

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 April 2007 (26.04.2007)

PCT

(10) International Publication Number
WO 2007/046548 A1

(51) International Patent Classification:

A61K 31/519 (2006.01) A61P 25/30 (2006.01)
C07D 487/04 (2006.01)

(74) Agents: TANAKA, Mitsuo et al.; AOYAMA & PARTNERS, IMP Building, 3-7, Shiromi 1-chome, Chuo-ku, Osaka-shi, Osaka 5400001 (JP).

(21) International Application Number:

PCT/JP2006/321441

(22) International Filing Date: 20 October 2006 (20.10.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2005-306816	21 October 2005 (21.10.2005)	JP
60/729,206	24 October 2005 (24.10.2005)	US
2006-151470	31 May 2006 (31.05.2006)	JP
60/810,149	2 June 2006 (02.06.2006)	US

(71) Applicant (for all designated States except US): TANABE SEIYAKU CO., LTD. [JP/JP]; 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MORITANI, Yasunori [JP/JP]; c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP). SHIRAI, Kimihiro [JP/JP]; c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP). OI, Mariko [JP/JP]; c/o TANABE SEIYAKU CO., LTD., 2-10, Dosho-machi 3-chome, Chuo-ku, Osaka-shi, Osaka, 5418505 (JP).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

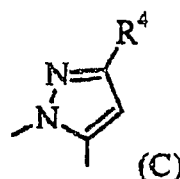
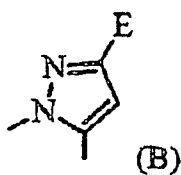
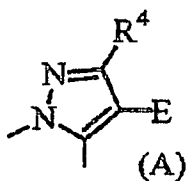
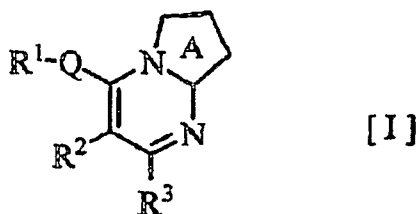
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRAZOLO[1,5-A]PYRIMIDINE COMPOUNDS AS CANNABINOID RECEPTOR ANTAGONISTS



(57) Abstract: The present invention relates to a novel pyrazolo[1,5-a]pyrimidine compound of the formula [I]: wherein Ring A is a substituted pyrazole ring fused to the adjacent pyrimidine ring having the following formula (A), (B) or (C), or a pharmaceutically acceptable salt thereof.

DESCRIPTION

A PYRAZOLO[1,5-a]PYRIMIDINE COMPOUND

5 TECHNICAL FIELD

The present invention relates to a novel pyrazolo[1,5-a]pyrimidine compound or a pharmaceutically acceptable salt thereof which has potent central cannabinoid receptor (CB1) antagonizing activity and hence is useful as a medicine.

10 BACKGROUND ART

It is well known that, by intake of marijuana, various psychiatric or neurological reactions such as confusion of temporal or space sense, euphoria, alteration of memories, analgesia, hallucination and the like would be produced. The compounds generally referred to as "cannabinoid" including Δ^9 -tetrahydrocannabinol (15 Δ^9 -THC) are responsible for many of such reactions. The effect of cannabinoid is considered to be produced by an interaction between the compound and its endogenous specific/high-affinity receptors. Two subtypes of cannabinoid receptors (CB1 and CB2) have been identified and cloned. The CB1 receptor is distributed in central nervous system (CNS) regions including brain (Nature, Vol. 346, 1990, pp 561-564) while the CB2 receptor is distributed in immune system including spleen (Nature, Vol. 20 365, 1993, pp 61-65).

Substances having affinity to such cannabinoid receptors (agonists, antagonists or inverse agonists) may produce various pharmacological effects like marijuana. In particular, substances having affinity to central CB1 receptor may be useful for 25 treatment of a CNS disease such as a psychotic disorder, a neurological disorder and the like.

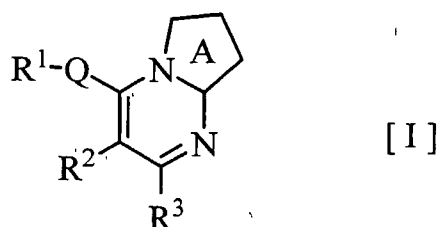
There have been known various compounds, including pyrazol-3-carboxamide compounds such as SR141716 (Life Science, Vol. 63, 1998, PL113-PL117), 4,5-dihydropyrazole compounds such as SLV-319 (Journal of Medicinal Chemistry, Vol. 30 47(3), 2004, pp.627-643), dihydropyrazolo[3,4-c] pyridin-7-one compounds, 2H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (WO2004/094417) and the like as the substances having affinity to such cannabinoid receptors. Among them, at least SR141716 and SLV-319 are under clinical studies on the efficacy thereof as anorexigenics (anti-obesity agent).

35

DISCLOSURE OF INVENTION

The object of the present invention is to provide a novel pyrazolo[1,5-a]-pyrimidine compound which has potent CB1 receptor-antagonizing activity and hence is useful as a medicine.

The present invention relates to a pyrazolo[1,5-a]pyrimidine compound of the formula [I]:



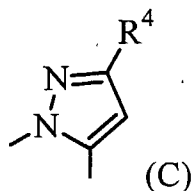
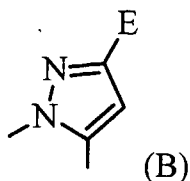
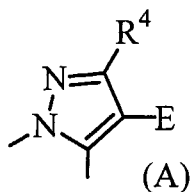
wherein

R^1 and R^2 are the same or different and an optionally substituted aryl group or an optionally substituted saturated or unsaturated heterocyclic group,

Q is single bond, a methylene group or a group of the formula: $-N(R^Q)-$,

R^Q is an alkyl group,

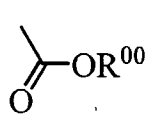
Ring A is a substituted pyrazole ring fused to the adjacent pyrimidine ring having the following formula (A), (B) or (C),



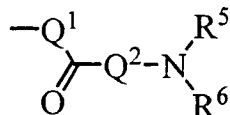
R^3 and R^4 are the same or different and (a) a hydrogen atom, (b) a cyano group, (c) an alkyl group optionally substituted by one to three halogen atom(s), (d) an alkyloxy group (the alkyl moiety of said group being optionally substituted by one to three group(s) selected from a halogen atom, a hydroxyl group, an amino group optionally substituted by one or two alkyl group(s), an alkyloxy group and an alkylsulfonyl group) or (e) an alkylthio group, (f) an alkylsulfinyl group, (g) an alkylsulfonyl group or (h) a group of the formula: $-N(R')(R'')$,

R' and R'' are the same or different and (a) a hydrogen atom, (b) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, an amino group optionally substituted by one or two alkyl group(s) and an alkyloxy group, (c) an acyl group, (d) an alkylsulfonyl group or (e) an amino sulfonyl group optionally substituted by one to two alkyl group(s), or both R' and R'' combine each other at their termini to form together with an adjacent nitrogen atom an optionally substituted, saturated or unsaturated nitrogen-containing heterocyclic group,

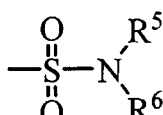
E is one of the following groups (i) to (v):



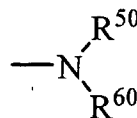
(i)



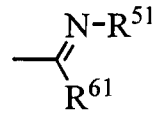
(ii)



(iii)



(iv)



(v)

R^{00} is an alkyl group,

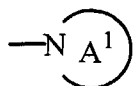
Q^1 is a single bond, an alkylene group or a group of the formula: $\text{—N}(\text{R}^7)\text{—}$, R^7 is a hydrogen atom or an alkyl group,

Q^2 is a single bond or an alkylene group,

one of R^5 and R^6 is a hydrogen atom or an alkyl group and the other is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyloxy group, an optionally substituted cycloalkyl group, an amino group optionally substituted by one or two alkyl group(s), an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an acyl group, an optionally substituted aryl group and optionally substituted saturated or unsaturated heterocyclic group, (b) an optionally substituted cycloalkyl group, (c) a group of the formula: $\text{—N}(\text{R}^8)(\text{R}^9)$, (d) an optionally substituted aryl group or (e) an optionally substituted, saturated or unsaturated heterocyclic group, or both of R^5 and R^6 combine each other to form together with an adjacent nitrogen atom an optionally substituted, saturated or unsaturated nitrogen-containing heterocyclic group,

one of R^8 and R^9 is a hydrogen atom or an alkyl group and the other is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group and an aryl group, (b) a cycloalkyl group, (c) an optionally substituted aryl group or (d) an acyl group or (e) an optionally substituted saturated or unsaturated heterocyclic group,

one of R^{50} and R^{60} is a hydrogen atom or an alkyl group and the other is a hydrogen atom, an alkyl group or an acyl group, or both of them combine together with the adjacent nitrogen atom to form a cyclic group of the following formula:



in which Ring A^1 is a 5- to 7-membered aliphatic nitrogen-containing heterocyclic group optionally substituted by an oxo group,

R^{51} is an alkyl group or an optionally substituted arylsulfonyl group,

R^{61} is an alkylamino group or an azido group,

or a pharmaceutically acceptable salt thereof.

BEST MODE TO CARRY OUT INVENTION

With regard to the compound [I] of the present invention, in case that each of R^1 and R^2 is an aryl group, examples of such aryl group include a 6- to 10-membered monocyclic or bicyclic aryl group such as a phenyl group or a naphthyl group. Among them, preferred example of such aryl group is a phenyl group.

With regard to the compound [I] of the present invention, in case that R^1 , R^2 , R^3 or R^4 is a saturated or unsaturated heterocyclic group, examples of such heterocyclic group include a 5- to 7-membered heteromonocyclic group including one to three heteroatom(s) selected from a sulfur atom, an oxygen atom and a nitrogen atom. More concretely, such heterocyclic group may be a saturated or unsaturated 5- to 6-membered oxygen-containing heterocyclic group such as a furyl group, a tetrahydrofuryl group, a pyranyl group or a tetrahydropyranyl group, a saturated or unsaturated 5- to 6-membered sulfur-containing heterocyclic group such as thienyl group, a tetrahydrothienyl group, a thiopyranyl group or a tetrahydrothiopyranyl group or a saturated or unsaturated 5- to 7-membered nitrogen-containing heterocyclic group such as a pyrrolidinyl group, an imidazolyl group, a pyrazolyl group, an oxazolyl group, an isoxazolyl group, a thiazolyl group, an isothiazolyl group, a pyridyl group, a piperidyl group, a pyrimidinyl group, a pyrazinyl group, a pyridazinyl group, a morpholinyl group, a thiomorpholinyl group or an azacycloheptyl group. Among them, preferred example of R^1 or R^2 is a saturated or unsaturated 5- or 6-membered sulfur- or nitrogen-containing heterocyclic group such as a thienyl group, a pyrrolidinyl group, a piperidyl group or a pyridyl group, and preferred example of R^3 or R^4 is a unsaturated 5- or 6-membered sulfur-, oxygen- or nitrogen-containing heterocyclic group such as a pyrrolidinyl group, a piperidyl group, a morpholino group or a thiomorpholino group.

The aryl group and/or the saturated or unsaturated heterocyclic group in R^1 , R^2 , R^3 or R^4 mentioned above may be substituted by one to three groups selected from a halogen atom, a cyano group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group optionally substituted by one to three halogen atom(s), an amino group optionally substituted by one to two alkyl group(s), an alkylthio group, an alkylsulfinyl group and an alkylsulfonyl group.

In case that R^5 , R^6 , R^8 or R^9 is a cycloalkyl group, such cycloalkyl group may be substituted by one to two group(s) selected from a cyano group and an alkyl group.

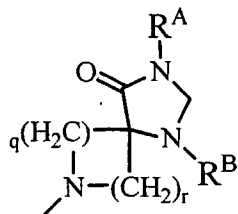
The aryl group in R^5 , R^6 , R^8 or R^9 mentioned above may be a 6- to 10-membered monocyclic or bicyclic aryl group such as a phenyl group, a naphthyl group and the like, preferably a phenyl group. The aryl group may be substituted by

one to two halogen atom(s).

In case that R⁵, R⁶, R⁸ or R⁹ is a saturated or unsaturated heterocyclic group, examples of such heterocyclic group include (a) a saturated or unsaturated, 4- to 7-membered heteromonocyclic group, said heteromonocyclic group containing one to four heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom; (b) a saturated or unsaturated, 8- to 15-membered nitrogen-containing bicyclic or tricyclic heterocyclic group formed by fusing the aforementioned heteromonocyclic group with one or two other cyclic group(s) selected from a C₃₋₈ cycloalkyl group, a 5- to 6-membered monocyclic aryl group and a saturated or unsaturated, 4- to 7-membered heteromonocyclic group, said heteromonocyclic group containing one to four heteroatom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom; or (c) a saturated or unsaturated, 8- to 11-membered nitrogen-containing spiro-heterocyclic group.

Examples of the saturated or unsaturated heterocyclic group in R⁵, R⁶, R⁸ or R⁹ is (A) an oxygen- or sulfur-containing heterocyclic group selected from a furyl group, a tetrahydrofuranlyl group, a pyranlyl group, a tetrahydropyranlyl group, a thiacyclobutyl group, a thienyl group, a tetrahydrothienyl group, a thiopyranlyl group, a tetrahydrothiopyranlyl group, a benzofuranlyl group, a dihydrobenzofuranlyl group, an isobenzofuranlyl group, a chromanlyl group, an isochromanlyl group, a chromenyl group, an isochromenyl group, a benzothienyl group and a dihydrobenzothienyl group; or (B) a nitrogen-containing heterocyclic group selected from an azetidyl group, a pyrrolidinyl group, a pyrrolinyl group, an imidazolidinyl group, an imidazoliny group, a pyrazolidinyl group, a pyrazolinyl group, a pyrrolyl group, a 2H-pyrrolyl group, an imidazolyl group, a pyrazolyl group, a dihydropyrazolyl group, a thiazolidinyl group, a thiazolyl group, an isothiazolyl group, an isoxazolyl group, an oxazolidinyl group, a pyridyl group, a dihydropyridyl group, a tetrahydropyridyl group, a piperidyl group, a pyrazinyl group, a piperazinyl group, a pyrimidinyl group, a tetrahydropyrimidinyl group, a pyridazinyl group, a morpholinyl group, an azocinyl group, an azacycloheptyl group, an indolizinyl group, a benzimidazolyl group, a benzotriazolyl group, a benzotriazolyl group, an indolyl group, an isoindolyl group, a 3H-indolyl group, an indolinyl group, an isoindolinyl group, a 1H-indazolyl group, a pyrrolopyridyl group, a pyrrolopyrimidinyl group, a purinyl group, a pteridinyl group, a 4H-quinolizinyl group, a quinolyl group, a dihydroquinolyl group, a tetrahydroquinolyl group, an isoquinolyl group, a dihydroisoquinolyl group, a tetrahydroisoquinolyl group, a phthalazinyl group, a dihydrophthalazinyl group, a naphthyridinyl group, a dihydronaphthyridinyl group, a tetrahydronaphthyridinyl group, a quinoxalinyl group, a quinazolinyl group, a

dihydroquinazolinyl group, a dihydrobenzothiazinyl group, a dihydrobenzoxazinyl group, a cinnolinyl group, a xanthenyl group, a carbazolyl group, a beta-carbolinyl group, a phenanthridinyl group, an acridinyl group, a 5H-dihydro-dibenzazepinyl group and a spiro-heterocyclic group of the formula:



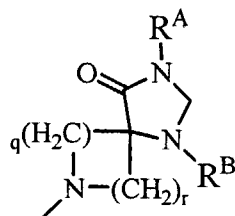
wherein R^A and R^B are the same or different and a hydrogen atom or an alkyl group, and q and r are an integer of 1 or 2.

Among them, preferred examples of the saturated or unsaturated heterocyclic group include a tetrahydrofuranyl group, a pyrrolyl group, a pyrrolidinyl group, a piperidyl group, an azacycloheptyl group, a tetrahydropyranyl group, piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a thiacyclobutyl group, a tetrahydrothienyl group, a tetrahydrothiopyranyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, an indolyl group, a pyrrolopyridyl group or a tetrahydronaphthyridinyl group.

In case that R^5 and R^6 combine each other to form a saturated or unsaturated nitrogen-containing heterocyclic group, examples of such nitrogen-containing heterocyclic group include (a) a saturated or unsaturated, 4- to 7-membered nitrogen-containing heteromonocyclic group, said heteromonocyclic group optionally containing two or more nitrogen atoms and optionally containing one to two heteroatoms other than such nitrogen atoms selected from oxygen atom and sulfur atom; (b) a saturated or unsaturated, 8- to 15-membered nitrogen-containing bicyclic or tricyclic heterocyclic group formed by fusing the aforementioned heteromonocyclic group with one or two other cyclic group(s) selected from a C_{3-8} cycloalkyl group, a 5- to 6-membered monocyclic aryl group and a saturated or unsaturated, 4- to 7-membered heteromonocyclic group, said heteromonocyclic group containing one to four heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom; or (c) a saturated or unsaturated, 8- to 11-membered nitrogen-containing spiro-heterocyclic group.

Examples of the saturated or unsaturated nitrogen-containing heterocyclic group mentioned above include a nitrogen-containing heterocyclic group selected from an azetidyl group, a pyrrolidinyl group, a pyrrolinyl group, an imidazolidinyl group, an imidazolinyl group, a pyrazolidinyl group, a pyrazolinyl group, a pyrrolyl group, an

imidazolyl group, a pyrazolyl group, a dihydropyrazolyl group, a thiazolidinyl group, an oxazolidinyl group, a dihydropyridyl group, a tetrahydropyridyl group, a piperidyl group, a piperazinyl group, a tetrahydropyrimidinyl group, a morpholinyl group, an azacycloheptyl group, a benzimidazolyl group, a benzotriazolyl group, an indolyl group, an isoindolyl group, an indolinyl group, an isoindolinyl group, a 1H-indazolyl group, a purinyl group, a dihydroquinolyl group, a tetrahydroquinolyl group, a dihydroisoquinolyl group, a tetrahydroisoquinolyl group, a dihydropthalazinyl group, a dihydroquinazolinyl group, a dihydrobenzothiazinyl group, a dihydrobenzoxazinyl group, a carbazolyl group, a beta-carbolinyl group, a 5H-dihydro-dibenzazepinyl group and a spiro-heterocyclic group of the formula:



wherein R^A and R^B are the same or different and a hydrogen atom or an alkyl group, and q and r are an integer of 1 or 2.

Among them, preferred examples of the saturated or unsaturated heterocyclic group include a saturated 5- to 7-membered, nitrogen-containing heteromonocyclic group such as a morpholino group, a thiomorpholino group, a piperidino group, a piperazino group or an azacycloheptyl group.

Moreover, the saturated or unsaturated heterocyclic group in R^5 , R^6 , R^8 or R^9 (and the saturated or unsaturated nitrogen-containing heterocyclic group formed by combining R^5 with R^6) may be substituted by one to four group(s) selected from a halogen atom, a hydroxyl group, a cyano group, an oxo group, an alkyl group, an alkyl group substituted by one to three halogen atom(s), an alkyloxyalkyl group, an aminoalkyl group, a cycloalkyl group, an arylalkyl group, an alkyloxy group, an alkyloxy group substituted by one to three halogen atom(s), an acyl group, an amino group optionally substituted by one to two alkyl group(s), an acylamino group, an alkylsulfonyl group, an aminosulfonyl group optionally substituted by one to two alkyl group(s), an aryl group optionally substituted by one to two halogen atom(s) and a saturated or unsaturated 5- to 6-membered, nitrogen-containing heterocyclic group.

Examples of the acyl group in R^4 , R^5 , R^6 , R^8 or R^9 include a group formed by removing a hydroxyl group from a carboxylic acid having the following formula [Ac-I]: $R^X\text{-COOH}$ [Ac-I], namely a group of the formula: $R^X\text{-CO-}$, in which R^X is (a) a hydrogen atom, (b) an alkyl group optionally substituted by one to

three group(s) selected from a halogen atom, a cyano group, an alkylsulfonyl group and a pyridyl group, (c) an alkyloxy group optionally substituted by an aryl group, (d) a cycloalkyl group, (e) an aryl group optionally substituted by a halogen atom, a cyano group, an alkyl group, a trihalogenoalkyl group and an alkyloxy group, (f) an amino group optionally substituted by one to two alkyl group(s) or (g) a saturated or unsaturated heterocyclic group. Concrete examples of such acyl group include (a1) a formyl group, (b1) a C₁₋₆ alkyl-carbonyl group such as an acetyl group, a propionyl group and the like, a trihalogeno-C₁₋₆ alkyl-carbonyl group such as a trifluoroacetyl group and the like, a cyano-C₁₋₆ alkyl-carbonyl group such as cyanoacetyl group and the like, a pyridyl-C₁₋₆ alkyl-carbonyl group such as a pyridylacetyl group and the like, (c1) a C₁₋₆ alkyloxy-carbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, a tert-butoxycarbonyl group and the like, an aryl-C₁₋₆ alkyloxy-carbonyl group such as a benzyloxycarbonyl group, (d1) a C₃₋₈ cycloalkyl-carbonyl group such as a cyclopropylcarbonyl group, a cyclopentylcarbonyl group and the like, (e1) an aryl-carbonyl group such as a benzoyl group and the like, a mono- or di-halogeno-aryl-carbonyl group such as a chlorobenzoyl group, a fluorobenzoyl group, a difluorobenzoyl group and the like, a cyano-aryl-carbonyl group such as a cyanobenzoyl group, a trihalogeno-C₁₋₆ alkyl-aryl-carbonyl group such as a trifluoromethylbenzoyl group and the like, a C₁₋₆ alkyloxy-aryl-carbonyl group such as a methoxybenzoyl group and the like, (f) a carbamoyl group, a N-(C₁₋₆ alkyl)carbamoyl group, or (g1) a furoyl group, a thenoyl group, a bromothenoyl group, a cyanothenoyl group, a pyridylcarbonyl group, a chloropyridylcarbonyl group, a cyanopyridylcarbonyl group, a trifluoromethyl-pyridylcarbonyl group or a pyrazinylcarbonyl group.

In case that E is a group of the formula (ii) in the compound [I] of the present invention, examples of the group (ii) include a group of the following formula:

- (a) $-\text{C}(=\text{O})-\text{N}(\text{R}^5)(\text{R}^6)$,
- (b) $-\text{C}(=\text{O})-\text{Alk}-\text{N}(\text{R}^5)(\text{R}^6)$,
- (c) $-\text{Alk}-\text{C}(=\text{O})-\text{N}(\text{R}^5)(\text{R}^6)$, or
- (d) $-\text{N}(\text{R}^7)-\text{C}(=\text{O})-\text{N}(\text{R}^5)(\text{R}^6)$

wherein Alk is a straight or branched chain C₁₋₆ alkylene group and other symbols are the same as defined above.

Among the compounds [I] of the present invention, examples of preferred compound include a compound of the following Group A to E.

Group A: Compound [I] in which

R¹ and R² are the same or different and (a) a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl

group,

Q is a single bond,

Ring A is a substituted pyrazole ring of the formula (A),

E is a group of the following formula: $-C(=O)O-R^{00}$ (i)

5 R^4 is (a) an amino group optionally substituted by one to two group(s) selected from an alkyl group and an alkylsulfonyl group or (b) an aminosulfonyl group optionally substituted by one to two alkyl group(s).

Among the compounds of Group A, preferred examples include a compound wherein R^1 is a chlorophenyl group or a trifluoro- C_{1-4} alkyl-phenyl group, R^2 is a
10 chlorophenyl group, R^a is a C_{1-4} alkyl group and R^4 is an amino group substituted by one to two group(s) selected from a C_{1-4} alkyl group and a C_{1-4} alkylsulfonyl group or a pharmaceutically acceptable salt thereof.

Group B: Compound [I] in which

15 R^1 and R^2 are the same or different and (a) a phenyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group optionally substituted by one to three halogen atom(s), an amino group optionally substituted by one to two alkyl group(s) and an alkylsulfonyl group or (b) a saturated or
20 unsaturated 5- to 7-membered heterocyclic group optionally substituted by one to three group(s) selected from a halogen atom, an oxo group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group, an alkyloxyalkyl group and an alkyloxyalkyloxy group,

Ring A is a substituted pyrazole ring of the formula (A) or (B),

E is one of the groups of the following formula (a) to (e):

- 25 a) $-C(=O)-N(R^5)(R^6)$,
b) $-C(=O)-Alk-N(R^5)(R^6)$,
c) $-Alk-C(=O)-N(R^5)(R^6)$,
d) $-N(R^7)-C(=O)-Alk-N(R^5)(R^6)$,
e) $-C(=NR^{51})-R^{61}$,

30 R^3 is a hydrogen atom, a cyano group or an alkyloxy group,

R^4 is (a) a hydrogen atom, (b) a cyano group, (c) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom and a hydroxyl group, (d) an alkyloxy group optionally substituted by one to three group(s) selected from a halogen atom, a hydroxyl group, an amino group optionally substituted by one to two
35 alkyl group(s), an alkyloxy group and an alkylsulfonyl group, (e) an alkylthio group, (f) an alkylsulfinyl group, (g) an alkylsulfonyl group or (h) a group of the formula:

-N(R')(R''),

R' and R'' are the same or different and (a) a hydrogen atom, (b) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, an amino group optionally substituted by one to two alkyl group(s) and an alkyloxy group, (c) an acyl group, (d) an alkylsulfonyl group or (e) an aminosulfonyl group optionally substituted by one to two alkyl group(s), or (f) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heteromonocyclic group optionally substituted by a hydroxyl group or an alkyloxy group,

one of R⁵ and R⁶ is a hydrogen atom or an alkyl group and the other is

(1) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, an alkyloxy group, a cycloalkyl group, an alkylthio group, an alkylsulfonyl group, an amino group optionally substituted by one or two alkyl group(s), a morpholinocarbonyl group, a phenyl group optionally substituted by a cyano group and a saturated or unsaturated 5- to 6-membered nitrogen-containing heteromonocyclic group, said heteromonocyclic group being optionally substituted by a group selected from a halogen atom, an alkyl group and a trihalogenoalkyl group;

(2) a cycloalkyl group optionally substituted by a cyano group or an alkyl group;

(3) a group of the formula: -N(R⁸)(R⁹); or

(4) a phenyl group; or

(5) a saturated or unsaturated 4- to 10-membered monocyclic- or bicyclic heterocyclic group optionally substituted by one to four group(s) selected from a halogen atom, a cyano group, a hydroxyl group, an oxo group, an alkyl group optionally substituted by one to three halogen atom(s), a cycloalkyl group, an alkylcarbonyl group, an alkyloxycarbonyl group, an alkylsulfonyl group, an aminosulfonyl group optionally substituted by one or two alkyl group(s), a carbamoyl group optionally substituted by one to two alkyl group(s), an alkyloxycarbonyl group, an alkyloxycarbonylamino group a phenyl group optionally substituted by one to two halogen atom(s) and saturated or unsaturated 5- to 6-membered heteromonocyclic group; or

(6) both of R⁵ and R⁶ combine each other together with the adjacent nitrogen atom to form a saturated or unsaturated 4- to 7-membered nitrogen-containing heterocyclic group optionally substituted by one to two group(s) selected from a halogen atom and an oxo group,

R⁸ is hydrogen atom or an alkyl group,

R⁹ is (a) an alkyl group optionally substituted by one to three group(s) selected

from a halogen atom, a cyano group and a phenyl group; (b) a phenyl group optionally substituted by a group selected from a halogen atom, a cyano group, an alkyl group, a trihalogenoalkyl group, a cycloalkyl group, a trihalogenoalkyloxy group, an alkyloxy group, an alkylthio group and an alkylsulfonyl group; (c) an alkyloxycarbonyl group; or
5 (d) a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by a group selected from a halogen atom, a cyano group, an alkyl group, an alkyloxy group and a trihalogenoalkyl group,

R^7 is a hydrogen atom,

10 R^{51} is an alkyl group or a phenylsulfonyl group optionally substituted by one to two halogen atom(s) and R^{61} is an alkylamino group or an azido group or a pharmaceutically acceptable salt thereof.

Among the compounds of the Group B, examples of more preferred compound include a compound wherein R^1 is (a) a phenyl group optionally substituted by one or two group(s) selected from a halogen atom, a cyano group, a dihalogenoalkyl group, a trihalogenoalkyl group, an alkyloxy group, an alkyloxyalkyl group and di(alkyl)amino
15 group or (b) a saturated or unsaturated 5- to 7-membered heterocyclic group optionally substituted by one to two group(s) selected from an oxo group, an alkyl group, a trihalogenoalkyl group, an alkyloxy group, an alkyloxyalkyl, an alkyloxyalkyloxy group and a di(alkyl)amino group,

20 R^2 is (a) a phenyl group optionally substituted by one or two group(s) selected from a halogen atom and a cyano group or (b) a saturated or unsaturated 5- to 6-membered heterocyclic group optionally substituted by a halogen atom,

R^3 is a hydrogen atom,

25 R^4 is a hydrogen atom, an alkyl group, a dihalogenoalkyl group, a hydroxyalkyl group, a trihalogenoalkyl group, an alkyloxyalkyl group, a hydroxyalkyloxy group, an alkyloxyalkyloxy group, an alkylsulfonylalkyl group or a group of the formula: $-N(R')(R'')$,

one of R' and R'' is a hydrogen atom or an alkyl group and the other is an acyl group or an alkylsulfonyl group,

30 E is one of the groups of the following formula (a), (b) and (e):

(a) $-C(=O)-N(R^5)(R^6)$,

(b) $-C(=O)-Alk-N(R^5)(R^6)$,

(e) $-C(=NR^{51})-R^{61}$,

35 one of R^5 and R^6 is a hydrogen atom or an alkyl group, the other is (a) an alkyl group, (b) a cycloalkyl group, (c) a phenyl group, (d) a saturated or unsaturated 4- to 10-membered mono- or bi-cyclic heterocyclic group optionally substituted by one to

four group(s) selected from a halogen atom, an oxo group, a cyano group, a hydroxyl group, an alkyl group, a trihalogenoalkyl group, an alkyloxy group, an alkyloxyalkyl group, an alkylcarbonyl group, a di(alkyl)carbonyl group, an alkylsulfonyl group, a di(alkyl)aminosulfonyl group, a phenyl group, a halogenophenyl group and a pyridyl group or (e) a group of the formula: $-N(R^8)(R^9)$, or (f) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by one to two group(s) selected from a halogen atom and an oxo group,

R^8 is an alkyl group,

R^9 is (a) an alkyl group, (b) a phenyl group optionally substituted by a halogen atom, (c) an alkyl group optionally substituted by a pyridyl group or (d) a saturated or unsaturated 4- to 6-membered heteromonocyclic group optionally substituted by a group selected from a halogen atom, an alkyl group, a trihalogenoalkyl group and an alkyloxy group,

R^{51} is an alkyl group or a halogenophenyl-sulfonyl group, and R^{61} is an alkylamino group or an azido group.

Among the compounds of the Group B, examples of further preferred compound include a compound wherein R^1 is (a) a phenyl group optionally substituted by a group selected from a chlorine atom, a fluorine atom, a cyano group, a difluoro- C_{1-4} alkyl group and a trifluoro- C_{1-4} alkyl group or (b) a pyridyl group optionally substituted by a trifluoro- C_{1-4} alkyl group,

R^2 is a phenyl group optionally substituted by one to two groups selected from a chlorine atom, a fluorine atom, a bromine atom and a cyano group,

R^3 is a hydrogen atom,

R^4 is a hydrogen atom, a C_{1-4} alkyl group, a difluoro- C_{1-4} alkyl group, a trifluoro- C_{1-4} alkyl group, a C_{1-4} alkyloxy- C_{1-4} alkyl group or a C_{1-4} alkyl-carbonyl-amino group,

E is one of the groups of the following formula (a) and (b):

(a) $-C(=O)-N(R^5)(R^6)$,

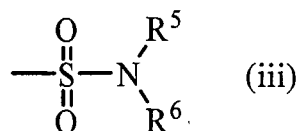
(b) $-C(=O)-Alk-N(R^5)(R^6)$,

one of R^5 and R^6 is a hydrogen atom and the other is a C_{1-4} alkyl group, a pyridyl- C_{1-4} alkyl group, a C_{5-7} cycloalkyl group, a chlorophenyl group, a saturated or unsaturated 4- to 6-membered heteromonocyclic group optionally substituted by one to two group(s) selected from a halogen atom, an oxo group and C_{1-4} alkyloxy- C_{1-4} alkyl group or a group of the formula: $-N(R^8)(R^9)$, or both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered

heteromonocyclic group optionally substituted by one to two oxo group(s),

R^8 is a C_{1-4} alkyl group and R^9 is a C_{1-4} alkyl group, a chlorophenyl group, a pyridyl group or a C_{1-4} alkyloxy-pyridyl group.

Group C: A compound [I] wherein R^1 and R^2 are the same or different and a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group, Q is a single bond, Ring A is a substituted pyrazole ring of the formula (A), R^3 is a hydrogen atom, R^4 is a hydrogen atom or an alkyl group, E is a group of the formula (iii):



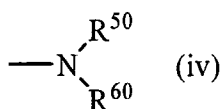
one of R^5 and R^6 is a hydrogen atom or an alkyl group and the other is (a) an alkyl group, (b) a cycloalkyl group or (c) a saturated or unsaturated 5- to 6-membered sulfur- or nitrogen-containing heteromonocyclic group, or (d) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group optionally substituted by one to two oxo group(s) or a pharmaceutically acceptable salt thereof.

Among the compounds of the Group C, examples of more preferred compound include a compound wherein R^1 is a trihalogenoalkyl-phenyl group, R^2 is a halogenophenyl group,

R^4 is an alkyl group,

one of R^5 and R^6 is a hydrogen atom or an alkyl group, the other is (a) an alkyl group, (b) a cycloalkyl group, (c) a saturated or unsaturated 5- to 6-membered sulfur- or nitrogen-containing heteromonocyclic group optionally substituted by one to two oxo group(s), or (d) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by one to two oxo group(s).

Group D: A compound [I] wherein R^1 and R^2 are the same or different and a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group, Q is a single bond, Ring A is a substituted pyrazole ring of the formula (A), R^3 is a hydrogen atom, R^4 is a hydrogen atom or an alkyl group, E is a group of the formula (iv):



one of R^{50} and R^{60} is a hydrogen atom or an alkyl group and the other is an alkyl group

or an acyl group, or both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group optionally substituted by one to two oxo group(s) or a pharmaceutically acceptable salt thereof.

5 Group E: A compound [I] wherein R^1 and R^2 are the same or different and a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group, Q is a single bond, Ring A is a substituted pyrazole ring of the formula (C), R^3 is a hydrogen atom, R^4 is a group of the formula -N(R')(R''), R' and R'' are the same or different and a hydrogen atom or an alkyl group,
10 or both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group or a pharmaceutically acceptable salt thereof.

Among the compounds [I] of the present invention, examples of particularly preferred compound include a compound selected from the group consisting of:

15 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-piperidinocarbamoyl)pyrazolo[1,5-a]-pyrimidine;

 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(N'-methyl-N'-phenylhydrazino)-carbonyl]pyrazolo[1,5-a]pyrimidine;

 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclohexylcarbamoyl)pyrazolo[1,5-a]-
20 pyrimidine;

 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(N',N'-dimethylhydrazino)carbonyl]-pyrazolo[1,5-a]pyrimidine;

 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-pyrrolidinocarbamoyl)pyrazolo[1,5-a]-pyrimidine;

25 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(4-tetrahydropyranyl)carbamoyl]-pyrazolo[1,5-a]pyrimidine;

 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)-carbamoyl]pyrazolo[1,5-a]pyrimidine;

30 (R)-6-(2-chlorophenyl)-7-(4-difluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

 (R)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

35 (S)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[2-(2-pyridyl)ethyl]carbamoyl]-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2-methoxy-pyrazolo[1,5-a]pyrimidine;

5 (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

10 6-(2-bromophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine;

(R, S)-6-(2-bromophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

15 (R)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[N-(3-chlorophenyl)-N-methylamino]-carbamoyl]pyrazolo[1,5-a]pyrimidine;

20 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-[N-methyl-N-(2-pyridyl)amino]-carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-isobutylcarbamoyl)pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

25 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-(N-cyclopentylcarbamoyl)-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-[N-methyl-N-(2-pyridyl)-amino]carbamoyl]pyrazolo[1,5-a]pyrimidine;

30 (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-cyanophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine;

(R,S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

35 6-(2-chlorophenyl)-7-(4-fluorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[N-methyl-N-(2-pyridyl)amino]-
carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)- 6-(2-chlorophenyl)-7-(4-chlorophenyl)- 3-[N-(1,1-dioxo-tetrahydrothiophen-
3-yl]carbamoyl]pyrazolo[1,5-a]pyrimidine;

5 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-ethylcarbamoyl)pyrazolo[1,5-a]-
pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopropylcarbamoyl)-
pyrazolo[1,5-a]pyrimidine;

10 (S)-6-(2-chlorophenyl)-7-(4-chloro-2-fluorophenyl)-3-[N-(1,1-dioxotetrahydro-
thiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-difluoromethylphenyl)-3-[N-(1,1-dioxotetrahydro-
thiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-cyanophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydro-
thiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

15 (S)-6-(2-cyanophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydro-
thiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-methoxypyridin-5-yl)-
hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine;

20 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]-
pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(2-trifluoromethylpyridin-5-yl)-3-(N-cyclopentylcarbamoyl)-
pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydro-
thiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

25 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-
carbonyl]-2-methylpyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydro-
thiophen-3-yl)carbamoyl]-2-trifluoromethylpyrazolo[1,5-a]pyrimidine;

30 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[(N',N'-dimethylhydrazino)-
carbonyl]-2-acetylaminopyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-
carbonyl]-2-acetylaminopyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-
carbonyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine;

35 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]-
-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

5 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-(N-piperidinocarbamoyl)-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxothiacyclobutan-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

10 7-(4-chlorophenyl)-6-(2-cyano-4-fluorophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

7-(4-chlorophenyl)-6-(2-cyanophenyl)-3-(N-piperidinocarbamoyl)-2-methylpyrazolo[1,5-a]pyrimidine;

7-(4-chlorophenyl)-6-(2-cyanophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

15 (S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(2-methoxymethyl-1-pyrrolidinyl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(4-fluoropiperidino)carbamoyl]pyrazolo[1,5-a]pyrimidine;

20 (R)-7-(4-chloro-2-fluorophenyl)-6-(2-cyanophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-ethoxypyridin-5-yl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

25 (S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

30 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

7-(4-chloro-2-fluorophenyl)-6-(2-cyanophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[2-(1,1-dioxothiomorpholino)acetyl]-2-methylpyrazolo[1,5-a]pyrimidine;

35 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-(4-fluoropiperidino)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine; and

6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(tetrahydrothiophen-3-yl)-carbamoyl] pyrazolo[1,5-a]pyrimidine
or a pharmaceutically acceptable salt thereof.

When the compound [I] of the present invention has an asymmetric carbon atom(s) in its molecule, it may exist in the form of a stereoisomer thereof (diastereoisomers, optical isomers) owing to said asymmetric carbon atom(s) thereof, and the present invention also includes one of the stereoisomers and a mixture thereof.

A compound [I] of the present invention shows a potent antagonistic activity against CB1 receptor and may be useful as an agent for prevention and/or treatment of a CB1 receptor-mediated diseases such as psychosis including schizophrenia, anxiety disorders, stress, depression, epilepsy, neurodegenerative disorders, spinocerebellar disorders, cognitive disorders, craniocerebral trauma, panic attack, peripheral neuropathy, glaucoma, migraine, Parkinson's disease, Alzheimer's disease, Huntington's disease, Raynaud's syndrome, tremor, obsessive-compulsive disorders, amnesia, geriatric dementia, thymic disorders, Tourette's syndrome, tardive dyskinesia, bipolar disorders, cancer, drug-induced dyskinesia, dystonia, septic shock, hemorrhagic shock, hypotension, insomnia, immunological diseases including inflammations, multiple sclerosis, emesis, diarrhea, asthma, appetite disorders such as bulimarexia, anorexia and the like, obesity, non insulin-dependent diabetes mellitus (NIDDM), memory disorders, urinary disorders, cardiovascular disorders, infertility disorders, infections, demyelination-related diseases, neuroinflammation, viral encephalitis, cerebral vascular incidents, cirrhosis of the liver or gastrointestinal disorders including intestinal transit disorders.

In addition, a compound [I] of the present invention may be useful as an agent for withdrawal from a chronic treatment, alcohol dependence or drug abuse (e.g., an opioid, barbiturate, marijuana, cocaine, anphetamine, phencyclidine, a hallucinogenic agent, a benzodiazepine compound and the like).

Furthermore, a compound [I] of the present invention may be useful as an agent for enhancing analgesic activity of analgesic or narcotic drugs and the like; or an agent for smoking cessation (withdrawal from smoking or nicotine dependence).

Moreover, a compound [I] of the present invention can be useful for treatment of a condition relating to metabolic diseases including obesity, diabetes, impaired glucose tolerance, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, cardiovascular disease, coronary heart disease, depression, anxiety, drug addiction, and substance addiction.

Besides, the compound [I] of the present invention can be advantageous as a medicine due to its low toxicity.

The compound [I] of the present invention can be clinically used either in the free form or in the form of a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt of the compound [I] includes a salt with an inorganic acid such as hydrochloride, sulfate, phosphate or hydrobromide, or a salt with an organic acid such as acetate, fumarate, oxalate, citrate, methanesulfonate, benzenesulfonate, tosylate or maleate. Besides, when the compound [I] of the present invention has a carboxyl group(s) and the like in its molecule, examples of the pharmaceutically acceptable salt include, salts with a base such as alkaline metal (e.g., sodium salt, potassium salt) or alkaline earth metal (e.g., calcium salt).

The compound [I] or a pharmaceutically acceptable salt thereof includes either intramolecular salt or an additive thereof, and solvates or hydrates thereof.

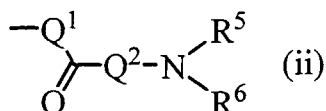
The present compound [I] or a pharmaceutically acceptable salt thereof can be either orally or parenterally, and can be formulated into a conventional pharmaceutical preparation such as tablets, granules, capsules, powders, injections or inhalants.

The dose of the compound [I] of the present invention or a pharmaceutically acceptable salt thereof may vary in accordance with the administration routes, and the ages, weights and conditions of the patients. For example, when administered in an injection preparation, it is usually in the range of about 0.0001 to 1.0 mg/kg/day, preferably in the range of about 0.001 to 0.1 mg/kg/day. When administered in an oral preparation, it is usually in the range of about 0.001 to 100 mg/kg/day, preferably in the range of 0.01 to 10 mg/kg/day.

A compound [I] of the present invention may also be useful as adjunctive, add-on or supplementary therapy for the treatment of the above-mentioned diseases/disorders. Said adjunctive, add-on or supplementary therapy means the concomitant or sequential administration of a compound of the present invention to a patient who has already received administration of, who is receiving administration of, or who will receive administration of one or more additional therapeutic agents for the treatment of the indicated conditions, for example, one or more known anti-depressant, anti-psychotics or anxiolytic agents.

The compound [I] of the present invention can be prepared by the following methods but should not be construed to be limited thereto.

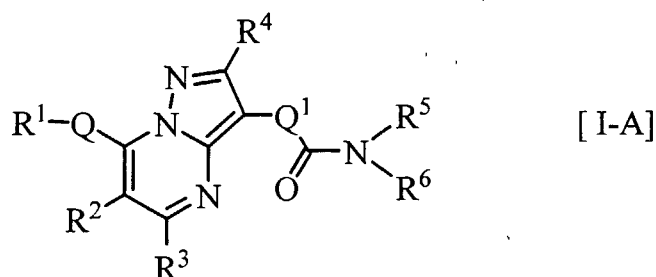
(1) Among the compound of the present invention, a compound [I] in which Ring A is a substituted pyrazole ring of the formula (A) and E is a group of the following formula (ii):



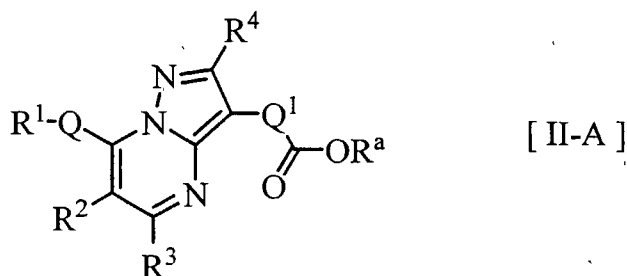
can be prepared in accordance with, for example, the following methods A to D.

(Method A)

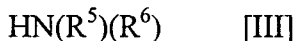
A compound [I] in which Q² is a single bond, namely having the following
5 formula [I-A]:



wherein the symbols are the same as defined above can be prepared by reacting a compound of the formula [II-A]:



10 wherein R^a is a hydrogen atom, an alkyl group or a benzyl group and the other symbols are the same as defined above with an amine compound of the following formula [III]:



wherein the symbols are the same as defined above or a salt thereof.

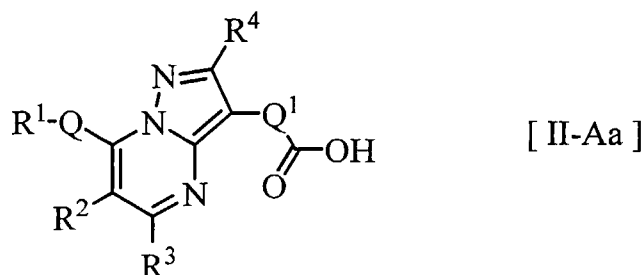
When R^a is a hydrogen atom, the above-mentioned reaction can be carried out
15 in a solvent in the presence of a condensing agent, and in the presence or absence of an activating agent and a base. Examples of the solvent include any solvent which does not disturb the reaction, such as methylene chloride, chloroform, dimethylformamide, dimethylacetamide, tetrahydrofuran, dioxane, toluene, benzene, 1,2-dichloroethane, 1-methylpyrrolidinone, 1,2-dimethoxyethane and the like. The condensing agent may
20 be dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (WSC HCl), diphenylphosphoryl azide (DPPA), carbonyldiimidazole (CDI), diethylcyanophosphonate (DEPC), diisopropylcarbodiimide (DIPCI), benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP), carbonylditriazole, N-cyclohexylcarbodiimide-N'-propyloxymethylpolystyrene (PS-

carbodiimide), N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), bromotrispyrrolidinophosphonium hexafluorophosphate (PyBroP), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), chloro-1,1,3,3-tetramethyluronium hexachloroantimonate (ACTU) and the like. Examples of the activating agent include 1-hydroxybenzotriazole (HOBt), 1-hydroxysuccinimide (HOSu), dimethylaminopyridine (DMAP), 1-hydroxy-7-azabenzotriazole (HOAt), hydroxyphthalimide (HOPht), pentafluorophenol (Pfp-OH), 1-hydroxybenzotriazole-6-sulfonamidomethylpolystyrene (PS-HOBt) and the like. The base includes, for example, pyridine, triethylamine, diisopropylethylamine, 4-methylmorpholine, 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) and the like.

