SUMMARY

[0005] The present disclosure is based on the determination that activators of sirtuin 6 (SIRT6) provide a significant lowering of blood glucose levels.

[0005a] In an aspect, there is provided the use of a therapeutically effective amount of a sirtuin 6 (SIRT6) activator in the manufacture of a medicament for improving glucose homeostasis in a subject in need thereof.

[0005b] In another aspect, there is provided the use of a therapeutically effective amount of a SIRT6 activator, in the manufacture of a medicament for lowering plasma glucose concentration in a subject in need thereof.

[0005c] In another aspect, there is provided the use of a therapeutically effective amount of a SIRT6 activator, in the manufacture of a medicament for treating hyperglycemia in a subject in need thereof.

[0005d] In another aspect, there is provided the use of a therapeutically effective amount of a SIRT6 activator, in the manufacture of a medicament for the treatment of prediabetes or diabetes in a subject in need thereof.

[0006] Thus, one example of the disclosure relates to a method of improving glucose homeostasis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a SIRT6 activator, thereby improving glucose homeostasis.

[0007] Another example of the disclosure relates to a method of lowering plasma glucose levels in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a SIRT6 activator, thereby lowering plasma glucose levels.

[0008] A further example of the disclosure relates to a method of treating hyperglycemia, prediabetes, or diabetes (*e.g.*, Type I, Type II or gestational) in a subject in need

thereof, comprising administering to the subject a therapeutically effective amount of a SIRT6 activator, thereby treating the hyperglycemia, prediabetes, or diabetes.

[0009] These and other examples of the disclosure are set forth in more detail in the description of the examples below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **FIG. 1.** Fasting glucose mean values by visit. Subjects received either placebo or a SIRT6 activator (Compound **1**).

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0011] The present invention is explained in greater detail below. This description is not intended to be a detailed catalog of all the different ways in which the invention may be implemented, or all the features that may be added to the instant invention. For example, features illustrated with

We Claim:

1. Use of a therapeutically effective amount of a sirtuin 6 (SIRT6) activator in the manufacture of a medicament for improving glucose homeostasis in a subject in need thereof.

2. Use of a therapeutically effective amount of a SIRT6 activator, in the manufacture of a medicament for lowering plasma glucose concentration in a subject in need thereof.

3. Use of a therapeutically effective amount of a SIRT6 activator, in the manufacture of a medicament for treating hyperglycemia in a subject in need thereof.

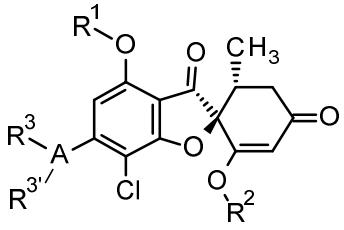
4. Use of a therapeutically effective amount of a SIRT6 activator, in the manufacture of a medicament for the treatment of prediabetes or diabetes in a subject in need thereof.

5. The use of claim 4, wherein the diabetes is Type I diabetes, Type II diabetes or gestational diabetes.

6. The use of any one of claims 1-5, wherein the SIRT6 activator is quercetin, isoquercetin, kaempferol, luteolin, cyanidin, fisetin, delphinidin, icariin, N-acetylethanolamines, oleic acid, linoleic acid, fucoidan, MDL-800 (CAS No. 2275619-53-7), MDL-811 (CAS No. 2275619-98-0), UBCS038 (CAS No. 358721-70-7), UBCS039 (CAS No. 358721-70-7), UBCS040 (1-(4,5-Dihydropyrrolo[1,2-*a*]quinoxalin-4-yl)naphthalen-2-ol), UBCS058 (4-(Pyridin-3-yl)pyrrolo[1,2-*a*]quinoxaline), UBCS060 (4-(Pyridin-2-yl)-4,5-dihydropyrrolo[1,2-*a*]quinoxaline), UBCS068 (1-(5-((3-(Trifluoromethyl)phenyl)sulfonyl)-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-4-yl)naphthalen-2-ol), myristic acid, oleoylethanolamide,

CL5D (CAS No. 2488745-53-3), or 10b (2-(1-benzofuran-2-yl)-*N*-(diphenylmethyl) quinoline-4-carboxamide).

