

COMBINATION COMPRISING A THRBETA AGONIST AND A GLP-1R AGONIST FOR USE IN TREATING A LIVER DISORDER OR A CARDIOMETABOLIC DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application Nos. 63/495,049, filed on April 7, 2023, 63/526,362, filed on July 12, 2023, and 63/615,985, filed on December 29, 2023, each of which are incorporated by reference herein in their entirety for all purposes.

BACKGROUND

[0002] GLP-1 is a 30 amino acid long incretin hormone secreted by the L-cells in the intestine in response to ingestion of food. GLP-1 has been shown to stimulate insulin secretion in a physiological and glucose-dependent manner, decrease glucagon secretion, inhibit gastric emptying, decrease appetite, and stimulate proliferation of beta-cells. Marketed GLP-1R agonists are peptides that are typically administered by subcutaneous injection. Liraglutide and semaglutide were the first GLP-1 peptides to be approved for both the treatment of type II diabetes mellitus (T2DM) and obesity. Semaglutide has also been approved for the treatment of T2DM as a bioavailable oral formulation.

[0003] In a healthy subject, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption.

[0004] Thyroid hormone (TH) is synthesized in the thyroid gland in response to the thyroid stimulating hormone (TSH) secreted by the pituitary. Thyroid hormones function by binding to the thyroid hormone receptors (THR). The thyroid hormone receptor belongs to a family of nuclear receptors and regulates the target gene expressions. Thyroid hormone receptors include two different subtypes, i.e., $THR\alpha$ and $THR\beta$. $THR\alpha$ is mainly distributed in cardiac tissues and plays an important role in regulating heart function. The $THR\beta$ subtype is mainly expressed in the liver and the pituitary, and regulates cholesterol metabolism and thyrotropin secretion.

[0005] At normal levels, thyroid hormones THs maintain body weight, metabolic rate, body temperature, and mood, and are responsible for regulating serum cholesterol. Attempts have been made to use thyroid hormones to regulate serum cholesterol. However, given the possible side effects on the heart from taking natural thyroid hormone (e.g., tachycardia and arrhythmia,

heart failure, and thyroid axis function, muscle metabolism, and osteoporosis,) they are unsuitable for treating high cholesterol and obesity. Research results regarding the study of animals with selective knock-out of the THR gene, and research results of some selective THR ligands show that the side effects on the heart caused by these thyroid hormones can be attributed to THR α but not THR β . Therefore, THR β -selective ligands may provide the benefits of THR agonism (e.g., cholesterol lowering) without the undesirable effects associated with THR α .

[0006] Combination therapies of known agonists can yield unexpected synergies and improved effects to a significantly greater extent than administration of either agent alone but effects of combination therapies are highly unpredictable. Developing new combination therapies for the treatment of various liver disorders and cardiometabolic diseases, including obesity, remains a critical unmet clinical need.

[0007] GLP-1R regulates post prandial blood glucose and satiety, which can induce weight loss but efficacy is limited by metabolic adaptation, a compensatory process that lowers energy expenditure (EE). Moreover, the higher dose levels of GLP-1R needed to achieve clinical meaningful weight loss, are associated with more severe and frequent GI-related side effects including nausea and emesis, which can negatively impact patient compliance. In a meta-analysis evaluating the efficacy and safety of orforglipron as an anti-obesity medication it has been shown that the total adverse events were significantly higher with all the doses of orforglipron compared to placebo, with the hazard ratios being higher with higher doses. Gastrointestinal side-effects were predominant side effects, being dose-dependent, with nausea, vomiting, constipation, and gastroesophageal reflux being the predominant ones (Dutta et al., *Obes Sci Pract.* 2024 Apr; 10(2):e743 PMID: 38414573). Compared to placebo, the occurrence of total adverse events was significantly higher with orforglipron 12 mg, 24 mg, 36 mg and 45 mg daily doses. (Frias et al., *Lancet.* 2023;402(10400):472-483, Wharton et al., *N Engl J Med.* 2023;389(10):877-888, Pratt et al., *Diabetes Obes Metabol.* 2023;25:2642-2649). Therefore, dose dependent gastrointestinal side effects are a persistent challenge in the field of GLP-1 therapeutics.

[0008] Mechanisms to improve the effectiveness of GLP-1 based therapies at lower doses, could mitigate GI-related side effects and improve patient compliance and outcomes.

SUMMARY

[0009] In one aspect, the present disclosure is directed to a combination of a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically

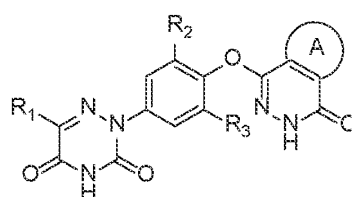
acceptable salt thereof, for the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.

[0010] In one aspect, the present disclosure is directed to a method of administering a THR β agonist, or a pharmaceutically acceptable salt thereof, and administering a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.

[0011] In one aspect, the present disclosure is directed to a method of administering a pharmaceutical composition comprising a THR β agonist, or a pharmaceutically acceptable salt thereof, and administering a pharmaceutical composition comprising a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.

[0012] In one aspect, the present disclosure is directed to a method of administering a pharmaceutical composition comprising a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.

[0013] In some embodiments, the THR β agonist of the combination of the present disclosure is a compound of Formula (II-1)



(II-1)

wherein:

R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

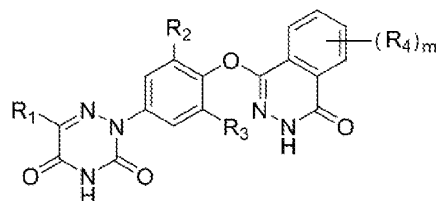
R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -

NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br,
or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the THR β agonist of the combination of the present disclosure is a compound of Formula (II-1a)



(II-1a)

wherein:

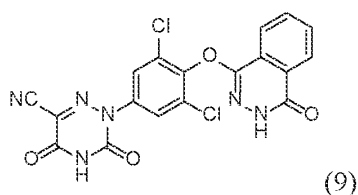
R₁ to R₃ are defined as detailed herein for Formula (II-1);

R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.
or a pharmaceutically acceptable salt thereof.

[0015] In some embodiments, the THR β agonist of the combination of the present disclosure is Compound 9:

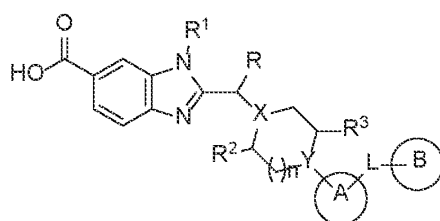


(9)

or a pharmaceutically acceptable salt thereof.

[0016] In some embodiments, the THR β agonist of the combination of the present disclosure is a potassium salt of Compound 9.

[0017] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is a compound of Formula (I-1):



(I-1)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH, or C₁-C₆ alkyl;

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom of R⁵ is S, and further wherein R⁵ is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁-C₆ haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene of L is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

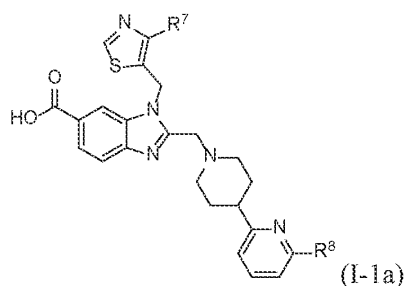
when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L,1}, wherein each R^{L,1} is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^{L,1} are taken together with

the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

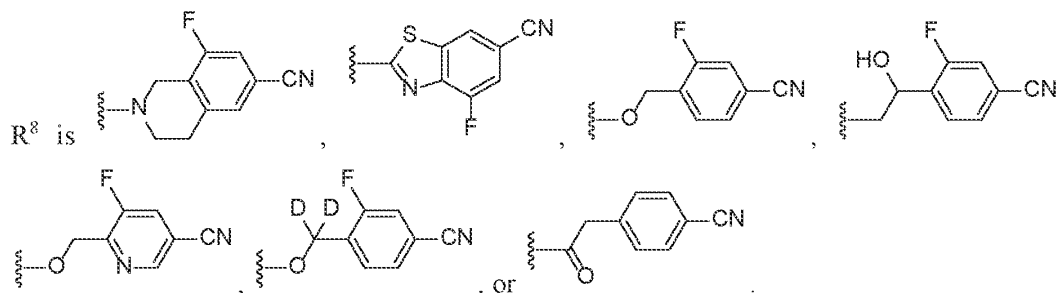
R⁶ is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

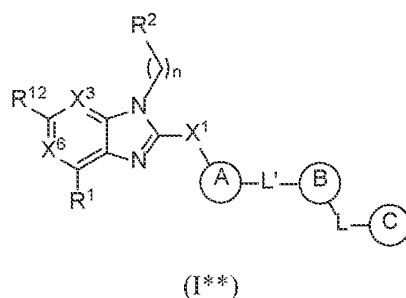
[0018] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is a compound of Formula (I-1a):



wherein R⁷ is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



[0019] In some embodiments, the GLP-1R agonist is a compound of Formula (I**):



or a pharmaceutically acceptable salt thereof; wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, halogen, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, C₃₋₁₀ cycloalkyl, or C₆₋₁₀ aryl, wherein the alkyl, alkylene, heteroalkyl, or haloalkyl group is optionally substituted with one or more deuterium, C₁₋₆ alkoxy, hydroxyl, -CN, or oxo, and the cycloalkyl, heterocyclyl, or aryl group is optionally substituted with one or more halogen, C₁₋₆ alkoxy, or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

C₁₋₆ alkyl optionally substituted with deuterium;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

-CN;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, $\text{HN} \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$, or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

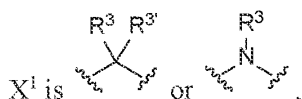
R² and R⁷, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R⁴ is halogen, hydrogen, -C(O)OH, or -O-R⁸,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

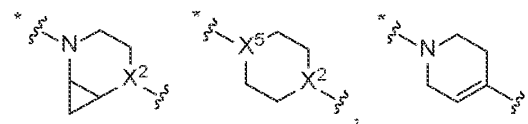
R^{12} is hydrogen, $-C(O)OH$, $-C(O)NR^{N12}R^{N12'}$, $-C(O)NR^{12}S(O)_2R^{12'}$, $-(C_{2-6} \text{ alkynylene})-C(O)OH$, $-(C_{1-6} \text{ alkylene})-C(O)OH$, $-NR^{N12}-(C_{1-6} \text{ alkylene})-C(O)OH$, 5-10 membered heteroaryl or 5- to 10-membered heterocyclyl optionally substituted with one or more oxo, C_{1-6} alkyl or C_{1-6} haloalkyl;

R^{N12} and $R^{N12'}$ independently are H or C_{1-6} alkyl;



wherein R^3 and $R^{3'}$ independently are H, D or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with deuterium;

Ring A is



one or more halo or C_{1-6} alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C_{1-6} alkyl;

wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or $-O-$;

Ring B is a C_{6-10} arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $-(C_{1-6} \text{ alkylene})-$, $-NR^L-(C_{1-6} \text{ alkylene})-$, $-O-(C_{1-6} \text{ alkylene})-$, or $-(C_{1-6} \text{ alkylene})-O-$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium;

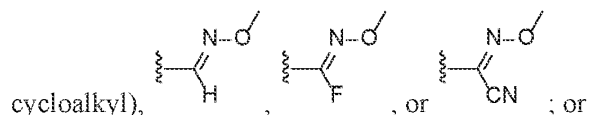
wherein R^L is H or C_{1-6} alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-10 membered heterocyclyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CN$, C_{3-10} cycloalkyl, or $-C(O)NR'^2$;

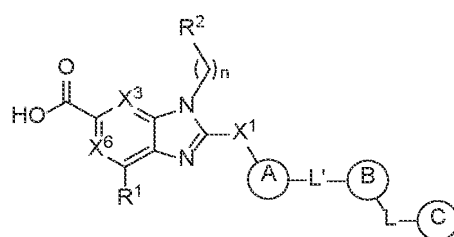
wherein R^1 is H or C_{1-6} alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, -CN, C_{1-6} haloalkyl, -O- C_{1-6} alkyl, C_{3-10} cycloalkyl, -C(=O)-(C₃₋₁₀



a bicyclic 9- or 10-membered heteroaryl or heterocyclyl optionally substituted with one or more C_{1-6} alkyl, halogen, -CN, or oxo.

[0020] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is a compound of Formula (I-5)



(I-5)

or a pharmaceutically acceptable salt thereof; wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, -O- X^4 , or -NR⁸R⁹, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R^6 is hydrogen, halogen, or -O- R^7 ;

wherein R^7 and R^2 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or -S(O)₂- C_{1-6} alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

branched C_{1-6} alkyl;

C_{1-6} haloalkyl;

-(O)- C_{1-6} alkyl;

a C_{3-10} cycloalkyl optionally substituted with one or more -CN, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

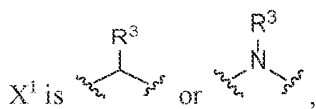
oxo, , or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

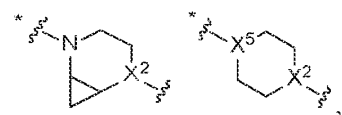
R^4 is hydrogen or -O- R^8 ,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



, phenylene optionally substituted with one or more halo or C_{1-6} alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C_{1-6} alkyl;

wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or -O-;

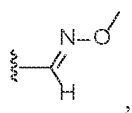
Ring B is a C_{6-10} arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

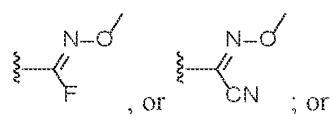
L is a bond, *-CH₂-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₁₋₆ alkyl, 3-10 membered heterocyclyl, halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

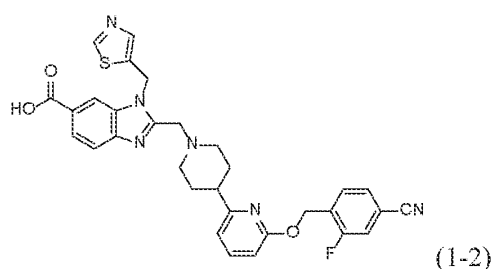
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0021] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

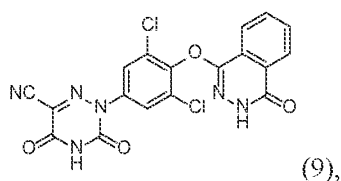
[0022] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is a meglumine salt of Compound 1-2.

[0023] In some embodiments, the THRβ agonist of the combination of the present disclosure is selected from those listed in Tables 6-11.

[0024] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is selected from those listed in Tables 1-5.

[0025] In some embodiments, the GLP-1R agonist of the combination of the present disclosure is selected from those listed in Table 5A.

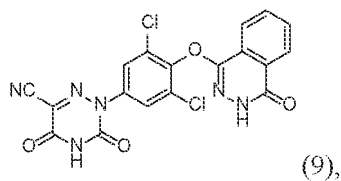
[0026] In some embodiments, the THRβ agonist of the combination of the present disclosure is compound 9



(9),

and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

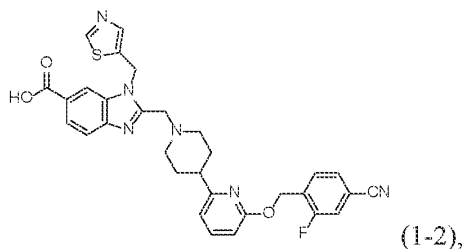
[0027] In some embodiments, the THR β agonist of the combination of the present disclosure is compound 9



(9),

and the GLP-1R agonist is orforglipron, or a pharmaceutically acceptable salt thereof.

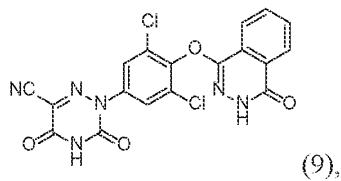
[0028] In some embodiments, the THR β agonist of the combination of the present disclosure is resmetirom, VK2809, sobetirome, eprotrirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is compound 1-2



(1-2),

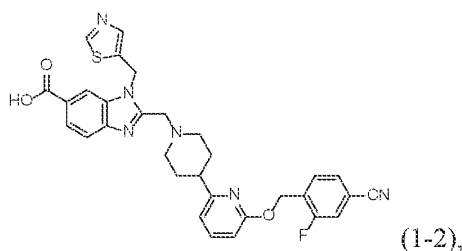
or a pharmaceutically acceptable salt thereof.

[0029] In some embodiments, the THR β agonist of the combination of the present disclosure is compound 9



(9),

or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is compound 1-2



or a pharmaceutically acceptable salt thereof.

[0030] In one aspect, the present disclosure is directed to a method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a combination disclosed herein.

[0031] In one aspect, the present disclosure is directed to a method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a combination disclosed herein.

[0032] In one aspect, the present disclosure is directed to a method of increasing the proportion of lean body mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination disclosed herein.

[0033] In one aspect, the present disclosure is directed to a method of decreasing the proportion of fat mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination disclosed herein.

[0034] In one aspect, the present disclosure is directed to a method of effectuating weight loss in a patient in need thereof, comprising administering to the patient a combination disclosed herein.

[0035] In some embodiments, the patient has a Body Mass Index (BMI) of 20 kg/m² to 25 kg/m².

[0036] In some embodiments, the patient has a BMI of 25 kg/m² to 30 kg/m².

[0037] In some embodiments, the patient has a BMI of 20 kg/m² or greater.

[0038] In some embodiments, the patient has a BMI of 25 kg/m² or greater.

[0039] In some embodiments, the patient has a BMI of 27 kg/m² or greater.

[0040] In some embodiments, the patient has a BMI of 30 kg/m² or greater.

[0041] In some embodiments, the cardiometabolic disease is obesity.

[0042] In some embodiments, the liver disorder is NASH.

[0043] In some embodiments, the liver disorder is liver fibrosis.

[0044] In some embodiments, the THR β agonist is administered at substantially the same time as the GLP-1R agonist.

[0045] In some embodiments, the THR β agonist is administered after the GLP-1R agonist.

[0046] In some embodiments, the THR β agonist is administered prior to the GLP-1R agonist.

[0047] In some embodiments, the THR β agonist is selective to THR β .

BRIEF DESCRIPTION OF THE FIGURES

[0048] FIG. 1 depicts the study design for usage of a THR β agonist (Compound 9) and a GLP-1R agonist (semaglutide) in combination to treat NASH.

[0049] FIG. 2 depicts a graph showing the change from baseline in the body weight (%) of DIO-NASH mice over days of treatment with Compound 9 alone and in combination with semaglutide.

[0050] FIG. 3 depicts the study design for usage of a THR β agonist (Compound 9) and a GLP-1R agonist (semaglutide) in combination for chronic weight management.

[0051] FIG. 4A depicts a graph showing the change in weight loss in Diet Induced Obese (DIO) mice over days of treatment with semaglutide alone or in combination with Compound 9.

[0052] FIG. 4B depicts a graph showing the change in weight loss in DIO mice following treatment with semaglutide alone or in combination with Compound 9.

[0053] FIG. 5A depicts a graph showing the daily food intake in DIO mice over days of treatment with semaglutide alone or in combination with Compound 9.

[0054] FIG. 5B depicts a graph showing the cumulative food intake in DIO mice over days of treatment with semaglutide alone or in combination with Compound 9.

[0055] FIG. 6A depicts a graph showing the change in lean mass in DIO mice following treatment with semaglutide alone or in combination with Compound 9. **** Indicates p-value <0.0001 vs. Vehicle

[0056] FIG. 6B depicts a graph showing the change in fat mass in DIO mice following treatment with semaglutide alone or in combination with Compound 9. **** Indicates p-value <0.0001 vs. Vehicle; ##### indicates p-value <0.001 vs. Semaglutide.

[0057] FIG. 7A depicts a graph showing the change in lean mass as a percent of bodyweight in DIO mice following treatment with semaglutide alone or in combination with Compound 9. The proportion of lean mass to total body mass increased by 3.9% following treatment by semaglutide alone and by 13.9% following treatment by semaglutide in combination with Compound 9. ** indicates p-value of 0.0028 and **** indicates p-value <0.0001.

[0058] FIG. 7B depicts a graph showing the change in fat mass as a percent of bodyweight in DIO mice following treatment with semaglutide alone or in combination with Compound 9.

[0059] FIG. 8 depicts a graph showing the percent change from baseline in bodyweight in DIO mice following treatment with semaglutide alone or in combination with Compound 9, wherein Compound 9 is added after 14 days of semaglutide monotherapy.

[0060] FIGs. 9A-C depict a graph showing the percent change from baseline in bodyweight (BW) in DIO mice following treatment with semaglutide alone or semaglutide in combination with Compound 9. In a Post hoc analysis mice were divided into two subgroups based on their initial starting body weight (FIG. 9A). Body weights ranged from 50-54.9g (Low BW) and 55-60g (High BW). Compound 9 + Semaglutide has greater efficacy in mice with higher initial body weight (FIG. 9C) compared to those with lower initial body weight (FIG. 9B).

[0061] FIG. 10 depicts the design of a study to evaluate the effects of 6 weeks treatment with Compound 9 alone and in combination with Semaglutide on metabolic parameters, energy expenditure and glycemic control in male DIO mice at thermoneutrality.

[0062] FIG. 11 depicts a graph showing the percent change from baseline in body weight in DIO mice following treatment with semaglutide alone, Compound 9 alone, semaglutide in combination with Compound 9, or tirzepatide alone. After 6 weeks of treatment, Compound 9 + Semaglutide induced additional weight loss that was comparable to tirzepatide. ****p-value <0.0001; *p-value <0.05.

[0063] FIG. 12 depicts a graph showing the percent change from baseline in body weight in DIO mice following treatment with semaglutide alone, Compound 9 alone, semaglutide in combination with Compound 9, or tirzepatide alone. Compound 9 + Semaglutide induced an additional ~7% weight loss compared with semaglutide treatment alone.

[0064] FIG. 13 depicts a pair of graphs showing the percent change in fat mass and lean mass following treatment with semaglutide alone, Compound 9 alone, semaglutide in combination with Compound 9, or tirzepatide. The body composition of mice was assessed on weeks 1 and 6 of the study using an EchoMRI 3-1 Body composition analyzer. Compound 9 + Semaglutide enhanced fat loss compared with Semaglutide treatment alone while lean mass loss was similar between semaglutide alone and the combination of Compound 9 + Semaglutide. ****p-value <0.0001; *p-value <0.05.

[0065] FIG. 14 depicts a graph showing the average food intake in DIO mice following treatment with semaglutide alone, Compound 9 alone, semaglutide in combination with Compound 9, or tirzepatide. Compound 9 normalized semaglutide-induced reduction in food intake. ****p-value <0.0001; ***p-value <0.001; **p-value <0.01.

[0066] FIG. 15 depicts three graphs showing the energy expenditure (EE) assessed after week 4 in DIO mice following treatment with semaglutide alone, Compound 9 alone, semaglutide in

combination with Compound 9, or tirzepatide. Compound 9+semaglutide prevented lowering of energy expenditure (EE) induced by weight Loss. Compound 9 restored energy expenditure to normal (DIO Veh) levels when combined with semaglutide. ****p-value <0.0001; *p-value <0.05.

[0067] FIG. 16 depicts a graph showing uncoupling protein 1 (UCP-1) expression in DIO mice following treatment with semaglutide alone, Compound 9 alone, semaglutide in combination with Compound 9, or tirzepatide. Obesity lowered uncoupling protein 1 (UCP-1) expression in subcutaneous adipose tissue. Compound 9 partially restored the obesity induced lowering of UCP-1. *p<0.05, one way ANOVA followed by Fisher's LSD test.

[0068] FIG. 17 depicts a graph showing the results of a glucose tolerance test (GTT) administered at week 4 to DIO mice following treatment with semaglutide alone, Compound 9 alone, semaglutide in combination with Compound 9, or tirzepatide. Compound 9+semaglutide further enhanced glucose tolerance compared with semaglutide treatment alone. ***p-value <0.001; **p-value <0.01; *p-value <0.05.

[0069] FIG. 18 depicts a graph showing body weight changes from baseline over time in DIO hGLP-1R mice following treatment with Compound 9 alone, orforglipron alone, or orforglipron in combination with Compound 9. Daily change from baseline in body weight (g) shown as mean (SE) with n = 6-7 mice per group. Vehicle, Compound 9 (3 mg/kg), and orforglipron (0.2 mg/kg and 2 mg/kg) were dosed once daily by oral gavage.

[0070] FIG. 19 depicts a graph showing body weight change from baseline in DIO hGLP-1R mice following treatment with Compound 9 alone, orforglipron alone, or orforglipron in combination with Compound 9. Change from baseline at 20 day in body weight (g) shown as mean (SD) with n = 6-7 mice per group. Statistical significance determined by ordinary one-way ANOVA with correction for multiple comparisons. *p-value <0.05, ***p-value <0.001, ****p-value <0.0001. ns = not significant.

[0071] FIG. 20 depicts a graph showing daily food intake over time in DIO hGLP-1R mice following treatment with Compound 9 alone, orforglipron alone, or orforglipron in combination with Compound 9. Daily food intake (g) shown as mean (SE) with n = 6-7 mice per group. Measurement of body mass composition on Day 19 leading to acute food intake decrease is denoted.

[0072] FIGs. 21A-B depict two graphs showing body mass composition change from baseline in DIO hGLP-1R mice following treatment with Compound 9 alone, orforglipron alone, or orforglipron in combination with Compound 9. Day 19 change from baseline in fat (FIG. 21A) and lean (FIG. 21B) mass (g) shown as mean (SD) with n = 6-7 mice per group. Statistical

significance determined by ordinary one-way ANOVA with correction for multiple comparisons. *p-value <0.05, **p-value <0.01, ***p-value <0.001, ****p-value <0.0001. ns = not significant.

[0073] FIG. 22 depicts a graph showing terminal subcutaneous fat in DIO hGLP-1R mice following treatment with Compound 9 alone, orforglipron alone, or orforglipron in combination with Compound 9. Data represents mean (SD) subcutaneous fat (mg) collected at study termination with n = 6-7 mice per group. Statistical significance determined by ordinary one-way ANOVA with correction for multiple comparisons. *p-value <0.05. ns = not significant.

[0074] FIG. 23 depicts a graph showing terminal liver weights in DIO hGLP-1R mice following treatment with Compound 9 alone, orforglipron alone, or orforglipron in combination with Compound 9. Data represents mean (SD) liver weight (mg) collected at study termination with n = 6-7 mice per group. Statistical significance determined by ordinary one-way ANOVA with correction for multiple comparisons. *p-value <0.05, **p-value <0.01, ***p-value <0.01, ****p-value <0.0001. ns = not significant.

[0075] FIGs. 24A-B depict two graphs showing concentration-time profiles of Compound 9 and orforglipron in DIO hGLP-1R mice. Compound concentration shown as mean (SD) over time for Compound 9 (FIG. 24A) or orforglipron (FIG. 24B) alone and in combination. Data represent sparse sampling across each treatment cohort as follows: predose (0-hour post dose), n = 3; 2-hour post dose, n = 3; 4-hour post dose, n = 4; 8-hour post dose, n = 4; 24-hour post dose, n = 7. Nominal doses and times are shown.

[0076] FIG. 25 depicts a graph showing weight loss induced by combination treatment of Compound 9 + Compound (1-2) compared to monotherapy in diet induced obese transgenic hGLP1R mice.

[0077] FIG. 26 depicts a graph showing the weight loss induced by combination treatment of Compound 9 + Compound (1-2) compared to monotherapy in diet induced obese transgenic hGLP1R mice. Percent change in body weight after 15 days of treatment.

DETAILED DESCRIPTION

Definitions

[0078] As used herein, the following definitions shall apply unless otherwise indicated. Further, if any term or symbol used herein is not defined as set forth below, it shall have its ordinary meaning in the art.

[0079] “Comprising” is intended to mean that the compositions and methods include the recited elements, but not exclude others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination. For example, a composition consisting essentially of the elements as defined herein would not exclude other elements that do not materially affect the basic and novel characteristic(s) of the claimed invention. “Consisting of” shall mean excluding more than trace amount of, e.g., other ingredients and substantial method steps recited. Embodiments defined by each of these transition terms are within the scope of this invention.

[0080] “Combination therapy” or “combination treatment” (also referred to herein as a combinational therapy) refers to the use of two or more drugs or agents in treatment, e.g., the use of a compound of formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I'''), (I''), (I*), (I'), (I), (I-P01), (II**), (II*), (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6) as utilized herein together with another agent (e.g., one useful to treat liver disorders, such as NAFLD, NASH, and symptoms and manifestations of each thereof) is a combination therapy.

[0081] Administration in “combination” refers to the administration of two agents (e.g., a compound of formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I'''), (I''), (I*), (I'), (I), (I-P01), (II**), (II*), (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6) as utilized herein, and another agent) in any manner in which the pharmacological effects of both manifest in the patient at the same time. Thus, administration in combination does not require that a single pharmaceutical composition, the same dosage form, or even the same route of administration be used for administration of both agents or that the two agents be administered at precisely the same time. The agents can be formulated in two separate pharmaceutically acceptable compositions. Both agents can also be formulated in a single pharmaceutically acceptable composition. A non-limiting example of such a single composition is an oral composition or an oral dosage form. For example, and without limitation, it is contemplated that a compound of formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I'''), (I''), (I*), (I'), (I), (I-P01), (II**), (II*),

(II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6) can be administered in combination therapy with another agent in accordance with the present invention.

[0082] The term “excipient” as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the invention as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, *e.g.*, carbomers, povidone, xanthan gum, etc.; coatings include, *e.g.*, cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, *e.g.*, calcium carbonate, dextrose, fructose dc (dc = “directly compressible”), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, *e.g.*, croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, *e.g.*, maltodextrin, carrageenans, etc.; lubricants include, *e.g.*, magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, *e.g.*, dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, *e.g.*, carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, *e.g.*, aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, *e.g.*, calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0083] “Patient” refers to mammals and includes humans and non-human mammals. Examples of patients include, but are not limited to mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, patient refers to a human.

[0084] “Patient’s response” as used herein refers to magnitude of treatment efficacy (*e.g.*, amount of weight loss, percentage of fat loss, etc.). Improving a “patient’s response” to a treatment can include, but are not limited to, increasing the magnitude of efficacy of the treatment (*e.g.* increasing weight loss, increasing fat loss, etc.). In some embodiments, improving a patient’s response to a treatment (*e.g.* the combinations and methods of the present disclosure) comprises maintaining the efficacy while decreasing side effects.

[0085] “Pharmaceutically acceptable” refers to safe and non-toxic, preferably for *in vivo*, more preferably, for human administration.

[0086] “Pharmaceutically acceptable salt” refers to a salt that is pharmaceutically acceptable. A compound described herein may be administered as a pharmaceutically acceptable salt.

[0087] “Salt” refers to an ionic compound formed between an acid and a base. When the compound provided herein contains an acidic functionality, such salts include, without limitation, alkali metal, alkaline earth metal, and ammonium salts. As used herein, ammonium salts include, salts containing protonated nitrogen bases and alkylated nitrogen bases. Exemplary and non-limiting cations useful in pharmaceutically acceptable salts include Na, K, Rb, Cs, NH₄, Ca, Ba, imidazolium, and ammonium cations based on naturally occurring amino acids. When the compounds utilized herein contain basic functionality, such salts include, without limitation, salts of organic acids, such as carboxylic acids and sulfonic acids, and mineral acids, such as hydrogen halides, sulfuric acid, phosphoric acid, and the likes. Exemplary and non-limiting anions useful in pharmaceutically acceptable salts include oxalate, fumarate, maleate, acetate, propionate, succinate, tartrate, chloride, sulfate, bisulfate, mono-, di-, and tribasic phosphate, mesylate, tosylate, and the likes.

[0088] “Therapeutically effective amount” or dose of a compound or a composition refers to that amount of the compound or the composition that results in reduction or inhibition of symptoms or a prolongation of survival in a patient. The results may require multiple doses of the compound or the composition.

[0089] “Treatment” or “treating” refers to an approach for obtaining beneficial or desired results including clinical results. For purposes of this invention, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease or disorder, diminishing the extent of the disease or disorder, stabilizing the disease or disorder (*e.g.*, preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delaying or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by “treatment” is a reduction of pathological consequence of the disease or disorder. The methods of the invention contemplate any one or more of these aspects of treatment.

[0090] As used herein, “delaying” development of a disease means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease and/or slowing the progression or

altering the underlying disease process and/or course once it has developed. This delay can be of varying lengths of time, depending on the history of the disease and/or subject being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the subject does not develop clinical symptoms associated with the disease. A method that "delays" development of a disease is a method that reduces probability of disease development in a given time frame and/or reduces extent of the disease in a given time frame, when compared to not using the method, including stabilizing one or more symptoms resulting from the disease.

[0091] A subject who is "at risk" of developing a disease may or may not have detectable disease, and may or may not have displayed detectable disease prior to the treatment methods described herein. "At risk" denotes that a subject has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease. A subject having one or more of these risk factors has a higher probability of developing the disease than a subject without these risk factor(s). These risk factors include, but are not limited to, age, sex, race, diet, history of previous disease, presence of precursor disease and genetic (*i.e.*, hereditary) considerations. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0092] "Stereoisomer" or "stereoisomers" refer to compounds that differ in the stereogenicity of the constituent atoms such as, without limitation, in the chirality of one or more stereocenters or related to the *cis* or *trans* configuration of a carbon-carbon or carbon-nitrogen double bond. Stereoisomers include enantiomers and diastereomers.

[0093] "Alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 12 carbon atoms, from 1 to 10 carbon atoms, or from 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH₃-), ethyl (CH₃CH₂-), *n*-propyl (CH₃CH₂CH₂-), isopropyl ((CH₃)₂CH-), *n*-butyl (CH₃CH₂CH₂CH₂-), isobutyl ((CH₃)₂CHCH₂-), *sec*-butyl ((CH₃)(CH₃CH₂)CH-), *t*-butyl ((CH₃)₃C-), *n*-pentyl (CH₃CH₂CH₂CH₂CH₂-), and neopentyl ((CH₃)₃CCH₂-). C_x alkyl refers to an alkyl group having x number of carbon atoms.

[0094] "Alkylene" refers to a divalent saturated aliphatic hydrocarbyl group having from 1 to 12 carbon atoms, for example from 1 to 10 carbon atoms, and from 1 to 6 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methylene (-CH₂-), ethylene (-CH₂CH₂- or -CH(Me)-), propylene (-CH₂CH₂CH₂- or -CH(Me)CH₂- or -CH(Et)-) and the like.

[0095] “Alkenyl” refers to straight or branched monovalent hydrocarbyl groups having from 2 to 6 carbon atoms, for example 2 to 4 carbon atoms and having at least 1, or from 1 to 2 sites of vinyl ($>C=C<$) unsaturation. Such groups are exemplified, for example, by vinyl, allyl, and but-3-en-1-yl. Included within this term are the *cis* and *trans* isomers or mixtures of these isomers. C_x alkenyl refers to an alkenyl group having x number of carbon atoms.

[0096] “Alkynyl” refers to straight or branched monovalent hydrocarbyl groups having from 2 to 6 carbon atoms, for example 2 to 3 carbon atoms and having at least 1 or from 1 to 2 sites of acetylenic ($-C\equiv C-$) unsaturation. Examples of such alkynyl groups include acetylenyl ($-C\equiv CH$), and propargyl ($-CH_2C\equiv CH$). C_x alkynyl refers to an alkynyl group having x number of carbon atoms.

[0097] “Alkoxy” refers to the group $-O$ -alkyl wherein alkyl is defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, *sec*-butoxy, and *n*-pentoxy.

[0098] “Aryl” refers to a monovalent aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (*e.g.*, phenyl (Ph)) or multiple condensed rings (*e.g.*, naphthyl or anthryl) which condensed rings may or may not be aromatic (*e.g.*, 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7-yl, and the like) provided that the point of attachment is at an aromatic carbon atom. Exemplary aryl groups include phenyl and naphthyl. A divalent aryl group is referred to herein as “arylene.” A divalent phenyl group is referred to herein as “phenylene”.

[0099] “Cyano” refers to the group $-C\equiv N$.

[0100] “Cycloalkyl” refers to saturated or unsaturated but nonaromatic cyclic alkyl groups of, for example, from 3 to 10 carbon atoms, from 3 to 8 carbon atoms, or from 3 to 6 carbon atoms, having single or multiple cyclic rings including fused, bridged, and spiro ring systems. C_x cycloalkyl refers to a cycloalkyl group having x number of ring carbon atoms. Examples of suitable cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclooctyl. One or more the rings can be aryl, heteroaryl, or heterocyclic provided that the point of attachment is through the non-aromatic, non-heterocyclic ring saturated carbocyclic ring. “Substituted cycloalkyl” refers to a cycloalkyl group having from 1 to 5 or 1 to 3 substituents selected from the group consisting of oxo, thione, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aminosulfonyl, aminosulfonyloxy, aminosulfonylamino, amidino, aryl, substituted aryl, aryloxy, substituted

aryloxy, arylthio, substituted arylthio, carboxyl, carboxyl ester, (carboxyl ester)amino, (carboxyl ester)oxy, cyano, cycloalkyl, substituted cycloalkyl, cycloalkyloxy, substituted cycloalkyloxy, cycloalkylthio, substituted cycloalkylthio, guanidino, substituted guanidino, halo, hydroxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylthio, substituted heteroarylthio, heterocyclic, substituted heterocyclic, heterocyclyloxy, substituted heterocyclyloxy, heterocyclylthio, substituted heterocyclylthio, nitro, SO₃H, substituted sulfonyl, sulfonyloxy, thioacyl, thiol, alkylthio, and substituted alkylthio, wherein said substituents are defined herein.

[0101] “Halo” or “halogen” refers to fluoro, chloro, bromo and iodo and in some embodiments is fluoro or chloro.

[0102] “Hydroxy” or “hydroxyl” refers to the group -OH.

[0103] “Heteroaryl” refers to an aromatic group of from 1 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (*e.g.*, pyridinyl or furyl) or multiple condensed rings (*e.g.*, indolizinyl or benzothienyl) wherein the condensed rings may or may not be aromatic and/or contain a heteroatom provided that the point of attachment is through an atom of the aromatic heteroaryl group. In one embodiment, the nitrogen and/or the sulfur ring atom(s) of the heteroaryl group are optionally oxidized to provide for the N-oxide (N→O), sulfinyl, or sulfonyl moieties. Exemplary heteroaryls include 5 or 6 membered heteroaryls such as pyridinyl, pyrrolyl, thiophenyl, and furanyl. Other exemplary heteroaryls include 9 or 10 membered heteroaryls, such as indolyl, quinolinyl, quinolonyl, isoquinolinyl, and isoquinolonyl. A divalent heteroaryl group is referred to herein as “heteroarylene.”

[0104] “Heterocycle” or “heterocyclic” or “heterocycloalkyl” or “heterocyclyl” refers to a saturated or partially saturated, but not aromatic, group having from 1 to 10 ring carbon atoms, from 1 to 8 carbon atoms, and from 1 to 6 carbon atoms, from 1 to 4 ring heteroatoms, from 1 to 3 heteroatoms, and from 1 to 2 heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen. C_x heterocycloalkyl refers to a heterocycloalkyl group having x number of ring atoms including the ring heteroatoms. Heterocycle encompasses single ring or multiple condensed rings, including fused bridged and spiro ring systems. In fused ring systems, one or more the rings can be cycloalkyl, aryl or heteroaryl provided that the point of attachment is through the non-aromatic ring. In one embodiment, the nitrogen and/or sulfur atom(s) of the heterocyclic group are optionally oxidized to provide for the N-oxide, sulfinyl, sulfonyl moieties. A divalent heterocyclyl group is referred to herein as “heterocyclene.”

[0105] Examples of heterocyclyl and heteroaryl include, but are not limited to, azetidiny, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, indolizyl, isoindolyl, indolyl, dihydroindolyl, indazolyl, purinyl, quinoliziny, isoquinoliny, quinoliny, phthalazinyl, naphthylpyridinyl, quinoxaliny, quinazoliny, cinnoliny, pteridinyl, carbazolyl, carboliny, phenanthridinyl, acridinyl, phenanthroliny, isothiazolyl, phenazinyl, isoxazolyl, phenoxazinyl, phenothiazinyl, imidazolidinyl, imidazoliny, piperidinyl, piperazinyl, indoliny, phthalimidyl, 1,2,3,4-tetrahydroisoquinoliny, 4,5,6,7-tetrahydrobenzo[b]thiophenyl, thiazolyl, thiazolidinyl, thiophenyl, benzo[b]thiophenyl, morpholiny, thiomorpholiny (also referred to as thiamorpholiny), 1,1-dioxothiomorpholiny, piperidinyl, pyrrolidinyl, and tetrahydrofuranly.

[0106] “Oxo” refers to the atom (=O) or (O).

[0107] The terms “optional” or “optionally” as used throughout the specification means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “the nitrogen atom is optionally oxidized to provide for the N-oxide (N→O) moiety” means that the nitrogen atom may but need not be oxidized, and the description includes situations where the nitrogen atom is not oxidized and situations where the nitrogen atom is oxidized.

[0108] The dosage amount of a compound as described herein is determined based on the free acid or free base of a compound, as appropriate.

[0109] Provided herein are compositions and methods for treating obesity and/or related comorbidities. The methods comprise administering to the patient a glucagon-like peptide-1 receptors (GLP-1R) agonist and a thyroid hormone receptor beta (THRβ) agonist, as described herein. In some embodiments, provided herein is a method of treating a cardiometabolic disease in a subject (e.g., a human patient) in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

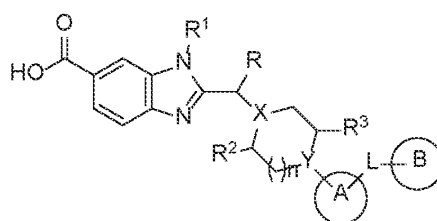
GLP-1R Agonists

[0110] Suitable GLP-1R agonists that can be used in accordance with the combinations and/or methods described herein include, but are not limited to orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, orforglipron, or semaglutide, or a pharmaceutically acceptable salt of the GLP-1R agonist, or a pharmaceutically acceptable solvates of either the GLP-1R agonist or the salt of the GLP-1R agonist. Suitable GLP-1R agonists that can be used in accordance with the combinations and/or methods described herein

also include danuglipron tromethamine, SAL-0112, exenatide biobetter, E-2HSA, ECC-5004, dapiglutide, HDM-1002, AZD-9550, BGM-0504, VK2735, AMG-133, HL-08, HZ-010, exenatide SR, DD-01, CT-388, CT-868, CT-996, GL-0034, GMA-105, GMA-106, GLP-06, SCO-094, CagriSema, amycretin (*e.g.*, oral amycretin), ZT-002, DR-10624, DR-10627, retatrutide, NN-6177, NN-9490, NN-9847, NN-9904, efocipegtrutide, GSB-1290, HB-1085, 4P-004, HM15211, survodutide, froniglutide, efinopegdutide, PF-06954522, YH-25724, YN-012, YN-015, mazdutide, MDR-001, KN-056, MWN-101, emvidutide ALT-801, AP-026, PEG-loxenate, PEGylated exenatide, ITCA 650, XW-004, XW-014, or efpeglenatide, or a pharmaceutically acceptable salt of the GLP-1R agonist, or a pharmaceutically acceptable solvates of either the GLP-1R agonist or the salt of the GLP-1R agonist.

[0111] Suitable GLP-1R agonists that can be used in accordance with the combinations and/or methods described herein are also described in, *e.g.*, PCT Pub. Nos. WO/2023/049518, WO/2022/040600, WO/2023/076237, WO/2023/164050, PCT Application Nos. PCT/US2022/047687, PCT/US2023/013700, PCT/US2024/022311, or US Provisional Application No. 63/492,895, incorporated herein by reference.

[0112] In some embodiments, the GLP-1R agonist is a compound of Formula (I-1)



(I-1)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH, or C₁-C₆ alkyl;

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom

of R^5 is S, and further wherein R^5 is optionally substituted by halo, $-O-C_{1-6}$ alkyl, C_{1-6} alkyl, C_{1-6} alkenyl, or C_{1-6} haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylne, each of which is independently optionally substituted by halo, CN, C_3-C_6 cycloalkyl, or C_{1-6} alkyl optionally substituted by halo or OH;

L is a bond, $-O-$, C_{1-6} alkylene, $^*-O-C_{1-6}$ alkylene- ** , $^*-C_{1-6}$ alkylene- $O-^{**}$, or $^*-NR^6-C_{1-6}$ alkylene- ** , wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

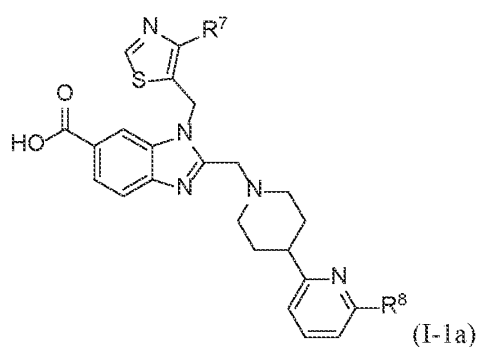
when L is $^*-O-C_{1-6}$ alkylene- ** , the C_{1-6} alkylene of L is optionally substituted by R^L , wherein each R^L is independently C_{1-6} alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C_{1-6} alkylene, the C_{1-6} alkylene is optionally substituted by R^{L1} , wherein each R^{L1} is independently halo, OH, oxo, or C_{1-6} alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

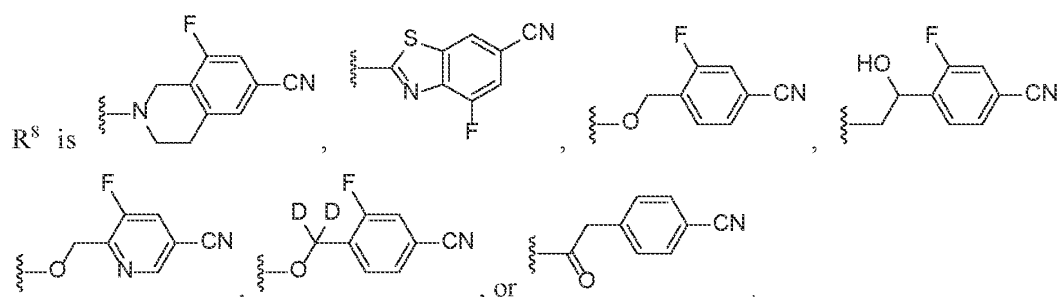
R^6 is hydrogen or C_{1-6} alkyl; and

Ring B is C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_{1-6} alkyl, C_{1-6} haloalkyl, $-COCH_3$, $-CONH_2$, $-S(O)_2CH_3$, and phenyl.

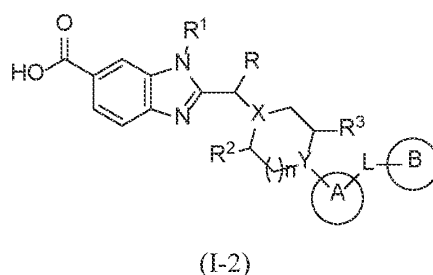
[0113] In some embodiments, the GLP-1R agonist is a compound of Formula (I-1a)



wherein R^7 is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



[0114] In some embodiments, the GLP-1R agonist is a compound of Formula (I-2)



or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X is N or CH;

Y is N or CR^4 , wherein R^4 is hydrogen, OH or C_1 - C_6 alkyl;

n is 0 or 1;

R is hydrogen;

R^1 is $-C_1$ - C_6 alkylene- R^5 , wherein R^5 is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by C_1 - C_6 alkyl, or

R^1 is taken together with R and the intervening atoms to form a Ring C, wherein Ring C is a 5- to 7-membered heterocyclyl optionally substituted by C_1 - C_6 alkyl;

R^2 and R^3 are independently hydrogen, oxo, or C_1 - C_6 alkyl, wherein when Y is CR^4 , R^3 and R^4 are optionally taken together with the carbon atoms to which they are attached to form C_3 - C_6 cycloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkyl optionally substituted by halo or OH;

L is a bond, -O-, C_1 - C_6 alkylene, *-O- C_1 - C_6 alkylene-**, *- C_1 - C_6 alkylene-O-**, or *- NR^6 - C_1 - C_6 alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B,

when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene is optionally substituted by R^L, wherein:

each R^L is independently C₁-C₆ alkyl or halo, or

two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl,

when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L1}, wherein:

each R^{L1} is independently halo, OH, or C₁-C₆ alkyl; or

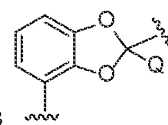
two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

R⁶ is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl, with the proviso that

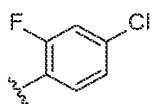
when R¹ is -C₁-C₆ alkylene-R⁵, wherein R⁵ is 3- to 6-membered heterocyclyl or 3- to 6-membered heteroaryl, each of which is optionally substituted by C₁-C₆ alkyl, Y is N or CH, n is 1, R² and R³ are independently hydrogen or C₁-C₆ alkyl, ring A is 6-membered heteroaryl optionally substituted one or two substituents each independently selected from the group consisting of F, Cl and CN, and L is *-OCH₂-**, then ring B is not phenyl optionally substituted by one or two substituents each independently selected from the group consisting of halo, CN, and C₁-C₆ alkyl;

when R¹ is -C₁-C₆ alkylene-R⁵, wherein R⁵ is 3- to 6-membered heterocyclyl or 3- to 6-membered heteroaryl, each of which is optionally substituted by C₁-C₆ alkyl, Y is N or CH,



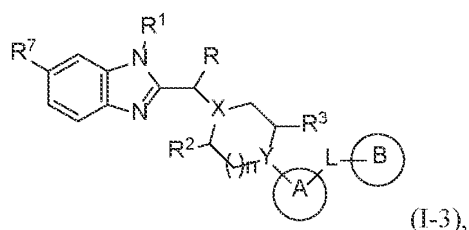
n is 1, R² and R³ are independently hydrogen or C₁-C₆ alkyl, ring A is , wherein Q is H or CH₃, and L is a bond, then ring B is neither phenyl or pyridinyl, each of which is optionally substituted by one or two substituents each independently selected from the group consisting of halo, CN, and C₁-C₆ alkyl; and

when R¹ is -C₁-C₆ alkylene-R⁵, wherein R⁵ is 4-membered heterocyclyl or 5-membered heteroaryl, each of which is optionally substituted by C₁-C₆ alkyl, X is N, Y is N or CH, n is 1, and R² and R³ are independently hydrogen or oxo, then ring B is not



. In some such embodiments of Formula (I-2), Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl. In some such embodiments of Formula (I-2), when L is *-O-C₁-C₆ alkylene-*, the C₁-C₆ alkylene is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl. In some such embodiments of Formula (I-2), when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is unsubstituted.

[0115] In some embodiments, the GLP-1R agonist is a compound of Formula (I-3)



or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

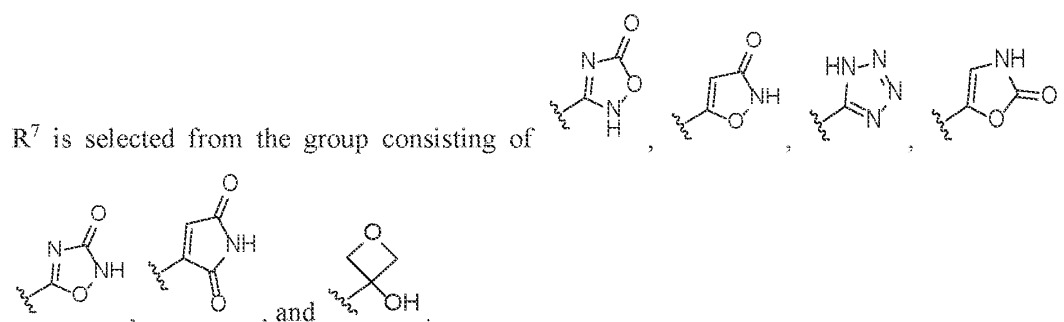
R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH or C₁-C₆ alkyl,

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl, wherein the 3- to 6-membered heterocyclyl or 5- to 6-membered heteroaryl of R⁵ is independently optionally substituted by halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkenyl, or C₁-C₆ haloalkyl;



or R^7 is $-\text{C}(\text{O})\text{NH}-R^8$, wherein R^8 is hydrogen, $-\text{OH}$, $-\text{S}(\text{O})_2-\text{C}_1-\text{C}_6$ alkyl, or $-\text{C}_1-\text{C}_6$ alkyl optionally substituted by halo;

Ring A is 5- to 12-membered heterocyclene, 5- to 12-membered heteroarylene, or C_6-C_{14} arylene, each of which is independently optionally substituted by halo, oxo, $-\text{CN}$, C_3-C_6 cycloalkyl, or C_1-C_6 alkyl optionally substituted by halo or OH ;

L is a bond, $-\text{O}-$, C_1-C_6 alkylene, $^*-\text{O}-\text{C}_1-\text{C}_6$ alkylene- ** , $^*-\text{C}_1-\text{C}_6$ alkylene- $\text{O}-^{**}$, or $^*-\text{NR}^6-\text{C}_1-\text{C}_6$ alkylene- ** , wherein:

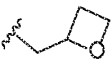
* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

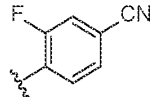
when L is $^*-\text{O}-\text{C}_1-\text{C}_6$ alkylene- ** , the C_1-C_6 alkylene is optionally substituted by R^L , wherein each R^L is independently C_1-C_6 alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C_1-C_6 alkylene, the C_1-C_6 alkylene is optionally substituted by R^{L1} , wherein each R^{L1} is independently halo, OH , oxo, or C_1-C_6 alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C_3-C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

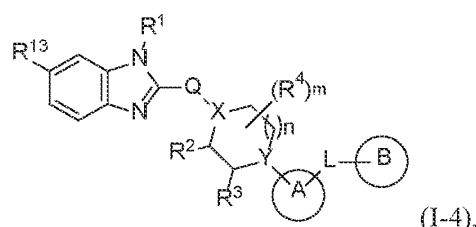
R^6 is hydrogen or C_1-C_6 alkyl; and

Ring B is C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN , oxo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{S}(\text{O})_2\text{CH}_3$, cyclopropyl, and phenyl, with the proviso that:

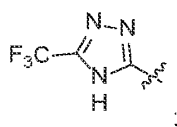
when R^7 is $-C(O)NH-R^8$, R^1 is , X is N, Y is CH, n is 1, R^2 and R^3 are each hydrogen,

ring A is 6-membered heteroaryl, and L is $^*-OCH_2-^*$, then ring B is not .

[0116] In some embodiments, the GLP-1R agonist is a compound of Formula (I-4)



or a pharmaceutically acceptable salt, wherein:



R^{13} is $-C(O)OH$ or

X is N or CR^x , wherein R^x is hydrogen, OH or C_1-C_6 alkyl;

Y is N or CR^y , wherein R^y is hydrogen, OH or C_1-C_6 alkyl;

n is 0 or 1;

Q is selected from the group consisting of $-C(R^7)(R^8)-$, $-O-$, $-N(R^9)-$, and $-S-$, wherein

R^7 and R^8 are independently hydrogen, halogen, or C_1-C_6 alkyl; and

R^9 is hydrogen or C_1-C_6 alkyl;

R^1 is optionally substituted $-C_1-C_6$ alkyl or $-C_1-C_6$ alkylene- R^5 , wherein R^5 is C_3-C_6 cycloalkyl, 3- to 6-membered heterocyclyl, or 5- to 6-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, oxo, CN, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl, wherein each C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and $-OC_1-C_6$ alkyl substituent is independently optionally substituted by halo or CN;

R^2 and R^3 are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3-C_4 cycloalkyl ring; or

R^2 and R^x , when present, are taken together with the carbon atoms to which they are attached to form an optionally substituted C_3-C_5 cycloalkyl ring, and R^3 is hydrogen, oxo, or C_1-C_6 alkyl;

m is 0, 1, 2, or 3;

R^4 is oxo or C_1-C_6 alkyl;

Ring A is C₆-C₁₄ arylene, 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, OH, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

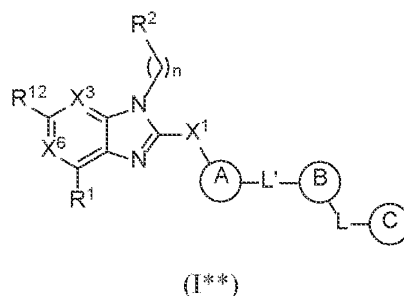
L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein * represents the point of attachment to ring A and ** represents the point of attachment to ring B, and wherein:

when L is C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, L is optionally substituted by one to three R^L substituents, wherein each R^L is independently halo, OH, or C₁-C₆ alkyl; or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

R⁶, when present, is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl optionally substituted by halo or CN, -OC₁-C₆ alkyl optionally substituted by halo or CN, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl optionally substituted by halo or CN.

[0117] In some embodiments, the GLP-1R agonist is a compound of Formula (I**):



or a pharmaceutically acceptable salt thereof; wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, halogen, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, C₃₋₁₀ cycloalkyl, or C₆₋₁₀ aryl, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted

with one or more deuterium, C₁₋₆ alkoxy, hydroxyl, -CN, or oxo, and the cycloalkyl, heterocyclyl, or aryl group is optionally substituted with one or more halogen, C₁₋₆ alkoxy, or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

C₁₋₆ alkyl optionally substituted with deuterium;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

-CN;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, , or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

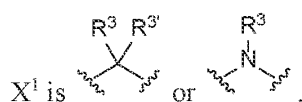
R² and R⁷, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R⁴ is halogen, hydrogen, -C(O)OH, or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

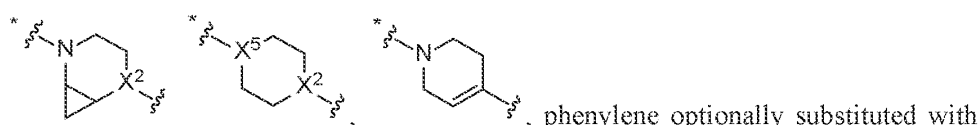
R¹² is hydrogen, -C(O)OH, -C(O)NR^{N12}R^{N12'}, -C(O)NR¹²S(O)₂R^{12'}, -(C₂₋₆ alkynylene)-C(O)OH, -(C₁₋₆ alkylene)-C(O)OH, -NR^{N12}-(C₁₋₆ alkylene)-C(O)OH, 5-10 membered heteroaryl or 5- to 10-membered heterocyclyl optionally substituted with one or more oxo, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R^{N12} and R^{N12'} independently are H or C₁₋₆ alkyl;



wherein R^3 and $R^{3'}$ independently are H, D or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with deuterium;

Ring A is



one or more halo or C_{1-6} alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C_{1-6} alkyl;

wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or $-O-$;

Ring B is a C_{6-10} arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $-(C_{1-6} \text{ alkylene})-$, $-(NR^L)-(C_{1-6} \text{ alkylene})-$, $-(O-(C_{1-6} \text{ alkylene})-$, or $-(C_{1-6} \text{ alkylene})-O-$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium;

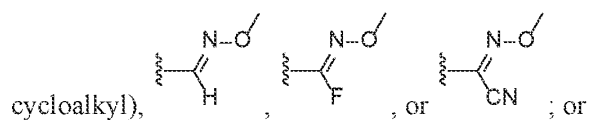
wherein R^L is H or C_{1-6} alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-10 membered heterocyclyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CN$, C_{3-10} cycloalkyl, or $-C(O)NR'^2$;

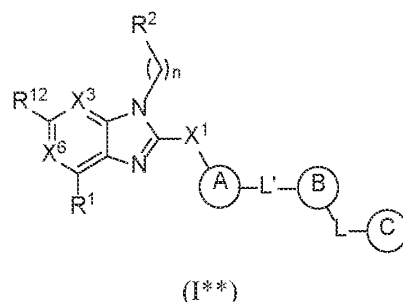
wherein R' is H or C_{1-6} alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, $-CN$, C_{1-6} haloalkyl, $-O-C_{1-6}$ alkyl, C_{3-10} cycloalkyl, $-C(=O)-(C_{3-10}$



a bicyclic 9- or 10-membered heteroaryl or heterocyclyl optionally substituted with one or more C_{1-6} alkyl, halogen, $-CN$, or oxo.

[0118] In some embodiments, the GLP-1R agonist is a compound of Formula (I**):



or a pharmaceutically acceptable salt thereof; wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, halogen, $-O-X^4$, or $-NR^8R^9$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$, or $-(C_{1-6} \text{ alkylene})-(3\text{- to } 8\text{-membered heterocyclyl})$, 3- to 8-membered heterocyclyl, $-(CH_2CH_2-O)_{1-5}-CH_3$, or $-(CH_2-CH(-OCH_3)-CH_2-O)_{1-5}-CH_3$, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, C_{1-6} alkoxy, hydroxyl, $-CN$, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or $-CN$;

R^6 is hydrogen, halogen, or $-O-R^7$;

wherein R^7 and R^2 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or $-S(O)_2-C_{1-6}$ alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

C_{1-6} alkyl optionally substituted with deuterium;

C_{1-6} haloalkyl;

$-(O)-C_{1-6}$ alkyl;

$-CN$;

a C_{3-10} cycloalkyl optionally substituted with one or more $-CN$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-CN$;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with

one or more oxo, $\text{HN}=\text{N}$, or C_{1-6} alkyl;

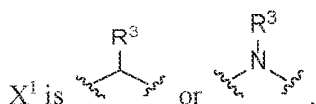
a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R^4 is hydrogen, $-\text{C}(\text{O})\text{OH}$, or $-\text{O}-\text{R}^8$,

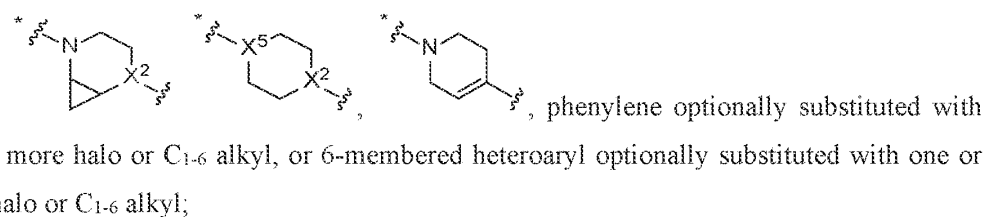
wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^{12} is hydrogen, $-\text{C}(\text{O})\text{OH}$ or 5-10 membered heteroaryl optionally substituted with one or more oxo, C_{1-6} alkyl or C_{1-6} haloalkyl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or $-\text{O}-$;

Ring B is a C_{6-10} arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $-(\text{C}_{1-6} \text{ alkylene})-$, $-\text{NR}^{\text{L}}-(\text{C}_{1-6} \text{ alkylene})-$, $-\text{O}-(\text{C}_{1-6} \text{ alkylene})-$, or $-(\text{C}_{1-6} \text{ alkylene})-\text{O}-$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium;

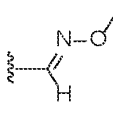
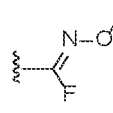
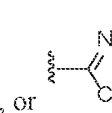
wherein R^{L} is H or C_{1-6} alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-10 membered heterocyclyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -CN, C₃₋₁₀ cycloalkyl, or -C(O)NR'²;

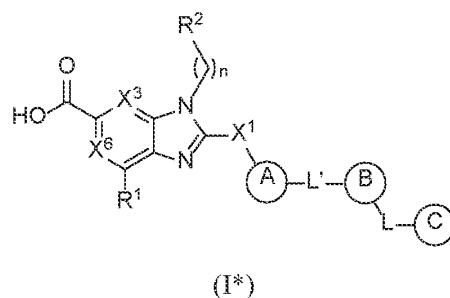
wherein R' is H or C₁₋₆ alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, -CN, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀

cycloalkyl), , , or ; or

a bicyclic 9- or 10-membered heteroaryl optionally substituted with one or more C₁₋₆ alkyl, halogen, or oxo.

[0119] In some embodiments, the GLP-1R agonist is a compound of Formula I*:



or a pharmaceutically acceptable salt thereof, wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or $-S(O)_2-C_{1-6}$ alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocycl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

C_{1-6} alkyl;

C_{1-6} haloalkyl;

$-(O)-C_{1-6}$ alkyl;

a C_{3-10} cycloalkyl optionally substituted with one or more $-CN$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-CN$;

a 4 or 5-membered heterocycl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocycl is optionally substituted with one or more

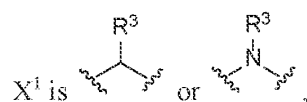
oxo, $\text{HN}=\text{N}$, or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocycl;

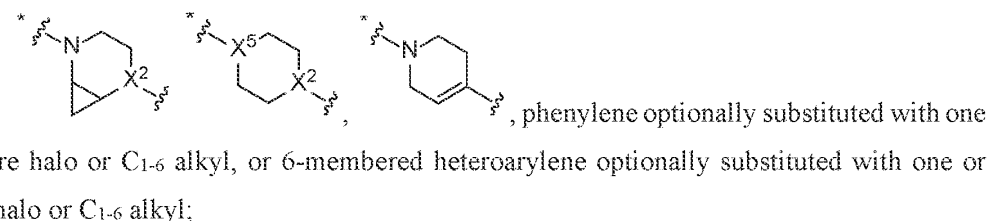
R^4 is hydrogen or $-O-R^8$,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocycl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or -O-;

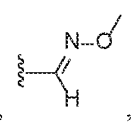
Ring B is a C₆₋₁₀ arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C₆₋₁₀ arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;

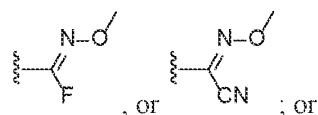
L is a bond, *-CH₂-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₁₋₆ alkyl, 3-10 membered heterocyclyl, halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

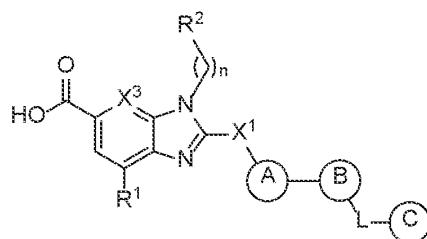
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0120] In some embodiments, the compound of Formula (I*) is of Formula (I'):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

X³ is CH or N;

R¹ is -C₁₋₆ haloalkyl or -O-X⁴;

wherein X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more -CN, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is hydrogen;

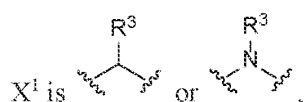
-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

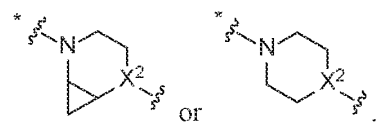
oxo, $\text{HN}=\text{C}$, or C₁₋₆ alkyl; or

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S;



wherein R^3 is H or C₁₋₆ alkyl;

Ring A is



wherein * indicates attachment to X^1 , and

wherein X^2 is CH or N;

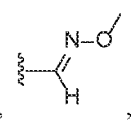
Ring B is a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene optionally substituted with one or more C₁₋₆ alkyl;

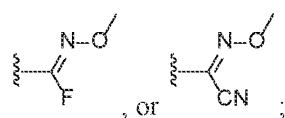
L is a bond or *-O-(C₁₋₆ alkylene)-, wherein * indicates attachment to Ring B;

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

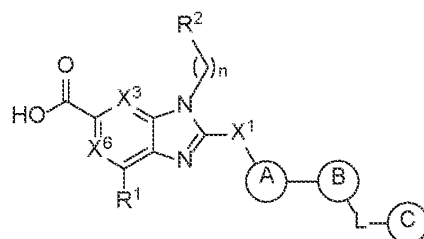
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0121] In some embodiments, the GLP-1R agonist is a compound of Formula I'':



(I'')

or a pharmaceutically acceptable salt thereof, wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

wherein X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

C₁₋₆ alkyl;

-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

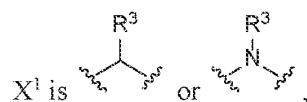
oxo, , or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

R² and R⁷, together with the atoms to which they are attached, combine to form a C₂₋₉ heterocyclyl;

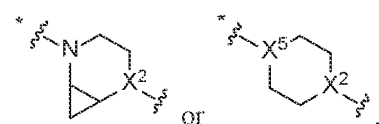
R⁴ is hydrogen or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



wherein * indicates attachment to X¹,

X⁵ is CH or N, and

X² is CH or N;

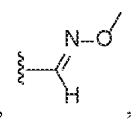
Ring B is a 6-10 membered heteroarylene, or a 3-10 membered heterocyclylene optionally substituted with one or more C₁₋₆ alkyl;

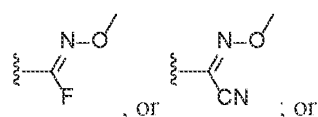
L is a bond or *-O-(C₁₋₆ alkylene)-, wherein * indicates attachment to Ring B; and

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

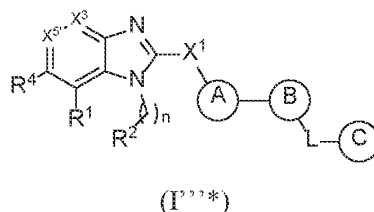
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0122] In some embodiments, the GLP-1R agonist is a compound of Formula (I'''):



or a pharmaceutically acceptable salt thereof, wherein:

X³ is CR^{X3} or N;

wherein R^{X3} is H, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkoxy, -O-(CH₂CH₂-O)₁₋₅-CH₃, or C₁₋₆ alkoxy;

X⁵ is CR⁵

R¹ is -C₁₋₆ haloalkyl or -O-X⁴, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

wherein X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, halogen, or -CN, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

halogen;

branched C₃₋₆ alkyl;

-(O)-C₁₋₆ alkyl;

C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, , or C₁₋₆ alkyl; or

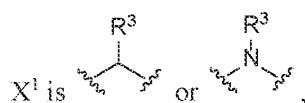
5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

R² and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁵ is hydrogen or -C(O)-OH;

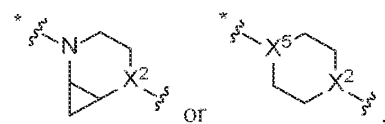
R⁴ is hydrogen, halogen, -C(O)-OH, or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



wherein * indicates attachment to X¹,

wherein X⁵ is CH or N, and

X² is CH or N;

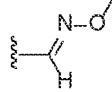
Ring B is a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene optionally substituted with one or more C₁₋₆ alkyl;

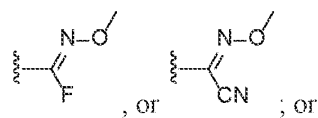
L is a bond or *-O-(C₁₋₆ alkylene)-, wherein * indicates attachment to Ring B;

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

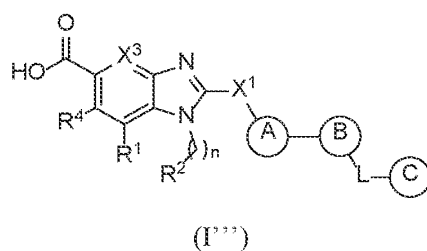
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0123] In some embodiments, the GLP-1R agonist is a compound of Formula (I''')



or a pharmaceutically acceptable salt thereof, wherein:

X^3 is CR^{X3} or N;

wherein R^{X3} is H, halogen, C_{1-6} alkyl, C_{1-6} haloalkoxy, or C_{1-6} alkoxy;

R^1 is $-C_{1-6}$ haloalkyl or $-O-X^4$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

wherein X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6}$ alkylene)-(C_{3-10} cycloalkyl), or $-(C_{1-6}$ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, $-(CH_2CH_2-O)_{1-5}-CH_3$, or $-(CH_2-CH(-OCH_3)-CH_2-O)_{1-5}-CH_3$, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, $-CN$, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or $-CN$;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

halogen;

C_{3-6} alkyl;

$-(O)-C_{1-6}$ alkyl;

a C_{3-10} cycloalkyl optionally substituted with one or more $-CN$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-CN$;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

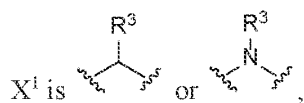
oxo, $\begin{matrix} \text{HN} \\ \diagup \diagdown \end{matrix}$, or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

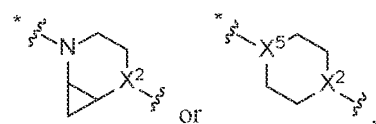
R^4 is hydrogen or $-O-R^8$,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



wherein * indicates attachment to X^1 ,

wherein X^5 is CH or N, and

X^2 is CH or N;

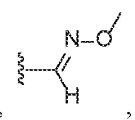
Ring B is a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene optionally substituted with one or more C_{1-6} alkyl;

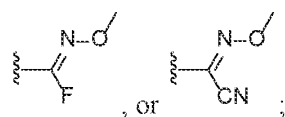
L is a bond or *-O-(C_{1-6} alkylene)-, wherein * indicates attachment to Ring B;

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C_{3-10} cycloalkyl;

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O- C_{1-6} alkyl, C_{3-10} cycloalkyl, -C(=O)-(C_{3-10} cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C_{1-6} alkyl, or oxo.