In the above-mentioned process, the compound [II-A] can be used in an amount of 0.33 to 1.5 moles, preferably 0.5 to 1.2 moles per one mole of the compound [III]. The condensing agent can be used in an amount of 1.0 to 3.0 moles, preferably 1.0 to 1.2 moles per one mole of the compound [II-A] or [III]. The base can be used in an amount of 1.0 to 3.0 moles, preferably 1.0 to 1.2 moles per one mole of the compound [II-A] or [III]. The activating agent can be used in an amount of 0.01 to 2.0 moles, preferably 0.1 to 1.0 moles per one mole of the compound [II-A] or [III]. The reaction can be carried out at 0 to 150°C, preferably 20 to 80°C.

When R^a in the compound [II-A] is hydrogen atom, the compound [I-A] can be prepared by converting the compound [II-A] to a corresponding reactive derivative (e.g., an acid halide, a mixed acid anhydride) and reacting such reactive derivative with the compound [III] in the presence of the base in or without the solvent.

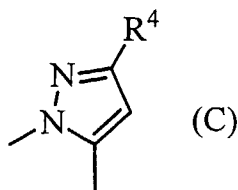
When R^a in the compound [II-A] is an alkyl group or a benzyl group, the present process A can be also carried out by converting the ester compound to a corresponding carboxylic acid compound of the following formula [II-Aa]:



wherein the symbols are the same as defined above by a conventional manner such as hydrolysis, acidolysis with hydrochloric acid, formic acid, trifluoroacetic acid and the like or hydrogenation and then reacting the carboxylic acid compound [II-Aa] with the

compound [III] in the same manner as described above.

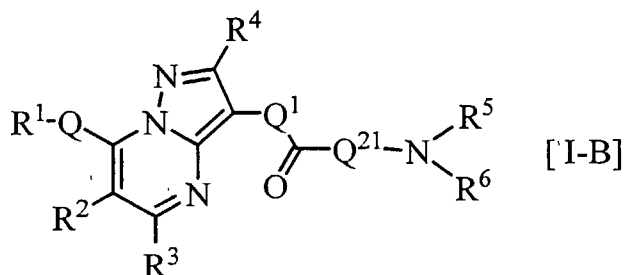
Meanwhile, a compound [I] in which Ring A is a group of the following formula (C):



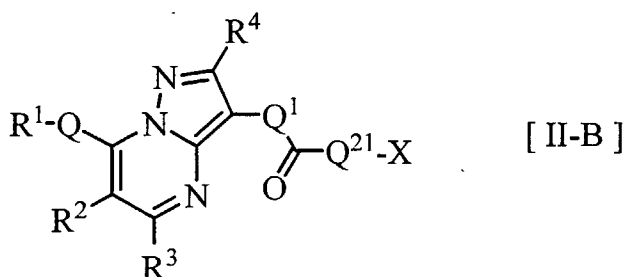
5 wherein the symbol is the same as defined above, can be obtained as a bi-product in the reaction of the compound [II-Aa] and the compound [III].

(Method B)

A compound [I] in which Q^2 is an alkylene group, namely a compound of the following formula [I-B]:



10 wherein Q^{21} is an alkylene group and the other symbols are the same as defined above can be prepared by reacting a compound of the following formula [II-B]:



15 wherein X is a halogen atom and the other symbols are the same as defined above with the compound [III] or a salt thereof.

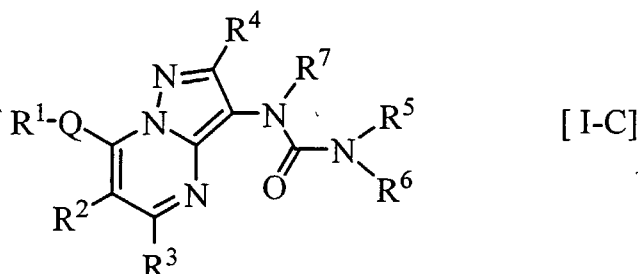
The reaction of the compound [II-B] with the compound [III] can be carried out in a solvent in the presence or absence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as methylene chloride, chloroform, dimethylformamide, dimethylacetamide, dimethylsulfoxide, tetrahydrofuran, dioxane, toluene, benzene, 1,2-dichloroethane, 1-methyl-pyrrolidinone, 1,2-dimethoxyethane and the like. The base includes, for example, sodium hydride, potassium carbonate, pyridine, triethylamine, diisopropylethylamine, 4-methylmorpholine, 1,8-diazabicyclo[5,4,0]-7-

undecene (DBU) and the like.

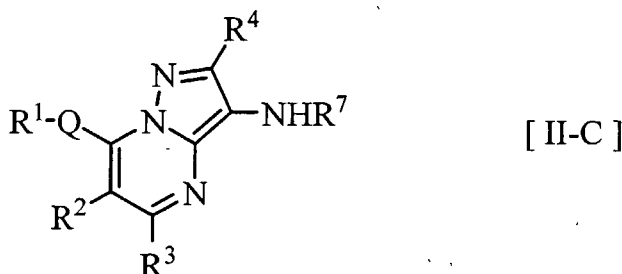
In the above-mentioned process, the compound [III] can be used in an amount of 1.0 to 20 moles, preferably 1.0 to 3.0 moles per one mole of the compound [II-B]. The base can be used in an amount of 0 to 20 moles, preferably 1.0 to 3.0 moles per one mole of the compound [III] or [II-B]. The reaction can be carried out at -20 to 100°C, preferably 0 to 50°C.

(Method C)

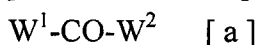
Among the compounds [I] of the present invention, a compound in which Q^1 is a group of the formula: $-N(R^7)-$ and Q^2 is a single bond, namely, a compound of the following formula [I-C]:



wherein the symbols are the same as defined above can be prepared by reacting a compound of the following formula [II-C]:



wherein the symbols are the same as defined above with the compound [III] in the presence of a compound of the formula [a]:

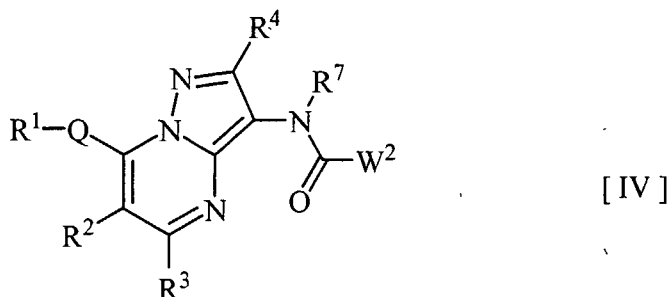


wherein W^1 and W^2 are the same or different and a removing group.

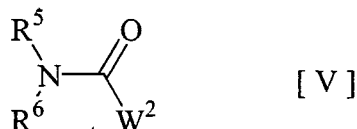
In the compound [a], examples of W^1 and W^2 include an imidazolyl group, a halogen atom, a phenoxy group and the like. Concrete examples of such compound include 1,1'-carbonyldiimidazole, phosgene, triphosgene and the like. Examples of the solvent include any solvent which does not disturb the reaction, such as acetonitrile, dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran, dioxane, benzene, toluene, dimethylformamide and the like. The compound [III] can be used in an amount of 1.0 to 5.0 moles, preferably 1.0 to 1.2 moles per one mole of the compound [II-C]. The compound [a] can be used in an amount of 0.33 to 5.0 moles, preferably 1.0 to 2.0

moles per one mole of the compound [II-C] or [III]. The reaction can be carried out at -20 to 100°C, preferably 0 to 50°C.

Moreover, the compound [I-C] can be also prepared by reacting the compound [II-C] with the compound [a] to obtain a compound of the formula [IV]:



wherein the symbols are the same as defined above and reacting the product or a reactive derivative thereof with the compound [III], or reacting the compound [III] with the compound [a] to obtain a compound of the formula [V]:



wherein the symbols are the same as defined above and reacting the product or a reactive derivative thereof with the compound [II-C].

Examples of the reactive derivative of the compound [IV] or [V] include those in which W² is converted to a group of the formula:



and such reactive derivative can be obtained by reacting a compound [IV] or [V] in which W² is an imidazolyl group with methyl iodide.

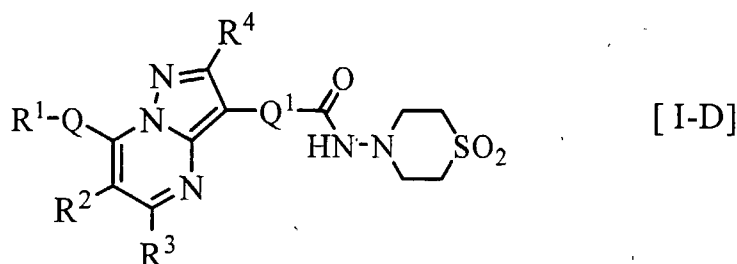
The reaction of the compound [II-C] or the compound [III] with the compound [a] can be carried in a solvent. Examples of the solvent include any solvent which does not disturb the reaction, such as acetonitrile, dichloromethane, 1,2-dichloroethane, benzene, toluene, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, dimethylformamide and the like. The compound [a] can be used in an amount of 1.0 to 3.0 moles, preferably 1.0 to 2.0 moles per one mole of the compound [II-C] or compound [III]. The present reaction can be carried out at 0 to 150°C, preferably at 20 to 80°C.

The reactive derivative of the compound [IV] or [V] can be prepared by, for example, treating such compound [IV] or [V] with an alkyl halide such as methyl iodide in a solvent. The present reaction can be carried out at 0 to 150°C, preferably at 20 to 80°C.

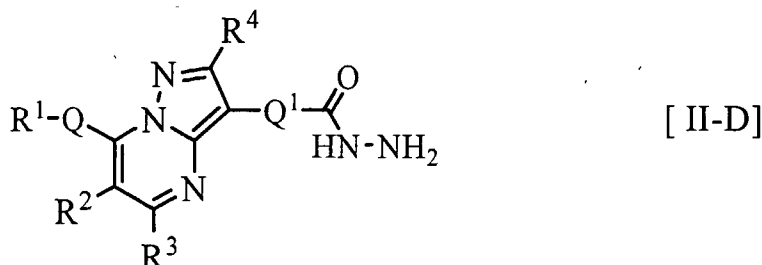
The reaction of the compound [IV] (or its reactive derivative) with the compound [III] or the reaction of the compound [V] (or its reactive derivative) with the compound [II-C] can be conducted in a solvent in the presence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as methylene chloride, chloroform, dimethylformamide, dimethylacetamide, dimethylsulfoxide, tetrahydrofuran, dioxane, toluene, benzene, 1,2-dichloroethane, 1-methylpyrrolidinone, 1,2-dimethoxyethane and the like. Examples of the base include pyridine, triethylamine, diisopropylethylamine, 4-methylmorpholine, 1,8-diazabicyclo[5,4,0]undecene and the like. Such reactive derivative can be used in an amount of 0.33 to 3.0 moles, preferably 0.5 to 1.2 moles per one mole of the compound [III] or [II-C]. The present reaction can be conducted at -30 to 100°C, preferably at 0 to 50°C.

(Method D)

A compound of the following formula [I-D]:



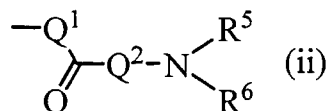
wherein the symbols are the same as defined above can be prepared by a compound of the following formula [II-D]:



wherein the symbols are the same as defined above with divinylsulfone in an appropriate solvent in the presence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as ethanol, isopropyl alcohol, dioxane, toluene, N,N-dimethylformamide, dimethylsulfoxide and the like. Examples of the base include triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine and the like. The divinylsulfone can be used in an amount of 1.0 to 3.0 moles, preferably 1.2 to 1.5 moles per one mole of the compound [II-D]. The present reaction can be conducted at 60 to 200°C, preferably at 80 to 150°C.

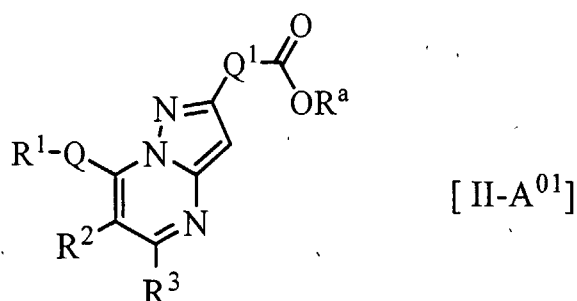
(2) Among the compound of the present invention, a compound [I] in which

Ring A is a substituted pyrazole ring of the formula (B) and E is a group of the following formula (ii):



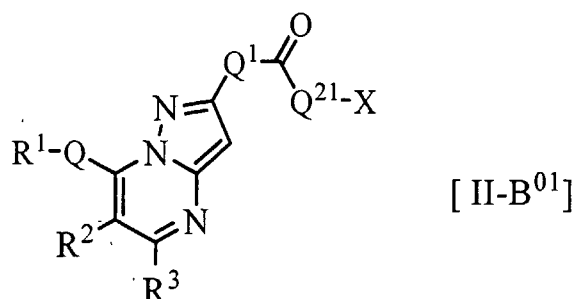
can be prepared in accordance with, for example,

5 a) treating a compound [II-A⁰¹]:



wherein the symbols are the same as define above in the same manner as described in Method A mentioned above, or

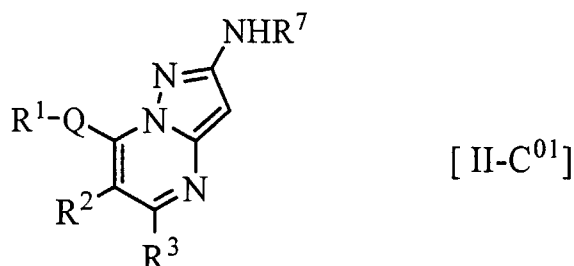
b) treating a compound [II-B⁰¹]:



10

wherein the symbols are the same as define above in the same manner as described in Method B mentioned above, or

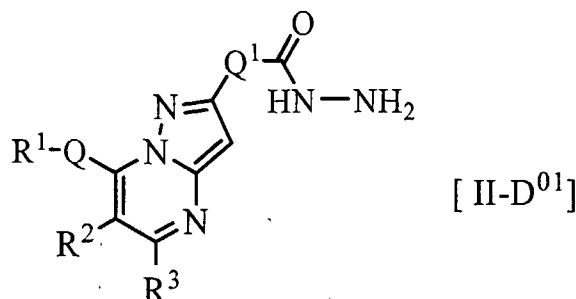
c) treating a compound [II-C⁰¹]:



15

wherein the symbols are the same as define above in the same manner as described in Method C mentioned above, or

d) treating a compound [II-D⁰¹]:



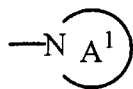
wherein the symbols are the same as define above in the same manner as described in Method D mentioned above.

Besides, a compound [I] in which R⁵⁰ and R⁶⁰ in the group of the formula (iv) is an alkyl group can be prepared by, for example, reacting a compound [II-C] or a compound [II-C⁰¹] in which R⁷ is a hydrogen atom (compound [II-Ca] or compound [II-Ca⁰¹]) with an aldehyde compound of the formula [a-1]:



wherein R^y is a hydrogen atom or an alkyl group in the presence of a reducing agent in the presence or absence of a base (Method E). Examples of the reducing agent include sodium triacetoxyborohydride, sodium borohydride, sodium cyanoborohydride and the like. Examples of the reducing agent include triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine and the like. The compound [a-1] can be used in an amount of 1.0 to 3.0 moles, preferably 1.2 to 1.5 moles per one mole of the compound [II-Ca]. The base can be used in an amount of 1.2 to 5.0 moles, preferably 1.5 to 2.0 moles per one mole of the compound [II-Ca]. The present reaction can be conducted at -50 to 100°C, preferably at -10 to 40°C.

Moreover, a compound [I] in which R⁵⁰ and R⁶⁰ in the group of the formula (iv) is a cyclic group of the following formula:



in which Ring A¹ is a 5- to 7-membered aliphatic nitrogen-containing heteromonocyclic group optionally substituted by an oxo group, can be prepared by, for example,

a) reacting a compound [II-C] or a compound [II-C⁰¹] in which R⁷ is a hydrogen atom (a compound [II-Ca] or a compound [II-Ca⁰¹]) with a compound of the following formula:



wherein X⁰¹ and X⁰² are a halogen atom and Alk¹ is a C₄₋₆ alkylene group in a solvent such as acetonitrile and the like in the presence of a base such as potassium carbonate

and in the presence or absence of an additive such as sodium iodide and the like, or

b) reacting a compound [II-Ca] or a compound [II-Ca⁰¹] with divinylsulfone. The reaction of the compound [II-Ca] or the compound [II-Ca⁰¹] with divinylsulfone can be conducted in the same manner as described in Method D mentioned above.

(3) Among the compounds [I] of the present invention, a compound in which Ring A is a substituted pyrazole ring of the formula (A) or (B) and E is group of the formula (v) can be prepared by, for example, reacting the compound [II-Aa] or the compound [II-Da] with an alkylamine such as methylamine and the like in a solvent such as methanol and the like in the presence of a condensing agent such as water-soluble carbodiimide and the like and an activating agent such as 1-hydroxybenzotriazole and the like, and then treating the resultant product with Lawsson's reagent, and further reacting the reaction product with a sulfoneazide compound of the following formula:



wherein Ar is an optionally substituted aryl group in a solvent such as pyridine and the like. Meanwhile, examples of the substituent in Ar include a halogen atom.

The objective compound [I] of the present invention can be also prepared by, for example, intramolecularly converting the substituent(s) in R¹, R² and the like of such a compound [I] as obtained above to the other desired substituent(s). The intramolecular conversion processes can be selected according to the kinds of the objective substituents, and may be carried out, for example, in the following methods (a) to (h).

Method (a): A compound [I] having a cyano group (or a group containing a cyano group) as a substituent can be obtained by reacting a corresponding compound [I] having a halogen atom or an alkylsulfonyl group (or a halogen- or alkylsulfonyl group-containing group) as a substituent with cyanide compound (e.g., zinc cyanide, copper cyanide, trimethylsilyl cyanide, potassium cyanide and the like) in the presence or absence of a catalyst, a base and an additive. Examples of the base include triethylamine, N-methylpiperidine, diisopropylethylamine and the like. Examples of said catalyst include a palladium catalyst such as palladium acetate, tris(dibenzylideneacetone)dipalladium, *trans*-dichlorobis-(tricyclohexylphosphine)-palladium, tetrakis-(triphenylphosphine)palladium and the like or a nickel catalyst such as dibromobis(triphenylphosphine)nickel and the like. Examples of the additive include a phosphine compound such as 1,1'-bis-(diphenylphosphino)ferrocene, racemic 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl, 2-(di-tert-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, 2-dicyclohexylphosphino-2'-(N,N'-dimethyl-

amino)biphenyl, tri-tert-butylphosphine and the like. Examples of the additive include a phosphine compound such as triphenylphosphine, 1,1'-bis(diphenylphosphino)-ferrocene, racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2-(di-tert-butylphosphino)biphenyl, 2-(dicyclohexylphosphino)biphenyl, 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl or tri-tert-butylphosphine and the like.

Method (b): A compound [I] having an alkylamino group or a cycloalkylamino group as a substituent (or an alkylamino- or cycloalkylamino-containing group) can be obtained by reacting a corresponding compound [I] having a halogen atom with a mono- or di-alkylamine or a cycloalkylamine in an appropriate solvent in the presence of a catalyst, an additive and a base. Examples of the catalyst may be the palladium compounds or copper compounds used in Method (a). Examples of the additive may be the phosphine compounds used in Method (a). Examples of the base include potassium acetate, potassium carbonate, cesium carbonate, potassium tert-butoxide and the like.

Method (c): A compound [I] having an alkyloxy group as a substituent (or an alkyloxy-containing group) can be obtained by, for example, (i) reacting a corresponding compound [I] having a hydroxyl group as a substituent (or a hydroxy-containing group) with an alkyl halide in a solvent, or (ii) reacting a corresponding compound [I] having a hydroxyl group as a substituent (or a hydroxy-containing group) with an alkanol in a solvent in the presence of a base (e.g., potassium carbonate, cesium carbonate, sodium hydride and the like) or an activating agent (e.g., diethyl azodicarboxylate and the like) and in the presence of a tri-substituted phosphine or (iii) reacting a corresponding compound [I] having an alkylsulfonyl group (or an alkylsulfonyl-containing group) with an alkali metal alkoxide in an appropriate solvent.

Method (d): A compound [I] having an alkylsulfinyl group or an alkylsulfonyl group as a substituent (or an alkylsulfinyl- or alkylsulfonyl-containing group) can be obtained by reacting a corresponding compound [I] having an alkylthio group as a substituent (or an alkylthio-containing group) with an oxidizing agent such as 3-chloroperbenzoic acid in an appropriate solvent.

Method (e): A compound [I] having an acylamino group such as an alkylcarbonylamino group as a substituent (or an acylamino-containing group) can be obtained by reacting a corresponding compound [I] having an amino group (or an amino-containing group) with a carboxylic acid compound of the following formula:



wherein R^x is an alkyl group optionally substituted by an aryl group or an optionally

substituted aryl group or a reactive derivative thereof (e.g., a corresponding acid anhydride or a corresponding acid halide). The present reaction can be carried out in a solvent in the presence of a base such as triethylamine and the like or a condensing agent such as water-soluble carbodiimide and in the presence or absence of an activating agent such as 1-hydroxybenzotriazole. Besides, such acyl group can be removed, in accordance with the kind of said acyl group, by a conventional manner such as acid treatment or catalytic hydrogenation.

Method (f): A compound [I] having a carbamoyl group as a substituent (or a carbamoyl-containing group) can be obtained by reacting a corresponding compound [I] having an alkyloxycarbonyl group as a substituent (or an alkyloxycarbonyl-containing group) with an aqueous ammonia in an appropriate solvent.

Method (g): A compound [I] having an alkylcarbamoylamino group as a substituent (or an alkylcarbamoylamino-containing group) can be obtained by reacting a corresponding compound [I] having an amino group as a substituent (or an amino-containing group) with an alkyl isocyanate in an appropriate solvent.

Method (h): A compound [I] having a group of the formula:



wherein Ring A¹ is a 5- to 7-membered nitrogen-containing aliphatic heterocyclic group can be obtained by reacting a corresponding compound [I] having an amino group with a compound of the formula:



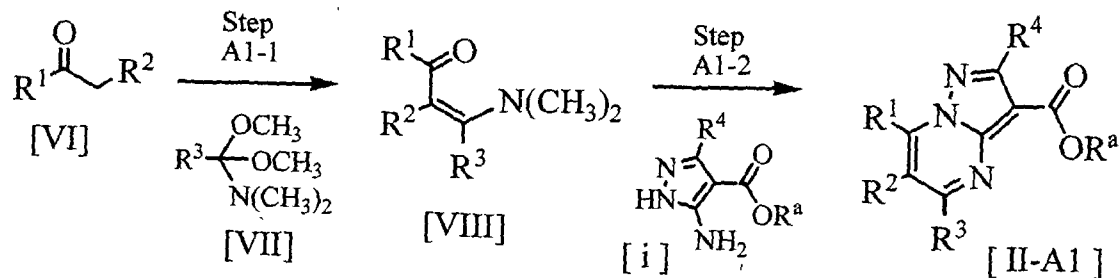
wherein the symbols are the same as defined above in a solvent such as acetonitrile in the presence of a base such as potassium carbonate and in the presence or absence of an additive such as sodium iodide. Examples of such nitrogen-containing aliphatic heterocyclic group include 1-pyrrolidinyl group, 1-piperidyl group and the like.

If necessary, the compounds [I] of the present invention obtained in the aforementioned Processes can be converted to a pharmaceutically acceptable salt thereof by a conventional manner.

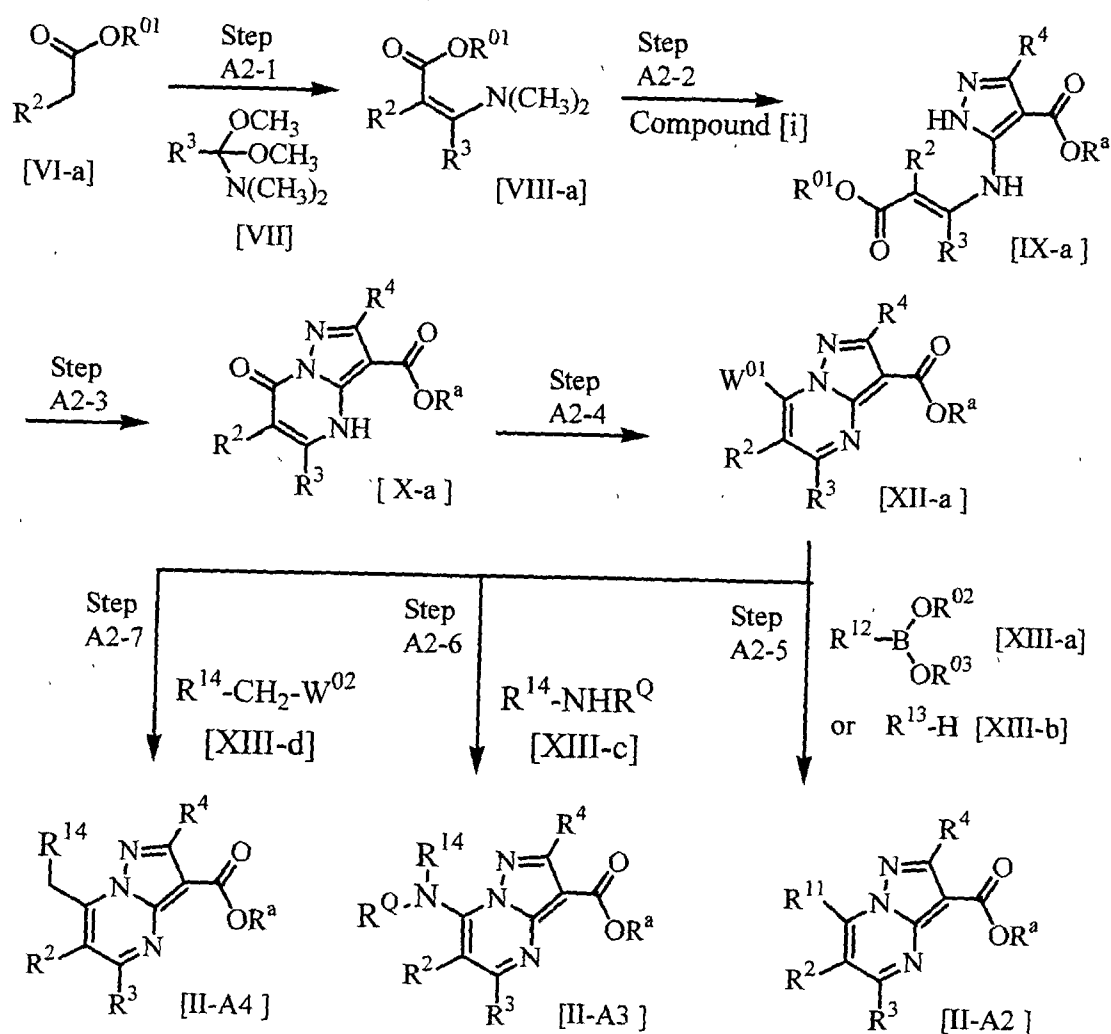
[Preparation of Intermediate compound]

i) For example, a compound [II-A] in which Q¹ is a single bond or an alkylene group can be prepared in a manner as described in the following reaction scheme A1 to A4.

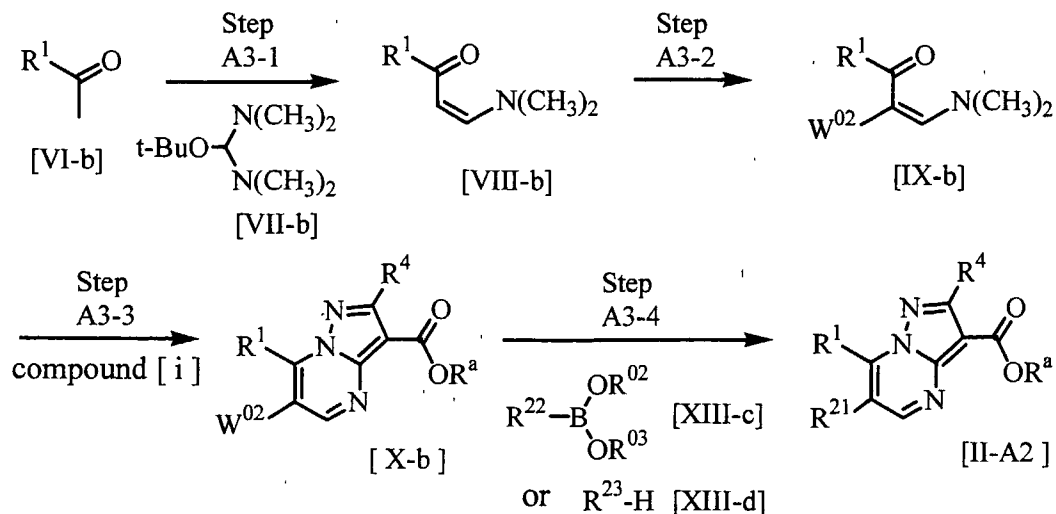
(Reaction Scheme A1)



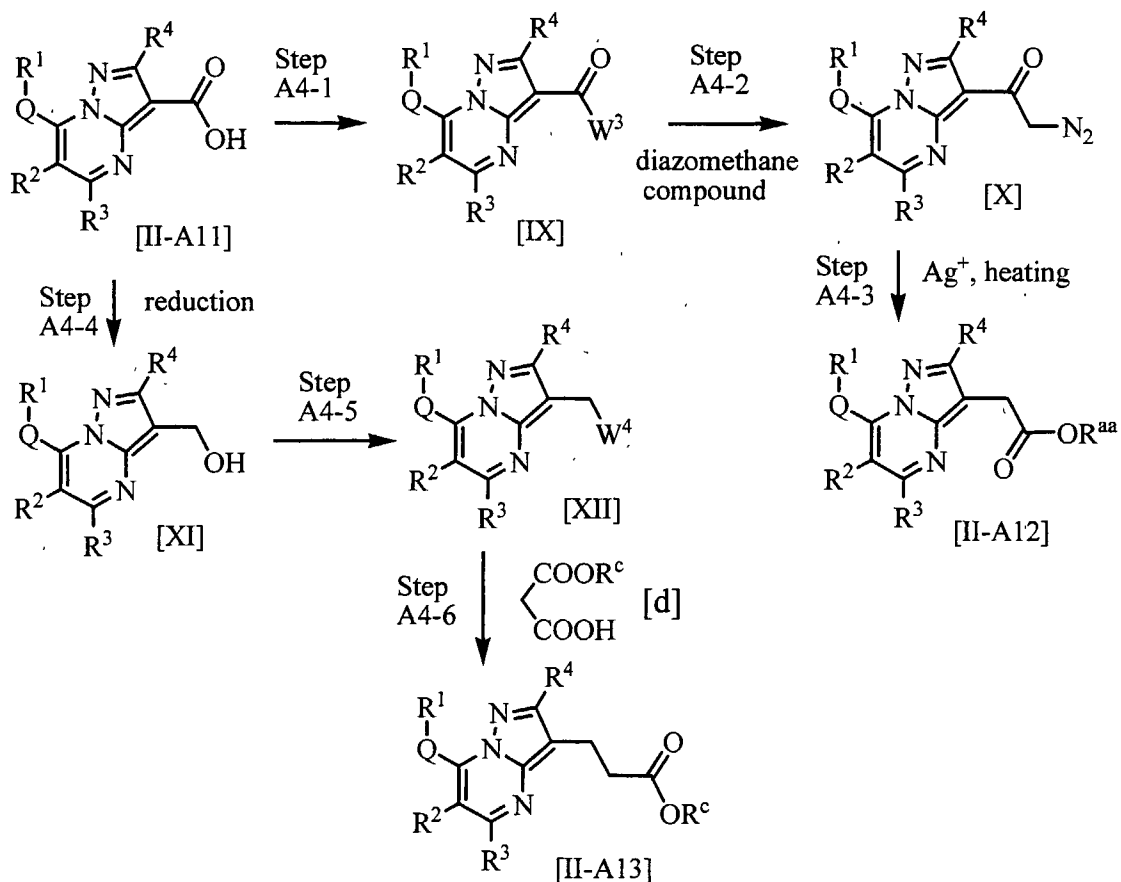
(Reaction Scheme A2)



(Reaction Scheme A3)



(Reaction Scheme A4)



5

In the above-mentioned reaction scheme A1 to A2, R^{aa} is hydrogen atom or an alkyl group, R^c is an alkyl group, W³ and W⁴ are a reactive residue, R⁰¹ is an alkyl group, R¹¹ and R²¹ are an optionally substituted aryl group, an optionally substituted heteroaryl group or an optionally substituted nitrogen-containing aliphatic heterocyclic

group, R^{12} and R^{22} are an optionally substituted aryl group or an optionally substituted heteroaryl group, R^{13} and R^{23} are an optionally substituted nitrogen-containing aliphatic heterocyclic group, R^{14} is an optionally substituted aryl group or an optionally substituted heteroaryl group, R^{02} and R^{03} are the same or different and a hydrogen atom or an alkyl group or both of them combine each other to form an alkylene group, t-Bu is a tert-butyl group, W^{01} and W^{02} are a halogen atom and the other symbols are the same as defined above.

Examples of the aryl group in R^{11} , R^{12} , R^{21} or R^{22} include a 6- to 10-membered mono- or bicyclic aryl group such as a phenyl group or a naphthyl group. Among them, phenyl group is preferable.

Examples of the heteroaryl group in R^{11} , R^{12} , R^{21} or R^{22} include a 5- to 10-membered mono- or bicyclic heteroaryl group having one to three heteroatom(s) selected from oxygen atom, sulfur atom and nitrogen atom. Among them, a furyl group, a thienyl group or a pyridyl group is preferable.

Examples of the nitrogen-containing aliphatic heterocyclic group in R^{11} , R^{12} , R^{21} or R^{22} include a 5- to 10-membered mono- or bicyclic aliphatic heterocyclic group further having one or two heteroatom(s) selected from oxygen atom, sulfur atom and nitrogen atom. Among them, a furyl group, a 1-pyrrolidinyl group, 1-piperidyl group, a morpholino group or a thiomorpholino group is preferable.

Each of the aryl group, heteroaryl group or nitrogen-containing aliphatic heterocyclic group in R^{11} , R^{12} , R^{21} or R^{22} may be substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group optionally substituted by one to three halogen atom(s) and an alkylsulfonyl group.

The alkylene group formed by combining R^{02} with R^{03} may be a straight or branched chain C_{2-6} alkylene group such as ethylene group, trimethylene group or 1,1,2,2-tetramethylethylene group. Example of the substituent of said alkylene group include an alkyl group such as methyl group.

Each reaction described in the above-mentioned scheme A1 to A4 can be carried out, for example, in accordance with the manner as illustrated bellow.

Step A1-1:

The reaction of the compound [VI] with the compound [VII] can be carried out in an appropriate solvent under heating. Examples of the solvent include any solvent which does not disturb the reaction, such as dimethylformamide, dimethylacetamide, dioxane, 1,2-dichloroethane, toluene, xylene and the like. The compound [VII] can be used in an amount of 1.0 to 10 moles, preferably 1.0 to 3.0 moles per one mole of the

compound [VI]. The reaction can be carried out at 50 to 200°C, preferably 80 to 150°C.

Step A1-2:

The reaction of the compound [VIII] with the compound [i] can be conducted in an appropriate solvent in the presence or absence of a base. Examples of the base include piperidine, morpholine, N-methylpiperazine, diethylamine and the like. Examples of the solvent include any solvent which does not disturb the reaction, such as acetic acid, methanol, ethanol, isopropanol, ethyleneglycol and the like. The compound [i] can be used in an amount of 0.5 to 2.0 moles, preferably 0.8 to 1.2 moles per one mole of the compound [VIII]. The base can be used in an amount of 0.01 to 2.0 moles, preferably 0.1 to 1.0 moles per one mole of the compound [VIII]. The reaction can be carried out at 50 to 150°C, preferably 70 to 100°C.

Besides, the present reaction can be carried out in a solvent in the presence or absence of an acid. Examples of the acid include hydrobromic acid, hydrochloric acid, acetic acid and the like. Examples of the solvent include any solvent which does not disturb the reaction, such as acetic acid, methanol, ethanol, isopropanol, ethyleneglycol and the like. The compound [i] can be used in an amount of 0.5 to 2.0 moles, preferably 0.8 to 1.2 moles per one mole of the compound [VIII]. The acid can be used in an amount of 0.1 to 3.0 moles, preferably 0.3 to 1.0 moles per one mole of the compound [VIII]. The reaction can be carried out at 0 to 150°C, preferably 60 to 100°C.

Step A2-1:

The reaction of the compound [VI-a] with the compound [VII] can be carried out in the same manner as described in Step A1-1.

Step A2-2:

The reaction of compound [VIII-a] with compound [i] can be carried out in the same manner as described in Step A1-2. Besides, the compound [X-a] can be obtained without conducting the next step A2-3, when the present reaction is conducted in the presence of acetic acid .

Step A2-3:

The intramolecular cyclization of the compound [IX-a] can be carried out in a solvent in the presence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as ethanol, acetonitrile, chloroform, tetrahydrofuran, dioxane, toluene, N,N-dimethylformamide and the like. Examples of the base include sodium carbonate, cesium carbonate, triethylamine, diisopropylethylamine, dimethylaminopyridine and the like. The base can be used in an amount of 0.1 to 10.0

moles, preferably 1.2 to 3.0 moles per one mole of the compound [IX-a]. The reaction can be carried out at 30 to 150°C, preferably 60 to 100°C.

Step A2-4:

The conversion of the compound [X-a] to the compound [XII-a] can be carried out in a solvent in the presence of a halogenating agent and in the presence or absence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as acetonitrile, chloroform, tetrahydrofuran, dioxane, toluene, N,N-dimethylformamide and the like. Examples of the halogenating agent include phosphorus oxychloride, thionyl chloride, phosphorus pentachloride, oxalyl chloride and the like. Examples of the base include N,N-dimethylaniline, diisopropylethylamine, N-methylmorpholine and the like. The halogenating agent can be used in an amount of 1.1 to 5.0 moles, preferably 1.2 to 1.5 moles per one mole of the compound [X-a]. The base can be used in an amount of 1.2 to 10.0 moles, preferably 1.5 to 2.0 moles per one mole of the compound [X-a]. The reaction can be carried out at 50 to 200°C, preferably 80 to 150°C.

Step A2-5:

(1) The reaction of the compound [XII-a] with the boronate compound [XIII-a] can be carried out in a solvent in the presence of a catalyst and a base. Examples of the boronate compound [XIII-a] include a compound in which R^{02} and R^{03} are a hydrogen atom or an alkyl group such as methyl group, ethyl group, isopropyl group and the like, or both R^{02} and R^{03} combine each other to form an alkylene group such as ethylene group, propylene group, 1,1,2,2-tetramethylethylene group and the like. Among them, a preferable example includes a compound [XIII-a] in which R^{02} and R^{03} are hydrogen atom or a corresponding boroxin compound of the formula: $[R^{12}-BO]_3$. Examples of the solvent include any solvent which does not disturb the reaction, such as dioxane, toluene, dimethoxyethane, ethanol, N, N-dimethylformamide, tetrahydrofuran, water and the like. Examples of the catalyst include a palladium catalyst such as tetrakis(triphenylphosphine)palladium (0), palladium acetate (II), bis(dibenzylideneacetone)palladium (0), bis(triphenylphosphine)palladium (II) dichloride, bis(tri-o-tolylphosphine)palladium (II) dichloride, bis(tricyclohexylphosphine)palladium (II) dichloride or [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloride, a nickel catalyst such as 1,3-bis(diphenylphosphino)propane nickel (II) dichloride or bis(triphenylphosphine)nickel (II) dichloride and the like. Examples of the base include potassium phosphate, sodium carbonate, cesium carbonate, sodium hydrogencarbonate, potassium fluoride, triethylamine, lithium chloride and the like. The compound [XIII-a] can be used in an amount of 1.0 to 5.0 moles, preferably 1.1 to

2.0 moles per one mole of the compound [XII-a]. The catalyst can be used in an amount of 0.001 to 0.5 moles, preferably 0.01 to 0.05 moles per one mole of the compound [XII-a]. The base can be used in an amount of 1.0 to 10.0 moles, preferably 2.0 to 5.0 moles per one mole of the compound [XII-a]. The reaction can be carried out at 20 to 150°C, preferably 60 to 120°C.

(2) The reaction of the compound [XII-a] with the nitrogen-containing heterocyclic compound [XIII-b] can be carried out in a solvent in the presence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as N, N-dimethylformamide, toluene, dioxane, tetrahydrofuran and the like. Examples of the base include potassium carbonate, sodium carbonate, cesium carbonate, sodium hydrogencarbonate, potassium fluoride, triethylamine, diisopropylethylamine, dimethylaminopyridine and the like. The compound [XIII-b] can be used in an amount of 0.8 to 5.0 moles, preferably 1.0 to 1.5 moles per one mole of the compound [XII-a]. The base can be used in an amount of 1.0 to 10.0 moles, preferably 2.0 to 5.0 moles per one mole of the compound [XII-a]. The reaction can be carried out at 80 to 200°C, preferably 120 to 180°C.

Step A2-6:

The reaction of the compound [XII-a] and the compound [XIII-c] can be carried out in a solvent in the presence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as N, N-dimethylformamide, dimethylsulfoxide, dimethoxyethane, tetrahydrofuran and the like. Examples of the base include sodium hydride, potassium hydride, sodium ethoxide, potassium tert-butoxide and the like. The compound [XIII-c] can be used in an amount of 0.5 to 5.0 moles, preferably 1.0 to 3.0 moles per one mole of the compound [XII-a]. The base can be used in an amount of 0.5 to 10.0 moles, preferably 1.2 to 6.0 moles per one mole of the compound [XII-a]. The reaction can be carried out at 40 to 200°C, preferably 60 to 120°C.

Step A2-7:

The reaction of the compound [XII-a] and the compound [XIII-d] can be carried out in a solvent in the presence of a catalyst and zinc. Examples of the solvent include any solvent which does not disturb the reaction, such as dimethoxyethane, tetrahydrofuran, N, N-dimethylformamide and the like. Examples of the catalyst include a palladium catalyst such as bis(triphenylphosphine)palladium (II) dichloride, tetrakis(triphenylphosphine)palladium (0), palladium acetate (II), bis(dibenzylideneacetone)palladium (0), bis(tri-o-tolylphosphine)palladium (II) dichloride, bis(tricyclohexylphosphine)palladium (II) dichloride or [1,1'-bis(diphenylphosphino)-

ferrocene]palladium (II) dichloride and the like. The compound [XIII-d] can be used in an amount of 0.5 to 5.0 moles, preferably 1.0 to 3.0 moles per one mole of the compound [XII-a]. The catalyst can be used in an amount of 0.001 to 1.0 moles, preferably 0.01 to 0.3 moles per one mole of the compound [XII-a]. Zinc can be used in an amount of 1.0 to 5.0 moles, preferably 1.5 to 3.0 moles per one mole of the compound [XII-a]. The reaction can be carried out at 40 to 200°C, preferably 60 to 120°C.

Step A3-1:

The reaction of the compound [VI-b] with the compound [VII-b] can be carried out in a solvent or without any solvent. Examples of the solvent include any solvent which does not disturb the reaction, such as dimethylformamide, toluene, dioxane, tetrahydrofuran, dimethoxyethane and the like. The compound [VII-b] can be used in an amount of 0.5 to 5.0 moles, preferably 0.9 to 1.5 moles per one mole of the compound [VI-b]. The reaction can be carried out at 0 to 150°C, preferably 50 to 80°C.

Step A3-2:

The halogenation of the compound [VIII-b] can be carried out in a solvent in the presence of a halogenating agent and in the presence or absence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as methylene chloride, carbon tetrachloride, chloroform, acetic acid, tetrahydrofuran and the like. Examples of the halogenating agent include bromine, N-bromosuccinimide, N-chlorosuccinimide and the like. Examples of the base include triethylamine, diisopropylethylamine, potassium carbonate, sodium carbonate and the like. The halogenating agent can be used in an amount of 0.5 to 10.0 moles, preferably 1.0 to 3.0 moles per one mole of the compound [VIII-b]. The reaction can be carried out at -40 to 100°C, preferably -5 to 20°C.

Step A3-3:

The reaction of the compound [IX-b] with the compound [i] can be carried out in the same manner as described in Step A1-2.

Step A3-4:

The reaction of the compound [X-b] with the boronate compound [XIII-c] or the nitrogen-containing heterocyclic compound [XIII-d] can be carried out in the same manner as described in Step A2-5 (1) or (2), respectively.

