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[Summary of the Invention]

[Problems to be Solved by the Invention]

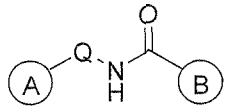
An objective of the present invention is to provide low molecular weight compounds that can selectively inhibit Discoidin Domain Receptor 1 (DDR1) and to provide pharmaceuticals effective for diseases associated with abnormalities of DDR1, such as cancer, cancer metastasis and invasion, fibrosis, and inflammation.

[Means for Solving the Problems]

Specifically, the present ~~invention~~ disclosure comprises:

[1]

In one aspect, ~~A~~a compound represented by general formula (I) below:



(I)

[wherein

Q represents CH_2 or NH;

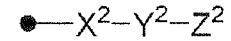
Ring A represents formula (1) or (2) below:

Rk represents a hydrogen atom, C_{1-6} alkyl group, amino group, mono-C_{1-6} alkylamino group, or di-C_{1-6} alkylamino group, wherein the C_{1-6} alkyl group may be substituted with 1 to 3 hydroxyl, amino, mono-C_{1-6} alkylamino, and/or di-C_{1-6} alkylamino groups; and

Rl and Rm are identical or different, each representing a hydrogen atom, C_{1-6} alkyl group, or 3- to 12-membered heterocycle, wherein the C_{1-6} alkyl group may be independently substituted with 1 to 3 amino, mono-C_{1-6} alkylamino, and/or di-C_{1-6} alkylamino groups;

B^4 represents N or CR^7;

R^7 represents a hydrogen atom, halogen atom, cyano group, C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{2-6} alkenyl group, or C_{3-8} cycloalkyl group (wherein the C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{2-6} alkenyl group, or C_{3-8} cycloalkyl group may be substituted with 1 to 5 halogen atoms), or a group represented by formula (ii) below:



(ii)

wherein X^2 represents $-(CH_2)_p-$;

p represents 0, 1, 2, or 3;

Y^2 represents a 4- to 10-membered aromatic ring, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle, wherein the 4- to 10-membered aromatic ring, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle may be substituted with 1 to 5 C_{1-6} alkyl groups;

Z^2 represents a hydrogen atom, a C_{1-6} alkyl group, hydroxyl group, -NRfRg, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle, wherein the C_{1-6} alkyl group may be substituted with 1 to 5 halogen atoms, and the 3- to 12-membered heterocycle or 4- to 10-membered aromatic heterocycle may be substituted with 1 to 5 C_{1-6} alkyl groups; and

Rf and Rg are identical or different, each representing a hydrogen atom, C_{1-6} alkyl group, $-COCH_3$, or $-SO_2CH_3$;

B^5 represents N or CR^8; and

R^8 represents a hydrogen atom, a C_{1-6} alkyl group, or halogen atom, wherein the C_{1-6} alkyl group may be substituted with 1 to 5 halogen atoms],

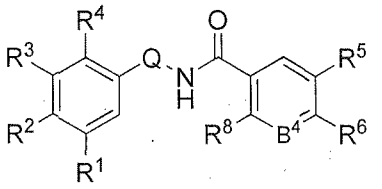
wherein "4- to 10-membered aromatic heterocycle" refers to an aromatic monovalent or divalent heterocycle containing 1 to 5 heteroatoms in the ring-forming atoms, and heteroatom is a nitrogen atom (N), an oxygen atom (O) or a sulfur atom (S),

wherein "3- to 12-membered heterocycle" refers to a non-aromatic monovalent or divalent heterocycle containing 1 to 5 heteroatoms in the ring-forming atoms, and heteroatom is a nitrogen atom (N), an oxygen atom (O) or a sulfur atom (S),

a pharmaceutically acceptable salt thereof, or a solvate thereof.

