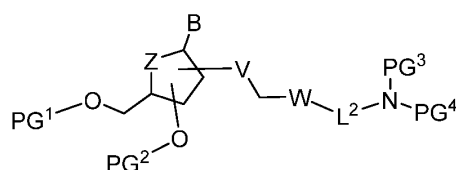


CLAIMS

We claim:

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



F-4-a

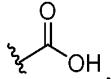
or a pharmaceutically acceptable salt thereof, wherein:

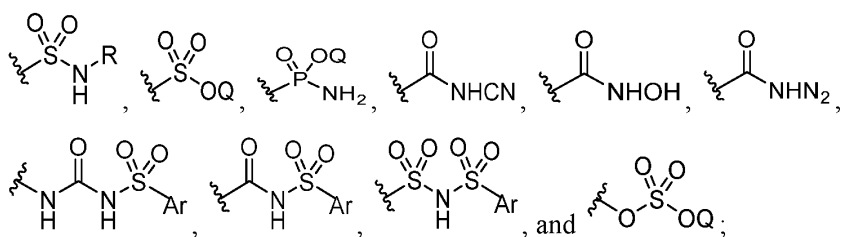
PG¹ and PG² are independently hydrogen or a suitable hydroxyl protecting group;

PG³ and PG⁴ are independently hydrogen or a suitable nitrogen protecting group, provided both PG³ and PG⁴ are not hydrogen at the same time;

B is a nucleobase or hydrogen;

L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ 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, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_m-heteroaryl where m is 1-10 and any of the aryl or

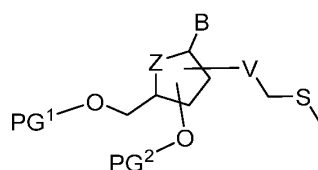
heteroaryl rings may be substituted with one to three independently selected Cl, F, CF₃, C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ or C(O)NHY;

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

Z is -CH₂-, -O-, -S-, or -NR-,

comprising the steps of:

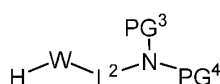
- (a) providing a fragment compound of formula **F-1-a**:



F-1-a

or a pharmaceutically acceptable salt thereof, and

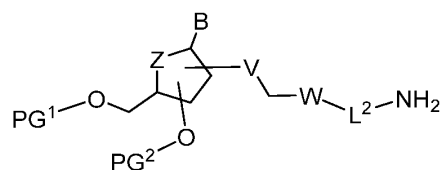
- (b) alkylating said compound with a compound of formula **F-2**:



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

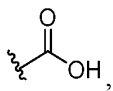
or a pharmaceutically acceptable salt thereof, wherein:

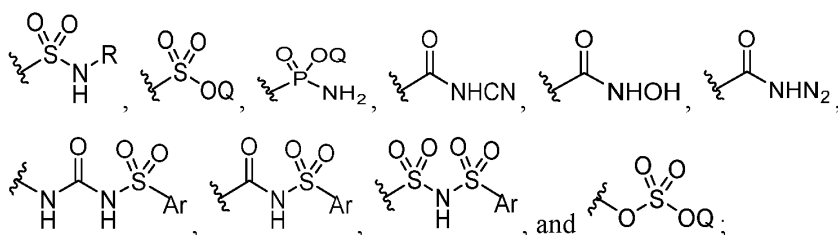
PG¹ and PG² are independently hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ alkenyl or aryl, including ,



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

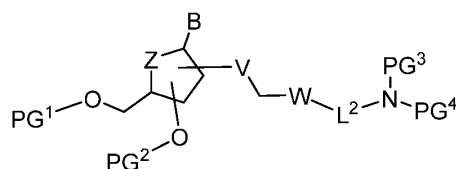
Q is H or a pharmaceutically acceptable salt, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_m-heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl, F, CF₃, C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ or C(O)NHY;

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

Z is -CH₂-, -O-, -S-, or -NR-,

comprising the steps of:

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

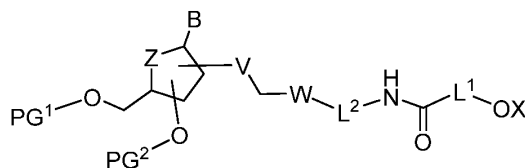


F-4-a

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**

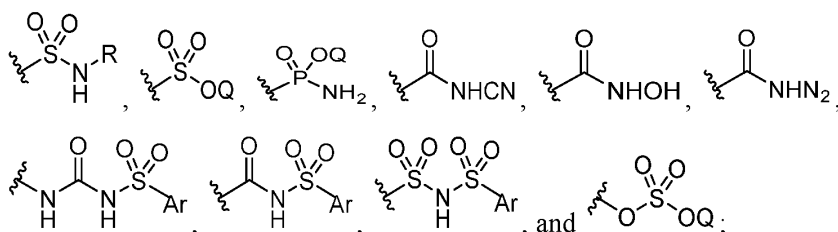
or a pharmaceutically acceptable salt thereof, wherein:

PG¹ and PG² are independently hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

each L¹ and L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ alkenyl or aryl, including

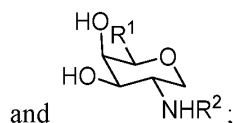


each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_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, CF₃, C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ 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,



R¹ is selected from CF₃, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

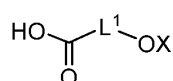
R² is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, P(O)₂, P(O)₄, polyethyleneglycol (PEG), OR³, S, S(OR³), SO₂(R³), (C=O)OR³, NY₂, NH, and NH(C=OR³);

R³ is H, C₁-C₆ alkanyl, C₁-C₆ alkenyl, or aryl; and

Z is -CH₂-, -O-, -S-, or -NR-,

comprising the steps of:

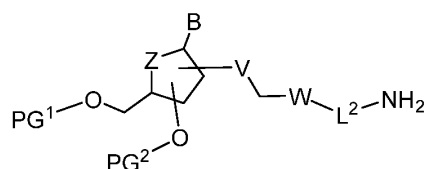
(a) providing a compound of formula **F-3**:



F-3

or a pharmaceutically acceptable salt thereof, and

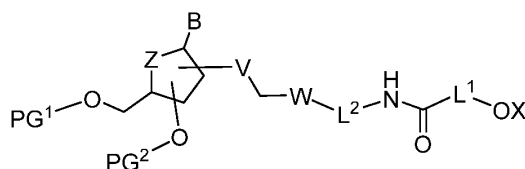
(b) reacting said fragment compound of formula **F-3** with a fragment compound of formula **F-5-a**:



F-5-a

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

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



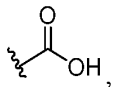
D-a

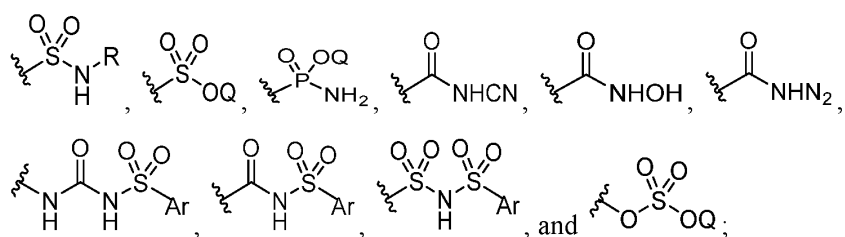
or a salt thereof, wherein:

PG¹ and PG² are independently hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

each L¹ and L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ alkenyl or aryl, including ,

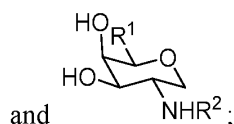


each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_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, CF₃, C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ 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,



