DESCRIPTION

HETEROCYCLIC COMPOUND

Technical Field

The present invention relates to heterocyclic compounds, and more particularly, to heterocyclic compounds useful as HSD1 inhibitors.

Background Art

As typically observed in the Cushing's syndrome, excess systemic glucocorticoid effect causes metabolic abnormalities such as accumulation of visceral fat, characteristic changes in body fat distribution, insulin resistance, diabetes, hyperlipidemia, elevation of blood pressure and the like.

It has been known for more than half a century that glucocorticoid plays a key role in diabetes and, for example, removal of hypophysis or adrenal gland from diabetic animal results in the relief of most serious conditions of diabetes and lower blood glucose concentration (see Long, C.D. and F.D.W. Leukins (1936), J. Exp. Med. 63: 465-490 and Houssay, B.A. (1942), Endocrinology, 30: 884-892).

Glucocorticoid is known to (1) be essential for adipocyte differentiation program and inhibit, as a representative insulin-antagonistic hormone, glucose and lipid metabolism by insulin in various steps, (2) raise blood pressure via induction of the production of renin substrate, that is angiotensinogen, enhancement of angiotensin II receptor expression and the like, (3) cause hyperorexia and obesity as a potent leptin antagonistic hormone and the like (see *Rinshoi*, vol. 30 no 9, 2004; 1782-1787).

In addition, it has been drawing attention that abnormally activated glucocorticoid effect in adipose tissue is involved in the pathology of metabolic syndrome clustered multiple metabolic diseases such as diabetes hyperlipidemia, hypertension, fatty liver and the like in a single individual (see Moller DE. New drug targets for 2 diabetes and the metabolic syndrome, Nature 2001; 414: 821-7).

These facts suggest that reduction of the effect of glucocorticoid is beneficial for the treatment or prophylaxis of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like and metabolic syndrome clustered metabolic diseases in a single individual, and further, fatal vascular events represented by cardiac infarction and cerebral apoplexy based on these diseases.

Active glucocorticoid (cortisol in human and corticosterone in rodents) exhibiting the glucocorticoid effect is produced from cortisone or 11-dehydrocorticosterone, both of which are inactive 11-ketometabolites, by the action of a converting enzyme, 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1), in not only adrenal gland but also various tissues and cells (see Agurwal et al., J. Biol. Chem 264, 18939-46, 1989). Since 11βHSD1 knockout mouse cannot convert an administered inactive glucocorticoid to an active type, this enzyme has been demonstrated to be the only active glucocorticoid converting enzyme in vivo (see Kotelevtsev, Y et al.: Proc. Natl. Acad. Sci. USA, 94: 14924, 1997). There is a report on a case of hypophyseal Cushing's disease with hyperglucocorticoidemia where the conditions of the Cushing's syndrome was not observed due to an markedly lowered 11βHSD1 activity by chance (see Tomlinson, JW et al.: J. Clin. Endocrinol. Metab., 87: 57, 2002).

These results reveal that the regulation of the 11βHSD1 activity is significant for the action of glucocorticoid. In other words, regulation of the 11βHSD1 activity is beneficial for the treatment or prophylaxis of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like and metabolic syndrome clustered metabolic diseases in a single individual, and further, fatal vascular events represented by cardiac infarction and cerebral apoplexy based on these diseases.

It has been clarified that transgenic mouse, which exhibits overexpression of 11βHSD1, the same level as obese individuals, only in the adipose tissue, also has major factors of metabolic syndromes such as visceral fat-type obesity, insulin-resistant diabetes, hyperlipidemia, hypertension, fatty liver and the like (see Masuzaki, H et al.: Science 2001; 294: 2166-70 and Masuzaki H et al.: J. Clin. Invest 2003; 112: 83-90). In addition, while transgenic mouse exhibiting liver-specific overexpression of 11βHSD1 does not show a phenotype of visceral fat-type obesity but shows insulin resistance and the pathology of hypertension, fatty liver and the like (see Janice M. Paterson et al.: PNAS 2004; 101: 7088-7093). In contrast, 11βHSD1 knockout mouse shows resistance to the induction of hepatic gluconeogenesis enzyme (PEPCK, G6Pase etc.) due to stress-loading or high fat diet-loading, and shows clear resistance to the onset of diabetes (see Kotelevtsev, Y et al.: Proc. Natl. Acad. Sci. USA, 94: 14924, 1997).

Furthermore, 11βHSD1 knockout mouse shows decreased blood triglyceride level and increased blood HDL-cholesterol level, because the expressions of molecular group relating to fat catabolism and their coordinating transcription factor PPARα markedly increased. It has been reported that 11βHSD1 knockout mouse shows clear attenuation of the accumulation of visceral adipose tissue and the onset of metabolic abnormalities induced by high fat diet-loading (see Morton NM et al. J. Biol. Chem. 2001; 44: 41293-301).

In fact, since insulin sensitivity is increased in 11βHSD1 deficiency, inhibition of the effect of this enzyme is expected to be useful for the treatment or prophylaxis of non-insulin dependent diabetes and obesity (see Seckl, JR et al. Eur. J. Biochem. 249: 361, 1997 and Morton NM et al. Diabetes 2004; 53: 931-938).

These findings support that reduction of the effect of 11βHSD1 is beneficial for the treatment or prophylaxis of metabolic diseases such as diabetes, insulin resistance,

diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like and metabolic syndrome clustered metabolic diseases in a single individual, and further, fatal vascular events represented by cardiac infarction and cerebral apoplexy based on those diseases.

Removal of adrenal gland weakens the effect of fasting which increases food intake and expression of hypothalamic neuropeptide Y. This supports the role of glucocorticoid to increase food intake and suggests that inhibition of 11βHSD1 in the brain will increase the satirety level, and therefore, decrease the food intake (see Woods, S.C. et al. (1998) Science, 280:1378-1383). That is, it is suggested that the reduction of the effect of 11βHSD1 is beneficial for the treatment or prophylaxis of hyperorexia.

Stress and glucocorticoids affect the cognitive function (see de Quervain, D.J.-F., B. Roozendaal, and J.L. McGaugh (1998), Nature, 394: 787-790). In fact, 11βHSD1 knockout mouse shows marked improvement in the cognitive dysfunction caused by aging (see Yau J L et al. PNAS 2001; 98: 4716-4721), and a recent report has documented that a 11βHSD1 non-specific inhibitor, carbenoxolone, is effective for cognitive dysfunction of elderly human (see Sandeep T C et al. PNAS 2004; 101: 6734-6739). Furthermore, 11βHSD1 controls the level of action of glucocorticoid in the brain, thereby contributing to the neurotoxicity (see Rajan, V., C.R.W. Edwards, and J.R. Seckl, J. (1996), Neuroscience, 16:65-70 and Seckl, J.R., Front. (2000), Neuroendocrinol, 18:49-99). Moreover, inhibition of 11βHSD1 in the brain results in the reduction of anxiety, which is based on the above-mentioned and known effect of glucocorticoid in the brain (see Tronche, F. et al. (1999), Nature Genetics, 23:99-103). Taken together, therefore, they suggest that the reduction of the 11βHSD1 effect in human brain prevents reactivation of cortisone to cortisol, and is useful for the treatment or prophylaxis of dysgnosia, neurodegenerative diseases accompanied by disappearance of

nerve cells, emotional disorders such as anxiety, depression, mania and the like, schizophrenia, neurodysfunction including appetite stimulation and the like.

It is a well-known fact that glucocorticoid suppresses the immune system. Therefore, reduction of the effect of 11βHSD1 is suggested to be beneficial for the treatment or prophylaxis of diseases showing lowered immunity such as immunodeficiency and the like or for the treatment or prophylaxis of diseases requiring increase of immunity.

Recent data suggest that the levels of glucocorticoid target receptor and 11βHSD1 enzyme determine the susceptibity to glaucoma (see Stokes, J. et al. (2000), Invest. Ophthalmol. 41: 1629-1638). Hence, reduction of the effect of 11βHSD1 is suggested to be beneficial for the treatment or prophylaxis of glaucoma.

Although glucocorticoid plays an essential part in the growth and function of the skeleton, excess glucocorticoid is harmful. Glucocorticoids-induced bone loss is at least partly induced via inhibition of bone formation including suppression of osteoblast growth and collagen synthesis (see Kim, C.H., S.L. Cheng, and G.S. Kim (1999), J. Endocrinol, 162: 371-379).

The negative effect on the bone nodule formation can be blocked by a non-specific 11βHSD1 inhibitor, carbenoxolone, which suggests the important role of 11βHSD1 in the glucocorticoid effect (see Bellows, C.G., A. Ciaccia, and J.N.M. Heersche, (1998), Bone, 23: 119-125). Therefore, reduction of the effect of 11βHSD1 is suggested to be beneficial for the treatment or prophylaxis of osteoporosis.

Accordingly, it can be said that a substance having an activity to reduce the effect of 11βHSD1 is useful as a drug for the treatment or prophylaxis of the pathology involving glucocorticoid, such as

1) metabolic diseases including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension and fatty liver,

2) metabolic syndrome,

3) fatal vascular events represented by cardiac infarction and cerebral apoplexy based on such diseases,

4) hyperorexia,

5) diseases including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders such as anxiety, depression, mania and the like, schizophrenia and neurodysfunction including appetite stimulation,

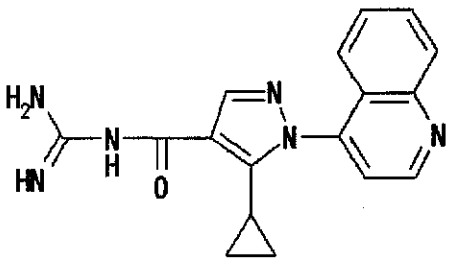
6) diseases requiring treatment or prophylaxis of lowered immunity or increase of immunity, such as immunodeficiency and the like,

7) glaucoma,

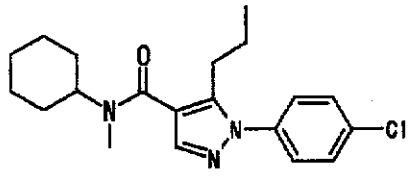
8) osteoporosis

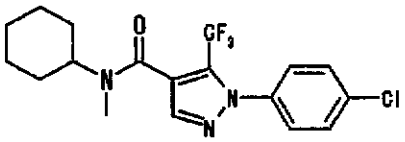
and the like.

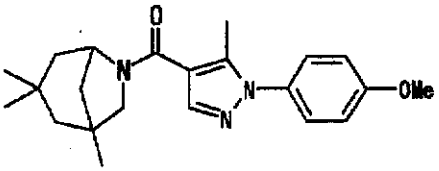
As a heterocyclic compound, for example, the following are known. For example, WO99/43663 discloses the following heterocyclic compound as a compound having am NHE1 inhibitory action.



As known 11βHSD1 inhibitors, for example, the following can be mentioned. WO2004/089470 discloses the following compounds as compounds having an inhibitory action on 11βHSD1:







Disclosure of the Invention

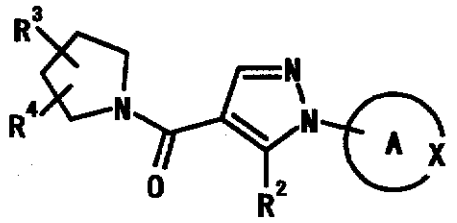
There is a strong demand for the development of a compound useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like, which has more superior properties as a pharmaceutical product in terms of efficacy, duration of action, specificity, low toxicity, oral absorbability, pharmacokinetics and the like.

It is therefore an object of the present invention to provide a compound having an HSD1 inhibitory action and the like and useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like, which has a different chemical structure from that of known compounds including the aforementioned compounds, and use thereof.

The present inventors have first found that a heterocyclic compound mentioned below has a superior HSD1 inhibitory action, and is useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity,

hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like. The present inventors have conducted intensive studies based on these findings and completed the present invention. Accordingly, the present invention specifically provides the following.

1. A compound represented by the following formula [1']:



[1']

wherein

ring A is

(1) a nitrogen-containing saturated monocyclic heterocyclic group, or

(2) a cycloalkyl group,

said ring A is optionally substituted by one or more, same or different substituents R^1,

said substituent R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$

alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a $-CO$-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen

atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group);

-X- is

(1) $-N(R^1)-$ wherein R^1 is as defined above, or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, 3) a C_{1-6} alkoxy group, and 4) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

4) a carboxyl group,

5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group),

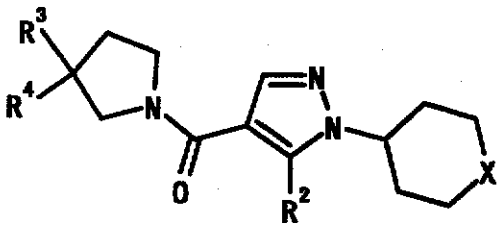
(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(5) a hydroxyl group, or

(6) a C_{1-6} alkoxy group],

or a salt thereof.

2. A compound represented by the following formula [1]:



[1]

wherein

-X- is

(1) $-N(R^1)-$ wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or

different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic

heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted

by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic

group is optionally substituted by one or more oxo groups)),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group), or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally

form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, 3) a C_{1-6} alkoxy group, and 4) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is optionally substituted by

one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

4) a carboxyl group,

5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group),

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(5) a hydroxyl group, or

(6) a C_{1-6} alkoxy group],

or a salt thereof.

3. The compound of any of the above-mentioned 1 and 2, wherein -X- is $-C(R^7R^8)-$ wherein R^7 and R^8 are as defined in the above-mentioned 1, or a salt thereof.

4. The compound of any of the above-mentioned 1 to 3, wherein R^8 is

1) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

2) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded

thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

5. The compound of the above-mentioned 1 or 2, wherein -X- is $-N(R^1)-$ wherein R^1 is as defined in the above-mentioned 1, or a salt thereof.

6. The compound of any of the above-mentioned 1, 2 and 5, wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group) and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms),

or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded

thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-

$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group, and

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group),

or a salt thereof.

7. The compound of any of the above-mentioned 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic

heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not any combination of substituents selected from the following group: (i) a hydrogen atom, and (ii) an unsubstituted C_{1-6} alkyl group),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from

the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) -$S(=O)_2$-R^{12} wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) -C(=NCN)-R^{13} wherein R^{13} is a C_{1-6} alkyl group,

8) -C(=NCN)$NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a $-COO-C_{1-6}$ alkyl group,

(f) a cyano group, and

(g) a C_{1-6} alkoxy group),

or a salt thereof.

8. The compound of any of the above-mentioned 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a

hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl

group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group, and

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the

nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a

C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a $-COO-C_{1-6}$ alkyl group,

(f) a cyano group, and

(g) a C_{1-6} alkoxy group),

or a salt thereof.

9. The compound of any of the above-mentioned 1 to 8, wherein R^2 is a cyclopropyl group or a 1-methylcyclopropyl group, or a salt thereof.

10. The compound of any of the above-mentioned 1 to 9, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following 1) to 5):

1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a hydroxyl group),

2) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is substituted by one or more, same or different halogen atoms),

3) a carboxyl group,

4) a $-COO-C_{1-6}$ alkyl group, and

5) a cyano group), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(provided that R^3 and R^4 are not simultaneously hydrogen atoms),

or a salt thereof.

11. The compound of the above-mentioned 1, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl

group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group)),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl

group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6}

alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

9) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a -COO-C_{1-6} alkyl group), or

10) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) -CO-$NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a -COO-C_{1-6} alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group),

or a salt thereof.

12. The compound of the above-mentioned 1, or a salt thereof, which is selected from the following:

(1) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(2) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(3) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(4) 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-

4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(5) 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(6) 1-{5-cyclopropyl-1-[1-(2-hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(7) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(8) 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(9) 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(10) 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(11) 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(12) 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(13) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(14) 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(15) 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(16) 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(17) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(18) 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(19) 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(20) 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(21) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(22) 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(23) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(24) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(25) 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(26) 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(27) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine,

(28) 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(29) 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(30) 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(31) 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(32) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(33) 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(34) 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(35) 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(36) 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(37) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(38) 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(39) 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-

yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(40) 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(41) 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(42) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(43) 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(44) 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(45) 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(46) 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(47) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(48) 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(49) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(50) 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(51) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(52) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(53) 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(54) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(55) 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(56) 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(57) 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(58) 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(59) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(60) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(61) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(62) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-

oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(63) 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(64) 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(65) 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(66) 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(67) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(68) 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(69) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(70) 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(71) 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(72) 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(73) 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(74) 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(75) 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(76) 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(77) 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(78) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(79) 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(80) 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(81) 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(82) 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(83) 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(84) 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(85) 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(86) 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(87) 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(88) 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(89) 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(90) 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(91) 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(92) 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(93) 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(94) 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(95) 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(96) 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(97) 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-

1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(98) 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(99) 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(100) 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(101) 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(102) 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(103) 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(104) 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(105) 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(106) 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(107) 1-(5-cyclopropyl-1-{1-[1-(2-hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(108) 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine,

(109) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(110) 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(111) 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(112) 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(113)4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(114)3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(115)5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid,

(116)2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid,

(117) 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(118) 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(119) 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(120) 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-

[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(121) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(122) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(123) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(124) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(125) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(126) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(127) (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(128) (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(129) 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(130) 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(131) 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(132) 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(133) 1-{5-(1-methylcyclopropyl)-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(134) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methoxycyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(135) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenyl-3-trifluoromethyl-pyrrolidine,

(136) 3-(2-chlorophenyl)-1-{5-cyclopropyl-1-[1-(2,4-difluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(137) 3-(2-chloropyridin-3-yl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(138) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(2,2,3,3-tetramethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(139) 1-{5-cyclohexyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(140) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethoxyphenyl)pyrrolidine,

(141) 1-{5-cyclopropyl-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(142) 1-(5-cyclopropyl-1-{1-[((S)-1-carboxy-2-methyl-propyl)methylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,

(143) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-methoxy-3-(2-trifluoromethylphenyl)pyrrolidine,

(144) 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-hydroxymethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(145) 1-{5-cyclopropyl-1-[1-(thiazol-2-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(146) 1-{1-[1-(isopropoxycarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(147) 1-{5-cyclopropyl-1-[1-(4-fluorobenzylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(148) 1-{1-[1-(2,3-dihydroindole-1-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(149) 1-{1-[1-(2,3-dihydro[1,4]oxazine-4-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(150) 1-{5-cyclopropyl-1-[1-(2,6-dichloropyridin-3-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(151) 1-{5-(1-methylcyclopropyl)-1-[1-(2,3,4,5-tetrahydrobenzo[b]azepine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(152) ethyl 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate,

(153) 1-[1-(1-benzyloxycarbonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(154) 1-{1-[1-(3-carboxy-3-methyl-butyryl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(155) 1-{5-cyclopropyl-1-[1-(2-phenoxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(156) 1-{1-[1-(3-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-

1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(157) 1-{1-[1-(2-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(158) 1-[5-cyclopropyl-1-(1-oxalylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(159) 1-{1-[1-(4-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(160) 1-(5-cyclopropyl-1-{1-[2-(4-fluorophenyl)acetyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(pyridin-3-yl)pyrrolidine,

(161) 1-{5-cyclopropyl-1-[1-(3-trifluoromethylbenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(162) 1-{5-cyclopropyl-1-[1-(3-methoxybenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(163) 1-{1-[1-(4-fluorobenzyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine hydrochloride,

(164) 1-[1-(1-benzenesulfonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(165) 1-{1-[1-(4-carbamoylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(166) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(167) 1-{1-[1-(5-carbamoyl-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(168) 1-{1-[1-(4-aminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(169) 1-(5-cyclopropyl-1-{1-[4-(2-oxooxazolidin-3-yl)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine,

(170) 1-(5-cyclopropyl-1-{1-[4-(3-methoxyureido)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-

(2-trifluoromethylphenyl)pyrrolidine,

(171) 1-{5-cyclopropyl-1-[1-(4-methanesulfonylaminophenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(172) 1-[1-(1-ethoxycarbamoylpiperidin-4-yl)-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(173) 1-[1-(5-chloropyridin-2-yl)azetidin-3-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine,

(174) 1-{1-[1-(5-chloro-pyridin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-methoxymethyl-3-phenylpyrrolidine,

(175) 1-{1-[1-(5-cyano-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(176) 3-(2-acetoxyethyl)-3-(4-fluorophenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(177) {(3S*,4R*)-3-methyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-4-phenylpyrrolidine hydrochloride,

(178) methyl 6-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)nicotinate,

(179) methyl 2-{1-[5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]pyrrolidin-3-yl}benzoate,

(180) 3-(2-hydroxymethylphenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(181) 1-[5-cyclopropyl-1-(1-pyridin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-hydroxy-3-(pyridin-3-yl)pyrrolidine,

(182) 1-{1-[1-(4-acetylaminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine,

(183) sodium 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)-3-fluorobenzoate,

(184) 3-(2-cyanophenyl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine,

(185) 3-hydroxymethyl-1-{1-[1-(4-methoxypyrimidin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenylpyrrolidine hydrochloride,

(186) 3-(3,5-difluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,

(187) 1-{1-[1-(3-chloro-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(188) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(thiazol-2-yl)pyrrolidine,

(189) (S)-2-[(trans-4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarbonyl)-methyl-amino]-3-methylbutyric acid,

(190) 1-{5-(1-methylcyclopropyl)-1-[trans-4-(2-fluorophenylcarbamoyl)cyclohexyl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine, and

(191) cis-4-{5-(1-methylcyclopropyl)-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl)-cyclohexanecarboxylic acid.

13. A pharmaceutical composition comprising a compound of any of the above-mentioned 1 to 12 or a salt thereof.

14. A 11βHSD1 inhibitor comprising a compound of any of the above-mentioned 1 to 12 or a salt thereof.

15. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises a compound of any of the above-mentioned 1 to 12 or a salt thereof.

16. The agent of the above-mentioned 15, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

17. A method of inhibiting 11βHSD1, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 1 to 12 or a salt thereof.

18. A method of treating or preventing a pathology involving glucocorticoid, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 1 to 12 or a salt thereof.

19. The method of the above-mentioned 18, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

20. Use of a compound of any of the above-mentioned 1 to 12 or a salt thereof for the production of a 11βHSD1 inhibitor.

21. Use of a compound of any of the above-mentioned 1 to 12 or a salt thereof for the production of an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

22. Use of the above-mentioned 21, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

23. A commercial package comprising a written matter stating that the pharmaceutical composition of the above-mentioned 13 can or should be used for the treatment or prophylaxis of a disease selected from

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

24. The pharmaceutical composition of the above-mentioned 13 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

25. The 11βHSD1 inhibitor of the above-mentioned 14, to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

26. The agent of the above-mentioned 15 or 16, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

27. The method of the above-mentioned 17, further comprising administering 1 to 3 agents selected from the

following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

28. A pharmaceutical agent comprising 1 to 3 agents selected from the following (1) to (5) and a compound of any of the above-mentioned 1 to 12 or a salt thereof in combination:

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

29. A method of treating or preventing the pathology involving glucocorticoid of the above-mentioned 18 or 19, which further comprises administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

30. The use of the above-mentioned 20, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

31. The use of the above-mentioned 21 or 22, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

32. The pharmaceutical composition of the above-mentioned 13, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

33. The 11βHSD1 inhibitor of the above-mentioned 14, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

34. The method of the above-mentioned 17, which further comprises administering a pharmaceutical agent raising the blood glucocorticoid level.

35. The use of the above-mentioned 21 for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

36. A method for suppressing the blood glucocorticoid level from rising, which comprises administering a pharmaceutical agent raising the blood glucocorticoid level and the 11βHSD1 inhibitor of the above-mentioned 14.

37. Dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

38. Methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

39. (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one.

40. (S)-3-(2-trifluoromethylphenyl)pyrrolidine or a salt thereof.

41. A method for producing dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate, which comprises a step for reacting 1-((E)-2-nitrovinyl)-2-trifluoromethylbenzene with dimethyl malonate in the presence of 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea.

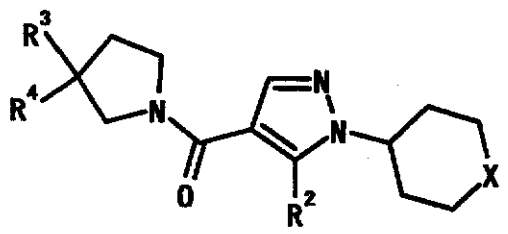
42. A method for producing methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate, which comprises a step for reduction and ring closure of dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

43. A method for producing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one, which comprises a step for hydrolysis and decarbonation of methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

44. A method for producing a salt of (S)-3-(2-trifluoromethylphenyl)pyrrolidine, which comprises a step for reducing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one and a step for treating the resulting compound with an acid to form a salt.

The present invention also encompasses the following.

45. A compound represented by the following formula [2]:



[2]

wherein

-X- is

(1) $-N(R^1)-$ wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated

monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

c) a C_{1-6} alkoxy group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

g) a carboxyl group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different

substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a -COO-C_{1-6} alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) -CO-$NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a -COO-C_{1-6} alkyl group, and

(g) a cyano group), or

(2) -$C(R^7R^8)$- wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) -$NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or -CO-$NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) -$CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl

group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group)); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, 2) a hydroxyl group, and 3) a C_{1-6} alkoxy group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) to 6):

1) a halogen atom,

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, (b) a hydroxyl group, and (c) a C_{1-6} alkoxy group),

3) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms),

4) a carboxyl group,

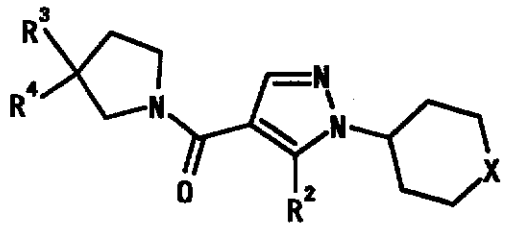
5) a $-COO-C_{1-6}$ alkyl group, and

6) a cyano group), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

or a salt thereof.

46. The compound of the above-mentioned 45, which is represented by the following formula [2]:



[2]

wherein

-X- is

(1) $-N(R^1)-$ wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is,

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

c) a C_{1-6} alkoxy group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is,

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

e) a C_{1-6} alkoxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different

substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a carboxyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group), and

(c) a cycloalkyl group), or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$

wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following 1) and 2):

1) a halogen atom, and

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

47. The compound of the above-mentioned 45 or 46, wherein

-X- is $-C(R^7R^8)-$ wherein R^7 and R^8 are as defined in the above-mentioned 46, or a salt thereof.

48. The compound of any of the above-mentioned 45 to 47, wherein R^8 is

1) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

2) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group),

or a salt thereof.

49. The compound of the above-mentioned 45 or 46, wherein -X- is $-N(R^1)-$ wherein R^1 is as defined in the above-mentioned 46), or a salt thereof.

50. The compound of any of the above-mentioned 45, 46 and 49, wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a

hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or

different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

c) a C_{1-6} alkoxy group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

e) a C_{1-6} alkoxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or

different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a carboxyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group), and

(c) a cycloalkyl group),

or a salt thereof.

51. The compound of any of the above-mentioned 45, 46 and 49, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is

optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or

R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms and unsubstituted C_{1-6} alkyl groups),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

c) a C_{1-6} alkoxy group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

e) a C_{1-6} alkoxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from

the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) and (b):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group), and

(b) a cycloalkyl group),

or a salt thereof.

52. The compound of any of the above-mentioned 45, 46 and 49, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally

substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group), or

(g) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms and unsubstituted C_{1-6} alkyl groups),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

c) a C_{1-6} alkoxy group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to e):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

e) a C_{1-6} alkoxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (c):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different $-CO-NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group), and

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by

one or more, same or different substituents selected from the following (a) and (b):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group), and

(b) a cycloalkyl group),

or a salt thereof.

53. The compound of any of the above-mentioned 45 to 52, wherein R^2 is a cyclopropyl group or a 1-methylcyclopropyl group, or a salt thereof.

54. The compound of any of the above-mentioned 45 to 53, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

(3) a phenyl group (said phenyl group is optionally substituted by one or more, same or different substituents selected from the following 1) and 2):

1) a halogen atom, and

2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

55. The compound of the above-mentioned 45 or a salt thereof, which is selected from the following:

(1) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine,

(2) 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-

carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(3) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine,

(4) 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(5) 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(6) 1-{5-cyclopropyl-1-[1-(2-hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(7) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(8) 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(9) 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(10) 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(11) 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(12) 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(13) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(14) 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-

carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(15) 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(16) 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(17) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(18) 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(19) 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(20) 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(21) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(22) 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(23) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(24) 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(25) 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(26) 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(27) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(28) 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(29) 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(30) 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(31) 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(32) 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(33) 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(34) 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(35) 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(36) 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(37) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,

(38) 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(39) 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(40) 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(41) 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(42) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(43) 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(44) 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(45) 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(46) 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(47) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(48) 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(49) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-

methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(50) 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(51) 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(52) 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(53) 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(54) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(55) 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(56) 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(57) 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(58) 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(59) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(60) 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-

(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(61) 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(62) 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(63) 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(64) 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(65) 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(66) 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(67) 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(68) 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(69) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(70) 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(71) 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(72) 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-

yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(73) 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(74) 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(75) 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(76) 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(77) 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(78) 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(79) 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(80) 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(81) 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(82) 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(83) 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(84) 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(85) 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(86) 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(87) 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(88) 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(89) 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(90) 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(91) 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(92) 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(93) 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(94) 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(95) 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(96) 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(97) 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(98) 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(99) 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(100) 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(101) 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(102) 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(103) 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(104) 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(105) 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(106) 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(107) 1-(5-cyclopropyl-1-{1-[1-(2-

hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(108) 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(109) 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(110) 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(111) 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(112) 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(113) 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(114) 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(115) 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid,

(116) 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid,

(117) 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,

(118) 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine hydrochloride,
(119) 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(120) 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(121) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(122) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(123) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(124) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(125) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(126) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,
(127) (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,
(128) (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride,
(129) 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride,
(130) 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-

pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine,

(131) 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine, and

(132) 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine.

56. A pharmaceutical composition comprising a compound of any of the above-mentioned 45 to 55 or a salt thereof.

57. A 11βHSD1 inhibitor comprising a compound of any of the above-mentioned 45 to 55 or a salt thereof.

58. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises a compound of any of the above-mentioned 45 to 55 or a salt thereof.

59. The agent of the above-mentioned 58, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

60. A method of inhibiting 11βHSD1, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 45 to 55 or a salt thereof.

61. A method of treating or preventing a pathology involving glucocorticoid, which comprises administering a pharmaceutically effective amount of a compound of any of the above-mentioned 45 to 55 or a salt thereof.

62. The method of the above-mentioned 61, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

63. Use of a compound of any of the above-mentioned 45 to 55 or a salt thereof for the production of a 11βHSD1 inhibitor.

64. Use of a compound of any of the above-mentioned 45 to 55 or a salt thereof for the production of an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

65. Use of the above-mentioned 64, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or

cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

66. A commercial package comprising a written matter stating that the pharmaceutical composition of the above-mentioned 56 can or should be used for the treatment or prophylaxis of a disease selected from

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, and

(8) osteoporosis.

67. The pharmaceutical composition of the above-mentioned 56 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

68. The 11βHSD1 inhibitor of the above-mentioned 57, to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

69. The agent of the above-mentioned 58 or 59, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

70. The method of the above-mentioned 60, further comprising administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

71. A pharmaceutical agent comprising 1 to 3 agents

selected from the following (1) to (5) and a compound of any of the above-mentioned 45 to 55 or a salt thereof in combination:

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

72. A method of treating or preventing the pathology involving glucocorticoid of the above-mentioned 61 or 62, which further comprises administering 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

73. The use of the above-mentioned 63, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

74. The use of the above-mentioned 64 or 65, which is to be combined with the use of 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

75. The pharmaceutical composition of the above-mentioned 56, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

76. The 11βHSD1 inhibitor of the above-mentioned 57, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

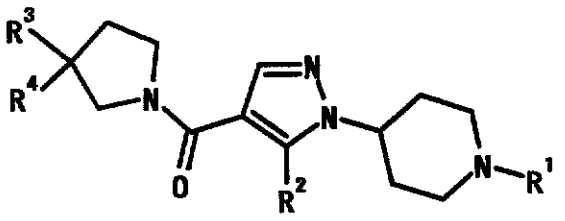
77. The method of the above-mentioned 60, which further comprises administering a pharmaceutical agent raising the blood glucocorticoid level.

78. The use of the above-mentioned 64 for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

79. A method for suppressing the blood glucocorticoid level from rising, which comprises administering a pharmaceutical agent raising the blood glucocorticoid level and the 11βHSD1 inhibitor of the above-mentioned 57.

The present invention further comprises the following.

80. A compound represented by the following formula [3]:



[3]

wherein

R^1 is

(1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and

each is

1) a hydrogen atom,

2) a C_{1-6} alkyl group,

3) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups), or

4) an aryl group (said aryl group is optionally substituted by one or more, same or different halogen atoms),

(2) an aryl group (said aryl group is optionally substituted by one or more carboxyl groups), or

(3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more carboxyl groups);

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups),

(3) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from a halogen atom and a C_{1-6} alkyl group optionally substituted by one or more halogen atoms), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a pharmaceutically acceptable salt thereof.

81. The compound of the above-mentioned 80, wherein R^1 is

(1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

1) a hydrogen atom,

2) a C_{1-6} alkyl group,

3) a cyclopropyl group (said cyclopropyl group is optionally substituted by one or more, same or different C_{1-6}

alkyl groups), or

4) a phenyl group (said phenyl group is optionally substituted by one or more, same or different halogen atoms),

(2) a phenyl group (said phenyl group is optionally substituted by one or more carboxyl groups), or

(3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more carboxyl groups), or a pharmaceutically acceptable salt thereof.

82. The compound of the above-mentioned 80, wherein R^2 is a cyclopropyl group or a methylcyclopropyl group, or a pharmaceutically acceptable salt thereof.

83. The compound of the above-mentioned 80, wherein R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups),

(3) a phenyl group (said phenyl group is optionally substituted by one or more, same or different substituents selected from a halogen atom and a C_{1-6} alkyl group optionally substituted by one or more halogen atoms), or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or a pharmaceutically acceptable salt thereof.

84. The compound of the above-mentioned 80 or a pharmaceutically acceptable salt thereof, which is selected from the following:

(1) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-(3-pyridin-3-yl)pyrrolidine,

(2) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(3) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(4) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(5) 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(S)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(6) 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(S)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(7) 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(S)-3-(2-trifluoromethylphenyl)}pyrrolidine,

(8) (-)1-{5-(1-methylcyclopropyl)-1-[(1-pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine hydrochloride,

(9) (+)1-{5-(1-methylcyclopropyl)-1-[(1-pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine hydrochloride,

(10) 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(11) 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid,

(12) 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid, and

(13) 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid.

85. A pharmaceutical composition comprising the compound of any of the above-mentioned 80 to 84, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

86. A 11βHSD1 inhibitor comprising the compound of any of

the above-mentioned 80 to 84, or a pharmaceutically acceptable salt thereof, as an active ingredient.

87. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises the compound of any of the above-mentioned 80 to 84, or a pharmaceutically acceptable salt thereof, as an active ingredient.

88. The agent of the above-mentioned 87, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy based on such diseases,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases accompanied by disappearance of nerve cells, emotional disorders including anxiety, depression or mania, schizophrenia or appetite stimulation,

(6) a disease requiring treatment or prophylaxis of lowered immunity or increase of immunity, including immunodeficiency,

(7) glaucoma, or

(8) osteoporosis.

89. The pharmaceutical composition of the above-mentioned 85 to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

90. The 11βHSD1 inhibitor of the above-mentioned 86, to

be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

91. The agent of the above-mentioned 87 or 88, which is to be used in combination with 1 to 3 agents selected from the following (1) to (5):

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension.

92. The pharmaceutical composition of the above-mentioned 85, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

93. The 11βHSD1 inhibitor of the above-mentioned 86, which is used for suppressing the blood glucocorticoid level from rising by using in combination with a pharmaceutical agent raising the blood glucocorticoid level.

Best Mode for Embodying the Invention

The present invention is described in detail in the following.

In the present invention, the definitions of the substituents to be used are as follows.

The "C_{1-6} alkyl group" is a linear or branched chain alkyl group having 1 to 6 carbon atoms and, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl group,

isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, 1,2-dimethyl-propyl group, hexyl group, 1,3-dimethyl-butyl group and the like can be mentioned, with preference given to a linear or branched chain alkyl group having 1 to 4 carbon atoms.

For R^1, preferable "C_{1-6} alkyl group" is methyl group, ethyl group, isopropyl group or isobutyl group.

For R^3 or R^4, preferable "C_{1-6} alkyl group" is methyl group.

For R^5 or R^6, preferable "C_{1-6} alkyl group" is ethyl group, isopropyl group, tert-butyl group, 1,2-dimethyl-propyl group or 1,3-dimethyl-butyl group.

For R^9, preferable "C_{1-6} alkyl group" is methyl group.

For R^{10}, preferable "C_{1-6} alkyl group" is methyl group or ethyl group.

For R^{11}, preferable "C_{1-6} alkyl group" is methyl group, ethyl group, propyl group, isopropyl group, isobutyl group or tert-butyl group.

For R^{12}, preferable "C_{1-6} alkyl group" is methyl group or ethyl group.

For R^{13}, preferable "C_{1-6} alkyl group" is methyl group.

For R^{14} or R^{15}, preferable "C_{1-6} alkyl group" is methyl group.

The "C_{2-6}alkenyl group" is a linear or branched chain alkenyl group having 2 to 6 carbon atoms and, for example, vinyl group, n-propenyl group, isopropenyl group, n-butenyl group, isobutenyl group, sec-butenyl group, tert-butenyl group, n-pentenyl group, isopentenyl group, neopentenyl group, 1-methylpropenyl group, n-hexenyl group, isohexenyl group, 1,1-dimethylbutenyl group, 2,2-dimethylbutenyl group, 3,3-dimethylbutenyl group, 3,3-dimethylpropenyl group, 2-ethylbutenyl group and the like can be mentioned.

The "C_{1-6} alkoxy group" is an alkoxy group wherein the alkyl moiety is the "C_{1-6} alkyl group" defined above and, for

example, methoxy group, ethoxy group, propoxy group, isopropyloxy group, butoxy group, isobutyloxy group, tert-butyloxy group, pentyloxy group, hexyloxy group and the like can be mentioned.

The "halogen atom" is fluorine atom, chlorine atom, bromine atom or iodine atom. Preferred is fluorine atom or chlorine atom and more preferred is fluorine atom.

The "aryl group" is an aromatic hydrocarbon group having 6 to 14 carbon atoms and, for example, phenyl group, naphthyl group, anthryl group, azulenyl group, phenanthryl group and the like can be mentioned. Preferred is phenyl group.

The "aryloxy group" is an aryloxy group wherein the aryl moiety is the "aryl group" defined above and, for example, phenoxy group, naphthyloxy group and the like can be mentioned.

The "cycloalkyl group" is a cycloalkyl group having 3 to 8 carbon atoms and, for example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like can be mentioned. Preferred is cycloalkyl group having 3 to 6 carbon atoms, such as cyclopropyl group, cyclobutyl group, cyclopentyl group and cyclohexyl group. Particularly preferred is cyclopropyl group and cyclopentyl group.

The "5-membered or 6-membered unsaturated monocyclic heterocyclic group" is a 5-membered or 6-membered unsaturated monocyclic heterocyclic group having, besides carbon atom, at least one, preferably 1 to 4, hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom. The unsaturated includes partial unsaturation and complete unsaturation. For example, a 5-membered monocyclic aromatic heterocyclic group such as furyl group, thienyl group, pyrrolyl group, pyrazolyl group, imidazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, triazolyl group, oxadiazolyl group, tetrazolyl group, thiadiazolyl group and the like, and a 6-membered monocyclic aromatic heterocyclic group

such as pyridyl group, pyridazinyl group, pyrimidinyl group, pyrazinyl group, triazinyl group, thiazinyl group, oxadiazinyl group, pyranyl group, thiopyranyl group and the like can be mentioned. As the 5-membered monocyclic aromatic heterocyclic group, preferred is thienyl group or thiazolyl group. As the 6-membered monocyclic aromatic heterocyclic group, preferred is pyridyl group or pyrimidinyl group.

For R^1, preferable "5-membered or 6-membered unsaturated monocyclic heterocyclic group" is pyridyl group, thienyl group, thiazolyl group, triazolyl group (particularly preferably 1,2,4-triazolyl group), tetrazolyl group, pyrimidinyl group or pyrazinyl group.

For R^3 or R^4, preferable "5-membered or 6-membered unsaturated monocyclic heterocyclic group" is pyridyl group or thiazolyl group. More preferred is pyridyl group.

The "nitrogen-containing saturated monocyclic heterocyclic group" is, for example, a 4-membered to 6-membered saturated monocyclic heterocycle having at least one nitrogen atom, such as azetidinyl group, pyrrolidinyl group, imidazolidinyl group, pyrazolidinyl group, oxazolidinyl group, 2-oxopyrrolidinyl group, thiazolidinyl group, isothiazolidinyl group, piperidyl group, piperazinyl group, morpholinyl group, thiomorpholinyl group, 2-oxopiperidinyl group, 4-oxopiperidinyl group, 2,6-dioxopiperidinyl group and the like.
preferable "nitrogen-containing saturated monocyclic heterocyclic group" is azetidinyl group, pyrrolidinyl group, piperidyl group, piperazinyl group or thiomorpholinyl group.

For $-NR^5R^6$, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is azetidinyl group, pyrrolidinyl group, piperidyl group, piperazinyl group or thiomorpholinyl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following group:
halogen atom,
hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,
carboxyl group,
acetyl group,
carbamoyl group,
amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and
oxo group).

For $-NR^{20}R^{21}$, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is azetidinyl group, pyrrolidinyl group or piperidyl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from halogen atom and hydroxyl group).

For $-NR^{26}R^{27}$, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is piperidyl group or pyrrolidinyl group, more preferably piperidyl group.

For R^{10}, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is piperidyl group.

For R^{11}, preferable "nitrogen-containing saturated monocyclic heterocyclic group" is pyrrolidinyl group or piperidyl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group, $-CO-C_{1-6}$ alkyl group and oxo group).

Being "optionally substituted by one or more substituents" means being unsubstituted or optionally substituted by at least one to the acceptable maximum number of substituents. For example, in the case of methyl group, it means being optionally substituted by 1 to 3 substituents, and in the case of ethyl group, it means being optionally substituted by 1 to 5 substituents. The substituents in the case of substitution with two or more substituents may be the same or different and the positions of the substituents are not particularly limited and may be any.

The "C_{1-6} alkyl group optionally substituted by one or more, same or different substituents" is preferably C_{1-6} alkyl group optionally substituted by the same or different 1 to 3 substituents. Particularly, "C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms " is preferably C_{1-6} alkyl group optionally substituted by 1 to 3 halogen atoms, more preferably C_{1-6} alkyl group optionally substituted by three halogen atoms, and more preferably trifluoromethyl group or 2,2,2-trifluoroethyl group.

Preferable groups of each group are as follows.

[Preferable ring A]

Ring A is

(1) a nitrogen-containing saturated monocyclic heterocyclic group (i.e., -X- is $-N(R^1)-$), or

(2) a cycloalkyl group (i.e., -X- is $-C(R^7R^8)-$), and preferably

(1) an azetidinyl group or a piperidyl group, or

(2) a cyclohexyl group.

[Preferable R^2]

R^2 is preferably a cyclopropyl group or a cyclohexyl group optionally substituted by one or more, same or different substituents selected from a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by a hydroxyl group) and a C_{1-6} alkoxy group. More preferably, it is a cyclopropyl group or a cyclohexyl group optionally substituted by one or more methyl groups (said methyl group is optionally substituted by a hydroxyl group) or methoxy groups. Particularly preferably, it is cyclopropyl group, methylcyclopropyl group, methoxycyclopropyl group, tetramethylcyclopropyl group, hydroxymethylcyclopropyl group or cyclohexyl group.

[Preferable R^3 and R^4]

R^3 and R^4 are preferably not hydrogen atoms at the same time.

More preferably, one of R^3 and R^4 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different

substituents selected from halogen atom, hydroxyl group, methoxy group and acetyloxy group) or a C_{1-6} alkoxy group, and the other is not a hydrogen atom.

Further preferably, one of R^3 and R^4 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from halogen atom, hydroxyl group, methoxy group and acetyloxy group) or a C_{1-6} alkoxy group, and the other is a substituent selected from the following group, which is optionally substituted by one or more, same or different substituents selected from halogen atom, C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms or hydroxyl group), C_{1-6} alkoxy group (said C_{1-6} alkoxy group is optionally substituted by one or more, same or different halogen atoms), C_{1-6} alkoxycarbonyl group and cyano group:

- phenyl group,
- pyridyl group, and
- thiazolyl group.

Particularly preferably, one of R^3 and R^4 is a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from halogen atom, hydroxyl group, methoxy group and acetyloxy group) or a methoxy group, and the other is a substituent selected from the following group, which is optionally substituted by one or more, same or different substituents selected from halogen atom, trifluoromethyl group, trifluoromethoxy group, methoxycarbonyl group, hydroxymethyl group and cyano group:

- phenyl group,
- pyridyl group, and
- thiazolyl group.

[Preferable R^5 and R^6]

R^5 and R^6 are preferably the same or different and each is

- a hydrogen atom,

· a phenyl group optionally substituted by one or more, same or different substituents selected from hydroxyl group, halogen atom, carboxyl group and C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups or halogen atoms),

· a cycloalkyl group having 3 to 6 carbon atoms (said cycloalkyl group is optionally substituted by C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· a C_{1-6} alkyl group optionally substituted by one or more, same or different substituents selected from hydroxyl group, halogen atom, phenyl group (said phenyl group is optionally substituted by halogen atom), carboxyl group and $-NR^{20}R^{21}$ (wherein R^{20} and R^{21} are as defined for the formula [1]),

· $-S(=O)_2-R^9$ wherein R^9 is phenyl group or C_{1-6} alkyl group,

· optionally substituted C_{1-6} alkoxy group,

· a pyridinyl group optionally substituted by halogen atom at the 2-position and the 6-position,

· an optionally substituted nitrogen-containing unsaturated heterocyclic group, or

· a nitrogen-containing saturated monocyclic heterocyclic group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group, or

· R^5 and R^6 may form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group selected from azetidinyl group, pyrrolidinyl group, piperidyl group, piperazinyl group, and thiomorpholinyl group, or a heterocyclic group selected from dihydroindolyl group, dihydro[1,4]oxazinyl group, and tetrahydrobenzo[b]azepinyl group, which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following group:
halogen atom,
hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,
carboxyl group,
acetyl group,
carbamoyl group,
amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and
oxo group).

More preferably, R^5 and R^6 are the same or different and each is

- a hydrogen atom,
- a phenyl group optionally substituted at the ortho-position and/or the para-position by substituents selected from hydroxyl group, halogen atom, carboxyl group and C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups or halogen atoms),
- a cyclopropyl group or a cyclopentyl group optionally substituted by C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,
- a C_{1-6} alkyl group substituted by one or more, same or different substituent selected from hydroxyl group, halogen atom, phenyl group (said phenyl group is optionally substituted by halogen atom), carboxyl group and $-NR^{20}R^{21}$ (wherein R^{20} and R^{21} are as defined for the formula [1]),
- $-S(=O)_2-R^9$ wherein R^9 is a phenyl group or a methyl group,
- a C_{1-6} alkoxy group,
- a pyridinyl group substituted by halogen atom at the 2-position and the 6-position,
- an optionally substituted thiazolyl group, or
- a piperidin-4-yl group optionally substituted at the 1-position by one substituent selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group, or
- R^5 and R^6 may form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group selected from azetidin-1-yl group, pyrrolidin-1-yl group, piperidin-1-yl group, piperazin-1-yl group, and thiomorpholin-4-yl group, or a heterocyclic group selected from dihydroindol-1-yl group, dihydro[1,4]oxazin-1-yl group, and tetrahydrobenzo[b]azepin-1-yl group, which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following group:

halogen atom,

hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,

carboxyl group,

acetyl group,

carbamoyl group,

amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and

oxo group).

Further preferably, R^5 and R^6 are the same or different and each is

· a hydrogen atom,

· a phenyl group substituted at the ortho-position and/or the para-position by substituents selected from hydroxyl group, halogen atom, carboxyl group and C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more hydroxyl groups or halogen atoms),

· a cyclopropyl group or a cyclopentyl group substituted by C_{1-6} alkyl group substituted by one or more hydroxyl groups,

· a C_{1-6} alkyl group substituted by one substituent selected from hydroxyl group, halogen atom, phenyl group (said phenyl group is optionally substituted by halogen atom), carboxyl group and $-NR^{20}R^{21}$ (wherein R^{20} and R^{21} are as defined for the formula [1]),

• $-S(=O)_2-R^9$ wherein R^9 is a phenyl group or a methyl group,

• a C_{1-6} alkoxy group,

• a pyridin-3-yl group substituted by halogen atom at the 2-position and the 6-position,

• a thiazolyl group, or

• a piperidin-4-yl group optionally substituted at the 1-position by $-CO-C_{1-6}$ alkyl group, or

• R^5 and R^6 may form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group selected from azetidin-1-yl group, pyrrolidin-1-yl group, piperidin-1-yl group, piperazin-1-yl group, and thiomorpholin-4-yl group, or a heterocyclic group selected from dihydroindol-1-yl group, dihydro[1,4]oxazin-1-yl group, and tetrahydrobenzo[b]azepin-1-yl group, which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following group:

halogen atom,

hydroxyl group,

C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups,

carboxyl group,

acetyl group,

carbamoyl group,

amino group optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and acetyl group, and

oxo group).

Particularly preferably, R^5 and R^6 are the same or different and each is

• hydrogen atom,

• 2-fluorophenyl group,

• 2-carboxyphenyl group,

• 2-hydroxymethylphenyl group,

- 1-hydroxymethylcyclopropyl group,
- 2-hydroxyethyl group,
- 2-hydroxy-1,1-dimethylethyl group,
- 2-acetylaminoethyl group,
- 2-aminoethyl group,
- 2-dimethylaminoethyl group,
- 2-piperidin-1-yl-ethyl group,
- 2-hydroxy-1-methylethyl group,
- piperidin-4-yl group,
- 1-methyl-piperidin-4-yl group,
- 1-acetyl-piperidin-4-yl group,
- 2,2,2-trifluoroethyl group,
- 1-hydroxymethyl-2-methylpropyl group,
- 1-hydroxymethyl-2-phenylethyl group,
- 2-hydroxy-1-phenylethyl group,
- 1-hydroxymethyl-3-methylbutyl group,
- 2-hydroxyphenyl group,
- 1-hydroxymethyl-cyclopentyl group,
- benzenesulfonyl group,
- 4-trifluoromethylphenyl group,
- 2,4-difluorophenyl group,
- 1-carboxy-2-methylpropyl group,
- thiazol-2-yl group,
- isopropoxy group,
- 4-fluorobenzyl group,
- 2,6-dichloropyridin-3-yl group,
- ethoxy group, or
- mesyl group, or
- R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring, which is selected from the following group:

azetidin-1-yl group,

3-hydroxyazetidin-1-yl group,

3-hydroxymethylazetidin-1-yl group,
3-acetylazetidin-1-yl group,
3-acetylaminoazetidin-1-yl group,
3-hydroxypyrrolidin-1-yl group,
3,3-difluoropyrrolidin-1-yl group,
3,3,4,4-tetrafluoropyrrolidin-1-yl group,
2-hydroxymethylpyrrolidin-1-yl group,
2-aminopyrrolidin-1-yl group,
2-acetylaminopyrrolidin-1-yl group,
2-dimethylaminopyrrolidin-1-yl group,
3-oxo-pyrrolidin-1-yl group,
4-hydroxypiperidin-1-yl group,
4,4-difluoropiperidin-1-yl group,
4-hydroxymethylpiperidin-1-yl group,
4-carboxypiperidin-1-yl group,
3-hydroxypiperidin-1-yl group,
4-carbamoylpiperidin-1-yl group,
4-aminopiperidin-1-yl group,
4-dimethylaminopiperidin-1-yl group,
4-acetylaminopiperidin-1-yl group,
4-methylpiperazin-1-yl group,
4-isopropylpiperazin-1-yl group,
4-acetylpiperazin-1-yl group,
1,1-dioxothiomorpholin-4-yl group,
3-oxo-piperidin-1-yl group,
4-oxo-piperidin-1-yl group,
2,3-dihydroindol-1-yl group,
2,3-dihydro[1,4]oxazin-1-yl group, and
2,3,4,5-tetrahydrobenzo[b]azepin-1-yl group.

Further preferably, R^5 and R^6 are not hydrogen atoms at the same time. More preferably, one of R^5 and R^6 is a hydrogen atom and the other is not a hydrogen atom.

[Preferable R^{10}]

R^{10} is preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally

substituted by one or more, same or different substituents selected from hydroxyl group, phenyl group and $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form a piperidyl group together with the nitrogen atom bonded thereto), or

· a piperidyl group (said piperidyl group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group).

R^{10} is more preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from hydroxyl group, phenyl group and $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is C_{1-6} alkyl group, or R^{26} and R^{27} optionally form a piperidyl group together with the nitrogen atom bonded thereto), or

· a piperidin-4-yl group (said piperidin-4-yl group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group).

R^{10} is further preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from hydroxyl group, phenyl group and $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is C_{1-6} alkyl group, or R^{26} and R^{27} optionally form a piperidyl group together with the nitrogen atom bonded thereto), or

· a piperidin-4-yl group (said piperidin-4-yl group is optionally substituted by one or more, same or different substituents selected from C_{1-6} alkyl group and $-CO-C_{1-6}$ alkyl group).

R^{10} is particularly preferably

· methyl group,

· 2-hydroxyethyl group,

· 2-dimethylaminoethyl group,

· 2-piperidin-1-yl-ethyl group,

· piperidin-4-yl group,

· 1-methyl-piperidin-4-yl group,

· benzyl group, or

· 1-acetyl-piperidin-4-yl group.

[Preferable R^{11}]

R^{11} is preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, -CO-cycloalkyl group, or $-S(=O)_2-C_{1-6}$ alkyl group,

d) a carbamoyl group,

e) a carboxyl group,

f) a phenoxy group, and

g) a fluorophenyl group),

· a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group optionally substituted by one or more, same or different halogen atoms, and

b) a C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) one or more, same or different halogen atoms,

b) a C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms, and

c) a C_{1-6} alkoxy group),

· a carboxyl group, or

· a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or

more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group).