[2]

The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to [1], wherein the compound is represented by the following general formula (II):



(II)

[wherein Q, R^1, R^2, R^3, R^4, R^5, R^6, B^4, and R^8 are as defined in [1], respectively].

independently substituted with 1 to 2 amino, mono-C_{1-2} alkylamino, and/or di-C_{1-2} alkylamino groups;

Rd represents a hydrogen atom or C_{1-2} alkyl group, wherein the C_{1-2} alkyl group may be substituted with an amino group or hydroxyl group;

Re represents a C_{1-2} alkyl group or 4- to 6-membered heterocycle, wherein the C_{1-2} alkyl group may be substituted with an amino group or hydroxyl group; and

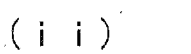
Rl and Rm are identical or different, each representing a hydrogen atom, C_{1-3} alkyl group, or 4- to 6-membered heterocycle, wherein the C_{1-3} alkyl group independently substituted with 1 to 3 amino, mono-C_{1-3} alkylamino, and/or di-C_{1-3} alkylamino groups.

[8]

The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of [1] to [7], wherein

B^4 represents CR^7, and

R^7 represents a chlorine atom, bromine atom, hydrogen atom, cyano group, C_{1-3} alkyl group, C_{1-3} alkoxy group, C_{2-3} alkenyl group, C_{3-6} cycloalkyl group (wherein the C_{1-3} alkyl group, C_{1-3} alkoxy group, C_{2-3} alkenyl group, or C_{3-6} cycloalkyl group may be substituted with 1 to 3 halogen atoms), or group represented by formula (ii) below,:



$$\bullet\!\!-X^2-Y^2-Z^2 \quad (ii)$$

wherein X^2 represents $-(CH_2)_p-$, p represents 0 or 1;

Y^2 represents piperazine, pyrrolidine, piperidine, morpholine, or 3,3-dimethylpiperazine;

Z^2 represents a hydrogen atom, a C_{1-3} alkyl group, -NRfRg, pyrrolidine, morpholine, or tetrahydropyran, wherein the C_{1-3} alkyl group may be substituted with 1 to 3 halogen atoms; and

Rf and Rg are identical or different, each representing a hydrogen atom, C_{1-3} alkyl group, $-COCH_3$, or $-SO_2CH_3$.

[9]

The compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of [1] to [8], wherein R^8 represents a hydrogen atom.

[10]

In another aspect, ~~A~~a pharmaceuticals comprising the compound~~,~~ or a pharmaceutically acceptable salt thereof~~, or a solvate thereof~~ as disclosed above ~~according to any one of [1] to [9]~~ as an active ingredient.

[11]

The pharmaceuticals according to [10], wherein the pharmaceuticals is used for treatment of cancer and/or cancer invasion/metastasis.

[12]

The pharmaceuticals according to [10], wherein the pharmaceuticals is used for treatment of fibrosis and/or inflammation.

[13]

A method for treating cancer, and/or cancer invasion/metastasis, comprising administering a pharmaceutically effective amount of a composition comprising the compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of [1] to [9] to a patient in need thereof.

[14]

A method for treating fibrosis and/or inflammation, comprising administering a pharmaceutically effective amount of a composition comprising the compound, a pharmaceutically acceptable salt thereof, or a solvate thereof according to any one of [1] to [9] to a patient in need thereof.

[15]

In another aspect, the u~~U~~se of the compound~~,~~ or a pharmaceutically acceptable salt thereof~~, or a solvate thereof~~ as disclosed above ~~according to any one of [1] to [9]~~ for the manufacture of an agent for treating cancer, and/or cancer invasion/metastasis.

[16]

In another aspect, the u~~U~~se of the compound~~,~~ or a pharmaceutically acceptable salt thereof~~, or a solvate thereof~~ as disclosed above ~~according to any one of [1] to [9]~~ for the manufacture of an agent for treating fibrosis and/or inflammation.

[17]

In another aspect, ~~T~~the compound~~,~~ or a pharmaceutically acceptable salt thereof~~, or a solvate thereof~~ as disclosed above ~~according to any one of [1] to [9]~~ for use in treating cancer, and/or cancer invasion/metastasis.

[18]

In another aspect, ~~T~~the compound~~,~~ or a pharmaceutically acceptable salt thereof~~, or a solvate thereof~~ as disclosed above ~~according to any one of [1] to [9]~~ for use in treating fibrosis and/or inflammation.