[0124] In some embodiments of Formula (I'''), or a pharmaceutically acceptable salt thereof,

X^3 is CH or N;

R^1 is - C_{1-6} haloalkyl or -O- X^4 , or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

wherein X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, -(C_{1-6} alkylene)-(C_{3-10} cycloalkyl), or -(C_{1-6} alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl,

heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, -CN, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

C₃₋₆ alkyl;

-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

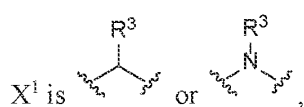
oxo, , or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

R² and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

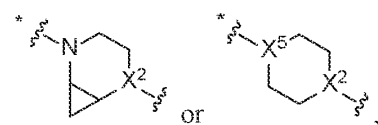
R⁴ is hydrogen or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



wherein * indicates attachment to X¹,

wherein X⁵ is CH or N, and

X² is CH or N;

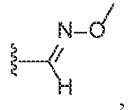
Ring B is a 6-10 membered heteroarylene, or a 3-10 membered heterocyclylene optionally substituted with one or more C₁₋₆ alkyl;

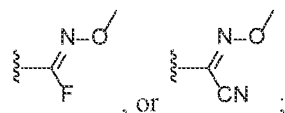
L is a bond or *-O-(C₁₋₆ alkylene)-, wherein * indicates attachment to Ring B;

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

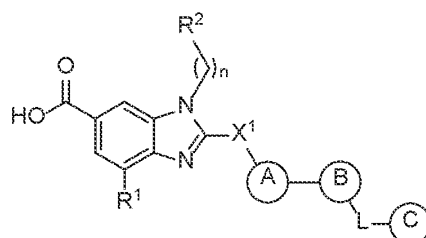
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0125] In some embodiments, the compound of Formula (I'') is of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

R¹ is -C₁₋₆ haloalkyl or -O-X⁴,

wherein X⁴ is C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), -(-CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more -CN, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

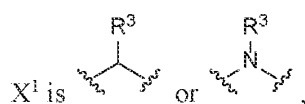
-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

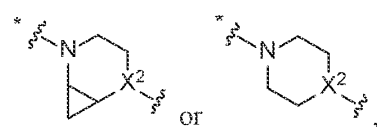
oxo, , or C₁₋₆ alkyl; or

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



wherein * indicates attachment to X¹, and

wherein X² is CH or N;

Ring B is:

a 6-membered heteroarylene comprising nitrogen;

a 9-membered heterocyclylene comprising two oxygen atoms optionally substituted with one or more C₁₋₆ alkyl; or

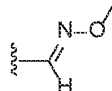
a 10-membered heterocyclylene comprising two oxygen atoms;

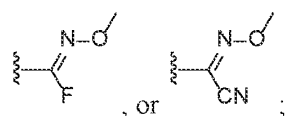
L is a bond or *-O-(C₁₋₆ alkylene)-, wherein * indicates attachment to Ring B;

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

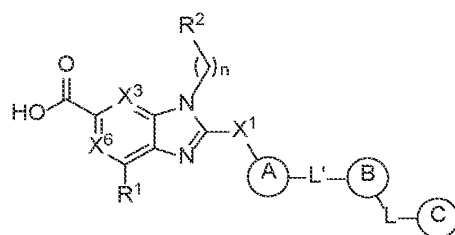
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0126] In some embodiments, the GLP-1R agonist is a compound of Formula (I-5)



(I-5)

or a pharmaceutically acceptable salt thereof, wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, $-O-X^4$, or $-NR^8R^9$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$, or $-(C_{1-6} \text{ alkylene})-(3\text{- to }8\text{-membered heterocyclyl})$, 3- to 8-membered heterocyclyl, $-(CH_2CH_2-O)_{1-5}-CH_3$, or $-(CH_2-CH(-OCH_3)-CH_2-O)_{1-5}-CH_3$, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, $-CN$, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or $-CN$;

R^6 is hydrogen, halogen, or $-O-R^7$;

wherein R^7 and R^2 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or $-S(O)_2-C_{1-6}$ alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

branched C_{1-6} alkyl;

C_{1-6} haloalkyl;

$-(O)-C_{1-6}$ alkyl;

a C_{3-10} cycloalkyl optionally substituted with one or more $-CN$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-CN$;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

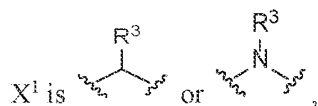
oxo, $\text{HN}=\text{C}$, or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

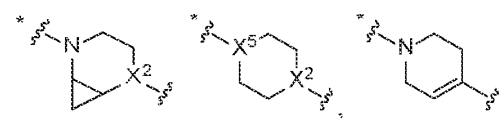
R^4 is hydrogen or $-\text{O}-\text{R}^8$,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



phenylene optionally substituted with one or more halo or C_{1-6} alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C_{1-6} alkyl;

wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or $-\text{O}-$;

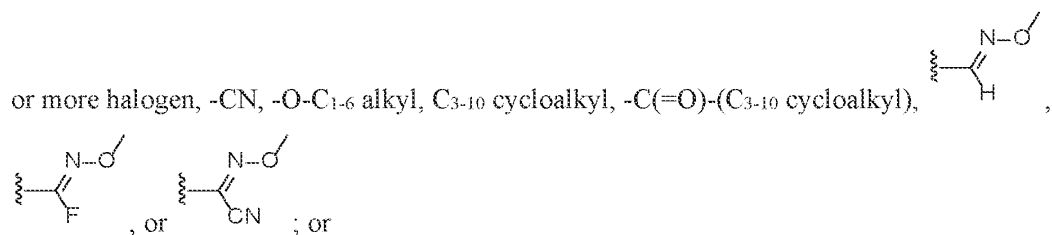
Ring B is a C_{6-10} arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $^*-\text{CH}_2-$, $^*-\text{O}-(\text{C}_{1-6} \text{ alkylene})-$, or $^*-(\text{C}_{1-6} \text{ alkylene})-\text{O}-$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium; and

Ring C is:

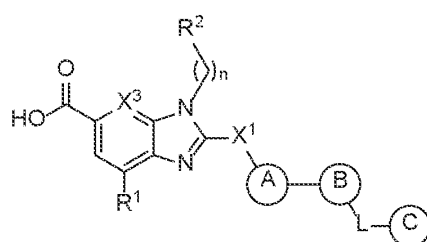
a 6-membered aryl optionally substituted with one or more C_{1-6} alkyl, 3-10 membered heterocyclyl, halogen, $-\text{OCH}_3$, $-\text{CN}$, or C_{3-10} cycloalkyl;

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

[0127] In some embodiments, the GLP-1R agonist is a compound of Formula (I-P01):



(I-P01)

or a pharmaceutically acceptable salt thereof, wherein:

X³ is CH or N;

R¹ is -C₁₋₆ haloalkyl or -O-X⁴;

wherein X⁴ is C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more -CN, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

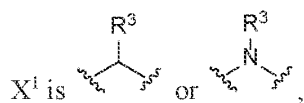
-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

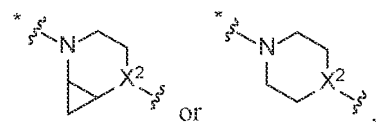
oxo, , or C₁₋₆ alkyl; or

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



wherein * indicates attachment to X¹, and

wherein X² is CH or N;

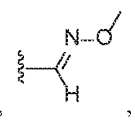
Ring B is a 6-10 membered heteroarylene, or a 3-10 membered heterocyclylene optionally substituted with one or more C₁₋₆ alkyl;

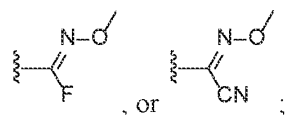
L is a bond or *-O-(C₁₋₆ alkylene)-, wherein * indicates attachment to Ring B;

Ring C is:

a 6-membered aryl optionally substituted with one or more halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

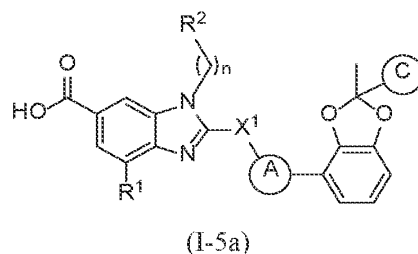
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

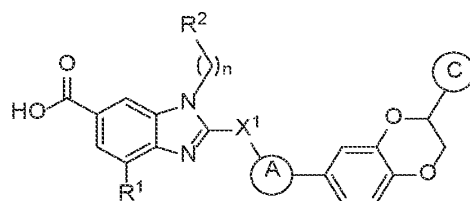
[0128] In some embodiments the compound of Formula (I-5) is of Formula (I-5a):



or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , Ring A, and Ring C are as defined for Formula (I-5).

[0129] In some embodiments, the compound of Formula (I-5) is of Formula (I-5b):

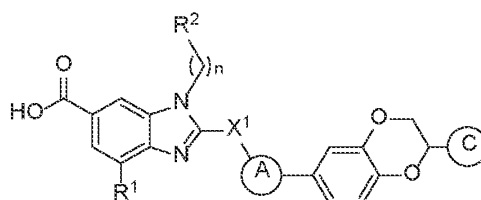


(I-5b)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , Ring A, and Ring C are as defined for Formula (I-5).

[0130] In some embodiments, the compound of Formula (I-5) is of Formula (I-5c):

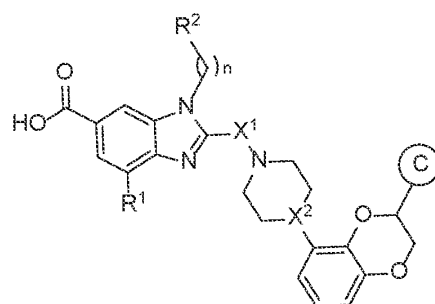


(I-5c)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , Ring A, and Ring C are as defined for Formula (I-5).

[0131] In some embodiments, the compound of Formula (I-5) is of Formula (I-5d):

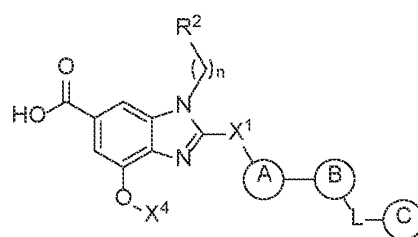


(I-5d)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , X^2 , and Ring C are as defined for Formula (I-5).

[0132] In some embodiments, the compound of Formula (I-5) is of Formula (I-5e):

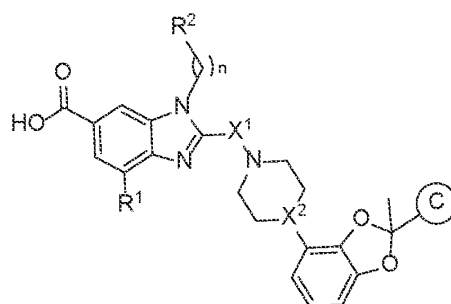


(I-5e)

or a pharmaceutically acceptable salt thereof;

wherein X^4 , n , R^2 , X^1 , Ring A, Ring B, and Ring C are as defined for Formula (I-5).

[0133] In some embodiments, the compound of Formula (I-5) is of Formula (I-5f):

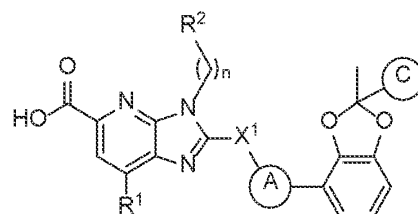


(I-5f)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , and Ring C are as defined for Formula (I-5).

[0134] In some embodiments, the compound of Formula (I-5) is of Formula (I-5g):

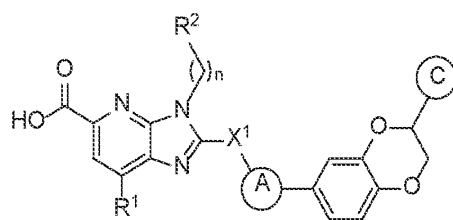


(I-5g)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , Ring A, and Ring C are as defined for Formula (I-5).

[0135] In some embodiments, the compound of Formula (I-5) is of Formula (I-5h):

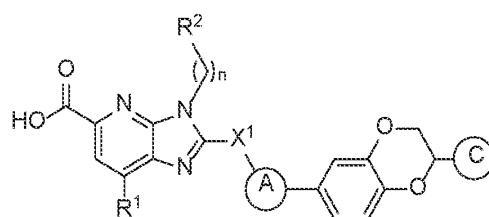


(I-5h)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , Ring A, and Ring C are as defined for Formula (I-5).

[0136] In some embodiments, the compound of Formula (I-5) is of Formula (I-5i):

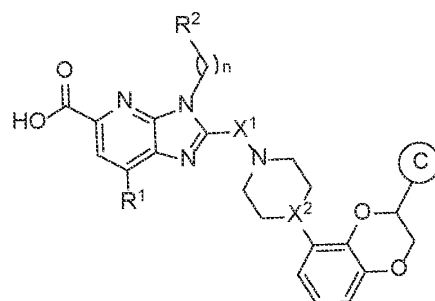


(I-5i)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , and Ring A, Ring C are as defined for Formula (I-5).

[0137] In some embodiments, the compound of Formula (I-5) is of Formula (I-5j)

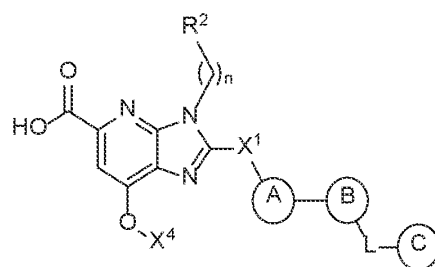


(I-5j)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , n , R^2 , X^1 , and Ring C are as defined for Formula (I-5).

[0138] In some embodiments, the compound of Formula (I-5) is of Formula (I-5k)

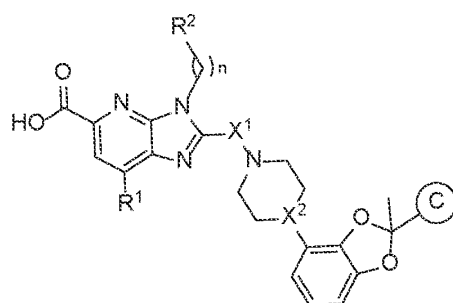


(I-5k)

or a pharmaceutically acceptable salt thereof;

wherein X^4 , R^2 , X^1 , n , Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0139] In some embodiments, the compound of Formula (I-5) is of Formula (I-5l)

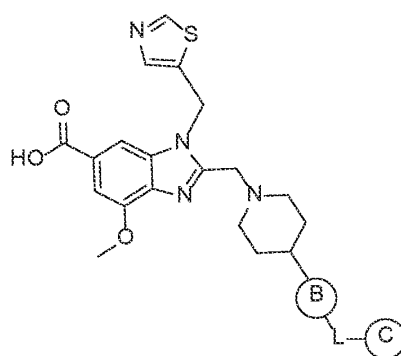


(I-5l)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , R^2 , X^1 , n , and Ring C are as defined for Formula (I-5).

[0140] In some embodiments, the compound of Formula (I-5) is of Formula (I-5m)

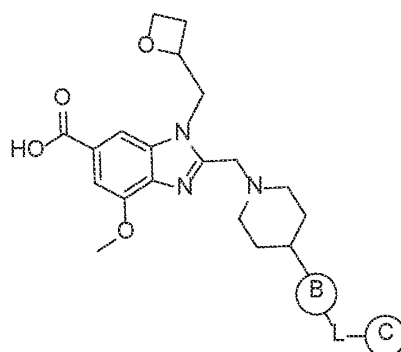


(I-5m)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0141] In some embodiments, the compound of Formula (I-5) is of Formula (I-5n)

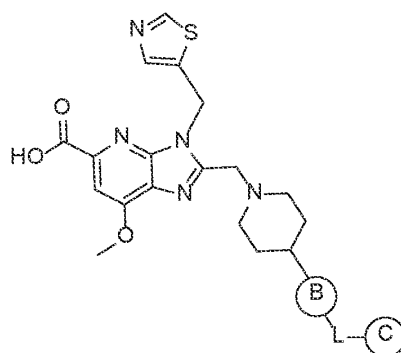


(I-5n)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0142] In some embodiments, the compound of Formula (I-5) is of Formula (I-5o)

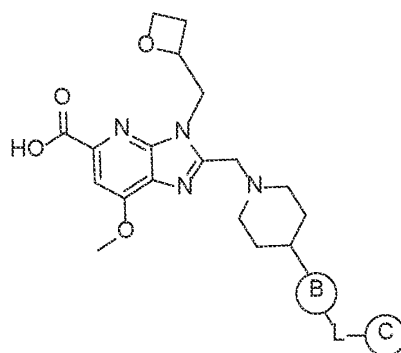


(I-5o)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0143] In some embodiments, the compound of Formula (I-5) is of Formula (I-5p)

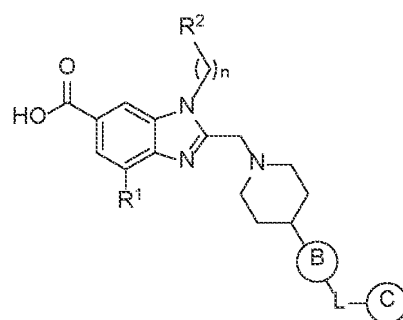


(I-5p)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0144] In some embodiments, the compound of Formula (I-5) is of Formula (IQ)

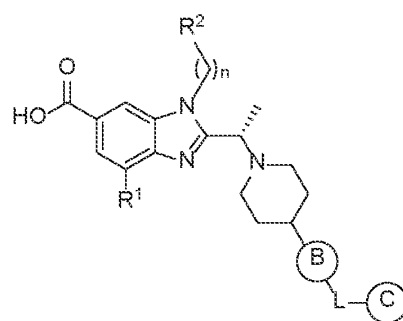


(IQ)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , R^2 , n , Ring B, L, and Ring C are as defined for Formula (I-5).

[0145] In some embodiments, the compound of Formula (I-5) is of Formula (IR)

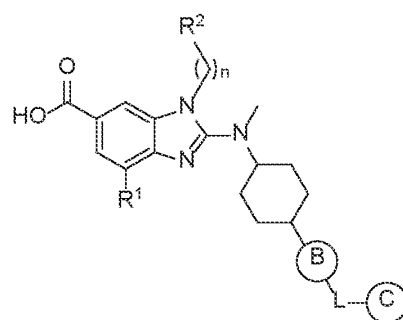


(IR)

or a pharmaceutically acceptable salt thereof;

wherein R^1 , R^2 , n , Ring B, L, and Ring C are as defined for Formula (I-5).

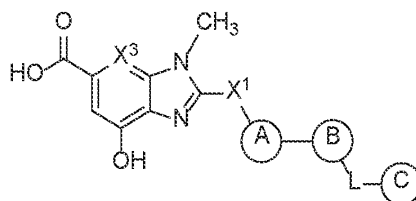
[0146] In some embodiments, the compound of Formula (I-5) is of Formula (IS)



(IS)

Wherein R^1 , R^2 , n , Ring B, L, and Ring C are as defined for Formula (I-5).

[0147] In some embodiments, the compound of Formula (I-5) is of Formula (IT)

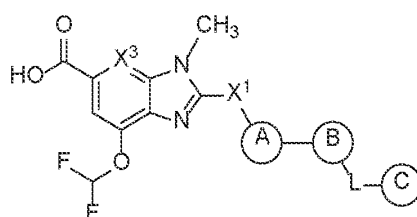


(IT)

or a pharmaceutically acceptable salt thereof;

wherein X^1 , X^3 , Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0148] In some embodiments, the compound of Formula (I-5) is of Formula (IU)



(IU)

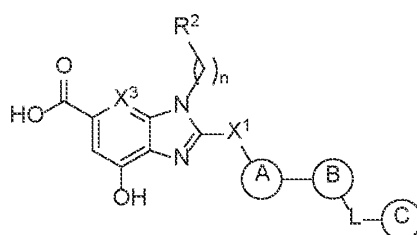
or a pharmaceutically acceptable salt thereof;

wherein X^3 , X^1 , Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

or a pharmaceutically acceptable salt thereof;

wherein X^3 , R^4 , R^1 , n , and R^2 are as defined for Formula (I-5).

[0149] In some embodiments, the compound of Formula (I-5) is of Formula (IX)

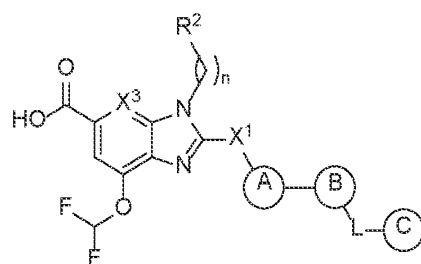


(IX)

or a pharmaceutically acceptable salt thereof;

wherein X^3 , n , R^2 , X^1 , Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0150] In some embodiments, the compound of Formula (I-5) is of Formula (IY)

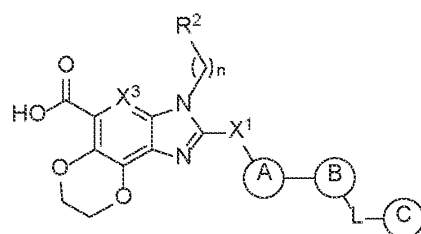


(IY)

or a pharmaceutically acceptable salt thereof;

wherein X³, n, R², X¹, Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0151] In some embodiments, the compound of Formula (I-5) is of Formula (IZ)

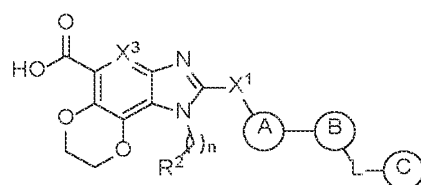


(IZ)

or a pharmaceutically acceptable salt thereof;

wherein X³, n, R², X¹, Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0152] In some embodiments, the compound of Formula (I'') is of Formula (IAA)

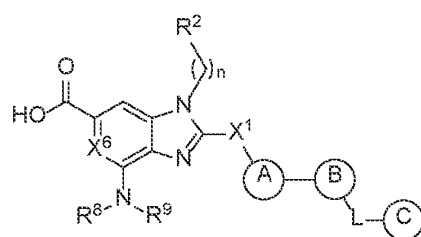


(IAA)

or a pharmaceutically acceptable salt thereof;

wherein X³, n, R², X¹, Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0153] In some embodiments, the compound of Formula (I-5) is of Formula (IAB)

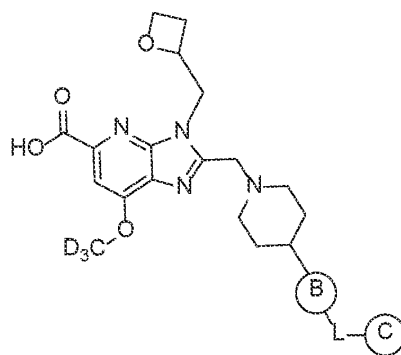


(IAB)

or a pharmaceutically acceptable salt thereof;

wherein X6, R8, R9, n, R2, X1, Ring A, Ring B, L, and Ring C are as defined for Formula (I-5).

[0154] In some embodiments, the compound of Formula (I-5) is of Formula (IAC)

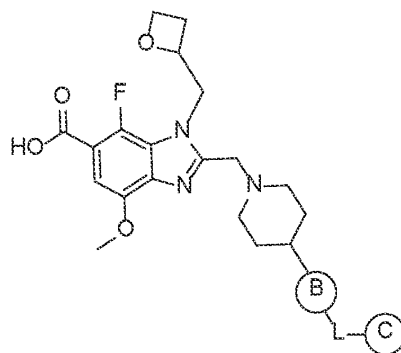


(IAC)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0155] In some embodiments, the compound of Formula (I-5) is of Formula (IAD)

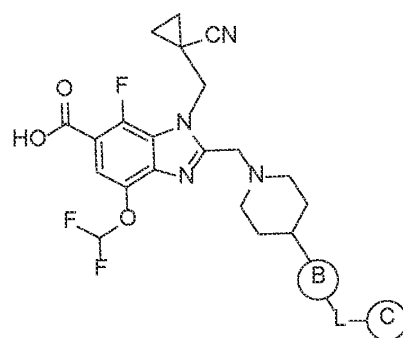


(IAD)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0156] In some embodiments, the compound of Formula (I-5) is of Formula (IAE)

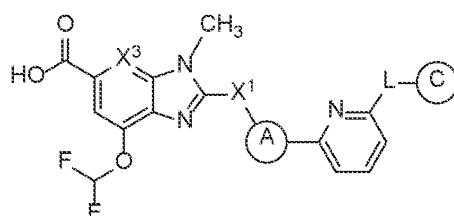


(IAE)

or a pharmaceutically acceptable salt thereof;

wherein Ring B, L, and Ring C are as defined for Formula (I-5).

[0157] In some embodiments, the compound of Formula (I-5) is of Formula (IAG)

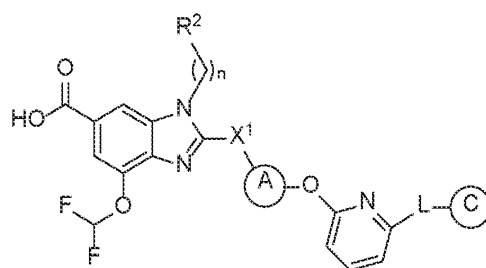


(IAG)

or a pharmaceutically acceptable salt thereof;

wherein X3, X1, Ring A, L, and Ring C are as defined for Formula (I-5).

[0158] In some embodiments, the compound of Formula (I-5) is of Formula (IAH):

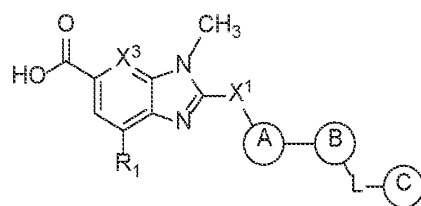


(IAH)

or a pharmaceutically acceptable salt thereof;

wherein n, R2, X1, Ring A, L, and Ring C are as defined for Formula (I-5).

[0159] In some embodiments, the compound of Formula (I-5) is of Formula (IAI):



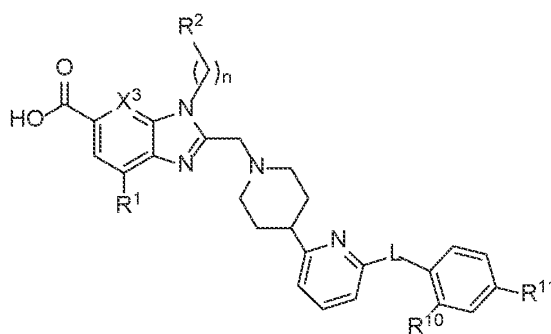
(IAI)

wherein R^1 is $-O-(C_{1-6}$ haloalkyl);

X^3 , X^1 , Ring A, Ring B, L, and Ring C are as defined for Formula (I-5);

or a pharmaceutically acceptable salt thereof.

[0160] In some embodiments, the compound of Formula (I-5) is of Formula (IAJ):



(IAJ)

wherein R^2 is hydrogen, thiazolyl, oxetanyl, cyclopropyl optionally substituted with cyano, or methoxy;

n is 1 or 2;

R^1 is $-O-C_{1-6}$ alkyl, $-OH$, or $-NH_2$, wherein the C_{1-6} alkyl is optionally substituted with one or more halo or deuterium;

X^3 is CR^6 , wherein R^6 is halo or hydrogen;

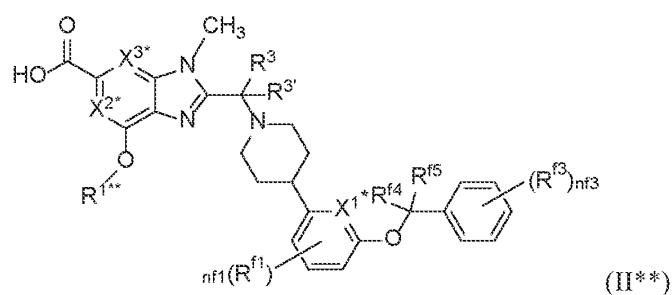
L is $^*-O-(C_{1-6}$ alkylene)-, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium;

R^{10} is halo; and

R^{11} is halo or cyano;

or a pharmaceutically acceptable salt thereof.

[0161] In some embodiments, the compound of Formula (I**) is of Formula (II**):



or a pharmaceutically acceptable salt thereof; wherein

R^{f4} and R^{f5} are each independently selected from C₁₋₆ alkyl, H and D

nf1 is 0, 1, 2, 3, or 4:

nf3 is 0, 1, 2, 3, 4, or 5;

each R^{fi} is halogen;

R^3 and $R^{3'}$ independently are H or D;

$$X^{1*} \text{ is } N \text{ or } CR^{fl},$$

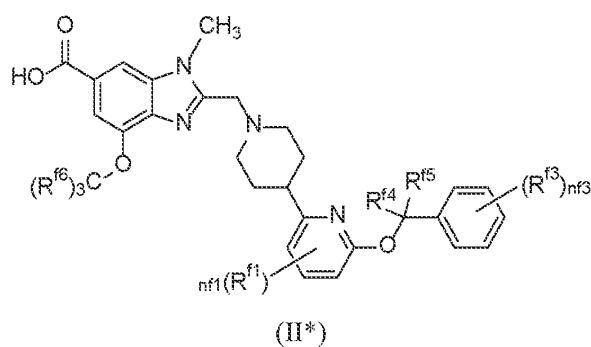
X^{2*} and X^{3*} independently are CH or CF;

each R³ is independently selected from halogen, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or -C(O)N(R³)₂,

each R^{f3'} is independently selected from H or C₁₋₆ alkyl; and

R^{1**} is H or C₁₋₂ alkyl optionally substituted with one or more deuterium or halogen.

[0162] In some embodiments, the compound of Formula (I**) is of Formula (II*):



or a pharmaceutically acceptable salt thereof;

each R^{fi} is independently selected from halogen

R^{f4} and R^{f5} are each independently selected from C₁₋₆ alkyl, H and D

nf1 is 0, 1, 2, or 3;

nf3 is 0, 1, 2, 3, 4, or 5;

each R^{fi} is halogen;

each R^{13} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or $-C(O)N(R^{13'})_2$,

each $R^{13'}$ is independently selected from H or C_{1-6} alkyl;

each R^{16} is independently selected from H, D or F.

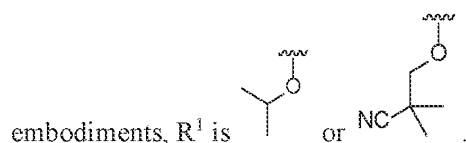
[0163] In some embodiments, R^{14} and R^{15} are each independently selected from CH_3 , H, and D.

[0164] In some embodiments, each R^{11} is fluorine.

[0165] In some embodiments, X^3 is N. In some embodiments, X^3 is CH.

[0166] In some embodiments, X^6 is N. In some embodiments, X^6 is CR^4 .

[0167] In some embodiments, R^1 is R^1 is $-O-C_{1-6}$ alkyl. In some embodiments, the alkyl group is linear. In some embodiments, the alkyl group is branched. In some embodiments, the alkyl group is linear and is optionally substituted with one or more deuterium, -CN or $-O-C_{1-6}$ alkyl. In some embodiments, the alkyl group is unsubstituted. In some embodiments, the alkyl group is substituted with one or more -CN or $-O-C_{1-6}$ alkyl. In some embodiments, R^1 is $-O-CH_2-CH_3$, $-O-CH_3$, $-O-CH_2-CN$, $-O-CH_2-CH_2-O-CH_3$, or $-O-CH_2CH(-O-CH_3)-CH_3$. In some embodiments, R^1 is branched and optionally substituted with one or more -CN. In some

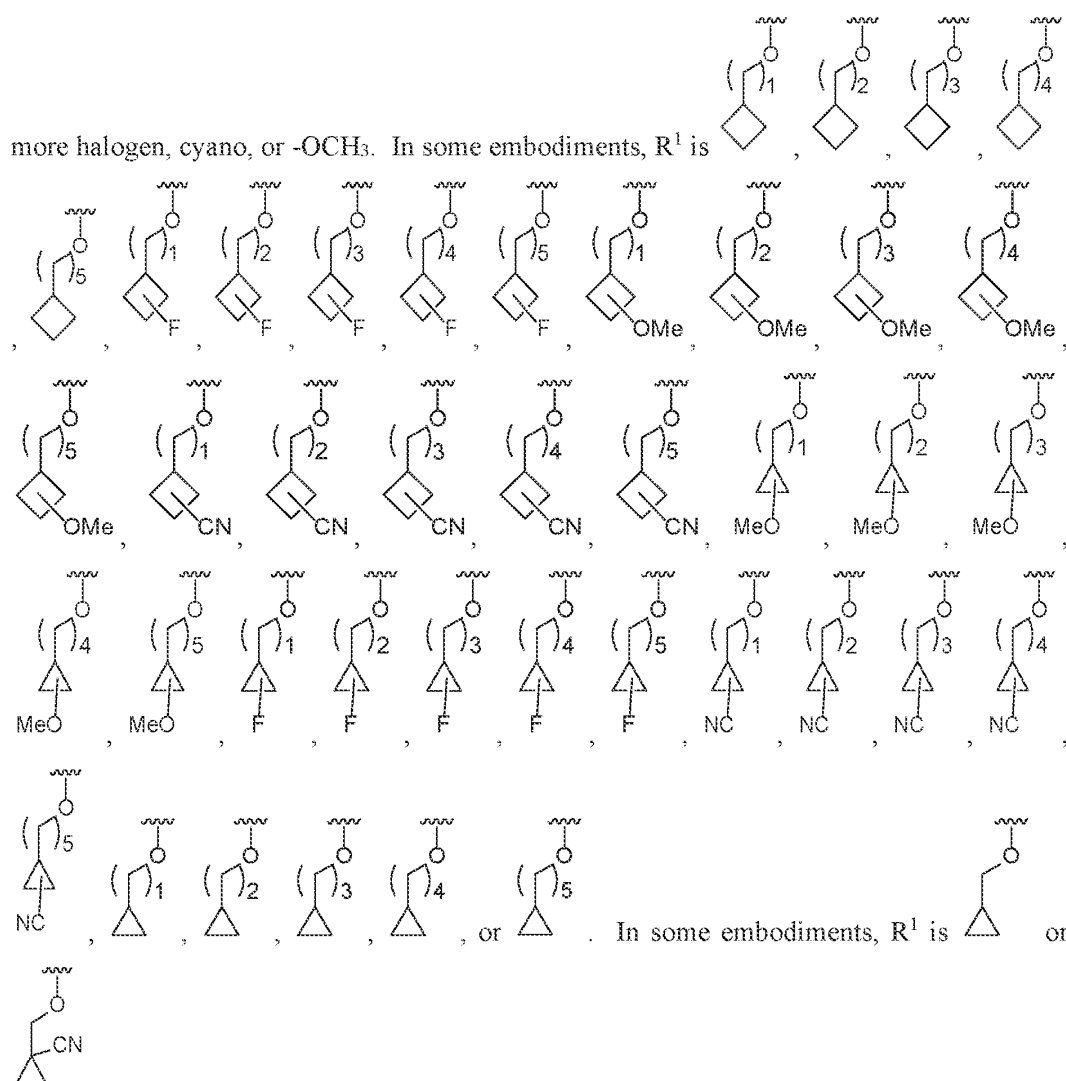


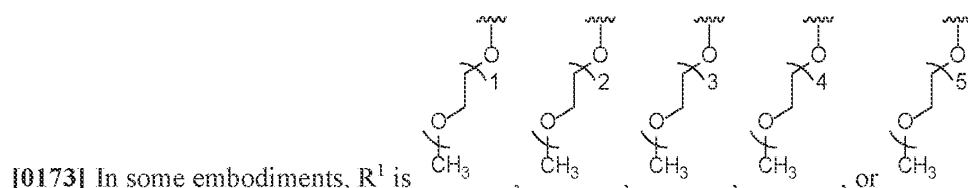
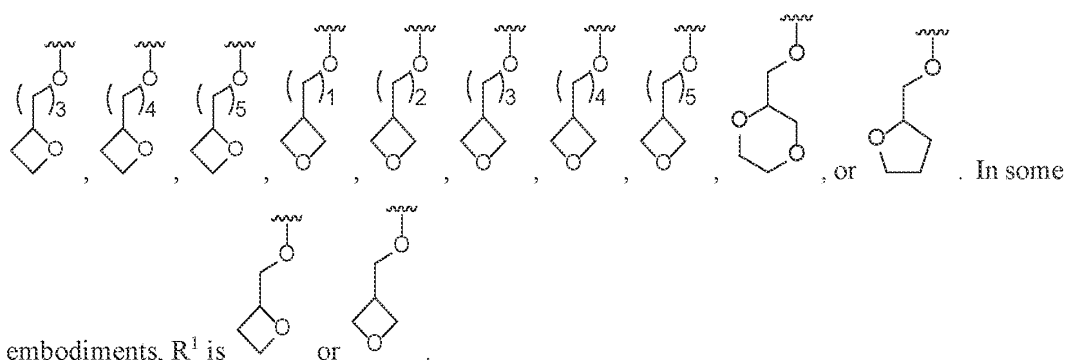
[0168] In some embodiments, R^1 is $-O-C_{1-6}$ haloalkyl, wherein the haloalkyl group is linear. In some embodiments, the haloalkyl group is substituted with one or more fluorine. In some embodiments, R^1 is $-O-CHF_2$, $-O-CF_3$, $-O-CH_2-CH_2F$, $-O-CH_2-CF_3$, $-O-CH_2-CHF-CH_3$, $-O-CHF-CH_3$, $-O-CHF-CH_2F$, or $-O-CH_2-CH_2F$.

[0169] In some embodiments, R^1 is $-O-C_{3-10}$ cycloalkyl optionally substituted with C_{1-6} alkoxy or halogen. In some embodiments, R^1 is $-O$ -cyclopropyl or $-O$ -cyclobutyl, wherein the cyclopropyl or cyclobutyl is optionally substituted with fluorine or methoxy. In some embodiments, R^1 is $-O-C_{3-10}$ cycloalkyl optionally substituted with one or more halogen, e.g., fluorine, $-OCH_3$, or -CN.

[0170] In some embodiments, R^1 is $-O$ -(3- to 8-membered heterocyclyl). In some embodiments, the 3- to 8-membered heterocyclyl comprises one oxygen atom. In some embodiments, the 3- to 8-membered heterocyclyl comprises two oxygen atoms. In some embodiments, the R^1 is $-O-CH_2$ -(1,4-dioxan-2-yl) or $-O-CH_2$ -tetrahydrofuran-2-yl.

[0171] In some embodiments, R^1 is $-O-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$. In some embodiments, R^1 is $-O-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$ optionally substituted with one or

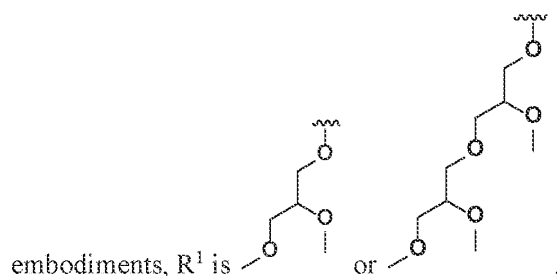




[0174] In some embodiments, R^1 is C_{1-6} haloalkyl. In some embodiments, R^1 is $-\text{CF}_2\text{-CH}_3$.

[0175] In some embodiments, R^1 is $-\text{O}-(3\text{- to } 8\text{-membered heterocycl})$. In some embodiments, R^1 is oxetanyl. In some embodiments, R^1 is oxetan-3-yl.

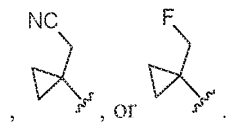
[0176] In some embodiments, R^1 is $-\text{O}-(\text{CH}_2\text{-CH}(\text{OCH}_3)\text{-CH}_2\text{-O})_{1-5}\text{-CH}_3$. In some



[0177] In some embodiments, R^1 is $-\text{NR}^8\text{R}^9$. In some embodiments, R^8 and R^9 combine with the atom to which they are attached to form a 6-membered heterocycl. In some embodiments, R^8 and R^9 combine with the atom to which they are attached to form morpholine. In some embodiments, R^8 and R^9 are hydrogen. In some embodiments, R^1 is NH_2 . In some embodiments, R^1 is NR^8R^9 , wherein R^8 is H and R^9 is C_{1-6} alkyl optionally substituted with oxo.

[0178] In some embodiments, R^2 is C_{3-10} cycloalkyl optionally substituted with one or more $-\text{CN}$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-\text{CN}$. In some embodiments, R^2 is cyclopropyl optionally substituted with one or more $-\text{CN}$, C_{1-6} haloalkyl,

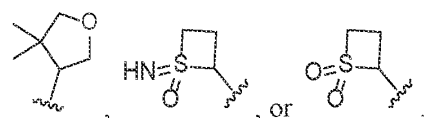
or C₁₋₆ alkyl optionally substituted with one or more -CN. In some embodiments, R² is 



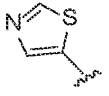
[0179] In some embodiments, R² is 4- or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more oxo, , or C₁₋₆ alkyl. In some embodiments, R² is (i) thietane

optionally substituted with one or more oxo or , (ii) oxetane, or (iii) tetrahydrofuran

optionally substituted with one or more C₁₋₆ alkyl. In some embodiments, R² is ,



[0180] In some embodiments, R² is 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R² is S. In some

embodiments, R² is thiazole. In some embodiments, R² is .

[0181] In some embodiments, R² is H. In some embodiments, R² is -OCH₃.

[0182] In some embodiments, n is 1.

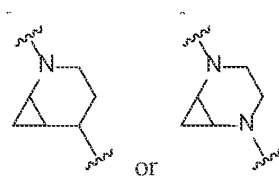
[0183] In some embodiments, X¹ is . In some embodiments, X¹ is . In some

embodiments, X¹ is . In some embodiments, R³ is methyl. In some embodiments, R³ is hydrogen. In some embodiments, R³ and R^{3'} independently are CH₃, CD₃, deuterium, or

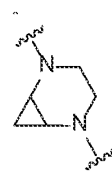
hydrogen. In some embodiments, X¹ is . In some embodiments, X¹ is . In

some embodiments, X¹ is . In some embodiments, X¹ is .

[0184] In some embodiments, Ring A is

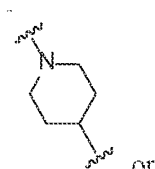


or

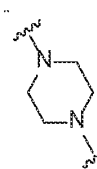


, wherein * indicates

attachment to X^1 . In some embodiments, Ring A is

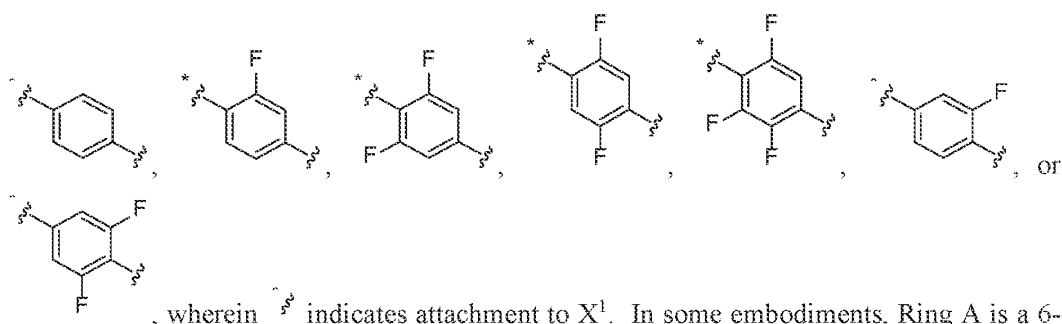


or



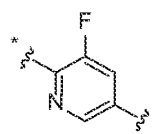
, wherein *

indicates attachment to X^1 . In some embodiments, Ring A is a phenylene ring optionally substituted with one or more halogen or C_{1-6} alkyl. In some embodiments, Ring A is

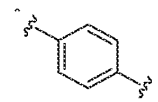


, wherein * indicates attachment to X^1 . In some embodiments, Ring A is a 6-membered heteroarylene ring optionally substituted with one or more halogen. In some

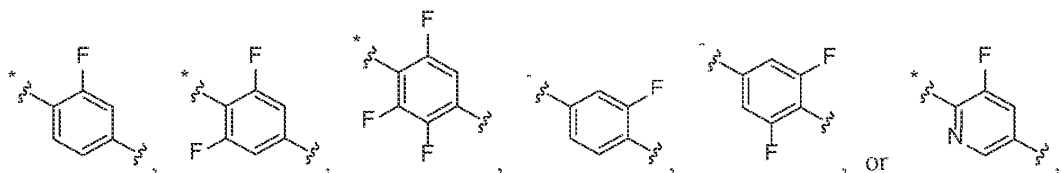
embodiments, Ring A is



. In some embodiments, Ring A is



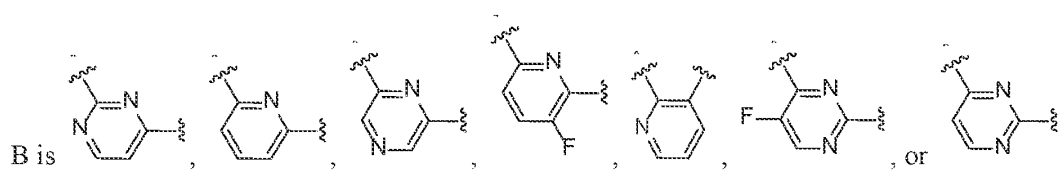
embodiments, Ring A is



wherein * indicates attachment to X^1 .

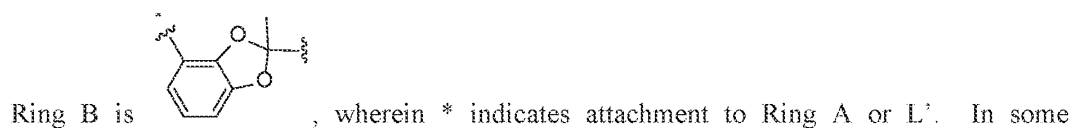
[0185] In some embodiments, Ring B is a 6-membered heteroarylene comprising nitrogen. In some embodiments, Ring B is pyridinylene or pyrimidinylene optionally substituted with one or more halogen. In some embodiments, Ring B is pyridinylene. In some embodiments, Ring

B is , wherein * indicates attachment to Ring A or L^1 . In some embodiments, Ring

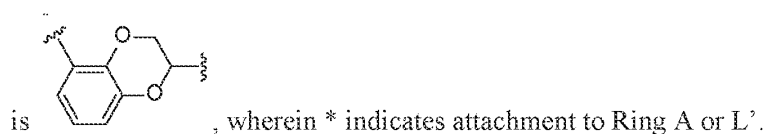


wherein * indicates attachment to Ring A or L'.

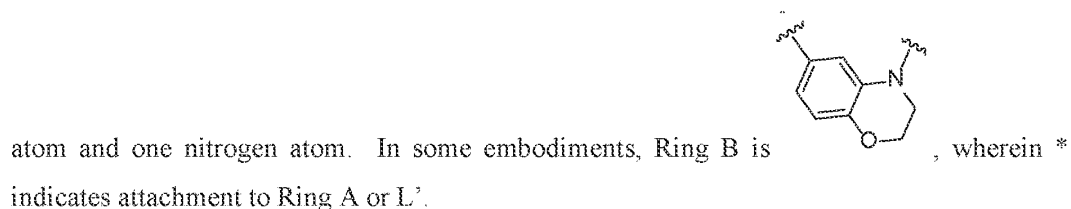
[0186] In some embodiments, Ring B is a 9-membered heterocyclene comprising two oxygen atoms optionally substituted with one or more C₁₋₆ alkyl. In some embodiments, Ring B is benzodioxolene optionally substituted with one or more C₁₋₆ alkyl. In some embodiments,



embodiments, Ring B is a 10-membered heterocyclene comprising two oxygen atoms. In some embodiments, Ring B is benzodioxanylene. In some embodiments, Ring B is

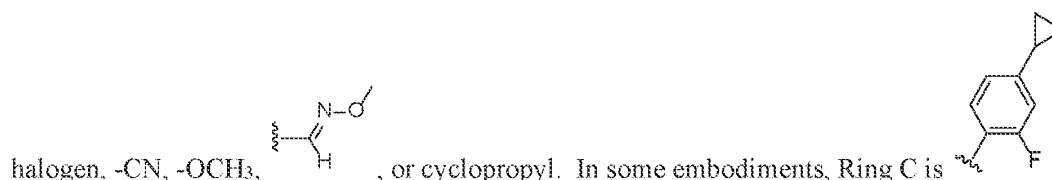


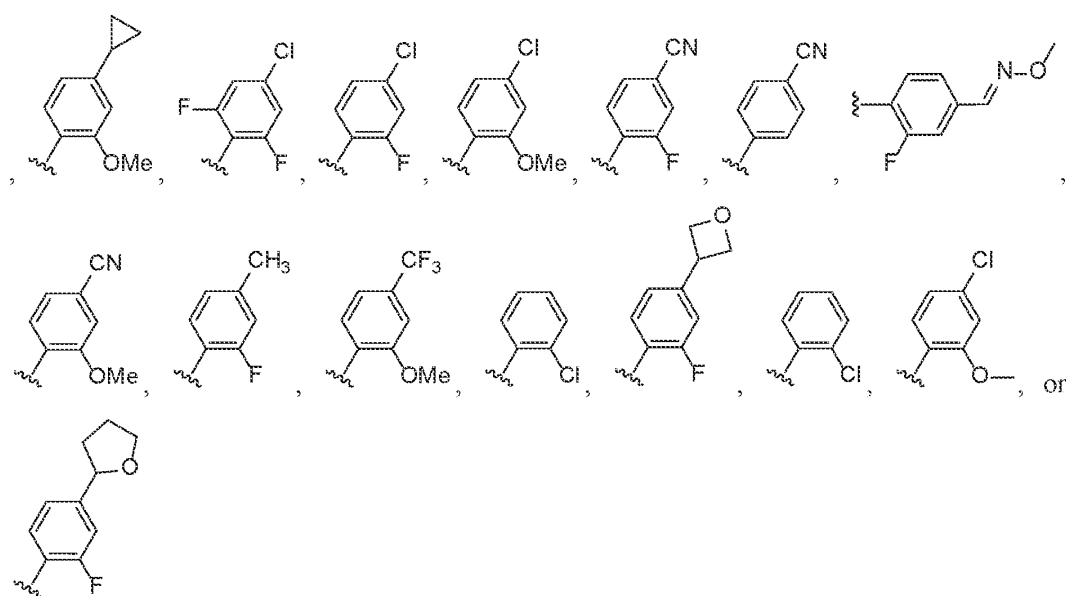
[0187] In some embodiments, Ring B is a 10-membered heterocyclene comprising one oxygen



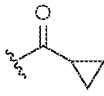
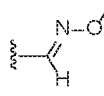
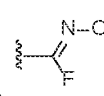
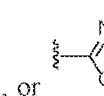
[0188] In some embodiments, L is a bond. In some embodiments, L is *-O-CH₂-, wherein * indicates attachment to Ring B.

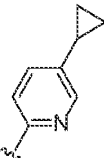
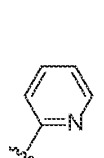
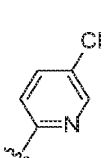
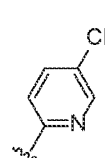
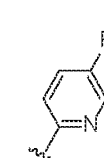
[0189] In some embodiments, Ring C is phenyl optionally substituted with one or more

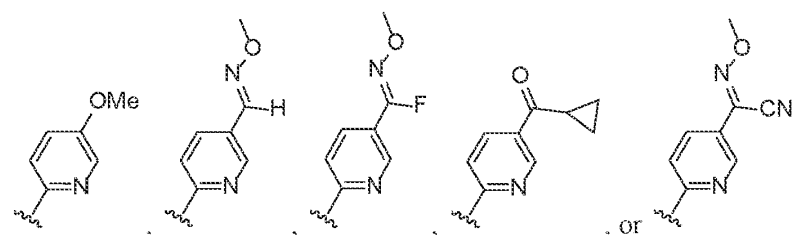




[0190] In some embodiments, Ring C is a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, -CN, -O-C₁₋₆ alkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), or C₃₋₁₀ cycloalkyl. In some embodiments, Ring C is pyridinyl optionally substituted with one

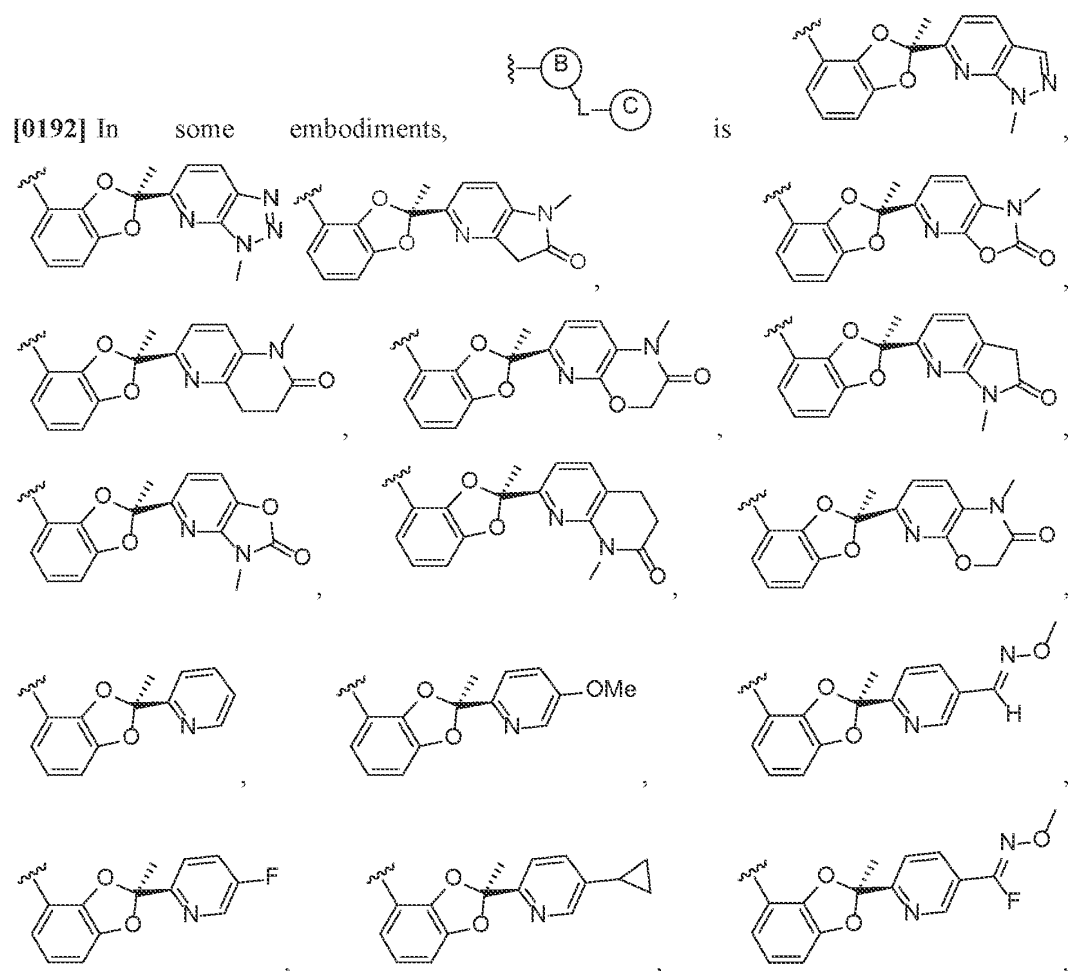
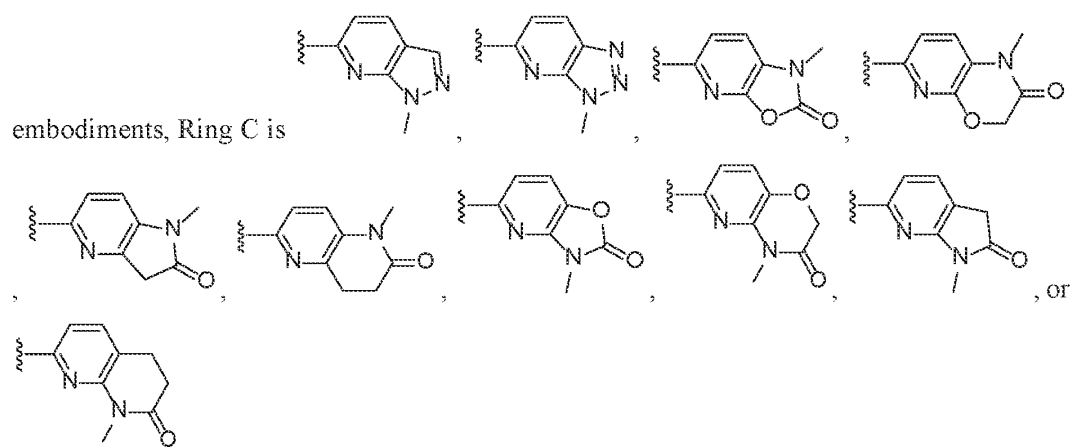
or more -Cl, -F, -CN, -OCH₃, cyclopropyl, , , , or . In

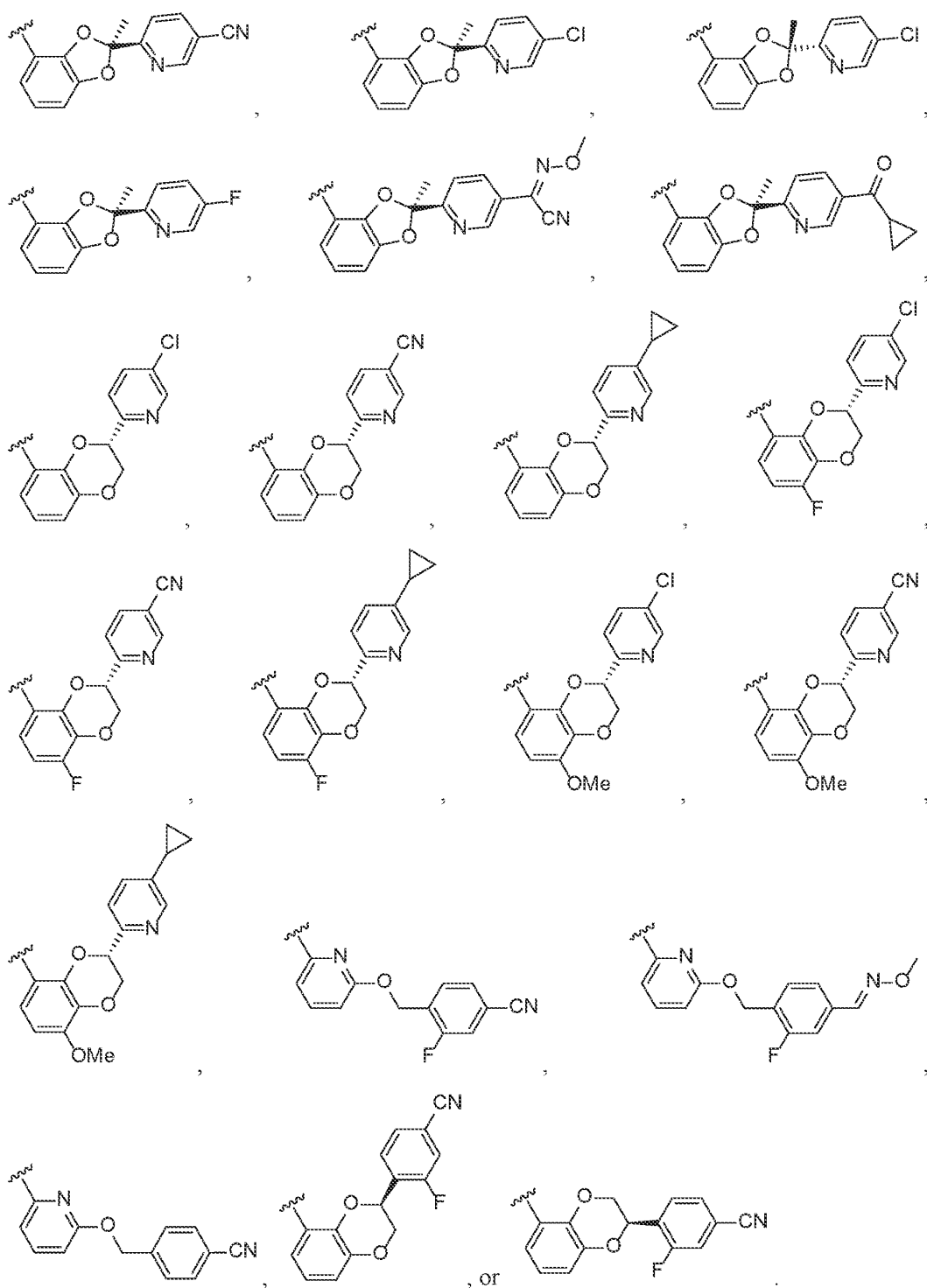
some embodiments, Ring C is , , , , ,



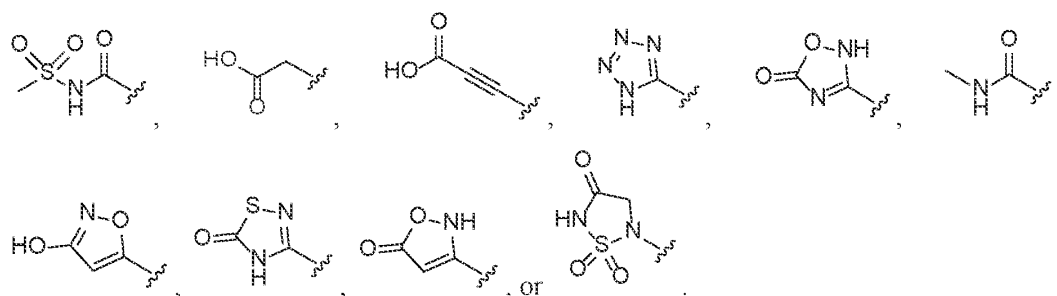
[0191] In some embodiments, Ring C is a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo. In some embodiments, Ring C is pyrazolopyridine, triazolopyridine, 2,3-dihydro-1*H*-pyrrolopyridine, 1,2-dihydrooxazolopyridine, 1,2,3,4-tetrahydronaphthyridine, 2,3-dihydro-pyridooxazine, 2,3-dihydro-1*H*-pyrrolopyridine, or 2,3-dihydrooxazolopyridine, wherein the pyrazolopyridine, triazolopyridine, 2,3-dihydro-1*H*-pyrrolopyridine, 1,2-dihydrooxazolopyridine, 1,2,3,4-

tetrahydronaphththyridine, 2,3-dihydro-pyridooxazine, 2,3-dihydro-1*H*-pyrrolopyridine, or 2,3-dihydrooxazolopyridine is optionally substituted with one or more C₁₋₆ alkyl or oxo. In some





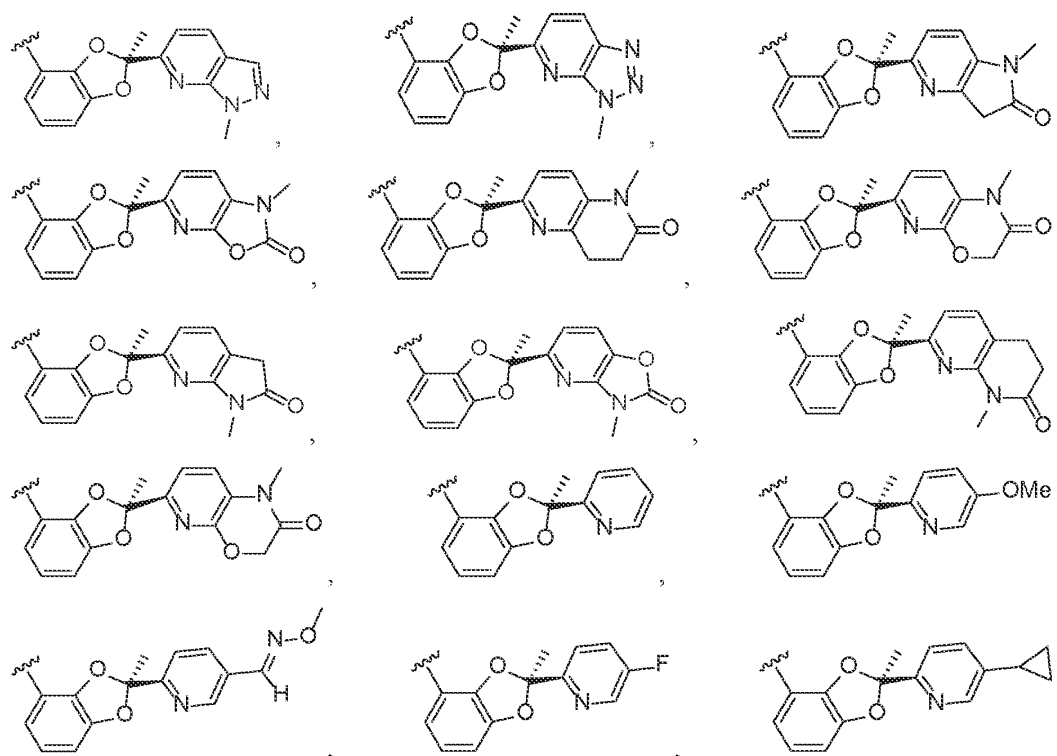
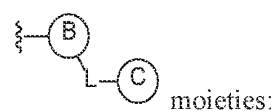
[0193] In some embodiments, R^{12} is $-\text{COOH}$. In some embodiments, R^{12} is $\text{HO}-\text{CH}_2-\text{CH}_2-\text{NH}-$,

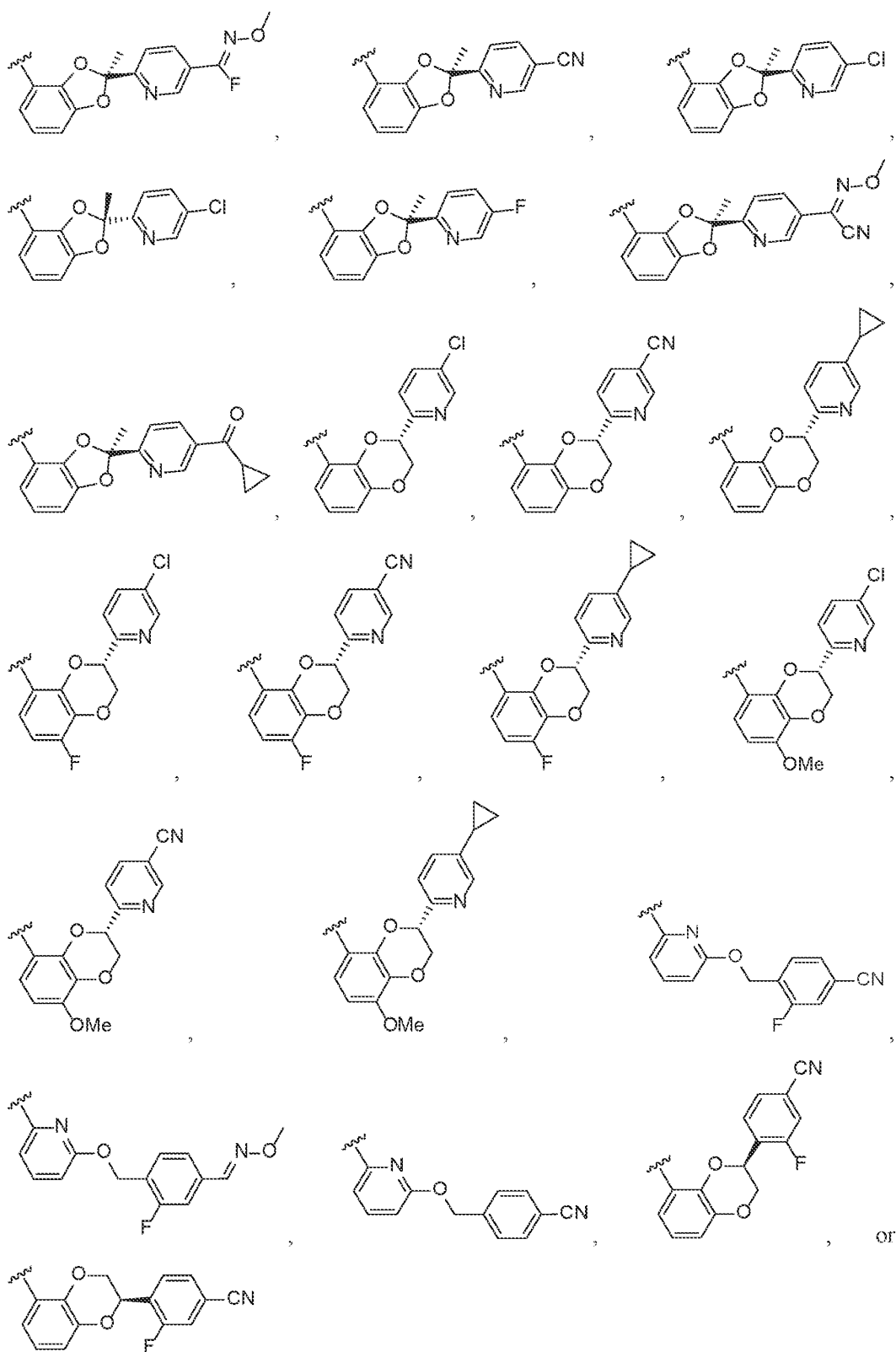


[0194]

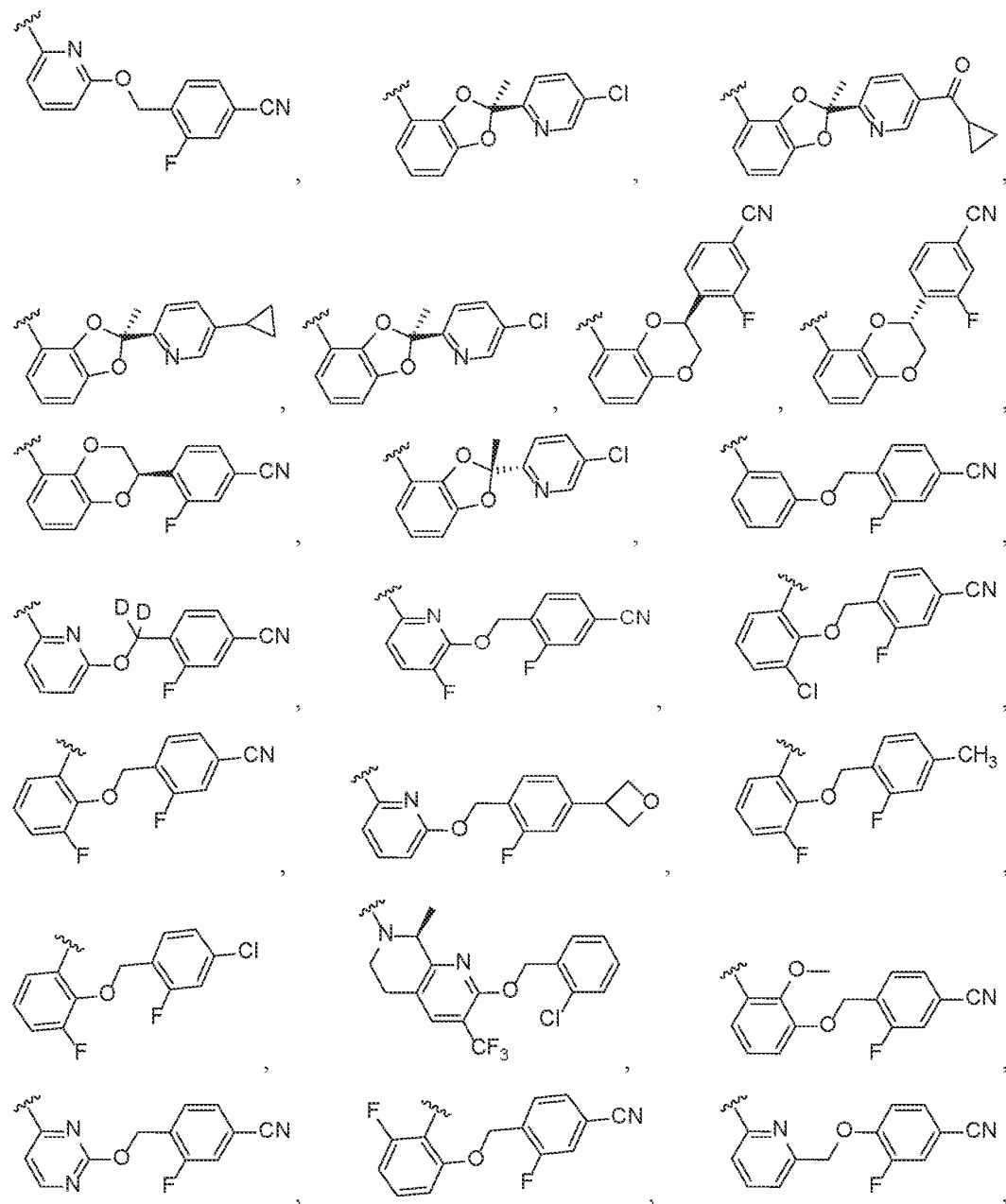
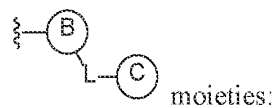
[0195]

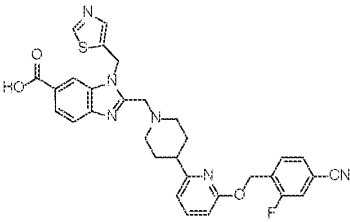
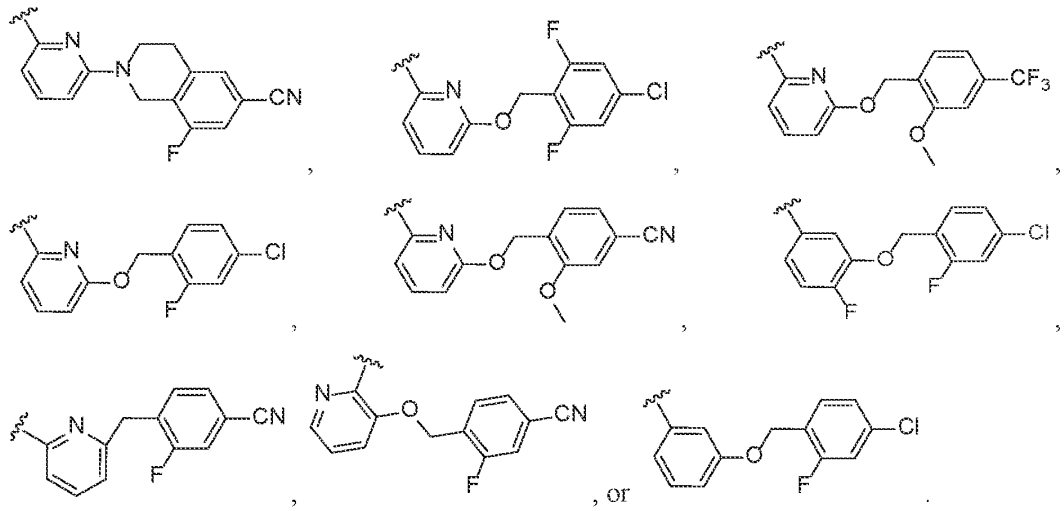
[0196] The present disclosure contemplates the combination of any one of Formula (I-5e), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (I-5q), (I-5r), (I-5s), (I-5t), (I-5u), (I-5v), (I-5w), (I-5x), (I-5y), (I-5z), (I-5aa), (I-5ab), (I-5ac), or (I-5af) with any one of the following





[0197] The present disclosure contemplates the combination of any one of Formula (I-5e), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (I-5q), (I-5r), (I-5s), (I-5t), (I-5u), (I-5v), (I-5w), (I-5x), (I-5y), (I-5z), (I-5aa), (I-5ab), (I-5ac), or (I-5af) with any one of the following



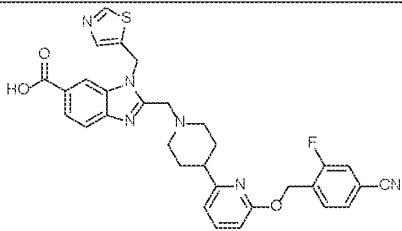
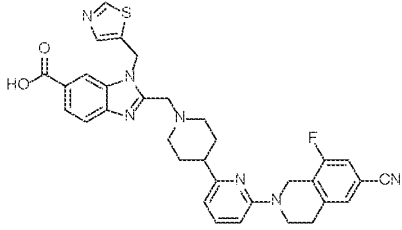
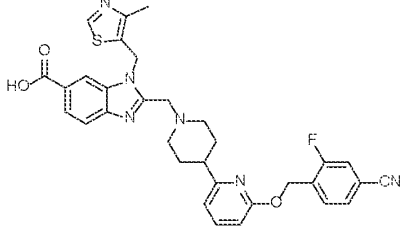
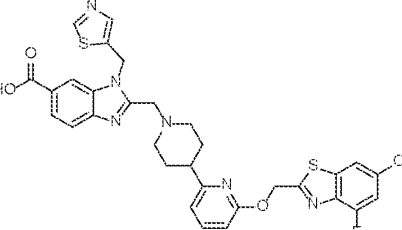
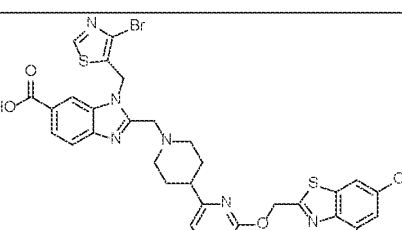
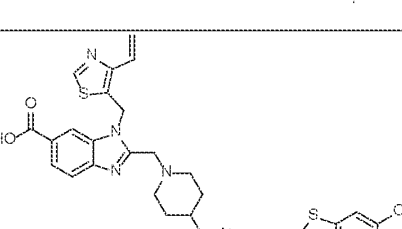


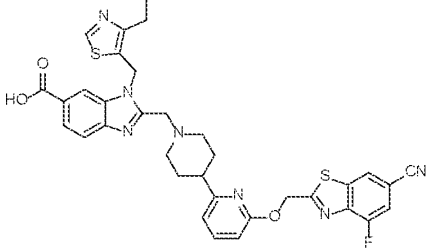
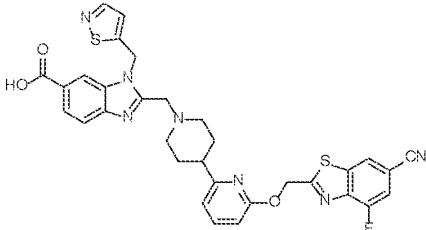
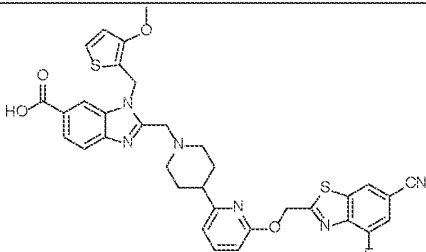
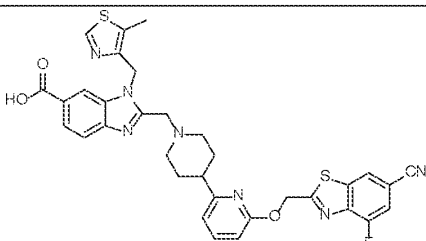
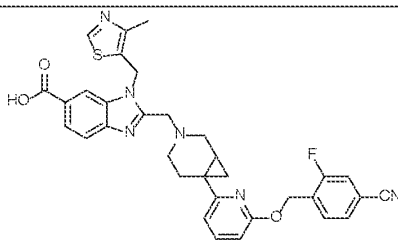
[0198] In some embodiments, the GLP-1R agonist is 2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid, or a pharmaceutically acceptable salt thereof. In some embodiments, the GLP-1R agonist is 2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid meglumine salt.

