they did not believe that GS-7340 (**41**) has a profile that differentiates it to an extent that supports its continued development.

GS-9131 (**42**) is a phosphoramidate prodrug of the novel nucleoside analogue 2'- α -fluoro-2',3'-didehydro-2',3'-dideoxyadenosine. In fact, it is the phenyl L-alanine ethyl ester derivative of this nucleoside that was chosen for development and clinical studies. The encouraging factors for the Gilead group, which are also responsible for the development of GS-9131 (**42**), were: a) the good anti-HIV potency of this agent against HIV-1-resistant virus strains, b) the favourable in vivo pharmacological properties of GS-9131 and c) the ability of GS-9131 (**42**) to effectively deliver the active diphosphate metabolite into PBMC.^[94,105] GS-9131 (**42**) is currently under clinical evaluation.

Thymectacin

As mentioned above, the phenyl L-alanine methoxy derivative of BVDU (**43**) surprisingly showed potent antitumour activities. Developed by NewBiotics, this BVDU phosphoramidate, known as thymectacin, is currently undergoing combined phase I/II clinical trials for the treatment of colon cancer. It is a novel agent that selectively targets tumour cells with a high expression of thymidylate synthase (TS).^[106–109] It is non-cross-resistant with TS-targeted agents and was found to be at least 10-fold more cytotoxic to 5-FU-resistant, TS over-expressing colorectal tumour cells than to normal cells.^[108] Monotherapy trials are complete, and thymectacin (**43**) was found to be active and feasible in fluoropyrimidine-resistant metastatic CRC.^[109]

Stampidine

Stampidine (**44**) is a *para*-bromophenyl methoxy-L-alaninyl phosphoramidate derivative of d4T. As well as showing good anti-HIV activity against wild-type HIV-1 strains, stampidine (**44**) also displayed good anti-HIV-1 activity against virus strains carrying NNRTI mutations.^[110,111] This compound also showed good activity, tolerability and toxicity profiles in vivo.^[112–114] Stampidine (**44**) has been proposed as a treatment for patients infected with highly drug-resistant strains of HIV-1. Despite the impressive in vitro and in vivo activities of stampidine (**44**), there have been no recent reports regarding its further development, and no clinical trials are underway at present.

Conclusions and Outlook

The phosphoramidate triester protide approach has been well investigated and established as a viable method for the intracellular delivery of monophosphate nucleoside analogues. This approach has been proven to considerably improve the antiviral and anticancer profiles of many nucleoside analogues. Unlike other pronucleotide approaches, phosphoramidate

triesters are activated intracellularly by enzymes to release the phosphorylated biomolecule. Although some of the enzymes involved in this activation process have been identified, more work is needed in this area to confirm the full activation mechanism.

Nevertheless, the phosphoramidate triester pronucleotide technology has proved effective as a tool for drug discovery, and so far at least four phosphoramidate triester-based drugs are undergoing clinical trials (one anticancer and three antiviral agents). In the future, we can expect to see this technology applied to non-nucleoside phosphorylated compounds, either as therapeutic molecules or as biochemical tools to study biological phenomena. In addition, phosphoramidate-based compounds may be explored as treatments of a wide range of diseases that are not just limited to viral infections and cancers.

Keywords: drug delivery · nucleosides · nucleotides · phosphoramidates · prodrugs

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**BEFORE THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, NEW DELHI**

In the matter of Post-grant opposition under Section 25(2) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55A of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

In the matter of Indian Patent number 332280 (formerly Application number 201727012821) dated 11/04/2017 in the name of GILEAD SCIENCES Inc.

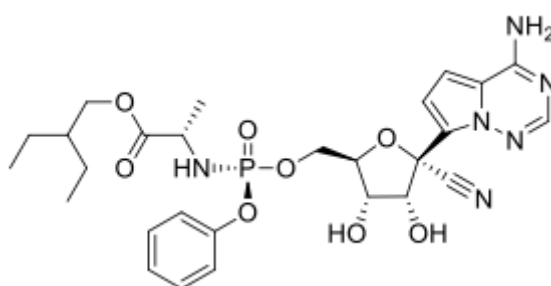
REPRESENTATION BY:

Low Cost Standard Therapeutics OPPONENT

GILEAD SCIENCES Inc APPLICANT

[A] INTRODUCTION:

1. I, Dr.UmeshRewajiZope, aged about 58 years, residing at 145B, Kanchanjunga Apartment, NOIDA UP 201301, India, do hereby solemnly affirm and declare as under:
2. I have been approached by **Low Cost Standard Therapeutics** (hereinafter referred as the “Petitioner”) regarding an Indian patent 332280 (formerly Indian Patent Application No. 201727012821) (hereinafter referred as “impugned patent”) in the name of GILEAD SCIENCES INC (hereinafter referred as “thePatentee”). The impugned Patent covers and claims a compound, Remdesivir, having the following structure:



3. I have been requested to independently review impugned patent and express my opinion on the claimed matter made therein against the prior-art documents.