7. The use of any one of claims 1-5, wherein the SIRT6 activator is a compound of Formula 1 or a pharmaceutically acceptable salt thereof:



(1)

wherein:

R^1 is a C1-C6 alkyl group optionally substituted with the same or different one to two substituents selected from a substituent group X,

a C3-C6 cycloalkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X, or

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X;

R^2 is a C1-C6 alkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C3-C6 cycloalkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X, or

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X;

A is a 5-membered aromatic heterocyclic ring,

a 6-membered aromatic heterocyclic ring,

an 8-10 membered condensed aromatic heterocyclic ring,

a 5-7 membered unsaturated heterocyclic ring,

a 4-7 membered saturated heterocyclic ring,

a benzene ring, -CH=, or a cyano group, wherein when A is a cyano group, R^3 and $R^{3'}$ do not exist;

R^3 and $R^{3'}$ are each independently a hydrogen atom, a halogen atom, a cyano group, a hydroxy group, an oxo group,

a C1-C6 alkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C1-C6 alkoxy group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C2-C6 alkenyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C2-C6 alkynyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C3-C6 cycloalkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

an amino group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C1-C6 alkoxycarbonyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a carbamoyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a phenyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 5-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 6-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 5-7 membered unsaturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

an 8-10 membered condensed aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X, or

R^3 and $R^{3'}$ may form a 5-7 membered unsaturated heterocyclic ring, a 4-7 membered saturated heterocyclic ring, or a C3-C6 cycloalkyl ring as a ring that binds to each other and condenses with A, and the ring is optionally substituted with the same or different one to two substituents selected from the substituent group X;

substituent group X is a halogen atom, a cyano group, a hydroxy group, an oxo group, a C1-C6 alkyl group, a hydroxy C1-C6 alkyl group, a C1-C6 alkoxy C1-C6 alkyl group, a C1-C6 haloalkyl group, a C3-C6 cycloalkyl group, a C3-C6 halocycloalkyl group,

a phenyl group optionally substituted with the same or different one to two substituents selected from a substituent group Y,

a 5-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 6-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a C1-C6 alkoxy group, a C1-C6 haloalkoxy group, a C3-C6 cycloalkoxy group, a C3-C6 halocycloalkoxy group,

a phenoxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 5-membered aromatic heterocyclic oxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 6-membered aromatic heterocyclic oxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 4-7 membered saturated heterocyclic oxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a C1-C6 alkoxycarbonyl group, a C3-C6 cycloalkoxycarbonyl group, a carboxy group, a C1-C6 alkylcarbonyl group, a C3-C6 cycloalkylcarbonyl group,

a phenylcarbonyl group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a carbamoyl group, a mono (C1-C6 alkyl) aminocarbonyl group, a di (C1-C6 alkyl) aminocarbonyl group, a mono (C1-C6 alkyl) aminosulfonyl group, a di (C1-C6 alkyl) aminosulfonyl group, an amino group, a mono (C1-C6 alkyl) amino group, a di (C1-C6 alkyl) amino group, a C1-C6 alkoxycarbonylamino group, a mono (C1-C6 alkyl) aminocarbonylamino group, a di (C1-C6 alkyl) aminocarbonylamino group, a C1-C6 alkylcarbonylamino group,

a phenylcarbonylamino group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

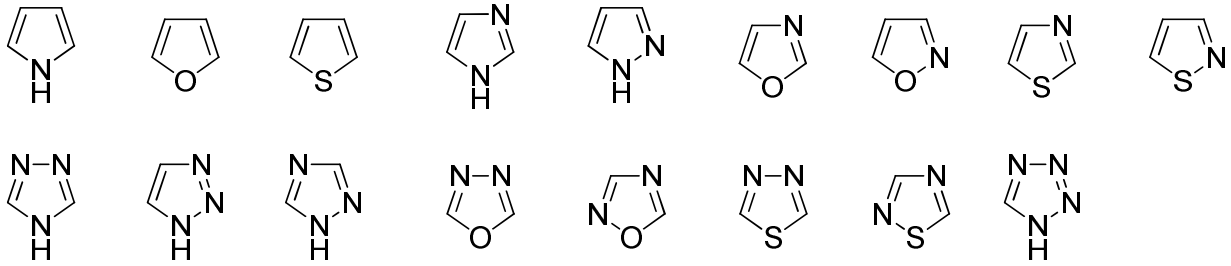
a 5-membered aromatic heterocyclic carbonylamino group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 6-membered aromatic heterocyclic carbonylamino group optionally substituted with the same or different one to two substituents selected from the substituent group Y, or