R^{11} is more preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, -CO-cycloalkyl group, or $-S(=O)_2-C_{1-6}$ alkyl group,

d) a carbamoyl group,

e) a carboxyl group,

f) a phenoxy group, and

g) a fluorophenyl group),

· a cyclopropyl group (said cyclopropyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group optionally substituted by one or more, same or different halogen atoms, and

b) a C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· a phenyl group (said phenyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) one or more, same or different halogen atoms,

b) a C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms, and

c) a C_{1-6} alkoxy group),

· a carboxyl group, or

· a nitrogen-containing saturated monocyclic heterocyclic group selected from a pyrrolidinyl group and a piperidyl group (said

heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group).

R^{11} is further preferably

· a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to g):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, -CO-cycloalkyl group, or $-S(=O)_2-C_{1-6}$ alkyl group,

d) a carbamoyl group,

e) a carboxyl group,

f) a phenoxy group, and

g) a fluorophenyl group),

· a cyclopropyl group (said cyclopropyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group optionally substituted by one or more, same or different halogen atoms, and

b) a C_{1-6} alkyl group optionally substituted by one or more hydroxyl groups),

· a phenyl group (said phenyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) one or more, same or different halogen atoms,

b) a C_{1-6} alkyl group optionally substituted by one or more, same or different halogen atoms, and

c) a C_{1-6} alkoxy group),

· a carboxyl group, or

· a nitrogen-containing saturated monocyclic heterocyclic group

selected from a pyrrolidin-2-yl group and a piperidin-4-yl group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group).

R^{11} is particularly preferably

- 2,2,2-trifluoroethyl group,
- hydroxymethyl group,
- 3-hydroxy-propyl group,
- 2-hydroxy-1,1-dimethyl-ethyl group,
- aminomethyl group,
- 2-amino-ethyl group,
- 1-amino-1-methyl-ethyl group,
- 1-amino-2-methyl-propyl group,
- methylamino-methyl group,
- dimethylamino-methyl group,
- acetylamino-methyl group,
- 1-acetylamino-ethyl group,
- 2-acetylamino-ethyl group,
- 1-acetylamino-1-methyl-ethyl group,
- 1-acetylamino-2-methyl-propyl group,
- isobutyrylamino-methyl group,
- cyclopropanecarbonyl-amino-methyl group,
- methanesulfonylamino-methyl group,
- 2-carbamoyl-ethyl group,
- cyclopropyl group,
- 1-(4-fluoro-phenyl)-cyclopropyl group,
- 1-methyl-cyclopropyl group,
- 1-hydroxymethyl-cyclopropyl group,
- pyrrolidin-1-yl group,
- pyrrolidin-2-yl group,
- piperidin-4-yl group,
- 1-methyl-pyrrolidin-2-yl group,

- 1-methyl-piperidin-4-yl group,
- 1-acetyl-pyrrolidin-2-yl group,
- 1-acetyl-piperidin-4-yl group,
- 2-carboxy-2-methylpropyl group,
- phenoxymethyl group,
- 2-chlorophenyl group,
- 3-chlorophenyl group,
- 4-chlorophenyl group,
- carboxyl group,
- 4-fluorobenzyl group,
- 3-trifluoromethylphenyl group,
- 3-methoxyphenyl group, or
- 5-oxo-pyrrolidin-2-yl group.

The salt of the compound of the present invention is preferably a pharmaceutically acceptable salt. The salt of the compound of the present invention represented by the formula [1'] can be produced by a conventional method. The salt of the compound of the present invention represented by the formula [1'] can be mentioned by reacting compound [1'] (hereinafter compound [1'] and salts thereof are also to be collectively referred to as the compound of the present invention) with, for example, inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids such as oxalic acid, malonic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid, trifluoroacetic acid, gluconic acid, ascorbic acid, methanesulfonic acid, benzenesulfonic acid and the like; inorganic bases such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonium hydroxide and the like; organic bases such as methylamine, diethylamine, triethylamine, triethanolamine, ethylenediamine, tris(hydroxymethyl)methylamine, guanidine, choline, cinchonine and the like; amino acids such as lysine, arginine, alanine and the like, and the like. The present invention also encompasses water-containing products, hydrates and solvates of the

compound of the present invention.

In addition, the compound of the present invention has various isomers. For example, E form and Z form can be present as geometric isomers, when an asymmetric carbon atom is present, enantiomer and diastereomer are present as stereoisomers based thereon, and tautomers can also be present. Therefore, the present invention encompasses all of these isomers and mixtures thereof. Moreover, the present invention encompasses, besides the compound of the present invention, prodrug compounds and metabolite compounds of these compounds as equivalent compounds.

As used herein, the "prodrug" is a derivative having a chemically or metabolically decomposable group, which shows a pharmaceutical activity upon decomposition by hydrolysis or solvolysis, or under physiological conditions. A prodrug is used for, for example, improving absorption by oral administration or targeting the object site. Inasmuch as what the chemically or metabolically decomposable group is, and how to introduced the group into a compound have been sufficiently established in the field of pharmaceutical agents, such known techniques can be employed in the present invention. As the moiety to be modified for producing a prodrug, for example, highly reactive functional groups such as a hydroxyl group, a carboxyl group, an amino group, a thiol group and the like in the compound of the present invention can be mentioned.

For example, a derivative wherein a substituent such as -CO-C_{1-6} alkyl group, -CO_2-C_{1-6} alkyl group, -CONH-C_{1-6} alkyl group, -CO-C_{2-6} alkenyl group, -CO_2-C_{2-6} alkenyl group, -CONH-C_{2-6} alkenyl group, -CO-aryl group, -CO_2-aryl group, -CONH-aryl group, -CO-heterocyclic group, -CO_2-heterocyclic group, -CONH-heterocyclic group (the C_{1-6} alkyl group, C_{2-6} alkenyl group, aryl group and heterocyclic group are each optionally substituted by halogen atom, C_{1-6} alkyl group, hydroxyl group, C_{1-6} alkoxy group, carboxyl group, amino group, amino acid residue, -PO_3H_2, -SO_3H, -CO-polyethylene glycol residue, -CO_2-

polyethylene glycol residue, -CO-polyethylene glycol monoalkyl ether residue, $-CO_2$-polyethylene glycol monoalkyl ether residue and the like) and the like has been introduced into a hydroxyl group can be mentioned.

In addition, a derivative wherein a substituent such as -CO-C_{1-6} alkyl group, $-CO_2-C_{1-6}$ alkyl group, -CO-C_{2-6} alkenyl group, $-CO_2-C_{2-6}$ alkenyl group, -CO-aryl group, $-CO_2$-aryl group, -CO-heterocyclic group, $-CO_2$-heterocyclic group (the C_{1-6} alkyl group, C_{2-6} alkenyl group, aryl group and heterocyclic group are each optionally substituted by halogen atom, C_{1-6} alkyl group, hydroxyl group, C_{1-6} alkoxy group, carboxyl group, amino group, amino acid residue, $-PO_3H_2$, $-SO_3H$, -CO-polyethylene glycol residue, $-CO_2$-polyethylene glycol residue, -CO-polyethylene glycol monoalkyl ether residue, $-CO_2$-polyethylene glycol monoalkyl ether residue, $-PO_3H_2$ and the like) and the like has been introduced into an amino group can be mentioned.

Furthermore, a derivative wherein a substituent such as C_{1-6} alkoxy group, aryloxy group (the C_{1-6} alkoxy group and aryloxy group are each optionally substituted by halogen atom, C_{1-6} alkyl group, hydroxyl group, C_{1-6} alkoxy group, carboxyl group, amino group, amino acid residue, $-PO_3H_2$, $-SO_3H$, polyethylene glycol residue, polyethylene glycol monoalkyl ether residue and the like) and the like has been introduced into a carboxyl group can be mentioned.

In the above, the "heterocyclic group" is a 5-membered or 6-membered saturated or unsaturated (including partial unsaturation and complete unsaturation) monocyclic heterocyclic group having, besides carbon atom, at least one, preferably 1 to 4, hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom, or a fused ring group of the heterocycles or a fused ring group of the heterocycle and a carbon ring selected from benzene, cyclopentane and cyclohexane.

As the "5-membered or 6-membered saturated monocyclic heterocyclic group", for example, pyrrolidinyl group, tetrahydrofuryl group, tetrahydrothienyl group, imidazolidinyl

group, pyrazolidinyl group, 1,3-dioxolanyl group, 1,3-oxathioranyl group, oxazolidinyl group, thiazolidinyl group, piperidinyl group, piperazinyl group, tetrahydropyranyl group, tetrahydrothiopyranyl group, dioxanyl group, morpholinyl group, thiomorpholinyl group, 2-oxopyrrolidinyl group, 2-oxopiperidinyl group, 4-oxopiperidinyl group, 2,6-dioxopiperidinyl group and the like can be mentioned.

As the "5-membered or 6-membered unsaturated monocyclic heterocyclic group", for example, pyrrolyl group, furyl group, thienyl group, imidazolyl group, 1,2-dihydro-2-oxoimidazolyl group, pyrazolyl group, diazolyl group, oxazolyl group, isoxazolyl group, thiazolyl group, isothiazolyl group, triazolyl group(1,2,4-triazolyl group, 1,2,3-triazolyl group), tetrazolyl group, 1,3,4-oxadiazolyl group, 1,2,4-oxadiazolyl group, 1,3,4-thiadiazolyl group, 1,2,4-thiadiazolyl group, furazanyl group, pyridyl group, pyrimidinyl group, 3,4-dihydro-4-oxopyrimidinyl group, pyridazinyl group, pyrazinyl group, 1,3,5-triazinyl group, imidazolinyl group, pyrazolinyl group, oxazolinyl group(2-oxazolinyl group, 3-oxazolinyl group, 4-oxazolinyl group), isooxazolinyl group, thiazolinyl group, isothiazolinyl group, pyranyl group, 2-oxopyranyl group, 2-oxo-2,5-dihydrofuranyl group and 1,1-dioxo-1H-isothiazolyl group can be mentioned.

As the "heterocyclic group which is a fused ring", for example, indolyl group (e.g., 4-indolyl group, 7-indolyl group etc), isoindolyl group, 1,3-dihydro-1,3-dioxoisoindolyl group, benzofuranyl group (e.g., 4-benzofuranyl group, 7-benzofuranyl group etc), indazolyl group, isobenzofuranyl group, benzothiophenyl group (e.g., 4-benzothiophenyl group, 7-benzothiophenyl group etc), benzooxazolyl group (e.g., 4-benzooxazolyl group, 7-benzooxazolyl group etc), benzimidazolyl group (e.g., 4-benzimidazolyl group, 7-benzimidazolyl group etc), benzothiazolyl group (e.g., 4-benzothiazolyl group, 7-benzothiazolyl group etc), indolizinyl group, quinolyl group, isoquinolyl group, 1,2-dihydro-2-oxoquinolyl group,

quinazolinyl group, quinoxalinyl group, cinnolinyl group, phthalazinyl group, quinolizinyl group, puryl group, pteridinyl group, indolinyl group, isoindolinyl group, 5,6,7,8-tetrahydroquinolyl group, 1,2,3,4-tetrahydroquinolyl group, 2-oxo-1,2,3,4-tetrahydroquinolyl group, benzo[1,3]dioxolyl group, 3,4-methylenedioxypyridyl group, 4,5-ethylenedioxypyrimidinyl group, chromenyl group, chromanyl group, isochromanyl group and the like can be mentioned.

The "pharmaceutical composition" includes, besides what is called a "composition" comprising an active ingredient as a pharmaceutical agent and a combination drug and the like, a combination agent with other drug, and the like. It is needless to say that the pharmaceutical composition of the present invention can be concurrently used with any other drug within the range acceptable in clinical situations. Therefore, the present pharmaceutical composition can also be considered a pharmaceutical composition to be combined with other drug.

Moreover, the pharmaceutical composition of the present invention can be administered to not only human but also other mammals (mouse, rat, hamster, rabbit, cat, dog, bovine, horse, sheep, monkey etc.). Therefore, the pharmaceutical composition of the present invention is also useful as a pharmaceutical product for animals, not to mention human.

The compound of the present invention or a salt thereof can be mixed with a pharmaceutically acceptable carrier, and administered orally or parenterally as tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like.

As the "pharmaceutically acceptable carrier", various organic or inorganic carrier substances conventionally used as preparation materials are employed, which are added as excipient, lubricant, binder, disintegrant, solvent, dissolution aids, suspending agent, isotonicity agent, buffer, soothing agent and the like. Where necessary,

preparation additives such as preservative, antioxidant, coloring agent, sweetening agent and the like can also be used. As examples of the above-mentioned excipient, lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic anhydride and the like can be mentioned. As the above-mentioned lubricant, for example, magnesium stearate, calcium stearate, talc, colloidal silica and the like can be mentioned. As examples of the above-mentioned binder, polymer compound such as crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone and the like can be mentioned. As examples of the above-mentioned disintegrant, starch, carboxymethylcellulose, carboxymethylcellulose calcium, croscarmellose sodium, sodium carboxymethyl starch and the like can be mentioned. As examples of the above-mentioned solvent, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, propylene glycol esters of fatty acids and the like can be mentioned. As examples of the above-mentioned dissolution aids, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like can be mentioned. As examples of the above-mentioned suspending agent, surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate and the like; polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose and the like can be mentioned. As examples of the above-mentioned isotonicity agent, sodium chloride, glycerol, D-mannitol and the like can be mentioned. As examples of the above-mentioned buffer, buffers such as phosphate, acetate, carbonate, citrate and the like, and the like can be mentioned. As examples of the

above-mentioned soothing agent, benzyl alcohol and the like can be mentioned. As examples of the above-mentioned preservative, paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid and the like can be mentioned. As examples of the above-mentioned antioxidant, sulfite, ascorbic acid and the like can be mentioned. As examples of the above-mentioned sweetening agent, aspartam, saccharin sodium, stevia and the like can be mentioned. As examples of the above-mentioned coloring agent, foodcolors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2 and the like, food lake colors, iron oxide and the like can be mentioned.

The "11βHSD1 inhibitor" means disappearance or attenuation of the activity of 11βHSD1 by specifically inhibiting the function thereof as an enzyme, and means, for example, specific inhibition of the function of 11βHSD1 under the conditions of the below-mentioned Experimental Example 1, and preferably means the concentration necessary to achieve 50% inhibition of 11βHSD1 under the conditions of the below-mentioned Experimental Example 1 of less than 10 μM, preferably less than 1 μM, more preferably less than 100 nM, and still more preferably less than 10 nM.

The "pathology involving glucocorticoid" means, for example,

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis

and the like.

When the compound of the present invention is used as the drug for the treatment or prophylaxis of pathology showing involvement of glucocorticoid, it can be systemically or topical, and orally or parenterally administered. While the dose varies depending on the age, body weight, condition, treatment effect and the like, for example, it can be generally administered within the range of 0.1 mg to 1 g per administration to an adult once to several times a day. The compound of the present invention can also be used as a drug for the treatment or prophylaxis of the aforementioned diseases in, not to mention human, animals other than human, particularly mammals. The same applies to the use of the compound of the present invention as a drug for the treatment or prophylaxis of

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis

and the like.

To produce a preparation of the compound of the present invention such as a solid composition or liquid composition for oral administration, or an injection for parenteral administration and the like, the compound can be admixed

additives such as a suitable diluent, a dispersing agent, an adsorbent, a solubilizer and the like. In addition, the pharmaceutical composition of the present invention may have known form such as tablet, pill, powder, granule, suppository, injection, eye drop, liquid, capsule, troche, aerosol, elixir, suspension, emulsion, syrup and the like.

When the pharmaceutical composition of the present invention is, for example, a solid preparation such as tablet, pill, powder, granule etc., the additive includes, for example, lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium aluminometasilicate, silicic anhydride powder and the like. When a tablet or pill is to be prepared, a film coating of gastrosoluble or enteric substance such as sucrose, gelatin, hydroxypropylcellulose, or hydroxymethylcellulose phthalate etc. may be applied as necessary, or a multi-layer tablet having two or more layers may be produced.

The compound, pharmaceutical composition, or drug of the present invention can be used in combination with (hereinafter to be also referred to combined use) other pharmaceutical composition or drug (hereinafter to be also referred to as a combination drug).

The timing of administration of the pharmaceutical composition or drug of the present invention, and a combination drug is not limited, and they may be administered to the administration subject in the form of a combined drug, simultaneously administered, or administered in a staggered manner. Moreover, a pharmaceutical agent which is characteristically a kit containing the pharmaceutical composition or drug of the present invention and a combination drug may be administered. The dose of the combination drug may be one clinically employed, which can be appropriately determined depending on the subject of administration, age and body weight of the administration subject, condition, administration time, dosage form, administration method,

combination and the like. The mode of administration of the combination drug is not particularly limited, and may be any as long as the pharmaceutical composition or drug of the present invention, and a combination drug are combined.

A pharmaceutical agent comprising 1 to 3 agents selected from the following (1) to (5) and the compound of the present invention or a salt thereof in combination:

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications,

(5) an agent for the treatment or prophylaxis of hypertension

means pharmaceutical agents such as a case in which the "pharmaceutical agent" is a combined drug, a case in which the "pharmaceutical agent" is a kit containing a drug containing said "1 to 3 agents selected from (1) to (5)" and a drug containing the compound of the present invention, a case in which the "pharmaceutical agent" and the drug containing the compound of the present invention are administered simultaneously or at certain intervals, and the like. This pharmaceutical agent is preferably an agent for the treatment or prophylaxis of a pathology involving glucocorticoid.

As the combination drug,

(1) an agent for the treatment or prophylaxis of hyperlipidemia,

(2) an agent for the treatment or prophylaxis of obesity,

(3) an agent for the treatment or prophylaxis of diabetes,

(4) an agent for the treatment or prophylaxis of diabetic complications, and

(5) an agent for the treatment or prophylaxis of hypertension,

can be mentioned, and 1 to 3 agents therefrom and the compound of the present invention can be used in combination.

As the "agent for the treatment or prophylaxis of

hyperlipidemia", for example,

(1) fibrate drugs (PPAR α receptor agonists),

(2) PPAR-δ receptor agonists,

(3) microsomal triglyceride transfer protein (MTP) inhibitors,

(4) cholesteryl ester transfer protein (CETP) inhibitors,

(5) statin drugs (HMG-CoA reductase inhibitors),

(6) anion exchange resins,

(7) probucol,

(8) nicotinic acid drugs,

(9) phytosterol,

(10) apolipoprotein-A1 (Apo-A1) inducers,

(11) lipoprotein lipase (LPL) activators,

(12) endothelial lipase inhibitors,

(13) ezetimibe,

(14) IBAT inhibitors,

(15) squalene synthase inhibitors,

(16) ACAT inhibitors,

(17) LXR receptor agonists,

(18) FXR receptor agonists,

(19) FXR receptor antagonists, and

(20) adenosine A1 agonists

can be mentioned, and specifically, clofibrate, bezafibrate, fenofibrate, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, cerivastatin, cholestyramine, colestimide, tocopherol nicotinate, nicomol, niceritrol, soysterol, gamma oryzanol and the like can be mentioned.

As the "agent for the treatment or prophylaxis of obesity", for example,

(1) leptin drugs,

(2) pancreatic lipase inhibitors,

(3) noradrenaline serotonin reuptake inhibitors,

(4) cannabinoid receptor antagonists,

(5) monoamine reuptake inhibitors,

(6) diacylglycerol acyltransferase (DGAT) inhibitors,

(7) glucose-dependent insulinotropic polypeptide (GIP) receptor antagonists,

(8) leptin receptor agonists,

(9) bombesin receptor subtype 3 (BRS-3) agonists,

(10) perilipin inhibitors,

(11) acetyl-CoA carboxylase 1 (ACC1) inhibitors,

(12) acetyl-CoA carboxylase 2 (ACC2) inhibitors,

(13) fatty acid synthase inhibitors,

(14) sn-1-acyl-glycerol-3-phosphate acyltransferase (AGPAT) inhibitors,

(15) pancreatic phospholipase A2 (pPLA2) inhibitors,

(16) melanocortin (MC) receptor agonists,

(17) neuropeptide Y5 (NPY5) receptor antagonists,

(18) uncoupling protein (UCP) inducer or activators,

(19) carnitine O-palmitoyltransferase 1 (CPT-1) activators,

(20) CCK1 (CCKA) agonists,

(21) Ciliary Neurotrophic Factor (CNTF),

(22) CRF 2 agonists,

(23) neuropeptide Y2 (NPY2) receptor antagonists,

(24) neuropeptide Y4 (NPY4) receptor antagonists,

(25) thyroid hormone receptor beta agonists,

(26) growth hormones,

(27) ATP citrate lyase inhibitors,

(28) 5-HT6 antagonists, and

(29) 5-HT2C agonists

can be mentioned, and specifically, leptin, orlistat, sibutramine, rimonabant, and mazindol and the like can be mentioned.

As the "agent for the treatment or prophylaxis of diabetes", for example,

(1) insulin preparations (injection),

(2) low molecular insulin oral preparations,

(3) sulfonylurea receptor agonists (SU agents),

(4) non-sulfonylurea insulin secretagogues (SU agents),

(5) potassium dependent ATP (KATP) channel openers,

(6) α glucosidase inhibitors,

(7) α amylase inhibitors,

(8) insulin sensitizer,

(9) low molecular tGLP-1 receptor agonists,

(10) tGLP-1 peptide analogs,

(11) dipeptidyl peptidase IV (DPP-IV) inhibitors,

(12) glucagon receptor antagonists,

(13) glucocorticoid receptor antagonists,

(14) biguanides,

(15) SGLUT inhibitors,

(16) fructose-1,6-bisphosphatase (FBPase) inhibitors,

(17) glycogen synthase kinase 3 (GSK-3) inhibitors,

(18) phosphoenolpyruvate carboxykinase (PEPCK) inhibitors,

(19) protein tyrosine phosphatase 1B (PTPase 1B) inhibitors,

(20) SH2 domain-containing inositol phosphatase (SHIP2) inhibitors,

(21) glycogen phosphorylase (GP) inhibitors,

(22) glucokinase activators,

(23) GPR40 receptor agonists,

(24) pyruvate dehydrogenase kinase (PDHK) inhibitors,

(25) glutamine: fructose-6-phosphate aminotransferase (GFAT) inhibitors,

(26) antioxidants; nitric oxide scavengers,

(27) carnitine O-palmitoyltransferase 1 (CPT-1) inhibitors,

(28) growth hormone-releasing factors (GHRF),

(29) triacylglycerol lipase (hormone sensitive lipase) inhibitors,

(30) PPAR γ receptor agonists,

(31) PPAR γ receptor antagonists,

(32) PPAR α/γ receptor agonists,

(33) AMP-activated protein kinase (AMPK) activators,

(34) adiponectin receptor agonists, and

(35) β3 adrenaline receptor agonists

can be mentioned, and specifically, insulin, tolbutamide, glyclopyramide, acetohexamide, chlorpropamide, glybuzole,

glibenclamide, gliclazide, glimepiride, mitiglinide, repaglinide, nateglinide, voglibose, acarbose, miglitol, rosiglitazone maleate, metformin hydrochloride, pioglitazone hydrochloride, buformin hydrochloride and the like can be mentioned.

As the "agent for the treatment or prophylaxis of diabetic complications", for example,

(1) protein kinase C β (PKCβ) inhibitor,

(2) angiotensin II receptor antagonist,

(3) aldose reductase inhibitor,

(4) angiotensin converting enzyme (ACE) inhibitor,

(5) advanced glycation end products (AGE) production inhibitors,

(6) therapeutic agents for neuropathy, and

(7) therapeutic agents for diabetic nephropathy

can be mentioned, and specifically, epalrestat (kinedak), mexiletine hydrochloride, imidapril hydrochloride and the like can be mentioned.

As the "agent for the treatment or prophylaxis of hypertension", for example,

(1) thiazide diuretics,

(2) thiazide-like diuretics,

(3) loop diuretics,

(4) K maintenance diuretics,

(5) β blockers,

(6) α,β blockers,

(7) α blockers,

(8) central sympathetic neurosuppressants,

(9) peripheral sympathetic neurosuppressants (rauwolfia preparations),

(10) Ca antagonist (benzothiazepin),

(11) Ca antagonists (dihydropyridine),

(12) vasodilators,

(13) angiotensin converting enzyme (ACE) inhibitors,

(14) angiotensin II receptor antagonists,

(15) nitrate drug,

(16) endothelin ETA receptor antagonists,

(17) endothelin-converting enzyme inhibitors; Neprilysin inhibitors,

(18) prostaglandin; prostanoid FP agonists,

(19) renin inhibitors,

(20) NOS3 expression enhancers; prostacyclin analogs,

(21) phosphodiesterase V (PDE5A) inhibitors,

(22) prostacyclin analogs, and

(23) aldosterone antagonists

can be mentioned, and specifically, hydrochlorothiazide, trichlormethiazide, benzylhydrochlorothiazide, meticrane, indapamide, tripamide, chlorthalidone, mefruside, furosemide, spironolactone, triamterene, atenolol, bisoprolol fumarate, betaxolol hydrochloride, bevantolol hydrochloride, metoprolol tartrate, acebutolol hydrochloride, celiprolol hydrochloride, nipradilol, tilisolol hydrochloride, Nadolol, propranolol hydrochloride, indenolol hydrochloride, carteolol hydrochloride, pindolol, pindolol sustained-release preparation, bunitrolol hydrochloride, penbutolol sulfate, bopindolol malonate, amosulalol hydrochloride, arotinolol hydrochloride, carvedilol, labetalol hydrochloride, urapidil, terazosin hydrochloride, doxazosin mesylate, bunazosin hydrochloride, prazosin hydrochloride, phentolamine mesylate, clonidine hydrochloride, guanfacine hydrochloride, guanabenz acetate, methyldopa, reserpine, rescinnamine, amlodipine besilate, aranidipine, efonidipine hydrochloride, cilnidipine, nicardipine hydrochloride, nisoldipine, nitrendipine, nifedipine, nifedipine sustained-release preparation, nilvadipine, barnidipine hydrochloride, felodipine, benidipine hydrochloride, manidipine hydrochloride, azelnidipine, diltiazem hydrochloride, hydrazine hydrochloride, todoralazine hydrochloride, budralazine, cadralazine, captopril, enalapril maleate, alacepril, delapril hydrochloride, cilazapril, lisinopril, benazepril hydrochloride, imidapril hydrochloride,

temocapril hydrochloride, quinapril hydrochloride, trandolapril, perindopril erbumine, candesartancilexetil, valsartan, termisartan, olmesartan medoxomil, sodium nitroprusside, nitroglycerin and the like can be mentioned.

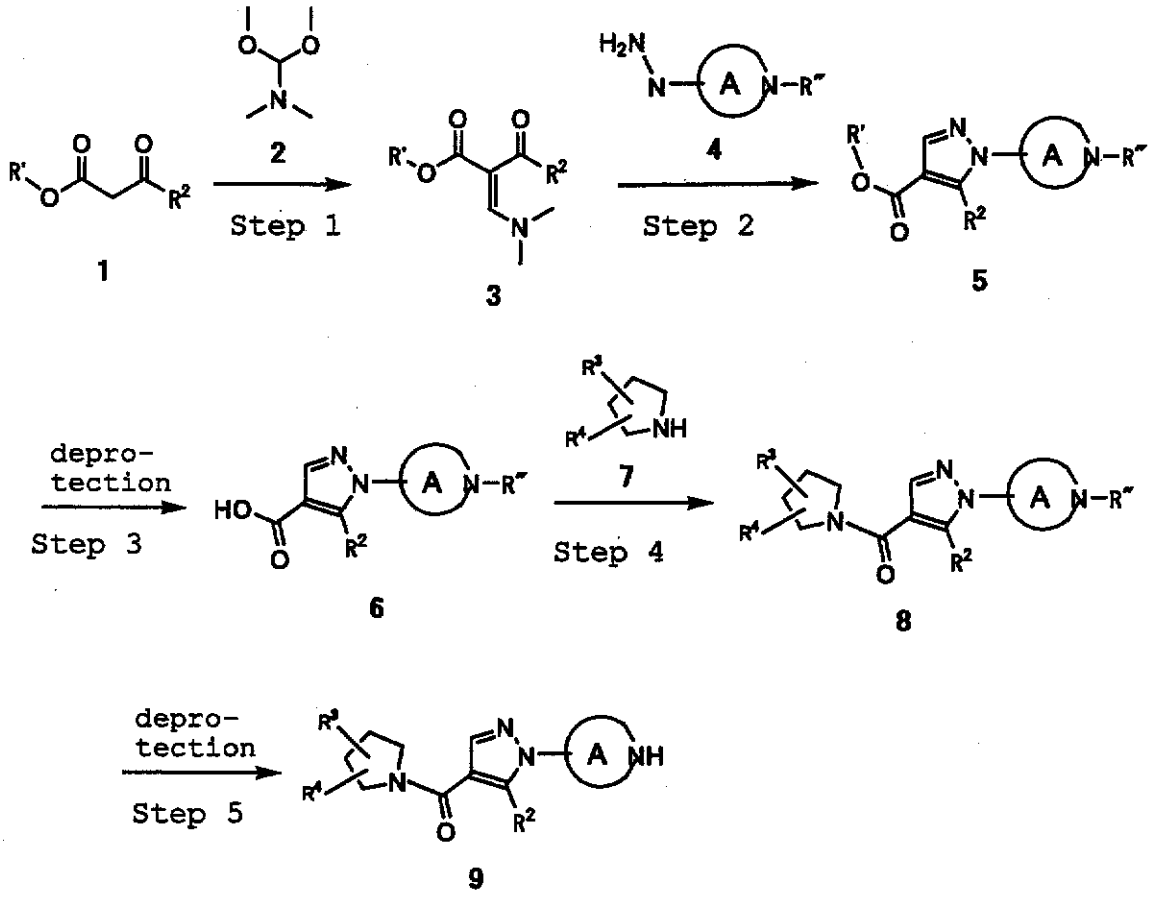
As the combination drug, a drug that raises the blood glucocorticoid level, such as adrenal corticosteroid and the like can be mentioned. The blood glucocorticoid means not only endogenous glucocorticoids, such as corticosterone, cortisol and the like, but also exogenous glucocorticoids due to the administration of adrenal corticosteroid. One to three agents therefrom and the compound of the present invention can be used in combination.

Some examples of the production methods of the compounds of the present invention are shown in the following. However, the production methods of the compounds of the present invention are not limited to these examples. Even in the absence of description in the production method, efficient production can be afforded, where necessary, by introducing a protecting group into a functional group followed by deprotection in a subsequent step, by exchanging the order of respective steps. As the protecting group, for example, a carboxy-protecting group (here, the carboxy-protecting group means those generally used in the field of synthetic organic chemistry, such as methyl group, ethyl group, propyl group, tert-butyl group, benzyl group, p-methoxybenzyl group and the like, which are in the form of esters capable of being easily led to carboxylic acid by hydrolysis, catalytic hydrogenation and the like), an amino-protecting group (here, the amino-protecting group means those generally used in the field of organic synthesis chemistry, such as tert-butoxycarbonyl group, benzyloxycarbonyl group, benzyl group and the like, which can be easily led to an amino group by hydrolysis, catalytic hydrogenation and the like), a hydroxyl group-protecting group (here, the hydroxyl group-protecting group means those generally used in the field of organic synthesis chemistry,

such as tetrahydropyranyl group, methoxymethyl group, methoxyethoxymethyl group, benzyloxymethyl group, benzyl group, p-methoxybenzyl group, p-nitrobenzyl group, trimethylsilyl group, t-butyldimethylsilyl group, acetyl group, benzoyl group, allyl group, t-butyl group and the like, which can be easily led to a hydroxyl group by hydrolysis, catalytic hydrogenation and the like), and the like can be mentioned. The workup after reaction in each step can be applied by a typical method, wherein isolation and purification is performed by selecting or combining conventional methods as necessary, such as crystallization, recrystallization, silica gel chromatography, preparative HPLC and the like.

Production Method 1

In the compound [1'] of the present invention, a compound wherein -X- is -NH- can be produced by the following steps.



1 3 5 6 8 9

wherein R' is a carboxy-protecting group (here, the carboxy-protecting group means those generally used in the field of organic synthesis chemistry, such as methyl group, ethyl group,

propyl group, tert-butyl group, benzyl group, p-methoxybenzyl group and the like), which is in the form of esters capable of being easily led to carboxylic acid by hydrolysis, catalytic hydrogenation and the like, R″ is an amino protecting group (here, the amino-protecting group means those generally used in the field of organic synthesis chemistry, such as tert-butoxycarbonyl group, benzyloxycarbonyl group, benzyl group and the like) which can be easily removed by hydrolysis, catalytic hydrogenation and the like, and other symbols are as defined above.

Step 1

Compound (3) can be obtained by reacting β-ketoester (1) synthesized by a known method with dimethylformamide dimethylacetal (2) in a solvent or in the absence of a solvent. As the solvent, methanol, ethanol, benzene, toluene, xylene, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of dimethylformamide dimethylacetal (2) to be used is generally about 1.5 - about 3 mol, per 1 mol of β-ketoester (1). The amount of the solvent to be used is not particularly limited and can be appropriately determined depending on the kind and the amount of use of the reaction substrate (β-ketoester (1) and dimethylformamide dimethylacetal (2)), reaction temperature, reaction time and the like (the same applies to the amount of the solvent to be used in each Step to be explained below).

Step 2: Step for constructing pyrazole ring

Compound (5) is obtained by reacting hydrazine (4) synthesized by a known method with compound (3) in a solvent. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the

like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of hydrazine (4) to be used is generally about 1 - about 2 mol, per 1 mol of compound (3). When hydrazine (4) is a salt, the reaction is carried out in the presence of a base (the amount of the base to be used is generally about 1 - about 2 mol, per 1 mol of compound (3)), such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like.

Step 3: Deprotection step of carboxyl-protecting group

Compound (6) is obtained by eliminating the carboxyl-protecting group R' of compound (5) by a known method.

Step 4: Amidation step

Compound (8) is obtained by reacting compound (6) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (6). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (6). When amine (7) is a

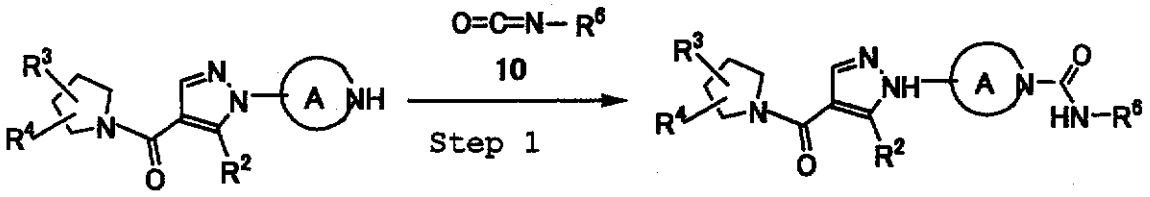
salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. Alternatively, carboxylic acid (6) may be led to an acid halide or a mixed acid anhydride and reacted with amine (7) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (6).

Step 5: Deprotection step of amino protecting group

Compound (9) is obtained by eliminating the amino protecting group R‴ of compound (8) by a known method. Where necessary, it may be converted to a salt by a known method.

Production Method 2

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-CONR^5R^6$ wherein R^5 is a hydrogen atom can be produced by the following Steps.



9 11

wherein each symbol is as defined above.

Step 1: Ureation step

1) When R^6 is other than hydrogen

Compound (11) is obtained by reacting compound (9) with isocyanate (10) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of isocyanate (10) to be used is generally about 1 - about 2 mol per 1 mol of compound

(9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9)). Alternatively, compound (9) may be reacted with 1,1'-carbonyldiimidazole (CDI) (The amount of CDI to be used is generally about 1 - about 3 mol per 1 mol of compound (9)), and then reacted with the corresponding amine.

When R^6 is an alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, it may be appropriately protected with a protecting group and, after ureation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituents, they may be converted, after ureation, to other functional groups by known methods. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

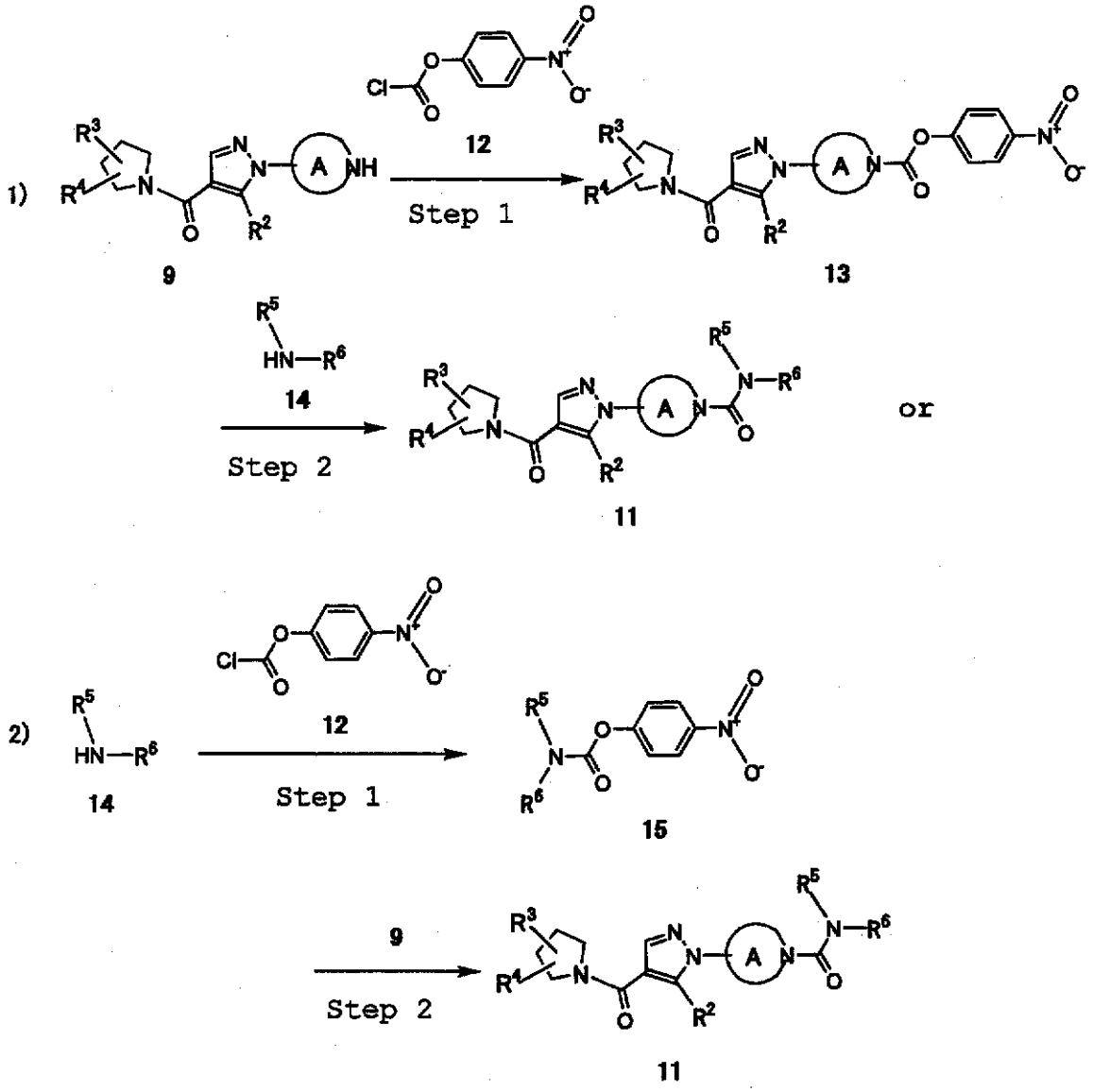
2) When R^6 is hydrogen

Compound (11) is obtained by reacting compound (9) with cyanate in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, water, acetic acid, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of cyanate to be used is generally about 1 - about 10 mol, per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is

generally about 1 - about 2 mol, per 1 mol of compound (9)).

Production Method 3

The compound of the present invention [1'] wherein -X- is $-N(R^1)-$ and R^1 is $-CONR^5R^6$ can be produced by the following steps.



wherein each symbol is as defined above.

Step 1: Phenylcarbamation step

Compound (13) is obtained by reacting compound (9) with 4-nitrophenyl chloroformate (12) in a solvent in the presence of a base. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be

mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of 4-nitrophenyl chloroformate (12) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol, per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9).

Step 2: Ureation step

Compound (11) is obtained by reacting phenylcarbamate intermediate (13) with amine (14) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (14) to be used is generally about 1 - about 3 mol per 1 mol of compound (9). When amine (14) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 3 mol per 1 mol of compound (13)).

As a different method, as shown in the formula 2), compound (15) is obtained in Step 1 by reacting amine (14) with 4-nitrophenyl chloroformate (12) in a solvent, and compound (15) is reacted with amine (9) in Step 2 to give compound (11).

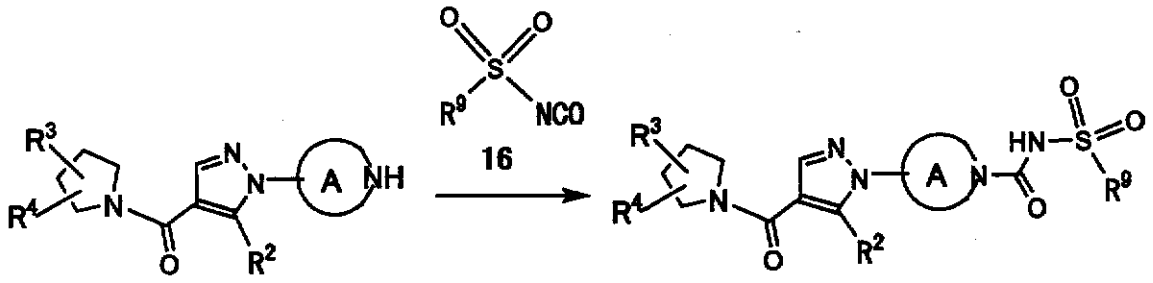
Moreover, other chloroformate or 1,1'-carbonyldiimidazole (CDI) may be used instead of 4-nitrophenyl chloroformate (12).

When R^5 and/or R^6 are/is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are appropriately protected with a protecting group and, after ureation, deprotected. When the alkyl group, cycloalkyl

group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional groups after ureation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 4

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$, R^1 is $-CONR^5R^6$ wherein R^5 is a hydrogen atom, and R^6=$-S(=O)_2R^9$) can be produced by the following Steps.



wherein each symbol is as defined above.

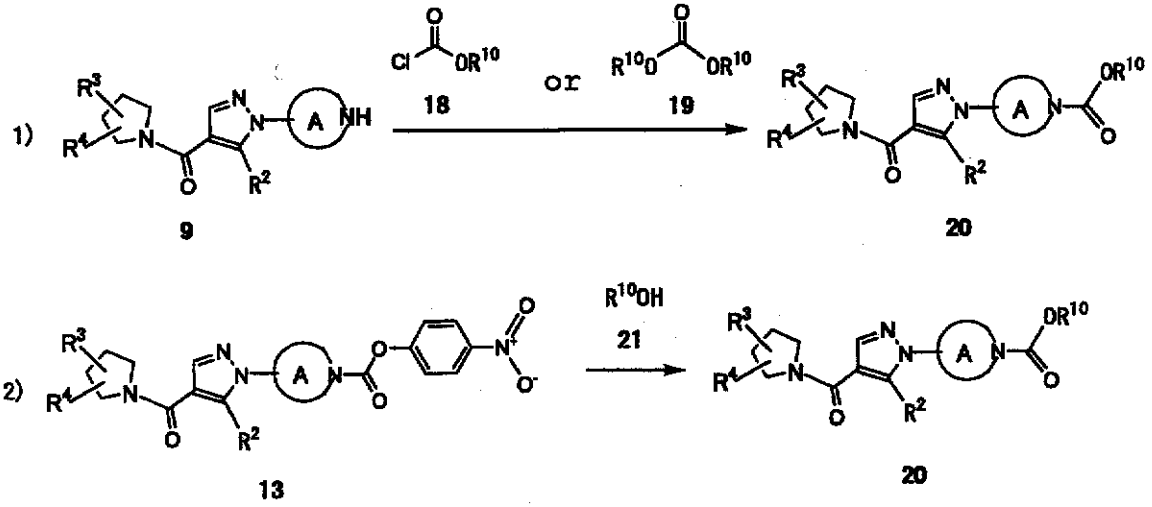
Step 1: Sulfonylureation step

Compound (17) is obtained by reacting compound (9) with sulfonylisocyanate (16) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of sulfonylisocyanate (16) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1

mol of compound (9)).

Production Method 5

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-COOR^{10}$ can be produced by the following Steps.



wherein each symbol is as defined above.

Step 1: Carbamation step

Compound (20) is obtained by reacting compound (9) with chlorocarbonate (18) or carbonate (19) in the presence of a base, in a solvent or without solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of chlorocarbonate (18) or carbonate (19) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9).

When R^{10} is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are

appropriately protected with a protecting group and, after carbamation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional groups after carbamation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

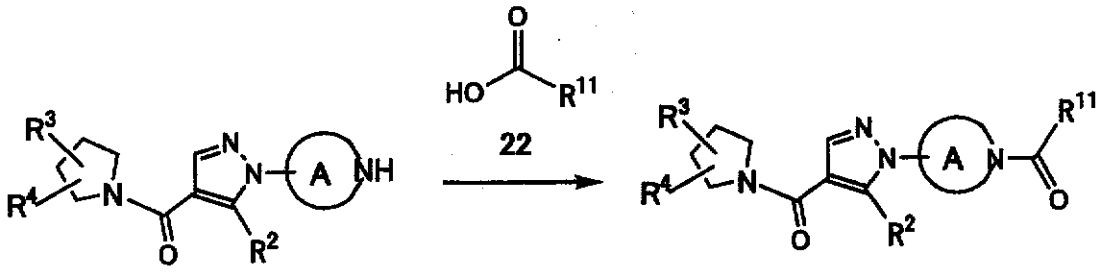
As a different method, as shown in the formula 2), phenylcarbamate intermediate (13) obtained in Production Method 3, Step 1 is reacted with alcohol (21) in a solvent, in the presence of a base to give Compound (20). As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. As the base, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of alcohol (21) to be used is generally about 1 - about 3 mol per 1 mol of phenylcarbamate intermediate (13). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of phenylcarbamate intermediate (13).

When R^{10} is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are appropriately protected with a protecting group and, after carbamation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional

groups after carbamation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 6

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$, and R^1 is $-COR^{11}$ can be produced by the following Steps.



9 23

wherein each symbol is as defined above.

Step 1: Amidation step

Compound (23) is obtained by reacting compound (9) with carboxylic acid (22) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of carboxylic acid (22) to be used is

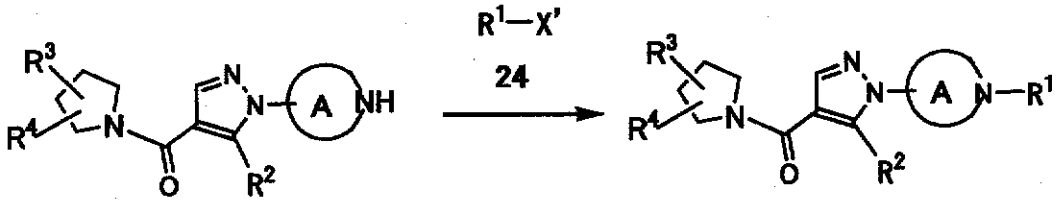
generally about 1 - about 1.5 mol per 1 mol of compound (9). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (9). When compound (9) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. Moreover, carboxylic acid (22) may be led to an acid halide or a mixed acid anhydride and reacted with compound (9) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (9).

When R^{11} is alkyl group, cycloalkyl group, aryl group, heterocyclic group etc. having a functional group, they are appropriately protected with a protecting group and, after amidation, deprotected. When the alkyl group, cycloalkyl group, aryl group, heterocyclic group and the like have substituent(s), they can be converted to other functional groups after amidation by a known method.

For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 7

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is C_{1-6} alkyl group or cycloalkyl group can be produced by the following Steps.



9 25

wherein X' is a halogen atom and other symbols are as defined above.

Step 1: N-alkylation step

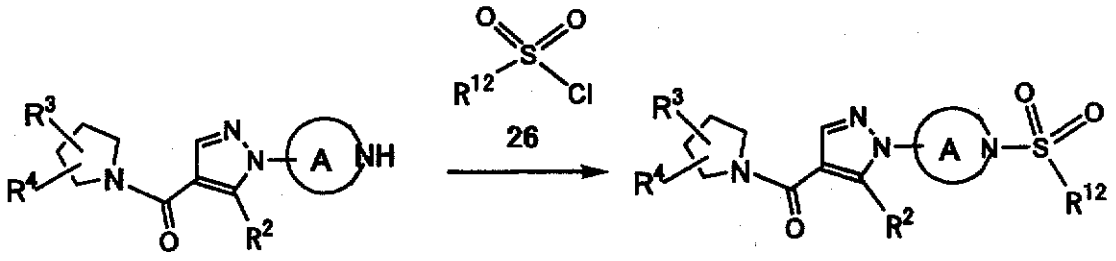
Compound (25) is obtained by reacting compound (9) with alkylhalide (24) in a solvent in the presence of a base. As the base, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. As the solvent, acetonitrile, acetone, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 30 min to 24 hr. The amount of alkylhalide (24) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9). It is also possible to perform reductive amination of compound (9) with the corresponding aldehyde, ketone, or an equivalent thereof.

When R^1 is alkyl group having a functional group, it is appropriately protected with a protecting group and, after N-alkylation, deprotected. When the alkyl group has substituent(s), it can be converted to other functional group after N-alkylation by a known method. For example, conversion

from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 8

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-S(=O)_2R^{12}$ can be produced by the following Steps.



9 27

wherein each symbol is as defined above.

Step 1: Sulfonylation step

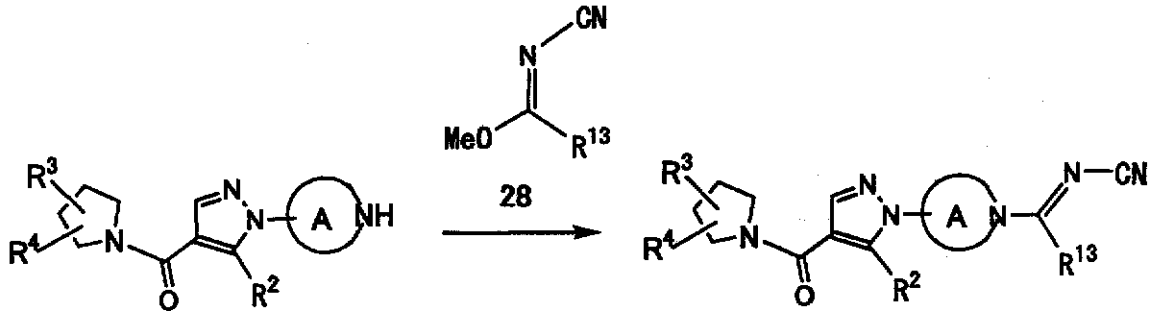
Compound (27) can be obtained by reacting compound (9) with sulfonyl chloride (26) in a solvent in the presence of a base. As the base, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. As the solvent, acetonitrile, acetone, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 30 min to 24 hr. The amount of sulfonyl chloride (26) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine

(9) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of compound (9). In addition, compound (9) may be reacted with the corresponding sulfonic anhydride.

When R^{12} is alkyl group having a functional group, it is appropriately protected with a protecting group and, after sulfonylation, deprotected. When the alkyl group has substituent(s), it can be converted to other functional group after sulfonylation by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 9

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-C(=NCN)R^{13}$ can be produced by the following Steps.



wherein each symbol is as defined above.

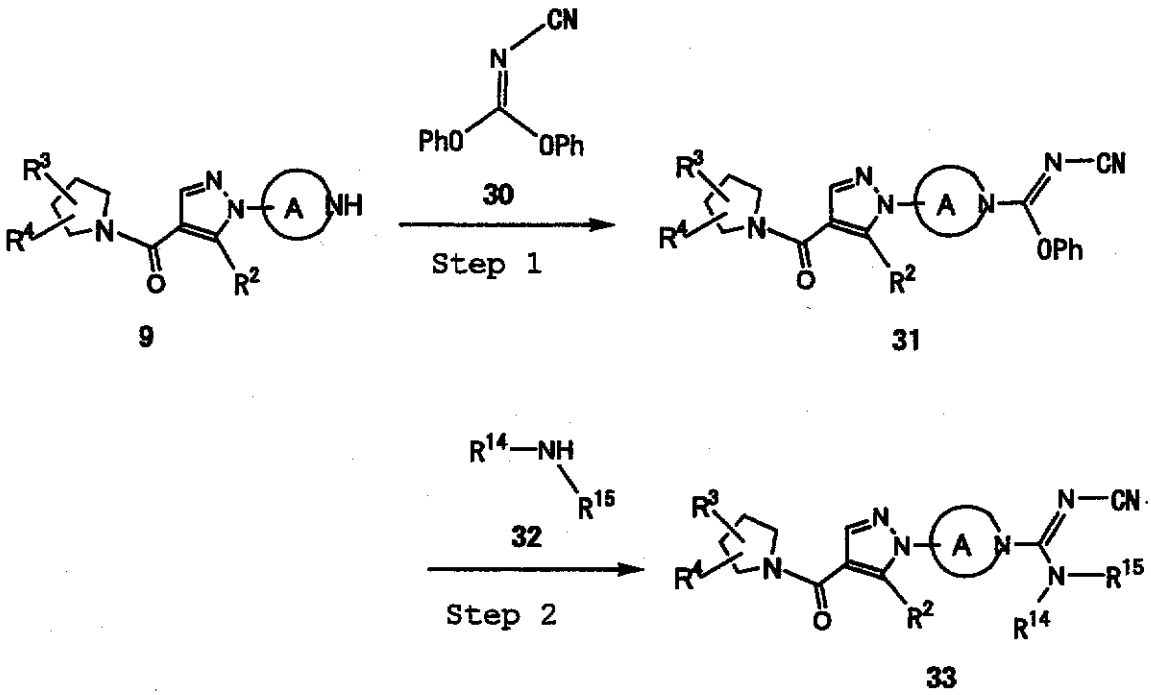
Step 1: Production step of N-cyanoamidine

Compound (29) is obtained by reacting compound (9) with N-cyanoimidoacetate (28) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction

temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of N-cyanoimidoacetate (28) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9)).

