

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. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier *et al.*, *Biodrugs*. 17(2): 93-102, 2013).

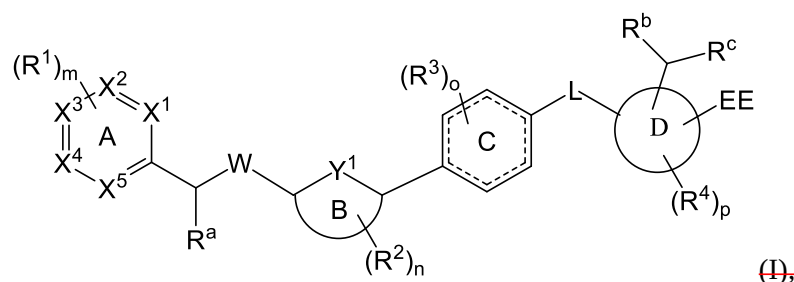
In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll *et al.*, *Diabetes*. 50:609-613, 2001).

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 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

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



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;

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

ring B is 6-membered heteroaryl, 6-membered monocyclic heterocyclyl, or phenyl, wherein

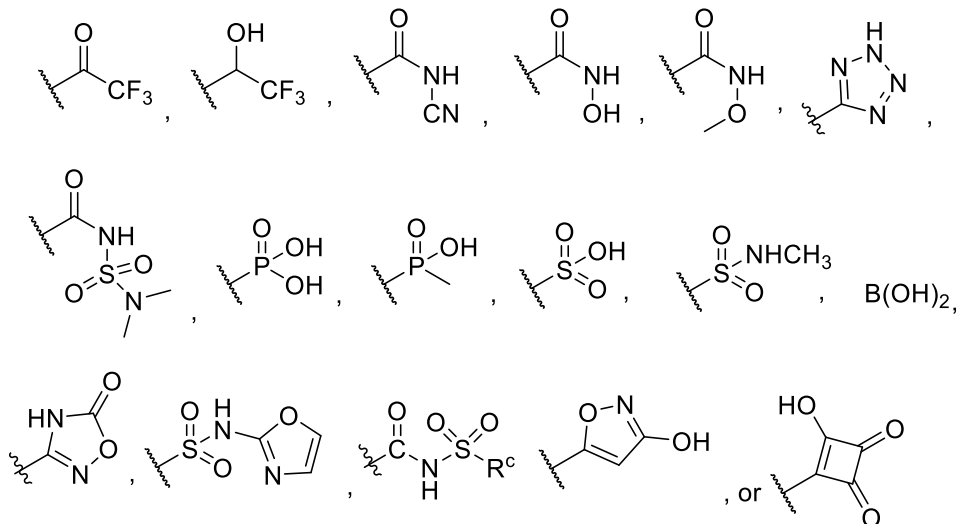
Y^1 is selected from N, NH, CH, and CH_2 ;

ring C is cyclohexyl, phenyl, or pyridyl;

L is CHR^d, O, S, or NR^{5'};

ring D is bicyclic heteroaryl;

EE is -COOH or a carboxylic group surrogate, optionally, the carboxylic group surrogate is:



each R^a and R^b are independently selected from hydrogen, deuterium, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR^{5'}R^{6'}, 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/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^a/R^b or in the group represented by R^a/R^b is optionally substituted with one or more groups selected from halogen, oxo (as appropriate), 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 NR^{5'}R^{6'};

each R^c and R^d are independently selected from hydrogen, deuterium, halogen, -CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR^{5'}R^{6'}, 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/R^d 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/R^d or in the group represented by R^c/R^d is optionally substituted with one or more groups selected from halogen, oxo (as appropriate), CN, and NR^{5'}R^{6'};

each R¹ is independently selected from H, deuterium, halogen, -CN, OH, C₁-C₆ alkyl, C₁-C₆

~~alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NR⁵R^{6'}, 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, C₂-C₆ alkenyl, or C₂-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 (as appropriate), 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 NR⁵R^{6'}.~~

~~each R² is independently selected from H, deuterium, halogen, -CN, OH, oxo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁵R^{6'}, 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 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 (as appropriate), 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 NR⁵R^{6'};~~

~~each R³ is independently selected from H, deuterium, halogen, -CN, OH, oxo, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR⁵R^{6'}, 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 (as appropriate), 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 NR⁵R^{6'};~~

~~each R⁴ is independently selected from H, deuterium, halogen, OH, -CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, and NR⁵R^{6'}, 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, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR^{5'}R^{6'}, 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 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 (as appropriate), 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 NR^{5'}R^{6'}.~~

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

~~wherein optionally two R¹; two R²; two R³; two R⁴; R¹ and R²; R² and R³; R^a and R¹; R^a and R²; R¹ and any of R⁵, R^{5'} (in the group represented by W), or R⁶; R^a and any of R⁵, R^{5'} (in the group represented by W), or R⁶; R² and any of R⁵, R^{5'} (in the group represented by W), or R⁶; R⁵ and R⁶; any of two groups selected from R^c, R^d, R^e, and R^f; or R⁴ and any one of R^c, 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, and each of which is optionally substituted with one or more groups selected from halogen, -CN, -OH, CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy, -NH₂, -NHC₁-C₆ alkyl, N(C₁-C₆ alkyl)₂, oxo, and saturated or partially saturated C₃-C₆ cycloalkyl, wherein the C₁-C₆ alkyl and C₁-C₆ alkoxy 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, wherein the cycloalkyl is optionally substituted with one or more 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;~~

~~o is an integer selected from 0, 1, 2, 3, and 4; and~~

~~p is an integer selected from 0, 1, 2, 3, and 4.~~

~~In another aspect of the present disclosure, there is provided a compound selected from any one of the compounds of 74-102 and 246-334 in Table 1 or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof.~~