R¹ is selected from CF₃, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

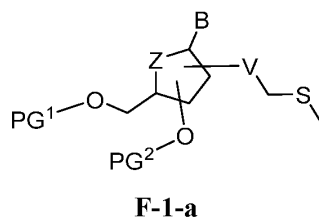
R^2 is selected from one or more methylenes interrupted or terminated by one or more of $P(O)H$, $P(O_2)$, $P(O_4)$, polyethyleneglycol (PEG), OR^3 , S, $S(OR^3)$, $SO_2(R^3)$, $(C=O)OR^3$, NY_2 , NH, and $NH(C=OR^3)$;

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

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

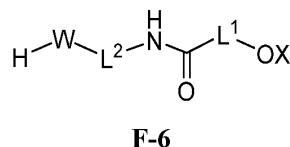
comprising the steps of:

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



or a salt thereof, and

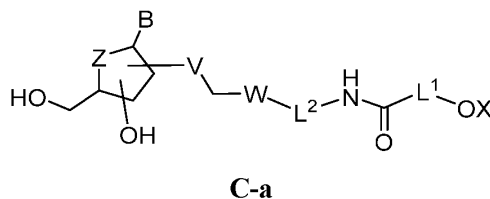
(b) reacting said fragment compound of formula **F-1-a** with a fragment compound of formula **F-6**:



or a salt thereof,

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

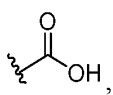
5. The method any one of claims 3-4, further comprising the step of preparing a compound of formula **C-a**:

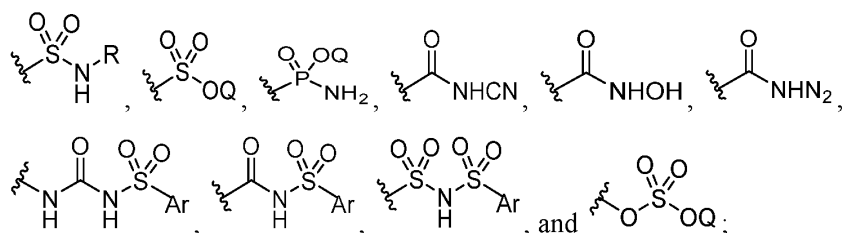


or a pharmaceutically acceptable salt thereof, wherein:

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 $P(O)H$, $P(O)_2$, $P(O)_4$, polyethyleneglycol (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 ,

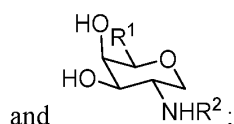


each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl;

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,



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

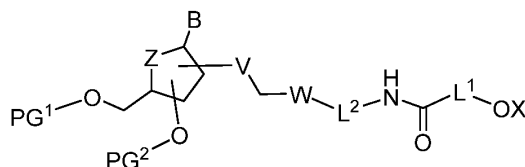
R^2 is selected from one or more methylenes interrupted or terminated by one or more of $P(O)H$, $P(O)_2$, $P(O)_4$, polyethyleneglycol (PEG), OR^3 , S , $S(OR^3)$, $SO_2(R^3)$, $(C=O)OR^3$, NY_2 , NH , and $NH(C=OR^3)$;

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**:

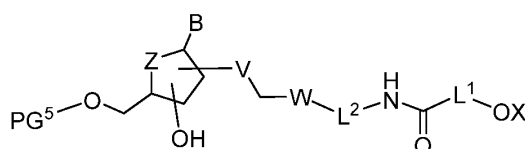


D-a

or a pharmaceutically acceptable salt thereof, and

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

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



B-a

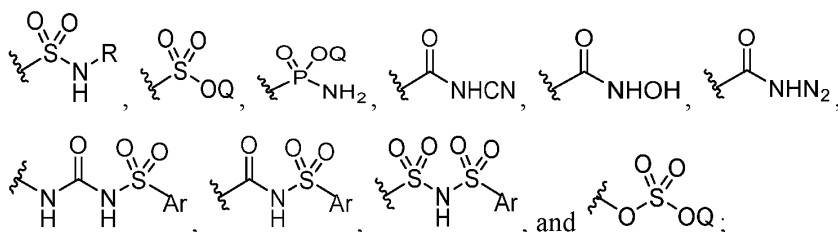
or a pharmaceutically acceptable salt thereof, wherein:

PG⁵ is hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

each L¹ and L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ alkenyl or aryl, including

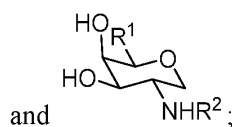


each R is independently selected from hydrogen, alkyl, alkenyl, aromatic, heterocycle, substituted alkyl, and substituted alkenyl;

Q is H or a pharmaceutically acceptable salt, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_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, CF₃, C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ 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,



R¹ is selected from CF₃, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

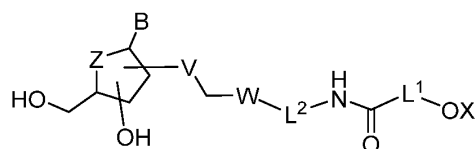
R² is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, P(O₂), P(O₄), polyethyleneglycol (PEG), OR³, S, S(OR³), SO₂(R³), (C=O)OR³, NY₂, NH, and NH(C=OR³);

R³ is H, C₁-C₆ alkanyl, C₁-C₆ alkenyl, or aryl; and

Z is -CH₂-, -O-, -S-, or -NR-,

comprising the steps of:

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

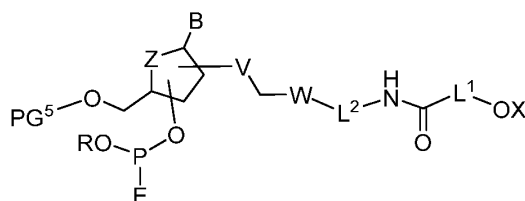


C-a

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

**A-a**

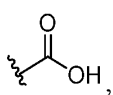
or a pharmaceutically acceptable salt thereof, wherein:

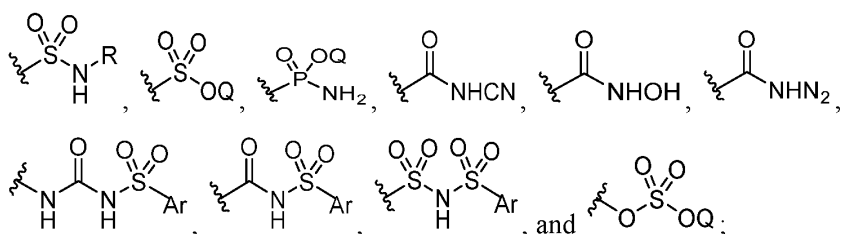
PG⁵ is hydrogen or a suitable hydroxyl protecting group;

B is a nucleobase or hydrogen;

E is a halogen or NR₂;

each L¹ and L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ alkenyl or aryl, including ,



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

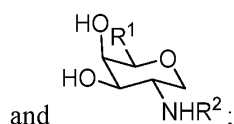
two R groups on the same nitrogen are optionally taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated heterocyclic ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

Q is H or a pharmaceutically acceptable salt, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_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, CF₃,

C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ 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,



R¹ is selected from CF₃, alkyl, alkenyl, alkynyl, aromatic, heterocycle, substituted alkyl, substituted alkenyl, and substituted alkynyl;

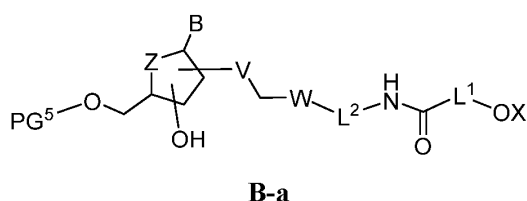
R² is selected from one or more methylenes interrupted or terminated by one or more of P(O)H, P(O₂), P(O₄), polyethyleneglycol (PEG), OR³, S, S(OR³), SO₂(R³), (C=O)OR³, NY₂, NH, and NH(C=OR³);

R³ is H, C₁-C₆ alkanyl, C₁-C₆ alkenyl, or aryl; and

Z is -CH₂-, -O-, -S-, or -NR-,

comprising the steps of:

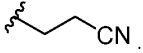
(a) providing a compound of formula **B-a**:



or a pharmaceutically acceptable salt thereof, and

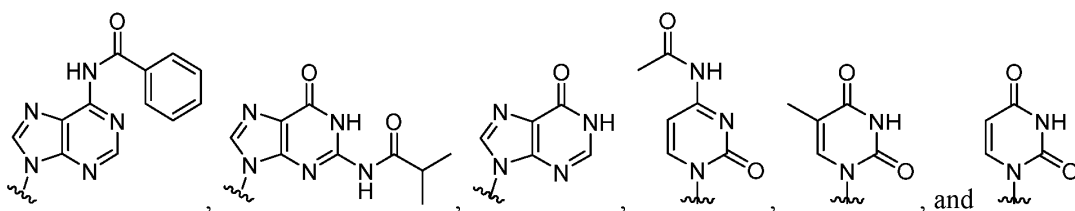
(b) reacting said compound of formula **B-a** with a P(III) forming reagent to form a compound of formula **A-a**.

8. The method of claim 7, wherein E is NR₂.

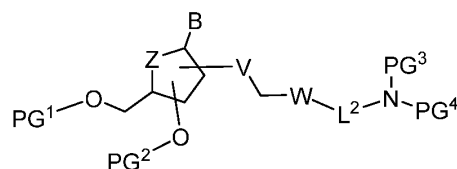
9. The method of claim 8, wherein R is selected from isopropyl and .

10. The method of claim 1, wherein PG³ is H and PG⁴ is Fmoc.

11. The method of any one of claims 1-4, wherein PG¹ and PG² are taken together with their intervening atoms to form a cyclic diol protecting group.
12. The method of claim 11, wherein the cyclic diol protecting group comprises 1,1,3,3-tetraisopropylidisiloxanylidene.
13. The method of any one of claims 6-7, wherein PG⁵ is 4,4'-dimethoxytrityl.
14. The method of any one of claims 1-13, wherein B is a purine or pyrimidine base.
15. The method of claim 14, wherein the purine or pyrimidine base is G, A, or C comprising a protecting group.
16. The method of claim 14, wherein purine or pyrimidine base is selected from



17. The method of any one of claims 1-16, wherein V is —O—.
18. The method of any one of claims 1-17, wherein W is —O—.
19. The method of any one of claims 1-18, wherein Z is —O—.
20. A compound of formula **F-4-a**:



F-4-a

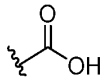
or a pharmaceutically acceptable salt thereof, wherein:

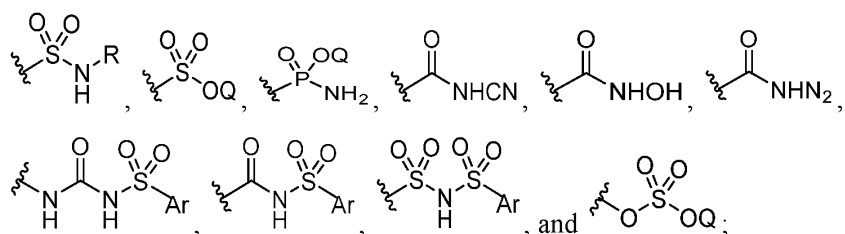
PG¹ and PG² are independently hydrogen or a suitable hydroxyl protecting group;

PG³ and PG⁴ are independently hydrogen or a suitable nitrogen protecting group, provided both PG³ and PG⁴ are not hydrogen at the same time;

B is a nucleobase or hydrogen;

L² 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(O₂), P(O₄), polyethyleneglycol (PEG), OY, S, S(OY), SO₂(Y), (C=O)OY, NY₂, NH, and NH—(C=OY);

Y is independently selected from H, C₁-C₆ alkanyl, C₁-C₆ 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, C₁-C₆ alkanyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, aryl, heteroaryl, (CH₂)_m-aryl or (CH₂)_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, CF₃, C₁-C₈ alkoxy, NO₂, C₁-C₆ alkanyl, C₁-C₆ alkenyl, aryl or OY, C(O)OY, NY₂ or C(O)NHY;

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

Z is -CH₂-, -O-, -S-, or -NR-.