Step A4-1:

The conversion of the compound [II-A11] to a corresponding reactive derivative (compound [IX]) can be carried out in a conventional manner. Examples of

such reactive derivative include a corresponding acid halide (a compound [IX] in which W^3 is a halogen atom) or a corresponding mixed acid anhydride (a compound [IX] in which W^3 is an alkyloxycarbonyloxy group and the like). The corresponding acid halide can be prepared by, for example, reacting the compound [II-A11] with a halogenating agent (e.g., thionyl chloride, phosphorus oxychloride, phosphorus pentachloride, oxalyl chloride and the like) in or without a solvent in the presence or absence of a catalytic amount of dimethylformamide. Examples of the solvent include any solvent which does not disturb the reaction, such as methylene chloride, chloroform, tetrahydrofuran, benzene, toluene and the like. The present reaction can be conducted at -20 to 150°C, preferably 0 to 120°C. Besides, the corresponding mixed acid anhydride can be prepared by, for example, reacting the compound [II-A11] with an alky chloroformate (e.g., ethyl chloroformate and the like) in a solvent in the presence of a base (e.g., triethylamine, diisopropylethylamine and the like). Examples of the solvent include any solvent which does not disturb the reaction, such as methylene chloride, chloroform, tetrahydrofuran, benzene, toluene and the like. The present reaction can be conducted at -60 to 100°C, preferably -40 to 80°C.

Step A4-2:

The conversion of the compound [IX] to the compound [X] can be carried out in a solvent in the presence of a diazomethane compound (e.g., diazomethane, trimethylsilyl diazomethane and the like). Examples of the solvent include any solvent which does not disturb the reaction, such as diethylether, dioxane, benzene, toluene and the like. The diazomethane compound can be used in an amount of 1.0 to 10 moles, preferably 1.0 to 3.0 moles per one mole of the compound [IX]. The reaction can be carried out at -50 to 80°C, preferably -10 to 50°C.

Step A4-3:

The conversion of the compound [X] to the compound [II-A12] can be carried out in a solvent in the presence or absence of a silver salt under heating. Examples of the solvent include any solvent which does not disturb the reaction, such as water, an alkanol (e.g., methanol, ethanol) and the like. Examples of the silver salt include silver oxide, silver benzoate and the like. The silver salt can be used in an amount of 1.0 to 20 moles, preferably 1.0 to 5.0 moles per one mole of the compound [X]. The reaction can be carried out at 50 to 200°C, preferably 80 to 150°C.

Step A4-4:

The reaction to obtain the compound [XI] by reducing the compound [II-A11] can be carried out in a solvent in the presence of a reducing agent (e.g., lithium aluminum hydride and the like). Examples of the solvent include any solvent which

does not disturb the reaction, such as diethylether, tetrahydrofuran and the like. The reducing agent can be used in an amount of 0.25 to 20 moles, preferably 2.0 to 5.0 moles per one mole of the compound [II-A11]. The reaction can be carried out at -50 to 100°C, preferably -10 to 40°C.

5 Meanwhile, the compound [XI] can be also prepared by reducing a compound [II-A1] in which R^a is an alkyl group. The present reaction can be conducted in a solvent in the presence of a reducing agent such as sodium borohydride and the like. Examples of the solvent include any solvent which does not disturb the reaction, such as a mixture of tetrahydrofuran and methanol and the like. The reducing agent can be
10 used in an amount of 1.0 to 20 moles, preferably 2.0 to 5.0 moles per one mole of the compound [II-A1]. The reaction can be carried out at 30 to 100°C, preferably 50 to 80°C.

Step A4-5:

The conversion of the compound [XI] to a corresponding reactive derivative
15 (compound [XII]) can be carried out in a conventional manner. For example, a compound [XII] in which W⁴ is a halogen atom or an alkylsulfonyloxy group can be prepared by treating the compound [XI] with a thionyl halide such as thionyl chloride or an alkylsulfonylhalide such as methanesulfonylchloride, respectively.

Step A4-6:

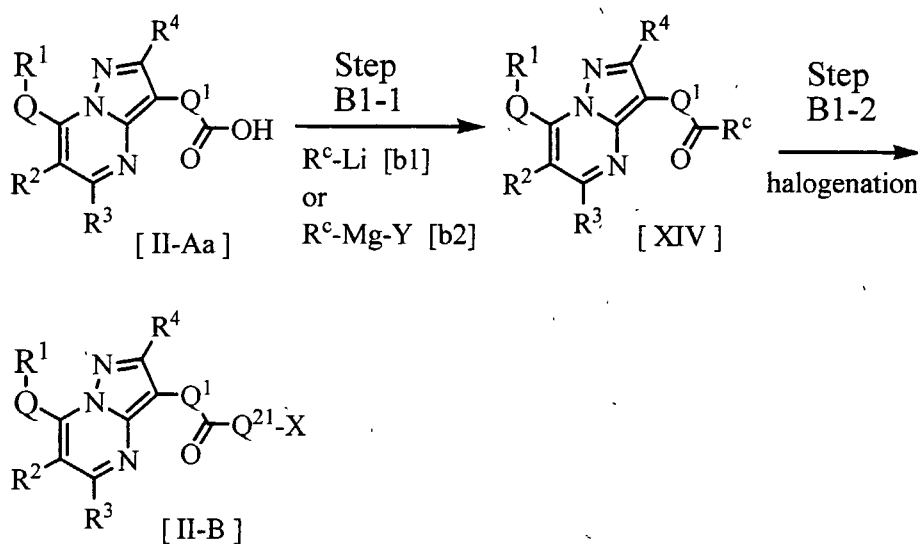
20 The reaction of the compound [XII] with the compound [d] or a salt thereof can be carried out in a solvent in the presence of a base. Examples of the salt of the compound [d] include a metal salt such as potassium salt. Examples of the solvent include any solvent which does not disturb the reaction, such as diethylether, tetrahydrofuran, benzene, dimethylformamide, dimethylacetamide, methanol, ethanol
25 and the like. Examples of the base include sodium hydride, potassium hydride, sodium methoxide, sodium ethoxide, lithium diisopropylamide, lithium hexamethyldisilazane and the like. The compound [d] or a salt thereof can be used in an amount of 1.0 to 10.0 moles, preferably 1.5 to 3.0 moles per one mole of the compound [XII]. The base can be used in an amount of 1.0 to 10.0 moles, preferably 1.5 to 3.0 moles per
30 one mole of the compound [XII]. The reaction can be carried out at -20 to 200°C, preferably 20 to 100°C.

A compound [II-A] in which Q¹ is an alkylene group having 3 or more carbon atoms can be obtained by, for example, converting an objective compound obtained in the above Step A4-3 (or Step A4-6) to a corresponding carboxylic acid compound by
35 deesterification, if necessary, and then subjecting such carboxylic acid compound to a serial reaction process of Step A4-1, A4-2 and A4-3 (or Step A4-4, A4-5 and A4-6),

repeatedly in desired times.

Besides, a compound [II-A] in which Q^1 is a group of the formula: $-N(R^7)-$ can be obtained by, for example, subjecting the compound [II-Ae] or the compound [II-Af] (cf., Reaction Step C1-4 described bellow) to a conventional deesterification reaction.

- 5 ii) The compound [II-B] can be prepared, for example, in the manner as described bellow (Reaction Scheme B1) by using a compound [II-Aa] or a corresponding amide compound (e.g., a corresponding dimethylamide, a corresponding N-alkyl-N-alkyloxyamide compound and the like).
(Reaction Scheme B1)



In the above scheme B1, R^c is an alkyl group, Y is a halogen atom and the other symbols are the same as defined above.

Each reaction described in Scheme B1 can be carried out, for example, in accordance with a manner as illustrated bellow.

Step B1-1:

The reaction of the compound [II-Aa] or a corresponding amide compound with the compound [b1] or compound [b2] can be carried out in a solvent. Examples of the solvent include any solvent which does not disturb the reaction, such as diethylether, tetrahydrofuran, dioxane, dimethoxyethane, benzene, toluene and the like.

The compound [b1] or compound [b2] can be used in an amount of 1.0 to 3.0 moles, preferably 1.0 to 2.2 moles per one mole of the compound [II-Aa] or a corresponding amide compound. The reaction can be carried out at -78 to 50°C , preferably -40 to 30°C .

Step B1-2:

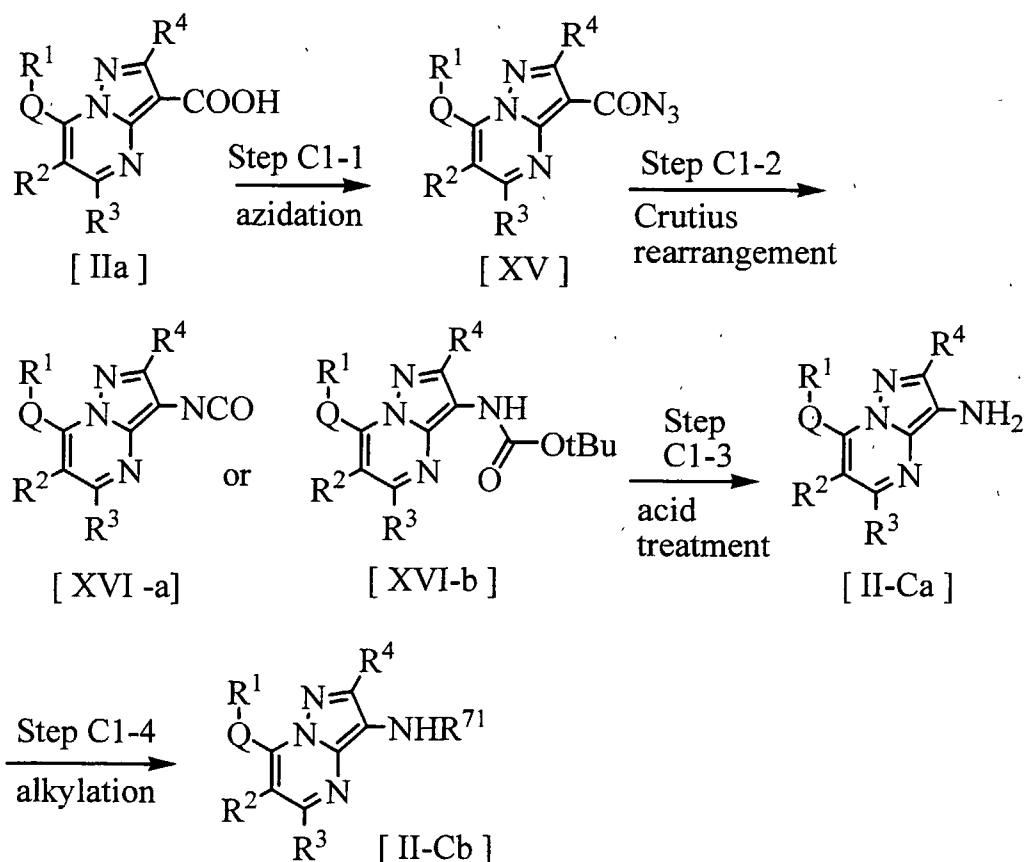
The halogenation of the compound [XIV] can be carried out in a solvent.

Examples of the halogenating agent include bromine, N-bromosuccinimide, bis(dimethylacetamide)dibromobromate hydride and the like. Examples of the solvent include any solvent which does not disturb the reaction, such as diethylether, dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like.

5 The halogenating agent can be used in an amount of 1.0 to 3.0 moles, preferably 1.0 to 2.0 moles per one mole of the compound [XIV]. The reaction can be carried out at -10 to 50°C, preferably 0 to 30°C.

iii) The compound [II-C] can be prepared, for example, by using a compound [II-Aa] in which Q¹ is a single bond (compound [IIa]) and in a manner as described in the following Reaction Scheme C1.

(Reaction Scheme C1)



In the above Reaction Scheme, R⁷¹ is an alkyl group, and tBu is a tert-butyl group and the other symbols are the same as defined above.

Each reaction described in Scheme C1 can be carried out, for example, in accordance with a manner as illustrated bellow.

Step C1-1:

The reaction of the compound [IIa] with an azidating agent can be carried out

in a solvent in the presence or absence of a base. Examples of the solvent include any solvent which does not disturb the reaction, such as acetone, benzene, toluene, tetrahydrofuran, diethylether and the like. Examples of the azidating agent include diphenyl phosphorylazide, sodium azide and the like. Examples of the base include
5 pyridine, triethylamine, diisopropylethylamine, 4-methylmorpholine, 1,8-diazabicyclo-5,4,0]undecene (DBU) and the like. The azidating agent can be used in an amount of 1.1 to 5.0 moles, preferably 1.2 to 1.5 moles per one mole of the compound [IIa]. The base can be used in an amount of 1.2 to 10.0 moles, preferably 1.5 to 3.0 moles per one mole of the compound [IIa]. The reaction can be carried out at -30 to 50°C, preferably
10 -10 to 10°C.

Step C1-2:

The preparation of the compound [XVI-a] by Crutius rearrangement reaction can be carried out in a solvent under heating. Examples of the solvent include any solvent which does not disturb the reaction, such as benzene, toluene, dioxane,
15 chloroform and the like. The reaction can be carried out at 40 to 200°C, preferably 60 to 120°C. Besides, the compound [XVI-b] can be obtained by carrying out the present reaction in tert-buthanol.

Step C1-3:

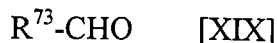
The treatment of the compound [XVI-a] or [XVI-b] with an acid can be carried
20 out in or without a solvent. Examples of the solvent include water, ethyl acetate, tetrahydrofuran, dioxane, methylene chloride, chloroform, toluene and the like. Examples of the acid include a strong acid such as sulfuric acid, hydrochloric acid, nitric acid, trifluoroacetic acid, hydrobromic acid and the like. The acid can be used in an amount of 1.0 to 50.0 moles, preferably 5.0 to 10.0 moles per one mole of the
25 compound [XVI-a] or [XVI-b]. The reaction can be carried out at -20 to 200°C, preferably 20 to 120°C.

Step C1-4:

The alkylation of the compound [II-Ca] can be carried out in a solvent by, for example, 1) in the presence of a base (e.g., sodium hydride, potassium carbonate,
30 pyridine, triethylamine, diisopropylethylamine, 4-methylmorpholine, 1,8-diazabicyclo-[5,4,0]undecene and the like) and an alkylhalide of the formula [XVIII]:



wherein R^{72} is an alkyl group and X^4 is a halogen atom; or 2) in the presence of a reducing agent (e.g., lithium aluminum hydride, sodium borohydride, sodium
35 cyanoborohydride, sodium triacetoxyborohydride and the like), an acid (e.g., acetic acid, formic acid and the like) and an aldehyde compound [XIX]:



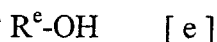
wherein R^{73} is an alkyl group; or 3) in the presence of an activating agent (e.g., diethyl azodicarboxylate and the like), a tri-substituted phosphine (e.g., triphenylphosphine, tributylphosphine and the like) and an alkanol compound of the formula [XX]:



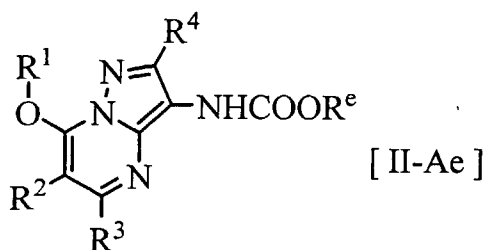
wherein R^{74} is an alkyl group. Examples of the solvent include methylene chloride, chloroform, dimethylformamide, dimethylacetamide, dimethylsulfoxide, tetrahydrofuran, dioxane, toluene, benzene, 1,2-dichloroethane, 1-methylpyrrolidinone, 1,2-dimethoxyethane and the like. The reaction can be carried out at -20 to 100°C , preferably 0 to 40°C .

Meanwhile, if required, an appropriate protecting group (e.g., an alkyloxycarbonyl group such as tert-butoxycarbonyl group, an arylalkyloxycarbonyl group such as benzyloxycarbonyl group and the like) may be introduced to 3-amino group in the compound [II-Ca] prior to the alkylation thereof. Such protecting group can be introduced or removed by a conventional manner depending on the kind of said protecting group.

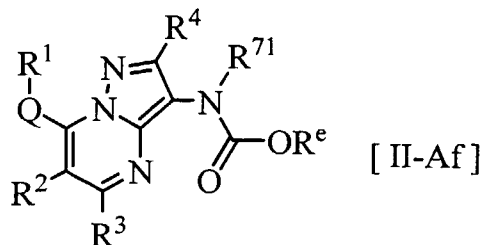
The compound [II-Cb] can be also prepared by conducting the above Crutius rearrangement reaction in an alkanol of the formula [e]:



wherein R^e is tert-butyl group or benzyl group to obtain a compound of the following formula [II-Ae]:



and reacting such compound [II-Ae] with the alkylhalide compound [XVIII] mentioned above or the alkanol compound [XX] to give a compound [II-Af]:



wherein the symbols are the same as defined above, and then removing the acyl group

represented by the group of the formula: $R^e\text{OCO}-$. The removal of said acyl group can be conducted by (1) treating the product [II-Af] with an acid such as hydrochloric acid, trifluoroacetic acid, hydrobromic acid and the like; or (2) heating such product at about 150°C; or (3) subjecting such product to catalytic hydrogenation.

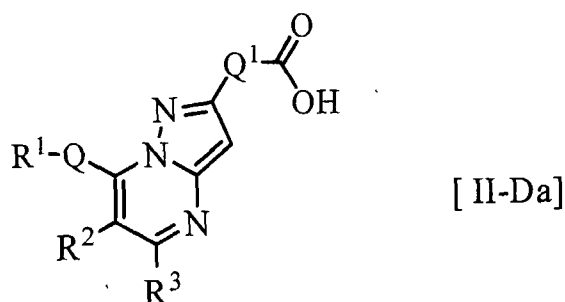
iv) The compound [II-D] can be prepared by reacting the compound [II-Aa] with a hydrazine compound of the following formula [c]:



wherein Z is an acyl group or a salt thereof in accordance with the same manner as described in Method A mentioned above, and then removing the acyl group (Z) from the reaction product in a conventional manner.

The intermediate compound [II-A⁰¹], [II-B⁰¹] or [II-C⁰¹] can be prepared by, for example, treating the corresponding starting compound having a desired substituent at 2-position of the pyrazolo[1,5-a]pyrimidine moiety in the same manner as illustrated in Reaction scheme A1, B1 or C1.

Furthermore, the compound [II-D⁰¹] can be prepared by, for example, reacting a compound of the following formula [II-Da]:



wherein the symbols are the same as defined above with a hydrazine compound [c] in the same manner as described in Method A, and then removing the acyl group (Z) by a conventional method.

Among the above-mentioned intermediates, each of the compound [i], the compound [VI], the compound [VI-a], the compound [VI-b], the compound [VII], the compound [XIII-a], the compound [XIII-b], the compound [XIII-c] and the compound [XIII-d] is a known compound or a compound obtainable from a known compound by using a conventional process in synthetic chemistry.

Throughout the present description and claims, the “halogen atom” means fluorine, chlorine, iodine or bromine atom. The “alkyl group” means a straight or branched chain alkyl group having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. The “cycloalkyl group” means a cycloalkyl group having 3 to 8 carbon atoms,

preferably 5 to 7 carbon atoms. The "alkylene group" means a straight or branched chain alkylene group having 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms.

EXAMPLES

The compounds of the present invention are illustrated in more detail by the following Examples but should not be construed to be limited thereto.

Example 1

To a suspension of 3-carboxyl-6-(2-chlorophenyl)-7-(4-chlorophenyl)-pyrazolo[1,5-a]pyrimidine (200 mg, compound obtained in Reference Example 1) in toluene (1.5 mL) was added thionyl chloride (114 μ L), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo and the resultant crude product was dissolved in methylene chloride (1.5 mL). To a solution was added triethylamine (217 μ L) and 1-aminopiperidine (56 μ L) and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: chloroform/methanol = 100/0 to 19/5 and hexane/ethyl acetate = 67/3 to 2/3) to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-piperidinocarbamoyl)-pyrazolo[1,5-a]pyrimidine (162 mg; yield: 67 %) as a powder.

MS(APCI)m/z; 466/468[M+H]⁺

Example 2

To a suspension of the compound obtained in Reference Example 1 (200 mg,) in toluene (2 mL) was added oxalyl chloride (136 μ L), and the mixture was stirred at 60°C for 1 hours. The reaction mixture was concentrated in vacuo and the resultant crude product was dissolved in methylene chloride (2 mL). To a solution was added triethylamine (217 μ L) and 1-methyl-1-phenylhydrazine (61 μ L) and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added water and methylene chloride and the organic layer was washed with saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 4/1 to 7/3) to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(N'-methyl-N'-phenylhydrazino)carbonyl]pyrazolo[1,5-a]pyrimidine (204 mg; yield: 80 %) as a powder.

MS(APCI)m/z; 488/490[M+H]⁺

Example 3

To a solution of the compound obtained in Reference Example 1 (57.6 mg) and 1-aminopyrrolidine HCl (24.5 mg) in chloroform (1.0 mL containing amylene) was added 1-hydroxybenzotriazole monohydrate (0.23 mL, 0.5M chloroform solution

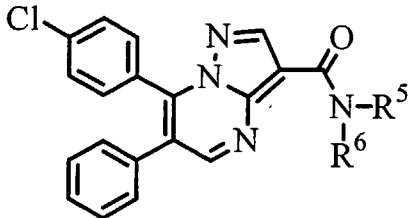
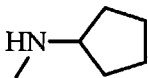
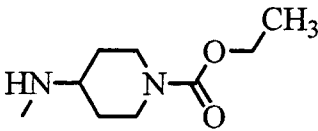
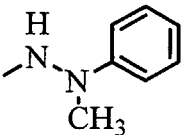
containing amylene), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (0.23 mL, 0.5M N, N-dimethylformamide solution) and triethylamine (63 μ L) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution (2 mL), water (2 mL) and chloroform (5 mL) and the mixture was stirred vigorously for 15 minutes. After separating the organic layer, the aqueous layer was extracted with chloroform (3 mL). The combined organic layer was washed successively with an aqueous saturated sodium hydrogencarbonate solution (3 mL) and saturated brine (3 mL) and concentrated in vacuo. The resultant crude product was purified by liquid chromatograph-mass spectrometer (LCMS) (column; XTerra MS C18, solvent; 10 mM ammonium carbonate/methanol = 40/60 to 10/90). The eluted fraction was concentrated and the residue was dissolved in tert-buthanol and lyophilized to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-pyrrolidinocarbamoyl)pyrazolo[1,5-a]pyrimidine (47.2 mg; yield: 70 %) as a powder.

MS(APCI)m/z; 452 $[M+H]^+$

Examples 4 to 27

The corresponding starting materials were treated in the same manner as described in either one of Examples 1 to 3 to obtain the compounds as shown in the following Table 1.

Table 1 (No. 1)

		
Ex. Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
4		powder MS(ESI):417 $[M+H]^+$
5		powder MS(ESI):504 $[M+H]^+$
6		powder MS(ESI):454 $[M+H]^+$

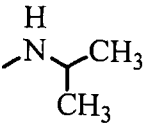
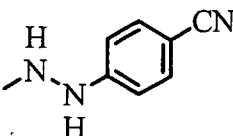
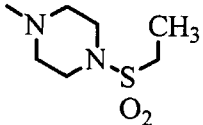
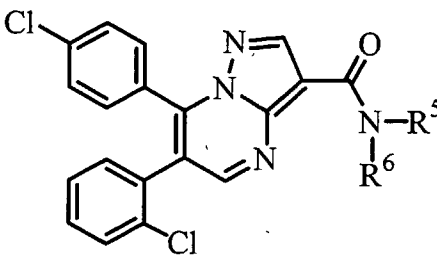
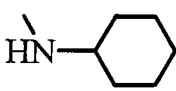
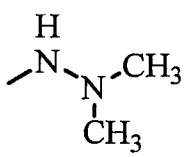
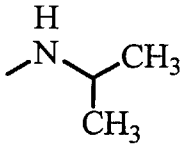
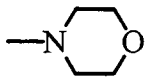
7		powder MS(ESI):391[M+H] ⁺
8		powder MS(APCI):465/467[M+H] ⁺
9		powder MS(APCI):510/512[M+H] ⁺

Table 1 (No. 2)

		
Ex. Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
10		powder MS(ESI):465.07[M] ⁺
11		powder MS(ESI):426.07[M] ⁺
12		powder MS(ESI):425.06[M] ⁺
13		powder MS(ESI):453.09[M] ⁺

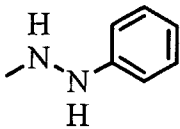
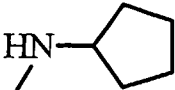
14		powder MS(ESI):474.01[M] ⁺
15		powder MS(ESI):451.07[M] ⁺

Table 1 (No. 3)

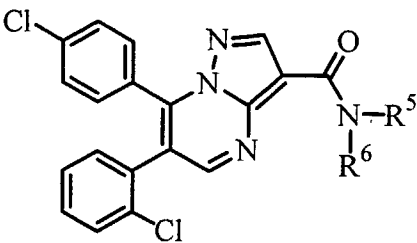
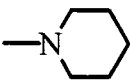
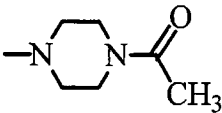
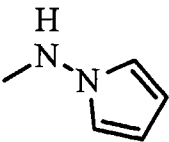
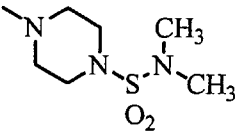
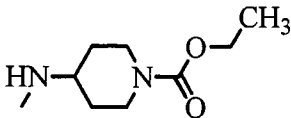
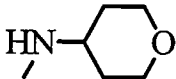
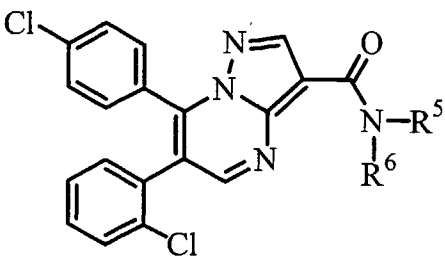
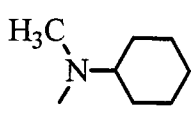
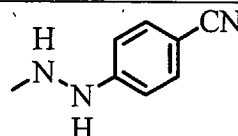
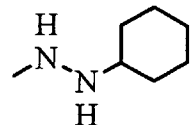
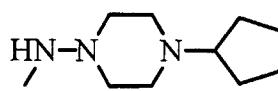
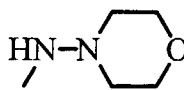
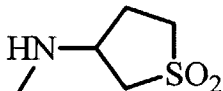
		
Ex. Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
16		powder MS(ESI):451.08[M] ⁺
17		powder MS(ESI):494.11[M] ⁺
18		powder MS(ESI):477.99[M] ⁺
19		powder MS(ESI):559.07[M] ⁺
20		powder MS(ESI):538.09[M] ⁺
21		powder MS(ESI):457.08[M] ⁺

Table 1 (No. 4)

		
Ex. Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
22		powder MS(ESI):479.12[M] ⁺
23		powder MS(ESI):499.02[M] ⁺
24		powder MS(ESI):480.06[M] ⁺
25		powder MS(ESI):535.17[M] ⁺
26		powder MS(APCI):468/470[M+H] ⁺
27		powder MS(APCI):501/503[M+H] ⁺

Example 28

5 To a solution of 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-pyrazolo[1,5-a]pyrimidine (compound obtained in Reference Example 1(4), 165 mg) in chloroform (1.0 mL containing amylene) was added the compound obtained in Reference Example 13(2), water-soluble carbodiimide HCl (123 mg), 1-hydroxybenzotriazole monohydrate (97 mg), and triethylamine (178 μ L) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution (2 mL) and the mixture was

10

stirred and extracted with chloroform. The extract was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 90/10 to 70/30) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(4-tetrahydrothiopyranyl)carbamoyl]pyrazolo[1,5-a]pyrimidine (50 mg; yield: 24 %) as a pale yellow powder.

MS(APCI)m/z; 483/485 [M+H]⁺

Example 29

To a solution of the compound obtained in Example 28 in methylene chloride (1.0 mL) was added methanesulfonic acid (20 μ L) and 3-chloroperbenzoic acid (57 mg) and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and the mixture was stirred. The organic layer was extracted and the extract was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; chloroform/ethyl acetate = 100/0 to 70/30) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[4-(1,1-dioxo)tetrahydrothiopyranyl]carbamoyl]pyrazolo[1,5-a]pyrimidine (37.3 mg; yield: 73 %) as a pale yellow powder.

MS(APCI)m/z; 515/517 [M+H]⁺

Example 30

To a solution of the compound obtained in Reference Example 9(2) (50 mL) in methanol (1 mL) was added 36% formaldehyde solution (118 μ L), sodium triacetoxyborohydride (75 mg) and triethylamine (39 μ L) and the mixture was stirred at room temperature for 3 hour. The reaction mixture was diluted with chloroform and thereto was added an aqueous sodium hydrogencarbonate solution. The mixture was extracted with chloroform and the extract was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; chloroform/ethyl acetate = 100/0 to 70/30), dissolved in tert-butanol and lyophilized to give 3-dimethylamino-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine (13.5 mg; yield: 26 %) as a red powder.

MS(APCI)m/z; 383/385 [M+H]⁺

Example 31

(1) The corresponding material (200 mg) was treated in the same manner as described in Example 3 to give 6-(2-bromophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (249 mg) as a yellow powder.

MS(APCI)m/z; 533/535 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (80 mg) in

dimethylformamide (1 mL) was added zinc cyanide (20 mg) and tetrakis-(triphenylphosphine)palladium (0) (17 mg) and the mixture was stirred under nitrogen gas atmosphere at 110°C for 19 hours. The reaction mixture was cooled to room temperature and thereto was added water and ethyl acetate and the mixture was stirred.

5 The organic layer was extracted and the extract was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 50/50 to 25/75), dissolved in tert-butanol and lyophilized to give 7-(4-chlorophenyl)-6-(2-cyanophenyl)-3-[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl-pyrazolo[1,5-a]pyrimidine (42 mg; yield: 58 %) as a colorless solid.

10 MS(APCI)m/z; 480/482 [M+H]⁺

Example 32

To a solution of the compound obtained in Reference Example 6 (1.0 g) in chloroform (20 mL) was added cyclopentylamine (260 mg), water-soluble carbodiimide HCl salt (620 mg) and 1-hydroxybenzotriazole (540 mg) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and chloroform and the mixture was stirred. The organic layer was extracted and the extract was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 82/18 to 67/33) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2-methylthiopyrazolo[1,5-a]pyrimidine (940 mg; yield: 81 %) as a yellow solid.

20 MS(APCI)m/z; 497/499 [M+H]⁺

Example 33

To a solution of the compound obtained in Example 32 (940 mg) in methylene chloride (40 mL) was added 3-chloroperbenzoic acid (1.09 g) under ice-cooling and the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added an aqueous sodium thiosulfate solution and the mixture was stirred and extracted with chloroform. The extract was concentrated in vacuo and the resultant crude product was purified by a column chromatography on NH-silica gel (Chromatorex NH silica gel/Fuji Silicia Chem., solvent; hexane/ethyl acetate = 50/50 to 0/100) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2-methylsulfonyl-pyrazolo[1,5-a]pyrimidine (1.0 g; yield: 100 %) as a colorless solid.

30 MS(APCI)m/z; 529/531 [M+H]⁺

Example 34

35 To a solution of the compound obtained in Example 33 (100 mg) in tetrahydrofuran/methanol (3 mL/3 mL) was added sodium methoxide (102 mg) and the

mixture was stirred at 50°C overnight. After cooling to room temperature, to the reaction mixture was added water and ethyl acetate and the mixture was stirred. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 60/40) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2-methoxypyrazolo[1,5-a]pyrimidine (57.2 mg; yield: 63 %) as a pale yellow powder.

MS(APCI)m/z; 481/483 [M+H]⁺

Example 35

To a solution of the compound obtained in Example 33 (300 mg) in dimethylformamide (7 mL) was added sodium cyanide (167 mg) and the mixture was stirred at 50°C overnight. After cooling to room temperature, to the reaction mixture was added ethyl acetate and a sodium hydrogencarbonate solution and the mixture was stirred. After separating the organic layer, the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 90/10 to 70/30) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-5-cyano-2-methylsulfonyl-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine (compound (a), 138 mg; yield: 44 %) and 6-(2-chlorophenyl)-7-(4-chlorophenyl)-2,5-dicyano-3-(N-cyclopentylcarbamoyl)-pyrazolo[1,5-a]pyrimidine (compound (b), 18.3 mg; yield: 6 %) as a pale yellow solid, respectively.

Compound (a): MS(APCI)m/z; 554/556 [M+H]⁺

Compound (b): MS(APCI)m/z; 501/503 [M+H]⁺

Example 36

To a solution of the compound (a) obtained in Example 35 (50 mg) in methanol/tetrahydrofuran (3 mL/3 mL) was added sodium methoxide (49 mg) and the mixture was stirred at room temperature overnight. To the reaction mixture was added ethyl acetate and a saturated brine and the organic layer was separated. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 30/70) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-5-methoxy-2-methylsulfonylpyrazolo[1,5-a]pyrimidine (50.5 mg; yield: 100 %) as a colorless solid.

MS(APCI)m/z; 559/561 [M+H]⁺

Example 37

To a solution of the compound obtained in Example 36 (24 mg) in methanol/tetrahydrofuran (2 mL/1 mL) was added sodium methoxide (23 mg) and the mixture was stirred at 100°C for 2 hours in a microwave reactor. After cooling to room temperature, to the reaction mixture was added chloroform and water and the organic layer was separated and concentrated in vacuo and the resultant crude product was purified by a column chromatography on NH-silica gel (Chromatorex NH-silica gel/Fuji Silicia Chem.; solvent; hexane/ethyl acetate = 65/35 to 30/70) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2,5-dimethoxypyrazolo[1,5-a]pyrimidine (17.8 mg; yield: 81 %) as a colorless solid.

MS(APCI)m/z; 511/513 [M+H]⁺

Example 38

To a solution of the compound obtained in Example 33 (300 mg) in dimethylformamide (10 mL) was added sodium cyanide (42.1 mg) and the mixture was stirred at 100°C for 1.5 hours in a microwave reactor. After cooling to room temperature, to the reaction mixture was added ethyl acetate and an aqueous sodium hydrogencarbonate solution and the mixture was stirred. The organic layer was washed with water and concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 65/35) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-cyano-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine (17.8 mg; yield: 81 %) as a pale yellow solid.

MS(APCI)m/z; 476/478 [M+H]⁺

Example 39

To a solution of the compound obtained in Reference Example 10(2) (138 mg) in ethanol (7 mL) was added divinylsulfone (42 µL) and triethylamine (72 µL) and the mixture was refluxed under heating for 6 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. To the residue was added water and methylene chloride and the mixture was stirred and the organic layer was extracted. The extract was washed with a brine, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; chloroform/methanol = 100/0 to 95/5) and then on NH-silica gel (Chromatorex NH-silica gel/Fuji Silicia Chem., solvent; hexane/ethyl acetate = 50/50 to 20/80), dissolved in tert-butanol and lyophilized to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[4-(1,1-dioxo)thiomorpholino]carbamoyl]pyrazolo[1,5-a]pyrimidine (57 mg; yield: 31 %) as a pale yellow powder.

MS(APCI)m/z; 516/518 [M+H]⁺

Example 40

To a solution of the compound obtained in Reference Example 11 (1.1 g) in tetrahydrofuran/water (2.8 mL/4.2 mL) was added acetic acid (7 mL) and the mixture was stirred at 100°C for 1 hours in a microwave reactor. After cooling to room temperature, to the reaction mixture was an aqueous 2N sodium hydroxide solution and the mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 60/40) to give 2-amino-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine (529 mg; yield: 75 %) as a yellow solid.

MS(APCI)m/z; 466/468 [M+H]⁺

Example 42

A mixture of the compound obtained in Example 40 (60 mg), pyridine (600 µL) and acetic anhydride (200 µL) was stirred at 100°C for 3 days. After cooling to room temperature, to the reaction mixture was added an aqueous 1N HCl and ethyl acetate and the mixture was stirred. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on NH-silica gel (Chromatorex NH-silica gel/Fuji Silicia Chem., solvent; hexane/ethyl acetate = 90/10 to 50/50) to give 2-acetyl-amino-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine (38.2 mg; yield: 58 %) as a pale yellow solid.

MS(APCI)m/z; 508/510 [M+H]⁺

Example 43

To a solution of the compound obtained in Example 40 (60 mg) in water/acetonitrile (0.3 mL/2.4 mL) was added 1,4-dichlorobutane (81.6 mg), potassium carbonate (88.8 mg) and sodium iodide (6.8 mg) and the mixture was stirred at 150°C for 3 hours in a microwave reactor. After cooling to room temperature, to the reaction mixture was added ethyl acetate and water and the mixture was stirred. The organic layer was extracted and dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 90/10 to 70/30) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2-(1-pyrrolidinyl)-pyrazolo[1,5-a]pyrimidine (25 mg; yield: 37 %) as a yellow solid.

MS(APCI)m/z; 520/522 [M+H]⁺

Example 44

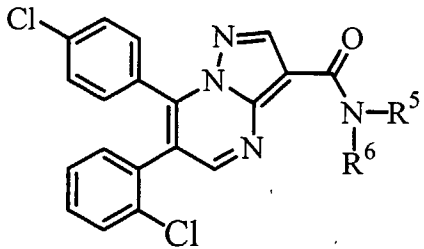
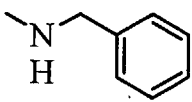
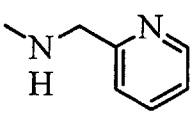
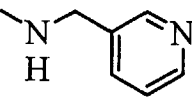
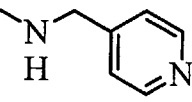
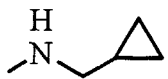
To a solution of the compound obtained in Reference Example 1(4) (77 mg) in methylene chloride (1 mL) was added water-soluble carbodiimide HCl (58 mg), 1-hydroxybenzotriazole (46 mg) and triethylamine (84 μ L) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous sodium hydrogencarbonate solution and methylene chloride and the mixture was stirred. The organic layer was separated and concentrated in vacuo to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(4-cyano-tetrahydrothiopyran-4-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (50.8 mg; yield: 50 %) as a pale yellow powder.

MS(APCI)m/z; 508/510 $[M+H]^+$

Examples 45 to 202

The corresponding materials were treated in the same manner as described in either one of Examples 1, 2 and 3 to obtain the compounds as shown in the following Tables 2 to 4.

Table 2 (No. 1)

		
Ex. Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
45		powder MS(APCI):473/475 $[M+H]^+$
46		powder MS(APCI):474/476 $[M+H]^+$
47		powder MS(APCI):474/476 $[M+H]^+$
48		powder MS(APCI):474/476 $[M+H]^+$
49		powder MS(APCI):423/425 $[M+H]^+$

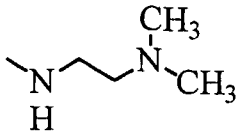
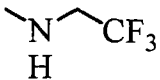
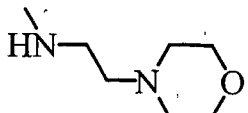
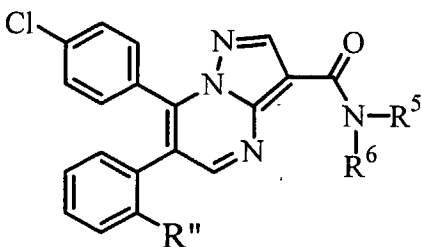
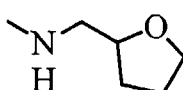
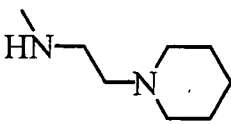
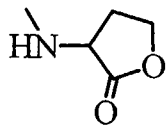
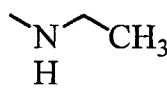
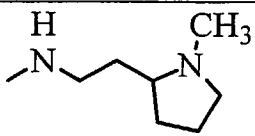
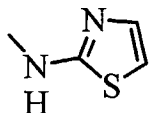
50		powder MS(APCI):454/456 [M+H] ⁺
51		powder MS(APCI):465/467 [M+H] ⁺
52		powder MS(APCI):496/498 [M+H] ⁺

Table 2 (No. 2)

			
Ex. Nos.	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
53	Cl		powder MS(APCI):467/469 [M+H] ⁺
54	Cl		powder MS(APCI):494/496 [M+H] ⁺
55	Cl		powder MS(APCI):467/469 [M+H] ⁺
56	Cl		powder MS(ESI):411 [M+H] ⁺
57	Cl		powder MS(APCI):494/496 [M+H] ⁺
58	Cl		powder MS(APCI):466/468 [M+H] ⁺

59	-OCH ₃		powder MS(APCI):484/486 [M+H] ⁺
60	-OCH ₃		powder MS(APCI):447/449 [M+H] ⁺

Table 2 (No. 3)

Ex. Nos.	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
61	-CH ₃		powder MS(APCI):446/448 [M+H] ⁺
62	-CH ₃		powder MS(APCI):468/470 [M+H] ⁺
63	-CH ₃		powder MS(APCI):445/447 [M+H] ⁺
64	-CH ₃		powder MS(APCI):431/433 [M+H] ⁺
65	-CH ₃		powder MS(APCI):447/449 [M+H] ⁺
66	-CH ₃		powder MS(APCI):481/483 [M+H] ⁺
67	F		powder MS(APCI):450/452 [M+H] ⁺

68	F		powder MS(APCI):472/474 [M+H] ⁺
----	---	--	---

Table 2 (No. 4)

Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
69	H	F		powder MS(APCI):449/451 [M+H] ⁺
70	H	F		powder MS(APCI):435/437 [M+H] ⁺
71	H	F		powder MS(APCI):451/453 [M+H] ⁺
72	H	F		powder MS(APCI):485/487 [M+H] ⁺
73	F	Cl		powder MS(APCI):484/486 [M+H] ⁺
74	F	Cl		powder MS(APCI):506/508 [M+H] ⁺
75	F	Cl		powder MS(APCI):483/485 [M+H] ⁺
76	F	Cl		powder MS(APCI):469/471 [M+H] ⁺

Table 2 (No. 5)

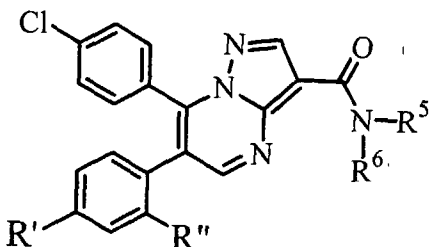
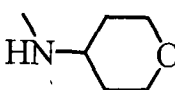
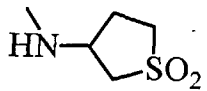
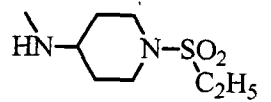
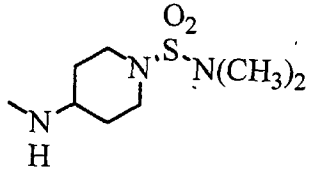
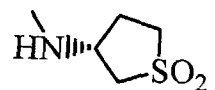
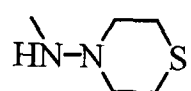
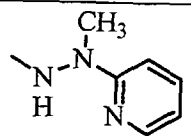
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
77	F	Cl		powder MS(APCI):485/487 [M+H] ⁺
78	F	Cl		powder MS(APCI):519/521 [M+H] ⁺
79	H	Cl		powder MS(APCI):558/560 [M+H] ⁺
80	H	Cl		powder MS(APCI):573/575 [M+H] ⁺
81	H	Cl		powder MS(APCI):501/503 [M+H] ⁺
82	H	Cl		powder MS(APCI):484/486 [M+H] ⁺
83	H	Cl		powder MS(APCI):489/491 [M+H] ⁺

Table 2 (No. 6)

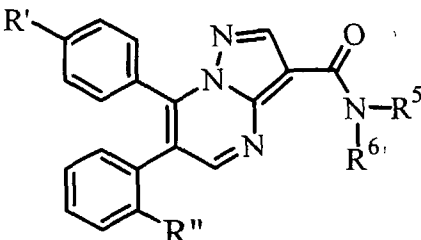
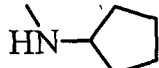
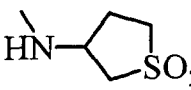
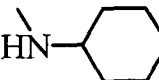
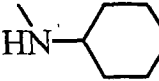
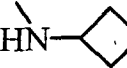
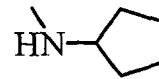
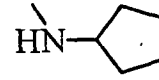
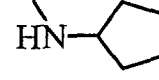
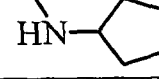
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
84	F	Cl		powder MS(APCI):435/437 [M+H] ⁺
85	F	Cl		powder MS(APCI):485/487 [M+H] ⁺
86	Cl	Br		powder MS(APCI):509/511 [M+H] ⁺
87	Cl	CN		powder MS(APCI):456/458 [M+H] ⁺
88	Cl	Cl		powder MS(APCI):437/439 [M+H] ⁺
89	CN	Cl		powder MS(APCI):442/444 [M+H] ⁺
90	CH ₃ -	Cl		powder MS(APCI):431/433 [M+H] ⁺
91	CH ₃ O-	Cl		powder MS(APCI):447/449 [M+H] ⁺
92	CH ₃ SO ₂ -	Cl		powder MS(APCI):495/497 [M+H] ⁺

Table 2 (No. 7)

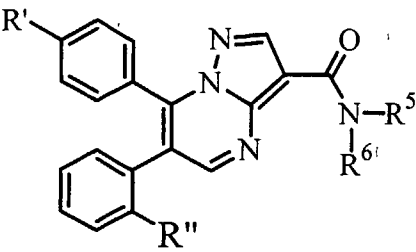
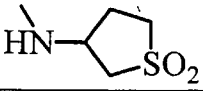
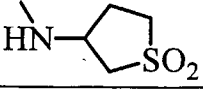
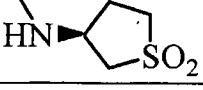
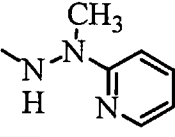
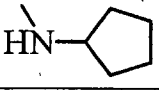
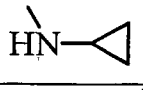
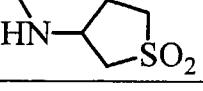
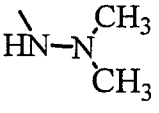
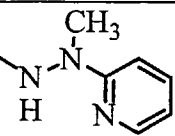
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
93	CN	Cl		powder MS(APCI):492/494 [M+H] ⁺
94	CH ₃ -	Cl		powder MS(APCI):481/483 [M+H] ⁺
95	Cl	Cl		powder MS(APCI):501/503 [M+H] ⁺
96	CF ₃ -	Cl		powder MS(APCI):523/525 [M+H] ⁺
97	CF ₃ -	Cl		powder MS(APCI):485/487 [M+H] ⁺
98	CF ₃ -	Cl		powder MS(APCI):457/459 [M+H] ⁺
99	CF ₃ -	Cl		powder MS(APCI):535/537 [M+H] ⁺
100	CF ₃ -	Cl		powder MS(APCI):460/462 [M+H] ⁺
101	Cl	F		powder MS(APCI):473/475 [M+H] ⁺

