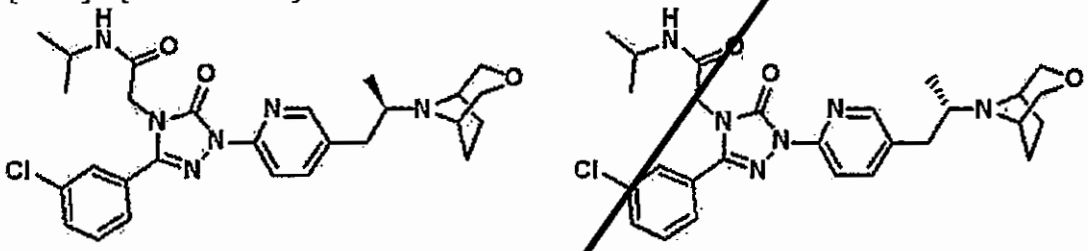
m), 3.34-3.41 (2H, m), 3.45-3.55 (2H, m), 3.71-3.82 (3H, m), 3.97-4.04 (2H, m), 4.39 (2H, s), 7.42 (2H, d, J = 8.6 Hz), 7.57-7.62 (1H, m), 7.64-7.70 (2H, m), 7.72-7.75 (1H, m), 7.96 (2H, d, J = 8.2 Hz), 8.22-8.28 (1H, m), 10.52-10.64 (1H, m).

Synthesis of Example Ad-19-1: (-)-2-[3-(3-Chlorophenyl)-1-{5-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)ethyl]pyridin-2-yl}-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N-(propan-2-yl)acetamide and Example Ad-19-2: (+)-2-[3-(3-chlorophenyl)-1-{5-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl)ethyl]pyridin-2-yl}-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N-(propan-2-yl)acetamide

[0452] [Formula 177]



[0453] Racemic resolution of the compound (50 mg) prepared in Example Ad-16 was performed.

Fractionation conditions

Solvent: n-hexane/EtOH = 100/0 to 85/15 (v/v)

Column: CHIRALPAK AD

Flow rate: 5 mL/min

The compound (5 × 10 mg/EtOH 1 mL) prepared in Example Ad-16 was applied to the column. Each fraction was collected by a fraction collector (time mode) to yield the title compound: Ad-19-1 (peak at a shorter retention time, 11 mg, colorless amorphous compound) and the title compound: Ad-19-2 (peak at a longer retention time, 10 mg, light yellow oily compound).

Example Ad-19-1: $[\alpha]_D^{27}$ = -2.26° (c = 0.2, MeOH)

Retention Time: 13.486 min

MS (ESI pos.) m/z: 525 ($[M+H]^+$).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm); 0.92 (3H, d, J = 6.2 Hz), 1.19 (6H, d, J =

R^4 and R^5 optionally, together with the adjoining nitrogen atom, form a 4- to 8-membered saturated or unsaturated heterocycle optionally containing one or more nitrogen, oxygen, or sulfur atoms, in addition to the adjoining nitrogen atom, in the ring (the 4- to 8-membered saturated or unsaturated heterocycle is optionally substituted by one or two groups selected from the group consisting of hydroxy, C_{1-5} alkyl (the C_{1-5} alkyl is optionally substituted by one or two hydroxy), C_{1-5} alkoxy, halogen atoms, cyano, C_{2-5} alkanoyl, oxo, aminocarbonyl, mono-C_{1-5} alkylaminocarbonyl, di-C_{1-5} alkylaminocarbonyl, trifluoromethyl, and amino (the amino is optionally substituted by one or two groups selected from the group consisting of C_{1-5} alkyl and C_{2-5} alkanoyl), and the 4- to 8-membered saturated or unsaturated heterocycle optionally has a C_{1-5} alkylene group crosslinking two different carbon atoms in the ring) or form 2-oxa-6-azaspiro[3.3]hept-6-yl or 7-oxa-2-azaspiro[3.5]non-2-yl;

A represents phenylene or 6-membered heteroarylene (the phenylene and 6-membered heteroarylene are optionally substituted by one or two groups selected from halogen atoms and C_{1-5} alkoxy);

X represents a single bond, -O-, or -NR^6-;

R^6 represents a hydrogen atom, C_{1-5} alkyl, or C_{2-5} alkanoyl;

R^a represents a hydrogen atom or C_{1-5} alkyl; and

n is an integer of 0 to 3],

or a pharmaceutically acceptable salt of the 1,2,4-triazolone derivative.