~~In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, and a pharmaceutically acceptable excipient.~~

~~In another aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, for use in 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 a further aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, 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.~~

~~In one example, the present disclosure provides a compound of any one of the formulae described herein (e.g., Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof.~~

~~In one example, the present disclosure provides a pharmaceutical composition comprising a compound of any one of the formulae described herein (e.g., Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, as defined in any one of the examples described herein, in a mixture with at least one pharmaceutically acceptable excipient.~~

~~In another example, the present disclosure provides a compound of any one of the formulae described herein (e.g., Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, as defined in any one of the examples described herein, for use as a medicament.~~

~~In another example, the present disclosure provides a compound of any one of the formulae~~

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. In non-clinical experiments GLP-1 promotes continued beta-cell competence by stimulating transcription of genes important for glucose-dependent insulin secretion and by promoting beta-cell neogenesis (Meier *et al.*, *Biodrugs*. 17(2): 93-102, 2013).

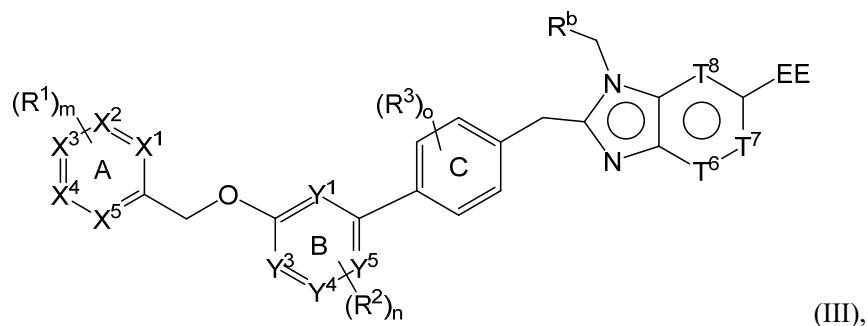
In a healthy individual, GLP-1 plays an important role regulating post-prandial blood glucose levels by stimulating glucose-dependent insulin secretion by the pancreas resulting in increased glucose absorption in the periphery. GLP-1 also suppresses glucagon secretion, leading to reduced hepatic glucose output. In addition, GLP-1 delays gastric emptying and slows small bowel motility delaying food absorption. In people with T2DM, the normal post-prandial rise in GLP-1 is absent or reduced (Vilsboll *et al.*, *Diabetes*. 50:609-613, 2001).

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 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

In one aspect of the present disclosure, there is provided a compound represented by structural formula (III):



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

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

ring B is 6-membered heteroaryl or phenyl, wherein Y¹, Y³, Y⁴, and Y⁵ are each independently

selected from N or CH; wherein there are no more than 3 nitrogen ring atoms in ring B and ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;

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

EE is -COOH;

R^b is independently selected from hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, NR^{5'}R^{6'}, 6-10 membered aryl, 5-6 membered heteroaryl, 3-6 membered saturated or partially saturated cycloalkyl and 3-7 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 (when R^b is non-aromatic), 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 NR^{5'}R^{6'};

each R¹ is independently selected from H, halogen, -CN, OH, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, NR^{5'}R^{6'}, 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, C₂-C₆ alkenyl, or C₂-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 (as appropriate), 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 NR^{5'}R^{6'}.

each R² is independently selected from halogen, -CN, OH, C₁-C₂ alkyl, C₁-C₂ haloalkyl, and C₁-C₂ alkoxy;

each R³ is independently selected from halogen, CN, OH, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and NR^{5'}R^{6'};

each R⁴ is independently selected from H, F, Cl, methyl, and methoxy;

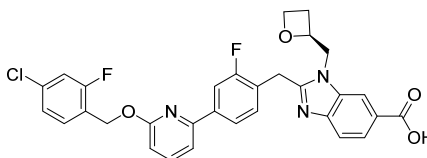
R^{5'} and R^{6'} are each independently selected from hydrogen and C₁-C₆ alkyl;

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

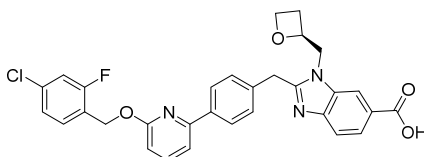
n is an integer selected from 0, 1, 2, 3, and 4

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

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 a further 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 pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a compound disclosed herein or a pharmaceutically acceptable salt thereof, for use in treating cardiometabolic and associated diseases, wherein the disease is type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.

In another aspect of the present disclosure, there is provided a use of a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for of treating a subject in need of with cardiometabolic and associated diseases, wherein the disease is type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.

In one example, the present disclosure provides a compound of any one of the formulae described herein (*e.g.*, Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof.

In one example, the present disclosure provides a pharmaceutical composition comprising a compound of any one of the formulae described herein (*e.g.*, Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, as defined in any one of the examples

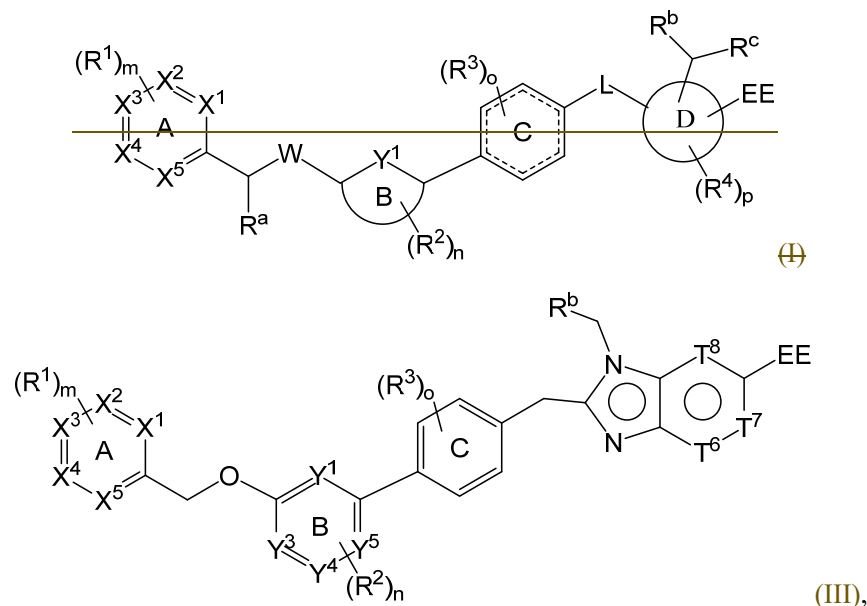
described herein, in a mixture with at least one pharmaceutically acceptable excipient.

