

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2003294183 B2**

(54) Title
Pyrrolopyridazine derivatives

(51) International Patent Classification(s)
C07D 487/04 (2006.01) **A61P 31/00** (2006.01)

(21) Application No: **2003294183** (22) Date of Filing: **2003.12.26**

(87) WIPO No: **WO04/063197**

(30) Priority Data

(31) Number	(32) Date	(33) Country
2003900189	2003.01.09	AU
2003903628	2003.07.14	AU

(43) Publication Date: **2004.08.10**

(43) Publication Journal Date: **2004.09.09**

(44) Accepted Journal Date: **2009.06.18**

(71) Applicant(s)
Astellas Pharma Inc.

(72) Inventor(s)
Ohne, Kazuhiko;IMAMURA, Kenichiro;Mizutani, Tsuyoshi;Abe, Yoshito;OKUMURA, Mitsuaki;Sawada, Kozo;SAWADA, Yuki;Inoue, Makoto

(74) Agent / Attorney
Davies Collison Cave, 255 Elizabeth Street, Sydney, NSW, 2000

(56) Related Art
WO 1991/018903 A1
Flitsch, W. and Kramer, U., Tetrahedron Letters, 1968, 12, 1479-1484

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
29 July 2004 (29.07.2004)

PCT

(10) International Publication Number
WO 2004/063197 A1

(51) International Patent Classification⁷: **C07D 487/04**,
A61P 31/00

(21) International Application Number:
PCT/JP2003/017091

(22) International Filing Date:
26 December 2003 (26.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2003900189 9 January 2003 (09.01.2003) AU
2003903628 14 July 2003 (14.07.2003) AU

(71) Applicant (*for all designated States except US*): **FUJISAWA PHARMACEUTICAL CO., LTD.** [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ABE, Yoshito** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **INOUE, Makoto** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **MIZUTANI, Tsuyoshi** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **SAWADA, Kozo** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **OHNE, Kazuhiko** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi,

Osaka 541-8514 (JP). **OKUMURA, Mitsuaki** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **SAWADA, Yuki** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). **IMAMURA, Kenichiro** [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(74) Agent: **TABUSHI, Eiji**; c/o Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

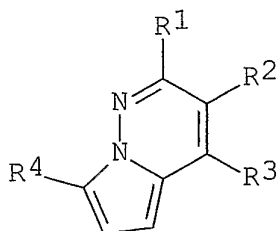
(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF,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

Published:

— with international search report

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: PYRROLOPYRIDAZINE DERIVATIVES



(I)

(57) Abstract: The invention relates to compound of the formula (I) or its salt, in which R¹, R², R³ and R⁴ are as defined in the description, their use as medicament, the process for their preparation and use for the treatment of PDE-IV or TNF- α mediated diseases.



WO 2004/063197 A1

DESCRIPTION

PYRROLOPYRIDAZINE DERIVATIVES

5

TECHNICAL FIELD

This invention relates to new pyrrolopyridazine derivatives and pharmaceutically acceptable salts thereof which inhibit enzymatic activity of phosphodiesterase IV (PDE IV) and production of tumor necrosis factor- α (TNF- α).

10

BACKGROUND ART

Cyclic adenosine monophosphate (adenosine 3', 5'-cyclic monophosphate, "cAMP" or "cyclic AMP") is known as an intracellular second messenger, which is intermediated by a first messenger (hormone, neurotransmitter or autacoid) and the cellular responses. The first messenger stimulates the enzyme responsible for synthesis of cAMP, and then the cAMP intervenes in many functions such as metabolic, contractile or secretory. The effect of cAMP ends when it is degraded by cyclic nucleotide phosphodiesterases, in particular phosphodiesterase-4 (PDE4 or PDE-IV), which is specific for cAMP. PDE-IV has been identified in many tissues including the central nervous systems, the heart, vascular smooth muscle, airway smooth muscle, myeloid lines, lymphoid, and the like. Evaluation of cAMP level by using the PDE-IV inhibitor would produce beneficial effect on inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells.

A major concern with the use of PDE-IV inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C. Burnouf et al., (Ann. Rep. In Med. Chem., 33:91-109(1998)). Burnouf describes the wide variation of the severity of the undesirable side effects exhibited by various compounds.

Some condensed heterocyclic derivatives having the inhibitory activity of PDE-IV have been known, for example in WO03/016279, WO03/018579, WO03/000679 and the like. However, there remains a need for novel compounds that inhibit PDE-IV with minimal side effects. Although some pyrrolopyridazine derivatives having the inhibitory activity of hydroxymethylglutaryl (HMG) CoA reductase have been known, for example, in WO91/18903, pyrrolopyridazine derivatives having the inhibitory activity of PDE-IV have not been known.

DISCLOSURE OF INVENTION

This invention relates to new pyrrolopyridazine derivatives.

The compounds of this invention inhibit cAMP phosphodiesterase enzymes, in particular phosphodiesterase-4 enzyme, and also inhibit the production of tumor necrosis factor- α (TNF- α), a serum glycoprotein.

Accordingly, this invention seeks to provide the new and useful pyrrolopyridazine derivatives and pharmaceutically acceptable salts thereof which possess a strong phosphodiesterase-4 (PDE IV)-inhibitory activity and a strong inhibitory activity on the production of tumor necrosis factor (TNF).

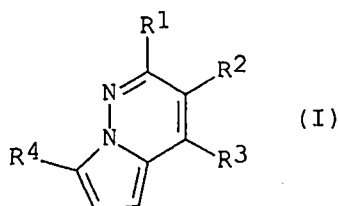
This invention further seeks to provide processes for preparation of the pyrrolopyridazine derivatives and salts thereof.

This invention also seeks to provide a pharmaceutical composition comprising said pyrrolopyridazine derivatives or a pharmaceutically acceptable salt thereof.

This invention still further seeks to provide a use of said pyrrolopyridazine derivatives or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of PDE-IV and TNF mediated diseases such as chronic inflammatory diseases, specific autoimmune diseases, sepsis-induced organ injury, and the like in human being and animals.

The invention subject of this application is set out in the claims that follow. These and other aspects and embodiments are described below.

Pyrrolopyridazine derivatives can be represented by the following general formula (I):



in which

- R¹ is (1) carboxy or protected carboxy,
 (2) -CONR⁵R⁶,
 (3) hydroxy or lower alkoxy,

- (4) amino, cyclo(lower)alkylamino or mono- or di(lower)alkylamino optionally substituted by lower alkoxy,
- (5) trihalo(lower)alkyl,
- (6) trihalo(lower)alkylsulfonyloxy or arylsulfonylamino,
- 5 (7) substituted or unsubstituted lower alkyl,
- (8) substituted or unsubstituted aryl, or
- (9) substituted or unsubstituted heterocyclic group,
- R^2 is R^7 or $-(A^1)_p-X-A^2-R^7$,
- wherein
- 10 p is integer of 0 or 1;
- A^1 is (C_1-C_2) alkylene or $-CH=CH-$;
- A^2 is $-(CH_2)_n-$ or $-(CH=CH)_m-$ [wherein n is integer which may range from 1 to 6 and m is integer which may range from 1 to 3];
- X is single bond, $-O-$, $-NR^8-$, $-C(=O)-$, $-C(=NR^9)-$ or hydroxy (C_1-C_2) alkylene
- 15 [wherein R^8 is hydrogen or lower alkyl, and R^9 is substituted or unsubstituted N-containing heterocyclic group]; and
- R^7 is
- (1) hydrogen,
- (2) substituted or unsubstituted aryl,
- 20 (3) substituted or unsubstituted heterocyclic group,
- (4) carboxy, protected carboxy or $CONR^{10}R^{11}$,
- (5) acyl or halocarbonyl,
- (6) cyano,
- (7) amino, protected amino, or mono- or di(lower)alkylamino,
- 25 (8) hydroxy, aryloxy, acyloxy or lower alkoxy optionally substituted by hydroxy or acyloxy,
- (9) lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl, or
- (10) $-O-R^{12}$,
- or
- 30 R^1 and R^2 are combined together to form lower alkylene or lower alkenylene group, which is optionally interrupted by amino or sulfonyl and optionally fuse with benzene ring, and also is optionally substituted by the group consisting of lower alkyl, hydroxy, oxo and lower alkoxy,

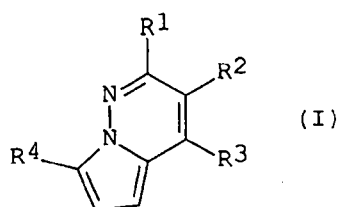
2003294183 21 May 2009

R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heterocyclic group,
 R^4 is hydrogen, halogen, cyano, carbamoyl, acyl, thiocyanate, lower alkylthio, lower alkenyl, hydroxyl(lower)alkyl, trihalo(lower)alkyl or lower alkyl,
 R^5 , R^6 , R^{10} and R^{11} each independently represents hydrogen, lower alkylsulfonyl, heterocyclic group or lower alkyl optionally substituted by hydroxy, alkoxy, sulfo, carboxy, protected carboxy or $-R^{17}$,
 or alternatively R^5 and R^6 or R^{10} and R^{11} , together with the nitrogen atom to which they are attached, represent N-containing heterocyclic group, and
 R^{12} and R^{17} are each independently a group derived from protected or unprotected sugar by removal of the hydroxy group therefrom,
 or a pharmaceutically acceptable salt thereof, or prodrug thereof.

Suitable pharmaceutically acceptable salts of compound (I) are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

The "prodrug" means the derivatives of compound (I) having a chemically or metabolically degradable group, which became pharmaceutically active after chemo- or biotransformation.

Preferred embodiments of compound (I) are as follows.



in which

- R¹ is (1) carboxy or esterified carboxy (more preferably, ethoxycarbonyl),
 (2) -CONR⁵R⁶ [wherein R⁵ and R⁶ each independently represents lower alkyl, or alternatively R⁵ and R⁶, together with nitrogen atom to which they are attached represents saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s).] (more preferably, dimethylcarbamoyl or 1-pyrrolidinylcarbonyl),
 (3) hydroxy or lower alkoxy,
 (4) amino, cyclo(lower)alkylamino, or mono- or di(lower)alkylamino optionally substituted by lower alkoxy,
 (5) trihalo(lower)alkyl,
 (6) trihalo(lower)alkylsulfonyloxy or arylsulfonylamino,
 (7) lower alkyl optionally substituted by (i) halogen; (ii) carboxy; (iii) protected carboxy; (iv) cyano; (v) carbamoyl; (vi) -OCONR¹⁵R¹⁶ [wherein R¹⁵ and R¹⁶ each independently represents hydrogen, aryl or lower alkyl optionally substituted by aryl, or R¹⁵ and R¹⁶, together with the nitrogen atom to which they are attached, represents saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and also optionally containing oxygen atom.] (more preferably, dimethylcarbamoyloxy, methyl-phenylcarbamoyloxy, morpholinylcarbonyloxy or pyrrolidinylcarbonyloxy); (vii) lower alkylthio; (viii) lower alkylsulfonyl; (ix) lower alkylsulfonyloxy; (x) lower alkylsulfonylamino; (xi) mono- or di(lower)alkylamino optionally substituted by hydroxy, lower alkoxy, aryloxy, or substituted or unsubstituted aryl; (xii) amino; (xiii) acylamino (more preferably, lower alkanoylamino such as acetylamino, aroylamino such as benzoylamino, or heterocycliccarbonylamino such as pyrazinylcarbonylamino); (xiv) protected amino such as phthalimide, benzylamino or lower alkoxycarbonylamino; (xv) hydroxy; (xvi) acyloxy (more preferably, lower alkanoyloxy such as acetyloxy); (xvii) cyclo(lower)alkyloxy; (xviii) aryloxy; (xix) substituted or unsubstituted aryl (more preferably, phenyl); (xx) saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to

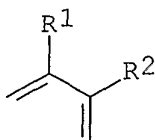
- 3 nitrogen atom(s) and also optionally containing oxygen atom or sulfur atom (more preferably, piperazinyl, morpholinyl, oxazolidinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl or triazolyl) optionally substituted by lower alkyl, hydroxy(lower)alkyl, aryl or oxo; or (xxi) lower alkoxy optionally substituted by carboxy, protected carboxy, hydroxy, protected hydroxy, lower alkoxy, cyclo(lower)alkyl, substituted or unsubstituted aryl (more preferably, phenyl optionally substituted by cyano, carboxy, protected carboxy or carbamoyl), saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) (more preferably, pyridinyl, pyrazinyl or piperazinyl) optionally substituted by lower alkyl, or -CONR¹³R¹⁴ [wherein R¹³ and R¹⁴ each independently represents hydrogen or lower alkyl optionally substituted by aryl, or R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, represents saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and also optionally containing oxygen atom.] (more preferably, carbamoyl, methylcarbamoyl, benzylcarbamoyl or morpholinylcarbonyl),
- (8) aryl (more preferably, phenyl) optionally substituted by the substituent(s) selected from the group consisting of halogen, or
- (9) saturated or unsaturated 5- or 6-membered heteromonocyclic group (more preferably, pyrrolidinyl, pyrrolyl, oxazolyl, isooxazolyl, thiazolyl, furanyl, thienyl, pyridinyl) optionally substituted by lower alkyl or halogen,
- 25 R² is R⁷ or -(A¹)_p-X-A²-R⁷
 wherein
 p is 0 or 1,
 A¹ is (C₁-C₂)alkylene or -CH=CH-;
 A² is -(CH₂)_n- or -(CH=CH)_m- [wherein n is integer which may range from 1 to 6 and m is integer which may range from 1 to 3];
 X is single bond, -O-, -NR⁸-, -C(=O)-, -C(=NR⁹)- or hydroxy(C₁-C₂)alkylene; [wherein R⁸ is hydrogen or lower alkyl, and R⁹ is substituted or unsubstituted pyrrolyl such as 2-ethyl-5-(4-fluorobenzoyl)pyrrolyl]

R⁷ is

- (1) hydrogen,
- (2) aryl (more preferably, phenyl) optionally substituted by lower alkoxy,
- (3) unsaturated heteromonocyclic group containing 1 to 2 nitrogen atom(s),
(more preferably, pyridinyl),
- (4) carboxy, esterified carboxy (more preferably, lower alkoxycarbonyl) or -
CONR¹⁰R¹¹ [wherein R¹⁰ and R¹¹ each independently represents hydrogen,
lower alkylsulfonyl, unsaturated heteromonocyclic group containing 1 to 2
nitrogen atom(s) such as pyridinyl or lower alkyl optionally substituted by
hydroxy, alkoxy, carboxy, protected carboxy, sulfo or -R¹⁷, or alternatively
R¹⁰ and R¹¹, together with the nitrogen atom to which they are attached,
represents saturated 5- or 6-membered heteromonocyclic group containing 1
to 2 nitrogen atom(s) and also optionally containing oxygen atom such as
morpholinyl.],
- (5) acyl (e.g. lower alkanoyl such as formyl or acetyl, and heterocycliccarbonyl
such as pyridinylcarbonyl) or halocarbonyl,
- (6) cyano,
- (7) amino, protected amino such as lower alkoxycarbonylamino, or mono- or
di(lower)alkylamino,
- (8) hydroxy, aryloxy, acyloxy or lower alkoxy optionally substituted by hydroxy
or acyloxy (e.g. lower alkanoyloxy),
- (9) lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl, or
- (10) -O-R¹²,

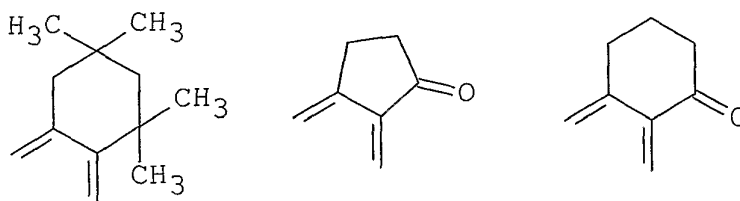
or

- R¹ and R² are combined together to form lower alkylene or lower alkenylene group which
is optionally interrupted by amino or sulfonyl and also is optionally substituted by
the group consisting of lower alkyl, hydroxy, oxo and lower alkoxy,
which is represented by the following formula:

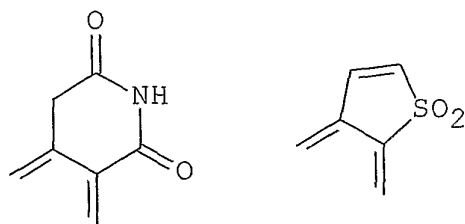


that may include the following ones;

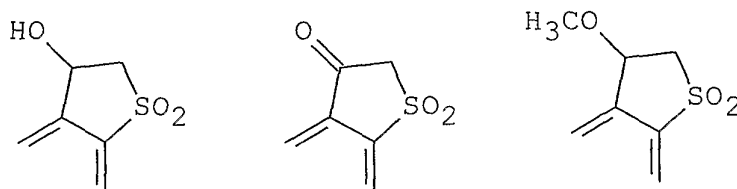
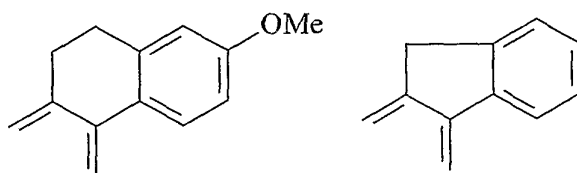
5



10



15



- 25 R^3 is (1) aryl (more preferably, phenyl or naphthyl) optionally substituted by at least one substituent(s) selected from the group consisting of (i) halogen, (ii) carboxy, (iii) protected carboxy, (iv) cyano, (v) $-CONR^{15}R^{16}$ [wherein R^{15} and R^{16} each independently represents hydrogen, lower alkyl optionally substituted by hydroxy], (vi) lower alkyl, (vii) cyclo(lower)alkyl, (viii) hydroxy(lower)alkyl,
- 30 (ix) lower alkoxy, (x) trihalo(lower)alkyl, (xi) unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 2 nitrogen atom(s) such as oxazolyl, (xii) lower alkylsulfonyl, (xiii) nitro, (xiv) sulfamoyl, and (xv) protected sulfamoyl; or
- (2) heterocyclic group selected from the group consisting of pyridinyl, pyrazinyl,
- 35 oxazolyl, isooxazolyl, furanyl, thienyl, quinolyl, benzofuranyl and benzothienyl, wherein said heterocyclic group is optionally substituted by at least one substituent(s) selected from the group consisting of (i) lower alkyl, (ii)

cyclo(lower)alkyl, (iii) lower alkoxy, (iv) acyl such as lower alkanoyl, (v) amino, (vi) mono- or di(lower)alkylamino, (vii) protected amino such as lower alkoxycarbonylamino, (viii) cyano, (ix) carboxy, (x) protected carboxy such as ethoxycarbonyl or methoxycarbonyl, (xi) $-\text{CONR}^{15}\text{R}^{16}$ [wherein R^{15} and R^{16} each independently represents hydrogen, lower alkyl optionally substituted by hydroxy], (xii) lower alkenyl optionally substituted by lower alkoxy, (xiii) halogen, (xiv) lower alkylthio and (xv) hydroxy;

R^4 is hydrogen, halogen, cyano, carbamoyl, lower alkanoyl, thiocyanate, lower alkylthio, lower alkenyl, hydroxyl(lower)alkyl, trihalo(lower)alkyl or lower alkyl, and

R^{12} and R^{17} are each independently a group derived from protected or unprotected sugar such as galactose by removal of the hydroxy group therefrom, or a pharmaceutically acceptable salt thereof.

More preferred compounds of formula (I) are those in which:

R^1 is (1) mono- or di(lower)alkylamino, (2) aryl such as phenyl, (3) saturated or unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 2 hetero atom(s) selected from nitrogen, oxygen or sulfur atom(s) (more preferably, pyrrolidinyl, pyrrolyl, oxazolyl, isooxazolyl, thiazolyl, furanyl, thienyl, pyridinyl, etc), or (4) lower alkyl optionally substituted by lower alkoxy or saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and also optionally containing oxygen atom (more preferably, piperazinyl or morpholinyl), wherein lower alkoxy is optionally substituted by cyclo(lower)alkyl or unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) (more preferably, pyridinyl),

R^2 is R^7 or $-\text{A}^2-\text{R}^7$, wherein

A^2 is $-(\text{CH}_2)_n-$ or $-(\text{CH}=\text{CH})_m-$ [wherein n is integer which may range 2 to 6 and m is integer of 1 or 2, and

R^7 is hydrogen, lower alkylsulfonyl, carboxy, protected carboxy or unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) (more preferably, pyridinyl),

R^3 is (1) aryl optionally substituted by lower alkyl, cyclo(lower)alkyl, halogen, cyano or

carbamoyl; or

- (2) unsaturated condensed heterocyclic group containing 1 to 2 nitrogen atom(s) (more preferably, quinolinyl); or unsaturated 5 to 6 membered heteromonocyclic group containing at least one nitrogen atom(s) (more preferably, 3-pyridinyl and 4-pyridinyl) substituted by lower alkyl, cyclo(lower)alkyl or halogen, and R⁴ is lower alkyl.

Most preferred compounds of formula (I) are those in which:

- R¹ is phenyl, saturated or unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 2 hetero atom(s) selected from nitrogen, oxygen or sulfur atom(s) (more preferably, pyrrolyl, isooxazolyl, furanyl, thienyl, etc.) or lower alkyl optionally substituted by lower alkoxy or saturated or saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and also optionally containing oxygen atom (more preferably, piperazinyl or morpholinyl), wherein lower alkoxy is optionally substituted by cyclo(lower)alkyl or unsaturated 5 to 6 membered heteromonocyclic group containing at least one nitrogen atom(s) (more preferably, pyridinyl),
- R² is -(CH₂)_n-R⁷, wherein n is integer which may range 2 to 5, and R⁷ is carboxy or protected carboxy,
- R³ is (1) phenyl optionally substituted by lower alkyl, cyclo(lower)alkyl, lower alkoxy, halogen, cyano or carbamoyl; or (2) unsaturated 5 to 6 membered heteromonocyclic group containing at least one nitrogen atom(s) (more preferably, 3-pyridinyl and 4-pyridinyl) substituted by lower alkyl, cyclo(lower)alkyl, lower alkoxy, carbamoyl or halogen, and
- R⁴ is lower alkyl.

Preferred concrete compound of formula (I) is:

- (1) 3-[7-Ethyl-2-methyl-3-(4-pyridinyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
- (2) 3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
- (3) 4-[7-Ethyl-2-methyl-3-(methylsulfonyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
- (4) 3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzamide,
- (5) Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate,
- (6) 2-{[4-(3-Chlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methyl}-1,3-

- propanediol,
- (7) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (8) 5-[7-Ethyl-2-methyl-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (9) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic
5 acid,
- (10) 5-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (11) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- 10 (12) 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (13) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (14) Ethyl (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-
15 2-propenoate,
- (15) 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid
- (16) 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- 20 (17) 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- (18) 5-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (19) 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid.
25
- (20) 4-{4-(5-chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid,
- (21) 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- 30 (22) 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- (23) 5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid, or

(24) 5-{4-(3-cyanophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid,
or a pharmaceutically acceptable salt thereof.

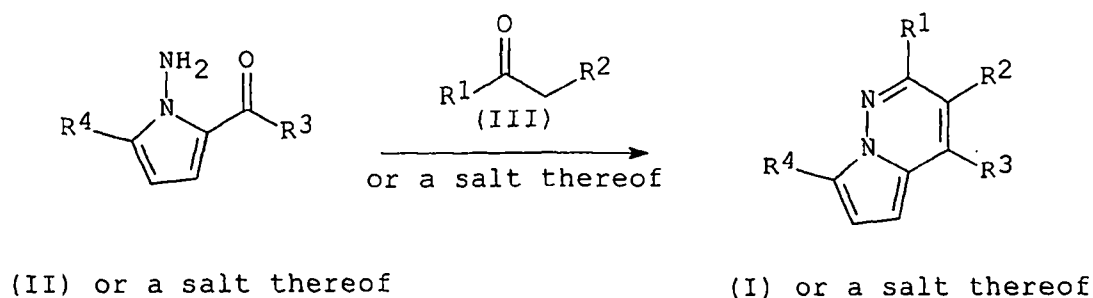
5 More preferred concrete compound of formula (I) is:

- (1) Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate,
 - (2) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
 - (3) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
 - 10 (4) 5-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
 - (5) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
 - (6) 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
 - 15 (7) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
 - (8) 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid
 - 20 (9) 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
 - (10) 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
 - (11) 5-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid, and
 - 25 (12) 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid,
 - (13) 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid, or
 - 30 (14) 5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- or a pharmaceutically acceptable salt thereof.

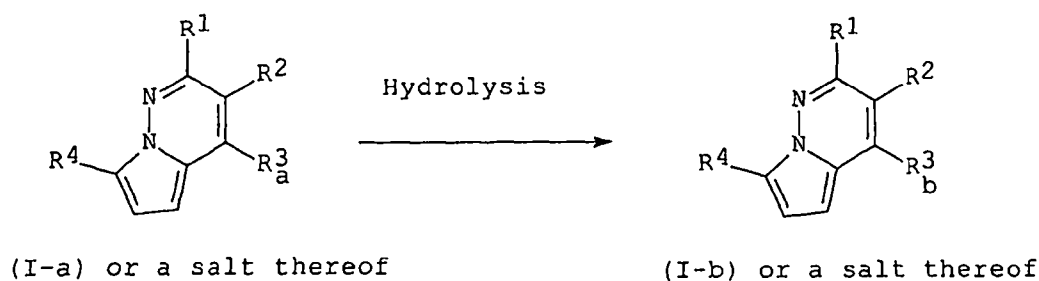
2003294183 21 May 2009

Compound (I) of the present invention can be prepared by the following processes

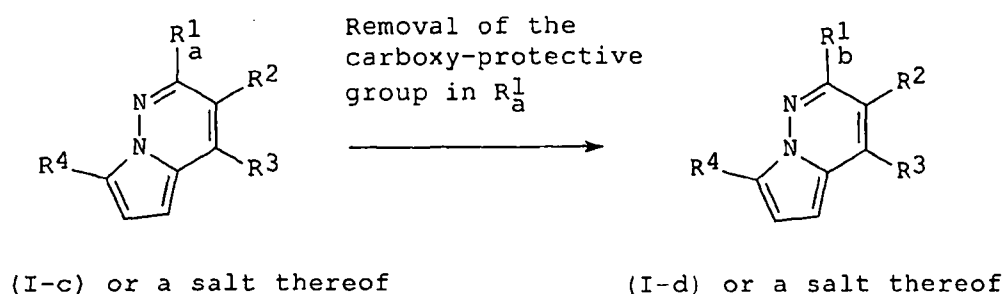
Process 1



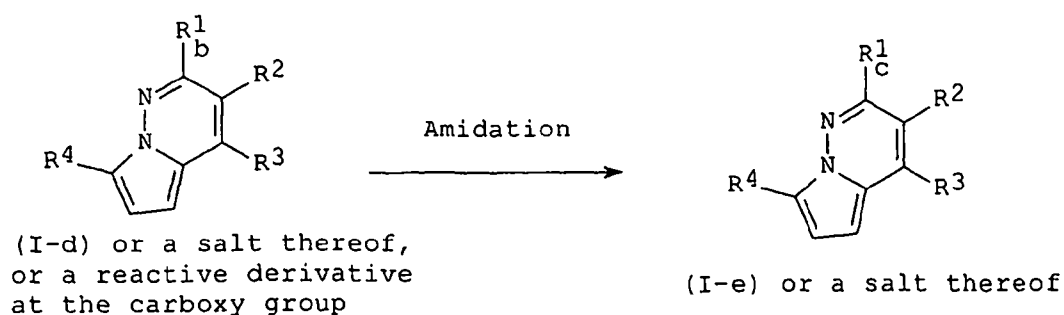
Process 2

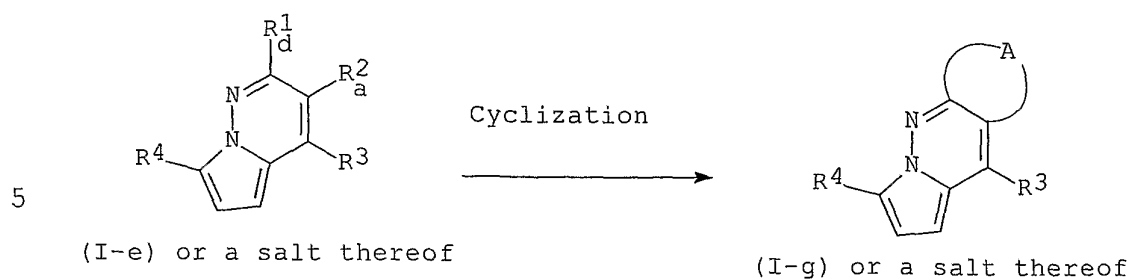
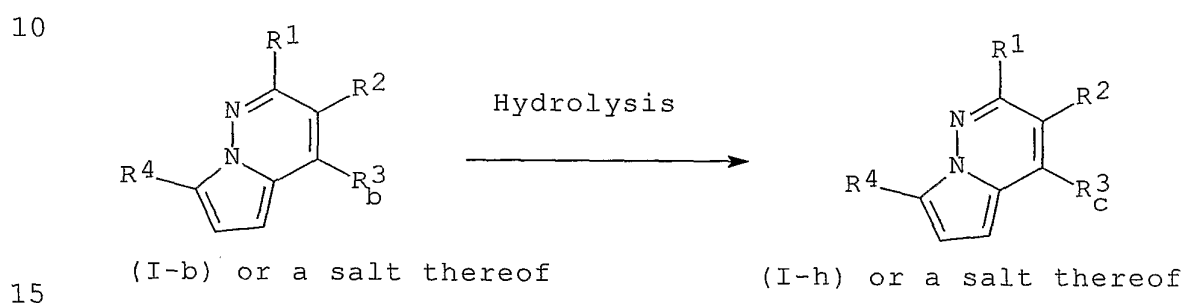
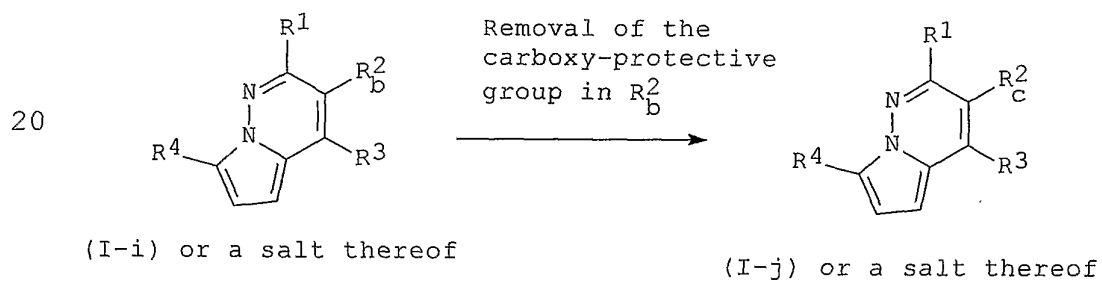
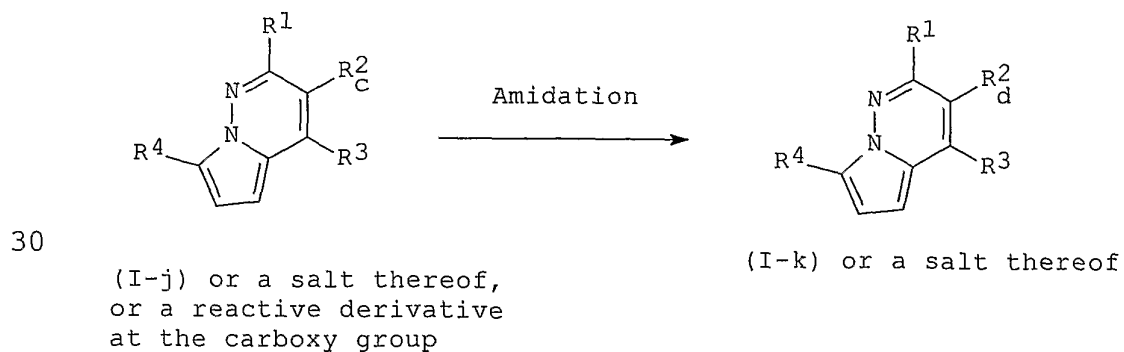


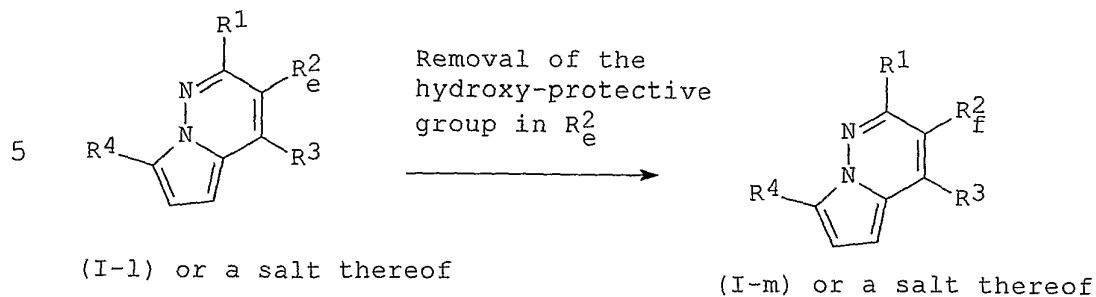
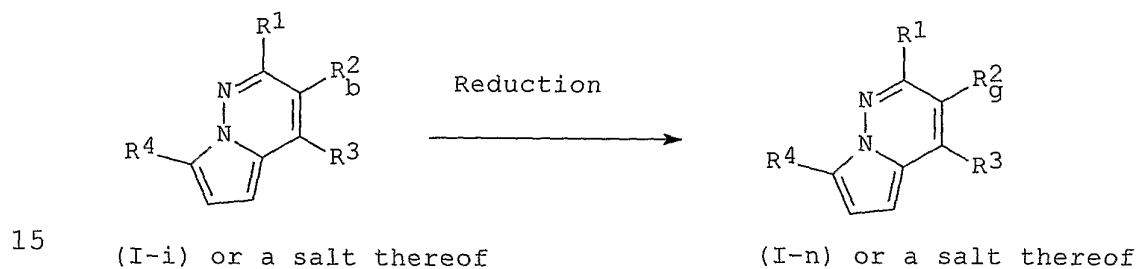
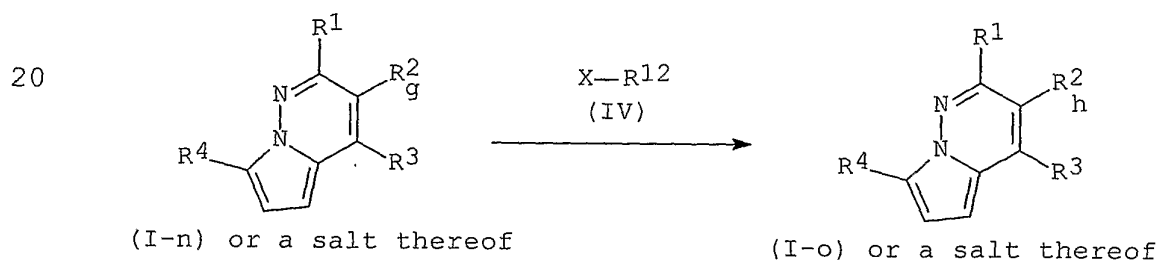
Process 3



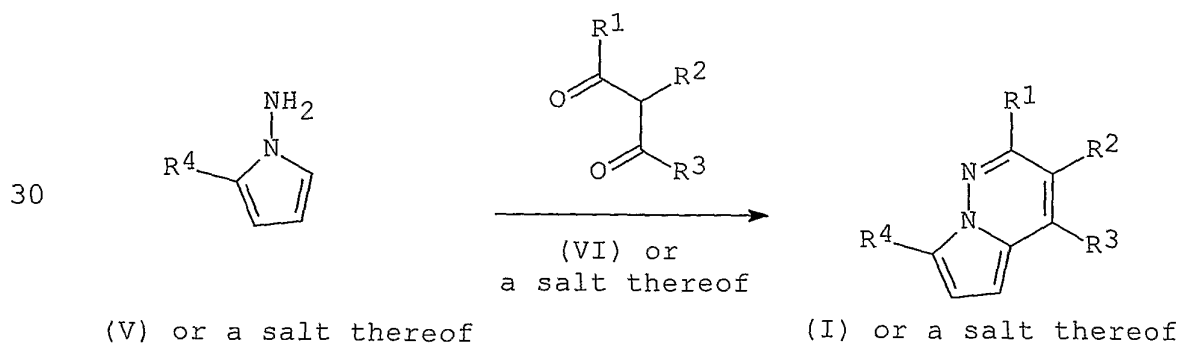
Process 4

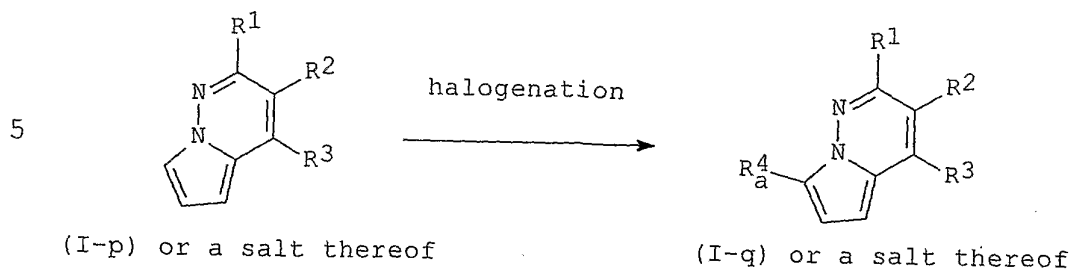
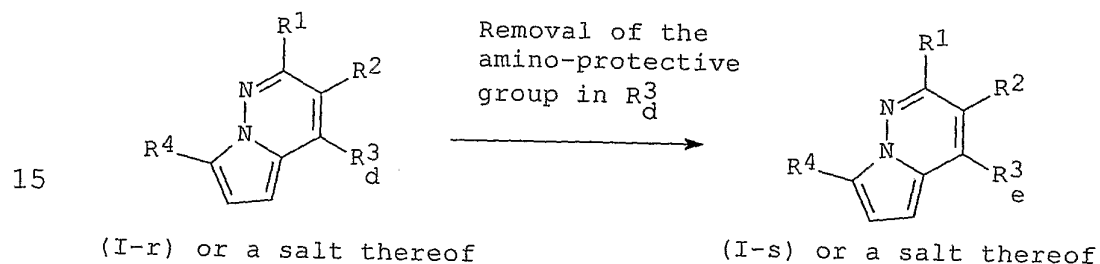
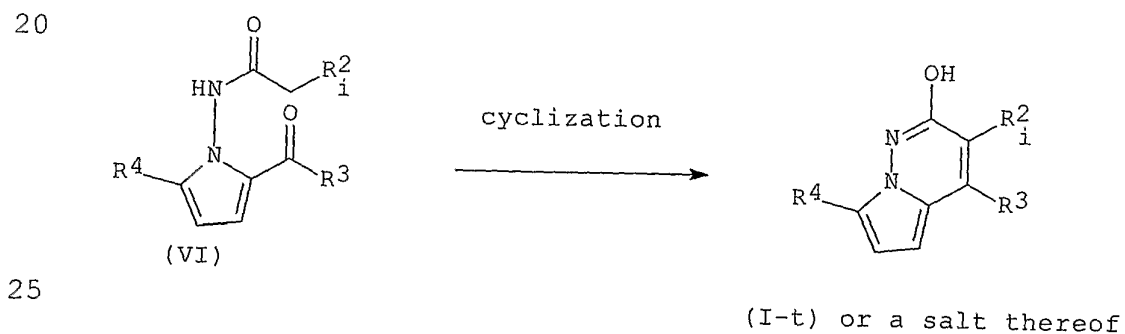
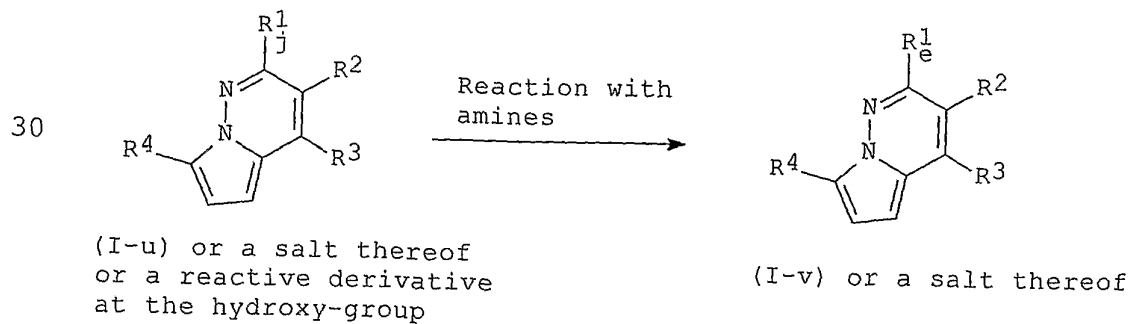


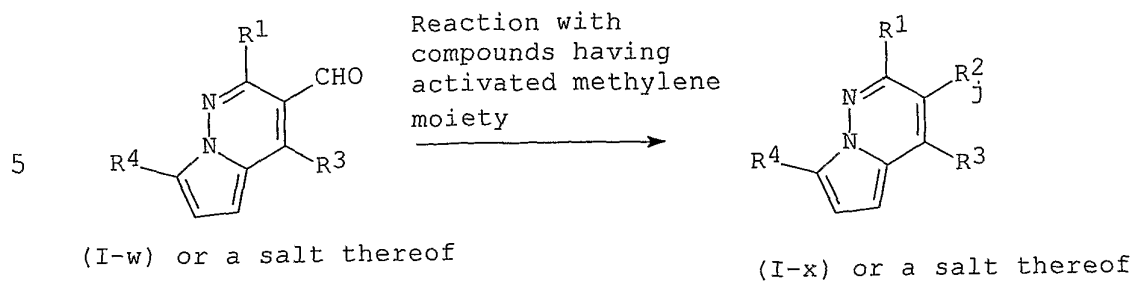
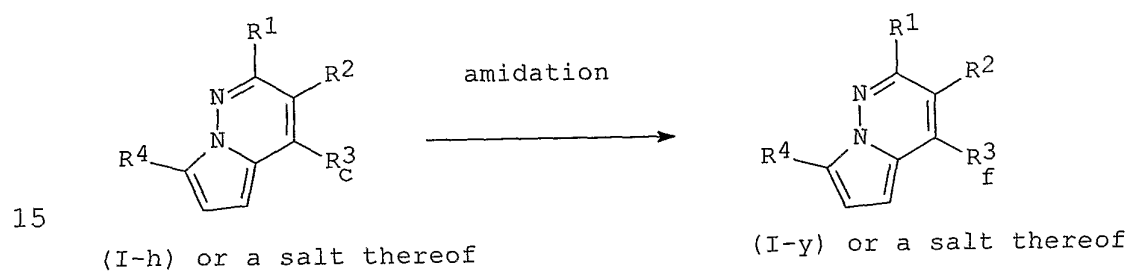
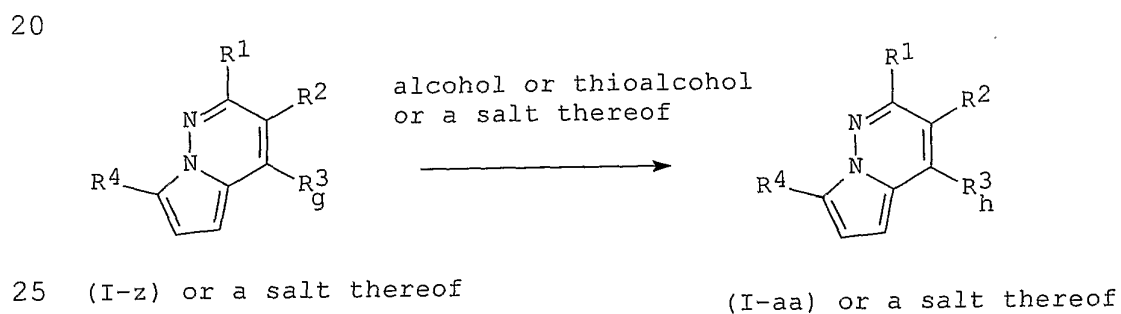
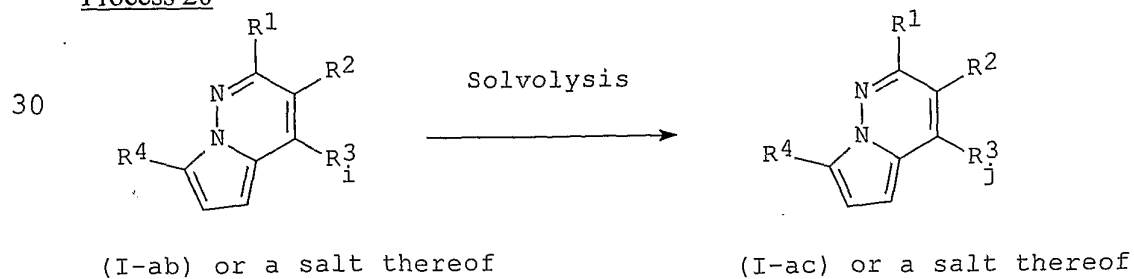
Process 5Process 6Process 7Process 8

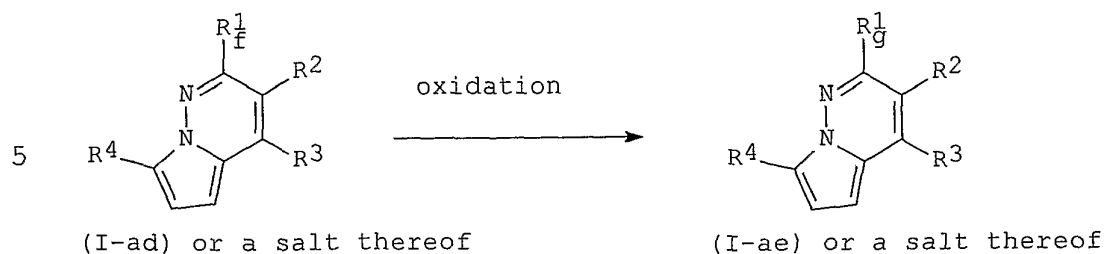
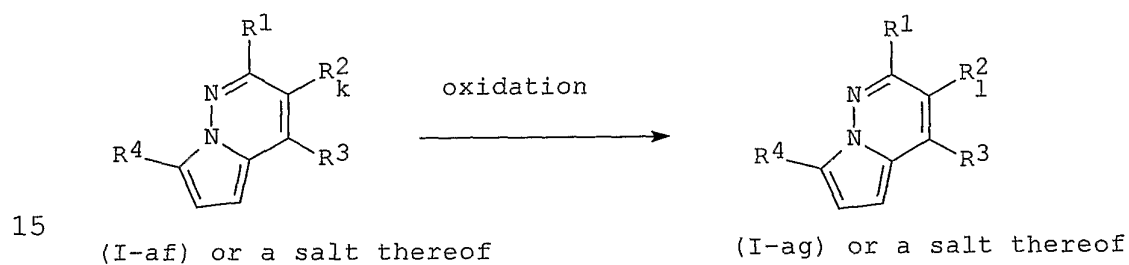
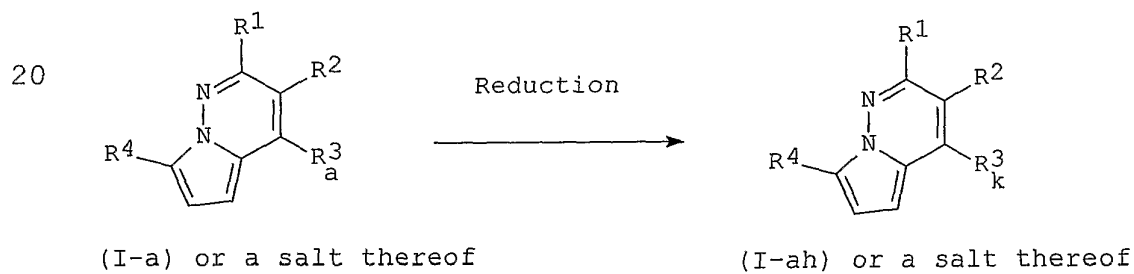
Process 910 Process 10Process 11

25

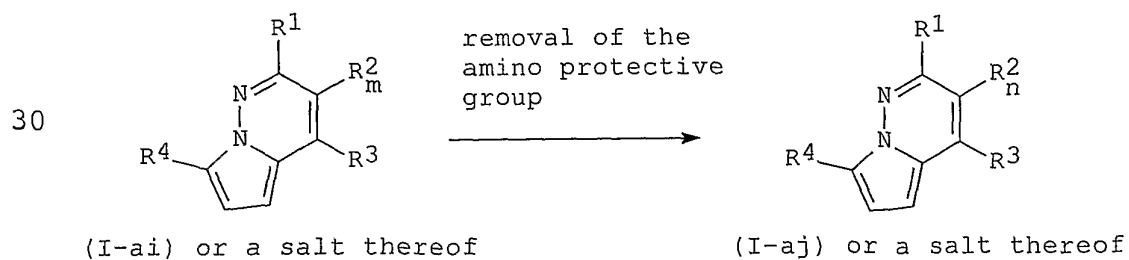
Process 12

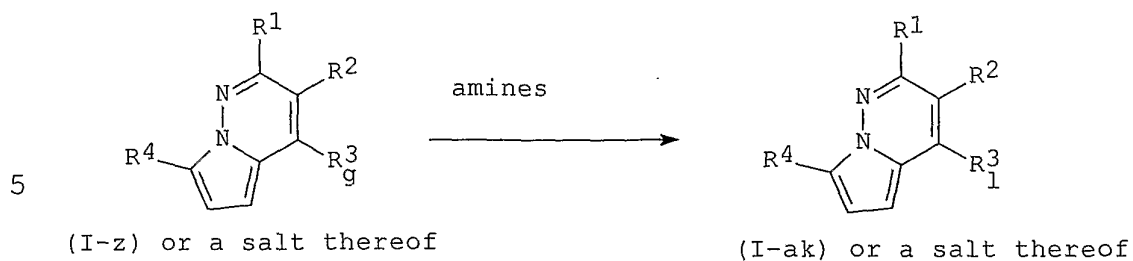
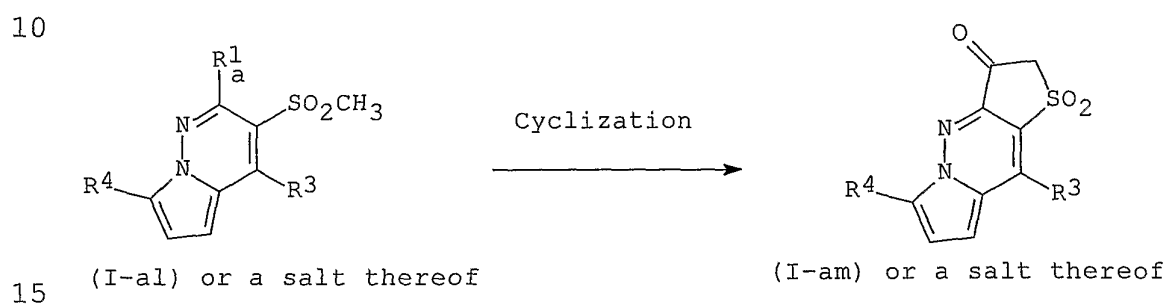
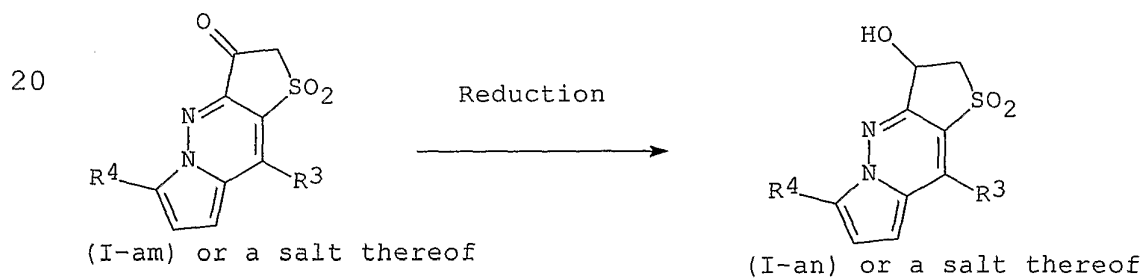
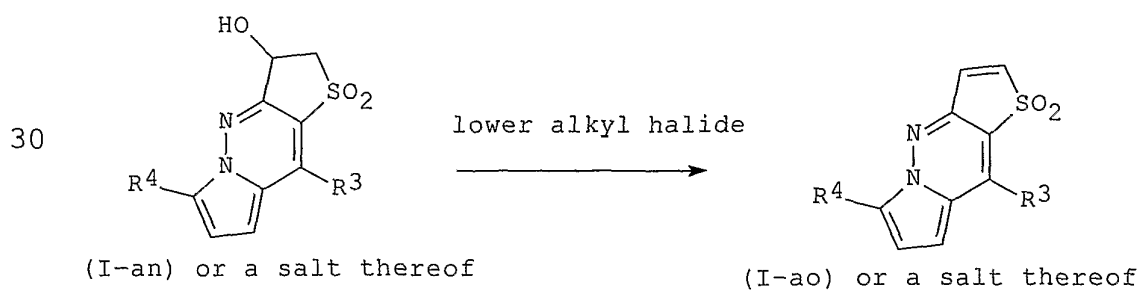
Process 1310 Process 14Process 15Process 16

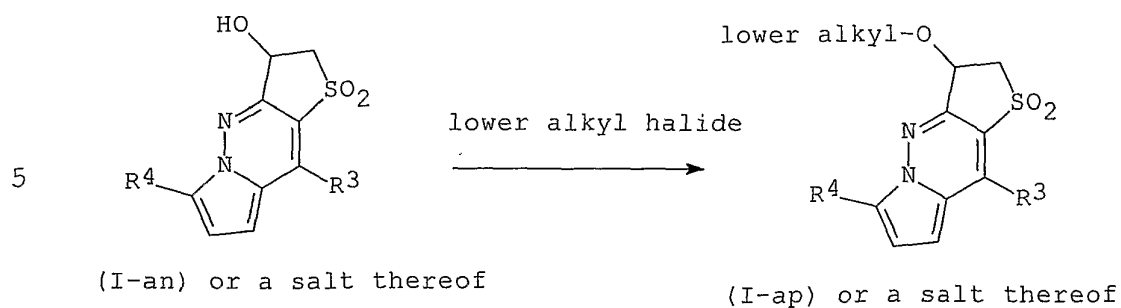
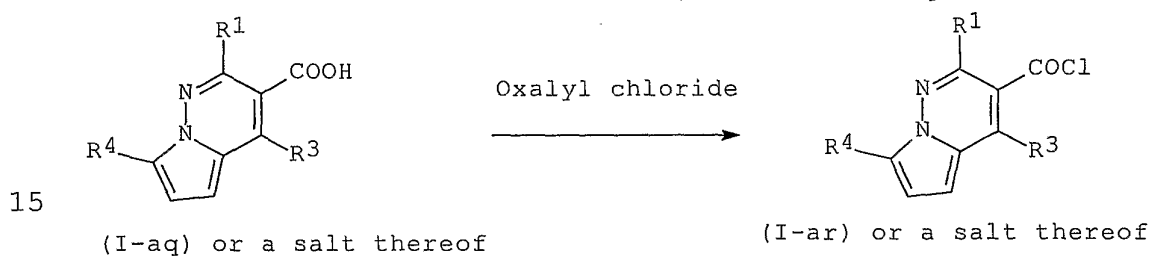
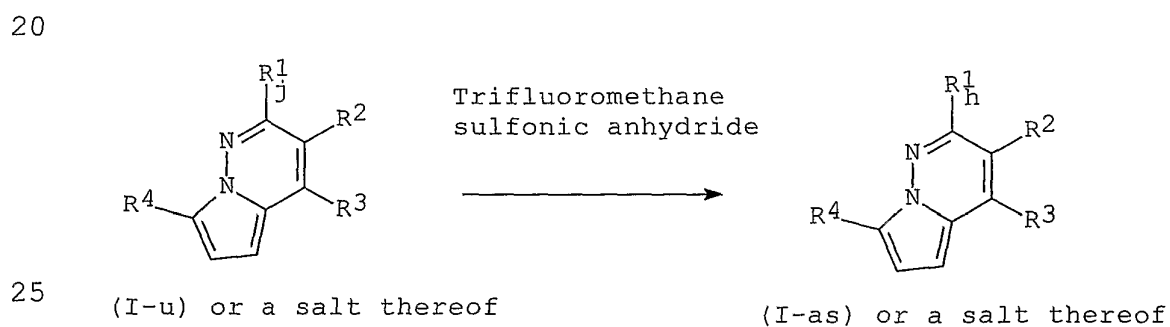
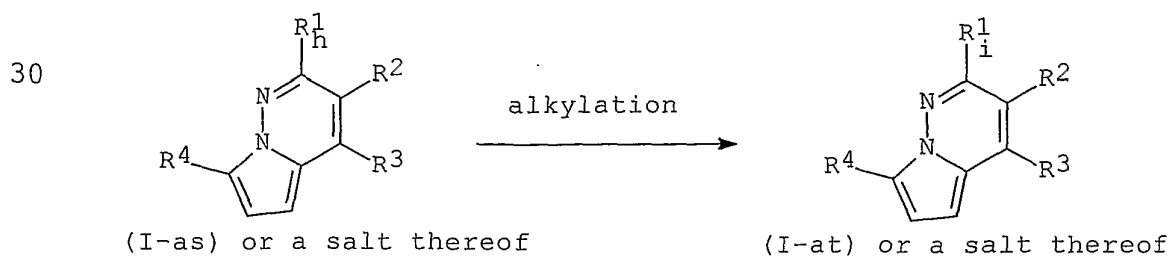
Process 1710 Process 18Process 19Process 20

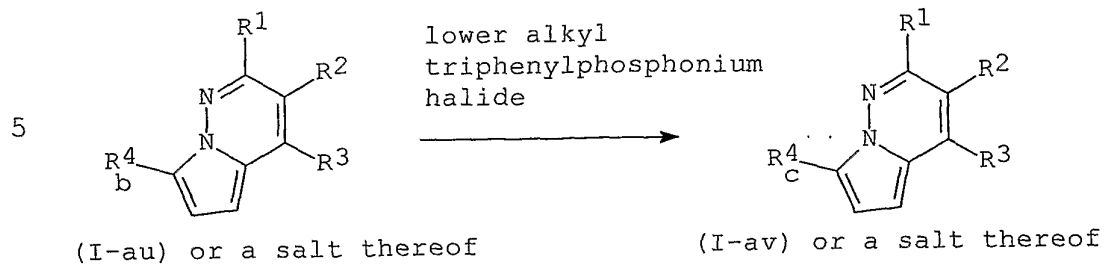
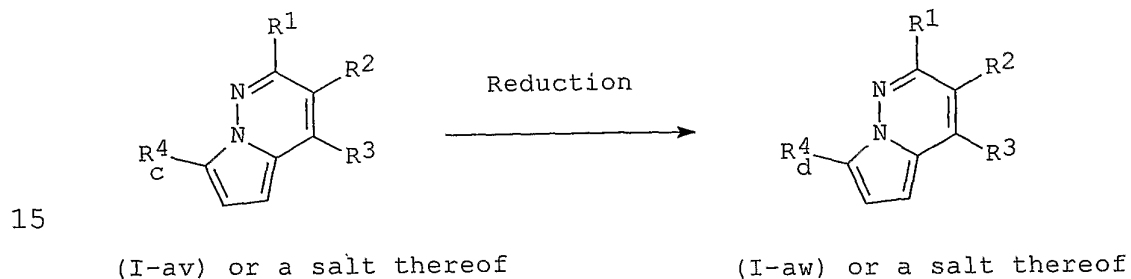
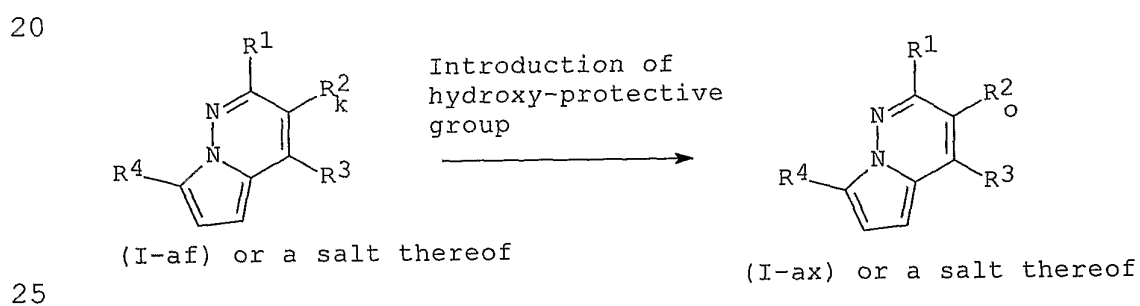
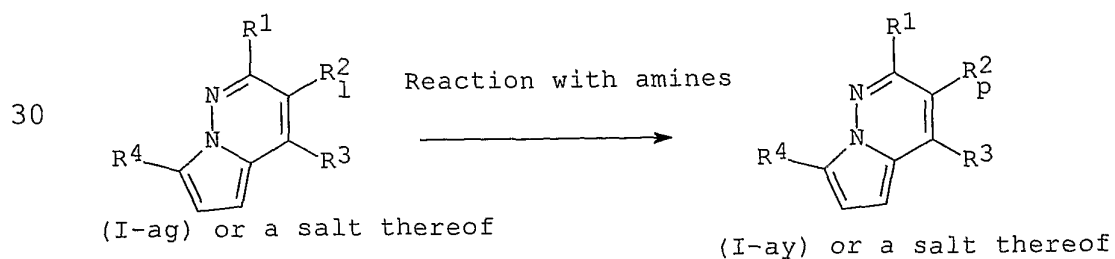
Process 2110 Process 22Process 23

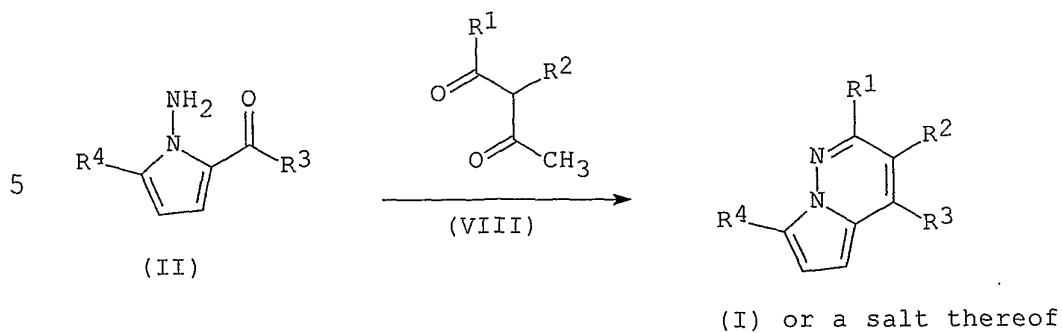
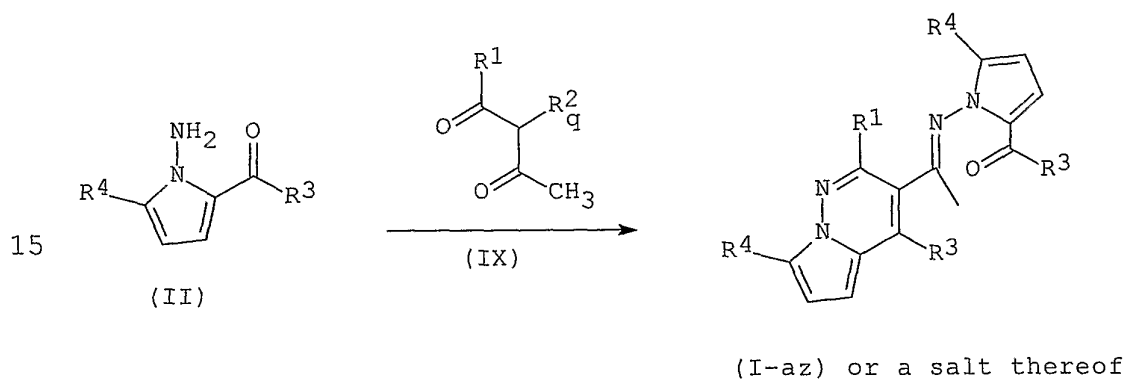
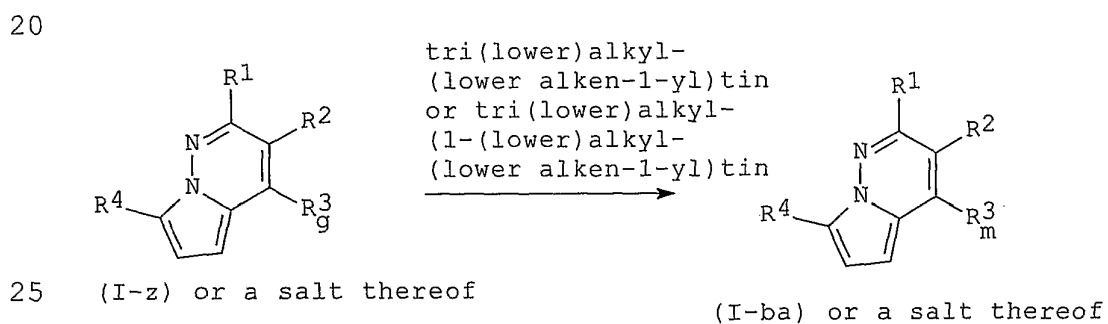
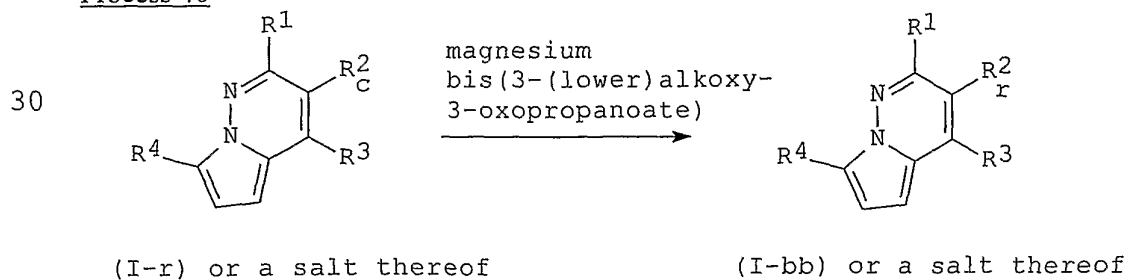
25

Process 24

Process 25Process 26Process 27Process 28

Process 2910 Process 30Process 31Process 32

Process 3310 Process 34Process 35Process 36

Process 3710 Process 38Process 39Process 40

wherein R^1 , R^2 , R^3 and R^4 are each as defined above,

R^1_a is the same as above R^1 having protected carboxy moiety,

R^1_b is the same as above R^1 having carboxy moiety,

R^1_c is $-\text{CONR}^5\text{R}^6$,

5 R^1_d is carbamoyl(lower)alkyl,

R^1_e is amino, mono- or di(lower)alkylamino-, lower alkoxy(lower)alkylamino,
nitrogen-containing heterocyclic group, amino(lower)alkyl, mono- or
di(lower)alkylamino(lower)alkyl, lower
alkoxy(lower)alkylamino(lower)alkyl, nitrogen-containing
10 heterocyclic(lower)alkyl,

R^1_f is lower alkylthio(lower)alkyl,

R^1_g is lower alkylsulfonyl(lower)alkyl,

R^1_h is trifluoromethanesulfonyloxy or trifluoromethanesulfonyloxy(lower)alkyl,

R^1_i is lower alkoxy or lower alkoxy(lower)alkyl,

15 R^1_j is hydroxy or hydroxy(lower)alkyl,

R^2_a is lower alkoxycarbonyl,

R^2_b is the same as above R^2 having protected carboxy moiety,

R^2_c is the same as above R^2 having carboxy moiety,

R^2_d is the same as above R^2 having carbamoyl moiety,

20 R^2_e is the same as above R^2 having protected hydroxy moiety,

R^2_f is the same as above R^2 having hydroxy moiety,

R^2_g is the same as above R^2 having hydroxymethyl moiety,

R^2_h is $-\text{OR}^{12}$,

R^2_i is lower alkoxycarbonyl or lower alkylsulfonyl,

25 R^2_j is substituted or unsubstituted lower alkenyl as mentioned in the above R^2 ,

wherein said lower alkenyl is lower 1-alken-1-yl,

R^2_k is the same as above R^2 having hydroxy(lower)alkyl moiety,

R^2_l is the same as above R^2 having oxo(lower)alkyl moiety,


R^2_m is the same as above R^2 having protected amino moiety,

30 R^2_n is the same as above R^2 having amino moiety,

R^2_o is the same as above R^2 having protected hydroxy moiety,

R^2_p is the same as above R^2 having hydroxy(lower)alkylamino(lower)alkyl moiety,

R^2_q is the same as above R^2 having lower alkoxycarbonyl(lower)alkyl moiety,

- R^2_f is the same as above R^2 having lower alkoxycarbonylmethylcarbonyl moiety,
 R^3_a is the same as above R^3 having cyano moiety,
 R^3_b is the same as above R^3 having carbamoyl moiety,
 R^3_c is the same as above R^3 having carboxy moiety,
5 R^3_d is the same as above R^3 having protected sulfamoyl moiety,
 R^3_e is the same as above R^3 having sulfamoyl moiety,
 R^3_f is the same as above R^3 having $-\text{CONR}^{10}\text{R}^{11}$ moiety,
 R^3_g is the same as above R^3 having haloheterocyclic moiety,
 R^3_h is the same as above R^3 having alkoxyheterocyclic, thioalkoxyheterocyclic or
10 hydroxy moiety,
 R^3_i is the same as above R^3 having 1-(lower)alkoxy(lower)alken-1-ylheterocyclic moiety,
 R^3_j is the same as above R^3 having lower alkanoylheterocyclic moiety,
 R^3_k is the same as above R^3 having aminomethylheterocyclic moiety,
15 R^3_l is the same as above R^3 having mono- or di(lower)alkylaminoheterocyclic moiety,
 R^3_m is the same as above R^3 having (lower)alken-1-ylheterocyclic group or 1-(lower)alkoxy-1-(lower)alken-1-yl-heterocyclic moiety,
 R^4_a is halogen,
20 R^4_b is formyl,
 R^4_c is lower 1-alken-1-yl,
 R^4_d is lower alkyl,
 R^{12} is lower alkyl or a group derived from protected or unprotected sugar by removal of the hydroxy group therefrom,
25 X is a leaving group, and
a group of the formula:  is lower alkylene interrupted by imino moiety and substituted by oxo groups.

The starting compound (II) of the present invention can be prepared according to
 30 a conventional manner or in a similar manner as described in the following Preparations and/or Examples.

Another point to be noted is that the pyrrolopyridazine moiety of the compound

2003294183 21 May 2009

(I) can also exist in the tautomeric form, and such tautomeric equilibrium can be represented, for example, by the following formula.



wherein R^1 , R^2 , R^3 and R^4 are each as defined above.

Both of the above tautomeric isomers are included within the scope of the present invention, and in the present specification and claims, however, compound (I) is represented for convenience' sake by one expression of the possible tautomeric forms of pyrrolopyridazine ring.

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, hexyl, and the like, and in which more preferable example may be C_1 - C_4 alkyl.

Suitable "lower alkenyl" may include vinyl(ethenyl), 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, 1-methylvinyl, 1-ethylvinyl, 1-(or 2-)methyl-1-(or 2-)propenyl, 1-(or 2-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be C_2 - C_4 alkenyl.

Suitable "lower alkynyl" may include ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-pentynyl, 1 or 2 or 3 or 4 or 5-hexynyl, and the like.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, propylene, and the like, in which more preferable example may be C₁-C₄ alkylene and the most preferable one may be methylene.

5 Example of hydroxy(C₁-C₂)alkylene is hydroxymethylene, (hydroxymethyl)methylene or 1-(or 2-)hydroxyethylene.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

10 Suitable "halogen" and "halogen moiety" may include fluorine, bromine, chlorine and iodine.

Suitable "trihalo(lower)alkyl" may include trichloromethyl, trifluoromethyl, trichloroethyl, tribromoethyl, and the like.

Suitable "mono- or di(lower)alkylamino" may include amino group substituted by one or two lower alkyl such as methylamino, ethylamino, dimethylamino, and the like.

15 Example of "mono- or di(lower)alkylamino substituted by lower alkoxy" may be methoxymethylamino, methoxyethylamino, methoxyethyl(methyl)amino, methoxyethyl(ethyl)amino, di(methoxyethyl)amino, ethoxymethylamino, ethoxyethylamino, and the like.

20 Suitable "lower alkylthio" may include conventional ones such as methylthio, ethylthio, propylthio, butylthio, and the like.

Suitable "lower alkylsulfinyl" may include conventional ones such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, and the like.

Suitable "lower alkylsulfonyl" may include conventional ones such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, and the like.

25 Suitable "trihalo(lower)alkylsulfonyloxy" may include sulfonyloxy group substituted by trihalo(lower)alkyl such as trifluoromethylsulfonyloxy, trifluoroethylsulfonyloxy, trichloromethylsulfonyloxy, and the like.

Suitable "protected carboxy" and "protected carboxy moiety" may include esterified carboxy and the like.

30 And suitable example of said ester may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, etc.); lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.);

- lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.);
- lower alkoxy(lower)alkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.);
- lower alkylthio(lower)alkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester,
- 5 ethylthioethyl ester, isopropoxythiomethyl ester, etc.);
- mono(or di or tri)halo(lower)alkyl ester (e.g., 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.);
- lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester,
- 10 hexanoyloxymethyl ester, 1-acetoxyethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.);
- lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, 1-(or 2)-
- [methoxycarbonyloxy]ethyl ester, 1-(or 2)-[ethoxycarbonyloxy]ethyl ester, 1-(or 2)-
- 15 [propoxycarbonyloxy]ethyl ester, 1-(or 2)-[isopropoxycarbonyloxy]ethyl ester, etc.);
- lower alkanesulfonyl(lower)alkyl ester (e.g., mesylmethyl ester, 2-mesylethyl ester, etc.);
- lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, t-butoxycarbonyloxymethyl ester, 1-(or 2)-methoxycarbonyloxyethyl ester, 1-(or 2-
- 20)ethoxycarbonyloxyethyl ester, 1-(or 2)-isopropoxycarbonyloxyethyl ester, etc.);
- phthalidylidene(lower)alkyl ester;
- (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];
- 25 mono(or di or tri)aryl(lower)alkyl ester, for example, mono(or di or tri)phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.);
- 30 aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.);
- tri(lower)alkylsilyl ester (e.g. trimethylsilyl ester, triethylsilyl ester, etc.);

tri(lower)alkylsilyl(lower)alkyl ester (e.g. 2-trimethylsilylethyl ester, etc.); and the like, in which more preferable example may be lower alkyl ester, i.e., lower alkoxy carbonyl (e.g. ethoxy carbonyl, etc.).

The term "protected amino" means an amino group bonded to the amino-
5 protecting group. Example of such amino-protecting group include lower alkoxy carbonyl (e.g. methoxy carbonyl, ethoxy carbonyl, t-butoxy carbonyl, etc.); lower alkenyloxy carbonyl (e.g. vinyloxy carbonyl, allyloxy carbonyl, etc.); optionally substituted aryl(lower)alkoxy carbonyl (e.g. benzyloxy carbonyl, etc.); phthalimide; and the like. Further example of amino-protecting group are well-known in organic synthesis and are
10 described by T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, N.Y., which is herein incorporated by reference.

The term "protected sulfamoyl" means sulfamoyl group having the amino-protecting group mentioned above on the nitrogen atom. A preferred amino-protecting
15 group is aryl(lower)alkoxy carbonyl (e.g. benzyloxy carbonyl, etc.); and the like.

Suitable "acyl" and "acyl moiety" may include aliphatic acyl group, and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows:

20 Aliphatic acyl such as
lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.); in which preferable
25 "lower alkanoyl" may include straight or branched one such as formyl, acetyl, propionyl, butyryl, and the like.
lower or higher alkenoyl (e.g., acryloyl, 2-(or 3-)-butenoyl, 2-(or 3- or 4-)pentenoyl, 2-(or 3- or 4- or 5-)-hexenoyl, etc.);
lower alkadienoyl (e.g., heptadienoyl, hexadienoyl, etc.);
30 cyclo(lower)alkyl carbonyl (e.g., cyclopropyl carbonyl, cyclopentyl carbonyl, cyclohexyl carbonyl, etc.);
lower alkylglyoxyloyl (e.g., methylglyoxyloyl, ethylglyoxyloyl, propylglyoxyloyl, etc.);
lower alkoxyglyoxyloyl (e.g., methoxyglyoxyloyl, ethoxyglyoxyloyl, propoxyglyoxyloyl,

etc.);

or the like;

Aromatic acyl such as

aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);

- 5 ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

- 10 ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];

aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);

arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);

heterocyclic acyl such as

- 15 heterocycliccarbonyl;
heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);
heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);

- 20 heterocyclicglyoxyloyl; heterocyclicoxycarbonyl; or the like;

in which suitable "heterocyclic moiety" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like, as mentioned below and preferable "heterocyclic-carbonyl" may include carbonyl group substituted by heterocyclic group as mentioned

- 25 below such as pyrrolidinylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, and the like..

Suitable "halocarbonyl" may include chlorocarbonyl, bromocarbonyl, and the like.

Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl moiety" may include one having 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

- 30 Suitable "aryl" and "aryl moiety" may include C₆-C₁₀ aryl such as phenyl, naphthyl and the like.

Suitable "heterocyclic moiety" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen,

sulfur, nitrogen atom and the like.

Preferable heterocyclic group may be heterocyclic group such as

- (1) unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl, dihydropyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 1H-1,2,4-triazolyl, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;
- (2) saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;
- (3) unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, tetrahydroquinolyl (e.g., 1,2,3,4-tetrahydroquinolyl, etc.), isoquinolyl, indazolyl, benzotriazolyl, benzopyrimidinyl (e.g., benzo[b]pyrimidinyl, etc.), etc.;
- (4) unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;
- (5) saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;
- (6) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;
- (7) unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;
- (8) saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
- (9) unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

- (10) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;
- (11) unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furanyl, etc.;
- 5 (12) unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzodioxolyl (e.g. methylenedioxyphenyl, etc.), benzofuranyl, etc.;
- (13) unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;
- 10 (14) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothieryl (e.g., benzo[b]thienyl, etc.), benzodithieryl, etc.;
- (15) unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathieryl, etc.; and the like.

Suitable "heterocyclic group" and "heterocyclic moiety" in the terms
 15 "heterocycliccarbonyl" can be referred to the ones as mentioned above.

Suitable "N-containing heterocyclic group" and "N-containing heterocyclic moiety" can be referred to the ones as mentioned above, wherein the heterocyclic group is containing at least one nitrogen atom such as 1-pyrrolidinyl, morpholinyl and the like.

A group derived from a sugar may be the group derived from, for example,
 20 glycerinaldehydes; an aldose such as erythrose, threose, arabinose, ribose, xylose, lyxose, glucose, mannose or galactose; a ketose such as fructose or sorbose; or a disaccharide such as maltose, lactose or sucrose.

Protecting groups for the hydroxy group of the above-mentioned sugars are an aliphatic acyl group, such as formyl, or acetyl; a cyclic ether group such as tetrahydro-2-
 25 furanyl or tetrahydro-2-pyranyl; a 1-alkoxyethyl group such as 1-methoxyethyl or 1-ethoxyethyl; and a silyl group such as trimethylsilyl, triethylsilyl or t-butyltrimethylsilyl.

Suitable "substituted or unsubstituted lower alkyl" for R^1 may include straight or branched lower alkyl (e.g. methyl, isopropyl, neopentyl, etc.) optionally substituted by;
 30 (1) halogen (e.g. fluoro, bromo, etc.), (2) carboxy, (3) protected carboxy (e.g. esterified carboxy such as ethoxycarbonyl, etc.), (4) cyano, (5) carbamoyl, (6) $-OCONR^{15}R^{16}$ [wherein R^{15} and R^{16} each independently represents hydrogen, aryl or lower alkyl optionally substituted by aryl, or R^{13} and R^{14} , together with the nitrogen atom to which

they are attached, represents saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 nitrogen atom(s) and also optionally containing oxygen atom.] (more preferably, dimethylcarbamoyloxy, methyl-phenylcarbamoyloxy, morpholinylcarbonyloxy, pyrrolidinylcarbonyloxy, etc.); (7) lower alkylthio (e.g. methylthio, etc.), (8) lower alkylsulfonyl (e.g. methylsulfonyl, etc.), (9) lower alkylsulfonyloxy (e.g. methylsulfonyloxy, etc.), (10) lower alkylsulfonylamino (e.g. methylsulfonylamino, etc.), (11) mono- or di(lower)alkylamino optionally substituted by hydroxy, lower alkoxy, acyloxy (e.g. phenoxy, etc.), or substituted or unsubstituted aryl (e.g. benzylamino, etc.), (12) amino; (13) acylamino (more preferably, lower alkanoylamino such as acetylamino, aroylamino such as benzoylamino, or heterocycliccarbonylamino such as pyrazinylcarbonylamino, or the like), (14) protected amino (e.g., methoxycarbonylamino, phthalimide, etc.), (15) hydroxy, (16) acyloxy (more preferably, lower alkanoyloxy such as acetyloxy, or the like), (17) cyclo(lower)alkyloxy, (18) aryloxy (e.g. phenoxy, etc.) (19) substituted or unsubstituted aryl (more preferably, phenyl), (20) saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 3 nitrogen atom(s) and also optionally containing oxygen atom or sulfur atom (more preferably, piperazinyl, morpholinyl, oxazolidinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl or triazolyl) optionally substituted by lower alkyl, hydroxy(lower)alkyl, aryl or oxo, (21) lower alkoxy (e.g. methoxy, ethoxy, iso-propoxy, etc.) optionally substituted by carboxy, protected carboxy (e.g. tert-butoxycarbonyl, etc.), hydroxy, protected hydroxy (e.g. tetrahydro-2H-pyran-2-yloxy, etc.), cyclo(lower)alkyl (e.g. cyclopropyl, cyclohexyl, etc.), substituted or unsubstituted aryl (e.g. phenyl optionally substituted by cyano, carboxy, protected carboxy or carbamoyl, such as phenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-carboxyphenyl, 2-, 3- or 4-(methoxycarbonyl)phenyl, 2-, 3- or 4-carbamoylphenyl, etc.), saturated or unsaturated 5- or 6-membered heterocyclic group containing 1 to 2 nitrogen atom(s) optionally substituted by lower (more preferably, 2-, 3- or 4-pyridinyl, pyrazinyl or 4-methylpiperazinyl)(e.g. 2-, 3- or 4-pyridinyl, pyrazinyl, etc.), or $\text{-CONR}^{13}\text{R}^{14}$ [wherein R^{13} and R^{14} each independently hydrogen or lower alkyl optionally substituted by aryl, or R^{13} and R^{14} , together with the nitrogen atom to which they are attached, represents N-containing heterocyclic group] (e.g. morpholinocarbonyl, dimethylcarbamoyl, etc.), and the like.

Suitable "substituted or unsubstituted aryl" may include $\text{C}_6\text{-C}_{10}$ aryl (e.g. phenyl, naphthyl, etc.) optionally substituted by the substituent(s) selected from the group

consisting of (1) halogen (e.g. fluoro, chloro, etc.), (2) carboxy, (3) protected carboxy, (4) cyano, (5) $-\text{CONR}^{15}\text{R}^{16}$ [wherein R^{15} and R^{16} are each independently represents hydrogen, lower alkyl optionally substituted by hydroxy] (e.g. carbamoyl, hydroxyethylcarbamoyl, etc.), (6) lower alkyl (e.g. methyl, etc.), (7) cyclo(lower)alkyl (e.g. cyclopropyl, etc.) (8) lower alkoxy (e.g. methoxy, etc.), (9) trihalo(lower)alkyl (e.g. trifluoromethyl, etc.), (10) heterocyclic group such as oxazolyl, (11) lower alkylsulfonyl (e.g. methylsulfonyl, etc.), (12) nitro, (13) amino, (14) sulfamoyl, and (15) protected sulfamoyl such as ar(lower)alkoxycarbonylsulfamoyl, and the like.

In which,

- 10 preferable example of "substituted or unsubstituted aryl" for R^1 is aryl optionally substituted by the substituent(s) selected from the group consisting of halogen (e.g. phenyl, 4-fluorophenyl, etc.);
- preferable example of "substituted or unsubstituted aryl" for R^3 is aryl optionally substituted by the substituent(s) selected from the group consisting of (1) halogen, (2) carboxy, (3) protected carboxy such as esterified carboxy (e.g. benzyloxycarbonyl, etc.), (4) cyano, (5) $-\text{CONR}^{15}\text{R}^{16}$ [wherein R^{15} and R^{16} are each independently represents hydrogen, lower alkyl optionally substituted by hydroxy], (6) lower alkyl, (7) cyclo(lower)alkyl, (8) lower alkoxy, (9) trihalo(lower)alkyl, (10) heterocyclic group, (11) lower alkylsulfonyl, (12) nitro, (13) amino, (14) sulfamoyl, and (15) protected sulfamoyl, and the like. (e.g. phenyl, 2-naphthyl, 2- or 3-chlorophenyl, 2,3-, 2,4-, 3,4- or 3,5-dichlorophenyl, 3- or 4-fluorophenyl, 3- or 4-cyanophenyl, 3- or 4-carbamoylphenyl, 4-sulfamoylphenyl, 4-(benzyloxycarbonylsulfamoyl)phenyl, 3-carboxyphenyl, 3-(N-(2-hydroxyethyl)carbamoyl)phenyl, 3-nitrophenyl, 3-trifluoromethylphenyl, 3-methylsulfonylphenyl, 3-(5-oxazolyl)phenyl, 3-methoxyphenyl, 3-methylphenyl, etc.);
- 25 and
- preferable example of "substituted or unsubstituted aryl" for R^7 is aryl optionally substituted by lower alkoxy (e.g. phenyl, 2-, 3- or 4-methoxyphenyl, etc.).

- Suitable "substituted or unsubstituted heterocyclic group" may include heterocyclic group mentioned above (more preferably, pyridinyl, pyrazinyl, oxazolyl, isooxazolyl, furanyl, thienyl, quinolinyl, benzofuranyl and benzothienyl), which is
- 30 optionally substituted by the substituent(s) selected from the group consisting of (1) lower alkyl (e.g. methyl, etc.), (2) cyclo(lower)alkyl (e.g. cyclopropyl, etc.) (3) lower alkoxy (e.g. methoxy, etc.), (4) acyl (e.g. lower alkanoyl such as acetyl, etc.), (5) amino,

(6) mono- or di(lower)alkylamino (e.g. dimethylamino, etc.), (7) protected amino (e.g. lower alkoxy-carbonylamino such as tert-butoxycarbonylamino, etc.), (8) cyano, (9) carboxy, (10) protected carboxy (e.g. benzyloxycarbonyl, etc.), (11) $-\text{CONR}^{15}\text{R}^{16}$ [wherein R^{15} and R^{16} are each independently represents hydrogen, lower alkyl optionally substituted by hydroxy] (e.g. carbamoyl, hydroxyethylcarbamoyl, etc.), (12) lower alkenyl optionally substituted by lower alkoxy (e.g. vinyl, 1-ethoxyvinyl, etc.), (13) halogen (e.g. chloro, bromo, etc.), (14) lower alkylthio, (15) hydroxy, and the like.

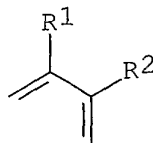
In which,

preferable example of "substituted or unsubstituted heterocyclic group" for R^1 is
 10 heterocyclic group optionally substituted by lower alkyl or halogen (e.g. 2-pyridinyl, 5-bromo-3-pyridinyl, 1-methyl-2-pyrrolyl, 1-pyrrolyl, 1-pyrrolidinyl, 3-methyl-2-thienyl, 2-thienyl, 2- or 3-furanyl, 2-thiazolyl, 5-oxazolyl, 5-methyl-isooxazolyl, 3,5-dimethyl-4-isoxazolyl, etc.); and
 preferable example of "substituted or unsubstituted heterocyclic group" for R^3 is
 15 heterocyclic group optionally substituted by at least one substituent(s) selected from the group consisting of (1) lower alkyl, (2) cyclo(lower)alkyl, (3) lower alkoxy, (4) acyl such as lower alkanoyl, (5) amino, (6) mono- or di(lower)alkylamino, (7) protected amino such as lower alkoxy-carbonylamino, (8) cyano, (9) carboxy, (10) protected carboxy such as esterified carboxy (e.g. benzyloxycarbonyl), (11) carbamoyl, (12) lower alkenyl
 20 optionally substituted by lower alkoxy, (13) halogen, (14) lower alkylthio, and (15) hydroxy (e.g. 3- or 4-pyridyl, 2-pyrazinyl, 6-methoxy-2-pyrazinyl, 4- or 5-oxazolyl, 2-benzofuranyl, 2-benzothienyl, 3- or 6-quinolinyl, 2-chloro-4-pyridyl, 5-bromo-3-pyridyl, 5-chloro-2-thienyl, 5,6-dichloro-2-pyridyl, 4-chloro-2-pyridyl, 5-cyano-3-pyridyl, 5-carboxy-3-pyridinyl, 5-carbamoyl-3-pyridyl, 5-(benzyloxycarbonyl)-3-pyridyl, 5-(tert-butoxycarbonylamino)-3-pyridinyl, 5-amino-3-pyridinyl, 2-methoxy-4-pyridyl, 3-methoxy-5-isoxazolyl, 2-methylthio-4-pyridinyl, 2-hydroxy-4-pyridyl, 5-methyl-3-pyridyl, 5-ethyl-3-pyridyl, 5-methyl-3-isoxazolyl, 5-vinyl-3-pyridyl, 2-vinyl-4-pyridyl, 5-acetyl-3-pyridyl, 2-dimethylamino-4-pyridyl, 5-(1-ethoxyvinyl)-3-pyridyl, 2-oxo-1,2-dihydro-4-pyridyl, or 2-methylthio-4-pyridyl, etc.).

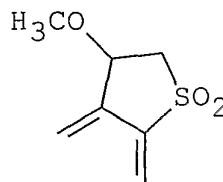
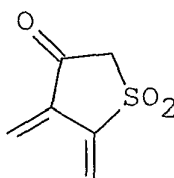
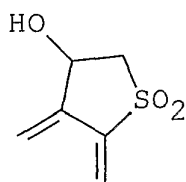
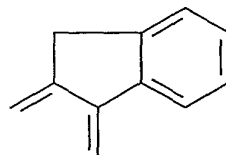
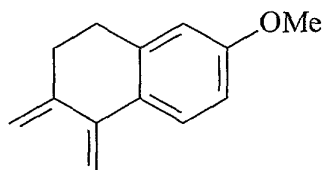
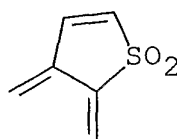
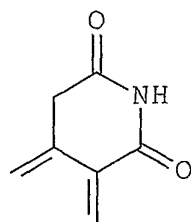
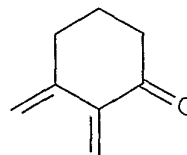
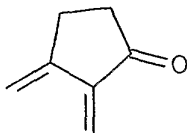
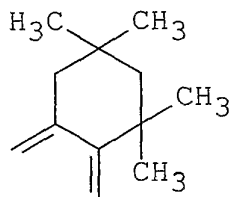
30

R^1 and R^2 are combined together to form lower alkylene or lower alkenylene group which is optionally interrupted by amino or sulfonyl and also is optionally substituted by the group consisting of lower alkyl, hydroxy, oxo and lower alkoxy, which is represented

by the following formula:



The above formula may include following ones;



Suitable "substituted or unsubstituted aryl(lower)alkenyl" may include C₆-C₁₀ aryl(lower)alkenyl which is optionally substituted by halogen (e.g. 2-phenylvinyl, 2-(2- or 3-chlorophenyl)vinyl, etc.).

Suitable "leaving group" may include acid residue, lower alkoxy as exemplified above, and the like.

The above Processes can be carried out according to a conventional manner such

2003294183 21 May 2009

as the one described in Preparations and/or Examples, or in a similar manner thereto. Among the above Processes, fused heterocyclic ring forming processes (such as Process 1 and Process 12) are important for carrying out of this invention and are explained in more detail.

According to the Process 1, pyrrolopyridazine derivatives (I) can be prepared by reacting the 1-amino-2-acylpyrrole derivative (II) or a salt thereof and the compound (III) or a salt thereof in the presence of a catalytic amount of acid catalyst in an inert solvent, preferably with concomitant removal of the water being produced by physical (e.g. Dean-Stark trap) or chemical (e.g. molecular sieves) means. Suitable acid catalyst is, for example p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, trifluoroacetic acid and so on. Suitable inert solvent is, for example, benzene, toluene, tetrahydrofuran and the like.

Another ring forming process is described in Process 12, in this process pyrrolopyridazine derivatives (I) can be also prepared reacting 1-aminopyrrole derivative (V) or a salt thereof and β -diketone derivative or a salt thereof under the similar condition before mentioned Process 1, and therefore the reaction conditions can be referred to those of the Process 1.

The compounds of the present invention can be purified by any conventional purification methods employed for purifying organic compounds, such as re-crystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. The compounds can be identified by conventional methods such as NMR spectrography, mass spectrography, IR spectrography, elemental analysis, and measurement of melting point.

Suitable salts of the compounds of formula I and the starting compounds in Processes 1 to 40 can be referred to the ones as exemplified for the compound (I).

The new pyrrolopyridazine derivatives (I) and pharmaceutically acceptable salts thereof hardly possess a strong inhibitory activity against phosphodiesterase III (PDE III), but possess a strong inhibitory activity against phosphodiesterase IV (PDE IV) and a strong inhibitory activity on the tumor necrosis factor (TNF).

That is, the pyrrolopyridazine derivatives (I) and pharmaceutically acceptable salts thereof are selective inhibitors of phosphodiesterase IV (PDE IV) and inhibitors on

the production of tumor necrosis factor (TNF).

Accordingly, the new pyrrolopyridazine derivatives (I) and a pharmaceutically acceptable salt thereof can be used for prophylactic and therapeutic treatment of PDE-IV and TNF mediated diseases such as chronic inflammatory diseases (e.g., rheumatoid arthritis, osteoarthritis, emphysema, chronic bronchiolitis, allergic rhinitis, etc.), osteoporosis, rejection by transplantation, asthma, chronic obstructive pulmonary disease (COPD), eosinophilia, fibrotic disease (e.g., cystic fibrosis, pulmonary fibrosis, hepatic fibrosis, renal fibrosis, etc.), (viral alcoholic, drug-induced) acute and fulminant hepatitis, hepatic steatosis (alcoholic and non-alcoholic steato-hepatitis), chronic (viral and non-viral) hepatitis, hepatic cirrhosis, autoimmune hepatitis, pancreatitis, nephritis, endotoxin shock, specific autoimmune diseases [e.g., ankylosing spondylitis, autoimmune encephalomyelitis, autoimmune hematological disorders (e.g., hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, etc.), systemic lupus erythematosus (SLE), polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis (Wilson's disease, etc.), myasthenia gravis, idiopathic sprue, autoimmune inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease, etc.), endocrine ophthalmopathy, Grave's disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), Reiter's syndrome, non infection uveitis, autoimmune keratitis (e.g., keratoconjunctivitis sicca, vernal keratoconjunctivitis, etc.), interstitial lung fibrosis, psoriatic arthritis, etc.], dermatological disorders associated with PDE-IV enzyme (such as psoriasis and other benign or malignant proliferative skin diseases, atopic dermatitis, and urticaria), neurodegenerative disorders such as Parkinson disease, Alzheimer's disease, acute and chronic multiple sclerosis, cancer cachexia, viral infection, AIDS cachexia, thrombosis, and the like.

