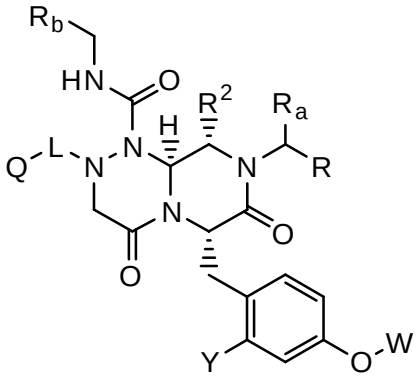
CLAIMS

1. A compound of formula (Ia):



(Ia)

and pharmaceutically acceptable salts thereof, wherein:

R_a is hydrogen or $-CH_3$;

R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and which may have one or more substituents selected from a group consisting of halide, cyano, and lower alkyl;

R is a phenyl group; a substituted phenyl group having one or more substituents wherein the one or more substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl groups; a benzyl group; a substituted benzyl group with one or more substituents where the one or more substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl group; or a bicyclic aryl group, or substituted bicyclic aryl, having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur, where the substituted bicyclic aryl may have one or more substituents independently selected from amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl group;

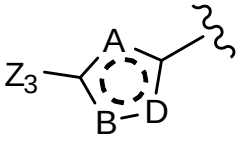
R^2 is hydrogen, or $-CH_3$;

Y is selected from: hydrogen, deuterium, or halogen;

W is hydrogen, phosphate or phosphate salt, an ester of an alkyl acid or of a fatty acid;

L is $-CH_2-$, $-CF_2-$, or $-C(CH_3)_2-$; and

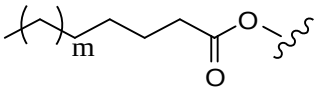
Q is a 5-membered nitrogen-containing heteroaryl substituted by 0 - 2 substituents, selected from:



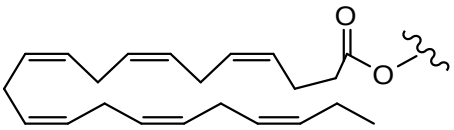
, wherein A, B, and D are independently selected from O, N, or -CH, wherein at least one of A, B, and D is O and at least one of A, B, and D is N

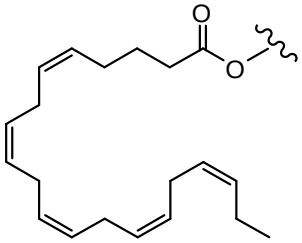
and wherein Z_3 is selected from hydrogen, halogen, or a direct-bonded, or -NH-linked, $-OC_1-C_3$ alkyl linked, or $-NHC_1-C_3$ alkyl linked aryl, heteroaryl, cycloalkyl, heterocycloalkyl, or a nitrogen-bonded cycloalkyl, heterocycloalkyl, or $-NHC_1-C_4$ alkyl, $-N(C_1-C_4$ alkyl$)_2$, each of which is substituted by 0 - 4 substituents independently selected from hydrogen, deuterium, halogen, C_1-C_4 alkyl, C_1-C_3 haloalkyl, -OH, $-OC_1-C_6$ alkyl, $-OC_1-C_6$ alkyl-C(O)NH-OH, $-NH_2$, -C(O)NH- C_1-C_6 alkyl-heteroaryl, $-NHC(O)C_1-C_6$ alkyl-C(O)NH-OH, heteroaryl, cycloalkyl, heterocycloalkyl, or a nitrogen-bonded cycloalkyl or heterocycloalkyl, $-NHC_1-C_4$ alkyl, or $-N(C_1-C_4$ alkyl$)_2$.

2. The compound of claim 1, wherein the ester of the alkyl acid or of the fatty acid is selected from:



wherein m is 1 to 14,





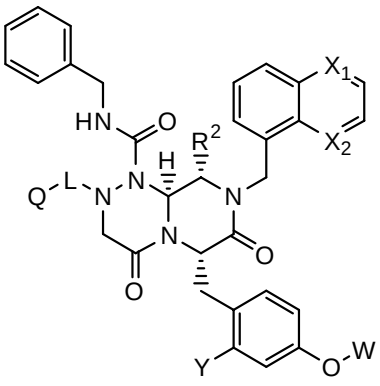
, or ;

and/or

wherein R is a bicyclic aryl selected from naphthyl, quinolinyl, isoquinolinyl, quinoxaline, phthalazine, quinazoline, cinnoline, naphthyridine, or substituted variants thereof.

