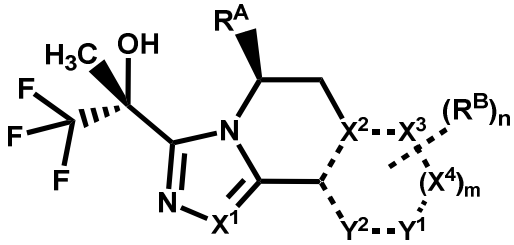
CLAIMS

1. A compound of the formula [I-a], or a pharmaceutically acceptable salt thereof:



[I-a]

wherein

a bond in a dotted line is a single bond or a double bond,

X^1, X^2, X^3 and X^4 are each independently C or N, Y^1 and Y^2 are each independently C, N or O (wherein the total number of N and O for X^2, X^3, X^4, Y^1 or Y^2 is 0 to 3),

R^A is C_{1-4} alkyl,

R^B is

(1) halogen,

(2) cyano,

(3) hydroxy,

(4) oxo,

(5) $-COR^1$ {wherein R^1 is

(A) hydrogen,

(B) -OH,

(C) $-NR^2R^3$ (wherein R^2 and R^3 are each independently hydrogen or C_{1-4} alkyl), or

(D) a 4- to 6-membered saturated heterocyclyl having one nitrogen atom (wherein the saturated heterocyclyl is optionally substituted by 1 or 2 halogens)},

(6) C_{1-8} alkyl {wherein the C_{1-8} alkyl is optionally substituted by 1 to 8 substituents independently selected from the group consisting of

(A) halogen,

(B) hydroxy,

(C) phenyl optionally substituted by halogen,

(D) pyridyl optionally substituted by haloC_{1-4} alkyl, and

(E) -OR^4 (wherein R^4 is

(a) C_{1-4} alkyl,

(b) phenyl optionally substituted by halogen, or

(c) benzyl optionally substituted by C_{1-4} alkoxy)},

(7) C_{1-8} alkoxy {wherein the C_{1-8} alkoxy is optionally substituted by 1 to 8 substituents independently selected from the group consisting of

(A) halogen,

(B) cyano,

(C) hydroxy,

(D) C_{1-4} alkoxy optionally substituted by 1 to 3 halogens,

(E) C_{1-4} alkylsulfonyl,

(F) C_{3-6} cycloalkyl optionally substituted by one substituent selected from the group consisting of cyano and cyano C_{1-4} alkyl,

(G) phenyl optionally substituted by cyano,

(H) -$COCy^1$ (wherein Cy^1 is a 4- to 6-membered saturated heterocyclyl having one nitrogen atom, and the saturated heterocyclyl is optionally substituted by 1 or 2 halogens), and

(I) a 4- to 6-membered saturated heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom (wherein the saturated heterocyclyl is optionally substituted by 1 to 4 substituents independently selected from

(a) C_{1-4} alkyl,

(b) oxo,

(c) C_{1-4} alkylcarbonyl,

(d) benzoyl optionally substituted by halogen, and

(e) C_{1-4} alkylsulfonyl,

when the saturated heterocyclyl is substituted by two C_{1-4} alkyls, the two C_{1-4} alkyls are optionally bonded to each other

to form a bridged ring together with the atoms bonded thereto)},

(8) -Cy^2 {wherein Cy^2 is

(A) C_{3-6} cycloalkyl (wherein the C_{3-6} cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from

(a) halogen,

(b) C_{1-4} alkyl,

(c) haloC_{1-4} alkyl, and

(d) phenyl optionally substituted by halogen),

(B) phenyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, haloC_{1-4} alkyl, and C_{1-4} alkoxy, or

(C) a 4- to 6-membered saturated heterocyclyl having one nitrogen atom or oxygen atom (wherein the saturated heterocyclyl is optionally substituted by one substituent selected from the group consisting of (a) phenyl optionally substituted by halogen and (b) C_{1-4} alkylcarbonyl)}, or

(9) -OCy^3 {wherein Cy^3 is

(A) a 4- to 6-membered saturated heterocyclyl having one nitrogen atom or oxygen atom (wherein the saturated heterocyclyl is optionally substituted by one substituent selected from the group consisting of (a) benzoyl optionally substituted by halogen and (b) C_{1-4} alkylcarbonyl), or

