

INHIBITING CREB BINDING PROTEIN (CBP)

Cross-Reference to Related Applications

[0001] This application claims the benefit of U.S. Provisional Application No. 62/692,593, filed June 29, 2018, International Application No. PCT/US2018/051235, filed September 14, 2018, International Application No. PCT/US2018/051214, filed September 14, 2018, and U.S. Provisional Application No. 62/819,490, filed March 15, 2019, each of which is incorporated by reference in its entirety.

Technical Field

[0002] This disclosure relates to novel chemical compositions for inhibiting the CREB binding protein (CBP), useful in the treatment of diseases or disorders associated with the inhibition of CBP/p300 family of bromodomains.

Background

[0003] CBP/p300 are lysine acetyltransferases that catalyze the attachment of an acetyl group to a lysine side chain of histones and other protein substrates. p300 (also known as EP300 and KAT3B) is a protein with multiple domains that bind to diverse proteins including many DNA-binding transcription factors. The cyclic AMP-responsive element-binding protein (CREB) binding protein (CBP, also known as KAT3A) is a cellular paralog of p300. p300 and CBP share extensive sequence identity and functional similarity and are often referred to as CBP/p300. CBP/p300-catalyzed acetylation of histones and other proteins is pivotal to gene activation. Heightened p300 expression and activities have been observed in advanced human cancers such as prostate and in human primary breast cancer specimens. Chemical inhibition of CBP/p300 that possesses intrinsic acetyltransferase enzymatic activity is more feasible than blocking transcription factors with small molecules, as discovery of chemical inhibitors of transcription factors has proven extremely challenging. Accordingly, there is a need for novel and potent compounds for inhibiting CBP/p300, useful as therapies for treating certain related forms of cancer.

Summary

[0004] A first aspect of the present disclosure relates to compounds of Formula (I):

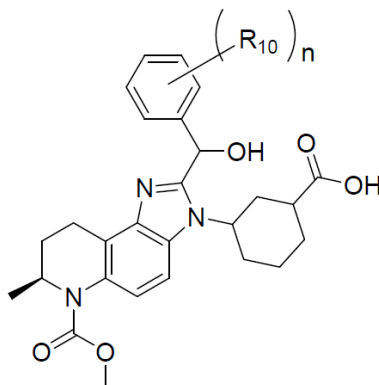
–C(O)OC₁–C₆alkyl, –N(C₁–C₆alkyl)SO₂C₁–C₆alkyl, –S(O)(C₁–C₆alkyl), –S(O)N(C₁–C₆alkyl)₂, or –N(C₁–C₆alkyl)S(O)(C₁–C₆alkyl), wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, or aryl is optionally substituted with one or more –R¹²;

wherein any two R¹⁰ when on non-adjacent atoms, can combine to form a bridging cycloalkyl or heterocyclyl;

wherein any two R¹⁰ when on adjacent atoms, can combine to form a cycloalkyl, heterocyclyl, aryl or heteroaryl; and

R¹² is independently, at each occurrence, –C₁–C₆alkyl, –C₂–C₆alkenyl, –C₂–C₆alkynyl, –C₃–C₈cycloalkyl, –C₄–C₈cycloalkenyl, heterocyclyl, heteroaryl, aryl, –OH, halogen, oxo, –NO₂, –CN, –NH₂, –OC₁–C₆alkyl, –NHC₁–C₆alkyl, –N(C₁–C₆alkyl)₂, –S(O)₂NH(C₁–C₆alkyl), –S(O)₂N(C₁–C₆alkyl)₂, –S(O)₂C₁–C₆alkyl, –C(O)C₁–C₆alkyl, –C(O)NH₂, –C(O)NH(C₁–C₆alkyl), –C(O)N(C₁–C₆alkyl)₂, –C(O)OC₁–C₆alkyl, –N(C₁–C₆alkyl)SO₂C₁–C₆alkyl, –S(O)(C₁–C₆alkyl), –S(O)N(C₁–C₆alkyl)₂, or –N(C₁–C₆alkyl)S(O)(C₁–C₆alkyl).

[0005] Preferably, the compounds of Formula (I) are a compound of Formula (IV):

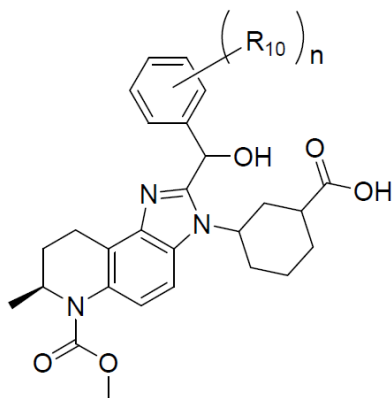


(IV),

or a pharmaceutically acceptable salt thereof, wherein:

