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(54) Title: ORGANOPHOSPHATE DERIVATIVES

(57) Abstract: Provided herein are organophosphates and pharmaceutical compositions comprising said compounds.



## ORGANOPHOSPHATE DERIVATIVES

## CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/538,879, filed on July 31, 2017, and U.S. Provisional Application No. 62/637,960, filed on March 2, 2018, each of which is herein incorporated by reference in its entirety.

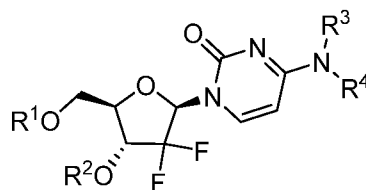
## BACKGROUND

[0002] Cancer is among the leading causes of death worldwide. The number of new cancer cases is expected to rise to 22 million within the next two decades. Improved therapies are needed to treat this increasing patient population.

## BRIEF SUMMARY OF THE INVENTION

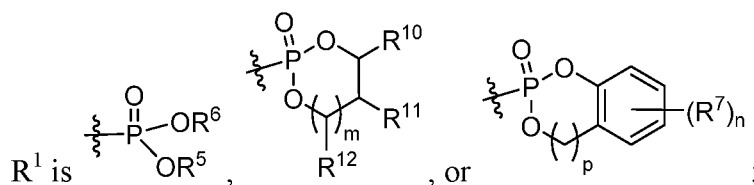
[0003] This disclosure provides, for example, organophosphate compounds, their use as medicinal agents for the treatment of cancer, processes for their preparation, and pharmaceutical compositions that include disclosed compounds as at least one active ingredient. The disclosure also provides for the use of compounds described herein as medicaments and/or in the manufacture of medicaments for the treatment of cancer.

[0004] In one aspect is a compound of Formula (I):



Formula (I);

wherein:



$R^1$  is  $-P(=O)(OR^5)_2$ ,

$R^2$  is  $-C(O)R^8$ ;

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^5$  is H,  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-6}$ alkyl- $OC(O)C_{1-22}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-}$

$\text{9heteroaryl}$ , wherein  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$  are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

$\text{R}^6$  is  $\text{C}_{3-22}\text{alkyl}$ ,  $\text{C}_{3-22}\text{alkenyl}$ ,  $\text{C}_{3-22}\text{alkynyl}$ ,  $\text{C}_{3-22}\text{haloalkyl}$ ,  $-\text{C}_{1-6}\text{alkyl}-\text{OC}(\text{O})\text{C}_{1-22}\text{alkyl}$ ,  $\text{C}_{3-8}\text{cycloalkyl}$ ,  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$ , wherein  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$  are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

each  $\text{R}^7$  is independently selected from halogen,  $\text{C}_{1-8}\text{alkyl}$ ,  $\text{C}_{1-8}\text{haloalkyl}$ , and  $\text{C}_{1-8}\text{alkoxy}$ ;

$\text{R}^8$  is  $\text{C}_{3-22}\text{alkyl}$ ,  $\text{C}_{3-22}\text{alkenyl}$ ,  $\text{C}_{3-22}\text{alkynyl}$ ,  $\text{C}_{3-22}\text{haloalkyl}$ ,  $\text{C}_{3-8}\text{cycloalkyl}$ ,  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$ , wherein  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$  are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

$\text{R}^9$  is  $\text{C}_{1-12}\text{alkyl}$ ;

$\text{R}^{10}$  and  $\text{R}^{11}$  are each independently H or  $\text{C}_{1-12}\text{alkyl}$ ; or  $\text{R}^{10}$  and  $\text{R}^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $\text{R}^{13}$ ;

$\text{R}^{12}$  is H or  $\text{C}_{1-12}\text{alkyl}$ ;

each  $\text{R}^{13}$  is independently selected from  $\text{C}_{1-12}\text{alkyl}$ ;

each  $\text{R}^{14}$  is independently selected from halogen,  $\text{C}_{1-8}\text{alkyl}$ ,  $\text{C}_{1-8}\text{haloalkyl}$ ,  $\text{C}_{1-8}\text{alkoxy}$ , and  $-\text{C}(\text{O})\text{R}^{13}$ ;

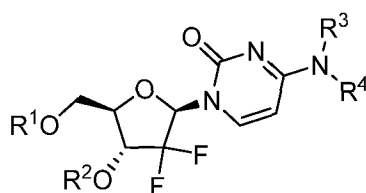
m is 0 or 1;

n is 0, 1, 2, 3, or 4; and

p is 0 or 1;

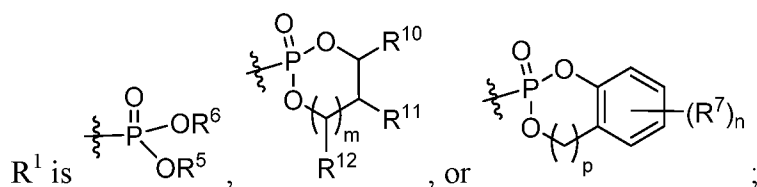
or a pharmaceutically acceptable salt thereof.

**[0005]** In another aspect is a compound of Formula (I'):



Formula (I');

wherein:



$R^2$  is  $-\text{C}(\text{O})\text{R}^8$ ;

$R^3$  is H,  $-\text{C}(\text{O})\text{R}^9$ , or  $-\text{C}(\text{O})\text{OR}^9$ ;

$R^4$  is H;

$R^5$  is H,  $\text{C}_{3-22}$ alkyl,  $\text{C}_{3-22}$ alkenyl,  $\text{C}_{3-22}$ alkynyl,  $\text{C}_{3-22}$ haloalkyl,  $-\text{C}_{1-4}$ alkyl- $\text{OC}(\text{O})\text{C}_{1-8}$ alkyl,  $\text{C}_{3-8}$ cycloalkyl,  $\text{C}_{6-10}$ aryl,  $-\text{C}_{1-8}$ alkyl- $\text{C}_{6-10}$ aryl,  $\text{C}_{2-9}$ heteroaryl, or  $-\text{C}_{1-8}$ alkyl- $\text{C}_{2-9}$ heteroaryl, wherein  $\text{C}_{6-10}$ aryl,  $-\text{C}_{1-8}$ alkyl- $\text{C}_{6-10}$ aryl,  $\text{C}_{2-9}$ heteroaryl, or  $-\text{C}_{1-8}$ alkyl- $\text{C}_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

$R^6$  is  $\text{C}_{3-22}$ alkyl,  $\text{C}_{3-22}$ alkenyl,  $\text{C}_{3-22}$ alkynyl,  $\text{C}_{3-22}$ haloalkyl,  $-\text{C}_{1-4}$ alkyl- $\text{OC}(\text{O})\text{C}_{1-8}$ alkyl,  $\text{C}_{3-8}$ cycloalkyl,  $\text{C}_{6-10}$ aryl,  $-\text{C}_{1-8}$ alkyl- $\text{C}_{6-10}$ aryl,  $\text{C}_{2-9}$ heteroaryl, or  $-\text{C}_{1-8}$ alkyl- $\text{C}_{2-9}$ heteroaryl, wherein  $\text{C}_{6-10}$ aryl,  $-\text{C}_{1-8}$ alkyl- $\text{C}_{6-10}$ aryl,  $\text{C}_{2-9}$ heteroaryl, or  $-\text{C}_{1-8}$ alkyl- $\text{C}_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

each  $\text{R}^7$  is independently selected from halogen,  $\text{C}_{1-8}$ alkyl,  $\text{C}_{1-8}$ haloalkyl, and  $\text{C}_{1-8}$ alkoxy;

$R^8$  is  $\text{C}_{3-22}$ alkyl,  $\text{C}_{3-22}$ alkenyl,  $\text{C}_{3-22}$ alkynyl,  $\text{C}_{3-22}$ haloalkyl,  $\text{C}_{3-8}$ cycloalkyl,  $\text{C}_{6-10}$ aryl,  $-\text{C}_{1-8}$ alkyl- $\text{C}_{6-10}$ aryl,  $\text{C}_{2-9}$ heteroaryl, or  $-\text{C}_{1-8}$ alkyl- $\text{C}_{2-9}$ heteroaryl, wherein  $\text{C}_{6-10}$ aryl,  $-\text{C}_{1-8}$ alkyl- $\text{C}_{6-10}$ aryl,  $\text{C}_{2-9}$ heteroaryl, or  $-\text{C}_{1-8}$ alkyl- $\text{C}_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

$R^9$  is  $\text{C}_{1-12}$ alkyl;

$R^{10}$  and  $R^{11}$  are each independently H or  $\text{C}_{1-12}$ alkyl; or  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $\text{R}^{13}$ ;

$R^{12}$  is H or  $\text{C}_{1-12}$ alkyl;

each  $\text{R}^{13}$  is independently selected from  $\text{C}_{1-12}$ alkyl;

each  $\text{R}^{14}$  is independently selected from halogen,  $\text{C}_{1-8}$ alkyl,  $\text{C}_{1-8}$ haloalkyl,  $\text{C}_{1-8}$ alkoxy, and  $-\text{C}(\text{O})\text{R}^{13}$ ;

$m$  is 0 or 1;

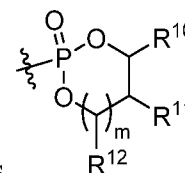
$n$  is 0, 1, 2, 3, or 4; and

$p$  is 0 or 1;

or a pharmaceutically acceptable salt thereof.

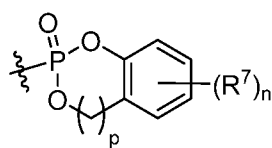
[0006] In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{P} \\ \swarrow \quad \searrow \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $C_{3-16}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $C_{3-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $C_{6-14}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $C_{6-10}$ alkyl. In another embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-16}$ alkyl. In another embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-\text{CH}_2\text{-OC(O)C}(\text{CH}_3)_3$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $C_{3-16}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $C_{3-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $C_{6-10}$ alkyl. In another embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-16}$ alkyl. In another embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-\text{CH}_2\text{-OC(O)C}(\text{CH}_3)_3$ . In another embodiment is a compound of



Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is

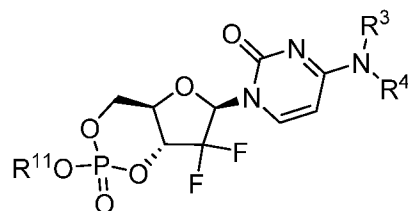
. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  is H. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  is  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is H. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



thereof, wherein  $R^1$  is

. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein each  $R^7$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein each  $R^7$  is independently selected from  $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $n$  is 1 or 2. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $n$  is 0. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 0. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-15}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-18}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_7CH_2$ .

[0007] In another aspect is a compound of Formula (II):



Formula (II);

wherein:

$R^3$  is H, H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^9$  is  $C_{1-8}$ alkyl;

$R^{11}$  is  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{12}$ ;

each  $R^{12}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ ; and

each  $R^{13}$  is independently selected from  $C_{1-12}$ alkyl;

or a pharmaceutically acceptable salt thereof.

[0008] In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{3-15}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-12}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{8-10}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{8-22}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{16-22}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-2}$ alkyl- $OC(O)C_{1-6}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-OC(O)C(CH_3)_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is

phenyl optionally substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl optionally substituted with 1, 2, or 3  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl optionally substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2$ -phenyl optionally substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2$ -phenyl optionally substituted with 1, 2, or 3  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2$ -phenyl optionally substituted with 1, 2, or 3  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (I), (I'), or (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H. In another embodiment is a compound of Formula (I), (I'), or (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$ . In another embodiment is a compound of Formula (I), (I'), or (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$ .

**[0009]** In another embodiment is a pharmaceutical composition comprising a compound of Formula (I), (I'), or (II) described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

**[0010]** In another embodiment is a method of treating cancer in a patient, comprising administering to the patient in need thereof a therapeutically effective amount of a compound of Formula (I), (I'), or (II) described herein, or a pharmaceutically acceptable salt thereof. In another embodiment is a method of treating an infectious disease in a patient, comprising administering to the patient in need thereof a therapeutically effective amount of a compound of Formula (I), (I'), or (II) described herein, or a pharmaceutically acceptable salt thereof.

## DETAILED DESCRIPTION OF THE INVENTION

**[0011]** Nucleoside analogues constitute a major class of chemotherapeutic agents and are used for the treatment of patients with cancer. This group of agents, known as antimetabolites, includes a variety of pyrimidine and purine nucleoside derivatives with



cytotoxic activity in both hematological and solid tumors. Gemcitabine (2',2'-difluoro-2'-deoxycytidine) is a pyrimidine nucleoside analogue, shown to be active against several solid tumor types.

**[0012]** Both innate and acquired resistance to nucleoside analogues is a problem in the treatment of cancer and is regarded as a driver of poor patient survival outcomes. Gemcitabine faces inherent and acquired cancer resistance mechanisms that limit its effectiveness. These include (i) poor conversion of gemcitabine into the active forms, dFdCDP and dFdCTP; (ii) rapid degradation into toxic byproducts; and (iii) limited uptake by cancer cells. These effects are due to the following: (i) down-regulation of the key initial phosphorylating enzyme deoxycytidine kinase (dCK) required to convert gemcitabine into the monophosphate form; (ii) expression of the key deactivating enzyme cytidine deaminase; and (iii) deficiency of nucleoside transporter proteins. In addition, increased expression and/or activity of cytidine deaminase (CDA) increases the degradation of gemcitabine into the toxic metabolite 2',2'-difluoro-2'-deoxyuridine (dFdU). Because of these processes, single agent gemcitabine has limited activity in cancer treatment.

**[0013]** As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range varies between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that which in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

### **Definitions**

**[0014]** As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0015] As used herein, C<sub>1</sub>-C<sub>x</sub> includes C<sub>1</sub>-C<sub>2</sub>, C<sub>1</sub>-C<sub>3</sub> . . . C<sub>1</sub>-C<sub>x</sub>. C<sub>1</sub>-C<sub>x</sub> refers to the number of carbon atoms that make up the moiety to which it designates (excluding optional substituents).

[0016] "Amino" refers to the -NH<sub>2</sub> radical.

[0017] "Cyano" refers to the -CN radical.

[0018] "Nitro" refers to the -NO<sub>2</sub> radical.

[0019] "Oxa" refers to the -O- radical.

[0020] "Oxo" refers to the =O radical.

[0021] "Thioxo" refers to the =S radical.

[0022] "Imino" refers to the =N-H radical.

[0023] "Oximo" refers to the =N-OH radical.

[0024] "Alkyl" or "alkylene" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eighteen carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>18</sub> alkyl). In certain embodiments, an alkyl comprises three to eighteen carbon atoms (*e.g.*, C<sub>3</sub>-C<sub>18</sub> alkyl). In certain embodiments, an alkyl comprises one to fifteen carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>15</sub> alkyl). In certain embodiments, an alkyl comprises one to twelve carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>12</sub> alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>8</sub> alkyl). In other embodiments, an alkyl comprises one to six carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>6</sub> alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>5</sub> alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>4</sub> alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>3</sub> alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C<sub>1</sub>-C<sub>2</sub> alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C<sub>1</sub> alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C<sub>5</sub>-C<sub>15</sub> alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C<sub>5</sub>-C<sub>8</sub> alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C<sub>2</sub>-C<sub>5</sub> alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C<sub>3</sub>-C<sub>5</sub> alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), and 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, -OR<sup>a</sup>, -SR<sup>a</sup>, -OC(O)-R<sup>f</sup>, -N(R<sup>a</sup>)<sub>2</sub>, -C(O)R<sup>a</sup>, -C(O)OR<sup>a</sup>, -C(O)N(R<sup>a</sup>)<sub>2</sub>, -

$N(R^a)C(O)OR^f$ ,  $-OC(O)-NR^aR^f$ ,  $-N(R^a)C(O)R^f$ ,  $-N(R^a)S(O)_tR^f$  (where  $t$  is 1 or 2),  $-S(O)_tOR^a$  (where  $t$  is 1 or 2),  $-S(O)_tR^f$  (where  $t$  is 1 or 2) and  $-S(O)_tN(R^a)_2$  (where  $t$  is 1 or 2) where each  $R^a$  is independently hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, and each  $R^f$  is independently alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl.

**[0025]** "Alkoxy" refers to a radical bonded through an oxygen atom of the formula  $-O$ -alkyl, where alkyl is an alkyl chain as defined above.

**[0026]** "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to eighteen carbon atoms. In certain embodiments, an alkenyl comprises three to eighteen carbon atoms. In certain embodiments, an alkenyl comprises three to twelve carbon atoms. In certain embodiments, an alkenyl comprises six to twelve carbon atoms. In certain embodiments, an alkenyl comprises six to ten carbon atoms. In certain embodiments, an alkenyl comprises eight to ten carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilyl,  $-OR^a$ ,  $-SR^a$ ,  $-OC(O)-R^f$ ,  $-N(R^a)_2$ ,  $-C(O)R^a$ ,  $-C(O)OR^a$ ,  $-C(O)N(R^a)_2$ ,  $-N(R^a)C(O)OR^f$ ,  $-OC(O)-NR^aR^f$ ,  $-N(R^a)C(O)R^f$ ,  $-N(R^a)S(O)_tR^f$  (where  $t$  is 1 or 2),  $-S(O)_tOR^a$  (where  $t$  is 1 or 2),  $-S(O)_tR^f$  (where  $t$  is 1 or 2) and  $-S(O)_tN(R^a)_2$  (where  $t$  is 1 or 2) where each  $R^a$  is independently hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, and each  $R^f$  is independently alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl.

**[0027]** "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to eighteen carbon atoms. In certain embodiments, an alkynyl comprises three to eighteen carbon atoms. In certain embodiments, an alkynyl comprises three to twelve carbon atoms. In certain embodiments, an alkynyl comprises six to twelve carbon atoms. In certain embodiments, an alkynyl comprises six to ten carbon atoms. In certain embodiments, an alkynyl comprises eight to ten carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to

four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thio, imino, oximo, trimethylsilyl,  $-OR^a$ ,  $-SR^a$ ,  $-OC(O)-R^f$ ,  $-N(R^a)_2$ ,  $-C(O)R^a$ ,  $-C(O)OR^a$ ,  $-C(O)N(R^a)_2$ ,  $-N(R^a)C(O)OR^f$ ,  $-OC(O)-NR^aR^f$ ,  $-N(R^a)C(O)R^f$ ,  $-N(R^a)S(O)_tR^f$  (where  $t$  is 1 or 2),  $-S(O)_tOR^a$  (where  $t$  is 1 or 2),  $-S(O)_tR^f$  (where  $t$  is 1 or 2) and  $-S(O)_tN(R^a)_2$  (where  $t$  is 1 or 2) where each  $R^a$  is independently hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, and each  $R^f$  is independently alkyl, haloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl.

**[0028]** "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from six to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized  $(4n+2)$   $\pi$ -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl,  $-R^b-OR^a$ ,  $-R^b-OC(O)-R^a$ ,  $-R^b-OC(O)-OR^a$ ,  $-R^b-OC(O)-N(R^a)_2$ ,  $-R^b-N(R^a)_2$ ,  $-R^b-C(O)R^a$ ,  $-R^b-C(O)OR^a$ ,  $-R^b-C(O)N(R^a)_2$ ,  $-R^b-O-R^c-C(O)N(R^a)_2$ ,  $-R^b-N(R^a)C(O)OR^a$ ,  $-R^b-N(R^a)C(O)R^a$ ,  $-R^b-N(R^a)S(O)_tR^a$  (where  $t$  is 1 or 2),  $-R^b-S(O)_tOR^a$  (where  $t$  is 1 or 2),  $-R^b-S(O)_tR^a$  (where  $t$  is 1 or 2), and  $-R^b-S(O)_tN(R^a)_2$  (where  $t$  is 1 or 2), where each  $R^a$  is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, each  $R^b$  is independently a direct bond or a straight or branched alkylene or alkenylene chain, and  $R^c$  is a straight or branched alkylene or alkenylene chain.

**[0029]** "Aryloxy" refers to a radical bonded through an oxygen atom of the formula  $-O$ -aryl, where aryl is as defined above.

**[0030]** "Aralkyl" refers to a radical of the formula  $-R^c$ -aryl where  $R^c$  is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the

aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

**[0031]** "Aralkyloxy" refers to a radical bonded through an oxygen atom of the formula  $\text{-O-}$ aralkyl, where aralkyl is as defined above.

**[0032]** "Aralkenyl" refers to a radical of the formula  $\text{-R}^d\text{-aryl}$  where  $\text{R}^d$  is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

**[0033]** "Aralkynyl" refers to a radical of the formula  $\text{-R}^e\text{-aryl}$ , where  $\text{R}^e$  is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

**[0034]** "Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a cycloalkyl comprises three to ten carbon atoms. In other embodiments, a cycloalkyl comprises five to seven carbon atoms. The cycloalkyl is attached to the rest of the molecule by a single bond. Cycloalkyls are saturated, (*i.e.*, containing single C-C bonds only) or partially unsaturated (*i.e.*, containing one or more double bonds or triple bonds.) Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*,  $\text{C}_3\text{-C}_8$  cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*,  $\text{C}_3\text{-C}_7$  cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*,  $\text{C}_3\text{-C}_6$  cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*,  $\text{C}_3\text{-C}_5$  cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*,  $\text{C}_3\text{-C}_4$  cycloalkyl). A partially unsaturated cycloalkyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless stated otherwise specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, oxo, thioxo, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl,  $\text{-R}^b\text{-OR}^a$ ,  $\text{-R}^b\text{-OC(O)-R}^a$ ,  $\text{-R}^b\text{-}$

OC(O)-OR<sup>a</sup>, -R<sup>b</sup>-OC(O)-N(R<sup>a</sup>)<sub>2</sub>, -R<sup>b</sup>-N(R<sup>a</sup>)<sub>2</sub>, -R<sup>b</sup>-C(O)R<sup>a</sup>, -R<sup>b</sup>-C(O)OR<sup>a</sup>, -R<sup>b</sup>-C(O)N(R<sup>a</sup>)<sub>2</sub>, -R<sup>b</sup>-O-R<sup>c</sup>-C(O)N(R<sup>a</sup>)<sub>2</sub>, -R<sup>b</sup>-N(R<sup>a</sup>)C(O)OR<sup>a</sup>, -R<sup>b</sup>-N(R<sup>a</sup>)C(O)R<sup>a</sup>, -R<sup>b</sup>-N(R<sup>a</sup>)S(O)<sub>t</sub>R<sup>a</sup> (where t is 1 or 2), -R<sup>b</sup>-S(O)<sub>t</sub>OR<sup>a</sup> (where t is 1 or 2), -R<sup>b</sup>-S(O)<sub>t</sub>R<sup>a</sup> (where t is 1 or 2), and -R<sup>b</sup>-S(O)<sub>t</sub>N(R<sup>a</sup>)<sub>2</sub> (where t is 1 or 2), where each R<sup>a</sup> is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, each R<sup>b</sup> is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R<sup>c</sup> is a straight or branched alkylene or alkenylene chain.

**[0035]** "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

**[0036]** "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above.

**[0037]** "Haloalkoxy" refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above.

**[0038]** "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical are optionally substituted as defined above for an alkyl group.

**[0039]** "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused, spiro, or bridged ring systems. The heteroatoms in the heterocycloalkyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized.

The heterocycloalkyl radical is partially or fully saturated. In some embodiments, the heterocycloalkyl is attached to the rest of the molecule through any atom of the ring(s).

Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolynyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholynyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholynyl, thiamorpholynyl, 1-oxo-thiomorpholynyl, and 1,1-dioxo-thiomorpholynyl. Unless stated otherwise specifically in the specification, the term "heterocycloalkyl" is meant to include heterocycloalkyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, oxo, thioxo, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl,

heterocycloalkyl, heteroaryl, heteroarylalkyl,  $-R^b-OR^a$ ,  $-R^b-OC(O)-R^a$ ,  $-R^b-OC(O)-OR^a$ ,  $-R^b-OC(O)-N(R^a)_2$ ,  $-R^b-N(R^a)_2$ ,  $-R^b-C(O)R^a$ ,  $-R^b-C(O)OR^a$ ,  $-R^b-C(O)N(R^a)_2$ ,  $-R^b-O-R^c-C(O)N(R^a)_2$ ,  $-R^b-N(R^a)C(O)OR^a$ ,  $-R^b-N(R^a)C(O)R^a$ ,  $-R^b-N(R^a)S(O)_tR^a$  (where  $t$  is 1 or 2),  $-R^b-S(O)_tOR^a$  (where  $t$  is 1 or 2),  $-R^b-S(O)_tR^a$  (where  $t$  is 1 or 2), and  $-R^b-S(O)_tN(R^a)_2$  (where  $t$  is 1 or 2), where each  $R^a$  is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, each  $R^b$  is independently a direct bond or a straight or branched alkylene or alkenylene chain, and  $R^c$  is a straight or branched alkylene or alkenylene chain.

**[0040]** "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises one to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized  $(4n+2)$   $\pi$ -electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, haloalkyl, oxo, thioxo, cyano, nitro, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl,  $-R^b-OR^a$ ,  $-R^b-OC(O)-R^a$ ,  $-R^b-OC(O)-OR^a$ ,  $-R^b-OC(O)-N(R^a)_2$ ,  $-R^b-N(R^a)_2$ ,  $-R^b-C(O)R^a$ ,  $-R^b-C(O)OR^a$ ,  $-R^b-C(O)N(R^a)_2$ ,  $-R^b-O-R^c-C(O)N(R^a)_2$ ,  $-R^b-N(R^a)C(O)OR^a$ ,  $-R^b-N(R^a)C(O)R^a$ ,  $-R^b-N(R^a)S(O)_tR^a$  (where  $t$  is 1 or 2),  $-R^b-S(O)_tOR^a$  (where  $t$  is 1 or 2),  $-R^b-S(O)_tR^a$  (where  $t$  is 1 or 2), and  $-R^b-S(O)_tN(R^a)_2$  (where  $t$  is 1 or 2), where each  $R^a$  is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl, or heteroarylalkyl, each  $R^b$  is independently a direct bond or a straight or branched alkylene or alkenylene chain, and  $R^c$  is a straight or branched alkylene or alkenylene chain.

