# LIGAND-2'-MODIFIED NUCLEIC ACIDS, SYNTHESIS THEREOF AND INTERMEDIATE COMPOUNDS THEREOF

## CROSS-REFERENCE TO RELATED APPLICATION

**[0001]** This application claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application no. 62/894,071, filed August 30, 2019, the content of which is incorporated by reference herein in its entirety.

## TECHNICAL FIELD OF THE INVENTION

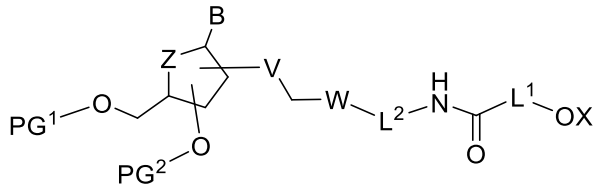
**[0002]** The present invention relates to method for synthesizing compounds useful as potent and stable RNA interference agents, derivatives thereof, and intermediates thereto.

## BACKGROUND OF THE INVENTION

**[0003]** Double-stranded RNA (dsRNA) agents possessing strand lengths of 25 to 35 nucleotides have been described as effective inhibitors of target gene expression in mammalian cells (Rossi et al., U.S. Patent Publication Nos. 2005/0244858 and 2005/0277610). dsRNA agents of such length are believed to be processed by the Dicer enzyme of the RNA interference (RNAi) pathway, leading such agents to be termed "Dicer substrate siRNA" ("DsiRNA") agents. Certain modified structures of DsiRNA agents were previously described (Rossi et al., U.S. Patent Publication No. 2007/0265220).

## SUMMARY

**[0003a]** In an aspect of the present disclosure, there is provided a method for preparing a compound of formula **D-a**:



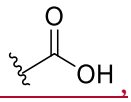
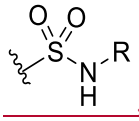
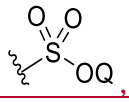
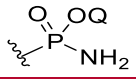
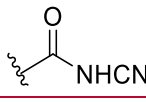
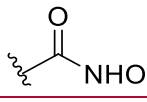
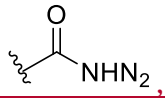
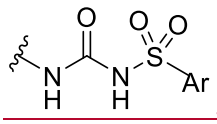
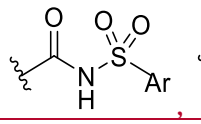
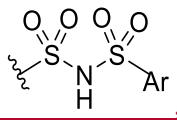
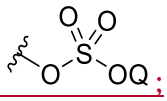

**D-a**

or a salt thereof, wherein:

$PG^1$ and $PG^2$ are independently hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

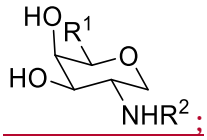
each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including , , , , , , , , , , and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols, and ;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

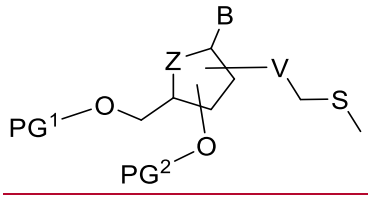
$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$;

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl; and

Z is $-CH_2-$, -O-, -S-, or -NR-,

comprising the steps of:

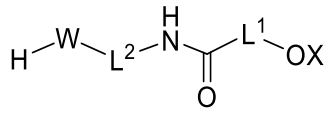
(a) providing a compound of formula **F-1-a**:




**F-1-a**

or a salt thereof, and

(b) reacting said fragment compound of formula **F-1-a** with a fragment compound of formula **F-6**:

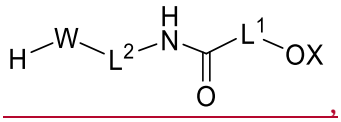



**F-6**

or a salt thereof,

to provide the compound of formula **D-a**.

**[0003b]** In another aspect of the present disclosure, there is provided a compound, wherein the compound is of formula **F-6:**

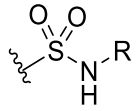
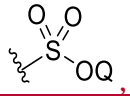
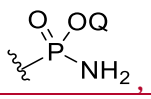
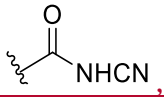
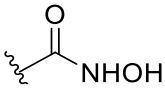
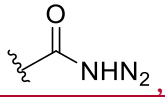
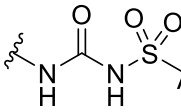
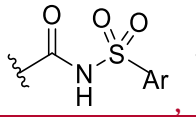
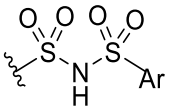
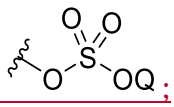



,

**F-6**

or a pharmaceutically acceptable salt thereof, wherein:

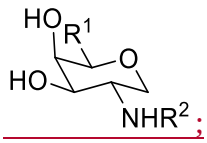
each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including , , , , , , , , , , and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

W is -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols, and ;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$; and

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl.

