

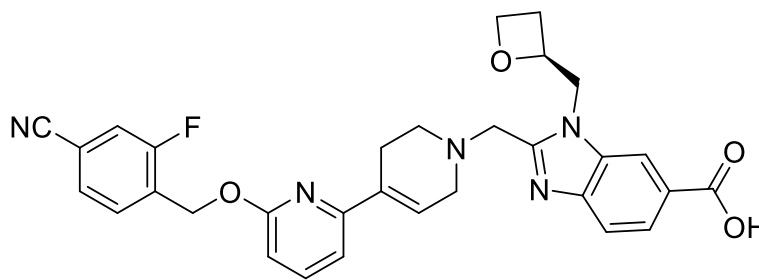
absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll *et al.*, *Diabetes*. 50:609-613, 2001).

5 Hoist (*Physiol. Rev.* 87:1409, 2007) and Meier (*Nat. Rev. Endocrinol.* 8:728, 2012) describe that GLP-1 receptor agonists, such as GLP-1, liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients with T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying
10 rate resulting in retarded absorption of meal-derived glucose.

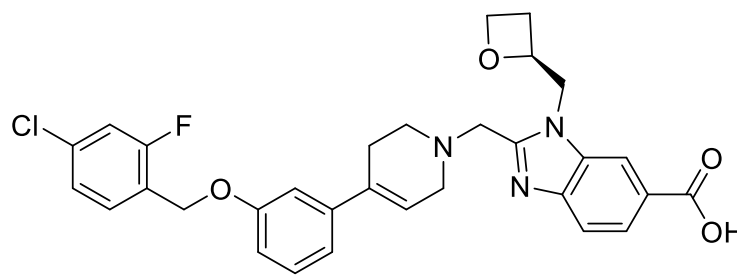
There remains a need for an easily-administered prevention and/or treatment for cardiometabolic and associated diseases.

SUMMARY ~~OF THE INVENTION~~

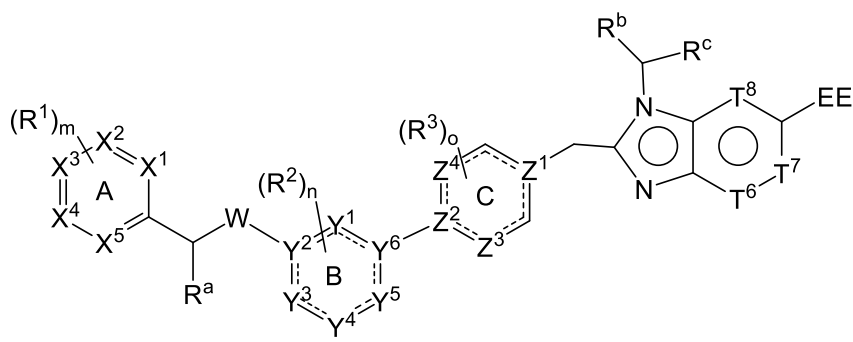
In a first aspect of the present disclosure, there is provided a compound or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



In another aspect of the present disclosure, there is provided a compound or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



In yet another aspect of the present disclosure, there is provided a compound represented by the structural formula (I'):



or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof; or a pharmaceutical composition comprising the compound, the pharmaceutically acceptable salt, the stereoisomer, the solvate, or the hydrate thereof, and a pharmaceutically acceptable excipient; wherein

===== indicates a single bond or a double bond;

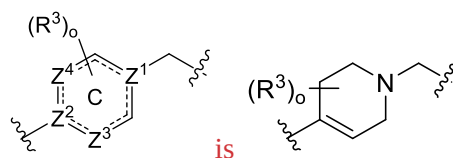
X^1 , X^2 , X^3 , X^4 , and X^5 are each independently selected from N, C, and CH; wherein no more than three of X^1 , X^2 , X^3 , X^4 , and X^5 are N and ring A does not contain 3 nitrogen ring atoms at 3 contiguous positions;

W is selected from O, NH and CH_2 ;

Y^1 , Y^3 , Y^4 , and Y^5 are each independently selected from N, NH, C, CH, and CH_2 ;

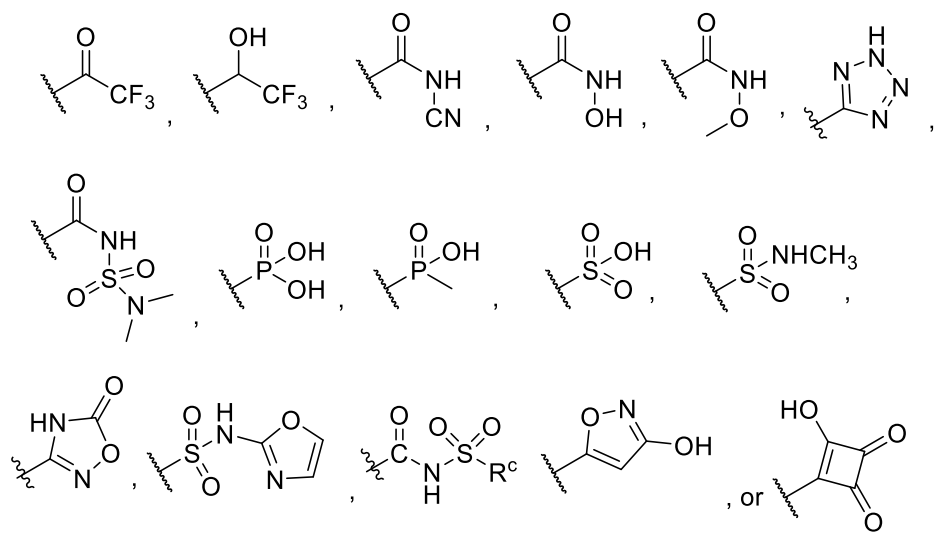
Y^2 and Y^6 are each independently selected from N, C, or CH;

wherein there is no more than 3 nitrogen ring atoms in ring B and wherein ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;



T^6 , T^7 , and T^8 are each independently selected from N and CR^4 ; and no more than 2 of T^6 , T^7 , and T^8 are selected from N;

EE is $-COOH$.



R^a is hydrogen;

R^b is 5-6 membered heteroaryl or 4-7 membered saturated or partially saturated heterocyclyl, wherein the heteroaryl or saturated or partially saturated heterocyclyl represented by R^b is optionally substituted with one or more groups selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, and C₁-C₃ haloalkoxy;

R^c is hydrogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

each R¹ is independently halogen, -CN, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NR^{5'}R^{6'}, phenyl, 5-6 membered heteroaryl, 4-6 membered saturated or partially saturated cycloalkyl and 3-7 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, or C₂-C₆ alkynyl represented by R¹ is optionally substituted with one or more groups selected from halogen, CN, OH, and C₃-C₆ cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R¹ or in the group represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ hydroxyalkoxy, and NR^{5'}R^{6'};

each R² is independently selected from halogen, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, and NR^{5'}R^{6'};

R³ is independently halogen, C₁-C₄ alkyl, or C₁-C₄ haloalkyl;

each R⁴ is independently H, halogen, or C₁-C₆ alkyl optionally substituted with one or more groups selected from halogen;

R^{5'} and R^{6'} are each independently selected from hydrogen and C₁-C₆ alkyl;

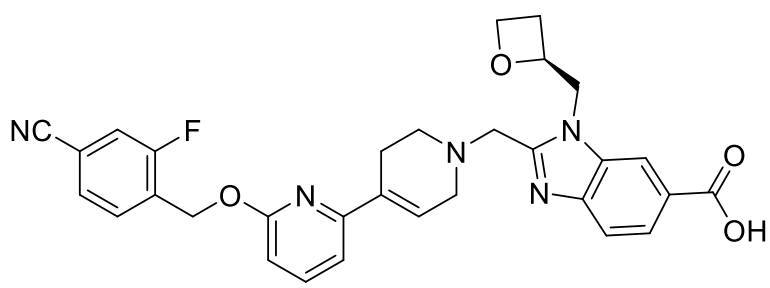
m is 0, 1, 2, 3, or 4;

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

o is 0, 1, or 2.

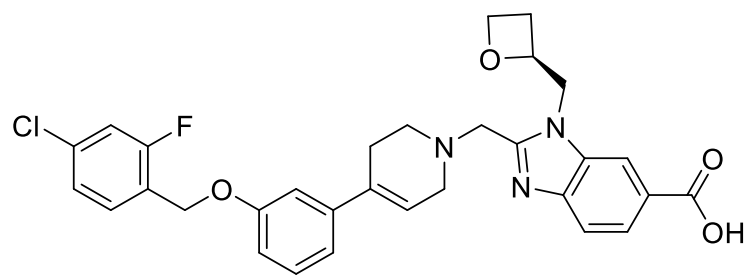
In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, in the manufacture of a medicament for treating cardiometabolic and associated diseases, wherein the disease is T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, 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, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome Crohn's disease, colitis, irritable bowel syndrome, prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable excipient, and a compound represented by the following structure:



or a pharmaceutically acceptable salt thereof.

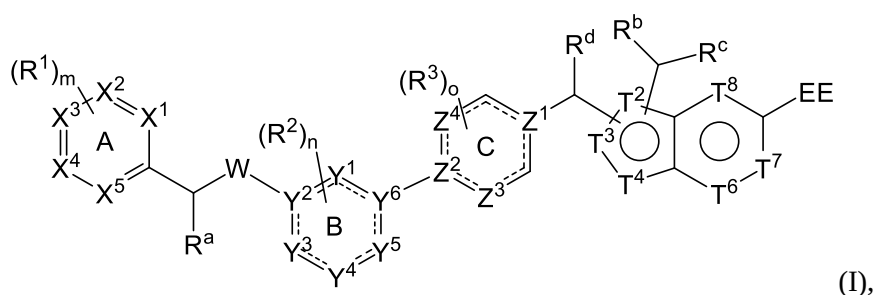
In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable excipient, and a compound represented by the following structure:



or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound as disclosed herein or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, for use in therapy.

5 In a first ~~embodiment~~ example, the ~~invention~~ present disclosure provides a compound represented by structural formula (I):



(I),

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

----- indicates a single bond or a double bond;

10 X^1 , X^2 , X^3 , X^4 , and X^5 are each independently selected from N and CH; wherein no more than three of X^1 , X^2 , X^3 , X^4 , and X^5 are N and wherein ring A does not contain 3 nitrogen ring atoms at 3 contiguous positions;

W is selected from O, S, CR^5R^6 , and $NR^{5'}$;

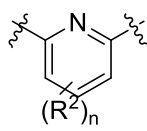
Y^1 , Y^3 , Y^4 , and Y^5 are each independently selected from N, NH, CH, and CH_2 ;

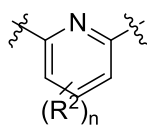
15 Y^2 and Y^6 are each independently selected from N, C, or CH;

wherein there is no more than 3 nitrogen ring atoms in ring B and wherein ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;

Z^1 and Z^2 are each independently selected from N, C, and CH; wherein at least one of Z^1 and Z^2 is N; Z^3 and Z^4 are each independently selected from a bond, CH, CH_2 , $CH=CH$, CH_2CH_2 , CH_2CH , and

20 $CHCH_2$; wherein ring C contains no more than two double bonds;



provided that when ring B is , then (1) W is not O, and/or (2) ring C is not

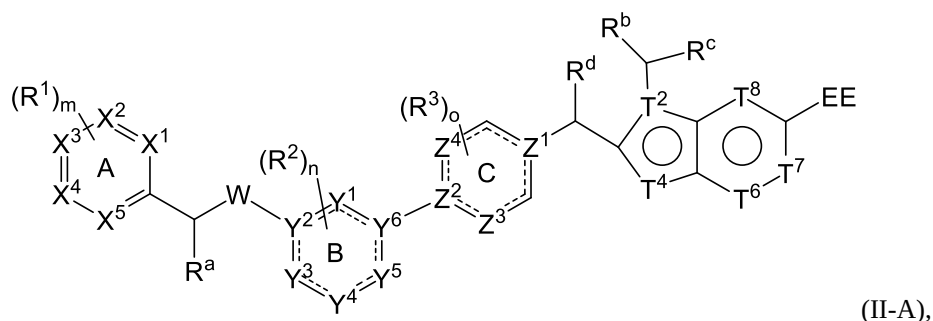
groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃;

m is an integer selected from 0, 1, 2, 3, and 4,

n is an integer selected from 0, 1, 2, 3, 4, and 5, and

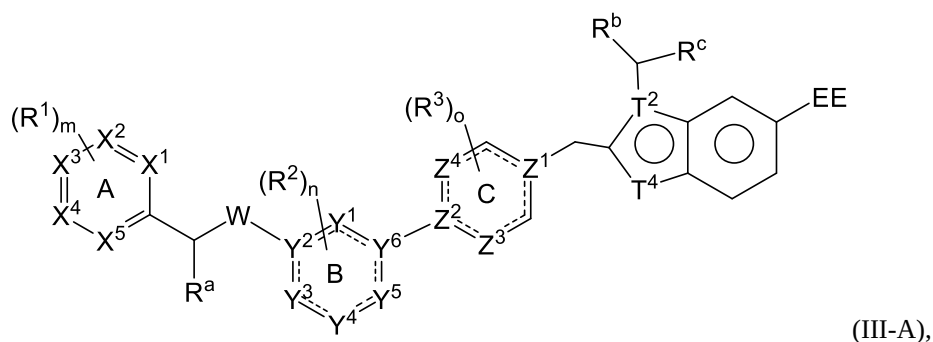
o is an integer selected from 0, 1, 2, 3, 4, and 5.

