protected with appropriate protective groups. Examples of such functional groups can include a hydroxy group, a carboxy group, and an amino group. For the types of their protective groups as well as conditions for the introduction and removal of these protective groups, see those described in, for example, Protective Groups in Organic Synthesis (T.W. Greene and P.G.M. Wuts, John Wiley & Sons, Inc., New York, 2006).

Production method

~~Next, typical methods for producing the compound represented by the general formula (I) will be described. The compound of the present invention can be produced by various production methods. The production methods shown below are given for illustrative purposes. It should be understood that the present invention is not limited by these examples.~~ Each reaction can be carried out with a substituent protected with an appropriate protective group, if necessary. The type of the protective group is not particularly limited.

General formula (I)

[0086]

hexane/ethyl acetate = 100/0 to 75/25) to obtain the title compound (1.73 g, yield: 67.9%) as a solid.

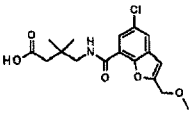
[0222]

^{1}H-NMR ($CDCl_3$) δ: 7.90 (1H, d, J = 2.0 Hz), 7.71 (1H, d, J = 2.0 Hz), 6.71 (1H, s), 4.62 (2H, s), 4.00 (3H, s), 3.48 (3H, s).

The following intermediate 3g was subsequently synthesized through the same reaction as in step 5 and the subsequent steps of intermediate 3a and is shown in Table 7.

[0223]

[Table 7]

Intermediate 3 g		^{1}H-NMR ($CDCl_3$) δ: 8.07 (1H, d, J = 2.0 Hz), 7.91 (1H, br s), 7.66 (1H, d, J = 2.0 Hz), 6.78 (1H, s), 4.72 (2H, s), 3.62 (2H, d, J = 6.8 Hz), 3.47 (3H, s), 2.32 (2H, s), 1.15 (6H, s).

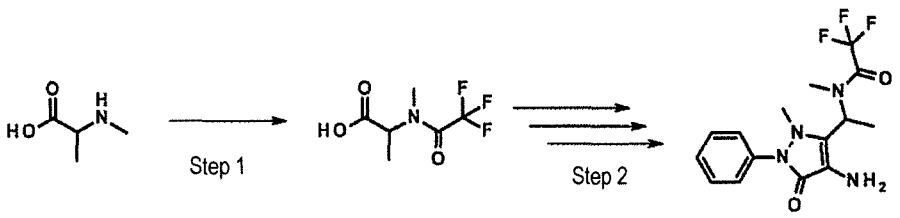
[0224]

(Example 1) 5-Chloro-N-[2,2-dimethyl-4-({1-methyl-5-[1-(methylamino)ethyl]-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxybenzamide;

(Example 2)

[0225]

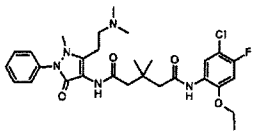
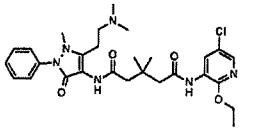
[Formula 44]



[0226]

(Step 1) N-Methyl-N-trifluoroacetylalanine

[Table 10-3]

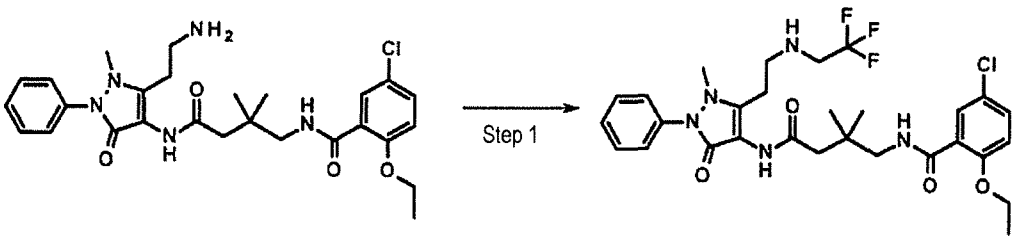
24		2c	^{1}H-NMR ($CDCl_3$) δ: 8.51 (2H, d, J = 3.1 Hz), 8.36 (1H, d, J = 7.9 Hz), 7.46-7.38 (4H, m), 7.30-7.27 (1H, m), 6.65 (1H, d, J = 10.4 Hz), 4.02 (2H, q, J = 7.0 Hz), 3.11 (3H, s), 2.85 (2H, t, J = 7.6 Hz), 2.67-2.63 (4H, m), 2.48 (2H, s), 2.31 (6H, s), 1.40 (3H, t, J = 7.0 Hz), 1.17 (6H, s). MS (APCI) m/z : 574 [(M+H)$^+$].
25		2a	^{1}H-NMR ($CDCl_3$) δ: 8.76 (1H, s), 8.62 (1H, s), 8.34 (1H, s), 7.77 (1H, t, J = 2.1 Hz), 7.47-7.26 (5H, m), 4.37 (2H, q, J = 7.0 Hz), 3.11 (3H, s), 2.86 (2H, t, J = 7.3 Hz), 2.68-2.63 (4H, m), 2.47 (2H, s), 2.31 (6H, s), 1.35 (3H, t, J = 7.0 Hz), 1.17 (6H, s). MS (APCI) m/z : 557 [(M+H)$^+$].

[0243]

(Example 26) 5-Chloro-N-[2,2-dimethyl-4-({1-methyl-3-oxo-2-phenyl-5-[2-(2,2,2-trifluoroethylamino)ethyl]-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxybenzamide

[0244]

[Formula 50]

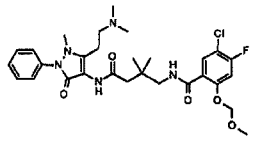
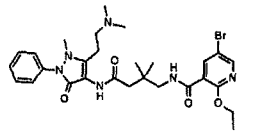
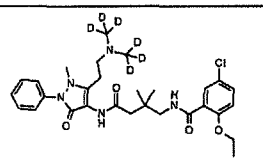
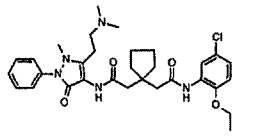


[0245]

(Step 1) 5-Chloro-N-[2,2-dimethyl-4-({1-methyl-3-oxo-2-phenyl-5-[2-(2,2,2-trifluoroethylamino)ethyl]-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxybenzamide

To a solution of N-(4-{[5-(2-aminoethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl]amino}-2,2-

[Table 12]

