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DERIVES DE PYRROLOPYRIDAZINE

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(56) References cited:
WO-A-91/18903 **FR-A- 2 792 938**

- **W. FLITSCH, U. KRÄMER: "Synthesen und Reaktionen von 5-Aza-Indolizinen und 5-Aza-Cycl[3.2.2]azin-Derivaten" TETRAHEDRON LETTERS, vol. 12, 1968, pages 1479-1484, XP002273465**

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(Cont. next page)

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

TECHNICAL FIELD

[0001] 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).

BACKGROUND ART

[0002] Gyclic 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 cellar 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 end when it is degraded by cyclic nucleotide phosphodiesterases, in particular phosphodiesterase-4 (PDE4 or PDE-JV), which is specific for cAMP. PDE-IV have 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.

[0003] A major concern with the use of PDE-1V inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C.Bumouf et al., (Ann. Rep. In Med. Chem., 33:91-109(1998)). Burnouf describe the wide variation of the severity of the undesirable side effects exhibited by various compounds.

[0004] Some condensed heterocyclic derivatives having the inhibitory activity of PDE-IV have been known, for example in FR-A-279293 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.

[0005] A further document which describes pyrrolopyridazine compounds is the publication of Plitsch and Krämer in Tetrahedron letters 1968; 12: 1479-1484. A specific compound contains an unsubstituted phenyl group in the 4-position of the pyrrolopyridazine nucleus. There is no reference to any specific biological activity.

DISCLOSURE OF INVENTION

[0006] This invention relates to new pyrrolopyridazine derivatives.

[0007] The compounds of this invention inhibit cAMP phosphodiesterase enzymes, in particular phosphodieslerase-4 enzyme, and also inhibit the production of tumor necros factor-α (TNF-α), a serum glycoprotein.

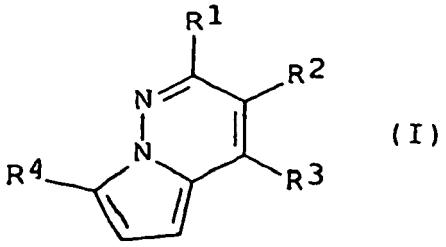
[0008] Accordingly, one object of this invention is to provide the new and useful pyrrolopyridazine derivatives and pharmaceutically acceptable salts thereof which possess a strong phosphodiesterase-4 (PDE IV)-inhibitory activity and a strong inhibitor activity on the production of tumor necrosis factor (TNF).

[0009] Another object of this invention is to provide processes for preparation of the pyrrolopyridazine derivatives and salts thereof.

[0010] A further object of this invention is to provide a pharmaceutical composition comprising said pyrrolopyridazine derivatives or a pharmaceutically acceptable salt thereof.

[0011] Still further object of this invention is 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-induccd organ injury, and the like in human being and animals.

[0012] The object pyrrolopyridazine derivatives of the present invention are novel and can be represented by the following general formula (J):



(I)

in which

R^1 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

R^2 is R^7 or $-A^2-R^7$, wherein
A^2 is $-(CH_2)_n-$ or $-(CH=CH)_m-$ [wherein n is integer which may range 2 to 6 and m is integer of 1 or 2, and
R^7 is hydrogen, lower alkyl sulfonyl, carboxy, esterified carboxy or pyridinyl,

R^3 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

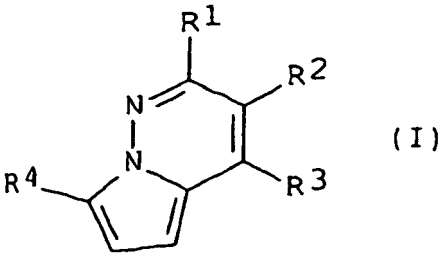
R^4 is lower alkyl,

or a pharmaceutically acceptable salt thereof, or prodrug thereof.

[0013] Suitable pharmaceutically acceptable salts of the object 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'-dibenzylelhylenediamine 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.).

[0014] The "prodrug" means the derivatives of the object compound (1) having a chemically or metabolically degradable group, which became pharmaceutically active after chemo- or biotransformation.

[0015] Preferred embodiments of the object compound (1) are as follows.



(I)

R^1 is phenyl, satulated 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),

R^2 is $-(CH_2)n-R^7$, wherein n is integer which may range 2 to 5, and R^7 is carboxy or protected carboxy,

R^3 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

R^4 is lower alkyl.

[0016] 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 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-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)pyrirolo[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.

[0017] More preferred concrete compound of formula (I) is:

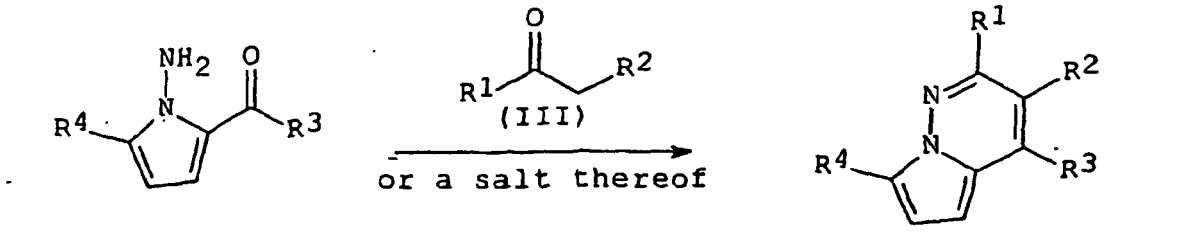
(1) Ethyl 5-[4-(3-cyanophenyl)-7-ethyl-2-methy]pyrrolo[1,2-b]pyridazin-3-yl]pentanoate,
(2) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid,
(3) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid,
(4) 5-[7-Ethyl-2-(metboxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic 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-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[l,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
(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.

[0018] The object compound (I) of the present invention can be prepared by the following processes.

Process 1

[0019]

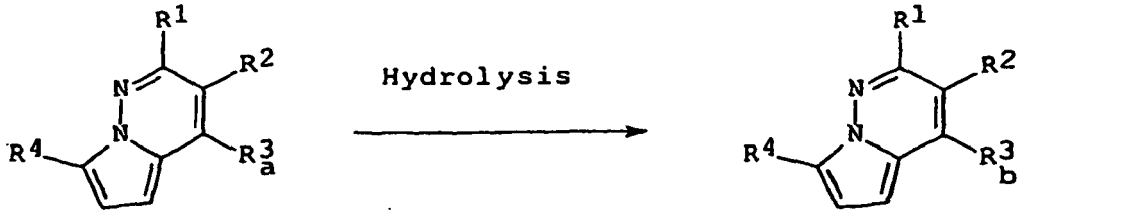


(II) or a salt thereof

(I) or a salt thereof

Process 2

[0020]

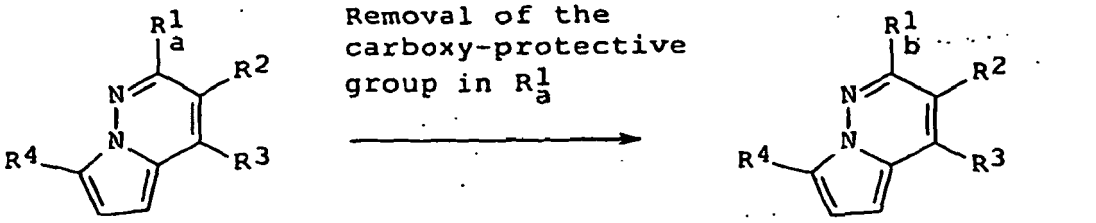


(I-a) or a salt thereof

(I-b) or a salt thereof

Process 3

[0021]

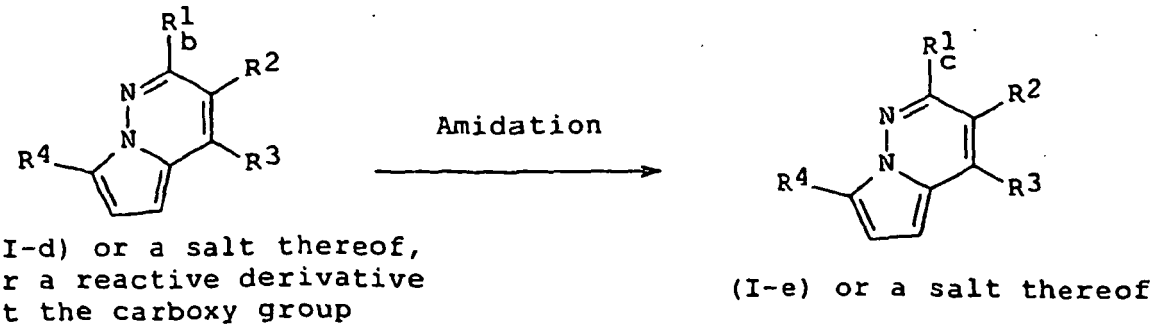


(I-c) or a salt thereof

(I-d) or a salt thereof

Process 4

[0022]

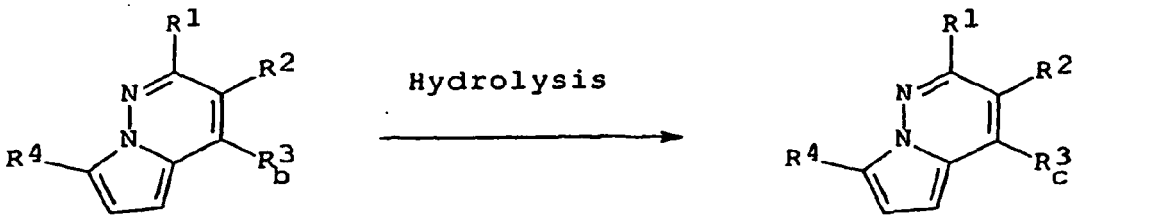


(I-d) or a salt thereof, or a reactive derivative at the carboxy group

(I-e) or a salt thereof

Process 6

[0023]

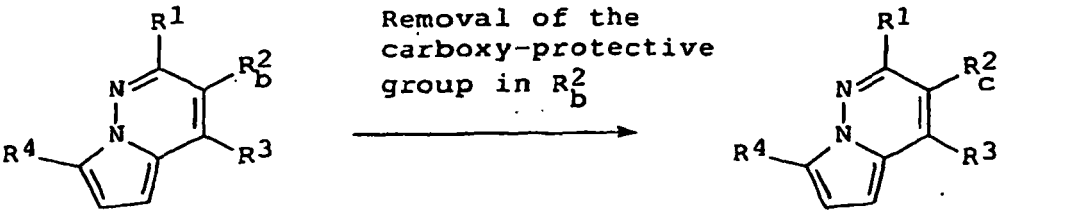


(I-b) or a salt thereof

(I-h) or a salt thereof

Process 7

[0024]

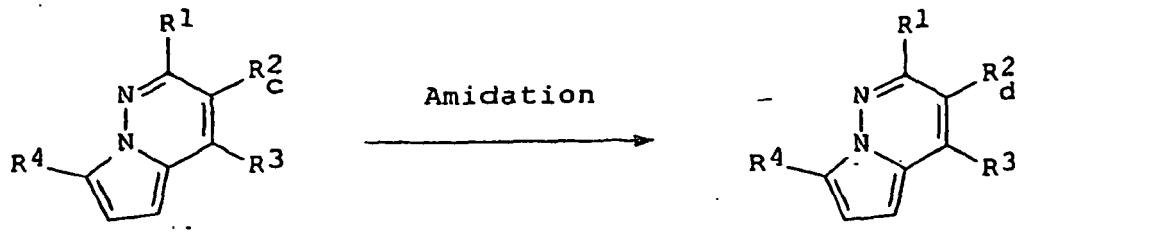


(I-i) or a salt thereof

(I-j) or a salt thereof

Process 8

[0025]

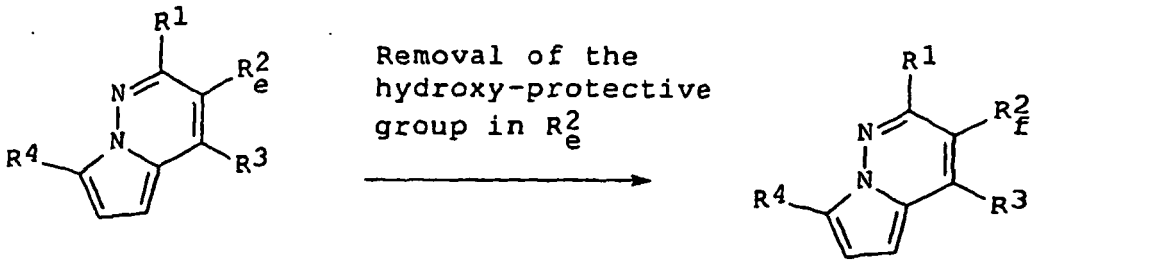


(I-j) or a salt thereof, or a reactive derivative at the carboxy group

(I-k) or a salt thereof

Process 9

[0026]

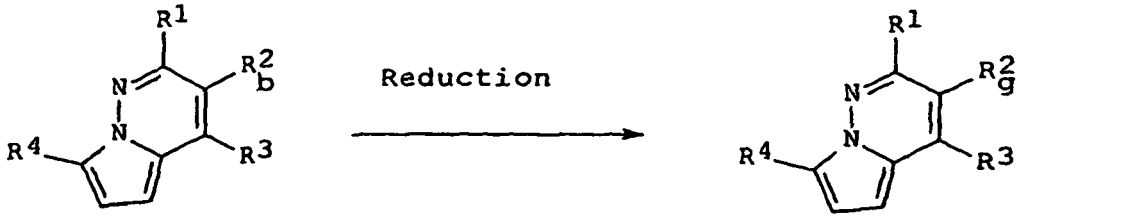


(I-l) or a salt thereof

(I-m) or a salt thereof

Process 10

[0027]

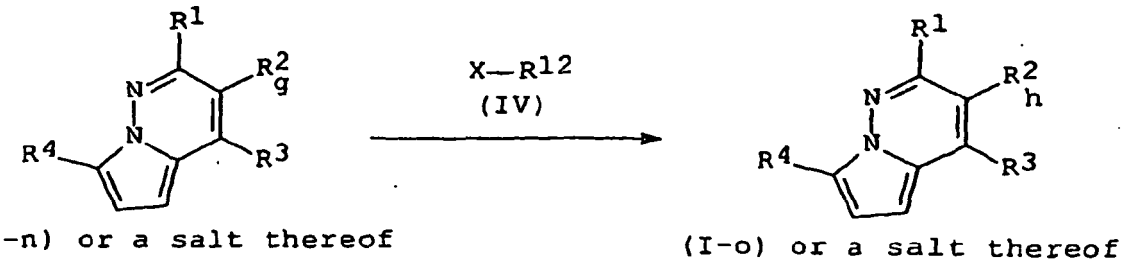


(I-i) or a salt thereof

(I-n) or a salt thereof

Process 11

[0028]

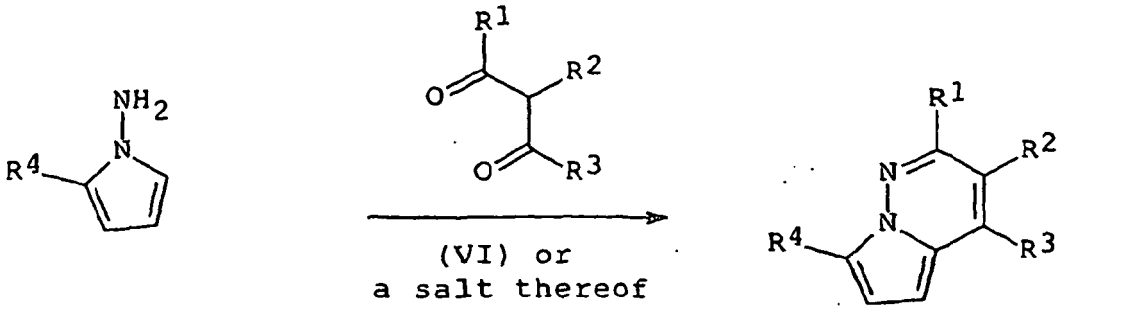


(I-n) or a salt thereof

(I-o) or a salt thereof

Process 12

[0029]

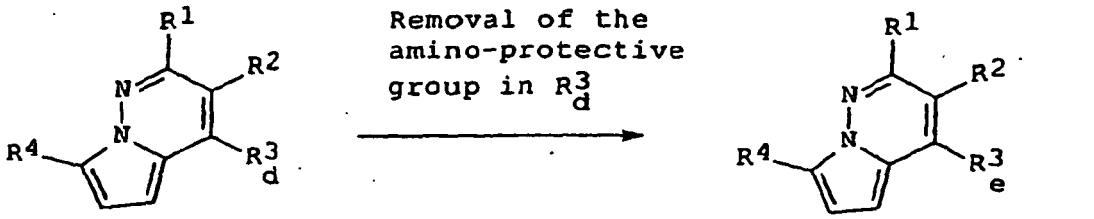


(V) or a salt thereof

(I) or a salt thereof

Process 14

[0030]

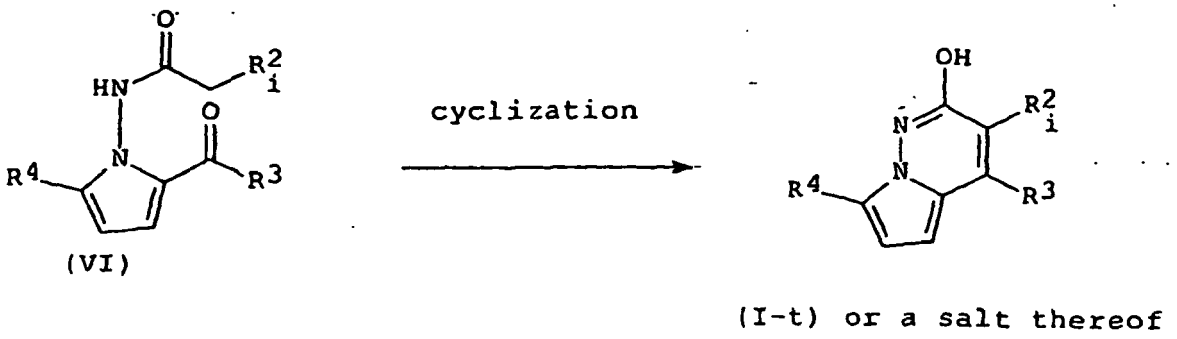


(I-r) or a salt thereof

(I-s) or a salt thereof

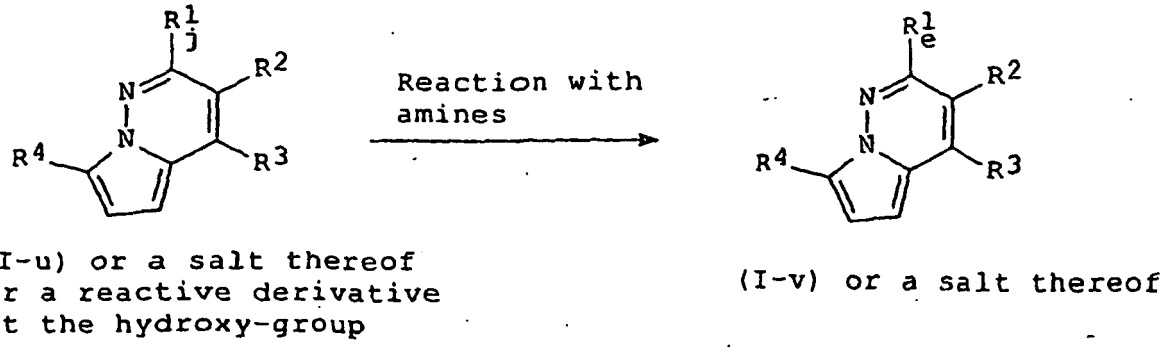
Process 15

[0031]



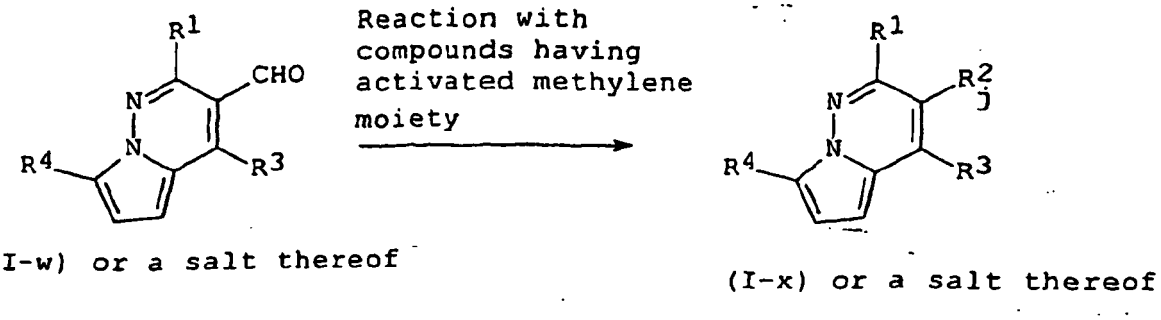
Process 16

[0032]