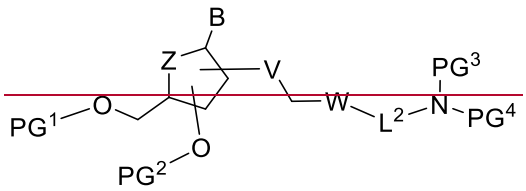
## DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

**[0004]** The methods and intermediates of the present disclosure are useful for preparing various analogues of compounds as described in, e.g. Brown et al., U.S. Patent Publication No. 2017/0305956, the entirety of which is herein incorporated by reference. The compounds provided herein are useful as pharmaceutical agents for the treatment of disease. In certain embodiments, a compound of formula **A** is generally prepared by the assembly of three fragments **F-1**, **F-2**, and **F-3** as shown by **Scheme 1** set forth below:

## CLAIMS

**We claim:**

1. A method for preparing a fragment compound of formula **F-4-a**:




**F-4-a**

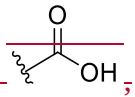
or a pharmaceutically acceptable salt thereof, wherein:

$PG^1$ and $PG^2$ are independently hydrogen or a suitable hydroxyl protecting group;

$PG^3$ and $PG^4$ are independently hydrogen or a suitable nitrogen protecting group, provided both $PG^3$ and $PG^4$ are not hydrogen at the same time;

B is a nucleobase or hydrogen;

$L^2$ is a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, $(C{=}O)OY$, $NY_2$, NH, and NH (C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including 

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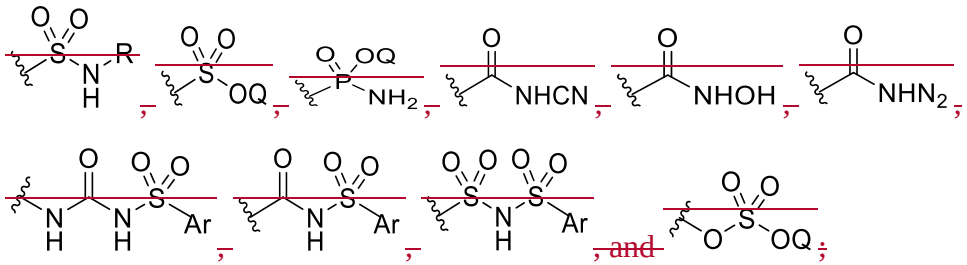



, and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$ aryl or $(CH_2)_m$ heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$,

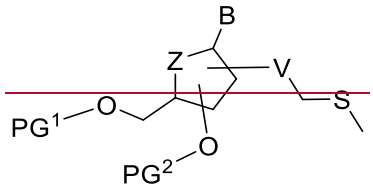
~~$C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;~~

~~V and W are independently -O-, -S-, or -NR-; and~~

~~Z is $-CH_2-$, -O-, -S-, or -NR-,~~

~~comprising the steps of:~~

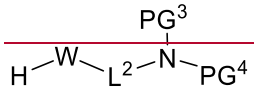
~~(a) providing a fragment compound of formula **F-1-a**:~~




~~**F-1-a**~~

~~or a pharmaceutically acceptable salt thereof, and~~

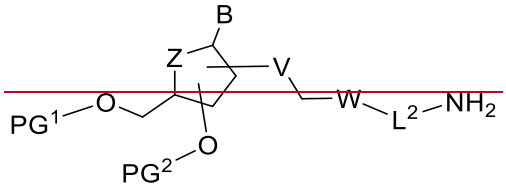
~~(b) alkylating said compound with a compound of formula **F-2**:~~




~~**F-2**~~

~~or a pharmaceutically acceptable salt thereof, to form a fragment compound of formula **F-4-a**.~~

~~2. The method according to claim 1, further comprising the step of preparing a compound of formula **F-5-a**:~~



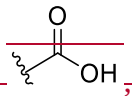

~~**F-5-a**~~

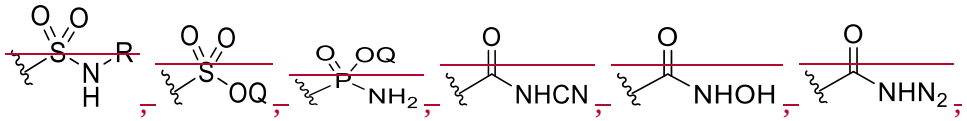
~~or a pharmaceutically acceptable salt thereof, wherein:~~

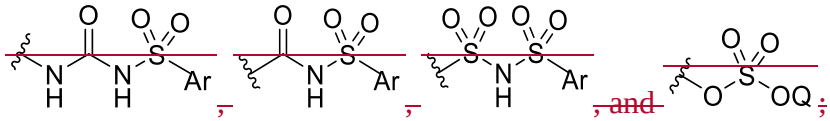
~~$PG^1$ and $PG^2$ are independently hydrogen or a suitable hydroxyl protecting group;~~

~~B is a nucleobase or hydrogen;~~

~~$L^2$ is a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH-(C=OY);~~

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,



, and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl;

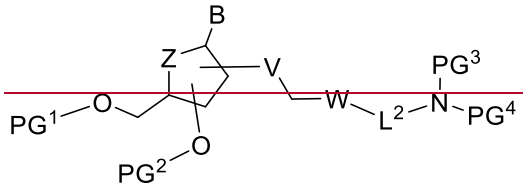
Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-; and

Z is $-CH_2-$, -O-, -S-, or -NR-,

comprising the steps of:

(a) providing a compound of formula **F-4-a**:

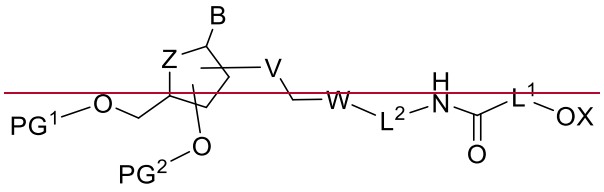


**F-4-a**

or a pharmaceutically acceptable salt thereof, and

(b) deprotecting said fragment compound of formula **F-4-a** to form the fragment compound of formula **F-5-a**.