2. A 1,2,4-triazolone derivative represented by Formula (1A):

saturated or unsaturated heterocycle is optionally substituted by one or two groups selected from the group consisting of hydroxy, C_{1-5} alkyl (the C_{1-5} alkyl is optionally substituted by one or two hydroxy), C_{1-5} alkoxy, halogen atoms, cyano, C_{2-5} alkanoyl, oxo, aminocarbonyl, mono-C_{1-5} alkylaminocarbonyl, di-C_{1-5} alkylaminocarbonyl, and trifluoromethyl, and the 4- to 8-membered saturated or unsaturated heterocycle optionally has a C_{1-5} alkylene group crosslinking two different carbon atoms in the ring) or form 2-oxa-6-azaspiro[3.3]hept-6-yl;

A represents phenylene or 6-membered heteroarylene (the phenylene and 6-membered heteroarylene are optionally substituted by one or two groups selected from halogen atoms and C_{1-5} alkoxy);

X represents a single bond, -O-, or -NR^6-;

R^6 represents a hydrogen atom, C_{1-5} alkyl, or C_{2-5} alkanoyl;

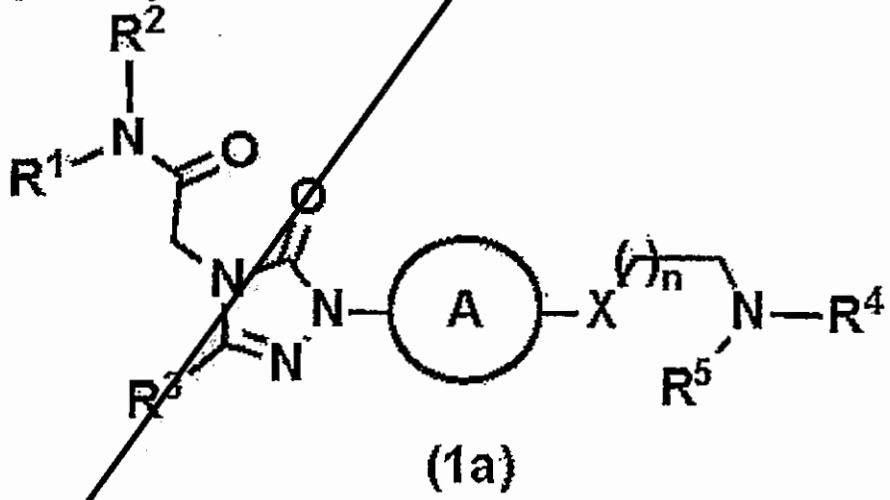
R^a represents a hydrogen atom or C_{1-5} alkyl; and

n is an integer of 1 to 3],

or a pharmaceutically acceptable salt of the 1,2,4-triazolone derivative.

3. A 1,2,4-triazolone derivative represented by Formula (1a):

[Formula 3]



(1a)

