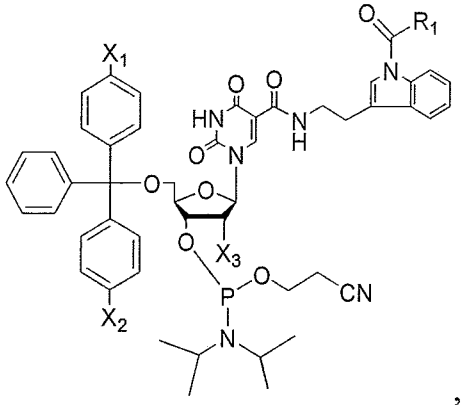
chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, X_1 and X_2 are each independently selected from methoxy and hydrogen. In some embodiments, X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy.

[0005a] In one aspect, there is provided a compound comprising:



, or a salt thereof; wherein,

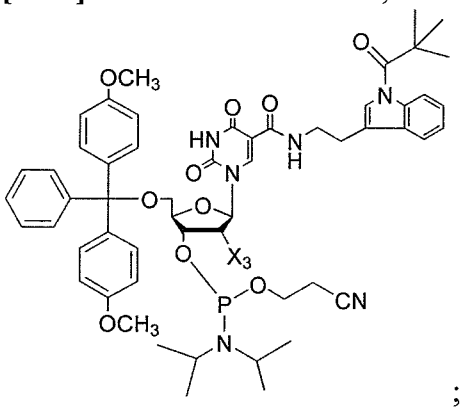
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_1 and X_2 are each independently selected from methoxy and hydrogen;

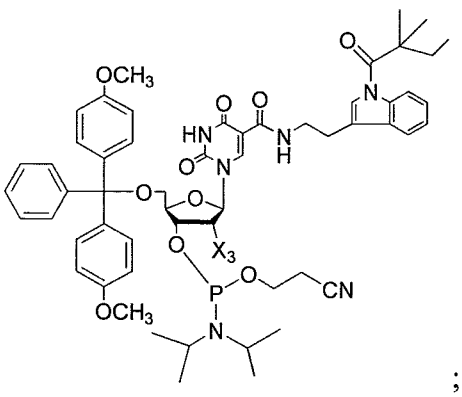
X_3 is selected from methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy.

[0006] In some embodiments, R_1 is *tert*-butyl. In some embodiments, R_1 is 1,1-dimethyl-propyl. In some embodiments, R_1 is 1,1-dimethyl-butyl; 2-chlorophenyl. In some embodiments, R_1 is 2-cyanophenyl. In some embodiments, R_1 is 1-methyl-cyclopentyl. In some embodiments, R_1 is 1-methyl-cyclohexyl. In some embodiments, X_1 and X_2 are methoxy. In some embodiments, X_3 is hydrogen. In some embodiments, X_3 is methoxy. In some embodiments, X_3 is fluoro. In some embodiments, X_3 is *tert*-butyldimethylsilyloxy.

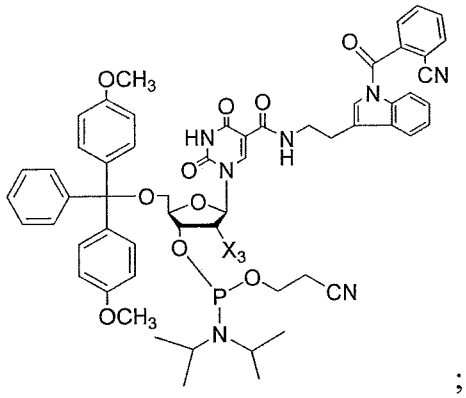
[0007] In some embodiments, a compound provided herein is selected from:



;



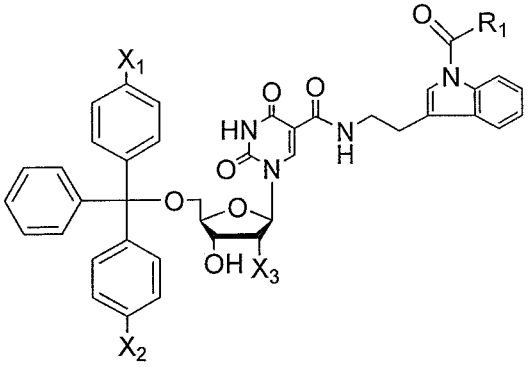
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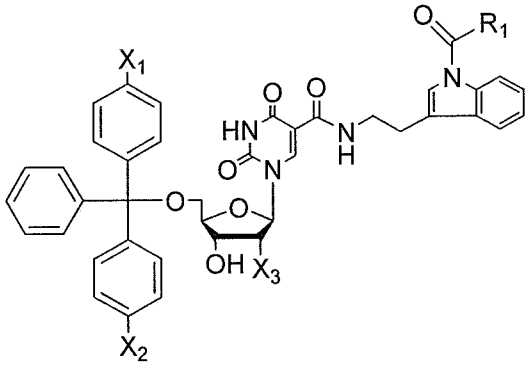
and salts thereof.