3. The method of claim 2, further comprising the steps of preparing a compound of formula **D-a**:



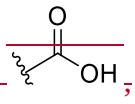

**D-a**

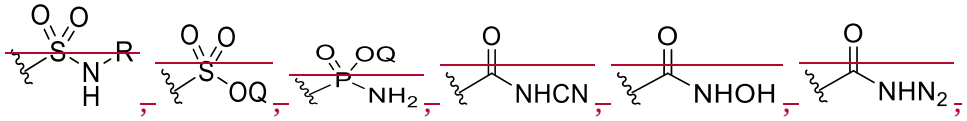
or a pharmaceutically acceptable salt thereof, wherein:

$PG^1$ and $PG^2$ are independently hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH−(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ;

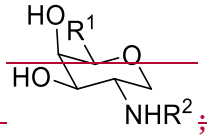



each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-;

~~X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols,~~



~~and ;~~

~~$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;~~

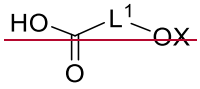
~~$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$;~~

~~$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl; and~~

~~Z is $-CH_2-$, $-O-$, $-S-$, or $-NR-$,~~

~~comprising the steps of:~~

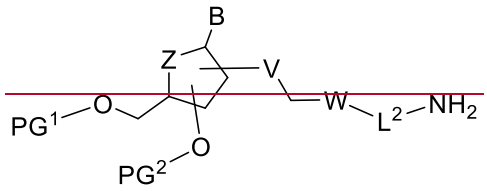
~~(a) providing a compound of formula **F-3**:~~



~~**F-3**~~

~~or a pharmaceutically acceptable salt thereof, and~~

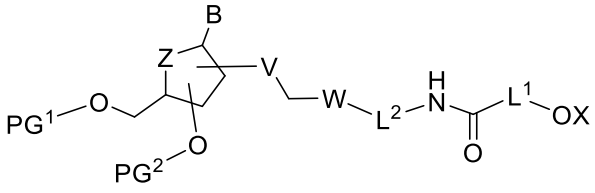
~~(b) reacting said fragment compound of formula **F-3** with a fragment compound of formula **F-5-a**:~~



~~**F-5-a**~~

~~or a pharmaceutically acceptable salt thereof, to provide the compound of formula **D-a**.~~

~~4~~1. A method for preparing a compound of formula **D-a**:



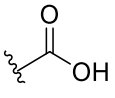
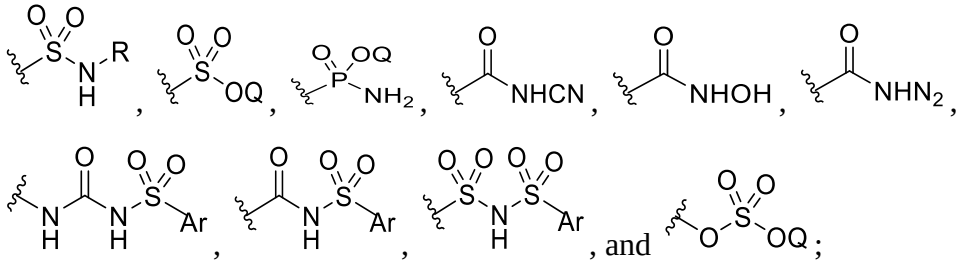
**D-a**

or a salt thereof, wherein:

$PG^1$ and $PG^2$ are independently hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

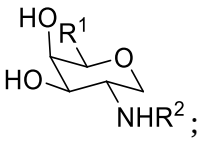
each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including , , and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols, and ;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

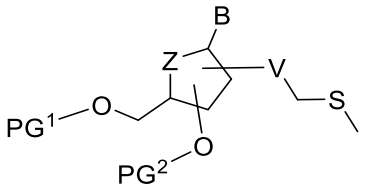
$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$;

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl; and

Z is $-CH_2-$, -O-, -S-, or -NR-,

comprising the steps of:

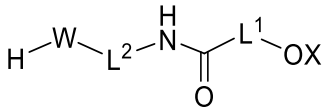
(a) providing a compound of formula **F-1-a**:




**F-1-a**

or a salt thereof, and

(b) reacting said fragment compound of formula **F-1-a** with a fragment compound of formula **F-6**:

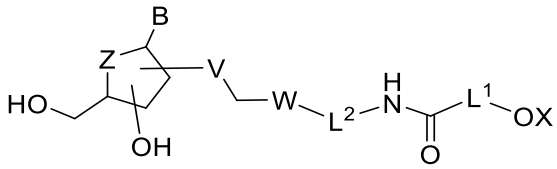



**F-6**

or a salt thereof,

to provide the compound of formula **D-a**.