**[0041]** "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0042] "C-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A C-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0043] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

[0044] "Heteroarylalkyl" refers to a radical of the formula –R<sup>c</sup>-heteroaryl, where R<sup>c</sup> is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

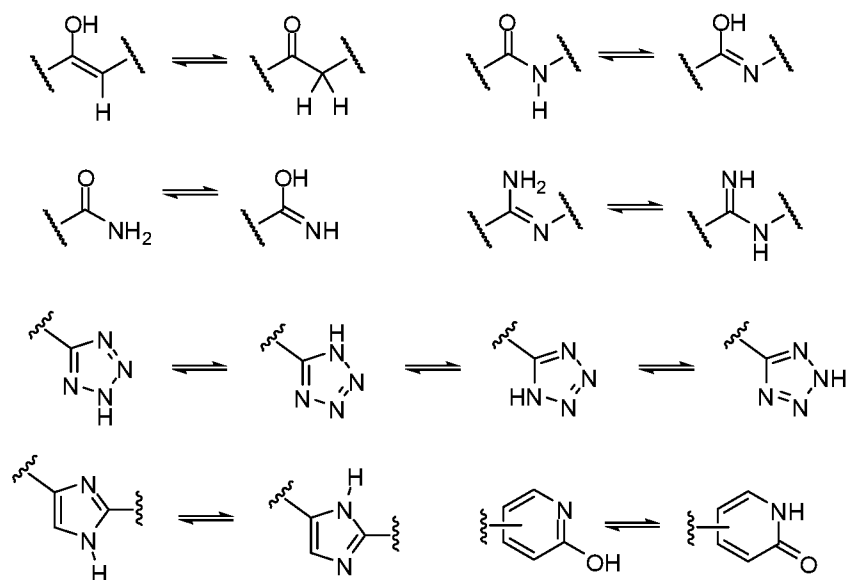
[0045] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R<sup>c</sup>-heteroaryl, where R<sup>c</sup> is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0046] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and *Z* geometric isomers (*e.g.*, *cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or *Z* geometric isomers (*e.g.*, *cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0047] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. In certain embodiments, the compounds presented herein exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers



depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



**[0048]** "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical are or are not substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

**[0049]** "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the pyrazole compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts, and pharmaceutically acceptable base addition salts.

**[0050]** "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites,

bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66:1-19 (1997)). Acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt.

**[0051]** "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

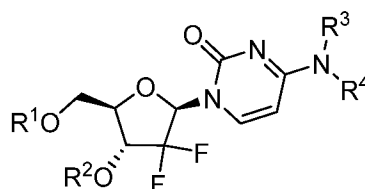
**[0052]** As used herein, "treatment" or "treating" or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are administered to a

patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

### Compounds

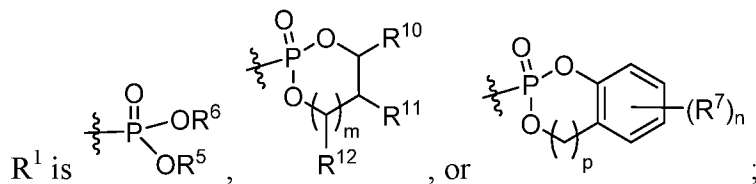
**[0053]** In some embodiments, the compounds of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, and compositions comprising these compounds, are useful for the treatment of cancer. In some embodiments, the compounds of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, and compositions comprising these compounds, are useful for the treatment of an infectious disease.

**[0054]** In some embodiments is a compound of Formula (I):



Formula (I);

wherein:



$R^1$  is  $-P(=O)(OR^5)OR^6$ ,

$R^2$  is  $-C(O)R^8$ ;

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^5$  is H,  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-6}$ alkyl-OC(O) $C_{1-22}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^6$  is  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-6}$ alkyl-OC(O) $C_{1-22}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

each  $R^7$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy;

R<sup>8</sup> is C<sub>3-22</sub>alkyl, C<sub>3-22</sub>alkenyl, C<sub>3-22</sub>alkynyl, C<sub>3-22</sub>haloalkyl, C<sub>3-8</sub>cycloalkyl, C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl, wherein C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl are optionally substituted with 1, 2, 3, or 4 R<sup>14</sup>;

R<sup>9</sup> is C<sub>1-12</sub>alkyl;

R<sup>10</sup> and R<sup>11</sup> are each independently H or C<sub>1-12</sub>alkyl; or R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two R<sup>13</sup>;

R<sup>12</sup> is H or C<sub>1-12</sub>alkyl;

each R<sup>13</sup> is independently selected from C<sub>1-12</sub>alkyl;

each R<sup>14</sup> is independently selected from halogen, C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, C<sub>1-8</sub>alkoxy, and -C(O)R<sup>13</sup>;

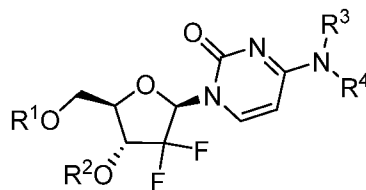
$m$  is 0 or 1;

$n$  is 0, 1, 2, 3, or 4; and

$p$  is 0 or 1;

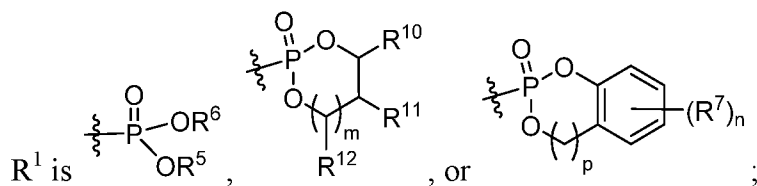
or a pharmaceutically acceptable salt thereof.

**[0055]** In some embodiments is a compound of Formula (I'):



Formula (I');

wherein:


$$R^2 \text{ is } -C(O)R^8;$$

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

 $R^4$  is  $H$ ;

R<sup>5</sup> is H, C<sub>3-18</sub>alkyl, C<sub>3-18</sub>alkenyl, C<sub>3-18</sub>alkynyl, C<sub>3-18</sub>haloalkyl, -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-8</sub>alkyl, C<sub>3-8</sub>cycloalkyl, C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-</sub>

$\text{C}_{2-9}\text{heteroaryl}$ , wherein  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$  are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

$\text{R}^6$  is  $\text{C}_{3-18}\text{alkyl}$ ,  $\text{C}_{3-18}\text{alkenyl}$ ,  $\text{C}_{3-18}\text{alkynyl}$ ,  $\text{C}_{3-18}\text{haloalkyl}$ ,  $-\text{C}_{1-4}\text{alkyl}-\text{OC}(\text{O})\text{C}_{1-8}\text{alkyl}$ ,  $\text{C}_{3-8}\text{cycloalkyl}$ ,  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$ , wherein  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$  are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

each  $\text{R}^7$  is independently selected from halogen,  $\text{C}_{1-8}\text{alkyl}$ ,  $\text{C}_{1-8}\text{haloalkyl}$ , and  $\text{C}_{1-8}\text{alkoxy}$ ;

$\text{R}^8$  is  $\text{C}_{3-18}\text{alkyl}$ ,  $\text{C}_{3-18}\text{alkenyl}$ ,  $\text{C}_{3-18}\text{alkynyl}$ ,  $\text{C}_{3-18}\text{haloalkyl}$ ,  $\text{C}_{3-8}\text{cycloalkyl}$ ,  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$ , wherein  $\text{C}_{6-10}\text{aryl}$ ,  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{6-10}\text{aryl}$ ,  $\text{C}_{2-9}\text{heteroaryl}$ , or  $-\text{C}_{1-8}\text{alkyl}-\text{C}_{2-9}\text{heteroaryl}$  are optionally substituted with 1, 2, 3, or 4  $\text{R}^{14}$ ;

$\text{R}^9$  is  $\text{C}_{1-12}\text{alkyl}$ ;

$\text{R}^{10}$  and  $\text{R}^{11}$  are each independently H or  $\text{C}_{1-12}\text{alkyl}$ ; or  $\text{R}^{10}$  and  $\text{R}^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $\text{R}^{13}$ ;

$\text{R}^{12}$  is H or  $\text{C}_{1-12}\text{alkyl}$ ;

each  $\text{R}^{13}$  is independently selected from  $\text{C}_{1-12}\text{alkyl}$ ;

each  $\text{R}^{14}$  is independently selected from halogen,  $\text{C}_{1-8}\text{alkyl}$ ,  $\text{C}_{1-8}\text{haloalkyl}$ ,  $\text{C}_{1-8}\text{alkoxy}$ , and  $-\text{C}(\text{O})\text{R}^{13}$ ;

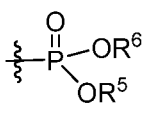
m is 0 or 1;

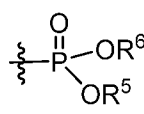
n is 0, 1, 2, 3, or 4; and

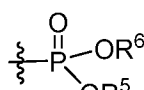
p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

[0056] In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein  $\text{R}^1$  is . In another embodiment is a compound of

Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $\text{R}^1$  is ,  $\text{R}^5$  is  $\text{C}_{3-18}\text{alkyl}$ , and  $\text{R}^6$  is  $\text{C}_{3-18}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or

(I'), or a pharmaceutically acceptable salt thereof, wherein  $\text{R}^1$  is ,  $\text{R}^5$  is  $\text{C}_{3-16}\text{alkyl}$ , and  $\text{R}^6$  is  $\text{C}_{3-16}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{3-15}$ alkyl, and  $R^6$  is  $C_{3-15}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{3-12}$ alkyl, and  $R^6$  is  $C_{3-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{6-15}$ alkyl, and  $R^6$  is  $C_{6-15}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{6-14}$ alkyl, and  $R^6$  is  $C_{6-14}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{6-12}$ alkyl, and  $R^6$  is  $C_{6-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

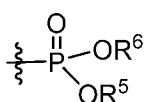
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{6-10}$ alkyl, and  $R^6$  is  $C_{6-10}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

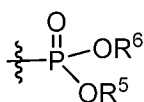
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{3-18}$ alkenyl, and  $R^6$  is  $C_{3-18}$ alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a

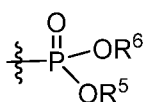
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{3-15}$ alkenyl, and  $R^6$  is  $C_{3-15}$ alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a

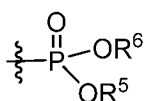
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{6-15}$ alkenyl, and  $R^6$  is  $C_{6-15}$ alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a

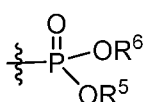
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{OR}^5 \end{array}$ ,  $R^5$  is  $C_{6-12}$ alkenyl, and  $R^6$  is  $C_{6-12}$ alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a

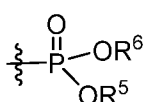
pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>6-10</sub>alkenyl, and R<sup>6</sup> is C<sub>6-10</sub>alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a

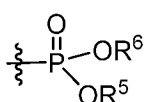
pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>3-18</sub>alkynyl, and R<sup>6</sup> is C<sub>3-18</sub>alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a

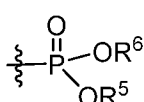
pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>3-15</sub>alkynyl, and R<sup>6</sup> is C<sub>3-15</sub>alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a

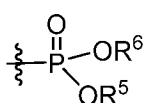
pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>6-15</sub>alkynyl, and R<sup>6</sup> is C<sub>6-15</sub>alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a

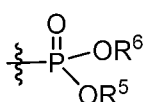
pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>6-12</sub>alkynyl, and R<sup>6</sup> is C<sub>6-12</sub>alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>6-10</sub>alkynyl, and R<sup>6</sup> is C<sub>6-10</sub>alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>3-18</sub>haloalkyl, and R<sup>6</sup> is C<sub>3-18</sub>haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>3-15</sub>haloalkyl, and R<sup>6</sup> is C<sub>3-15</sub>haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>6-15</sub>haloalkyl, and R<sup>6</sup> is C<sub>6-15</sub>haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>6-12</sub>haloalkyl, and R<sup>6</sup> is C<sub>6-12</sub>haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $C_{6-10}$ haloalkyl, and  $R^6$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-6}$ alkyl- $OC(O)C_{1-22}$ alkyl, and  $R^6$  is  $-C_{1-6}$ alkyl- $OC(O)C_{1-22}$ alkyl. In another embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is

$\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-16}$ alkyl, and  $R^6$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-16}$ alkyl. In another embodiment is a compound of Formula (I), or a pharmaceutically acceptable salt

thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-12}$ alkyl, and  $R^6$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl, and  $R^6$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl. In another embodiment is a compound

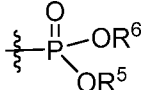
of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-2}$ alkyl- $OC(O)C_{1-8}$ alkyl, and  $R^6$  is  $-C_{1-2}$ alkyl- $OC(O)C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

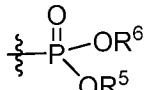
thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-CH_2OC(O)C_{1-8}$ alkyl, and  $R^6$  is  $-CH_2OC(O)C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

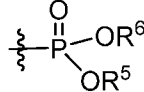
acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-6}$ alkyl, and  $R^6$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-6}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

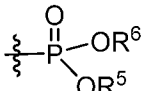
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-2}$ alkyl- $OC(O)C_{1-6}$ alkyl, and  $R^6$  is  $-C_{1-2}$ alkyl- $OC(O)C_{1-6}$ alkyl. In another embodiment is a compound

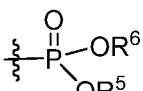


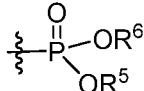
of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is -CH<sub>2</sub>OC(O)C<sub>1-6</sub>alkyl, and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C<sub>1-6</sub>alkyl. In another embodiment is a

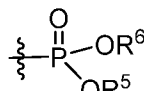
compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl, and R<sup>6</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

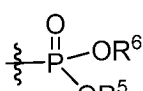
thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl, and R<sup>6</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

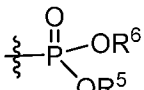
pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is -CH<sub>2</sub>OC(O)C<sub>1-4</sub>alkyl, and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula

(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>, and R<sup>6</sup> is -C<sub>1-4</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is

, R<sup>5</sup> is -C<sub>1-2</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>, and R<sup>6</sup> is -C<sub>1-2</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is -CH<sub>2</sub>OC(O)C(CH<sub>3</sub>)<sub>3</sub>, and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>3-8</sub>cycloalkyl, and R<sup>6</sup> is C<sub>3-8</sub>cycloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is , R<sup>5</sup> is C<sub>3-6</sub>cycloalkyl, and R<sup>6</sup> is C<sub>3-6</sub>cycloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is unsubstituted  $C_{6-10}$ aryl, and  $R^6$  is unsubstituted  $C_{6-10}$ aryl. In another embodiment is a compound of Formula

(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ , and  $R^6$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is unsubstituted phenyl, and  $R^6$  is unsubstituted phenyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is phenyl substituted with 1 or 2  $R^{14}$ , and  $R^6$  is phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of

Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is unsubstituted  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl, and  $R^6$  is unsubstituted  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable

salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ , and  $R^6$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is

$\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is unsubstituted  $-\text{CH}_2$ -phenyl, and  $R^6$  is unsubstituted  $-\text{CH}_2$ -phenyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable

salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is  $-\text{CH}_2$ -phenyl substituted with 1 or 2  $R^{14}$ , and  $R^6$  is  $-\text{CH}_2$ -phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of

Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is unsubstituted  $C_{2-9}$ heteroaryl, and  $R^6$  is unsubstituted  $C_{2-9}$ heteroaryl. In another

embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>. In another embodiment is a compound of Formula

(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl, and R<sup>6</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable

salt thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>.

**[0057]** In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is H, and R<sup>6</sup> is C<sub>3-18</sub>alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is H, and R<sup>6</sup> is C<sub>6-15</sub>alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is

$\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is H, and R<sup>6</sup> is C<sub>6-10</sub>alkyl. In another embodiment is a compound of Formula

(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is H, and R<sup>6</sup> is C<sub>3-18</sub>alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is H, and R<sup>6</sup> is C<sub>6-15</sub>alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein R<sup>1</sup> is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ , R<sup>5</sup> is H, and R<sup>6</sup> is C<sub>6-10</sub>alkenyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt

thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $C_{3-18}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$

is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $C_{6-15}$ alkynyl. In another embodiment is a compound of

Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $C_{6-10}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'),

or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $C_{3-18}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $C_{6-15}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

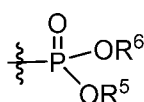
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a

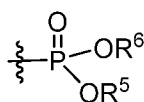
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

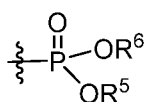
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

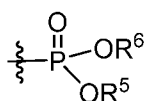
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $-\text{CH}_2\text{OC(O)}C_{1-8}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

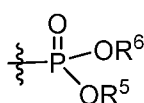
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\begin{array}{c} \text{O} \\ \parallel \\ \text{---P---} \\ \diagup \quad \diagdown \\ \text{OR}^5 \quad \text{OR}^6 \end{array}$ ,  $R^5$  is H, and  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $R^5$  is H, and  $R^6$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

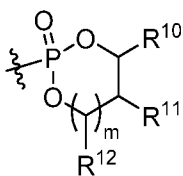
pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $R^5$  is H, and  $R^6$  is  $-CH_2OC(O)C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

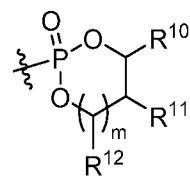
pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $R^5$  is H, and  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C(CH_3)_3$ . In another embodiment is a compound of Formula (I) or (I'), or a

pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $R^5$  is H, and  $R^6$  is  $-C_{1-2}$ alkyl-OC(O) $C(CH_3)_3$ . In another embodiment is a compound of Formula (I) or (I'), or a

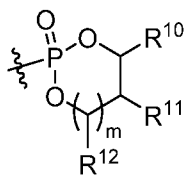
pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $R^5$  is H, and  $R^6$  is  $-CH_2OC(O)C(CH_3)_3$ .

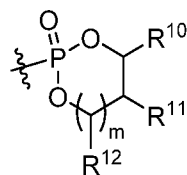
**[0058]** In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

acceptable salt thereof, wherein  $R^1$  is . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is

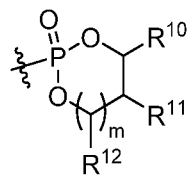


and  $m$  is 1. In another embodiment is a compound of Formula (I) or (I'), or a

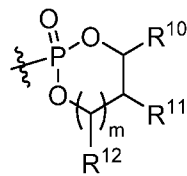
pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $m$  is 1, and  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula (I) or (I'), or a



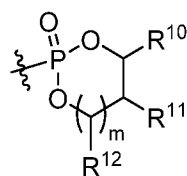
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1, and  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a



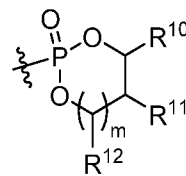
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1, and  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a



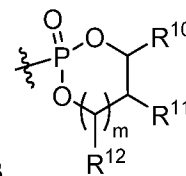
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1, and  $R^{10}$ ,  $R^{11}$  and  $R^{12}$  are each  $-CH_3$ . In another embodiment is a compound of Formula (I) or (I'), or a



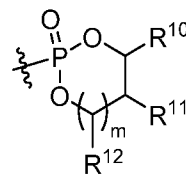
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1,  $R^{10}$  is  $C_{1-12}$ alkyl, and  $R^{11}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula (I) or



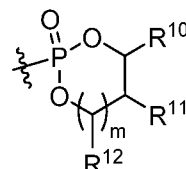
(I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1,  $R^{10}$  is  $C_{1-4}$ alkyl, and  $R^{11}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula (I)



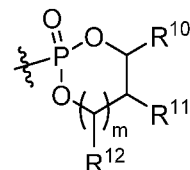
or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1,  $R^{10}$  is  $-CH_3$ , and  $R^{11}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula (I) or



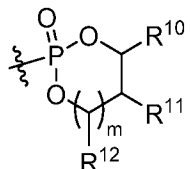
(I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1,  $R^{11}$  is  $C_{1-12}$ alkyl, and  $R^{10}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula (I)



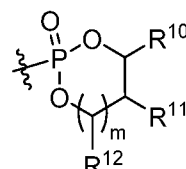
or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\text{C}_{1-4}\text{alkyl}$ , and  $R^{10}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula



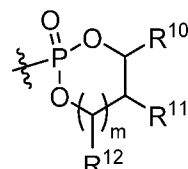
(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_3$ , and  $R^{10}$  and  $R^{12}$  are each H. In another embodiment is a compound of Formula (I) or



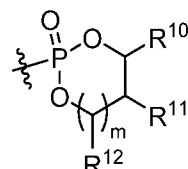
(I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\text{C}_{1-12}\text{alkyl}$ ,  $R^{10}$  is H, and  $R^{11}$  and  $R^{12}$  are each  $\text{C}_{1-12}\text{alkyl}$ . In another embodiment is a compound of Formula (I)



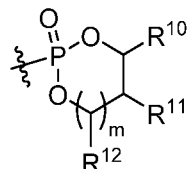
or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is H, and  $R^{11}$  and  $R^{12}$  are each  $\text{C}_{1-4}\text{alkyl}$ . In another embodiment is a compound of Formula



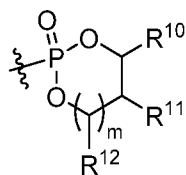
(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\text{C}_{1-4}\text{alkyl}$ ,  $R^{10}$  is H, and  $R^{11}$  and  $R^{12}$  are each  $-\text{CH}_3$ . In another embodiment is a compound of Formula



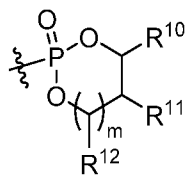
(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is H, and  $R^{10}$  and  $R^{12}$  are each  $\text{C}_{1-12}\text{alkyl}$ . In another embodiment is a compound of



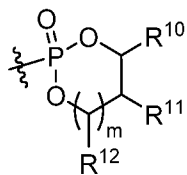
Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\text{C}_{1-4}\text{alkyl}$ ,  $R^{11}$  is H, and  $R^{10}$  and  $R^{12}$  are each  $\text{C}_{1-4}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is



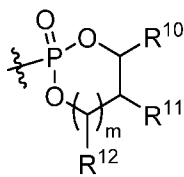
, m is 1, R<sup>11</sup> is H, and R<sup>10</sup> and R<sup>12</sup> are each -CH<sub>3</sub>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is



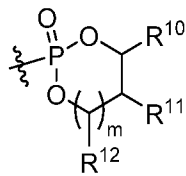
, m is 1, R<sup>12</sup> is H, and R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two R<sup>13</sup>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable



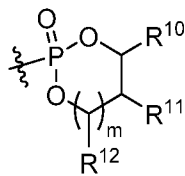
salt thereof, wherein R<sup>1</sup> is , m is 1, R<sup>12</sup> is H, and R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered cycloalkyl ring optionally substituted with one or two R<sup>13</sup>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein



R<sup>1</sup> is , m is 1, R<sup>12</sup> is H, and R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered heterocycloalkyl ring optionally substituted with one or two R<sup>13</sup>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein R<sup>1</sup> is



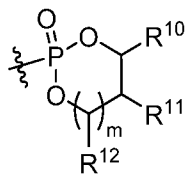
, m is 1, R<sup>12</sup> is C<sub>1-12</sub>alkyl, and R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two R<sup>13</sup>. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically



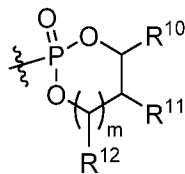
acceptable salt thereof, wherein R<sup>1</sup> is , m is 1, R<sup>12</sup> is C<sub>1-12</sub>alkyl, and R<sup>10</sup> and R<sup>11</sup>



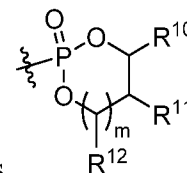
form a 5- or 6-membered cycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable



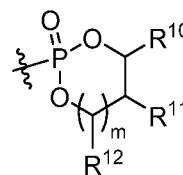
salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 1,  $R^{12}$  is  $C_{1-12}$ alkyl, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered heterocycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



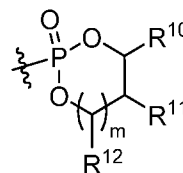
thereof, wherein  $R^1$  is  $R^{12}$  and  $m$  is 0. In another embodiment is a compound of



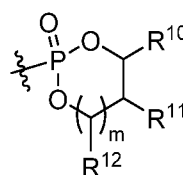
Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  are each H. In another embodiment is a compound of Formula (I) or



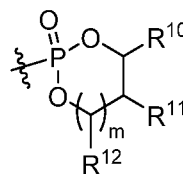
(I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  are each  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a



pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  are each  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a

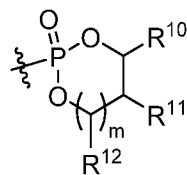


pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  are each  $-CH_3$ . In another embodiment is a compound of Formula (I) or (I'), or a

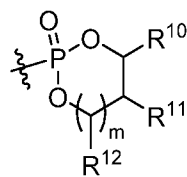


pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $R^{12}$ ,  $m$  is 0,  $R^{10}$  is H, and

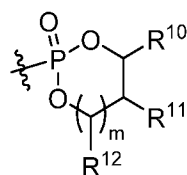
$R^{11}$  is  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a



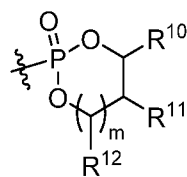
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-4}$ alkyl,  $m$  is 0,  $R^{10}$  is H, and  $R^{11}$  is  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a



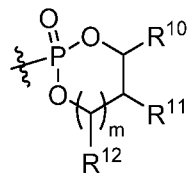
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-4}$ alkyl,  $m$  is 0,  $R^{10}$  is H, and  $R^{11}$  is  $-CH_3$ . In another embodiment is a compound of Formula (I) or (I'), or a



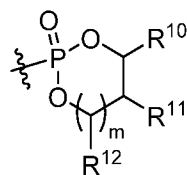
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-12}$ alkyl,  $m$  is 0,  $R^{10}$  is  $C_{1-12}$ alkyl, and  $R^{11}$  is H. In another embodiment is a compound of Formula (I) or (I'), or a



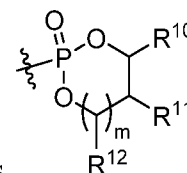
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-4}$ alkyl,  $m$  is 0,  $R^{10}$  is  $C_{1-4}$ alkyl, and  $R^{11}$  is H. In another embodiment is a compound of Formula (I) or (I'), or a

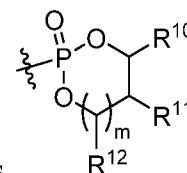


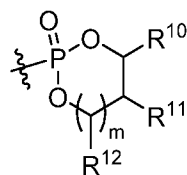
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-4}$ alkyl,  $m$  is 0,  $R^{10}$  is  $-CH_3$ , and  $R^{11}$  is H. In another embodiment is a compound of Formula (I) or (I'), or a

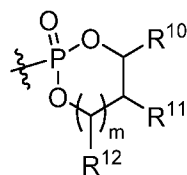


pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-4}$ alkyl,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of

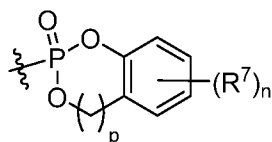


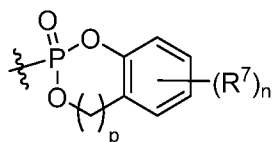
Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (I) or (I'), or a

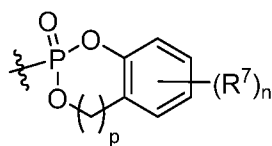


pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $m$  is 0, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered heterocycloalkyl ring optionally substituted with one or two  $R^{13}$ .