Production Method 10

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is $-C(=NCN)NR^{14}R^{15}$ can be produced by the following Steps.



wherein Ph is a phenyl group and other symbols are as defined above.

Step 1

Compound (31) is obtained by reacting compound (9) with diphenyl N-cyanocarbonimidate (30) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction

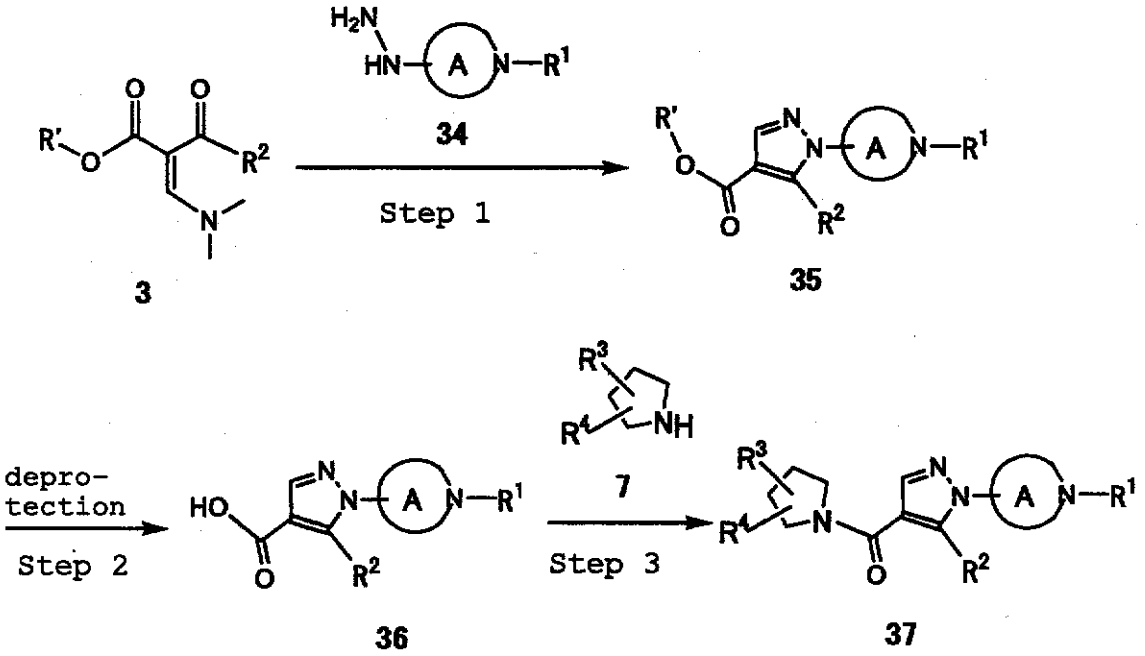
time is generally 1 hr to 24 hr. The amount of diphenyl N-cyanocarbonimidate (30) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). When amine (9) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (9)).

Step 2: Production step of N-cyanoguanidine

Compound (33) is obtained by reacting compound (31) with amine (32) in a solvent. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, N-methylpyrrolidone, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (32) to be used is generally about 1 - about 5 mol per 1 mol of compound (31). When amine (32) is a salt, the reaction is carried out in the presence of a base such as triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 20 mol per 1 mol of compound (31)).

Production Method 11

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is an aryl group or 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



wherein each symbol is as defined above.

Step 1: Step for constructing pyrazole ring from hydrazine (34) and compound (3)

Compound (35) is obtained by reacting hydrazine (34) synthesized by a known method with compound (3) obtained in Production Method 1, Step 1, in a solvent. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of hydrazine (34) to be used is generally about 1.5 - about 3 mol per 1 mol of compound (3). When hydrazine (34) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1.5 - about 3 mol per 1 mol of compound (3)).

Step 2: Deprotection step of carboxyl-protecting group R'

Compound (36) is obtained by eliminating carboxyl-protecting group R' by a known method.

Step 3: Amidation step

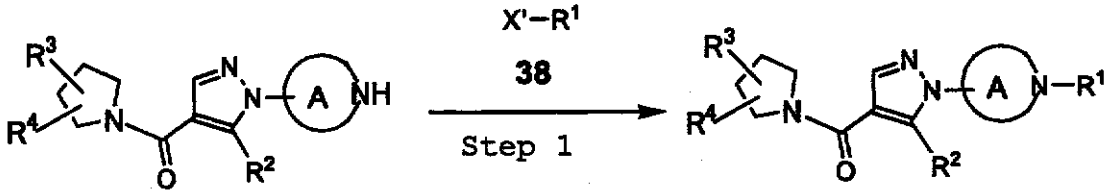
Compound (37) is obtained by reacting compound (36) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (36). In addition, the amount of the condensing agent and the additive to be used is generally about 1- about 1.5 mol and about 1- about 1.5 mol, respectively, per 1 mol of compound (36). When amine (7) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. In addition, carboxylic acid (36) may be led to an acid halide and then reacted with amine (7) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (36).

When R^1 is aryl group or a 5-membered or 6-membered unsaturated monocyclic heterocyclic group having a functional group, it is appropriately protected with a protecting group and thereafter deprotected. When the aryl group or 5-membered

or 6-membered unsaturated monocyclic heterocyclic group has substituent(s), it can be converted to other functional group by a known method after this step. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 12

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is an aryl group or 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



9 39

wherein each symbol is as defined above.

Step 1: Palladium catalyzed Buchwald/Hartwig type amination step

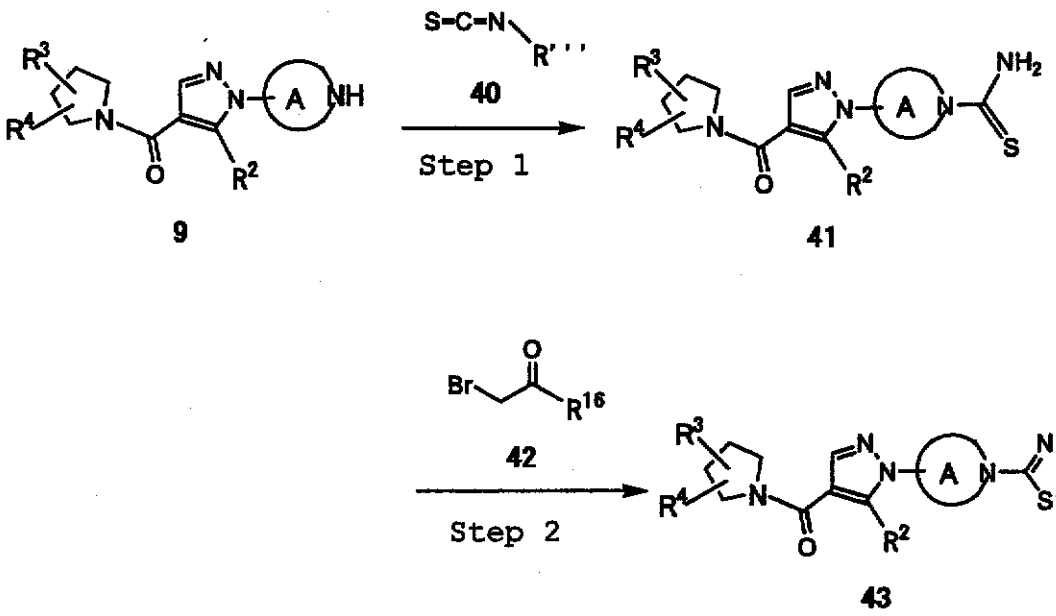
Compound (39) is obtained by reacting compound (9) obtained in Production Method 1 and aromatic halide (38) in a solvent in the presence of a palladium catalyst and a base. As the palladium catalyst, a mixture of palladium acetate and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bis(diphenylphosphino)ferrocene palladium (II) dichloride, tris(dibenzylideneacetone) dipalladium and the like can be mentioned. As the base, tripotassium phosphate (K_3PO_4), sodium carbonate, potassium carbonate, cesium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, potassium tert-butoxide and the like can be mentioned. As the solvent, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane, benzene, toluene, xylene, tert-butanol, and a mixed solvent thereof and

the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of aromatic halide (38) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (9). The amount of the palladium catalyst and the base to be used is generally about 0.01- about 0.1 mol and about 1- about 2 mol, respectively, per 1 mol of compound (9).

When R^1 is an aryl group or a 5-membered or 6-membered unsaturated monocyclic heterocyclic group having a functional group, it is appropriately protected with a protecting group and thereafter deprotected. When the aryl group or a 5-membered or 6-membered unsaturated monocyclic heterocyclic group has substituent(s), it can be converted to other functional group after this step by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 13

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is an aryl group or 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



wherein R‴ is a substituent (e.g., ethoxycarbonyl group, benzoyl group, 9-fluorenylmethoxycarbonyl group and the like) on nitrogen atom, and other symbols are as defined above.

Step 1: Thioureation step

Compound (41) is obtained by reacting compound (9) obtained in Production Method 1 with isothiocyanate (40) in a solvent and eliminating the substituent (R‴) on the nitrogen atom by a known method. As isothiocyanate (40), ethoxycarbonylisothiocyanate, benzoylisothiocyanate, 9-fluorenylmethoxycarbonylisothiocyanate and the like can be mentioned. As the solvent, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of isothiocyanate (40) to be used is generally about 1 - about 2 mol per 1 mol of compound (9). It is possible to react compound (9) with thiophosgene (the amount of thiophosgene to be used is generally about 1 - about 1.5 mol per 1 mol of compound (9)), followed by an ammonia treatment.

Step 2: Step for constructing thiazole ring

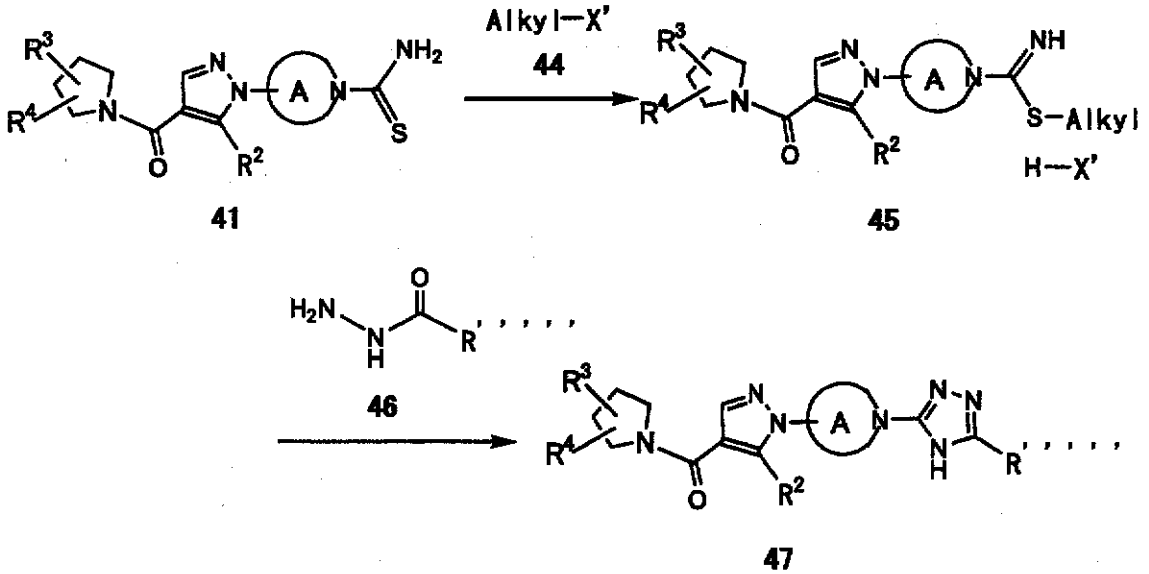
Compound (43) is obtained by reacting compound (41) with

halomethylketone (42) in a solvent. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of halomethylketone (42) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (41).

A thiazolyl group having a functional group can be appropriately protected with a protecting group and thereafter deprotected. When the thiazolyl group has substituent(s), it can be converted to other functional group after this step by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 14

In the compound [1'] of the present invention, a compound wherein -X- is $-N(R^1)-$ and R^1 is a 5-membered or 6-membered unsaturated monocyclic heterocyclic group can be produced by the following Steps.



wherein X' is a halogen atom, Alkyl is a C_{1-6} alkyl group, R''''' is a carboxyl group, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from halogen atom and hydroxyl group), or a cycloalkyl group and other symbols are as defined above.

Step 1

Isothiourea hydrohalide (45) is obtained by reacting compound (41) obtained in Production Method 13, Step 1 with alkylhalide (44) in a solvent. As the solvent, acetonitrile, acetone, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 30 min to 24 hr. The amount of alkylhalide (44) to be used is generally about 1 - about 2 mol per 1 mol of compound (41).

Step 2: Step for constructing triazole ring from isothiourea and hydrazide

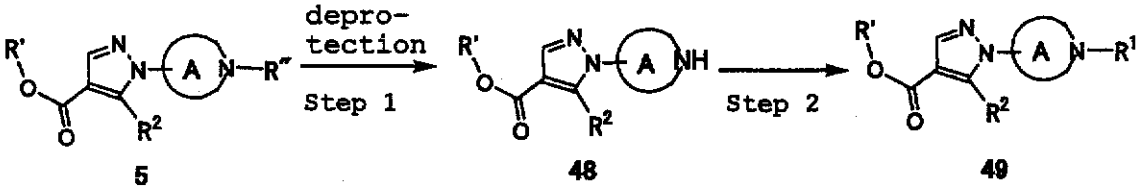
Compound (47) can be obtained by reacting isothiourea hydrohalide (45) with hydrazide (46) synthesized by a known method in a solvent in the presence of a base. As the solvent, methanol, ethanol, n-propanol, isopropanol, n-butanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, dichloromethane, 1,2-dichloroethane, chloroform, benzene, chlorobenzene, O-dichlorobenzene, toluene, xylene, pyridine, 2,6-lutidine, 2,4,6-collidine, acetic acid, water, and a mixed solvent thereof and the like can be mentioned. As the base, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydride, potassium hydride, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The

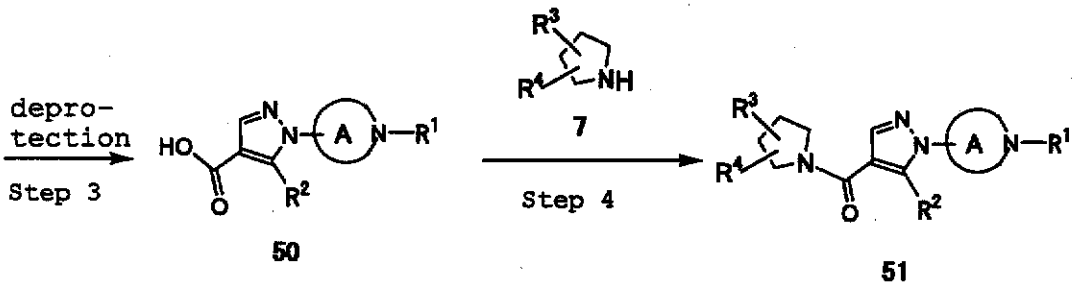
reaction time is generally 30 min to 24 hr. The amount of hydrazide (46) to be used is generally about 1 - about 2 mol per 1 mol of isothiourea hydrohalide (45). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of isothiourea hydrohalide (45). When hydrazide (46) is a salt, the reaction is carried out with a base in an amount of about 2 - about 4 mol per 1 mol of isothiourea hydrohalide (45).

A triazolyl group having a functional group can be appropriately protected with a protecting group and thereafter deprotected. When the triazolyl group has substituent(s), the substituent(s) can be converted by a known method to other functional group after this step. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 15

In the compound [1'] of the present invention, a compound wherein -X- is -N(R^1)- can be produced by the following Steps.





wherein each symbol is as defined above.

Step 1: Deprotection step of amino protecting group

Compound (48) is obtained by eliminating the amino protecting group R" of compound (5) obtained in Production

Method 1, Step 2.

Step 2: Introduction of R^1

Compound (49) is obtained by introducing R^1 into compound (48) by a method similar to Production Methods 2 to 10, and Production Methods 12 to 14.

Step 3: Deprotection step of carboxyl-protecting group

Compound (50) is obtained by eliminating the carboxyl-protecting group R' of compound (49) by a known method.

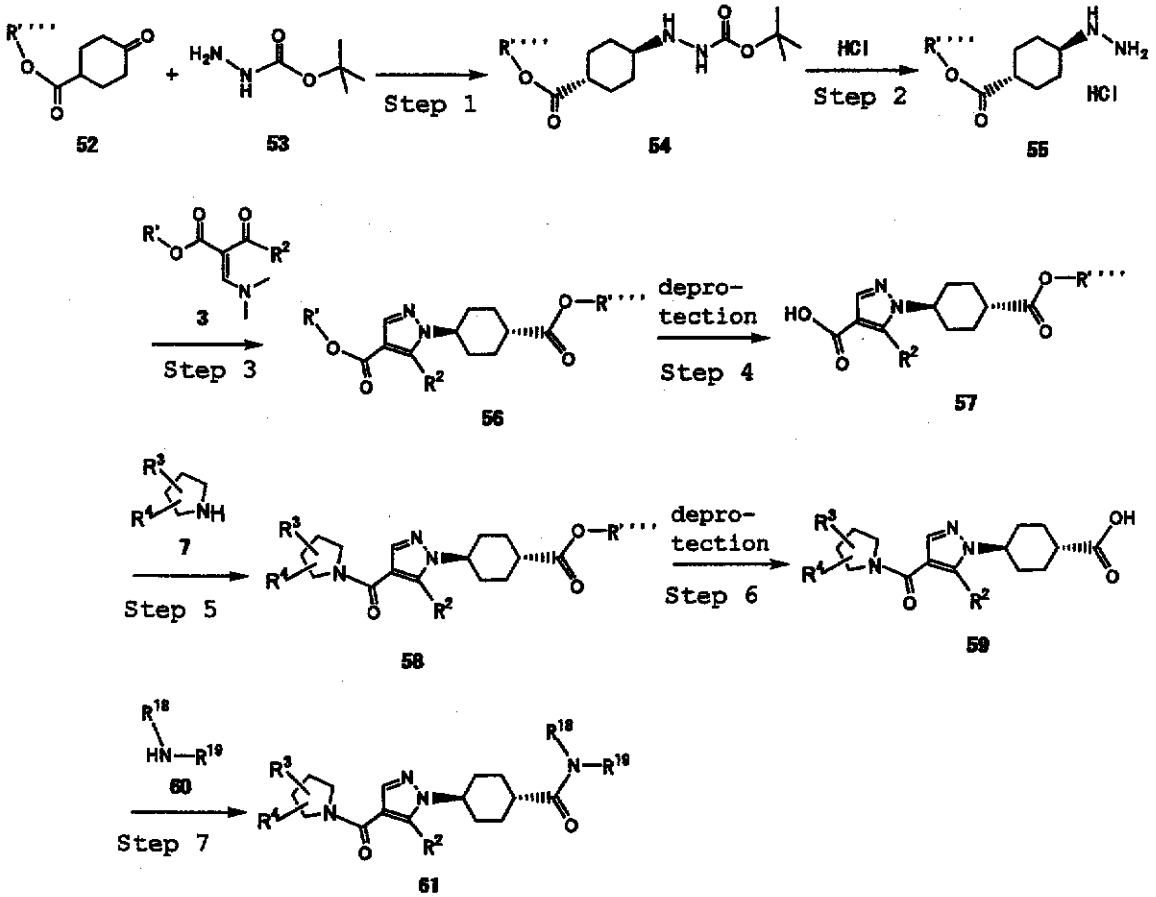
Step 4: Amidation step

Compound (51) is obtained by reacting compound (50) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (50). In addition, the amount of the condensing agent and the additive to be used is generally about 1- about 1.5 mol and about 1- about 1.5 mol, respectively, per 1 mol of compound (50). When amine (7) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like (the amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (50)).

R^1 having a functional group is appropriately protected with a protecting group and thereafter deprotected. When R^1 has substituent(s), it can be converted to other functional group after this step by a known method. For example, conversion from hydroxyl group to alkoxy group or ketone, from amino group to alkylamino group, alkylcarbonylamino group or alkylsulfonylamino group, from alkoxycarbonyl group to carboxyl group, aminocarbonyl group, alkylaminocarbonyl group or hydroxymethyl group, and from sulfide to sulfone or sulfoxide can be mentioned.

Production Method 16

In the compound [1'] of the present invention, a compound wherein -X- is $-C(R^7R^8)-$ can be produced by the following Steps.



wherein each symbol is as defined above where R'''' is a carboxy-protecting group (here, the carboxy-protecting group means those generally used in the field of organic synthesis chemistry, such as methyl group, ethyl group, propyl group,

tert-butyl group, benzyl group, p-methoxybenzyl group and the like, which is in the form of esters capable of being easily led to carboxylic acid by hydrolysis, catalytic hydrogenation and the like)

Step 1: Reductive alkylation

Compound (54) is obtained by reacting ketone (52) with tert-butyl carbazate (53) in a solvent in the presence of a reducing agent. As the reducing agent, sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride, borane complex and the like can be mentioned. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, dichloromethane, chloroform, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, benzene, toluene, xylene, acetic acid, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of the reducing agent to be used is generally about 2- about 5 mol, per 1 mol of compound (52).

Step 2: de-BOC (tert-butoxycarbonyl group)

Compound (54) is reacted with 4N hydrochloric acid ethyl acetate solution, or 4N hydrochloric acid 1,4-dioxane solution to give hydrazine hydrochloride (55). In addition, after de-BOC by the action of trifluoroacetic acid in a solvent, it may be converted to hydrochloride. As the solvent, dichloromethane, chloroform and the like can be mentioned.

Step 3: Step for constructing pyrazole ring from hydrazine hydrochloride (55) and compound (3)

Compound (56) is obtained by reacting hydrazine hydrochloride (55) with compound (3) in a solvent in the presence of a base. As the solvent, methanol, ethanol, n-propanol, n-butanol, isopropanol, acetonitrile, diethyl ether, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, dichloromethane, chloroform, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. As the base, sodium carbonate, potassium carbonate, sodium hydrogen

carbonate, potassium hydrogencarbonate, sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature is generally 20°C to 250°C. The reaction time is generally 1 hr to 24 hr. The amount of hydrazine hydrochloride (55) to be used is generally about 1 - about 2 mol per 1 mol of compound (3). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of compound (3).

Step 4: Deprotection step of carboxyl-protecting group

Compound (57) is obtained by eliminating carboxyl-protecting group R' of compound (56) by a known method.

Step 5: Amidation step

Compound (58) is obtained by reacting compound (57) with amine (7) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (7) to be used is generally about 1 - about 1.5 mol per 1 mol of compound (57). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (57). When amine (7) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogencarbonate, sodium acetate,

potassium acetate, sodium hydroxide, potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. In addition, carboxylic acid (57) may be led to an acid halide or a mixed acid anhydride and reacted with amine (7) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of compound (57).

Step 6: Deprotection step of carboxyl-protecting group

Carboxylic acid (59) is obtained by eliminating the carboxyl-protecting group R"" of compound (58) by a known method.

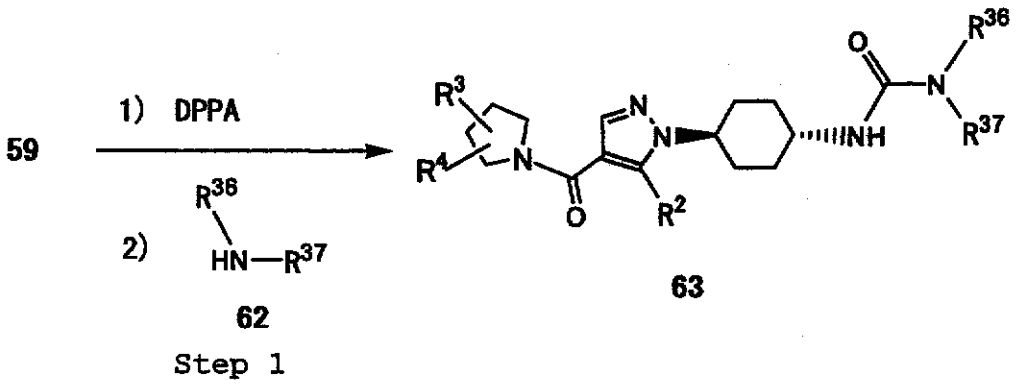
Step 7: Amidation step

Compound (61) is obtained by reacting carboxylic acid (59) with amine (60) in a solvent in the presence of a condensing agent and an additive. As the condensing agent, dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI) or, diphenylphosphoryl azide (DPPA) and the like can be mentioned. As the additive, 1-hydroxybenzotriazole (HOBT), N-hydroxysuccinic imide (HOSu), 4-dimethylaminopyridine (DMAP) and the like can be mentioned. As the solvent, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of amine (60) to be used is generally about 1 - about 1.5 mol per 1 mol of carboxylic acid (59). In addition, the amount of the condensing agent and the additive to be used is generally about 1 - about 1.5 mol and about 1 - about 1.5 mol, respectively, per 1 mol of compound (59). When amine (60) is a salt, the reaction is carried out in the presence of a base such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium acetate, potassium acetate, sodium hydroxide,

potassium hydroxide, lithium hydroxide, triethylamine, N,N-diisopropylethylamine, pyridine and the like. Moreover, carboxylic acid (59) may be led to an acid halide or a mixed acid anhydride and reacted with amine (60) in the presence of a base. The amount of the base to be used is generally about 1 - about 1.5 mol per 1 mol of carboxylic acid (59).

Production Method 17

In the compound [1'] of the present invention, a compound wherein -X- is $-C(R^7R^8)-$ can be produced by the following Steps.



wherein each symbol is as defined above.

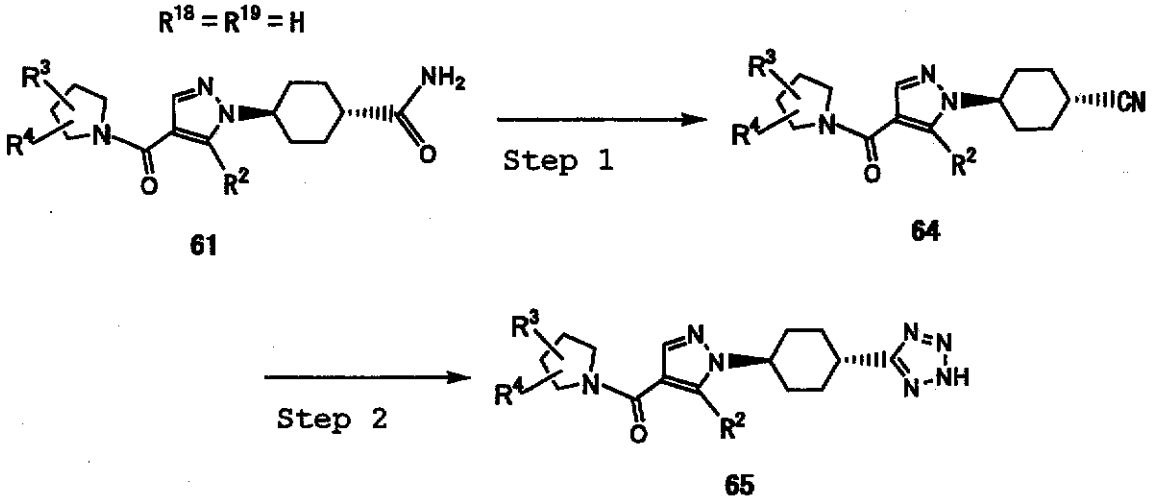
Step 1: Ureation step

Carboxylic acid (59) is reacted with diphenylphosphoryl azide (DPPA) in a solvent in the presence of a base to lead to isocyanate, which is reacted with amine (62) to give urea (63). As the solvent, dichloromethane, chloroform, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, benzene, toluene, xylene and the like can be mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. The reaction temperature for the step to give isocyanate is generally 20°C to 150°C, and the step to give urea is generally 0°C to 100°C. The reaction time is generally 1 hr to 24 hr for both steps. The amount of DPPA to be used is generally about 1- about 2 mol per 1 mol of carboxylic acid (59). The amount of the base to be used is generally about 1 - about 2 mol per 1 mol of carboxylic acid (59). The amount of amine (62) to be used is generally about 1 - about 5 mol per 1

mol of carboxylic acid (59).

Production Method 18

In the compound [1'] of the present invention, a compound wherein -X- is $-C(R^7R^8)-$ can be produced by the following Steps.



61 64 65

wherein each symbol is as defined above.

Step 1: Cyanation step

Nitrile (64) is obtained by reacting amide (61) with a dehydrating agent in a solvent in the presence of a base. As the dehydrating agent, trifluoromethanesulfonic acid anhydride, p-toluenesulfonyl chloride, trichloroacetyl chloride, trifluoroacetic acid anhydride, phosphorus oxychloride, thionyl chloride and the like can be mentioned. As the base, triethylamine, N,N-diisopropylethylamine, pyridine and the like can be mentioned. As the solvent, dichloromethane, chloroform, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, pyridine, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 100°C. The reaction time is generally 1 hr to 24 hr. The amount of the dehydrating agent to be used is generally about 1 - about 2 mol per 1 mol of amide (61). The amount of the base to be used is generally about 1 - about 2 mol, per 1 mol of amide (61).

Step 2: Step for constructing tetrazole ring

Nitrile (64) is reacted in a solvent in the presence of an azidating reagent to give tetrazole (65). As the azidating

reagent, sodium azide, azidotrimethyltin, azidotributyltin, azidotrimethylsilane and the like can be mentioned. As the solvent, dichloromethane, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, N,N-dimethylformamide, benzene, toluene, xylene, and a mixed solvent thereof and the like can be mentioned. The reaction temperature is generally 20°C to 150°C. The reaction time is generally 1 hr to 24 hr. The amount of the azidating reagent to be used is generally about 1 - about 2 mol per 1 mol of nitrile (64).

The production methods described in this specification are examples of the production methods of the compound of the present invention, and compounds other than those explained above can be produced by combining known conventional methods in the field of organic synthesis chemistry.

Examples

The heterocyclic compounds and production methods thereof of the present invention are explained in detail in the following by referring to Examples, which are not to be construed as limitative.

Example 1

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

Step 1

Production of methyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate

Methyl 3-cyclopropyl-3-oxopropionate (2.0 g) was dissolved in toluene (20 ml). To the obtained solution was added dimethylformamide dimethylacetal (3.0 ml) and the mixture was refluxed for 3 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:acetone=2:1) to give the title compound as a yellow oil (2.61 g).

Step 2

Production of methyl 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-

cyclopropyl-1H-pyrazole-4-carboxylate

Methyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate (1.0 g) produced in the previous step and benzyl 4-hydrazinopiperidine-1-carboxylate hydrochloride (1.49 g) synthesized by a known method were suspended in ethanol. To the obtained suspension was added triethylamine (0.78 ml) and the mixture was refluxed for 3.5 hr. Water was added to the reaction mixture and the mixture was extracted with diethyl ether. The diethyl ether layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2.5:1) to give the title compound as a yellow oil (1.58 g).

Step 3

Production of 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

Methyl 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate (1.58 g) produced in the previous step was dissolved in tetrahydrofuran (5 ml), methanol (5 ml) and water (10 ml), lithium hydroxide monohydrate (834 mg) was added and the mixture was stirred at 50°C for 6 hr. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, acidified with 2N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the obtained residue were added diethyl ether and n-hexane, and the precipitated solid was collected by filtration, and dried to give the title compound as a white amorphous solid (1.27 g).

Step 4

Production of 1-[1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid (800 mg) produced in the previous step, 1-hydroxybenzotriazole (332 mg) and 1-ethyl-3-(3-

dimethylaminopropyl)-carbodiimide hydrochloride (498 mg) were dissolved in N,N-dimethylformamide (10 ml), and the mixture was stirred for 15 min. To the obtained solution were added 3-(pyridin-3-yl)pyrrolidine (330 mg) and 4-dimethylaminopyridine (catalytic amount) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=11:1) to give the title compound as a white amorphous solid (1.06 g).

Step 5

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

1-[1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine (970 mg) produced in the previous step was dissolved in methanol (12 ml), 10% palladium carbon (50% water content) (200 mg) was added, and the mixture was stirred under a hydrogen atmosphere for 2.5 hr. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by chromatography (neutral alumina) (chloroform:methanol=7:1) to give the title compound as a white amorphous solid (718 mg).

Example 2

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Step 1

Production of (S)-3-acetyl-4-isopropyl-5,5-diphenyloxazolidin-2-one

Under an argon atmosphere, (S)-4-isopropyl-5,5-diphenyloxazolidin-2-one (1.56 g) was suspended in

tetrahydrofuran (22 ml), and 1.6M n-butyllithium/n-hexane solution (3.64 ml) was added under ice-cooling. After 10 min, acetyl chloride (0.47 ml) was added, and the mixture was stirred overnight while allowing the mixture to gradually return to room temperature. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was concentrated under reduced pressure. Water was added to the obtained residue and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous magnesium sulfate. The ethyl acetate layer was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=4:1) to give the title compound as white crystals (1.69 g).

Step 2

Production of (S)-4-isopropyl-3-[(S)-4-nitro-3-(2-trifluoromethylphenyl)butyryl]-5,5-diphenyloxazolidin-2-one

(S)-3-Acetyl-4-isopropyl-5,5-diphenyloxazolidin-2-one (4.74 g) produced in the previous step was dissolved in dichloromethane (73 ml) under an argon atmosphere, and titanium tetrachloride (3.17 ml) and N,N-diisopropylethylamine (3.06 ml) were added at -78°C. The mixture was gradually warmed to 0°C over 30 min, again cooled to -78°C and a solution of 1-[(E)-2-nitrovinyl]-2-trifluoromethylbenzene (3.50 g) in dichloromethane (27 ml) was added. titanium tetrachloride (3.17 ml) was added and, 2 hr later, saturated aqueous ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=5:1) and crystallized from diethyl ether:n-pentane to give the title

compound as white crystals (2.62 g).

Step 3

Production of (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one

To (S)-4-isopropyl-3-[(S)-4-nitro-3-(2-trifluoromethylphenyl)butyryl]-5,5-diphenyloxazolidin-2-one (2.51 g) produced in the previous step were added ethanol (35 ml) and ethyl acetate (35 ml), and Raney nickel (50% in water) (2.8 g) was added. After stirring overnight under a hydrogen atmosphere, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as white crystals (850 mg).

Step 4

Production of (S)-3-(2-trifluoromethylphenyl)pyrrolidine

To (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one (803 mg) produced in the previous step was added tetrahydrofuran (7 ml), and aluminum lithium hydride (200 mg) was added. After heating under reflux for 1.5 hr, water (0.2 ml), 4N aqueous sodium hydroxide solution (0.2 ml) and water (0.4 ml) were added under ice-cooling. Anhydrous magnesium sulfate was added, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound as a pale-yellow oil (722 mg).

$[\alpha]^{25}D$=+23.9 (c=0.504, EtOH)

Step 5

Production of 1-[1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid (235 mg) produced in Example 1, Step 3, 1-hydroxybenzotriazole (127 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (159 mg) were dissolved in N,N-dimethylformamide (6 ml), and the mixture was stirred for 15 min. To the obtained solution were added (S)-3-

(2-trifluoromethylphenyl)pyrrolidine (151 mg) produced in the previous step and 4-dimethylaminopyridine (78 mg), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, 1N aqueous potassium hydrogensulfate, saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=40:1) to give the title compound as a white amorphous solid (287 mg).

Step 6

Production of 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-[1-(1-Benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (2.0 g) produced in the previous step was dissolved in methanol (14 ml), palladium hydroxide carbon (0.2 g) was added, and the mixture was stirred under a hydrogen atmosphere for 15 hr. The catalyst was filtered off with celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol (6.4 ml), and 4N hydrochloric acid ethyl acetate solution (1.32 ml) was added. The mixture was concentrated under reduced pressure, and crystallized from ethyl acetate+diisopropyl ether to give the title compound as white crystals (1.45 g).

Step 7

(S)-3-(2-trifluoromethylphenyl)pyrrolidine produced in the above-mentioned Step 4 and a hydrochloride thereof can also be produced according to the following Step.

Step 7-1

Production of dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate

Toluene (40 ml) was added to 1-((E)-2-nitrovinyl)-2-trifluoromethylbenzene (4.34 g), and dimethyl malonate (3.4 ml) and 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea (413 mg) disclosed in WO2005/000803 and J. Am. Chem. Soc., 2005, 127, 119-125 were added under ice-cooling. The mixture was stirred under ice-cooling for 24 hr. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from 2-propanol to give the title compound (5.31 g) as white crystals.

This reaction can also be carried out using catalysts disclosed in J. Am. Chem. Soc., 1999, 121, 10215-10216, J. Am. Chem. Soc., 2005, 127, 9958-9959, J. Am. Chem. Soc., 2006, 128, 1454-1455 and the like, instead of 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea.

Step 7-2

Production of methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate

Dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate (4.0 g) produced in the previous Step was added to a suspension of Raney nickel (2.0 g) in tetrahydrofuran (10 ml)/methanol (10 ml), and the mixture was stirred under 3.5 atm hydrogen atmosphere at room temperature for 24 hr. Insoluble materials were filtered off through celite. The filtrate and washing were combined and concentrated under reduced pressure. Toluene was added to the residue, and the mixture was washed with 10% aqueous potassium carbonate solution and water, and the organic layer was concentrated under reduced pressure. The residue was crystallized from toluene+n-hexane to give the title compound (2.38 g) as white crystals.

This reaction can also be carried out using palladium carbon instead of Raney nickel with an acid such as acetic acid, tosylic acid, mesylic acid and the like.

Step 7-3

Production of (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one

Methanol (3.8 ml) was added to methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate (1.0 g) produced in the previous Step, 1N-aqueous sodium hydroxide solution (3.8 ml) was further added, and the mixture was stirred at 65°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was acidified with 1N-hydrochloric acid under ice-cooling and extracted twice with butyl acetate. The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Butyl acetate (10 ml) was newly added to the residue, and the mixture was stirred overnight at 100°C. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from n-hexane to give the title compound (667 mg) as white crystals.

Step 7-4

Production of (S)-3-(2- trifluoromethylphenyl)pyrrolidine hydrochloride

To a solution of (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one (22.9 g) produced in the previous Step in THF (100 ml) was added dropwise 1M lithium aluminium hydride THF solution (100 ml) under an argon atmosphere at 85°C over 1 hr, and the mixture was further stirred at said temperature for 1 hr. After allowing to cool, 50% aqueous Rochelle salt solution was added under ice-cooling, and the mixture was partitioned between water and ethyl acetate. The organic layer was separated and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, and the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Ethyl acetate (60 ml) was added to the residue, 4N-hydrochloric acid ethyl acetate solution (37.5 ml) was further added under ice-cooling, and the mixture was stirred at room temperature. The precipitated crystals were collected by filtration to give

the title compound (20.6 g) as white crystals.

$[\alpha]^{25}D$ = +10.3 (c = 0.55, MeOH)

Example 3

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine (100 mg) produced in Example 1, Step 5 was dissolved in chloroform (2 ml), triethylamine (38 µl) and 2-fluorophenylisocyanate (34 µl) were added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=11:1) to give the title compound as a white amorphous solid (111 mg).

Example 4

Production of 1-[1-(1-carbamoylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (1.0 g) produced by a method similar to that of Example 1, Step 5 was dissolved in acetic acid (3 ml) and water (6 ml), and an aqueous solution (6 ml) of sodium cyanide (300 mg) was added dropwise at room temperature. The mixture was stirred at room temperature for 6 hr, during which sodium cyanide (750 mg total) was further added. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, water and brine, and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). Diethyl ether (10 ml) was added, and the mixture was stirred at room temperature for 2 hr. The precipitated solid was collected by filtration

and dried to give the title compound as white crystals (581 mg).

Example 5

Production of 1-{1-[1-(2-carboxyphenylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (703 mg) of Example 2 was suspended in chloroform (7 ml), and triethylamine (0.23 ml) was added. Under ice-cooling, 2-methoxycarbonylphenylisocyanate (292 mg) was added, and the mixture was stirred at room temperature for 2 hr. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=30:1) to give 1-{5-cyclopropyl-1-[1-(2-methoxycarbonylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (992 mg) as a white amorphous solid.

The obtained 1-{5-cyclopropyl-1-[1-(2-methoxycarbonylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (244 mg) was dissolved in tetrahydrofuran (0.4 ml) and methanol (0.2 ml), 4N aqueous sodium hydroxide solution (0.4 ml) was added, and the mixture was stirred at 60°C for 4 hrs. The mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water. Under ice-cooling, the mixture was acidified with 2N hydrochloric acid and extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. n-Hexane was added to the residue to allow crystal precipitation. The obtained crystal was washed with n-hexane and dried under reduced pressure to give the title compound as a white amorphous solid (181 mg).

Example 6

Production of 1-{5-cyclopropyl-1-[1-(2-

hydroxymethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-{5-Cyclopropyl-1-[1-(2-methoxycarbonylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (213 mg) obtained in Example 5 was dissolved in tetrahydrofuran (2 ml) and ethanol (2 ml), and lithium chloride (30 mg) and sodium borohydride (26 mg) were added under ice-cooling. The mixture was stirred overnight at room temperature. The precipitated insoluble material was collected by filtration, and washed with chloroform. The filtrate and washing were combined, and the mixture was washed with water, saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=30:1) to give the title compound as a white amorphous solid (109 mg).

Example 7

Production of 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 5, the title compound was obtained as a white amorphous solid (530 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (1.07 g) of Example 2.

Example 8

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 5, the title compound was obtained as a white amorphous solid (202 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (206 mg) of Example 2.

Example 9

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxy-1,1-dimethylethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 5, the title compound was obtained as a white amorphous solid (341 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (350 mg) of Example 2.

Example 10

Production of 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

To 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (5.04 g) of Example 2 was added chloroform (50 ml), N,N-diisopropylethylamine (4.68 ml) and 4-nitrophenyl chloroformate (2.39 g) was added under ice-cooling, and the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, acidified with 1N hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a pale-yellow amorphous form (5.41 g).

Step 2

Production of 1-{1-[1-(2-acetylaminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-

4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg) produced in the previous step was dissolved in N-methylpyrrolidone (1 ml), and N-(2-aminoethyl)-acetamide (96 µl) was added. The mixture was stirred overnight at 80°C. After allowing to cool, 10% aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, 1N hydrochloric acid and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous form (65 mg).

Example 11

Production of 1-{1-[1-(2-aminoethylcarbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-{5-Cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg) produced in Example 10, Step 1 and t-butyl (2-aminoethyl)carbamate (160 mg) were dissolved in acetonitrile (1 ml), and the mixture was heated under reflux overnight. The mixture was diluted with chloroform, and the mixture was washed with water, saturated aqueous potassium hydrogencarbonate solution, water and brine, and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). The obtained amorphous solid was dissolved in ethyl acetate (1 ml), and 4N hydrochloric acid ethyl acetate solution (4 ml) was added. The precipitated solid was collected by filtration and dried to give the title compound as a white amorphous solid (111 mg).

Example 12

Production of 1-{5-cyclopropyl-1-[1-(1,1-dioxothiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine

1-{5-Cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (250 mg) produced in Example 10, Step 1 and thiomorpholine (0.13 ml) were dissolved in N-methylpyrrolidone (1 ml), and the mixture was stirred overnight at 100°C. After allowing to cool, the mixture was diluted with diethyl ether, washed with water, 5% aqueous potassium carbonate solution and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=30:1) to give 1-{5-cyclopropyl-1-[1-(thiomorpholine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine as a white amorphous solid (224 mg). This was dissolved in chloroform (4 ml), and m-chloroperbenzoic acid (319 mg) was added under ice-cooling. The mixture was stirred for 3 hr while allowing it to gradually return to room temperature. Saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution were added, and the mixture was extracted with chloroform. The chloroform layer was washed with brine and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=30:1) to give the title compound as a white amorphous solid (198 mg).

Example 13

Production of 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (130 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-

1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 14

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxypiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (176 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 15

Production of 1-{1-[1-(azetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (150 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 16

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxypyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (175 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 17

Production of 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a pale-yellow amorphous solid (170 mg)

from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 18

Production of 1-{5-cyclopropyl-1-[1-(4,4-difluoropiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a pale-yellow amorphous solid (132 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 19

Production of 1-{5-cyclopropyl-1-[1-(3,3-difluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a pale-yellow amorphous solid (152 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 20

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxyazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (158 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 21

Production of 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title

compound was obtained as a white amorphous solid (171 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 22

Production of 1-(5-cyclopropyl-1-{1-[(S)-3-hydroxypyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (172 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 23

Production of 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-methylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (60 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 24

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxymethylpiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (94 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 25

Production of 1-{1-[1-(4-carboxypiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (65 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (172 mg).

Example 26

Production of 1-{5-cyclopropyl-1-[1-(3-oxopiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (143 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 27

Production of 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxymethylpyrrolidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (150 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 28

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxymethylazetidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (178 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 29

Production of 1-{5-cyclopropyl-1-[1-(4-methylpiperazine-1-

carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (66 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 30

Production of 1-{5-cyclopropyl-1-[1-(4-isopropylpiperazine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (50 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 31

Production of 1-{1-[1-(4-acetylpiperazine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (56 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 32

Production of 1-(5-cyclopropyl-1-{1-[(R)-3-hydroxypiperidine-1-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a yellow amorphous solid (170 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg).

Example 33

Production of 1-{1-[1-(4-carbamoylpiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (108 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg).

Example 34

Production of 1-{1-[1-(3-carbamoylazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (93 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (171 mg).

Example 35

Production of 1-{1-[1-(4-aminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a white amorphous solid (302 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 36

Production of 1-{1-[1-(3-aminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a pale-brown yellow amorphous solid (635 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 37

Production of 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a white amorphous solid (59 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 38

Production of 1-{5-cyclopropyl-1-[1-(4-dimethylaminopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (74 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 39

Production of 1-{1-[1-(4-acetylaminopiperidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (100 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 40

Production of 1-{1-[1-(3-acetylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (127 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-

trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 41

Production of 1-{5-cyclopropyl-1-[1-(3-dimethylaminopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title compound was obtained as a pale-brown yellow amorphous solid (141 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (478 mg).

Example 42

Production of 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (116 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (181 mg).

Example 43

Production of 1-{1-[1-(1-acetylpiperidin-4-yl-carbamoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (41 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (181 mg).

Example 44

Production of 1-{5-cyclopropyl-1-[1-(4-oxopiperidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (155 mg) from

1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (540 mg).

Example 45

Production of 1-{1-[1-(3-acetylaminoazetidine-1-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (68 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (90 mg).

Example 46

Production of 1-{5-cyclopropyl-1-[1-(3-oxopyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (155 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg).

Example 47

Production of 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 4-nitrophenyl (2,2,2-trifluoroethyl)carbamate

2,2,2-Trifluoroethylamine (392 mg) was dissolved in chloroform (4 ml), and pyridine (0.35 ml) and 4-nitrophenyl chloroformate (2.39 g) were added under ice-cooling. The mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 1N hydrochloric acid and water, dried over anhydrous magnesium

sulfate, and concentrated under reduced pressure. Diisopropylether was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (501 mg).

Step 2

Production of 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

4-Nitrophenyl (2,2,2-trifluoroethyl)carbamate (113 mg) produced in the previous step and 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 were dissolved in pyridine (1 ml), and the mixture was stirred at 80°C for 2 hr. After allowing to cool, toluene was added and the mixture was concentrated under reduced pressure. 10% Aqueous potassium carbonate solution was added, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with 10% aqueous potassium carbonate solution, water, 1N hydrochloric acid and water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a pale-yellow amorphous form (162 mg).

Example 48

Production of 1-{5-cyclopropyl-1-[1-(3,3,4,4-tetrafluoropyrrolidine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a pale-yellow amorphous solid (138 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (468 mg) of Example 2.

Example 49

Production of 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-2-methylpropylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-

[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (166 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 50

Production of 1-(1-{1-[(S)-1-benzyl-2-hydroxyethylcarbamoyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (140 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (300 mg) of Example 2.

Example 51

Production of 1-(5-cyclopropyl-1-{1-[(S)-2-hydroxy-1-phenylethylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (170 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (300 mg) of Example 2.

Example 52

Production of 1-(5-cyclopropyl-1-{1-[(S)-1-hydroxymethyl-3-methylbutylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a yellow amorphous solid (256 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 53

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (125 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 54

Production of 1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopentylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 47, the title compound was obtained as a white amorphous solid (92 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 55

Production of 1-[1-(1-benzenesulfonylaminocarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (3 ml) was added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2, triethylamine (81 µl) and toluenesulfonylisocyanate (78 µl) were added and the mixture was stirred for 2 hr. The mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with chloroform. The chloroform layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). The obtained solid was recrystallized from ethyl acetate to give the title compound as a pale-yellow solid (40 mg).

Example 56

Production of 1-[5-cyclopropyl-1-(1-methanesulfonylaminocarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 55, the title compound was obtained as a pale-yellow amorphous solid (200 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (500 mg) of Example 2.

Example 57

Production of 1-[5-cyclopropyl-1-(1-methoxycarbonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 was suspended in chloroform (2.0 ml), and potassium carbonate (177 mg) was added under ice-cooling. Methyl chloroformate (49.4 μl) was added, and the mixture was allowed to return to room temperature and stirred for 1.5 hr. Methyl chloroformate (49.4 μl) was further added, and the mixture was stirred at room temperature for 15.5 hr. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=30:1) to give the title compound as a white amorphous solid (210 mg).

Example 58

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 57, the title compound was obtained as a white amorphous solid (214 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-

[(S)3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (300 mg) of Example 2.

Example 59

Production of 1-{5-cyclopropyl-1-[1-(2-dimethylaminoethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (166 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg).

Example 60

Production of 1-{5-cyclopropyl-1-[1-(2-piperidin-1-yl-ethoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 10, the title compound was obtained as a white amorphous solid (219 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg).

Example 61

Production of 1-{5-cyclopropyl-1-[1-(piperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 11, the title compound was obtained as a pale-yellow amorphous solid (53 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (102 mg).

Example 62

Production of 1-{5-cyclopropyl-1-[1-(1-methylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 12, the title

compound was obtained as a white amorphous solid (64 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (124 mg).

Example 63

Production of 1-{1-[1-(1-acetylpiperidin-4-yl-oxycarbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 12, the title compound was obtained as a white amorphous solid (65 mg) from 1-{5-cyclopropyl-1-[1-(4-nitrophenoxycarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (122 mg).

Example 64

Production of 1-[1-(1-cyclopropanecarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (5 ml) and triethylamine (0.13 ml) were added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 and cyclopropanecarboxylic chloride (0.047 ml) was added under ice-cooling. After stirring overnight at room temperature, the solvent was removed under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=10:1) to give the title compound as a white amorphous solid (170 mg).

Example 65

Production of 1-{5-cyclopropyl-1-[1-(2-hydroxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (5 ml) and triethylamine (0.16 ml) were added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2 and acetoxyacetyl chloride (0.069 ml) was added under ice-cooling. After stirring overnight at room temperature, the mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=10:1). The obtained amorphous solid was dissolved in tetrahydrofuran (2 ml), methanol (2 ml) and water (4 ml), and lithium hydroxide monohydrate (103 mg) was added. The mixture was stirred at 60°C for 4 hrs. The mixture was concentrated under reduced pressure, 5% aqueous potassium hydrogensulfate was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, and dried over anhydrous sodium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (ethyl acetate:methanol=20:1) to give the title compound as a white amorphous solid (30 mg).

Example 66

Production of 1-(5-cyclopropyl-1-{1-[1-(4-fluorophenyl)cyclopropanecarbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (193 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 67

Production of 1-{5-cyclopropyl-1-[1-(2-dimethylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (217 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 68

Production of 1-{1-[1-(2-acetylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-brown yellow amorphous solid (119 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 69

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (178 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 70

Production of 1-{1-[1-(2-acetylamino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-brown yellow amorphous solid (94 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 71

Production of 1-(1-{1-[(S)-2-acetylaminopropionyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a white amorphous solid (183 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 72

Production of 1-(1-{1-[(S)-2-acetylamino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (212 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 73

Production of 1-{5-cyclopropyl-1-[1-(3,3,3-trifluoropropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (151 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 74

Production of 1-(5-cyclopropyl-1-{1-[(S)-5-oxopyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a white amorphous solid (127 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200

mg) of Example 2.

Example 75

Production of 1-{1-[1-(3-acetylaminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 64, the title compound was obtained as a pale-yellow amorphous solid (263 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (355 mg) of Example 2.

Example 76

Production of 1-{5-cyclopropyl-1-[1-(3-hydroxy-2,2-dimethylpropionyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (238 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 77

Production of 1-{1-[1-(2-aminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (219 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 78

1-{5-cyclopropyl-1-[1-(1-hydroxymethylcyclopropanecarbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as while crystals (168 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-

(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (250 mg) of Example 2.

Example 79

Production of 1-{1-[1-(2-amino-2-methylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (154 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 80

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxybutyryl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (166 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 81

Production of 1-(5-cyclopropyl-1-{1-[(S)-pyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (569 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (450 mg).

Example 82

Production of 1-(5-cyclopropyl-1-{1-[(S)-1-methylpyrrolidine-2-carbonyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (192 mg)

from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (450 mg).

Example 83

Production of 1-{1-[1-(3-aminopropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (414 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (355 mg) of Example 2.

Example 84

Production of 1-(1-{1-[(S)-2-amino-3-methylbutyryl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (182 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 85

Production of 1-{5-cyclopropyl-1-[1-(2-methylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (183 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 86

Production of 1-{5-cyclopropyl-1-[1-(piperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title

compound was obtained as a pale-yellow amorphous solid (478 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (404 mg) of Example 2.

Example 87

Production of 1-{5-cyclopropyl-1-[1-(2-isobutyrylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (214 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 88

Production of 1-{1-[1-(2-cyclopropanecarbonylaminoacetyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (190 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 89

Production of 1-(1-{1-[(S)-1-acetylpyrrolidine-2-carbonyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (189 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (450 mg).

Example 90

Production of 1-{5-cyclopropyl-1-[1-(2-methanesulfonylaminoacetyl)piperidin-4-yl]-1H-pyrazole-4-

carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (134 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (152 mg).