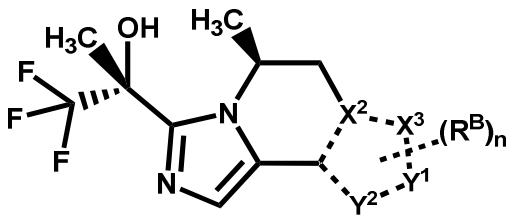
(B) a 6-membered heteroaryl having 1 or 2 nitrogen atoms (wherein the heteroaryl is optionally substituted by 1 or 2 substituents independently selected from cyano, haloC_{1-4} alkyl, and C_{3-6} cycloalkyl)},

m is 0 or 1, and

n is 0, 1 or 2, when n is 2, each R^B may be the same or different.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is a compound of the formula

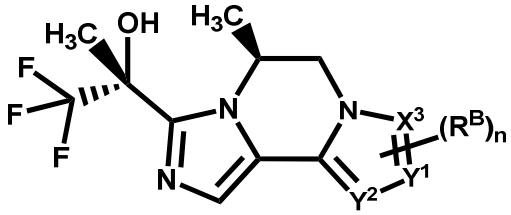
[I-b]:



[I-b]

wherein each symbol is as defined in claim 1, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof, which is a compound of the formula [I-c]:

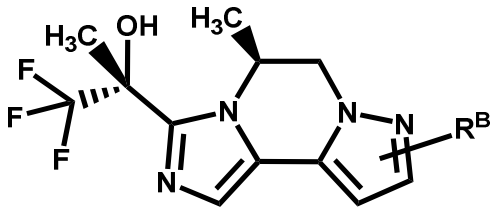


[I-c]

wherein each symbol is as defined in claim 1, or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1 to 3, wherein n is 1, or a pharmaceutically acceptable salt thereof.

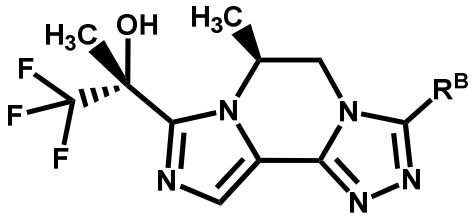
5. The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, which is a compound of the formula [I-d]:



[I-d]

wherein the symbol is as defined in claim 1, or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, which is a compound of the formula [I-e]:



[I-e]

wherein the symbol is as defined in claim 1, or a pharmaceutically acceptable salt thereof.

7. The compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein R^B is
(1) C_{1-8} alkyl {wherein the C_{1-8} alkyl is optionally substituted by 1 to 8 substituents independently selected from the group consisting of
(A) halogen,
(B) hydroxy,
(C) phenyl optionally substituted by halogen,
(D) pyridyl optionally substituted by haloC_{1-4} alkyl, and
(E) -OR^4 (wherein R^4 is
(a) C_{1-4} alkyl,
(b) phenyl optionally substituted by halogen, or
(c) benzyl optionally substituted by C_{1-4} alkoxy)}, or
(2) C_{1-8} alkoxy {wherein the C_{1-8} alkoxy is optionally substituted by 1 to 8 substituents independently selected from the group consisting of
(A) halogen,
(B) cyano,
(C) hydroxy,

(D) C_{1-4} alkoxy optionally substituted by 1 to 3 halogens,

(E) C_{1-4} alkylsulfonyl,

(F) C_{3-6} cycloalkyl optionally substituted by one substituent selected from the group consisting of cyano and cyano C_{1-4} alkyl,

(G) phenyl optionally substituted by cyano,

(H) $-COCy^1$ (wherein Cy^1 is a 4- to 6-membered saturated heterocyclyl having one nitrogen atom, and the saturated heterocyclyl is optionally substituted by 1 or 2 halogens), and

(I) a 4- to 6-membered saturated heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom, an oxygen atom and a sulfur atom (wherein the saturated heterocyclyl is optionally substituted by 1 to 4 substituents independently selected from