- 5 In a second embodimentexample, the inventionpresent disclosure provides a compound according to the first embodimentexample, wherein the compound is represented by the structural formula (II-A):



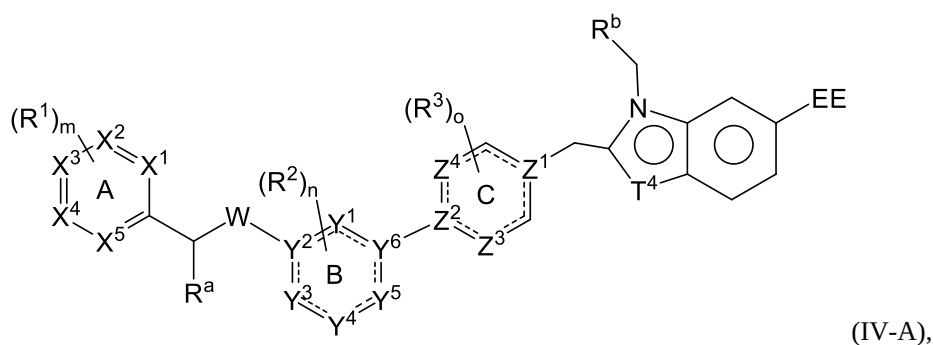
or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R^d is H, F, CH₃, or CF₃, wherein the remainder of the variables are as defined in the first embodimentexample.

- 10 In a third embodimentexample the inventionpresent disclosure provides a compound according to the first or second embodimentexample, wherein the compound is represented by structural formula (III-A):



or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein T² is N, and T⁴ is N or CR⁴, wherein R⁴ is H, halogen, OH, CN, C₁-C₃ alkyl, C₁-C₃ haloalkyl, or C₁-C₃ alkoxy; or T² is C, and T⁴ is NR⁴, wherein R⁴ is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, wherein the remainder of the variables are as defined in the first or second embodimentexample.

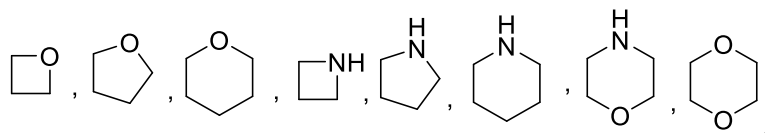
In a fourth embodimentexample the inventionpresent disclosure provides a compound according to the first, second, or third embodimentexamples, wherein the compound is represented by structural formula (IV-A):



or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein T⁴ is N

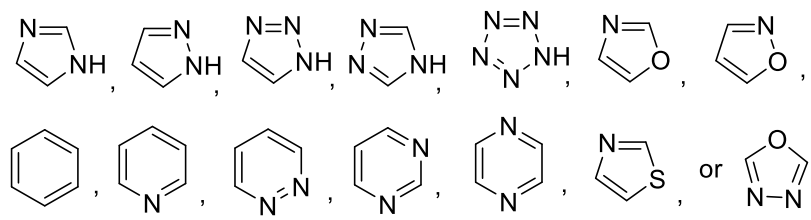
or CH; and R^a is H, CH₃, or CF₃; or R^a, R¹ and X⁵, taken together with their respective intervening carbons, form 5-7 membered cycloalkenyl or 5-7 membered partially saturated monoheterocyclyl, wherein the remainder of the variables are as defined in the first, second, or third [embodimentexample](#).

5 In a fifth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third or fourth [embodimentexamples](#), wherein R^b is



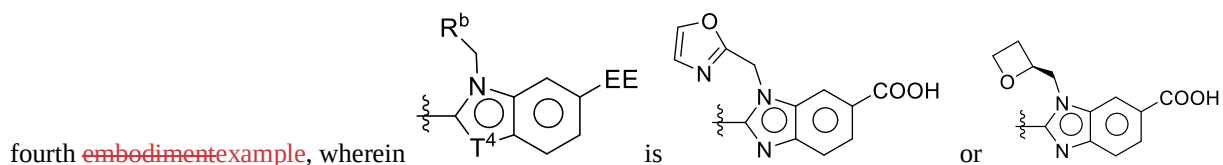
10 wherein R^b is optionally substituted with 1 or 2 groups selected from oxo, CN, F, Cl, C₁-C₃ alkyl, and C₁-C₃ alkoxy, wherein the C₁-C₃ alkyl or C₁-C₃ alkoxy in the group represented by R^b is optionally substituted with 1 or 2 groups selected from F, OH, and OCH₃, wherein the remainder of the variables are as defined in the first, second, third or fourth [embodimentexample](#).

In a sixth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third or fourth [embodimentexamples](#), wherein R^b is



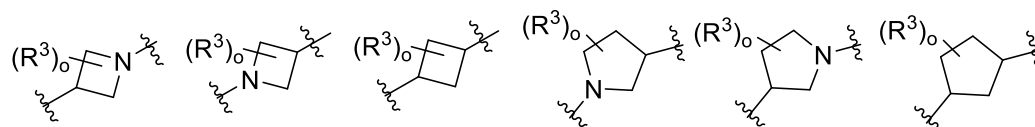
15 wherein R^b is optionally substituted with 1 or 2 groups selected from halogen, OH, NR⁵R⁶, C₁-C₃ alkyl, and C₁-C₃ alkoxy, wherein the C₁-C₃ alkyl or C₁-C₃ alkoxy in the group represented by R^b is optionally substituted with 1 or 2 groups selected from F, OH, and OCH₃, wherein the remainder of the variables are as defined in the first, second, third or fourth [embodimentexample](#).

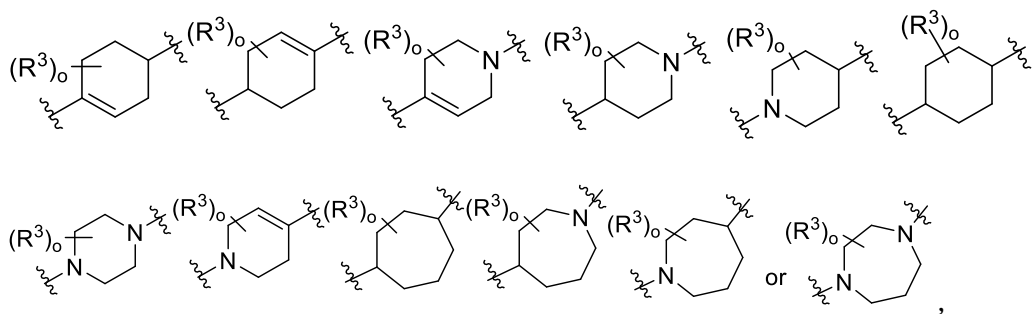
In a seventh [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the



20 wherein the remainder of the variables are as defined in the first, second, third or fourth [embodimentexample](#).

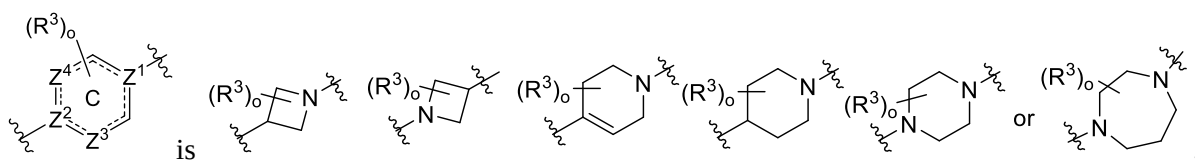
In an eighth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first,





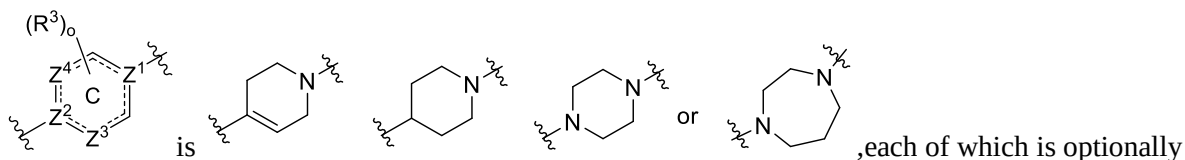
wherein R^3 is halogen, CN, OH, oxo, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, or $NR^{5'}R^{6'}$; and o is an integer selected from 0, 1, 2, and 3, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, or seventh [embodimentexample](#).

In a ninth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third, fourth, fifth, sixth, seventh, or eighth [embodimentexample](#), wherein



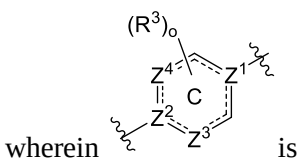
wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, or eighth [embodimentexample](#).

In a tenth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third, fourth, fifth, sixth, seventh, eighth, or ninth [embodimentexample](#), wherein

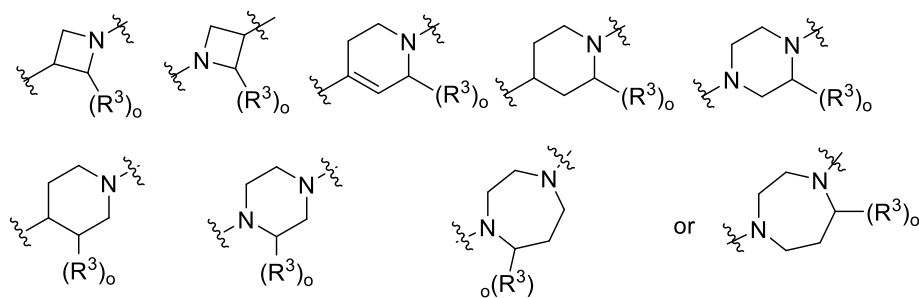


each of which is optionally substituted with 1 or 2 groups selected from halogen, CN, and oxo; or two R^3 groups taken together with ring C, form bridged (C_5 - C_8)heterocyclene or bridged (C_5 - C_8)cycloalkylene, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, or ninth [embodimentexample](#).

In an eleventh [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third, fourth, fifth, sixth, seventh, eighth, or ninth [embodimentexample](#),



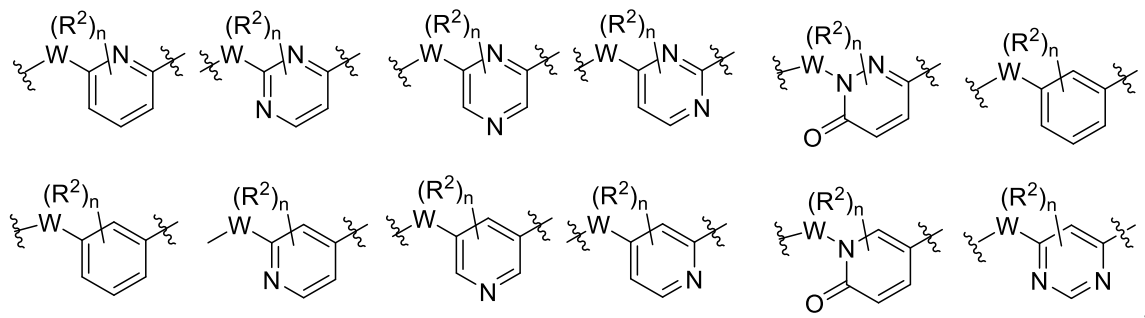
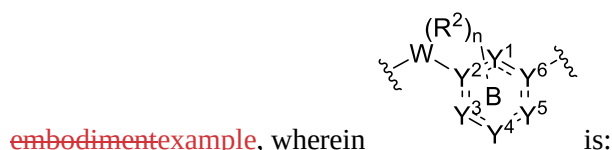
wherein



, wherein R^3 is halogen,

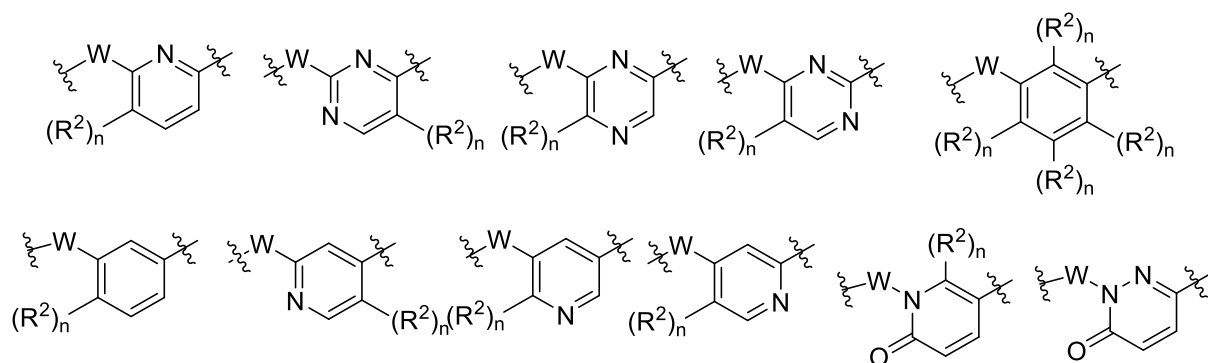
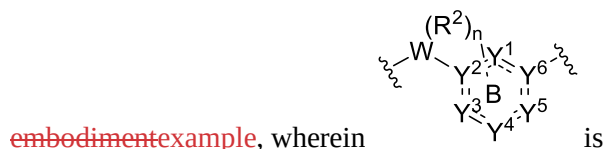
CN, oxo, CH_3 , CF_3 , CH_2CH_3 , or CH_2CF_3 ; and o is 0 or 1, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, or ninth [embodimentexample](#).

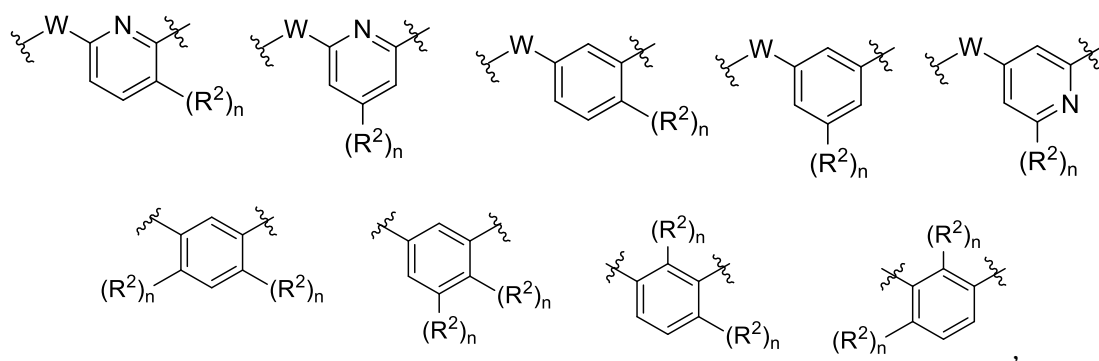
In a twelfth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh



wherein each R^2 is independently selected from halogen, -CN, OH, oxo, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, and C_1 - C_2 alkoxy; and n is an integer selected from 0, 1, 2, and 3, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, or eleventh [embodimentexample](#).