a C1-C6 alkylsulfonylamino group; and

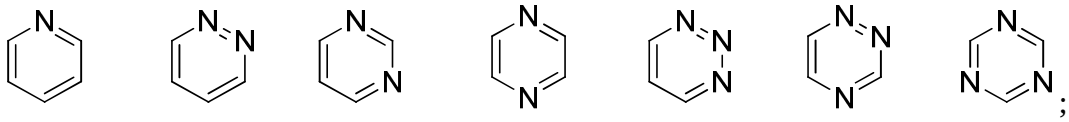
substituent group Y is a C1-C6 alkyl group, a C1-C6 alkoxy group, a halogen atom, or a hydroxy group.

8. The use of claim 7, wherein the 5-membered aromatic heterocyclic ring or the 5-membered aromatic heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:



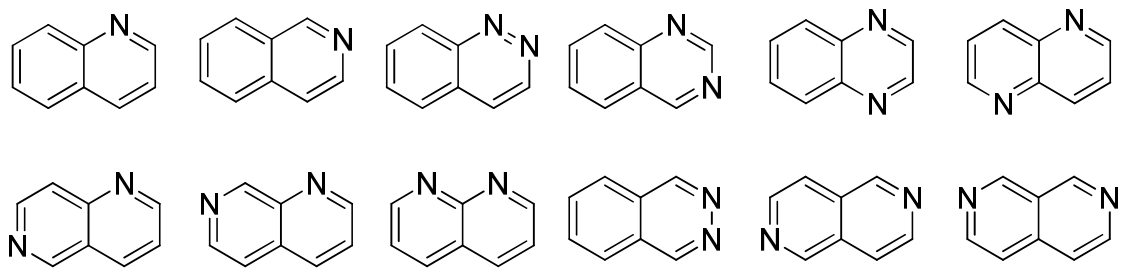
;

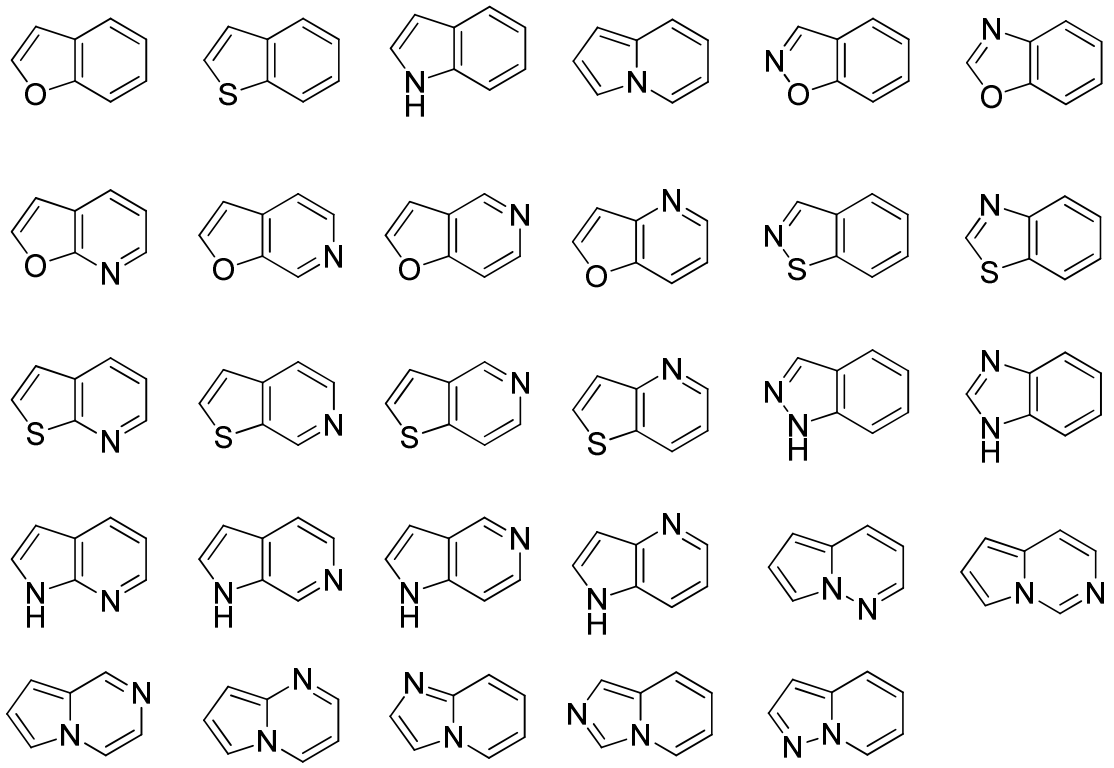
the 6-membered aromatic heterocyclic ring or the 6-membered aromatic heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:



;

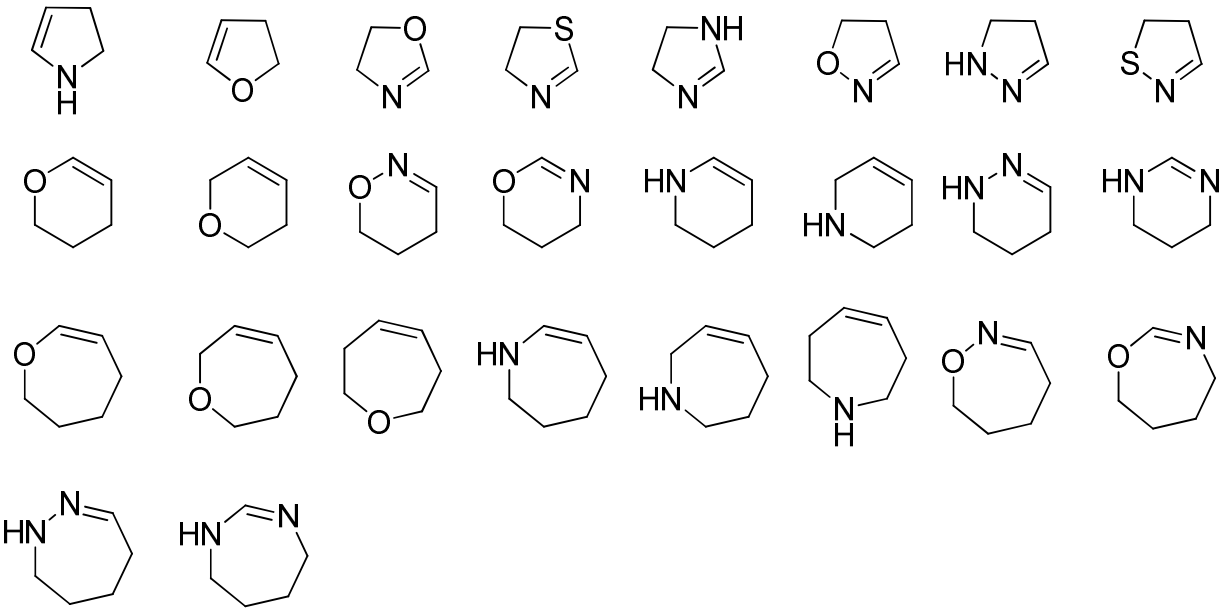
the 8-10 membered condensed aromatic heterocyclic ring or the 8-10 membered condensed aromatic heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:





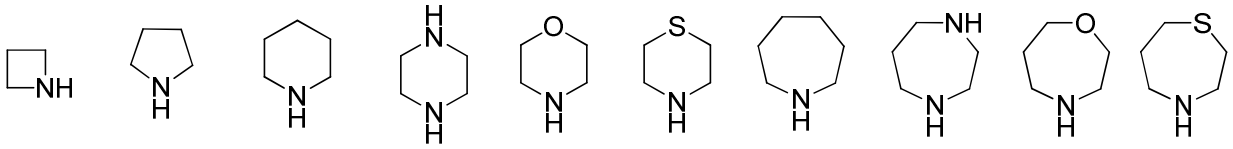
;

the 5-7 membered unsaturated heterocyclic ring or 5-7 membered unsaturated heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:

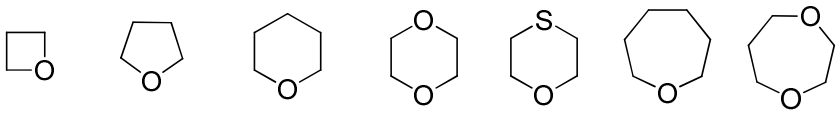


; and

the 4-7 membered saturated heterocyclic ring or the 4-7 membered saturated heterocyclic group in A, R^1, R^2, or R^3 is any one selected from the group:



.