4. I state that my opinion is purely based on my education, knowledge, training and experiences in the relevant scientific field.
5. I also declare that I am being compensated for consultation in this case, however, neither my compensation is related to outcome of this proceedings nor I have personal interest in the matter.
6. Further, I also hereby admit that I have provided expert opinion in several patent litigation and related cases and therefore, I am familiar with basic concepts of patent law including novelty and inventive step which shall be assessed on the priority date of impugned patent or patent application by a person having ordinary skilled in the art (herein after referred as “PHOSITA”).
7. Importantly, I am well aware that hindsight approach is not permissible in these deliberations. In addition to above all, I firmly believe that the inventions filed without merits shall loudly be opposed.

8. I am no stranger to the requirements of an invention as per Indian Patents Act, 1970 (herein after referred as “the Patents Act”) that to be patentable; it must be novel, inventive/non-obvious and have industrial applicability. More importantly, the invention shall also cross the barrier of non-patentable subject matters those are described in Section-3 and Section-4 of the Patents Act.
9. As per the Patents Act new invention means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject matter has not fallen in public domain or that it does not form part of the state of the art.
10. I am quite acquainted with the definition of inventive step which is also known as non-obviousness that it is a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art (PSITA).

11. Thus, from above information, it may be clear to the Learned Controller that I am well mindful of Indian patents law, also. I further describe my educational and professional background in following paragraphs.

[B] EDUCATIONAL AND PROFESSIONAL BACKGROUND:

12. My educational qualifications, work experience, associations are more particularly stated in Exhibit-1, hereto. In view thereof, I am the ordinarily skilled person in the art who is the addressee of the invention disclosed and claimed in the opposed patent and I am competent to make this Affidavit inter alia expressing an opinion, as an expert in the field of pharmaceutical chemistry, on the issue stated herein below.

13. I state that I have about 30 years of experience in Chemistry. I hold a Ph. D. degree in Chemistry.

14. I deliberate on professional experience stating from present to old. Also, write about projects, publications, etc. My previous work experiences are mentioned in detail in the form of curriculum vitae enclosed herewith as Exhibit-1. I

have several patents and publications to my credit. A representative list of my career achievements is also attached herewith as Exhibit-1.

15. I view of my position, qualifications, experience and knowledge in the field of Pharmaceutical chemistry, I am competent to depose this Affidavit by expressing my opinions on the discussed matter.

[C] TECHNICAL:

16. I understand that the impugned patent claims various antiviral compounds. One of the claimed compounds is known as Remdesivir.

PRIOR CLAIMING BY IN 332280 (IN'280)

17. The claims of the impugned Patent IN 332280 are prior claimed in IN 319927 herein reproduced as IN'927. IN'927 (formerly 1328/CHENP/2013) was filed on 19.02.2013 and granted on 05.9.2019. It has a PCT application PCT/US2011/045102 that was filed on 22.07.2011. The conditions for prior claiming is fulfilled in IN'927 because:-

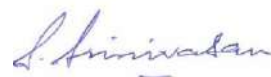
FORM 26
THE PATENTS ACT, 1970
(39 of 1970)
&
The Patent Rules, 2003
FORM OF AUTHORISATION OF A PATENT AGENT/OR ANY PERSON IN A
MATTER OR PROCEEDING UNDER THE ACT
[See sections 127 and 132 and rule 135]

We, **LOW COST STANDARD THERAPEUTICS**, I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390 001, Gujarat, India; hereby authorize Rajeshwari H., Gopalan Deepak Srinivas, Sweetly Sharma and Pragya Singh Thakur, all Indian citizens, Advocates / Patent Agents of **RAJESHWARI & ASSOCIATES**, A – 202, FIRST FLOOR, SHIVALIK COLONY, MALVIYA NAGAR, NEW DELHI – 110017, INDIA, jointly or severally to act on our behalf for filing an opposition and/or representation by the way of opposition against an invention entitled: "**COMPOUNDS FOR TREATING FILOVIRIDAE INFECTIONS**" **Indian Patent No. 332280 (having Indian Application No: 201727012821)** by GILEAD SCIENCES INC. is a National Phase of PCT Application No. PCT/US2015/057933 dated 29/10/2015 under the above mentioned Act and in all matters and proceedings relating to the patent applications before the Controller of Patents or the Government of India in connection therewith or incidental thereto and in general to do all acts or things including filing of representation, statements, replies, extensions, fees, evidence and any or all documents or pleadings, attending hearings and appointment of a substitute or substitutes as the said Agent(s) may deem necessary or expedient and request that all notices, requisitions and communication relating thereto may be sent to such Agent(s) at Rajeshwari & Associates, India.

We hereby revoke all previous authorization, if any made, in respect of same matter or proceeding.

We hereby assent to the action already taken by the said person in the above matter.

Dated this 30th day of June, 2020



S.SRINIVASAN
MANAGING TRUSTEE

To
The Controller of Patents
The Patent Office, Mumbai