



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/495 // (C07D 471/04, 241:00, 221:00)	A1	(11) International Publication Number: WO 96/01825 (43) International Publication Date: 25 January 1996 (25.01.96)
(21) International Application Number: PCT/JP95/01366 (22) International Filing Date: 10 July 1995 (10.07.95) (30) Priority Data: 9413975.5 11 July 1994 (11.07.94) GB (71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP). (71) Applicant (for US only): HEMMI, Mitsue (heirress of the deceased inventor) [JP/JP]; 668-37, Shimohirooka, Tsukuba-shi, Ibaraki 305 (JP). (72) Inventor: HEMMI, Keiji (deceased). (72) Inventors; and (75) Inventors/Applicants (for US only): SHIMAZAKI, Norihiko [JP/JP]; 1157-20, Nagakuni, Tsuchiura-shi, Ibaraki 300 (JP). WATANABE, Shinya [JP/JP]; 4-13-1, Ninomiya, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Akihiko [JP/JP]; 1-602-208, Azuma, Tsukuba-shi, Ibaraki 305 (JP).		(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP). (81) Designated States: AU, BR, CA, CN, FI, HU, JP, KR, MX, NO, NZ, RU, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: HETEROBICYCLIC DERIVATIVES (57) Abstract Heterobicyclic derivatives of formula (I) wherein R¹ is aryl which may have suitable substituent(s), ar(lower)alkyl which may have suitable substituent(s), halo(lower)alkyl, protected carboxy(lower)alkyl, acyl(lower)alkyl, heterocyclic group or heterocyclic(lower)alkyl which may have suitable substituent(s), R² is aryl which may have suitable substituent(s) or heterocyclic group, and R³ is hydrogen, lower alkoxy or arylthio, and a pharmaceutically acceptable salt thereof which are useful as PDE IV and TNF inhibitors. (I)		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

D E S C R I P T I O N
HETEROBICYCLIC DERIVATIVES

TECHNICAL FIELD

5 This invention relates to new heterobicyclic derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

10 Some heterobicyclic derivatives have been known as described, for example, in EP 0 008 864 A2.

DISCLOSURE OF INVENTION

15 This invention relates to new heterobicyclic derivatives.

 One object of this invention is to provide the new and useful pyridopyrazine derivatives and pharmaceutically acceptable salts thereof which possess a strong phosphodiesterase IV (PDE IV)-inhibitory activity and a
20 strong inhibitory activity on the production of tumor necrosis factor (TNF).

 Another object of this invention is to provide processes for preparation of the pyridopyrazine derivatives and salts thereof.

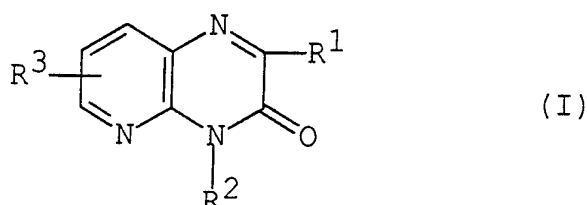
25 A further object of this invention is to provide a pharmaceutical composition comprising said pyridopyrazine derivatives or a pharmaceutically acceptable salt thereof.

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

35

- 2 -

The object pyridopyrazine derivatives of the present invention are novel and can be represented by the following general formula (I) :



10

wherein R¹ is aryl which may have suitable substituent(s), ar(lower)alkyl which may have suitable substituent(s), halo(lower)alkyl, protected carboxy(lower)alkyl, acyl(lower)alkyl, heterocyclic group or heterocyclic(lower)alkyl which may have suitable substituent(s),

15

R² is aryl which may have suitable substituent(s) or heterocyclic group, and

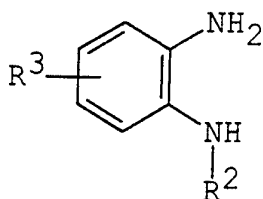
20

R³ is hydrogen, lower alkoxy or arylthio.

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

25

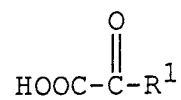
Process (1)



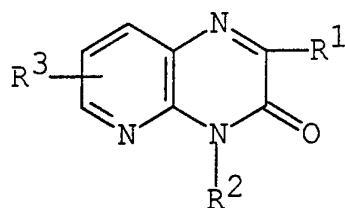
(II)
or a salt thereof

35

- 3 -

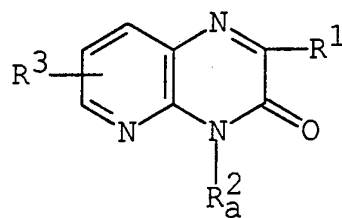


(III)
or a salt thereof



(I)
or a salt thereof

Process (2)

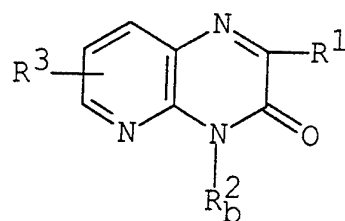


(Ia)

or its reactive derivative
at the amino group, or a salt thereof

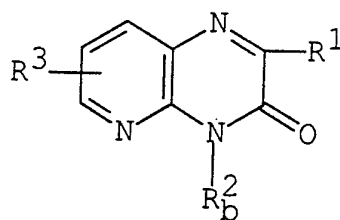
- 4 -

acylation



(Ib)

or a salt thereof

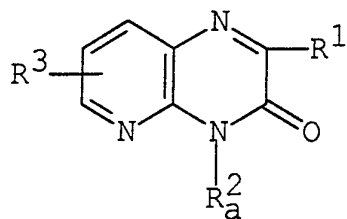
Process (3)