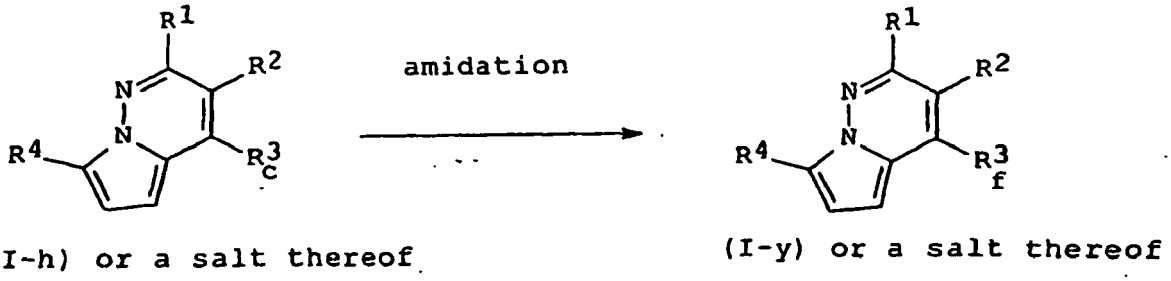
Process 17

[0033]



Process 18

[0034]

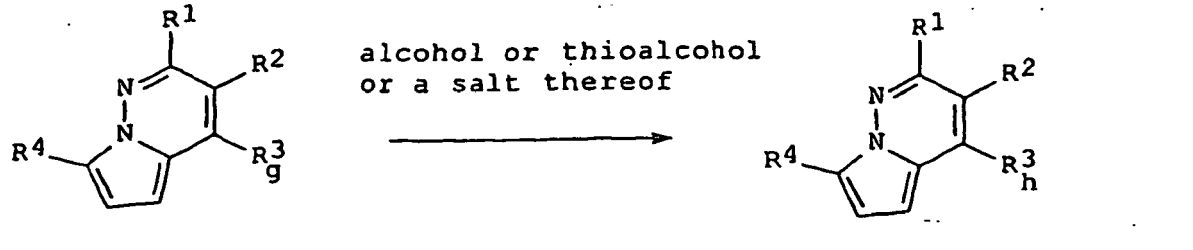


(I-h) or a salt thereof

(I-y) or a salt thereof

Process 19

[0035]

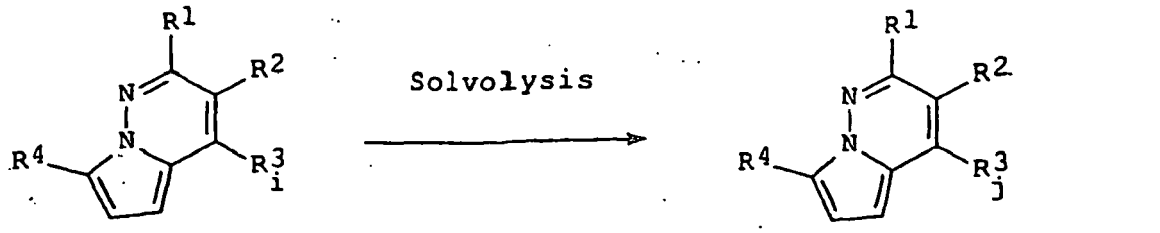


(I-z) or a salt thereof

(I-aa) or a salt thereof

Process 20

[0036]

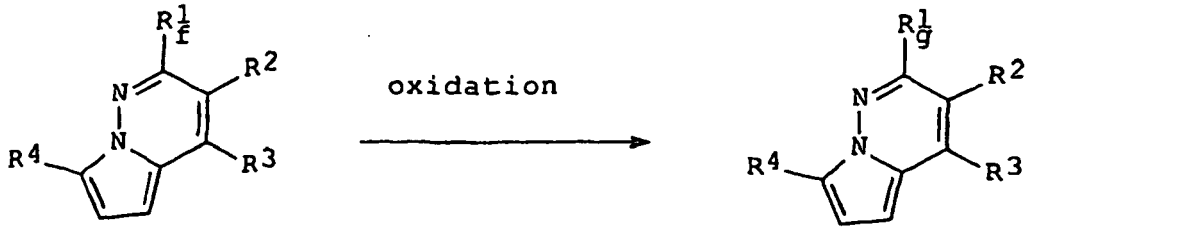


(I-ab) or a salt thereof

(I-ac) or a salt thereof

Process 21

[0037]

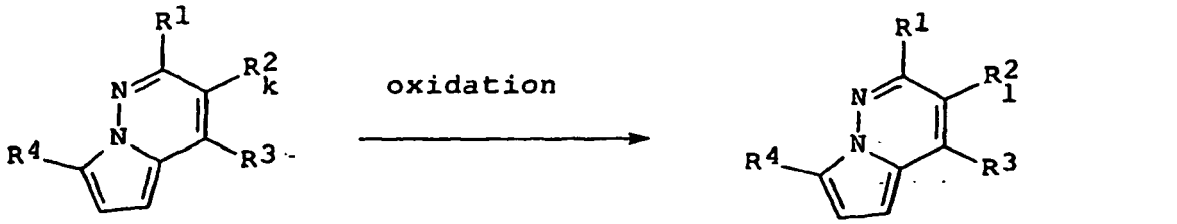


(I-ad) or a salt thereof

(I-ae) or a salt thereof

Process 22

[0038]

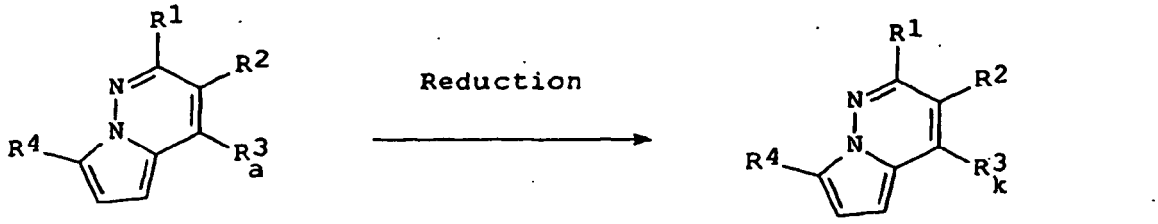


(I-af) or a salt thereof

(I-ag) or a salt thereof

Process 23

[0039]

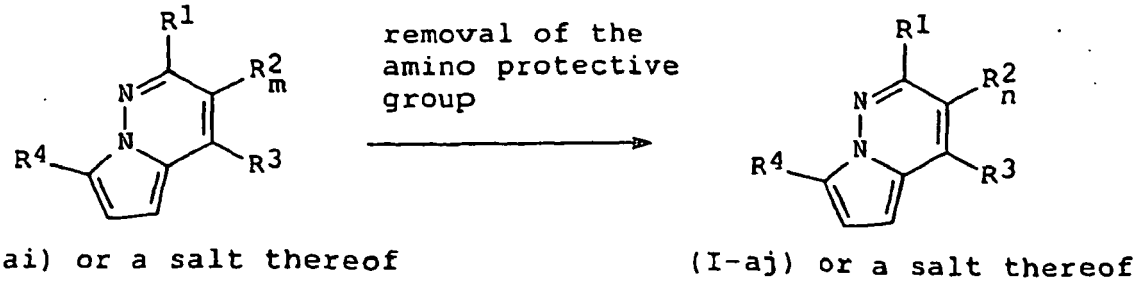


(I-a) or a salt thereof

(I-ah) or a salt thereof

Process 24

[0040]

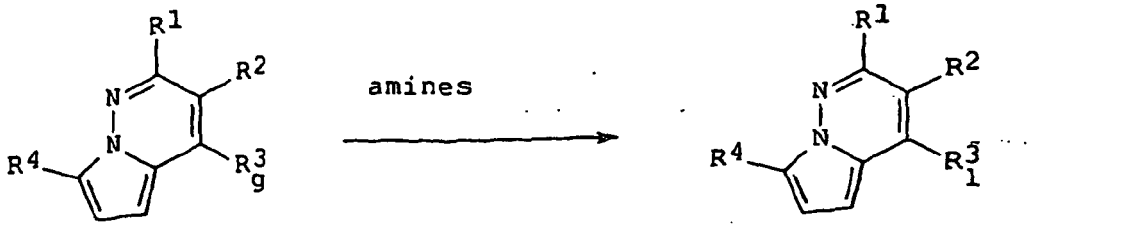


(I-ai) or a salt thereof

(I-aj) or a salt thereof

Process 25

[0041]

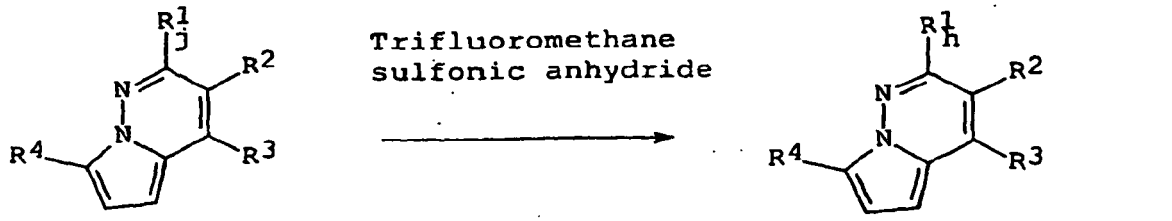


(I-z) or a salt thereof

(I-ak) or a salt thereof

Process 31

[0042]

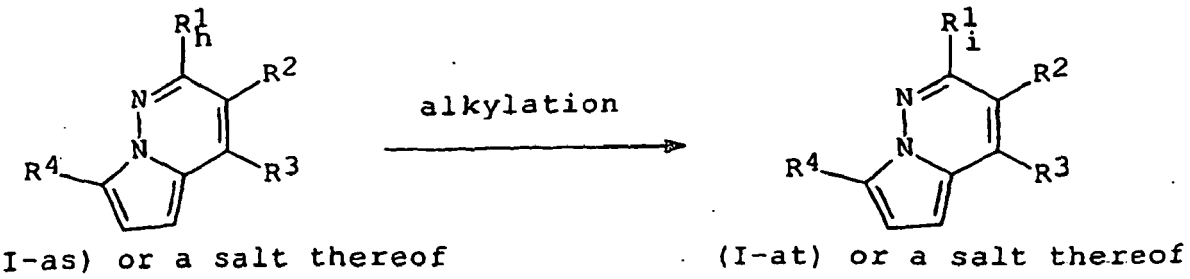


(I-u) or a salt thereof

(I-as) or a salt thereof

Process 32

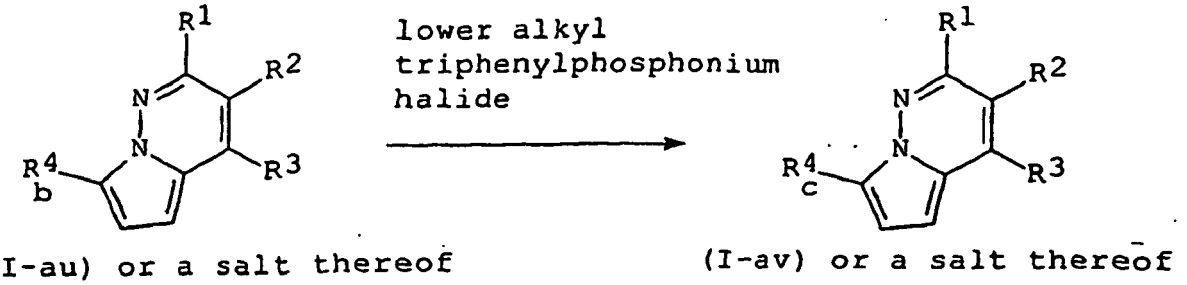
[0043]



(I-as) or a salt thereof (I-at) or a salt thereof

Process 33

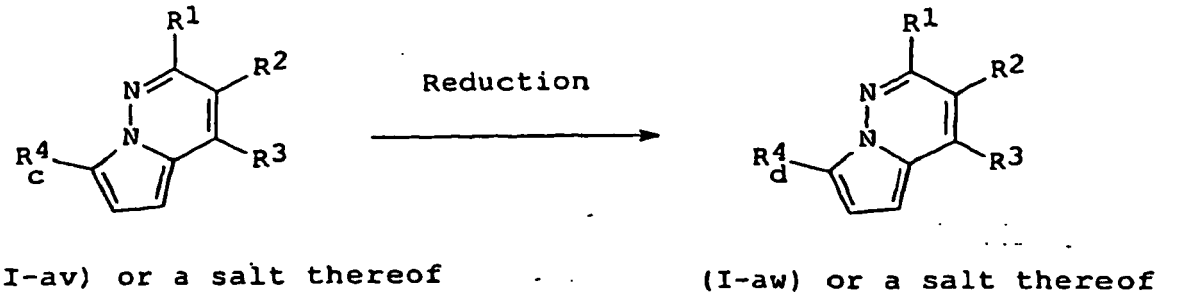
[0044]



(I-au) or a salt thereof (I-av) or a salt thereof

Process 34

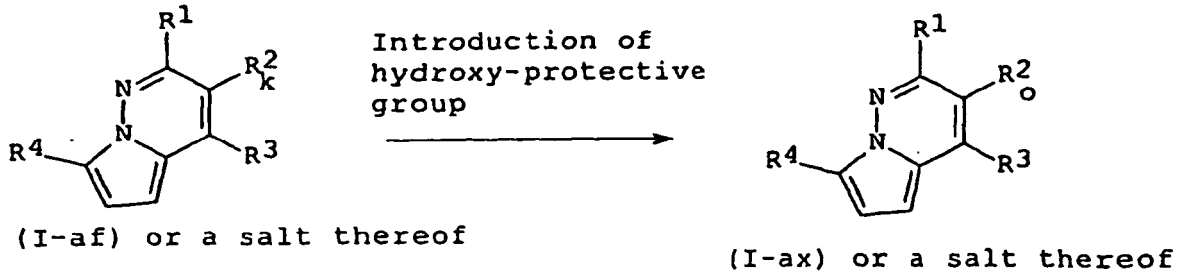
[0045]



(I-av) or a salt thereof (I-aw) or a salt thereof

Process 35

[0046]

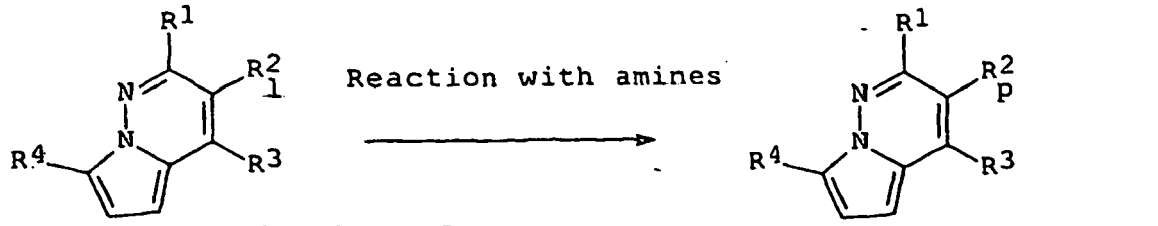


(I-af) or a salt thereof

(I-ax) or a salt thereof

Process 36

[0047]

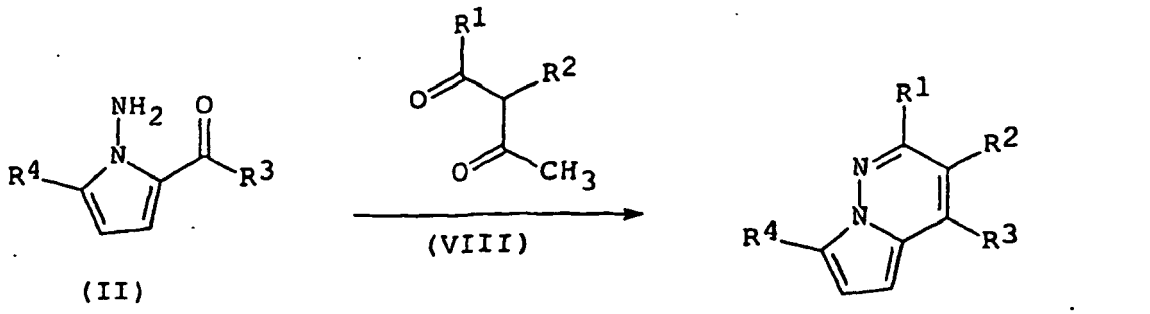


(I-ag) or a salt thereof

(I-ay) or a salt thereof

Process 37

[0048]

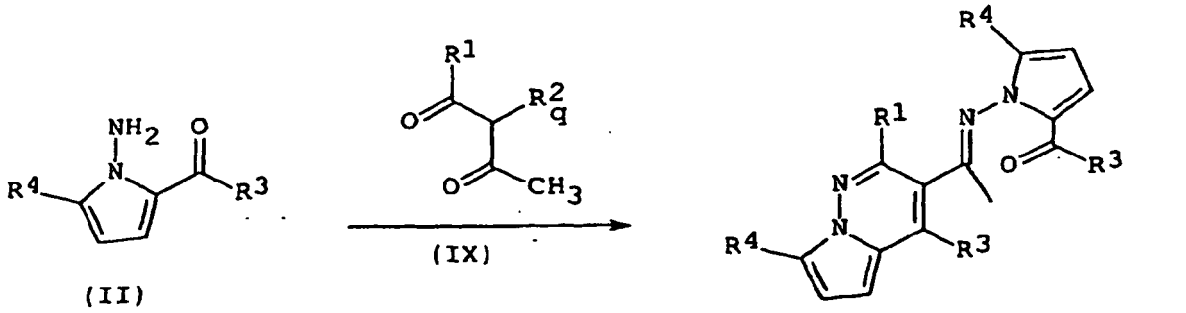


(II)

(I) or a salt thereof

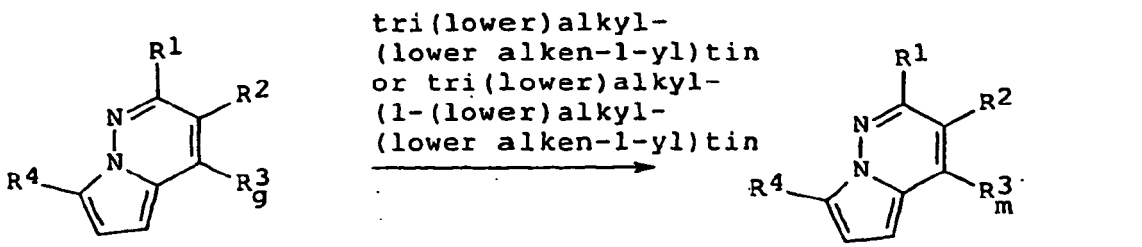
Process 38

[0049]



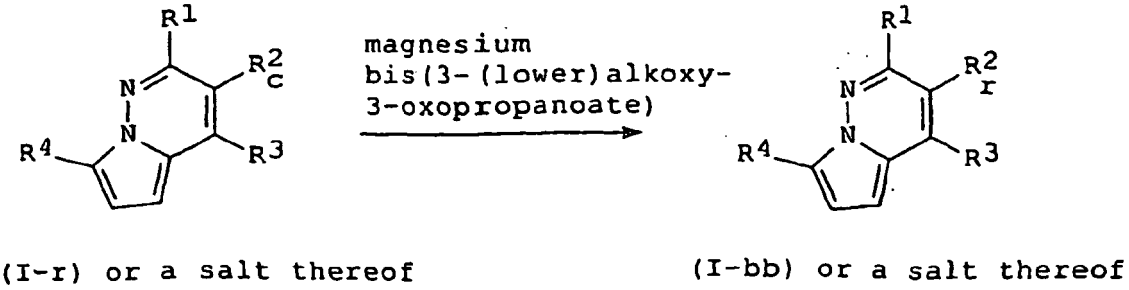
Process 39

[0050]



Process 40

[0051]

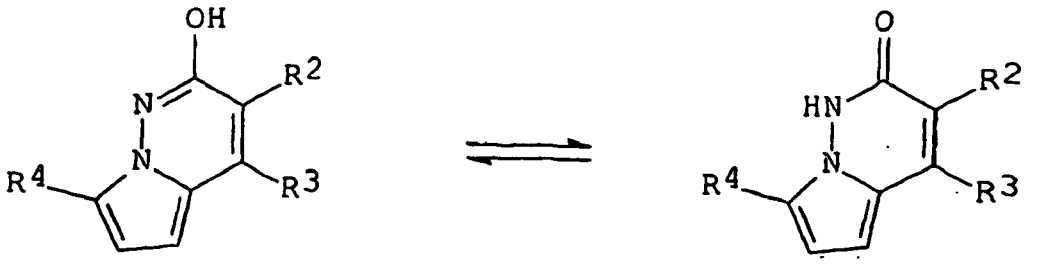


wherein R^1, R^2, R^3 and R^4 are each as defined above,
$R^1{}_a$ is the same as above R^1 having protected carboxy moiety,
$R^1{}_b$ is the same as above R^1 having carboxy moiety,
$R^1{}_c$ is $-CONR^5R^6$,
$R^1{}_e$ is amino, mono- or di(lower)alkylamino-, lower alkoxy(lower)alkylamino, nitrogen-containing heterocyclic group, amino(lower)alkyl, mono- or di(lower)alkylamino(lower)alkyl, lower alkoxy(lower)alkylamino(lower)alkyl, nitrogen-containing 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,
R^{1}_{j} is hydroxy or hydroxy(lower)alkyl,
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,
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 $-OR^{12}$,
R^{2}_{i} is lower alkoxycarbonyl or lower alkylsulfonyl,
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,
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}, 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,
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 $-CONR^{10}R^{11}$ 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 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,
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}_{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, and
X is a leaving group

[0052] The starting compound (II) of the present invention can be prepared according to a conventional manner or in a similar manner as described in the following Preparations and/or Examples.