3. The compound of claim 1 or claim 2, wherein the compound is of the

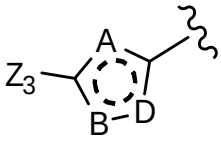
formula (Ib):

(Ib) 

, wherein X_1 and X_2 are independently selected from: N, or -CH.

4. The compound of claim 3, wherein:

L is $-CH_2-$;

Q is 

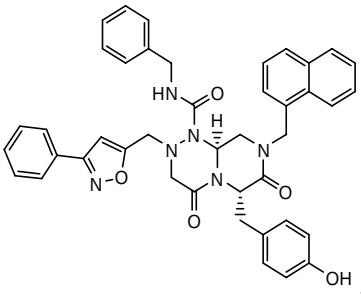
, wherein A, B, and D are independently selected from O, N, or -CH, wherein at least one of A, B, and D is O and at least one of A, B, and D is N.

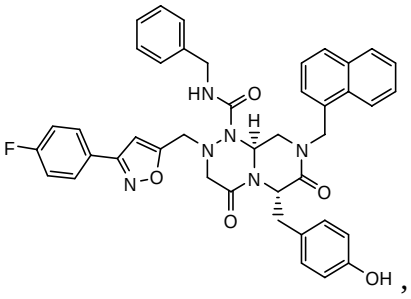
5. The compound of claim 4, wherein A is -CH, B is N, and D is O (Z_3-isoxazole-), and wherein W is hydrogen, phosphate or phosphate salt, an ester of an alkyl acid or of a fatty acid,;

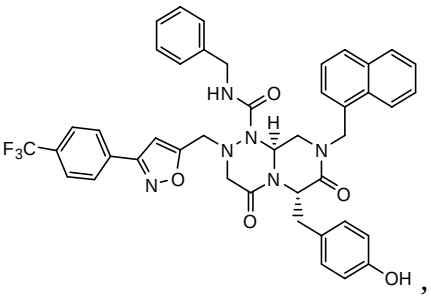
preferably wherein Z_3 is selected from aryl or heteroaryl, each of which is substituted by 0 - 4 substituents independently selected from hydrogen, deuterium, halogen, C_1-C_4 alkyl, C_1-C_3 haloalkyl, -OH, $-OC_1$-C_6 alkyl, $-OC_1$-C_6 alkyl-C(O)NH-OH, $-NH_2$, -C(O)NH- C_1-C_6 alkyl-heteroaryl, $-NHC(O)C_1$-C_6 alkyl-C(O)NH-OH, heteroaryl, cycloalkyl, heterocycloalkyl, or a nitrogen-bonded cycloalkyl or heterocycloalkyl, $-NHC_1$-C_4 alkyl, or $-N(C_1$-C_4 alkyl$)_2$;

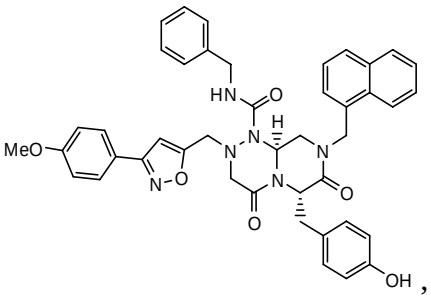
preferably wherein Z_3 is selected from aryl or heteroaryl, substituted by 0 - 4 substituents independently selected from hydrogen, deuterium, halogen, C_1-C_4 alkyl, C_1-C_3 haloalkyl, -OH, $-OC_1$-C_6 alkyl, or nitrogen-bonded heterocycloalkyl.

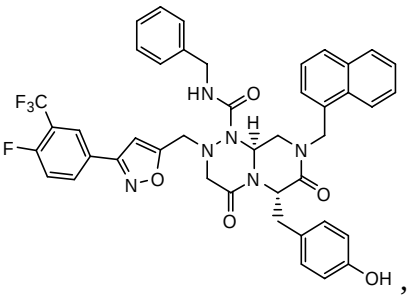
6. The compound of claim 4, wherein the compound is:

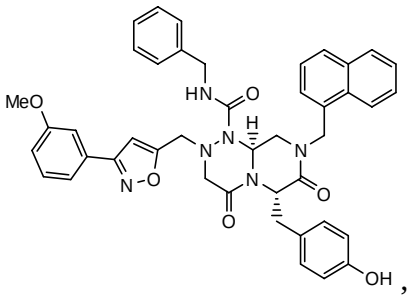


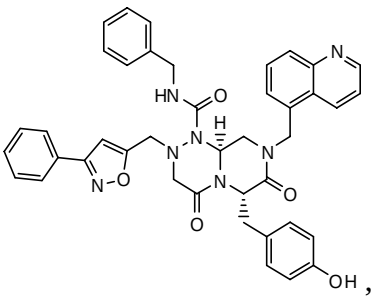


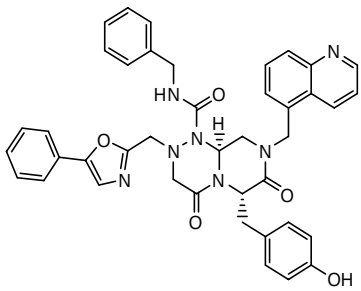


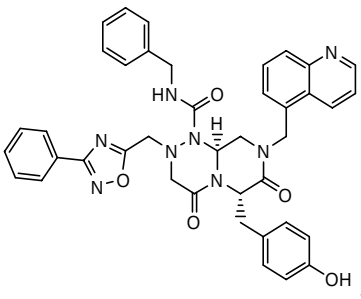


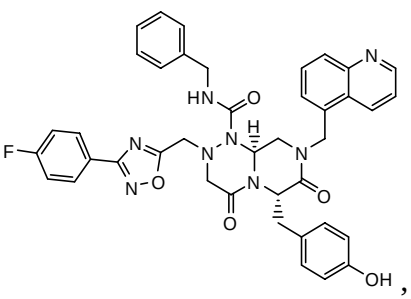


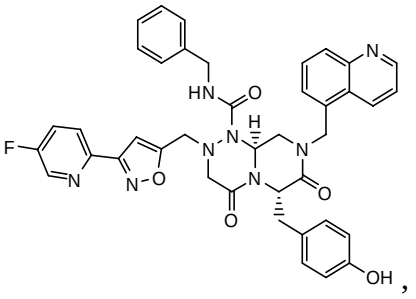
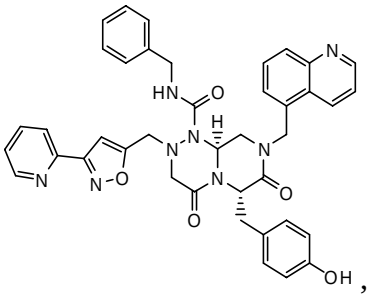
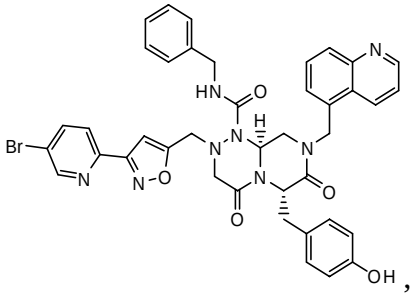
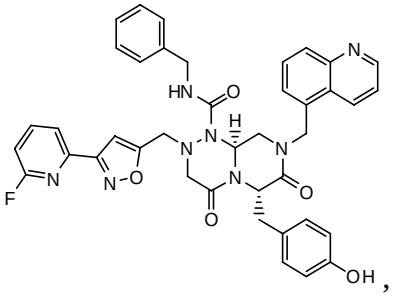
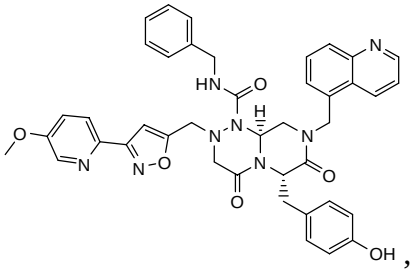
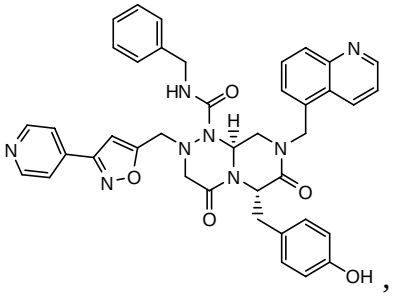
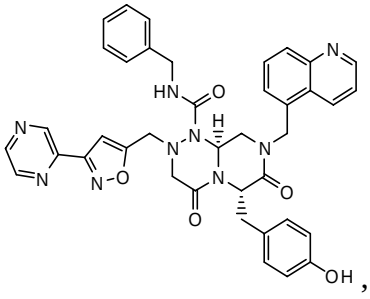
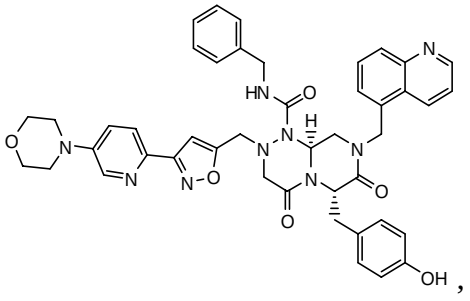
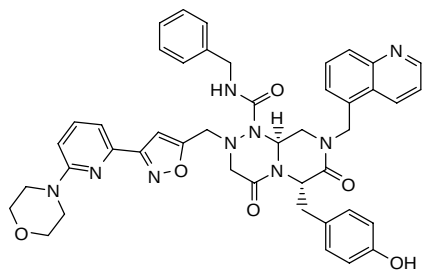