9. The use of claim 7 or 8, wherein the compound of Formula 1 is any compound selected from the following group:

(2S,5'R)-7-chloro-6-(5-ethyl-1,3,4-oxadiazol-2-yl)-3',4-dimethoxy-5'-methyl-spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-3',4-dimethoxy-5'-methyl-6-(5-tetrahydropyran-4-yl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-3',4-dimethoxy-5'-methyl-6-[5-(1-methyl-4-piperidyl)-1,3,4-oxadiazol-2-yl] spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-6-[5-(4-fluoro-1-methyl-4-piperidyl)-1,3,4-oxadiazol-2-yl]-3',4-dimethoxy-5'-methyl-spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-3',4-dimethoxy-6-[5-[(1S)-1-methoxyethyl]-1,3,4-oxadiazol-2-yl]-5'-methyl-spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-4-ethoxy-3'-methoxy-5'-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-4-(difluoromethoxy)-3'-methoxy-5'-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-[3-(1-methoxyethyl)-1,2,4-oxadiazol-5-yl]-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[3-(1-hydroxy-1-methyl-ethyl)-1,2,4-oxadiazol-5-yl]-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(1H-pyrazol-5-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-[1-(2-methoxyethyl) pyrazol-3-yl]-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-(1,8-dioxa-2-azaspiro [4.5] dec-2-en-3-yl)-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

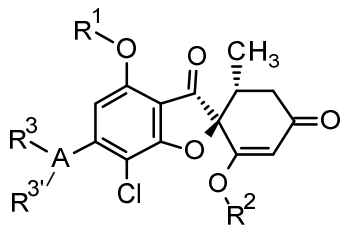
(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(8-methyl-1-oxa-2,8-diazaspiro [4.5] dec-2-en-3-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-(2-methoxypyrimidin-5-yl)-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-(6-methoxy-3-pyridyl)-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione; or

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(3-pyridyl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione.

10. The use of any one of claims 7-9, wherein the compound of Formula 1 is a compound of Formula 1′ or a pharmaceutically acceptable salt thereof:



(1')

wherein:

R^1 is a C1-C6 alkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C3-C6 cycloalkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X, or

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X;

R^2 is a C1-C6 alkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C3-C6 cycloalkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X, or

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X;

A is a 5-membered aromatic heterocyclic ring,

a 6-membered aromatic heterocyclic ring,

an 8-10 membered condensed aromatic heterocyclic ring,

a 5-7 membered unsaturated heterocyclic ring,

a 4-7 membered saturated heterocyclic ring,

a benzene ring, or a single bond, wherein when it is a single bond, one or the other of R^3 and $R^{3'}$ is not present;

R^3 and $R^{3'}$ are each independently a hydrogen atom, a halogen atom, a cyano group, a hydroxy group,

a C1-C6 alkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C1-C6 alkoxy group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C2-C6 alkenyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C2-C6 alkynyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C3-C6 cycloalkyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

an amino group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a C1-C6 alkoxycarbonyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a carbamoyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a phenyl group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 5-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 6-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 5-7 membered unsaturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X,

an 8-10 membered condensed aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group X, or

R^3 and $R^{3'}$ may form a 5-7 membered unsaturated heterocyclic ring, a 4-7 membered saturated heterocyclic ring, or a C3-C6 cycloalkyl ring as a ring that binds to each other and condenses with A, and the ring is optionally substituted with the same or different one to two substituents selected from the substituent group X;

substituent group X is a halogen atom, a cyano group, a hydroxy group, an oxo group, a C1-C6 alkyl group, a hydroxy C1-C6 alkyl group, a C1-C6 alkoxy C1-C6 alkyl group, a C1-C6 haloalkyl group, a C3-C6 cycloalkyl group, a C3-C6 halocycloalkyl group,

a phenyl group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 5-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 6-membered aromatic heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 4-7 membered saturated heterocyclic group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a C1-C6 alkoxy group, a C1-C6 haloalkoxy group, a C3-C6 cycloalkoxy group, a C3-C6 halocycloalkoxy group,

a phenoxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 5-membered aromatic heterocyclic oxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 6-membered aromatic heterocyclic oxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 4-7 membered saturated heterocyclic oxy group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a C1-C6 alkoxycarbonyl group, a C3-C6 cycloalkoxycarbonyl group, a carboxy group, a C1-C6 alkylcarbonyl group, a C3-C6 cycloalkylcarbonyl group,