[0053] Another point to be noted is that the pyrrolopyridazine moiety of the compound (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.

[0054] Both of the above tautomeric isomers are included within the scope of the present invention, and in the present specification and claims, however, the object compound (I) is represented for convenience sake by one expression of the possible tautomeric forms of pyrrolopyridazine ring.

[0055] 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.

[0056] The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

[0057] 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.

[0058] 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-l-(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.

[0059] Suitable "lower alkynyl" may include ethynyl,1-propynyl, propargyl, 1-methylpropargyl, 1 or 2 or 3-butynyl, 1 or 2 or 3 or 4-penlynyl, 1 or 2 or 3 or 4 or 5-hexynyl, and the like.

[0060] 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 C_1-C_4 alkylene and the most preferable one may be methylene.

[0061] Example of hydroxy(C_1-C_2)alkylene is hydroxymethylene, (hydroxymethyl)methylene or 1-(or 2-)hydroxyethylene.

[0062] Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

[0063] Suitable "halogen" and "halogen moiety" may include fluorine, bromine, chlorine and iodine.

[0064] Suitable "trihalo(lower)alkyl" may include trichloromethyl, trifluoromethyl, trichloroethyl, tribromoethyl, and the like.

[0065] 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.

[0066] Example of "mono- or di(lower)alkylamino substituted by lower alkoxy" may be methoxymetylamino, methoxyethylamino, methoxyethyl(methyl)amino, methoxyethyl(ethyl)amino, di(methoxyethyl)amino, ethoxymethylamino, ethoxyethylamino, and the like.

[0067] Suitable "lower alkylthio" may include conventional ones such as methylthio, ethylthio, propylthio, butylthio, and the like.

[0068] Suitable "lower alkylsulfinyl" may include conventional ones such as methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, and the like.

[0069] Suitable "lower alkylsulfonyl" may include conventional ones such as methylsulfonyl, ethylsulfonyl, propylsulfonyl, bytylsulfonyl, and the like.

[0070] Suitable "trihalo(lower)alkylsulfonyloxy" may include sulfonyloxy group substituted by trihalo(lower)alkyl such as trifluoromethylsulfonyloxy, trifluoroethylsulfonyloxy, trichloromethylsulfonyloxy, and the like.

[0071] Suitable "protected carboxy" and "protected carboxy moiety" may include esterified carboxy and the like.

[0072] 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, 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,
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-)-[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, pro-

poxycarbonyloxymethyl ester, t-butoxycarbonyloxymethyl ester, 1-(or 2-)methoxycarbonyloxyethyl ester,1-(or 2-)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.];
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.);
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 alkoxycarbonyl (e.g. ethoxycarbonyl, etc.).

[0073] The term "protected amino" means an amino group bonded to the amino-protecting group. Example of such amino-protecting group include lower alkoxycarbon (e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, etc.); lower alkenyloxycarbonyl (e.g. vinyloxycarbonyl, allyloxycarbonyl, etc.); optionally substituted aryl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.); phthalimide; and the like. Further examples of amino-protecting groups are well-known in organic synthesis and are 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.

[0074] The term "protected sulfamoyl" means sulfamoyl group having the amino-protecting group mentioned above on the nitrogen atom. A preferred amino-protecting group is aryl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.); and the like.

[0075] 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.

[0076] Suitable example of said acyl may be illustrated as follows:

Aliphatic acyl such as
lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-diinethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl; tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.); in which preferable "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.);
cyclo(lower)alkylcarbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, 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.);
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.];
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
heterocycliccarbonyl;
heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl,
heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);
heterocyclic(lower)alkenoyl(e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);
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 "heterocycliccarbonyl" may include carbonyl group substituted by heterocyclic group as mentioned below such as pyrrolidinylcarbonyl, pyridinylcarbonyl, pyrazinylcarbonyl, and the like..

[0077] Syitable "halocarbonyl" may include chlorocarbonyl, bromocarbonyl, and the like.

[0078] Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl moeity" may include one having 3 to 7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[0079] Suitable "aryl" and "aryl moiety" may include C_6-C_{10} aryl such as phenyl, naphthyl and the like.

[0080] 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.

[0081] 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.;
(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.;
(14) unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl (e.g., benzo[b]thienyl, etc.), benzodithiinyl, etc.;
(15) unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

[0082] Suitable "heterocyclic group" and "heterocyclic moiety" in the terms "heterocycliccarbonyl" can be referred to the ones as mentioned above.

[0083] 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.

[0084] A group derived from a sugar may be the group derived from, for example, glyceraldehydes; an aldose such as erythrose, threose, arabinose, ribose, xylose, lyxose, glucose, mannose or galactose; a ketose such as fructose or sorbose; or a disccharide such as maltose, lactose or sucrose.

[0085] 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-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-butyldimethylsilyl.

[0086] 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; (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, pyrrolidinylcarnbonyloxy, etc); (7) lower alkylthio (e.g. methylthio, etc.), (8) lower alkylsulfonyl (e.g. methylsulfonyl, etc.), (9) lower alkylsulfonyloxy (e.g. methylsulfonyoxyl, 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-(rnethoxycarbonyl)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 $-CONR^{13}R^{14}$ [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.

[0087] Suitable "substituted or unsubstituted aryl" may include C_6-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) $-CONR^{15}R^{16}$ [wherein R^{15} and R^{16} are each independently represents hydrogen lower alkyl optionally substituted by hydroxy] (e.g. carbamoyl, hydroxyethylcarbamoyl, elc.), (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.

[0088] In which,

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 aryl" for R^3 is aryl 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) $-CONR^{15}R^{16}$ [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. 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.); and

preferable example of "substituted or unsubstituted aryl" for R^7 is aryl substituted by lower alkoxy (e.g. phenyl, 2-, 3- or 4-methoxyphenyl, etc.).

[0089] 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 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 alkoxycarbonylamino such as tert-butoxycarbonylamino, etc.), (8) cyano, (9) carboxy, (10) protected carboxy (e.g. benzyloxycarbonyl, etc.), (11)-$CONR^{15}R^{16}$ [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.

[0090] In which,

preferable example of "substituted or unsubstituted heterocyclic group" for R^1 is heterocyclic group optionally substituted by lower alkyl or halogen (e.g. 2-pyridinyl, 5-blomo-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 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 alkoxycarbonylamino, (8) cyano, (9) carboxy, (10) protected carboxy such as esterified carboxy (e.g. benzyloxycarbonyl), (11) carbamoyl, (12) lower alkenyl optionally substituted by lower alkoxy, (13) halogen, (14) lower alkylthio, and (15) hydroxy (e.g. 3- or 4-pyridyl, 2-pyraziny), 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.).

[0091] Suitable "substituted or unsubstituted aryl(lower)alkenyl" may include C_6-C_{10} aryl(lower)alkenyl which is optionally substituted by halogen (e.g. 2-phenylvinyl, 2-(2- or 3-chlorophenyl)vinyl, etc.).

[0092] Suitable "leaving group" may include acid residue, lower alkoxy as exemplified above, and the like.

[0093] The above Processes can be carried out according to a conventional manner such 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.

[0094] 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.

[0095] Another ring forming process is described in Process 12, in this process pyrrolopyridazine derivatives (1) can be also prepared reacting 1-aminopyrole 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.

[0096] The compounds of the present invention can be purified by any conventional purification methods employed for purifying organic compounds, such as recrystallization, 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.

[0097] Suitable salts of the object and the starting compounds in Processes 1 to 40 can be referred to the ones as exemplified for the compound (I).

[0098] 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).

[0099] 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).

[0100] 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.

[0101] 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.

[0102] 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 intramucous 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 (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, 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.

[0103] 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.

[0104] Further, the compound of this invention can be used in combination with other 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, 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 grouth factor (HGF), xvi) aminosalicylic acid such as salazosulfapyridine, mesalazin, or the like, xvii) steroids such as prednisolone famesylate, xviii) immunosuppressant such as azathioprine, 6-mercaptopurine, tacrolimus, and the like.

[0105] 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.

[0106] 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.

[0107] 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:

[0108] 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 μM leupeptin, 100 μM PMSF, 20 μM 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.

[0109] 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 μCi/well of [^{3}H]cAMP to the enzyme mixture containing 50 mM Tris-HCI (pH 75), 8.3 mM $MgCl_2$,1.7 mM EGTA, and various concentrations of the test compound or vehicle. CI-930 (10 μM in final), a specific PDE3, inhibitor, was also added in the reaction mixture. After incubation at 30°C for 15 minutes, 50 μL of SPA beads suspension was added to each well . The well-plate was then shaken for 20 minutes by a plate mixer. Rndio-nctivity in each well was counted by a Top Counter.

[0110] Test compounds were dissolved in 100% dimethylsulfoxide (DMSO) and diluted into respective concentrations with the final solution containing 1% v/v of DMSO.

[0111] IC_{50} values of test compounds for the enzyme activity of PDE4 were 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)} x 100; in which A, B and C means mean values of radio-activity counts (dpm) of control, blank and the compound-treated tubes, respectively.

2. Test results

[0112] The following table illustrates the inhibitory activity on PDE-IV of the representative compound of formula (I):

Example	Compound name	IC50 (μM)
107	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

1. Test method

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

[0113] Blood (30 ml for each person) 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 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 cell counting, final suspension at 3 x 10^6cells/mL in culture medium was prepared.

(2) TNF-alpha production from stimulated PBMCs

[0114] Human PBMCs prepared by the density gradient method using Ficoll-Paque PLUS were suspended in the culture medium mentioned above with the concentration of 3 x 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 CO_2 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 stored at -80°C until assay. TNF-alpha levels in the medium were measured by ELISA.

[0115] The IC_{50} 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.

2. Test results

[0116]

Example	Compound name	IC50 (nM)
107	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

[0117] 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.

[0118] 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.

[0119] 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
Et3N	Triethylamine
MeOH	Methanol
EtOH	Ethanol
BuOH	Butanol
DCM	Dichloromethane
Pd/C	Palladium on carbon powder

Preparation 1

[0120] To a suspension of 2-pyridinethiol (17 g) in tetrahydrofuran (200 mL) was added triethylamine (155 g) in an ice-water bath under N_2. 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.

S-(2-Pyridinyl) 4-cyanobenzenecarbothioate

[0121] NMR ($CDCl_3$, 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)

[0122] 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

[0123] NMR ($CDCl_3$, 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 3

S-(2-Pyridinyl) 3-cyanobenzenecarbothioate

[0124] NMR ($CDCl_3$, 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 4

S-(2-Pyridinyl) 3-methoxybenzenecarbothioate

[0125] NMR ($CDCl_3$, 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 5

[0126] To a solution of 2-ethyl-1H-pyrrole in toluene (120 mL) was added dropwise 1M 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 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.

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

[0127] NMR ($CDCl_3$, 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)

[0128] The following compound was obtained in substantially the same manner as that of Preparation 5.

Preparation 6

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

[0129] NMR($CDCl_3$, 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)
MS (ESI^+): m/z 226 (M+H)

Preparation 7

[0130] 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 N_2. 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 an 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

[0131] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 240 (M+H)

[0132] The following compounds were obtained in substantially the same manner as that of Preparation 7.

Preparation 8

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

[0133] NMR ($CDCl_3$, 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)

Preparation 9

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

[0134] NMR ($CDCl_3$, 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)

Preparation 10

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

[0135] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 241 (M+H)

Preparation 11

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

[0136] NMR ($CDCl_3$, 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 12

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

[0137] NMR ($CDCl_3$, 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 13

[0138] 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 N_2. 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 cooled mixture was partitined 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%) as colorless oil.

1-tert-Butyl 7-ethyl 2-acetylheptanedioate

[0139] NMR ($CDCl_3$, 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)
[0140] The following compounds were obtained in substantially the same manner as that of Preparation 13.

Preparation 14

tert-Butyl 2-acetylhexanoate

[0141] NMR ($CDCl_3$, 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 15

1-tert-Butyl 8-ethyl 2-acetyloctanedioate

[0142] NMR ($CDCl_3$, δ): 1.21-133 (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 16

[0143] To a suspension of magnesium chloride (133 g) in dichloromethane (40 mL) was added 1-tert-butyl 7-ethyl 2-acetylheptanedioate (4.0 g) at ambient temperature under N_2. 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.

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

[0144] NMR ($CDCl_3$, 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, $J=8_{Hz}$), 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)

[0145] The following compounds were obtained in substantially the same manner as that of Preparation 16.

Preparation 17

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

[0146] NMR ($CDCl_3$, 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)

Preparation 18

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

[0147] NMR ($CDCl_3$, 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)

Preparation 31

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

[0148] NMR ($CDCl_3$, δ): 1.23 (3H, t, J=7Hz), 1.33 (9H, s), 1.30-1.43 (2H, m), 1.62-1.76 (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 19

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

[0149] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 426 (M+H)

Preparation 20

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

[0150] NMR ($CDCl_3$, δ): 1.21 (3H; t, J=7Hz),1.30 (9H, s), 1.32-1.47 (2H, m), 1.64-1.77 (2H, m), 2.26-238 (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)

Preparation 21

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

[0151] NMR ($CDCl_3$, 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 22

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

[0152] NMR ($CDCl_3$, 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 23

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

[0153] NMR ($CDCl_3$, 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)

Preparation 24

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

[0154] NMR ($CDCl_3$, 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 25

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

[0155] NMR ($CDCl_3$, 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 26

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

[0156] NMR ($CDCl_3$, 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

Preparation 27

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

[0157] NMR ($CDCl_3$, 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)

Preparation 28

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

[0158] NMR ($CDCl_3$, δ): 1.23 (3H, t, J=7.Hz), 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)

Preparation 29

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

[0159] NMR ($CDCl_3$, 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 442

Preparation 30

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

[0160] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 456

Preparation 31

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

[0161] NMR ($CDCl_3$, 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

Preparation 32

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

[0162] NMR ($CDCl_3$, 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, J=8Hz), 8.28 (1H, d, J=8Hz), 8.27 (1H, s), 9.01 (1H, m)
MS (ESI^+): m/z 472

Preparation 33

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

[0163] NMR ($CDCl_3$, 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, J =8Hz), 7.73 (1H, m)

Preparation 34

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

[0164] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 405

Preparation 35

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

[0165] NMR ($CDCl_3$, 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 36

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

[0166] NMR ($CDCl_3$, 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

Preparation 37

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

[0167] NMR ($CDCl_3$, 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 38

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

[0168] NMR ($CDCl_3$, 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), 2.28-237 (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 39

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

[0169] NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7Hz), 1.36 (9H, s), 1.60-1.80 (2H, m), 2.20-2.45 (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 40

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

[0170] NMR ($CDCl_3$, 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

Preparation 41

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

[0171] NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7Hz),134 (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), 8.73 (1H, s)
MS (ESI^+): m/z 392

Preparation 42

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

[0172] NMR ($CDCl_3$, 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

Preparation 43

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

[0173] NMR ($CDCl_3$, 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 44

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

[0174] NMR ($CDCl_3$, 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)

Preparation 45

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

[0175] NMR ($CDCl_3$, 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)

Preparation 46

[0176] 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.

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

[0177] NMR ($CDCl_3$, 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)
MS (ESI^-): m/z 314 (M-H)

[0178] The following compounds were obtained in substantially the same manner as that of Preparation 46.

Preparation 47

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

[0179] NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7Hz), 1.32-1.43 (2H, m), 1.62-1.77 (2H, m), 1.96-2.17 (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 48

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

[0180] NMR ($CDCl_3$, 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)

Preparation 49

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

[0181] NMR ($CDCl_3$, 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)

Preparation 50

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

[0182] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 342 (M+H)

Preparation 51

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

[0183] NMR ($CDCl_3$, δ): 1.25 (3H, t, J=7Hz), 1.41 (2H, m), 1.76 (2H, m), 2.03 (2H, m), 2.31 (2H, m), 3.20 (2H, m), 4.10 (2H, q, J=7Hz), 7.94 (1H, s), 8.10 (1H, s)

Preparation 52

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

[0184] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 326 (M+H)

Preparation 53

4-(2-Acetylhexanoyl)benzonitrile

[0185] NMR ($CDCl_3$, 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 54

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

[0186] NMR ($CDCl_3$, 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)

Preparation 55

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

[0187] NMR ($CDCl_3$, 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)

Preparation 56

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

[0188] NMR ($CDCl_3$,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 (1 H, d, J=8Hz)
MS (ESI^+): m/z 326

Preparation 57

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

[0189] NMR ($CDCl_3$, 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 58

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

[0190] NMR ($CDCl_3$, 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), 7.43-752 (1H, m), 7.63-7.68 (1H, m), 7.76 (1H, d, J=8Hz)
MS (ESI^+): m/z 309

Preparation 59

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

[0191] NMR ($CDCl_3$, 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

Preparation 60

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

[0192] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 356, MS (ESI^-): m/z 354

Preparation 61

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

[0193] NMR ($CDCl_3$, 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 62

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

[0194] NMR ($CDCl_3$, 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

Preparation 63

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

[0195] NMR ($CDCl_3$, 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)

Preparation 64

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

[0196] NMR ($CDCl_3$, 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)

Preparation 65

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

[0197] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 336

Preparation 66

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

[0198] NMR ($CDCl_3$, 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

Preparation 67

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

[0199] NMR ($CDCl_3$, 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 (1H, m), 8.88 (1H, m), 9.07 (1H, m)
MS (ESI^+): m/z 400, 402

Preparation 68

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

[0200] NMR ($CDCl_3$, 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 69

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

[0201] NMR ($CDCl_3$, 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

Preparation 70

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

[0202] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 308

Preparation 71

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

[0203] NMR ($CDCl_3$, 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)
MS (FSI^+): m/z 292

Preparation 72

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

[0204] NMR ($CDCl_3$, 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

Preparation 73

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

[0205] NMR ($CDCl_3$, 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 74

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

[0206] NMR ($CDCl_3$, 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=l6Hz), 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)

Preparation 75

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

[0207] NMR ($CDCl_3$, 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)

Preparation 76

[0208] 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 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 hydrochoric acid (600 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, 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

[0209] NMR ($CDCl_3$, δ): 1.75 (6H, s), 3.53 (3H, s), 4.87 (2H, s)

Preparation 77

[0210] 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 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

[0211] NMR ($CDCl_3$, δ): 1.50 (9H, s), 3.41 (2H, s), 3.43 (3H, s), 4.08 (2H, s)

Preparation 78

[0212] 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 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 an yellow oil (614 mg).

