cancer therapy using ^{211}At-AAMT targeting LAT1.Cancer Sci. 2021 Mar;112(3):1132-1140. doi: 10.1111/cas.14761.

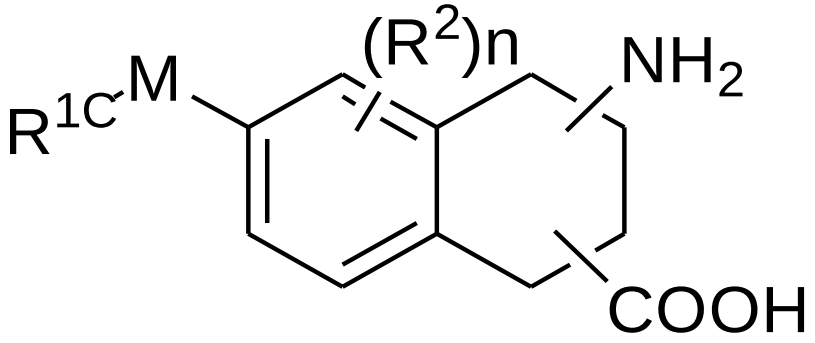
Non-Patent Document 4: Watabe T, Kaneda-Nakashima K, Shirakami Y, Liu Y, Ooe K, Teramoto T, Toyoshima A, Shimosegawa E, Nakano T,Kanai Y, Shinohara A, Hatazawa J. Targeted alpha therapy using astatine (^{211}At)-labeled phenylalanine: A preclinical study in glioma bearing mice. Oncotarget. 2020 Apr 14;11(15):1388-1398. doi: 10.18632/oncotarget.27552.

SUMMARY

[0008a]

In an aspect of the present disclosure, there is provided a compound represented by Formula (I) below or a pharmaceutically acceptable salt thereof:

[Formula 179]



(I)

wherein in Formula (I),

M represents S, O, or NH;

R^{1C} represents any structure selected from the group consisting of a 5- to 7-membered aromatic heterocyclic group having a substituent, a C5- to 7-membered aromatic cyclic group having a substituent, and a substituted or unsubstituted 8- to 16-membered polycyclic group,

where, the substituent of the 5- to 7-membered aromatic heterocyclic group having the substituent or the C5- to 7-membered aromatic cyclic group having the substituent is 1 to 5 groups independently selected from the group consisting of substituted or unsubstituted benzyloxy, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyl C1-6 alkyl, substituted or unsubstituted biphenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted naphthyl, halogen, hydroxy, cyano, amino, C1-6 alkylamino, di-(C1-6 alkyl)amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6

haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, sulfamoyl, ^{18}F, ^{123}I, boron containing substituents, alpha-emitting nuclides and beta-emitting nuclides,

where, the substituent of the polycyclic group is 1 to 6 groups independently selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, di-(C1-6 alkyl)amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, sulfamoyl, ^{18}F, ^{123}I, boron containing substituents, alpha-emitting nuclides and beta-emitting nuclides;

or,

M is S, O, NH, or absent (simply represents a single bond), R^{1C} represents ^{18}F, ^{123}I, a substituent including

boron, an α radioactive nucleus and/or a β radioactive nucleus;

R^2 represents a group independently selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, and sulfamoyl; and

n represents any integer of 0 to 5.

[0008b]

In another aspect of the present disclosure, there is provided an L-type amino acid transporter LAT1 selective inhibitor containing the compound or pharmaceutically acceptable salt thereof as described herein.

[0008c]

In a further aspect of the present disclosure, there is provided a use of a compound or pharmaceutically

acceptable salt thereof as described herein in the manufacture of a medicament for treating cancer.

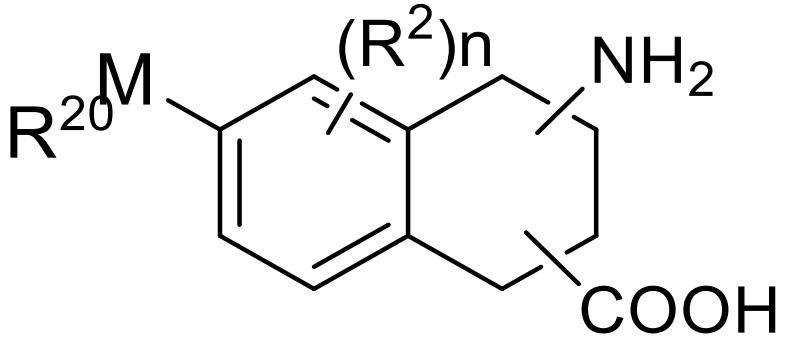
[0008d]

In another aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for retaining L-BPA in a cell.