~~5~~2. The method ~~any one~~ of claim 1~~s 3-4~~, further comprising the step of preparing a compound of formula **C-a**:



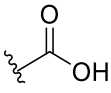

**C-a**

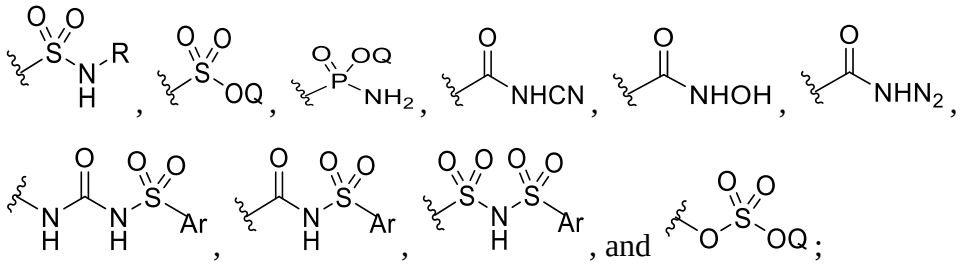
or a pharmaceutically acceptable salt thereof, wherein:

B is a nucleobase or hydrogen;

each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl,

wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,

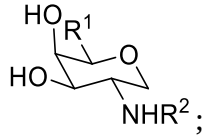


each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols,

and ;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

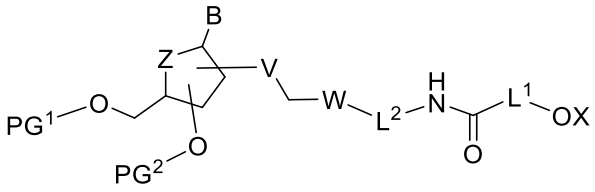
$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$;

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl; and

Z is -$CH_2$-, -O-, -S-, or -NR-,

comprising the steps of:

(a) providing a compound of formula **D-a**:

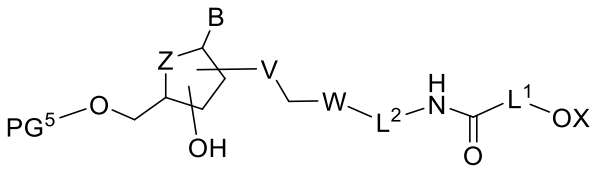


**D-a**

or a pharmaceutically acceptable salt thereof, and

(b) deprotecting said compound of formula **D-a** to form a compound of formula **C-a**.

~~6~~3. The method of~~according to~~ claim ~~5~~2, further comprising the step of preparing a compound of formula **B-a**:



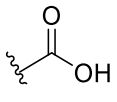
**B-a**

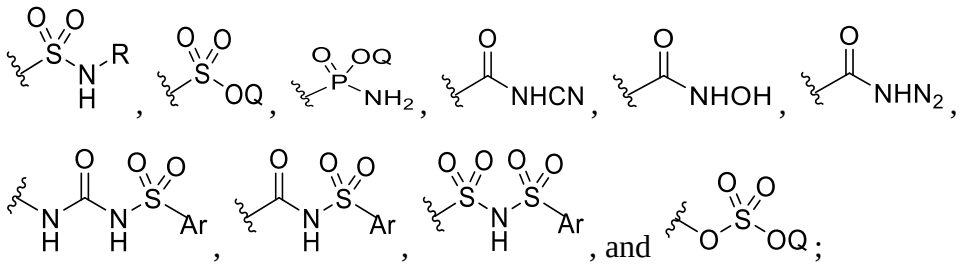
or a pharmaceutically acceptable salt thereof, wherein:

$PG^5$ is hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,

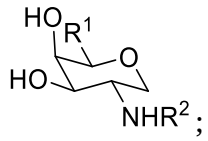


each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols,

and 

;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

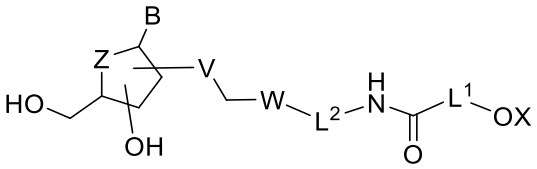
$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$;

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl; and

Z is $-CH_2-$, -O-, -S-, or -NR-,

comprising the steps of:

(a) providing a compound of formula **C-a**:

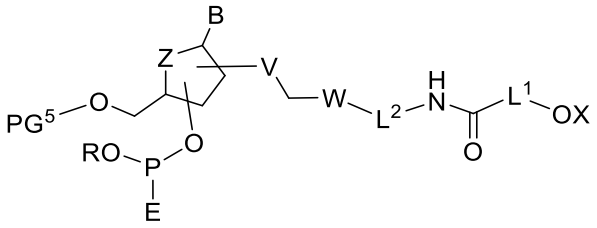



**C-a**

or a pharmaceutically acceptable salt thereof, and

(b) protecting said compound of formula **C-a** with a suitable protecting group to form a compound of formula **B-a**.