Table 2 (No. 8)

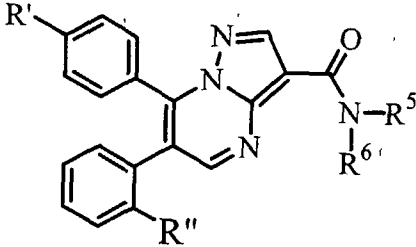
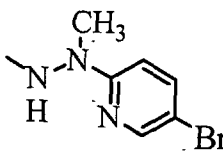
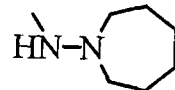
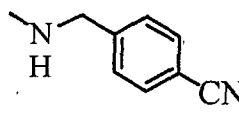
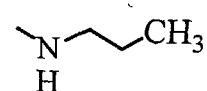
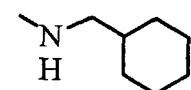
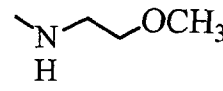
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
102	Cl	Cl		powder MS(APCI):567/569 [M+H] ⁺
103	Cl	Cl		powder MS(ESI):480 [M+H] ⁺
104	Cl	Cl		solid MS(ESI):498 [M+H] ⁺
105	Cl	Cl		solid MS(ESI):425 [M+H] ⁺
106	Cl	Cl		solid MS(ESI):479 [M+H] ⁺
107	Cl	Cl		solid MS(ESI):441 [M+H] ⁺

Table 2 (No. 9)

Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
108	Cl	Cl		solid MS(ESI):439 [M+H] ⁺
109	Cl	Cl		solid MS(ESI):437 [M+H] ⁺
110	Cl	Cl		powder MS(ESI):501 [M+H] ⁺
111	Cl	Cl		powder MS(ESI):487 [M+H] ⁺
112	Cl	Cl		solid MS(ESI):429 [M+H] ⁺
113	Cl	Cl		solid MS(ESI):447 [M+H] ⁺
114	Cl	Cl		solid MS(ESI):508 [M+H] ⁺
115	Cl	Cl		solid MS(ESI):542 [M+H] ⁺
116	Cl	Cl		solid MS(ESI):480 [M+H] ⁺

Table 2 (No. 10)

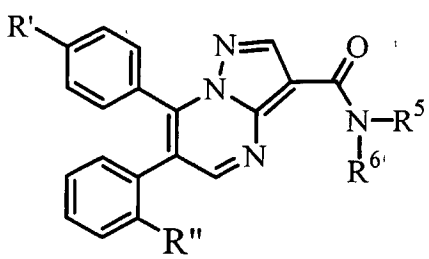
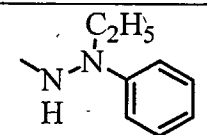
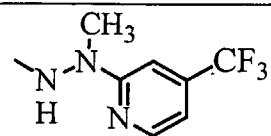
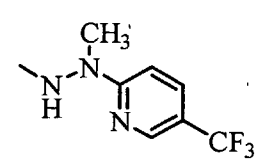
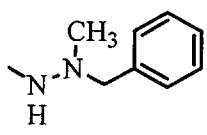
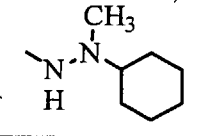
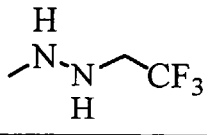
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
117	Cl	Cl		powder MS(APCI):502/504 [M+H] ⁺
118	Cl	Cl		powder MS(APCI):557/559 [M+H] ⁺
119	Cl	Cl		powder MS(APCI):557/559 [M+H] ⁺
120	Cl	Cl		powder MS(APCI):502/504 [M+H] ⁺
121	Cl	Cl		powder MS(APCI):494/496 [M+H] ⁺
122	Cl	Cl		powder MS(APCI):480/482 [M+H] ⁺

Table 2 (No. 11)

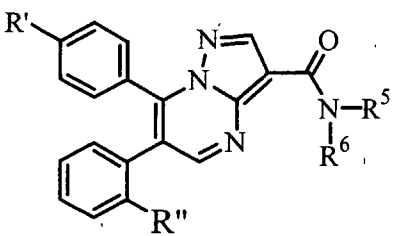
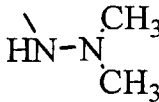
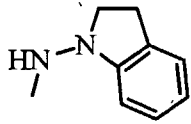
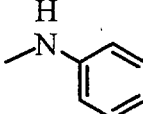
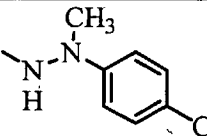
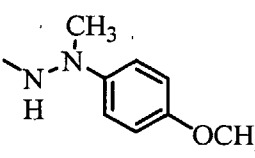
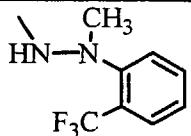
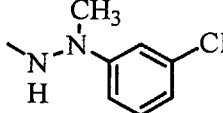
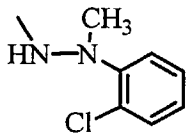
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
123	Cl	Cl		powder MS(APCI):440/442 [M+H] ⁺
124	Cl	Cl		powder MS(APCI):500/502 [M+H] ⁺
125	Cl	Cl		powder MS(ESI):459/461 [M+H] ⁺
126	Cl	Cl		powder MS(APCI):522/524 [M+H] ⁺
127	Cl	Cl		powder MS(APCI):518/520 [M+H] ⁺
128	Cl	Cl		powder MS(APCI):556/558 [M+H] ⁺
129	Cl	Cl		powder MS(APCI):522/524 [M+H] ⁺
130	Cl	Cl		powder MS(APCI):522/524 [M+H] ⁺

Table 2 (No. 12)

Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
131	CF ₃ -	Cl		powder MS(APCI):535/537 [M+H] ⁺
132	CF ₃ -	Cl		powder MS(APCI):535/537 [M+H] ⁺
133	Cl	Cl		powder MS(APCI):460/462 [M+H] ⁺
134	Cl	Br		powder MS(APCI):545/547 [M+H] ⁺
135	Cl	Br		powder MS(APCI):495/497 [M+H] ⁺
136	Cl	CN		powder MS(APCI):442/444 [M+H] ⁺
137	Cl	Cl		powder MS(APCI):502/504 [M+H] ⁺
138	Cl	CN		powder MS(APCI):492/494 [M+H] ⁺
139	Cl	CF ₃ -		powder MS(APCI):535/537 [M+H] ⁺
140	Cl	CF ₃ -		powder MS(APCI):485/487 [M+H] ⁺
141	Cl	CF ₃ -		powder MS(APCI):500/502 [M+H] ⁺

Table 2 (No. 13)

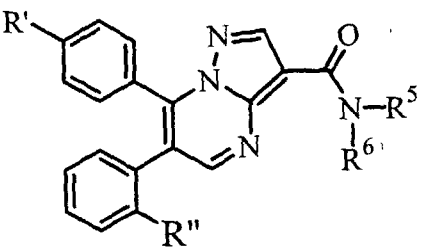
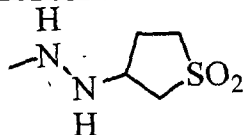
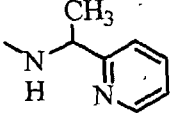
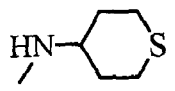
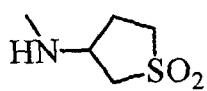
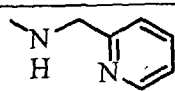
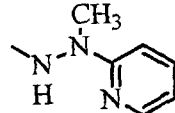
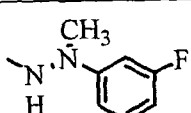
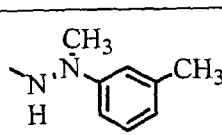
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
142	Cl	Cl		powder MS(APCI):516/518 [M+H] ⁺
143	Cl	Cl		powder MS(APCI):488/490 [M+H] ⁺
144	CF ₃ O-	Cl		powder MS(APCI):533/535 [M+H] ⁺
145	CF ₃ O-	Cl		powder MS(APCI):551/553 [M+H] ⁺
146	CF ₃ O-	Cl		powder MS(APCI):524/526 [M+H] ⁺
147	CF ₃ O-	Cl		powder MS(APCI):539/541 [M+H] ⁺
148	Cl	Cl		powder MS(APCI):506/508 [M+H] ⁺
149	Cl	Cl		powder MS(APCI):502/504 [M+H] ⁺

Table 2 (No. 14)

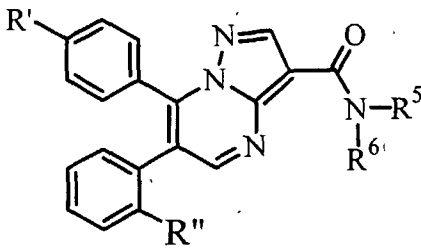
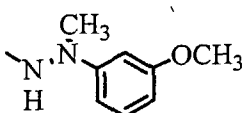
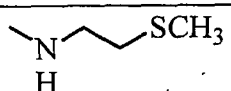
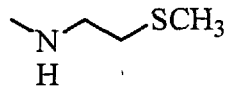
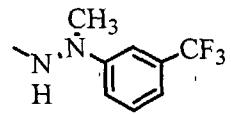
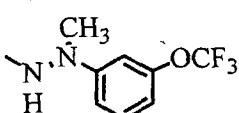
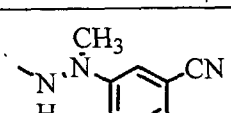
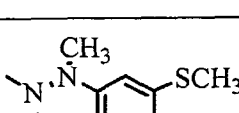
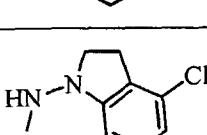
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
150	Cl	Cl		powder MS(APCI):518/520 [M+H] ⁺
151	Cl	Cl		powder MS(APCI):457/459 [M+H] ⁺
152	CF ₃ -	Cl		powder MS(APCI):491/493 [M+H] ⁺
153	Cl	Cl		powder MS(APCI):556/558 [M+H] ⁺
154	Cl	Cl		powder MS(APCI):572/574 [M+H] ⁺
155	Cl	Cl		powder MS(APCI):513/515 [M+H] ⁺
156	Cl	Cl		powder MS(APCI):534/536 [M+H] ⁺
157	Cl	Cl		powder MS(APCI):534/536 [M+H] ⁺

Table 2 (No. 15)

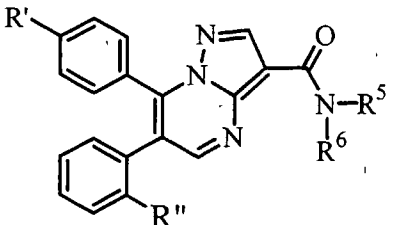
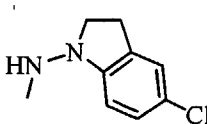
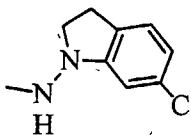
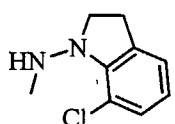
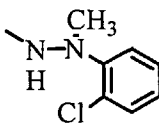
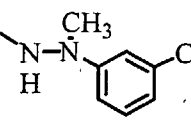
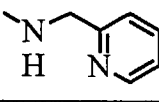
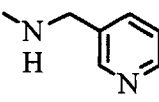
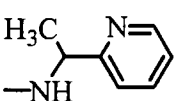
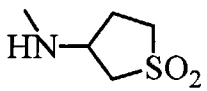
				
Ex. Nos.	R'	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
158	Cl	Cl		powder MS(APCI):534/536 [M+H] ⁺
159	Cl	Cl		powder MS(APCI):534/536 [M+H] ⁺
160	Cl	Cl		powder MS(APCI):534/536 [M+H] ⁺
161	CF ₃ -	Cl		powder MS(APCI):556/558 [M+H] ⁺
162	CF ₃ -	Cl		powder MS(APCI):556/558 [M+H] ⁺
163	CF ₃ -	Cl		powder MS(APCI):508/510 [M+H] ⁺
164	CF ₃ -	Cl		powder MS(APCI):508/510 [M+H] ⁺
165	CF ₃ -	Cl		powder MS(APCI):522/524 [M+H] ⁺
166	CF ₃ -	CN		powder MS(APCI):526 [M+H] ⁺

Table 2 (No. 16)

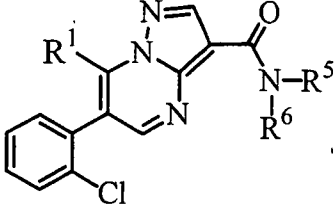
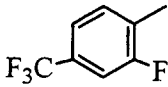
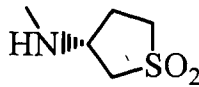
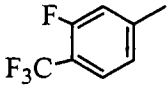
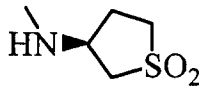
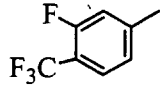
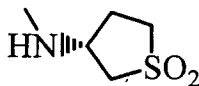
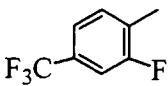
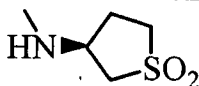
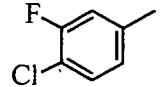
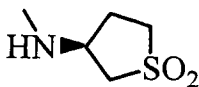
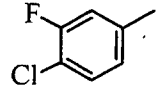
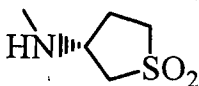
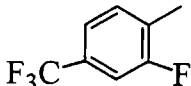
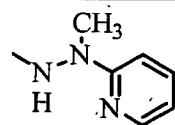
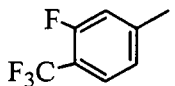
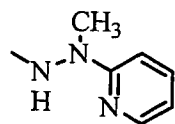
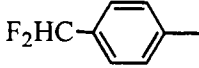
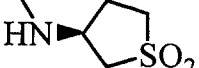
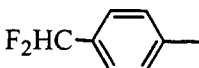
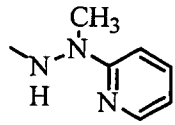
			
Ex. Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc
167			powder MS(APCI):553/555 [M+H] ⁺
168			powder MS(APCI):553/555 [M+H] ⁺
169			powder MS(APCI):553/555 [M+H] ⁺
170			powder MS(APCI):553/555 [M+H] ⁺
171			powder MS(APCI):519/521 [M+H] ⁺
172			powder MS(APCI):519/521 [M+H] ⁺
173			powder MS(APCI):541/543 [M+H] ⁺
174			powder MS(APCI):541/543 [M+H] ⁺
175			powder MS(APCI):517/519 [M+H] ⁺
176			powder MS(APCI):505/507 [M+H] ⁺

Table 3 (No. 1)

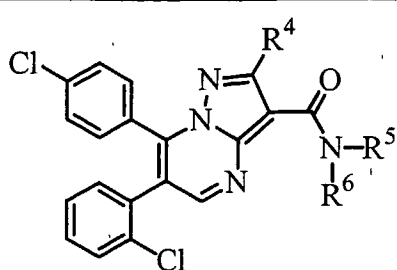
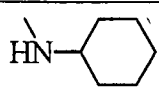
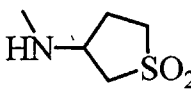
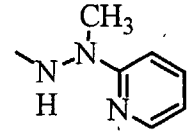
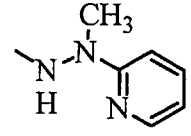
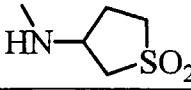
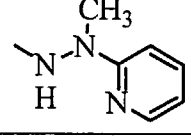
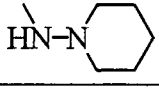
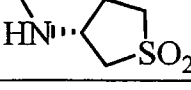
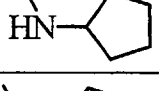
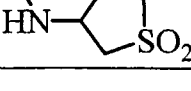
			
Ex. Nos.	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc
177	CH ₃ -		powder MS(APCI):479/481 [M+H] ⁺
178	CH ₃ -		powder MS(APCI):515/517 [M+H] ⁺
179	CH ₃ -		powder MS(APCI):503/505 [M+H] ⁺
180	CH ₃ S-		powder MS(APCI):535/537 [M+H] ⁺
181	CH ₃ S-		powder MS(APCI):547/549 [M+H] ⁺
182	C ₂ H ₅ -		powder MS(APCI):533/535 [M+H] ⁺
183	CH ₃ S-		powder MS(APCI):512/514 [M+H] ⁺
184	CH ₃ -		powder MS(APCI):515/517 [M+H] ⁺
185	CH ₃ -		powder MS(APCI):515/517 [M+H] ⁺
186	C ₂ H ₅ -		powder MS(APCI):495/497 [M+H] ⁺
187	C ₂ H ₅ -		powder MS(APCI):545/547 [M+H] ⁺

Table 3 (No. 2)

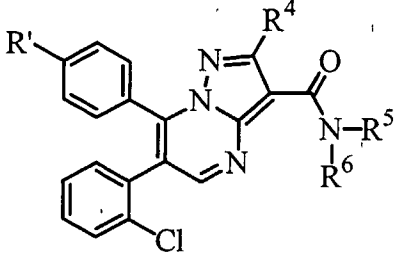
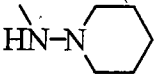
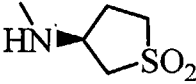
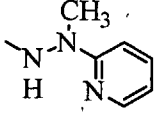
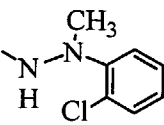
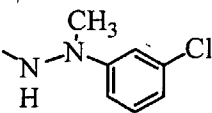
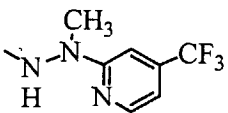
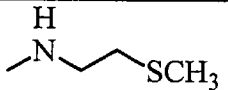
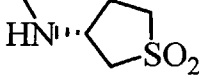
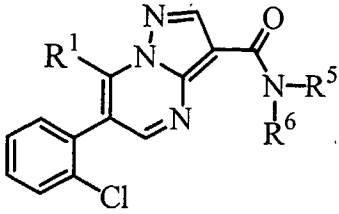
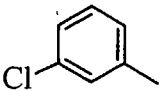
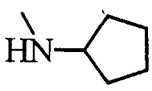
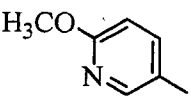
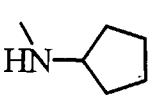
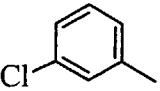
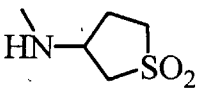
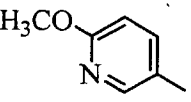
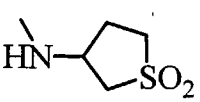
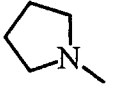
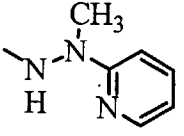
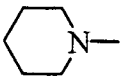
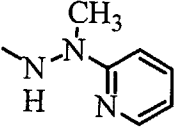
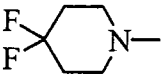
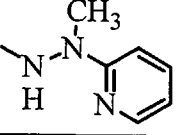
				
Ex. Nos.	R'	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc
188	Cl	C ₂ H ₅ -		powder MS(APCI):510/512 [M+H] ⁺
189	CF ₃ -	CH ₃ -		powder MS(APCI):549/551 [M+H] ⁺
190	CF ₃ -	CH ₃ -		powder MS(APCI):537/539 [M+H] ⁺
191	CF ₃ -	CH ₃ -		powder MS(APCI):570/572 [M+H] ⁺
192	CF ₃ -	CH ₃ -		powder MS(APCI):570/572 [M+H] ⁺
193	CF ₃ -	CH ₃ -		powder MS(APCI):605/607 [M+H] ⁺
194	CF ₃ -	CH ₃ -		powder MS(APCI):505/507 [M+H] ⁺
195	CF ₃ -	CH ₃ -		powder MS(APCI):549/551 [M+H] ⁺

Table 4

			
Ex. Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc
196			powder MS(APCI):451/453 [M+H] ⁺
197			powder MS(APCI):448/450 [M+H] ⁺
198			powder MS(APCI):501/503 [M+H] ⁺
199			powder MS(APCI):498/500 [M+H] ⁺
200			powder MS(APCI):448/450 [M+H] ⁺
201			powder MS(APCI):462/464 [M+H] ⁺
202			powder MS(APCI):498/500 [M+H] ⁺

Example 203

5

The corresponding materials were treated in the same manner as described in Example 3 to obtain 6-(2-chloropyridin-3-yl)-7-(4-chlorophenyl)-3-(N-cyclopentyl-carbamoyl)pyrazolo[1,5-a]pyrimidine (39 mg, yield: 67%) as a pale yellow powder. MS(APCI)m/z: 452/454 [M+H]⁺

Example 204

The compound obtained in Example 181 (36 mg) was treated in the same manner as described in Example 33 to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methylsulfonyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]-pyrimidine (33.1 mg, yield: 86%) as a colorless solid.

MS(APCI)m/z: 579/581 [M+H]⁺

Example 205

The compound obtained in Example 204 was treated in the same manner as described in Example 34 to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methoxy-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (72 mg, yield: 79%) as a powder.

MS(APCI)m/z: 531/533 [M+H]⁺

Example 206

The compound obtained in Example 144 (80 mg) was treated in the same manner as described in Example 29 to obtain 6-(2-chlorophenyl)-7-(4-trifluoromethoxyphenyl)-3-[N-(1,1-dioxo-tetrahydrothiopyran-4-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (61.1 mg, yield: 72%) as a pale yellow powder.

MS(APCI)m/z: 565/567 [M+H]⁺

Example 207

(1) The compound obtained in Example 204 (300 mg) was treated in the same manner as described in Example 35 to obtain 5-cyano-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methylsulfonyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (60 mg, yield: 19%) as a pale yellow solid.

MS(APCI)m/z: 604/606 [M+H]⁺

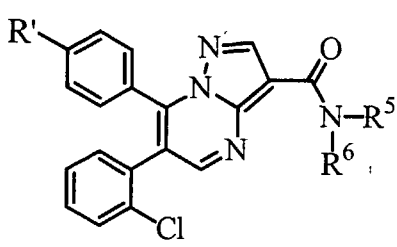
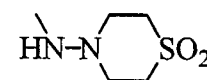
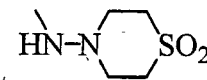
(2) The compound obtained in the above step (1) (60 mg) was treated in the same manner as described in Example 36 to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-5-methoxy-2-methylsulfonyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (29 mg, yield: 49%) as a pale yellow powder.

MS(APCI)m/z: 609/611 [M+H]⁺

Examples 208 to 209

The compound obtained in Reference Example 18 or 19 was treated in the same manner as described in Example 39 to obtain the compounds as shown in the following Table 5.

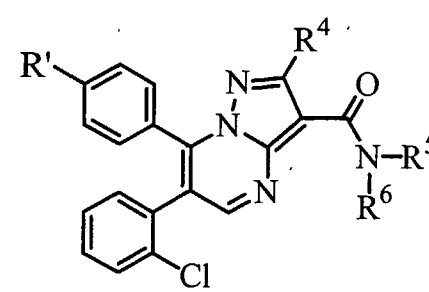
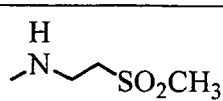
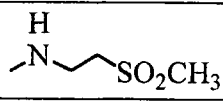
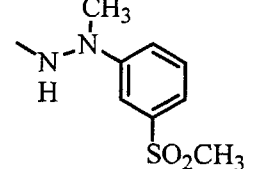
Table 5

			
Ex. Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc
208	CF ₃ O-		powder MS(APCI):566/568 [M+H] ⁺
209	CF ₃ -		powder MS(APCI):550/552 [M+H] ⁺

Examples 210 to 212

- 5 The compound obtained in Example 152, 194 or 156 was treated in the same manner as described in Example 29 to obtain the compounds as shown in the following Table 6.

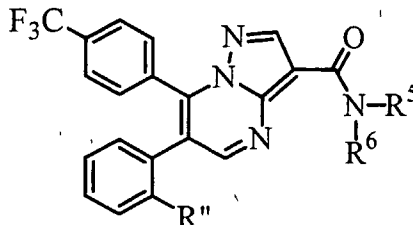
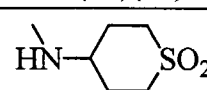
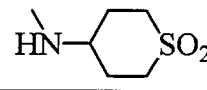
Table 6

				
Ex. Nos.	R'	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc
210	CF ₃ -	H		powder MS(APCI):523/525 [M+H] ⁺
211	CF ₃ -	CH ₃ -		powder MS(APCI):537/539 [M+H] ⁺
212	Cl	H		powder MS(APCI):566/568 [M+H] ⁺

Examples 213 to 214

The corresponding starting materials were treated in the same manner as described in Example 28 and then the product was treated in the same manner as described in Example 29 to obtain the compounds as shown in the following Table 7.

Table 7

			
Ex. Nos.	R''	-N(R ⁵)(R ⁶)	Physicochemical properties etc
213	Cl		powder MS(APCI):549/551 [M+H] ⁺
214	CN		powder MS(APCI):540 [M+H] ⁺

Examples 215

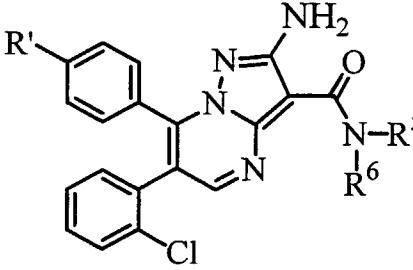
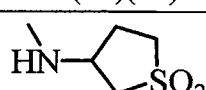
The compound obtained in Example 40 and 2-chloroethylether were treated in the same manner as described in Example 43 to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-morpholino-3-(N-pentylcarbamoyl)pyrazolo[1,5-a]pyrimidine (23 mg, yield: 33%) as a powder.

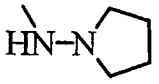
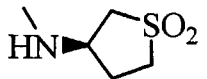
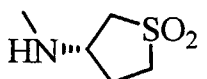
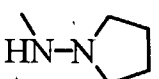
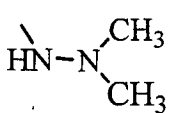
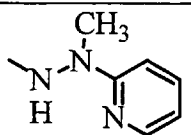
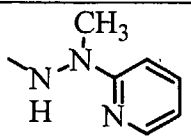
MS(APCI)m/z: 536/538 [M+H]⁺

Examples 216 to 223

The corresponding starting materials were treated in the same manner as described in Example 11 and then the product was treated in the same manner as described in Example 40 to obtain the compounds as shown in the following Table 8.

Table 8

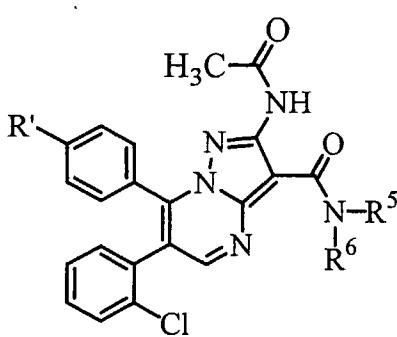
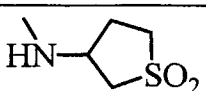
			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
216	Cl		powder MS(APCI):516/518 [M+H] ⁺

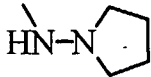
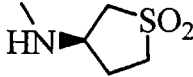
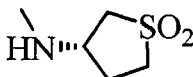
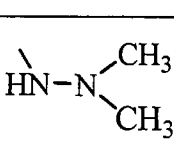
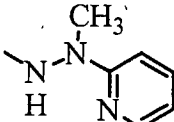
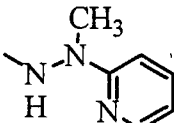
217	Cl		powder MS(APCI):467/469 [M+H] ⁺
218	CF ₃		powder MS(APCI):550/552 [M+H] ⁺
219	CF ₃		powder MS(APCI):550/552 [M+H] ⁺
220	CF ₃		powder MS(APCI):501/503 [M+H] ⁺
221	CF ₃		powder MS(APCI):475/477 [M+H] ⁺
222	CF ₃		powder MS(APCI):538/540 [M+H] ⁺
223	Cl		powder MS(APCI):504/506 [M+H] ⁺

Examples 224 to 231

The corresponding starting materials were treated in the same manner as described in Example 42 to obtain the compounds as shown in the following Table 9.

Table 9.

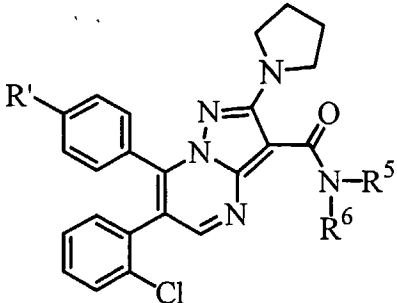
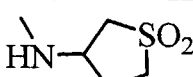
			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
224	Cl		powder MS(APCI):558/560 [M+H] ⁺

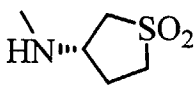
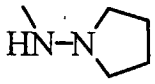
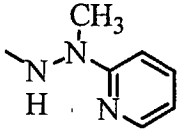
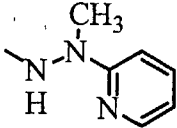
225	Cl		powder MS(APCI):509/511 [M+H] ⁺
226	CF ₃		powder MS(APCI):592/594 [M+H] ⁺
227	CF ₃		powder MS(APCI):592/594 [M+H] ⁺
228	CF ₃		powder MS(APCI):543/545 [M+H] ⁺
229	CF ₃		powder MS(APCI):517/519 [M+H] ⁺
230	CF ₃		powder MS(APCI):580/582 [M+H] ⁺
231	Cl		powder MS(APCI):546/548 [M+H] ⁺

Examples 232 to 237

The corresponding starting materials were treated in the same manner as described in Example 43 to obtain the compounds as shown in the following Table 10.

Table 10.

			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
232	Cl		powder MS(APCI):570/572 [M+H] ⁺
233	CF ₃		powder MS(APCI):604/606 [M+H] ⁺

234	CF ₃		powder MS(APCI):604/606 [M+H] ⁺
235	CF ₃		powder MS(APCI):555/557 [M+H] ⁺
236	CF ₃		powder MS(APCI):592/594 [M+H] ⁺
237	Cl		powder MS(APCI):558/560 [M+H] ⁺

Example 238

To a solution of pyrrolidine (15.5 μ L) and pyridine (20 μ L) in chloroform (2 mL) was added dropwise a solution of the compound (60 mg) obtained in Reference Example 54 in chloroform (1 mL) under ice-cooling and the mixture was stirred at room temperature for 2.5 hours. To the reaction mixture was further added pyrrolidine (15.5 μ L) and the mixture was stirred for 2.5 hours. To the reaction mixture was added water and the mixture was extracted with chloroform. The organic layer was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 82/18 to 67/33) to obtain 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methyl-3-(1-pyrrolidinyl)sulfonylpyrazolo[1,5-a]pyrimidine (43.8 mg; yield: 68 %) as a colorless solid.

MS(APCI)m/z; 521/523 [M+H]⁺

Example 239

To a solution of the compound obtained in Reference Example 53 (60 mg) in ethanol (0.5 mL) was added divinylsulfone (20 μ L) and the mixture was stirred at 120°C for 1 hour and at 130°C for 4 hours in a microwave reactor. After cooling to room temperature, to the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 70/30 to 55/45) to obtain 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-(1,1-dioxothiomorpholino)pyrazolo[1,5-a]pyrimidine (40 mg; yield: 51 %) as a red solid.

MS(APCI)m/z; 507/509 [M+H]⁺

Example 240

To a solution of the compound obtained in Reference Example 55 (128 mg) in

chloroform (2 mL) was added a solution of bromine (21 μ L) in chloroform (1.3 mL) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo and to the residue was added dimethylformamide (2 mL) and N-methylaniline (181 μ L) and the mixture was stirred at room temperature for 2 hours.

To the reaction mixture was added water and an aqueous saturated sodium hydrogencarbonate solution and the mixture was extracted with ethyl acetate. The organic layer was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 88/12 to 75/25) to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[2-(N-methyl-N-phenylamino)acetyl]-pyrazolo[1,5-a]pyrimidine (115 mg; yield: 70 %) as a yellow solid.

MS(APCI)m/z; 487/489 [M+H]⁺

Example 241

To a solution of the compound obtained in Example 434 (125 mg) in dichloromethane (2 mL) was added m-chloro-perbenzoic acid (146 mg) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent: hexane/ethyl acetate = 50/50). The eluted fraction was concentrated and the precipitates were washed with hexane to obtain 6-(2-chlorophenyl)-7-(1,1-dioxothiomorpholino)-2-methyl-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (70 mg; yield: 53 %) as a solid.

MS(APCI)m/z; 526/528 [M+H]⁺

Example 242

(1) The corresponding starting materials were treated in the same manner as described in Reference Example 2 to obtain 6-(2-bromophenyl)-7-(4-chloro-2-fluorophenyl)-3-carboxy-2-methylpyrazolo[1,5-a]pyrimidine (1.51 g; yield: 20 %) as a pale yellow powder.

MS(APCI)m/z; 460/462 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (100 mg) in methylene chloride (3 mL) was added 1-methyl-1-(2-pyridyl)hydrazine (37 mg), water-soluble carbodiimide hydrochloride (58 mg) and 1-hydroxybenzotriazole hydrate (46 mg) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and the mixture was stirred and extracted with chloroform. The extract was concentrated in

vacuo and the resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent: hexane/ethyl acetate = 80/20 to 55/45) to obtain 6-(2-bromophenyl)-7-(4-chloro-2-fluorophenyl)-2-methyl-3-
5 [[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (119.5 mg; yield: 96 %) as a pale yellow solid.

MS(APCI)m/z; 565/567 [M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (119 mg) in dimethylformamide (2 mL) was added zinc cyanide (15.5 mg), tris(dibenzylidene-acetone)dipalladium (4.2 mg) and 1,1'-bis(diphenylphosphino)ferrocene (5.1 mg) and
10 the mixture was stirred at 180°C for 20 minutes in a microwave reactor. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and the mixture was stirred and extracted with chloroform. The extract was washed with water and concentrated in vacuo. The resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent:
15 hexane/ethyl acetate = 70/30 to 55/45) to obtain 6-(2-cyanophenyl)-7-(4-chloro-2-fluorophenyl)-2-methyl-3-[[N'-methyl-N'-(2-pyridyl)-hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (22.1 mg; yield: 21 %) as a yellow solid.
MS(APCI)m/z; 512/514 [M+H]⁺

Example 243

(1) To a solution of the compound obtained in Reference Example 33 (2.08 g) in N,N-dimethylformamide (20 mL) was added 2M methylamine-methanol solution (5 mL), water-soluble carbodiimide (1.92 g) and 1-hydroxybenzotriazole (1.53 g) and triethylamine (1.01 g) and the mixture was stirred at room temperature overnight. To
20 the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent: chloroform/methanol = 100/0 to 95/5) to obtain 6-(2-chlorophenyl)-7-
25 (4-trifluoromethylphenyl)-3-(N-methylcarbamoyl)pyrazolo[1,5-a]pyrimidine (1.83 g; yield: 85 %) as a yellow powder.

MS(APCI)m/z; 431/433 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (832 mg) in toluene (10 mL) was added Lawesson reagent (809 mg) and the mixture was stirred at 110°C for 2 hours. After cooling, to the reaction mixture was added NH-silica gel (2.0
35 g) and the mixture was filtered. The residue was washed with ethyl acetate and the organic layers were combined and concentrated in vacuo. The resultant crude product

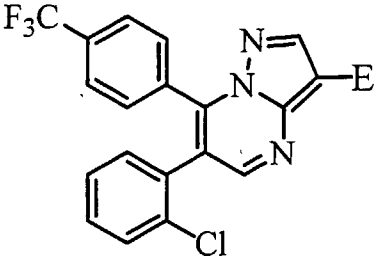
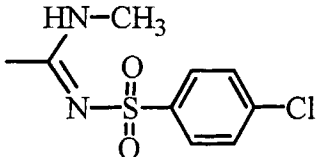
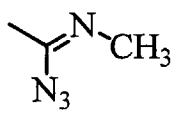
was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 80/20 to 60/40) to obtain 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(methyl)thiocarbamoyl]pyrazolo[1,5-a]pyrimidine (730 mg; yield: 82 %) as a yellow powder.

5 MS(APCI)m/z; 447/449 [M+H]⁺

(3) To a solution of 4-chlorobenzenesulfonyl chloride (5.28 g) in tetrahydrofuran (25 mL) was added a solution of sodium azide (1.79 g) in water (12.5 mL) and the mixture was stirred at room temperature overnight. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to give 4-chlorobenzenesulfonyl azide (4.27 g, yield: 78%) as a colorless liquid.

(4) A solution of the compound obtained in the above step (2) (223 mg) and the compound obtained in the above step (3) (326 mg) in pyridine (5 mL) was stirred at 110°C for 2 days. After cooling, to the reaction mixture was added water and the mixture was extracted with chloroform. The organic layer was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 30/70 to 50/50) to obtain the compound a (24 mg; yield: 8 %) and the compound b (0.8 mg, yield: 0.4%) as shown in the following Table 11.

Table 11

		
Example Nos.	E	Physicochemical properties etc.
243		Compound a yellow powder MS(APCI):604/606 [M+H] ⁺
		Compound b yellow powder MS(APCI):456/458 [M+H] ⁺

Example 244

The compound obtained in Example 332 was treated in the same manner as described in Example 31(2) to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(6-cyanopyridin-3-yl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine.

5 MS(APCI)m/z; 514/516 [M+H]⁺

Example 245

To a solution of the compound obtained in Example 292 (6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(6-fluoropyridin-2-yl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine) in N-methylpiperidine (1 mL) was added diisopropylethylamine (52 μL) and morpholine (26 μL) and the mixture was stirred at 90°C overnight and 120°C for 4 hours in a shield container. After cooling to room temperature, to the reaction mixture was added morpholine (60 μL) and the mixture was stirred at 120°C overnight in a shield container and 100°C for 15 minutes in a microwave reactor. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 70/30 to 40/60) and the eluted fraction was concentrated. The residue was purified by gel-permeation chromatography (mobile phase: chloroform) and the eluted fraction was concentrated. The resultant residue was dissolved in tert-butanol and the solution was lyophilized to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(6-morpholinopyridin-2-yl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (12.9 mg; yield: 23%) as a pale yellow powder.

20 MS(APCI)m/z; 574/576 [M+H]⁺

Example 246

25 (1) The corresponding starting materials were treated in the same manner as described in Reference Example 2 to obtain 6-(2-bromophenyl)-7-(4-chloro-2-fluorophenyl)-3-carboxypyrazolo[1,5-a]pyrimidine (2.09 g; yield: 22 %) as a pale yellow powder.

MS(APCI)m/z; 446/448 [M+H]⁺

30 (2) The compound obtained in the above step (1) and the corresponding starting materials were treated in the same manner as described in Example 3 to obtain 6-(2-bromophenyl)-7-(4-chloro-2-fluorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (148 mg, yield: 89%) as a pale yellow solid.

MS(APCI)m/z; 551/553 [M+H]⁺

35 (3) The compound obtained in the above step (2) (119 mg) was treated in the same manner as described in Example 242(3) to give 6-(2-cyanophenyl)-7-(4-chloro-

2-fluorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (compound a: 51.6 mg, yield: 40%) as a yellow solid and 6-(2-cyanophenyl)-7-(4-cyano-2-fluorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine (compound b: 34.1 mg, yield: 27%) as a yellow solid.

5 Compound a: MS(APCI)m/z; 498/500 [M+H]⁺

Compound b: MS(APCI)m/z; 489 [M+H]⁺

Example 247

10 (1) The corresponding starting material (3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine; 576 mg) was treated in the same manner as described in Example 3 to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]carbamoyl]pyrazolo[1,5-a]pyrimidine (656 mg, yield: 79%) as a yellow solid.

MS(APCI)m/z; 552/554 [M+H]⁺

15 (2) A solution of the compound obtained in the above step (1) (650 mg) in 4N-HCl-dioxane (5 mL) was stirred at room temperature overnight. The reaction mixture was neutralized (pH 7 to 8) with an aqueous saturated sodium hydrogencarbonate solution under ice cooling. The mixture was extracted with methylene chloride and the organic layer was dried over magnesium sulfate and concentrated in vacuo. The resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent: chloroform/methanol = 100/0 to 95/5) and dried in vacuo to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(pyrrolidin-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (515.8 mg; yield: 97 %) as a pale yellow solid.

MS(APCI)m/z; 452/454 [M+H]⁺

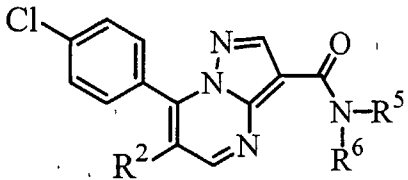
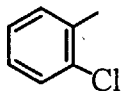
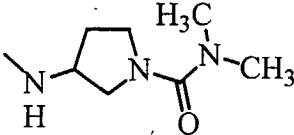
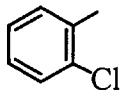
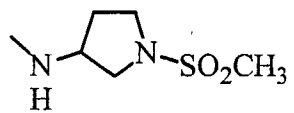
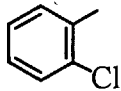
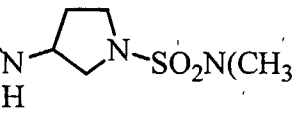
25 (3) To a solution of the compound obtained in the above step (2) (46 mg) in dichloromethane (1 mL containing amylen) was added triethylamine (28 μ L) and thereto was added dropwise acetyl chloride (9 μ L) under nitrogen-gas atmosphere and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and the mixture was
30 extracted with methylene chloride. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: chloroform/methanol = 100/0 to 95/5) and the eluted fraction was concentrated in vacuo. The resultant residue was dissolved in tert-butanol and lyophilized to obtain
35 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1-acetylpyrrolidin-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (50.7 mg; yield: 100 %) as a pale yellow powder.

MS(APCI)m/z; 494/496 [M+H]⁺

Examples 248 to 250

The corresponding starting materials were treated in the same manner as described in Example 247 to obtain the compounds as shown in the following Table 12.

Table 12

			
Example Nos.	R ²	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
248			powder MS(APCI):523/525 [M+H] ⁺
249			powder MS(APCI):530/532 [M+H] ⁺
250			powder MS(APCI):559/561 [M+H] ⁺

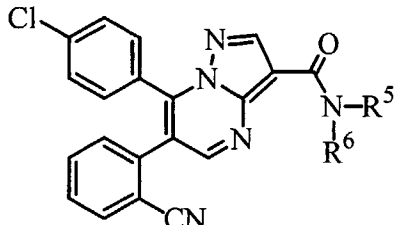
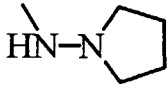
5

Examples 251 to 278

The corresponding starting materials were treated in the same manner as described in Example 31 or 242 to obtain the compounds as shown in the following Table 13.

10

Table 13 (No. 1)

		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
251		powder MS(APCI):443/445 [M+H] ⁺

252		powder MS(APCI):471/473 [M+H] ⁺
253		powder MS(APCI):513/515 [M+H] ⁺
254		powder MS(APCI):548/550 [M+H] ⁺
255		powder MS(APCI):417/419 [M+H] ⁺
256		powder MS(APCI):457/459 [M+H] ⁺
257		solid MS(APCI):511/513 [M+H] ⁺

Table 13 (No. 2)

Example Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
258			powder MS(APCI):515 [M+H] ⁺
259			solid MS(APCI):510/512 [M+H] ⁺

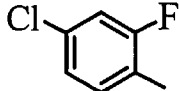
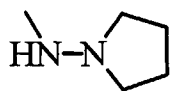
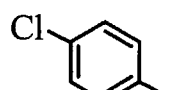
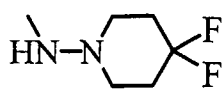
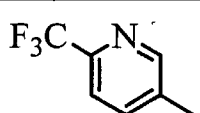
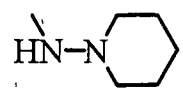
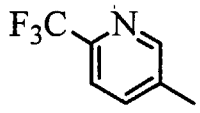
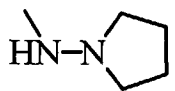
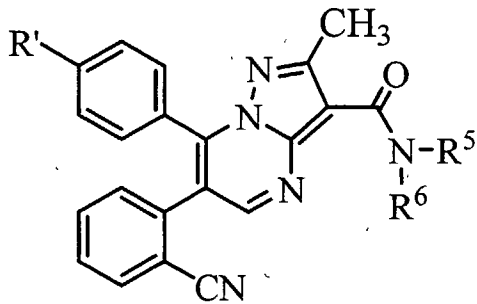
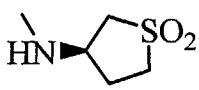
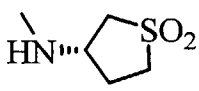
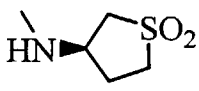
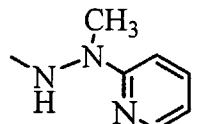
260			solid MS(APCI):461/463 [M+H] ⁺
261			solid MS(APCI):493/495 [M+H] ⁺
262			powder MS(APCI):492 [M+H] ⁺
263			powder MS(APCI):478 [M+H] ⁺

Table 13 (No. 3)

			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
264	CF ₃		powder MS(APCI):540 [M+H] ⁺
265	CF ₃		powder MS(APCI):540 [M+H] ⁺
266	Cl		powder MS(APCI):506/508 [M+H] ⁺
267	Cl		powder MS(APCI):494/496 [M+H] ⁺

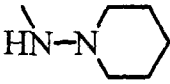
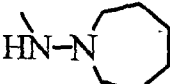
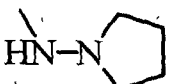
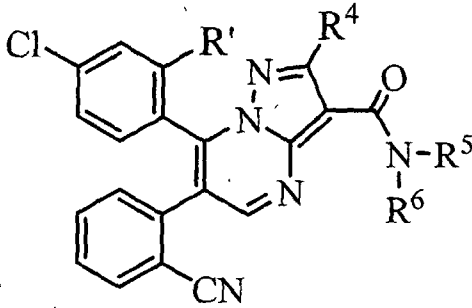
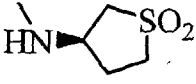
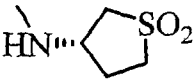
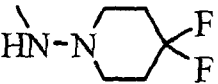
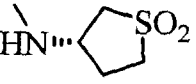
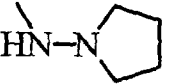
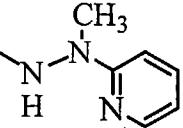
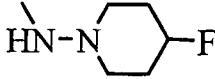
268	Cl		powder MS(APCI):471/473 [M+H] ⁺
269	Cl		powder MS(APCI):485/487 [M+H] ⁺
270	Cl		powder MS(APCI):457/459 [M+H] ⁺

Table 13 (No. 4)

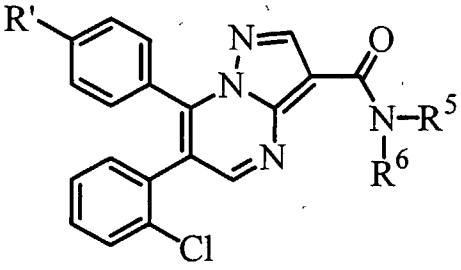
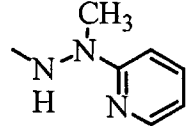
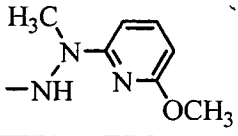
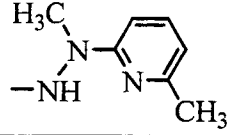
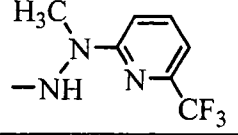
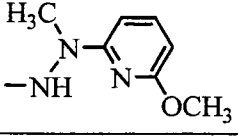
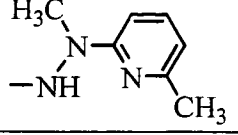
				
Example Nos.	R'	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
271	F	CH ₃		solid MS(APCI):524/526 [M+H] ⁺
272	F	CH ₃		solid MS(APCI):524/526 [M+H] ⁺
273	H	CH ₃		solid MS(APCI):507/509 [M+H] ⁺
274	H	CF ₃		powder MS(APCI):560/562 [M+H] ⁺
275	H	CF ₃		powder MS(APCI):560/562 [M+H] ⁺
276	H	CF ₃		powder MS(APCI):511/513 [M+H] ⁺

277	H	CF ₃		powder MS(APCI):548/550 [M+H] ⁺
278	H	CH ₃		solid MS(APCI):489/491 [M+H] ⁺

Examples 279 to 423

The corresponding starting materials were treated in the same manner as described in Example 3 to obtain the compounds as shown in the following Table 14.