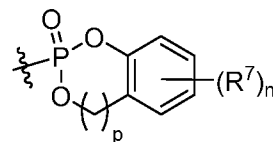
**[0059]** In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically

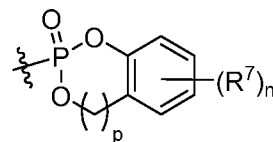


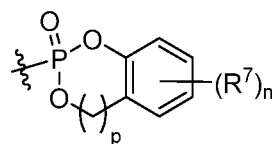
acceptable salt thereof, wherein  $R^1$  is . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is

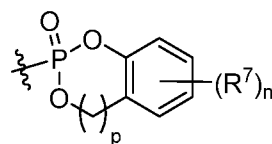


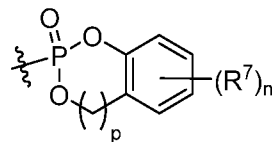
and  $p$  is 1. In another embodiment is a compound of Formula (I) or

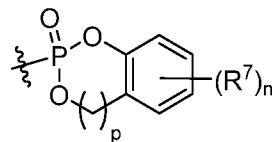


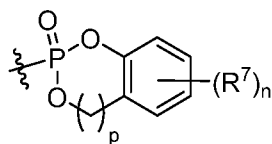
(I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $p$  is 1, and  $n$  is 0. In another embodiment is a compound of Formula (I) or (I'), or a



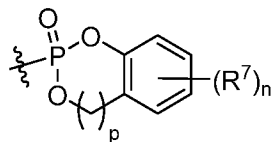
pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $p$  is 1, and  $n$  is 1, 2, 3, or 4. In another embodiment is a compound of Formula (I) or (I'), or a



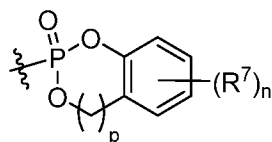
pharmaceutically acceptable salt thereof, wherein  $R^1$  is ,  $p$  is 1, and  $n$  is 1 or 2. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically



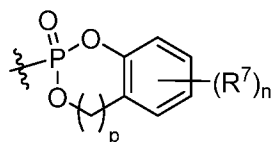
acceptable salt thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkyl,  $p$  is 1, and  $n$  is 1. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



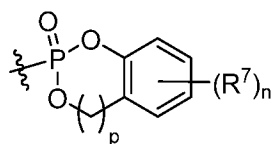
thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkoxy,  $p$  is 1,  $n$  is 1, and  $R^7$  is halogen. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



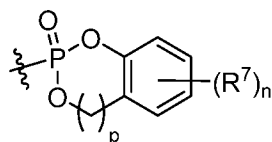
thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkoxy,  $p$  is 1,  $n$  is 1, and  $R^7$  is  $\text{C}_1\text{-}_8$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



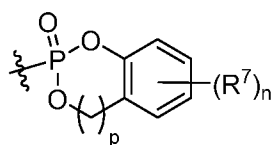
thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkoxy,  $p$  is 1,  $n$  is 1, and  $R^7$  is  $\text{C}_1\text{-}_8$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



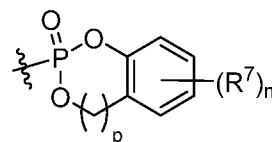
thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkoxy,  $p$  is 1,  $n$  is 1, and  $R^7$  is  $\text{C}_1\text{-}_8$ alkoxy. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



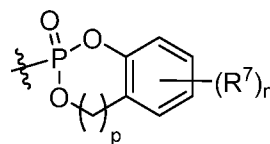
thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkoxy and  $p$  is 0. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is



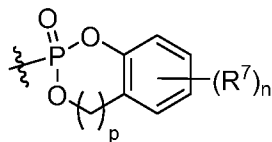
$\text{C}_1\text{-}_8$ alkoxy,  $p$  is 0, and  $n$  is 0. In another embodiment is a compound of Formula



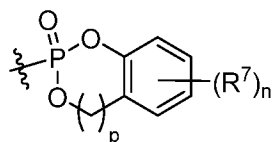
(I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\text{C}_1\text{-}_8$ alkoxy,  $p$  is 0, and  $n$  is 1, 2, 3, or 4. In another embodiment is a compound of Formula (I) or (I'), or a



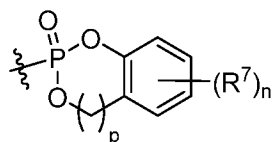
pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $p$  is 0, and  $n$  is 1 or 2. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically



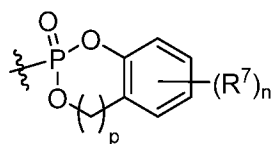
acceptable salt thereof, wherein  $R^1$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $p$  is 0, and  $n$  is 1. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



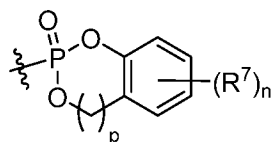
thereof, wherein  $R^1$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $p$  is 0,  $n$  is 1, and  $R^7$  is halogen. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



thereof, wherein  $R^1$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $p$  is 0,  $n$  is 1, and  $R^7$  is  $\text{C}_{1-8}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



thereof, wherein  $R^1$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $p$  is 0,  $n$  is 1, and  $R^7$  is  $\text{C}_{1-8}\text{haloalkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt



thereof, wherein  $R^1$  is  $\text{C}_{1-6}\text{alkyl}$ ,  $p$  is 0,  $n$  is 1, and  $R^7$  is  $\text{C}_{1-8}\text{alkoxy}$ .

**[0060]** In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $\text{C}_{3-18}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $\text{C}_{3-15}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $\text{C}_{3-12}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $\text{C}_{6-18}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $\text{C}_{6-12}\text{alkyl}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $\text{C}_{6-10}\text{alkyl}$ . In another

[illegible]

thereof, wherein  $R^8$  is  $C_{3-18}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ alkynyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-18}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ haloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-8}$ cycloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-6}$ cycloalkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{6-10}$ aryl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted phenyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a

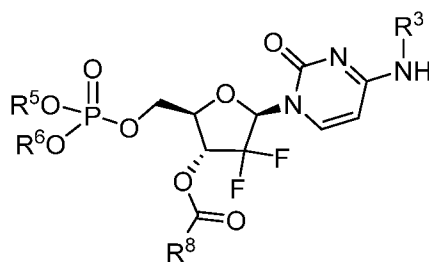
pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ -phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2$ -phenyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ -phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{2-9}$ heteroaryl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}$ heteroaryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-C_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2-C_{2-9}$ heteroaryl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-C_{2-9}$ heteroaryl substituted with 1 or 2  $R^{14}$ .

**[0061]** In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-10}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_2CH_3$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-10}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-4}$ alkyl. In another embodiment



is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (I) or (I'), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_2CH_3$ .

**[0062]** In some embodiments is a compound of Formula (I') having the structure of Formula (Ia):



Formula (Ia);

wherein:

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^5$  is H,  $C_{3-18}$ alkyl,  $C_{3-18}$ alkenyl,  $C_{3-18}$ alkynyl,  $C_{3-18}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^6$  is  $C_{3-18}$ alkyl,  $C_{3-18}$ alkenyl,  $C_{3-18}$ alkynyl,  $C_{3-18}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^8$  is  $C_{3-18}$ alkyl,  $C_{3-18}$ alkenyl,  $C_{3-18}$ alkynyl,  $C_{3-18}$ haloalkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^9$  is  $C_{1-12}$ alkyl;

each  $R^{13}$  is independently selected from  $C_{1-12}$ alkyl; and

each  $R^{14}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ ;

or a pharmaceutically acceptable salt thereof.

**[0063]** In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $C_{3-18}$ alkyl and  $R^6$  is  $C_{3-18}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is

C<sub>3-15</sub>alkyl and R<sup>6</sup> is C<sub>3-15</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-15</sub>alkyl and R<sup>6</sup> is C<sub>6-15</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-12</sub>alkyl and R<sup>6</sup> is C<sub>6-12</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-10</sub>alkyl and R<sup>6</sup> is C<sub>6-10</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-18</sub>alkenyl and R<sup>6</sup> is C<sub>3-18</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-15</sub>alkenyl and R<sup>6</sup> is C<sub>3-15</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-15</sub>alkenyl and R<sup>6</sup> is C<sub>6-15</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-12</sub>alkenyl and R<sup>6</sup> is C<sub>6-12</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-10</sub>alkenyl and R<sup>6</sup> is C<sub>6-10</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-18</sub>alkynyl and R<sup>6</sup> is C<sub>3-18</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-15</sub>alkynyl and R<sup>6</sup> is C<sub>3-15</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-15</sub>alkynyl and R<sup>6</sup> is C<sub>6-15</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-12</sub>alkynyl and R<sup>6</sup> is C<sub>6-12</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-10</sub>alkynyl and R<sup>6</sup> is C<sub>6-10</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-18</sub>haloalkyl and R<sup>6</sup> is C<sub>3-18</sub>haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-15</sub>haloalkyl and R<sup>6</sup> is C<sub>3-15</sub>haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-15</sub>haloalkyl and R<sup>6</sup> is C<sub>6-15</sub>haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-12</sub>haloalkyl and R<sup>6</sup> is C<sub>6-12</sub>haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-10</sub>haloalkyl and R<sup>6</sup> is C<sub>6-10</sub>haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-8</sub>alkyl and R<sup>6</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-2</sub>alkyl-

OC(O)C<sub>1-8</sub>alkyl and R<sup>6</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -CH<sub>2</sub>OC(O)C<sub>1-8</sub>alkyl and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-6</sub>alkyl and R<sup>6</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-6</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-6</sub>alkyl and R<sup>6</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-6</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -CH<sub>2</sub>OC(O)C<sub>1-6</sub>alkyl and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C<sub>1-6</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl and R<sup>6</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl and R<sup>6</sup> is -C<sub>1-2</sub>alkyl-OC(O)C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -CH<sub>2</sub>OC(O)C<sub>1-4</sub>alkyl and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub> and R<sup>6</sup> is -C<sub>1-4</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-2</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub> and R<sup>6</sup> is -C<sub>1-2</sub>alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -CH<sub>2</sub>OC(O)C(CH<sub>3</sub>)<sub>3</sub>, and R<sup>6</sup> is -CH<sub>2</sub>OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-8</sub>cycloalkyl and R<sup>6</sup> is C<sub>3-8</sub>cycloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-6</sub>cycloalkyl and R<sup>6</sup> is C<sub>3-6</sub>cycloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is unsubstituted C<sub>6-10</sub>aryl and R<sup>6</sup> is unsubstituted C<sub>6-10</sub>aryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-10</sub>aryl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is C<sub>6-10</sub>aryl substituted with 1 or 2 R<sup>14</sup>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is unsubstituted phenyl, and R<sup>6</sup> is unsubstituted phenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is phenyl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is phenyl substituted with 1 or 2 R<sup>14</sup>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, and R<sup>6</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>6-</sub>

<sub>10</sub>aryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 or 2 R<sup>14</sup>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is unsubstituted -CH<sub>2</sub>-phenyl, and R<sup>6</sup> is unsubstituted -CH<sub>2</sub>-phenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -CH<sub>2</sub>-phenyl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is -CH<sub>2</sub>-phenyl substituted with 1 or 2 R<sup>14</sup>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is unsubstituted C<sub>2-9</sub>heteroaryl, and R<sup>6</sup> is unsubstituted C<sub>2-9</sub>heteroaryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl, and R<sup>6</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>, and R<sup>6</sup> is -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl substituted with 1 or 2 R<sup>14</sup>.

**[0064]** In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>3-18</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>6-15</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>6-10</sub>alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>3-18</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>6-15</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>6-10</sub>alkenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>3-18</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>6-15</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>6-10</sub>alkynyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is H and R<sup>6</sup> is C<sub>3-18</sub>haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof,

wherein  $R^5$  is H and  $R^6$  is  $C_{6-15}$ haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-CH_2OC(O)C_{1-8}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-CH_2OC(O)C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-C_{1-4}$ alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-C_{1-2}$ alkyl-OC(O)C(CH<sub>3</sub>)<sub>3</sub>. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H and  $R^6$  is  $-CH_2OC(O)C(CH_3)_3$ .

**[0065]** In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-18}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ alkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_2CH_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_3CH_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_4CH_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_5CH_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_6CH_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_7CH_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is -

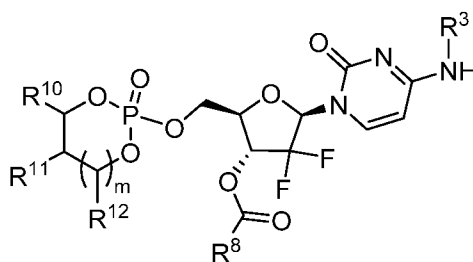
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pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ haloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-8}$ cycloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-6}$ cycloalkyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{6-10}$ aryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted phenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ -phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2$ -phenyl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ -phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{2-9}$ heteroaryl. In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}$ heteroaryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ - $C_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2$ - $C_{2-9}$ heteroaryl. In

another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-\text{CH}_2-\text{C}_{2-9}\text{heteroaryl}$  substituted with 1 or 2  $R^{14}$ .

**[0066]** In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H,  $-\text{C}(\text{O})\text{R}^9$ , or  $-\text{C}(\text{O})\text{OR}^9$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{R}^9$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{R}^9$  and  $\text{R}^9$  is  $\text{C}_{1-10}\text{alkyl}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{R}^9$  and  $\text{R}^9$  is  $\text{C}_{1-6}\text{alkyl}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{R}^9$  and  $\text{R}^9$  is  $\text{C}_{1-4}\text{alkyl}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{R}^9$  and  $\text{R}^9$  is  $-\text{CH}_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{R}^9$  and  $\text{R}^9$  is  $-\text{CH}_2\text{CH}_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{OR}^9$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{OR}^9$  and  $\text{R}^9$  is  $\text{C}_{1-10}\text{alkyl}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{OR}^9$  and  $\text{R}^9$  is  $\text{C}_{1-6}\text{alkyl}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{OR}^9$  and  $\text{R}^9$  is  $\text{C}_{1-4}\text{alkyl}$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{OR}^9$  and  $\text{R}^9$  is  $-\text{CH}_3$ . In another embodiment is a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-\text{C}(\text{O})\text{OR}^9$  and  $\text{R}^9$  is  $-\text{CH}_2\text{CH}_3$ .

**[0067]** In some embodiments is a compound of Formula (I') having the structure of Formula (Ib):



Formula (Ib);

wherein:

$R^3$  is H,  $-\text{C}(\text{O})\text{R}^9$ , or  $-\text{C}(\text{O})\text{OR}^9$ ;



R<sup>8</sup> is C<sub>3-18</sub>alkyl, C<sub>3-18</sub>alkenyl, C<sub>3-18</sub>alkynyl, C<sub>3-18</sub>haloalkyl, C<sub>3-8</sub>cycloalkyl, C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl, wherein C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl are optionally substituted with 1, 2, 3, or 4 R<sup>14</sup>;

R<sup>9</sup> is C<sub>1-12</sub>alkyl;

R<sup>10</sup> and R<sup>11</sup> are each independently H or C<sub>1-12</sub>alkyl; or R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two R<sup>13</sup>;

R<sup>12</sup> is H or C<sub>1-12</sub>alkyl;

each R<sup>13</sup> is independently selected from C<sub>1-12</sub>alkyl;

each R<sup>14</sup> is independently selected from halogen, C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, C<sub>1-8</sub>alkoxy, and -C(O)R<sup>13</sup>; and

m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

**[0068]** In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1 and R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1 and R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each C<sub>1-12</sub>alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1 and R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each C<sub>1-4</sub>alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1 and R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are each -CH<sub>3</sub>. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1, R<sup>10</sup> is C<sub>1-12</sub>alkyl, and R<sup>11</sup> and R<sup>12</sup> are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1, R<sup>10</sup> is C<sub>1-4</sub>alkyl, and R<sup>11</sup> and R<sup>12</sup> are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1, R<sup>10</sup> is -CH<sub>3</sub>, and R<sup>11</sup> and R<sup>12</sup> are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1, R<sup>11</sup> is C<sub>1-12</sub>alkyl, and R<sup>10</sup> and R<sup>12</sup> are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1, R<sup>11</sup> is C<sub>1-4</sub>alkyl, and R<sup>10</sup> and R<sup>12</sup> are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein m is 1, R<sup>11</sup> is -CH<sub>3</sub>, and R<sup>10</sup> and R<sup>12</sup> are

each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{10}$  is H, and  $R^{11}$  and  $R^{12}$  are each  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{10}$  is H, and  $R^{11}$  and  $R^{12}$  are each  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{10}$  is H, and  $R^{11}$  and  $R^{12}$  are each  $-CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{11}$  is H, and  $R^{10}$  and  $R^{12}$  are each  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{11}$  is H, and  $R^{10}$  and  $R^{12}$  are each  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{11}$  is H, and  $R^{10}$  and  $R^{12}$  are each  $-CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{12}$  is H, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{12}$  is H, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{12}$  is H, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered heterocycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{12}$  is  $C_{1-12}$ alkyl, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1,  $R^{12}$  is  $C_{1-12}$ alkyl, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered heterocycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0 and  $R^{10}$  and  $R^{11}$  are each H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0 and  $R^{10}$  and  $R^{11}$  are each  $C_{1-12}$ alkyl.

In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0 and  $R^{10}$  and  $R^{11}$  are each  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0 and  $R^{10}$  and  $R^{11}$  are each  $-CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0,  $R^{10}$  is H, and  $R^{11}$  is  $C_{1-12}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0,  $R^{10}$  is H, and  $R^{11}$  is  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0,  $R^{10}$  is H, and  $R^{11}$  is  $-CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0,  $R^{10}$  is  $C_{1-12}$ alkyl, and  $R^{11}$  is H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0,  $R^{10}$  is  $C_{1-4}$ alkyl, and  $R^{11}$  is H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0,  $R^{10}$  is  $-CH_3$ , and  $R^{11}$  is H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring optionally substituted with one or two  $R^{13}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0, and  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered heterocycloalkyl ring optionally substituted with one or two  $R^{13}$ .

**[0069]** In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-18}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_2CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_3CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_4CH_3$ . In another embodiment is a compound of Formula (Ib),

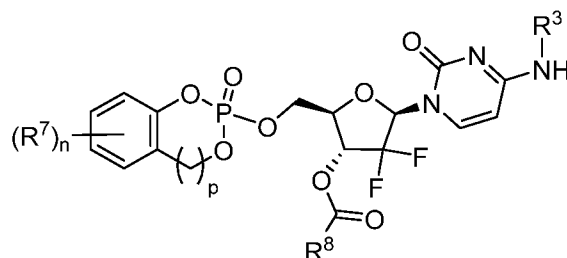
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embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ haloalkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ haloalkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ haloalkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-8}$ cycloalkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-6}$ cycloalkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{6-10}$ aryl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted phenyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ -phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2$ -phenyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2$ -phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{2-9}$ heteroaryl. In another embodiment is a compound of

Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}$ heteroaryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-C_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2-C_{2-9}$ heteroaryl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-C_{2-9}$ heteroaryl substituted with 1 or 2  $R^{14}$ .

**[0070]** In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-10}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_2CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-10}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_2CH_3$ .

**[0071]** In some embodiments is a compound of Formula (I') having the structure of Formula (Ic):



Formula (Ic);

wherein:

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

each  $R^7$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy;

$R^8$  is  $C_{3-18}$ alkyl,  $C_{3-18}$ alkenyl,  $C_{3-18}$ alkynyl,  $C_{3-18}$ haloalkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^9$  is  $C_{1-12}$ alkyl;

each  $R^{13}$  is independently selected from  $C_{1-12}$ alkyl;

each  $R^{14}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ ;

$n$  is 0, 1, 2, 3, or 4; and

$p$  is 0 or 1;

or a pharmaceutically acceptable salt thereof.

**[0072]** In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1 and  $n$  is 0. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1 and  $n$  is 1, 2, 3, or 4. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1,  $n$  is 1, 2, 3, or 4, and each  $R^7$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1 and  $n$  is 1 or 2. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1,  $n$  is 1 or 2, and each  $R^7$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1,  $n$  is 2. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof,

wherein p is 1, n is 2, and each R<sup>7</sup> is independently selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 1 and n is 1. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 1, n is 1, and R<sup>7</sup> is selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 1, n is 1, and R<sup>7</sup> is halogen. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 1, n is 1, and R<sup>7</sup> is C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 1, n is 1, and R<sup>7</sup> is C<sub>1-8</sub>haloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 1, n is 1, and R<sup>7</sup> is C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0 and n is 0. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0 and n is 1, 2, 3, or 4. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1, 2, 3, or 4, and each R<sup>7</sup> is independently selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0 and n is 1 or 2. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1 or 2, and each R<sup>7</sup> is independently selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 2. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 2, and each R<sup>7</sup> is independently selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0 and n is 1. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1, and R<sup>7</sup> is selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1, and R<sup>7</sup> is halogen. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1, and R<sup>7</sup> is C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1, and R<sup>7</sup> is C<sub>1-8</sub>haloalkyl. In another embodiment is a compound



of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein p is 0, n is 1, and R<sup>7</sup> is C<sub>1-8</sub>alkoxy.

**[0073]** In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is C<sub>3-18</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is C<sub>3-12</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is C<sub>6-12</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is C<sub>6-10</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is C<sub>8-10</sub>alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>6</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>13</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>14</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>15</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>16</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is -(CH<sub>2</sub>)<sub>17</sub>CH<sub>3</sub>. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein R<sup>8</sup> is C<sub>3-18</sub>alkenyl. In another embodiment is a compound of Formula (Ic),

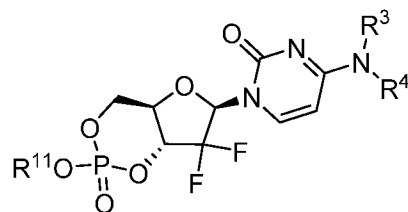
or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ alkenyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkenyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ alkenyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ alkenyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-18}$ alkynyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ alkynyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkynyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ alkynyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ alkynyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-18}$ haloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-12}$ haloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ haloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{8-10}$ haloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-8}$ cycloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-6}$ cycloalkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{6-10}$ aryl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted phenyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is phenyl substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable

salt thereof, wherein  $R^8$  is  $-C_{1-8}alkyl-C_{6-10}aryl$  optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-C_{1-8}alkyl-C_{6-10}aryl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-C_{1-8}alkyl-C_{6-10}aryl$  substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-phenyl$  optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2-phenyl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-phenyl$  substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}heteroaryl$  optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $C_{2-9}heteroaryl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-C_{2-9}heteroaryl$  optionally substituted with 1, 2, 3, or 4  $R^{14}$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is unsubstituted  $-CH_2-C_{2-9}heteroaryl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-CH_2-C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{14}$ .

**[0074]** In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-10}alkyl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-6}alkyl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-4}alkyl$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_2CH_3$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$ . In another embodiment is a compound of Formula (Ic), or

a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-10}$ alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_2CH_3$ .

**[0075]** In another embodiment is a compound of Formula (II):



Formula (II);

wherein:

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^9$  is  $C_{1-8}$ alkyl;

$R^{11}$  is  $C_{3-18}$ alkyl,  $C_{3-18}$ alkenyl,  $C_{3-18}$ alkynyl,  $C_{3-18}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{12}$ ;

each  $R^{12}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ ; and

each  $R^{13}$  is independently selected from  $C_{1-12}$ alkyl;

or a pharmaceutically acceptable salt thereof.