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

[0213] NMR ($CDCl_3$, δ): 1.39 (6H, s), 1.70 (1H, m), 1.91-2.15 (2H, m), 2.16 (3H, s), 3.61 (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)

[0214] The following compounds were obtained in substantially the same manner as that of Preparation 78.

Preparation 79

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

[0215] NMR ($CDCl_3$, 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)

Preparation 80

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

[0216] NMR ($CDCl_3$, 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; J=7Hz)

Preparation 81

[0217] 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 partitoned 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 (55 g) as an oil.

Ethyl 7-acetyl-8-oxononanoate

[0218] (mixture of tautomers, too complicated to be assigned)

Preparation 82

[0219] To a mixture of ethyl 7-acetyl-8-oxononanoate (4.0 g) and magnesium chloride (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 was chromatographed on silica gel eluting with a mixture of ethyl acetate and hexane (1:5) to give ethyl 7-acetyl-7-(4-cyanobenzoyi)-8-oxononanoate (3.52 g) as an oil.

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

[0220] NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7Hz), 1.25-1.45 (4H, m), 1.30 (9H, s), 1.55-1.70 (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 83

[0221] Ethyl 7-acetyl-7-(4-cyanobenzoyl)-8-oxononanoate (35 g) was dissolved in trifluoroacetic acid (12.6 ml) and the mixture was stirred at 20°C for 15 minutes. The mixture was partitoned between ethyl acetate and water. The organic layer was separated, washed with water, aqueous sodium bicarbonate and brine, dried over $MgSO_4$ (magnesium sulfate), and evaporated to give ethyl 7-(4-cyanobenzoyl)-8-oxononanoate (2.25 g) as an oil.

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

[0222] NMR ($CDCl_3$, δ): 1.25 (3H, t, J=7Hz), 1.25-1.45 (4H, m), 1.55-1.70 (2H, m), 1.80-2.10 (2H, m), 2.16 (3H, s), 2.28 (2H, t, J=7Hz), 4.12 (2H, q, J=7Hz), 4.40 (1 H, t, J=7Hz), 7.80 (2H, t, J=9Hz), 8.07 (2H, d, J=9Hz)

Preparation 84

[0223] A mixture of methyl 4-(aminosulfonyl)benzoate (5.10 g) and potassium carbonate (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 evaporated to give a pale yellow oil, which was solidified upon standing. The solid was triturated 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

[0224] NMR ($CDCl_3$, 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 85

[0225] A suspension of methyl 4-({[(benzyloxy)carbonyl]amino}-sulfonyl)benzoate (3.38 g) and 85% pottasium 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 (2.92 g).

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

[0226] NMR (DMSO-d_6, δ): 5.06 (2H, s), 7.25 (2H, m), 7.33 (3H, m), 8.00 (2H, d, J=9Hz), 8.15 (2H, d, J=9Hz)
MS (ESI^-): m/z 334 (M-H)

Preparation 86

[0227] 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 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 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

[0228] NMR ($CDCl_3$, δ): 1.33 (3H, t, J=7Hz), 2.75 (2H, q, J=7Hz), 6.12 (1H, m), 6.78 (1H, -m), 7.60 (1H, t, J=8Hz), 7.82 (1H, d, J=8Hz), 8.07 (1H, d, J=8Hz), 8.14 (1H, s), 9.50 (1H, s, br)

Preparation 87

[0229] To a suspension of magnesium chloride (3.01 g) in tetrahydrofuran (30 mL) was 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 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

[0230] NMR ($CDCl_3$, δ): mixture of tautomers: 1.20 and 1.27 (9H, s), 2.16 and 2.44 (3H, s), 7.33-7.71 (4H, m), 13.66 (1H, s)

Preparation 88

[0231] 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 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 (533 g).

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

[0232] NMR ($CDCl_3$, 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 89

[0233] To a mixture of 2-(trimethylsilyl)ethanol (205 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 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

[0234] NMR ($CDCl_3$, δ): 0.08 (18H, s), 1.12 (4H, m), 4.38 (4H, m)

Preparation 90

[0235] 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 sufate, 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

[0236] NMR ($CDCl_3$, 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 91

[0237] 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 15 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

[0238] NMR ($CDCl_3$, 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)

[0239] The following compound was obtained in substantially the same manner as that of Preparation 91.

Preparation 92

Ethyl 5-oxo-5-phenylpentanoate

[0240] NMR ($CDCl_3$, 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 93

[0241] A mixture of 2-benzoylcyclohexanone (1.00 g), sodium ethoxide (404 mg) in ethanol (5 mL) was stirred for 35 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).

Ethyl 7-oxo-7-phenylheptanoate

[0242] NMR ($CDCl_3$, 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)

Preparation 94

[0243] To a solution of ethyl 7-chloro-7-oxoheptanoate (131 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).

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

[0244] NMR ($CDCl_3$, δ): 1.25 (3H, 1, 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)

Preparation 95

[0245] 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 OS 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 brmown 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).

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

[0246] NMR ($CDCl_3$, 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)

Preparation 96

[0247] 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.

Benzyl [4-(chlorocarbonyl)phenyl]sulfonylcarbamate

Preparation 97

[0248] 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 (aminooxy)(diphenyl)phosphine oxide as a white crystal (15.3 g).

(Aminooxy)(diphenyl)phosphine oxide

[0249] NMR ($CDCl_3$, δ): 7.54-7.58 (6H, m), 7.74-7.83 (4H, m), 8.20-8.33 (2H, m)

Preparation 98

[0250] 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

[0251] NMR ($CDCl_3$, δ): 2.37 (3H, s), 5.22 (2H, s, br), 6.07 (1H, m), 6.99 (1H, m), 7.15 (1H, m)

Preparation 99

[0252] 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).

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

[0253] NMR ($CDCl_3$, 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)

Preparation 100

[0254] To a suspension of (1E)-1-(1-amino-1H-pyrrol-2-yl)ethanone hydrazone (110 g) in toluene (1.1 L) was added potassium teri-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 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).

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

[0255] NMR ($CDCl_3$, δ): 1.26 (3H, t, J=7Hz), 21.62 (2H, q, J=7Hz), 4.53 (2H, s, br), 5.80 (1H, m), 5.99 (1H, m), 6.67 (1H, m)

Preparation 101

[0256] To a suspension of tert-butyl 4-methoxy-3-oxobutanoate (3.09 g) and potassium carbonate (250 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 (433 g).

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

[0257] NMR ($CDCl_3$, 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), 4.02 (4H, m)
MS: (m/z) 317 (M+H)

[0258] The following compounds were obtained in substantially the same manner as that of Preparation 101.

Preparation 102

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

[0259] NMR ($CDCl_3$, 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)

Preparation 103

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

[0260] NMR ($CDCl_3$, 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)

Preparation 104

1-tert-Butyl 6-ethyl 2-acetylhexanedioate

[0261] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 273

Preparation 105

1-tert-Butyl 5-ethyl 2-acetylpentanedioate

[0262] NMR ($CDCl_3$, 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 106

[0263] 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 an 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

[0264] NMR ($CDCl_3$, 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 107

[0265] 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

[0266] NMR ($CDCl_3$, 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 82H, q, J=7Hz), 4.73 (1H, d, J=17Hz), 4.82 (1H, d, J=17Hz)

Preparation 108

[0267] To a solution of ethyl thiophene (2.00 g) and ethyl 7-chloro-7-oxoheptanoate (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 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

[0268] NMR ($CDCl_3$, 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)

[0269] The following compounds were obtained in substantially the same manner as those of Preparations 76 and 77.

Preparation 109

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

[0270] NMR ($CDCl_3$, δ): 1.47 (9H, s), 2.46 (3H, s), 2.68 (3H, s), 3.68 (2H, s)

Preparation 110

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

[0271] NMR ($CDCl_3$, 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)

[0272] The following compounds were obtained in substantially the same manner as that of Preparation 86.

Preparation 111

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

[0273] NMR ($CDCl_3$, δ): 1.32 (3H, t, J=7Hz), 2.74 (2H, q, J=7Hz), 6.13 (1H, m), 6.79 (1H, m), 7.56 (1H, d, J=5Hz), 7.69 (1H, s), 8.54 (1H, d, J=5Hz), 9.40 (1H, br)

Preparation 112

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

[0274] NMR ($CDCl_3$, δ): 1.32 (3H, t, J=7Hz), 2.74 (2H, q, J=7Hz), 3.87 (3H, s), 6.08 (1H, 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 113

[0275] 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 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

[0276] NMR ($CDCl_3$, 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)

Example 1

[0277] 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-toluenesulfonic 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 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 an yellow solid.

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

[0278] NMR ($CDCl_3$, δ): 1.40 (3H, t, J=8Hz), 231 (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)

[0279] The following compounds were obtained in substantially the same manner as that of Example 1.

Example 2

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

[0280] NMR ($CDCl_3$, 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)

Example 3

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

[0281] NMR ($CDCl_3$, 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)

Example 4

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

[0282] NMR ($CDCl_3$, 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 5

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

[0283] NMR ($CDCl_3$, 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 5-2

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

[0284] NMR ($CDCl_3$, 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 6

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

[0285] NMR ($CDCl_3$, 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 7

[0286] 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 an yellow solid.

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

[0287] NMR ($CDCl_3$, 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)

[0288] The following compound was obtained in substantially the same manner as that of Example 7.

Example 8

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

[0289] NMR ($CDCl_3$, 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), 7.52-756 (2H, m), 7.90 (1H, s), 7.94-8.06 (2H, m)
MS (ESI^+): m/z 387 (M+H)

Example 9

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

[0290] NMR ($CDCl_3$, 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)

Example 10

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

[0291] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 332 (M+H)

Example 11

[0292] 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 an yellow oil.

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

[0293] NMR ($CDCl_3$, δ): 1.23 (3H, 1, 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=8Nz), 5.79 (1H, d, J=5Hz), 6.51 (1H, d, J=5Hz), 7.57-7.67 (3H, m), 7.75 (1 H, m)

[0294] The following compounds were obtained in substantially the same manner as that of Example 11.

Example 12

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

[0295] NMR ($CDCl_3$, 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), 839 (1H, s), 8.53 (1H, s)
MS (ESI^+): m/z 380 (M+H)

Example 13

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

[0296] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 400 (M+H)

Example 14

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

[0297] NMR ($CDCl_3$, 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), 651 (1H, d, J=4Hz), 7.45-752 (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)

Example 15

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

[0298] NMR ($CDCl_3$, 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)

Example 16

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

[0299] NMR ($CDCl_3$, 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)

Example 17

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

[0300] NMR ($CDCl_3$, 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 18

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

[0301] NMR ($CDCl_3$, 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 19

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

[0302] NMR ($CDCl_3$, 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: (m/z) 444, 446 (M+H)

Example 20

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

[0303] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 404 (M+H)

Example 21

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

[0304] NMR ($CDCl_3$, 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

Example 22

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

[0305] NMR ($CDCl_3$, 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), 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 23

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

[0306] NMR ($CDCl_3$, 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

Example 24

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

[0307] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 416

Example 25

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

[0308] NMR ($CDCl_3$, 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), 7.37 (1H, s), 8.53 (1H, d, J=5Hz)
MS (ESI^+): m/z 430

Example 26

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

[0309] NMR ($CDCl_3$, 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=4.Hz), 6.87-7.00 (3H, m), 7.38 (1H, t, J=8Hz)
MS (ESI^+): m/z 425

Example 27

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

[0310] NMR ($CDCl_3$, 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)

Example 28

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

[0311] NMR ($CDCl_3$, 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)

Example 29

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

[0312] NMR ($CDCl_3$, 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), 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 30

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

[0313] NMR ($CDCl_3$, 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 (1H, s), 8.41 (1H, s), 8.53 (1H, s)
MS (ESI^+): m/z 410

Example 31

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

[0314] NMR ($CDCl_3$, 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 (1 H, d, J=2Hz)
MS (ESI^+): m/z 444, 446

Example 32

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

[0315] NMR ($CDCl_3$, 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 33

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

[0316] NMR ($CDCl_3$, 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 34

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

[0317] NMR ($CDCl_3$, 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

Example 35

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

[0318] NMR ($CDCl_3$, 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), 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 36

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

[0319] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 366

Example 37

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

[0320] NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7Hz),1.37 (3H, t, J=7Hz), 2.30-2.43 (2H, m), 2.42 (3H, s), 258 (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

Example 38

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

[0321] NMR ($CDCl_3$, δ): 1.21 (3H, t, J=7Hz), 139 (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)
MS: (m/z) 416 (M^+), 418 (M^+-2), 85(bp)

Example 39

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

[0322] NMR ($CDCl_3$, 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)

Example 40

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

[0323] NMR ($CDCl_3$, 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 41

[0324] 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 partitined 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 an 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 yellow crystals (795 mg, 71.4%).

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

[0325] mp: 109-110°C
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)

[0326] The following compounds were obtained in substantially the same manner as that of Example 41.

Example 42

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

[0327] NMR ($CDCl_3$, 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 43

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

[0328] NMR ($CDCl_3$, 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 (BSI^+): m/z 352 (M+H)

Example 44

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

[0329] NMR ($CDCl_3$, δ): 136 (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 45

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

[0330] NMR ($CDCl_3$, 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 (1 H. 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)
MS (ESI^+): m/z 386 (M-H), 388(M+H)

Example 46

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

[0331] 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)
MS (ESI^+): m/z 372 (M+H)

Example 47

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

[0332] NMR ($CDCl_3$, 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)

Example 48

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0333] NMR ($CDCl_3$, 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), 7.31 (1H, d, J=5Hz), 7.39-7.53 (6H, m), 8.55 (1H, d, J=5Hz)

Example 49

5-[4-(6-Chloro-2-pyridinyl)-7-ethyl-2-methylpyrrolo-[1,2-b]pyridazin-3-yl]pentanoic acid

[0334] NMR ($CDCl_3$, 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 (1 H, 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

Example 50

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

[0335] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 367, MS (ESI^-): m/z 365

Example 51

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

[0336] NMR ($CDCl_3$, 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

Example 52

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

[0337] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 388, MS (ESI): m/z 386

Example 53

5-[7-Ethyl-4-(3-methoxyphenyl)-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0338] NMR ($CDCl_3$, 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=4.Hz), 6.59 (1H, d, J=4Hz), 6.93-7.02 (3H, m), 7.36-7.54 (6H, m)
MS (ESI^+): m/z 429

Example 54

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0339] NMR ($CDCl_3$,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

Example 55

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

[0340] NMR ($CDCl_3$,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 56

5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0341] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 440

Example 57

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

[0342] NMR ($CDCl_3$. 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

Example 58

5-[4-(3-Chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0343] NMR ($CDCl_3$, 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 59

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

[0344] NMR ($CDCl_3$, 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), 732-7.38 (1H, m)
MS (ESI^+): m/z 351

Example 60

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

[0345] NMR ($CDCl_3$, 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 61

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

[0346] NMR ($CDCl_3$, 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 62

5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0347] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 446, 448

Example 63

5-[4-(5,6-Dichloro-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0348] NMR ($CDCl_3$, 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

Example 64

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

[0349] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 364

Example 65

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

[0350] NMR ($CDCl_3$, 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

Example 66

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

[0351] NMR ($CDCl_3$, δ): 138 (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)
MS (ESI^+): m/z 368

Example 67

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

[0352] NMR ($CDCl_3$, 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

Example 68

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

[0353] NMR ($CDCl_3$, δ): 1.37 (3H, t, J=7Hz), 1.70-1.88 (2H, m), 2.22-23.2 (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

Example 69

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

[0354] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 324, MS (ESI^-): m/z 322

Example 70

3-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0355] mp: 181-182°C
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)

Example 71

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

[0356] NNMR ($CDCl_3$, 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, J=5Hz), 7.59-7.64 (2H, m), 7.68 (1H, br s), 7.75 (1H, m)
MS (ESI^+): 392 (M+H)

Example 72

5-[4-[3-(Aminocarbonyl)phenyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0357] NMR ($CDCl_3$, δ): 1.30-1.70 (5H, overlappoed with H_2O), 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 73

5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0358] NMR ($CDCl_3$,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)

Example 74

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

[0359] NMR ($CDCl_3$, 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)

Example 75

5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0360] NMR ($CDCl_3$, δ): 1.25-1.48 (7H, m), 2.12 (2H, t, J=7Hz), 2.62 (2H, m), 3.03 (2H, q, 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 76

5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0361] NMR ($CDCl_3$, 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 81H, m), 8.78 (1H, m)

Example 77

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

[0362] NMR ($CDCl_3$, 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 78

5-[4-[5-(Aminocarbonyl)-3-pyridinyl]-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0363] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 411

Example 79

[0364] 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, 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 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

[0365] NMR (300 MHz, $CDCl_3$, 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)
MS (ESI^+): m/z 379 (M+H)
[0366] The following compounds were obtained in substantially the same manner as that of Example 79.

Example 80

Ethyl (2E)-3-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propenoate

[0367] NMR ($CDCl_3$, 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)

Example 81

[0368] 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.

Ethyl (2E,4E)-5-[7-chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2,4-pentadienoate

[0369] NMR (300 MHz, $CDCl_3$, 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)

Example 82

[0370] 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 methylate 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°Cfor I 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 an 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

[0371] NMR ($CDCl_3$, 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)

[0372] The following compounds were obtained in substantially the same manner as that of Example 82.

Example 83

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

[0373] NMR ($CDCl_3$, 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 84

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

[0374] NMR ($CDCl_3$, 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)

Example 85

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

[0375] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 430

Example 86

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

[0376] NMR ($CDCl_3$, 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

Example 87

[0377] 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%).

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

[0378] NMR ($CDCl_3$, 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)

[0379] The following compound was obtained in substantially the same manner as that of Example 87.

Example 88

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

[0380] NMR ($CDCl_3$, 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)
MS: (m/z) 468 (M+H)

Example 89

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

[0381] NMR ($CDCl_3$, δ): 1.05-1.17 (2H, m),1.19-130 (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)

Example 90

Ethyl [4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]acetate

[0382] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 419 (M+H)

Example 91

Ethyl 4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

[0383] NMR ($CDCl_3$, 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), 752 (2H, m)
MS (ESI^+): m/z 395 (M+H)

Example 92

Ethyl 4-(3-chlorophenyl)-7-ethyl-2-(2-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

[0384] NMR ($CDCl_3$, 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), 7.26-755 (4H, m), 7.84 (1H, m), 8.15 (1H, m), 8.57 (1H, m)
MS (ESI^+): m/z 406 (M+H)

Example 93

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

[0385] NMR ($CDCl_3$, 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 (1 H, 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 94

Ethyl 3-[4-(3-chlorophenyl)-7-ethyl-2-phenylpyrrolo(1,2-b)pyridazin-3-yl]propanoate

[0386] NMR ($CDCl_3$, 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)

Example 95

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

[0387] NMR ($CDCl_3$, 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 96

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

[0388] NMR ($CDCl_3$, 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, J=7Hz), 6.02 (1H, d, J=4Hz), 6.60 (1H, d, J=4Hz), 6.95-7.02 (3H, m), 736-7.56 (6H, m)

Example 97

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

[0389] NMR ($CDCl_3$, 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 98

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

[0390] NMR ($CDCl_3$, 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)

Example 99

[0391] 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 (531 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).

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

[0392] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 424 (M+H)

[0393] The following compounds were obtained in substantially the same manner as that of Example 99.

Example 100

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

[0394] NMR ($CDCl_3$, 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)

Example 101

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

[0395] NMR ($CDCl_3$, 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)

Example 102

[0396] To a solution of N-[2-(3-cyanobenzoyl)-5-ethyl-IH-pyrrol-1-yi]-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 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 an yellow powder (231 g, 90.1%).

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

[0397] NMR ($CDCl_3$, 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)

Example 103

[0398] 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

[0399] NMR ($CDCl_3$, 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 104

[0400] 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 15 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 an yellow oil, which was crystalyzed upon standing (112 mg, 89.6%).

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

[0401] NMR ($CDCl_3$, 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)

[0402] The following compounds were obtained in substantially the same manner as that of Example 104.