Example No.	Structure	Intermediate used	Instrumental analysis data
29		1f	^{1}H-NMR ($CDCl_3$) δ: 8.54 (1H, s), 8.31-8.26 (2H, m), 7.47-7.40 (4H, m), 7.31-7.27 (1H, m), 7.07 (1H, d, J = 10.4 Hz), 5.33 (2H, s), 3.56-3.51 (5H, m), 3.11 (3H, s), 2.86-2.82 (2H, m), 2.68-2.64 (2H, m), 2.31 (6H, s), 2.27 (2H, s), 1.12 (6H, s). MS (APCI) m/z : 590 [(M+H)$^+$].
30		1j	^{1}H-NMR ($CDCl_3$) δ: 8.83 (1H, s), 8.63 (1H, d, J = 2.4 Hz), 8.40 (1H, br t, J = 6.4 Hz), 8.28 (1H, d, J = 2.4 Hz), 7.48-7.40 (4H, m), 7.31-7.24 (1H, m), 4.54 (2H, q, J = 6.9 Hz), 3.59 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 2.89-2.81 (2H, m), 2.71-2.64 (2H, m), 2.32 (6H, s), 2.26 (2H, s), 1.48 (3H, t, J = 7.0 Hz), 1.13 (6H, s). MS (ESI) m/z : 601 [(M+H)$^+$].
31		1a	^{1}H-NMR ($CDCl_3$) δ: 9.13 (1H, s), 8.38 (1H, br t, J = 6.4 Hz), 8.21 (1H, d, J = 2.4 Hz), 7.46-7.41 (4H, m), 7.38 (1H, dd, J = 8.8, 2.7 Hz), 7.29-7.22 (1H, m), 6.91 (1H, d, J = 9.1 Hz), 4.20 (2H, q, J = 6.9 Hz), 3.59 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 2.87-2.80 (2H, m), 2.72-2.65 (2H, m), 2.27 (2H, s), 1.52 (3H, t, J = 7.0 Hz), 1.13 (6H, s). MS (ESI) m/z: 562 [(M+H)$^+$].
32		2h	^{1}H-NMR ($CDCl_3$) δ: 8.54 (1H, s), 8.53 (1H, s), 8.33 (1H, d, J = 2.4 Hz), 7.45-7.39 (4H, m), 7.29-7.27 (1H, m), 6.98 (1H, dd, J = 8.8, 2.4 Hz), 6.74 (1H, d, J = 8.8 Hz), 4.04 (2H, q, J = 7.0 Hz), 3.10 (3H, s), 2.86-2.83 (2H, m), 2.75 (2H, s), 2.66-2.64 (2H, m), 2.53 (2H, s), 2.31 (6H, s), 1.71-1.66 (8H, m), 1.39 (3H, t, J = 7.0 Hz). MS (ESI) m/z: 582 [(M+H)$^+$].

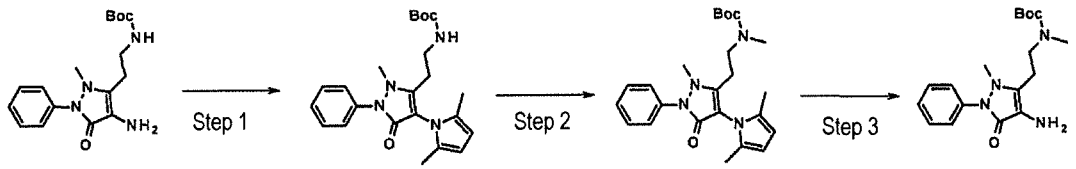
[0251]

(Example 33) 5-Chloro-N-[2,2-dimethyl-4-({1-methyl-5-[2-(methylamino)ethyl]-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxybenzamide;

(Examples 34 and 35)

[0252]

[Formula 51]



[0253]

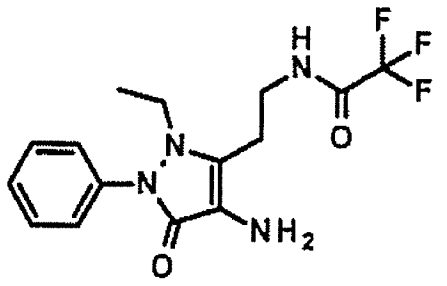
[0261]

(Example 40) 5-Chloro-N-[4-({5-[2-(dimethylamino)ethyl]-1-ethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Examples 41 and 42)

[0262]

[Formula 58]



[0263]

(Step 1) N-[2-(4-Amino-2-ethyl-5-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)ethyl]-2,2,2-trifluoroacetamide

The title compound was obtained as a solid by using ethyl iodide instead of methyl iodide in step 3 of Example 28 and subsequently performing the same reaction as in Example 28 up to step 5.

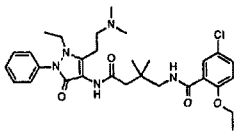
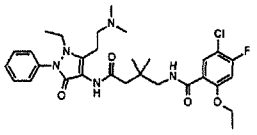
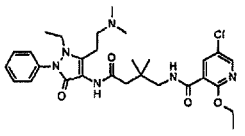
[0264]

^{1}H-NMR ($CDCl_3$) δ: 8.26 (1H, s), 7.48-7.41 (4H, m), 7.31-7.28 (1H, m), 3.63-3.62 (2H, m), 3.44 (2H, q, J = 7.0 Hz), 3.05 (2H, br s), 2.79 (2H, t, J = 6.7 Hz), 0.71 (3H, t, J = 7.0 Hz).

The following compounds of Examples 40 to 42 were subsequently synthesized in the same way as in steps 6 to 8 of Example 28 and are shown in Table 16.

[0265]

[Table 16]

Example No.	Structure	Intermediate used	Instrumental analysis data
40		Ia	^{1}H-NMR ($CDCl_3$) δ: 8.99 (1H, s), 8.37 (1H, t, J = 6.7 Hz), 8.22 (1H, d, J = 2.4 Hz), 7.46-7.36 (5H, m), 7.28-7.24 (1H, m), 6.91 (1H, d, J = 8.5 Hz), 4.20 (2H, q, J = 7.0 Hz), 3.64-3.58 (4H, m), 2.83-2.69 (4H, m), 2.33 (6H, s), 2.27 (2H, s), 1.52 (3H, t, J = 7.0 Hz), 1.12 (6H, s), 0.89 (3H, t, J = 7.0 Hz). MS (APCI) m/z :570 [(M+H)$^+$].
41		Ic	^{1}H-NMR ($CDCl_3$) δ: 8.80 (1H, s), 8.31 (1H, d, J = 9.2 Hz), 8.23 (1H, t, J = 6.4 Hz), 7.48-7.41 (4H, m), 7.31-7.22 (1H, m), 6.78 (1H, d, J = 10.4 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.64-3.56 (4H, m), 2.83-2.79 (2H, m), 2.71-2.68 (2H, m), 2.32 (6H, s), 2.26 (2H, s), 1.53 (3H, t, J = 7.0 Hz), 1.12 (6H, s), 0.88 (3H, t, J = 7.0 Hz). MS (APCI) m/z :588 [(M+H)$^+$].
42		Ih	^{1}H-NMR ($CDCl_3$) δ: 8.64 (1H, s), 8.51 (1H, d, J = 2.4 Hz), 8.41 (1H, t, J = 6.7 Hz), 8.19 (1H, d, J = 2.4 Hz), 7.45-7.40 (4H, m), 7.30-7.23 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.64-3.57 (4H, m), 2.83-2.79 (2H, m), 2.71-2.67 (2H, m), 2.32 (6H, s), 2.27 (2H, s), 1.47 (3H, t, J = 7.0 Hz), 1.12 (6H, s), 0.88 (3H, t, J = 7.0 Hz). MS (APCI) m/z :571 [(M+H)$^+$].