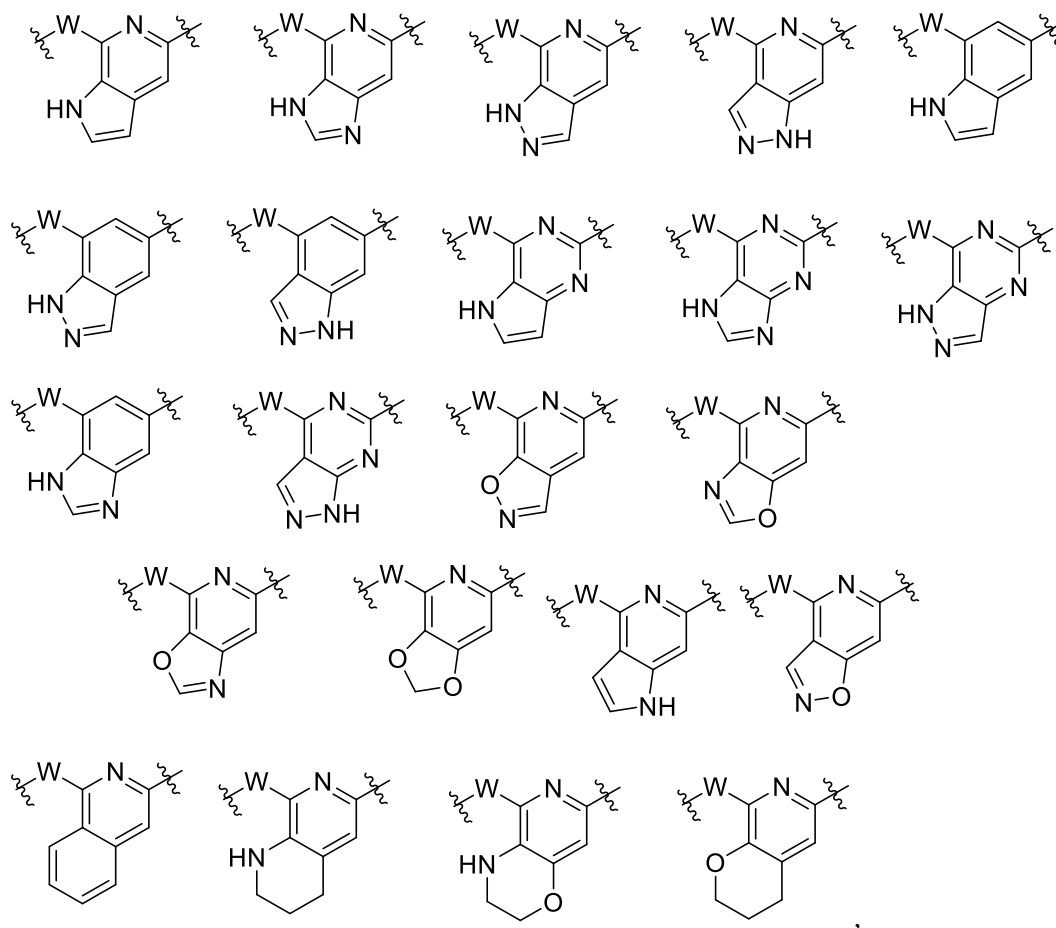
In a thirteenth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, or twelfth





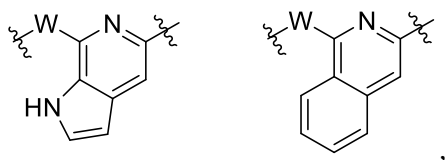
wherein R^2 is halogen, -CN, OH, oxo, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, or C_1 - C_2 alkoxy, n is 0 or 1, and no more than two R^2 are attached to ring B, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, or twelfth [embodiment example](#).

In a fourteenth [embodiment example](#), the [invention present disclosure](#) provides a compound according to the twelfth [embodiment example](#), wherein two R^2 groups together with ring B form a bicyclic structure:



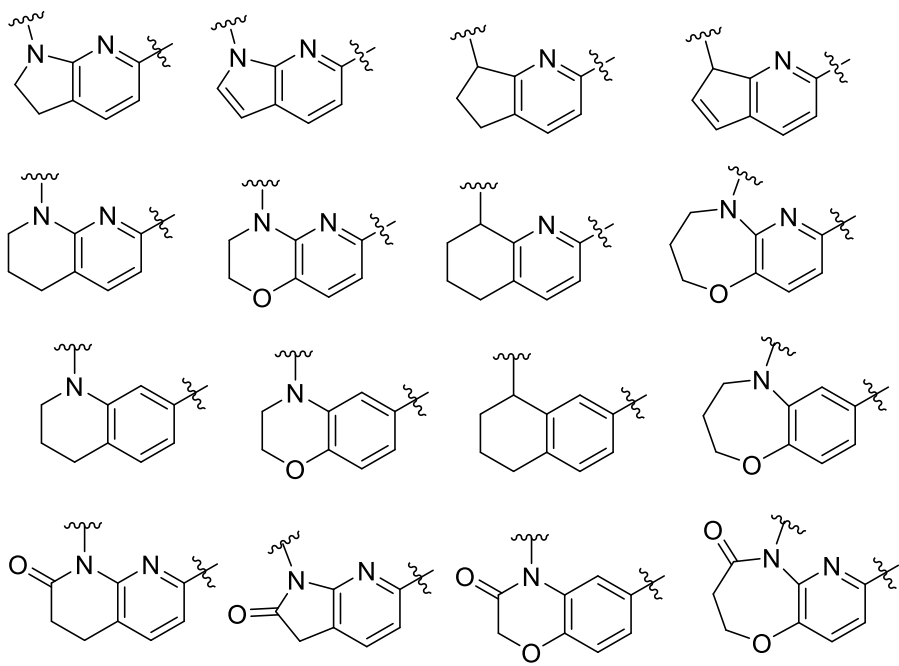
each of which is optionally substituted with 1 or 2 groups selected from halogen, oxo, CN, CF_3 , C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, C_1 - C_2 alkoxy, $-NH_2$, $-NHC_1$ - C_2 alkyl, and $-N(C_1$ - C_2 alkyl) $_2$, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, or twelfth [embodiment example](#).

In a fifteenth [embodiment example](#), the [invention present disclosure](#) provides a compound according to the fourteenth [embodiment example](#), wherein two R^2 groups together with ring B form a bicyclic structure:



each of which is optionally substituted with halogen, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, or twelfth embodimentexample.

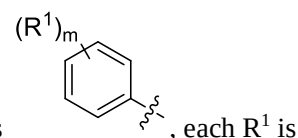
5 In a sixteenth embodimentexample, the inventionpresent disclosure provides a compound according to the twelfth embodimentexample, wherein W and ring B form a bicyclic structure:



10 each of which is optionally substituted with 1 or 2 groups selected from halogen, oxo, CN, CF₃, -NH₂, -NHC₁-C₂ alkyl, and -N(C₁-C₂ alkyl)₂, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, or twelfth embodimentexample.

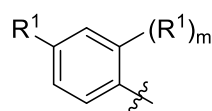
In a seventeenth embodimentexample, the inventionpresent disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth,

15 thirteenth, fourteenth, fifteenth, or sixteenth embodimentexample, wherein ring A is independently selected from halogen, OH, CN, CF₃, C₁-C₂ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, -NH₂, -NHC₁-C₂ alkyl, -N(C₁-C₂ alkyl)₂, and C₂-C₄alkynyl optionally substituted with cyclopropane; and m is an integer selected from 0, 1, 2, and 3, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or
20 sixteenth embodimentexample.



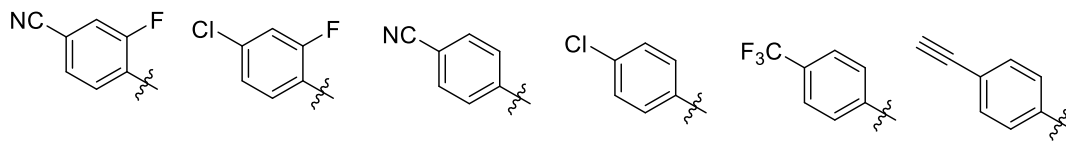
In an eighteenth embodimentexample, the inventionpresent disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth,

sixteenth, or seventeenth [embodimentexample](#), wherein ring A is



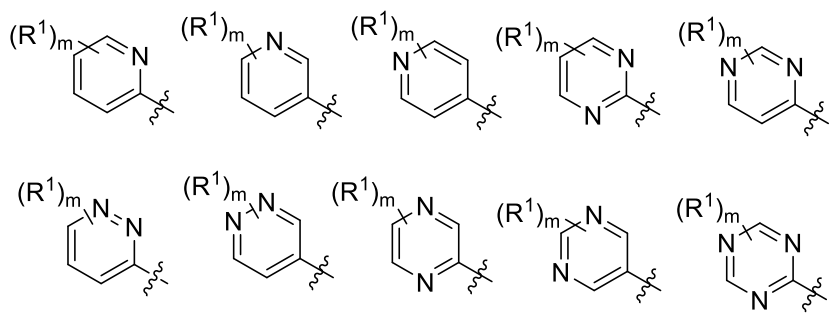
, and m is 0 or 1, and R¹

is halogen, CN, CH₃, CF₃, OH, or C₂-C₄alkynyl optionally substituted with cyclopropane; preferably ring A is



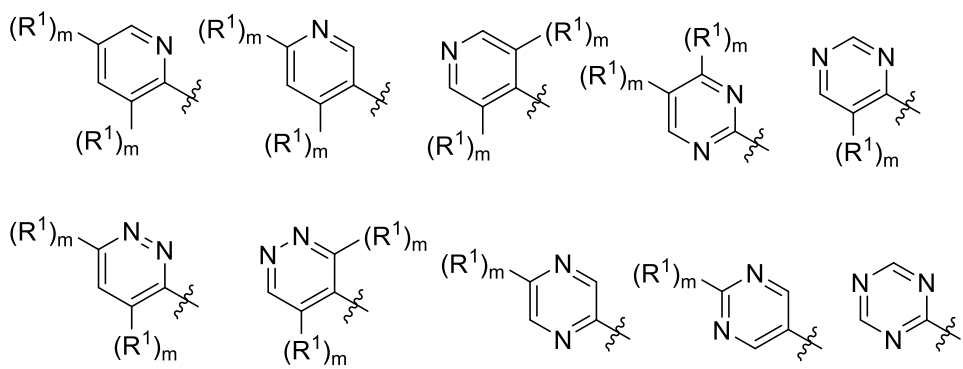
wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, or seventeenth [embodimentexample](#).

In a nineteenth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth [embodimentexample](#), wherein ring A is



each R¹ is independently selected from halogen, OH, CN, CF₃, C₁-C₂ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, -NH₂, -NHC₁-C₂ alkyl, -N(C₁-C₂ alkyl)₂, and C₂-C₄alkynyl optionally substituted with cyclopropane; and m is an integer selected from 0, 1, and 2, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, or sixteenth [embodimentexample](#).

In a twentieth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the nineteenth [embodimentexample](#), wherein ring A is



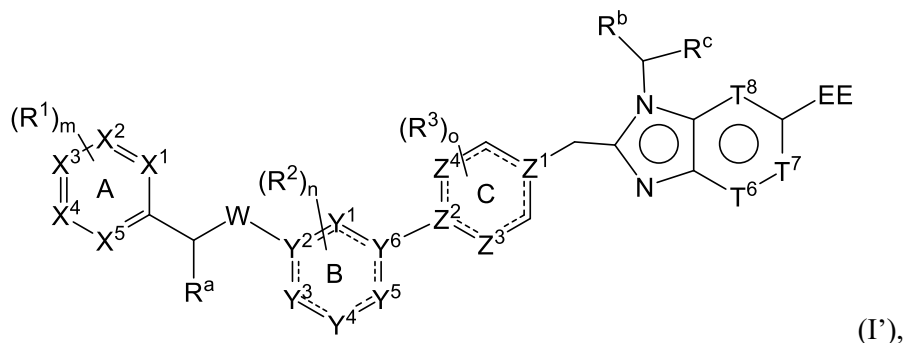
each of which is optionally substituted with halogen, OH, CN, C≡CH, CH₃, or CF₃, m is 0 or 1, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, or nineteenth

embodimentexample.

In a twenty-first embodimentexample, the inventionpresent disclosure provides a compound according to any one of the first through fifteenth and the seventeenth through twentieth embodimentexamples, wherein W is O, NH or CH₂, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth or twentieth embodimentexample.

In a twenty-second embodimentexample, the inventionpresent disclosure provides a compound according to any one of the first through twentieth embodimentexamples, wherein R¹ is selected from halogen, CN, CH₃, CF₃, and C≡CH, wherein the remainder of the variables are as defined in the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, or twenty-first embodimentexample.