Example 105

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

[0403] NMR ($CDCl_3$, 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 106

[0404] 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 partioned 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 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

[0405] NMR ($CDCl_3$, 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)

Example 107

[0406] To a solution of ethyl 6-[4-(4-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]hexanoate (15 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 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 chromatograpy eluting with a mixture of ethyl acetate and hexane (1:1) and triturated with isopropyl ether to give 6-[4-(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

[0407] NMR ($CDCl_3$, δ): 1.15-1.30 (2H, m), 1.35-1.45 (2H, m), 1.38 (3H, t, 1=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

[0408] NMR ($CDCl_3$, 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)

Example 108

[0409] 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 15 M diisobutylalminum hydride (0.277 mL) in toluene (24 mL) in a dryice-acetone bath. After addition, the mixture was stirred for 2 hours (-10°C). The reaction mixture was quenched with sodium, potassium-tartarate 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 an yellow solid (30 mg).

(2E)-3-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propen-1-ol

[0410] NMR ($CDCl_3$, 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).

[0411] The following compounds were obtained in substantially the same manner as that of Example 108.

Example 109

[4-(4-Fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methanol

[0412] NMR ($CDCl_3$, 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), 7.43-751 (2H, m), 7.70 (1H, m)
MS (ESI^+): m/z 257 (M+H)

Example 110

[0413] 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

[0414] NMR ($CDCl_3$, 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 111

[0415] 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 25 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

[0416] NMR ($CDCl_3$, 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 112

[0417] 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 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 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-Cblorophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoyl}amino)ethanesulfonic acid

[0418] NMR ($CDCl_3$, 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 113

[0419] 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 diisobulylaluminum hydride in toluene (0.816 mL) under an ice-bath. After stirring for hour at room temperature, additional 1 M diisobutylaluminum hydride (0.41 m L) 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 (1C 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 crystalyzed upon standing (107 mg, 104%).

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

[0420] NMR ($CDCl_3$, 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 114 (comparative)

[0421] 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 mixtrure 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 partioned 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

[0422] NMR ($CDCl_3$, δ): 1.35 (3H, t, J=7Hz), J .70 (3H, m), 1.94 (3H, s), 2.04 (3H, s), 2.17 (3H, s), 2.78 (2H, m), 3.01 (2H, q, J=7Hz), 3.10 (1 H, 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 115 (comparative)

[0423] 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

[0424] NMR ($CDCl_3$, 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)

[0425] The following compounds were obtained in substantially the same manner as that of Example 115.

Example 116

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

[0426] NMR ($CDCl_3$, 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 117

[0427] 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 mixure became clear solution. The solution was filtered through membrane filter, washed with water (0.4 mL x3), and was freezedried 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

[0428] NMR (DMSO-d_6, δ): 1.10-1.15 (2H, m), 1.20-1.40 (7H, m), 1.74 (2H, t, J=8Hz), 2.25-238 (2H, m), 250 (3H, s), 2.91 (2H, q, J=8Hz), 5.72 (1H, d, J=5Hz), 6.50 (1H, d, J=5Hz), 7.39-7.46 (3H, m), 7.97 (2H, d, J=8Hz), 8.26 (1H, br s)

Example 118

[0429] A solution of 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid (100 mg), triethylamime (29.4 mg), and diphenylphosphoryl azide (79.9 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-b]pyridazin-3-yl]butylcarbamate (28 mg, 23.4%) as an yellow oil.

tert-Butyl 4-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butylcarbamate

[0430] NMR ($CDCl_3$, 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 433 (M+H)

Example 119

[0431] 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 (18 mg).

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

[0432] NMR ($CDCl_3$, 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)

Example 120

[0433] 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(O) (1.9 mg) was added. After refluxed over night, the reaction mixture was quenched with potassium fluoride (1.8 mmol) in H_2O. 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.

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

[0434] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 392 (M+H)

[0435] The following compounds were obtained in substantially the same manner as that of Example 120.

Example 121

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

[0436] NMR ($CDCl_3$, 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 122

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

[0437] NMR ($CDCl_3$, 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)

Example 123

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

[0438] NMR ($CDCl_3$, 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)

Example 124

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

[0439] NMR ($CDCl_3$, 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)

Example 125

[0440] To a solution of [4-(4-fluorophenyl)-2-methylpyrrolo-[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 arnbient-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 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 an yelow solid (340 ing, 67.9%).

4-(4-Fluorophenyl)-2-methylpyrrolo[1,2-b]pyridazine-3-carbaldehyde

[0441] NMR ($CDCl_3$, 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 126

[0442] 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 atomosphere (3.5 atm) at ambient temperature. After 10 hours, the mixture was stood overnight. To the mixture was added 10% palladium on carbon (900 mg) and was stirred under hydrogen atomosphere (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 atomosphere (35 atm) at ambient temperature for 8 hours. The mixture was filtered 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 an yellow oil (9.0 g, 100.5%).

Ethyl 7-ethyl-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazine-3-carboxylate

[0443] NMR ($CDCl_3$, 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)

[0444] The following compounds were obtained in substantially the same manner as that of Example 126.

Example 127

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 acid

[0445] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 366 (M+H), MS (ESI^-): m/z 364

Example 128

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

[0446] NMR ($CDCl_3$, 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 129

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

[0447] NMR ($CDCl_3$, 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 130

[0448] 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 an yellow oil (160 mg).

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

[0449] NMR ($CDCl_3$, δ): 1.24 (3H, t, J=7Hz), 1.38 (3H, t, 1=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)

Example 131

[0450] A mixture of ethyl 5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-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 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 an yellow oil (88 mg).

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

[0451] NMR ($CDCl_3$, 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)
MS (ESI^+): m/z 391.

Example 132

[0452] 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.

5-[4-(3-Cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]-N-(2-pyridinyl)pentanamide

[0453] mp:67-70°C
NMR ($CDCl_3$, 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=75Hz), 8.24 (1H, d, J=4Hz)
MS: (m/z) 499 (M+), 45 (bp)

Example 133

[0454] 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 25 hour, the reaction was quenched by adding 1N hydrochloric acid (1 mL), and the mixture was partitioend 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 an 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

[0455] NMR ($CDCl_3$, 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)

[0456] The following compound was obtained in substantially the same manner as that of Example 133.

Example 134

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

[0457] NMR ($CDCl_3$, 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)

Example 135

[0458] 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 mixrure 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 an 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

[0459] NMR ($CDCl_3$, 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 136

[0460] 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 dichloromathane (1 mL) was stirred for 20 hour 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 an yellow gum (19.1 mg).

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

[0461] NMR ($CDCl_3$, 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)

[0462] The following compound was obtained in substantially the same manner as that of Example 136.

Example 137

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

[0463] NMR ($CDCl_3$, 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)

Preparation 114

[0464] To a suspension of 60% sodium hydride (8.79 g) in tetrahydrofuran (500 mL) was addded 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 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

[0465] ^{1}H NMR ($CDCl_3$) 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).

[0466] The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 114.

Preparation 115

isopropoxyacetic acid

[0467] ^{1}H NMR ($CDCl_3$) δ 1.24 (6H, d, J= 7 Hz), 3.68-3.82 (1H, m), 4.11 (2H, s).

[0468] The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 76 and Preparation 77.

Preparation 116

tert-butyl 4-isopropoxy-3-oxobutanoate

[0469] ^{1}H 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).

[0470] The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 101.

Preparation 117

1-tert-butyl 7-ethyl 2-(isopropoxyacetyl)heptanedioate

[0471] ^{1}H 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.

[0472] The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 16.

Preparation 118

ethyl 2-[(5-methyl-3-pyridinyl)carbonyl]-3-oxobutanoate

[0473] ^{1}H 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 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 119

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

[0474] ^{1}H 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 (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 120

1-tert-butyl 5-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(methoxyacetyl)pentanedioate

[0475] ^{1}H 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.

Preparation 121

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

[0476] ^{1}H NMR ($CDCl_3$) 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.

Preparation 122

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

[0477] ^1H NMR ($CDCl_3$) 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.

Preparation 123

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

[0478] ^1H NMR ($CDCl_3$) 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.

[0479] The following compound(s) was(were) obtained in substantially the same manner as that of Preparation 46.

Preparation 124

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-6-oxoheptanoate

[0480] ^1H NMR ($CDCl_3$) 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 125

ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-6-methoxy-5-oxohexanoate

[0481] ^1HNMR ($CDCl_3$) 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 126

ethyl 8-isopropoxy-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

[0482] ^1H NMR ($CDCl_3$) 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), 3.44-354 (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), 8.63 (1H, s), 9.02 (1H, s).
MS (ESI^+): m/z 364.

Preparation 127

ethyl 6-[(5-bromo-3-pyxidinyl)carbonyl]-8-isopropoxy-7-oxooctanoate

[0483] ^1H NMR ($CDCl_3$) 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 128

ethyl 8-(acetyloxy)-6-[(5-methyl-3-pyridinyl)carbonyl]-7-oxooctanoate

[0484] ^{1}H NMR ($CDCl_3$) 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.

[0485] The following compound(s) was(were) obtained in substantially the same manner as that of Example 11.

Example 138

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

[0486] ^{1}H NMR ($CDCl_3$) 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 139

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

[0487] ^{1}H NMR ($CDCl_3$) 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), 653 (1H, d, J= 4 Hz), 7.87 (1H, m), 8.54 (1H, d, J= 2 Hz), 8.77 (1H, d, J= 2 Hz).
MS (ESI$^+$): m/z 430 432.

Example 140

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

[0488] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI$^+$): m/z 446 448.

Example 141

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

[0489] ^{1}H NMR ($CDCl_3$) 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.

Example 142

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

[0490] ^{1}H NMR ($CDCl_3$) 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.

Example 143

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

[0491] ^{1}H NMR ($CDCl_3$) 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 144

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

[0492] ^{1}H NMR ($CDCl_3$) 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.

Example 145

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

[0493] ^{1}H NMR ($CDCl_3$) 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.

[0494] The following compound(s) was(were) obtained in substantially the same manner as that of Example 120.

Example 146

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

[0495] ^{1}H NMR ($CDCl_3$) 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 (1H, d, J= 2-Hz), 8.72 (1H, d, J= 2 Hz).
MS (ESI^+): m/z 394.

Example 147

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

[0496] ^{1}H NMR ($CDCl_3$) 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 Hz), 8.71 (1H, d, J= 2 Hz).
MS (ESI^+): m/z 394.

[0497] The following compound(s) was(were) obtained in substantially the same manner as that of Example 125.

Example 148

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

[0498] ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, J= 7 Hz), 1.37 (3H, t, J= 7 Hz), 2.45-2.58 (2H, m), 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 (ESr): m/z 366, MS (ESI^+): m/z 368.

Example 149

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

[0499] ^{1}H NMR ($CDCl_3$) 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.

[0500] The following compound(s) was(were) obtained in substantially the same manner as that of Example 115.

Example 150

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

[0501] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 432 434.

Example 151

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

[0502] ^{1}H NMR ($CDCl_3$) 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.

[0503] The following compound(s) was(were) obtained in substantially the same manner as that of Example 133.

Example 152

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

[0504] ^{1}H 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 153

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

[0505] ^{1}H 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 154

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

[0506] ^{1}H 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.

Example 155

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

[0507] ^{1}H NMR ($CDCl_3$) 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.

Example 156

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

[0508] ^{1}H NMR ($CDCl_3$) 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.

Example 157

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

[0509] ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J= 7 Hz), 1.39 (3H, t, J= 7 Hz), 1.38-157 (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 158

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

[0510] ^{1}H NMR ($CDCl_3$) δ 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 (1J, d, J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 7.60 (2H, m), 7.67 (1H, s), 7.75 (1H, m)

Example 159

[0511] 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%).

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

[0512] ^{1}H NMR ($CDCl_3$): 1.23 (3H, t, J = 7 Hz), 1.33-1.60 (7 H, m), 2.16 (2H, t, J = 7 Hz), 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 Hz9, 7.87 (1H, m), 8.54 (1H, m), 8.77 (1H, m).

[0513] The following compound(s) was(were) obtained in substantially the same manner as that of Example 44.

Example 160

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

[0514] ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J= 7 Hz), 1.65-1.85 (2H, m), 2.31 (2H, t, J= 7 Hz), 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.

Example 161

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

[0515] ^{1}H 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).
MS (ESI^-): m/z 416 418, MS (ESI^+): m/z 418 420.

Example 162

3-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0516] ^{1}H 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.

Example 163

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

[0517] ^{1}H 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 164

4-[7-ethyl-2-(methoxymethyl)-4-(5-vinyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0518] ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, t, J= 7 Hz), 1.72-1.87 (2H, m), 2.26 (2H, t, J= 7 Hz), 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.

Example 165

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

[0519] ^{1}H 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).
MS (ESI^-): m/z 408, MS (ESI^+): m/z 410.

Example 166

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isopropoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0520] ^{1}H 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), 658 (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.

Example 167

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

[0521] ^1H NMR ($CDCl_3$) δ 0.23-033 (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, 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 168

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

[0522] ^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).
MS (ESI^-): m/z 462, MS (ESI^+): m/z 464.

Example 169

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

[0523] ^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), 7.28-736 (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 170

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

[0524] ^1H NMR ($CDCl_3$) 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 Hz).
MS (ESI^-): m/z 457, MS (ESI^+): m/z 459.

Example 171

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

[0525] ^1H NMR ($CDCl_3$) 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).
MS (ESI^-): m/z 457, MS (ESI^+): m/z 459.

Example 172

[0526] To a solution of ethyl 7-ethyl-2-rnethyl-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 produt 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

[0527] ^{1}H NMR ($CDCl_3$) 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), 858 (1H, s).
MS (ESI^-): m/z 294 , MS (ESI^+): m/z 296.

[0528] The following compound(s) was(were) obtained in substantially the same manner as that of Example 99.

Example 173

5-[4-(3-cyanophenyl)-2-(ethoxymethyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0529] ^{1}H 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)

[0530] The following compound(s) was(were) obtained in a similar manner to that of Preparation 13.

Preparation 129

1-tert-butyl 7-ethyl 2-(isobutoxyacetyl)heptanedioate

[0531] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Preparation 130

1-tert-butyl 6-ethyl 2-(isobutoxyacetyl)hexanedioate

[0532] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

[0533] The following compound(s) was(were) obtained in a similar manner to that of Preparation 16.

Preparation 131

1-tert-butyl 6-ethyl 2-acetyl-2-(2-chloroisonicotinoyl)hexanedioate

[0534] ^{1}H NMR ($CDCl_3$) 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.

Preparation 132

1-tert-butyl 5-ethyl 2-acetyl-2-(2-chloroisonicotinoyl)pentanedioate

[0535] ^{1}H NMR ($CDC1_3$) 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.

Preparation 133

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

[0536] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 436.

Preparation 134

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

[0537] ^{1}H 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.

Preparation 135

1-tert-butyl 7-ethyl 2-[(acetyloxy)acetyl]-2-(3-cyanobenzoyl)heptanedioate

[0538] ^{1}H 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).

Preparation 136

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-[(5-bromo-3-pyridinyl)carbonyl]hexanedioate

[0539] ^{1}H 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).

Preparation 137

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

[0540] ^{1}H 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), 822 (1H, m), 8.82 (2H, m).
MS (ESI^+): m/z 500 502.

Preparation 138

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

[0541] ^{1}H 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).
MS (ESI^+): m/z 490.

Preparation 139

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

[0542] ^{1}H 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.

Preparation 140

1-tert-butyl 6-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-[(cyclohexylmethoxy)acetyl]hexanedioate

[0543] ^{1}H 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.

Preparation 141

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

[0544] ^{1}H 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 142

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

[0545] ^{1}H NMR ($CDCl_3$) δ 0.15-0.23 (2H, m), 0.48-056 (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.

Preparation 143

tert-butyl 2-[(5-bromo-3-pyridinyl)carbonyl]-3-oxobutanoate

[0546] ^{1}H NMR ($CDCl_3$) 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 144

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-[(5-chloro-3-pyridinyl)carbonyl]hexanedioate

[0547] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Preparation 145

1-tert-butyl 7-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-[(cyclopropylmethoxy)acetyl]heptanedioate

[0548] ^{1}H NMR (300 MHz, $CDCl_3$) 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, m), 3.26-3.29 (2H, m), 4.07-4.19 (4H, m), 431 (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 146

1-tert-butyl 6-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-[(cyclopropylmethoxy)acetyl]hexanedioate

[0549] ^{1}H NMR (300 MHz, $CDCl_3$) 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), 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 147

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

[0550] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Preparation 148

1-tert-butyl 5-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-(isobutoxyacetyl)pentanedioate

[0551] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Preparation 149

1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]-2-(3-chlorobenzoyl)peritanedioate

[0552] ^{1}H NMR (300 MHz, $CDCl_3$) 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), 738 (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 150

1-tert-butyl 6-ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-2-(isobutoxyacetyl)hexanedioate

[0553] ^{1}H NMR (300 MHz, $CDCl_3$) 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, 7Hz), 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 151

1-tert-butyl 6-ethyl 2-[(acetyloxy)acetyl]-2-(3-chlorobenzoyl)hexanedioate

[0554] ^{1}H 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).

Preparation 152

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

[0555] ^{1}H 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).

Preparation 153

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

[0556] ^{1}H 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).

Preparation 154

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

[0557] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI+): m/z 438 (M + H).

Preparation 155

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

[0558] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 442 (M + H).

Preparation 156

1-tert-butyl 5-ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-2-(methoxyacetyl)pentanedioate

[0559] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 428 (M + H).

Preparation 157

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

[0560] ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 8 Hz), 1.31-1.48 (11H, m), 1.55-1.75 (2H, m), 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).

Preparation 158

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

[0561] ^{1}H NMR ($CDCl_3$) 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.

Preparation 159

ethyl 2-(2-chloroisonicotinoyl)-3-oxobutanoate

[0562] ^{1}H NMR ($CDCl_3$) 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).
[0563] The following compound(s) was(were) obtained in a similar manner to that of Prepatration 46.

Preparation 160

ethyl 5-(2-chloroisonicotinoyl)-6-oxoheptanoate

[0564] ^{1}H NMR ($CDCl_3$) 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 (1H, d, J= 5 Hz), 7.77 (1H, s), 8.59 (1H, d, J= 5 Hz).
MS (ESI^+): m/z 312.

Preparation 161

ethyl 4-(2-chloroisonicotinoyl)-5-oxohexanoate

[0565] ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, t, J= 7 Hz), 221 (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.

Preparation 162

ethyl 6-(acetyloxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

[0566] ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J= 7 Hz), 1.98 (3H, s), 2.23-234 (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).
MS (ESI^+): m/z 336.

Preparation 163

ethyl 7-(acetyloxy)-5-[(5-methyl-3-pyridinyl)carbonyl]-6-oxoheptanoate

[0567] ^{1}H 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.

Preparation 164

ethyl 8-(acetyloxy)-6-(3-cyanobenzoyl)-7-oxooctanoate

[0568] ^{1}H 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.

Preparation 165

ethyl 7-(acetyloxy)-5-[(5-bromo-3-pyridinyl)carbonyl]-6-oxoheptanoate

[0569] ^{1}H 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).
MS (ESI^-): m/z 4.14 4.16, MS (ESI^+): m/z 414 416.

Preparation 166

ethyl 6-(acetyloxy)-4-[(5-bromo-3-pyridinyl)carbonyl]-5-oxohexanoate

[0570] ^{1}H 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 167

ethyl 6-(cyclohexylmethoxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

[0571] ^{1}H 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).
MS (ESI^+): m/z 390.

Preparation 168

ethyl 4-[(5-bromo-3-pyridinyl)carbonyl]-6-(cyclohexylmethoxy)-5-oxohexanoate

[0572] ^{1}H 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 169

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-7-(cyclohexylmethoxy)-6-oxoheptanoate

[0573] ^1H NMR (300 MHz, $CDCl_3$) 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.

Preparation 170

ethyl 7-(cyclopropylmethoxy)-5-[(5-methyl-3-pyridinyl)carbonyl]-6-oxoheptanoate

[0574] ^1H NMR ($CDCl_3$) δ -0.08-0.00 (1H, m), 0.00-0.15 (1H, m), 028-0.49 (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 171

ethyl 6-(cyclopropylmethoxy)-4-[(5-methyl-3-pyridinyl)carbonyl]-5-oxohexanoate

[0575] ^1H NMR ($CDCl_3$) 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), 2.22-236 (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.

Preparation 172

1-(5-bromo-3-pyridinyl)-1,3-butanedione

[0576] ^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.