[0266]

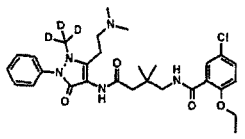
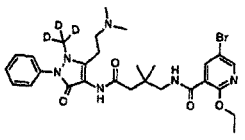
(Example 43) 5-Chloro-N-[4-({3-[2-(dimethylamino)ethyl]-5-oxo-1-phenyl-2-(trideuteriomethyl)pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Example 44)

[0267]

[Formula 59]

[Table 17]

Example No.	Structure	Intermediate used	Instrumental analysis data
43		1a	^{1}H-NMR ($CDCl_3$) δ: 9.12 (1H, s), 8.38 (1H, br t, J = 6.4 Hz), 8.21 (1H, d, J = 1.8 Hz), 7.48-7.35 (5H, m), 7.29-7.22 (1H, m), 6.91 (1H, d, J = 8.5 Hz), 4.20 (2H, q, J = 6.9 Hz), 3.59 (2H, d, J = 6.7 Hz), 2.88-2.80 (2H, m), 2.72-2.65 (2H, m), 2.33 (6H, s), 2.27 (2H, s), 1.52 (3H, t, J = 6.7 Hz), 1.13 (6H, s). MS (ESI) m/z: 559 [(M+H)$^+$].
44		1j	^{1}H-NMR ($CDCl_3$) δ: 8.81 (1H, s), 8.63 (1H, d, *J* = 3.1 Hz), 8.39 (1H, br t, *J* = 6.4 Hz), 8.28 (1H, d, *J* = 2.4 Hz), 7.48-7.40 (4H, m), 7.30-7.24 (1H, m), 4.54 (2H, q, *J* = 7.1 Hz), 3.59 (2H, d, *J* = 6.7 Hz), 2.88-2.81 (2H, m), 2.71-2.63 (2H, m), 2.32 (6H, s), 2.26 (2H, s), 1.48 (3H, t, *J* = 7.0 Hz), 1.13 (6H, s). MS (ESI) m/z: 604 [(M+H)$^+$].

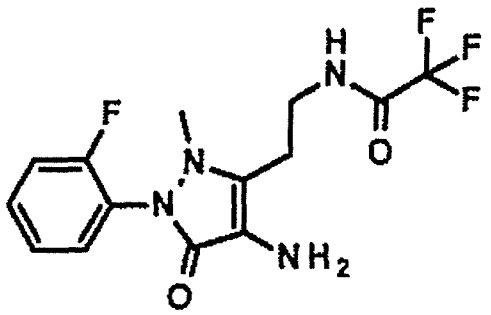
[0270]

(Example 45) 5-Chloro-N-[4-({3-[2-(dimethylamino)ethyl]-1-(2-fluorophenyl)-2-methyl-5-oxopyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Example 46)

[0271]

[Formula 60]



[0272]

(Step 1) N-{2-[4-Amino-1-(2-fluorophenyl)-2-methyl-5-oxopyrazol-3-yl]ethyl}-2,2,2-trifluoroacetamide

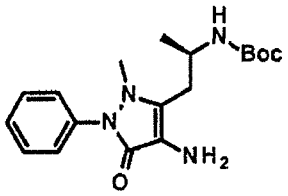
[0278]

(Example 48) 5-Chloro-N-[4-({5-[(2R)-2-(dimethylamino)propyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Examples 49 and 50)

[0279]

[Formula 63]



[0280]

(Step 1) tert-Butyl-N-[(1R)-2-(4-amino-2-methyl-5-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)-1-methylethyl]carbamate

The title compound was obtained as a solid by using (3R)-3-(tert-butoxycarbonylamino)butanoic acid instead of 3-(tert-butoxycarbonylamino)propionic acid in step 1 of Example 10 and subsequently performing the same reaction as in Example 10 up to step 6.

^{1}H-NMR ($CDCl_3$) δ: 7.49-7.42 (4H, m), 7.27-7.23 (1H, m), 4.74 (1H, s), 4.00-3.93 (1H, m), 3.11 (2H, s), 2.89-2.82 (4H, m), 2.63 (1H, dd, J = 14.6, 7.3 Hz), 1.45 (9H, s), 1.23 (3H, d, J = 6.7 Hz).

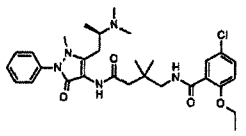
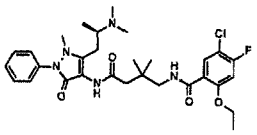
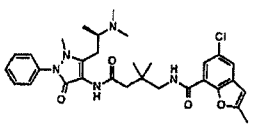
MS (APCI) m/z :347[$(M+H)^+$].

The following compounds of Examples 48 to 50 were subsequently synthesized in the same way as in step 7 of

Example 10 and steps 1 and 2 of Example 11 and are shown in Table 20.

[0281]

[Table 20]

Example No.	Structure	Intermediate used	Instrumental analysis data
48		1a	^{1}H-NMR ($CDCl_3$) δ: 8.98 (1H, s), 8.37 (1H, t, *J* = 6.4 Hz), 8.19 (1H, d, *J* = 3.1 Hz), 7.46-7.36 (5H, m), 7.28-7.23 (1H, m), 6.91 (1H, d, *J* = 9.2 Hz), 4.20 (2H, q, *J* = 7.0 Hz), 3.62-3.52 (2H, m), 3.10 (3H, s), 3.06-2.97 (1H, m), 2.90 (1H, dd, *J* = 14.0, 4.9 Hz), 2.66 (1H, dd, *J* = 14.6, 9.2 Hz), 2.33 (6H, s), 2.27 (2H, s), 1.52 (3H, t, *J* = 7.0 Hz), 1.15-1.10 (9H, m). MS (APCI) m/z :570 [(M+H)$^+$]. $[\alpha]_D^{20}$ -1.76 (c = 1.08, MeOH).
49		1c	^{1}H-NMR ($CDCl_3$) δ: 8.84 (1H, s), 8.28 (1H, d, J = 9.2 Hz), 8.22 (1H, t, J = 6.7 Hz), 7.46-7.41 (4H, m), 7.29-7.24 (1H, m), 6.78 (1H, d, J = 10.4 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.56 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 3.05-3.00 (1H, m), 2.92 (1H, dd, J = 14.6, 4.6 Hz), 2.68 (1H, dd, J = 14.6, 9.2 Hz), 2.34 (6H, s), 2.27 (2H, s), 1.54 (3H, t, J = 7.0 Hz), 1.14-1.10 (9H, m). MS (APCI) m/z :588 [(M+H)$^+$]. $[\alpha]_D^{20}$ -1.33 (c = 1.05, MeOH).
50		3a	^{1}H-NMR ($CDCl_3$) δ: 8.51 (1H, s), 7.96-7.92 (2H, m), 7.56 (1H, d, J = 1.8 Hz), 7.47-7.40 (4H, m), 7.29-7.25 (1H, m), 6.43 (1H, d, J = 1.2 Hz), 3.65 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 3.03-2.97 (1H, m), 2.91 (1H, dd, J = 14.6, 4.9 Hz), 2.67 (1H, dd, J = 14.6, 9.2 Hz), 2.51 (3H, d, J = 1.2 Hz), 2.33-2.32 (8H, m), 1.18 (3H, s), 1.18 (3H, s), 1.09 (3H, d, J = 6.1 Hz). MS (APCI) m/z :588 [(M+H)$^+$]. $[\alpha]_D^{20}$ -2.05 (c = 1.02, MeOH).