In a twenty-third embodimentexample, the inventionpresent disclosure provides a compound according to the first embodimentexample, wherein the compound is represented by the structural formula (I'):



C₁-C₆ haloalkoxy, and NR⁵R⁶;

each R³ is independently halogen, -CN, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl,

C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy; and/or

two R³ taken together with Ring C, form 6-10 membered bridged heterocyclyl optionally substituted with

one or more groups selected from halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy;

each R⁴ is independently H, halogen, or C₁-C₆ alkyl optionally substituted with one or more groups selected from halogen;

R⁵ and R⁶ are each independently hydrogen or C₁-C₆ alkyl;

wherein optionally two R¹; two R²; two R³; R^a and R¹; R^a and R²; R¹ and R⁵; R² and R⁵; taken together with their respective intervening carbon or hetero atom(s), form phenyl, 5-6 membered heteroaryl, 4-6 membered saturated or partially saturated cycloalkyl or 4-7 membered saturated or partially saturated heterocyclyl, each of which is optionally substituted with one or more groups selected from halogen, -CN, -OH,

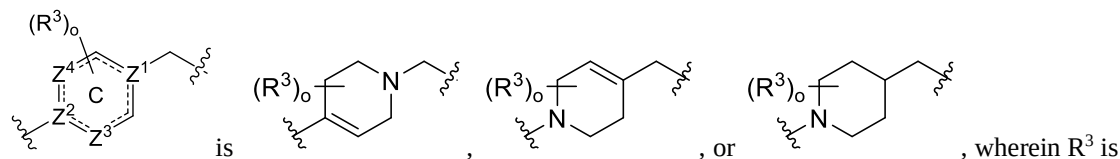
C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, and NR⁵R⁶;

m is 0, 1, 2, 3, or 4;

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

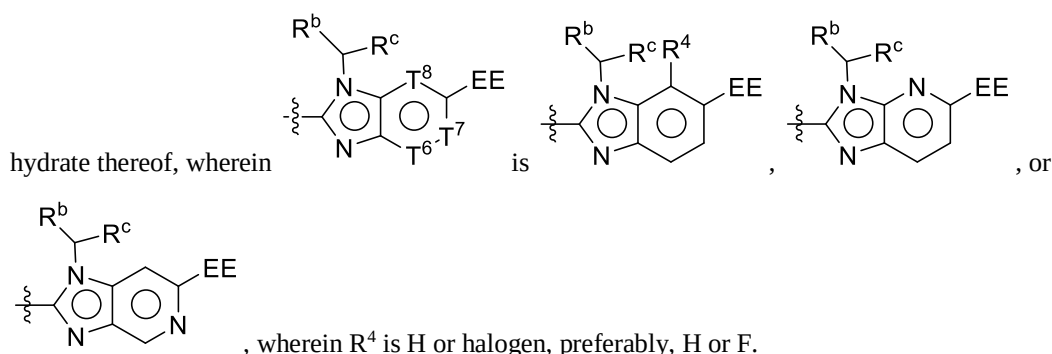
o is 0, 1, 2, 3, or 4, wherein the remainder of the variables are as defined in the first [embodimentexample](#).

In a twenty-fourth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, or twenty-third (*e.g.*, twenty-third) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein



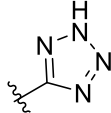
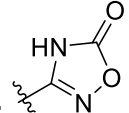
independently halogen, C₁-C₄ alkyl, or C₁-C₄ haloalkyl; and o is 0, 1, or 2.

In a twenty-fifth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, or twenty-fourth (*e.g.*, twenty-third or twenty-fourth) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or



, wherein R⁴ is H or halogen, preferably, H or F.

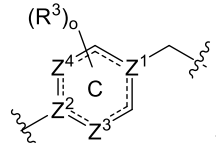
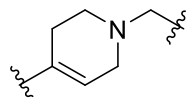
In a twenty-sixth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, or twenty-fifth (*e.g.*, twenty-third, twenty-fourth or twenty-fifth) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof,

wherein EE is $-\text{COOH}$, $-\text{C}(\text{O})\text{NHOH}$, $-\text{C}(\text{O})\text{NHSO}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NHSO}_2\text{CF}_3$, , or .

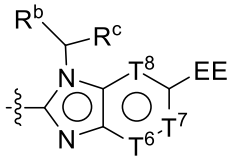
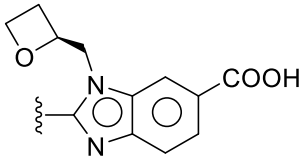
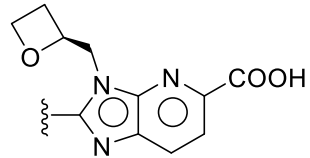
In a twenty-seventh [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, or twenty-sixth (*e.g.*, twenty-third, twenty-fourth, twenty-fifth, or twenty-sixth) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer,

solvate, or hydrate thereof, wherein R^b is , , or ; each of which is optionally substituted with one or more groups selected from $\text{C}_1\text{-C}_3$ alkyl; and R^c is H or $\text{C}_1\text{-C}_3$ alkyl.

In a twenty-eighth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, or twenty-seventh (*e.g.*, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, or twenty-seventh) [embodimentexample](#), or a pharmaceutically

acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein  is .

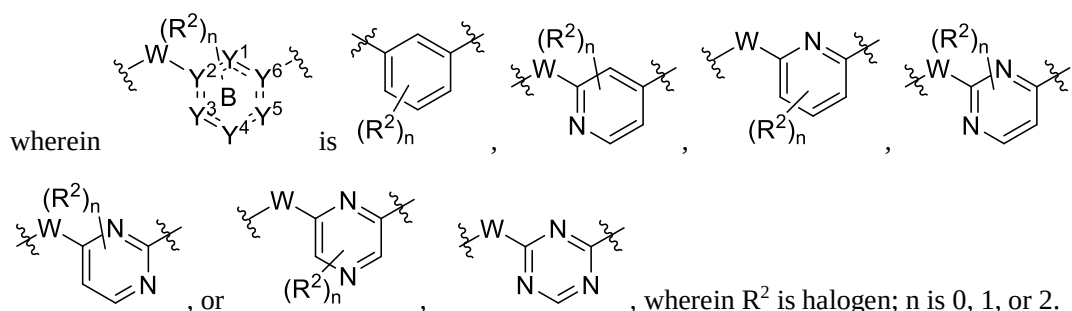
In a twenty-ninth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, or twenty-eighth (*e.g.*, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, or twenty-eighth) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof,

wherein  is  or .

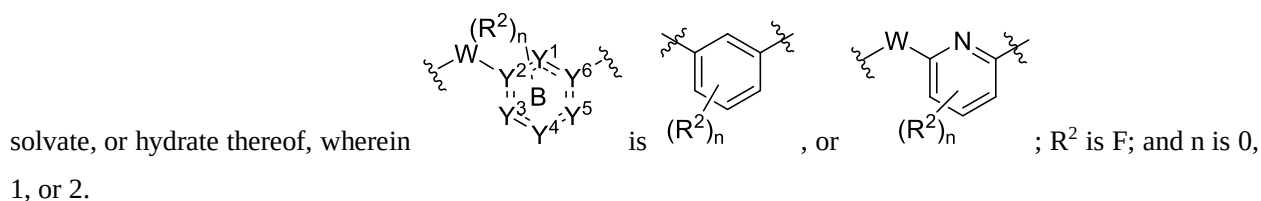
In a thirtieth [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third,

fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, or twenty-ninth (e.g., twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, or twenty-ninth) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein W is O, NH or CH₂, and R^a is H.

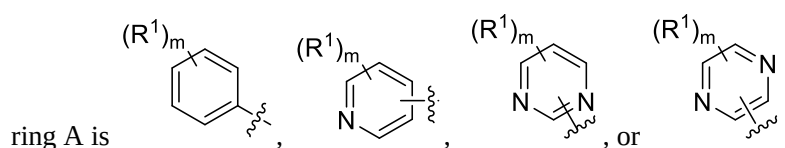
In a thirty-first [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, or thirtieth (e.g., twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, or thirtieth) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof,



In a thirty-second [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, or thirty-first (e.g., twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, or thirty-first) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer,



In a thirty-third [embodimentexample](#), the [inventionpresent disclosure](#) provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, or thirty-second (e.g., twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, or thirty-second) [embodimentexample](#), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein



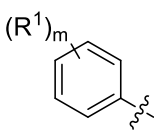
each R¹ is independently selected from halogen, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₂-C₄alkynyl optionally substituted with cyclopropyl, 5-6 membered heteroaryl (wherein the hetero ring atom is nitrogen) optionally substituted with C₁-C₄ alkyl; and/or

two R¹, taken together with and their respective intervening carbon atoms, form 4-7 membered heterocyclyl (wherein the hetero ring atom is nitrogen and/or oxygen) optionally substituted with C₁-C₄ alkyl; and

m is 0, 1, 2, or 3.

In a thirty-fourth embodimentexample, the inventionpresent disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, or thirty-third (*e.g.*, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second or thirty-third) embodimentexample, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein W is O.

In a thirty-fifth embodimentexample, the inventionpresent disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, or thirty-fourth (*e.g.*, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, or thirty-fourth) embodimentexample, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein

ring A is , each R¹ is independently selected from halogen, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, imidazolyl, triazolyl, pyridyl, and C₂-C₄alkynyl optionally substituted with cyclopropyl; and m is 0, 1, or 2.

In a thirty-sixth embodimentexample, the inventionpresent disclosure provides a compound according to the first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, thirty-fourth, or thirty-fifth (*e.g.*, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, thirty-fourth, or thirty-fifth) embodimentexample, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R¹ is selected from halogen and CN.

In a thirty-seventh embodimentexample, the compound, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, is selected from the compounds disclosed in examples and Table 1.

In one embodimentexample, the inventionpresent disclosure provides a pharmaceutical composition comprising the compound according to any one of the first through thirty-seventh embodimentexamples, and a pharmaceutically acceptable excipient.

In another aspectexample, the inventionpresent disclosure provides a method of treating

5 cardiometabolic and associated diseases comprising administering to a subject in need of such treatment a therapeutically effective amount of any one of the compound according to any one of the first through twenty-second embodimentexamples, wherein the disease is T1D, T2DM, pre-diabetes, idiopathic T1D (Type 1b), LADA (latent autoimmune diabetes in adults), EOD (early-onset T2DM), YOAD (youth-onset atypical diabetes), MODY (maturity onset diabetes of the young), malnutrition-related diabetes, gestational diabetes,

10 hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity (including hypothalamic obesity and monogenic obesity) and related comorbidities (e.g., osteoarthritis and urine incontinence), eating disorders (including binge eating syndrome, bulimia nervosa, and syndromic obesity such as Prader-Willi and Bardet-Biedl syndromes), weight gain from use of other agents

15 (e.g., from use of steroids and antipsychotics), excessive sugar craving, dyslipidemia (including hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, and low HDL cholesterol), excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD (including related diseases such as steatosis, NASH, fibrosis, cirrhosis, and hepatocellular carcinoma), NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis (including coronary artery disease), coronary

20 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, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract,

25 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, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome

30 Crohn's disease, colitis, irritable bowel syndrome, prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction (e.g., alcohol and/or drug abuse).

In a further aspectexample, the inventionpresent disclosure includes use of a therapeutically effective amount of the compound according to any one of the first through twenty-second embodimentexamples in the manufacture of a medicament for treating a subject in need of with cardiometabolic and associated diseases,

35 wherein the disease is T1D, T2DM, pre-diabetes, idiopathic T1D (Type 1b), LADA (latent autoimmune diabetes in adults), EOD (early-onset T2DM), YOAD (youth-onset atypical diabetes), MODY (maturity onset diabetes of the young), malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin

resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity (including hypothalamic obesity and monogenic obesity) and related comorbidities (e.g., osteoarthritis and urine incontinence), eating disorders (including binge eating syndrome, bulimia nervosa, and syndromic obesity such as Prader-Willi and Bardet-Biedl syndromes), weight gain from use of other agents (e.g., from use of steroids and antipsychotics), excessive sugar craving, dyslipidemia (including hyperlipidemia, hypertriglyceridemia, increased total cholesterol, high LDL cholesterol, and low HDL cholesterol), excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD (including related diseases such as steatosis, NASH, fibrosis, cirrhosis, and hepatocellular carcinoma), NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis (including coronary artery disease), 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, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, 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, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome Crohn's disease, colitis, irritable bowel syndrome, prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction (e.g., alcohol and/or drug abuse).

It should be understood that any ~~embodiment~~example of the ~~invention~~present disclosure, including those described only in the Examples or claims, or only in one section of the specification, can be combined with one or more additional ~~embodiment~~examples of the ~~invention~~present disclosure, to the extent that such combinations are not expressly disclaimed or are improper.

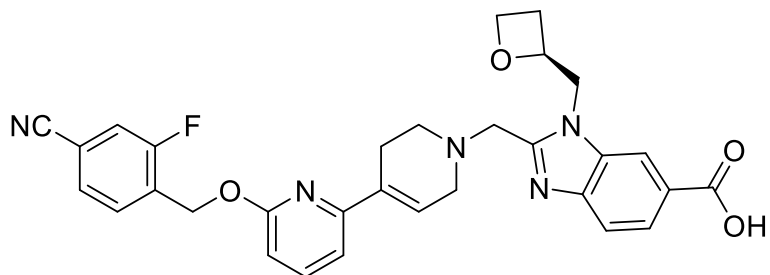
BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1A and 1B show dose-response curves for the GLP-1R/ β -Arrestin recruitment assay using certain compounds of the invention and GLP-1 (7-37) as control. The vertical axis represents relative effects of the test compounds normalized to percentage of effect by the natural ligand GLP-1 (7-37). FIG. 1A compares Compounds 1, 10, 11, 19, and 35 to GLP-1 (7-37). The two panels of FIG. 1B compare Compounds 225, 237, & 239 (left panel) and 236 & 238 (right panel) to GLP-1 (7-37).