Example 91

Production of 1-{1-[1-(1-acetylpiperidine-4-carbonyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a pale-yellow amorphous solid (145 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (404 mg) of Example 2.

Example 92

Production of 1-{5-cyclopropyl-1-[1-(1-methylpiperidine-4-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 65, the title compound was obtained as a pale-brown yellow amorphous solid (151 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (404 mg) of Example 2.

Example 93

Production of 1-{1-[1-(3-carbamoylpropionyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 65, the title compound was obtained as a white amorphous solid (61 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 94

Production of 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-

cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 was dissolved in N,N-dimethylformamide (2.5 ml), and potassium carbonate (93 mg) and 2-bromoacetamide (50.7 mg) were added. The mixture was stirred at room temperature for 2 hr. Water was added to the reaction mixture, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give 1-[1-(1-carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (167 mg) as a white amorphous solid.

1-[1-(1-Carbamoylmethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (154 mg)obtained in the previous step was dissolved in ethyl acetate (2 ml), and 4N hydrochloric acid ethyl acetate solution (159 µl) was added. The mixture was stirred for 10 min. The precipitated crystals were collected by filtration and dried to give the title compound as a white amorphous solid (109 mg).

Example 95

Production of 1-[5-cyclopropyl-1-(1-methylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (2.5 g) of Example 2 was dissolved in N,N-dimethylformamide (20 ml), and potassium carbonate (1.62 g) and ethyl bromoacetate (0.98 g) were added. The mixture was stirred at room temperature for 1 hr. Water was added to the reaction mixture, and the mixture was extracted twice with

ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=25:1) to give 1-{5-cyclopropyl-1-[1-(ethoxycarbonylmethyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (2.79 g) as a white amorphous solid.

1-{5-Cyclopropyl-1-[1-(ethoxycarbonylmethyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (1.4 g) obtained in the previous step was dissolved in tetrahydrofuran (5.5 ml) and methanol (2.7 ml), and 4N aqueous sodium hydroxide solution (1.4 ml) was added. The mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water. The aqueous layer was washed twice with diethyl ether, adjusted to pH 5-6 with 2N hydrochloric acid under ice-cooling, and extracted 3 times with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and n-hexane was added to the obtained residue. The precipitated solid was collected by filtration, and dried to give 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (1.17 g) as a white solid.

N,N-Dimethylformamide (3.0 ml) was added to 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (150 mg) obtained in the previous step, 1-hydroxybenzotriazole (61 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (76 mg) was added, and the mixture was stirred at room temperature for 1 hr. 40% Aqueous methylamine solution (106 µl) was added, and the mixture was stirred for 5 hr, 40% methylamine aqueous solution (318 µl) was further added, and the mixture was stirred at room temperature for 13 hr. Water

was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1). The obtained amorphous solid was dissolved in ethyl acetate (2.0 ml), 4N hydrochloric acid ethyl acetate solution (100 µl) was added, and the mixture was stirred for 10 min. The precipitated crystals were collected by filtration and dried to give the title compound as a white amorphous solid (16.9 mg).

Example 96

Production of 1-{1-[1-(1-carbamoyl-1-methylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Cumylamine (1.1 g) and triethylamine (1.2 ml) were dissolved in chloroform (10 ml), and a solution of 2-bromoisobutyryl bromide (1.0 ml) in chloroform (2 ml) was added under ice-cooling over 5 min. The mixture was stirred at room temperature for 15 min. The mixture was concentrated under reduced pressure, ethyl acetate was added to the obtained residue, and the mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained white solid was washed with diisopropyl ether, and dried to give 2-bromo-2-methyl-N-(1-methyl-1-phenylethyl)-propylamide as a white solid (1.73 g).

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 was dissolved in tetrahydrofuran (5.5 ml), and 60% sodium hydride (104 mg) was added. The mixture was stirred at 60°C for 1 hr and at room temperature for 5 min. 2-Bromo-2-methyl-N-(1-methyl-1-phenylethyl)-propylamide (329 mg) produced in the previous step was added, and the mixture was stirred at 60°C for 22 hr. After allowing to cool, water was added to the reaction mixture, and the

mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give 1-(5-cyclopropyl-1-{1-[1-methyl-1-(1-methyl-1-phenylethylcarbamoyl)ethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine as a pale-yellow amorphous form (78 mg).

1-(5-Cyclopropyl-1-{1-[1-methyl-1-(1-methyl-1-phenylethylcarbamoyl)ethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine produced in the previous step was dissolved in trifluoroacetic acid (2 ml), and the mixture was stirred at 80°C for 8 hr. Trifluoroacetic acid (1 ml) was further added and the mixture was further stirred at 80°C for 8 hr. After allowing to cool, and the mixture was concentrated under reduced pressure, and the obtained residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:acetone=4:5→chloroform:methanol=10:1). The obtained residue was dissolved in ethyl acetate (1 ml), and 4N hydrochloric acid ethyl acetate solution (1 ml) and diethyl ether (1.5 ml) were added. The obtained solid was collected by filtration and dried to give the title compound as a pale-yellow solid (36 mg).

Example 97

Production of 1-{1-[1-(2-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained as a white amorphous solid (149 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-

[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 98

Production of 1-[5-cyclopropyl-1-(1-cyclopropylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained as while crystals (133 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (150 mg) of Example 2.

Example 99

Production of 1-[5-cyclopropyl-1-(1-cyclopropylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained as a pale-brown yellow amorphous solid (144 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 100

Production of 1-[5-cyclopropyl-1-(1-dimethylcarbamoylmethylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a white amorphous solid (20 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (2.5 g) of Example 2.

Example 101

Production of 1-[1-(1-carboxymethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

The title compound was obtained as a white amorphous solid (24 mg) from 1-[1-(1-carboxymethylpiperidin-4-yl)-5-

cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (112 mg) produced in Example 95.

Example 102

Production of 1-[1-(1-carboxyethylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a pale-yellow amorphous solid (295 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (350 mg).

Example 103

Production of 1-{1-[1-(1-carbamoylethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a pale-yellow amorphous solid (146 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (350 mg).

Example 104

Production of 1-{1-[1-(2-carboxy-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a pale-yellow amorphous solid (71 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 105

Production of 1-{1-[1-(2-carbamoyl-2-methylpropyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title

compound was obtained as a white amorphous solid (52 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 106

Production of 1-{1-[1-(1-carbamoylcyclopropylmethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a white amorphous solid (82 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 107

Production of 1-(5-cyclopropyl-1-{1-[1-(2-hydroxyethylcarbamoyl)cyclopropylmethyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 95, the title compound was obtained as a white amorphous solid (84 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (400 mg).

Example 108

Production of 1-[5-cyclopropyl-1-(1-trifluoromethanesulfonylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2 was dissolved in methylene chloride (2.0 ml), and under an argon atmosphere, the solution was cooled to -78°C, triethylamine (178 µl) and trifluoromethanesulfonic acid anhydride (78.8 µl) were added, and the mixture was stirred for 2.5 hr.

Trifluoromethanesulfonic acid anhydride (78.8 µl) was further

added and the mixture was stirred for 2 hr. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture at -78°C, and the mixture was extracted with chloroform. The organic layer was washed with 1N hydrochloric acid, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a yellow amorphous form (192 mg).

Example 109

Production of 1-{5-cyclopropyl-1-[1-(2,2,2-trifluoroethanesulfonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 108, the title compound was obtained as a yellow amorphous solid (29 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride (200 mg) of Example 2.

Example 110

Production of 1-{1-[1-(1-cyanoiminoethyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (300 mg) was dissolved in chloroform (5 ml), and triethylamine (97 µl) and methyl N-cyanoacetoimidate (66 µl) were added. After stirring at room temperature for 30 min and at 45°C for 1.5 hr, triethylamine (97 µl) and methyl N-cyanoacetoimidate (66 µl) were further added, and the mixture was stirred at 45°C for 2 hr. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a pale-yellow amorphous form (214 mg).

Example 111

Production of 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 1-(1-{1-[cyanoimino(phenoxy)-methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Chloroform (5 ml) was added to 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (500 mg) and triethylamine (0.162 ml) and diphenyl N-cyanocarbonimidate (284 mg) were added. The mixture was stirred for 1.5 hr. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:acetone=1:1→2:3→1:2) to give the title compound as a pale-yellow amorphous form (575 mg).

Step 2

Production of 1-(1-{1-[cyanoimino(methylamino)methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-(1-{1-[Cyanoimino(phenoxy)-methyl]piperidin-4-yl}-5-cyclopropyl-1H-pyrazole-4-carbonyl)-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (575 mg) produced in the previous step was dissolved in chloroform (10 ml), methylamine hydrochloride (81 mg) and triethylamine (0.31 ml) were added, and the mixture was stirred at room temperature for 30 min and at 55°C for 5 hr. Methylamine hydrochloride (81 mg) and triethylamine (2 ml) further added and the mixture was stirred at 55°C for 1 hr and at 60°C for 30 min. Methylamine hydrochloride (162 mg) was further added and the mixture was stirred at 60°C for 2.5 hr. After allowing to cool, the mixture was concentrated under reduced pressure, and the obtained residue was dissolved in chloroform, and the mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained

residue was purified by silica gel chromatography (chloroform:methanol=10:1) to give the title compound as a white amorphous solid (242 mg).

Example 112

Production of 1-{1-[1-(N-cyanocarbamimidoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 111, the title compound was obtained as a pale-yellow amorphous solid (249 mg) from 1-[5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride of Example 2 (302 mg).

Example 113

Production of 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid

Step 1

Production of tert-butyl 1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carboxylate

tert-Butyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate (1.12 g) produced by a method similar to that of Example 1, Step 1 and ethyl 4-(4-hydrazinopiperidin-1-yl)benzoate hydrochloride (692 mg) produced by a known method were suspended in ethanol (15 ml). Triethylamine (0.81 ml) was added to the obtained suspension, and the mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=3:1) to give the title compound as a yellow oil (673 mg).

Step 2

Production of 1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

tert-Butyl 1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carboxylate (673 mg) produced in the previous step was dissolved in chloroform (4 ml), trifluoroacetic acid (4 ml) was added under ice-cooling, and the mixture was stirred at 40°C for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. To the obtained residue were added diethyl ether and n-hexane, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (556 mg).

Step 3

Production of 5-cyclopropyl-1-{1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{3-(2-trifluoromethylphenyl)}pyrrolidine

5-Cyclopropyl-1-[1-(4-ethoxycarbonylphenyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (550 mg) produced in the previous step, 1-hydroxybenzotriazole (285 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (357 mg) were dissolved in N,N-dimethylformamide (8 ml). 3-(2-Trifluoromethylphenyl)pyrrolidine (308 mg) was added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (ethyl acetate) to give the title compound as a white amorphous solid (757 mg).

Step 4

Production of 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid

1-{1-[1-(4-Ethoxycarbonylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-{3-(2-trifluoromethylphenyl)}pyrrolidine (720 mg) produced in the previous step was dissolved in tetrahydrofuran (3 ml) and methanol (1.5 ml), and 4N aqueous sodium hydroxide solution (1.2 ml) was added. The mixture was stirred at room temperature for 4 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water. The aqueous layer was washed with diethyl ether, acidified with 2N hydrochloric acid under ice-cooling, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Diethyl ether:n-hexane (1:1) was added to the obtained residue and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (600 mg).

Example 114

Production of 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoic acid

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine (195 mg) produced by a method similar to that of Example 1 and ethyl 3-iodobenzoate (142 mg) were dissolved in 1,4-dioxane (1 ml) and tert-butanol (1 ml), and tris(dibenzylideneacetone)dipalladium (14.2 mg), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (24.3 mg) and cesium carbonate (235 mg) were added. The mixture was heated under reflux overnight. After allowing to cool, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and the mixture was

extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:acetone=1:1) to give ethyl 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate as a white amorphous solid (179 mg).

Ethyl 3-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate (179 mg) produced in the previous step was dissolved in tetrahydrofuran (1 ml) and ethanol (1 ml), and 4N aqueous sodium hydroxide solution (1 ml) was added. The mixture was heated under reflux for 2 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water, and acidified with 2N hydrochloric acid under ice-cooling. The precipitated solid was collected by filtration, washed with water and dried under reduced pressure to give the title compound as a white solid (165 mg).

Example 115

Production of 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylic acid

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine (220 mg) produced by a method similar to that of Example 1 and ethyl 5-bromothiophene-2-carboxylate (137 mg) were dissolved in toluene (4 ml), and palladium acetate (13 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (36 mg) and cesium carbonate (265 mg) were added. The mixture was heated under reflux for 6 hr. After allowing to cool, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The

ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:acetone=1:1) to give ethyl 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylate (162 mg) as a white amorphous solid.

Ethyl 5-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiophene-2-carboxylate (162 mg) produced in the previous step was dissolved in tetrahydrofuran (1 ml) and ethanol (1 ml), and a 4N aqueous sodium hydroxide solution (1 ml) was added. The mixture was heated under reflux for 3 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was dissolved in water, and acidified with 2N hydrochloric acid under ice-cooling. The precipitated solid was collected by filtration, washed with water and dried under reduced pressure. The obtained solid was purified by silica gel chromatography (chloroform:acetone=6:1), and recrystallized from ethyl acetate to give the title compound as a pale-green solid (28 mg).

Example 116

Production of 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid

Step 1

Production of 4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-thiocarboxamide

1-[5-Cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine (420 mg) produced by a method similar to that of Example 1 was dissolved in chloroform (10 ml), and triethylamine (0.139 ml) and 9-fluorenylmethoxycarbonylisothiocyanate (285 mg) were added at room temperature. The mixture was stirred for 1 hr. The

reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=50:1). The obtained purified product was dissolved in N,N-dimethylformamide (7 ml), and piperidine (0.7 ml) was added at room temperature. The mixture was stirred for 1 hr and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the mixture was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration, washed with water and dried under reduced pressure to give the title compound as a white solid (287 mg).

Step 2

Production of 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylic acid

4-{5-Cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-thiocarboxamide (280 mg) produced in the previous step was suspended in ethanol (5 ml), and ethyl bromopyruvate (0.09 ml) was added to the obtained suspension. The mixture was refluxed for 2 hr. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give ethyl 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)thiazole-4-carboxylate (361 mg) as a white amorphous solid.

Ethyl 2-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-

yl}piperidin-1-yl)thiazole-4-carboxylate (355 mg) produced in the previous step was dissolved in tetrahydrofuran (0.6 ml) and methanol (0.3 ml), and 4N aqueous sodium hydroxide solution (0.57 ml) was added at room temperature. The mixture was stirred for 3 hr. The reaction mixture was concentrated under reduced pressure, and a 1N aqueous sodium hydroxide solution was added to the obtained residue, and the mixture was washed with diethyl ether. The aqueous layer was acidified with 2N hydrochloric acid, and the precipitated solid was collected by filtration, washed with water and dried under reduced pressure to give the title compound as a white solid (272 mg).

Example 117

Production of 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Step 1

Production of methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide

4-{5-Cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-thiocarboxamide (500 mg) produced by a method similar to that of Example 116, Step 1 was dissolved in chloroform (5 ml), and methyl iodide (0.1 ml) was added. The mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure, diethyl ether was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a pale-yellow solid (654 mg).

Step 2

Production of 1-{5-cyclopropyl-1-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

Methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-

yl}piperidine-1-imidothiocarboxylate hydroiodide (317 mg) produced in the previous step, acetic acid hydrazide (50 mg) and sodium acetate (43 mg) were suspended in dioxane (2 ml) and water (0.4 ml), and the mixture was heated under reflux overnight. The solvent was removed under reduced pressure, water was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine and dried over anhydrous magnesium sulfate. The mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). The obtained amorphous solid was dissolved in ethyl acetate (1 ml), and a 4N hydrochloric acid ethyl acetate solution (0.4 ml) was added. The precipitated solid was collected by filtration and dried to give the title compound as white crystals (72 mg).

Example 118

Production of 1-{5-cyclopropyl-1-[1-(5-cyclopropyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 117, the title compound was obtained as while crystals (253 mg) from methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide (475 mg).

Example 119

Production of 1-{5-cyclopropyl-1-[1-(5-hydroxymethyl-4H-[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 117, the title compound was obtained as while crystals (25 mg) from methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide (317 mg).

Example 120

Production of 1-{5-cyclopropyl-1-[1-(5-trifluoromethyl-4H-

[1,2,4]triazol-3-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

By a method similar to that of Example 117, the title compound was obtained as while crystals (130 mg) from methyl 4-{5-cyclopropyl-4-[(S)-3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidine-1-imidothiocarboxylate hydroiodide (317 mg).

Example 121

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate

Methyl 1-(1-benzyloxycarbonylpiperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate (15.9 g) produced in Example 1, Step 2 was dissolved in methanol (12 ml), and palladium carbon (1.5 g) was added. The mixture was stirred overnight under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. n-Hexane was added to the obtained residue, and filtration gave the title compound as a white amorphous solid (9.66 g).

Step 2

Production of methyl 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate

Methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (2.82 g) produced in the previous step was dissolved in chloroform (28 ml) and triethylamine (1.58 ml) was added.

2-Fluorophenylisocyanate (1.4 ml) was added to the obtained mixture under ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:3) to

give the title compound as a white amorphous solid (4.23 g).

Step 3

Production of 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid

Methyl 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate (4.23 g) produced in the previous step was dissolved in tetrahydrofuran (11 ml) and methanol (5 ml), and a 4N aqueous sodium hydroxide solution (11 ml) was added. The mixture was stirred at 60°C for 6 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure. The obtained residue was dissolved in water. The aqueous layer was washed with diethyl ether, and acidified with concentrated hydrochloric acid under ice-cooling. The precipitated solid was collected by filtration, washed with water and n-hexane and dried under reduced pressure to give the title compound as a white solid (3.89 g).

Step 4

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-{(R)-3-(2-trifluoromethylphenyl)}pyrrolidine

5-Cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (101 mg) produced in the previous step, 1-hydroxybenzotriazole (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (57 mg) were dissolved in N,N-dimethylformamide (15 ml). (R)-3-(2-Trifluoromethylphenyl)pyrrolidine (65 mg)* and 4-dimethylaminopyridine (37 mg) were added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained

residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a white amorphous solid (136 mg).

$[\alpha]^{25}D$=+10.9 (c=0.495, EtOH)

*(R)-3-(2-Trifluoromethylphenyl)pyrrolidine was produced by a method similar to the method of Example 2, Step 1 to Step 4 and using (R)-4-isopropyl-5,5-diphenyloxazolidin-2-one. $[\alpha]^{25}D$=-21.0 (c=0.500, EtOH)

Example 122

Production of 1-(5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl)-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of methyl 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate

1-Methylcyclopropane-1-carboxylic acid (1.81 g), diphenylphosphoryl azide (4.67 ml) and triethylamine (2.77 ml) were dissolved in toluene (30 ml), and the mixture was heated under reflux for 1 hr to produce isocyanate.

Methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (1.50 g) produced in Example 121, Step 1 and triethylamine (0.84 ml) were dissolved in tetrahydrofuran (15 ml) and the toluene solution of isocyanate prepared in advance was added until the starting material, (methyl 1-(piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carboxylate), disappeared. The reaction mixture was concentrated under reduced pressure, water was added to the obtained residue, and the mixture was extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over anhydrous magnesium sulfate. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (1.92 g).

Step 2

Production of 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid

Methyl 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate (1.92 g) produced in the previous step was dissolved in tetrahydrofuran (20 ml) and methanol (10 ml), and 4N aqueous sodium hydroxide solution (15 ml) was added. The mixture was stirred at 60°C for 6 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure. The obtained residue was dissolved in water and the aqueous layer was washed with diethyl ether. Under ice-cooling, and the mixture was acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Ethyl acetate was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (1.68 g).

Step 3

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

5-Cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (91 mg) produced in the previous step, 1-hydroxybenzotriazole (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (57 mg) were dissolved in N,N-dimethylformamide (1.5 ml). (R)-3-(2-Trifluoromethylphenyl)pyrrolidine (65 mg) and 4-dimethylaminopyridine (37 mg) were added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen

carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (123 mg).

$[\alpha]^{25}D$=+13.1 (c=0.495, EtOH)

Example 123

Production of 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of methyl 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate

Methyl 5-cyclopropyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (1.87 g) produced in Example 121, Step 1 was dissolved in chloroform (20 ml), and triethylamine (1.05 ml) was added. Isopropylisocyanate (0.7 ml) was added to the obtained mixture under ice-cooling and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (2.00 g).

Step 2

Production of 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid

Methyl 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylate (2.00 g) produced in the previous step was dissolved in tetrahydrofuran (6 ml) and methanol (3 ml), and 4N aqueous sodium hydroxide solution (6 ml) was added. The mixture was stirred at 60°C for 4.5 hr. The reaction mixture was allowed to cool and concentrated under reduced pressure. The obtained residue was dissolved in water and the aqueous layer was washed

with diethyl ether, and acidified with concentrated hydrochloric acid under ice-cooling. The mixture was extracted with chloroform. The chloroform layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.

n-Hexane was added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a white solid (1.58 g).

Step 3

Production of 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(R)-3-(2-trifluoromethylphenyl)]pyrrolidine

5-Cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (88 mg) produced in the previous step, 1-hydroxybenzotriazole (46 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (57 mg) were dissolved in N,N-dimethylformamide (1.5 ml). (R)-3-(2-Trifluoromethylphenyl)pyrrolidine (65 mg) and 4-dimethylaminopyridine (37 mg) was added to the obtained solution and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=15:1) to give the title compound as a white amorphous solid (120 mg).

$[\alpha]^{25}D$=+14.2 (c=0.500, EtOH)

Example 124

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 121, Step 4, the title compound was obtained as a white amorphous solid (127 mg)

from 5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (123 mg), (S)-3-(2-trifluoromethylphenyl)pyrrolidine (78 mg).

$[\alpha]^{25}D$=-10.8 (c=0.510, EtOH)

Example 125

Production of 1-{5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 123, Step 3, the title compound was obtained as a white amorphous solid (123 mg) from 5-cyclopropyl-1-[1-(1-isopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (107 mg), (S)-3-(2-trifluoromethylphenyl)pyrrolidine (79 mg).

$[\alpha]^{25}D$=-13.2 (c=0.515, EtOH)

Example 126

Production of 1-{5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

By a method similar to that of Example 122, Step 3, the title compound was obtained as a white amorphous solid (149 mg) from 5-cyclopropyl-1-[1-(1-methylcyclopropylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carboxylic acid (107 mg), (S)-3-(2-trifluoromethylphenyl)pyrrolidine (76 mg).

$[\alpha]^{25}D$=-13.6 (c=0.500, EtOH)

Example 127

Production of (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

Step 1

Production of ethyl cyano-(4-fluorophenyl)acetate

Toluene (40 ml) was added to 4-fluorophenylacetonitrile (15.0 g) and diethyl carbonate (66.9 ml) and sodium ethoxide (8.30 g) were added. The mixture was stirred for 2 hr while evaporating the solvent at 110°C to 130°C. After allowing to

cool, the reaction mixture was poured into water, and acetic acid (13 ml) was added. The mixture was stirred for 5 min, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound as a pale-yellow oil (25.0 g).

Step 2

Production of diethyl 2-cyano-2-(4-fluorophenyl)succinate

Tetrahydrofuran (40 ml) was added to 60% sodium hydride (2.12 g), and a solution of ethyl cyano-(4-fluorophenyl) acetate (10.0 g) produced in the previous step in tetrahydrofuran (40 ml) was added dropwise under ice-cooling. The mixture was stirred for 40 min and ethyl bromoacetate (6.4 ml) was added under ice-cooling. The mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=5:1) to give the title compound as a pale-yellow oil (14.7 g).

Step 3

Production of ethyl 3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate

A solution of diethyl 2-cyano-2-(4-fluorophenyl)succinate (7.0 g) produced in the previous step in ethanol (50 ml) was added to Raney nickel (7.0 g), and the mixture was stirred overnight under a hydrogen atmosphere. The reaction mixture was filtered through celite, and the filtrate and washing were combined and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=25:1) and a mixed solvent of diethyl ether and n-hexane was added to the obtained solid residue. The

mixture was filtered and dried to give the title compound as white crystals (3.96 g).

Step 4

Production of ethyl 1-benzyl-3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate

Tetrahydrofuran (25 ml) was added to 60% sodium hydride (1.63 g), and a solution of ethyl 3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate (10.3 g) produced in the previous step in tetrahydrofuran (30 ml)/N,N-dimethylformamide (10 ml) was added dropwise under ice-cooling. The mixture was stirred for 10 min. Under ice-cooling, benzyl bromide (4.86 ml) was added. The mixture was stirred at the same temperature for 30 min and at room temperature for 3.5 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to give the title compound as a pale-yellow oil (12.1 g).

Step 5

Production of 1-benzyl-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

Tetrahydrofuran (20 ml) was added to aluminum lithium hydride (1.16 g) and a solution of ethyl 1-benzyl-3-(4-fluorophenyl)-5-oxo-pyrrolidine-3-carboxylate (4.16 g) produced in the previous step in tetrahydrofuran (20 ml) was added dropwise under ice-cooling. The mixture was stirred under reflux for 3.5 hr. After allowing to cool, water (0.9 ml), 4N aqueous sodium hydroxide solution (0.9 ml) and water (2.7 ml) were successively added under ice-cooling, and diethyl ether and magnesium sulfate were added. The mixture was stirred for 20 min and filtered through celite. The filtrate and washing were combined and concentrated under reduced pressure to give the title compound as a pale-yellow oil (3.18 g).

Step 6

Production of 3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

To a solution of 1-benzyl-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine (3.18 g) produced in the previous step in methanol (30 ml) was added palladium hydroxide (300 mg), and the mixture was stirred overnight under a hydrogen atmosphere (3 atm). The reaction mixture filtered through celite, and the filtrate and washing were combined and concentrated under reduced pressure to give the title compound as a pale-yellow oil (2.30 g).

Step 7

Production of tert-butyl 3-(4-fluorophenyl)-3-hydroxymethyl-pyrrolidine-1-carboxylate

To 3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine (2.30 g) produced in the previous step were added tetrahydrofuran (40 ml) and triethylamine (5.7 ml), and di-tert-butyldicarbonate (4.60 g) was added under ice-cooling. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and ethyl acetate was added. The mixture was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to give the title compound as a colorless oil (2.70 g).

Step 8

Production of (-)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

To tert-butyl 3-(4-fluorophenyl)-3-hydroxymethyl-pyrrolidine-1-carboxylate (1.02 g) produced in the previous step were added chloroform (10 ml), triethylamine (962 µl) and 4-dimethylaminopyridine (421 mg), and (S)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (969 µl) was added under ice-cooling. The mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, water was added to the residue, and the mixture was extracted 3 times with ethyl acetate. The organic layer was

washed with aqueous potassium hydrogensulfate solution, water, aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:diethyl ether=5:3) to give less polar diastereomer as a colorless oil (871 mg). In addition, a more polar diastereomer was obtained as a colorless oil (781 mg).

The colorless oil (871 mg) of the less polar diastereomer was dissolved in tetrahydrofuran (4 ml) and methanol (2 ml), and 4N aqueous sodium hydroxide solution (2.6 ml) was added. The mixture was stirred at 60°C for 40 min. The reaction mixture was concentrated under reduced pressure and water was added to the residue. The mixture was extracted 3 times with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a colorless oil (481 mg).

Methanol (3 ml) and a 4N hydrochloric acid ethyl acetate solution (3.3 ml) were added to the obtained colorless oil (481 mg) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure and water was added to the residue. The mixture was washed with diethyl ether, and the aqueous layer was alkalified with a 2N aqueous sodium hydroxide solution. The mixture was extracted 5 times with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure to give the title compound as a colorless oil (312 mg).

$[\alpha]^{25}D$=-9.70 (c=0.598, EtOH)

Production of (+)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine

By a method similar to the method for the production of (-)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine and using a colorless oil (781 mg) of a more polar diastereomer, the title compound was obtained as a colorless oil (251 mg).

$[\alpha]^{25}D$=+10.37 (c=0.588, EtOH)

Step 9

Production of tert-butyl 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylate

tert-Butyl 5-(1-methylcyclopropyl)-1-(piperidin-4-yl)-1H-pyrazole-4-carboxylate (1.15 g) produced by a method similar to that of Example 121, Step 1 and 2-chloropyrimidine (700 mg) were dissolved in 1,4-dioxane (12 ml), and palladium acetate (85 mg), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (352 mg) and cesium carbonate (1.84 g) were added. The mixture was heated under reflux for 3 hr. After allowing to cool, the insoluble material was filtered through celite, and the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the obtained residue, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=2:1) to give the title compound as a white amorphous solid (922 mg).

Step 10

Production of 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride

tert-Butyl 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylate (922 mg) produced in the previous step was dissolved in chloroform (2 ml), and trifluoroacetic acid (4 ml) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the obtained crystal was dissolved in tetrahydrofuran. A 4N hydrochloric acid ethyl acetate solution (2 ml) was added, and the mixture was concentrated under reduced pressure. The obtained crystalline residue was slurry washed with ethyl acetate (10 ml) for 1 hr to give the title compound as a white solid (800 mg).

Step 11

Production of (-)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-

pyrazole-4-carbonyl}pyrrolidine hydrochloride

5-(1-Methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride (150 mg) produced in the previous step, 1-hydroxybenzotriazole (81 mg) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (102 mg) were dissolved in N,N-dimethylformamide (3 ml).

(-)-3-(4-Fluorophenyl)-3-hydroxymethylpyrrolidine (88 mg) produced in Step 8, triethylamine (0.057 ml) and 4-dimethylaminopyridine (50 mg) were added to the obtained solution, and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (chloroform:methanol=20:1) and the obtained free base was dissolved in methanol (3 ml). A 4N hydrochloric acid 1,4-dioxane solution (0.2 ml) was added, and the mixture was concentrated under reduced pressure. The obtained crystalline residue was washed in the slurry with ethyl acetate (3 ml) for 15 min to give the title compound as white crystals (203 mg).

$[\alpha]^{25}D$=-21.3 (c=0.506, MeOH)

Example 128

Production of (+)-3-(4-fluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 127, Step 11, the title compound was obtained as white crystals (198 mg) from 5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride (150 mg), (+)-3-(4-fluorophenyl)-3-hydroxymethylpyrrolidine (88 mg) produced in Example 127, Step 8.

$[\alpha]^{25}D$=+26.0 (c=0.508, MeOH)

Example 129

Production of 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine hydrochloride

The title compound was obtained as a yellow amorphous solid (165 mg) from 1-[5-cyclopropyl-1-(1-pyrazin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carboxylic acid hydrochloride (281 mg) produced by a method similar to that of Example 127.

Example 130

Production of 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of ethyl trans-4-(2-tert-butoxycarbonylhydrazino)cyclohexanecarboxylate

Ethyl 4-cyclohexanonecarboxylate (8.0 g) and tert-butyl carbazate (6.2 g) were dissolved in chloroform (150 ml), and acetic acid (5.4 ml) and sodium triacetoxyborohydride (30 g) were added under ice-cooling. The mixture was allowed to gradually return to room temperature, and the mixture was stirred for 7 hr. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=4:1) to give the title compound as a white solid (4.63 g).

Step 2

Production of ethyl trans-4-hydrazinocyclohexanecarboxylate hydrochloride

Ethyl trans-4-(2-tert-butoxycarbonylhydrazino)cyclohexanecarboxylate (4.63 g) produced in the previous step was dissolved in ethanol (30 ml), and a 4N hydrochloric acid ethyl acetate solution (82 ml) was

added. The mixture was stirred for 5.5 hr. The mixture was concentrated under reduced pressure, and diethyl ether was added to the obtained residue. The mixture was filtered and dried to give the title compound as a white powder (3.86 g).

Step 3

Production of tert-butyl 1-(trans-4-ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylate

Ethyl trans-4-hydrazinocyclohexanecarboxylate hydrochloride (3.80 g) obtained in the previous step and tert-butyl 2-cyclopropylcarbonyl-3-dimethylaminoacrylate (3.71 g) synthesized by a method similar to that of Example 1, Step 1 were dissolved in ethanol (50 ml), and triethylamine (4.32 ml) was added. The mixture was stirred under reflux for 1 hr. After allowing to cool, the mixture was concentrated under reduced pressure, and water was added to the residue. The mixture was extracted 3 times with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (n-hexane:ethyl acetate=5:1) to give the title compound as a yellow liquid (4.80 g).

Step 4

Production of 1-(trans-4-ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid

To a solution of tert-butyl 1-(trans-4-ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylate (4.80 g) obtained in the previous step in chloroform (14 ml) was added trifluoroacetic acid (14 ml), and the mixture was heated to 40°C and stirred for 1.5 hr. After allowing to cool, the mixture was concentrated under reduced pressure and azeotroped with toluene. Ethyl acetate was added to the residue to allow crystal precipitation. The mixture was once concentrated under reduced pressure, n-hexane was added to the residue, and the crystals were collected by filtration and dried to give the title compound as a white powder (3.09 g).

Step 5

Production of 1-{5-cyclopropyl-1-(trans-4-ethoxycarbonylcyclohexyl)-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-(trans-4-Ethoxycarbonylcyclohexane)-5-cyclopropyl-1H-pyrazole-4-carboxylic acid (1.50 g) produced in the previous step and (S)-3-(2-trifluoromethylphenyl)pyrrolidine (1.16 g) were dissolved in N,N-dimethylformamide (15 ml), and 1-hydroxybenzotriazole (825 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.03 g) and 4-dimethylaminopyridine (658 mg) were added. The mixture was stirred at room temperature for 14 hrs. Ethyl acetate was added to the reaction mixture and the mixture was washed twice with water. The organic layer was washed with 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=20:1) to give the title compound as a brown amorphous (2.34 g).

Step 6

Production of 1-[1-(trans-4-carboxycyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-{5-Cyclopropyl-1-(trans-4-ethoxycarbonylcyclohexyl)-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (2.34 g) produced in the previous step was dissolved in tetrahydrofuran (12 ml) and methanol (6 ml), and a solution of lithium hydroxide monohydrate (973 mg) in water (12 ml) was added. The mixture was stirred at 45°C for 1 hr. The mixture was concentrated under reduced pressure, and water was added to the obtained residue. The mixture was washed twice with diethyl ether, and the aqueous layer was acidified with 2N hydrochloric acid and extracted 3 times with ethyl acetate. The organic layer was

washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Ethyl acetate and n-hexane were added to the obtained residue, and the precipitated solid was collected by filtration and dried to give the title compound as a milky white solid (2.13 g).

Step 7

Production of 1-[1-(trans-4-carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[1-(trans-4-Carboxycyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (300 mg) produced in the previous step was dissolved in N,N-dimethylformamide (3.5 ml), and 1-hydroxybenzotriazole (106 mg), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (133 mg), ammonium chloride (80 mg) and triethylamine (0.105 ml) were added. The mixture was stirred at room temperature for 15 hr. Ethyl acetate was added to the reaction mixture, and the mixture was washed successively with water, 1N hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Diethyl ether was added to the obtained solid residue and the mixture was stirred for 10 min. The solid was collected by filtration and dried to give the title compound as a white amorphous solid (171 mg).

Example 131

Production of 1-[5-cyclopropyl-1-(trans-4-ureidocyclohexyl)-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Toluene (3.0 ml) was added to 1-[1-(trans-4-carboxycyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (200 mg) produced in Example 130, Step 6, and triethylamine (76 µl) and diphenylphosphonic azide (118 µl) were added under an argon atmosphere. The mixture was heated under reflux for 2 hr.

After allowing to cool, the toluene solution was added dropwise to a solution of 28% aqueous ammonia (10 ml) and ethyl acetate (4 ml) under ice-cooling, and the mixture was stirred at the same temperature for 30 min. Water was added to the reaction mixture, and the mixture was extracted 3 times with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (chloroform:methanol=10:1). Diethyl ether was added to the obtained solid residue and the mixture was stirred for 10 min. The solid was collected by filtration and dried to give the title compound as a white amorphous solid (135 mg).

Example 132

Production of 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

Step 1

Production of 1-[1-(trans-4-cyanocyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[1-(trans-4-Carbamoylcyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (514 mg) produced in Example 130, Step 7 was dissolved in tetrahydrofuran (6 ml), and pyridine (180 µl) and trifluoromethanesulfonic acid anhydride (220 µl) were added. The mixture was stirred at room temperature for 1 hr. Pyridine (180 µl) and trifluoromethanesulfonic acid anhydride (220 µl) were further added, and the mixture was stirred at room temperature for 1 hr. The mixture was concentrated under reduced pressure, and 1N aqueous potassium hydrogensulfate solution was added. The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by chromatography

(chloroform:methanol=15:1) to give the title compound as a pale-yellow amorphous form (207 mg).

Step 2

Production of 1-{5-cyclopropyl-1-[trans-4-(1H-tetrazol-5-yl)cyclohexyl]-1H-pyrazole-4-carbonyl}-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine

1-[1-(trans-4-Cyanocyclohexyl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-[(S)-3-(2-trifluoromethylphenyl)]pyrrolidine (207 mg) produced in the previous step was dissolved in 1,4-dioxane (2.5 ml), and azidotributyltin (188 mg) was added. The mixture was heated under reflux overnight. Azidotributyltin (94 mg) was further added and the mixture was heated under reflux for 4 hr. The mixture was concentrated under reduced pressure, 1N hydrochloric acid was added, and the mixture was extracted twice with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by chromatography (chloroform:methanol=25:2) and concentrated under reduced pressure. Diisopropyl ether was added to the obtained residue, and the precipitated solid was collected by filtration, and dried to give the title compound as a white amorphous solid (122 mg).

Example 133

Production of 1-{5-(1-methylcyclopropyl)-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 134

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methoxycyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 135

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenyl-3-trifluoromethyl-pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 136

Production of 3-(2-chlorophenyl)-1-{5-cyclopropyl-1-[1-(2,4-difluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 137

Production of 3-(2-chloropyridin-3-yl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 138

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(2,2,3,3-tetramethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 139

Production of 1-{5-cyclohexyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 140

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethoxyphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 141

Production of 1-{5-cyclopropyl-1-[1-(4-trifluoromethylphenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 142

Production of 1-(5-cyclopropyl-1-{1-[((S)-1-carboxy-2-methyl-propyl)methylcarbamoyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 12, the title compound was obtained from the corresponding starting compound.

Example 143

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-methoxy-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 144

Production of 1-{1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-5-(1-hydroxymethylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 3, the title compound was obtained from the corresponding starting compound.

Example 145

Production of 1-{5-cyclopropyl-1-[1-(thiazol-2-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 146

Production of 1-{1-[1-(isopropoxycarbamoyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title

compound was obtained from the corresponding starting compound.

Example 147

Production of 1-{5-cyclopropyl-1-[1-(4-fluorobenzylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 148

Production of 1-{1-[1-(2,3-dihydroindole-1-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 149

Production of 1-{1-[1-(2,3-dihydro[1,4]oxazine-4-carbonyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 150

Production of 1-{5-cyclopropyl-1-[1-(2,6-dichloropyridin-3-ylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 151

Production of 1-{5-(1-methylcyclopropyl)-1-[1-(2,3,4,5-tetrahydrobenzo[b]azepine-1-carbonyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 152

Production of ethyl 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)benzoate

By a method similar to that of Example 114, the title compound was obtained from the corresponding starting compound.

Example 153

Production of 1-[1-(1-benzyloxycarbonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 1, Step 4, the title compound was obtained.

Example 154

Production of 1-{1-[1-(3-carboxy-3-methyl-butyryl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 65, the title compound was obtained from the corresponding starting compound.

Example 155

Production of 1-{5-cyclopropyl-1-[1-(2-phenoxyacetyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 156

Production of 1-{1-[1-(3-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 157

Production of 1-{1-[1-(2-chlorobenzoyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 158

Production of 1-[5-cyclopropyl-1-(1-oxalylpiperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 65, the title compound was obtained from the corresponding starting compound.

Example 159

Production of 1-{1-[1-(4-chlorobenzoyl)piperidin-4-yl]-5-

cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 160

Production of 1-(5-cyclopropyl-1-{1-[2-(4-fluorophenyl)acetyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 161

Production of 1-{5-cyclopropyl-1-[1-(3-trifluoromethylbenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 162

Production of 1-{5-cyclopropyl-1-[1-(3-methoxybenzoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 64, the title compound was obtained from the corresponding starting compound.

Example 163

Production of 1-{1-[1-(4-fluorobenzyl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine hydrochloride

By a method similar to that of Example 94, the title compound was obtained from the corresponding starting compound.

Example 164

Production of 1-[1-(1-benzenesulfonyl-piperidin-4-yl)-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 108, the title compound was obtained from the corresponding starting compound.

Example 165

Production of 1-{1-[1-(4-carbamoylphenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-

trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 166

Production of 1-{5-cyclopropyl-1-[1-(4-hydroxymethylphenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 167

Production of 1-{1-[1-(5-carbamoyl-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 168

Production of 1-{1-[1-(4-aminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 169

Production of 1-(5-cyclopropyl-1-{1-[4-(2-oxooxazolidin-3-yl)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 170

Production of 1-(5-cyclopropyl-1-{1-[4-(3-methoxyureido)phenyl]piperidin-4-yl}-1H-pyrazole-4-carbonyl)-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 171

Production of 1-{5-cyclopropyl-1-[1-(4-

methanesulfonylaminophenyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 172

Production of 1-[1-(1-ethoxycarbamoylpiperidin-4-yl)-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 10, the title compound was obtained from the corresponding starting compound.

Example 173

Production of 1-[1-(5-chloropyridin-2-yl)azetidin-3-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl]-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 174

Production of 1-{1-[1-(5-chloro-pyridin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-methoxymethyl-3-phenylpyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 175

Production of 1-{1-[1-(5-cyano-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 176

Production of 3-(2-acetoxyethyl)-3-(4-fluorophenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 177

Production of {(3S*,4R*)-3-methyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-4-phenylpyrrolidine hydrochloride

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 178

Production of methyl 6-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)nicotinate

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 179

Production of methyl 2-{1-[5-(1-methylcyclopropyl)-1-(1-pyrimidin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]pyrrolidin-3-yl}benzoate

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 180

Production of 3-(2-hydroxymethylphenyl)-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 181

Production of 1-[5-cyclopropyl-1-(1-pyridin-2-yl-piperidin-4-yl)-1H-pyrazole-4-carbonyl]-3-hydroxy-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 182

Production of 1-{1-[1-(4-acetylaminophenyl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 114, the title compound was obtained from the corresponding starting compound.

Example 183

Production of Sodium 4-(4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)pyrrolidine-1-carbonyl]pyrazol-1-yl}piperidin-1-yl)-3-fluorobenzoate

By a method similar to that of Example 114, the title compound was obtained from the corresponding starting compound.

Example 184

Production of 3-(2-cyanophenyl)-1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine

By a method similar to that of Example 121, the title compound was obtained from the corresponding starting compound.

Example 185

Production of 3-hydroxymethyl-1-{1-[1-(4-methoxypyrimidin-2-yl)piperidin-4-yl]-5-(1-methylcyclopropyl)-1H-pyrazole-4-carbonyl}-3-phenylpyrrolidine hydrochloride

By a method similar to that of Example 127, the title compound was obtained from the corresponding starting compound.

Example 186

Production of 3-(3,5-difluorophenyl)-3-hydroxymethyl-1-{5-(1-methylcyclopropyl)-1-[1-(pyrimidin-2-yl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}pyrrolidine hydrochloride

By a method similar to that of Example 127, the title compound was obtained from the corresponding starting compound.

Example 187

Production of 1-{1-[1-(3-chloro-pyridin-2-yl)piperidin-4-yl]-5-cyclopropyl-1H-pyrazole-4-carbonyl}-3-(pyridin-3-yl)pyrrolidine

By a method similar to that of Example 113, the title compound was obtained from the corresponding starting compound.

Example 188

Production of 1-{5-cyclopropyl-1-[1-(2-fluorophenylcarbamoyl)piperidin-4-yl]-1H-pyrazole-4-carbonyl}-3-(thiazol-2-yl)pyrrolidine

By a method similar to that of Example 121, the title compound was obtained from the corresponding starting compound.

Example 189

Production of (S)-2-[(trans-4-{5-cyclopropyl-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarbonyl)-methyl-amino]-3-methylbutyric acid

By a method similar to that of Example 130, the title compound was obtained from the corresponding starting compound.

Example 190

Production of 1-{5-(1-methylcyclopropyl)-1-[trans-4-(2-fluorophenylcarbamoyl)cyclohexyl]-1H-pyrazole-4-carbonyl}-3-(2-trifluoromethylphenyl)pyrrolidine

By a method similar to that of Example 130, the title compound was obtained from the corresponding starting compound.

Example 191

Production of cis-4-{5-(1-methylcyclopropyl)-4-[3-(2-trifluoromethylphenyl)-pyrrolidine-1-carbonyl]-pyrazol-1-yl}-cyclohexanecarboxylic acid

By a method similar to that of Example 130, the title compound was obtained from the corresponding starting compound.

The structural formula and property values of the compound of each Example are shown in the following Table 1-1 to Table 1-45.

Table 1-1

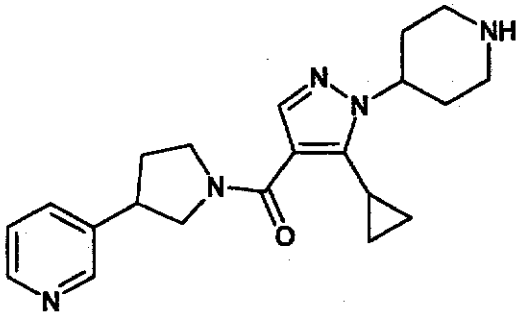
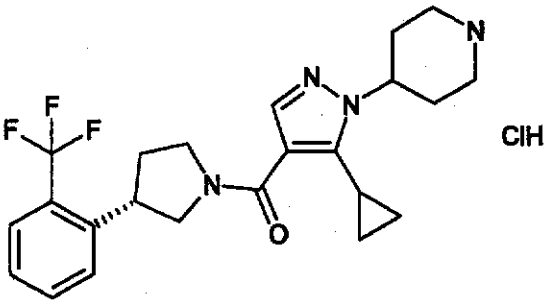
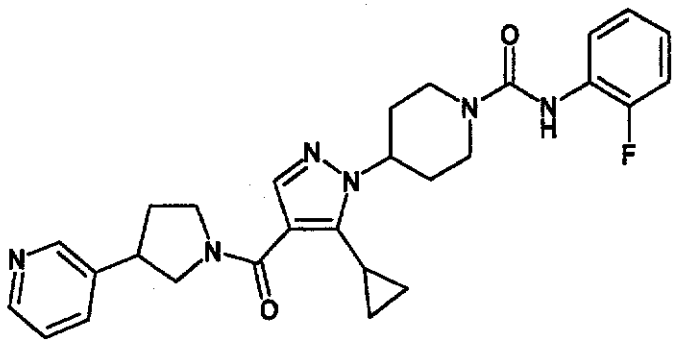
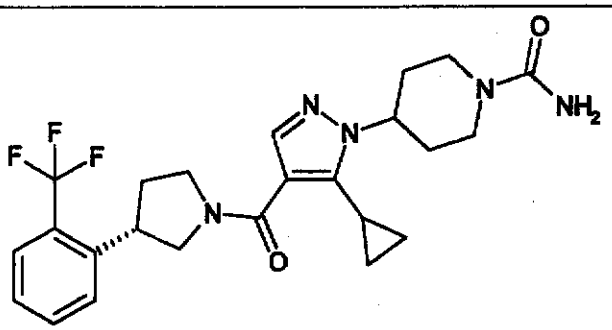
Ex. No.	structural formula	NMR
1		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.77 (2H, m), 0.97-1.11 (2H, m), 1.70-1.82 (1H, m), 1.96-2.67 (8H, m), 2.83-2.97 (2H, m), 3.33-3.53 (3H, m), 3.55-4.17 (3H, m), 4.50-4.64 (1H, m), 7.23-7.32 (1H, m), 7.48-7.64 (2H, m), 8.46-8.61 (2H, m)
2		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.75 (2H, m), 0.94-1.07 (2H, m), 1.86-2.36 (8H, m), 3.00-3.21 (2H, m), 3.30-3.93 (6H, m), 4.69-4.88 (1H, m), 7.44-7.64 (2H, m), 7.66-7.78 (3H, m), 8.83 (1H, brs), 9.22 (1H, brs)
3		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.83 (2H, m), 0.99-1.15 (2H, m), 1.73-1.84 (1H, m), 1.90-2.50 (6H, m), 3.02-3.20 (2H, m), 3.36-3.55 (1.5H, m), 3.56-3.80 (2H, m), 3.83-3.99 (1H, m), 4.06-4.17 (0.5H, m), 4.18-4.36 (2H, m), 4.54-4.71 (1H, m), 6.71 (1H, brs), 6.93-7.00 (1H, m), 7.02-7.14 (2H, m), 7.24-7.32 (1H, m), 7.50-7.62 (2H, m), 8.02-8.09 (1H, m), 8.47-8.59 (2H, m)
4		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.84 (2H, m), 1.03-1.14 (2H, m), 1.54-2.47 (7H, m), 2.94-3.14 (2H, m), 3.40-4.20 (7H, m), 4.47-4.67 (2H, m), 7.32-7.72 (6H, m)

Table 1-2

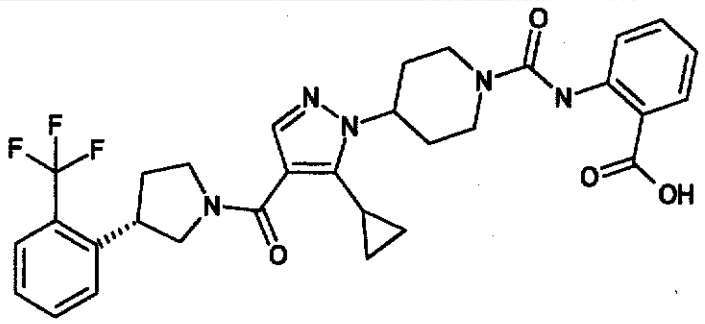
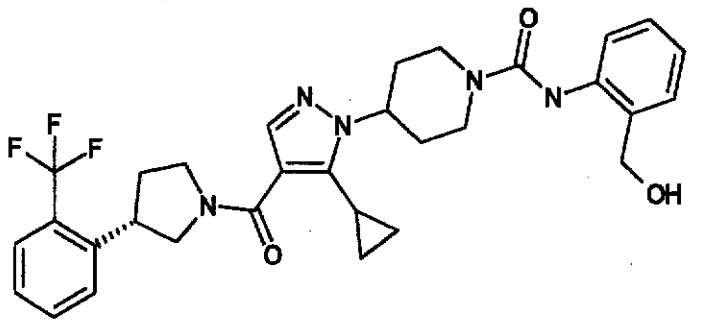
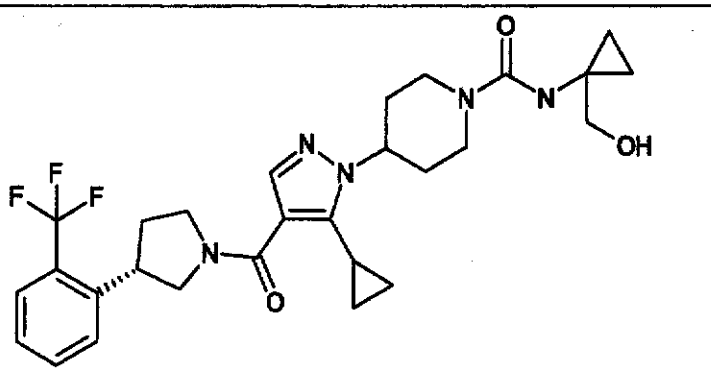
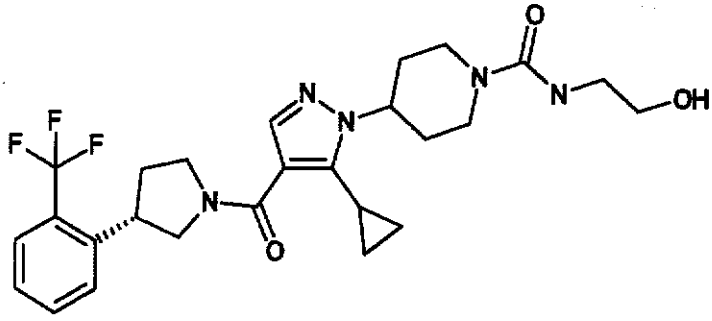
Ex. No.	structural formula	NMR
5		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.75 (2H, m), 0.92-1.07 (2H, m), 1.81-2.36 (6H, m), 3.04-3.23 (2H, m), 3.44-3.93 (6H, m), 4.10-4.27 (2H, m), 4.65-4.83 (1H, m), 6.98-7.07 (1H, m), 7.39-7.61 (3H, m), 7.63-7.79 (3H, m), 7.92-8.02 (1H, m), 8.37-8.40 (1H, m), 11.0-11.2 (1H, m), 13.6 (1H, brs)
6		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.01-1.14 (2H, m), 1.70-2.44 (7H, m), 2.72-2.86(1H, m), 2.97-3.13 (2H, m), 3.41-4.09 (5H, m), 4.20-4.35 (2H, m), 4.51-4.75 (3H, m), 6.97-7.04 (1H, m), 7.11-7.19 (1H, m), 7.28-7.60 (5H, m), 7.64-7.72 (1H, m), 7.92-7.98 (1H, m), 8.13-8.23 (1H, m)
7		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.94 (6H, m), 0.98-1.17 (2H, m), 1.64-1.86 (3H, m), 1.93-2.23 (3H, m), 2.24-2.48 (1H, m), 2.79-2.99 (2H, m), 3.32-4.22 (9H, m), 4.38-4.63 (1H, m), 5.64-5.87 (1H, m), 7.29-7.60 (4H, m), 7.60-7.71 (1H, m)
8		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.82 (2H,m), 0.99-1.12 (2H, m), 1.20-1.34 (1H, m), 1.67-1.88 (4H, m), 1.95-2.21 (3H,m), 2.23-2.46 (1H, m), 2.82-3.02 (2H, m), 3.28-3.48 (3H, m), 3.52-3.99 (5H, m), 3.99-4.22 (2H, m), 4.41-4.63 (1H, m), 5.16-5.33 (1H, m), 7.28-7.71 (5H, m)