[0008] In some embodiments, a compound having the structure



, or a salt thereof, is provided. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, X_1 and X_2 are each independently selected from methoxy and hydrogen. In some embodiments, X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy.

[0008a] In another aspect, there is provided a compound comprising:



, or a salt thereof; wherein,

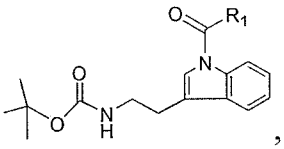
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_1 and X_2 are each independently selected from methoxy and hydrogen;

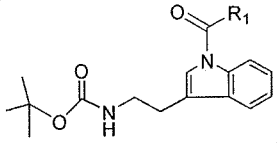
X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy.

[0009] In some embodiments, R_1 is *tert*-butyl. In some embodiments, R_1 is 1,1-dimethyl-propyl. In some embodiments, R_1 is 1,1-dimethyl-butyl; 2-chlorophenyl. In some embodiments, R_1 is 2-cyanophenyl. In some embodiments, R_1 is 1-methyl-cyclopentyl. In some embodiments, R_1 is 1-methyl-cyclohexyl. In some embodiments, X_1 and X_2 are methoxy. In some embodiments, X_3 is hydrogen. In some embodiments, X_3 is methoxy. In some embodiments, X_3 is fluoro. In some embodiments, X_3 is *tert*-butyldimethylsilyloxy.

[0010] In some embodiments, the compound is selected from:

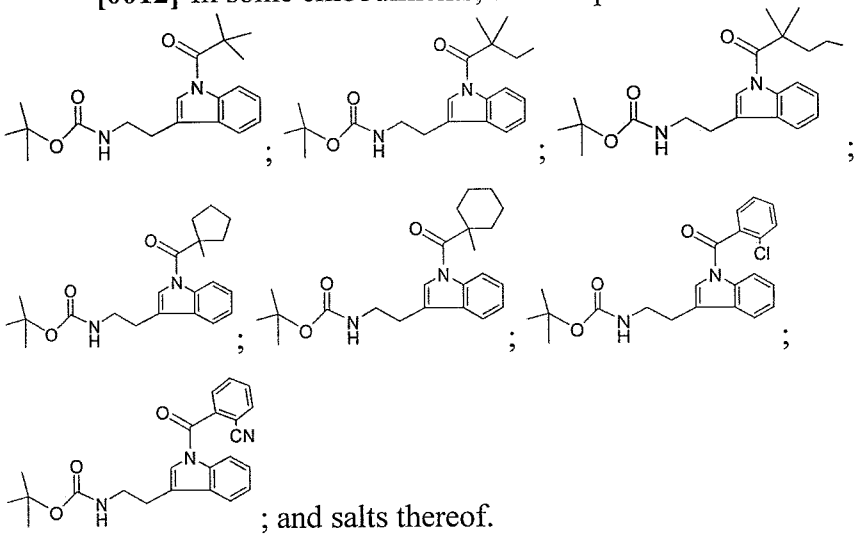

, or a salt thereof, is provided. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, R_1 is *tert*-butyl. In some embodiments, R_1 is 1,1-dimethyl-propyl. In some embodiments, R_1 is 1,1-dimethyl-butyl; 2-chlorophenyl. In some embodiments, R_1 is 2-cyanophenyl. In some embodiments, R_1 is 1-methyl-cyclopentyl. In some embodiments, R_1 is 1-methyl-cyclohexyl.

[0011a] In another aspect, there is provided a compound comprising:

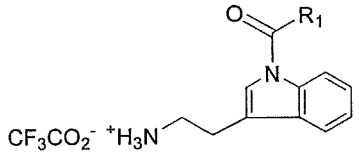

, or a salt thereof; wherein,

R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl.

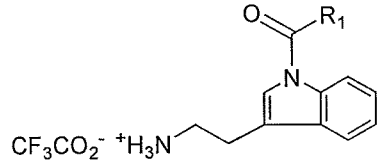
[0012] In some embodiments, the compound has a structure selected from:


; and salts thereof.

[0013] In some embodiments, a compound having the structure:


is provided. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, R_1 is *tert*-butyl. In some embodiments, R_1 is 1,1-dimethyl-propyl. In some embodiments, R_1 is 1,1-dimethyl-butyl; 2-chlorophenyl. In some embodiments, R_1 is 2-cyanophenyl. In some embodiments, R_1 is 1-methyl-cyclopentyl. In some embodiments, R_1 is 1-methyl-cyclohexyl.

[0013a] In another aspect, there is provided a compound comprising:

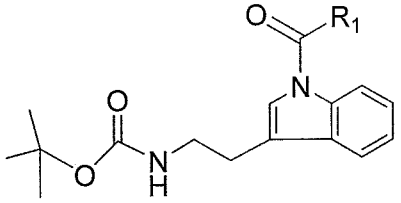

wherein,

R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl.