In another example, the present disclosure provides a compound of any one of the formulae described herein (*e.g.*, Structural Formula (I), (I-1), (I-2), (II), (III), (I-A), (I-B), (I-C), (I-D), (II-A), (II-B), (II-B'), (II-C), or (II-D)), or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, as defined in any one of the examples described herein, for use as a medicament.

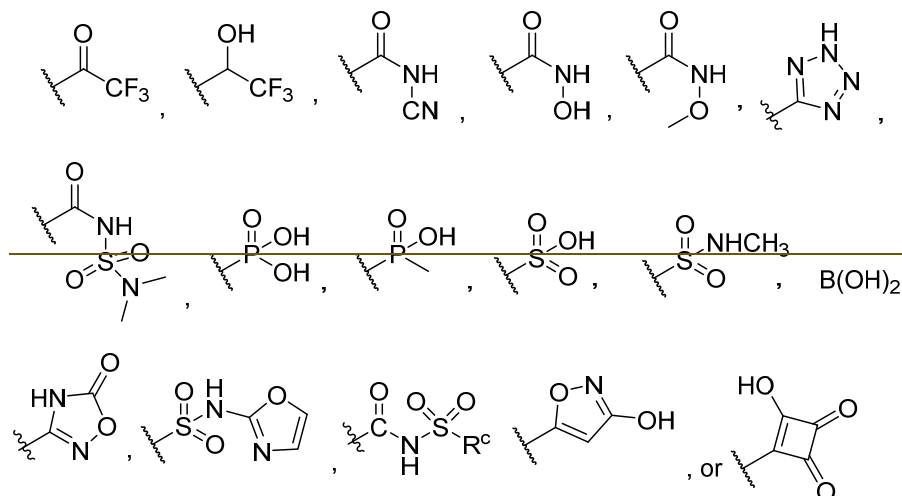
In another example, the present disclosure provides a compound of any one of the formulae

CLAIMS

1. A compound represented by structural formula (III):



- 5 or a pharmaceutically acceptable salt, or 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;
10 ~~W is selected from O, S, CR^5R^6 , and NR^{5z} ;~~
ring B is 6-membered heteroaryl, ~~6-membered monocyclic heterocyclyl~~, or phenyl, wherein Y^1 ~~is selected~~, Y^3 , Y^4 , and Y^5 are each independently selected from N, ~~NH~~, or CH, ~~and CH_2~~ ; wherein there are no more than 3 nitrogen ring atoms in ring B and ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;
15 T^6 , T^7 , and T^8 are each independently selected from N and CR^4 ;
ring C is cyclohexyl, phenyl, or pyridyl;
L is CHR^d , O, S, or NR^{5z} ;
ring D is bicyclic heteroaryl;
EE is $-COOH$; ~~or a carboxylic group surrogate, optionally, the carboxylic group surrogate is;~~
20 ~~surrogate is:~~



each R^a and R^b are independently selected from hydrogen, ~~deuterium, halogen, CN,~~
 C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $NR^{5'}R^{6'}$, 6-10 membered aryl, 5-86 membered heteroaryl, 3-86
 5 membered saturated or partially saturated cycloalkyl and 3-87 membered saturated or
 partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl or C_1 - C_6 alkoxy represented by R^a/R^b
 is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and
 C_3 - C_6 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/R^b or in the group represented by R^a/R^b is optionally substituted with one or more groups
 10 selected from halogen, oxo (~~as appropriate when R^b is non-aromatic~~), CN, OH, C_1 - C_3 alkyl
 (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and C_1 - C_3 alkoxy
 (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and $NR^{5'}R^{6'}$;

each R^e and R^d are independently selected from hydrogen, ~~deuterium, halogen, CN,~~
 C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $NR^{5'}R^{6'}$, 6-10 membered aryl, 5-8 membered heteroaryl,
 15 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or
 partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl or C_1 - C_6 alkoxy represented by R^e/R^d
 is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and
 C_3 - C_6 saturated or partially saturated cycloalkyl; and wherein the aryl, heteroaryl, saturated or
 partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by
 R^e/R^d or in the group represented by R^e/R^d is optionally substituted with one or more groups
 20 selected from halogen, oxo (~~as appropriate~~), CN, and $NR^{5'}R^{6'}$;

each R^1 is independently selected from H, ~~deuterium,~~ halogen, -CN, OH, C_1 - C_6 alkyl,
 C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $NR^{5'}R^{6'}$, 6-10 membered aryl, 5-8 membered
 heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered
 25 saturated or partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6
 alkenyl, or C_2 - C_6 alkynyl represented by R^1 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 (as appropriate), 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 ~~H, deuterium, halogen, -CN, OH, oxo, C₁-C₂ alkyl, C₁-C₂ haloalkyl, and C₁-C₂ alkoxy~~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 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 (as appropriate), 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 ~~H, deuterium, halogen, -CN, OH, oxo, C₁-C₆ alkyl, C₁-C₆ alkoxy, CN, OH, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, and 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 (as appropriate), 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 independently selected from ~~H, F, Cl, methyl, and methoxy~~deuterium, halogen, OH, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, and 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, C₁-C₆-alkyl, C₁-C₆-alkoxy, NR^{5'}R^{6'}, 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 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 (as appropriate), 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 NR^{5'}R^{6'}.

