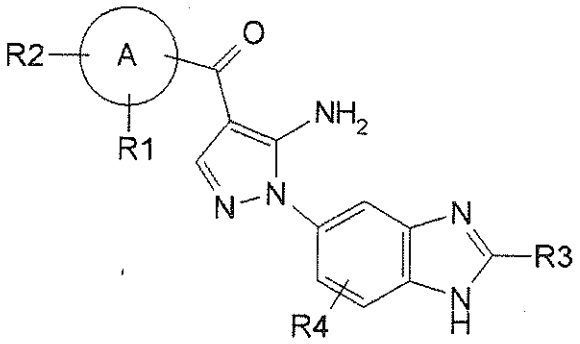
involved in cancer. Thus, the inhibition of the FGFR family kinases in cancer tissues may be a promising therapeutic method for treating the above types of cancer.

[Prior Art Documents]

[Non-patent Document 1] Cytokine & Growth Factor Reviews 16 (2005) 139-149
[Non-patent Document 2] Breast Cancer Research 2007, 9:R23
[Non-patent Document 3] Cancer Res 2005; 65(13): 5561-70
[Non-patent Document 4] PNAS (2005), 102(40), 14344-14349.
[Non-patent Document 5] Acta Haematol 2002;107:101-107
[Non-patent Document 6] Nature Medicine 3, 887-89, 1997
[Non-patent Document 7] J Pathol. 2003 Nov;201(3):439-50
[Non-patent Document 8] Anal Cell Pathol. 2001;22(4):229-34
[Non-patent Document 9] Cancer Res 2008;68(17):6902-7
[Non-patent Document 10] Blood. 2003;101: 4569-4575
[Non-patent Document 11] Nat Genet. 1999 Sep;23(1):18-20.

Summary ~~of the Invention~~

In a first aspect, there is provided a compound represented by following general formula (I), isomer thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-3} perfluoroalkyl, cyano, methanesulfonyl, hydroxyl, C_{1-4} alkoxy, or amino;

A represents indole or pyrrole;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, C_{6-10} aryl, C_{6-10} aryl C_{1-3} alkyl, or 3- to 10-membered heterocyclyl C_{1-3} alkyl, 3- to 10-membered heterocyclyl, 5- to 10-membered heteroaryl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, or C_{1-6}

trihydroxy alkyl which is optionally substituted by one or more groups independently selected from group Q;

R_6 and R_7, which are the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl C_{1-3} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl, C_{1-4} aminoalkyl, C_{1-4} alkylamino C_{1-4} alkyl, di(C_{1-4} alkyl)amino C_{1-4} alkyl, or cyano(C_{1-3} alkyl); or R_6 and R_7, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

n represents 1 to 3;

R_8 and R_9, which are the same or different, each represents hydrogen, C_{1-4} alkyl, or halogen; or alternatively, R_8 and R_9, together with a carbon atom linked thereto, form a cycloaliphatic ring;

Z_1 represents hydrogen, $NR_{10}R_{11}$, -OH, or 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{10} and R_{11}, which are the same or different, each represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, cyano(C_{1-3} alkyl), or C_{1-3} alkylsulfonyl C_{1-4} alkyl; or alternatively, R_{10} and R_{11}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{12} and R_{13}, which are the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, 3- to 10-membered cycloaliphatic ring, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; or alternatively, R_{12} and R_{13}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl which is optionally substituted by one or more groups independently selected from group Q;

R_{14} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{15} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{16} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered

heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{17} represents hydrogen or C_{1-4} alkyl;

R_{18} represents C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{19} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q;

R_{20} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{21} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{22} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{23} represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{24} represents hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

R_{25} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{26} and R_{27}, which are the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively, R_{26} and R_{27}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{28} and R_{29}, which are the same or different, each represents hydrogen, C_{1-4} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxyl C_{1-4} alkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, 3- to 10-membered heterocyclyl, C_{6-10} aryl C_{1-4} alkyl, 3- to 10-membered heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively, R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

<group P>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

<group Q>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, $-SO_2R_{16}$, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl;

wherein the heteroaryl, heterocyclyl, and heterocyclylamino groups include one to five hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom;

with the proviso that said compound represented by general formula (I) does not include [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-trifluoromethyl-phenyl)-1H-indol-2-yl]-methanone.

In a second aspect, there is provided a pharmaceutical composition comprising the compound, isomer thereof, or a pharmaceutically acceptable salt thereof as defined above; and a carrier.

In a third aspect, there is provided an agent for inhibiting FGFR activity, which comprises as an active ingredient the compound, isomer thereof, or a pharmaceutically acceptable salt thereof as defined above.

In a fourth aspect, there is provided an agent for preventing or treating cancer, which comprises as an active ingredient the compound, isomer thereof, or a pharmaceutically acceptable salt thereof as defined above.

In a fifth aspect, there is provided the use of the compound, isomer thereof, or a pharmaceutically acceptable salt thereof as defined above in the production of an agent for preventing or treating cancer.

In a sixth aspect, there is provided the compound, isomer thereof, or a pharmaceutically acceptable salt thereof as defined above, for use in preventing or treating cancer.

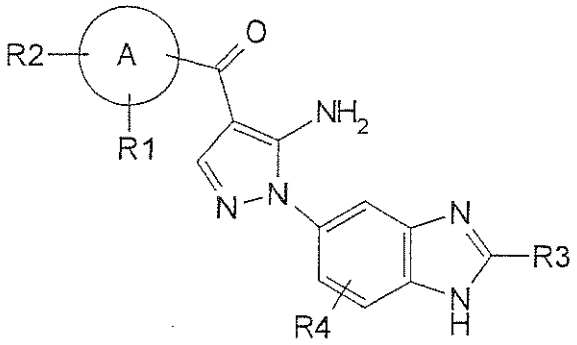
[Problems to be Solved by the Invention]

An objective of the present invention is to provide low molecular weight compounds capable of inhibiting fibroblast growth factor receptor (FGFR) family kinases in cancer tissues.

