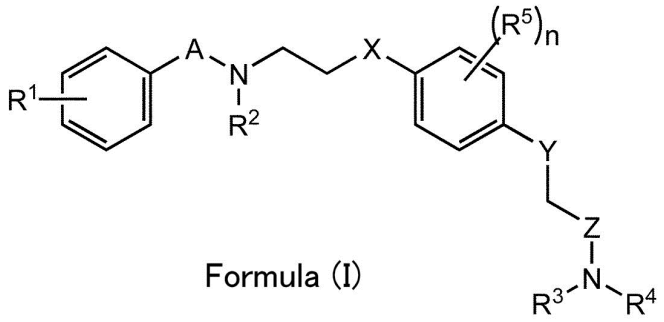
The compound of the present invention can specifically bind to an AMPA receptor and has extremely high brain uptake. In particular, the compound of the present invention can be used as a molecular probe, for example, a PET probe, and can image the AMPA receptor in living organisms in vivo. Further, the compound of the present invention is easily synthesized and can be obtained with a high yield.

SUMMARY

[0007a]

In one aspect, there is provided a compound represented by Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

in the formula,

each of A and Z independently represents CO, SO, or SO_2;

each of X and Y independently represents S or O;

each of R^1 , R^3 and R^4 independently represents hydrogen, alkyl, alkenyl, alkynyl, or halo;

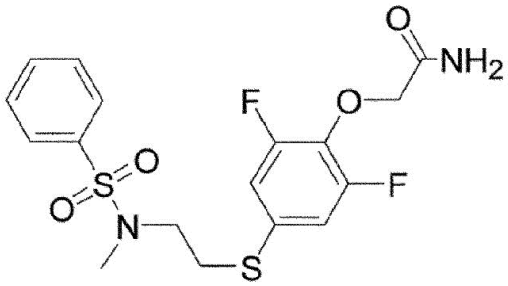
R^2 represents alkyl;

each R^5 independently represents alkyl, alkenyl, alkynyl, or halo; and

n represents an integer of 0 to 4

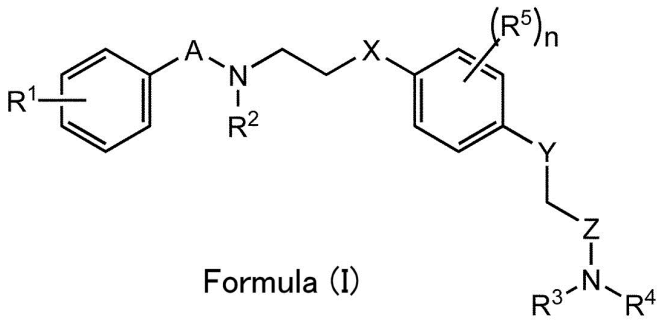
[0007b]

In another aspect, there is provided the {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof:



[0007c]

In another aspect, there is provided a compound represented by Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

in the formula,

each of A and Z independently represents CO, SO, or SO_2;

each of X and Y independently represents S or O;

each of R^1, R^3 and R^4 independently represents hydrogen, alkyl, alkenyl, alkynyl, or halo;

R^2 represents alkyl;

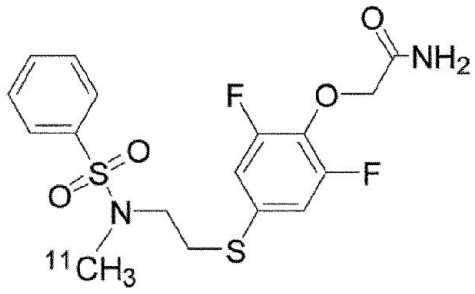
each R^5 independently represents alkyl, alkenyl, alkynyl, or halo;

n represents an integer of 0 to 4; and

one or more atoms are a radioisotope of the atom or atoms.

[0007d]

In another aspect, there is provided the radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following or a pharmaceutically acceptable salt or solvate thereof:



[0007e]

In another aspect, there is provided a composition comprising the compound or the pharmaceutically acceptable salt or solvate thereof as described in paragraph [0007a]-[0007d].