[Effects of the Invention]

The compounds or pharmaceutically acceptable salts thereof, or solvates thereof according to the present invention have an effect of selectively inhibiting the Discoidin Domain Receptor 1 (DDR1). The compounds of the present application may be able to have efficacy for diseases associated with abnormalities of DDR1, such as cancer, cancer metastasis and invasion, fibrosis, and inflammation, and can prevent and/or treat diseases for which previous therapeutic agents are not sufficiently effective.

[Brief Description of the Drawings]

Fig. 1 is a graph showing an antitumor effect of Compound B-2.

Fig. 2 shows a DDR1 phosphorylation inhibitory effect of Compound B-2 in tumors.

[Mode for Carrying Out the Invention]

Re represents a C_{1-6} alkyl group, hydroxyl group, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle, wherein the C_{1-6} alkyl group may be substituted with 1 to 3 hydroxyl and/or amino groups;

Ri represents a hydrogen atom or a C_{1-6} alkyl group, wherein the C_{1-6} alkyl group may be substituted with 1 to 5 halogen atoms;

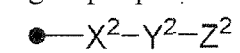
Rj represents a hydrogen atom or C_{1-6} alkyl group, wherein the C_{1-6} alkyl group may be substituted with 1 to 5 halogen atoms;

Rk represents a hydrogen atom, C_{1-6} alkyl group, amino group, mono-C_{1-6} alkylamino group, or di-C_{1-6} alkylamino group, wherein the C_{1-6} alkyl group may be substituted with 1 to 3 hydroxyl, amino, mono-C_{1-6} alkylamino, and/or di-C_{1-6} alkylamino groups; and

Rl and Rm are identical or different, each representing a hydrogen atom, C_{1-6} alkyl group, or 3- to 12-membered heterocycle, wherein the C_{1-6} alkyl group may be independently substituted with 1 to 3 amino, mono-C_{1-6} alkylamino, and/or di-C_{1-6} alkylamino groups;

B^4 represents N or CR^7;

R^7 represents a hydrogen atom, halogen atom, cyano group, C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{2-6} alkenyl group, or C_{3-8} cycloalkyl group (wherein the C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{2-6} alkenyl group, or C_{3-8} cycloalkyl group may be substituted with 1 to 5 halogen atoms), or a group represented by formula (ii) below:



(ii)

wherein X^2 represents $-(CH_2)_p-$;

p represents 0, 1, 2, or 3;

Y^2 represents a 4- to 10-membered aromatic ring, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle, wherein the 4- to 10-membered aromatic ring, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle may be substituted with 1 to 5 C_{1-6} alkyl groups;

Z^2 represents a hydrogen atom, a C_{1-6} alkyl group, hydroxyl group, -NRfRg, 3- to 12-membered heterocycle, or 4- to 10-membered aromatic heterocycle, wherein the C_{1-6} alkyl group may be substituted with 1 to 5 halogen atoms, and the 3- to 12-membered heterocycle or 4- to 10-membered aromatic heterocycle may be substituted with 1 to 5 C_{1-6} alkyl groups; and

Rf and Rg are identical or different, each representing a hydrogen atom, C_{1-6} alkyl group, $-COCH_3$, or $-SO_2CH_3$;

B^5 represents N or CR^8; and

R^8 represents a hydrogen atom, a C_{1-6} alkyl group, or halogen atom, wherein the C_{1-6} alkyl group may be substituted with 1 to 5 halogen atoms],

wherein "4- to 10-membered aromatic heterocycle" refers to an aromatic monovalent or divalent heterocycle containing 1 to 5 heteroatoms in the ring-forming atoms, and heteroatom is a nitrogen atom (N), an oxygen atom (O) or a sulfur atom (S),
wherein "3- to 12-membered heterocycle" refers to a non-aromatic monovalent or divalent heterocycle containing 1 to 5 heteroatoms in the ring-forming atoms, and heteroatom is a nitrogen atom (N), an oxygen atom (O) or a sulfur atom (S),
or a pharmaceutically acceptable salt thereof.