[0008e]

In a further aspect of the present disclosure, there is provided a use of a compound represented by Formula (II) below or a pharmaceutically acceptable salt thereof:

[Formula 180]



(II)

in the manufacture of a medicament for treating cancer,

wherein, in Formula (II),

M represents S, O, NH, or absent (single bond); and

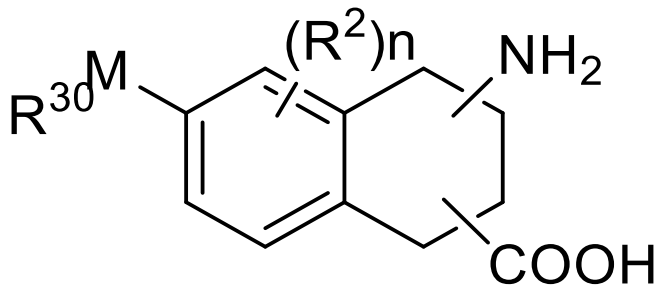
R^{20} represents a radioisotope.

[0008f]

In another aspect of the present disclosure, there is provided a use of a compound represented by Formula (III)

below or a pharmaceutically acceptable salt thereof:

[Formula 181]



(III)

in the manufacture of a medicament for BNCT,

wherein, in Formula (III),

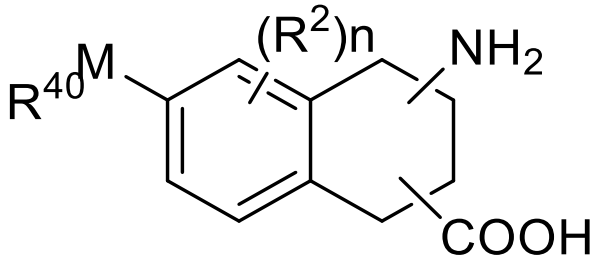
M represents S, O, NH, or absent (single bond); and

R^{30} represents a substituent including boron.

[0008g]

In a further aspect of the present disclosure, there is provided a use of a compound represented by Formula (IV) below or a pharmaceutically acceptable salt thereof:

[Formula 182]



(IV)

in the manufacture of a medicament for diagnosing cancer,

wherein, in Formula (IV),

M represents S, O, NH, or absent (single bond); and

R^{40} represents a radioisotope.

[0008h]

In another aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for sustained inhibition of LAT1.

[0008i]

In a further aspect of the present disclosure, there is provided a use of a compound or pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for enhancing a BNCT effect.

[0008j]

In another aspect of the present disclosure, there is provided a compound or pharmaceutically acceptable salt thereof as described herein for use in therapy.

Problems to be solved

[0009]

A drug having an ability to inhibit the uptake of amino acids into cancer cells via LAT1 and exhibiting anticancer action is also known, but development of a drug having high LAT1 affinity, a drug having a sustained LAT1 inhibitory effect, or a drug capable of effectively maintaining a blood concentration is required.

[0010]

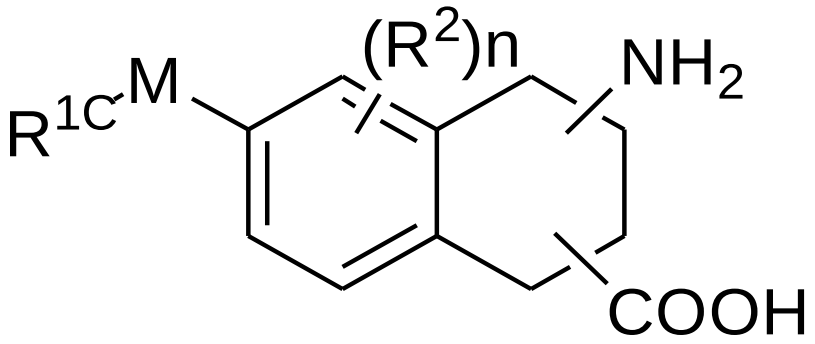
LAT1 has an exchange transport function, and when there is an amino acid outside the cell, even if an existing drug such as L-BPA is once delivered into the cell by exchange transport, LAT1 is rapidly released outside the cell.

Claims

[Claim 1]

A compound represented by Formula (I) below or a pharmaceutically acceptable salt thereof:

[Formula 179]



(I)

wherein in Formula (I),

M represents S, O, or NH;