Preparation 173

ethyl 7-(acetyloxy)-5-[(5-chloro-3-pyridinyl)carbonyl]-6-oxoheptanoate

[0577] ^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).

Preparation 174

ethyl 6-[(5-chloro-3-pyridinyl)carbonyl]-8-(cyclopropylmethoxy)-7-oxooctanoate

[0578] ^1H NMR (300 MHz, $CDCl_3$) δ -0.09-0.11 (2H, m), 0.25-035 (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).

Preparation 175

ethyl 5-[(5-chloro-3-pyridinyl)carbonyl]-7-(cyclopropylmethoxy)-6-oxoheptanoate

[0579] ^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).

Preparation 176

ethyl 6-[(5-bromo-3-pyridinyl)carbonyl]-8-isobutoxy-7-oxooctanoate

[0580] ^{1}H 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, J = 2 Hz), 8.87 (1H, d, J = 2 Hz), 9.08 (1H, d, J = 2 Hz).

Preparation 177

ethyl 4-[(5-chloro-3-pyridinyl)carbonyl]-6-isobutoxy-5-oxohexanoate

[0581] ^{1}H 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).

Preparation 178

ethyl 6-(acetyloxy)-4-(3-chlorobenzoyl)-5-oxohexanoate

[0582] ^{1}H 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).

Preparation 179

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-7-isobutoxy-6-oxoheptanoate

[0583] ^{1}H 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 = 2Hz), 9.10 (1H, d, J = 2Hz).

Preparation 180

ethyl 7-(acetyloxy)-5-(3-chlorobenzoyl)-6-oxoheptanoate

[0584] ^{1}H 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 181

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

[0585] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 352 (M + H).

Preparation 182

ethyl 6-[(5-methoxy-3-pyridinyl)carbonyl]-7-oxooctanoate

[0586] ^{1}H NMR ($CDCl_3$) 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 183

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

[0587] ^{1}H NMR ($CDCl_3$) 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 184

ethyl 5-[(5-chloro-3-pyridinyl)carbonyl]-7-methoxy-6-oxoheptanoate

[0588] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 342 (M + H).

Preparation 185

ethyl 4-[(5-chloro-3-pyridinyl)carbonyl]-6-methoxy-5-oxohexanoate

[0589] ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, t, J = 8 Hz), 2.09 (1H, m), 2.25 (1H, m), 2.38-2.49 (2H, 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 186

ethyl 6-[(5-chloro-3-pyridinyl)carbonyl]-8-methoxy-7-oxooctanoate

[0590] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 356 (M + H).

Preparation 187

ethyl 5-[(5-bromo-3-pyridinyl)carbonyl]-7-methoxy-6-oxoheptanoate

[0591] ^{1}H 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).
MS (ESI^+): m/z 386 388.
[0592] The following compound(s) was(were) obtained in a similar manner to that of Preparation 76 and 77.

Preparation 188

tert-butyl 4-(cyclohexylmethoxy)-3-oxobutanoate

[0593] ^{1}H 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).

Preparation 189

tert-butyl 4-(cyclopropylmethoxy)-3-oxobutanoate

[0594] ^{1}H 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 190

tert-butyl 4-isobutoxy-3-oxobutanoate

[0595] ^{1}H 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 191

tert-butyl 3-(3-methyl-2-thienyl)-3-oxopropanoate

[0596] ^{1}H-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 192

tert-butyl 3-(5-methyl-3-isoxazolyl)-3-oxopropanoate

[0597] ^{1}H-NMR ($CDCl_3$) δ 1.475-1.57 (9H, m), 2.49 (3H, m), 3.95 (2H, s), 6.40 (1H, s).
[0598] The following compound(s) was(were) obtained in a similar manner to that of Preparation 78.

Preparation 193

1-tert-butyl 7-ethyl 2-[(3-methyl-2-thienyl)carbonyl]heptanedioate

[0599] ^{1}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).

Preparation 194

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

[0600] ^{1}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).
[0601] The following compound(s) was(were) obtained in a similar manner to that of Preparation 96.

Preparation 195

5-methoxynicotinoyl chloride hydrochloride

Preparation 196

5-pyrimidinecarbonyl chloride hydrochloride

Preparation 197

5-chloronicotinoyl chloride hydrochloride

[0602] The following compound(s) was(were) obtained in a similar manner to that of Preparation 101.

Preparation 198

1-tert-butyl 5-ethyl 2-[(cyclohexylmethoxy)acetyl]pentanedioate

[0603] ^{1}H 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).

Preparation 199

1-tert-buty) 6-ethyl 2-[(cyclohexylmethoxy)acetyl]hexanedioate

[0604] ^{1}H 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 200

1-tert-butyl 6-ethyl 2-[(cyclopropylmethoxy)acetyl]hexanedioate

[0605] ^{1}H NMR ($CDCl_3$) δ 0.22-033 (2H, m), 054-0.64 (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.

Preparation 201

1-tert-butyl 5-ethyl 2-[(cyclopropylmethoxy)acetyl]pentanedioate

[0606] ^{1}H NMR ($CDCl_3$) 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 202

1-tert-butyl 5-ethyl 2-[(2-methoxyethoxy)acetyl]pentanedioate

[0607] ^{1}H NMR ($CDCl_3$) 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.

[0608] The following compound(s) was(were) obtained in a similar manner to that of Preparation 106.

Preparation 203

methyl 2-bromo-4-[(5-ethyl-1H-pyrrol-2-yl)carbonyl]benzoate

[0609] ^{1}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).

Preparation 204

[0610] 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, 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).

methyl [2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]acetate

[0611] ^{1}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 205

[0612] 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

[0613] ^{1}H NMR ($CDCl_3$) δ 3.69 (2H, m), 3.76 (2H, m), 3.78 (3H, s), 4.16 (2H, s).

Preparation 206

[0614] To solution of methyl (2-hydroxyethoxy)acetate (540 mg), imidazole (411 mg) and triphenylphosphine (137 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 filterred off, the filtrates were diluted with AcOEt, washed with aq Na_2S0_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).

methyl (2-iodoethoxy)acetate

[0615] ^{1}H 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 207

[0616] 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 05 hour. To this added ethyl 3-iodopropanoate (554 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).

1-tert-butyl 5-ethyl 2-[(acetyloxy)acetyl]pentanedioate

[0617] ^{1}H 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).

Preparation 208

[0618] 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).

benzyl 4-thiomorpholinecarboxylate 1,1-dioxide

[0619] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02 (4H, br s), 4.01 (4H, t, J = 5 Hz), 5.16 (2H, s), 733-7.40 (5H, m).

Preparation 209

[0620] 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 betwwen EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with water three times, dried over $MgSO_4$ 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

[0621] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (3H, t, J = 7 Hz), 4.43 (2H, q, J = 7 Hz), 8.28 (1 H, dd, J = 3, 3 Hz), 8.74 (1H, d, J = 3 Hz), 9.09 (1H, d, J = 3 Hz).

Preparation 210

[0622] 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.
^{1}H NMR (300 MHz, DMSO-d_6) 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

[0623] ^{1}H NMR (300 MHz, DMSO-d_6) 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).

[0624] The following compound(s) was(were) obtained in a similar manner to that of Preparation 210.

Preparation 211

5-pyrimidinecarboxylic acid

[0625] ^{1}H NMR (DMSO-d_6) δ 9.20 (2H, s), 9.37 (1H, s).
MS (ESI^+): m/z 148 (M+ + Na).

Preparation 212

[0626] To a solution of diisopropylamine (5.41 g) in THF (30 mL) was added 15 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 NH_4Cl solution. The organic layer was separated, washed with aq $NaHCO_3$ solution and brine, dried over $MgSO_4$, 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

[0627] Enol form: ^{1}H NMR ($CDCl_3$) 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: ^{1}H NMR ($CDCl_3$) 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 213

[0628] 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 miutes. After stirring for 1 hour, -(aminooxy)(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 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 acetatec-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-bro-

mobenzoate as an orange solid (310 mg).

methyl 4-[(1-amino-5-ethyl-1H-pyrrol-2-yl)carbonyl]-2-bromobenzoate

[0629] ^{1}H-NMR ($CDCl_3$) 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), 7.84 (1H, d, J = 8 Hz), 8.02 (1H, s).

Preparation 214

[0630] A solution of 1-tert-butyl 7-ethyl 2-[(5-methyl-3-isoxazolyl)carbonyl]heptanedioate (12.6 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).

7-ethoxy-2-[(5-methyl-3-isoxazotyl)carbonyl]-7-oxoheptanoic acid

[0631] ^{1}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).
MS (ESI^+): m/z 296.22 (M-H) and 593.52 (2M-H)

Preparation 215

[0632] To a suspension of dimethyl sulfone (5.43 g) in tetrahydrofuran (10 mL) was addded 1.59 M n-butyl lithium (36.3 mL) in a dryice-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 $MgSO_4$, and evaporated. Flash silicagel column chromatography (EtOAc-hexane = 50-200 to 300-100) afforded 2-(methylsulfonyl)-1-methoxyethanone as a colorless oil (2.24 g).

1-methoxy-3-(methylsulfonyl)acetone

[0633] ^{1}H-NMR ($CDCl_3$) δ 2.99 (3H, s), 3.08 (2H, s), 3.47 (3H, s), 4.19 (2H, s).
[0634] The following compound(s) was(were) obtained in a similar manner to that of Example 1.

Example 174

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

[0635] ^{1}H-NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 370 (M + H)
[0636] The following compound(s) was(were) obtained in a similar manner to that of Example 7.

Example 175

5-{4-[3-(aminocarbonyl)phenyl]-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0637] ^{1}H-NMR ($CDCl_3$) 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).
[0638] The following compound(s) was(were) obtained in a similar manner to that of Example 11.

Example 176

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

[0639] ^{1}H NMR ($CDCl_3$) 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), 2.40-252 (2H, m), 2.58 (3H, s), 3.03 (2H, q, J= 7 Hz), 4.05 (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), 736 (1H, s), 8.53 (1H, d, J= 5 Hz).
MS (ESI^+): m/z 386.

Example 177

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

[0640] ^1H NMR ($CDCl_3$) 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), 724 (1H, d, J= 5 Hz), 735 (1H, s), 8.53 (1H, d, J= 5 Hz).
MS (ESI^+): m/z 372.

Example 178

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

[0641] ^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 179

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

[0642] ^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).
MS (ESI^+): m/z 424.

Example 180

ethyl 5-[2-[(acetyloxy)methyl]-4-(3-cyanophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate

[0643] ^1H NMR ($CDCl_3$) 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), 7.60-7.68 (3H, m), 7.75-7.83 (1H, m).
MS (ESI^+): m/z 448.

Example 181

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

[0644] ^1H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 488 490.

Example 182

ethyl 3-[2-[(acetyloxy)methyl]-4-(5-bromo-3-pyridinyl)-7-ethylpyzrolo[1,2-b]pyridazin-3-yl]propanoate

[0645] ^1H NMR ($CDCl_3$) 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.

Example 183

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

[0646] ^{1}H NMR ($CDCl_3$) 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 184

ethyl 3-4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoate

[0647] ^{1}H NMR ($CDCl_3$) 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=2Hz).
MS (ESI^+): m/z 528 530.

Example 185

ethyl 4-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0648] ^{1}H NMR ($CDCl_3$) 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), 8.79 (1H, d, J= 2 Hz).
MS (ESI^+): m/z 542 544.

Example 186

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

[0649] ^{1}H NMR ($CDCl_3$) 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, s), 8.43 (1H, s), 8.54 (1H, s).
MS (ESI^+): m/z 436.

Example 187

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

[0650] ^{1}H NMR ($CDCl_3$) 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.

Example 188

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

[0651] ^{1}H NMR ($CDCl_3$) 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.

Example 189

ethyl 4-[2-[(acetyloxy)methyl]-4-(5-chloro-3-pyridinyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0652] ^{1}H NMR (300 MHz, $CDCl_3$) 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 190

ethyl 5-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoate

[0653] ^{1}H 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).

Example 191

ethyl 4-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0654] ^{1}H 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).

Example 192

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

[0655] ^{1}H 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).

Example 193

ethyl 3-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0656] ^{1}H 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 H), 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).

Example 194

ethyl 3-[2-[(acetyloxy)methyl]-4-(3-chlorophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0657] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Example 195

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0658] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Example 196

ethyl 4=[2-[(acetyloxy)methyl]-4-(3-chlorophenyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0659] ^{1}H NMR ($CDCl_3$) 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 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 $CDCl_3$), 7.36 (1H, br s), 7.38-7.46 (2H, m).
MS (ESI^+): m/z 443 (M + H).

Example 197

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

[0660] ^{1}H NMR ($CDCl_3$) 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), 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 198

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

[0661] ^{1}H NMR ($CDCl_3$) 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), 721 (1H, m), 8.21 (1H, d, J = 1 Hz), 8.40 (1H, d, J = 3 Hz).
MS (ESI^+): m/z 396 (M + H).

Example 199

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

[0662] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 398 (M + H).

Example 200

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

[0663] ^{1}H NMR ($CDCl_3$) 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, J=5Hz), 7.23 (1H, m), 8.22 (1H, d, J=1Hz), 8.40 (1H, d, J=3Hz).
MS (ESI^+): m/z 412 (M + H).

Example 201

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

[0664] ^{1}H NMR ($CDCl_3$) 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).

Example 202

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

[0665] ^{1}H NMR ($CDCl_3$) 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 203

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

[0666] ^{1}H 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).

Example 204

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

[0667] ^{1}H 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 205

ethyl 4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylate

[0668] ^{1}H 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).

[0669] The following compound(s) was(were) obtained in a similar manner to that of Example 41.

Example 206

[0670] 4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid ^{1}H 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 (EST): m/z 356, MS (ESI^+): m/z 358.

Example 207

3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0671] ^{1}H 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 208

4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0672] ^{1}H 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 209

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

[0673] ^{1}H 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 210

3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0674] ^{1}H 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), 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 211

3-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0675] ^{1}H 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 212

4-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0676] ^{1}H NMR ($CDCl_3$) 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.

Example 213

5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0677] ^{1}H NMR ($CDCl_3$) 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 214

5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0678] ^{1}H NMR ($CDCl_3$) 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 215

5-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0679] ^{1}H NMR ($CDCl_3$) 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.

Example 216

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl)butanoic acid

[0680] ^1H NMR ($CDCl_3$) 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).
MS (ESI^-): m/z 507 509, MS (ESI^+): m/z 509 511.

Example 217

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0681] ^1H NMR ($CDCl_3$) 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.

Example 218

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0682] ^1H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 509 511.

Example 219

4-{4-(5-bromo-3-pyridiny1)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0683] ^1H NMR ($CDCl_3$) 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.

Example 220

3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0684] ^1H NMR ($CDCl_3$) 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).
MS (ESI^-): m/z 493 495, MS (ESI^+): m/z 495 497.

Example 221

3-[2-[(cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0685] ^1H NMR ($CDCl_3$) 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, 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 222

3-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0686] ^{1}H NMR ($CDCl_3$) 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), 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 223

4-{4-(5-bromo-3-pyridinyl)-2-[(cyclohexylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0687] ^{1}H NMR ($CDCl_3$) 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 224

4-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0688] ^{1}H NMR ($CDCl_3$) δ 0.22-032 (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).
MS (ESI^+): m/z 408.

Example 225

3-[2-[(cyclopropylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0689] ^{1}H NMR ($CDCl_3$) δ 0.23-035 (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).
MS (ESI^-): m/z 392, MS (ESI^+): m/z 394.

Example 226

4-{4-(5-chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0690] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H,t, J = 7 Hz), 1.73 (2H, tt, J = 7, 7 Hz), 2.25 (2H, t, J = 7 Hz), 2.37-2.73 (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), 731 (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 227

4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0691] ^{1}H NMR (300 MHz, $CDCl_3$) 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 228

5-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0692] ^{1}H NMR (300 MHz, $CDCl_3$) 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 229

4-{4-(5-chloro-3-pyridinyl)-2-[(cyclopropylmethoxy)methyl]-7-ethylpyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0693] ^{1}H NMR (300 MHz, $CDCl_3$) 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 230

5-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0694] ^{1}H NMR (300 MHz, $CDCl_3$) 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 231

3-(4-(5-chloro-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid .

[0695] ^{1}H NMR (300 MHz, $CDCl_3$) 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 232

3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0696] ^{1}H NMR (300 MHz, $CDCl_3$) 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 233

4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0697] ^{1}H NMR (300 MHz, $CDCl_3$) 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 234

4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(isobutoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0698] ^{1}H 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 235

3-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0699] ^{1}H 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), 735 (1H, br s), 7.40-7.46 (2H, m). MS (ESI^+): m/z 373 (M + H).

Example 236

4-[4-(3-chlorophenyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0700] ^{1}H NMR ($CDCl_3$) 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, overlappled with $CDCl_3$), 7.36 (1H, br s), 7.39-7.46 (2H, m).
MS (ESI^+): m/z 387 (M + H).

Example 237

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

[0701] mp 111-112°C
^{1}H 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) .
MS (ESI^+): m/z 398 (M + H).

Example 238

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

[0702] mp 133-134°C
^{1}H 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 (1 H, d, J = 1 Hz), 8.39 (1H, d, J = 3 Hz).
MS (ESI^+): m/z 369 (M + H).

Example 239

3-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0703] mp 164-165°C
^{1}H 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).
MS (ESI^+): m/z 370 (M + H).

Example 240

4-[7-ethyl-2-(methoxymethyl)-4-(5-methoxy-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0704] mp 140-141°C
^{1}H 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).

Example 241

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

[0705] mp 112-113°C
^{1}H NMR ($CDCl_3$) 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 242

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

[0706] mp 159-160°C
^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 374,376 (M + H).

Example 243

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

[0707] mp 118-119°C
^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 8 Hz), 1.40-1.62 (7H, m), 2.24 (2H, t, J = 8 Hz), 2.45-2.64 (2H, m), 3.04 (2H, d, J = 8 Hz), 3.45 (3H, s), 4.63 (2H, s), 5.91 (1H, d, 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=2Hz).
MS (ESI^+): m/z 402, 404 (M + H).

Example 244

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

[0708] ^{1}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 (1 H, d, J= 4 Hz), 6.62 (1H, d, J= 4 Hz), 7.92 (1H, m), 857 (1H, d, J= 2 Hz), 8.78 (1H, d, J= 2 Hz).
MS (ESI^-): m/z 430 432, MS (ESI^+): m/z 432 434.
[0709] The following compound(s) was(were) obtained in a similar manner to that of Example 87.

Example 245

ethyl 4-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0710] ^{1}H NMR ($CDCl_3$) 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.

Example 246

ethyl 3-[4-(2-chloro-4-pyridinyl)-7-ethy]-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0711] ^{1}H NMR ($CDCl_3$) 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.

Example 247

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

[0712] ^{1}H-NMR ($CDCl_3$) 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).

Example 248

ethyl 3-[4-(3-cyanophenyl)-7-ethyl-2-phenylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0713] ^{1}H-NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 424 (M + H)

Example 249

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

[0714] ^{1}H-NMR ($CDCl_3$) 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

[0715] The following compound(s) was(were) obtained in a similar manner to that of Example 99.

Example 250

5-{4-(3-cyanophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0716] ^{1}H NMR ($CDCl_3$) 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, 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 251

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

[0717] ^{1}H NMR ($CDCl_3$) 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 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 252

5-{4-(3-cyanophenyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentanoic acid

[0718] ^{1}H NMR ($CDCl_3$) δ1.38 (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, 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 253

5-[4-(3-cyanophenyl)-7-ethyl-2-(2-thienyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0719] ^{1}H-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, m), 7.43 (1H, d, J = 5 Hz), 7.62 (2H, m), 7.70 (1H, s), 7.76 (1H, m).

Example 254

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

[0720] ^{1}H-NMR ($CDCl_3$) δ 1.36 (3H, t, J = 7 Hz), 1.99 (2H, m), 2.75 (2H, m), 3.00 (2H, q, J = 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 255

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

[0721] ^{1}H-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 (IH, m), 7.35-7.54 (8H, m).
MS (ESI^+): m/z 433 (M+H)

[0722] The following compound(s) was(were) obtained in a similar manner to that of Example 104.

Example 256

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

[0723] ^{1}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).

Example 257

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

[0724] ^{1}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).

[0725] The following compound(s) was(were) obtained in a similar manner to that of Example 113.