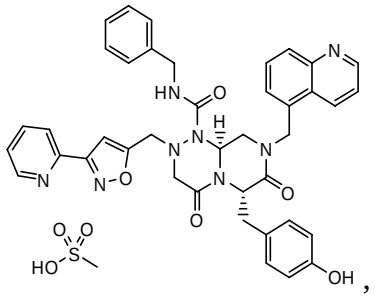




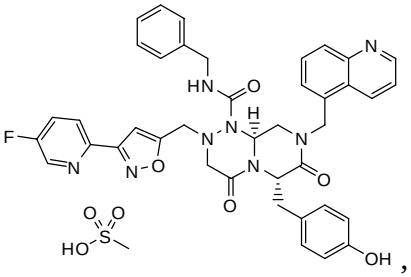





,

,

,

,

,

,

,

,

,

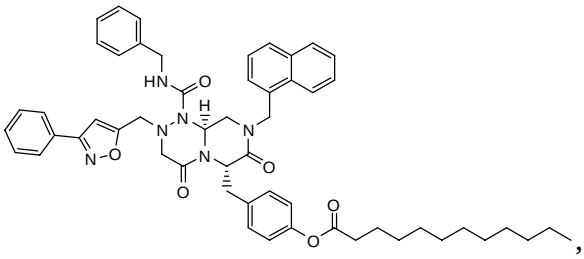


,

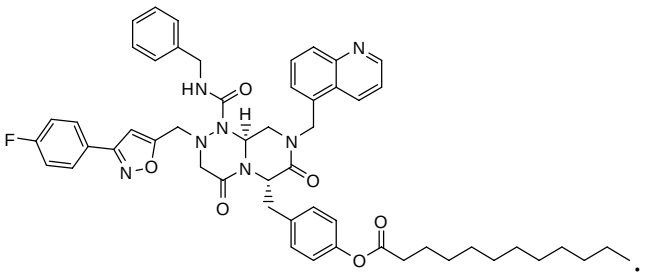


,

,



,



.

7. A composition or pharmaceutical composition comprising the compound of any one of claims 1 to 6, and a pharmaceutically acceptable carrier.

8. Use of a compound, composition or pharmaceutical composition of any one of claims 1 to 7 in the manufacture of a medicament for treating a disease or disorder in a patient or a warm-blooded mammal having a disease or disorder mediated by CREB binding protein (CBP)/β-catenin signaling, wherein the disease or disorder is one or more of fibrosis, cancer, neurological conditions, metabolic disorders, skin conditions, and aging.

9. The use of claim 8, wherein, in the compound, W is hydrogen, phosphate or phosphate salt.

10. The use of claim 8 or claim 9, wherein the disease or disorder comprises one or more of:

fibrosis, cancer, neurological conditions, metabolic disorders, and skin conditions.

11. The use of claim 10, wherein the metabolic disorder comprises one or more of diabetes and/or fatty liver disease.

12. The use of claim 11, wherein the fatty liver disease comprises one or more of alcoholic hepatic steatosis (ALD), non-alcoholic hepatic steatosis (NAFLD), and/or non-alcoholic steatohepatitis (NASH).

13. The use of claim 10, wherein the fibrosis is fibrosis of the lung, liver, kidney, heart, endometrium, skin or systemic fibrosis.