R^{1C} represents any structure selected from the group consisting of a 5- to 7-membered aromatic heterocyclic group having a substituent, a C5- to 7-membered aromatic cyclic group having a substituent, and a substituted or unsubstituted 8- to 16-membered polycyclic group,

where, the substituent of the 5- to 7-membered aromatic heterocyclic group having the substituent or the C5- to 7-membered aromatic cyclic group having the substituent is 1 to 5 groups independently selected from the group consisting of substituted or unsubstituted benzyloxy, substituted or unsubstituted benzyl, substituted

or unsubstituted phenyl, substituted or unsubstituted phenyl C1-6 alkyl, substituted or unsubstituted biphenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted naphthyl, halogen, hydroxy, cyano, amino, C1-6 alkylamino, di-(C1-6 alkyl)amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, sulfamoyl, ^{18}F, ^{123}I, boron containing substituents, alpha-emitting nuclides and beta-emitting nuclides,

where, the substituent of the polycyclic group is 1 to 6 groups independently selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, di-(C1-6 alkyl)amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6

alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, sulfamoyl, ^{18}F, ^{123}I, boron containing substituents, alpha-emitting nuclides and beta-emitting nuclides;

or,

M is S, O, NH, or absent (simply represents a single bond), R^{1C} represents ^{18}F, ^{123}I, a substituent including boron, an α radioactive nucleus and/or a β radioactive nucleus;

R^2 represents a group independently selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino,

3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, and sulfamoyl; and

n represents any integer of 0 to 5.

[Claim 2]

The compound or pharmaceutically acceptable salt thereof of claims 1, wherein the R^{1C} is a substituted or unsubstituted 8- to 16-membered polycyclic group, and the polycyclic group is a ring which may optionally contain N, O and/or S in addition to a C atom.

[Claim 3]

The compound or pharmaceutically acceptable salt thereof of claim 1, wherein

the R^{1C} is a 5- to 7-membered aromatic group having a substituent, and necessarily contains, as the substituent, at least one group selected from the group consisting of substituted or unsubstituted benzyloxy, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyl C1-6 alkyl, substituted or unsubstituted pyridyl, substituted or unsubstituted naphthyl, and substituted or unsubstituted biphenyl, and

where, when the benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, pyridyl, naphthyl, or biphenyl is substituted, the benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, pyridyl,

naphthyl, or biphenyl is substituted with 1 to 5 groups independently selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, di-(C1-6 alkyl)amino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxyl, benzyloxy, benzyl, phenyl, phenyl C1-6 alkyl, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino, or di-(C1-6 alkyl)amino), a 3- to 8-membered non-aromatic heterocycle, morpholinocarbonyl, C3-8 cycloalkyl, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, and sulfamoyl.

[Claim 4]

The compound or pharmaceutically acceptable salt thereof of claim 1, wherein

the R^{1C} is one selected from the group consisting of substituted or unsubstituted pyridylphenyl, substituted or unsubstituted biphenyl, substituted or unsubstituted biphenyl-substituted phenyl, substituted or unsubstituted naphthyl-substituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted quinoline-substituted phenyl, substituted or unsubstituted

isoquinoline, substituted or unsubstituted isoquinoline-substituted phenyl, substituted or unsubstituted anthracene, substituted or unsubstituted anthracene-substituted phenyl, substituted or unsubstituted dithiazole ylideneaminonaphthyl, substituted or unsubstituted dithiazole ylideneaminobiphenyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted acenaphthene, and substituted or unsubstituted dithiazole ylideneaminophenyl, and

the substituent in the case of the substitution is 1 to 5 groups selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino), morpholinocarbonyl, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, C3-8 cycloalkyl, 3- to 8-membered non-aromatic heterocycle, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, dialkylamino, and sulfamoyl.

[Claim 5]

The compound or pharmaceutically acceptable salt thereof of claim 1, wherein in Formula (I),

M represents O,

R^{1C} is a 5- to 7-membered aromatic group having a substituent, and necessarily contains, as the substituent, at least one group selected from the group consisting of substituted or unsubstituted benzyloxy, substituted or unsubstituted benzyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenyl C1-6 alkyl, substituted or unsubstituted pyridyl, substituted or unsubstituted naphthyl, and substituted or unsubstituted biphenyl,

the substituent in the case of substitution is 1 to 5 groups selected from the group consisting of halogen, hydroxy, cyano, amino, C1-6 alkylamino, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, C1-6 alkoxy C1-6 alkyl, nitro, C1-6 haloalkyl, carbamoyl, C1-6 alkylaminocarbonyl, di-(C1-6 alkyl)aminocarbonyl, C1-6 alkoxycarbonyl, C1-6 alkylcarbonyl, $COOR^{10}$ (R^{10} is H or C1-6 alkyl, amino, C1-6 alkylamino), morpholinocarbonyl, C1-6 haloalkylsulfanyl, C1-6 haloalkylsulfinyl, C1-6 haloalkylsulfonyl, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-6 alkylsulfonyl, aminosulfonyl, sulfo, C3-8 cycloalkyl, 3- to 8-membered non-aromatic heterocycle, C3-8 cycloalkylamino, 3- to 8-membered non-aromatic heterocycle-substituted amino, dialkylamino, and sulfamoyl, and

n represents 0.