**[0076]** In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{3-18}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{3-12}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-12}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is

[illegible]

pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-12}$ alkynyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ alkynyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{8-10}$ alkynyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{3-18}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{3-12}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-12}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{8-10}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2OC(O)C_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-6}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2OC(O)C_{1-6}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-4}$ alkyl-OC(O) $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-2}$ alkyl-OC(O) $C_{1-4}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2OC(O)C_{1-4}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-4}$ alkyl-OC(O) $C(CH_3)_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-2}$ alkyl-OC(O) $C(CH_3)_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2OC(O)C(CH_3)_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is unsubstituted  $C_{6-10}$ aryl. In another

embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}$ alkyl and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is halogen. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is -F. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is -Cl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-CH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically

acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-CF_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-OCH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}$ aryl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is unsubstituted phenyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1 or 2  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}$ alkyl and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ . In another embodiment is a



compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}$ alkyl and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is halogen. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is -F. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is -Cl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is -CH<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is -CF<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is -OCH<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is -C(O) $R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is - $C_{1-8}$ alkyl- $C_{6-10}$ aryl optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is unsubstituted - $C_{1-8}$ alkyl- $C_{6-10}$ aryl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is - $C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is - $C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is - $C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is - $C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is - $C_{1-8}$ alkyl- $C_{6-10}$ aryl substituted with 1

or 2 R<sup>12</sup> and each R<sup>12</sup> is independently selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy, and -C(O)R<sup>13</sup>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 or 2 R<sup>12</sup> and each R<sup>12</sup> is independently selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 or 2 R<sup>12</sup> and each R<sup>12</sup> is independently selected from C<sub>1-8</sub>alkyl and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is selected from halogen, C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy, and -C(O)R<sup>13</sup>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is selected from C<sub>1-8</sub>alkyl and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is halogen. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -F. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -Cl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -CH<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is C<sub>1-8</sub>haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -CF<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -OCH<sub>3</sub>. In another embodiment is a compound of Formula (II), or a

pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{6-10}aryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is unsubstituted  $-CH_2-phenyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1 or 2  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from halogen,  $C_{1-8}alkyl$ ,  $C_{1-8}haloalkyl$ , and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}alkyl$ ,  $C_{1-8}alkoxy$ , and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}alkyl$ ,  $C_{1-8}haloalkyl$ , and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}alkyl$  and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1  $R^{12}$  and  $R^{12}$  is selected from halogen,  $C_{1-8}alkyl$ ,  $C_{1-8}haloalkyl$ , and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}alkyl$ ,  $C_{1-8}alkoxy$ , and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}alkyl$  and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1  $R^{12}$  and  $R^{12}$  is halogen. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-CH_2-phenyl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-F$ . In another embodiment is a compound of Formula (II), or a

pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-\text{Cl}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $\text{C}_{1-8}$ alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-\text{CH}_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $\text{C}_{1-8}$ haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-\text{CF}_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $\text{C}_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-\text{OCH}_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2$ -phenyl substituted with 1  $R^{12}$  and  $R^{12}$  is  $-\text{C}(\text{O})\text{R}^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl optionally substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is unsubstituted  $\text{C}_{2-9}$ heteroaryl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1, 2, 3, or 4  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1 or 2  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from halogen,  $\text{C}_{1-8}$ alkyl,  $\text{C}_{1-8}$ haloalkyl, and  $\text{C}_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $\text{C}_{1-8}$ alkyl,  $\text{C}_{1-8}$ alkoxy, and  $-\text{C}(\text{O})\text{R}^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $\text{C}_{1-8}$ alkyl,  $\text{C}_{1-8}$ haloalkyl, and  $\text{C}_{1-8}$ alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $\text{C}_{2-9}$ heteroaryl substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently

selected from C<sub>1-8</sub>alkyl and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is selected from halogen, C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is selected from C<sub>1-8</sub>alkyl, C<sub>1-8</sub>alkoxy, and -C(O)R<sup>13</sup>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is selected from C<sub>1-8</sub>alkyl and C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is halogen. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -F. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -Cl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is C<sub>1-8</sub>alkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -CH<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is C<sub>1-8</sub>haloalkyl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -CF<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is C<sub>1-8</sub>alkoxy. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -OCH<sub>3</sub>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is C<sub>2-9</sub>heteroaryl substituted with 1 R<sup>12</sup> and R<sup>12</sup> is -C(O)R<sup>13</sup>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl optionally substituted with 1, 2, 3, or 4 R<sup>12</sup>. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is unsubstituted -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> is -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl substituted with 1, 2, 3, or 4

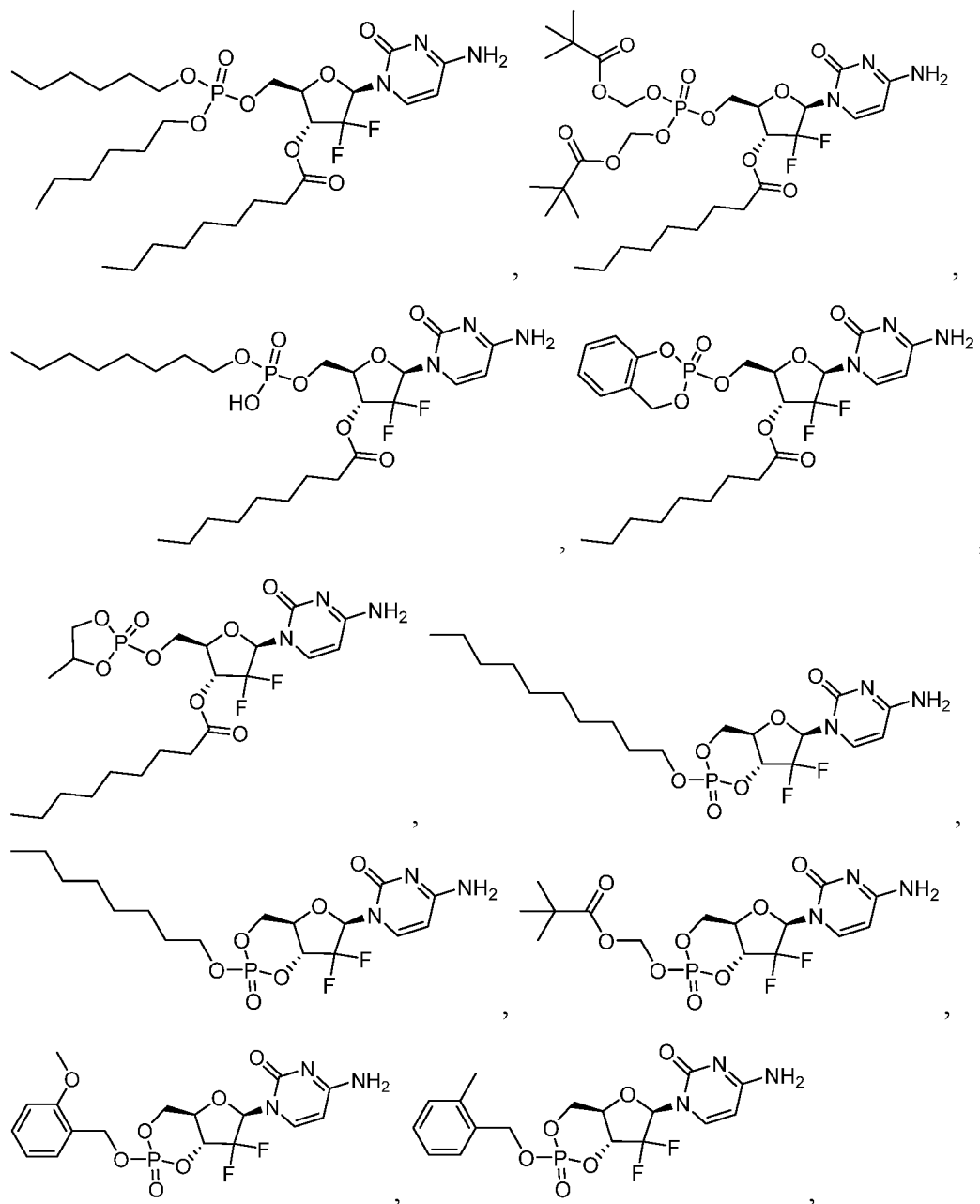
$R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1, 2, or 3  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from halogen,  $C_{1-8}alkyl$ ,  $C_{1-8}haloalkyl$ , and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}alkyl$ ,  $C_{1-8}alkoxy$ , and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}alkyl$ ,  $C_{1-8}haloalkyl$ , and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1 or 2  $R^{12}$  and each  $R^{12}$  is independently selected from  $C_{1-8}alkyl$  and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is selected from halogen,  $C_{1-8}alkyl$ ,  $C_{1-8}haloalkyl$ , and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}alkyl$ ,  $C_{1-8}alkoxy$ , and  $-C(O)R^{13}$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is selected from  $C_{1-8}alkyl$  and  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is halogen. In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-F$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-Cl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$

substituted with 1  $R^{12}$  and  $R^{12}$  is  $-CH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}haloalkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-CF_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $C_{1-8}alkoxy$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-OCH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}alkyl-C_{2-9}heteroaryl$  substituted with 1  $R^{12}$  and  $R^{12}$  is  $-C(O)R^{13}$ .

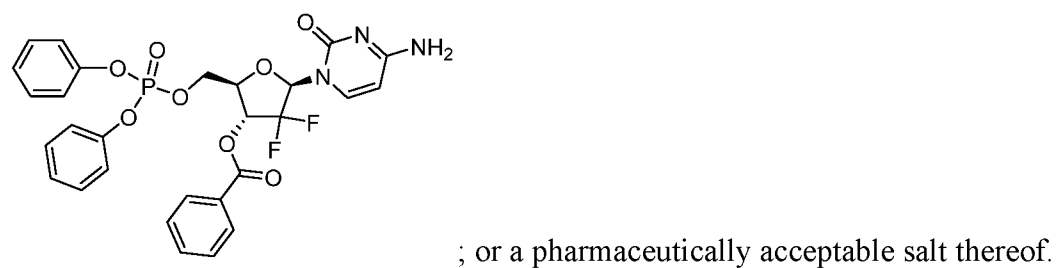
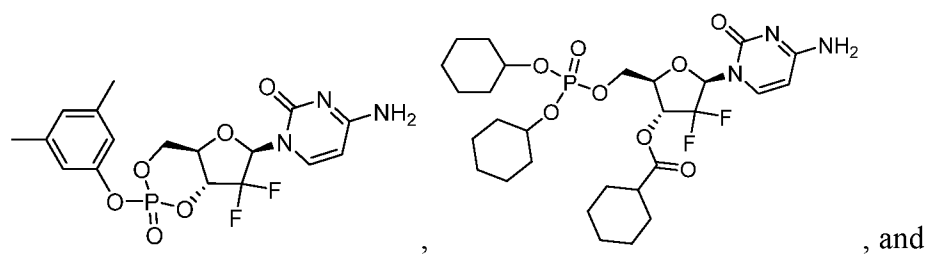
**[0077]** In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-10}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-6}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $C_{1-4}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$  and  $R^9$  is  $-CH_2CH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-10}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-6}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $C_{1-4}alkyl$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_3$ . In another embodiment is a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$  and  $R^9$  is  $-CH_2CH_3$ .

**[0078]** Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

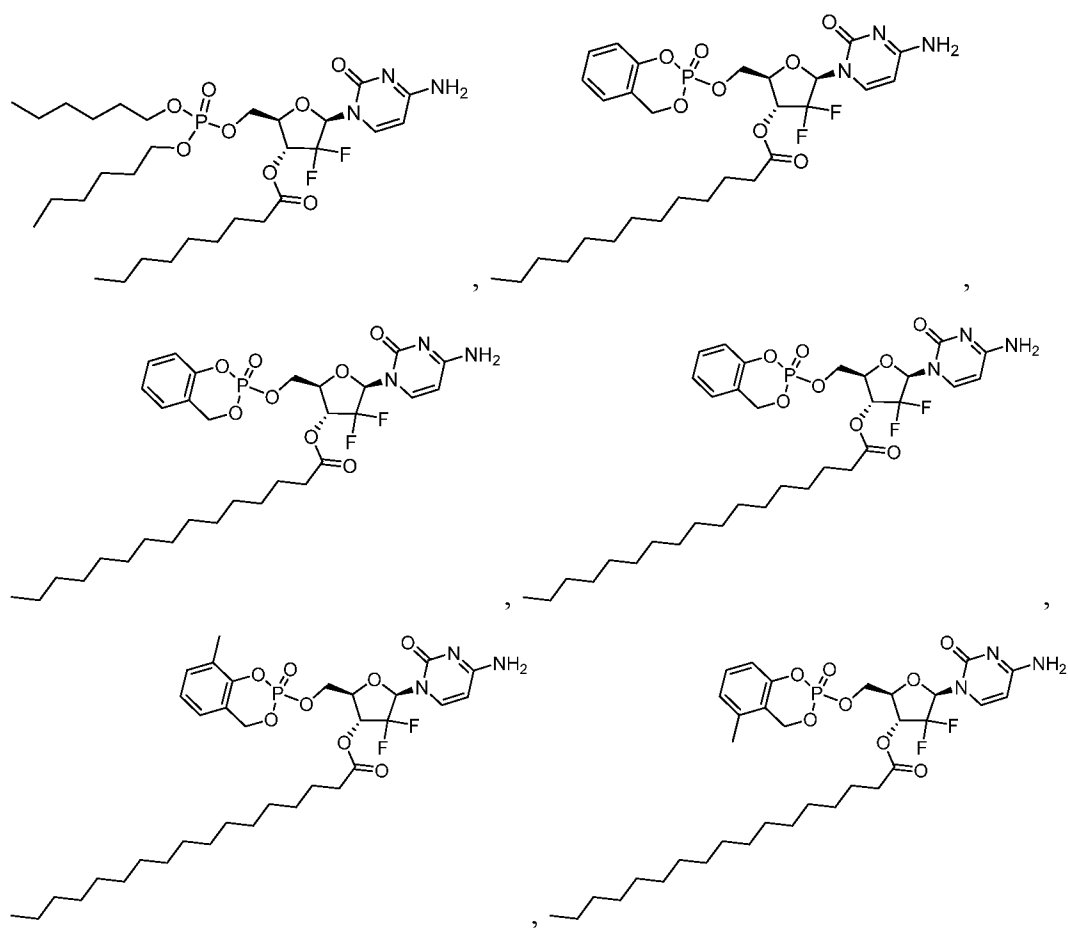
[0079] In some embodiments is a compound selected from:

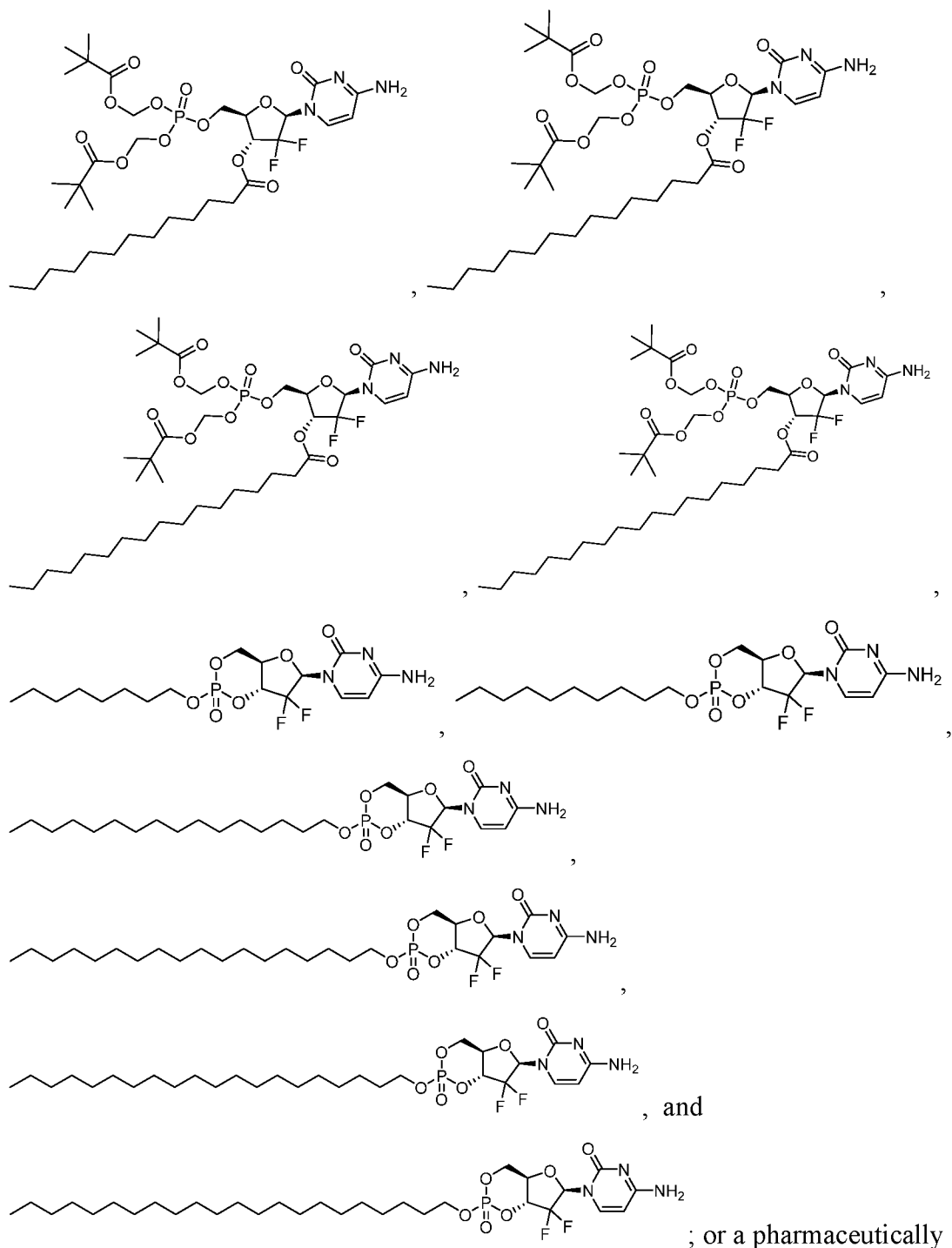






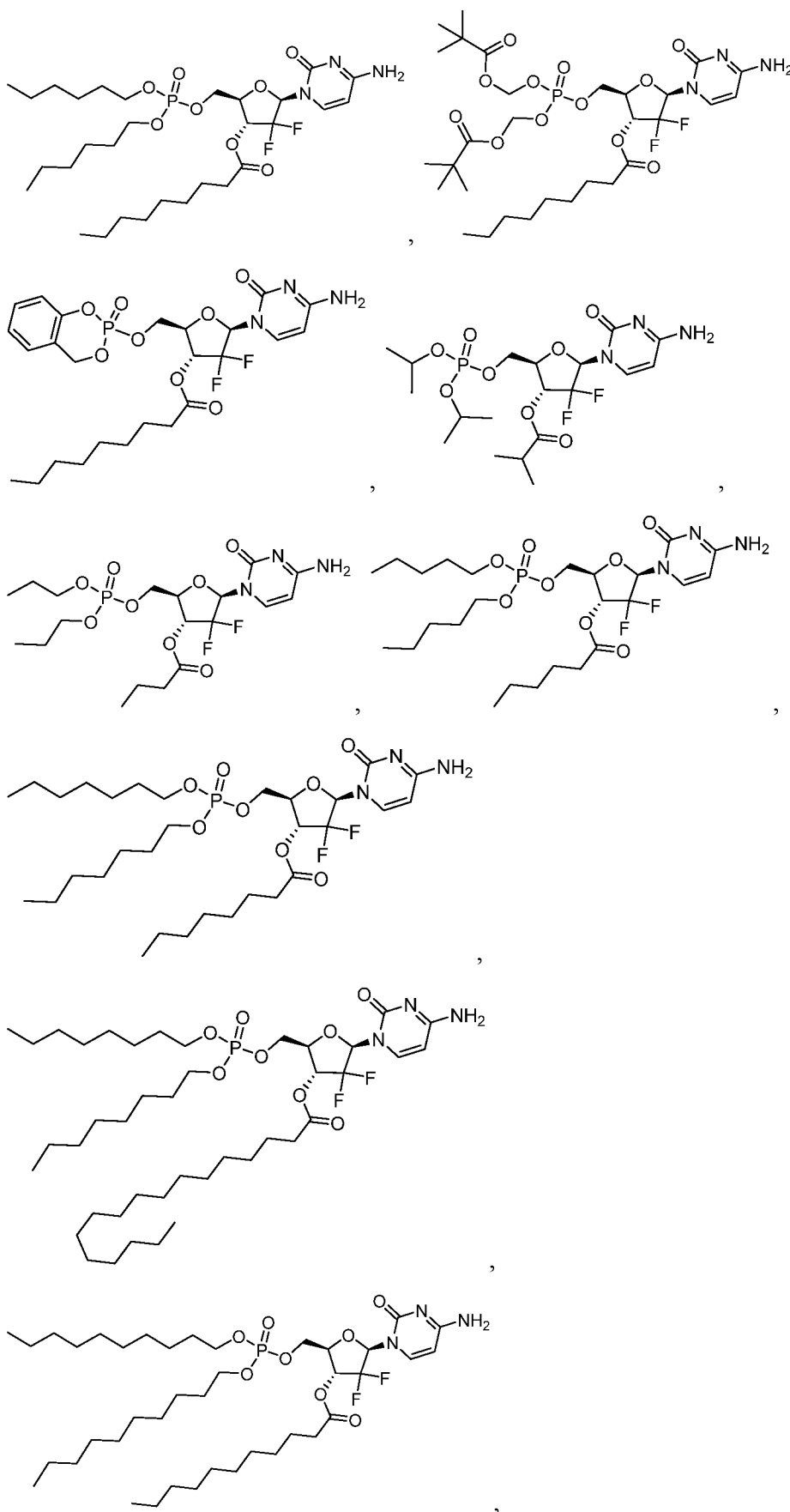
[0080] In some embodiments is a compound selected from:

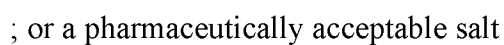




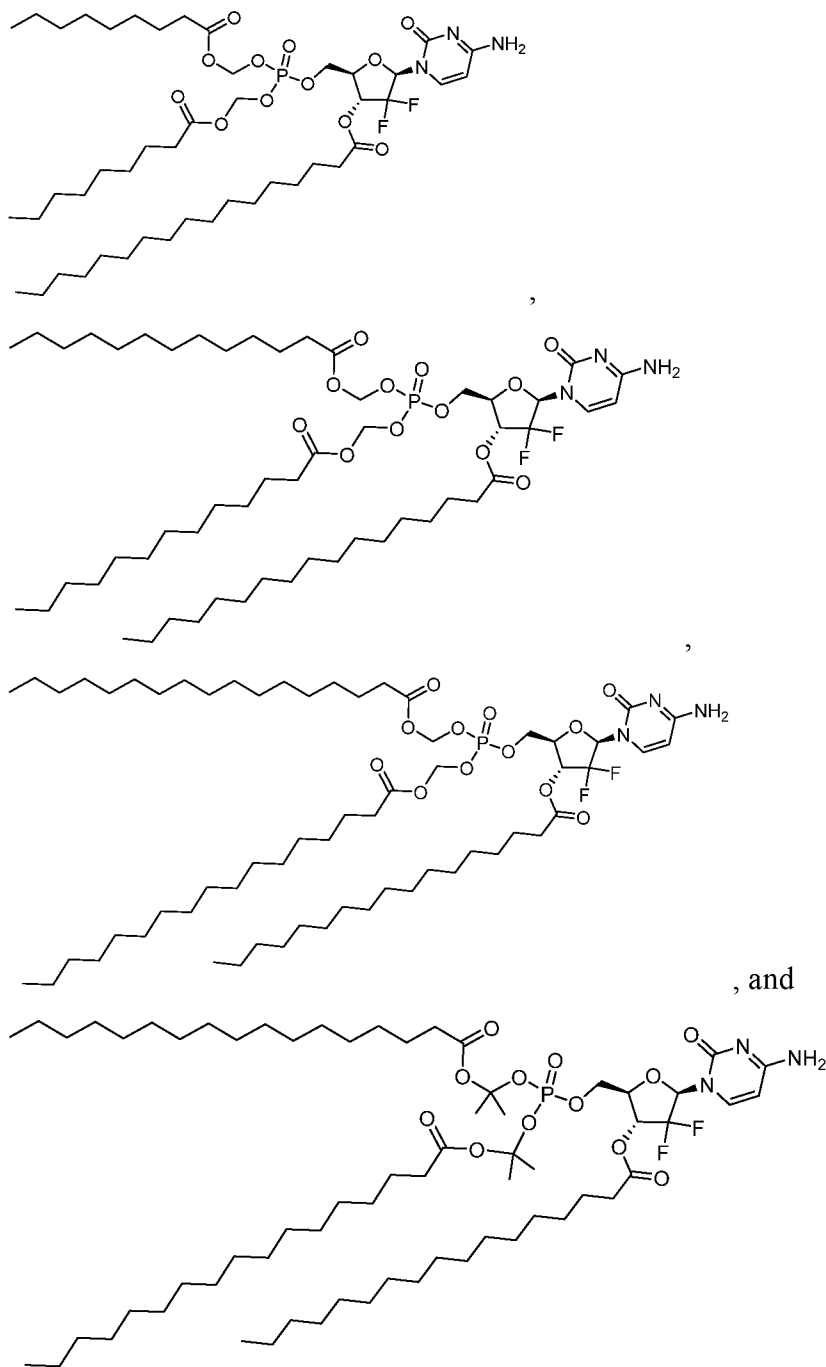
acceptable salt thereof.

**[0081]** In some embodiments is a compound selected from:





**[0082]** In some embodiments is a compound selected from:



; or a pharmaceutically acceptable salt thereof.

### Preparation of Compounds

**[0083]** The compounds used in the reactions described herein are made according to organic synthesis techniques, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Geel, Belgium), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Ark Pharm, Inc. (Libertyville, IL), Avocado Research (Lancashire, U.K.), BDH Inc.

(Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Combi-blocks (San Diego, CA), Crescent Chemical Co. (Hauppauge, NY), eMolecules (San Diego, CA), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Matrix Scientific, (Columbia, SC), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Ryan Scientific, Inc. (Mount Pleasant, SC), Spectrum Chemicals (Gardena, CA), Sundia Meditech, (Shanghai, China), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and WuXi (Shanghai, China).

**[0084]** Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley &

Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

**[0085]** Specific and analogous reactants are also identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C.). Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

### **Further Forms of Compounds Disclosed Herein**

#### Isomers

**[0086]** Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (*E*), and *zusammen* (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion, are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as optically pure enantiomers by chiral chromatographic resolution of the racemic mixture. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred (*e.g.*, crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by

chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that does not result in racemization.

#### Labeled compounds

**[0087]** In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that are incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as  $^2\text{H}$ ,  $^3\text{H}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{18}\text{O}$ ,  $^{17}\text{O}$ ,  $^{31}\text{P}$ ,  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^{18}\text{F}$ , and  $^{36}\text{Cl}$ , respectively. Compounds described herein, and pharmaceutically acceptable salts, esters, solvate, hydrates or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as  $^3\text{H}$  and  $^{14}\text{C}$  are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e.,  $^3\text{H}$  and carbon-14, i. e.,  $^{14}\text{C}$ , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, i.e.,  $^2\text{H}$ , produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, solvate, hydrate, or derivative thereof is prepared by any suitable method.

**[0088]** In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

#### Pharmaceutically acceptable salts

**[0089]** In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein



include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

**[0090]** In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds described herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

#### Solvates

**[0091]** In some embodiments, the compounds described herein exist as solvates. In some embodiments are methods of treating diseases by administering such solvates. Further described herein are methods of treating diseases by administering such solvates as pharmaceutical compositions.

**[0092]** Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein are conveniently prepared or formed during the processes described herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran or MeOH. In addition, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

#### **Pharmaceutical Compositions**

**[0093]** In certain embodiments, the compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) as described herein is administered as a pure chemical. In some embodiments, the compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21<sup>st</sup> Ed. Mack Pub. Co., Easton, PA (2005)).

**[0094]** Accordingly, provided herein is a pharmaceutical composition comprising at least one compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.*, the subject) of the composition.

**[0095]** One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (I'), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (II), or a pharmaceutically acceptable salt thereof.