Table 1-3

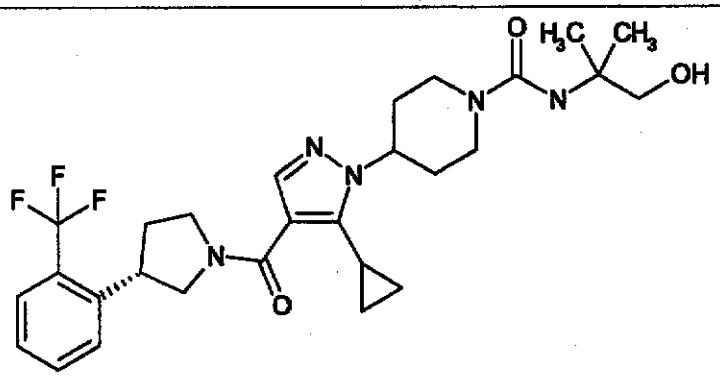
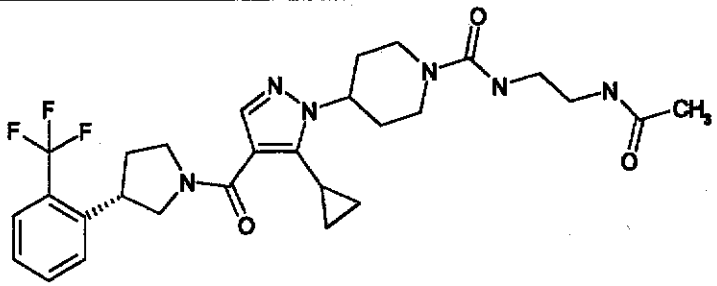
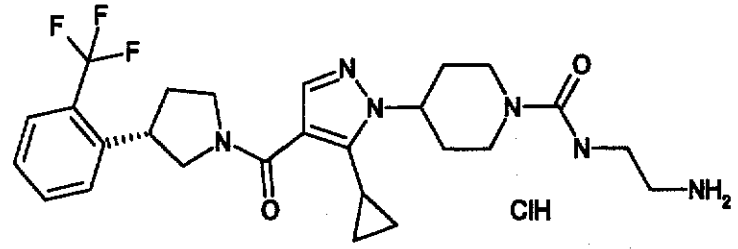
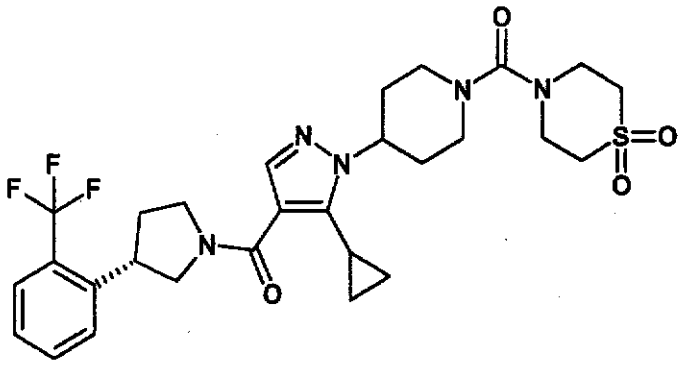
Ex. No.	structural formula	NMR
9		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.87 (2H, m), 0.98-1.17 (2H, m), 1.31 (3H, s), 1.32 (3H, s), 1.66-2.25 (6H, m), 2.26-2.47 (1H, m), 2.83-3.02 (2H, m), 3.39-4.20 (9H, m), 4.43-4.64 (1H, m), 4.67-4.84 (1H, m), 5.00-5.46 (1H, brs), 7.32-7.40 (1H, m), 7.41-7.60 (3H, m), 7.61-7.72 (1H, m)
10		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.82 (2H, m), 1.00-1.11 (2H, m), 1.70-1.83 (1H, m), 1.83-1.95 (3H, m), 1.99 (3H, br s), 2.04-2.22 (3H, m), 2.27-2.43 (1H, m), 2.86-3.01 (2H, m), 3.33-3.43 (4H, m), 3.54-4.18 (6H, m), 4.44-4.63 (1H, m), 5.42-5.53 (1H, m), 6.33-6.41 (1H, m), 7.32-7.71 (5H, m)
11		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.58-0.74 (2H,m), 0.91-1.05 (2H, m), 1.78-2.34 (7H, m), 2.78-2.99 (5H, m), 3.22-3.94 (6H,m), 4.06-4.21 (2H, m), 4.54-4.72 (1H, m), 6.46-6.95 (1H,m), 7.42-7.77 (5H, m), 7.88-8.03 (3H,m)
12		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.86 (2H, m), 1.01-1.16 (2H, m), 1.71-1.86 (1H, m), 1.89-2.46 (6H, m), 2.91-3.15 (6H, m), 3.40-4.14 (11H, m), 4.47-4.67 (1H, m), 7.32-7.73 (5H, m)

Table 1-4

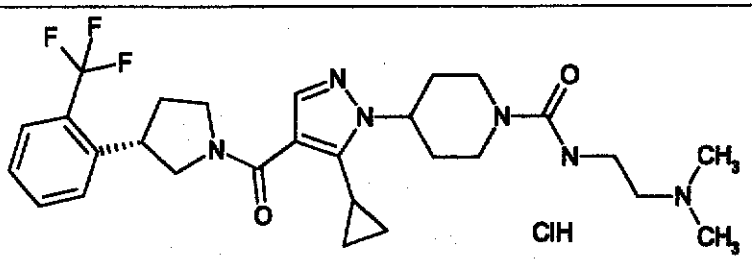
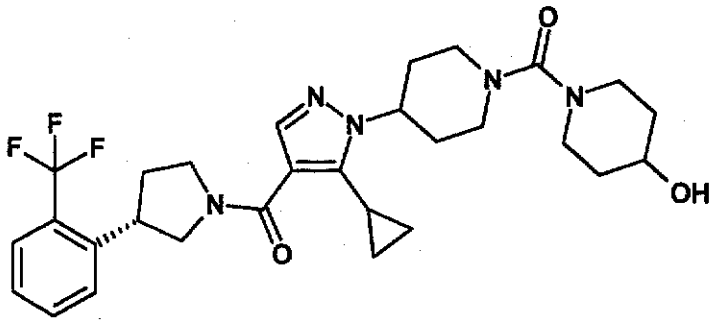
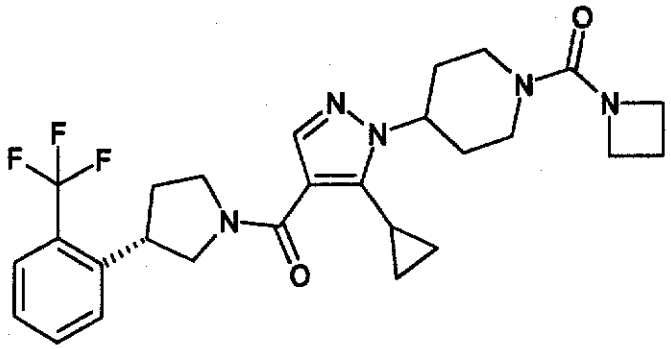
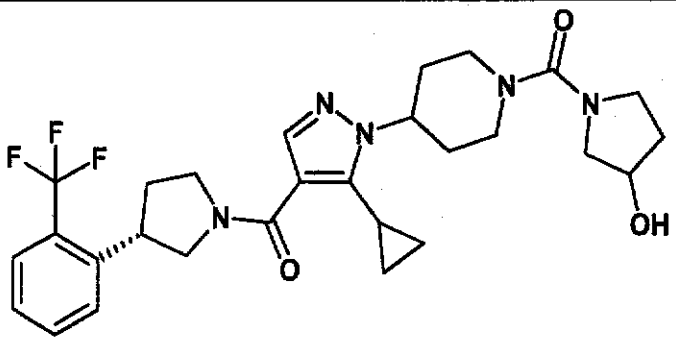
Ex. No.	structural formula	NMR
13		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.68-0.86 (2H,m), 1.00-1.15 (2H, m), 1.58-2.49 (15H, m), 2.84-3.03 (2H, m), 3.20-3.39 (2H,m), 3.41-4.25 (7H, m), 4.44-4.65 (1H, m), 5.13-5.29 (1H, m), 7.31-7.73 (5H, m)
14		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.82 (2H, m), 1.03-1.12 (2H, m), 1.46-1.60 (3H, m), 1.72-1.97 (5H, m), 2.00-2.44 (4H, m), 2.80-3.07 (4H, m), 3.42-4.10 (10H, m), 4.43-4.61 (1H, m), 7.32-7.71 (5H, m)
15		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.02-1.14 (2H, m), 1.71-2.45 (9H, m), 2.81-2.96 (2H, m), 3.42-4.22 (11H, m), 4.45-4.63 (1H, m), 7.32-7.72 (5H, m)
16		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.85 (2H, m), 0.99-1.17 (2H, m), 1.71-2.45 (10H, m), 2.79-3.00 (2H, m), 3.27-4.11 (11H, m), 4.39-4.63 (2H, m), 7.32-7.73 (5H, m)

Table 1-5

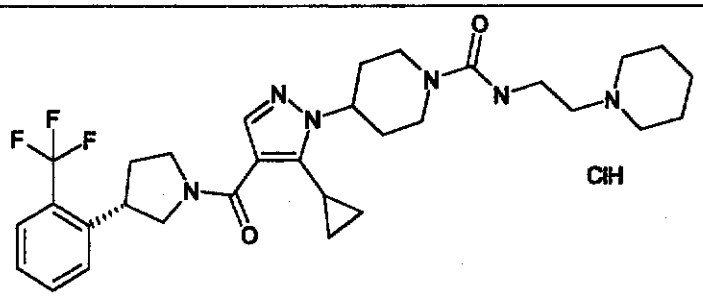
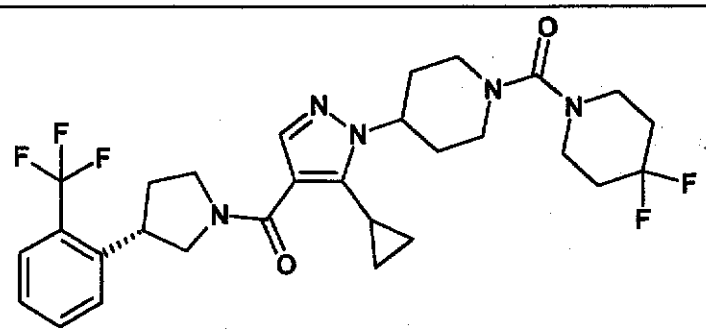
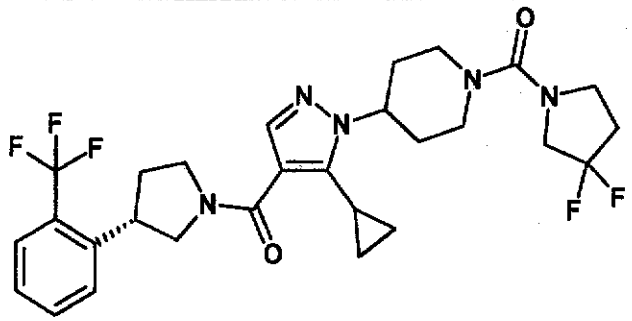
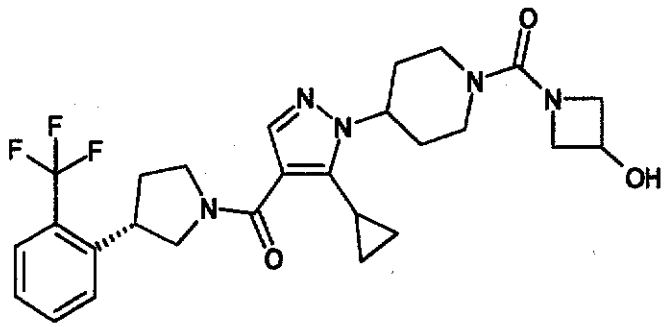
Ex. No.	structural formula	NMR
17		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.75 (2H, m), 0.92-1.06 (2H, m), 1.32-1.47 (1H, m), 1.63-1.98 (6H, m), 2.02-2.39 (2H,m), 2.78-3.00 (4H, m), 3.02-3.16 (2H, m), 3.38-3.54 (4H, m), 3.54-3.78 (3H, m), 3.80-4.55 (8H, m), 4.55-4.72 (1H, m), 7.01-7.20 (1H, brs), 7.41-7.60 (2H, m), 7.65-7.78 (3H, m), 9.99-10.16 (1H, brs)
18		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.01-1.15 (2H, m), 1.71-2.45 (11H, m), 2.83-3.01 (2H, m), 3.33-3.51 (4H, m), 3.57-4.11 (7H, m), 4.45-4.62 (1H, m), 7.31-7.73 (5H, m)
19		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.86 (2H, m), 1.02-1.15 (2H, m), 1.70-2.46 (9H, m), 2.83-3.01 (2H, m), 3.41-4.12 (11H, m), 4.46-4.65 (1H, m), 7.31-7.73 (5H, m)
20		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.84 (2H, m), 1.00-1.16 (2H, m), 1.71-2.26 (6H, m), 2.27-2.45 (1H, m), 2.50-2.59 (1H, m), 2.81-3.00 (2H, m), 3.42-4.12 (9H, m), 4.46-4.68 (2H, m), 7.31-7.72 (5H, m)

Table 1-6

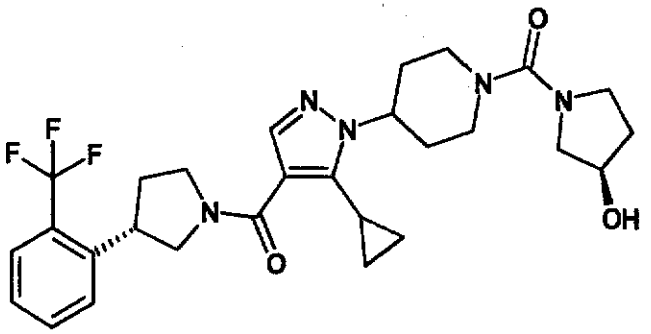
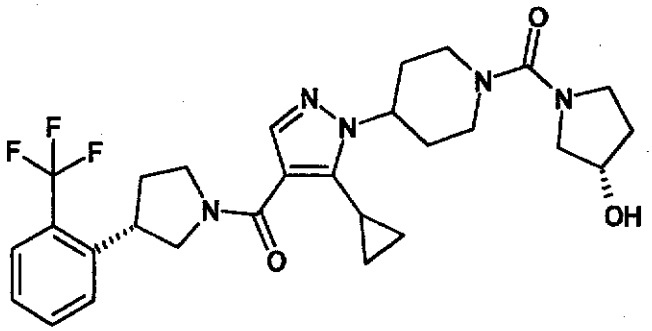
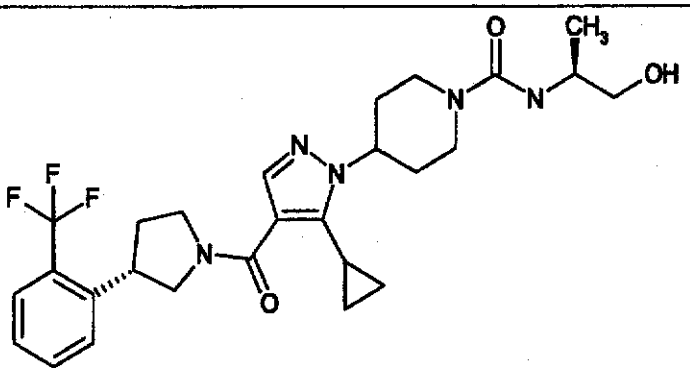
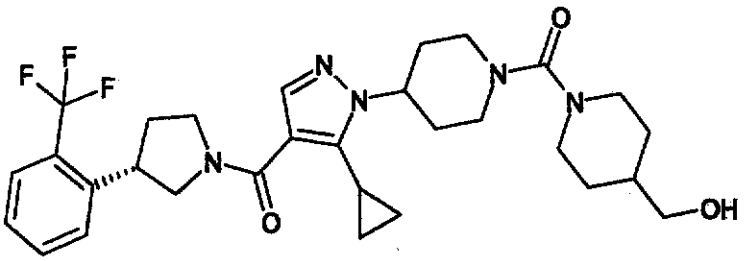
Ex. No.	structural formula	NMR
21		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.84 (2H, m), 0.99-1.15 (2H, m), 1.71-2.44 (10H, m), 2.78-2.99 (2H, m), 3.26-4.12 (11H, m), 4.42-4.62 (2H, m), 7.31-7.72 (5H, m)
22		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.85 (2H, m), 0.99-1.16 (2H, m), 1.68-2.47 (10H, m), 2.76-2.99 (2H, m), 3.27-4.11 (11H, m), 4.41-4.62 (2H, m), 7.32-7.73 (5H, m)
23		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.81 (2H,m), 1.05-1.15 (2H, m), 1.71-2.45 (7H, m), 1.94-2.44 (6H, m), 2.85-3.05 (2H, m), 3.35-4.20 (9H, m), 4.45-4.65 (1H, m), 4.65-4.75 (1H, m), 7.30-8.30 (5H, m)
24		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.83 (2H, m), 1.02-1.13 (2H, m), 1.15-1.32 (3H, m), 1.35-1.46 (1H, m), 1.63-2.45 (9H, m), 2.73-2.98 (4H, m), 3.40-4.12 (11H, m), 4.42-4.63 (1H, m), 7.29-7.74 (5H, m)

Table 1-7

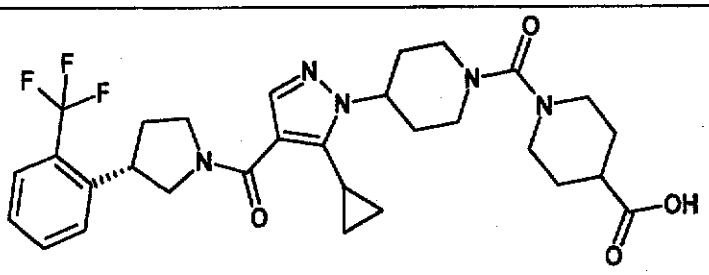
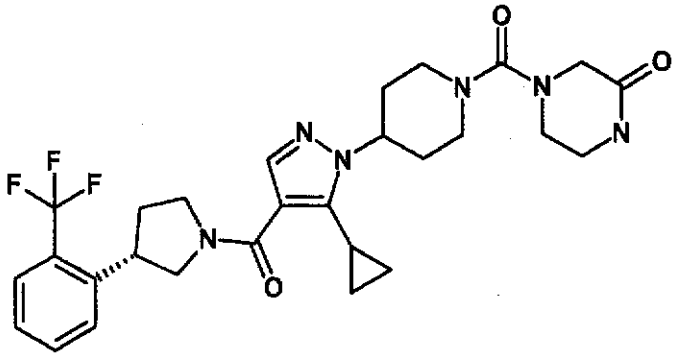
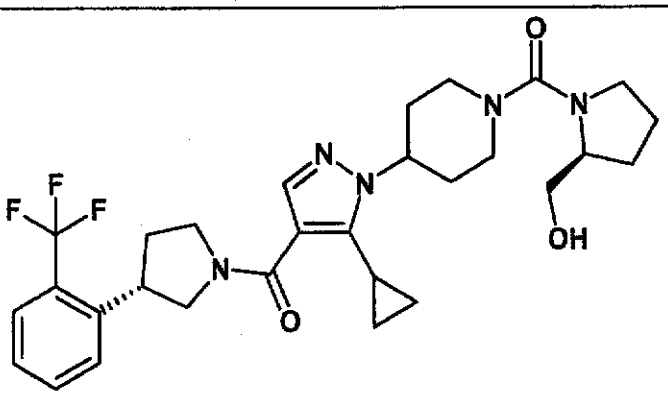
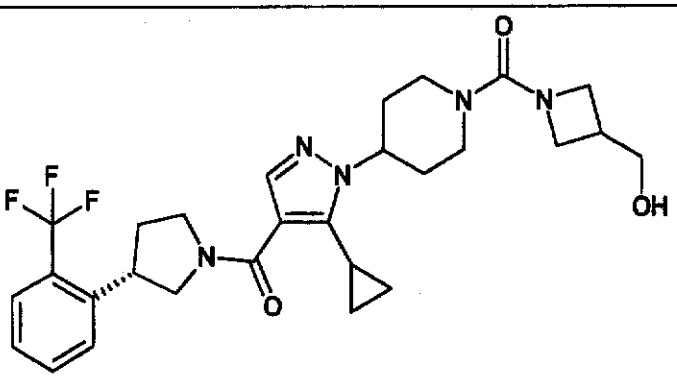
Ex. No.	structural formula	NMR
25		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.74 (2H, m), 0.91-1.06 (2H, m), 1.42-1.63 (2H, m), 1.72-2.46 (10H, m), 2.75-3.03 (4H, m), 3.43-3.96 (9H, m), 4.48-4.72 (1H, m), 7.38-7.83 (5H, m), 12.1-12.4 (1H, m)
26		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.85 (2H, m), 0.97-1.17 (2H, m), 1.68-2.46 (7H, m), 2.84-3.08 (2H, m), 3.36-4.13 (13H, m), 4.44-4.67 (1H, m), 6.54-6.71 (1H, m), 7.30-7.73 (5H, m)
27		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.84 (2H, m), 1.00-1.15 (2H, m), 1.43-1.59 (1H, m), 1.61-2.45 (10H, m), 2.78-3.01 (2H, m), 3.32-4.10 (11H, m), 4.18-4.31 (1H, m), 4.45-4.63 (1H, m), 7.31-7.72 (5H, m)
28		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.83 (2H, m), 0.96-1.16 (2H, m), 1.70-2.29 (6H, m), 2.29-2.39 (1H, m), 2.67-2.69 (1H, m), 2.82-2.97 (2H, m), 3.38-4.18 (13H, m), 4.41-4.65 (1H, m), 7.30-7.74 (5H, m)

Table 1-8

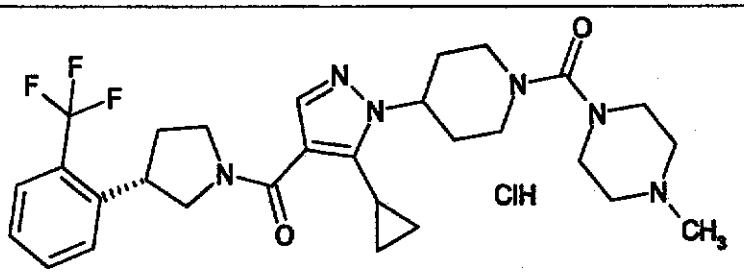
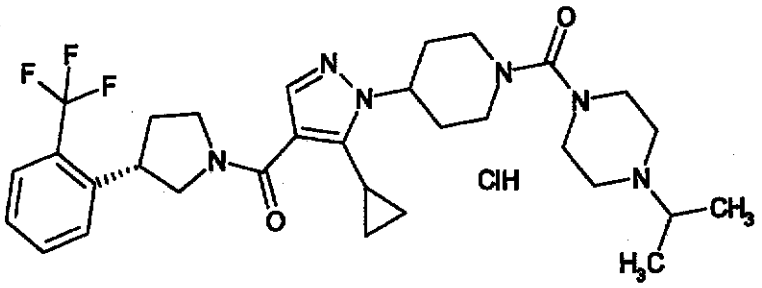
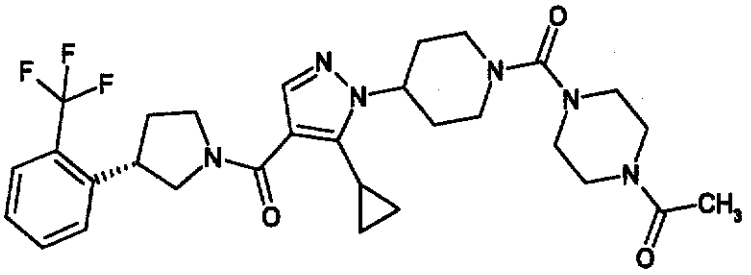
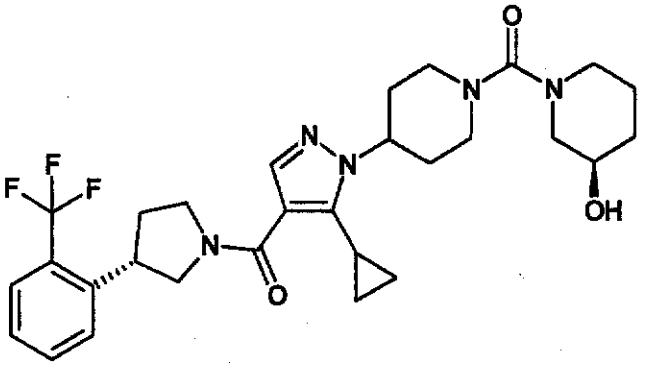
Ex. No.	structural formula	NMR
29		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.73 (2H, m), 0.94-1.06 (2H, m), 1.79-2.34 (7H, m), 2.74-2.82 (3H, m), 2.89-3.93 (17H, m), 4.55-4.74 (1H, m), 7.42-7.80 (5H, m), 10.4-10.6 (1H, m)
30		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.75 (2H, m), 0.92-1.06 (2H, m), 1.22-1.35 (6H, m), 1.77-2.46 (7H, m), 2.85-3.11 (5H, m), 3.21-3.96 (13H, m), 4.52-4.74 (1H, m), 7.42-7.82 (5H, m), 10.3-10.5 (1H, m)
31		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.85 (2H, m), 1.02-1.16 (2H, m), 1.71-2.47 (10H, m), 2.87-3.03 (2H, m), 3.20-4.15 (15H, m), 4.45-4.66 (1H, m), 7.31-7.73 (5H, m)
32		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.84 (2H, m), 0.97-1.15 (2H, m), 1.37-1.55 (1H, m), 1.55-1.96 (6H, m), 1.99-2.46 (5H, m), 2.77-3.03 (1H, m), 3.15-4.12 (12H, m), 4.38-4.65 (1H, m), 7.30-7.74 (5H, m)

Table 1-9

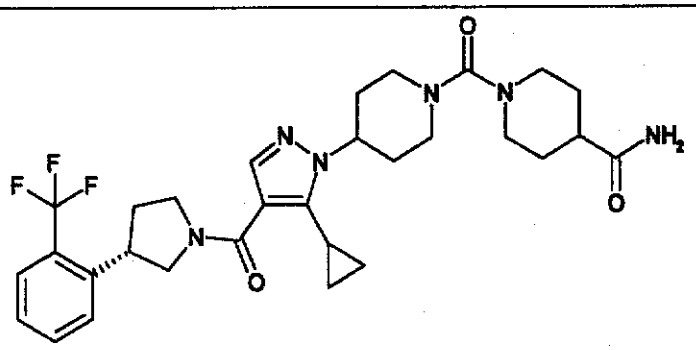
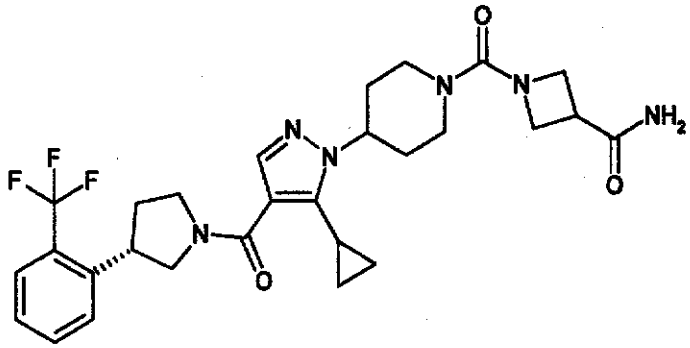
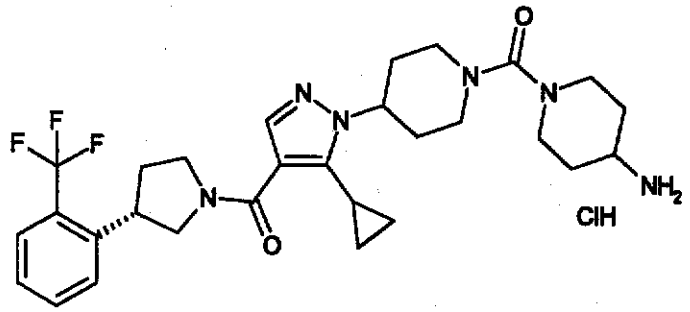
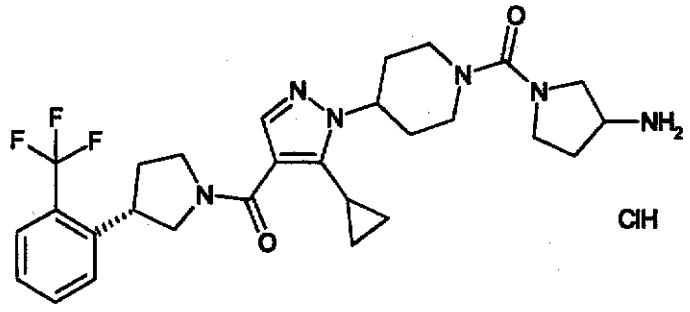
Ex. No.	structural formula	NMR
33		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.01-1.14 (2H, m), 1.62-1.99 (7H, m), 1.99-2.47 (5H, m), 2.74-3.00 (4H, m), 3.41-3.53 (0.6H, m), 3.56-4.11 (8.4H, m), 4.43-4.61 (1H, m), 5.44 (1H, brs), 5.56 (1H, brs), 7.32-7.38 (1H, m), 7.39-7.60 (3H, m), 7.62-7.71 (1H, m)
34		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.83 (2H, m), 0.99-1.15 (2H, m), 1.67-1.96 (3H, m), 1.98-2.24 (3H, m), 2.25-2.44 (1H, m), 2.78-3.00 (2H, m), 3.20-3.39 (1H, m), 3.40-3.53 (0.5H, m), 3.53-4.09 (6.5H, m), 4.10-4.25 (4H, m), 4.40-4.66 (1H, m), 5.59 (1H, brs), 5.77 (1H, brs), 7.31-7.39 (1H, m), 7.40-7.60 (3H, m), 7.62-7.71 (1H, m)
35		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.72 (2H, m), 0.94-1.06 (2H, m), 1.39-1.56 (2H, m), 1.78-2.01 (6H, m), 2.05-2.34 (2H, m), 2.72-3.01 (4H, m), 3.24-3.27 (1H, m), 3.43-4.01 (9H, m), 4.53-4.70 (1H, m), 7.43-7.60 (2H, m), 7.66-7.77 (3H, m), 8.33 (3H, brs)
36		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.55-0.73 (2H, m), 0.89-1.08 (2H, m), 1.69-2.38 (10H, m), 2.77-3.02 (2H, m), 3.12-4.15 (11H, m), 4.52-4.73 (1H, m), 7.41-7.77 (3H, m), 8.18-8.40 (3H, m), 8.42-8.61 (1H, m), 9.36-9.63 (1H, m)

Table 1-10

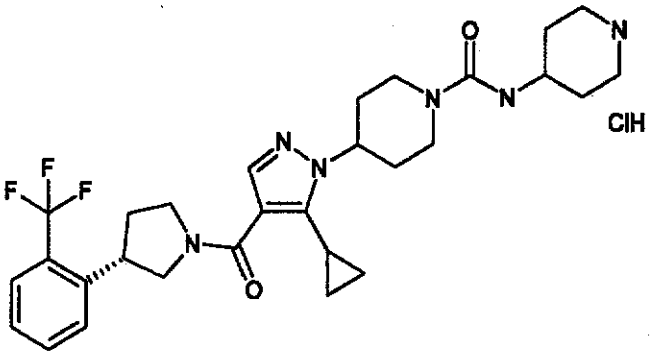
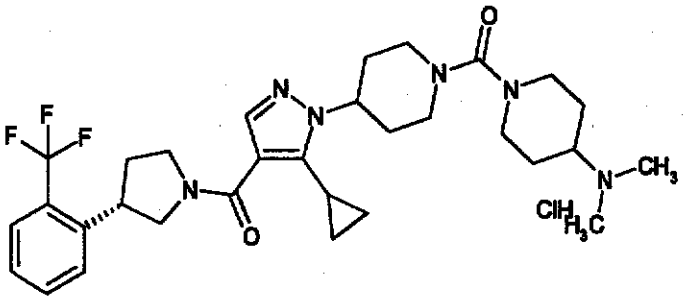
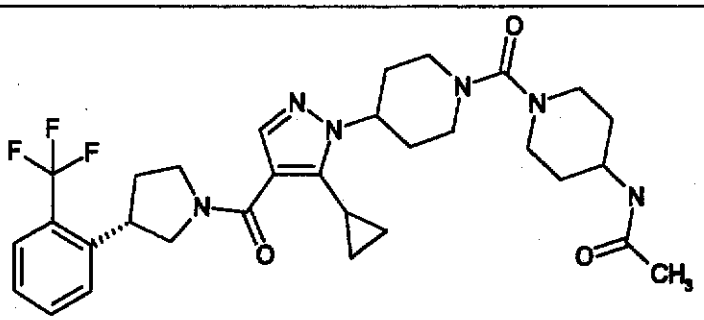
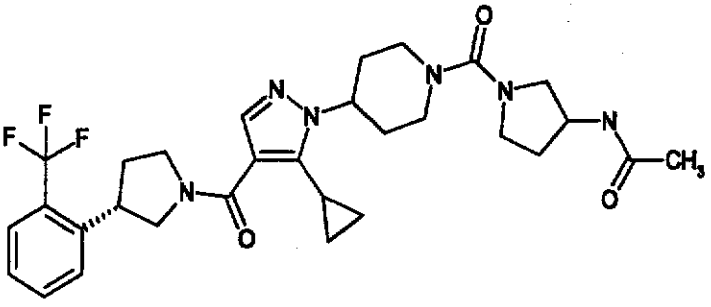
Ex. No.	structural formula	NMR
37		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.73 (2H, m), 0.92-1.04 (2H, m), 1.55-1.70 (2H, m), 1.74-1.98 (7H, m), 2.02-2.36 (2H, m), 2.73-3.02 (4H, m), 3.19-3.33 (2H, m), 3.45-4.32 (8H, m), 4.53-4.72 (1H, m), 6.44-6.62 (1H, m), 7.42-7.79 (5H, m), 8.62 (1H, br s), 8.72 (1H, br s)
38		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.74 (2H, m), 0.92-1.06 (2H, m), 1.47-1.68 (2H, m), 1.78-2.56 (8H, m), 2.62-3.03 (4H, m), 2.77 (6H, s), 3.24-3.94 (10H, m), 4.54-4.70 (1H, m), 7.42-7.62 (2H, m), 7.63-7.79 (3H, m), 10.2-10.4 (1H, m)
39		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.02-1.14 (2H, m), 1.31-1.46 (2H, m), 1.71-2.45 (9H, m), 1.97 (3H, s), 2.81-3.00 (4H, m), 3.42-4.10 (10H, m), 4.44-4.61 (1H, m), 5.29-5.43 (1H, m), 7.33-7.72 (5H, m)
40		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.83 (2H, m), 1.00-1.13 (2H, m), 1.68-2.46 (13H, m), 2.81-3.00 (2H, m), 3.28-4.10 (10H, m), 4.36-4.63 (2H, m), 5.61-5.72 (1H, m), 7.31-7.70 (5H, m)

Table 1-11

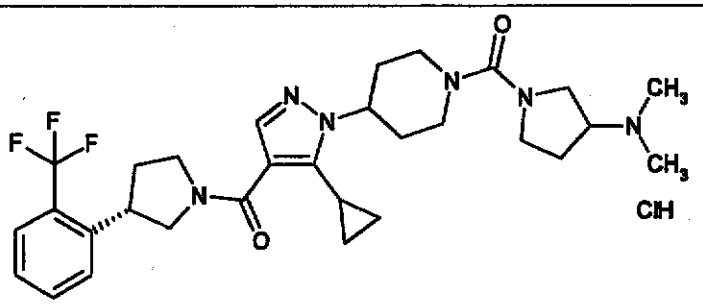
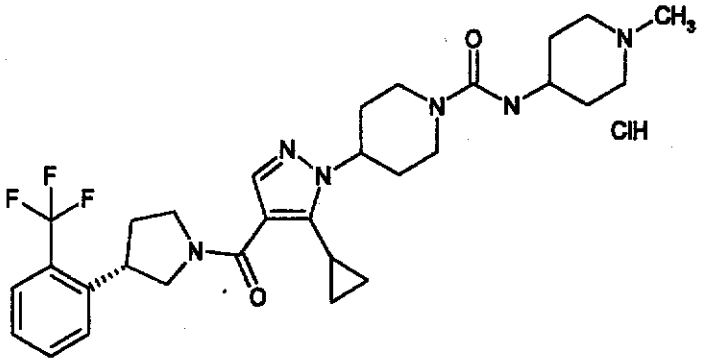
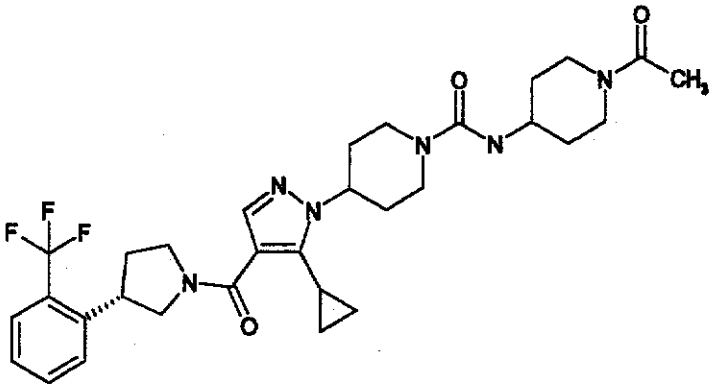
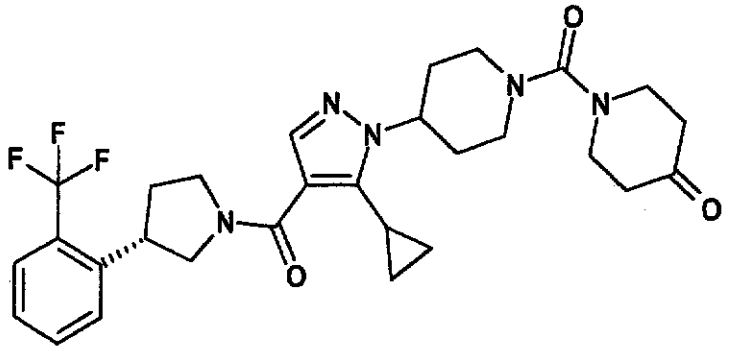
Ex. No.	structural formula	NMR
41		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.71 (2H, m), 0.92-1.03 (2H, m), 1.76-2.36 (8H, m), 2.70-2.80 (6H, brs), 2.81-3.03 (2H, m), 3.24-3.92 (13H, m), 4.52-4.71 (1H, m), 7.41-7.77 (5H, m), 10.76-10.91 (1H, brs)
42		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.74 (2H, m), 0.92-1.05 (2H, m), 1.60-2.00 (9H, m), 2.03-2.38 (2H, m), 2.65-3.93 (15H, m), 4.04-4.24 (2H, m), 4.51-4.73 (1H, m), 6.28-6.65 (1H, m), 7.41-7.81 (5H, m), 9.88 (1H, br s)
43		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.02-1.15 (2H, m), 1.22-1.38 (2H, m), 1.70-2.26 (11H, m), 2.28-2.46 (1H, m), 2.67-2.79 (1H, m), 2.86-3.04 (2H, m), 3.10-3.24 (1H, m), 3.40-4.21 (9H, m), 4.32-4.45 (1H, m), 4.47-4.64 (2H, m), 7.32-7.72 (5H, m)
44		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.85 (2H, m), 1.02-1.18 (2H, m), 1.70-2.57 (11H, m), 2.91-3.08 (2H, m), 3.38-4.13 (11H, m), 4.74-4.66 (1H, m), 7.32-7.76 (5H, m)

Table 1-12

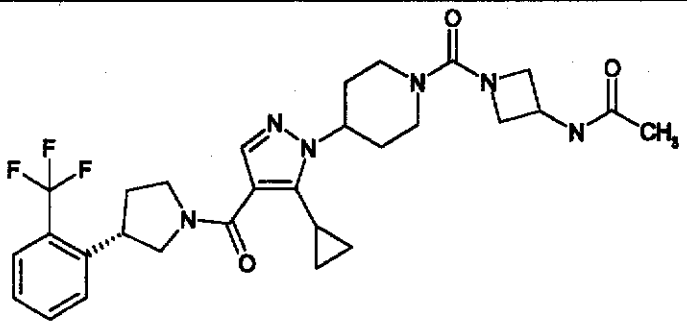
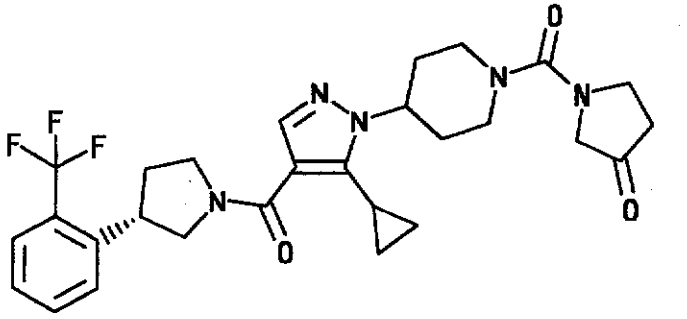
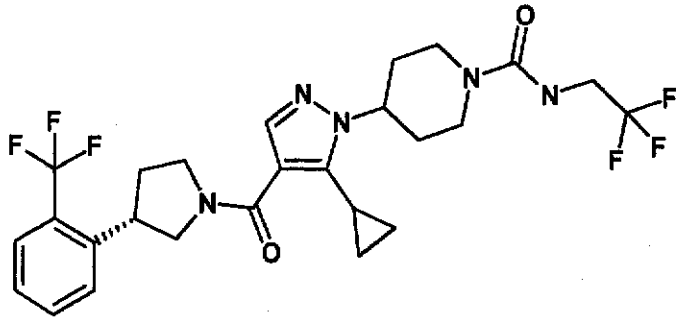
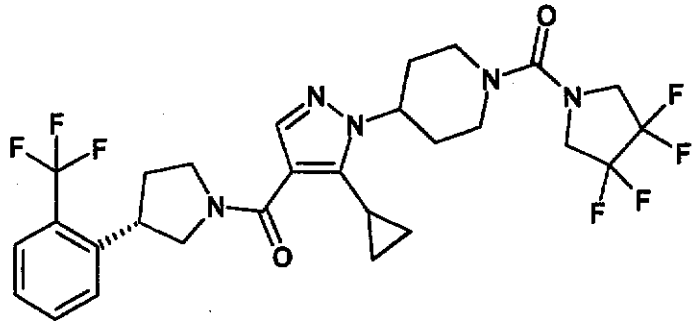
Ex. No.	structural formula	NMR
45		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.85 (2H, m), 0.96-1.17 (2H, m), 1.65-1.95 (3H, m), 1.96-2.22 (3H, m), 1.99 (3H, s), 2.25-2.48 (1H, m), 2.81-3.02 (2H, m), 3.38-3.5 (0.6H, m), 3.54-4.14 (8.4H, m), 4.19-4.37 (2H, m), 4.43-4.72 (2H, m), 6.24-6.40 (1H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.70 (1H, m)
46		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.88 (2H, m), 1.02-1.17 (2H, m), 1.71-1.87 (1H, m), 1.88-2.45 (6H, m), 2.48-2.60 (2H, m), 2.90-3.06 (2H, m), 3.43-4.11 (11H, m), 4.49-4.66 (1H, m), 7.33-7.72 (5H, m)
47		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.81 (2H, m), 1.01-1.12 (2H, m), 1.71-1.82 (1H, m), 1.83-1.96 (3H, m), 1.99-2.25 (3H, m), 2.26-2.43 (1H, m), 2.93-3.08 (2H, m), 3.41-4.00 (6H, m), 4.00-4.20 (2H, m), 4.49-4.64 (1H, m), 4.85-4.97 (1H, m), 7.30-7.70 (5H, m)
48		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.01-1.17 (2H, m), 1.71-2.45 (7H, m), 2.86-3.06 (2H, m), 3.42-4.12 (11H, m), 4.49-4.67 (1H, m), 7.31-7.73 (5H, m)

Table 1-13

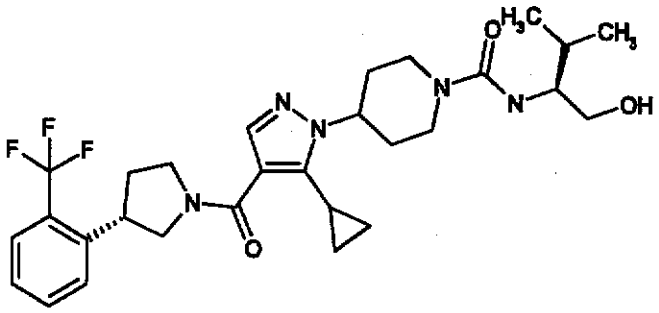
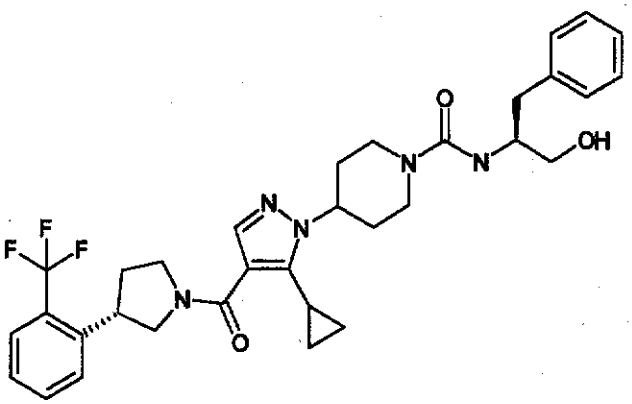
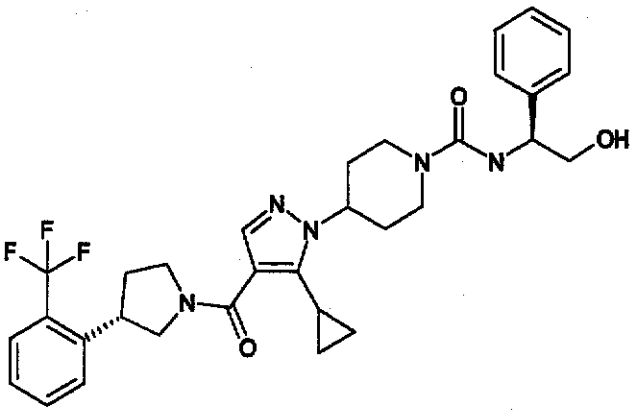
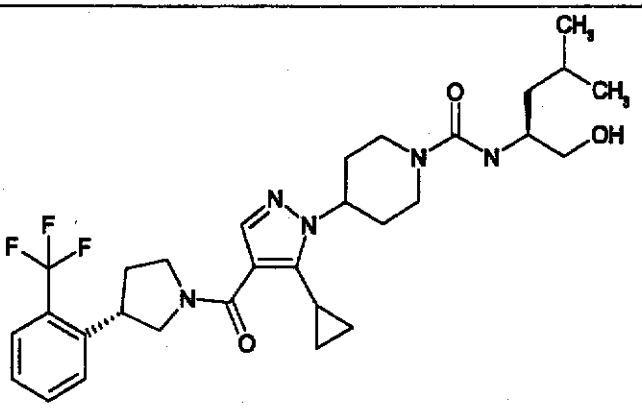
Ex. No.	structural formula	NMR
49		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.83 (2H,m), 0.92-1.02 (6H, m), 1.02-1.13 (2H, m), 1.22-1.33 (2H, m), 1.71-1.98 (4H,m), 1.99-2.45 (4H, m), 2.88-3.08 (2H, m), 3.14-3.28 (1H, brs), 3.38-4.24 (8H, m), 4.47-4.73 (2H, m), 7.32-7.72 (5H, m)
50		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.81 (2H, m), 0.96-1.13 (2H, m), 1.60-1.81 (3H, m), 1.90-2.21 (3H, m), 2.26-2.46 (1H, m), 2.72-2.98 (4H, m), 3.38-4.13 (9H, m), 4.37-4.59 (1H, m), 4.94-5.04 (1H, m), 7.16-7.73 (10H, m)
51		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.82 (2H, m), 1.00-1.12 (2H, m), 1.69-1.85 (3H, m), 1.96-2.22 (3H, m), 2.25-2.45 (1H, m), 2.84-3.01 (2H, m), 3.39-3.50 (2H, m), 3.54-4.27 (7H, m), 4.41-4.61 (1H, m), 4.93-5.04 (1H, m), 5.38-5.55 (1H, m), 7.23-7.73 (10H, m)
52		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.79 (2H, m), 0.89-0.99 (6H, m), 1.02-1.12 (2H, m), 1.31-1.43 (2H, m), 1.60-1.85 (4H, m), 2.00-2.20 (3H, m), 2.25-2.45 (1H, m), 2.81-3.00 (2H, m), 3.39-4.21 (10H, m), 4.42-4.60 (1H, m), 4.79-4.92 (1H, m), 7.30-7.73 (5H, m)

Table 1-14

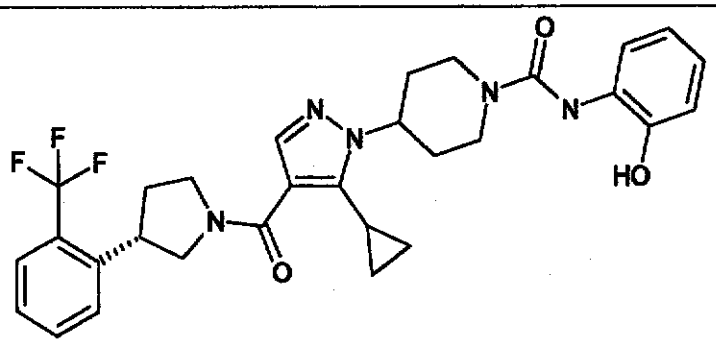
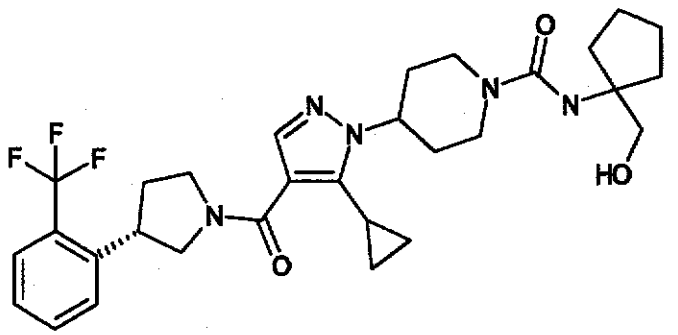
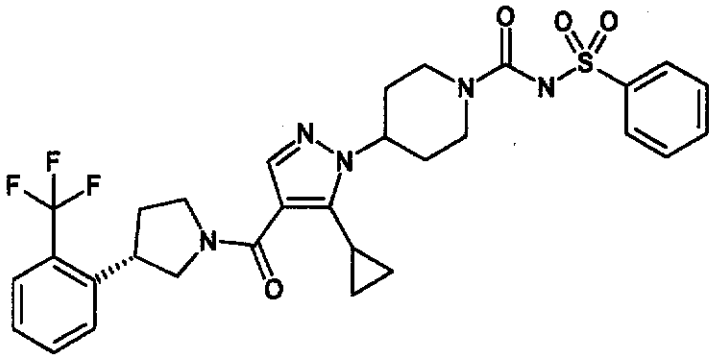
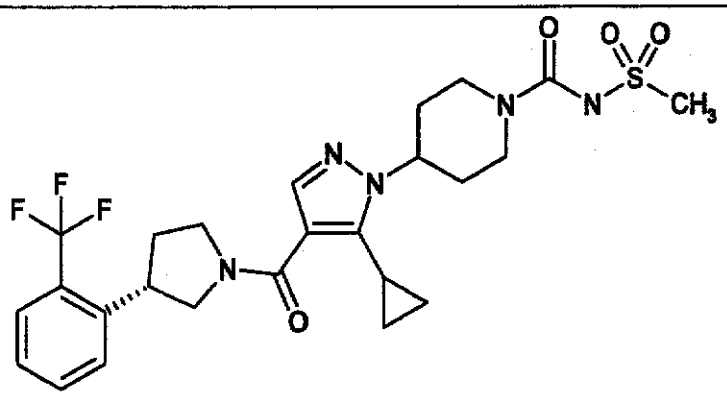
Ex. No.	structural formula	NMR
53		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.83 (2H, m), 1.00-1.14 (2H, m), 1.67-1.90 (3H, m), 1.98-2.27 (3H, m), 2.27-2.24 (1H, m), 2.98-3.14 (2H, m), 3.42-4.11 (5H, m), 4.22-4.40 (2H, m), 4.50-4.66 (1H, m), 6.78-6.88 (1H, m), 6.98-7.13 (3H, m), 7.14-7.21 (1H, m), 7.34-7.61 (4H, m), 7.64-7.73 (1H, m), 9.24-9.36 (1H, m)
54		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.85 (2H, m), 0.97-1.16 (2H, m), 1.51-2.46 (15H, m), 2.84-3.07 (2H, m), 3.42-4.19 (9H, m), 4.47-4.64 (1H, m), 4.65-4.75 (1H, m), 5.14-5.24 (1H, m), 7.31-7.73 (5H, m)
55		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.85 (2H, m), 0.95-1.18 (2H, m), 1.36-2.25 (7H, m), 2.25-2.44 (1H, m), 2.76-3.05 (2H, m), 3.38-3.47 (0.5H, m), 3.52-3.91 (3.5H, m), 3.95-4.31 (3H, m), 4.34-4.60 (1H, m), 7.29-7.73 (8H, m), 8.00-8.13 (2H, m)
56		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.83 (2H, m), 0.98-1.16 (2H, m), 1.65-1.91 (3H, m), 1.92-2.23 (3H, m), 2.24-2.50 (1H, m), 2.80-3.05 (2H, m), 3.16-3.34 (3H, m), 3.39-3.51 (0.6H, m), 3.52-4.13 (5.4H, m), 4.19-4.43 (2H, m), 4.44-4.64 (1H, m), 7.30-7.39 (1H, m), 7.41-7.60 (3H, m), 7.61-7.70 (1H, m)