For therapeutic administration, the compound (I), or its prodrug, or a salt thereof can be administered alone or in the form of a mixture, preferably, with a pharmaceutical vehicle or carrier.

The active ingredient of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains a compound (I), as an active ingredient, in admixture with an organic or

inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, parenteral or intra-mucous applications. The active ingredient can be formulated, for example, with the conventional non-toxic, pharmaceutically acceptable carriers for ointment, cream, plaster, tablets, pellets, capsules, suppositories, solution
5 (saline, for example), emulsion, suspension (olive oil, for example), aerosols, pills, powders, syrups, injections, troches, cataplasms, aromatic waters, lotions, buccal tablets, sublingual tablets, nasal drops and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch,
10 urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

15 The active ingredient can be formulated into, for example, preparations for oral application, preparations for injection, preparations for external application, preparations for inhalation, and preparations for application to mucous membranes.

Further, the compound of this invention can be used in combination with other
20 therapeutic compounds. In particular, the combinations of the PDE4 inhibiting compound of this invention can be advantageously used in combination with i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) COX-2 selective inhibitors, iv) statins, v) NSAIDs, vi) M2/M3 antagonists, vii) corticosteroids, viii) Hi (histamine) receptor antagonists, ix) beta 2 adrenoceptor agonist, x) interferon,
25 xi) antiviral drugs for hepatitis C virus (HCV) such as protease inhibitor, helicase inhibitor, polymerase inhibitor, or the like, xii) antiviral drug for hepatitis B virus such as lamivudine, xiii) ursodesoxycholic acid, xiv) glycyrrhizin, xv) human growth factor (HGF), xvi) aminosalicilyc acid such as salazosulfapyridine, mesalazin, or the like, xvii) steroids such as prednisolone farnesylate, xviii) immunosuppressant such as azathioprine,
30 6-mercaptopurine, tacrolimus, and the like.

Mammals which may be treated by the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and

humans, preferably humans.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose to a human patient of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utilities of the pyrrolopyridazine derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the pyrrolopyridazine derivatives (I) are illustrated in the following.

(a) Inhibition of U937 phosphodiesterase IV (PDE IV)

1. Test method:

Cultured U937 cells were washed twice and harvested with phosphate-buffered saline (PBS) by cell-scraper. After centrifugation, the cell pellet was suspended in homogenizing buffer (0.5 % deoxycholate [DOC], 5 mM 2-mercaptoethanol, 1 μ M leupeptin, 100 μ M PMSF, 20 μ M p-tosyl-L-lysine-chloromethyl ketone [TLCK] in PBS). The cell suspension was then sonicated for a couple of minutes and homogenized by a glass-Teflon homogenizer with twenty strokes. The homogenate was centrifuged at 200g for 30 minutes, and the supernatant was further ultra-centrifuged at 100,000 x g for 90 minutes (4°C). The final supernatant was dialyzed against dialysis buffer, which was the same component as homogenizing buffer without DOC. The dialysate of enzyme preparation was stored at -20°C until assay.

PDE4, activity was estimated with a Phosphodiesterase [3 H]cAMP SPA Enzyme Assay System (Amersham Pharmacia Biotech), using a 96 well Opti-plate. Reactions were initiated by addition of 0.025 μ Ci/well of [3 H]cAMP to the enzyme mixture containing 50 mM Tris-HCl (pH 7.5), 8.3 mM MgCl_2 , 1.7 mM EGTA, and various concentrations of the test compound or vehicle. CI-930 (10 μ M in final), a specific PDE3, inhibitor, was also added in the reaction mixture. After incubation at 30°C for 15 minutes, 50 μ L of SPA beads suspension was added to each well. The well-plate was then shaken

for 20 minutes by a plate mixer. Radio-activity in each well was counted by a Top Counter.

Test compounds were dissolved in 100% dimethylsulfoxide (DMSO) and diluted into respective concentrations with the final solution containing 1% v/v of DMSO.

- 5 IC_{50} values of test compounds for the enzyme activity of PDE4 was determined from regression analysis for log-logit conversion values of percent inhibition in the compound-treated tubes compared to that of the control. Percent inhibition was calculated with the following equation: Inhibition (%) = $\{1-(C-B)/(A-B)\} \times 100$; in which A, B and C means mean values of radio-activity counts (dpm) of control, blank and the
10 compound-treated tubes, respectively.

2. Test results

The following table illustrates the inhibitory activity on PDE-IV of the representative compound of formula (I):

15

Example	Compound name	IC ₅₀ (μM)
198	6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid	<1

(b) Inhibition on TNF-alpha production in human mononuclear cells

20 1. Test method

(1) Human peripheral blood mononuclear cells (PBMCs) preparation

- Blood (30 ml for each person) was collected from the median cubital vein of healthy volunteer was divided 15 mL each in heparin containing conical tube and the same volume of RPMI1640 was added to each tube. Diluted blood was then piled up to
25 20 mL of Ficoll-Paque PLUS (Amersham Pharmacia Biotech) in polystyrene centrifuge tube. After centrifugation at 1,600rpm for 30 minutes, cells gathering in the center area of the gradient were collected by capillary and washed with 40 mL of RPMI1640 in several times with centrifugation at 1,200 rpm for 10 minutes. PBMC finally precipitated were suspended in RPMI1640 containing 1% fetal bovine serum and antibiotics. After
30 cell counting, final suspension at 3×10^6 cells/mL in culture medium was prepared.

(2) TNF-alpha production from stimulated PBMCs

Human PBMCs prepared by the density gradient method using Ficoll-Paque PLUS were suspended in the culture medium mentioned above with the concentration of 5 3×10^6 cells/mL and 0.5 mL of the suspension was sowed into each well of a 24-well culture plate. Cells were incubated in the CO₂ incubator for 24 hours with 0.25 mL of LPS in addition of 0.25 mL of concentrations of drugs or vehicle at the start of the incubation. Final concentration of LPS in the incubation medium was 1 µg/mL. After 24 hours, the supernatant of each well by centrifugation at 1,700 rpm for 10 minutes was 10 stored at -80°C until assay. TNF-alpha levels in the medium were measured by ELISA.

The IC₅₀ values of drugs on cytokine productions in LPS stimulated PBMC were estimated by the regression analysis for the relative values of cytokine level in the drug-treated wells compared to those of the vehicle-treated ones.

15 2. Test results

Example	Compound name	IC50 (nM)
198	6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid	<100

Best Mode for carrying out the Invention

The following examples are provided to further illustrate details for the preparation of the compounds of the present invention. The examples are not intended to be limitations on the scope of the instant invention in any way, and they should not be so construed. Furthermore, the compounds described in the following examples are not to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

The abbreviations, symbols and terms used in the Preparations, Examples and Formulae have the following meanings.

DMF	N,N-dimethylformamide
EtOAc or AcOEt	Ethyl acetate
THF	Tetrahydrofuran
Et ₃ N	Triethylamine
MeOH	Methanol
EtOH	Ethanol
BuOH	Butanol
DCM	Dichloromethane
Pd/C	Palladium on carbon powder

Preparation 1

To a suspension of 2-pyridinethiol (17 g) in tetrahydrofuran (200 mL) was added triethylamine (15.5 g) in an ice-water bath under N₂. To this was added a solution of 4-cyanobenzoyl chloride (25.3 g) in tetrahydrofuran (80 mL) below 10°C over 30 minutes. After 15 minutes, the bath was removed and the mixture was stirred overnight at ambient temperature. The mixture was concentrated in vacuo. The residue was partitioned between chloroform and water. The organic layer was washed with saturated sodium

bicarbonate and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue (38 g) was triturated with isopropyl ether to give S-(2-pyridinyl) 4-cyanobenzenecarbothioate (32.5 g) as a pale brown solid.

5 S-(2-Pyridinyl) 4-cyanobenzenecarbothioate

NMR (CDCl₃, δ): 7.38 (1H, t, J=7Hz), 7.72 (1H, d, J=8Hz), 7.75-7.87 (3H, m), 8.11 (2H, d, J=8Hz), 8.71 (1H, d, J=2Hz)

MS (ESI⁺): m/z 241 (M+H)

10 The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 1.

Preparation 2

S-(2-Pyridinyl) 2-chloro-4-pyridinecarbothioate

15 NMR (CDCl₃, δ): 7.40 (1H, m), 7.65-7.75 (2H, m), 7.75-7.90 (2H, m), 8.62 (1H, d, J=5Hz), 8.70 (1H, m)

Preparation 4

S-(2-Pyridinyl) 3-cyanobenzenecarbothioate

20 NMR (CDCl₃, δ): 7.39 (1H, m), 7.66 (1H, t, J=8Hz), 7.72 (1H, t, J=8Hz), 7.83 (1H, m), 7.91 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 8.29 (1H, s), 8.71 (1H, m)
MS (ESI⁺): m/z 241 (M+H)

Preparation 5

25 S-(2-Pyridinyl) 3-methoxybenzenecarbothioate

NMR (CDCl₃, δ): 3.87 (3H, s), 7.16 (1H, m), 7.32-7.44 (2H, m), 7.51 (1H, m), 7.63 (1H, d, J=8Hz), 7.71-7.83 (2H, m), 8.69 (1H, m)

Preparation 6

30 S-(2-Pyridinyl) 4-pyridinecarbothioate

NMR (CDCl₃, δ): 7.35-7.43 (1H, m), 7.73 (1H, d, J=8Hz), 7.77-7.88 (3H, m), 8.70 (1H, d, J=7Hz), 8.85 (2H, d, J=8Hz)

MS (ESI⁺): m/z 217

Preparation 7

S-(2-Pyridinyl) 2-pyrazinecarbothioate

5 NMR (CDCl₃, δ): 7.38 (1H, m), 7.71 (1H, d, J=8Hz), 7.82 (1H, m), 8.73 (2H, m),
8.86 (1H, m), 9.17 (1H, s)

Preparation 8

S-(2-Pyridinyl) 3-pyridinecarbothioate

10 NMR (CDCl₃, δ): 7.37 (1H, m), 7.46 (1H, m), 7.73 (1H, m), 7.83 (1H, m), 8.27 (1H,
m), 8.68 (1H, m), 8.84 (1H, m), 9.23 (1H, m)

Preparation 9

To a solution of 2-ethyl-1H-pyrrole in toluene (120 mL) was added dropwise 1M
15 methylmagnesium bromide in tetrahydrofuran (170 mL) in a dry ice-acetone bath below
-60°C over 30 minutes. Then the mixture was stirred in an ice-water bath for 40 minutes.
To this reaction mixture was added S-(2-pyridinyl) 4-cyanobenzenecarbothioate (15.2 g)
portionwise over 10 minutes in a dryice-acetone bath. After 1.5 hours stirring, saturated
ammonium chloride (100 mL) was added therein and the reaction mixture was allowed to
20 ambient temperature. The mixture was partitioned between ethyl acetate and water. The
organic layer was washed with 1N sodium hydroxide (100 mL) twice, water, and brine,
dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with
isopropyl ether to give 4-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (12.7 g) as a pale
yellow solid.

25

4-[(5-Ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile

NMR (CDCl₃, δ): 1.32 (3H, t, J=8Hz), 2.75 (2H, q, J=8Hz), 6.11 (1H, d, J=5Hz),
6.76 (1H, d, J=5Hz), 7.77 (2H, d, J=8Hz), 7.94 (2H, d, J=8Hz), 9.49 (1H, br s)

MS (ESI⁺): m/z 225 (M+H)

30

The following compound was obtained in substantially the same manner as that of
Preparation 9.

Preparation 10

(2E)-1-(5-Ethyl-1H-pyrrol-2-yl)-3-phenyl-2-propen-1-one

NMR (CDCl₃, δ): 1.31 (3H, t, J=7Hz), 2.73 (2H, q, J=7Hz), 6.10 (1H, m), 7.02 (1H, m), 7.27 (1H, d, J=16Hz), 7.35-7.43 (3H, m), 7.63 (2H, m), 7.79 (1H, d, J=16Hz)

5 MS (ESI⁺): m/z 226 (M+H)

Preparation 11

To a solution of 4-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]-benzonitrile (12.5 g) in N,N-dimethylformamide (63 mL) was added 60% sodium hydride in oil (2.68 g) in an ice-water bath under N₂. After 30 minutes, to the mixture was added 1-(aminooxy)-2,4-dinitrobenzene (13.3 g). After 2 hours, the mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water (100 mL) 3 times, 1N sodium hydroxide (100 mL), and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 500 mL) eluted with hexane-chloroform = 1-2, 1-5, and 1-10 followed by triturated with isopropyl ether to give 4-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (8.1 g, 60.7%) as a yellow solid. The mixed fraction and the mother layer (7 g) were repurified by flash silica gel chromatography (silica gel, 200 mL) eluted with hexane-chloroform = 2-1 and 1-1 followed by triturated with isopropyl ether to give 4-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (2.0 g, 15%) as a pale yellow solid.

4-[(1-Amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-benzonitrile

NMR (CDCl₃, δ): 1.29 (3H, t, J=8Hz), 2.77 (2H, q, J=8Hz), 5.75 (2H, br s), 5.94 (1H, d, J=5Hz), 6.59 (1H, d, J=5Hz), 7.76 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz)

25 MS (ESI⁺): m/z 240 (M+H)

The following compounds were obtained in substantially the same manner as that of Preparation 11.

30 Preparation 12

(1-Amino-5-ethyl-1H-pyrrol-2-yl)(2-chloro-4-pyridinyl)methanone

NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.77 (2H, q, J=7Hz), 5.71 (2H, s), 5.96 (1H, d,

J=4Hz), 6.63 (1H, d, J=4Hz), 7.50 (1H, d, J=4Hz), 7.61 (1H, s), 8.52 (1H, d, J=4Hz)

MS: (m/z) 250 (M+H)

5 Preparation 13

3-[(1-Amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-benzonitrile

NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.77 (2H, q, J=7Hz), 5.74 (2H, s), 5.94 (1H, d, J=5Hz), 6.59 (1H, d, J=5Hz), 7.59 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.06 (1H, s)

10

Preparation 14

(2E)-1-(1-Amino-5-ethyl-1H-pyrrol-2-yl)-3-phenyl-2-propen-1-one

NMR (CDCl₃, δ): 1.28 (3H, t, J=7Hz), 2.73 (2H, q, J=7Hz), 5.93 (1H, d, J=5Hz), 6.99 (1H, d, J=5Hz), 7.30 (1H, d, J=16Hz), 7.37-7.43 (3H, m), 7.62 (2H, m), 7.74 (1H, d, J=16Hz)

15

MS (ESI⁺): m/z 241 (M+H)

Preparation 15

(1-Amino-5-ethyl-1H-pyrrol-2-yl)(3-methoxyphenyl)-methanone

20 NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 2.75 (2H, q, J=7Hz), 3.86 (3H, s), 5.79 (2H, s), 5.89 (1H, d, J=4Hz), 6.67 (1H, d, J=4Hz), 7.07 (1H, m), 7.29-7.40 (3H, m)

MS (ESI⁺): m/z 245

Preparation 16

25 (1-Amino-5-ethyl-1H-pyrrol-2-yl)(4-pyridinyl)methanone

NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.77 (2H, q, J=7Hz), 5.76 (2H, s), 5.94 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 7.58 (2H, d, J=7Hz), 8.75 (2H, d, J=7Hz)

MS (ESI⁺): m/z 216

30 Preparation 17

(1-Amino-5-ethyl-1H-pyrrol-2-yl)(2-pyrazinyl)methanone

NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.77 (2H, q, J=7Hz), 5.79 (2H, s), 5.98 (1H, d,

J=4Hz), 7.27 (1H, d, J=4Hz), 8.63 (1H, m), 8.71 (1H, m), 9.17 (1H, m)

Preparation 18

(1-Amino-5-ethyl-1H-pyrrol-2-yl)(3-pyridinyl)methanone

- 5 NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.77 (2H, q, J=7Hz), 5.78 (2H, s), 5.94 (1H, d, J=4Hz), 6.65 (1H, d, J=4Hz), 7.39 (1H, m), 8.06 (1H, m), 8.74 (1H, m), 8.99 (1H, m)

Preparation 19

- 10 (1-Amino-5-ethyl-1H-pyrrol-2-yl)(5-bromo-3-pyridinyl)-methanone

NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.76 (2H, q, J=7Hz), 5.72 (2H, s), 5.96 (1H, m), 6.65 (1H, m), 8.19 (1H, m), 8.70 (1H, m), 8.89 (1H, m)

Preparation 20

- 15 To a solution of tert-butyl 3-oxobutanoate (20.0 g) in tetrahydrofuran (200 mL) was added 60% sodium hydride in oil (5.56 g) portionwise over 20 minutes in an ice-water bath under N₂. After 40 minutes, to the mixture was added ethyl 5-iodopentanoate (35.6 g) at the temperature. After 15 minutes, the mixture was stirred at ambient temperature. After 1 hour, the reaction mixture was heated at 50°C for 24 hours. The
20 cooled mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 1 L) eluting with hexane-ethyl acetate = 50-1, 20-1, 10-1, and 8-1 to give 1-tert-butyl 7-ethyl 2-acetylheptanedioate (27.3 g, 75.4%)
25 as colorless oil.

1-tert-Butyl 7-ethyl 2-acetylheptanedioate

- NMR (CDCl₃, δ): 1.20-1.38 (5H, m), 1.46 (9H, s), 1.54-1.71 (2H, m), 1.75-1.87 (2H, m), 2.12 (3H, s), 2.30 (2H, t, J=8Hz), 3.30 (12H, t, J=8Hz), 4.11 (2H, q, J=8Hz)
30

The following compounds were obtained in substantially the same manner as that of Preparation 20.

Preparation 21

1-tert-Butyl 9-ethyl 2-acetylnonanedioate

NMR (CDCl₃, δ): 1.23-1.33 (9H, m), 1.46 (9H, s), 1.55 (2H, m), 1.77 (2H, m), 2.21 (3H, s), 2.28 (2H, t, J=7Hz), 3.27 (1H, t, J=7Hz), 4.12 (2H, q, J=7Hz)

5 MS (ESI⁺): m/z 315 (M+H)

Preparation 22

tert-Butyl 2-acetylhexanoate

NMR (CDCl₃, δ): 0.90 (3H, t, J=8Hz), 1.28-1.40 (4H, m), 1.46 (9H, s), 1.73-1.89 (2H, m), 2.22 (3H, s), 3.30 (1H, t, J=8Hz)

Preparation 23

1-tert-Butyl 8-ethyl 2-acetyloctanedioate

NMR (CDCl₃, δ): 1.21-1.33 (7H, m), 1.46 (9H, s), 1.54-1.69 (2H, m), 1.74-1.85 (2H, m), 2.21 (3H, s), 2.28 (2H, t, J=8Hz), 3.29 (1H, t, J=8Hz), 4.12 (2H, q, J=8Hz)

Preparation 24

To a suspension of magnesium chloride (1.33 g) in dichloromethane (40 mL) was added 1-tert-butyl 7-ethyl 2-acetylheptanedioate (4.0 g) at ambient temperature under N₂.

20 To this mixture was added dropwise pyridine (2.26 mL) in an ice-water bath. Then the mixture was stirred at ambient temperature for 40 minutes. To the reaction mixture was added a solution of 3-cyanobenzoyl chloride (3.01 g) in dichloromethane (6 mL) dropwise over 2 minutes. The reaction mixture was stirred at ambient temperature for 2 hours. To the mixture was added 1N hydrogen chloride and ethyl acetate in an ice-water bath. The organic layer was washed with 1N hydrogen chloride, water, and brine, dried over magnesium sulfate, and evaporated in vacuo to give a solid. The residue was purified by flash silica gel chromatography (silica gel, 300 mL) eluting with hexane-ethyl acetate = 10-1, 8-1, 5-1, and 3-1 to give 1-tert-butyl 7-ethyl 2-acetyl-2-(3-cyanobenzoyl)heptanedioate (4.23 g, 72.9%) as colorless oil.

30

1-tert-Butyl 7-ethyl 2-acetyl-2-(3-cyanobenzoyl)-heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=8Hz), 1.28-1.40 (11H, m), 1.63-1.75 (2H, m), 2.19-

2.28 (2H, m), 2.32 (2H, t, J=8Hz), 2.45 (3H, s), 4.11 (2H, q, J=8Hz), 7.56 (1H, t, J=8Hz), 7.80 (2H, dd, J=8, 1Hz), 7.95 (2H, dd, J=8, 1Hz), 8.06 (1H, br s)

MS (ESI⁺): m/z 416 (M+H)

- 5 The following compounds were obtained in substantially the same manner as that of Preparation 24.

Preparation 25

Ethyl 2-isobutyryl-4-methyl-3-oxopentanoate

10 NMR (300 MHz, CDCl₃, δ): 1.10-1.23 (12H, m), 1.30-1.43 (3H, m), 2.91-3.10 (2H, m), 4.21-4.36 (2H, m)

Preparation 26

Ethyl 2-(2-chlorobenzoyl)-4-methyl-3-oxopentanoate

15 NMR (300 MHz, CDCl₃, δ): 0.79 (3H, t, J=7.5Hz), 1.22 (6H, d, J=7.5Hz), 3.36-3.54 (1H, m), 3.88 (2H, q, J=7.5Hz), 7.26-7.44 (4H, m)

Preparation 27

Ethyl 4-methyl-2-(2-naphthoyl)-3-oxopentanoate

20 NMR (300 MHz, CDCl₃, δ): 0.76-1.03 (3H, m), 1.10-1.30 (6H, m), 2.56-2.71 (1/2H, m), 2.88-3.04 (1/6H, m), 3.20-3.35 (1/3H, m), 3.72-4.336 (3H, m), 7.50-7.68 (2+1/3H, m), 7.82-8.01 (3+2/3H, m), 8.09 (1/3H, s), 8.35 (1/2H, s), 8.41 (1/6H, s)
MS (ES⁺): m/e 313.45

Preparation 28

- 25 1-tert-Butyl 7-ethyl 2-acetyl-2-[3-(trifluoromethyl)benzoyl]heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.32 (9H, s), 1.36-1.75 (4H, m), 2.15-2.36 (4H, m), 2.45 (3H, s), 4.11 (2H, q, J=7Hz), 7.56 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 7.93 (1H, d, J=8Hz), 8.04 (1H, s)

- 30 Preparation 29

1-tert-Butyl 7-ethyl 2-acetyl-2-[(5-methyl-3-pyridinyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.27-1.42 (2H, m), 1.34 (9H, s), 1.65-1.77

(2H, m), 2.16-2.35 (4H, m), 2.39 (3H, s), 2.43 (3H, s), 4.10 (2H, q, J=7Hz), 7.87 (1H, s), 8.56 (1H, s), 8.73 (1H, s)

MS (ESI⁺): m/z 406 (M+H)

5 Preparation 30

1-tert-Butyl 7-ethyl 2-(methoxyacetyl)-2-[(3-methoxy-5isoxazolyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.39 (9H, s), 1.35-1.50 (2H, m), 1.64-1.75

(2H, m), 2.15-2.23 (2H, m), 2.32 (2H, t, J=7Hz), 3.40 (3H, s), 4.01 (3H, s), 4.12

10 (2H, q, J=7Hz), 4.57 (2H, s), 6.54 (1H, s)

Preparation 31

1-tert-Butyl 7-ethyl 2-acetyl-2-[3-(1,3-oxazol-5-yl)benzoyl]heptanedioate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.33 (9H, s), 1.30-1.43 (2H, m), 1.62-1.76

15 (2H, m), 2.17-2.35 (4H, m), 2.44 (3H, s), 4.09 (2H, q, J=7Hz), 7.42 (1H, s), 7.48

(1H, t, J=8Hz), 7.69 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 7.94 (1H, s), 8.09 (1H, m)

Preparation 32

20 1-tert-Butyl 7-ethyl 2-acetyl-2-(3,4-dichlorobenzoyl)heptanedioate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.43 (2H, m), 1.35 (9H, s), 1.63-1.74

(2H, m), 2.15-2.34 (4H, m), 2.41 (3H, s), 4.10 (2H, q, J=7Hz), 7.48 (1H, d,

J=8Hz), 7.56 (1H, dd, J=2, 8Hz), 7.88 (1H, d, J=2Hz)

25 Preparation 33

1-tert-Butyl 7-ethyl 2-acetyl-2-[(4-chloro-2-pyridinyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.23-1.30 (3H, m), 1.25 (9H, s), 1.40-1.58 (2H, m), 1.65-1.77 (2H,

m), 2.10-2.21 (2H, m), 2.35 (2H, t, J=7Hz), 2.61 (3H, s), 4.12 (2H, q, J=7Hz),

7.39 (1H, m), 8.04 (1H, m), 8.43 (1H, d, J=5Hz)

30 MS (ESI⁺): m/z 426 (M+H)

Preparation 34

1-tert-Butyl 7-ethyl 2-[(5-chloro-2-thienyl)carbonyl]-2-(methoxyacetyl)heptanedioate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.25-1.40 (2H, m), 1.41 (9H, s), 1.62-1.74

(2H, m), 2.26-2.37 (4H, m), 3.37 (3H, s), 4.11 (2H, q, J=7Hz), 4.30 (1H, d,

J=17Hz), 4.42 (1H, d, J=17Hz), 6.92 (1H, d, J=4Hz), 7.39 (1H, d, J=4Hz)

5

Preparation 35

1-tert-Butyl 7-ethyl 2-acetyl-2-[(6-methoxy-2-pyrazinyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.26 (9H, s), 1.38-1.49 (2H, m), 1.66-1.80

(2H, m), 2.14-2.26 (2H, m), 2.33 (2H, t, J=7Hz), 2.57 (3H, s), 3.90 (3H, s), 4.12

10 (2H, q, J=7Hz), 8.37 (1H, s), 8.83 (1H, s)

Preparation 36

1-tert-Butyl 7-ethyl 2-acetyl-2-(1-benzofuran-2-ylcarbonyl)heptanedioate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.33 (9H, s), 1.38-1.55 (2H, m), 1.64-1.77

15 (2H, m), 2.23-2.36 (4H, m), 2.49 (3H, s), 4.08 (2H, q, J=7Hz), 7.32 (1H, m), 7.46

(2H, m), 7.54 (1H, s), 7.71 (1H, d, J=8Hz)

Preparation 37

1-tert-Butyl 7-ethyl 2-acetyl-2-(1-benzothien-2-ylcarbonyl)heptanedioate

20 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.45 (2H, m), 1.39 (9H, s), 1.62-1.75

(2H, m), 2.25-2.38 (4H, m), 2.40 (3H, s), 4.10 (2H, q, J=7Hz), 7.36-7.51 (2H, m),

7.76 (1H, s), 7.82-7.88 (2H, m)

Preparation 38

25 1-tert-Butyl 7-ethyl 2-acetyl-2-(1,3-oxazol-5-ylcarbonyl)heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.30-1.45 (2H, m), 1.38 (9H, s), 1.63-1.77

(2H, m), 2.15-2.27 (2H, m), 2.30 (2H, t, J=7Hz), 2.43 (3H, s), 4.10 (2H, q,

J=7Hz), 7.80 (1H, s), 7.93 (1H, s)

30 Preparation 39

1-tert-Butyl 7-ethyl 2-acetyl-2-benzoylheptanedioate

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.20-1.40 (2H, m), 1.32 (9H, s), 1.60-1.73

(2H, m), 2.26-2.38 (4H, m), 2.40 (3H, s), 4.12 (2H, q, J=7Hz), 7.36-7.78 (5H, m)

Preparation 40

1-tert-Butyl 7-ethyl 2-acetyl-2-(6-quinolinylcarbonyl)heptanedioate

- 5 NMR (CDCl₃, δ): 1.21 (3H, t, J=7Hz), 1.30 (9H, s), 1.32-1.47 (2H, m), 1.64-1.77 (2H, m), 2.26-2.38 (4H, m), 2.46 (3H, s), 4.08 (2H, q, J=7Hz), 7.48 (1H, m), 8.04 (1H, dd, J=2 Hz, 8Hz), 8.13 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.28 (1H, d, J=2Hz), 9.00 (1H, m)
- MS (ESI⁺): m/z 442 (M+H)

10

Preparation 41

1-tert-Butyl 9-ethyl 2-acetyl-2-[4-({[(benzyloxy)carbonyl]amino}sulfonyl)benzoyl]-nonanedioate

- NMR (CDCl₃, δ): 1.23-1.37 (11H, m), 1.60 (9H, s), 2.15-2.31 (4H, m), 2.46 (3H, s),
- 15 4.12 (2H, q, J=7Hz), 5.10 (2H, s), 7.26-7.40 (5H, m), 7.65 (1H, s, br), 7.84 (2H, d, J=9Hz), 8.06 (2H, d, J=9Hz)

Preparation 42

1-tert-Butyl 7-ethyl 2-acetyl-2-(2-chloroisonicotinoyl)heptanedioate

- 20 NMR (CDCl₃, δ): 1.20-1.40 (14H, m), 1.61-1.75 (2H, m), 2.19-2.28 (2H, m), 2.20 (2H, t, J=8Hz), 2.31 (2H, t, J=8Hz), 2.46 (3H, s), 4.11 (2H, q, J=8Hz), 7.41 (1H, dd, J=7, 1Hz), 7.55 (1H, d, J=1Hz), 8.50 (1H, d, J=7Hz)

Preparation 43

25 1-tert-Butyl 7-ethyl 2-acetyl-2-[3-(methylsulfonyl)benzoyl]heptanedioate

- NMR (CDCl₃, δ): 1.24 (3H, t, J=8Hz), 1.27-1.40 (11H, m), 1.61-1.75 (2H, m), 2.19-2.35 (4H, m), 2.46 (3H, s), 3.07 (3H, s), 4.10 (2H, q, J=8Hz), 7.65 (1H, t, J=8Hz), 7.99 (1H, dd, J=8, 1Hz), 8.09 (2H, br d, J=8Hz), 8.34 (1H, br s)

Preparation 44

1-tert-Butyl 7-ethyl 2-acetyl-2-(3-nitrobenzoyl)heptanedioate

- NMR (CDCl₃, δ): 1.30-1.39 (12H, m), 1.61-1.75 (2H, m), 2.19-2.35 (4H, m),

2.47(3H, s), 4.10 (2H, q, J=8Hz), 7.63 (1H, t, J=8Hz), 8.09 (1H, br d, J=8Hz),
8.39 (1H, br d, J=8Hz), 8.60 (1H, br s)

Preparation 45

5 tert-Butyl 2-acetyl-2-(4-cyanobenzoyl)hexanoate

NMR (CDCl₃, δ): 0.90 (3H, t, J=8Hz), 1.20-1.44 (13H, m), 2.15-2.25 (2H, m), 2.45
(3H, s), 7.70 (2H, d, J=8Hz), 7.83 (2H, d, J=8Hz)

Preparation 46

10 1-tert-Butyl 7-ethyl 2-acetyl-2-[(5-bromo-3-pyridinyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (9H, s), 1.32-1.45 (2H, m), 1.65-1.77
(2H, m), 2.18-2.28 (2H, m), 2.32 (2H, t, J=7Hz), 2.45 (3H, s), 4.11 (2H, q,
J=7Hz), 8.20 (1H, m), 8.80 (2H, m)

MS: (m/z) 470, 472 (M+H)

15

Preparation 47

1-tert-Butyl 7-ethyl 2-(2-chloroisonicotinoyl)-2-[(methylthio)acetyl]heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (9H, s), 1.23-1.45 (2H, m), 1.63-1.77
(2H, m), 2.05 (3H, s), 2.16-2.28 (2H, m), 2.32 (2H, t, J=7Hz), 3.16 (1H, d,
20 J=17Hz), 4.07 (1H, d, J=17Hz), 4.11 (2H, q, J=7Hz), 7.68 (1H, d, J=5Hz), 7.87
(1H, s), 8.49 (1H, d, J=5Hz)

Preparation 48

Ethyl 2-(4-fluorobenzoyl)-3-oxobutanoate

25 NMR (CDCl₃, δ): (mixture of tautomers) 0.97 and 1.02 (3H, t, J=7Hz), 2.07 and 2.42
(3H, s), 4.01 and 4.13 (2H, q, J=7Hz), 7.06-7.18, 7.56, and 7.85 (4H, m)
MS (ESI⁺): m/z 275 (M+H)

Preparation 49

30 1-tert-Butyl 8-ethyl 2-acetyl-2-(3-cyanobenzoyl)octanedioate

NMR (CDCl₃, δ): 1.21-1.46 (16H, m), 1.56-1.70 (2H, m), 2.15-2.25 (2H, m), 2.29
(2H, t, J=8Hz), 2.45 (3H, s), 4.12 (2H, q, J=8Hz), 7.56 (1H, t, J=8Hz), 7.80 (2H,

dd, J=8, 1Hz), 7.95 (2H, dd, J=8, 1Hz), 8.05 (1H, br s)

Preparation 50

1-tert-Butyl 7-ethyl 2-acetyl-2-[(6-chloro-2-pyridinyl)carbonyl]heptanedioate

- 5 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.27 (9H, s), 1.20-1.78 (4H, m), 2.08 (2H, t, J=7Hz), 2.26-2.40 (2H, m), 2.69 (3H, s), 4.12 (2H, q, J=7Hz), 7.43 (1H, d, J=8Hz), 7.81 (1H, t, J=8Hz), 7.96 (1H, d, J=8Hz)
MS (ESI⁺): m/z 426

10 Preparation 51

1-tert-Butyl 7-ethyl 2-acetyl-2-(3-methoxybenzoyl)heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, m), 1.34 (9H, s), 1.20-1.92 (4H, m), 2.10-2.38 (4H, m), 2.41 (3H, s), 3.84 (3H, s), 4.04-4.22 (2H, m), 7.08 (1H, br), 7.23-7.40 (3H, m)

15 Preparation 52

1-tert-Butyl 7-ethyl 2-acetyl-2-(3,5-dichlorobenzoyl)heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.26-1.40 (2H, m), 1.36 (9H, s), 1.63-1.76 (2H, m), 2.15-2.36 (4H, m), 2.43 (3H, s), 4.10 (2H, q, J=7Hz), 7.51 (1H, m), 7.60 (2H, m)

20

Preparation 53

1-tert-Butyl 7-ethyl 2-acetyl-2-[(5-chloro-2-thienyl)carbonyl]heptanedioate

- NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.40 (9H, s), 1.30-1.90 (4H, m), 2.20-2.35 (4H, m), 2.38 (3H, s), 4.11 (2H, q, J=7Hz), 6.91 (1H, d, J=4Hz), 7.32 (1H, d, J=4Hz)
25

Preparation 54

1-tert-Butyl 7-ethyl 2-acetyl-2-(3-fluorobenzoyl)heptanedioate

- NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.35 (9H, s), 1.35-1.45 (2H, m), 1.64-1.74 (2H, m), 2.16-2.35 (4H, m), 2.42 (3H, s), 4.09 (2H, q, J=7Hz), 7.24 (1H, m), 7.35-7.43 (1H, m), 7.46-7.53 (2H, m)
30

Preparation 55

1-tert-Butyl 7-ethyl 2-acetyl-2-(3-quinolinylcarbonyl)heptanedioate

NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.33 (9H, s), 1.33-1.53 (2H, m), 1.65-1.78 (2H, m), 2.25-2.43 (4H, m), 2.47 (3H, s), 4.08 (2H, q, J=7Hz), 7.63 (1H, t, J=8Hz), 7.81-7.87 (1H, t, J=8Hz), 7.91 (1H, d, J=8Hz), 8.56 (1H, m), 9.24 (1H, m)

MS (ESI⁺): m/z 442Preparation 56

10 1-tert-Butyl 7-ethyl 2-acetyl-2-isonicotinoylheptanedioate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.31 (9H, s), 1.30-1.45 (2H, m), 1.65-1.76 (2H, m), 2.18-2.28 (2H, m), 2.31 (2H, t, J=7Hz), 2.45 (3H, s), 4.10 (2H, q, J=7Hz), 7.52 (2H, d, J=7Hz), 8.75 (2H, d, J=7Hz)

15 Preparation 57

1-tert-Butyl 7-ethyl 2-acetyl-2-[(3-methoxy-5-isoxazolyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.39 (9H, s), 1.35-1.50 (2H, m), 1.62-1.75 (2H, m), 2.11-2.23 (2H, m), 2.33 (2H, t, J=7Hz), 2.49 (3H, s), 4.01 (3H, s), 4.11 (2H, q, J=7Hz), 6.53 (1H, s)

20

Preparation 58

1-tert-Butyl 7-ethyl 2-acetyl-2-[(5-methyl-3-isoxazolyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.31-1.48 (2H, m), 1.37 (9H, s), 1.63-1.75 (2H, m), 2.18-2.26 (2H, m), 2.31 (2H, t, J=7Hz), 2.47 (3H, s), 2.50 (3H, s), 4.11 (2H, q, J=7Hz), 6.38 (1H, s)

25

Preparation 59

1-tert-Butyl 7-ethyl 2-(2-chloroisonicotinoyl)-2-(methoxyacetyl)heptanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.32-1.45 (2H, m), 1.36 (9H, s), 1.64-1.78 (2H, m), 2.16-2.28 (2H, m), 2.31 (2H, t, J=7Hz), 3.36 (3H, s), 4.11 (2H, q, J=7Hz), 4.25 (1H, d, J=17Hz), 4.39 (1H, d, J=17Hz), 7.39 (1H, d, J=5Hz), 7.54 (1H, s), 8.50 (1H, d, J=5Hz)

30

MS (ESI⁺): m/z 456

Preparation 60

1-tert-Butyl 7-ethyl 2-(methoxyacetyl)-2-(3-methoxybenzoyl)heptanedioate

5 NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.25-1.33 (2H, m), 1.34 (9H, s), 1.60-1.75
 (2H, m), 2.15-2.40 (4H, m), 3.38 (3H, s), 3.83 (3H, s), 4.08 (2H, q, J=7Hz), 4.39
 (1H, d, J=17Hz), 4.55 (1H, d, J=17Hz), 7.07 (1H, m), 7.26-7.34 (3H, m)

MS (ESI⁺): m/z 451

10 Preparation 61

1-tert-Butyl 7-ethyl 2-(methoxyacetyl)-2-(6-quinolinylcarbonyl)heptanedioate

 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.32 (9H, s), 1.30-1.50 (2H, m), 1.65-1.78
 (2H, m), 2.26-2.44 (4H, m), 3.38 (3H, s), 4.11 (2H, q, J=7Hz), 4.38 (1H, d,
 J=17Hz), 4.57 (1H, d, J=17Hz), 7.47 (1H, m), 8.03 (1H, d, J=8Hz), 8.13 (1H, d,
15 J=8Hz), 8.28 (1H, d, J=8Hz), 8.27 (1H, s), 9.01 (1H, m)

MS (ESI⁺): m/z 472

Preparation 62

1-tert-Butyl 7-ethyl 2-(methoxyacetyl)-2-(3-pyridinylcarbonyl)heptanedioate

20 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.47 (2H, m), 1.35 (9H, s), 1.63-1.78
 (2H, m), 2.22-2.38 (4H, m), 3.37 (3H, s), 4.10 (2H, q, J=7Hz), 4.32 (1H, d,
 J=17Hz), 4.45 (1H, d, J=17Hz), 7.37 (1H, m), 8.03 (1H, m), 8.73 (1H, m), 8.92
 (1H, m)

25 Preparation 63

1-tert-Butyl 7-ethyl 2-(3-chlorobenzoyl)-2-(methoxyacetyl)heptanedioate

 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.35 (9H, s), 1.20-1.50 (2H, m), 1.60-1.73
 (2H, m), 2.25-2.35 (4H, m), 3.37 (3H, s), 4.12 (2H, q, J=7Hz), 4.35 (1H, d,
 J=17Hz), 4.50 (1H, d, J=17Hz), 7.34 (1H, m), 7.48 (1H, d, J=8Hz), 7.59 (1H, d,
30 J=8Hz), 7.73 (1H, m)

Preparation 64

1-tert-Butyl 7-ethyl 2-acetyl-2-(3-methylbenzoyl)heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.30-1.40 (2H, m), 1.33 (9H, s), 1.60-1.72 (2H, m), 2.10-2.38 (4H, m), 2.21 (3H, s), 2.39 (3H, s), 4.10 (2H, q, J=7Hz), 7.26-7.36 (2H, m), 7.48-7.62 (2H, m)

5 MS (ESI⁺): m/z 405

Preparation 67

1-tert-Butyl 7-ethyl 2-(methoxyacetyl)-2-[(5-methyl-3-pyridinyl)carbonyl]heptanedioate

10 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (9H, s), 1.30-1.45 (2H, m), 1.62-1.76 (2H, m), 2.20-2.36 (4H, m), 2.40 (3H, s), 3.38 (3H, s), 4.10 (2H, q, J=7Hz), 4.34 (1H, d, J=17Hz), 4.49 (1H, d, J=17Hz), 7.86 (1H, s), 8.56 (1H, s), 8.73 (1H, s)

MS (ESI⁺): m/z 436

Preparation 68

15 1-tert-Butyl 7-ethyl 2-acetyl-2-[(5-bromo-3-pyridinyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (9H, s), 1.32-1.45 (2H, m), 1.65-1.77 (2H, m), 2.18-2.28 (2H, m), 2.32 (2H, t, J=7Hz), 2.45 (3H, s), 4.11 (2H, q, J=7Hz), 8.20 (1H, m), 8.80 (2H, m)

MS (ESI⁺): m/z 470, 472

20

Preparation 69

1-tert-Butyl 7-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(methoxyacetyl)heptanedioate

25 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.30-1.44 (2H, m), 1.37 (9H, s), 1.65-1.77 (2H, m), 2.18-2.36 (4H, m), 3.36 (3H, s), 4.10 (2H, q, J=7Hz), 4.28 (1H, d, J=17Hz), 4.40 (1H, d, J=17Hz), 8.18 (1H, m), 8.80 (2H, m)

MS (ESI⁺): m/z 500, 502

Preparation 70

1-tert-Butyl 7-ethyl 2-acetyl-2-[(5,6-dichloro-3-pyridinyl)carbonyl]heptanedioate

30 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.25-1.40 (2H, m), 1.38 (9H, s), 1.65-1.75 (2H, m), 2.18-2.27 (2H, m), 2.28-2.37 (2H, m), 2.44 (3H, s), 4.12 (2H, q, J=7Hz), 8.13 (1H, d, J=2Hz), 8.57 (1H, d, J=2Hz)

Preparation 71

1-tert-Butyl 6-ethyl 2-(methoxyacetyl)-2-[(5-methyl-3-pyridinyl)carbonyl]hexanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.36 (9H, s), 1.60-1.80 (2H, m), 2.20-2.45
5 (4H, m), 2.39 (3H, s), 3.38 (3H, s), 4.12 (2H, q, J=7Hz), 4.38 (1H, d, J=18Hz),
4.50 (1H, d, J=18Hz), 7.87 (1H, s), 8.55 (1H, s), 8.73 (1H, s)
MS (ESI⁺): m/z 422

Preparation 72

10 1-tert-Butyl 5-ethyl 2-(methoxyacetyl)-2-[(5-methyl-3-pyridinyl)carbonyl]pentanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (9H, s), 2.23-2.70 (4H, m), 2.39 (3H, s),
3.37 (3H, s), 4.12 (2H, q, J=7Hz), 4.32 (1H, d, J=18Hz), 4.43 (1H, d, J=18Hz),
7.84 (1H, s), 8.55 (1H, s), 8.73 (1H, s)
MS (ESI⁺): m/z 408

15

Preparation 73

1-tert-Butyl 6-ethyl 2-acetyl-2-[(5-methyl-3-pyridinyl)carbonyl]hexanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.34 (9H, s), 1.60-1.75 (2H, m), 2.20-2.39
(4H, m), 2.39 (3H, s), 2.46 (3H, s), 4.11 (2H, q, J=7Hz), 7.87 (1H, s), 8.56 (1H, s),
20 8.73 (1H, s)
MS (ESI⁺): m/z 392

Preparation 74

1-tert-Butyl 5-ethyl 2-acetyl-2-[(5-methyl-3-pyridinyl)carbonyl]pentanedioate

25 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.36 (9H, s), 2.39 (3H, s), 2.44 (3H, s), 2.35-
2.47 (2H, m), 2.56-2.70 (2H, m), 4.11 (2H, q, J=7Hz), 7.88 (1H, s), 8.56 (1H, s),
8.74 (1H, s)
MS (ESI⁺): m/z 378

30 Preparation 75

1-tert-Butyl 5-ethyl 2-acetyl-2-[(5-bromo-3-pyridinyl)carbonyl]pentanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (9H, s), 2.40 (2H, t, J=7Hz), 2.59 (2H, t,

J=7Hz), 2.46 (3H, s), 4.13 (2H, q, J=7Hz), 8.20 (1H, t, J=3Hz), 8.81 (2H, dd, J=7, 3Hz)

Preparation 76

5 1-tert-Butyl 7-ethyl 2-(3-cyanobenzoyl)-2-(methoxyacetyl)heptanedioate

NMR (CDCl₃, δ): 1.20-1.41 (14H, m), 1.60-1.74 (2H, m), 2.27-2.34 (4H, m), 3.37 (83H, s), 4.10 (2H, q, J=8Hz), 4.29 (1H, d, J=16Hz), 4.46 (1H, d, J=16Hz), 7.55 (1H, t, J=8Hz), 7.80 (1H, dd, J=8, 1Hz), 7.93 (1H, dd, J=8, 1Hz), 8.04 (1H, br s)

10 Preparation 77

1-tert-Butyl 7-ethyl 2-[(acetyloxy)acetyl]-2-[(5-bromo-3-pyridinyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.22-1.28 (5H, m), 1.36 (9H, s), 1.68 (2H, m), 2.14 (3H, s), 2.32 (2H, m), 4.11 (2H, q, J=7Hz), 5.07 (1H, d, J=18Hz), 5.34 (1H, d, J=18Hz), 8.21 (1H, m), 8.81 (2H, m)

15

Preparation 78

To 1-tert-butyl 7-ethyl 2-acetyl-2-(3-cyanobenzoyl)-heptanedioate (4.2 g) was added trifluoroacetic acid (20 mL) in an ice-water bath. After 30 minutes, the bath was removed and the reaction mixture was stirred at ambient temperature. After 1 hour, the mixture was concentrated. The residue was dissolved in toluene and was evaporated in vacuo to give ethyl 6-(3-cyanobenzoyl)-7-oxooctanoate (3.20 g, 100.4%) as colorless oil.

20

25 Ethyl 6-(3-cyanobenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=8Hz), 1.28-1.40 (2H, m), 1.60-1.74 (2H, m), 1.91-2.14 (2H, m), 2.17 (3H, s), 2.31 (2H, t, J=8Hz), 4.11 (2H, q, J=8Hz), 4.39 (1H, t, J=8Hz), 7.64 (1H, t, J=8Hz), 7.87 (2H, dd, J=8, 1Hz), 8.20 (2H, dd, J=8, 1Hz), 8.26 (1H, br s)

30

MS (ESI): m/z 314 (M-H)

The following compounds were obtained in substantially the same manner as that

of Preparation 78.

Preparation 79

Ethyl 7-oxo-6-[3-(trifluoromethyl)benzoyl]octanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.32-1.43 (2H, m), 1.62-1.77 (2H, m), 1.96-
 5 2.17 (2H, m), 2.17 (3H, s), 2.30 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.44 (1H, t,
 J=7Hz), 7.64 (1H, t, J=8Hz), 7.86 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz), 8.24 (1H,
 s)

Preparation 80

10 Ethyl 6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.27-1.44 (2H, m), 1.65-1.75 (2H, m), 1.90-
 2.12 (2H, m), 2.17 (3H, s), 2.25-2.34 (2H, m), 2.43 (3H, s), 4.10 (2H, q, J=7Hz),
 4.42 (1H, t, J=7Hz), 8.03 (1H, s), 8.63 (1H, s), 8.98 (1H, s)

MS (ESI⁺): m/z 306 (M+H)

15

Preparation 81

Ethyl 8-methoxy-6-[(3-methoxy-5-isoxazolyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.34-1.47 (2H, m), 1.65-1.74 (2H, m), 1.83-
 2.03 (2H, m), 2.29 (2H, t, J=7Hz), 3.31 (3H, s), 4.05 (5H, s), 4.11 (2H, q, J=7Hz),
 20 4.51 (1H, t, J=7Hz), 6.56 (1H, s)

MS (ESI⁺): m/z 342 (M+H)

Preparation 82

Ethyl 6-[3-(1,3-oxazol-5-yl)benzoyl]-7-oxooctanoate

25 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.33-1.46 (2H, m), 1.63-1.77 (2H, m), 1.95-
 2.17 (2H, m), 2.17 (3H, s), 2.30 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.46 (1H, t,
 J=7Hz), 7.47 (1H, s), 7.56 (1H, t, J=8Hz), 7.85-7.96 (2H, m), 7.98 (1H, s), 8.27
 (1H, m)

30 Preparation 83

Ethyl 6-(3,4-dichlorobenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.30-1.43 (2H, m), 1.60-1.74 (2H, m), 1.91-

2.14 (2H, m), 2.14 (3H, s), 2.30 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.34 (1H, t, J=7Hz), 7.57 (1H, d, J=8Hz), 7.78 (1H, dd, J=2, 8Hz), 8.06 (1H, d, J=2Hz)

Preparation 84

5 Ethyl 6-[(4-chloro-2-pyridinyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.34-1.48 (2H, m), 1.62-1.77 (2H, m), 1.80-2.10 (2H, m), 2.31 (2H, t, J=7Hz), 2.34 (3H, s), 4.12 (2H, q, J=7Hz), 4.83-4.92 (1H, m), 7.49 (1H, dd, J=2 Hz, 5Hz), 8.04 (1H, d, J=2Hz), 8.57 (1H, d, J=5Hz)
MS (ESI⁺): m/z 326 (M+H)

10

Preparation 85

Ethyl 6-[(5-chloro-2-thienyl)carbonyl]-8-methoxy-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.32-1.42 (2H, m), 1.60-1.73 (2H, m), 1.84-2.06 (2H, m), 2.28 (2H, t, J=7Hz), 3.30 (3H, s), 3.97 (1H, d, J=17Hz), 4.06 (1H, d, J=17Hz), 4.11 (2H, q, J=7Hz), 4.40 (1H, t, J=7Hz), 6.99 (1H, d, J=4Hz), 7.56 (1H, d, J=4Hz)

15

Preparation 86

Ethyl 6-[(6-methoxy-2-pyrazinyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.34-1.48 (2H, m), 1.60-1.78 (2H, m), 1.88-2.08 (2H, m), 2.31 (3H, s), 2.32 (2H, t, J=7Hz), 4.01 (3H, s), 4.11 (2H, q, J=7Hz), 4.62 (1H, t, J=7Hz), 8.44 (1H, s), 8.81 (1H, s)
MS (ESI⁺): m/z 323 (M+H)

20

25 Preparation 87

Ethyl 6-(1-benzofuran-2-ylcarbonyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.34-1.48 (2H, m), 1.62-1.76 (2H, m), 1.93-2.19 (2H, m), 2.24 (3H, s), 2.30 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 4.37 (1H, t, J=7Hz), 7.34 (1H, t, J=8Hz), 7.51 (1H, t, J=8Hz), 7.56-7.65 (2H, m), 7.73 (1H, d, J=8Hz)
MS (ESI⁺): m/z 895 (M+H)

30

Preparation 88

Ethyl 6-(1-benzothien-2-ylcarbonyl)-7-oxooctanoate

5 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.35-1.48 (2H, m), 1.60-1.80 (2H, m), 1.95-2.17 (2H, m), 2.19 (3H, s), 2.30 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 4.36 (1H, t, J=7Hz), 7.38-7.53 (2H, m), 7.82-7.93 (2H, m), 8.05 (1H, s)

Preparation 89

Ethyl 6-(1,3-oxazol-5-ylcarbonyl)-7-oxooctanoate

10 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.30-1.43 (2H, m), 1.65-1.78 (2H, m), 1.92-2.10 (2H, m), 2.21 (3H, s), 2.32 (2H, t, J=7Hz), 4.11 (3H, m), 7.88 (1H, s), 8.05 (1H, s)

Preparation 90

Ethyl 6-benzoyl-7-oxooctanoate

15 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.29-1.42 (2H, m), 1.60-1.75 (2H, m), 1.92-2.12 (2H, m), 2.14 (3H, s), 2.29 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 4.43 (1H, t, J=7Hz), 7.42-7.53 (2H, m), 7.55-7.64 (1H, m), 7.98 (2H, d, J=8Hz)

Preparation 91

20 Ethyl 7-oxo-6-(6-quinolinylcarbonyl)octanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.36-1.48 (2H, m), 1.65-1.78 (2H, m), 2.00-2.18 (2H, m), 2.18 (3H, s), 2.30 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 4.58 (1H, t, J=8Hz), 7.54 (1H, m), 8.18 (1H, d, J=8Hz), 8.28 (1H, dd, J=2 Hz, 8Hz), 8.32 (1H, d, J=8Hz), 8.51 (1H, d, J=2Hz), 9.05 (1H, m)

25 MS (ESI⁺): m/z 342 (M+H)

Preparation 92

Ethyl 8-[4-({[(benzyloxy)carbonyl]amino}sulfonyl)benzoyl]-9-oxodecanoate

30 NMR (CDCl₃, δ): 1.23-1.37 (9H, m), 1.55-1.68 (11H, s), 2.01 (2H, m), 2.18 (3H, s), 2.29 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.39 (1H, t, J=7Hz), 5.11 (2H, s), 7.30-7.49 (5H, m), 7.74 (1H, s, br), 8.04-8.13 (4H, m)

MS (ESI): m/z 530 (M-H)

Preparation 93

Ethyl 7-(1,3-oxazol-5-yl)-7-oxoheptanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.41 (2H, m), 1.76 (2H, m), 2.03 (2H, m),
5 2.31 (2H, m), 3.20 (2H, m), 4.10 (2H, q, J=7Hz), 7.94 (1H, s), 8.10 (1H, s)

Preparation 94

Ethyl 6-[3-(methylsulfonyl)benzoyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=8Hz), 1.59-1.64 (2H, m), 1.91-2.15 (2H, m), 2.18
10 (3H, s), 2.30 (2H, t, J=8Hz), 3.11 (3H, s), 4.10 (2H, q, J=8Hz), 4.45 (1H, t,
J=8Hz), 7.23 (1H, t, J=8Hz), 8.17 (1H, dd, J=8, 1Hz), 8.25 (2H, br d, J=8Hz),
8.53 (1H, br s)

MS (ESI⁺): m/z 369 (M+H)15 Preparation 95

Ethyl 6-(2-chloroisonicotinoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=8Hz), 1.30-1.40 (2H, m), 1.60-1.71 (2H, m), 1.90-
2.14 (2H, m), 2.27 (3H, s), 2.25-2.74 (2H, m), 4.11 (2H, q, J=8Hz), 4.32 (1H, t,
J=8Hz), 7.15 (1H, dd, J=7, 1Hz), 7.76 (1H, d, J=1Hz), 8.09 (1H, d, J=7Hz)
20 MS (ESI⁺): m/z 326 (M+H)

Preparation 96

Ethyl 6-(3-nitrobenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=8Hz), 1.29-1.41 (2H, m), 1.60-1.74 (2H, m), 1.91-
25 2.16 (2H, m), 2.19 (3H, s), 2.30 (2H, t, J=8Hz), 4.11 (2H, q, J=8Hz), 4.46 (1H, t,
J=8Hz), 7.71 (1H, t, J=8Hz), 8.30 (1H, br d, J=8Hz), 8.45 (4H, br d, J=8Hz), 8.80
(1H, br s)

MS (ESI⁺): m/z 337 (M+H)30 Preparation 97

4-(2-Acetylhexanoyl)benzonitrile

NMR (CDCl₃, δ): 0.90 (3H, t, J=8Hz), 1.18-1.44 (4H, m), 1.90-2.12 (2H, m), 2.17

(3H, s), 4.40 (1H, t, J=8Hz), 7.80 (2H, d, J=8Hz), 8.08 (2H, d, J=8Hz)

MS (ESI): m/z 242 (M-H)

Preparation 98

5 Ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.32-1.43 (2H, m), 1.60-1.76 (2H, m), 1.96-2.15 (2H, m), 2.19 (3H, s), 2.30 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.36 (1H, t, J=7Hz), 8.37 (1H, s), 8.87 (1H, br), 9.07 (1H, br)

MS: (m/z) 370, 372 (M+H)

10

Preparation 99

Ethyl 6-(2-chloroisonicotinoyl)-8-(methylthio)-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.34-1.47 (2H, m), 1.60-1.77 (2H, m), 1.92 (3H, s), 1.93-2.05 (2H, m), 2.30 (2H, t, J=7Hz), 3.19 (1H, d, J=17Hz), 3.26 (1H, d, J=17Hz), 4.11 (2H, q, J=7Hz), 4.68 (1H, t, J=7Hz), 7.72 (1H, d, J=5Hz), 7.86 (1H, s), 8.57 (1H, d, J=5Hz)

15

MS: (m/z) 370 (M-H), 372 (M+H)

Preparation 100

20 Ethyl 7-(3-cyanobenzoyl)-8-oxononanoate

NMR (CDCl₃, δ): 1.21-1.44 (7H, m), 1.55-1.69 (2H, m), 1.89-2.15 (2H, m), 2.17 (3H, s), 2.29 (2H, t, J=8Hz), 4.12 (2H, q, J=8Hz), 4.39 (1H, t, J=8Hz), 7.64 (1H, t, J=8Hz), 7.87 (1H, dd, J=8, 1Hz), 8.20 (1H, dd, J=8, 1Hz), 8.27 (1H, br s)

MS (ESI⁺): m/z 330 (M+H)

25

Preparation 101

Ethyl 6-[(6-chloro-2-pyridinyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.36-1.52 (2H, m), 1.63-1.75 (2H, m), 1.77-2.06 (2H, m), 2.29 (2H, t, J=7Hz), 2.45 (3H, s), 4.12 (2H, q, J=7Hz), 4.82 (1H, t, J=7Hz), 7.51 (1H, d, J=8Hz), 7.82 (1H, t, J=8Hz), 7.97 (1H, d, J=8Hz)

30

MS (ESI⁺): m/z 326

Preparation 102

Ethyl 6-(3-methoxybenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.30-1.43 (2H, m), 1.60-1.77 (2H, m), 1.92-2.12 (2H, m), 2.15 (3H, s), 2.31 (2H, t, J=7Hz), 3.88 (3H, s), 4.12 (2H, q, J=7Hz), 4.42 (1H, t, J=7Hz), 7.14 (1H, dd, J=2Hz, 8Hz), 7.40 (1H, t, J=8Hz), 7.46-7.58 (2H, m)

MS (ESI⁺): m/z 321

Preparation 103

10 Ethyl 6-(3,5-dichlorobenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.32-1.42 (2H, m), 1.63-1.75 (2H, m), 1.90-2.12 (2H, m), 2.16 (3H, s), 2.30 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.32 (1H, t, J=7Hz), 7.58 (1H, m), 7.82 (2H, m)

15 Preparation 104

Ethyl 6-[(5-chloro-2-thienyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.30-1.40 (2H, m), 1.62-1.74 (2H, m), 1.90-2.12 (2H, m), 2.16 (3H, s), 2.29 (2H, t, J=7Hz), 4.13 (2H, q, J=7Hz), 4.14 (1H, m), 6.98 (1H, d, J=4Hz), 7.58 (1H, d, J=4Hz)

20

Preparation 105

Ethyl 6-(3-fluorobenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.28-1.42 (2H, m), 1.60-1.75 (2H, m), 1.90-2.13 (2H, m), 2.14 (3H, s), 2.29 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.37 (1H, t, J=7Hz), 7.26-7.33 (1H, m), 7.43-7.52 (1H, m), 7.63-7.68 (1H, m), 7.76 (1H, d, J=8Hz)

MS (ESI⁺): m/z 309

25

Preparation 106

30 Ethyl 7-oxo-6-(3-quinolinylcarbonyl)octanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.35-1.47 (2H, m), 1.63-1.77 (2H, m), 1.98-2.18 (2H, m), 2.20 (3H, s), 2.31 (2H, t, J=7Hz), 4.10 (2H, q, J=7Hz), 4.55 (1H, t,

J=7Hz), 7.66 (1H, t, J=8Hz), 7.87 (1H, t, J=8Hz), 7.97 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.78 (1H, d, J=2Hz), 9.43 (1H, d, J=2Hz)

MS (ESI⁺): m/z 342

5 Preparation 107

Ethyl 6-isonicotinoyl-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.26-1.45 (2H, m), 1.60-1.75 (2H, m), 1.94-2.07 (2H, m), 2.17 (3H, s), 2.27-2.35 (2H, m), 4.11 (2H, q, J=7Hz), 4.38 (1H, t, J=7Hz), 7.74 (2H, m), 8.83 (2H, m)

10

Preparation 108

Ethyl 6-[(3-methoxy-5-isoxazolyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.33-1.45 (2H, m), 1.60-1.80 (2H, m), 1.88-2.05 (2H, m), 2.28 (3H, s), 2.30-2.45 (2H, m), 4.03 (3H, s), 4.11 (2H, q, J=7Hz), 4.33 (1H, t, J=7Hz), 6.56 (1H, s)

15

MS (ESI⁺): m/z 312

Preparation 109

Ethyl 6-[(5-methyl-3-isoxazolyl)carbonyl]-7-oxooctanoate

20 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.32-1.44 (2H, m), 1.61-1.74 (2H, m), 1.85-2.07 (2H, m), 2.26-2.38 (2H, m), 2.29 (3H, s), 2.49 (3H, s), 4.11 (2H, q, J=7Hz), 4.64 (1H, m), 6.39 (1H, s)

MS (ESI⁺): m/z 296

25 Preparation 110

Ethyl 6-(2-chloroisonicotinoyl)-8-methoxy-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.28-1.43 (2H, m), 1.66 (2H, t, J=7Hz), 1.73-1.86 (1H, m), 1.93-2.07 (1H, m), 2.73 (2H, t, J=7Hz), 3.23 (3H, s), 3.89 (1H, d, J=17Hz), 4.00 (1H, d, J=17Hz), 4.10 (2H, q, J=7Hz), 4.58 (1H, t, J=7Hz), 7.66 (1H, d, J=5Hz), 7.78 (1H, s), 8.60 (1H, d, J=5Hz)

30

MS (ESI⁺): m/z 356, MS (ESI): m/z 354

Preparation 111

Ethyl 8-methoxy-6-(3-methoxybenzoyl)-7-oxooctanoate

5 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.30-1.43 (2H, m), 1.60-1.73 (2H, m), 1.79-2.04 (2H, m), 2.28 (2H, t, J=7Hz), 3.27 (3H, s), 3.87 (3H, s), 4.00 (2H, m), 4.12 (2H, q, J=7Hz), 4.66 (1H, t, J=7Hz), 7.13 (1H, m), 7.39 (1H, m), 7.45-7.55 (2H, m)

Preparation 112

Ethyl 8-methoxy-7-oxo-6-(6-quinolinylcarbonyl)octanoate

10 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.34-1.47 (2H, m), 1.60-1.75 (2H, m), 1.86-2.10 (2H, m), 2.27 (2H, t, J=7Hz), 3.24 (3H, s), 4.02-4.10 (2H, m), 4.12 (2H, q, J=7Hz), 4.83 (1H, t, J=7Hz), 7.48-7.55 (1H, m), 8.16-8.33 (3H, m), 8.49 (1H, m), 9.02 (1H, m)

MS (ESI⁺): m/z 372

15

Preparation 113

Ethyl 8-methoxy-7-oxo-6-(3-pyridinylcarbonyl)octanoate

20 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.31-1.45 (2H, m), 1.60-1.73 (2H, m), 1.75-2.08 (2H, m), 2.28 (2H, t, J=7Hz), 3.24 (3H, s), 3.94 (1H, d, J=17Hz), 4.00 (1H, d, J=17Hz), 4.10 (2H, q, J=7Hz), 4.67 (1H, t, J=7Hz), 7.44 (1H, m), 8.22 (1H, m), 8.81 (1H, d, J=5Hz), 9.18 (1H, m)

MS (ESI⁺): m/z 322Preparation 114

25 Ethyl 6-(3-chlorobenzoyl)-8-methoxy-7-oxooctanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.44 (2H, m), 1.60-1.74 (2H, m), 1.75-1.92 (1H, m), 1.94-2.10 (1H, m), 2.28 (2H, t, J=7Hz), 3.25 (3H, s), 3.93 (1H, d, J=17Hz), 4.02 (1H, d, J=17Hz), 4.12 (2H, q, J=7Hz), 4.63 (1H, t, J=7Hz), 7.43 (1H, t, J=8Hz), 7.57 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 7.94 (1H, s)

30

Preparation 115

Ethyl 6-(3-methylbenzoyl)-7-oxooctanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.29-1.42 (2H, m), 1.60-1.73 (2H, m), 1.90-2.06 (2H, m), 2.13 (3H, s), 2.28 (2H, t, J=7Hz), 2.42 (3H, s), 4.10 (2H, q, J=7Hz), 4.42 (1H, t, J=7Hz), 7.31-7.43 (2H, m), 7.73-7.78 (2H, m)

5 Preparation 118

Ethyl 8-methoxy-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.47 (2H, m), 1.60-1.74 (2H, m), 1.75-1.93 (1H, m), 1.93-2.08 (1H, m), 2.26 (2H, t, J=7Hz), 2.43 (3H, s), 3.25 (3H, s), 3.95 (1H, d, J=17Hz), 4.03 (1H, d, J=17Hz), 4.12 (2H, q, J=7Hz), 4.67 (1H, t, J=7Hz), 8.03 (1H, s), 8.63 (1H, s), 8.98 (1H, s)
10 MS (ESI⁺): m/z 336

Preparation 119

Ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-7-oxooctanoate

15 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.32-1.43 (2H, m), 1.60-1.76 (2H, m), 1.96-2.15 (2H, m), 2.19 (3H, s), 2.30 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.36 (1H, t, J=7Hz), 8.37 (1H, s), 8.87 (1H, br), 9.07 (1H, br)
MS (ESI⁺): m/z 370, 372

20 Preparation 120

Ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-8-methoxy-7-oxooctanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.47 (2H, m), 1.60-1.72 (2H, m), 1.75-1.93 (1H, m), 1.95-2.08 (1H, m), 2.27 (2H, t, J=7Hz), 3.25 (3H, s), 3.93 (1H, d, J=17Hz), 4.02 (1H, d, J=17Hz), 4.10 (2H, q, J=7Hz), 4.63 (1H, t, J=7Hz), 8.38
25 (1H, m), 8.88 (1H, m), 9.07 (1H, m)
MS (ESI⁺): m/z 400, 402

Preparation 121

Ethyl 6-[(5,6-dichloro-3-pyridinyl)carbonyl]-7-oxooctanoate

30 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.30-1.43 (2H, m), 1.60-1.77 (2H, m), 1.95-2.17 (2H, m), 2.19 (3H, s), 2.30 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.32 (1H, t, J=7Hz), 8.31 (1H, d, J=2Hz), 8.82 (1H, d, J=2Hz)

Preparation 122

Ethyl 7-methoxy-5-[(5-methyl-3-pyridinyl)carbonyl]-6-oxoheptanoate

5 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.60-1.75 (2H, m), 1.78-1.95 (1H, m), 1.95-2.12 (1H, m), 2.32 (2H, t, J=7Hz), 2.44 (3H, s), 3.25 (3H, s), 3.94 (1H, d, J=18Hz), 4.02 (1H, d, J=18Hz), 4.12 (2H, q, J=7Hz), 4.69 (1H, t, J=7Hz), 8.04 (1H, s), 8.63 (1H, s), 9.00 (1H, s)

MS (ESI⁺): m/z 322

10 Preparation 123

Ethyl 6-methoxy-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 2.08-2.55 (4H, m), 2.44 (3H, s), 3.23 (3H, s), 3.94 (1H, d, J=18Hz), 4.01 (1H, d, J=18Hz), 4.12 (2H, q, J=7Hz), 4.88 (1H, m), 8.12 (1H, s), 8.64 (1H, s), 9.04 (1H, s)

15 MS (ESI⁺): m/z 308

Preparation 124

Ethyl 5-[(5-methyl-3-pyridinyl)carbonyl]-6-oxoheptanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.60-1.75 (2H, m), 1.96-2.13 (2H, m), 2.18 (3H, s), 2.36 (2H, t, J=7Hz), 2.43 (3H, s), 4.12 (2H, q, J=7Hz), 4.43 (1H, t, J=7Hz), 8.04 (1H, s), 8.63 (1H, s), 8.97 (1H, s)

20 MS (ESI⁺): m/z 292

Preparation 125

25 Ethyl 4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 2.20 (3H, s), 2.26-2.48 (4H, m), 2.43 (3H, s), 4.13 (2H, q, J=7Hz), 4.62 (1H, t, J=7Hz), 8.08 (1H, s), 8.64 (1H, s), 9.02 (1H, s)

MS (ESI⁺): m/z 278

30 Preparation 126

Ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-5-oxohexanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 2.26 (3H, s), 2.30 (2H, t, J=7Hz), 2.43 (2H, t,

J=7Hz), 4.15 (2H, q, J=7Hz), 8.65(1H, s), 8.94 (1H, s), 9.22(1H, s)

Preparation 127

Ethyl 6-(3-cyanobenzoyl)-8-methoxy-7-oxooctanoate

- 5 NMR (CDCl₃, δ): 1.19-1.43 (12H, m), 1.57-1.70 (2H, m), 1.80 (1H, m), 1.99 (1H, m),
2.28 (2H, t, J=8Hz), 3.24 (3H, s), 3.91 (1H, d, J=16Hz), 4.01 (1H, d, J=16Hz),
4.09 (2H, q, J=8Hz), 4.65 (1H, t, J=8Hz), 7.64 (1H, t, J=8Hz), 7.87 (1H, dd, J=8,
1Hz), 8.18 (1H, dd, J=8, 1Hz), 8.25 (1H, br s)

10 Preparation 128

Ethyl 8-(acetyloxy)-6-[(5-bromo-3-pyridinyl)carbonyl]-7-oxooctanoate

- NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.37 (2H, m), 1.67 (2H, m), 1.98-2.06 (5H, m),
2.30 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.47 (1H, t, J=7Hz), 4.66 (d, J=17Hz),
4.74 (d, J=17Hz), 8.37 (1H, m), 8.88 (1H, m), 9.06 (1H, m)

15

Preparation 129

- To a solution of Meldrum's acid (30 g, 0.208 mol) in dichloromethane (420 mL) was added pyridine (33.7 mL, 0.416 mol) over 3 minutes in an ice-methanol bath under nitrogen atmosphere (-9°C). To this mixture was added dropwise a solution of
20 methoxyacetyl chloride (24.8 g) in dichloromethane (180 mL) over 1 hour period at the temperature. After addition, the reaction mixture was stirred at the temperature for 1 hour and at ambient temperature for 2 hours. The mixture was quenched with 1N hydrochloric acid (600 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine,
25 dried over magnesium sulfate, and evaporated in vacuo to give 5-(methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione as dark orange oil (38.1 g, 84.7%).

5-(Methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione

NMR (CDCl₃, δ): 1.75 (6H, s), 3.53 (3H, s), 4.87 (2H, s)

30

Preparation 130

A solution of 5-(methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (38 g) in

tert-butanol (120 mL) and toluene (120 mL) was refluxed for 2 hours under nitrogen atmosphere. The mixture was evaporated in vacuo to give brown oil (32.5 g). The residue was dissolved in hexane-ethyl acetate = 2-1 (200 mL) and was added silica gel (65 g) therein. After stirring for 30 minutes at ambient temperature, the mixture was
5 filtered and washed with hexane-ethyl acetate = 2-1 (200 mL). The filtrate was concentrated in vacuo to give tert-butyl 4-methoxy-3-oxobutanoate as pale yellow oil (30.1 g, 91.0%).

tert-Butyl 4-methoxy-3-oxobutanoate

10 NMR (CDCl₃, δ): 1.50 (9H, s), 3.41 (2H, s), 3.43 (3H, s), 4.08 (2H, s)

Preparation 131

To a mixture of 3-formylbenzoic acid (500 mg) and p-toluenesulfonylmethyl isocyanide (715 mg) in methanol (20 mL) was added potassium carbonate (1.38 g) and
15 the mixture was heated under reflux for 2 hours. After evaporation of solvent, the residue was partitioned between ethyl acetate and water. The aqueous layer was separated and acidified with 1N hydrochloric acid. The resulting precipitates were collected and washed with water, methanol and ether to give 3-(1,3-oxazol-5-yl)benzoic acid as a colorless amorphous powder (484 mg).

20

3-(1,3-Oxazol-5-yl)benzoic acid

NMR (DMSO-d₆, δ): 7.63 (1H, t, J=8Hz), 7.84 (1H, s), 7.89-8.02 (2H, m), 8.25 (1H, m), 8.50 (1H, s), 13.22 (1H, br)

MS (ESI⁺): m/z 188 (M-H)

25

Preparation 132

A mixture of 1-(3-chlorophenyl)-1,3-butanedione (500 mg), 5-(iodomethyl)-2,2-dimethyl-1,3-dioxane (716 mg), and potassium carbonate (351 mg) in dimethylsulfoxide (2.5 mL) was stirred for 14 hours at room temperature and 7 hours at 40°C. The mixture
30 was partitioned between ethyl acetate (20 mL) and water (10 mL). The organic layer was washed with water (10 x 2 mL) and brine, dried over magnesium sulfate, and evaporated to give a brown oil. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-10 to 2-5 afforded 1-(3-chlorophenyl)-2-[(2,2-dimethyl-1,3-dioxan-5-

yl)methyl]-1,3-butanedione as a yellow oil (614 mg).

1-(3-Chlorophenyl)-2-[(2,2-dimethyl-1,3-dioxan-5-yl)methyl]-1,3-butanedione

NMR (CDCl₃, δ): 1.39 (6H, s), 1.70 (1H, m), 1.91-2.15 (2H, m), 2.16 (3H, s), 3.61
5 (2H, m), 3.88 (2H, m), 4.46 (1H, t, J=7Hz), 7.44 (1H, t, J=9Hz), 7.57 (1H, m),
7.86 (1H, d, J=9Hz), 7.96 (1H, m)

The following compounds were obtained in substantially the same manner as that of Preparation 132.

10 Preparation 133

1-tert-Butyl 7-ethyl 2-(1,3-oxazol-5-ylcarbonyl)heptanedioate

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.32-1.38 (11H, m), 1.67 (2H, m), 1.97 (2H,
m), 2.30 (2H, m), 3.86 (1H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 7.86 (1H, s), 8.03 (1H,
s)

15

Preparation 134

1-tert-Butyl 7-ethyl 2-[(3,5-dimethyl-4-isoxazolyl)carbonyl]heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.33-1.41 (11H, m), 1.64 (2H, m), 1.93 (2H,
m), 2.30 (2H, m), 2.47 (3H, s), 2.69 (2H, s), 3.79 (1H, t, J=7Hz), 4.12 (2H, q,
20 J=7Hz)

Preparation 135

To a suspension of magnesium chloride (1.46 g) in tetrahydrofuran (10 ml) was added a solution of ethyl 3-oxo-4-phenylbutanoate (2.0 g) in tetrahydrofuran (10 ml) and
25 the mixture was cooled to 0°C, then pyridine (2.5 ml) was added. The mixture was stirred at 20°C for 30 minutes, then a solution of 4-fluorobenzoyl chloride (2.44 g) in tetrahydrofuran (10 ml) was added at 0°C. After stirring at 20°C for 2 hours, the mixture was partitioned between 0.5N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated.
30 The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give ethyl 2-(4-fluorobenzoyl)-3-oxo-4-phenylbutanoate (2.15 g) as an oil.

Ethyl 2-(4-fluorobenzoyl)-3-oxo-4-phenylbutanoate

(mixture of tautomers, too complicated to be assigned)

Preparation 136

- 5 A mixture of 1-(4-fluorophenyl)butane-1,3-dione (1.0 g), potassium carbonate (3.42 g), and tetrabutylammonium bromide (20 mg) in toluene (10 ml) was refluxed for 3 hours. After cooling to 20°C, ethyl bromoacetate (0.74 ml) was added to the mixture. After being allowed to stand at 20°C overnight, the mixture was partitioned between ethyl acetate and 0.5N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was
- 10 chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give ethyl 3-(4-fluorobenzoyl)-4-oxopentanoate (964 mg) as an oil.

Ethyl 3-(4-fluorobenzoyl)-4-oxopentanoate

- 15 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 2.18 (3H, s), 3.01 (2H, d, J=7Hz), 4.12 (2H, q, J=7Hz), 4.95 (1H, d, J=7Hz), 7.18 (2H, dt, J=2, 7Hz), 8.07 (2H, ddd, J=2, 5, 7Hz)

Preparation 137

- 20 A mixture of 1-(4-fluorophenyl)butane-1,3-dione (1.0 g), potassium carbonate (3.84 g), and tetrabutylammonium bromide (90 mg) in toluene (20 ml) was refluxed for 3 hours, then ethyl 6-bromohexanoate (1.18 ml) was added. After stirring at 100°C for 3 hours, the mixture was partitioned between ethyl acetate and 0.5N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of
- 25 ethyl acetate and hexane (1:5) to give ethyl 7-(4-fluorobenzoyl)-8-oxononanoate (983 mg) as an oil.

Ethyl 7-(4-fluorobenzoyl)-8-oxononanoate

- 30 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.25-1.45 (4H, m), 1.55-1.70 (2H, m), 1.90-2.10 (2H, m), 2.13 (3H, s), 2.27 (2H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.37 (1H, t, J=7Hz), 7.16 (2H, t, J=9Hz), 8.02 (2H, dd, J=5, 9Hz)

Preparation 138

A mixture of pentane-2,4-dione (5.0 g), ethyl 7-bromoheptanoate (11.1 g), potassium carbonate (13.8 g), and cesium carbonate (1.63 g) in a mixture of acetonitrile (150 ml) and dimethylsulfoxide (30 ml) was stirred at 20°C overnight, then pentane-2,4-dione (5 g) was added. After stirring at 20°C overnight, the mixture was partitioned
5 between ethyl acetate and 0.5N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give ethyl 8-acetyl-9-oxodecanoate (5.5 g) as an oil.

10 Ethyl 7-acetyl-8-oxononanoate
(mixture of tautomers, too complicated to be assigned)

Preparation 139

To a mixture of ethyl 7-acetyl-8-oxononanoate (4.0 g) and magnesium chloride
15 (1.27 g) in dichloromethane (70 ml) was added pyridine (2.15 ml) at 0°C. The mixture was stirred at 20°C for 1 hour, then a solution of 4-cyanobenzoyl chloride (2.87 g) in dichloromethane (10 ml) was added. After stirring for 3 hours at 20°C, the mixture was partitioned between ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue
20 was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give ethyl 7-acetyl-7-(4-cyanobenzoyl)-8-oxononanoate (3.52 g) as an oil.

1-tert-Butyl 8-ethyl 2-acetyl-2-(4-cyanobenzoyl)octanedioate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.25-1.45 (4H, m), 1.30 (9H, s), 1.55-1.70
25 (2H, m), 2.20 (2H, t, J=7Hz), 2.28 (2H, t, J=7Hz), 2.44 (3H, s), 4.12 (2H, q, J=7Hz), 7.72 (2H, t, J=9Hz), 7.83 (2H, d, J=9Hz)

Preparation 140

Ethyl 7-acetyl-7-(4-cyanobenzoyl)-8-oxononanoate (3.5 g) was dissolved in
30 trifluoroacetic acid (12.6 ml) and the mixture was stirred at 20°C for 15 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water, aqueous sodium bicarbonate and brine, dried over MgSO₄ (magnesium sulfate), and evaporated to give ethyl 7-(4-cyanobenzoyl)-8-oxononanoate

(2.25 g) as an oil.

Ethyl 7-(4-cyanobenzoyl)-8-oxononanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.25-1.45 (4H, m), 1.55-1.70 (2H, m), 1.80-
5 2.10 (2H, m), 2.16 (3H, s), 2.28 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.40 (1H, t,
J=7Hz), 7.80 (2H, t, J=9Hz), 8.07 (2H, d, J=9Hz)

Preparation 141

A mixture of methyl 4-(aminosulfonyl)benzoate (5.10 g) and potassium carbonate
10 (6.55 g) in dimethoxyethane (50 mL) was refluxed for 5 minutes. After cooling the
mixture, a solution of benzyl chloridocarbonate (5.25 g) in dimethoxyethane (30 mL),
and the resulting mixture was refluxed for 1 hour. The reaction was quenched by adding
1N hydrochloric acid (100 mL). The mixture was extracted with ethyl acetate (200 mL),
and the organic layer was washed with brine, dried over magnesium sulfate, and
15 evaporated to give a pale yellow oil, which was solidified upon standing. The solid was
trituated in diisopropyl ether (30 mL) to give methyl 4-
({[(benzyloxy)carbonyl]amino}sulfonyl)benzoate as a white powder (3.38 g).

Methyl 4-({[(benzyloxy)carbonyl]amino}sulfonyl)benzoate

20 NMR (CDCl₃, δ): 3.98 (3H, s), 5.10 (2H, s), 7.22 (2H, m), 7.34 (3H, m), 7.64 (1H, s,
br), 8.08 (2H, d, J=9Hz), 8.16 (2H, d, J=9Hz)

Preparation 142

A suspension of methyl 4-({[(benzyloxy)carbonyl]amino}-
25 sulfonyl)benzoate (3.38 g) and 85% potassium hydroxide (1.28 g) in methanol (40 mL)
was stirred for 35 minutes. Methanol was evaporated off, and to the mixture was added
1N hydrochloric acid (20 mL). A white crystal was formed, which was collected by
filtration and washed with water and diisopropyl ether, and dried under vacuum. 4-
({[(Benzyloxy)carbonyl]amino}sulfonyl)benzoic acid was obtained as a white crystal
30 (2.92 g).

4-({[(Benzyloxy)carbonyl]amino}sulfonyl)benzoic acid

NMR (DMSO- d_6 , δ): 5.06 (2H, s), 7.25 (2H, m), 7.33 (3H, m), 8.00 (2H, d, $J=9\text{Hz}$),
8.15 (2H, d, $J=9\text{Hz}$)
MS (ESI): m/z 334 (M-H)

5 Preparation 143

To a suspension of S-(2-pyridinyl) 3-cyanobenzenecarbothioate (2.40 g) in toluene (10 mL) was added titanium chloride (1.99 g) under an ice-methanol bath over 5 minutes (-7 to -2°C). After stirring for 10 minutes, a solution of 2-ethyl-1H-pyrrole (1.00 g) in toluene (10 mL) was added over 5 minutes (-4 to 0°C). The resulting heterogeneous
10 mixture was stirred for 1.5 hours at room temperature. Ethyl acetate (20 mL) and water (20 mL) were added, and the mixture was filtered through celite. The filtrate was diluted with ethyl acetate (80 mL) and water (30 mL), and organic extract was washed with water (30 mL), 1N sodium hydroxide (50 mL), and brine (50 mL), dried over magnesium sulfate, and evaporated to give a dark colored crystal (2.46 g). The crystal was triturated
15 in diisopropyl ether (10 mL) to give 3-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile as a brown crystal (1.57 g, 70.1%).

3-[(5-Ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile

NMR (CDCl_3 , δ): 1.33 (3H, t, $J=7\text{Hz}$), 2.75 (2H, q, $J=7\text{Hz}$), 6.12 (1H, m), 6.78 (1H,
20 m), 7.60 (1H, t, $J=8\text{Hz}$), 7.82 (1H, d, $J=8\text{Hz}$), 8.07 (1H, d, $J=8\text{Hz}$), 8.14 (1H, s),
9.50 (1H, s, br)

Preparation 144

To a suspension of magnesium chloride (3.01 g) in tetrahydrofuran (30 mL) was
25 added tert-butyl 3-oxobutanoate (5.00 g). The mixture was cooled under an ice-bath. Then, pyridine (5.00 g) was added over 15 minutes. After stirring for 1 hour at room temperature, the resulting mixture was cooled under the ice-bath. A solution of 2-chlorobenzoyl chloride (4.98 g) in tetrahydrofuran (30 mL) was added over 15 minutes. The mixture was stirred for 1 hour at room temperature. The reaction was quenched by
30 adding 1N hydrochloric acid (65 mL). The mixture was filtered, and the solvent was evaporated off. The residue was extracted with ethyl acetate (150 mL). The extract was washed with water (100 mL), saturated sodium bicarbonate (100 mL), and brine, dried over magnesium sulfate, and evaporated to give tert-butyl 2-(3-chlorobenzoyl)-3-

oxobutanoate as an yellow oil (8.82 g).

tert-Butyl 2-(3-chlorobenzoyl)-3-oxobutanoate

NMR (CDCl₃, δ): mixture of tautomers: 1.20 and 1.27 (9H, s), 2.16 and 2.44 (3H, s),
5 7.33-7.71 (4H, m), 13.66 (1H, s)

Preparation 145

A solution of tert-butyl 2-(3-chlorobenzoyl)-3-oxobutanoate (8.82 g) in
trifluoroacetic acid (40 mL) was stirred for 1 hour under an ice-bath. The volatile was
10 removed in vacuo, and the residue was partitioned between ethyl acetate (150 mL) and
saturated sodium bicarbonate. The organic layer was washed with brine, dried over
magnesium sulfate, and evaporated to give 1-(3-chlorophenyl)-1,3-butanedione as a pale
orange crystal (5.33 g).

15 1-(3-Chlorophenyl)-1,3-butanedione

NMR (CDCl₃, δ): 2.21 (3H, s), 6.14 (1H, s), 7.38 (1H, t, J=9Hz), 7.48 (1H, d, J=9Hz),
7.75 (1H, d, J=9Hz), 7.85 (1H, s)

Preparation 146

20 To a mixture of 2-(trimethylsilyl)ethanol (20.5 g) and pyridine (18.7 g) in
dichloromethane (40 mL) was added a solution of ethanedioyl dichloride (10.0 g) in
dichloromethane (20 mL) over 30 minutes under an ice-bath (6 to 20°C). The bath was
removed, and the mixture was stirred for 0.5 hour. The mixture was filtered, and the
filtrate was partitioned between ethyl acetate (200 mL) and 1N hydrochloric acid (200
25 mL). The organic layer was washed with saturated sodium bicarbonate and brine, dried
over magnesium sulfate, and evaporated to give bis[2-(trimethylsilyl)ethyl] oxalate as a
pale yellow oil (25.1 g).

bis[2-(Trimethylsilyl)ethyl]oxalate

30 NMR (CDCl₃, δ): 0.08 (18H, s), 1.12 (4H, m), 4.38 (4H, m)

Preparation 147

To a suspension of dimethyl sulfone (7.00 g) in diethyl ether (50 mL) was added potassium tert-butoxide (8.76 g). To the resulting mixture was added bis[2-(trimethylsilyl)ethyl]oxalate (23.8 g). The resulting mixture was stirred for 36 hours at room temperature. The mixture was partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a dark orange oil. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-25 to 8-5 afforded 2-(trimethylsilyl)ethyl 3-(methylsulfonyl)-2-oxopropanoate as a pale brown oil (8.37 g).

2-(Trimethylsilyl)ethyl 3-(methylsulfonyl)-2-oxopropanoate

NMR (CDCl₃, δ): 0.08 (9H, s), 1.14 (2H, m), 3.11 (3H, s), 4.43 (4H, m), 4.56 (2H, s)

MS (ESI): m/z 265 (M-H)

Preparation 148

A mixture of 4-oxo-4-phenylbutanoic acid (5.00 g), ethanol (2.59 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.46 g), and 4-(dimethylamino)pyridine (171 mg) in N,N-dimethylformamide (25 mL) was stirred for 1.5 hours at room temperature. The mixture was partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (75 mL), and the organic layer was washed with water (75 x 3 mL), saturated sodium bicarbonate (75 mL), and brine (75 mL), dried over magnesium sulfate, and evaporated to give ethyl 4-oxo-4-phenylbutanoate as a colorless oil (4.19 g).

Ethyl 4-oxo-4-phenylbutanoate

NMR (CDCl₃, δ): 1.27 (3H, t, J=7Hz), 2.76 (2H, t, J=7Hz), 3.32 (2H, t, J=7Hz), 4.16 (2H, q, J=7Hz), 7.47 (2H, t, J=9Hz), 7.55 (1H, d, J=9Hz), 7.98 (2H, d, J=9Hz)

MS (ESI⁺): m/z 207 (M+H)

The following compound was obtained in substantially the same manner as that of Preparation 148.

Preparation 149

Ethyl 5-oxo-5-phenylpentanoate

5 NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 2.08 (2H, m), 2.44 (2H, t, J=7Hz), 3.06 (2H, t, J=7Hz), 4.14 (2H, q, J=7Hz), 7.46 (2H, t, J=9Hz), 7.56 (1H, d, J=9Hz), 7.97 (2H, d, J=9Hz)
MS (ESI⁺): m/z 221 (M+H)

Preparation 150

10 A mixture of 2-benzoylcyclohexanone (1.00 g), sodium ethoxide (404 mg) in ethanol (5 mL) was stirred for 3.5 hours at room temperature. The reaction was quenched by adding 1N hydrochloric acid (1 mL). The solvent was evaporated off, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give ethyl 7-oxo-7-phenylheptanoate as a brown oil (1.33 g).

15

Ethyl 7-oxo-7-phenylheptanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.42 (2H, m), 1.63-1.81 (4H, m), 2.32 (2H, t, J=7Hz), 2.98 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 7.47 (2H, t, J=9Hz), 7.54 (1H, d, J=7Hz), 7.95 (2H, d, J=9Hz)

20

Preparation 151

25 To a solution of ethyl 7-chloro-7-oxoheptanoate (1.31 g) in dichloromethane (25 mL) was added a solution of 2-(trimethylsilyl)-1,3-thiazole (500 mg) in dichloromethane (5 mL) under nitrogen. After stirring for 3 hours, the reaction was quenched by adding saturated sodium bicarbonate (5 mL). The mixture was partitioned between ethyl acetate (30 mL) and saturated sodium bicarbonate (30 mL), and the organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a colorless oil. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-10 to 2-5 afforded ethyl 7-oxo-7-(1,3-thiazol-2-yl)heptanoate as a colorless oil (778 mg).

30

Ethyl 7-oxo-7-(1,3-thiazol-2-yl)heptanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.44 (2H, m), 1.64-1.85 (4H, m), 2.32 (2H, t,

J=7Hz), 3.17 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 7.66 (1H, d, J=3Hz), 8.00 (1H, d, J=3Hz)

MS (ESI⁺): m/z 256 (M+H)

5 Preparation 152

To a solution of 7-methoxy-7-oxoheptanoic acid (1.00 g) in dichloromethane (10 mL) was added a solution of trifluoroacetic anhydride (1.33 g) in dichloromethane (2 mL). After stirring for 0.5 hour, a solution of 1-methyl-1H-pyrrole (1.49 g) in dichloromethane (2 mL) was added. The mixture was stirred for 2 hours 40 minutes at room temperature and 2 hours at 35°C. The mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a brown oil. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-20 to 4-5 afforded methyl 7-(1-methyl-1H-pyrrol-2-yl)-7-oxoheptanoate as a colorless oil (615 mg).

15

Methyl 7-(1-methyl-1H-pyrrol-2-yl)-7-oxoheptanoate

NMR (CDCl₃, δ): 1.34 (2H, m), 1.61-1.77 (4H, m), 2.32 (2H, t, J=7Hz), 2.77 (2H, t, J=7Hz), 3.66 (3H, s), 3.94 (3H, s), 6.13 (1H, m), 6.79 (1H, m), 6.93 (1H, m)

MS (ESI⁺): m/z 238 (M+H)

20

Preparation 153

To a suspension of 4-({[(benzyloxy)carbonyl]amino}-sulfonyl)benzoic acid (2.90 g) in dichloromethane (30 mL) was added N,N-dimethylformamide (19.0 mg) and followed by oxalyl chloride (1.15 g) under an ice-bath. The mixture was stirred for 0.5 hour at room temperature and refluxed for 1 hour. The resulting mixture was refluxed further for 5 minutes after adding oxalyl chloride (439 mg). The volatile was evaporated off to give a white solid. The solid was triturated in diisopropyl ether to give benzyl [4-(chlorocarbonyl)phenyl]sulfonylcarbamate as a white powder (2.40 g), which was used for the next reaction without further purification.

30

Benzyl [4-(chlorocarbonyl)phenyl]sulfonylcarbamate

Preparation 154

To a solution of tert-butyl 4-(methylthio)-3-oxobutanoate (5.00 g) and potassium carbonate (3.72 g) in dimethylformamide (25 mL) was added ethyl 5-iodopentanoate (6.89 g) and the mixture was stirred at ambient temperature for 15 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 10:1) to give 1-tert-butyl 7-ethyl 2-[(methylthio)acetyl]heptanedioate as colorless oil (5.88 g).

10 1-tert-butyl 7-ethyl 2-[(methylthio)acetyl]heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.30-1.42 (2H, m), 1.45 (9H, s), 1.63-1.74 (2H, m), 1.81-1.93 (2H, m), 2.05 (3H, s), 2.30 (2H, t, J=7Hz), 3.23 (1H, d, J=17Hz), 3.38 (1H, d, J=17Hz), 3.74 (1H, t, J=7Hz), 4.11 (2H, q, J=7Hz)

15 Preparation 155

To a suspension of hydroxylamine hydrochloride (29.4 g) in dichloromethane (200 mL) was added diisopropylethylamine (54.6 g) over 3 minutes in a methanol-ice bath under a nitrogen atmosphere. A white precipitate was formed upon the addition. After stirring for 1 hour under the bath, a solution of diphenylphosphinic chloride (20.0 g) in dichloromethane (20 mL) was added over 60 minutes. A white crystal was formed upon the addition. The mixture was warmed to 0°C over 1 hour with stirring. The reaction was quenched by adding water (200 mL) over 3 minutes. After stirring the mixture for 0.5 hour, the crystal was collected by filtration. The crystal was washed with water (50 x 3 mL) followed by diisopropyl ether (50 x 3 mL). The collected crystal was dried overnight in the air and 3 hours under a reduced pressure with slight warming (4°C) to give a crude product. The crude product was triturated in EtOH (ethanol) to give (aminoxy)(diphenyl)phosphine oxide as a white crystal (15.3 g).