Table 14 (No. 1)

			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
279	CHF ₂		powder MS(APCI):505/507 [M+H] ⁺
280	Cl		powder MS(APCI):519/521 [M+H] ⁺
281	Cl		powder MS(APCI):503/505 [M+H] ⁺
282	Cl		powder MS(APCI):557/559 [M+H] ⁺
283	CF ₃		powder MS(APCI):553/555 [M+H] ⁺
284	CF ₃		powder MS(APCI):537/539 [M+H] ⁺

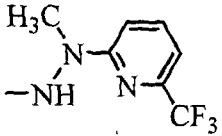
285	CF ₃		powder MS(APCI):591/593 [M+H] ⁺
-----	-----------------	---	---

Table 14 (No. 2)

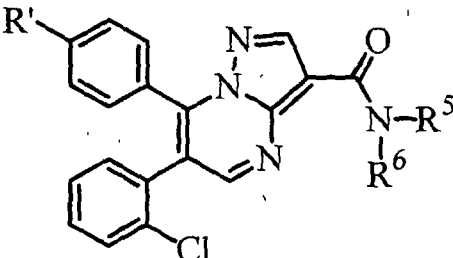
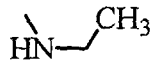
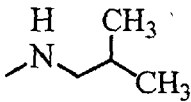
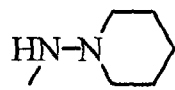
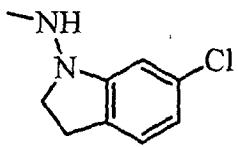
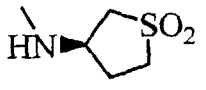
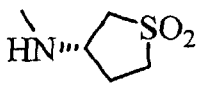
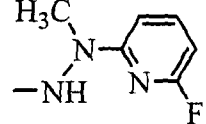
			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
286	CF ₃		powder MS(APCI):445/447 [M+H] ⁺
287	CF ₃		powder MS(APCI):473/475 [M+H] ⁺
288	CF ₃		powder MS(APCI):500/502 [M+H] ⁺
289	CF ₃		powder MS(APCI):557/559 [M+H] ⁺
290	CH ₂ F		powder MS(APCI):499/501 [M+H] ⁺
291	CH ₂ F		powder MS(APCI):499/501 [M+H] ⁺
292	Cl		powder MS(APCI):507/509 [M+H] ⁺

Table 14 (No. 3)

Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
293	Cl		powder MS(APCI):495/497 [M+H] ⁺
294	CF ₃		powder MS(APCI):529/531 [M+H] ⁺
295	Cl		powder MS(APCI):519/521 [M+H] ⁺
296	Cl		powder MS(APCI):489/491 [M+H] ⁺
297	CF ₃		powder MS(APCI):553/555 [M+H] ⁺
298	CF ₃		powder MS(APCI):523/525 [M+H] ⁺

Table 14 (No. 4)

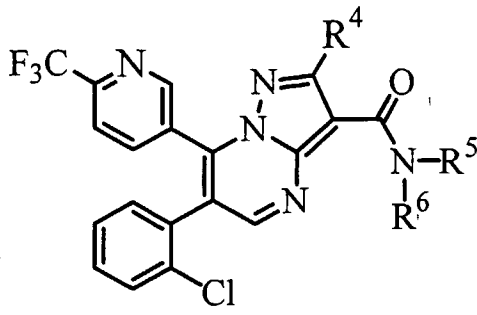
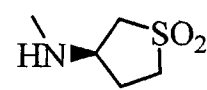
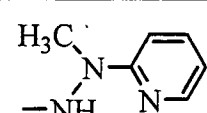
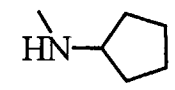
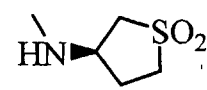
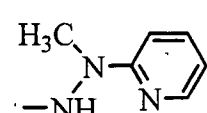
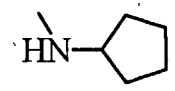
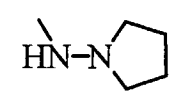
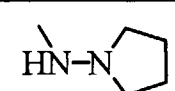
			
Example Nos.	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
299	H		powder MS(APCI):536/538 [M+H] ⁺
300	H		powder MS(APCI):524/526 [M+H] ⁺
301	H		powder MS(APCI):486/488 [M+H] ⁺
302	CH ₃		powder MS(APCI):550/552 [M+H] ⁺
303	CH ₃		powder MS(APCI):538/540 [M+H] ⁺
304	CH ₃		powder MS(APCI):500/502 [M+H] ⁺
305	H		solid MS(APCI):487/489 [M+H] ⁺
306	CH ₃		powder MS(APCI):501/503 [M+H] ⁺

Table 14 (No. 5)

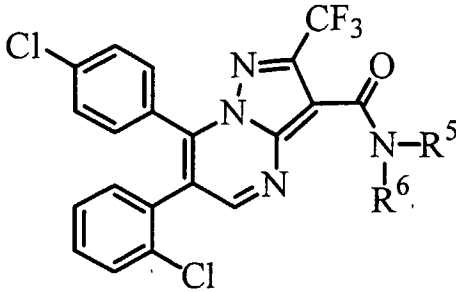
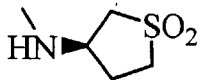
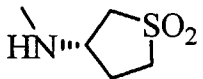
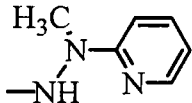
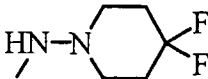
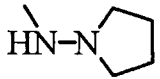
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
307		powder MS(APCI):569/571 [M+H] ⁺
308		powder MS(APCI):569/571 [M+H] ⁺
309		powder MS(APCI):557/559 [M+H] ⁺
310		powder MS(APCI):570/572 [M+H] ⁺
311		powder MS(APCI):520/522 [M+H] ⁺

Table 14 (No. 6)

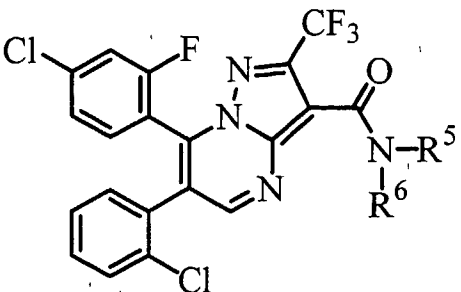
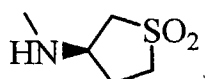
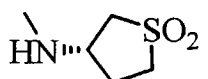
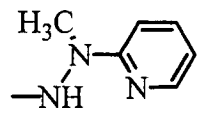
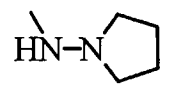
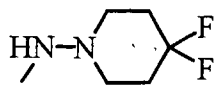
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
312		powder MS(APCI):587/589 [M+H] ⁺
313		powder MS(APCI):587/589 [M+H] ⁺
314		powder MS(APCI):575/577 [M+H] ⁺
315		powder MS(APCI):538/540 [M+H] ⁺
316		powder MS(APCI):588/590 [M+H] ⁺

Table 14 (No. 7)

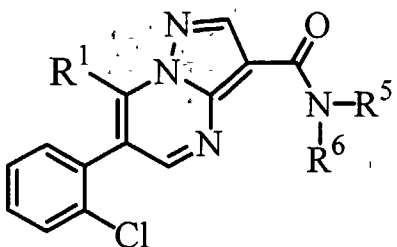
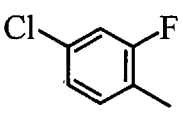
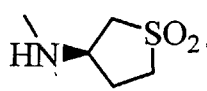
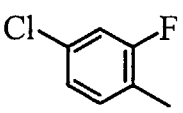
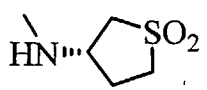
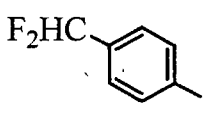
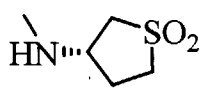
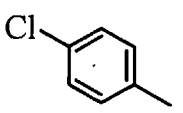
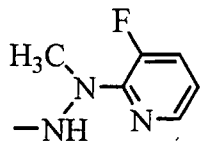
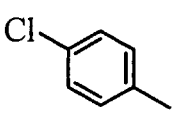
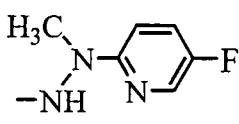
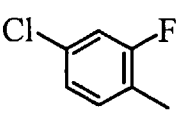
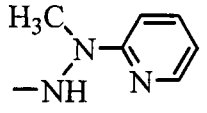
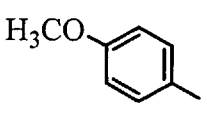
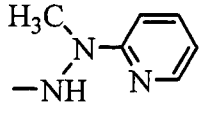
			
Example Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
317			powder MS(APCI):519/521 [M+H] ⁺
318			powder MS(APCI):519/521 [M+H] ⁺
319			powder MS(APCI):517/519 [M+H] ⁺
320			powder MS(APCI):507/509 [M+H] ⁺
321			powder MS(APCI):507/509 [M+H] ⁺
322			powder MS(APCI):507/509 [M+H] ⁺
323			powder MS(APCI):485/487 [M+H] ⁺

Table 14 (No. 8)

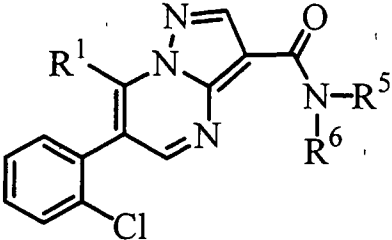
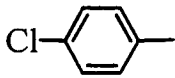
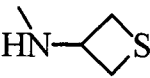
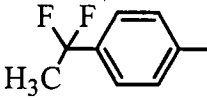
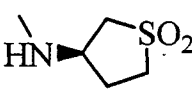
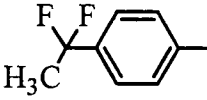
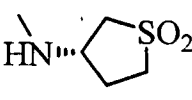
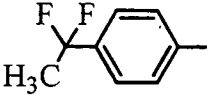
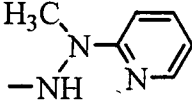
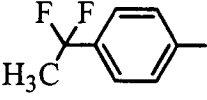
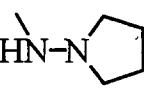
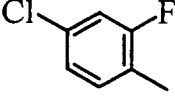
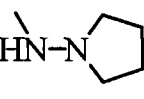
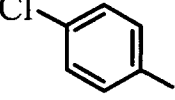
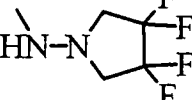
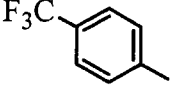
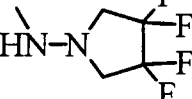
			
Example Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
324			powder MS(APCI):455/457[M+H] ⁺
325			powder MS(APCI):531/533[M+H] ⁺
326			powder MS(APCI):531/533[M+H] ⁺
327			powder MS(APCI):519/521[M+H] ⁺
328			powder MS(APCI):482/484[M+H] ⁺
329			solid MS(APCI):470/472[M+H] ⁺
330			powder MS(APCI):524/526[M+H] ⁺
331			powder MS(APCI):558/560[M+H] ⁺

Table 14 (No. 9)

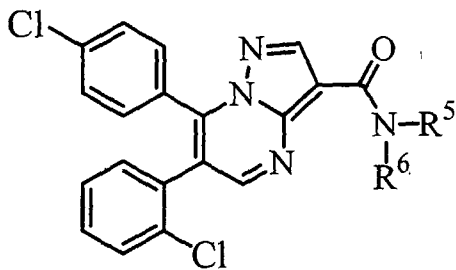
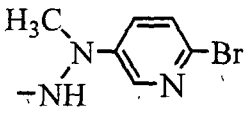
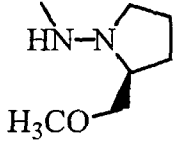
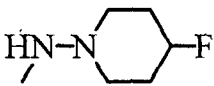
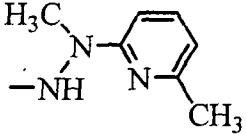
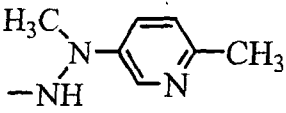
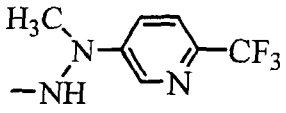
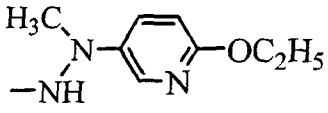
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
332		powder MS(APCI):569/571 [M+H] ⁺
333		powder MS(APCI):496/498 [M+H] ⁺
334		solid MS(APCI):484/486 [M+H] ⁺
335		powder MS(APCI):474/476 [M+H] ⁺
336		powder MS(APCI):503/505 [M+H] ⁺
337		powder MS(APCI):557/559 [M+H] ⁺
338		powder MS(APCI):533/535 [M+H] ⁺

Table 14 (No. 10)

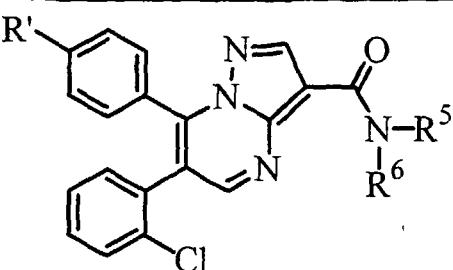
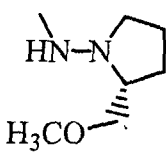
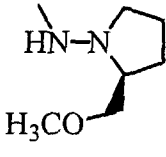
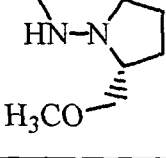
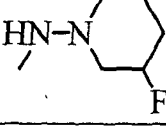
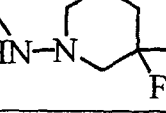
			
Example Nos.	R'	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
339	Cl		powder MS(APCI):496/498 [M+H] ⁺
340	CF ₃		powder MS(APCI):530/532 [M+H] ⁺
341	CF ₃		powder MS(APCI):530/532 [M+H] ⁺
342	Cl		solid MS(APCI):484/486 [M+H] ⁺
343	Cl		solid MS(APCI):502/504 [M+H] ⁺
344	Cl		solid MS(APCI):480/482 [M+H] ⁺

Table 14 (No. 11)

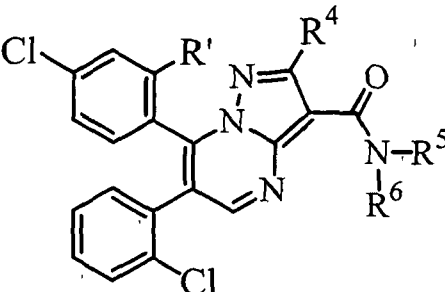
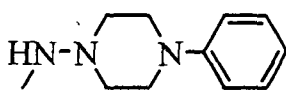
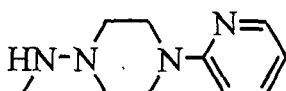
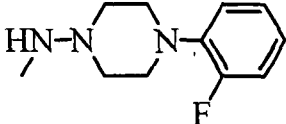
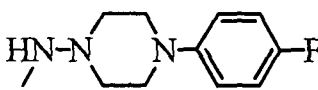
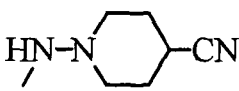
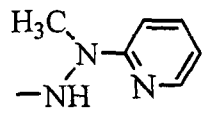
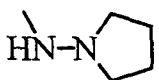
				
Example Nos.	R'	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
345	H	H		solid MS(APCI):543/545 [M+H] ⁺
346	H	H		solid MS(APCI):544/546 [M+H] ⁺
347	H	H		solid MS(APCI):561/563 [M+H] ⁺
348	H	H		solid MS(APCI):561/563 [M+H] ⁺
349	H	H		solid MS(APCI):491/493 [M+H] ⁺
350	F	CH ₃		solid MS(APCI):521/523 [M+H] ⁺
351	F	CH ₃		solid MS(APCI):484/486 [M+H] ⁺

Table 14 (No. 12)

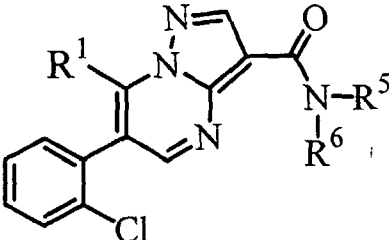
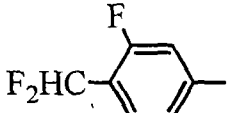
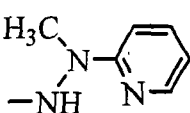
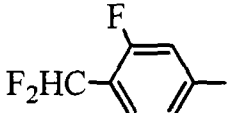
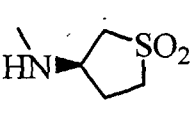
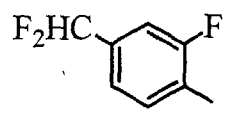
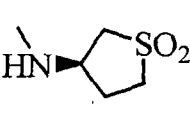
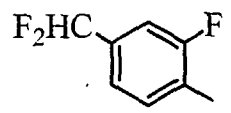
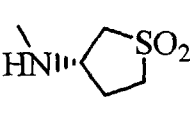
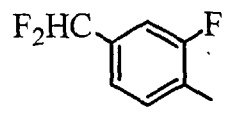
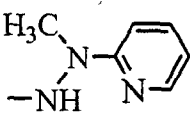
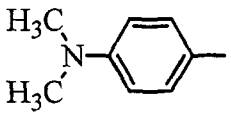
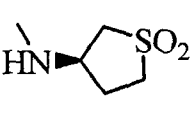
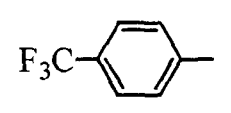
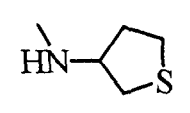
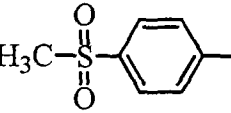
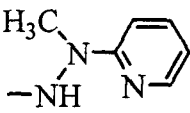
			
Example Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
352			powder MS(APCI):523/525 [M+H] ⁺
353			powder MS(APCI):535/537 [M+H] ⁺
354			powder MS(APCI):535/537 [M+H] ⁺
355			powder MS(APCI):535/537 [M+H] ⁺
356			powder MS(APCI):523/525 [M+H] ⁺
357			powder MS(APCI):510/512 [M+H] ⁺
358			powder MS(APCI):503/505 [M+H] ⁺
359			powder MS(APCI):533/535 [M+H] ⁺

Table 14 (No. 13)

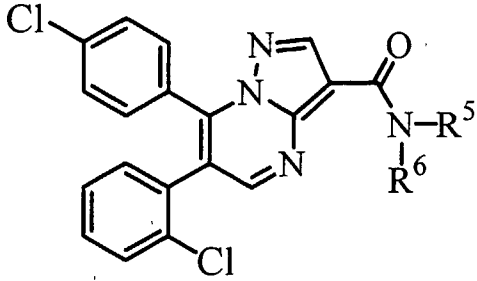
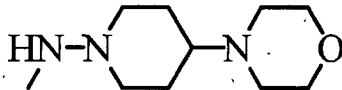
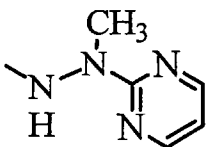
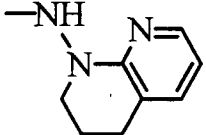
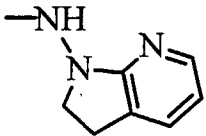
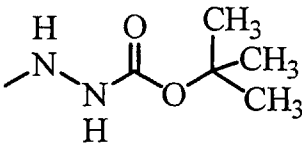
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
360		solid MS(APCI):551/553 [M+H] ⁺
361		powder MS(APCI):490/492 [M+H] ⁺
362		powder MS(APCI):515/517 [M+H] ⁺
363		powder MS(APCI):501/503 [M+H] ⁺
364		powder MS(APCI):498/500 [M+H] ⁺

Table 14 (No. 14)

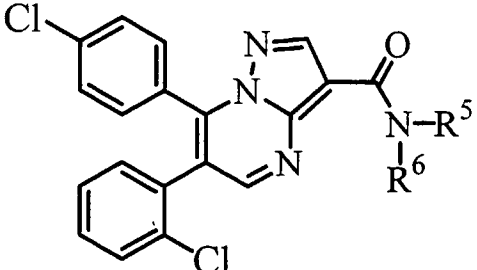
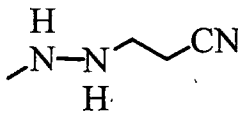
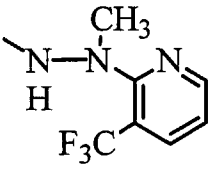
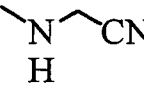
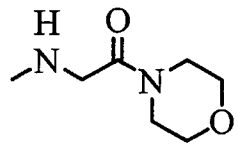
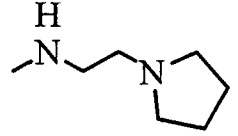
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
365		powder MS(APCI):451/453 [M+H] ⁺
366		powder MS(APCI):557/559 [M+H] ⁺
367		solid MS(ESI):422 [M+H] ⁺
368		solid MS(ESI): 510 [M+H] ⁺
369		powder MS(APCI):480/482 [M+H] ⁺

Table 14 (No. 15)

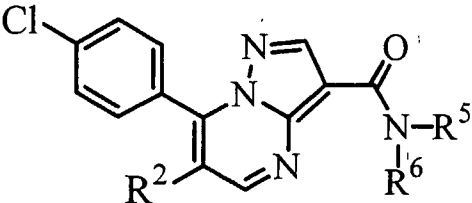
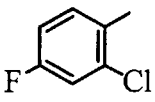
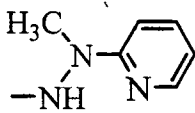
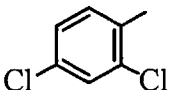
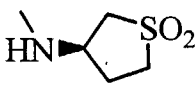
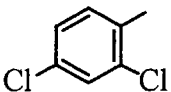
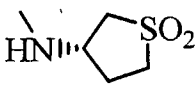
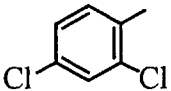
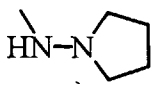
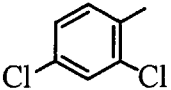
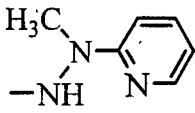
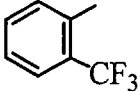
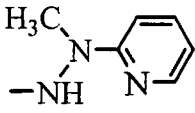
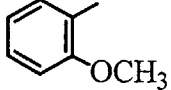
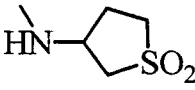
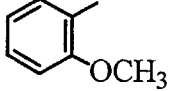
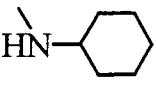
			
Example Nos.	R ²	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
370			solid MS(APCI):507/509 [M+H] ⁺
371			powder MS(APCI):535/537 [M+H] ⁺
372			powder MS(APCI):535/537 [M+H] ⁺
373			powder MS(APCI):486/488 [M+H] ⁺
374			powder MS(APCI):523/525 [M+H] ⁺
375			powder MS(APCI):523/525 [M+H] ⁺
376			powder MS(APCI):497/499 [M+H] ⁺
377			powder MS(APCI):461/463 [M+H] ⁺

Table 14 (No. 16)

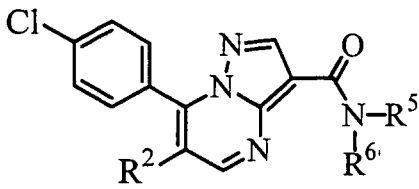
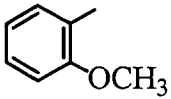
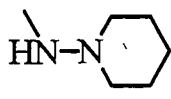
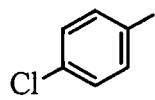
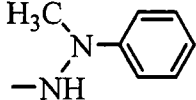
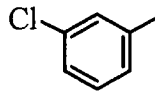
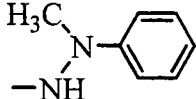
			
Example Nos.	R ²	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
378			powder MS(APCI):462/464 [M+H] ⁺
379			powder MS(APCI):488/490 [M+H] ⁺
380			powder MS(APCI):488/490 [M+H] ⁺

Table 14 (No. 17)

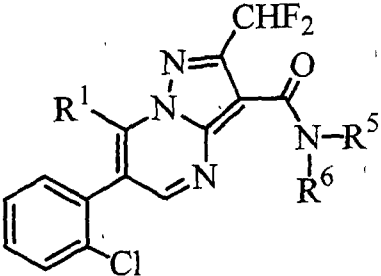
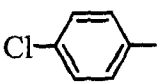
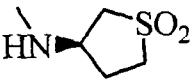
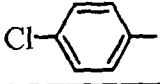
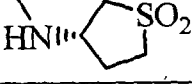
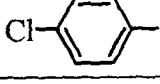
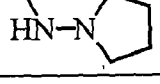
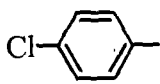
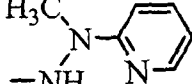
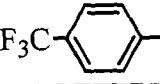
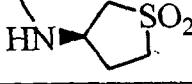
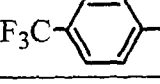
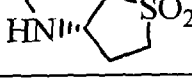
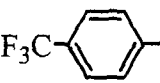
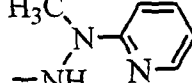
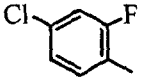
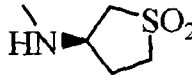
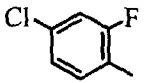
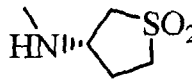
			
Example Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
381			powder MS(APCI):551/553 [M+H] ⁺
382			powder MS(APCI):551/553 [M+H] ⁺
383			powder MS(APCI):502/504 [M+H] ⁺
384			powder MS(APCI):539/541 [M+H] ⁺
385			powder MS(APCI):585/587 [M+H] ⁺
386			powder MS(APCI):585/587 [M+H] ⁺
387			powder MS(APCI):573/575 [M+H] ⁺
388			solid MS(APCI):569/571 [M+H] ⁺
389			solid MS(APCI):569/571 [M+H] ⁺

Table 14 (No. 18)

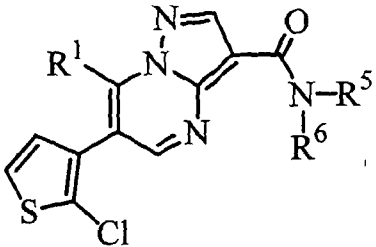
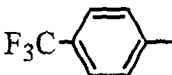
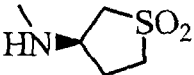
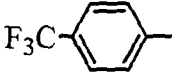
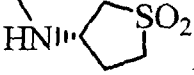
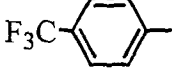
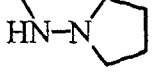
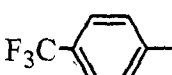
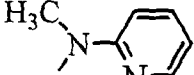
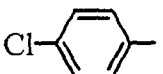
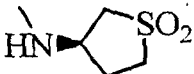
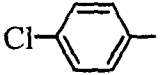
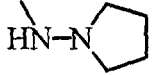
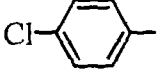
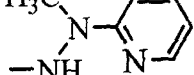
			
Example Nos.	R¹	-N(R⁵)(R⁶)	Physicochemical properties etc.
390			powder MS(APCI):541/543 [M+H] ⁺
391			powder MS(APCI):541/543 [M+H] ⁺
392			powder MS(APCI):492/494 [M+H] ⁺
393			powder MS(APCI):529/531 [M+H] ⁺
394			powder MS(APCI):507/509 [M+H] ⁺
395			powder MS(APCI):458/460 [M+H] ⁺
396			powder MS(APCI):495/497 [M+H] ⁺

Table 14 (No. 19)

Example Nos.	R'	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
397	CHF ₂	H		powder MS(APCI):468/470 [M+H] ⁺
398	CHF ₂	H		powder MS(APCI):482/484 [M+H] ⁺
399	CHF ₂	H		powder MS(APCI):442/444 [M+H] ⁺
400	CHF ₂	H		powder MS(APCI):484/486 [M+H] ⁺
401	Cl	CH ₃ OCH ₂		powder MS(APCI):545/547 [M+H] ⁺
402	Cl	CH ₃ OCH ₂		powder MS(APCI):545/547 [M+H] ⁺
403	Cl	CH ₃ OCH ₂		powder MS(APCI):533/535 [M+H] ⁺
404	Cl	CH ₃ OCH ₂		powder MS(APCI):496/498 [M+H] ⁺

Table 14 (No. 20)

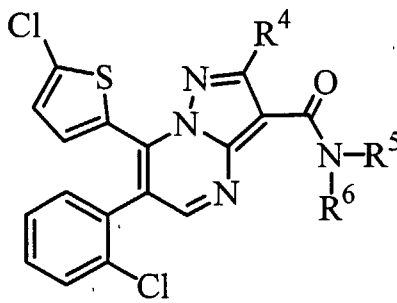
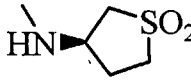
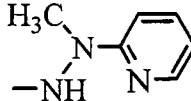
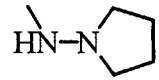
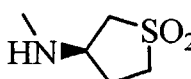
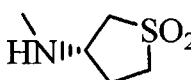
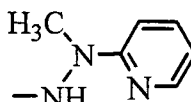
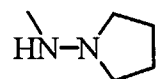
			
Example Nos.	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
405	H		powder MS(APCI):507/509 [M+H] ⁺
406	H		powder MS(APCI):495/497 [M+H] ⁺
407	H		powder MS(APCI):458/460 [M+H] ⁺
408	CH ₃		powder MS(APCI):521/523 [M+H] ⁺
409	CH ₃		powder MS(APCI):521/523 [M+H] ⁺
410	CH ₃		powder MS(APCI):509/511 [M+H] ⁺
411	CH ₃		powder MS(APCI):472/474 [M+H] ⁺

Table 14 (No. 21)

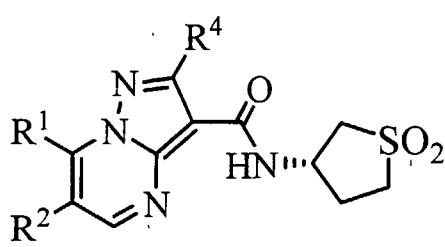
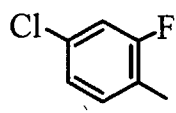
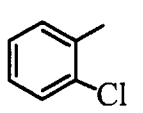
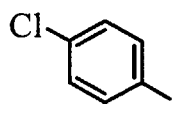
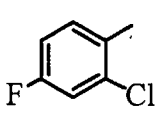
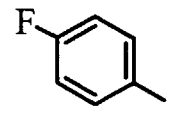
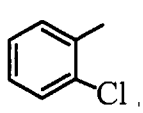
				
Example Nos.	R ¹	R ²	R ⁴	Physicochemical properties etc.
412			CH ₃	solid MS(APCI):533/535 [M+H] ⁺
413			CH ₃	powder MS(APCI):533/535 [M+H] ⁺
414			CH ₃	powder MS(APCI):499/501 [M+H] ⁺

Table 14 (No. 22)

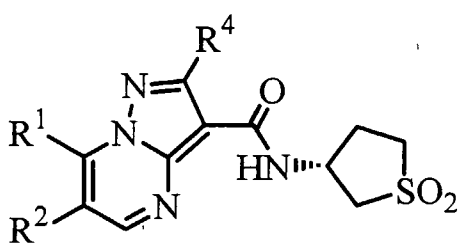
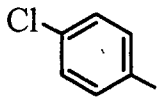
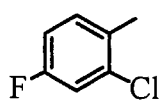
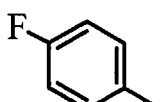
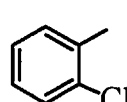
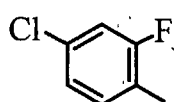
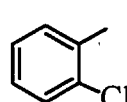
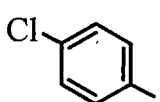
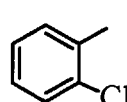
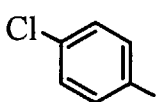
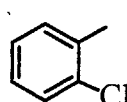
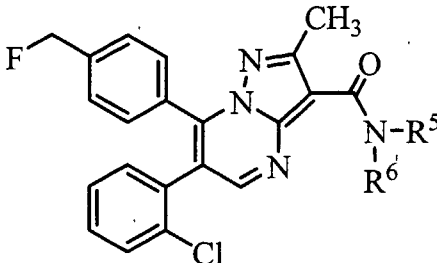
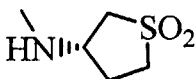
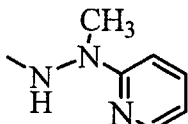
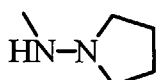
				
Et: ethyl group				
Example Nos.	R ¹	R ²	R ⁴	Physicochemical properties etc.
415			CH ₃	powder MS(APCI):533/535 [M+H] ⁺
416			CH ₃	powder MS(APCI):499/501 [M+H] ⁺
417			CH ₃	solid MS(APCI):533/535 [M+H] ⁺
418			C ₂ H ₅	solid MS(APCI):529/531 [M+H] ⁺
419			EtOCH ₂	powder MS(APCI):559/561 [M+H] ⁺

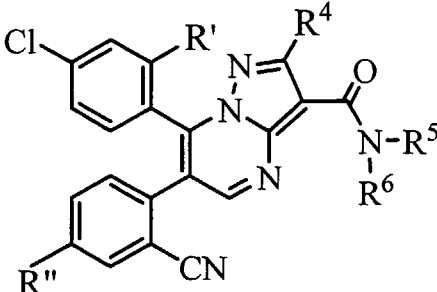
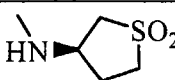
Table 14 (No. 23)

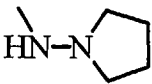
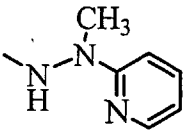
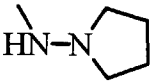
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
420		powder MS(APCI):513/515 [M+H] ⁺
421		powder MS(APCI):513/515 [M+H] ⁺
422		powder MS(APCI):501/503 [M+H] ⁺
423		powder MS(APCI):464/466 [M+H] ⁺

Examples 424 to 427

The corresponding starting materials were treated in the same manner as described in Example 3 or 242 to obtain the compounds as shown in the following Table 15.

Table 15

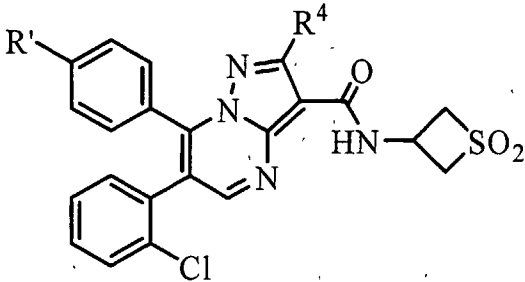
					
Example Nos.	R'	R''	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
424	H	F	H		powder MS(APCI):510/512 [M+H] ⁺

425	H	F	H		powder MS(APCI):461/463 [M+H] ⁺
426	H	F	H		powder MS(APCI):498/500 [M+H] ⁺
427	F	H	CH ₃		solid MS(APCI):475/477 [M+H] ⁺

Examples 428 to 430

The corresponding starting materials were treated in the same manner as described in Example 28 to obtain the compounds as shown in the following Table 16.

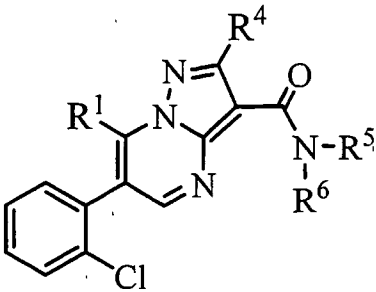
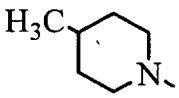
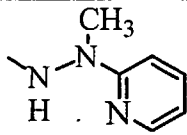
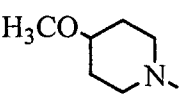
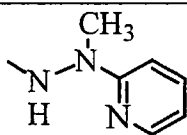
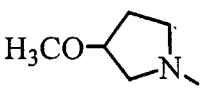
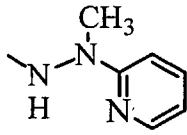
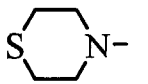
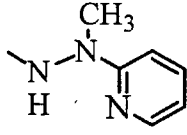
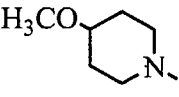
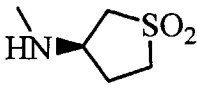
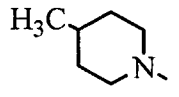
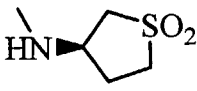
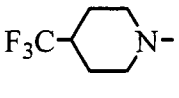
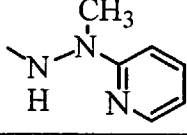
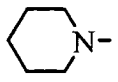
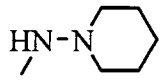
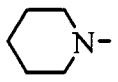
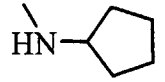
Table 16

			
Example Nos.	R'	R ⁴	Physicochemical properties etc.
428	Cl	H	powder MS(APCI):487/489 [M+H] ⁺
429	CF ₃	H	powder MS(APCI):521/523 [M+H] ⁺
430	Cl	CH ₃	powder MS(APCI):501/503 [M+H] ⁺

Examples 431 to 439

The corresponding starting materials were treated in the same manner as described in Example 1 to obtain the compounds as shown in the following Table 17.

Table 17

				
Example Nos.	R ¹	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
431		H		powder MS(APCI):476/478 [M+H] ⁺
432		H		powder MS(APCI):492/494 [M+H] ⁺
433		H		powder MS(APCI):478/480 [M+H] ⁺
434		CH ₃		powder MS(APCI):494/496 [M+H] ⁺
435		H		powder MS(APCI):504/506 [M+H] ⁺
436		H		powder MS(APCI):488/490 [M+H] ⁺
437		H		powder MS(APCI):530/532 [M+H] ⁺
438		H		powder MS(APCI):439/441 [M+H] ⁺
439		H		powder MS(APCI):424/425 [M+H] ⁺

Example 440

(1) To a solution the compound obtained in Example 484(2) (1.0 g) and triethylamine (1.81 mL) in tetrahydrofuran (20 mL) was added gradually methanesulfonyl chloride (1.0 g) under ice-cooling and the mixture was stirred at room temperature for 40 minutes. The reaction mixture was diluted with ethyl acetate and thereto was added water under ice-cooling. After stirring, the aqueous layer was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent: hexane/ethyl acetate = 80/20 to 60/40) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonyl-2-[N,N-bis(methylsulfonyl)amino]-pyrazolo[1,5-a]pyrimidine (1.01 g, yield: 75%) as a pale yellow solid.

MS(APCI)m/z; 617/619 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (1.01 g) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride trihydrate (1.03 g) and the mixture was stirred at room temperature for 15 minutes. To the reaction mixture was added water and the mixture was stirred and extracted with chloroform. The extract was dried over magnesium sulfate and filtered and the filtrate was concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 70/30 to 50/50) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonyl-2-(methylsulfonyl-amino)pyrazolo[1,5-a]pyrimidine (0.71 g, yield: 81%) as a pale yellow powder.

MS(APCI)m/z; 539/541 [M+H]⁺

(3) A solution of the compound obtained in the above step (2) (0.69 g) and sodium ethoxide (0.87 g) in ethanol (20 mL) was stirred at 80°C for 10 minutes. To the reaction mixture was added dropwise methyl iodide (1.59 mL) and the mixture was stirred overnight. The reaction mixture was concentrated in vacuo and to the residue was added water. The mixture was extracted with ethyl acetate and the organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on NH-silica gel (Chromatorex NH-silica gel, solvent: hexane/ethyl acetate = 75/25 to 60/40) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonyl-2-[N-methyl-N-(methylsulfonyl)amino]pyrazolo[1,5-a]pyrimidine (0.70 g, yield: 99%) as a powder.

MS(APCI)m/z; 553/555 [M+H]⁺

Examples 441 to 452

The corresponding starting materials were treated in the same manner as

described in Reference Example 1(3) and Example 3 to obtain the compounds as shown in the following Table 18.

Table 18 (No. 1)

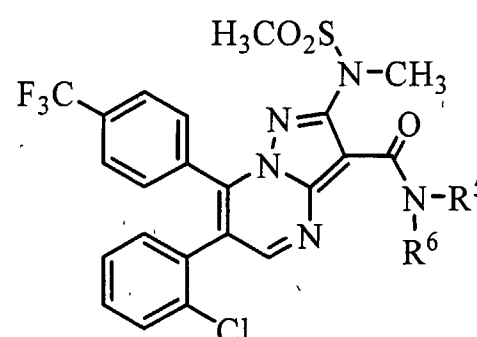
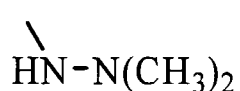
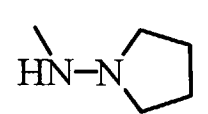
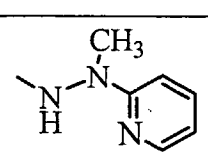
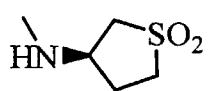
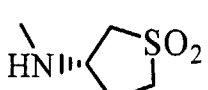
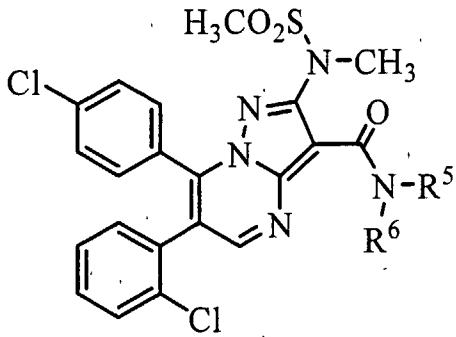
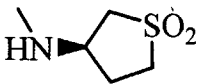
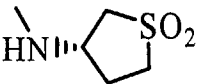
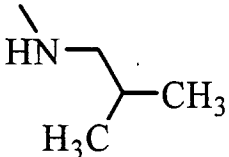
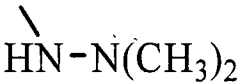
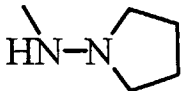
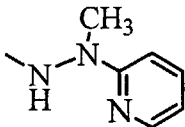
		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
441		powder MS(APCI):567/569 [M+H] ⁺
442		powder MS(APCI):593/595 [M+H] ⁺
443	-NH(C ₂ H ₅)	powder MS(APCI):552/554 [M+H] ⁺
444		powder MS(APCI):630/632 [M+H] ⁺
445		powder MS(APCI):642/644 [M+H] ⁺
446		powder MS(APCI):642/644 [M+H] ⁺

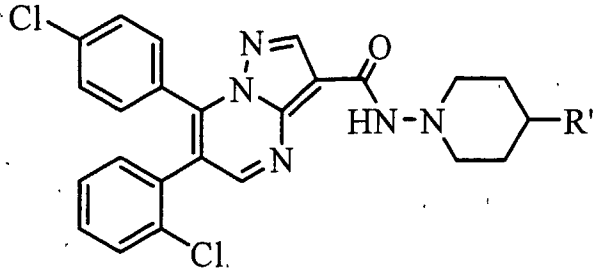
Table 18 (No. 2)

		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
447		powder MS(APCI):608/610 [M+H] ⁺
448		powder MS(APCI):608/610 [M+H] ⁺
449		powder MS(APCI):546/548 [M+H] ⁺
450		powder MS(APCI):533/535 [M+H] ⁺
451		powder MS(APCI):559/561 [M+H] ⁺
452		powder MS(APCI):596/598 [M+H] ⁺

Examples 453 to 454

The corresponding starting materials were treated in the same manner as described in Example 3 to obtain the compounds as shown in the following Table 19.