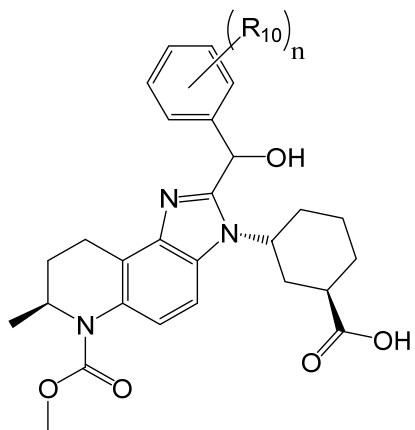
n is 0, 1, 2, 3, 4, or 5;

each R¹⁰ is independently, at each occurrence, –C₁–C₆alkyl, –C₂–C₆alkenyl, –C₂–C₆alkynyl, –C₃–C₈cycloalkyl, –C₄–C₈cycloalkenyl, heterocyclyl, heteroaryl, aryl, –OH, halogen, –NO₂, –CN, –NH₂, –OC₁–C₆alkyl, –OC₃–C₆cycloalkyl, –Oaryl, –Oheteroaryl, –NHC₁–C₆alkyl, –N(C₁–C₆alkyl)₂, –S(O)₂NH(C₁–C₆alkyl), –S(O)₂N(C₁–C₆alkyl)₂, –S(O)₂C₁–C₆alkyl, –C(O)C₁–C₆alkyl, –C(O)NH₂, –C(O)NH(C₁–C₆alkyl), –C(O)N(C₁–C₆alkyl)₂,



(IV),

or a pharmaceutically acceptable salt thereof, wherein *n* is an integer of 0, 1, 2, 3, 4, or 5 (preferably, 0, 1 or 2) and R₁₀ is as defined above. Preferably, the compound of Formula (IV) is a compound of Formula (IV-a) (including, for example, compounds of Formula (IV-b), Formula (IV-c) or mixtures thereof), or pharmaceutically acceptable salts thereof, wherein *n* is an integer of 0, 1, 2, 3, 4 or 5 (preferably 0, 1 or 2) and R₁₀ is as defined above.

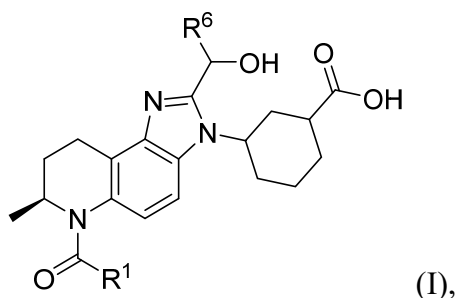


(IV-a)

wherein any two R¹⁰ when on adjacent atoms, can combine to form a cycloalkyl, heterocyclyl, aryl or heteroaryl; and

R¹² is independently, at each occurrence, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -C₄-C₈cycloalkenyl, heterocyclyl, heteroaryl, aryl, -OH, halogen, oxo, -NO₂, -CN, -NH₂, -OC₁-C₆alkyl, -NHC₁-C₆alkyl, -N(C₁-C₆alkyl)₂, -S(O)₂NH(C₁-C₆alkyl), -S(O)₂N(C₁-C₆alkyl)₂, -S(O)₂C₁-C₆alkyl, -C(O)C₁-C₆alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆alkyl), -C(O)N(C₁-C₆alkyl)₂, -C(O)OC₁-C₆alkyl, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, -S(O)(C₁-C₆alkyl), -S(O)N(C₁-C₆alkyl)₂, or -N(C₁-C₆alkyl)S(O)(C₁-C₆alkyl).

[0016] In some embodiments, compounds of the disclosure have the Formula (I)



or a pharmaceutically acceptable salt, enantiomer, hydrate, solvate, isomer, or tautomer thereof, wherein:

R¹ is -OR⁵;

R⁵ is -C₁-C₃alkyl;

R⁶ is phenyl optionally substituted with one or more R¹⁰;

R¹⁰ is each independently, at each occurrence halogen, -OC₁-C₆alkyl, -OC₃-C₆cycloalkyl, -Oaryl, or -Oheteroaryl, wherein each alkyl, cycloalkyl, aryl or heteroaryl is optionally substituted with one or more -R¹²;

R¹² is halogen.

[0017] In some embodiments, compounds of the disclosure have the Formula (III):

[0036] Preferably, the compound is a CBP Inhibitor Compound of Formula (I) wherein R₁ is –OCH₃. In some embodiments, a CBP Inhibitor Compound of Formula (I) includes R₁ is –OCH₃ and R₆ is C₆ aryl (phenyl) optionally substituted with one or more R₁₀. In some embodiments, a CBP Inhibitor Compound of Formula (I) includes R₁ is –OCH₃ and R₆ is C₆ aryl (phenyl) optionally substituted with one or more R₁₀ being selected from the group consisting of halogen (e.g., fluorine) and methoxy, wherein the methoxy is optionally substituted with one or more R₁₂. In some embodiments, a CBP Inhibitor Compound of Formula (I) includes R₁ is –OCH₃ and R₆ is C₆ aryl (phenyl) optionally substituted with one or more R₁₀ being selected from the group consisting of halogen (e.g., fluorine) and methoxy, wherein the methoxy is optionally substituted with one or more R₁₂ and R₁₂ is a halogen (preferably, fluorine).

[0037] In some embodiments, a compound of the disclosure is a compound selected from Figure 1, or a pharmaceutically acceptable salt thereof.