FIGs. 2A and 2B show dose-response curves for the GLP-1R/ β -Arrestin internalization assay using certain compounds of the invention and GLP-1 (7-37) as control. The vertical axis represents relative effects of the test compounds normalized to percentage of effect by the natural ligand GLP-1 (7-37). The two panels in FIG. 2A compare Compounds 19 & 28 (left panel), and Compounds 9, 33, & 35

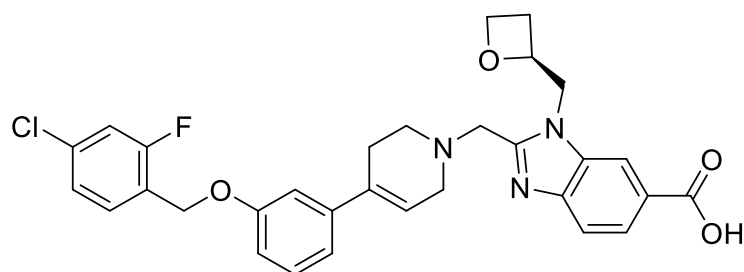
WHAT IS CLAIMED IS:

1. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:

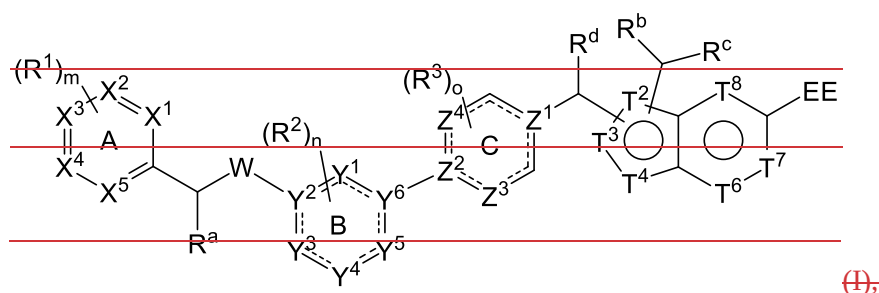


5

2. A compound or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



1. ~~A compound represented by structural formula (I):~~



10

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

~~----- indicates a single bond or a double bond;~~

~~X^1, X^2, X^3, X^4 , and X^5 are each independently selected from N and CH; wherein no more than three of X^1, X^2, X^3, X^4 , and X^5 are N and wherein ring A does not contain 3 nitrogen ring atoms at 3 contiguous positions;~~

15

~~W is selected from O, S, CR^5R^6 , and $NR^{5'}$;~~

~~Y^1, Y^3, Y^4 , and Y^5 are each independently selected from N, NH, CH, and CH_2 ;~~

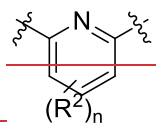
~~Y^2 and Y^6 are each independently selected from N, C, or CH;~~

~~wherein there is no more than 3 nitrogen ring atoms in ring B and wherein ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;~~

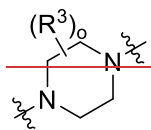
20

~~Z^1 and Z^2 are each independently selected from N, C, and CH; wherein at least one of Z^1 and Z^2 is N; Z^3 and Z^4 are each independently selected from a bond, CH, CH_2 , $CH=CH$, CH_2CH_2 , CH_2CH , and $CHCH_2$; wherein ring C contains no more than two double bonds;~~

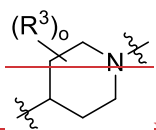
provided that when ring B is



, then (1) W is not O, and/or (2) ring C is not



, and/or (3) ring C is not



wherein Z¹ is N, and/or (4) ring A is not

phenyl;

wherein:

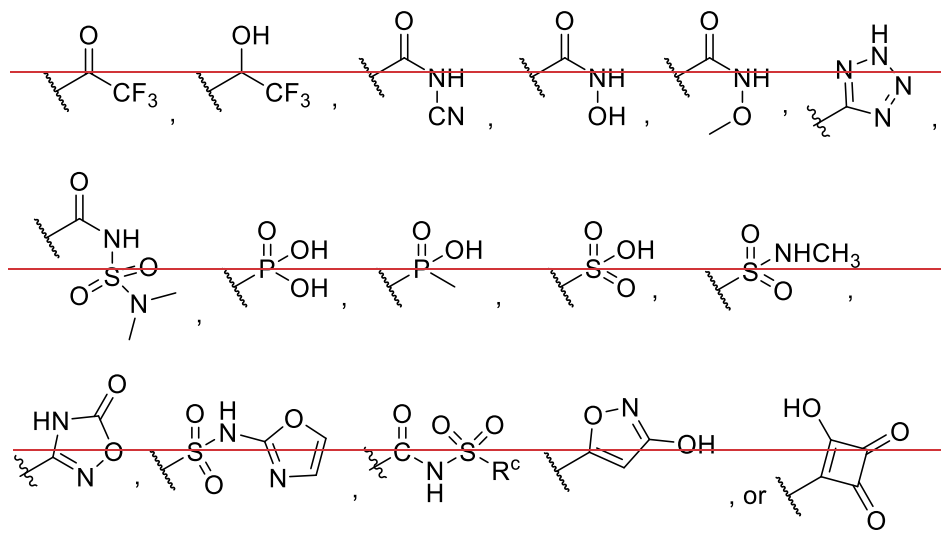
T², T³, and T⁴ are each independently selected from N, NR⁴, O, S, C, and CR⁴;

T⁶, T⁷, and T⁸ are each independently selected from N and CR⁴;

wherein no more than 4 of T², T³, T⁴, T⁶, T⁷, and T⁸ are selected from N, O, and S;

EE is ~~COOH or a carboxylic group surrogate, optionally, the carboxylic group~~

surrogate is:



R^a is selected from hydrogen, deuterium, halogen, ~~CN, C₁-C₆ alkyl, C₁-C₆ alkoxy,~~

NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the

C₁-C₆ alkyl or C₁-C₆ alkoxy represented by R^a is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and C₃-C₆ saturated or partially saturated cycloalkyl; and

wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^a or in the group represented by R^a is optionally

substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃ alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃ alkoxy (optionally

substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR⁵R⁶;

R^b is selected from hydrogen, deuterium, halogen, ~~CN, C₁-C₆ alkyl, C₁-C₆ alkoxy,~~

NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the

C₁-C₆ alkyl or C₁-C₆ alkoxy represented by R^b is optionally substituted with one or more groups

selected from halogen, oxo, CN, OH, and C₃-C₆-saturated or partially saturated cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^b or in the group represented by R^b is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃-alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃-alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR⁵R⁶;

R^c is selected from hydrogen, deuterium, halogen, CN, C₁-C₆-alkyl, C₁-C₆-alkoxy, NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆-alkyl or C₁-C₆-alkoxy represented by R^c is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and C₃-C₆-saturated or partially saturated cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^c or in the group represented by R^c is optionally substituted with one or more groups selected from halogen, oxo, CN, and NR⁵R⁶;

R^d is selected from hydrogen, deuterium, halogen, CN, C₁-C₆-alkyl, C₁-C₆-alkoxy, NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆-alkyl or C₁-C₆-alkoxy represented by R^d is optionally substituted with one or more groups selected from halogen, oxo, CN, and saturated or partially saturated C₃-C₆-cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^d or in the group represented by R^d is optionally substituted with one or more groups selected from halogen, oxo, CN, and NR⁵R⁶;

each R¹ is independently selected from halogen, CN, OH, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkenyl, C₁-C₆-alkynyl, NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkenyl, or C₁-C₆-alkynyl represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃, and saturated or partially saturated C₃-C₆-cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R¹ or in the group represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃-alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃-alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR⁵R⁶;

each R² is independently selected from halogen, CN, OH, oxo, C₁-C₆-alkyl, C₁-C₆-alkoxy, NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆-alkyl or C₁-C₆-alkoxy represented by R² is optionally substituted with one or

more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃, and saturated or partially saturated C₃-C₆-cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R² or in the group represented by R² is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃-alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃-alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR⁵R⁶;

each R³ is independently selected from halogen, CN, OH, oxo, C₁-C₆-alkyl, C₁-C₆-alkoxy, NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆-alkyl or C₁-C₆-alkoxy represented by R³ is optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃, and saturated or partially saturated C₃-C₆-cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R³ or in the group represented by R³ is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃-alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃-alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR⁵R⁶;

each R⁴ is H, deuterium, halogen, OH, CN, C₁-C₆-alkyl, C₁-C₆-alkoxy, or NR⁵R⁶; wherein the C₁-C₆-alkyl and C₁-C₆-alkoxy represented by R⁴ is optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, and saturated or partially saturated C₃-C₆-cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃);

R⁵ and R⁶ are each independently selected from hydrogen, deuterium, halogen, CN, OH, oxo, C₁-C₆-alkyl, C₁-C₆-alkoxy, NR⁵R⁶, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkenyl, or C₁-C₆-alkynyl represented by R⁵ or R⁶ is optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃, and saturated or partially saturated C₃-C₆-cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R⁵ or R⁶ or in the group represented by R⁵ or R⁶ is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃-alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and C₁-C₃-alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH₃), and NR⁵R⁶;

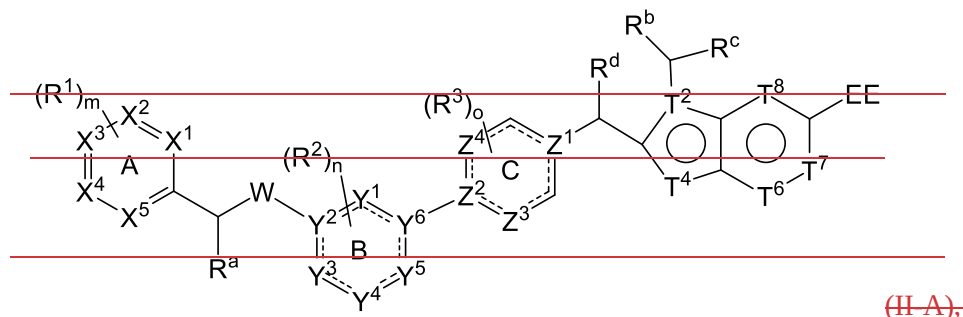
R^{5+} and R^{6+} are each independently selected from hydrogen, deuterium, and C_1 - C_6 alkyl;
 wherein optionally two R^1 ; two R^2 ; two R^3 ; two R^4 ; R^1 and R^2 ; R^2 and R^3 ; R^a and R^1 ; R^a
 and R^2 ; R^1 and any of R^5 , R^{5+} (in the group represented by W), or R^6 ; R^a and any of R^5 , R^{5+} (in the
 group represented by W), or R^6 ; R^2 and any of R^5 , R^{5+} (in the group represented by W), or R^6 ; R^5
 and R^6 ; any of two groups selected from R^e , R^d , R^e , and R^f ; or R^4 and any one of R^e , R^d , R^e , and
 R^f ; taken together with their respective intervening carbon or hetero atom(s), form phenyl, 5-6
 membered heteroaryl, 4-8 membered saturated or partially saturated cycloalkyl or 4-8 membered
 saturated or partially saturated heterocyclyl, each of which is optionally substituted with one or
 more groups selected from halogen, CN, OH, CF_3 , C_1 - C_6 alkyl, C_1 - C_6 alkoxy, NH_2 , NHC_1 - C_6
 alkyl, $N(C_1$ - C_6 alkyl) $_2$, oxo, and saturated or partially saturated C_3 - C_6 cycloalkyl, wherein the
 C_1 - C_6 alkyl and C_1 - C_6 alkoxy is optionally substituted with one or more groups selected from
 halogen, oxo, CN, CF_3 , OH, OCH_3 , OCH_2CH_3 , and saturated or partially saturated C_3 - C_6
 cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more groups selected
 from halogen, oxo, CN, CF_3 , OH, OCH_3 , OCH_2CH_3 ;

m is an integer selected from 0, 1, 2, 3, and 4,

n is an integer selected from 0, 1, 2, 3, 4, and 5, and

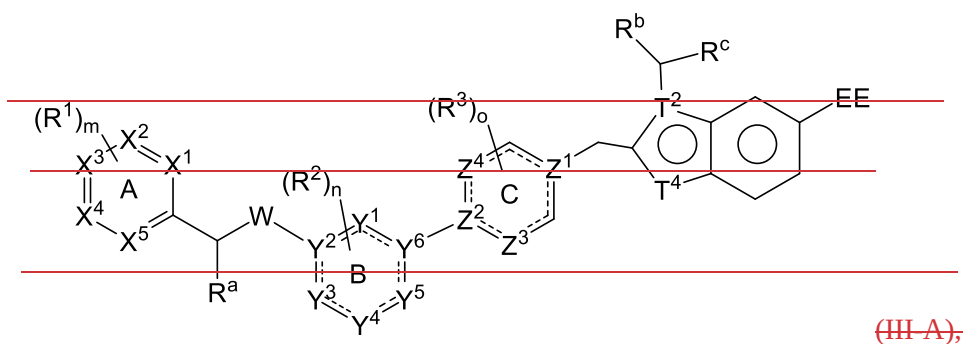
o is an integer selected from 0, 1, 2, 3, 4, and 5.

2. The compound according to claim 1, wherein the compound is represented by the structural
 formula (II-A):



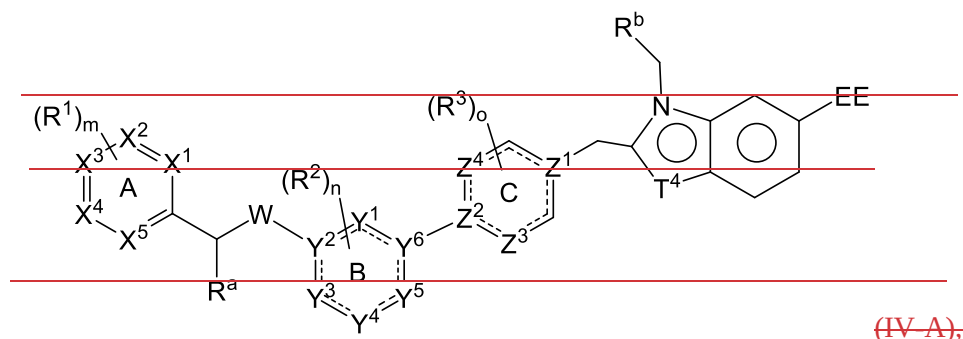
or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R^d is H,
 F, CH_3 , or CF_3 .

3. The compound according to claim 1 or 2, wherein the compound is represented by structural
 formula (III-A):



or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein T^2 is N, and T^4 is N or CR^4 , wherein R^4 is H, halogen, OH, CN, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, or C_1 - C_3 alkoxy; or T^2 is C, and T^4 is NR^4 , wherein R^4 is H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl.

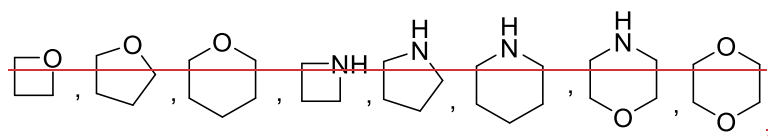
- 5 4. The compound according to any one of claims 1-3, wherein the compound is represented by structural formula (IV-A):



or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein T^4 is N or CH; and

- 10 R^a is H, CH_3 , or CF_3 ; or R^a , R^1 and X^5 , taken together with their respective intervening carbons, form 5-7 membered cycloalkenyl or 5-7 membered partially saturated monoheterocyclyl.