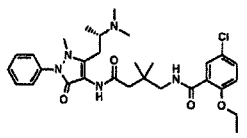
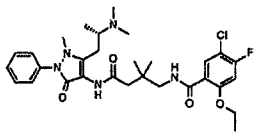
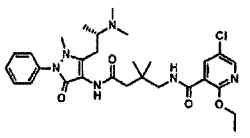
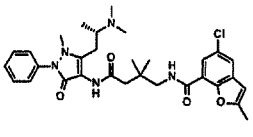
[0282]

(Example 51) 5-Chloro-N-[4-({5-[(2*S*)-2-(dimethylamino)propyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Examples 52, 53 and 54)

[0283]

[Table 21]

Example No.	Structure	Intermediate used	Instrumental analysis data
5 1		1 a	^{1}H-NMR ($CDCl_3$) δ: 8.97 (1H, s), 8.37 (1H, t, J = 6.4 Hz), 8.19 (1H, d, J = 3.1 Hz), 7.46-7.36 (5H, m), 7.29-7.22 (1H, m), 6.91 (1H, d, J = 9.2 Hz), 4.20 (2H, q, J = 7.0 Hz), 3.62-3.52 (2H, m), 3.10 (3H, s), 3.06-2.97 (1H, m), 2.91 (1H, dd, J = 14.6, 4.9 Hz), 2.66 (1H, dd, J = 14.6, 9.5 Hz), 2.33 (6H, s), 2.27 (2H, s), 1.52 (3H, t, J = 7.0 Hz), 1.15 (3H, s), 1.14 (3H, s), 1.11 (3H, d, J = 6.7 Hz). MS (APCI) m/z :570 [(M+H)$^+$]. $[\alpha]_D^{20}$ +1.69 (c = 1.00, MeOH).
5 2		1 c	^{1}H-NMR ($CDCl_3$) δ: 8.83 (1H, s), 8.28 (1H, d, J = 8.5 Hz), 8.22 (1H, t, J = 6.7 Hz), 7.46-7.41 (4H, m), 7.28-7.24 (1H, m), 6.78 (1H, d, J = 10.3 Hz), 4.18 (2H, q, J = 7.0 Hz), 3.56 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 3.05-2.96 (1H, m), 2.90 (1H, dd, J = 14.3, 5.2 Hz), 2.66 (1H, dd, J = 14.0, 9.1 Hz), 2.32 (6H, s), 2.26 (2H, s), 1.54 (3H, t, J = 7.0 Hz), 1.14 (3H, s), 1.13 (3H, s), 1.10 (3H, d, J = 6.7 Hz). MS (APCI) m/z :588 [(M+H)$^+$]. $[\alpha]_D^{20}$ +1.66 (c = 1.02, MeOH).
5 3		1 h	^{1}H-NMR ($CDCl_3$) δ: 8.64 (1H, s), 8.48 (1H, d, J = 3.0 Hz), 8.40 (1H, t, J = 6.7 Hz), 8.19 (1H, d, J = 3.0 Hz), 7.47-7.41 (4H, m), 7.29-7.25 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.57 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 3.04-2.89 (2H, m), 2.67 (1H, dd, J = 14.6, 9.1 Hz), 2.32 (6H, s), 2.27 (2H, s), 1.48 (3H, t, J = 7.0 Hz), 1.14 (6H, s), 1.09 (3H, d, J = 6.7 Hz). MS (APCI) m/z :571 [(M+H)$^+$]. $[\alpha]_D^{20}$ -+2.26 (c = 1.02, MeOH).
5 4		3 a	^{1}H-NMR ($CDCl_3$) δ: 8.50 (1H, s), 7.96-7.93 (2H, m), 7.55 (1H, d, J = 1.8 Hz), 7.47-7.40 (4H, m), 7.29-7.25 (1H, m), 6.43 (1H, s), 3.65 (2H, d, J = 6.7 Hz), 3.10 (3H, s), 3.04-2.96 (1H, m), 2.90 (1H, dd, J = 14.3, 4.9 Hz), 2.67 (1H, dd, J = 14.3, 8.9 Hz), 2.51 (3H, s), 2.33-2.31 (8H, m), 1.18 (3H, s), 1.18 (3H, s), 1.09 (3H, d, J = 6.7 Hz). MS (ESI) m/z :580 [(M+H)$^+$]. $[\alpha]_D^{20}$ +2.27 (c = 1.02, MeOH).

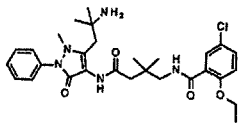
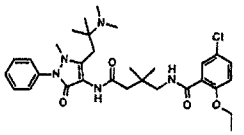
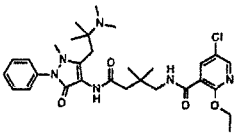
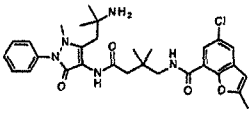
[0286]

(Example 55) N-(4-{[5-(2-Amino-2-methylpropyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl]amino}-2,2-dimethyl-4-oxobutyl)-5-chloro-2-ethoxybenzamide;

(Examples 56, 57 and 58)

[0287]

[Table 22]

Example No.	Structure	Intermediate used	Instrumental analysis data
55		1a	^{1}H-NMR ($CDCl_3$) δ: 9.07 (1H, s), 8.39 (1H, t, J = 6.6 Hz), 8.15 (1H, d, J = 3.1 Hz), 7.47-7.43 (4H, m), 7.39-7.36 (1H, m), 7.29-7.25 (1H, m), 6.91 (1H, d, J = 9.0 Hz), 4.20 (2H, q, J = 7.0 Hz), 3.57 (2H, d, J = 6.6 Hz), 3.12 (3H, s), 2.81 (2H, s), 2.27 (2H, s), 1.53 (3H, t, J = 7.0 Hz), 1.29 (6H, s), 1.16 (6H, s). MS (ESI) m/z : 556 [(M+H)$^+$].
56		1a	^{1}H-NMR ($CDCl_3$) δ: 8.94 (1H, s), 8.36 (1H, t, J = 6.5 Hz), 8.16 (1H, d, J = 3.1 Hz), 7.46-7.41 (4H, m), 7.39-7.35 (1H, m), 7.28-7.24 (1H, m), 6.90 (1H, d, J = 8.6 Hz), 4.20 (2H, q, J = 7.0 Hz), 3.57 (2H, d, J = 6.5 Hz), 3.09 (3H, s), 2.85 (2H, s), 2.36 (6H, s), 2.27 (2H, s), 1.52 (3H, t, J = 7.0 Hz), 1.20 (6H, s), 1.16 (6H, s). MS (ESI) m/z : 584 [(M+H)$^+$].
57		1h	^{1}H-NMR ($CDCl_3$) δ: 8.60 (1H, s), 8.45 (1H, d, J = 2.9 Hz), 8.39 (1H, br s), 8.18 (1H, d, J = 2.9 Hz), 7.46-7.42 (4H, m), 7.28-7.28 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.57 (2H, d, J = 6.8 Hz), 3.09 (3H, s), 2.86 (2H, s), 2.35 (6H, s), 2.27 (2H, s), 1.48 (3H, t, J = 7.0 Hz), 1.18 (6H, s), 1.16 (6H, s). MS (ESI) m/z : 585 [(M+H)$^+$].
58		3a	^{1}H-NMR ($CDCl_3$) δ: 8.57 (1H, s), 7.94-7.94 (2H, m), 7.56 (1H, d, J = 2.0 Hz), 7.48-7.43 (4H, m), 7.29-7.28 (1H, m), 6.43 (1H, d, J = 1.2 Hz), 3.66 (2H, d, J = 7.0 Hz), 3.12 (3H, s), 2.81 (2H, s), 2.53 (3H, d, J = 1.2 Hz), 2.33 (2H, s), 1.28 (6H, s), 1.21 (6H, s). MS (ESI) m/z : 566 [(M+H)$^+$].