Method of Synthesizing the Compounds

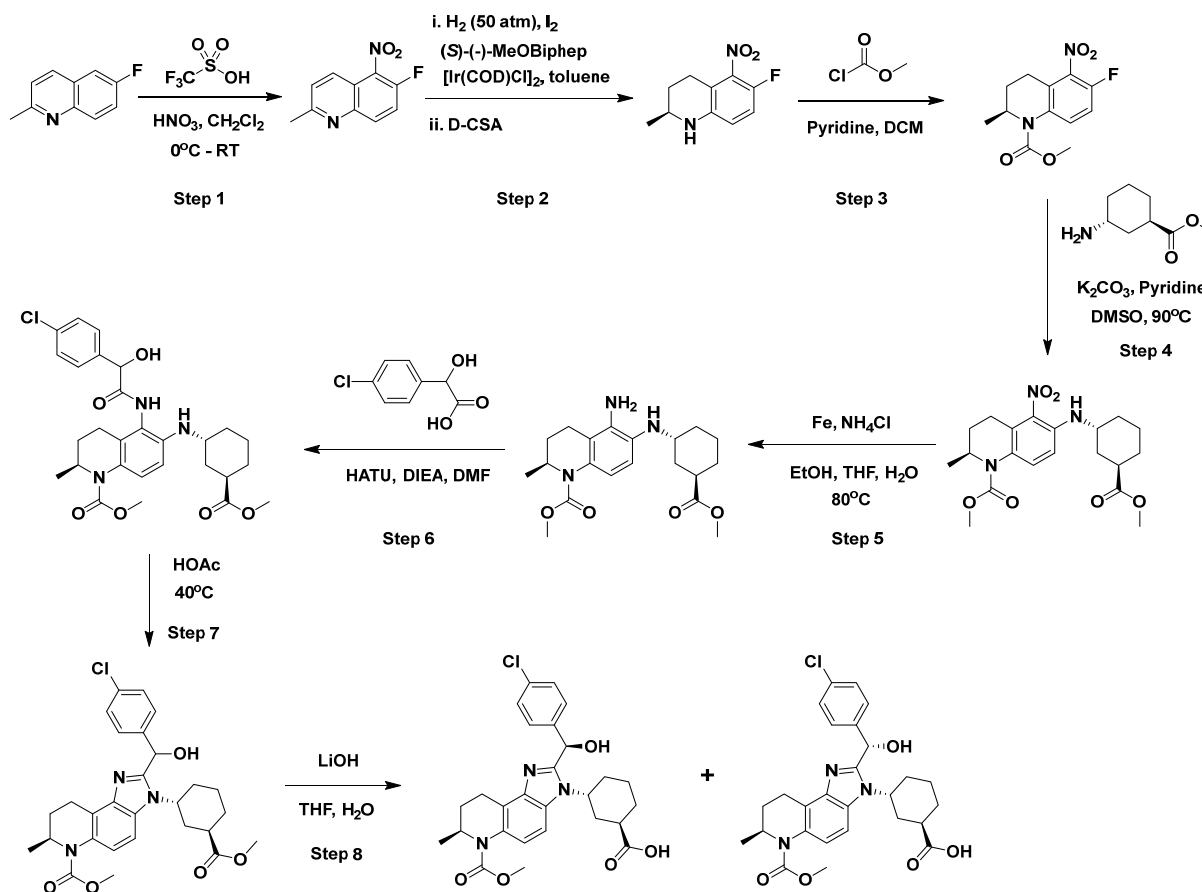
[0038] The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the examples given below.

[0039] The compounds of the present disclosure, *i.e.*, compounds of Formula (I), or a pharmaceutically acceptable salt, enantiomer, hydrate, solvate, prodrug, isomer, or tautomer thereof, may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula (I).

[0040] Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula (I). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or

[0062] The synthetic schemes are presented for the synthesis of certain compounds herein disclosed. The process and results for the assays testing BET family bromodomain inhibition are also described.

Example 1: methyl (S)-2-(2-(1H-pyrazol-1-yl)ethyl)-7-methyl-3-(2-(((1-methyl-1H-pyrazol-3-yl)methyl)amino)ethyl)-3,7,8,9-tetrahydro-6H-imidazo[4,5-f]quinoline-6-carboxylate



Step 1. 6-fluoro-2-methyl-5-nitroquinoline

[0063] A solution of trifluoromethanesulfonic acid (82.0 mL, 0.923 mol) in HNO_3 (19.6 mL, 0.437 mol) was stirred for 20 min at 0°C . This was followed by the addition of 6-fluoro-2-methylquinoline (50.0 g, 0.310 mol) in dichloromethane (300 mL) at 0°C . The resulting mixture was stirred for 15 hours at room temperature (25°C). The reaction mixture was diluted with water (300 mL). The pH value of the solution was adjusted to 8 with sodium bicarbonate (saturated aqueous solution). The resulting solution was extracted with dichloromethane (3 x 300 mL). The

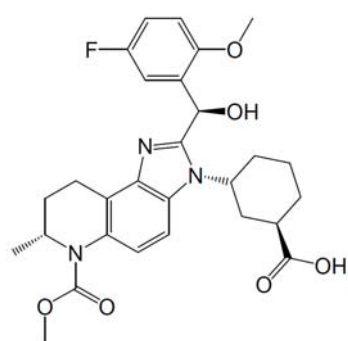
layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:1 ethyl acetate/petroleum ether) to afford methyl (2S)-5-[2-(4-chlorophenyl)-2-hydroxyacetamido]-6-[[(1R,3R)-3-(methoxycarbonyl)cyclohexyl]amino]-2-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylate as yellow oil (70.0 mg, 32%). LCMS (ES, m/z): 544 $[M+H]^+$.