**[0096]** Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable excipient and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable excipient and a compound of Formula (I'), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable excipient and a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable excipient and a compound of Formula (Ib), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable excipient and a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof. Another embodiment provides a pharmaceutical

composition consisting essentially of a pharmaceutically acceptable excipient and a compound of Formula (II), or a pharmaceutically acceptable salt thereof.

**[0097]** In certain embodiments, the compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) as described herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

**[0098]** In certain embodiments, the compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein is formulated for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous), vaginal, ophthalmic, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions are formulated as a unit dose, and/or are formulated for oral or subcutaneous administration.

**[0099]** Exemplary pharmaceutical compositions are used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which includes one or more of a disclosed compound, as an active ingredient, in a mixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. In some embodiments, the active ingredient is compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

**[00100]** In some embodiments for preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition is readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

**[00101]** In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more

pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, cellulose, microcrystalline cellulose, silicified microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, hypromellose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as crospovidone, croscarmellose sodium, sodium starch glycolate, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, docusate sodium, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, in some embodiments, the compositions comprise buffering agents. In some embodiments, solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

**[00102]** In some embodiments, a tablet is made by compression or molding, optionally with one or more accessory ingredients. In some embodiments, compressed tablets are prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. In some embodiments, molded tablets are made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. In some embodiments, tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, are scored or prepared with coatings and shells, such as enteric coatings and other coatings.

**[00103]** Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the subject composition, in some embodiments, the liquid dosage forms contain inert diluents, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (optionally, cottonseed, groundnut, corn, germ,

olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins, and mixtures thereof.

**[00104]** In some embodiments, suspensions, in addition to the subject composition, contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

**[00105]** In some embodiments, formulations for rectal or vaginal administration are presented as a suppository, which are prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

**[00106]** Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In some embodiments, the active component is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants as required.

**[00107]** In some embodiments, the ointments, pastes, creams and gels contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

**[00108]** In some embodiments, powders and sprays contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. In some embodiments, sprays additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

**[00109]** In some embodiments, the compounds described herein are formulated as eye drops for ophthalmic administration.

**[00110]** Compositions and compounds disclosed herein alternatively are administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. In some embodiments, a non-aqueous (*e.g.*, fluorocarbon propellant) suspension is used. In some embodiments, sonic nebulizers are used because they minimize exposing the agent to shear, which results in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by

formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

**[00111]** Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which are reconstituted into sterile injectable solutions or dispersions just prior to use, which, in some embodiments, contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

**[00112]** Examples of suitable aqueous and non-aqueous carriers which are employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate and cyclodextrins. Proper fluidity is maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

**[00113]** Also contemplated are enteral pharmaceutical formulations including a disclosed compound, an enteric material, and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5.

Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate

(HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (*e.g.*, Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*.

**[00114]** The dose of the composition comprising at least one compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) as described herein differs, depending upon the patient's (*e.g.*, human) condition, that is, stage of the disease, general health status, age, and other factors.

**[00115]** Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). Optimal doses are generally determined using experimental models and/or clinical trials. In some embodiments, the optimal dose depends upon the body mass, weight, or blood volume of the patient.

**[00116]** Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

## Methods

**[00117]** In some embodiments is a method of treating cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt

thereof, wherein the cancer is breast cancer, ovarian cancer, non-small cell lung cancer, pancreatic cancer, or bladder cancer. In some embodiments is a method of treating breast cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating ovarian cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating non-small cell lung cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating pancreatic cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof. In some embodiments is a method of treating bladder cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof.

**[00118]** In some embodiments is a method of treating an infectious disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II) described herein, or a pharmaceutically acceptable salt thereof.

**[00119]** In certain embodiments, a disclosed compound utilized by one or more of the foregoing methods is one of the generic, subgeneric, or specific compounds described herein, such as a compound of Formula (I), (I'), (Ia), (Ib), (Ic), or (II).

**[00120]** Disclosed compounds are administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted above, a contemplated compound disclosed herein is administered orally, subcutaneously, topically, parenterally, by



inhalation spray, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Parenteral administration include subcutaneous injections, intravenous, or intramuscular injections or infusion techniques.

[00121] The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

## EXAMPLES

### List of abbreviations

[00122] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN	acetonitrile
Bn	benzyl
BOC or Boc	<i>tert</i> -butyl carbamate
DCC	dichloroethane (ClCH <sub>2</sub> CH <sub>2</sub> Cl)
DCM	N,N'-dicyclohexylcarbodiimide
DIPEA	N,N-diisopropylethylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMF	dimethylformamide
DMA	N,N-dimethylacetamide
DMSO	dimethylsulfoxide
equiv	equivalent(s)
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Et	ethyl
EtOH	ethanol
EtOAc	ethyl acetate
HF	hydrofluoric acid
HMDS	bis(trimethylsilyl)amine
HPLC	high performance liquid chromatography
Me	methyl
MeOH	methanol
MMTr	4-methoxytrityl

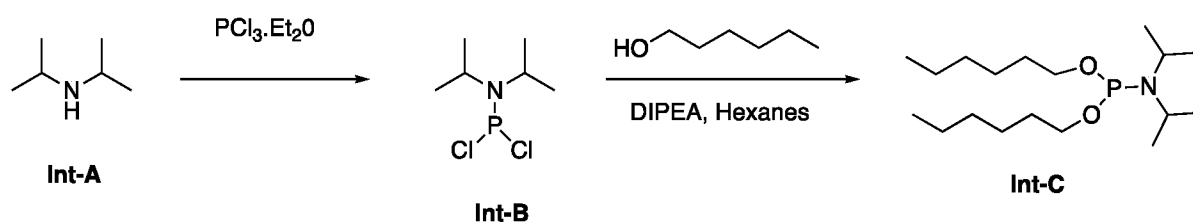
MMTrCl	4-methoxytrityl chloride
MS	mass spectroscopy
NMM	<i>N</i> -methylmorpholine
NMR	nuclear magnetic resonance
TBHP	tert-butyl hydroperoxide
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate

### Chemical Synthesis

[00123] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times are approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted. Spectra are given in ppm ( $\delta$ ) and coupling constants ( $J$ ) are reported in Hertz. For proton spectra the solvent peak was used as the reference peak.

### Synthesis of Intermediates:

#### Synthesis of Int-C:

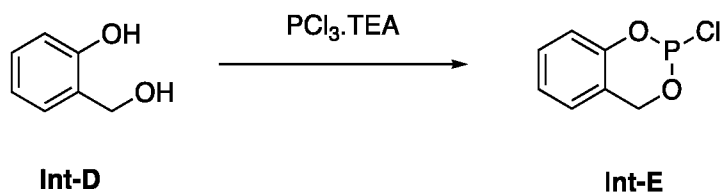


[00124] To a solution of  $\text{PCl}_3$  (7.7 mL, 87.9 mmol) in diethyl ether (60 mL) was added **Int-A** (16.7 mL, 118.8 mmol) in diethyl ether (60 mL) dropwise over a period of 1h at  $0^\circ\text{C}$ . The reaction mixture was stirred at room temperature for 4h under argon atmosphere. The reaction mixture was then filtered and washed with diethyl ether (20 mL). The filtrate was

concentrated under reduced pressure to give **Int-B** (13 g) as a colorless liquid. The compound was used directly in the next step without any further purification.

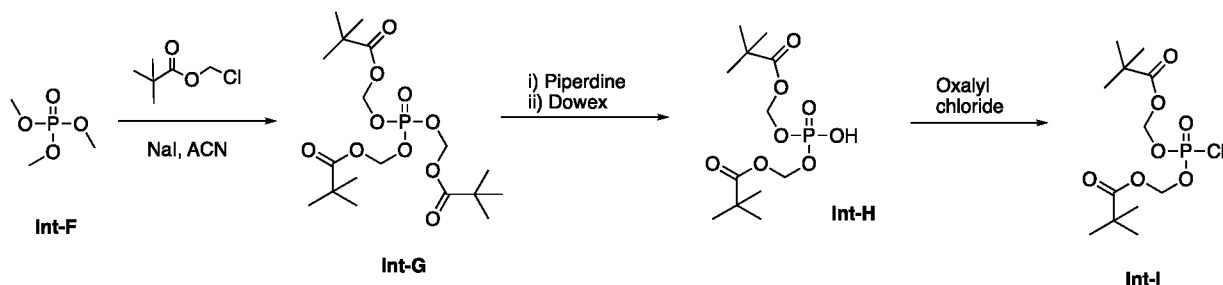
[00125] To a solution of 1-hexanol (13.13 g, 128.0 mmol) in hexane (65 mL) was added DIPEA (67.2 mL, 386.0 mmol) followed by **Int-B** (13.0 g, 64.0 mmol) in hexane (65 mL) dropwise over a period of 1h at 10 °C. The reaction mixture was stirred at room temperature for 4h and then concentrated under reduced pressure to afford **Int-C** (16 g) as a light green liquid. The compound was used directly in the next step without any further purification.

#### Synthesis of Int-E:



[00126] To a solution of **Int-D** (10.0 g, 80.0 mmol) in diethyl ether (300 mL) was added  $\text{PCl}_3$  (8.2 mL, 94.2 mmol) over a period of 15 min at -20°C, and then pyridine (19.1 mL, 241.9 mmol) in diethyl ether (200 mL) was added dropwise over a period of 2h at -20°C. The reaction mixture was allowed to warm to room temperature and maintained at room temperature for 2h. The reaction mixture was stored at 0°C for 12h and filtered. The filtrate was concentrated under reduced pressure to afford crude **Int-E** (12 g, 80%) as a yellow oil. The compound was used directly in the next step without any further purification.

#### Synthesis of Int-I:

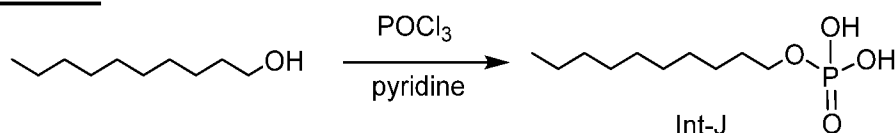


[00127] To a stirred solution of **Int-F** (20 g, 142.8 mmol) in ACN (200 mL) was added NaI (63.8 g, 428.4 mmol) and chloromethylpivalate (85.7 g, 571.4 mmol) at room temperature. The resulting reaction mixture was heated to 80°C for 3 days. The reaction mixture was cooled and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and filtered. The solvent was evaporated under reduced pressure and the residue was purified by silica gel chromatography to afford **Int-G** (40 g, 62%) as a light green liquid.

**[00128]** A solution of **Int-G** (40 g, 90.0 mmol) in piperidine (280 mL) was stirred at room temperature for 12h. The reaction mixture was distilled. The crude compound was dissolved in water (240 mL) and Dowex H<sup>+</sup> resin was added till pH ~ 2 and stirred for 2h at room temperature. The reaction mixture was filtered and washed with water (2 x 50 mL). The filtrate was concentrated under reduced pressure to afford pure **Int-H** (15 g, 51%) as an off-white solid.

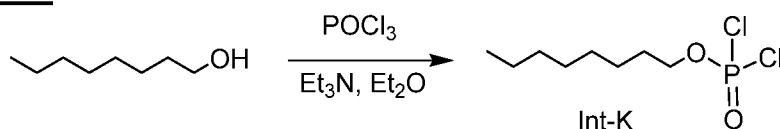
**[00129]** To a solution of **Int-H** (10 g, 30.6 mmol) in DCM (100 mL) was added oxalyl chloride in DCM (100 mL) dropwise at room temperature under argon atmosphere. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was concentrated under reduced pressure to afford **Int-I** (10 g) as a yellow oil. The compound was used directly in the next step without any further purification.

#### **Synthesis of Int-J:**



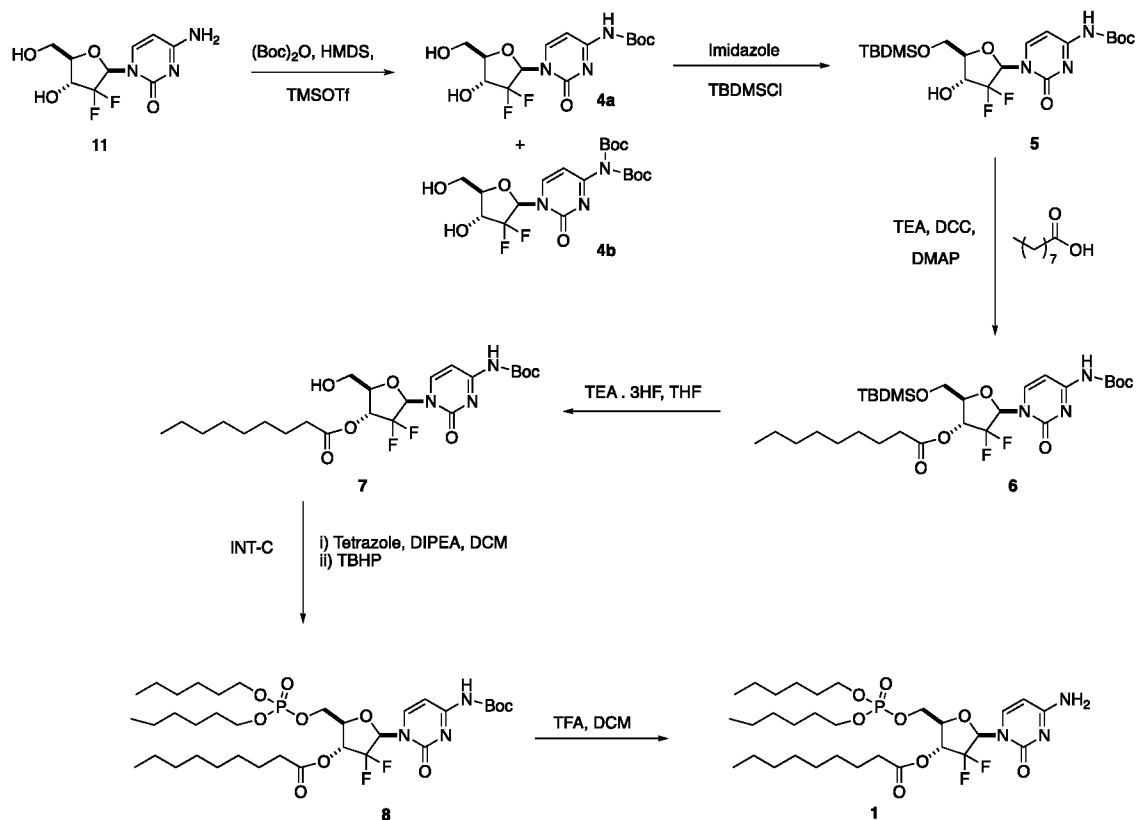
**[00130]** To a stirred solution of phosphorus oxychloride (3.7 mL, 39.7 mmol) in distilled tetrahydrofuran (50 mL) was added 1-decanol (5.0 g, 31.59 mmol) as a solution in pyridine (7.7 mL, 95.6 mmol) at 0°C under argon. The reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by dropwise addition of saturated aqueous sodium bicarbonate (140 mL) at 0°C. The mixture was poured onto ice water (150 mL) and the mixture was acidified to pH 2 by addition of 6 M hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate and evaporated to give **Int-J** (6.50 g, 86%) as a pale yellow semi-solid.

#### **Synthesis of Int-K:**



**[00131]** Dry Et<sub>3</sub>N (15.54 g, 153.58 mmol, 1 *eq.*) and octan-1-ol (20 g, 153.58 mmol, 1 *eq.*) in Et<sub>2</sub>O (150 mL) was added dropwise with vigorous stirring to POCl<sub>3</sub> (23.55 g, 153.58 mmol, 1 *eq.*) in Et<sub>2</sub>O (150 mL) at -78°C under N<sub>2</sub>. After addition, the reaction mixture was allowed to warm to 25°C and stirred for 12 h. The mixture was filtered and the filtrate was concentrated in reduced pressure to yield 1-dichlorophosphoryloxyoctane (20 g, 53% yield) as a yellow liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.36 (td, *J* = 6.4, 9.8 Hz, 2H), 1.90-1.78 (m, 2H), 1.51-1.42 (m, 2H), 1.39-1.28 (m, 8H), 1.02-0.81 (m, 3H).

**Example 1: Synthesis of (2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((bis(hexyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl nonanoate (Compound 1)**



**[00132]** To a suspension of **11** (40 g, 152.0 mmol) in HMDS (73.46 g, 456.2 mmol) were added DMAP (1.8 g, 15.2 mmol) and TMSOTf (1.01 g, 4.56 mmol) at 0°C. The resulting mixture was stirred at room temperature for 12h. Boc-anhydride (165 g, 760 mmol) was then added dropwise over a period of 1h at 0 °C. The resulting reaction mixture was stirred at room temperature for 16h and then methanol (400 mL) and TEA (200 mL) were added at 0°C for 1h. The resulting reaction mixture was stirred at room temperature for 20h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated under reduced pressure. The crude compound was purified by silica gel chromatography to afford **4a** (35.0 g, 63 %) and **4b** (12 g, 17%) as off-white solids.

**[00133]** To a stirred solution of **4a** (35.0 g, 96.4 mmol) in pyridine (350 mL) at 0° C were added imidazole (9.18 g, 134.9 mmol) and TBDMSCl (26.03 g, 173.5 mmol). The reaction mixture was stirred at room temperature for 8h. The pyridine was evaporated under reduced pressure and the residue was co-distilled with toluene repeatedly 3 times. The crude reaction mass was diluted with water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel chromatography to afford **5** (30 g, 65%) as an off-white solid.

**[00134]** To a solution of **5** (30 g, 62.8 mmol) in 1,4-dioxane (300 mL) at 0 °C was added TEA (43.7 mL, 314.4 mmol), DCC (38.86 g, 188.0 mmol), and DMAP (767 mg, 6.2 mmol) followed by nonanoic acid (29.81 g, 188 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM (500 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure to give the crude compound which was purified by silica gel chromatography to afford **6** (30 g, 77%) as a light brown liquid.

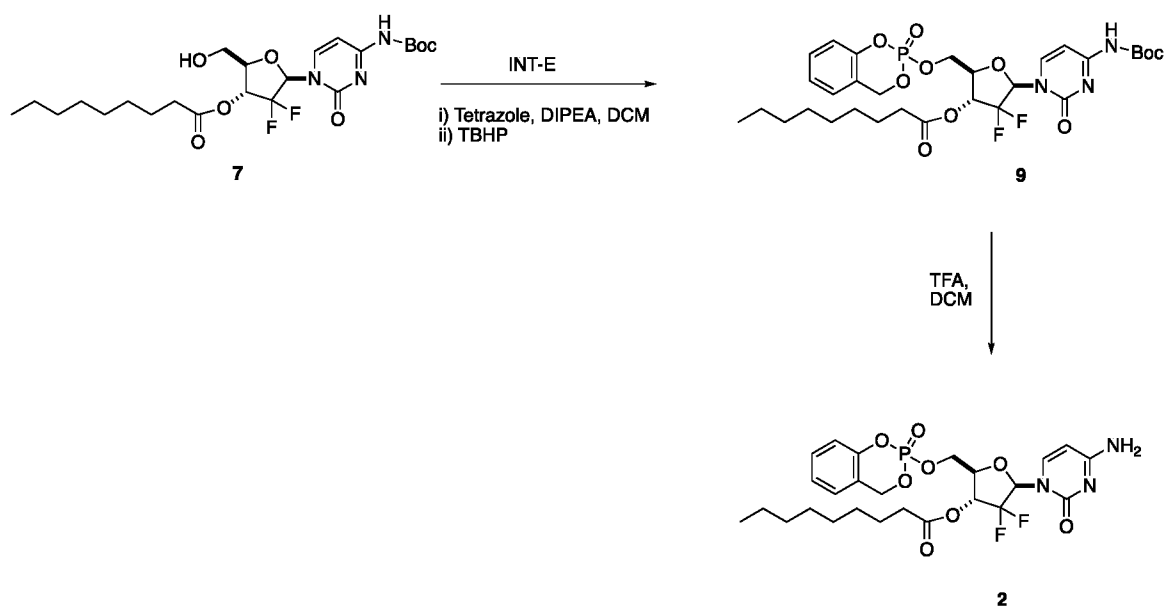
**[00135]** To a solution of **6** (30 g, 48.6 mmol) in THF (300 mL), was added TEA.3HF (39.14 g, 243 mmol) dropwise at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 12h at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (500 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure to give the crude compound which was purified by silica gel chromatography to afford **7** (20 g, 82%) as a light brown liquid.

**[00136]** To a stirred solution of **7** (5 g, 9.9 mmol) in DCM (100 mL), was added DIPEA (8.65 mL, 49.6 mmol) and tetrazole (1.74 g, 24.8 mmol). **Int-C** (8.27 g, 24.8 mmol) in DCM (20 mL) was then added dropwise at 0°C over 15 min. The reaction mixture was stirred at room temperature for 16 h and then TBHP (5.96 mL; 5M in decane, 29.8 mmol) was added to the reaction mixture dropwise at 0°C. The resulting reaction mixture was stirred for 6h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> filtered solvent was evaporated under

reduced pressure to give the crude compound which was purified by silica gel chromatography to afford **8** (2.8 g, 38%) as a red liquid.

[00137] To a solution of **8** (2.8 g, 3.72 mmol) in DCM (28 mL) was added TFA (1.42 mL, 18.6 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 16h. The solvent was evaporated under reduced pressure and the residue was diluted in ethyl acetate (200 mL) and washed with saturated NaHCO<sub>3</sub> (2 x 50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure to give the crude compound which was purified by silica gel chromatography to afford the title compound (**1**) (1.3 g, 54%) as a colorless liquid. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ 0.83-0.87 (9H, m); 1.25 (22H, broad s); 1.54-1.61 (6H, m); 2.42-2.47 (2H, t); 3.93-3.99 (4H, q); 4.25-4.37 (3H, m); 5.41 (1H, broad m); 5.78-5.80 (1H, d); 6.26 (1H, broad m); 7.48 (2H, broad s); 7.57-7.60 (1H, d). LC-MS (ESI) *m/z* (M+H)<sup>+</sup>: 652.5.

**Example 2: Synthesis of (2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-4,4-difluoro-2-(((2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)methyl)tetrahydrofuran-3-yl nonanoate (Compound 2)**

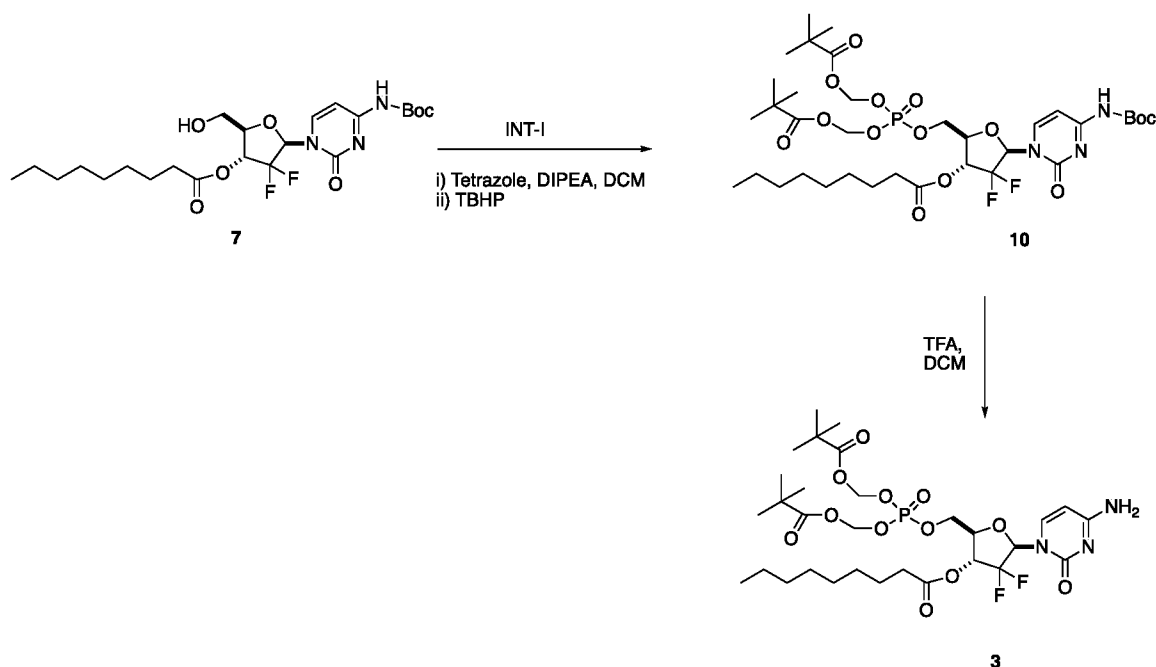


[00138] To a solution of **7** (4.5 g, 8.8 mmol) in ACN (90 mL) was added DIPEA (8.8 mL, 49.6 mmol) and a solution of **Int-E** (3.36 g, 17.8 mmol) in DCM (20 mL) dropwise at 0°C over 15 min. The reaction mixture was stirred at room temperature for 30 min. TBHP (5.37 mL; 5M in decane, 26.8 mmol) was then added dropwise at 0°C. The reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered.

The solvent was evaporated under reduced pressure to give the crude compound which was purified by silica gel chromatography to afford **9** (1.74 g, 29%) as an off-white solid.

**[00139]** To a solution of **9** (1.74 g, 2.59 mmol) in DCM (34.8 mL) was added TFA (0.98 mL, 12.9 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL) and washed with saturated NaHCO<sub>3</sub> (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure to give the crude compound which was purified by silica gel chromatography to afford the title compound (**2**) (0.83 g, 56%) as an off-white solid. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ 0.84-0.87 (3H, t); 1.25 (10H, broad s); 1.51-1.54 (2H, m); 2.37-2.41 (2H, m); 4.37-4.41 (1H, m); 4.44-4.51 (2H, m); 5.37 (1H, broad s); 5.42-5.57 (2H, m); 5.72-5.75 (1H, m); 6.22 (1H, broad m); 7.11-7.14 (1H, m); 7.19-7.23 (1H, m); 7.28-7.30 (1H, m); 7.35-7.47 (4H, m). LC-MS (ESI) *m/z* (M+H)<sup>+</sup>: 572.2.