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

wherein optionally two R¹; two R²; two R³; two R⁴; R¹ and R²; R² and R³; R^a and R¹; R^a and R²; R¹ and any of R⁵, R^{5'} (in the group represented by W), or R⁶; R^a and any of R⁵, R^{5'} (in the group represented by W), or R⁶; R² and any of R⁵, R^{5'} (in the group represented by W), or R⁶; R⁵ and R⁶; any of two groups selected from R^e, R^d, R^e, and R^f; or R⁴ 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, and each of which is optionally substituted with one or more groups selected from halogen, CN, OH, CF₃, C₁-C₆-alkyl, C₁-C₆-alkoxy, NH₂, NHC₁-C₆-alkyl, N(C₁-C₆-alkyl)₂, oxo, and saturated or partially saturated C₃-C₆-cycloalkyl, wherein the C₁-C₆-alkyl and C₁-C₆-alkoxy 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, wherein the cycloalkyl is optionally substituted with one or more groups selected from halogen, oxo, CN, CF₃, OH, OCH₃, OCH₂CH₃;

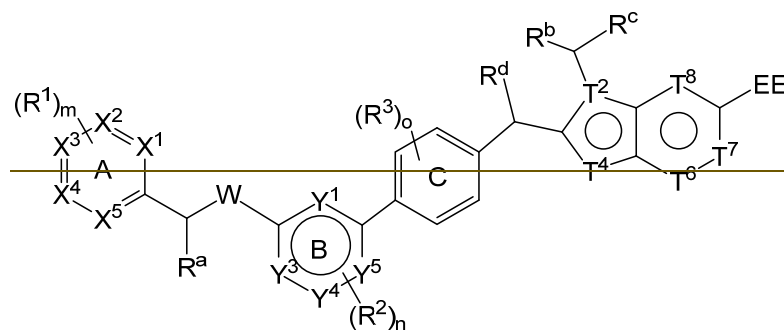
m is an integer selected from 0, 1, 2, 3, and 4;

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

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

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

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



(H);

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

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;

ring B is 6 membered heteroaryl or phenyl, wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each independently selected from N or CH; wherein there are no more than 3 nitrogen ring atoms in ring B and ring B does not contain 3 nitrogen ring atoms at 3 contiguous positions;

T^2 is selected from N and C;

T^4 is selected from N, NR^4 , O, S, and CR^4 ;

T^6 , T^7 , and T^8 are each independently selected from N and CR^4 ;

wherein no more than 4 of T^2 , T^4 , T^6 , T^7 , and T^8 are selected from N, O, and S.

3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein:

W is O, NH or CH_2 ;

R^a is H, CH_3 , or CF_3 ;

R^b is selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $NR^{51}R^{61}$, 6-10 membered aryl, 5-6 membered heteroaryl, 3-6 membered saturated or partially saturated cycloalkyl and 3-7 membered saturated or partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl or C_1 - C_6 alkoxy represented by R^b is optionally substituted with one or more groups selected from halogen, oxo, CN, OH, and C_3 - C_6 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 (when R^b is non-aromatic), CN, OH, C_1 - C_3 alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and C_1 - C_3 alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and $NR^{52}R^{62}$;

R^e is selected from hydrogen, halogen, and C_1 - C_4 alkyl optionally substituted with one or more groups selected from halogen and hydroxy;

R^d is H, F, CH_3 , or CF_3 ; and

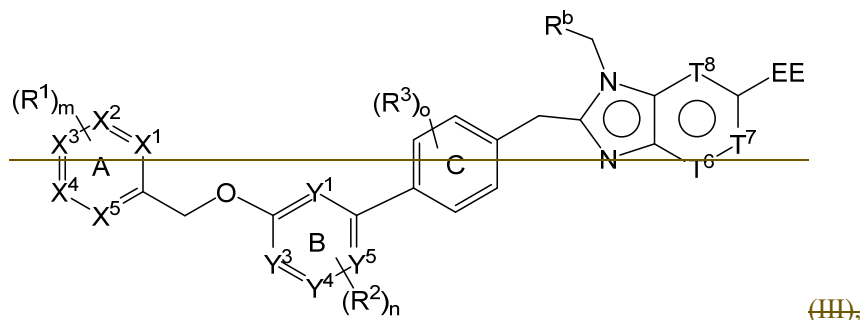
each R^1 is independently selected from H, deuterium, halogen, ~~CN~~, OH, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $NR^{5:}R^{6:}$, 6-10 membered aryl, 5-8 membered heteroaryl, 3-8 membered saturated or partially saturated cycloalkyl and 3-8 membered saturated or partially saturated heterocyclyl, wherein the C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl represented by R^1 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 (optionally substituted with one or more groups selected from halogen, oxo, CN, CF_3 , OH, OCH_3 , OCH_2CH_3); and wherein the aryl, heteroaryl, saturated or partially saturated cycloalkyl, or saturated or partially saturated heterocyclyl represented by R^1 or in the group represented by R^1 is optionally substituted with one or more groups selected from halogen, oxo (when R^1 is non-aromatic), CN, OH, C_1 - C_3 alkyl (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and C_1 - C_3 alkoxy (optionally substituted with 1 to 3 groups selected from F, OH, and OCH_3), and $NR^{5:}R^{6:}$.