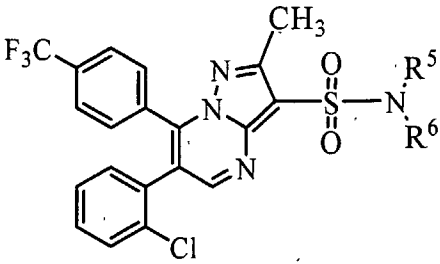
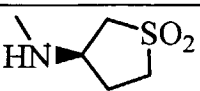
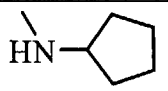
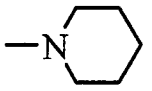
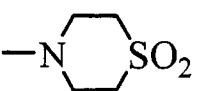
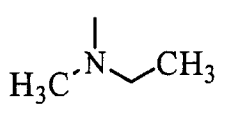
Table 19

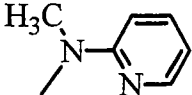
		
Example Nos.	R'	Physicochemical properties etc.
453	-OCH ₃	yellow solid MS(APCI): 496/498 [M+H] ⁺
454	-OH	solid MS(APCI): 482/484 [M+H] ⁺

Examples 455 to 460

The corresponding starting materials were treated in the same manner as described in Example 238 to obtain the compounds as shown in the following Table 20.

Table 20

		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
455		powder MS(APCI): 585/587 [M+H] ⁺
456		powder MS(APCI): 535/537 [M+H] ⁺
457		powder MS(APCI): 535/537 [M+H] ⁺
458		powder MS(APCI): 585/587 [M+H] ⁺
459		powder MS(APCI): 509/511 [M+H] ⁺

460		powder MS(APCI):558/560 [M+H] ⁺
-----	---	---

Example 461

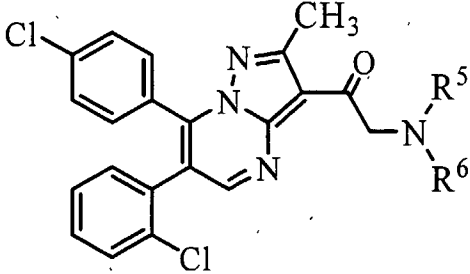
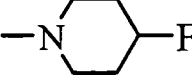
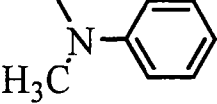
To a solution of the compound obtained in Reference Example 53 (60 mg) in tetrahydrofuran (1 mL)-dimethylacetamide (0.2 mL) was added diiodopentane (34.5 μ L) and sodium carbonate (24.5 mg) and the mixture was stirred at 70°C for 17 hours. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 85/15 to 60/40) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-(piperidin-1-yl)pyrazolo[1,5-a]pyrimidine (17 mg, yield: 24%) as a red powder.

MS(APCI)m/z; 457/459 [M+H]⁺

Examples 462 to 465

The corresponding starting materials were treated in the same manner as described in Example 240 to obtain the compounds as shown in the following Table 21.

Table 21

		
Example Nos.	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
462		solid MS(APCI):529/531 [M+H] ⁺
463		solid MS(APCI):497/499 [M+H] ⁺
464		solid MS(APCI):515/517 [M+H] ⁺
465		solid MS(APCI):501/503 [M+H] ⁺

Example 466

(1) The compound obtained in Reference Example 33 was treated in the same manner as described in Example 1 to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1-hydroxy-4-methylthio-2-butyl)carbamoyl]pyrazolo[1,5-a]pyrimidine (357 mg, yield: 56%) as a yellow powder.

MS(APCI)m/z; 535/537 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (349 mg) in methylene chloride (2 mL) was added thionyl chloride (170 μ L) and the mixture was stirred at room temperature for 23 hours. To the reaction mixture was added chloroform (2 mL) and the mixture was stirred at 60°C for 5 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 85/15 to 60/40) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[(tetrahydrothiophene-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (106 mg, yield: 32%) as a pale yellow powder.

MS(APCI)m/z; 503/505 [M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (96 mg) in methylene chloride (3 mL) was added m-chloro-perbenzoic acid (75%, 44 mg) under ice-cooling and the mixture was stirred at the same temperature for 15 minutes. To the reaction mixture was added sodium sulfite and an aqueous sodium hydrogencarbonate solution and the mixture was extracted with chloroform. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: chloroform/methanol = 100/0 to 92/8) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[(1-oxo-tetrahydrothiophene-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine (81 mg, yield: 82%) as a colorless powder.

MS(APCI)m/z; 519/520 [M+H]⁺

Example 467

The compound obtained in Reference Example 47 was treated in the same manner as described in Example 3 to give (R)- 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(1,1-dioxo-tetrahydrothiophene-3-yl)carbamoyl]-2-(2-methoxyethoxy)pyrazolo[1,5-a]pyrimidine (77 mg, yield: 67%) as a powder.

MS(APCI)m/z; 575/577 [M+H]⁺

Example 468

The corresponding starting materials were treated in the same manner as described in Example 3 to give (R)- 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(1,1-dioxo-tetrahydrothiophene-3-yl)carbamoyl]-2-(2-hydroxyethoxy)pyrazolo[1,5-

a]pyrimidine (91 mg, yield: 84%) as a powder.

MS(APCI)m/z; 561/563 [M+H]⁺

Example 469

(1) The compound obtained in Reference Example 59 was treated in the same manner as described in Example 3 to give (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(1,1-dioxo-tetrahydrothiophene-3-yl)carbamoyl]-2-methylthiomethylpyrazolo[1,5-a]pyrimidine (183.6 mg, yield: 91%) as a pale yellow powder.

MS(APCI)m/z; 561/563 [M+H]⁺

(2) The compound obtained in the above step (1) (183 mg) was treated in the same manner as described in Example 29 to give (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(1,1-dioxo-tetrahydrothiophene-3-yl)carbamoyl]-2-(methylsulfonylmethyl)pyrazolo[1,5-a]pyrimidine (91.6 mg, yield: 47%) as a powder.

MS(APCI)m/z; 593/595 [M+H]⁺

Example 470

The compound obtained in Reference Example 9 (50 mg) and 3-pyridylacetate hydrochloride (31.8 mg) were treated in the same manner as described in Example 3 to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[2-(2-pyridyl)acetyl]amino]pyrazolo[1,5-a]pyrimidine (52.6 mg, yield: 79%) as a yellow powder.

MS(APCI)m/z; 474/476 [M+H]⁺

Example 471

(1) The compound obtained in Reference Example 5 (7.3 g) was treated in the same manner as described in Example 484 to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-aminopyrazolo[1,5-a]pyrimidine (1.43 g).

MS(APCI)m/z; 427/429 [M+H]⁺

(2) The compound obtained in the above step (1) (2.64 g) was treated in the same manner as described in Example 440(1) to (2) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-(methylsulfonylamino)pyrazolo[1,5-a]pyrimidine (2.20 g).

MS(APCI)m/z; 505/507 [M+H]⁺

(3) The compound obtained in the above step (2) (70 mg) was treated in the same manner as described in Reference Example 1(3) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-carboxy-2-(methylsulfonylamino)pyrazolo[1,5-a]pyrimidine as a crude product.

MS(APCI)m/z; 477/479 [M+H]⁺

(4) The compound obtained in the above step (3) was treated in the same manner as described in Example 3 to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-

[[N'-methyl-N'-(2-pyridyl)hydrazino]carbonyl]-2-(methylsulfonylamino)pyrazolo[1,5-a]pyrimidine (27 mg, yield: 32%) as a powder.

MS(APCI)m/z; 596/598 [M+H]⁺

Example 472

5 The corresponding starting materials were treated in the same manner as described in Example 471 to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-isobutylcarbonyl)-2-(methylsulfonylamino)pyrazolo[1,5-a]pyrimidine (52 mg, yield: 79%) as a powder.

MS(APCI)m/z; 546/548 [M+H]⁺

10 Example 473

To a solution of the compound obtained in Reference Example 9(2) (50 mg) in tetrahydrofuran (1.5 mL) was added phenyl isocyanate (30.5 μ L) and triethylamine (49 μ L) and the mixture was stirred at 60°C overnight. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 75/25 to 65/35) to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N'-phenylureido)pyrazolo[1,5-a]pyrimidine (37.8 mg, yield: 57%) as a powder.

MS(APCI)m/z; 474/476 [M+H]⁺

20 Examples 474

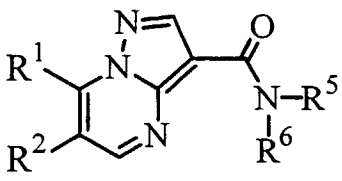
The corresponding starting materials were treated in the same manner as described in Example 473 to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N'-cyclopentylureido)pyrazolo[1,5-a]pyrimidine (48.3 mg, yield: 74%) as a powder.

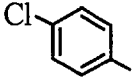
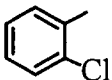
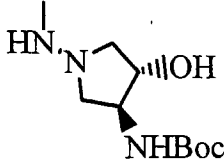
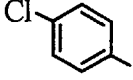
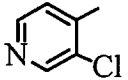
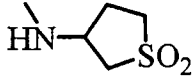
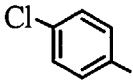
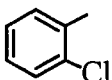
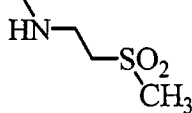
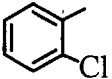
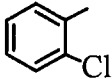
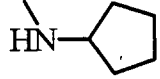
MS(APCI)m/z; 466/468 [M+H]⁺

25 Examples 475 to 478

The corresponding starting materials were treated in the same manner as described in Example 3 to obtain the compounds as shown in the following Table 22.

Table 22

 Boc: tert-butoxycarbonyl group				
Example Nos.	R ¹	R ²	-N(R ⁵)(R ⁶)	Physicochemical properties etc.

475				solid MS(APCI):583/585 [M+H] ⁺
476				powder MS(APCI):502/504 [M+H] ⁺
477				powder MS(APCI):489/491 [M+H] ⁺
478				powder MS(APCI):451/453 [M+H] ⁺

Examples 479

The corresponding starting materials were treated in the same manner as described in Example 31 to obtain 6-(2-cyanophenyl)-7-(4-trifluoromethylphenyl)-3-

5 [N-(1,1-dioxothiomorpholino)carbamoyl]pyrazolo[1,5-a]pyrimidine as a powder.

MS(APCI)m/z; 541 [M+H]⁺

Example 480

(1) The compound obtained in Example 471(1) (440 mg) was treated in the same manner as described in Reference Example 1(3) to give 6-(2-chlorophenyl)-7-

10 (4-chlorophenyl)-3-carboxy-2-aminopyrazolo[1,5-a]pyrimidine as a crude product.

MS(APCI)m/z; 399/401 [M+H]⁺

(2) The compound obtained in the above step (1) was treated in the same manner as described in Example 3 to give (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-

15 3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-aminopyrazolo[1,5-a]pyrimidine

(254 mg, yield: 48%) as a powder.

(3) The compound obtained in the above step (2) (250 mg) was treated in the same manner as described in Example 43 to give (R)-6-(2-chlorophenyl)-7-(4-chloro-

20 phenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-(pyrrolidin-1-yl)-

pyrazolo[1,5-a]pyrimidine (106 mg, yield: 38%) as a powder.

MS(APCI)m/z; 570/572 [M+H]⁺

(4) The compound obtained in the above step (3) (95 mg) was treated in the same manner as described in Example 33 to give the compound as shown in the following Table 23.

described in Reference Example 5(1) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-methylthiopyrazolo[1,5-a]pyrimidine (11.4 g, yield: 45%) as a colorless powder.

MS(APCI)m/z; 492/494 [M+H]⁺

5 Example 484

(1) The compound obtained in Example 483 (11 g) was treated in the same manner as described in Reference Example 5(2) to give 2-azido-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (10.6 g, yield: 91%) as a crude product (colorless powder). The product (10.6 g) was treated in the same manner as described in Reference Example 11 to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-(triphenylphosphoranylidenamino)pyrazolo[1,5-a]-pyrimidine (11.4 g) as a colorless powder.

(2) The compound obtained in the above step (1) (11.1 g) and acetic acid (70 mL) were treated in the same manner as described in Example 40 to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonyl-2-aminopyrazolo[1,5-a]pyrimidine (5.2 g, yield: 73%) as a colorless solid.

MS(APCI)m/z; 461/463 [M+H]⁺

15 Example 485

The compound obtained in Example 484 (2.1 g) and 1,4-dichlorobutane (2.9 g) were treated in the same manner as described in Example 43 to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonyl-2-(pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine (0.61 g, yield: 26%) as a yellow oil.

MS(APCI)m/z; 515/517 [M+H]⁺

20 Example 486

The compound obtained in Example 485 (0.61 g) was treated in the same manner as described in Reference Example 8 to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-carboxy-2-(pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine (0.45 g) as a crude product. The product (70 mg) and 1-aminopyrrolidine hydrochloride (17.6 mg) were treated in the same manner as described in Example 3 to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(pyrrolidin-1-yl)carbamoyl]-2-(pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine (14.8 mg; compound a) and 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-(pyrrolidin-1-yl)pyrazolo[1,5-a]-pyrimidine (32.6 mg; compound b) as a yellow powder, respectively.

Compound a: MS(APCI)m/z; 555/557 [M+H]⁺

Compound b: MS(APCI)m/z; 443/445 [M+H]⁺

35 Example 487

(1) To a solution of the compound obtained in Reference Example 4B (300 mg) in dimethylformamide (5 mL) was added portionwise sodium hydride (60%, 137 mg) under nitrogen-gas atmosphere and the mixture was stirred. To the mixture was gradually added 4-chloro-N-methylaniline (125 μ L) and the mixture was stirred at 80°C for 30 minutes. After cooling to room temperature, to the reaction mixture was added water and ethyl acetate and the aqueous layer was neutralized with 2N HCl. The organic layer was washed with water, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: chloroform/methanol = 98/2 to 85/15) to obtain 6-(2-chlorophenyl)-7-[N-methyl-N-(4-chlorophenyl)amino]-3-carboxy-2-methylpyrazolo[1,5-a]pyrimidine (54.2 mg, yield: 15%) as a colorless powder.

MS(APCI)m/z; 427/429 [M+H]⁺

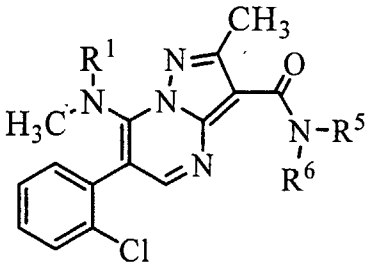
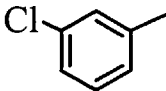
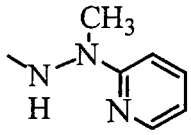
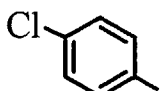
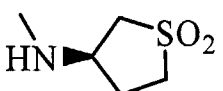
(2) The compound obtained in the above step (1) (27 mg) was treated in the same manner as described in Example 3 to give 6-(2-chlorophenyl)-7-[N-methyl-N-(4-chlorophenyl)amino]-3-[N'-methyl-N'-(pyridin-2-yl)hydrazino]-2-methylpyrazolo[1,5-a]pyrimidine (18.5 mg, yield: 55%) as a colorless powder.

MS(APCI)m/z; 532/533 [M+H]⁺

Examples 488 to 489

The corresponding starting materials were treated in the same manner as described in Example 487 to obtain the compounds as shown in the following Table 24.

Table 24

			
Example Nos.	R ¹	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
488			powder MS(APCI): 532/534 [M+H] ⁺
489			powder MS(APCI): 544/546 [M+H] ⁺

Examples 490 to 500

The corresponding starting materials were treated in the same manner as described in Example 487 to obtain the compounds as shown in the following Table 25.

Table 25 (No. 1)

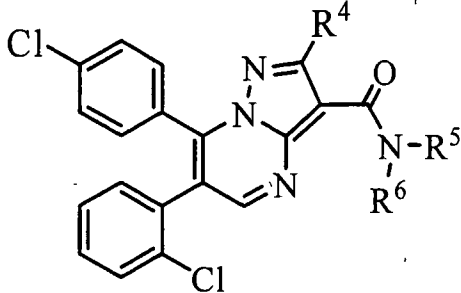
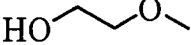
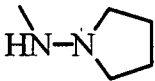
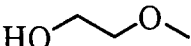
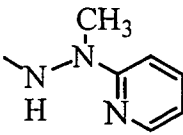
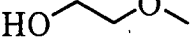
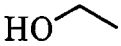
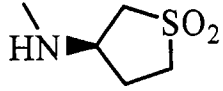
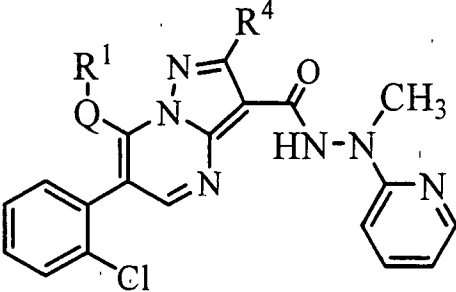
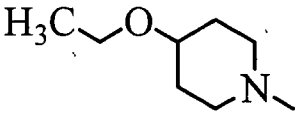
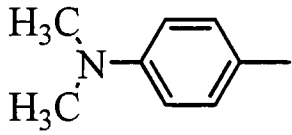
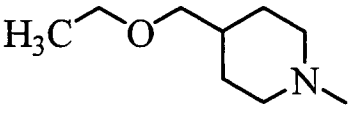
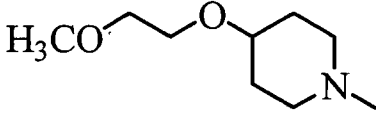
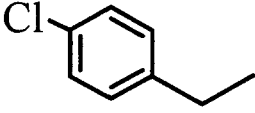
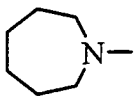
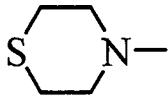
			
Example Nos.	R ⁴	-N(R ⁵)(R ⁶)	Physicochemical properties etc.
490			powder MS(APCI): 512/514 [M+H] ⁺
491			powder MS(APCI): 549/551 [M+H] ⁺
492			powder MS(APCI): 561/563 [M+H] ⁺
493			powder MS(APCI): 531/533 [M+H] ⁺

Table 25 (No. 2)

			
Example Nos.	R ¹ -Q-	R ⁴	Physicochemical properties etc.
494		H	powder MS(APCI): 506/508 [M+H] ⁺
495		H	powder MS(APCI): 498/500 [M+H] ⁺
496		H	powder MS(APCI): 520/522 [M+H] ⁺
497		H	powder MS(APCI): 544/546 [M+H] ⁺
498		CH ₃	powder MS(APCI): 517/519 [M+H] ⁺
499		H	powder MS(APCI): 476/478 [M+H] ⁺
500		H	powder MS(APCI): 464/466 [M+H] ⁺

Reference Example 1

- 5 (1) To diethylether (250 mL) was added magnesium (6.04 g) and a catalytic amount of iodine and the mixture was stirred and thereto was gradually added dropwise 2-chlorobenzyl chloride (20.0 g). After stirring for 1 hour from the time when the

temperature of such mixture began to rise, thereto was added a solution of 4-chlorobenzonitrile (18.8 g) in tetrahydrofuran/diethylether (20 mL/50 mL) and the mixture was stirred for 3 hours. To the reaction mixture was added 2N HCl (150 mL) under ice-cooling and the mixture was stirred at room temperature for 2 hours. The reaction mixture was extracted with ethyl acetate and the organic layer was washed with 1N HCl, water and saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 40/1 to 20/1) to obtain 2-(chlorobenzyl)(4-chlorophenyl)methanone (24.40 g; yield: 74 %) as a powder.

MS(APCI)m/z; 265/267 [M+H]⁺

(2) A solution of the compound obtained in the above step (1) (6.4 g) and N, N-dimethylformamide dimethylacetal (6.4 mL) in N, N-dimethylformamide (24 mL) was stirred at 150°C for 4 hours. After cooling the reaction mixture to room temperature, thereto was added water and the mixture was extracted with a mixture of ethyl acetate and hexane (x 3). The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to obtain 3-(N, N-dimethylamino)-1-(4-chlorophenyl)-2-(2-chlorophenyl)-2-propen-1-one as an oil. To a solution of the compound in acetic acid (8 mL) was added 3-amino-4-ethoxycarbonyl-1H-pyrazole (3.75 g) and piperidine (0.48 mL) and the mixture was heated at 80°C for 16 hours. After cooling the reaction mixture to room temperature, thereto was added water and ethyl acetate and the organic layer was washed with saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 17/3 to 67/33) to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (5.02 g, yield: 50 %) as a powder.

MS(APCI)m/z; 412/414 [M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (2.5 g) in ethanol (30 mL) was added 2N sodium hydroxide (6 mL) and the mixture was stirred at room temperature for 5 hour. To the reaction mixture was 2N HCl (6 mL) and the mixture was stirred and concentrated in vacuo. The residue was extracted with ethyl acetate and the organic layer was washed with saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to obtain 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-carboxypyrazolo[1,5-a]pyrimidine (2.1 g, yield: 90%) as a powder.

MS(APCI)m/z; 384/386 M+H]⁺

Reference Example 2

(1) To dimethoxyethane (100 mL) was added 4-chlorobenzylbromide (4.1 g), 4-chlorobenzoylchloride (2.56 mL), bis(triphenylphosphine)palladium dichloride (702 mg) and zinc powder (2.6 g) and the mixture was stirred for 2 hours under nitrogen gas atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent: hexane/ethyl acetate = 49/1 to 9/1) to obtain (4-chlorobenzyl) (4-chlorophenyl)methanone (4.85 g, yield: 91 %) as a powder.

MS(GC-EI)m/z; 264 [M]⁺

(2) The compound obtained in the above step (1) was treated in the same manner as described in Reference Example 1(2) and (3) to give 3-carboxyl-6-(4-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine (165 mg, yield: 20%) as a powder.

MS(APCI)m/z; 384/386 M+H]⁺

Reference Example 3

The corresponding starting materials were treated in the same manner as described in Reference Example 1 to give 3-carboxyl-6-phenyl-7-(4-chlorophenyl)-pyrazolo[1,5-a]pyrimidine (2.06 g, yield: 22%) as a powder.

MS(APCI)m/z; 350/352 M+H]⁺

Reference Example 4

(1) To a solution of methyl 2-chlorophenylacetate (10 g) in dimethylformamide (150 mL) was added N,N-dimethylformamide dimethylacetal (14.4 mL) and the mixture was stirred at 85°C overnight. After cooling to room temperature, to the reaction mixture was added ethyl acetate and water and the mixture was stirred. The organic layer was extracted, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the residue was diluted with acetic acid (18 mL). Thereto was added 3-amino-4-ethoxycarbonyl-1H-pyrazole (8.4 g) and piperidine (1.1 mL) and the mixture was stirred at 80°C for 3.5 hours. After cooling to room temperature, to the reaction mixture was added ethyl acetate and water and the mixture was stirred and filtered. The resultant solid materials were dried to obtain 5-[2-(2-chlorophenyl)-2-methoxycarbonylvinylamino]-4-methoxycarbonyl-1H-pyrazole (11.8 g, yield: 62 %) as a powder.

MS(APCI)m/z; 350/352 M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (10.7 g) in

ethanol (250 mL) was added sodium carbonate 3.24 g and the mixture was refluxed under heating for 4 days. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo. To the residue was added water and the mixture was stirred and filtered (such filtration step was repeated in 5 times). The resultant solid materials were dried to obtain 6-(2-chlorophenyl)-3-ethoxycarbonyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine (8.5 g, yield: 87 %) as a powder.

MS(APCI)m/z; 318/320 M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (300 mg) in acetonitrile (2 mL) was added N,N-dimethylanilin (319 μ L) and phosphorus oxychloride (270 μ L) and the mixture was refluxed under heating for 1 day. After cooling to room temperature, the reaction mixture was poured to water with ice and extracted with methylene chloride. The extract was dried over magnesium sulfate and filtered and the filtrate was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 60/40) to give 7-chloro-6-(2-chlorophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (108 mg, yield: 34 %) as a powder.

MS(APCI)m/z; 336/338 M+H]⁺

(4) A solution of the compound obtained in the above step (3) (100 mg), [1,1'-bis(diphenylphosphio)ferrocene]palladium (II) dichloride-methylene chloride complex (7.3 mg), potassium phosphate (189 mg) and 4-fluorophenylboronic acid 846 mg in 1,4-dioxane (3 mL) was stirred at 80°C for 5 hours under nitrogen gas atmosphere. After cooling to room temperature, to the reaction mixture was added methylene chloride and a brine and the mixture was stirred. The organic layer was extracted and the extract was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 65/35) to give 6-(2-chlorophenyl)-3-ethoxycarbonyl-7-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidine (106 mg, yield: 90 %) as a powder.

MS(APCI)m/z; 396/398 M+H]⁺

Reference Example 4B

A solution of methyl 2-chlorophenylacetate (25 g) in dimethylformamide (400 mL) was added N,N-dimethylformamide dimethylacetal (36 mL) and the mixture was stirred at 90°C overnight. After cooling to room temperature, to the reaction mixture was added ethyl acetate and water and the mixture was stirred and extracted. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the residue was diluted with acetic acid (60 mL). Thereto

was added 3-amino-4-ethoxycarbonyl-2-methyl-1H-pyrazole (19.7 g) and the mixture was stirred at 120°C overnight. After cooling to room temperature, the precipitates were collected by filtration and washed to give 6-(2-chlorophenyl)-3-ethoxycarbonyl-2-methyl-7-oxo-4,7-dihydropyrazolo[1,5-a]pyrimidine (26.0 g, yield in the two steps: 62%) as a powder.

MS(APCI)m/z; 332/334 [M+H]⁺

Reference Example 5

(1) A solution of 5-amino-4-ethoxycarbonyl-3-methylthio-1H-pyrazole (compound obtained in Reference Example 18, 6.8 g), 3-(N,N-dimethylamino)-1-(4-chlorophenyl)-2-(2-chlorophenyl)-2-propene-1-one (10.9 g) and piperidine (578 mg) in acetic acid (13 mL) was stirred at 80°C overnight. After cooling to room temperature, to the reaction mixture was added water and ethyl acetate. The organic layer was washed with a brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 85/15 to 70/30) to give 6-(2-chlorophenyl)-7-(4-fluorophenyl)-3-ethoxycarbonyl-2-methylthiopyrazolo[1,5-a]pyrimidine (5.88 g, yield: 38 %) as a yellow solid.

(2) To a solution of the compound obtained in the above step (1) (5.86 g) in methylene chloride (200 mL) was added 3-chloroperbenzoic acid (70 %, 9.46 g) under ice-cooling and the mixture was stirred at the same temperature for 10 minutes and at room temperature for 3 hours. To the reaction mixture was added an aqueous sodium thiosulfate solution. The mixture was stirred at room temperature and thereto was added ethyl acetate and water. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crystals were washed with ice-cooled ethanol and dried to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-methylsulfonylpyrazolo[1,5-a]pyrimidine (5.52 g, yield: 88 %) as a pale yellow solid.

(3) To a solution of the compound obtained in the above step (2) (1.0 g) in ethanol/tetrahydrofuran (26 mL/30 mL) was added sodium ethoxide (1.66 g) and the mixture was refluxed under heating. After cooling to room temperature, to the reaction mixture was added water and sodium acetate. The organic layer was washed with a brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 40/60) to give 6-(2-chlorophenyl)-7-(4-fluorophenyl)-2-ethoxy-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (86 mg, yield: 9.2 %) as a pale yellow solid.

MS(APCI)m/z; 456/458 M+H]⁺

(4) The compound obtained in the above step (3) (455 mg) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-fluorophenyl)-2-ethoxypyrazolo[1,5-a]pyrimidine (490 mg) as a pale yellow solid.

MS(APCI)m/z; 4528/430 M+H]⁺

Reference Example 6

(1) A mixture of 1-(4-chlorophenyl)ethanone (13.1 g) and C-tert-butoxy-N,N,N',N'-tetramethylmethylenediamine (16.3 g) was stirred at 60°C overnight. After cooling to room temperature, the reaction mixture was concentrated in vacuo to give 1-(4-chlorophenyl)-3-(N,N-dimethylamino)-2-propen-1-one (18.4 g, yield: 100 %) as a yellow solid.

MS(APCI)m/z; 210/212 M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (18.4 g) in methylene chloride (105 mL) was added dropwise bromine (13.6 g) under ice-cooling over a period of 10 minutes and the mixture was stirred at the same temperature for 30 minutes. To the reaction mixture was added dropwise a solution of triethylamine (11.8 mL) in diethylether (130 mL) over a period of 5 minutes and the mixture was stirred for 2 hours. After warming to room temperature, the reaction mixture was filtered and to the residue was added methylene chloride (20 mL) and diisopropylether (50 mL). After stirring for 1 hour, the resultant crystals were collected by filtration and dried in vacuo to give 2-bromo-1-(4-chlorophenyl)-3-(N,N-dimethylamino)-2-propene-1-one (20.2 g, yield: 82 %) as a pale yellow solid.

MS(APCI)m/z; 288/290 M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (20.2 g) and 3-amino-4-ethoxycarbonylpyrazole (10.9 g) in ethanol (65 mL) was added 25% hydrogen bromide/acetic acid solution (13 mL) and the mixture was refluxed under heating for 1 hour. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform (200 mL). The solution was washed with an aqueous saturated sodium hydrogencarbonate solution and a brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; ethyl acetate/chloroform = 0/100 to 10/90) and crystallized from diisopropylether to give 6-bromo-7-(4-fluorophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (13.8 g, yield: 52 %) as a colorless solid.

MS(APCI)m/z; 380/382 M+H]⁺

(4) A solution of the compound obtained in the above step (3) (1.0 g), 2-(trifluoromethyl)phenylboronic acid (549 mg), [1,1'-bis(diphenylphosphio)ferrocene] palladium(II) dichloride-methylene chloride complex (77 mg) and potassium phosphate (1.55 g) in 1,4-dioxane (51 mL) was stirred at 80°C overnight and at 90°C for 8 hours under nitrogen gas atmosphere. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated in vacuo and the residue was diluted with tetrahydrofuran (34 mL). Thereto was added an aqueous 1N lithium hydroxide solution (16 mL) and the mixture was stirred at 55°C overnight. After cooling to room temperature, to the reaction mixture was added chloroform, water and an aqueous 1N HCl and the organic layer was separated. The organic layer was washed with a brine, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant product was recrystallized to give 3-carboxy-7-(4-chlorophenyl)-6-(2-trifluoromethylphenyl)pyrazolo[1,5-a]pyrimidine (370 mg, yield: 34 %) as a pale yellow solid.

MS(APCI)m/z; 418/420 M+H]⁺

Reference Example 7

To a solution of the compound obtained in Reference Example 4(3) (168 mg) in dimethylformamide (5 mL) was added pyrrolidine (50 µL) and potassium carbonate (138 mg) and the mixture was stirred at 160°C for 5 minutes in a microwave reactor. After cooling to room temperature, to the reaction mixture was added water and the mixture was stirred and extracted with methylene chloride. The extract was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 65/35) to give 6-(2-chlorophenyl)-3-ethoxycarbonyl-7-(1-pyrrolidinyl)pyrazolo[1,5-a]pyrimidine (116 mg, yield: 63 %) as a powder.

MS(APCI)m/z; 371/373 M+H]⁺

Reference Example 7B

(1) The corresponding starting materials were treated in the same manner as described in Reference Example 4B and 4(3) to give 6-(2-chlorophenyl)-7-chloro-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]pyrimidine.

(2) To a solution of the compound obtained in the above step (1) (300 mg) in dimethylformamide (3 mL) was added thiomorpholine (103 µL) and potassium carbonate (237 mg) and the mixture was stirred at 80°C for 40 minutes. After cooling to room temperature, to the reaction mixture was added water and the mixture was stirred and extracted with ethyl acetate. The extract was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product

was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 5/2) to give 6-(2-chlorophenyl)-7-thiomorpholino-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]pyrimidine (324 mg, yield: 91 %) as a powder.

MS(APCI)m/z; 417/419 M+H]⁺

5 Reference Example 8

To a solution of the compound obtained in Reference Example 5(1) (11.5 g) in ethanol/tetrahydrofuran (58 mL/58 mL) was added an aqueous 2N sodium hydroxide solution (50.2 mL) and the mixture was stirred at 60°C for 8 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. To the residue was added chloroform, a brine and an aqueous 2N HCl and the mixture was stirred (pH 2 to 3). The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the precipitated crystals were diethylether to give 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methylthiopyrazolo[1,5-a]pyrimidine (11.1 g, yield: 100 %) as a pale yellow solid.

15 MS(APCI)m/z; 430/432 M+H]⁺

Reference Example 9

(1) To a solution of the compound obtained in Reference Example 1(4) (2.0 g) in tert-butyl alcohol (15 mL) was added diphenyl phosphoryl azide (1.15 mL) and triethylamine (725 µL) and the mixture was stirred at 80°C overnight. After cooling to room temperature, to the reaction mixture was added water and ethyl acetate and the mixture was stirred. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 55/45) to give 3-tert-butoxycarbonylamino-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine (1.0 g, yield: 42 %) as a powder.

25 MS(APCI)m/z; 455/457 M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (1.0 g) in 1,4-dioxane (8 mL) was added 4N HCl-1,4-dioxane (16 mL) and the mixture was stirred at room temperature for 1.5 hours. To the reaction mixture was added methanol (2 mL) and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was concentrated in vacuo and the residue was crystallized from diisopropylether to give 3-amino-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine hydrochloride (809 mg, yield: 94 %) as a pale orange powder.

30 MS(APCI)m/z; 355/357 M+H]⁺

35 Reference Example 10

(1) To a solution of the compound obtained in Reference Example 1(4) (300

mg) in methylene chloride (4.0 mg) was added N-tert-butoxycarbonylhydrazine (135 mL), water-soluble carbodiimide HCl (224 mg), 1-hydroxybenzotriazole (179 mg) and triethylamine (326 mg) and the mixture was stirred at room temperature overnight. To the reaction mixture was an aqueous sodium hydrogencarbonate solution and methylene chloride and the mixture was stirred. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on NH-silica gel (Chromatorex NH-silica gel/Fuji Silicia Chem., solvent; hexane/ethyl acetate = 70/30 to 40/60) to give 3-(N'-tert-butoxycarbonylhydrazino)carbonyl-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine (379 mg, yield: 97 %) as a powder.

MS(APCI)m/z; 498/500 M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (345 mg) in 1,4-dioxane (5 mL) was added 4N HCl-1,4-dioxane (500 μ L) and the mixture was stirred at 40°C overnight. To the reaction mixture was added 2N HCl and the mixture was at 40°C for 8 hours. To the reaction mixture was added an aqueous sodium hydrogencarbonate solution and methylene chloride and the mixture was stirred. The organic layer was extracted and the extract was dried and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 0/100) to give 3-hydrazinocarbonyl-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine (142 mg, yield: 52 %) as a yellow gum.

MS(APCI)m/z; 398/400 M+H]⁺

Reference Example 11

(1) To a solution of the compound obtained in Example 33 (1.5 g) in dimethylformamide (20 mL) was added sodium azide (1.11 g) and the mixture was stirred at 110°C overnight. After cooling to room temperature, to the reaction mixture was a saturated brine and the mixture was stirred and extracted with ethyl acetate. The organic layer was washed with water and concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 30/70) to give 2-azido-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]pyrimidine (1.15 g, a yellow viscosity). To a solution of the product (870 mg) in tetrahydrofuran (16 mL) was added triphenylphosphine (896 mg) and the mixture was stirred at 40°C for 1 hour. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; chloroform/methanol = 100/0 to 97/3) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-

2-triphenylphosphoranylidenamino-pyrazolo[1,5-a]pyrimidine (942 mg, yield: 58 %) as a yellow solid

MS(APCI)m/z; 726/728 M+H]⁺

Reference Example 12

5 (1) 7-Chloro-6-(2-chlorophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (1 g) was treated in the same manner as described in Reference Example 4(5) to give 6-(2-chlorophenyl)-3-ethoxycarbonyl-7-(4-formylphenyl)pyrazolo[1,5-a]pyrimidine (910 mg) as a pale yellow powder.

MS(APCI)m/z; 428/430 M+H]⁺

10 (2) To a solution of the compound obtained in the above step (1) (406 mg) in methylene chloride (1 mL) was added bis-(2-methoxyethyl)aminosulfur trifluoride (trade name: Deoxo-Fluor, Scott Inc.) (184 μ L) and the mixture was stirred at room temperature for 4 hours. The organic layer was washed with a brine and extracted with methylene chloride. The extract was dried over sodium sulfate and filtered. The
15 filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 70/30 to 60/40) to give 6-(2-chlorophenyl)-7-(4-difluoromethylphenyl)-3-ethoxycarbonylpyrazolo[1,5-a]-pyrimidine (25 mg, yield: 37 %) as a pale yellow solid.

MS(APCI)m/z; 428/430 M+H]⁺

20 (3) The compound obtained in the above step (2) (278 mg) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-difluoromethylphenyl)pyrazolo[1,5-a]pyrimidine (223 mg, yield: 86%) as a pale yellow solid.

MS(APCI)m/z; 400/402 M+H]⁺

25 Reference Example 13

(1) To a solution of tetrahydro-4H-thiopyran-4-one (2.32 g) in ethanol (100 mL) was added sodium acetate (3.28 g) and hydroxylamine HCl (1.81 g) at room temperature and the mixture was stirred at the same temperature for 2 hours. The reaction mixture was concentrated in vacuo and to the residue was added ethyl acetate
30 and an aqueous sodium hydrogencarbonate solution. After stirring, the mixture was extracted with ethyl acetate and the organic layer was washed with a brine, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to give 4-hydroxyimino-tetrahydro-4H-thiopyrane (2.53 g, yield: 96 %) as a colorless solid.

MS(APCI)m/z; 132 M+H]⁺

35 (2) To a solution of the compound obtained in the above step (1) (500 mg) in diethylether (10 mL) was added lithium aluminum hydride (289 mg) under nitrogen gas

atmosphere and ice-cooling and the mixture was stirred at the same temperature for 30 minutes and at room temperature for 1 hour. To the reaction mixture was added lithium aluminum hydride (72 mg) and the mixture was stirred at 40°C for 2 hours. To the reaction mixture was added water (1 mL) and an aqueous 2N sodium hydroxide solution (1 mL) at room temperature and the mixture was stirred and filtered. The filtrate was concentrated in vacuo to give 4-amino-tetrahydro-4H-thiopyrane (150 mg, yield: 34 %) as a yellow fluid.

MS(APCI)m/z; 118 M+H]⁺

Reference Example 14A

(1) A mixture of (R)-methioninol (4.95 g), benzonitrile (8.3 mL) and zinc bromide (250 mg) was stirred at 120°C for 90 hours under nitrogen gas atmosphere. After cooling to room temperature, the reaction mixture was filtered and the filtrate was washed with water and a brine, dried over magnesium sulfate and filtered again. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 5/1 to 3/1) to give (R)-4-(2-methylthioethyl)-2-phenyl-4,5-dihydrooxazole (3.94 g, yield: 48.6 %) as a colorless oil.

MS(APCI)m/z; 222 M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (3.94 g) in acetic acid (65 mL) was added conc. hydrochloric acid (7.7 mL) and the mixture was refluxed under heating overnight. After cooling to room temperature, the reaction mixture was concentrated in vacuo. To the residue was added an aqueous sodium hydroxide solution (50 mL) and chloroform (100 mL) and the mixture was stirred. To the organic layer was added magnesium sulfate and silica gel and the mixture was stirred and filtered. The filtrate was concentrated in vacuo and the resultant crude product was washed with isopropylether and dried to give (R)-N-(tetrahydrothiophen-3-yl)benzamide (2.80 g, yield: 76 %) as a colorless solid.

MS(APCI)m/z; 208 M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (3.59 g) in methylene chloride (70 mL) was gradually added 3-chloroperbenzoic acid (75 %, 10 g) under ice-cooling and the mixture was stirred at room temperature overnight. To the reaction mixture was added water (35 mL), sodium sulfite (3.5 g) and an aqueous saturated sodium hydrogencarbonate solution (100 mL) and the mixture was stirred for 30 minutes and extracted with chloroform. The extract was washed with an aqueous saturated sodium hydrogencarbonate solution and the organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant

solid materials were washed with ethyl acetate to give (R)-N-(1,1-dioxo-tetrahydrothiophen-3-yl)benzamide (3.5 g, yield: 85 %) as a colorless solid.

MS(APCI)m/z; 240 M+H]⁺

(4) To a solution of the compound obtained in the above step (3) (3.51 g) in ethanol (13 mL) was added 6N HCl (52 mL) and the mixture was refluxed under heating for 1 day. After cooling to room temperature, the aqueous layer was washed with ethyl acetate and concentrated in vacuo. The precipitated solid materials were washed with ethanol/diethylether, collected by filtration and further washed with diethylether to give (R)-N-(1,1-dioxo-tetrahydrothiophen-3-yl)amine hydrochloride (2.52 g, yield: 100 %) as a colorless solid.

MS(APCI)m/z; 136 M+H]⁺

Reference Example 14B

(S)-Methioninol (4.83 g) was treated in the same manner as described in Reference Example 14A to give (S)-N-(1,1-dioxo-tetrahydrothiophen-3-yl)amine hydrochloride (3.86 g,) as a colorless solid.

MS(APCI)m/z; 136 M+H]⁺

Reference Example 15

(1) To a solution of 4,4-difluoropiperidine hydrochloride (2.0 g) in water was added 2N sodium hydroxide (7.6 mL) and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added sodium nitrite (1.75 g) at room temperature and added acetic acid (1.27 mL) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added an aqueous sodium hydrogencarbonate solution and the mixture was extracted with chloroform. The extract was dried over magnesium sulfate and filtered, and the filtrate was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 4/1) to give 4,4-difluoro-1-nitrosopiperidine (1.89 g, yield: 99 %) as a pale yellow solid.

MS(APCI)m/z; 151 M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (1.89 g) in tetrahydrofuran was added portionwise lithium aluminum hydride (837 mg) under ice-cooling and the mixture was refluxed under heating for 1 hour. To the reaction mixture was added water under ice-cooling and the mixture was refluxed under heating for 30 minutes. After cooling to room temperature, the reaction mixture was filtered and the filtrate was concentrated in vacuo. To the residue was added an aqueous sodium hydrogencarbonate solution and chloroform and the mixture was stirred. The organic layer was dried over sodium sulfate and filtered and the filtrate was

concentrated in vacuo to give 1-amino-4,4-difluoropiperidine (500 mg, yield: 29 %) as a pale yellow oil.

MS(APCI)m/z; 137 M+H]⁺

Reference Example 16

5 (1) To a solution of 3-fluoromethoxyphenylmethylamine (278 mg) in water (400 µL) was added acetic acid (125 µL) and a solution of sodium nitrite (201 mg) in water (600 µL) under ice-cooling and the mixture was stirred. Thereto was added methanol (500 µL) and tetrahydrofuran (500 µL) and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated
10 sodium hydrogencarbonate solution and the mixture was stirred and extracted with ethyl acetate. The extract was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 100/0 to 87/13) to give N-(3-trifluoromethoxyphenyl)methyl nitrosoamine (282 mg, yield: 88 %) as a pale yellow oil.

15 MS(APCI)m/z; 192 M+H]⁺

(2) To a solution of lithium aluminum hydride (82.7 mg) in tetrahydrofuran (5 mL) was added a solution of the compound obtained in the above step (1) (282 mg) in tetrahydrofuran (2.5 mL) under ice-cooling and the mixture was stirred at room temperature for 1 hour under nitrogen gas atmosphere. To the reaction mixture was
20 added water (90 µL), an aqueous 15 % sodium hydroxide solution (90 µL) and water (180 µL) and the mixture was stirred and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 85/15 to 65/35) to give N-methyl-N-(3-trifluoromethoxyphenyl)hydrazine (187 mg, yield: 71 %) as an orange viscosity.

25 MS(APCI)m/z; 207 M+H]⁺

Reference Example 17

To a solution of tetrahydro-4H-thiopyran-4-one (500 mg) in water/ethanol (10 mL/10 mL) was added potassium cyanide (1.4 g) and ammonium chloride (1.15 g) and the mixture was stirred at room temperature for 4 days. To the reaction mixture was
30 added diethylether and an aqueous 1N sodium hydroxide solution and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted with diethylether and ethyl acetate. The combined organic layer was dried over calcium chloride and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 70/30 to 30/70) to give 4-amino-4-cyano-tetrahydro-4H-thiopyrane (315 mg)
35 as a colorless solid.

Reference Example 18

A solution of ethyl 2-cyano-3,3-bismethylthioacrylate (40 g), hydrazine hydrochloride (12.6 g) and sodium acetate (22.6 g) in ethanol was stirred at 90°C for 2 hours. After cooling to room temperature, the reaction mixture was concentrated in vacuo. To the residue was added water and ethyl acetate and the organic layer was separated, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and to the residue was added ethyl acetate and hexane. The precipitated solid materials were collected by filtration and dried to give 5-amino-4-ethoxycarbonyl-3-methylthio-1H-pyrazole (17.4 g, yield: 47 %) as a colorless solid.

Reference Examples 19 to 20

3-Carboxy-6-(2-chlorophenyl)-7-(4-trifluoromethoxyphenyl)pyrazolo[1,5-a]pyrimidine or 3-carboxy-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)pyrazolo[1,5-a]pyrimidine was treated in the same manner as described in Reference Example 10 to give the following compound.

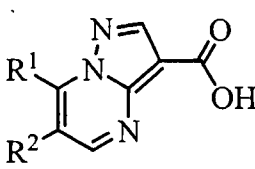
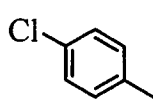
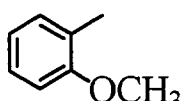
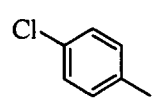
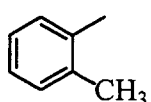
(Ref. Ex. 19) 3-hydrazinocarbonyl-6-(2-chlorophenyl)-7-(4-trifluoromethoxyphenyl)pyrazolo[1,5-a]pyrimidine; MS(APCI)m/z; 448/450 M+H]⁺

(Ref. Ex. 20) 3-hydrazinocarbonyl-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)pyrazolo[1,5-a]pyrimidine; MS(APCI)m/z; 432/434 M+H]⁺

Reference Examples 21 to 40

The corresponding starting materials were treated in the same manner as described in either one of Reference Examples 1, 4 and 6 to give the compound as shown in the following Table B1.