Table 1-15

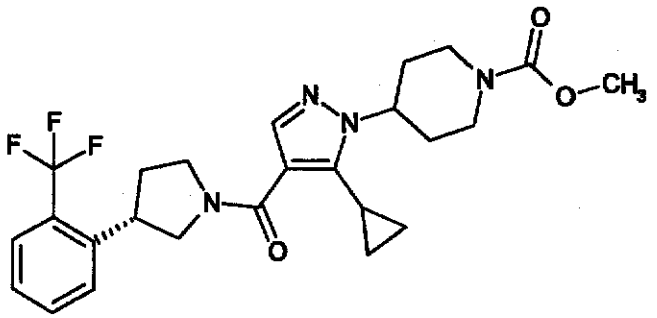
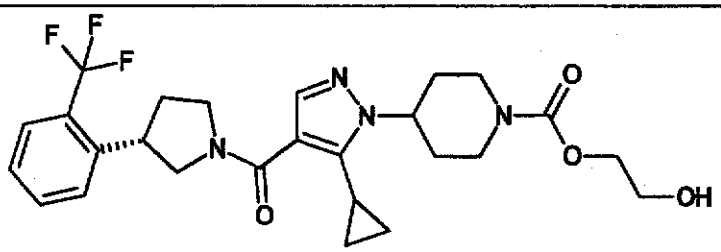
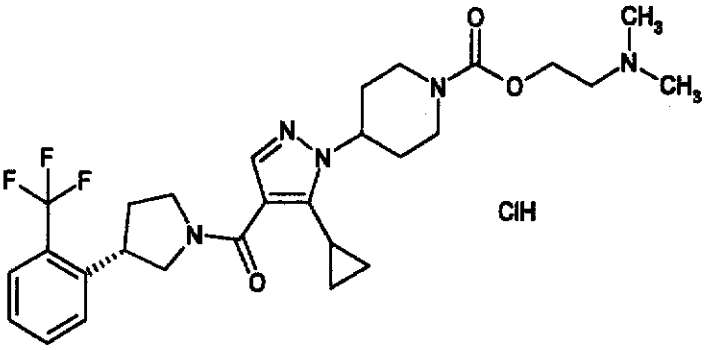
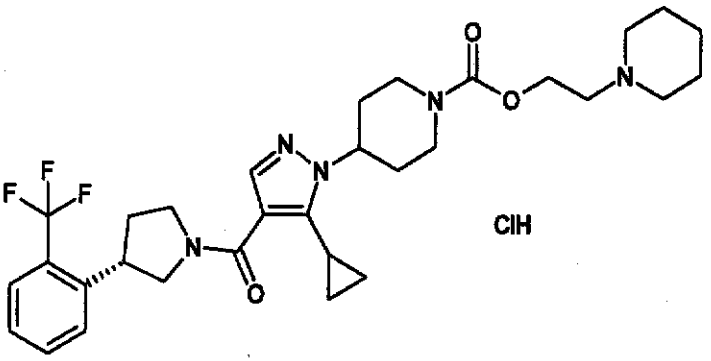
Ex. No.	structural formula	NMR
57		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.83 (2H, m), 0.98-1.15 (2H, m), 1.65-1.94 (3H, m), 1.94-2.25 (3H,m), 2.25-2.45 (1H, m), 2.77-3.05 (2H, m), 3.43-4.07 (8H, m), 4.11-4.45 (2H, m), 4.45-4.65 (1H, m), 7.30-7.72 (5H, m)
58		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.67-0.84 (2H, m), 1.03-1.15 (2H, m), 1.69-2.59 (8H, m), 2.86-3.11 (2H, m), 3.38-4.13 (7H, m), 4.19-4.44 (4H, m), 4.48-4.66 (1H, m), 7.30-7.74 (5H, m)
59		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.87 (2H, m), 0.99-1.18 (2H, m), 1.72-1.86 (1H, m), 1.87-1.99 (2H, m), 2.06-2.47 (4H, m), 2.63-3.23 (10H, m), 3.26-3.42 (2H, m), 3.43-4.13 (3H, m), 4.20-4.75 (5H, m), 7.33-7.39 (1H, m), 7.40-7.63 (3H, m), 7.64-7.69 (1H, m), 12.69 (1H, brs)
60		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.83 (2H, m), 1.07-1.23 (2H, m), 1.35-1.56 (1H, m), 1.79-2.00 (4H, m), 2.06-2.45 (6H, m), 2.68-3.20 (4H, m), 3.27-3.41 (2H, m), 3.43-4.08 (9H, m), 4.22-4.48 (2H, m), 4.58-4.82 (3H, m), 7.34-7.40 (1H, m), 7.44-7.50 (1H, m), 7.53-7.60 (1H, m), 7.65-7.72 (2H, m), 12.22 (1H, brs)

Table 1-16

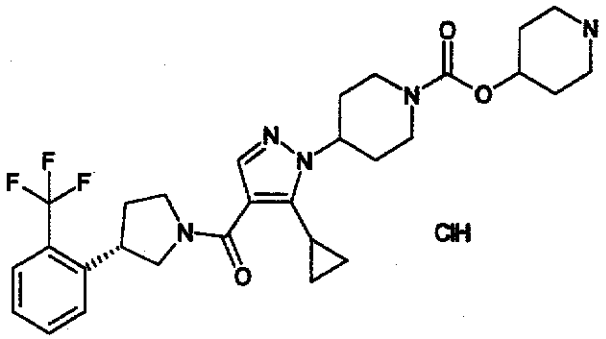
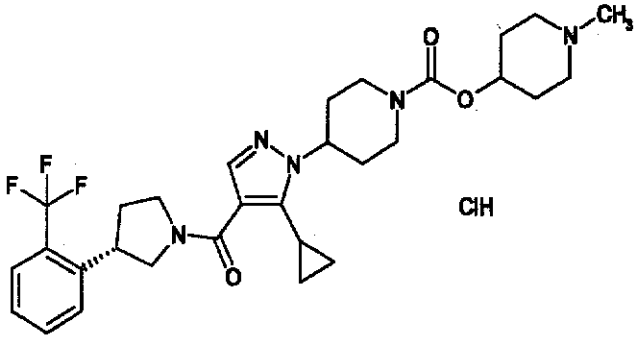
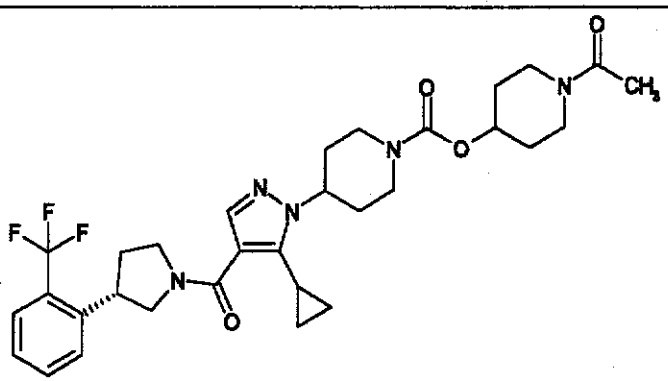
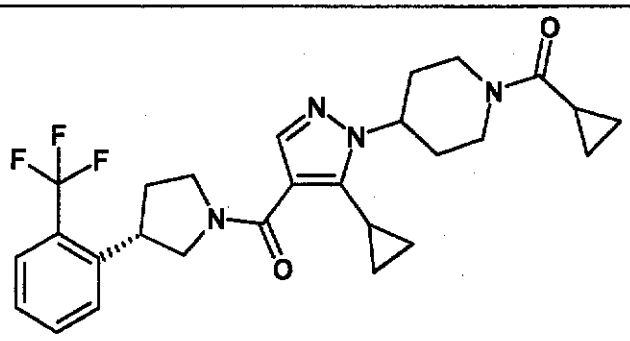
Ex. No.	structural formula	NMR
61		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.88 (2H, m), 1.03-1.21 (2H, m), 1.79-2.01 (3H, m), 2.01-2.32 (7H, m), 2.33-2.45 (1H, m), 2.81-3.12 (2H, m), 3.11-4.14 (9H, m), 4.15-4.49 (2H, m), 4.54-4.75 (1H, m), 4.92-5.09 (1H, m), 7.33-7.41 (1H, m), 7.44-7.61 (2H, m), 7.63-7.75 (2H, m), 9.45-9.81 (2H, m)
62		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.87 (2H, m), 1.04-1.21 (2H, m), 1.78-2.01 (3H, m), 2.03-2.49 (7H, m), 2.50-2.68 (1H, m), 2.72-3.14 (7H, m), 3.23-4.07 (7H, m), 4.17-4.44 (2H, m), 4.57-4.75 (1H, m), 4.76-4.89 (0.5H, m), 5.01-5.09 (0.5H, m), 7.33-7.41 (1H, m), 7.43-7.52 (1H, m), 7.52-7.61 (1H, m), 7.62-7.73 (2H, m), 12.38-12.70 (1H, m)
63		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.85 (2H, m), 0.99-1.16 (2H, m), 1.57-2.25 (13H, m), 2.26-2.46 (1H, m), 2.79-3.11 (2H, m), 3.27-3.54 (2.6H, m), 3.55-4.12 (6.4H, m), 4.14-4.66 (3H, m), 4.85-5.00 (1H, m), 7.31-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.71 (1H, m)
64		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.87 (4H, m), 0.91-1.18 (4H, m), 1.70-1.86 (2H, m), 1.88-2.48 (6H, m), 2.65-2.89 (1H, m), 3.13-3.39 (1H, m), 3.41-4.13 (5H, m), 4.27-4.89 (3H, m), 7.31-7.76 (5H, m)

Table 1-17

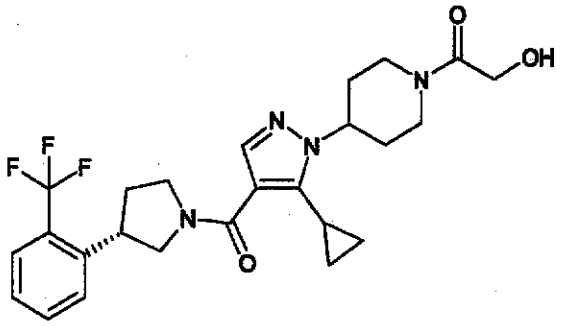
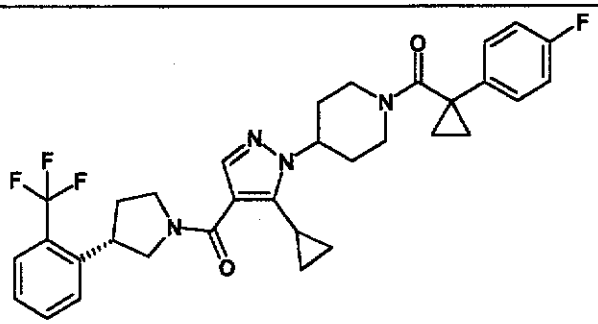
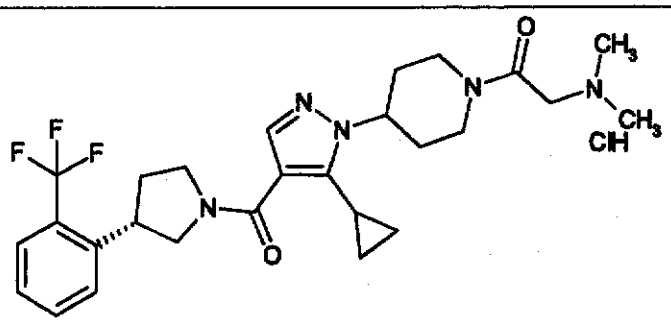
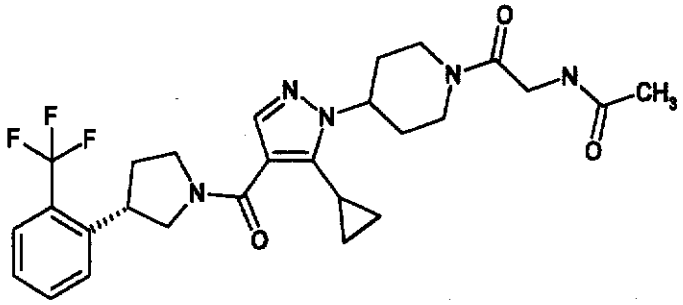
Ex. No.	structural formula	NMR
65		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.87 (2H, m), 1.01-1.16 (2H, m), 1.69-1.86 (1H, m), 1.90-2.49 (6H, m), 2.85-3.02 (1H, m), 3.07-3.26 (1H, m), 3.40-4.12 (7H, m), 4.16-4.29 (2H, m), 4.54-4.82 (2H, m), 7.31-7.77 (5H, m)
66		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.63-0.83 (2H, m), 0.98-1.10 (2H, m), 1.12-1.23 (2H, m), 1.38-1.51 (2H, m), 1.66-2.22 (6H, m), 2.27-2.45 (1H, m), 2.73-3.03 (2H, m), 3.37-4.11 (5H, m), 4.15-4.95 (3H, m), 6.94-7.73 (9H, m)
67		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.92-1.06 (2H, m), 1.15-1.20 (1H, m), 1.75-2.36 (4H, m), 2.78-2.87 (6H, brs), 3.14-3.36 (1H, m), 3.40-3.92 (9H, m), 4.22-4.56 (3H, m), 4.64-4.86 (1H, m), 7.40-7.62 (2H, m), 7.64-7.77 (3H, m), 9.61-9.74 (1H, brs)
68		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.84 (2H, m), 1.04-1.16 (2H, m), 1.72-1.86 (1H, m), 1.90-2.28 (8H, m), 2.28-2.45 (1H, m), 2.81-2.96 (1H, m), 3.15-3.29 (1H, m), 3.42-3.51 (0.5H, m), 3.58-4.21 (7.5H, m), 4.58-4.79 (2H, m), 6.58-6.67 (1H, br s), 7.33-7.42 (1H, m), 7.42-7.62 (3H, m), 7.63-7.72 (1H, m)

Table 1-18

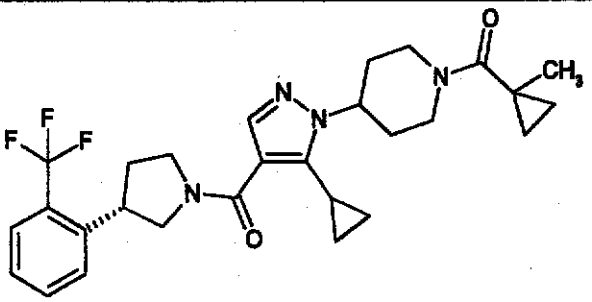
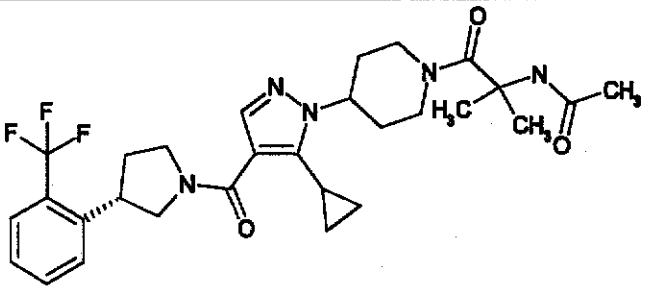
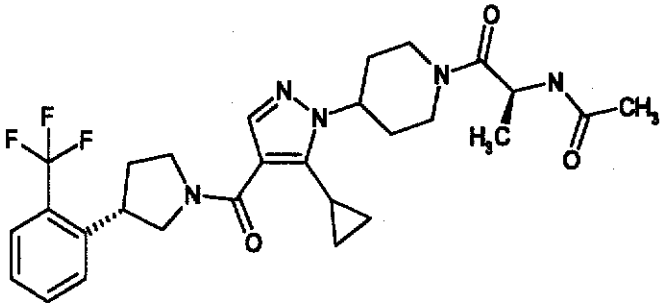
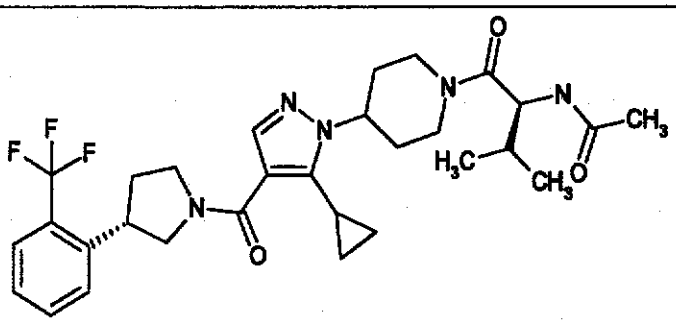
Ex. No.	structural formula	NMR
69		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.54-0.67 (2H, m), 0.71-0.86 (2H, m), 0.92-1.02 (2H, m), 1.04-1.14 (2H, m), 1.28-1.40 (3H, m), 1.72-1.86 (1H, m), 1.89-2.24 (5H, m), 2.27-2.46 (1H, m), 2.86-3.13 (2H, m), 3.41-4.12 (5H, m), 4.51-4.71 (3H, m), 7.32-7.75 (5H, m)
70		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.82 (2H, m), 1.01-1.12 (2H, m), 1.60-1.71 (7H, m), 1.71-2.45 (10H, m), 2.93-3.12 (1H, m), 3.37-4.10 (6H, m), 4.47-4.70 (2H, m), 6.70-6.79 (1H, brs), 7.28-7.71 (5H, m)
71		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.02-1.13 (2H, m), 1.29-1.41 (4H, m), 1.71-1.84 (1H, m), 1.89-2.45 (7H, m), 2.76-2.96 (2H, m), 3.16-3.34 (2H, m), 3.39-4.15 (5H, m), 4.56-4.79 (2H, m), 4.85-4.99 (1H, m), 6.55-6.67 (1H, m), 7.31-7.70 (5H, m)
72		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.83 (2H, m), 0.84-1.03 (6H, m), 1.03-1.14 (2H, m), 1.22-1.34 (2H, m), 1.71-2.44 (9H, m), 2.76-2.92 (1H, m), 3.17-4.79 (9H, m), 4.84-4.95 (1H, m), 6.19-6.30 (1H, m), 7.31-7.71 (5H, m)

Table 1-19

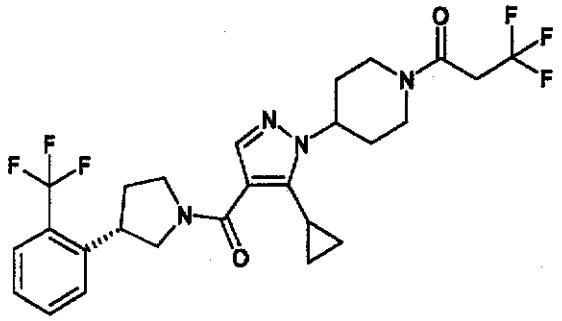
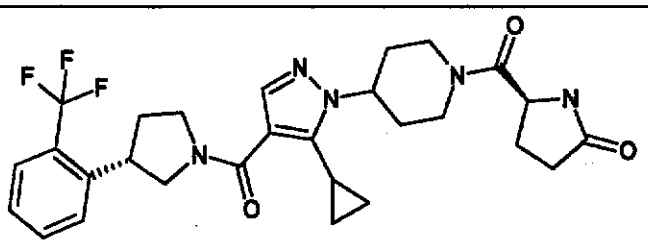
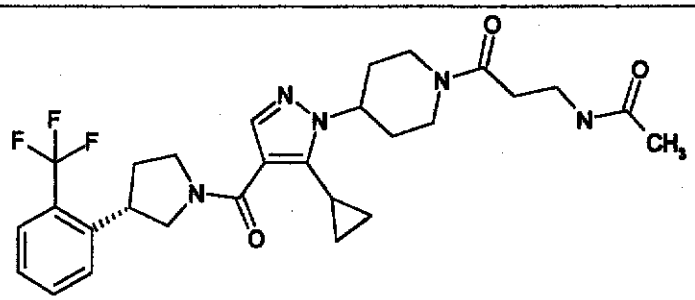
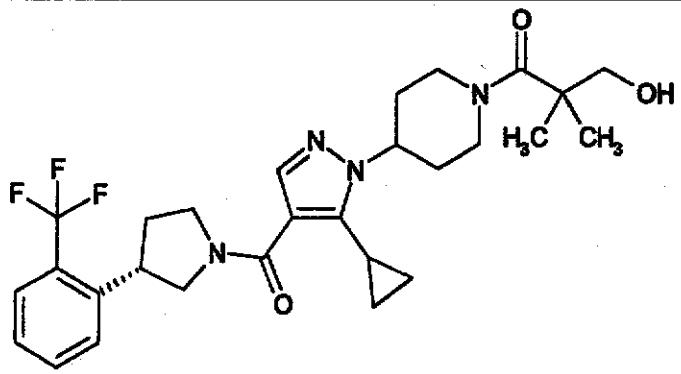
Ex. No.	structural formula	NMR
73		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.86 (2H, m), 0.99-1.18 (2H, m), 1.69-1.85 (1H, m), 1.89-2.45 (6H, m), 2.78-2.94 (1H, m), 3.19-3.39 (3H, m), 3.41-3.50 (0.6H, m), 3.56-4.10 (5.4H, m), 4.56-4.83 (2H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.71 (1H, m)
74		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.85 (2H, m), 1.03-1.15 (2H, m), 1.69-1.86 (1H, m), 1.91-2.61 (9H, m), 2.76-2.95 (1H, m), 3.18-4.11 (8H, m), 4.44-4.83 (3H, m), 5.76-5.93 (1H, m), 7.32-7.75 (5H, m)
75		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.82 (2H, m), 1.02-1.13 (2H, m), 1.69-1.84 (1H, m), 1.85-2.01 (6H, m), 2.02-2.23 (2H, m), 2.26-2.46 (1H, m), 2.47-2.60 (2H, m), 2.71-2.84 (1H, m), 3.11-3.26 (1H, m), 3.41-4.10 (8H, m), 4.54-4.68 (1H, m), 4.69-4.82 (1H, m), 6.32-6.40 (1H, brs), 7.31-7.70 (5H, m)
76		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.87 (2H, m), 1.02-1.18 (2H, m), 1.31 (3H, s), 1.33 (3H, s), 1.72-1.88 (1H, m), 1.90-2.48 (6H, m), 2.88-3.10 (2H, m), 3.42-4.15 (8H, m), 4.47-4.75 (3H, m), 7.32-7.74 (5H, m)

Table 1-20

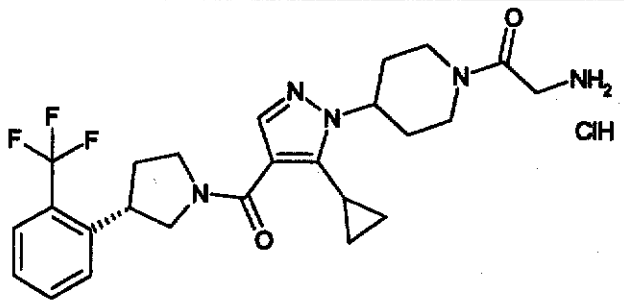
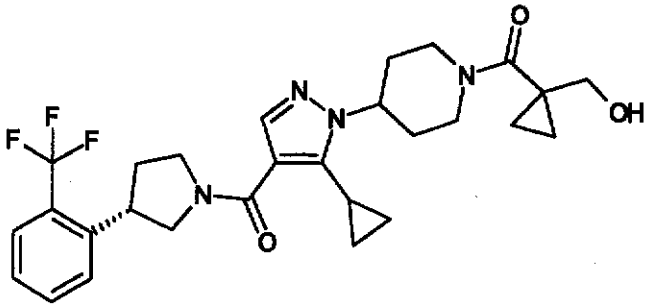
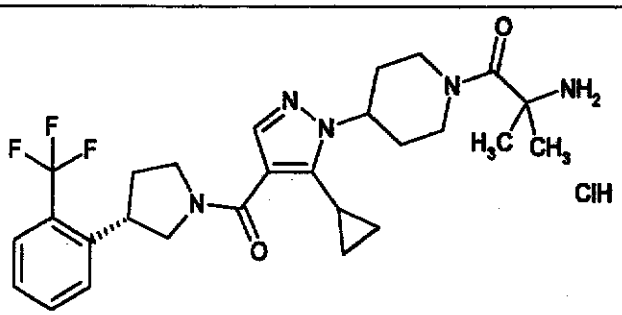
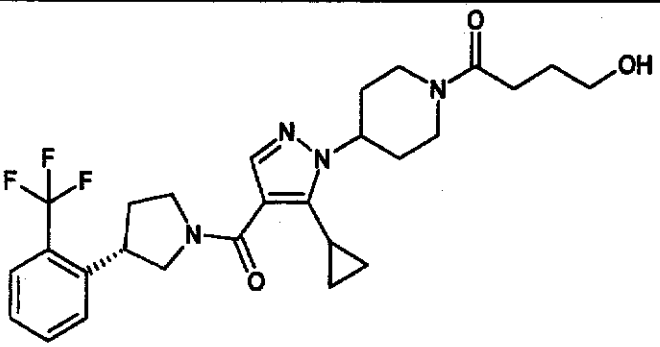
Ex. No.	structural formula	NMR
77		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.74 (2H, m), 0.93-1.05 (2H, m), 1.21-1.32 (1H, m), 1.72-2.34 (5H, m), 2.79-2.98 (1H,m), 3.13-3.34 (1H, m), 3.39-4.36 (9H, m), 4.38-4.55 (1H, m), 4.63-4.84 (1H, m), 7.40-7.60 (2H, m), 7.63-7.74 (3H, m), 8.80-8.18 (3H, brs)
78		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.89 (4H, m), 0.97-1.16 (4H, m), 1.71-1.86 (1H, m), 1.88-2.24 (6H, m), 2.27-2.46 (1H, m), 2.90-3.11 (2H, m), 3.41-4.11 (7H, m), 4.54-4.74 (3H, m), 7.33-7.74 (5H, m)
79		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.94-1.03 (2H, m), 1.50-1.65 (7H, m), 1.74-2.38 (5H, m), 2.99-3.28 (2H,m), 3.37-3.90 (5H, m), 3.94-4.65 (3H, m), 4.67-4.89 (1H, m), 7.40-7.78 (5H, m), 8.12-8.32 (3H, brs)
80		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.83 (2H, m), 1.02-1.14 (2H, m), 1.70-1.85 (1H, m), 1.85-2.46 (8H, m), 2.49-2.60 (2H, m), 2.69-2.85 (2H, m), 3.13-3.29 (1H, m), 3.41-3.50 (0.5H, m), 3.55-4.14 (7.5H, m), 4.53-4.70 (1H, m), 4.71-4.85 (1H, m), 7.31-7.40 (1H, m), 7.40-7.61 (3H, m), 7.62-7.73 (1H, m)

Table 1-21

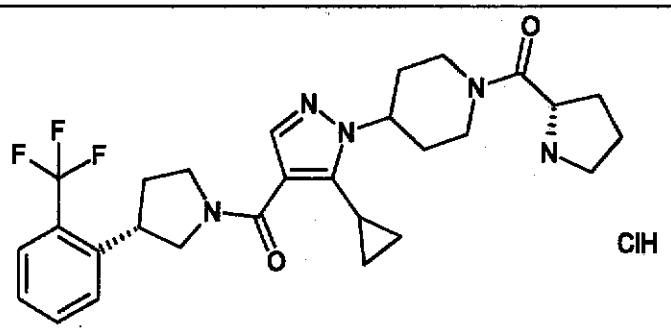
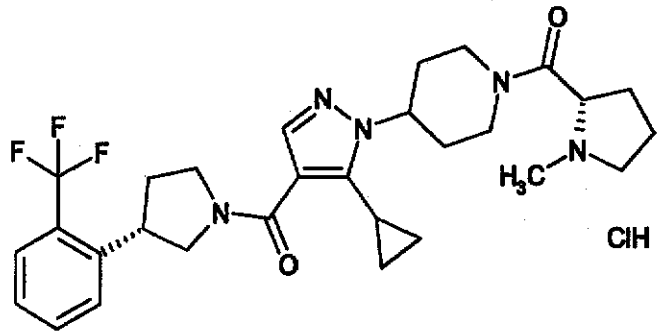
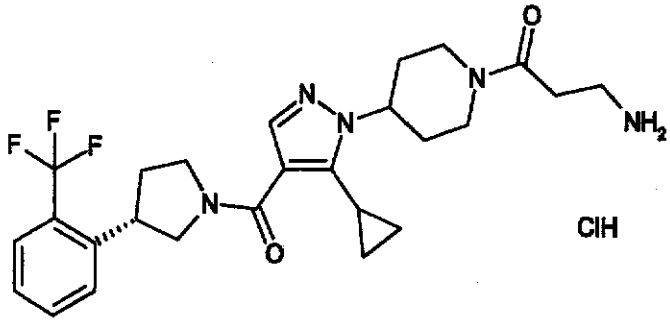
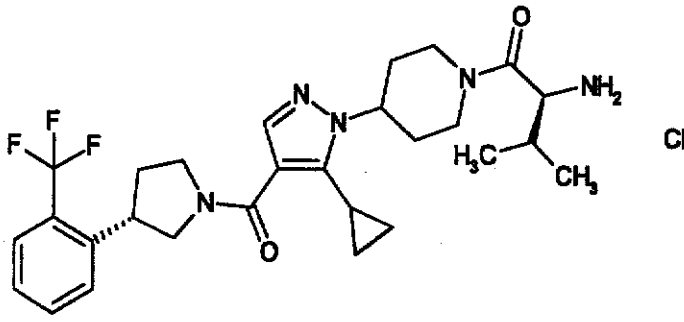
Ex. No.	structural formula	NMR
81		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.74 (2H, m), 0.93-1.10 (2H, m), 1.70-2.48 (12H, m), 2.83-3.03 (1H, m), 3.11-4.08 (9H, m), 4.41-4.85 (2H, m), 7.42-7.53 (2H, m), 7.65-7.78 (3H, m), 9.91-10.05 (1H, brs), 10.12-10.24 (1H, brs)
82		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.75 (2H, m), 0.92-1.03 (2H, m), 1.74-2.17 (11H, m), 2.18-2.35 (1H, m), 2.73-2.87 (3H, m), 2.88-3.90 (10H, m), 4.43-4.56 (1H, m), 4.60-4.85 (1H, m), 7.41-7.76 (5H, m), 9.53-9.70 (1H, brs)
83		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.58-0.72 (2H, m), 0.93-1.04 (2H, m), 1.69-2.02 (5H, m), 2.03-2.16 (1H, m), 2.17-2.34 (1H, m), 2.64-2.87 (3H, m), 2.91-3.07 (2H, m), 3.16-3.32 (1H, m), 3.42-3.78 (6H, m), 3.80-3.99 (1H, m), 4.44-4.58 (1H, m), 7.42-7.94 (8H, m)
84		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.73 (2H, m), 0.87-1.10 (8H, m), 1.73-2.17 (8H, m), 2.18-2.34 (1H, m), 2.81-2.98 (1H, m), 3.21-3.37 (1H, m), 3.40-3.92 (4H, m), 4.04-4.19 (1H, m), 4.23-4.41 (1H, m), 4.46-4.61 (1H, m), 4.66-4.85 (1H, m), 7.43-7.61 (2H, m), 7.64-7.77 (3H, m), 8.07-8.24 (3H, m)

Table 1-22

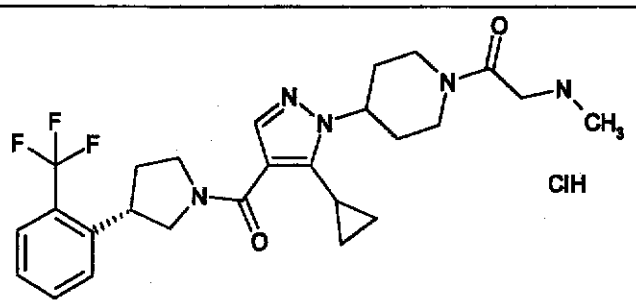
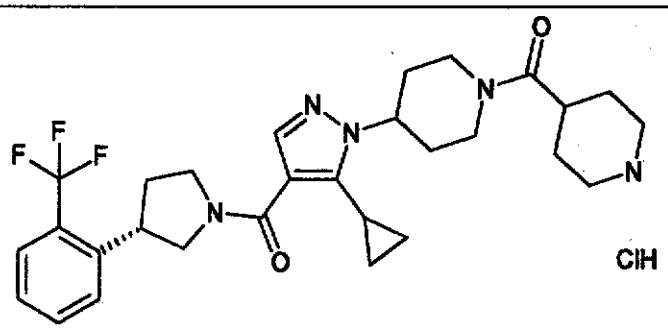
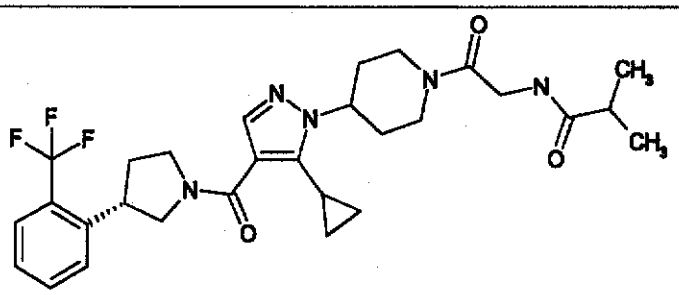
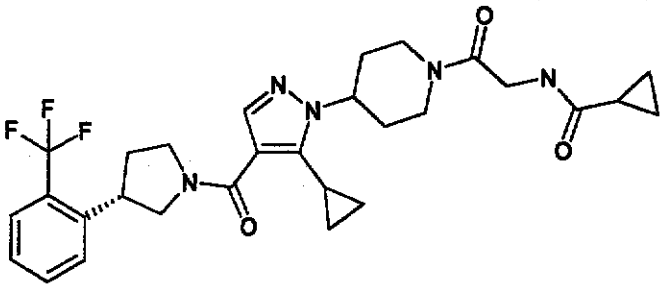
Ex. No.	structural formula	NMR
85		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.92-1.06 (2H, m), 1.72-2.35 (8H, m), 2.53-2.62 (3H, m), 2.80-2.98 (1H, m), 3.18-3.34 (1H, m), 3.42-3.90 (5H, m), 3.98-4.23 (2H, m), 4.40-4.54 (1H, m), 4.66-4.82 (1H, m), 7.42-7.78 (5H, m), 8.77-9.02 (2H, m)
86		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.72 (2H, m), 0.93-1.02 (2H, m), 1.67-1.84 (6H, m), 1.85-2.00 (4H, m), 2.03-2.17 (1H, m), 2.18-2.33 (1H, m), 2.65-2.81 (1H, m), 2.84-3.08 (3H, m), 3.16-3.32 (4H, m), 3.52-3.90 (3H, m), 4.05-4.19 (1H, m), 4.44-4.57 (1H, m), 4.63-4.79 (1H, m), 7.40-7.75 (5H, m), 8.62-8.78 (1H, m), 9.04-9.16 (1H, m)
87		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.03-1.12 (2H, m), 1.14-1.22 (7H, m), 1.66-2.24 (6H, m), 2.27-2.54 (2H, m), 2.79-2.96 (1H, m), 3.13-3.27 (1H, m), 3.39-3.50 (1H, m), 3.55-4.18 (6H, m), 4.53-4.79 (2H, m), 6.58-6.61 (1H, m), 7.31-7.71 (5H, m)
88		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.83 (4H, m), 0.92-1.01 (2H, m), 1.01-1.13 (2H, m), 1.45-1.54 (1H, m), 1.68-2.44 (8H, m), 2.80-2.95 (1H, m), 3.12-3.29 (1H, m), 3.41-3.50 (1H, m), 3.57-4.22 (6H, m), 4.56-4.79 (2H, m), 6.68-6.76 (1H, m), 7.31-7.70 (5H, m)

Table 1-23

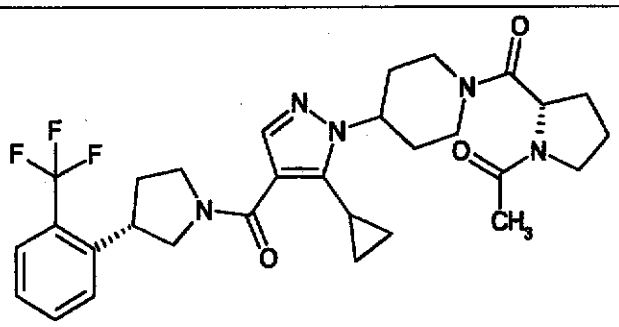
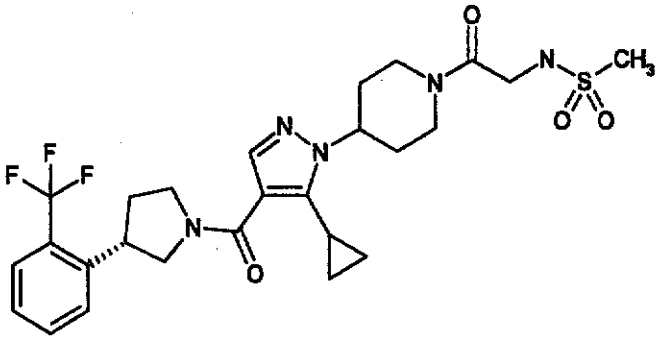
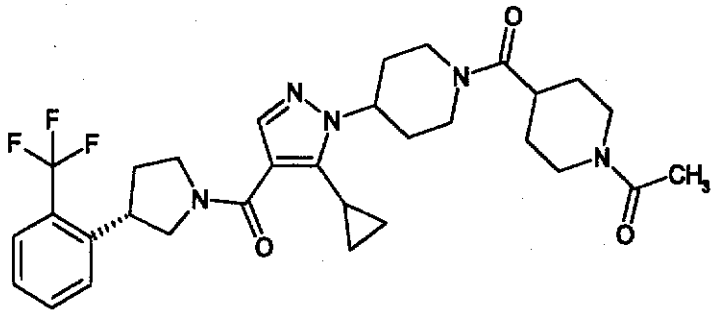
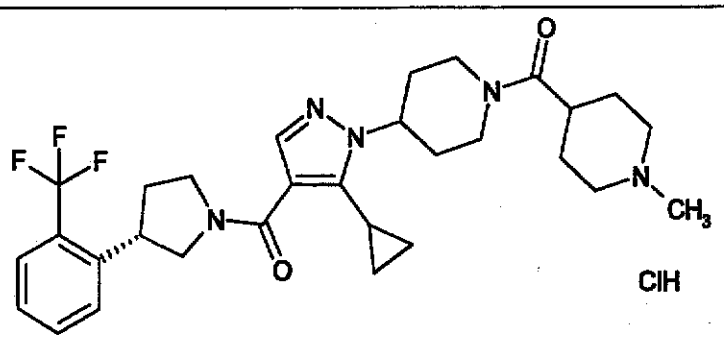
Ex. No.	structural formula	NMR
89		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.82 (2H, m), 1.03-1.14 (2H, m), 1.70-1.84 (1H, m), 1.85-2.25 (12H, m), 2.25-2.42 (1H, m), 2.75-2.95 (1H, m), 3.18-4.21 (9H, m), 4.54-4.78 (2H, m), 4.87-4.97 (1H, m), 7.32-7.71 (5H, m)
90		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.02-1.16 (2H, m), 1.70-1.86 (1H, m), 1.89-2.45 (6H, m), 2.83-2.96 (1H, m), 2.96-3.03 (3H, m), 3.16-3.31 (1H, m), 3.41-3.50 (0.6H, m), 3.56-4.12 (7.4H, m), 4.57-4.77 (2H, m), 5.35-5.44 (1H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.62-7.71 (1H, m)
91		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.81 (2H, m), 1.04-1.12 (2H, m), 1.62-2.44 (11H, m), 2.09 (3H, brs), 2.66-2.82 (3H, m), 3.05-3.17 (1H, m), 3.18-3.31 (1H, m), 3.39-3.50 (1H, m), 3.55-3.99 (5H, m), 4.00-4.15 (1H, m), 4.51-4.70 (2H, m), 4.71-4.84 (1H, m), 7.31-7.70 (5H, m)
92		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.72 (2H, m), 0.93-1.05 (2H, m), 1.67-2.02 (11H, m), 2.04-2.16 (1H, m), 2.18-2.34 (1H, m), 2.66-2.75 (3H, brs), 2.86-3.01 (2H, m), 3.09-3.32 (1H, m), 3.36-3.91 (6H, m), 3.99-4.16 (1H, m), 4.44-4.58 (2H, m), 4.63-4.80 (1H, m), 7.43-7.76 (5H, m), 10.21-10.33 (1H, m)

Table 1-24

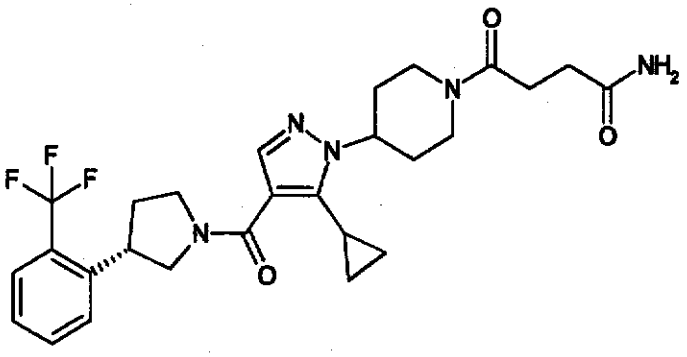
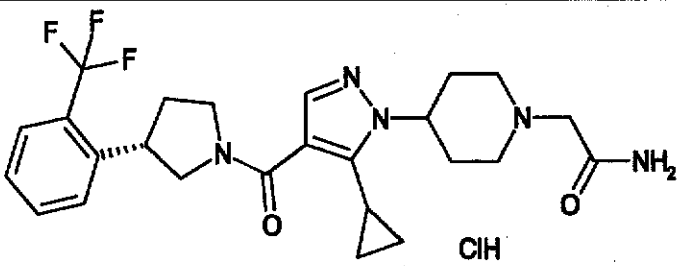
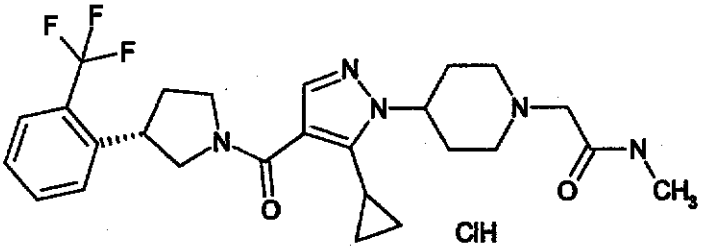
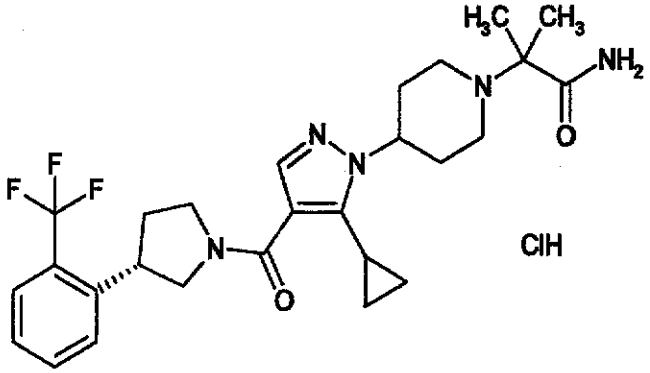
Ex. No.	structural formula	NMR
93		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.03-1.12 (2H, m), 1.14-1.22 (7H, m), 1.66-2.24 (6H, m), 2.27-2.54 (2H, m), 2.79-2.96 (1H, m), 3.13-3.27 (1H, m), 3.39-3.50 (1H, m), 3.55-4.18 (6H, m), 4.53-4.79 (2H, m), 6.58-6.61 (1H, m), 7.31-7.71 (5H, m)
94		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.57-0.73 (2H, m), 0.90-1.05 (2H, m), 1.82-2.53 (8H, m), 3.23-3.79 (6H, m), 3.81-4.24 (4H, m), 4.63-4.97 (1H, m), 7.39-7.77 (6H, m), 7.98-8.17 (1H, m), 9.99-10.27 (1H, m)
95		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.59-0.75 (2H, m), 0.91-1.07 (2H, m), 1.82-2.46 (8H, m), 2.64-2.76 (3H, m), 3.21-3.99 (10H, m), 4.61-4.82 (1H, m), 7.41-7.79 (5H, m), 8.48-8.69 (1H, m), 9.99-10.24 (1H, m)
96		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.82 (2H, m), 1.02-1.18 (2H, m), 1.69 (6H, s), 1.70-1.84 (1H, m), 2.05-2.23 (3H, m), 2.29-2.46 (1H, m), 3.03-4.07 (11H, m), 5.02 (1H, brs), 5.74 (1H, brs), 7.34-7.41 (1H, m), 7.44-7.50 (1H, m), 7.51-7.60 (2H, m), 7.65-7.70 (1H, m), 9.13 (1H, brs), 11.80 (1H, brs)

Table 1-25

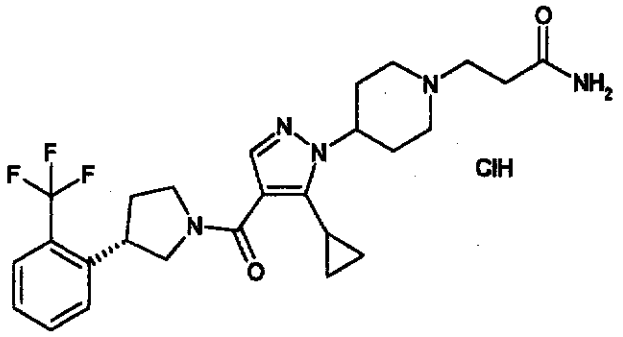
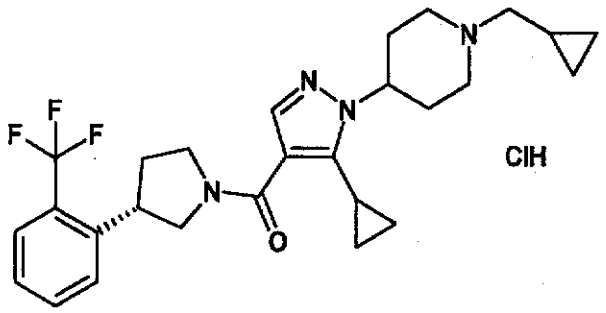
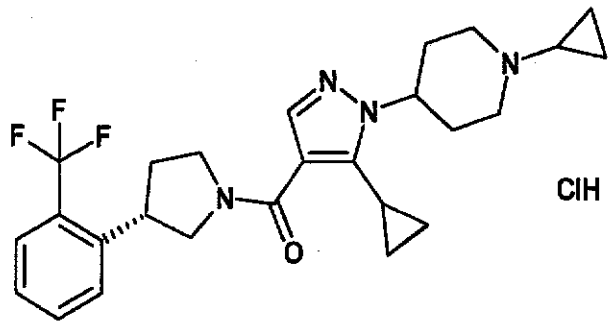
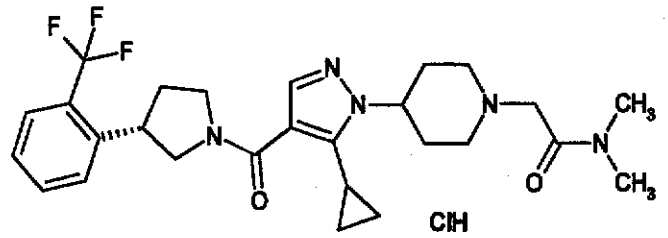
Ex. No.	structural formula	NMR
97		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.58-0.77 (2H, m), 0.90-1.06 (2H, m), 1.83-1.98 (1H, m), 2.04-2.74 (6H, m), 3.07-3.96 (13H, m), 4.64-4.97 (1H, m), 7.20-7.85 (7H, m), 10.09-10.49 (1H, m)
98		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.30-0.49 (2H, m), 0.56-0.76 (4H, m), 0.88-1.05 (2H, m), 1.07-1.22 (1H, m), 1.81-1.98 (1H, m), 1.99-2.38 (6H, m), 2.88-3.04 (2H, m), 3.09-3.26 (2H, m), 3.41-3.95 (7H, m), 4.58-4.86 (1H, m), 7.34-7.85 (5H, m), 10.17-10.53 (1H, m)
99		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.74 (2H, m), 0.75-0.85 (2H, m), 0.93-1.04 (2H, m), 1.12-1.23 (2H, m), 1.86-2.54 (7H, m), 2.71-2.82 (1H, m), 3.28-3.92 (9H, m), 4.66-4.83 (1H, m), 7.42-7.77 (5H, m), 10.60-10.79 (1H, m)
100		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.57-0.75 (2H, m), 0.91-1.05 (2H, m), 1.82-2.53 (7H, m), 2.85-3.01 (6H, m), 3.18-4.44 (11H, m), 4.62-4.83 (1H, m), 7.41-7.78 (5H, m), 9.66-9.97 (1H, br)

Table 1-26

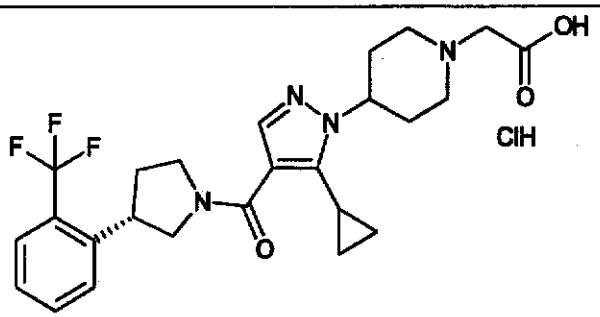
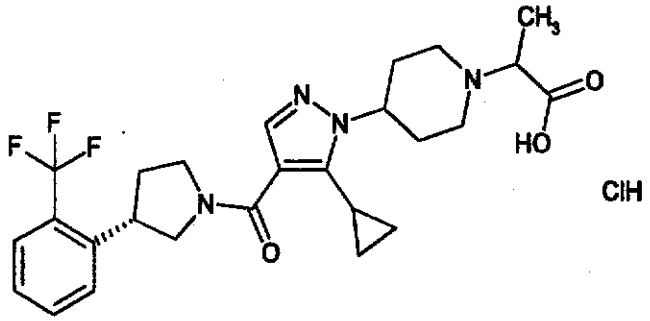
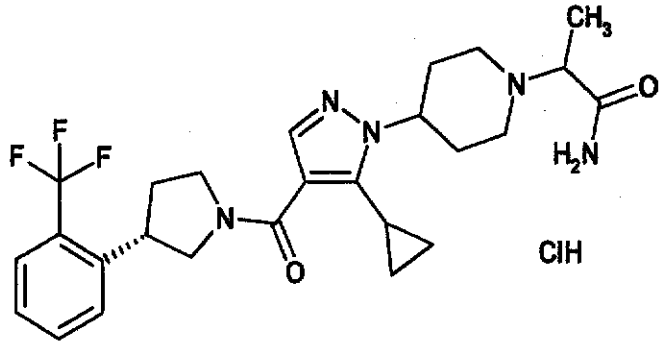
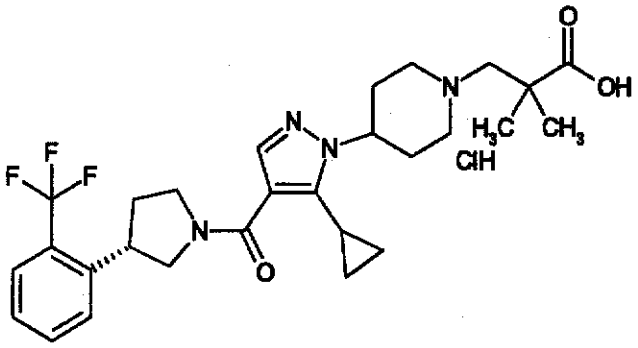
Ex. No.	structural formula	NMR
101		^{1}H-NMR (400MHz, DMSO-d_6) δ: 0.59-0.75 (2H, m), 0.91-1.06 (2H, m), 1.84-2.00 (1H, m), 2.03-2.45 (6H, m), 3.15-3.95 (9H, m), 4.06-4.23 (2H, m), 4.63-4.83 (1H, m), 7.41-7.80 (5H, m)
102		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.75 (2H, m), 0.91-1.06 (2H, m), 1.46-1.62 (4H, m), 1.84-2.60 (7H, m), 3.23-3.94 (7H,m), 4.16-4.32 (1H, m), 4.51-5.06 (2H, m), 7.40-7.79 (6H, m), 10.11-10.42 (1H, brs)
103		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.60-0.73 (2H, m), 0.92-1.04 (2H, m), 1.43-1.54 (3H, m), 2.00-2.58 (8H, m), 3.14-4.17 (9H, m), 4.68-4.85 (1H, m), 7.42-7.79 (6H, m), 8.08-8.20 (1H, m), 10.09 (1H, brs)
104		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.61-0.75 (2H, m), 0.94-1.06 (2H, m), 1.22-1.38 (6H, m), 1.82-2.62 (7H, m), 3.13-3.96 (11H, m), 4.69-4.95 (1H, m), 7.38-7.82 (6H, m), 9.23-9.88 (1H, m)