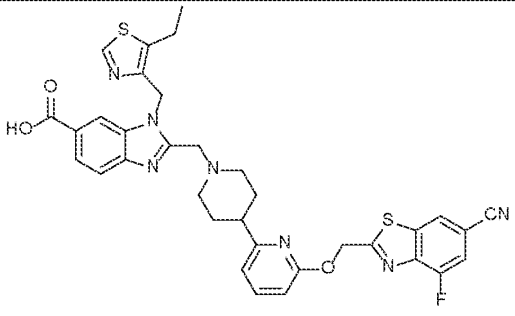
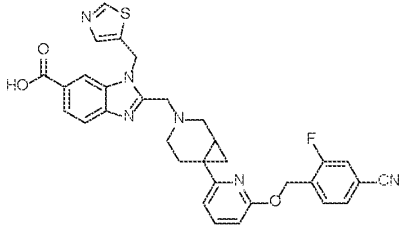
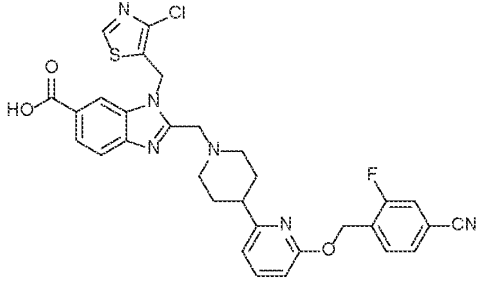
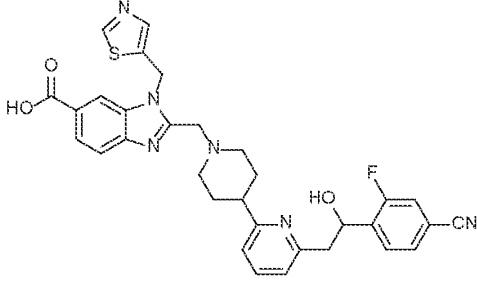
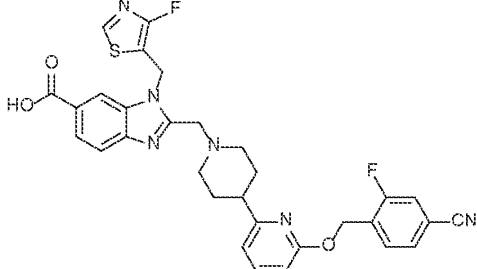
[0199] In some embodiments, the GLP-1R agonist is selected from those listed in Table 1 below, or a pharmaceutically acceptable salt thereof.

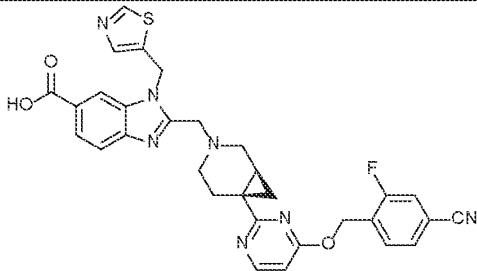
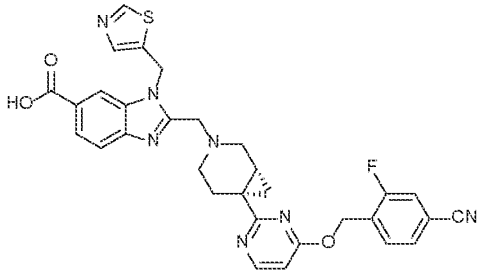
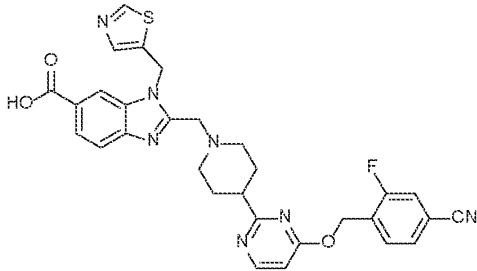
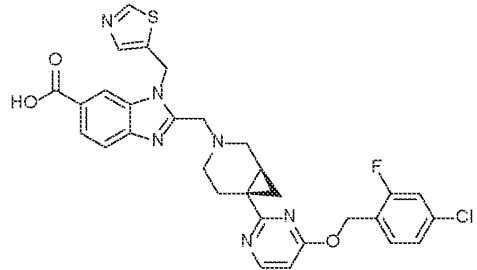
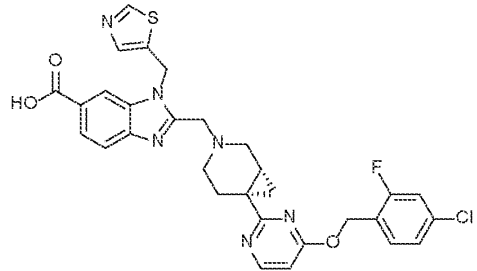
Table 1

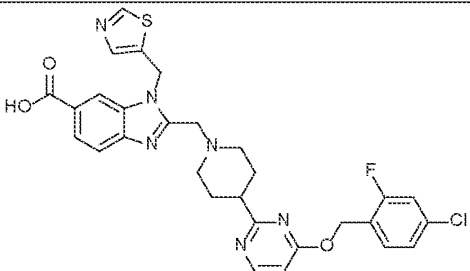
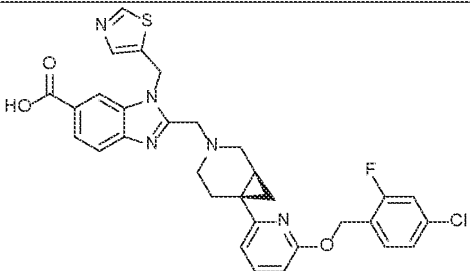
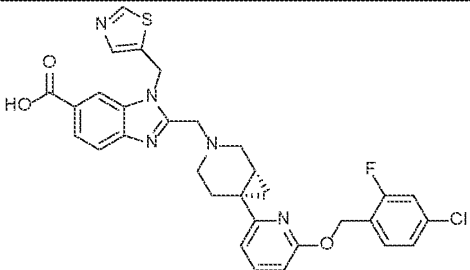
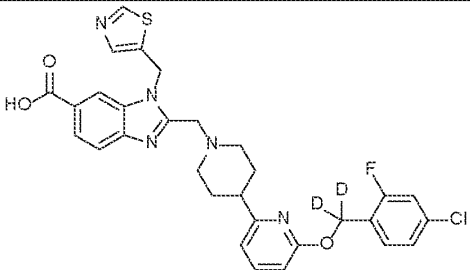
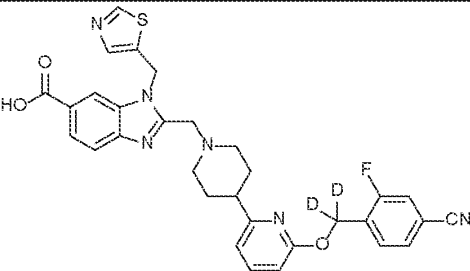
Compound No.	Structure
1-1	

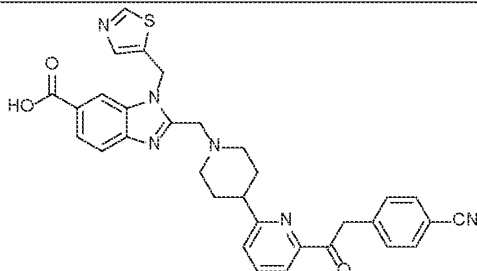
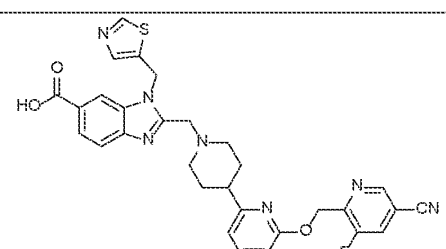
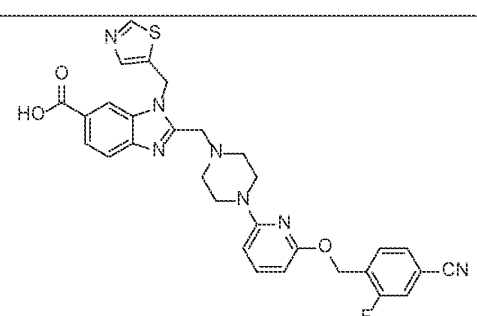
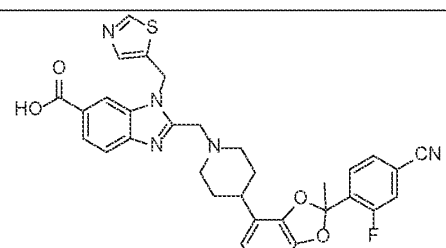
Compound No.	Structure
I-2	
I-3	
I-4	
I-5	
I-6	
I-7	

<i>Compound No.</i>	<i>Structure</i>
<i>1-8</i>	
<i>1-9</i>	
<i>1-10</i>	
<i>1-11</i>	
<i>1-12</i>	

<i>Compound No.</i>	<i>Structure</i>
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<i>1-14</i>	
<i>1-15</i>	
<i>1-16</i>	
<i>1-17</i>	

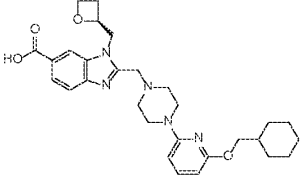
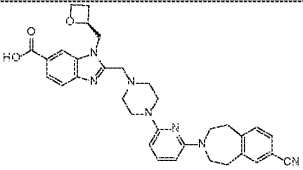
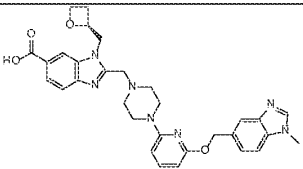
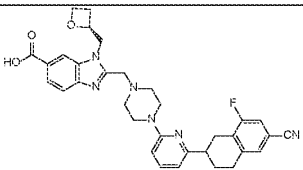
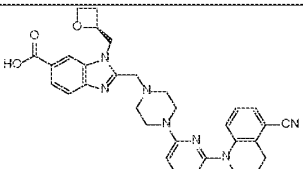
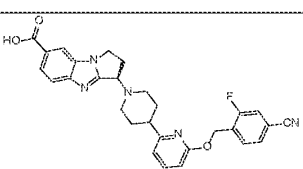
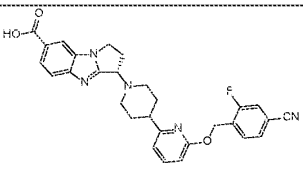
Compound No.	Structure
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<i>1-19</i>	
<i>1-20</i>	
<i>1-21</i>	
<i>1-22</i>	

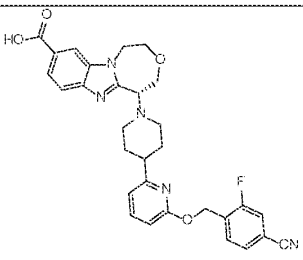
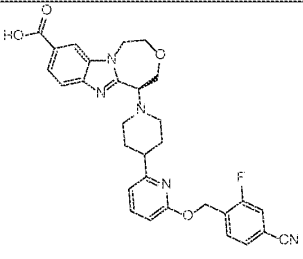
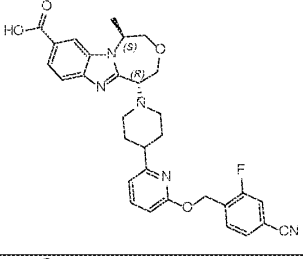
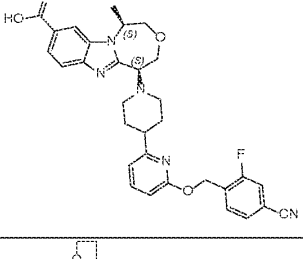
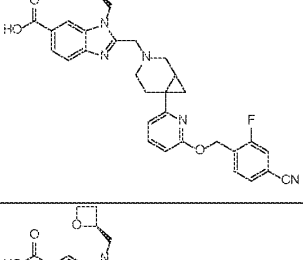
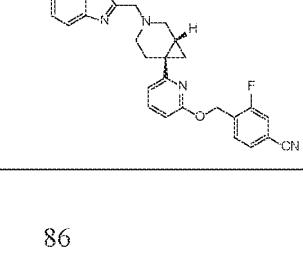
<i>Compound No.</i>	<i>Structure</i>
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<i>1-24</i>	
<i>1-25</i>	
<i>1-26</i>	
<i>1-27</i>	

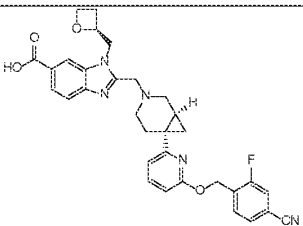
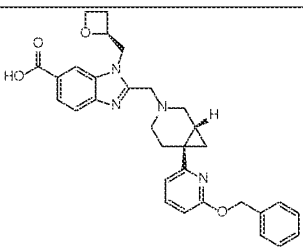
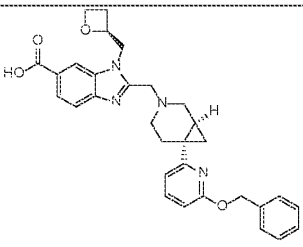
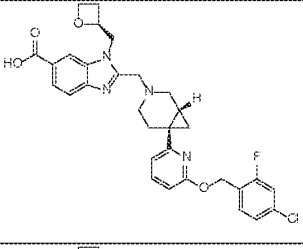
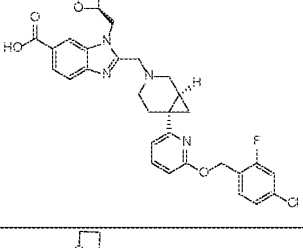
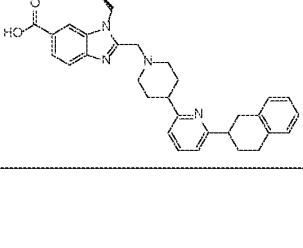
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<i>1-29</i>	
<i>1-30</i>	
<i>1-31</i>	

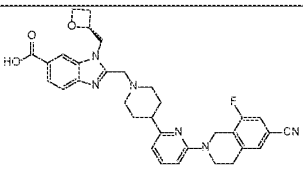
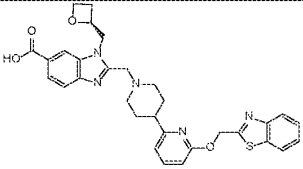
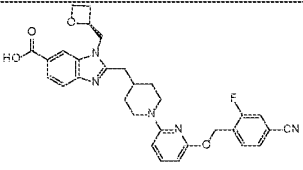
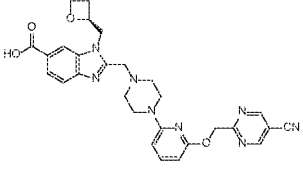
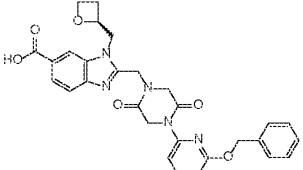
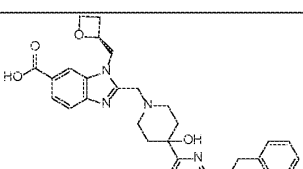
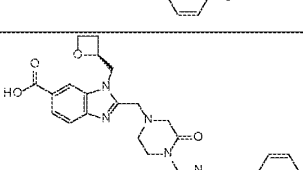
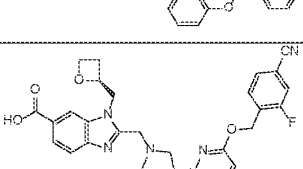
[0200] In some embodiments, the GLP-1R agonist is selected from those listed in Table 2 below, or a pharmaceutically acceptable salt thereof:

Table 2

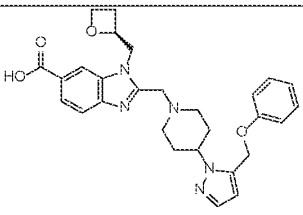
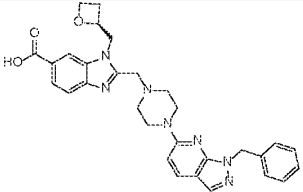
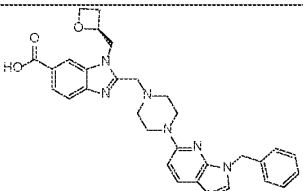
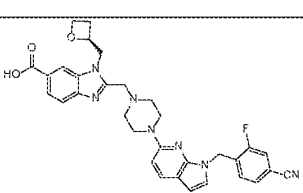
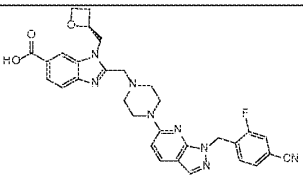
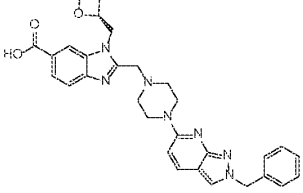
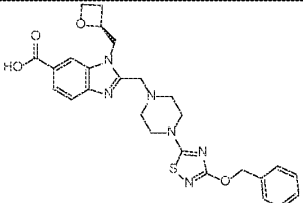
Compound No.	Structure
2-1	
2-2	
2-3	
2-4	
2-5	
2-6-P1	
2-6-P2	

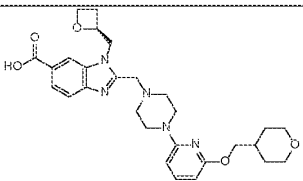
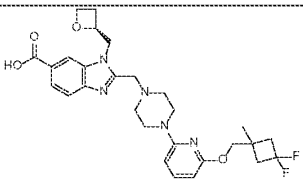
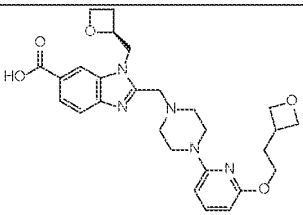
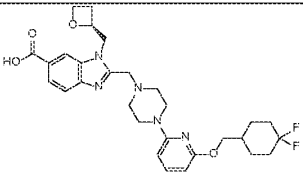
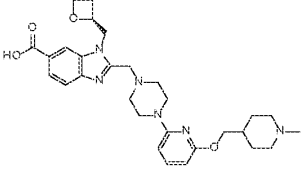
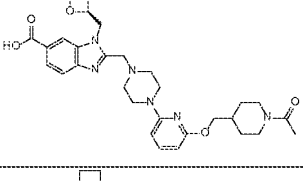
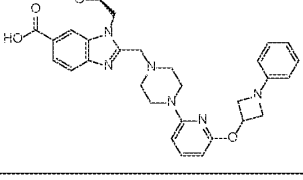
Compound No.	Structure
2-7-P1	
2-7-P2	
2-8-P1	
2-8-P2	
2-9	
2-9-P1	

Compound No.	Structure
2-9-P2	
2-10-P1	
2-10-P2	
2-11-P1	
2-11-P2	
2-12	

Compound No.	Structure
2-13	
2-14	
2-15	
2-16	
2-17	
2-18	
2-19	
2-20-P1	

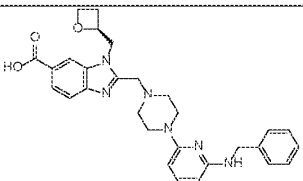
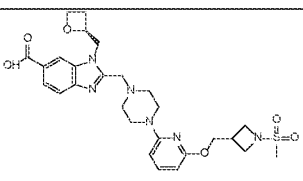
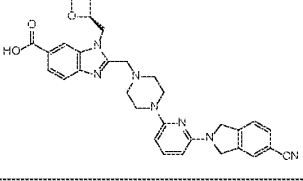
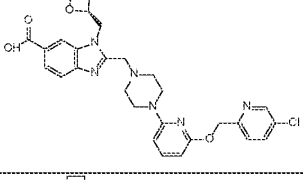
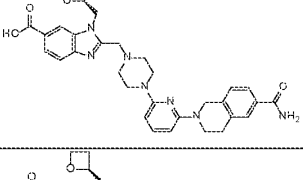
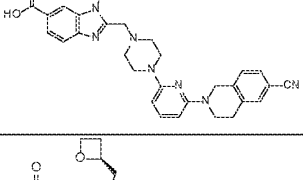
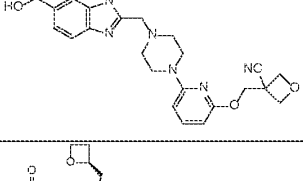
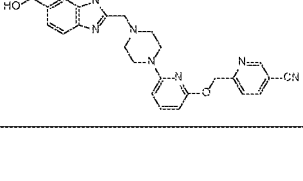
Compound No.	Structure
2-20-P2	
2-21	
2-22	
2-23	
2-24	
2-25	
2-26-P1	

Compound No.	Structure
2-26-P2	
2-27	
2-28	
2-29	
2-30	
2-31	
2-32	

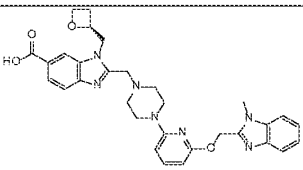
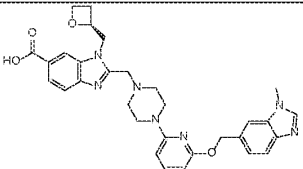
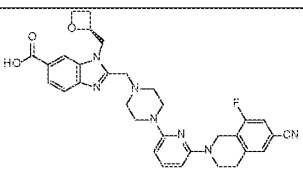
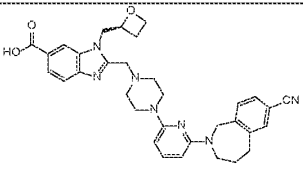
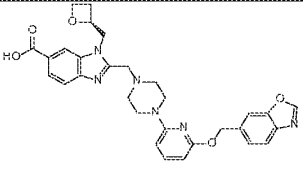
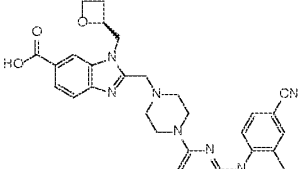
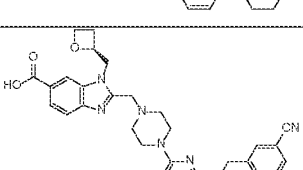
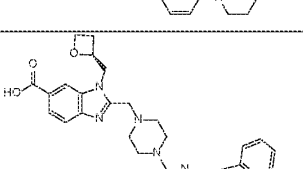
Compound No.	Structure
2-33	
2-34	
2-35	
2-36	
2-37	
2-38	
2-39	

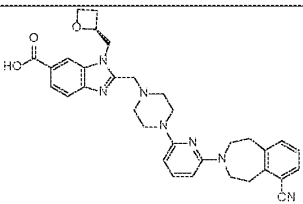
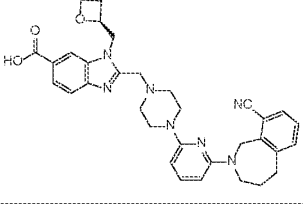
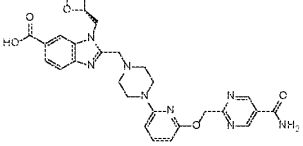
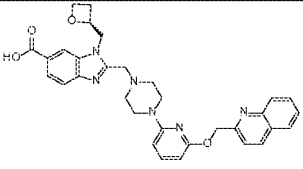
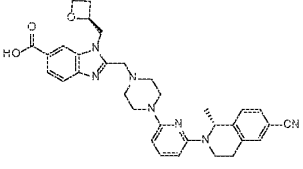
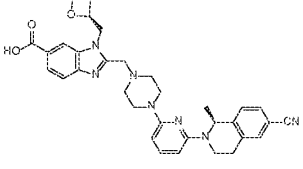
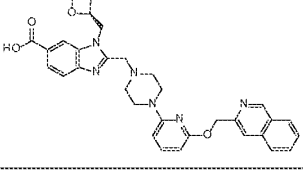
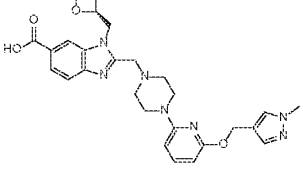
Compound No.	Structure
2-40	
2-41	
2-42	
2-43	
2-44	
2-45	
2-46	

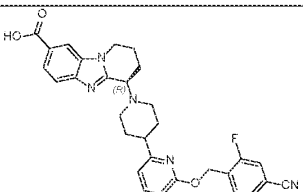
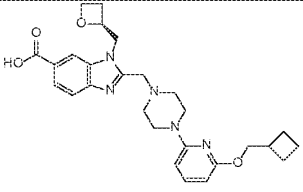
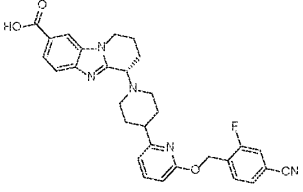
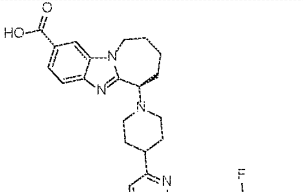
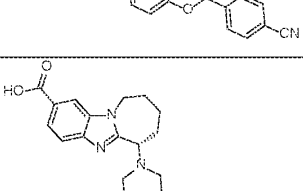
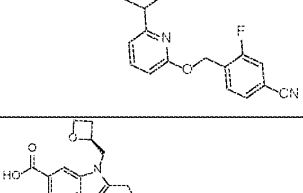
Compound No.	Structure
2-47	
2-48	
2-49	
2-50	
2-51	
2-52	
2-53	
2-54	

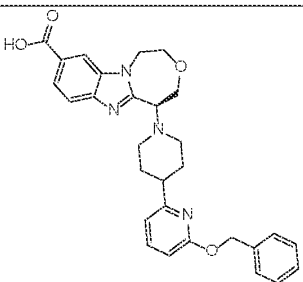
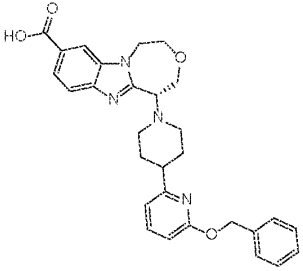
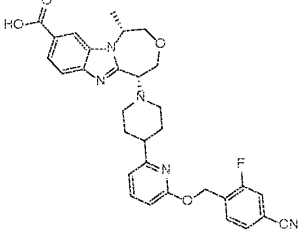
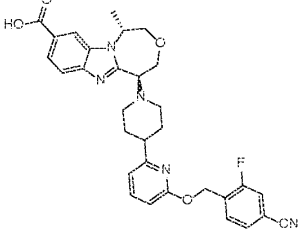
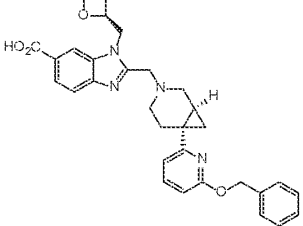
Compound No.	Structure
2-55	
2-56	
2-57	
2-58	
2-59	
2-60	
2-61	
2-62	

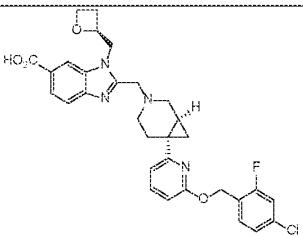
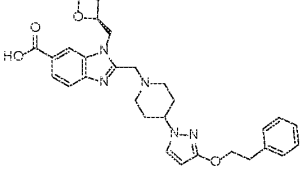
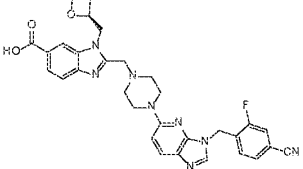
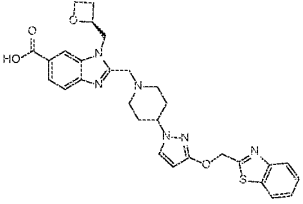
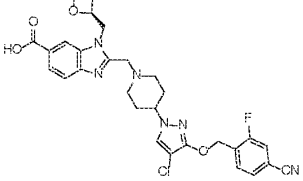
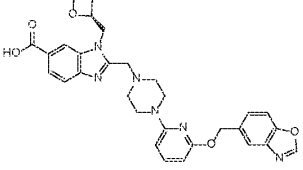
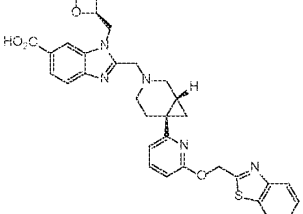
Compound No.	Structure
2-63	<chem>N#Cc1ccc(cc1)CN2CCN(CC2)c3cc4c(cc3)nc(C5COC5)c6ccccc46C(=O)O</chem>
2-64	<chem>Nc1ccc(cc1)CN2CCN(CC2)c3cc4c(cc3)nc(C5COC5)c6ccccc46C(=O)O</chem>
2-65	<chem>c1ccc2c(c1)sc(C3CCN(CC3)c4cc5c(cc4)nc(C6COC6)c7ccccc57C(=O)O)c2</chem>
2-66	<chem>N#Cc1ccc(cc1)CN2CCN(CC2)c3cc4c(cc3)nc(C5COC5)c6ccccc46C(=O)O</chem>
2-67	<chem>c1ccc2c(c1)oc(C3CCN(CC3)c4cc5c(cc4)nc(C6COC6)c7ccccc57C(=O)O)c2</chem>
2-68	<chem>c1ccc2c(c1)oc(C3CCN(CC3)c4cc5c(cc4)nc(C6COC6)c7ccccc57C(=O)O)c2</chem>
2-69	<chem>c1ccc2c(c1)sc(C3CCN(CC3)c4cc5c(cc4)nc(C6COC6)c7ccccc57C(=O)O)c2</chem>
2-70	<chem>c1ccc2c(c1)sc(C3CCN(CC3)c4cc5c(cc4)nc(C6COC6)c7ccccc57C(=O)O)c2</chem>

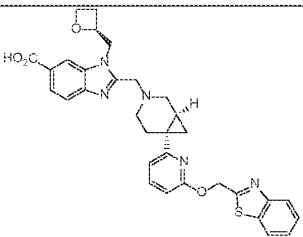
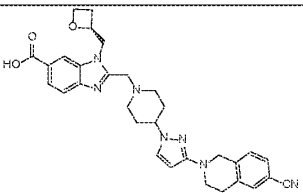
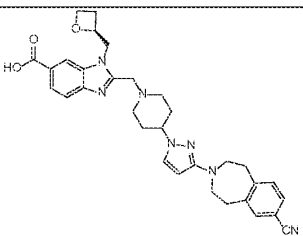
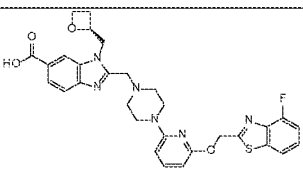
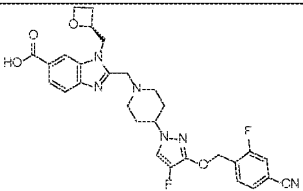
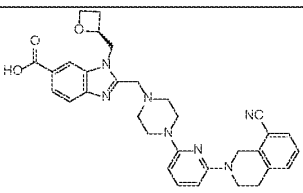
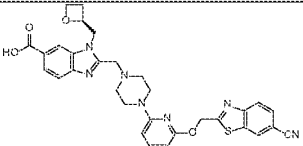
Compound No.	Structure
2-71	
2-72	
2-73	
2-74	
2-75	
2-76	
2-77	
2-78	

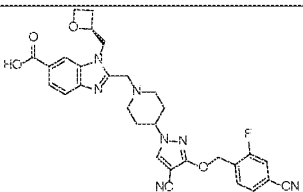
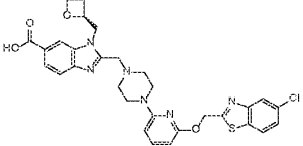
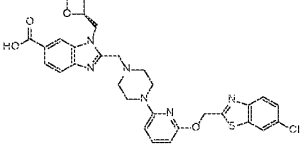
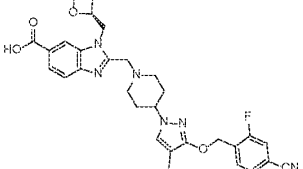
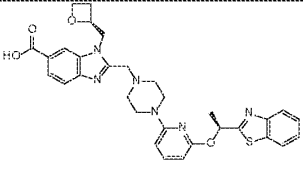
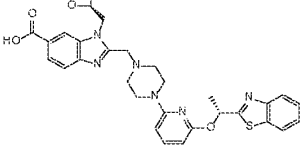
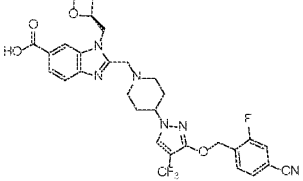
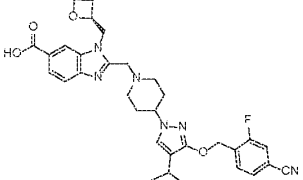
Compound No.	Structure
2-79	
2-80	
2-81	
2-82	
2-83	
2-84	
2-85	
2-86	

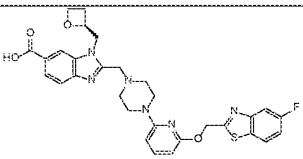
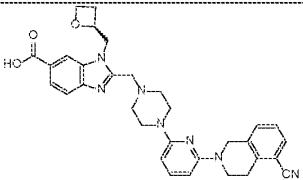
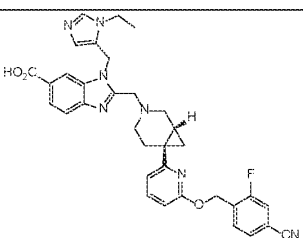
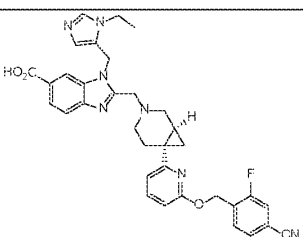
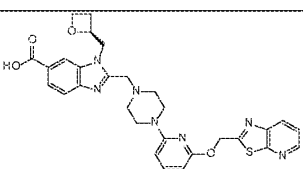
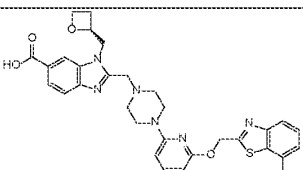
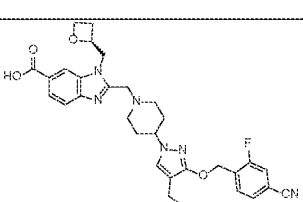
Compound No.	Structure
2-87	
2-88	
2-89	
2-90	
2-91	
2-92	

Compound No.	Structure
2-93	
2-94	
2-95	
2-96	
2-97	

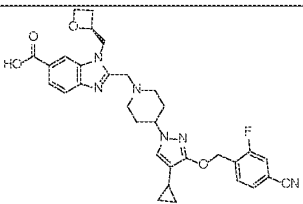
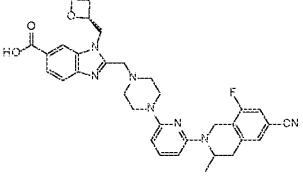
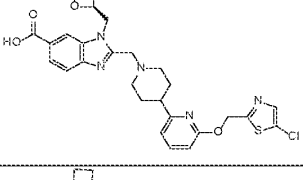
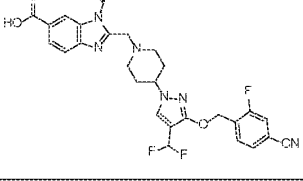
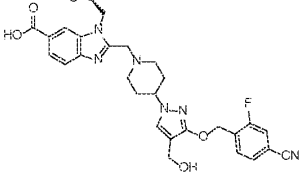
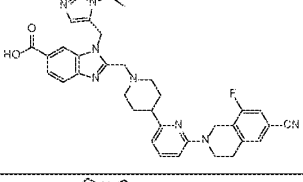
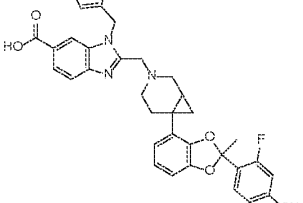
Compound No.	Structure
2-98	
2-99	
2-100	
2-101	
2-102	
2-103	
2-104-P1	

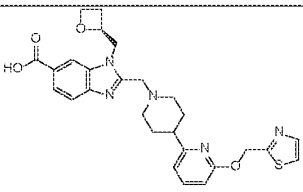
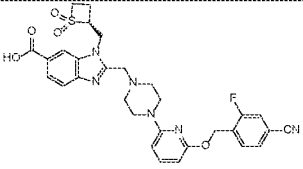
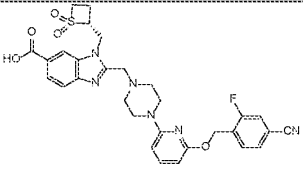
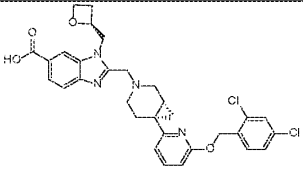
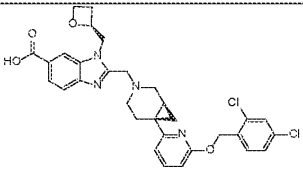
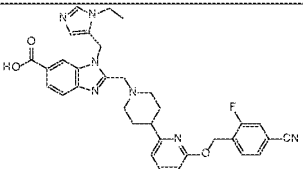
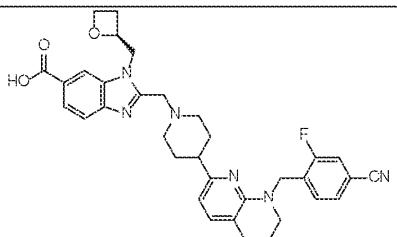
Compound No.	Structure
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2-105	
2-106	
2-107	
2-108	
2-109	
2-110	

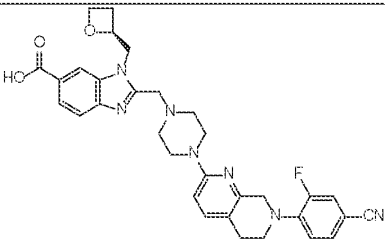
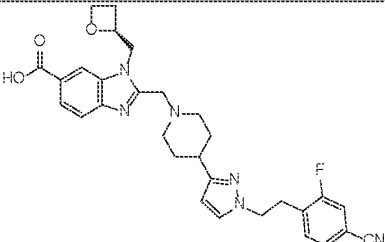
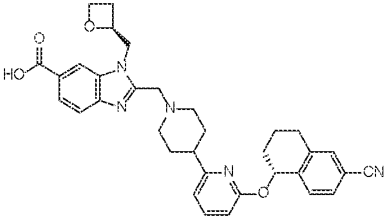
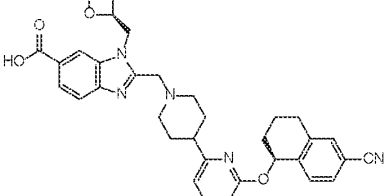
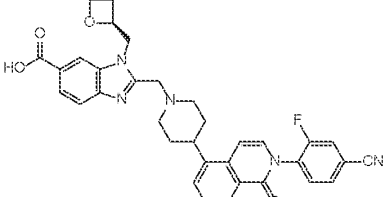
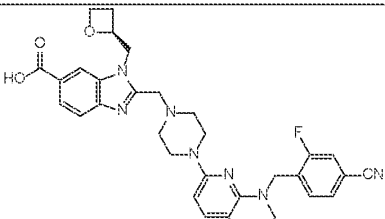
Compound No.	Structure
2-111	
2-112	
2-113	
2-114	
2-115	
2-116	
2-117	
2-118	

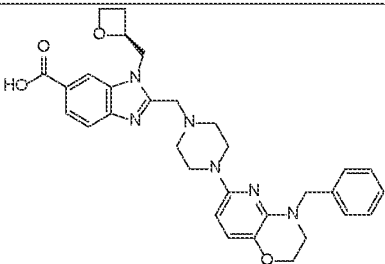
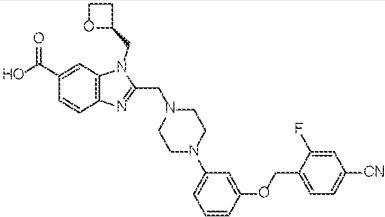
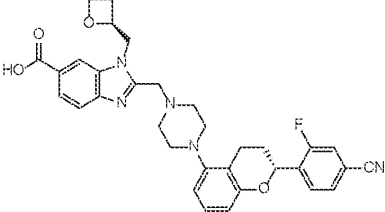
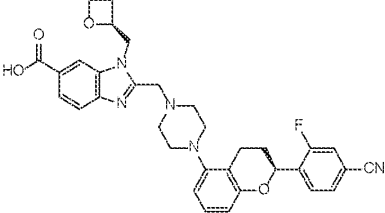
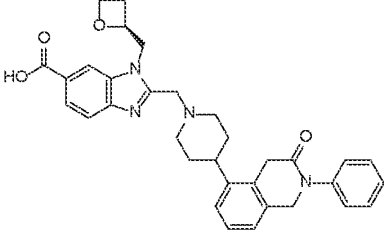
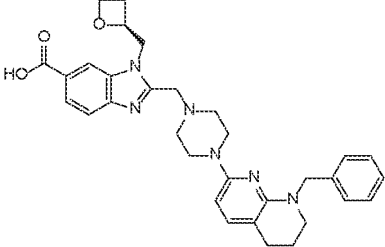
Compound No.	Structure
2-119	
2-120	
2-121-P1	
2-121-P2	
2-122	
2-123	
2-124	

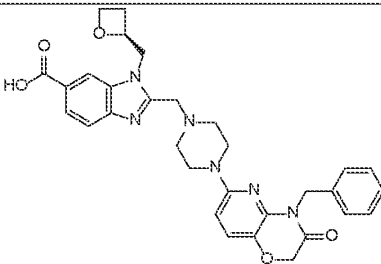
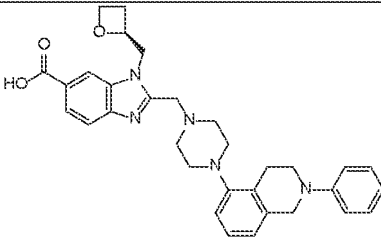
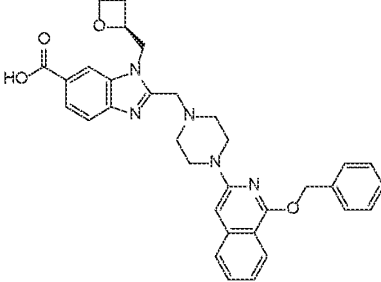
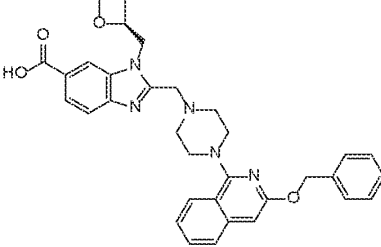
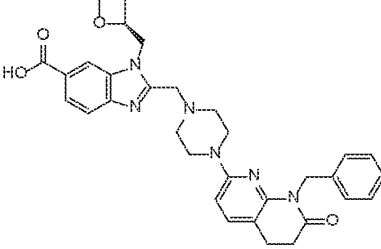
Compound No.	Structure
2-125	
2-126-P1	
2-126-P2	
2-127	
2-128	
2-129	
2-130	
2-131	

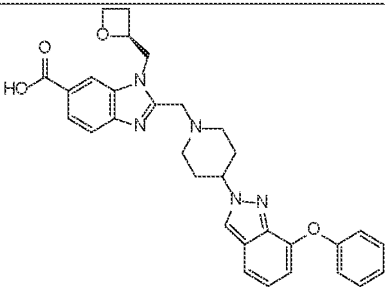
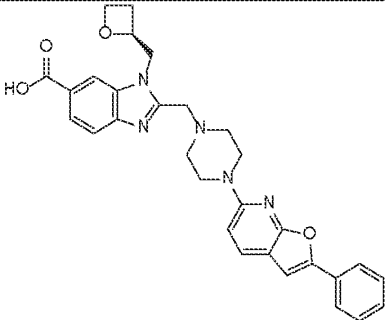
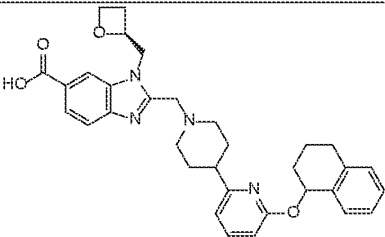
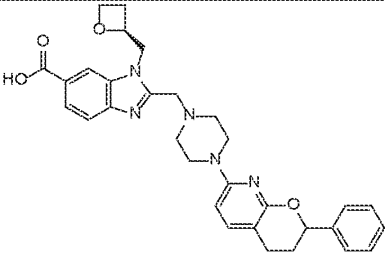
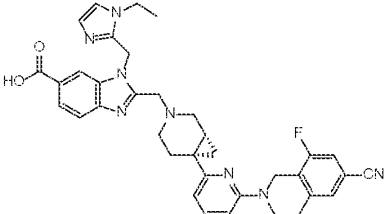
Compound No.	Structure
2-132	
2-133	
2-134	
2-135	
2-136	
2-137	
2-138	

Compound No.	Structure
2-139	
2-140-P1	
2-140-P2	
2-141-P1	
2-141-P2	
2-142	
2-143	

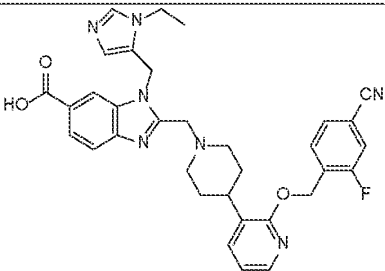
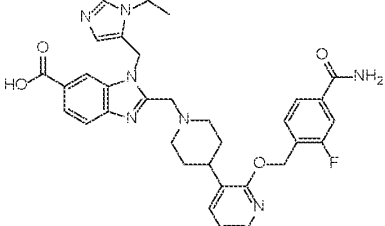
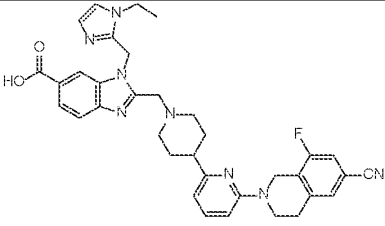
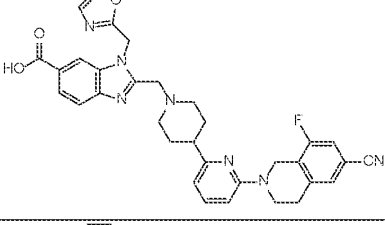
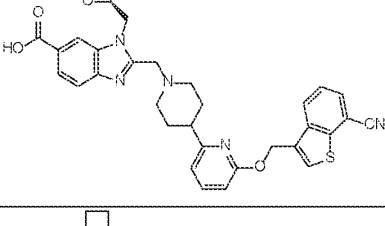
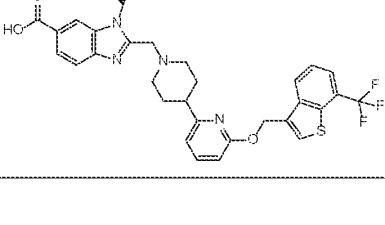
Compound No.	Structure
2-144	
2-145	
2-146-P1	
2-146-P2	
2-147	
2-148	

Compound No.	Structure
2-149	
2-150	
2-151-P1	
2-151-P2	
2-152	
2-153	

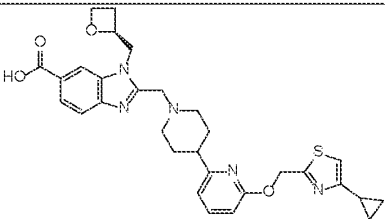
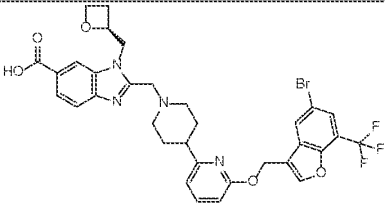
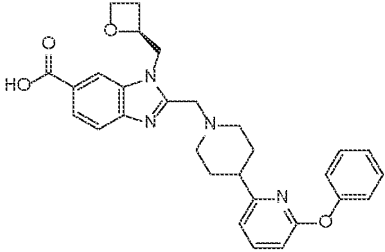
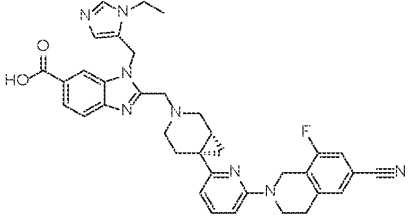
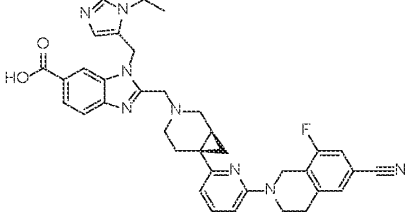
Compound No.	Structure
2-154	
2-155	
2-156	
2-157	
2-158	

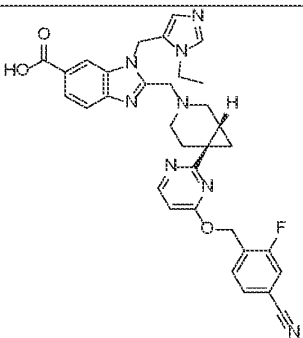
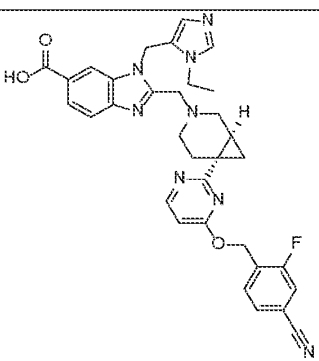
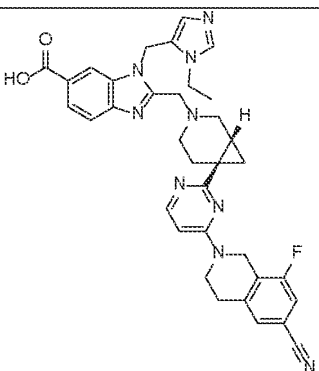
Compound No.	Structure
2-159	
2-160	
2-161	
2-162	
2-163-P1	

Compound No.	Structure
2-163-P2	
2-164	
2-165	
2-166	
2-167	
2-168	

Compound No.	Structure
2-169	
2-170	
2-171	
2-172	
2-173	
2-174	

Compound No.	Structure
2-175	
2-176	
2-177	
2-178	
2-179	
2-180	

Compound No.	Structure
2-181	
2-182	
2-183	
2-184-P1	
2-184-P2	

Compound No.	Structure
2-185-P1	 Chemical structure of 2-185-P1: A complex molecule featuring a central bicyclic system (a benzimidazole derivative) substituted with a carboxylic acid group (HO-C=O) and a fluorophenyl group (F-C₆H₄-CN). The structure includes a piperidine ring and a pyridine ring, with a fluorophenyl group (F-C₆H₄-CN) attached via an ether linkage.
2-185-P2	 Chemical structure of 2-185-P2: A complex molecule featuring a central bicyclic system (a benzimidazole derivative) substituted with a carboxylic acid group (HO-C=O) and a fluorophenyl group (F-C₆H₄-CN). The structure includes a piperidine ring and a pyridine ring, with a fluorophenyl group (F-C₆H₄-CN) attached via an ether linkage.
2-186-P1	 Chemical structure of 2-186-P1: A complex molecule featuring a central bicyclic system (a benzimidazole derivative) substituted with a carboxylic acid group (HO-C=O) and a fluorophenyl group (F-C₆H₄-CN). The structure includes a piperidine ring and a pyridine ring, with a fluorophenyl group (F-C₆H₄-CN) attached via an ether linkage.

Compound No.	Structure
2-186-P2	
2-187	

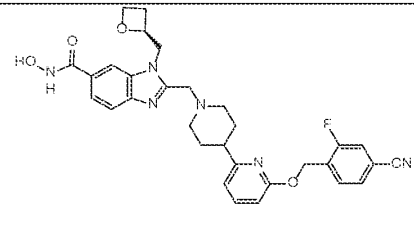
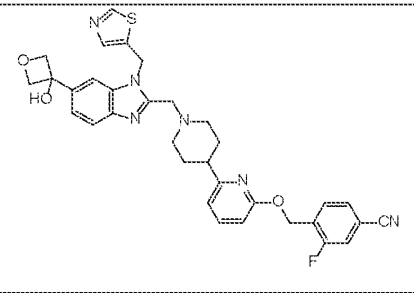
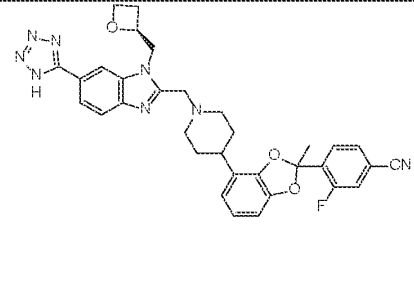
[0201] In some embodiments, the GLP-1R agonist is selected from those listed in Table 3 below, or a pharmaceutically acceptable salt thereof:

Table 3

Compound No.	Structure	Name
3-1		2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)-N-methyl-1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxamide

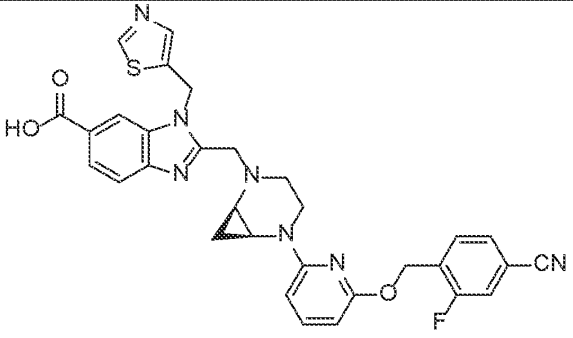
3-2		2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)-1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxamide
3-3		2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)-1-(oxazol-2-ylmethyl)-N-(2,2,2-trifluoroethyl)-1H-benzo[d]imidazole-6-carboxamide
3-4		2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)-N-(dioxo[5-sulfaneyl]-1-(oxazol-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxamide
3-5		(S)-3-fluoro-4-(((6-(1-((1-(oxetan-2-ylmethyl)-6-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)benzonitrile
3-6		(S)-5-(2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazol-6-yl)isoxazol-3(2H)-one
3-7		(S)-3-(2-((4-(6-((4-bromo-2-fluorobenzyl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazol-6-yl)-1,2,4-oxadiazol-5(2H)-one

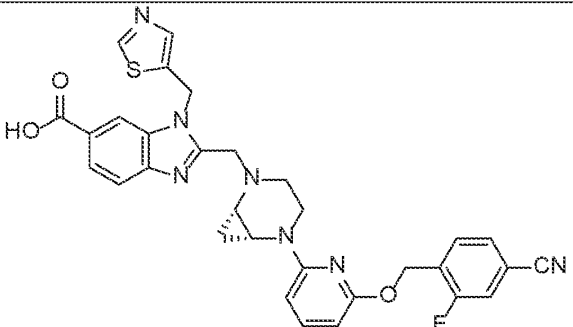
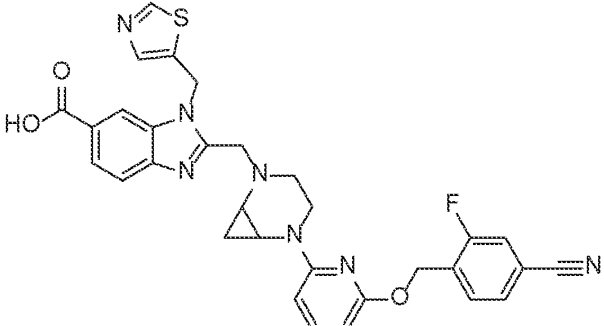
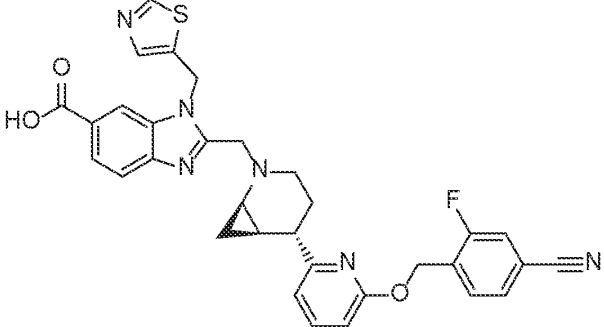
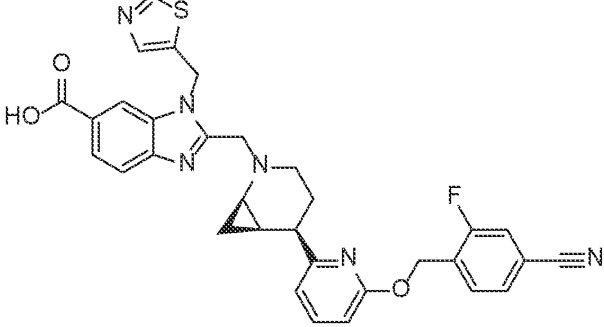
3-8		(S)-3-fluoro-4-(((6-(1-((1-(oxetan-2-ylmethyl)-6-(1H-tetrazol-5-yl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)benzonitrile
3-9		4-(((6-(1-((6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile
3-10		4-(((6-(3-((6-(1H-tetrazol-5-yl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile
3-11		4-(((6-(1-((6-(1H-tetrazol-5-yl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile
3-12		3-fluoro-4-(((6-(1-((6-(2-oxo-2,3-dihydrooxazol-5-yl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)benzonitrile
3-13		3-fluoro-4-(((6-(1-((6-(3-oxo-2,3-dihydro-1,2,4-oxadiazol-5-yl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)benzonitrile

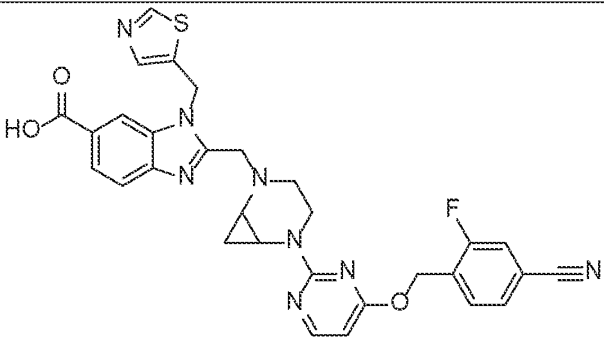
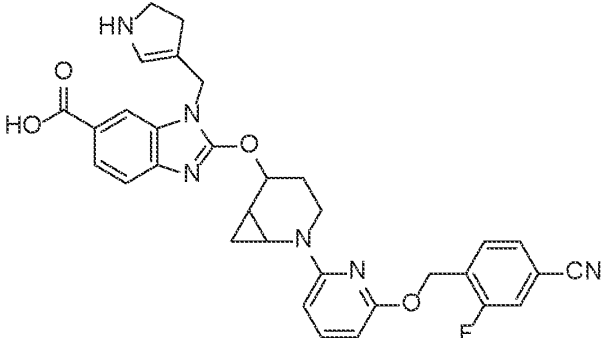
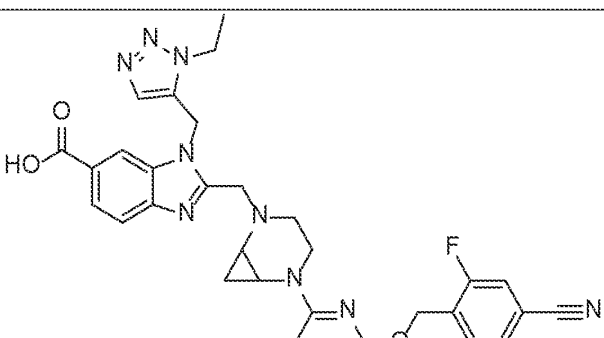
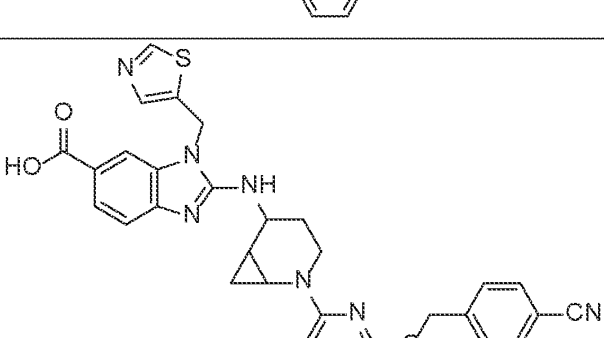
3-14		(S)-2-((4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-N-hydroxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxamide
3-15		3-fluoro-4-(((6-(1-((6-(3-hydroxyoxetan-3-yl)-1-(thiazol-5-ylmethyl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)benzonitrile
3-16		3-fluoro-4-(2-methyl-4-(1-(((1-(((S)-oxetan-2-yl)methyl)-6-(1H-tetrazol-5-yl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)benzo[d][1,3]dioxol-2-yl)benzonitrile

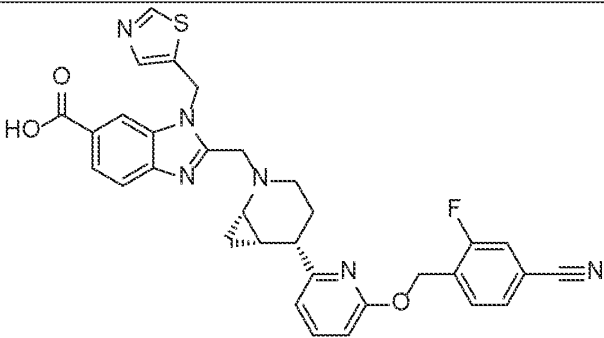
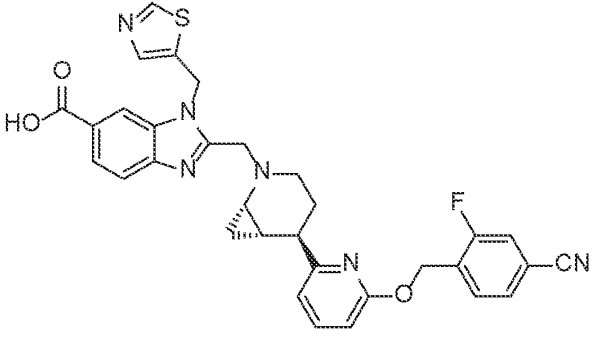
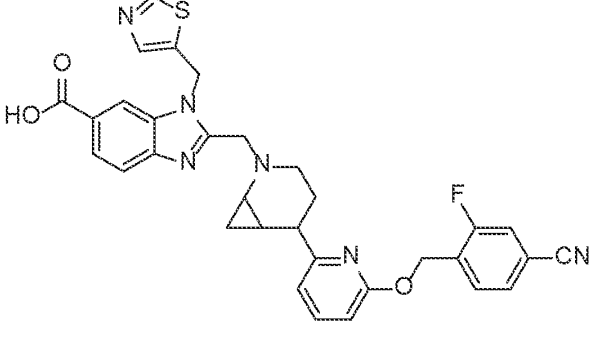
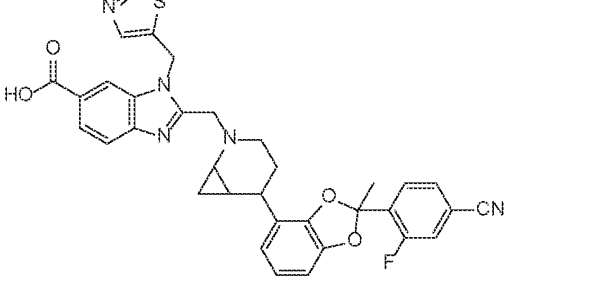
[0202] In some embodiments, the GLP-1R agonist is selected from those listed in Table 4 below, or a pharmaceutically acceptable salt thereof:

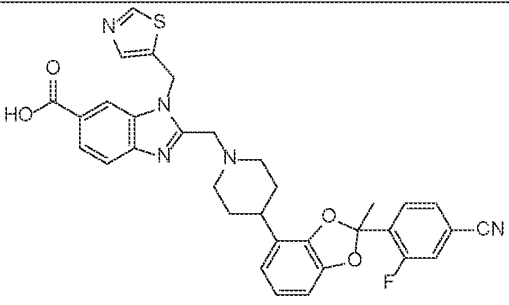
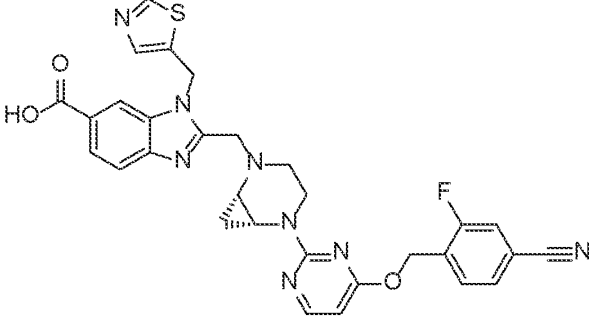
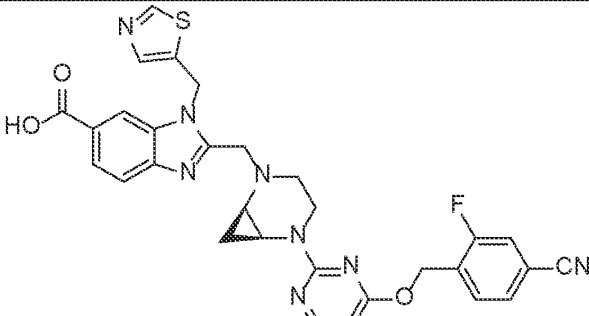
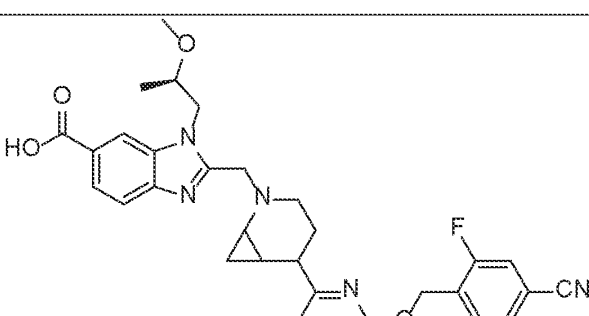
Table 4

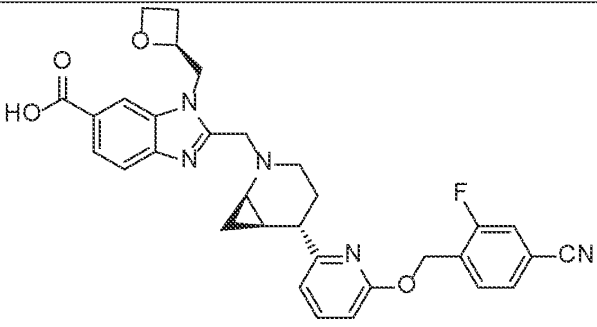
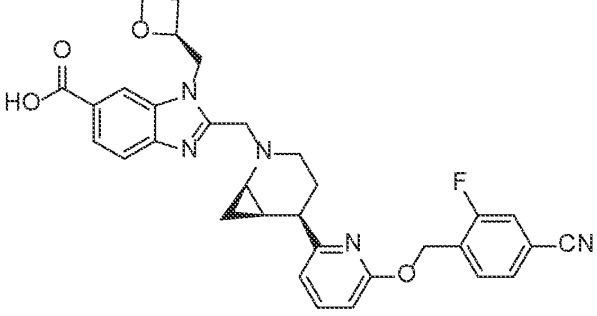
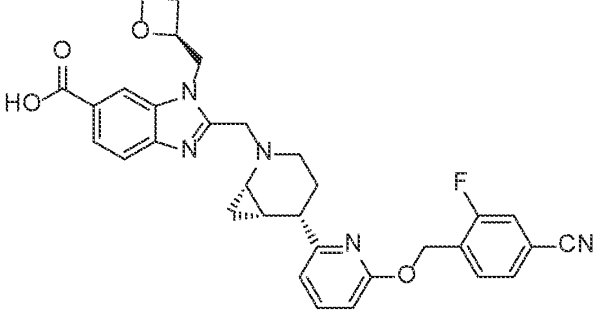
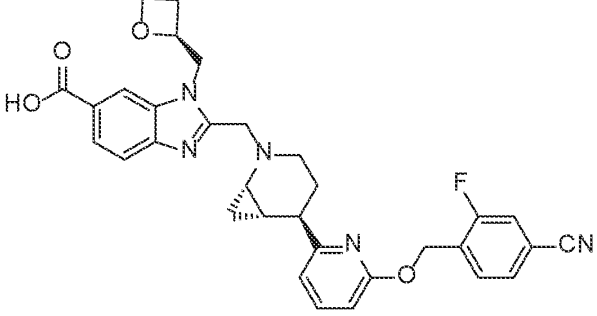
Compound No.	Structure
4-1	

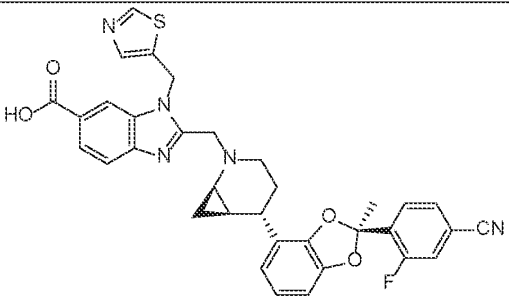
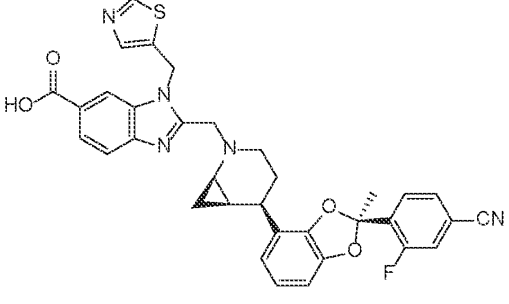
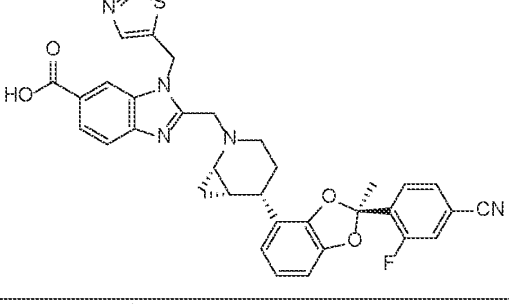
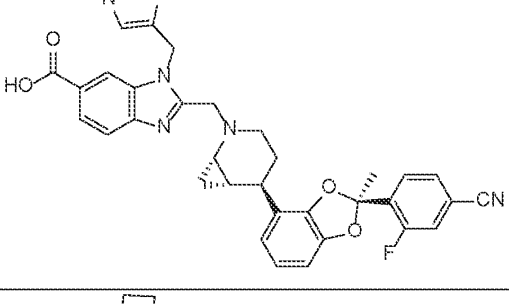
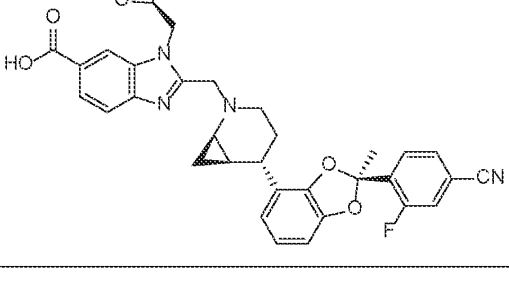
Compound No.	Structure
4-2	
4-3	
4-4	
4-5	

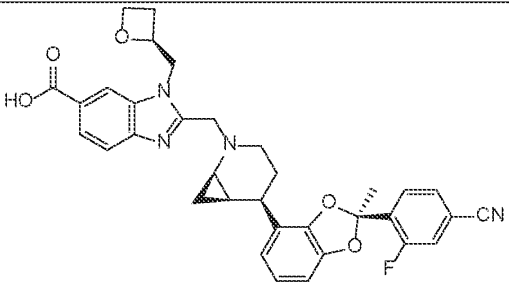
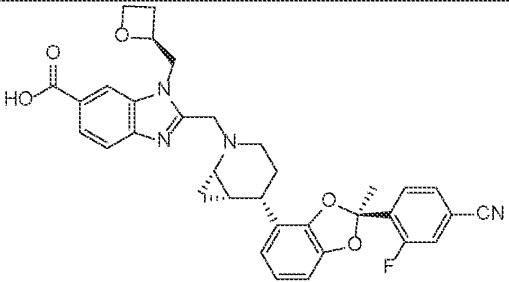
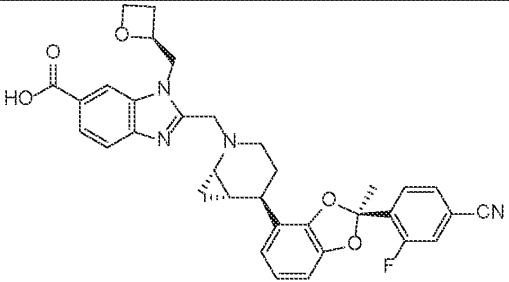
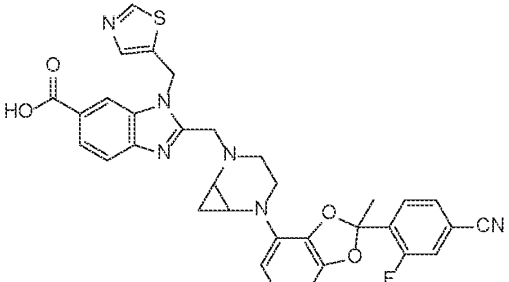
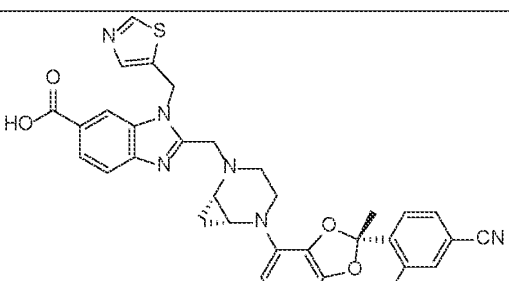
Compound No.	Structure
4-6	
4-7	
4-8	
4-9	

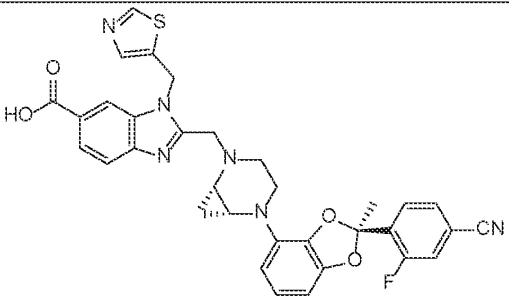
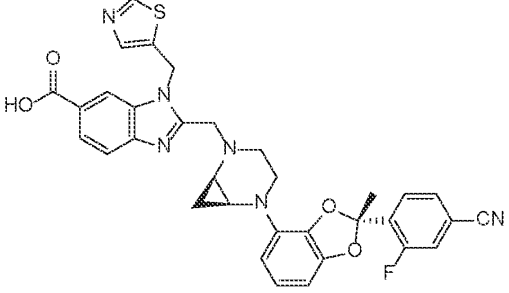
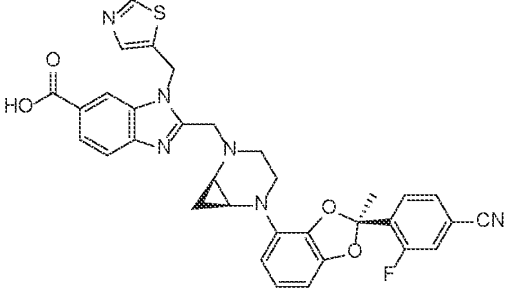
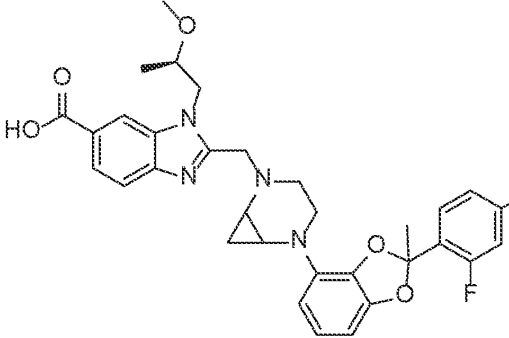
Compound No.	Structure
4-14	
4-15	
4-16	
4-17	

Compound No.	Structure
4-18	
4-19	
4-20	
4-21	

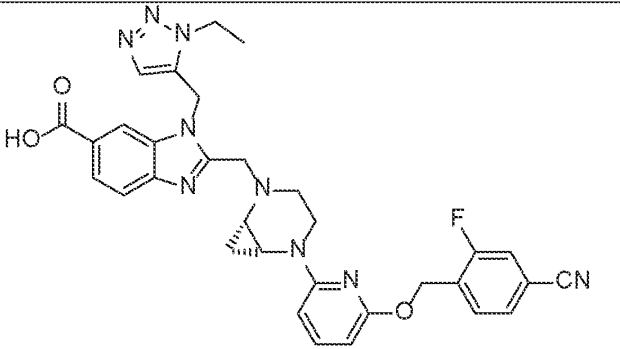
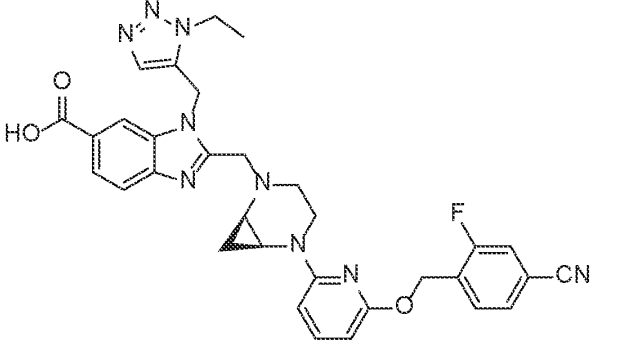
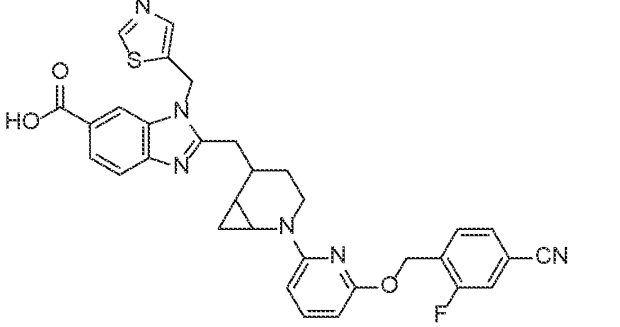
Compound No.	Structure
4-22	 Chemical structure of compound 4-22: A 1H-indazole-3-carboxylic acid derivative. The indazole ring has a carboxylic acid group at position 3 and a 4-oxaspiro[3.3]hept-2-ylmethyl group at position 2. The nitrogen at position 1 of the indazole is connected via a methylene group to a piperidine ring. The piperidine ring is substituted with a 2-(4-cyano-3-fluorophenoxy)pyridin-3-yl group at the 4-position and a 4-oxaspiro[3.3]hept-2-yl group at the 3-position.
4-23	 Chemical structure of compound 4-23: A 1H-indazole-3-carboxylic acid derivative. The indazole ring has a carboxylic acid group at position 3 and a 4-oxaspiro[3.3]hept-2-ylmethyl group at position 2. The nitrogen at position 1 of the indazole is connected via a methylene group to a piperidine ring. The piperidine ring is substituted with a 2-(4-cyano-3-fluorophenoxy)pyridin-3-yl group at the 4-position and a 4-oxaspiro[3.3]hept-2-yl group at the 3-position.
4-24	 Chemical structure of compound 4-24: A 1H-indazole-3-carboxylic acid derivative. The indazole ring has a carboxylic acid group at position 3 and a 4-oxaspiro[3.3]hept-2-ylmethyl group at position 2. The nitrogen at position 1 of the indazole is connected via a methylene group to a piperidine ring. The piperidine ring is substituted with a 2-(4-cyano-3-fluorophenoxy)pyridin-3-yl group at the 4-position and a 4-oxaspiro[3.3]hept-2-yl group at the 3-position.
4-25	 Chemical structure of compound 4-25: A 1H-indazole-3-carboxylic acid derivative. The indazole ring has a carboxylic acid group at position 3 and a 4-oxaspiro[3.3]hept-2-ylmethyl group at position 2. The nitrogen at position 1 of the indazole is connected via a methylene group to a piperidine ring. The piperidine ring is substituted with a 2-(4-cyano-3-fluorophenoxy)pyridin-3-yl group at the 4-position and a 4-oxaspiro[3.3]hept-2-yl group at the 3-position.

Compound No.	Structure
4-26	 Chemical structure of compound 4-26: A thiazole ring is connected via a methylene group to the 2-position of an indazole ring. The indazole ring has a carboxylic acid group at the 6-position. The 3-position of the indazole ring is connected via a methylene group to a piperidine ring. The piperidine ring is further connected to a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a fluorine atom and a cyano group on the benzene ring, and a methyl group on the five-membered ring.
4-27	 Chemical structure of compound 4-27: A thiazole ring is connected via a methylene group to the 2-position of an indazole ring. The indazole ring has a carboxylic acid group at the 6-position. The 3-position of the indazole ring is connected via a methylene group to a piperidine ring. The piperidine ring is further connected to a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a fluorine atom and a cyano group on the benzene ring, and a methyl group on the five-membered ring.
4-28	 Chemical structure of compound 4-28: A thiazole ring is connected via a methylene group to the 2-position of an indazole ring. The indazole ring has a carboxylic acid group at the 6-position. The 3-position of the indazole ring is connected via a methylene group to a piperidine ring. The piperidine ring is further connected to a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a fluorine atom and a cyano group on the benzene ring, and a methyl group on the five-membered ring.
4-29	 Chemical structure of compound 4-29: A thiazole ring is connected via a methylene group to the 2-position of an indazole ring. The indazole ring has a carboxylic acid group at the 6-position. The 3-position of the indazole ring is connected via a methylene group to a piperidine ring. The piperidine ring is further connected to a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a fluorine atom and a cyano group on the benzene ring, and a methyl group on the five-membered ring.
4-30	 Chemical structure of compound 4-30: A thiazole ring is connected via a methylene group to the 2-position of an indazole ring. The indazole ring has a carboxylic acid group at the 6-position. The 3-position of the indazole ring is connected via a methylene group to a piperidine ring. The piperidine ring is further connected to a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a fluorine atom and a cyano group on the benzene ring, and a methyl group on the five-membered ring.

Compound No.	Structure
4-31	
4-32	
4-33	
4-34	
4-35	

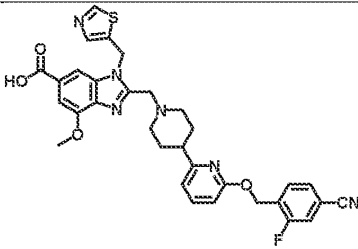
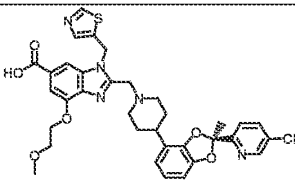
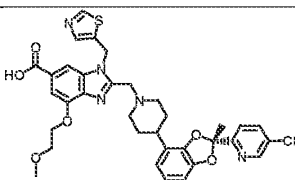
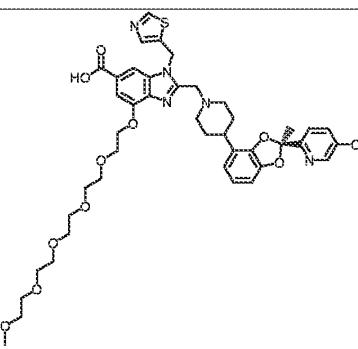
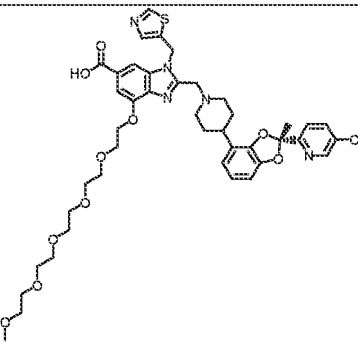
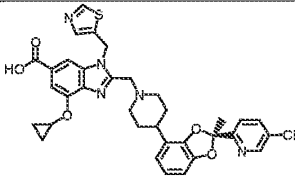
Compound No.	Structure
4-36	 Chemical structure of compound 4-36: A benzimidazole ring system with a carboxylic acid group at position 6 and a thiazole ring at position 2. The benzimidazole is connected via a methylene bridge to a piperazine ring. The piperazine ring is further connected to a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a cyano group and a fluorine atom.
4-37	 Chemical structure of compound 4-37: Similar to 4-36, but the piperazine ring is replaced by a bicyclic system (a benzene ring fused to a five-membered ring containing an oxygen atom). This bicyclic system is substituted with a cyano group and a fluorine atom.
4-38	 Chemical structure of compound 4-38: Similar to 4-37, but the bicyclic system is substituted with a cyano group and a fluorine atom.
4-39	 Chemical structure of compound 4-39: Similar to 4-38, but the bicyclic system is substituted with a cyano group and a fluorine atom.

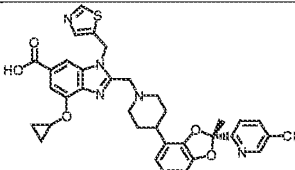
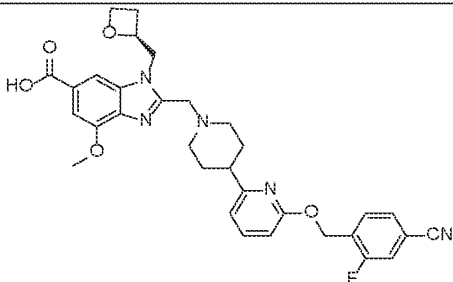
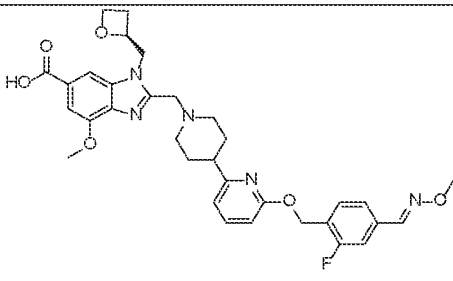
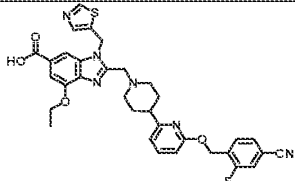
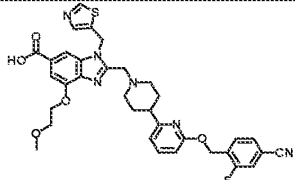
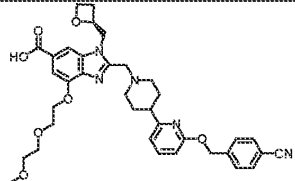
Compound No.	Structure
4-40	
4-41	
4-42	
4-43	

Compound No.	Structure
4-44	
4-45	
4-46	

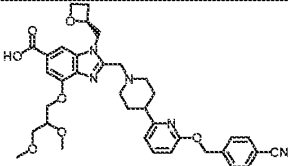
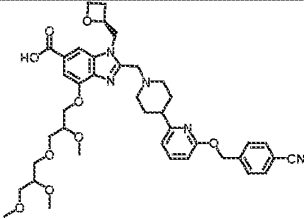
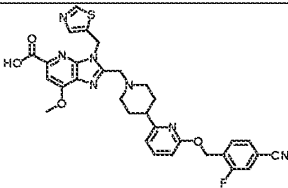
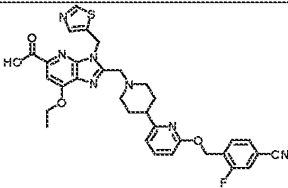
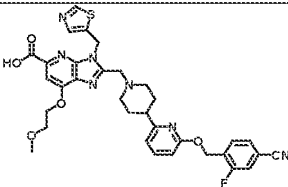
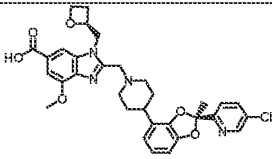
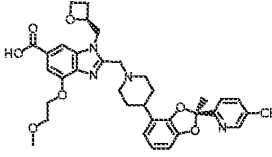
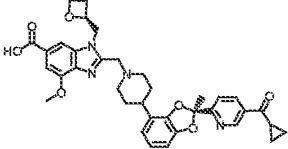
[0203] In some embodiments, the GLP-1R agonist is selected from those listed in Table 5 below, or a pharmaceutically acceptable salt thereof:

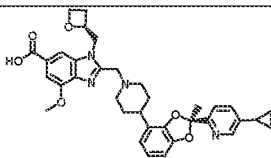
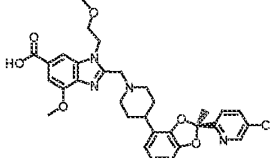
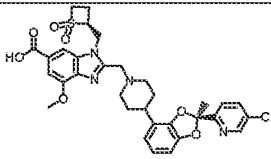
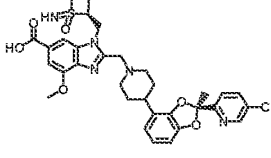
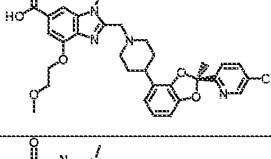
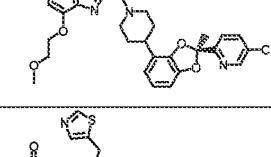
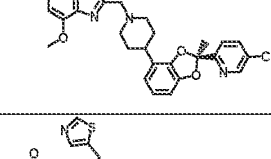
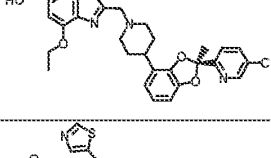
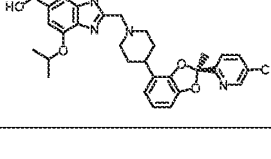
Table 5

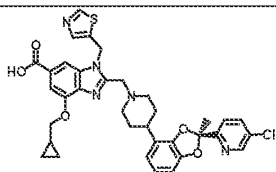
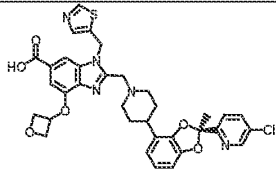
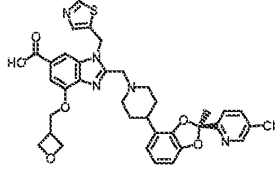
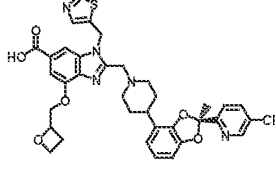
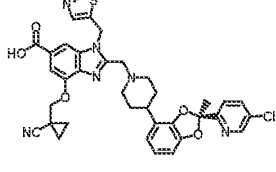
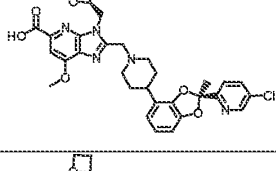
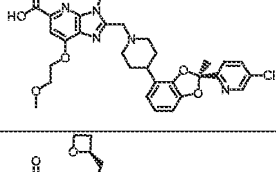
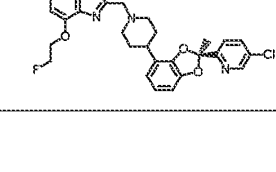
Compound No.	Structure
5-1	
5-2	
5-3	
5-4	
5-5	
5-6	

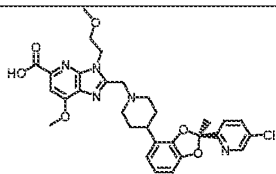
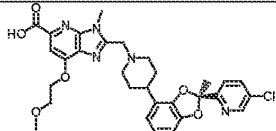
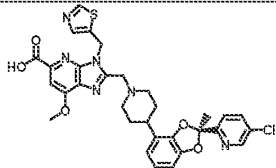
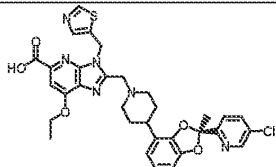
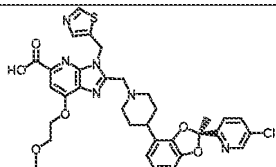
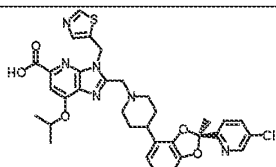
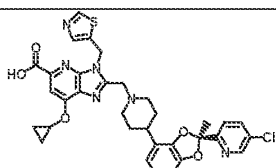
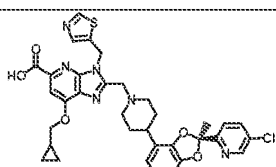
Compound No.	Structure
5-7	
5-8	
5-9	
5-10	
5-11	
5-12	

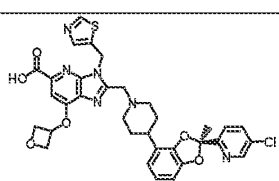
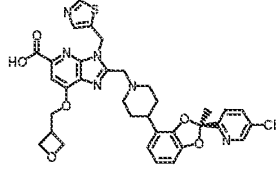
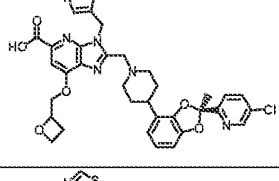
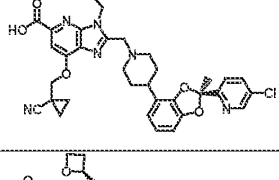
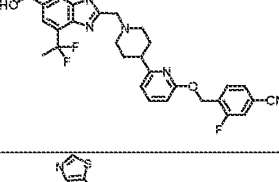
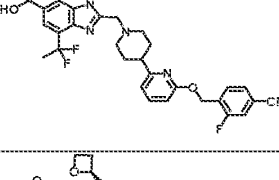
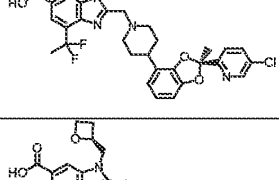
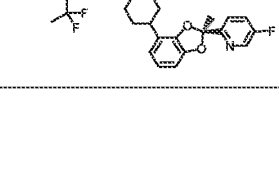
Compound No.	Structure
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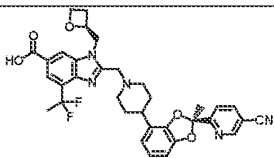
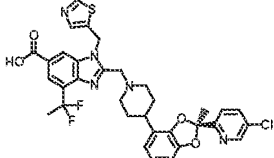
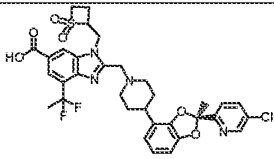
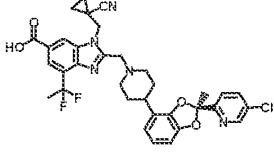
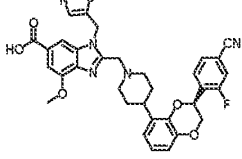
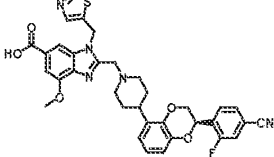
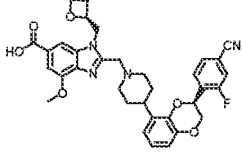
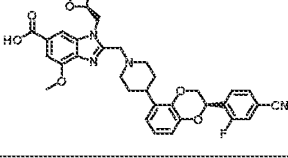
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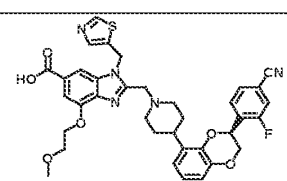
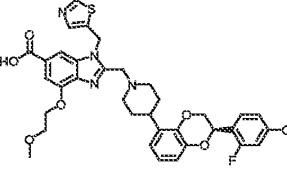
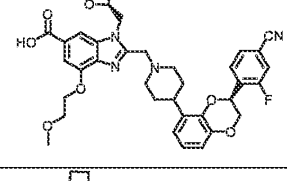
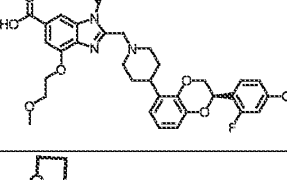
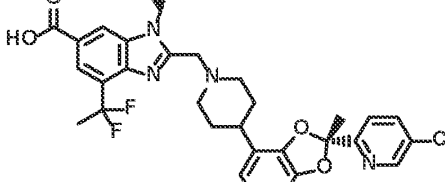
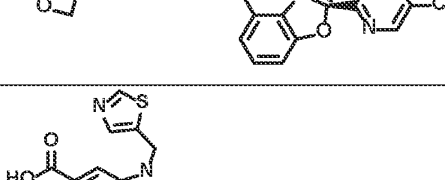
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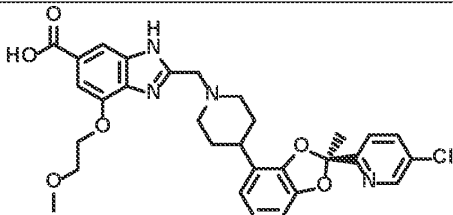
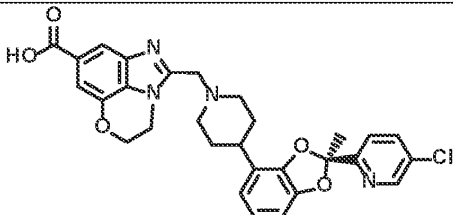
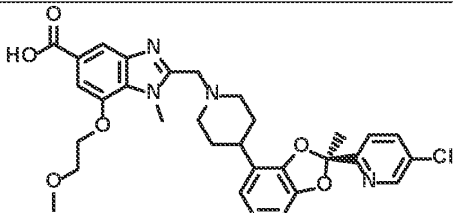
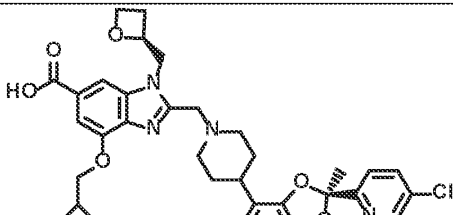
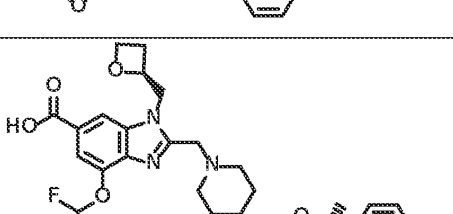
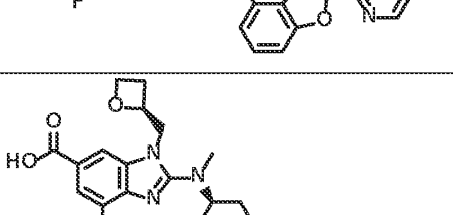
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Compound No.	Structure
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Compound No.	Structure
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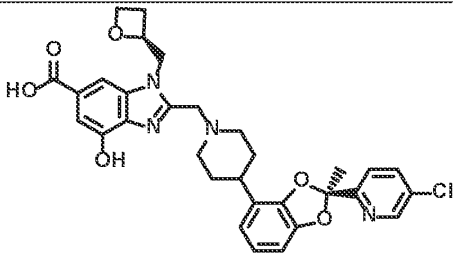
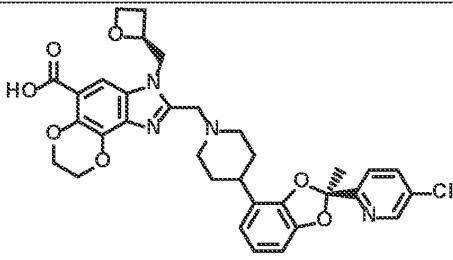
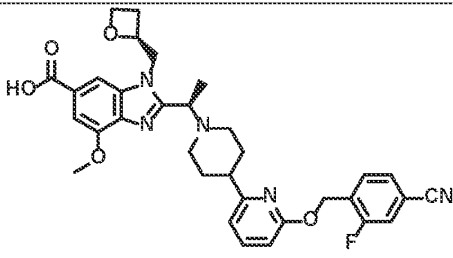
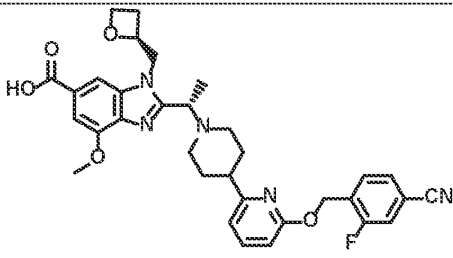
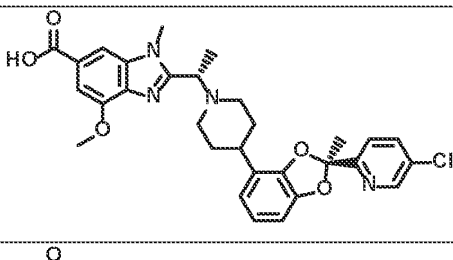
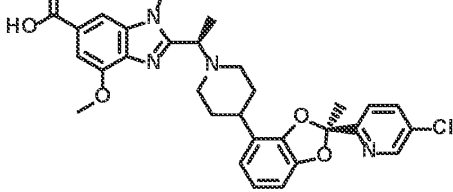
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Compound No.	Structure
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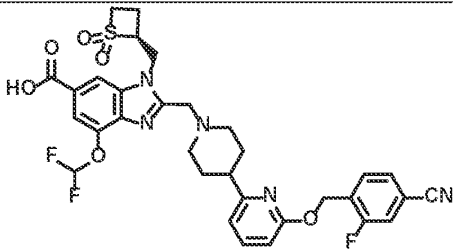
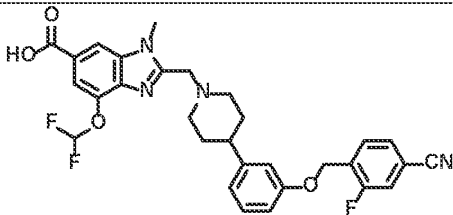
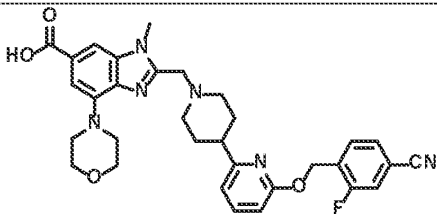
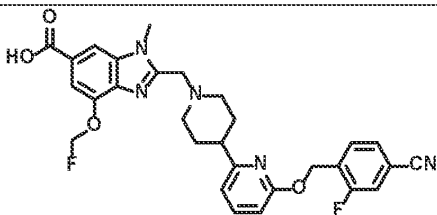
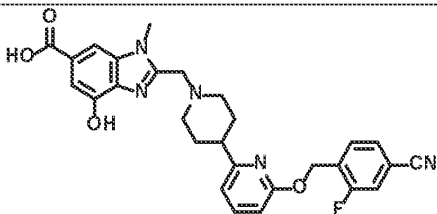
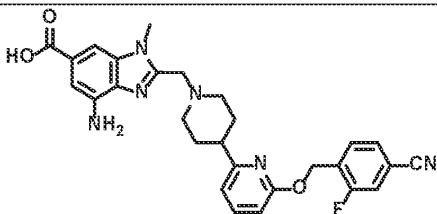
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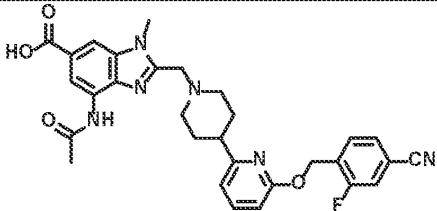
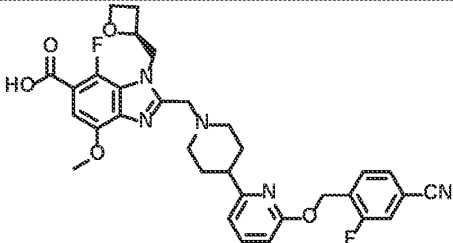
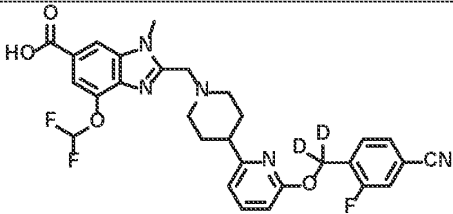
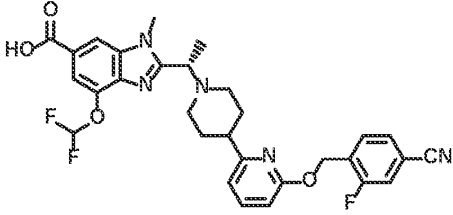
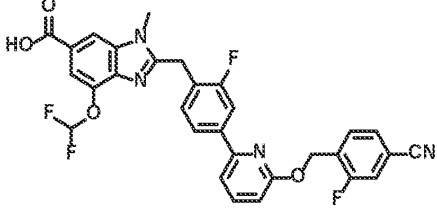
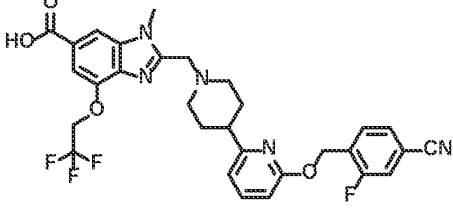
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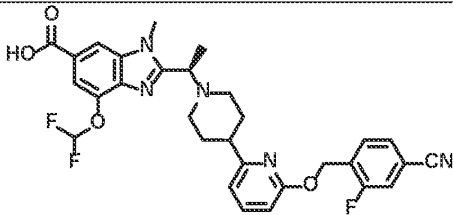
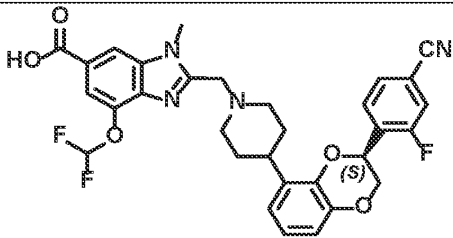
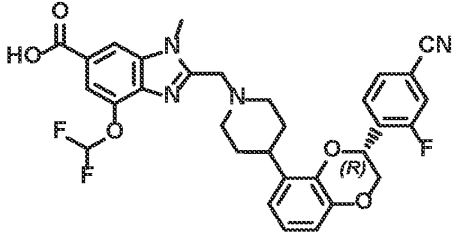
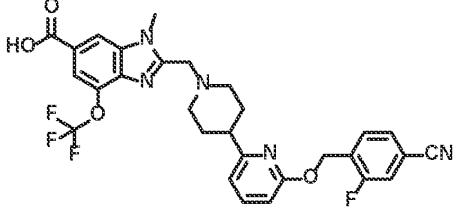
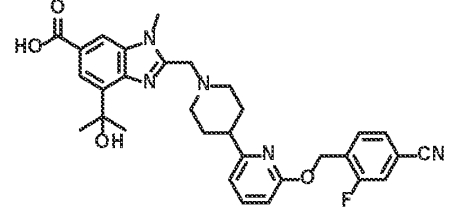
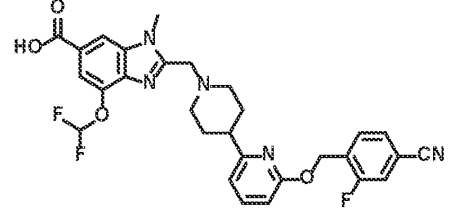
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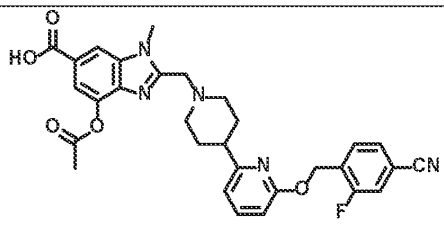
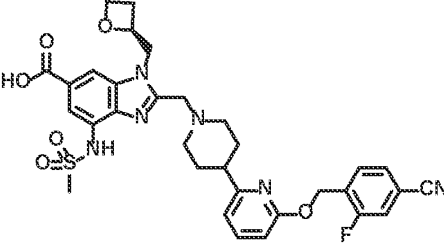
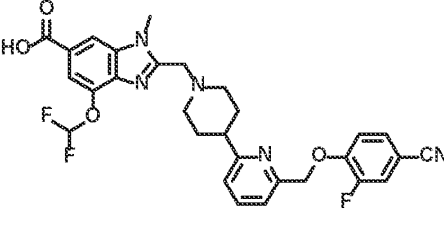
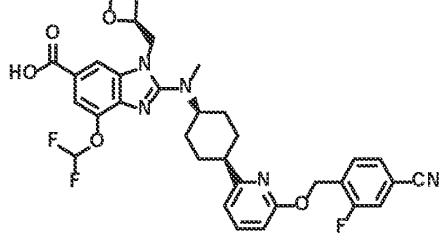
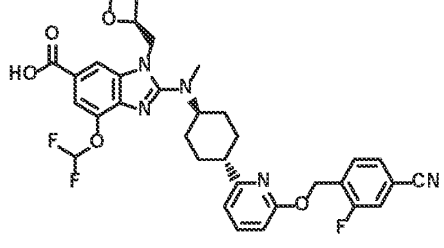
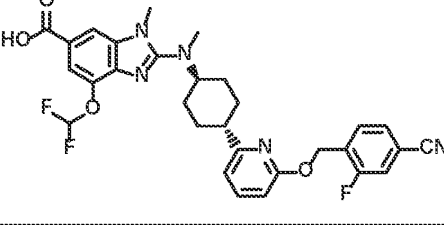
Compound No.	Structure
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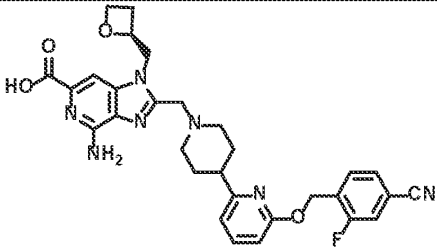
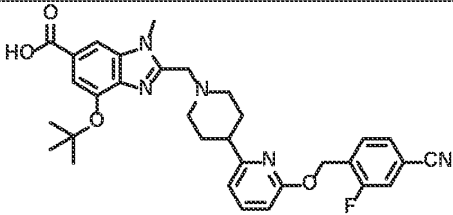
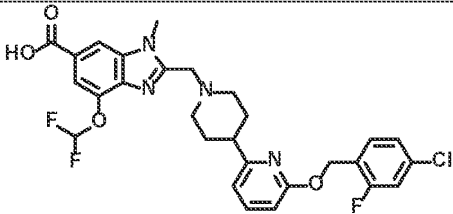
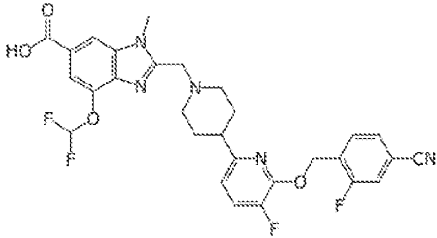
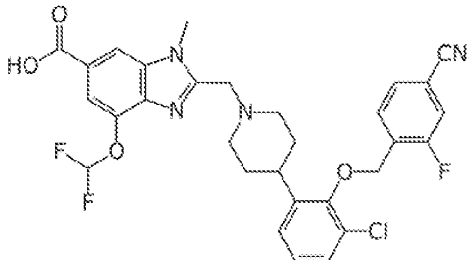
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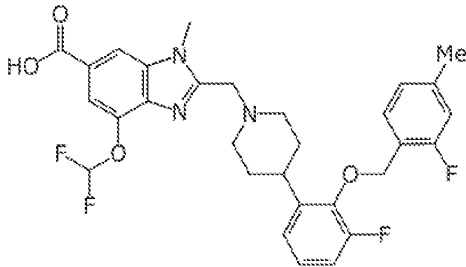
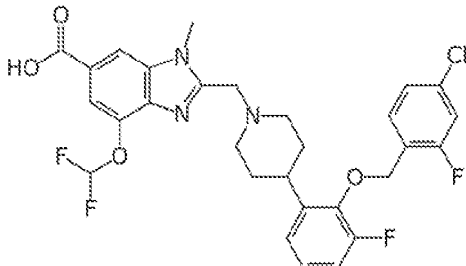
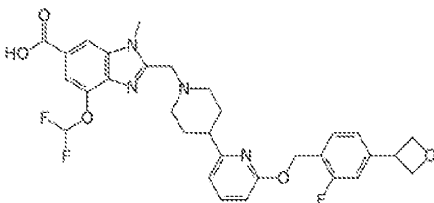
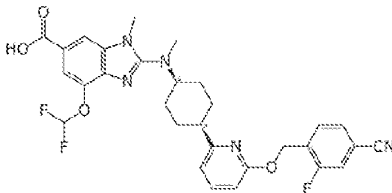
Compound No.	Structure
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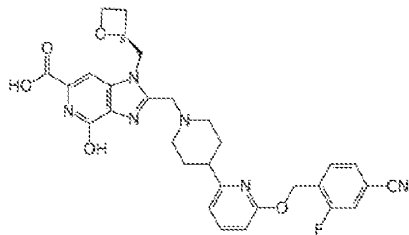
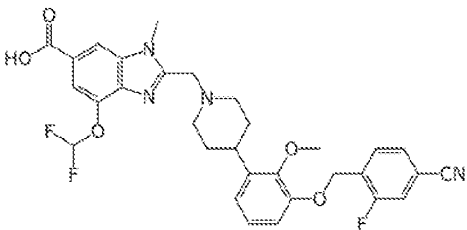
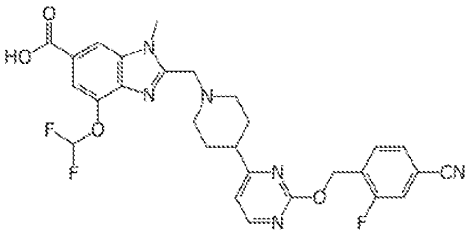
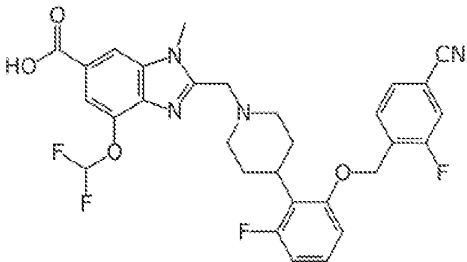
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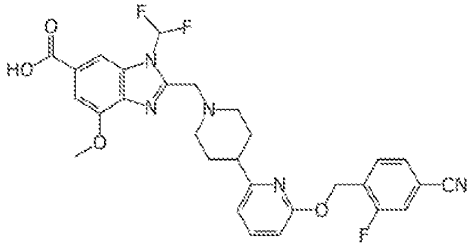
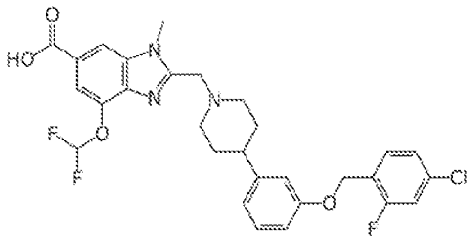
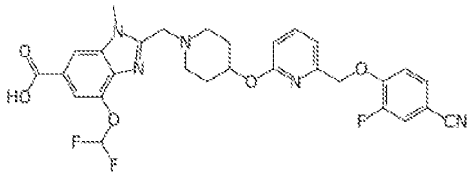
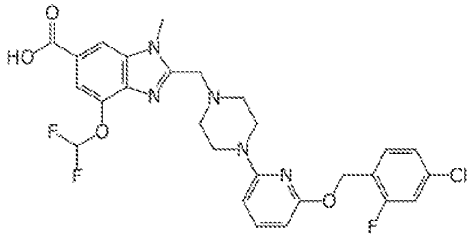
Compound No.	Structure
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Compound No.	Structure
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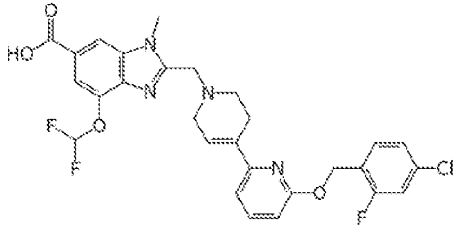
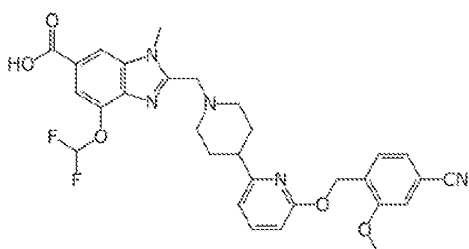
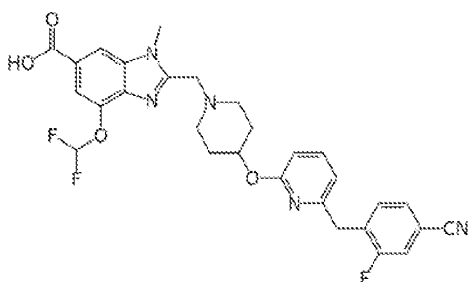
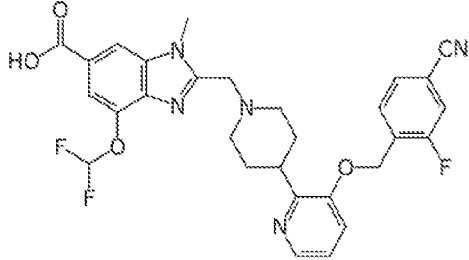
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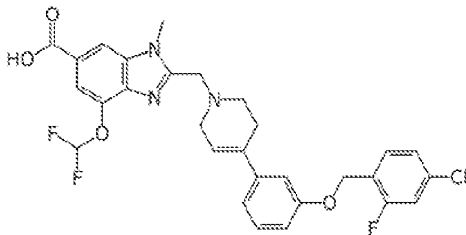
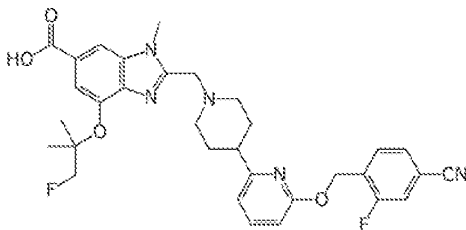
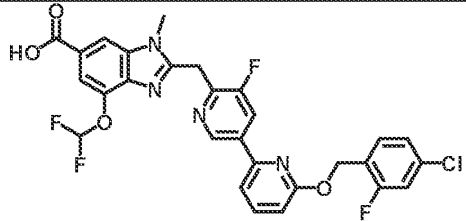
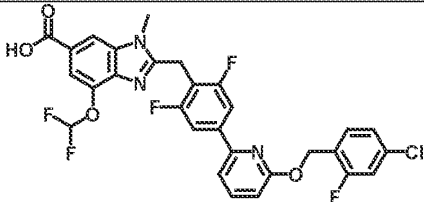
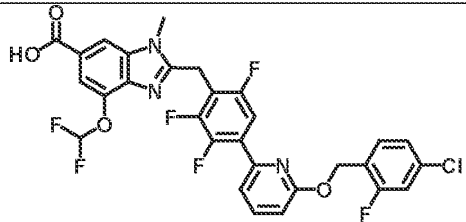
Compound No.	Structure
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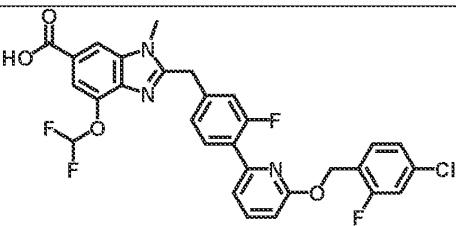
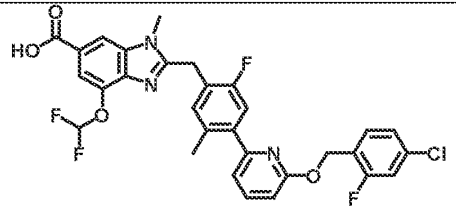
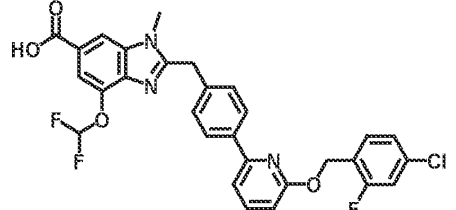
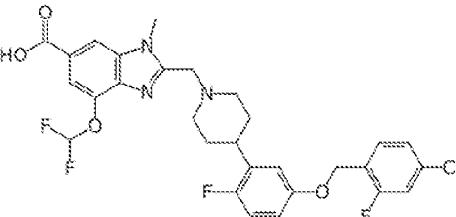
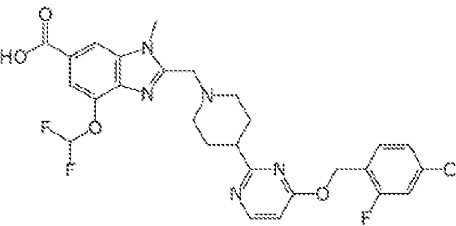
Compound No.	Structure
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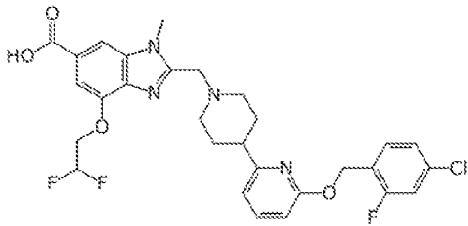
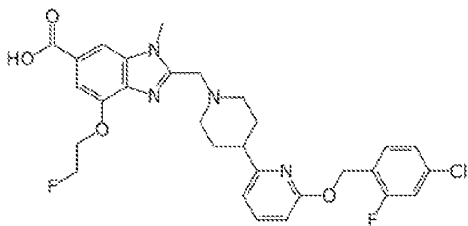
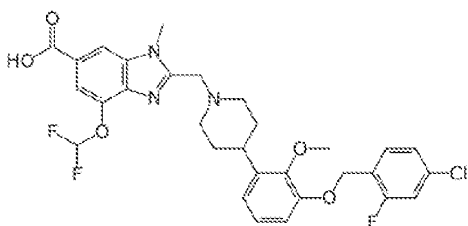
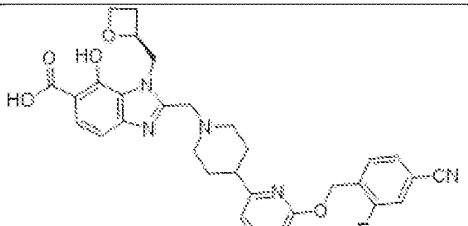
Compound No.	Structure
5-147	
5-148	
5-149	
5-150	

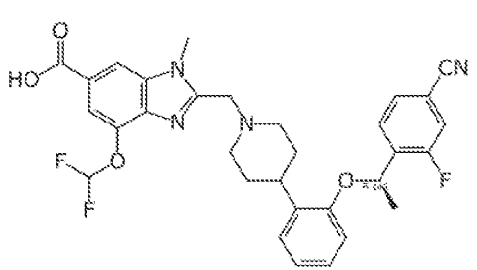
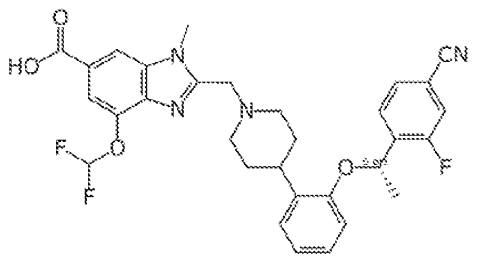
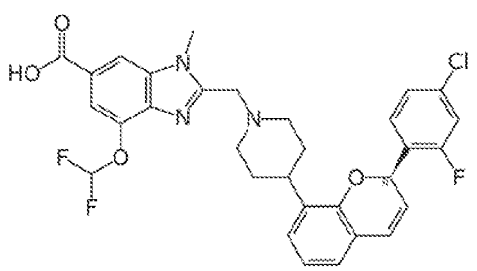
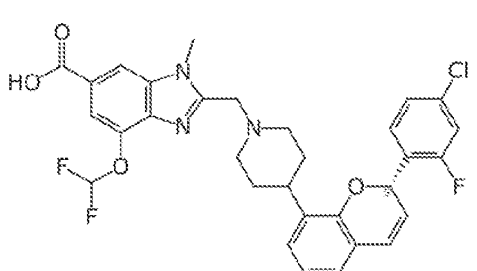
Compound No.	Structure
5-151	 <chem>CN1C=NC2=C(C(=O)O)C(OC(F)F)=CC=C2N1CCN3CCCCC3c4cccnc4-c5ccc(F)c(C#N)c5</chem>
5-152	 <chem>CN1C=NC2=C(C(=O)O)C(OC(F)F)=CC=C2N1CCN3CCCCC3c4ccc(F)cc4COc5ccc(F)c(Cl)c5</chem>
5-153	 <chem>CN1C=NC2=C(C(=O)O)C(OC(F)F)=CC=C2N1CCN3CCCCC3c4cccnc4COc5cc(F)c(Cl)c(F)c5</chem>
5-154	 <chem>CN1C=NC2=C(C(=O)O)C(OC(F)F)=CC=C2N1CCN3CCCCC3c4cccnc4COc5ccc(OC)c(C(F)(F)F)c5</chem>

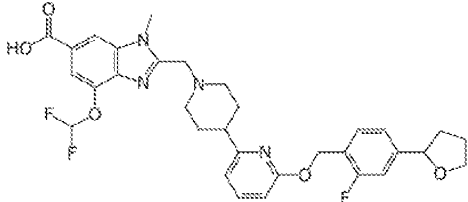
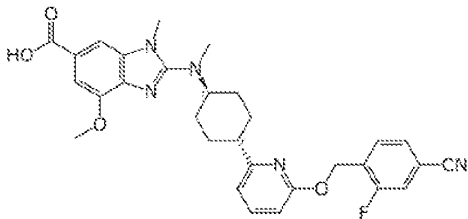
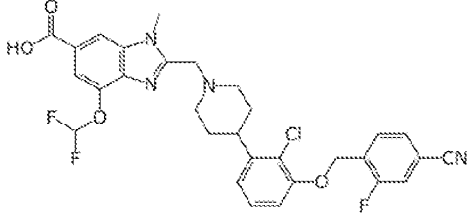
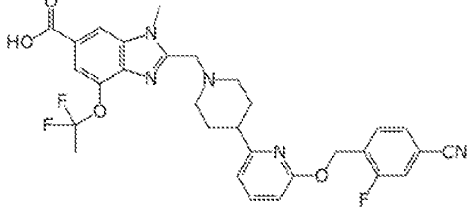
Compound No.	Structure
5-155	
5-156	
5-157	
5-158	

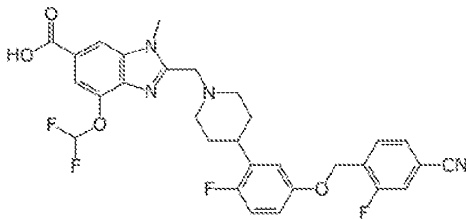
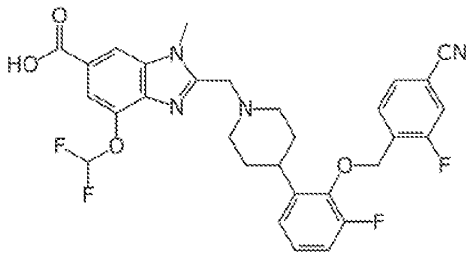
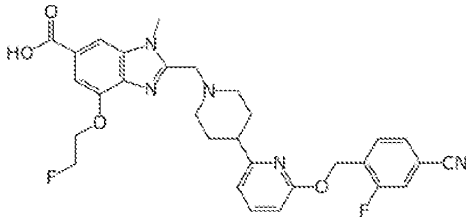
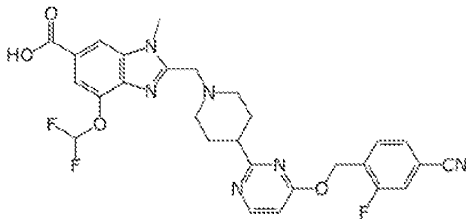
Compound No.	Structure
5-159	
5-160	
5-161	
5-162	
5-163	

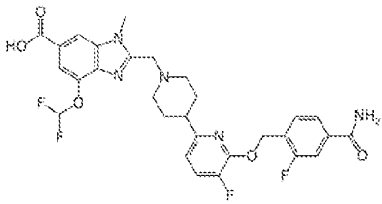
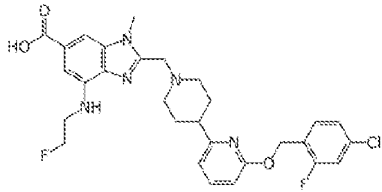
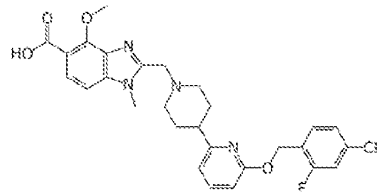
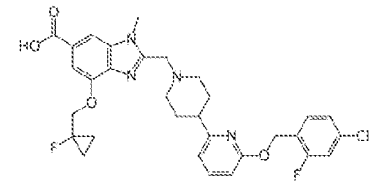
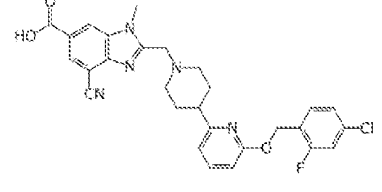
Compound No.	Structure
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5-165	
5-166	
5-167	
5-168	

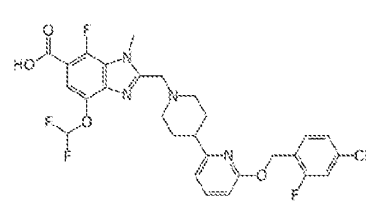
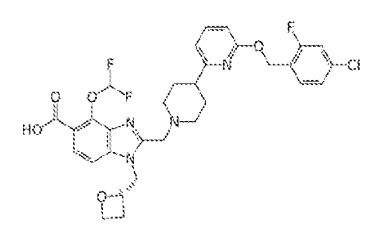
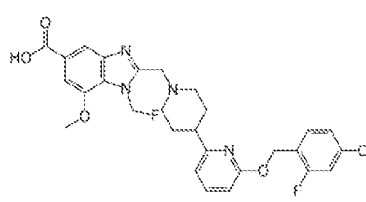
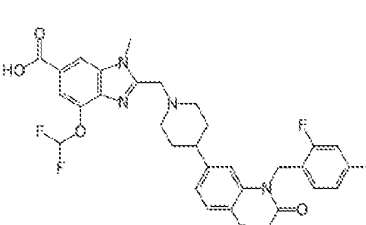
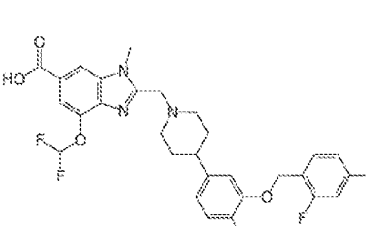
Compound No.	Structure
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5-170	
5-171	
5-172	

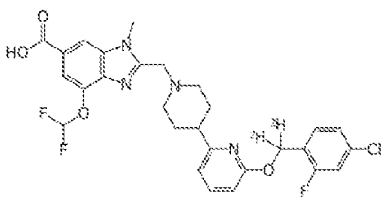
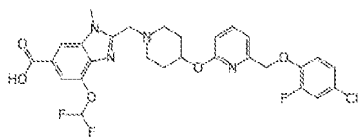
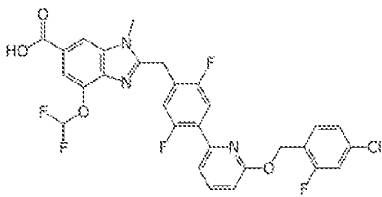
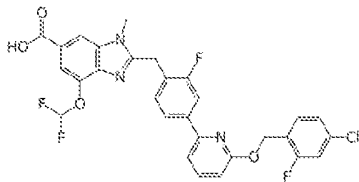
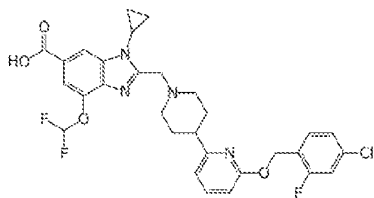
Compound No.	Structure
5-173	
5-174	
5-175	
5-176	

Compound No.	Structure
5-177	 Chemical structure of compound 5-177: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a 2,2,2-trifluoroethoxy group, and a 1-(4-(4-cyano-2-fluorophenyl)pyridin-2-yl)piperidin-4-yl group.
5-178	 Chemical structure of compound 5-178: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a methoxy group, and a 1-(4-(4-cyano-2-fluorophenyl)pyridin-2-yl)piperidin-4-yl group.
5-179	 Chemical structure of compound 5-179: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a 2,2,2-trifluoroethoxy group, and a 1-(4-(4-cyano-2-fluorophenyl)-2-chlorophenyl)piperidin-4-yl group.
5-180	 Chemical structure of compound 5-180: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a 2,2,2-trifluoroethoxy group, and a 1-(4-(4-cyano-2-fluorophenyl)pyridin-2-yl)piperidin-4-yl group.