(Aminoxy)(diphenyl)phosphine oxide

30 NMR (CDCl₃, δ): 7.54-7.58 (6H, m), 7.74-7.83 (4H, m), 8.20-8.33 (2H, m)

Preparation 156

To a solution of 1-(1H-pyrrol-2-yl)ethanone (5.00 g) in tetrahydrofuran (100 mL) was added potassium tert-butoxide (6.17 g) in a water bath under a nitrogen atmosphere. After stirring for 1 hour, (aminooxy)(diphenyl)phosphine oxide (12.8 g) was added over 2 hours. After stirring for 2 hours at room temperature, water (4 mL) was added over 3 minutes to give a clear solution. The solvent was evaporated off, and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (25 x 5 mL), and the combined organic extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give a brown oil (6.01 g). The oil was dissolved in diisopropyl ether (30 mL), and to the solution was added hexane (15 mL) to afford a pale yellow crystal. After stirring for 1 hour, the crystal was removed by filtration. The filtrate was evaporated to give a brown oil (5.69 g). The oil was dissolved in ethyl acetate (45.5 mL), the solution was cooled under an ice-bath. To the cooled solution was added 4N hydrogen chloride in ethyl acetate (11.5 mL) over 15 minutes to afford a pale brown precipitate. After stirring the mixture for 0.5 hour under the bath, the precipitate was collected by filtration and washed with ethyl acetate (5 x 3 mL) to give a pale brown powder (5.33 g). The powder was suspended in ethyl acetate (37 mL) and warmed to 3°C. The suspension was stirred for 1 hour at room temperature. The powder was collected by filtration and washed with ethyl acetate (5 x 3 mL) to give 1-(1-amino-1H-pyrrol-2-yl)ethanone hydrochloride as a pale brown powder (5.25 g).

1-(1-Amino-1H-pyrrol-2-yl)ethanone hydrochloride

NMR (CDCl₃, δ): 2.37 (3H, s), 5.22 (2H, s, br), 6.07 (1H, m), 6.99 (1H, m), 7.15 (1H, m)

Preparation 157

Under a nitrogen atmosphere, hydrazine monohydrate (530 g) was added to ethanol (1.7 L) over 55 minutes. To the mixture was added 1-(1-amino-1H-pyrrol-2-yl)ethanone hydrochloride (170 g) over 20 minutes. The mixture was stirred for 10 minutes at room temperature and heated to refluxing temperature over 55 minutes, and refluxed for 15 minutes. After cooling the mixture under a water bath, water (1.7 L) was added to the mixture (30 to 31°C). Ethanol was evaporated off, and the resulting mixture was extracted with chloroform (0.85 x 4 mL). The combined organic extract was washed

with brine (1.3 L). The brine was extracted with chloroform (0.85 L). The combined organic extract was dried over anhydrous magnesium sulfate, and evaporated to give (1E)-1-(1-amino-1H-pyrrol-2-yl)ethanone hydrazone as a brown crystal (112 g).

5 (1E)-1-(1-Amino-1H-pyrrol-2-yl)ethanone hydrazone

NMR (CDCl₃, δ): 2.10 (3H, s), 5.11 (2H, s, br), 5.83 (2H, s, br), 5.98 (1H, m), 6.25

(1H, m), 6.79 (1H, m)

MS (ESI⁺): m/z 139 (M+H)

10 Preparation 158

To a suspension of (1E)-1-(1-amino-1H-pyrrol-2-yl)ethanone hydrazone (110 g) in toluene (1.1 L) was added potassium tert-butoxide (93.8 g) over 5 minutes under a nitrogen atmosphere, and the mixture was heated to refluxing temperature over 45 minutes. After refluxing for 15 minutes, the mixture was cooled to room temperature and partitioned between ethyl acetate (1.1 L) and water (1.1 L). The aqueous layer was extracted with ethyl acetate (1.1 L) again. The combined organic extract was washed with brine (1.1 L), and the brine was extracted with ethyl acetate (0.5 L). All the organic layer was combined, dried over anhydrous magnesium sulfate, and evaporated to give 2-ethyl-1H-pyrrol-1-amine as a brown oil (94.4 g).

20

2-Ethyl-1H-pyrrol-1-amine

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 2.16 (2H, q, J=7Hz), 4.53 (2H, s, br), 5.80

(1H, m), 5.99 (1H, m), 6.67 (1H, m)

25 Preparation 159

To a suspension of tert-butyl 4-methoxy-3-oxobutanoate (3.09 g) and potassium carbonate (2.50 g) in dimethylformamide (20 mL) was added ethyl 5-iodopentanoate (4.62 g) and the mixture was stirred at ambient temperature for 15 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 5:1) to give 1-tert-butyl 7-ethyl 2-(methoxyacetyl)heptanedioate as colorless oil (4.33 g).

30

1-tert-Butyl 7-ethyl 2-(methoxyacetyl)heptanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.30-1.44 (2H, m), 1.45 (9H, s), 1.60-1.73 (2H, m), 1.80-1.93 (2H, m), 2.29 (2H, t, J=7Hz), 3.41 (3H, s), 3.47 (1H, t, J=7Hz),
5 4.02 (4H, m)
MS: (m/z) 317 (M+H)

The following compounds were obtained in substantially the same manner as that of Preparation 159.

10 Preparation 160

1-tert-Butyl 6-ethyl 2-(methoxyacetyl)hexanedioate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.46 (9H, s), 1.52-1.73 (2H, m), 1.82-1.94 (2H, m), 2.33 (2H, t, J=7Hz), 3.42 (3H, s), 3.50 (1H, t, J=7Hz), 4.10 (2H, s), 4.12 (2H, q, J=7Hz)

15

Preparation 161

1-tert-Butyl 5-ethyl 2-(methoxyacetyl)pentanedioate

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.47 (9H, s), 2.10-2.25 (2H, m), 2.37 (2H, t, J=7Hz), 3.42 (3H, s), 3.62 (1H, t, J=7Hz), 4.12 (2H, s), 4.13 (2H, q, J=7Hz)

20

Preparation 162

1-tert-Butyl 6-ethyl 2-acetylhexanedioate

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.47 (9H, s), 1.57-1.75 (2H, m), 1.79-1.93 (2H, m), 2.23 (3H, s), 2.33 (2H, t, J=7Hz), 3.33 (1H, t, J=7Hz), 4.12 (2H, q, J=7Hz)

25

MS (ESI⁺): m/z 273

Preparation 163

1-tert-Butyl 5-ethyl 2-acetylpentanedioate

30 NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.47 (9H, s), 2.08-2.22 (2H, m), 2.24 (3H, s), 2.33-2.42 (2H, m), 3.45 (1H, t, J=7Hz), 4.13 (2H, q, J=7Hz)

Preparation 164

To a solution of 2-ethyl-1H-pyrrole (7.00 g) in tetrahydrofuran (14 mL) was added 0.93 M ethyl magnesium bromide (198 mL) under an ice-bath. The mixture was stirred for 1 hour at room temperature. Then the resulting solution was added to a suspension of 5-bromonicotinoyl chloride (22.3 g) in tetrahydrofuran (110 mL) over 50 minutes under an ice-bath. After stirring for 15 minutes under the bath, the reaction was quenched by adding saturated ammonium chloride (30 mL). The mixture was partitioned between ethyl acetate (350 mL) and water (350 mL). The organic layer was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give a dark colored gum (33.9 g). The gum was dispersed in ethyl acetate/hexane (1:3, 150 mL) in the presence of silica gel (150 mL). The mixture was filtered, and the filtrate was concentrated to give a yellow crystal (20.6 g). Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-20 to 4-5 afforded (5-bromo-3-pyridinyl)(5-ethyl-1H-pyrrol-2-yl)methanone as a pale yellow solid (7.11 g).

(5-Bromo-3-pyridinyl)(5-ethyl-1H-pyrrol-2-yl)methanone

NMR (CDCl₃, δ): 1.33 (3H, t, J=7Hz), 2.75 (2H, q, J=7Hz), 6.14 (1H, m), 6.83 (1H, m), 8.27 (1H, m), 8.82 (1H, m), 8.98 (1H, m)

MS (ESI⁺): m/z 279 (M+H)

Preparation 165

To a solution of tert-butyl 4-(acetyloxy)-3-oxobutanoate (30.0 g) and ethyl 5-iodopentanoate (35.5 g) in N,N-dimethylformamide (150 mL) was added potassium carbonate (19.2 g) at room temperature. After stirring for 4 hours, the mixture was quenched by adding 1N hydrochloric acid (140 mL) under an ice-bath. The mixture was partitioned between ethyl acetate (450 mL) and water (300 mL). The organic extract was washed with water (500 mL, three times) and brine, dried over magnesium sulfate, and evaporated to give a brown oil containing 1-tert-butyl 7-ethyl 2-[(acetyloxy)acetyl]heptanedioate (63.4 g, 43% wt purity).

1-tert-Butyl 7-ethyl 2-[(acetyloxy)acetyl]heptanedioate

NMR (CDCl₃, δ): 1.20-1.37 (5H, m), 1.46 (9H, s), 1.63 (2H, m), 1.85 (2H, m), 2.17 (3H, s), 2.30 (2H, t, J=7Hz), 3.39 (1H, t, J=7Hz), 4.11 (2H, q, J=7Hz), 4.73 (1H,

d, J=17Hz), 4.82 (1H, d, J=17Hz)

Preparation 166

To a solution of ethyl thiophene (2.00 g) and ethyl 7-chloro-7-oxoheptanoate
5 (5.39 g) in dichloromethane (20 mL) was added 1 M tin chloride in dichloromethane
(38.9 mL) over 0.5 hour under an ice-bath (5 to 8°C). After stirring for 0.5 hour, the
mixture was stirred for 0.5 hour at room temperature. The mixture was poured into ice-
water (100 mL), and extracted with ethyl acetate (100 mL). The organic extract was
washed with water (100 mL) and brine, dried over magnesium sulfate, and evaporated to
10 give a brown oil. Flash silica gel column chromatography eluting with ethyl acetate-
hexane = 1-10 to 3-10 afforded ethyl 7-oxo-7-(2-thienyl)heptanoate as a brown oil (5.79
g).

Ethyl 7-oxo-7-(2-thienyl)heptanoate

15 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.42 (2H, m), 1.63-1.72 (4H, m), 2.31 (2H, t,
J=7Hz), 2.91 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 7.13 (1H, m), 7.612 (1H, m),
7.70 (1H, m)

The following compounds were obtained in substantially the same manner as
20 those of Preparations 129 and 130.

Preparation 167

tert-Butyl 3-(3,5-dimethyl-4-isoxazolyl)-3-oxopropanoate

NMR (CDCl₃, δ): 1.47 (9H, s), 2.46 (3H, s), 2.68 (3H, s), 3.68 (2H, s)

25 Preparation 168

Ethyl 4-methyl-3-oxopentanoate

NMR (CDCl₃, δ): 1.14 (6H, d, J=7Hz), 1.28 (3H, t, J=7Hz), 2.71 (1H, quintet,
J=7Hz), 3.50 (s, 2H), 4.19 (2H, q, J=7Hz), 7.06-7.18, 7.56, and 7.85 (4H, m)

30 Preparation 169

tert-Butyl 4-(methylthio)-3-oxobutanoate

NMR (CDCl₃, δ): 1.47 (9H, s), 2.07 (3H, s), 3.31 (2H, s), 3.58 (2H, s)

Preparation 170

5 tert-Butyl 3-(1,3-oxazol-5-yl)-3-oxopropanoate

NMR (CDCl₃, δ): (a mixture of keto- and enol-form); keto-form: 1.45 (9H, s), 3.77

(2H, s), 7.85 (1H, s), 8.04 (1H, s); enol-form: d 1.45 (9H, s), 5.54 (1H, s), 7.53

(1H, s), 7.91 (1H, s)

10 The following compounds were obtained in substantially the same manner as that of Preparation 143.

Preparation 171

(2-Chloro-4-pyridinyl)(5-ethyl-1H-pyrrol-2-yl)methanone

NMR (CDCl₃, δ): 1.32 (3H, t, J=7Hz), 2.74 (2H, q, J=7Hz), 6.13 (1H, m), 6.79 (1H,

15 m), 7.56 (1H, d, J=5Hz), 7.69 (1H, s), 8.54 (1H, d, J=5Hz), 9.40 (1H, br)

Preparation 172

(5-Ethyl-1H-pyrrol-2-yl)(3-methoxyphenyl)methanone

NMR (CDCl₃, δ): 1.32 (3H, t, J=7Hz), 2.74 (2H, q, J=7Hz), 3.87 (3H, s), 6.08 (1H,

20 m), 6.83 (1H, m), 7.08 (1H, dd, J=2 Hz, 8Hz), 7.33-7.42 (2H, m), 7.47 (1H, d,

J=8Hz), 9.58 (1H, br)

MS (ESI⁺): m/z 230

Preparation 173

25 (5-Ethyl-1H-pyrrol-2-yl)(4-pyridinyl)methanone

NMR (CDCl₃, δ): 1.32 (3H, t, J=7Hz), 2.72 (2H, q, J=7Hz), 6.13 (1H, m), 6.81 (1H,

m), 7.65 (2H, d, J=7Hz), 8.77 (2H, d, J=7Hz), 9.39 (1H, br)

Preparation 174

30 (5-Ethyl-1H-pyrrol-2-yl)(2-pyrazinyl)methanone

NMR (CDCl₃, δ): 1.33 (3H, t, J=7Hz), 2.77 (2H, q, J=7Hz), 6.14 (1H, m), 7.51 (1H,

m), 8.65 (1H, m), 8.74 (1H, m), 9.36 (1H, br)

Preparation 175

(5-Ethyl-1H-pyrrol-2-yl)(3-pyridinyl)methanone

5 NMR (CDCl₃, δ): 1.33 (3H, t, J=7Hz), 2.76 (2H, q, J=7Hz), 6.12 (1H, m), 6.81 (1H, m), 7.42 (1H, m), 8.13 (1H, m), 8.76 (1H, m), 9.08 (1H, m), 9.36 (1H, br)

Preparation 176

10 A mixture of 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (300 mg), methanesulfonylacetic acid (208 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (361 mg), and 1-hydroxybenzotriazole (254 mg) in N,N-dimethylformamide (1 mL) was stirred for 1.5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with water two times, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated to give a pale brown solid. Flash silica gel column chromatography eluting with ethyl
15 acetate-hexane = 1/2 to 1/0 afforded N-[2-(3-cyanobenzoyl)-5-ethyl-1H-pyrrol-1-yl]-2-(methylsulfonyl)acetamide as a pale brown foam, which was solidified upon standing (505 mg).

N-[2-(3-Cyanobenzoyl)-5-ethyl-1H-pyrrol-1-yl]-2-(methylsulfonyl)acetamide

20 NMR (CDCl₃, δ): 1.29 (3H, t, J=7Hz), 2.62 (2H, q, J=7 Hz), 3.28 (3H, s), 4.15 (2H, s), 6.12 (1H, d, J=5Hz), 6.75 (1H, d, J=5Hz), 7.58 (1H, t, J=9Hz), 7.82 (1H, d, J=9Hz), 8.01 (1H, d, J=9Hz), 8.06 (1H, s)

The following compound was obtained in substantially the same manner as that of

25 Preparation 176.

Preparation 177

Ethyl 3-{[2-(4-cyanobenzoyl)-5-ethyl-1H-pyrrol-1-yl]amino}-3-oxopropanoate

30 NMR (CDCl₃, δ): 1.20-1.37 (6H, m), 2.56 (2H, q, J=7Hz), 3.57 (2H, s), 4.30 (2H, q, J=7Hz), 6.06 (1H, d, J=5Hz), 6.68 (1H, d, J=5Hz), 7.54 (2H, d, J=9Hz), 7.84 (2H, d, J=9Hz)

Example 1

To a solution of 4-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (100 mg) in toluene (1 mL) were added 1-(4-methoxyphenyl)acetone (103 mg) and p-toluene-sulfonic acid monohydrate (16 mg) at ambient temperature. The reaction mixture was heated at 80°C for 3 hours. The mixture was evaporated in vacuo. The residue was
5 purified by flash silica gel column chromatography eluting with hexane-ethyl acetate = 20-1 and 15-1 to give 4-[7-ethyl-3-(4-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile (31 mg, 20.2%) as a yellow solid.

4-[7-Ethyl-3-(4-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

10 NMR (CDCl₃, δ): 1.40 (3H, t, J=8Hz), 2.31 (3H, s), 3.16 (2H, q, J=8Hz), 3.77 (3H, s),
6.10 (1H, d, J=5Hz), 6.60 (1H, d, J=5Hz), 6.75 (2H, d, J=8Hz), 6.93 (2H, d,
J=8Hz), 7.33 (2H, d, J=8Hz), 7.53 (2H, d, J=8Hz)

MS (ESI⁺): m/z 368 (M+H)

15 The following compounds were obtained in substantially the same manner as that of Example 1.

Example 2

Ethyl 4-(4-cyanophenyl)-2-(2-ethoxy-2-oxoethyl)-7-ethylpyrrolo[1,2-b]pyridazine-3-carboxylate

20 NMR (CDCl₃, δ): 0.84 (3H, t, J=7Hz), 1.28 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 3.04
(2H, q, J=7Hz), 3.93 (2H, q, J=7Hz), 4.13 (3H, s), 4.19 (2H, q, J=7Hz), 6.24 (1H,
d, J=5Hz), 6.62 (1H, d, J=5Hz), 7.13 (2H, d, J=9Hz), 7.76 (2H, d, J=9Hz)

Example 3

25 Ethyl 4-(4-cyanophenyl)-7-ethyl-2-(trifluoromethyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (CDCl₃, δ): 1.08 (3H, t, J=7Hz), 1.41 (3H, t, J=7Hz), 3.11 (2H, q, J=7Hz), 4.11
(2H, q, J=7Hz), 6.43 (1H, d, J=5Hz), 6.93 (1H, d, J=5Hz), 7.62 (2H, d, J=9Hz),
7.80 (2H, d, J=9Hz)

30

Example 4

4-[7-Ethyl-2-methyl-3-(3-pyridinylcarbonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.43 (t, J=7 Hz, 3H), 2.47 (s, 3H), 3.09 (q, J=7 Hz, 2 H), 6.35 (d, J=5 Hz, 1H), 6.74 (d, J=5 Hz, 1H), 7.23 (1H, m), 7.48 (2H, d, J=9Hz), 7.55 (2H, d, J=9Hz), 7.93 (1H, m), 8.62 (1H, m), 8.74 (1H, m)

5 Example 5

3-[7-Ethyl-2-methyl-3-(4-pyridinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.42 (3H, t, J=7Hz), 2.32 (3H, s), 3.08 (2H, q, J=7Hz), 6.15 (1H, d, J=5Hz), 6.67 (1H, d, J=5Hz), 7.00 (2H, d, J=9Hz), 7.37 (2H, m), 7.57 (2H, m), 8.50 (2H, d, J=9Hz)

10

Example 6

4-(3-Benzyl-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl)benzonitrile

NMR (CDCl₃, δ): 1.40 (3H, t, J=8Hz), 2.35 (3H, s), 3.04 (2H, q, J=8Hz), 3.83 (3H, s), 5.94 (1H, d, J=5Hz), 6.57 (1H, d, J=5Hz), 6.98 (2H, d, J=8Hz), 7.14-7.30 (3H, m), 7.46 (2H, d, J=8Hz), 7.68 (2H, d, J=8Hz)

15

MS (ESI⁺): m/z 352 (M+H)

Example 7

4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazine-3-carbonitrile

20 mp: 172-173°C

NMR (CDCl₃, δ): 1.41 (3H, t, J=8Hz), 3.10 (2H, q, J=8Hz), 6.65 (1H, d, J=5Hz), 6.88 (1H, d, J=5Hz), 7.47-7.64 (6H, m), 7.70 (1H, br s), 7.81-7.90 (2H, m)

Example 8

25 3-(3-Ethyl-7,7,9,9-tetramethyl-6,7,8,9-tetrahydropyrrolo[1,2-b]cinnolin-10-yl)benzonitrile

NMR (CDCl₃, δ): 1.00-1.15 (12H, m), 1.37 (3H, t, J=8Hz), 2.81 (3H, s), 3.00 (2H, q, J=8Hz), 3.82 (2H, t, J=5Hz), 5.46 (1H, d, J=5Hz), 6.46 (1H, d, J=5Hz), 7.50-7.65 (3H, m), 7.72 (1H, m)

30

Example 9

3-(3-Ethyl-9-oxo-6,7,8,9-tetrahydropyrrolo[1,2-b]cinnolin-10-yl)benzonitrile

NMR (CDCl₃, δ): 1.40 (3H, t, J=8Hz), 2.08-2.22 (2H, m), 2.60 (2H, t, J=7Hz), 3.00-3.15 (4H, m), 6.26 (1H, d, J=5Hz), 6.74 (1H, d, J=5Hz), 7.49-7.61 (3H, m), 7.74 (1H, m)

MS (ESI⁺): m/z 316 (M+H)

5

Example 10

3-(6-Ethyl-1-oxo-2,3-dihydro-1H-cyclopenta[e]pyrrolo[1,2-b]pyridazin-9-yl)benzonitrile
mp: 150-154°C

10 NMR (CDCl₃, δ): 1.43 (3H, t, J=8Hz), 2.75 (2H, t, J=7Hz), 3.10 (2H, q, J=8Hz), 3.24 (2H, t, J=7Hz), 6.67 (1H, d, J=5Hz), 6.87 (1H, d, J=5Hz), 7.60 (1H, t, J=8Hz), 7.75-7.90 (3H, m)

MS (ESI⁺): m/z 324 (M+Na)

Example 11

15 3-(7-Ethyl-2-neopentylpyrrolo[1,2-b]pyridazin-4-yl)benzonitrile

NMR (CDCl₃, δ): 1.05 (9H, s), 1.39 (3H, t, J=8Hz), 2.68 (2H, s), 3.04 (2H, q, J=8Hz), 6.36 (1H, s), 6.48 (1H, d, J=5Hz), 6.67 (1H, d, J=5Hz), 7.51 (1H, t, J=8Hz), 7.75 (1H, br d, J=8Hz), 7.92-8.01 (2H, m)

MS (ESI⁺): m/z 318 (M+H)

20

Example 12

3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

25 NMR (CDCl₃, δ): 1.44 (3H, t, J=8Hz), 3.11 (2H, q, J=8Hz), 6.52-6.60 (2H, m), 6.74 (1H, d, J=5Hz), 6.98 (1H, s), 7.09 (1H, d, J=5Hz), 7.56-7.68 (2H, m), 7.78 (1H, dd, J=8, 1Hz), 7.96-8.08 (2H, m)

MS (ESI⁺): m/z 314 (M+H)

Example 13

4-[7-Ethyl-2-methyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

30 NMR (CDCl₃, δ): 1.38 (3H, t, J=8Hz), 2.89 (3H, s), 3.00-3.11 (5H, m), 6.09 (1H, d, J=5Hz), 6.73 (1H, d, J=5Hz), 7.45 (2H, d, J=8Hz), 7.76 (2H, d, J=8Hz)

MS (ESI⁺): m/z 340 (M+H)

Example 13-2

4-{7-Ethyl-2-[(methylsulfonyl)methyl]pyrrolo[1,2-b]pyridazin-4-yl}benzonitrile

NMR (CDCl₃, δ): 1.39 (3H, t, J=8Hz), 2.96-3.09 (5H, m), 4.44 (2H, s), 6.63 (1H, d, J=5Hz), 6.71 (1H, s), 6.81 (1H, d, J=5Hz), 7.79 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz)

MS (ESI⁺): m/z 340 (M+H)

Example 15

3-[7-Ethyl-2-methyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.39 (3H, t, J=8Hz), 2.89 (3H, s), 3.00-3.11 (5H, m), 6.09 (1H, d, J=5Hz), 6.73 (1H, d, J=5Hz), 7.54-7.63 (3H, m), 7.77 (1H, m)

Example 16

To a solution of 4-[7-ethyl-3-(4-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile (22 mg) in N,N-dimethylformamide (1 mL) were added 1N sodium hydroxide (0.12 mL) and 30% hydrogen peroxide (0.07 mL) at ambient temperature. After 1 hour stirring, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water three times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (silica gel, 30 mL) eluting with hexane-ethyl acetate = 5-1 and 0-1 to give 4-[7-ethyl-3-(4-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzamide (18 mg, 78.0%) as a yellow solid.

4-[7-Ethyl-3-(4-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzamide

NMR (CDCl₃, δ): 1.41 (3H, t, J=8Hz), 2.31 (3H, s), 3.17 (2H, q, J=8Hz), 3.77 (3H, s), 5.61 (0.2H, br s), 6.02 (0.4H, br s), 6.13 (1H, d, J=5Hz), 6.60 (1H, d, J=5Hz), 6.75 (2H, d, J=8Hz), 6.95 (2H, d, J=8Hz), 7.31 (2H, d, J=8Hz), 7.68 (2H, d, J=8Hz)

MS (ESI⁺): m/z 386 (M+H)

The following compound was obtained in substantially the same manner as that of Example 16.

Example 17

3-[2-(Dimethylamino)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzamide

NMR (CDCl₃, δ): 1.32 (3H, t, J=7Hz), 2.90 (6H, s), 2.95 (2H, q, J=7Hz), 3.36 (3H, s),

6.21 (1H, d, J=5Hz), 6.79 (1H, d, J=5Hz), 7.44 (1H, s, br), 7.52-7.56 (2H, m),

5 7.90 (1H, s), 7.94-8.06 (2H, m)

MS (ESI⁺): m/z 387 (M+H)Example 18

3-(7-Ethyl-2-neopentylpyrrolo[1,2-b]pyridazin-4-yl)benzamide

10 NMR (CDCl₃, δ): 1.05 (9H, s), 1.39 (3H, t, J=8Hz), 2.68 (2H, s), 3.04 (2H, q, J=8Hz),

5.70 (1H, br s), 6.11 (1H, br s), 6.41 (1H, s), 6.52 (1H, d, J=5Hz), 6.65 (1H, d,

J=5Hz), 7.59 (1H, t, J=8Hz), 7.85-7.93 (2H, m), 8.15 (1H, br s)

MS (ESI⁺): m/z 336 (M+H)15 Example 19

3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzamide

NMR (CDCl₃, δ): 1.43 (3H, t, J=8Hz), 3.10 (2H, q, J=8Hz), 5.70 (1H, br s), 6.13 (1H,

br s), 6.53-6.60 (2H, m), 6.71 (1H, d, J=5Hz), 7.02 (1H, s), 7.06 (1H, d, J=5Hz),

7.55-7.65 (2H, m), 7.79-7.98 (2H, m), 8.02 (1H, br s)

20 MS (ESI⁺): m/z 332 (M+H)Example 20

5-[2-({[4-(Aminocarbonyl)benzyl]oxy}methyl)-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

25 NMR (DMSO-d₆, δ): 1.27-1.45 (7H, m), 1.99 (2H, m), 2.96 (2H, m), 3.40 (2H, m),

4.67 (2H, s), 4.72 (2H, s), 5.88 (1H, d, J=5Hz), 6.67 (1H, d, J=5Hz), 7.35 (1H, s,

br), 7.44 (2H, d, J=8Hz), 7.86 (2H, d, J=8Hz), 7.96 (1H, s, br), 8.21 (1H, m), 8.60

(1H, m), 8.86 (1H, m)

30 Example 21

To a solution of ethyl 6-(3-cyanobenzoyl)-7-oxooctanoate (3.18 g) in toluene (30 mL) was added 2-ethyl-1H-pyrrol-1-amine (1.17 g) and p-toluenesulfonic acid

monohydrate (96 mg) at ambient temperature. The reaction mixture was refluxed for 1 hour. The mixture was evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 200 mL) eluting with hexane-ethyl acetate = 20-1, 15-1, and 10-1 to give ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (3.29 g, 83.8%) as a yellow oil.

Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=8Hz), 1.32-1.58 (7H, m), 2.18 (2H, t, J=8Hz), 2.35-2.45 (2H, m), 3.01 (2H, q, J=8Hz), 4.10 (2H, q, J=8Hz), 5.79 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.57-7.67 (3H, m), 7.75 (1H, m)

The following compounds were obtained in substantially the same manner as that of Example 21.

Example 22

Ethyl 2,4-diisopropylpyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (300 MHz, CDCl₃, δ): 1.32 (6H, d, J=7.5Hz), 1.39 (3H, t, J=7.5Hz), 1.46 (6H, d, J=7.5Hz), 2.91-3.05 (1H, m), 3.05-3.20 (1H, m), 4.38 (2H, q, J=7.5Hz), 6.64-6.68 (1H, m), 6.76-6.80 (1H, m), 7.65-7.68 (1H, m)

MS (ES+) m/e 275.33

Example 23

Ethyl 4-(2-chlorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (300 MHz, CDCl₃, δ): 0.89 (3H, t, J=7.5Hz), 1.30-1.40 (6H, m), 3.36-3.51 (1H, m), 4.00 (2H, q, J=7.5Hz), 6.10-6.18 (1H, m), 6.75-6.84 (1H, m), 7.28-7.45 (3H, m), 7.45-7.55 (1H, m), 7.75-7.81 (1H, m)

Example 24

Ethyl 2-isopropyl-4-(2-naphthyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (300 MHz, CDCl₃, δ): 0.78 (3H, t, J=7.5Hz), 1.38 (6H, d, J=7.5Hz), 3.24-3.35 (1H, m), 3.95 (2H, q, J=7.5Hz), 6.36-6.40 (1H, m), 6.80-6.85 (1H, m), 7.50-7.54 (3H, m), 7.78-7.82 (1H, m), 7.82-8.00 (4H, m)

MS (ES+) m/e 359.56

Example 25

Ethyl 5-{7-ethyl-2-methyl-4-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

5 NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.59 (4H, m), 2.14 (2H, t, J=7Hz), 2.38-2.46 (2H, m), 2.55 (3H, s), 3.01 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz), 5.83 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.53-7.64 (3H, m), 7.71 (1H, d, J=8Hz)

MS (ESI⁺): m/z 433 (M+H)

10

Example 26

Ethyl 5-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

15 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.38-1.60 (4H, m), 2.18 (2H, t, J=7Hz), 2.42 (3H, s), 2.38-2.50 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.50 (1H, s), 8.39 (1H, s), 8.53 (1H, s)

MS (ESI⁺): m/z 380 (M+H)

20 Example 27

Ethyl 5-[7-ethyl-4-(3-methoxy-5-isoxazolyl)-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.55-1.64 (2H, m), 1.64-1.80 (2H, m), 2.33 (2H, t, J=7Hz), 2.74-2.85 (2H, m), 3.03 (2H, q, J=7Hz), 3.43 (3H, s), 4.08 (3H, s), 4.12 (2H, q, J=7Hz), 4.62 (2H, s), 6.28 (1H, s), 6.38 (1H, d, J=4Hz), 6.65 (1H, d, J=4Hz)

MS (ESI⁺): m/z 416 (M+H)

Example 28

30 Ethyl 5-{7-ethyl-2-methyl-4-[3-(1,3-oxazol-5-yl)phenyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

NMR (CDCl₃, δ): 1.20 (3H, t, J=7Hz), 1.35 (3H, t, J=7Hz), 1.40-1.63 (4H, m), 2.17

(2H, t, J=7Hz), 2.44-2.57 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 4.05 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.50 (1H, d, J=4Hz), 7.33 (1H, d, J=8Hz), 7.39 (1H, s), 7.53 (1H, t, J=8Hz), 7.66 (1H, m), 7.74 (1H, d, J=8Hz), 7.93 (1H, s)

5 Example 29

Ethyl 5-[4-(3,4-dichlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.38-1.48 (2H, m), 1.50-1.65 (2H, m), 2.20 (2H, t, J=7Hz), 2.38-2.47 (2H, m), 2.54 (3H, s), 3.00 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.19 (1H, dd, J=2 Hz, 8Hz), 7.46 (1H, d, J=2Hz), 7.56 (1H, d, J=8Hz)

MS (ESI⁺): m/z 433 (M+H)

Example 30

Ethyl 5-[4-(4-chloro-2-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-

15 yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.44-1.67 (4H, m), 2.15-2.26 (2H, m), 2.42-2.56 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz), 5.95 (1H, d, J=3Hz), 6.54 (1H, d, J=3Hz), 7.40 (1H, dd, J=2 Hz, 4Hz), 7.54 (1H, d, J=2Hz), 8.67 (1H, d, J=4Hz)

20 MS (ESI⁺): m/z 400 (M+H)

Example 31

Ethyl 5-[4-(5-chloro-2-thienyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.48-1.74 (4H, m), 2.28 (2H, t, J=7Hz), 2.68-2.77 (2H, m), 3.02 (2H, q, J=7Hz), 3.44 (3H, s), 4.12 (2H, q, J=7Hz), 4.60 (2H, s), 6.25 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 6.97 (2H, m)

MS (ESI⁺): m/z 435 (M+H)

30 Example 32

Ethyl 5-[7-ethyl-4-(6-methoxy-2-pyrazinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.52-1.68 (4H, m), 2.23 (2H, t, J=7Hz), 2.48-2.55 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 3.98 (3H, s), 4.09 (2H, q, J=7Hz), 6.03 (1H, d, J=4Hz), 6.55 (1H, d, J=4Hz), 8.30 (1H, s), 8.33 (1H, s)

5 MS (ESI⁺): m/z 397 (M+H)

Example 33

Ethyl 5-[4-(1-benzofuran-2-yl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

10 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.62-1.83 (4H, m), 2.33 (2H, t, J=7Hz), 2.57 (3H, s), 2.69-2.78 (2H, m), 3.03 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 6.48 (1H, d, J=4Hz), 6.59 (1H, d, J=4Hz), 7.15 (1H, s), 7.26-7.42 (2H, m), 7.57 (1H, d, J=8Hz), 7.68 (1H, d, J=8Hz)

MS (ESI⁺): m/z 405 (M+H)

15 Example 34

Ethyl 5-[4-(1-benzothien-2-yl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

20 NMR (CDCl₃, δ): 1.21 (3H, t, J=7Hz), 1.35 (3H, t, J=7Hz), 1.52-1.69 (4H, m), 2.23 (2H, t, J=7Hz), 2.56 (3H, s), 2.61-2.70 (2H, m), 3.02 (2H, q, J=7Hz), 4.07 (2H, q, J=7Hz), 6.21 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.35-7.43 (3H, m), 7.81-7.92 (2H, m)

Example 35

Ethyl 5-[7-ethyl-2-methyl-4-(1,3-oxazol-5-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.53-1.66 (2H, m), 1.66-1.83 (2H, m), 2.34 (2H, t, J=7Hz), 2.56 (3H, s), 2.62-2.73 (2H, m), 3.02 (2H, q, J=7Hz), 4.13 (2H, q, J=7Hz), 6.42 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.50 (1H, s), 8.10 (1H, s)

MS (ESI⁺): m/z 356 (M+H)

30 Example 36

Ethyl 5-(7-ethyl-2-methyl-4-phenylpyrrolo[1,2-b]pyridazin-3-yl)pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.15

(2H, t, J=7Hz), 2.41-2.48 (2H, m), 2.55 (3H, s), 3.02 (2H, q, J=7Hz), 4.08 (2H, q, J=7Hz), 5.88 (1H, d, J=4Hz), 6.48 (1H, d, J=4Hz), 7.31-7.34 (2H, m), 7.40-7.49 (3H, m)

MS (ESI⁺): m/z 365 (M+H)

5

Example 37

Ethyl 5-[7-ethyl-2-methyl-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.18 (3H, t, J=7Hz), 1.39 (3H, t, J=7Hz), 1.39-1.55 (4H, m), 2.14

(2H, d, J=7Hz), 2.44-2.55 (2H, m), 2.58 (3H, s), 3.03 (2H, q, J=7Hz), 4.03 (2H, q, J=7Hz), 5.86 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.45-7.52 (1H, m), 7.69 (1H, dd, J=2Hz, 8Hz), 7.84 (1H, d, J=2Hz), 8.20 (2H, d, J=8Hz), 9.00 (1H, m)

10

Example 38

Ethyl 7-{4-[4-({[(benzyloxy)carbonyl]amino}sulfonyl)phenyl]-7-ethyl-2-

15 methylpyrrolo[1,2-b]pyridazin-3-yl}heptanoate

NMR (CDCl₃, δ): 1.12-1.23 (7H, m), 1.33-1.51 (7H, s), 2.17 (2H, t, J=7Hz), 2.35

(2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 4.11 (2H, q, J=7Hz), 5.17 (2H, s), 5.78 (1H, d, J=5Hz), 6.52 (1H, d, J=5Hz), 7.29-7.38 (5H, m), 7.49 (2H, d, J=9Hz), 7.87 (1H, s, br), 8.11 (2H, d, J=9Hz)

20 MS (ESI⁺): m/z 606 (M+H)

MS (ESI⁻): m/z 604 (M-H)

Example 39

2-{[4-(3-Chlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methyl}-1,3-

25 propanediol

NMR (CDCl₃, δ): 1.26 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.64-1.82 (3H, m), 2.59

(3H, s), 3.02 (2H, q, J=7Hz), 3.45 (2H, m), 3.63 (2H, m), 4.12 (2H, q, J=7Hz), 5.93 (1H, d, J=5Hz), 6.53 (1H, d, J=5Hz), 7.28 (1H, m), 7.42-7.44 (3H, m)

30 Example 40

Ethyl 5-{7-ethyl-2-methyl-4-[3-(methylsulfonyl)phenyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

NMR (CDCl₃, δ): 1.22 (3H, t, J=8Hz), 1.33-1.57 (7H, m), 2.18 (2H, t, J=8Hz), 2.35-2.45 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=8Hz), 3.12 (3H, s), 4.08 (2H, q, J=8Hz), 5.80 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.64-7.74 (2H, m), 7.96 (1H, br s), 8.04 (1H, m)

5 MS (ESI⁺): m/z 443 (M+H)

Example 41

Ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

10 NMR (CDCl₃, δ): 1.23 (3H, t, J=8Hz), 1.30-1.62 (7H, m), 2.21 (2H, t, J=8Hz), 2.35-2.45 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=8Hz), 4.10 (2H, q, J=8Hz), 5.85 (1H, d, J=5Hz), 6.53 (1H, d, J=5Hz), 7.24 (1H, dd, J=7, 1Hz), 7.35 (1H, br s), 8.53 (1H, d, J=7Hz)

MS (ESI⁺): m/z 400 (M+H)

15

Example 42

Ethyl 5-[7-ethyl-2-methyl-4-(3-nitrophenyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.21 (3H, t, J=8Hz), 1.34-1.59 (7H, m), 2.17 (2H, t, J=8Hz), 2.37-2.47 (2H, m), 2.57 (3H, s), 3.01 (2H, q, J=8Hz), 4.08 (2H, q, J=8Hz), 5.81 (1H, d, J=5Hz), 6.52 (1H, d, J=5Hz), 7.64-7.74 (2H, m), 8.25 (1H, br s), 8.33 (1H, m)

20

MS (ESI⁺): m/z 410 (M+H)

Example 43

Ethyl 4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylate

25 NMR (CDCl₃, δ): 0.98 (3H, t, J=8Hz), 2.55 (3H, s), 4.05 (2H, q, J=8Hz), 6.35 (1H, m), 6.81 (1H, m), 7.12-7.22 (2H, m), 7.41-7.50 (2H, m), 7.76 (1H, m)

MS (ESI⁺): m/z 359 (M+H)

Example 44

30 4-(3-Butyl-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl)benzonitrile

NMR (CDCl₃, δ): 0.78 (3H, t, J=8Hz), 1.12-1.43 (7H, m), 2.31-2.40 (2H, m), 2.56 (3H, s), 3.00 (2H, q, J=8Hz), 5.79 (1H, d, J=5Hz), 6.50 (1H, d, J=5Hz), 7.47 (2H,

d, J=8Hz), 7.77 (2H, d, J=8Hz)

MS (ESI⁺): m/z 318 (M+H)

Example 45

- 5 Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.65 (4H, m), 2.21 (2H, t, J=7Hz), 2.37-2.49 (2H, m), 2.56 (3H, s), 3.00 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.85 (1H, m), 8.53 (1H, d, J=2Hz), 8.77 (1H, d, J=2Hz)
 10 MS: (m/z) 444, 446 (M+H)

Example 46

- 15 Ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-[(methylthio)methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.40-1.63 (4H, m), 2.18 (3H, s), 2.20 (2H, t, J=7Hz), 2.48-2.58 (2H, m), 3.02 (2H, q, J=7Hz), 3.81 (2H, s), 4.10 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz), 7.27 (1H, m), 7.38 (1H, s), 8.53 (1H, d, J=4Hz)
 20 MS: (m/z) 446 (M+H)

Example 47

Ethyl 6-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate

NMR (CDCl₃, δ): 1.15-1.29 (5H, m), 1.32-1.61 (7H, m), 2.20 (2H, t, J=8Hz), 2.33-2.43 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=8Hz), 4.10 (2H, q, J=8Hz), 5.79 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.57-7.67 (3H, m), 7.75 (1H, m)
 25 MS (ESI⁺): m/z 404 (M+H)

Example 48

- 30 Ethyl 5-[4-(6-chloro-2-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.46-1.65 (4H, m), 2.22

(2H, t, J=7Hz), 2.46-2.57 (2H, m), 2.54 (3H, s), 3.00 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 5.95 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.38-7.47 (2H, m), 7.80 (1H, t, J=8Hz)

MS (ESI⁺): m/z 400

5

Example 49

Ethyl 5-[7-ethyl-4-(3-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.40-1.62 (4H, m), 2.17

(2H, t, J=7Hz), 2.43-2.52 (2H, m), 2.54 (3H, s), 3.00 (2H, q, J=7Hz), 3.83 (3H, s),

10 4.08 (2H, q, J=7Hz), 5.91 (1H, d, J=4Hz), 6.49 (1H, d, J=4Hz), 6.87-6.99 (3H, m),

7.37 (1H, t, J=8Hz)

MS (ESI⁺): m/z 395

Example 50

15 Ethyl 5-[4-(3,5-dichlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.39-1.52 (2H, m), 1.52-

1.64 (2H, m), 2.22 (2H, t, J=7Hz), 2.38-2.48 (2H, m), 2.54 (3H, s), 3.00 (2H, q,

J=7Hz), 4.10 (2H, q, J=7Hz), 5.88 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.25 (2H,

m), 7.45 (1H, m)

20 MS (ESI⁺): m/z 433

Example 51

Ethyl 5-[4-(5-chloro-2-thienyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.46-1.58 (2H, m), 1.60-

25 1.74 (2H, m), 2.28 (2H, t, J=7Hz), 2.53 (3H, s), 2.56-2.66 (2H, m), 2.98 (2H, q,

J=7Hz), 4.12 (2H, q, J=7Hz), 6.20 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 6.94 (1H,

d, J=4Hz), 6.98 (1H, d, J=4Hz)

MS (ESI⁺): m/z 405

30 Example 52

Ethyl 5-[7-ethyl-4-(3-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.39 (3H, t, J=7Hz), 1.38-1.50 (2H, m), 1.50-

1.63 (2H, m), 2.17 (2H, t, J=7Hz), 2.39-2.48 (2H, m), 2.54 (3H, s), 3.03 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 5.88 (1H, d, J=4Hz), 6.50 (1H, d, J=4Hz), 7.03-7.16 (3H, m), 7.38-7.47 (1H, m)

MS (ESI⁺): m/z 383

5

Example 53

Ethyl 5-[7-ethyl-2-methyl-4-(3-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.18 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.16 (2H, t, J=7Hz), 2.44-2.56 (2H, m), 2.59 (3H, s), 3.04 (2H, q, J=7Hz), 4.03 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.62 (1H, t, J=8Hz), 7.80 (1H, t, J=8Hz), 7.90 (1H, d, J=8Hz), 8.21 (2H, m), 8.90 (1H, d, J=2Hz)

10

MS (ESI⁺): m/z 416

Example 54

15 Ethyl 5-[7-ethyl-2-methyl-4-(4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.40-1.64 (4H, m), 2.19 (2H, t, J=7Hz), 2.38-2.52 (2H, m), 2.55 (3H, s), 3.02 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 5.83 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.29 (2H, m), 8.72 (2H, m)

MS (ESI⁺): m/z 366

20

Example 55

Ethyl 5-[7-ethyl-4-(3-methoxy-5-isoxazolyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.55-1.82 (4H, m), 2.33 (2H, t, J=7Hz), 2.55 (3H, s), 2.62-2.72 (2H, m), 2.99 (2H, q, J=7Hz), 4.08 (3H, s), 4.12 (2H, q, J=7Hz), 6.26 (1H, s), 6.34 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz)

25

Example 56

Ethyl 5-[7-ethyl-2-methyl-4-(5-methyl-3-isoxazolyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

30

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.50-1.75 (4H, m), 2.29 (2H, t, J=7Hz), 2.55 (6H, s), 2.56-2.65 (2H, m), 2.99 (2H, q, J=7Hz), 4.11 (2H, q,

J=7Hz), 6.16 (1H, d, J=4Hz), 6.22 (1H, s), 6.54 (1H, d, J=4Hz)

MS (ESI⁺): m/z 370

Example 57

- 5 Ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.36-1.63 (4H, m), 2.20 (2H, t, J=7Hz), 2.48-2.63 (2H, m), 3.03 (2H, q, J=7Hz), 3.45 (3H, s), 4.09 (2H, q, J=7Hz), 4.62 (2H, s), 5.89 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 7.26 (1H, m),
10 7.37 (1H, s), 8.53 (1H, d, J=5Hz)

MS (ESI⁺): m/z 430

Example 58

- 15 Ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(3-methoxyphenyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.63 (4H, m), 2.16 (2H, t, J=7Hz), 2.54-2.65 (2H, m), 3.04 (2H, q, J=7Hz), 3.45 (3H, s), 3.83 (3H, s), 4.08 (2H, q, J=7Hz), 4.62 (2H, s), 5.96 (1H, d, J=4Hz), 6.56 (1H, d, J=4Hz), 6.87-7.00 (3H, m), 7.38 (1H, t, J=8Hz)

20 MS (ESI⁺): m/z 425

Example 59

- 25 Ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.17 (3H, t, J=7Hz), 1.43 (3H, t, J=7Hz), 1.36-1.58 (4H, m), 2.10 (2H, m), 2.56-2.68 (2H, m), 3.07 (2H, q, J=7Hz), 3.48 (3H, s), 4.02 (2H, q, J=7Hz), 4.66 (2H, s), 5.90 (1H, d, J=4Hz), 6.56 (1H, d, J=4Hz), 7.45-7.50 (1H, m), 7.72 (1H, dd, J=2 Hz, 8Hz), 7.86 (1H, d, J=2Hz), 8.16-8.24 (2H, m), 8.98 (1H, m)

30

Example 60

Ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-

yl]pentanoate

NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.17
(2H, t, J=7Hz), 2.52-2.64 (2H, m), 3.04 (2H, q, J=7Hz), 3.46 (3H, s), 4.10 (2H, q,
J=7Hz), 4.63 (2H, s), 5.89 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.42 (1H, m),
5 7.71 (1H, m), 8.62 (1H, m), 8.70 (1H, m)

MS (ESI⁺): m/z 396

Example 61

Ethyl 5-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-

10 yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.58 (4H, m), 2.17
(2H, t, J=7Hz), 2.51-2.62 (2H, m), 3.03 (2H, q, J=7Hz), 3.45 (3H, s), 4.08 (2H, q,
J=7Hz), 4.61 (2H, s), 5.92 (1H, d, J=4Hz), 6.56 (1H, d, J=4Hz), 7.25 (1H, m),
7.37 (1H, s), 7.42 (2H, m)

15

Example 62

Ethyl 5-[7-ethyl-2-methyl-4-(3-methylphenyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.16
(2H, t, J=7Hz), 2.40 (3H, s), 2.40-2.50 (2H, m), 2.54 (3H, s), 3.03 (2H, q, J=7Hz),
20 4.08 (2H, q, J=7Hz), 5.90 (1H, d, J=4Hz), 6.49 (1H, d, J=4Hz), 7.10-7.15 (2H, m),
7.24 (1H, m), 7.33 (1H, m)

MS: (m/z) 379 (M+H)

Example 65

25 Ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.18
(2H, t, J=7Hz), 2.42 (3H, s), 2.48-2.63 (2H, m), 3.05 (2H, q, J=7Hz), 3.46 (3H, s),
4.08 (2H, q, J=7Hz), 4.62 (2H, s), 5.90 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz), 7.51
30 (1H, s), 8.41 (1H, s), 8.53 (1H, s)

MS (ESI⁺): m/z 410

Example 66

Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

5 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.65 (4H, m), 2.21 (2H, t, J=7Hz), 2.37-2.49 (2H, m), 2.56 (3H, s), 3.00 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.85 (1H, m), 8.53 (1H, d, J=2Hz), 8.77 (1H, d, J=2Hz)

MS (ESI⁺): m/z 444, 446

10 Example 67

Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

15 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.63 (4H, m), 2.19 (2H, t, J=7Hz), 2.50-2.66 (2H, m), 3.03 (2H, q, J=7Hz), 3.46 (3H, s), 4.10 (2H, q, J=7Hz), 4.62 (2H, s), 5.91 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 7.88 (1H, m), 8.55 (1H, d, J=2Hz), 8.77 (1H, d, J=2Hz)

MS (ESI⁺): m/z 474, 476

Example 68

20 Ethyl 5-[4-(5,6-dichloro-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.36-1.60 (4H, m), 2.23 (2H, t, J=7Hz), 2.37-2.50 (2H, m), 2.55 (3H, s), 3.02 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.81 (1H, d, J=2Hz), 8.30 (1H, d, J=2Hz)

MS (ESI⁺): m/z 434

Example 69

30 Ethyl 4-[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.65-1.78 (2H, m), 2.16-2.25 (2H, m), 2.42 (3H, s), 2.53-2.65 (2H, m), 3.04 (2H, q, J=7Hz), 3.46 (3H, s), 4.12 (2H, q, J=7Hz),

4.67 (2H, m), 5.91 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.53 (1H, s), 8.43 (1H, s),
8.54 (1H, s)

MS (ESI⁺): m/z 396

5 Example 70

Ethyl 3-[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 2.35-2.55 (2H, m), 2.42
(3H, s), 2.84-2.96 (2H, m), 3.04 (2H, q, J=7Hz), 3.46 (3H, s), 4.08 (2H, q, J=7Hz),
10 4.65 (2H, s), 5.91 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 7.51 (1H, s), 8.41 (1H, s),
8.52 (1H, s)

Example 71

Ethyl 4-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-

15 yl]butanoate

NMR (CDCl₃, δ): 1.20 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.66-1.82 (2H, m), 2.16-
2.28 (2H, m), 2.42 (3H, s), 2.44-2.53 (2H, m), 2.59 (3H, s), 3.02 (2H, q, J=7Hz),
4.12 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.51 (1H, s), 8.41
(1H, d, J=2Hz), 8.53 (1H, d, J=2Hz)

20 MS (ESI⁺): m/z 366

Example 72

Ethyl 3-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-

yl]propanoate

25 NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 2.30-2.43 (2H, m), 2.42
(3H, s), 2.58 (3H, s), 2.76-2.86 (2H, m), 3.02 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz),
5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.48 (1H, s), 8.40 (1H, d, J=2Hz), 8.53
(1H, d, J=2Hz)

MS (ESI⁺): m/z 352

30

Example 73

Ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-

yl]propanoate

NMR (CDCl₃, δ): 1.21 (3H, t, J=7Hz), 1.39 (2H, t, J=7Hz), 2.35 (2H, t, J=7Hz), 2.58 (3H, s), 2.74-2.83 (2H, m), 3.01 (2H, q, J=7Hz), 4.08 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.55 (1H, d, J=4Hz), 7.87 (1H, s), 8.53 (1H, s), 8.79 (1H, s)

5 MS: (m/z) 416 (M⁺), 418 (M⁺-2), 85(bp)

Example 74

Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

10 NMR (CDCl₃, δ): 1.23 (3H, t, J=8Hz), 1.32-1.55 (5H, m), 2.16 (2H, t, J=8Hz), 2.46-2.57 (2H, m), 3.03 (2H, q, J=8Hz), 3.46 (3H, s), 4.09 (1H, q, J=8Hz), 4.62 (2H, s), 5.34 (1H, d, J=5Hz), 6.57 (1H, d, J=5Hz), 7.59-7.64 (2H, m), 7.68 (1H, br s), 7.75 (1H, m)

MS (ESI⁺): 420 (M+H)

15

Example 75

Ethyl 5-[2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

20 NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.34-1.55 (7H, m), 2.11-2.22 (5H, m), 2.47 (2H, m), 3.02 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 5.29 (2H, s), 5.94 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.88 (1H, m), 8.56 (1H, m), 8.79 (1H, m)

Example 76

To a solution of ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (1.20 g) in ethanol (12 mL) was added 1N sodium hydroxide (4.62 mL) and was stirred at ambient temperature for 2 hours. The reaction mixture was acidified with 1N hydrogen chloride and was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 100 mL) eluted with hexane-ethyl acetate= 3-1, 2-1, and 1-1 to give a yellow solid (846 mg). The solid was recrystallized from hexane-ethyl acetate (5-1) to give 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid as a pale

25

30

yellow crystals (795 mg, 71.4%).

5-[4-(3-Cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

mp: 109-110°C

5 NMR (CDCl₃, δ): 1.33-1.60 (7H, m), 2.42 (2H, t, J=8Hz), 2.34-2.48 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=8Hz), 5.80 (1H, d, J=5Hz), 6.52 (1H, d, J=5Hz), 7.56-7.64 (2H, m), 7.66 (1H, br s), 7.76 (1H, m)

MS (ESI⁺): m/z 362 (M-H)

10 The following compounds were obtained in substantially the same manner as that of Example 76.

Example 77

3-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

15 NMR (CDCl₃, δ): 1.36 (3H, t, J=7 H), 1.56 (2H, m), 2.03 (2H, m), 2.79 (2H, m), 3.01 (2H, q, J=7Hz), 6.01 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.27 (1H, m), 7.40-7.53 (8H, m)

Example 78

5-{7-Ethyl-2-methyl-4-[3-(trifluoromethyl)phenyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

20 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.62 (4H, m), 2.22 (2H, t, J=7Hz), 2.38-2.46 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.84 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.53-7.64 (3H, m), 7.72 (1H, d, J=8Hz)

MS (ESI⁺): m/z 403 (M-H), 405 (M+H)

25

Example 79

5-[7-Ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

30 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.67 (4H, m), 2.22 (2H, t, J=7Hz), 2.42 (3H, s), 2.35-2.48 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.83 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.53 (1H, s), 8.39 (1H, s), 8.53 (1H, s)

MS (ESI⁺): m/z 352 (M+H)

Example 80

5-[7-Ethyl-4-(3-methoxy-5-isoxazolyl)-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.58-1.83 (4H, m), 2.38 (2H, t, J=7Hz), 2.74-
2.85 (2H, m), 3.03 (2H, q, J=7Hz), 3.43 (3H, s), 4.08 (3H, s), 4.62 (2H, s), 6.28
(1H, s), 6.41 (1H, d, J=4Hz), 6.67 (1H, d, J=4Hz)
MS (ESI⁺): m/z 386 (M-H), 388 (M+H)

Example 81

5-{7-Ethyl-2-methyl-4-[3-(1,3-oxazol-5-yl)phenyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.45-1.65 (4H, m), 2.21 (2H, t, J=7Hz), 2.43-
2.53 (2H, m), 2.56 (3H, s), 3.03 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.51 (1H, d,
J=4Hz), 7.32 (1H, d, J=8Hz), 7.39 (1H, s), 7.53 (1H, t, J=8Hz), 7.65 (1H, s), 7.73
(1H, d, J=8Hz), 7.93 (1H, s)
MS (ESI⁺): m/z 402 (M-H), 404 (M+H)

Example 82

5-[4-(3,4-Dichlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.42-1.65 (4H, m), 2.27 (2H, t, J=7Hz), 2.38-
2.48 (2H, m), 2.54 (3H, s), 3.02 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.51 (1H, d,
J=4Hz), 7.19 (1H, dd, J=2 Hz, 8Hz), 7.45 (1H, d, J=2Hz), 7.56 (1H, d, J=8Hz)
MS (ESI⁺): m/z 403 (M-H), 405 (M+H)

Example 83

5-[4-(4-Chloro-2-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.47-1.66 (4H, m), 2.24 (2H, t, J=7Hz), 1.45-
2.56 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=7Hz), 5.94 (1H, d, J=4Hz), 6.53 (1H, d,
J=4Hz), 7.39 (1H, dd, J=2 Hz, 7Hz), 7.53 (1H, d, J=2Hz), 8.67 (1H, d, J=7Hz)
MS (ESI⁺): m/z 372 (M+H)

Example 84

5-[4-(5-Chloro-2-thienyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.52-1.74 (4H, m), 2.33 (2H, t, J=7Hz), 2.69-2.78 (2H, m), 3.01 (2H, q, J=7Hz), 3.44 (3H, s), 4.60 (2H, s), 6.25 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 6.97 (2H, m)
MS (ESI⁺): m/z 405 (M-H), 407 (M+H)

Example 85

5-[7-Ethyl-4-(6-methoxy-2-pyrazinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.55-1.69 (4H, m), 2.28 (2H, m), 2.52 (2H, m), 2.56 (3H, s), 3.03 (2H, q, J=7Hz), 3.97 (3H, s), 6.03 (1H, d, J=4Hz), 6.54 (1H, d, J=4Hz), 8.30 (1H, s), 8.32 (1H, s)
MS (ESI⁺): m/z 369 (M+H)

Example 86

5-[4-(1-Benzofuran-2-yl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 1.66-1.86 (4H, m), 2.34-2.47 (2H, m), 2.58 (3H, s), 2.69-2.85 (2H, m), 3.03 (2H, q, J=7Hz), 6.47 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 7.16 (1H, s), 7.26-7.43 (2H, m), 7.57 (1H, d, J=8Hz), 7.68 (1H, d, J=8Hz)

Example 87

5-[4-(1-Benzothien-2-yl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.53-1.73 (4H, m), 2.30 (2H, t, J=7Hz), 2.56 (3H, s), 2.62-2.73 (2H, m), 3.02 (2H, q, J=7Hz), 6.19 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.34-7.45 (3H, m), 7.79-7.93 (2H, m)

Example 88

5-[7-Ethyl-2-methyl-4-(1,3-oxazol-5-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.57-1.70 (2H, m), 1.70-1.88 (2H, m), 2.43 (2H, t, J=7Hz), 2.56 (3H, s), 2.66-2.75 (2H, m), 3.02 (2H, q, J=7Hz), 6.41 (1H, d,

J=4Hz), 6.60 (1H, d, J=4Hz), 7.52 (1H, s), 8.13 (1H, s)

MS (ESI⁺): m/z 328 (M+H)

Example 89

5 5-(7-Ethyl-2-methyl-4-phenylpyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.62 (4H, m), 2.20 (2H, t, J=7Hz), 2.43-
2.52 (2H, m), 2.54 (3H, s), 3.01 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.48 (1H, d,
J=4Hz), 7.33 (2H, m), 7.38-7.52 (3H, m)

MS (ESI⁺): m/z 337 (M+H)

10

Example 90

5-[7-Ethyl-2-methyl-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 1.47-1.61 (4H, m), 2.14-2.23 (2H, m), 2.44-
2.55 (2H, m), 2.59 (3H, s), 3.05 (2H, q, J=7Hz), 5.86 (1H, d, J=4Hz), 6.51 (1H, d,
J=4Hz), 7.49 (1H, m), 7.73 (1H, dd, J=2 Hz, 8Hz), 7.85 (1H, d, J=2Hz), 8.23 (2H,
m), 8.97 (1H, m)

15

MS (ESI⁺): m/z 386 (M-H), 388 (M+H)

Example 91

20 7-{4-[4-(Aminosulfonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}heptanoic acid

NMR (CDCl₃, δ): 0.98 (2H, m), 1.17-1.48 (9H, m), 2.27 (2H, t, J=7Hz), 2.36 (2H, m),
2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.06 (2H, s, br), 5.84 (1H, d, J=5Hz), 6.52 (1H,
d, J=5Hz), 7.52 (2H, d, J=9Hz), 8.04 (2H, d, J=9Hz)

25

MS (ESI⁺): m/z 444 (M+H)

Example 92

({[4-(3-Chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-3-
yl]carbonyl}amino)acetic acid

30

NMR (CDCl₃, δ): 1.41 (3H, t, J=7Hz), 3.07 (2H, q, J=7Hz), 3.95 (2H, d, J=5Hz),
6.02 (1H, t, br, 5Hz), 6.37 (1H, d, J=5Hz), 6.50 (1H, m), 6.75 (1H, d, J=5Hz),
7.01 (1H, d, J=7Hz), 7.37-7.45 (3H, m), 7.51 (1H, m), 7.55 (1H, m)

Example 93

5- $\{7\text{-Ethyl-2-methyl-4-[3-(methylsulfonyl)phenyl]pyrrolo[1,2-b]pyridazin-3-yl}\}$ pentanoic acid

- 5 NMR (CDCl₃, δ): 1.30-1.59 (7H, m), 2.22 (2H, t, J=8Hz), 2.33-2.49 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=8Hz), 3.12 (3H, s), 5.80 (1H, d, J=5Hz), 6.50 (1H, d, J=5Hz), 7.63-7.74 (2H, m), 7.95 (1H, br s), 8.03 (1H, br d, J=8Hz)
MS (ESI⁺): m/z 415 (M+H)

10 Example 94

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid
mp: 139-140°C

- NMR (CDCl₃, δ): 1.32-1.64 (7H, m), 2.28 (2H, t, J=8Hz), 2.36-2.46 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=8Hz), 5.85 (1H, d, J=5Hz), 6.52 (1H, d, J=5Hz), 7.24 (1H, br d, J=7Hz), 7.36 (1H, br s), 8.53 (1H, d, J=7Hz)
15 MS (ESI⁺): m/z 372 (M+H)

Example 95

5-[7-Ethyl-2-methyl-4-(2-vinyl-4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

- 20 NMR (CDCl₃, δ): 1.36 (3H, t, J=8Hz), 1.40-1.62 (4H, m), 2.25 (2H, t, J=8Hz), 2.35-2.47 (2H, m), 2.56 (3H, s), 3.00 (2H, q, J=8Hz), 5.54 (1H, d, J=10Hz), 5.86 (1H, d, J=5Hz), 6.23 (1H, d, J=16Hz), 6.51 (1H, d, J=5Hz), 6.88 (1H, dd, J=16, 10Hz), 7.20 (1H, dd, J=6, 1Hz), 7.38 (1H, br s), 8.70 (1H, d, J=6Hz)

25 Example 96

5-[7-Ethyl-2-methyl-4-(3-nitrophenyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

- NMR (CDCl₃, δ): 1.37 (3H, t, J=8Hz), 1.41-1.59 (4H, m), 2.23 (2H, t, J=8Hz), 2.37-2.47 (2H, m), 2.57 (3H, s), 3.02 (2H, q, J=8Hz), 5.81 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.63-7.74 (2H, m), 8.25 (1H, br s), 8.32 (1H, m)

30

Example 97

$\{[7\text{-Ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methoxy\}$ acetic

acid

NMR (CDCl₃, δ): 1.33-1.45 (9 H, m), 3.04 (2H, q, J=8Hz), 3.43 (1H, m), 4.01 (2H, s), 4.45 (2H, s), 6.09 (1H, d, J=5Hz), 6.58 (1H, d, J=5Hz), 7.13-7.22 (2H, m), 7.40-7.49 (2H, m)

5

Example 98

5-[4-(5-Acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.43-1.63 (4H, m), 2.23 (2H, t, J=7Hz), 2.35-2.48 (2H, m), 2.57 (3H, s), 2.69 (3H, s), 3.03 (2H, q, J=7Hz), 5.80 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 8.26 (1H, m), 8.78 (1H, d, J=2Hz), 9.23 (1H, d, J=2Hz)
MS: (m/z) 378 (M-H), 380 (M+H)

10

Example 99

5-{4-(2-Chloro-4-pyridinyl)-7-ethyl-2-[(methylthio)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

15

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.42-1.65 (4H, m), 2.18 (3H, s), 2.28 (2H, t, J=7Hz), 2.48-2.60 (2H, m), 3.02 (2H, q, J=7Hz), 3.81 (2H, s), 5.89 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz), 7.27 (1H, m), 7.38 (1H, s), 8.53 (1H, d, J=5Hz)
MS: (m/z) 416 (M-H), 418 (M+H)

20

Example 100

5-{4-(2-Chloro-4-pyridinyl)-7-ethyl-2-[(methylsulfonyl)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.65 (4H, m), 2.29 (2H, t, J=7Hz), 2.56-2.67 (2H, m), 2.98 (2H, q, J=7Hz), 3.13 (3H, s), 4.54 (2H, s), 5.98 (1H, d, J=4Hz), 6.69 (1H, d, J=4Hz), 7.27 (1H, m), 7.38 (1H, s), 8.56 (1H, d, J=5Hz)
MS: (m/z) 448 (M-H), 450 (M+H)

25

Example 101

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.03-1.45 (4H, m), 1.36 (3H, t, J=7Hz), 1.97 (2H, t, J=7Hz), 2.36-2.48 (2H, m), 3.02 (2H, q, J=7Hz), 5.96 (1H, d, J=4Hz), 6.64 (1H, d, J=4Hz),

30

7.31 (1H, d, J=5Hz), 7.39-7.53 (6H, m), 8.55 (1H, d, J=5Hz)

Example 102

5-[4-(6-Chloro-2-pyridinyl)-7-ethyl-2-methylpyrrolo-[1,2-b]pyridazin-3-yl]pentanoic acid

5 NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.56-1.73 (4H, m), 2.29 (2H, t, J=7Hz), 2.46-2.56 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.96 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.38-7.48 (2H, m), 7.78 (1H, t, J=8Hz)

MS (ESI⁺): m/z 372 (M+H), MS (ESI⁻): m/z 370

10 Example 103

5-[7-Ethyl-4-(3-methoxyphenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.46-1.63 (4H, m), 2.22 (2H, t, J=7Hz), 2.44-2.53 (2H, m), 2.54 (3H, s), 3.01 (2H, q, J=7Hz), 3.82 (3H, s), 5.92 (1H, d, J=4Hz), 6.49 (1H, d, J=4Hz), 6.87-7.01 (3H, m), 7.37 (1H, t, J=8Hz)

15 MS (ESI⁺): m/z 367, MS (ESI⁻): m/z 365

Example 104

5-[4-(3,5-Dichlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

20 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.42-1.53 (2H, m), 1.53-1.66 (2H, m), 2.27 (2H, t, J=7Hz), 2.41-2.49 (2H, m), 2.54 (3H, s), 3.01 (2H, q, J=7Hz), 5.88 (1H, d, J=4Hz), 6.52 (1H, d, J=4Hz), 7.26 (2H, m), 7.45 (1H, m)

MS (ESI⁺): m/z 405, MS (ESI⁻): m/z 403

Example 105

25 5-[4-(5-Chloro-2-thienyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.48-1.62 (2H, m), 1.62-1.73 (2H, m), 2.34 (2H, t, J=7Hz), 2.53 (3H, s), 2.58-2.67 (2H, m), 2.99 (2H, q, J=7Hz), 6.20 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 6.94 (1H, d, J=4Hz), 6.98 (1H, d, J=4Hz)

MS (ESI⁺): m/z 377, MS (ESI⁻): m/z 375

30

Example 106

5-[7-Ethyl-4-(3-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.64 (4H, m), 2.23 (2H, t, J=7Hz), 2.41-2.49 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=7Hz), 5.88 (1H, d, J=4Hz), 6.50 (1H, d, J=4Hz), 7.03-7.16 (3H, m), 7.38-7.47 (1H, m)

MS (ESI⁺): m/z 355, MS (ESI⁻): m/z 353

5

Example 107

5-[7-Ethyl-2-methyl-4-(3-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 1.47-1.65 (4H, m), 2.20-2.30 (2H, m), 2.45-2.53 (2H, m), 2.59 (3H, s), 3.05 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.62 (1H, t, J=8Hz), 7.79 (1H, t, J=8Hz), 7.87 (1H, d, J=8Hz), 8.21 (2H, m), 8.88 (1H, d, J=2Hz)

10

MS (ESI⁺): m/z 388, MS (ESI⁻): m/z 386

Example 108

15 5-[7-Ethyl-2-methyl-4-(4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.70 (4H, m), 2.20-2.30 (2H, m), 2.37-2.53 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=7Hz), 5.84 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.39 (2H, d, J=7Hz), 8.74 (2H, d, J=7Hz)

20 Example 109

5-[7-Ethyl-4-(3-methoxy-5-isoxazolyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.57-1.84 (4H, m), 2.41 (2H, t, J=7Hz), 2.55 (3H, s), 2.63-2.72 (2H, m), 3.02 (2H, q, J=7Hz), 4.08 (3H, s), 6.27 (1H, s), 6.34 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz)

25

Example 110

5-[7-Ethyl-4-(3-methoxyphenyl)-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.06-1.33 (4H, m), 1.36 (3H, t, J=7Hz), 1.91 (2H, t, J=7Hz), 2.42-2.53 (2H, m), 3.01 (2H, q, J=7Hz), 3.83 (3H, s), 6.03 (1H, d, J=4Hz), 6.59 (1H, d, J=4Hz), 6.93-7.02 (3H, m), 7.36-7.54 (6H, m)

30

MS (ESI⁺): m/z 429

Example 111

5-[7-Ethyl-2-methyl-4-(5-methyl-3-isoxazolyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

- 5 NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.52-1.77 (4H, m), 2.35 (2H, t, J=7Hz), 2.55 (6H, s), 2.56-2.67 (2H, m), 3.01 (2H, q, J=7Hz), 6.16 (1H, d, J=4Hz), 6.23 (1H, s), 6.54 (1H, d, J=4Hz)
MS (ESI⁺): m/z 342, MS (ESI⁻): m/z 340

10 Example 112

5-[7-Ethyl-2-phenyl-4-(4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.11-1.33 (4H, m), 1.36 (3H, t, J=7Hz), 1.99 (2H, t, J=7Hz), 2.38-2.50 (2H, m), 3.03 (2H, q, J=7Hz), 5.94 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 7.38-7.56 (7H, m), 8.74 (2H, d, J=6Hz)

15

Example 113

5-[7-Ethyl-2-phenyl-4-(2-pyrazinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.10-1.33 (4H, m), 1.36 (3H, t, J=7Hz), 1.95 (2H, t, J=7Hz), 2.45-2.57 (2H, m), 3.02 (2H, q, J=7Hz), 6.05 (1H, d, J=4Hz), 6.66 (1H, d, J=4Hz), 7.40-7.55 (5H, m), 8.67 (1H, d, J=3Hz), 8.77 (1H, s), 8.85 (1H, s)

20

MS (ESI⁺): m/z 401, MS (ESI⁻): m/z 399

Example 114

5-[7-Ethyl-2-phenyl-4-(3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

- 25 NMR (CDCl₃, δ): 1.05-1.30 (4H, m), 1.36 (3H, t, J=7Hz), 1.95 (2H, t, J=7Hz), 2.35-2.48 (2H, m), 3.02 (2H, q, J=7Hz), 5.94 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.40-7.55 (6H, m), 7.76-7.83 (1H, m), 8.65-8.72 (2H, m)

MS (ESI⁺): m/z 400, MS (ESI⁻): m/z 398

30 Example 115

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.42-1.64 (4H, m), 2.27 (2H, t, J=7Hz), 2.48-2.62 (2H, m), 3.04 (2H, q, J=7Hz), 3.45 (3H, s), 4.62 (2H, s), 5.90 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 7.27 (1H, m), 7.38 (1H, s), 8.53 (1H, d, J=5Hz)

MS (ESI⁺): m/z 402

5

Example 116

5-[7-Ethyl-2-(methoxymethyl)-4-(3-methoxyphenyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.62 (4H, m), 2.19 (2H, t, J=7Hz), 2.55-2.66 (2H, m), 3.03 (2H, q, J=7Hz), 3.45 (3H, s), 3.82 (3H, s), 4.62 (2H, s), 5.96 (1H, d, J=4Hz), 6.56 (1H, d, J=4Hz), 6.87-7.00 (3H, m), 7.37 (1H, t, J=8Hz)

MS (ESI⁺): m/z 397, MS (ESI⁻): m/z 395

Example 117

15 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.20-1.50 (4H, m), 1.38 (3H, t, J=7Hz), 2.15 (2H, t, J=7Hz), 2.55-2.68 (2H, m), 3.04 (2H, q, J=7Hz), 5.93 (1H, d, J=4Hz), 6.64 (1H, d, J=4Hz), 7.13 (1H, t, J=5Hz), 7.28 (1H, d, J=5Hz), 7.35-7.47 (3H, m), 8.54 (1H, d, J=5Hz)

20 MS (ESI⁺): m/z 440

Example 118

5-[7-Ethyl-2-(methoxymethyl)-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

25 NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 1.45-1.60 (4H, m), 2.16 (2H, m), 2.55-2.75 (2H, m), 3.07 (2H, q, J=7Hz), 3.47 (3H, s), 4.66 (2H, s), 5.89 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz), 7.45-7.53 (1H, m), 7.72 (1H, d, J=8Hz), 7.86 (1H, s), 8.22 (2H, m), 8.94 (1H, m)

MS (ESI⁺): m/z 418, MS (ESI⁻): m/z 416

30

Example 119

5-[7-Ethyl-2-(methoxymethyl)-4-(3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic

acid

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.45-1.64 (4H, m), 2.22 (2H, t, J=7Hz), 2.48-2.68 (2H, m), 3.06 (2H, q, J=7Hz), 3.46 (3H, s), 4.63 (2H, s), 5.89 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.48 (1H, m), 7.78 (1H, m), 8.62 (1H, m), 8.69 (1H, m)

5 MS (ESI⁺): m/z 368

Example 120

5-[4-(3-Chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.63 (4H, m), 2.23 (2H, t, J=7Hz), 2.53-2.63 (2H, m), 3.04 (2H, q, J=7Hz), 3.45 (3H, s), 4.63 (2H, s), 5.93 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.25 (1H, m), 7.36 (1H, s), 7.42 (2H, m)

Example 121

15 5-[7-Ethyl-2-methyl-4-(3-methylphenyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.23-1.63 (4H, m), 1.37 (3H, t, J=7Hz), 2.22 (2H, t, J=7Hz), 2.40 (3H, s), 2.40-2.49 (2H, m), 2.54 (3H, s), 3.02 (2H, q, J=7Hz), 5.89 (1H, d, J=4Hz), 6.48 (1H, d, J=4Hz), 7.10-7.14 (2H, m), 7.23-7.27 (1H, m), 7.32-7.38 (1H, m)

MS (ESI⁺): m/z 351

20

Example 124

5-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

25 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.44-1.65 (4H, m), 2.16-2.26 (2H, m), 2.43 (3H, s), 2.47-2.69 (2H, m), 3.03 (2H, q, J=7Hz), 3.45 (3H, s), 4.63 (2H, m), 5.88 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz), 7.56 (1H, s), 8.42 (1H, s), 8.53 (1H, s)

MS (ESI⁺): m/z 382, MS (ESI⁻): m/z 380

Example 125

30 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.67 (4H, m), 2.27 (2H, t, J=7Hz), 2.38-2.52 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d,

J=4Hz), 7.88 (1H, m), 8.53 (1H, d, J=2Hz), 8.77 (1H, d, J=2Hz)

MS (ESI⁺): m/z 416, 418

Example 126

- 5 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.65 (4H, m), 2.25 (2H, t, J=7Hz), 2.49-2.68 (2H, m), 3.03 (2H, q, J=7Hz), 3.45 (3H, s), 4.63 (2H, s), 5.91 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.89 (1H, m), 8.51 (1H, s), 8.79 (1H, m)

- 10 MS (ESI⁺): m/z 446, 448

Example 127

- 5-[4-(5,6-Dichloro-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

- 15 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.43-1.68 (4H, m), 2.29 (2H, t, J=7Hz), 2.38-2.52 (2H, m), 2.57 (3H, s), 3.02 (2H, q, J=7Hz), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.81 (1H, d, J=2Hz), 8.31 (1H, d, J=2Hz)

MS (ESI⁺): m/z 406, MS (ESI⁻): m/z 404

- 20 Example 128

- 5-[7-Ethyl-2-methyl-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

- NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.68 (4H, m), 2.23 (2H, t, J=7Hz), 2.38-2.53 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.46 (1H, d, J=11Hz), 5.86 (1H, d, J=4Hz), 5.89 (1H, d, J=17Hz), 6.52 (1H, d, J=4Hz), 6.72-6.83 (1H, dd, J=11 Hz, 17Hz), 7.77 (1H, m), 8.47 (1H, d, J=2Hz), 8.68 (1H, d, J=2Hz)

- 25 MS (ESI⁺): m/z 364

Example 129

- 5-[7-Ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-

- 30 yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.45-1.65 (4H, m), 2.22 (2H, t, J=7Hz), 2.45-2.73 (2H, m), 3.04 (2H, q, J=7Hz), 3.46 (3H, s), 4.63 (2H, m), 5.44 (1H, d,

J=11Hz), 5.87 (1H, d, J=18Hz), 5.92 (1H, d, J=4Hz), 6.57 (1H, d, J=4Hz), 6.72-6.83 (1H, dd, J=11 Hz, 18Hz), 7.78 (1H, s), 8.48 (1H, s), 8.68 (1H, s)
MS (ESI⁺): m/z 394 (M+H), MS (ESI⁻): m/z 392

5 Example 130

5-[4-(5-Acetyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.44-1.60 (4H, m), 2.22 (2H, t, J=7Hz), 2.50-2.63 (2H, m), 2.69 (3H, s), 3.02 (2H, q, J=7Hz), 3.46 (3H, s), 4.64 (2H, s), 5.86
10 (1H, d, J=4Hz), 6.59 (1H, d, J=4Hz), 8.29 (1H, m), 8.79 (1H, d, J=2Hz), 9.23 (1H, d, J=2Hz)
MS (ESI⁺): m/z 410, MS (ESI⁻): m/z 408

Example 131

15 4-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.70-1.87 (2H, m), 2.26 (2H, t, J=7Hz), 2.45 (3H, s), 2.53-2.81 (2H, m), 3.06 (2H, q, J=7Hz), 3.46 (3H, s), 4.66 (2H, m), 5.90 (1H, d, J=4Hz), 6.59 (1H, d, J=4Hz), 7.61 (1H, s), 8.43 (1H, s), 8.46 (1H, s)
20 MS (ESI⁺): m/z 368

Example 132

3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

25 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 2.30-2.60 (2H, m), 2.42 (3H, s), 2.77-3.13 (2H, m), 3.05 (2H, q, J=7Hz), 3.47 (3H, s), 4.66 (2H, s), 5.91 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 7.58 (1H, s), 8.42 (1H, s), 8.54 (1H, s)
MS (ESI⁺): m/z 354

30 Example 133

4-[7-Ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.70-1.88 (2H, m), 2.22-2.32 (2H, m), 2.45

(3H, s), 2.50-2.62 (2H, m), 2.59 (3H, s), 3.02 (2H, q, J=7Hz), 5.86 (1H, d, J=4Hz),
6.53 (1H, d, J=4Hz), 7.60 (1H, s), 8.42 (2H, m)

MS (ESI⁺): m/z 338, MS (ESI⁻): m/z 336

5 Example 134

3-[7-Ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 2.42 (3H, s), 2.40-2.53 (2H, m), 2.59 (3H, s),
2.82 (2H, t, J=7Hz), 3.03 (2H, q, J=7Hz), 5.86 (1H, d, J=4Hz), 6.53 (1H, d,
J=4Hz), 7.57 (1H, s), 8.38 (1H, s), 8.52 (1H, s)

10 MS (ESI⁺): m/z 324, MS (ESI⁻): m/z 322

Example 135

3-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

mp: 181-182°C

15 NMR (CDCl₃, δ): 1.38(2H, t, J=7Hz), 2.4(2H, t, J=7Hz), 2.58(3H, s), 2.74-2.85(2H,
m), 3.01(2H, q, J=7Hz), 5.89(1H, d, J=4Hz), 6.55(1H, d, J=4Hz), 7.87(1H, s),
8.54(1H, s), 8.77(1H, s)

MS: (m/z) 388 (M⁺), 390(M⁺+2), 114(bp)

20 Example 136

5-[4-(3-Cyanophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NNMR (CDCl₃, δ): 1.30-1.57 (5H, m), 2.21 (2H, t, J=8Hz), 2.47-2.57 (2H, m), 3.03
(2H, q, J=8Hz), 3.45 (3H, s), 4.62 (2H, s), 5.84 (1H, d, J=5Hz), 6.57 (1H, d,
25 J=5Hz), 7.59-7.64 (2H, m), 7.68 (1H, br s), 7.75 (1H, m)

MS (ESI⁺): 392 (M+H)

Example 136-2

5-[4-[3-(Aminocarbonyl)phenyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

30 NMR (CDCl₃, δ): 1.30-1.70 (5H, overlapped with H₂O), 2.20-2.50 (4H, m), 2.80-
2.93 (2H, m), 3.03 (2H, q, J=8Hz), 3.46 (3H, s), 4.54 (1H, d, J=10Hz), 4.77 (1H,
d, J=10Hz), 5.80 (1H, d, J=5Hz), 6.55 (1H, d, J=5Hz), 7.43-7.50 (2H, m), 7.58

(1H, t, J=8Hz), 7.77 (1H, br s), 7.88 (1H, br s), 7.99 (1H, br d, J=8Hz)

MS (ESI⁺): 410 (M+H)

Example 137

5 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.06-1.26 (4H, m), 1.36 (3H, t, J=7Hz), 1.94 (2H, t, J=7Hz), 2.40

(2H, m), 2.99 (2H, q, J=7Hz), 5.96 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.40-

7.52 (5H, m), 7.93 (1H, s), 8.59 (1H, s), 8.77 (1H, s)

10 Example 138

5-[7-Ethyl-4-(5-ethyl-3-pyridinyl)-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.05-1.42 (10H, m), 1.92 (2H, m), 2.41 (2H, m), 2.75 (2H, q,

J=7Hz), 3.01 (2H, q, J=7Hz), 5.93 (1H, d, J=5Hz), 6.55 (1H, d, J=5Hz), 7.37-7.54

(5H, m), 7.62 (1H, m), 8.45 (1H, m), 8.52 (1H, m)

15

Example 139

5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.25-1.48 (7H, m), 2.12 (2H, t, J=7Hz), 2.62 (2H, m), 3.03 (2H, q,

20 J=7Hz), 5.93 (1H, d, J=5Hz), 6.64 (1H, d, J=5Hz), 7.14 (1H, m), 7.37 (1H, d,

J=5Hz), 7.43 (1H, d, J=5Hz), 7.92 (1H, s), 8.58 (1H, m), 8.79 (1H, m)

MS (ESI⁺): m/z 484 (M+H)

Example 140

25 5-[2-[(Benzyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.34-1.48 (5H, m), 2.09 (2H, m), 2.53 (2H, m),

3.04 (2H, q, J=7Hz), 4.07 (2H, J=7Hz), 4.65 (2H, s), 4.72 (2H, s), 5.90 (1H, d,

J=5Hz), 6.60 (1H, d, J=5Hz), 7.29-7.38 (5H, m), 7.86 (1H, s), 8.54 (1H, m), 8.77

30 (1H, m)

Example 141

5-(4-(5-Bromo-3-pyridinyl)-2-[[4-(4-cyanobenzyl)oxy]methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

NMR (CDCl₃, δ): 1.35-1.56 (7H, m), 2.18 (2H, m), 2.57 (2H, m), 3.03 (2H, q, J=7Hz), 4.69 (2H, s), 4.74 (2H, s), 5.92 (1H, d, J=5Hz), 6.62 (1H, d, J=5Hz), 7.47 (2H, d, J=8Hz), 7.64 (2H, d, J=8Hz), 7.88 (1H, s), 8.54 (1H, m), 8.79 (1H, m)

Example 142

5-[2-[(Benzylamino)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 NMR (CDCl₃, δ): 1.20-1.49 (7H, m), 2.17 (2H, m), 2.32 (2H, m), 3.04 (2H, q, J=7Hz), 4.29 (4H, s), 5.94 (1H, d, J=5Hz), 6.51 (1H, s, br), 6.12 (1H, d, J=5Hz), 7.27-7.36 (3H, m), 7.48 (2H, m), 7.84 (1H, m), 8.49 (1H, m), 8.75 (1H, m)

Example 143

15 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.20-1.38 (5H, m), 1.49 (4H, m), 2.24 (2H, q, J=7Hz), 2.59 (4H, m), 3.01 (2H, q, J=7Hz), 3.70 (4H, m), 5.88 (1H, d, J=5Hz), 6.55 (1H, d, J=5Hz), 7.90 (1H, m), 8.55 (1H, m), 8.78 (1H, m)

Example 144

5-{4-[5-(Aminocarbonyl)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid from ethyl 5-[4-(5-cyano-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 NMR (CDCl₃, δ): 1.10-1.70 (4H, m), 1.37 (3H, t, J=7Hz), 2.24-2.77 (4H, m), 2.59 (3H, s), 3.02 (2H, q, J=7Hz), 5.77 (1H, d, J=4Hz), 6.52 (1H, d, J=4Hz), 7.57 (1H, br), 7.97 (1H, br), 8.07 (1H, s), 8.68 (1H, s), 9.18 (1H, s)

MS (ESI⁺): m/z 381

Example 145

5-[4-[5-(Aminocarbonyl)-3-pyridinyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.16-1.72 (4H, m), 1.37 (3H, t, J=7Hz), 2.25-2.50 (3H, m), 2.83-2.97 (1H, m), 3.04 (2H, q, J=7Hz), 3.47 (3H, s), 4.56 (1H, d, J=17Hz), 4.77 (1H, d, J=17Hz), 5.81 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.52 (1H, br), 7.82 (1H, br), 8.11 (1H, m), 8.70 (1H, d, J=2Hz), 9.18 (1H, d, J=2Hz)

5 MS (ESI⁺): m/z 411

Example 146

To a solution of triethyl 4-phosphonocrotonate (2.13 g) in tetrahydrofuran (20 mL) was added dropwise lithium bis(trimethylsilyl)amide (1.1mol/L solution in hexanes, 10 15mL) at 2°C under nitrogen, and the mixture was stirred at the same temperature for 30 minutes. To the mixture was added dropwise a solution of 4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carbaldehyde (1.2 g) in tetrahydrofuran (20 mL). After being stirred for 3 hours at 2°C, the mixture was poured into saturated aqueous ammonium chloride, and the mixture was extracted with ethyl acetate. The organic layer 15 was washed with water, brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent; 3% ethyl acetate in n-hexane) to give the title compound (1.06 g) as an yellow crystals.

Ethyl (2E,4E)-5-[4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2,4-pentadienoate 20

NMR (300 MHz, CDCl₃, δ): 1.28(3H, t, J=7Hz), 1.35(6H, d, J=7Hz), 3.30(1H, quintet, J=7Hz), 4.19(2H, quartet, J=7Hz), 5.63(1H, d, J=16Hz), 5.94(1H, dd, J=16,11Hz), 6.16(1H, dd, J=4.4,1.5Hz), 6.76(1H, dd, J=4.4,2.6Hz), 6.78(1H, d, J=16Hz), 7.11-7.23(3H, m), 7.33-7.40(2H, m), 7.72(1H, dd, J=2.6,1.5Hz)

25 MS (ESI⁺): m/z 379 (M+H)

The following compounds were obtained in substantially the same manner as that of Example 146.

Example 147

30 Ethyl (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propenoate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 1.40 (6H, d, J=7Hz), 3.38 (1H, m), 4.16 (2H,

q, J=7Hz), 5.57 (1H, d, J=15Hz), 6.25 (1H, d, J=5Hz), 6.74 (1H, d, J=5Hz), 7.15 (1H, d, J=8.5Hz), 7.29 (1H, d, J=8.5Hz), 7.33 (1H, d, J=8.5Hz), 7.35 (1H, d, J=8.5Hz), 7.63 (1H, d, J=15Hz)

MS (ESI): m/z 385 (M-H)

5

Example 148

(2E)-3-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propenenitrile

NMR (CDCl₃, δ): 1.41 (6H, d, J=7Hz), 3.28 (1H, m), 4.99 (1H, d, J=15Hz), 6.24 (1H, d, J=5Hz), 6.76 (1H, d, J=15Hz), 7.17-7.27 (2H, m), 7.30-7.40 (3H, m)

10

MS (ESI): m/z 340 (M+H)

Example 149

To a solution of ethyl (2E,4E)-5-[4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2,4-pentadienoate (300 mg) in tetrahydrofuran (3 mL) and acetic acid (1mL) was added dropwise N-chlorosuccinimide (106 mg). The mixture was stirred at ambient temperature for 24 hours. The resulting mixture was concentrated and partitioned between saturated aqueous sodium hydrogencarbonate and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography (eluent; 1% ethyl acetate in n-hexane) to give the title compound (110mg) as an oil.

15

20

Ethyl (2E,4E)-5-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2,4-pentadienoate

NMR (300 MHz, CDCl₃, δ): 1.28(3H, t, J=7Hz), 1.40(6H, d, J=7Hz), 3.33(1H, quintet, J=7Hz), 4.19(2H, quartet, J=7Hz), 5.64(1H, d, J=16Hz), 5.94(1H, dd, J=16,11Hz), 6.18(1H, d, J=4.4Hz), 6.71(1H, d, J=4.4Hz), 6.79(1H, d, J=16Hz), 7.13-7.23(3H, m), 7.32-7.37(2H, m)

25

The following compounds were obtained in substantially the same manner as that of Example 149.

Example 151

Ethyl 7-chloro-4-(2-chlorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (300 MHz, CDCl₃, δ): 0.89 (3H, t, J=7.5Hz), 1.41 (6H, d, J=7.5Hz), 3.41-3.56 (1H, m), 4.00 (2H, q, J=7.5Hz), 6.16 (1H, d, J=5Hz), 6.76 (1H, d, J=5Hz), 7.25-7.53 (4H, m)

MS (ES⁺): m/e 377.44

5

Example 152

Ethyl 7-chloro-2-isopropyl-4-(2-naphthyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (300 MHz, CDCl₃, δ): 0.78 (3H, t, J=7.5Hz), 1.43 (6H, d, J=7.5Hz), 3.29-3.41 (1H, m), 3.95 (2H, q, J=7.5Hz), 6.40 (1H, d, J=5Hz), 6.79 (1H, d, J=5Hz), 7.50-7.60 (3H, m), 7.81-8.00 (4H, m)

10

Example 153

To a solution of ethyl (2E,4E)-5-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2,4-pentadienoate (82 mg) in ethanol (2 mL) was added 1N sodium hydroxide solution (0.5 mL), and the mixture was stirred at ambient temperature for 12 hours. The resulting mixture was concentrated in vacuo, and the residue was dissolved in water, acidified with 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent; 50% ethyl acetate in n-hexane) to give the title compound (14mg) as a brown amorphous solid, which was recrystallized from aqueous ethanol.

15

20

(2E,4E)-5-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2,4-pentadienoic acid

25

NMR (300 MHz, CDCl₃, δ): 1.40 (6H, d, J=7Hz), 1.30-1.90 (1H, br), 3.34 (1H, quintet, J=7Hz), 5.64 (1H, d, J=16Hz), 5.98 (1H, dd, J=16,11Hz), 6.19 (1H, d, J=4.4Hz), 6.72 (1H, d, J=4.4Hz), 6.84 (1H, d, J=16Hz), 7.14-7.37 (5H, m)

MS(ESI): m/z 383 (M-H)

Example 154

30

To a mixture of ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (130 mg) in toluene (5 mL) was added 28% sodium

methyrate metanol solution (536 mg) and the mixture was heated under reflux for 2 hours.

The solution was acidified to pH 4 with 1N hydrochloric acid and extracted with chloroform. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. To the residue in ethanol (5 mL) was added 1N sodium hydroxide solution (1 mL) and the mixture was heated at 60°C for 1 hour. The solution was acidified to pH 4 with 1N hydrochloric acid and extracted with chloroform. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (1:1) to give 5-[7-ethyl-4-(2-methoxy-4-pyridinyl)-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid as a yellow powder (50.0 mg).

5-[7-Ethyl-4-(2-methoxy-4-pyridinyl)-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.30-1.48 (4H, m), 1.38 (3H, t, J=7Hz), 2.13 (2H, t, J=7Hz), 2.58-

2.69 (2H, m), 3.02 (2H, q, J=7Hz), 4.02 (3H, s), 5.96 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 6.78 (1H, s), 6.90 (1H, d, J=5Hz), 7.12 (1H, m), 7.34 (1H, m), 7.42 (1H, d, J=5Hz), 8.29 (1H, d, J=5Hz)

The following compounds were obtained in substantially the same manner as that of Example 154.

Example 155

5-[7-Ethyl-4-(2-methoxy-4-pyridinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.31-1.64 (7H, m), 2.25 (2H, t, J=8Hz), 2.43 (2H, br t, J=8Hz),

2.54 (3H, s), 3.00 (2H, q, J=8Hz), 4.04 (3H, s), 5.60 (1H, br s), 5.90 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 6.81 (1H, br s), 6.93 (1H, br d, J=7Hz), 8.30 (1H, d, J=7Hz)

MS (ESI⁺): m/z 368 (M+H)

Example 155-2

5-[7-Ethyl-2-methyl-4-(2-oxo-1,2-dihydro-4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.29-1.67 (7H, m), 2.29 (2H, t, J=8Hz), 2.35-2.60 (5H, m), 3.00 (2H, q, J=8Hz), 5.94 (1H, d, J=5Hz), 6.54 (1H, d, J=5Hz), 6.64 (1H, br d, J=7Hz), 6.84 (1H, br s), 7.70 (1H, br d, J=7Hz)
MS (ESI⁺): m/z 354 (M+H)

5

The following compounds were obtained in substantially the same manner as that of Example 154.

Example 156

5-[7-Ethyl-4-(2-methoxy-4-pyridinyl)-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 acid

NMR (CDCl₃, δ): 1.08-1.30 (4H, m), 1.36 (3H, t, J=7Hz), 1.95 (2H, t, J=7Hz), 2.48-2.53 (2H, m), 3.03 (2H, q, J=7Hz), 4.01 (3H, s), 6.02 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 6.82 (1H, s), 6.94 (1H, d, J=5Hz), 7.42-7.54 (5H, m), 8.29 (1H, d, J=5Hz)

15 MS (ESI⁺): m/z 430

Example 157

5-[7-Ethyl-2-(methoxymethyl)-4-(2-methoxy-4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

20 NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.64 (4H, m), 2.24 (2H, t, J=7Hz), 2.53-2.64 (2H, m), 3.03 (2H, q, J=7Hz), 3.45 (3H, s), 4.01 (3H, s), 4.61 (2H, s), 5.94 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 6.77 (1H, s), 6.89 (1H, d, J=5Hz), 8.28 (1H, d, J=5Hz)

MS (ESI⁺): m/z 398, MS (ESI⁻): m/z 396

25

Example 158

To a solution of ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (120 mg) in toluene (5 mL) and tetrahydrofuran (10 mL) was added sodium thiomethoxide (91.0 mg) and the mixture was heated under reflux for 4
30 hours. The solution was acidified with 1N hydrochloric acid and extracted with chloroform. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column

chromatography eluting with a mixture of hexane and ethyl acetate (10:1 - 3:1) to give 5-{7-ethyl-4-[2-(methylthio)-4-pyridinyl]-2-phenylpyrrolo-[1,2-b]pyridazin-3-yl}pentanoic acid as a yellow powder (85.0 mg).