Table 1-27

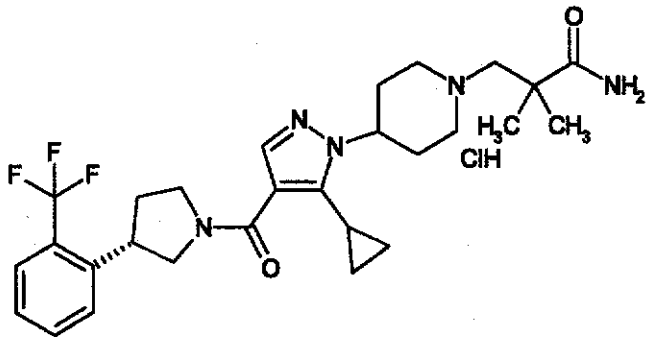
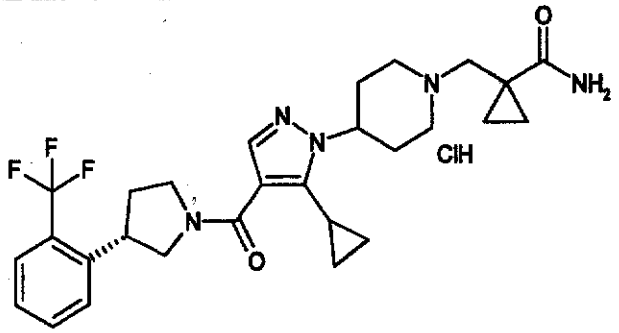
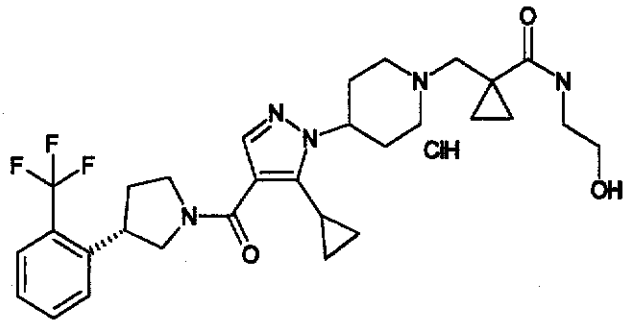
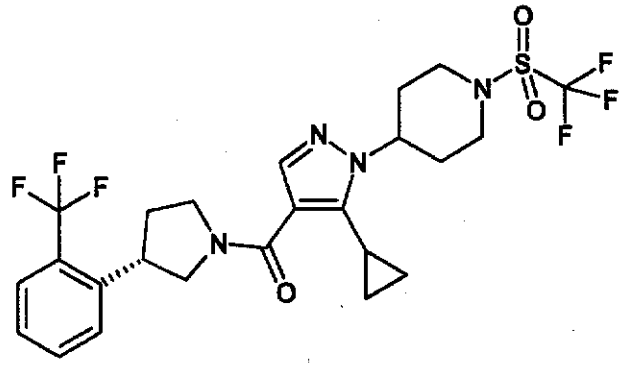
Ex. No.	structural formula	NMR
105		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.59-0.75 (2H, m), 0.93-1.06 (2H, m), 1.22-1.38 (6H, m), 1.83-1.98 (1H, m), 1.99-2.62 (6H, m), 3.14-3.94 (11H, m), 4.69-4.93 (1H, m), 7.27-7.80 (7H, m), 9.05-9.52 (1H, m)
106		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.56-0.77 (2H, m), 0.91-1.07 (2H, m), 1.15-1.39 (4H, m), 1.82-2.62 (7H, m), 3.13-4.03 (11H, m), 4.63-4.97 (1H, m), 7.06-7.32 (2H, m), 7.40-7.81 (5H, m), 9.76-10.08 (1H, m)
107		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.61-0.74 (2H, m), 0.93-1.04 (2H, m), 1.13-1.21 (2H, m), 1.25-1.34 (2H, m), 1.85-1.98 (1H, m), 2.01-2.54 (6H, m), 3.08-3.92 (16H, m), 4.64-4.84 (1H, m), 7.43-7.78 (6H, m), 9.57-9.92 (1H, m)
108		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.82 (2H, m), 1.01-1.14 (2H, m), 1.66-1.83 (1H, m), 1.94-2.44 (6H, m), 3.18-3.49 (2H, m), 3.54-4.20 (7H, m), 4.53-4.70 (1H, m), 7.28-7.72 (5H, m)

Table 1-28

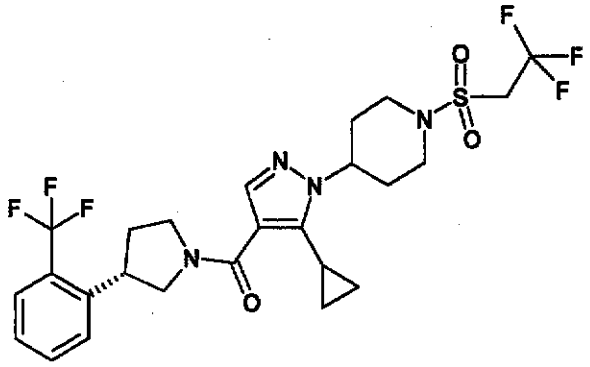
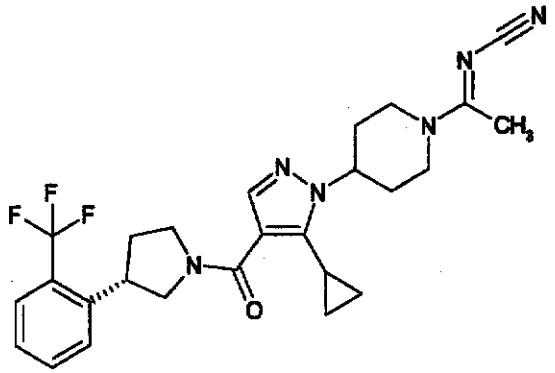
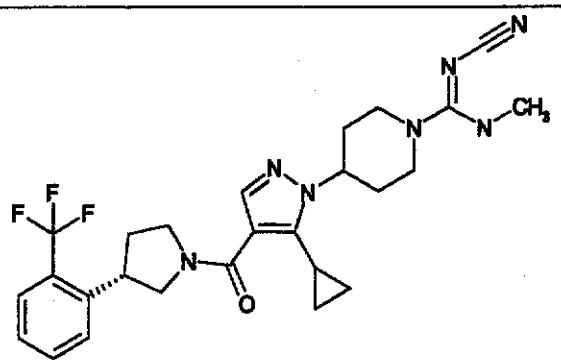
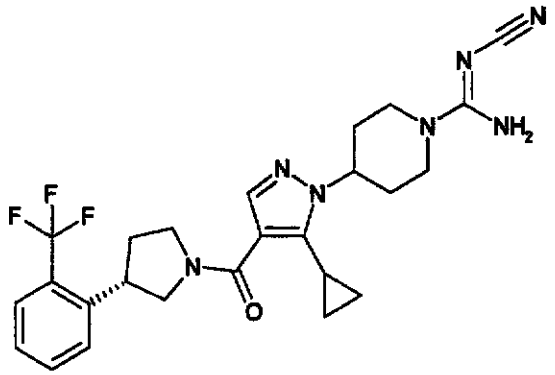
Ex. No.	structural formula	NMR
109		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.83 (2H, m), 0.99-1.11 (2H, m), 1.68-1.83 (1H, m), 1.91-2.45 (6H, m), 3.04-3.20 (2H, m), 3.38-4.11 (9H, m), 4.47-4.66 (1H, m), 7.72-8.35 (5H, m)
110		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.88 (2H, m), 0.98-1.21 (2H, m), 1.66-1.88 (1H, m), 1.89-2.54 (9H, m), 2.94-3.17 (1H, m), 3.26-3.53 (1.5H, m), 3.54-4.21 (5.5H, m), 4.58-4.93 (2H, m), 7.29-7.75 (5H, m)
111		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.83 (2H, m), 0.97-1.17 (2H, m), 1.63-1.95 (3H, m), 1.96-2.24 (3H, m), 2.25-2.47 (1H, m), 2.97-3.19 (5H, m), 3.40-3.49 (0.5H, m), 3.55-4.26 (6.5H, m), 4.46-4.69 (1H, m), 5.54-5.76 (1H, m), 7.30-7.60 (4H, m), 7.61-7.73 (1H, m)
112		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.60-0.81 (2H, m), 0.98-1.16 (2H, m), 1.62-1.82 (3H, m), 1.93-2.25 (3H, m), 2.26-2.47 (1H, m), 2.90-3.08 (2H, m), 3.35-3.50 (0.5H, m), 3.53-4.09 (4.5H, m), 4.17-4.34 (2H, m), 4.45-4.65 (1H, m), 5.94-6.14 (2H, m), 7.29-7.61 (4H, m), 7.62-7.74 (1H, m)

Table 1-29

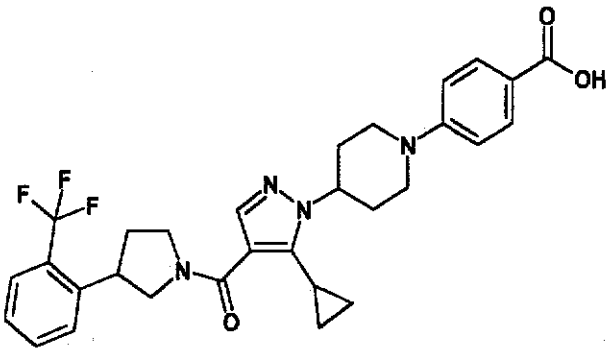
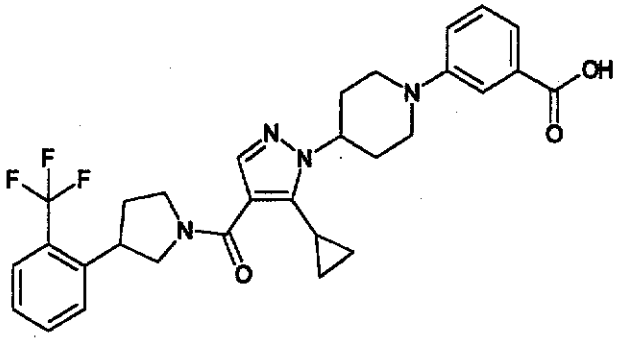
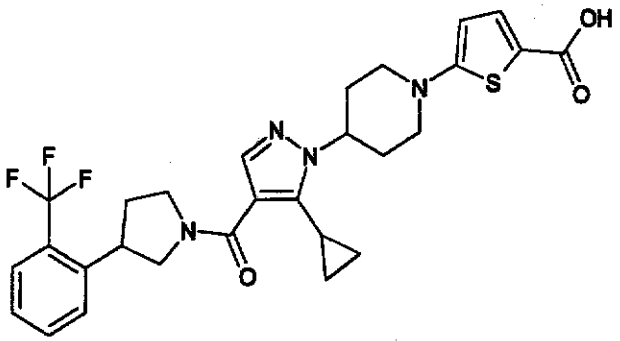
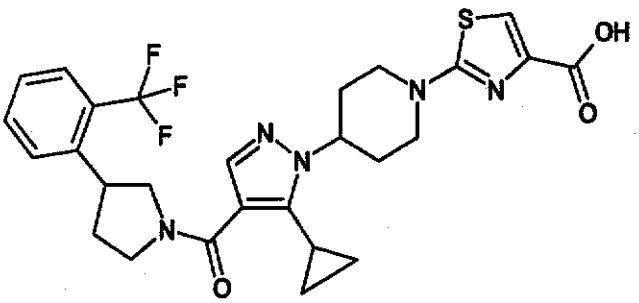
Ex. No.	structural formula	NMR
113		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.87 (2H, m), 1.03-1.18 (2H, m), 1.71-2.47 (7H, m), 3.00-3.18 (2H, m), 3.42-4.17 (7H, m), 4.56-4.75 (1H, m), 6.85-6.97 (2H, m), 7.32-7.71 (5H, m), 7.92-8.00 (2H, m)
114		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.87 (2H, m), 1.02-1.19 (2H, m), 1.74-2.50 (7H, m), 2.81-3.19 (2H, m), 3.44-4.14 (7H, m), 4.48-4.80 (1H, m), 7.07-7.85 (9H, m)
115		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.77 (2H, m), 0.92-1.08 (2H, m), 1.87-2.36 (7H, m), 3.08-3.94 (9H, m), 4.60-4.81 (1H, m), 6.16-6.29 (1H, m), 7.38-7.80 (6H, m), 12.25(1H, bs)
116		^{1}H-NMR (300MHz, DMSO-D6) δ: 0.62-0.73 (2H, m), 0.96-1.04 (2H, m), 1.87-2.33 (7H, m), 3.18-3.32 (3H, m), 3.44-3.91 (4H, m), 3.97-4.10 (2H, m), 4.66-4.80 (1H, m), 7.41-7.60 (2H, m), 7.63-7.78 (4H, m), 12.6 (1H, brs)

Table 1-30

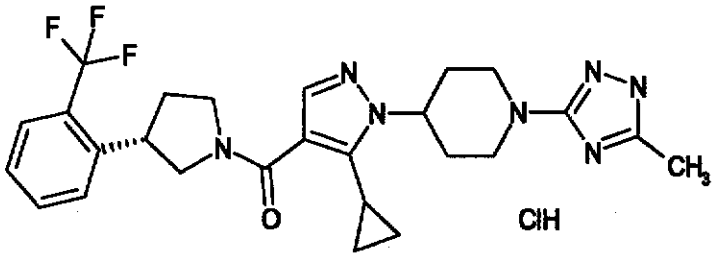
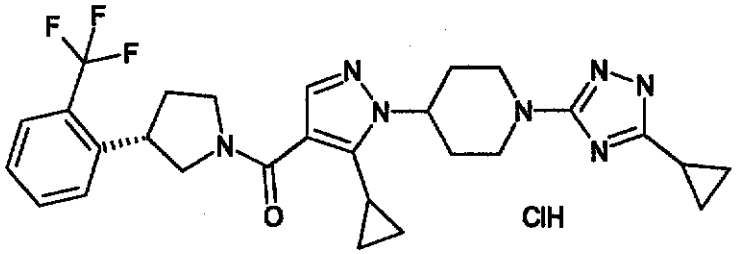
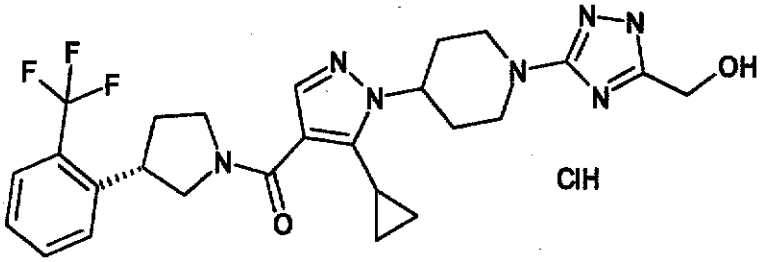
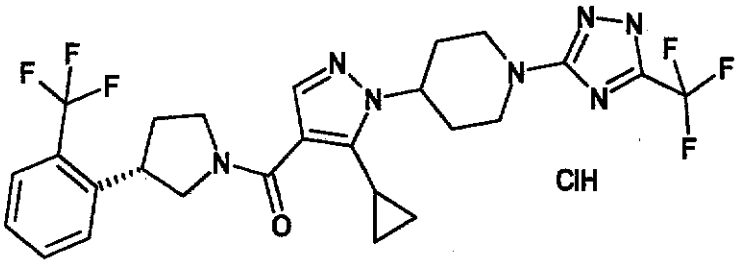
Ex. No.	structural formula	NMR
117		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.59-0.77 (2H, m), 0.93-1.08(2H, m), 1.88-2.39 (10H, m), 3.21-4.12 (11H, m), 4.64-4.84 (1H, m), 7.41-7.80 (5H, m)
118		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.60-0.75 (2H, m), 0.89-1.09 (6H, m), 1.86-2.36 (8H, m), 3.11-4.11 (11H, m), 4.61-4.82 (1H, m), 7.41-7.80 (5H, m)
119		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.60-0.76 (2H, m), 0.92-1.06 (2H, m), 1.88-2.38 (8H, m), 3.15-4.15 (10H, m), 4.42-4.53 (2H, m), 4.63-4.82 (1H, m), 7.39-7.79 (6H, m)
120		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.58-0.77 (2H, m), 0.92-1.06 (2H, m), 1.85-2.41 (7H, m), 3.11-4.10 (9H, m), 4.31-5.07 (2H, m), 7.41-7.79 (5H, m), 13.3-13.5 (1H, m)

Table 1-31

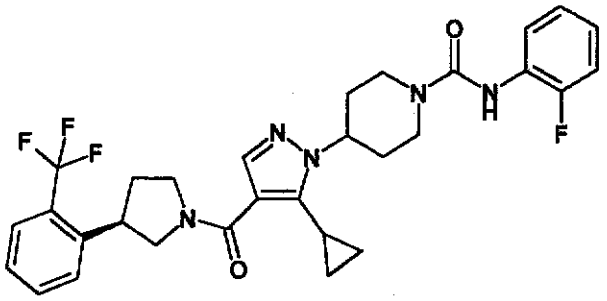
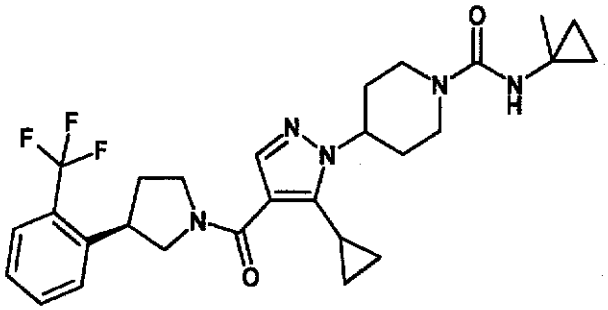
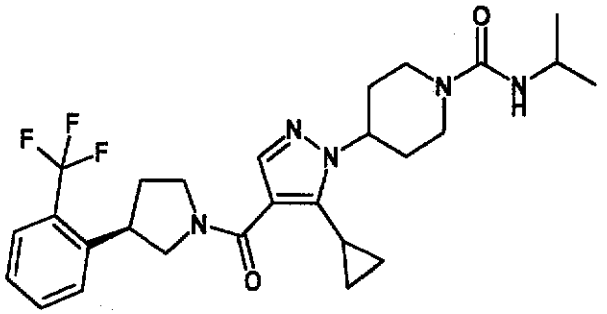
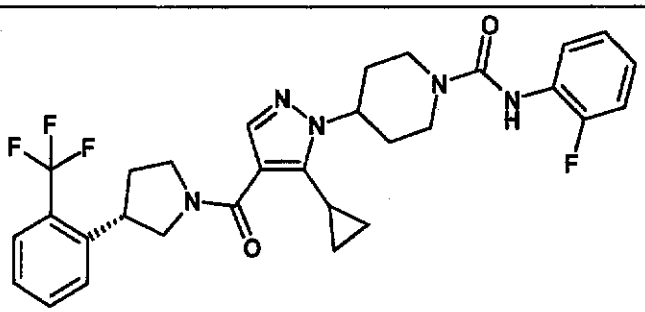
Ex. No.	structural formula	NMR
121		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.87 (2H, m), 1.05-1.15 (2H, m), 1.49-2.48 (7H, m), 3.05-3.22 (2H, m), 3.40-4.14 (5H, m), 4.20-4.36 (2H, m), 4.52-4.73 (1H, m), 6.60-6.71 (1H, m), 6.94-7.16 (3H, m), 7.33-7.72 (5H, m), 8.04-8.14 1H, m)
122		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.57-0.66 (2H, m), 0.66-0.84 (4H, m), 1.01-1.13 (2H, m), 1.32-1.45 (3H, m), 1.55-2.48 (7H, m), 2.81-3.00 (2H, m), 3.41-4.15 (5H, m), 4.44-4.63 (2H, m), 4.85-4.96 (1H, m), 7.33-7.71 (6H, m)
123		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.82 (2H, m), 1.02-1.13 (2H, m), 1.13-1.22 (6H, m),1.55-2.47 (8H, m), 2.84-3.01 (2H, m), 3.41-4.34 (9H, m), 4.45-4.63 (1H, m), 7.30-7.71 (6H, m)
124		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.87 (2H, m), 1.04-1.17 (2H, m), 1.53-2.46 (7H, m), 3.05-3.21 (2H, m), 3.42-4.11 (5H, m), 4.20-4.35 (2H, m), 4.55-4.71 (1H, m), 6.62-6.70 (1H, m), 6.93-7.16 (3H, m), 7.33-7.72 (5H, m), 8.04-8.14 (1H, m)

Table 1-32

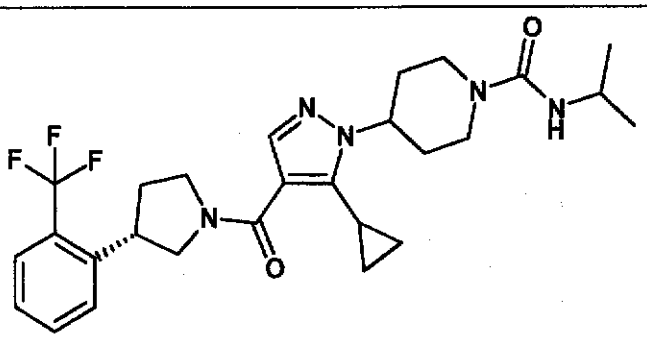
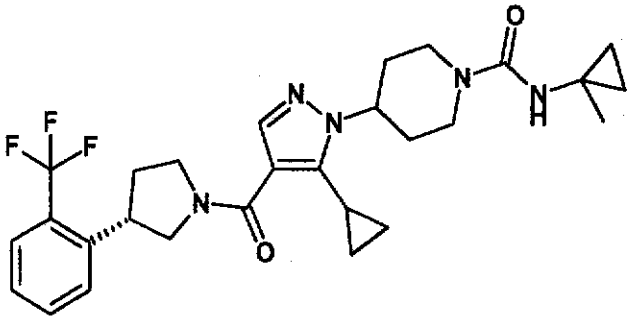
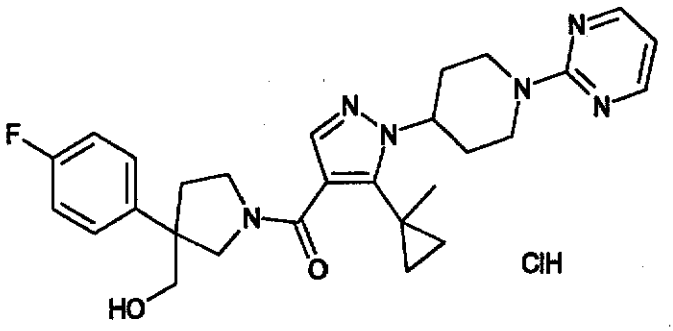
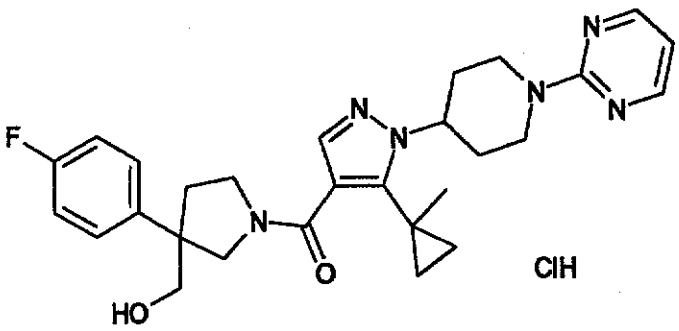
Ex. No.	structural formula	NMR
125		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.84 (2H, m), 1.03-1.13 (2H, m), 1.13-1.21 (6H, m), 1.55-2.47 (8H, m), 2.84-3.01 (2H, m), 3.41-4.31 (9H, m), 4.45-4.63 (1H, m), 7.33-7.72 (6H, m)
126		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.58-0.66 (2H, m), 0.66-0.83 (4H, m), 1.02-1.11 (2H, m), 1.36-1.43 (3H, m), 1.53-2.46 (7H, m), 2.83-2.99 (2H, m), 3.41-4.15 (5H, m), 4.45-4.61 (2H, m), 4.85-4.92 (1H, m), 7.32-7.72 (6H, m)
127		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.56-0.86 (4H, m), 1.32-1.43 (3H, m), 1.85-2.12 (6H, m), 2.28-2.39 (1H, m), 3.09-3.26 (2H, m), 3.31-4.94 (6H, m), 4.74-4.91 (3H, m), 6.30 (1H, bs), 6.69-6.75 (1H, m), 7.07-7.37 (4H, m), 7.53-7.62 (1H, m), 8.40-8.50 (2H, m)
128		^{1}H-NMR (400MHz, DMSO-D6) δ: 0.56-0.88 (4H, m), 1.32-1.48 (3H, m), 1.85-2.12 (6H, m), 2.28-2.39 (1H, m), 3.09-3.24 (2H, m), 3.30-4.95 (6H, m), 4.73-4.93 (3H, m), 5.81 (1H, bs), 6.64-6.73 (1H, m), 7.06-7.40 (4H, m), 7.50-7.67 (1H, m), 8.39-8.49 (2H, m)

Table 1-33

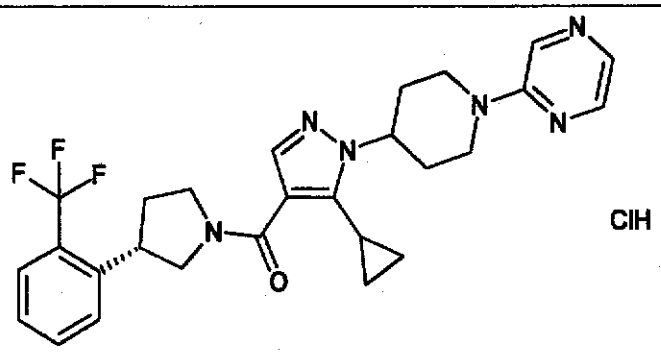
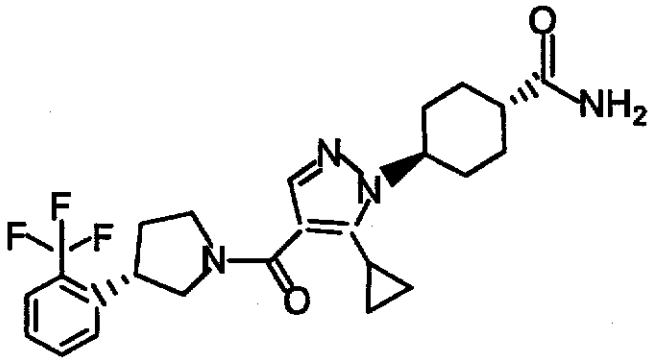
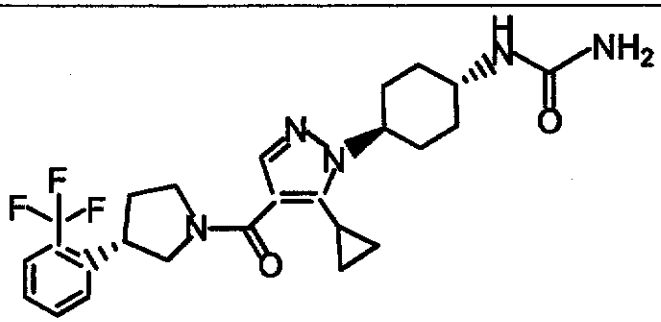
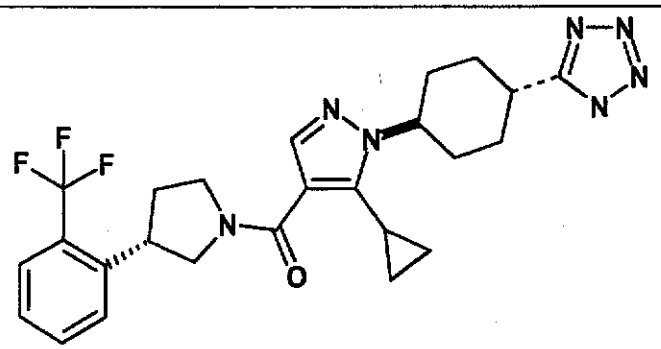
Ex. No.	structural formula	NMR
129		^{1}H-NMR (400MHz, DMSO-d6) δ: 0.66-0.69 (2H, m), 0.99-1.01 (2H, m), 1.91-2.33 (7H, m), 3.11-3.14 (2H, m), 3.46-3.89 (5H, m), 4.49-4.52 (2H, m), 4.75-4.77 (1H, m), 7.48-7.74 (6H, m), 7.85-7.90 (1H, m), 8.17 (1H, brs), 8.43-8.45 (1H, m)
130		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.79 (2H, m), 0.94-1.10 (2H, m), 1.63-2.44 (12H, m), 3.38-4.10 (5H, m), 4.32-4.51 (1H, m), 5.33 (1H, br), 5.51 (1H, br), 7.27-7.70 (5H, m)
131		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.82 (2H, m), 0.95-1.10 (2H, m), 1.23-1.39 (2H, m), 1.65-2.45 (8H, m), 3.40-4.10 (6H, m), 4.26-4.60 (4H, m), 7.27-7.71 (6H, m)
132		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.79 (2H, m), 0.84-0.92 (2H, m), 1.06-1.15 (2H, m), 1.22-1.35 (3H, m), 1.73-2.49 (8H, m), 3.05-3.19 (1H, m), 3.39-3.55 (1H, m), 3.61-4.17 (3H, m), 4.46-4.61 (1H, m), 7.33-7.71 (5H, m)

Table 1-34

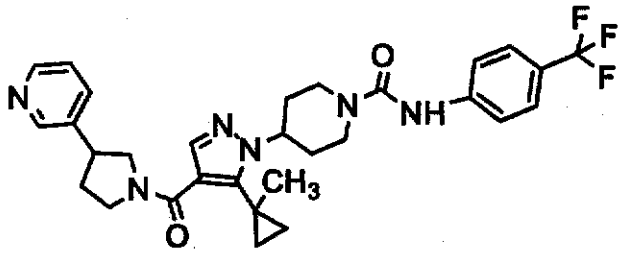
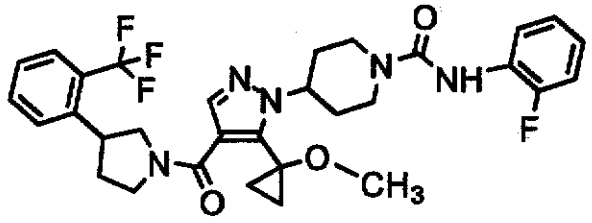
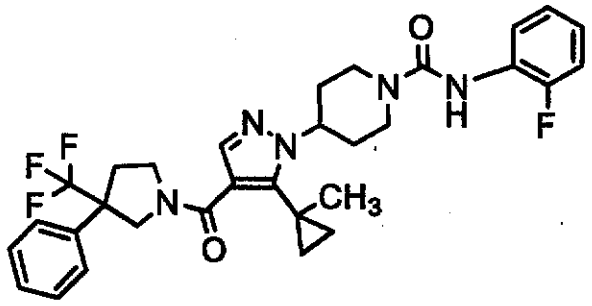
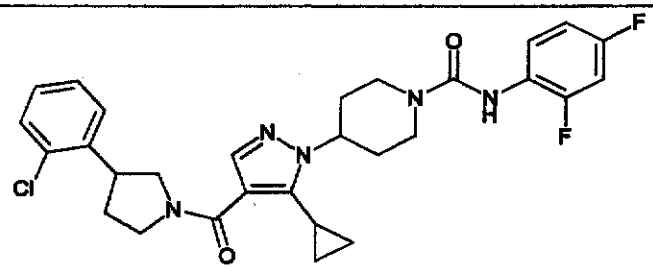
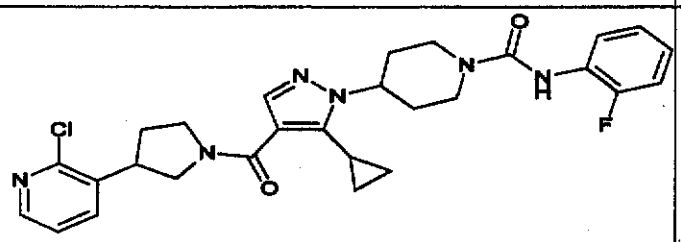
Ex. No.	structural formula	NMR
133		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.95 (4H, m), 1.38-1.47 (3H, m), 1.61-1.88 (2H, m), 1.99-2.29 (3H, m), 2.34-2.50 (1H, m), 2.94-3.12 (2H, m), 3.36-4.18 (5H, m), 4.25-4.40 (2H, m), 4.54-4.72 (1H, m), 6.99-7.33 (2H, m), 7.44-7.65 (6H, m), 8.44-8.61 (2H, m)
134		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.89-1.05 (2H, m), 1.22-1.34 (2H, m), 1.94-2.44 (6H, m), 3.05-3.21 (2H, m), 3.28-3.39 (3H, m), 3.42-4.11 (5H, m), 4.20-4.35 (2H, m), 4.77-4.93 (1H, m), 6.62-6.71 (1H, m), 6.93-7.18 (3H, m), 7.32-7.72 (5H, m), 8.05-8.14 (1H, m)
135		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.57-0.95 (4H, m), 1.34-1.54 (3H, m), 1.83-2.08 (2H, m), 2.18-2.41 (2H, m), 2.45-2.61 (1H, m), 2.73-2.92 (1H, m), 3.02-3.24 (2H, m), 3.51-4.86 (7H, m), 6.60-6.78 (1H, m), 6.93-7.18 (3H, m), 7.20-7.46 (5H, m), 7.46-7.57 (1H, m), 8.01-8.15 (1H, m)
136		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.81 (2H, m), 1.00-1.14 (2H, m), 1.71-1.85 (1H, m), 1.93-2.43 (6H, m), 3.05-3.19 (2H, m), 3.40-4.10 (5H, m), 4.20-4.33 (2H, m), 4.55-4.69 (1H, m), 6.48-6.57 (1H, m), 6.81-6.92 (2H, m), 7.17-7.45 (4H, m), 7.50-7.60 (1H, m), 7.94-8.03 (1H, m)
137		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.01-1.14 (2H, m), 1.75-1.86 (1H, m), 1.94-2.36 (6H, m), 2.37-2.49 (1H, m), 3.07-3.20 (2H, m), 3.40-4.14 (4H, m), 4.22-4.34 (2H, m), 4.57-4.71 (1H, m), 6.61-6.70 (1H, m), 6.93-7.03 (1H, m), 7.03-7.17 (3H, m), 7.51-7.70 (2H, m), 8.02-8.15 (1H, m), 8.28-8.37 (1H, brs)

Table 1-35

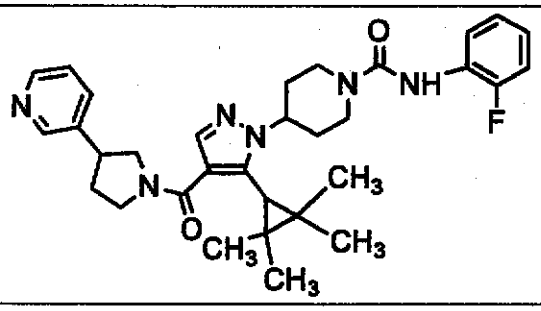
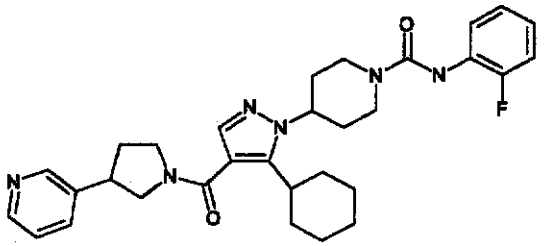
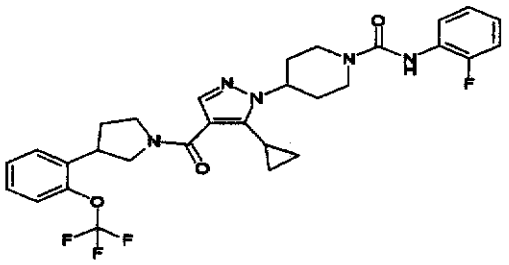
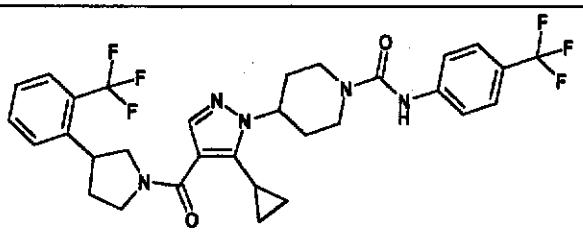
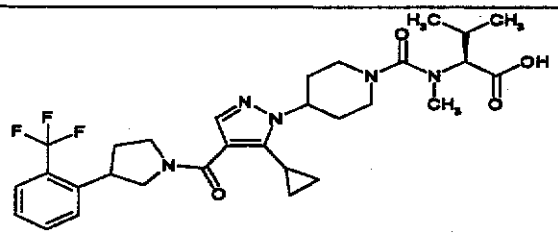
Ex. No.	structural formula	NMR
138		^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, s), 1.33 (6H, s), 2.03-2.11 (4H, m), 2.36-2.39 (2H, m), 3.07-3.09 (2H, m), 3.37-3.76 (4H, m), 3.89-3.96 (1H, m), 4.28-4.32 (4H, m), 6.65 (1H, s), 7.01-7.08 (3H, m), 7.24-7.32 (1H, m), 7.53-7.63 (2H, m), 8.07-8.09 (1H, m), 8.53-8.57 (2H, m)
139		^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.25-1.48 (3H, m), 1.69-2.48 (13H, m), 2.85-3.19 (3H, m), 3.33-4.41 (8H, m), 6.59-6.69 (1H, m), 6.89-7.14 (3H, m), 7.23-7.36 (1H, m), 7.43-7.68 (2H, m), 8.05 (1H, t, J = 8.1 Hz), 8.44-8.59 (2H, m)
140		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.83 (2H, m), 1.01-1.15 (2H, m), 1.72-1.86 (1H, m), 1.92-2.43 (6H, m), 3.03-3.20 (2H, m), 3.36-4.11 (5H, m), 4.20-4.34 (2H, m), 4.55-4.71 (1H, m), 6.66 (1H, br s), 6.93-7.16 (3H, m), 7.20-7.42 (4H, m), 7.48-7.63 (1H, m), 8.03-8.14 (1H, m)
141		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.66-0.80 (2H, m), 1.00-1.12 (2H, m), 1.58-1.82 (3H, m), 1.97-2.23 (3H, m), 2.27-2.47 (1H, m), 2.90-3.06 (2H, m), 3.40-4.11 (5H, m), 4.24-4.41 (2H, m), 4.46-4.62 (1H, m), 7.32-7.73 (10H, m)
142		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.57-0.74 (2H, m), 0.81-1.03 (8H, m), 1.79-2.36 (8H, m), 2.82-2.90 (8H, m), 3.44-3.92 (9H, m), 4.50-4.70 (1H, s), 7.42-7.53 (2H, m), 7.55-7.61 (1H, m), 7.66-7.78 (2H, m)

Table 1-36

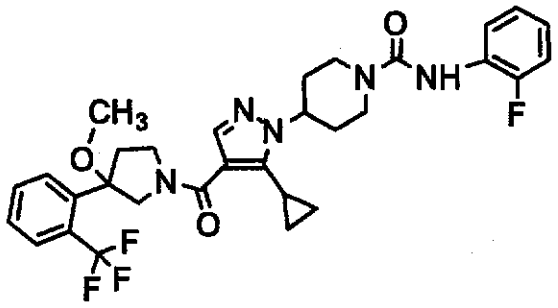
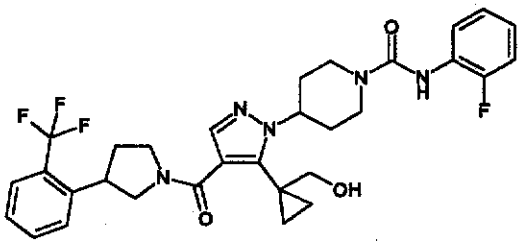
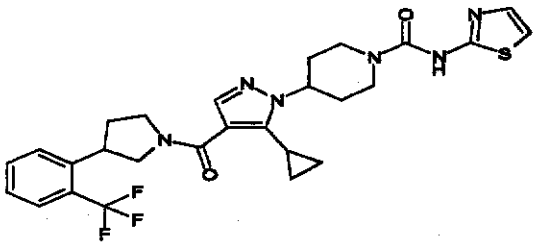
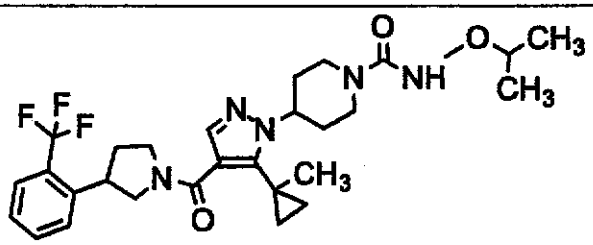
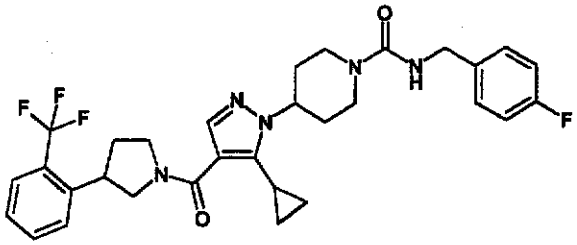
Ex. No.	structural formula	NMR
143		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.84 (2H, m), 0.91-1.17 (2H, m), 1.67-1.88 (1H, m), 1.91-2.08 (2H, m), 2.14-2.42 (2.5H, m), 2.43-2.56 (0.5H, m), 2.57-2.72 (1H, m), 2.88-3.21 (5H, m), 3.45-3.61 (0.6H, m), 3.64-3.91 (2H, m), 3.98-4.13 (1H, m), 4.19-4.36 (2.4H, m), 4.53-4.72 (1H, m), 6.63-6.79 (1H, m), 6.89-7.18 (3H, m), 7.40-7.64 (4H, m), 7.75-7.93 (1H, m), 8.00-8.13 (1H, m)
144		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.97 (2H, m), 0.97-1.35 (2H, m), 1.85-2.54 (6H, m), 2.87-3.21 (2H, m), 3.21-4.14 (7H, m), 4.16-4.46 (2H, m), 4.51-4.79 (1H, m), 5.98-6.35 (1H, m), 6.56-6.78 (1H, m), 6.85-7.20 (3H, m), 7.20-7.79 (5H, m), 7.95-8.16 (1H, m)
145		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.84 (2H, m), 1.01-1.16 (2H, m), 1.68-1.85 (1H, m), 1.88-2.46 (6H, m), 3.02-3.19 (2H, m), 3.40-4.11 (5H, m), 4.24-4.41 (2H, m), 4.53-4.71 (1H, m), 6.82-6.91 (1H, m), 7.30-7.72 (7H, m)
146		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.99 (4H, m), 1.15-1.31 (6H, m), 1.35-1.52 (3H, m), 1.73-1.98 (2H, m), 1.98-2.47 (4H, m), 2.86-3.08 (2H, m), 3.42-4.11 (6H, m), 4.12-4.31 (2H, m), 4.53-4.72 (1H, m), 7.08-7.21 (1H, m), 7.30-7.40 (1H, m), 7.41-7.61 (3H, m), 7.61-7.74 (1H, m)
147		^{1}H-NMR (300MHz, $CDCl_3$) δ: 0.64-0.81 (2H, m), 0.96-1.13 (2H, m), 1.55-1.93 (3H, m), 1.95-2.44 (4H, m), 2.84-3.02 (2H, m), 3.36-4.22 (7H, m), 4.30-4.41 (2H, m), 4.43-4.62 (1H, m), 4.83-4.99 (1H, m), 6.91-7.05 (2H, m), 7.17-7.71 (7H, m)

Table 1-37

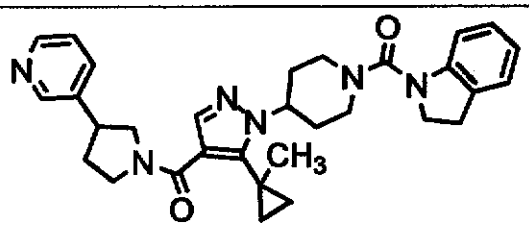
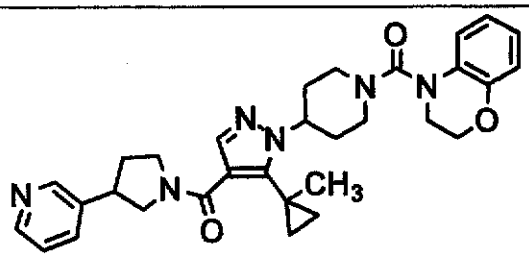
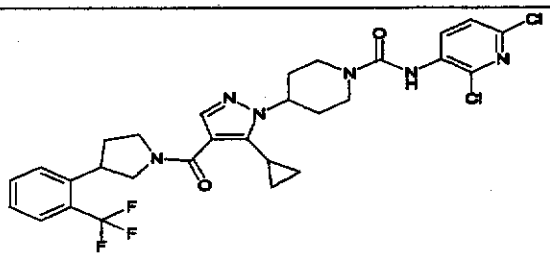
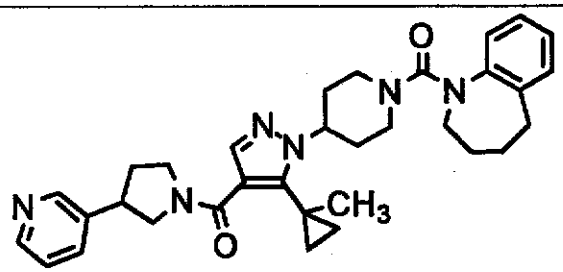
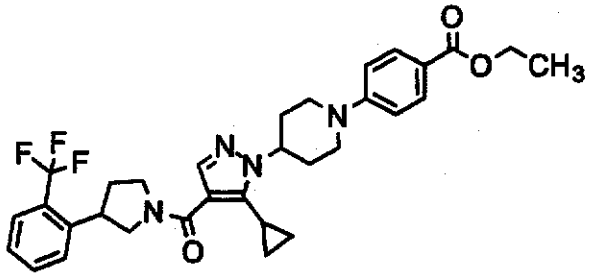
Ex. No.	structural formula	NMR
148		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.84 (2H, m), 0.85-0.96 (2H, m), 1.45 (3H, s), 1.84-1.97 (2H, m), 2.01-2.20 (1H, m), 2.26-2.49 (3H, m), 2.97-3.12 (4H, m), 3.37-4.19 (9H, m), 4.61-4.75 (1H, m), 6.86-6.95 (1H, m), 7.08-7.22 (3H, m), 7.25-7.33 (1H, m), 7.48-7.65 (2H, m), 8.46-8.63 (2H, m)
149		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.82 (2H, m), 0.82-0.96 (2H, m), 1.42 (3H, s), 1.79-1.97 (2H, m), 1.98-2.19 (4H, m), 2.93-3.08 (2H, m), 3.33-3.82 (5.5H, m), 3.84-4.01 (1H, m), 4.04-4.23 (2.5H, m), 4.26-4.40 (2H, m), 4.55-4.73 (1H, m), 6.81-6.97 (3H, m), 7.11-7.22 (1H, m), 7.23-7.35 (1H, m), 7.46-7.67 (2H, m), 8.44-8.62 (2H, m)
150		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.02-1.18 (2H, m), 1.72-1.87 (1H, m), 1.94-2.46 (6H, m), 3.08-3.26 (2H, m), 3.41-4.11 (5H, m), 4.18-4.33 (2H, m), 4.57-4.75 (1H, m), 6.97-7.07 (1H, m), 7.23-7.61 (5H, m), 7.64-7.72 (1H, m), 8.53-8.60 (1H, m)
151		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.89 (4H, m), 1.36 (3H, s), 1.55-1.83 (6H, m), 1.89-2.17 (3H, m), 2.32-2.47 (1H, m), 2.59-2.82 (4H, m), 3.33-4.18 (9H, m), 4.38-4.52 (1H, m), 7.03-7.14 (2H, m), 7.16-7.32 (3H, m), 7.43-7.64 (2H, m), 8.44-8.61 (2H, m)
152		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.85 (2H, m), 1.03-1.16 (2H, m), 1.33-1.42 (3H, m), 1.73-1.88 (1H, m), 1.93-2.22 (3H, m), 2.25-2.45 (3H, m), 2.96-3.13 (2H, m), 3.41-4.11 (7H, m), 4.28-4.39 (2H, m), 4.52-4.71 (1H, m), 6.85-6.96 (2H, m), 7.32-7.40 (1H, m), 7.41-7.61 (3H, m), 7.63-7.71 (1H, m), 7.89-7.99 (2H, m)

Table 1-38

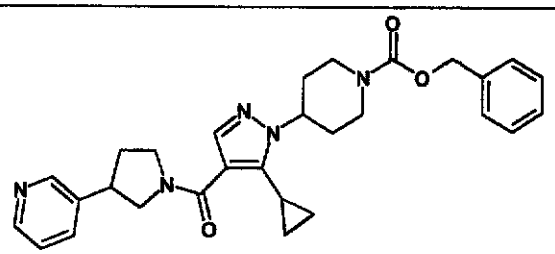
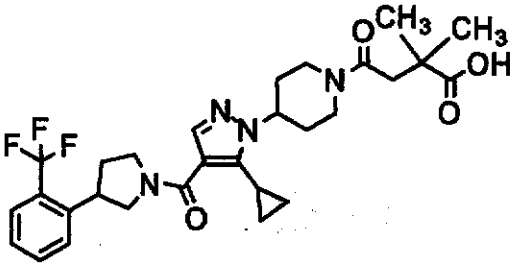
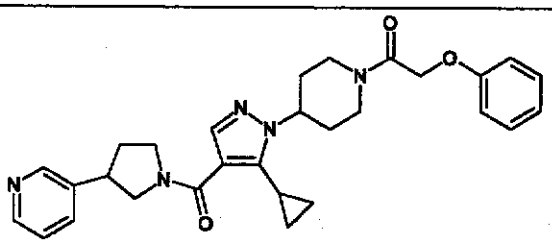
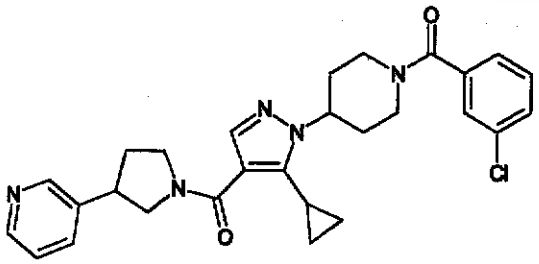
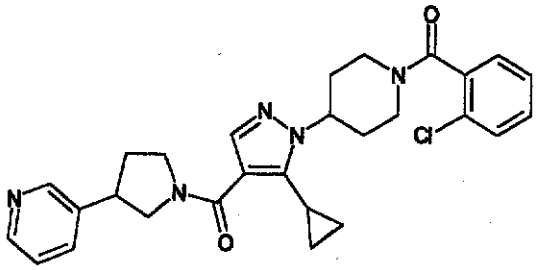
Ex. No.	structural formula	NMR
153		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.79 (2H, m), 1.00-1.09 (2H, m), 1.70-1.97 (3H, m), 2.00-2.26 (3H, m), 2.31-2.47 (1H, m), 2.86-3.05 (2H, m), 3.35-3.53 (1.5H, m), 3.56-3.77 (2H, m), 3.84-3.94 (1H, m), 4.08-4.16 (0.5H, m), 4.25-4.61 (3H, m), 5.14 (2H, s), 7.23-7.40 (6H, m), 7.49-7.61 (2H, m), 8.47-8.57 (2H, m)
154		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.61-0.86 (2H, m), 0.98-1.18 (2H, m), 1.23-1.41 (6H, m), 1.67-1.86 (1H, m), 1.87-2.47 (6H, m), 2.52-2.88 (3H, m), 3.06-3.32 (1H, m), 3.35-4.15 (6H, m), 4.49-4.85 (2H, m), 7.28-7.73 (5H, m)
155		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-0.83 (2H, m), 0.97-1.14 (2H, m), 1.66-2.50 (8H, m), 2.78-2.95 (1H, m), 3.16-3.34 (1H, m), 3.37-3.54 (1H, m), 3.57-3.79 (2H, m), 3.83-3.97 (1H, m), 4.09-4.29 (1H, m), 4.54-4.80 (4H, m), 6.89-7.04 (3H, m), 7.21-7.38 (3H, m), 7.48-7.68 (2H, m), 8.42-8.70 (2H, m)
156		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.82 (2H, m), 1.00-1.13 (2H, m), 1.67-2.30 (9H, m), 2.32-2.51 (1H, m), 2.72-3.34 (2H, m), 3.36-4.03 (4H, m), 4.56-4.99 (1H, m), 7.20-7.46 (5H, m), 7.49-7.65 (2H, m), 8.42-8.62 (2H, m)
157		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.85 (2H, m), 0.98-1.13 (2H, m), 1.57-1.92 (3H, m), 1.96-2.50 (5H, m), 2.90-3.54 (3H, m), 3.56-3.81 (3H, m), 3.83-3.98 (1H, m), 4.53-4.73 (1H, m), 4.85-5.04 (1H, m), 7.21-7.47 (5H, m), 7.49-7.65 (2H, m), 8.45-8.62 (2H, m)

Table 1-39

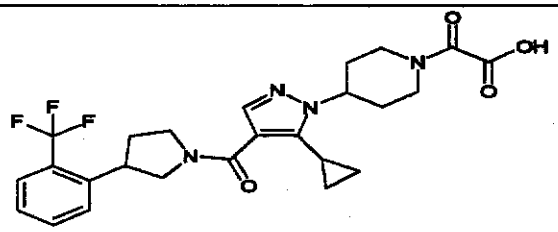
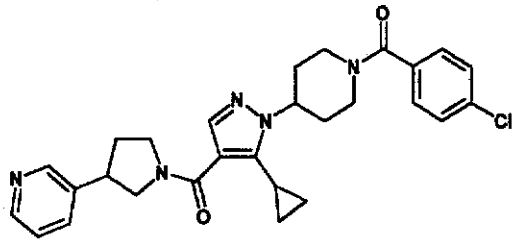
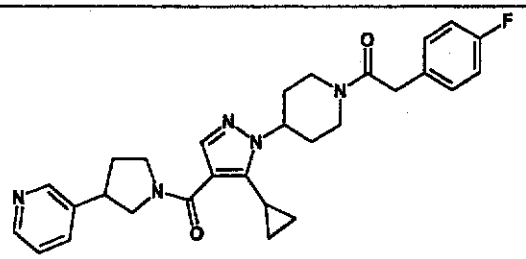
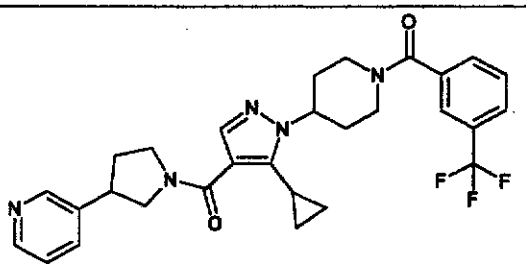
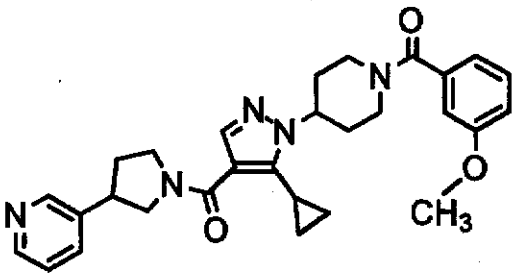
Ex. No.	structural formula	NMR
158		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.62-1.19 (4H, m), 1.62-2.53 (7H, m), 2.70-2.92 (1H, m), 3.08-3.29 (1H, m), 3.33-4.21 (6H, m), 4.51-4.75 (2H, m), 7.31-7.62 (4H, m), 7.63-7.73 (1H, m)
159		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.82 (2H, m), 0.98-1.12 (2H, m), 1.65-2.32 (9H, m), 2.34-2.50 (1H, m), 3.08 (2H, brs), 3.34-4.00 (4H, m), 4.56-4.95 (1H, m), 7.23-7.32 (1H, m), 7.35-7.44 (4H, m), 7.48-7.65 (2H, m), 8.45-8.61 (2H, m)
160		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.59-0.83 (2H, m), 0.95-1.14 (2H, m), 1.62-2.20 (6H, m), 2.30-2.50 (1H, m), 2.69-2.91 (1H, m), 3.06-3.27 (1H, m), 3.33-4.20 (6H, m), 3.73 (2H, s), 4.50-4.66 (1H, m), 4.71-4.85 (1H, m), 6.93-7.10 (2H, m), 7.15-7.34 (3H, m), 7.45-7.64 (2H, m), 8.41-8.62 (2H, m)
161		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.65-0.81 (2H, m), 0.99-1.13 (2H, m), 1.72-2.50 (9H, m), 2.85-3.33 (2H, m), 3.35-3.78 (3H, m), 3.81-4.96 (3H, m), 7.22-7.33 (1H, m), 7.47-7.77 (6H, m), 8.44-8.63 (2H, m)
162		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.64-0.82 (2H, m), 1.00-1.12 (2H, m), 1.71-2.32 (8H, m), 2.33-2.51 (1H, m), 2.85-3.28 (2H, m), 3.32-4.05 (5H, m), 3.83 (3H, s), 4.57-4.99 (1H, m), 6.90-7.04 (3H, m), 7.24-7.38 (2H, m), 7.50-7.69 (2H, m), 8.53 (2H, brs)