[0290]

(Example 59) 5-Chloro-N-[2,2-dimethyl-4-({1-methyl-5-[2-methyl-2-(methylamino)propyl]-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxybenzamide;

(Examples 60 and 61)

[0291]

The reaction solution was concentrated, and the obtained crude amine form was suspended in methylene chloride (5.0 mL). To the suspension, triethylamine (0.342 mL, 0.298 g, 2.95 mmol) and 5-chloro-2-ethoxybenzoyl chloride (0.139 g, 0.640 mmol) were added, and the mixture was stirred for 1 hour. Water was added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with saturated saline and then dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated, and the obtained crude product was purified by silica gel column chromatography (Shoko Scientific Co., Ltd., eluting solvent: methanol/ethyl acetate = 1/99 to 10/90) to obtain the title compound (0.174 g, yield: 60.0%) as a solid.

^{1}H-NMR ($CDCl_3$) δ: 9.04 (1H, s), 8.45-8.40 (1H, m), 8.18 (1H, s), 7.48-7.37 (5H, m), 6.91 (1H, d, J= 9.0 Hz), 4.67-4.57 (2H, m), 4.54-4.46 (2H, m), 4.23-4.16 (2H, m), 3.87-3.83 (2H, m), 3.11 (3H, s), 2.85-2.80 (2H, m), 2.70-2.64 (2H, m), 2.39 (2H, s), 2.33 (6H, s), 1.52 (4H, t, J = 6.8 Hz).

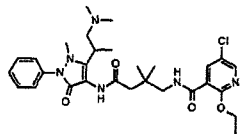
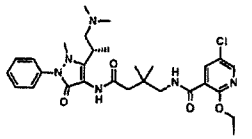
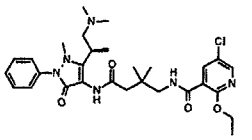
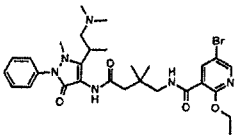
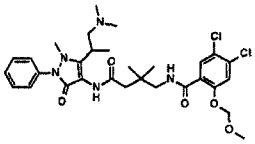
MS (ESI) m/z : 592 [$(M+H)^+$].

(Example 63) 5-Chloro-N-[4-({5-[3-(dimethylamino)propyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Examples 64 and 65)

[0297]

[Table 25-2]

7 1		1 h 6 6 a	^{1}H-NMR ($CDCl_3$) δ: 8.74 (1H, s), 8.46 (1H, d, J = 2.4 Hz), 8.42 (1H, t, J = 6.7 Hz), 8.19 (1H, d, J = 2.4 Hz), 7.46-7.41 (4H, m), 7.29-7.23 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.67-3.55 (2H, m), 3.14 (3H, s), 3.10-3.01 (1H, m), 2.74 (1H, dd, J = 12.2, 7.3 Hz), 2.56 (1H, dd, J = 12.2, 7.9 Hz), 2.29 (6H, s), 2.24 (2H, s), 1.47 (3H, t, J = 7.0 Hz), 1.41 (3H, d, J = 6.7 Hz), 1.17 (3H, s), 1.16 (3H, s). MS (APCI) m/z :571 [(M+H)$^+$].
7 2		1 h 6 6 b	^{1}H-NMR ($CDCl_3$) δ: 8.72 (1H, s), 8.46-8.39 (2H, m), 8.19 (1H, d, J = 2.4 Hz), 7.45-7.41 (4H, m), 7.27-7.22 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.67-3.55 (2H, m), 3.14 (3H, s), 3.09-3.01 (1H, m), 2.73 (1H, dd, J = 12.5, 7.0 Hz), 2.55 (1H, dd, J = 12.5, 7.9 Hz), 2.29 (6H, s), 2.24 (2H, s), 1.47 (3H, t, J = 7.0 Hz), 1.41 (3H, d, J = 6.7 Hz), 1.16 (3H, s), 1.16 (3H, s). MS (APCI) m/z :571 [(M+H)$^+$]. $[\alpha]_D^{20}$ +6.66 (c = 1.01, MeOH).
7 3		1 h 6 6 c	^{1}H-NMR ($CDCl_3$) δ: 8.71 (1H, s), 8.46-8.39 (2H, m), 8.19 (1H, d, J = 2.4 Hz), 7.45-7.41 (4H, m), 7.27-7.23 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.67-3.55 (2H, m), 3.14 (3H, s), 3.10-3.01 (1H, m), 2.73 (1H, dd, J = 12.2, 7.3 Hz), 2.55 (1H, dd, J = 12.2, 7.9 Hz), 2.29 (6H, s), 2.24 (2H, s), 1.47 (3H, t, J = 7.0 Hz), 1.41 (3H, d, J = 7.3 Hz), 1.17 (3H, s), 1.16 (3H, s). MS (APCI) m/z :571 [(M+H)$^+$]. $[\alpha]_D^{20}$ -6.95 (c = 1.01, MeOH).
7 4		1 j 6 6 a	^{1}H-NMR ($CDCl_3$) δ: 8.73 (1H, s), 8.59 (1H, d, J = 2.4 Hz), 8.39 (1H, t, J = 6.4 Hz), 8.28 (1H, d, J = 3.1 Hz), 7.45-7.41 (4H, m), 7.28-7.23 (1H, m), 4.54 (2H, q, J = 7.0 Hz), 3.67-3.54 (2H, m), 3.14 (3H, s), 3.08-3.01 (1H, m), 2.73 (1H, dd, J = 12.2, 7.3 Hz), 2.56 (1H, dd, J = 12.2, 7.9 Hz), 2.29 (6H, s), 2.24 (2H, s), 1.47 (3H, t, J = 7.0 Hz), 1.41 (3H, d, J = 7.3 Hz), 1.16 (3H, s), 1.15 (3H, s). MS (APCI) m/z :615 [(M+H)$^+$].
7 5		1 g 6 6 a	^{1}H-NMR ($CDCl_3$) δ: 8.35-8.34 (1H, br m), 8.24 (1H, s), 7.45-7.39 (4H, m), 7.34 (1H, s), 7.28-7.28 (1H, m), 5.32 (2H, s), 3.60-3.54 (2H, m), 3.50 (3H, s), 3.13 (3H, s), 3.06-3.03 (1H, m), 2.75-2.73 (1H, m), 2.54-2.51 (1H, m), 2.28 (6H, s), 2.25 (2H, d, J = 2.4 Hz), 1.40 (3H, d, J = 6.8 Hz), 1.15 (3H, s), 1.14 (3H, s). MS (ESI+APCI) m/z : 620 [(M+H)$^+$].