[0014] In some embodiments, a compound has a structure selected from:

embodiments, R_1 is 1,1-dimethyl-propyl and the acid chloride is 2,2-dimethylbutyroyl chloride. In some embodiments, R_1 is 1,1-dimethyl-butyl and the acid chloride is 2,2-dimethylvaleroyl chloride. In some embodiments, R_1 is 2-chlorophenyl and the acid chloride is 2-chlorobenzoyl chloride. In some embodiments, R_1 is 2-cyanophenyl and the acid chloride is 2-cyanobenzoyl chloride. In some embodiments, R_1 is 1-methyl-cyclopentyl and the acid chloride is 1-methylcyclopentane-1-carbonyl chloride. In some embodiments, R_1 is 1-methyl-cyclohexyl and the acid chloride is 1-methylcyclohexane-1-carbonyl chloride.

[0015a] In another aspect, there is provided a method of producing a compound comprising:

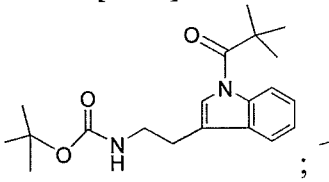
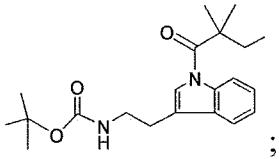
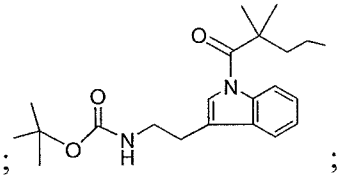
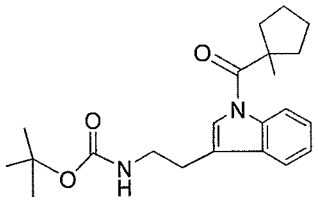
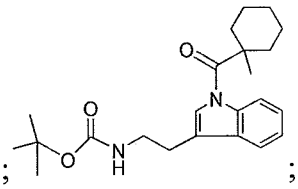
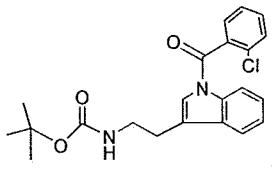
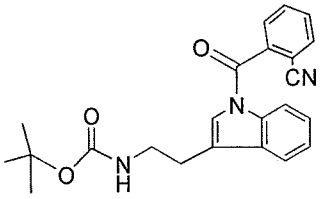


, or a salt thereof; wherein,

R1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

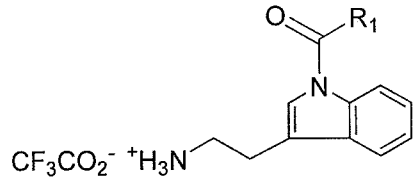
the method comprising reacting N-α-BOC-tryptamine with an acid chloride selected from pivaloyl chloride, 2,2-dimethylbutyroyl chloride, 2,2-dimethylvaleroyl chloride, 1-methylcyclopentane-1-carbonyl chloride, 1-methylcyclohexane-1-carbonyl chloride, 2-chlorobenzoyl chloride, and 2-cyanobenzoyl chloride.

[0016] In some embodiments, the method produces a compound selected from

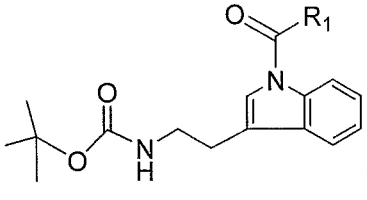

;

;

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;

;


; and salts thereof.

[0017] In some embodiments, a method of producing a compound having the structure:

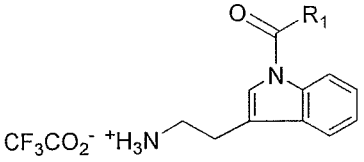


is provided. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, the method comprises reacting the compound



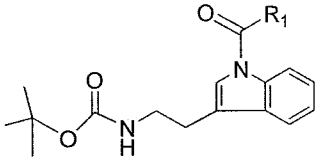
with trifluoroacetic acid.

[0017a] In another aspect, there is provided a method of producing a compound comprising:

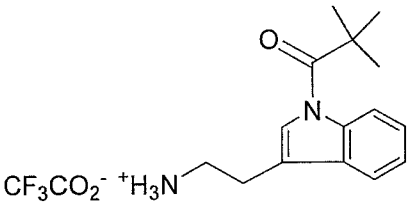


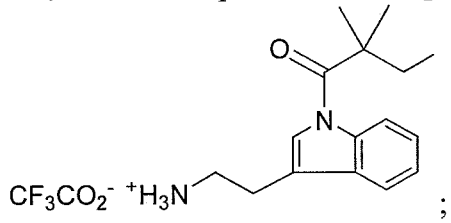
wherein,

R1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

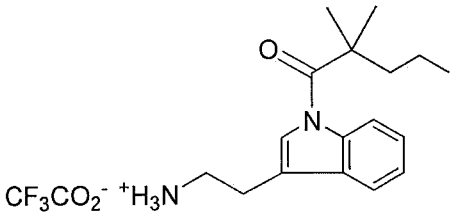
the method comprising reacting the compound  with trifluoroacetic acid.