~~7~~4. The method of claim ~~6~~3, further comprising the steps of preparing a compound of formula **A-a**:



**A-a**

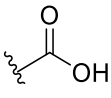
or a pharmaceutically acceptable salt thereof, wherein:

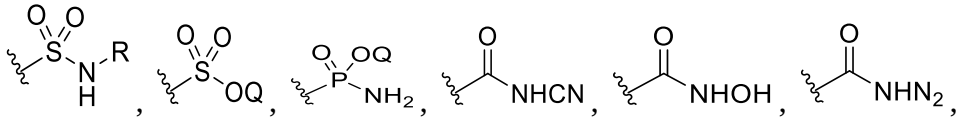
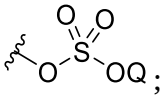
$PG^5$ is hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

E is a halogen or $NR_2$;

each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,

, and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl, or:

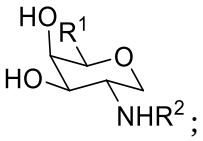
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated heterocyclic ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$,

$C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols,

and ;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

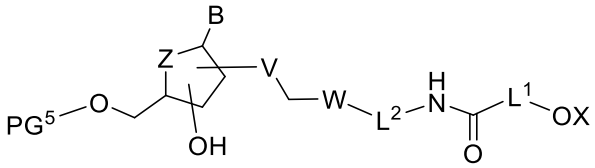
$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$;

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl; and

Z is $-CH_2-$, -O-, -S-, or -NR-,

comprising the steps of:

(a) providing a compound of formula **B-a**:

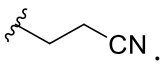


**B-a**

or a pharmaceutically acceptable salt thereof, and

(b) reacting said compound of formula **B-a** with a P(III) forming reagent to form a compound of formula **A-a**.

~~8~~5. The method of claim ~~7~~4, wherein E is $NR_2$.

~~9~~6. The method of claim ~~8~~5, wherein R is selected from isopropyl and .

~~10. The method of claim 1, wherein $PG^3$ is H and $PG^4$ is Fmoc.~~

~~11~~7. The method of claim 1~~any one of claims 1-4~~, wherein $PG^1$ and $PG^2$ are taken together with their intervening atoms to form a cyclic diol protecting group.

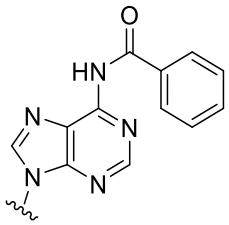
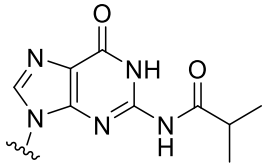
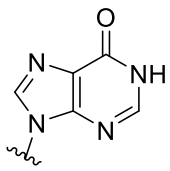
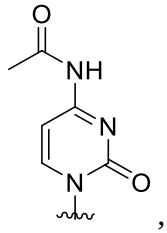
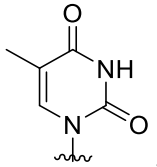
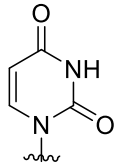
~~12~~8. The method of claim ~~11~~7, wherein the cyclic diol protecting group comprises 1,1,3,3-tetraisopropylidisiloxanylidene.

~~13~~9. The method of any one of claims ~~6~~3-~~7~~4, wherein $PG^5$ is 4,4'-dimethyoxytrityl.

~~14~~10. The method of any one of claims 1-~~13~~9, wherein B is a purine or pyrimidine base.

~~15~~11. The method of claim ~~14~~10, wherein the purine or pyrimidine base is G, A, or C comprising a protecting group.

~~16~~12. The method of claim ~~14~~10, wherein purine or pyrimidine base is selected from

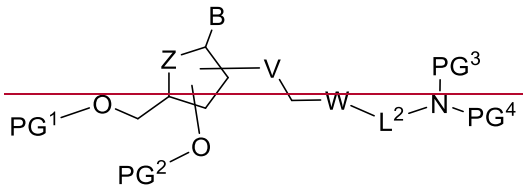

, 
, 
, 
, 
, and 
.

~~17~~13. The method of any one of claims 1-~~16~~12, wherein V is –O–.

~~18~~14. The method of any one of claims 1-~~17~~13, wherein W is –O–.

~~19~~15. The method of any one of claims 1-~~18~~14, wherein Z is –O–.

~~20. A compound of formula **F-4-a:**~~



~~**F-4-a**~~

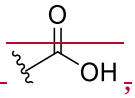
or a pharmaceutically acceptable salt thereof, wherein:

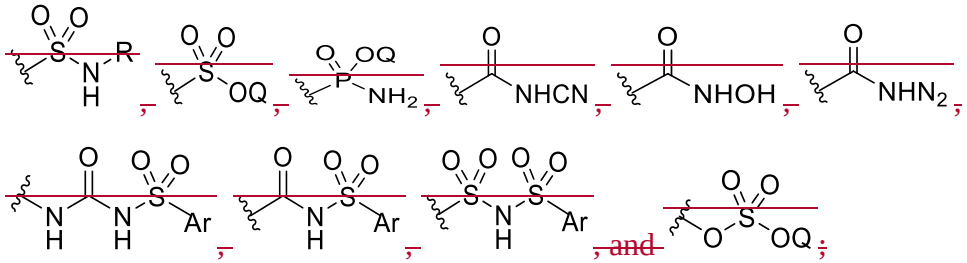
$PG^1$ and $PG^2$ are independently hydrogen or a suitable hydroxyl protecting group;

$PG^3$ and $PG^4$ are independently hydrogen or a suitable nitrogen protecting group, provided both $PG^3$ and $PG^4$ are not hydrogen at the same time;

B is a nucleobase or hydrogen;

$L^2$ is a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,



each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-; and

Z is $-CH_2-$, -O-, -S-, or -NR-.