14. The use of claim 13, wherein the fibrosis comprises fibrosis in a SARS-CoV-2 (COVID-19) patient tissue.

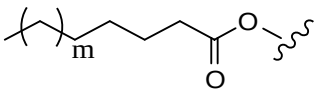
15. The use of claim 10, wherein the disease is cancer, and wherein the CBP/β-catenin antagonist is to be administered in combination with, or as an adjunctive therapy with, one or more of cytotoxic and/or directed chemotherapy, and/or radiotherapy, and/or immunotherapy, including checkpoint inhibition, chimeric antigen receptor (CAR-T) and/or CAR-NK.

16. The use of claim 10, wherein the neurological condition comprises one or more of Huntington’s (HD), Parkinson’s (PD), Alzheimer’s (AD), Multiple sclerosis (MS), and/or amyotrophic lateral sclerosis (ALS), muscular dystrophy (MD), and/or spinal muscular atrophy (SMA).

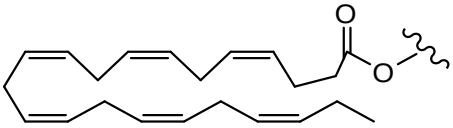
17. The use of claim 10, wherein the skin condition comprises one or more of atopic dermatitis, psoriasis, acne, fibrosis, wounding, scarring, burns, sun or U.V. damage, diabetic ulceration, chronic ulceration, and/or alopecia.

18. The use of claim 17, wherein W is an ester of an alkyl acid or of a fatty acid, and wherein the medicament is to be administered topically or transdermally.

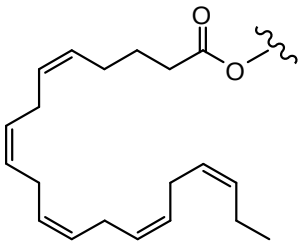
19. A cosmetic method for treating a skin condition, comprising topically administering to a patient or a warm-blooded mammal, having a skin condition, a cosmeceutically effective amount of the compound or composition of any one of claims 1 to 7, wherein W is an ester of an alkyl acid or of a fatty acid, preferably, wherein the ester of the alkyl acid or of the fatty acid is selected from:



wherein m is 1 to 14,



, or

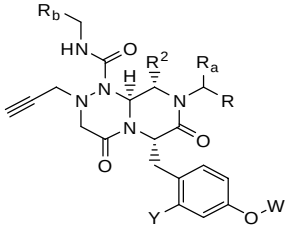


;

preferably wherein the skin condition comprises one or more aging skin conditions selected from wrinkles, hyperpigmentation, redness, rosacea, dryness, cracking, loss of vibrance, loss of elasticity, thinning, loss of vibrance, scarring, acne, sun damage, hair loss, and/or loss of hair coloration.

20. A method for efficiently synthesizing a clinical grade drug, comprising use, in a penultimate, or last reaction step under GMP conditions, of an intermediate 2-propynyl-compound to form a clinical grade isoxazole derivative via 3 + 2 cycloaddition; preferably

wherein preparing the clinical grade isoxazole derivative comprises preparing a compound according to claim 5 using, in the penultimate, or last reaction step, said step prior to any optional formation of a final pharmaceutically acceptable salt, phosphate or phosphate salt, an intermediate 2-propynyl-compound of formula (IIa):



(IIa)

wherein:

R_a is hydrogen or -CH_3;

R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and which may have one or more substituents selected from a group consisting of halide, cyano, and lower alkyl;

R is a phenyl group; a substituted phenyl group having one or more substituents wherein the one or more substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl groups; a benzyl group; a substituted benzyl group with one or more substituents where the one or more substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl group; or a bicyclic aryl group having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur;

R^2 is hydrogen, or -CH_3;

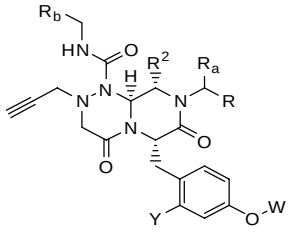
Y is selected from: hydrogen, deuterium, or halogen;

W is hydrogen, an ester of an alkyl acid or of a fatty acid;

and/or

wherein the last or penultimate step, performed under GMP conditions, is preceded by one or more reaction steps under non-GMP conditions, as part of an overall reaction scheme for preparing the clinical grade isoxazole derivative.