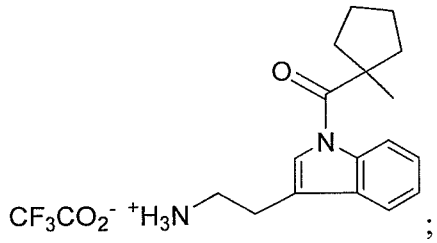
[0018] In some embodiments, the method produces a compound selected from:



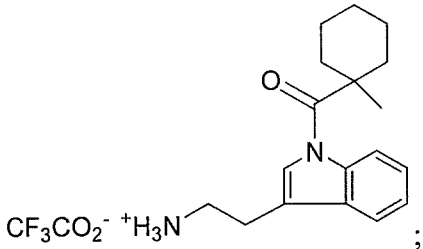
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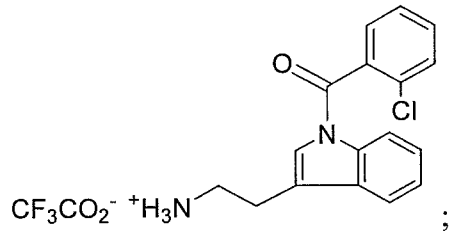
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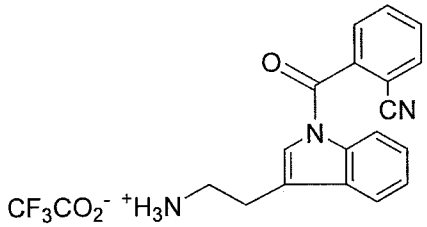
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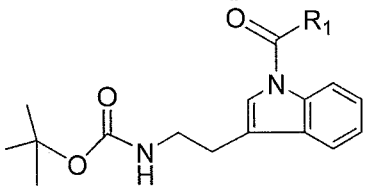
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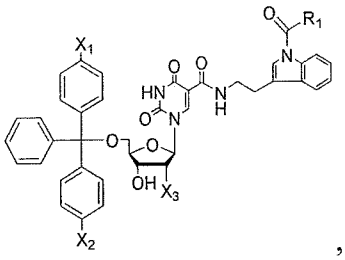
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[0019] In some embodiments, the method further comprises reacting N-α-BOC-tryptamine with an acid chloride selected from pivaloyl chloride, 2,2-dimethylbutyroyl chloride, 2,2-dimethylvaleroyl chloride, 1-methylcyclopentane-1-carbonyl chloride, 1-methylcyclohexane-1-carbonyl chloride, 2-chlorobenzoyl chloride, and 2-cyanobenzoyl chloride, to form the compound

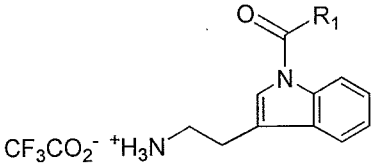


.

[0020] In some embodiments, a method of producing a compound having the structure:

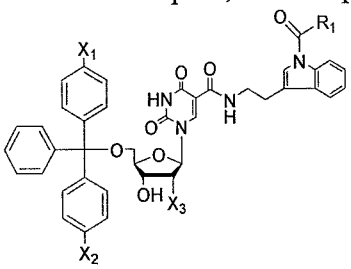


, or a salt thereof, is provided. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, X_1 and X_2 are each independently selected from methoxy and hydrogen. In some embodiments, X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy. In some embodiments, the method comprising reacting the compound



with 5'-*O*-DMT-5-(2,2,2-trifluoroethyoxy-carbonyl)-2'-deoxyuridine (TFEdU).

[0020a] In another aspect, there is provided a method of producing a compound comprising:

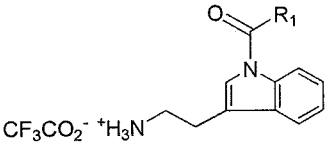


, or a salt thereof; wherein,

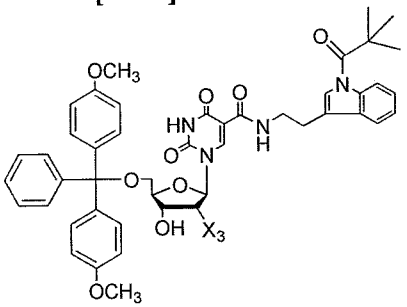
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_1 and X_2 are each independently selected from methoxy and hydrogen;

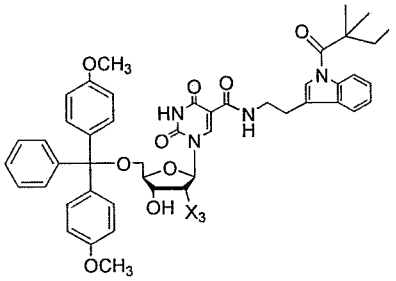
X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy;

the method comprising reacting the compound  with 5'-*O*-DMT-5-(2,2,2-trifluoroethyoxy-carbonyl)-2'-deoxyuridine (TFEdU).