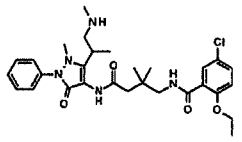
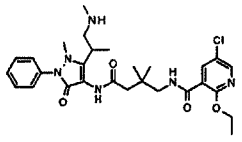
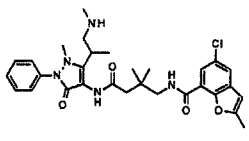
[0309]

(Example 76) 5-Chloro-N-[2,2-dimethyl-4-({1-methyl-5-[1-methyl-2-(methylamino)ethyl]-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxybenzamide;

(Examples 77 and 78)

[0310]

[Table 26]

Example No.	Structure	Intermediate used	Instrumental analysis data
76		1a	^{1}H-NMR ($CDCl_3$) δ: 9.36 (1H, s), 8.40 (1H, t, J = 6.7 Hz), 8.17 (1H, d, J = 3.0 Hz), 7.44-7.38 (5H, m), 7.28-7.22 (1H, m), 6.92 (1H, d, J = 9.1 Hz), 4.20 (2H, q, J = 7.0 Hz), 3.75 (1H, dd, J = 14.6, 7.3 Hz), 3.51 (1H, dd, J = 14.6, 6.7 Hz), 3.15-3.06 (5H, m), 2.82-2.75 (1H, m), 2.46 (3H, s), 2.30-2.19 (2H, m), 1.66 (1H, br s), 1.52 (3H, t, J = 7.0 Hz), 1.42 (3H, d, J = 6.7 Hz), 1.17 (3H, s), 1.15 (3H, s). MS (APCI) m/z :556 [(M+H)$^+$].
77		1h	^{1}H-NMR ($CDCl_3$) δ: 9.00 (1H, s), 8.46-8.40 (2H, m), 8.20 (1H, d, J = 3.0 Hz), 7.46-7.41 (4H, m), 7.29-7.23 (1H, m), 4.55 (2H, q, J = 7.1 Hz), 3.75 (1H, dd, J = 14.3, 7.3 Hz), 3.52 (1H, dd, J = 14.3, 6.7 Hz), 3.15-3.04 (5H, m), 2.78 (1H, dd, J = 11.2, 5.8 Hz), 2.45 (3H, s), 2.24 (2H, q, J = 12.6 Hz), 1.64 (1H, br s), 1.48 (3H, t, J = 7.1 Hz), 1.41 (3H, d, J = 7.3 Hz), 1.17 (3H, s), 1.16 (3H, s). MS (APCI) m/z :557 [(M+H)$^+$].
78		3a	^{1}H-NMR ($CDCl_3$) δ: 8.87 (1H, s), 7.94 (1H, d, J = 2.4 Hz), 7.87 (1H, t, J = 6.7 Hz), 7.57 (1H, d, J = 2.4 Hz), 7.46-7.41 (4H, m), 7.29-7.22 (1H, m), 6.44 (1H, d, J = 1.2 Hz), 3.82 (1H, dd, J = 14.3, 7.0 Hz), 3.61 (1H, dd, J = 14.3, 6.4 Hz), 3.15-3.05 (5H, m), 2.79 (1H, dd, J = 11.0, 5.5 Hz), 2.52 (3H, d, J = 1.2 Hz), 2.45 (3H, s), 2.30 (2H, q, J = 12.8 Hz), 1.42 (3H, d, J = 6.7 Hz), 1.22 (3H, s), 1.20 (3H, s). MS (APCI) m/z :566 [(M+H)$^+$].

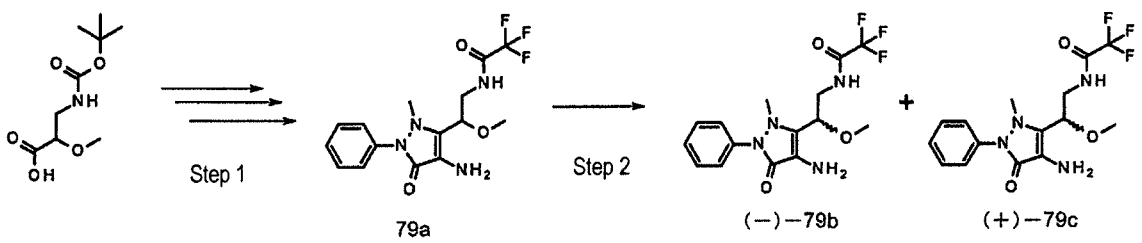
[0313]

(Example 79) 5-Chloro-N-[4-({5-[2-(dimethylamino)-1-methoxyethyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Examples 80, 81, 82 and 83)

[0314]

[Formula 72]



performing the same reaction as in Example 28 from step 1 up to step 5.

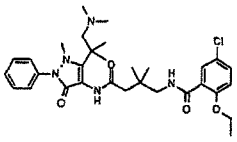
^{1}H-NMR ($CDCl_3$) δ: 8.14 (1H, s), 7.51-7.44 (4H, m), 7.30-7.26 (1H, m), 3.68 (2H, d, J = 6.7 Hz), 3.24 (2H, s), 2.95 (3H, s), 1.43 (6H, s).

MS (APCI) m/z :357 [$(M+H)^+$].

The following compound of Example 84 was subsequently synthesized in the same way as in steps 7 to 9 of Example 66 and is shown in Table 28.

[0321]

[Table 28]

Example No.	Structure	Intermediate used	Instrumental analysis data
84		1a	^{1}H-NMR ($CDCl_3$) δ: 9.19 (1H, s), 8.38 (1H, t, J = 6.7 Hz), 8.16 (1H, d, J = 2.4 Hz), 7.50-7.36 (5H, m), 7.24-7.21 (1H, m), 6.91 (1H, d, J = 8.5 Hz), 4.19 (2H, q, J = 6.9 Hz), 3.63 (2H, d, J = 6.7 Hz), 3.23 (3H, s), 2.67 (2H, s), 2.35 (6H, s), 2.23 (2H, s), 1.54-1.50 (9H, m), 1.18 (6H, s). MS (APCI) m/z :584 [$(M+H)^+$]

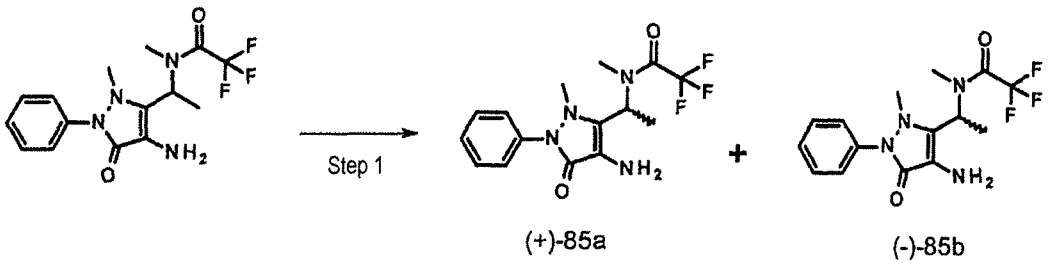
[0322]