- 5 5-{7-Ethyl-4-[2-(methylthio)-4-pyridinyl]-2-phenylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

NMR (CDCl₃, δ): 1.07-1.17 (2H, m), 1.17-1.30 (2H, m), 1.36 (3H, t, J=7Hz), 1.97 (2H, t, J=7Hz), 2.38-2.48 (2H, m), 2.61 (3H, s), 3.02 (2H, q, J=7Hz), 5.98 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 7.03 (1H, dd, J=1 Hz, 5Hz), 7.25 (1H, m), 7.43-7.55 (5H, m), 8.57 (1H, d, J=5Hz)

10

MS (ESI⁺): m/z 446 (M+H)

Example 159

- A mixture of 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (3.00 g), ethyl 6-benzoylhexanoate (5.07 g), and trifluoromethanesulfonic acid (376 mg) in toluene (60 mL) was refluxed for 1 hour and 20 minutes with Dean-Stark equipment. The mixture was partitioned between ethyl acetate (60 mL) and water (60 mL), and the organic layer was washed with saturated sodium bicarbonate (60 mL) and brine (60 mL), dried over magnesium sulfate, and evaporated to give a dark colored oil. Flash silica gel column chromatography eluting with acetone = 1-100 to 7-100 afforded ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo-[1,2-b]pyridazin-3-yl]pentanoate as an orange oil (4.45 g, 78.6%).
- 15
- 20

Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

- 25 NMR (CDCl₃, δ): 1.01-1.27 (7H, m), 1.36 (3H, t, J=7Hz), 1.86 (2H, t, J=7Hz), 2.40 (2H, m), 3.02 (2H, q, J=7Hz), 4.02 (2H, q, J=7Hz), 5.90 (1H, d, J=5Hz), 6.61 (1H, d, J=5Hz), 7.44-7.53 (5H, s), 7.60-7.69 (2H, m), 7.74-7.79 (2H, m)

- The following compound was obtained in substantially the same manner as that of Example 159.
- 30

Example 160

Ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.21 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.25-1.48 (4H, m), 2.07 (2H, t, J=7Hz), 2.57-2.68 (2H, m), 3.04 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.93 (1H, d, J=4Hz), 6.64 (1H, d, J=4Hz), 7.12 (1H, m), 7.28 (1H, dd, J=1 Hz, 5Hz), 7.37 (1H, m), 7.41 (1H, s), 7.45 (1H, d, J=5Hz), 8.55 (1H, d, J=5Hz)

5 MS: (m/z) 468 (M+H)

Example 161

Ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

10 NMR (CDCl₃, δ): 1.05-1.17 (2H, m), 1.19-1.30 (2H, m), 1.28 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.91 (2H, t, J=7Hz), 2.38-2.48 (2H, m), 3.02 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.96 (1H, d, J=4Hz), 6.64 (1H, d, J=4Hz), 7.31 (1H, dd, J=2 Hz, 5Hz), 7.41-7.54 (6H, m), 8.56 (1H, d, J=5Hz)

MS (ESI⁺): m/z 462 (M+H)

15

Example 162

Ethyl [4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]acetate

NMR (CDCl₃, δ): 1.08 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 3.03 (2H, q, J=7Hz), 3.36 (2H, s), 3.93 (2H, q, J=7Hz), 6.09 (1H, d, J=5Hz), 6.66 (1H, d, J=5Hz), 7.33 (1H, m), 7.41-7.50 (8H, m)

20

MS (ESI⁺): m/z 419 (M+H)

Example 163

Ethyl 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

25 NMR (CDCl₃, δ): 1.06 (3H, t, J=7Hz), 1.41 (3H, t, J=7Hz), 3.08 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 6.34 (1H, d, J=5Hz), 6.53 (1H, m), 6.74 (1H, d, J=5Hz), 6.97 (1H, m), 7.39-7.46 (3H, m), 7.52 (2H, m)

MS (ESI⁺): m/z 395 (M+H)

30 Example 164

Ethyl 4-(3-chlorophenyl)-7-ethyl-2-(2-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (CDCl₃, δ): 0.94 (3H, m), 1.41 (3H, m), 3.08 (2H, q, J=7Hz), 3.11 (2H, m),

4.00 (2H, m), 6.36 (1H, m), 6.76 (1H, m), 7.26-7.55 (4H, m), 7.84 (1H, m), 8.15 (1H, m), 8.57 (1H, m)

MS (ESI⁺): m/z 406 (M+H)

5 Example 165

Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(1,3-thiazol-2-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.21 (3H, t, J=7Hz), 1.33-1.50 (7H, m), 2.14 (2H, t, J=7Hz), 2.46 (2H, m), 2.97 (2H, q, J=7Hz), 3.06 (2H, q, J=7Hz), 4.05 (2H, q, J=7Hz), 5.88 (1H, d, J=5Hz), 6.67 (1H, d, J=5Hz), 7.43 (1H, d, J=3Hz), 7.64-7.67 (2H, m), 7.70 (1H, m), 7.78 (1H, m), 7.93 (1H, d, J=3Hz)

Example 166

Methyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(1-methyl-1H-pyrrol-2-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.04 (2H, m), 1.21-1.41 (5H, m), 1.99 (2H, t, J=7Hz), 2.46 (2H, m), 3.02 (2H, q, J=7Hz), 3.60 (3H, s), 3.68 (3H, s), 5.89 (1H, d, J=5Hz), 6.23 (1H, m), 6.35 (1H, m), 6.62 (1H, d, J=5Hz), 6.76 (1H, m), 7.62-7.79 (4H, m)

20 Example 167

Ethyl 3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

NMR (CDCl₃, δ): 1.08 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 2.02 (2H, m), 2.80 (2H, m), 3.02 (2H, q, J=7Hz), 3.89 (2H, q, J=7Hz), 6.01 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.31 (1H, m), 7.41-7.54 (8H, m)

25 Example 168

Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(1,3-oxazol-5-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.17-1.49 (10H, m), 2.08 (2H, t, J=7Hz), 2.57 (2H, m), 3.03 (2H, q, J=7Hz), 4.06 (2H, q, J=7Hz), 5.91 (1H, d, J=5Hz), 6.66 (1H, d, J=5Hz), 7.55 (1H, s), 7.62-7.68 (3H, m), 7.78 (1H, m), 8.04 (1H, s)

Example 169

Ethyl 5-[7-ethyl-4-(3-methoxyphenyl)-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.05-1.29 (4H, m), 1.18 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.86
(2H, t, J=7Hz), 2.42-2.52 (2H, m), 3.02 (2H, q, J=7Hz), 3.84 (3H, s), 4.02 (2H, q,
5 J=7Hz), 6.02 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 6.95-7.02 (3H, m), 7.36-7.56
(6H, m)

Example 170

Ethyl 5-[7-ethyl-2-phenyl-4-(4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

10 NMR (CDCl₃, δ): 1.04-1.29 (4H, m), 1.19 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.88
(2H, t, J=7Hz), 2.38-2.48 (2H, m), 3.02 (2H, q, J=7Hz), 4.04 (2H, q, J=7Hz), 5.95
(1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.36 (2H, m), 7.42-7.54 (5H, m), 8.76 (2H,
m)

15 Example 171

Ethyl 5-[7-ethyl-2-phenyl-4-(2-pyrazinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.10-1.32 (4H, m), 1.18 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 1.90
(2H, t, J=7Hz), 2.45-2.55 (2H, m), 3.02 (2H, q, J=7Hz), 4.02 (2H, q, J=7Hz), 6.05
(1H, d, J=4Hz), 6.66 (1H, d, J=4Hz), 7.43-7.56 (5H, m), 8.66 (1H, m), 8.77 (1H,
20 m), 8.86 (1H, m)

Example 172

Ethyl 5-[7-ethyl-2-phenyl-4-(3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.04-1.30 (4H, m), 1.18 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.87
25 (2H, t, J=7Hz), 2.38-2.50 (2H, m), 3.02 (2H, q, J=7Hz), 4.01 (2H, q, J=7Hz), 5.96
(1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 7.42-7.55 (6H, m), 7.77 (1H, m), 8.66-8.73
(2H, m)

Example 173

30 Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-
yl]pentanoate

NMR (CDCl₃, δ): 1.12-1.28 (7H, m), 1.36 (3H, t, J=7Hz), 1.89 (2H, t, J=7Hz), 2.43

(2H, m), 3.01 (2H, m), 4.02 (2H, q, J=7Hz), 5.97 (1H, d, J=5Hz), 6.65 (1H, d, J=5Hz), 7.43-7.55 (5H, m), 7.93 (1H, m), 8.61 (1H, m), 8.79 (1H, m)

Example 174

- 5 Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.16-1.46 (10H, m), 1.57 (2H, t, J=7Hz), 2.62 (2H, m), 2.30 (2H, m), 3.03 (2H, q, J=7Hz), 4.05 (2H, q, J=7Hz), 5.93 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.36 (1H, m), 7.44 (1H, m), 7.91 (1H, m)

10

Example 175

- To a solution of ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (1.00 g) in dimethylsulfoxide (20 mL) was added 1N sodium hydroxide (5.31 mL) over 1.5 hours. The reaction was quenched by adding 1N hydrochloric acid (6 mL) under an ice-bath. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 x 2 mL) and brine, dried over magnesium sulfate, and evaporated. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1/3 to 1/1 afforded 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid as an yellow solid (668 mg).

20

5-[4-(3-Cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.03-1.25 (4H, m), 1.36 (3H, t, J=7Hz), 1.93 (2H, t, J=7Hz), 2.39 (2H, m), 3.02 (2H, q, J=7Hz), 5.91 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.26-7.53 (5H, s), 7.56-7.69 (2H, m), 7.72-7.79 (2H, m)

25

MS (ESI⁺): m/z 424 (M+H)

The following compounds were obtained in substantially the same manner as that of Example 175.

30 Example 176

5-[4-(3-Cyanophenyl)-7-ethyl-2-(1,3-thiazol-2-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.20-1.52 (7H, m), 2.19 (2H, m), 2.98 (2H, m), 3.04 (2H, q, J=7Hz), 4.05 (2H, q, J=7Hz), 5.38 (1H, d, J=5Hz), 6.67 (1H, d, J=5Hz), 7.43 (1H, d, J=3Hz), 7.60-7.64 (2H, m), 7.67 (1H, m), 7.76 (1H, m), 7.92 (1H, d, J=3Hz)
MS (ESI⁺): m/z 431 (M+H)

5

Example 177

5-[4-(3-Cyanophenyl)-7-ethyl-2-(1-methyl-1H-pyrrol-2-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.12 (2H, m), 1.23-1.41 (5H, m), 2.04 (2H, t, J=7Hz), 2.48 (2H, m),
10 3.02 (2H, q, J=7Hz), 3.68(3H, s), 5.90 (1H, d, J=5Hz), 6.22 (1H, m), 6.35 (1H, m),
6.62 (1H, d, J=5Hz), 6.75 (1H, m), 7.57-7.789 (4H, m)
MS (ESI⁺): m/z 427 (M+H)

Example 178

15 5-[4-(3-Cyanophenyl)-7-ethyl-2-(1,3-oxazol-5-yl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.31-1.49 (7H, m), 2.17 (2H, t, J=7Hz), 2.57 (2H, m), 3.04 (2H, q, J=7Hz), 5.42 (1H, d, J=5Hz), 6.67 (1H, d, J=5Hz), 7.56 (1H, s), 7.64 (2H, m),
7.67 (1H, s), 7.78 (1H, m), 8.07 (1H, s)

20

Example 179

5-[4-(3-Cyanophenyl)-2-(3,5-dimethyl-4-isoxazolyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.04-1.30 (7H, m), 1.97 (2H, t, J=7Hz), 2.26-2.35 (5H, m), 2.41
25 (3H, s), 3.00 (2H, q, J=7Hz), 4.06 (2H, q, J=7Hz), 5.97 (1H, d, J=5Hz), 6.68 (1H, d, J=5Hz), 7.61-7.68 (2H, m), 7.73 (1H, s), 7.79 (1H, m)

Example 180

A solution of 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (120 mg),
30 1-tert-butyl 7-ethyl 2-[(3,5-dimethyl-4-isoxazolyl)carbonyl]heptanedioate (203 mg), and
toluenesulfonic acid monohydrate (3.76 mg) in toluene (1 mL) was refluxed for 1 hour.
Additional p-toluenesulfonic acid monohydrate (14.5 mg) was added, and the mixture

was refluxed for 1 hour. The mixture was stirred further for 0.5 hour after adding trifluoromethanesulfonic acid (3.76 mg). The mixture was partitioned between ethyl acetate (20 mL) and saturated sodium bicarbonate (10 mL). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. Flash silica gel
5 column chromatography eluting with ethyl acetate-hexane = 1/40 to 2/5 afforded ethyl 5-[4-(3-cyanophenyl)-2-(3,5-dimethyl-4-isoxazolyl)-7-ethylpyrrolo-[1,2-b]pyridazin-3-yl]pentanoate as a yellow gum (75.7 mg, 19.1%).

Ethyl 5-[4-(3-cyanophenyl)-2-(3,5-dimethyl-4-isoxazolyl)-7-ethylpyrrolo[1,2-
10 b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.04-1.30 (7H, m), 1.97 (2H, t, J=7Hz), 2.26-2.35 (5H, m), 2.41 (3H, s), 3.00 (2H, q, J=7Hz), 4.06 (2H, q, J=7Hz), 5.97 (1H, d, J=5Hz), 6.68 (1H, d, J=5Hz), 7.61-7.68 (2H, m), 7.73 (1H, s), 7.79 (1H, m)

15 Example 181

To a solution of N-[2-(3-cyanobenzoyl)-5-ethyl-1H-pyrrol-1-yl]-2-(methylsulfonyl)acetamide (2.70 g) in tetrahydrofuran (30 mL) was added sodium hydride (601 mg, 60% in oil) under an ice-bath. After stirring for 40 minutes, the reaction was quenched by adding 1N hydrochloric acid (15 mL). The mixture was
20 extracted with ethyl acetate (50 mL), and the extract was washed with water (50 x 2 mL) and brine (50 mL), dried over magnesium sulfate, and evaporated to give a brownish yellow solid (3.36 g). The solid was triturated in diisopropyl ether (20 mL) to give 3-[7-ethyl-3-(methylsulfonyl)-2-oxo-1,2-dihydropyrrolo[1,2-b]pyridazin-4-yl]benzonitrile as a yellow powder (2.31 g, 90.1%).

25

3-[7-Ethyl-3-(methylsulfonyl)-2-oxo-1,2-dihydropyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 2.46-3.07 (5H, m), 6.81 (1H, d, J=5Hz), 6.70 (1H, d, J=5Hz), 7.60-7.69 (3H, m), 7.83 (1H, d, J=9Hz)

30

The following compound was obtained in substantially the same manner as that of Example 181.

Example 182

Ethyl 4-(4-cyanophenyl)-7-ethyl-2-oxo-1,2-dihydropyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (CDCl₃, δ): 0.78 (3H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 3.02 (2H, q, J=7Hz), 4.02 (2H, q, J=7Hz), 6.15 (1H, d, J=5Hz), 6.64 (1H, d, J=5Hz), 7.42 (2H, d, J=9Hz), 7.77 (2H, d, J=9Hz), 11.74 (1H, s, br)

MS (ESI⁺): m/z 336 (M+H)

Example 183

To a solution of 3-[7-ethyl-3-(methylsulfonyl)-2-oxo-1,2-dihydropyrrolo[1,2-b]pyridazin-4-yl]benzonitrile (1.30 g) and triethylamine (578 mg) in dichloromethane (18 mL) was added trifluoromethanesulfonic anhydride (1.61 g) under an ice-bath over 30 minutes (3 to 7°C). After stirring for 0.5 hour, the reaction was quenched by adding water (100 mL). The mixture was partitioned between ethyl acetate (200 mL) containing chloroform (200 mL) and 1N hydrochloric acid (50 mL). An insoluble yellow solid was collected by filtration (0.542 g). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a dark yellow solid (1.27 g). Both the solid was combined, and triturated in diisopropyl ether (30 mL) to give 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-2-yl trifluoromethanesulfonate as a brownish yellow powder (1.67 g, 92.6%).

4-(3-Cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-2-yl trifluoromethanesulfonate

NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 3.02 (2H, q, J=7 Hz), 3.22 (3H, s), 6.40 (1H, d, J=5Hz), 6.93 (1H, d, J=5Hz), 7.63 (3H, m), 7.82 (1H, m)

Example 184

A mixture of 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-2-yl trifluoromethanesulfonate (150 mg) and pyrrolidine (45.6 mg) in tetrahydrofuran (1 mL) was refluxed for 1.5 hours. The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (10 mL). The organic extract was washed with brine, dried over magnesium sulfate, and evaporated to give a dark colored solid. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-4 to 1-2 afforded 3-[7-ethyl-3-(methylsulfonyl)-2-(1-pyrrolidinyl)-

pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile as a yellow oil, which was crystallized upon standing (112 mg, 89.6%).

3-[7-Ethyl-3-(methylsulfonyl)-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

5 NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.99 (4H, m), 3.99 (2H, q, J=7Hz), 3.22 (3H, s), 3.42-3.70 (4H, m), 6.28 (1H, d, J=5Hz), 6.68 (1H, d, J=5Hz), 7.57 (1H, t, J=9Hz), 7.69- 7.78 (3H, m)

MS (ESI⁺): m/z 395 (M+H)

10 The following compounds were obtained in substantially the same manner as that of Example 184.

Example 185

3-[2-(Dimethylamino)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

15 NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 2.97 (6H, s), 3.02 (2H, q, J=7Hz), 3.26 (3H, s), 6.28 (1H, d, J=5Hz), 6.69 (1H, d, J=5Hz), 7.57 (1H, t, J=9Hz), 7.66- 7.79 (3H, m)

MS (ESI⁺): m/z 369 (M+H)

Example 186

20 3-[7-Ethyl-2-[(2-methoxyethyl)amino]-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.35 (3H, t, J=7Hz), 2.96 (2H, q, J=7Hz), 3.07 (3H, s), 3.43 (3H, s), 3.61-3.73 (4H, m), 5.96 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 6.75 (1H, m, br), 7.51- 7.60 (3H, m), 7.74 (1H, m)

25 MS (ESI⁺): m/z 399 (M+H)

Example 187

A mixture of ethyl 2-(4-fluorobenzoyl)-3-oxo-4-phenylbutanoate (1.4 g), 1H-pyrrol-1-amine (350 mg), and p-toluenesulfonic acid monohydrate (41 mg) in ethanol (10
30 ml) was refluxed for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of

ethyl acetate and hexane (1:4) to give ethyl 2-benzyl-4-(4-fluorophenyl)pyrrolo[1,2-b]pyridazine-3-carboxylate (828 mg) as an oil.

Ethyl 2-benzyl-4-(4-fluorophenyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

- 5 NMR (CDCl₃, δ): 0.70 (3H, t, J=7Hz), 3.71 (2H, q, J=7Hz), 4.29 (2H, s), 6.37 (1H, dd, J=1, 4Hz), 6.85 (1H, dd, J=2, 4Hz), 7.10-7.30 (7H, m), 7.38-7.46 (2H, m), 7.83 (1H, dd, 1, 2Hz)

Example 188

- 10 To a solution of ethyl 2-benzyl-4-(4-fluorophenyl)pyrrolo[1,2-b]pyridazine-3-carboxylate (730 mg) in tetrahydrofuran (10 ml) was added N-chlorosuccinimide (260 mg) and the mixture was stirred at 20°C for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with aqueous sodium thiosulfate, water and brine, dried over magnesium sulfate, and evaporated. The
15 residue was purified by silica gel column chromatography eluting with a mixture of toluene and ethyl acetate (10:1) to give ethyl 2-benzyl-7-chloro-4-(4-fluorophenyl)pyrrolo[1,2-b]pyridazine-3-carboxylate (285 mg) as a yellow oil.

Ethyl 2-benzyl-7-chloro-4-(4-fluorophenyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

- 20 NMR (CDCl₃, δ): 0.69 (3H, t, J=7Hz), 3.70 (2H, q, J=7Hz), 4.37 (2H, s), 6.39 (1H, d, J=4Hz), 6.82 (1H, d, J=4Hz), 7.10-7.30 (7H, m), 7.35-7.45 (2H, m)

Example 189

- 25 A mixture of ethyl 3-(4-fluorobenzoyl)-4-oxopentanoate (800 mg), 1H-pyrrol-1-amine (265 mg), and p-toluenesulfonic acid monohydrate (31 mg) in ethanol (5 ml) was refluxed for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:4) to give ethyl [4-(4-fluorophenyl)-2-methylpyrrolo[1,2-
30 b]pyridazin-3-yl]acetate (1.09 g) as an oil.

Ethyl [4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 2.45 (3H, s), 3.45 (2H, s), 4.16 (2H, q, J=7Hz), 6.03 (1H, dd, J=1, 4Hz), 6.72 (1H, dd, J=2, 4Hz), 7.17 (2H, dt, J=2, 7Hz), 7.40 (2H, ddd, J=2, 5, 7Hz), 7.68 (1H, dd, J=1, 2Hz)

5 Example 190

To a solution of ethyl [4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate (100 mg) in tetrahydrofuran (2 ml) was added N-chlorosuccinimide (43 mg) and the mixture was stirred at 20°C for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with aqueous ethyl acetate, water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography eluting with a mixture of toluene and ethyl acetate (10:1) to give ethyl [7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate (34 mg) as a yellow oil.

15 Ethyl [7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 2.54 (3H, s), 3.47 (2H, s), 4.16 (2H, q, J=7Hz), 6.05 (1H, d, J=4Hz), 6.68 (1H, d, J=4Hz), 7.18 (2H, dt, J=2, 7Hz), 7.38 (2H, ddd, J=2, 5, 7Hz)

20 Example 191

To a solution of ethyl [7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate (300 mg) in tetrahydrofuran (4 ml) was added 1N sodium hydroxide (1.7 ml), followed by methanol (2 ml). After standing at 20°C overnight, the mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was triturated with ether to give [7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetic acid (250 mg) as a yellow powder.

[7-Chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetic acid

30 NMR (CDCl₃, δ): 2.57 (3H, s), 3.54 (2H, s), 6.06 (1H, d, J=4Hz), 6.69 (1H, d, J=4Hz), 7.19 (2H, t, J=7Hz), 7.38 (2H, dd, J=5, 7Hz)

Example 192

To a solution of [7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetic acid (220 mg) in tetrahydrofuran (10 ml) was added 1,1'-carbonyldiimidazole (18 mg) and the mixture was stirred at 20°C for 1 hour, then magnesium bis(3-ethoxy-3-oxo-propanoate) (109 mg) was added. After the mixture was stirred overnight at 20°C, magnesium bis(3-ethoxy-3-oxo-propanoate) (109 mg) was added. After stirring for 3 hours, the mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give the product (237 mg) as an oil, which was triturated with ethyl acetate and washed with isopropyl ether to give ethyl 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-oxobutanoate (212 mg) as a yellow powder.

Ethyl 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-oxobutanoate

mp 116-118°C

NMR (CDCl₃, δ): 1.25 (3H, t, J=7Hz), 2.46 (3H, s), 3.40 (2H, s), 3.75 (2H, s), 4.16 (2H, q, J=7Hz), 6.04 (1H, d, J=4Hz), 6.68 (1H, d, J=4Hz), 7.20 (2H, t, J=7Hz), 7.28 (2H, dd, J=5, 7Hz)

Example 193

To a solution of ethyl 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-oxo-butanoate (160 mg) in methanol (5 ml) was added sodium borohydride (23.4 mg) at 0°C and the mixture was stirred at the same temperature for 1 hour. The mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by preparative thin-layer chromatography eluting with a mixture of ethyl acetate and hexane (1:3) and triturated with ethyl acetate to give ethyl 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-hydroxybutanoate (95 mg) as a yellow powder.

Ethyl 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-

hydroxybutanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 2.18-2.38 (2H, m), 2.67 (3H, s), 2.70-2.85 (2H, m), 4.03 (1H, m), 4.09 (2H, q, J=7Hz), 5.96 (1H, d, J=4Hz), 6.65 (1H, d, J=4Hz), 7.19 (2H, t, J=7Hz), 7.30-7.45 (2H, m)

5

Example 194

To a solution of ethyl 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-hydroxybutanoate (52 mg) in tetrahydrofuran (1 ml) was added 1N sodium hydroxide (0.27 ml), followed by methanol (1 ml). After standing at 20°C overnight, the mixture was partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated to give 4-[7-chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-hydroxybutanoic acid (45 mg) as a yellow oil.

10 4-[7-Chloro-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-3-hydroxybutanoic acid

NMR (CDCl₃, δ): 2.125-2.45 (2H, m), 2.66 (3H, s), 2.70-2.88 (2H, m), 4.02 (1H, m), 5.97 (1H, d, J=4Hz), 6.65 (1H, d, J=4Hz), 7.20 (2H, t, J=7Hz), 7.30-7.45 (2H, m)

20 Example 195

A mixture of ethyl 7-(4-fluorobenzoyl)-8-oxononanoate (300 mg), (1-amino-5-ethyl-1H-pyrrol-2-yl)(4-fluorophenyl)methanone (216 mg), and p-toluenesulfonic acid monohydrate (35.4 mg) in ethanol (6 ml) was refluxed for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:4) to give ethyl 6-[7-ethyl-2,4-bis(4-fluorophenyl)pyrrolo[1,2-b]pyridazin-3-yl]hexanoate (83 mg) and ethyl 6-[7-ethyl-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate (40 mg) as an oil.

30

Ethyl 6-[7-ethyl-2,4-bis(4-fluorophenyl)pyrrolo[1,2-b]pyridazin-3-yl]hexanoate

NMR (CDCl₃, δ): 0.85-1.00 (2H, m), 1.00-1.10 (2H, m), 1.16-1.30 (2H, m), 1.21 (3H,

t, J=7Hz), 1.36 (3H, t, J=7Hz), 2.00 (2H, t, J=7Hz), 2.40 (2H, t, J=7Hz), 3.01 (2H, q, J=7Hz), 4.06 (2H, q, J=7Hz), 5.97 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 7.12-7.24 (4H, m), 7.38 (2H, dd, J=5, 9Hz), 7.50 (2H, dd, J=5, 9Hz)

5 Ethyl 6-[7-ethyl-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate

NMR (CDCl₃, δ): 1.15-1.30 (2H, m), 1.23 (3H, t, J=7Hz), 1.35-1.45 (2H, m), 1.37 (3H, t, J=7Hz), 1.45-1.55 (2H, m), 2.18 (2H, t, J=7Hz), 2.40 (2H, t, J=7Hz), 2.54 (3H, s), 3.01 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz), 5.85 (1H, d, J=4Hz), 6.49 (1H, d, J=4Hz), 7.16 (2H, t, J=9Hz), 7.32 (2H, dd, J=5, 9Hz)

10

Example 196

A mixture of (1-amino-5-ethyl-1H-pyrrol-2-yl)(4-fluorophenyl)methanone (500 mg), ethyl 8-acetyl-9-oxodecanoate (678 mg), and p-toluenesulfonic acid monohydrate (82 mg) in ethanol (5 ml) was refluxed for 2 hours. The mixture was partitioned between
 15 ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel eluting with toluene to give ethyl 6-[7-ethyl-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate (130 mg) as an oil and
 20 [5-ethyl-1-((1E)-1-[7-ethyl-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethylidene)amino)-1H-pyrrol-2-yl](4-fluorophenyl)-methanone (70 mg) as a yellow crystal.

[5-Ethyl-1-((1E)-1-[7-ethyl-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethylidene)amino)-1H-pyrrol-2-yl](4-fluorophenyl)methanone

25 NMR (CDCl₃, δ): 1.13 (3H, t, J=7Hz), 1.39 (3H, t, J=7Hz), 1.80-2.00 (2H, m), 1.91 (3H, s), 2.86 (3H, s), 3.06 (2H, q, J=7Hz), 5.97 (1H, d, J=4Hz), 6.11 (1H, d, J=4Hz), 6.62 (2H, t, J=4Hz), 7.11 (4H, t, J=9Hz), 7.48 (2H, dd, J=5, 9Hz), 7.82 (2H, dd, J=5, 9Hz)

30 Ethyl 6-[7-ethyl-4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate

NMR (CDCl₃, δ): 1.15-1.30 (2H, m), 1.23 (3H, t, J=7Hz), 1.35-1.45 (2H, m), 1.37 (3H, t, J=7Hz), 1.45-1.55 (2H, m), 2.18 (2H, t, J=7Hz), 2.40 (2H, t, J=7Hz), 2.54

(3H, s), 3.01 (2H, q, J=7Hz), 4.10 (2H, q, J=7Hz), 5.85 (1H, d, J=4Hz), 6.49 (1H, d, J=4Hz), 7.16 (2H, t, J=9Hz), 7.32 (2H, dd, J=5, 9Hz)

Example 197

5 A mixture of ethyl 7-(4-cyanobenzoyl)-8-oxononanoate (2.2 g), 2-ethyl-1H-pyrrol-1-amine (809 mg), and p-toluenesulfonic acid monohydrate (64 mg) in toluene (40 ml) was refluxed for 20 minutes. The mixture was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on
10 silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give the product, which was triturated with hexane to give ethyl 6-[4-(4-cyanophenyl)-7-ethyl-2-methylpyrrolo-[1,2-b]pyridazin-3-yl]hexanoate (2.21 g) as an yellow crystals.

Ethyl 6-[4-(4-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate

15 NMR (CDCl₃, δ): 1.15-1.25 (2H, m), 1.25 (3H, t, J=7Hz), 1.30-1.45 (2H, m), 1.38 (3H, t, J=7Hz), 1.45-1.65 (2H, m), 2.19 (2H, t, J=7Hz), 2.38 (2H, t, J=7Hz), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.80 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.48 (2H, t, J=9Hz), 7.78 (2H, d, J=9Hz)

20 Example 198

To a solution of ethyl 6-[4-(4-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate (1.5 g) in tetrahydrofuran (15 ml) was added 2N potassium hydroxide (7.4 ml), followed by methanol (7.4 ml). After stirring at 50°C for 2 hours and 60°C for 3 hours, the mixture was partitioned between 1N hydrochloric acid and ethyl
25 acetate. The precipitates were filtered and washed with ethyl acetate. The organic layer and the washings were combined, washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was triturated with ethyl acetate and the precipitates were filtered. The filtrate was purified by silica gel column chromatography eluting with a mixture of ethyl acetate and hexane (1:1) and triturated with isopropyl ether to give 6-[4-
30 (4-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoic acid (650 mg) as an yellow crystals. The two precipitates were combined and recrystallized from ethyl acetate to give 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid (550 mg, 37.6%) as an yellow crystals.

6-[4-(4-Cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoic acid

NMR (CDCl₃, δ): 1.15-1.30 (2H, m), 1.35-1.45 (2H, m), 1.38 (3H, t, J=7Hz), 1.45-1.60 (2H, m), 2.26 (2H, t, J=7Hz), 2.38 (2H, t, J=7Hz), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 5.80 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.48 (2H, t, J=9Hz), 7.79 (2H, d, J=9Hz)

6-{4-[4-(Aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid

NMR (CDCl₃, δ): 1.1-1.20 (2H, m), 1.29 (3H, t, J=7Hz), 1.30-1.45 (4H, m), 2.10 (2H, t, J=7Hz), 2.37 (2H, t, J=7Hz), 2.51 (3H, s), 2.92 (2H, q, J=7Hz), 5.73 (1H, d, J=4Hz), 6.51 (1H, d, J=4Hz), 7.45 (2H, t, J=9Hz), 7.47 (1H, s), 7.80 (2H, d, J=9Hz), 8.09 (1H, s)

15 Example 199

To a solution of 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (200 mg) in toluene (6 mL) was added 2,4-pentanedione (837 mg) and p-toluenesulfonic acid monohydrate (32 mg) at ambient temperature. The reaction mixture was refluxed for 1 hour. The residue was purified by flash silica gel chromatography (silica gel, 80 mL) eluted with hexane-ethyl acetate = 10-1 to give 3-(3-acetyl-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl)benzonitrile (63 mg, 24.8%) as a yellow solid.

3-(3-Acetyl-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl)benzonitrile

NMR (CDCl₃, δ): 1.39 (3H, t, J=8Hz), 1.95 (3H, s), 2.50 (3H, s), 3.04 (2H, q, J=8Hz), 6.27 (1H, d, J=5Hz), 6.69 (1H, d, J=5Hz), 7.59-7.72 (2H, m), 7.76-7.84 (2H, m)
MS (ESI⁺): m/z 304 (M+H)

Example 200

To a solution of ethyl (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propenoate (50 mg) in toluene was added dropwise 1.5 M diisobutylaluminum hydride (0.277 mL) in toluene (24 mL) in a dry ice-acetone bath. After addition, the mixture was stirred for 2 hours (-10°C). The reaction

mixture was quenched with sodium, potassium-tartrate and was filtered through Celite. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 40 mL) eluted with hexane-ethyl acetate = 10-1, 5-1, and 3-1 to give (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propen-1-ol as a yellow solid (30 mg).

(2E)-3-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propen-1-ol

NMR (CDCl₃, δ): 1.38 (6H, d, J=7Hz), 3.31 (1H, m), 4.05-4.11 (2H, m), 5.48 (1H, dt, J=15, 6Hz), 6.11 (1H, d, J=5Hz), 6.45 (1H, d, J=15Hz), 6.68 (1H, d, J=5Hz), 7.08-7.18 (2H, m), 7.29-7.40 (2H, m)

MS (ESI⁺): m/z 345 (M+H)

The following compounds were obtained in substantially the same manner as that of Example 200.

Example 201

[4-(4-Fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methanol

NMR (CDCl₃, δ): 1.45 (1H, t, J=5Hz), 2.65 (3H, s), 4.47 (2H, d, J=5Hz), 6.13 (1H, m), 6.73 (1H, m), 7.14-7.28 (2H, m), 7.43-7.51 (2H, m), 7.70 (1H, m)

MS (ESI⁺): m/z 257 (M+H)

Example 202

[7-Ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methanol

NMR (CDCl₃, δ): 1.31-1.46 (10 H, m), 3.04 (2H, q, J=8Hz), 3.46 (1H, m), 4.49 (2H, d, J=5Hz), 6.05 (1H, d, J=5Hz), 6.56 (1H, d, J=5Hz), 7.12-7.22 (2H, m), 7.41-7.50 (2H, m)

MS (ESI⁺): m/z 313 (M+H)

Example 203

2-[[7-Ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methoxy]ethanol

NMR (CDCl₃, δ): 1.30-1.45 (9 H, m), 3.04 (2H, q, J=8Hz), 3.35 (1H, m), 3.46 (2H, t,

J=6Hz), 3.69 (2H, br t, J=8Hz), 4.30 (2H, s), 6.07 (1H, d, J=5Hz), 6.55 (1H, d, J=5Hz), 7.11-7.22 (2H, m), 7.41-7.51 (2H, m)

MS (ESI⁺): m/z 357 (M+H)

5 Example 204

- To a solution of (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propen-1-ol (30 mg) in N,N-dimethylformamide (1 mL) was added 60% sodium hydride in oil (3.8 mg) in an ice-water bath under nitrogen atmosphere. After 20 minutes, to the mixture was added methyl iodide (18.5 mg) at the temperature.
- 10 After 15 minutes, the reaction mixture was stirred at ambient temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water three times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by p-TLC (hexane-ethyl acetate = 10-1) to give 7-chloro-4-(4-fluorophenyl)-2-isopropyl-3-[(1E)-3-methoxy-1-propenyl]pyrrolo[1,2-
- 15 b]pyridazine as a brown oil (3.5 mg, 10.2 %).

7-Chloro-4-(4-fluorophenyl)-2-isopropyl-3-[(1E)-3-methoxy-1-propenyl]pyrrolo[1,2-b]pyridazine

- NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 3.31 (1H, m), 4.05-4.11 (2H, m), 5.48 (1H, dt, J=15, 6Hz), 6.11 (1H, d, J=5Hz), 6.45 (1H, d, J=15Hz), 6.68 (1H, d, J=5Hz), 7.08-7.18 (2H, m), 7.29-7.40 (2H, m)
- 20 MS (ESI⁺): m/z 345 (M+H)

Example 205

- 25 To dimethylsulfoxide (0.5 mL) was added 60% sodium hydride in oil (27 mg) and was heated at 60°C for 40 minutes. To this mixture was added (3-carboxypropyl)(triphenyl)phosphonium bromide (124 mg) at ambient temperature and was stirred for 40 minutes. 7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carbaldehyde (40 mg) was added therein at ambient temperature. After 4
- 30 hours, the reaction mixture was acidified with 1N hydrogen chloride and was partitioned between ethyl acetate and water. The organic layer was washed with water three times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by p-TLC (hexane-ethyl acetate = 1-1) to give (4E)-5-[7-chloro-4-(4-

fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-4-pentenoic acid as a yellow oil (21 mg, E:Z=16:1, 56.3%).

(4E)-5-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-4-pentenoic acid

NMR (CDCl₃, δ): 1.40 (6H, d, J=7Hz), 2.20-2.37 (4H, m), 3.25 (1H, m), 5.30 (0.94H, dt, J=15, 7Hz), 5.01 (0.06H, m), 6.09 (1H, d, J=5Hz), 6.24 (0.94H, d, J=15Hz), 6.84 (0.06H, d, J=10Hz), 6.67 (0.94H, d, J=5Hz), 6.70 (0.06H, d, J=5Hz), 7.07-7.17 (2H, m), 7.26-7.35 (2H, m).

MS (ESI): m/z 385 (M-H)

Example 206

To a solution of 7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carbaldehyde (40 mg) was added 1N sodium hydroxide (19.3 mg) and acetone (0.425 mL) at ambient temperature. After 8 hours, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by p-TLC (hexane-ethyl acetate = 5-1) to give (3E)-4-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-3-buten-2-one as a yellow solid (33 mg).

(3E)-4-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-3-buten-2-one

NMR (CDCl₃, δ): 1.40 (6H, d, J=7Hz), 2.13 (3H, s), 3.38 (1H, m), 5.89 (1H, d, J=15Hz), 6.23 (1H, d, J=5Hz), 6.75 (1H, d, J=5Hz), 7.13-7.23 (2H, m), 7.30-7.39 (2H, m), 7.49 (1H, d, J=15Hz)

Example 207

A solution of ethyl 4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (100 mg) in tetrahydrofuran (1 mL) was purged with nitrogen gas under a dry ice-acetone bath. To the mixture was added 2,2'-azobisisobutyronitrile (0.5 mg) was added to the mixture. After 5 minutes, was added 1,3-dibromo-5,5-dimethyl-2,4-imidazolidinedione (43.8 mg). The resulting mixture was stirred for 3 hours (-78 to -

- 30°C). Water (5 mL) was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give an yellow gum. Flash silica gel column chromatography eluting with toluene-hexane = 1-5 to 2-3 afforded ethyl 7-bromo-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate product as an yellow gum (90.0 mg, 72.5%).

Ethyl 7-bromo-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate
NMR (CDCl₃, δ): 0.98 (3H, t, J=7Hz), 1.40 (6H, d, J=7Hz), 3.31 (1H, septet, J=7Hz),
4.05 (2H, q, J=7Hz), 6.39 (1H, d, J=5Hz), 6.87 (1H, d, J=5Hz), 7.16 (2H, t, J=9Hz), 7.45 (2H, dd, J=4 and 9Hz)
MS (ESI⁺): m/z 405 (M+H)

Example 208

- A suspension of sodium hydride (74.4 mg) in dimethylsulfoxide (1.4 mL) was stirred for 1 hour at 60°C. The mixture was added to a solution of methyl triphenylphosphonium bromide (1.11 g) in dimethylsulfoxide (1.0 mL) at room temperature. After stirring for 0.5 hour, the mixture was added ethyl 4-(4-fluorophenyl)-7-formyl-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (500 mg). After stirring for 15 hours, the mixture was partitioned between ethyl acetate (20 mL) and water (5 mL). The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, and evaporated to give an orange gum. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-7 to 3-1 afforded ethyl 4-(4-fluorophenyl)-2-isopropyl-7-vinylpyrrolo[1,2-b]pyridazine-3-carboxylate an yellow gum, which was solidified upon standing (361 mg, 72.6%).

Ethyl 4-(4-fluorophenyl)-2-isopropyl-7-vinylpyrrolo[1,2-b]pyridazine-3-carboxylate
NMR (CDCl₃, δ): 0.97 (3H, t, J=7Hz), 1.38 (6H, d, J=7Hz), 3.32 (1H, septet, J=7Hz),
4.03 (2H, q, J=7Hz), 5.35 (1H, dd, J=2 and 12Hz), 6.11 (1H, dd, J=2 and 18Hz),
6.34 (1H, d, J=5Hz), 6.99 (1H, d, J=5Hz), 7.16 (1H, t, J=9Hz), 7.25 (1H, dd, J=12 and 18Hz), 7.45 (2H, d, J=4 and 9Hz)

Example 209

To a solution of ethyl 7-{4-[4-({[(benzyloxy)carbonyl]-amino}sulfonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}heptanoate (169 mg) in ethanol (2 mL) was added 10% palladium on activated carbon (1.6 mg), and the mixture was stirred under hydrogen pressure (3 kg/cm²) for 2 hours. The resulting mixture was filtered through celite, and the filtrate was concentrated to give an yellow gum. Preparative silica gel thin layer chromatography eluting with ethyl acetate-hexane = 1-1 afforded ethyl 7-{4-[4-(aminosulfonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}heptanoate as an yellow gum (76.8 mg, 58.4%).

10

Ethyl 7-{4-[4-(aminosulfonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}heptanoate

NMR (CDCl₃, δ): 1.07-1.25 (7H, m), 1.30-1.46 (7H, m), 2.18 (2H, t, J=7Hz), 2.36

(2H, m), 2.55 (3H, s), 3.00 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.21 (2H, s),

15 5.82 (1H, d, J=5Hz), 6.50 (1H, d, J=5Hz), 7.52 (2H, d, J=9Hz), 8.05 (2H, d,

J=9Hz)

MS (ESI⁺): m/z 472 (M+H)

Example 210

To a solution of ethyl 4-(4-cyanophenyl)-2-(2-ethoxy-2-oxoethyl)-7-ethylpyrrolo[1,2-b]pyridazine-3-carboxylate (77.9 mg) in ethanol (0.5 mL)-tetrahydrofuran (0.5 mL) was added 1N potassium hydroxide. The resulting solution was stirred for 2.5 hours at room temperature. The mixture was stirred for further 1 hour after adding 1N potassium hydroxide (0.04 mL). The reaction was quenched by adding 1N hydrochloric acid (0.23 mL). The volatile was evaporated off, and the resulting residue was partitioned between ethyl acetate (10 mL) and 1N hydrochloric acid (6 mL). The organic layer was washed with brine, dried, and evaporated to give [4-(4-cyanophenyl)-3-(ethoxycarbonyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]acetic acid as an yellow solid (67.7 mg, 93.4%).

30

[4-(4-Cyanophenyl)-3-(ethoxycarbonyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]acetic acid

NMR (CDCl₃, δ): 0.84 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 3.05 (2H, q, J=7Hz), 3.93

(2H, q, J=7Hz), 4.18 (3H, s), 6.27 (1H, d, J=5Hz), 6.74 (1H, d, J=5Hz), 7.52 (2H,

d, J=9Hz), 7.76 (2H, d, J=9Hz)

MS (ESI⁺): m/z 378 (M+H)

Example 211

5 To a solution of ethyl 2-(2-amino-2-oxoethyl)-4-(4-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazine-3-carboxylate (35.0 mg) in tetrahydrofuran (1 mL) was added 60% sodium hydride (4.50 mg) under an ice-bath. The resulting mixture was stirred for 1 hour. The reaction was quenched by adding 1N HCl (4 mL). The mixture was extracted with ethyl acetate (10 mL), and the organic layer was washed with water
10 and brine, dried over magnesium sulfate, and evaporated. Preparative silica gel thin layer chromatography eluting with ethyl chloroform-methanol = 10-1 afforded 4-(7-ethyl-1,3-dioxo-1,2,3,4-tetrahydropyrido[3,4-e]pyrrolo[1,2-b]-pyridazin-10-yl)benzonitrile as an yellow solid (3.86 mg, 12.6%).

15 4-(7-Ethyl-1,3-dioxo-1,2,3,4-tetrahydropyrido[3,4-e]pyrrolo[1,2-b]pyridazin-10-yl)benzonitrile

NMR (CDCl₃, δ): 1.40 (3H, t, J=7Hz), 3.08 (2H, q, J=7Hz), 4.16 (3H, s), 6.38 (1H, d, J=5Hz), 6.85 (1H, d, J=5Hz), 7.46 (2H, d, J=9Hz), 7.78 (2H, d, J=9Hz), 7.92 (1H, s, br)

20

Example 212

To methanol (1 mL) was added 60% sodium hydride (6.51 mg) at room temperature. Then, 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-2-yl trifluoromethanesulfonate (70.0 mg) was added to the mixture. The
25 resulting mixture was stirred for 2 hours at room temperature and 1 hour at 50°C. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. Preparative silica gel thin layer chromatography eluting with ethyl acetate-hexane = 1-1 afforded 3-[7-ethyl-2-methoxy-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile as an yellow solid
30 (1.92 mg, 3.7%).

3-[7-Ethyl-2-methoxy-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 3.01 (2H, q, J=7Hz), 3.24 (3H, s), 4.18 (3H,

s), 6.12 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.53-7.64 (3H, m), 7.76 (1H, m)

Example 213

To a solution of ethyl 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylate (92.6 mg) in tetrahydrofuran (1 mL) and ethanol (0.5 mL) was added 1N sodium hydroxide (0.349 mL). The resulting mixture was stirred for 3 hours at room temperature. The resulting mixture was stirred further for 40 minutes after adding 1N sodium hydroxide (0.1 mL). The mixture was stirred further for 1.5 hours after adding 1N sodium hydroxide (0.1 mL). The reaction was quenched by adding 1N hydrochloric acid (1 mL), and the mixture was partitioned between ethyl acetate (20 mL) and water (10 mL). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a red oil. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-1 afforded 3-(6-ethyl-1,1-dioxido-3-oxo-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]-pyridazin-9-yl)benzonitrile as a red foam (52.4 mg, 64.0%).

3-(6-Ethyl-1,1-dioxido-3-oxo-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile

NMR (CDCl₃, δ): 1.45 (3H, t, J=7Hz), 3.21, (3H, s), 4.28 (2H, s), 6.91 (1H, d,

J=5Hz), 7.26 (1H, d, J=5Hz), 7.75 (1H, t, J=9Hz), 7.91 (1H, d, J=9Hz), 8.08-8.16

(2H, m)

MS (ESI⁺): m/z 352 (M+H)

Example 214

To a solution of 3-(6-ethyl-1,1-dioxido-3-oxo-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile (60.0 mg) in tetrahydrofuran (0.2 mL) was added 1 M solution of borane-tetrahydrofuran complex in tetrahydrofuran (0.487 mL) under an ice-bath. After stirring for 1 hour, the reaction was quenched by adding 1N hydrochloric acid (1 mL). The mixture was partitioned between ethyl acetate (20 mL) and water (10 mL), and the organic layer was washed with brine, dried, and evaporated to give 3-(6-ethyl-3-hydroxy-1,1-dioxido-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile as a yellow foam (576 mg, 99.8%).

3-(6-Ethyl-3-hydroxy-1,1-dioxido-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile

NMR (CDCl₃, δ): 1.45 (3H, t, J=7Hz), 3.21, (3H, s), 4.28 (2H, s), 6.91 (1H, d, J=5Hz), 7.26 (1H, d, J=5Hz), 7.75 (1H, t, J=9Hz), 7.91 (1H, d, J=9Hz), 8.08-8.16 (2H, m)

Example 215

To a solution of 3-(6-ethyl-3-hydroxy-1,1-dioxido-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile (54.0 mg) in tetrahydrofuran (1 mL) was added 60% sodium hydride (6.69 mg) under an ice-bath. After stirring for 0.5 hour, methyl iodide (25.9 mg) was added, and the mixture was stirred for 3 hours 20 minutes at room temperature. The mixture was stirred for another 6 hours after adding methyl iodide (25.9 mg). The mixture was further stirred for 1 hour after adding 60% sodium hydride (3.0 mg) and methyl iodide (25.9 mg). The mixture was partitioned between ethyl acetate and 1N hydrochloric acid, and the organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give an yellow oil. Preparative silica gel thin layer chromatography eluting with ethyl acetate-hexane = 1-2 afforded 3-(6-ethyl-1,1-dioxidopyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile (5.9 mg, 10.5%, an yellow solid) and 3-(6-ethyl-3-methoxy-1,1-dioxido-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile (16.8 mg, 30.0%, an orange gum).

3-(6-Ethyl-1,1-dioxidopyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile

NMR (CDCl₃, δ): 1.40 (3H, t, J=7Hz), 3.07 (2H, q, J=7Hz), 6.68 (1H, d, J=5Hz), 6.82 (1H, d, J=5Hz), 7.02 (1H, d, J=7Hz), 7.37 (1H, d, J=7Hz), 7.72 (1H, t, J=9Hz), 7.87 (1H, d, J=9Hz), 8.11-8.16 (2H, m)

3-(6-Ethyl-3-methoxy-1,1-dioxido-2,3-dihydropyrrolo[1,2-b]thieno[2,3-e]pyridazin-9-yl)benzonitrile

NMR (CDCl₃, δ): 1.42 (3H, t, J=7Hz), 3.12 (2H, q, J=7Hz), 3.67 (3H, s), 3.73 (2H, m), 5.02 (1H, m), 6.74 (1H, d, J=5Hz), 6.97 (1H, d, J=5Hz), 7.70 (1H, t, J=9Hz), 7.85 (1H, d, J=9Hz), 8.04-8.13 (2H, m)

MS (ESI⁺): m/z 368 (M+H)

Example 216

A mixture of 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]benzonitrile (1.00 g), ethyl 3-(methylsulfonyl)-2-oxopropanoate (1.34 g), and p-toluenesulfonic acid monohydrate (79.5 mg) in toluene (20 mL) was refluxed for 1 hour with Dean-Stark condenser. The volatile was removed in vacuo. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-10 to 9-15 afforded the intermediate imine (1.38 g, 67.7%) as an orange foam. The foam was dissolved in N-methylmorpholine (10 mL), and the solution was stirred for 1 hour at 130°C. The mixture was partitioned between ethyl acetate (50 mL) and water (30 mL). The organic layer was washed with water (30 x 2 mL) and brine, dried over magnesium sulfate, and evaporated to give a dark orange solid. The solid was triturated in diisopropyl ether (10 mL) to give 2-(trimethylsilyl)ethyl 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylate as an yellow powder (1.11 g, 67.7%).

15

2-(Trimethylsilyl)ethyl 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylate

NMR (CDCl₃, δ): 0.12 (9H, s), 1.22 (2H, m), 1.39 (3H, t, J=7Hz), 3.09 (2H, q,

J=7Hz), 3.23 (3H, s), 4.53 (2H, m), 6.30 (1H, d, J=5Hz), 6.89 (1H, d, J=5Hz),

20 7.50-7.67 (3H, m), 7.82 (1H, m)

MS (ESI⁺): m/z 470 (M+H)

The following compound was obtained in substantially the same manner as that of Example 216.

25 Example 217

Ethyl 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylate

NMR (CDCl₃, δ): 1.39 (3H, t, J=7Hz), 1.47 (3H, t, J=7Hz), 3.10 (2H, q, J=7Hz), 3.21,

(3H, s), 4.51 (2H, q, J=7Hz), 6.30 (1H, d, J=5Hz), 6.90 (1H, d, J=5Hz), 7.61-7.67

30 (3H, m), 7.72 (1H, m)

Example 218

A solution of 2-(trimethylsilyl)ethyl 4-(3-cyanophenyl)-7-ethyl-3-

(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylate (1.09) in trifluoroacetic acid (5 mL) was stirred for 1.5 hours under an ice-bath. The reaction was quenched by adding water (20 mL). An yellow crystal was formed upon the addition, which was collected by filtration. The crystal was washed with water (5 mL) and hexane (3 mL) to give 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylic acid as an yellow crystal (756 mg, 88.2%).

4-(3-Cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylic acid
NMR (CDCl₃, δ): 1.41 (2H, m), 3.10 (2H, q, J=7Hz), 3.30 (3H, s), 6.36 (1H, d, J=5Hz), 6.94 (1H, d, J=5Hz), 7.53-7.67 (3H, m), 7.82 (1H, m)
MS (ESI⁺): m/z 370 (M+H)

Example 219

A mixture of 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylic acid (40.0 mg), diethylamine hydrochloride (12.4 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (25.2 mg), and 1-hydroxybenzotriazole (21.9 mg) in N,N-dimethylformamide (1 mL) was stirred for 3 hours at room temperature. The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (10 mL). The organic layer was washed with water (10 x 3 mL), saturated sodium bicarbonate (10 mL), and brine, dried over magnesium sulfate, and evaporated to give 4-(3-cyanophenyl)-7-ethyl-N,N-dimethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxamide as an yellow solid (43.4 mg, 101%).

4-(3-Cyanophenyl)-7-ethyl-N,N-dimethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxamide
NMR (CDCl₃, δ): 1.38 (2H, m), 3.07 (2H, q, J=7Hz), 3.12 (3H, s), 3.18 (3H, s), 3.27 (3H, s), 6.27 (1H, d, J=5Hz), 6.85 (1H, d, J=5Hz), 7.57-7.67 (3H, m), 7.81 (1H, m)
MS (ESI⁺): m/z 397 (M+H)

Example 220

A mixture of ethyl 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carboxylate (450 mg) and 85% potassium hydroxide (3.01 g) in a mixture

of ethanol (3 mL) and water (2 mL) was refluxed for 2.5 hours. The reaction mixture was cooled under an ice-bath, and quenched by adding concentrated hydrochloric (5 mL). The mixture was partitioned between ethyl acetate (20 mL) and water (10 mL), and the organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give an yellow solid (388 mg). The solid was triturated in hexane to give 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid as an yellow powder (361 mg, 86.4%).

4-(3-Chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid

10 NMR (CDCl₃, δ): 1.41 (3H, t, J=7Hz), 3.08 (2H, q, J=7Hz), 6.37 (1H, d, J=5Hz), 6.55 (1H, m), 6.76 (1H, d, J=5Hz), 7.02 (1H, d, J=3Hz), 7.40-7.55 (5H, m)
MS (ESI⁺): m/z 367 (M+H)

Example 221

15 To a solution of 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid (358 mg,) and N,N-dimethylformamide (1.39 mg) in dichloromethane (3 mL) was added oxalyl chloride (157 mg) at room temperature. After stirring for 30 minutes, the volatile was removed in vacuo, and the residue was azeotroped with toluene three times to afford 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carbonyl chloride as an yellow gum (396 mg, 106%).

4-(3-Chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carbonyl chloride

25 NMR (CDCl₃, δ): 1.42 (3H, t, J=7Hz), 3.10 (2H, q, J=7Hz), 6.45 (1H, d, J=5Hz), 6.59 (1H, m), 6.82 (1H, d, J=5Hz), 7.06 (1H, d, J=7Hz), 7.38-7.55 (4H, m), 7.63 (1H, m)

Example 222

To a solution of methyl aminoacetate hydrochloride (26.1 mg) and triethylamine (42.0 mg) in dichloromethane (0.5 mL) was added a solution of 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carbonyl chloride (40.0 mg) in dichloromethane (0.5 mL) under an ice-bath. The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (10 mL), and the organic layer was washed with brine (10 mL), dried over magnesium sulfate, and evaporated to give methyl ({[4-(3-

chlorophenyl)-7-ethyl-2-(3-furyl)pyrrolo[1,2-b]pyridazin-3-yl]carbonyl}amino)acetate as an yellow gum (50.6 mg, 111%).

Methyl ({[4-(3-chlorophenyl)-7-ethyl-2-(3-furyl)pyrrolo[1,2-b]pyridazin-3-

5 yl]carbonyl}amino)acetate

NMR (CDCl₃, δ): 1.41 (3H, t, J=7Hz), 3.10 (2H, q, J=7Hz), 3.69 (3H, s), 3.95 (2H, d, J=5Hz), 6.01 (1H, t, br, 5Hz), 6.35 (1H, d, J=5Hz), 6.51 (1H, m), 6.75 (1H, d, J=5Hz), 7.01 (1H, d, J=7Hz), 7.37-7.48 (3H, m), 7.53 (1H, m), 7.58 (1H, m)

MS (ESI⁺): m/z 438 (M+H)

10

The following compound was obtained in substantially the same manner as that of Example 222.

Example 223

4-(3-Chlorophenyl)-7-ethyl-2-(2-furyl)-N,N-bis(2-hydroxyethyl)pyrrolo[1,2-

15 b]pyridazine-3-carboxamide

NMR (CDCl₃, δ): 1.42 (3H, t, J=7Hz), 2.35-2.72 (4H, m), 3.08 (2H, d, J=5Hz), 3.20-3.63 (4H, m), 3.82 (2H, m), 6.40 (1H, t, br, 5Hz), 6.54 (1H, m), 6.75 (1H, d, J=5Hz), 7.04 (1H, d, J=3Hz), 7.40-7.48 (2H, m), 7.53-7.60 (2H, m), 7.71 (1H, m)

MS (ESI⁺): m/z 454 (M+H)

20

Example 224

To a solution of 3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid (100 mg) in dioxane (0.5 mL) was added triethylamine (25.2 mg)

followed by a solution of pivaloyl chloride (30.1 mg) in dioxane (0.5 mL). A white

25 precipitate was formed. After stirring for 40 minutes at room temperature, the precipitate

was removed by filtration, and washed with dioxane (2 mL). To the combined washing

was added a solution of 2-aminoethanesulfonic acid (38.6 mg) in 1N sodium hydroxide

(0.247 mL). The resulting mixture was stirred for 1 hour at room temperature. The

mixture was partitioned between ethyl acetate (15 mL) and water (5 mL). The organic

30 layer was washed with brine, dried over magnesium sulfate, and evaporated. Preparative

silica gel thin layer chromatography eluting with chloroform-methanol = 5-1 afforded 2-

({3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo-

[1,2-b]pyridazin-3-yl]propanoyl}amino)ethanesulfonic acid as an yellow solid (104 mg,

82.0%).

2-({3-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoyl}amino)ethanesulfonic acid

5 NMR (CDCl₃, δ): 1.27 (5H, m), 2.59 (4H, m), 2.90-3.14 (4H, m), 5.96 (1H, m), 6.06 (1H, m), 7.06-7.40 (9H, m)

Example 225

A solution of 3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid (100 mg), (2R,3R,4S,5S,6R)-2-amino-3,5-bis[(2,2-dimethylpropanoyl)-oxy]-6-{[(2,2-dimethylpropanoyl)oxy]methyl}tetrahydro-2H-pyran-4-yl pivalate (255 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.494 mmol), and 1-hydroxybenzotriazole (66.7 mg) in N,N-dimethylformamide (1 mL) was stirred for 1
10 hour at room temperature. The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (10 mL). The organic layer was washed with water (10 x 3 mL), saturated sodium bicarbonate (10 mL), and brine, dried over magnesium sulfate, and evaporated to give an yellow foam (339 mg). Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-10 to 2-5 afforded
20 (2R,3R,4S,5S,6R)-2-({3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoyl}amino)-3,5-bis[(2,2-dimethylpropanoyl)oxy]-6-{[(2,2-dimethylpropanoyl)oxy]methyl}tetrahydro-2H-pyran-4-yl pivalate an yellow foam (240 mg, 108%).

(2R,3R,4S,5S,6R)-2-({3-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoyl}amino)-3,5-bis[(2,2-dimethylpropanoyl)oxy]-6-{[(2,2-dimethylpropanoyl)oxy]methyl}tetrahydro-2H-pyran-4-yl pivalate
25 NMR (CDCl₃, δ): 0.97-1.26 (36H, m), 1.35 (3H, t, J=7Hz), 1.83 (2H, m), 2.81 (2H, m), 3.01 (2H, q, J=7Hz), 3.87-4.16 (3H, m), 4.90-5.27 (3H, m), 5.36-5.51 (2H, m), 6.01 (1H, d, J=5Hz), 6.52 (1H, d, J=5Hz), 7.29 (1H, m), 7.40-7.59 (8H, m)

30

Example 226

To a solution of ethyl [4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]acetate (114 mg) in tetrahydrofuran (2 mL) was added 1 M

diisobutylaluminum hydride in toluene (0.816 mL) under an ice-bath. After stirring for 1 hour at room temperature, additional 1 M diisobutylaluminum hydride (0.41 mL) was added. The reaction was quenched by adding 1N hydrochloric acid (1 mL) after 1 hour. The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (10 mL), and filtered through celite. The organic layer was washed with water (10 mL) and brine, dried over magnesium sulfate, and evaporated to give an yellow gum. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-20 to 2-50 afforded 2-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethanol as an yellow oil, which was crystallized upon standing (107 mg, 104%).

2-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethanol

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 2.77 (2H, t, J=7Hz), 3.01 (2H, q, J=7Hz), 3.26 (2H, m), 3.26 (2H, m), 6.00 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.34 (1H, m), 7.41-7.55 (8H, m)

Example 227

To a mixture of 2-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethanol (105 mg), 2,3,4,6-tetra-O-acetyl-beta-D-galactosyl bromide (299 mg), silver carbonate (154 mg) in toluene (2 mL) was added silver triflate (3.58 mg) under an ice bath. After 40 minutes, 2,3,4,6-tetra-O-acetyl-beta-D-galactosyl bromide (114 mg), silver carbonate (229 mg) was added, and the mixture was stirred for 50 minutes. The mixture was further stirred for 50 minutes after adding 2,3,4,6-tetra-O-acetyl-beta-D-galactosyl bromide (114 mg), silver carbonate (154 mg). The mixture was filtered through celite, and the filtrate was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give an yellow gum. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-10 to 7/10 afforded (2R,3R,4S,5S,6R)-4,5-bis(acetyloxy)-6-[(acetyloxy)methyl]-2-{2-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}tetrahydro-2H-pyran-3-yl acetate as an yellow gum (115 mg, 58.4%).

(2R,3R,4S,5S,6R)-4,5-bis(Acetyloxy)-6-[(acetyloxy)methyl]-2-{2-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}tetrahydro-2H-pyran-3-yl acetate

NMR (CDCl₃, δ): 1.35 (3H, t, J=7Hz), 1.70 (3H, m), 1.94 (3H, s), 2.04 (3H, s), 2.11 (3H, s), 2.78 (2H, m), 3.01 (2H, q, J=7Hz), 3.10 (1H, m), 3.46 (1H, m), 3.62 (1H, t, J=6Hz), 3.79 (1H, d, J=8Hz), 3.98 (2H, m), 4.83 (1H, dd, J=3 and 10Hz), 4.97 (1H, dd, J=8 and 10Hz), 5.28 (1H, d, J=3Hz), 6.02 (1H, d, J=5Hz), 6.64 (1H, d, J=5Hz), 7.31 (1H, m), 7.41-7.56 (8H, m)

Example 228

To a solution of (2R,3R,4S,5S,6R)-4,5-bis(acetyloxy)-6-[(acetyloxy)methyl]-2-{2-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}tetrahydro-2H-pyran-3-yl acetate (113 mg) in methanol (2 mL) was added sodium methoxide (0.86 mg) at room temperature. After stirring for 2 hours, the solvent was evaporated off, and the mixture was partitioned between ethyl acetate (20 mL) and water (10 mL). The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give an yellow foam (77.3 mg). The foam was triturated in hexane to give (2R,3R,4S,5R,6R)-2-{2-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol as an yellow powder (48.3 mg, 89.7%).

(2R,3R,4S,5R,6R)-2-{2-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

NMR (CDCl₃, δ): 1.36 (3H, t, J=7Hz), 1.92 (1H, m), 2.06 (1H, m), 2.56 (1H, s, br), 2.76-2.92 (3H, m), 3.02 (2H, q, J=7Hz), 3.24 (2H, m), 3.38-3.50 (3H, m), 3.63-3.84 (3H, m), 2.41 (1H, s, br), 6.01 (1H, d, J=5Hz), 6.63 (1H, d, J=5Hz), 7.32 (1H, m), 7.41-7.57 (8H, m)

The following compounds were obtained in substantially the same manner as that of Example 228.

Example 229

3-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]propanamide

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.97 (2H, m), 2.83 (2H, m), 3.01 (2H, q,

J=7Hz), 3.31-3.52 (3H, m), 3.61-3.76 (2H, m), 3.88 (1H, m), 4.63 (1H, d, J=9Hz), 6.01 (1H, d, J=5Hz), 6.64 (1H, d, J=5Hz), 7.34 (1H, m), 7.42-7.59 (8H, m)

Example 230

5 Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate from ethyl 5-[2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.34-1.50 (5H, m), 1.54 (2H, m), 2.19 (2H, t, J=7Hz), 2.37 (2H, m), 3.02 (2H, q, J=7Hz), 3.71 (1H, t, J=5Hz), 4.10 (2H, q, J=7Hz), 4.86 (2H, d, J=5Hz), 5.97 (1H, d, J=5Hz), 6.60 (1H, d, J=5Hz), 7.88 (1H, m), 8.55 (1H, m), 8.79 (1H, m)

Example 231

To a solution of 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (50 mg) in N,N-dimethylformamide (1 mL) was added 1,1'-carbonyldiimidazole (33.6 mg) at ambient temperature. After 1 hour stirring, to the mixture was added methanesulfonamide (19.7 mg) and 1,8-diazabicyclo[5.4.0]undec-7-ene (31.6 mg). The mixture was heated at 50°C for 2 hours. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was acidified with 1N hydrogen chloride and was extracted with ethyl acetate. The organic layer was washed with water 3 times and brine, dried over magnesium sulfate, and evaporated in vacuo to give a yellow solid. The residue was crystallized from IPE to give yellow solid (45 mg). The solid was recrystallized from ethanol to give N-{5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoyl}methanesulfonamide (25 mg,) as an yellow solid.

N-{5-[4-(3-Cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoyl}methanesulfonamide

NMR (CDCl₃, δ): 1.33-1.61 (7H, m), 2.21 (2H, t, J=8Hz), 2.40 (2H, t, J=8Hz), 2.55 (3H, s), 3.00 (2H, q, J=8Hz), 3.29 (3H, s), 5.80 (1H, d, J=5Hz), 6.52 (1H, d, J=5Hz), 7.58-7.67 (3H, m), 7.76 (1H, m), 7.86 (1H, br s)

MS (ESI⁺): m/z 439 (M+H)

Example 232

To a solution of ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (45 mg) in tetrahydrofuran (1 mL) was added lithium borohydride (5 mg) in an ice-water bath. Then the reaction mixture was stirred at ambient temperature. After 2 hours, another lithium borohydride (5 mg) was added therein and was stirred overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and was evaporated in vacuo. The residue was purified by p-TLC (hexane-ethyl acetate = 1-1) to give 3-[7-ethyl-3-(6-hydroxyhexyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile (26 mg, 64.5%) as a yellow oil and 6-{4-[3-(aminomethyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}-1-hexanol (13 mg, 31.9%) as a yellow solid.

3-[7-Ethyl-3-(6-hydroxyhexyl)-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.15-1.53 (11H, m), 2.32-2.41 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J=8Hz), 3.58 (2H, br t, J=8Hz), 5.58 (1H, br t, J=8Hz), 5.79 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.57-7.63 (2H, m), 7.65 (1H, br s), 7.75 (1H, m)

MS (ESI⁺): m/z 362 (M+H)

6-{4-[3-(Aminomethyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}-1-hexanol

NMR (CDCl₃, δ): 1.03-1.43 (11H, m), 2.41 (2H, t, J=8Hz), 2.55 (3H, s), 3.01 (2H, q, J=8Hz), 3.39-3.61 (2H, m), 3.88-4.04 (2H, m), 4.25 (2H, br s), 5.31 (1H, d, J=5Hz), 6.49 (1H, d, J=5Hz), 7.28-7.40 (3H, m), 7.51 (1H, t, J=8Hz)

MS (ESI⁺): m/z 366 (M+H)

Example 233

To a suspension of 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid (590 mg) in water (3 mL) was added 1N sodium hydroxide (1.5 mL) at ambient temperature. After 5 hours, the mixture became clear solution. The solution was filtered through membrane filter, washed with water (0.4 mL x3), and was freeze-dried for 15 hours to give 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid sodium salt (612 mg, 98.2%) as a pale yellow powder.

6-{4-[4-(Aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid sodium salt

NMR (DMSO-d₆, δ): 1.10-1.15 (2H, m), 1.20-1.40 (7H, m), 1.74 (2H, t, J=8Hz),
2.25-2.38 (2H, m), 2.50 (3H, s), 2.91 (2H, q, J=8Hz), 5.72 (1H, d, J=5Hz), 6.50
5 (1H, d, J=5Hz), 7.39-7.46 (3H, m), 7.97 (2H, d, J=8Hz), 8.26 (1H, br s)

Example 234

A solution of 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (100 mg), triethylamine (29.4 mg), and diphenylphosphoryl azide (79.9
10 mg) in tert-butanol (2 mL) was heated at 80°C for 8 hours. The cooled reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by p-TLC (hexane-ethyl acetate = 3-1) to give tert-butyl 4-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-
15 b]pyridazin-3-yl]butylcarbamate (28 mg, 23.4%) as a yellow oil.

tert-Butyl 4-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butylcarbamate

NMR (CDCl₃, δ): 1.27-1.47 (14H, m), 2.34-2.45 (2H, m), 2.55 (3H, s), 2.91-3.02
20 (4H, m), 4.39 (1H, br s), 5.79 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.56-7.67 (3H, m), 7.75 (1H, m)
MS (ESI⁺): m/z 433 (M+H)

Example 235

To tert-butyl 4-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butylcarbamate (25 mg) was added 4N hydrogen chloride in ethyl acetate (1 mL) at ambient temperature. After 1 hour, the mixture was evaporated in vacuo. The residue was triturated with isopropyl ether to give 3-[3-(4-aminobutyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile hydrochloride as dark green amorphous
30 (18 mg).

3-[3-(4-Aminobutyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile hydrochloride

NMR (CDCl₃, δ): 1.27-1.47 (14H, m), 2.34-2.45 (2H, m), 2.55 (3H, s), 2.91-3.02 (4H, m), 4.39 (1H, br s), 5.79 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.56-7.67 (3H, m), 7.75 (1H, m)

MS (ESI⁺): m/z 333 (M+H)

5

Example 236

To lithium chloride (16.5 mg) was added a solution of ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (65 mg) and tributyl(vinyl)stannane (56.7 mg) in dioxane (1 mL) and tetrakis(triphenylphosphine)palladium(0) (1.9 mg). The mixture was refluxed. After 4 hours, tributyl(vinyl)stannane (50 mg) and tetrakis(triphenylphosphine)palladium(0) (1.9 mg) was added. After refluxed over night, the reaction mixture was quenched with potassium fluoride (1.8 mmol) in H₂O. The mixture was filtered through Celite and was washed with ethyl acetate. The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 50 mL) eluted with hexane-ethyl acetate = 5-1 and 3-1 to give ethyl 5-[7-ethyl-2-methyl-4-(2-vinyl-4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (18 mg, 28.3%) as an yellow oil.

20

Ethyl 5-[7-ethyl-2-methyl-4-(2-vinyl-4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.15-1.70 (10H, m), 2.18 (2H, t, J=8Hz), 2.36-2.46 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=8Hz), 4.08 (2H, q, J=8Hz), 5.54 (1H, d, J=10Hz), 5.86 (1H, d, J=5Hz), 6.25 (1H, d, J=16Hz), 6.51 (1H, d, J=5Hz), 6.87 (1H, dd, J=16, 10Hz), 7.16 (1H, dd, J=6, 1Hz), 7.33 (1H, br s), 8.70 (1H, d, J=6Hz)

25

MS (ESI⁺): m/z 392 (M+H)

The following compounds were obtained in substantially the same manner as that of Example 236.

30 Example 237

Ethyl 5-{4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.42 (3H, t, J=7Hz),
 1.40-1.60 (4H, m), 2.20 (2H, t, J=7Hz), 2.38-2.52 (2H, m), 2.56 (3H, s), 3.03 (2H,
 q, J=7Hz), 3.96 (2H, q, J=7Hz), 4.09 (2H, q, J=7Hz), 4.34 (1H, d, J=2Hz), 4.76
 (1H, d, J=2Hz), 5.87 (1H, d, J=4Hz), 6.52 (1H, d, J=4Hz), 7.89 (1H, m), 8.53 (1H,
 d, J=2Hz), 8.93 (1H, d, J=2Hz)
 MS: (m/z) 436 (M+H)

Example 238

Ethyl 5-[7-ethyl-2-methyl-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

10 NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.65 (4H, m), 2.18
 (2H, t, J=7Hz), 2.40-2.53 (2H, m), 2.56 (3H, s), 3.02 (2H, q, J=7Hz), 4.08 (2H, q,
 J=7Hz), 5.43 (1H, d, J=11Hz), 5.88 (1H, d, J=4Hz), 5.89 (1H, d, J=18Hz), 6.52
 (1H, d, J=4Hz), 6.71-6.83 (1H, dd, J=11 Hz, 18Hz), 7.73 (1H, m), 8.47 (1H, d,
 J=2Hz), 8.68 (1H, d, J=2Hz)

15

Example 239

Ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

20 NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.17
 (2H, t, J=7Hz), 2.52-2.65 (2H, m), 3.04 (2H, q, J=7Hz), 3.46 (3H, s), 4.08 (2H, q,
 J=7Hz), 4.63 (2H, s), 5.43 (1H, d, J=11Hz), 5.88 (1H, d, J=18Hz), 5.91 (1H, d,
 J=4Hz), 6.58 (1H, d, J=4Hz), 6.71-6.83 (1H, dd, J=11 Hz, 18Hz), 7.75 (1H, m),
 8.49 (1H, d, J=2Hz), 8.71 (1H, d, J=2Hz)

25 Example 240

Ethyl 5-[4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

30 NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.42 (3H, t, J=7Hz),
 1.40-1.63 (4H, m), 2.18 (2H, t, J=7Hz), 2.51-2.63 (2H, m), 3.03 (2H, q, J=7Hz),
 3.47 (3H, s), 3.93 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 4.35 (1H, d, J=3Hz), 4.63
 (2H, s), 4.77 (1H, d, J=3Hz), 5.92 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.92 (1H,
 m), 8.53 (1H, d, J=2Hz), 8.93 (1H, d, J=2Hz)

MS (ESI⁺): m/z 466

Example 241

Ethyl 5-[7-ethyl-2-phenyl-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

5 NMR (CDCl₃, δ): 1.15-1.31 (7H, m), 1.37 (3H, t, J=7Hz), 1.87 (2H, t, J=7Hz), 2.43 (2H, m), 3.01 (2H, q, J=7Hz), 3.98 (2H, q, J=7Hz), 5.45 (1H, d, J=11Hz), 5.88 (1H, d, J=18Hz), 5.98 (1H, d, J=5Hz), 6.62 (1H, d, J=5Hz), 6.78 (1H, dd, J=11 and 18Hz), 7.44-7.55 (5H, m), 7.81 (1H, m), 8.55 (1H, m), 8.72 (1H, m)

10 Example 242

A solution of 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (50 mg) in dioxane (1.5 mL) in a sealed tube was added 50% dimethylamine in water (1.5 mL). The mixture was heated at 175°C overnight. The cooled reaction mixture was concentrated in vacuo. The residue was dissolved in water
15 (1 mL) and the pH was adjusted to 7-8. The mixture was extracted with chloroform three times. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 50 mL) eluted with chloroform-ethyl acetate = 1-1 and chloroform-methanol = 20-1 to give yellow oil (43 mg). The oil was crystallized from isopropyl ether to give 5-{4-[2-(dimethylamino)-
20 4-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid as a yellow solid (27 mg, 52.8%).

5-{4-[2-(Dimethylamino)-4-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

25 NMR (CDCl₃, δ): 1.36 (3H, t, J=8Hz), 1.40-1.65 (4H, m), 2.25 (2H, t, J=8Hz), 1.86-1.96 (2H, m), 2.55 (3H, s), 3.00 (2H, q, J=8Hz), 4.08 (2H, q, J=8Hz), 5.54 (1H, d, J=10Hz), 5.86 (1H, d, J=5Hz), 6.25 (1H, d, J=16Hz), 6.51 (1H, d, J=5Hz), 6.87 (1H, dd, J=16, 10Hz), 7.16 (1H, dd, J=6, 1Hz), 7.33 (1H, br s), 8.70 (1H, d, J=6Hz)

30

Example 243

To a suspension of 7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carbaldehyde (40 mg) in ethanol (1 mL) was added 2-aminoethanol (11.8

mg), sodium cyanoborohydride (12.1 mg), and acetic acid (1 drop) in an ice-water bath. After 10 minutes, the mixture was stirred at ambient temperature. After 2 hours, sodium cyanoborohydride (11.8 mg) was added and the reaction mixture was acidified to pH4 with acetic acid (5 drops). After stirring overnight, the reaction mixture was partitioned
5 between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate, water, and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by p-TLC (chloroform-methanol = 10-1) to give 2-([7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methyl}amino)ethanol as pale yellow oil (21 mg).

10

2-([7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methyl}amino)ethanol

NMR (CDCl₃, δ): 1.43 (6H, d, J=7Hz), 2.65 (2H, t, J=7Hz), 3.42 (1H, m), 3.53 (2H, t, J=7Hz), 3.59 (2H, s), 6.01 (1H, d, J=5Hz), 6.77 (1H, d, J=5Hz), 7.14-7.24 (2H, m), 7.35-7.44 (2H, m)
15 MS (ESI⁺): m/z 362 (M+H)

Example 244

To a solution of [4-(4-fluorophenyl)-2-methylpyrrolo-
20 [1,2-b]pyridazin-3-yl]methanol (505 mg) and triethylamine (997 mg) in dichloromethane (4 mL) and dimethyl sulfoxide (2 mL) was added sulfur trioxide pyridine complex (941 mg) in an ice-water bath under nitrogen. After 30 minutes, the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated to about 1/3 volume. The mixture was partitioned between ethyl acetate and water. The organic layer
25 was washed with water three times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 30 mL) eluted with hexane-chloroform = 3-1 and 2-1 to give 4-(4-fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazine-3-carbaldehyde as a yellow solid (340 mg, 67.9%).

30 4-(4-Fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazine-3-carbaldehyde

NMR (CDCl₃, δ): 2.77 (3H, s), 6.50 (1H, m), 6.86 (1H, m), 7.20-7.30 (2H, m), 7.44-7.54 (2H, m), 8.89 (1H, br s), 9.79 (1H, s)

Example 245

A mixture of ethyl 4-(4-fluorophenyl)-2-isopropyl-7-vinylpyrrolo[1,2-b]pyridazine-3-carboxylate (8.9 g) and 10% palladium on carbon (900 mg) in ethanol (180 mL) was stirred under hydrogen atmosphere (3.5 atm) at ambient temperature.

- 5 After 10 hours, the mixture was stood overnight. To the mixture was added 10% palladium on carbon (900 mg) and was stirred under hydrogen atmosphere (3.5 atm) at ambient temperature. After 12 hours, the mixture was stood overnight. To the mixture was added 10% palladium on carbon (900 mg) and was stirred under hydrogen atmosphere (3.5 atm) at ambient temperature for 8 hours. The mixture was filtered
10 through Celite. The filtrate was concentrated in vacuo to give ethyl 7-ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow oil (9.0 g, 100.5%).

Ethyl 7-ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate

- 15 NMR (CDCl₃, δ): 0.96 (3H, t, J=8Hz), 1.38 (3H, t, J=8Hz), 3.05 (2H, q, J=8Hz), 4.01 (2H, q, J=8Hz), 6.27 (1H, d, J=5Hz), 6.64 (1H, d, J=5Hz), 7.10-7.19 (2H, m), 7.41-7.49 (2H, m)
MS (ESI⁺): m/z 362 (M +H)

- 20 The following compounds were obtained in substantially the same manner as that of Example 245.

Example 246

5-[7-Ethyl-4-(5-ethyl-3-pyridinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid
from 5-[7-ethyl-2-methyl-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic
25 acid

NMR (CDCl₃, δ): 1.30 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.45-1.65 (4H, m), 2.22 (2H, m), 2.35-2.50 (2H, m), 2.56 (3H, s), 2.75 (2H, q, J=7Hz), 3.00 (2H, q, J=7Hz), 5.84 (1H, d, J=4Hz), 6.52 (1H, d, J=4Hz), 7.57 (1H, s), 8.42 (1H, d, J=2Hz), 8.53 (1H, d, J=2Hz)

- 30 MS (ESI⁺): m/z 366 (M+H), MS (ESI): m/z 364

Example 247

5-[7-Ethyl-4-(5-ethyl-3-pyridinyl)-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-

yl]pentanoic acid

NMR (CDCl₃, δ): 1.30 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.45-1.64 (4H, m), 2.17 (2H, m), 2.45-2.67 (2H, m), 2.73 (2H, q, J=7Hz), 3.04 (2H, q, J=7Hz), 3.45 (3H, s), 4.62 (2H, m), 5.89 (1H, d, J=4Hz), 6.58 (1H, d, J=4Hz), 7.59 (1H, s), 8.44 (1H, s), 8.54 (1H, s)

MS (ESI⁺): m/z 396

Example 248

Ethyl 5-[7-ethyl-4-(5-ethyl-3-pyridinyl)-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.04-1.23 (7H, m), 1.32 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.86 (2H, t, J=7Hz), 2.42 (2H, m), 2.74 (2H, q, J=7Hz), 3.01 (2H, q, J=7Hz), 3.99 (2H, q, J=7Hz), 5.97 (1H, d, J=5Hz), 6.62 (1H, d, J=5Hz), 7.45-7.53 (5H, m), 7.60 (1H, m), 8.50 (1H, m), 8.56 (1H, m)

Example 249

To a solution of 3-(7-ethyl-2-neopentylpyrrolo[1,2-b]pyridazin-4-yl)benzamide (35 mg) in ethanol (1 mL) was added water (0.2 mL) and potassium hydroxide (68.9 mg) at ambient temperature. The reaction mixture was heated at 60°C. After 2 hours, potassium hydroxide (100 mg) was added. After 5 hours, potassium hydroxide (100 mg) was added. After 12 hours, the mixture was acidified with 1N hydrogen chloride. The precipitate was filtered, washed with water and ethyl acetate to give 3-(7-ethyl-2-neopentylpyrrolo[1,2-b]pyridazin-4-yl)benzoic acid as a yellow solid (19 mg, 54.1%).

3-(7-Ethyl-2-neopentylpyrrolo[1,2-b]pyridazin-4-yl)benzoic acid

NMR (CDCl₃, δ): 1.05 (9H, s), 1.39 (3H, t, J=8Hz), 2.69 (2H, s), 3.04 (2H, q, J=8Hz), 6.42 (1H, s), 6.54 (1H, d, J=5Hz), 6.65 (1H, d, J=5Hz), 7.62 (1H, t, J=8Hz), 7.97 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz), 8.46 (1H, br s)

MS (ESI⁺): m/z 337 (M+H)

The following compound was obtained in substantially the same manner as that of Example 249.

Example 250

3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoic acid

NMR (CDCl₃, δ): 1.44 (3H, t, J=8Hz), 3.11 (2H, q, J=8Hz), 6.56 (1H, m), 6.61 (1H, d, J=5Hz), 6.72 (1H, d, J=5Hz), 7.03 (1H, br s), 7.07 (1H, d, J=5Hz), 7.55-7.69 (2H, m), 8.03 (1H, br d, J=8Hz), 8.23 (1H, br d, J=8Hz), 8.52 (1H, br s)

Example 251

A solution of ethyl 5-{4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate (190 mg) in methanol (5 mL) and 1N hydrochloric acid (5 mL) was stirred at ambient temperature for 2 hours. The solution was diluted with brine and extracted with chloroform. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (10:1 - 2:1) to give ethyl 5-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate as a yellow oil (160 mg).

Ethyl 5-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.19 (2H, t, J=7Hz), 2.36-2.47 (2H, m), 2.57 (3H, s), 2.70 (3H, s), 3.02 (2H, q, J=7Hz), 4.08 (2H, q, J=7Hz), 5.81 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 8.23 (1H, m), 8.78 (1H, d, J=2Hz), 9.23 (1H, d, J=2Hz)
MS: (m/z) 408 (M+H)

The following compound was obtained in substantially the same manner as that of Example 251.

Example 252

Ethyl 5-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 1.40-1.59 (4H, m), 2.17 (2H, t, J=7Hz), 2.50-2.63 (2H, m), 2.70 (3H, s), 3.03 (2H, q, J=7Hz), 3.46 (3H, s), 4.12 (2H, q, J=7Hz), 4.63 (2H, s), 5.86 (1H, d, J=4Hz), 6.59 (1H, d, J=4Hz), 8.26

(1H, m), 8.79 (1H, d, J=2Hz), 9.24 (1H, d, J=2Hz)

MS (ESI⁺): m/z 438

Example 253

5 To a solution of ethyl 5-{4-(2-chloro-4-pyridinyl)-7-ethyl-2-
[(methylthio)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate (139 mg) in
tetrahydrofuran (4 mL) and water (1 mL) was added oxone (287 mg) and the mixture was
stirred at ambient temperature for 4 hours. The solution was diluted with water and
extracted with ethyl acetate. The organic layer was separated, washed with saturated
10 sodium bicarbonate solution, sodium thiosulfate solution and brine, dried over
magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel
column chromatography eluting with a mixture of hexane and ethyl acetate (10:1 - 1:1) to
give ethyl 5-{4-(2-chloro-4-pyridinyl)-7-ethyl-2-[(methylsulfonyl)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}pentanoate as a yellow oil (124 mg).

15

Ethyl 5-{4-(2-chloro-4-pyridinyl)-7-ethyl-2-[(methylsulfonyl)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.63 (4H, m), 2.21
(2H, t, J=7Hz), 2.57-2.68 (2H, m), 3.02 (2H, q, J=7Hz), 3.12 (3H, s), 4.10 (2H, q,
20 J=7Hz), 4.53 (2H, s), 5.98 (1H, d, J=4Hz), 6.68 (1H, d, J=4Hz), 7.27 (1H, m),
7.38 (1H, s), 8.56 (1H, d, J=5Hz)

Example 254

A mixture of ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-
25 b]pyridazin-3-yl]pentanoate (167 mg) and copper(I) cyanide (37 mg) in 1-methyl-2-
pyrrolidinone (3 mL) was stirred at 170°C for 4 hours. The mixture was partitioned
between ethyl acetate and water. The organic layer was separated, washed with water
and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was
purified by silica gel column chromatography eluting with a mixture of hexane and ethyl
30 acetate (20:1 - 5:1) to give ethyl 5-[4-(5-cyano-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-
b]pyridazin-3-yl]pentanoate as a yellow oil (88 mg).

Ethyl 5-[4-(5-cyano-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-
yl]pentanoate

NMR (CDCl₃, δ): 1.24 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.62 (4H, m), 2.21 (2H, t, J=7Hz), 2.35-2.47 (2H, m), 2.57 (3H, s), 3.02 (2H, q, J=7Hz), 4.12 (2H, q, J=7Hz), 5.79 (1H, d, J=4Hz), 6.54 (1H, d, J=4Hz), 7.98 (1H, m), 8.80 (1H, d, J=2Hz), 8.97 (1H, d, J=2Hz)

5 MS (ESI⁺): m/z 391.

The following compounds were obtained in substantially the same manner as that of Example 254.

Example 255

10 5-[4-(5-Cyano-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.40-1.67 (4H, m), 2.28 (2H, m), 2.37-2.47 (2H, m), 2.57 (3H, s), 3.01 (2H, q, J=7Hz), 5.80 (1H, d, J=4Hz), 6.55 (1H, d, J=4Hz), 8.01 (1H, s), 8.81 (1H, br), 8.98 (1H, br)

15 Example 256

Ethyl 5-[4-(5-cyano-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.37 (3H, t, J=7Hz), 1.40-1.60 (4H, m), 2.19 (2H, t, J=7Hz), 2.49-2.60 (2H, m), 3.04 (2H, q, J=7Hz), 3.46 (3H, s), 4.12 (2H, q, J=7Hz), 4.63 (2H, s), 5.84 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 8.02 (1H, m), 8.83 (1H, d, J=2Hz), 8.98 (1H, d, J=2Hz)

20

Example 257

25 5-[4-(5-Cyano-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.38 (3H, t, J=7Hz), 1.40-1.65 (4H, m), 2.27 (2H, t, J=7Hz), 2.48-2.64 (2H, m), 3.03 (2H, q, J=7Hz), 3.46 (3H, s), 4.64 (2H, s), 5.84 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 8.03 (1H, s), 8.82 (1H, s), 8.97 (1H, s)

30 Example 258

5-[4-(5-Cyano-3-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

NMR (CDCl₃, δ): 1.06-1.24 (4H, m), 1.36 (3H, t, J=7Hz), 1.94 (2H, t, J=7Hz), 2.38

(2H, m), 2.99 (2H, q, J=7Hz), 5.88 (1H, d, J=5Hz), 6.64 (1H, d, J=5Hz), 7.44-7.52 (5H, m), 8.06 (1H, s), 8.87 (1H, s), 8.98 (1H, s)

MS (ESI⁺): m/z 425 (M+H)

5 Example 259

To a suspension of lithium aluminum hydride (98.8 mg) in tetrahydrofuran (10 mL) was added ethyl 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (600 mg) in tetrahydrofuran (10 mL) under ice-water cooling and the mixture was stirred at 0°C for 2 hours. The reaction was quenched with saturated
10 potassium sodium tartrate solution and the insolubles were filtered off and washed with ethyl acetate. The filtrates were washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (10:1 - 2:1) to give 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-1-pentanol as a yellow oil
15 (478 mg).

5-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-1-pentanol

NMR (CDCl₃, δ): 0.90-1.22 (6H, m), 1.27 (1H, t, J=7Hz), 1.36 (3H, t, J=7Hz), 2.37-2.47 (2H, m), 3.02 (2H, q, J=7Hz), 3.29-3.41 (2H, m), 5.97 (1H, d, J=4Hz), 6.61
20 (1H, d, J=4Hz), 7.32 (1H, m), 7.40-7.55 (8H, m)

Example 260

To a solution of 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-1-pentanol (63.0 mg) and triethylamine (22.8 mg) in dichloromethane (3 mL) was
25 added methanesulfonyl chloride (18.9 mg) under ice-water cooling and the mixture was stirred at 0°C for 1 hour. The solution was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was added to sodium cyanide (14.7 mg) in dimethylformamide (2 mL) and the mixture was stirred at 60°C for 5 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was separated,
30 washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 5:1) to give 6-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]

pyridazin-3-yl]hexanenitrile as a yellow oil (58.5 mg).

6-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]hexanenitrile

NMR (CDCl₃, δ): 1.00-1.15 (4H, m), 1.17-1.28 (2H, m), 1.36 (3H, t, J=7Hz), 1.98

5 (2H, t, J=7Hz), 2.38-2.47 (2H, m), 3.03 (2H, q, J=7Hz), 5.99 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.32 (1H, m), 7.38-7.56 (8H, m)

MS (ESI⁺): m/z 428

Example 261

10 A mixture of 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-1-pentanol (65 mg), trimethyloxonium tetrafluoroborate (27.5 mg) and 2,6-di-*t*-butyl-4-methylpyridine (47.8 mg) in 1,2-dichloroethane (3 mL) was stirred at ambient temperature for 4 hours. The solution was washed with water, 1N hydrochloric acid, water, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate,
15 and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 5:1) to give 4-(3-chlorophenyl)-7-ethyl-3-(5-methoxypentyl)-2-phenylpyrrolo[1,2-b]pyridazine as a yellow oil (60 mg).

4-(3-chlorophenyl)-7-ethyl-3-(5-methoxypentyl)-2-phenylpyrrolo[1,2-b]pyridazine

20 NMR (CDCl₃, δ): 0.90-1.32 (6H, m), 1.36 (3H, t, J=7Hz), 2.37-2.47 (2H, m), 3.03 (2H, q, J=7Hz), 3.08 (2H, t, J=7Hz), 3.31 (3H, s), 5.97 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 7.27-7.33 (1H, m), 7.38-7.53 (8H, m)

MS (ESI⁺): m/z 433

25 Example 262

To a solution of 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-1-pentanol (55 mg) and triethylamine (19.9 mg) in dichloromethane (3 mL) was added methanesulfonyl chloride (16.5 mg) under ice-water cooling and the mixture was stirred at 0°C for 1 hour. The solution was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. To the residue in 1,2-dichloroethane (3 mL) was added
30 2 M dimethylamine in tetrahydrofuran (3 mL) and the mixture was stirred at 60°C for 120 hours. The solution was diluted with chloroform, washed with brine, dried over

magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 5:1) to give 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N,N-dimethyl-1-pentanamine as an yellow oil (38 mg).

5

N-{5-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentyl}-N,N-dimethylamine

NMR (CDCl₃, δ): 0.86-0.97 (2H, m), 1.02-1.15 (4H, m), 1.36 (3H, t, J=7Hz), 1.97-

2.04 (2H, m), 2.11 (6H, s), 2.37-2.47 (2H, m), 3.02 (2H, q, J=7Hz), 5.97 (1H, d,

10 J=4Hz), 6.61 (1H, d, J=4Hz), 7.31 (1H, m), 7.39-7.54 (8H, m)

MS (ESI⁺): m/z 446

Example 263

To a stirred solution of 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (60 mg) in dichloromethane (2 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (35.3 mg) and 2-animopyridine (20 mg) and the reaction mixture was stirred for 10 minutes. 4-Dimethylaminopyridine (2 mg) was added and the reaction mixture was stirred at room temperature for 15 hours. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and n-hexane (1:2) to give 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-(2-pyridinyl)pentanamide(55.7mg) as an yellow amorphous.

25

5-[4-(3-Cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-(2-pyridinyl)pentanamide

mp: 67-70°C

NMR (CDCl₃, δ): 1.12 (2H, quintet, J=7Hz), 1.30 (2H, quintet, J=7Hz), 1.36 (3H, t, J=7Hz), 1.95 (2H, t, J=7Hz), 2.43 (2H, q, J=7Hz), 3.02 (2H, q, J=7Hz), 5.90 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.00-7.05 (1H, m), 7.43-7.54 (5H, m), 7.59-7.77 (6H, m), 8.11 (1H, d, J=7.5Hz), 8.24 (1H, d, J=4Hz)

30

MS: (m/z) 499 (M⁺), 45 (bp)

The following compounds were obtained in substantially the same manner as that of Example 263.