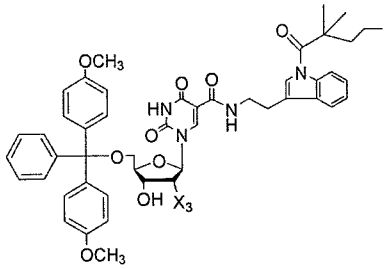
[0021] In some embodiments, the method produces a compound selected from:



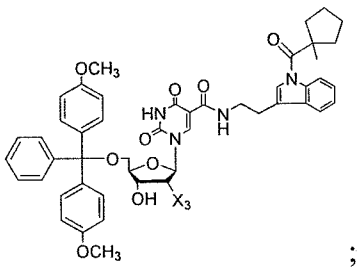
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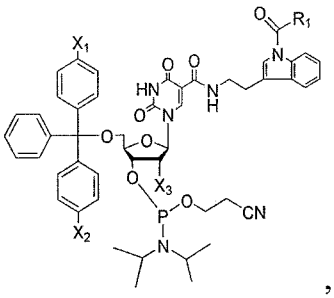
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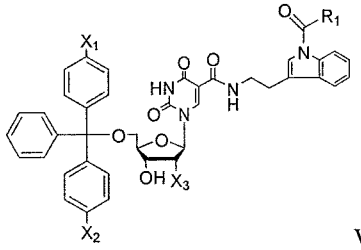
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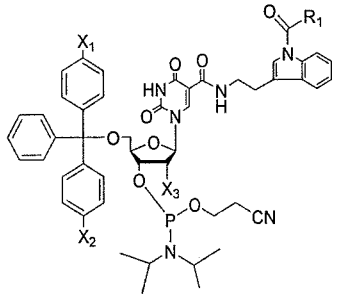


, or a salt thereof, is provided. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, X_1 and X_2 are each independently selected from methoxy and hydrogen. In some embodiments, X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy. In some embodiments, the method comprises reacting the compound



with 2-cyanoethyl-N,N,N',N'-tetraisopropylphosphor-amidite.

[0023a] In another aspect, there is provided a method of producing a compound comprising:

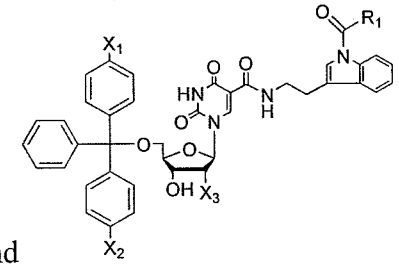


, or a salt thereof; wherein,

R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

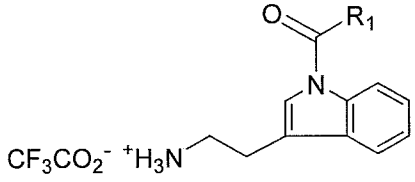
X_1 and X_2 are each independently selected from methoxy and hydrogen;

X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy;

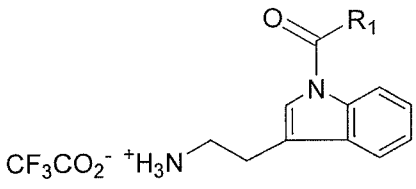


the method comprising reacting the compound with 2-cyanoethyl-N,N,N',N'-tetraisopropylphosphor-amidite.

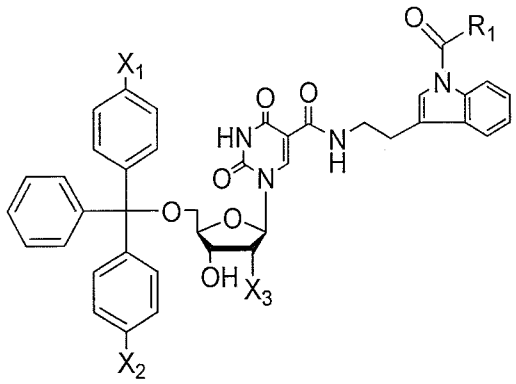
[0024] In some embodiments, the method comprises reacting the compound



with 5'-*O*-DMT-5-(2,2,2-trifluoroethyoxy-carbonyl)-2'-deoxyuridine (TFEdU) to form the compound

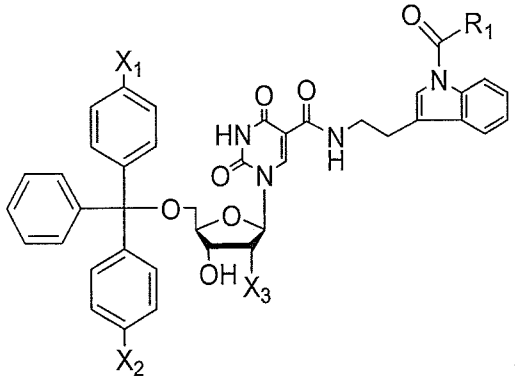


with 5'-*O*-DMT-5-(2,2,2-trifluoroethyoxy-carbonyl)-2'-deoxyuridine (TFEdU) to form the compound