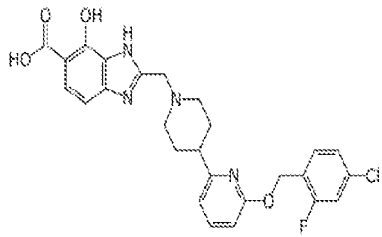
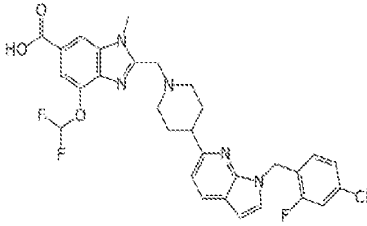
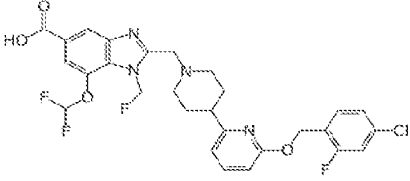
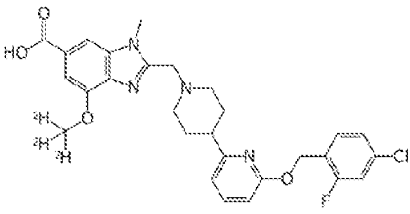
Compound No.	Structure
5-181	
5-182	
5-183	
5-184	

Compound No.	Structure
5-185	
5-186	
5-187	
5-188	
5-189	

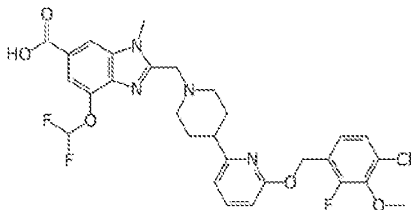
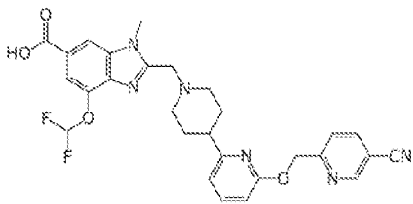
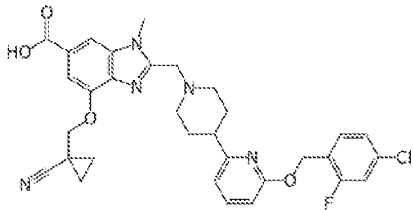
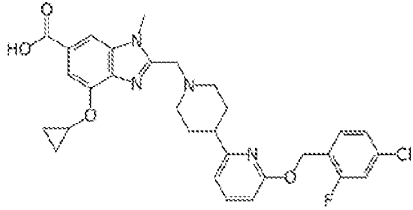
Compound No.	Structure
5-190	
5-191	
5-192	
5-193	
5-194	

Compound No.	Structure
5-195	
5-196	
5-197	
5-198	
5-199	

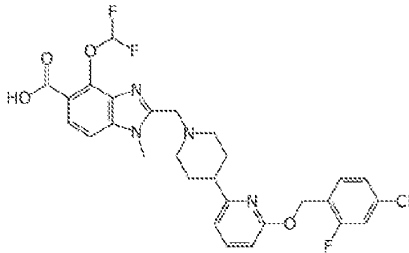
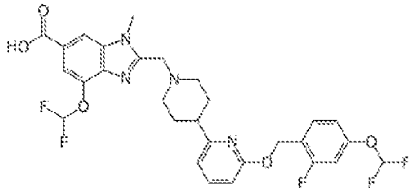
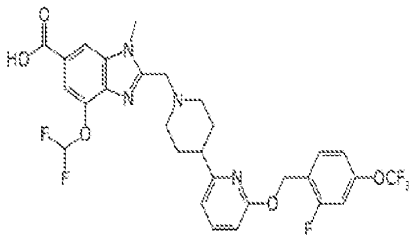
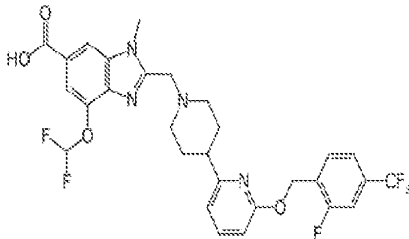
Compound No.	Structure
5-200	
5-201	
5-202	
5-203	

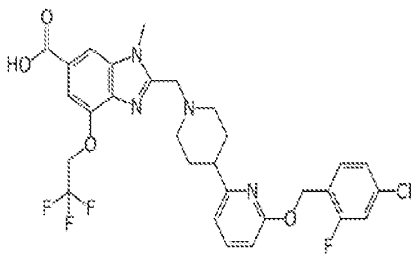
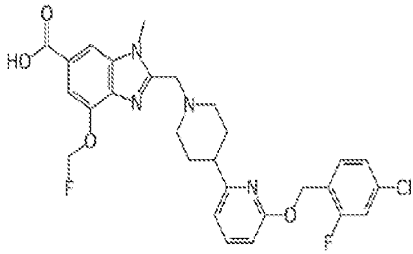
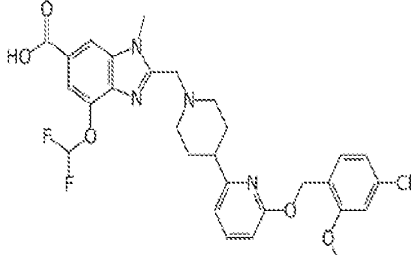
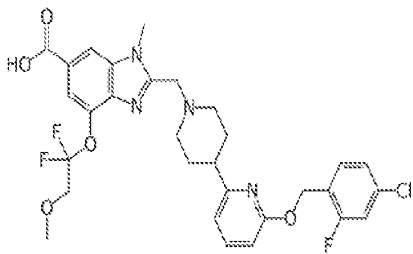
Compound No.	Structure
5-204	
5-205	
5-206	
5-207	

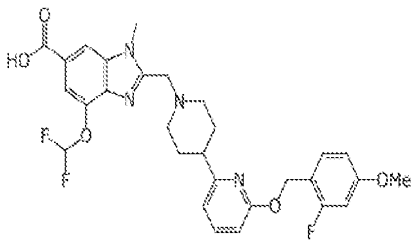
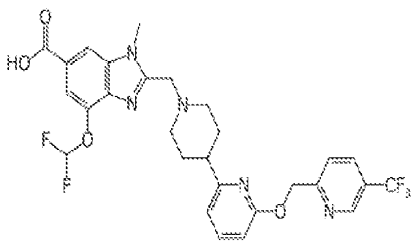
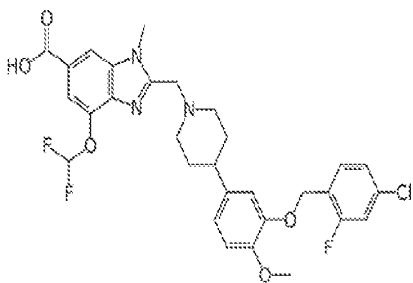
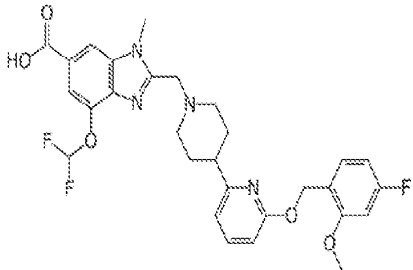
Compound No.	Structure
5-208	 <chem>COc1nc2cc(C(=O)O)c(OC(F)(F)F)c2n1Cc3ccccc3n3c(Cc4ccc(Cl)c(F)c4)cc3</chem>
5-209	 <chem>COc1nc2cc(C(=O)O)c(OC)c2n1Cc3ccccc3n3c(Cc4ccc(Cl)c(F)c4)cc3</chem>
5-210	 <chem>COc1nc2cc(C(=O)O)c(OC(F)(F)F)c2n1Cc3ccccc3n3c(Cc4ccc(Cl)c(F)c4)cc3</chem>
5-211	 <chem>COc1nc2cc(C(=O)O)c(OC3CCOC3)c2n1Cc3ccccc3n3c(Cc4ccc(Cl)c(F)c4)cc3</chem>

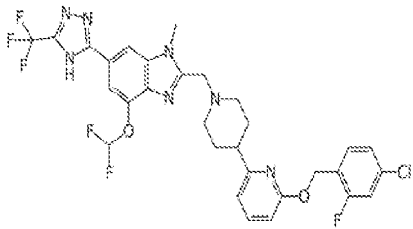
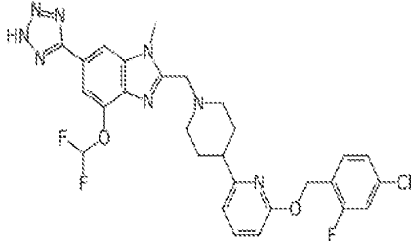
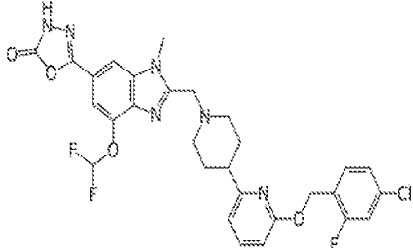
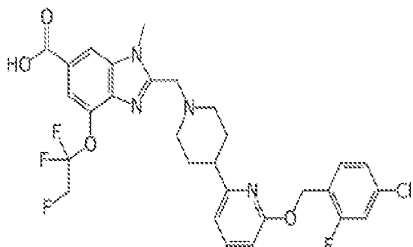
Compound No.	Structure
5-212	
5-213	
5-214	
5-215	

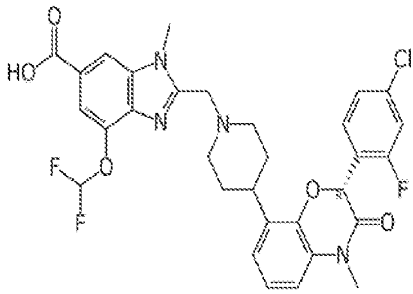
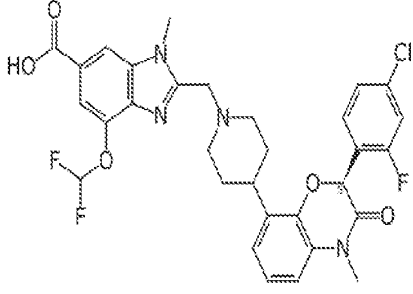
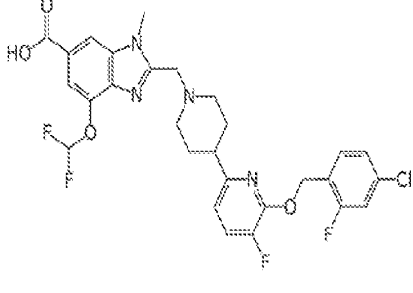
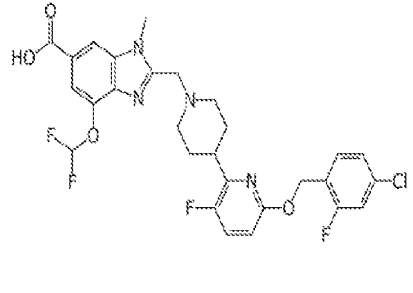
Compound No.	Structure
5-216	 <chem>CN1C=NC2=C(C(=O)O)C=C(C=C2OC(F)F)C1CN3CCCCC3c4ccc(Oc5cc(F)cc(Cl)c5)cc4</chem>
5-217	 <chem>CN1C=NC2=C(C(=O)O)C=C(C=C2OC(F)F)C1CN3CCCCC3c4cc5nn(Cc6cc(F)cc(Cl)c6)cc5cc4</chem>
5-218	 <chem>CN1C=NC2=C(C(=O)O)C=C(C=C2OC(F)F)C1CN3CCCCC3c4cccc(Cc5cc(F)cc(Cl)c5)n4</chem>
5-219	 <chem>CN1C=NC2=C(C(=O)O)C=C(C=C2OC(F)F)C1CN3CCCCC3c4cccc(Cc5cc(Cl)cc(C)cc5)n4</chem>

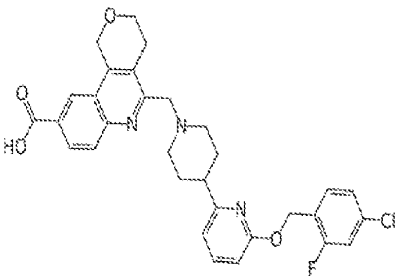
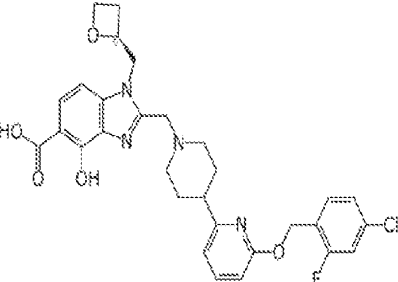
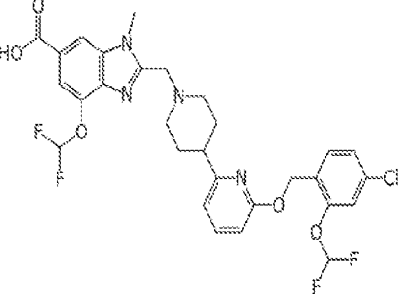
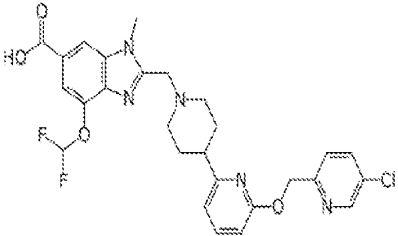
Compound No.	Structure
5-220	
5-221	
5-222	
5-223	

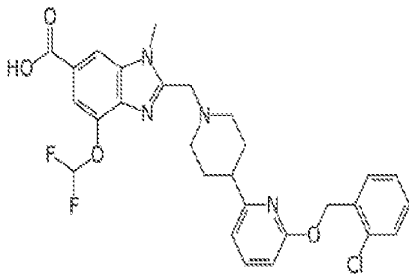
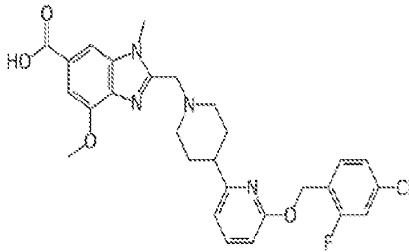
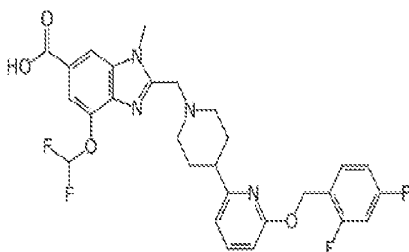
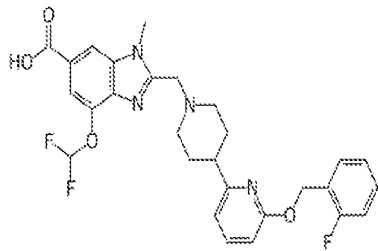
Compound No.	Structure
5-224	 Chemical structure of compound 5-224: A quinazolin-4(1H)-one derivative. The quinazolinone core has a methyl group at position 2, a carboxylic acid group at position 6, and a 2,2,2-trifluoroethoxy group at position 7. The nitrogen at position 4 is connected via a methylene bridge to a piperidine ring. The piperidine ring is further connected via a methylene bridge to a pyridine ring. The pyridine ring is connected via a methylene bridge to a 4-chloro-2-fluorophenyl group.
5-225	 Chemical structure of compound 5-225: A quinazolin-4(1H)-one derivative. The quinazolinone core has a methyl group at position 2, a carboxylic acid group at position 6, and a 2-fluoroethoxy group at position 7. The nitrogen at position 4 is connected via a methylene bridge to a piperidine ring. The piperidine ring is further connected via a methylene bridge to a pyridine ring. The pyridine ring is connected via a methylene bridge to a 4-chloro-2-fluorophenyl group.
5-226	 Chemical structure of compound 5-226: A quinazolin-4(1H)-one derivative. The quinazolinone core has a methyl group at position 2, a carboxylic acid group at position 6, and a 1,1-difluoroethoxy group at position 7. The nitrogen at position 4 is connected via a methylene bridge to a piperidine ring. The piperidine ring is further connected via a methylene bridge to a pyridine ring. The pyridine ring is connected via a methylene bridge to a 4-chloro-2-methoxyphenyl group.
5-227	 Chemical structure of compound 5-227: A quinazolin-4(1H)-one derivative. The quinazolinone core has a methyl group at position 2, a carboxylic acid group at position 6, and a 1,1,1-trifluoro-2-methoxyethoxy group at position 7. The nitrogen at position 4 is connected via a methylene bridge to a piperidine ring. The piperidine ring is further connected via a methylene bridge to a pyridine ring. The pyridine ring is connected via a methylene bridge to a 4-chloro-2-fluorophenyl group.

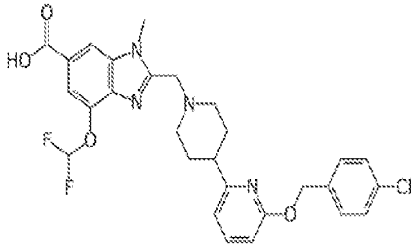
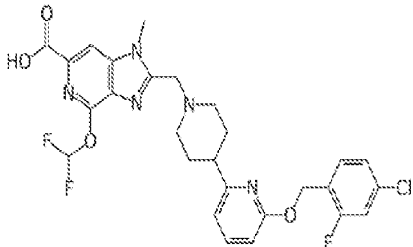
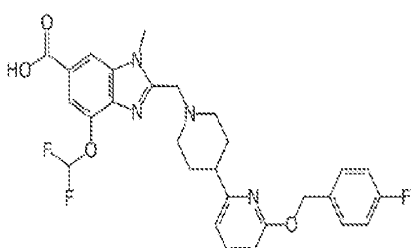
Compound No.	Structure
5-228	 Chemical structure of compound 5-228: A 7-fluoro-2-methyl-4-((4-methoxy-3-(trifluoromethyl)phenyl)methyl)piperidine-1-carboxamide derivative. The structure features a central piperidine ring connected via its nitrogen to a carbonyl group. This carbonyl is part of a larger system where the piperidine ring is also connected to a 4-methoxy-3-(trifluoromethyl)phenyl group through a methylene bridge. The piperidine ring has a methyl group at position 2 and a carboxamide group at position 1.
5-229	 Chemical structure of compound 5-229: A 7-fluoro-2-methyl-4-((4-(trifluoromethyl)pyridin-2-yl)methyl)piperidine-1-carboxamide derivative. The structure features a central piperidine ring connected via its nitrogen to a carbonyl group. This carbonyl is part of a larger system where the piperidine ring is also connected to a 4-(trifluoromethyl)pyridin-2-yl group through a methylene bridge. The piperidine ring has a methyl group at position 2 and a carboxamide group at position 1.
5-230	 Chemical structure of compound 5-230: A 7-fluoro-2-methyl-4-((4-chloro-3-(methoxymethyl)phenyl)methyl)piperidine-1-carboxamide derivative. The structure features a central piperidine ring connected via its nitrogen to a carbonyl group. This carbonyl is part of a larger system where the piperidine ring is also connected to a 4-chloro-3-(methoxymethyl)phenyl group through a methylene bridge. The piperidine ring has a methyl group at position 2 and a carboxamide group at position 1.
5-231	 Chemical structure of compound 5-231: A 7-fluoro-2-methyl-4-((4-fluoro-3-methoxyphenyl)methyl)piperidine-1-carboxamide derivative. The structure features a central piperidine ring connected via its nitrogen to a carbonyl group. This carbonyl is part of a larger system where the piperidine ring is also connected to a 4-fluoro-3-methoxyphenyl group through a methylene bridge. The piperidine ring has a methyl group at position 2 and a carboxamide group at position 1.

Compound No.	Structure
5-232	 Chemical structure of compound 5-232: A pyrazolo[1,5-a]pyridine core substituted with a 1,1,1-trifluoroethoxy group at position 6, a methyl group at position 7, and a (4-(2-chloro-4-fluorophenyl)pyridin-2-yl)methyl group at position 3. The pyridine ring is connected to the pyrazolo[1,5-a]pyridine core via a methylene bridge.
5-233	 Chemical structure of compound 5-233: A pyrazolo[1,5-a]pyridine core substituted with a 1,1,1-trifluoroethoxy group at position 6, a methyl group at position 7, and a (4-(2-chloro-4-fluorophenyl)pyridin-2-yl)methyl group at position 3. The pyridine ring is connected to the pyrazolo[1,5-a]pyridine core via a methylene bridge.
5-234	 Chemical structure of compound 5-234: A pyrazolo[1,5-a]pyridine core substituted with a 1,1,1-trifluoroethoxy group at position 6, a methyl group at position 7, and a (4-(2-chloro-4-fluorophenyl)pyridin-2-yl)methyl group at position 3. The pyridine ring is connected to the pyrazolo[1,5-a]pyridine core via a methylene bridge.
5-235	 Chemical structure of compound 5-235: A pyrazolo[1,5-a]pyridine core substituted with a 1,1,1-trifluoroethoxy group at position 6, a methyl group at position 7, and a (4-(2-chloro-4-fluorophenyl)pyridin-2-yl)methyl group at position 3. The pyridine ring is connected to the pyrazolo[1,5-a]pyridine core via a methylene bridge.

Compound No.	Structure
5-240	 Chemical structure of compound 5-240: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a difluoromethoxy group, and a methyl group. It is linked via a piperidine ring to a benzimidazole system, which is further substituted with a 4-chlorophenyl group and a 2-fluorophenyl group.
5-241	 Chemical structure of compound 5-241: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a difluoromethoxy group, and a methyl group. It is linked via a piperidine ring to a benzimidazole system, which is further substituted with a 4-chlorophenyl group and a 2-fluorophenyl group.
5-242	 Chemical structure of compound 5-242: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a difluoromethoxy group, and a methyl group. It is linked via a piperidine ring to a pyridine ring, which is further substituted with a 4-chlorophenyl group and a 2-fluorophenyl group.
5-243	 Chemical structure of compound 5-243: A pyrazolo[1,5-a]pyridine core substituted with a carboxylic acid group, a difluoromethoxy group, and a methyl group. It is linked via a piperidine ring to a pyridine ring, which is further substituted with a 4-chlorophenyl group and a 2-fluorophenyl group.

Compound No.	Structure
5-244	
5-245	
5-246	
5-247	

Compound No.	Structure
5-248	
5-249	
5-250	
5-251	

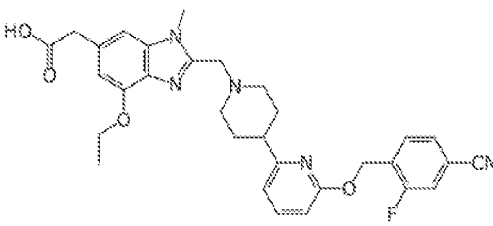
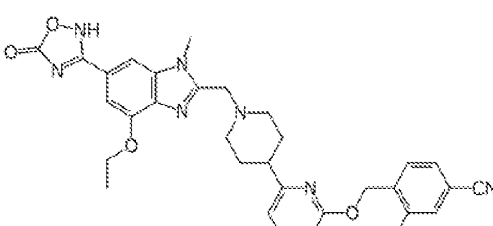
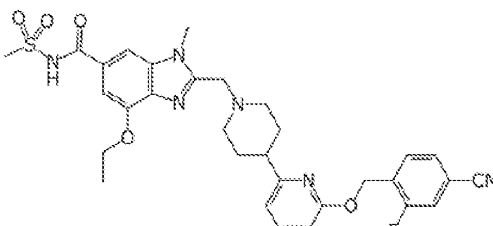
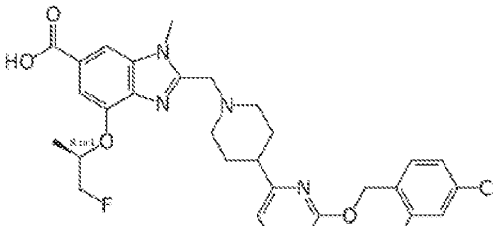
Compound No.	Structure
5-252	
5-253	
5-254	

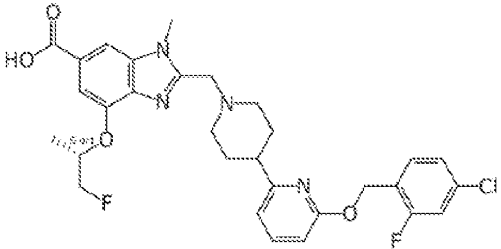
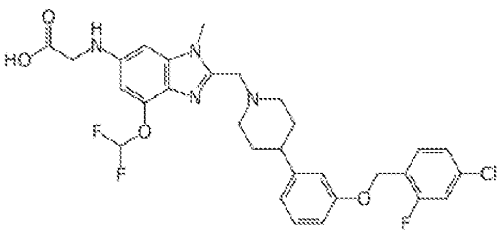
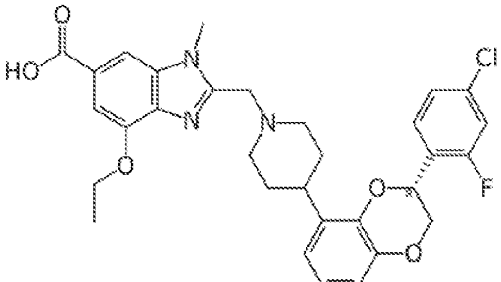
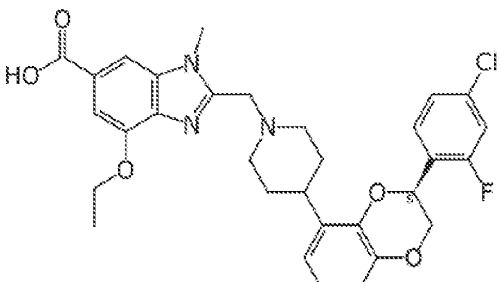
[0204] In some embodiments, the GLP-1R agonist is selected from those listed in Table 5A below, or a pharmaceutically acceptable salt thereof:

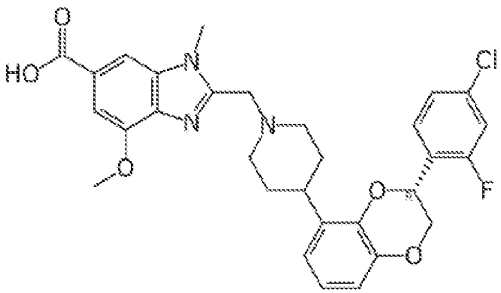
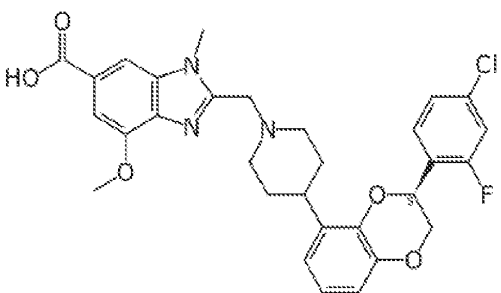
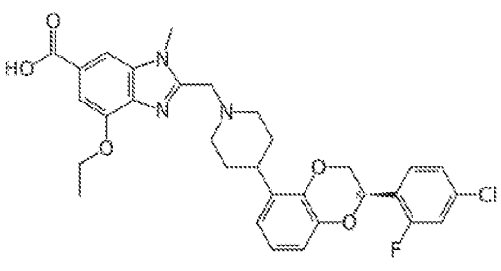
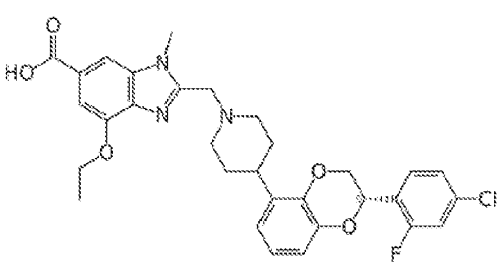
Table 5A

Compound No.	Name	Structure
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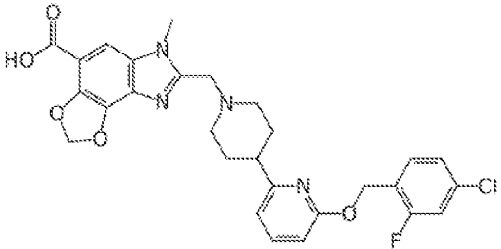
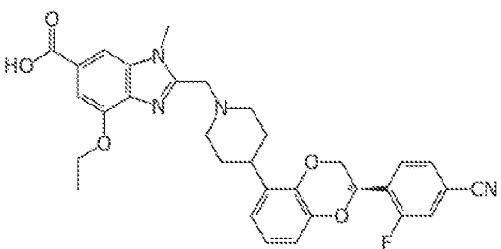
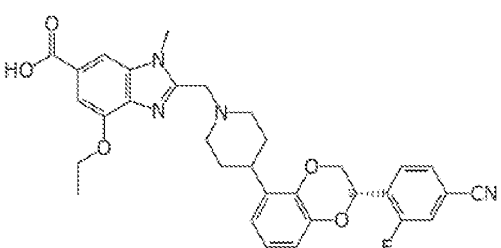
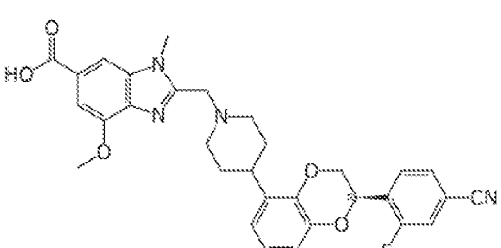
5-255	(2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazol-6-yl)glycine	
5-256	2-((4-((6-((4-chloro-2-fluorophenoxy)methyl)pyridin-2-yl)oxy)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-257	(S)-3-(2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazol-6-yl)propionic acid	
5-258	(S)-2-((4-(2-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

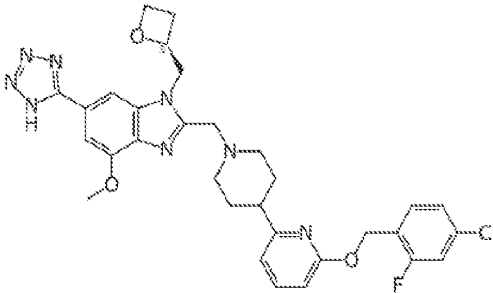
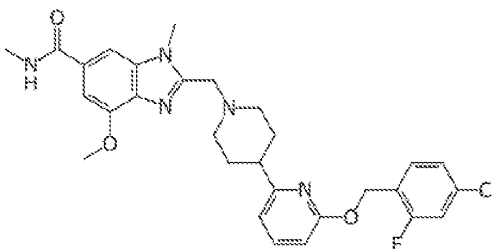
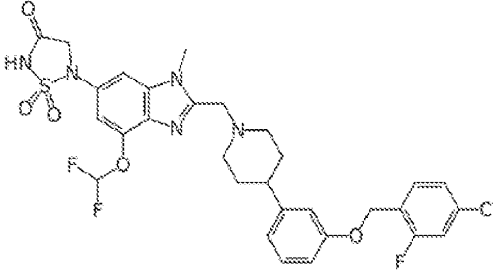
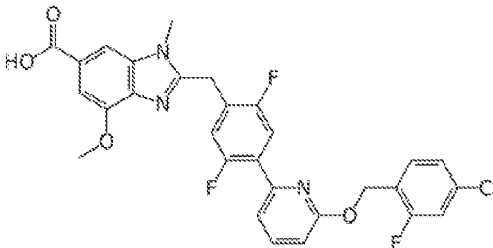
5-259	2-(2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazol-6-yl)acetic acid	
5-260	4-(((6-(1-((4-ethoxy-1-methyl-6-(5-oxo-2,5-dihydro-1,2,4-oxadiazol-3-yl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile	
5-261	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-N-(methylsulfonyl)-1H-benzo[d]imidazole-6-carboxamide	
5-262	rel-(R)-2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1-fluoropropan-2-yl)oxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

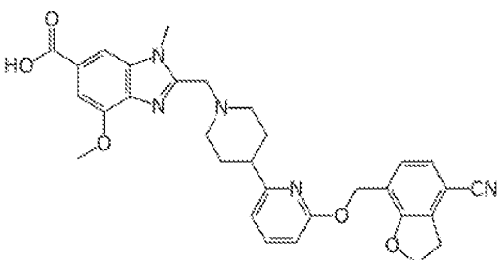
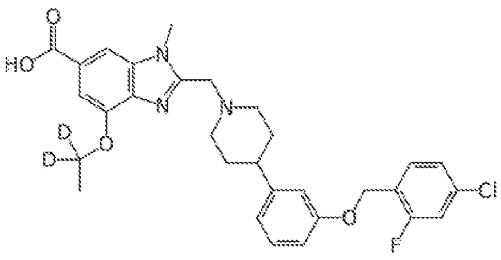
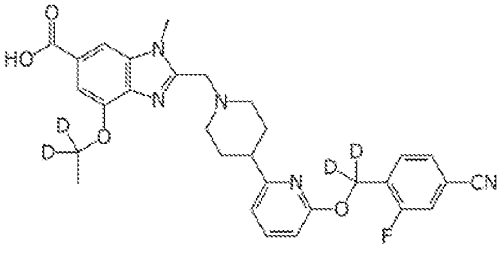
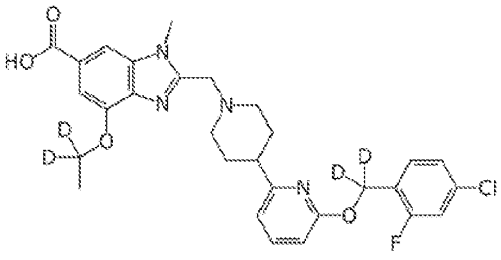
5-263	rel-(S)-2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1-fluoropropan-2-yl)oxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-264	(2-((4-(3-((4-chloro-2-fluorobenzyl)oxy)phenyl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazol-6-yl)glycine	
5-265	(R)-2-((4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-266	(S)-2-((4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

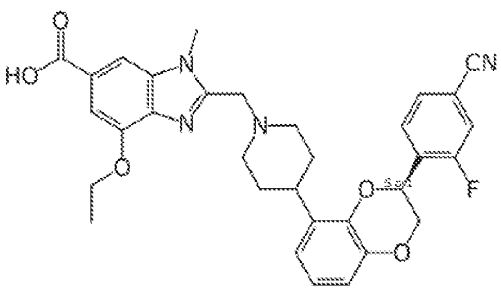
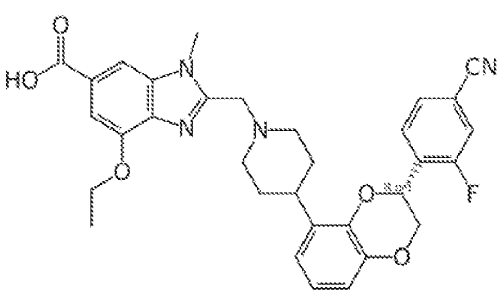
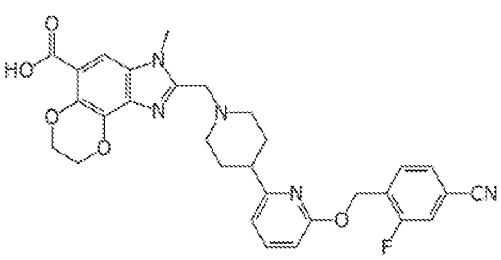
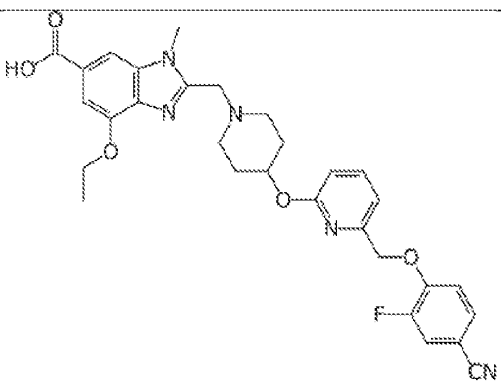
5-267	(R)-2-((4-(3-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-268	(S)-2-((4-(3-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-269	(R)-2-((4-(2-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-270	(S)-2-((4-(2-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

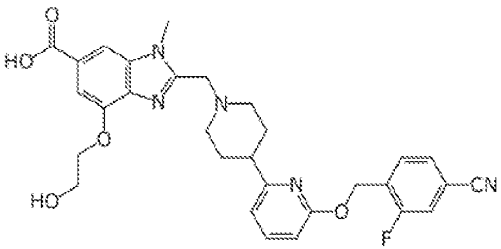
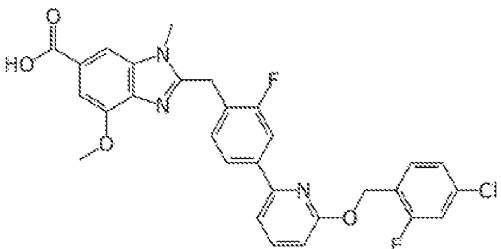
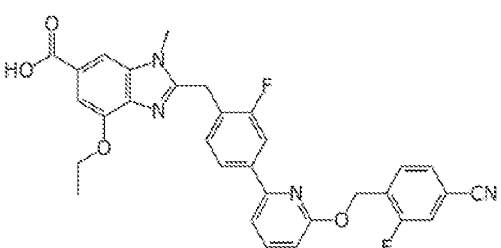
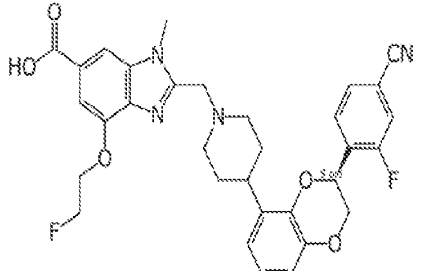
5-271	(R)-2-((4-(2-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-272	2-((4-(6-((4-Chloro-2,5-difluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-273	4-(((6-(1-((4-ethoxy-1-methyl-6-(1H-tetrazol-5-yl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile	
5-274	(S)-2-((4-(2-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

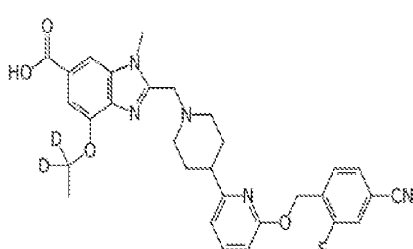
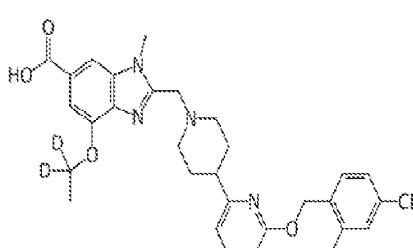
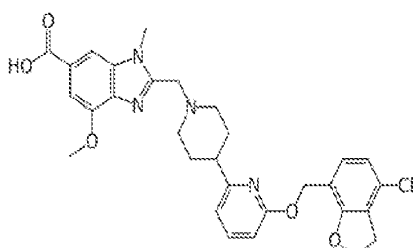
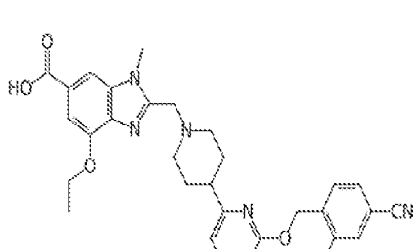
5-275	7-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-6-methyl-6H-[1,3]dioxolo[4',5':3,4]benzo[1,2-d]imidazole-4-carboxylic acid	
5-276	(R)-2-((4-(2-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-277	(S)-2-((4-(2-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-278	(R)-2-((4-(2-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-279	(S)-2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-(oxetan-2-ylmethyl)-6-(1H-tetrazol-5-yl)-1H-benzo[d]imidazole	
5-280	2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-N,1-dimethyl-1H-benzo[d]imidazole-6-carboxamide	
5-281	5-(2-((4-(3-((4-Chloro-2-fluorobenzyl)oxy)phenyl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazol-6-yl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide	
5-282	2-(4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

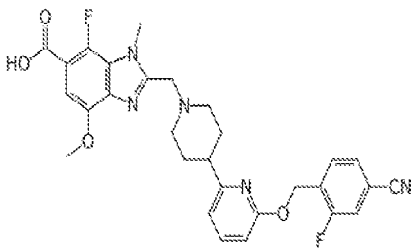
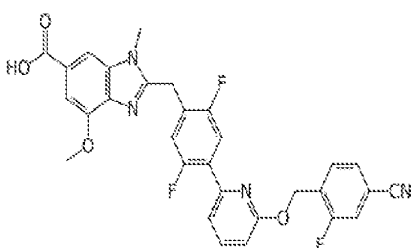
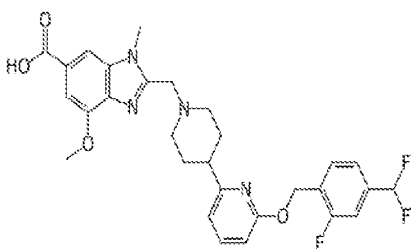
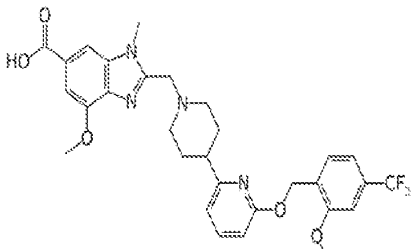
5-283	2-((4-(6-((4-Cyano-2,3-dihydrobenzofuran-7-yl)methoxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-284	2-((4-(3-((4-Chloro-2-fluorobenzyl)oxy)phenyl)piperidin-1-yl)methyl)-4-(ethoxy-1,1-d2)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-285	2-((4-(6-((4-Cyano-2-fluorophenyl)methoxy-d2)pyridin-2-yl)piperidin-1-yl)methyl)-4-(ethoxy-1,1-d2)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-286	2-((4-(6-((4-Chloro-2-fluorophenyl)methoxy-d2)pyridin-2-yl)piperidin-1-yl)methyl)-4-(ethoxy-1,1-d2)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

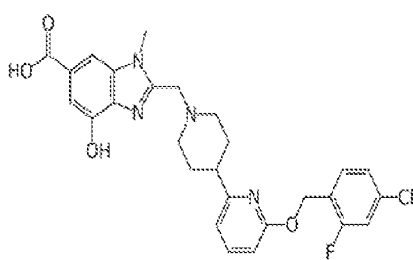
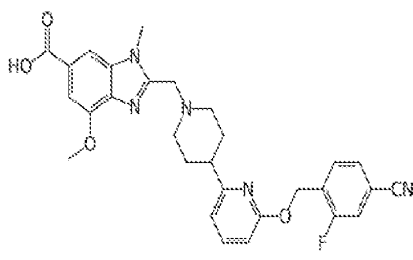
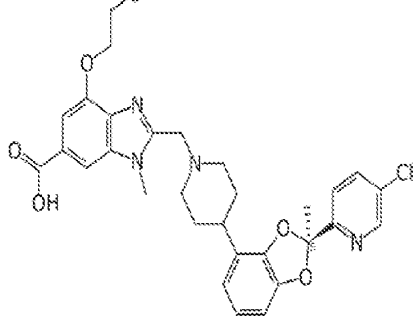
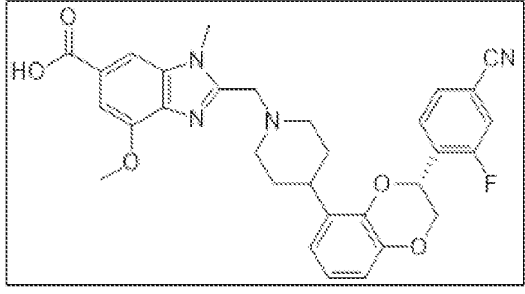
5-287	(S)-2-((4-(3-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-288	(R)-2-((4-(3-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-289	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-3-methyl-7,8-dihydro-3H-[1,4]dioxino[2',3':3,4]benzo[1,2-d]imidazole-5-carboxylic acid	
5-290	2-((4-(((6-((4-Cyano-2-fluorophenoxy)methyl)pyridin-2-yl)oxy)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-291	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(2-hydroxyethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-292	2-(4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)-2-fluorobenzyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-293	2-(4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-fluorobenzyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-294	(S)-2-((4-(3-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(2-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

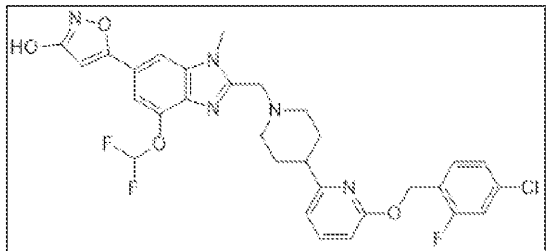
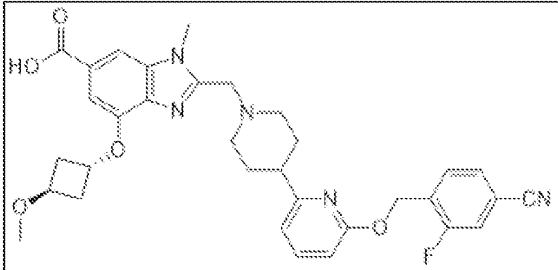
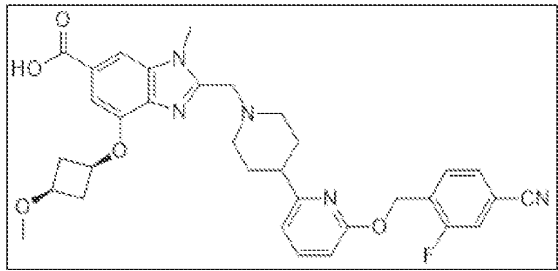
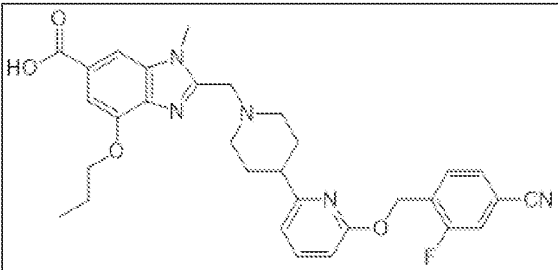
5-295	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(ethoxy-1,1-d ₂)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-296	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(ethoxy-1,1-d ₂)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-297	2-((4-(6-((4-Chloro-2,3-dihydrobenzofuran-7-yl)methoxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-298	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

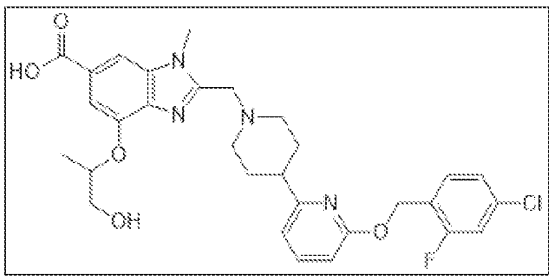
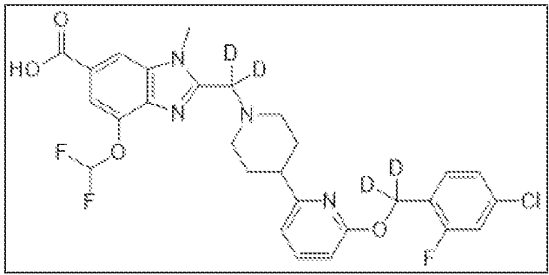
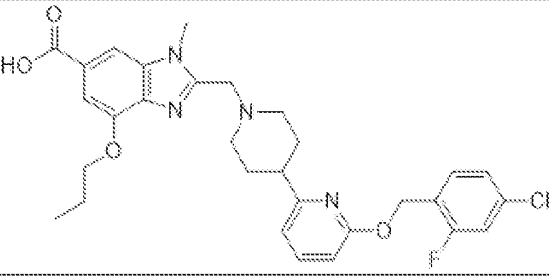
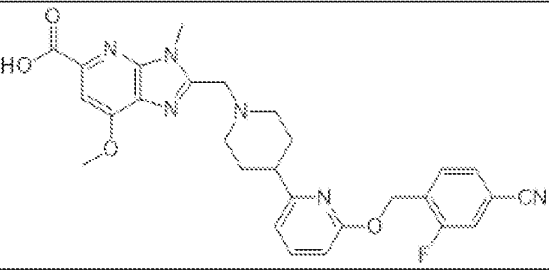
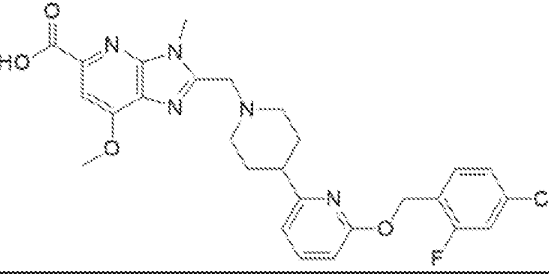
5-299	(S)-2-((4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(2-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-300	(R)-2-((4-(2-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-301	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-5-fluoro-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-302	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-fluoro-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

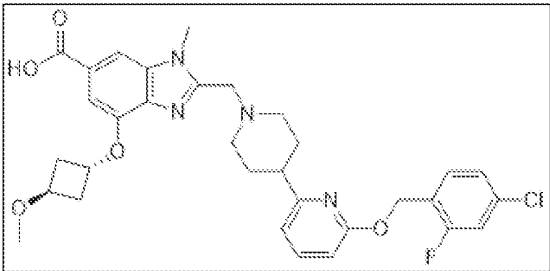
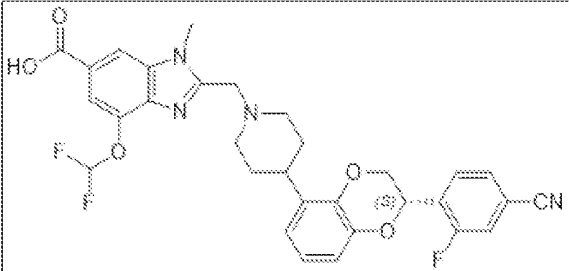
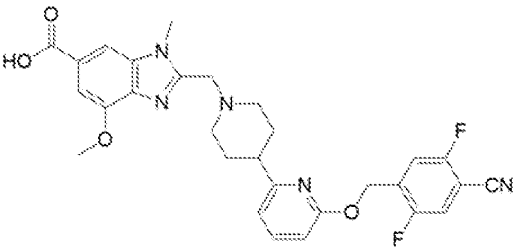
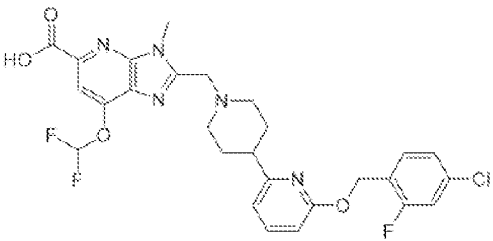
5-303	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-fluoro-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-304	2-(4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-305	2-((4-(6-((4-(Difluoromethyl)-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-306	4-Methoxy-2-((4-(6-((2-methoxy-4-(trifluoromethyl)benzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

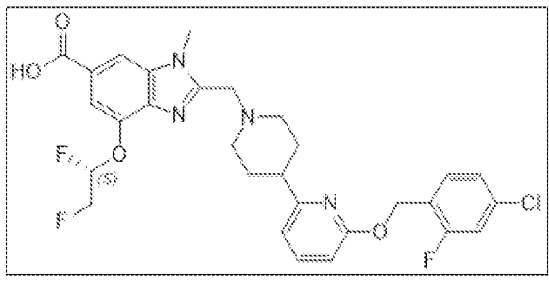
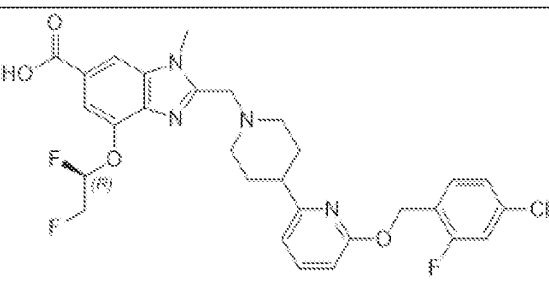
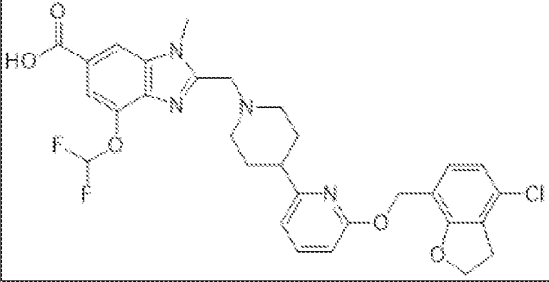
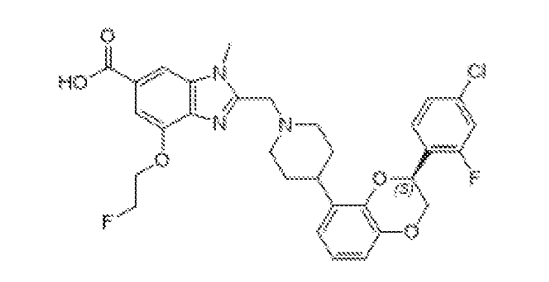
5-307	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-hydroxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-308	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-309	(S)-2-((4-(2-(5-Chloropyridin-2-yl)-2-methylbenzo[d][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-4-(2-methoxyethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-310	(R)-2-((4-(3-(4-cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

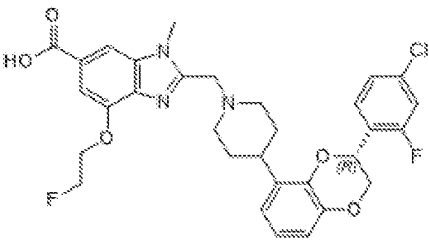
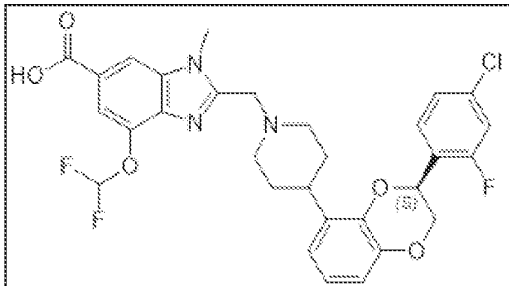
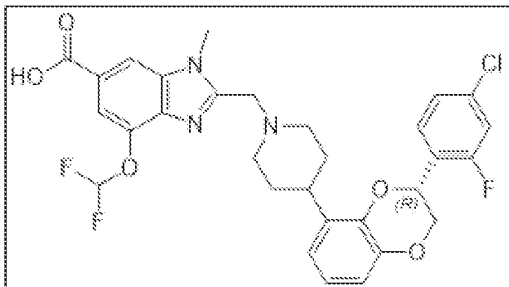
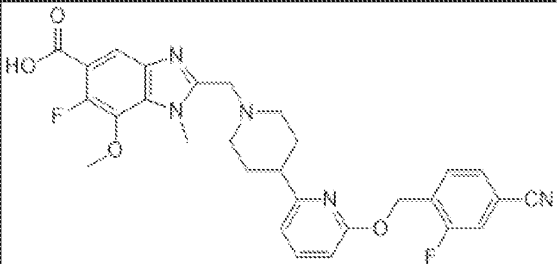
5-311	2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-3-methyl-7,8-dihydro-3H-[1,4]dioxino[2',3':3,4]benzo[1,2-d]imidazole-5-carboxylic acid	
5-312	(R)-2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-313	(S)-2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-314	(S)-2-((4-(3-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-315	(R)-2-((4-(3-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(2-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-316	5-(2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazol-6-yl)isoxazol-3-ol	
5-317	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1r,3r)-3-methoxycyclobutoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-318	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1s,3s)-3-methoxycyclobutoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-319	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-methyl-4-propoxy-1H-benzo[d]imidazole-6-carboxylic acid	

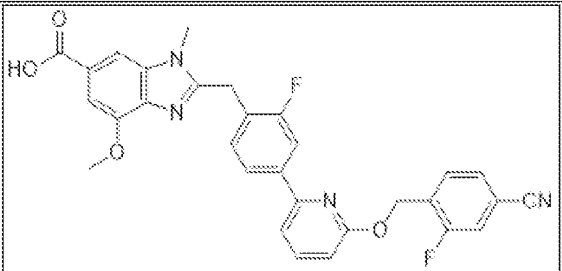
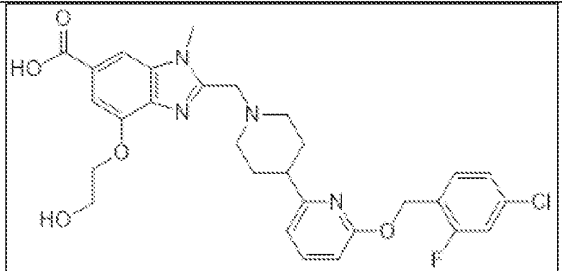
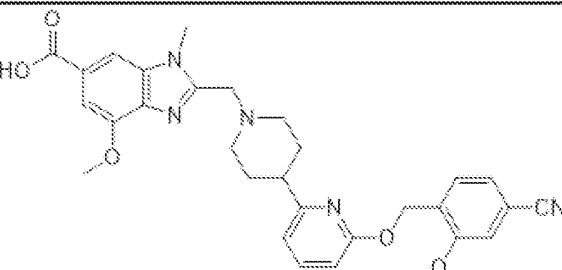
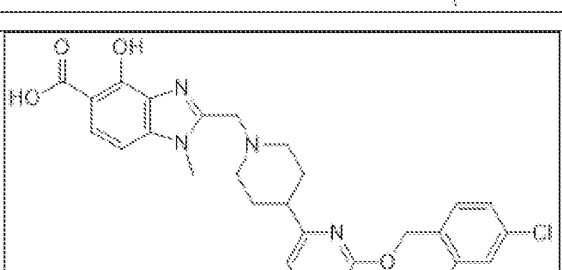
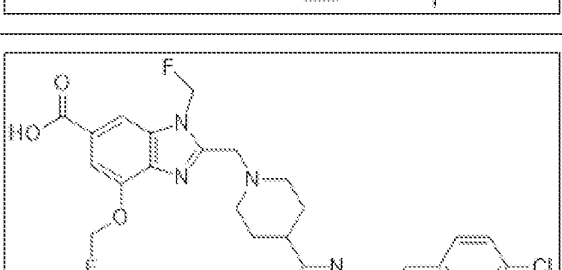
5-320	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1-hydroxypropan-2-yl)oxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-321	2-((4-(6-((4-Chloro-2-fluorophenyl)methoxy-d2)pyridin-2-yl)piperidin-1-yl)methyl-d2)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-322	2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-methyl-4-propoxy-1H-benzo[d]imidazole-6-carboxylic acid	
5-323	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylic acid	
5-324	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-methoxy-3-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylic acid	

5-325	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1r,3r)-3-methoxycyclobutoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-326	(S)-2-((4-(2-(4-Cyano-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-327	2-((4-(6-((4-Cyano-2,5-difluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-328	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-(difluoromethoxy)-3-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylic acid	

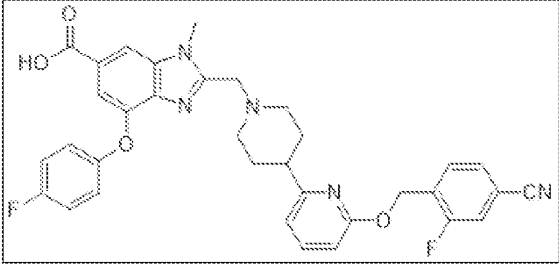
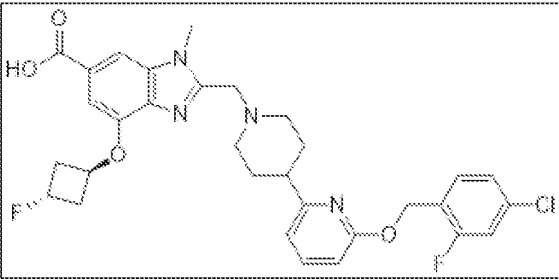
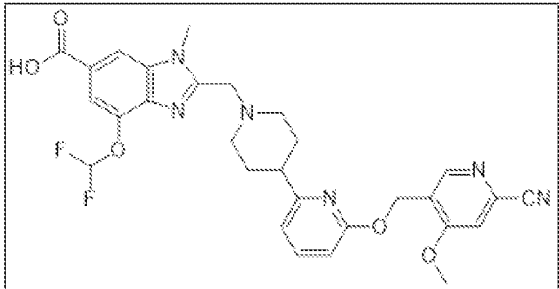
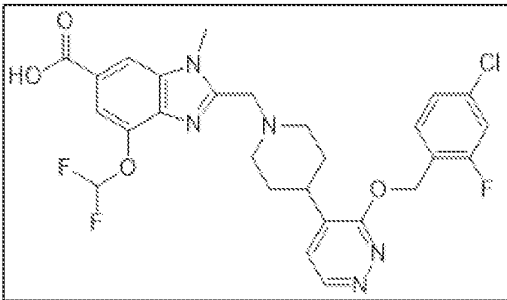
5-329	(S)-2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1,2-difluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-330	(R)-2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1,2-difluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-331	2-((4-(6-((4-Chloro-2,3-dihydrobenzofuran-7-yl)methoxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-332	(S)-2-((4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(2-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-333	(R)-2-((4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(2-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-334	(S)-2-((4-(3-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-335	(R)-2-((4-(3-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxin-5-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-336	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-6-fluoro-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid	

5-337	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-5-fluoro-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-338	2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-6-fluoro-7-methoxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid	
5-339	2-((4-(3-((4-Cyano-2-fluorobenzyl)oxy)-4-fluorophenyl)piperidin-1-yl)methyl)-7-fluoro-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-340	2-((4-(3-((4-Chloro-2-fluorobenzyl)oxy)-4-fluorophenyl)piperidin-1-yl)methyl)-7-fluoro-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-341	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-hydroxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

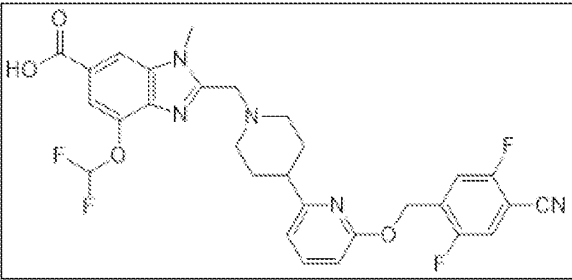
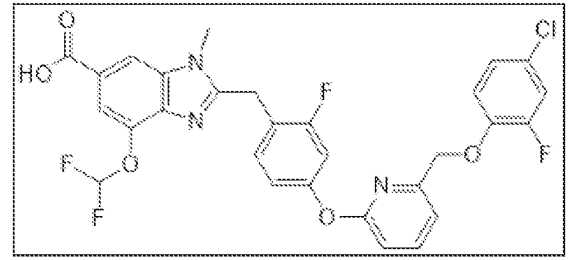
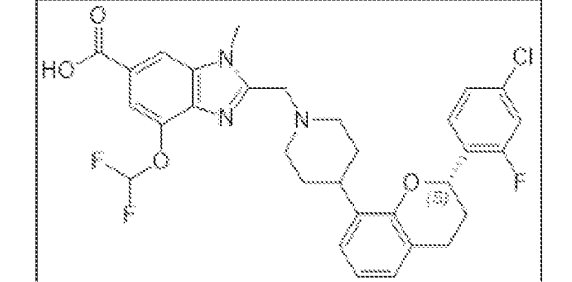
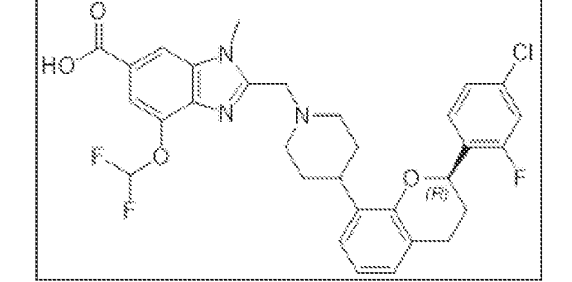
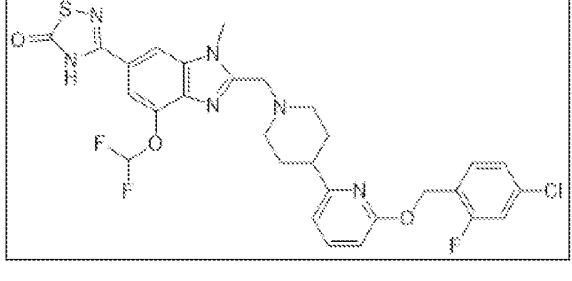
5-342	2-(4-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-fluorobenzyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-343	2-(4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(2-hydroxyethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-344	2-(4-(6-((4-Cyano-2-methoxybenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-345	2-(4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-hydroxy-1-methyl-1H-benzo[d]imidazole-5-carboxylic acid	
5-346	2-(4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(fluoromethoxy)-1-(fluoromethyl)-1H-benzo[d]imidazole-6-carboxylic acid	

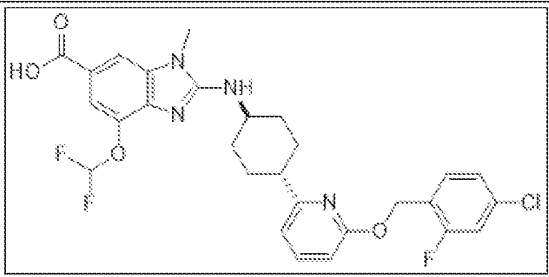
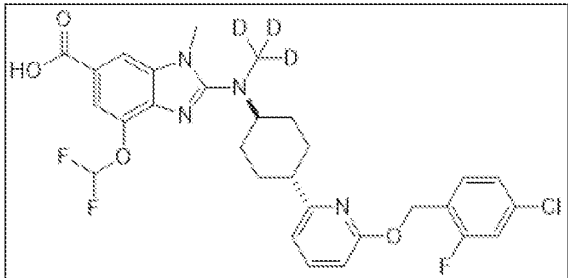
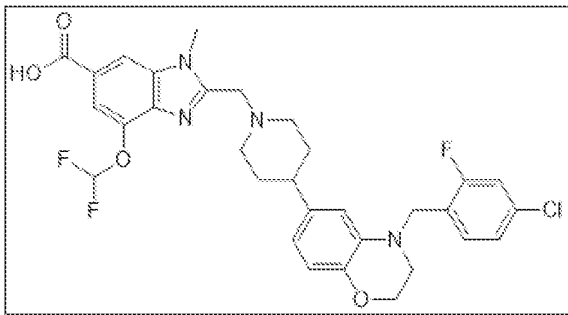
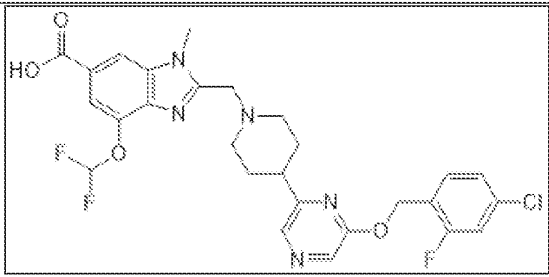
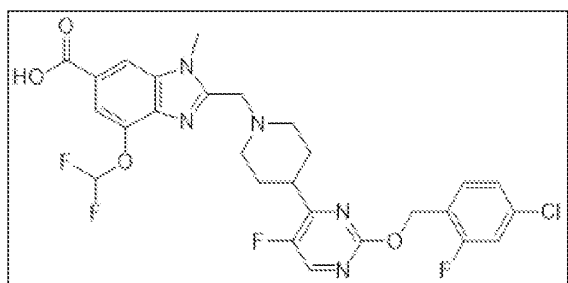
5-347	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-(fluoromethoxy)-1-(fluoromethyl)-1H-benzo[d]imidazole-5-carboxylic acid	
5-348	2-((4-(6-((4-Chloro-2-methoxybenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-349	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(methoxy-d3)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-350	2-((4-(6-((6-Cyano-4-fluoropyridin-3-yl)methoxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-351	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1-fluoropropoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-352	2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(4-fluorophenoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-353	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1r,3r)-3-fluorocyclobutoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-354	2-((4-(2-((4-Chloro-2-fluorobenzyl)oxy)-5-fluoropyrimidin-4-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-355	2-((4-(3-((4-Chloro-2-fluorobenzyl)oxy)pyridazin-4-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

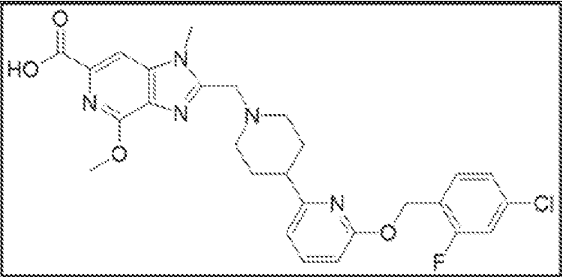
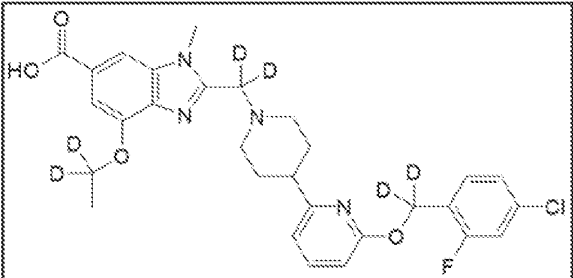
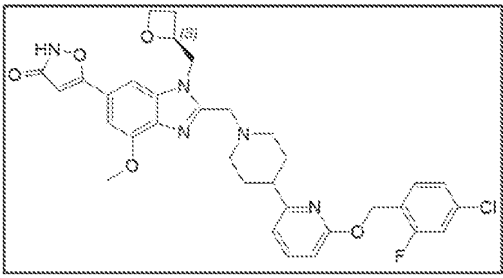
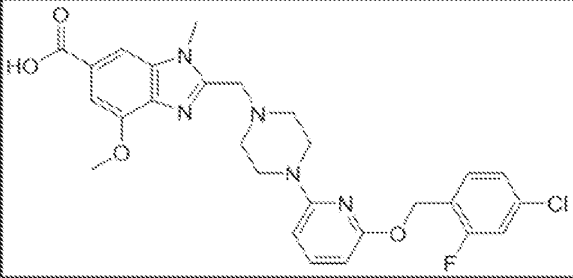
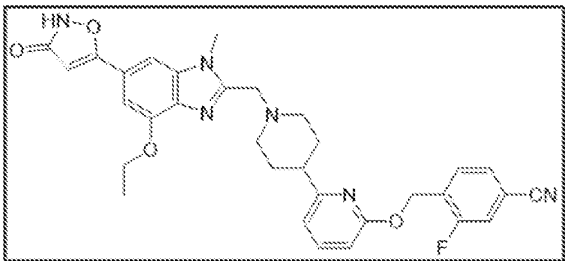
5-356	2-((4-(4-((4-Chloro-2-fluorobenzyl)oxy)-5-fluoropyrimidin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-357	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(cyclopropylmethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-358	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-ethoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-359	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-360	(S)-2-((4-(6-((4-chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

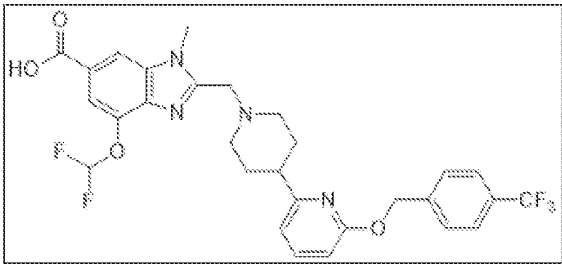
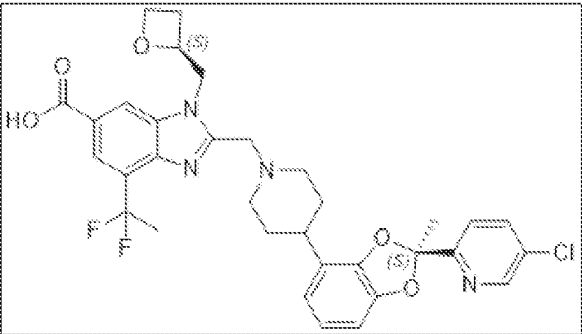
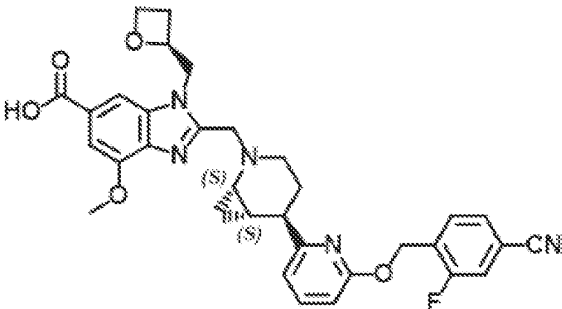
5-361	(R)-2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(1-fluoroethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-362	2-((3-(6-((4-Chloro-2-fluorophenoxy)methyl)pyridin-2-yl)pyrrolidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-363	2-(((1r,4r)-4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)cyclohexyl)(methyl)amino)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-364	2-((4-(2-((4-Chloro-2-fluorobenzyl)oxy)pyridin-3-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-365	2-((4-(6-((4-Cyclopropyl-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-366	2-((4-(6-((4-Cyano-2,5-difluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-367	2-(4-((6-((4-chloro-2-fluorophenoxy)methyl)pyridin-2-yl)oxy)-2-fluorobenzyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-368	S)-2-((4-(2-(4-Chloro-2-fluorophenyl)chroman-8-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-369	(R)-2-((4-(2-(4-Chloro-2-fluorophenyl)chroman-8-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-370	3-(2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazol-6-yl)-1,2,4-thiadiazol-5(4H)-one	

5-371	2-(((1r,4r)-4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)cyclohexyl)amino)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-372	2-(((1r,4r)-4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)cyclohexyl)(methyl-d3)amino)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-373	2-((4-(4-(4-Chloro-2-fluorobenzyl)-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-374	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyrazin-2-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-375	2-((4-(2-((4-Chloro-2-fluorobenzyl)oxy)-5-fluoropyrimidin-4-yl)piperidin-1-yl)methyl)-4-(difluoromethoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-376	(S)-2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-hydroxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-5-carboxylic acid	
5-377	(S)-2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-7-hydroxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid	
5-378	(S)-2-((4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1-(oxetan-2-ylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid	
5-379	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-((1s,3s)-3-fluorocyclobutoxy)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	

5-380	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-methyl-1H-imidazo[4,5-c]pyridine-6-carboxylic acid	
5-381	2-((4-(6-((4-Chloro-2-fluorophenyl)methoxy-d2)pyridin-2-yl)piperidin-1-yl)methyl-d2)-4-(ethoxy-1,1-d2)-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-382	(S)-5-(2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-4-methoxy-1-(oxetan-2-yl)methyl)-1H-benzo[d]imidazol-6-yl)isoxazol-3(2H)-one	
5-383	2-((4-(6-((4-Chloro-2-fluorobenzyl)oxy)pyridin-2-yl)piperazin-1-yl)methyl)-4-methoxy-1-methyl-1H-benzo[d]imidazole-6-carboxylic acid	
5-384	4-(((6-(1-((4-Ethoxy-1-methyl-6-(3-oxo-2,3-dihydroisoxazol-5-yl)-1H-benzo[d]imidazol-2-yl)methyl)piperidin-4-yl)pyridin-2-yl)oxy)methyl)-3-fluorobenzonitrile	

5-385	4-(Difluoromethoxy)-1-methyl-2-((4-(6-((4-(trifluoromethyl)benzyl)oxy)pyridin-2-yl)piperidin-1-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid	
5-386	2-((4-((S)-2-(5-Chloropyridin-2-yl)-2-methylbenzo[d][1,3]dioxol-4-yl)piperidin-1-yl)methyl)-4-(1,1-difluoroethyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid	
5-387	2-(((1S,5R,6S)-5-(6-((4-cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2-azabicyclo[4.1.0]heptan-2-yl)methyl)-4-methoxy-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid	

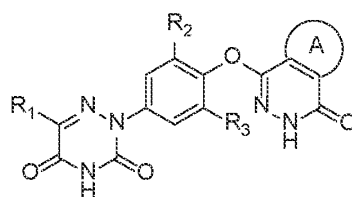
THRβ Agonists

[0205] In some embodiments, the THRβ agonist administered to the patient in need thereof is resmetirom (MGL-3196, Madrigal Therapeutics). In some embodiments, the THRβ agonist administered to the patient in need thereof is VK2809 (Viking Therapeutics). In some embodiments, the THRβ agonist administered to the patient in need thereof is sobetirome. In some embodiments, the THRβ agonist administered to the patient in need thereof is eprotrirome. In some embodiments, the THRβ agonist administered to the patient in need thereof is ALG-055009 (Aligo). In some embodiments, the THRβ agonist administered to the patient in need

thereof is CNPT-101101. In some embodiments, the THR β agonist administered to the patient in need thereof is CNPT-101207. In some embodiments, the THR β agonist administered to the patient in need thereof is ASC41 (Ascletis).