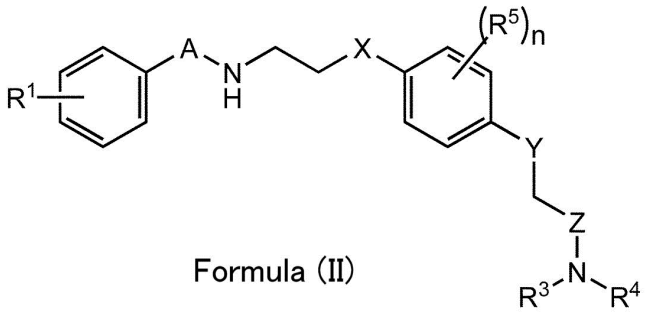
[0007f]

In another aspect, there is provided the use of a composition in the manufacture of a medicament for imaging an

α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the composition comprising the compound or the pharmaceutically acceptable salt or solvate thereof as described in paragraph [0007a]-[0007b].

[0007g]

In another aspect, there is provided a method for producing the compound or the pharmaceutically acceptable salt or solvate thereof as described in paragraph [0007a]-[0007d], the method comprising reacting a compound represented by Formula (II), or a pharmaceutically acceptable salt or solvate thereof with X^1-R^2, wherein R^2 represents alkyl and X^1 represents halo:



Formula (II)

in the formula,

each of A and Z independently represents CO, SO, or SO_2;

each of X and Y independently represents S or O;

each of R^1, R^3 and R^4 independently represents hydrogen, alkyl, alkenyl, alkynyl, or halo;

each R^5 independently represents alkyl, alkenyl, alkynyl, or halo; and

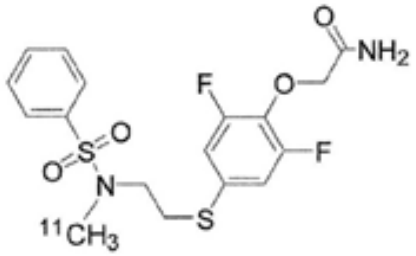
n represents an integer of 0 to 4.

[0007h]

In another aspect, there is provided a method for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the method comprising a step of detecting radiation emitted from the brain in living subjects to which the compound or the pharmaceutically acceptable salt or solvate thereof as described in paragraph [0007c]-[0007d] has been administered.

[0007i]

In another aspect, there is provided a composition comprising radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof:



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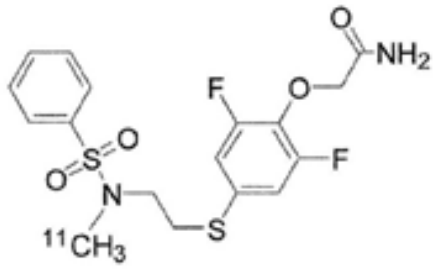
[0007j]

In another aspect, there is provided the use of a composition in the manufacture of a medicament for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the composition comprising radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof:



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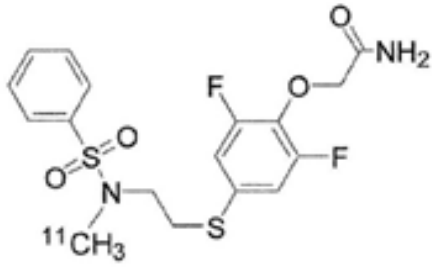
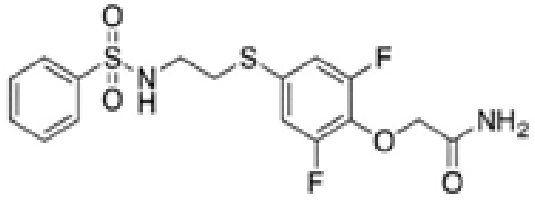
[0007k]