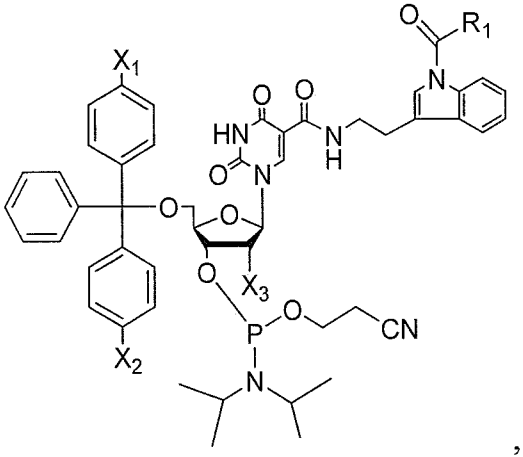
; and

d) reacting the compound



with 2-cyanoethyl-N,N,N',N'-tetraisopropylphosphor-amidite.

[0026a] In another aspect, there is provided a method of producing a compound comprising:



, or a salt thereof; wherein,

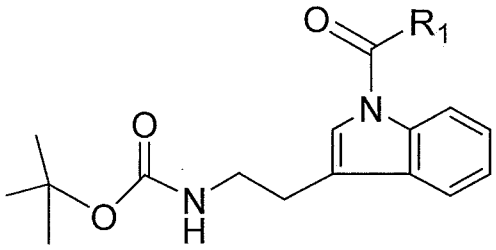
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_1 and X_2 are each independently selected from methoxy and hydrogen;

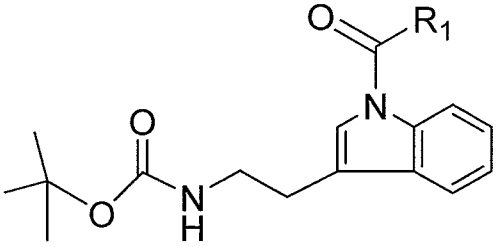
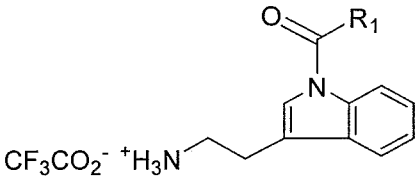
X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy;

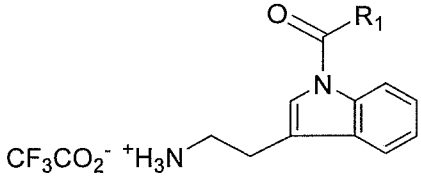
comprising the steps of:

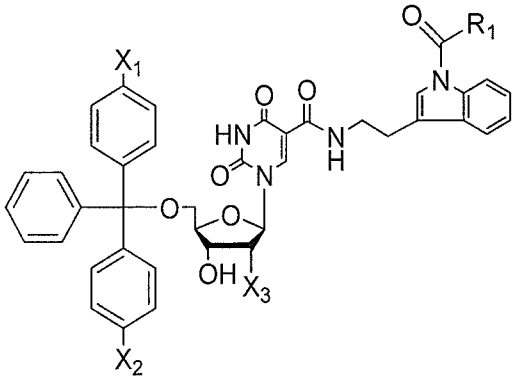
a) reacting N-α-BOC-tryptamine with an acid chloride selected from pivaloyl chloride, 2,2-dimethylbutyroyl chloride, 2,2-dimethylvaleroyl chloride, 1-methylcyclopentane-1-carbonyl chloride, 1-methylcyclohexane-1-carbonyl chloride, 2-chlorobenzoyl chloride, and 2-cyanobenzoyl chloride, to form the compound



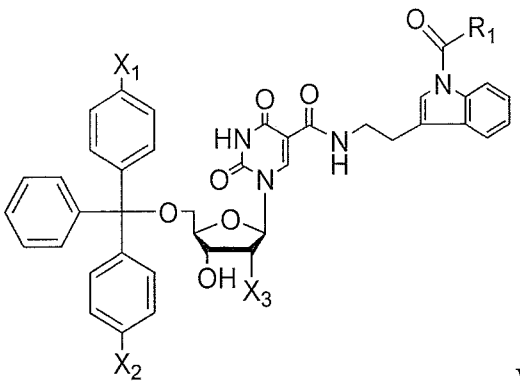
;

b) reacting the compound  with trifluoroacetic acid to form the compound ;

c) reacting the compound  with 5'-*O*-DMT-5-(2,2,2-trifluoroethyoxy-carbonyl)-2'-deoxyuridine (TFEdU) to form the compound