21. A compound of formula (IIa):



(IIa)

wherein:

R_a is methyl or hydrogen;

R_b is a monocyclic aryl group having 5 to 7 ring members, which may have 1 to 2 heteroatoms selected from nitrogen, oxygen or sulfur, and which may have one or more substituents selected from a group consisting of halide, cyano, and lower alkyl;

R is a phenyl group; a substituted phenyl group having one or more substituents wherein the one or more substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl groups; a benzyl group; a substituted benzyl group with one or more substituents where the one or more substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, and hydroxyl group; or a bicyclic aryl group having 8 to 11 ring members, which may have 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur;

R^2 is hydrogen, or $-CH_3$;

Y is selected from: hydrogen, deuterium, or halogen;

W is X, wherein X is selected from: an alkyl acid or fatty acid.

22. Use of a compound, composition or pharmaceutical composition of any one of claims 1 to 7 in the manufacture of a medicament for enhancing anti-viral vaccine efficacy, wherein an amount of said compound, composition or pharmaceutical composition sufficient to inhibit CBP/β-catenin mediated signaling and/or enhance p300/catenin mediated signaling is to be administered to a subject, prior to, and/or during, and/or after vaccination; preferably

wherein enhancing vaccine efficacy comprises one or more of: increased levels of vaccine antigen-specific antibodies; an increase in the percent protection afforded; an increase in the number or and/or persistence of differentiated memory T-cells; and/or an increase in the duration of protection; and/or

wherein inhibiting the CBP/β-catenin mediated signaling and/or enhancing the p300/catenin mediated signaling comprises one or more of: metabolic maintenance of cell asymmetry following division in activated T cells of the subject; enhancing antigen-specific immunity by increasing the number and/or persistence of differentiated memory T-cells: and/or enhancing the presentation of antigens to T-cells by antigen

presenting cells to enhance cooperativity between the innate and acquired immune systems.

23. The use of claim 22,

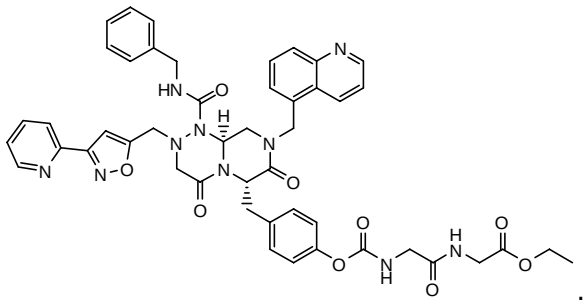
wherein an anti-viral vaccine is to be administered in the vaccination; and/or

wherein an anti-viral vaccine selected from influenza, SARS, SARS-CoV-2, HPV-A, HPV-B, and/or Herpes Zoster is to be administered in the vaccination; and/or

wherein the subject is a human having an age of 55-75 yr, 55-85 yr, ≥ 50 yr, ≥60 yr, or ≥ 65 yrs; and/or

wherein an anti-viral vaccine is to be administered as a primer before vaccination; and/or co-administered with vaccination; and/or administered or co-administered subsequent to initial vaccine.

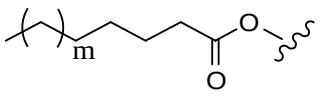
24. A compound having the structure or a pharmaceutically acceptable salt thereof,

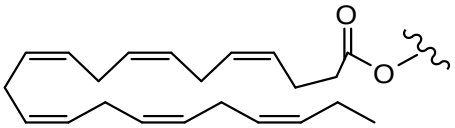


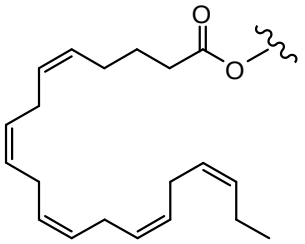
.

25. A composition or pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt thereof of claim 24, and a pharmaceutically acceptable carrier.

26. A cosmetic method for treating reduced cuticle growth or reduced nail growth, comprising topically administering to a patient or a warm-blooded mammal, having reduced cuticle growth or reduced nail growth, a cosmeceutically effective amount of the compound or composition of any one of claims 1 to 7, wherein W is an ester of an alkyl acid or of a fatty acid, preferably, wherein the ester of the alkyl acid or of the fatty acid is selected from:



wherein m is 1 to 14,


, or


.