Example 258

[4-(3-chlorophenyl)-7-ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-3-yl]methanol

[0726] ^{1}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).

[0727] The following compound(s) was(were) obtained in a similar manner to that of Example 114.

Example 259 (comparative)

(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

[0728] ^{1}H-NMR ($CDCl_3$) 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), 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).

[0729] The following compound(s) was(were) obtained in a similar manner to that of Example 115.

Example 260

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

[0730] ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, J= 7 Hz), 1.39 (3H, t, J= 7 Hz), 233 (2H, t, J= 7 Hz), 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.

Example 261

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

[0731] ^{1}H NMR ($CDCl_3$) 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 (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 262

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

[0732] ^{1}H NMR ($CDCl_3$) 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.

Example 263

ethyl 4-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0733] ^{1}H NMR ($CDCl_3$) 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 264

ethyl 3-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0734] ^{1}H NMR ($CDCl_3$) 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).
MS (ESI^+): m/z 432 434.

Example 265

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0735] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, J = 7 Hz), 1.38 (3H, t, J = 7 Hz), 1.67 (2H, tt, 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).

Example 266

ethyl 3-[4-(3-chlorophenyl)-7-ethyl-2-(hydroxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0736] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, 1, 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).

[0737] The following compound(s) was(were) obtained in a similar manner to that of Example 119.

Example 267

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

[0738] ^{1}H-NMR ($CDCl_3$) δ 1.37 (3H, 1, J = 7 Hz), 2.29 (2H, m), 2.72-3.07 (6H, m), 3.33 (2H, 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)

[0739] The following compound(s) was(were) obtained in a similar manner to that of Example 133.

Example 268

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

[0740] ^{1}H NMR ($CDCl_3$) δ 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 (1 H, m), 8.48-8-55 (3H, m), 8.76 (1 H, s).
MS (ESI^+): m/z 460.

Example 269

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

[0741] ^{1}H NMR ($CDCl_3$) δ 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.

Example 270

ethyl 4-{7-ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0742] ^{1}H NMR ($CDCl_3$) δ 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.

Example 271

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

[0743] ^{1}H NMR ($CDCl_3$) 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.

Example 272

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

[0744] ^{1}H NMR ($CDCl_3$) 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.

Example 273

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

[0745] ^{1}H NMR ($CDCl_3$) 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 274

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

[0746] ^{1}H 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), 7.24-738 (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.

Example 275

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

[0747] ^{1}H 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), 855 (1H, d, J= 2 Hz), 8.74 (1H, m), 8.79 (1H, d, J= 2 Hz).
MS (ESI^+): m/z 552 554.

Example 276

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0748] ^{1}H 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.

Example 277

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(3-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0749] ^{1}H NMR ($CDCl_3$) 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 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 278

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0750] ^{1}H NMR ($CDCl_3$) 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 (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 279

ethyl 4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0751] ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, J= 7 Hz), 1.38 (3H, t, J= 7 Hz), 1.70-1.82 (2H, m), 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.

Example 280

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

[0752] ^1H NMR ($CDCl_3$) 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), 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 281

ethyl 4-{4-(5-chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoate

[0753] ^1H NMR (300 MHz, $CDCl_3$) 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 282

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

[0754] ^1H NMR ($CDCl_3$) 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, overlappled with $CDCl_3$), 7.36 (1H, br s), 7.38-7.46 (2H, m).

[0755] The following compound(s) was(were) obtained in a similar manner to that of Example 137.

Example 283

ethyl 5-(4-(5-bromo-3-pyridinyl)-7-ethyl-2-{[4-(2-hydroxyethyl)-1-piperazinyl]methyl}pyrrolo[1,2-b]pyridazin-3-yl)pentanoate

[0756] ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7 Hz), 136 (3H, t, J = 7 H_2), 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 284

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-thiomorpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0757] ^1H NMR (300 MHz, $CDCl_3$) 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 285

ethyl 4-[4-(5-chloro-3-pyridinyl)-7-ethyl-2-(4-moipholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate

[0758] ^1H NMR (300 MHz, $CDCl_3$) 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 286

Example 287

[0759] 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 (0576 mL) in BuOH (30 mL) was heated under reflux for 2 hours. After evaporation of solvent, the residue was partitioned between AcOEt and water. The organic layer was separated, washed with aq $NaHCO_3$ 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 - 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 yellow oil (450 mg).

tert-butyl {2-[4-(5-bromo-3-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]ethyl}carbamate

[0760] ^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).

Example 288

[0761] 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 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 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

[0762] ^1H NMR ($CDCl_3$) 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).

[0763] The following compound(s) was(were) obtained in a similar manner to that of Example 288.

Example 289

4-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-methoxyethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butanoic acid

[0764] ^1H NMR ($CDCl_3$) 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.

Example 290

3-{4-(5-bromo-3-pyridinyl)-7-ethyl-2-[(2-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0765] ^1H NMR ($CDCl_3$) 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 291

[0766] 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 $MgSO_4$, and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with a mixture of hexane and AcOEt (20:1 - 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-pyxidinyl)-3-(5-ethoxy-5-oxopentyl)-7-ethylpyrrolo[1,2-b]pyridazin-2-yl]methyl 4-morpholinecarboxylate

[0767] ^1H NMR ($CDCl_3$) 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.
[0768] The following compound(s) was(were) obtained in a similar manner to that of Example 291

Example 292

ethyl 3-[4-(5-bromo-3-pyridinyl)-2-({[(dimethylamino)carbonyl]oxy}methyl)-7-ethylpyrrolo[1,2-b]pyridazin-3-yl]propanoate

[0769] ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J= 7 Hz), 1.36 (3H, t, J= 7 Hz), 237 (2H, t, J= 7 Hz), 2.82-2.93 (2H, m), 2.97 (6H, s), 3.03 (2H, q, J= 7 Hz), 4.05 (2H, q, J= 7 Hz), 532 (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 293

[0770] 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. The mixture was extracted with $CHCl_3$. 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 $CHCl_3$-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.

3-{4-(3-chlorophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0771] ^1H NMR (300 MHz, $CDCl_3$) δ 139 (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), 6.62 (1H, d, J = 5 Hz), 7.23-7.26 (1H, m), 736-738 (3H, m), 7.42-7.44 (2H, m), 8.41 (2H, d, J = 5 Hz).
MS (m/z) 450 (M+H).
[0772] The following compound(s) was(were) obtained in a similar manner to that of Example 293.

Example 294

3-{4-(3-chlorophenyl)-7-ethyl-2-[(2-pyrazinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}propanoic acid

[0773] ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 7 Hz), 2.4 (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).

Example 295

[0774] 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 1N 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 an yellow gum (77.5 mg, 108%).

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

[0775] ^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 (1 H, m).
MS (ESI^+): m/z 482 (M + H)

[0776] The following compound(s) was(were) obtained in a similar manner to that of Preparation 16.

Preparation 216

ethyl 2-[(5-bromo-3-pyridinyl)carbonyl]-4-methoxy-3-oxobutanoate

[0777] ^1H NMR ($CDCl_3$) 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).

[0778] The following compound(s) was(were) obtained in a similar manner to that of Preparation 77.

Preparation 217

ethyl 4-methoxy-3-oxobutanoate

[0779] ^1H NMR ($CDCl_3$) 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).

[0780] The following compound(s) was(were) obtained in a similar manner to that of Example 11.

Example 296

ethyl 4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

[0781] ^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).

[0782] The following compound(s) was(were) obtained in a similar manner to that of Example 41.

Example 297

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

[0783] ^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).

[0784] The following compound(s) was(were) obtained in a similar manner to that of Example 80.

Example 298

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

[0785] ^1H NMR ($CDCl_3$) 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), 751 (1H, d, J = 15 Hz), 7.91 (1H, br s), 8.57 (1H, br s), 8.70 (1H, br s).
MS (ESI^+): m/z 444, 446 (M + H).

[0786] The following compound(s) was(were) obtained in a similar manner to that of Example 108.

Example 299

[4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxyrnethyl)pyrrolo[1,2-b]pyridazin-3-yl]methanol.

[0787] ^1H 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 376, 378 (M + H).

[0788] The following compound(s) was(were) obtained in a similar manner to that of Example 111.

Example 300

4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylic acid

[0789] ^{1}H NMR ($CDCl_3$) 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 301

4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carboxylic acid

[0790] ^{1}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).
[0791] The following compound(s) was(were) obtained in a similar manner to that of Example 125.

Example 302

4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo [1,2-b]pyridazine-3-carbaldehyde

[0792] ^{1}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 (1 H, 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 303

4-(5-bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde

[0793] ^{1}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 (1 H, d, J = 5 Hz), 7.95 (1H, br s), 8.12 (1H, brs), 8.84 (1H, brs), 9.85 (1H, s).
MS (ESI^+): m/z 374, 376 (M + H).

Example 304

[0794] 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 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 an yellow oil, which was crystalized upon standing (360 mg, 77.5%).
^{1}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), 7.45 - 7.51 (3H, m), 10.56 (1H ,s).
MS (ESI^+): m/z 355 (M + H)
[0795] The following compound(s) was(were) obtained in a similar manner to that of Preparation 16.

Preparation 218

ethyl 4-methoxy-2-[(5-methyl-3-pyridinyl)carbonyl]-3-oxobutanoate

[0796] ^{1}H NMR ($CDCl_3$) 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).

Preparation 219

ethyl 2-[(5-chloro-3-pyridinyl)carbonyl]-4-methoxy-3-oxobutanoate

[0797] ^{1}H NMR ($CDCl_3$) 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, 822, 8.29, 8.58-8.82, 8.85, 9.01, 9,10 (3H, m).

Preparation 220

[0798] 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 nitrogen atmosphere. The mixture was stirred for 0.5 hour in an ice bath. The mixture was cooled in a dry ice-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 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 hexane to give cyclopropylboronic acid as a white powder (789 mg).

cyclopropylboronic acid

[0799] ^{1}H-NMR (DMSO-d_6) δ -0.40 (1H. m), 0.32 (2H, m), 0.39 (2H, m), 7.28 (2N, s).

[0800] The following compound(s) was(were) obtained in a similar manner to that of Example 11.

Example 305

ethyl 7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

[0801] ^{1}H 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.

Example 306

ethyl 4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carboxylate

[0802] ^{1}H 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).

[0803] The following compound(s) was(were) obtained in a similar manner to that of Example 41.

Example 307

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

[0804] ^{1}H 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.

Example 308

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

[0805] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (3H, t, J = 7 Hz), 3.07 (2H, q, J = 7 Hz), 351 (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).

Example 309

4-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoic acid

[0806] 1H-NMR ($CDCl_3$) δ 0.78 (2H, m),1.10 (2H, m), 1.37 (3H, t, J = 7 Hz), 1.73 (2H, m), 1.98 (1H, m), 2.23 (2H, m), 2.62 (2H, m), 3.02 (2H, q, J = 7 Hz9, 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 310

5-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(metboxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentanoic acid

[0807] ^{1}H-NMR ($CDCl_3$) 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, do J = 5 Hz), 6.56 (1H, d, J = 5 Hz), 7.34 (1H, m), 8.39 (1H, m), 8.50 (1H, m).

Example 311

3-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propanoic acid

[0808] ^{1}H-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).

Example 312

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

[0809] ^{1}H NMR ($CDCl_3$) 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 313

(2E)-3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acrylic acid

[0810] ^{1}H NMR ($CDCl_3$) 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, overlappled with $CDCl_3$), 7.40 (1H, br s), 7.51 (1H, d, J = 15 Hz), 8.55 (1H, d, J = 5 Hz).

[0811] The following compound(s) was(were) obtained in a similar manner to that of Example 79.

Example 314

ethyl (2E)-3-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]acrylate

[0812] ^{1}H NMR ($CDCl_3$) 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, overlappled with $CDCl_3$), 7.40 (1H, br s), 7.53 (1H, d, J = 15 Hz), 8.53 (1H, d, J = 5 Hz).
MS (ESI^+): m/z 370 (M + H).

[0813] The following compound(s) was(were) obtained in a similar manner to that of Example 80.

Example 315

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

[0814] ^{1}H NMR (300 MHz, $CDCl_3$) 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).

[0815] The following compound(s) was(were) obtained in a similar manner to that of Preparation 96.

Example 316

4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazine-3-carbonyl chloride

[0816] The following compound(s) was(were) obtained in a similar manner to that of Example 244.

Example 307

7-ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde

[0817] ^{1}H 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.

Example 318

4-(5-chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazine-3-carbaldehyde

[0818] ^{1}H 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).

[0819] The following compound(s) was(were) obtained in a similar manner to that of Example 258.

Example 319

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

[0820] ^{1}H 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), 854 (1H, s), 8.60 (1H, s).
MS (ESI^+): m/z 312.

Example 320

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

[0821] ^{1}H 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).

Example 321

[0822] 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
^{1}H NMR ($CDCl_3$) δ 126 (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 322

[0823] 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]butanoateas an yellow gum (60.9 mg).
ethyl 4-[4-(5-cyclopropyl-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butanoate
^{1}H-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).

[0824] The following compound(s) was(were) obtained in a similar manner to that of Example 322.

Example 323

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

[0825] ^{1}H-NMR ($CDCl_3$) δ 0.76 (2H, m), 1.08 (2H, m), 1.23 (3H, 1, J = 7 Hz), 1.35-1.57 (7 m), 1.96 (1H, m), 2.16 (2H, t, J = 7 Hz), 2.53 (2H, m), 3.03 (2H, q, J = 7 Hz), 3.46 (3H, s), 4.08 (2H, q, J = 7 Hz), 4.62 (2H, s), 5.89 (1H, d, J = 5 Hz), 6.56 (J H d, J = 5 Hz), 7.29 (1H, m), 8.40 (1H, m), 8.52 (1H, m).

Example 324

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

[0826] ^{1}H-NMR ($CDCl_3$) 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).

Example 325

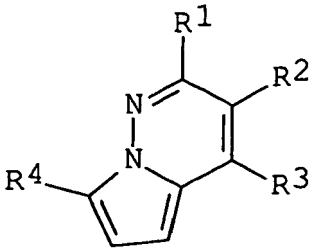
[0827] To a 3-necked flash containing Zn-Cu couple was added a solution of ethyl 4-iodobutanoate (369 mg) in toluene (3 mL) and N,N-dimethylacetarnide (0.2 mL), at ambient temperature under N_2. The mixture was stirred at the temperature for 1 h and then at 60°C for 3 h. A suspension of tetrakis(triphenylphosphine)palladium (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 temperature for 2 h. The reaction mixture was partitioned between AcOEt and H_2O. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, 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(7,2-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
^{1}H NMR ($CDCl_3$) δ 1.23(3H, t, j = 8 Hz), 1.38 (3H, t, J = 8Hz), 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, brs), 8.53 (1H, d, J = 5 Hz).

Example 326

[0828] 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 N_2. After 10 min, the mixture was Stirred at ambient temperature. After 1 h, another sodium borohydride (5 mg) was added. After 2 h, the reaction mixture was partitioned between $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$ twice. The combined organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by p-TLC ($CHCl_3$-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).
5-[4-(2-chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]-5-hydroxypentanoic acid
^{1}H NMR ($CDCl_3$) 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 $CDCl_3$), 7.34 (1H, d, J = 2 Hz), 8.49 (1H, d, J = 5 Hz).

Claims

1. A compound of the formula :



(I)

in which

R^1 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

R^2 is R^7 or $-A^2-R^7$, wherein
A^2 is $-(CH_2)_n-$ or $-(CH=CH)_m-$ [wherein n is integer which may range 2 to 6 and m is integer of 1 or 2], and
R^7 is hydrogen, lower alkyl sulfonyl, carboxy, esterified carboxy or pyridinyl,
R^3 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

R^4 is lower alkyl,

or a pharmaceutical acceptable salt thereof, or prodrug thereof.

2. A compound of claim 1, wherein

R^1 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,
R^2 is $-(CH_2)_n-R^7$, wherein n is integer which may range 2 to 5, and R^7 is carboxy or esterified carboxy, and
R^3 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-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.

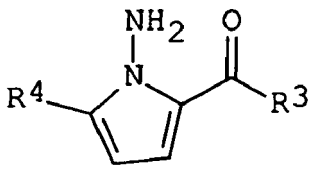
4. A compound of claim 1, which is

(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-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.

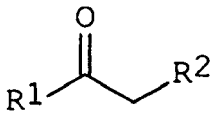
5. A process for preparing a compound of any of claims 1 to 4 comprising

(1) the reaction of a compound (II) of general formula

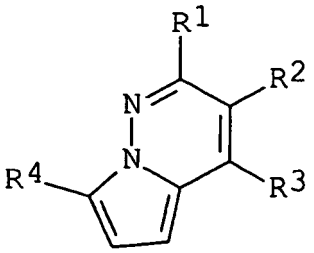


[wherein R^3 and R^4 are as defined in claim 1] or a salt thereof

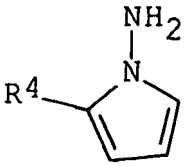
with a compound (III) of general formula



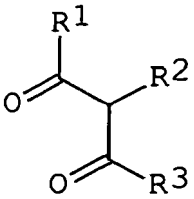
[wherein R^1 and R^2 are as defined in claim 1] or a salt thereof
to obtain a compound (I) of general formula



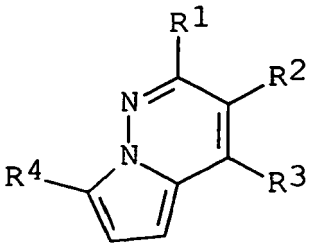
[wherein R^1, R^2, R^3 and R^4 are as defined in claim 1] or a salt thereof, or
(2) the reaction of a compound (V) of general formula



[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 of claims 1 to 4 in admixture with pharmaceutically acceptable carriers.

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.

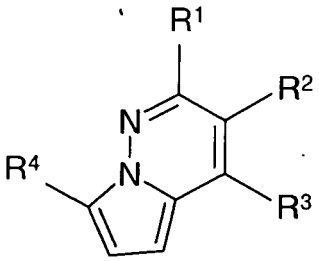
9. A pharmaceutical composition of claim 6, for prevention or treatment of asthma, chronic obstructive pulmonary disease (COPD), fibrotic disease, acute and fulminant hepatitis, hepatic steatosis (alcoholic or non-alcoholic steatohepatitis), chronic (viral or non-viral) hepatitis, hepatic cirrhosis, autoimmune hepatitis, autoimmune inflammatory bowel disease, atopic dermatitis, Alzheimer's diseases and viral infection.

10. Use of a compound of any 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.

11. Use of a compound of any of claims 1 to 4 for the manufacture of a medicament for the 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.

Patentansprüche

1. Verbindung der Formel



(I)

wobei

R^1

(1) Mono- oder Di(nieder)alkylamio,
(2) Phenyl,
(3) gesättigte oder ungesättigte 5- bis 6-gliedrige hetermonozyklische Gruppe, die ausgewählt wird aus der

aus Pyrrolidinyl, Pyrrolyl, Oxazolyl, Isooxazolyl, Thiazolyl, Furanyl, Thienyl und Pyridinyl bestehenden Gruppe oder
(4) Niederalkyl, gegebenenfalls substituiert durch (i) Niederalkoxy oder (ii) gesättigte 5- oder 6-gliedrige hetermonozyklische Gruppe, ausgewählt aus der aus Piperazinyl und Morpholinyl bestehenden Gruppe, wobei Niederalkoxy gegebenenfalls durch Cyclo(nieder)alkyl oder Pyridinyl substituiert ist,

ist,
R^2, R^7 oder $-A^2-R^7$ ist, wobei
A^2 $-(CH_2)_n-$ oder $-(CH=CH)_m-$ ist [wobei n eine ganze Zahl ist, die zwischen 2 und 6 liegt, und m eine ganze Zahl von 1 oder 2 ist], und
R^7 Wasserstoff, Niederalkylsulfonyl, Carboxy, verestertes Carboxy oder Pyridinyl ist,
R^3

(1) Phenyl ist, gegebenenfalls substituiert durch Niederalkyl, Cyclo(nieder)alkyl, Niederalkoxy, Halogen, Cyano oder Carbamoyl; oder
(2) Chinolinyl; oder Pyridinyl, substituiert durch Niederalkyl, Cyclo(nieder)alkyl, Niederalkoxy, Carbamoyl oder Halogen, und

R^4 Niederalkyl ist,
oder ein pharmazeutisch verträgliches Salz davon, oder ein Prodrug davon.