Step 7. methyl (7S)-2-[(4-chlorophenyl)(hydroxy)methyl]-3-[(1R,3R)-3-(methoxycarbonyl)cyclohexyl]-7-methyl-3H,6H,7H,8H,9H-imidazo[4,5-f]quinoline-6-carboxylate

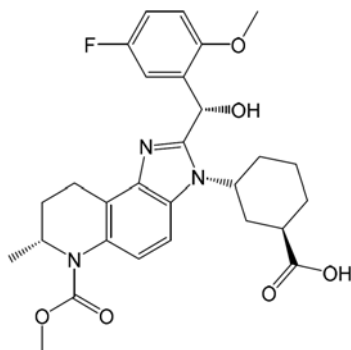
[0068] A solution of methyl (2S)-5-[2-(4-chlorophenyl)-2-hydroxyacetamido]-6-[[(1R,3R)-3-(methoxycarbonyl)cyclohexyl]amino]-2-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (60.0 mg, 0.11 mmol) in AcOH (2 mL) was stirred for 15 h at 40 °C and then cooled to room temperature. The reaction mixture was diluted with water (10 mL). The pH value of the solution was adjusted to 8 with sodium bicarbonate (saturated aqueous solution). The resulting solution was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined and dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:1 ethyl acetate/petroleum ether) to afford methyl (7S)-2-[(4-chlorophenyl)(hydroxy)methyl]-3-[(1R,3R)-3-(methoxycarbonyl)cyclohexyl]-7-methyl-3H,6H,7H,8H,9H-imidazo[4,5-f]quinoline-6-carboxylate as yellow oil (46.0 mg, 79%). LCMS (ES, m/z): 526 $[M+H]^+$.

Step 8. (1R,3R)-3-[(7S)-2-[(R)-(4-chlorophenyl)(hydroxy)methyl]-6-(methoxycarbonyl)-7-methyl-3H,6H,7H,8H,9H-imidazo[4,5-f]quinolin-3-yl]cyclohexane-1-carboxylic acid; (1R,3R)-3-[(7S)-2-[(S)-(4-chlorophenyl)(hydroxy)methyl]-6-(methoxycarbonyl)-7-methyl-3H,6H,7H,8H,9H-imidazo[4,5-f]quinolin-3-yl]cyclohexane-1-carboxylic acid

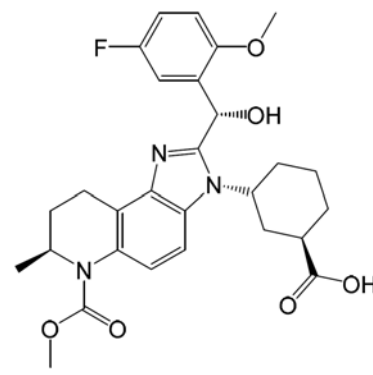
[0069] A solution of methyl (7S)-2-[(4-chlorophenyl)(hydroxy)methyl]-3-[(1R,3R)-3-(methoxycarbonyl)cyclohexyl]-7-methyl-3H,6H,7H,8H,9H-imidazo[4,5-f]quinoline-6-carboxylate (50.0 mg, 0.10 mmol), and LiOH (11.4 mg, 0.48 mmol) in tetrahydrofuran (1 mL) and water (1 mL) was stirred for 15 h at 25 °C. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: ACN (10%



(II-m)



(II-n)



(II-o)/compound 660

[0084] In any of the foregoing embodiments, the percentage purity recited may be determined by HPLC. In some embodiments the percentage purity is determined using the following HPLC method:

Sample Preparation:

Prepare 0.2mg/mL in 70/30 Water/Acetonitrile.

LCMS Information:

Instruments:

MS: Waters QDa MS

HPLC: Waters Alliance e2695

UV: Waters 2998 PDA

Conditions:

Mobile Phase A: 10mM Ammonium acetate

Mobile Phase B: Acetonitrile

Column: Waters XSelect Phenyl-Hexyl, 3.5 μ m, 4.6x150 mm

Column Temperature: 35°C

LC Gradient:

Runtime: 25 min

LC Flow Rate: 1 mL/min

UV Wavelength: 238 nm

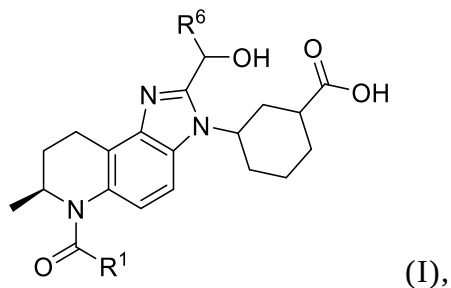
Ionization Mode: Electrospray Ionization +ive

Injection Volume: 8 μ L

[0085] For instance, the disclosure provides a pharmaceutical composition comprising compound 424 or a pharmaceutically acceptable salt thereof at a purity of at least 95% as determined by the above HPLC method. The disclosure also provides a pharmaceutical composition comprising compound 424 at a purity of at least 95% as determined by the above HPLC method.