### Example 3: Synthesis of Compound 3



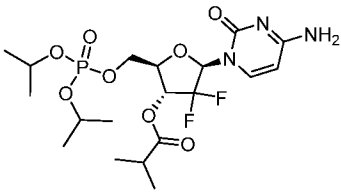
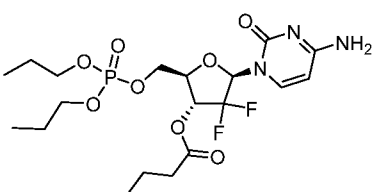
**[00140]** To a solution of **7** (4 g, 7.9 mmol) in DCM (80 mL) was added DIPEA (1.65 mL, 9.4 mmol), DMAP (57 mg, 0.47 mmol), and a solution of **Int-I** (3.2 g, 9.5 mmol) in DCM (20 mL) dropwise at 0°C for 15 min. The reaction mixture was stirred at room temperature for 16h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated

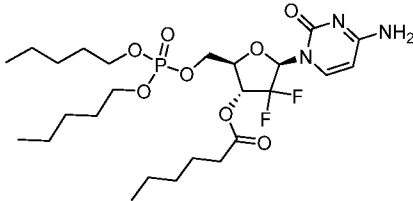
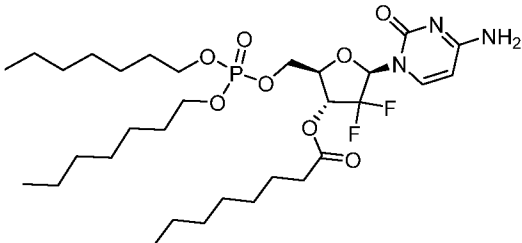
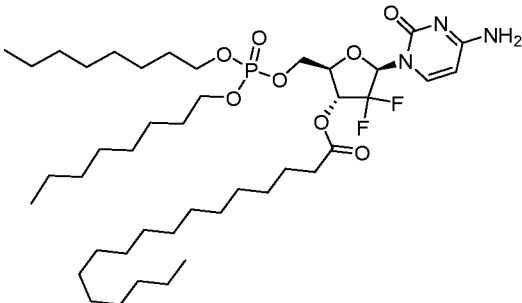
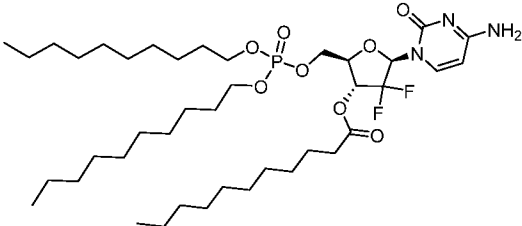


under reduced pressure to afford **10** (3.0 g) as a brown liquid which was used in the next step without further purification.

**[00141]** To a solution of **10** (3.0 g, 3.6 mmol) in DCM (30 mL) was added TFA (1.41 mL, 18.45 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 16h. The solvent was evaporated under reduced pressure and the residue was diluted in ethyl acetate (100 mL) and washed with saturated NaHCO<sub>3</sub> (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure to give crude compound which was purified by silica gel chromatography to afford **Compound 3** (0.58 g, 33%) as a colorless liquid. <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO): δ 0.83-0.87 (3H, m); 1.09-1.16 (18H, m); 1.25 (10H, broad s); 1.53-1.60 (2H, m); 2.41-2.46 (2H, t); 4.35-4.37 (3H, broad d); 5.40 (1H, broad s); 5.58-5.63 (4H, d); 5.79-5.82 (1H, d); 6.25 (1H, broad s); 7.46-7.48 (2H, m); 7.57-7.59 (1H, d). LC-MS (ESI) *m/z* (M+H)<sup>+</sup>: 712.4.

**[00142] Examples 4-14:** The following compounds were synthesized in a similar manner as described in Example 1.

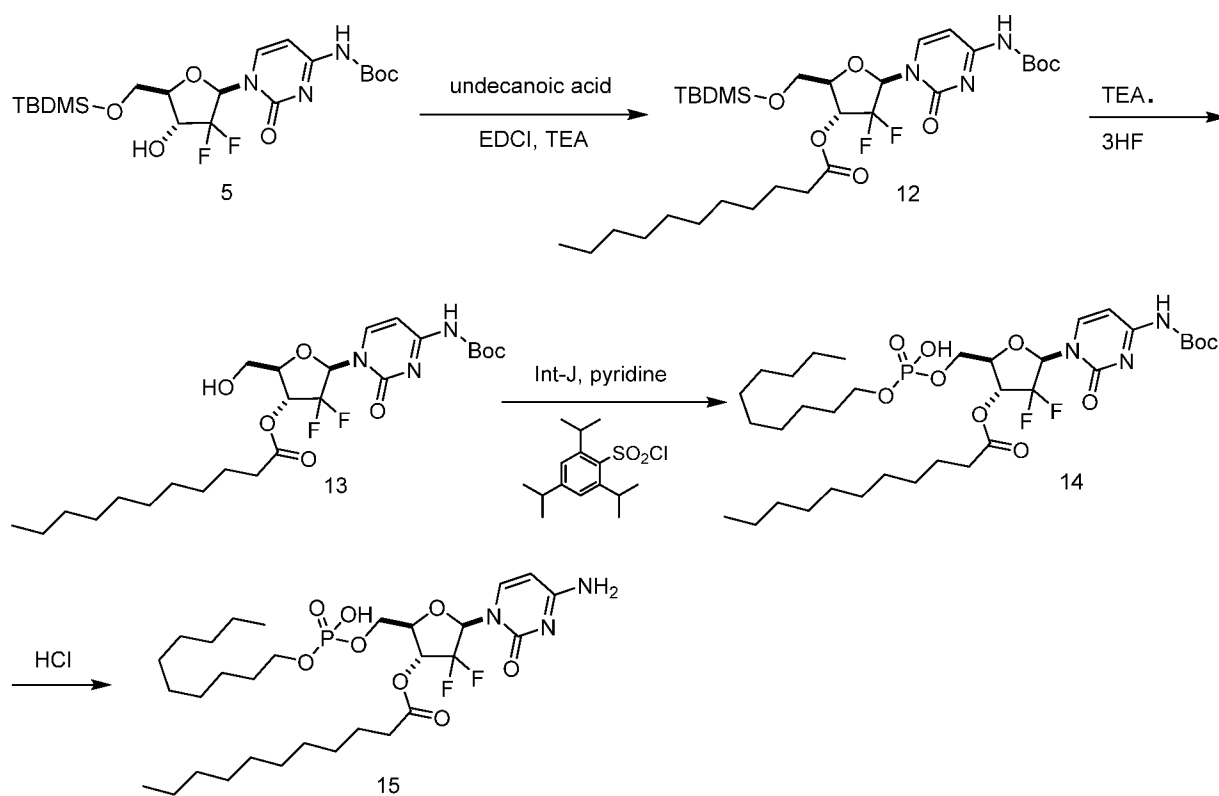
Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) <i>m/z</i> (M+H) <sup>+</sup>
4	16		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((diisopropoxyphosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl isobutyrate	498.4
5	17		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((dipropoxyphosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl butyrate	498.4

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
6	18		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((bis(pentyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl hexanoate	582.5
7	19		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((bis(heptyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl octanoate	666.7
8	20		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((bis(octyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl heptadecanoate	820.7
9	21		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((bis(decyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl undecanoate	792.7

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
10	22		(2R,3R,5R)-5-(4-amino-2-oxypyrimidin-1(2H)-yl)-2-(((bis(dodecyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl tridecanoate	876.7
11	23		(2R,3R,5R)-5-(4-amino-2-oxypyrimidin-1(2H)-yl)-2-(((bis(tetradecyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl pentadecanoate	960.8
12	24		(2R,3R,5R)-5-(4-amino-2-oxypyrimidin-1(2H)-yl)-2-(((bis(cyclohexyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl cyclohexanecarboxylate	618.5
13	25		(2R,3R,5R)-5-(4-amino-2-oxypyrimidin-1(2H)-yl)-2-(((diphenoxyphosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl benzoate	600.4

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
14	26		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((bis(hexyloxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl nonanoate	652.5

**Example 15: Synthesis of (2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((decyloxy)(hydroxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl undecanoate (Compound 15)**



**[00143]** To a stirred solution of *tert*-butyl *N*-[1-[(2*R*,5*R*)-5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3,3-difluoro-4-hydroxytetrahydrofuran-2-yl]-2-oxopyrimidin-4-yl]carbamate (**5**) (3.64 g, 7.6 mmol) in dry 1,4-dioxane (60 mL) was added undecanoic acid (4.71 g, 25.3 mmol), triethylamine (6.8 mL, 48.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.39 g, 22.90 mmol) and 4-

dimethylaminopyridine (91 mg, 0.7 mmol) while maintaining the temperature between 5-10 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated. The residue was partitioned between water (100 mL) and dichloromethane (150 mL) and the aqueous layer was extracted with dichloromethane (150 mL). The combined organic layers were washed with water (100 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. The crude product was purified by silica gel column chromatography to give **12** (5.26 g) as a colorless oil.

**[00144]** To a stirred solution of **12** (5.2 g, 8.1 mmol) in distilled tetrahydrofuran (52 mL) was added triethylamine trihydrofluoride (7.6 mL, 46.6 mmol) at 0°C under argon. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was evaporated. The residue was taken up in ethyl acetate (100 mL) and the organic layer was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The crude product was purified by silica gel column chromatography to give **13** (3.38 g, 83%) as a colorless oil.

**[00145]** A solution of **13** (540 mg, 2.3 mmol) in freshly distilled pyridine (17 mL) was stirred at 50 °C for 2 h under argon. The solution was evaporated and the residue was taken up in freshly distilled pyridine (8 mL). To the mixture was added 2,4,6-triisopropylbenzenesulfonyl chloride (1.37 g, 4.5 mmol) as a solution in freshly distilled pyridine (20 mL) and **Int-J** (1.20 g, 2.3 mmol) as a solution in freshly distilled pyridine (7 mL) at 40°C under argon. The reaction mixture was stirred at 40°C for 28 h. To the reaction mixture was added water (1.65 mL) and isopropanol (6.5 mL) and the mixture was stirred at room temperature for 15 min. The mixture was evaporated. To the residue was added toluene (10 mL) and the mixture was evaporated. This evaporation sequence was repeated 4 times. The crude product was purified by silica gel chromatography to give **14** (860 mg, 50%) as a white solid.

**[00146]** A suspension of **14** (1.18 g, 1.58 mmol) and hydrogen chloride (5.3 M in 1,4-dioxane, 11.6 mL, 61.48 mmol) was stirred at room temperature for 29 h under argon. The reaction mixture was evaporated and the residue was purified by preparative HPLC to give the title compound (**15**) (260 mg, 25%) as an off-white solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 7.75 – 7.58 (m, 2H), 7.43 – 6.95 (m, 2H), 6.24 (t, *J* = 9.1 Hz, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 5.46 – 5.25 (m, 1H), 4.34 – 4.24 (m, 1H), 4.14 – 3.96 (m, 2H), 3.81 – 3.68 (m, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.61 – 1.44 (m, 4H), 1.32 – 1.16 (m, 28H), 0.90 – 0.81 (m, 6H). LC-MS (ESI) *m/z* (M+H)<sup>+</sup>: 652.2.

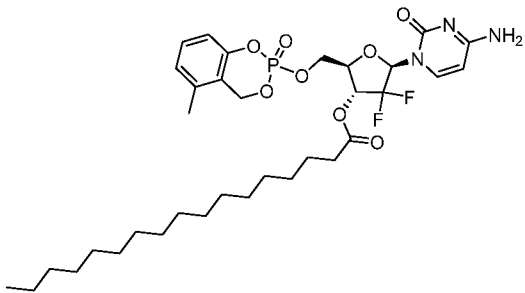
**[00147] Example 16 (Compound 27)** was synthesized in a similar manner as described in Example 15.

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
16	27		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-(((dodecyloxy)(hydroxy)phosphoryl)oxy)methyl)-4,4-difluorotetrahydrofuran-3-yl tridecanoate	708.3

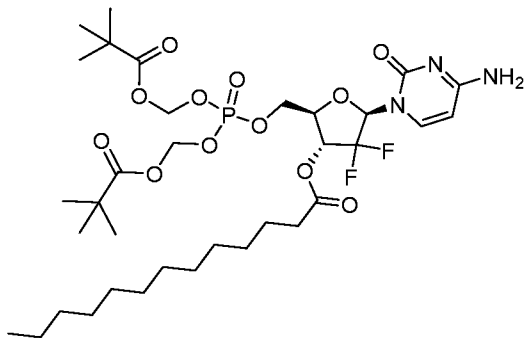
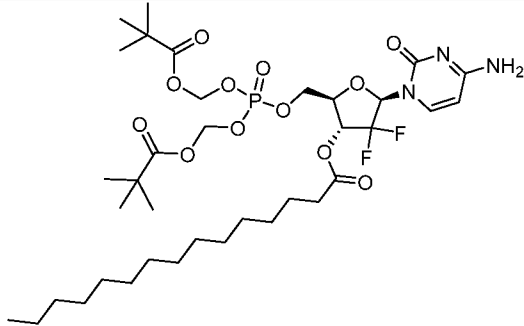
**[00148] Examples 17-21:** The following compounds (**Compounds 28-32**) were synthesized in a similar manner as described in Example 2.

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
17	28		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-4,4-difluoro-2-(((2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)methyl)tetrahydrofuran-3-yl tridecanoate	628.5

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
18	29		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-4,4-difluoro-2-(((2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)methyl)tetrahydrofuran-3-yl pentadecanoate	654.6
19	30		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-4,4-difluoro-2-(((2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)methyl)tetrahydrofuran-3-yl heptadecanoate	682.6
20	31		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-4,4-difluoro-2-(((8-methyl-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)methyl)tetrahydrofuran-3-yl heptadecanoate	698.6

Ex. No.	Compound No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
21	32		(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-4,4-difluoro-2-(((5-methyl-2-oxido-4H-benzo[d][1,3,2]dioxaphosphinin-2-yl)oxy)methyl)tetrahydrofuran-3-yl heptadecanoate	698.6

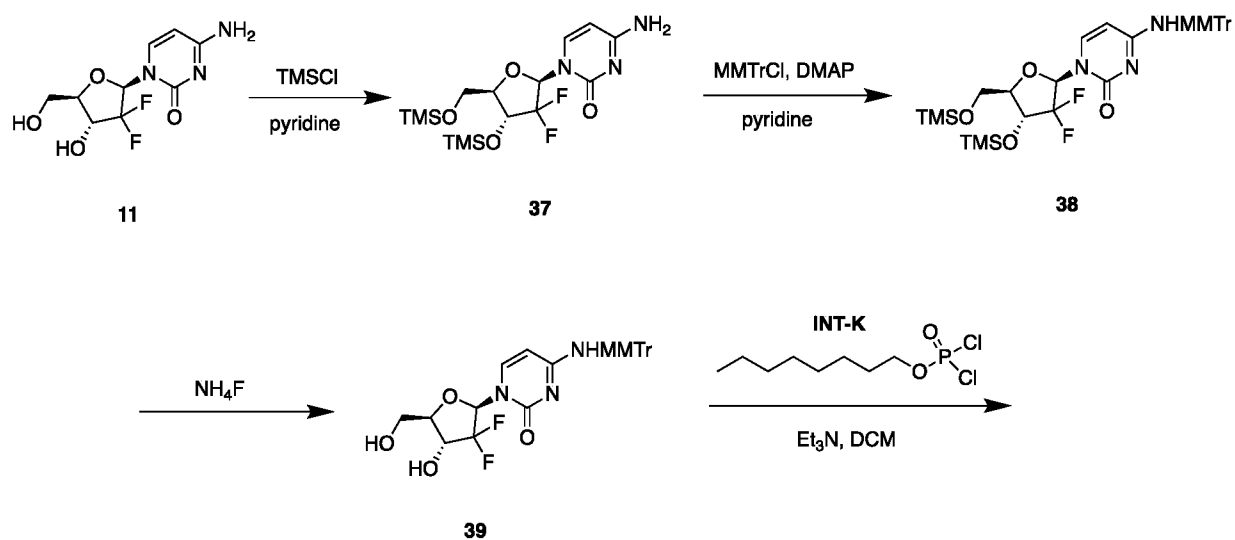
**[00149] Examples 22-25:** The following compounds (**Compounds 33-36**) were synthesized in a similar manner as described in Example 3.

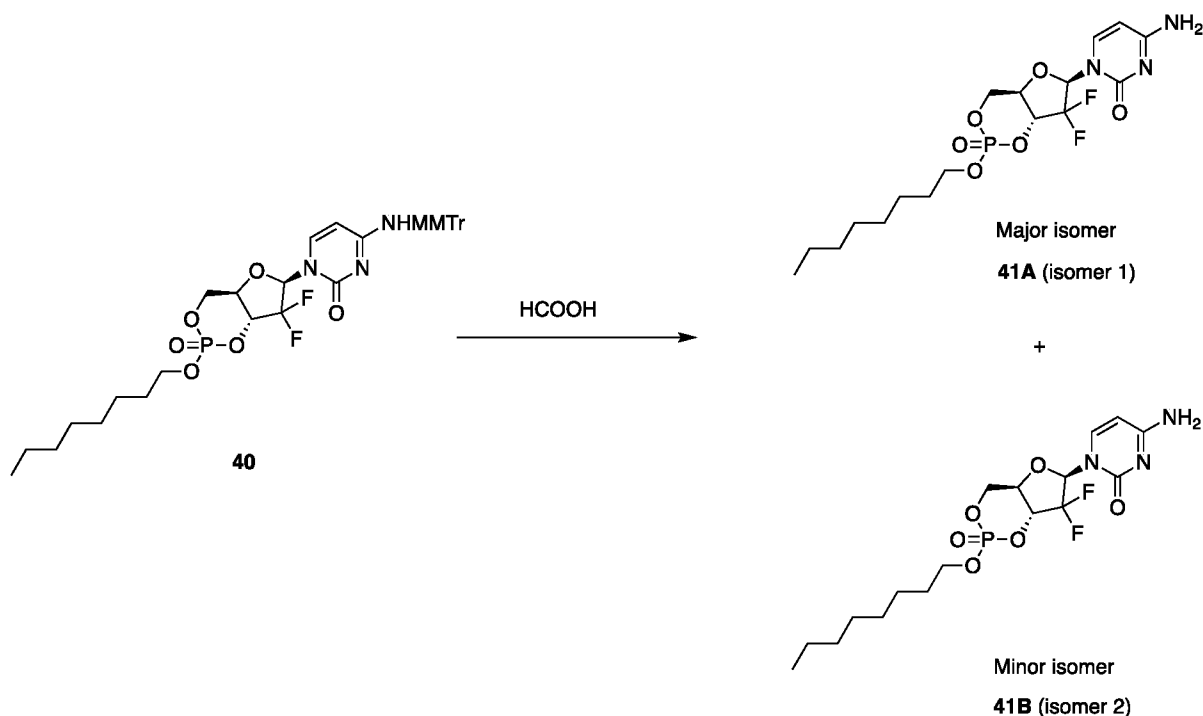
Ex. No.	Compound No.	Structure	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
22	33		768.6
23	34		796.7



Ex. No.	Compound No.	Structure	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
24	35		824.8
25	36		852.8

**Example 26: Synthesis of isomers 1-[(4aR,6R,7aR)-7,7-difluoro-2-octoxy-2-oxo-4,4a,6,7a-tetrahydrofuro[3,2-d][1,3,2]dioxaphosphinin-6-yl]-4-amino-pyrimidin-2-one (Compound 41A) and (Compound 41B)**





**[00150]** 4-amino-1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]pyrimidin-2-one (20 g, 75.99 mmol, 1 *eq.*) was dissolved in pyridine (500 mL) and the mixture was cooled down to 0°C. TMSCl (49.53 g, 455.93 mmol, 6 *eq.*) was added and the mixture was stirred at 25°C for 12h. DMAP (9.28 g, 75.99 mmol, 1 *eq.*) and MMTTrCl (46.93 g, 151.98 mmol, 2 *eq.*) were added and the reaction mixture was stirred at 50°C for 16h. The reaction mixture was quenched with cold sat.aq.NaHCO<sub>3</sub> slowly and extracted with EtOAc (500 mL x 3). The organic layer was washed with brine (200 ml), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuum. The crude product was combined with toluene (100 mL) and then concentrated again to yield 1-[(2R,4R,5R)-3,3-difluoro-4-trimethylsilyloxy-5-(trimethylsilyloxymethyl)tetrahydrofuran-2-yl]-4-[[[4-methoxyphenyl)-diphenyl-methyl]amino]pyrimidin-2-one (38) (103 g, crude, two parallel batches) as a yellow oil, which was used into the next step without further purification.

**[00151]** To a solution of 1-[(2R,4R,5R)-3,3-difluoro-4-trimethylsilyloxy-5-(trimethylsilyloxymethyl)tetrahydrofuran-2-yl]-4-[[[4-methoxyphenyl)-diphenyl-methyl]amino]pyrimidin-2-one (38) (103 g, 151.49 mmol, 1 *eq.*) in MeOH (1 L) was added NH<sub>4</sub>F (28.05 g, 757.47 mmol, 5 *eq.*). The reaction mixture was stirred at 70°C for 1hr and then concentrated in vacuum. The residue was purified by column chromatography to yield 1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-4-[[[4-methoxyphenyl)-diphenylmethyl]amino]pyrimidin-2-one (39) (56 g, 69%) as a white solid. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26-7.21 (m, 8H), 7.19-7.12 (m, 4H), 7.10-7.12 (m, 2H),

7.02-6.75 (m, 2H), 6.01 (s, 1H), 5.07 (m, 1H), 4.38-4.36 (m, 1H), 3.86-3.81 (m, 2H), 3.72 (s, 3H).

**[00152]** To a mixture of 1-[(2R,4R,5R)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl]-4-[[[(4-methoxyphenyl)-diphenyl-methyl]amino]pyrimidin-2-one (39) (14.5 g, 27.08 mmol, 1 *eq.*) in DCM (300 mL) was added Et<sub>3</sub>N (19.18 g, 189.53 mmol, 7 *eq.*). The reaction was cooled to -20°C, and then 1-dichlorophosphoryloxyoctane (Int-K) (13.38 g, 54.15 mmol, 2 *eq.*) was added dropwise over 10 min. The mixture was stirred at -20°C for 0.5h, and then 1-methylimidazole (8.89 g, 108.30 mmol, 4 *eq.*) was added dropwise over 15 min. The mixture was stirred at -15°C for 1h and then slowly warmed to 25°C and stirred for 12h. The mixture was concentrated and the residue was purified by column chromatography to yield 1-[(4aR,6R,7aR)-7,7-difluoro-2-octoxy-2-oxo-4,4a,6,7a-tetrahydrofuro[3,2-d][1,3,2]dioxaphosphinin-6-yl]-4-[[[(4-methoxyphenyl)-diphenyl-methyl]amino]pyrimidin-2-one (40) (7.8 g, 41%) as a white solid. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33-7.25 (m, 10H), 7.20-7.18 (m, 2H), 7.12-7.10 (m, 1H), 6.84-6.82 (m, 3H), 5.12-5.09 (m, 1H), 4.60-4.57 (m, 2H), 4.18-4.10 (m, 4H), 3.80 (s, 3H), 1.77-1.68 (m, 2H), 1.26-1.23 (m, 10H), 0.88-0.84 (m, 3H).

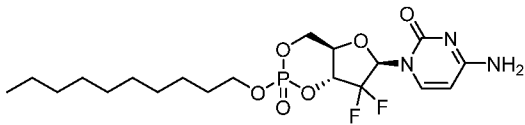
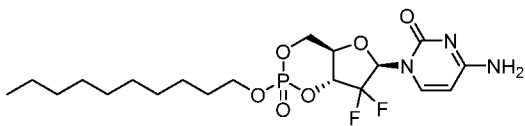
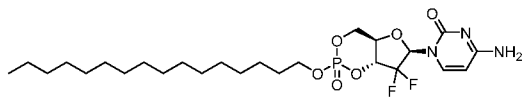
**[00153]** To a solution of 1-[(4aR,6R,7aR)-7,7-difluoro-2-octoxy-2-oxo-4,4a,6,7a-tetrahydrofuro[3,2-d][1,3,2]dioxaphosphinin-6-yl]-4-[[[(4-methoxyphenyl)-diphenyl-methyl]amino]pyrimidin-2-one (40) (7.8 g, 10.99 mmol, 1 *eq.*) in water (20 mL) was added HCOOH (80 mL) and the mixture was stirred at 25°C for 12 hrs. The mixture was concentrated in vacuum and the residue was purified by prep-HPLC to yield two stereoisomers (two stereoisomers at phosphorous) of 1-[(4aR,6R,7aR)-7,7-difluoro-2-octoxy-2-oxo-4,4a,6,7a-tetrahydrofuro[3,2-d][1,3,2]dioxaphosphinin-6-yl]-4-aminopyrimidin-2-one: major isomer (41A) (1.91 g, 39%) and minor isomer (41B) (1.55 g, 31%) as white solids.

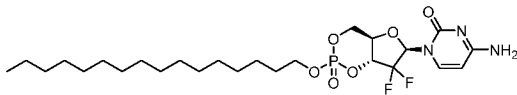
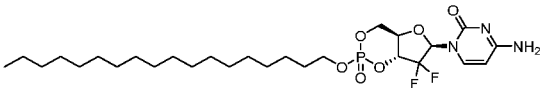
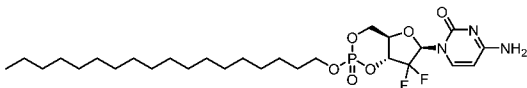
The stereochemistry at phosphorous was not assigned for Compounds 41A and 41B.

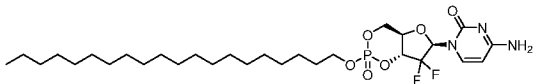
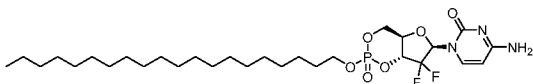
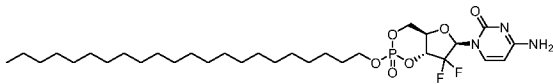
Major isomer (41A): <sup>1</sup>H-NMR (400 MHz, DMSO) δ 7.80 (s, 1H), 7.52 (d, 2H, *J* = 11.6 Hz), 6.45 (s, 1H), 5.81 (d, 1H, *J* = 7.6 Hz), 4.95 (s, 1H), 4.75-4.71 (m, 2H), 4.28 (s, 1H), 4.15-4.09 (s, 2H), 1.76-1.66 (m, 2H), 1.37-1.35 (m, 2H), 1.27-1.26 (m, 8H), 0.87-0.84 (m, 3H). QC (ESI+): 438.16 (M+H). Minor isomer (41B): <sup>1</sup>H-NMR (400 MHz, DMSO) δ 7.80 (s, 1H), 7.53 (d, 2H, *J* = 6.8 Hz), 6.45 (s, 1H), 5.80 (d, 1H, *J* = 8.0 Hz), 5.30 (s, 1H), 4.76-4.64 (m, 2H), 4.38 (s, 1H), 4.13-4.08 (s, 2H), 1.65-1.60 (m, 2H), 1.32-1.26 (m, 10H), 0.88-0.85 (m, 3H). QC (ESI+): 438.16 (M+H).