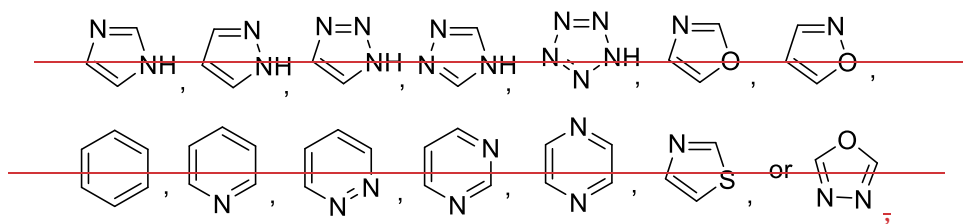
5. The compound according to any one of claims 1-4, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R^b is



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wherein R^b is optionally substituted with 1 or 2 groups selected from oxo, CN, F, Cl, C_1 - C_3 alkyl, and C_1 - C_3 alkoxy, wherein the C_1 - C_3 alkyl or C_1 - C_3 alkoxy in the group represented by R^b is optionally substituted with 1 or 2 groups selected from F, OH, and OCH_3 .

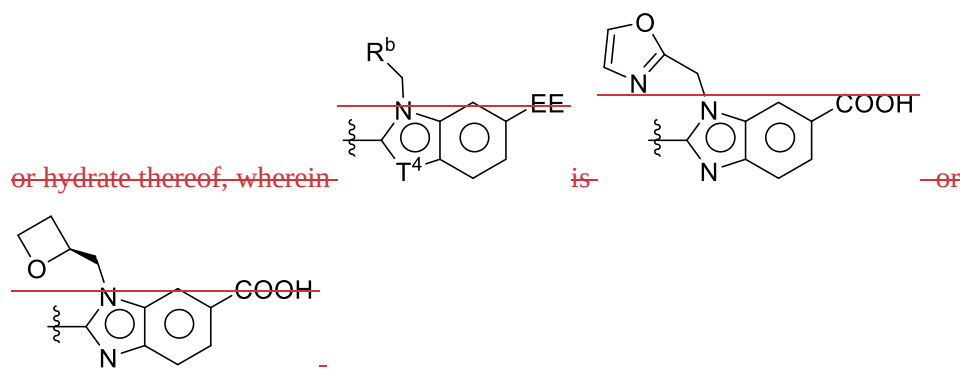
- 20 6. The compound according to any one of claims 1-4, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R^b is



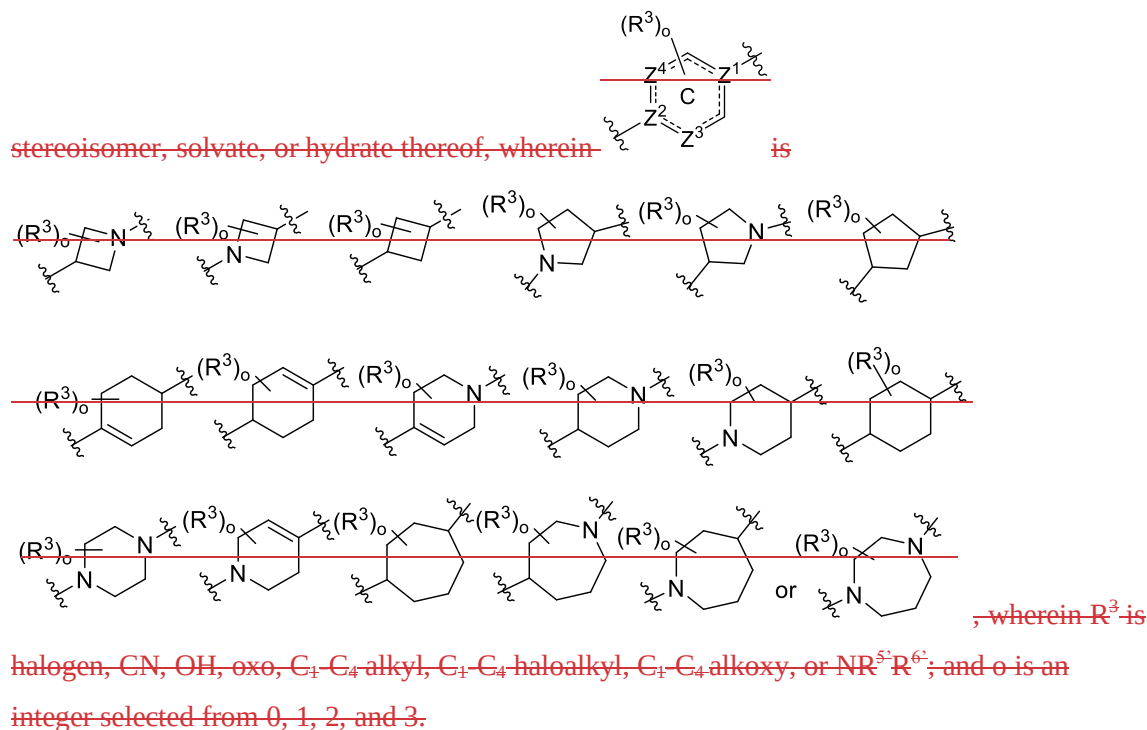
wherein R^b is optionally substituted with 1 or 2 groups selected from halogen, OH, $NR^{5'}R^{6'}$, C_1 - C_3 alkyl, and C_1 - C_3 alkoxy, wherein the C_1 - C_3 alkyl or C_1 - C_3 alkoxy in the group represented by R^b is optionally substituted with 1 or 2 groups selected from F, OH, and OCH_3 .

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7. The compound according to claim 4, or a pharmaceutically acceptable salt, stereoisomer, solvate,

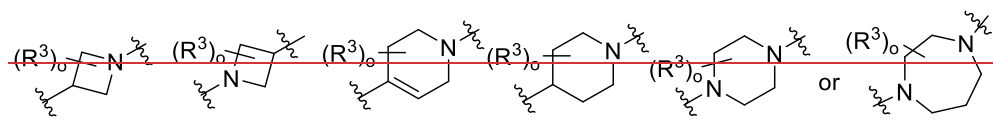


10 8. The compound according to any one of claims 1-7, or a pharmaceutically acceptable salt,



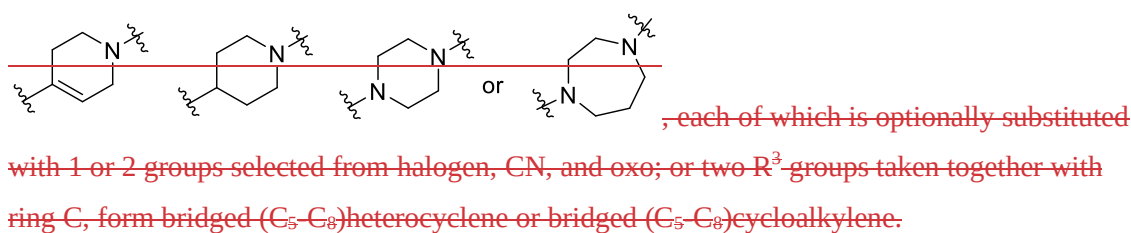
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9. The compound according to any one of claims 1-8, or a pharmaceutically acceptable salt,



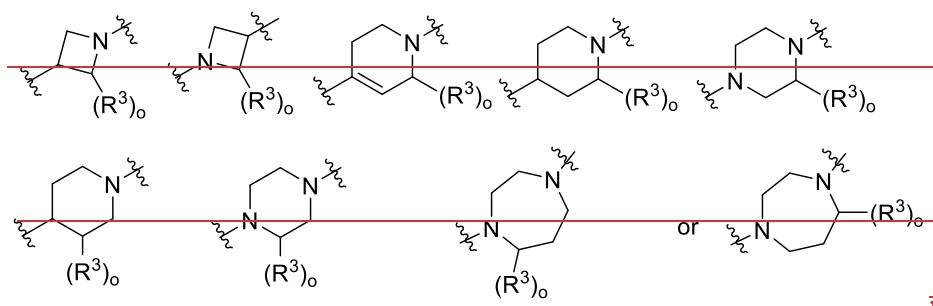
10. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt,

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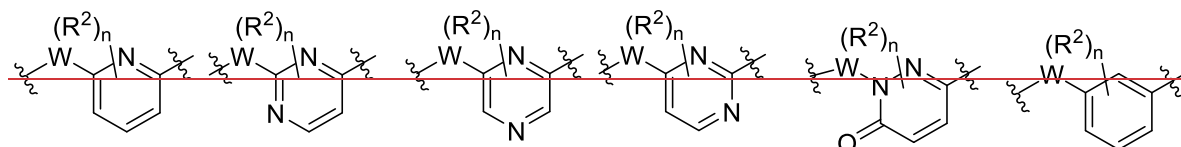
11. The compound according to any one of claims 1-9, or a pharmaceutically acceptable salt,

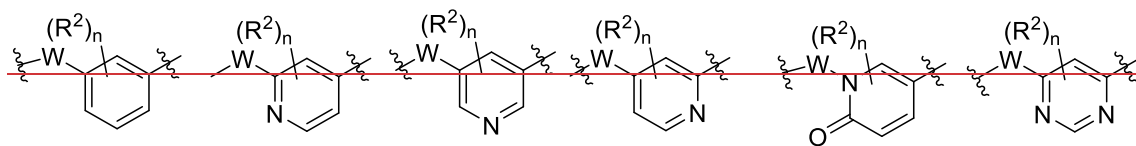


halogen, CN, oxo, CH₃, CF₃, CH₂CH₃, or CH₂CF₃; and o is 0 or 1.

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12. The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt,

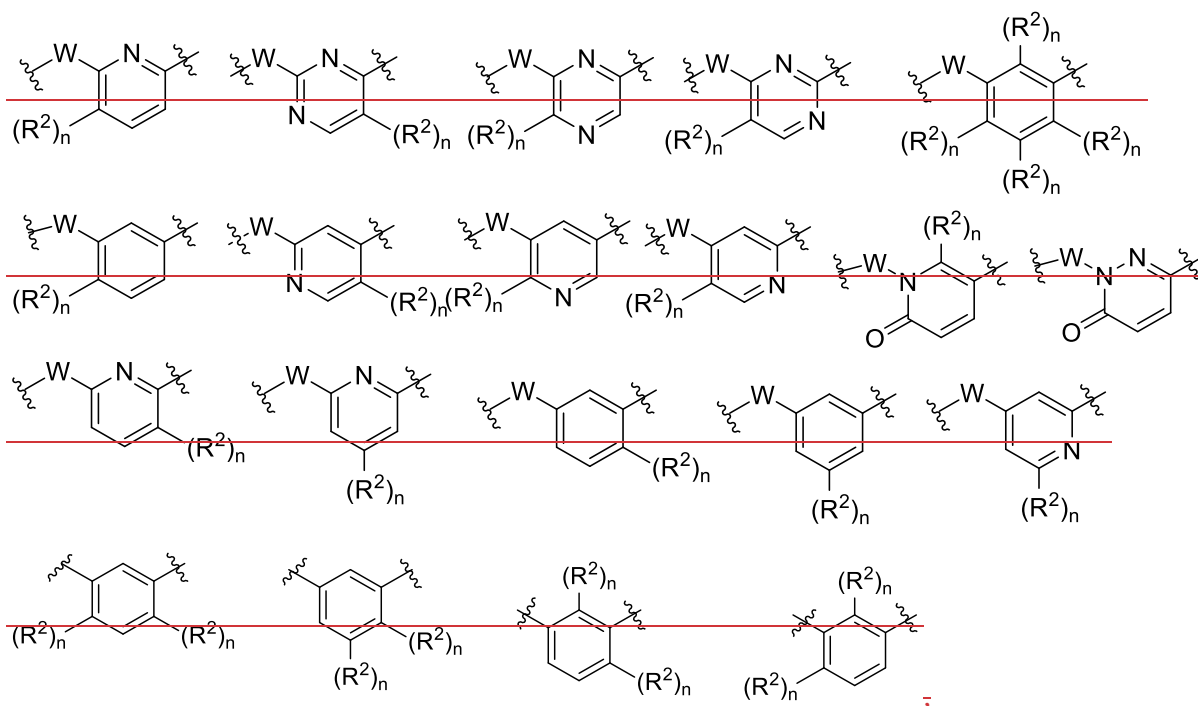




wherein each R^2 is independently selected from halogen, CN, OH, oxo, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, and C_1 - C_2 alkoxy; and n is an integer selected from 0, 1, 2, and 3.

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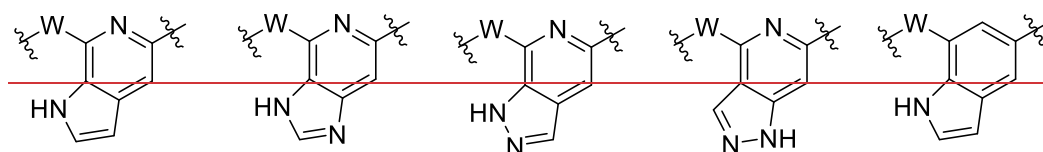
13. The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt,

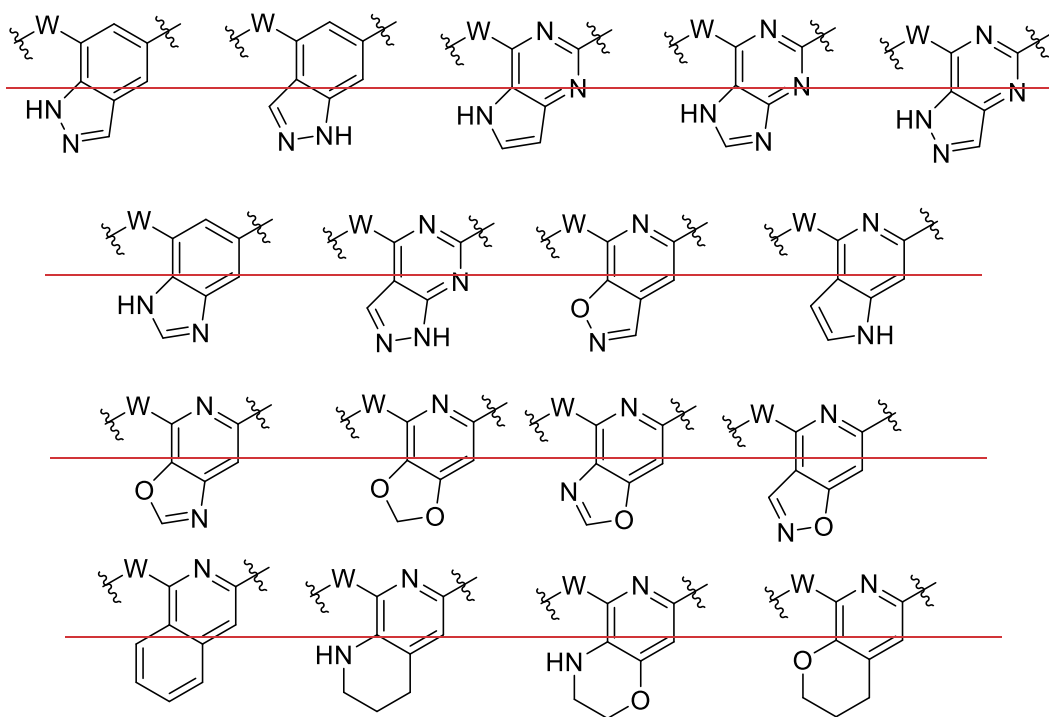


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wherein R^2 is halogen, CN, OH, oxo, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, or C_1 - C_2 alkoxy, n is 0 or 1, and no more than two R^2 are attached to ring B.