Claims:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt, enantiomer, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

R¹ is -OR⁵;

R⁵ is -C₁-C₆alkyl;

R⁶ is phenyl optionally substituted with one or more R¹⁰;

R¹⁰ is each independently, at each occurrence, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -C₄-C₈cycloalkenyl, heterocyclyl, heteroaryl, aryl, -OH, halogen, -NO₂, -CN, -NH₂, -OC₁-C₆alkyl, -OC₃-C₆cycloalkyl, -Oaryl, -Oheteroaryl, -NHC₁-C₆alkyl, -N(C₁-C₆alkyl)₂, -S(O)₂NH(C₁-C₆alkyl), -S(O)₂N(C₁-C₆alkyl)₂, -S(O)₂C₁-C₆alkyl, -C(O)C₁-C₆alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆alkyl), -C(O)N(C₁-C₆alkyl)₂, -C(O)OC₁-C₆alkyl, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, -S(O)(C₁-C₆alkyl), -S(O)N(C₁-C₆alkyl)₂, or -N(C₁-C₆alkyl)S(O)(C₁-C₆alkyl), wherein each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, or aryl is optionally substituted with one or more -R¹²;

wherein any two R¹⁰ when on non-adjacent atoms, can combine to form a bridging cycloalkyl or heterocyclyl;

wherein any two R¹⁰ when on adjacent atoms, can combine to form a cycloalkyl, heterocyclyl, aryl or heteroaryl;

R¹² is independently, at each occurrence, -C₁-C₆alkyl, -C₂-C₆alkenyl, -C₂-C₆alkynyl, -C₃-C₈cycloalkyl, -C₄-C₈cycloalkenyl, heterocyclyl, heteroaryl, aryl,

–OH, halogen, oxo, –NO₂, –CN, –NH₂, –OC₁–C₆alkyl, –NHC₁–C₆alkyl, –N(C₁–C₆alkyl)₂, –S(O)₂NH(C₁–C₆alkyl), –S(O)₂N(C₁–C₆alkyl)₂, –S(O)₂C₁–C₆alkyl, –C(O)C₁–C₆alkyl, –C(O)NH₂, –C(O)NH(C₁–C₆alkyl), –C(O)N(C₁–C₆alkyl)₂, –C(O)OC₁–C₆alkyl, –N(C₁–C₆alkyl)SO₂C₁–C₆alkyl, –S(O)(C₁–C₆alkyl), –S(O)N(C₁–C₆alkyl)₂, or –N(C₁–C₆alkyl)S(O)(C₁–C₆alkyl).

2. The compound of claim 1 or a pharmaceutically acceptable salt, enantiomer, hydrate, solvate, stereoisomer, or tautomer thereof, wherein

R⁵ is –C₁–C₃alkyl;

R¹⁰ is each independently, at each occurrence halogen, –OC₁–C₆alkyl, –OC₃–C₆cycloalkyl, –Oaryl, or –Oheteroaryl, wherein each alkyl, cycloalkyl, aryl or heteroaryl is optionally substituted with one or more –R¹²;

R¹² is halogen.

3. The compound of any one of claims 1-2, or a pharmaceutically acceptable salt thereof, wherein R⁵ is methyl.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein at least one R¹⁰ is halogen.

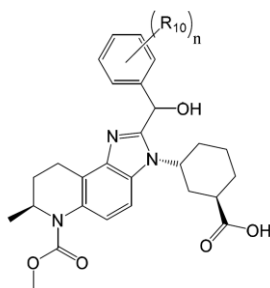
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein at least one R¹⁰ is –OC₁–C₆alkyl.

6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein any two R¹⁰ when on non-adjacent atoms, can combine to form a bridging cycloalkyl or heterocyclyl.

7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein any two R¹⁰ when on adjacent atoms, can combine to form a cycloalkyl, heterocyclyl, aryl or heteroaryl.

8. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R⁶ is phenyl optionally substituted with one or two R¹⁰ and each R¹⁰ is independently, at each occurrence, halogen or –OC₁–C₆alkyl, wherein the –OC₁–C₆alkyl is optionally substituted with halogen.