In another aspect, there is provided a method for producing radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following radio-labeled K-2, or a pharmaceutically acceptable salt or solvate thereof,

the method comprising reacting 2-[2,6-difluoro-4-({2-[(phenylsulfonyl)amino]ethyl}thio)phenoxy]acetamide represented by the following PEPA, or a pharmaceutically acceptable salt or solvate thereof with X^1-R^2, wherein R^2 represents [^{11}C]methyl group and X^1 represents halo:



Radio-labeled K-2



PEPA

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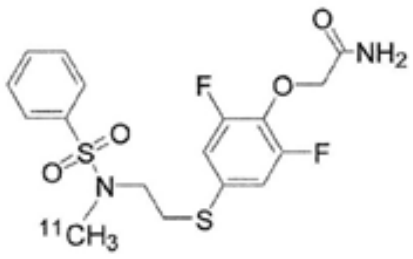
[00071]

In another aspect, there is provided a method for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the method comprising a step of detecting radiation emitted from the brain in living subjects to which radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof has been administered:



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BRIEF DESCRIPTION OF THE DRAWINGS

[0008]

Fig. 1 is a graph showing accumulation ratios of various compounds in hippocampal tissues.

Fig. 2 is a graph showing a ratio of an AMPA current to a reference value after administration of PEPA or K-2.

Fig. 3 is a graph showing a change in the amount of an AMPA receptor when K-2 or a vehicle is administered to a living organism. Left diagram: An amount of the AMPA receptor presented on the surface of the cell membrane, Right diagram: A total amount of the AMPA receptor.

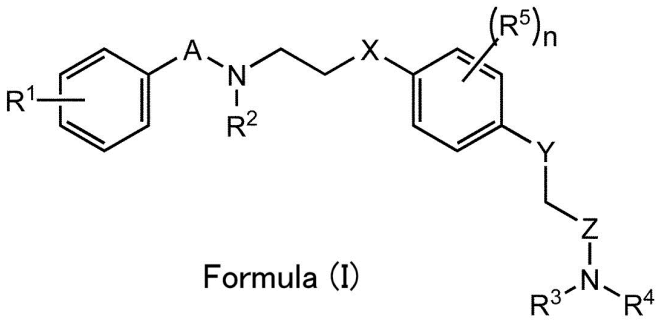
Fig. 4 is an in vivo PET image of a rat using radio-labeled K-2. Left diagram: A rat to which a vehicle is administered, Right diagram: A rat which is subjected to blocking by 0.5 mg/kg of non-radio-labeled K-2.

Fig. 5 shows time-activity curves (TAC) of K-2 of the hippocampus and the brain stem of a rat.

(a) Hippocampus after administration of the vehicle, (b) Hippocampus after blocking, (c) Brain stem after

CLAIMS

1. A compound represented by Formula (I), or a



Formula (I)

pharmaceutically acceptable salt or solvate thereof:

in the formula,

each of A and Z independently represents CO, SO, or SO_2;

each of X and Y independently represents S or O;

each of R^1 , R^3 and R^4 independently represents hydrogen, alkyl, alkenyl, alkynyl, or halo;

R^2 represents alkyl;

each R^5 independently represents alkyl, alkenyl, alkynyl, or halo; and

n represents an integer of 0 to 4.

2. The compound or the pharmaceutically acceptable salt or solvate according to claim 1, wherein each of A and Z independently represents CO or SO_2.

3. The compound or the pharmaceutically acceptable salt or solvate according to claims 1 or 2, wherein A represents SO_2 and Z represents CO.

4. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 3, wherein X represents S and Y represents O.

5. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 4, wherein R^1 represents hydrogen, alkyl or halo.

6. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 5, wherein both of R^3 and R^4 represent hydrogen, each of R^3 and R^4 independently represents alkyl, or one of R^3 and R^4 represents hydrogen and the other one is alkyl.

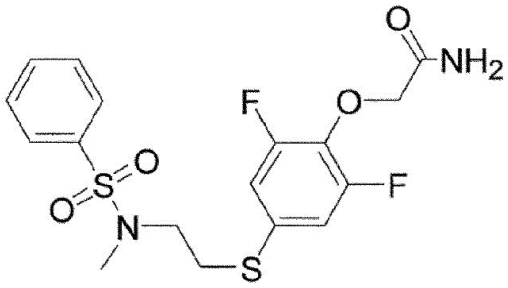
7. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 6, wherein the alkyl is C_1–C_5 alkyl.

8. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 7, wherein R^5 represents halo.

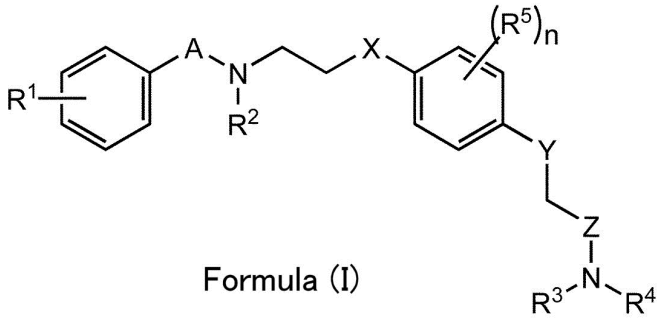
9. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 8, wherein the halo is fluoro.

10. The compound or the pharmaceutically acceptable salt or solvate according to any one of claims 1 to 9, wherein n is 2.

11. {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof:



12. A compound represented by Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

in the formula,

each of A and Z independently represents CO, SO, or SO_2;

each of X and Y independently represents S or O;

each of R^1, R^3 and R^4 independently represents hydrogen, alkyl, alkenyl, alkynyl, or halo;

R^2 represents alkyl;

each R^5 independently represents alkyl, alkenyl, alkynyl, or halo;

n represents an integer of 0 to 4; and

one or more atoms are a radioisotope of the atom or atoms.

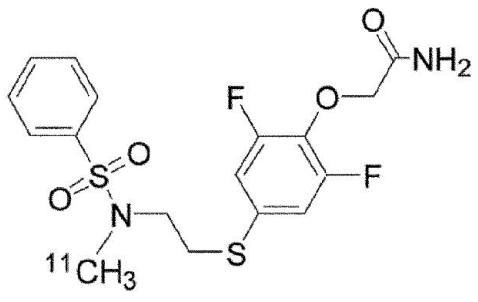
13. The compound or the pharmaceutically acceptable salt or solvate thereof according to claim 12, wherein the radioisotope is ^{11}C or ^{18}F.

14. The compound or the pharmaceutically acceptable salt or solvate thereof according to claim 13, wherein a group containing a radioisotope is R^1.

15. The compound or the pharmaceutically acceptable salt or solvate thereof according to claim 13, wherein a group containing a radioisotope is R^2.

16. The compound or the pharmaceutically acceptable salt or solvate thereof according to claim 13, wherein a group containing a radioisotope is at least one of R^3 and R^4.

17. Radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following or a pharmaceutically acceptable salt or solvate thereof:



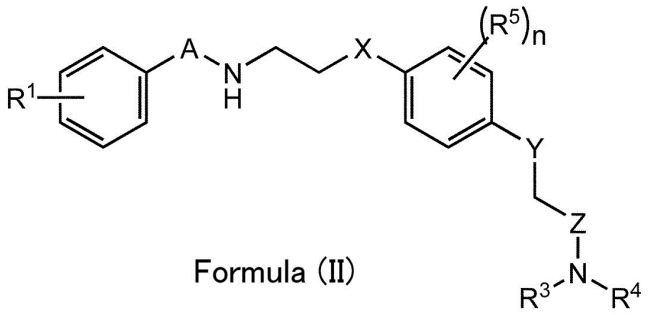
18. A composition comprising the compound or the pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 17.

19. Use of a composition in the manufacture of a medicament for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the composition comprising the compound or the pharmaceutically acceptable salt or solvate thereof according to any one of claims 12 to 17.