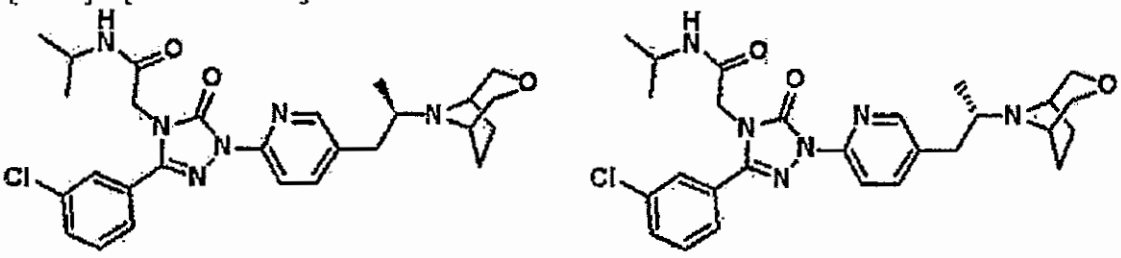
[in Formula (1a),

R^1 represents a C_{1-5} alkyl (the C_{1-5} alkyl is optionally substituted by one to three groups selected from the group consisting of hydroxy, halogen atoms, cyano, C_{3-7} cycloalkyl, and C_{1-}

m), 3.34-3.41 (2H, m), 3.45-3.55 (2H, m), 3.71-3.82 (3H, m), 3.97-4.04 (2H, m), 4.39 (2H, s), 7.42 (2H, d, J = 8.6 Hz), 7.57-7.62 (1H, m), 7.64-7.70 (2H, m), 7.72-7.75 (1H, m), 7.96 (2H, d, J = 8.2 Hz), 8.22-8.28 (1H, m), 10.52-10.64 (1H, m).

Synthesis of Example Ad-19-1: (-)-2-[3-(3-Chlorophenyl)-1-{5-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl) propyl]pyridin-2-yl}-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N-(propan-2-yl)acetamide and Example Ad-19-2: (+)-2-[3-(3-chlorophenyl)-1-{5-[2-(3-oxa-8-azabicyclo[3.2.1]oct-8-yl) propyl]pyridin-2-yl}-5-oxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-N-(propan-2-yl)acetamide

[0452] [Formula 177]



[0453] Racemic resolution of the compound (50 mg) prepared in Example Ad-16 was performed.

Fractionation conditions

Solvent: n-hexane/EtOH = 100/0 to 85/15 (v/v)

Column: CHIRALPAK AD

Flow rate: 5 mL/min

The compound (5 × 10 mg/EtOH 1 mL) prepared in Example Ad-16 was applied to the column. Each fraction was collected by a fraction collector (time mode) to yield the title compound: Ad-19-1 (peak at a shorter retention time, 11 mg, colorless amorphous compound) and the title compound: Ad-19-2 (peak at a longer retention time, 10 mg, light yellow oily compound).

Example Ad-19-1: $[\alpha]_D^{27}$ = -2.26° (c = 0.2, MeOH)

Retention Time: 13.486 min

MS (ESI pos.) m/z: 525 ($[M+H]^+$).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm); 0.92 (3H, d, J = 6.2 Hz), 1.19 (6H, d, J =

R^4 and R^5 optionally, together with the adjoining nitrogen atom, form a 4- to 8-membered saturated or unsaturated heterocycle optionally containing one or more nitrogen, oxygen, or sulfur atoms, in addition to the adjoining nitrogen atom, in the ring (the 4- to 8-membered saturated or unsaturated heterocycle is optionally substituted by one or two groups selected from the group consisting of hydroxy, C_{1-5} alkyl (the C_{1-5} alkyl is optionally substituted by one or two hydroxy), C_{1-5} alkoxy, halogen atoms, cyano, C_{2-5} alkanoyl, oxo, aminocarbonyl, mono-C_{1-5} alkylaminocarbonyl, di-C_{1-5} alkylaminocarbonyl, trifluoromethyl, and amino (the amino is optionally substituted by one or two groups selected from the group consisting of C_{1-5} alkyl and C_{2-5} alkanoyl), and the 4- to 8-membered saturated or unsaturated heterocycle optionally has a C_{1-5} alkylene group crosslinking two different carbon atoms in the ring) or form 2-oxa-6-azaspiro[3.3]hept-6-yl or 7-oxa-2-azaspiro[3.5]non-2-yl;

A represents phenylene or 6-membered heteroarylene (the phenylene and 6-membered heteroarylene are optionally substituted by one or two groups selected from halogen atoms and C_{1-5} alkoxy);

X represents a single bond, -O-, or -NR^6-;

R^6 represents a hydrogen atom, C_{1-5} alkyl, or C_{2-5} alkanoyl;

R^a represents a hydrogen atom or C_{1-5} alkyl; and

n is an integer of 0 to 3],

or a pharmaceutically acceptable salt of the 1,2,4-triazolone derivative.