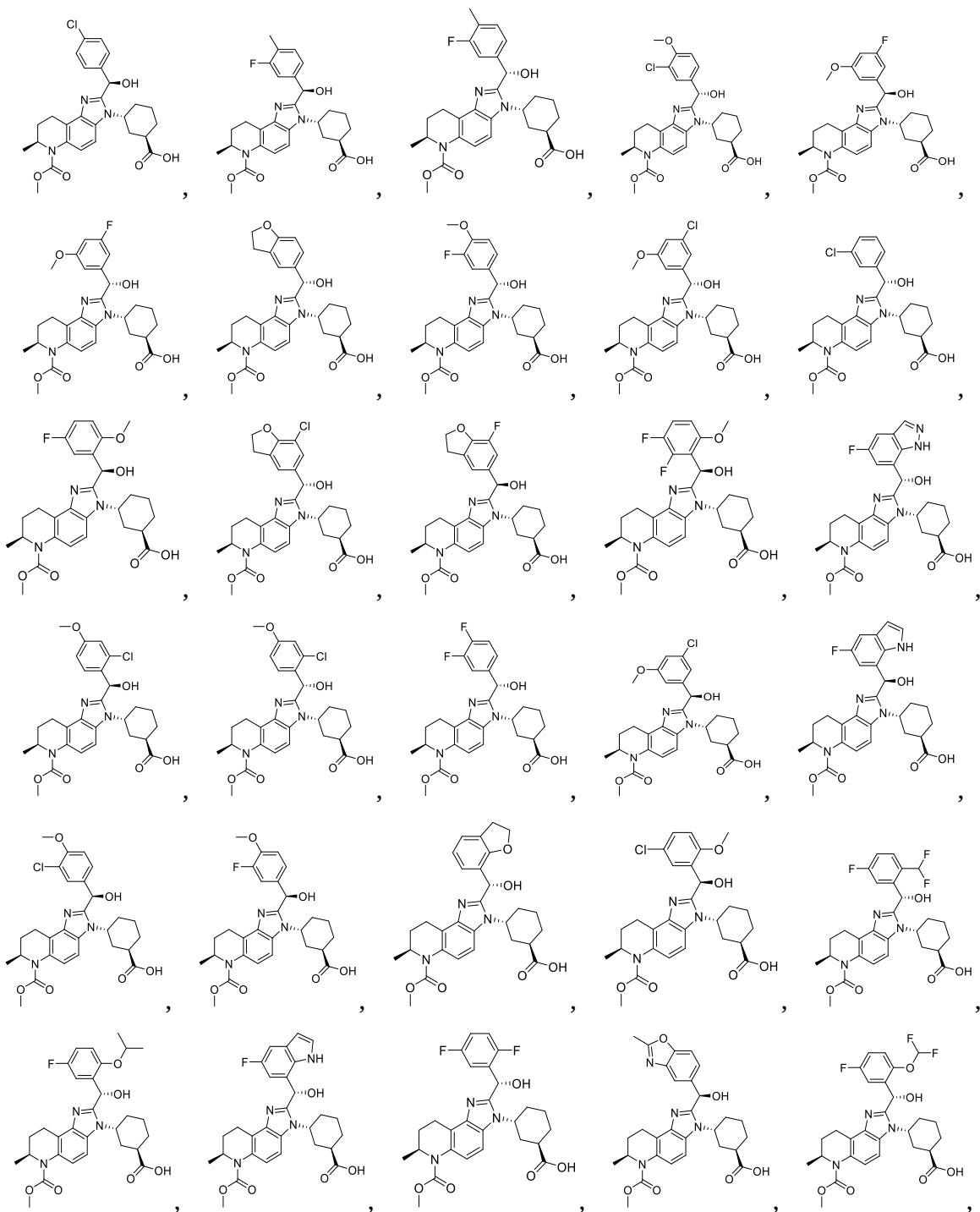
9. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently, at each occurrence halogen or $-OC_1$ alkyl optionally substituted with one or more R^{12} , wherein R^{12} is halogen.
10. The compound of claim 9, or a pharmaceutically acceptable salt thereof, wherein each R^{12} is independently, at each occurrence, fluoro.
11. The compound of claim 1, wherein the compound is a compound of Formula (IV-a):