Example 264

- 5 5-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-(2-pyridinyl)pentanamide

NMR (CDCl₃, δ): 1.15 (2H, quintet, J=7Hz), 1.24(2H, quintet, J=7Hz), 1.36(3H, t, J=7Hz), 1.91(2H, t, J=7Hz), 2.45(2H, t, J=7Hz), 3.00(2H, q, J=7Hz), 5.97(1H, d, J=5Hz), 6.60(1H, d, J=4Hz), 7.00(1H, t, J=7Hz), 7.30(1H, s), 7.38-7.53(7H, m),
10 7.65-7.73(2H, m), 8.11(1H, d, J=7Hz), 8.25(1H, d, J=5Hz)
MS: (m/z) 509 (M⁺+H), 74 (bp)

Example 265

- 15 N-{5-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoyl}methanesulfonamide

NMR (CDCl₃, δ): 1.08 (2H, quintet, J=7Hz), 1.23 (2H, quintet, J=7Hz), 1.36 (3H, t, J=7Hz), 1.85 (2H, t, J=7Hz), 2.44 (2H, t, J=7Hz), 3.02 (2H, q, J=7Hz), 3.21 (3H, s), 5.99 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.30-7.33 (1H, m), 7.43-7.55 (8H, m)
20

Example 266

- 25 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-(2-pyridinyl)pentanamide

NMR (CDCl₃, δ): 1.12 (2H, quintet, J=7Hz), 1.27 (2H, quintet, J=7Hz), 1.36 (3H, t, J=7Hz), 1.97 (2H, t, J=7Hz), 2.45 (2H, t, J=7Hz), 3.01 (2H, q, J=7Hz), 5.95 (1H, d, J=5Hz), 6.63 (1H, d, J=4Hz), 7.01 (1H, t, J=7Hz), 7.31 (1H, d, J=7Hz), 7.41-7.53 (6H, m), 7.68 (1H, ddd, J=7,7,1Hz), 7.77 (1H, s), 8.12 (1H, d, J=7.5Hz), 8.24 (1H, d, J=5Hz), 8.53 (1H, d, J=6Hz)
MS: (m/z) 510 (M⁺⁺H), 80 (bp)
30

Example 267

- N-{5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-

yl]pentanoyl}methanesulfonamide

mp: 124-125°C

NMR (CDCl₃, δ): 1.37 (3H, t, J=7Hz), 1.43-1.49 (2H, m), 1.55-1.65 (2H, m), 2.23 (2H, t, J=7Hz), 2.34-2.48 (2H, m), 2.55 (3H, s), 3.01 (2H, q, J=7Hz), 3.28 (3H, s), 5.87 (1H, d, J=4Hz), 6.53 (1H, d, J=4Hz), 7.09 (1H, s), 7.40 (1H, s), 8.53 (1H, s), 8.77 (1H, s)

MS: (m/z) 493(M⁺), 491 (M⁺-2), 137 (bp)

Example 268

To a solution of ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (100.0 mg) and (bromomethyl)benzene (111 mg) in N,N-dimethylformamide (1 mL) was added 60% sodium hydride (17.4 mg) under an ice-bath. After stirring for 2.5 hour, the reaction was quenched by adding 1N hydrochloric acid (1 mL), and the mixture was partitioned between ethyl acetate (10 mL) and water (5 mL). The organic layer was washed with 1N hydrochloric acid (5 mL), water (5 mL, three times), and brine, dried over magnesium sulfate, and evaporated. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1/40 to 20/40 afforded ethyl 5-[2-[(benzyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate as a yellow gum (47.7 mg, 39.9%).

Ethyl 5-[2-[(benzyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.34-1.48 (5H, m), 2.09 (2H, m), 2.53 (2H, m), 3.04 (2H, q, J=7Hz), 4.07 (2H, J=7Hz), 4.65 (2H, s), 4.72 (2H, s), 5.90 (1H, d, J=5Hz), 6.60 (1H, d, J=5Hz), 7.29-7.38 (5H, m), 7.86 (1H, s), 8.54 (1H, m), 8.77 (1H, m)

The following compound was obtained in substantially the same manner as that of Example 268.

Example 269

Ethyl 5-(4-(5-bromo-3-pyridinyl)-2-[[4-(cyanobenzyl)oxy]methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl)pentanoate

NMR (CDCl₃, δ): 1.23 (3H, J=7Hz), 1.35-1.55 (7H, m), 2.12 (2H, t, J=7Hz), 2.57 (2H, m), 3.02 (2H, q, J=7Hz), 4.07 (2H, q, J=7Hz), 4.49 (2H, s), 4.76 (2H, s), 5.93 (1H, d, J=7Hz), 6.62 (1H, d, J=7Hz), 7.48 (2H, d, J=8Hz), 7.65 (2H, d, J=8Hz), 7.86 (1H, m), 8.54 (1H, m), 8.78 (1H, m)

5

Example 270

To a solution of ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (200 mg) and triethylamine (65.9 mg) in dichloromethane (2 mL) was added methanesulfonyl chloride (54.7 mg) under an ice-bath. After stirring for 1 hour, the reaction was quenched by adding 1N hydrochloric acid (1 mL). The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (5 mL). The organic layer was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to give ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[[methylsulfonyl]oxy]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoate as a yellow gum (247 mg).

Ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[[methylsulfonyl]oxy]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoate

NMR (CDCl₃, δ): 1.22 (3H, t, J=7Hz), 1.34-1.65 (7H, m), 2.20 (2H, t, J=7Hz), 2.55 (2H, m), 3.02 (2H, q, J=7Hz), 3.15 (3H, s), 4.07 (2H, q, J=7Hz), 5.42 (2H, s), 5.99 (1H, d, J=5Hz), 6.68 (1H, d, J=5Hz), 7.87 (1H, m), 8.54 (1H, m), 8.81 (1H, m)

Example 271

A mixture of ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[[methylsulfonyl]oxy]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoate (50.0 mg), benzylamine (29.8 mg) in dichloromethane (1 mL) was stirred for 20 hours at room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried, and evaporated. Preparative thin layer chromatography eluting with ethyl acetate-hexane = 1:2 afforded ethyl 5-[2-[(benzylamino)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate as a yellow gum (19.1 mg).

Ethyl 5-[2-[(benzylamino)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.30-1.50 (7H, m), 2.13 (2H, t, J=7Hz), 2.42 (2H, m), 3.03 (2H, q, J=7Hz), 3.96 (4H, m), 4.09 (2H, q, J=7Hz), 5.89 (1H, d, J=5Hz), 6.57 (1H, d, J=5Hz), 7.23-7.42 (5H, m), 7.86 (1H, m), 8.53 (1H, m), 8.77 (1H, m)

The following compound was obtained in substantially the same manner as that of Example 271.

10 Example 272

Ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

NMR (CDCl₃, δ): 1.23 (3H, t, J=7Hz), 1.31-1.56 (7H, m), 2.19 (2H, t, J=7Hz), 2.45-2.65 (6H, m), 3.02 (2H, q, J=7Hz), 3.60-3.75 (6H, m), 4.09 (2H, q, J=7Hz), 5.88 (1H, d, J=5Hz), 6.57 (1H, d, J=5Hz), 7.89 (1H, m), 8.55 (1H, m), 8.78 (1H, m)

Example 273

To a solution of (7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl)methanol (40 mg) in N,N-dimethylformamide (1 mL) was added 40% sodium hydride in oil (5.5 mg) in an ice-water bath. After 20 minutes, to the mixture was added 2-bromoethyl acetate (31 mg) at the temperature. After 15 minutes, the reaction mixture was stirred at ambient temperature for 5 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water three times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by p-TLC (hexane-ethyl acetate = 10-1) to give [7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methyl acetate as a pale yellow solid (42 mg).

[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methyl acetate

NMR (CDCl₃, δ): 1.41 (6H, d, J=8Hz), 2.06 (3H, s), 3.21 (1H, m), 4.92 (2H, s), 6.14 (1H, d, J=5Hz), 6.72 (1H, d, J=5Hz), 7.13-7.24 (2H, m), 7.34-7.43 (2H, m)
MS (ESI⁺): m/z 361 (M+H)

The following compound was obtained in substantially the same manner as that of Preparation 20.

Example 274

Ethyl {[7-ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]methoxy}acetate

NMR (CDCl₃, δ): 1.25 (3H, t, J=8Hz), 1.30-1.45 (9 H, m), 3.04 (2H, q, J=8Hz), 3.51 (1H, m), 3.97 (2H, s), 4.15 (2H, q, J=8Hz), 4.40 (2H, s), 6.06 (1H, d, J=5Hz), 6.56 (1H, d, J=5Hz), 7.11-7.22 (2H, m), 7.41-7.51 (2H, m)

MS (ESI⁺): m/z 399 (M+H)

10

The following compound was obtained in substantially the same manner as that of Preparation 276.

Example 275

Ethyl 2-(2-amino-2-oxoethyl)-4-(4-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazine-3-carboxylate

NMR (CDCl₃, δ): 0.84 (3H, t, J=7Hz), 1.38 (3H, t, J=7Hz), 3.06 (2H, q, J=7Hz), 3.96 (2H, q, J=7Hz), 4.02 (3H, s), 5.41 (1H, s, br), 6.09 (1H, s, br), 6.28 (1H, d, J=5Hz), 6.75 (1H, d, J=5Hz), 7.53 (2H, d, J=9Hz), 7.77 (2H, d, J=9Hz)

MS (ESI⁺): m/z 753 (2M + H)

20

Example 276

A mixture of 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazine-2-carboxylic acid (40.0 mg), pyrrolidine (10.8 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (31.1 mg), and 1-hydroxybenzotriazole (21.9 mg) in N,N-dimethylformamide (1 mL) was stirred for 6 hour at room temperature. The mixture was partitioned between ethyl acetate (20 mL) and 1N hydrochloric acid (10 mL). The organic layer was washed with water (10 mL) three times, saturated sodium bicarbonate (10 mL), and brine, dried, and evaporated to give 3-[7-ethyl-3-(methylsulfonyl)-2-(1-pyrrolidinylcarbonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile as an yellow solid (35.6 mg).

30

3-[7-Ethyl-3-(methylsulfonyl)-2-(1-pyrrolidinylcarbonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

NMR (CDCl₃, δ): 1.38 (2H, m), 1.99 (4H, m), 3.07 (2H, q, J=7Hz), 3.23 (3H, s), 3.59 (2H, t, J=7Hz), 3.68 (2H, t, J=7Hz), 6.27 (1H, d, J=5Hz), 6.83 (1H, d, J=5Hz), 7.57-7.66 (3H, m), 7.79 (1H, m)
MS (ESI⁺): m/z 423 (M+H)

5

Example 277

To a solution of 3-[7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoic acid (40 mg) in N,N-dimethylformamide (4 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 mg), 1-hydroxybenzotriazole (24 mg), and 2-aminoethanol (15 mg) at ambient temperature. After stirring overnight, the reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with water 3 times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (silica gel, 40 mL) eluted with chloroform-methanol = 50-1 and 20-1 to give a yellow solid (42 mg). The solid was triturated with isopropyl ether to give 3-[7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]-N-(2-hydroxyethyl)benzamide as a yellow solid (35 mg).

3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]-N-(2-hydroxyethyl)benzamide
NMR (CDCl₃, δ): 1.43 (3H, t, J=8Hz), 2.39-2.49 (2H, m), 3.10 (2H, q, J=8Hz), 3.60-3.74 (2H, m), 3.80-3.94 (2H, m), 6.53-6.86 (4H, m), 7.00 (1H, s), 6.61 (1H, d, J=5Hz), 6.72 (1H, d, J=5Hz), 7.03 (1H, br s), 7.07 (1H, d, J=5Hz), 7.55-7.65 (2H, m), 7.86-7.97 (2H, m), 8.17 (1H, br s)
MS (ESI⁺): m/z 376 (M+H)

25

The following compounds were obtained in substantially the same manner as that of Example 283.

Example 278

5-[4-(3-Cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-methylpentanamide

30

mp: 60°C

NMR (CDCl₃, δ): 1.02-1.12 (2H, m), 1.17-1.25 (2H, m), 1.36 (3H, t, J=7Hz), 1.73 (2H, t, J=7Hz), 2.40 (2H, t, J=7Hz), 2.71 (3H, d, J=7Hz), 3.03 (2H, q, J=7Hz),

5.09 (1H, broad s), 5.90 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 7.45-7.55 (5H, m),
7.60-7.78 (4H, m)

MS: (m/z) 437 ($M^+ + H$), 115 (bp)

5 Example 279

4-(3-Chlorophenyl)-7-ethyl-3-[5-(4-morpholinyl)-5-oxopentyl]-2-phenylpyrrolo[1,2-b]pyridazine

mp: 55-58°C

10 NMR (CDCl₃, δ): 1.05-1.14 (2H, m), 1.17-1.23 (2H, m), 1.35 (3H, t, J=7Hz), 1.84 (2H, t, J=7Hz), 2.45 (2H, t, J=7Hz), 3.02 (2H, q, J=7Hz), 3.24 (2H, t, J=6Hz), 3.50 (2H, t, J=6Hz), 3.55-3.62 (4H, m), 5.99 (1H, d, J=4Hz), 6.62 (1H, d, J=4Hz), 7.30-7.35 (1H, m), 7.40-7.55 (8H, m)

MS: (m/z) 502 ($M^+ + H$), 115 (bp)

15 Example 280

5-[4-(3-Chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-methylpentanamide

mp: 70-72°C

20 NMR (CDCl₃, δ): 1.06 (2H, quintet, J=7Hz), 1.22 (2H, quintet, J=7Hz), 1.36 (3H, t, J=7Hz), 1.72 (2H, t, J=7Hz), 2.43 (2H, t, J=7Hz), 2.70 (3H, d, J=7Hz), 3.03 (2H, q, J=7Hz), 5.08 (1H, broad s), 5.99 (1H, d, J=4Hz), 6.61 (1H, d, J=4Hz), 7.29-7.33 (1H, m), 7.41-7.55 (8H, m)

MS: (m/z) 446 ($M^+ + H$), 115 (bp)

25 Example 281

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-methylpentanamide

30 NMR (CDCl₃, δ): 1.07 (2H, quintet, J=7Hz), 1.23 (2H, quintet, J=7Hz), 1.36 (3H, t, J=7Hz), 1.74 (2H, t, J=7Hz), 2.41 (2H, t, J=7Hz), 2.71 (3H, d, J=7Hz), 3.02 (2H, q, J=7Hz), 5.10 (1H, broad s), 5.95 (1H, d, J=4Hz), 6.64 (1H, d, J=4Hz), 7.31 (1H, d, J=7Hz), 7.42 (1H, s), 7.46-7.52 (1H, m), 7.41-7.55 (1H, d, J=7Hz)

MS: (m/z) 447 ($M^+ + H$), 115 (bp)

Example 282

3-{7-Ethyl-3-[5-(4-morpholinyl)-5-oxopentyl]-2-phenylpyrrolo[1,2-b]pyridazin-4-yl}benzonitrile from 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid
 mp: 66-69°C
 NMR (CDCl₃, δ): 1.04-1.12 (2H, m), 1.17-1.23 (2H, m), 1.36 (3H, t, J=7Hz), 1.84 (2H, t, J=7Hz), 2.42 (2H, t, J=7Hz), 3.03 (2H, q, J=7Hz), 3.23 (2H, t, J=6Hz), 3.50 (2H, t, J=6Hz), 3.55-3.63 (4H, m), 5.90 (1H, d, J=4Hz), 6.63 (1H, d, J=4Hz), 7.43-7.55 (5H, m), 7.60-7.78 (4H, m)
 MS: (m/z) 493 (M⁺+H), 126 (bp)

Example 283

To a solution of 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (50 mg) in N,N-dimethylformamide (1 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (35 mg) and 1-hydroxybenzotriazole (28 mg) at ambient temperature. After 30 minutes, to the mixture was added morpholine (24 mg). After 5 hours, the reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with water three times and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by flash silica gel column chromatography (silica gel, 40 mL) eluted with hexane-ethyl acetate = 3-1, 2-1, 1-1, 1-3, and 0-1 to give 3-{7-ethyl-2-methyl-3-[5-(4-morpholinyl)-5-oxopentyl]pyrrolo[1,2-b]pyridazin-4-yl}benzonitrile as an yellow gum (53 mg).

3-{7-Ethyl-2-methyl-3-[5-(4-morpholinyl)-5-oxopentyl]pyrrolo[1,2-b]pyridazin-4-yl}benzonitrile
 NMR (CDCl₃, δ): 1.15-1.61 (7H, m), 2.18 (2H, t, J=8Hz), 2.41 (2H, t, J=8Hz), 2.56 (3H, s), 3.00 (2H, q, J=8Hz), 3.82 (2H, t, J=5Hz), 3.51-3.68 (6H, m), 5.78 (1H, d, J=5Hz), 6.50 (1H, d, J=5Hz), 7.56-7.67 (3H, m), 7.74 (1H, m)
 MS (ESI⁺): m/z 431 (M+H)

The following compound was obtained in substantially the same manner as that of

Example 283.

Example 284

5-[4-(3-Cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanamide

NMR (CDCl₃, δ): 1.31-1.61 (7H, m), 2.11 (2H, t, J=8Hz), 2.40 (2H, t, J=8Hz), 2.56
5 (3H, s), 3.00 (2H, q, J=8Hz), 5.36 (2H, br s), 5.79 (1H, d, J=5Hz), 6.50 (1H, d,
J=5Hz), 7.56-7.67 (3H, m), 7.75 (1H, m)

MS (ESI⁺): m/z 361 (M+H)

Preparation 178

10 To a suspension of 60% sodium hydride (8.79 g) in tetrahydrofuran (500 mL) was
added cyclohexanol (10 g) and the mixture was stirred at 0 °C for 0.5 hour. To the
mixture was added bromoacetic acid (13.9 g) under ice-water cooling and the mixture
was heated under reflux for 2 hours. After adding water to the mixture and organic
solvent was evaporated in vacuo. The aqueous solution was diluted with water, washed
15 with ether, acidified with 1 N hydrochloric acid, and extracted with ether. The organic
layer was separated, dried over magnesium sulfate, and evaporated in vacuo to give
(cyclohexyloxy)acetic acid as colorless oil (13.3 g).

(cyclohexyloxy)acetic acid

20 ¹H NMR (CDCl₃) δ 1.18-1.47 (5H, m), 1.52-1.63 (1H, m), 1.72-1.85 (2H, m), 1.90-
2.03 (2H, m), 3.36-3.47 (1H, m), 4.13 (2H, s).

The following compound(s) was(were) obtained in substantially the same manner
as that of Preparation 178.

25 Preparation 179

isopropoxyacetic acid

¹H NMR (CDCl₃) δ 1.24 (6H, d, J= 7 Hz), 3.68-3.82 (1H, m), 4.11 (2H, s).

The following compound(s) was(were) obtained in substantially the same manner
30 as that of Preparation 129 and Preparation 130.

Preparation 180

tert-butyl 4-(benzyloxy)-3-oxobutanoate

¹H NMR (CDCl₃) δ 1.44 (9H, s), 3.45 (2H, s), 4.14 (2H, s), 4.60 (2H, s), 7.28-7.40

(5H, m).

Preparation 181

tert-butyl 4-(cyclohexyloxy)-3-oxobutanoate

- 5 ^1H NMR (CDCl_3) δ 1.18-1.43 (5H, m), 1.47 (9H, s), 1.53-1.63 (1H, m), 1.69-1.85 (2H, m), 1.87-1.97 (2H, m), 3.24-3.38 (1H, m), 3.46 (2H, s), 4.11 (2H, s).

Preparation 182

tert-butyl 4-isopropoxy-3-oxobutanoate

- 10 ^1H NMR (CDCl_3) δ 1.20 (6H, d, $J = 7$ Hz), 1.47 (9H, s), 3.45 (2H, s), 3.60-3.70 (1H, m), 4.08 (2H, s).

The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 159.

15 Preparation 183

1-tert-butyl 4-ethyl 2-acetylsuccinate

- ^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.47 (9H, s), 2.35 (3H, s), 3.08 (2H, m), 3.93 (1H, m), 4.12 (2H, q, $J = 7$ Hz).

20 Preparation 184

1-tert-butyl 7-ethyl 2-[(benzyloxy)acetyl]heptanedioate

- ^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.30-1.50 (2H, m), 1.40 (9H, s), 1.56-1.72 (2H, m), 1.75-1.95 (2H, m), 2.28 (2H, t, $J = 7$ Hz), 3.52 (1H, t, $J = 7$ Hz), 4.11 (2H, q, $J = 7$ Hz), 4.16 (2H, s), 4.59 (2H, s), 7.27-7.40 (5H, m).

25

Preparation 185

1-tert-butyl 5-ethyl 2-[(benzyloxy)acetyl]pentanedioate

- ^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.41 (9H, s), 2.10-2.23 (2H, m), 2.36 (2H, t, $J = 7$ Hz), 3.66 (1H, t, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.18 (2H, s), 4.60 (2H, s), 7.26-7.38 (5H, m).

30

Preparation 186

1-tert-butyl 7-ethyl 2-[(cyclohexyloxy)acetyl]heptanedioate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.44 (9H, s), 1.15-1.92 (16H, m), 2.29 (2H, t, $J = 7$ Hz), 3.24-3.38 (1H, m), 3.56 (1H, t, $J = 7$ Hz), 4.12 (4H, m),

Preparation 187

5 1-tert-butyl 7-ethyl 2-(isopropoxyacetyl)heptanedioate

^1H NMR (CDCl_3) δ 1.20 (6H, d, $J = 7$ Hz), 1.25 (3H, t, $J = 7$ Hz), 1.25-1.45 (2H, m), 1.45 (9H, s), 1.60-1.72 (2H, m), 1.75-1.95 (2H, m), 2.29 (2H, t, $J = 7$ Hz), 3.54 (1H, t, $J = 7$ Hz), 3.60-3.68 (1H, m), 4.11 (2H, s), 4.12 (2H, q, $J = 7$ Hz).

MS (ESI^+): m/z 345.

10

The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 20.

Preparation 188

1-tert-butyl 5-ethyl 2-[(cyclohexyloxy)acetyl]pentanedioate

15 ^1H NMR (CDCl_3) δ 1.26 (3H, t, $J = 7$ Hz), 1.45 (9H, s), 1.18-1.62 (6H, m), 1.66-1.78 (2H, m), 1.84-1.98 (2H, m), 2.10-2.23 (2H, m), 2.38 (2H, t, $J = 7$ Hz), 3.25-3.38 (1H, m), 3.69 (1H, t, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.15 (2H, s).

MS (ESI^+): m/z 357.

20 Preparation 189

To a suspension of 60% sodium hydride (527 mg) in dimethylformamide (20 mL) was added 3,5-pyridinedicarboxylic acid (2.00 g) under ice-water cooling and the mixture was stirred at 0 °C for 1 hour. To the mixture was added (bromomethyl)benzene (2.05 g) and the mixture was stirred at 60 °C for 2 hours. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with ethyl acetate to give 5-[(benzyloxy)carbonyl]nicotinic acid as a pale yellow powder (722 mg).

25 5-[(benzyloxy)carbonyl]nicotinic acid

^1H NMR ($\text{DMSO}-d_6$) δ 5.42 (2H, s), 7.34-7.54 (5H, m), 8.63 (1H, m), 9.23-9.34 (2H, m).

30

The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 24.

Preparation 190

1-tert-butyl 4-ethyl 2-acetyl-2-[(5-methyl-3-pyridinyl)carbonyl]succinate

^1H NMR (CDCl_3) δ 1.23 (3H, t, $J = 7$ Hz), 1.40 (9H, s), 2.38 (3H, s), 2.45 (3H, s),
3.20 (2H, m), 4.13 (2H, q, $J = 7$ Hz), 7.88 (1H, s), 8.57 (1H, s), 8.74 (1H, s).

5 MS (ESI^+): m/z 363.Preparation 191

ethyl 2-[(5-methyl-3-pyridinyl)carbonyl]-3-oxobutanoate

^1H NMR (CDCl_3) δ 0.96 (3H, t, $J = 7$ Hz), 2.15 (3H, s), 2.45 (3H, s), 4.03 (2H, q, $J = 7$
10 Hz), 4.12 (1H, t, $J = 7$ Hz), 7.89 (1H, s), 8.54 (1H, s), 8.72 (1H, s).

MS (ESI^+): m/z 250.Preparation 192

1-tert-butyl 6-ethyl 2-acetyl-2-[(5-bromo-3-pyridinyl)carbonyl]hexanedioate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.36 (9H, s), 1.60-1.73 (2H, m), 2.23-2.35
15 (2H, m), 2.38 (2H, t, $J = 7$ Hz), 2.48 (3H, s), 4.12 (2H, q, $J = 7$ Hz), 8.20 (1H, m),
8.78 (1H, m), 8.81 (1H, m).

Preparation 193

20 1-tert-butyl 5-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(methoxyacetyl)pentanedioate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.39 (9H, s), 2.40-2.47 (2H, m), 2.55-2.67
(2H, m), 3.36 (3H, s), 4.12 (2H, q, $J = 7$ Hz), 4.27 (1H, d, $J = 17$ Hz), 4.40 (1H, d,
 $J = 17$ Hz), 8.21 (1H, m), 8.79 (1H, d, $J = 2$ Hz), 8.82 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 472 474.

25

Preparation 194

1-tert-butyl 7-ethyl 2-acetyl-2-({5-[(benzyloxy)carbonyl]-3-pyridinyl}carbonyl)heptanedioate

^1H NMR (CDCl_3) δ 1.23 (3H, t, $J = 7$ Hz), 1.20-1.40 (2H, m), 1.32 (9H, s), 1.65-1.76
30 (2H, m), 2.19-2.26 (2H, m), 2.32 (2H, t, $J = 7$ Hz), 2.44 (3H, s), 4.12 (2H, q, $J = 7$
Hz), 5.41 (2H, s), 7.35-7.48 (5H, m), 8.62 (1H, m), 9.07 (1H, d, $J = 2$ Hz), 9.33
(1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 526.

Preparation 195

1-tert-butyl 7-ethyl 2-[(benzyloxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]heptanedioate

- 5 ^1H NMR (CDCl_3) δ 1.23 (3H, t, J = 7 Hz), 1.20-1.46 (2H, m), 1.32 (9H, s), 1.60-1.74 (2H, m), 2.10-2.36 (4H, m), 2.35 (3H, s), 4.10 (2H, q, J = 7 Hz), 4.38 (1H, d, J = 18 Hz), 4.53 (1H, d, J = 18 Hz), 4.54 (2H, m), 7.27-7.40 (5H, m), 7.79 (1H, m), 8.54 (1H, d, J = 2 Hz), 8.72 (1H, d, J = 2 Hz).

MS (ESI^+): m/z 512.

10

Preparation 196

1-tert-butyl 5-ethyl 2-[(benzyloxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]pentanedioate

- 15 ^1H NMR (CDCl_3) δ 1.26 (3H, t, J = 7 Hz), 1.34 (9H, s), 2.35 (3H, s), 2.40-2.72 (4H, m), 4.12 (2H, q, J = 7 Hz), 4.38 (1H, d, J = 17 Hz), 4.50 (1H, d, J = 17 Hz), 4.53 (2H, m), 7.25-7.38 (5H, m), 7.81 (1H, s), 8.54 (1H, s), 8.73 (1H, s).

MS (ESI^+): m/z 484.

Preparation 197

- 20 1-tert-butyl 7-ethyl 2-[(cyclohexyloxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]heptanedioate

- 25 ^1H NMR (CDCl_3) δ 1.25 (3H, t, J = 7 Hz), 1.16-1.55 (10H, m), 1.37 (9H, s), 1.60-1.76 (2H, m), 1.78-1.90 (2H, m), 2.15-2.28 (2H, m), 2.31 (2H, t, J = 7 Hz), 2.39 (3H, s), 3.17-3.29 (1H, m), 4.12 (2H, q, J = 7 Hz), 4.34 (1H, d, J = 18 Hz), 4.44 (1H, d, J = 18 Hz), 7.86 (1H, s), 8.56 (1H, s), 8.76 (1H, s).

MS (ESI^+): m/z 504.

Preparation 198

- 30 1-tert-butyl 7-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-[(cyclohexyloxy)acetyl]heptanedioate

- ^1H NMR (CDCl_3) δ 1.24 (3H, t, J = 7 Hz), 1.39 (9H, s), 1.16-1.88 (14H, m), 2.15-2.40 (4H, m), 3.16-3.28 (1H, m), 4.10 (2H, q, J = 7 Hz), 4.28 (1H, d, J = 18 Hz), 4.38 (1H, d, J = 18 Hz), 8.20 (1H, m), 8.78 (1H, d, J = 2 Hz), 8.84 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 568 570.

Preparation 199

1-tert-butyl 5-ethyl 2-[(cyclohexyloxy)acetyl]-2-[(5-methyl-3-

5 pyridinyl)carbonyl]pentanedioate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.15-1.38 (4H, m), 1.39 (9H, s), 1.45-1.75 (4H, m), 1.76-1.93 (2H, m), 2.39 (3H, s), 2.45-2.75 (4H, m), 3.17-3.30 (1H, m), 4.12 (2H, q, J= 7 Hz), 4.32 (1H, d, J= 17 Hz), 4.41 (1H, d, J= 17 Hz), 7.88 (1H, s), 8.55 (1H, s), 8.77 (1H, s).

10 MS (ESI⁺): m/z 476.

Preparation 200

1-tert-butyl 5-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-

[(cyclohexyloxy)acetyl]pentanedioate

15 ¹H NMR (CDCl₃) δ 1.26 (3H, t, J= 7 Hz), 1.15-1.35 (4H, m), 1.40 (9H, s), 1.40-1.65 (2H, m), 1.65-1.75 (2H, m), 1.75-1.92 (2H, m), 2.35-2.85 (4H, m), 3.16-3.32 (1H, m), 4.12 (2H, q, J= 7 Hz), 4.28 (1H, d, J= 17 Hz), 4.35 (1H, d, J= 17 Hz), 8.22 (1H, t, J= 2 Hz), 8.78 (1H, d, J= 2 Hz), 8.87 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 540 542.

20

Preparation 201

1-tert-butyl 7-ethyl 2-(isopropoxyacetyl)-2-[(5-methyl-3-

pyridinyl)carbonyl]heptanedioate

25 ¹H NMR (CDCl₃) δ 1.12 (6H, d, J= 7 Hz), 1.23 (3H, t, J= 7 Hz), 1.30-1.55 (2H, m), 1.37 (9H, s), 1.63-1.77 (2H, m), 2.19-2.28 (2H, m), 2.28 (2H, t, J= 7 Hz), 2.39 (3H, s), 3.53-3.64 (1H, m), 4.10 (2H, q, J= 7 Hz), 4.31 (1H, d, J= 18 Hz), 4.42 (1H, d, J= 18 Hz), 7.86 (1H, s), 8.55 (1H, s), 8.74 (1H, s).

MS (ESI⁺): m/z 464.

30 Preparation 202

1-tert-butyl 7-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(isopropoxyacetyl)heptanedioate

¹H NMR (CDCl₃) δ 1.10 (6H, d, J= 7 Hz), 1.24 (3H, t, J= 7 Hz), 1.39 (9H, s), 1.18-1.48 (2H, m), 1.64-1.77 (2H, m), 2.18-2.37 (4H, m), 3.52-3.64 (1H, m), 4.12 (2H,

q, J= 7 Hz), 4.25 (1H, d, J= 17 Hz), 4.36 (1H, d, J= 17 Hz), 8.19 (1H, t, J= 2 Hz), 8.77 (1H, d, J= 2 Hz), 8.83 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 528 530.

5 Preparation 203

1-tert-butyl 7-ethyl 2-[(acetyloxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]heptanedioate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.33 (9H, s), 1.20-1.42 (2H, m), 1.63-1.74 (2H, m), 2.14 (3H, s), 2.27-2.38 (4H, m), 2.40 (3H, s), 4.10 (2H, q, J= 7 Hz), 5.08 (1H, d, J= 18 Hz), 5.36 (1H, d, J= 18 Hz), 7.84 (1H, s), 8.56 (1H, s), 8.75 (1H, s).
MS (ESI⁺): m/z 464.

The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 78.

15 Preparation 204

ethyl 3-[(5-methyl-3-pyridinyl)carbonyl]-4-oxopentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 2.21 (3H, s), 2.44 (3H, s), 3.03 (2H, t, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 4.96 (1H, t, J= 7 Hz), 8.08 (1H, s), 8.66 (1H, s), 9.03 (1H, s).
MS (ESI⁺): m/z 264.

Preparation 205

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-6-oxoheptanoate

¹H NMR (CDCl₃) δ 1.25 (3H, t, J= 7 Hz), 1.60-1.78 (2H, m), 1.98-2.12 (2H, m), 2.20 (3H, s), 2.36 (2H, t, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 4.39 (1H, t, J= 7 Hz), 8.38 (1H, m), 8.87 (1H, d, J= 2 Hz), 9.08 (1H, d, J= 2 Hz).

Preparation 206

ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-6-methoxy-5-oxohexanoate

¹H NMR (CDCl₃) δ 1.25 (3H, t, J= 7 Hz), 2.04-2.16 (1H, m), 2.20-2.34 (1H, m), 2.40-2.48 (2H, m), 3.22 (3H, s), 3.93 (1H, d, J= 17 Hz), 4.00 (1H, d, J= 17 Hz), 4.12 (2H, q, J= 7 Hz), 4.85 (1H, m), 8.47 (1H, m), 8.88 (1H, s), 9.16 (1H, s).
MS (ESI⁺): m/z 372 374.

Preparation 207

benzyl 5-(2-acetyl-7-ethoxy-7-oxoheptanoyl)nicotinate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.30-1.43 (2H, m), 1.65-1.75 (2H, m),
5 1.93-2.15 (2H, m), 2.19 (3H, s), 2.29 (2H, t, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 4.44
(1H, t, J= 7 Hz), 5.43 (2H, s), 7.35-7.50 (5H, m), 8.81 (1H, m), 9.28 (1H, d, J= 2
Hz), 9.39 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 426.10 Preparation 208

ethyl 8-(benzyloxy)-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.30-1.43 (2H, m), 1.60-1.69 (2H, m),
1.73-1.86 (1H, m), 1.95-2.08 (1H, m), 2.25 (2H, t, J= 7 Hz), 2.34 (3H, s), 4.05
(2H, s), 4.07 (2H, q, J= 7 Hz), 4.35-4.45 (2H, m), 4.69 (1H, t, J= 7 Hz), 7.09 (2H,
15 m), 7.17-7.25 (3H, m), 7.93 (1H, s), 8.58 (1H, d, J= 2 Hz), 8.94 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 412.Preparation 209

ethyl 6-(benzyloxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 2.07-2.35 (2H, m), 2.34 (3H, s), 2.38-2.48
20 (2H, m), 4.05 (2H, s), 4.12 (2H, q, J= 7 Hz), 4.34 (1H, d, J= 17 Hz), 4.41 (1H, d,
J= 17 Hz), 4.90 (1H, m), 7.03 (2H, m), 7.15-7.25 (3H, m), 8.00 (1H, s), 8.57 (1H,
s), 9.02 (1H, s).

MS (ESI⁺): m/z 384.

25

Preparation 210

ethyl 8-(cyclohexyloxy)-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

¹H NMR (CDCl₃) δ 0.91-1.70 (12H, m), 1.23 (3H, t, J= 7 Hz), 1.70-1.85 (2H, m),
1.96-2.04 (2H, m), 2.27 (2H, t, J= 7 Hz), 2.43 (3H, s), 3.14-3.28 (1H, m), 4.00
30 (2H, s), 4.12 (2H, q, J= 7 Hz), 4.76 (1H, t, J= 7 Hz), 8.04 (1H, s), 8.62 (1H, s),
9.00 (1H, s).

MS (ESI⁺): m/z 404.

Preparation 211

ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-8-(cyclohexyloxy)-7-oxooctanoate

¹H NMR (CDCl₃) δ 0.95-1.87 (14H, m), 1.23 (3H, t, J= 7 Hz), 1.96-2.07 (2H, m),
2.28 (2H, t, J= 7 Hz), 3.16-3.27 (1H, m), 3.96-4.07 (2H, m), 4.12 (2H, q, J= 7 Hz),
5 4.72 (1H, t, J= 7 Hz), 8.38 (1H, m), 8.87 (1H, d, J= 2 Hz), 9.08 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 468 470.

Preparation 212

ethyl 6-(cyclohexyloxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

10 ¹H NMR (CDCl₃) δ 0.88-1.25 (5H, m), 1.24 (3H, t, J= 7 Hz), 1.40-1.83 (5H, m),
2.04-2.14 (1H, m), 2.18-2.34 (1H, m), 2.42 (2H, m), 2.44 (3H, s), 3.13-3.27 (1H,
m), 4.00 (2H, s), 4.12 (2H, q, J= 7 Hz), 4.93 (1H, m), 8.13 (1H, s), 8.63 (1H, d, J=
2 Hz), 9.07 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 376.

15

Preparation 213

ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-6-(cyclohexyloxy)-5-oxohexanoate

¹H NMR (CDCl₃) δ 0.88-1.85 (10H, m), 1.25 (3H, t, J= 7 Hz), 2.02-2.14 (1H, m),
2.18-2.34 (1H, m), 2.40-2.50 (2H, m), 3.15-3.27 (1H, m), 3.97 (1H, d, J= 17 Hz),
20 4.02 (1H, d, J= 17 Hz), 4.13 (2H, q, J= 7 Hz), 4.87-4.95 (1H, m), 8.48 (1H, t, J= 2
Hz), 8.88 (1H, d, J= 2 Hz), 9.19 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 440 442.

Preparation 214

25 ethyl 8-isopropoxy-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

¹H NMR (CDCl₃) δ 0.86 (3H, d, J= 7 Hz), 1.02 (3H, d, J= 7 Hz), 1.23 (3H, t, J= 7
Hz), 1.30-1.48 (2H, m), 1.60-1.72 (2H, m), 1.72-1.88 (1H, m), 1.95-2.07 (1H, m),
2.27 (2H, t, J= 7 Hz), 2.43 (3H, s), 3.44-3.54 (1H, m), 3.95 (1H, d, J= 18 Hz),
4.03 (1H, d, J= 18 Hz), 4.08 (2H, q, J= 7 Hz), 4.73 (1H, t, J= 7 Hz), 8.06 (1H, s),
30 8.63 (1H, s), 9.02 (1H, s).
MS (ESI⁺): m/z 364.

Preparation 215

ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-8-isopropoxy-7-oxooctanoate

- ¹H NMR (CDCl₃) δ 0.88 (3H, d, J= 7 Hz), 1.03 (3H, t, J= 7 Hz), 1.23 (3H, t, J= 7 Hz), 1.20-1.46 (2H, m), 1.58-1.72 (2H, m), 1.73-1.87 (1H, m), 1.95-2.07 (1H, m), 2.27 (2H, t, J= 7 Hz), 3.46-3.58 (1H, m), 3.94 (1H, d, J= 17 Hz), 4.03 (1H, d, J= 17 Hz), 4.10 (2H, q, J= 7 Hz), 4.68 (1H, t, J= 7 Hz), 8.40 (1H, t, J= 2 Hz), 8.86 (1H, d, J= 2 Hz), 9.08 (1H, d, J= 2 Hz).
- MS (ESI⁺): m/z 428 430.

Preparation 216

- ethyl 8-(acetyloxy)-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

- ¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.37-1.47 (2H, m), 1.60-1.77 (2H, m), 2.01 (3H, s), 1.97-2.08 (2H, m), 2.29 (2H, t, J= 7 Hz), 2.44 (3H, s), 4.10 (2H, q, J= 7 Hz), 4.52 (1H, t, J= 7 Hz), 4.68 (1H, d, J= 18 Hz), 4.76 (1H, d, J= 18 Hz), 8.04 (1H, s), 8.66 (1H, s), 8.98 (1H, s).
- MS (ESI⁺): m/z 364.

The following compound(s) was(were) obtained in substantially the same manner as that of Example 21.

Example 285

- ethyl [7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]acetate

- ¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.40 (3H, s), 2.50 (3H, s), 3.02 (2H, q, J= 7 Hz), 3.44 (2H, s), 4.14 (2H, q, J= 7 Hz), 5.98 (1H, d, J= 4 Hz), 6.56 (1H, d, J= 4 Hz), 7.55 (1H, s), 8.45 (1H, s), 8.54 (1H, s).
- MS (ESI⁺): m/z 338.

Example 286

ethyl 7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

- ¹H NMR (CDCl₃) δ 0.96 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.41 (3H, s), 2.61 (3H, s), 3.04 (2H, q, J= 7 Hz), 4.05 (2H, q, J= 7 Hz), 6.30 (1H, d, J= 4 Hz), 6.67 (1H, d, J= 4 Hz), 7.58 (1H, s), 8.48 (1H, d, J= 2 Hz), 8.51 (1H, d, J= 2 Hz).
- MS (ESI⁺): m/z 324.

Example 287

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.21 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.67-1.78 (2H, m),
2.22 (2H, t, J= 7 Hz), 2.42-2.54 (2H, m), 2.59 (3H, s), 3.01 (2H, q, J= 7 Hz), 4.06
(2H, q, J= 7 Hz), 5.87 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 7.87 (1H, m), 8.54
5 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 430 432.

Example 288

ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-
10 yl]propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 2.42 (2H, t, J= 7 Hz),
2.85-2.97 (2H, m), 3.06 (2H, q, J= 7 Hz), 3.46 (3H, s), 4.08 (2H, q, J= 7 Hz), 4.65
(2H, s), 5.94 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.87 (1H, m), 8.54 (1H, d,
J= 2 Hz), 8.78 (1H, d, J= 2 Hz).
15 MS (ESI⁺): m/z 446 448.

Example 289

ethyl 4-[2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-
yl]butanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.60-1.75 (2H, m),
2.17 (3H, s), 2.10-2.28 (2H, m), 2.45-2.60 (2H, m), 3.02 (2H, q, J= 7 Hz), 4.05
(2H, q, J= 7 Hz), 5.32 (2H, s), 5.95 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.88
(1H, m), 8.55 (1H, m), 8.78 (1H, m).
MS (ESI⁺): m/z 488 490.

25

Example 290

benzyl 5-[3-(5-ethoxy-5-oxopentyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-
yl]nicotinate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.33-1.60 (4H, m),
30 2.18 (2H, t, J= 7 Hz), 2.35-2.47 (2H, m), 2.56 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.10
(2H, q, J= 7 Hz), 5.42 (2H, s), 5.82 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 7.36-
7.47 (5H, m), 8.33 (1H, m), 8.77 (1H, d, J= 2 Hz), 9.33 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 500.

Example 291

ethyl 5-[2-[(benzyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

5 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.22 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.20-1.50 (4H, m),
2.06 (2H, t, J= 7 Hz), 2.42 (3H, s), 2.47-2.63 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.08
(2H, q, J= 7 Hz), 4.64 (2H, s), 4.73 (2H, s), 5.90 (1H, d, J= 4 Hz), 6.58 (1H, d, J=
4 Hz), 7.27-7.39 (5H, m), 7.51 (1H, s), 8.41 (1H, d, J= 2 Hz), 8.53 (1H, d, J= 2
Hz).

10

Example 292

ethyl 3-[2-[(benzyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

15 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.16 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.36 (2H, t, J= 7 Hz),
2.42 (3H, s), 2.80-3.00 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.03 (2H, q, J= 7 Hz), 4.65
(2H, s), 4.75 (2H, s), 5.92 (1H, d, J= 2 Hz), 6.59 (1H, d, J= 2 Hz), 7.26-7.38 (5H,
m), 7.48 (1H, s), 8.40 (1H, d, J= 2 Hz), 8.53 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 458.

20 Example 293

ethyl 5-[2-[(cyclohexyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.20-1.60 (10H, m), 1.25 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz),
1.70-1.83 (2H, m), 1.96-2.07 (2H, m), 2.15 (2H, t, J= 7 Hz), 2.43 (3H, s), 2.53-
2.68 (2H, m), 3.04 (2H, q, J= 7 Hz), 3.42-3.53 (1H, m), 4.08 (2H, q, J= 7 Hz),
4.69 (2H, s), 5.88 (1H, d, J= 4 Hz), 6.55 (1H, d, J= 4 Hz), 7.53 (1H, s), 8.42 (1H,
d, J= 2 Hz), 8.53 (1H, d, J= 2 Hz).

Example 294

30 ethyl 5-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexyloxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate

$^1\text{H NMR (CDCl}_3\text{)}$ δ 1.22-1.62 (10H, m), 1.23 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz),
1.73-1.86 (2H, m), 1.98-2.07 (2H, m), 2.18 (2H, t, J= 7 Hz), 2.53-2.70 (2H, m),

3.03 (2H, q, J= 7 Hz), 3.42-3.56 (1H, m), 4.12 (2H, q, J= 7 Hz), 4.69 (2H, s), 5.88 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.88 (1H, m), 8.54 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).

5 Example 295

ethyl 3-[2-[(cyclohexyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.16-1.45 (4H, m), 1.52-1.65 (2H, m), 1.73-1.83 (2H, m), 1.98-2.07 (2H, m), 2.35-2.47 (2H, m), 2.42 (3H, s), 2.84-2.98 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.45-3.56 (1H, m), 4.06 (2H, q, J= 7 Hz), 4.71 (2H, s), 5.89 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.50 (1H, s), 8.42 (1H, s), 8.53 (1H, s).

MS (ESI⁺): m/z 450.

15 Example 296

ethyl 3-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexyloxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.15-1.60 (6H, m), 1.73-1.85 (2H, m), 1.97-2.08 (2H, m), 2.45 (2H, t, J= 7 Hz), 2.83-2.97 (2H, m), 3.05 (2H, q, J= 7 Hz), 3.42-3.56 (1H, m), 4.08 (2H, q, J= 7 Hz), 4.71 (2H, s), 5.90 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.86 (1H, t, J= 2 Hz), 8.53 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 514 516.

25 Example 297

ethyl 5-[7-ethyl-2-(isopropoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.26 (6H, d, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.38-1.62 (4H, m), 2.17 (2H, t, J= 7 Hz), 2.43 (3H, s), 2.53-2.68 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.76-3.88 (1H, m), 4.08 (2H, q, J= 7 Hz), 4.66 (2H, s), 5.88 (1H, d, J= 4 Hz), 6.57 (1H, d, J= 4 Hz), 7.52 (1H, s), 8.42 (1H, s), 8.53 (1H, s).

MS (ESI⁺): m/z 438.

Example 298

ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isopropoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.25 (6H, d, J= 7 Hz), 1.37 (3H, t, J= 7 Hz),
1.37-1.64 (4H, m), 2.15 (2H, t, J= 7 Hz), 2.54-2.72 (2H, m), 3.02 (2H, q, J= 7 Hz),
3.75-3.87 (1H, m), 4.09 (2H, q, J= 7 Hz), 4.66 (2H, s), 5.89 (1H, d, J= 4 Hz), 6.58
(1H, d, J= 4 Hz), 7.88 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 502 504.

10 Example 299

ethyl 5-[2-[(acetyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.30-1.58 (4H, m),
2.13 (2H, t, J= 7 Hz), 2.18 (3H, s), 2.44 (3H, s), 2.40-2.55 (2H, m), 3.02 (2H, q,
J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 5.29 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.62 (1H, d,
J= 4 Hz), 7.52 (1H, s), 8.42 (1H, s), 8.53 (1H, s).

MS (ESI⁺): m/z 438.

The following compound(s) was(were) obtained in substantially the same manner
as that of Example 236.

Example 300

ethyl 4-{4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.41 (3H, t, J= 7 Hz),
1.68-1.80 (2H, m), 2.22 (2H, t, J= 7 Hz), 2.44-2.54 (2H, m), 2.59 (3H, s), 3.03
(2H, q, J= 7 Hz), 3.95 (2H, q, J= 7 Hz), 4.10 (2H, q, J= 7 Hz), 4.36 (1H, d, J= 3
Hz), 4.77 (1H, d, J= 3 Hz), 5.88 (1H, d, J= 4 Hz), 6.52 (1H, d, J= 4 Hz), 7.92 (1H,
m), 8.53 (1H, d, J= 2 Hz), 8.93 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 422.

30

Example 301

ethyl 3-[4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J= 7 Hz), 1.26 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz),
2.42 (2H, t, J= 7 Hz), 2.84-2.97 (2H, m), 3.07 (2H, q, J= 7 Hz), 3.47 (3H, s), 3.97
(2H, q, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.36 (1H, d, J= 3 Hz), 4.66 (2H, s), 4.77
(1H, d, J= 3 Hz), 5.95 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.92 (1H, m), 8.54
5 (1H, d, J= 2 Hz), 8.95 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 438.

Example 302

ethyl 3-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-
10 yl]propanoate

¹H NMR (CDCl₃) δ 1.18 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.40 (2H, t, J= 7 Hz),
2.84-2.98 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.47 (3H, s), 4.04 (2H, q, J= 7 Hz), 4.65
(2H, s), 5.46 (1H, d, J= 11 Hz), 5.87 (1H, d, J= 18 Hz), 5.94 (1H, d, J= 4 Hz),
6.60 (1H, d, J= 4 Hz), 6.72-6.83 (1H, dd, J= 11 Hz, 18 Hz), 7.74 (1H, m), 8.49
15 (1H, d, J= 2 Hz), 8.72 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 394.

Example 303

methyl 4-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-
20 yl]butanoate

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.65-1.78 (2H, m), 2.23 (2H, t, J= 7 Hz),
2.54-2.70 (2H, m), 3.05 (2H, q, J= 7 Hz), 3.47 (3H, s), 3.58 (3H, s), 4.67 (2H, s),
5.46 (1H, d, J= 11 Hz), 5.88 (1H, d, J= 18 Hz), 5.93 (1H, d, J= 4 Hz), 6.58 (1H, d,
J= 4 Hz), 6.73-6.83 (1H, dd, J= 11 Hz, 18 Hz), 7.77 (1H, m), 8.51 (1H, d, J= 2
25 Hz), 8.71 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 394.

Example 304

methyl 4-[4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-
30 b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.26 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.67-1.82 (2H, m),
2.22 (2H, t, J= 7 Hz), 2.53-2.67 (2H, m), 3.04 (2H, q, J= 7 Hz), 3.47 (3H, s), 3.58
(3H, s), 3.95 (2H, q, J= 7 Hz), 4.34 (1H, d, J= 2 Hz), 4.67 (2H, s), 4.77 (1H, d, J=

2 Hz), 5.93 (1H, d, J= 4 Hz), 6.59 (1H, d, J= 4 Hz), 7.92 (1H, m), 8.54 (1H, d, J= 2 Hz), 8.95 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 438.

5 Example 305

ethyl 3-{4-[5-(1-ethoxyvinyl)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}propanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.44 (3H, t, J= 7 Hz), 2.33-2.43 (2H, m), 2.58 (3H, s), 2.76-2.87 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.96 (2H, q, J= 7 Hz), 4.06 (2H, q, J= 7 Hz), 4.36 (1H, d, J= 2 Hz), 4.77 (1H, d, J= 2 Hz), 5.91 (1H, d, J= 4 Hz), 6.54 (1H, d, J= 4 Hz), 7.91 (1H, m), 8.53 (1H, d, J= 2 Hz), 8.96 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 408.

15 The following compound(s) was(were) obtained in substantially the same manner as that of Example 251.

Example 306

ethyl 4-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.66-1.82 (2H, m), 2.21 (2H, t, J= 7 Hz), 2.41-2.51 (2H, m), 2.60 (3H, s), 2.69 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.03 (2H, q, J= 7 Hz), 5.83 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 8.25 (1H, m), 8.79 (1H, d, J= 2 Hz), 9.25 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 394.

25 Example 307

ethyl 3-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.18 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.41 (2H, t, J= 7 Hz), 2.70 (3H, s), 2.83-2.96 (2H, m), 3.06 (2H, q, J= 7 Hz), 3.47 (3H, s), 4.03 (2H, q, J= 7 Hz), 4.66 (2H, s), 5.88 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 8.26 (1H, m), 8.79 (1H, d, J= 2 Hz), 9.25 (1H, d, J= 2 Hz).

Example 308

methyl 4-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.64-1.80 (2H, m), 2.20 (2H, t, J= 7 Hz),
2.53-2.65 (2H, m), 2.70 (3H, s), 3.05 (2H, q, J= 7 Hz), 3.47 (3H, s), 3.57 (3H, s),
5 4.67 (2H, s), 5.87 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 8.27 (1H, s), 8.81 (1H,
d, J= 2 Hz), 9.26 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 410.

Example 309

10 ethyl 3-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.33-2.42 (2H, m),
2.59 (3H, s), 2.69 (3H, s), 2.75-2.83 (2H, m), 3.02 (2H, q, J= 7 Hz), 4.05 (2H, q,
J= 7 Hz), 5.83 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 8.25 (1H, m), 8.78 (1H, d,
15 J= 2 Hz), 9.26 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 380.

Example 310

A mixture of benzyl 5-[3-(5-ethoxy-5-oxopentyl)-7-ethyl-2-methylpyrrolo[1,2-
20 b]pyridazin-4-yl]nicotinate (330 mg) and 10% palladium on carbon (33 mg) in methanol
(10 mL) was stirred under 4 atm hydrogen atmosphere at ambient temperature for 2 hours.
The catalysts were filtered off and washed with chloroform. The filtrates were
evaporated in vacuo to give 5-[3-(5-ethoxy-5-oxopentyl)-7-ethyl-2-methylpyrrolo[1,2-
b]pyridazin-4-yl]nicotinic acid as yellow oil (272 mg).

25

5-[3-(5-ethoxy-5-oxopentyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl]nicotinic acid

¹H NMR (CDCl₃) δ 1.21 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.35-1.63 (4H, m),
2.19 (2H, t, J= 7 Hz), 2.38-2.49 (2H, m), 2.57 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.11
(2H, q, J= 7 Hz), 5.85 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 8.40 (1H, m), 8.83
30 (1H, d, J= 2 Hz), 9.37 (1H, d, J= 2 Hz).

MS (ESI⁻): m/z 408, MS (ESI⁺): m/z 410.

Example 311

To a solution of 5-[3-(5-ethoxy-5-oxopentyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl]nicotinic acid (235 mg) and triethylamine (87.1 mg) in t-butanol (10 mL) was added diphenylphosphoryl azide (237 mg) and the mixture was heated under reflux for 2 hours. After evaporation of solvent, the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 2:1) to give ethyl 5-(4-{5-[(tert-butoxycarbonyl)amino]-3-pyridinyl}-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl)pentanoate as yellow oil (190 mg).

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.42-1.67 (4H, m), 1.52 (9H, s), 2.19-2.28 (2H, m), 2.38-2.50 (2H, m), 2.55 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 5.92 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 6.93 (1H, br), 7.87 (1H, s), 8.30 (1H, d, J= 2 Hz), 8.70 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 481.

Example 312

A solution of ethyl 5-(4-{5-[(tert-butoxycarbonyl)amino]-3-pyridinyl}-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl)pentanoate (190 mg) in 2 N hydrogen chloride ethyl acetate solution (4 mL) was stirred at ambient temperature for 2 hours. After evaporation of solvent, the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of chloroform and methanol (100:1 - 20:1) to give ethyl 5-[4-(5-amino-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (140 mg).

ethyl 5-[4-(5-amino-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.40-1.65 (4H, m), 2.23 (2H, t, J= 7 Hz), 2.45 (2H, t, J= 7 Hz), 2.54 (3H, s), 3.03 (2H, q, J= 7 Hz), 3.97 (2H, br), 4.12 (2H, q, J= 7 Hz), 5.94 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz),

7.02 (1H, m), 8.02 (1H, d, J= 2 Hz), 8.17 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 381 (M+H).

Example 313

5 To a solution of ethyl 5-[4-(5-amino-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (55 mg), 37% formaldehyde solution (277 mg) and sodium cyanoborohydride (27.3 mg) in acetonitrile (1 mL) and methanol (1 mL) was added acetic acid (2 drops) and the mixture was stirred at ambient temperature for 2 hours. The solution was diluted with saturated sodium bicarbonate solution and extracted with
10 chloroform. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative silica gel column chromatography eluting with a mixture of chloroform and methanol (20:1) to give ethyl 5-{4-[5-(dimethylamino)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate as yellow oil (36.5 mg).

15

ethyl 5-{4-[5-(dimethylamino)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.40-1.63 (4H, m),
2.19 (2H, t, J= 7 Hz), 2.40-2.53 (2H, m), 2.55 (3H, s), 3.02 (6H, s), 3.03 (2H, q,
20 J= 7 Hz), 4.09 (2H, q, J= 7 Hz), 5.93 (1H, d, J= 4 Hz), 6.50 (1H, d, J= 4 Hz), 6.96 (1H, m), 7.95 (1H, d, J= 2 Hz), 8.20 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 409.

The following compound(s) was(were) obtained in substantially the same manner
25 as that of Example 245.

Example 314

3-[7-ethyl-4-(5-ethyl-3-pyridinyl)-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

¹H NMR (CDCl₃) δ 1.29 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 2.45-2.58 (2H, m),
30 2.73 (2H, q, J= 7 Hz), 2.82-3.02 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.47 (3H, s), 4.67 (2H, s), 5.91 (1H, d, J= 4 Hz), 6.59 (1H, d, J= 4 Hz), 7.58 (1H, m), 8.43 (1H, d, J= 2 Hz), 8.53 (1H, d, J= 2 Hz).

MS (ESI): m/z 366, MS (ESI⁺): m/z 368.

Example 315

4-[7-ethyl-4-(5-ethyl-3-pyridinyl)-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

5 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.31 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.69-1.85 (2H, m), 2.20-2.31 (2H, m), 2.52-2.75 (2H, m), 2.77 (2H, q, J= 7 Hz), 3.06 (2H, q, J= 7 Hz), 3.46 (3H, s), 4.60-4.80 (2H, m), 5.91 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.61 (1H, s), 8.44-8.53 (2H, m).

MS (ESI⁺): m/z 382.

10

The following compound(s) was(were) obtained in substantially the same manner as that of Example 228.

Example 316

15 methyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

$^1\text{H NMR (CDCl}_3\text{)}$ δ 1.38 (3H, t, J= 7 Hz), 1.65-1.79 (2H, m), 2.25 (2H, t, J= 7 Hz), 2.39-2.53 (2H, m), 3.06 (2H, q, J= 7 Hz), 3.61 (3H, s), 4.90 (2H, s), 5.96 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.88 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.79 (1H, d, J= 2 Hz).

20 MS (ESI⁺): m/z 432 434 .

Example 317

ethyl 5-[7-ethyl-2-(hydroxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.23 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.35-1.60 (4H, m), 2.17 (2H, t, J= 7 Hz), 2.35-2.45 (2H, m), 2.43 (3H, s), 3.04 (2H, q, J= 7 Hz), 3.83 (1H, t, J= 7 Hz), 4.10 (2H, q, J= 7 Hz), 4.85 (2H, d, J= 7 Hz), 5.96 (1H, d, J= 4 Hz), 6.57 (1H, d, J= 4 Hz), 7.50 (1H, s), 8.42 (1H, s), 8.54 (1H, s).

MS (ESI⁺): m/z 396.

30

The following compound(s) was(were) obtained in substantially the same manner as that of Example 268.

Example 318

methyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.65-1.79 (2H, m), 2.24 (2H, t, $J = 7$ Hz),
2.52-2.70 (2H, m), 3.04 (2H, q, $J = 7$ Hz), 3.46 (3H, s), 3.60 (3H, s), 4.76 (2H, s),
5.93 (1H, d, $J = 4$ Hz), 6.62 (1H, d, $J = 4$ Hz), 7.88 (1H, m), 8.56 (1H, d, $J = 2$ Hz),
8.79 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 446 448.

Example 319

ethyl 5-[2-[(2-tert-butoxy-2-oxoethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.30-1.60 (4H, m),
1.47 (9H, s), 2.17 (2H, t, $J = 7$ Hz), 2.43 (3H, s), 2.58-2.72 (2H, m), 3.03 (2H, q,
 $J = 7$ Hz), 4.08 (2H, s), 4.12 (2H, q, $J = 7$ Hz), 4.81 (2H, s), 5.91 (1H, d, $J = 4$ Hz),
6.58 (1H, d, $J = 4$ Hz), 7.53 (1H, s), 8.43 (1H, s), 8.53 (1H, s).

MS (ESI^+): m/z 510.

Example 320

ethyl 5-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

^1H NMR (CDCl_3) δ 0.20-0.32 (2H, m), 0.53-0.63 (2H, m), 1.07-1.20 (1H, m), 1.22
(3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.40-1.60 (4H, m), 2.15 (2H, t, $J = 7$ Hz),
2.43 (3H, s), 2.53-2.68 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.41 (2H, d, $J = 7$ Hz), 4.08
(2H, q, $J = 7$ Hz), 4.70 (2H, s), 5.89 (1H, d, $J = 4$ Hz), 6.56 (1H, d, $J = 4$ Hz), 7.52
(1H, s), 8.43 (1H, s), 8.53 (1H, s).

MS (ESI^+): m/z 450.

Example 321

ethyl 5-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

^1H NMR (CDCl_3) δ 0.88-1.05 (2H, m), 1.16-1.35 (4H, m), 1.25 (3H, t, $J = 7$ Hz), 1.37
(3H, t, $J = 7$ Hz), 1.38-1.59 (4H, m), 1.60-1.87 (5H, m), 2.16 (2H, t, $J = 7$ Hz), 2.43
(3H, s), 2.54-2.67 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.35 (2H, d, $J = 7$ Hz), 4.10 (2H,

q, J= 7 Hz), 4.64 (2H, s), 5.89 (1H, d, J= 4 Hz), 6.56 (1H, d, J= 4 Hz), 7.52 (1H, s), 8.43 (1H, d, J= 2 Hz), 8.53 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 492.

5 Example 322

ethyl 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.39 (3H, t, J= 7 Hz), 1.35-1.54 (4H, m), 2.12 (2H, t, J= 7 Hz), 2.43 (3H, s), 2.50-2.63 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.66 (2H, s), 4.76 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.28 (1H, m), 7.52 (1H, s), 7.72 (1H, d, J= 8 Hz), 8.42 (1H, d, J= 2 Hz), 8.54 (2H, m), 8.62 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 487.

15 Example 323

ethyl 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (CDCl₃) δ 1.21 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.36-1.54 (4H, m), 2.12 (2H, t, J= 7 Hz), 2.42 (3H, s), 2.56-2.68 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.77 (2H, s), 4.85 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.22 (1H, m), 7.43-7.54 (2H, m), 7.66-7.74 (1H, m), 8.42 (1H, d, J= 2 Hz), 8.54 (1H, d, J= 2 Hz), 8.57 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 487.

25 Example 324

ethyl 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.39 (3H, t, J= 7 Hz), 1.38-1.57 (4H, m), 2.12 (2H, t, J= 7 Hz), 2.43 (3H, s), 2.52-2.68 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.66 (2H, s), 4.77 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 2 Hz), 7.28 (2H, d, J= 7 Hz), 7.52 (1H, s), 8.42 (1H, d, J= 2 Hz), 8.53 (1H, d, J= 2 Hz), 8.58 (2H, d, J= 7 Hz).

MS (ESI⁺): m/z 487.

Example 325

ethyl 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

- 5 $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.22 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.38-1.57 (4H, m), 2.13 (2H, t, J = 7 Hz), 2.43 (3H, s), 2.52-2.68 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.07 (2H, q, J = 7 Hz), 4.82 (2H, s), 4.88 (2H, m), 5.92 (1H, d, J = 4 Hz), 6.60 (1H, d, J = 4 Hz), 7.52 (1H, s), 8.43 (1H, d, J = 2 Hz), 8.48-8.57 (3H, m), 8.75 (1H, m).
MS (ESI⁺): m/z 488.

10

Example 326

ethyl 5-[4-(3-cyanophenyl)-2-(ethoxymethyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

- 15 $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.18-1.29 (6H, m), 1.34-1.53 (7H, m), 2.14 (2H, t, J = 7 Hz), 2.52 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.53 (2H, q, J = 7 Hz), 4.07 (2H, q, J = 7 Hz), 4.66 (1H, s), 5.73 (1H, d, J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 7.60 (2H, m), 7.67 (1H, s), 7.75 (1H, m)

Example 327

- 20 ethyl 5-[2-[(benzyloxy)methyl]-4-(3-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

- $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.22 (3H, t, J = 7 Hz), 1.30-1.46 (7H, m), 2.06 (2H, t, J = 7 Hz), 2.51 (2H, m), 3.02 (2H, q, J = 7 Hz), 4.07 (2H, q, J = 7 Hz), 4.64 (3H, s), 4.72 (3H, s), 5.83 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz), 7.25-7.38 (5H, m), 7.57 (2H, d, J = 9 Hz), 7.65 (1H, s), 7.74 (1H, m).

25

Example 328

methyl 4-({[4-(3-cyanophenyl)-3-(5-ethoxy-5-oxopentyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methoxy)methyl}benzoate

- 30 $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.22 (3H, t, J = 7 Hz), 1.32-1.49 (7H, m), 2.01 (2H, t, J = 7 Hz), 2.52 (2H, m), 3.02 (2H, t, J = 7 Hz), 3.92 (3H, s), 4.07 (2H, t, J = 7 Hz), 4.69 (2H, s), 4.75 (2H, s), 6.84 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.43 (2H, d, J = 9 Hz), 7.60 (2H, m), 7.65 (1H, s), 7.75 (1H, m), 8.02 (2H, d, J = 9 Hz).

Example 329

A solution of ethyl 5-[2-[(2-tert-butoxy-2-oxoethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (60 mg) in trifluoroacetic acid
 5 (2 mL) was stirred at ambient temperature for 2 hours, and evaporated in vacuo to give
 {[3-(5-ethoxy-5-oxopentyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-2-yl]methoxy}acetic acid as brown oil (55 mg).

10 {[3-(5-ethoxy-5-oxopentyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-2-yl]methoxy}acetic acid

¹H NMR (CDCl₃) δ 1.25 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.35-1.60 (4H, m),
 2.23 (2H, t, J= 7 Hz), 2.50-2.58 (2H, m), 2.67 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.08
 (2H, q, J= 7 Hz), 4.30 (2H, s), 4.87 (2H, s), 5.86 (1H, d, J= 4 Hz), 6.67 (1H, d, J=
 4 Hz), 8.15 (1H, s), 8.69 (1H, s), 8.85 (1H, s).

15 MS (ESI⁺): m/z 452, MS (ESI⁺): m/z 454.

Example 330

To a solution of {[3-(5-ethoxy-5-oxopentyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-2-yl]methoxy}acetic acid (55 mg), 1-ethyl-3-(3'-
 20 dimethylaminopropyl)carbodiimide hydrochloride (34.9 mg) and 1-hydroxybenotriazole
 (24.6 mg) in dimethylformamide (2 mL) was added morpholine (12.7 mg) and the
 mixture was stirred at ambient temperature for 1 hour. The mixture was partitioned
 between ethyl acetate and water. The organic layer was separated, washed with saturated
 sodium bicarbonate solution, water and brine, dried over magnesium sulfate, and
 25 evaporated in vacuo. The residue was purified by silica gel column chromatography
 eluting with a mixture of ethyl acetate and methanol (50:1 - 20:1) to give ethyl 5-(7-ethyl-
 4-(5-methyl-3-pyridinyl)-2-{[2-(4-morpholinyl)-2-oxoethoxy]methyl}pyrrolo[1,2-
 b]pyridazin-3-yl)pentanoate as yellow oil (50 mg).

30 ethyl 5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-{[2-(4-morpholinyl)-2-oxoethoxy]methyl}pyrrolo[1,2-b]pyridazin-3-yl)pentanoate

¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.40-1.63 (4H, m),
 2.15 (2H, t, J= 7 Hz), 2.43 (3H, s), 2.54-2.68 (2H, m), 3.02 (2H, q, J= 7 Hz), 3.48-

3.57 (2H, m), 3.63-3.78 (6H, m), 4.08 (2H, q, J= 7 Hz), 4.30 (2H, s), 4.78 (2H, s),
5.93 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.52 (1H, s), 8.43 (1H, d, J= 2 Hz),
8.54 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 523.

5

The following compound(s) was(were) obtained in substantially the same manner as that of Example 330.

Example 331

ethyl 5-[7-ethyl-2-{[2-(methylamino)-2-oxoethoxy]methyl}-4-(5-methyl-3-
10 pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.38-1.62 (4H, m),
2.18 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.48-2.62 (2H, m), 2.88 (3H, d, J= 7 Hz), 3.03
(2H, q, J= 7 Hz), 4.11 (2H, q, J= 7 Hz), 4.13 (2H, s), 4.77 (2H, s), 5.94 (1H, d, J=
4 Hz), 6.63 (1H, d, J= 4 Hz), 6.79 (1H, br), 7.53 (1H, s), 8.44 (1H, s), 8.56 (1H, s).

15 MS (ESI⁺): m/z 467.

The following compound(s) was(were) obtained in substantially the same manner as that of Example 271.

Example 332

20 ethyl 5-[2-[(benzylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-
b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.30-1.50 (2H, m),
1.60-1.85 (2H, m), 2.12 (2H, t, J= 7 Hz), 2.30-2.45 (2H, m), 2.42 (3H, s), 3.03
(2H, q, J= 7 Hz), 3.96 (2H, s), 3.98 (2H, s), 4.08 (2H, q, J= 7 Hz), 5.87 (1H, d, J=
25 4 Hz), 6.54 (1H, d, J= 4 Hz), 7.27-7.43 (5H, m), 7.48 (1H, s), 8.38 (1H, d, J= 2
Hz), 8.53 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 485.

Example 333

30 A mixture of ethyl 5-[7-ethyl-2-(hydroxymethyl)-4-(5-methyl-3-
pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (100 mg), 1H-isoindole-1,3(2H) dione
(44.6 mg) diisopropyl azodicarboxylate (76.7 mg) and triphenylphosphine (99.5 mg) in
tetrahydrofuran (2 mL) was stirred at ambient temperature for 1 hour. After evaporation

of solvent, the residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate (20:1 - 1:1) to give ethyl 5-[2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (107 mg).

5

ethyl 5-[2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 0.89 (3H, t, J= 7 Hz), 1.26 (3H, t, J= 7 Hz), 1.20-1.40 (2H, m), 1.53-1.75 (2H, m), 2.24 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.47 (2H, q, J= 7 Hz), 2.50-2.64 (2H, m), 4.12 (2H, q, J= 7 Hz), 5.10 (2H, s), 5.85 (1H, d, J= 4 Hz), 6.43 (1H, d, J= 4 Hz), 7.51 (1H, s), 7.78 (2H, m), 7.96 (2H, m), 8.43 (1H, s), 8.55 (1H, s).
MS (ESI⁺): m/z 525.

10

Example 334

15

A mixture of ethyl 5-[2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (107 mg) and hydrazine monohydrate (51.1 mg) in ethanol (2 mL) was heated under reflux for 2 hours. After evaporation of solvent, the residue was partitioned between chloroform and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo to give ethyl 5-[2-(aminomethyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (67.6 mg).

20

ethyl 5-[2-(aminomethyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.38-1.62 (4H, m), 2.14 (2H, t, J= 7 Hz), 2.42 (3H, s), 2.38-2.56 (2H, m), 3.04 (2H, q, J= 7 Hz), 4.06 (2H, s), 4.08 (2H, q, J= 7 Hz), 5.90 (1H, d, J= 4 Hz), 6.55 (1H, d, J= 4 Hz), 7.51 (1H, s), 8.41 (1H, s), 8.53 (1H, s).

30

MS (ESI⁺): m/z 395.

Example 335

A mixture of ethyl 5-[2-(aminomethyl)-7-ethyl-4-(5-methyl-3-

pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (67.6 mg) and acetic anhydride (19.2 mg) in dichloromethane (3 mL) was stirred at ambient temperature for 1 hour. The solution was diluted with chloroform, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was
5 purified by preparative silica gel column chromatography eluting with a mixture of chloroform and methanol (20:1) to give ethyl 5-[2-[(acetylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (70 mg).

ethyl 5-[2-[(acetylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-
10 b]pyridazin-3-yl]pentanoate

^1H NMR (CDCl_3) δ 1.22 (3H, t, $J = 7$ Hz), 1.40 (3H, t, $J = 7$ Hz), 1.40-1.63 (4H, m),
2.12 (2H, m), 2.15 (3H, s), 2.43 (3H, s), 2.40-2.53 (2H, m), 3.03 (2H, q, $J = 7$ Hz),
4.10 (2H, q, $J = 7$ Hz), 4.66 (2H, m), 5.94 (1H, d, $J = 4$ Hz), 6.59 (1H, d, $J = 4$ Hz),
6.85 (1H, br), 7.50 (1H, s), 8.40 (1H, d, $J = 2$ Hz), 8.54 (1H, d, $J = 2$ Hz).

15 MS (ESI^+): m/z 437.

Example 336

To a solution of ethyl 5-[2-(aminomethyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (80 mg) and pyridine (1 mL) in
20 dichloromethane (2 mL) was added methanesulfonyl chloride (34.8 mg) under ice-water cooling and the mixture was stirred at ambient temperature for 1 hour. The solution was diluted with chloroform, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative silica gel column chromatography eluting with a mixture of chloroform and
25 methanol (20:1) to give ethyl 5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[[(methylsulfonyl)amino]methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (62.8 mg)

ethyl 5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[[(methylsulfonyl)amino]methyl]pyrrolo[1,2-
30 b]pyridazin-3-yl]pentanoate

^1H NMR (CDCl_3) δ 1.23 (3H, t, $J = 7$ Hz), 1.39 (3H, t, $J = 7$ Hz), 1.40-1.62 (4H, m),
2.19 (2H, t, $J = 7$ Hz), 2.44 (3H, s), 2.38-2.51 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.06
(3H, s), 4.08 (2H, q, $J = 7$ Hz), 4.58 (2H, s), 5.63 (1H, br), 5.97 (1H, d, $J = 4$ Hz),

6.61 (1H, d, J= 4 Hz), 7.50 (1H, s), 8.41 (1H, d, J= 2 Hz), 8.54 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 473.

Example 337

- 5 A mixture of ethyl 5-[2-(aminomethyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (75 mg), benzoic acid (27.9 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (54.7 mg) and 1-hydroxybenotriazole (38.5 mg) in dimethylformamide (2 mL) was stirred at ambient temperature for 2 hours. The mixture was partitioned between ethyl acetate and water.
- 10 The organic layer was separated, washed with saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative silica gel column chromatography eluting with a mixture of chloroform and methanol (20:1) to give ethyl 5-[2-[(benzoylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (60 mg).
- 15 ethyl 5-[2-[(benzoylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate
- ¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.42 (3H, t, J= 7 Hz), 1.42-1.65 (4H, m), 2.17 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.44-2.58 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.86 (2H, m), 5.96 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.46-7.59 (4H, m), 7.78 (1H, br), 7.91-7.97 (2H, m), 8.44 (1H, d, J= 2 Hz), 8.56 (1H, d, J= 2 Hz).
- 20 MS (ESI⁺): m/z 499.

- 25 The following compound(s) was(were) obtained in substantially the same manner as that of Example 337.

Example 338

- ethyl 5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[2-pyrazinylcarbonyl]amino]methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate
- 30 ¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.41 (3H, t, J= 7 Hz), 1.42-1.64 (4H, m), 2.18 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.47-2.59 (2H, m), 3.08 (2H, q, J= 7 Hz), 4.09 (2H, q, J= 7 Hz), 4.89 (2H, d, J= 7 Hz), 5.96 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.53 (1H, s), 8.43 (1H, d, J= 2 Hz), 8.55 (1H, d, J= 2 Hz), 8.62 (1H, m), 8.79

(1H, m), 9.15 (1H, br), 9.46 (1H, m).

MS (ESI⁺): m/z 501.

Example 339

- 5 To a solution of ethyl 5-[2-(aminomethyl)-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (80 mg) and pyridine (1 mL) in dichloromethane (2 mL) was added methyl chloridocarbonate (34.8 mg) under ice-water cooling and the mixture was stirred at ambient temperature for 2 hours. After evaporation of solvent, the residue was partitioned between ethyl acetate and water.
- 10 The organic layer was separated, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by preparative silica gel column chromatography eluting with a mixture of chloroform and methanol (20:1) to give ethyl 5-[7-ethyl-2-[(methoxycarbonyl)amino]methyl]-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as yellow oil (70 mg).
- 15 ethyl 5-[7-ethyl-2-[(methoxycarbonyl)amino]methyl]-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate
- ¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.39 (3H, t, J= 7 Hz), 1.40-1.63 (4H, m), 2.19 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.40-2.55 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.07 (3H, s), 4.12 (2H, q, J= 7 Hz), 4.57 (2H, m), 5.72 (1H, br), 5.97 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.51 (1H, s), 8.41 (1H, s), 8.56 (1H, s).
- 20

Example 340

- To a solution of ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (70.0 mg) and triethyl amine (18.5 mg) in dichloromethane (1 mL) was added methanesulfonyl chloride (20.9 mg) under an ice bath. After stirring for 1 hour, to the mixture was added 1-methylpiperazine (27.0 mg). The mixture was stirred for 0.5 hour under an ice bath and overnight at room temperature. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. Preparative silicagel thin layer chromatography (chloroform-methanol = 20-1) afforded ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-methyl-1-piperazinyl)methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as an yellow gum (52.4 mg, 63.5%).
- 25
- 30

ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-methyl-1-piperazinyl)methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃): 1.23 (3H, t, J = 7 Hz), 1.33-1.60 (7 H, m), 2.16 (2H, t, J = 7 Hz),
5 2.29 (3H, s), 2.34-2.65 (6H, m), 3.00 (2H, q, J = 7 Hz), 3.54 (2H, s), 4.08 (2H, q, J = 7 Hz), 5.86 (1H, d, J = 5 Hz), 6.55 (1H, d, J = 5 Hz), 7.87 (1H, m), 8.54 (1H, m), 8.77 (1H, m).

Example 341

10 To a solution of ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (300 mg, 0.652 mmol) and tetrabromomethane (432 mg, 1.30 mmol) in tetrahydrofuran (3 mL) was added triphenylphosphine (308 mg, 1.17 mmol) over 40 minutes. The mixture was concentrated, and the residue was chromatographed on a flash silica gel column
15 chromatography (ethyl acetate-hexane = 1-8 to 1-5) to afford ethyl 5-[2-(bromomethyl)-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate as a yellow gum (229 mg, 50.4%).

ethyl 5-[2-(bromomethyl)-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

20 ¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.41-1.50 (4H, m), 2.19 (2H, t, J = 7 Hz), 2.58 (2H, m), 3.01 (2H, q, J = 7 Hz), 4.08 (2H, q, J = 7 Hz), 4.66 (2H, s), 5.94 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 7.88 (1H, m), 8.55 (1H, m), 8.79 (1H, m).

Example 342

25 A mixture of ethyl 5-[2-(bromomethyl)-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (70.0 mg) and potassium cyanide (13.1 mg) in N,N-dimethylformamide (1 mL) was stirred for 28 hours at room temperature. The
30 mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (two times), brine, dried over magnesium sulfate, and evaporated to give ethyl 5-[4-(5-bromo-3-pyridinyl)-2-(cyanomethyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate as a yellow gum (28.8 mg, 45.9%).

ethyl 5-[4-(5-bromo-3-pyridinyl)-2-(cyanomethyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 7 Hz), 1.46-1.65 (7H, m), 2.22 (2H, t, J = 7 Hz),
5 2.48 (2H, m), 3.04 (2H, q, J = 7 Hz), 3.98 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.98
 (1H, d, J = 5 Hz), 6.65 (1H, d, J = 5 Hz), 7.88 (1H, m), 8.55 (1H, m), 8.81 (1H,
 m).

The following compound(s) was(were) obtained in substantially the same manner
10 as that of Example 76.

Example 343

[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]acetic acid

¹H NMR (CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 2.45 (3H, s), 2.56 (3H, s), 3.02 (2H, q, J = 7
 Hz), 3.28 (1H, d, J = 17 Hz), 3.53 (1H, d, J = 17 Hz), 5.91 (1H, d, J = 4 Hz), 6.52
15 (1H, d, J = 4 Hz), 7.71 (1H, s), 8.47 (1H, s), 8.59 (1H, s).

MS (ESI): m/z 308, MS (ESI⁺): m/z 310.

Example 344

4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 1.65-1.85 (2H, m), 2.31 (2H, t, J = 7 Hz),
20 2.45-2.63 (2H, m), 2.59 (3H, s), 3.03 (2H, q, J = 7 Hz), 5.88 (1H, d, J = 4 Hz), 6.53
 (1H, d, J = 4 Hz), 7.90 (1H, s), 8.53 (1H, s), 8.75 (1H, s).

MS (ESI): m/z 400 402, MS (ESI⁺): m/z 402 404.

25 Example 345

4-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 1.68-1.82 (2H, m), 2.26 (2H, t, J = 7 Hz),
2.45-2.58 (2H, m), 2.60 (3H, s), 2.70 (3H, s), 3.03 (2H, q, J = 7 Hz), 5.83 (1H, d,
 J = 4 Hz), 6.54 (1H, d, J = 4 Hz), 8.28 (1H, m), 8.77 (1H, d, J = 2 Hz), 9.19 (1H, d,
30 J = 2 Hz).

Example 346

3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-

yl]propanoic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.49 (2H, t, $J = 7$ Hz), 2.80-3.00 (2H, m), 3.05 (2H, q, $J = 7$ Hz), 3.46 (3H, s), 4.66 (2H, s), 5.94 (1H, d, $J = 4$ Hz), 6.62 (1H, d, $J = 4$ Hz), 7.88 (1H, s), 8.55 (1H, s), 8.77 (1H, s).

5 MS (ESI): m/z 416 418, MS (ESI^+): m/z 418 420.

Example 347

3-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

10 ^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 2.48 (2H, t, $J = 7$ Hz), 2.68 (3H, s), 2.85-2.97 (2H, m), 3.05 (2H, q, $J = 7$ Hz), 3.47 (3H, s), 4.67 (2H, s), 5.88 (1H, d, $J = 4$ Hz), 6.62 (1H, d, $J = 4$ Hz), 8.27 (1H, m), 8.78 (1H, d, $J = 2$ Hz), 9.23 (1H, d, $J = 2$ Hz).

MS (ESI): m/z 380, MS (ESI^+): m/z 382.

15

Example 348

3-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

20 ^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 2.46-2.58 (2H, m), 2.83-3.03 (2H, m), 3.05 (2H, q, $J = 7$ Hz), 3.47 (3H, s), 4.68 (2H, s), 5.46 (1H, d, $J = 11$ Hz), 5.88 (1H, d, $J = 18$ Hz), 5.93 (1H, d, $J = 4$ Hz), 6.60 (1H, d, $J = 4$ Hz), 6.68-6.82 (1H, dd, $J = 11$ Hz, 18 Hz), 7.78 (1H, m), 8.47 (1H, d, $J = 2$ Hz), 8.68 (1H, d, $J = 2$ Hz).

MS (ESI): m/z 364, MS (ESI^+): m/z 366.

25 Example 349

4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

30 ^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.68-1.82 (2H, m), 2.29 (2H, t, $J = 7$ Hz), 2.55-2.75 (2H, m), 3.04 (2H, q, $J = 7$ Hz), 3.45 (3H, s), 4.64 (2H, s), 5.93 (1H, d, $J = 4$ Hz), 6.61 (1H, d, $J = 4$ Hz), 7.91 (1H, m), 8.56 (1H, d, $J = 2$ Hz), 8.77 (1H, d, $J = 2$ Hz).

MS (ESI): m/z 430 432, MS (ESI^+): m/z 432 434.

Example 350

4-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.72-1.87 (2H, m), 2.26 (2H, t, J= 7 Hz),
5 2.53-2.80 (2H, m), 3.06 (2H, q, J= 7 Hz), 3.46 (3H, s), 4.68 (2H, m), 5.47 (1H, d,
J= 11 Hz), 5.88 (1H, d, J= 18 Hz), 5.93 (1H, d, J= 4 Hz), 6.59 (1H, d, J= 4 Hz),
6.72-6.83 (1H, dd, J= 11 Hz, 18 Hz), 7.81 (1H, m), 8.50 (1H, d, J= 2 Hz), 8.63
(1H, d, J= 2 Hz).

MS (ESI): m/z 378, MS (ESI⁺): m/z 380.

10

Example 351

4-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.66-1.83 (2H, m), 2.26 (2H, t, J= 7 Hz),
15 2.55-2.70 (2H, m), 2.70 (3H, s), 3.05 (2H, q, J= 7 Hz), 3.46 (3H, s), 4.67 (2H, s),
5.88 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 8.29 (1H, m), 8.80 (1H, d, J= 2 Hz),
9.22 (1H, d, J= 2 Hz).

MS (ESI): m/z 394 , MS (ESI⁺): m/z 396.

20 Example 352

5-[4-(5-amino-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H NMR (CDCl₃) δ 1.34 (3H, t, J= 7 Hz), 1.44-1.65 (4H, m), 2.16-2.32 (2H, m),
2.34-2.46 (2H, m), 2.53 (3H, s), 3.02 (2H, q, J= 7 Hz), 5.06 (2H, br), 5.86 (1H, d,
J= 4 Hz), 5.98 (1H, d, J= 4 Hz), 7.45 (1H, s), 7.84 (1H, s), 8.58 (1H, s).

25 MS (ESI): m/z 351, MS (ESI⁺): m/z 353.

Example 353

5-{4-[5-(dimethylamino)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

30 ¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 1.40-1.70 (4H, m), 2.23 (2H, m), 2.36-2.50
(2H, m), 2.56 (3H, s), 3.03 (2H, q, J= 7 Hz), 3.06 (6H, s), 5.88 (1H, d, J= 4 Hz),
6.53 (1H, d, J= 4 Hz), 7.13 (1H, s), 7.90 (1H, s), 8.14 (1H, m).

MS (ESI⁺): m/z 381.

Example 354

3-[4-(5-acetyl-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 2.40-2.53 (2H, m), 2.60 (3H, s), 2.68 (3H, s), 2.83 (2H, t, J= 7 Hz), 3.03 (2H, q, J= 7 Hz), 5.83 (1H, d, J= 4 Hz), 6.53 (1H, d, J= 4 Hz), 8.27 (1H, m), 8.78 (1H, d, J= 2 Hz), 9.22 (1H, d, J= 2 Hz).

MS (ESI): m/z 350, MS (ESI⁺): m/z 352.

Example 355

10 5-[2-[(benzyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 1.35-1.55 (4H, m), 2.05-2.20 (2H, m), 2.42 (3H, s), 2.40-2.70 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.63 (2H, s), 4.74 (2H, m), 5.88 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.27-7.42 (5H, m), 7.53 (1H, s), 8.40 (1H, s), 8.53 (1H, s).

MS (ESI⁺): m/z 458.

Example 356

20 3-[2-[(benzyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 2.40 (3H, s), 2.40-2.54 (2H, m), 2.80-3.08 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.65 (2H, s), 4.77 (2H, m), 5.89 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.26-7.42 (5H, m), 7.54 (1H, s), 8.39 (1H, d, J= 2 Hz), 8.48 (1H, d, J= 2 Hz).

25 MS (ESI): m/z 428, MS (ESI⁺): m/z 430.

Example 357

5-[2-[(cyclohexyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

30 ¹H NMR (CDCl₃) δ 1.20-1.45 (6H, m), 1.36 (3H, t, J= 7 Hz), 1.45-1.63 (4H, m), 1.70-1.83 (2H, m), 1.95-2.08 (2H, m), 2.14-2.28 (2H, m), 2.42 (3H, s), 2.46-2.60 (1H, m), 2.60-2.75 (1H, m), 3.03 (2H, q, J= 7 Hz), 3.42-3.54 (1H, m), 4.72 (2H, m), 5.87 (1H, d, J= 4 Hz), 6.54 (1H, d, J= 4 Hz), 7.55 (1H, s), 8.41 (1H, s), 8.53

(1H, s).

MS (ESI⁻): m/z 448, MS (ESI⁺): m/z 450.

Example 358

5 5-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexyloxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (CDCl₃) δ 1.18-1.60 (10H, m), 1.36 (3H, t, J= 7 Hz), 1.70-1.80 (2H, m),
1.95-2.05 (2H, m), 2.22 (2H, t, J= 7 Hz), 2.50-2.70 (2H, m), 3.03 (2H, q, J= 7 Hz),
3.42-3.53 (1H, m), 4.68 (2H, s), 5.89 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.88
10 (1H, s), 8.54 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 514 516.

Example 359

15 3-[2-[(cyclohexyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

¹H NMR (CDCl₃) δ 1.20-1.45 (5H, m), 1.37 (3H, t, J= 7 Hz), 1.50-1.60 (1H, m),
1.72-1.84 (2H, m), 1.96-2.08 (2H, m), 2.42 (3H, s), 2.48-2.62 (2H, m), 2.80-3.10
(2H, m), 3.03 (2H, q, J= 7 Hz), 3.44-3.66 (1H, m), 4.73 (2H, s), 5.88 (1H, d, J= 4
Hz), 6.57 (1H, d, J= 4 Hz), 7.55 (1H, s), 8.40 (1H, s), 8.51 (1H, s).

20 MS (ESI⁺): m/z 422.

Example 360

25 3-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexyloxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

¹H NMR (CDCl₃) δ 1.18-1.47 (5H, m), 1.37 (3H, t, J= 7 Hz), 1.52-1.63 (1H, m),
1.72-1.85 (2H, m), 1.97-2.07 (2H, m), 2.48-2.62 (2H, m), 2.80-3.10 (2H, m), 3.03
(2H, q, J= 7 Hz), 3.44-3.57 (1H, m), 4.73 (2H, s), 5.91 (1H, d, J= 4 Hz), 6.61 (1H,
d, J= 4 Hz), 7.88 (1H, t, J= 2 Hz), 8.55 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).

MS (ESI⁻): m/z 484 486, MS (ESI⁺): m/z 486 488.

30

Example 361

5-[7-ethyl-2-(isopropoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 1.25 (6H, d, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.44-1.63 (4H, m), 2.15-2.27 (2H, m), 2.43 (3H, s), 2.47-2.60 (1H, m), 2.60-2.73 (1H, m), 3.03 (2H, q, $J = 7$ Hz), 3.75-3.87 (1H, m), 4.67 (2H, s), 5.87 (1H, d, $J = 4$ Hz), 6.56 (1H, d, $J = 4$ Hz), 7.55 (1H, s), 8.41 (1H, s), 8.53 (1H, s).

5 MS (ESI): m/z 408, MS (ESI $^+$): m/z 410.

Example 362

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isopropoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 ^1H NMR (CDCl_3) δ 1.25 (6H, d, $J = 7$ Hz), 1.36 (3H, t, $J = 7$ Hz), 1.45-1.65 (4H, m), 2.23 (2H, t, $J = 7$ Hz), 2.50-2.60 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.75-3.85 (1H, m), 4.66 (2H, s), 5.89 (1H, d, $J = 4$ Hz), 6.58 (1H, d, $J = 4$ Hz), 7.89 (1H, m), 8.54 (1H, d, $J = 2$ Hz), 8.77 (1H, d, $J = 2$ Hz).

MS (ESI $^+$): m/z 474 476.

15

Example 363

5-[7-ethyl-2-(hydroxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

20 ^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 1.40-1.65 (4H, m), 2.22 (2H, t, $J = 7$ Hz), 2.33-2.45 (2H, m), 2.43 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 4.87 (2H, s), 5.94 (1H, d, $J = 4$ Hz), 6.57 (1H, d, $J = 4$ Hz), 7.56 (1H, s), 8.43 (1H, s), 8.54 (1H, s).

MS (ESI): m/z 366, MS (ESI $^+$): m/z 368.

Example 364

25 5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[2-(4-morpholinyl)-2-oxoethoxy]methyl]pyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

30 ^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.40-1.63 (4H, m), 2.22 (2H, t, $J = 7$ Hz), 2.43 (3H, s), 2.50-2.72 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.51 (2H, m), 3.57-3.75 (6H, m), 4.32 (2H, s), 4.70-4.86 (2H, m), 5.90 (1H, d, $J = 4$ Hz), 6.59 (1H, d, $J = 4$ Hz), 7.53 (1H, s), 8.42 (1H, s), 8.53 (1H, s).

MS (ESI): m/z 493, MS (ESI $^+$): m/z 495.

Example 365

5-[7-ethyl-2-{[2-(methylamino)-2-oxoethoxy]methyl}-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.40-1.65 (4H, m), 2.22 (2H, t, $J = 7$ Hz),
2.44 (3H, s), 2.45-2.64 (2H, m), 2.87 (3H, m), 3.03 (2H, q, $J = 7$ Hz), 4.13 (2H, s),
5 4.74 (2H, m), 5.93 (1H, d, $J = 4$ Hz), 6.60 (1H, d, $J = 4$ Hz), 6.83 (1H, br), 7.57
(1H, s), 8.42 (1H, s), 8.53 (1H, s).

MS (ESI $^+$): m/z 437, MS (ESI $^+$): m/z 439.

Example 366

10 5-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 0.23-0.33 (2H, m), 0.55-0.64 (2H, m), 1.07-1.22 (1H, m), 1.36
(3H, t, $J = 7$ Hz), 1.45-1.68 (4H, m), 2.19 (2H, t, $J = 7$ Hz), 2.43 (3H, s), 2.50-2.75
(2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.40 (2H, d, $J = 7$ Hz), 4.70 (2H, m), 5.87 (1H, d,
15 $J = 4$ Hz), 6.56 (1H, d, $J = 4$ Hz), 7.57 (1H, s), 8.40 (1H, s), 8.54 (1H, s).

MS (ESI $^+$): m/z 422.

Example 367

20 5-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 0.87-1.04 (2H, m), 1.10-1.82 (13H, m), 1.37 (3H, t, $J = 7$ Hz),
2.18 (2H, t, $J = 7$ Hz), 2.43 (3H, s), 2.47-2.72 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.33
(2H, d, $J = 7$ Hz), 4.63 (2H, m), 5.87 (1H, d, $J = 4$ Hz), 6.56 (1H, d, $J = 4$ Hz), 7.56
(1H, s), 8.42 (1H, s), 8.53 (1H, s).

25 MS (ESI $^+$): m/z 462, MS (ESI $^+$): m/z 464.

Example 368

30 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 1.35-1.57 (4H, m), 2.13 (2H, t, $J = 7$ Hz),
2.42 (3H, s), 2.47-2.66 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 4.68 (2H, s), 4.77 (2H, m),
5.90 (1H, d, $J = 4$ Hz), 6.59 (1H, d, $J = 4$ Hz), 7.28-7.36 (1H, m), 7.53 (1H, s), 7.73
(1H, d, $J = 8$ Hz), 8.41 (1H, d, $J = 2$ Hz), 8.53 (2H, m), 8.63 (1H, s).

MS (ESI): m/z 457, MS (ESI⁺): m/z 459.

Example 369

5- $\{7\text{-ethyl-4-(5-methyl-3-pyridinyl)-2-}[(2\text{-pyridinylmethoxy)methyl}]\text{pyrrolo}[1,2\text{-}$
5 $\text{b}]\text{pyridazin-3-yl}\}$ pentanoic acid

¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 1.45-1.65 (4H, m), 2.23 (2H, t, J= 7 Hz),
2.41 (3H, s), 2.48-2.74 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.80 (2H, s), 4.82 (2H, m),
5.88 (1H, d, J= 4 Hz), 6.57 (1H, d, J= 4 Hz), 7.26 (1H, m), 7.47-7.53 (2H, m),
7.69-7.77 (1H, m), 8.42 (1H, d, J= 2 Hz), 8.50 (1H, d, J= 2 Hz), 8.58 (1H, d, J= 7
10 Hz).

MS (ESI): m/z 457, MS (ESI⁺): m/z 459.

Example 370

5- $\{7\text{-ethyl-4-(5-methyl-3-pyridinyl)-2-}[(4\text{-pyridinylmethoxy)methyl}]\text{pyrrolo}[1,2\text{-}$
15 $\text{b}]\text{pyridazin-3-yl}\}$ pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.40-1.62 (4H, m), 2.16 (2H, t, J= 7 Hz),
2.43 (3H, s), 2.48-2.71 (2H, m), 3.02 (2H, q, J= 7 Hz), 4.68 (2H, s), 4.79 (2H, m),
5.91 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.32 (2H, d, J= 7 Hz), 7.54 (1H, s),
8.42 (1H, d, J= 2 Hz), 8.54 (1H, d, J= 2 Hz), 8.55 (2H, d, J= 7 Hz).