Table B1 (No. 1)

			
Ref. Ex.	R ¹	R ²	Physicochemical properties etc
21			MS(APCI):380/382 [M+H] ⁺
22			MS(APCI):364/366 [M+H] ⁺

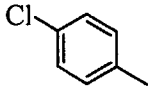
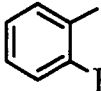
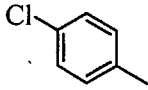
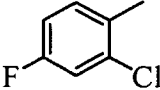
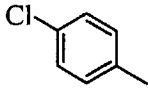
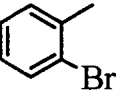
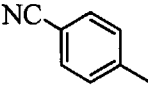
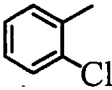
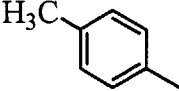
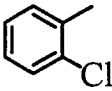
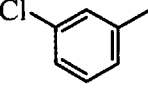
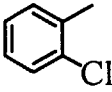
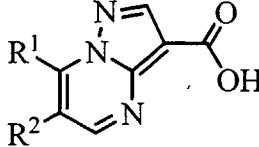
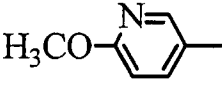
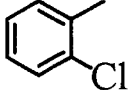
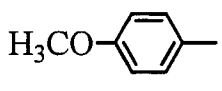
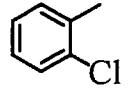
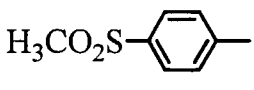
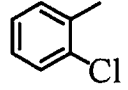
23			MS(APCI):368/370 [M+H] ⁺
24			MS(APCI):402/404 [M+H] ⁺
25			MS(APCI):428/430 [M+H] ⁺
26			MS(APCI):375/377 [M+H] ⁺
27			MS(APCI):364/366 [M+H] ⁺
28			MS(APCI):384/386 [M+H] ⁺

Table B1 (No. 2)

			
Ref. Ex.	R ¹	R ²	Physicochemical properties etc
29			MS(APCI):381/383 [M+H] ⁺
30			MS(APCI):380/382[M+H] ⁺
31			MS(APCI):428/430 [M+H] ⁺

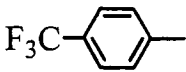
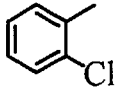
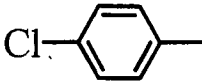
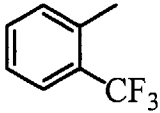
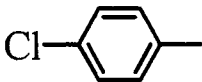
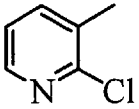
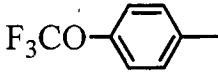
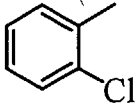
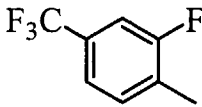
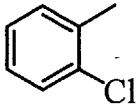
32			MS(APCI):418/420 [M+H] ⁺
33			MS(APCI):418/420 [M+H] ⁺
34			MS(APCI):385/387 [M+H] ⁺
35			MS(APCI):434/436 [M+H] ⁺
36			MS(ESI):434/436 [M-H] ⁻

Table B1 (No. 3)

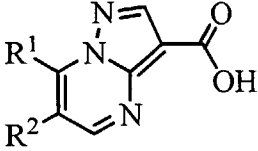
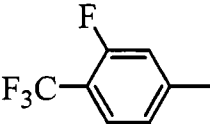
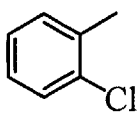
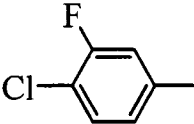
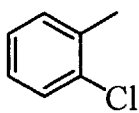
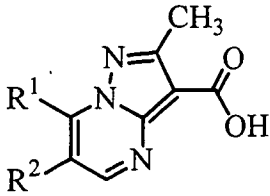
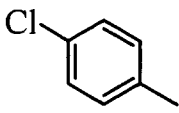
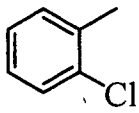
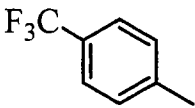
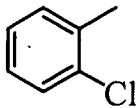
			
Ref. Ex.	R ¹	R ²	Physicochemical properties etc
37			MS(ESI):434/436 [M-H] ⁻
38			MS(APCI):402/404 [M+H] ⁺

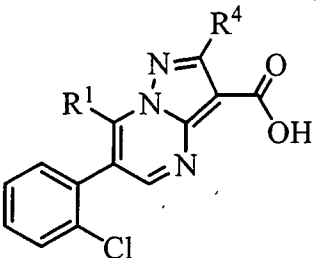
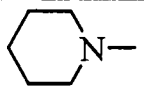
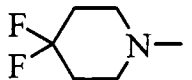
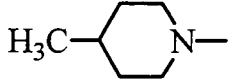
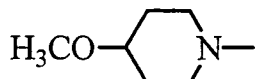
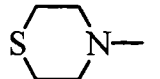
Table B1 (No. 4)

			
Ref. Ex.	R ¹	R ²	Physicochemical properties etc
39			MS(APCI):398/400 [M+H] ⁺
40			MS(APCI):432/434 [M+H] ⁺

Reference Examples 41 to 45

The corresponding starting materials were treated in the same manner as described in Reference Example 7 to give the compound as shown in the following Table B2.

Table B2

			
Ref. Ex.	R ¹	R ⁴	Physicochemical properties etc
41		H	MS(APCI):357/359[M+H] ⁺
42		H	MS(APCI):393/395 [M+H] ⁺
43		H	MS(APCI):351/373[M+H] ⁺
44		H	MS(APCI):387/389[M+H] ⁺
45		CH ₃	MS(APCI):389/391 [M+H] ⁺

Reference Example 46

(1) To a solution of 5-nitropyrazol-3-carboxylic acid (19.9 g) in ethanol (200 mL) was added dropwise thionyl chloride (9.7 mL) over a period of 5 minutes and the mixture was refluxed for 4 hours. After cooling to room temperature, the reaction mixture was diluted with water (25 mL) and ethanol (50 mL) and to the mixture was neutralized with sodium hydrogencarbonate (54 g). The mixture was filtered and the residue was washed with ethanol. The filtrate and the washings were combined and concentrated in vacuo. The residue was azeotropically distilled with ethanol and the residue was dissolved in ethyl acetate, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and to the residue was added isopropylether. The precipitates were collected by filtration and washed with ethyl acetate/diisopropylether (1/2) to give ethyl 5-nitropyrazol-3-carboxylate (20 g, yield: 85%) as a colorless solid. MS(APCI): 186 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (22.5 g) in acetic acid (130 mL) and tetrahydrofuran (130 mL) was added 10% palladium-carbon (4.1 g) and the mixture was stirred under hydrogen-gas atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo. To the residue was added hexane and the mixture was stirred and decanted to remove hexane. To the residue was added ether/diisopropylether (1/1) and the precipitates were collected by filtration to give ethyl 5-aminopyrazol-3-carboxylate (17.2 g, yield: 91%) as a colorless solid.

MS(APCI): 156 [M+H]⁺

Reference Example 47

(1) To a solution of 2-[(cyano)(ethoxycarbonyl)vinyl]-1,3-dioxolane (2.0 g) in ethanol (20 mL) was added hydrazine hydrochloride (748 mg) and sodium acetate (1.34 g) and the mixture was stirred at 80°C (external temperature) for 1 hour. After cooling to room temperature, the reaction mixture was filtered through Cerite and the filtrate was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; chloroform/methanol = 100/0 to 85/15) to give 3-amino-4-ethoxycarbonyl-5-(2-hydroxy)ethoxypyrazole (2.01 g, yield: 86 %) as a pale pink solid.

MS(APCI)m/z; 216 M+H]⁺

(2) To the compound obtained in the above step (1) (2.65 g) and 3-(N,N-dimethylamino)-1-(4-chlorophenyl)-2-(2-chlorophenyl)-2-propen-1-one (cf. Reference Example 1(2)) was added ethanol (20 mL) and 21% sodium ethoxide in ethanol (5 mL) and the mixture was stirred at room temperature for 15 minutes. To the

reaction mixture was added ethyl acetate and water and the mixture was acidified with 2N HCl and extracted with ethyl acetate. The organic layer was washed with a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 72/28 to 30/70) and triturated in diethylether to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-(2-hydroxyethoxy)pyrazolo[1,5-a]pyrimidine (2.25 g, yield: 39%) as a colorless solid.

MS(APCI)m/z; 472/474 M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (100 mg) in acetonitrile (10 mL) was added silver(I) oxide (320 mg) and methyl iodide (350 µL) and the mixture was stirred at room temperature for 3 days. The reaction mixture was filtered through Cerite and the filtrate was concentrated in vacuo. The resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 50/50) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-(2-methoxyethoxy)pyrazolo[1,5-a]pyrimidine (98.6 mg, yield: 96%) as a colorless powder.

MS(APCI)m/z; 486/488 M+H]⁺

(4) The compound obtained in the above step (3) (98 mg) was treated in the same manner as described in Reference Example 1(3) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-carboxy-2-(2-hydroxyethoxy)pyrazolo[1,5-a]pyrimidine (92 mg, yield: 99%) as a colorless powder.

MS(APCI)m/z; 458/460 M+H]⁺

Reference Example 48

(1) To a solution 1,3-dibromo-2,2-dimethoxypropane (26.45 g) in dimethylsulfoxide (200 mL) was added sodium sulfate (9.46 g) and the mixture was stirred at 110 to 140°C (external temperature) for 30 minutes. The reaction mixture was diluted with diethylether under ice-cooling and thereto was added an aqueous saturated sodium hydrogencarbonate solution and water. The mixture was extracted with diethylether (x 2). The organic layer was washed with a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by a column chromatography on silica gel (solvent; hexane/diethylether = 100/0 to 15/1) to give 3,3-dimethoxythiacyclobutane (10.55 g, yield: 78%) as a pale yellow liquid.

MS(APCI)m/z; 103 [M+H-MeOH]⁺

(2) To a solution of the compound obtained in the above step (1) (9.0 g) in

acetone (70 mL) was added ion-exchange resin (Amberlyt 15E, 3.5 g) and the mixture was stirred at room temperature for 21 hours. The reaction mixture was filtered through Cerite and the residue was washed with acetone. The filtrate and the washings were combined and concentrated in vacuo. The precipitates were collected by filtration and washed with cooled hexane to give 3-oxothiacyclobutane (1.58 g, yield: 27%) as colorless crystals.

(3) To a solution of the compound obtained in the above step (2) (100 mg) in ethanol (3 mL) was added hydroxylamine hydrochloride (236 mg) and sodium carbonate (360 mg) and the mixture was refluxed under heating for 17 hours. After cooling to room temperature, to the reaction mixture was added an aqueous sodium hydrogencarbonate solution and water. The mixture was extracted with chloroform. The organic layer was concentrated in vacuo the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/diethylether = 90/10 to 50/50) to give 3-hydroxyiminothiacyclobutane (93 mg, yield: 80%) as a colorless solid.

(4) To a solution of lithium aluminum hydride (58 mg) in tetrahydrofuran (2 mL) was added dropwise a solution of the compound obtained in the above step (3) (93 mg) in tetrahydrofuran (1.5 mL) under ice-cooling and nitrogen-gas atmosphere. The mixture was stirred at room temperature for 1 hour. To the reaction mixture was successively added water (60 μ L), 15% sodium hydroxide solution (60 μ L) and water (120 μ L) under ice-cooling and the mixture was stirred at room temperature and filtered through Cerite. The filtrate was concentrated in vacuo to give 3-aminothiacyclobutane as crude product.

Reference Example 49

(1) To a solution of sodium ethoxide (14.32 g) in ethanol (20 mL) was added dropwise ethyl cyanoacetate (4.7 mL) and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added difluoroacetic acid (4.85 mL) and the mixture was stirred at room temperature for 4 hours and then stirred at 60°C (external temperature) for 17 hours. The reaction mixture was concentrated in vacuo and to the residue was added toluene (10 mL) and phosphorus chloride (3.2 g) and the mixture was stirred at 45°C for 1 hour. To the reaction mixture was added phosphorus chloride (1.9 g) and the mixture was stirred at 55°C for 2 hours. The reaction mixture was cooled with ice and filtered through Cerite and the filtrate was concentrated in vacuo. To the residue was added ethanol (20 mL), hydrazine monohydrate (0.8 mL) and triethylamine (3.0 mL) and the mixture was stirred at 60°C for 2 hours. After cooling to room temperature, to the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and water. The mixture was extracted with chloroform (x

4) and the organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; chloroform/methanol = 100/0 to 94/6) and washed with chloroform to give 3-amino-4-ethoxycarbonyl-5-difluoromethylpyrazole (1.26 g, yield: 41%) as a colorless solid.

MS(APCI)m/z; 206 [M+H]⁺

(2) The compound obtained in the above step (1) (400 mg) was treated in the same manner as described in Reference Example 1(2) to (3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-difluoromethylpyrazolo[1,5-a]pyrimidine (405 mg, yield: 48%) as a powder.

MS(APCI)m/z; 434/436 [M+H]⁺

Reference Example 50

(1) To a solution of methyl cyanoacetate (14.6 g) in methylene chloride (260 mL) was added trifluoroacetic anhydride (37.2 g) and the mixture was stirred at room temperature. To the mixture was added dropwise triethylamine (51.7 mL) at 0°C and the mixture was stirred at room temperature overnight. To the reaction mixture was added water and the mixture was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to give methyl 2-cyano-2-(2-trifluoroacetyl)acetate (compound 2a) and methyl 2-cyano-4,4,4-trifluoro-3-trifluoromethoxycarbonyl-2-butenate (compound 2b) as a mixture (55.3 g).

Compound 2a: MS(APCI)m/z; 196 [M+H]⁺

Compound 2b: MS(APCI)m/z; 292 [M+H]⁺

(2) To a solution of the mixture of the compound 2a and 2b (27.6 g) in methylene chloride (200 mL) was added dropwise oxalyl chloride (31.6 mL) and a few drops of pyridine and the mixture was refluxed under heating for 4 hours. The reaction mixture was poured to water gradually and the mixture was extracted with methylene chloride. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to give methyl 2-cyano-3-chloro-4,4,4-trifluoro-2-butenate as a crude product.

(3) To the compound obtained in the above step (2) was added water (20 mL) and thereto was added dropwise hydrazine monohydrate (80 %, 6.74 g) at 0°C. To the mixture was added triethylamine (2 mL) at room temperature and the mixture was stirred for 1 hour. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and to the residue was added

chloroform and the precipitates were collected by filtration to give 3-amino-4-ethoxycarbonyl-5-trifluoromethylpyrazole (3.96 g) as an orange solid.

MS(APCI)m/z; 210 [M+H]⁺

(4) The compound obtained in the above step (3) (2.37 g) was treated in the same manner as described in Reference Example 1(2) to (3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-trifluoromethylpyrazolo[1,5-a]pyrimidine (1.81 g) as a crude product (powder).

MS(APCI)m/z; 452/454 [M+H]⁺

Reference Example 51

(1) To a solution of 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]pyrimidine (1.50 g; corresponding ethyl ester of the compound obtained in Reference Example 39) in carbon tetrachloride (20 mL) was added N-bromosuccinimide (1.88 g) and 2,2'-azobisisobutyronitrile (30 mg). The mixture was stirred at 85°C (external temperature) for 26 hours. After cooling to room temperature, the reaction mixture was filtered through Cerite and the filtrate was concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent; hexane/diethylether = 85/15 to 67/33) to give 2-bromomethyl-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (827 mg, yield: 47%) as a pale yellow solid.

MS(APCI)m/z; 504/506 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (825 mg) in methanol/tetrahydrofuran (7 mL/4 mL) was added 28% sodium methoxide-methanol solution (3 mL) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and thereto was added water. The mixture was extracted with ethyl acetate and the organic layer was washed with a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 75/25 to 60/40) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-methoxycarbonyl-2-methoxymethylpyrazolo[1,5-a]pyrimidine (404 mg, yield: 56%) as a pale yellow solid.

MS(APCI)m/z; 442/444 [M+H]⁺

(3) The compound obtained in the above step (2) (404 mg) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methoxymethylpyrazolo[1,5-a]pyrimidine (367 mg, yield: 94%) as a colorless solid.

MS(APCI)m/z; 428/430 [M+H]⁺

Reference Example 52

(1) To dimethylformamide (75 mL) was added sodium hydride (60%, 6.77 g) under nitrogen-gas atmosphere and thereto was added dropwise a solution of ethyl cyanoacetate (9.57 g) in dimethylformamide (15 mL) over a period of 15 minutes and the mixture was stirred at room temperature for 10 minutes. To the mixture was added dropwise a solution of carbon disulfide (5.09 mL) in dimethylformamide (12 mL) under cooling at 0°C (internal temperature $\leq 10^{\circ}\text{C}$) over a period of 20 minutes. The mixture was stirred at room temperature overnight and to the reaction mixture was added dropwise a solution of benzyl bromide (20.1 mL) in dimethylformamide (23 mL) under cooling at 0°C (internal temperature $\leq 25^{\circ}\text{C}$) and the mixture was stirred at 70°C for 7 hours and then stirred at room temperature overnight. The reaction mixture was poured to water with ice and the mixture was stirred. The precipitates were collected by filtration, recrystallized from hot ethanol and washed with cooled ethanol to give ethyl 2-cyano-3,3-bisbenzylthioacrylate (25.63 g, yield: 82%) as a colorless solid.

MS(APCI)m/z; 370 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (15.0 g) in tetrahydrofuran/ethanol (16 mL/41 mL) was added a solution of hydrazine monohydrate (2.04 g) in ethanol (18 mL) over a period of 5 minutes and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was crystallized from diisopropylether/hexane. The precipitated crystals were collected by filtration and washed to give 3-amino-4-ethoxycarbonyl-5-benzylthio-pyrazole (9.45 g, yield 84%) as a colorless solid.

MS(APCI)m/z; 278 [M+H]⁺

(3) The compound obtained in the above step (2) (8.15 g) was treated in the same manner as described in Reference Example 5(1) to give 2-benzylthio-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (8.24 g, yield: 51%) as a pale yellow solid.

MS(APCI)m/z; 534/536 [M+H]⁺

Reference Example 53

(1) The compound obtained in Reference Example 33 (3.0 g) was treated in the same manner as described in Reference Example 9(1) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-(tert-butoxycarbonylamino)pyrazolo[1,5-a]pyrimidine (1.06 g, yield: 30%) as an orange powder.

MS(APCI)m/z; 489/491 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (1.06 g) in dioxane (5 mL) was added 4N HCl-dioxane (10 mL) and the mixture was stirred at

room temperature for 7 hours. The reaction mixture was concentrated in vacuo and to the residue was added an aqueous saturated sodium hydrogencarbonate solution. The mixture was extracted with chloroform and the organic layer was concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 70/30 to 40/60) to give 3-amino-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)pyrazolo[1,5-a]pyrimidine (850 mg, yield: 80%) as a pale yellow solid.

MS(APCI)m/z; 389/391 [M+H]⁺

Reference Example 54

(1) The corresponding starting materials were treated in the same manner as described in Reference Example 1(1) to give (2-chlorobenzyl)(4-trifluoromethylphenyl) methanone.

(2) The compound obtained in the above step (1) (3.0 g) and 3-amino-5-methylpyrazole (977 mg) were treated in the same manner as described in Reference Example 1(2) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methylpyrazolo[1,5-a]pyrimidine (2.63 g, yield: 67%) as a brown oil.

MS(APCI)m/z; 388/390 [M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (2.27 g) in chloroform (50 mL) was added gradually dropwise chlorosulfonic acid (1.35 mL) and the mixture was stirred at 70°C for 3.5 hours. The reaction mixture was concentrated in vacuo and to the residue was added thionyl chloride (20 mL) and the mixture was refluxed under heating for 2 hours. The reaction mixture was concentrated in vacuo and to the residue was added ice-water and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 85/15 to 60/40) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-chlorosulfonyl-2-methylpyrazolo[1,5-a]pyrimidine (2.71 g, yield: 95%) as a pale yellow solid.

MS(APCI)m/z; 486/488 [M+H]⁺

Reference Example 55

(1) To a solution of ethyl potassium malonate (465 mg) in acetonitrile (3.5 mL) was added magnesium chloride (309 mg) and triethylamine (580 μ L) and the mixture was stirred at room temperature for 2 hours (solution A). To a solution of the compound obtained in Reference Example 1 (500 mg) in acetonitrile (3 mL) was added carbonyldiimidazole (232 mg) and tetrahydrofuran (2 mL) at room temperature and the mixture was stirred at the same temperature for 2 hours. To the reaction mixture was

added the above obtained solution A at room temperature and the mixture was stirred for 4 hours. To the reaction mixture was added 2N HCl and the mixture was extracted with ethyl acetate. The organic layer was washed with water and a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 90/10 to 75/25) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(2-ethoxycarbonylacetyl)pyrazolo[1,5-a]pyrimidine (488 mg, yield: 83%).

MS(APCI)m/z; 454/456 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (475 mg) in ethanol/tetrahydrofuran (2.5 mL/2.5 mL) was added an aqueous 2N sodium hydroxide solution (1.05 mL) and the mixture was stirred at 60°C for 1 hour. To the reaction mixture was added an aqueous 2N sodium hydroxide solution (1.05 mL) and ethanol (2.5 mL) and the mixture was stirred at the same temperature for 18 hours. After cooling to room temperature, to the reaction mixture was added an aqueous 2N HCl (2.1 mL) and the mixture was diluted with ethyl acetate. To the solution was added water and the mixture was extracted with ethyl acetate. The organic layer was concentrated in vacuo the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 70/30) to give 3-acetyl-6-(2-chlorophenyl)-7-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidine (233 mg, yield: 58%) as a pale yellow solid.

MS(APCI)m/z; 382/384 [M+H]⁺

Reference Example 56

(1) The corresponding starting materials were treated in the same manner as described in Reference Example 2(1) to give (2-chlorobenzyl)(5-chlorothiophen-2-yl) methanone (5.06 g, yield: 61%).

(2) The compound obtained in the above step (1) (2.92 g) was treated in the same manner as described in Reference Example 1(2) to give 3-(N,N-dimethylamino)-2-(2-chlorophenyl)-1-(5-chlorothiophen-2-yl)-2-propen-1-one as a crude product.

(3) To a solution of the compound obtained in the above step (2) in acetic acid (2 mL) was added 3-amino-4-ethoxycarbonyl-5-methylpyrazole (1.3 g) and piperidine (153 µL) and the mixture was stirred at 80°C overnight. To the reaction mixture was added acetic acid (3 mL) and toluene (30 mL) and the mixture was stirred at the same temperature for 7 hours. After cooling to room temperature, to the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution under ice-cooling. The mixture was extracted with ethyl acetate and the organic layer was washed

successively with water and a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the precipitates were collected by filtration and washed with diethylether. The filtrate was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 60/40) and the eluted fraction was concentrated. The precipitates were washed with ethyl acetate/hexane (1/10) and combined with the above-mentioned precipitates to give 6-(2-chlorophenyl)-7-(5-chlorothiophen-2-yl)-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]pyrimidine (1.52 g, yield in the two steps: 45%) as a yellow solid.

MS(APCI)m/z; 432/434 [M+H]⁺

(4) The compound obtained in the above step (3) (1.51 g) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(5-chlorothiophen-2-yl)-2-methylpyrazolo[1,5-a]pyrimidine (1.18 g, yield: 84%) as a yellow solid.

MS(APCI)m/z; 404/406 [M+H]⁺

Reference Example 57

(1) The corresponding starting materials were treated in the same manner as described in Reference Example 4(1) to (4) to give 6-(2-chlorophenyl)-7-chloro-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine.

(2) To a solution of the compound obtained in the above step (1) (672 mg) in tetrahydrofuran (6 mL) was added palladium acetate (2.2 mg), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (4.1 mg), potassium phosphate trihydrate (1.27 g) and water (120 µL) under nitrogen-gas atmosphere and the mixture was stirred at room temperature for 2 hours and then stirred at 100°C for 24 hours. After cooling to room temperature, to the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed successively with an aqueous 1N sodium hydroxide solution, water and a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 50/50). The eluted fraction was concentrated and the precipitates were washed with diethyl ether/hexane to give 6-(2-chlorophenyl)-7-(4-dimethylaminophenyl)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (288 mg, yield: 34%) as a yellow powder.

MS(APCI)m/z; 421/423 [M+H]⁺

Reference Example 58

The compound obtained in Example 440 (0.67 g) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-

7-(4-trifluoromethylphenyl)-2-[N-methyl-N-(methylsulfonyl)amino]pyrazolo[1,5-a]-pyrimidine (0.64 g) as a crude product (powder).

MS(APCI)m/z; 525/527 [M+H]⁺

Reference Example 59

5 (1) The compound obtained in Reference Example 51(1) (200 mg) in dimethylsulfoxide (2 mL) was added sodium thiomethoxide (15 mg) and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water and the mixture was extracted with ethyl acetate. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica
10 gel (solvent; hexane/ethyl acetate = 87/13 to 60/40) to give 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-ethoxycarbonyl-2-methylthiopyrazolo[1,5-a]pyrimidine (170 mg, yield: 91%) as a pale yellow solid.

MS(APCI)m/z; 472/474 [M+H]⁺

(2) The compound obtained in the above step (1) (170 mg) was treated in the
15 same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methylthiomethylpyrazolo[1,5-a]-pyrimidine as a pale yellow powder.

MS(APCI)m/z; 444/446 [M+H]⁺

Reference Example 60

20 (1) To a solution of 1-benzyloxycarbonyl-3-pyrroline (5.0 g) in methylene chloride (125 mL) was added m-chloroperbezoic acid (12.17 g) and the mixture was stirred at room temperature for 3 days. To the reaction mixture was added an aqueous saturated sodium thiosulfate solution (100 mL) and the mixture was stirred for 30
25 minutes. The reaction mixture was extracted with chloroform (x 2) and the organic layer was washed successively with an aqueous 2N sodium hydroxide solution (100 mL x 2) and a saturated brine, dried over magnesium sulfate and concentrated in vacuo to give benzyl 6-oxa-3-azabicyclo[3,1,0]hexan-3-carboxylate (5.58 g, yield: 100%) as an oil.

MS(APCI)m/z; 220 [M+H]⁺

30 (2) A mixture of the compound obtained in the above step (1) (26.5 g), (1R, 2R)-(-)-[1,2-cyclohexanediamino-N,N'-bis(3,5-di-tert-butylsalicylidene)]chromium chloride (1.57 g) and trimethylsilylazide (17.7 mL) was stirred at room temperature for 2 days. To the reaction mixture was added chloroform and the mixture was washed successively with water and a saturated brine and dried over magnesium sulfate. The
35 organic layer was concentrated in vacuo and the residue was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 10/1 to 2/1 →

chloroform/methanol = 20/1 to 9/1) to give (3S, 4S)-4-azido-1-benzyloxycarbonyl-3-trimethylsilyloxypyrrolidine (compound a: 20.6 g, yield: 55%) and (3S, 4S)-4-azido-1-benzyloxycarbonyl-3-hydroxypyrrolidine (compound b: 8.16 g, yield: 28%) as an oil, respectively.

5 Compound a: MS(APCI)m/z; 335 [M+H]⁺

Compound b: MS(APCI)m/z; 263 [M+H]⁺

(3) To a solution of the compound a (20.6 g) and compound b (8.16 g) in tetrahydrofuran (740 mL) was added triphenylphosphine (26.67 g) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and to the residue was added methanol (380 mL) and an aqueous 0.5N sodium hydroxide solution (380 mL) and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and to the residue was added an aqueous 6N HCl (pH 3). The mixture was washed with chloroform and the aqueous layer was basified (pH 9) with an aqueous 5N sodium hydroxide solution. The mixture was extracted with chloroform (x 3) and the organic layer was dried over magnesium sulfate and concentrated in vacuo to give (3S, 4S)-4-amino-1-benzyloxycarbonyl-3-hydroxypyrrolidine (19.6 g, yield: 90%) as an oil
MS(APCI)m/z; 237 [M+H]⁺

(4) To a solution of the compound obtained in the above step (3) (14.61 g) in chloroform (135 mL) was added dropwise a solution of di-tert-butyl dicarboxylate (16.18 g) in chloroform (20 mL) under ice-cooling and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution (100 mL) and the mixture was stirred. The mixture was extracted with chloroform and the organic layer was dried over magnesium sulfate. Thereto was added NH-silica gel (2 g) and the mixture was stirred and filtered. The filtrate was concentrated in vacuo and the resultant crude product was triturated in hexane/ethyl acetate to give (3S, 4S)-1-benzyloxycarbonyl-3-hydroxy-4-(tert-butoxycarbonyl)pyrrolidine (18.59 g, yield: 94%) as crystals.
MS(APCI)m/z; 337 [M+H]⁺

(5) To a solution of the compound obtained in the above step (4) (18.56 g) in methanol (200 mL) was added 10% palladium-carbon (1.16 g) and the mixture was stirred at room temperature under hydrogen-gas atmosphere for 3 hours. The reaction mixture was filtered through Cerite and the filtrate was concentrated in vacuo. The residue was triturated in methanol/diisopropylether to give (3S, 4S)-3-hydroxy-4-(tert-butoxycarbonyl)pyrrolidine (10.8 g, yield: 97%) as crystals.
MS(APCI)m/z; 203 [M+H]⁺

Reference Example 61 to 83

The corresponding starting materials were treated in the same manner as described in Reference Example 1, 4 or 6 to obtain the compounds as shown in the following Table B3.

5

Table B3 (No. 1)

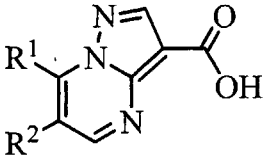
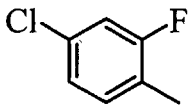
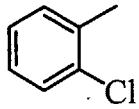
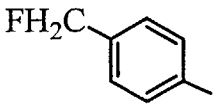
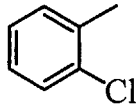
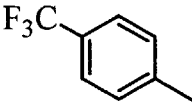
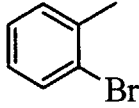
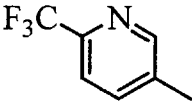
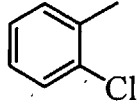
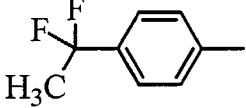
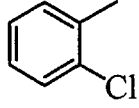
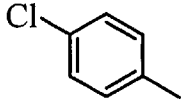
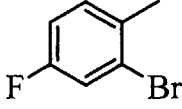
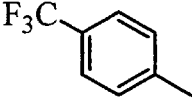
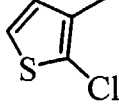
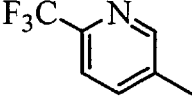
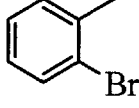
			
Ref. Ex. Nos.	R ¹	R ²	Physicochemical properties etc.
61			MS(APCI):402/404 [M+H] ⁺
62			MS(APCI):382/384 [M+H] ⁺
63			MS(APCI):462/464 [M+H] ⁺
64			MS(APCI):419/421 [M+H] ⁺
65			MS(APCI):414/416 [M+H] ⁺
66			MS(APCI):446/448 [M+H] ⁺
67			MS(APCI):424/426 [M+H] ⁺
68			MS(APCI):463/465 [M+H] ⁺

Table B3 (No. 2)

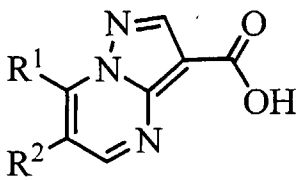
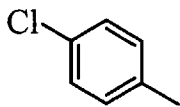
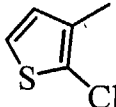
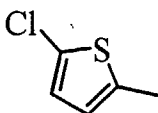
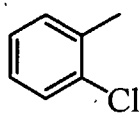
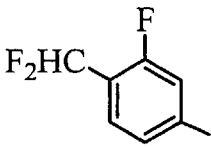
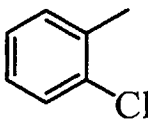
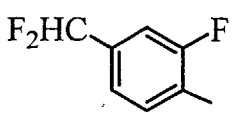
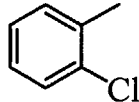
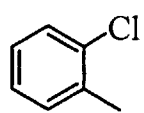
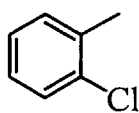
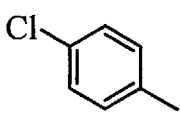
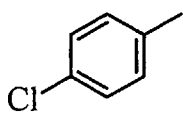
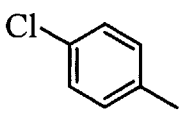
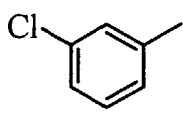
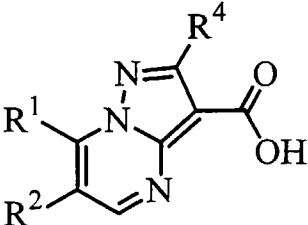
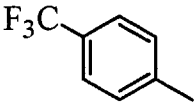
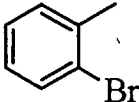
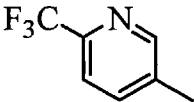
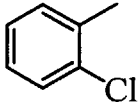
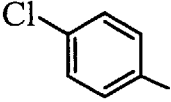
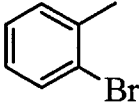
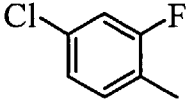
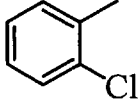
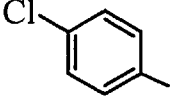
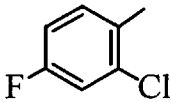
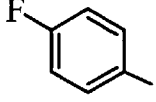
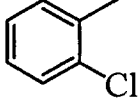
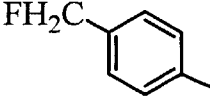
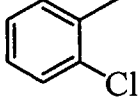
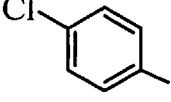
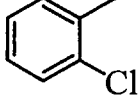
			
Ref. Ex. Nos.	R ¹	R ²	Physicochemical properties etc.
69			MS(APCI):390/392 [M+H] ⁺
70			MS(APCI):390/392 [M+H] ⁺
71			MS(APCI): 418/420 [M+H] ⁺
72			MS(APCI):418/420 [M+H] ⁺
73			MS(APCI):384/386 [M+H] ⁺
74			MS(APCI): 384/386 [M+H] ⁺
75			MS(APCI): 384/386 [M+H] ⁺

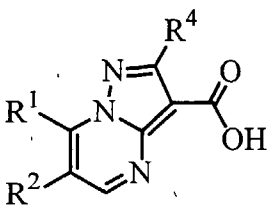
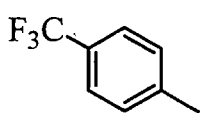
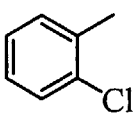
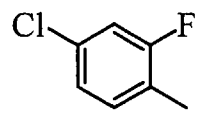
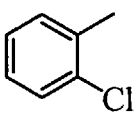
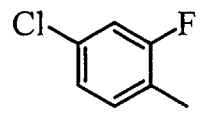
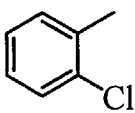
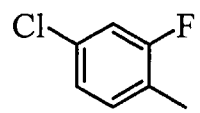
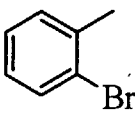
Table B3 (No. 3)

				
Ref. Ex. Nos.	R ¹	R ²	R ⁴	Physicochemical properties etc.
76			CH ₃	MS(APCI):476/478 [M+H] ⁺
77			CH ₃	MS(APCI):433/435 [M+H] ⁺
78			CH ₃	MS(APCI):442/444 [M+H] ⁺
79			CH ₃	MS(APCI):416/418 [M+H] ⁺
80			CH ₃	MS(APCI):416/418 [M+H] ⁺
81			CH ₃	MS(APCI):382/384 [M+H] ⁺
82			CH ₃	MS(APCI):396/398 [M+H] ⁺
83			C ₂ H ₅	MS(APCI):412/414 [M+H] ⁺

Reference Example 84 to 87

The corresponding starting materials were treated in the same manner as described in Reference Example 40 or 50 to obtain the compounds as shown in the following Table B4.

Table B4

				
Ref. Ex. Nos.	R ¹	R ²	R ⁴	Physicochemical properties etc.
84			CHF ₂	MS(APCI):468/470 [M+H] ⁺
85			CF ₃	MS(APCI):470/472 [M+H] ⁺
86			CHF ₂	MS(APCI):452/454 [M+H] ⁺
87			CF ₃	MS(APCI):497/499 [M+H] ⁺

Reference Example 88

The corresponding starting materials were treated in the same manner as described in Reference Example 51 to obtain 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-ethoxymethylpyrazolo[1,5-a]pyrimidine (602 mg, yield: 95%) as a colorless solid..

MS(APCI)m/z; 442/444 [M+H]⁺

Reference Example 89

(1) To a solution of 4-methoxypiperidine (202 mg) in water (4 mL) was added acetic acid (200 μ L) under ice-cooling and the mixture was stirred at room temperature overnight. To the reaction mixture was added an aqueous saturated sodium hydrogencarbonate solution and the mixture was stirred and extracted with chloroform. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; ethyl acetate) to give 4-methoxy-

1-nitrosopiperidine (260 mg, yield: 100%) as a pale yellow oil.

MS(APCI)m/z; 145 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (280 mg) in methanol (3 mL) was added zinc powder (654 mg). Thereto was added dropwise acetic acid (3 mL) under ice-cooling and the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo. To the residue was added an aqueous saturated sodium hydrogencarbonate solution and chloroform, and the mixture was stirred and extracted with chloroform. The extract was concentrated in vacuo to give 1-amino-4-methoxypiperidine (119 mg, yield: 57%) as a pale yellow oil.

MS(APCI)m/z; 131 [M+H]⁺

Reference Example 90

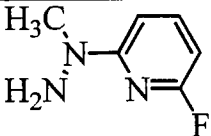
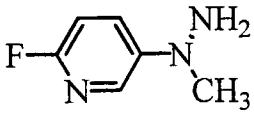
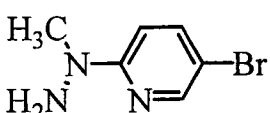
A mixture of 2,5-dibromopyridine (500 mg) and methylhydrazine (1 mL) was heated at 100°C. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with a saturated brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent; chloroform) and the eluted fraction was concentrated. The residue was dissolved in tert-butanol and lyophilized to give 5-bromo-2-(N-methylhydrazino)pyridine (460 mg) as an oil.

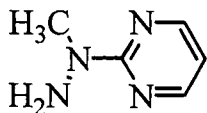
MS(APCI)m/z; 202/204 [M+H]⁺

Reference Example 91 to 93

The corresponding starting materials were treated in the same manner as described in Reference Example 90 to obtain the compounds as shown in the following Table B5.

Table B5

Ref. Ex. Nos.	Chemical structure	Physicochemical properties etc.
91		MS(APCI): 142 [M+H] ⁺
92		MS(APCI): 142 [M+H] ⁺
		MS(APCI): 202/204 [M+H] ⁺

93		MS(APCI): 125 [M+H] ⁺
----	---	----------------------------------

Reference Example 94

(1) To a solution of the compound obtained in Reference Example 4(2) (1.0 g) in tetrahydrofuran (10 mL) was added 4-hydroxypiperidine (361 mg) and triethylamine (830 μ L) and the mixture was stirred at 60°C for 2 hours. After cooling to room temperature, to the reaction mixture was added water and the mixture was extracted with ethyl acetate. The extract was washed with a saturated brine, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was triturated in diisopropylether to give 6-(2-chlorophenyl)-7-(4-hydroxy-1-piperidiny)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (646 mg, yield: 54%) as a colorless solid.

MS(APCI)m/z; 401/403 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (200 mg) in dimethylformamide (3 mL) was added sodium hydride (48 mg) under ice-cooling and the mixture was stirred at room temperature for 15 minutes. To the reaction mixture was added ethyl iodide (120 μ L) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and thereto was added an aqueous diluted HCl. The mixture was extracted with ethyl acetate and the extract was concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 82/18 to 60/40) to give 6-(2-chlorophenyl)-7-(4-ethoxy-1-piperidiny)-3-ethoxycarbonylpyrazolo[1,5-a]pyrimidine (65 mg, yield: 30%) as a colorless viscosity.

MS(APCI)m/z; 429/431 [M+H]⁺

(3) The compound obtained in the above step (2) (65 mg) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-ethoxy-1-piperidiny)pyrazolo[1,5-a]pyrimidine as a colorless powder.

MS(APCI)m/z; 401/403 [M+H]⁺

Reference Example 95

(1) The corresponding starting materials were treated in the same manner as described in Reference Example 4(3) to obtain 6-chloro-7-(4-chlorobenzyl)-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]pyrimidine.

(2) To a solution of the compound obtained in the above step (1) (525 mg) in dimethoxyethane (5 mL) was added p-chlorobenzyl bromide (370 mg), bis(triphenyl-

phosphine)palladium dichloride (53 mg) and zinc powder (235 mg) and the mixture was refluxed under heating and nitrogen-gas atmosphere for 2 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo. To the residue was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 4/1) to give 7-(4-chlorobenzyl)-6-(2-chlorophenyl)-3-ethoxycarbonyl-2-methylpyrazolo[1,5-a]-pyrimidine (113 mg, yield: 17%) as a pale yellow powder.

MS(APCI)m/z; 440/442 [M+H]⁺

Reference Example 96

(1) To a solution of the compound obtained in Reference Example 51(1) (200 mg) in dimethylformamide (2 mL) was added potassium acetate (116 mg) and the mixture was stirred at 60°C for 1 hours. After cooling to room temperature, to the reaction mixture was diluted with ethyl acetate and thereto was added water. The organic layer was separated and concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 55/45) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-acetoxymethylpyrazolo[1,5-a]pyrimidine (109.4 mg, yield: 57%) as a colorless powder.

MS(APCI)m/z; 484/486 [M+H]⁺

(2) To a solution of the compound obtained in the above step (1) (109 mg) in ethanol/tetrahydrofuran (3 mL/3 mL) was added 21% sodium ethoxide/ethanol (0.2 mL) and the mixture was stirred at 60°C for 30 minutes. After cooling to room temperature, to the reaction mixture was diluted with ethyl acetate and thereto was added water. The mixture was extracted with ethyl acetate and the organic layer was concentrated in vacuo. The resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 80/20 to 50/50) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-hydroxymethylpyrazolo[1,5-a]pyrimidine (75 mg, yield: 75%) as a colorless solid.

MS(APCI)m/z; 442/444 [M+H]⁺

(3) To a solution of the compound obtained in the above step (2) (75 mg) in dimethylformamide (2 mL) was added imidazole (23 mg) and tert-butyldimethylsilyl chloride (31 mg) and the mixture was stirred at room temperature for 22 hours. To the reaction mixture was added imidazole (10 mg) and tert-butyldimethylsilyl chloride (15 mg) and the mixture was stirred for 6 hours. To the reaction mixture was added water

and the mixture was extracted with ethyl acetate. The extract was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 85/15 to 60/40) to give 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-ethoxycarbonyl-2-(tert-butyldimethylsilyloxymethyl)pyrazolo[1,5-a]pyrimidine (66.8 mg, yield: 71%) as a colorless solid.

MS(APCI)m/z; 556/558 [M+H]⁺

(4) The compound obtained in the above step (3) (66.8 mg) was treated in the same manner as described in Reference Example 1(3) to give 3-carboxy-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-hydroxymethylpyrazolo[1,5-a]pyrimidine as a colorless powder.

MS(APCI)m/z; 414/416 [M+H]⁺

Reference Example 97

(1) To a solution of benzyl 4-hydroxy-1-piperidinecarboxylate (1.0 g) in toluene/aqueous 2N sodium hydroxide solution (10 mL/10 mL) was added tetrabutylammonium bromide (550 mg) and methoxyethyl bromide (1.2 mL) and the mixture was stirred at 60°C for 2.5 hours and then stirred at 80°C for 17 hours. To the reaction mixture was added sodium hydroxide (0.95 g) and methoxyethyl bromide (1.2 mL) and the mixture was stirred at 80°C for 24 hours. After cooling to room temperature, to the reaction mixture was added water and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the resultant crude product was purified by column chromatography on silica gel (solvent; hexane/ethyl acetate = 75/25 to 40/60) to give benzyl 4-(2-methoxyethoxy)-1-piperidinecarboxylate (266 mg, yield: 21%) as a pale yellow liquid.

MS(APCI)m/z; 294 [M+H]⁺

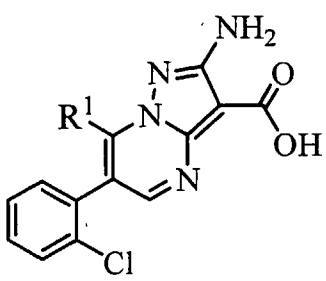
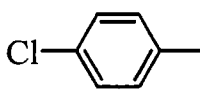
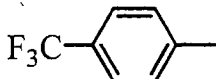
(2) To a solution of the compound obtained in the above step (1) (266 mg) in ethanol (5 mL) was added 10% palladium-carbon (30 mg) and the mixture was stirred at room temperature under hydrogen-gas atmosphere. The reaction mixture was filtered and the filtrate was concentrated in vacuo to give 4-(2-methoxyethoxy)piperidine (138 mg, yield: 96%) as a colorless liquid.

MS(APCI)m/z; 160 [M+H]⁺

Reference Example 98 to 99

The corresponding starting materials were treated in the same manner as described in Example 484 and then the resultant product was treated in Reference Example 1(3) to obtain the compounds as shown in the following Table B6.

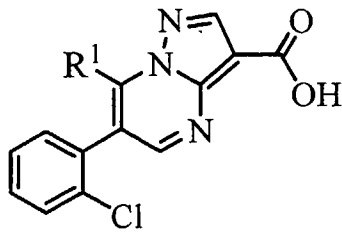
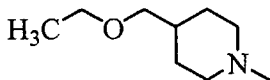
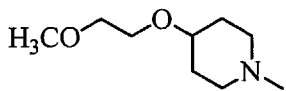
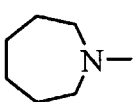
Table B6

		
Ref. Ex. Nos.	R ¹	Physicochemical properties etc.
98		MS(APCI):399/4.1 [M+H] ⁺
99		MS(APCI):433/435 [M+H] ⁺

Reference Example 100 to 102

The corresponding starting materials were treated in the same manner as described in Reference Example 7B to obtain the compounds as shown in the following Table B7.