each R^2 and R^3 are independently selected from H, deuterium, halogen, ~~CN~~, OH, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $NR^{5:}R^{6:}$, wherein the C_1 - C_6 alkyl or C_1 - C_6 alkoxy represented by R^2 and/or R^3 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 (optionally substituted with one or more groups selected from halogen, oxo, CN, CF_3 , OH, OCH_3 , OCH_2CH_3);

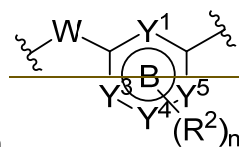
each R^4 is independently selected from H, deuterium, halogen, OH, ~~CN~~, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and $NR^{5:}R^{6:}$, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkoxy represented by R^4 is optionally substituted with one or more groups selected from halogen, oxo, CN, CF_3 , and saturated or partially saturated C_3 - C_6 cycloalkyl (optionally substituted with one or more groups selected from halogen, oxo, CN, CF_3 , OH, OCH_3 , OCH_2CH_3); and

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

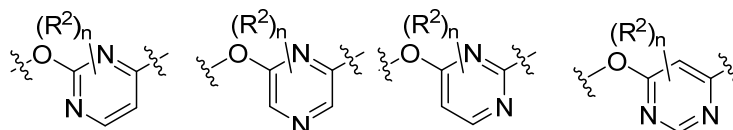
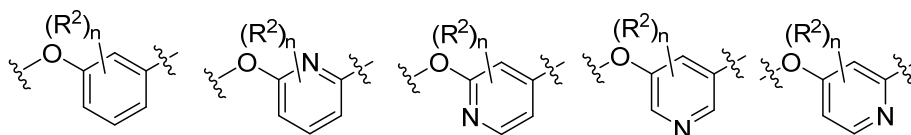
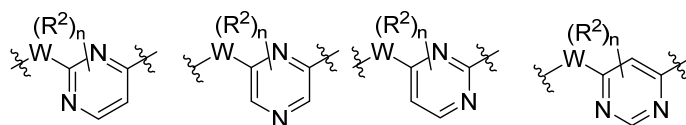
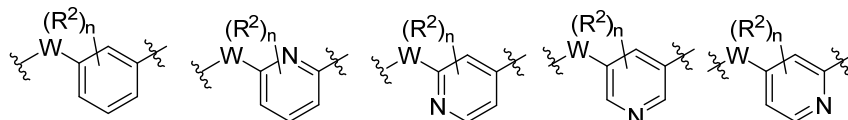
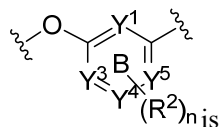
4. The compound according to any one of claims 1-3, wherein the compound is represented by structural formula (III):



52. The compound according to ~~any one of claims 2-4~~claim 1, or a pharmaceutically acceptable



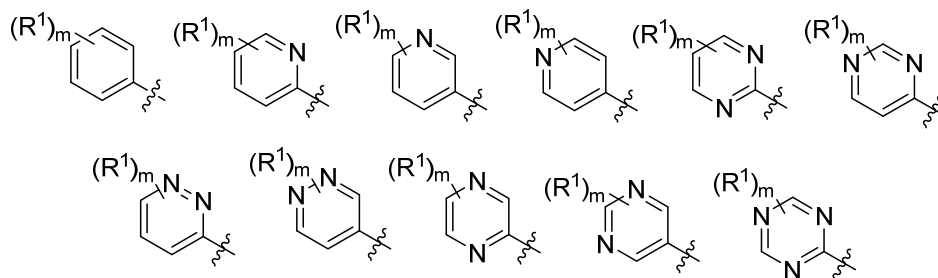
salt, or stereoisomer, ~~solvate, or hydrate~~ thereof, wherein



5

wherein n is an integer selected from 0, 1, 2, ~~and 3, and 4,~~ as appropriate.

63. The compound according to ~~any one of claims 1-5~~claim 1 or 2, or a pharmaceutically acceptable salt, or stereoisomer, ~~solvate, or hydrate~~ thereof, wherein ring A is



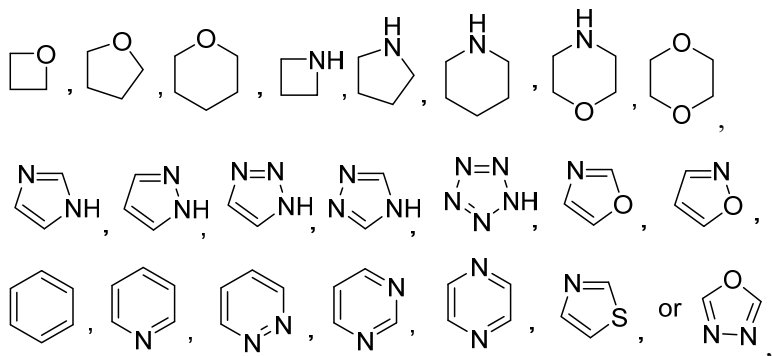
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each R¹ is independently selected from halogen, OH, CN, CF₃, C₁-C₄₂ alkyl, C₁-C₄₂ haloalkyl, ~~C₁-C₄ hydroxyalkyl~~, C₁-C₄₂ alkoxy, ~~C₁-C₄ haloalkoxy~~, ~~C₁-C₄ hydroxyalkoxy~~, ~~C₂-C₄ alkenyl~~, ~~NH₂~~, ~~-NHC₁-C₂ alkyl~~, ~~-N(C₁-C₂ alkyl)₂~~, and C₂-C₄ alkynyl, ~~NH₂~~, ~~NHC₁-C₄ alkyl~~, ~~N(C₁-C₄ alkyl)₂~~, optionally substituted with cyclopropane; and m is an integer selected from 0, 1, and 2.