2. The 1,2,4-triazolone derivative according to claim 1, which is represented by Formula (1A):

saturated or unsaturated heterocycle is optionally substituted by one or two groups selected from the group consisting of hydroxy, C_{1-5} alkyl (the C_{1-5} alkyl is optionally substituted by one or two hydroxy), C_{1-5} alkoxy, halogen atoms, cyano, C_{2-5} alkanoyl, oxo, aminocarbonyl, mono-C_{1-5} alkylaminocarbonyl, di-C_{1-5} alkylaminocarbonyl, and trifluoromethyl, and the 4- to 8-membered saturated or unsaturated heterocycle optionally has a C_{1-5} alkylene group crosslinking two different carbon atoms in the ring) or form 2-oxa-6-azaspiro[3.3]hept-6-yl;

A represents phenylene or 6-membered heteroarylene (the phenylene and 6-membered heteroarylene are optionally substituted by one or two groups selected from halogen atoms and C_{1-5} alkoxy);

X represents a single bond, -O-, or -NR^6-;

R^6 represents a hydrogen atom, C_{1-5} alkyl, or C_{2-5} alkanoyl;

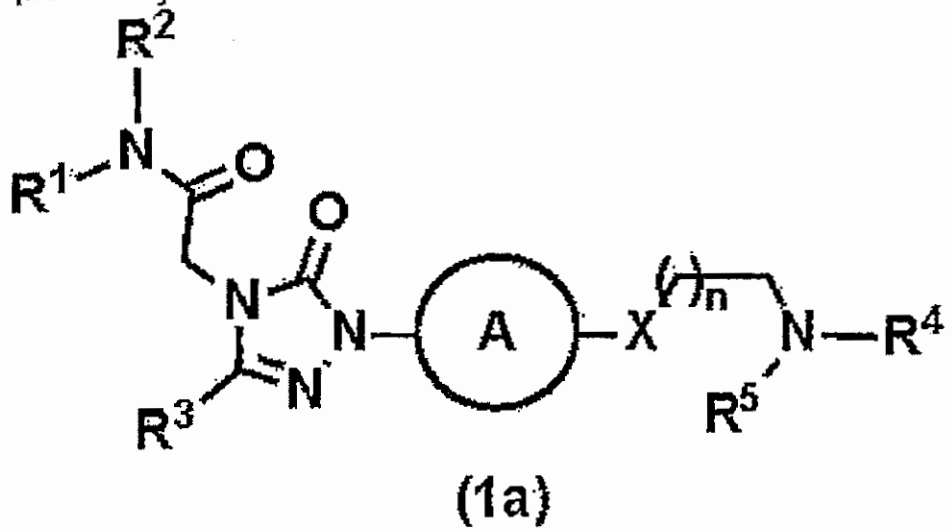
R^a represents a hydrogen atom or C_{1-5} alkyl; and

n is an integer of 1 to 3],

or a pharmaceutically acceptable salt of the 1,2,4-triazolone derivative.

3. The 1,2,4-triazolone derivative according to claim 1, which is represented by Formula (1a):

[Formula 3]



(1a)

[in Formula (1a),

R^1 represents a C_{1-5} alkyl (the C_{1-5} alkyl is optionally substituted by one to three groups selected from the group consisting of hydroxy, halogen atoms, cyano, C_{3-7} cycloalkyl, and C_1.