20. The use according to claim 19, wherein the imaging is conducted by molecular imaging.

21. A method for producing the compound or the pharmaceutically acceptable salt or solvate thereof according to any one of claims 1 to 17, the method comprising reacting a compound represented by Formula (II), or a pharmaceutically acceptable salt or solvate thereof with X^1–R^2, wherein R^2

represents alkyl and X^1 represents halo:



Formula (II)

in the formula,

each of A and Z independently represents CO, SO, or SO_2;

each of X and Y independently represents S or O;

each of R^1, R^3 and R^4 independently represents hydrogen, alkyl, alkenyl, alkynyl, or halo;

each R^5 independently represents alkyl, alkenyl, alkynyl, or halo; and

n represents an integer of 0 to 4.

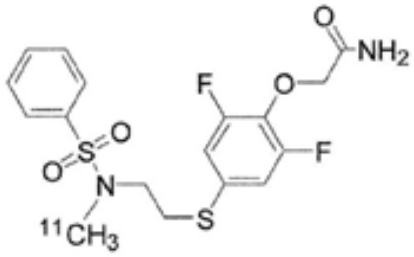
22. The method according to claim 21, wherein the R^2 represents [^{11}C]alkyl.

23. The method according to claim 21 or 22, wherein both the R^3 and the R^4 in Formula (II) represent hydrogen.

24. A method for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the method comprising a step of detecting radiation emitted from the brain in living subjects to which the compound or the pharmaceutically acceptable salt or solvate thereof according to any one of claims 12 to 17 has

been administered.

25. A composition comprising radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof:



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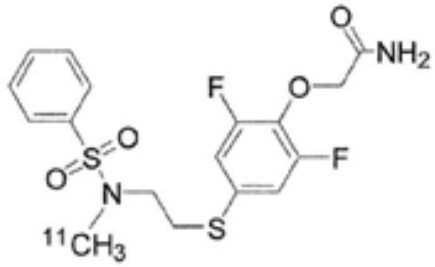
26. Use of a composition in the manufacture of a medicament for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the composition comprising radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof:



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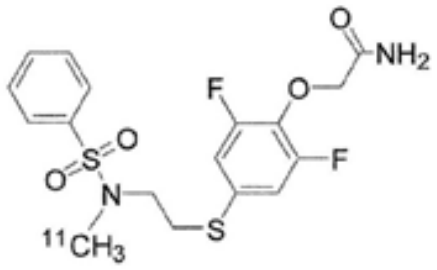
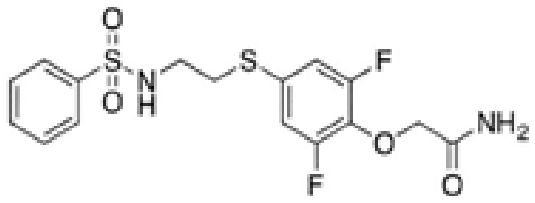
27. The use according to claim 26, wherein the imaging is conducted by molecular imaging.

28. A method for producing radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following radio-labeled K-2, or a pharmaceutically acceptable salt or solvate thereof,

the method comprising reacting 2-[2,6-difluoro-4-({2-[(phenylsulfonyl)amino]ethyl}thio)phenoxy]acetamide represented by the following PEPA, or a pharmaceutically acceptable salt or solvate thereof with X^1-R^2, wherein R^2 represents [^{11}C]methyl group and X^1 represents halo:



Radio-labeled K-2



PEPA

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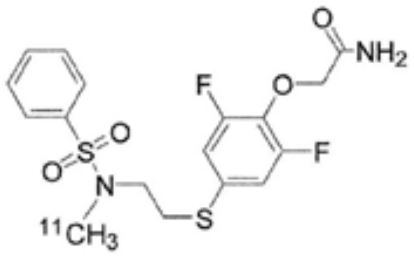
29. A method for imaging an α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor in the brain in living subjects, the method comprising a step of detecting radiation emitted from the brain in living subjects to which radio-labeled {4-[2-(benzenesulfonyl-methyl-amino)-

ethylsulfanil]-2,6-difluoro-phenoxy}-acetamide represented by the following, or a pharmaceutically acceptable salt or solvate thereof has been administered:



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