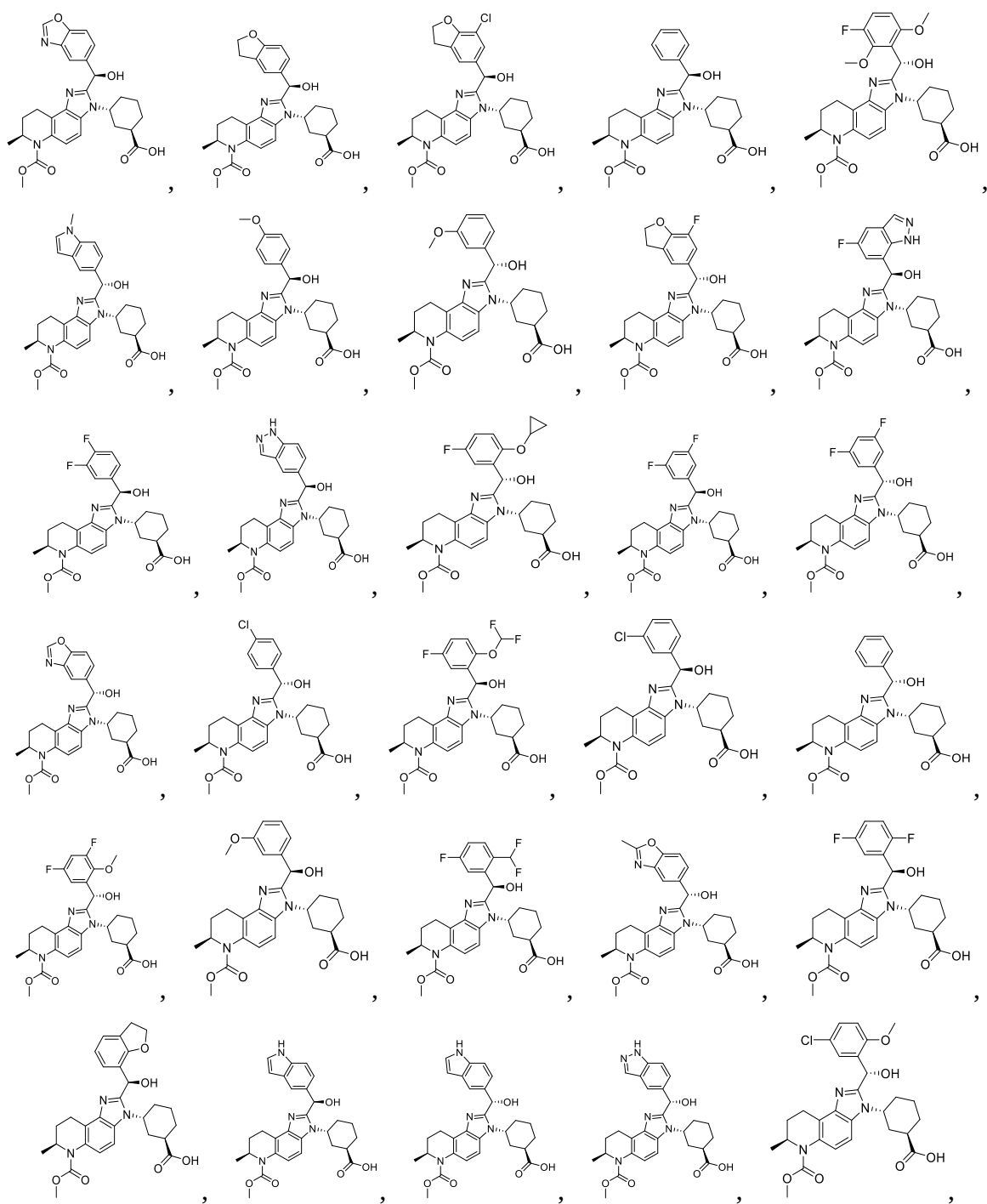


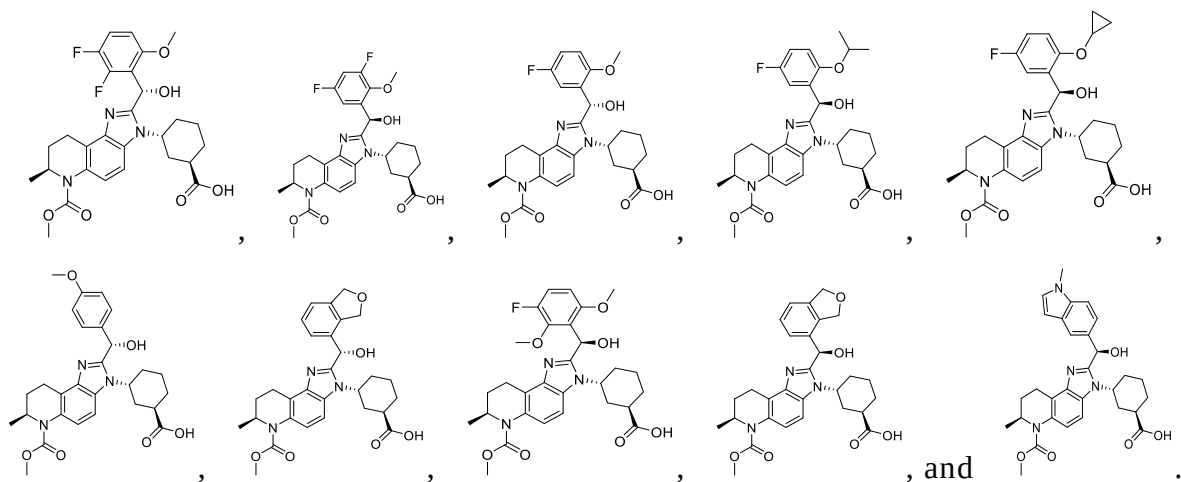
or a pharmaceutically acceptable salt thereof, wherein:

- n is an integer of 0, 1, 2, 3, 4 or 5; and
- each R^{10} is independently, at each occurrence, selected from the group consisting of: $-C_1$ - C_6 alkyl, halogen, $-OC_1$ - C_6 alkyl, and $-OC_3$ - C_6 cycloalkyl, wherein each alkyl or cycloalkyl is optionally substituted with one or more halogen or C_1 - C_6 alkyl; or
- any two R^{10} when on non-adjacent atoms, can combine to form a bridging cycloalkyl or heterocyclyl; or
- any two R^{10} when on adjacent atoms, can combine to form a cycloalkyl, heterocyclyl, aryl or heteroaryl.
12. The compound of claim 11, wherein n is 0, 1, or 2.
13. The compound of claim 11 or claim 12, wherein each R^{10} is independently, at each occurrence, selected from the group consisting of: $-C_1$ - C_6 alkyl, halogen, $-OC_1$ - C_6 alkyl, and $-OC_3$ - C_6 cycloalkyl, wherein each alkyl or cycloalkyl is optionally substituted with one or more halogen or methyl.
14. The compound of any one of claims 11 to 13, wherein each halogen is independently selected from the group consisting of fluorine and chlorine.