15 14. The compound according to claim 12, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein two R^2 groups together with ring B form a bicyclic structure:

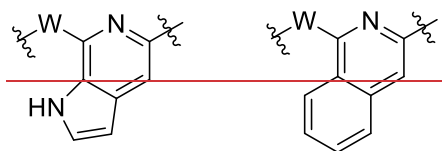




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~~each of which is optionally substituted with 1 or 2 groups selected from halogen, oxo, CN, CF₃, C₁-C₂ alkyl, C₁-C₂ haloalkyl, C₁-C₂ alkoxy, NH₂, NHC₁-C₂ alkyl, and N(C₁-C₂ alkyl)₂.~~

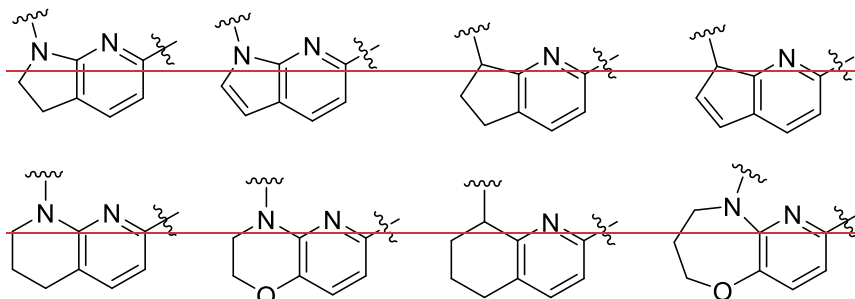
- 5 15. ~~The compound according to claim 14, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein two R² groups together with ring B form a bicyclic structure:~~

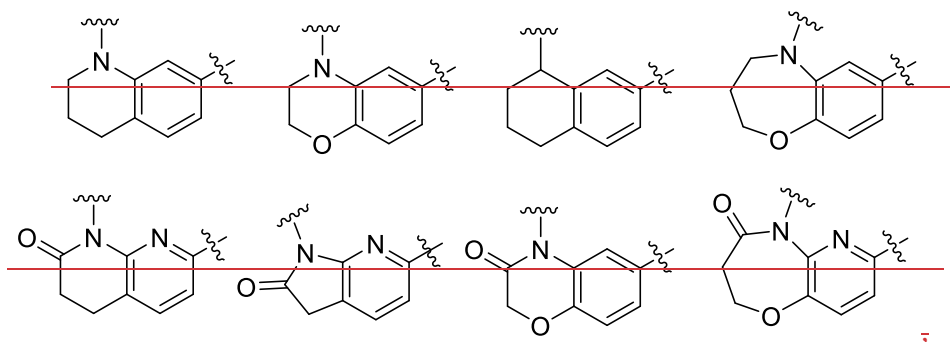


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~~each of which is optionally substituted with halogen.~~

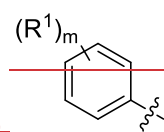
- 10 16. ~~The compound according to claim 12, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein W and ring B form a bicyclic structure:~~





each of which is optionally substituted with 1 or 2 groups selected from halogen, oxo, CN, CF₃, NH₂, NHC₁-C₂-alkyl, and N(C₁-C₂-alkyl)₂.

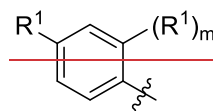
- 5 17. The compound according to any one of claims 1-16, or a pharmaceutically acceptable salt,



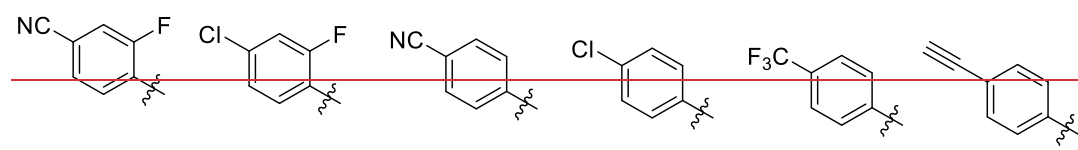
stereoisomer, solvate, or hydrate thereof, wherein ring A is independently selected from halogen, OH, CN, CF₃, C₁-C₂-alkyl, C₁-C₂-haloalkyl, C₁-C₂-alkoxy, NH₂, NHC₁-C₂-alkyl, N(C₁-C₂-alkyl)₂, and C₂-C₄alkynyl optionally substituted with cyclopropane; and m is an integer selected from 0, 1, 2, and 3.

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18. The compound according to any one of claims 1-17, or a pharmaceutically acceptable salt,

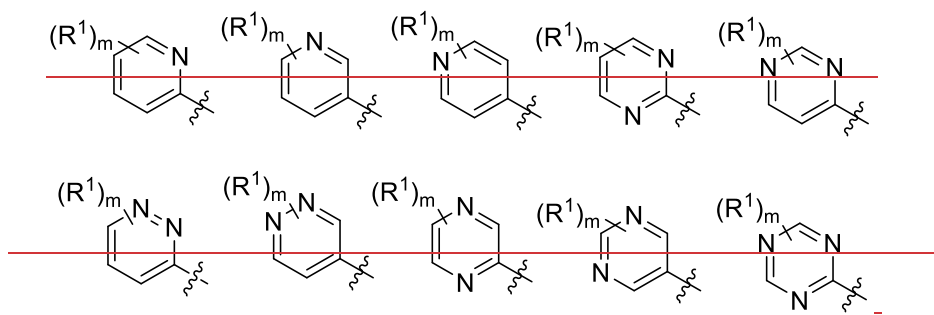


stereoisomer, solvate, or hydrate thereof, wherein ring A is and R¹ is halogen, CN, CH₃, CF₃, OH, or C₂-C₄alkynyl optionally substituted with cyclopropane; preferably ring A is



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19. The compound according to any one of claims 1-16, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein ring A is

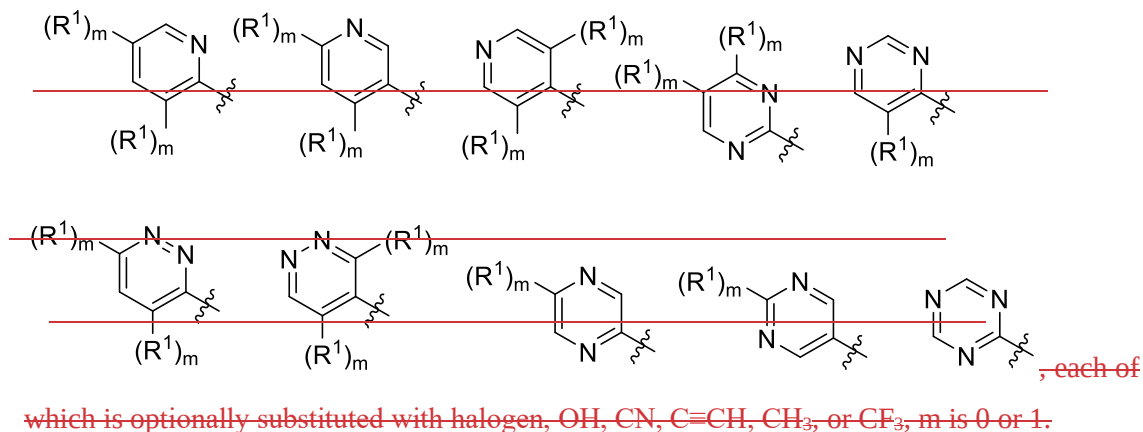


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each R¹ is independently selected from halogen, OH, CN, CF₃, C₁-C₂-alkyl, C₁-C₂-haloalkyl, C₁-

~~C₂-alkoxy, NH₂, NHC(1-C₂-alkyl), N(C₁-C₂-alkyl)₂, and C₂-C₄alkynyl optionally substituted with cyclopropane; and m is an integer selected from 0, 1, and 2.~~

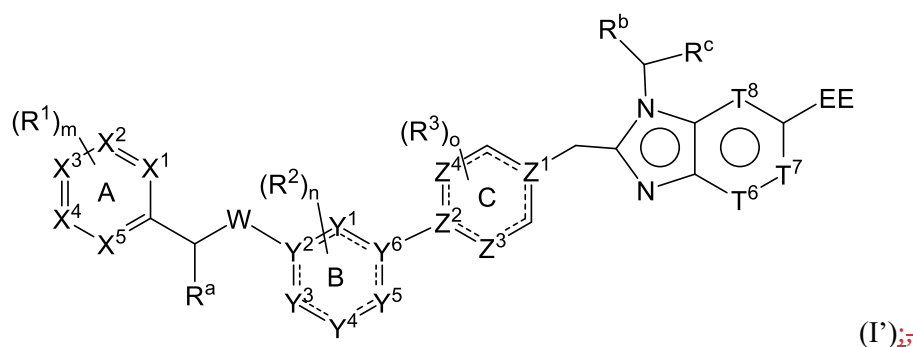
20. ~~The compound according to claim 19, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein ring A is~~



21. ~~The compound according to any one of claims 1-15 and 17-20, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein W is O, NH or CH₂.~~

22. ~~The compound according to any one of claims 1-21, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R¹ is selected from halogen, CN, CH₃, CF₃, and C≡CH.~~

233. ~~The A compound according to claim 1, wherein the compound is~~ represented by the structural formula (I'):



or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof;

or a pharmaceutical composition comprising the compound, the pharmaceutically acceptable salt, the stereoisomer, the solvate, or the hydrate thereof, and a pharmaceutically acceptable excipient;

wherein

----- indicates a single bond or a double bond;

X¹, X², X³, X⁴, and X⁵ are each independently selected from N, C, and CH; wherein no more than three of X¹, X², X³, X⁴, and X⁵ are N and ring A does not contain 3 nitrogen ring atoms

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Y^1 , Y^3 , Y^4 , and Y^5 are each independently selected from N, NH, C, CH, and CH_2 ;

wherein there is no more than 3 nitrogen ring atoms in ring B and wherein ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;



T^6 , T^7 , and T^8 are each independently selected from N and CR⁴; and no more than 2 of T^6 , T^7 , and T^8 are selected from N;

*C(=O)C(F)(F)F, *C(O)C(F)(F)F, *C(=O)NC#N, *C(=O)NO, *C(=O)NOC, *c1nn[nH]1,
*C(=O)NS(=O)(=O)N(C)C, *P(=O)(O)O, *P(=O)(O)C, *S(=O)(=O)O, *S(=O)(=O)NC,
*c1nc2c(=O)[nH]cnc12, *S(=O)(=O)Nc1ccoc1, *C(=O)NS(=O)(=O)R^c, *c1cc2c(c1)oc(=O)[nH]2, or *C1=C(C(=O)O)C(=O)C1=O

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by R^b is optionally substituted with one or more groups selected from halogen, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, and C₁-C₃ haloalkoxy;

R^c is hydrogen, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

each R¹ is independently halogen, -CN, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₂-C₆ alkenyl, C₂-C₆ alkynyl, NR⁵R⁶, phenyl, 5-6 membered heteroaryl, 4-6 membered saturated or partially saturated cycloalkyl and 3-7 membered saturated or partially saturated heterocyclyl, wherein the C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, or C₂-C₆ alkynyl represented by R¹ is optionally substituted with one or more groups selected from halogen, CN, OH, and C₃-C₆ cycloalkyl; and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R¹ or in the group represented by R¹ is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ hydroxyalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ hydroxyalkoxy, and NR⁵R⁶;

each R² is independently selected from halogen, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, and NR⁵R⁶;

~~each R³ is independently halogen, -CN, -oxo-, C₁-C₄₆ alkyl, or C₁-C₄₆ haloalkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy; and/or~~

~~two R³ taken together with Ring C, form 6-10 membered bridged heterocyclyl optionally substituted with one or more groups selected from halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy;~~

each R⁴ is independently H, halogen, or C₁-C₆ alkyl optionally substituted with one or more groups selected from halogen;

R⁵ and R⁶ are each independently selected from hydrogen ~~and/or~~ C₁-C₆ alkyl;

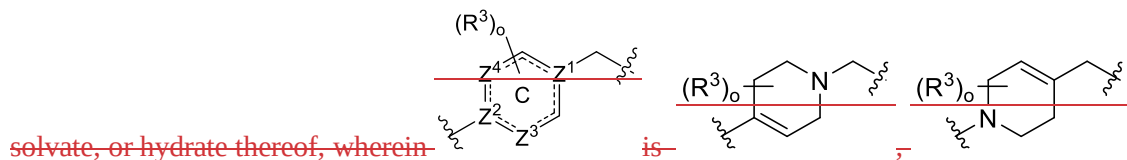
~~wherein optionally two R¹; two R²; two R³; R^a and R¹; R^a and R²; R¹ and R⁵; R² and R⁵; taken together with their respective intervening carbon or hetero atom(s), form phenyl, 5-6 membered heteroaryl, 4-6 membered saturated or partially saturated cycloalkyl or 4-7 membered saturated or partially saturated heterocyclyl, each of which is optionally substituted with one or more groups selected from halogen, -CN, -OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, and NR⁵R⁶;~~

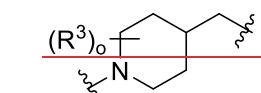
m is 0, 1, 2, 3, or 4;

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

o is 0, 1, or 2, 3, or 4.