20 MS (ESI): m/z 457, MS (ESI⁺): m/z 459.

Example 371

5- $\{7\text{-ethyl-4-(5-methyl-3-pyridinyl)-2-}[(2\text{-pyrazinylmethoxy)methyl}]\text{pyrrolo}[1,2\text{-}$
 $\text{b}]\text{pyridazin-3-yl}\}$ pentanoic acid

25 ¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 1.45-1.62 (4H, m), 2.18 (2H, t, J= 7 Hz),
2.43 (3H, s), 2.48-2.73 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.83 (2H, s), 4.88 (2H, m),
5.90 (1H, d, J= 4 Hz), 6.59 (1H, d, J= 4 Hz), 7.54 (1H, s), 8.42 (1H, s), 8.48-8.56
(3H, m), 8.76 (1H, s).

MS (ESI): m/z 458, MS (ESI⁺): m/z 460.

30

Example 372

5-[2-[(benzylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H NMR (DMSO-d₆) δ 1.33 (3H, t, J= 7 Hz), 1.28-1.48 (4H, m), 2.03-2.13 (2H, m), 2.30-2.45 (2H, m), 2.40 (3H, s), 3.06 (2H, q, J= 7 Hz), 4.37 (2H, s), 4.46 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.68 (1H, d, J= 4 Hz), 7.40-7.52 (3H, m), 7.56-7.67 (3H, m), 8.36 (1H, d, J= 2 Hz), 8.57 (1H, d, J= 2 Hz).

5 MS (ESI⁺): m/z 457.

Example 373

5-[2-[(acetylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 ¹H NMR (CDCl₃) δ 1.40 (3H, t, J= 7 Hz), 1.40-1.64 (4H, m), 2.16 (3H, s), 2.23 (2H, t, J= 7 Hz), 2.35-2.50 (2H, m), 2.43 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.63-4.72 (2H, m), 5.92 (1H, d, J= 4 Hz), 6.57 (1H, d, J= 4 Hz), 6.88-6.97 (1H, br), 7.53 (1H, s), 8.41 (1H, s), 8.53 (1H, s).

MS (ESI): m/z 407, MS (ESI⁺): m/z 409.

15

Example 374

5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[[(methylsulfonyl)amino]methyl]pyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

20 ¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.46-1.66 (4H, m), 2.23 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.39-2.53 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.05 (3H, s), 4.57 (2H, s), 5.72 (1H, br), 5.96 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.54 (1H, s), 8.41 (1H, d, J= 2 Hz), 8.55 (1H, d, J= 2 Hz).

MS (ESI): m/z 443, MS (ESI⁺): m/z 445.

25 Example 375

5-[2-[(benzoylamino)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

30 ¹H NMR (CDCl₃) δ 1.42 (3H, t, J= 7 Hz), 1.50-1.68 (4H, m), 2.25 (2H, t, J= 7 Hz), 2.44 (3H, s), 2.40-2.60 (2H, m), 3.07 (2H, q, J= 7 Hz), 4.89 (2H, m), 5.95 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.46-7.60 (4H, m), 7.83 (1H, br), 7.93 (2H, d, J= 8 Hz), 8.44 (1H, d, J= 2 Hz), 8.56 (1H, d, J= 2 Hz).

MS (ESI): m/z 469, MS (ESI⁺): m/z 471.

Example 376

5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[2-pyrazinylcarbonyl]amino]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

¹H NMR (CDCl₃) δ 1.41 (3H, t, J= 7 Hz), 1.51-1.72 (4H, m), 2.24 (2H, t, J= 7 Hz),
2.44 (3H, s), 2.45-2.58 (2H, m), 3.10 (2H, q, J= 7 Hz), 4.90 (2H, m), 5.94 (1H, d,
J= 4 Hz), 6.59 (1H, d, J= 4 Hz), 7.55 (1H, s), 8.43 (1H, s), 8.53 (1H, s), 8.62 (1H,
m), 8.79 (1H, d, J= 2 Hz), 9.20 (1H, br), 9.45 (1H, d, J= 2 Hz).

MS (ESI): m/z 471, MS (ESI⁺): m/z 473.

10 Example 377

5-[7-ethyl-2-[[methoxycarbonyl]amino]methyl]-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.45-1.65 (4H, m), 2.23 (2H, t, J= 7 Hz),
2.40-2.53 (2H, m), 2.44 (3H, s), 3.02 (2H, q, J= 7 Hz), 3.05 (3H, s), 4.58 (2H, s),
5.69 (1H, br), 5.96 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.53 (1H, s), 8.41 (1H,
d, J= 2 Hz), 8.54 (1H, d, J= 2 Hz).

Example 378

To a solution of ethyl 7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylate (682 mg) in ethanol (20 mL) was added potassium hydroxide (5 g) solution (10 mL) and the mixture was heated under reflux for 1 hour. The solution was acidified with 1 N hydrochloric acid to pH 3-4 and diluted with brine, and extracted with chloroform twice. The organic layer was separated, dried over magnesium sulfate, and evaporated in vacuo. The crude product was triturated with ethyl acetate to give 7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid as a yellow powder (590 mg)

7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid

¹H NMR (CDCl₃) δ 1.39 (3H, t, J= 7 Hz), 2.44 (3H, s), 2.69 (3H, s), 3.05 (2H, q, J= 7 Hz), 6.29 (1H, d, J= 4 Hz), 6.67 (1H, d, J= 4 Hz), 7.97 (1H, s), 8.41 (1H, s), 8.58 (1H, s).

MS (ESI): m/z 294, MS (ESI⁺): m/z 296.

The following compound(s) was(were) obtained in substantially the same manner as that of Example 175.

Example 379

5-[4-(3-cyanophenyl)-2-(ethoxymethyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic

5 acid

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.34-1.53 (7H, m), 2.20 (2H, t, $J = 7$ Hz),
2.53 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.62 (2H, q, $J = 7$ Hz), 4.66 (2H, s), 5.33 (1H,
d, $J = 5$ Hz), 6.57 (1H, d, $J = 5$ Hz), 7.60 (2H, m), 7.66 (1H, s), 7.74 (1H, m)

10 Example 380

5-[2-[(benzyloxy)methyl]-4-(3-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 1.30-1.46 (7H, m), 2.11 (2H, t, $J = 7$ Hz), 2.50 (2H, m), 3.02 (2H,
q, $J = 7$ Hz), 4.64 (3H, s), 4.71 (3H, s), 5.83 (1H, d, $J = 5$ Hz), 6.56 (1H, d, $J = 5$
15 Hz), 7.25-7.34 (5H, m), 7.57 (2H, d, $J = 9$ Hz), 7.65 (1H, s), 7.74 (1H, m).

MS (ESI^+): m/z 468 ($M + H$)

Example 381

4-([3-(4-carboxybutyl)-4-(3-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-

20 yl]methoxy)methyl)benzoic acid

^1H -NMR (CDCl_3) δ 1.05-1.43 (7H, m), 1.92 (2H, m), 2.31 (2H, m), 3.04 (2H, m),
4.65 (2H, s), 4.72 (2H, s), 5.82 (1H, m), 6.58 (1H, m), 7.46-7.77 (6H, m), 8.09
(2H, d, $J = 8$ Hz).

MS (ESI^+): m/z 510 ($M - H$)

25 Example 381-2

4-([4-[3-(carbamoyl)phenyl]-3-(4-carboxybutyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methoxy)methyl)benzoic acid

^1H -NMR (CDCl_3) δ 1.20-1.45 (7H, m), 2.03 (2H, m), 2.52 (2H, m), 3.03 (2H, q, $J = 7$
Hz), 4.69 (2H, s), 4.73 (2H, s), 5.36 (1H, d, $J = 5$ Hz), 6.57 (1H, d, $J = 5$ Hz),
30 7.39-7.60 (4H, m), 7.77 (1H, s), 7.93 (1H, d, $J = 8$ Hz), 7.98 (2H, d, $J = 8$ Hz).

MS (ESI^+): m/z 528 ($M - H$)

The following compound(s) was(were) obtained in substantially the same manner

as that of Example 77.

Example 382

5- $\{4-(5\text{-bromo-3-pyridinyl})\text{-7-ethyl-2-}[(4\text{-methyl-1-piperazinyl})\text{methyl}]\text{pyrrolo}[1,2\text{-b}]\text{pyridazin-3-yl}\}$ pentanoic acid

- 5 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.34 (3H, t, $J = 7$ Hz), 1.38-1.59 (4H, m), 2.22 (2H, m), 2.43-2.60 (5H, m), 2.83-3.04 (8H, m), 3.74 (3H, s), 5.88 (1H, d, $J = 5$ Hz), 6.56 (1H, d, $J = 5$ Hz), 7.87 (1H, m), 8.54 (1H, m), 8.76 (1H, m).

Example 383

- 10 5- $\{4-(5\text{-bromo-3-pyridinyl})\text{-2-(cyanomethyl)-7-ethylpyrrolo}[1,2\text{-b}]\text{pyridazin-3-yl}\}$ pentanoic acid

$^1\text{H NMR (CDCl}_3\text{)}$ δ 1.35-1.60 (7H, m), 2.27 (2H, m), 2.46 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.98 (2H, s), 3.97 (1H, d, $J = 5$ Hz), 6.65 (1H, d, $J = 5$ Hz), 7.90 (1H, m), 8.54 (1H, s, br), 8.79 (1H, s, br).

15

Example 384

5- $\{4-(5\text{-bromo-3-pyridinyl})\text{-7-ethyl-2-(hydroxymethyl)}\}$ pyrrolo $[1,2\text{-b}]\text{pyridazin-3-yl}$ pentanoic acid

- 20 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.35-1.60 (7H, m), 2.22 (2H, t, $J = 7$ Hz), 2.38 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 4.86 (2H, s), 5.95 (1H, d, $J = 5$ Hz), 6.60 (1H, d, $J = 5$ Hz), 7.88 (1H, m), 8.54 (1H, s, br), 8.79 (1H, s, br).

Example 385

- To a solution of 7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo $[1,2\text{-b}]\text{pyridazine-3-carboxylic acid}$ (70 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (68.2 mg) and 1-hydroxybenotriazole (48 mg) in dimethylformamide (2 mL) was added 2-aminoethanol (17.4 mg) and the mixture was stirred at ambient temperature for 1 hour. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated sodium bicarbonate solution, water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of chloroform and methanol (50:1 - 10:1). The crude product was triturated with isopropylether to give 7-ethyl-N-(2-hydroxyethyl)-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo $[1,2\text{-b}]\text{pyridazine-}$
- 25
- 30

3-carboxamide as a yellow powder (47 mg).

7-ethyl-N-(2-hydroxyethyl)-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxamide

5 ^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 2.39 (3H, s), 2.57 (3H, s), 3.02 (2H, q, $J = 7$ Hz), 3.33 (2H, m), 3.45 (2H, m), 6.03 (1H, br), 6.31 (1H, d, $J = 4$ Hz), 6.66 (1H, d, $J = 4$ Hz), 7.71 (1H, s), 8.47 (1H, s), 8.58 (1H, s).

MS (ESI): m/z 337, MS (ESI^+): m/z 339.

10 The following compound(s) was(were) obtained in substantially the same manner as that of Example 385.

Example 386

N-butyl-7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxamide

15 ^1H NMR (CDCl_3) δ 0.80 (3H, t, $J = 7$ Hz), 0.96-1.08 (2H, m), 1.08-1.25 (2H, m), 1.38 (3H, t, $J = 7$ Hz), 2.40 (3H, s), 2.56 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 3.16 (2H, m), 5.36 (1H, br), 6.31 (1H, d, $J = 4$ Hz), 6.63 (1H, d, $J = 4$ Hz), 7.69 (1H, s), 8.53 (1H, s), 8.62 (1H, s).

MS (ESI^+): m/z 351.

20

Example 387

ethyl 3-({[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]carbonyl}amino)propanoate

25 ^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 2.21 (2H, t, $J = 7$ Hz), 2.40 (3H, s), 2.55 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 3.43 (2H, q, $J = 7$ Hz), 4.04 (2H, q, $J = 7$ Hz), 6.08 (1H, br), 6.30 (1H, d, $J = 4$ Hz), 6.65 (1H, d, $J = 4$ Hz), 7.67 (1H, s), 8.50 (1H, d, $J = 1$ Hz), 8.60 (1H, d, $J = 1$ Hz).

MS (ESI^+): m/z 395.

30 The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 176.

Example 388

4-(5-bromo-3-pyridinyl)-7-ethyl-2-methyl-3-[3-(4-morpholinyl)-3-oxopropyl]pyrrolo[1,2-

b]pyridazine

$^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.37(3H, t, J=7Hz), 2.41(2H, t, J=7Hz),
 2.60(3H, s), 2.72-2.82(2H, m), 3.01(2H, q, J=7Hz), 3.19(2H, t, J=5Hz), 3.55(4H, t,
 J=5Hz), 3.63(2H, t, J=5Hz), 5.89(1H, d, J=4Hz), 6.55(1H, d, J=4Hz), 7.87(1H, t,
 5 J=1Hz), 8.54(1H, d, J=1Hz), 8.77(1H, d, J=1Hz)
 MS(m/z) 457(M^+), 459(M^{++2}), 115(bp)
 mp. 178-180°C

Example 389

10 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-N-
 methylpropanamide
 $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.38(3H, t, J=7Hz), 2.20(2H, t, J=7Hz),
 2.60(3H, s), 2.75(3H, d, J=6Hz), 2.78-2.89(2H, m), 3.01(2H, q, J=7Hz), 5.21-
 5.27(1H, m), 5.88(1H, d, J=4Hz), 6.54(1H, d, J=4Hz), 7.86(1H, t, J=1Hz),
 15 8.53(1H, d, J=1Hz), 8.78(1H, d, J=1Hz)
 MS(m/z) 401(M^++1), 403(M^++1), 115(bp)
 mp. 172-174°C

The following compound(s) was(were) obtained in substantially the same manner as
 20 that of Example 263.

Example 390

N-{3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-
 yl]propanoyl}methanesulfonamide
 $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.36(3H, t, J=7Hz), 2.33-2.45(2H, m), 2.58(3H, s), 2.84-2.95(2H,
 25 m), 3.01(2H, q, J=7Hz), 3.26(3H, s), 5.89(1H, d, J=4Hz), 6.56(1H, d, J=4Hz),
 7.90(1H, s), 8.50(1H, s), 8.77(1H, s)
 MS(m/z) 465(M^+ , bp), 467(M^+-2 , bp)
 mp. 196.5-197.5°C

30 The following compound(s) was(were) obtained in substantially the same manner
 as that of Example 224.

Example 391

2-[{3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoyl}(methylamino)ethanesulfonic acid

¹H NMR (CDCl₃) δ 1.32 (3H, t, J = 7 Hz), 1.90 (2H, m), 2.26 (3H, s), 2.57-2.2.78 (4H, m), 2.98 (2H, q, J = 7 Hz), 3.31 (2H, m), 6.00 (1H, d, J = 5 Hz), 6.61 (1H, d, J = 5 Hz), 7.20-7.52 (5H, m).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 20.

Preparation 217

10 1-tert-butyl 7-ethyl 2-(isobutoxyacetyl)heptanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.95 (6H, d, J = 7 Hz), 1.27 (3H, t, J = 7 Hz), 1.31-1.41 (2H, m), 1.46 (9H, s), 1.66 (2H, tt, J = 7, 7 Hz), 1.75-1.98 (3H, m), 2.31 (2H, t, J = 8 Hz), 3.26 (2H, d, J = 7 Hz), 3.56 (1H, t, J = 7 Hz), 4.06-4.17 (4H, m).

15 Preparation 218

1-tert-butyl 6-ethyl 2-(isobutoxyacetyl)hexanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.93 (6H, d, J = 7 Hz), 1.25 (3H, t, J = 7 Hz), 1.45 (9H, s), 1.59-1.69 (2H, m), 1.80-1.95 (3H, m), 2.32 (2H, t, J = 7 Hz), 2.25 (2H, d, J = 7 Hz), 3.57 (1H, t, J = 7 Hz), 4.10 (2H, s), 4.12 (2H, q, J = 7 Hz).

20

The following compound(s) was(were) obtained in a similar manner to that of Preparation 24.

Preparation 219

1-tert-butyl 6-ethyl 2-acetyl-2-(2-chloroisonicotinoyl)hexanedioate

25 ¹H NMR (CDCl₃) δ 1.26 (3H, t, J = 7 Hz), 1.34 (9H, s), 1.60-1.73 (2H, m), 2.22-2.32 (2H, m), 2.39 (2H, t, J = 7 Hz), 2.49 (3H, s), 4.12 (2H, q, J = 7 Hz), 7.43 (1H, d, J = 5 Hz), 7.57 (1H, s), 8.50 (1H, d, J = 5 Hz).

MS (ESI⁺): m/z 412.

30 Preparation 220

1-tert-butyl 5-ethyl 2-acetyl-2-(2-chloroisonicotinoyl)pentanedioate

¹H NMR (CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.72-1.84 (2H, m), 2.33 (2H, t, J = 7 Hz), 2.47-2.57 (2H, m), 2.58 (3H, s), 3.03 (2H, q, J = 7 Hz), 5.88 (1H, d, J = 4 Hz), 6.53

(1H, d, J= 4 Hz), 7.27 (1H, m), 7.38 (1H, s), 8.53 (1H, d, J= 5 Hz).

MS (ESI): m/z 356, MS (ESI⁺): m/z 358.

Preparation 221

- 5 1-tert-butyl 7-ethyl 2-(2-chloroisonicotinoyl)-2-(phenylacetyl)heptanedioate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.35 (9H, s), 1.63-1.76 (2H, m), 2.22-2.37 (4H, m), 3.93 (1H, d, J= 17 Hz), 4.12 (2H, q, J= 7 Hz), 4.29 (1H, d, J= 17 Hz), 7.22 (2H, d, J= 8 Hz), 7.26-7.36 (4H, m), 7.50 (1H, s), 8.42 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 502.

10

Preparation 222

tert-butyl 2-[2-(2-methoxy-2-oxoethoxy)ethyl]-2-[(5-methyl-3-pyridinyl)carbonyl]-3-oxobutanoate

- 15 ¹H NMR (CDCl₃) δ 1.33 (9H, s), 2.39 (3H, s), 2.47 (3H, s), 2.62 (2H, t, J= 7 Hz), 3.66 (2H, m), 3.70 (3H, s), 3.90 (2H, s), 7.87 (1H, s), 8.56 (1H, s), 8.75 (1H, s).

MS (ESI⁺): m/z 394.

Preparation 223

1-tert-butyl 4-ethyl 2-acetyl-2-[(5-bromo-3-pyridinyl)carbonyl]succinate

- 20 ¹H NMR (CDCl₃) δ 1.27 (3H, t, J= 7 Hz), 1.41 (9H, s), 2.45 (3H, s), 3.22 (2H, m), 4.12 (2H, q, J= 7 Hz), 8.22 (1H, m), 8.80 (1H, m), 8.82 (1H, m).

MS (ESI⁺): m/z 428 430.

Preparation 224

- 25 1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]pentanedioate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.35 (9H, s), 2.14 (3H, s), 2.40 (3H, s), 2.40-2.48 (2H, m), 2.62-2.70 (2H, m), 4.12 (2H, q, J= 7 Hz), 5.12 (1H, d, J= 18 Hz), 5.34 (1H, d, J= 18 Hz), 7.85 (1H, s), 8.58 (1H, s), 8.78 (1H, s).

- 30 MS (ESI⁺): m/z 436.

Preparation 225

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]hexanedioate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.34 (9H, s), 1.60-1.75 (2H, m), 2.14 (3H, s), 2.26-2.39 (4H, m), 2.40 (3H, s), 4.12 (2H, q, $J = 7$ Hz), 5.13 (1H, d, $J = 18$ Hz), 5.40 (1H, d, $J = 18$ Hz), 7.86 (1H, s), 8.57 (1H, s), 8.78 (1H, s).

MS (ESI^+): m/z 450.

5

Preparation 226

1-tert-butyl 7-ethyl 2-[(acetyloxy)acetyl]-2-(3-cyanobenzoyl)heptanedioate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.32 (9H, s), 1.26-1.46 (2H, m), 1.66-1.77 (2H, m), 2.14 (3H, s), 2.26-2.38 (4H, m), 4.12 (2H, q, $J = 7$ Hz), 5.06 (1H, d, $J = 18$ Hz), 5.42 (1H, d, $J = 18$ Hz), 7.57 (1H, t, $J = 8$ Hz), 7.81 (1H, d, $J = 8$ Hz), 7.92 (1H, d, $J = 8$ Hz), 8.09 (1H, s).

10

Preparation 227

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-[(5-bromo-3-pyridinyl)carbonyl]hexanedioate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.36 (9H, s), 1.60-1.74 (2H, m), 1.85-1.96 (2H, m), 2.14 (3H, s), 2.28-2.42 (2H, m), 4.12 (2H, q, $J = 7$ Hz), 5.12 (1H, d, $J = 17$ Hz), 5.42 (1H, d, $J = 17$ Hz), 8.23 (1H, m), 8.81 (1H, m), 8.83 (1H, m).

15

Preparation 228

20 1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]-2-[(5-bromo-3-pyridinyl)carbonyl]pentanedioate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.37 (9H, s), 2.14 (3H, s), 2.41-2.51 (2H, m), 2.66 (2H, t, $J = 7$ Hz), 4.13 (2H, q, $J = 7$ Hz), 5.11 (1H, d, $J = 18$ Hz), 5.33 (1H, d, $J = 18$ Hz), 8.22 (1H, m), 8.82 (2H, m).

MS (ESI^+): m/z 500 502.

25

Preparation 229

1-tert-butyl 5-ethyl 2-[(cyclohexylmethoxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]pentanedioate

^1H NMR (CDCl_3) δ 0.80-0.98 (2H, m), 1.00-1.32 (3H, m), 1.23 (3H, t, $J = 7$ Hz), 1.38 (9H, s), 1.46-1.62 (6H, m), 2.39 (3H, s), 2.40-2.72 (4H, m), 3.19 (2H, d, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.31 (1H, d, $J = 17$ Hz), 4.39 (1H, d, $J = 17$ Hz), 7.88 (1H, s), 8.56 (1H, s), 8.77 (1H, s).

30

MS (ESI^+): m/z 490.

Preparation 230

1-tert-butyl 5-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-
[(cyclohexylmethoxy)acetyl]pentanedioate

5 ^1H NMR (CDCl_3) δ 0.78-0.98 (2H, m), 1.10-1.33 (3H, m), 1.25 (3H, t, $J = 7$ Hz), 1.40 (9H, s), 1.38-1.83 (6H, m), 2.35-2.75 (4H, m), 3.22 (2H, d, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.25 (1H, d, $J = 17$ Hz), 4.37 (1H, d, $J = 17$ Hz), 8.22 (1H, s), 8.78 (1H, s), 8.86 (1H, s).

MS (ESI^+): m/z 554 556.

10

Preparation 231

1-tert-butyl 6-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-
[(cyclohexylmethoxy)acetyl]hexanedioate

15 ^1H NMR (CDCl_3) δ 0.80-0.97 (2H, m), 1.12-1.35 (3H, m), 1.25 (3H, t, $J = 7$ Hz), 1.39 (9H, s), 1.46-1.80 (10H, m), 2.22-2.45 (2H, m), 3.20 (2H, d, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.30 (1H, d, $J = 17$ Hz), 4.38 (1H, d, $J = 17$ Hz), 8.22 (1H, s), 8.78 (1H, s), 8.85 (1H, s).

MS (ESI^+): m/z 568 570.

20 Preparation 232

1-tert-butyl 6-ethyl 2-[(cyclopropylmethoxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]hexanedioate

25 ^1H NMR (CDCl_3) δ 0.16-0.28 (2H, m), 0.48-0.59 (2H, m), 0.98-1.12 (1H, m), 1.24 (3H, t, $J = 7$ Hz), 1.37 (9H, s), 1.55-1.80 (4H, m), 2.18-2.40 (2H, m), 2.39 (3H, s), 3.31 (2H, m), 4.12 (2H, q, $J = 7$ Hz), 4.38 (1H, d, $J = 17$ Hz), 4.53 (1H, d, $J = 17$ Hz), 7.88 (1H, s), 8.55 (1H, d, $J = 2$ Hz), 8.75 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 462.

Preparation 233

30 1-tert-butyl 5-ethyl 2-[(cyclopropylmethoxy)acetyl]-2-[(5-methyl-3-pyridinyl)carbonyl]pentanedioate

^1H NMR (CDCl_3) δ 0.15-0.23 (2H, m), 0.48-0.56 (2H, m), 0.95-1.10 (1H, m), 1.24 (3H, t, $J = 7$ Hz), 1.39 (9H, s), 2.39 (3H, s), 2.40-2.68 (4H, m), 3.28 (2H, m), 4.12

(2H, q, J = 7 Hz), 4.36 (1H, d, J = 17 Hz), 4.48 (1H, d, J = 17 Hz), 7.88 (1H, s),
8.55 (1H, s), 8.75 (1H, s).

MS (ESI⁺): m/z 448.

5 Preparation 234

1-tert-butyl 5-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-[(2-methoxyethoxy)acetyl]pentanedioate

¹H NMR (CDCl₃) δ 1.26 (3H, t, J = 7 Hz), 1.46 (9H, s), 2.15-2.25 (2H, m), 2.42-2.72
(2H, m), 3.38 (3H, s), 3.48-3.72 (4H, m), 4.12 (2H, q, J = 7 Hz), 4.43 (1H, d, J =
10 17 Hz), 4.58 (1H, d, J = 17 Hz), 8.22 (1H, s), 8.78 (1H, s), 8.82 (1H, s).

MS (ESI⁺): m/z 516 518.

Preparation 235

tert-butyl 2-[(5-bromo-3-pyridinyl)carbonyl]-3-oxobutanoate

15 ¹H NMR (CDCl₃) δ 1.22, 1.30 (9H, s), 2.22, 2.45 (3H, s), 7.96, 8.13 (1H, s), 8.66,
8.76-8.80 (2H, m).

Preparation 236

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-[(5-chloro-3-pyridinyl)carbonyl]hexanedioate

20 ¹H NMR (300 MHz, CDCl₃) δ 1.25 (3H, t, J = 7 Hz), 1.36 (9H, s), 1.63-1.71 (2H, m),
2.14 (3H, s), 2.27-2.40 (4H, m), 4.13 (2H, q, J = 7 Hz), 5.11 (1H, d, J = 18 Hz),
5.38 (1H, d, J = 18 Hz), 8.07 (1H, dd, J = 2 Hz), 8.71 (1H, d, J = 2 Hz), 8.80 (1H,
d, J = 2 Hz).

25 Preparation 237

1-tert-butyl 7-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-
[(cyclopropylmethoxy)acetyl]heptanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.15-0.20 (2H, m), 0.49-0.58 (2H, m), 0.95-1.04 (1H,
m), 1.24 (3H, t, J = 7 Hz), 1.38 (9H, s), 1.68 (2H, tt, J = 7, 7 Hz), 2.14-2.33 (4H,
30 m), 3.26-3.29 (2H, m), 4.07-4.19 (4H, m), 4.31 (1H, d, J = 17 Hz), 4.45 (1H, d, J
= 17 Hz), 8.05 (1H, dd, J = 2 Hz), 8.68 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

Preparation 238

1-tert-butyl 6-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-
[(cyclopropylmethoxy)acetyl]hexanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.14-0.21 (2H, m), 0.49-0.55 (2H, m), 0.92-1.04 (1H, m), 1.25 (3H, t, J = 7 Hz), 1.39 (9H, s), 1.62-1.74 (2H, m), 1.82-1.90 (2H, m),
5 2.21-2.33 (2H, m), 3.27-3.31 (2H, m), 4.12 (2H, q, J = 7 Hz), 4.34 (1H, d, J = 18 Hz), 4.46 (1H, d, J = 18 Hz), 8.07 (1H, dd, J = 2, 2 Hz), 8.68 (1H, d, J = 2 Hz), 8.80 (1H, d, J = 2 Hz).

Preparation 239

10 1-tert-butyl 7-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(isobutoxyacetyl)heptanedioate
¹H NMR (300 MHz, CDCl₃) δ 0.85 (6H, d, J = 7 Hz), 1.24 (3H, t, J = 7 Hz), 1.38 (9H, s), 1.67 (2H, t, J = 7 Hz), 1.75-1.93 (3H, m), 2.24-2.33 (4H, m), 3.17 (2H, d, J = 7 Hz), 4.11 (2H, q, J = 7 Hz), 4.28 (1H, d, J = 17 Hz), 4.38 (1H, d, J = 17 Hz), 8.20 (1H, dd, J = 2, 2 Hz), 8.79 (1H, d, J = 2 Hz), 8.84 (1H, d, J = 2 Hz).

15

Preparation 240

1-tert-butyl 5-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-(isobutoxyacetyl)pentanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.84 (6H, d, J = 7 Hz), 1.24 (3H, t, J = 7 Hz), 1.39 (9H, s), 1.80 (1H, qt, J = 7 Hz), 2.34-2.71 (4H, m), 3.17 (2H, d, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 4.28 (1H, d, J = 18 Hz), 4.36 (1H, d, J = 18 Hz), 8.07 (1H, s), 8.69 (1H, s), 8.83 (1H, s).

20

Preparation 241

1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]-2-(3-chlorobenzoyl)pentanedioate

25 ¹H NMR (300 MHz, CDCl₃) δ 1.24 (3H, t, J = 7 Hz), 1.34 (9H, s), 2.14 (3H, s), 2.35-2.44 (2H, m), 2.60-2.68 (2H, m), 4.11 (2H, q, J = 7 Hz), 5.11 (1H, d, J = 18 Hz), 5.35 (1H, d, J = 18 Hz), 7.38 (1H, dd, J = 8, 8 Hz), 7.53 (1H, d, J = 8 Hz), 7.60 (1H, d, J = 8 Hz), 7.79 (1H, s).

Preparation 242

1-tert-butyl 6-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(isobutoxyacetyl)hexanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.85 (6H, d, J = 7 Hz), 1.25 (3H, t, J = 7 Hz), 1.39 (9H, s), 1.59-1.72 (2H, m), 1.80 (1H, qt, J = 7, 7 Hz), 2.19-2.39 (4H, m), 3.18 (2H, d, J

= 7 Hz), 4.12 (2H, q, J = 7 Hz), 4.31 (1H, d, J = 17 Hz), 4.40 (1H, d, J = 17 Hz), 8.22 (1H, dd, J = 2, 2 Hz), 8.79 (1H, d, J = 2 Hz), 8.85 (1H, d, J = 2 Hz).

Preparation 243

- 5 tert-butyl 3-(5-bromo-3-pyridinyl)-2-[(5-bromo-3-pyridinyl)carbonyl]-3-oxopropanoate
 ^1H NMR (CDCl_3) δ 1.05 (9H, s), 7.86 (2H, s), 8.46 (2H, s), 8.61 (2H, s).
 MS (ESI): m/z 481 483 485.

Preparation 244

- 10 1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-(3-chlorobenzoyl)hexanedioate
 ^1H NMR (CDCl_3) δ 1.24 (3H, t, J = 8 Hz), 1.33 (9H, s), 1.56-1.72 (2H, m), 2.15 (3H, s), 2.20-2.41 (4H, m), 4.11 (2H, q, J = 8 Hz), 5.13 (1H, d, J = 18 Hz), 5.40 (1H, d, J = 18 Hz), 7.38 (1H, t, J = 8 Hz), 7.52 (1H, br d, J = 8 Hz), 7.60 (1H, br d, J = 8 Hz), 7.79 (1H, br s).

15

Preparation 245

- 1-tert-butyl 7-ethyl 2-(methoxyacetyl)-2-[(5-methoxy-3-pyridinyl)carbonyl]heptanedioate
 ^1H NMR (CDCl_3) δ 1.23 (3H, t, J = 8 Hz), 1.27-1.43 (11H, m), 1.60-1.74 (2H, m), 2.15-2.34 (4H, m), 3.37 (3H, s), 3.90 (3H, s), 4.10 (2H, q, J = 8 Hz), 4.35 (1H, d, J = 18 Hz), 4.48 (1H, d, J = 18 Hz), 7.58 (1H, m), 8.43 (1H, d, J = 3 Hz), 8.50 (1H, d, J = 1 Hz).
 MS (ESI⁺): m/z 452 (M + H).

20

Preparation 246

- 25 1-tert-butyl 7-ethyl 2-acetyl-2-[(5-methoxy-3-pyridinyl)carbonyl]heptanedioate
 ^1H NMR (CDCl_3) δ 1.24 (3H, t, J = 8 Hz), 1.27-1.40 (11H, m), 1.60-1.74 (2H, m), 2.15-2.34 (4H, m), 2.44 (3H, s), 3.89 (3H, s), 4.10 (2H, q, J = 8 Hz), 7.61 (1H, m), 8.43 (1H, d, J = 3 Hz), 8.49 (1H, d, J = 1 Hz).
 MS (ESI⁺): m/z 422 (M + H).

30

Preparation 247

- 1-tert-butyl 5-ethyl 2-(methoxyacetyl)-2-[(5-methoxy-3-pyridinyl)carbonyl]pentanedioate
 ^1H NMR (CDCl_3) δ 1.24 (3H, t, J = 8 Hz), 1.38 (9H, s), 2.36-2.48 (2H, m), 2.53-2.67

(2H, m), 3.37 (3H, s), 3.90 (3H, s), 4.11 (2H, q, J = 8 Hz), 4.33 (1H, d, J = 18 Hz), 4.45 (1H, d, J = 18 Hz), 7.59 (1H, m), 8.43 (1H, d, J = 3 Hz), 8.51 (1H, d, J = 1 Hz).

MS (ESI⁺): m/z 446 (M + Na).

5

Preparation 248

1-tert-butyl 6-ethyl 2-(methoxyacetyl)-2-[(5-methoxy-3-pyridinyl)carbonyl]hexanedioate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 8 Hz), 1.37 (9H, s), 1.52-1.75 (2H, m), 2.18-2.39 (4H, m), 3.38 (3H, s), 3.90 (3H, s), 4.11 (2H, q, J = 8 Hz), 4.37 (1H, d, J = 18 Hz), 4.51 (1H, d, J = 18 Hz), 7.60 (1H, m), 8.43 (1H, d, J = 3 Hz), 8.50 (1H, d, J = 1 Hz).

10

MS (ESI⁺): m/z 438 (M + H).

Preparation 249

15 1-tert-butyl 7-ethyl 2-(methoxyacetyl)-2-(5-pyrimidinylcarbonyl)heptanedioate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 8 Hz), 1.30-1.44 (11H, m), 1.62-1.75 (2H, m), 2.16-2.35 (4H, m), 3.35 (3H, s), 4.11 (2H, q, J = 8 Hz), 4.20 (1H, d, J = 18 Hz), 4.33 (1H, d, J = 18 Hz), 9.01 (2H, s), 9.31 (1H, s).

MS (ESI⁺): m/z 423 (M + H).

20

Preparation 250

1-tert-butyl 6-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-(methoxyacetyl)hexanedioate

¹H NMR (CDCl₃) δ 1.26 (3H, t, J = 8 Hz), 1.39 (9H, s), 1.57-1.74 (2H, m), 1.78 (2H, br t, J = 8 Hz), 2.23-2.41 (2H, m), 3.38 (3H, s), 4.14 (2H, q, J = 8 Hz), 4.33 (1H, d, J = 18 Hz), 4.45 (1H, d, J = 18 Hz), 8.07 (1H, m), 8.71 (1H, br s), 8.80 (1H, br s).

25

MS (ESI⁺): m/z 442 (M + H).

Preparation 251

1-tert-butyl 5-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-(methoxyacetyl)pentanedioate

¹H NMR (CDCl₃) δ 1.25 (3H, t, J = 8 Hz), 1.39 (9H, s), 2.37-2.48 (2H, m), 2.53-2.65 (2H, m), 3.36 (3H, s), 4.13 (2H, q, J = 8 Hz), 4.26 (1H, d, J = 18 Hz), 4.40 (1H, d, J = 18 Hz), 8.06 (1H, br s), 8.70 (1H, br s), 8.80 (1H, br s).

30

MS (ESI⁺): m/z 428 (M + H).

Preparation 252

1-tert-butyl 7-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-(methoxyacetyl)heptanedioate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 8 Hz), 1.31-1.48 (11H, m), 1.55-1.75 (2H, m),
5 2.15-2.35 (4H, m), 3.36 (3H, s), 4.10 (2H, q, J = 8 Hz), 4.27 (1H, d, J = 18 Hz),
 4.43 (1H, d, J = 18 Hz), 8.03 (1H, t, J = 2 Hz), 8.69 (1H, d, J = 2 Hz), 8.77 (1H, d,
 J = 2 Hz).

MS (ESI⁺): m/z 456 (M + H).

10 Preparation 253

methyl 4-(acetyloxy)-2-[(5-bromo-3-pyridinyl)carbonyl]-3-oxobutanoate

¹H NMR (CDCl₃) δ 2.21 (3H, s), 3.58 (3H, br s), 4.87 (1H, br s), 5.19 (2H, br s), 7.98
 (1H, br s), 8.58 (1H, br s), 8.79 (1H, br s).

MS (ESI⁺): m/z 358, 360 (M + H).

15

Preparation 254

tert-butyl 2-(2-{2-[2-(acetyloxy)ethoxy]ethoxy}ethyl)-2-[(5-methyl-3-pyridinyl)carbonyl]-3-oxobutanoate

¹H-NMR (CDCl₃) δ 1.32 (9H, s), 2.07 (3H, s), 2.38 (3H, s), 2.45 (3H, s), 2.57 (2H, t,
20 J = 7 Hz), 3.43 (4H, m), 3.57 (4H, m), 4.16 (2H, m), 7.84 (1H, m), 8.53 (1H, m),
 8.75 (1H, m).

Preparation 255

1-tert-butyl 6-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(methoxyacetyl)hexanedioate

25 ¹H NMR (CDCl₃) δ 1.26 (3H, t, J = 7 Hz), 1.39 (9H, s), 1.55-1.75 (2H, m), 2.23-2.45
 (4H, m), 3.38 (3H, s), 4.12 (2H, q, J = 7 Hz), 4.34 (1H, d, J = 18 Hz), 4.47 (1H, d,
 J = 18 Hz), 8.22 (1H, m), 8.81 (1H, d, J = 2 Hz), 8.83 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 486 488.

30 Preparation 256

ethyl 2-(2-chloroisonicotinoyl)-3-oxobutanoate

¹H NMR (CDCl₃) δ 0.91-1.00 (3H, m), 2.24 (1.2H, s), 2.48 (1.8H, s), 4.02 (1.2H, q, J
 = 8 Hz), 4.10 (0.8H, q J = 8 Hz), 7.24 (0.6H, m), 7.39 (0.6H, s), 7.45 (0.4H, m),

7.54 (1H, s), 8.49 (1H, m).

MS (ESI⁺): m/z 298 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of

5 Preparation 78.

Preparation 257

ethyl 5-(2-chloroisonicotinoyl)-6-oxoheptanoate

¹H NMR (CDCl₃) δ 1.25 (3H, t, J= 7 Hz), 1.60-1.73 (2H, m), 1.98-2.10 (2H, m), 2.20
(3H, s), 2.35 (2H, t, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 4.37 (1H, t, J= 7 Hz), 7.67
10 (1H, d, J= 5 Hz), 7.77 (1H, s), 8.59 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 312 .

Preparation 258

ethyl 4-(2-chloroisonicotinoyl)-5-oxohexanoate

15 ¹H NMR (CDCl₃) δ 1.26 (3H, t, J= 7 Hz), 2.21 (3H, s), 2.22-2.35 (2H, m), 2.36-2.47
(2H, m), 4.12 (2H, q, J= 7 Hz), 4.57 (1H, t, J= 7 Hz), 7.76 (1H, dd, J= 2 Hz, 5 Hz),
7.83 (1H, d, J= 2 Hz), 8.61 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 298.

20 Preparation 259

ethyl 6-(2-chloroisonicotinoyl)-7-oxo-8-phenyloctanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.20-1.38 (2H, m), 1.60-1.72 (2H, m),
1.95-2.06 (2H, m), 2.28 (2H, t, J= 7 Hz), 3.71 (1H, d, J= 17 Hz), 3.80 (1H, d, J=
17 Hz), 4.12 (2H, q, J= 7 Hz), 4.41 (1H, t, J= 7 Hz), 7.10 (2H, m), 7.20-7.33 (4H,
25 m), 7.39 (1H, s), 8.42 (1H, d, J= 5 Hz).

Preparation 260

methyl ({3-[(5-methyl-3-pyridinyl)carbonyl]-4-oxopentyl}oxy)acetate

¹H NMR (CDCl₃) δ 2.23 (3H, s), 2.23-2.40 (2H, m), 2.44 (3H, s), 3.58 (2H, m), 3.71
30 (3H, s), 4.02 (2H, s), 4.89 (1H, t, J= 7 Hz), 8.12 (1H, s), 8.64 (1H, s), 9.07 (1H, s).

MS (ESI⁺): m/z 294.

Preparation 261

methyl (4-oxo-4-phenylbutoxy)acetate

^1H NMR (CDCl_3) δ 2.04-2.16 (2H, m), 3.15 (2H, t, $J = 7$ Hz), 3.64 (2H, t, $J = 7$ Hz), 3.73 (3H, s), 4.09 (2H, s), 7.46 (2H, t, $J = 8$ Hz), 7.56 (1H, t, $J = 8$ Hz), 7.99 (2H, d, $J = 8$ Hz).

5 MS (ESI^+): m/z 237.

The following compound(s) was(were) obtained in a similar manner to that of Preparation 78.

Preparation 262

10 ethyl 3-[(5-bromo-3-pyridinyl)carbonyl]-4-oxopentanoate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 2.22 (3H, s), 2.97-3.17 (2H, m), 4.12 (2H, q, $J = 7$ Hz), 4.91 (1H, m), 8.41 (1H, m), 8.88 (1H, m), 9.12 (1H, m).

MS (ESI^+): m/z 328 330.

15 Preparation 263

ethyl 6-(acetyloxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.98 (3H, s), 2.23-2.34 (2H, m), 2.40-2.50 (2H, m), 2.45 (3H, s), 4.12 (2H, q, $J = 7$ Hz), 4.69 (2H, m), 4.82 (1H, t, $J = 7$ Hz), 8.14 (1H, s), 8.67 (1H, s), 9.07 (1H, s).

20 MS (ESI^+): m/z 336.

Preparation 264

ethyl 7-(acetyloxy)-5-[(5-methyl-3-pyridinyl)carbonyl]-6-oxoheptanoate

25 ^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.60-1.80 (2H, m), 2.02 (3H, s), 1.97-2.13 (2H, m), 2.35 (2H, t, $J = 7$ Hz), 2.45 (3H, s), 4.12 (2H, q, $J = 7$ Hz), 4.56 (1H, t, $J = 7$ Hz), 4.69 (1H, d, $J = 17$ Hz), 4.78 (1H, d, $J = 17$ Hz), 8.06 (1H, s), 8.66 (1H, s), 9.00 (1H, s).

MS (ESI^+): m/z 350.

30 Preparation 265

ethyl 8-(acetyloxy)-6-(3-cyanobenzoyl)-7-oxooctanoate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.35-1.50 (2H, m), 1.60-1.78 (2H, m), 2.04 (3H, s), 2.00-2.12 (2H, m), 2.29 (2H, t, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.49 (1H,

t, J= 7 Hz), 4.68 (1H, d, J= 17 Hz), 4.75 (1H, d, J= 17 Hz), 7.66 (1H, t, J= 8 Hz), 7.88 (1H, d, J= 8 Hz), 8.16 (1H, d, J= 8 Hz), 8.26 (1H, s).

MS (ESI): m/z 372.

5 Preparation 266

ethyl 7-(acetyloxy)-5-[(5-bromo-3-pyridinyl)carbonyl]-6-oxoheptanoate

^1H NMR (CDCl_3) δ 1.25 (3H, t, J= 7 Hz), 1.60-1.82 (2H, m), 2.04 (3H, s), 2.03-2.15 (2H, m), 2.35 (2H, t, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 4.51 (1H, t, J= 7 Hz), 4.70 (1H, d, J= 17 Hz), 4.75 (1H, d, J= 17 Hz), 8.39 (1H, m), 8.88 (1H, s), 9.07 (1H, s).

10 MS (ESI): m/z 414 416, MS (ESI⁺): m/z 414 416.

Preparation 267

ethyl 6-(acetyloxy)-4-[(5-bromo-3-pyridinyl)carbonyl]-5-oxohexanoate

15 ^1H NMR (CDCl_3) δ 1.26 (3H, t, J= 7 Hz), 2.00 (3H, s), 2.22-2.36 (2H, m), 2.43-2.53 (2H, m), 4.13 (2H, q, J= 7 Hz), 4.70 (2H, m), 4.80 (1H, t, J= 7 Hz), 8.48 (1H, s), 8.90 (1H, s), 9.19 (1H, s).

MS (ESI⁺): m/z 400 402.

Preparation 268

20 ethyl 6-(cyclohexylmethoxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

^1H NMR (CDCl_3) δ 0.60-0.82 (2H, m), 0.93-1.10 (3H, m), 1.12-1.65 (6H, m), 1.25 (3H, t, J= 7 Hz), 2.07-2.17 (1H, m), 2.22-2.35 (1H, m), 2.42 (2H, m), 2.44 (3H, s), 3.05-3.23 (2H, m), 3.96 (2H, s), 4.12 (2H, q, J= 7 Hz), 4.92 (1H, m), 8.16 (1H, s), 8.66 (1H, s), 9.08 (1H, s).

25 MS (ESI⁺): m/z 390.

Preparation 269

ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-6-(cyclohexylmethoxy)-5-oxohexanoate

30 ^1H NMR (CDCl_3) δ 0.63-0.84 (2H, m), 0.93-1.88 (3H, m), 1.25 (3H, t, J= 7 Hz), 1.35-1.90 (6H, m), 2.02-2.14 (1H, m), 2.20-2.36 (1H, m), 2.44 (2H, t, J= 7 Hz), 3.04-3.20 (2H, m), 3.95 (2H, s), 4.13 (2H, q, J= 7 Hz), 4.85-4.93 (1H, m), 8.50 (1H, m), 8.88 (1H, d, J= 2 Hz), 9.20 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 454 456.

Preparation 270

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-7-(cyclohexylmethoxy)-6-oxoheptanoate

¹H NMR (300 MHz, CDCl₃) δ 0.75-0.86 (2H, m), 0.95-1.15 (3H, m), 1.24 (3H, t, J= 7 Hz), 1.40-1.90 (10H, m), 2.36 (2H, t, J= 7 Hz), 3.12 (2H, q, J= 7 Hz), 3.97 (2H, s), 4.12 (2H, q, J= 7 Hz), 4.71 (1H, t, J= 7 Hz), 8.41 (1H, s), 8.88 (1H, s), 9.12 (1H, s).

MS (ESI⁺): m/z 468 470.10 Preparation 271

ethyl 7-(cyclopropylmethoxy)-5-[(5-methyl-3-pyridinyl)carbonyl]-6-oxoheptanoate

¹H NMR (CDCl₃) δ -0.08-0.00 (1H, m), 0.00-0.15 (1H, m), 0.28-0.49 (2H, m), 0.72-0.87 (1H, m), 1.23 (3H, t, J= 7 Hz), 1.58-2.13 (4H, m), 2.32 (2H, t, J= 7 Hz), 2.44 (3H, s), 3.10-3.26 (2H, m), 4.02 (2H, m), 4.12 (2H, q, J= 7 Hz), 4.77 (1H, t, J= 7 Hz), 8.07 (1H, s), 8.63 (1H, s), 9.03 (1H, s).

MS (ESI⁺): m/z 362.Preparation 272

ethyl 6-(cyclopropylmethoxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

¹H NMR (CDCl₃) δ -0.08-0.00 (1H, m), 0.00-0.13 (1H, m), 0.23-0.47 (2H, m), 0.68-0.84 (1H, m), 1.24 (3H, t, J= 7 Hz), 2.03-2.17 (1H, m), 2.22-2.36 (1H, m), 2.40 (2H, m), 2.44 (3H, s), 3.12 (2H, m), 3.98 (1H, d, J= 17 Hz), 4.06 (1H, d, J= 17 Hz), 4.12 (2H, q, J= 7 Hz), 4.93 (1H, m), 8.12 (1H, s), 8.65 (1H, s), 9.08 (1H, s).

MS (ESI⁺): m/z 348.

25

Preparation 273

ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-6-(2-methoxyethoxy)-5-oxohexanoate

¹H NMR (CDCl₃) δ 1.25 (3H, t, J= 7 Hz), 1.90-2.37 (2H, m), 2.43 (2H, t, J= 7 Hz), 3.18 (3H, s), 3.16-3.73 (4H, m), 4.06 (2H, q, J= 7 Hz), 4.10-4.24 (2H, m), 4.86-4.93 (1H, m), 8.51 (1H, m), 8.87 (1H, d, J= 2 Hz), 9.20 (1H, d, J= 2 Hz).

MS (ESI): m/z 414 416, MS (ESI⁺): m/z 416 418.Preparation 274

1-(5-bromo-3-pyridinyl)-1,3-butanedione

 ^1H NMR (CDCl_3) δ 2.25 (3H, s), 6.18 (1H, s), 8.31 (1H, s), 8.78 (1H, s), 8.96 (1H, s).MS (ESI^+): m/z 242 244.5 Preparation 275

ethyl 7-(acetyloxy)-5-[(5-chloro-3-pyridinyl)carbonyl]-6-oxoheptanoate

 ^1H NMR (300 MHz, CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.60-1.70 (4H, m), 2.04 (3H, s), 2.35 (2H, t, $J = 6$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.52 (1H, t, $J = 7$ Hz), 4.69 (1H, d, $J = 18$ Hz), 4.78 (1H, d, $J = 18$ Hz), 8.24 (1H, s), 8.78 (1H, s), 9.05 (1H, s).

10

Preparation 276

ethyl 6-[(5-chloro-3-pyridinyl)carbonyl]-8-(cyclopropylmethoxy)-7-oxooctanoate

 ^1H NMR (300 MHz, CDCl_3) δ -0.09-0.11 (2H, m), 0.25-0.35 (1H, m), 0.37-0.46 (1H, m), 0.70-0.79 (1H, m), 1.24 (3H, t, $J = 7$ Hz), 1.29-1.41 (2H, m), 1.64 (2H, t, $J = 7$ Hz), 1.72-1.84 (1H, m), 1.96-2.08 (1H, m), 2.28 (2H, t, $J = 7$ Hz), 3.12 (1H, dd, $J = 10, 7$ Hz), 3.21 (1H, dd, $J = 10, 7$ Hz), 3.97 (1H, d, $J = 12$ Hz), 4.05 (1H, d, $J = 12$ Hz), 4.11 (2H, q, $J = 7$ Hz), 4.70 (1H, t, $J = 7$ Hz), 8.26 (1H, dd, $J = 2, 2$ Hz), 8.77 (1H, dd, $J = 2$ Hz), 9.09 (1H, dd, $J = 2$ Hz).

15

20 Preparation 277

ethyl 5-[(5-chloro-3-pyridinyl)carbonyl]-7-(cyclopropylmethoxy)-6-oxoheptanoate

 ^1H NMR (300 MHz, CDCl_3) δ -0.07-0.09 (2H, m), 0.24-0.46 (2H, m), 0.68-0.79 (1H, m), 1.23 (3H, t, $J = 7$ Hz), 1.47-1.84 (3H, m), 1.98-2.10 (1H, m), 2.33 (2H, t, $J = 7$ Hz), 3.12 (1H, dd, $J = 10, 7$ Hz), 3.21 (1H, dd, $J = 10, 7$ Hz), 3.97 (1H, d, $J = 17$ Hz), 4.06 (1H, d, $J = 17$ Hz), 4.10 (2H, q, $J = 7$ Hz), 4.73 (1H, t, $J = 6$ Hz), 8.27 (1H, dd, $J = 2, 2$ Hz), 8.77 (1H, d, $J = 2$ Hz), 9.10 (1H, d, $J = 2$ Hz).

25

Preparation 278

ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-8-isobutoxy-7-oxooctanoate

 ^1H NMR (300 MHz, CDCl_3) δ 0.72 (3H, d, $J = 7$ Hz), 0.77 (3H, d, $J = 7$ Hz), 1.24 (3H, t, $J = 7$ Hz), 1.30-1.42 (2H, m), 1.54-1.70 (3H, m), 1.75-1.87 (1H, m), 1.95-2.08 (1H, m), 2.28 (2H, t, $J = 8$ Hz), 3.10 (1H, dd, $J = 9, 7$ Hz), 3.14 (1H, dd, $J = 9, 7$ Hz), 3.98 (2H, s), 4.11 (2H, q, $J = 7$ Hz), 4.70 (1H, t, $J = 6$ Hz), 8.39 (1H, dd,

30

$J = 2$ Hz), 8.87 (1H, d, $J = 2$ Hz), 9.08 (1H, d, $J = 2$ Hz).

Preparation 279

ethyl 4-[(5-chloro-3-pyridinyl)carbonyl]-6-isobutoxy-5-oxohexanoate

5 ^1H NMR (300 MHz, CDCl_3) δ 0.68 (3H, d, $J = 7$ Hz), 0.72 (3H, d, $J = 7$ Hz), 1.25 (3H, t, $J = 7$ Hz), 1.52 (1H, qt, $J = 7, 7$ Hz), 2.02-2.13 (1H, m), 2.20-2.32 (1H, m), 2.44 (2H, t, $J = 7$ Hz), 3.07 (1H, dd, $J = 9, 7$ Hz), 3.12 (1H, dd, $J = 9, 7$ Hz), 3.98 (2H, s), 4.14 (2H, q, $J = 7$ Hz), 4.90 (1H, d, $J = 9$ Hz), 4.92 (1H, d, $J = 9$ Hz), 8.34 (1H, dd, $J = 2$ Hz), 8.78 (1H, d, $J = 2$ Hz), 9.15 (1H, d, $J = 2$ Hz).

10

Preparation 280

ethyl 6-(acetyloxy)-4-(3-chlorobenzoyl)-5-oxohexanoate

^1H NMR (300 MHz, CDCl_3) δ 1.26 (3H, t, $J = 7$ Hz), 1.95 (3H, s), 2.20-2.29 (2H, m), 2.41-2.47 (2H, m), 4.15 (2H, q, $J = 7$ Hz), 4.64 (1H, d, $J = 17$ Hz), 4.71 (1H, d, $J = 17$ Hz), 4.78 (1H, t, $J = 6$ Hz), 7.48 (1H, dd, $J = 8, 8$ Hz), 7.60 (1H, d, $J = 8$ Hz), 7.96 (1H, d, $J = 8$ Hz), 8.04 (1H, s).

15

Preparation 281

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-7-isobutoxy-6-oxoheptanoate

20 ^1H NMR (300 MHz, CDCl_3) δ 0.72 (3H, d, $J = 7$ Hz), 0.77 (3H, d, $J = 7$ Hz), 1.23 (3H, t, $J = 7$ Hz), 1.61-1.73 (3H, m), 1.77-1.88 (1H, m), 1.98-2.10 (1H, m), 2.33 (2H, t, $J = 7$ Hz), 3.10 (1H, dd, $J = 9, 7$ Hz), 3.15 (1H, dd, $J = 9, 7$ Hz), 3.99 (2H, s), 4.11 (2H, q, $J = 7$ Hz), 4.73 (1H, t, $J = 7$ Hz), 8.40 (1H, dd, $J = 2, 2$ Hz), 8.87 (1H, d, $J = 2$ Hz), 9.10 (1H, d, $J = 2$ Hz).

25

Preparation 282

1,3-bis(5-bromo-3-pyridinyl)-1,3-propanedione

^1H NMR ($\text{DMSO}-d_6$) δ 7.60 (1H, s), 8.78 (2H, s), 8.88 (2H, s), 9.30 (2H, s).

30 Preparation 283

ethyl 7-(acetyloxy)-5-(3-chlorobenzoyl)-6-oxoheptanoate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 8$ Hz), 1.57-1.75 (2H, m), 1.90-2.12 (5H, m), 2.34 (2H, t, $J = 8$ Hz), 4.11 (2H, q, $J = 8$ Hz), 4.52 (1H, t, $J = 8$ Hz), 4.71 (2H, q, J

= 8 Hz), 4.65 (1H, d, J = 16 Hz), 4.75 (1H, d, J = 16 Hz), 7.43 (1H, t, J = 8 Hz), 7.60 (1H, br d, J = 8 Hz), 7.84 (1H, br d, J = 8 Hz), 7.96 (1H, br s).

Preparation 284

5 ethyl 8-methoxy-6-[(5-methoxy-3-pyridinyl)carbonyl]-7-oxooctanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.27-1.43 (2H, m), 1.55-1.70 (2H, m), 1.84 (1H, m), 2.00 (1H, m), 2.27 (2H, d, J = 8 Hz), 3.26 (3H, s), 3.92 (3H, s), 3.98 (2H, d, J = 5 Hz), 4.10 (2H, q, J = 8 Hz), 4.67 (1H, t, J = 8 Hz), 7.71 (1H, m), 8.50 (1H, d, J = 3 Hz), 8.78 (1H, br s).

10 MS (ESI⁺): m/z 352 (M + H).

Preparation 285

ethyl 6-[(5-methoxy-3-pyridinyl)carbonyl]-7-oxooctanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 8 Hz), 1.27-1.41 (2H, m), 1.60-1.73 (2H, m), 1.90-2.14 (2H, m), 2.18 (3H, s), 2.24-2.84 (2H, m), 3.26 (3H, s), 3.92 (3H, s), 4.10 (2H, q, J = 8 Hz), 4.40 (1H, t, J = 8 Hz), 7.71 (1H, m), 8.51 (1H, d, J = 3 Hz), 8.78 (1H, br s).

Preparation 286

20 ethyl 6-methoxy-4-[(5-methoxy-3-pyridinyl)carbonyl]-5-oxohexanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 8 Hz), 2.10 (1H, m), 2.25 (1H, m), 2.38-2.47 (2H, m), 3.24 (3H, s), 3.94 (3H, s), 3.95 (1H, d, J = 16 Hz), 4.00 (1H, d, J = 16 Hz), 4.12 (2H, q, J = 8 Hz), 4.38 (1H, m), 7.83 (1H, m), 8.52 (1H, d, J = 3 Hz), 8.87 (1H, d, J = 1 Hz).

25 MS (ESI⁺): m/z 346 (M+ + Na).

Preparation 287

ethyl 7-methoxy-5-[(5-methoxy-3-pyridinyl)carbonyl]-6-oxoheptanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.54-1.74 (2H, m), 1.84 (1H, m), 2.02 (1H, m), 2.32 (2H, d, J = 8 Hz), 3.26 (3H, s), 3.92 (3H, s), 3.99 (2H, d, J = 5 Hz), 4.10 (2H, q, J = 8 Hz), 4.70 (1H, t, J = 8 Hz), 7.71 (1H, m), 8.51 (1H, d, J = 3 Hz), 8.79 (1H, br s).

MS (ESI⁺): m/z 338 (M + H).

Preparation 288

ethyl 8-methoxy-7-oxo-6-(5-pyrimidinylcarbonyl)octanoate

- ¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.25-1.45 (2H, m), 1.55-1.70 (2H, m),
 5 1.81 (1H, m), 2.03 (1H, m), 2.28 (2H, t, J = 8 Hz), 3.24 (3H, s), 3.92 (1H, d, J =
 18 Hz), 4.01 (1H, d, J = 18 Hz), 4.10 (2H, q, J = 8 Hz), 9.26 (2H, s), 9.40 (1H, s).
 MS (ESI⁺): m/z 323 (M + H).

Preparation 289

- 10 ethyl 5-[(5-chloro-3-pyridinyl)carbonyl]-7-methoxy-6-oxoheptanoate

- ¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 8 Hz), 1.52-1.74 (2H, m), 1.83 (1H, m), 2.02 (1H,
 m), 2.34-2.40 (2H, m), 3.25 (3H, s), 3.92 (1H, d, J = 16 Hz), 4.01 (1H, d, J = 16
 Hz), 4.11 (2H, q, J = 8 Hz), 4.68 (1H, t, J = 8 Hz), 8.23 (1H, br s), 8.78 (1H, br s),
 9.05 (1H, br s).
 15 MS (ESI⁺): m/z 342 (M + H).

Preparation 290

ethyl 4-[(5-chloro-3-pyridinyl)carbonyl]-6-methoxy-5-oxohexanoate

- ¹H NMR (CDCl₃) δ 1.25 (3H, t, J = 8 Hz), 2.09 (1H, m), 2.25 (1H, m), 2.38-2.49 (2H,
 20 m), 3.22 (3H, s), 3.91 (1H, d, J = 18 Hz), 4.00 (1H, d, J = 18 Hz), 4.14 (2H, q, J =
 8 Hz), 4.85 (1H, m), 8.33 (1H, br s), 8.78 (1H, br s), 9.14 (1H, br s).
 MS (ESI⁺): m/z 328 (M + H).

Preparation 291

- 25 ethyl 6-[(5-chloro-3-pyridinyl)carbonyl]-8-methoxy-7-oxooctanoate

- ¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.27-1.43 (2H, m), 1.50-1.71 (2H, m),
 1.82 (1H, m), 2.00 (1H, m), 2.27 (2H, d, J = 8 Hz), 3.25 (3H, s), 3.92 (1H, d, J =
 16 Hz), 4.02 (1H, d, J = 16 Hz), 4.10 (2H, q, J = 8 Hz), 4.63 (1H, t, J = 8 Hz),
 8.23 (1H, br s), 8.78 (1H, br s), 9.03 (1H, br s).
 30 MS (ESI⁺): m/z 356 (M + H).

Preparation 292

2-[2-({3-[(5-methyl-3-pyridinyl)carbonyl]-4-oxopentyl}oxy)ethoxy]ethyl acetate

trifluoroacetate

^1H -NMR (CDCl_3) δ 2.06 (3H, s), 2.28 (3H, s), 2.33 (2H, m), 2.65 (3H, s), 3.47-3.67 (8H, m), 4.17 (2H, m), 4.71 (1H, t, $J = 7$ Hz), 8.66 (1H, m), 8.88 (1H, m), 9.31 (1H, m).

5

Preparation 293

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-7-methoxy-6-oxoheptanoate

^1H NMR (CDCl_3) δ 1.23 (3H, t, $J = 7$ Hz), 1.56-1.73 (2H, m), 1.77-1.92 (1H, m), 1.96-2.10 (1H, m), 2.32 (2H, t, $J = 7$ Hz), 3.25 (3H, s), 3.92 (1H, d, $J = 17$ Hz), 4.02 (1H, d, $J = 17$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.67 (1H, t, $J = 7$ Hz), 8.39 (1H, m), 8.87 (1H, d, $J = 2$ Hz), 9.09 (1H, d, $J = 2$ Hz).

10

MS (ESI^+): m/z 386 388.

The following compound(s) was(were) obtained in a similar manner to that of

15

Preparation 129 and 130.

Preparation 294

tert-butyl 3-oxo-4-phenylbutanoate

^1H NMR (CDCl_3) δ 1.46 (9H, s), 3.37 (2H, s), 3.82 (2H, s), 7.21 (2H, d, $J = 8$ Hz), 7.25-7.37 (3H, m).

20

Preparation 295

tert-butyl 3-oxo-3-phenylpropanoate

^1H NMR (CDCl_3) δ 1.43 (9H, s), 3.81 (2H, s), 7.40-7.52 (2H, m), 7.56-7.63 (1H, m), 7.94 (2H, d, $J = 8$ Hz).

25

Preparation 296

tert-butyl 4-(cyclohexylmethoxy)-3-oxobutanoate

^1H NMR (CDCl_3) δ 0.89-1.07 (2H, m), 1.13-1.40 (3H, m), 1.47 (9H, s), 1.60-1.83 (6H, m), 3.28 (2H, d, $J = 7$ Hz), 3.45 (2H, s), 4.06 (2H, s).

30

Preparation 297

tert-butyl 4-(cyclopropylmethoxy)-3-oxobutanoate

^1H NMR (CDCl_3) δ 0.20-0.28 (2H, m), 0.55-0.64 (2H, m), 1.03-1.17 (1H, m), 1.47

(9H, s), 3.36 (2H, d, J = 7 Hz), 3.45 (2H, s), 4.15 (2H, s).

Preparation 298

tert-butyl 4-(2-methoxyethoxy)-3-oxobutanoate

- 5 ^1H NMR (CDCl_3) δ 1.47 (9H, s), 3.38 (3H, s), 3.44 (2H, s), 3.57 (2H, m), 3.70 (2H, m), 4.20 (2H, s).

Preparation 299

tert-butyl 4-isobutoxy-3-oxobutanoate

- 10 ^1H NMR (300 MHz, CDCl_3) δ 0.93 (6H, d, J = 7 Hz), 1.45 (9H, s), 1.91 (1H, qt, J = 7, 7 Hz), 3.26 (2H, d, J = 7 Hz), 3.45 (2H, s), 4.07 (2H, s).

Preparation 300

tert-butyl 3-(3-methyl-2-thienyl)-3-oxopropanoate

- 15 ^1H -NMR (CDCl_3) δ 1.47 (9H, s), 2.57 (3H, s), 3.79 (2H, s), 6.96 (1H, d, J = 5 Hz), 7.44 (1H, d, J = 5 Hz).

Preparation 301

tert-butyl 3-(5-methyl-3-isoxazolyl)-3-oxopropanoate

- 20 ^1H -NMR (CDCl_3) δ 1.475-1.57 (9H, m), 2.49 (3H, m), 3.95 (2H, s), 6.40 (1H, s).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 132.

Preparation 302

- 25 ethyl (2E)-5-(3-cyanobenzoyl)-6-oxo-2-heptenoate

^1H -NMR (CDCl_3) δ 1.28 (3H, t, J = 7 Hz), 2.20 (3H, s), 2.88 (2H, m), 4.16 (2H, q, J = 7 Hz), 4.54 (1H, t, J = 7 Hz), 5.88 (1H, d, J = 16 Hz), 6.82 (1H, dt, J = 7 and 16 Hz), 7.65 (1H, t, J = 8 Hz), 7.89 (1H, d, J = 8 Hz), 8.20 (1H, d, J = 8 Hz), 8.27 (1H, s).

- 30 MS (ESI^+): m/z 300.14 (M + H)

Preparation 303

1-tert-butyl 7-ethyl 2-[(3-methyl-2-thienyl)carbonyl]heptanedioate

$^1\text{H-NMR}$ (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.35-1.51 (11H, m), 1.65 (2H, m), 1.96 (2H, m), 2.30 (2H, t, $J = 7$ Hz), 2.58 (3H, s), 3.94 (1H, t, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 6.97 (1H, d, $J = 5$ Hz), 7.44 (1H, d, $J = 5$ Hz).

5 Preparation 304

1-tert-butyl 7-ethyl 2-[(5-methyl-3-isoxazolyl)carbonyl]heptanedioate

$^1\text{H-NMR}$ (CDCl_3) δ 11.24 (3H, t, $J = 7$ Hz), 1.39 (9H, s), 1.67 (2H, m), 1.98 (2H, m), 2.49 (3H, s), 4.10 (2H, q, $J = 7$ Hz), 4.26 (1H, t, $J = 7$ Hz), 6.37 (1H, s).

10 The following compound(s) was(were) obtained in a similar manner to that of Preparation 152.

Preparation 305

methyl 7-oxo-7-(2-thienyl)heptanoate

15 $^1\text{H-NMR}$ (CDCl_3) δ 1.41 (2H, m), 1.63-1.82 (4H, m), 2.33 (2H, t, $J = 7$ Hz), 2.91 (2H, t, $J = 7$ Hz), 3.67 (3H, s), 1.73 (1H, m), 7.62 (1H, m), 7.70 (1H, m).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 153.

Preparation 306

20 5-methoxynicotinoyl chloride hydrochloride

Preparation 307

5-pyrimidinecarbonyl chloride hydrochloride

25 Preparation 308

5-chloronicotinoyl chloride hydrochloride

Preparation 309

methyl 2-bromo-4-(chlorocarbonyl)benzoate

30

The following compound(s) was(were) obtained in a similar manner to that of Preparation 159.

Preparation 310

1-tert-butyl 7-ethyl 2-(phenylacetyl)heptanedioate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.18-1.50 (2H, m), 1.46 (9H, s), 1.50-1.75 (2H, m), 1.75-1.88 (2H, m), 2.24 (2H, t, $J = 7$ Hz), 3.47 (1H, t, $J = 7$ Hz), 3.81 (2H, s), 4.10 (2H, q, $J = 7$ Hz), 7.20 (2H, d, $J = 8$ Hz), 7.25-7.37 (3H, m).

5

Preparation 311

tert-butyl 2-[2-(2-methoxy-2-oxoethoxy)ethyl]-3-oxobutanoate

^1H NMR (CDCl_3) δ 1.46 (9H, s), 2.04-2.23 (2H, m), 2.29 (3H, s), 3.54 (2H, t, $J = 7$ Hz), 3.69 (1H, t, $J = 7$ Hz), 3.74 (3H, s), 4.04 (2H, s).

10

Preparation 312

tert-butyl 2-benzoyl-4-(2-methoxy-2-oxoethoxy)butanoate

^1H NMR (CDCl_3) δ 1.34 (9H, s), 2.26-2.40 (2H, m), 3.55-3.67 (2H, m), 3.70 (3H, s), 4.04 (2H, s), 4.57 (1H, t, $J = 7$ Hz), 7.47 (2H, t, $J = 8$ Hz), 7.56 (1H, m), 8.01 (2H, d, $J = 8$ Hz).

15

Preparation 313

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]hexanedioate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.48 (9H, s), 1.60-1.73 (2H, m), 1.82-1.95 (2H, m), 2.17 (3H, s), 2.32 (2H, t, $J = 7$ Hz), 3.43 (1H, t, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.72 (1H, d, $J = 17$ Hz), 4.83 (1H, d, $J = 17$ Hz).

20

Preparation 314

1-tert-butyl 5-ethyl 2-[(cyclohexylmethoxy)acetyl]pentanedioate

^1H NMR (CDCl_3) δ 0.85-1.06 (2H, m), 1.13-1.34 (3H, m), 1.26 (3H, t, $J = 7$ Hz), 1.45 (9H, s), 1.60-1.85 (6H, m), 2.08-2.23 (2H, m), 2.36 (2H, t, $J = 7$ Hz), 3.27 (2H, d, $J = 7$ Hz), 3.67 (1H, t, $J = 7$ Hz), 4.10 (2H, s), 4.12 (2H, q, $J = 7$ Hz).

25

Preparation 315

30 1-tert-butyl 6-ethyl 2-[(cyclohexylmethoxy)acetyl]hexanedioate

^1H NMR (CDCl_3) δ 0.88-1.06 (2H, m), 1.12-1.34 (3H, m), 1.25 (3H, t, $J = 7$ Hz), 1.45 (9H, s), 1.54-1.94 (10H, m), 2.32 (2H, t, $J = 7$ Hz), 3.27 (2H, d, $J = 7$ Hz), 3.56 (1H, t, $J = 7$ Hz), 4.09 (2H, s), 4.11 (2H, q, $J = 7$ Hz).

MS (ESI⁺): m/z 385.

Preparation 316

1-tert-butyl 6-ethyl 2-[(cyclopropylmethoxy)acetyl]hexanedioate

5 ¹H NMR (CDCl₃) δ 0.22-0.33 (2H, m), 0.54-0.64 (2H, m), 1.04-1.18 (1H, m), 1.25 (3H, t, J = 7 Hz), 1.45 (9H, s), 1.60-1.73 (2H, m), 1.83-1.95 (2H, m), 2.33 (2H, t, J = 7 Hz), 3.33 (2H, d, J = 7 Hz), 3.53 (1H, t, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 4.18 (2H, m).

MS (ESI⁺): m/z 343.

10

Preparation 317

1-tert-butyl 5-ethyl 2-[(cyclopropylmethoxy)acetyl]pentanedioate

15 ¹H NMR (CDCl₃) δ 0.20-0.35 (2H, m), 0.56-0.64 (2H, m), 1.04-1.16 (1H, m), 1.26 (3H, t, J = 7 Hz), 1.45 (9H, s), 2.12-2.24 (2H, m), 2.38 (2H, t, J = 7 Hz), 3.36 (2H, m), 3.65 (1H, t, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 4.19 (2H, s).

Preparation 318

1-tert-butyl 5-ethyl 2-[(2-methoxyethoxy)acetyl]pentanedioate

20 ¹H NMR (CDCl₃) δ 1.25 (3H, t, J = 7 Hz), 1.46 (9H, s), 2.10-2.23 (2H, m), 2.38 (2H, t, J = 7 Hz), 3.37 (3H, s), 3.60 (2H, m), 3.62 (1H, t, J = 7 Hz), 3.70 (2H, m), 4.12 (2H, q, J = 7 Hz), 4.23 (1H, d, J = 17 Hz), 4.30 (1H, d, J = 17 Hz).

MS (ESI⁺): m/z 333.

Preparation 319

25 1-tert-butyl 5-ethyl 2-(isobutoxyacetyl)pentanedioate

¹H NMR (300 MHz, CDCl₃) δ 0.93 (6H, d, J = 7 Hz), 1.26 (3H, t, J = 7 Hz), 1.45 (9H, s), 1.91 (1H, qt, J = 7, 7 Hz), 2.13 (2H, m), 2.37 (2H, t, J = 7 Hz), 3.25 (2H, d, J = 7 Hz), 3.67 (1H, t, J = 7 Hz), 4.12 (2H, s), 4.13 (2H, q, J = 7 Hz).

30 The following compound(s) was(were) obtained in a similar manner to that of Preparation 164.

Preparation 320

methyl 2-bromo-4-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.32 (3H, t, $J = 7$ Hz), 2.72 (2H, q, $J = 7$ Hz), 3.97 (3H, s), 6.10 (1H, m), 6.77 (1H, m), 7.81 (1H, d, $J = 8$ Hz), 7.85 (1H, d, $J = 8$ Hz), 8.11 (1H, s), 9.32 (1H, s, br).

5 The following compound(s) was(were) obtained in a similar manner to that of Preparation 165.

Preparation 321

tert-butyl 2-(2-{2-[2-(acetyloxy)ethoxy]ethoxy}ethyl)-3-oxobutanoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.46 (9H, s), 2.00-2.17 (5H, m), 2.25 (3H, s), 3.45-3.70 (10H, m),
10 4.22 (2H, m).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 178.

Preparation 322

15 isobutoxyacetic acid

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 0.94 (6H, d, $J = 7$ Hz), 1.93 (1H, qt, $J = 7, 7$ Hz), 3.34 (2H, d, $J = 7$ Hz), 4.12 (2H, s).

Preparation 323

20 To a suspension of 60% NaH (2.66 g) in DMF (20 mL) was added methyl hydroxyacetate (5.00 g) under ice-water cooling, and the mixture was stirred at 0 °C for 0.5 hour. To this was added 2-(2-bromoethoxy)tetrahydro-2H-pyran (12.8 g) under ice-water cooling, and the mixture was stirred at ambient temperature for 2 hours. The mixture was partitioned between AcOEt and water. The organic layer was separated,
25 washed with water and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (10:1 - 3:1) to give methyl [2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]acetate pale yellow oil (4.45 g).

30 methyl [2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]acetate

$^1\text{H NMR}$ (CDCl_3) δ 1.48-1.95 (6H, m), 3.46-3.57 (2H, m), 3.64-3.75 (2H, m), 3.76 (3H, s), 3.82-3.97 (2H, m), 4.20 (2H, s), 4.66 (1H, m).

Preparation 324

A mixture of methyl [2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]acetate (1.07 g) and pyridinium p-toluenesulfonate (24.6 mg) in MeOH (10 mL) was heated under reflux for 2 hours. After evaporation of solvent, the residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (10:1 - 1:3) to give methyl (2-hydroxyethoxy)acetate as colorless oil (555 mg).

methyl (2-hydroxyethoxy)acetate

^1H NMR (CDCl_3) δ 3.69 (2H, m), 3.76 (2H, m), 3.78 (3H, s), 4.16 (2H, s).

10

Preparation 325

To solution of methyl (2-hydroxyethoxy)acetate (540 mg), imidazole (411 mg) and triphenylphosphine (1.37 g) in ether (2 mL) and CH_3CN (1 mL) was added iodine (1.43 g) under ice-water cooling and the mixture was stirred at 0 °C for 2 hours. After insolubles were filtered off, the filtrates were diluted with AcOEt, washed with aq Na_2SO_3 solution and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (20:1 - 5:1) to give methyl (2-iodoethoxy)acetate as colorless oil (898 mg).

20 methyl (2-iodoethoxy)acetate

^1H NMR (CDCl_3) δ 3.30 (2H, t, $J = 7$ Hz), 3.77 (3H, s), 3.84 (2H, t, $J = 7$ Hz), 4.17 (2H, s).

Preparation 326

25 To a suspension of 60% NaH (1.02 g) in THF (50 mL) was added tert-butyl 4-(acetyloxy)-3-oxobutanoate (5.00 g) under ice-water cooling and the mixture was stirred at 0 °C for 0.5 hour. To this added ethyl 3-iodopropanoate (5.54 g) and the mixture was stirred at 50 °C for 8 hours. The mixture was partitioned between AcOEt and water. The organic layer was separated, washed with brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (20:1 - 3:1) to give 1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]pentanedioate as yellow oil (4.27 g).

30

1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]pentanedioate

^1H NMR (CDCl_3) δ 1.26 (3H, t, $J = 7$ Hz), 1.46 (9H, s), 2.14-2.24 (2H, m), 2.17 (3H, s), 2.36 (2H, t, $J = 7$ Hz), 3.60 (1H, t, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.73 (1H, d, $J = 18$ Hz), 4.83 (1H, d, $J = 18$ Hz).

5

Preparation 327

To a solution of benzyl 4-thiomorpholinecarboxylate (4.8 g) in methanol (30 mL) and H_2O (20 mL) was added oxone (16.2 g) under ice water cooling and the mixture was stirred at ambient temperature for 2 hours. The solution was evaporated in vacuo and partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine, dried over MgSO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and EtOAc to give benzyl 4-thiomorpholinecarboxylate 1,1-dioxide as a colorless solid (3.8 g).

15

benzyl 4-thiomorpholinecarboxylate 1,1-dioxide

^1H NMR (300 MHz, CDCl_3) δ 3.02 (4H, br s), 4.01 (4H, t, $J = 5$ Hz), 5.16 (2H, s), 7.33-7.40 (5H, m).

20 Preparation 328

To a solution of thiomorpholine (2 g) in 1N NaOH (11.6 mL) was added benzyl chloridocarbonate (1.66 mL) under ice water cooling and the mixture was stirred at ambient temperature for 2 hours. The solution was neutralized with 1N HCl and extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over MgSO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography to give benzyl 4-thiomorpholinecarboxylate as a colorless solid (4.8 g).

25

benzyl 4-thiomorpholinecarboxylate

^1H NMR (300 MHz, CDCl_3) δ 2.59 (4H, br s), 3.77 (4H, t, $J = 5$ Hz), 5.14 (2H, s), 7.30-7.41 (5H, m).

30

Preparation 329

To a solution of benzyl 4-thiomorpholinecarboxylate 1,1-dioxide (3.8 g) in methanol (32 mL) and 1,4-dioxane (8 mL) was added Palladium, 10 wt. % on activated carbon (380 mg) at ambient temperature. The mixture was stirred at ambient temperature for 4 hours under H₂ (3.4 atom). The mixture was filtered and evaporated in vacuo to give thiomorpholine 1,1-dioxide as a colorless solid (2.22 g).

thiomorpholine 1,1-dioxide

¹H NMR (300 MHz, CDCl₃) δ 3.03 (4H, t, J = 5 Hz), 3.33 (4H, t, J = 5 Hz).

MS (m/z) 136 (M+H).

10

Preparation 330

To a suspension of [(5-chloro-4-mercapto-6-methyl-3-pyridinyl)oxy]acetic acid (10 g) in dichloromethane (100 mL) was added Et₃N (14 mL) in ice-MeOH bath. To this was added trifluoromethanesulfonic anhydride (14.3 mL) dropwise below 10°C over 30 min. After 2 hours the mixture was partitioned between CHCl₃ and water. The aqueous layer was extracted with CHCl₃ twice. The combined organic layer was dried over MgSO₄ and evaporated in vacuo to give brown oil. The residue was purified by silica gel column chromatography (silica gel, 100 mL) eluted with hexane-EtOAc = 15-1 and 10-1 to give 5-chloro-3-pyridinyl trifluoromethanesulfonate (15.8 g) as a pale brown oil.

20

5-chloro-3-pyridinyl trifluoromethanesulfonate

¹H NMR (300 MHz, CDCl₃) δ 7.69 (1H, dd, J = 4, 4 Hz), 8.52 (1H, d, J = 4 Hz), 8.65 (1H, d, J = 4 Hz).

Preparation 331

To ethanol (66 mL) and DMF (66 mL) was added Et₃N (29.4 mL), 1,3-propanediylbis(diphenylphosphine) (3.48 g) and palladium acetate (1.9 g) in ice-water bath. To this was added 5-chloro-3-pyridinyl trifluoromethanesulfonate (22.1 g) at the temperature. The mixture was stirred at 50°C for 4 hours under CO (1 atom). The mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water three times, dried over MgSO₄ and evaporated in vacuo. The residue was purified by silica gel column chromatography (silica gel, 200 mL) eluted with hexane-EtOAc = 15-1 and 10-1 to give ethyl 5-

chloronicotinate (10.5 g) as a pale brown oil.

ethyl 5-chloronicotinate

¹H NMR (300 MHz, CDCl₃) δ 1.42 (3H, t, J = 7 Hz), 4.43 (2H, q, J = 7 Hz), 8.28 (1H, dd, J = 3, 3 Hz), 8.74 (1H, d, J = 3 Hz), 9.09 (1H, d, J = 3 Hz).

Preparation 332

To 5-chloronicotinate (10.5 g) was added 1N NaOH (84.9 mL) at ambient temperature. The mixture was heated at 60°C for 1 hour. The reaction mixture was adjusted to pH 4-5 with HCl. The precipitate was filtered to give 5-chloronicotinic acid (6.9 g) a colorless solid.

¹H NMR (300 MHz, DMSO-d₆) δ 8.30 (1H, dd, J = 3 Hz), 8.88 (1H, d, J = 3 Hz), 9.01 (1H, d, J = 3 Hz), 13.8 (1H, br s).

5-chloronicotinic acid

¹H NMR (300 MHz, DMSO-d₆) δ 8.30 (1H, dd, J = 3, 3 Hz), 8.88 (1H, d, J = 3 Hz), 9.01 (1H, d, J = 3 Hz), 13.8 (1H, br s).

The following compound(s) was(were) obtained in a similar manner to that of

Preparation 332.

Preparation 333

5-methoxynicotinic acid

¹H NMR (DMSO-d₆) δ 3.87 (3H, s), 7.73 (1H, m), 8.48 (1H, d, J = 3 Hz), 8.65 (1H, d, J = 1 Hz).

MS (ESI⁺): m/z 154 (M + H).

Preparation 334

5-pyrimidinecarboxylic acid

¹H NMR (DMSO-d₆) δ 9.20 (2H, s), 9.37 (1H, s).

MS (ESI⁺): m/z 148 (M + Na).

Preparation 335

To a solution of diisopropylamine (5.41 g) in THF (30 mL) was added 1.5 M n-

butyllithium hexane solution (35 mL) under dryice acetone cooling and the mixture was stirred at -78 °C for 10 minutes. To this was added tert-butyl acetate (5.87 g) under dryice acetone cooling and the mixture was stirred at -78 °C for 10 minutes and added dropwise to a solution of 5-bromonicotinic acid (3.00 g) and N, N-carbonyldiimidazole (2.65 g) in THF (30 mL) under dryice acetone cooling. The mixture was stirred at -78 °C for 0.5 hour. The mixture was partitioned between ethyl acetate and aq NH₄Cl solution. The organic layer was separated, washed with aq NaHCO₃ solution and brine, dried over MgSO₄, and evaporated in vacuo. The residue was triturated with isopropyl ether to give tert-butyl 3-(5-bromo-3-pyridinyl)-3-oxopropanoate as a colorless powder (3.71 g).

tert-butyl 3-(5-bromo-3-pyridinyl)-3-oxopropanoate

Enol form: ¹H NMR (CDCl₃) δ 1.54 (9H, s), 5.62 (1H, s), 8.19 (1H, m), 8.72 (1H, d, J= 2 Hz), 8.86 (1H, d, J= 2 Hz).

Keto form: ¹H NMR (CDCl₃) δ 1.44 (9H, s), 3.90 (2H, s), 8.37 (1H, m), 8.86 (1H, d, J= 2 Hz), 9.03 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 300 302.

Preparation 336

To a suspension of NaH in DMF (50 mL) which was washed with hexane 3 times was added methyl 5-hydroxynicotinate (10.2 g) portionwise below 10°C in an ice-water bath under nitrogen atmosphere. After 30 min, methyl iodide (4.56 mL) was added dropwise therein. The precipitate appeared and the mixture was hard to be stirred. DMF (30 mL) was added. After 20 min, the mixture was stirred at ambient temperature for 3 h. The reaction mixture was quenched with MeOH and was concentrated in vacuo. To the residue was added CHCl₃, sat. NaHCO₃, and brine. The organic layer was separated and the aqueous layer was extracted with CHCl₃. The combined organic layer was dried over MgSO₄ and was evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 200 mL) eluted with hexane-AcOEt = 5-1 and 3-1 to give methyl 5-methoxynicotinate (3.47 g) as a pale brown solid .

methyl 5-methoxynicotinate

¹H NMR (CDCl₃) δ 3.91 (3H, s), 3.96 (3H, s), 7.76 (1H, m), 8.47 (1H, d, J = 3 Hz),

8.83 (1H, d, J = 1 Hz).

MS (ESI⁺): m/z 168 (M + H).

Preparation 337

- 5 To a solution of methyl 2-bromo-4-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzoate (330 mg) in N,N-dimethylformamide (5 mL) was added 60% sodium hydride in oil (58.4 mg) in an ice-bath over 5 minutes. After stirring for 1 hour, (aminoxy)(diphenyl)phosphine oxide (340 mg) was added portionwise over 40 minutes. The resulting mixture was stirred for 1 hour in the bath. The reaction was quenched by
10 adding water (10 mL). The mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (two times) and brine, dried over magnesium sulfate, and evaporated. The residue was dissolved in ethyl acetate-hexane (1-5), and to the solution was added silicagel. The mixture was filtered, and the filtrate was evaporated to give methyl 4-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-2-
15 bromobenzoate as an orange solid (310 mg).

methyl 4-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-2-bromobenzoate

- ¹H-NMR (CDCl₃) δ 1.29 (3H, t, J = 7 Hz), 2.76 (2H, q, J = 7 Hz), 3.97 (3H, s), 5.73 (2H, s, br), 5.93 (1H, d, J = 5 Hz), 6.62 (1H, d, J = 5 Hz), 7.73 (1H, d, J = 8 Hz),
20 7.84 (1H, d, J = 8 Hz), 8.02 (1H, s).

Preparation 338

- To a solution of dimethyl 2-bromoterephthalate (1.04 g) in methanol (10 mL) was added 1 N sodium hydroxide (5.71 mL) at room temperature. After stirring for 1.5 hour,
25 the reaction was quenched by adding 1 N hydrochloric acid (7 mL). White crystals were formed. Water (10 mL) was added to aid crystallization. The crystals were collected by filtration, washed with water, and dried in the air. 3-Bromo-4-(methoxycarbonyl)benzoic acid was obtained as white crystals (532 mg).

- 30 3-bromo-4-(methoxycarbonyl)benzoic acid

¹H-NMR (DMSO-d₆) δ 3.89 (3H, s), 7.87 (1H, d, J = 8 Hz), 8.01 (1H, d, J = 8 Hz), 8.17 (1H, s).

Preparation 339

A mixture of 2-[2-(2-chloroethoxy)ethoxy]ethyl acetate (6.23 g) and sodium iodide (22.2 g) in acetone (60 mL) was refluxed for 4 hours. The mixture was further refluxed for 4 hours after adding sodium iodide (11.0 g). The solvent was evaporated off, and the residue was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was washed with 10% sodium thiosulfate and brine, dried over MgSO_4 , and evaporated to give 2-[2-(2-iodoethoxy)ethoxy]ethyl acetate as a pale yellow oil (9.74 g).

2-[2-(2-iodoethoxy)ethoxy]ethyl acetate

$^1\text{H-NMR}$ (CDCl_3) δ 2.09 (3H, s), 3.27 (2H, t, $J = 7$ Hz), 3.65-3.78 (8H, m), 4.24 (2H, m).

Preparation 340

A solution of 1-tert-butyl 7-ethyl 2-[(5-methyl-3-isoxazolyl)carbonyl]heptanedioate (126 mg) in trifluoroacetic acid (1 mL) was stirred for 1.5 hour at room temperature. The volatile was evaporated off, and azeotroped with toluene to give 7-ethoxy-2-[(5-methyl-3-isoxazolyl)carbonyl]-7-oxoheptanoic acid as a pale orange oil (106 mg).

20

7-ethoxy-2-[(5-methyl-3-isoxazolyl)carbonyl]-7-oxoheptanoic acid

$^1\text{H-NMR}$ (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.41 (2H, m), 1.65 (2H, m), 2.02 (2H, m), 2.30 (2H, m), 2.50 (3H, s), 2.55 (1H, s, br), 4.10 (2H, q, $J = 7$ Hz), 4.47 (1H, t, $J = 7$ Hz), 6.40 (1H, s).

25 MS (ESI^+): m/z 296.22 (M-H) and 593.52 (2M-H)

Preparation 341

To a suspension of dimethyl sulfone (5.43 g) in tetrahydrofuran (10 mL) was added 1.59 M n-butyl lithium (36.3 mL) in a dry ice-acetone bath under a nitrogen atmosphere. After stirring for 0.5 hour, a solution of methyl methoxyacetate (2.00 g) in tetrahydrofuran (5 mL) was added. The resulting mixture was stirred for 2 hours in the bath and allowed to warm to room temperature over 2 hours. The mixture was partitioned between EtOAc and 4 N hydrochloric acid. The reaction was quenched by

adding 4 N hydrochloric acid in EtOAc (15 mL). The mixture was partitioned between EtOAc (100 mL) and brine (100 mL). The aqueous layer was washed with EtOAc (100 mL, five times). The organic layer was combined, and the combined extracts were dried over MgSO₄, and evaporated. Flash silicagel column chromatography (EtOAc-hexane = 5 50-200 to 300-100) afforded 2-(methylsulfonyl)-1-methoxyethanone as a colorless oil (2.24 g).

1-methoxy-3-(methylsulfonyl)acetone

¹H-NMR (CDCl₃) δ 2.99 (3H, s), 3.08 (2H, s), 3.47 (3H, s), 4.19 (2H, s).

10

The following compound(s) was(were) obtained in a similar manner to that of Example 1.

Example 392

ethyl 4-[3-bromo-4-(methoxycarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-15 3-carboxylate

¹H-NMR (CDCl₃) δ 0.98 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 2.61 (3H, s), 3.04 (2H, q, J = 7 Hz), 3.98 (3H, s), 4.05 (2H, q, J = 7 Hz), 6.29 (1H, d, J = 5 Hz), 6.67 (1H, d, J = 7 Hz), 7.44 (1H, d, J = 8 Hz), 7.76 (1H, s), 7.89 (1H, d, J = 8 Hz).

20 Example 393

3-[7-ethyl-2-(methoxymethyl)-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

¹H-NMR (CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 2.98 (2H, q, J = 7 Hz), 3.18 (3H, s), 3.45 (3H, s), 4.59 (2H, s), 6.25 (1H, d, J = 5 Hz), 6.71 (1H, d, J = 5 Hz), 7.65 (1H, t, J = 8 Hz), 7.78 (1H, d, J = 8 Hz), 7.94 (1H, d, J = 8 Hz), 7.99 (1H, s).

25

MS (ESI⁺): m/z 370 (M + H)

The following compound(s) was(were) obtained in a similar manner to that of Example 16.

30 Example 394

5-{4-[3-(aminocarbonyl)phenyl]-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H-NMR (CDCl₃) δ 1.02 (4H, m), 1.28 (3H, t, J = 7 Hz), 1.70 (2H, m), 2.37 (2H, m),

2.92 (2H, q, J = 7 Hz), 5.87 (1H, d, J = 5 Hz), 6.66 (1H, d, J = 5 Hz), 7.46-7.67 (5H, m), 7.96-8.08 (3H, m).

The following compound(s) was(were) obtained in a similar manner to that of

5 Example 21.

Example 395

ethyl 4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.65-1.78 (2H, m),
2.22 (2H, t, J = 7 Hz), 2.40-2.52 (2H, m), 2.58 (3H, s), 3.03 (2H, q, J = 7 Hz), 4.05
10 (2H, q, J = 7 Hz), 5.86 (1H, d, J = 4 Hz), 6.53 (1H, d, J = 4 Hz), 7.25 (1H, d, J = 5
Hz), 7.36 (1H, s), 8.53 (1H, d, J = 5 Hz).

MS (ESI⁺): m/z 386 .

Example 396

15 ethyl 3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 2.30-2.39 (2H, m),
2.57 (3H, s), 2.74-2.83 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 5.88
(1H, d, J = 4 Hz), 6.55 (1H, d, J = 4 Hz), 7.24 (1H, d, J = 5 Hz), 7.35 (1H, s), 8.53
20 (1H, d, J = 5 Hz).

MS (ESI⁺): m/z 372.

Example 397

25 ethyl 5-[2-benzyl-4-(2-chloro-4-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.30-1.50 (4H, m),
2.10 (2H, t, J = 7 Hz), 2.23-2.35 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.09 (2H, q, J = 7
Hz), 4.21 (2H, s), 5.88 (1H, d, J = 4 Hz), 6.58 (1H, d, J = 4 Hz), 7.14-7.32 (7H, m),
8.50 (1H, d, J = 5 Hz).

30

Example 398

methyl {2-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]ethoxy}acetate

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.42 (3H, s), 2.61 (3H, s), 2.78-2.88 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.46-3.57 (2H, m), 3.71 (3H, s), 3.95 (2H, s), 5.87 (1H, d, $J = 4$ Hz), 6.52 (1H, d, $J = 4$ Hz), 7.54 (1H, s), 8.43 (1H, d, $J = 2$ Hz), 8.53 (1H, d, $J = 2$ Hz).

5 MS (ESI^+): m/z 368.

Example 399

ethyl [4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate

^1H NMR (CDCl_3) δ 1.26 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 2.51 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 3.43 (2H, s), 4.12 (2H, q, $J = 7$ Hz), 5.99 (1H, d, $J = 4$ Hz), 6.58 (1H, d, $J = 4$ Hz), 7.94 (1H, m), 8.58 (1H, d, $J = 2$ Hz), 8.78 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 402 404.

Example 400

15 ethyl 3-[2-[(acetyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 2.16 (3H, s), 2.32-2.42 (2H, m), 2.44 (3H, s), 2.77-2.90 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 5.31 (2H, s), 5.96 (1H, d, $J = 4$ Hz), 6.63 (1H, d, $J = 4$ Hz), 7.53 (1H, s), 8.42 (1H, d, $J = 2$ Hz), 8.55 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 410.