Table B7

		
Ref. Ex. Nos.	R ¹	Physicochemical properties etc.
100		MS(APCI): 415/417 [M+H] ⁺
101		MS(APCI): 431/433 [M+H] ⁺
102		MS(APCI): 371/373 [M+H] ⁺

Experiment 1

[Human CB1 receptor binding assay]

10

(1) Preparation of human CB1 receptor (membrane fraction):

Materials)

Human CB1-expressing cell line: hCB1/CHO#C3 (Euroscreen)

Medium: F-12 (GIBCO#11765-062), 10% fetal calf serum, antibiotics (400 µg, Geneticin (GIBCO#11811-031)

5 Buffer A: 50 mM tris-HCl (pH 7.5) containing ethylenediaminetetraacetic acid (2.5 mM), MgCl₂ (5 mM) and sucrose (200 mM)

Procedure)

The receptor-expressing cells cultivated in the above medium were washed with phosphate buffer (x 2) and thereto was added Buffer A (2 mL) under ice-cooling or
10 4°C (the following procedures were also carried out at the same temperature). The cells were collected by using a cell-scraper, treated by a microtip-type ultrasonicator for 20 seconds (pulse-on: 2 sec, pulse-off: 1 sec) and centrifuged (500 x g, 15 min). The supernatant was separated and centrifuged (43000 x g, 60 min). The resultant pellet was suspended in Buffer A and homogenized with a potter-type homogenizer. To the
15 homogenate was added an equal volume of 80% glycerol and stored at -80°C.

(2) Procedure of CB1 receptor binding assay:

Materials)

Buffer B: 50 mM tris-HCl (pH 7.5) containing ethylenediaminetetraacetic acid (2.5 mM), MgCl₂ (5 mM) and bovine serum albumine (2 mg/mL, fatty acid-free,
20 SIGMA-A7030)

Buffer C: 50 mM tris-HCl (pH 7.5) containing ethylenediaminetetraacetic acid (2.5 mM), MgCl₂ (5 mM) and bovine serum albumine (2 mg/mL, SIGMA-A7906)

Coating solution: 0.3 % ethyleneimine polymer

Radioligand: [³H]-CP55940 (30 nM/7992 dpm/µL) prepared by diluting 8.3
25 µM solution of the radioligand with Buffer B

Method)

Each well of the assay plate (96-well, Costar Code#3371) was filled with Buffer B (140 µL), a solution of each test compound in dimethylsulfoxide (20 µL, final concentration: 0.1%), radioligand (20 µL) and membrane preparation (20 µL, 0.5 µg/20
30 µL) and the mixture was incubated at 30°C for 90 minutes to proceed the binding reaction. The reaction mixture was harvested to each well of a plate presoaked with the above coating solution (Packard Unifilter GF/B, #6005177). The plate was washed with Buffer C (200 µL x 10) and dried at 50°C for 1 hour and Microscinti 40 (40 µL) was added to each well. The bound radiolabel was quantitated by scintillation counting
35 (Top Count NXT, Packard). IC₅₀ value of each test compound against the

radioligand-binding to CB1 receptors was calculated on the basis of the quantitated radiolabel activity by using Graphpad Prism3.02.

3) Results:

IC₅₀ value of each test compound is shown in the following Table C1.

5 Meanwhile, the symbols (++ and +++) are defined as follows:

++ : 10 nM < IC₅₀ < 100 nM

+++ : 10 nM > IC₅₀

Table C1

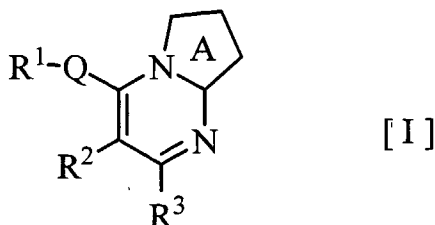
Test Compounds	IC ₅₀ (nM)
Compound of Example 10	++
Compound of Example 131	++
Compound of Example 185	++
Compound of Example 224	++
Compound of Example 238	++
Compound of Example 287	++
Compound of Example 289	++
Compound of Example 309	+++
Compound of Example 324	++
Compound of Example 410	++
Compound of Example 252	++
Compound of Example 253	+++
Compound of Example 427	++
Compound of Example 452	+++
Compound of Example 462	++

10 INDUSTRIAL APPLICABILITY

The compounds [I] of the present invention are useful for treatment and/or prophylaxis of various CB1 receptor-mediated diseases such as psychosis including schizophrenia. The compounds [I] of the present invention are also useful for withdrawal from a chronic treatment, alcohol dependence or drug abuse. Furthermore,
 15 the compounds [I] of the present invention are useful as an agent for enhancing analgesic activity or an agent for smoking cessation.

CLAIMS

1. A pyrazolo[1,5-a]pyrimidine compound of the formula [I]:



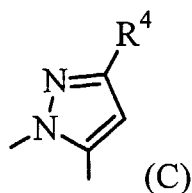
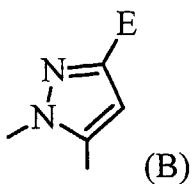
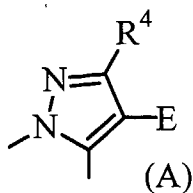
5 wherein

R^1 and R^2 are the same or different and an optionally substituted aryl group or an optionally substituted saturated or unsaturated heterocyclic group,

Q is single bond, a methylene group or a group of the formula: $-N(R^Q)-$,

R^Q is an alkyl group,

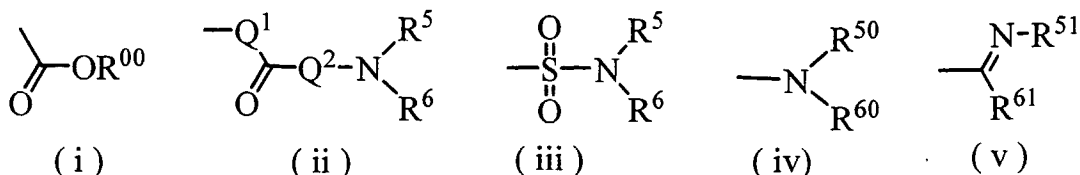
10 5-membered Ring A is a substituted pyrazole ring fused to the adjacent pyrimidine ring having the following formula (A), (B) or (C),



15 R^3 and R^4 are the same or different and (a) a hydrogen atom, (b) a cyano group, (c) an alkyl group optionally substituted by one to three halogen atom(s), (d) an alkyloxy group (the alkyl moiety of said group being optionally substituted by one to three group(s) selected from a halogen atom, a hydroxyl group, an amino group optionally substituted by one or two alkyl group(s), an alkyloxy group and an alkylsulfonyl group) or (e) an alkylthio group, (f) an alkylsulfinyl group, (g) an alkylsulfonyl group or (h) a group of the formula: $-N(R')(R'')$,

20 R' and R'' are the same or different and (a) a hydrogen atom, (b) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, an amino group optionally substituted by one or two alkyl group(s) and an alkyloxy group, (c) an acyl group, (d) an alkylsulfonyl group or (e) an amino sulfonyl group optionally substituted by one to two alkyl group(s), or both R' and R'' combine each other at their
25 termini to form together with an adjacent nitrogen atom an optionally substituted, saturated or unsaturated nitrogen-containing heterocyclic group,

E is one of the following groups (i) to (v):



R^{00} is an alkyl group,

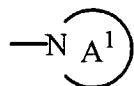
Q^1 is a single bond, an alkylene group or a group of the formula: $-\text{N}(\text{R}^7)-$, R^7 is a hydrogen atom or an alkyl group,

5 Q^2 is a single bond or an alkylene group,

one of R^5 and R^6 is a hydrogen atom or an alkyl group and the other is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyloxy group, an optionally substituted cycloalkyl group, an amino group optionally substituted by one or two alkyl group(s), an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an acyl group, an optionally substituted aryl group and optionally substituted saturated or unsaturated heterocyclic group, (b) an optionally substituted cycloalkyl group, (c) a group of the formula: $-\text{N}(\text{R}^8)(\text{R}^9)$, (d) an optionally substituted aryl group or (e) an optionally substituted, saturated or unsaturated heterocyclic group, or both of R^5 and R^6 combine each other to form together with an adjacent nitrogen atom an optionally substituted, saturated or unsaturated nitrogen-containing heterocyclic group,

one of R^8 and R^9 is a hydrogen atom or an alkyl group and the other is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group and an aryl group, (b) a cycloalkyl group, (c) an optionally substituted aryl group or (d) an acyl group or (e) an optionally substituted saturated or unsaturated heterocyclic group,

one of R^{50} and R^{60} is a hydrogen atom or an alkyl group and the other is a hydrogen atom, an alkyl group or an acyl group, or both of them combine together with the adjacent nitrogen atom to form a cyclic group of the following formula:



25

in which Ring A^1 is a 5- to 7-membered aliphatic nitrogen-containing heterocyclic group optionally substituted by an oxo group,

R^{51} is an alkyl group or an optionally substituted arylsulfonyl group,

R^{61} is an alkylamino group or an azido group,

30 or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein R^1 and R^2 are the same

or different and

(i) a 6- to 10-membered monocyclic or bicyclic aryl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group optionally substituted by one to three halogen atom(s), an amino group optionally substituted by one to two alkyl group(s), an alkylthio group, an alkylsulfinyl group and an alkylsulfonyl group, or

(ii) a 5- to 6-membered saturated or unsaturated, oxygen-, sulfur- or nitrogen-containing heteromonocyclic group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an oxo group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group optionally substituted by one to three halogen atom(s), an amino group optionally substituted by one to two alkyl group(s), an alkylthio group, an alkylsulfinyl group and an alkylsulfonyl group,

or a pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 wherein the saturated or unsaturated heterocyclic group in R^5 , R^6 , R^8 or R^9 is

(a) a saturated or unsaturated, 4- to 7-membered heteromonocyclic group, said heteromonocyclic group containing one to four heteroatoms selected from oxygen atom, sulfur atom and nitrogen atom;

(b) a saturated or unsaturated, 8- to 15-membered nitrogen-containing bicyclic or tricyclic heterocyclic group formed by fusing the aforementioned heteromonocyclic group with one or two other cyclic group(s) selected from a C_{3-8} cycloalkyl group, a 5- to 6-membered monocyclic aryl group and a saturated or unsaturated, 4- to 7-membered heteromonocyclic group, said heteromonocyclic group containing one to four heteroatom(s) selected from oxygen atom, sulfur atom and nitrogen atom; or

(c) a saturated or unsaturated, 8- to 11-membered nitrogen-containing spiro-heterocyclic group, or a pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 wherein the saturated or unsaturated nitrogen-containing heterocyclic group formed by combining R^5 with R^6 is

(a) a saturated or unsaturated, 4- to 7-membered nitrogen-containing heteromonocyclic group, said heteromonocyclic group optionally containing two or more nitrogen atoms and optionally containing one to two heteroatom(s) other than such nitrogen atom(s) selected from oxygen atom and sulfur atom;

(b) a saturated or unsaturated, 8- to 15-membered nitrogen-containing bicyclic

or tricyclic heterocyclic group formed by fusing the aforementioned heteromonocyclic group with one or two other cyclic group(s) selected from a C₃₋₈ cycloalkyl group, a 5- to 6-membered monocyclic aryl group and a saturated or unsaturated, 4- to 7-membered heteromonocyclic group, said heteromonocyclic group containing one to four
5 heteroatom(s) selected from oxygen atom, sulfur atom and nitrogen atom; or

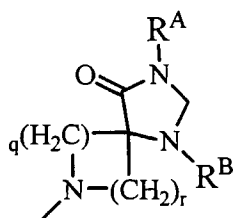
(c) a saturated or unsaturated, 8- to 11-membered nitrogen-containing spiro-heterocyclic group,
or a pharmaceutically acceptable salt thereof.

5. The compound according to Claim 3 wherein the saturated or
10 unsaturated heterocyclic group in R⁵, R⁶, R⁸ or R⁹ is a saturated or unsaturated heterocyclic group substituted by one to four groups selected from a halogen atom, a hydroxyl group, a cyano group, an oxo group, an alkyl group, an alkyl group substituted by one to three halogen atom(s), an alkyloxyalkyl group, an aminoalkyl group, a cycloalkyl group, an arylalkyl group, an alkyloxy group, an alkyloxy group substituted
15 by one to three halogen atom(s), an acyl group, an amino group optionally substituted by one to two alkyl group(s), an acylamino group, an alkylsulfonyl group, an aminosulfonyl group optionally substituted by one to two alkyl group(s), an aryl group optionally substituted by one to two halogen atom(s) and a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group, or a pharmaceutically acceptable
20 salt thereof.

6. The compound according to Claim 4 wherein the saturated or
unsaturated heterocyclic group formed by combining R⁵ with R⁶ is a saturated or
unsaturated nitrogen-containing heterocyclic group substituted by one to three group(s)
25 selected from a halogen atom, a hydroxyl group, a cyano group, an oxo group, an alkyl group, an alkyl group substituted by one to three halogen atom(s), an alkyloxyalkyl group, an aminoalkyl group, a cycloalkyl group, an arylalkyl group, an alkyloxy group, an alkyloxy group substituted by one to three halogen atom(s), an acyl group, an amino group optionally substituted by one to two alkyl group(s), an acylamino group, an alkylsulfonyl group, an aminosulfonyl group optionally substituted by one to two alkyl
30 group(s) and an aryl group, or a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 3 wherein the saturated or
unsaturated heterocyclic group in R⁵, R⁶, R⁸ or R⁹ is (A) a saturated or unsaturated oxygen- or sulfur-containing heterocyclic group selected from a furyl group, a tetrahydrofuran-yl group, a pyran-yl group, a tetrahydropyran-yl group, a thiacyclobutyl
35 group, a thienyl group, a tetrahydrothienyl group, a thiopyran-yl group, a tetrahydrothiopyran-yl group, a benzofuran-yl group, a dihydrobenzofuran-yl group, an

isobenzofuranyl group, a chromanyl group, an isochromanyl group, a chromenyl group, an isochromenyl group, a benzothienyl group and a dihydrobenzothienyl group; or (B) a saturated or unsaturated nitrogen-containing heterocyclic group selected from an azetidyl group, a pyrrolidinyl group, a pyrrolinyl group, an imidazolidinyl group, an imidazoliny group, a pyrazolidinyl group, a pyrazolinyl group, a pyrrolyl group, a 2H-pyrrolyl group, an imidazolyl group, a pyrazolyl group, a dihydropyrazolyl group, a thiazolidinyl group, a thiazolyl group, an isothiazolyl group, an isoxazolyl group, an oxazolidinyl group, a pyridyl group, a dihydropyridyl group, a tetrahydropyridyl group, a piperidyl group, a pyrazinyl group, a piperazinyl group, a pyrimidinyl group, a tetrahydropyrimidinyl group, a pyridazinyl group, a morpholinyl group, an azocinyl group, an azacycloheptyl group, an indoliziny group, a benzimidazolyl group, a benzotriazolyl group, an indolyl group, an isoindolyl group, a 3H-indolyl group, an indolinyl group, an isoindolinyl group, a 1H-indazolyl group, a pyrrolopyridyl group, a pyrrolopyrimidinyl group, a tetrazolyl group, a purinyl group, a pteridinyl group, a 4H-quinoliziny group, a quinolyl group, a dihydroquinolyl group, a tetrahydroquinolyl group, an isoquinolyl group, a dihydroisoquinolyl group, a tetrahydroisoquinolyl group, a phthalazinyl group, a dihydrophthalazinyl group, a naphthyridinyl group, a dihydronaphthyridinyl group, a tetrahydronaphthyridinyl group, a quinoxalinyl group, a quinazolinyl group, a dihydrobenzothiazinyl group, a dihydrobenzoxazinyl group, a cinnolinyl group, a pteridinyl group, a xanthenyl group, a carbazolyl group, a beta-carbolinyl group, a phenanthridinyl group, an acridinyl group, a 5H-dihydro-dibenzazepinyl group and a spiro-heterocyclic group of the formula:

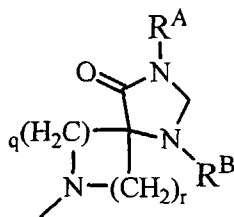


wherein R^A and R^B are the same or different and a hydrogen atom or an alkyl group, and q and r are an integer of 1 or 2, or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 3 wherein the saturated or unsaturated heterocyclic group in R^5 , R^6 , R^8 or R^9 is a tetrahydrofuranyl group, a pyrrolyl group, a pyrrolidinyl group, a piperidyl group, an azacycloheptyl group, a tetrahydropyranyl group, piperazinyl group, a morpholinyl group, a thiomorpholinyl group, a thiacyclobutyl group, a tetrahydrothienyl group, a tetrahydrothiopyranyl group, a thiazolyl group, a pyridyl group, a pyrimidinyl group, an indolinyl group, a

pyrrolopyridyl group or a tetrahydronaphthyridinyl group, or a pharmaceutically acceptable salt thereof.

9. The compound according to Claim 4 wherein the saturated or unsaturated nitrogen-containing heterocyclic group formed by combining R^5 with R^6 is a saturated or unsaturated nitrogen-containing heterocyclic group selected from an azetidyl group, a pyrrolidinyl group, a pyrrolinyl group, an imidazolidinyl group, an imidazoliny group, a pyrazolidinyl group, a pyrazolinyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a dihydropyrazolyl group, a thiazolidinyl group, an oxazolidinyl group, a dihydropyridyl group, a tetrahydropyridyl group, a piperidyl group, a piperazinyl group, a tetrahydropyrimidinyl group, a morpholinyl group, an azacycloheptyl group, a benzimidazolyl group, a benzotriazolyl group, an indolyl group, an isoindolyl group, an indolinyl group, an isoindolinyl group, a 1H-indazolyl group, a tetrazolyl group, a purinyl group, a dihydroquinolyl group, a tetrahydroquinolyl group, a dihydroisoquinolyl group, a tetrahydroisoquinolyl group, a dihydropthalazinyl group, a dihydroquinazolinyl group, a dihydrobenzothiazinyl group, a dihydrobenzoxazinyl group, a carbazolyl group, a beta-carbolinyl group, a 5H-dihydro-dibenzazepinyl group and a spiro-heterocyclic group of the formula:



wherein R^A and R^B are the same or different and a hydrogen atom or an alkyl group, and q and r are an integer of 1 or 2, or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 4 wherein the saturated or unsaturated nitrogen-containing heterocyclic group formed by combining R^5 with R^6 is a morpholino group, a thiomorpholino group, a piperidino group, a piperazino group or an azacycloheptyl group, or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 1 wherein the group of the formula (ii) is one of the following groups (a) to (d):

- (a) $-C(=O)-N(R^5)(R^6)$,
- (b) $-C(=O)-Alk-N(R^5)(R^6)$,
- (c) $-Alk-C(=O)-N(R^5)(R^6)$,
- (d) $-N(R^7)-C(=O)-N(R^5)(R^6)$

in which Alk is a straight or branched chain C_{1-6} alkylene group, or a pharmaceutically

acceptable salt thereof.

12. The compound according to Claim 1 wherein

R^1 and R^2 are the same or different and (a) a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group,

Q is a single bond,

Ring A is a substituted pyrazole ring of the formula (A),

E is a group of the following formula: $-C(=O)O-R^{00}$ (i)

R^4 is an amino group optionally substituted by one to two group(s) selected from an alkyl group and an alkylsulfonyl group, or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 12 wherein R^1 is a chlorophenyl group or a trifluoro- C_{1-4} alkyl-phenyl group, R^2 is a chlorophenyl group, R^3 is a C_{1-4} alkyl group and R^4 is (a) an amino group substituted by one to two group(s) selected from a C_{1-4} alkyl group and a C_{1-4} alkylsulfonyl group or (b) an aminosulfonyl group substituted by one to two C_{1-4} alkyl group(s), or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 1 wherein

R^1 and R^2 are the same or different and (a) a phenyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group optionally substituted by one to three halogen atom(s), an amino group optionally substituted by one to two alkyl group(s) and an alkylsulfonyl group or (b) a saturated or unsaturated 5- to 7-membered heterocyclic group optionally substituted by one to three group(s) selected from a halogen atom, an oxo group, an alkyl group optionally substituted by one to three halogen atom(s), an alkyloxy group, an alkyloxyalkyl group and an alkyloxyalkyloxy group,

Ring A is a substituted pyrazole ring of the formula (A) or (B),

E is one of the groups of the following formula (a) to (e):

a) $-C(=O)-N(R^5)(R^6)$,

b) $-C(=O)-Alk-N(R^5)(R^6)$,

c) $-Alk-C(=O)-N(R^5)(R^6)$,

d) $-N(R^7)-C(=O)-Alk-N(R^5)(R^6)$,

e) $-C(=NR^{51})-R^{61}$,

R^3 is a hydrogen atom, a cyano group or an alkyloxy group,

R^4 is (a) a hydrogen atom, (b) a cyano group, (c) an alkyl group optionally

substituted by one to three group(s) selected from a halogen atom and a hydroxyl group, (d) an alkyloxy group optionally substituted by one to three group(s) selected from a halogen atom, a hydroxyl group, an amino group optionally substituted by one to two alkyl group(s), an alkyloxy group and an alkylsulfonyl group, (e) an alkylthio group, (f) an alkylsulfinyl group, (g) an alkylsulfonyl group or (h) a group of the formula: $-N(R')(R'')$,

R' and R'' are the same or different and (a) a hydrogen atom, (b) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, an amino group optionally substituted by one to two alkyl group(s) and an alkyloxy group, (c) an acyl group, (d) an alkylsulfonyl group or (e) an aminosulfonyl group optionally substituted by one to two alkyl group(s), or (f) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heteromonocyclic group optionally substituted by a hydroxyl group or an alkyloxy group,

one of R^5 and R^6 is a hydrogen atom or an alkyl group and the other is

(1) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, an alkyloxy group, a cycloalkyl group, an alkylthio group, an alkylsulfonyl group, an amino group optionally substituted by one or two alkyl group(s), a morpholinocarbonyl group, a phenyl group optionally substituted by a cyano group and a saturated or unsaturated 5- to 6-membered nitrogen-containing heteromonocyclic group, said heteromonocyclic group being optionally substituted by a group selected from a halogen atom, an alkyl group and a trihalogenoalkyl group;

(2) a cycloalkyl group optionally substituted by a cyano group or an alkyl group;

(3) a group of the formula: $-N(R^8)(R^9)$; or

(4) a phenyl group; or

(5) a saturated or unsaturated 4- to 10-membered monocyclic- or bicyclic heterocyclic group optionally substituted by one to four group(s) selected from a halogen atom, a cyano group, a hydroxyl group, an oxo group, an alkyl group optionally substituted by one to three halogen atom(s), a cycloalkyl group, an alkylcarbonyl group, an alkyloxycarbonyl group, an alkylsulfonyl group, an aminosulfonyl group optionally substituted by one or two alkyl group(s), a carbamoyl group optionally substituted by one to two alkyl group(s), an alkyloxycarbonyl group, an alkyloxycarbonylamino group a phenyl group optionally substituted by one to two halogen atom(s) and saturated or unsaturated 5- to 6-membered heteromonocyclic group; or

(6) both of R^5 and R^6 combine each other together with the adjacent nitrogen

atom to form a saturated or unsaturated 5- to 7-membered nitrogen-containing heterocyclic group optionally substituted by one to two group(s) selected from a halogen atom and an oxo group,

R^8 is hydrogen atom or an alkyl group,

R^9 is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group and a phenyl group; (b) a phenyl group optionally substituted by a group selected from a halogen atom, a cyano group, an alkyl group, a trihalogenoalkyl group, a cycloalkyl group, a trihalogenoalkyloxy group, an alkyloxy group, an alkylthio group and an alkylsulfonyl group; (c) an alkyloxycarbonyl group; or (d) a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by a group selected from a halogen atom, a cyano group, an alkyl group, an alkyloxy group and a trihalogenoalkyl group,

R^7 is a hydrogen atom,

R^{51} is an alkyl group or a phenylsulfonyl group optionally substituted by one to two halogen atom(s) and R^{61} is an alkylamino group or an azido group, or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 14 wherein R^1 is (a) a phenyl group optionally substituted by one or two group(s) selected from a halogen atom, a cyano group, a dihalogenoalkyl group, a trihalogenoalkyl group, an alkyloxy group, an alkyloxyalkyl group and di(alkyl)amino group or (b) a saturated or unsaturated 5- to 7-membered heterocyclic group optionally substituted by one to two group(s) selected from an oxo group, an alkyl group, a trihalogenoalkyl group, an alkyloxy group, an alkyloxyalkyl, an alkyloxyalkyloxy group and a di(alkyl)amino group,

R^2 is (a) a phenyl group optionally substituted by one or two group(s) selected from a halogen atom and a cyano group or (b) a saturated or unsaturated 5- to 6-membered heterocyclic group optionally substituted by a halogen atom,

R^3 is a hydrogen atom,

R^4 is a hydrogen atom, an alkyl group, a dihalogenoalkyl group, a hydroxyalkyl group, a trihalogenoalkyl group, an alkyloxyalkyl group, a hydroxyalkyloxy group, an alkyloxyalkyloxy group, an alkylsulfonylalkyl group or a group of the formula: $-N(R')(R'')$,

one of R' and R'' is a hydrogen atom or an alkyl group and the other is an acyl group or an alkylsulfonyl group,

E is one of the groups of the following formula (a), (b) and (e):

(a) $-C(=O)-N(R^5)(R^6)$,

(b) $-C(=O)-Alk-N(R^5)(R^6)$,

(e) $-C(=NR^{51})-R^{61}$,

one of R^5 and R^6 is a hydrogen atom or an alkyl group, the other is (a) an alkyl group, (b) a cycloalkyl group, (c) a phenyl group, (d) a saturated or unsaturated 4- to 10-membered mono- or bi-cyclic heterocyclic group optionally substituted by one to four group(s) selected from a halogen atom, an oxo group, a cyano group, a hydroxyl group, an alkyl group, a trihalogenoalkyl group, an alkyloxy group, an alkyloxyalkyl group, an alkylcarbonyl group, a di(alkyl)carbonyl group, an alkylsulfonyl group, a di(alkyl)aminosulfonyl group, a phenyl group, a halogenophenyl group and a pyridyl group or (e) a group of the formula: $-N(R^8)(R^9)$, or (f) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by one to two group(s) selected from a halogen atom and an oxo group,

R^8 is an alkyl group,

R^9 is (a) an alkyl group, (b) a phenyl group optionally substituted by a halogen atom, (c) an alkyl group optionally substituted by a pyridyl group or (d) a saturated or unsaturated 4- to 6-membered heteromonocyclic group optionally substituted by a group selected from a halogen atom, an alkyl group, a trihalogenoalkyl group and an alkyloxy group,

R^{51} is an alkyl group or a halogenophenyl-sulfonyl group, and R^{61} is an alkylamino group or an azido group, or a pharmaceutically acceptable salt thereof.

16. The compound according to Claim 14 wherein R^1 is (a) a phenyl group optionally substituted by a group selected from a chlorine atom, a fluorine atom, a cyano group, a difluoro- C_{1-4} alkyl group and a trifluoro- C_{1-4} alkyl group or (b) a pyridyl group optionally substituted by a trifluoro- C_{1-4} alkyl group,

R^2 is a phenyl group optionally substituted by one to two groups selected from a chlorine atom, a fluorine atom, a bromine atom and a cyano group,

R^3 is a hydrogen atom,

R^4 is a hydrogen atom, a C_{1-4} alkyl group, a difluoro- C_{1-4} alkyl group, a trifluoro- C_{1-4} alkyl group, a C_{1-4} alkyloxy- C_{1-4} alkyl group or a C_{1-4} alkyl-carbonyl-amino group,

E is one of the groups of the following formula (a) and (b):

(a) $-C(=O)-N(R^5)(R^6)$,

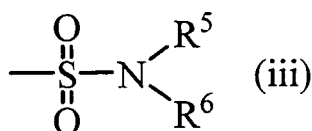
(b) $-C(=O)-Alk-N(R^5)(R^6)$,

one of R^5 and R^6 is a hydrogen atom and the other is a C_{1-4} alkyl group, a pyridyl- C_{1-4} alkyl group, a C_{5-7} cycloalkyl group, a chlorophenyl group, a saturated or

unsaturated 4- to 6-membered heteromonocyclic group optionally substituted by one to two group(s) selected from a halogen atom, an oxo group and C₁₋₄ alkyloxy-C₁₋₄ alkyl group or a group of the formula: -N(R⁸)(R⁹), or both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by one to two oxo group(s),

R⁸ is a C₁₋₄ alkyl group and R⁹ is a C₁₋₄ alkyl group, a chlorophenyl group, a pyridyl group or a C₁₋₄ alkyl-pyridyl group, or a pharmaceutically acceptable salt thereof.

17. The compound according to Claim 1 wherein R¹ and R² are the same or different and a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group, Q is a single bond, Ring A is a substituted pyrazole ring of the formula (A), R³ is a hydrogen atom, R⁴ is a hydrogen atom or an alkyl group, E is a group of the formula (iii):



one of R⁵ and R⁶ is a hydrogen atom or an alkyl group and the other is (a) an alkyl group, (b) a cycloalkyl group or (c) a saturated or unsaturated 5- to 6-membered sulfur- or nitrogen-containing heteromonocyclic group, or (d) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group optionally substituted by one to two oxo group(s), or a pharmaceutically acceptable salt thereof.

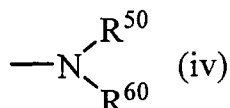
18. The compound according to Claim 17 wherein R¹ is a trihalogenoalkyl-phenyl group, R² is a halogenophenyl group,

R⁴ is an alkyl group,

one of R⁵ and R⁶ is a hydrogen atom or an alkyl group, the other is (a) an alkyl group, (b) a cycloalkyl group, (c) a saturated or unsaturated 5- to 6-membered sulfur- or nitrogen-containing heteromonocyclic group optionally substituted by one to two oxo group(s), or (d) both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered heteromonocyclic group optionally substituted by one to two oxo group(s), or a pharmaceutically acceptable salt thereof.

19. The compound according to Claim 1 wherein R¹ and R² are the same or different and a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group, Q is a single bond, Ring A is a

substituted pyrazole ring of the formula (A), R^3 is a hydrogen atom, R^4 is a hydrogen atom or an alkyl group, E is a group of the formula (iv):



one of R^{50} and R^{60} is a hydrogen atom or an alkyl group and the other is an alkyl group or an acyl group, or both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group optionally substituted by one to two oxo group(s), or a pharmaceutically acceptable salt thereof.

20. The compound according to Claim 1 wherein R^1 and R^2 are the same or different and a phenyl group optionally substituted by one to two group(s) selected from a halogen atom and a trihalogenoalkyl group, Q is a single bond, Ring A is a substituted pyrazole ring of the formula (C), R^3 is a hydrogen atom, R^4 is a group of the formula -N(R')R'' , R' and R'' are the same or different and a hydrogen atom or an alkyl group, or both of them combine together with the adjacent nitrogen atom to form a saturated or unsaturated 5- to 6-membered nitrogen-containing heterocyclic group, or a pharmaceutically acceptable salt thereof.

21. A compound selected from the group consisting of:

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-piperidinocarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(N'-methyl-N'-phenylhydrazino)-carbonyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclohexylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[(N',N'-dimethylhydrazino)carbonyl]-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-pyrrolidinocarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(4-tetrahydropyranyl)carbamoyl]-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)-carbamoyl]pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-difluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydro-

thiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

5 (S)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[2-(2-pyridyl)ethyl]carbamoyl]-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)-2-methoxy-pyrazolo[1,5-a]pyrimidine;

10 (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

15 6-(2-bromophenyl)-7-(4-chlorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

(R, S)-6-(2-bromophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

20 (R)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[N-(3-chlorophenyl)-N-methylamino]-carbamoyl]pyrazolo[1,5-a]pyrimidine;

25 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-[N-methyl-N-(2-pyridyl)amino]-carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-isobutylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

30 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-(N-cyclopentylcarbamoyl)-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-[N-methyl-N-(2-pyridyl)-amino]carbamoyl]pyrazolo[1,5-a]pyrimidine;

35 (R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-cyanophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]-

pyrimidine;

(R,S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-2-methyl-3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

5 6-(2-chlorophenyl)-7-(4-fluorophenyl)-3-(N-cyclopentylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-[N-methyl-N-(2-pyridyl)amino]-carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)- 6-(2-chlorophenyl)-7-(4-chlorophenyl)- 3-[N-(1,1-dioxo-tetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

10 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-ethylcarbamoyl)pyrazolo[1,5-a]-pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-(N-cyclopropylcarbamoyl)-pyrazolo[1,5-a]pyrimidine;

15 (S)-6-(2-chlorophenyl)-7-(4-chloro-2-fluorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-difluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-cyanophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

20 (S)-6-(2-cyanophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-methoxypyridin-5-yl)-hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine;

25 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-(1-pyrrolidinyl)carbamoyl]-pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(2-trifluoromethylpyridin-5-yl)-3-(N-cyclopentylcarbamoyl)-pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

30 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-carbonyl]-2-methylpyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-trifluoromethylpyrazolo[1,5-a]pyrimidine;

35 6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[(N',N'-dimethylhydrazino)-carbonyl]-2-acetylaminopyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-

carbonyl]-2-acetylaminopyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-carbonyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine;

5 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1-pyrrolidiny)carbamoyl]-
-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

(S)-6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

10 6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-(N-piperidinocarbamoyl)-
-2-difluoromethylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxothiacyclobutan-3-yl)-carbamoyl] pyrazolo[1,5-a]pyrimidine;

15 7-(4-chlorophenyl)-6-(2-cyano-4-fluorophenyl)-3-[N-(1-pyrrolidiny)carbamoyl]-
pyrazolo[1,5-a]pyrimidine;

7-(4-chlorophenyl)-6-(2-cyanophenyl)-3-(N-piperidinocarbamoyl)-2-methylpyrazolo[1,5-a]pyrimidine;

7-(4-chlorophenyl)-6-(2-cyanophenyl)-3-[N-(1-pyrrolidiny)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

20 (S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(2-methoxymethyl-1-pyrrolidiny)-carbamoyl]pyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(4-fluoropiperidino)carbamoyl]-pyrazolo[1,5-a]pyrimidine;

25 (R)-7-(4-chloro-2-fluorophenyl)-6-(2-cyanophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-ethoxypyridin-5-yl)-hydrazino]carbonyl]pyrazolo[1,5-a]pyrimidine;

(R)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

30 (S)-6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1,1-dioxotetrahydrothiophen-3-yl)carbamoyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[[N'-methyl-N'-(2-pyridyl)hydrazino]-carbonyl]-2-methoxymethylpyrazolo[1,5-a]pyrimidine;

35 6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[N-(1-pyrrolidiny)carbamoyl]-
2-methoxymethylpyrazolo[1,5-a]pyrimidine;

7-(4-chloro-2-fluorophenyl)-6-(2-cyanophenyl)-3-[N-(1-pyrrolidiny)carbamoyl]-

2-methylpyrazolo[1,5-a]pyrimidine;

6-(2-chlorophenyl)-7-(4-chlorophenyl)-3-[2-(1,1-dioxothiomorpholino)acetyl]-
2-methylpyrazolo[1,5-a]pyrimidine;

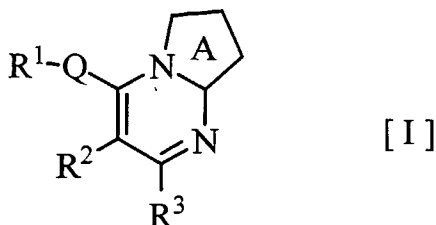
6-(2-cyanophenyl)-7-(4-chlorophenyl)-3-[N-(4-fluoropiperidino)carbamoyl]-

5 2-methylpyrazolo[1,5-a]pyrimidine; and

6-(2-chlorophenyl)-7-(4-trifluoromethylphenyl)-3-[N-(tetrahydrothiophen-3-yl)-
carbamoyl] pyrazolo[1,5-a]pyrimidine,

or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising as an active ingredient a
10 pyrazolo[1,5-a]pyrimidine compound of the formula [I]:



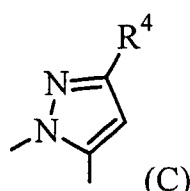
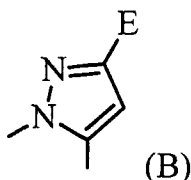
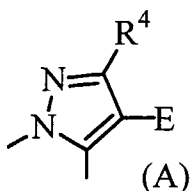
wherein

R^1 and R^2 are the same or different and an optionally substituted aryl group or
an optionally substituted saturated or unsaturated heterocyclic group,

15 Q is single bond, a methylene group or a group of the formula: $-N(R^Q)-$,

R^Q is an alkyl group,

5-membered Ring A is a substituted pyrazole ring fused to the adjacent
pyrimidine ring having the following formula (A), (B) or (C),

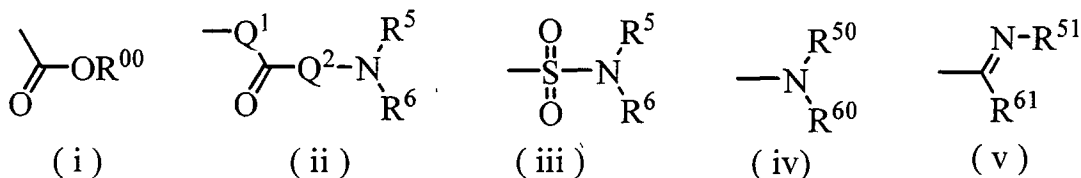


20 R^3 and R^4 are the same or different and (a) a hydrogen atom, (b) a cyano group,
(c) an alkyl group optionally substituted by one to three halogen atom(s), (d) an
alkyloxy group (the alkyl moiety of said group being optionally substituted by one to
three group(s) selected from a halogen atom, a hydroxyl group, an amino group
optionally substituted by one or two alkyl group(s), an alkyloxy group and an
25 alkylsulfonyl group) or (e) an alkylthio group, (f) an alkylsulfinyl group, (g) an
alkylsulfonyl group or (h) a group of the formula: $-N(R')(R'')$,

R' and R'' are the same or different and (a) a hydrogen atom, (b) an alkyl group
optionally substituted by one to three group(s) selected from a halogen atom, an amino

group optionally substituted by one or two alkyl group(s) and an alkyloxy group, (c) an acyl group, (d) an alkylsulfonyl group or (e) an amino sulfonyl group optionally substituted by one to two alkyl group(s), or both R' and R'' combine each other at their termini to form together with an adjacent nitrogen atom an optionally substituted, saturated or unsaturated nitrogen-containing heterocyclic group,

E is one of the following groups (i) to (v):



R⁰⁰ is an alkyl group,

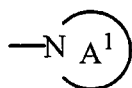
Q¹ is a single bond, an alkylene group or a group of the formula: -N(R⁷)-, R⁷ is a hydrogen atom or an alkyl group,

Q² is a single bond or an alkylene group,

one of R⁵ and R⁶ is a hydrogen atom or an alkyl group and the other is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group, an alkyloxy group, an optionally substituted cycloalkyl group, an amino group optionally substituted by one or two alkyl group(s), an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, an acyl group, an optionally substituted aryl group and optionally substituted saturated or unsaturated heterocyclic group, (b) an optionally substituted cycloalkyl group, (c) a group of the formula: -N(R⁸)(R⁹), (d) an optionally substituted aryl group or (e) an optionally substituted, saturated or unsaturated heterocyclic group, or both of R⁵ and R⁶ combine each other to form together with an adjacent nitrogen atom an optionally substituted, saturated or unsaturated nitrogen-containing heterocyclic group,

one of R⁸ and R⁹ is a hydrogen atom or an alkyl group and the other is (a) an alkyl group optionally substituted by one to three group(s) selected from a halogen atom, a cyano group and an aryl group, (b) a cycloalkyl group, (c) an optionally substituted aryl group or (d) an acyl group or (e) an optionally substituted saturated or unsaturated heterocyclic group,

one of R⁵⁰ and R⁶⁰ is a hydrogen atom or an alkyl group and the other is a hydrogen atom, an alkyl group or an acyl group, or both of them combine together with the adjacent nitrogen atom to form a cyclic group of the following formula:



in which Ring A¹ is a 5- to 7-membered aliphatic nitrogen-containing heterocyclic group optionally substituted by an oxo group,

R⁵¹ is an alkyl group or an optionally substituted arylsulfonyl group, R⁶¹ is an alkylamino group or an azido group,

5 or a pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition according to Claim 22 which is an agent for prevention and/or treatment of a CB1 receptor-mediated diseases.

24. The pharmaceutical composition according to Claim 23 wherein the
10 CB1 receptor-mediated disease is psychosis including schizophrenia, anxiety disorder, stress, depression, epilepsy, neurodegenerative disorders, spinocerebellar disorder, cognitive disorder, craniocerebral trauma, panic attack, peripheral neuropathy, glaucoma, migraine, Parkinson's disease, Alzheimer's disease, Huntington's disease, Raynaud's syndrome, tremor, obsessive-compulsive disorder, amnesia, geriatric dementia, thymic disorder, Tourette's syndrome, tardive dyskinesia, bipolar disorder, cancer, drug-induced
15 dyskinesia, dystonia, septic shock, hemorrhagic shock, hypotension, insomnia, immunological disease including inflammation, multiple sclerosis, emesis, diarrhea, asthma, appetite disorder including bulimarexia and anorexia, obesity, non insulin-dependent diabetes mellitus (NIDDM), memory disorder, urinary disorder, cardiovascular disorder, infertility disorder, infection, demyelination-related disease, neuroinflammation, viral encephalitis, cerebral vascular incident, cirrhosis of the liver
20 or gastrointestinal disorder including intestinal transit disorder.

25. The pharmaceutical composition according to Claim 22 which is an agent for withdrawal from a chronic treatment, alcohol dependence or drug abuse.

26. The pharmaceutical composition according to Claim 22 which is an
25 agent for enhancing analgesic activity of an analgesic or narcotic drug.

27. The pharmaceutical composition according to Claim 22 which is an agent for smoking cessation (withdrawal from smoking or nicotine dependence).

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2006/321441

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/519 C07D487/04 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/106341 A (BASF AG [DE]; WAGNER OLIVER [DE]; GROTE THOMAS [DE]; BLETNER CARSTEN) 9 December 2004 (2004-12-09) compounds with rn: 632342-92-8, 632342-94-0, 805227-82-1, 805227-85-4, 805227-92-3, 805227-93-4, 805227-94-5, 805227-95-6, 805227-96-7, 805227-97-8, 805228-06-2, page 43; claims ----- -/--	1-22

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

7 February 2007

Date of mailing of the international search report

20/02/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Gavriliu, Daniela

INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2006/321441

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/101993 A (NEOGENESIS PHARMACEUTICALS INC [US]) 11 December 2003 (2003-12-11) compounds with rn: 632361-74-1, 632361-66-1, 632361-67-2, 632361-68-3, 632361-69-4, 632361-70-7, 632361-71-8, 632361-72-9, 632361-73-0, 632361-75-2, 632361-76-3, 632361-77-4, 632361-78-5, 632361-79-6, 632361-80-9, 632361-81-0, 632361-82-1, 632361-83-2, 632361-84-3, 632361-85-4, 632361-86-5, 632361-87-6, 632361-97-8, 632361-98-9, 632361-99-0, 632362-00-6, 632362-01-7, 632362-02-8, 632362-09-5, 632362-10-8, 632362-11-9, 632362-12-0, 632362-17-5, 632362-18-6, 632363-01-0, 632363-02-1, 632363-03-2, 632363-04-3, 632363-05-4, 632363-06-5, 632363-07-6, 632363-08-7, 632365-58-3, 632365-55-0, 632365-72-1, 632365-76-5 claims; example 43	1-22
Y	WO 2004/069838 A (PFIZER PROD INC [US]; GRIFFITH DAVID ANDREW [US]) 19 August 2004 (2004-08-19) the whole document	1-27
Y	WO 2005/018645 A (PFIZER PROD INC [US]; COE JOTHAM WADSWORTH [US]; IREDALE PHILIP ANDREW) 3 March 2005 (2005-03-03) compounds with rn: 737827-71-3, 737827-73-5, 737827-74-6, 737827-77-9, 737827-81-5, 737827-84-8, 737828-12-5, 737828-13-6, 737828-23-8, 737828-25-0, 845670-46-4, 845670-47-5, 845670-48-6, 845670-49-7, 845670-50-0, 845670-51-1, 845670-52-2, 845670-53-3, 845670-54-4, 845670-55-5, 845670-56-6, 845670-57-7, 845670-58-8 page 19 - page 26; claims	1-27
P,X	WO 2006/072828 A2 (PFIZER PROD INC [US]; VERHOEST PATRICK ROBERT [US]; HELAL CHRISTOPHER) 13 July 2006 (2006-07-13) see compounds with rn: 898563-07-0	1-27
P,X	WO 2006/016715 A (TEIJIN PHARMA LTD [JP]; KOSUGI TOMOMI [JP]; IMAI MINORU [JP]; MAKINO H) 16 February 2006 (2006-02-16) see compounds with rn: 876391-14-9, 876391-15-0, 876391-16-1	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/JP2006/321441

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004106341	A	09-12-2004	AU 2004242850 A1	09-12-2004
			BR PI0410610 A	04-07-2006
			CA 2527136 A1	09-12-2004
			EP 1633755 A1	15-03-2006
			JP 2006526583 T	24-11-2006
			MX PA05012288 A	30-01-2006
			US 2006258685 A1	16-11-2006
WO 03101993	A	11-12-2003	AU 2003240488 A1	19-12-2003
			CA 2487211 A1	11-12-2003
			CN 1671710 A	21-09-2005
			EP 1511751 A1	09-03-2005
			JP 2005533040 T	04-11-2005
			MX PA04012245 A	30-09-2005
WO 2004069838	A	19-08-2004	BR PI0407305 A	07-02-2006
			CA 2515596 A1	19-08-2004
			EP 1594872 A1	16-11-2005
			JP 2006517220 T	20-07-2006
			MX PA05007938 A	30-09-2005
WO 2005018645	A	03-03-2005	BR PI0413693 A	24-10-2006
			CA 2536280 A1	03-03-2005
			EP 1658082 A1	24-05-2006
			MX PA06002035 A	17-05-2006
WO 2006072828	A2	13-07-2006	NL 1030863 A1	10-07-2006
WO 2006016715	A	16-02-2006	NONE	