[Claim 6]

An L-type amino acid transporter LAT1 selective inhibitor containing the compound or pharmaceutically acceptable salt thereof described in any one of claims 1 to 5.

[Claim 7]

Use of a compound or pharmaceutically acceptable salt thereof described in any one of claims 1 to 5 in the manufacture of a medicament for treating cancer.

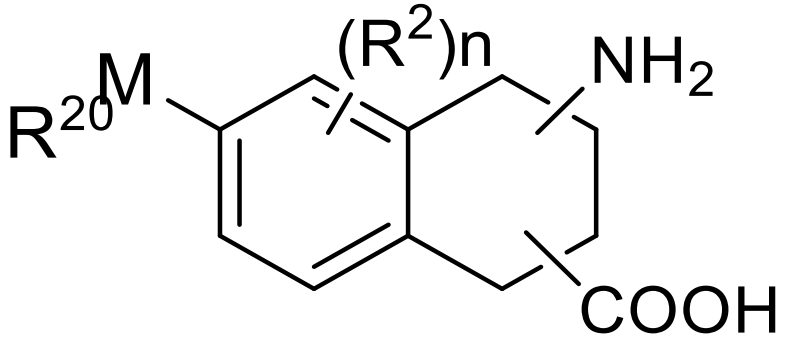
[Claim 8]

Use of a compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 5 in the manufacture of a medicament for retaining L-BPA in a cell.

[Claim 9]

Use of a compound represented by Formula (II) below or a pharmaceutically acceptable salt thereof:

[Formula 180]



(II)

in the manufacture of a medicament for treating cancer,

wherein, in Formula (II),

M represents S, O, NH, or absent (single bond); and

R^{20} represents a radioisotope.

[Claim 10]

The use of claim 9, wherein the R^{20} represents an α radioactive nucleus and/or a β radioactive nucleus.

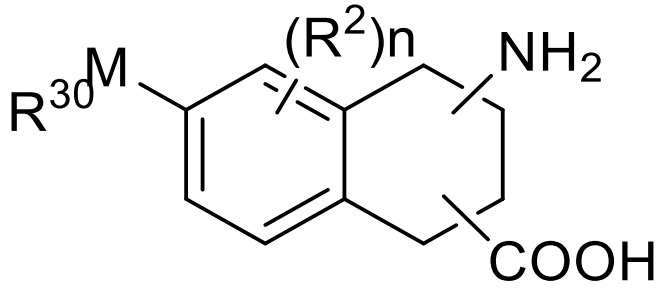
[Claim 11]

The use of claim 10, wherein the α radioactive nucleus is ^{211}At, and the β radioactive nucleus is ^{131}I.

[Claim 12]

Use of a compound represented by Formula (III) below or a pharmaceutically acceptable salt thereof:

[Formula 181]



(III)

in the manufacture of a medicament for BNCT,

wherein, in Formula (III),

M represents S, O, NH, or absent (single bond); and

R^{30} represents a substituent including boron.

[Claim 13]

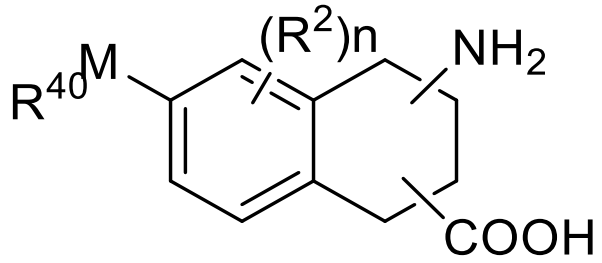
The use of claim 12, wherein the R^{30} represents

boronic acid (-$B(OH)_2$), a boronic acid ester, a boronic acid amide, or a boron cluster.

[Claim 14]

Use of a compound represented by Formula (IV) below or a pharmaceutically acceptable salt thereof:

[Formula 182]



(IV)

in the manufacture of a medicament for diagnosing cancer,

wherein, in Formula (IV),

M represents S, O, NH, or absent (single bond); and

R^{40} represents a radioisotope.

[Claim 15]

The use of claim 14, wherein the R^{40} is ^{18}F or ^{123}I.

[Claim 16]

The use of claim 14 or 15, wherein the medicament is a probe for PET or a probe for SPECT.

[Claim 17]

Use of a compound or pharmaceutically acceptable salt thereof described in any one of claims 1 to 5 in the manufacture of a medicament for sustained inhibition of

LAT1.

[Claim 18]

Use of a compound or pharmaceutically acceptable salt thereof described in any one of claims 1 to 5 in the manufacture of a medicament for enhancing a BNCT effect.

[Claim 19]

A compound or pharmaceutically acceptable salt thereof described in any one of claims 1 to 5 for use in therapy.