Ra and Rb are identical or different, each representing a hydrogen atom, C_{1-6} alkyl group, C_{3-6} cycloalkyl group , or $-SO_2CH_3$, wherein the C_{1-6} alkyl group or C_{3-6} cycloalkyl group may be substituted with 1 to 5 halogen atoms, hydroxyl groups, C_{1-6} alkoxy groups, amino groups, $-CONH_2$, mono- C_{1-6} alkylamino groups, di-C_{1-6} alkylamino groups, or cyano groups;

Rc represents a C_{1-4} alkyl group, C_{1-4} alkoxy group, 4- to 6-membered heterocycle, 4- to 6-membered aromatic heterocycle, or amino group, wherein the C_{1-4} alkyl group may be independently substituted with 1 to 2 amino, mono-C_{1-2} alkylamino, and/or di-C_{1-2} alkylamino groups;

Rd represents a hydrogen atom or C_{1-2} alkyl group, wherein the C_{1-2} alkyl group may be substituted with an amino group or hydroxyl group;

Re represents a C_{1-2} alkyl group or 4- to 6-membered heterocycle, wherein the C_{1-2} alkyl group may be substituted with an amino group or hydroxyl group; and

Rl and Rm are identical or different, each representing a hydrogen atom, C_{1-3} alkyl group, or 4- to 6-membered heterocycle, wherein the C_{1-3} alkyl group independently substituted with 1 to 3 amino, mono-C_{1-3} alkylamino, and/or di-C_{1-3} alkylamino groups,

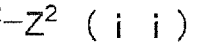
wherein "4- to 6-membered aromatic heterocycle" refers to an aromatic monovalent or divalent heterocycle containing 1 to 5 heteroatoms in the ring-forming atoms, and heteroatom is a nitrogen atom (N), an oxygen atom (O) or a sulfur atom (S),

wherein "4- to 6-membered heterocycle" refers to a non-aromatic monovalent or divalent heterocycle containing 1 to 5 heteroatoms in the ring-forming atoms, and heteroatom is a nitrogen atom (N), an oxygen atom (O) or a sulfur atom (S).

8. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7, wherein

B^4 represents CR^7, and

R^7 represents a chlorine atom, bromine atom, hydrogen atom, cyano group, C_{1-3} alkyl group, C_{1-3} alkoxy group, C_{2-3} alkenyl group, C_{3-6} cycloalkyl group (wherein the C_{1-3} alkyl group, C_{1-3} alkoxy group, C_{2-3} alkenyl group, or C_{3-6} cycloalkyl group may be substituted with 1 to 3 halogen atoms), or group represented by formula (ii) below,:



(ii)

wherein X^2 represents $-(CH_2)_p-$, p represents 0 or 1;

Y^2 represents piperazine, pyrrolidine, piperidine, morpholine, or 3,3-dimethylpiperazine;

Z^2 represents a hydrogen atom, a C_{1-3} alkyl group, -NRfRg, pyrrolidine, morpholine, or tetrahydropyran, wherein the C_{1-3} alkyl group may be substituted with 1 to 3 halogen atoms; and

Rf and Rg are identical or different, each representing a hydrogen atom, C_{1-3} alkyl group, $-COCH_3$, or $-SO_2CH_3$.

9. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 8, wherein R^8 represents a hydrogen atom.

10. A pharmaceuticals comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 as an active ingredient.

11. The pharmaceuticals according to claim 10, wherein the pharmaceuticals is to be used for treatment of cancer and/or cancer invasion/metastasis.

12. The pharmaceuticals according to claim 10, wherein the pharmaceuticals is to be used for treatment of fibrosis and/or inflammation.

~~13. A method for treating cancer, and/or cancer invasion/metastasis, comprising administering a pharmaceutically effective amount of a composition comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 to a patient in need thereof.~~

~~14. A method for treating fibrosis and/or inflammation, comprising administering a pharmaceutically effective amount of a composition comprising the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 to a patient in need thereof.~~

~~15~~13. Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for the manufacture of an agent for treating cancer, and/or cancer invasion/metastasis.

~~16~~14. Use of the compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for the manufacture of an agent for treating fibrosis and/or inflammation.

~~17~~15. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for use in treating cancer, and/or cancer invasion/metastasis.

~~18~~16. The compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9 for use in treating fibrosis and/or inflammation.