(a) C_{1-4} alkyl,

(b) oxo,

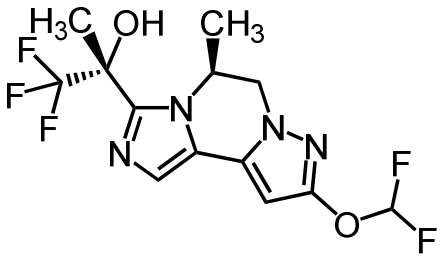
(c) C_{1-4} alkylcarbonyl,

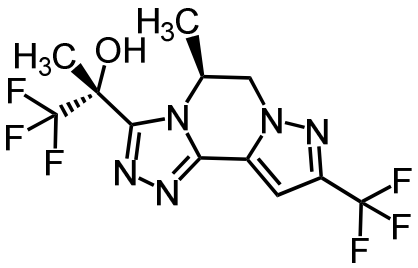
(d) benzoyl optionally substituted by halogen, and

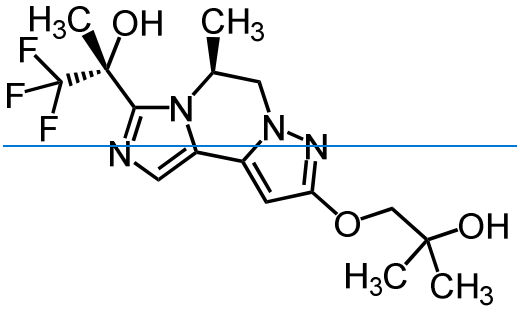
(e) C_{1-4} alkylsulfonyl,

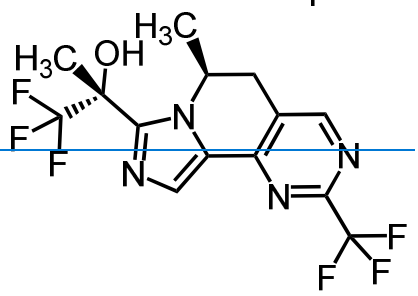
when the saturated heterocyclyl is substituted by two C_{1-4} alkyls, the two C_{1-4} alkyls are optionally bonded to each other to form a bridged ring together with the atoms bonded thereto)}.

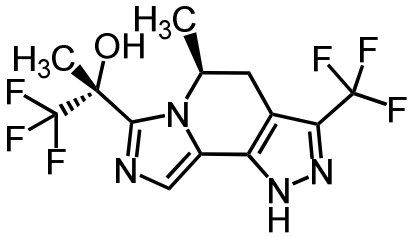
~~8. A compound selected from the following formulas:~~

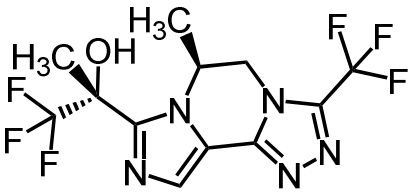






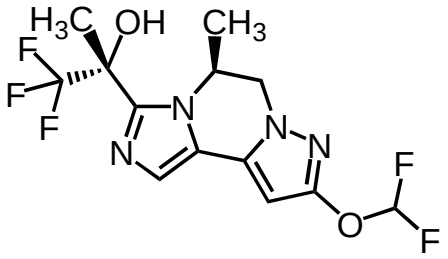






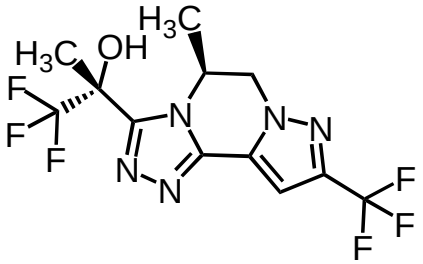
~~or a pharmaceutically acceptable salt thereof.~~

8. A compound of the formula:



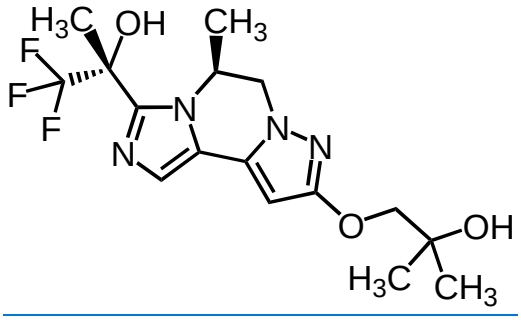
or a pharmaceutically acceptable salt thereof.