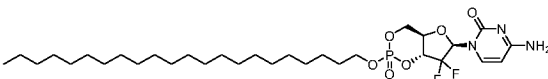
**[00154] Examples 27-31:** The following compounds (**Compounds 42A, 42B, 43A, 43B, 44A, 44B, 45A, 45B, 46A, and 46B**) were synthesized in a similar manner as described in

Example 26. As in Example 26, the stereochemistry at phosphorous was not assigned for the compounds of Examples 27-31.

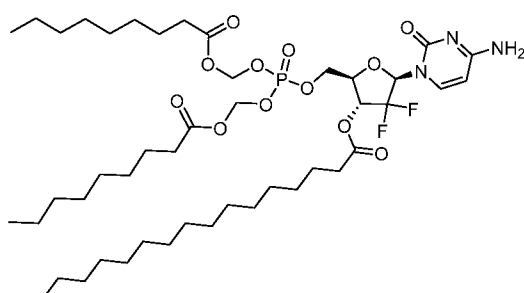
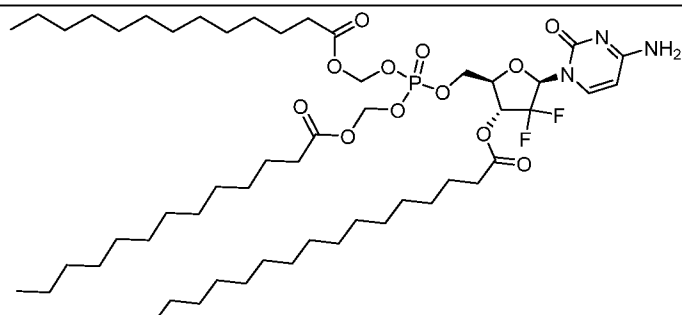
Ex. No.	Compd. No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
27	42A (isomer 1)		4-amino-1- ((4aR,6R,7aR)-2- (decyloxy)-7,7-difluoro- 2-oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	466.2
	42B (isomer 2)		4-amino-1- ((4aR,6R,7aR)-2- (decyloxy)-7,7-difluoro- 2-oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	466.2
28	43A (isomer 1)		4-amino-1- ((4aR,6R,7aR)-7,7- difluoro-2- (hexadecyloxy)-2- oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	550.3

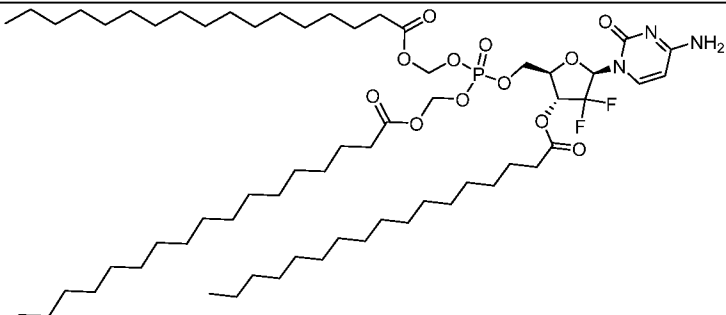
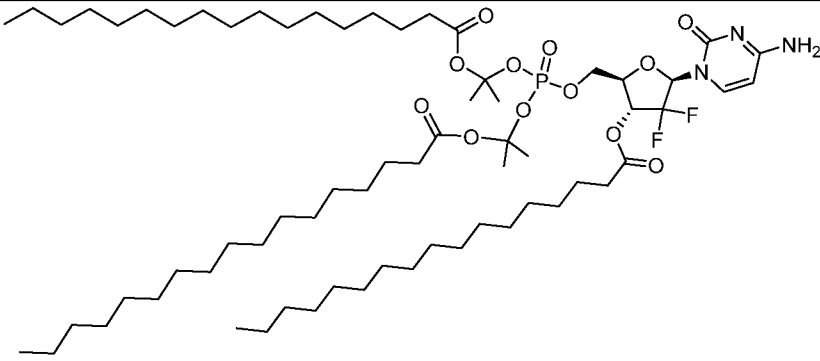
Ex. No.	Compd. No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
	43b (isomer 2)		4-amino-1- ((4aR,6R,7aR)-7,7- difluoro-2- (hexadecyloxy)-2- oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	550.3
29	44A (isomer 1)		4-amino-1- ((4aR,6R,7aR)-7,7- difluoro-2- (octadecyloxy)-2- oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	578.3
	44B (isomer 2)		4-amino-1- ((4aR,6R,7aR)-7,7- difluoro-2- (octadecyloxy)-2- oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	578.3

Ex. No.	Compd. No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
30	45A (isomer 1)		4-amino-1- ((4aR,6R,7aR)-7,7- difluoro-2-(icosyloxy)- 2-oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	606.3
	45B (isomer 2)		4-amino-1- ((4aR,6R,7aR)-7,7- difluoro-2-(icosyloxy)- 2-oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	606.3
31	46A (isomer 1)		4-amino-1- ((4aR,6R,7aR)-2- (docosyloxy)-7,7- difluoro-2- oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	634.4

Ex. No.	Compd. No.	Structure	Chemical Name	LC-MS (ESI) $m/z$ (M+H) <sup>+</sup>
	46B (isomer 2)		4-amino-1- ((4aR,6R,7aR)-2- (docosyloxy)-7,7- difluoro-2- oxidotetrahydro-4H- furo[3,2- d][1,3,2]dioxaphosphini n-6-yl)pyrimidin-2(1H)- one	634.4

**[00155] Examples 32-35:** The following compounds are synthesized in a similar manner as described in Example 3.

Ex. No.	Structure
32	
33	

Ex. No.	Structure
34	
35	

### Cellular Pharmacology

**[00156]** Compounds are tested for their ability to impair cancer cell proliferation and/or induce cell death. For cellular proliferation studies, cultured cells are treated with the test compound for 24-120 hours. After compound treatment, cell proliferation is assessed by using methods including, but not limited to, Cell-Titer-Glo® (Promega), Alamar Blue, LIVE/DEAD® (ThermoFisher), BrdU incorporation, and live-cell imaging.

**[00157]** The cancer lines used include, but are not limited to, PANC-1, MiaPaCa-2, BxPC-3 (pancreatic cancer), RT112 (bladder cancer), MCF-7 (breast cancer), and A549 (non-small cell lung cancer). Gemcitabine Hydrochloride serves as a control for activity.

**[00158]** Protocol for the Cellular Proliferation assay in BxPC-3 Cells

**[00159]** BxPC-3 (pancreatic adenocarcinoma) cell line was purchased from the American Type Culture Collection (Catalog# CRL-1687) and grown in RPMI-1640 medium (e.g. Corning #10-040-CV) with 10% Heat Inactivated Fetal Calf Serum at 37°C and 5% CO<sub>2</sub> (as recommended by the ATCC).

**[00160]** Cultures were grown in 175 mm<sup>2</sup> plates to 80% confluence, and cells were trypsinized to a single-cell suspension. Cells were then resuspended in growth medium to a density of 25,00 cells/ml. They were then plated into 96-well assay plates (Corning #3917)



in a volume of 100  $\mu$ l/well (2,500 cells/well). Cells were allowed to adhere to plates for 24h at 37° C and 5% CO<sub>2</sub>). Compounds were then added to the wells using an 11-fold serial dilution scheme (over 9 dilutions, generally ranging from 30  $\mu$ M-30 pM), and the cells were incubated for an additional 120 hours. After 120 h, 90  $\mu$ l of Cell-Titer Glo reagent (Promega #G7572) was added, and the plates were read using a luminescence counter (e.g., BioTek Synergy HTX at 100 ms read time).

**[00161]** Potency determination were performed by 4-parameter fit of the dose vs. luminescence data using XLFit software (IDBS) with a one site dose response model (Model 205; fit =  $(A + ((B-A)/(1+((C/x)^D))))$ ). The EC<sub>50</sub> was generally expressed as the inflection point (C parameter) for the fit when the upper and lower portions of the response curve were well-defined. In cases where full inhibition of cell growth was not observed at the highest concentration used, EC<sub>50</sub> was reported as the concentration that resulted in 50% loss of Cell-Titer-Glo signal (compared to untreated control).

**[00162]** Potency of compounds in BxPC-3 cells is shown in Table 1:

Table 1

Compound	EC <sub>50</sub>
Gemcitabine Hydrochloride	+++
1	+++
2	++++
3	++++
16	++
17	+
18	++
19	++
20	+
21	+
22	+
23	+
24	+
25	+
28	++++
29	++++
30	++++
31	++++

32	++++
33	++++
34	++++
35	++++
36	++++
42A	++++
43A	+++
44A	+++
45A	++
46A	+

++++ =  $EC_{50} < 1 \text{ nM}$ ; +++ =  $1 \text{ nM} \leq EC_{50} < 100 \text{ nM}$ ; ++ =  $100 \text{ nM} \leq EC_{50} < 1 \text{ }\mu\text{M}$ ;  
 + =  $1 \text{ }\mu\text{M} \leq EC_{50} < 25 \text{ }\mu\text{M}$

### Animal Pharmacology

**[00163]** Compounds are tested to impair tumor growth in rodents using several “xenograft” model systems. Initially, immune-deficient (e.g. SCID) mice are implanted subcutaneously with tumor cells (using either tumor cell lines or human patient-derived tumor tissue) until tumors are palpable ( $\sim 100\text{-}200 \text{ mm}^3$ ). Test article is administered intravenously at varying doses and schedules, and anti-tumor effect is determined by physical measurement of tumors using standard methods (i.e., caliper measurements). Additional measures of anti-tumor effect include time of survival, gain/loss of body weight, non-invasive visualization of tumor mass (i.e., ultrasound, positron emission tomography, optical imaging), or direct visualization of tumor growth/metastasis by necropsy.

**[00164]** In addition to the aforementioned xenograft models, a variety of genetically-engineered mouse models (GEMM) of cancer are employed. In these models, GEMM mice are allowed to spontaneously grow tumors, at which time test article administration is initiated. Determination of anti-tumor effect is implemented by caliper measurement of lesions, time of survival, gain/loss of body weight, non-invasive visualization of tumor mass (i.e., ultrasound, positron emission tomography, optical imaging), or direct visualization of tumor growth/metastasis by necropsy.

**[00165]** In both types of models, gemcitabine hydrochloride is used as a comparator. Additionally, other common anti-neoplastic compounds (e.g., paclitaxel, 5-fluorouracil, erlotinib etc.) are used as control compounds depending on the tumor type being studied.

### Additional Measurements

**[00166]** In addition to the functional assays described above, a series of cell- and animal-based experiments are performed to determine the uptake (i.e., in tumor vs. normal tissue) and catabolism/metabolism of test compounds. For instance, test compounds are applied to cells growing in culture for varying amounts of time. Subsequently, cells (and media) are collected and analyzed to determine the concentration of parent compound and metabolites.

**[00167]** For example, compounds were evaluated for the liberation of gemcitabine in both human liver microsomes and human hepatocytes.

**[00168]** Protocol for metabolic stability in human liver microsomes:

[Compound] = 1  $\mu$ M

[LM] = 0.5 mg/mL

[NADPH] = 0 or 1 mM

Buffer = 100 mM Potassium Phosphate, pH 7.4

Time = 0, 15, 30, and 60 min

Temperature = 37°C

**[00169]** Liver microsomes tissue fractions were used for in vitro assessment of metabolic stability of various compounds by cytochrome P450 (CYP450) mediated phase I oxidation, and metabolism through other pathways. Human liver microsomes tissue fractions were obtained from Corning Gentest.

**[00170]** The assay is carried out in 96-well microtiter plates. Compounds were incubated at 37°C in the presence of human liver microsomes. Reaction mixtures (25  $\mu$ L) contain a final concentration of 1  $\mu$ M test compound, 0.5 mg/mL liver microsomes protein, and 1 mM NADPH in 100 mM potassium phosphate, pH 7.4 buffer. At each of the time points (0, 15, 30, and 60 minutes), 150  $\mu$ L of quench solution (100% acetonitrile with 0.1% formic acid) with internal standard bucefin was transferred to each well. Verapamil was included as a positive control to verify assay performance. The extent of metabolism is determined as the formation of the drug gemcitabine. Plates were sealed and centrifuged at 4°C for 15 minutes at 4000 rpm. The supernatant was transferred to fresh plates for LC/MS/MS analysis.

**[00171]** All samples were analyzed on LC/MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Analytical samples were separated using a Waters Atlantis T3 dC18 reverse phase HPLC column (50 mm x 2.1 mm, 3  $\mu$ m) at a flow rate of 0.3 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in 100% acetonitrile (solvent B).

**[00172]** Results:

Compound	Relative Peak Area Ratio (gemcitabine/internal standard)			
	0 min	15 min	30 min	60 min
1	7.7	15.1	12.7	18.1
2	10.0	17.8	17.4	47.5
3	0.0	0.0	0.0	8.3
21	0.0	0.0	0.0	1.9
24	0.0	0.0	0.0	0.0
28	0.0	14.8	18.7	58.1
30	0.0	4.9	8.2	25.5
31	0.0	1.6	6.5	23.7
33	0.0	21.1	19.7	26.0
35	0.0	0.0	1.6	6.3
42A	0.0	0.0	4.2	7.4
43A	0.0	0.0	0.0	9.7

**[00173]** Protocol for metabolic stability in human hepatocytes:

[Compound] = 1  $\mu$ M

[Hepatocytes] = 0.5 million cells/mL

Time = 0, 60, 120, and 180 min

Temperature = 37°C

**[00174]** Metabolic stability of testing compound was evaluated using human hepatocytes to determine the formation of gemcitabine. Human LiverPool™ 20-donor cryopreserved hepatocytes are obtained from BioIVT.

**[00175]** Cryopreserved hepatocytes were removed from the liquid nitrogen tank and thawed in a 37°C water bath. As soon as the cells pull away from the vial wall, they were decanted into 48 mL of warm HT medium. Cells were centrifuged for four minutes at 420 rpm (50 g). After removing the supernatant, pellet was re-suspended in warm DMEM medium. Cell density was counted by a hemacytometer.

**[00176]** The assay was carried out in 96-well microtiter plates. Compounds were incubated for 0, 60, 120, and 180 minutes at 37°C with hepatocytes. Reaction mixtures (50  $\mu$ L) contained a final concentration of 1  $\mu$ M test compound, 0.5 million cells/mL hepatocytes in the DMEM medium. At each of the time points (0, 1, 2, and 3 hours), 150  $\mu$ L of quench solution (100% acetonitrile with 0.1% formic acid) with internal standard bucin was transferred to each well. Midazolam was included as a positive control to verify assay performance. The extent of metabolism was determined as the formation of the drug

gemcitabine. Plates were sealed and centrifuged at 4°C for 15 minutes at 4000 rpm. The supernatant was transferred to fresh plates for LC/MS/MS analysis.

**[00177]** All samples were analyzed on LC/MS/MS using an AB Sciex API 4000 instrument, coupled to a Shimadzu LC-20AD LC Pump system. Analytical samples were separated using a Waters Atlantis T3 dC18 reverse phase HPLC column (50 mm x 2.1 mm, 3  $\mu$ m) at a flow rate of 0.3 mL/min. The mobile phase consisted of 0.1% formic acid in water (solvent A) and 0.1% formic acid in 100% acetonitrile (solvent B).

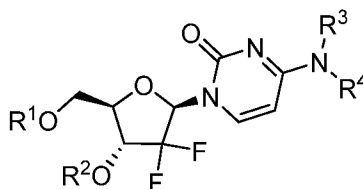
Compound	Relative Peak Area Ratio (gemcitabine/internal standard)			
	0 min	15 min	30 min	60 min
1	0.0	0.0	0.0	2.4
2	0.0	55.6	58.8	49.2
3	0.0	54.7	55.8	47.1
21	0.0	0.0	0.0	0.0
24	0.0	0.0	0.0	0.0
28	0.0	41.4	54.8	42.3
30	0.0	0.0	0.0	6.4
31	0.0	0.0	7.5	6.3
33	0.0	18.3	24.2	23.8
35	0.0	0.0	0.0	0.0
42A	0.0	0.0	3.7	8.6
43A	0.0	0.0	0.0	0.0

**[00178]** Other experiments are performed in tumor-bearing animals to determine the distribution of test article as well as active (and inactive) metabolites in blood, normal tissue, and tumor.

## CLAIMS

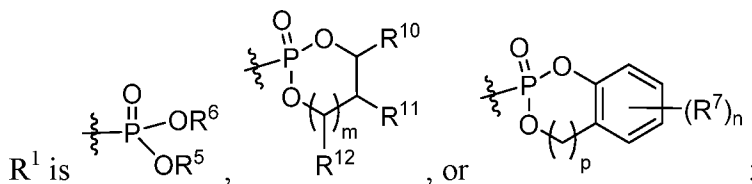
What is claimed is:

1. A compound having the structure of Formula (I):



Formula (I);

wherein:



$R^2$  is  $-C(O)R^8$ ;

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^5$  is H,  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-6}$ alkyl- $OC(O)C_{1-22}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^6$  is  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-6}$ alkyl- $OC(O)C_{1-22}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

each  $R^7$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy;

$R^8$  is  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^9$  is  $C_{1-12}$ alkyl;

$R^{10}$  and  $R^{11}$  are each independently H or  $C_{1-12}$ alkyl; or  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the

5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ ;

$R^{12}$  is H or  $C_{1-12}$ alkyl;

each  $R^{13}$  is independently selected from  $C_{1-12}$ alkyl;

each  $R^{14}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ ;

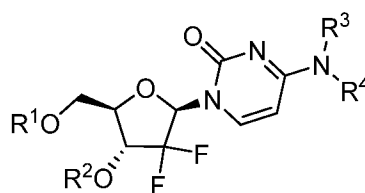
m is 0 or 1;

n is 0, 1, 2, 3, or 4; and

p is 0 or 1;

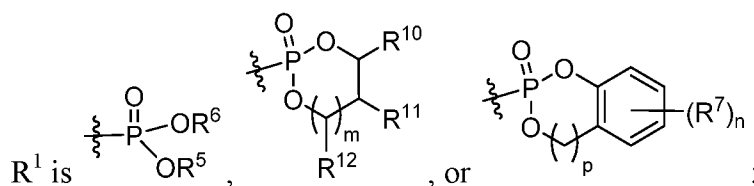
or a pharmaceutically acceptable salt thereof.

2. A compound having the structure of Formula (I'):



Formula (I');

wherein:



$R^2$  is  $-C(O)R^8$ ;

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^5$  is H,  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

$R^6$  is  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{3-8}$ cycloalkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{14}$ ;

each  $R^7$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy;

R<sup>8</sup> is C<sub>3-22</sub>alkyl, C<sub>3-22</sub>alkenyl, C<sub>3-22</sub>alkynyl, C<sub>3-22</sub>haloalkyl, C<sub>3-8</sub>cycloalkyl, C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl, wherein C<sub>6-10</sub>aryl, -C<sub>1-8</sub>alkyl-C<sub>6-10</sub>aryl, C<sub>2-9</sub>heteroaryl, or -C<sub>1-8</sub>alkyl-C<sub>2-9</sub>heteroaryl are optionally substituted with 1, 2, 3, or 4 R<sup>14</sup>;

R<sup>9</sup> is C<sub>1-12</sub>alkyl;

R<sup>10</sup> and R<sup>11</sup> are each independently H or C<sub>1-12</sub>alkyl; or R<sup>10</sup> and R<sup>11</sup> form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two R<sup>13</sup>;

R<sup>12</sup> is H or C<sub>1-12</sub>alkyl;

each R<sup>13</sup> is independently selected from C<sub>1-12</sub>alkyl;

each R<sup>14</sup> is independently selected from halogen, C<sub>1-8</sub>alkyl, C<sub>1-8</sub>haloalkyl, C<sub>1-8</sub>alkoxy, and -C(O)R<sup>13</sup>;

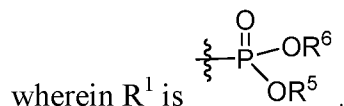
m is 0 or 1;

n is 0, 1, 2, 3, or 4; and

p is 0 or 1;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof,



4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-16</sub>alkyl.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>3-12</sub>alkyl.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-14</sub>alkyl.

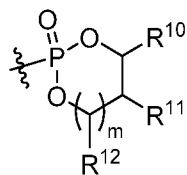
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is C<sub>6-10</sub>alkyl.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-16</sub>alkyl.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R<sup>5</sup> is -C<sub>1-4</sub>alkyl-OC(O)C<sub>1-12</sub>alkyl.



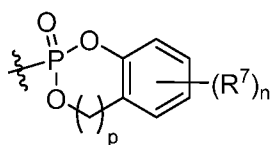
10. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-C_{1-4}\text{alkyl-OC(O)C}_{1-8}\text{alkyl}$ .
11. The compound of claim 10, or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-C_{1-2}\text{alkyl-OC(O)C}_{1-6}\text{alkyl}$ .
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is  $-\text{CH}_2-\text{OC(O)C}(\text{CH}_3)_3$ .
13. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein  $R^5$  is H.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $C_{3-16}\text{alkyl}$ .
15. The compound of any one of claims 1-14, or pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $C_{3-12}\text{alkyl}$ .
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $C_{6-10}\text{alkyl}$ .
17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-4}\text{alkyl-OC(O)C}_{1-16}\text{alkyl}$ .
18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-4}\text{alkyl-OC(O)C}_{1-12}\text{alkyl}$ .
19. The compound of any one of claims 1-18, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-4}\text{alkyl-OC(O)C}_{1-8}\text{alkyl}$ .
20. The compound of claim 19, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-C_{1-2}\text{alkyl-OC(O)C}_{1-6}\text{alkyl}$ .
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is  $-\text{CH}_2-\text{OC(O)C}(\text{CH}_3)_3$ .
22. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof,



wherein  $R^1$  is

23. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein  $m$  is 0.
24. The compound of claim 22, or a pharmaceutically acceptable salt thereof, wherein  $m$  is 1.

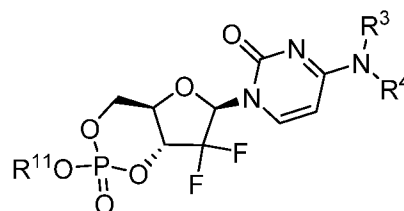
25. The compound of any one of claims 22-24, or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  is H.
26. The compound of any one of claims 22-24, or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  is  $C_{1-12}$ alkyl.
27. The compound of any one of claims 22-26, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is H.
28. The compound of any one of claims 22-24, or a pharmaceutically acceptable salt thereof, wherein  $R^{10}$  and  $R^{11}$  form a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocycloalkyl ring, wherein the 5- or 6-membered cycloalkyl ring or the 5- or 6-membered heterocycloalkyl ring are optionally substituted with one or two  $R^{13}$ .
29. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof,



wherein  $R^1$  is

30. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein each  $R^7$  is independently selected from  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl, and  $C_{1-8}$ alkoxy.
31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein each  $R^7$  is independently selected from  $C_{1-8}$ alkyl.
32. The compound of any one of claims 29-31, or a pharmaceutically acceptable salt thereof, wherein  $n$  is 1 or 2.
33. The compound of claim 29, or a pharmaceutically acceptable salt thereof, wherein  $n$  is 0.
34. The compound of any one of claims 29-33, or a pharmaceutically acceptable salt thereof, wherein  $p$  is 0.
35. The compound of any one of claims 29-33, or a pharmaceutically acceptable salt thereof, wherein  $p$  is 1.
36. The compound of any one of claims 1-35, or pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{3-15}$ alkyl.
37. The compound of any one of claims 1-35, or pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-18}$ alkyl.
38. The compound of any one of claims 1-37, or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $C_{6-12}$ alkyl.