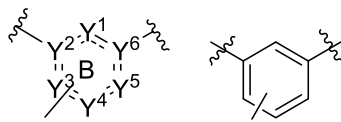
~~24. The compound according to claim 23, or a pharmaceutically acceptable salt, stereoisomer,~~





or ~~wherein R^3 is independently halogen, C_1 - C_4 alkyl, or C_1 - C_4 haloalkyl; and θ is 0, 1, or 2.~~

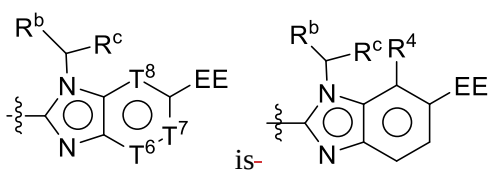
4. The compound according to claim 3, or a pharmaceutically acceptable salt, stereoisomer, solvate,



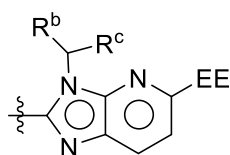
or hydrate thereof, wherein $(R^2)_n$ is $(R^2)_n$, wherein R^2 is halogen; n is 0, 1, or 2.

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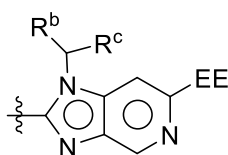
255. The compound according to claim ~~23 or 24~~, or a pharmaceutically acceptable salt, stereoisomer,



solvate, or hydrate thereof, wherein



, or



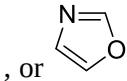
, wherein R^4 is H or halogen, ~~preferably, H or F.~~

10

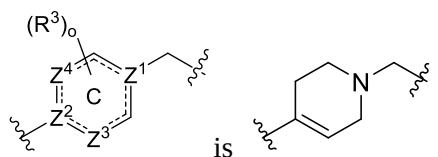
26. The compound according to ~~any one of claims 23-25~~, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein EE is $-\text{COOH}$, $-\text{C}(\text{O})\text{NHOH}$,



15 27. The compound according to ~~any one of claims 23-26~~, or a pharmaceutically acceptable salt,

stereoisomer, solvate, or hydrate thereof, wherein R^b is , , or ; each of which is optionally substituted with one or more groups selected from C_1 - C_3 alkyl; and R^c is H or C_1 - C_3 alkyl.

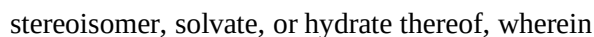
20 28. The compound according to ~~any one of claims 23-27~~, or a pharmaceutically acceptable salt,



stereoisomer, solvate, or hydrate thereof, wherein

is

29. The compound according to ~~any one of claims 23-28~~, or a pharmaceutically acceptable salt,



5

~~31. The compound according to any one of claims 23-30, or a pharmaceutically acceptable salt,~~



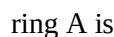
10

~~32. The compound according to any one of claims 23-31, or a pharmaceutically acceptable salt,~~



15

1033. The compound according to ~~any one of claims 23-32~~ 9, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein

alkoxy, C₁-C₄ haloalkoxy, C₂-C₄alkynyl optionally substituted with cyclopropyl,

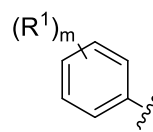
5-6 membered heteroaryl (wherein the heteroaryl comprises nitrogen as hetero ring atom and is nitrogen)-optionally substituted with C₁-C₄ alkyl; and/or

two R¹, taken together with and their respective intervening carbon atoms, form 4-7 membered heterocyclyl (wherein the hetero ring atom is nitrogen and/or oxygen)-optionally substituted with C₁-C₄ alkyl; and

m is 0, 1, 2, or 3.

3411. The compound according to ~~any one of claims 23-33~~ 10, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein W is O.

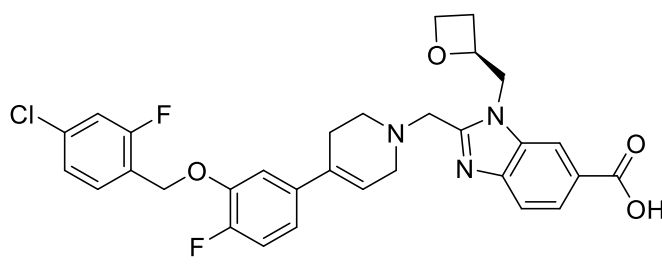
3512. The compound according to ~~any one of claims 23-34~~ 11, or a pharmaceutically acceptable salt,



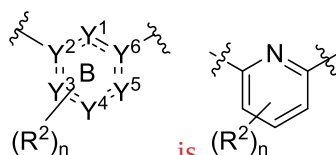
stereoisomer, solvate, or hydrate thereof, wherein ring A is independently selected from halogen, CN, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, imidazolyl, triazolyl, pyridyl, and C₂-C₄alkynyl optionally substituted with cyclopropyl; and m is 0, 1, or 2.

3613. The compound according to ~~any one of claims 23-35~~ 12, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R¹ is selected from halogen and CN.

14. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:

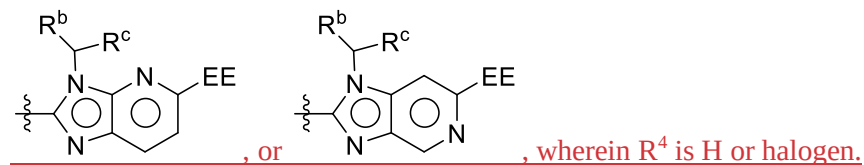
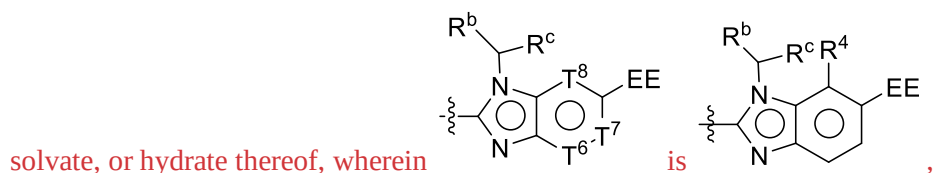


15. The compound according to claim 3, or a pharmaceutically acceptable salt, stereoisomer,



solvate, or hydrate thereof, wherein (R²)_n is (R²)_n, wherein R² is halogen; n is 0, 1, or 2.

16. The compound according to claim 15, or a pharmaceutically acceptable salt, stereoisomer,



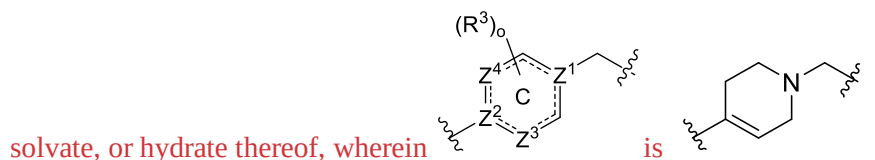
5 17. The compound according to claim 16, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein EE is -COOH, -C(O)NHOH,



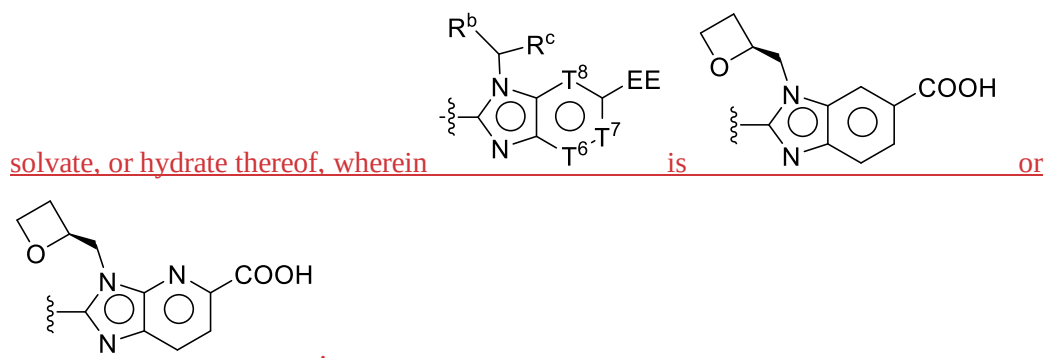
18. The compound according to claim 17, or a pharmaceutically acceptable salt, stereoisomer,

10 solvate, or hydrate thereof, wherein R^b is , , or ; each of which is optionally substituted with one or more groups selected from C₁-C₃ alkyl; and R^c is H or C₁-C₃ alkyl.

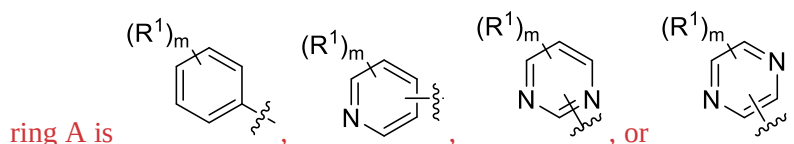
19. The compound according to claim 18, or a pharmaceutically acceptable salt, stereoisomer,



20. The compound according to claim 19, or a pharmaceutically acceptable salt, stereoisomer,



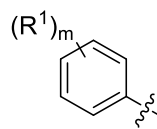
20 21. The compound according to claim 20, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein

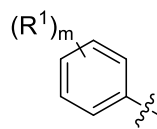


each R^1 is independently selected from halogen, CN, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_2 - C_4 alkynyl optionally substituted with cyclopropyl, 5-6 membered heteroaryl wherein the heteroaryl comprises nitrogen as hetero ring atom and is optionally substituted with C_1 - C_4 alkyl; and m is 0, 1, 2, or 3.

22. The compound according to claim 21, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein W is O.

23. The compound according to claim 22, or a pharmaceutically acceptable salt, stereoisomer,



solvate, or hydrate thereof, wherein ring A is , each R^1 is independently selected from halogen, CN, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, imidazolyl, triazolyl, pyridyl, and C_2 - C_4 alkynyl optionally substituted with cyclopropyl; and m is 0, 1, or 2.

24. The compound according to claim 23, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein R^1 is selected from halogen and CN.

~~37. The compound according to claim 1, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein the compound is a compound listed in Table 1.~~

~~38. A pharmaceutical composition comprising the compound of any of claims 1-37, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, and a pharmaceutically acceptable excipient.~~

3925. Use of a compound of claim 3 or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, in the manufacture of a medicament for ~~A method of~~ treating cardiometabolic and associated diseases ~~comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of any of claims 1-37 or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, or the pharmaceutical composition of claim 38,~~ wherein the disease is T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose

deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, 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, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome Crohn's disease, colitis, irritable bowel syndrome, prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction.

~~40. — Use of a therapeutically effective amount of a compound of any of claims 1-37 or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, or the pharmaceutical composition of claim 38, in the manufacture of a medicament for of treating a subject in need of with cardiometabolic and associated diseases, wherein the disease is T1D, T2DM, pre-diabetes, idiopathic T1D, LADA, EOD, YOAD, MODY, malnutrition-related diabetes, gestational diabetes, hyperglycemia, insulin resistance, hepatic insulin resistance, impaired glucose tolerance, diabetic neuropathy, diabetic nephropathy, kidney disease, diabetic retinopathy, adipocyte dysfunction, visceral adipose deposition, sleep apnea, obesity, eating disorders, weight gain from use of other agents, excessive sugar craving, dyslipidemia, hyperinsulinemia, NAFLD, NASH, fibrosis, cirrhosis, hepatocellular carcinoma, cardiovascular disease, atherosclerosis, coronary artery disease, peripheral vascular disease, hypertension, endothelial dysfunction, impaired vascular compliance, congestive heart failure, myocardial infarction, stroke, hemorrhagic stroke, ischemic stroke, traumatic brain injury, pulmonary hypertension, restenosis after angioplasty, intermittent claudication, post-prandial lipemia, metabolic acidosis, ketosis, arthritis, osteoporosis, Parkinson's Disease, left ventricular hypertrophy, peripheral arterial disease, macular degeneration, cataract, 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, hyper apo B lipoproteinemia, Alzheimer's Disease, schizophrenia, impaired cognition, inflammatory bowel disease, short bowel syndrome~~

Crohn's disease, colitis, irritable bowel syndrome, prevention or treatment of Polycystic Ovary Syndrome and treatment of addiction.

26. The use of claim 25, wherein the disease is type 1 diabetes (T1D) or type 2 diabetes mellitus (T2DM).

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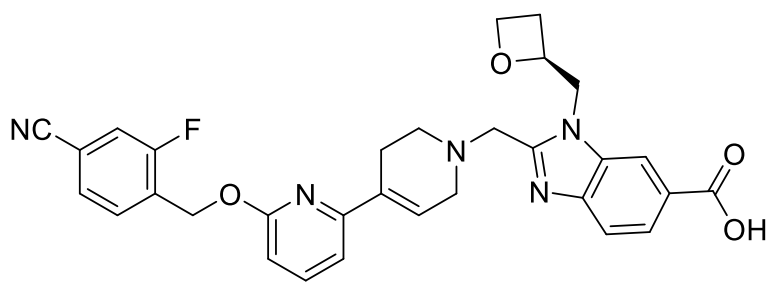
27. The use of claim 25, wherein the disease is obesity.

28. The use of claim 25, wherein the disease is a cardiovascular disease.

10 29. The use of claim 25, wherein disease is non-alcoholic steatohepatitis (NASH).

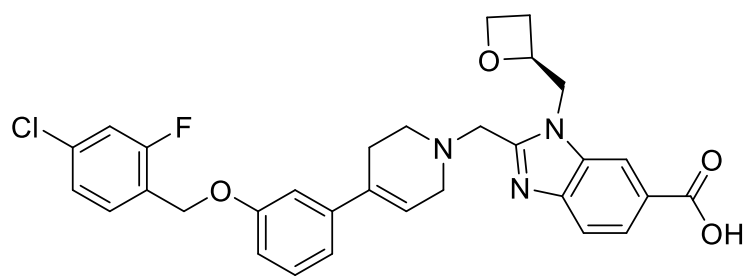
30. The use of claim 25, wherein the disease is Alzheimer's Disease.

15 31. A pharmaceutical composition comprising a pharmaceutically acceptable excipient, and a compound represented by the following structure:



or a pharmaceutically acceptable salt thereof.

20 32. A pharmaceutical composition comprising a pharmaceutically acceptable excipient, and a compound represented by the following structure:



or a pharmaceutically acceptable salt thereof.

25 33. A compound of claim 3 or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, for use in therapy.