21. The compound of claim 20, wherein $PG^3$ is H and $PG^4$ is Fmoc or trifluoroacetyl.

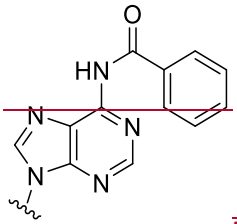
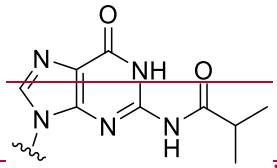
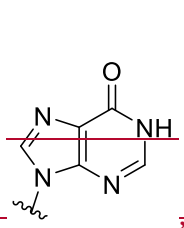
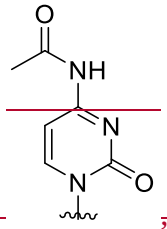
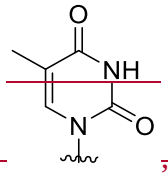
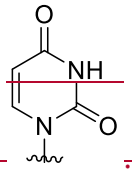
22. The compound of any one of claims 20-21, wherein $PG^1$ and $PG^2$ are taken together with their intervening atoms to form a cyclic diol protecting group.

23. The compound of claim 23, wherein the cyclic diol protecting group comprises 1,1,3,3-tetraisopropylidisiloxanylidene.

24. The compound of any one of claims 20-24, wherein B is a purine or pyrimidine base.

25. The method of claim 24, wherein the purine or pyrimidine base is G, A, or C comprising a protecting group.

26. The compound of claim 24, wherein purine or pyrimidine base is selected from


, 
, 
, 
, 
, and 
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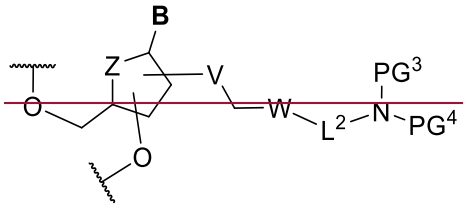
27. The compound of any one of claims 20-26, wherein V is O .

28. The compound of any one of claims 20-27, wherein W is O .

29. The compound of any one of claims 20-28, wherein Z is O .

30. A nucleic acid or analogue thereof compound **P2-a**, or a pharmaceutically acceptable salt thereof, comprising:

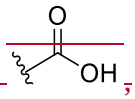


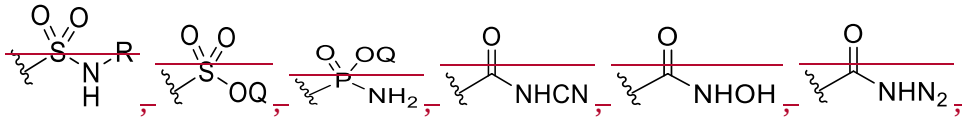

wherein

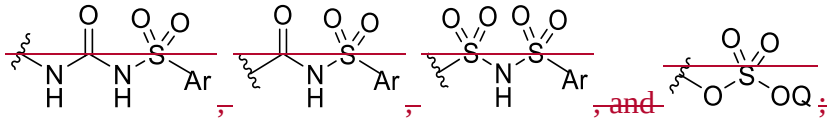
$PG^3$ and $PG^4$ are independently hydrogen or a suitable nitrogen protecting group, provided both $PG^3$ and $PG^4$ are not hydrogen at the same time;

B is a nucleobase or hydrogen;

$L^2$ is a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,



, and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl, or:

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

V and W are independently -O-, -S-, or -NR-; and

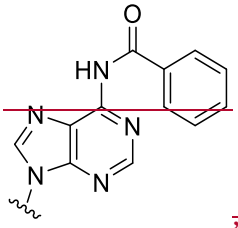
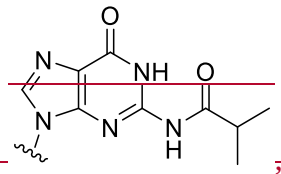
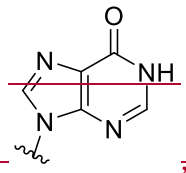
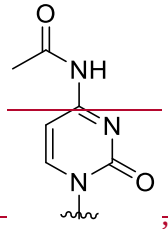
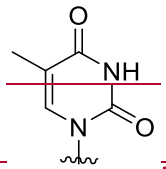
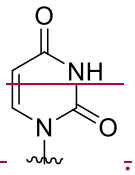
Z is $-CH_2-$, -O-, -S-, or -NR-.

31. The compound of claim 30, wherein $PG^3$ is H and $PG^4$ is Fmoc or trifluoroacetyl.

32. The compound of any one of claims 30-31, wherein B is a purine or pyrimidine base.

33. The method of claim 32, wherein the purine or pyrimidine base is G, A, or C comprising a protecting group.

~~34. The compound of claim 32, wherein purine or pyrimidine base is selected from~~