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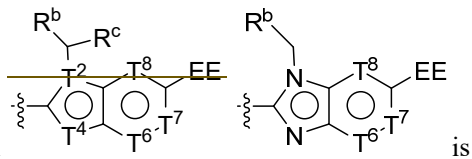
~~7. The compound according to any one of claims 1-6, or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof, wherein EE is COOH.~~

~~84.~~ The compound according to any one of claims 1-~~73~~, or a pharmaceutically acceptable salt, or stereoisomer, ~~solvate, or hydrate~~ thereof, wherein R^b is

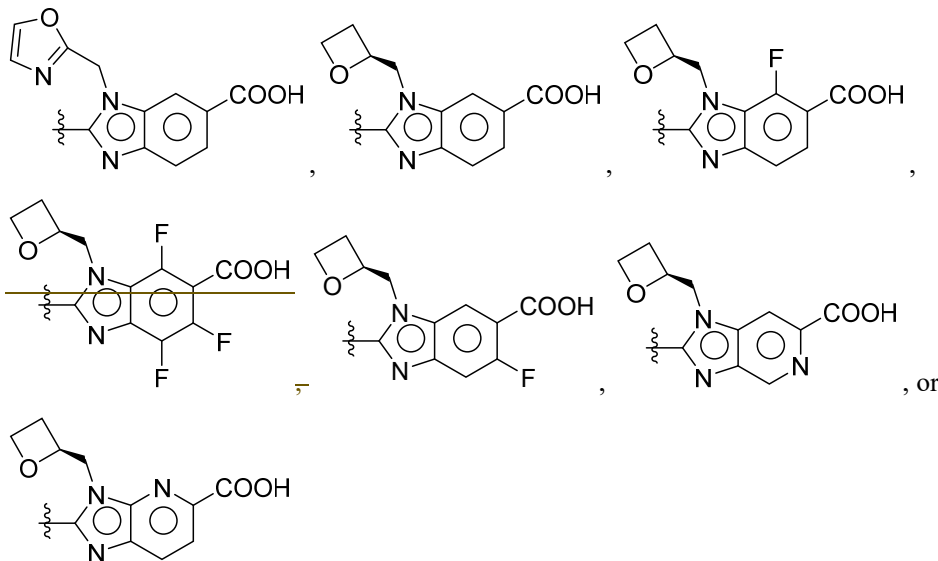


each of which is optionally substituted with 1 or 2 groups selected from ~~halogen~~ F, Cl, oxo (when R^b is non-aromatic), ~~CN, NR⁵R⁶~~, C₁-C₄₃ alkyl, and C₁-C₄₃ alkoxy, wherein the C₁-C₄₃ alkyl or C₁-C₄₃ alkoxy in the group represented by R^b is optionally substituted with 1 or 2 groups selected from F, OH, and OCH₃.

~~95.~~ The compound according to any one of claims 2-~~84~~, or a pharmaceutically acceptable salt, or



stereoisomer, ~~solvate, or hydrate~~ thereof, wherein



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

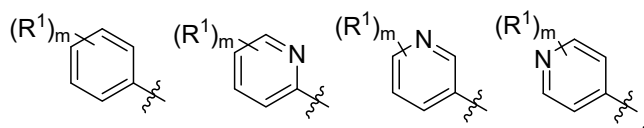
stereoisomer, solvate, or hydrate thereof, wherein

R^3 is halogen, CN, OH, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, or $NR^{52}R^{62}$; and

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

11. The compound according to any one of claims 1-10, wherein each R^2 is independently selected from deuterium, halogen, CN, OH, 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, 3, and 4.

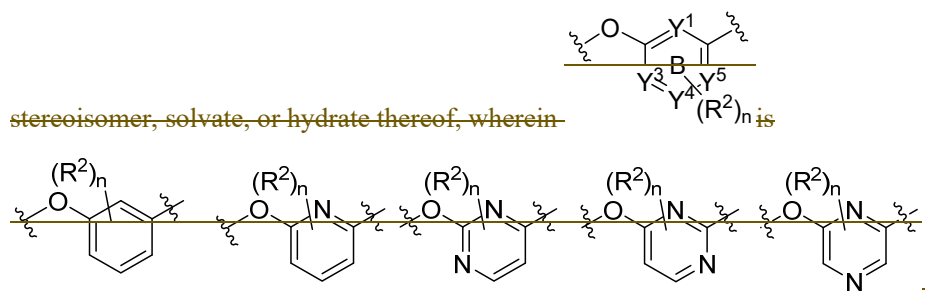
126. The compound according to any one of claims 1-115, or a pharmaceutically acceptable salt, or stereoisomer, solvate, or hydrate thereof, wherein ring A is



each R^1 is independently selected from halogen, OH, CN, C_1 - C_2 alkyl, C_1 - C_2 haloalkyl, C_1 - C_2 hydroxyalkyl, C_1 - C_2 alkoxy, C_1 - C_2 haloalkoxy, C_1 - C_2 hydroxyalkoxy, and C_2 - C_4 alkynyl; and m is an integer selected from 0, 1, and 2.

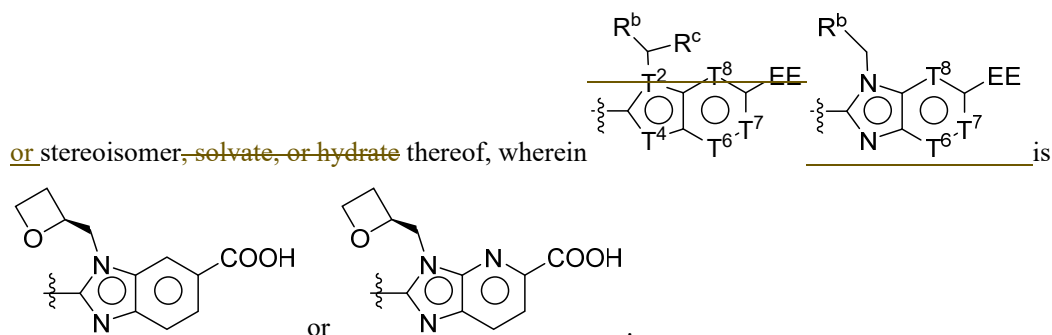
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13. The compound according to any one of claims 4-12, or a pharmaceutically acceptable salt,