Example 401

25 ethyl 4-[2-[(acetyloxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

^1H NMR (CDCl_3) δ 1.25 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.64-1.78 (2H, m), 2.10-2.23 (2H, m), 2.17 (3H, s), 2.43 (3H, s), 2.43-2.58 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 4.12 (2H, q, $J = 7$ Hz), 5.33 (2H, s), 5.93 (1H, d, $J = 4$ Hz), 6.60 (1H, d, $J = 4$ Hz), 7.53 (1H, s), 8.43 (1H, s), 8.55 (1H, s).

30 MS (ESI^+): m/z 424.

Example 402

ethyl 5-[2-[(acetyloxy)methyl]-4-(3-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-

yl]pentanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.40-1.60 (4H, m),
2.16 (2H, t, J= 7 Hz), 2.17 (3H, s), 2.40-2.52 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.12
(2H, q, J= 7 Hz), 5.29 (2H, s), 5.88 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.60-
5 7.68 (3H, m), 7.75-7.83 (1H, m).
MS (ESI⁺): m/z 448.

Example 403

ethyl 4-[2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-
10 yl]butanoate
¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.65-1.82 (2H, m),
2.17 (3H, s), 2.21 (2H, t, J= 7 Hz), 2.45-2.63 (2H, m), 3.02 (2H, q, J= 7 Hz), 4.05
(2H, q, J= 7 Hz), 5.33 (2H, s), 5.95 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.90
(1H, m), 8.57 (1H, d, J= 2 Hz), 8.80 (1H, d, J= 2 Hz).
15 MS (ESI⁺): m/z 488 490.

Example 404

ethyl 3-[2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-
yl]propanoate
20 ¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 2.16 (3H, s), 2.36
(2H, t, J= 7 Hz), 2.77-2.95 (2H, m), 3.02 (2H, q, J= 7 Hz), 4.06 (2H, q, J= 7 Hz),
5.31 (2H, s), 5.96 (1H, d, J= 4 Hz), 6.64 (1H, d, J= 4 Hz), 7.88 (1H, s), 8.56 (1H,
m), 8.80 (1H, m).
MS (ESI⁺): m/z 474 476.

25

Example 405

ethyl 3-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-
b]pyridazin-3-yl]propanoate
30 ¹H NMR (CDCl₃) δ 0.88-1.06 (2H, m), 1.19 (3H, t, J= 7 Hz), 1.15-1.36 (3H, m), 1.37
(3H, t, J= 7 Hz), 1.58-1.85 (6H, m), 2.42 (2H, m), 2.43 (3H, s), 2.83-2.97 (2H, m),
3.05 (2H, q, J= 7 Hz), 3.38 (2H, d, J= 7 Hz), 4.06 (2H, q, J= 7 Hz), 4.66 (2H, s),
5.91 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.52 (1H, s), 8.42 (1H, d, J= 2 Hz),
8.54 (1H, d, J= 2 Hz).

Example 406

ethyl 3-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoate

5 $^1\text{H NMR (CDCl}_3\text{)}$ δ 0.85-1.06 (2H, m), 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz),
1.16-1.46 (3H, m), 1.55-1.84 (6H, m), 2.43 (2H, t, J= 7 Hz), 2.82-3.00 (2H, m),
3.06 (2H, q, J= 7 Hz), 3.37 (2H, d, J= 7 Hz), 4.06 (2H, q, J= 7 Hz), 4.66 (2H, s),
5.93 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.87 (1H, m), 8.55 (1H, d, J= 2 Hz),
8.78 (1H, d, J= 2 Hz).

10

MS (ESI⁺): m/z 528 530.

Example 407

ethyl 4-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

15 $^1\text{H NMR (CDCl}_3\text{)}$ δ 0.87-1.06 (2H, m), 1.21 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz),
1.16-1.46 (3H, m), 1.50-1.85 (8H, m), 2.23 (2H, t, J= 7 Hz), 2.55-2.75 (2H, m),
3.04 (2H, q, J= 7 Hz), 3.38 (2H, d, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.67 (2H, s),
5.92 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.56 (1H, d, J= 2 Hz),
20 8.79 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 542 544.

Example 408

ethyl 4-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

25 $^1\text{H NMR (CDCl}_3\text{)}$ δ 0.22-0.32 (2H, m), 0.53-0.65 (2H, m), 1.10-1.20 (1H, m), 1.19
(3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.65-1.80 (2H, m), 2.14-2.30 (2H, m), 2.43
(3H, s), 2.57-2.74 (2H, m), 3.05 (2H, q, J= 7 Hz), 3.43 (2H, d, J= 7 Hz), 4.03 (2H,
q, J= 7 Hz), 4.74 (2H, s), 5.90 (1H, d, J= 4 Hz), 6.57 (1H, d, J= 4 Hz), 7.53 (1H,
30 s), 8.43 (1H, s), 8.54 (1H, s).

MS (ESI⁺): m/z 436.

Example 409

ethyl 3-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 0.22-0.32 (2H, m), 0.54-0.63 (2H, m), 1.10-1.20 (1H, m), 1.21 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 2.40-2.50 (2H, m), 2.43 (3H, s), 2.86-2.98 (2H, m), 3.05 (2H, q, J = 7 Hz), 3.42 (2H, d, J = 7 Hz), 4.06 (2H, q, J = 7 Hz), 4.71 (2H, s), 5.92 (1H, d, J = 4 Hz), 6.60 (1H, d, J = 4 Hz), 7.52 (1H, s), 8.42 (1H, s), 8.54 (1H, s).

MS (ESI⁺): m/z 422.

10 Example 410

ethyl 3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-methoxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 2.44 (2H, t, J = 7 Hz), 2.82-2.98 (2H, m), 3.05 (2H, q, J = 7 Hz), 3.38 (3H, s), 3.58 (2H, m), 3.76 (2H, m), 4.05 (2H, q, J = 7 Hz), 4.76 (2H, s), 5.93 (1H, d, J = 4 Hz), 6.62 (1H, d, J = 4 Hz), 7.87 (1H, m), 8.54 (1H, s), 8.79 (1H, s).

MS (ESI⁺): m/z 490 492.

Example 411

20 4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine

¹H NMR (CDCl₃) δ 1.39 (3H, t, J = 7 Hz), 2.54 (3H, s), 3.04 (2H, q, J = 7 Hz), 6.39 (1H, s), 6.51 (1H, d, J = 4 Hz), 6.67 (1H, d, J = 4 Hz), 8.17 (1H, m), 8.76 (1H, d, J = 2 Hz), 8.86 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 316 318.

25

Example 412

ethyl 4-[2-[(acetyloxy)methyl]-4-(5-chloro-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (300 MHz, CDCl₃) δ 1.20 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.70 (2H, tt, J = 7, 7 Hz), 2.17 (3H, s), 2.20 (2H, t, J = 7 Hz), 2.45-2.54 (2H, m), 3.02 (2H, q, J = 7 Hz), 4.04 (2H, q, J = 7 Hz), 5.33 (2H, s), 5.94 (1H, d, J = 4 Hz), 6.63 (1H, d, J = 4 Hz), 7.74 (1H, dd, J = 2, 2 Hz), 8.53 (1H, d, J = 2 Hz), 8.70 (1H, d, J = 2 Hz).

Example 413

ethyl 5-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate

- 5 ^1H NMR (300 MHz, CDCl_3) δ 0.23-0.26 (2H, m), 0.54-0.59 (2H, m), 1.07-1.16 (1H, m), 1.23 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.41-1.56 (4H, m), 2.17 (2H, t, $J = 7$ Hz), 2.53-2.64 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.41 (2H, d, $J = 7$ Hz), 4.09 (2H, q, $J = 7$ Hz), 4.70 (2H, s), 5.90 (1H, d, $J = 5$ Hz), 6.58 (1H, d, $J = 5$ Hz), 7.72 (1H, s), 8.51 (1H, s), 8.68 (1H, s).

10

Example 414

ethyl 4-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

- 15 ^1H NMR (300 MHz, CDCl_3) δ 0.24 (2H, dt, $J = 7, 7$ Hz), 0.56 (2H, dt, $J = 7, 7$ Hz), 1.07-1.15 (1H, m), 1.20 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.72 (2H, tt, $J = 7, 7$ Hz), 2.21 (2H, t, $J = 7$ Hz), 2.55-2.66 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.43 (2H, d, $J = 7$ Hz), 4.04 (2H, q, $J = 7$ Hz), 4.73 (2H, s), 5.91 (1H, d, $J = 5$ Hz), 6.59 (1H, d, $J = 5$ Hz), 7.74 (1H, dd, $J = 2, 2$ Hz), 8.52 (1H, d, $J = 2$ Hz), 8.68 (1H, d, $J = 2$ Hz).

20

Example 415

ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

- 25 ^1H NMR (300 MHz, CDCl_3) δ 0.92 (6 H, d, $J = 7$ Hz), 1.26 (3H, t, $J = 7$ Hz), 1.34 (3H, t, $J = 7$ Hz), 1.38-1.56 (4H, m), 1.92 (1H, qt, $J = 7, 7$ Hz), 2.15 (2H, t, $J = 7$ Hz), 2.51-2.63 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.33 (2H, d, $J = 7$ Hz), 4.09 (2H, q, $J = 7$ Hz), 4.65 (2H, s), 5.90 (1H, d, $J = 7$ Hz), 6.59 (1H, d, $J = 7$ Hz), 7.88 (1H, dd, $J = 2, 2$ Hz), 8.55 (1H, d, $J = 2$ Hz), 8.77 (1H, d, $J = 2$ Hz).

30 Example 416

ethyl 3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

- ^1H NMR (300 MHz, CDCl_3) δ 0.92 (6H, d, $J = 7$ Hz), 1.19 (3H, t, $J = 7$ Hz), 1.37 (3H,

t, J = 7 Hz), 1.91 (1H, qt, J = 7, 7 Hz), 2.41 (2H, t, J = 8 Hz), 2.84-2.94 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.35 (2H, d, J = 7 Hz), 4.05 (2H, q, J = 7 Hz), 4.68 (2H, s), 5.92 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.72 (1H, dd, J = 2, 2 Hz), 8.51 (1H, d, J = 2 Hz), 8.69 (1H, d, J = 2 Hz).

5

Example 417

ethyl 3-[2-[(acetyloxy)methyl]-4-(3-chlorophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (300 MHz, CDCl₃) δ 1.19 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 2.15 (3H, s), 2.33 (2H, t, J = 8 Hz), 2.82 (2H, t, J = 8 Hz), 3.02 (2H, q, J = 7 Hz), 4.06 (2H, q, J = 7 Hz), 5.31 (2H, s), 5.97 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.23-7.26 (1H, m), 7.37 (1H, s), 7.44-7.46 (2H, m).

10

Example 418

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (300 MHz, CDCl₃) δ 0.92 (6H, d, J = 7 Hz), 1.20 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.71 (2H, tt, J = 8, 8 Hz), 1.91 (1H, qt, J = 7, 7 Hz), 2.20 (2H, t, J = 8 Hz), 2.56-2.66 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.34 (2H, d, J = 7 Hz), 4.05 (2H, q, J = 7 Hz), 4.69 (2H, s), 5.91 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.89 (1H, s), 8.56 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

20

Example 419

2,4-bis(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazine

¹H NMR (CDCl₃) δ 1.45 (3H, t, J = 7 Hz), 3.14 (2H, q, J = 7 Hz), 6.66 (1H, d, J = 4 Hz), 6.86 (1H, d, J = 4 Hz), 6.91 (1H, s), 8.23 (1H, m), 8.48 (1H, m), 8.77 (1H, m), 8.83 (1H, m), 8.94 (1H, d, J = 2 Hz), 9.18 (1H, d, J = 2 Hz).

25

Example 420

ethyl 4-[2-[(acetyloxy)methyl]-4-(3-chlorophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J = 8 Hz), 1.34 (3H, t, J = 8 Hz), 1.63-1.76 (2H, m), 2.10-2.22 (5H, m), 2.45-2.55 (2H, m), 3.01 (2H, q, J = 8 Hz), 4.04 (2H, q, J = 8

30

Hz), 5.32 (2H, s), 5.95 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.21-7.29 (1H, overlapped with CDCl₃), 7.36 (1H, br s), 7.38-7.46 (2H, m).
MS (ESI⁺): m/z 443 (M + H).

5 Example 421

ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.33-1.60 (7H, m), 1.55-1.70 (2H, m),
2.17 (2H, t, J = 8 Hz), 2.46-2.64 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.46 (3H, s),
10 3.90 (3H, s), 4.09 (2H, q, J = 8 Hz), 4.62 (2H, s), 5.93 (1H, d, J = 5 Hz), 6.59 (1H,
d, J = 5 Hz), 7.23 (1H, m), 8.22 (1H, d, J = 1 Hz), 8.40 (1H, d, J = 3 Hz).
MS (ESI⁺): m/z 426 (M + H).

Example 422

15 ethyl 5-[7-ethyl-4-(5-methoxy-3-pyridinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.33-1.62 (7H, m), 2.18 (2H, t, J = 8 Hz),
2.38-2.49 (2H, m), 2.56 (3H, s), 3.01 (2H, q, J = 8 Hz), 3.90 (3H, s), 4.08 (2H, q,
J = 8 Hz), 5.89 (1H, d, J = 5 Hz), 6.51 (1H, d, J = 5 Hz), 7.21 (1H, m), 8.21 (1H,
20 d, J = 1 Hz), 8.40 (1H, d, J = 3 Hz).
MS (ESI⁺): m/z 396 (M + H).

Example 423

25 ethyl 3-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 8 Hz), 1.38 (3H, t, J = 8 Hz), 2.40 (2H, t, J = 8
Hz), 2.81-2.96 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.47 (3H, s), 3.90 (3H, s), 4.05
(2H, q, J = 8 Hz), 4.65 (2H, s), 5.96 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.21
(1H, m), 8.23 (1H, br s), 8.40 (1H, d, J = 3 Hz).
30 MS (ESI⁺): m/z 398 (M + H).

Example 424

ethyl 4-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-

yl]butanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 8 Hz), 1.38 (3H, t, J = 8 Hz), 1.64-1.79 (2H, m),
2.14-2.24 (2H, m), 2.53-2.66 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.47 (3H, s), 3.90
(3H, s), 4.04 (2H, q, J = 8 Hz), 4.67 (2H, br s), 5.94 (1H, d, J = 5 Hz), 6.59 (1H, d,
5 J = 5 Hz), 7.23 (1H, m), 8.22 (1H, d, J = 1 Hz), 8.40 (1H, d, J = 3 Hz).
MS (ESI⁺): m/z 412 (M + H).

Example 425

ethyl 5-[7-ethyl-2-(methoxymethyl)-4-(5-pyrimidinyl)pyrrolo[1,2-b]pyridazin-3-

10 yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.30-1.62 (7H, m), 2.19 (2H, t, J = 8 Hz),
2.46-2.60 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.47 (3H, s), 3.90 (3H, s), 4.09 (2H, q,
J = 8 Hz), 4.63 (2H, s), 5.90 (1H, d, J = 5 Hz), 6.61 (1H, d, J = 5 Hz), 8.80 (2H, s),
9.34 (1H, s).
15 MS (ESI⁺): m/z 397 (M + H).

Example 426

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-
yl]butanoate

20 ¹H NMR (CDCl₃) δ 1.21 (3H, t, J = 8 Hz), 1.37 (3H, t, J = 8 Hz), 1.62-1.76 (2H, m),
2.21 (2H, t, J = 8 Hz), 2.49-2.67 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.46 (3H, s),
4.06 (2H, q, J = 8 Hz), 4.67 (2H, br s), 5.92 (1H, d, J = 5 Hz), 6.61 (1H, d, J = 5
Hz), 7.74 (1H, m), 8.53 (1H, d, J = 1 Hz), 8.69 (1H, d, J = 2 Hz).
MS (ESI⁺): m/z 414 (M - H).

25

Example 427

ethyl 3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-
yl]propanoate

30 ¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 8 Hz), 1.38 (3H, t, J = 8 Hz), 2.40 (2H, t, J = 8
Hz), 2.82-2.94 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.47 (3H, s), 4.06 (2H, q, J = 8
Hz), 4.65 (2H, s), 5.93 (1H, d, J = 5 Hz), 6.67 (1H, d, J = 5 Hz), 7.73 (1H, br s),
8.51 (1H, br s), 8.70 (1H, br s).
MS (ESI⁺): m/z 402 (M + H).

Example 428

ethyl 5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

- 5 ^1H NMR (CDCl_3) δ 1.23 (3H, t, J = 8 Hz), 1.34-1.60 (7H, m), 2.19 (2H, t, J = 8 Hz), 2.47-2.64 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.46 (3H, s), 4.10 (2H, q, J = 8 Hz), 4.62 (2H, s), 5.90 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.73 (1H, m), 8.51 (1H, br s), 8.68 (1H, br s).

MS (ESI^+): m/z 426 (M + H).

10

Example 429

methyl 2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazine-3-carboxylate

mp 122-123 deg.

- 15 ^1H NMR (CDCl_3) δ 1.38 (3H, t, J = 8 Hz), 2.12 (3H, s), 3.06 (2H, t, J = 8 Hz), 3.61 (3H, s), 5.43 (2H, s), 6.37 (1H, d, J = 5 Hz), 6.78 (1H, d, J = 5 Hz), 7.93 (1H, t, J = 1 Hz), 8.57 (1H, d, J = 1 Hz), 8.78 (1H, d, J = 1 Hz).

MS (ESI^+): m/z 432, 434 (M + H).

20 Example 430

2-(2-{2-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]ethoxy}ethoxy)ethyl acetate

- 25 ^1H -NMR (CDCl_3) δ 1.37 (3H, t, J = 7 Hz), 2.05 (3H, s), 2.42 (3H, s), 2.59 (3H, s), 2.75 (2H, m), 3.00 (2H, q, J = 7 Hz), 3.39-3.48 (4H, m), 3.54 (2H, m), 3.63 (2H, m), 4.16 (2H, m), 5.86 (1H, d, J = 5 Hz), 6.52 (1H, d, J = 5 Hz), 7.50 (1H, m), 8.43 (1H, m), 8.52 (1H, m).

Example 431

ethyl (2E)-4-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-2-

30 butenoate

- ^1H -NMR (CDCl_3) δ 1.27 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 2.49 (3H, s), 3.02 (2H, q, J = 7 Hz), 3.30 (2H, m), 4.16 (2H, q, J = 7 Hz), 5.58 (1H, d, J = 16 Hz), 5.90 (1H, d, J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 6.97 (1H, dt, J = 7 and 16 Hz), 7.58

(2H, m), 7.65 (1H, s), 7.75 (1H, m).

Example 432

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

^1H NMR (300 MHz, CDCl_3) δ 1.23 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.65-1.78 (2H, m), 2.23 (2H, t, $J = 7$ Hz), 2.54-2.72 (2H, m), 3.04 (2H, q, $J = 7$ Hz), 3.46 (3H, s), 4.06 (2H, q, $J = 7$ Hz), 4.66 (2H, s), 5.93 (1H, d, $J = 4$ Hz), 6.62 (1H, d, $J = 4$ Hz), 7.89 (1H, m), 8.55 (1H, d, $J = 2$ Hz), 8.77 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 460 462.

Example 433

ethyl 4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylate

^1H NMR (CDCl_3) δ 0.99 (3H, t, $J = 8$ Hz), 1.38 (3H, t, $J = 8$ Hz), 2.63 (3H, s), 3.05 (2H, q, $J = 8$ Hz), 4.07 (2H, q, $J = 8$ Hz), 6.27 (1H, d, $J = 5$ Hz), 6.70 (1H, d, $J = 5$ Hz), 7.30 (1H, dd, $J = 5, 1$ Hz), 7.41 (1H, br s), 8.49 (1H, d, $J = 5$ Hz).

MS (ESI^+): m/z 344 ($M + H$).

The following compound(s) was(were) obtained in a similar manner to that of Example 76.

Example 434

4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.72-1.84 (2H, m), 2.33 (2H, t, $J = 7$ Hz), 2.47-2.57 (2H, m), 2.58 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 5.88 (1H, d, $J = 4$ Hz), 6.53 (1H, d, $J = 4$ Hz), 7.27 (1H, m), 7.38 (1H, s), 8.53 (1H, d, $J = 5$ Hz).

MS (ESI): m/z 356, MS (ESI^+): m/z 358.

Example 435

3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.36-2.47 (2H, m), 2.58 (3H, s), 2.76-2.88 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 5.89 (1H, d, $J = 4$ Hz), 6.55 (1H, d, $J = 4$ Hz), 7.25 (1H, d, $J = 5$ Hz), 7.35 (1H, s), 8.53 (1H, d, $J = 5$ Hz).

Example 436

4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

^1H NMR (CDCl_3) δ 1.24 (3H, t, $J = 7$ Hz), 1.30-1.42 (2H, m), 1.35 (9H, s), 1.63-1.76 (2H, m), 2.22-2.37 (4H, m), 3.93 (1H, d, $J = 17$ Hz), 4.12 (2H, q, $J = 7$ Hz), 4.29 (1H, d, $J = 17$ Hz), 7.22 (2H, d, $J = 8$ Hz), 7.26-7.36 (4H, m), 7.50 (1H, s), 8.42 (1H, d, $J = 5$ Hz).

MS (ESI): m/z 418, MS (ESI $^+$): m/z 420.

Example 437

3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

^1H NMR (CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 2.06 (2H, t, $J = 7$ Hz), 2.78 (2H, t, $J = 7$ Hz), 3.04 (2H, q, $J = 7$ Hz), 5.99 (1H, d, $J = 4$ Hz), 6.67 (1H, d, $J = 4$ Hz), 7.28 (1H, d, $J = 5$ Hz), 7.41 (1H, s), 7.45-7.55 (5H, m), 8.53 (1H, d, $J = 5$ Hz).

MS (ESI): m/z 404, MS (ESI $^+$): m/z 406.

Example 438

5-[2-benzyl-4-(2-chloro-4-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 1.16-1.32 (2H, m), 1.39 (3H, t, $J = 7$ Hz), 1.38-1.53 (2H, m), 2.15 (2H, t, $J = 7$ Hz), 2.30-2.40 (2H, m), 3.06 (2H, q, $J = 7$ Hz), 4.21 (2H, s), 5.88 (1H, d, $J = 4$ Hz), 6.58 (1H, d, $J = 4$ Hz), 7.18-7.35 (7H, m), 8.49 (1H, d, $J = 5$ Hz).

MS (ESI): m/z 446, MS (ESI $^+$): m/z 448.

Example 439

{2-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]ethoxy}acetic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.44 (3H, s), 2.59 (3H, s), 2.74-2.92 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.54-3.66 (2H, m), 3.93 (2H, m), 5.82 (1H, d, $J = 4$ Hz), 6.53 (1H, d, $J = 4$ Hz), 7.63 (1H, s), 8.52 (1H, s), 8.56 (1H, s).

Example 440

{2-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}acetic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.80 (2H, t, $J = 7$ Hz), 3.03 (2H, q, $J = 7$ Hz),

3.20 (2H, t, J= 7 Hz), 3.72 (3H, s), 6.01 (1H, d, J= 4 Hz), 6.67 (1H, d, J= 4 Hz),
7.42 (1H, d, J= 5 Hz), 7.45-7.60 (6H, m), 8.57 (1H, d, J= 5 Hz).

Example 441

- 5 [4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetic acid
 ^1H NMR (CDCl_3) δ 1.37 (3H, t, J= 7 Hz), 2.55 (3H, s), 2.97-3.10 (2H, m), 3.30-3.62
(2H, m), 5.97 (1H, m), 6.57 (1H, m), 8.03 (1H, s), 8.69 (1H, s), 8.77 (1H, s).
MS (ESI^+): m/z 374 376.

10 Example 442

3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}propanoic acid

- ^1H NMR (CDCl_3) δ 1.38 (3H, t, J= 7 Hz), 2.33-2.50 (2H, m), 2.42 (3H, s), 2.80-3.00
(2H, m), 3.06 (2H, q, J= 7 Hz), 4.72 (2H, s), 4.83 (2H, s), 5.92 (1H, d, J= 4 Hz),
15 6.62 (1H, d, J= 4 Hz), 7.36 (2H, d, J= 7 Hz), 7.55 (1H, s), 8.41 (1H, s), 8.44 (2H,
d, J= 7 Hz), 8.53 (1H, s).
MS (ESI^+): m/z 429 431.

Example 443

- 20 3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}propanoic acid

- ^1H NMR (CDCl_3) δ 1.38 (3H, t, J= 7 Hz), 2.42 (3H, s), 2.40-2.55 (2H, m), 2.83-3.12
(2H, m), 3.03 (2H, q, J= 7 Hz), 4.84 (2H, s), 4.91 (2H, m), 5.92 (1H, d, J= 4 Hz),
6.61 (1H, d, J= 4 Hz), 7.57 (1H, s), 8.42 (1H, s), 8.48-8.55 (3H, m), 8.76 (1H, s).
25 MS (ESI^+): m/z 432.

Example 444

3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}propanoic acid

- 30 ^1H NMR (CDCl_3) δ 1.37 (3H, t, J= 7 Hz), 2.43 (3H, s), 2.50-2.60 (2H, m), 2.88-3.05
(2H, m), 3.03 (2H, q, J= 7 Hz), 4.81 (2H, s), 4.87 (2H, s), 5.82 (1H, d, J= 4 Hz),
6.58 (1H, d, J= 4 Hz), 7.27 (1H, m), 7.48 (1H, d, J= 8 Hz), 7.56 (1H, s), 7.77 (1H,
t, J= 8 Hz), 8.43 (1H, s), 8.54 (2H, m).

Example 445

4-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

5 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.40 (3H, t, J= 7 Hz), 1.70-1.85 (2H, m), 2.16-2.31 (2H, m), 2.44 (3H, s), 2.53-2.83 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.72 (2H, s), 4.83-4.98 (2H, m), 5.92 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.30 (2H, d, J= 7 Hz), 7.57 (1H, s), 8.38-8.55 (4H, m).

MS (ESI): m/z 443, MS (ESI⁺): m/z 445.

10

Example 446

5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

15 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.38 (3H, t, J= 7 Hz), 1.40-1.63 (4H, m), 2.20 (2H, t, J= 7 Hz), 2.52-2.68 (2H, m), 3.04 (2H, q, J= 7 Hz), 4.69 (2H, s), 4.78 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.35 (2H, d, J= 6 Hz), 7.88 (1H, m), 8.54 (2H, d, J= 6 Hz), 8.55 (1H, m), 8.79 (1H, m).

Example 447

20 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

25 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.38 (3H, t, J= 7 Hz), 1.40-1.62 (4H, m), 2.17 (2H, t, J= 7 Hz), 2.50-2.67 (2H, m), 3.04 (2H, q, J= 7 Hz), 4.69 (2H, s), 4.76 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.32-7.38 (1H, m), 7.77 (1H, d, J= 8 Hz), 7.88 (1H, m), 8.55 (2H, m), 8.65 (1H, m), 8.78 (1H, m).

MS (ESI): m/z 521 523, MS (ESI⁺): m/z 523 525.

Example 448

30 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

$^1\text{H NMR (CDCl}_3\text{)}$ δ 1.37 (3H, t, J= 7 Hz), 1.48-1.67 (4H, m), 2.26 (2H, t, J= 7 Hz), 2.53-2.75 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.82 (2H, s), 4.83 (2H, s), 5.90 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.26-7.34 (1H, m), 7.53 (1H, d, J= 8 Hz), 7.75-

7.83 (1H, m), 7.87 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.62 (1H, m), 8.77 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 523 525.

5 Example 449

5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.45-1.64 (4H, m), 2.23 (2H, t, J= 7 Hz),
2.53-2.72 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.83 (2H, s), 4.87 (2H, s), 5.93 (1H, d,
10 J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.88 (1H, m), 8.53 (3H, m), 8.77 (2H, m).

MS (ESI): m/z 522 524, MS (ESI⁺): m/z 524 526.

Example 450

15 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

¹H NMR (CDCl₃) δ 1.39 (3H, t, J= 7 Hz), 1.69-1.84 (2H, m), 2.27 (2H, t, J= 7 Hz),
2.56-2.80 (2H, m), 3.02 (2H, q, J= 7 Hz), 4.73 (2H, s), 4.92 (2H, m), 5.94 (1H, d,
J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 6 Hz), 7.90 (1H, m), 8.46 (2H, d,
J= 6 Hz), 8.57 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

20 MS (ESI): m/z 507 509, MS (ESI⁺): m/z 509 511.

Example 451

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

25 ¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.66-1.83 (2H, m), 2.26 (2H, t, J= 7 Hz),
2.53-2.77 (2H, m), 3.04 (2H, q, J= 7 Hz), 4.71 (2H, s), 4.86 (2H, m), 5.92 (1H, d,
J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.33 (1H, m), 7.78 (1H, d, J= 8 Hz), 7.90 (1H, m),
8.50 (1H, m), 8.56 (1H, d, J= 2 Hz), 8.60 (1H, s), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 509 511.

30

Example 452

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

- ¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 1.70-1.85 (2H, m), 2.23-2.34 (2H, m), 2.57-2.76 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.81 (2H, s), 4.90 (2H, m), 5.91 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.28 (1H, m), 7.49 (1H, d, J= 7 Hz), 7.77 (1H, t, J= 8 Hz), 7.88 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.57 (1H, m), 8.74 (1H, d, J= 2 Hz).
- 5 MS (ESI⁺): m/z 509 511.

Example 453

4-{4-(5-bromo-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

- 10 ¹H NMR (CDCl₃) δ 0.22 (2H, m), 0.57 (2H, m), 1.07-1.22 (1H, m), 1.37 (3H, t, J= 7 Hz), 1.72-1.87 (2H, m), 2.28 (2H, t, J= 7 Hz), 2.58-2.77 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.41 (2H, d, J= 7 Hz), 4.72 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.93 (1H, m), 8.56 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).
- MS (ESI): m/z 470 472, MS (ESI⁺): m/z 472 474.

15

Example 454

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

- ¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.68-1.83 (2H, m), 2.27 (2H, t, J= 7 Hz), 2.56-2.78 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.84 (2H, s), 4.92 (2H, m), 5.94 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.91 (1H, m), 8.51 (2H, m), 8.56 (1H, d, J= 2 Hz), 8.76 (2H, m).
- 20 MS (ESI): m/z 508 510, MS (ESI⁺): m/z 510 512.

25 Example 455

3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

- ¹H NMR (CDCl₃) δ 1.39 (3H, t, J= 7 Hz), 2.38 (2H, t, J= 7 Hz), 2.83-2.98 (2H, m), 3.07 (2H, q, J= 7 Hz), 4.74 (2H, s), 4.83 (2H, s), 5.95 (1H, d, J= 4 Hz), 6.65 (1H, d, J= 4 Hz), 7.38 (2H, d, J= 6 Hz), 7.88 (1H, s), 8.43 (2H, d, J= 6 Hz), 8.55 (1H, s), 8.78 (1H, s).
- 30 MS (ESI): m/z 493 495, MS (ESI⁺): m/z 495 497.

Example 456

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-hydroxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

$^1\text{H NMR (CDCl}_3\text{)}$ δ 1.37 (3H, t, J= 7 Hz), 1.68-1.83 (2H, m), 2.28 (2H, t, J= 7 Hz),
5 2.53-2.76 (2H, m), 3.02 (2H, q, J= 7 Hz), 3.75 (2H, m), 3.79 (2H, m), 4.78 (2H, s),
5.93 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.90 (1H, s), 8.56 (1H, s), 8.78 (1H, s).

MS (ESI): m/z 460 462, MS (ESI⁺): m/z 462 464.

10 Example 457

3-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

$^1\text{H NMR (CDCl}_3\text{)}$ δ 0.88-1.06 (2H, m), 1.10-1.36 (3H, m), 1.37 (3H, t, J= 7 Hz),
1.58-1.85 (6H, m), 2.42 (3H, s), 2.48-2.60 (2H, m), 2.80-3.02 (2H, m), 3.04 (2H,
15 q, J= 7 Hz), 3.39 (2H, d, J= 7 Hz), 4.67 (2H, m), 5.89 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.57 (1H, s), 8.42 (1H, s), 8.53 (1H, s).

MS (ESI): m/z 434, MS (ESI⁺): m/z 436.

Example 458

20 3-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

$^1\text{H NMR (CDCl}_3\text{)}$ δ 0.88-1.05 (2H, m), 1.10-1.36 (3H, m), 1.37 (3H, t, J= 7 Hz),
1.56-1.83 (6H, m), 2.51 (2H, t, J= 7 Hz), 2.80-3.07 (2H, m), 3.06 (2H, q, J= 7 Hz),
3.37 (2H, d, J= 7 Hz), 4.67 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz),
25 7.89 (1H, m), 8.55 (1H, s), 8.79 (1H, s).

MS (ESI): m/z 498 500, MS (ESI⁺): m/z 500 502.

Example 459

30 4-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

$^1\text{H NMR (CDCl}_3\text{)}$ δ 0.86-1.03 (2H, m), 1.10-1.35 (3H, m), 1.37 (3H, t, J= 7 Hz),
1.60-1.82 (8H, m), 2.28 (2H, t, J= 7 Hz), 2.55-2.76 (2H, m), 3.05 (2H, q, J= 7 Hz),
3.36 (2H, d, J= 7 Hz), 4.67 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz),

7.91 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.76 (1H, d, J= 2 Hz).

MS (ESI⁻): m/z 512 514, MS (ESI⁺): m/z 514 516.

Example 460

- 5 4-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 0.22-0.32 (2H, m), 0.55-0.63 (2H, m), 1.10-1.22 (1H, m), 1.37 (3H, t, J= 7 Hz), 1.73-1.86 (2H, m), 2.20-2.35 (2H, m), 2.46 (3H, s), 2.55-2.86 (2H, m), 3.04 (2H, q, J= 7 Hz), 3.43 (2H, d, J= 7 Hz), 4.70-4.85 (2H, m), 5.88 (1H, d, J= 4 Hz), 6.57 (1H, d, J= 4 Hz), 7.62 (1H, s), 8.42 (1H, s), 8.46 (1H, s).
10 MS (ESI⁺): m/z 408.

Example 461

- 3-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid
15

¹H NMR (CDCl₃) δ 0.23-0.35 (2H, m), 0.54-0.65 (2H, m), 1.08-1.24 (1H, m), 1.37 (3H, t, J= 7 Hz), 2.43 (3H, s), 2.50-2.65 (2H, m), 2.70-3.05 (2H, m), 3.04 (2H, q, J= 7 Hz), 3.44 (2H, d, J= 7 Hz), 4.74 (2H, s), 5.89 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4 Hz), 7.56 (1H, s), 8.42 (1H, s), 8.53 (1H, s).
20 MS (ESI⁻): m/z 392, MS (ESI⁺): m/z 394.

Example 462

- 3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-methoxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

25 ¹H NMR (CDCl₃) δ 1.37 (3H, t, J= 7 Hz), 2.48-2.62 (2H, m), 2.83-3.02 (2H, m), 3.02 (2H, q, J= 7 Hz), 3.37 (3H, s), 3.60 (2H, m), 3.73 (2H, m), 4.75 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁻): m/z 460 462, MS (ESI⁺): m/z 462 464.

30

Example 463

- 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[[4-(morpholinylcarbonyl)oxy]methyl]pyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.35-1.65 (4H, m), 2.23 (2H, t, $J = 7$ Hz), 2.40-2.56 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.48-3.57 (4H, m), 3.60-3.78 (4H, m), 5.33 (2H, s), 5.93 (1H, d, $J = 4$ Hz), 6.62 (1H, d, $J = 4$ Hz), 7.89 (1H, m), 8.56 (1H, d, $J = 2$ Hz), 8.79 (1H, d, $J = 2$ Hz).

5

Example 464

5-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H NMR (CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 1.45-1.65 (4H, m), 2.22 (2H, t, $J = 7$ Hz), 2.42-2.57 (2H, m), 2.97 (6H, s), 3.03 (2H, q, $J = 7$ Hz), 5.30 (2H, s), 5.93 (1H, d, $J = 4$ Hz), 6.62 (1H, d, $J = 4$ Hz), 7.89 (1H, s), 8.54 (1H, s), 8.78 (1H, s).

10

MS (ESI^+): m/z 503 505.

Example 465

15 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-{{[(1-pyrrolidinylcarbonyl)oxy]methyl}pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

^1H NMR (CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 1.40-1.63 (4H, m), 1.82-1.97 (4H, m), 2.23 (2H, t, $J = 7$ Hz), 2.43-2.58 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.37-3.52 (4H, m), 5.31 (2H, s), 5.93 (1H, d, $J = 4$ Hz), 6.60 (1H, d, $J = 4$ Hz), 7.88 (1H, m), 8.54 (1H, d, $J = 2$ Hz), 8.78 (1H, d, $J = 2$ Hz).

20

MS (ESI): m/z 527 529, MS (ESI^+): m/z 529 531.

Example 466

5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-

25 [({[methyl(phenyl)amino]carbonyl}oxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 1.40-1.58 (4H, m), 2.18 (2H, t, $J = 7$ Hz), 2.32-2.53 (2H, m), 3.04 (2H, q, $J = 7$ Hz), 3.37 (3H, s), 5.36 (2H, s), 5.92 (1H, d, $J = 4$ Hz), 6.63 (1H, d, $J = 4$ Hz), 7.16-7.40 (5H, m), 7.87 (1H, s), 8.52 (1H, s), 8.79 (1H, s).

30

Example 467

4-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-{{[(4-morpholinylcarbonyl)oxy]methyl}pyrrolo[1,2-

b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.65-1.84 (2H, m), 2.27 (2H, t, J = 7 Hz),
2.45-2.68 (2H, m), 3.04 (2H, q, J = 7 Hz), 3.53 (4H, m), 3.69 (4H, m), 5.36 (2H, s),
5.95 (1H, d, J = 4 Hz), 6.63 (1H, d, J = 4 Hz), 7.91 (1H, m), 8.55 (1H, d, J = 2 Hz),
8.78 (1H, d, J = 2 Hz).

Example 468

4-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 1.66-1.82 (2H, m), 2.27 (2H, t, J = 7 Hz),
2.46-2.68 (2H, m), 2.97 (6H, s), 3.04 (2H, q, J = 7 Hz), 5.33 (2H, s), 5.94 (1H, d,
J = 4 Hz), 6.62 (1H, d, J = 4 Hz), 7.92 (1H, m), 8.56 (1H, d, J = 2 Hz), 8.78 (1H, d,
J = 2 Hz).

Example 469

3-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

¹H NMR (CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 2.45 (2H, t, J = 7 Hz), 2.82-2.96 (2H, m),
2.97 (6H, s), 3.03 (2H, q, J = 7 Hz), 5.33 (2H, s), 5.96 (1H, d, J = 4 Hz), 6.63 (1H,
d, J = 4 Hz), 7.89 (1H, m), 8.55 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

MS (ESI): m/z 473 475, MS (ESI⁺): m/z 475 477.

Example 470

5-{4-(5-bromo-3-pyridinyl)-2-[(1,1-dioxido-4-thiomorpholinyl)methyl]-7-

ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 1.42-1.56 (4H, m), 2.26 (2H, t,
J = 7 Hz), 2.48-2.61 (2H, m), 3.01 (2H, q, J = 7 Hz), 3.10 (4H, t, J = 6 Hz), 3.19
(4H, t, J = 6 Hz), 3.85 (2H, s), 5.92 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.89
(1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

MS (m/z) 550 (M+H).

Example 471

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-

3-yl]pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.43-1.58 (4H, m), 2.24 (2H, t, J = 7 Hz), 2.49-2.61 (2H, m), 2.66 (4H, t, J = 4 Hz), 2.86 (4H, t, J = 4 Hz), 3.02 (2H, q, J = 7 Hz), 3.68 (2H, s), 5.89 (1H, d, J = 5 Hz), 6.58 (1H, d, J = 5 Hz), 7.90 (1H, s), 8.56 (1H, s), 8.79 (1H, s).
MS (m/z) 518 (M+H).

Example 472

5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.34 (3H, t, J = 7 Hz), 1.41-1.57 (4H, m), 2.21 (2H, t, J = 6 Hz), 2.43-2.57 (2H, m), 2.80-2.84 (4H, m), 2.91-3.00 (6H, m), 3.65 (2H, s), 3.83 (2H, m), 5.88 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz), 7.88 (1H, s), 8.55 (1H, s), 8.77 (1H, s).
MS (m/z) 545 (M+H).

Example 473

4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid
¹H NMR (300 MHz, CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.72 (2H, tt, J = 7, 7 Hz), 2.26 (2H, t, J = 7 Hz), 2.53-2.68 (6H, m), 2.87-2.90 (4H, m), 3.02 (2H, q, J = 7 Hz), 3.72 (2H, s), 5.91 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.78 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.68 (1H, d, J = 2 Hz).
MS (m/z) 460 (M+H).

Example 474

4-{4-(5-chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid
¹H NMR (300 MHz, CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 1.73 (2H, tt, J = 7, 7 Hz), 2.25 (2H, t, J = 7 Hz), 2.57-2.73 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.72 (2H, s), 4.89 (2H, s), 5.93 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 7.31 (2H, d, J = 6 Hz), 7.76 (1H, dd, J = 2, 2 Hz), 8.46 (2H, d, J = 6 Hz), 8.53 (1H, d, J = 2 Hz), 8.67 (1H, d, J = 2 Hz).

MS (m/z) 465 (M+H).

Example 475

4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.73 (2H, tt, J = 7, 7 Hz), 2.26 (2H, t, J = 7 Hz), 2.54-2.72 (6H, m), 3.03 (2H, q, J = 7 Hz), 3.66-3.73 (6H, m), 5.90 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.79 (1H, s), 8.53 (1H, s), 8.67 (1H, s).

MS (m/z) 443 (M+H).

Example 476

5-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 0.24 (2H, dt, J = 7, 7 Hz), 0.57 (2H, dt, J = 7, 7 Hz), 1.07-1.17 (1H, m), 1.38 (3H, t, J = 7 Hz), 1.45-1.61 (4H, m), 2.23 (2H, t, J = 7 Hz), 2.52-2.66 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.41 (2H, d, J = 7 Hz), 4.70 (2H, s), 5.90 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.74 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.68 (1H, d, J = 2 Hz).

MS (m/z) 442 (M+H).

Example 477

4-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

¹H NMR (300 MHz, CDCl₃) δ 0.23 (2H, dt, J = 6, 6 Hz), 0.56 (2H, dt, J = 6, 6 Hz), 1.05-1.17 (1H, m), 1.37 (3H, t, J = 7 Hz), 1.75 (2H, tt, J = 7, 7 Hz), 2.28 (2H, t, J = 7 Hz), 2.57-2.70 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.42 (2H, d, J = 7 Hz), 4.73 (2H, s), 5.91 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.77 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.66 (1H, d, J = 2 Hz).

MS (m/z) 428 (M+H).

Example 478

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-

yl]pentanoic acid

- ¹H NMR (300 MHz, CDCl₃) δ 0.93 (6H, d, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.42-1.59 (4H, m), 1.92 (1H, qt, J = 7, 7 Hz), 2.24 (2H, t, J = 7 Hz), 2.48-2.69 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.33 (2H, d, J = 7 Hz), 4.66 (2H, s), 5.91 (1H, d, J = 4 Hz), 6.60 (1H, d, J = 4 Hz), 7.90 (1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.77 (1H, d, J = 2 Hz).
- MS (m/z) 489 (M+H).

Example 479

- 3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

- ¹H NMR (300 MHz, CDCl₃) δ 0.92 (6H, d, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.91 (1H, qt, J = 7, 7 Hz), 2.49 (2H, t, J = 8 Hz), 2.82-2.98 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.35 (2H, d, J = 7 Hz), 4.69 (2H, s), 5.92 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.72 (1H, dd, J = 2, 2 Hz), 8.51 (1H, d, J = 2 Hz), 8.69 (1H, d, J = 2 Hz).
- MS (m/z) 416 (M+H).

Example 480

- 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

- ¹H NMR (300 MHz, CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 2.55 (2H, t, J = 8 Hz), 2.66 (4H, br s), 2.79-2.97 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.70-3.74 (6H, m), 5.92 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.90 (1H, dd, J = 2, 2 Hz), 8.55 (1H, d, J = 2 Hz), 8.79 (1H, d, J = 2 Hz).
- MS (m/z) 474 (M+H).

Example 481

- 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

- ¹H NMR (300 MHz, CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 1.73 (2H, tt, J = 7, 7 Hz), 2.26 (2H, t, J = 7 Hz), 2.57-2.70 (6H, m), 3.02 (2H, q, J = 7 Hz), 3.69 (6H, m), 5.90 (1H, d, J = 4 Hz), 6.58 (1H, d, J = 4 Hz), 7.93 (1H, dd, J = 2, 2 Hz), 8.57 (1H, d, J = 2 Hz), 8.77 (1H, d, J = 2 Hz).

MS (m/z) 488 (M+H).

Example 482

4-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylamino)methyl]-7-ethylpyrrolo[1,2-

5 b]pyridazin-3-yl}butanoic acid

¹H NMR (300 MHz, CDCl₃) δ 0.54-0.60 (2H, m), 0.74-0.79 (2H, m), 1.38 (3H, t, J = 7 Hz), 1.65 (2H, tt, J = 6, 6 Hz), 2.21 (2H, t, J = 6 Hz), 2.45-2.55 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.30 (2H, s), 5.04 (1H, br s), 5.93 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.73 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.69 (1H, d, J = 2 Hz).

MS (m/z) 413 (M+H).

Example 483

5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-phenoxyethyl)amino]methyl)pyrrolo[1,2-

15 b]pyridazin-3-yl}pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 1.42-1.56 (4H, m), 2.22 (2H, br s), 2.34-2.48 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.38-3.43 (2H, br s), 4.23-4.50 (4H, m), 5.93 (1H, d, J = 4 Hz), 6.60 (1H, d, J = 4 Hz), 6.89-6.97 (3H, m), 7.23-7.30 (2H, m), 7.85 (1H, s), 8.52 (1H, s), 8.78 (1H, s).

MS (m/z) 552 (M+H).

Example 484

5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-

hydroxyethyl)(methyl)amino]methyl)pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 1.34-1.54 (4H, m), 2.15-2.26 (2H, m), 2.33-2.52 (2H, m), 2.98 (2H, q, J = 7 Hz), 3.16 (3H, s), 3.59-3.72 (2H, m), 3.99-4.10 (2H, m), 4.70 (2H, s), 5.94 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.85 (1H, s), 8.51 (1H, s), 8.73 (1H, s).

MS (m/z) 490 (M+H).

Example 485

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(1-piperidinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

^1H NMR (300 MHz, CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 1.39-1.51 (6H, m), 1.62-1.71 (4H, m), 2.19 (2H, t, $J = 6$ Hz), 2.52-2.65 (2H, m), 2.78-2.91 (4H, m), 3.10 (2H, q, $J = 7$ Hz), 3.65 (2H, s), 5.89 (1H, d, $J = 5$ Hz), 6.58 (1H, d, $J = 5$ Hz), 7.88 (1H, s), 8.55 (1H, s), 8.76 (1H, s).

5 MS (m/z) 500 (M+H).

Example 486

3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

10 ^1H NMR (300 MHz, CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.52 (2H, t, $J = 8$ Hz), 2.68 (4H, t, $J = 5$ Hz), 2.81-2.95 (6H, m), 3.02 (2H, q, $J = 7$ Hz), 3.74 (2H, s), 5.92 (1H, d, $J = 5$ Hz), 6.61 (1H, d, $J = 5$ Hz), 7.89 (1H, dd, $J = 2, 2$ Hz), 8.55 (1H, d, $J = 2$ Hz), 8.79 (1H, d, $J = 2$ Hz).

MS (m/z) 490 (M+H).

15

Example 487

3-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[[4-(2-hydroxyethyl)-1-piperazinyl]methyl]pyrrolo[1,2-b]pyridazin-3-yl)propanoic acid

20 ^1H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, t, $J = 7$ Hz), 2.40-2.56 (12H, m), 2.58-2.65 (2H, m), 2.94 (2H, q, $J = 7$ Hz), 3.52 (2H, t, $J = 5$ Hz), 3.67 (2H, s), 5.83 (1H, d, $J = 5$ Hz), 6.62 (1H, d, $J = 5$ Hz), 8.25 (1H, dd, $J = 2, 2$ Hz), 8.63 (1H, d, $J = 2$ Hz), 8.86 (1H, d, $J = 2$ Hz).

MS (m/z) 517 (M+H).

25 Example 488

4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

30 ^1H NMR (300 MHz, CDCl_3) δ 0.91 (6H, d, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.74 (2H, tt, $J = 8, 8$ Hz), 1.91 (1H, qt, $J = 7, 7$ Hz), 2.27 (2H, t, $J = 8$ Hz), 2.56-2.73 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.33 (2H, d, $J = 7$ Hz), 4.68 (2H, s), 5.92 (1H, d, $J = 5$ Hz), 6.60 (1H, d, $J = 5$ Hz), 7.92 (1H, dd, $J = 7, 7$ Hz), 8.56 (1H, d, $J = 2$ Hz), 8.77 (1H, d, $J = 2$ Hz).

MS (m/z) 475 (M+H).

Example 489

5-[2-{[2-(benzylamino)-2-oxoethoxy]methyl}-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

5 ^1H NMR (CDCl_3) δ 1.33 (3H, t, $J = 7$ Hz), 1.39-1.60 (4H, m), 2.15 (2H, t, $J = 7$ Hz), 2.42 (3H, s), 2.40-2.58 (2H, m), 2.95 (2H, q, $J = 7$ Hz), 4.19 (2H, s), 4.50 (2H, d, $J = 7$ Hz), 4.75 (2H, m), 5.91 (1H, d, $J = 4$ Hz), 6.59 (1H, d, $J = 4$ Hz), 7.07 (1H, br), 7.22-7.34 (5H, m), 7.54 (1H, s), 8.40 (1H, s), 8.53 (1H, s).

MS (ESI): m/z 513, MS (ESI $^+$): m/z 515.

10

Example 490

5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[phenylsulfonyl]amino]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoic acid

15 ^1H NMR (CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 1.23-1.60 (4H, m), 2.19 (2H, t, $J = 7$ Hz), 2.28-2.46 (2H, m), 2.42 (3H, s), 2.97 (2H, q, $J = 7$ Hz), 4.37 (2H, m), 5.89 (1H, d, $J = 4$ Hz), 5.90 (1H, m), 6.57 (1H, d, $J = 4$ Hz), 7.42-7.53 (4H, m), 7.90 (2H, d, $J = 8$ Hz), 8.34 (1H, s), 8.53 (1H, s).

MS (ESI): m/z 505, MS (ESI $^+$): m/z 507.

20 Example 491

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(1-pyrrolidinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

25 ^1H NMR (300 MHz, CDCl_3) δ 1.35 (3H, t, $J = 7$ Hz), 1.39-1.57 (4H, m), 1.79-1.88 (4H, m), 2.18 (2H, t, $J = 7$ Hz), 2.84-2.89 (6H, m), 3.00 (2H, q, $J = 7$ Hz), 3.89-4.02 (2H, m), 5.88 (1H, d, $J = 5$ Hz), 6.56 (1H, d, $J = 5$ Hz), 7.87 (1H, s), 8.55 (1H, s), 8.75 (1H, s).

MS (m/z) 486 (M+H).

Example 492

30 3-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 8$ Hz), 2.39-2.48 (2H, m), 2.83-2.94 (2H, m), 3.03 (2H, q, $J = 8$ Hz), 3.45 (3H, s), 4.65 (2H, s), 5.95 (1H, d, $J = 5$ Hz), 6.60 (1H,

d, J = 5 Hz), 7.24 (1H, m), 7.35 (1H, br s), 7.40-7.46 (2H, m).

MS (ESI⁺): m/z 373 (M + H).

Example 493

- 5 4-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H NMR (CDCl₃) δ 1.37 (3H, t, J = 8 Hz), 1.64-1.78 (2H, m), 2.24 (2H, t, J = 8 Hz),
2.56-2.66 (2H, m), 3.04 (2H, q, J = 8 Hz), 3.45 (3H, s), 4.65 (2H, s), 5.94 (1H, d,
J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.21-7.29 (1H, overlapped with CDCl₃), 7.36
10 (1H, br s), 7.39-7.46 (2H, m).

MS (ESI⁺): m/z 387 (M + H).

Example 494

- 15 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-phenyl-1-piperazinyl)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.41-1.61 (4H, m), 2.22 (2H, t,
J = 7 Hz), 2.49-2.67 (2H, m), 2.76 (4H, t, J = 5 Hz), 3.03 (2H, q, J = 7 Hz), 3.20
(4H, t, J = 5 Hz), 3.73 (2H, s), 5.89 (1H, d, J = 5 Hz), 6.58 (1H, d, J = 5 Hz), 6.85
(1H, dd, J = 8, 8 Hz), 6.93 (2H, J = 8 Hz), 7.25 (2H, J = 8 Hz), 7.90 (1H, dd, J = 2,
20 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.77 (1H, d, J = 2 Hz).

Example 495

- 25 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-methoxyethyl)amino]methyl)pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.28 (3H, t, J = 7 Hz), 1.32-1.43 (4H, m), 2.03-2.17
(2H, m), 2.23-2.41 (2H, m), 2.49-2.88 (2H, m), 2.98 (2H, q, J = 7 Hz), 3.37 (3H,
s), 3.89-3.99 (2H, m), 4.51 (2H, s), 5.91 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz),
7.82 (1H, s), 8.47 (1H, s), 8.72 (1H, s).

- 30 Example 496

5-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

mp 111-112°C

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 8$ Hz), 1.41-1.60 (4H, m), 2.21 (2H, br t, $J = 8$ Hz), 2.30-2.70 (2H, m), 3.04 (2H, d, $J = 8$ Hz), 3.46 (3H, s), 3.90 (3H, s), 4.63 (2H, br d, $J = 5$ Hz), 5.92 (1H, d, $J = 5$ Hz), 6.58 (2H, d, $J = 8$ Hz), 7.25 (1H, m), 8.22 (1H, d, $J = 1$ Hz), 8.40 (1H, d, $J = 3$ Hz).

5 MS (ESI^+): m/z 398 ($M + H$).

Example 497

5-[7-ethyl-4-(5-methoxy-3-pyridinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 mp 133-134°C

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 8$ Hz), 1.40-1.62 (7H, m), 2.24 (2H, t, $J = 8$ Hz), 2.35-2.49 (2H, m), 2.56 (3H, s), 3.01 (2H, q, $J = 8$ Hz), 3.89 (3H, s), 5.87 (1H, d, $J = 5$ Hz), 6.51 (1H, d, $J = 5$ Hz), 7.23 (1H, m), 8.20 (1H, d, $J = 1$ Hz), 8.39 (1H, d, $J = 3$ Hz).

15 MS (ESI^+): m/z 369 ($M + H$).

Example 498

3-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

20 mp 164-165°C

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 8$ Hz), 2.44-2.54 (2H, m), 2.80-3.00 (2H, m), 3.04 (2H, d, $J = 8$ Hz), 3.47 (3H, s), 3.89 (3H, s), 4.66 (2H, br s), 5.95 (1H, d, $J = 5$ Hz), 6.60 (1H, d, $J = 5$ Hz), 7.25 (1H, m), 8.22 (1H, d, $J = 1$ Hz), 8.38 (1H, d, $J = 3$ Hz).

25 MS (ESI^+): m/z 370 ($M + H$).

Example 499

4-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

30 mp 140-141°C

^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 8$ Hz), 1.68-1.82 (2H, m), 2.25 (2H, t, $J = 8$ Hz), 2.52-2.75 (2H, m), 3.04 (2H, d, $J = 8$ Hz), 3.46 (3H, s), 3.92 (3H, s), 4.65 (2H, br

d, J = 7 Hz), 5.94 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.29 (1H, m), 8.23 (1H, d, J = 1 Hz), 8.37 (1H, d, J = 3 Hz).

MS (ESI⁺): m/z 384 (M + H).

5 Example 500

5-[7-ethyl-2-(methoxymethyl)-4-(5-pyrimidinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 1.40-1.64 (4H, m), 2.25 (2H, t, J = 8 Hz), 2.49-2.61 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.47 (3H, s), 4.65 (2H, s), 5.91 (1H, d, J = 5 Hz), 6.62 (1H, d, J = 5 Hz), 8.82 (2H, s), 9.32 (1H, s).

MS (ESI⁺): m/z 369 (M + H).

Example 501

15 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

mp 112-113°C

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 1.66-1.79 (2H, m), 2.28 (2H, t, J = 8 Hz), 2.52-2.71 (2H, m), 3.05 (2H, d, J = 8 Hz), 3.46 (3H, s), 4.66 (2H, br s), 5.92 (1H, d, J = 5 Hz), 6.61 (1H, d, J = 5 Hz), 7.77 (1H, m), 8.53 (1H, d, J = 1 Hz), 8.67 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 388 (M + H).

Example 502

25 3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

mp 159-160°C

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 2.47 (2H, br t, J = 8 Hz), 2.79-2.98 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.47 (3H, s), 4.66 (2H, s), 5.93 (1H, d, J = 5 Hz), 6.67 (1H, d, J = 5 Hz), 7.74 (1H, m), 8.51 (1H, d, J = 1 Hz), 8.68 (1H, d, J = 3 Hz).

30 MS (ESI⁺): m/z 374, 376 (M + H).

Example 503

5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-

yl]pentanoic acid

mp 118-119°C

¹H NMR (CDCl₃) δ 1.37 (3H, t, J = 8 Hz), 1.40-1.62 (7H, m), 2.24 (2H, t, J = 8 Hz),
2.45-2.64 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.45 (3H, s), 4.63 (2H, s), 5.91 (1H, d,
5 J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.74 (1H, m), 8.51 (1H, d, J = 1 Hz), 8.67 (1H,
d, J = 2 Hz).
MS (ESI⁺): m/z 402, 404 (M + H).

Example 504

10 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4H-1,2,4-triazol-4-ylmethyl)pyrrolo[1,2-
b]pyridazin-3-yl]butanoic acid

¹H-NMR (CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 1.60 (2H, m), 2.32 (2H, m), 2.46 (2H, m),
3.01 (2H, q, J = 7 Hz), 5.75 (2H, m), 5.97 (1H, d, J = 5 Hz), 6.66 (1H, d, J = 5
Hz), 7.87 (1H, m), 7.97 (1H, s), 8.53 (1H, s), 8.65 (1H, s), 8.69 (1H, s).

15

Example 505

4-{4-(5-bromo-3-pyridinyl)-2-[(cyclopropylamino)methyl]-7-ethylpyrrolo[1,2-
b]pyridazin-3-yl}butanoic acid

¹H-NMR (CDCl₃) δ 0.56 (2H, m), 0.75 (2H, m), 1.38 (3H, t, J = 7 Hz), 1.65 (2H, m),
20 2.21 (2H, m), 2.50 (2H, m), 3.01 (2H, q, J = 7 Hz), 3.27 (3H, br), 4.29 (2H, s),
5.93 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.98 (1H, m), 8.55 (1H, m), 8.78
(1H, m).

MS (ESI⁺) m/z: 457 and 459 (M + H)

25 Example 506

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-oxo-1,3-oxazolidin-3-yl)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}butanoic acid

¹H-NMR (CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.68 (2H, m), 2.31 (2H, m), 2.53 (2H, m),
2.98 (2H, q, J = 7 Hz), 3.77 (2H, m), 4.42 (2H, t, J = 7 Hz), 4.67 (2H, m), 5.94
30 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 7.89 (1H, m), 8.55 (1H, m), 8.78 (1H, m).

Example 507

2-bromo-4-[3-(ethoxycarbonyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzoic

acid

$^1\text{H-NMR}$ (CDCl_3) δ 1.00 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 2.62 (3H, s), 3.04 (2H, q, $J = 7$ Hz), 4.06 (2H, q, $J = 7$ Hz), 6.29 (1H, d, $J = 5$ Hz), 6.68 (1H, d, $J = 5$ Hz), 7.49 (2H, dd, $J = 2$ and 8 Hz), 7.82 (1H, d, $J = 2$ Hz), 8.07 (1H, d, $J = 8$ Hz).

5 MS (ESI^+) m/z : 431 and 433 ($M + H$)

Example 508

5-[4-(3-cyanophenyl)-7-ethyl-2-(phenoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

10 $^1\text{H-NMR}$ (CDCl_3) δ 1.25-1.49 (7H, m), 2.15 (2H, m), 2.54 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 5.23 (2H, s), 5.86 (1H, d, $J = 5$ Hz), 6.60 (1H, d, $J = 5$ Hz), 6.98 (1H, t, $J = 8$ Hz), 7.06 (2H, d, $J = 8$ Hz), 7.28 (2H, t, $J = 8$ Hz), 7.60 (2H, m), 7.67 (1H, s), 7.77 (1H, m).

15 Example 509

5-[4-(3-cyanophenyl)-7-ethyl-2-(3-methyl-2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

$^1\text{H-NMR}$ (CDCl_3) δ 1.14-1.28 (4H, m), 1.37 (3H, t, $J = 7$ Hz), 2.01 (2H, t, $J = 7$ Hz), 2.23 (3H, s), 2.40 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 5.92 (1H, d, $J = 5$ Hz), 6.64 (1H, d, $J = 5$ Hz), 6.94 (1H, d, $J = 5$ Hz), 7.33 (1H, d, $J = 5$ Hz), 7.57-7.66 (2H, m), 7.73-7.76 (2H, m).

Example 510

(2E)-4-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-2-butenic acid

25 $^1\text{H-NMR}$ (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 2.55 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 3.09 (2H, d, $J = 7$ Hz), 5.45 (1H, dt, $J = 7$ and 16 Hz), 6.05 (1H, d, $J = 5$ Hz), 6.25 (1H, d, $J = 16$ Hz), 6.57 (1H, d, $J = 5$ Hz), 7.55 (1H, t, $J = 8$ Hz), 7.66+-7.72 (3H, m).

MS (ESI^+): m/z 345 ($M+H$)

30 Example 511

4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

$^1\text{H NMR}$ (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.68-1.84 (2H, m), 2.28 (2H, t, $J = 7$ Hz),

2.56-2.74 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.46 (3H, s), 4.66 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.92 (1H, m), 8.57 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 430 432, MS (ESI⁺): m/z 432 434.

5

The following compound(s) was(were) obtained in a similar manner to that of Example 159.

Example 512

ethyl 4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

10 ¹H NMR (CDCl₃) δ 1.26 (3H, t, J= 7 Hz), 1.36 (3H, t, J= 7 Hz), 1.35-1.45 (2H, m), 1.88 (2H, t, J= 7 Hz), 2.43-2.55 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.12 (2H, q, J= 7 Hz), 5.98 (1H, d, J= 4 Hz), 6.65 (1H, d, J= 4 Hz), 7.33 (1H, d, J= 5 Hz), 7.42-7.55 (6H, m), 8.55 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 448.

15

Example 513

ethyl 3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

20 ¹H NMR (CDCl₃) δ 1.09 (3H, t, J= 7 Hz), 1.36 (3H, t, J= 7 Hz), 1.98-2.08 (2H, m), 2.75-2.85 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.92 (2H, q, J= 7 Hz), 6.00 (1H, d, J= 4 Hz), 6.67 (1H, d, J= 4 Hz), 7.32 (1H, d, J= 5 Hz), 7.42 (1H, s), 7.43-7.57 (5H, m), 8.55 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 434.

25 Example 514

methyl {2-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]ethoxy}acetate

30 ¹H NMR (CDCl₃) δ 1.36 (3H, t, J= 7 Hz), 2.73-2.85 (2H, t, J= 7 Hz), 3.03 (2H, t, J= 7 Hz), 3.15 (2H, t, J= 7 Hz), 3.74 (2H, s), 4.09 (3H, s), 6.02 (1H, d, J= 4 Hz), 6.67 (1H, d, J= 4 Hz), 7.39 (1H, m), 7.42-7.60 (6H, m), 8.53 (1H, d, J= 5 Hz).

MS (ESI⁺): m/z 450.

Example 515

ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(3-methyl-2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H-NMR (CDCl₃) δ 1.09-1.26 (7H, m), 1.36 (3H, t, J = 7 Hz), 1.93 (2H, t, J = 7 Hz), 2.23 (3H, s), 2.39 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.03 (2H, q, J = 7 Hz), 5.93 (1H, d, J = 5 Hz), 6.64 (1H, d, J = 7 Hz), 6.96 (1H, d, J = 5 Hz), 7.33 (1H, d, J = 5 Hz), 7.60-7.67 (2H, m), 7.72-7.79 (2H, m).

Example 516

10 methyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H-NMR (CDCl₃) δ 1.21-1.47 (7H, m), 2.04 (2H, t, J = 7 Hz), 2.60 (2H, m), 3.05 (2H, q, J = 7 Hz), 3.61 (3H, s), 5.37 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 7.13 (1H, m), 7.36 (1H, m), 7.44 (1H, m), 7.62-7.78 (4H, m).

15 Example 517

ethyl 3-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H-NMR (CDCl₃) δ 1.08 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.98 (2H, m), 2.75 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.89 (2H, q, J = 7 Hz), 5.93 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 7.41-7.55 (5H, m), 7.57-7.78 (4H, m).

20 MS (ESI⁺): m/z 424 (M + H)

Example 518

ethyl 5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

25 ¹H-NMR (CDCl₃) δ 1.02-1.25 (7H, m), 1.37 (3H, t, J = 7 Hz), 1.88 (2H, t, J = 7 Hz), 2.43 (2H, m), 3.01 (2H, q, J = 7 Hz), 4.00 (2H, q, J = 7 Hz), 5.96 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.29 (1H, m), 7.37-7.54 (8H, m).

MS (ESI⁺): m/z 461

Example 519

30 4-(5-bromo-3-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazine-3-carbonitrile

¹H NMR (CDCl₃) δ 1.42 (3H, t, J = 8 Hz), 3.12 (2H, t, J = 8 Hz), 6.65 (1H, d, J = 5 Hz), 6.94 (1H, d, J = 5 Hz), 7.51-7.59 (3H, m), 7.83-7.91 (2H, m), 8.19 (1H, m), 8.85-8.92 (2H, m).

MS (ESI⁺): m/z 403, 405 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of Example 175.

5 Example 520

5-{4-(3-cyanophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.36-1.57 (4H, m), 2.16 (2H, t, J= 7 Hz),
2.51-2.62 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.69 (2H, s), 4.78 (2H, s), 5.87 (1H, d,
10 J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.35 (2H, d, J= 5 Hz), 7.61 (2H, d, J= 5 Hz), 7.67
(1H, s), 7.77 (1H, m), 8.54 (2H, d, J= 5 Hz).

MS (ESI): m/z 467, MS (ESI⁺): m/z 469.

Example 521

15 5-{4-[3-(aminocarbonyl)phenyl]-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.47-1.68 (4H, m), 2.15-2.40 (2H, m),
2.40-2.56 (1H, m), 2.82-2.96 (1H, m), 3.05 (2H, q, J= 7 Hz), 4.68 (2H, s), 4.72
(1H, d, J= 17 Hz), 4.93 (1H, d, J= 17 Hz), 5.83 (1H, d, J= 4 Hz), 6.58 (1H, d, J= 4
20 Hz), 7.31 (2H, d, J= 5 Hz), 7.39 (1H, br), 7.45 (1H, d, J= 8 Hz), 7.58 (1H, t, J= 8
Hz), 7.69 (1H, br), 7.77 (1H, br), 7.98 (1H, d, J= 8 Hz), 8.57 (2H, d, J= 5 Hz).

MS (ESI): m/z 485, MS (ESI⁺): m/z 487.

Example 522

25 5-{4-(3-cyanophenyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J= 7 Hz), 1.30-1.57 (4H, m), 2.18 (2H, m), 2.48-2.65
(2H, m), 3.03 (2H, q, J= 7 Hz), 4.83 (2H, s), 4.85 (2H, s), 5.86 (1H, d, J= 4 Hz),
6.58 (1H, d, J= 4 Hz), 7.61 (2H, d, J= 5 Hz), 7.68 (1H, s), 7.77 (1H, m), 8.53 (2H,
30 d, J= 5 Hz), 8.76 (1H, s).

MS (ESI): m/z 468, MS (ESI⁺): m/z 470.

Example 523

5-{4-(3-cyanophenyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 1.38-1.57 (4H, m), 2.15 (2H, t, $J = 7$ Hz),
2.49-2.62 (2H, m), 3.04 (2H, q, $J = 7$ Hz), 4.69 (2H, s), 4.76 (2H, s), 5.85 (1H, d,
5 $J = 4$ Hz), 6.61 (1H, d, $J = 4$ Hz), 7.33 (1H, m), 7.62 (2H, m), 7.67 (1H, s), 7.73-
7.82 (2H, m), 8.53 (1H, d, $J = 5$ Hz), 8.67 (1H, s).

MS (ESI): m/z 467, MS (ESI $^+$): m/z 469.

Example 524

10 5-[4-(3-cyanophenyl)-7-ethyl-2-(5-methyl-3-isoxazolyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H -NMR (CDCl_3) δ 1.34-1.52 (7H, m), 2.17 (2H, t, $J = 7$ Hz), 2.53 (3H, s), 2.77 (2H,
m), 3.03 (2H, q, $J = 7$ Hz), 5.89 (1H, d, $J = 5$ Hz), 6.54 (1H, s), 6.67 (1H, d, $J = 5$
Hz), 7.63 (2H, m), 7.68 (1H, s), 7.78 (1H, m).

15

Example 525

5-[4-(3-cyanophenyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

^1H -NMR (CDCl_3) δ 1.23-1.42 (7H, m), 2.07 (2H, t, $J = 7$ Hz), 2.58 (2H, m), 3.03 (2H,
q, $J = 7$ Hz), 5.87 (1H, d, $J = 5$ Hz), 6.56 (1H, d, $J = 5$ Hz), 7.13 (1H, m), 7.36 (1H,
20 m), 7.43 (1H, d, $J = 5$ Hz), 7.62 (2H, m), 7.70 (1H, s), 7.76 (1H, m).

Example 526

3-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

^1H -NMR (CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 1.99 (2H, m), 2.75 (2H, m), 3.00 (2H, q, J
25 $= 7$ Hz), 5.93 (1H, d, $J = 5$ Hz), 6.63 (1H, d, $J = 5$ Hz), 7.42-7.55 (5H, m), 7.57-
7.78 (4H, m).

Example 527

5-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

30 ^1H -NMR (CDCl_3) δ 1.03-1.25 (4H, m), 1.36 (3H, t, $J = 7$ Hz), 1.90 (2H, t, $J = 7$ Hz),
2.41 (2H, m), 3.00 (2H, q, $J = 7$ Hz), 5.97 (1H, d, $J = 5$ Hz), 6.59 (1H, d, $J = 5$
Hz), 7.28 (1H, m), 7.35-7.54 (8H, m).

MS (ESI $^+$): m/z 433 (M+H)

The following compound(s) was(were) obtained in a similar manner to that of Example 180.

Example 528

- 5 ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(5-methyl-3-isoxazolyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.22 (3H, t, $J = 7$ Hz), 1.32-1.46 (5H, m), 1.72 (2H, m), 2.10 (2H, t, $J = 7$ Hz), 2.54 (3H, s), 2.78 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 4.06 (2H, q, $J = 7$ Hz), 5.89 (1H, d, $J = 5$ Hz), 6.54 (1H, s), 6.66 (1H, d, $J = 5$ Hz), 7.62 (2H, m),
10 7.67 (1H, s), 7.77 (1H, m).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 176.

Example 529

- 15 ethyl 4-[4-(aminocarbonyl)-3-bromophenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylate

$^1\text{H-NMR}$ (CDCl_3) δ 1.03 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 2.60 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 4.07 (2H, q, $J = 7$ Hz), 5.83 (1H, s, br), 6.19 (1H, s, br), 6.28 (1H, d, $J = 5$ Hz), 6.67 (1H, d, $J = 5$ Hz), 7.46 (1H, d, $J = 8$ Hz), 7.72 (1H, s), 7.77
20 (1H, d, $J = 8$ Hz).

The following compound(s) was(were) obtained in a similar manner to that of Example 184.

Example 530

- 25 3-[2-(cyclopentylamino)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ 1.36 (3H, t, $J = 7$ Hz), 1.51-1.80 (6H, m), 2.15 (2H, m), 2.96 (2H, q, $J = 7$ Hz), 3.05 (3H, s), 4.27 (1H, m), 5.94 (1H, d, $J = 5$ Hz), 6.47-6.53 (2H, m), 7.53-7.59 (3H, m), 7.74 (1H, m).

30

Example 531

- 3-[7-ethyl-2-(methylamino)-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile

$^1\text{H-NMR}$ (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.94-3.07 (8H, m), 5.95 (1H, d, $J = 5$ Hz),

6.50 (2H, m), 7.54-7.59 (3H, m), 7.74 (1H, m).

The following compound(s) was(were) obtained in a similar manner to that of Example 225.

5 Example 532

(2R,3R,4S,5S,6R)-2-({3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoyl}amino)-6-[(2,2-dimethylpropanoyl)oxy]methyl}tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate)

10 $^1\text{H-NMR}$ (CDCl_3) δ 1.07 (9H, s), 1.11 (9H, s), 1.16 (9H, s), 1.18 (9H, s), 1.37 (3H, t, $J = 7$ Hz), 2.23 (2H, m), 2.84 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.48 (3H, s), 3.91-4.21 (3H, m), 4.62-4.67 (2H, m), 5.00-5.26 (3H, m), 5.43 (2H, m), 5.91 (1H, d, $J = 5$ Hz), 6.55 (1H, m, br), 6.62 (1H, d, $J = 5$ Hz), 7.84 (1H, m), 8.51 (1H, m), 8.77 (1H, m).

15

The following compound(s) was(were) obtained in a similar manner to that of Example 226.

Example 533

[4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-3-yl]methanol

20 $^1\text{H-NMR}$ (CDCl_3) δ 1.40 (3H, t, $J = 7$ Hz), 2.53 (1H, t, $J = 7$ Hz), 3.07 (2H, q, $J = 7$ Hz), 4.48 (2H, m), 6.23 (1H, d, $J = 5$ Hz), 6.62 (1H, m), 6.71 (1H, d, $J = 5$ Hz), 7.10 (1H, d, $J = 5$ Hz), 7.46-7.52 (3H, m), 7.61 (1H, m), 7.64 (1H, m).

Example 534

25 [4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methanol

$^1\text{H NMR}$ (CDCl_3) δ 1.38 (3H, t, $J = 8$ Hz), 3.05 (2H, q, $J = 8$ Hz), 3.45-3.55 (4H, m), 4.40 (2H, br d, $J = 7$ Hz), 4.77 (2H, br s), 6.22 (1H, d, $J = 5$ Hz), 6.70 (1H, d, $J = 5$ Hz), 8.11 (1H, m), 8.74 (1H, br s), 8.80 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 302 ($M + H$).

30

The following compound(s) was(were) obtained in a similar manner to that of Example 227.

Example 535

(2R,3S,4S,5R,6R)-2-[(acetyloxy)methyl]-6-({5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentyl}oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate

¹H-NMR (CDCl₃) δ 0.82-1.18 (6H, m), 1.37 (3H, t, J = 7 Hz), 1.92-2.17 (14H, m),
 2.35 (2H, m), 3.01 (2H, q, J = 7 Hz), 3.16 (1H, m), 3.62 (1H, m), 3.85 (1H, m),
 5 4.11 (2H, m), 4.10 (2H, m), 4.30 (1H, d, J = 8.1 Hz), 4.96 (1H, m), 5.11 (1H, m),
 5.35 (1H, m), 5.90 (1H, d, J = 5 Hz), 6.62 (1H, d, J = 5 Hz), 7.44-7.53 (5H, m),
 7.60-7.80 (4H, m).

The following compound(s) was(were) obtained in a similar manner to that of

10 Example 228.

Example 536

ethyl 3-[7-ethyl-2-(hydroxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J = 7 Hz), 1.39 (3H, t, J = 7 Hz), 2.33 (2H, t, J = 7 Hz),
 15 2.43 (3H, s), 2.70-2.82 (2H, m), 3.04 (2H, q, J = 7 Hz), 3.71 (1H, t, J = 5 Hz), 4.05
 (2H, q, J = 7 Hz), 4.89 (2H, d, J = 5 Hz), 5.98 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4
 Hz), 7.52 (1H, s), 8.42 (1H, d, J = 2 Hz), 8.56 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 368.

20 Example 537

ethyl 4-[7-ethyl-2-(hydroxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.24 (3H, t, J = 7 Hz), 1.39 (3H, t, J = 7 Hz), 1.62-1.78 (2H, m),
 2.16-2.28 (2H, m), 2.36-2.53 (2H, m), 2.44 (3H, s), 3.06 (2H, q, J = 7 Hz), 3.86
 25 (1H, t, J = 7 Hz), 4.12 (2H, q, J = 7 Hz), 4.90 (2H, m), 5.96 (1H, d, J = 4 Hz), 6.60
 (1H, d, J = 4 Hz), 7.53 (1H, s), 8.44 (1H, s), 8.56 (1H, s).

MS (ESI⁺): m/z 382.

Example 538

30 ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.26 (3H, t, J = 7 Hz), 1.39 (3H, t, J = 7 Hz), 1.46-1.65 (4H, m),
 2.16 (2H, t, J = 7 Hz), 2.32-2.44 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.12 (2H, q, J = 7

Hz), 4.86 (2H, s), 5.91 (1H, d, J = 4 Hz), 6.60 (1H, d, J = 4 Hz), 7.58-7.68 (3H, m), 7.75-7.82 (1H, m).

MS (ESI⁺): m/z 406.

5 Example 539

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.25 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.64-1.79 (2H, m), 2.23 (2H, t, J = 7 Hz), 2.42-2.53 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.10 (2H, q, J = 7 Hz), 4.91 (2H, s), 5.97 (1H, d, J = 4 Hz), 6.62 (1H, d, J = 4 Hz), 7.89 (1H, m), 8.56 (1H, d, J = 2 Hz), 8.80 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 446 448.

Example 540

15 ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 2.32 (2H, m), 2.68-2.90 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.10 (2H, m), 4.89 (2H, s), 6.03 (1H, m), 6.65 (1H, m), 7.90 (1H, m), 8.58 (1H, m), 8.83 (1H, m).

20 MS (ESI⁺): m/z 432 434.

Example 541

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

25 ¹H NMR (300 MHz, CDCl₃) δ 1.22 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.67 (2H, t, J = 7, 7 Hz), 2.20 (2H, t, J = 7 Hz), 2.37-2.79 (2H, m), 3.04 (2H, q, J = 7 Hz), 3.77 (1H, t, J = 4 Hz), 4.07 (2H, q, J = 7 Hz), 4.91 (2H, d, J = 4 Hz), 5.96 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.73 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.70 (1H, d, J = 2 Hz).

30

Example 542

ethyl 3-[4-(3-chlorophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

^1H NMR (300 MHz, CDCl_3) δ 1.20 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 2.31 (2H, t, $J = 8$ Hz), 2.85 (2H, t, $J = 8$ Hz), 3.04 (2H, q, $J = 7$ Hz), 3.69-3.75 (1H, br s), 4.06 (2H, q, $J = 7$ Hz), 4.88 (2H, s), 6.00 (1H, d, $J = 4$ Hz), 6.59 (1H, d, $J = 4$ Hz), 7.23-7.26 (1H, m), 7.36 (1H, s), 7.44-7.46 (2H, m).

5

Example 543

ethyl 4-[4-(3-chlorophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

^1H NMR (CDCl_3) δ 1.21 (3H, t, $J = 8$ Hz), 1.38 (3H, t, $J = 8$ Hz), 1.57 (3H, s), 1.59-1.74 (2H, m), 2.20 (2H, t, $J = 8$ Hz), 2.37-2.47 (2H, m), 3.03 (2H, q, $J = 8$ Hz), 3.84 (1H, t, $J = 5$ Hz), 4.06 (2H, q, $J = 8$ Hz), 4.39 (2H, d, $J = 5$ Hz), 5.32 (2H, s), 5.96 (1H, d, $J = 5$ Hz), 6.56 (1H, d, $J = 5$ Hz), 7.21-7.29 (1H, overlapped with CDCl_3), 7.36 (1H, br s), 7.39-7.47 (2H, m).

10

15 Example 544

9-(5-bromo-3-pyridinyl)-6-ethyl-1H,3H-furo[3,4-e]pyrrolo[1,2-b]pyridazin-1-one

^1H NMR (CDCl_3) δ 1.42 (3H, t, $J = 8$ Hz), 3.11 (2H, q, $J = 8$ Hz), 5.32 (2H, s), 6.87 (1H, d, $J = 5$ Hz), 6.99 (1H, d, $J = 5$ Hz), 8.20 (1H, m), 8.83-8.87 (2H, m).

MS (ESI^+): m/z 358, 360 ($M + H$).

20

4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid

^1H NMR (CDCl_3 - CD_3OD) δ 1.40 (3H, t, $J = 8$ Hz), 3.09 (2H, q, $J = 8$ Hz), 4.93 (2H, s), 6.34 (1H, d, $J = 5$ Hz), 6.79 (1H, d, $J = 5$ Hz), 7.96 (1H, m), 8.55 (1H, br s), 8.73 (1H, br s).

25

MS (ESI^+): m/z 376, 378 ($M + H$).

Example 545

30 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]-N-[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]propanamide

^1H -NMR ($\text{DMSO}-d_6$) δ 1.30 (3H, t, $J = 7$ Hz), 2.21 (1H, m), 2.96 (2H, q, $J = 7$ Hz),

3.25-3.45 (8H, m), 3.66 (1H, m), 4.40 (1H, m), 4.55-4.67 (5H, m), 4.75 (1H, m),
5.85 (1H, d, J = 5 Hz), 6.66 (1H, d, J = 5 Hz), 8.23 (1H, m), 8.33 (1H, d, br, J = 7
Hz), 8.61 (1H, m), 8.84 (1H, m).

5 Example 546

3-[7-ethyl-2-phenyl-3-(5-[[[(2R,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(
(hydroxymethyl)tetrahydro-2H-pyran-2-yl]oxy}pentyl]pyrrolo[1,2-b]pyridazin-4-
yl]benzonitrile

¹H-NMR (CDCl₃) δ 0.85-1.38 (6H, m), 1.46 (3H, t, J = 7 Hz), 2.13 (2H, m), 2.38 (2H,
10 m), 2.65 (1H, m), 2.73 (1H, m), 3.02 (2H, q, J = 7 Hz), 3.23 (1H, m), 3.48-3.70
(4H, m), 3.80-4.01 (3H, m), 4.13 (1H, m), 5.90 (1H, d, J = 5 Hz), 6.63 (1H, d, J =
5 Hz), 7.42-7.55 (5H, m), 7.60-7.79 (4H, m).

The following compound(s) was(were) obtained in a similar manner to that of

15 Example 235.

Example 547

N-(2-aminoethyl)-3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-
b]pyridazin-3-yl]propanamide

¹H-NMR (CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 2.29 (2H, m), 2.72-3.07 (6H, m), 3.33 (2H,
20 q, J = 7 Hz), 3.49 (3H, s), 4.68 (2H, s), 5.93 (1H, d, J = 5 Hz), 6.06 (1H, m, br),
6.62 (1H, d, J = 5 Hz), 7.89 (1H, m), 8.55 (1H, m), 8.77 (1H, m).

MS (ESI⁺) m/z: 460 and 462 (M + H)

The following compound(s) was(were) obtained in a similar manner to that of

25 Example 268.

Example 548

ethyl 3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-
b]pyridazin-3-yl}propanoate

¹H NMR (CDCl₃) δ 1.15 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 2.37 (2H, t, J = 7 Hz),
30 2.43 (3H, s), 2.86-3.01 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.99 (2H, q, J = 7 Hz), 4.68
(2H, s), 4.81 (2H, s), 5.95 (1H, d, J = 4 Hz), 6.62 (1H, d, J = 4 Hz), 7.27 (2H, d, J =
7 Hz), 7.51 (1H, s), 8.43 (1H, s), 8.56 (1H, s), 8.57 (2H, d, J = 7 Hz).

MS (ESI⁺): m/z 459.

Example 549

ethyl 3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoate

- 5 $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.16 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.39 (2H, t, J= 7 Hz), 2.43 (3H, s), 2.88-3.03 (2H, m), 3.04 (2H, q, J= 7 Hz), 4.01 (2H, q, J= 7 Hz), 4.83 (2H, s), 4.90 (2H, s), 5.94 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.53 (1H, s), 8.42 (1H, m), 8.48-8.55 (3H, m), 8.76 (1H, s).

MS (ESI⁺): m/z 460.

10

Example 550

ethyl 3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoate

- 15 $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.15 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.40 (2H, t, J= 7 Hz), 2.42 (3H, s), 2.88-3.00 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.99 (2H, q, J= 7 Hz), 4.79 (2H, s), 4.86 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.16-7.23 (1H, m), 7.45-7.53 (2H, m), 7.68 (1H, m), 8.42 (1H, m), 8.53 (2H, m).

MS (ESI⁺): m/z 459.

20 Example 551

ethyl 4-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

- 25 $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.18 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.60-1.80 (2H, m), 2.13-2.25 (2H, m), 2.43 (3H, s), 2.53-2.76 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.03 (2H, q, J= 7 Hz), 4.68 (2H, s), 4.83 (2H, m), 5.92 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.27 (2H, d, J= 5 Hz), 7.53 (1H, s), 8.42 (1H, s), 8.53 (1H, s), 8.55 (2H, d, J= 5 Hz).

MS (ESI⁺): m/z 473.

30 Example 552

ethyl 5-{4-(3-cyanophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

- $^1\text{H NMR (CDCl}_3\text{)} \delta$ 1.22 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.35-1.57 (4H, m),

2.11 (2H, t, J= 7 Hz), 2.53-2.65 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.03 (2H, q, J= 7 Hz), 4.67 (2H, s), 4.78 (2H, s), 5.87 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.28 (2H, d, J= 5 Hz), 7.61 (2H, m), 7.66 (1H, s), 7.78 (1H, m), 8.58 (2H, d, J= 5 Hz).

5 MS (ESI⁺): m/z 497.

Example 553

ethyl 5-{4-(3-cyanophenyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

10 ¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.35-1.58 (4H, m), 2.11 (2H, t, J= 7 Hz), 2.55-2.65 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.10 (2H, q, J= 7 Hz), 4.82 (2H, s), 4.86 (2H, s), 5.86 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.62 (2H, m), 7.67 (1H, s), 7.78 (1H, m), 8.51 (2H, m), 8.74 (1H, s).

MS (ESI⁺): m/z 498.

15

Example 554

ethyl 5-{4-(3-cyanophenyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

20 ¹H NMR (CDCl₃) δ 1.22 (3H, t, J= 7 Hz), 1.39 (3H, t, J= 7 Hz), 1.32-1.66 (4H, m), 2.10 (2H, t, J= 7 Hz), 2.48-2.60 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.08 (2H, q, J= 7 Hz), 4.66 (2H, s), 4.75 (2H, s), 5.86 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.28 (1H, m), 7.58-7.63 (2H, m), 7.66 (1H, s), 7.66-7.80 (2H, m), 8.54 (1H, m), 8.62 (1H, m).

MS (ESI⁺): m/z 497.

25

Example 555

ethyl 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

30 ¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.40-1.62 (4H, m), 2.16 (2H, t, J= 7 Hz), 2.53-2.71 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.09 (2H, q, J= 7 Hz), 4.67 (2H, s), 4.78 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 5 Hz), 7.88 (1H, m), 8.56 (1H, d, J= 2 Hz), 8.58 (2H, d, J= 5 Hz), 8.79 (1H, d, J= 2 Hz).

Example 556

ethyl 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

- 5 ^1H NMR (CDCl_3) δ 1.23 (3H, t, J= 7 Hz), 1.40 (3H, t, J= 7 Hz), 1.30-1.60 (4H, m),
2.15 (2H, t, J= 7 Hz), 2.50-2.68 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.12 (2H, q, J= 7
Hz), 4.68 (2H, s), 4.78 (2H, s), 5.95 (1H, m), 6.63 (1H, m), 7.24-7.38 (1H, m),
7.75 (1H, m), 7.89 (1H, m), 8.58 (2H, s), 8.64 (1H, s), 8.80 (1H, s).

MS (ESI^+): m/z 551 553.

10

Example 557

ethyl 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

- 15 ^1H NMR (CDCl_3) δ 1.24 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.40-1.58 (4H, m),
2.12 (2H, t, J= 7 Hz), 2.53-2.68 (2H, m), 3.03 (2H, q, J= 7 Hz), 4.10 (2H, q, J= 7
Hz), 4.78 (2H, s), 4.84 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.22
(1H, m), 7.48 (1H, d, J= 8 Hz), 7.68-7.75 (1H, m), 7.88 (1H, m), 8.57 (2H, m),
8.78 (1H, d, J= 2 Hz).

20 Example 558

ethyl 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

- 25 ^1H NMR (CDCl_3) δ 1.22 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.40-1.62 (4H, m),
2.15 (2H, t, J= 7 Hz), 2.53-2.72 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.08 (2H, q, J= 7
Hz), 4.82 (2H, s), 4.86 (2H, s), 5.94 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.88
(1H, m), 8.52 (2H, m), 8.55 (1H, d, J= 2 Hz), 8.74 (1H, m), 8.79 (1H, d, J= 2 Hz).

MS (ESI^+): m/z 552 554.

Example 559

- 30 ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

^1H NMR (CDCl_3) δ 1.19 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.60-1.80 (2H, m),
2.22 (2H, t, J= 7 Hz), 2.55-2.74 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.06 (2H, q, J= 7

Hz), 4.69 (2H, s), 4.83 (2H, s), 5.96 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.30 (2H, d, J= 6 Hz), 7.88 (1H, m), 8.56 (2H, d, J= 6 Hz), 8.57 (1H, m), 8.80 (1H, m).
MS (ESI⁺): m/z 537 539.

5 Example 560

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (CDCl₃) δ 1.26 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.55-1.82 (2H, m),
2.18 (2H, t, J= 7 Hz), 2.52-2.72 (2H, m), 3.05 (2H, q, J= 7 Hz), 4.05 (2H, q, J= 7
10 Hz), 4.68 (2H, s), 4.83 (2H, s), 5.94 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.28 (1H, m), 7.73 (1H, d, J= 8 Hz), 7.88 (1H, m), 8.54 (2H, m), 8.62 (1H, s), 8.79 (1H, s)

Example 561

15 ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (CDCl₃) δ 1.26 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.63-1.82 (2H, m),
2.18 (2H, t, J= 7 Hz), 2.55-2.75 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.00 (2H, q, J= 7
Hz), 4.80 (2H, s), 4.88 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.22
20 (1H, m), 7.48 (1H, d, J= 8 Hz), 7.71 (1H, t, J= 8 Hz), 7.89 (1H, m), 8.55 (2H, m), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 537 539.

Example 562

25 ethyl 4-{4-(5-bromo-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (CDCl₃) δ 0.25 (2H, m), 0.60 (2H, m), 1.08-1.22 (1H, m), 1.22 (3H, t, J= 7
Hz), 1.37 (3H, t, J= 7 Hz), 1.69-1.82 (2H, m), 2.21 (2H, t, J= 7 Hz), 2.56-2.72
(2H, m), 3.03 (2H, q, J= 7 Hz), 3.42 (2H, d, J= 7 Hz), 4.04 (2H, q, J= 7 Hz), 4.73
30 (2H, s), 5.91 (1H, d, J= 4 Hz), 6.59 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.56 (1H, d, J= 2 Hz), 8.79 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 500 502.

Example 563

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (CDCl₃) δ 1.19 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.70-1.82 (2H, m),
 5 2.23 (2H, t, J= 7 Hz), 2.56-2.76 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.04 (2H, q, J= 7 Hz), 4.84 (2H, s), 4.95 (2H, m), 5.94 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.50 (2H, m), 8.56 (1H, s), 8.74 (1H, s), 8.79 (1H, m).

MS (ESI⁺): m/z 538 540.

10 Example 564

ethyl 3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoate

¹H NMR (CDCl₃) δ 1.16 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 2.41 (2H, t, J= 7 Hz),
 2.85-3.07 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.02 (2H, q, J= 7 Hz), 4.68 (2H, s), 4.81
 15 (2H, s), 5.95 (1H, d, J= 4 Hz), 6.65 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 6 Hz), 7.87 (1H, m), 8.55 (1H, m), 8.56 (2H, d, J= 6 Hz), 8.79 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 523 525.

Example 565

20 ethyl 4-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-{[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]methyl}pyrrolo[1,2-b]pyridazin-3-yl)butanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.46-1.93 (8H, m),
 2.21 (2H, t, J= 7 Hz), 2.55-2.76 (2H, m), 3.02 (2H, q, J= 7 Hz), 3.46-3.56 (1H, m),
 3.60-3.68 (1H, m), 3.74-3.82 (2H, m), 3.83-3.96 (2H, m), 4.03 (2H, q, J= 7 Hz),
 25 4.63 (1H, m), 4.77 (2H, s), 5.91 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.56 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

Example 566

30 ethyl 4-{4-(5-chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (300 MHz, CDCl₃) δ 1.19 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.70 (2H, t, J = 7 Hz), 2.19 (2H, t, J = 7 Hz), 2.55-2.67 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.03 (2H, q, J = 7 Hz), 4.69 (2H, s), 4.83 (2H, s), 5.94 (1H, d, J = 5 Hz), 6.63 (1H, d, J

= 5 Hz), 7.29 (2H, d, J = 6 Hz), 7.73 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.58 (2H, d, J = 6 Hz), 8.69 (1H, d, J = 2 Hz).

Example 567

5 ethyl 3-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 8 Hz), 1.37 (3H, t, J = 8 Hz), 2.33-2.44 (2H, m), 2.84-2.94 (2H, m), 3.03 (2H, q, J = 8 Hz), 3.45 (3H, s), 4.05 (2H, q, J = 8 Hz), 4.64 (2H, s), 5.94 (1H, d, J = 5 Hz), 6.58 (1H, d, J = 5 Hz), 7.21-7.29 (1H, overlapped with CDCl₃), 7.36 (1H, br s), 7.38-7.46 (2H, m).

Example 568

ethyl 4-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

15 ¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 8 Hz), 1.37 (3H, t, J = 8 Hz), 1.62-1.78 (2H, m), 2.14-2.28 (2H, m), 2.53-2.66 (2H, m), 3.04 (2H, q, J = 8 Hz), 3.46 (3H, s), 4.04 (2H, q, J = 8 Hz), 4.65 (2H, s), 5.93 (1H, d, J = 5 Hz), 6.58 (1H, d, J = 5 Hz), 7.21-7.29 (1H, overlapped with CDCl₃), 7.36 (1H, br s), 7.39-7.46 (2H, m).

20 The following compound(s) was(were) obtained in a similar manner to that of Example 272.

Example 569

ethyl 5-{4-(5-bromo-3-pyridinyl)-2-[(1,1-dioxido-4-thiomorpholinyl)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate

25 ¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 1.39-1.53 (4H, m), 2.19 (2H, t, J = 7 Hz), 2.50-2.61 (2H, m), 3.00 (2H, q, J = 7 Hz), 3.10 (4H, t, J = 6 Hz), 3.21 (4H, t, J = 6 Hz), 3.85 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.92 (1H, d, J = 4 Hz), 6.61 (1H, d, J = 4 Hz), 7.88 (1H, dd, J = 2, 2 Hz), 8.55 (1H, d, J = 2 Hz), 8.80 (1H, d, J = 2 Hz).