[0206] Suitable THR β agonists that can be used in accordance with the methods described herein are also described in, e.g., PCT Pub. Nos. WO/2020/123827, WO/2020/041741, WO/2020/077123, WO/2021/041237, WO/2021/050945, or WO/2022/187403, incorporated herein by reference.

[0207] In some embodiments, the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

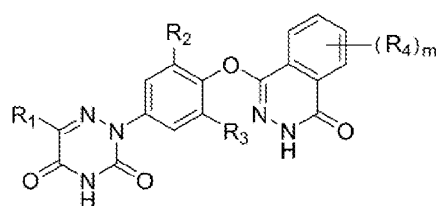
R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br, or a pharmaceutically acceptable salt thereof.

[0208] In some embodiments, the THR β agonist administered to the patient in need thereof is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

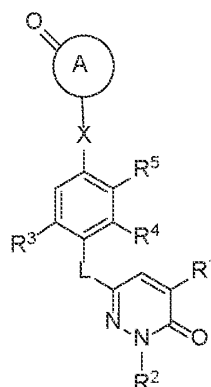
the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

[0209] In some embodiments, wherein R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl; and m is an integer from the range 1 to 3.

[0210] In some embodiments, wherein R₁ is selected from the group consisting of hydrogen, cyano, and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy; and the halogen atoms are selected from the group consisting of F, Cl and Br.

[0211] In some embodiments, the THRβ agonist administered to the patient in need thereof is a compound of Formula (II-2)



(II-2)

or a pharmaceutically acceptable salt thereof, wherein:

ring A together with the carbonyl (keto) group within the ring form a 5 membered heterocycle containing 1-3 ring heteroatoms selected from the group consisting of N, O, and S, wherein the heterocycle is optionally substituted with 1-2 C₁-C₃ alkyl or C₃-C₄ cycloalkyl groups, and wherein the carbonyl (keto) group is not adjacent to the atom attached to X;

R¹ is C₁-C₄ alkyl optionally substituted with 1-5 halo or hydroxyl groups, C₃-C₅ cycloalkyl, CON(R¹⁰)₂, or NR¹⁰COR¹⁰;

R² is H or C₁-C₃ alkyl;

L is O, CH₂, S, SO, SO₂, CO, CHF, CF₂, C(R¹¹)CN, CHR¹¹, or C(R¹¹)R¹¹;

R³ and R⁴ are independently Cl, Br, methyl, or ethyl;

R⁵ is H, halo, C₁-C₄ alkyl, or C₃-C₄ cycloalkyl;

or R⁵ together with R⁴ and the intervening atoms form a 5-7 membered cycloalkyl or a 5-7 membered heterocycle containing 1-2 ring heteroatoms;

X is absent, O, NR¹², C(O)NR¹², NR¹²C(O), CR¹²R¹², OCR¹²R¹², CR¹²R¹²O, NR¹²CR¹²R¹², CR¹²R¹²NR¹², SO₂NR¹², or NR¹²SO₂;

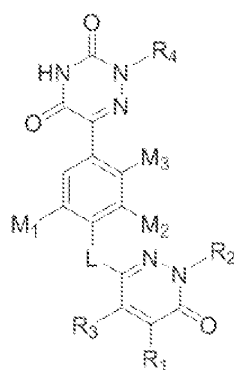
each R¹⁰ is independently C₁-C₃ alkyl or H;

each R¹¹ is independently C₁-C₂ alkyl optionally substituted with 1-5 halo,

or two R¹¹ groups together with the carbon atom to which they are attached form a cyclopropyl or cyclobutyl ring; and

each R¹² is independently H or methyl.

[0212] In some embodiments, the THRβ agonist administered to the patient in need thereof is a compound of Formula (II-3)

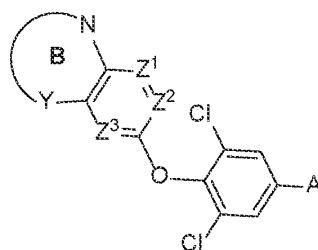


(II-3)

wherein:

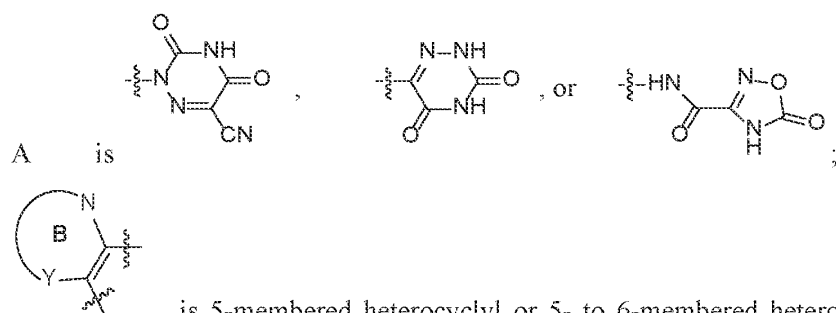
R₁ is substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, -C(O)N(R₇)(R₈), -N(R₉)C(O)(R₁₀), or halo;

- R₂ is H, substituted or unsubstituted C₁-C₆ alkyl, or substituted or unsubstituted C₃-C₆ cycloalkyl;
- R₃ is H or halo;
- R₄ is H, or substituted or unsubstituted linear C₁-C₃ alkyl;
- L is -O-, -S-, -S(O)-, -S(O)₂-, -C(O)-, or -C(R₅)(R₆)-;
- R₅ and R₆ are independently H, halo, -CN, or substituted or unsubstituted C₁-C₆ alkyl, or R₅ and R₆ are taken together with the carbon atom to which they are attached to form a substituted or unsubstituted C₃-C₆ cycloalkyl;
- R₇ and R₈ are independently H, or substituted or unsubstituted C₁-C₆ alkyl, or R₇ and R₈ are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted 3- to 7-membered heterocycloalkyl;
- R₉ is H, substituted or unsubstituted C₁-C₆ alkyl, or substituted or unsubstituted C₃-C₆ cycloalkyl;
- R₁₀ is substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, -N(R₇)(R₈), or -O(R₁₁);
- R₁₁ is substituted or unsubstituted C₁-C₆ alkyl, or substituted or unsubstituted C₃-C₆ cycloalkyl;
- M₁ and M₂ are independently halo, or substituted or unsubstituted C₁-C₆ alkyl; and
- M₃ is H, halo, or substituted or unsubstituted C₁-C₆ alkyl, or M₃ is taken together with M₂ and the carbon atoms to which they are attached to form a 5- to 7-membered ring containing 0, 1, or 2 heteroatoms selected from the group consisting of N, O, and S, or a pharmaceutically acceptable salt thereof.
- [0213]** In some embodiments, the THRβ agonist administered to the patient in need thereof is a compound of Formula (II-4)



(II-4)

or a tautomer or an N-oxide thereof, or an isotopomer of each thereof, or a stereoisomer of the aforesaid, or a pharmaceutically acceptable salt of each of the foregoing, or a solvate of each of the preceding, wherein:



wherein each heteroatom of the heterocyclyl or heteroaryl is bound to one R¹ group if needed to complete the valency of the heteroatom, and

wherein each carbon atom of the heterocyclyl or heteroaryl is bound to one R² group if needed to complete the valency of the carbon atom, provided that no

more than one R² group is needed to complete the valency of each carbon atom;

Z¹, Z², and Z³ are independently N or CH;

Y is N or C;

each R¹ is independently H, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl,

wherein each C₁-C₆ alkyl or C₃-C₆ cycloalkyl group is optionally substituted by 1-5 R³ groups;

each R² is independently H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -O(C₁-C₆ alkyl), -O(C₃-C₆ cycloalkyl), hydroxyl, or oxo,

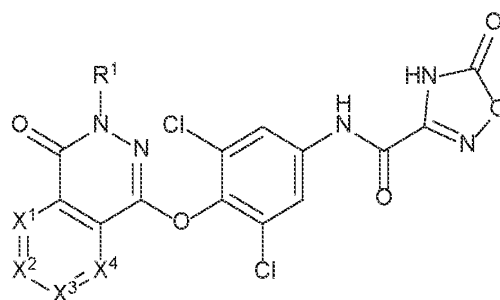
wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -O(C₁-C₆ alkyl), or -O(C₃-C₆ cycloalkyl) group is optionally substituted by 1-5 R³ groups;

or R¹ and R² are taken together to form a 5- to 6-membered heteroaryl or 5- to 7-membered heterocyclyl;

or two R² groups are taken together to form a 5- to 6-membered heteroaryl, 5- to 7-membered heterocyclyl, C₅-C₇ cycloalkyl, or C₆ aryl;

each R³ is independently halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkyl-OH, -NH₂, -CN, or hydroxyl.

[0214] In some embodiments, the THRβ agonist administered to the patient in need thereof is a compound of Formula (II-5)



(II-5)

or a tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

R^1 is H or $-CH_3$;

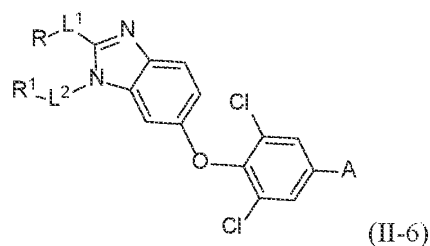
X^1 , X^2 , X^3 , and X^4 are each independently CR^2 or N, wherein at least two of X^1 , X^2 , X^3 , and X^4 are CR^2 ;

each R^2 is independently H, halo, C_1 - C_6 alkyl, C_1 - C_6 alkyl-CN, C_1 - C_6 alkyl-OH, C_1 - C_6 haloalkyl, -CN, hydroxyl, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, $-O(C_1-C_6 \text{ alkyl})$, C_3 - C_6 cycloalkyl, 5- to 6-membered heteroaryl, 5- to 7-membered heterocyclyl, or C_6 aryl, wherein each C_1 - C_6 alkyl, $-O(C_1-C_6 \text{ alkyl})$, C_3 - C_6 cycloalkyl, 5- to 6-membered heteroaryl, 5- to 7-membered heterocyclyl, or C_6 aryl is optionally substituted by 1-5 R^3 groups;

or two R^2 groups are taken together with the carbon atoms to which they are attached to form a 5- to 6-membered heteroaryl, 5- to 7-membered heterocyclyl, C_5 - C_7 cycloalkyl, or C_6 aryl, each of which is optionally substituted by 1-5 R^3 groups; and

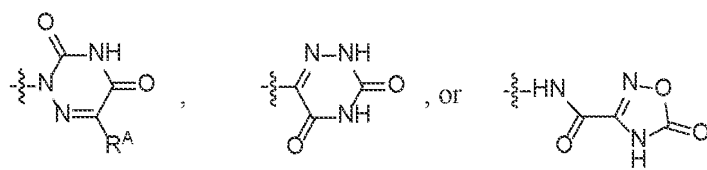
each R^3 is independently C_1 - C_6 alkyl, $-O(C_1-C_6 \text{ alkyl})$, halo, -CN, hydroxyl, $-NH_2$, $-NH(C_1-C_6 \text{ alkyl})$, $-N(C_1-C_6 \text{ alkyl})_2$, or CO_2H .

[0215] In some embodiments, the THR β agonist administered to the patient in need thereof is a compound of Formula (II-6)



(II-6)

or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein:



A is , wherein R^A is H or -CN;

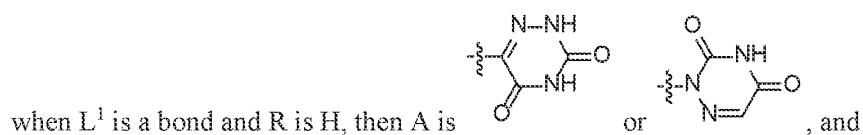
L^1 is a bond, -NR¹-, -O-, -S-, or -S(O)₂-, wherein R¹ is H or C₁-C₆ alkyl;

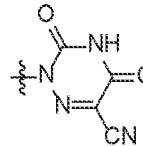
L^2 is a bond or -S(O)₂-;

R¹ is H, C₁-C₆ alkyl, C₆-C₁₀ aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C₃-C₆ cycloalkyl, wherein the C₁-C₆ alkyl, C₆-C₁₀ aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C₃-C₆ cycloalkyl are each independently optionally substituted by 1-5 R² groups;

R is H, C₁-C₆ alkyl, C₆-C₁₀ aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C₃-C₆ cycloalkyl, wherein the C₁-C₆ alkyl, C₆-C₁₀ aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C₃-C₆ cycloalkyl are each independently optionally substituted by 1-5 R² groups; and

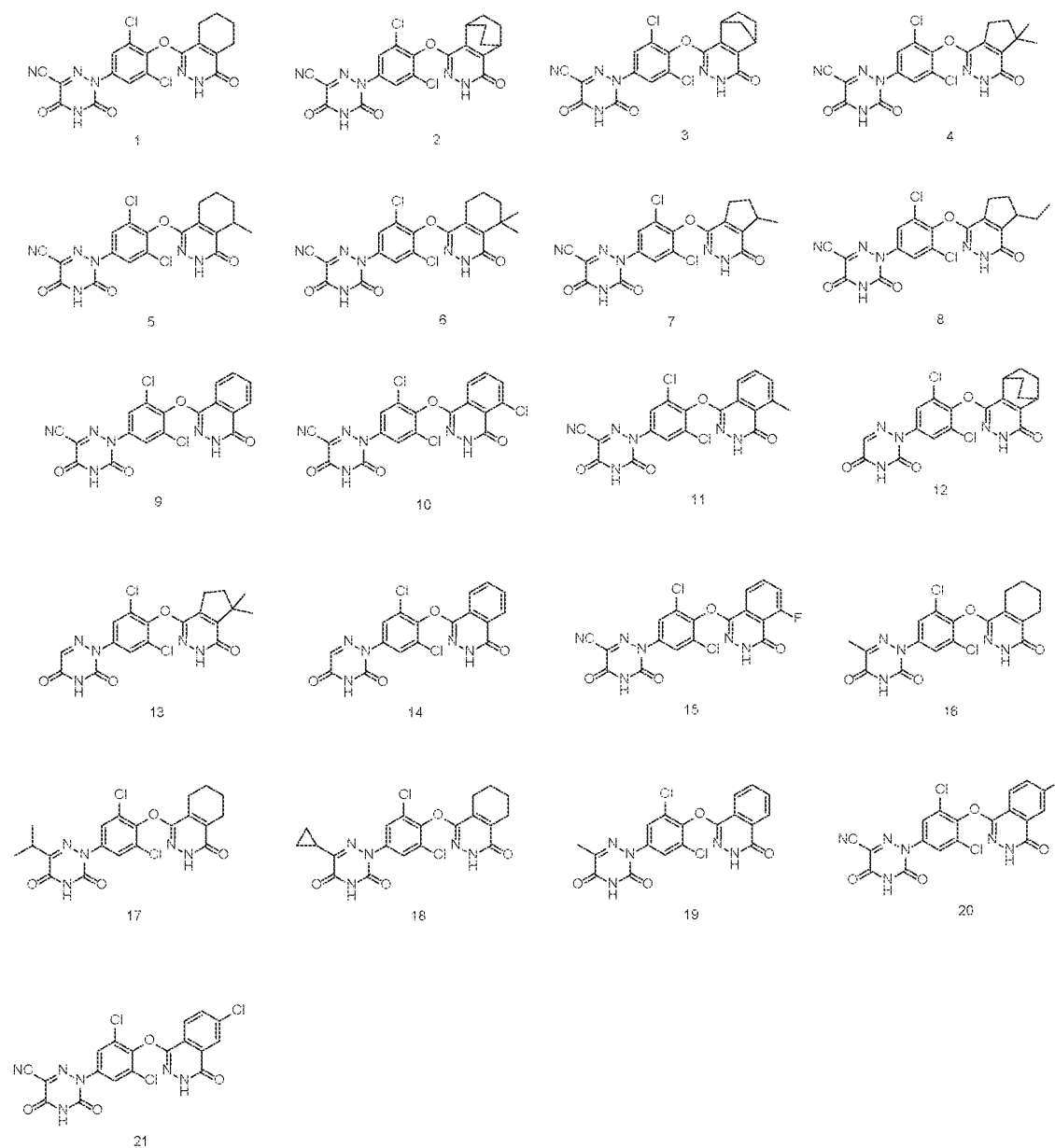
each R² is independently halogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkyl-OH, -NH₂, -CN, or hydroxyl, provided that



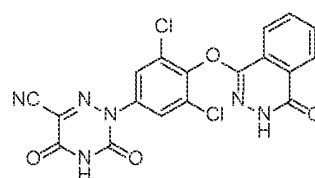
when L^1 is -O-, R is H, and A is , then R¹ is C₂-C₆ alkyl, C₆-C₁₀ aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C₃-C₆ cycloalkyl, wherein the C₂-C₆ alkyl, C₆-C₁₀ aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C₃-C₆ cycloalkyl are each independently optionally substituted by 1-5 R² groups.

[0216] In some embodiments, the THR β agonist is selected from those listed in Table 6 below, or a pharmaceutically acceptable salt thereof:

Table 6



[0217] In some embodiments, the THR β agonist is (Compound 9) which is 2-(3,5-dichloro-4-((4-oxo-3,4-dihydrophthalazin-1-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile, or a pharmaceutically acceptable salt thereof. In some embodiments, the THR β agonist is 2-(3,5-dichloro-4-((4-oxo-3,4-dihydrophthalazin-



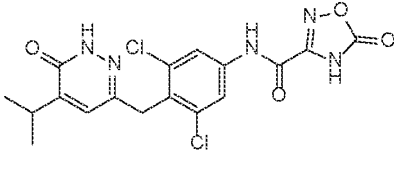
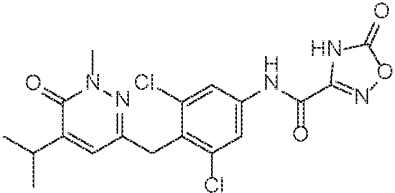
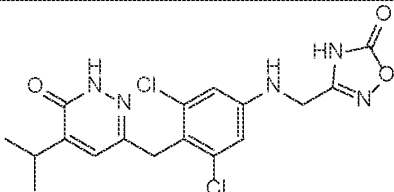
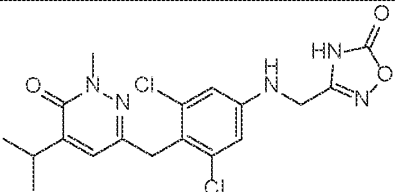
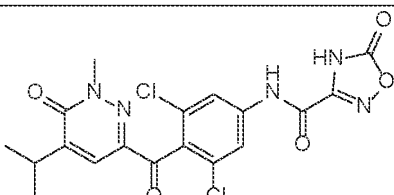
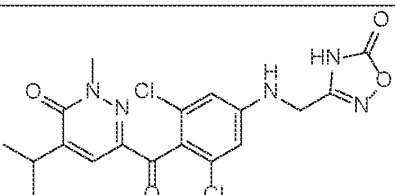
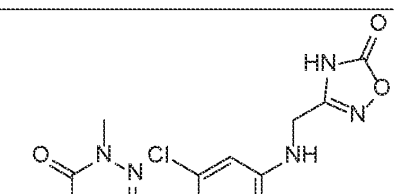
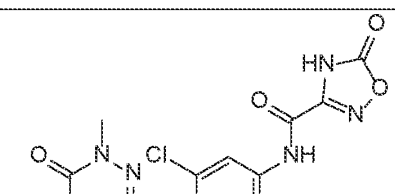
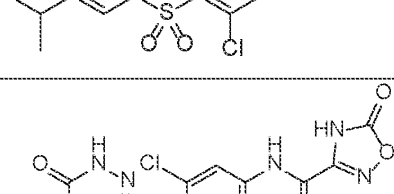
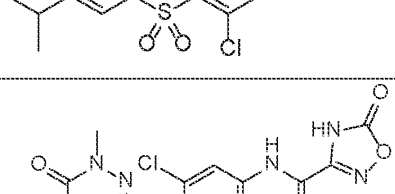
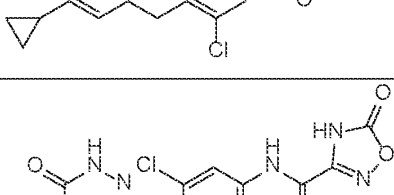
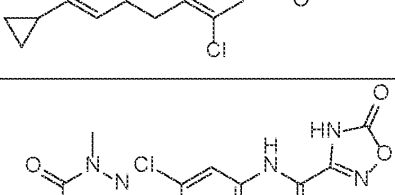
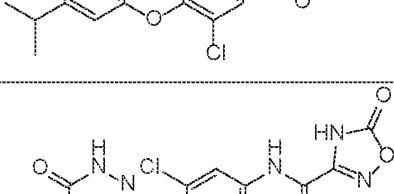
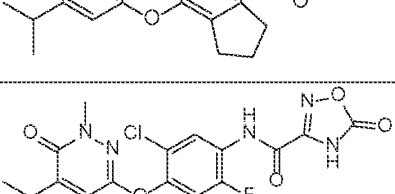
(Compound 9)

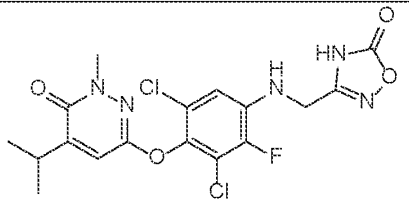
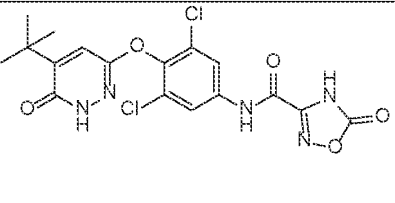
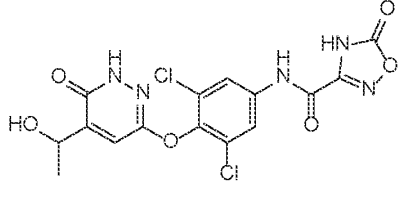
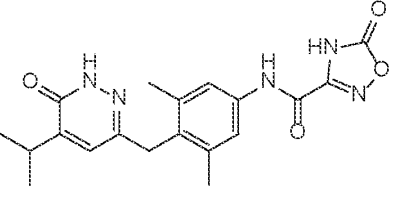
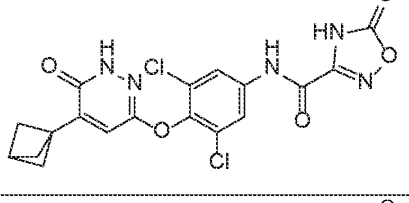
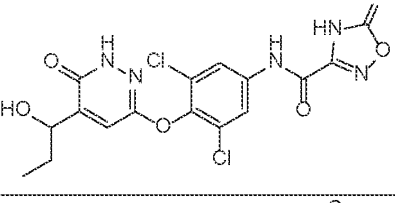
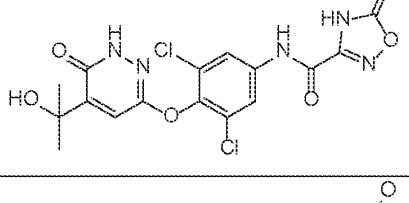
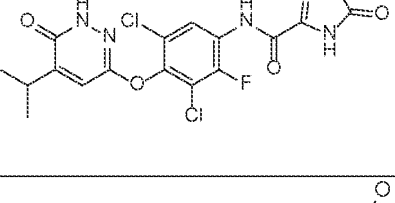
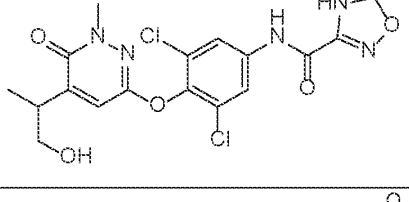
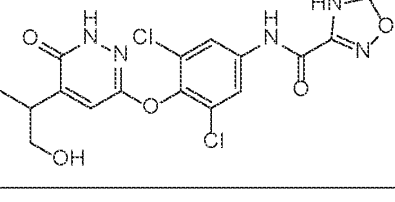
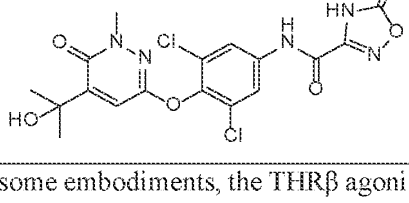
1-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile potassium salt. In some embodiments, the THR β agonist is 2-(3,5-dichloro-4-((4-oxo-3,4-dihydrophthalazin-1-yl)oxy)phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile sodium salt.

[0218] In some embodiments, the THR β agonist is selected from those listed in Table 7 below, or a pharmaceutically acceptable salt thereof.

Table 7

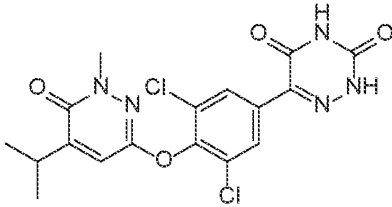
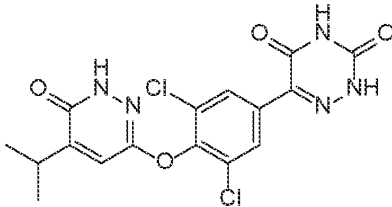
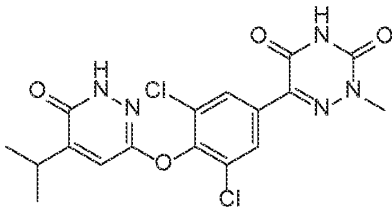
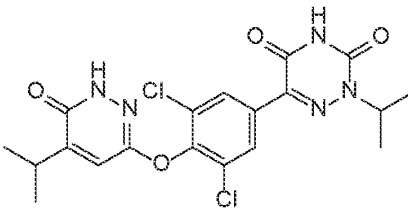
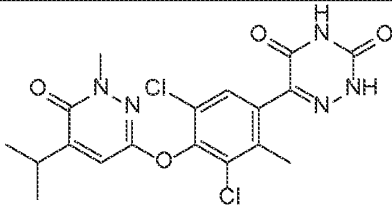
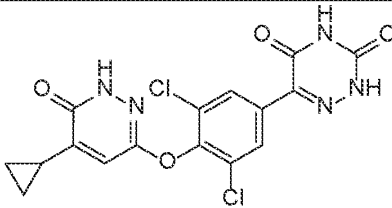
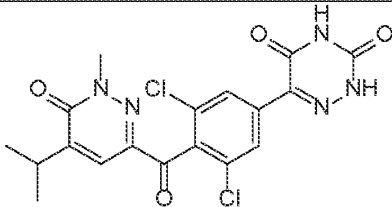
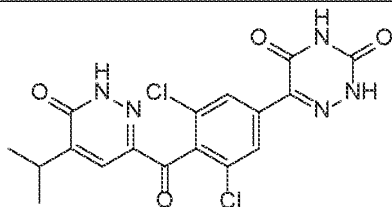
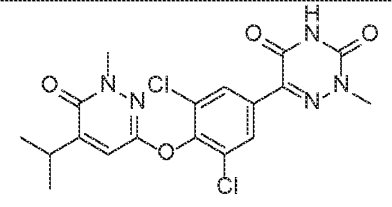
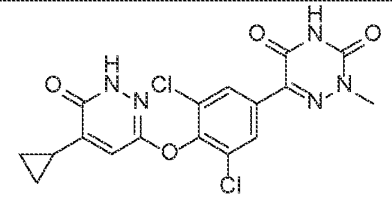
Example	Structure	Example	Structure
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7-5		7-6	
7-7		7-8	
7-9		7-10	
7-11		7-12	

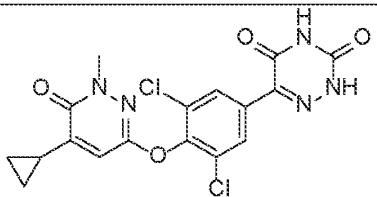
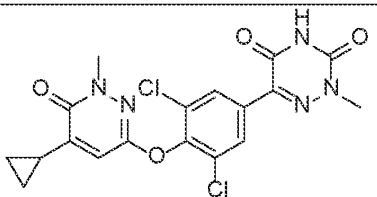
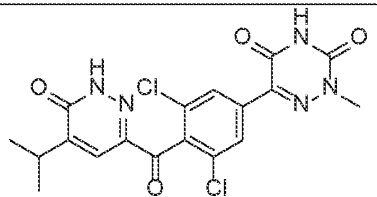
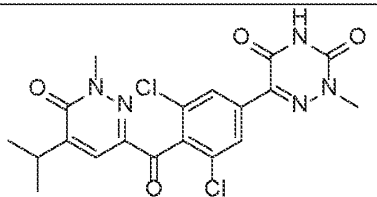
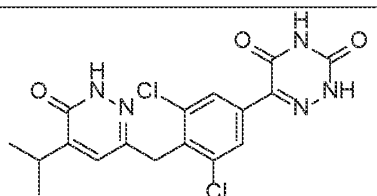
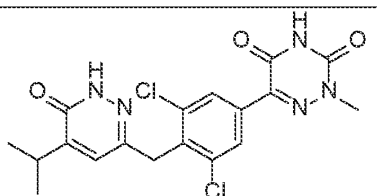
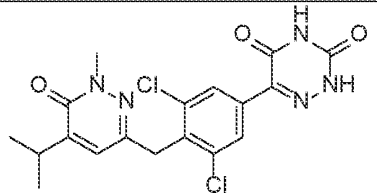
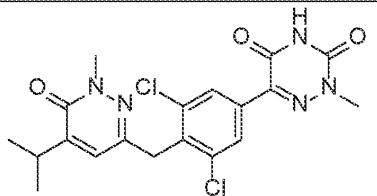
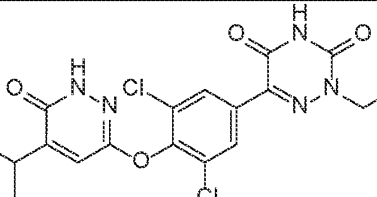
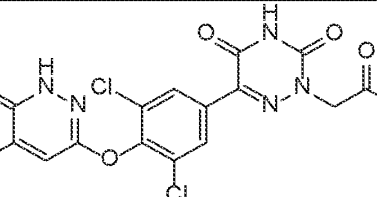
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7-15		7-16	
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7-21		7-22	
7-23		7-24	
7-25		7-26	

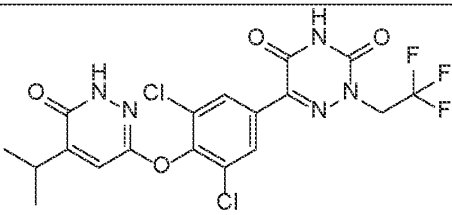
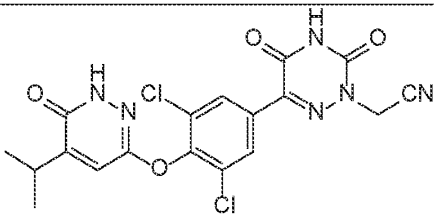
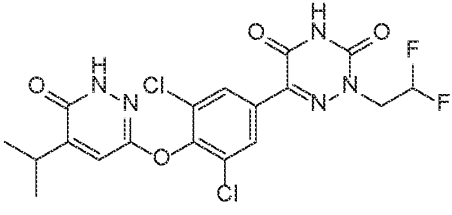
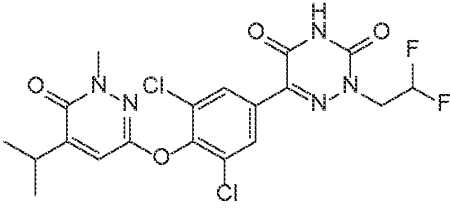
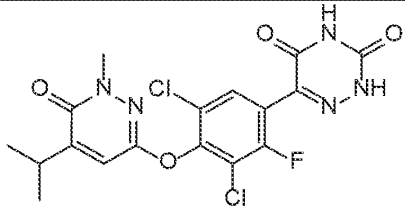
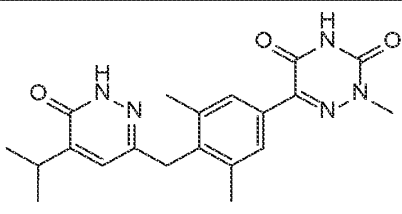
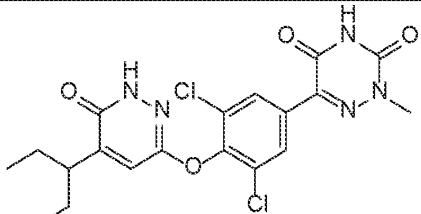
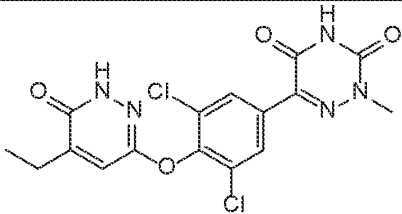
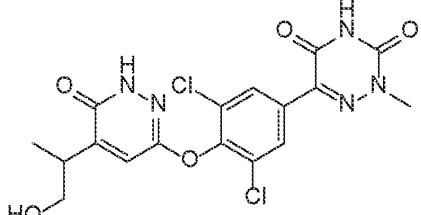
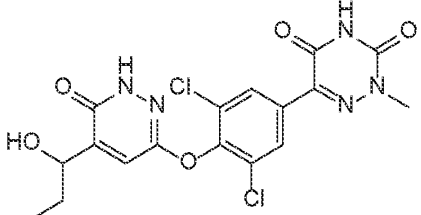
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7-29		7-30	
7-31		7-32	
7-33		7-34	
7-35		7-36	
7-37			

[0219] In some embodiments, the THR β agonist is selected from those listed in Table 8 below, or a pharmaceutically acceptable salt thereof:

Table 8

Compound Structure and Number	Compound Structure and Number
 8-1	 8-2
 8-3	 8-4
 8-5	 8-6
 8-7	 8-8
 8-9	 8-10

Compound Structure and Number	Compound Structure and Number
 8-11	 8-12
 8-13	 8-14
 8-15	 8-16
 8-17	 8-18
 8-19	 8-20

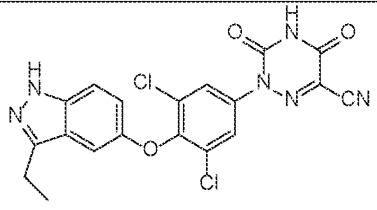
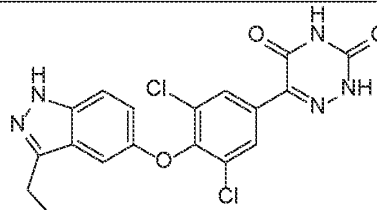
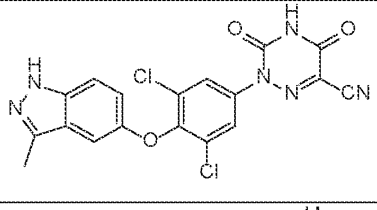
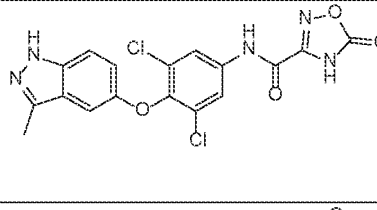
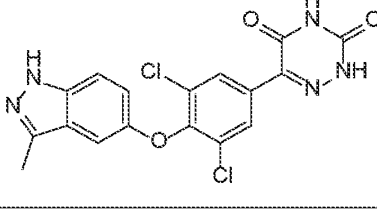
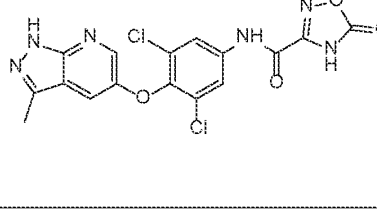
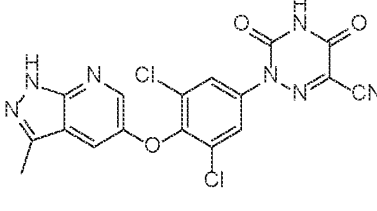
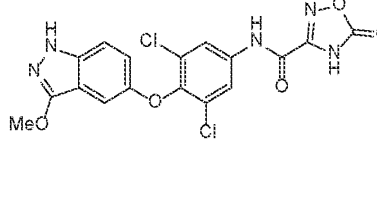
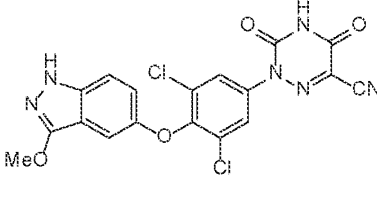
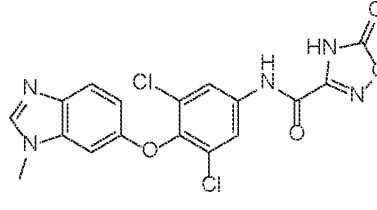
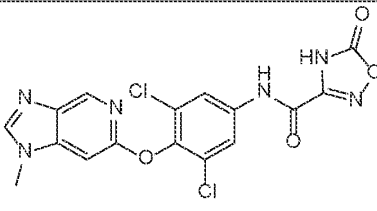
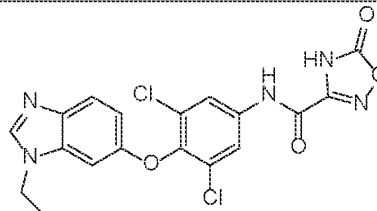
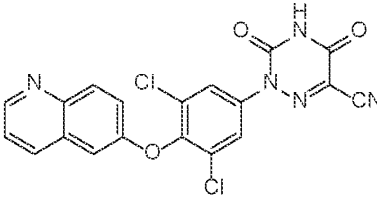
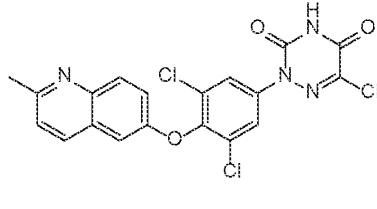
Compound Structure and Number	Compound Structure and Number
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 8-23	 8-24
 8-25	 8-26
 8-27	 8-28
 8-29	 8-30

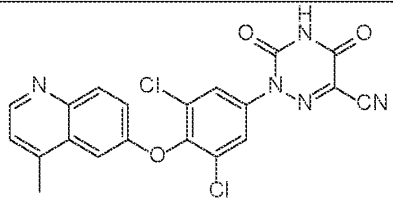
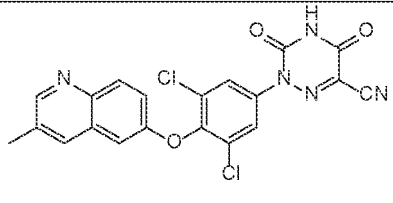
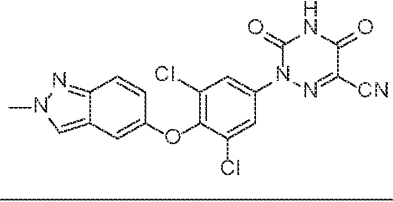
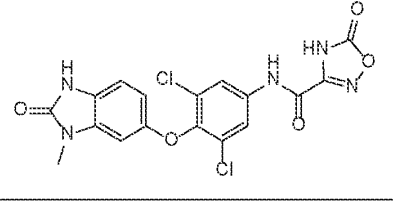
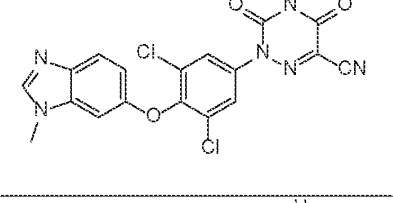
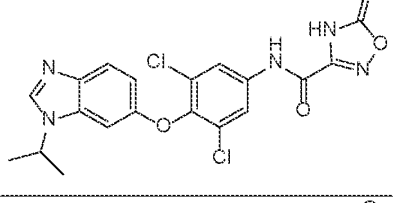
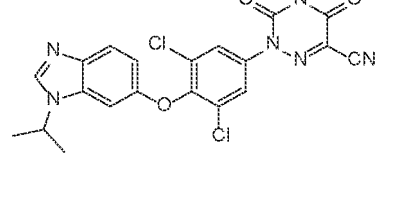
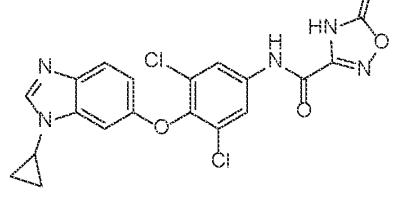
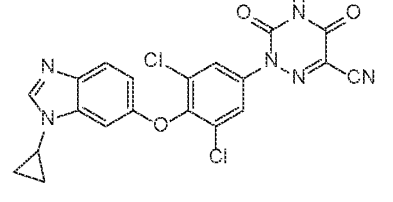
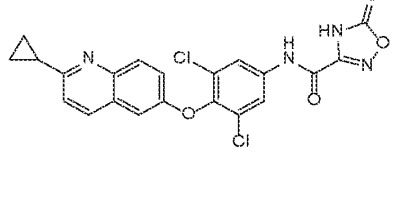
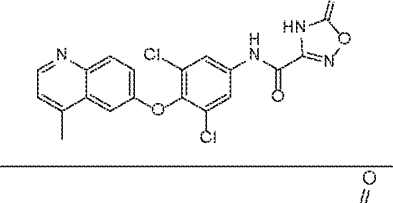
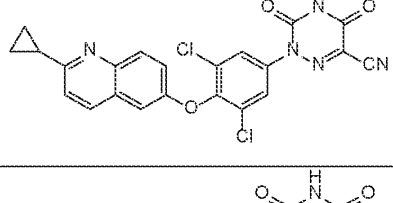
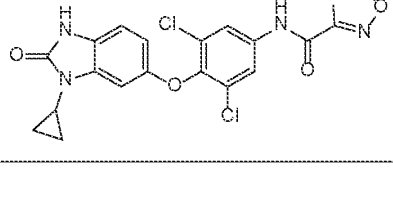
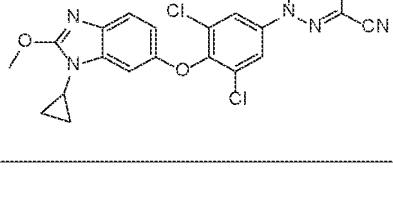
Compound Structure and Number	Compound Structure and Number
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 8-31 P2	 8-32
 8-33 P1	 8-33 P2
 8-34	 8-35

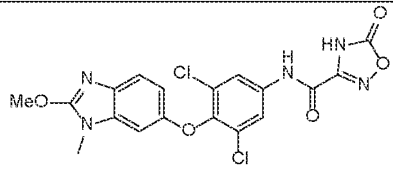
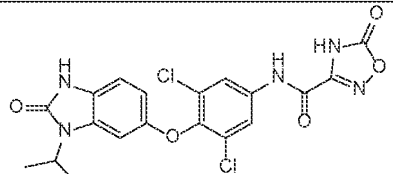
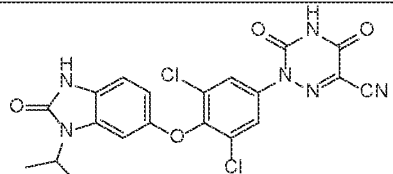
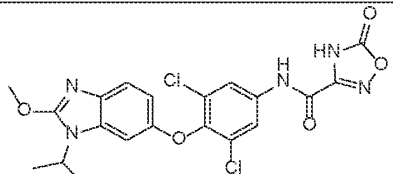
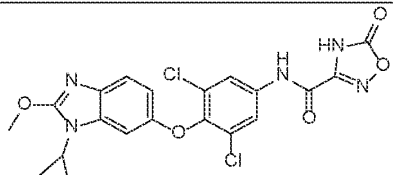
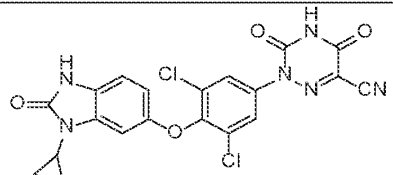
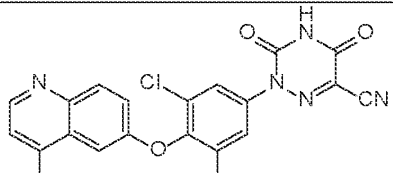
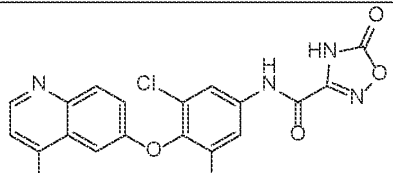
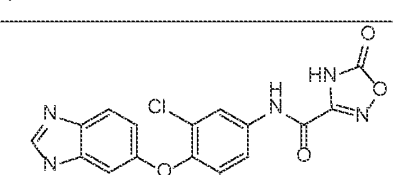
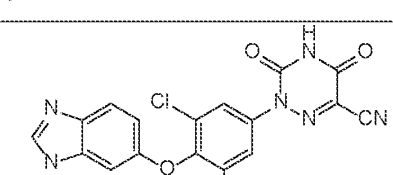
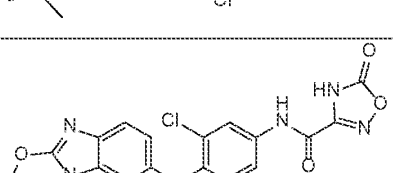
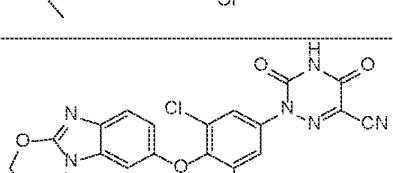
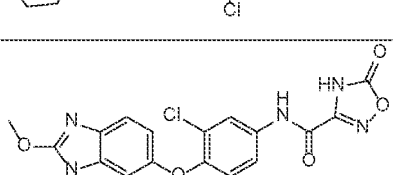
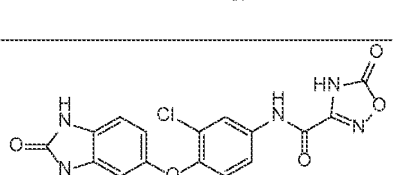
[0220] In some embodiments, the THR β agonist is selected from those listed in Table 9 below, or a pharmaceutically acceptable salt thereof.

Table 9

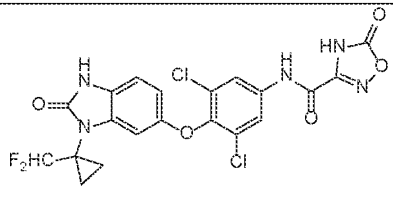
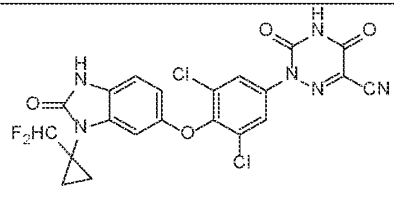
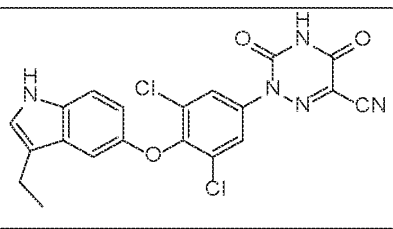
Example	Structure	Example	Structure
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9-1		9-2	
9-3		9-4	
9-5		9-6	
9-7		9-8	
9-9		9-10	
9-11		9-12	
9-13		9-14	

9-15		9-16	
9-17		9-18	
9-19		9-20	
9-21		9-22	
9-23		9-24	
9-25		9-26	
9-27		9-28	

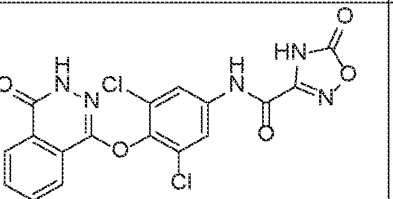
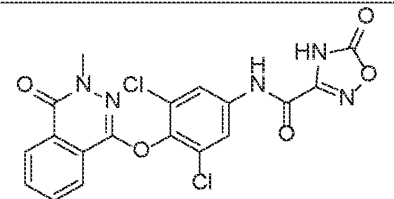
9-29		9-30	
9-31		9-32	
9-33		9-34	
9-35		9-36	
9-37		9-38	
9-39		9-40	
9-41		9-42	

9-43		9-44	
9-45		9-46	
9-47		9-48	
9-49		9-50	
9-51		9-52	
9-53		9-54	
9-55		9-56	

9-57		9-58	
9-59			

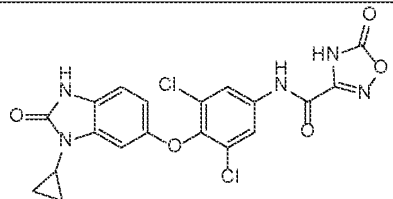
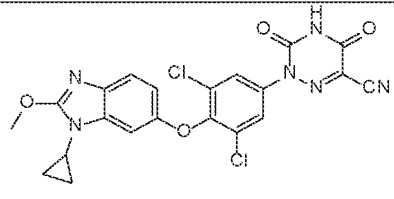
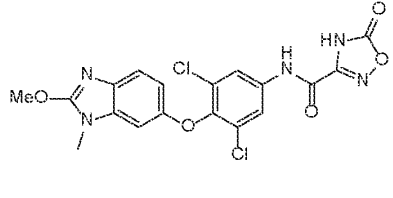
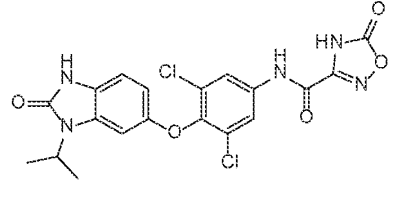
[0221] In some embodiments, the THR β agonist is selected from those listed in Table 10 below, or a pharmaceutically acceptable salt thereof:

Table 10

Example	Structure	Example	Structure
10-1		10-2	

[0222] In some embodiments, the THR β agonist is selected from those listed in Table 11 below, or a pharmaceutically acceptable salt thereof:

Table 11

Example	Structure	Example	Structure
11-1		11-2	
11-3		11-4	

11-5		11-6	
11-7		11-8	
11-9		11-10	
11-11		11-12	
11-13		11-14	
11-15		11-16	
11-17		11-18	

11-19		11-20	
11-21		11-22	
11-23		11-24	
11-25		11-26	
11-27		11-28	
11-29		11-30	
11-31		11-32	

11-33		11-34	
11-35		11-36	
11-37		11-38	
11-39		11-40	
11-41		11-42	

Pharmaceutically Acceptable Compositions and Formulations

[0223] Pharmaceutically acceptable compositions or simply “pharmaceutical compositions” of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising an GLP-1R agonist (such as the compound of Formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAD), (IAJ), (I**), (I'), (I''), (I'''), (I*), (I'), (I), (I-P01), (II**), or (II*), or a pharmaceutically acceptable salt thereof), a THRβ agonist (such as the compounds of Formula (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6), or a pharmaceutically acceptable salt thereof), and a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutically acceptable salt is

an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[0224] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In some embodiments, “substantially pure” intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. For example, a composition of a substantially pure compound intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound or a salt thereof. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 20% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 10% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 5% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 1% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 0.5% impurity. In some embodiments, a composition of substantially pure compound means that the composition contains no more than 15%, in some embodiments no more than 10%, in some embodiments no more than 5%, in some embodiments no more than 3% and, in some embodiments no more than 1% impurity, which impurity may be the compound in a different stereochemical form.

[0225] In some embodiments, the compounds herein are synthetic compounds prepared for administration to a subject such as a human. In some embodiments, compositions are provided containing a compound in substantially pure form. In some embodiments, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a

pharmaceutically acceptable carrier or excipient. In some embodiments, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0226] The compounds may be formulated for any available delivery route, including an oral, mucosal (e.g., nasal, sublingual, vaginal, buccal or rectal), parenteral (e.g., intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (e.g., nasal spray or inhalers), gels, suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0227] Compounds described herein can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compounds as active ingredients with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (e.g., transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, e.g., in Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, 21st ed. (2005), which is incorporated herein by reference.

[0228] Compounds as described herein may be administered to a subject (e.g., a human) in a form of generally accepted oral compositions, such as tablets, coated tablets, and gel capsules in a hard or in soft shell, emulsions or suspensions. Examples of carriers, which may be used for the preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its salts, etc. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax, fats, semisolid and liquid polyols, and so on. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, and salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

Methods of Use and Uses

[0229] The combinations described herein may in some aspects be used in treatment or prevention of liver disorders. In some embodiments, the method of treating or preventing a liver disorder in a patient in need thereof comprises administering to the patient a GLP-1R agonist and administering a THR β agonist.

[0230] Liver disorders include, without limitation, liver inflammation, fibrosis, and steatohepatitis. In some embodiments, the liver disorder is selected from liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). In certain embodiments, the liver disorder is selected from: liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, NAFLD, and NASH. In one embodiment, the liver disorder is NASH. In another embodiment, the liver disorder is liver inflammation. In another embodiment, the liver disorder is liver fibrosis. In another embodiment, the liver disorder is alcohol induced fibrosis. In another embodiment, the liver disorder is steatosis. In another embodiment, the liver disorder is alcoholic steatosis. In another embodiment, the liver disorder is NAFLD. In one embodiment, the treatment methods provided herein impedes or slows the progression of NAFLD to NASH. In one embodiment, the treatment methods provided herein impedes or slows the progression of NASH. NASH can progress, e.g., to one or more of liver cirrhosis, hepatic cancer, etc. In some embodiments, the liver disorder is NASH. In some embodiments, the patient has had a liver biopsy. In some embodiments, the method further comprising obtaining the results of a liver biopsy.

[0231] In some embodiments, the method of treating a liver disorder in a patient in need thereof, wherein the liver disorder is selected from the group consisting of liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

[0232] In some embodiments, the disease or condition to be treated and/or prevented is a cardiometabolic disorder, e.g., diabetes (T1 D and/or T2DM, including pre-diabetes), idiopathic T1 D (Type 1 b), latent autoimmune diabetes in adults (LADA), early-onset T2DM (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease (e.g., acute kidney disorder, tubular dysfunction, proinflammatory changes to the proximal tubules), diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition,

obesity (including hypothalamic obesity and monogenic obesity) and related comorbidities (e.g., osteoarthritis and urine incontinence), overweight without obesity (e.g., BMI between 25 kg/m² and 30 kg/m²), eating disorders (including binge eating syndrome, bulimia nervosa, and syndromic obesity such as Prader-Willi and Bardet-Biedl syndromes), excessive sugar craving, dyslipidemia (including hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, and low HDL cholesterol), hyperinsulinemia, liver diseases such as NAFLD, steatosis, NASH, fibrosis, cirrhosis, and hepatocellular carcinoma, cardiovascular disease, atherosclerosis (including coronary artery disease), peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction (e.g., necrosis and apoptosis), stroke, hemorrhagic stroke, ischemic stroke, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, left ventricular hypertrophy, peripheral arterial disease, glomerulosclerosis, chronic renal failure, metabolic syndrome, syndrome X, premenstrual syndrome, angina pectoris, thrombosis, atherosclerosis, transient ischemic attacks, vascular restenosis, impaired glucose metabolism, conditions of impaired fasting plasma glucose, hyperuricemia, gout, erectile dysfunction, skin and connective tissue disorders, psoriasis, foot ulcerations, ulcerative colitis, or hyper apo B lipoproteinemia.

[0233] In some embodiments, the disease or condition to be treated includes sleep apnea, weight gain from use of other agents (e.g., from use of steroids and antipsychotics), traumatic brain injury, Parkinson's Disease, macular degeneration, cataract, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome, Crohn's disease, colitis, irritable bowel syndrome Polycystic Ovary Syndrome and addiction (e.g., alcohol and/or drug abuse), prevention or treatment of Polycystic Ovary Syndrome or treatment of addiction (e.g., alcohol and/or drug abuse).

[0234] In some embodiments, the present disclosure is directed to co-administration of a GLP-1R agonist and THR β agonist to a subject resulting in a loss in fat mass in the subject with little or no reduction in lean mass in the subject. In some embodiments, provided herein is a method of treating a cardiometabolic disorder in a subject (e.g., a human patient) in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof.

[0235] In one embodiment the methods and combinations of the present disclosure are directed to a) the reduction of HbA1c; b) the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) the prevention or treatment

of obesity, for reducing body weight and/or food intake, or for inducing satiety in a subject in need thereof.

[0236] In some embodiments, the combinations and methods of the present disclosure are directed to treating or preventing obesity, reducing body fat percentage, increasing lean mass percentage of total weight, or for inducing satiety in a subject in need thereof.

[0237] In some embodiments, the combinations and methods of the present disclosure are directed to treating or preventing obesity, reducing body fat percentage, increasing lean mass percentage of total weight, or for inducing satiety in a subject in need thereof.

[0238] In some embodiments, the combinations and methods of the present disclosure are directed to treating obesity in a subject in need thereof.

[0239] In some embodiments, the combinations and methods of the present disclosure are directed to treating or preventing obesity in a subject in need thereof.

[0240] In some embodiments, the combinations and methods of the present disclosure are directed to reducing body fat, increasing lean mass percentage of total weight, or inducing satiety in a subject in need thereof.

[0241] In some embodiments, the present disclosure provides methods of treating or preventing obesity, for reducing body fat, and/or for increasing lean mass percentage of total weight, in a subject in need thereof comprising the administration of a THR-B agonist (*e.g.*, Compound 9) and a GLP-1R agonist which results in a synergistic effect compared to the administration of a GLP-1R agonist alone.

[0242] In some embodiments, the present disclosure provides methods of treating obesity, for reducing body fat, and/or for increasing lean mass percentage of total weight, in a subject in need thereof comprising the administration of a THR-B agonist (*e.g.*, Compound 9) and a GLP-1R agonist which results in a synergistic effect compared to the administration of a GLP-1R agonist alone.

[0243] In some embodiments, provided herein is a method of treating a liver disorder in a subject (*e.g.*, a human patient) in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof. Exemplary liver disorders include, without limitation, liver inflammation, fibrosis, and steatohepatitis. In some embodiments, the liver disorder is selected from the list consisting of primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), drug induced cholestasis, intrahepatic cholestasis of pregnancy, parenteral nutrition associated cholestasis (PNAC), bacterial overgrowth or sepsis associated cholestasis, autoimmune hepatitis, viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease

(NAFLD), nonalcoholic steatohepatitis (NASH), graft versus host disease, transplant liver regeneration, congenital hepatic fibrosis, choledocholithiasis, granulomatous liver disease, intra- or extrahepatic malignancy, Sjogren's syndrome, sarcoidosis, Wilson's disease, Gaucher's disease, hemochromatosis, and α_1 -antitrypsin deficiency. In some embodiments, the liver disorder is selected from the list consisting of liver inflammation, liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH). In some embodiments, the liver disorder is selected from the group consisting of liver fibrosis, alcohol induced fibrosis, steatosis, alcoholic steatosis, NAFLD, and NASH. In one embodiment, the liver disorder is NASH. In another embodiment, the liver disorder is liver inflammation. In another embodiment, the liver disorder is liver fibrosis. In another embodiment, the liver disorder is alcohol induced fibrosis. In another embodiment, the liver disorder is steatosis. In another embodiment, the liver disorder is alcoholic steatosis. In another embodiment, the liver disorder is NAFLD. In one embodiment, the treatment methods provided herein impedes or slows the progression of NAFLD to NASH. In one embodiment, the treatment methods provided herein impedes or slows the progression of NASH. NASH can progress, e.g., to one or more of liver cirrhosis, hepatic cancer, etc. In some embodiments, the liver disorder is NASH. In some embodiments, the patient has had a liver biopsy. In some embodiments, the method further comprising obtaining the results of a liver biopsy.

[0244] In some embodiments, the present disclosure provides a method of decreasing food intake in a subject in need thereof, the method comprising administering an effective amount of any one of the compounds or pharmaceutical compositions disclosed herein to the subject. In some embodiments, administration of a compound disclosed herein causes the subject's food intake to be reduced at least 10%, e.g., at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% relative to the subject's food intake in the absence of a compound disclosed herein. In some embodiments, the subject's food intake is reduced, e.g., reduced by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%, for at least 1 hour following administration, e.g., at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 1 day, or at least 2 days following administration.

[0245] In some embodiments, the present disclosure provides a method of improving glucose tolerance in a subject in need thereof. In some embodiments, following glucose intake, e.g., glucose intake caused by consuming food, and the administration of a compound disclosed

herein, the concentration of glucose in the blood of a subject is lower, e.g., 10% lower, 20% lower, 30% lower, 40% lower, 50% lower, 60% lower, 70% lower, 80% lower, 90% lower, 100% lower, 200% lower, 500% lower, 1000% lower, than the blood glucose concentration would have been had the subject not been administered the compound disclosed herein.

[0246] In accordance with the present application, a compound described herein, or a pharmaceutically acceptable salt thereof, can be administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. In some embodiments, it is a compound of any embodiment of Formula (I) or selected from the compounds of Table 1, or a pharmaceutically acceptable salt thereof. The compounds and/or compositions described herein may be administered orally, rectally, vaginally, parenterally, or topically.

[0247] In some embodiments, the compounds and/or compositions may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

[0248] In some embodiments, the compounds and/or compositions may be administered directly into the bloodstream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

[0249] In some embodiments, the compounds and/or compositions may be administered topically to the skin or mucosa, that is, dermally or transdermally. In some embodiments, the compounds and/or compositions may be administered intranasally or by inhalation. In some embodiments, the compounds and/or compositions may be administered rectally or vaginally. In some embodiments, the compounds and/or compositions may be administered directly to the eye or ear.

[0250] The dosage regimen for the compounds and/or compositions described herein is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus, the dosage regimen may vary widely. In some embodiments, the total daily dose of the compounds of the present application is typically from about 0.001 to about 100 mg/kg (i.e., mg compound per kg body weight) for the treatment of the indicated conditions discussed herein. In one embodiment, total daily dose of the compounds of the

present application is from about 0.01 to about 30 mg/kg, and in another embodiment, from about 0.03 to about 10 mg/kg, and in yet another embodiment, from about 0.1 to about 3. It is not uncommon that the administration of the compounds of the present application will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

[0251] Suitable dosages of the THR β agonists described herein are also described in, e.g., PCT Pub. Nos. WO2021231646, WO2023086561, and WO2023083288, which are each incorporated herein by reference.

[0252] In some embodiments, about 0.5 mg to about 100 mg of the THR β agonist is administered to the subject. In some embodiments, about 0.5 mg to about 90 mg of the compound is administered to the subject. In some embodiments, about 1 mg to about 90 mg of the compound is administered to the subject. In some embodiments, about 3 mg to about 90 mg of the compound is administered to the subject. In some embodiments, about 0.5 mg to about 30 mg of the compound is administered to the subject. In some embodiments, about 1 mg to about 30 mg of the compound is administered to the subject. In some embodiments, about 3 mg to about 90 mg of the compound is administered to the subject. In some embodiments, about 1 mg to about 5 mg of the compound is administered to the subject. In some embodiments about 1 mg to about 3 mg of the compound is administered to the subject. In some embodiments about 5 mg to about 10 mg of the compound is administered to the subject. In some embodiments, about 10 mg to about 15 mg of the compound is administered to the subject. In some embodiments, about 15 mg to about 20 mg of the compound is administered to the subject. In some embodiments, about 20 mg to about 25 mg of the compound is administered to the subject. In some embodiments, about 25 mg to about 30 mg of the compound is administered to the subject. In some embodiments, about 1 mg of the compound is administered to the subject. In some embodiments, about 2 mg of the compound is administered to the subject. In some embodiments, about 3 mg of the compound is administered to the subject. In some embodiments, about 4 mg of the compound is administered to the subject. In some embodiments, about 5 mg of the compound is administered to the subject. In some embodiments, about 6 mg of the compound is administered to the subject. In some embodiments, about 7 mg of the compound is administered to the subject. In some embodiments, about 8 mg of the compound is administered to the subject. In some embodiments, about 9 mg of the compound is administered to the subject. In some embodiments, about 10 mg of the compound is administered to the subject. In some embodiments, about 15 mg of the compound is administered to the subject. In some

embodiments, about 20 mg of the compound is administered to the subject. In some embodiments, about 25 mg of the compound is administered to the subject. In some embodiments, about 30 mg of the compound is administered to the subject. In some embodiments, the compound is Compound 9 as described herein.

Combinations

[0253] In further embodiments, the pharmaceutical compositions provided herein may be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action. In some embodiments, the GLP-1R agonist and the THR β agonist are administered in temporal proximity (e.g., the GLP-1R agonist and the THR β agonist can be administered simultaneously). Accordingly, the present disclosure provides a method of treating or preventing a cardiometabolic disorder comprising administering the GLP-1R agonist and the THR β agonist in temporal proximity.

[0254] In some embodiments, a GLP-1R agonist of Formula (I-1), (I-1a), (I-5) (I**), or (II*), or a pharmaceutically acceptable salt thereof is administered in temporal proximity with a THR β agonist of Formula (II-1) or (II-1a), or a pharmaceutically acceptable salt thereof.

[0255] In some embodiments, a GLP-1R agonist of Formula (I-1), (I-1a), (I-5), (I**), or (II*), or a pharmaceutically acceptable salt thereof is administered in temporal proximity with a THR β agonist (such as the compounds of Formula (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6), or a pharmaceutically acceptable salt thereof).

[0256] In some embodiments, a GLP-1R agonist of Formula (I**), or a pharmaceutically acceptable salt thereof is administered in temporal proximity with a THR β agonist of Formula (II-1) or (II-1a), or a pharmaceutically acceptable salt thereof.

[0257] In some embodiments, a GLP-1R agonist of Formula (I**), or a pharmaceutically acceptable salt thereof is administered in temporal proximity with a THR β agonist (such as the compounds of Formula (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6), or a pharmaceutically acceptable salt thereof).

[0258] In some embodiments, a THR β agonist of Formula (II-1) or (II-1a), or a pharmaceutically acceptable salt thereof, is administered in temporal proximity with a GLP-1R agonist (such as the compound of Formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I''), (I'''), (I*), (I'), (I), (I-P01), (I**), or (II*), or a pharmaceutically acceptable salt thereof).

[0259] In some embodiments, “temporal proximity” means that administration of one therapeutic agent occurs within a time period before or after the administration of another therapeutic agent, such that the therapeutic effect of the one therapeutic agent overlaps with the therapeutic effect of the another therapeutic agent. In some embodiments, the therapeutic effect of the one therapeutic agent completely overlaps with the therapeutic effect of the other therapeutic agent. In some embodiments, “temporal proximity” means that administration of one therapeutic agent occurs within a time period before or after the administration of another therapeutic agent, such that there is a synergistic effect between the one therapeutic agent and the another therapeutic agent. “Temporal proximity” may vary according to various factors, including but not limited to, the age, gender, weight, genetic background, medical condition, disease history, and treatment history of the subject to which the therapeutic agents are to be administered; the disease or condition to be treated or ameliorated; the therapeutic outcome to be achieved; the dosage, dosing frequency, and dosing duration of the therapeutic agents; the pharmacokinetics and pharmacodynamics of the therapeutic agents; and the route(s) through which the therapeutic agents are administered. In some embodiments, “temporal proximity” means within 15 minutes, within 30 minutes, within an hour, within two hours, within four hours, within six hours, within eight hours, within 12 hours, within 18 hours, within 24 hours, within 36 hours, within 2 days, within 3 days, within 4 days, within 5 days, within 6 days, within a week, within 2 weeks, within 3 weeks, within 4 weeks, with 6 weeks, or within 8 weeks. In some embodiments, multiple administration of one therapeutic agent can occur in temporal proximity to a single administration of another therapeutic agent. In some embodiments, temporal proximity may change during a treatment cycle or within a dosing regimen.

[0260] In some embodiments, the THR β agonist is administered to the patient prior to the GLP-1R agonist. In some embodiments, the THR β agonist is administered to the patient 0-1 hours, 1-2 hours, 2-3 hours, 3-4 hours, 4-5 hours, or 5-6 hours prior to the GLP-1R agonist. In some embodiments, the THR β agonist is administered to the patient 0-1 days, 1-2 days, 2-3 days, 3-4 days, 4-5 days, or 5-6 days prior to the GLP-1R agonist. In some embodiments, the THR β agonist reaches a steady state in a patient prior to the administration of the GLP-1R agonist. In some embodiments, the GLP-1R agonist is administered to the patient prior to the THR β agonist. In some embodiments, the GLP-1R agonist is administered to the patient 0-1 days, 1-2 days, 2-3 days, 3-4 days, 4-5 days, or 5-6 days prior to the THR β agonist. In some embodiments, the GLP-1R agonist reaches a steady state in a patient prior to the administration

of the THR β agonist. In some embodiments, the THR- β agonist is administered to the patient at substantially the same time as the GLP-1R agonist.

Articles of Manufacture and Kits

[0261] The present disclosure further provides articles of manufacture comprising a compound described herein, or a salt thereof, a composition described herein, or one or more unit dosages described herein in suitable packaging. In certain embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging (e.g., containers) is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

[0262] The present disclosure further provides kits for carrying out the methods of the present disclosure, which comprises at least two compounds described herein, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof. The kits may employ any of the compounds disclosed herein or a pharmaceutically acceptable salt thereof. In some embodiments, the kit employs an GLP-1R agonist (such as the compound of Formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I''), (I'''), (I*), (I'), (I), (I-P01), (II**), or (II*), or a pharmaceutically acceptable salt thereof) and a THR β agonist (such as the compound of (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6), or a pharmaceutically acceptable salt thereof) described herein. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment as described herein.

[0263] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein or a pharmaceutically acceptable salt thereof. Each component can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit. In some embodiments, the kit includes a container comprising the GLP-1R agonist (such as the compound of Formula (I-1), (I-1a), (I-2), (I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I''), (I'''), (I*), (I'), (I), (I-P01), (II**), or (II*), or a pharmaceutically acceptable salt thereof) and THR β agonist (such as the compound of (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6), or a pharmaceutically acceptable salt thereof). In other embodiments, the kit includes a first container comprising GLP-1R agonist (such as the compound of Formula (I-1), (I-1a), (I-2),

(I-3), (I-4), (I-5), (I-5a), (I-5b), (I-5c), (I-5d), (I-5e), (I-5f), (I-5g), (I-5h), (I-5i), (I-5j), (I-5k), (I-5l), (I-5m), (I-5n), (I-5o), (I-5p), (IQ), (IR), (IS), (IT), (IU), (IX), (IY), (IZ), (IAA), (IAB), (IAC), (IAD), (IAE), (IAG), (IAH), (IAI), (IAJ), (I**), (I'), (I''*), (I'''), (I*), (I'), (I), (I-P01), (II**), or (II*), or a pharmaceutically acceptable salt thereof) and a second container comprising the THR β agonist (such as the compound of (II-1), (II-1a), (II-2), (II-3), (II-4), (II-5), or (II-6), or a pharmaceutically acceptable salt thereof).

[0264] The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein (e.g., Compound 9), or a pharmaceutically acceptable salt thereof, and/or an additional pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of a subject for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

[0265] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present disclosure. The instructions included with the kit generally include information as to the components and their administration to a subject.

General Biological Protocols

Non-alcoholic steatohepatitis (NASH) mouse model

[0266] This mouse model is fed a high fat diet that results in nonalcoholic steatohepatitis (NASH) disease and increased weight.

Liver biopsy

[0267] Mice are anesthetized and a small abdominal incision is made in the midline and the left lateral lobe of the liver is exposed. A cone shaped wedge of liver tissue is excised from the distal portion of the lobe and fixated in 10% neutral buffered formalin for histology. The cut surface of the liver is instantly electrocoagulated using bipolar coagulation.