(Example 85) (+)-/(-)-5-Chloro-N-[2,2-dimethyl-4-({1-methyl-5-[1-(methylamino)ethyl]-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-4-oxobutyl]-2-ethoxypyridine-3-carboxamide;

(Example 86)

[0323]

[Formula 74]

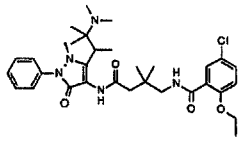


^{1}H-NMR ($CDCl_3$) δ: 9.01 (1H, s), 7.49-7.40 (4H, m), 7.32-7.27 (1H, m), 2.99-2.83 (6H, m), 1.64 (3H, s), 1.53-1.50 (6H, m). MS (APCI) m/z :371 [$(M+H)^+$].

The following compound of Example 87 was subsequently synthesized in the same way as in steps 7 to 9 of Example 66 and is shown in Table 30.

[0329]

[Table 30]

Example No.	Structure	Intermediate used	Instrumental analysis data
87		1a	^{1}H-NMR ($CDCl_3$) δ: 9.12 (1H, s), 8.38 (1H, t, J = 6.4 Hz), 8.13 (1H, d, J = 3.0 Hz), 7.45-7.36 (5H, m), 7.26-7.22 (1H, m), 6.90 (1H, d, J = 9.1 Hz), 4.19 (2H, q, J = 7.0 Hz), 3.72 (1H, dd, J = 14.3, 7.3 Hz), 3.46 (1H, dd, J = 14.3, 7.0 Hz), 3.18-3.08 (4H, m), 2.31 (6H, s), 2.26-2.18 (2H, m), 1.52 (3H, t, J = 7.0 Hz), 1.43 (3H, d, J = 7.3 Hz), 1.21-1.11 (12H, m). MS (APCI) m/z :598 [$(M+H)^+$].

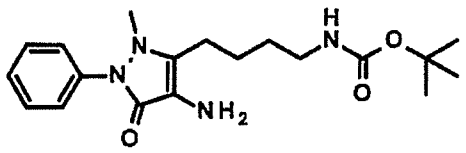
[0330]

(Example 88) 5-Chloro-N-[4-({5-[4-(dimethylamino)butyl]-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl}amino)-2,2-dimethyl-4-oxobutyl]-2-ethoxybenzamide;

(Examples 89 and 90)

[0331]

[Formula 76]



[0332]

(Step 1) tert-Butyl N-[4-(4-amino-2-methyl-5-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-3-yl)butyl]carbamate

8.2 Hz), 3.09 (3H, s), 3.05 (1H, dd, J = 14.2, 5.9 Hz), 2.25 (3H, s), 1.17 (3H, s), 1.10 (3H, s).

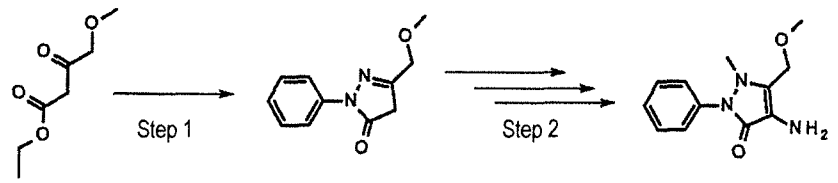
MS (APCI) m/z : 501 [(M+H)$^+$].

(Example 113) 5-Chloro-2-ethoxy-4-fluoro-N-(4-{[5-(methoxymethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl]amino}-2,2-dimethyl-4-oxobutyl)benzamide;

(Examples 114, 115, 116, 117, 118, 119, 120 and 121)

[0361]

[Formula 85]

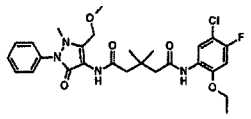
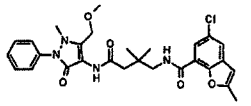
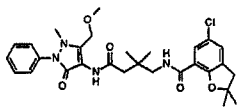


[0362]

(Step 1) 5-(Methoxymethyl)-2-phenyl-4H-pyrazol-3-one

To a solution of ethyl 4-methoxy-3-oxobutanoate (0.481 g, 3.00 mmol) in acetic acid (4.0 mL), phenylhydrazine (0.295 mL, 0.324 g, 3.00 mmol) was added, and the mixture was stirred at 110°C for 5 hours under a nitrogen atmosphere. The reaction solution was allowed to cool to room temperature and then concentrated under reduced pressure, and water was added to the residue, followed by extraction with ethyl acetate three times. The organic layer was washed with saturated saline and then dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and then, the obtained residue was purified by silica gel column chromatography (Yamazen Corp., eluting

[Table 33-2]

119		2c	^{1}H-NMR ($CDCl_3$) δ: 8.68 (1H, s), 8.47 (1H, s), 8.38 (1H, d, J = 7.9 Hz), 7.48-7.40 (4H, m), 7.33-7.28 (1H, m), 6.66 (1H, d, J = 10.4 Hz), 4.54 (2H, s), 4.03 (2H, q, J = 7.0 Hz), 3.44 (3H, s), 3.20 (3H, s), 2.64 (2H, s), 2.49 (2H, s), 1.41 (3H, t, J = 7.0 Hz), 1.15 (6H, s). MS (API) m/z : 547 [(M+H)$^+$].
120		3a	^{1}H-NMR ($CDCl_3$) δ: 8.73 (1H, s), 7.97 (1H, d, J = 2.4 Hz), 7.91 (1H, t, J = 6.3 Hz), 7.56 (1H, d, J = 2.4 Hz), 7.48-7.43 (4H, m), 7.31-7.28 (1H, m), 6.43 (1H, s), 4.53 (2H, s), 3.64 (2H, d, J = 6.3 Hz), 3.43 (3H, s), 3.19 (3H, s), 2.51 (3H, s), 2.34 (2H, s), 1.15 (6H, s). MS (ESI) m/z : 539 [(M+H)$^+$].
121		3c	^{1}H-NMR ($CDCl_3$) δ: 9.07 (1H, s), 7.98 (1H, t, J = 6.6 Hz), 7.90 (1H, d, J = 2.9 Hz), 7.45-7.44 (4H, m), 7.31-7.27 (1H, m), 7.22-7.21 (1H, m), 4.54 (2H, s), 3.56 (2H, d, J = 6.6 Hz), 3.45 (3H, s), 3.19 (3H, s), 3.06 (2H, s), 2.27 (2H, s), 1.55 (6H, s), 1.10 (6H, s). MS (ESI) m/z : 555 [(M+H)$^+$].

