An object of the present invention is to provide an antitumor agent that does not cause inhibition of wild-type EGFR and thus causes smaller side effects, serving as an inhibitor that can ensure high selectivity with respect to exon 18 and/or exon 21 mutant EGFR for which the therapeutic effects of the previously known EGFR inhibitors are insufficient.

Solution to Problem

[0009]

The inventors of the present invention conducted extensive research, and found that exon 18 and/or exon 21 mutant EGFR is an appropriate target in treating cancers, and that EGFR inhibitors conventionally used for the treatments have inferior selectivity between exon 18 and/or exon 21 mutant EGFR. Further, the inventors also confirmed that the compound of the present invention exerts superior selectivity and tumor growth inhibitory effects with respect to exon 18 and/or exon 21 mutant EGFR. With this finding, the inventors accomplished the present invention.

[0009a]

In one aspect, the present disclosure refers to the use of an antitumor agent in the manufacture of a medicament for treating a malignant tumor patient expressing EGFR having at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue, the antitumor agent comprising (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof.

In another aspect, the present disclosure refers to the use of (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in the manufacture of a medicament for treating a malignant tumor patient expressing EGFR having at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation ofexon 21, wherein X represents an arbitrary amino-acid residue.

In a further aspect, the present disclosure refers to the use of (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof for the production of a pharmaceutical agent for treating a malignant tumor patient expressing EGFR having at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue.

In a further aspect, the present disclosure refers to an *ex vivo* method for predicting therapeutic effects of chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in a malignant tumor patient, the method comprising steps (1) and (2) below:

(1) a step of detecting the presence or absence of mutation of EGFR gene contained in a biological sample obtained from the patient; and

(2) a step of predicting that the chemotherapy is highly likely to exhibit sufficient therapeutic effects with respect to the

CLAIMS

[Claim 1]

Use of an antitumor agent in the manufacture of a medicament for treating a malignant tumor patient expressing EGFR having at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue, the antitumor agent comprising (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof.

[Claim 2]

The use according to claim 1, wherein the exon 18 mutation is at least one mutation selected from the group consisting of G719A, G719S, G719C, E709K and E709A.

[Claim 3]

The use according to claim 1 or 2, wherein the exon 21 mutation is L861Q.

[Claim 4]

The use according to any one of claims 1 to 3, wherein the EGFR further has T790M mutation.

[Claim 5]

Use of (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in the manufacture of a medicament for treating a malignant tumor patient expressing EGFR having at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue.

[Claim 6]

The use according to claim 5, wherein the exon 18

mutation is at least one mutation selected from the group consisting of G719A, G719S, G719C, E709K and E709A.

[Claim 7]

The use according to claim 5 or 6, wherein the exon 21 mutation is L861Q.

[Claim 8]

The use according to any one of claims 5 to 7, wherein the EGFR further has T790M mutation.

[Claim 9]

Use of (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof for the production of a pharmaceutical agent for treating a malignant tumor patient expressing EGFR having at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue.

[Claim 10]

The use according to claim 9, wherein the exon 18 mutation is at least one mutation selected from the group consisting of G719A, G719S, G719C, E709K and E709A.

[Claim 11]

The use according to claim 9 or 10, wherein the exon 21 mutation is L861Q.

[Claim 12]

The use according to any one of claims 9 to 11, wherein the EGFR further has T790M mutation.

[Claim 13]

The use according to claim 9, wherein the

pharmaceutical agent comprises a pharmaceutical composition comprising (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof and a pharmaceutically acceptable carrier.

[Claim 14]

An *ex vivo* method for predicting therapeutic effects of chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in a malignant tumor patient, the method comprising steps (1) and (2) below:

(1) a step of detecting the presence or absence of mutation of EGFR gene contained in a biological sample obtained from the patient; and

(2) a step of predicting that the chemotherapy is highly likely to exhibit sufficient therapeutic effects with respect to the patient when the results of the detection in step (1) found that the EGFR gene has at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue.

[Claim 15]

The method according to claim 14, wherein the exon 18 mutation is at least one mutation selected from the group consisting of G719A, G719S, G719C, E709K and E709A.

[Claim 16]

The method according to claim 14 or 15, wherein the exon 21 mutation is L861Q.

[Claim 17]

The method according to any one of claims 14 to 16, wherein the EGFR further has T790M mutation.

[Claim 18]

Use of(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in the manufacture of a medicament for treating malignant tumor, wherein the medicament is to be administered to a malignant tumor patient who was predicted highly likely to sufficiently respond to the chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof, after a biological sample is to be obtained from the patient in a first step to detect the presence or absence of mutation of EGFR;

and wherein in a second step, chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof is predicted to highly likely to exhibit sufficient therapeutic effects with respect to the patient when the results of the detection in the first step found that the EGFR gene has at least one mutation selected from the group consisting of G719X mutation of exon 18, E709X mutation of exon 18, and L861X mutation of exon 21, wherein X represents an arbitrary amino-acid residue.

[Claim 19]

The use according to claim 18, wherein the exon 18 mutation is at least one mutation selected from the group consisting of G719A, G719S, G719C, E709K and E709A.

[Claim 20]

The use according to claim 18 or 19, wherein the exon 21 mutation is L861Q.

[Claim 21]

The use according to any one of claims 18 to 20, wherein the EGFR further has T790M mutation.