a phenylcarbonyl group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a carbamoyl group, a mono (C1-C6 alkyl) aminocarbonyl group, a di (C1-C6 alkyl) aminocarbonyl group, a mono (C1-C6 alkyl) aminosulfonyl group, a di (C1-C6 alkyl) aminosulfonyl group, an amino group, a mono (C1-C6 alkyl) amino group, a di (C1-C6 alkyl) amino group, a C1-C6 alkoxycarbonylamino group, a mono (C1-C6 alkyl) aminocarbonylamino group, a di (C1-C6 alkyl) aminocarbonylamino group, a C1-C6 alkylcarbonylamino group,

a phenylcarbonylamino group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 5-membered aromatic heterocyclic carbonylamino group optionally substituted with the same or different one to two substituents selected from the substituent group Y,

a 6-membered aromatic heterocyclic carbonylamino group optionally substituted with the same or different one to two substituents selected from the substituent group Y, or

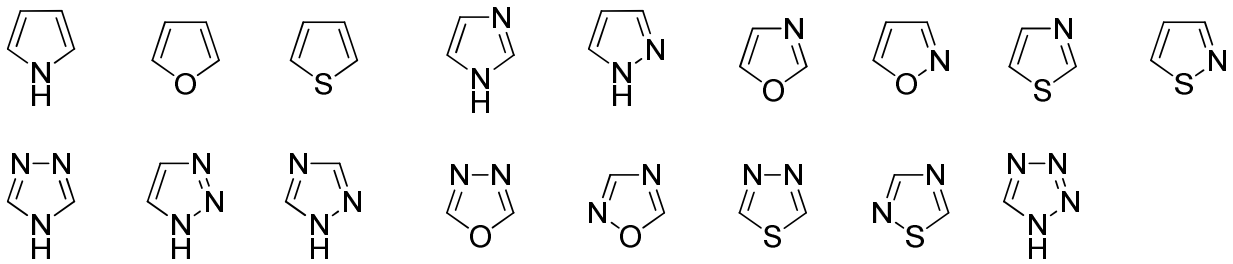
a C1-C6 alkylsulfonylamino group; and

substituent group Y is a C1-C6 alkyl group, a C1-C6 alkoxy group, a halogen atom, or a hydroxy group.

11. The use of claim 10, wherein R^1 is a methyl group, an ethyl group, or a hydroxyethyl group.

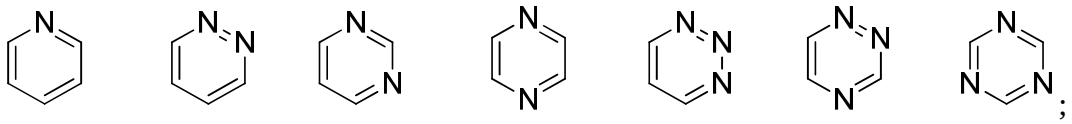
12. The use of claim 10 or 11, wherein R^2 is a methyl group.

13. The use of any one of claims 10-12, wherein the 5-membered aromatic heterocyclic ring or the 5-membered aromatic heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:



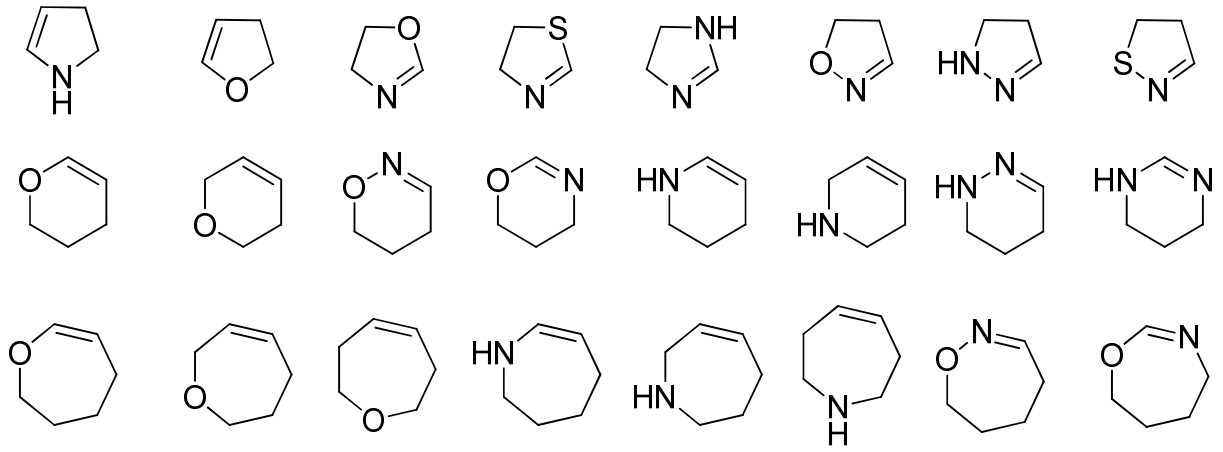
;