stereoisomer, solvate, or hydrate thereof, wherein

147. The compound according to any one of claims 2-136, or a pharmaceutically acceptable salt,

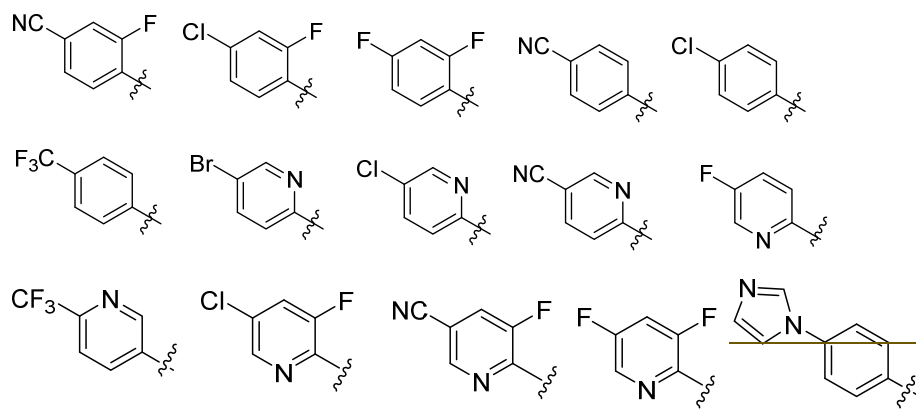


158. The compound according to any one of claims 1-147, or a pharmaceutically acceptable salt,

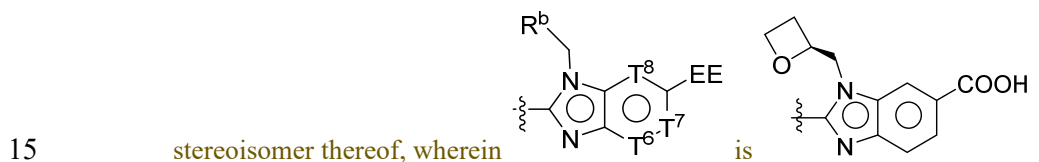
or stereoisomer, ~~solvate, or hydrate~~ thereof, wherein each R^2 is independently selected from halogen (e.g., F) ~~or deuterium~~; and n is an integer selected from 0, 1, and 2, ~~provided that when R^2 is deuterium, ring B is fully substituted with deuterium.~~

- 5 ~~169~~. The compound according to any one of claims 1-~~158~~, or a pharmaceutically acceptable salt, ~~or stereoisomer, solvate, or hydrate~~ thereof, wherein each R^3 is F, Cl or CH_3 ; and o is 0, 1, or 2.

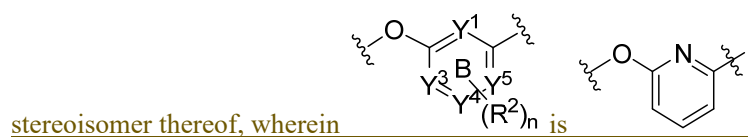
- 10 ~~1710~~. The compound according to any one of claims 1-~~169~~, or a pharmaceutically acceptable salt, ~~or stereoisomer, solvate, or hydrate~~ thereof, wherein ring A is



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



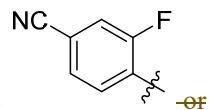
12. ~~The compound according to any one of claims 1-11, or a pharmaceutically acceptable salt or~~



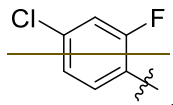
- 20 13. ~~The compound according to any one of claims 1-12, or a pharmaceutically acceptable salt or~~



- ~~1814~~. The compound according to any one of claims 1-~~1713~~, or a pharmaceutically acceptable salt,

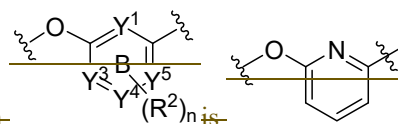


or stereoisomer, solvate, or hydrate thereof, wherein ring A is



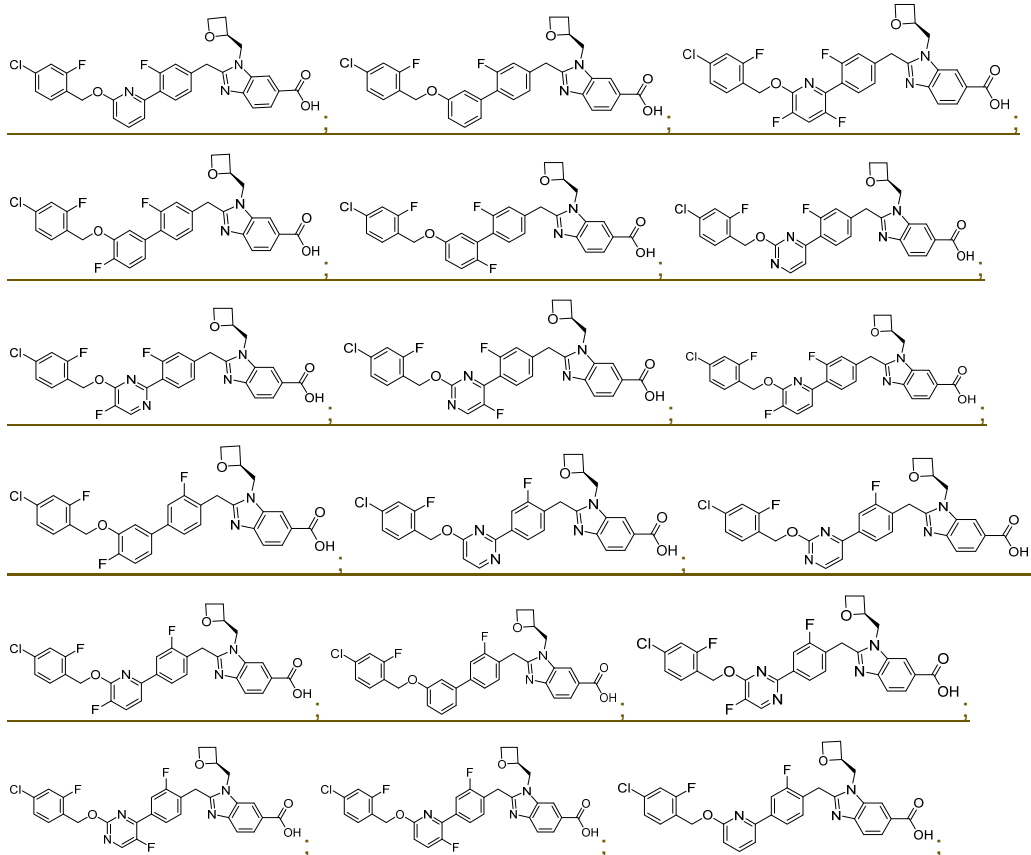
15. The compound according to any one of claims 1-14, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each R^3 is F or CH_3 ; and o is 2.