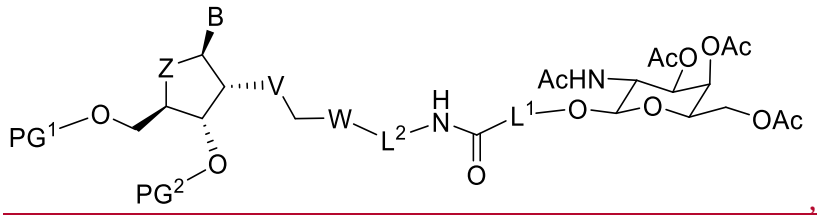

~~,~~ 
~~,~~ 
~~,~~ 
~~,~~ 
~~, and~~ 
~~.~~

~~35. The compound of any one of claims 30-34, wherein V is O .~~

~~36. The compound of any one of claims 30-35, wherein W is O .~~

~~37. The compound of any one of claims 30-36, wherein Z is O .~~

16. The method of claim 1, wherein the compound of formula **D-a** is a compound of any one of the following formulae: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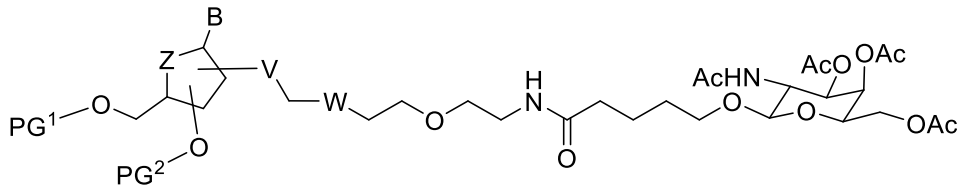
**D-b**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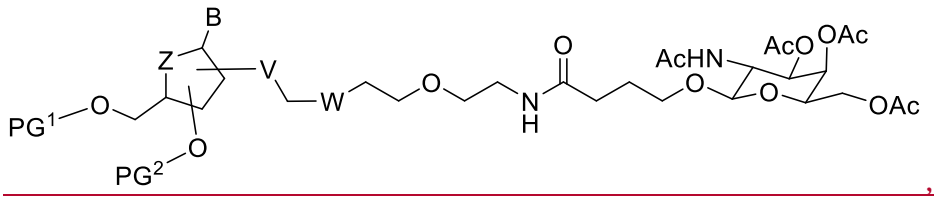
**D-c**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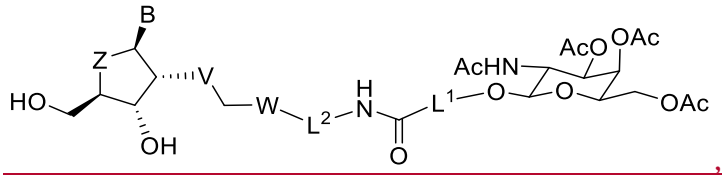
**D-d**

or a pharmaceutically acceptable salt thereof.

17. The method of claim 2, wherein the compound of formula **C-a** is a compound of any one of the following formulae:



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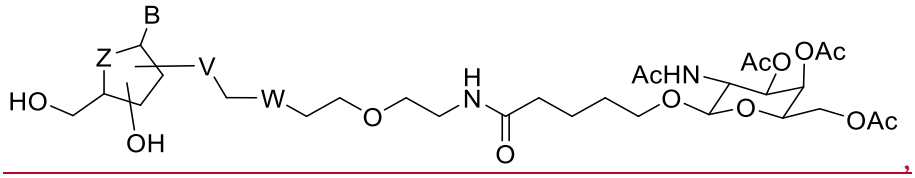
**C-b**



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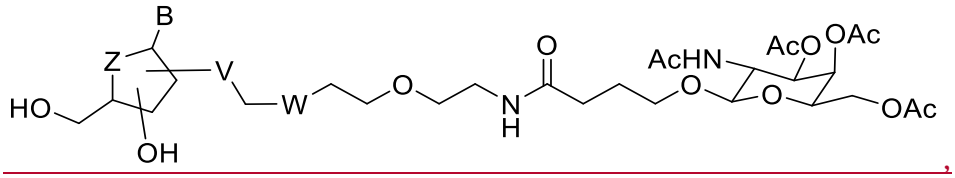
**C-c**

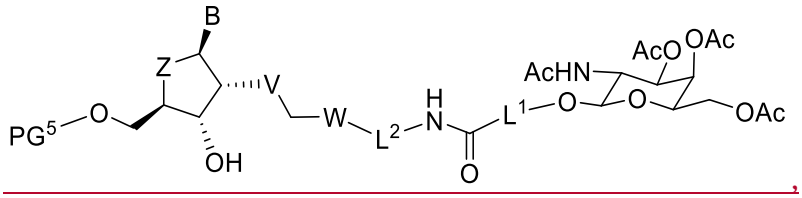


,

**C-d**

or a pharmaceutically acceptable salt thereof.

18. The method of claim 3, wherein the compound of formula **B-a** is a compound of any one of the following formulae:



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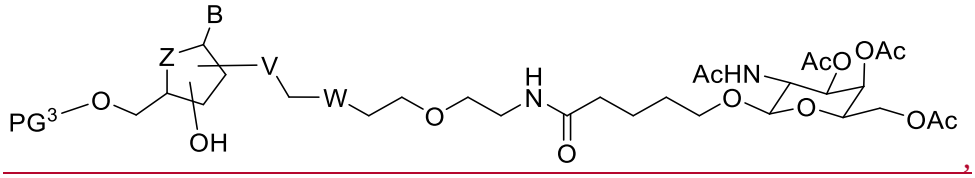
**B-b**



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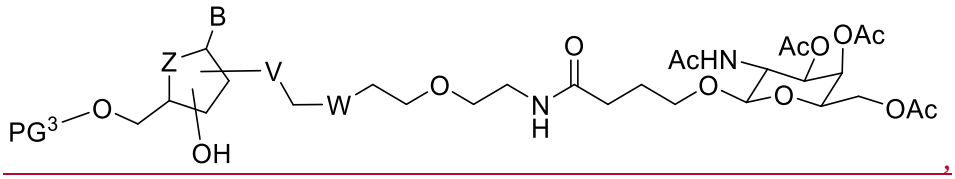
**B-c**