Blood sampling and plasma preparation

[0268] *In vivo* blood samples: Samples are collected at week 8, 30 minutes post-dose, 1 hour post-dose, 2 hours post-dose, 4 hours post-dose, 6 hours post-dose, and 24 hours post-dose (before the next dose). Tail-vein, tongue or cheek blood is collected in a Microvette tube of

appropriate dimensions with anticoagulant and mixed. Blood is centrifuged. The plasma supernatants are transferred to new tubes and immediately frozen on dry ice. Termination blood samples: During anesthesia, the abdominal cavity is opened, and cardiac blood is drawn with a syringe with anticoagulant and mixed. Blood is centrifuged and plasma supernatants are transferred to new tubes and immediately frozen on dry ice.

Tissue sampling

Liver (NASH)

[0269] After the animal has been terminated, the liver is collected and weighed.

[0270] The liver is divided into left lateral lobe, medial lobe, right lateral lobe, and caudate lobe.

[0271] The *Post-biopsy* piece is cut from the left lateral lobe, 4 mm from the prebiopsy site with an edge. The tissue is collected in paraformaldehyde.

The *Liver Sponsor* piece is dissected from the left medial lobe, put in a tube and placed directly into liquid nitrogen.

[0272] The *Liver RNA Sequencing (RNAseq)* piece is dissected from the center of the left lateral lobe, snap frozen (put directly in liquid nitrogen in Nunc filter) and collected in a pre-cooled tube which is put in liquid nitrogen.

[0273] The *Liver TG TC* piece is dissected from the right medial lobe, with no edges, on the opposite side of the sponsor piece. The samples are weighed individually and collected in tubes before placed in liquid nitrogen.

[0274] The *Liver Extra* piece is dissected from the right lateral lobe and collected in tubes before placed in liquid nitrogen, to have as backup tissue from the study and can be used for re-analysis if necessary.

Biopsy processing

Microtome sectioning of Formalin fixed paraffin-embedded (FFPE) biopsies

[0275] FFPE biopsies are placed in 10% neutral buffered formalin then transferred to 70% EtOH. The FFPE biopsies are then placed in the Histokinette to infiltrate prior to embedding in blocks. Biopsy tissues are cut at 3µm on a microtome and the sections are mounted on Superfrost Plus slides.

NAFLD Activity Score (NAS) and Fibrosis stage

[0276] Liver samples stained with Hematoxylin and Eosin (H&E) or Picro Sirius Red (PSR) are given a score for NAS and fibrosis stage respectively using the clinical criteria outlined by Kleiner *et al.* 2005. Total NAS represents the sum of scores for steatosis, inflammation, and ballooning, and ranges from 0-8. Adapted from: Design and validation of a histological scoring system for nonalcoholic fatty liver disease, Kleiner *et al.*, Hepatology 41; 2005

Histological staining procedures

[0277] Slides with paraffin embedded sections are deparaffinated in xylene and rehydrated in series of graded ethanol.

[0278] Hematoxylin & Eosin (H&E) staining: Slides are incubated in Mayer's Hematoxylin (Dako), washed in tap water, stained in Eosin Y solution (Sigma-Aldrich), dehydrated and cover slipped.

[0279] Sirius red (PSR) staining: Slides are incubated in Weigert's iron hematoxylin (Sigma-Aldrich), washed in tap water, stained in Picro-sirius red (Sigma-Aldrich) and washed twice in acidified water. Excess water is removed by shaking the slides and the slides are then dehydrated in three changes of 100% ethanol, cleared in xylene and cover slipped.

[0280] Immunohistochemistry using single chromogen: IHC is performed using standard procedures. Briefly, after antigen retrieval and blocking of endogenous peroxidase activity, slides are incubated with primary antibody. The primary antibody is detected using a polymeric HRP-linker antibody conjugate. Next, the primary antibody is visualized with DAB as chromogen. Finally, sections are counterstained in hematoxylin and cover slipped. Slides are scanned under a 20X objective in a ScanScope AT slide scanner (Aperio).

Gene expression analysis using RNAseq

[0281] *RNA isolation:* Tissue is collected and snap-frozen in liquid nitrogen. Samples are stored at -70°C until processing. RNA is isolated using the NucleoSpin® kit (MACHEREY-NAGEL).

[0282] *Library preparation and sequencing:* A total of 10 ng-1 µg purified RNA from each sample is used to generate a cDNA library using the NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina (New England Biolabs). cDNA libraries are then sequenced on a NextSeq 500 using NextSeq 500/550 High Output Kit V2 (Illumina).

[0283] *Data analysis:* The sequencing data is aligned to the genome of the animal species obtained from the Ensembl database using the Spliced Transcripts Alignment to a Reference (STAR) software. For the bioinformatic analysis, the quality of the data is evaluated using the

standard RNA-sequencing quality control parameters, the inter- and intra-group variability is evaluated using principal component analysis and hierarchical clustering and the differentially expressed genes are identified using the R-package DESeq2. Downstream analyses such as pathway analysis or target identification are performed as agreed with the sponsor.

Blood and plasma assays

[0284] Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG) and Total Cholesterol (TC): Blood samples are collected in heparinized tubes and plasma is separated and stored at -70°C until analysis. Samples are measured using commercial kits.

[0285] Cytokeratin 18 (CK18-M30): Blood samples are collected in EDTA tubes and plasma is separated and stored at -70°C until analysis. CK18 is measured using a commercial ELISA kit.

[0286] Insulin: Blood samples are collected in heparinized tubes and plasma is separated and stored at -70°C until analysis. Insulin is measured using a commercial MSD platform.

[0287] TIMP-1: Blood samples are collected in EDTA tubes and plasma is separated and stored at -70°C until analysis. TIMP-1 is measured using a commercial ELISA kit.

[0288] PIINP: Blood samples are collected in EDTA tubes and plasma is separated and stored at -70°C until analysis. PIINP is measured using a commercial ELISA kit.

Tissue assays

[0289] Triglycerides (TG) and Total cholesterol (TC): Liver samples are homogenized and TG and TC is extracted. The samples are centrifuged and the TG and TC content is measured in the supernatant using commercial kits.

Oral Glucose Tolerance Test (OGTT)

[0290] On the day of the OGTT, random blood glucose and body weight of the mice are measured, mice are dosed with corresponding compounds or vehicle in the morning before fasting, then the mice are fasted for 6 hours, basal fasting glucose is measured by tail vein nick thereafter. Glucose is orally gavaged with 2 g/kg at a dose volume of 5 mL/kg. Blood glucose levels are measured at 0 (pre-dose), 15-, 30-, 60-, and 120-min post glucose dosing. The second dose is administrated after OGTT treatment.

Terminal plasma and tissue collection

[0291] The body weight and food intake of all mice is measured and then fasted for 6 hours, all mice are euthanized with CO₂ and bled via cardiac puncture. Blood samples will be

processed for serum by centrifugation and stored for TC/TG/LDL/HDL/AST/ALT analysis. Blood samples are mixed with K₂EDTA anticoagulant and processed for plasma by centrifugation stored for insulin and other possible analysis.

[0292] The weight of whole liver and epididymal fat are weighed and recorded. Left lobule of liver is fixed in formalin. The remaining liver is flash frozen and stored. Pancreas is collected and fixed in formalin. Brown adipose, subcutaneous white adipose, and epididymal white adipose tissues and the brain hypothalamus region are frozen with liquid nitrogen and preserved and stored for optional qPCR analysis.

Hypothalamus collection procedure

[0293] The brain tissue is placed in the mold, and the olfactory bulb is placed in the center of the groove. The brain tissue is sliced into 8 coronal sections evenly spaced at 2 mm intervals. The third section (6-8mm) of the coronal brain tissue is taken out, and the section is cut along the boundary of the purple part with a scalpel to separate the cerebral cortex. The remaining tissue is hypothalamus.

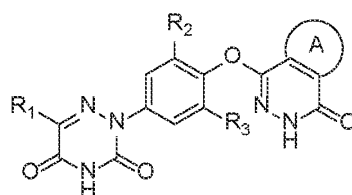
Weight loss analysis

[0294] Body weight, food and water intake are measured daily. Body composition is measured using EchoMRI. Subcutaneous fat is collected and weighed at study termination. Subcutaneous fat tissue samples are assessed for UCP-1 expression by qPCR and Western blot analyses.

NUMBERED EMBODIMENTS

Embodiments 1-169

1. A combination comprising a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.
2. A combination of THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for effectuating weight loss in a patient in need thereof.
3. The combination of embodiment 1 or 2, wherein the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

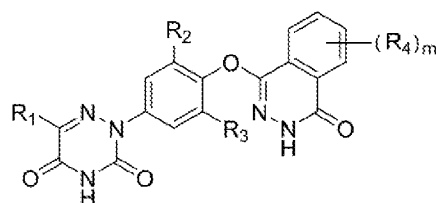
R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br;

or a pharmaceutically acceptable salt thereof.

4. The combination of any one of the preceding embodiments, wherein the THR β agonist is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

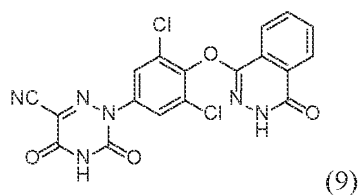
R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

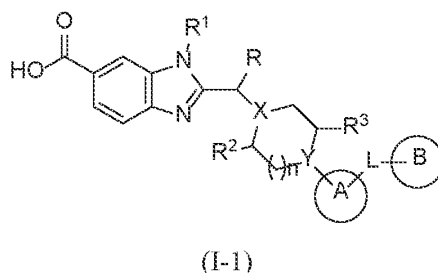
5. The combination of any one of the preceding embodiments, wherein the THRβ agonist is Compound 9:



or a pharmaceutically acceptable salt thereof.

6. The combination of any one of the preceding embodiments, wherein the THRβ agonist is a potassium salt of Compound 9.

7. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1):



or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R^3 is hydrogen, oxo, or C_1 - C_6 alkyl and R^4 is hydrogen, OH, or C_1 - C_6 alkyl;
or R^3 and R^4 are taken together with the carbon atoms to which they are attached to form C_3 - C_6 cycloalkyl optionally substituted by halo or C_1 - C_3 alkyl;

R^5 is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom of R^5 is S, and further wherein R^5 is optionally substituted by halo, -O- C_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkenyl, or C_1 - C_6 haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkyl optionally substituted by halo or OH;

L is a bond, -O-, C_1 - C_6 alkylene, *-O- C_1 - C_6 alkylene-**, *- C_1 - C_6 alkylene-O-**, or *-NR⁶- C_1 - C_6 alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

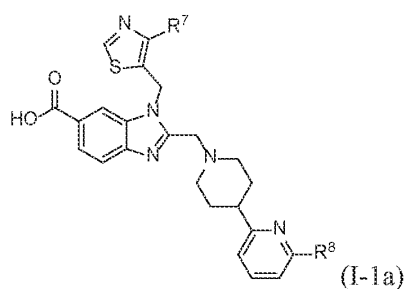
when L is *-O- C_1 - C_6 alkylene-**, the C_1 - C_6 alkylene of L is optionally substituted by R^L , wherein each R^L is independently C_1 - C_6 alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C_3 - C_6 cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C_1 - C_6 alkylene, the C_1 - C_6 alkylene is optionally substituted by R^{L1} , wherein each R^{L1} is independently halo, OH, oxo, or C_1 - C_6 alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C_3 - C_6 cycloalkyl or 3- to 6-membered heterocyclyl;

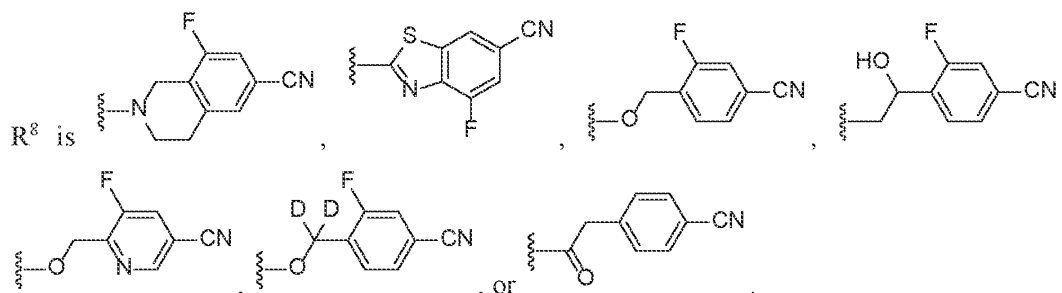
R^6 is hydrogen or C_1 - C_6 alkyl; and

Ring B is C_3 - C_{10} cycloalkyl, C_6 - C_{14} aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

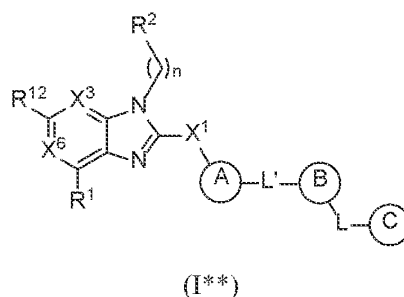
8. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1a):



wherein R^7 is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



9. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I**):



or a pharmaceutically acceptable salt thereof, wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, halogen, $-O-X^4$, or $-NR^8R^9$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$, or $-(C_{1-6} \text{ alkylene})-(3- \text{ to } 8\text{-membered heterocyclyl})$, 3- to 8-membered heterocyclyl, $-(CH_2CH_2-O)_{1-5}-CH_3$, $-(CH_2-CH(-OCH_3)-CH_2-O)_{1-5}-CH_3$, C_{3-10} cycloalkyl, or C_{6-10} aryl, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, C_{1-6} alkoxy, hydroxyl, $-CN$, or oxo, and the cycloalkyl,

heterocyclyl, or aryl group is optionally substituted with one or more halogen, C₁₋₆ alkoxy, or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

C₁₋₆ alkyl optionally substituted with deuterium;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

-CN;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, $\text{HN} \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$, or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

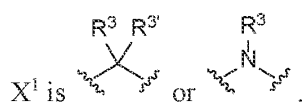
R² and R⁷, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R⁴ is halogen, hydrogen, -C(O)OH, or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

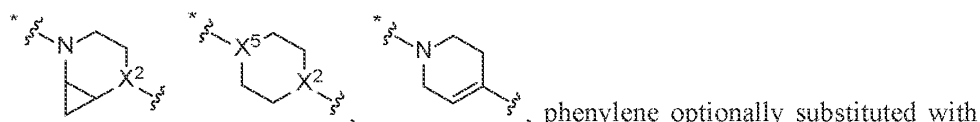
R¹² is hydrogen, -C(O)OH, -C(O)NR^{N12}R^{N12'}, -C(O)NR¹²S(O)₂R^{12'}, -(C₂₋₆ alkynylene)-C(O)OH, -(C₁₋₆ alkylene)-C(O)OH, -NR^{N12}-(C₁₋₆ alkylene)-C(O)OH, 5-10 membered heteroaryl or 5- to 10-membered heterocyclyl optionally substituted with one or more oxo, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R^{N12} and R^{N12'} independently are H or C₁₋₆ alkyl;



wherein R^3 and $R^{3'}$ independently are H, D or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with deuterium;

Ring A is



phenylene optionally substituted with one or more halo or C_{1-6} alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C_{1-6} alkyl;

wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or $-O-$;

Ring B is a C_{6-10} arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $-(C_{1-6} \text{ alkylene})-$, $-(NR^L)-(C_{1-6} \text{ alkylene})-$, $-(O-(C_{1-6} \text{ alkylene})-$, or $-(C_{1-6} \text{ alkylene})-O-$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium;

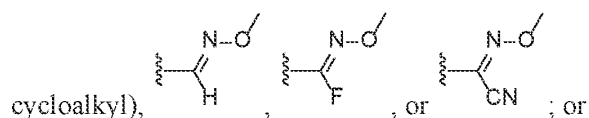
wherein R^L is H or C_{1-6} alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-10 membered heterocyclyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CN$, C_{3-10} cycloalkyl, or $-C(O)NR'^2$;

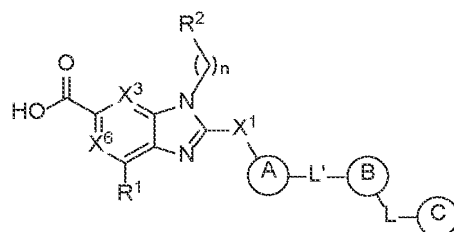
wherein R' is H or C_{1-6} alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, $-CN$, C_{1-6} haloalkyl, $-O-C_{1-6}$ alkyl, C_{3-10} cycloalkyl, $-C(=O)-(C_{3-10}$



a bicyclic 9- or 10-membered heteroaryl or heterocyclyl optionally substituted with one or more C_{1-6} alkyl, halogen, $-CN$, or oxo.

10. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-5)



(I-5)

or a pharmaceutically acceptable salt thereof; wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

branched C₁₋₆ alkyl;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

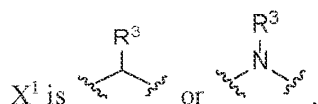
oxo, , or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

R² and R⁷, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

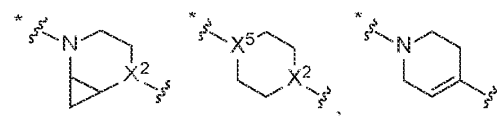
R⁴ is hydrogen or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



phenylene optionally substituted with one or more halo or C₁₋₆ alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C₁₋₆ alkyl;

wherein * indicates attachment to X¹,

X⁵ is CR³ or N, and

X² is CR³ or N;

L' is a bond or -O-;

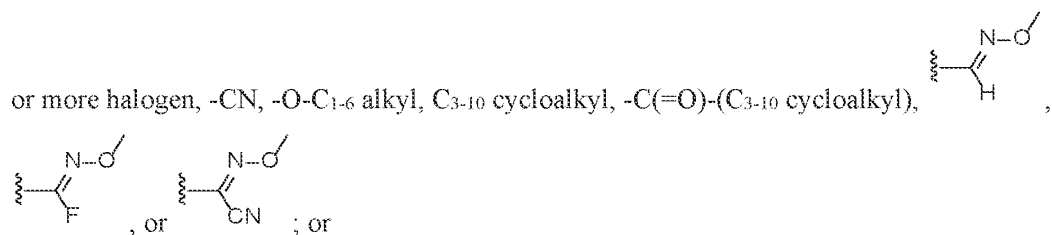
Ring B is a C₆₋₁₀ arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C₆₋₁₀ arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;

L is a bond, *-CH₂-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium; and

Ring C is:

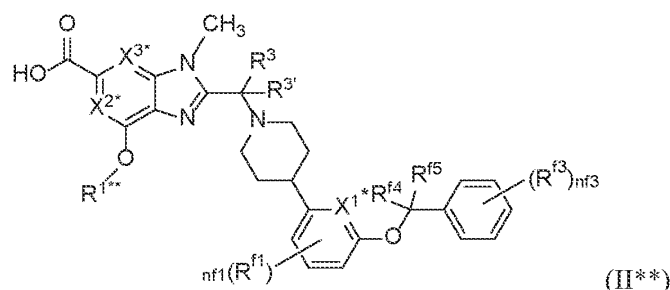
a 6-membered aryl optionally substituted with one or more C₁₋₆ alkyl, 3-10 membered heterocyclyl, halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

11. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (II**):



or a pharmaceutically acceptable salt thereof, wherein

R^{f4} and R^{f5} are each independently selected from C₁₋₆ alkyl, H and D

nf1 is 0, 1, 2, 3, or 4;

nf3 is 0, 1, 2, 3, 4, or 5;

each R^{f1} is halogen;

R³ and R^{3'} independently are H or D;

X^{1*} is N or CR^{f1};

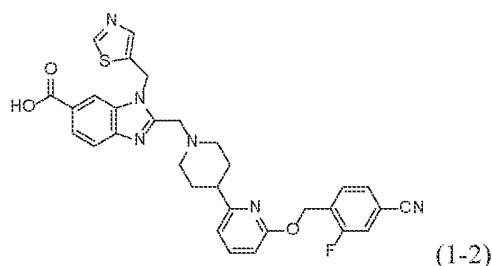
X^{2*} and X^{3*} independently are CH or CF;

each R^{f3} is independently selected from halogen, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or -C(O)N(R^{f3'})₂,

each R^{f3'} is independently selected from H or C₁₋₆ alkyl; and

R^{1**} is H or C₁₋₂ alkyl optionally substituted with one or more deuterium or halogen.

12. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

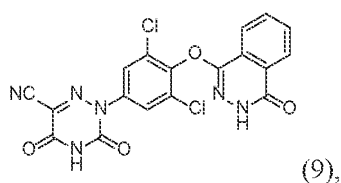
13. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a meglumine salt of Compound 1-2.

14. The combination of any one of the preceding embodiments, wherein the THR β agonist is selected from those listed in Tables 6-11.

15. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Tables 1-5.

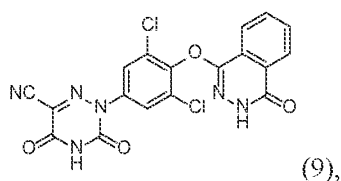
16. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Table 5A.

17. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



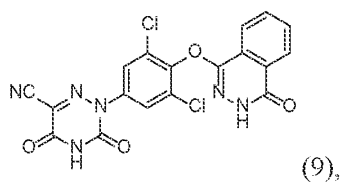
and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

17a. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



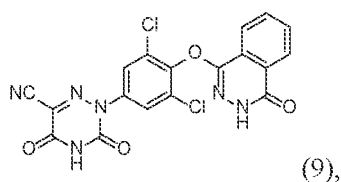
and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

17b. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



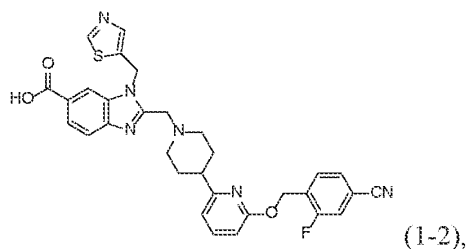
and the GLP-1R agonist is semaglutide or a pharmaceutically acceptable salt thereof.

17c. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



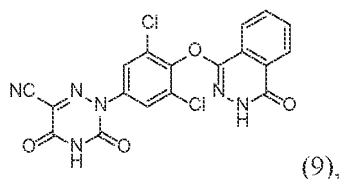
and the GLP-1R agonist is danuglipron or a pharmaceutically acceptable salt thereof.

18. The combination of any one of the preceding embodiments, wherein the THR β agonist is resmetirom, VK2809, sobetirome, eprotrirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is compound 1-2

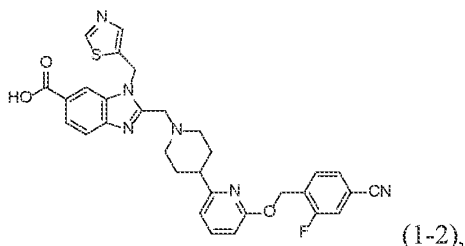


or a pharmaceutically acceptable salt thereof.

19. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



- or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is compound 1-2



- or a pharmaceutically acceptable salt thereof.

20. A method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a combination according to any one of the previous embodiments.

21. A method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the combination according to any one of the previous embodiments.

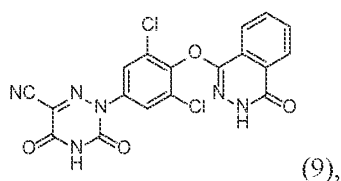
22. A method of increasing the proportion of lean body mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination according to any one of the previous embodiments.

23. A method of decreasing the proportion of fat mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination according to any one of the previous embodiments.

24. A method of effectuating weight loss in a patient in need thereof, comprising administering to the patient a combination according to any one of the previous embodiments.

25. The method of any one of the previous embodiments, wherein the patient has a Body Mass Index (BMI) of 20 kg/m² to 25 kg/m².
26. The method of any one of the previous embodiments, wherein the patient has a BMI of 25 kg/m² to 30 kg/m².
27. The method of any one of the previous embodiments, wherein the patient has a BMI of 30 kg/m² or greater.
28. The method of any one of the preceding embodiments, wherein the cardiometabolic disease is obesity.
29. The method of any one of the preceding embodiments, wherein the liver disorder is NASH.
30. The method of any one of the preceding embodiments, wherein the liver disorder is liver fibrosis.
31. The method of any one of the preceding embodiments, wherein the GLP-1R agonist element of the combination is administered to the subject more than once.
32. The method of any one of the preceding embodiments, wherein the THR- β agonist element of the combination is administered to the subject more than once.
33. The method of any one of the preceding embodiments, wherein both the GLP-1R agonist and THR β agonist elements of the combination are administered to the subject more than once.
34. The method of any one of the preceding embodiments, wherein the THR β agonist is administered prior to or concurrent with the GLP-1R agonist.
35. The method of any one of the preceding embodiments, wherein the THR β agonist is administered in temporal proximity to the GLP-1R agonist.

36. The method of any one of the preceding embodiments, wherein the THR β agonist is administered on the same day as the GLP-1R agonist.
37. The method of any one of the preceding embodiments, wherein the THR β agonist is administered at substantially the same time as the GLP-1R agonist.
38. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
39. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered on the same day as the GLP-1R agonist.
40. The method of any one of the preceding embodiments, wherein the wherein the initial dose of THR β agonist is at substantially the same time as the GLP-1R agonist.
41. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered prior to the initial dose of GLP-1R agonist.
42. The method of embodiment 40, wherein a subsequent dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
43. The method of embodiment 41 or 42, wherein a subsequent dose of THR β agonist is administered on the same day as the GLP-1R agonist.
44. The method of any one of embodiments 41 to 43, wherein a subsequent dose of THR β agonist is administered at substantially the same time as the GLP-1R agonist.
45. A method of improving a patient's response to the administration of a GLP-1R agonist in a patient in need thereof, comprising
- (i) administering to the patient compound 9



or a pharmaceutically acceptable salt thereof, and

(ii) administering a GLP-1R agonist, or a pharmaceutically acceptable salt thereof.

46. The method of embodiment 45, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, increases fat loss associated with administering the GLP-1R agonist.

47. The method of embodiment 45, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, increases fat loss associated with administering the GLP-1R agonist while maintaining lean mass.

48. The method of embodiment 45, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, is performed prior to or concurrent with the administration of the GLP-1R agonist.

49. The method of embodiment 45, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, is performed prior to the administration of the GLP-1R agonist.

50. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is administered to the subject more than once.

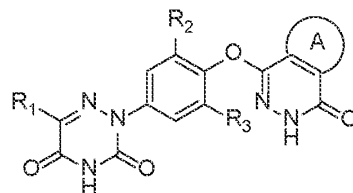
51. The method of any one the preceding embodiments, wherein the THR β agonist element is administered to the subject more than once.

52. The method of any one of the preceding embodiments, wherein both the GLP-1R agonist and THR- β agonist are administered to the subject more than once.

53. The method of any one of the preceding embodiments, wherein the THR β agonist is administered prior to or concurrent with the GLP-1R agonist.

54. The method of any one of the preceding embodiments, wherein the THR β agonist is administered in temporal proximity to the GLP-1R agonist.
55. The method of any one of the preceding embodiments, wherein the THR β agonist is administered on the same day as the GLP-1R agonist.
56. The method of any one of the preceding embodiments, wherein the THR β agonist is administered at substantially the same time as the GLP-1R agonist.
57. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
58. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered on the same day as the GLP-1R agonist.
59. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is at substantially the same time as the GLP-1R agonist.
60. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered prior to the initial dose of GLP-1R agonist.
61. The method of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
62. The method of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered on the same day as the GLP-1R agonist.
63. The method of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered at substantially the same time as the GLP-1R agonist.
64. A combinational therapy comprising a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for the treatment of obesity in a patient in need thereof.

65. The combinational therapy of embodiment 64, wherein the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

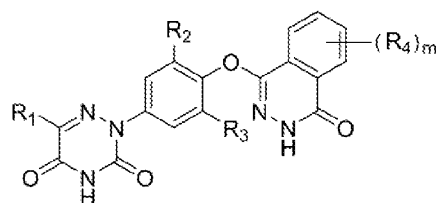
R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br,
or a pharmaceutically acceptable salt thereof.

66. The combinational therapy of embodiment 64 or 65, wherein the THR β agonist is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

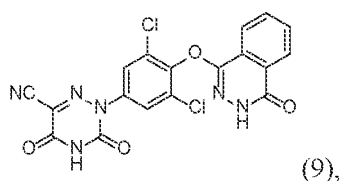
R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

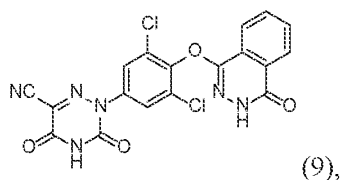
Or a pharmaceutically acceptable salt thereof.

67. The combinational therapy of any one of the preceding embodiments, wherein the THRβ agonist is compound 9



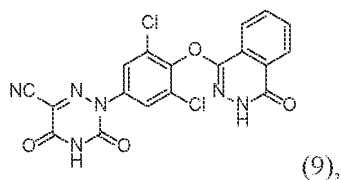
and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

67a. The combinational therapy of any one of the preceding embodiments, wherein the THRβ agonist is compound 9



and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

67b. The combinational therapy of any one of the preceding embodiments, wherein the THRβ agonist is compound 9



and the GLP-1R agonist is semaglutide or a pharmaceutically acceptable salt thereof.

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

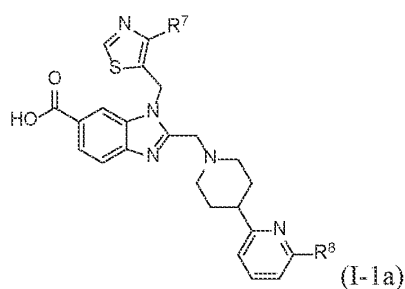
when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene of L is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L1}, wherein each R^{L1} is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

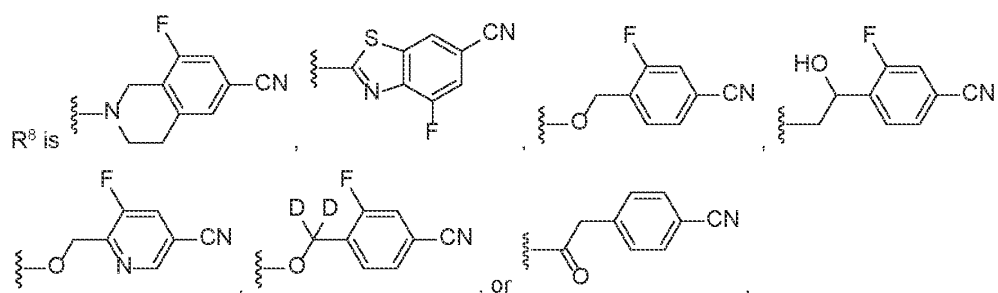
R⁶ is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

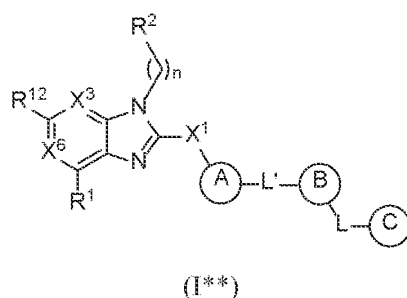
70. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1a):



wherein R⁷ is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



71. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I**):



or a pharmaceutically acceptable salt thereof, wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, halogen, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, C₃₋₁₀ cycloalkyl, or C₆₋₁₀ aryl, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, C₁₋₆ alkoxy, hydroxyl, -CN, or oxo, and the cycloalkyl, heterocyclyl, or aryl group is optionally substituted with one or more halogen, C₁₋₆ alkoxy, or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

C₁₋₆ alkyl optionally substituted with deuterium;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

-CN;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, , or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

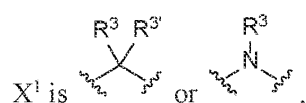
R² and R⁷, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R⁴ is halogen, hydrogen, -C(O)OH, or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

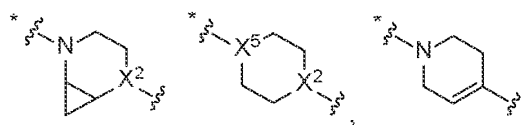
R¹² is hydrogen, -C(O)OH, -C(O)NR^{N12}R^{N12'}, -C(O)NR¹²S(O)₂R^{12'}, -(C₂₋₆ alkynylene)-C(O)OH, -(C₁₋₆ alkylene)-C(O)OH, -NR^{N12}-(C₁₋₆ alkylene)-C(O)OH, 5-10 membered heteroaryl or 5- to 10-membered heterocyclyl optionally substituted with one or more oxo, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R^{N12} and R^{N12'} independently are H or C₁₋₆ alkyl;



wherein R³ and R^{3'} independently are H, D or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with deuterium;

Ring A is



, phenylene optionally substituted with one or more halo or C₁₋₆ alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C₁₋₆ alkyl;

wherein * indicates attachment to X¹,

X⁵ is CR³ or N, and

X² is CR³ or N;

L' is a bond or -O-;

Ring B is a C₆₋₁₀ arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C₆₋₁₀ arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;

L is a bond, *-(C₁₋₆ alkylene)-, *-NR^L-(C₁₋₆ alkylene)-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium;

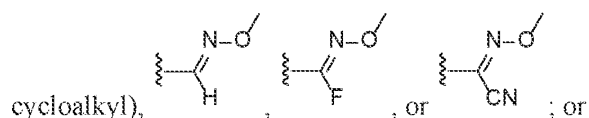
wherein R^L is H or C₁₋₆ alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₃₋₁₀ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-10 membered heterocyclyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -CN, C₃₋₁₀ cycloalkyl, or -C(O)NR'²;

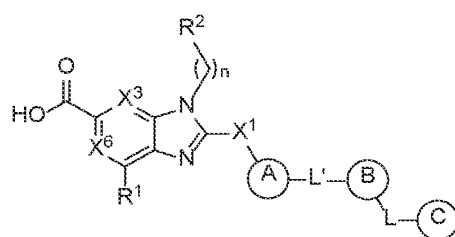
wherein R'² is H or C₁₋₆ alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, -CN, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀



a bicyclic 9- or 10-membered heteroaryl or heterocyclyl optionally substituted with one or more C₁₋₆ alkyl, halogen, -CN, or oxo.

72. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (1-5)



(I-5)

or a pharmaceutically acceptable salt thereof, wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

branched C₁₋₆ alkyl;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

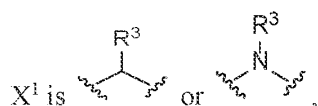
oxo, $\text{HN}=\text{O}$, or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

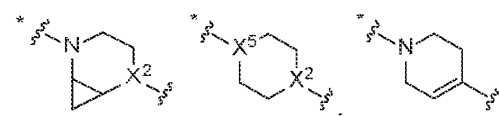
R^4 is hydrogen or $-\text{O}-\text{R}^8$,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



phenylene optionally substituted with one or more halo or C_{1-6} alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C_{1-6} alkyl;

wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L' is a bond or $-\text{O}-$;

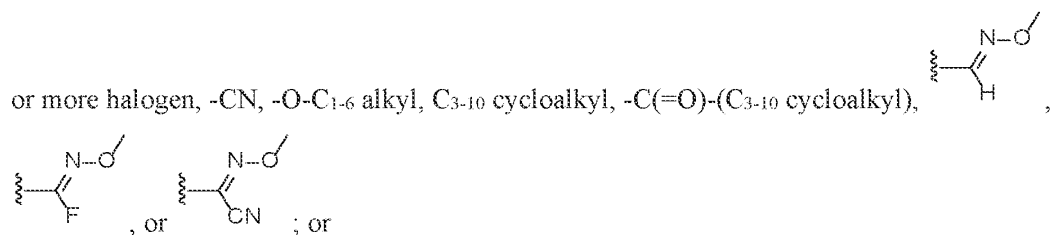
Ring B is a C_{6-10} arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $^*\text{-CH}_2\text{-}$, $^*\text{-O-(C}_{1-6}\text{ alkylene)-}$, or $^*\text{-(C}_{1-6}\text{ alkylene)-O-}$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium; and

Ring C is:

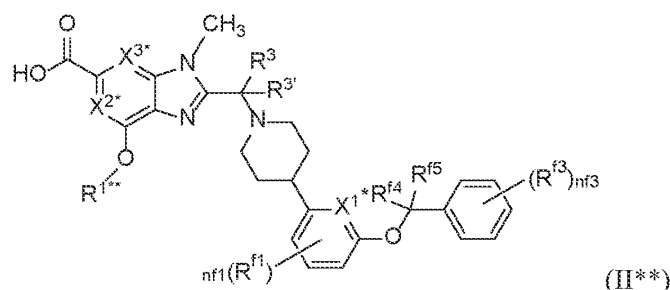
a 6-membered aryl optionally substituted with one or more C_{1-6} alkyl, 3-10 membered heterocyclyl, halogen, $-\text{OCH}_3$, $-\text{CN}$, or C_{3-10} cycloalkyl;

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

73. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (II**):



or a pharmaceutically acceptable salt thereof, wherein

R^{f4} and R^{f5} are each independently selected from C₁₋₆ alkyl, H and D

nf1 is 0, 1, 2, 3, or 4;

nf3 is 0, 1, 2, 3, 4, or 5;

each R^{f1} is halogen;

R³ and R^{3'} independently are H or D;

X^{1*} is N or CR^{f1};

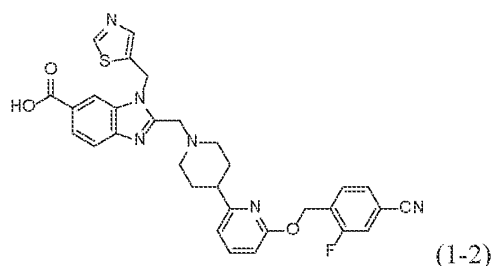
X^{2*} and X^{3*} independently are CH or CF;

each R^{f3} is independently selected from halogen, -CN, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, or -C(O)N(R^{f3'})₂,

each R^{f3'} is independently selected from H or C₁₋₆ alkyl; and

R^{1**} is H or C₁₋₂ alkyl optionally substituted with one or more deuterium or halogen.

74. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

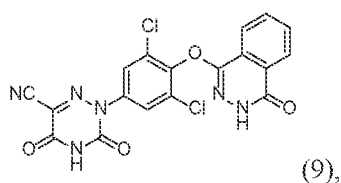
75. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is a meglumine salt of Compound 1-2.

76. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is selected from those listed in Tables 6-11.

77. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Tables 1-5.

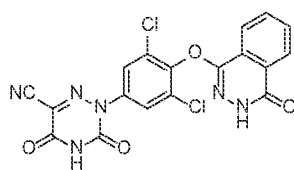
78. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Table 5A.

79. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is compound 9



and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

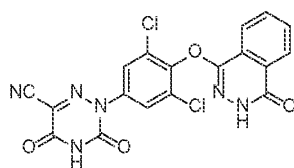
79a. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is compound 9



(9),

and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

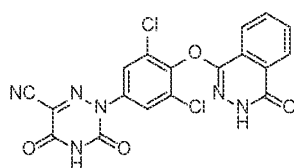
79b. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is compound 9



(9),

and the GLP-1R agonist is semaglutide or a pharmaceutically acceptable salt thereof.

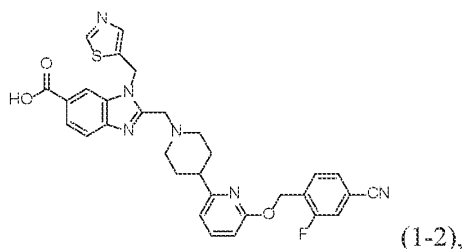
79c. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is compound 9



(9),

and the GLP-1R agonist is danuglipron or a pharmaceutically acceptable salt thereof.

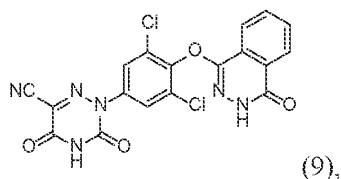
80. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is resmetirom, VK2809, sobetirome, eprotirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is compound 1-2



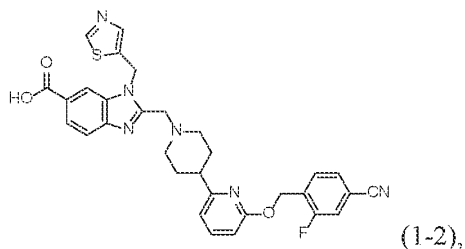
(1-2),

or a pharmaceutically acceptable salt thereof.

81. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is compound 9



or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is compound 1-2



or a pharmaceutically acceptable salt thereof.

82. The combinational therapy of any one of the preceding embodiments, wherein the patient has a body mass index (BMI) of 25 kg/m² to 30 kg/m².

83. The combinational therapy of any one of the preceding embodiments, wherein the patient has a BMI of 30 kg/m² or greater.

84. The combinational therapy of any one of the preceding embodiments, wherein the GLP-1R agonist element of the combinational therapy is administered to the subject more than once.

85. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist element of the combinational therapy is administered to the subject more than once.

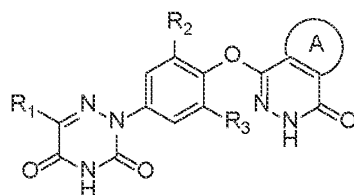
86. The combinational therapy of any one of the preceding embodiments, wherein both the GLP-1R agonist and THR- β agonist elements of the combination therapy are administered to the subject more than once.

87. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is administered prior to or concurrent with the GLP-1R agonist.

88. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is administered in temporal proximity to the GLP-1R agonist.
89. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is administered on the same day as the GLP-1R agonist.
90. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is administered at substantially the same time as the GLP-1R agonist.
91. The combinational therapy of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
92. The combinational therapy of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered on the same day as the GLP-1R agonist.
93. The combinational therapy of any one of the preceding embodiments, wherein the initial dose of THR β agonist is at substantially the same time as the GLP-1R agonist.
94. The combinational therapy of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered prior to the initial dose of GLP-1R agonist.
95. The combinational therapy of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
96. The combinational therapy of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered on the same day as the GLP-1R agonist.
97. The combinational therapy of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered at substantially the same time as the GLP-1R agonist.

98. A THR- β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, for use in a combinational therapy for the treatment of obesity in a patient in need thereof.

99. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to embodiment 98, wherein the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

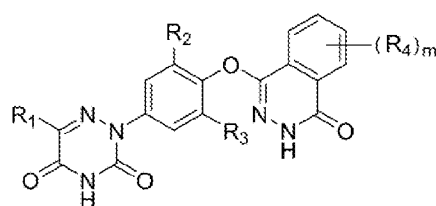
R_1 is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C_{1-6} alkyl, and substituted or unsubstituted C_{3-6} cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy;

R_2 and R_3 are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C_{1-6} alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C_{1-6} alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C_{5-10} aliphatic ring, or a substituted or unsubstituted C_{5-10} aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, $-OCF_3$, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4}$ alkyl) $_2$, $-CONH_2$, $-CONHC_{1-4}$ alkyl, $-CON(C_{1-4}$ alkyl) $_2$, $-NHCOC_{1-4}$ alkyl, C_{1-6} alkyl, C_{1-6} alkoxy or C_{3-6} cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br, or a pharmaceutically acceptable salt thereof.

100. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to embodiment 98 or 99, wherein the THR β agonist is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

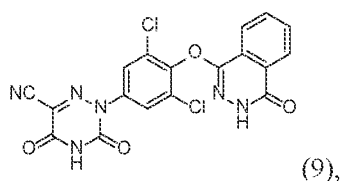
R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

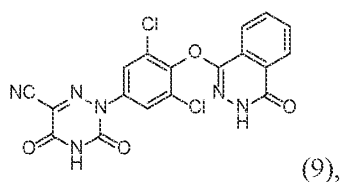
101. The THR-β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THRβ agonist is compound 9



(9),

and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

101a. The THR-β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THRβ agonist is compound 9



(9),

and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH, or C₁-C₆ alkyl;

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom of R⁵ is S, and further wherein R⁵ is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁-C₆ haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

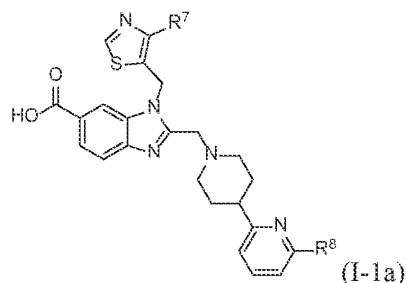
when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene of L is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L1}, wherein each R^{L1} is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

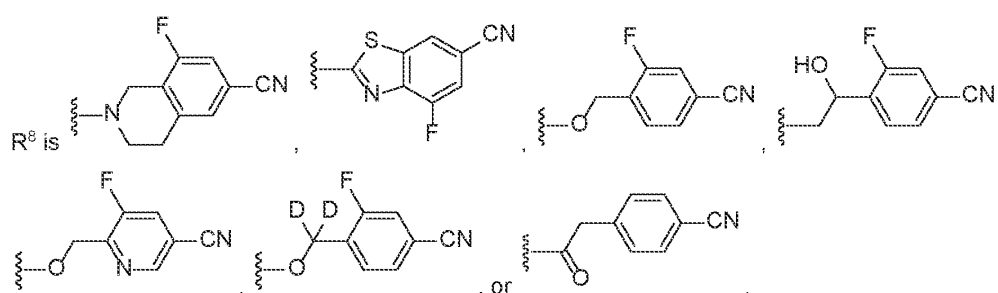
R⁶ is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

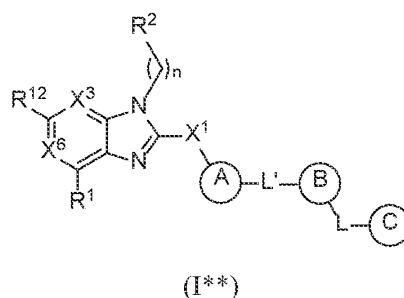
104. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1a):



wherein R^7 is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



105. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I**):



or a pharmaceutically acceptable salt thereof; wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, halogen, $-O-X^4$, or $-NR^8R^9$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$, or $-(C_{1-6} \text{ alkylene})-(3- \text{ to } 8\text{-membered heterocyclyl})$, 3- to 8-membered

heterocyclyl, $-(\text{CH}_2\text{CH}_2\text{-O})_{1-5}\text{-CH}_3$, $-(\text{CH}_2\text{-CH}(\text{-OCH}_3)\text{-CH}_2\text{-O})_{1-5}\text{-CH}_3$, C_{3-10} cycloalkyl, or C_{6-10} aryl, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, C_{1-6} alkoxy, hydroxyl, $-\text{CN}$, or oxo, and the cycloalkyl, heterocyclyl, or aryl group is optionally substituted with one or more halogen, C_{1-6} alkoxy, or $-\text{CN}$;

R^6 is hydrogen, halogen, or $-\text{O-R}^7$;

wherein R^7 and R^2 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or $-\text{S}(\text{O})_2\text{-C}_{1-6}$ alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

C_{1-6} alkyl optionally substituted with deuterium;

C_{1-6} haloalkyl;

$-(\text{O})\text{-C}_{1-6}$ alkyl;

$-\text{CN}$;

a C_{3-10} cycloalkyl optionally substituted with one or more $-\text{CN}$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-\text{CN}$;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, $\text{HN}=\text{N}$, or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

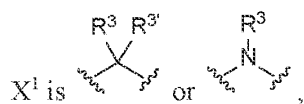
R^4 is halogen, hydrogen, $-\text{C}(\text{O})\text{OH}$, or $-\text{O-R}^8$,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^{12} is hydrogen, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}^{\text{N}12}\text{R}^{\text{N}12'}$, $-\text{C}(\text{O})\text{NR}^{\text{N}12}\text{S}(\text{O})_2\text{R}^{\text{N}12'}$, $-(\text{C}_{2-6}$ alkynylene)- $\text{C}(\text{O})\text{OH}$, $-(\text{C}_{1-6}$ alkylene)- $\text{C}(\text{O})\text{OH}$, $-\text{NR}^{\text{N}12}\text{-(C}_{1-6}$ alkylene)- $\text{C}(\text{O})\text{OH}$, 5-10 membered

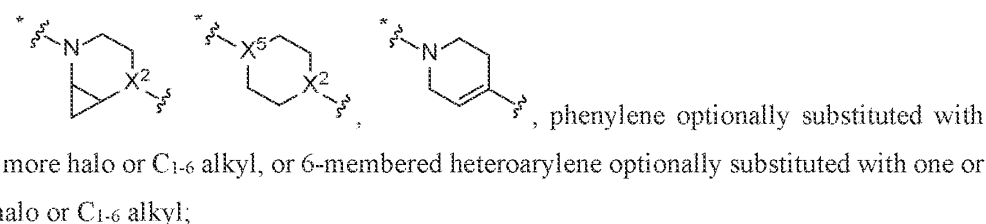
heteroaryl or 5- to 10-membered heterocyclyl optionally substituted with one or more oxo, C₁₋₆ alkyl or C₁₋₆ haloalkyl;

R^{N12} and R^{N12'} independently are H or C₁₋₆ alkyl;



wherein R³ and R^{3'} independently are H, D or C₁₋₆ alkyl, wherein the C₁₋₆ alkyl is optionally substituted with deuterium;

Ring A is



wherein * indicates attachment to X¹,

X⁵ is CR³ or N, and

X² is CR³ or N;

L' is a bond or -O-;

Ring B is a C₆₋₁₀ arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C₆₋₁₀ arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;

L is a bond, *-(C₁₋₆ alkylene)-, *-NR^L-(C₁₋₆ alkylene)-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium;

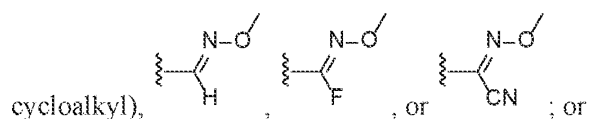
wherein R^L is H or C₁₋₆ alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₃₋₁₀ cycloalkyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, 3-10 membered heterocyclyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -CN, C₃₋₁₀ cycloalkyl, or -C(O)NR'₂;

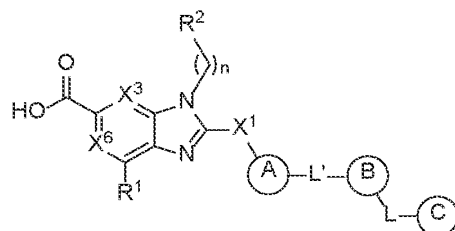
wherein R' is H or C₁₋₆ alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, -CN, C₁₋₆ haloalkyl, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀



a bicyclic 9- or 10-membered heteroaryl or heterocyclyl optionally substituted with one or more C₁₋₆ alkyl, halogen, -CN, or oxo.

106. The THR-β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-5)



(I-5)

or a pharmaceutically acceptable salt thereof, wherein:

X³ is CR⁶ or N;

X⁶ is CR⁴ or N;

R¹ is -C₁₋₆ haloalkyl, -O-X⁴, or -NR⁸R⁹, or R¹ and R⁴, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X⁴ is hydrogen, C₁₋₆ alkyl, C₁₋₆ heteroalkyl, C₁₋₆ haloalkyl, -(C₁₋₆ alkylene)-(C₃₋₁₀ cycloalkyl), or -(C₁₋₆ alkylene)-(3- to 8-membered heterocyclyl), 3- to 8-membered heterocyclyl, -(CH₂CH₂-O)₁₋₅-CH₃, or -(CH₂-CH(-OCH₃)-CH₂-O)₁₋₅-CH₃, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R⁶ is hydrogen, halogen, or -O-R⁷;

wherein R⁷ and R², together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R⁸ and R⁹ each independently are selected from hydrogen, C₁₋₆ alkyl, or -S(O)₂-C₁₋₆ alkyl, or R⁸ and R⁹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C₁₋₆ alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R² is:

hydrogen;

branched C₁₋₆ alkyl;

C₁₋₆ haloalkyl;

-(O)-C₁₋₆ alkyl;

a C₃₋₁₀ cycloalkyl optionally substituted with one or more -CN, C₁₋₆ haloalkyl, or C₁₋₆ alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

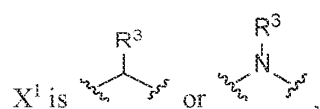
oxo, , or C₁₋₆ alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R⁵ is S; or

R² and R⁷, together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

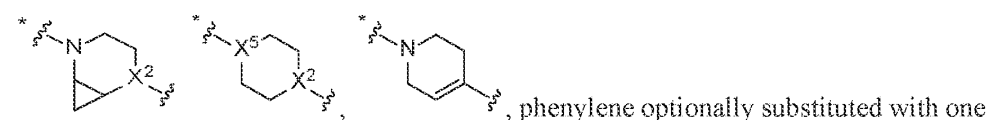
R⁴ is hydrogen or -O-R⁸,

wherein R⁸ and R¹, together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R³ is H or C₁₋₆ alkyl;

Ring A is



or more halo or C₁₋₆ alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C₁₋₆ alkyl;

wherein * indicates attachment to X¹,

X⁵ is CR³ or N, and

X² is CR³ or N;

L' is a bond or -O-;

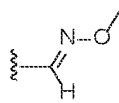
Ring B is a C₆₋₁₀ arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C₆₋₁₀ arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;

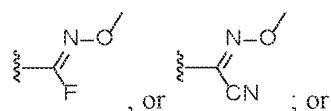
L is a bond, *-CH₂-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₁₋₆ alkyl, 3-10 membered heterocyclyl, halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

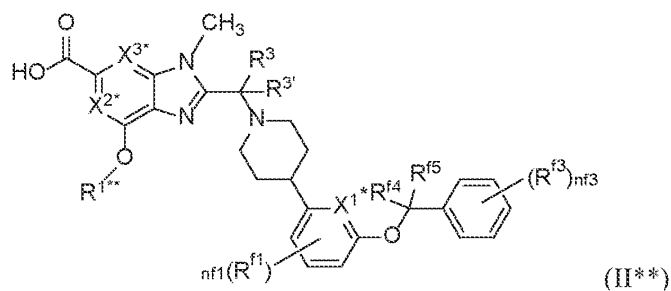
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl), ,



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

107. The THR-β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (II**):



or a pharmaceutically acceptable salt thereof, wherein

R^{f4} and R^{f5} are each independently selected from C₁₋₆ alkyl, H and D

nf1 is 0, 1, 2, 3, or 4;

nf3 is 0, 1, 2, 3, 4, or 5;

each R^{f1} is halogen;

R³ and R^{3'} independently are H or D;

X^{1*} is N or CR^{f1};

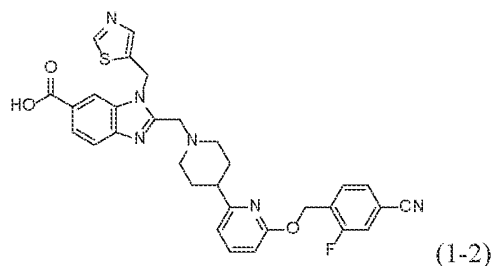
X^{2*} and X^{3*} independently are CH or CF;

each R^{13} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or $-C(O)N(R^{13})_2$,

each R^{13*} is independently selected from H or C_{1-6} alkyl; and

R^{1**} is H or C_{1-2} alkyl optionally substituted with one or more deuterium or halogen.

108. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

109. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is a meglumine salt of Compound 1-2.

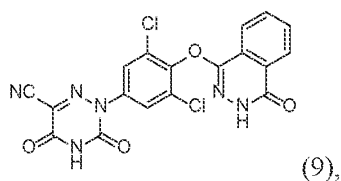
110. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is selected from those listed in Tables 6-11.

111. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Tables 1-5.

112. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the

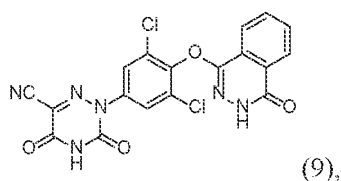
preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Table 5A.

113. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is Compound 9



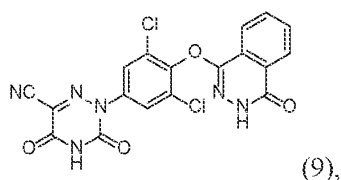
and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

113a. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is compound 9



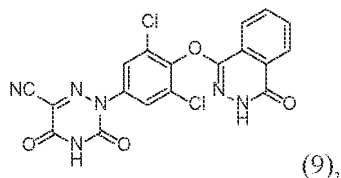
and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

113b. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is compound 9



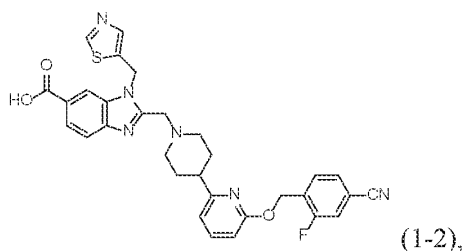
and the GLP-1R agonist is semaglutide or a pharmaceutically acceptable salt thereof.

113c. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is compound 9



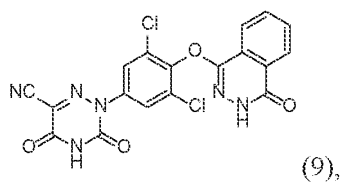
and the GLP-1R agonist is danuglipron or a pharmaceutically acceptable salt thereof.

114. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is resmetirom, VK2809, sobetirome, eprotirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is Compound 1-2

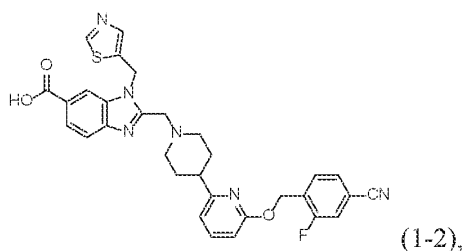


or a pharmaceutically acceptable salt thereof.

115. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is compound 9



or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is Compound 1-2



or a pharmaceutically acceptable salt thereof.

116. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the patient has a body mass index (BMI) of 25 kg/m² to 30 kg/m².

117a. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the patient has a BMI of 27 kg/m² or greater.

117b. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the patient has a BMI of 30 kg/m² or greater.

118. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the GLP-1R agonist is administered to the subject more than once.

119. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is administered to the subject more than once.

120. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein both the GLP-1R agonist and THR- β agonist are administered to the subject more than once.

121. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is administered prior to or concurrent with the GLP-1R agonist.

122. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is administered in temporal proximity to the GLP-1R agonist.

123. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is administered on the same day as the GLP-1R agonist.

124. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is administered at substantially the same time as the GLP-1R agonist.

125. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.

126. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered on the same day as the GLP-1R agonist.

127. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the

preceding embodiments, wherein the initial dose of THR β agonist is at substantially the same time as the GLP-1R agonist.

128. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered prior to the initial dose of GLP-1R agonist.

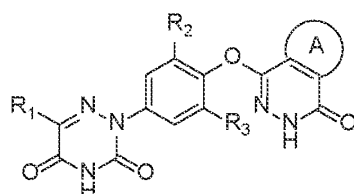
129. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.

130. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered on the same day as the GLP-1R agonist.

131. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered at substantially the same time as the GLP-1R agonist.

132. A method of treating obesity in a patient in need thereof, the method comprising administering a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof, to the patient.

133. The method of embodiment 132, wherein the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

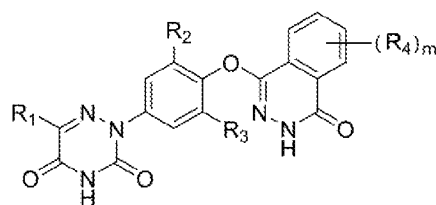
R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br, or a pharmaceutically acceptable salt thereof.

134. The method of embodiment 132 or 133, wherein the THRβ agonist is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

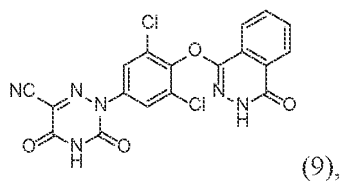
R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

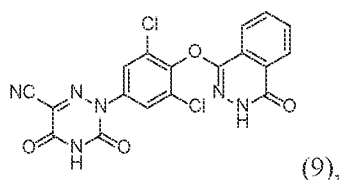
or a pharmaceutically acceptable salt thereof.

135. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



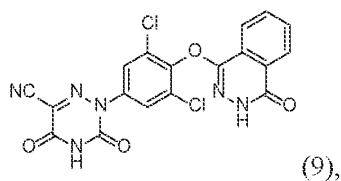
and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

135a. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



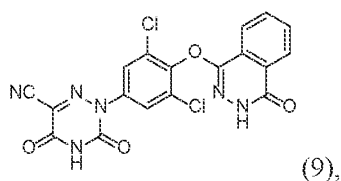
and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

135b. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



and the GLP-1R agonist is semaglutide or a pharmaceutically acceptable salt thereof.

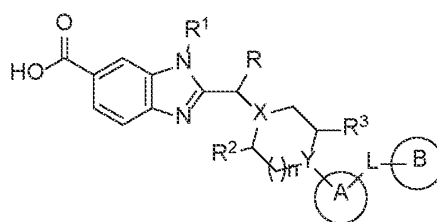
135c. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



and the GLP-1R agonist is danuglipron or a pharmaceutically acceptable salt thereof.

136. The method of any one of the preceding embodiments, wherein the THR β agonist is a potassium salt of Compound 9.

137. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1):



(I-1)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH, or C₁-C₆ alkyl;

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom of R⁵ is S, and further wherein R⁵ is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁-C₆ haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

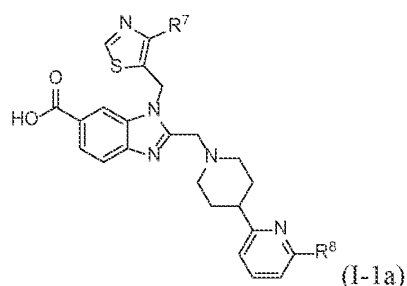
when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene of L is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L1}, wherein each R^{L1} is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

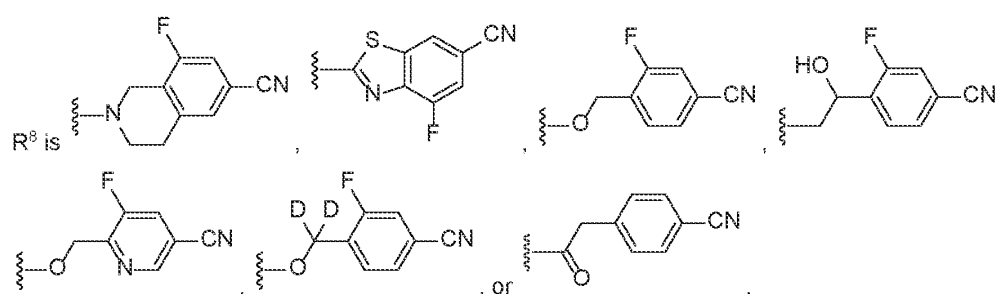
R⁶ is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

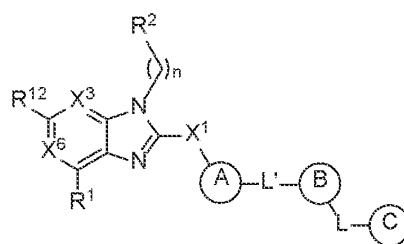
138. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1a):



wherein R⁷ is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



139. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I**):



(I**)

or a pharmaceutically acceptable salt thereof, wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, halogen, $-O-X^4$, or $-NR^8R^9$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$, or $-(C_{1-6} \text{ alkylene})-(3- \text{ to } 8\text{-membered heterocyclyl})$, 3- to 8-membered heterocyclyl, $-(CH_2CH_2-O)_{1-5}-CH_3$, $-(CH_2-CH(-OCH_3)-CH_2-O)_{1-5}-CH_3$, C_{3-10} cycloalkyl, or C_{6-10} aryl, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more deuterium, C_{1-6} alkoxy, hydroxyl, $-CN$, or oxo, and the cycloalkyl, heterocyclyl, or aryl group is optionally substituted with one or more halogen, C_{1-6} alkoxy, or $-CN$;

R^6 is hydrogen, halogen, or $-O-R^7$;

wherein R^7 and R^2 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or $-S(O)_2-C_{1-6}$ alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

C_{1-6} alkyl optionally substituted with deuterium;

C_{1-6} haloalkyl;

$-(O)-C_{1-6}$ alkyl;

$-CN$;

a C_{3-10} cycloalkyl optionally substituted with one or more $-CN$, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more $-CN$;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

oxo, $\text{HN}=\text{C}$, or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

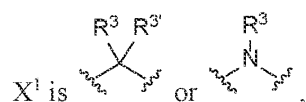
R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

R^4 is halogen, hydrogen, $-\text{C}(\text{O})\text{OH}$, or $-\text{O}-\text{R}^8$,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

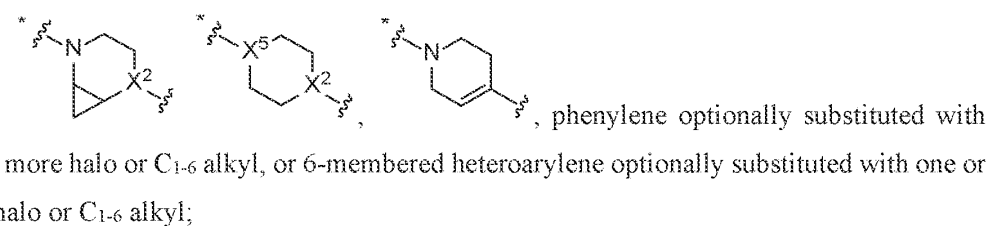
R^{12} is hydrogen, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NR}^{\text{N}12}\text{R}^{\text{N}12'}$, $-\text{C}(\text{O})\text{NR}^{\text{N}12}\text{S}(\text{O})_2\text{R}^{12'}$, $-(\text{C}_{2-6} \text{ alkynylene})-\text{C}(\text{O})\text{OH}$, $-(\text{C}_{1-6} \text{ alkylene})-\text{C}(\text{O})\text{OH}$, $-\text{NR}^{\text{N}12}-(\text{C}_{1-6} \text{ alkylene})-\text{C}(\text{O})\text{OH}$, 5-10 membered heteroaryl or 5- to 10-membered heterocyclyl optionally substituted with one or more oxo, C_{1-6} alkyl or C_{1-6} haloalkyl;

$\text{R}^{\text{N}12}$ and $\text{R}^{\text{N}12'}$ independently are H or C_{1-6} alkyl;



wherein R^3 and $\text{R}^{3'}$ independently are H, D or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with deuterium;

Ring A is



wherein * indicates attachment to X^1 ,

X^5 is CR^3 or N, and

X^2 is CR^3 or N;

L^1 is a bond or $-\text{O}-$;

Ring B is a C_{6-10} arylene, a 5-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C_{6-10} arylene, 5-10 membered heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more oxo, C_{1-6} alkyl, C_{1-6} alkoxy, or halogen;

L is a bond, $^{*}-(C_{1-6} \text{ alkylene})-$, $^{*}-NR^L-(C_{1-6} \text{ alkylene})-$, $^{*}-O-(C_{1-6} \text{ alkylene})-$, or $^{*}-(C_{1-6} \text{ alkylene})-O-$, wherein * indicates attachment to Ring B and the C_{1-6} alkylene is optionally substituted with deuterium;

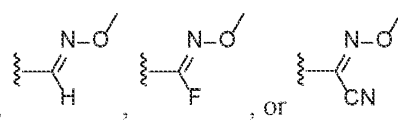
wherein R^L is H or C_{1-6} alkyl; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C_{3-10} cycloalkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, 3-10 membered heterocyclyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-CN$, C_{3-10} cycloalkyl, or $-C(O)NR'^2$;

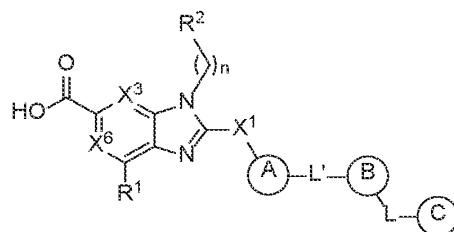
wherein R' is H or C_{1-6} alkyl

a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one or more halogen, $-CN$, C_{1-6} haloalkyl, $-O-C_{1-6}$ alkyl, C_{3-10} cycloalkyl, $-C(=O)-(C_{3-10}$

cycloalkyl), ; or

a bicyclic 9- or 10-membered heteroaryl or heterocyclyl optionally substituted with one or more C_{1-6} alkyl, halogen, $-CN$, or oxo.

140. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-5)



(I-5)

or a pharmaceutically acceptable salt thereof, wherein:

X^3 is CR^6 or N;

X^6 is CR^4 or N;

R^1 is $-C_{1-6}$ haloalkyl, $-O-X^4$, or $-NR^8R^9$, or R^1 and R^4 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

X^4 is hydrogen, C_{1-6} alkyl, C_{1-6} heteroalkyl, C_{1-6} haloalkyl, $-(C_{1-6} \text{ alkylene})-(C_{3-10} \text{ cycloalkyl})$, or $-(C_{1-6} \text{ alkylene})-(3- \text{ to } 8\text{-membered heterocyclyl})$, 3- to 8-membered heterocyclyl, $-(CH_2CH_2-O)_{1.5}-CH_3$, or $-(CH_2-CH(-OCH_3)-CH_2-O)_{1.5}-CH_3$, wherein the alkyl, heteroalkyl, alkylene, or haloalkyl group is optionally substituted with one or more

deuterium, hydroxyl, -CN, or oxo, and the cycloalkyl or heterocyclyl group is optionally substituted with one or more halogen or -CN;

R^6 is hydrogen, halogen, or -O- R^7 ;

wherein R^7 and R^2 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;

R^8 and R^9 each independently are selected from hydrogen, C_{1-6} alkyl, or -S(O)₂- C_{1-6} alkyl, or R^8 and R^9 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl; wherein the C_{1-6} alkyl is optionally substituted by one or more oxo;

n is 0, 1, 2, 3, 4, 5, or 6;

R^2 is:

hydrogen;

branched C_{1-6} alkyl;

C_{1-6} haloalkyl;

-(O)- C_{1-6} alkyl;

a C_{3-10} cycloalkyl optionally substituted with one or more -CN, C_{1-6} haloalkyl, or C_{1-6} alkyl optionally substituted with one or more -CN;

a 4 or 5-membered heterocyclyl comprising at least one oxygen or at least one sulfur atom, wherein the 4- or 5-membered heterocyclyl is optionally substituted with one or more

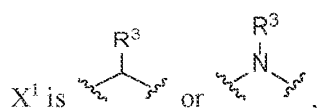
oxo, , or C_{1-6} alkyl;

a 5-membered heteroaryl, comprising 1 or 2 heteroatoms independently selected from N, and S, wherein at least one heteroatom of R^5 is S; or

R^2 and R^7 , together with the atoms to which they are attached, combine to form a 5- or 6-membered heterocyclyl;

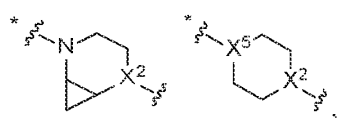
R^4 is hydrogen or -O- R^8 ,

wherein R^8 and R^1 , together with the atoms to which they are attached, combine to form a 6-membered heterocyclyl;



wherein R^3 is H or C_{1-6} alkyl;

Ring A is



, phenylene optionally substituted with one or more halo or C₁₋₆ alkyl, or 6-membered heteroarylene optionally substituted with one or more halo or C₁₋₆ alkyl;

wherein * indicates attachment to X¹,

X⁵ is CR³ or N, and

X² is CR³ or N;

L' is a bond or -O-;

Ring B is a C₆₋₁₀ arylene, a 6-10 membered heteroarylene, or a 3-10 membered heterocyclene, wherein the C₆₋₁₀ arylene, 6-10 heteroarylene, or 3-10 membered heterocyclene is optionally substituted with one or more C₁₋₆ alkyl, C₁₋₆ alkoxy, or halogen;

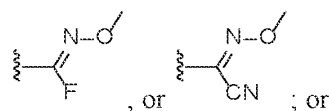
L is a bond, *-CH₂-, *-O-(C₁₋₆ alkylene)-, or *-(C₁₋₆ alkylene)-O-, wherein * indicates attachment to Ring B and the C₁₋₆ alkylene is optionally substituted with deuterium; and

Ring C is:

a 6-membered aryl optionally substituted with one or more C₁₋₆ alkyl, 3-10 membered heterocyclyl, halogen, -OCH₃, -CN, or C₃₋₁₀ cycloalkyl;

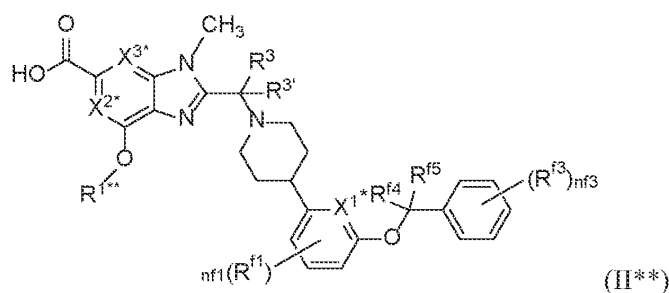
a 6-membered heteroaryl comprising a nitrogen atom optionally substituted with one

or more halogen, -CN, -O-C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, -C(=O)-(C₃₋₁₀ cycloalkyl),



a bicyclic 9- or 10-membered heteroaryl comprising two nitrogen atoms optionally substituted with one or more C₁₋₆ alkyl, or oxo.

141. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (II**):



or a pharmaceutically acceptable salt thereof, wherein

R^{f4} and R^{f5} are each independently selected from C_{1-6} alkyl, H and D

$nf1$ is 0, 1, 2, 3, or 4;

$nf3$ is 0, 1, 2, 3, 4, or 5;

each R^{f1} is halogen;

R^3 and $R^{3'}$ independently are H or D;

X^{1*} is N or CR^{f1} ;

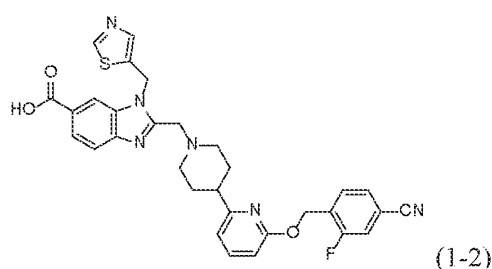
X^{2*} and X^{3*} independently are CH or CF;

each R^{f3} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or $-C(O)N(R^{f3'})_2$,

each $R^{f3'}$ is independently selected from H or C_{1-6} alkyl; and

R^{1**} is H or C_{1-2} alkyl optionally substituted with one or more deuterium or halogen.

142. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

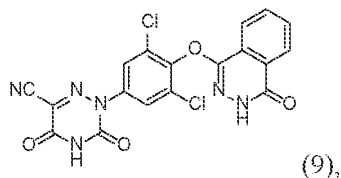
143. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is a meglumine salt of Compound 1-2.

144. The method of any one of the preceding embodiments, wherein the THR β agonist is selected from those listed in Tables 6-11.

145. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Tables 1-5.

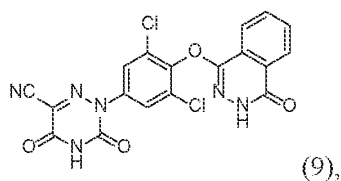
146. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Table 5A.

147. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



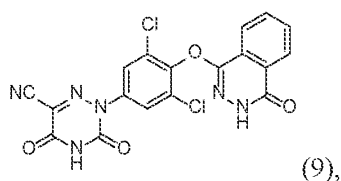
and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

147a. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



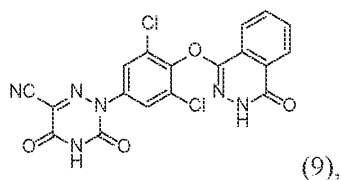
and the GLP-1R agonist is orforglipron or a pharmaceutically acceptable salt thereof.

147b. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



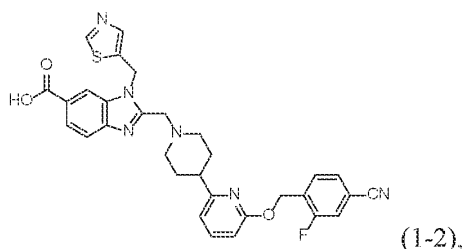
and the GLP-1R agonist is semaglutide or a pharmaceutically acceptable salt thereof.

147c. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



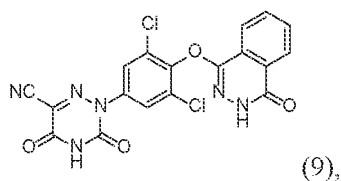
and the GLP-1R agonist is danuglipron or a pharmaceutically acceptable salt thereof.

148. The method of any one of the preceding embodiments, wherein the THR β agonist is resmetirom, VK2809, sobetirome, eprotirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is compound 1-2

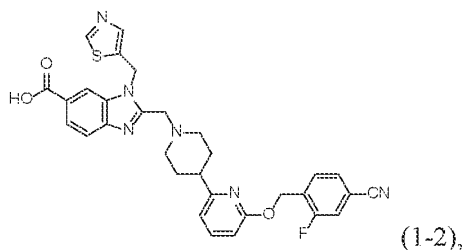


or a pharmaceutically acceptable salt thereof.

149. The method of any one of the preceding embodiments, wherein the THR β agonist is compound 9



or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is compound 1-2



or a pharmaceutically acceptable salt thereof.

150. The method of any one of the preceding embodiments, wherein the patient has a body mass index (BMI) of 25 kg/m² to 30 kg/m².

151. The method of any one of the preceding embodiments, wherein the patient has a BMI of 30 kg/m² or greater.

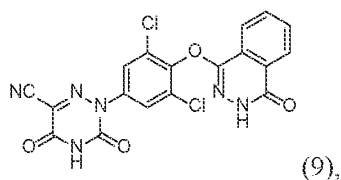
152. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is administered to the subject more than once.
153. The method of any one of the preceding embodiments, wherein the THR β agonist is administered to the subject more than once.
154. The method of any one of the preceding embodiments, wherein both the GLP-1R agonist and THR- β agonist are administered to the subject more than once.
155. The method of any one of the preceding embodiments, wherein the THR β agonist is administered prior to or concurrent with the GLP-1R agonist.
156. The method of any one of the preceding embodiments, wherein the THR β agonist is administered in temporal proximity to the GLP-1R agonist.
157. The method of any one of the preceding embodiments, wherein the THR β agonist is administered on the same day as the GLP-1R agonist.
158. The method of any one of the preceding embodiments, wherein the THR β agonist is administered at substantially the same time as the GLP-1R agonist.
159. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.
160. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered on the same day as the GLP-1R agonist.
161. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is at substantially the same time as the GLP-1R agonist.
162. The method of any one of the preceding embodiments, wherein the initial dose of THR β agonist is administered prior to the initial dose of GLP-1R agonist.

163. The method of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered in temporal proximity to the GLP-1R agonist.

164. The method of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered on the same day as the GLP-1R agonist.

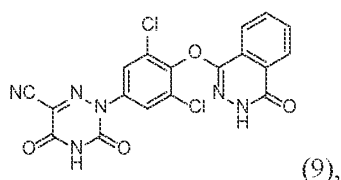
165. The method of any one of the preceding embodiments, wherein a subsequent dose of THR β agonist is administered at substantially the same time as the GLP-1R agonist.

166. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



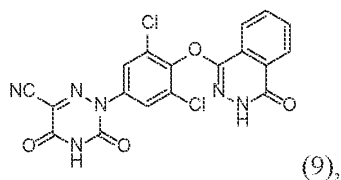
and the GLP-1R agonist is orforglipron, or a pharmaceutically acceptable salt thereof.

167. The combinational therapy of any one of the preceding embodiments, wherein the THR β agonist is compound 9



and the GLP-1R agonist is orforglipron, or a pharmaceutically acceptable salt thereof.

168. The THR- β agonist, or pharmaceutically acceptable salt thereof, and GLP-1R agonist, or pharmaceutically acceptable salt thereof, for use according to any one of the preceding embodiments, wherein the THR β agonist is compound 9



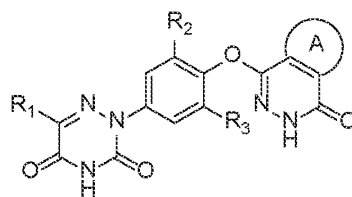
and the GLP-1R agonist is orforglipron, or a pharmaceutically acceptable salt thereof.

169. The method of any one of the preceding embodiments, wherein the GLP-1R agonist is orforglipron, or a pharmaceutically acceptable salt thereof.

Embodiments A1-A48

A1. A combination comprising a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof.

A2. The combination of embodiment A1, wherein the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

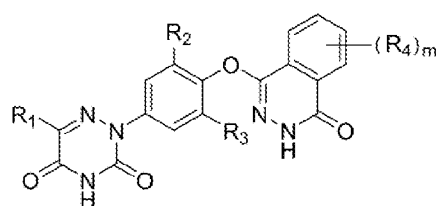
R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br;
or a pharmaceutically acceptable salt thereof.

A3. The combination of embodiment A1 or A2, wherein the THR β agonist is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

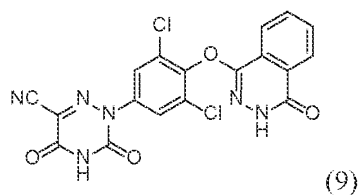
R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

A4. The combination of any one of the preceding embodiments, wherein the THRβ agonist is Compound 9:

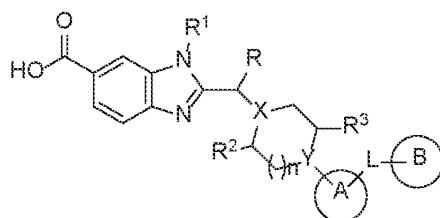


(9)

or a pharmaceutically acceptable salt thereof.

A5. The combination of any one of the preceding embodiments, wherein the THRβ agonist is a potassium salt of Compound 9.

A6. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1):



(I-1)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH, or C₁-C₆ alkyl;

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom of R⁵ is S, and further wherein R⁵ is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁-C₆ haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

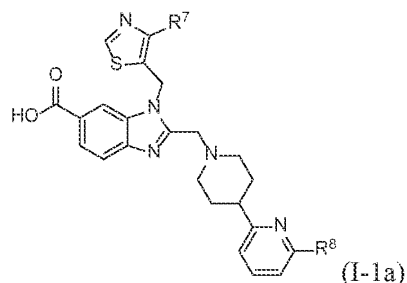
when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene of L is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L1}, wherein each R^{L1} is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

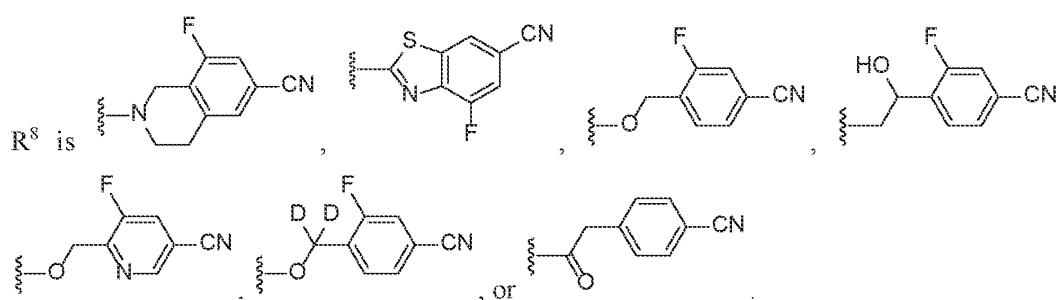
R⁶ is hydrogen or C₁-C₆ alkyl; and

Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

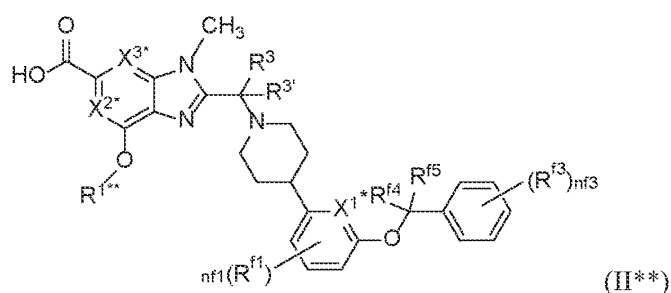
A7. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (I-1a):



wherein R⁷ is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



A8. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a compound of Formula (II**):



or a pharmaceutically acceptable salt thereof, wherein

R^{f4} and R^{f5} are each independently selected from C₁₋₆ alkyl, H and D

nf1 is 0, 1, 2, 3, or 4;

nf3 is 0, 1, 2, 3, 4, or 5;

each R^{f1} is halogen;

R³ and R^{3'} independently are H or D;

X^{1*} is N or CR^{f1};

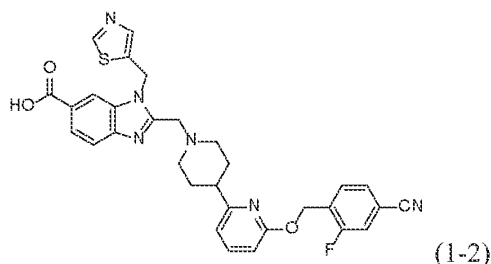
X^{2*} and X^{3*} independently are CH or CF;

each R^{13} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or -C(O)N(R^{13})₂,

each $R^{13'}$ is independently selected from H or C_{1-6} alkyl; and

R^{1**} is H or C_{1-2} alkyl optionally substituted with one or more deuterium or halogen.

A9. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

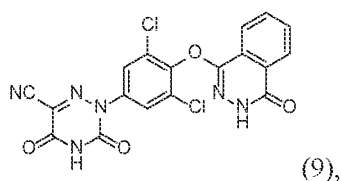
A10. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is a meglumine salt of Compound 1-2.

A11. The combination of any one of the preceding embodiments, wherein the THR β agonist is selected from those listed in Tables 6-11, or a pharmaceutically acceptable salt thereof.

A12. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Tables 1-5, or a pharmaceutically acceptable salt thereof.

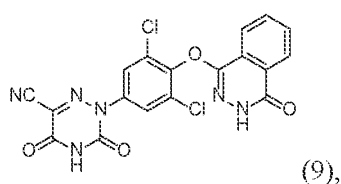
A13. The combination of any one of the preceding embodiments, wherein the GLP-1R agonist is selected from those listed in Table 5A, or a pharmaceutically acceptable salt thereof.

A14. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



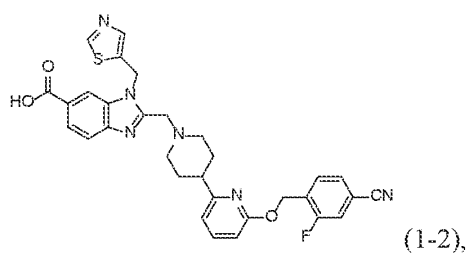
and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

A15. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



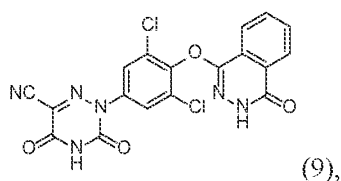
and the GLP-1R agonist is orforglipron, danuglipron, or semaglutide, or a pharmaceutically acceptable salt thereof.

A16. The combination of any one of the preceding embodiments, wherein the THR β agonist is resmetirom, VK2809, sobetirome, eprotrirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is compound 1-2

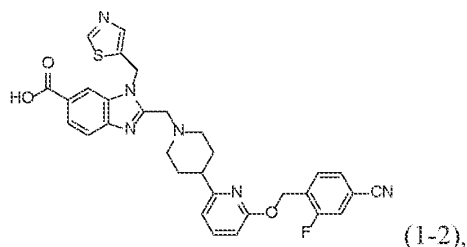


or a pharmaceutically acceptable salt thereof.

A17. The combination of any one of the preceding embodiments, wherein the THR β agonist is compound 9



or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is compound 1-2



or a pharmaceutically acceptable salt thereof.

A18. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is from about 0.5 mg to about 25 mg.

A19. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is from about 1 mg to about 15 mg.

A20. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is from about 2 mg to about 10 mg.

A21. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is about 1 mg.

A22. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is about 3 mg.

A23. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is about 6 mg.

A24. The combination of any one of the preceding embodiments, wherein the amount of the THR β agonist is about 10 mg.

A25. The combination of any one of the preceding embodiments for use in the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.

A26. The combination of any one of the preceding embodiments for use in effectuating weight loss in a patient in need thereof.

A27. The combination of any one of the preceding embodiments for use in a combinational therapy for the treatment of obesity in a patient in need thereof.

A28. A method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding embodiments.

A29. A method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the combination according to any one of the preceding embodiments.

A30. A method of increasing the proportion of lean body mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding embodiments.

A31. A method of decreasing the proportion of fat mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding embodiments.

A32. A method of effectuating weight loss in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding embodiments.

A33. The method of any one of the preceding embodiments, wherein the patient has a Body Mass Index (BMI) of 27 kg/m^2 or greater.

A34. The method of any one of the preceding embodiments, wherein the patient has a BMI of 30 kg/m^2 or greater.

A35. The method of any one of the preceding embodiments, wherein the administration of the THR β agonist allows for administration of a reduced dose of the GLP-1R agonist while maintaining equivalent weight loss.

A36. The method of any one of the preceding embodiments, wherein the administration of the THR β agonist increases weight loss compared to administration of a GLP-1R agonist at an equivalent dose.

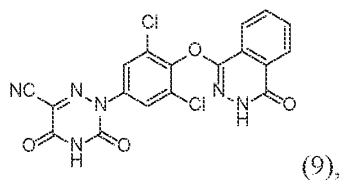
A37. The method of any one of the preceding embodiments, wherein the cardiometabolic disease is obesity or an obesity-associated condition.

A38. The method of any one of the preceding embodiments, wherein the cardiometabolic disease is diabetes.

A39. The method of any one of the preceding embodiments, wherein the combination or method improves glycemic control in adults with type 2 diabetes mellitus.

A40. A method of treating obesity or effectuating weight loss in a patient in need thereof, the method comprising

(i) administering to the patient compound 9



or a pharmaceutically acceptable salt thereof, and

(ii) administering to the patient a GLP-1R agonist, or a pharmaceutically acceptable salt thereof,

wherein administering to the patient compound 9, or a pharmaceutically acceptable salt thereof, improves the patient's response to the GLP-1R agonist or a pharmaceutically acceptable salt thereof.

A41. The combination or method of any one of the preceding embodiments, wherein the THR β agonist is administered once daily or twice daily.

A42. The combination or method of any one of the preceding embodiments, wherein the THR β agonist is administered orally.

A43. The combination or method of any one of the preceding embodiments, wherein the GLP-1R agonist is administered orally.

A44. The method of embodiment A40, wherein the GLP-1R agonist comprises compound 1-2, orforglipron, semaglutide, tirzepatide, or danuglipron.

A45. The method of any one of the preceding embodiments, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, increases fat loss associated with administering the GLP-1R agonist.

A46. The method of any one of the preceding embodiments, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, increases fat loss associated with administering the GLP-1R agonist while maintaining lean mass.

A47. The combination of any one of embodiments A1-A27 for the preparation of a medicament for the use in a method according to any one of embodiments A28-A46.

A48. Use of the combination of any one of embodiments A1-A27 in a method according to any one of embodiments A28-A46.

EXAMPLES

[0295] The combination treatment provided herein can be tested by administering the combination of the agents to a well-known mouse model and evaluating the results. Methods of such testing can be adapted from those known.

Example 1. Evaluating THR-B agonist Compound 9 in combination with a GLP-1R agonist (e.g., Semaglutide)

[0296] To evaluate the effect of 12 weeks of treatment with Compound 9 alone and in combination with semaglutide on metabolic parameters, hepatic pathology and NAFLD Activity Score including Fibrosis Stage in male biopsy-confirmed GAN DIO-NASH mice are determined.

Sample Formulation

Compound	Frequency of preparation	Dosing solution Stored at 4°C			Detailed instruction on compound preparation
		Conc.	Storage [temp]	pH	
Vehicle (Compound 9)	Weekly	NA	4°C	8	1% HP- β -CD (Cyclodextrin) and 90% 50 mM Tris buffer in reverse osmosis water (pH 8.0 $\pm$ 0.2 with NaOH or HCl)
Vehicle (Semaglutide)	Weekly	NA	4°C	7.4	PBS + 0.1% BSA
Compound 9	Daily	Gr. 3 and 6: 1.2 mg/ml Gr. 4 and 7: 0.6 mg/ml	4°C	8	Weigh out compound in amber colored vial, add vehicle and pH adjust to 8.0 with NaOH or HCL; stir and sonicate (if needed) for ~20 minutes. Solution may be slightly opaque. Dilute with vehicle to achieve the low concentration. Always protect from light.
Semaglutide	Weekly	6 nmol/ml*	4°C	7.4	Dilute in PBS + 0.1% BSA

* Titration: 0.12 nmol/ml day 1; 0.24 nmol/ml day 2; 0.48 nmol/ml day 3; 0.96 nmol/ml day 4; 2.4 nmol/ml day 5, 6 nmol/ml day 6

Groups of the study

Group		Compound	n	Model	Dosing conc.	Dosing 5ml/kg, QD, AM
#	Name					Route
1	Lean-chow Vehicle	Vehicle (Compound 9)	10	Lean chow	NA	PO
		Vehicle (Semaglutide)			NA	SC
2	DIO-NASH Vehicle	Vehicle (Compound 9)	18	DIO-NASH	NA	PO
		Vehicle (Semaglutide)			NA	SC
3	Compound 9 (6 mg/kg)	Compound 9	18	DIO-NASH	6 mg/kg	PO
		Vehicle (Semaglutide)			NA	SC
4	Compound 9 (3 mg/kg)	Compound 9	18	DIO-NASH	3 mg/kg	PO
		Vehicle (Semaglutide)			NA	SC
5	Semaglutide	Semaglutide*	18	DIO-NASH	30 nmol/kg	SC
		Vehicle (Compound 9)			NA	PO
6	Compound 9 (6 mg/kg)+ Semaglutide	Compound 9	18	DIO-NASH	6 mg/kg	PO
		Semaglutide*			30 nmol/kg	SC
7	Compound 9 (3 mg/kg)+ Semaglutide	Compound 9	18	DIO-NASH	3 mg/kg	PO
		Semaglutide*			30 nmol/kg	SC

*Titration: 0.6 nmol/kg day 1; 1.2 nmol/kg day 2; 2.4 nmol/kg day 3; 4.8 nmol/kg day 4; 12 nmol/kg day 5, 30 nmol/kg day 6.

Measurements (In vivo pharmacology)

Measurement Name	Groups	Sample Name	Periods or frequency	Comments
Body weight	All	NA	QD from day -3 to day 85/86	NA
Food intake	All	NA	QW from week 1 to week 12	NA
Fasting BG	All	4h Fasting blood glucose	Week 10	NA
EchoMRI	All	NA	Week 12	Whole body lean/fat tissue mass
Liver weight	All	Liver weight	Termination	NA

Measurements (Histology)

Measurement Name	Sample Name	Comments
Fibrosis quantification for randomization	Liver pre-biopsy Liver post biopsy	PSR staining
NAFLD Activity Score	Liver pre-biopsy Liver post biopsy	HE staining
Fibrosis stage	Liver pre-biopsy Liver post biopsy	PSR staining
Steatosis quantification	Liver post biopsy	HE staining
Fibrosis (PSR) quantification	Liver post biopsy	PSR staining
Gal-3 quantification	Liver post biopsy	IHC staining
Colla1 quantification	Liver post biopsy	IHC staining
α -SMA quantification	Liver post biopsy	IHC staining

Measurements (Assays)

Measurement	Sample Type
Plasma insulin	4h Fasting plasma insulin
Plasma ALT	Plasma ALT/AST/TG/TC
Plasma AST	Plasma ALT/AST/TG/TC
Plasma TG	Plasma ALT/AST/TG/TC
Plasma TC	Plasma ALT/AST/TG/TC
Plasma TIMP-1	Plasma TIMP-1
Plasma PIIINP	Plasma PIIINP
Plasma CK18-M30	Plasma CK18- M30

Liver TG	Liver TG/TC
Liver TC	Liver TG/TC
Liver RNAseq	Liver RNAseq n=10

Non-alcoholic steatohepatitis (NASH) mouse model

[0297] This mouse model is fed a high fat diet that results in nonalcoholic steatohepatitis (NASH) disease. The NASH mice are based on male C57BL/6JRj mice fed a 40% fat, 22% fructose and 2% cholesterol diet (D09100310, SSNIFF, Germany) for at least 28 weeks, respectively, prior to experiment.

Liver biopsy

[0298] Mice are anesthetized by inhalation anesthesia using isoflurane (2-3%). A small abdominal incision is made in the midline and the left lateral lobe of the liver is exposed. A cone shaped wedge of liver tissue (approximately 50 mg) is excised from the distal portion of the lobe and fixated in 10% neutral buffered formalin (10% NBF) for histology. The cut surface of the liver is instantly electrocoagulated using bipolar coagulation (ERBE VIO 100 electrosurgical unit). The liver is returned to the abdominal cavity, the abdominal wall is sutured and the skin is closed with staplers. For post-operative recovery mice receive carprofen (5 mg/kg) administered subcutaneously on OP day and post-OP day 1 and 2.

Blood sampling and plasma preparation

[0299] *In vivo* blood samples: Samples are collected at week 8, 30 minutes post-dose, 1 hour post-dose, 2 hours post-dose, 4 hours post-dose, 6 hours post-dose, and 24 hours post-dose (before the next dose). Tail-vein, tongue or cheek blood is collected in a Microvette tube of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood is placed at 4°C until it is centrifuged at 3000 g for 10 minutes. The plasma supernatants are transferred to new tubes and immediately frozen on dry ice. The samples are stored at -70°C.

[0300] Termination blood samples: During anesthesia with isoflurane, the abdominal cavity is opened, and cardiac blood is drawn with a syringe into a Microvette/Vacurette of appropriate dimensions with anticoagulant and mixed by inversion 5 times. Blood is placed at 4°C until it is centrifuged at 3000 g for 10 minutes. The plasma supernatants are transferred to new tubes and immediately frozen on dry ice. The samples are stored at -70°C.

*Tissue sampling**Liver (NASH)*

[0301] After the animal has been terminated by heart puncture, the liver is collected and weighed. Specific liver samples and biopsies are dissected and processed as specified in table “Termination samples” and further described below.

[0302] The liver is divided into left lateral lobe, medial lobe, right lateral lobe, and caudate lobe. The remaining lobes are not used unless specified in the protocol.

[0303] The *Post-biopsy* piece (~200 mg, less than 0.7 x 0.5 cm) is cut from the left lateral lobe, 4 mm from the prebiopsy site with an edge. The tissue is collected in paraformaldehyde.

[0304] The *Liver Sponsor* piece (~150 mg) is dissected from the left medial lobe, put in a tube and placed directly into liquid nitrogen. The samples are stored at -70°C. Please note that the size of the sponsor piece varies according to the size of the left medial lobe.

[0305] The *Liver RNA Sequencing (RNAseq)* piece (20±10 mg) is dissected from the center of the left lateral lobe, snap frozen (put directly in liquid nitrogen in Nunc filter) and collected in a pre-cooled tube which is put in liquid nitrogen. The samples are stored at -70°C.

[0306] The *Liver TG TC* piece (25±5 mg) is dissected from the right medial lobe, with no edges, on the opposite side of the sponsor piece. The samples are weighed individually and collected in tubes before placed in liquid nitrogen. The samples are stored at -70°C.

[0307] The *Liver Extra* piece (~100-300 mg) is dissected from the right lateral lobe and collected in tubes before placed in liquid nitrogen, to have as backup tissue from the study and can be used for re-analysis if necessary. The samples are stored at -70°C.

*Biopsy processing**Microtome sectioning of Formalin fixed paraffin-embedded (FFPE) biopsies*

[0308] FFPE biopsies are placed in 10% neutral buffered formalin (10% NBF) for approximately 24h and then transferred to 70% EtOH and stored at 4°C. The FFPE biopsies are then placed in the Histokinette to infiltrate prior to embedding in blocks. Biopsy tissues are cut at 3µm on a microtome and the sections are mounted on Superfrost Plus slides and stored at 4°C.

NAFLD Activity Score (NAS) and Fibrosis stage

[0309] Liver samples stained with Hematoxylin and Eosin (H&E) or Picro Sirius Red (PSR) are given a score for NAS and fibrosis stage respectively using the clinical criteria outlined by Kleiner et al. 2005. Total NAS represents the sum of scores for steatosis, inflammation, and ballooning, and ranges from 0-8. Adapted from: Design and validation of a histological scoring system for nonalcoholic fatty liver disease, Kleiner et al., Hepatology 41; 2005

Histological staining procedures

[0310] In brief, slides with paraffin embedded sections are deparaffinated in xylene and rehydrated in series of graded ethanol.

[0311] Hematoxylin & Eosin (H&E) staining: Slides are incubated in Mayer's Hematoxylin (Dako), washed in tap water, stained in Eosin Y solution (Sigma-Aldrich), dehydrated and cover slipped.

[0312] Sirius red (PSR) staining: Slides are incubated in Weigert's iron hematoxylin (Sigma-Aldrich), washed in tap water, stained in Picro-sirius red (Sigma-Aldrich) and washed twice in acidified water. Excess water is removed by shaking the slides and the slides are then dehydrated in three changes of 100% ethanol, cleared in xylene and cover slipped.

[0313] Immunohistochemistry using single chromogen: IHC is performed using standard procedures. Briefly, after antigen retrieval and blocking of endogenous peroxidase activity, slides are incubated with primary antibody. The primary antibody is detected using a polymeric HRP-linker antibody conjugate. Next, the primary antibody is visualized with DAB as chromogen. Finally, sections are counterstained in hematoxylin and cover slipped. Slides are scanned under a 20X objective in a ScanScope AT slide scanner (Aperio).

Gene expression analysis using RNAseq

[0314] RNA isolation: Tissue is collected and snap-frozen in liquid nitrogen. Samples are stored at -70°C until processing. RNA is isolated using the NucleoSpin® kit (MACHEREY-NAGEL).

[0315] Library preparation and sequencing: A total of 10 ng-1 µg purified RNA from each sample is used to generate a cDNA library using the NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina (New England Biolabs). cDNA libraries are then sequenced on a NextSeq 500 using NextSeq 500/550 High Output Kit V2 (Illumina).

[0316] Data analysis: The sequencing data is aligned to the genome of the animal species obtained from the Ensembl database using the Spliced Transcripts Alignment to a Reference (STAR) software. For the bioinformatic analysis, the quality of the data is evaluated using the standard RNA-sequencing quality control parameters, the inter- and intra-group variability is evaluated using principal component analysis and hierarchical clustering and the differentially expressed genes are identified using the R-package DESeq2. Downstream analyses such as pathway analysis or target identification are performed as agreed with the sponsor.

Blood and plasma assays

[0317] Alanine transaminase (ALT), Aspartate transaminase (AST), Triglycerides (TG) and Total Cholesterol (TC): Blood samples are collected in heparinized tubes and plasma is

separated and stored at -70°C until analysis. Samples are measured using commercial kits (Roche Diagnostics), on the cobas c 501 autoanalyzer.

[0318] Cytokeratin 18 (CK18-M30): Blood samples are collected in EDTA tubes and plasma is separated and stored at -70°C until analysis. CK18 is measured using a commercial ELISA kit (Cusabio).

[0319] Insulin: Blood samples are collected in heparinized tubes and plasma is separated and stored at -70°C until analysis. Insulin is measured using the commercial MSD platform (Meso Scale Diagnostics).

[0320] TIMP-1: Blood samples are collected in EDTA tubes and plasma is separated and stored at -70°C until analysis. TIMP-1 is measured using a commercial ELISA kit (R&D Systems).

[0321] PIINP: Blood samples are collected in EDTA tubes and plasma is separated and stored at -70°C until analysis. PIINP is measured using a commercial ELISA kit (Cusabio).

Tissue assays

[0322] Triglycerides (TG) and Total cholesterol (TC): Liver samples are homogenized and TG and TC is extracted in 5% NP-40 by heating twice to 90°C. The samples are centrifuged and the TG and TC content is measured in the supernatant using commercial kits (Roche Diagnostics) on the cobas c 501 autoanalyzer.

Example 2: In vivo efficacy of Compound (1-2) alone and in combination with Compound 9 on weight loss in a high fat diet-induced obesity model in hGLP1R-C57BL/6J mice

[0323] hGLP1R-C57BL/6J mice on >20 weeks high fat diet to induce obesity are administered Compound (1-2) alone or in combination with Compound 9. Other groups are administered alternative GLP-1R agonists, e.g., semaglutide. Body weight and food-intake are measured daily.

Animal Use

Species	C57BL6/J-h-GLP1-r
Level	SPF
Weight	~45 g
Age (Order)	6-7 weeks
Age (Start)	23-24 weeks
Sex	Male

Method of Identification	The mice are singly housed per cage with a unique cage
Animal Number	127
Animal Number (used)	88

Mouse Generation

[0324] 118 h-GLP1R-C57BL/6J mice at 6-7 weeks age old are fed a high fat diet (HFD, Research Diets D12492i 60%kcal) for ~20 weeks to obtain a diet induced obese (DIO) phenotype, while n=10 h-GLP1R-C57BL/6J mice are fed regular chow diet to serve as lean controls. All animals have ad libitum access to diet and water. The animal room environment is controlled (target conditions: temperature 20 to 24°C, relative humidity 30 to 70%). Temperature and relative humidity are monitored daily. An electronic time-controlled lighting system is used to provide a 12-hour light/12-hour dark cycle. 2-3 mice are housed per plastic cage, which is in accordance with the National Research Council "Guide for the Care and Use of Laboratory Animals." Enrichment toys are provided. Before the formal experiment, the animals are housed in a single cage and adapted to the environment for at least one week. Weight is measured once a week during modeling.

Study Procedure

Group Design

Group ID	Treatment	Number	Dose level (mg/kg)	Dose volume (mL/kg)	Dose Method	Dose Frequency¹ Study Days	Start Dosing time
1	Vehicle (Lean)	8	-	5	PO	BID*30	9:30am, 17:30pm
2	Vehicle (DIO)	10	-	5	PO	BID*30	9:30am, 17:30pm
3	Danuglipron	10	10	5	PO	BID*30	9:30am, 17:30pm
4	Compound (1-2) High	10	10	5	PO	BID*30	9:30am, 17:30pm

5	Compound (1-2) Low	10	3	5	PO	BID*30	9:30am, 17:30pm
6	Compound 9	10	3	5	PO	QD*30	9:30am
	Vehicle	10	-	5	PO	QD*30	17:30pm
7	Compound (1-2) High+ Compound 9	10	10+3	5	PO	QD*30	9:30am
	Compound (1-2) High+ Vehicle	10	10	5	PO	QD*30	17:30pm
8	Compound (1-2) Low+ Compound 9	10	3+3	5	PO	QD*30	9:30am
	Compound (1-2) Low+ Vehicle	10	3	5	PO	QD*30	17:30pm
9	Semaglutide	10	10 nmol/kg	2	SC	QD*30	9:30am
	Saline	10	-	2	SC	QD*30	17:30pm

¹Test article is administered in the morning (9:30 to 10:30 am) for the Groups 6 and 9, and then administered a dose of vehicle (10% Solutol HS15: 90% sterile water, [v/v]) or saline (semaglutide vehicle) in the evening (17:30 to 18:30 pm) to balance treatment. For combination groups (7 and 8), Compound (1-2) and Compound 9 are administered in the morning (9:30 to 10:30 am), and then administered Compound (1-2) and vehicle in the evening (17:30 to 18:30 pm). SC = subcutaneous injection.

Acclimation

[0325] Minus Day-14 to Day-1: After ~16 weeks of modeling to achieve an average model weight ~42 g, the mice are orally dosed with vehicle (10 % Solutol HS15: 90% sterile water, [v/v]) twice daily for 1~2 weeks to ensure a smooth dosing operation and to acclimate the mice to repeat dosing. Mice with body weights that have not stabilized by the end of the dosing acclimation are removed from the study.

Grouping

[0326] All animals on HFD are assigned into 8 groups based on baseline body weight, 3 day's food intake and body composition (Day-4).

Dose and Food Intake

[0327] Day1-30: Body weight and food intake are recorded daily before dosing in the morning.

[0328] BID dosing: Dosing time is 9:30 am-10:30 am and 17:30 pm-18:30 pm.

[0329] QD dosing (For group 6 and 9): The dosing time of Compound 9 (3 mg/kg, PO), or semaglutide (10 nmol/kg, SC) is between 9:30 am-10:30 am, while vehicle (10% Solutol HS15: 90% sterile water, [v/v]) or saline (semaglutide vehicle) is dosed between 17:30 pm-18:30 pm.

Body Composition

[0330] Baseline (Day-4), Day 24: Lean and fat mass are measured by Body composition analyzer (Bruker's minispec- LF90) in the morning.

Oral Glucose Tolerance Test (OGTT)

[0331] On day 28, random blood glucose and body weight of the mice are measured, mice are dosed with corresponding compounds or vehicle in the morning before fasting, then the mice are placed in new cages at 9:00 am and fasted for 6 hours, basal fasting glucose is measured by tail vein nick thereafter. Glucose is orally gavaged with 2 g/kg at a dose volume of 5 mL/kg. Blood glucose levels are measured at 0 (pre-dose), 15-, 30-, 60-, and 120-min post glucose dosing. The second dose is administrated after OGTT treatment.

Terminal plasma and tissue collection

[0332] Day 31: The body weight and food intake of all mice is measured and then fasted for 6 hours, all mice are euthanized with CO₂ and bled via cardiac puncture. 500 µL blood samples will be processed for serum by centrifugation at 4°C, 3200 x g for 10 min and stored at -80°C for TC/TG/LDL/HDL/AST/ALT analysis (Analyzed by Biochemical analyzer: Beckman AU480/Hitachi 7180). 200 µL – 300 µL blood samples are mixed with K₂EDTA anticoagulant and processed for plasma by centrifugation at 4°C, 3200 x g for 10 min and stored at -80°C for insulin and other possible analysis.

[0333] The weight of whole liver and epididymal fat are weighed and recorded. Left lobule of liver is fixed in formalin. The remaining liver is flash frozen and stored at -80°C. Pancreas is collected and fixed in formalin. Brown adipose, subcutaneous white adipose, and epididymal white adipose tissues and the brain hypothalamus region are frozen with liquid nitrogen and preserved and stored at -80°C for optional qPCR analysis.

Hypothalamus collection procedure

[0334] The brain tissue is placed in the mold, and the olfactory bulb is placed in the center of the groove. The brain tissue is sliced into 8 coronal sections evenly spaced at 2 mm intervals. The third section (6-8mm) of the coronal brain tissue is taken out, and the section is cut along the boundary of the purple part with a scalpel to separate the cerebral cortex. The remaining tissue is hypothalamus.

Blood Collection

[0335] Day 21: Animals in all groups are divided into 3 sub-groups respectively. All mice for PK sampling, except for the pre-dose mice, receive the first dose of corresponding compound in the morning between 9:30 am to 10:30 am, 60 μ L blood is collected from mice under the jaw into pre-chilled tubes containing 1.2 μ L K₂ EDTA, and placed on ice. For the evening dose, the 8-hour post-1st-dose samples are collected before the second dose of the day. Blood samples are processed to plasma within 1 hour of collection by centrifugation at 4°C, 3200 x g for 10 min. About 30 μ L of plasma is collected and stored at -80°C for further analysis.

Data Processing and Analysis

[0336] The significances of the differences among groups and within groups are evaluated by one-way or two-way ANOVA using Graph Pad statistic software. A p-value of less than 0.05 are considered statistically significant.

Example 3. Effects of 4 weeks of treatment with Semaglutide alone and in combination with Compound 9 on body weight regulation and composition in male DIO mice at thermoneutrality

Methods

[0337] Male C57BL/6JRj mice (n=48), 5 weeks of age were fed a high fat diet (HFD) for 24 weeks before treatment starts. Mice were randomized during week -1 into 7 groups (n= 12 each group) based on body weight and fat tissue mass. The DIO mice were dosed once a day per oral (PO) and subcutaneous (SC) for 28 days.

Group 1 received Vehicle (PO + SC),

Group 2 Semaglutide (30 nmol/kg, SC) + Vehicle (PO),

Group 3 Semaglutide (30 nmol/kg, SC) + Compound 9 (6 mg/kg, PO),

Group 4 Semaglutide (30 nmol/kg, SC) Wk1-4 + Compound 9 Wk2-4 (6 mg/kg, PO).

See Fig. 3.

[0338] Body weight, food intake and water intake were measured daily, EchoMRI was performed during week -1 and at week 4, and plasma samples were collected for sponsor at termination.

Results

[0339] Treatment with Compound 9 in combination with Semaglutide (Semaglutide + Compound 9), induced a reduction of absolute and relative body weight, compared Semaglutide alone. See Figs. 4-5.

Semaglutide + Compound 9 potentiated semaglutide-induced weight loss and led to a specific loss of fat mass without additional lean mass loss. See Figs. 6-9.

Example 4: Effect of 6 weeks of treatment with Compound 9 alone and in combination with Semaglutide on metabolic parameters, energy expenditure and glycemic control in male DIO mice at thermoneutrality.

Methods

[0340] Male C57BL/6JRj mice (5 weeks of age, n=70) were fed a high fat diet (n= 60, 60% HFD, D12492, Ssniff) for 24 weeks, or a lean-chow diet (n= 10, Altromin 1324) before treatment start. HFD animals were randomized during week -1 based on body weight, glucose levels and fat tissue mass into 5 treatments groups. Lean mice (group 1) were treated with vehicle (QD + QD, PO + SC) and DIO mice were treated (QD + QD, PO + SC) as follow: group 2 received vehicle (PO + SC), group 3 received Compound 9 6 mg/kg, PO + vehicle (SC), group 4 received Semaglutide (30 nmol/kg, SC) + vehicle (PO), group 5 received Compound 9 (6 mg/kg, PO) + Semaglutide (30 nmol/kg, SC) and group 6 received Tirzepatide (30 nmol/kg, SC) + vehicle (PO). Body weight, food and water intake were measured daily from day -3, body composition (EchoMRI) was measured during week -1 and week 6; energy expenditure was assessed at study day 5-7 and at study day 34-36. Fasting blood glucose and insulin levels were measured at baseline and termination, while an oral glucose tolerance test was performed at week 4. At termination, the *M. gastrocnemius* muscle was weighted and collected for RNAseq analysis, while plasma, brain, liver, BAT, epididymal and subcutaneous WAT depots were collected for sponsor. See Fig. 10

Table 4-1 – Study Groups

#	Group name	n in group	Animal model	Dose	Route of administration	Dosing frequency
1	Vehicle Lean	9	Lean mice	NA	PO + SC	QD + QD
2	Vehicle DIO	12	DIO mice	NA	PO + SC	QD + QD
3	Compound 9 + Vehicle	12	DIO mice	6 mg/kg + NA	PO + SC	QD + QD
4	Semaglutide + Vehicle	12	DIO mice	30 nmol/kg + NA	SC + PO	QD + QD
5	Compound 9 + Semaglutide	12	DIO mice	6 mg/kg + 30 nmol/kg	PO + SC	QD + QD
6	Tirzepatide + Vehicle	12	DIO mice	30 nmol/kg + NA	SC + PO	QD + QD

Results (See Figs. 11-17)

[0341] At week 1, compared to vehicle, Compound 9 in combination with Semaglutide reduced absolute and relative body weight, together with Semaglutide and Tirzepatide alone. Heat production was increased by Compound 9 + Semaglutide treatment in the light phase, together with Semaglutide and Tirzepatide alone, while the RER was reduced compared to vehicle during both dark and light phase in these three treatment groups. Compound 9 in combination with Semaglutide increased oxygen consumption both during dark and light phase.

[0342] The OGTT test indicated an increased glucose disposal for the Compound 9 + Semaglutide treated group, as well as Semaglutide and Tirzepatide alone; after 4 weeks of treatment, the combination of Compound 9 and Semaglutide reduced absolute and relative fat tissue mass compared to the vehicle-treated group, while absolute lean tissue mass was decreased and relative tissue mass was increased, and the same changes were observed for the Semaglutide and Tirzepatide treatment alone.

[0343] The energy expenditure measurement showed that after 5 weeks of treatment, Compound 9 alone increased both dark and light-phase heat production. Moreover, the oxygen consumption was significantly higher for the Compound 9 + Semaglutide group during both

dark and light phase, while only higher in the light phase for Semaglutide and Tirzepatide alone. Plasma insulin level was increased at week 6 upon Compound 9 treatment, while significantly lower in combination with Semaglutide, Semaglutide and Tirzepatide alone.

Example 5. Evaluating THR-B agonist Compound 9 in combination with a GLP-1R agonist (e.g., orforglipron)

Background

[0344] GLP-1R regulates post prandial blood glucose and satiety. The later effect can induce weight loss but efficacy is limited by metabolic adaptation, a compensatory process that lowers energy expenditure (EE). Moreover, the higher dose levels of GLP-1R needed to achieve clinical meaningful weight loss, are associated with more severe and frequent GI-related side effects including nausea and emesis, which can negatively impact patient compliance. Mechanisms to improve the effectiveness of GLP-1 based therapies at lower doses, could mitigate GI-related side effects and improve patient compliance and outcomes. In addition, combining these mechanisms in an all-oral medication could further improve patient compliance over injectable medications

[0345] Thyroid hormone receptor beta (THR β) plays a central role in regulating energy metabolism. Compound 9 is an orally bioavailable, highly selective, thyroid receptor beta agonist. In preclinical models of obesity, Compound 9 enhances the weight loss efficacy of the injectable peptide GLP-1R agonist semaglutide by mitigating the lowering of EE associated with weight loss and increasing fat mass loss, while preserving relative lean mass loss. In this example, Compound 9 was tested in combination with orforglipron, an orally bioavailable GLP-1R agonist in late-stage clinical development for the treatment of type II diabetes mellitus (T2DM) and obesity. Specifically, the combination of Compound 9 with a low dose of orforglipron was tested to see if it could achieve a similar weight loss efficacy as a 10-fold higher dose of orforglipron in monotherapy. Like other small molecule GLP-1R agonists, orforglipron is inactive on rodent GLP-1R. Therefore, for the current study, diet-induced obese (DIO) transgenic mice expressing human GLP-1R (hGLP-1R) were used to assess in vivo efficacy Compound 9 in combination with orforglipron.

Methods

[0346] DIO hGLP-1R mice were housed at room temperature (21-25°C) with a relative humidity of 40-70%. Temperature and relative humidity were monitored and recorded twice daily. An electronic time-controlled lighting system was used to provide a 12 h light/12 h dark cycle, 19:00 pm-7:00 am, lights out and enrichment toys were provided. The mice were fed high fat diet (HFD, Research Diets 12492, 60% kca, 1% fat) for >50 weeks to induce obesity.

Mice were acclimated to once-daily (QD) oral dosing (per os, PO) for 1 week with body weight and food intake measured on consecutive 4 days prior to dosing start (Day 1). Body mass composition was measured by EchoMRI (Bruker Minispec LF90II) on Day 0 and mice were randomized to treatment groups (Table 5-1) based on baseline body weight, food intake, and body composition.

[0347] Test compounds were formulated in vehicle (10% [v/v] Solutol HS15 + 90% [v/v] saline) and mice were treated QD PO for 21 days with vehicle, Compound 9 (3 mg/kg), orforglipron (0.2 and 2 mg/kg), and Compound 9 (3 mg/kg) in combination with orforglipron (0.2 mg/kg). Body weight and food intake were measured daily, and mice were maintained on HFD throughout the study period. On Day 20 of the study, plasma samples were collected at predose (0), 2-, 4-, 8-, and 24-hours postdose for pharmacokinetic analyses of Compound 9, orforglipron, and combination treatment groups. Body mass composition was assessed on Day 19. Liver was collected and weighed at study termination and portions were preserved for steatosis assessment by histology. Subcutaneous fat was collected and weighed at study termination. A sample of subcutaneous fat tissue was assessed for UCP-1 expression by qPCR and Western blot analyses.

Table 5-1: Treatment groups

Group ID	Treatment	n	Dose (mg/kg)	Dose volume (mL/kg)	Dose Method	Dose Frequency
1	Vehicle	6	-	5	PO	QD*21 days
2	Compound 9	6	3	5	PO	QD*21 days
3	Orforglipron	7	2	5	PO	QD*21 days
4	Orforglipron	7	0.2	5	PO	QD*21 days
5	Compound 9 + Orforglipron	7	0.2+3	5	PO	QD*21 days

Results

[0348] Treatment with orforglipron (0.2 mg/kg and 2 mg/kg PO QD) resulted in dose-dependent body weight decreases over time (FIG. 18), while body weights in mice treated with vehicle (PO QD) or Compound 9 (3 mg/kg PO QD) alone remained relatively unchanged during the study period. In contrast, mice treated with the combination of Compound 9 (3 mg/kg PO QD) and orforglipron (0.2 mg/kg PO QD) showed comparable weight loss to the

high dose of orforglipron (2 mg/kg PO QD) monotherapy. On Day 20 decreases in body weight were significant for mice treated with orforglipron (0.2 and 2 mg/kg) and Compound 9 in combination with orforglipron (0.2 mg/kg) (FIG. 19). Moreover, treatment with the combination resulted in significantly greater weight loss compared with the low dose of orforglipron (0.2 mg/kg) monotherapy. Daily food intake was profoundly reduced in a dose-dependent manner during the first few days in mice treated with orforglipron before steadily increasing towards vehicle control levels (FIG. 20). Daily food intake was similar between mice treated with low dose orforglipron (0.2 mg/kg PO QD) and those treated with Compound 9 (3 mg/kg PO QD) in combination with orforglipron (0.2 mg/kg PO QD). Daily food intake was similar in mice treated with vehicle and Compound 9 (3 mg/kg PO QD). All treatment groups showed acute decreases in food intake following body mass composition measurements on Day 19, suggestive of animal handling induced stress response.

[0349] Treatment with orforglipron (0.2 mg/kg and 2 mg/kg PO QD) resulted in a dose-dependent decrease in fat mass (FIG. 21A), while fat mass remained relatively unchanged in mice treated with vehicle (PO QD) or Compound 9 (3 mg/kg PO QD). In contrast, the mice treated with the combination of Compound 9 (3 mg/kg PO QD) and orforglipron (0.2 mg/kg PO QD) showed comparable fat mass loss to the high dose of orforglipron (2 mg/kg PO QD) monotherapy. Lean mass loss was statistically significant in mice treated with orforglipron (0.2 mg/kg and 2 mg/kg PO QD) compared to vehicle treatment (FIG. 21B). Mice treated Compound 9 in combination with orforglipron (0.2 mg/kg PO QD) showed a similar mean decrease in lean mass, which was not statistically significant relative to orforglipron (0.2 mg/kg PO QD) monotherapy. Lean mass loss was negligible in mice treated with vehicle or Compound 9 (3 mg/kg PO QD).

[0350] Treatment with orforglipron (0.2 mg/kg and 2 mg/kg PO QD) resulted in a dose-dependent decrease in subcutaneous fat, although only the high dose was significantly different from vehicle treatment (FIG. 22Error! Reference source not found.). Treatment with the combination of Compound 9 (3 mg/kg PO QD) and orforglipron (0.2 mg/kg PO QD) showed similar levels of subcutaneous fat compared to the high dose of orforglipron (2 mg/kg PO QD). The subcutaneous fat levels in mice treated Compound 9 (3 mg/kg PO QD) alone were not significantly different from mice treated with vehicle.

[0351] All treatment groups showed significantly lower liver weights at the end of study compared to vehicle control (FIG. 23). Mice treated with Compound 9 (3 mg/kg PO QD) in combination with orforglipron (0.2 mg/kg PO QD) showed trends towards further reductions in liver weight compared to mice treated with the low dose of orforglipron (0.2 mg/kg PO QD).

[0352] Concentration-time profiles of Compound 9 and orforglipron are shown in FIG. 24A and FIG. 24B, respectively, alone or in combination. Select derived pharmacokinetic parameters are shown in Table 5-2. Orforglipron exposure increased in a less than dose-proportional manner and exposure was largely unaffected when dosed in combination with Compound 9. Similarly, exposure to Compound 9 was unaffected when dosed in combination with orforglipron.

Table 5-2: Derived pharmacokinetic parameters

Analyte	Treatment group	AUC _{0-last} (h*ng/mL)	C _{max} (ng/mL)
Compound 9	Compound 9 (3 mg/kg)	19,000 (5310)	2480 (220)
	Compound 9 (3 mg/kg) + orforglipron (0.2 mg/kg)	17,600 (1810)	2780 (379)
Orforglipron	Orforglipron (0.2 mg/kg)	543 (34.8)	47.4 (6.47)
	Orforglipron (2 mg/kg)	2670 (428)	251 (39.8)
	Compound 9 (3 mg/kg) + orforglipron (0.2 mg/kg)	607 (23.7)	45.1 (3.45)

Abbreviations: AUC_{0-last} = area under the plasma concentration time curve from time 0 to time of the last measurable concentration; C_{max} = maximum observed concentration

Summary

[0353] Compound 9 enhanced the weight loss efficacy of a low dose of orforglipron to a level comparable to a 10-fold higher dose of orforglipron as monotherapy.

[0354] Daily doses of orforglipron at 0.2 mg/kg in mice provided equivalent unbound exposures (AUC_{24h,u} ~0.300 h.ng/mL) following daily doses of 6 mg/day in humans, while 2 mg/kg in mice provided equivalent unbound exposures (AUC_{24h,u} ~1.60 h.ng/mL) following daily doses of 45 mg/day in humans (Pratt et al (2023). The daily dose of 45 mg orforglipron in humans is associated with the highest change in body weight at week 26 compared to 12, 24, or 36 mg/day doses, however compared to placebo, the occurrence of total adverse events was significantly higher with orforglipron 12 mg [OR 2.49 (95% CI: 1.25, 4.98), $p = 0.01$, $I^2 = 12\%$], 24 mg [OR 2.23 (95% CI: 1.13, 4.43), $p = 0.02$, $I^2 = 10\%$], 36 mg [OR 2.04 (95% CI: 1.08, 3.84), $p = 0.03$, $I^2 = 0\%$] and 45 mg [OR 2.96 (95% CI: 1.41, 6.21), $p = 0.004$, $I^2 = 17\%$] daily doses; the highest rates seen with orforglipron 45 mg. (Frias et al., *Lancet*. 2023;402(10400):472-483, Wharton et al., *N Engl J Med*. 2023;389(10):877-888, Pratt et al, *Diabetes Obes Metabol*. 2023;25:2642-2649).

[0355] The enhanced weight loss observed did not appear to be driven by changes in food intake. The enhanced weight loss effects of Compound 9 in combination with orforglipron were driven by larger reductions in fat mass, including subcutaneous fat, without additional decreases in lean mass. Lastly, liver weights were reduced by the combination of Compound 9 and orforglipron, suggesting enhanced anti-steatotic effects with the combination. The ability of Compound 9 to substantially enhance the efficacy of a low dose of GLP-1R agonist may ultimately translate to improved GI tolerability, leading to improved patient compliance and better outcomes.

Example 6. Evaluating THR-B agonist Compound 9 in combination with a GLP-1R agonist (e.g., Compound 1-2)

[0356] Transgenic C57/BL6J male mice expressing the human glucagon-like peptide-1 receptor (hGLP-1R) were fed a high fat diet (HFD, Research Diets D12492i 60%kcal) for 17 weeks to obtain a diet induced obese (DIO) phenotype. Mice were randomly divided into groups (n=8-10 per group) based on baseline body weight. Mice were treated for 30 days with Compound 9 [3 mpk, PO, once daily], Compound (1-2) [10 mpk PO, twice daily], Compound 9 [3 mpk PO, once daily] + Compound (1-2) [10 mpk, twice daily], Semaglutide [10 nmol/kg SQ, once daily] or vehicle: 10% Solutol HS15: 90% sterile water, (v/v). Body weight was measured daily and the mean percent change from baseline was calculated for each treatment group (FIGs. 25 and 26). The combination of Compound 9 + Compound (1-2) exerted a greater effect on reducing body weight compared to mice treated with either Compound 9 or Compound (1-2) alone.

EQUIVALENTS

[0357] All publications, including patents, patent applications, and scientific articles, mentioned in this specification are herein incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, including patent, patent application, or scientific article, were specifically and individually indicated to be incorporated by reference.

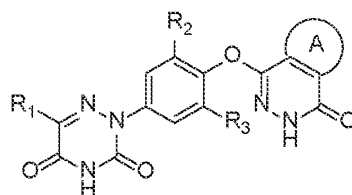
[0358] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced in light of the above

teaching. Therefore, the description and examples should not be construed as limiting the scope of the invention.

CLAIMS

What is claimed is:

1. A combination comprising a THR β agonist, or a pharmaceutically acceptable salt thereof, and a GLP-1R agonist, or a pharmaceutically acceptable salt thereof.
2. The combination of claim 1, wherein the THR β agonist is a compound of Formula (II-1)



(II-1)

wherein:

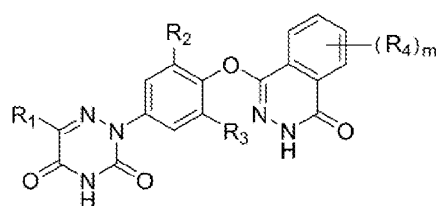
R₁ is selected from the group consisting of hydrogen, cyano, substituted or unsubstituted C₁₋₆ alkyl, and substituted or unsubstituted C₃₋₆ cycloalkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

R₂ and R₃ are each independently selected from the group consisting of halogen atoms and substituted or unsubstituted C₁₋₆ alkyl, the substituent being selected from the group consisting of halogen atoms, hydroxy, and C₁₋₆ alkoxy;

ring A is a substituted or unsubstituted saturated or unsaturated C₅₋₁₀ aliphatic ring, or a substituted or unsubstituted C₅₋₁₀ aromatic ring, the substituent being one or more substances selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₃₋₆ cycloalkyl, and when two substituents are contained, the two substituents can form a ring structure together with the carbon connected thereto; and

the halogen atoms are selected from the group consisting of F, Cl and Br;
or a pharmaceutically acceptable salt thereof.

3. The combination of claim 1 or 2, wherein the THR β agonist is a compound of Formula (II-1a)



(II-1a)

wherein:

R₁ to R₃ are defined as detailed herein for Formula (II-1);

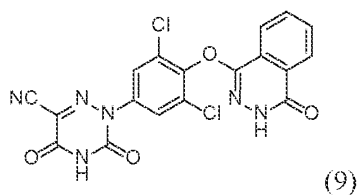
R₄ is selected from the group consisting of hydrogen, halogen atoms, hydroxy, -OCF₃, -NH₂, -NHC₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, -CONH₂, -CONHC₁₋₄ alkyl, -CON(C₁₋₄ alkyl)₂, -NHCOC₁₋₄ alkyl, C₁₋₆ alkyl, C₁₋₆ alkoxy and C₃₋₆ cycloalkyl;

m is an integer from the range 1 to 4; and

the halogen atoms are selected from the group consisting of F, Cl and Br.

or a pharmaceutically acceptable salt thereof.

4. The combination of any one of the preceding claims, wherein the THRβ agonist is Compound 9:

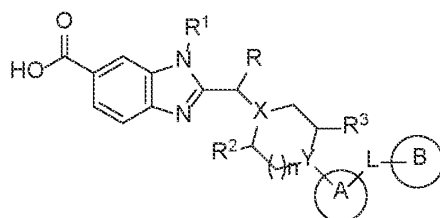


(9)

or a pharmaceutically acceptable salt thereof.

5. The combination of any one of the preceding claims, wherein the THRβ agonist is a potassium salt of Compound 9.

6. The combination of any one of the preceding claims, wherein the GLP-1R agonist is a compound of Formula (I-1):



(I-1)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CH;

Y is N or CR⁴;

n is 0 or 1;

R is hydrogen;

R¹ is -C₁-C₆ alkylene-R⁵;

R² is hydrogen, oxo, or C₁-C₆ alkyl;

R³ is hydrogen, oxo, or C₁-C₆ alkyl and R⁴ is hydrogen, OH, or C₁-C₆ alkyl;

or R³ and R⁴ are taken together with the carbon atoms to which they are attached to form C₃-C₆ cycloalkyl optionally substituted by halo or C₁-C₃ alkyl;

R⁵ is 5-membered heterocyclyl or 5-membered heteroaryl, each of which comprises 1, 2, or 3 heteroatoms independently selected from O, N, and S, wherein at least one heteroatom of R⁵ is S, and further wherein R⁵ is optionally substituted by halo, -O-C₁₋₆ alkyl, C₁₋₆ alkyl, C₁₋₆ alkenyl, or C₁-C₆ haloalkyl;

Ring A is 5- to 12-membered heterocyclene or 5- to 12-membered heteroarylene, each of which is independently optionally substituted by halo, CN, C₃-C₆ cycloalkyl, or C₁-C₆ alkyl optionally substituted by halo or OH;

L is a bond, -O-, C₁-C₆ alkylene, *-O-C₁-C₆ alkylene-**, *-C₁-C₆ alkylene-O-**, or *-NR⁶-C₁-C₆ alkylene-**, wherein

* represents the point of attachment to ring A and ** represents the point of attachment to ring B;

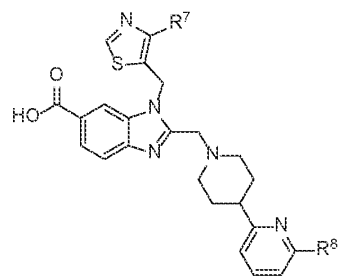
when L is *-O-C₁-C₆ alkylene-**, the C₁-C₆ alkylene of L is optionally substituted by R^L, wherein each R^L is independently C₁-C₆ alkyl or halo, or two R^L are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl; and

when L is C₁-C₆ alkylene, the C₁-C₆ alkylene is optionally substituted by R^{L1}, wherein each R^{L1} is independently halo, OH, oxo, or C₁-C₆ alkyl, or two R^{L1} are taken together with the carbon atom or atoms to which they are attached to form C₃-C₆ cycloalkyl or 3- to 6-membered heterocyclyl;

R⁶ is hydrogen or C₁-C₆ alkyl; and

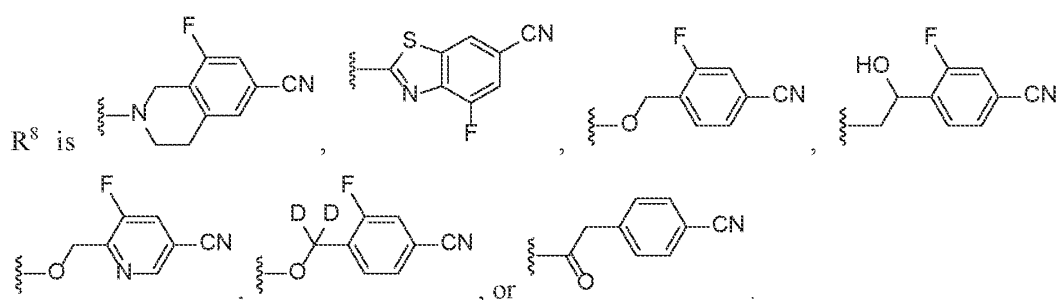
Ring B is C₃-C₁₀ cycloalkyl, C₆-C₁₄ aryl, 4- to 12-membered heterocyclyl, or 5- to 12-membered heteroaryl, each of which is independently optionally substituted by one to three substituents independently selected from the group consisting of halo, CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -COCH₃, -CONH₂, -S(O)₂CH₃, and phenyl.

7. The combination of any one of the preceding claims, wherein the GLP-1R agonist is a compound of Formula (I-1a):

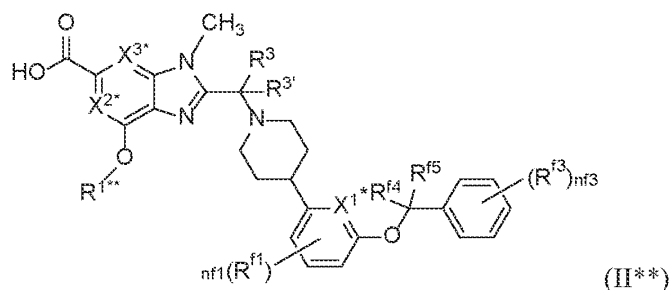


(I-1a), or a pharmaceutically acceptable salt thereof

wherein R^7 is hydrogen, chloro, bromo, fluoro, methyl, or vinyl; and



8. The combination of any one of the preceding claims, wherein the GLP-1R agonist is a compound of Formula (II**):



(II**)

or a pharmaceutically acceptable salt thereof, wherein

R^{f4} and R^{f5} are each independently selected from C_{1-6} alkyl, H and D

$nf1$ is 0, 1, 2, 3, or 4;

$nf3$ is 0, 1, 2, 3, 4, or 5;

each R^{f1} is halogen;

R^3 and $R^{3'}$ independently are H or D;

X^{1*} is N or CR^{f1} ;

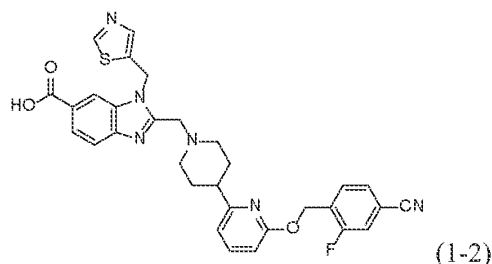
X^{2*} and X^{3*} independently are CH or CF;

each R^{13} is independently selected from halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or -C(O)N(R^{13})₂,

each $R^{13'}$ is independently selected from H or C_{1-6} alkyl; and

R^{1**} is H or C_{1-2} alkyl optionally substituted with one or more deuterium or halogen.

9. The combination of any one of the preceding claims, wherein the GLP-1R agonist is Compound 1-2:



or a pharmaceutically acceptable salt thereof.

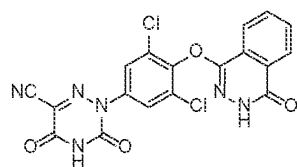
10. The combination of any one of the preceding claims, wherein the GLP-1R agonist is a meglumine salt of Compound 1-2.

11. The combination of any one of the preceding claims, wherein the THR β agonist is selected from those listed in Tables 6-11, or a pharmaceutically acceptable salt thereof.

12. The combination of any one of the preceding claims, wherein the GLP-1R agonist is selected from those listed in Tables 1-5, or a pharmaceutically acceptable salt thereof.

13. The combination of any one of the preceding claims, wherein the GLP-1R agonist is selected from those listed in Table 5A, or a pharmaceutically acceptable salt thereof.

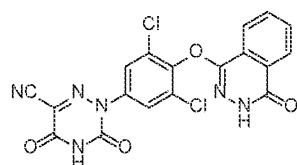
14. The combination of any one of the preceding claims, wherein the THR β agonist is compound 9



(9), or a pharmaceutically acceptable salt thereof

and the GLP-1R agonist is orforglipron, danuglipron, liraglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide, or semaglutide, or a pharmaceutically acceptable salt thereof.

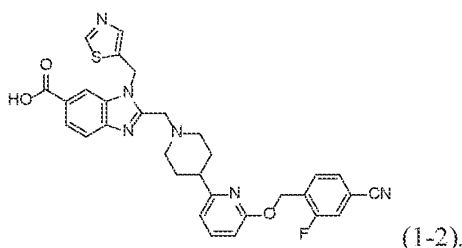
15. The combination of any one of the preceding claims, wherein the THR β agonist is compound 9



(9), or a pharmaceutically acceptable salt thereof

and the GLP-1R agonist is orforglipron, danuglipron, or semaglutide, or a pharmaceutically acceptable salt thereof.

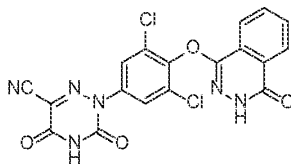
16. The combination of any one of the preceding claims, wherein the THR β agonist is resmetirom, VK2809, sobetirome, eprotrirome, ALG-055009, CNPT-101101, CNPT-101207, ASC41 or a pharmaceutically acceptable salt thereof and the GLP-1R agonist is compound 1-2



(1-2),

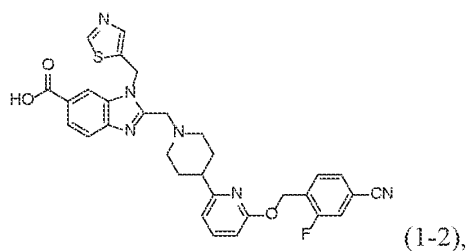
or a pharmaceutically acceptable salt thereof.

17. The combination of any one of the preceding claims, wherein the THR β agonist is compound 9



(9),

or a pharmaceutically acceptable salt thereof, and the GLP-1R agonist is compound 1-2



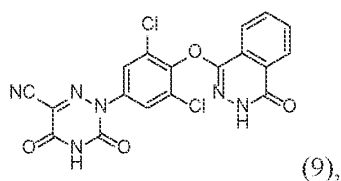
or a pharmaceutically acceptable salt thereof.

18. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is from about 0.5 mg to about 25 mg.
19. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is from about 1 mg to about 15 mg.
20. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is from about 2 mg to about 10 mg.
21. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is about 1 mg.
22. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is about 3 mg.
23. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is about 6 mg.
24. The combination of any one of the preceding claims, wherein the amount of the THR β agonist is about 10 mg.
25. The combination of any one of the preceding claims for use in the treatment of a liver disorder or a cardiometabolic disease in a patient in need thereof.
26. The combination of any one of the preceding claims for use in effectuating weight loss in a patient in need thereof.

27. The combination of any one of the preceding claims for use in a combinational therapy for the treatment of obesity in a patient in need thereof.
28. A method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding claims.
29. A method of treating a liver disorder or a cardiometabolic disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the combination according to any one of the preceding claims.
30. A method of increasing the proportion of lean body mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding claims.
31. A method of decreasing the proportion of fat mass relative to total body mass in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding claims.
32. A method of effectuating weight loss in a patient in need thereof, comprising administering to the patient a combination according to any one of the preceding claims.
33. The method of any one of the preceding claims, wherein the patient has a Body Mass Index (BMI) of 27 kg/m² or greater.
34. The method of any one of the preceding claims, wherein the patient has a BMI of 30 kg/m² or greater.
35. The method of any one of the preceding claims, wherein the administration of the THR β agonist allows for administration of a reduced dose of the GLP-1R agonist while maintaining equivalent weight loss.

36. The method of any one of the preceding claims, wherein the administration of the THR β agonist increases weight loss compared to administration of a GLP-1R agonist at an equivalent dose.
37. The method of any one of the preceding claims, wherein the cardiometabolic disease is obesity or an obesity-associated condition.
38. The method of any one of the preceding claims, wherein the cardiometabolic disease is diabetes.
39. The method of any one of the preceding claims, wherein the combination or method improves glycemic control in adults with type 2 diabetes mellitus.
40. A method of treating obesity or effectuating weight loss in a patient in need thereof, the method comprising

(i) administering to the patient compound 9



or a pharmaceutically acceptable salt thereof, and

(ii) administering to the patient a GLP-1R agonist, or a pharmaceutically acceptable salt thereof,

wherein administering to the patient compound 9, or a pharmaceutically acceptable salt thereof, improves the patient's response to the GLP-1R agonist or a pharmaceutically acceptable salt thereof.

41. The combination or method of any one of the preceding claims, wherein the THR β agonist is administered once daily or twice daily.
42. The combination or method of any one of the preceding claims, wherein the THR β agonist is administered orally.

43. The combination or method of any one of the preceding claims, wherein the GLP-1R agonist is administered orally.
44. The method of claim 40, wherein the GLP-1R agonist comprises compound 1-2, orforglipron, semaglutide, tirzepatide, or danuglipron.
45. The method of any one of the preceding claims, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, increases fat loss associated with administering the GLP-1R agonist.
46. The method of any one of the preceding claims, wherein administering compound 9, or a pharmaceutically acceptable salt thereof, increases fat loss associated with administering the GLP-1R agonist while maintaining lean mass.
47. The combination of any one of claims 1-27 for the preparation of a medicament for the use in a method according to any one of claims 28-46.
48. Use of the combination of any one of claims 1-27 in a method according to any one of claims 28-46.