9. A compound of the formula:



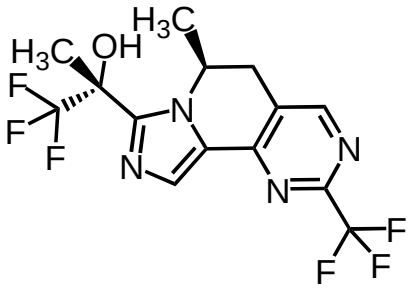
or a pharmaceutically acceptable salt thereof.

10. A compound of the formula:



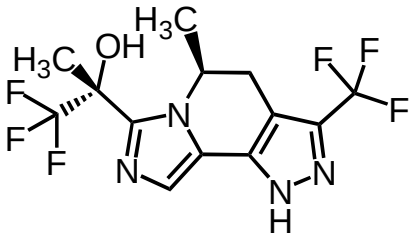
or a pharmaceutically acceptable salt thereof.

11. A compound of the formula:



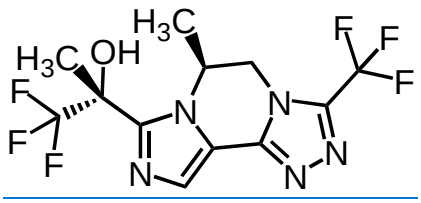
or a pharmaceutically acceptable salt thereof.

12. A compound of the formula:



or a pharmaceutically acceptable salt thereof.

13. A compound of the formula:



or a pharmaceutically acceptable salt thereof.

~~9~~14. A pharmaceutical composition comprising the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~10~~15. A PDHK inhibitor comprising the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof.

~~11~~16. A PDHK2 inhibitor comprising the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof.

~~12~~17. An agent for the treatment or prophylaxis of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy or chronic kidney disease, the agent comprising the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof.

~~13~~18. The agent according to claim ~~12~~ 17, wherein the diabetes is type 1 diabetes or type 2 diabetes.

~~14~~19. The agent according to claim ~~12~~ 17, wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

~~15~~20. The agent according to claim ~~12~~ 17, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

~~16~~21. The agent according to claim ~~12~~ 17, wherein the pulmonary hypertension is pulmonary arterial hypertension.

~~17~~22. A method for inhibiting PDHK, comprising administering a therapeutically effective amount of the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof to a mammal.

~~18~~23. A method for treating or preventing a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease, the method comprising administering a therapeutically effective amount of the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof to a mammal.

~~19~~24. The method according to claim ~~18~~ 23, wherein the diabetes is type 1 diabetes or type 2 diabetes.

~~20~~25. The method according to claim ~~18~~ 23, wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

~~21~~26. The method according to claim ~~18~~ 23, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

~~22~~27. The method according to claim ~~18~~ 23, wherein the pulmonary hypertension is pulmonary arterial hypertension.

~~23~~28. Use of the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof in the manufacture of a PDHK inhibitor.

~~24~~29. Use of the compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof in the manufacture of an agent for the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease.

~~25~~30. The use according to claim ~~24~~ 29, wherein the diabetes is type 1 diabetes or type 2 diabetes.

~~26~~31. The use according to claim ~~24~~ 29, wherein the vascular dementia is of a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

~~27~~32. The use according to claim ~~24~~ 29, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

~~28~~33. The use according to claim ~~24~~ 29, wherein the pulmonary hypertension is pulmonary arterial hypertension.

~~29~~34. The compound according to any one of claims 1 to ~~8~~ 13 or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease.

~~30~~35. The compound according to claim ~~29~~ 34 or a pharmaceutically acceptable salt thereof, wherein the diabetes is type 1 diabetes or type 2 diabetes.

~~31~~36. The compound according to claim ~~29~~ 34 or a

pharmaceutically acceptable salt thereof, wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

~~32~~37. The compound according to claim ~~29~~ 34 or a pharmaceutically acceptable salt thereof, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

~~33~~38. The compound according to claim ~~29~~ 34 or a pharmaceutically acceptable salt thereof, wherein the pulmonary hypertension is pulmonary arterial hypertension.