21. The compound of claim 20, wherein PG³ is H and PG⁴ is Fmoc or trifluoroacetyl.

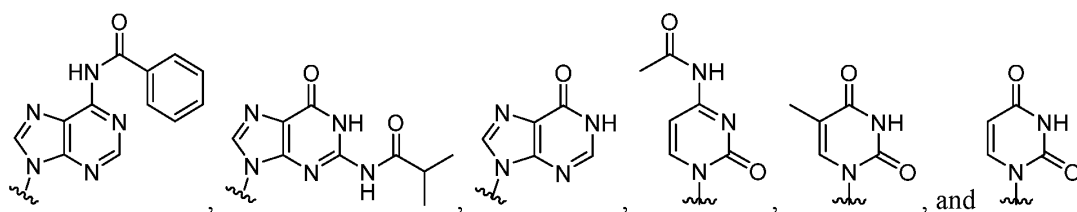
22. The compound of any one of claims 20-21, wherein PG¹ and PG² are taken together with their intervening atoms to form a cyclic diol protecting group.

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

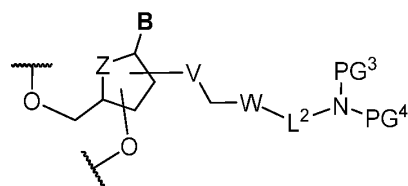


27. The compound of any one of claims 20-26, wherein V is -O-.

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:



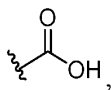
wherein

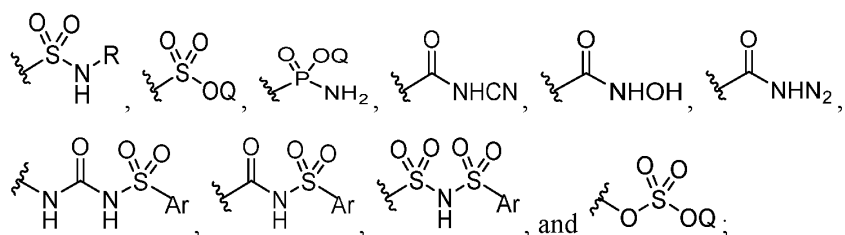
PG³ and PG⁴ are independently hydrogen or a suitable nitrogen protecting group, provided both

PG³ and PG⁴ 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 $P(O)H$, $P(O_2)$, $P(O_4)$, polyethyleneglycol (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, or:

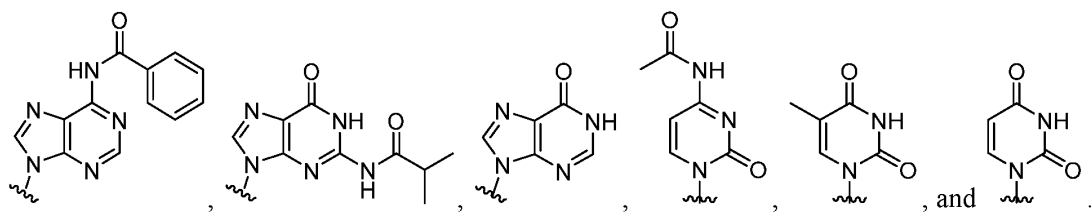
Q is H or a pharmaceutically acceptable salt, C_1 - C_6 alkanyl, C_1 - C_6 alkenyl, C_1 - C_6 alkynyl, aryl, heteroaryl, $(CH_2)_m$ -aryl or $(CH_2)_m$ -heteroaryl where m is 1-10 and any of the aryl or heteroaryl rings may be substituted with one to three independently selected Cl , F , CF_3 , C_1 -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



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-.