Table 1-40

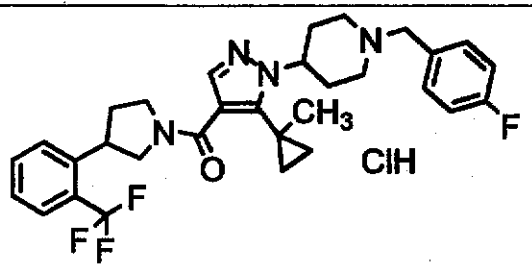
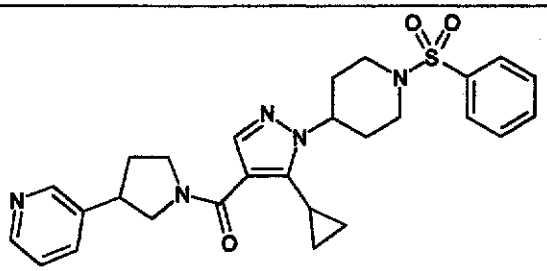
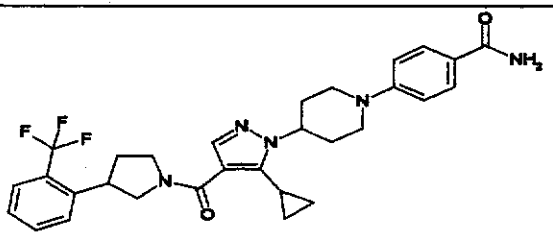
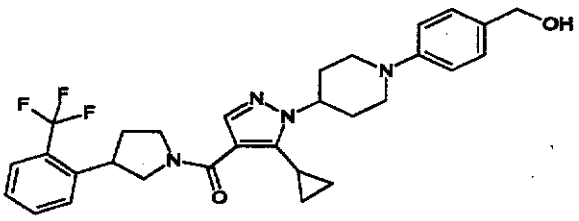
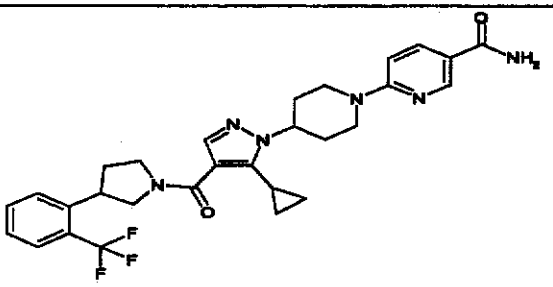
Ex. No.	structural formula	NMR
163		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.68-0.86 (4H, m), 1.29-1.38 (3H, m), 1.99-2.17 (2H, m), 2.18-2.66 (5H, m), 3.14-3.32 (2H, m), 3.39-4.50 (8H, m), 4.68-4.83 (1H, m), 7.30-7.40 (2H, m), 7.43-7.53 (1H, m), 7.60-7.82 (6H, m), 10.55-10.76 (1H, m)
164		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.59-0.74 (2H, m), 0.93-1.04 (2H, m), 1.61-1.73 (1H, m), 1.88-2.16 (3H, m), 2.25-2.59 (5H, m), 3.34-3.76 (3.5H, m), 3.83-4.01 (3H, m), 4.08-4.15 (0.5H, m), 4.27-4.39 (1H, m), 7.23-7.31 (1H, m), 7.49-7.67 (5H, m), 7.79-7.84 (2H, m), 8.46-8.58 (2H, m)
165		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.86 (2H, m), 1.00-1.19 (2H, m), 1.73-1.88 (1H, m), 1.92-2.21 (3H, m), 2.24-2.47 (3H, m), 2.92-3.12 (2H, m), 3.40-4.12 (7H, m), 4.51-4.69 (1H, m), 5.74 (2H, br s), 6.87-6.99 (2H, m), 7.31-7.40 (1H, m), 7.41-7.61 (3H, m), 7.63-7.78 (3H, m)
166		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.85 (2H, m), 1.01-1.16 (2H, m), 1.51-1.67 (1H, m), 1.75-1.89 (1H, m), 1.91-2.23 (3H, m), 2.26-2.49 (3H, m), 2.83-3.00 (2H, m), 3.40-4.12 (7H, m), 4.44-4.68 (3H, m), 6.88-7.04 (2H, m), 7.23-7.31 (2H, m), 7.32-7.40 (1H, m), 7.41-7.62 (3H, m), 7.63-7.72 (1H, m)
167		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.86 (2H, m), 1.06-1.12 (2H, m), 1.76-1.88 (1H, m), 1.94-2.08 (2H, m), 2.11-2.44 (5H, m), 3.05-3.19 (2H, m), 3.42-3.51 (0.5H, m), 3.59-4.10 (3.5H, m), 4.56-4.78 (3H, m), 5.40-5.94 (2H, brs), 6.67-6.74 (1H, m), 7.12-7.22 (1H, m), 7.31-7.40 (1H, m), 7.41-7.60 (2H, m), 7.64-7.73 (1H, m), 7.91-7.99 (1H, m), 8.56-8.63 (1H, m)

Table 1-41

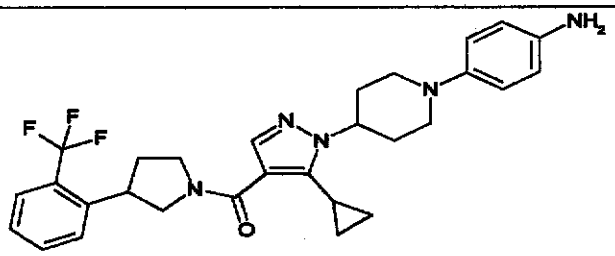
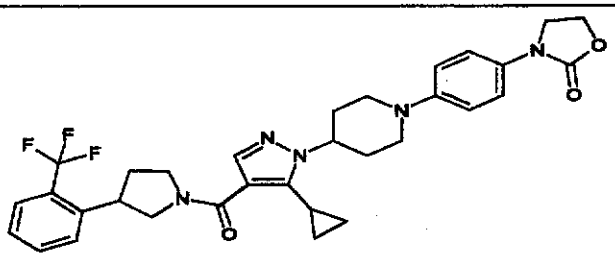
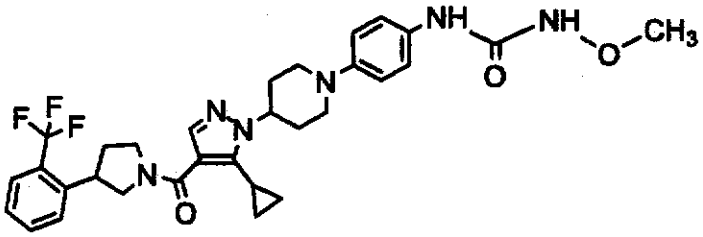
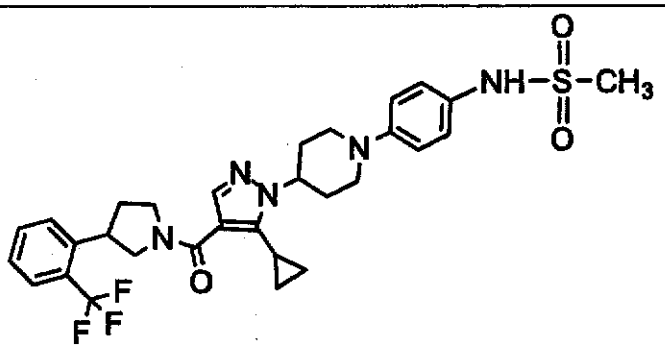
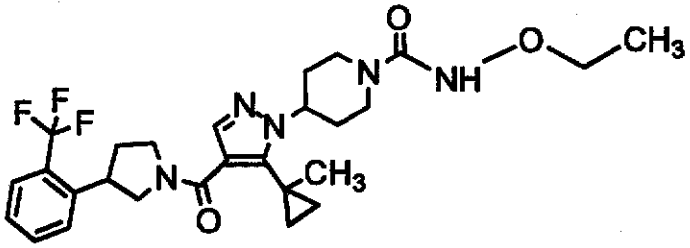
Ex. No.	structural formula	NMR
168		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.85 (2H, m), 1.02-1.14 (2H, m), 1.73-1.88 (1H, m), 1.90-2.22 (3H, m), 2.27-2.51 (3H, m), 2.71-2.88 (2H, m), 3.35-4.11 (9H, m), 4.38-4.56 (1H, m), 6.60-6.71 (2H, m), 6.78-6.91 (2H, m), 7.31-7.40 (1H, m), 7.41-7.62 (3H, m), 7.63-7.71 (1H, m)
169		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.71-0.88 (2H, m), 1.02-1.16 (2H, m), 1.73-1.88 (1H, m), 1.91-2.19 (3H, m), 2.27-2.50 (3H, m), 2.81-3.00 (2H, m), 3.40-4.17 (9H, m), 4.39-4.63 (3H, m), 6.92-7.04 (2H, m), 7.31-7.72 (7H, m)
170		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.01-1.16 (2H, m), 1.72-1.88 (1H, m), 1.91-2.23 (3H, m), 2.26-2.51 (3H, m), 2.76-2.98 (2H, m), 3.42-4.11 (10H, m), 4.42-4.62 (1H, m), 6.89-7.00 (2H, m), 7.16 (1H, s), 7.31-7.73 (8H, m)
171		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.00-1.16 (2H, m), 1.72-1.88 (1H, m), 1.92-2.23 (3H, m), 2.26-2.48 (3H, m), 2.84-3.02 (5H, m), 3.38-4.12 (7H, m), 4.45-4.65 (1H, m), 6.25-6.38 (1H, m), 6.88-6.99 (2H, m), 7.11-7.22 (2H, m), 7.32-7.40 (1H, m), 7.41-7.62 (3H, m), 7.63-7.71 (1H, m)
172		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-1.01 (4H, m), 1.16-1.35 (3H, m), 1.35-1.53 (3H, m), 1.71-1.97 (2H, m), 1.97-2.49 (4H, m), 2.86-3.09 (2H, m), 3.41-4.31 (9H, m), 4.53-4.75 (1H, m), 7.17-7.30 (1H, m), 7.30-7.40 (1H, m), 7.41-7.60 (3H, m), 7.61-7.74 (1H, m)

Table 1-42

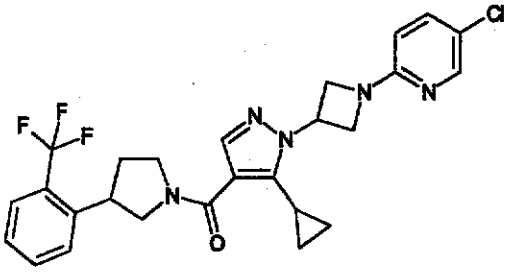
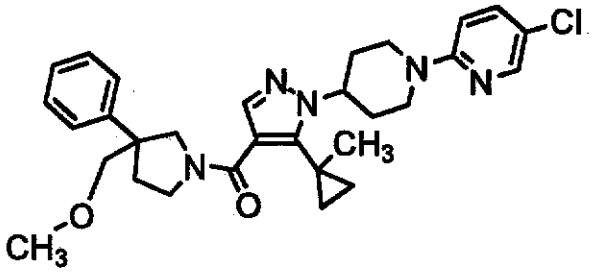
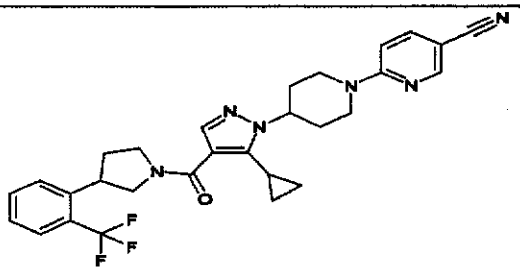
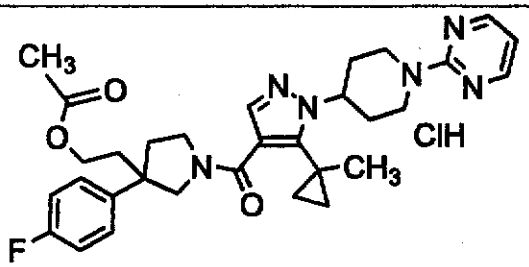
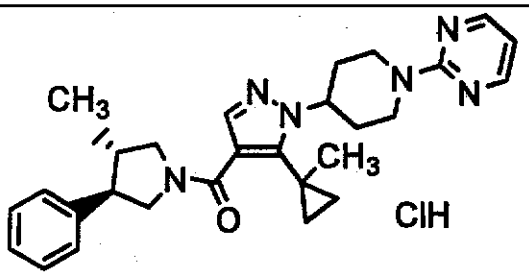
Ex. No.	structural formula	NMR
173		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.81-0.87 (2H, m), 1.00-1.19 (2H, m), 1.57-1.87 (1H, m), 1.93-2.25 (1H, m), 2.25-2.48 (1H, m), 3.31-4.15 (5H, m), 4.35-4.59 (4H, m), 5.44-5.66 (1H, m), 6.26-6.40 (1H, m), 7.30-7.76 (6H, m), 8.02-8.17 (1H, m)
174		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.69-0.93 (4H, m), 1.41-1.52 (3H, m), 1.83-2.01 (2H, m), 2.13-2.51 (4H, m), 2.97-3.11 (2H, m), 3.16-4.12 (9H, m), 4.41-4.54 (2H, m), 4.65-4.78 (1H, m), 6.62-6.71 (1H, m), 7.12-7.55 (7H, m), 8.10-8.16 (1H, m)
175		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.72-0.85 (2H, m), 1.04-1.16 (2H, m), 1.73-1.88 (1H, m), 1.94-2.09 (2H, m), 2.10-2.45 (5H, m), 3.07-3.22 (2H, m), 3.42-3.51 (0.5H, m), 3.57-4.10 (3.5H, m), 4.52-4.80 (3H, m), 6.62-6.71 (1H, m), 7.32-7.41 (1H, m), 7.41-7.72 (5H, m), 8.38-8.45 (1H, m)
176		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.46-0.86 (4H, m), 1.07-1.24 (2H, m), 1.27-1.41 (3H, m), 1.73-2.07 (7H, m), 2.15-2.30 (2H, m), 3.06-4.08 (8H, m), 4.72-4.88 (3H, m), 6.66-6.74 (1H, m), 7.08-7.61 (5H, m), 8.38-8.48 (2H, m)
177		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.70-0.97 (7H, m), 1.35-1.42 (3H, m), 1.86-2.03 (4H, m), 2.25-2.46 (1H, m), 2.84-2.95 (1H, m), 3.07-3.24 (3H, m), 3.39-3.57 (1H, m), 3.67-3.77 (1H, m), 3.81-3.94 (1H, m), 4.75-4.88 (3H, m), 6.64-6.72 (1H, m), 7.20-7.41 (5H, m), 7.53-7.61 (1H, m), 8.39-8.44 (2H, m)

Table 1-43

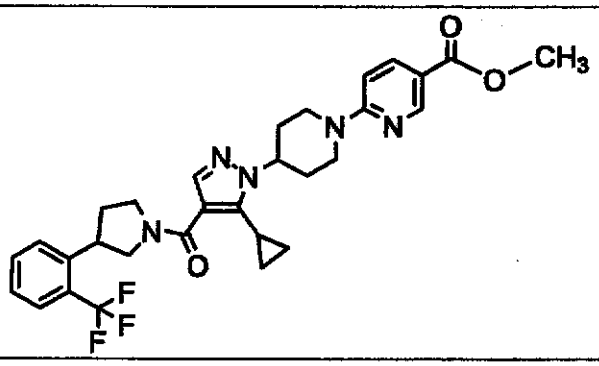
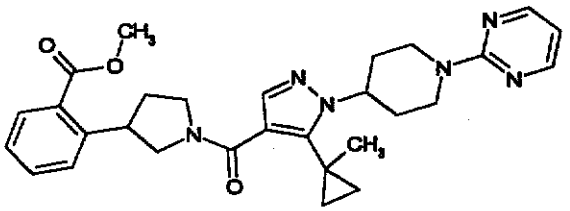
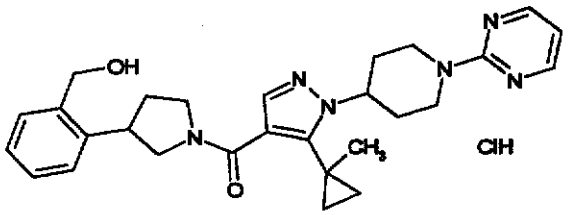
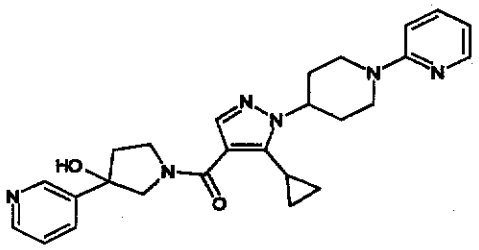
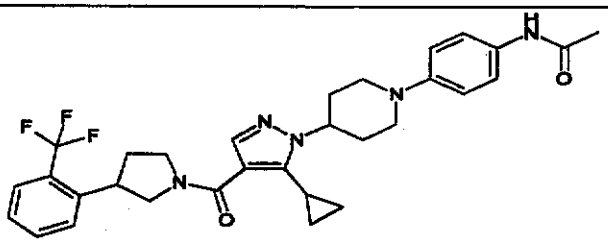
Ex. No.	structural formula	NMR
178		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.74-0.86 (2H, m), 1.05-1.15 (2H, m), 1.76-1.88 (1H, m), 1.93-2.09 (3H, m), 2.11-2.46 (4H, m), 3.04-3.19 (2H, m), 3.43-3.51 (0.5H, m), 3.59-4.09 (3.5H, m), 3.84-3.91 (3H, s), 4.58-4.78 (3H, m), 6.61-6.71 (1H, m), 7.32-7.61 (3.5H, m), 7.63-7.71 (1H, m), 7.98-8.08 (1.5H, m), 8.77-8.83 (1H, m)
179		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.77-0.98 (4H, m), 1.44-1.53 (3H, m), 1.86-2.46 (6H, m), 2.99-3.15 (2H, m), 3.45-4.06 (7H, m), 4.18-4.41 (1H, m), 4.68-4.85 (1H, m), 4.94-5.09 (2H, m), 6.48-6.55 (1H, m), 7.26-7.56 (4H, m), 7.82-7.92 (1H, m), 8.31-8.37 (2H, m)
180		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.67-0.91 (4H, m), 1.29-1.44 (3H, m), 1.74-2.34 (7H, m), 3.02-4.18 (7H, m), 4.47-4.69 (2H, m), 4.77-4.91 (3H, m), 6.60-6.71 (1H, m), 7.14-7.69 (5H, m), 8.34-8.46 (2H, m)
181		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.77 (2H, m), 0.99-1.15 (2H, m), 1.75-1.89 (1H, m), 1.92-2.05 (2H, m), 2.18-2.53 (4H, m), 2.96-3.09 (2H, m), 3.68-3.85 (2H, m), 3.87-4.04 (2H, m), 4.44-4.56 (2H, m), 4.58-4.72 (1H, m), 6.58-6.67 (1H, m), 6.68-6.76 (1H, m), 7.29-7.39 (1H, m), 7.45-7.53 (2H, m), 7.75-7.88 (1H, m), 8.17-8.23 (1H, m), 8.54-8.62 (1H, m), 8.69-8.83 (1H, m)
182		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.83 (2H, m), 1.01-1.15 (2H, m), 1.69-1.88 (1H, m), 1.90-2.21 (6H, m), 2.26-2.50 (3H, m), 2.77-3.00 (2H, m), 3.41-4.11 (7H, m), 4.40-4.62 (1H, m), 6.85-6.97 (2H, m), 7.31-7.71 (7H, m)

Table 1-44

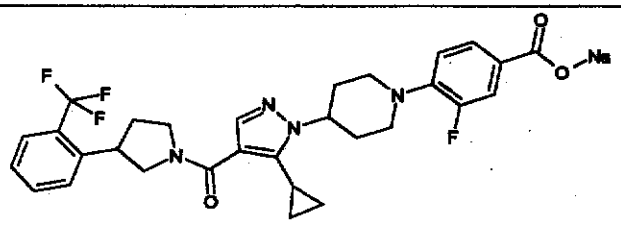
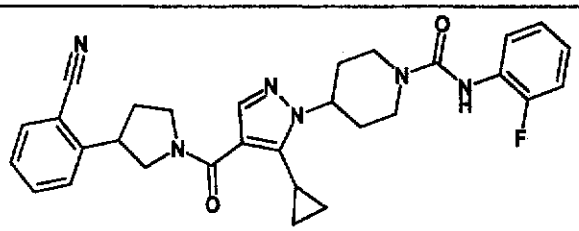
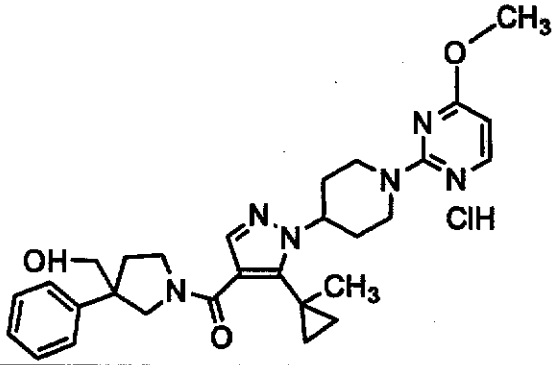
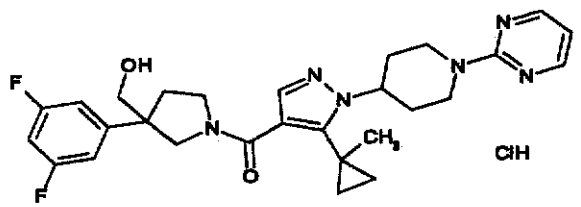
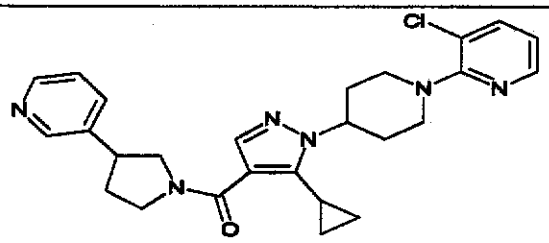
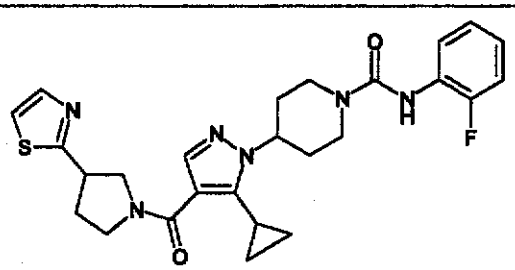
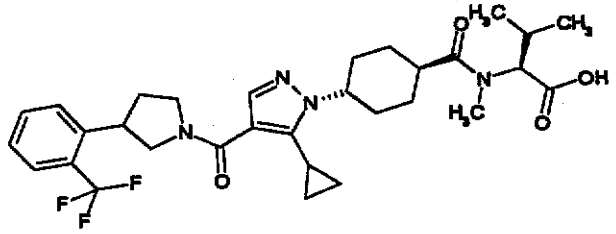
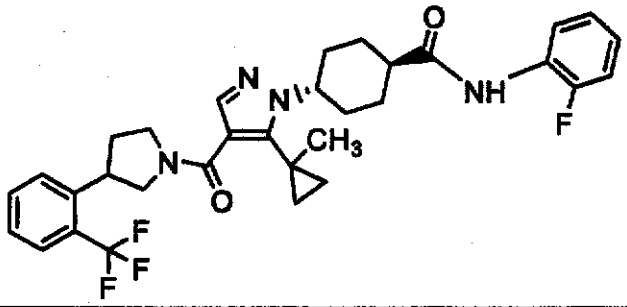
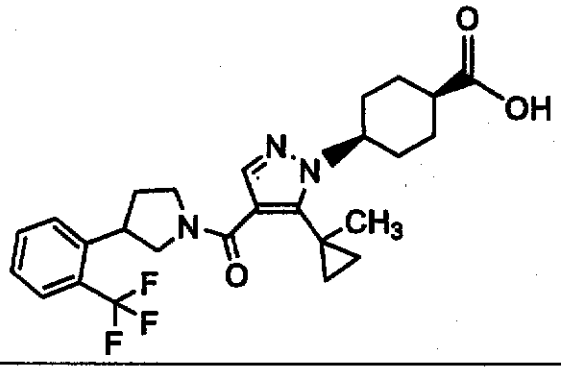
Ex. No.	structural formula	NMR
183		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.60-0.75 (2H, m), 0.94-1.06 (2H, m), 1.88-2.34 (7H, m), 2.79-2.98 (2H.m), 3.44-3.93 (7H, m), 4.50-4.68 (1H, m), 6.89-7.03 (1H, m), 7.43-7.80 (7H, m)
184		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.70-0.86 (2H, m), 1.05-1.16 (2H, m), 1.77-1.88 (1H, m), 1.94-2.53 (6H, m), 3.06-3.22 (2H, m), 3.45-4.16 (5H, m), 4.21-4.35 (2H, m), 4.57-4.73 (1H, m), 6.67 (1H, s), 6.95-7.17 (3H, m), 7.35-7.73 (5H, m), 8.05-8.13 (1H, m)
185		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.58-0.88 (4H, m), 1.29-1.44 (3H, m), 1.94-2.21 (5H, m), 2.28-2.41 (1H, m), 3.27-3.93 (8H, m), 3.95-4.05 (3H, m), 4.58-4.97 (3H, m), 5.42-6.26 (1H, m), 6.37-6.50 (1H, m), 7.14-7.41 (5H, m), 7.53-7.68 (1H, m), 8.11-8.23 (1H, m)
186		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.55-0.85 (4H, m), 1.32-1.41 (3H, m), 1.84-2.40 (7H, m), 3.06-3.23 (2H, m), 3.29-3.90 (5H, m), 4.72-4.88 (3H, m), 4.89-5.35 (2H, m), 6.66-6.72 (1H, m), 6.91-7.64 (4H, m), 8.39-8.44 (2H, m)
187		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.68-0.85 (2H, m), 1.01-1.13 (2H, m), 1.57-1.88 (2H, m), 1.93-2.20 (1H, m), 2.33-2.56 (3H, m), 2.94-3.07 (2H, m), 3.35-3.82 (4H, m), 3.86-4.21 (4H, m), 4.52-4.66 (1H, m), 6.82-6.88 (1H, m), 7.24-32 (3H, m), 7.55-7.64 (3H, m), 8.15-8.22 (1H, m), 8.47-8.61 (1H, m)

Table 1-45

Ex. No.	structural formula	NMR
188		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.67-0.78 (2H, m), 0.96-1.11 (2H, m), 1.71-1.85 (1H, m), 1.92-2.09 (3H, m), 2.16-2.57 (4H, m), 3.04-3.21 (2H, m), 3.55-4.00 (4H, m), 4.19-4.34 (2H, m), 4.54-4.68 (1H, m), 6.61-6.70 (1H, m), 6.91-7.15 (3H, m), 7.23-7.31 (1H, m), 7.51-7.58 (1H, m), 7.67-7.76 (1H, m), 8.03-8.12 (1H, m)
189		^{1}H-NMR (400MHz, DMSO-D_6) δ: 0.53-0.69 (2H, m), 0.71-0.88 (2H, m), 0.91-1.11 (6H, m), 1.43-2.39 (10H, m), 2.62-2.82 (2H, m), 2.92-3.06 (3H, m), 3.42-3.92 (6H, m), 4.10-4.74 (2H, m), 7.39-7.59 (2H, m), 7.63-7.81 (2H, m)
190		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.97 (4H, m), 1.36-1.51 (3H, m), 1.77-1.95 (2H, m), 1.97-2.26 (7H, m), 2.29-2.49 (2H, m), 3.47-4.11 (5H, m), 4.46-4.64 (1H, m), 7.00-7.20 (3H, m), 7.32-7.72 (6H, m), 8.29-8.42 (1H, m)
191		^{1}H-NMR (400MHz, $CDCl_3$) δ: 0.73-0.97 (4H, m), 1.38-1.49 (3H, m), 1.60-1.76 (1H, m), 1.77-1.90 (2H, m), 1.93-2.18 (2H, m), 2.19-2.56 (5H, m), 2.70-2.81 (1H, m), 3.47-4.09 (5H, m), 4.42-4.61 (1H, m), 7.31-7.72 (5H, m)

The present invention is now concretely explained by way of the following Formulation Examples, which are not to be construed as limitative.

Formulation Example 1 (production of capsule)

1)	Compound of Example 1	30 mg
2)	crystalline cellulose	10 mg
3)	lactose	19 mg
4)	magnesium stearate	1 mg

1), 2), 3) and 4) were mixed and filled in a gelatin capsule.

Formulation Example 2 (production of tablet)

1)	Compound of Example 1	30 g
2)	lactose	50 g
3)	cornstarch	15 g
4)	carboxymethylcellulose calcium	44 g
5)	magnesium stearate	1 g

The entire amount of 1), 2), 3) and 30 g of 4) are kneaded with water, dried under reduced pressure and sized. The sized powder is mixed with 14 g of 4) and 1 g of 5), and tableted with a tableting machine. In this way, 1000 tablets containing 30 mg of the compound of Example 1 per tablet are obtained.

In the same manner as in the above-mentioned Formulation Example 1 or Formulation Example 2, the compounds of Examples 2 to 191 can also be used to produce capsules or tablets.

Experimental Example 1: HSD-1 (hydroxysteroid dehydrogenase 1) activity inhibitory action in vitro

The HSD-1 activity inhibitory action was determined by quantitation of inhibition of conversion of cortisone to cortisol by SPA (scintillation proximity assay) system and using, as an enzyme source, human HSD-1 (hereinafter recombinant HSD-1) expressed using baculovirus system. Reagents (100 µl) were added to a 96 well plate (96 well Opti-plates™-96 (Packard)) to a final concentration shown below and the reaction was carried out at room temperature for 90 to 120 min. As a reaction mixture, 5-100 ng/well recombinant HSD-1, 500 µM NADPH and 10 nM ^{3}H cortisone (American Radiolabeled Chemicals Inc., 50 Ci/mmol) were dissolved in PBS containing

0.1% BSA (Sigma), and the test substance was 2 µl of a compound solution (dissolved in DMSO). After the reaction, 50 µl of PBS (containing 0.1% BSA (Sigma)) containing 0.2 µg of anti-cortisol mouse monoclonal antibody (East Coast Biologics), 500 µg of anti-mouse antibody bonded PVT SPA beads (Amersham Biosciences) and 133 µM carbenoxolone (Sigma) was added to the reaction mixture to stop the reaction. After completion of the reaction, the mixture was incubated at room temperature for not less than 2 hr, and the radioactivity was measured with Topcount (Packard). As the control, the value of the well added with 2 µl of DMSO instead of the test substance was used (0% inhibition) and, as the positive control, the value of the well added with carbenoxolone (final concentration 100 µM) instead of the test substance was used (100% inhibition). inhibition (%) of the test substance was calculated from ((value of control - value of test substance)/(value of control - value of positive control)) ×100(%). The IC_{50} value was calculated from the inhibition rates of two points across the 50% inhibition. The obtained results are shown in the following Table 2-1 to Table 2-3.

Table 2-1

Ex. No.	hHSD1 (IC_{50} (nM))	Ex. No.	hHSD1 (IC_{50} (nM))
2	++	41	++
3	++	42	++
4	++	43	++
6	++	44	++
7	++	45	++
8	++	47	++
9	++	48	++
10	++	49	++
11	++	50	++
12	++	51	++
13	++	52	++
14	++	53	++
15	++	54	++
16	++	55	++
17	++	56	++
18	++	57	++
19	++	58	++
20	++	59	++
21	++	60	++
22	++	61	++
23	++	63	++
24	++	64	++
25	++	65	++
26	++	66	++
27	++	67	++
28	++	68	++
29	++	69	++
30	++	71	++
31	++	72	++
32	++	73	++
33	++	74	++
34	++	75	++
35	++	76	++
36	++	77	++
37	++	78	++
39	++	79	++
40	++	80	++

Table 2-2

Ex. No.	hHSD1 (IC_{50} (nM))	Ex. No.	hHSD1 (IC_{50} (nM))
83	++	130	++
84	++	131	++
85	++	132	++
87	++	133	++
88	++	134	++
89	++	135	++
90	++	136	++
91	++	137	++
93	++	138	++
94	++	139	++
95	++	140	++
96	++	141	++
97	++	142	++
99	++	145	++
100	++	146	++
103	++	147	++
105	++	148	++
106	++	149	++
107	++	150	++
108	++	151	++
109	++	154	++
110	++	155	++
111	++	156	++
112	++	157	++
113	++	158	++
114	++	165	++
115	++	166	++
116	++	167	++
117	++	168	++
118	++	169	++
119	++	170	++
120	++	171	++
124	++	172	++
125	++	173	++
126	++	174	++
128	++	175	++
129	++	176	++

Table 2-3

Ex. No.	hHSD1 (IC_{50} (nM))	Ex. No.	hHSD1 (IC_{50} (nM))
177	++	185	++
178	++	186	++
179	++	187	++
180	++	189	++
182	++	190	++
183	++	191	++
184	++		

In the above-mentioned Tables, ++ means IC_{50} value of not more than 30 nM.

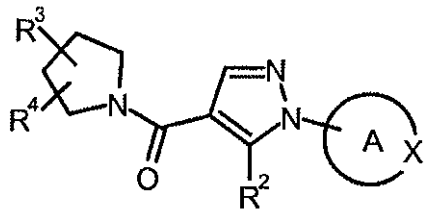
Industrial Applicability

The heterocyclic compound of the present invention has a superior HSD1 inhibitory action and is useful as an agent for the prophylaxis or treatment of metabolic diseases such as diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension, fatty liver and the like, and the like, and the like.

This application is based on patent application Nos. 2005-168901, 2006-027097 and 2006-138252 filed in Japan, and 60/692,039 and 60/772,734 filed in the US, the contents of which are incorporated in full herein by this reference.

CLAIMS

1. A compound represented by the following formula [1']:



[1']

wherein

ring A is

(1) a nitrogen-containing saturated monocyclic heterocyclic group, or

(2) a cycloalkyl group,

said ring A is optionally substituted by one or more, same or different substituents R^1,

said substituent R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the

following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) -S(=O)2-R9 wherein R9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C1-6 alkyl group (said C1-6 alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C1-6 alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a -CO-C_{1-6} alkyl group,

f) -CO-$NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) -$NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a -CO-C_{1-6} alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated

monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or

different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different

substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic

heterocyclic group, and

(f) a -COO-C_{1-6} alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) -CO-$NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a -COO-C_{1-6} alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group);

-X- is

(1) -N(R^1)- wherein R^1 is as defined above, or

(2) -C(R^7R^8)- wherein R^7 and R^8 are the same or different and each is

1) a hydrogen atom,

2) -$NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or -CO-$NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different $-OCO-C_{1-6}$ alkyl group),

(3) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following 1) to 4):

1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from

the following group: (a) a halogen atom, and (b) a hydroxyl group),

2) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is substituted by one or more, same or different halogen atoms),

3) a carboxyl group, and

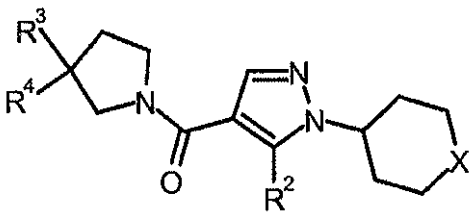
4) a -COO-C_{1-6} alkyl group, or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(provided that R^3 and R^4 are not simultaneously hydrogen atoms)],

or a salt thereof.

2. A compound represented by the following formula [1]:



[1]

wherein

-X- is

(1) -N(R^1)- wherein R^1 is

1) a hydrogen atom,

2) -CONR^{5}R^6 wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group,

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or a heterocyclic group which is a fused ring of said heterocycle and a carbon ring (both said heterocyclic groups are optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) -CO-$NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) -$NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a -CO-C_{1-6} alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group),

3) -$COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) -$NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

4) -COR^{11} wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the

nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group)), or

(2) $-C(R^7R^8)-$ wherein R^7 and R^8 are the same or different and

each is

1) a hydrogen atom,

2) $-NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or $-CO-NR^{36}R^{37}$ wherein R^{36} and R^{37} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{36} and R^{37} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

3) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more carboxyl groups), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group, or

5) a carboxyl group;

R^2 is

(1) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following group: 1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (a) a hydroxyl group, and (b) a C_{1-6} alkoxy group), and 2) a C_{1-6} alkoxy group); and

R^3 and R^4 are the same or different and each is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different -OCO-C_{1-6} alkyl group),

(3) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following 1) to 4):

1) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group: (a) a halogen atom, and (b) a hydroxyl group),

2) a C_{1-6} alkoxy group (said C_{1-6} alkoxy group is substituted by one or more, same or different halogen atoms),

3) a carboxyl group, and

4) a -COO-C_{1-6} alkyl group, or

(4) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following group: 1) a halogen atom, and 2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

(provided that R^3 and R^4 are not simultaneously hydrogen atoms)],

or a salt thereof.

3. The compound of any one of claims 1 and 2, wherein -X- is -C(R^7R^8)- wherein R^7 and R^8 are as defined in claim 1, or a salt thereof.

4. The compound of any one of claims 1 to 3, wherein R^8 is

1) -$NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{16} and R^{17} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

2) $-CONR^{18}R^{19}$ wherein R^{18} and R^{19} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{18} and R^{19} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

3) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group,

or a salt thereof.

5. The compound of any one of claims 1 and 2, wherein -X- is $-N(R^1)-$ wherein R^1 is as defined in claim 1, or a salt thereof.

6. The compound of any one of claims 1, 2 and 5, wherein R^1 is

1) a hydrogen atom,

2) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group) and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the

following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group), or

(g) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(h) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a -CO-C_{1-6} alkyl group,

f) -CO-$NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) -$NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a -CO-C_{1-6} alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

3) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

4) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom,

(2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

5) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

6) a cycloalkyl group,

7) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is

optionally substituted by one or more, same or different halogen atoms)),

8) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

9) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

10) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group, or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

11) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group, and

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(f) a $-COO-C_{1-6}$ alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group),

or a salt thereof.

7. The compound of any one of claims 1, 2 and 5, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a $-CO-C_{1-6}$ alkyl group,

f) $-CO-NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) $-NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not any combination of substituents selected from the following group: (i) a hydrogen atom, and (ii) an unsubstituted C_{1-6} alkyl group),

2) $-COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) $-NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents

selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents

selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) -CO-$NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or

9) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (g):

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(b) a cycloalkyl group,

(c) a halogen atom,

(d) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

(e) a -COO-C_{1-6} alkyl group,

(f) a cyano group, and

(g) a C_{1-6} alkoxy group),

or a salt thereof.

8. The compound of any one of claims 1, 2 and 5, wherein R^1 is $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a -CO-C_{1-6} alkyl group, a -CO-cycloalkyl group, or a $-S(=O)_2-C_{1-6}$ alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

or a salt thereof.

9. The compound of any one of claims 1 to 8, wherein R^2 is a cyclopropyl group or a 1-methylcyclopropyl group, or a salt thereof.

10. The compound of claim 1, wherein R^1 is

1) $-CONR^5R^6$ wherein R^5 and R^6 are the same or different and each is

(a) a hydrogen atom,

(b) an aryl group (said aryl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) a carboxyl group,

d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group), and

e) a C_{1-6} alkoxy group),

(c) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different C_{1-6} alkyl groups (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)),

(d) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following group:

a) a hydroxyl group,

b) a halogen atom,

c) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

d) $-NR^{20}R^{21}$ wherein R^{20} and R^{21} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a $-CO-C_{1-6}$ alkyl group, or R^{20} and R^{21} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated

monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following (i) to (iv):

(i) a halogen atom,

(ii) a hydroxyl group,

(iii) an oxo group, and

(iv) a C_{1-6} alkoxy group),

e) a C_{1-6} alkoxy group, and

f) a carboxyl group),

(e) $-S(=O)_2-R^9$ wherein R^9 is an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), or a C_{1-6} alkyl group, or

(f) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a $-CO-C_{1-6}$ alkyl group, and

c) an oxo group),

(g) a C_{1-6} alkoxy group, or

(h) a nitrogen-containing unsaturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different halogen atoms), or

(i) R^5 and R^6 optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to i):

a) a halogen atom,

b) a hydroxyl group,

c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, and (iii) a C_{1-6} alkoxy group),

d) a carboxyl group,

e) a -CO-C_{1-6} alkyl group,

f) -CO-$NR^{22}R^{23}$ wherein R^{22} and R^{23} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{22} and R^{23} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

g) an oxo group,

h) -$NR^{24}R^{25}$ wherein R^{24} and R^{25} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a -CO-C_{1-6} alkyl group, or R^{24} and R^{25} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

i) a C_{1-6} alkoxy group) (provided that R^5 and R^6 are not simultaneously hydrogen atoms),

2) -$COOR^{10}$ wherein R^{10} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to d):

a) a hydroxyl group,

b) -$NR^{26}R^{27}$ wherein R^{26} and R^{27} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{26} and R^{27} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

c) a C_{1-6} alkoxy group, and

d) an aryl group), or

(b) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents

selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

3) $-COR^{11}$ wherein R^{11} is

(a) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following a) to h):

a) a halogen atom,

b) a hydroxyl group,

c) $-NR^{28}R^{29}$ wherein R^{28} and R^{29} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a -CO-C_{1-6} alkyl group, a -CO-cycloalkyl group, or a -S(=O)$_2$-C_{1-6} alkyl group, or R^{28} and R^{29} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

d) $-CO-NR^{30}R^{31}$ wherein R^{30} and R^{31} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{30} and R^{31} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

e) a C_{1-6} alkoxy group,

f) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a halogen atom, (ii) a hydroxyl group, (iii) a C_{1-6} alkoxy group, and (iv) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

g) a carboxyl group, and

h) an aryloxy group),

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different substituents selected from the following a) and b):

a) an aryl group (said aryl group is optionally

substituted by one or more, same or different substituents selected from the following (1) and (2): (1) a halogen atom, and (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)), and

b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group)), or

(c) a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a C_{1-6} alkyl group,

b) a -CO-C_{1-6} alkyl group, and

c) an oxo group),

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (1) to (3): (1) a halogen atom, (2) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms), and (3) a C_{1-6} alkoxy group), or

(e) a carboxyl group,

4) a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different substituents selected from the following (a) to (d):

(a) a carboxyl group,

(b) a cycloalkyl group (said cycloalkyl group is optionally substituted by one or more, same or different -CO-$NR^{32}R^{33}$ wherein R^{32} and R^{33} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: (i) a hydroxyl group, and (ii) a C_{1-6} alkoxy group), or R^{32} and R^{33} optionally

form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

(c) $-CO-NR^{34}R^{35}$ wherein R^{34} and R^{35} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{34} and R^{35} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(d) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms))),

5) a cycloalkyl group,

6) $-S(=O)_2-R^{12}$ wherein R^{12} is a C_{1-6} alkyl group (said C_{1-6} alkyl group is substituted by one or more, same or different halogen atoms), or an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a halogen atom, and b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different halogen atoms)),

7) $-C(=NCN)-R^{13}$ wherein R^{13} is a C_{1-6} alkyl group,

8) $-C(=NCN)NR^{14}R^{15}$ wherein R^{14} and R^{15} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{14} and R^{15} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group,

9) an aryl group (said aryl group is optionally substituted by one or more, same or different substituents selected from the following (a) to (f):

(a) a carboxyl group,

(b) a halogen atom,

(c) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following group: a) a hydroxyl group, b) a

halogen atom, and c) a C_{1-6} alkoxy group),

(d) $-NR^{38}R^{39}$ wherein R^{38} and R^{39} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, a $-CO-C_{1-6}$ alkyl group, $-CO-NR^{40}R^{41}$ wherein R^{40} and R^{41} are the same or different and each is a hydrogen atom, a C_{1-6} alkyl group, or a C_{1-6} alkoxy group, or R^{40} and R^{41} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, or $-S(=O)_2-R^{42}$ wherein R^{42} is a C_{1-6} alkyl group), or R^{38} and R^{39} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group (said heterocyclic group is optionally substituted by one or more oxo groups),

(e) $-CO-NR^{43}R^{44}$ wherein R^{43} and R^{44} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{43} and R^{44} optionally form, together with the nitrogen atom bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group, and

(f) a $-COO-C_{1-6}$ alkyl group), or

10) a 5-membered or 6-membered unsaturated monocyclic heterocyclic group (said heterocyclic group is substituted by one or more, same or different substituents selected from the following (a) to (h):

(a) a carboxyl group,

(b) a C_{1-6} alkyl group (said C_{1-6} alkyl group is optionally substituted by one or more, same or different substituents selected from the following a) to c):

a) a halogen atom,

b) a hydroxyl group, and

c) a C_{1-6} alkoxy group),

(c) a cycloalkyl group,

(d) a halogen atom,

(e) $-CO-NR^{45}R^{46}$ wherein R^{45} and R^{46} are the same or different and each is a hydrogen atom, or a C_{1-6} alkyl group, or R^{45} and R^{46} optionally form, together with the nitrogen atom

bonded thereto, a nitrogen-containing saturated monocyclic heterocyclic group),

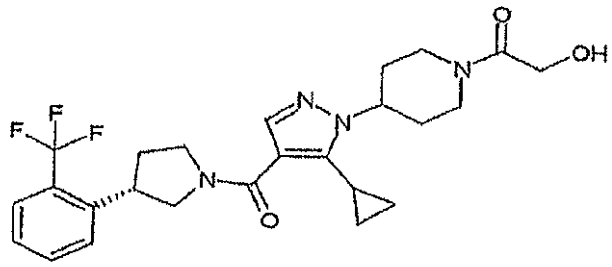
(f) a -COO-C_{1-6} alkyl group,

(g) a cyano group, and

(h) a C_{1-6} alkoxy group),

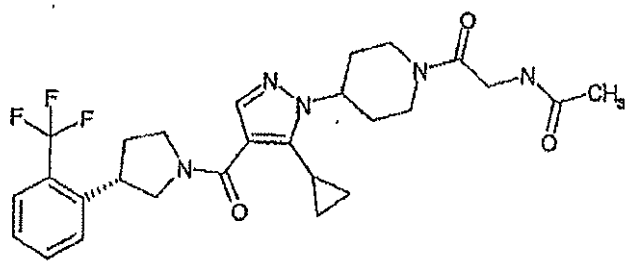
or a salt thereof.

11. A compound represented by the following formula:



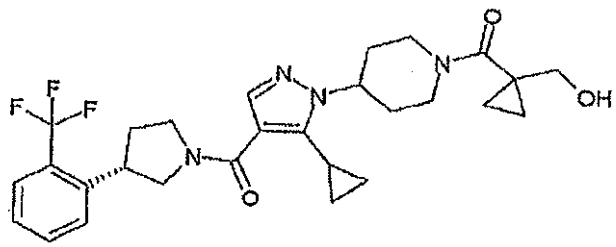
or a salt thereof.

12. A compound represented by the following formula:



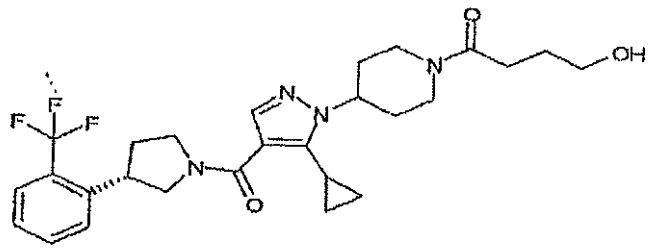
or a salt thereof.

13. A compound represented by the following formula:



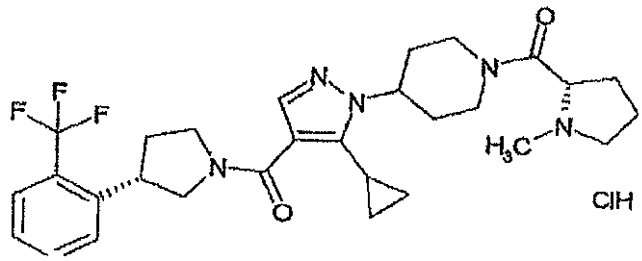
or a salt thereof.

14. A compound represented by the following formula:



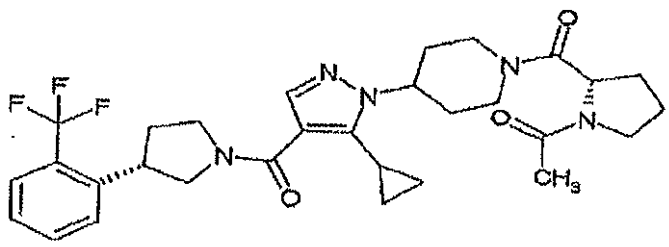
or a salt thereof.

15. A compound represented by the following formula:



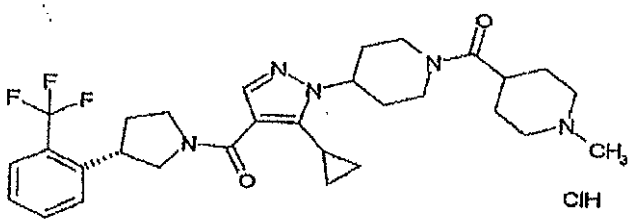
or a salt thereof.

16. A compound represented by the following formula:



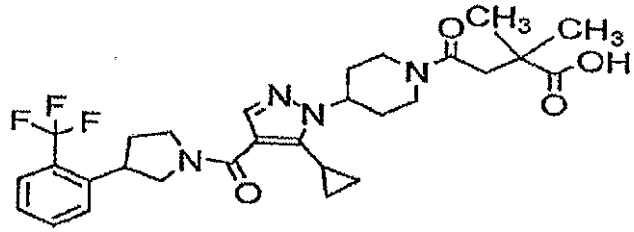
or a salt thereof.

17. A compound represented by the following formula:



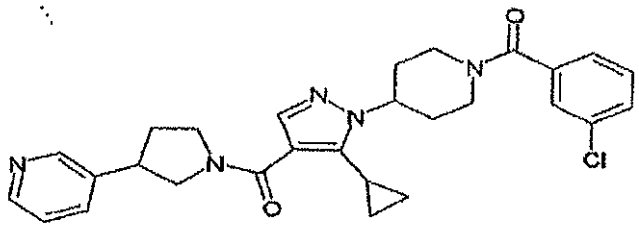
or a salt thereof.

18. A compound represented by the following formula:



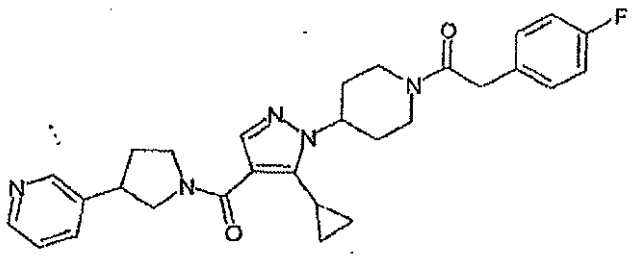
or a salt thereof.

19. A compound represented by the following formula:



or a salt thereof.

20. A compound represented by the following formula:



or a salt thereof.

21. A pharmaceutical composition comprising a compound of any one of claims 1 to 20 or a salt thereof.

22. A 11βHSD1 inhibitor comprising a compound of any one of claims 1 to 20 or a salt thereof.

23. An agent for the treatment or prophylaxis of a pathology involving glucocorticoid, which comprises a compound of any one of claims 1 to 20 or a salt thereof, wherein the

pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

24. A compound of any one of claims 1 to 20 or a salt thereof for treating or preventing a pathology involving glucocorticoid, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or apetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

25. Use of a compound of any one of claims 1 to 20 or a

salt thereof for the production of a 11βHSD1 inhibitor.

26. Use of a compound of any one of claims 1 to 20 or a salt thereof for the production of an agent for the treatment or prophylaxis of a pathology involving glucocorticoid, wherein the pathology involving glucocorticoid is

(1) a metabolic disease including diabetes, insulin resistance, diabetic complications, obesity, hyperlipidemia, hypertension or fatty liver,

(2) a metabolic syndrome,

(3) a fatal vascular event including cardiac infarction or cerebral apoplexy,

(4) hyperorexia,

(5) a neurodysfunctional disease including dysgnosia, neurodegenerative diseases, emotional disorders, schizophrenia or appetite stimulation,

(6) a disease associated with decreased immune function,

(7) glaucoma, or

(8) osteoporosis.

27. Dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

28. Methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

29. (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one.

30. (S)-3-(2-trifluoromethylphenyl)pyrrolidine or a salt thereof.

31. A method for producing dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate, which comprises a step for reacting 1-((E)-2-nitrovinyl)-2-trifluoromethylbenzene with

dimethyl malonate in the presence of 1-(3,5-bis-trifluoromethylphenyl)-3-((1S,2S)-2-dimethylaminocyclohexyl)-thiourea.

32. A method for producing methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate, which comprises a step for reduction and ring closure of dimethyl 2-[(S)-2-nitro-1-(2-trifluoromethylphenyl)ethyl]malonate.

33. A method for producing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one, which comprises a step for hydrolysis and decarbonation of methyl (S)-2-oxo-4-(2-trifluoromethylphenyl)pyrrolidine-3-carboxylate.

34. A method for producing a salt of (S)-3-(2-trifluoromethylphenyl)pyrrolidine, which comprises a step for reducing (S)-4-(2-trifluoromethylphenyl)pyrrolidin-2-one and a step for treating the resulting compound with an acid to form a salt.