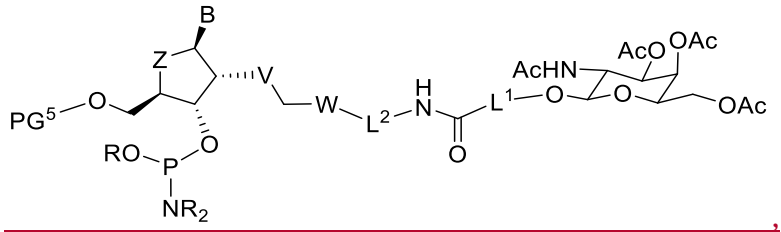



,

**B-d**

or a pharmaceutically acceptable salt thereof.

19. The method of claim 4, wherein the compound of formula **A-a** is a compound of any one of the following formulae:

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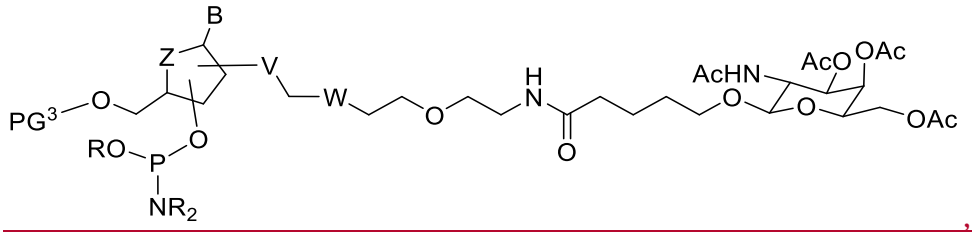
**A-b**

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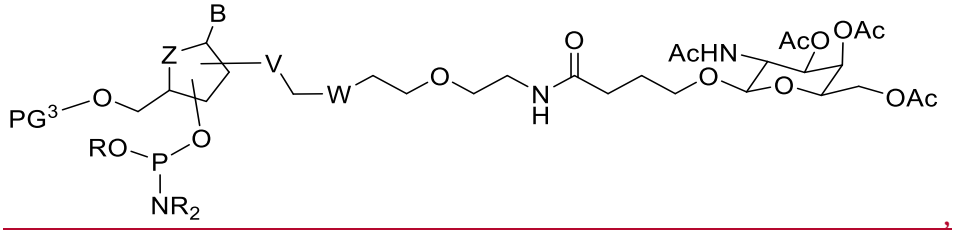
**A-c**

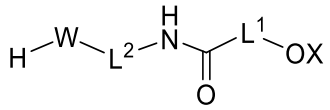



,

**A-d**

or a pharmaceutically acceptable salt thereof.

20. A compound, wherein the compound is of formula **F-6:**

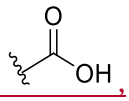


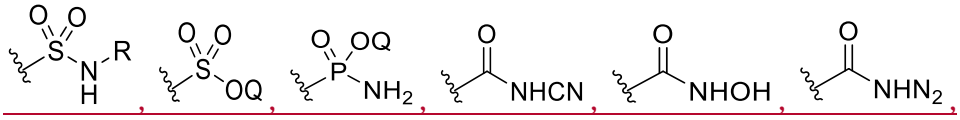

,

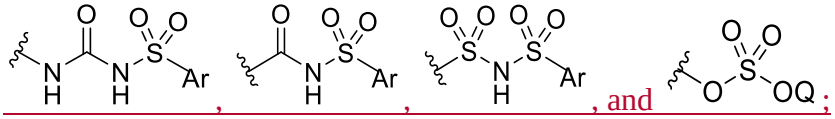
**F-6**

or a pharmaceutically acceptable salt thereof, wherein:

each $L^1$ and $L^2$ are independently a bivalent moiety selected from alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, or substituted alkynyl, wherein one or more methylenes can be interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), OY, S, S(OY), $SO_2(Y)$, (C=O)OY, $NY_2$, NH, and NH—(C=OY);

Y is independently selected from H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl or aryl, including ,

,

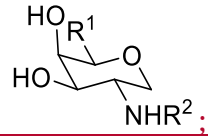
, and ;

each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, $C_1$-$C_6$ alkynyl, aryl, heteroaryl, $(CH_2)_m$-aryl or $(CH_2)_m$-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, $CF_3$, $C_1$-$C_8$ alkoxy, $NO_2$, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, aryl or OY, C(O)OY, $NY_2$ or C(O)NHY;

W is -O-, -S-, or -NR-;

X is a ligand selected from GalNAc, D-mannose, L-galactose, D-arabinose, L-fucose, polyols,

and ;

$R^1$ is selected from $CF_3$, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

$R^2$ is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, $P(O_2)$, $P(O_4)$, polyethylenegylcol (PEG), $OR^3$, S, $S(OR^3)$ , $SO_2(R^3)$, $(C=O)OR^3$, $NY_2$, NH, and $NH(C=OR^3)$; and

$R^3$ is H, $C_1$-$C_6$ alkanyl, $C_1$-$C_6$ alkenyl, or aryl.