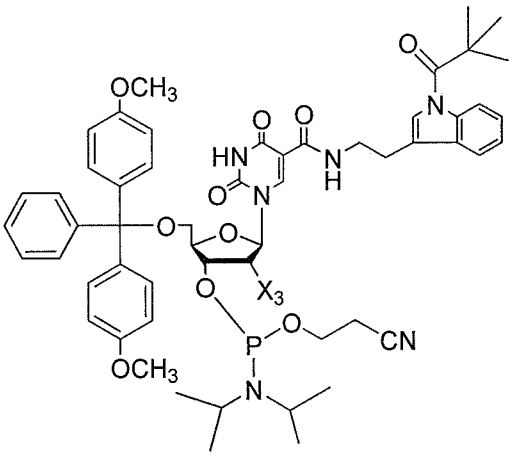


; and

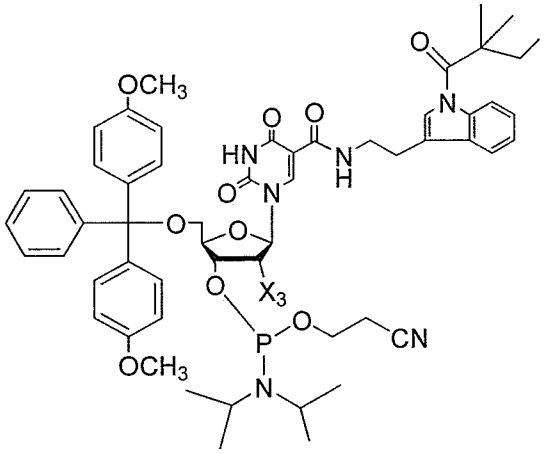


d) reacting the compound with 2-cyanoethyl-N,N,N',N'-tetraisopropylphosphor-amidite.

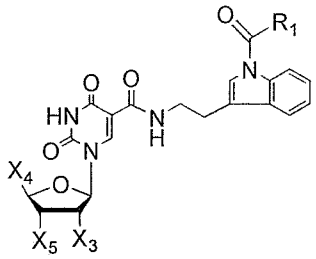
[0027] In some embodiments, the method produces a compound selected from:



;

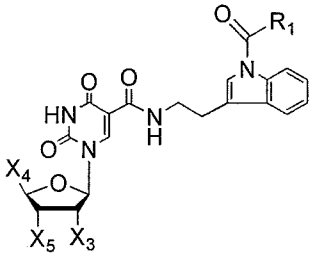


;



. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy. In some embodiments, X_4 is selected from OH, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide. In some embodiments, X_5 is selected from –O-ss, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein ss is a solid support, Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide. In some embodiments, the solid support is controlled-pore glass (CPG). In some embodiments, Z' is S and Z" is O. In some embodiments, Z' and Z" are O.

[0028a] In another aspect, there is provided an oligonucleotide comprising at least one protected TrpU nucleotide, wherein at least one protected TrpU nucleotide in the oligonucleotide has the structure:



; wherein,

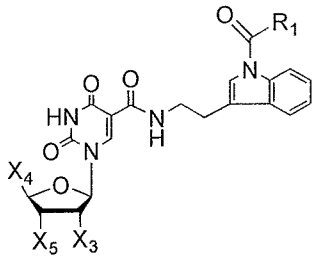
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy;

X_4 is selected from OH, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide; and

X_5 is selected from –O-ss, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein ss is a solid support, Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide.

[0029] In some embodiments, a method of producing an oligonucleotide comprising at least one TrpU nucleotide is provided, comprising incorporating at least one nucleotide having the structure:

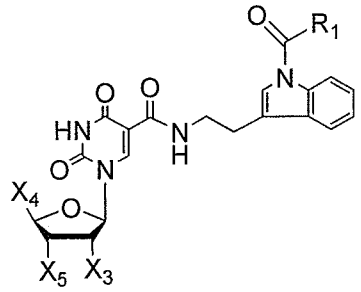


into a nucleotide sequence on a solid support; and removing the



protecting group from the at least one TrpU nucleotide incorporated into the oligonucleotide. In some embodiments, R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl. In some embodiments, X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy. In some embodiments, X_4 is selected from OH, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide. In some embodiments, X_5 is selected from –O-ss, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein ss is a solid support, Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide. In some embodiments, the solid support is controlled-pore glass (CPG). In some embodiments, Z' is S and Z" is O. In some embodiments, Z' and Z" are O.