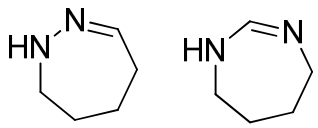
the 6-membered aromatic heterocyclic ring or the 6-membered aromatic heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:



;

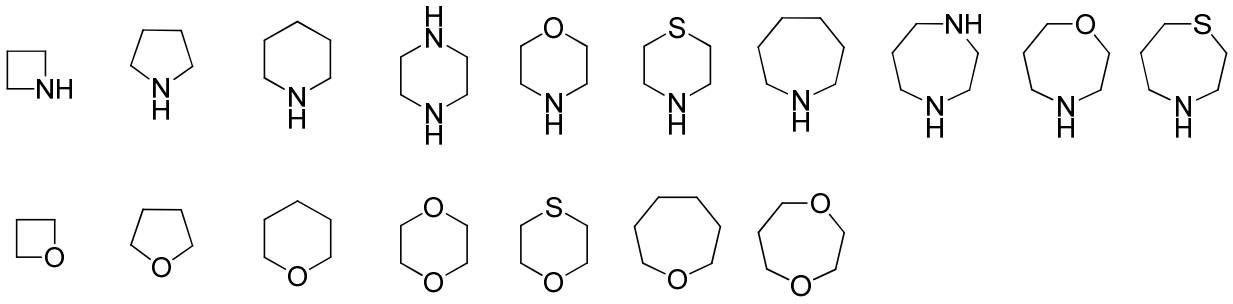
the 5-7 membered unsaturated heterocyclic ring or the 5-7 membered unsaturated heterocyclic group in A, R^3, or $R^{3'}$ is any one selected from the group:





; and

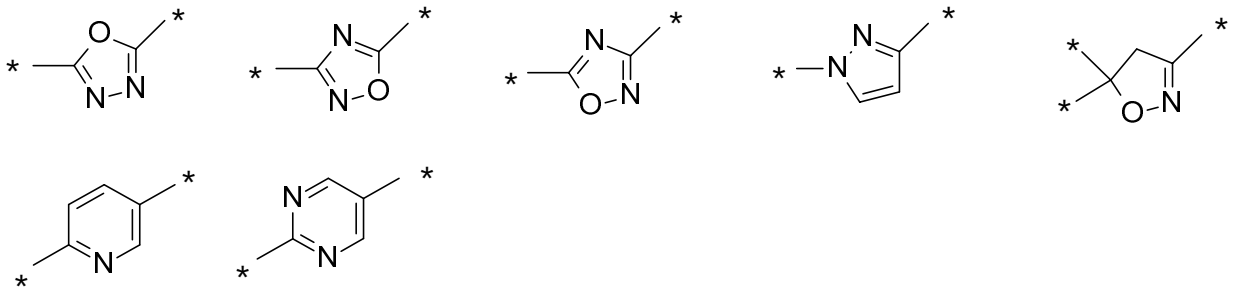
the 4-7 membered saturated heterocyclic ring or the 4-7 membered saturated heterocyclic group in A, R^1, R^2, or R^3 is any one selected from the group:



.

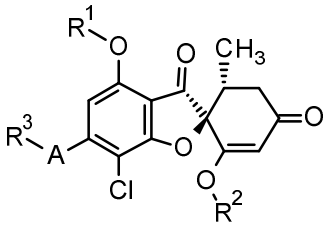
14. The use of any one of claims 10-13, wherein A is a 5-membered aromatic heterocyclic ring; R^3 is a methyl group, an ethyl group, a hydroxy C1-C3 alkyl group, or a methoxy C1-C3 alkyl group; and $R^{3'}$ is a hydrogen atom.