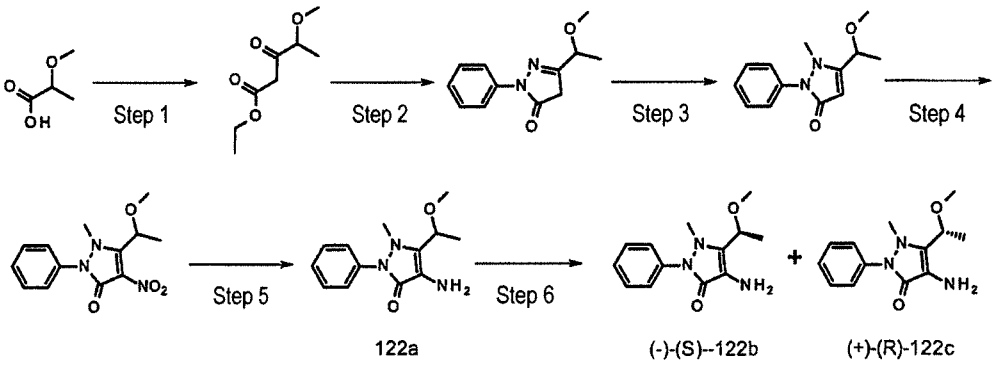
[0365]

(Example 122) 5-Chloro-2-ethoxy-4-fluoro-N-(4-{[5-(1-methoxyethyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl]amino}-2,2-dimethyl-4-oxobutyl)benzamide;

(Examples 123, 124, 125 and 126)

[0366]

[Formula 86]



[0367]

(Step 1) Ethyl 4-methoxy-3-oxopentanoate

pyrazolo-3-yl)ethyl]-2,2,2-trifluoroacetamide in step 1 of Example 62 and subsequently performing the same reaction as in steps 1 and 3 of Example 62.

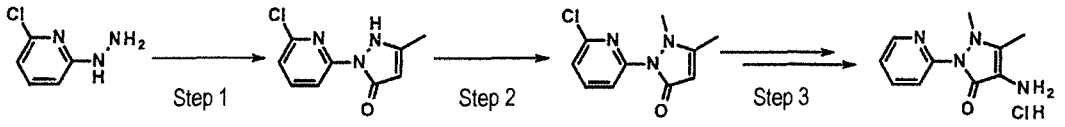
^{1}H-NMR ($CDCl_3$) δ: 9.07 (1H, s), 8.41 (1H, s), 8.18 (1H, s), 7.50-7.36 (4H, m), 7.34-7.28 (1H, m), 6.91 (1H, d, J= 8.6 Hz), 5.30 (1H, s), 4.64-4.56 (2H, m), 4.54-4.43 (4H, m), 4.23-4.15 (2H, m), 3.87-3.81 (2H, m), 3.45 (3H, s), 3.20 (3H, s), 2.41 (2H, s), 1.52 (3H, t, J = 6.8 Hz).

(Example 149) 5-Chloro-N-(4-{[1,5-dimethyl-3-oxo-2-(2-pyridyl)pyrazol-4-yl]amino}-2,2-dimethyl-4-oxobutyl)-2-ethoxybenzamide;

(Examples 150 and 151)

[0445]

[Formula 107]

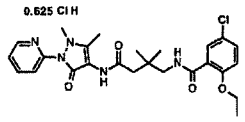
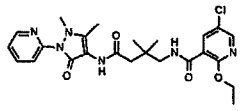
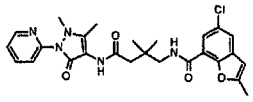


[0446]

(Step 1) 2-(6-Chloro-2-pyridyl)-5-methyl-4H-pyrazol-3-one

(6-Chloro-2-pyridyl)hydrazine (10.0 g, 69.7 mmol) was dissolved in ethanol (200 ml). To the solution, ethyl acetoacetate (9.24 ml, 73.1 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction solution was concentrated under reduced pressure to obtain an oil substance. This oil substance was dissolved in ethanol (140 ml). To the solution, potassium tert-butoxide (9.39 g, 83.6 mmol) was added,

[Table 49]

Example No.	Structure	Intermediate used	Instrumental analysis data
149		1a	^{1}H-NMR ($CDCl_3$) δ: 9.66 (1H, s), 8.60-8.57 (1H, m), 8.40-8.34 (1H, m), 8.19 (1H, d, J = 3.1 Hz), 8.01-7.90 (2H, m), 7.38 (1H, dd, J = 8.5, 3.1 Hz), 7.33-7.29 (1H, m), 6.91 (1H, d, J = 8.5 Hz), 4.21 (2H, q, J = 7.3 Hz), 3.57 (2H, d, J = 6.7 Hz), 3.46 (3H, s), 2.39 (3H, s), 2.38 (2H, s), 1.53 (3H, t, J = 7.3 Hz), 1.15 (6H, s). MS (ESI+APCI) m/z : 500 [(M+H)$^+$].
150		1h	^{1}H-NMR ($CDCl_3$) δ: 8.66 (1H, br s), 8.50-8.48 (2H, m), 8.42 (1H, t, J = 6.9 Hz), 7.98 (1H, d, J = 8.6 Hz), 7.80 (1H, td, J = 8.0, 1.5 Hz), 7.15 (1H, dd, J = 6.9, 5.2 Hz), 4.55 (2H, q, J = 7.2 Hz), 3.58 (2H, d, J = 6.9 Hz), 3.36 (3H, s), 2.28 (3H, s), 2.28 (2H, s), 1.48 (3H, t, J = 7.2 Hz), 1.14 (6H, s). MS (ESI) m/z : 501 [(M+H)$^+$].
151		3a	^{1}H-NMR (DMSO-D_6) δ: 9.11 (1H, s), 8.50 (1H, d, J = 4.4 Hz), 8.41 (1H, t, J = 6.3 Hz), 7.95-7.93 (1H, m), 7.77-7.76 (2H, m), 7.56 (1H, d, J = 2.0 Hz), 7.30-7.28 (1H, m), 6.68 (1H, s), 3.36 (2H, d, J = 6.3 Hz), 3.27 (3H, s), 2.46 (3H, s), 2.29 (2H, s), 2.13 (3H, s), 1.07 (6H, s). MS (ESI) m/z : 510 [(M+H)$^+$].

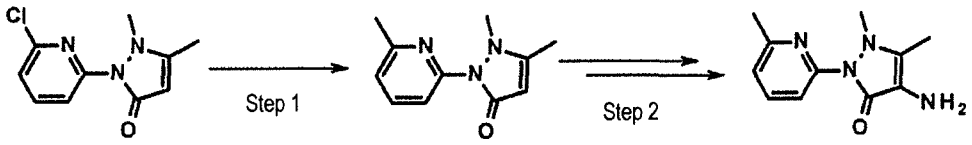
[0448]

(Example 152) 5-Chloro-N-(4-{[1,5-dimethyl-2-(6-methyl-2-pyridyl)-3-oxopyrazol-4-yl]amino}-2,2-dimethyl-4-oxobutyl)-2-ethoxybenzamide;

(Examples 153, 154 and 155)

[0449]

[Formula 108]



[0450]

(Step 1) 1,5-Dimethyl-2-(6-methyl-2-pyridyl)pyrazol-3-one

2-(6-Chloro-2-pyridyl)-1,5-dimethylpyrazol-3-one (0.447 g, 2.00 mmol) synthesized in step 2 of Example 149