39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof, wherein  $R^8$  is  $-(CH_2)_7CH_3$ .
40. A compound having the structure of Formula (II):



Formula (II);

wherein:

$R^3$  is H,  $-C(O)R^9$ , or  $-C(O)OR^9$ ;

$R^4$  is H;

$R^9$  is  $C_{1-8}$ alkyl;

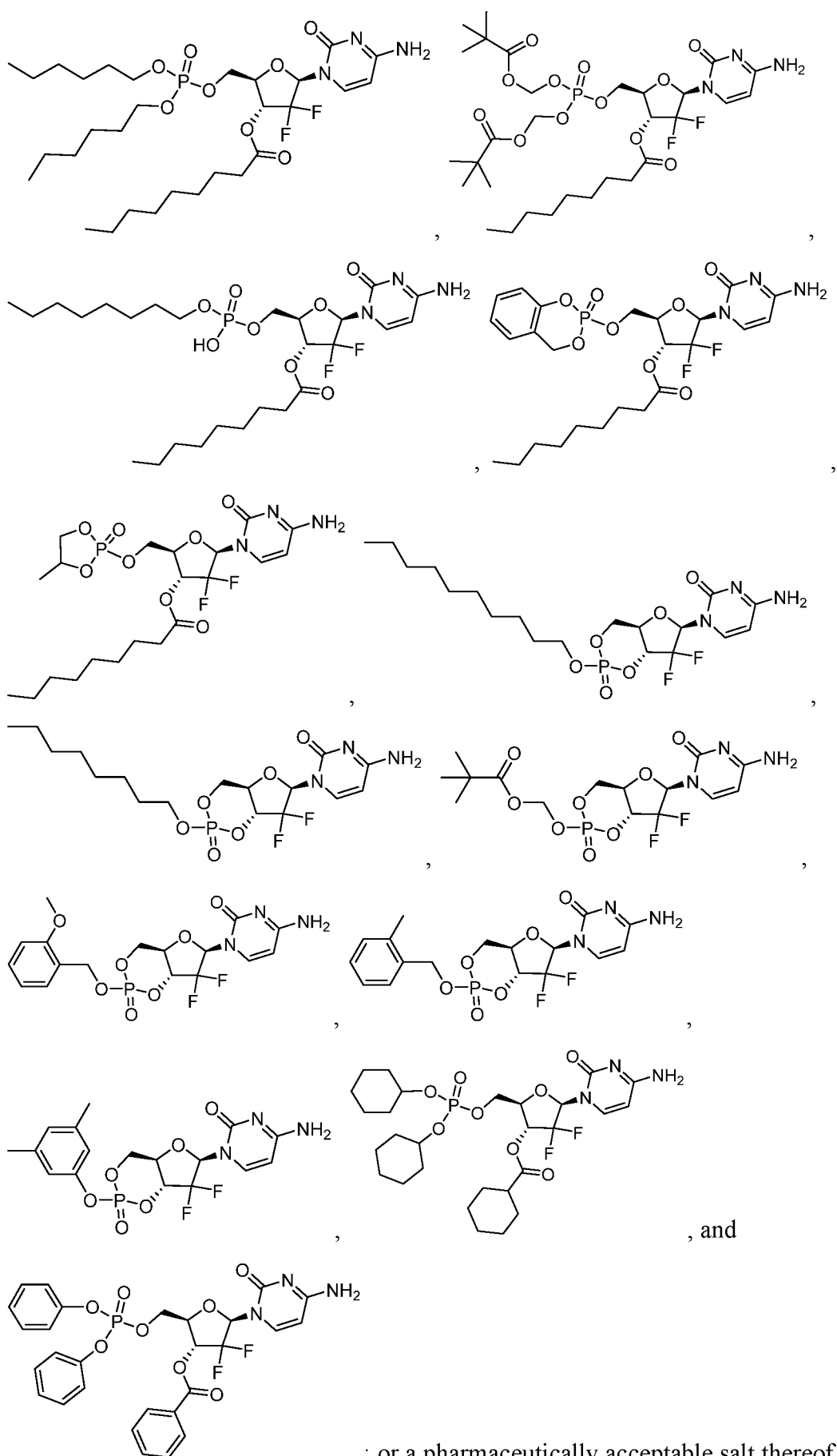
$R^{11}$  is  $C_{3-22}$ alkyl,  $C_{3-22}$ alkenyl,  $C_{3-22}$ alkynyl,  $C_{3-22}$ haloalkyl,  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl,  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl, wherein  $C_{6-10}$ aryl,  $-C_{1-8}$ alkyl- $C_{6-10}$ aryl,  $C_{2-9}$ heteroaryl, or  $-C_{1-8}$ alkyl- $C_{2-9}$ heteroaryl are optionally substituted with 1, 2, 3, or 4  $R^{12}$ ;

each  $R^{12}$  is independently selected from halogen,  $C_{1-8}$ alkyl,  $C_{1-8}$ haloalkyl,  $C_{1-8}$ alkoxy, and  $-C(O)R^{13}$ ; and

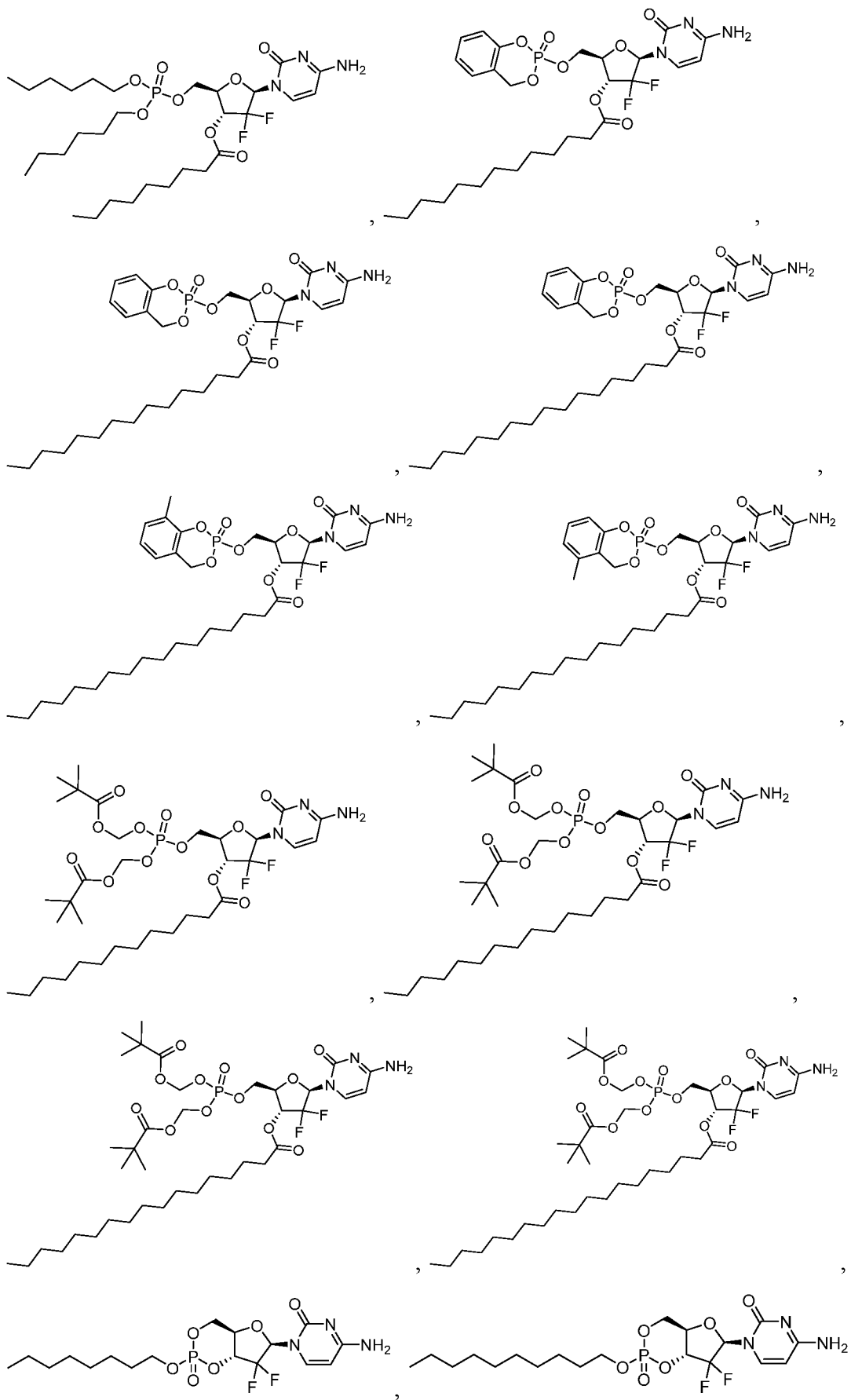
each  $R^{13}$  is independently selected from  $C_{1-12}$ alkyl;  
or a pharmaceutically acceptable salt thereof.

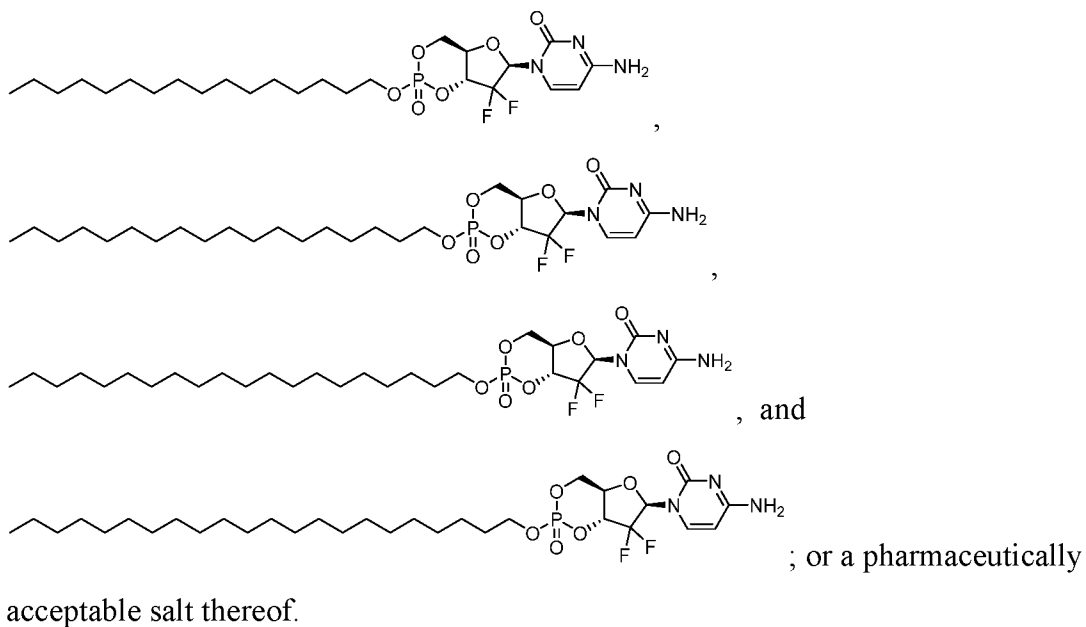
41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{3-15}$ alkyl.
42. The compound of claim 40 or claim 41, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-12}$ alkyl.
43. The compound of any one of claims 40-42, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{8-10}$ alkyl.
44. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{8-22}$ alkyl.
45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{16-22}$ alkyl.
46. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-4}$ alkyl- $OC(O)C_{1-8}$ alkyl.

47. The compound of claim 46, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-2}\text{alkyl}-OC(O)C_{1-6}\text{alkyl}$ .
48. The compound of claim 47, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2-OC(O)C(\text{CH}_3)_3$ .
49. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $C_{6-10}\text{aryl}$  optionally substituted with 1, 2, 3, or 4  $R^{12}$ .
50. The compound of claim 49, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl optionally substituted with 1, 2, or 3  $R^{12}$ .
51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl optionally substituted with 1, 2, or 3  $R^{12}$ , and each  $R^{12}$  is independently selected from  $C_{1-8}\text{alkyl}$ ,  $C_{1-8}\text{alkoxy}$ , and  $-C(O)R^{13}$ .
52. The compound of claim 51, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is phenyl optionally substituted with 1 or 2  $R^{12}$ , and each  $R^{12}$  is independently selected from  $C_{1-8}\text{alkyl}$  and  $C_{1-8}\text{alkoxy}$ .
53. The compound of claim 52, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-C_{1-8}\text{alkyl}-C_{6-10}\text{aryl}$  optionally substituted with 1, 2, 3, or 4  $R^{12}$ .
54. The compound of claim 53, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2\text{-phenyl}$  optionally substituted with 1, 2, or 3  $R^{12}$ .
55. The compound of claim 54, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2\text{-phenyl}$  optionally substituted with 1, 2, or 3  $R^{12}$ , and each  $R^{12}$  is independently selected from  $C_{1-8}\text{alkyl}$ ,  $C_{1-8}\text{alkoxy}$ , and  $-C(O)R^{13}$ .
56. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein  $R^{11}$  is  $-\text{CH}_2\text{-phenyl}$  optionally substituted with 1 or 2  $R^{12}$ , and each  $R^{12}$  is independently selected from  $C_{1-8}\text{alkyl}$  and  $C_{1-8}\text{alkoxy}$ .
57. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is H.
58. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)R^9$ .
59. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt thereof, wherein  $R^3$  is  $-C(O)OR^9$ .
60. A compound selected from:

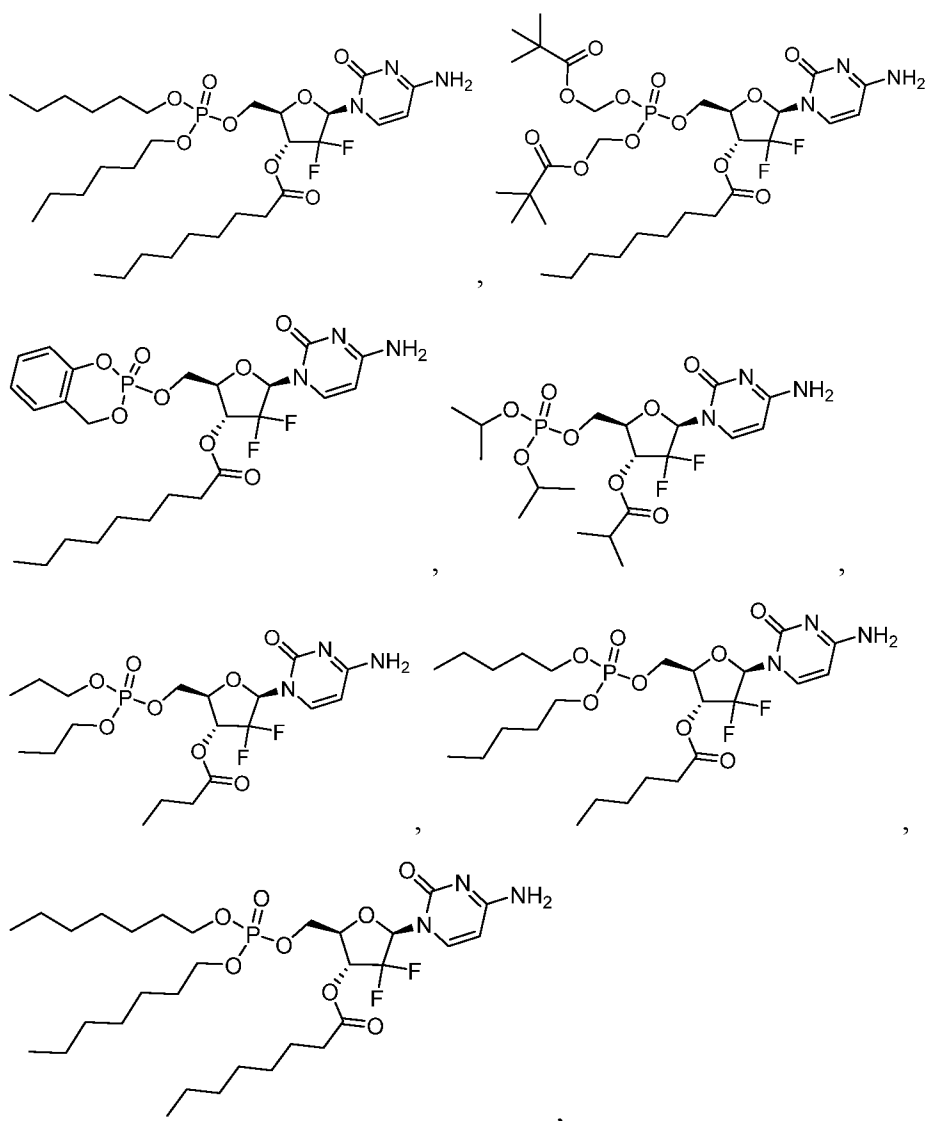


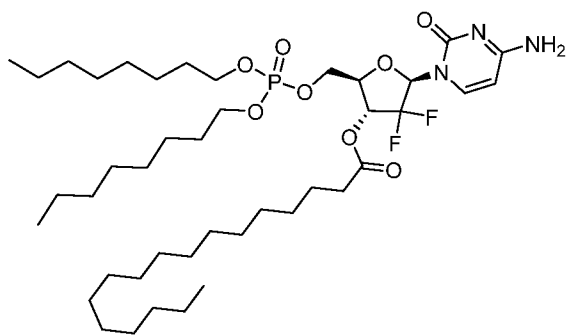
61. A compound selected from:



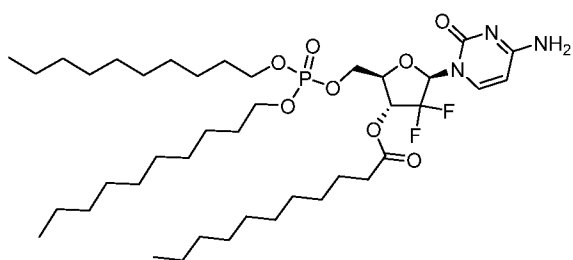


62. A compound selected from:

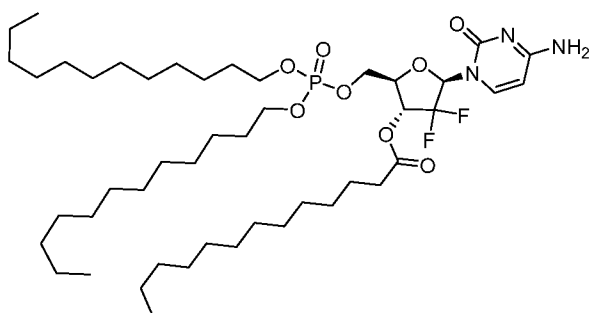




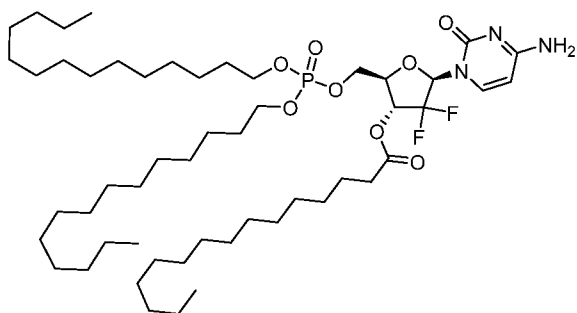
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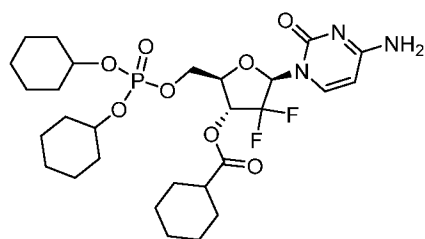
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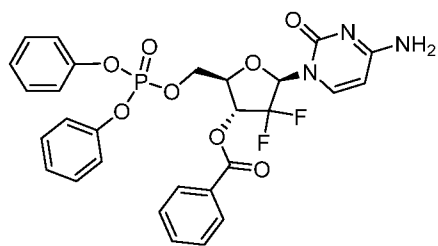
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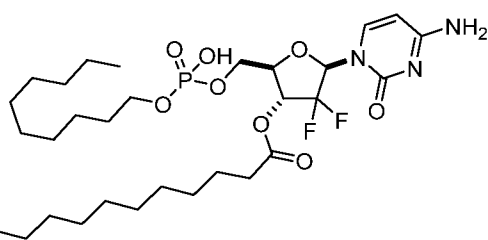
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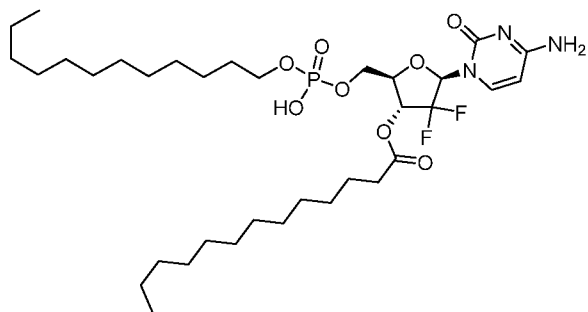


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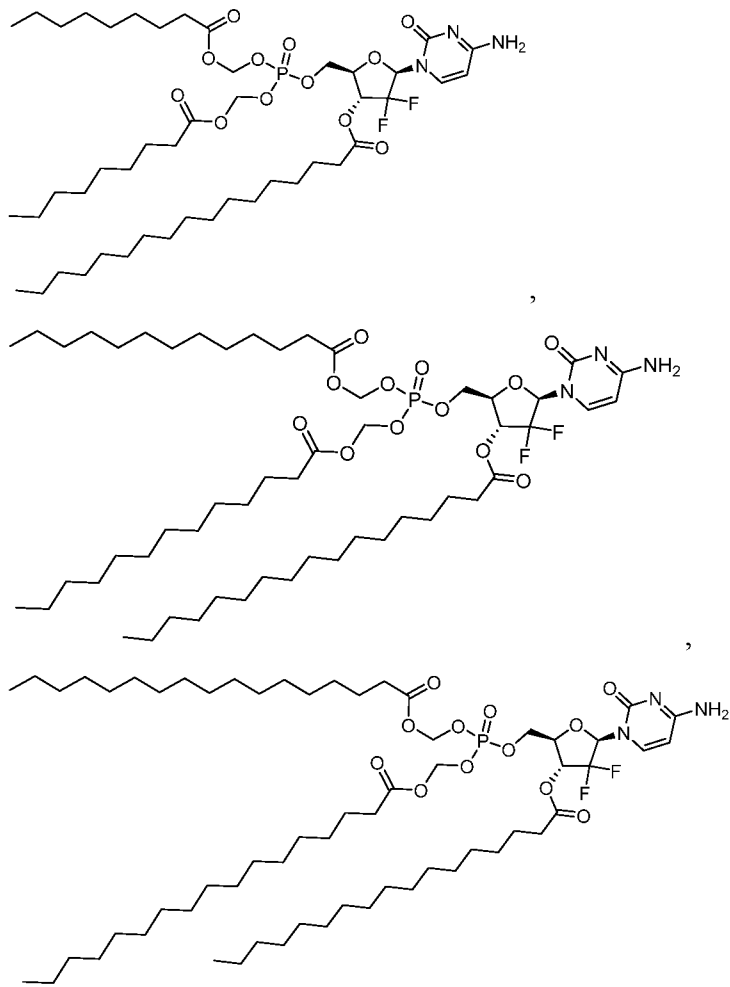


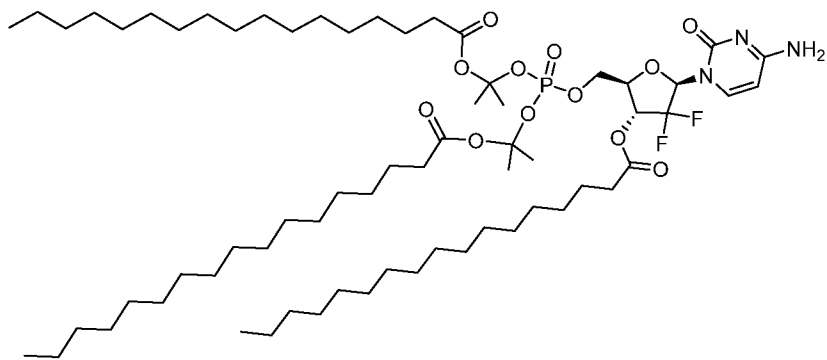


; or a pharmaceutically acceptable salt

thereof.

63. A compound selected from:





; or a

pharmaceutically acceptable salt thereof.

64. A pharmaceutical composition comprising a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
65. A method of treating cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof.
66. A method of treating an infectious disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/44389

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC(8) - A61K 31/5025, A61K 31/706 (2018.01)  
 CPC - A61K 2300/00, C07F 9/65583, C07F 9/65586

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)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/188943 A1 (IDENIX PHARMACEUTICALS LLC) 01 December 2016 (01.12.2016); pg. 30, ln 3	1-3, 13
A	WO 2016/068341 A1 (FUJIFILM CORPORATION) 06 May 2016 (06.05.2016); para [0244]	1-3, 13
A	US 2015/0105341 A1 (Alios BioPharma, Inc.) 16 April 2015 (16.04.2015); Figure 9(cont.)	1-3, 13

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"&" document member of the same patent family

Date of the actual completion of the international search

09 November 2018

Date of mailing of the international search report

**29 NOV 2018**

Name and mailing address of the ISA/US

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/44389

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-7, 14-16, 19-21, 25-28, 32, 34-39, 43, 57-59 and 64-66  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3 and 13

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-3, 8-13, 17-18, 22-24, 29-31, 33, 60-61(in part) and 62-63, directed to a compound of claim 1, a compound of formula I/I'. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of formula I wherein R1 is the first structure listed; R2 is C(O)R8; R3 is H; R4 is H; R5 is H; R6 is C3 alkyl. It is believed that claims 1-3 and 13 reads on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1 a compound of formula I wherein R1 is the first structure listed; R2 is C(O)R8; R3 is H; R4 is H; R5 is C3 alkyl; R6 is C3 alkyl (i.e., claims 1-3).

Group II+: Claims 40-42, 44-56, and 60-61(in part), directed to a compound of claim 40, a compound of formula II. The compound of claim 40 may be searched, for example, to the extent that it encompasses the first species of claim 40, represented by a compound according to Formula II wherein R3 is H; R4 is H and R11 is C3 alkyl; for payment of additional fee and election as such. It is believed that claims 40-41 read on this first named invention of Group II+. Applicant is invited to elect additional compounds of claim 40, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Another exemplary election would be a compound of claim 40, represented by a compound according to Formula II wherein R3 is H; R4 is H and R11 is C6 alkyl (i.e., claims 40-42).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

**Special Technical Features:**

Group I+ includes the technical feature of a unique compound of claim 1, formula I/I', which is not required by any other invention of Group I+ or II+.

Group II+ includes the technical feature of a unique compound of claim 40, formula II, which is not required by any other invention of Group I+ or II+.

**Common technical features:**

The inventions of Groups II+ share the technical feature of a compound of Formula (II).

The inventions of Groups I+ and II+ share the technical feature of a compound of comprising the core structure of Formula I and II.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by WO 2016/188943 A1 to IDENIX PHARMACEUTICALS LLC (hereinafter Idenix). Idenix discloses a compound of formula II (comprising the core structure of formula I and II) wherein R3 is H; R4 is H and R11 is C3 alkyl (pg. 30, ln 3: 2nd compound listed).

The inventions of Groups I+ share the technical feature of a compound of Formula (I).

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over WO 2016/068341 A1 to FUJIFILM CORPORATION (hereinafter Fujifilm). Fujifilm discloses a compound of formula I wherein R1 is the first structure listed; R3 is H; R4 is H; R5 is C1alkyl-OC(O)C4 alkyl; R6 is C1alkyl-OC(O)C4 alkyl (original-para [0244]: 4th compound listed) and further discloses precursor compounds comprising hydroxyl protecting groups bound in the position of substituent R2 (original para [0244]: 3rd compound listed (BOC)), but does not disclose wherein R2 is C(O)R8 and R8 is C6 aryl. However, Fujifilm further discloses similar nucleotide drug compounds prepared from compounds comprising similar hydroxy protecting groups (Bz) wherein R2 is C(O)R8 and R8 is C6 aryl (original-para [0228]: 2nd compound listed). It would have been obvious to one with skill in the art to prepare the compound disclosed by Fujifilm, utilizing similar precursor compounds utilizing similar routine hydroxy protecting groups, such as Bz instead of BOC (ie wherein R2 is C(O)R8 and R8 is C6 aryl), in order to optimize the synthetic scheme.

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+ or II+. The inventions of Group I+ and II+ thus lack unity under PCT Rule 13.

Note: Claims 4-7, 14-16, 19-21, 25-28, 32, 34-39, 43, 57-59 and 64-66 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).