15. The use of any one of claims 10-14, wherein A is any ring selected from the following group, and in the case of two binding groups, $R^{3'}$ is not present:



wherein * indicates a binding group.

16. The use of any one of claims 10-12, wherein the compound of Formula 1 is a compound of a Formula 1″ or a pharmaceutically acceptable salt thereof:



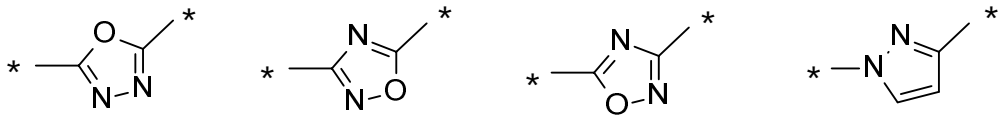
(1")

wherein

R^1 is a methyl group or an ethyl group;

R^2 is a methyl group;

A is any ring selected from the following group:



wherein * indicates a binding group; and

R^3 is a methyl group or an ethyl group.

17. The use of any one of claims 10-15, wherein the compound of Formula 1′ is any compound selected from the following group:

(2S,5'R)-7-chloro-6-(2-hydroxyethoxy)-3',4-dimethoxy-5'-methyl-spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-3',4-dimethoxy-6-(2-methoxyethoxy)-5'-methyl-spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-3',4-dimethoxy-5'-methyl-6-(1-methylpyrazol-3-yl) spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5'R)-7-chloro-6-(1-ethylpyrazol-3-yl)-3',4-dimethoxy-5'-methyl-spiro [benzofuran-2,4'-cyclohex-2-ene]-1',3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(3-methyl-1,2,4-oxadiazol-5-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(5-methyl)-1,2,4-oxadiazol-3-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[5-(1-hydroxy-1-methyl-ethyl)-1,3,4-oxadiazol-2-yl]-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[5-[(1R)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-ethoxy-6-[5-(1-hydroxy-1-methyl-ethyl)-1,3,4-oxadiazol-2-yl]-3’-methoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-ethoxy-6-[5-[(1S)-1-hydroxyethyl]-1,3,4-oxadiazol-2-yl]-3’-methoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[3-(1-hydroxyethyl)-1,2,4-oxadiazol-5-yl]-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-(2-hydroxyethoxy)-3’-methoxy-5’-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-(2-hydroxyethoxy)-3’-methoxy-5’-methyl-6-(3-methyl-1,2,4-oxadiazol-5-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-(2-hydroxyethoxy)-3’-methoxy-5’-methyl-6-(5-methyl-1,2,4-oxadiazol-3-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-(5-ethyl-1,3,4-oxadiazol-2-yl)-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(5-tetrahydropyran-4-yl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-[5-(1-methyl-4-piperidyl)-1,3,4-oxadiazol-2-yl] spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[5-(4-fluoro-1-methyl-4-piperidyl)-1,3,4-oxadiazol-2-yl]-3’,4-dimethoxy-5’- methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-[5-[(1S)-1-methoxyethyl]-1,3,4-oxadiazol-2-yl]-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-ethoxy-3’-methoxy-5’-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-4-(difluoromethoxy)-3’-methoxy-5’-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-[3-(1-methoxyethyl)-1,2,4-oxadiazol-5-yl]-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-[3-(1-hydroxy-1-methyl-ethyl)-1,2,4-oxadiazol-5-yl]-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(1H-pyrazol-5-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-[1-(2-methoxyethyl) pyrazol-3-yl]-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-6-(1,8-dioxa-2-azaspiro [4.5] dec-2-en-3-yl)-3’,4-dimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(8-methyl-1-oxa-2,8-diazaspiro [4.5] dec-2-en-3-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-(2-methoxypyrimidin-5-yl)-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-6-(6-methoxy-3-pyridyl)-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione;

(2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(3-pyridyl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione; or

(2S,5’R)-7-chloro-3’,4,6-trimethoxy-5’-methyl-spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione.

18. The use of claim 17, wherein the compound is (2S,5’R)-7-chloro-3’,4-dimethoxy-5’-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl) spiro [benzofuran-2,4’-cyclohex-2-ene]-1’,3-dione or a pharmacologically acceptable salt thereof.