[0029a] In another aspect, there is provided a method of producing an oligonucleotide comprising at least one TrpU nucleotide, comprising incorporating at least one nucleotide having the structure:



wherein,

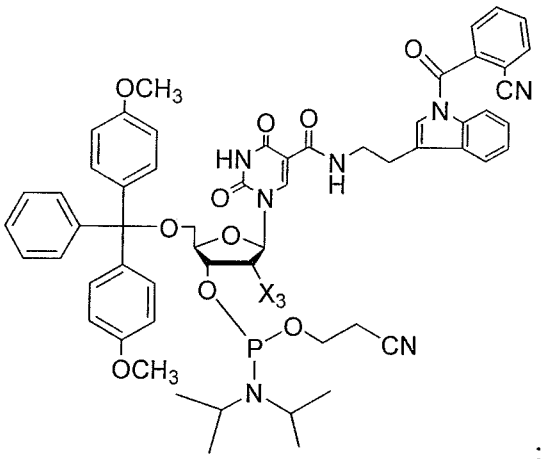
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy;

X_4 is selected from OH, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide; and

X_5 is selected from –O-ss, –OR, -SR, and –Z-P(Z')(Z")O-R, wherein ss is a solid support, Z, Z', and Z" are each independently selected from O and S, and R is an adjacent nucleotide in the oligonucleotide;

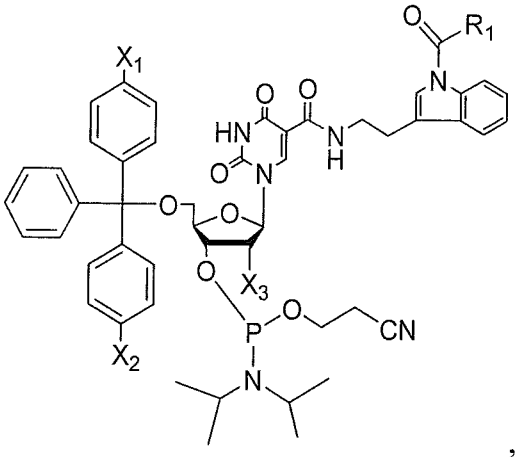
into a nucleotide sequence on a solid support; and removing the  protecting group from the at least one TrpU nucleotide incorporated into the oligonucleotide.



;

and salts thereof.

42. A method of producing a compound comprising:



, or a salt thereof;

wherein,

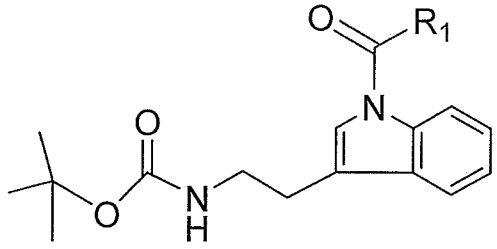
R_1 is selected from *tert*-butyl, 1,1-dimethyl-propyl; 1,1-dimethyl-butyl; 2-chlorophenyl; 2-cyanophenyl; 1-methyl-cyclopentyl; and 1-methyl-cyclohexyl;

X_1 and X_2 are each independently selected from methoxy and hydrogen;

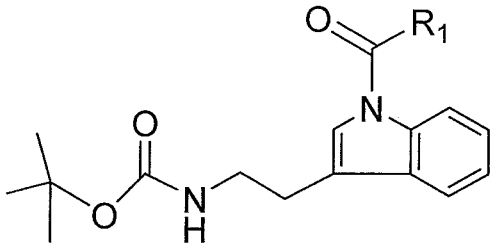
X_3 is selected from a methoxy, fluoro, hydrogen, and *tert*-butyldimethylsilyloxy;

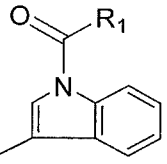
comprising the steps of:

a) reacting N-α-BOC-tryptamine with an acid chloride selected from pivaloyl chloride, 2,2-dimethylbutyroyl chloride, 2,2-dimethylvaleroyl chloride, 1-methylcyclopentane-1-carbonyl chloride, 1-methylcyclohexane-1-carbonyl chloride, 2-chlorobenzoyl chloride, and 2-cyanobenzoyl chloride, to form the compound

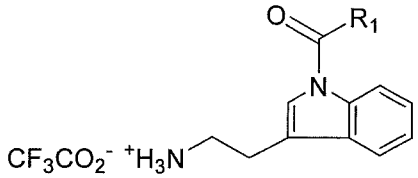

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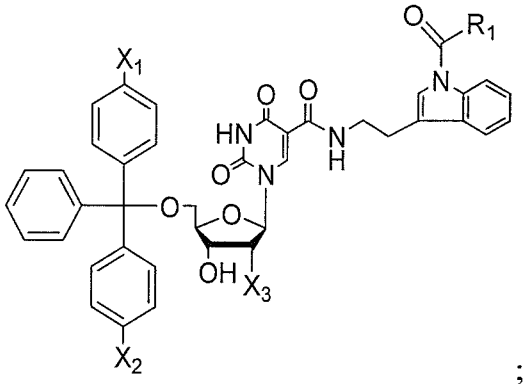
b) reacting the compound


with trifluoroacetic acid to form the


compound $CF_3CO_2^-$ ^+H_3N ;

c) reacting the compound


with 5'-*O*-DMT-5-(2,2,2-trifluoroethyoxy-carbonyl)-2'-deoxyuridine (TFEdU) to form the compound


; and

d) reacting the compound