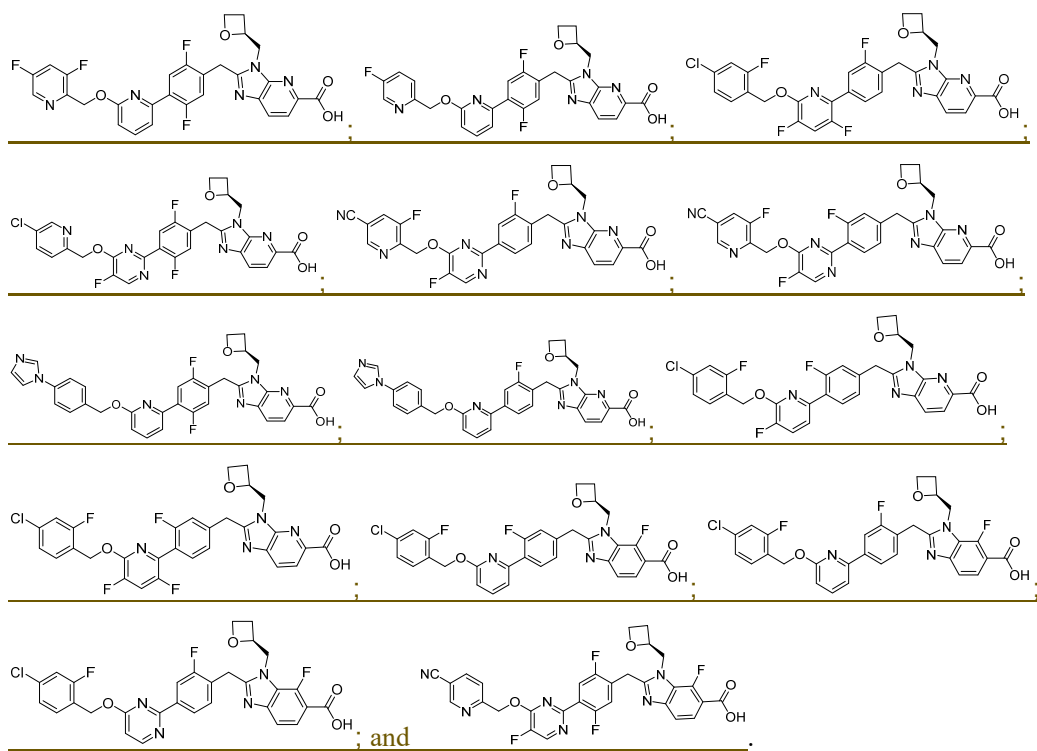
19. The compound according to any one of claims 2-18, or a pharmaceutically acceptable salt,



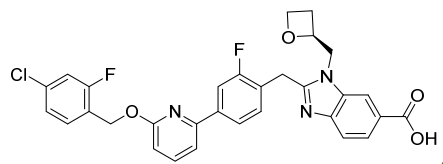
stereoisomer, solvate, or hydrate thereof, wherein

10 2016. A The compound according to claim 1, or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is selected from any one of the compounds of 74-102 and 246-334 in Table 1 or a pharmaceutically acceptable salt, stereoisomer, solvate, or hydrate thereof the group consisting of

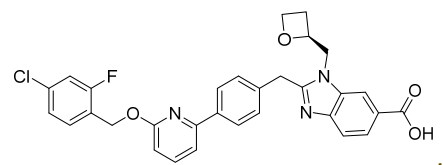




17. A compound, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structure:



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



2419. A pharmaceutical composition comprising the compound of any one of claims 1-2018, or a pharmaceutically acceptable salt, ~~stereoisomer, solvate, or hydrate~~ thereof, and a pharmaceutically acceptable excipient.

2220. A compound of any one of claims 1-2018 or a pharmaceutically acceptable salt, ~~stereoisomer, solvate, or hydrate~~ thereof, for use in treating cardiometabolic and associated diseases,

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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 type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.

2321. Use of a therapeutically effective amount of a compound of any one of claims 1-2018 or a pharmaceutically acceptable salt, ~~stereoisomer~~, ~~solvate~~, or ~~hydrate~~ thereof, 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 type 1 diabetes, type 2 diabetes mellitus, obesity, hyperglycemia, non-alcoholic steatohepatitis, Alzheimer's Disease, Parkinson's Disease, ulcerative colitis, or nonalcoholic fatty liver disease.