[Means for Solving the Problems]

Specifically, the present invention includes the following:

[1] A compound represented by following general formula (I), or a pharmaceutically acceptable salt thereof:



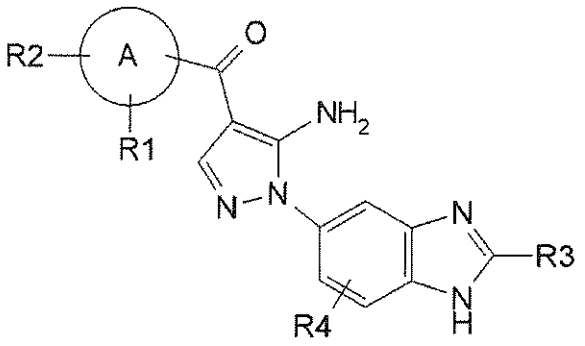
(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl,

CLAIMS

1. A compound represented by following general formula (I), isomer thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein R_1, R_2, R_3, and R_4 each independently represents the group listed below:

R_1 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$;

R_2 represents hydrogen, hydroxy, halogen, cyano, nitro, C_{1-4} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-10} aryl C_{1-4} alkyl, $-OR_5$, $-NR_6R_7$, $-(CR_8R_9)_nZ_1$, $-C(O)NR_{12}R_{13}$, $-SR_{14}$, $-SOR_{15}$, $-SO_2R_{16}$, $-NR_{17}SO_2R_{18}$, COOH, C_{6-10} aryl which is optionally substituted by one or more groups independently selected from group P, 5- to 10-membered heteroaryl or 3- to 10-membered heterocyclyl which is optionally substituted by one or more groups independently selected from group Q, $-COR_{19}$, $-COOR_{20}$, $-OC(O)R_{21}$, $-NR_{22}C(O)R_{23}$, $-NR_{24}C(S)R_{25}$, $-C(S)NR_{26}R_{27}$, $-SO_2NR_{28}R_{29}$, $-OSO_2R_{30}$, $-SO_3R_{31}$, or $-Si(R_{32})_3$; or

R_1 and R_2, together with an atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl, wherein the heterocyclyl or heteroaryl is optionally substituted by halogen;

R_3 represents hydrogen, C_{1-5} alkyl, C_{6-10} aryl C_{1-6} alkyl, or C_{1-4} haloalkyl;

R_4 represents hydrogen, halogen, C_{1-3} alkyl, C_{1-3} perfluoroalkyl, cyano, methanesulfonyl, hydroxyl, C_{1-4} alkoxy, or amino;

A represents indole or pyrrole;

R_5 represents C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-3} alkoxy C_{1-4} alkyl, C_{1-3} alkoxy C_{1-4} alkoxy C_{1-4} alkyl, C_{1-4} aminoalkyl, C_{1-4}

heterocyclyl C_{1-3} alkyl, 5- to 10-membered heteroaryl C_{1-3} alkyl, cyano(C_{1-3} alkyl), C_{1-3} alkylsulfonyl C_{1-4} alkyl, or 3- to 10-membered cycloaliphatic ring; or alternatively, R_{28} and R_{29}, together with a nitrogen atom linked thereto, form 3- to 10-membered heterocyclyl or 5- to 10-membered heteroaryl;

R_{30} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{31} represents C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} haloalkyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl;

R_{32} represents C_{1-4} alkyl or C_{6-10} aryl;

<group P>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, 3- to 10-membered heterocyclylamino, $-SO_2R_{16}$, -CN, $-NO_2$, and 3- to 10-membered heterocyclyl;

<group Q>

halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, -OH, C_{1-3} alkoxy, C_{1-6} monohydroxy alkyl, C_{1-6} dihydroxy alkyl, C_{1-6} trihydroxy alkyl, 3- to 10-membered heterocyclyl amine, $-SO_2R_{16}$, -CN, $-NO_2$, C_{3-7} cycloalkyl, $-COR_{19}$, and 3- to 10-membered heterocyclyl which is optionally substituted by C_{1-4} alkyl;

wherein the heteroaryl, heterocyclyl, and heterocyclylamino groups include one to five hetero atoms selected from the group consisting of a nitrogen atom, an oxygen atom, and a sulfur atom;

with the proviso that said compound represented by general formula (I) does not include [5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-[5-(4-trifluoromethyl-phenyl) -1H-indol-2-yl]-methanone.

2. The compound, isomer thereof, or a pharmaceutically acceptable salt thereof of claim 1, wherein R_3 represents hydrogen, C_{1-4} alkyl, C_{6-10} aryl C_{1-4} alkyl, or C_{1-3} perfluoroalkyl.

3. The compound, isomer thereof, or a pharmaceutically acceptable salt thereof of claim 1 or 2, which is selected from the group consisting of:

[5-amino-1-(2-methyl-1H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone, and

[5-amino-1-(2-methyl-3H-benzimidazol-5-yl)-1H-pyrazol-4-yl]-(1H-indol-2-yl)-methanone.

4. The compound, isomer thereof, or a pharmaceutically acceptable salt thereof of any one of claims 1-3, wherein the pharmaceutically acceptable salt is selected from the group consisting of acetate, succinate, fumarate, maleate, tartrate, citrate, lactate, malate, stearate, benzoate, methanesulfonate, and p-toluenesulfonate.