2. Verbindung nach Anspruch 1, wobei

R^1 Phenyl, Pyrrolyl, Isooxazolyl, Furanyl, Thienyl, Niederalkyl, gegebenenfalls substituiert durch Niederalkoxy, Piperazinyl oder Morpholinyl ist, wobei Niederalkoxy gegebenenfalls durch Cyclo(nieder)alkyl oder Pyrrolidinyl substituiert ist;
R^2 $-(CH_2)_n-R^7$ ist, wobei n eine ganze Zahl ist, die zwischen 2 und 5 liegt und R^7 Carboxy oder verestertes Carboxy ist, und
R^3 (1) Phenyl, gegebenenfalls substituiert durch Niederalkyl, Cyclo(nieder)alkyl, Niederalkoxy, Halogen, Cyano oder Carbamoyl ist; oder (2) Pyridinyl, substituiert durch Niederalkyl, Cyclo(nieder)alkyl, Niederalkoxy, Carbamoyl oder Halogen.

3. Verbindung nach Anspruch 1, welche

(1) 3-[7-Ethyl-2-methyl-3-(4-pyridinyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitril,
(2) 3-[7-Ethyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitril
(3) 4-[7-Ethyl-2-methyl-3-(methylsulfonyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitril,
(4) 3-[7-Ethyl-2-(2-furyl)pyrrolo[1 ,2-b]pyridazin-4-yl]benzamid,
(5) 5-[4-(3-cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentansäureethylester,
(6) 2-{[4-(3-Chlorophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]methyl}-1 ,3-propandiol,
(7) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propansäure,
(8) 5-[7-Ethyl-2-methyl-4-(6-chinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(9) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1 ,2-b]pyridazin-3-yl]pentansäure,
(10) 5-[7-Ethyl-2-(methoxymetyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(11) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymehtyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(12) 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propansäure,
(13) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(14) (2E)-3-[7-Chloro-4-(4-fluorophenyl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]2-propensäureethylester,
(15) 6-{4-[4-(Aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexansäure,
(16) 3-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]propansäure,
(17) 4-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butansäure,
(18) 5-[2-[(Cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(19) 5-{7-Ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentansäure,
(20) 4-{4-(5-Chloro-3-pyridinyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}butansäure,
(21) 4-[4-(5-Chloro-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]butansäure,
(22) 4-[4-(5-Chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butansäure,

(23) 5-[4-(5-Chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1 ,2-b]pyridazin-3-yl]pentansäure oder
(24) 5-{4-(3-Cyanophenyl)-7-ethyl-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentansäure,

oder ein pharmazeutisch verträgliches Salz davon ist.

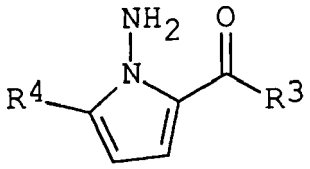
4. Verbindung nach Anspruch 1, welche

(1) 5-[4-(3-Cyanophenyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentansäureethylester,
(2) 3-[4-(3-Chlorophenyl)-7-ethyl-2-phenyl-pyrrolo[1,2-b]pyridazin-3-yl]propansäure,
(3) 5-[4-(2-Chloro-4-pyridinyl)-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(4) 5-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(5) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(6) 3-[7-Ethyl-2-(methoxymethyl)-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]propansäure,
(7) 5-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(4-morpholinylmethyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(8) 6-{4-[4-(Aminocarbonyl)phenyl]-7-ethyl-2-methylpyrrolo[1,2-b]pyridazin-3-yl}hexansäure,
(9) 3-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-]propansäure,
(10) 4-[4-(5-Bromo-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butansäure,
(11) 5-[2-[(Cyclohexylmethoxy)methyl]-7-ethyl-4-(5-methyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,
(12) 5-7{Ethyl-4-(5-methyl-3-pyridinyl)-2-[(4-pyridinylmethoxy)methyl]pyrrolo[1,2-b]pyridazin-3-yl}pentansäure,
(13) 4-[4-(5-Chloro-3-pyridinyl)-7-ethyl-2-(methoxymethyl)pyrrolo[1,2-b]pyridazin-3-yl]butansäure oder
(14) 5-[4-(5-Chloro-3-pyridinyl)-7-ethyl-2-(methoxymehyl)pyrrolo[1,2-b]pyridazin-3-yl]pentansäure,

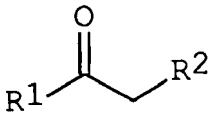
oder ein pharmazeutisch verträgliches Salz davon ist.

5. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 4, umfassend

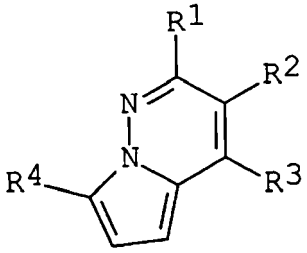
(1) die Reaktion einer Verbindung (II) der allgemeinen Formel



[wobei R^3 und R^4 wie in Anspruch 1 definiert sind] oder eines Salzes davon mit einer Verbindung (III) der allgemeinen Formel



[wobei R^1 und R^2 wie in Anspruch 1 definiert sind] oder einem Salz davon
zur Herstellung einer Verbindung (I) der allgemeinen Formel



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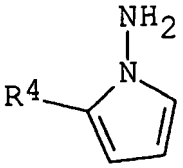
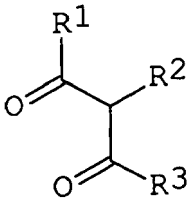
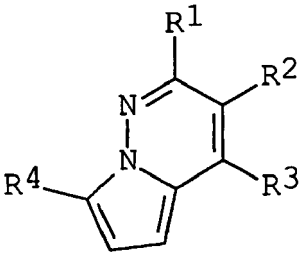
[wobei R^1, R^2, R^3 und R^4 wie in Anspruch 1 definiert sind] oder eines Salzes davon, oder
(2) die Reaktion einer Verbindung (V) der allgemeinen Formel



[wobei R^4 wie in Anspruch 1 definiert ist] oder eines Salzes davon mit einer Verbindung (VI) der allgemeinen Formel



[wobei R^1, R^2 und R^3 wie in Anspruch 1 definiert sind] oder einem Salz davon
zur Herstellung eines Verbindung (I) der allgemeinen Formel



[wobei R^1, R^2, R^3 und R^4 wie in Anspruch 1 definiert sind] oder eines Salzes davon.

6. Pharmazeutische Zusammensetzung, welche als aktiven Bestandteil eine Verbindung nach einem der Ansprüche 1 bis 4 im Gemisch mit pharmazeutisch verträglichen Trägern umfasst.

7. Pharmazeutische Zusammensetzung nach Anspruch 6 zur Inhibierung von Phosphodiesterase IV (PDE-IV)-En-

zymaktivität und/oder Inhibierung der Bildung von Tumornekrosefaktor (TNF).

8. Pharmazeutische Zusammensetzung nach 6 zur Vorbeugung oder Behandlung von Erkrankungen, für die Therapie durch einen PDE-IV-Inhibitor oder TNF-Bildungs-Inhibitor relevant ist.

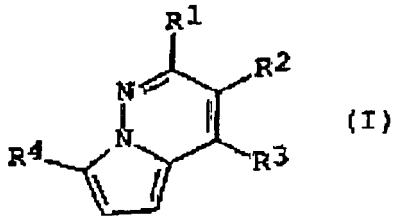
9. Pharmazeutische Zusammensetzung nach Anspruch 6 zur Vorbeugung oder Behandlung von Asthma, chronisch obstruktiver Lungenerkrankung (COPD), fibrotischer Erkrankung, akuter und fulminanter Hepatitis, hepatischer Steatose (alkoholische oder nicht-alkoholische Steatohepatitis), chronischer (viraler oder nicht-viraler) Hepatitis, hepatischer Zirrhose, Autoimmunhepatitis, entzündlicher Autoimmun-Darmerkrankung, atopischer Dermatitis, Alzheimer-Krankheit und Virusinfektion.

10. Verwendung einer Verbindung nach den Ansprüchen 1 bis 4 zur Herstellung eines Medikaments zur Vorbeugung oder Behandlung von Erkrankungen, für die Therapie durch einen PDE-IV-Inhibitor der TNF-Synthese-Inhibitor relevant ist.

11. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 zur Herstellung eines Medikaments zur Vorbeugung oder Behandlung von Asthma, chronisch obstruktiver Lungenerkrankung (COPD), fibrotischer Erkrankung, akuter und fulminanter Hepatitis, hepatischer Steatose (alkoholische oder nicht-alkoholische Steatohepatitis), chronischer (viraler oder nicht-viraler) Hepatitis, hepatischer Zirrhose, Autoimmunhepatitis, entzündlicher Autoimmun-Darmerkrankung, atopischer Dermatitis, Alzheimer-Krankheit und Virusinfektion.

Revendications

1. Composé de formule :



(I)

dans laquelle

R^1 est

(1) un mono- ou dialkylamino(inférieur),
(2) un phényle,
(3) un groupe hétéromonocyclique à 5 ou 6 membres saturé ou non saturé choisi parmi le groupe constitué de pyrrolidinyle, pyrrolyle, oxazolyle, isooxazolyle, thiazolyle, furanyle, thiényle et pyridinyle, ou
(4) un alkyle inférieur éventuellement substitué par (i) un alcoxy inférieur ou (ii) un groupe hétéromonocyclique à 5 ou 6 membres saturé choisi parmi le groupe constitué de pipérazinyle et morpholinyle, où l'alcoxy inférieur est éventuellement substitué par un cycloalkyl(inférieur) ou un pyridinyl,

R^2 est R^7 ou $-A^2-R^7$, où
A^2 est $-(CH_2)_n-$ ou $-(CH=CH)_m-$ [où n est un entier compris entre 2 et 6 et m est un entier égal à 1 ou 2], et
R^7 est un hydrogène, un alkyle sulfonyle inférieur, un carboxy, un carboxy estérifié ou un pyridinyle,
R^3 est

(1) un phényle éventuellement substitué par un alkyle inférieur, un cycloalkyle (inférieur), un alcoxy inférieur, un halogène, un cyano ou un carbamoyle ; ou
(2) un quinolinyle ; ou un pyridinyle substitué par un alkyle inférieur, un cycloalkyle (inférieur), un alcoxy inférieur, un carbamoyle ou un halogène, et

R^4 est un alkyle inférieur,

ou un sel pharmaceutiquement acceptable de celui-ci ou une prodrogue de celui-ci.

2. Composé selon la revendication 1, dans lequel

R^1 est un phényle, un pyrrolyle, un isooxazolyle, un furanyle, un thiényle, un alkyle inférieur éventuellement substitué par un alcoxy inférieur, un piperazinyle ou un morpholinyle, où l'alcoxy inférieur est éventuellement substitué par un cycloalkyle (inférieur) ou un pyridinyle,
R^2 est $-(CH_2)_n-R^7$, où n est un entier compris entre 2 et 5, et R^7 est un carboxy ou un carboxy estérifié, et
R^3 est (1) un phényle éventuellement substitué par un alkyle inférieur, un cycloalkyle (inférieur), un alcoxy inférieur, un halogène, un cyano ou un carbamoyle ; ou (2) un pyridinyl substitué par un alkyle inférieur, un cycloalkyle (inférieur), un alcoxy inférieur, un carbamoyle ou un halogène.

3. Composé selon la revendication 1, qui est

(1) 3-[7-éthyl-2-méthyl-3-(4-pyridinyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
(2) 3-[7-éthyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
(3) 4-[7-éthyl-2-méthyl-3-(méthylsulfonyl)-pyrrolo[1,2-b]pyridazin-4-yl]benzonitrile,
(4) 3-[7-éthyl-2-(2-furyl)pyrrolo[1,2-b]pyridazin-4-yl]benzamide,
(5) éthyl 5-[4-(3-cyanophényl)-7-éthyl-2-méthylpyrrolo[1,2,b]pyridazin-3-yl]pentanoate,
(6) 2-{[4-(3-chlorophényl)-7-éthyl-2-méthylpyrrolo[1,2-b]pyridazin-3-yl]méthyl}-1,3-propanediol,
(7) 3-[4-(3-chlorophényl)-7-éthyl-2-phényl-pyrrolo[1,2-b]pyridazin-3-yl] acide propanoïque,
(8) 5-[7-éthyl-2-méthyl-4-(6-quinolinyl)pyrrolo[1,2-b]pyridazin-3-yl]acide pentanoïque,
(9) 5-[4-(2-chloro-4-pyridinyl)-7-éthyl-2-méthylpyrrolo[1,2-b]pyridazin-3-yl]acide pentanoïque,
(10) 5-[7-éthyl-2-(méthoxyméthyl)-4-(5-méthyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl]acide pentanoïque,
(11) 5-[4-(5-bromo-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(12) 3-[7-éthyl-2-(méthoxyméthyl)-4-(5-méthyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl] acide propanoïque,
(13) 5- [4- (5-bromo-3-pyridinyl)-7-éthyl-2- (4-morpholinylméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(14) éthyl (2E)-3-[7-chloro-4-(4-fluorophényl)-2-isopropylpyrrolo[1,2-b]pyridazin-3-yl]-2-propanoate,
(15) 6-{4-[4-(aminocarbonyl)phényl]-7-éthyl-2-méthylpyrrolo[1,2-b]pyridazin-3-yl} acide hexanoïque,
(16) 3-[4-(5-bromo-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide propanoïque,
(17) 4-[4-(5-bromo-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide butanoïque,
(18) 5-[2-[(cyclahexylméthoxy)méthyl]-7-éthyl-9-(5-méthyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(19) 5-{7-éthyl-4-(5-méthyl-3-pyridinyl)-2-[(4-pyridinylméthoxy)méthyl]pyrrolo[1,2-b]pyridazin-3-yl} acide pentanoïque,
(20) 4-{4-(5-chloro-3-pyridinyl)-7-éthyl-2-[(4-pyridinylméthoxy)méthyl]pyrrolo[1,2-b]pyridazin-3-yl)acide butanoïque,
(21) 4-[4-(5-chloro-3-pyridinyl)-7-éthyl-2-(4-morpholinylméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide butanoïque,
(22) 4-[4-(5-chloro-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide butanoïque,
(23) 5-[4-(5-chloro-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque, ou
(24) 5-{4-(3-cyanophényl)-7-éthyl-2-[(4-pyridinylméthoxy)méthyl]pyrrolo[1,2-b]pyridazin-3-yl} acide pentanoïque,

ou un sel pharmaceutiquement acceptable de ceux-ci.

4. Composé selon la revendication 1, qui est

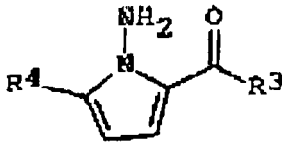
(1) éthyl 5-[4-(3-cyanophényl)-7-éthyl-2-méthylpyrrolo[1,2-b]pyridazin-3-yl]pentanoate,
(2) 3-[4-(3-chlorophényl)-7-éthyl-2-phényl-pyrrolo[1,2-b]pyridazin-3-yl] acide propanoïque,
(3) 5-[4-(2-chloro-4-pyridinyl)-7-éthyl-2-méthylpyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(4) 5-[7-éthyl-2-(méthoxyméthyl)-4,(5-méthyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(5) 5-[4-(5-bromo-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(6) 3-[7-éthyl-2-(méthoxyméthyl)-4-(5-méthyl-3-pyridinyl)pyrrolo[1,2-b] pyridazin-3-yl] acide propanoïque,
(7) 5-[4-(5-Bromo-3-pyridinyl)-7-éthyl-2-(4-morpholinylméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(8) 6-{4-[4-(aminocarbonyl)phényl]-7-éthyl-2-méthylpyrrolo[1,2-b]pyridazin-3-yl} acide hexanoïque,

(9) 3-[4-(5-bromo-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide propanoïque,
(10) 4-[4-(5-bromo-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide butanoïque,
(11) 5-[2-[(cyclohexylméthoxy)méthyl]-7-éthyl-4-(5-méthyl-3-pyridinyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,
(12) 5-{7-éthyl-4-(5-méthyl-3-pyridinyl)-2-[(4-pyridinylméthoxylméthoxy)méthyl]pyrrolo[1,2-b]pyridazin-3-yl} acide pentanoïque,
(13) 4-[4-(5-chloro-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide butanoïque, ou
(14) 5-[4-(5-chloro-3-pyridinyl)-7-éthyl-2-(méthoxyméthyl)pyrrolo[1,2-b]pyridazin-3-yl] acide pentanoïque,

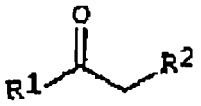
ou un sel pharmaceutiquement acceptable de ceux-ci.

5. Procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 4, comprenant

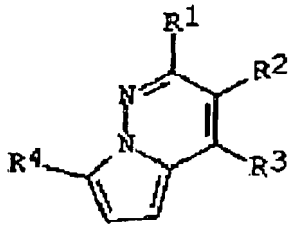
(1) la réaction d'un composé (II) de formule générale



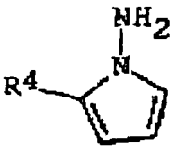
[dans laquelle R^3 et R^4 sont tels que définis dans la revendication 1] ou un sel de celui-ci avec un composé (III) de formule générale



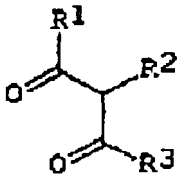
[dans laquelle R^1 et R^2 sont tels que définis dans la revendication 1] ou un sel de celui-ci pour obtenir un composé (I) de formule générale



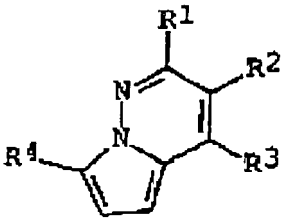
[dans laquelle R^1, R^2, R^3 et R^4 sont tels que définis dans la revendication 1] ou un sel de celui-ci, ou
(2) la réaction d'un composé (V) de formule générale



[dans laquelle R^4 est tel que défini dans la revendication 1] ou un sel de celui-ci,
avec un composé (VI) de formule générale



[dans laquelle R^1, R^2 et R^3 sont tels que définis dans la revendication 1] ou un sel de celui-ci,
pour obtenir un composé (I) de formule générale



[dans laquelle R^1, R^2, R^3 et R^4 sont tels que définis dans la revendication 1] ou un sel de celui-ci.

6. Composition pharmaceutique comprenant, en ingrédient actif, un composé selon l'une quelconque des revendications 1 à 4 dans un adjuvant avec des excipients pharmaceutiquement acceptables.

7. composition pharmaceutique selon la revendication 6, destinée à inhiber l'activité enzymatique de la phosphodiestérase IV (PDE-IV) et/ou inhiber la production du facteur de nécrose tumorale (TNF).

8. Composition pharmaceutique selon la revendication 6, destinée à la prévention ou au traitement de maladies pour lesquelles le traitement par un inhibiteur de PDE-IV ou un inhibiteur de la production de TNF est adapté.

9. Composition pharmaceutique selon la revendication 6, destinée à la prévention ou au traitement de l'asthme, la broncho-pneumopathie chronique obstructive (BPCO), la maladie fibrotique, l'hépatite aiguë et fuminante, la stéatose hépatique (stéatohépatite alcoolique ou non-alcoolique), l'hépatite chronique (virale ou non virale), la cirrhose hépatique, l'hépatite auto-immune, la maladie intestinale inflammatoire auto-immune, la dermatite atopique, la maladie d'Alzheimer et l'infection virale.

10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4 dans la fabrication d'un médicament destiné à la prévention ou au traitement des maladies pour lesquelles un traitement par un inhibiteur de PDE-IV ou un inhibiteur de la synthèse de TNF est adapté.

11. Utilisation d'un composé selon l'une quelconque des revendications 1 à 4 dans la fabrication d'un médicament destiné à la prévention ou au traitement de l'asthme, la broncho-pneumopathie chronique obstructive (BPCO), la maladie fibrotique, l'hépatite aiguë et fulminante, la stéatose hépatique (stéatohépatite alcoolique ou non-alcoolique), l'hépatite chronique (virale ou non virale), la cirrhose hépatique, l'hépatite auto-immune, la maladie intestinale inflammatoire auto-immune, la dermatite atopique, la maladie d'Alzheimer et l'infection virale.

REFERENCES CITED IN THE DESCRIPTION

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