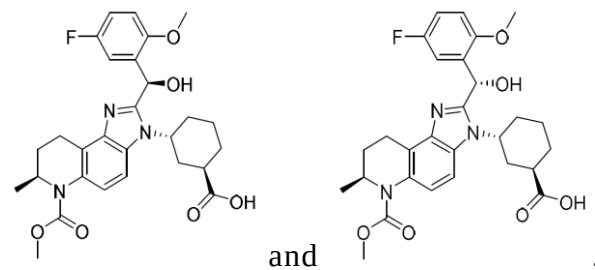
16. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



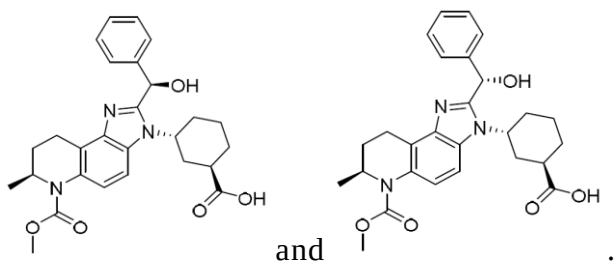




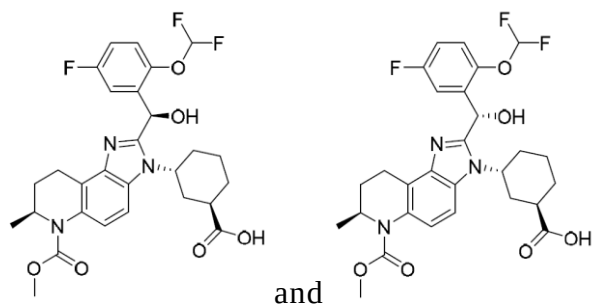
17. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



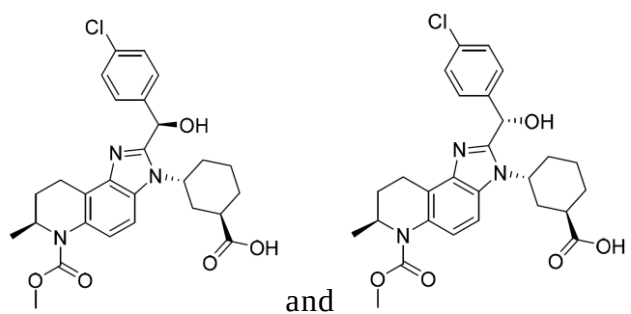
18. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



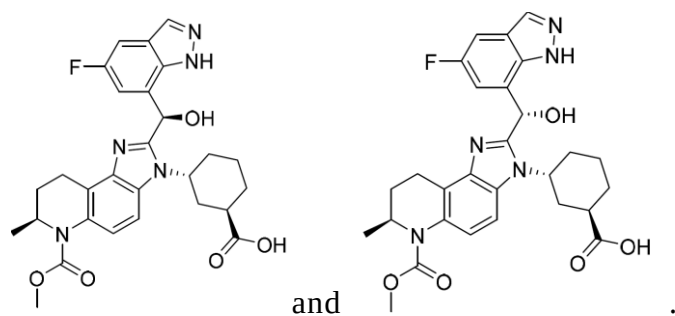
19. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



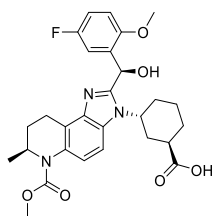
20. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



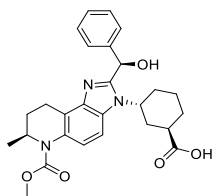
21. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from



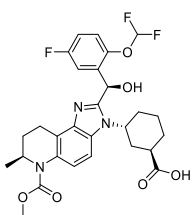
22. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure



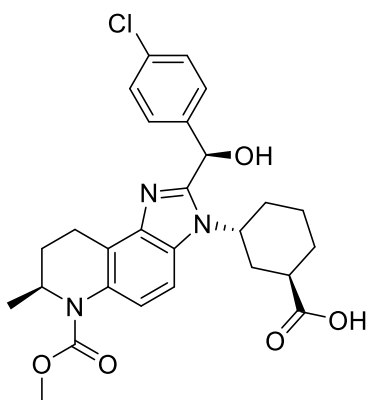
23. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure



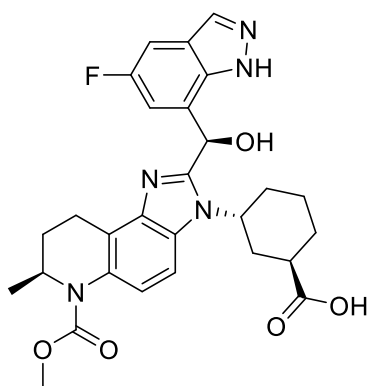
24. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure



25. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure



26. The compound of claim 1 or claim 11, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure



27. A pharmaceutical composition comprising a compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.