Example 570

ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.41-1.54 (4H, m), 2.19 (2H, t, J = 7 Hz), 2.50-2.61 (2H, m), 2.66 (4H, t, J = 4 Hz), 2.85 (4H, t, J = 4 Hz), 3.01 (2H, q, J = 7 Hz), 3.67 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.88 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz), 7.88 (1H, dd, J = 2, 2 Hz), 8.55 (1H, d, J = 2 Hz), 8.79 (1H, d, J = 2 Hz).

Example 571

ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-([4-(2-hydroxyethyl)-1-piperazinyl]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 1.40-1.55 (4H, m), 2.18 (2H, t, J = 7 Hz), 2.48-2.66 (12H, m), 3.02 (2H, q, J = 7 Hz), 3.61 (2H, t, J = 5 Hz), 3.66 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.88 (1H, d, J = 4 Hz), 6.57 (1H, d, J = 4 Hz), 7.88 (1H, dd, J = 2, 2 Hz), 8.55 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

Example 572

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.70 (2H, tt, J = 7, 7 Hz), 2.19 (2H, t, J = 7 Hz), 2.50-2.67 (6H, m), 2.86 (4H, t, J = 5 Hz), 3.02 (2H, q, J = 7 Hz), 3.70 (2H, s), 4.05 (2H, q, J = 5 Hz), 5.89 (1H, d, J = 4 Hz), 6.58 (1H, d, J = 4 Hz), 7.74 (1H, dd, J = 2, 2 Hz), 8.52 (1H, d, J = 2 Hz), 8.68 (1H, d, J = 2 Hz).

Example 573

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.72 (2H, tt, J = 7, 7 Hz), 2.20 (2H, t, J = 7 Hz), 2.56-2.69 (6H, m), 3.02 (2H, q, J = 7 Hz), 3.68-3.71 (6H, m), 4.05 (2H, q, J = 7 Hz), 5.89 (1H, d, J = 4 Hz), 6.58 (1H, d, J = 4 Hz), 7.74 (1H, dd, J = 2, 2 Hz), 8.53 (1H, d, J = 2 Hz), 8.69 (1H, d, J = 2 Hz).

Example 574

ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.34 (3H, t, J = 7 Hz), 2.47-2.54 (2H, m), 2.59 (4H, t, J = 5 Hz), 2.81-2.95 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.67 (4H, t, J = 5 Hz), 3.69 (2H, s), 4.07 (2H, q, J = 7 Hz), 5.90 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.88 (1H, dd, J = 2, 2 Hz), 8.55 (1H, d, J = 2 Hz), 8.79 (1H, d, J = 2 Hz).

Example 575

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 1.73 (2H, tt, J = 7, 7 Hz), 2.20 (2H, t, J = 7 Hz), 2.55-2.69 (6H, m), 3.02 (2H, q, J = 7 Hz), 3.69 (4H, t, J = 5 Hz), 4.05 (2H, q, J = 7 Hz), 5.89 (1H, d, J = 4 Hz), 6.58 (1H, d, J = 4 Hz), 7.89 (1H, dd, J = 2, 2 Hz), 8.57 (1H, d, J = 2 Hz), 8.79 (1H, d, J = 2 Hz).

Example 576

ethyl 4-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylamino)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

¹H NMR (300 MHz, CDCl₃) δ 0.46-0.52 (4H, m), 1.21 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.71 (2H, tt, J = 8, 8 Hz), 2.21 (2H, t, J = 8 Hz), 2.32-2.39 (1H, m), 2.45-2.54 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.06 (2H, q, J = 7 Hz), 4.07 (2H, s), 5.89 (1H, d, J = 4 Hz), 6.57 (1H, d, J = 4 Hz), 7.72 (1H, dd, J = 2, 2 Hz), 8.50 (1H, d, J = 2 Hz), 8.68 (1H, d, J = 2 Hz).

Example 577

ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-phenoxyethyl)amino]methyl)pyrrolo[1,2-b]pyridazin-3-yl)pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.40-1.56 (4H, m), 2.18 (2H, t, J = 8 Hz), 2.41-2.52 (2H, m), 3.04 (2H, q, J = 7 Hz), 3.19 (2H, t, J = 5 Hz), 4.07 (2H, s), 4.09 (2H, q, J = 7 Hz), 4.17 (2H, t, J = 5 Hz), 5.90 (1H, d, J = 4 Hz), 6.57 (1H, d, J = 4 Hz), 6.92-6.98 (3H, m), 7.29-7.32 (2H, m),

7.86 (1H, dd, J = 2, 2 Hz), 8.54 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

Example 578

ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-

5 hydroxyethyl)(methyl)amino]methyl}pyrrolo[1,2-b]pyridazin-3-yl)pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.42-1.63 (4H, m), 2.20 (2H, t, J = 8 Hz), 2.38 (3H, s), 2.53-2.64 (2H, m), 2.75 (2H, t, J = 5 Hz), 3.02 (2H, q, J = 7 Hz), 3.66 (2H, t, J = 5 Hz), 3.77 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.90 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.88 (1H, dd, J = 2, 2 Hz),
10 8.55 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

Example 579

ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(1-piperidinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

15 ¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 1.42-1.58 (6H, m), 1.69 (4H, tt, J = 5, 5 Hz), 2.18 (2H, t, J = 8 Hz), 2.53-2.64 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.19 (4H, t, J = 5 Hz), 3.60 (2H, s), 4.07 (2H, q, J = 7 Hz), 5.86 (1H, d, J = 5 Hz), 6.54 (1H, d, J = 5 Hz), 7.89 (1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.75 (1H, d, J = 2 Hz).

20

Example 580

ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

25 ¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 2.46 (2H, t, J = 8 Hz), 2.64 (4H, t, J = 5 Hz), 2.86 (6H, m), 3.02 (2H, q, J = 7 Hz), 3.69 (2H, s), 4.06 (2H, q, J = 7 Hz), 5.91 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.88 (1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.80 (1H, d, J = 2 Hz).

Example 581

30 ethyl 3-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}pyrrolo[1,2-b]pyridazin-3-yl)propanoate

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 2.46-2.63 (12H, m), 2.80-2.94 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.61 (2H, t, J = 5 Hz), 3.70

(2H, s), 4.08 (2H, q, J = 7 Hz), 5.90 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.88 (1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.79 (1H, d, J = 2 Hz).

Example 582

- 5 ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(1-pyrrolidinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.40-1.55 (4H, m), 1.75-1.80 (4H, m), 2.19 (2H, t, J = 7 Hz), 2.54-2.66 (6H, m), 3.02 (2H, q, J = 7 Hz), 3.76-3.81 (2H, m), 4.10 (2H, q, J = 7 Hz), 5.87 (1H, d, J = 5 Hz), 6.55 (1H, d, J = 5 Hz), 7.89 (1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.77 (1H, d, J = 2 Hz).

Example 583

- 15 ethyl 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-phenyl-1-piperazinyl)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.21 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.41-1.54 (4H, m), 2.17 (2H, t, J = 7 Hz), 2.53-2.68 (2H, m), 2.75 (4H, t, J = 5 Hz), 3.03 (2H, q, J = 7 Hz), 3.19 (4H, t, J = 5 Hz), 3.73 (2H, s), 4.07 (2H, q, J = 7 Hz), 5.89 (1H, d, J = 5 Hz), 6.58 (1H, d, J = 5 Hz), 6.85 (1H, dd, J = 8, 8 Hz), 6.93 (2H, J = 8 Hz), 7.25 (2H, J = 8 Hz), 7.89 (1H, dd, J = 2, 2 Hz), 8.56 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

Example 584

- 25 ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-methoxyethyl)amino]methyl)pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (300 MHz, CDCl₃) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.41-1.60 (4H, m), 2.19 (2H, t, J = 7 Hz), 2.43-2.52 (2H, m), 2.96 (2H, t, J = 5 Hz), 3.03 (2H, q, J = 7 Hz), 3.40 (3H, s), 3.58 (2H, t, J = 5 Hz), 3.99 (2H, s), 4.10 (2H, q, J = 7 Hz), 5.89 (1H, d, J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 7.87 (1H, dd, J = 2, 2 Hz), 8.54 (1H, d, J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

The following compound(s) was(were) obtained in a similar manner to that of Example 385.

Example 585

3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]-N-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]propanamide

¹H-NMR (CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 2.25-3.10 (6H, m), 3.49 (3H, s), 3.58 (4H, m), 3.81 (2H, m), 4.55 (2H, s), 5.97 (1H, d, J = 5 Hz), 6.54 (1H, s), 6.64 (1H, d, J = 5 Hz), 7.93 (1H, m), 8.52 (1H, m), 8.78 (1H, m).

Example 586

tert-butyl [2-({3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoyl}amino)ethyl]carbamate

¹H-NMR (CDCl₃) δ 1.37 (3H, t, J = 7 Hz), 1.43 (9H, s), 2.26 (2H, m), 2.88 (2H, m), 3.04 (2H, q, J = 7 Hz), 3.20 (2H, m), 3.28 (2H, m), 3.48 (3H, s), 4.67 (2H, s), 4.85 (1H, s, br), 5.93 (1H, d, J = 5 Hz), 6.20 (1H, s, br), 6.63 (1H, d, J = 5 Hz), 7.88 (1H, m), 8.53 (1H, m), 8.79 (1H, m).

15

The following compound(s) was(were) obtained in a similar manner to that of Example 330.

Example 587

ethyl 5-[2-{[2-(benzylamino)-2-oxoethoxy]methyl}-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.22 (3H, t, J = 7 Hz), 1.34 (3H, t, J = 7 Hz), 1.33-1.55 (4H, m), 2.12 (2H, t, J = 7 Hz), 2.43 (3H, s), 2.40-2.56 (2H, m), 2.96 (2H, q, J = 7 Hz), 4.07 (2H, q, J = 7 Hz), 4.19 (2H, s), 4.52 (2H, d, J = 7 Hz), 4.76 (2H, s), 5.93 (1H, d, J = 4 Hz), 6.59 (1H, d, J = 4 Hz), 7.06 (1H, br), 7.23-7.38 (5H, m), 7.49 (1H, s), 8.40 (1H, s), 8.54 (1H, s).

25

MS (ESI⁺): m/z 543.

The following compound(s) was(were) obtained in a similar manner to that of Example 333.

30 Example 588

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4H-1,2,4-triazol-4-ylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H-NMR (CDCl₃) δ 1.22-1.34 (6H, m), 1.67 (2H, m), 2.23 (2H, m), 2.51 (2H, m),

2.98 (2H, q, J = 7 Hz), 4.21 (2H, q, J = 7 Hz), 5.67 (2H, m), 5.97 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 7.85 (1H, m), 7.96 (1H, s), 8.34 (1H, s), 8.53 (1H, m), 8.79 (1H, m).

- 5 The following compound(s) was(were) obtained in a similar manner to that of Example 336.

Example 589

ethyl 5-(7-ethyl-4-(5-methyl-3-pyridinyl)-2-[[[(phenylsulfonyl)amino]methyl]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

- 10 ^1H NMR (CDCl_3) δ 1.23 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.26-1.57 (4H, m), 2.16 (2H, t, J = 7 Hz), 2.33-2.46 (2H, m), 2.42 (3H, s), 2.98 (2H, q, J = 7 Hz), 4.11 (2H, q, J = 7 Hz), 4.38 (2H, m), 5.91 (1H, br), 5.92 (1H, d, J = 4 Hz), 6.58 (1H, d, J = 4 Hz), 7.43-7.55 (4H, m), 7.93 (2H, d, J = 8 Hz), 8.33 (1H, d, J = 2 Hz), 8.54 (1H, d, J = 2 Hz).

- 15 MS (ESI^+): m/z 535.

The following compound(s) was(were) obtained in a similar manner to that of Example 340.

Example 590

- 20 ethyl 4-{4-(5-bromo-3-pyridinyl)-2-[(cyclopropylamino)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

- ^1H -NMR (CDCl_3) δ 0.48 (4H, m), 1.19 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.70 (2H, t, J = 7 Hz), 2.22 (2H, m), 2.50 (2H, m), 2.95-3.07 (3H, m), 3.96-4.12 (4H, m), 5.90 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz), 7.88 (1H, m), 8.54 (1H, m), 25 8.77 (1H, m).

Example 591

- To a suspension of LiAlH_4 (113 mg) in THF (10 mL) was added ethyl [4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acetate (600 mg) under
30 ice-water cooling and the mixture was stirred at 0 °C for 2 hours. To the mixture was added potassium sodium tartrate solution and the insolubles were filtered off. After evaporation of solvent, the residue was partitioned between AcOEt and water. The organic layer was separated, washed with brine, dried over MgSO_4 , and evaporated in

vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (5:1 - 1:1) to give 2-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethanol as yellow oil (246 mg).

5 2-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethanol

^1H NMR (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 2.60 (3H, s), 2.72-2.84 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.65 (2H, t, $J = 7$ Hz), 5.89 (1H, d, $J = 4$ Hz), 6.55 (1H, d, $J = 4$ Hz), 7.91 (1H, t, $J = 2$ Hz), 8.56 (1H, d, $J = 2$ Hz), 8.76 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 360 362.

10

Example 592

A mixture of 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid (1.07 g), diphenylphosphoryl azide (1.14 g) and Et₃N (0.576 mL) in BuOH (30 mL) was heated under reflux for 2 hours. After evaporation of
15 solvent, the residue was partitioned between AcOEt and water. The organic layer was separated, washed with aq NaHCO₃ solution and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (20:1 - 3:1) to give tert-butyl {2-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethyl}carbamate as
20 yellow oil (450 mg).

tert-butyl {2-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethyl}carbamate

^1H NMR (CDCl_3) δ 1.37 (9H, s), 1.37 (3H, t, $J = 7$ Hz), 2.64 (3H, s), 2.62-2.75 (2H, m), 3.03 (2H, q, $J = 7$ Hz), 3.10-3.27 (2H, m), 4.40-4.52 (1H, m), 5.89 (1H, d, $J = 4$ Hz), 6.55 (1H, d, $J = 4$ Hz), 7.89 (1H, m), 8.53 (1H, m), 8.77 (1H, m).
25

Example 593

To a suspension of 60% NaH (74 mg) in DMF (3 mL) was added ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate (200 mg) under ice-water cooling, and the mixture was stirred at 0 °C for 0.5 hour. To
30 this was added 3-(bromomethyl)pyridine hydrobromide (234 mg) under ice-water cooling, and the mixture was stirred at ambient temperature for 2 hours. The mixture was

partitioned between AcOEt and water. The aqueous layer was separated, acidified to pH 3-4 with HCl and extracted with AcOEt. The organic layer was washed with water and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of CHCl_3 and MeOH (100:1 - 20:1) to
5 give 3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid as a yellow powder (110 mg).

3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

10 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.39 (3H, t, $J=7$ Hz), 2.41 (2H, t, $J=7$ Hz), 2.80-2.98 (2H, m), 3.04 (2H, q, $J=7$ Hz), 4.70 (2H, s), 4.83 (2H, s), 5.93 (1H, d, $J=4$ Hz), 6.63 (1H, d, $J=4$ Hz), 7.32-7.38 (1H, m), 7.81 (1H, d, $J=8$ Hz), 7.87 (1H, m), 8.52 (1H, d, $J=8$ Hz), 8.53 (1H, d, $J=2$ Hz), 8.63 (1H, s), 8.77 (1H, d, $J=2$ Hz).

15 The following compound(s) was(were) obtained in a similar manner to that of Example 593.

Example 594

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-methoxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

20 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.37 (3H, t, $J=7$ Hz), 1.72-1.83 (2H, m), 2.28 (2H, t, $J=7$ Hz), 2.60-2.77 (2H, m), 3.03 (2H, q, $J=7$ Hz), 3.39 (3H, s), 3.62 (2H, m), 3.77 (2H, m), 4.75 (2H, s), 5.93 (1H, d, $J=4$ Hz), 6.62 (1H, d, $J=4$ Hz), 7.92 (1H, m), 8.56 (1H, d, $J=2$ Hz), 8.77 (1H, d, $J=2$ Hz).

MS (ESI): m/z 474 476, MS (ESI $^+$): m/z 476 478.

25

Example 595

3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

30 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.38 (3H, t, $J=7$ Hz), 2.48-2.62 (2H, m), 2.98-3.10 (2H, m), 3.05 (2H, q, $J=7$ Hz), 4.82 (2H, s), 4.88 (2H, s), 5.94 (1H, d, $J=4$ Hz), 6.63 (1H, d, $J=4$ Hz), 7.27 (1H, m), 7.48 (1H, d, $J=8$ Hz), 7.77 (1H, t, $J=8$ Hz), 7.90 (1H, m), 8.56 (2H, m), 8.80 (1H, m).

MS (ESI $^+$): m/z 495 497.

Example 596

3-{4-(5-bromo-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

5 $^1\text{H NMR (CDCl}_3\text{)}$ δ 0.25 (2H, m), 0.58 (2H, m), 1.12 (1H, m), 1.37 (3H, t, J= 7 Hz), 2.40-2.63 (2H, m), 2.85-3.05 (2H, m), 3.02 (2H, q, J= 7 Hz), 3.42 (2H, d, J= 7 Hz), 4.73 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 456 458, MS (ESI⁺): m/z 458 460.

10

Example 597

3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

15 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.38 (3H, t, J= 7 Hz), 2.48 (2H, t, J= 7 Hz), 2.85-3.09 (2H, m), 3.06 (2H, q, J= 7 Hz), 4.84 (2H, s), 4.92 (2H, s), 5.96 (1H, d, J= 4 Hz), 6.65 (1H, d, J= 4 Hz), 7.90 (1H, m), 8.48-8.62 (3H, m), 8.77 (2H, m).

Example 598

20 A mixture of ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-(tetrahydro-2H-pyran-2-yloxy)ethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate (89 mg) and pyridinium p-toluenesulfonate (0.8 mg) in MeOH (5 mL) was heated under reflux for 2 hours. After evaporation of solvent, the residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (10:1 - 1:1) to give ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-hydroxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate as yellow oil (69 mg).

25

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-hydroxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

30 $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.22 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.69-1.84 (2H, m), 2.22 (2H, t, J= 7 Hz), 2.53-2.72 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.76 (2H, m), 3.83 (2H, m), 4.07 (2H, q, J= 7 Hz), 4.79 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.89 (1H, m), 8.56 (1H, d, J= 2 Hz), 8.79 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 490 492.

Example 599

To a suspension of 60% NaH (69.5 mg) in DMF (3 mL) was added ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate (200 mg) under ice-water cooling and the mixture was stirred at 0 °C for 0.5 hour. To this was added 4-morpholinecarbonyl chloride (659 mg) and the mixture was stirred at ambient temperature for 15 hours. The mixture was partitioned between AcOEt and water. The organic layer was separated, washed with water and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (20:1 - 1:1) to give [4-(5-bromo-3-pyridinyl)-3-(5-ethoxy-5-oxopentyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methyl 4-morpholinecarboxylate as yellow oil (75 mg).

[4-(5-bromo-3-pyridinyl)-3-(5-ethoxy-5-oxopentyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methyl 4-morpholinecarboxylate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.40-1.60 (4H, m), 2.18 (2H, t, J= 7 Hz), 2.42-2.54 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.53-3.57 (4H, m), 3.63-3.78 (4H, m), 4.09 (2H, q, J= 7 Hz), 5.33 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.87 (1H, m), 8.54 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 573 575.

The following compound(s) was(were) obtained in a similar manner to that of Example 599.

Example 600

ethyl 5-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.36 (3H, t, J= 7 Hz), 1.35-1.60 (4H, m), 2.17 (2H, t, J= 7 Hz), 2.44-2.57 (2H, m), 2.98 (6H, s), 3.03 (2H, q, J= 7 Hz), 4.09 (2H, q, J= 7 Hz), 5.30 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.61 (1H, d, J= 4 Hz), 7.87 (1H, m), 8.54 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).
MS (ESI⁺): m/z 531 533.

Example 601

[4-(5-bromo-3-pyridinyl)-3-(5-ethoxy-5-oxopentyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methyl 1-pyrrolidinecarboxylate

¹H NMR (CDCl₃) δ 1.23 (3H, t, J= 7 Hz), 1.36 (3H, t, J= 7 Hz), 1.38-1.60 (4H, m),
1.86-1.98 (4H, m), 2.17 (2H, t, J= 7 Hz), 2.44-2.57 (2H, m), 3.03 (2H, q, J= 7 Hz),
5 3.36-3.52 (4H, m), 4.11 (2H, q, J= 7 Hz), 5.32 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.61
(1H, d, J= 4 Hz), 7.87 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

Example 602

ethyl 5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-

10 [({[methyl(phenyl)amino]carbonyl}oxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.32-1.57 (4H, m),
2.13 (2H, t, J= 7 Hz), 2.33-2.48 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.38 (3H, s), 4.08
(2H, q, J= 7 Hz), 5.34 (2H, s), 5.92 (1H, d, J= 4 Hz), 6.60 (1H, d, J= 4 Hz), 7.20-
7.38 (5H, m), 7.83 (1H, s), 8.49 (1H, s), 8.77 (1H, s).

15

Example 603

[4-(5-bromo-3-pyridinyl)-3-(4-ethoxy-4-oxobutyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methyl 4-morpholinecarboxylate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 1.63-1.80 (2H, m),
20 2.22 (2H, t, J= 7 Hz), 2.44-2.65 (2H, m), 3.03 (2H, q, J= 7 Hz), 3.54 (4H, m),
3.68 (4H, m), 4.05 (2H, q, J= 7 Hz), 5.37 (2H, s), 5.94 (1H, d, J= 4 Hz), 6.62 (1H,
d, J= 4 Hz), 7.87 (1H, m), 8.55 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 559 561.

25 Example 604

ethyl 4-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J= 7 Hz), 1.36 (3H, t, J= 7 Hz), 1.66-1.79 (2H, m),
2.20 (2H, t, J= 7 Hz), 2.46-2.62 (2H, m), 2.97 (6H, s), 3.03 (2H, q, J= 7 Hz), 4.04
30 (2H, q, J= 7 Hz), 5.34 (2H, s), 5.93 (1H, d, J= 4 Hz), 6.63 (1H, d, J= 4 Hz), 7.89
(1H, m), 8.56 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).

MS (ESI⁺): m/z 517 519.

Example 605

ethyl 3-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H NMR (CDCl₃) δ 1.20 (3H, t, J = 7 Hz), 1.36 (3H, t, J = 7 Hz), 2.37 (2H, t, J = 7 Hz),
 5 2.82-2.93 (2H, m), 2.97 (6H, s), 3.03 (2H, q, J = 7 Hz), 4.05 (2H, q, J = 7 Hz), 5.32
 (2H, s), 5.96 (1H, d, J = 4 Hz), 6.63 (1H, d, J = 4 Hz), 7.88 (1H, m), 8.54 (1H, d,
 J = 2 Hz), 8.78 (1H, d, J = 2 Hz).

Example 606

10 To a solution of sodium hydride (93.1 mg) in DMF (4 mL) was added ethyl 3-[4-(3-chlorophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate (150 mg) under ice water cooling and the mixture was stirred at this temperature for 1 hour. To this was added 4-(bromomethyl)pyridine hydrobromide (196 mg) and the mixture was stirred for 1 hour at ambient temperature. The reaction was quenched by adding water.

15 The mixture was extracted with CHCl₃. The organic layer was washed with water and brine, dried over MgSO₄ and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of CHCl₃-MeOH = 30-1 to give 3-{4-(3-chlorophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid (18 mg) as a yellow solid.

20 3-{4-(3-chlorophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.39 (3H, t, J = 7 Hz), 2.33 (2H, t, J = 7 Hz), 2.84-2.91
 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.73 (2H, s), 4.82 (2H, s), 5.96 (1H, d, J = 5 Hz),
 25 6.62 (1H, d, J = 5 Hz), 7.23-7.26 (1H, m), 7.36-7.38 (3H, m), 7.42-7.44 (2H, m),
 8.41 (2H, d, J = 5 Hz).

MS (m/z) 450 (M+H).

The following compound(s) was(were) obtained in a similar manner to that of

30 Example 606.

Example 607

3-{4-(3-chlorophenyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.39 (3H, t, J = 7 Hz), 2.32-2.38 (2H, m), 2.84-2.92 (2H, m), 3.04 (2H, q, J = 7 Hz), 4.70 (2H, s), 4.82 (2H, s), 5.94 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.21-7.24 (1H, m), 7.31-7.36 (2H, m), 7.40-7.42 (2H, m), 7.80 (2H, d, J = 8 Hz), 8.51 (1H, d, J = 5 Hz), 8.64 (1H, s).

5

Example 608

3-{4-(3-chlorophenyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 2.42 (2H, t, J = 7 Hz), 2.91-2.97 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.83 (2H, s), 4.90 (2H, s), 5.96 (2H, d, J = 5 Hz), 6.62 (2H, d, J = 5 Hz), 7.23-7.26 (1H, m), 7.36 (1H, s), 7.43-7.44 (2H, m), 8.51-8.53 (2H, m), 8.75 (1H, s).

10

Example 609

15 A solution of 5-[7-ethyl-2-methyl-4-(2-vinyl-4-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (15 mg) in MeOH was added 10% Pd/C (2 mg). The mixture was stirred under hydrogen atmosphere (1 atm) for 6 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was triturated with hexane to give 5-[7-ethyl-4-(2-ethyl-4-pyridinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (14 mg) as a yellow solid.

20

5-[7-ethyl-4-(2-ethyl-4-pyridinyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H NMR (CDCl₃) δ 1.29-1.64 (10H, m), 2.18-2.30 (2H, m), 2.45-2.48 (2H, m), 2.56 (3H, s), 2.91-3.06 (4H, m), 5.84 (1H, d, J = 5 Hz), 6.53 (1H, d, J = 16 Hz), 6.51 (1H, d, J = 5 Hz), 7.25-7.32 (2H, m), 8.69 (1H, br s).

25

Example 610

To a solution of ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate (70.0 mg) in toluene (1 mL) was added tributylphosphine (0.098 mL), 1,3-oxazolidin-2-one (34.1 mg) in that order in an ice bath. After stirring for 5 minutes, to the mixture was added 1,1'-(azodicarbonyl)dipiperidine (98.9 mg). The mixture was stirred for 10 minutes in the bath, and 8 hours at room temperature. Hexane (5 mL) was added, and the mixture was

30

filtered. The filtrate was evaporated. Preparative thin layer chromatography (ethyl acetate-hexane = 1-1) afforded ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-oxo-1,3-oxazolidin-3-yl)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate as a yellow gum (25.0 mg).

5

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-oxo-1,3-oxazolidin-3-yl)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.20 (3H, t, $J = 7$ Hz), 1.369 (3H, t, $J = 7$ Hz), 1.65 (3H, t, $J = 7$ Hz), 2.25 (2H, t, $J = 7$ Hz), 2.51 (2H, m), 2.99 (2H, q, $J = 7$ Hz), 3.79 (2H, t, $J = 7$ Hz), 4.04 (2H, q, $J = 7$ Hz), 4.43 (2H, t, $J = 7$ Hz), 4.69 (2H, m), 5.95 (1H, d, $J = 5$ Hz), 6.61 (1H, d, $J = 5$ Hz), 7.87 (1H, m), 8.55 (1H, m), 8.80 (1H, m).

10

Example 611

To a solution of 2-bromo-4-[3-(ethoxycarbonyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-4-yl]benzoic acid (50.0 mg) in tetrahydrofuran (1 mL) was added a solution of 1 M borane-tetrahydrofuran complex (0.348 mL) in an ice bath. After stirring for 2 hours at room temperature, additional solution of the borane-tetrahydrofuran complex (0.348 mL) was added. The mixture was stirred for 15 hours at room temperature. The mixture was partitioned between ethyl acetate and 1 N hydrochloric acid. The organic layer was washed with water, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated to give ethyl 4-[3-bromo-4-(hydroxymethyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow oil (54.2 mg).

20

ethyl 4-[3-bromo-4-(hydroxymethyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylate

25

$^1\text{H-NMR}$ (CDCl_3) δ 0.99 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 2.59 (3H, s), 3.03 (2H, q, $J = 7$ Hz), 4.07 (2H, q, $J = 7$ Hz), 4.82 (2H, s), 6.33 (1H, d, $J = 5$ Hz), 6.66 (1H, d, $J = 5$ Hz), 7.44 (1H, d, $J = 8$ Hz), 7.58 (1H, d, $J = 8$ Hz), 7.67 (1H, s).

30 Example 612

To a solution of 2-(2-{2-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]ethoxy}ethoxy)ethyl acetate (62.0 mg) in methanol (1 mL) was added potassium carbonate (22.2 mg). After stirring for 1.5 hour, The solvent was evaporated

off. Preparative thin layer chromatography (CHCl_3 -MeOH = 20-1) afforded the desired product as a yellow gum (54.1 mg). The gum was dissolved in 1 N HCl (1 mL), and the solution was lyophilized to give a dark green gum, which was crystallized upon standing. The crystal was triturated in diisopropyl ether to give 2-(2-{2-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]ethoxy}ethoxy)ethanol hydrochloride as an yellow powder (40.3 mg).

2-(2-{2-[7-ethyl-2-methyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]ethoxy}ethoxy)ethanol hydrochloride

¹H-NMR (DMSO-d_6): 1.29 (3H, t, J = 7 Hz), 2.51 (3H, s), 2.56 (3H, s), 2.62 (2H, m), 2.94 (2H, q, J = 7 Hz), 3.30-3.47 (10H, m), 5.84 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 8.26 (1H, m), 8.77 (1H, m), 8.85 (1H, m).

Example 613

A mixture of ethyl 5-[2-(bromomethyl)-4-(3-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate (70.0 mg), phenol (21.1 mg), and potassium carbonate (31.0 mg) in N,N-dimethylformamide was stirred for 2.5 hours at room temperature. The mixture was partitioned between ethyl acetate and 1 N hydrochloric acid. The organic layer was washed with water, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated to give ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(phenoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate as a yellow gum (77.5 mg, 108%).

ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-(phenoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H-NMR (CDCl_3) δ 1.21 (3H, t, J = 7 Hz), 1.35-1.53 (7H, m), 2.07 (2H, m), 2.54 (2H, m), 3.03 (2H, q, J = 7 Hz), 4.05 (2H, q, J = 7 Hz), 5.24 (2H, s), 5.86 (1H, d, J = 5 Hz), 6.65 (1H, d, J = 5 Hz), 6.80-7.01 (3H, m), 7.03 (2H, d, J = 9 Hz), 7.32 (2H, t, J = 9 Hz), 7.55-7.63 (2H, m), 7.67 (1H, s), 7.76 (1H, m).

MS (ESI^+): m/z 482 (M + H)

Example 614

A mixture of 4-(3-cyanophenyl)-7-ethyl-3-(methylsulfonyl)pyrrolo[1,2-

b]pyridazin-2-yl trifluoromethanesulfonate (50.0 mg), 3-furylboronic acid (23.6 mg), dichlorobis(triphenylphosphine)palladium (3.71 mg), and 2 N sodium carbonate (44.8 mg in 0.2 mL of water) in dioxane was stirred for 20 minutes at 85°C. The mixture was partitioned between EtOAc and water, and the organic layer was washed with brine, dried, and evaporated. Preparative thin layer chromatography (EtOAc-hexane = 1-1) afforded 3-[7-ethyl-2-(2-furyl)-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile as an orange solid (11.5 mg).

3-[7-ethyl-2-(2-furyl)-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile
10 ¹H-NMR (CDCl₃) δ 1.40 (3H, t, J = 7 Hz), 3.10 (2H, q, J = 7 Hz), 3.20 (3H, s), 6.30 (1H, d, J = 5 Hz), 6.63 (1H, m), 6.87 (1H, d, J = 5 Hz), 6.95 (1H, m), 7.60-7.73 (4H, m), 8.79 (1H, m).

Example 615

15 To a solution of 5-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (100 mg) in tetrahydrofuran (1 mL) was added 1 M borane-tetrahydrofuran complex (0.708 mL) in an ice bath under a nitrogen atmosphere. The mixture was stirred for 4 hours in the bath and 1 hour at room temperature. The reaction was quenched by adding 1 N hydrochloric acid (1 mL). The mixture was partitioned
20 between EtOAc (10 mL) and 1 N hydrochloric acid (5 mL). The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated. Preparative thin layer chromatography eluting with acetone-hexane = 1-2 afforded 3-[7-ethyl-3-(5-hydroxypentyl)-2-phenylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile as a yellow gum (104 mg).

25 3-[7-ethyl-3-(5-hydroxypentyl)-2-phenylpyrrolo[1,2-b]pyridazin-4-yl]benzonitrile
¹H-NMR (CDCl₃) δ 0.98-1.17 (6H, m), 1.36 (3H, t, J = 7 Hz), 2.38 (2H, m), 2.58 (2H, m), 3.34 (2H, m), 5.89 (1H, d, J = 5 Hz), 6.62 (1H, d, J = 5 Hz), 7.45-7.53 (5H, m), 7.55-7.67 (4H, m).

30 MS (ESI+): m/z 410 (M + H)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 24.

Preparation 343

ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-4-methoxy-3-oxobutanoate

¹H NMR (CDCl₃) δ 0.96-1.10 (3H, m), 3.23 (1.5H, s), 3.49 (1.5H, s), 4.00-4.34 (4H, m), 4.57 (1H, s), 8.00 (0.5H, br s), 8.23 (0.5H, br s), 8.60-8.91 (2H, m).

5

Preparation 344

1-tert-butyl 8-ethyl 2-acetyl-2-[(6-cyano-3-pyridinyl)carbonyl]octanedioate

¹H NMR (CDCl₃) δ 1.22-1.46 (16H, m), 1.55-1.70 (2H, m), 2.17-2.34 (4H, m), 2.48 (3H, s), 4.14 (2H, q, J = 8 Hz), 7.77 (1H, br d, J = 8 Hz), 8.17 (1H, dd, J = 8, 2 Hz), 8.97 (1H, d, J = 2 Hz).

10

The following compound(s) was(were) obtained in a similar manner to that of Preparation 78.

Preparation 345

15 ethyl 7-[(6-cyano-3-pyridinyl)carbonyl]-8-oxononanoate

¹H NMR (CDCl₃) δ 1.20-1.45 (7H, m), 1.52-1.70 (2H, m), 1.92-2.14 (2H, m), 2.17-2.39 (5H, m), 4.11 (2H, q, J = 8 Hz), 4.40 (1H, t, J = 8 Hz), 7.84 (1H, br d, J = 8 Hz), 8.39 (1H, m), 9.23 (1H, br s).

20 The following compound(s) was(were) obtained in a similar manner to that of Preparation 130.

Preparation 346

ethyl 4-methoxy-3-oxobutanoate

¹H NMR (CDCl₃) δ 1.28 (3H, t, J = 8 Hz), 3.42 (3H, s), 3.51 (2H, s), 4.09 (2H, s), 4.20 (2H, q, J = 8 Hz).

25

The following compound(s) was(were) obtained in a similar manner to that of Preparation 338.

Preparation 347

30 benzyl 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-5-bromobenzoate

¹H-NMR (CDCl₃) δ 1.28 (3H, t, J = 7 Hz), 2.75 (2H, q, J = 7 Hz), 5.37 (2H, s), 5.73 (2H, s), 5.94 (1H, d, J = 5 Hz), 6.66 (1H, d, J = 5 Hz), 7.35-7.48 (5H, m), 7.99 (1H, s), 8.33 (1H, s), 8.38 (1H, s).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 321.

Preparation 348

- 5 benzyl 3-bromo-5-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.29 (3H, t, $J = 7$ Hz), 2.72 (2H, q, $J = 7$ Hz), 5.37 (2H, s), 6.09 (1H, m), 6.78 (1H, m), 7.33-7.45 (5H, m), 8.15 (1H, s), 8.33 (1H, s), 8.45 (1H, s).

- 10 The following compound(s) was(were) obtained in a similar manner to that of Preparation 310.

Preparation 349

benzyl 3-bromo-5-(chlorocarbonyl)benzoate

- 15 Preparation 350

To a solution of benzyl 3-bromo-5-iodobenzoate (1.00 g) in THF (10 mL) was added 0.76 M isopropyl magnesium bromide (3.16 mL) in an ice bath under a nitrogen atmosphere. After stirring for 0.5 hour, the mixture was poured onto dryice. The mixture was warmed to room temperature over 1 hour. The mixture was partitioned between

- 20 EtOAc and 1 N HCl. The organic layer was washed with brine, dried over MgSO_4 , and evaporated. Flash silicagel column chromatography (chloroform-methanol = 50-0 to 50-2) afforded 3-benzyloxycarbonyl-5-bromobenzoic acid as a white solid (273 mg).

3-[(benzyloxy)carbonyl]-5-bromobenzoic acid

- 25 $^1\text{H-NMR}$ (DMSO-d_6) δ 5.39 (2H, s), 7.30-7.52 (5H, m), 8.29 (2H, s), 8.43 (1H, s).

Preparation 351

- 30 A mixture of 3-bromo-5-iodobenzoic acid (5.00 g) and N,N-dimethylformamide (0.059 mL) in dichloromethane (50 mL) was added oxalyl chloride (1.47 mL) in an ice bath under a nitrogen atmosphere. After stirring for 1 hour, the volatile was evaporated off. The residue was dissolved in dichloromethane (50 mL), and to the solution was added benzyl alcohol (1.82 g) followed by triethyl amine (3.2 mL) in the ice bath. The mixture was stirred for 2 hours at room temperature. The mixture was partitioned

between EtOAc and water. The organic layer was washed with water (two times), satd. NaHCO₃, and brine, dried over MgSO₄ and evaporated. Flash silicagel column chromatography (EtOAc-hexanes = 1/200 to 20/200) afforded benzyl 3-bromo-5-iodobenzoate as white crystals (5.95 g).

5

benzyl 3-bromo-5-iodobenzoate

¹H-NMR (CDCl₃) δ 5.35 (3H, s), 7.35-7.68 (5H, m), 8.04 (1H, s), 8.16 (1H, m), 8.30 (1H, s).

10 The following compound(s) was(were) obtained in a similar manner to that of Example 1.

Example 615

benzyl 3-bromo-5-[7-ethyl-2-methyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoate

15 ¹H-NMR (CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 2.88 (3H, s), 3.05 (3H, s), 3.06 (2H, q, J = 7 Hz), 5.35 (2H, s), 6.15 (1H, d, J = 5 Hz), 6.72 (1H, d, J = 5 Hz), 7.33-7.45 (5H, m), 7.68 (1H, m), 7.94 (1H, m), 8.28 (1H, m).

Example 616

20 4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazine-3-carbonitrile

¹H NMR (CDCl₃) δ 1.42 (3H, t, J = 8 Hz), 3.12 (2H, q, J = 8 Hz), 6.60 (1H, d, J = 5 Hz), 6.92 (1H, d, J = 5 Hz), 7.50-7.58 (3H, m), 7.73 (1H, t, J = 8 Hz), 7.82-7.91 (3H, m), 7.93-8.01 (2H, m).

25 Example 617

2-tert-butyl-4-(3-chlorophenyl)-7-ethylpyrrolo[1,2-b]pyridazine-3-carbonitrile

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 1.60 (9H, s), 3.05 (2H, q, J = 8 Hz), 6.48 (1H, d, J = 5 Hz), 6.77 (1H, d, J = 5 Hz), 7.45-7.54 (3H, m), 7.60 (1H, br s).

30 The following compound(s) was(were) obtained in a similar manner to that of Preparation 78.

Example 618

ethyl 6-[4-(6-cyano-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate

^1H NMR (CDCl_3) δ 1.15-1.64 (12H, m), 2.21 (1H, t, $J = 8$ Hz), 2.32-2.44 (2H, m), 2.56 (3H, s), 3.01 (2H, q, $J = 8$ Hz), 4.10 (2H, q, $J = 8$ Hz), 5.79 (1H, d, $J = 5$ Hz), 6.54 (1H, d, $J = 5$ Hz), 7.85 (1H, br s), 8.30 (1H, br d, $J = 8$ Hz), 8.72 (1H, br s).
MS (ESI^+): m/z 405 ($M + H$).

5

The following compound(s) was(were) obtained in a similar manner to that of Example 21.

Example 619

ethyl 4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

10

^1H NMR (CDCl_3) δ 1.04 (3H, t, $J = 8$ Hz), 1.38 (3H, t, $J = 8$ Hz), 3.06 (2H, q, $J = 8$ Hz), 3.39 (3H, s), 4.10 (2H, q, $J = 8$ Hz), 4.76 (2H, s), 6.33 (1H, d, $J = 5$ Hz), 6.74 (1H, d, $J = 5$ Hz), 7.96 (1H, br s), 8.61 (1H, br s), 8.78 (1H, d, $J = 2$ Hz).
MS (ESI^+): m/z 418, 420 ($M + H$).

15

The following compound(s) was(were) obtained in a similar manner to that of Example 76.

Example 620

3-bromo-5-[7-ethyl-2-methyl-3-(methylsulfonyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoic acid

20

^1H -NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 1.38 (3H, t, $J = 7$ Hz), 2.86 (3H, s), 3.05 (3H, s), 3.06 (2H, q, $J = 7$ Hz), 6.19 (1H, d, $J = 5$ Hz), 6.71 (1H, d, $J = 5$ Hz), 7.53 (1H, s), 7.90 (1H, s), 8.23 (1H, s).

25 Example 621

(2E)-3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylic acid

30

^1H NMR (CDCl_3) δ 1.39 (3H, t, $J = 8$ Hz), 3.07 (2H, q, $J = 8$ Hz), 3.51 (3H, s), 4.65 (2H, s), 5.96 (1H, d, $J = 15$ Hz), 6.27 (1H, d, $J = 5$ Hz), 6.74 (1H, d, $J = 5$ Hz), 7.68 (1H, d, $J = 15$ Hz), 7.93 (1H, m), 8.57 (1H, d, $J = 1$ Hz), 8.70 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 416, 418 ($M + H$).

Example 622

6-[4-(6-cyano-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoic acid

¹H NMR (CDCl₃) δ 1.15-1.69 (9H, m), 1.90-2.50 (4H, m), 2.56 (3H, s), 3.01 (2H, q, J = 8 Hz), 5.80 (1H, d, J = 5 Hz), 6.51 (1H, d, J = 5 Hz), 7.84 (1H, dd, J = 8, 2 Hz),
5 8.28 (1H, d, J = 8 Hz), 8.51 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 377 (M + H).

Example 622-2

6-{4-[6-(aminocarbonyl)-3-pyridinyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid

10 ¹H NMR (CDCl₃) δ 1.16-1.51 (9H, m), 2.10-2.24 (2H, m), 2.35-2.47 (2H, m), 2.58 (3H, s), 3.01 (2H, q, J = 8 Hz), 5.85 (1H, d, J = 5 Hz), 6.54 (1H, d, J = 5 Hz), 7.22 (1H, br s), 7.90 (1H, dd, J = 8, 1 Hz), 8.01 (1H, br s), 8.34 (1H, d, J = 8 Hz), 8.61 (1H, d, J = 1 Hz).

MS (ESI⁺): m/z 395 (M + H).

15

The following compound(s) was(were) obtained in a similar manner to that of Example 147.

Example 623

ethyl (2E)-3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylate

20 ¹H NMR (CDCl₃) δ 1.27 (3H, t, J = 8 Hz), 1.39 (3H, t, J = 8 Hz), 3.06 (2H, q, J = 8 Hz), 3.51 (3H, s), 4.17 (2H, q, J = 8 Hz), 4.64 (2H, s), 5.97 (1H, d, J = 15 Hz), 6.24 (1H, d, J = 5 Hz), 6.73 (1H, d, J = 5 Hz), 7.51 (1H, d, J = 15 Hz), 7.91 (1H, br s), 8.57 (1H, br s), 8.70 (1H, br s).

25 MS (ESI⁺): m/z 444, 446 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of Example 200.

Example 624

30 [4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]methanol

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 3.05 (2H, q, J = 8 Hz), 3.45-3.55 (4H, m), 4.40 (2H, br d, J = 7 Hz), 4.77 (2H, br s), 6.22 (1H, d, J = 5 Hz), 6.70 (1H, d, J =

5 Hz), 8.11 (1H, m), 8.74 (1H, br s), 8.80 (1H, d, J = 2 Hz).

MS (ESI⁺): m/z 376, 378 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of

5 Example 205.

Example 625

(4E)-5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-4-pentenoic acid

¹H NMR (CDCl₃) δ 1.37 (3H, t, J = 8 Hz), 2.26-2.43 (4H, m), 2.50 (3H, s), 3.01 (2H, q, J = 8 Hz), 5.40 (1H, dt, J = 15, 7 Hz), 6.05 (1H, d, J = 5 Hz), 6.20 (1H, d, J = 15 Hz), 6.56 (1H, d, J = 5 Hz), 7.28 (1H, br d, J = 5 Hz), 7.39 (1H, br s), 8.47 (1H, br d, J = 5 Hz).

MS (ESI⁺): m/z 370 (M + H).

15 Example 625-2

(4Z)-5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-4-pentenoic acid

¹H NMR (CDCl₃) δ 1.39 (3H, t, J = 8 Hz), 1.87-2.00 (2H, m), 2.12 (2H, t, J = 8 Hz), 2.42 (3H, s), 3.03 (2H, q, J = 8 Hz), 5.58 (1H, dt, J = 10, 8 Hz), 6.17 (1H, d, J = 5 Hz), 6.26 (1H, br d, J = 10 Hz), 6.60 (1H, d, J = 5 Hz), 7.35 (1H, br d, J = 5 Hz), 7.44 (1H, br s), 8.48 (1H, br d, J = 5 Hz).

MS (ESI⁺): m/z 370 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of

25 Example 220.

Example 626

4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid

¹H NMR (CDCl₃) δ 1.39 (3H, t, J = 8 Hz), 3.06 (2H, q, J = 8 Hz), 3.44 (3H, s), 4.82 (2H, s), 6.36 (1H, d, J = 5 Hz), 6.77 (1H, d, J = 5 Hz), 8.09 (1H, br s), 8.65 (1H, br s), 8.72 (1H, br s).

MS (ESI⁺): m/z 390, 392 (M + H).

Example 627

4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylic acid

- $^1\text{H NMR}$ (CDCl_3) δ 1.38 (3H, t, $J = 8$ Hz), 2.70 (3H, s), 3.06 (2H, q, $J = 8$ Hz), 6.26 (1H, d, $J = 5$ Hz), 6.72 (1H, d, $J = 5$ Hz), 7.32 (1H, dd, $J = 5, 1$ Hz), 7.43 (1H, br s), 8.50 (1H, d, $J = 5$ Hz).
MS (ESI^+): m/z 316 ($M + H$).

The following compound(s) was(were) obtained in a similar manner to that of Example 244.

10 Example 628

4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carbaldehyde

- $^1\text{H NMR}$ (CDCl_3) δ 1.39 (3H, t, $J = 8$ Hz), 2.81 (3H, s), 3.09 (2H, q, $J = 8$ Hz), 6.43 (1H, d, $J = 5$ Hz), 6.78 (1H, d, $J = 5$ Hz), 7.34 (1H, br d, $J = 5$ Hz), 7.46 (1H, br s), 8.56 (1H, d, $J = 5$ Hz), 9.76 (1H, s).
MS (ESI^+): m/z 300 ($M + H$).

Example 629

4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde

- $^1\text{H NMR}$ (CDCl_3) δ 1.41 (3H, t, $J = 8$ Hz), 3.14 (2H, q, $J = 8$ Hz), 3.55 (3H, s), 4.94 (2H, s), 6.50 (1H, d, $J = 5$ Hz), 6.84 (1H, d, $J = 5$ Hz), 7.95 (1H, br s), 8.12 (1H, br s), 8.84 (1H, br s), 9.85 (1H, s).
MS (ESI^+): m/z 374, 376 ($M + H$).

25 Example 630

- A solution of phosphorus oxychloride (241 mg, 1.57 mmol) in N,N -dimethylformamide (4 mL) was stirred for 10 min at room temperature. The resulting mixture was cooled to 0°C , and a solution of ethyl 4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (428 mg, 1.31 mmol) in N,N -dimethylformamide (0.7 mL) was added. The resulting mixture was warmed to 50°C , and stirred for 45 min. Since the starting material was remained, a solution of phosphorus oxychloride (621 mg, 0.67 mmol) in N,N -dimethylformamide (0.2 mL) was added, and the mixture was stirred for 15 min. The resulting mixture was poured into

ice-cooled water (10 mL), and extracted with ethyl acetate (30 mL). The organic layer was washed with water and saturated sodium bicarbonate. All the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give a blue oil. Flash silica gel
5 column chromatography eluting with ethyl acetate-hexane = 1-20 to 1-10 afforded ethyl 4-(4-fluorophenyl)-7-formyl-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow oil, which was crystalized upon standing (360 mg, 77.5%).

$^1\text{H-NMR}$ (CDCl_3) δ 1.02 (3H, t, $J = 7$ Hz), 1.41 (6H, d, $J = 7$ Hz), 3.29 (1H, septet, $J = 7$ Hz), 4.10 (2H, q, $J = 7$ Hz), 6.42 (1H, d, $J = 5$ Hz), 7.20 (2H, t, $J = 9$ Hz),
10 7.45 - 7.51 (3H, m), 10.56 (1H, s).

MS (ESI^+): m/z 355 ($M + H$)

Example 631

15 To a solution of N,N -dimethylacetamide (80.1 mg, 0.919 mmol) in dichloroethane (1 mL) was added phosphorus oxychloride (141 mg, 0.919 mmol) in dichloroethane (0.5 mL) at 0°C . After stirring for 0.5 h, a solution of ethyl 4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (200 mg, 0.613 mmol) in dichloroethane (0.5 mL) was added. The resulting mixture was stirred for 3 days at room
20 temperature. The mixture was partitioned between ethyl acetate (30 mL) and water (5 mL), and the organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, and evaporated to give an orange gum. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-20 to 1-10 afforded ethyl 7-acetyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate as
25 a yellow gum (144 mg, 63.8%).

$^1\text{H-NMR}$ (CDCl_3) δ 1.00 (3H, t, $J = 7$ Hz), 1.41 (6H, d, $J = 7$ Hz), 2.88 (3H, s), 3.09 (1H, septet, $J = 7$ Hz), 4.09 (2H, q, $J = 7$ Hz), 6.40 (1H, d, $J = 5$ Hz), 7.19 (2H, t, $J = 9$ Hz), 7.46 (2H, dd, $J = 3$ and 9 Hz), 7.57 (2H, d, $J = 7$ Hz).

30 MS (ESI^+): m/z 369 ($M + H$)

Example 632

A solution of ethyl 4-(4-fluorophenyl)-7-formyl-2-isopropylpyrrolo[1,2-

b]pyridazine-3-carboxylate (100 mg, 0.282 mmol) and sodium borohydride (10.7 mg, 0.282 mmol) in ethanol (1 mL) was stirred for 0.5 h under an ice bath. The mixture was partitioned between ethyl acetate (10 mL) and water (5 mL), and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give
5 ethyl 4-(4-fluorophenyl)-7-hydroxymethyl-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow gum (89.1 mg, 89.1%).

$^1\text{H-NMR}$ (CDCl_3) δ 0.97 (3H, t, $J = 7$ Hz), 1.37 (6H, , $J = 7$ Hz), 3.25-3.37 (2H, m),
4.04 (2H, q, $J = 7$ Hz), 5.06 (1H, d, $J = 7$ Hz), 6.32 (1H, d, $J = 5$ Hz), 6.78 (1H, d,
10 $J = 5$ Hz), 7.19 (2H, t, $J = 9$ Hz), 7.46 (2H, d, $J = 4$ and 9 Hz).

Example 633

To a solution of ethyl 4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (80.0 mg, 0.245 mmol) and N,N -dimethylaminopyridine (29.9 mg, 0.245
15 mmol) in N,N -dimethylformamide (0.5 mL) was added 3,7-dinitro-5-(trifluoromethyl)dibenzo[b,d]thiophenium trifluoromethanesulfonate (120 mg, 0.245 mmol) at -20°C . The resulting mixture was stirred for 45 min at 0°C and 12 h at room temperature. Water (5 mL) and ethyl acetate (10 mL) were added, and the resulting mixture was filtered. The organic layer was washed with brine, dried over anhydrous
20 magnesium sulfate, and evaporated to give a brown gum. Flash silica gel column chromatography eluting with toluene-hexane = 1-5 to 4-5 afforded ethyl 4-(4-fluorophenyl)-2-isopropyl-7-trifluoromethylpyrrolo[1,2-b]pyridazine-3-carboxylate product as a yellow gum (46.7 mg, 48.3%).

25 $^1\text{H-NMR}$ (CDCl_3) δ 1.00 (3H, t, $J = 7$ Hz), 1.38 (6H, d, $J = 7$ Hz), 3.26 (1H, septet, $J = 7$ Hz), 4.08 (2H, q, $J = 7$ Hz), 6.33 (1H, d, $J = 5$ Hz), 7.12 (1H, d, $J = 5$ Hz), 7.19 (2H, t, $J = 9$ Hz), 7.47 (2H, d, $J = 4$ and 9 Hz).

MS (ESI^+): m/z 395 ($M + H$)

30 Example 634

A solution of ethyl 4-(4-fluorophenyl)-7-formyl-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (200 mg, 0.564 mmol), hydroxylamine hydrochloride (51.0 mg, 0.734 mmol), and sodium formate (69.1 mg, 1.02 mmol) in formic acid (2 mL) were

refluxed for 2 h. The mixture was evaporated to give a green gum. The gum was partitioned between ethyl acetate (10 mL) and saturated sodium bicarbonate (5 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give a green gum. Flash silica gel column chromatography eluting with
5 ethyl acetate-hexane = 1-10 to 1-8 gave ethyl 7-cyano-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow crystal (144 mg, 72.6%).

$^1\text{H-NMR}$ (CDCl_3) δ 1.01 (3H, t, $J = 7$ Hz), 1.41 (6H, d, $J = 7$ Hz), 3.26 (1H, septet, $J = 7$ Hz), 4.09 (2H, q, $J = 7$ Hz), 6.36 (1H, d, $J = 5$ Hz), 7.20 (2H, t, $J = 9$ Hz), 7.28
10 (1H, d, $J = 5$ Hz), 7.47 (2H, d, $J = 4$ and 9 Hz).
 $\text{MS (ESI}^+)$: m/z 398 ($\text{M} + \text{HCOOH} + \text{H}$)

Example 635

A solution of ethyl 7-cyano-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-
15 b]pyridazine-3-carboxylate (70.4 mg, 0.200 mmol) in sulfuric acid (1 mL) was stirred for 50 min at 70°C. The solution was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give a brown gum. Preparative silica gel thin layer chromatography eluting with ethyl acetate-hexane = 1-1 afforded ethyl 7-aminocarbonyl-4-(4-fluorophenyl)-2-
20 isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate as an orange solid (5.2 mg, 7.0%).

$^1\text{H-NMR}$ (CDCl_3) δ 0.99 (3H, t, $J = 7$ Hz), 1.41 (6H, d, $J = 7$ Hz), 3.41 (1H, septet, $J = 7$ Hz), 4.08 (2H, q, $J = 7$ Hz), 5.93 (1H, br s), 6.46 (1H, d, $J = 5$ Hz), 7.45 (2H, t, $J = 9$ Hz), 7.28 (1H, d, $J = 5$ Hz), 8.90 (1H, br s).
25

Example 636

To a mixture of ethyl 4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate (100 mg, 0.306 mmol) and ammonium thiocyanate (28.0 mg, 0.368 mmol) in methanol (100 mL) was added cerium ammonium nitrate (386 mg, 0.705 mmol) under an
30 ice bath. The mixture was stirred for 30 min. The mixture was stirred for additional 10 min after adding ammonium thiocyanate (8.2 mg, 0.107 mmol). Water (5 mL) was added, and the mixture was extracted with ethyl acetate (20 mL). The organic extract was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give a

deep green gum. Flash silica gel column chromatography eluting with ethyl acetate-hexane = 1-10 to 3-20 afforded ethyl ethyl 4-(4-fluorophenyl)-2-isopropyl-7-thiocyanatopyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow gum (89.6 mg, 82.3%).

- 5 $^1\text{H-NMR}$ (CDCl_3) δ 1.01 (3H, t, $J = 7$ Hz), 1.46 (6H, d, $J = 7$ Hz), 3.36 (1H, septet, $J = 7$ Hz), 4.08 (2H, q, $J = 7$ Hz), 6.23 (1H, d, $J = 5$ Hz), 7.14-7.22 (3H, m), 7.16 (2H, t, $J = 9$ Hz), 7.46 (2H, dd, $J = 4$ and 9 Hz).

Example 637

- 10 To a solution of ethyl 4-(4-fluorophenyl)-2-isopropyl-7-thiocyanatopyrrolo[1,2-b]pyridazine-3-carboxylate (77.7 mg, 0.219 mmol) in methanol (0.7 mL) was added 85% potassium hydroxide (0.3 mg, 0.004 mmol) at room temperature. After stirring for 5 min, the mixture was partitioned between ethyl acetate (20 mL) and water (5 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and
15 evaporated to give a yellow gum. Preparative silica gel thin layer chromatography eluting with ethyl acetate-hexane = 1-7 afforded ethyl 4-(4-fluorophenyl)-2-isopropyl-7-(methylthio)pyrrolo[1,2-b]pyridazine-3-carboxylate as a yellow gum (35.9 mg, 44.1%).

- $^1\text{H-NMR}$ (CDCl_3) δ 0.98 (3H, t, $J = 7$ Hz), 1.41 (6H, d, $J = 7$ Hz), 2.52 (3H, s), 3.32
20 (1H, septet, $J = 7$ Hz), 4.05 (2H, q, $J = 7$ Hz), 6.35 (1H, d, $J = 5$ Hz), 6.89 (1H, d, $J = 5$ Hz), 7.16 (2H, t, $J = 9$ Hz), 7.44 (2H, d, $J = 4$ and 9 Hz).

MS (ESI^+): m/z 373 ($M + H$)

The following compound(s) was(were) obtained in a similar manner to that of

- 25 Example 1

Example 638

3-(9-ethyl-3-methoxy-5,6-dihydrobenzo[f]pyrrolo[1,2-b]cinnolin-12-yl)benzonitrile

- $^1\text{H NMR}$ (CDCl_3) δ 1.41 (3H, t, $J = 8$ Hz), 2.91-3.11 (6H, m), 3.78 (3H, s), 6.09 (1H, d, $J = 5$ Hz), 6.38 (1H, dd, $J = 8, 3$ Hz), 6.52 (1H, d, $J = 8$ Hz), 6.59 (1H, d, $J = 5$ Hz), 6.77 (1H, br s), 7.56 (1H, t, $J = 8$ Hz), 7.67 (1H, br d, $J = 8$ Hz), 7.70-7.77
30 (2H, m).

Example 639

4-(3-ethyl-6H-indeno[1,2-e]pyrrolo[1,2-b]pyridazin-11-yl)benzonitrile

- ¹H NMR (CDCl₃) δ 1.43 (3H, t, J = 8 Hz), 3.09 (2H, q, J = 8 Hz), 4.11 (3H, s), 6.14 (1H, d, J = 5 Hz), 6.64 (1H, d, J = 5 Hz), 6.71 (1H, d, J = 8 Hz), 7.07 (1H, t, J = 8 Hz), 7.20-7.30 (1H, overlapped with CDCl₃), 7.49 (1H, d, J = 8 Hz), 7.69 (2H, d, J = 8 Hz), 7.88 (2H, d, J = 8 Hz).
- MS (ESI⁺): m/z 336 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 24.

10 Preparation 352

ethyl 4-methoxy-2-[(5-methyl-3-pyridinyl)carbonyl]-3-oxobutanoate

- ¹H NMR (CDCl₃) δ 0.97, 1.26 (3H, t, J = 7 Hz), 2.40 (3H, s), 3.24, 3.35, 3.49 (3H, s), 3.98-4.20 (2H, m), 4.11, 4.20, 4.54 (2H, s), 5.70 (1H, s), 7.67, 7.92, 8.02, 8.50-8.66, 8.77, 8.89 (3H, m).

15 Preparation 353

ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-4-methoxy-3-oxobutanoate

- ¹H NMR (CDCl₃) δ 1.00, 1.06, 1.28, 1.35 (3H, t, J = 7 Hz), 3.23, 3.43, 3.49 (3H, s), 4.05-4.33 (2H, m), 4.56 (2H, s), 7.85, 8.05, 8.22, 8.29, 8.58-8.82, 8.85, 9.01, 9.10 (3H, m).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 176.

25 Preparation 354

tert-butyl 3-bromo-5-({1-[(cyanoacetyl)amino]-5-ethyl-1H-pyrrol-2-yl}carbonyl)benzoate

- ¹H-NMR (CDCl₃) δ 1.29 (3H, t, J = 7 Hz), 1.60 (9H, s), 2.61 (2H, q, J = 7 Hz), 3.64 (2H, s), 6.00 (1H, m), 6.80 (1H, m), 8.03 (1H, m), 8.26 (1H, m), 8.28 (1H, m).

30 Preparation 355

tert-butyl 3-bromo-5-[(5-ethyl-1-[(methylsulfonyl)acetyl]amino)-1H-pyrrol-2-yl]carbonyl]benzoate

- ¹H-NMR (CDCl₃) δ 1.29 (3H, t, J = 7 Hz), 1.60 (9H, s), 2.60 (2H, q, J = 7 Hz), 2.92

(3H, s), 4.04 (2H, s), 6.11 (1H, m), 6.78 (1H, m), 8.03 (1H, m), 8.25 (1H, m), 8.27 (1H, m).

The following compound(s) was(were) obtained in a similar manner to that of

5 Preparation 153.

Preparation 356

tert-butyl 3-bromo-5-(chlorocarbonyl)benzoate

The following compound(s) was(were) obtained in a similar manner to that of

10 Preparation 164.

Preparation 357

tert-butyl 3-bromo-5-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzoate

¹H-NMR (CDCl₃) δ 1.32 (3H, t, J = 7 Hz), 1.61 (9H, s), 2.74 (2H, q, J = 7 Hz), 6.10 (1H, m), 6.80 (1H, m), 8.13 (1H, m), 8.26 (1H, m), 8.39 (1H, m), 9.34 (1H, s, br).

15

The following compound(s) was(were) obtained in a similar manner to that of

Preparation 338.

Preparation 358

tert-butyl 3-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-5-bromobenzoate

20 ¹H-NMR (CDCl₃) δ 1.29 (3H, t, J = 7 Hz), 1.61 (9H, s), 2.76 (2H, q, J = 7 Hz), 5.74 (2H, s, br), 5.93 (1H, d, J = 5 Hz), 6.63 (1H, d, J = 5 Hz), 8.05 (1H, m), 8.25 (1H, m), 8.29 (1H, m).

Preparation 359

25 To a solution of tert-butyl 3-bromo-5-iodobenzoate (4.00 g) in tetrahydrofuran (30 mL) was added 0.76 M isopropylmagnesium bromide (13.7 mL) in an ice-methanol bath under a nitrogen atmosphere. After stirring for 0.5 hour, the mixture was poured onto dryice. The mixture was warmed to room temperature over 1 hour. The mixture was partitioned between EtOAc and 1 N hydrochloric acid. The organic layer was back
30 extracted with 1 N sodium hydroxide (two times). The extract was acidified by adding concentrated hydrochloric acid, and extracted with chloroform (two times). The organic extract was washed with brine, dried over MgSO₄, and evaporated to give 3-bromo-5-(tert-butoxycarbonyl)benzoic acid as a pale brown solid (529 mg).

3-bromo-5-(tert-butoxycarbonyl)benzoic acid

^1H -NMR (DMSO- d_6) δ 1.57 (9H, s), 8.21 (1H, s), 8.25 (1H, s), 8.37 (1H, s).

5 Preparation 360

To a vigorously stirred suspension of powdered MgSO_4 (7.36 g) in dichloromethane (50 mL) was added sulfuric acid (0.758 mL) at room temperature. After stirring for 15 minutes, to the mixture was added 3-bromo-5-iodobenzoic acid (5.00 g) followed by tert-butanol (7.31 mL). The mixture was stirred for 3 days at room
10 temperature. The mixture was partitioned between EtOAc and water. The organic layer was washed with satd. NaHCO_3 and brine, dried over MgSO_4 , and evaporated to give tert-butyl 3-bromo-5-iodobenzoate as pale purple crystals (4.44 g).

tert-butyl 3-bromo-5-iodobenzoate

15 ^1H -NMR (CDCl_3) δ 1.58 (9H, s), 8.00 (1H, m), 8.06 (1H, m), 8.22 (1H, m).

Preparation 361

To a suspension of lithium (316 mg) in ether (10 mL) was added cyclopropylbromide (2.50 g) in ether (10 mL) over 20 min in a methanol-ice bath under a
20 nitrogen atmosphere. The mixture was stirred for 0.5 hour in an ice bath. The mixture was cooled in a dryice-acetone bath. To the mixture was added a solution of triisopropoxyborane (5.05 g) in tetrahydrofuran (5 mL) over 15 minutes. The mixture was allowed to warm to room temperature over 2 hours. The reaction was quenched by adding hydrochloric acid. The organic solvent was evaporated off, and the residual
25 solution was extracted with ether (30 mL, five times). The combined extract was dried over MgSO_4 , and evaporated to give a white solid (968 mg). The solid was triturated in cold hexanes to give cyclopropylboronic acid as a white powder (789 mg).

cyclopropylboronic acid

30 ^1H -NMR (DMSO- d_6) δ -0.40 (1H, m), 0.32 (2H, m), 0.39 (2H, m), 7.28 (2H, s).

The following compound(s) was(were) obtained in a similar manner to that of Example 21.

Example 640

ethyl 7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

^1H NMR (CDCl_3) δ 0.99 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 2.41 (3H, s), 3.06 (2H, q, $J = 7$ Hz), 3.38 (3H, s), 4.06 (2H, q, $J = 7$ Hz), 4.75 (2H, s), 6.33 (1H, d, $J = 4$ Hz), 6.71 (1H, d, $J = 4$ Hz), 7.61 (1H, s), 8.52 (1H, d, $J = 2$ Hz), 8.54 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 354.

10 Example 641

ethyl 4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

^1H NMR (300 MHz, CDCl_3) δ 1.04 (3H, t, $J = 7$ Hz), 1.38 (3H, t, $J = 7$ Hz), 3.06 (2H, q, $J = 7$ Hz), 3.39 (3H, s), 4.09 (2H, q, $J = 7$ Hz), 4.76 (2H, s), 6.33 (1H, d, $J = 4$ Hz), 6.75 (1H, d, $J = 4$ Hz), 7.81 (1H, dd, $J = 2, 2$ Hz), 8.57 (1H, d, $J = 2$ Hz), 8.68 (1H, d, $J = 2$ Hz).

MS (m/z) 374 ($M+1$).

The following compound(s) was(were) obtained in a similar manner to that of

20 Example 076.Example 642

(2E)-3-[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylic acid

^1H NMR (CDCl_3) δ 1.39 (3H, t, $J = 7$ Hz), 2.43 (3H, s), 3.07 (2H, q, $J = 7$ Hz), 3.51 (3H, s), 4.65 (2H, s), 5.97 (1H, d, $J = 16$ Hz), 6.27 (1H, d, $J = 4$ Hz), 6.71 (1H, d, $J = 4$ Hz), 7.61 (1H, s), 7.72 (1H, d, $J = 16$ Hz), 8.46 (1H, d, $J = 2$ Hz), 8.57 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 352.

30 Example 643

(2E)-3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylic acid

^1H NMR (300 MHz, CDCl_3) δ 1.39 (3H, t, $J = 7$ Hz), 3.07 (2H, q, $J = 7$ Hz), 3.51

(3H, s), 4.65 (2H, s), 5.97 (1H, d, J = 16 Hz), 6.27 (1H, d, J = 4 Hz), 6.75 (1H, d, J = 4 Hz), 7.69 (1H, d, J = 16 Hz), 7.78 (1H, dd, J = 2, 2 Hz), 8.54 (1H, d, J = 2 Hz), 8.71 (1H, d, J = 2 Hz).

MS (m/z) 400 (M+1).

5

Example 644

4-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

¹H-NMR (CDCl₃) δ 0.78 (2H, m), 1.10 (2H, m), 1.37 (3H, t, J = 7 Hz), 1.73 (2H, m),
 10 1.98 (1H, m), 2.23 (2H, m), 2.62 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.46 (3H, s),
 4.65 (2H, q, J = 7 Hz), 5.88 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz), 7.36 (1H,
 m), 8.41 (1H, m), 8.47 (1H, m).

Example 645

15 5-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

¹H-NMR (CDCl₃) δ 0.75 (2H, m), 1.08 (2H, m), 1.37 (3H, t, J = 7 Hz), 1.40-1.57 (4H,
 m), 1.96 (1H, m), 2.18 (2H, m), 2.51 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.45 (3H, s),
 4.61 (2H, m), 5.87 (1H, d, J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 7.34 (1H, m), 8.39
 20 (1H, m), 8.50 (1H, m).

Example 646

3-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

25 ¹H-NMR (DMSO-d₆) δ 0.76 (2H, m), 1.08 (2H, m), 1.37 (3H, t, J = 7 Hz), 1.95 (1H,
 m), 2.48 (2H, m), 2.87 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.47 (3H, s), 4.66 (2H, m),
 5.90 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.35 (1H, m), 8.40 (1H, m), 8.48
 (1H, m).

30 Example 647

5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-oxopentanoic acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 1.73-1.85 (2H, m), 2.26 (2H, t, J = 8 Hz),

2.36 (2H, t, J = 8 Hz), 2.46 (3H, s), 3.04 (2H, q, J = 8 Hz), 6.33 (1H, d, J = 5 Hz),
6.70 (1H, d, J = 5 Hz), 7.34 (1H, br d), 7.45 (1H, br s), 8.53 (1H, d, J = 6 Hz).

Example 648

- 5 (2E)-3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acrylic
acid

¹H NMR (CDCl₃) δ 1.38 (3H, t, J = 8 Hz), 2.67 (3H, s), 3.05 (2H, q, J = 8 Hz), 5.79
(1H, d, J = 15 Hz), 6.19 (1H, d, J = 5 Hz), 6.67 (1H, d, J = 5 Hz), 7.24-7.29 (1H,
overlapped with CDCl₃), 7.40 (1H, br s), 7.51 (1H, d, J = 15 Hz), 8.55 (1H, d, J =
10 5 Hz).

The following compound(s) was(were) obtained in a similar manner to that of
Example 146.

Example 649

- 15 ethyl (2E)-3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-
yl]acrylate

¹H NMR (CDCl₃) δ 1.27 (3H, t, J = 8 Hz), 1.38 (3H, t, J = 8 Hz), 2.65 (3H, s), 3.04
(2H, q, J = 8 Hz), 4.17 (2H, q, J = 8 Hz), 5.76 (1H, d, J = 15 Hz), 6.16 (1H, d, J =
5 Hz), 6.65 (1H, d, J = 5 Hz), 7.24-7.29 (1H, overlapped with CDCl₃), 7.40 (1H,
20 br s), 7.53 (1H, d, J = 15 Hz), 8.53 (1H, d, J = 5 Hz).

MS (ESI⁺): m/z 370 (M + H).

The following compound(s) was(were) obtained in a similar manner to that of
Example 181.

- 25 Example 650

tert-butyl 3-bromo-5-(3-cyano-7-ethyl-2-oxo-1,2-dihydropyrrolo[1,2-b]pyridazin-4-
yl)benzoate

¹H-NMR (CDCl₃) δ 1.36 (3H, t, J = 7 Hz), 2.94 (2H, q, J = 7 Hz), 6.57 (1H, d, J = 5
Hz), 6.72 (1H, d, J = 5 Hz), 7.94 (1H, m), 8.20 (1H, m), 8.38 (1H, m).

30

Example 651

tert-butyl 3-bromo-5-[7-ethyl-3-(methylsulfonyl)-2-oxo-1,2-dihydropyrrolo[1,2-
b]pyridazin-4-yl]benzoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.35 (3H, t, $J = 7$ Hz), 3.02 (2H, q, $J = 7$ Hz), 3.06 (3H, s), 6.24 (1H, d, $J = 5$ Hz), 6.70 (1H, d, $J = 5$ Hz), 7.23 (1H, m), 7.94 (1H, m), 8.25 (1H, m).

- 5 The following compound(s) was(were) obtained in a similar manner to that of Example 183.

Example 652

tert-butyl 3-bromo-5-(3-cyano-7-ethyl-2-[[trifluoromethyl)sulfonyl]oxy]pyrrolo[1,2-b]pyridazin-4-yl)benzoate

- 10 $^1\text{H-NMR}$ (CDCl_3) δ 1.39 (3H, t, $J = 7$ Hz), 1.61 (9H, s), 3.02 (2H, q, $J = 7$ Hz), 6.81 (1H, d, $J = 5$ Hz), 7.00 (1H, d, $J = 5$ Hz), 7.96 (1H, m), 8.21 (1H, m), 8.33 (1H, m).

Example 653

tert-butyl 3-bromo-5-(7-ethyl-3-(methylsulfonyl)-2-

- 15 {[(trifluoromethyl)sulfonyl]oxy}pyrrolo[1,2-b]pyridazin-4-yl)benzoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 1.59 (9H, s), 3.01 (2H, q, $J = 7$ Hz), 3.22 (3H, s), 6.46 (1H, d, $J = 5$ Hz), 7.12 (1H, d, $J = 5$ Hz), 7.67 (1H, m), 7.90 (1H, m), 8.23 (1H, m).

- 20 The following compound(s) was(were) obtained in a similar manner to that of Example 184.

Example 654

tert-butyl 3-bromo-5-[3-cyano-7-ethyl-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoate

- 25 $^1\text{H-NMR}$ (CDCl_3) δ 1.35 (3H, t, $J = 7$ Hz), 1.60 (9H, s), 2.01 (4H, m), 2.93 (2H, q, $J = 7$ Hz), 3.73 (4H, m), 6.32 (1H, d, $J = 5$ Hz), 6.58 (1H, d, $J = 7$ Hz), 7.86 (1H, m), 8.12 (1H, m), 8.24 (1H, m).

Example 655

- 30 tert-butyl 3-bromo-5-[7-ethyl-3-(methylsulfonyl)-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoate

$^1\text{H-NMR}$ (CDCl_3) δ 1.37 (3H, t, $J = 7$ Hz), 1.58 (9H, s), 1.99 (4H, m), 2.98 (2H, q, $J = 7$ Hz), 3.21 (3H, s), 3.52 (4H, m), 6.30 (1H, d, $J = 5$ Hz), 6.66 (1H, d, $J = 5$ Hz),

7.76 (1H, m), 8.00 (1H, m), 8.19 (1H, m).

The following compound(s) was(were) obtained in a similar manner to that of Example 147.

5 Example 656

ethyl (2E)-3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylate

¹H NMR (300 MHz, CDCl₃) δ 1.27 (3H, t, J = 7 Hz), 1.39 (3H, t, J = 7 Hz), 3.07 (2H, q, J = 7 Hz), 3.51 (3H, s), 4.18 (2H, q, J = 7 Hz), 4.64 (2H, s), 5.97 (1H, d, J = 16 Hz), 6.24 (1H, d, J = 4 Hz), 6.72 (1H, d, J = 4 Hz), 7.61 (1H, d, J = 16 Hz), 7.76 (1H, dd, J = 2, 2 Hz), 8.54 (1H, d, J = 2 Hz), 8.68 (1H, d, J = 2 Hz).

The following compound(s) was(were) obtained in a similar manner to that of Example 205.

15 Example 657

(4E)-5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]-4-pentenoic acid

¹H NMR (300 MHz, CDCl₃) δ 1.38 (3H, t, J = 7 Hz), 2.25-2.41 (4H, m), 3.05 (2H, q, J = 7 Hz), 3.50 (3H, s), 4.57 (2H, s), 5.53 (1H, dd, J = 16, 7 Hz), 6.13 (1H, d, J = 4 Hz), 6.36 (1H, d, J = 16 Hz), 6.65 (1H, d, J = 4 Hz), 7.80 (1H, s), 8.54 (1H, br s), 8.62 (1H, br s).

MS (m/z) 400 (M+1).

The following compound(s) was(were) obtained in a similar manner to that of Preparation 153.

Example 658

4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carbonyl chloride

The following compound(s) was(were) obtained in a similar manner to that of Example 244.

Example 659

7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde

^1H NMR (CDCl_3) δ 1.40 (3H, t, $J = 7$ Hz), 2.45 (3H, s), 3.12 (2H, q, $J = 7$ Hz), 3.56 (3H, s), 4.96 (2H, s), 6.51 (1H, d, $J = 4$ Hz), 6.80 (1H, d, $J = 4$ Hz), 7.62 (1H, s), 8.54 (1H, s), 8.61 (1H, s), 9.79 (1H, s).

MS (ESI^+): m/z 310.

5

Example 660

4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde

^1H NMR (300 MHz, CDCl_3) δ 1.41 (3H, t, $J = 7$ Hz), 3.12 (2H, q, $J = 7$ Hz), 3.54 (3H, s), 4.94 (2H, s), 6.50 (1H, d, $J = 4$ Hz), 6.84 (1H, d, $J = 4$ Hz), 7.81 (1H, dd, $J = 2, 2$ Hz), 8.59 (1H, d, $J = 2$ Hz), 8.74 (1H, d, $J = 2$ Hz), 9.85 (1H, s).

10

The following compound(s) was(were) obtained in a similar manner to that of Example 533.

15 Example 661

[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]methanol

^1H NMR (CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 2.43 (3H, s), 3.05 (2H, q, $J = 7$ Hz), 3.52 (3H, s), 4.37-4.51 (2H, br), 4.66-4.78 (2H, br), 6.20 (1H, d, $J = 4$ Hz), 6.67 (1H, d, $J = 4$ Hz), 7.75 (1H, s), 8.54 (1H, s), 8.60 (1H, s).

20

MS (ESI^+): m/z 312.

Example 662

[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]methanol

25

^1H NMR (300 MHz, CDCl_3) δ 1.38 (3H, t, $J = 7$ Hz), 3.05 (2H, q, $J = 7$ Hz), 3.53 (3H, s), 4.41 (2H, d, $J = 6$ Hz), 4.77 (2H, s), 6.22 (1H, d, $J = 4$ Hz), 6.70 (1H, d, $J = 4$ Hz), 7.97 (1H, dd, $J = 2, 2$ Hz), 8.69-8.71 (2H, m).

MS (m/z) 332 ($M+1$).

30

Example 663

A mixture of 7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde (48 mg) and ethyl (triphenylphosphoranylidene)acetate

(56.8 mg) in THF (3 mL) was stirred at ambient temperature for 2 hours. After evaporation of solvent, the residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (5:1 - 2:1) to give ethyl (2E)-3-[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylate as a yellow powder (30 mg).

ethyl (2E)-3-[7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]acrylate

^1H NMR (CDCl_3) δ 1.26 (3H, t, $J = 7$ Hz), 1.39 (3H, t, $J = 7$ Hz), 2.42 (3H, s), 3.07 (2H, q, $J = 7$ Hz), 3.51 (3H, s), 4.12 (2H, q, $J = 7$ Hz), 4.64 (2H, s), 5.97 (1H, d, $J = 16$ Hz), 6.24 (1H, d, $J = 4$ Hz), 6.70 (1H, d, $J = 4$ Hz), 7.55 (1H, s), 7.63 (1H, d, $J = 16$ Hz), 8.47 (1H, d, $J = 2$ Hz), 8.55 (1H, d, $J = 2$ Hz).

MS (ESI^+): m/z 380.

Example 664

To a mixture of ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate (75.0 mg), cyclopropylboronic acid (18.2 mg), tricyclohexylphosphine (4.57 mg), and potassium phosphate (104 mg) in toluene-water (1 mL-0.2 mL) was added palladium acetate (1.83 mg). The mixture was stirred for 2 hours at 100°C . The mixture was partitioned between EtOAc and water.

The organic layer was washed with brine, dried over MgSO_4 , and evaporated. Preparative silicagel thin layer chromatography (EtOAc-hexanes = 1-3) afforded ethyl 4-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate as a yellow gum (60.9 mg).

ethyl 4-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

^1H -NMR (CDCl_3) δ 0.76 (2H, m), 1.07 (2H, m), 1.20 (3H, t, $J = 7$ Hz), 1.37 (3H, t, $J = 7$ Hz), 1.68 (2H, m), 1.96 (1H, m), 2.17 (2H, m), 2.56 (2H, m), 3.02 (2H, q, $J = 7$ Hz), 3.46 (3H, s), 4.03 (2H, q, $J = 7$ Hz), 4.65 (2H, m), 5.90 (1H, d, $J = 5$ Hz), 6.57 (1H, d, $J = 5$ Hz), 7.30 (1H, m), 8.40 (1H, m), 8.51 (1H, m).

The following compound(s) was(were) obtained in a similar manner to that of Example 664.

Example 665

ethyl 5-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoate

¹H-NMR (CDCl₃) δ 0.76 (2H, m), 1.08 (2H, m), 1.23 (3H, t, J = 7 Hz), 1.35-1.57 (7H, m), 1.96 (1H, m), 2.16 (2H, t, J = 7 Hz), 2.53 (2H, m), 3.03 (2H, q, J = 7 Hz),
5 3.46 (3H, s), 4.08 (2H, q, J = 7 Hz), 4.62 (2H, s), 5.89 (1H, d, J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 7.29 (1H, m), 8.40 (1H, m), 8.52 (1H, m).

Example 666

10 ethyl 3-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

¹H-NMR (CDCl₃) δ 0.76 (2H, m), 1.08 (2H, m), 1.19 (3H, t, J = 7 Hz), 1.37 (3H, t, J = 7 Hz), 1.97 (1H, m), 2.38 (2H, m), 2.85 (2H, m), 3.02 (2H, q, J = 7 Hz), 3.46 (3H, s), 4.04 (2H, q, J = 7 Hz), 4.64 (2H, s), 5.92 (1H, d, J = 5 Hz), 6.59 (1H, d, J = 5 Hz), 7.29 (1H, m), 8.40 (1H, m), 8.53 (1H, m).

15

Example 667

tert-butyl 3-[3-cyano-7-ethyl-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]-5-cyclopropylbenzoate

¹H-NMR (CDCl₃) δ 0.81 (2H, m), 1.03 (2H, m), 1.35 (3H, t, J = 7 Hz), 1.59 (9H, s),
20 1.94-2.08 (5H, m), 2.94 (2H, q, J = 7 Hz), 3.68-3.77 (4H, m), 6.35 (1H, j, J = 5 Hz), 6.55 (1H, d, J = 5 Hz), 7.43 (1H, s), 7.84 (1H, s), 7.97 (1H, s).

Example 668

A solution of tert-butyl 3-bromo-5-[3-cyano-7-ethyl-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoate (16.0 mg) in trifluoroacetic acid (0.5 mL) was stirred for 0.5 hour at room temperature. The reaction was quenched by adding water. The mixture was neutralized by adding NaOH (pH = 3). The mixture was extracted with EtOAc. The extract was washed with brine, dried over MgSO₄, and evaporated to give a greenish yellow solid. The solid was triturated in hexanes-CHCl₃
25 (2-1) to afford 3-bromo-5-[3-cyano-7-ethyl-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoic acid as a yellow powder (10.8 mg).
30

3-bromo-5-[3-cyano-7-ethyl-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoic acid

¹H-NMR (CDCl₃ + CD₃OD) δ 1.36 (3H, t, J = 7 Hz), 2.01 (4H, m), 2.94 (2H, q, J = 7 Hz), 3.72 (4H, m), 6.36 (1H, d, J = 5 Hz), 6.60 (1H, d, J = 5 Hz), 7.92 (1H, m), 8.23 (1H, m), 8.35 (1H, m).

5 The following compound(s) was(were) obtained in a similar manner to that of Example 668.

Example 669

3-[3-cyano-7-ethyl-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]-5-cyclopropylbenzoic acid

10 ¹H-NMR (CDCl₃ + CD₃OD) δ 0.81 (2H, m), 1.05 (2H, m), 1.35 (3H, t, J = 7 Hz), 2.01 (5H, m), 2.94 (2H, q, J = 7 Hz), 7.73 (4H, m), 6.37 (1H, d, J = 5 Hz), 6.57 (1H, d, J = 5 Hz), 6.98 (1H, s), 7.90 (1H, s), 8.08 (1H, s).

Example 670

15 3-bromo-5-[7-ethyl-3-(methylsulfonyl)-2-(1-pyrrolidinyl)pyrrolo[1,2-b]pyridazin-4-yl]benzoic acid

¹H-NMR (CDCl₃ + CD₃OD) δ 1.37 (3H, t, J = 7 Hz), 1.98 (4H, m), 2.99 (2H, q, J = 7 Hz), 3.20 (3H, s), 3.56 (4H, m), 6.32 (1H, d, J = 5 Hz), 6.67 (1H, d, J = 5 Hz), 7.80 (1H, m), 8.08 (1H, m), 8.30 (1H, m).

20

Example 671

To a 3-necked flask containing Zn-Cu couple was added a solution of ethyl 4-iodobutanoate (369 mg) in toluene (3 mL) and N,N-dimethylacetamide (0.2 mL) at ambient temperature under N₂. The mixture was stirred at the temperature for 1 h and
25 then at 60°C for 3 h. A suspension of tetrakis(triphenylphosphine)palladium (44 mg) in toluene (0.5 mL) was added and stirred for 5 min. After removal of an oil bath, the mixture was cooled in an ice-water bath. To this mixture was added a solution of 4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carbonyl chloride (212 mg) in DCM (1 mL) dropwise. After 10 min, the reaction mixture was stirred at ambient
30 temperature for 2 h. The reaction mixture was partitioned between AcOEt and H₂O. The organic layer was washed with sat. NaHCO₃ and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by flash silica gel chromatography (silica gel, 80 mL) eluted with hexane-AcOEt = 10-1 and 5-1 to give ethyl 5-[4-(2-chloro-4-

pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-oxopentanoate as yellow amorphous (143 mg).

ethyl 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-oxopentanoate

- 5 ¹H NMR (CDCl₃) δ 1.23 (3H, t, J = 8 Hz), 1.38 (3H, t, J = 8 Hz), 1.71-1.84 (2H, m), 2.17 (3H, t, J = 8 Hz), 2.32 (3H, t, J = 8 Hz), 2.46 (3H, s), 3.04 (2H, q, J = 8 Hz), 4.06 (2H, q, J = 8 Hz), 6.32 (1H, d, J = 5 Hz), 6.70 (1H, d, J = 5 Hz), 7.32 (1H, dd, J = 5, 1), 7.46 (1H, br s), 8.53 (1H, d, J = 5 Hz).

10 Example 672

- To a solution of 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-oxopentanoic acid (47 mg) in EtOH (1 mL) was added sodium borohydride (5 mg) in an ice-water bath under N₂. After 10 min, the mixture was stirred at ambient temperature. After 1 h, another sodium borohydride (5 mg) was added. After 15 2 h, the reaction mixture was partitioned between CHCl₃ and H₂O. The aqueous layer was extracted with CHCl₃ twice. The combined organic layer was dried over MgSO₄ and evaporated in vacuo. The residue was purified by p-TLC (CHCl₃-MeOH = 10-1) to give 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-hydroxypentanoic acid as yellow amorphous (28 mg).
- 20 5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-hydroxypentanoic acid

- 25 ¹H NMR (CDCl₃) δ 1.36 (3H, t, J = 8 Hz), 1.46-1.83 (3H, m), 1.95 (1H, m), 2.70 (3H, br s), 3.01 (2H, q, J = 8 Hz), 4.63 (1H, m), 5.85 (1H, m), 6.55 (1H, d, J = 5 Hz), 7.18-7.29 (1H, overlapped with CDCl₃), 7.34 (1H, d, J = 2 Hz), 8.49 (1H, d, J = 5 Hz).

2003294183 21 May 2009

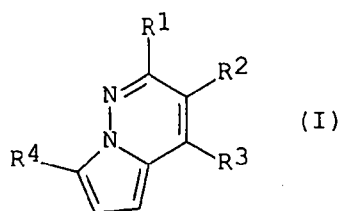
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as, an acknowledgement or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2003294183 21 May 2009

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula :



in which

R¹ is (1) mono- or di(lower)alkylamino,

(2) phenyl,

(3) saturated or unsaturated 5 to 6 membered heteromonocyclic group selected from the group consisting of pyrrolidinyl, pyrrolyl, oxazolyl, isooxazolyl, thiazolyl, furanyl, thienyl and pyridinyl, or

(4) lower alkyl optionally substituted by (i) lower alkoxy or (ii) saturated 5- or 6-membered heteromonocyclic group selected from the group consisting of piperazinyl and morpholinyl, wherein lower alkoxy is optionally substituted by cyclo(lower)alkyl or pyridinyl,

R² is R⁷ or -A²-R⁷, whereinA² is -(CH₂)_n- or -(CH=CH)_m- [wherein n is an integer from 2 to 6 and m is an integer of 1 or 2], andR⁷ is hydrogen, lower alkyl sulfonyl, carboxy, esterified carboxy or pyridinyl,R³ is (1) phenyl optionally substituted by lower alkyl, cyclo(lower)alkyl, lower alkoxy, halogen, cyano or carbamoyl; or

(2) quinolinyl; or pyridinyl substituted by lower alkyl, cyclo(lower)alkyl, lower alkoxy, carbamoyl or halogen, and

R⁴ is lower alkyl,

provided that

Ethyl 4-(4-fluorophenyl)-2-isopropyl-7-methylpyrrolo[1,2-b] pyridazine-3-carboxylate is excluded,

or a pharmaceutically acceptable salt thereof, or prodrug thereof.

2003294183 21 May 2009

2. A compound of claim 1, wherein

R¹ is phenyl, pyrrolyl, isooxazolyl, furanyl, thienyl, lower alkyl optionally substituted by lower alkoxy, piperazinyl or morpholinyl, wherein lower alkoxy is optionally substituted by cyclo(lower)alkyl or pyridinyl,

R² is -(CH₂)_n-R⁷, wherein n is an integer from 2 to 5, and R⁷ is carboxy or esterified carboxy, and

R³ is (1) phenyl optionally substituted by lower alkyl, cyclo(lower)alkyl, lower alkoxy, halogen, cyano or carbamoyl; or (2) pyridinyl substituted by lower alkyl, cyclo(lower)alkyl, lower alkoxy, carbamoyl or halogen.

3. A compound of claim 1, which is

- (1) 3-[7-Ethyl-2-methyl-3-(4-pyridinyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
- (2) 3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
- (3) 4-[7-Ethyl-2-methyl-3-(methylsulfonyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
- (4) 3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzamide,
- (5) Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate,
- (6) 2-[[4-(3-Chlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methyl]-1,3-propanediol,
- (7) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (8) 5-[7-Ethyl-2-methyl-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (9) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (10) 5-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (11) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (12) 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (13) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (14) Ethyl (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propenoate,
- (15) 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-

2003294183 21 May 2009

- yl}hexanoic acid
- (16) 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (17) 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- (18) 5-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (19) 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid,
- (20) 4-{4-(5-chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid,
- (21) 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- (22) 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- (23) 5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid, or
- (24) 5-{4-(3-cyanophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid,
- or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1, which is

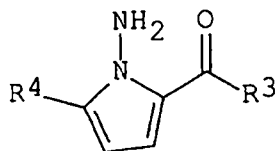
- (1) Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate,
- (2) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (3) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (4) 5-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (5) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (6) 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (7) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-

2003294183 21 May 2009

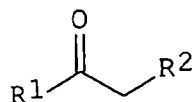
- b]pyridazin-3-yl]pentanoic acid,
- (8) 6-{4-[4-(aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexanoic acid,
- (9) 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
- (10) 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid,
- (11) 5-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- (12) 5-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid,
- (13) 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid, or
- (14) 5-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
- or a pharmaceutically acceptable salt thereof.

5. A process for preparing a compound of claim 1 comprising

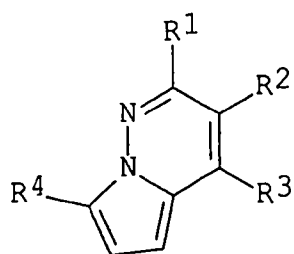
- (1) the reaction of a compound (II) of general formula



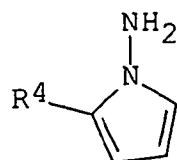
[wherein R³ and R⁴ are as defined in claim 1] or a salt thereof
with a compound (III) of general formula



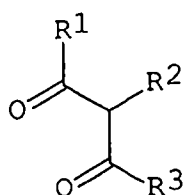
[wherein R¹ and R² are as defined in claim 1] or a salt thereof
to obtain a compound (I) of general formula



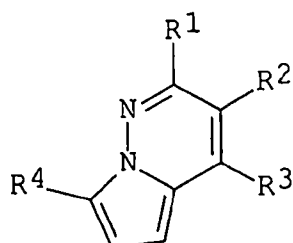
[wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1] or a salt thereof, or
(2) the reaction of a compound (V) of general formula



[wherein R^4 is as defined in claim 1] or a salt thereof
with a compound (VI) of general formula



[wherein R^1 , R^2 and R^3 are as defined in claim 1] or a salt thereof
to obtain a compound (I) of general formula



[wherein R^1 , R^2 , R^3 and R^4 are as defined in claim 1] or a salt thereof.

6. A pharmaceutical composition which comprises, as an active ingredient, a compound of any one of Claims 1 to 4 in admixture with pharmaceutically acceptable carriers.

21 May 2009
2003294183

7. A pharmaceutical composition of claim 6, for inhibiting phosphodiesterase IV (PDE-IV) enzyme activity and/or inhibiting the production of tumor necrosis factor (TNF).

8. A pharmaceutical composition of claim 6, for prevention or treatment of diseases for which therapy by a PDE-IV inhibitor or TNF production inhibitor is relevant.

9. A pharmaceutical composition of claim 6, for prevention or treatment of asthma, chronic obstructive pulmonary disease (COPD), fibrotic disease, acute and fulminant hepatitis, hepatic steatosis (alcoholic or non-alcoholic steatohepatitis), chronic (viral or non-viral) hepatitis, hepatic cirrhosis, autoimmune hepatitis, autoimmune inflammatory bowel disease, atopic dermatitis, Alzheimer's diseases and viral infection.

10. A method of prevention or treatment of diseases for which therapy by a PDE-IV inhibitor or TNF synthesis inhibitor is relevant, comprising the step of administering an effective amount of the compound of any one of Claims 1 to 4.

11. A method of prevention or treatment of asthma, chronic obstructive pulmonary disease (COPD), fibrotic disease, acute and fulminant hepatitis, hepatic steatosis (alcoholic or non-alcoholic steatohepatitis), chronic (viral or non-viral) hepatitis, hepatic cirrhosis, autoimmune hepatitis, autoimmune inflammatory bowel disease, atopic dermatitis, Alzheimer's diseases or viral infection, comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound of any one of Claims 1 to 4.

12. A use of a compound of any one of Claims 1 to 4 in the manufacture of a medicament for prevention or treatment of diseases for which therapy by a PDE-IV inhibitor or TNF synthesis inhibitor is relevant.