(Ib)

or a salt thereof

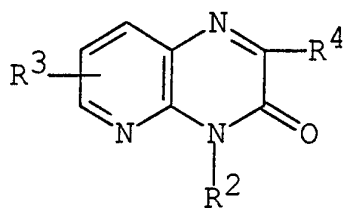
deacylation

- 5 -



(Ia)
or a salt thereof

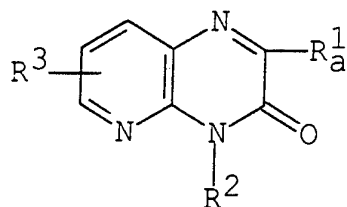
Process (4)



(XI)
or a salt thereof

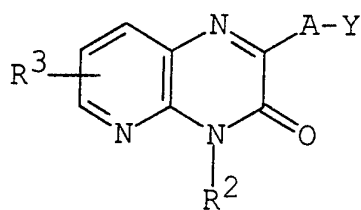
halogenation

- 6 -



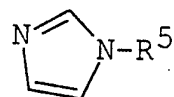
(Ic)
or a salt thereof

Process (5)



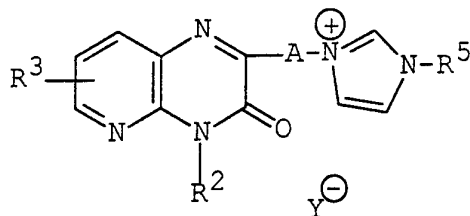
(Id)
or a salt thereof

①



(VIII)
or a salt thereof

- 7 -



(IX)
or a salt thereof

10

15

20

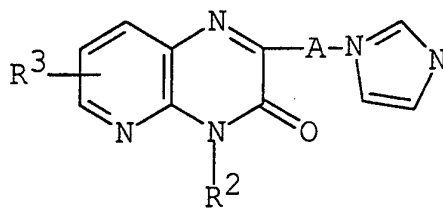
25

30

35

②

elimination of
N-protective group



(Ie)
or a salt thereof

- 8 -

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

R_a^1 is halo(lower)alkyl,

R_a^2 is aryl having amino or aryl having aminoaryl,

R_b^2 is aryl having acylamino or aryl having

5 acylaminoaryl,

R^4 is lower alkyl,

R^5 is N-protective group,

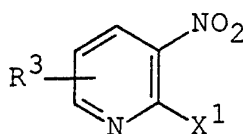
Y is halogen,

$Y^\ominus$ is halide, and

10 A is lower alkylene.

The starting compound (II) of the present invention can be prepared by the following processes.

15 Process (A)

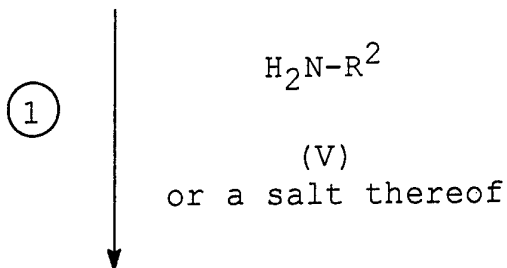


20

(IV)

or a salt thereof

25

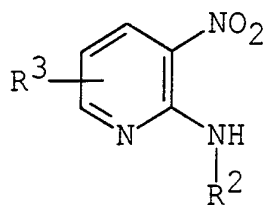


30

(V)
or a salt thereof

35

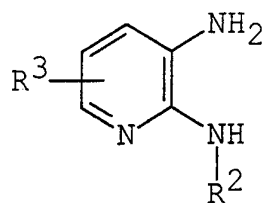
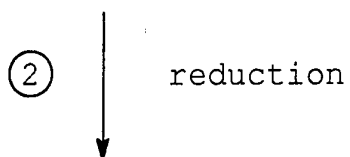
- 9 -



(VI)

or a salt thereof

10



(II)

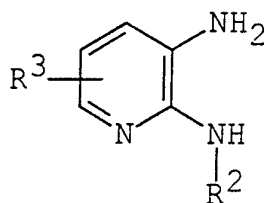
or a salt thereof

25

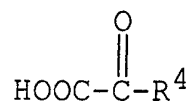
30

35

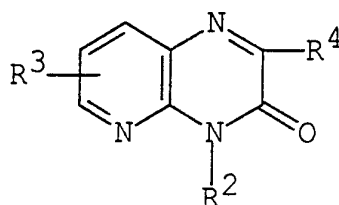
- 10 -

Process (B)

(II)
or a salt thereof

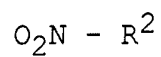


(X)
or a salt thereof



(XI)
or a salt thereof

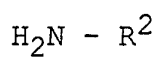
- 11 -

Process (C)

(XII)

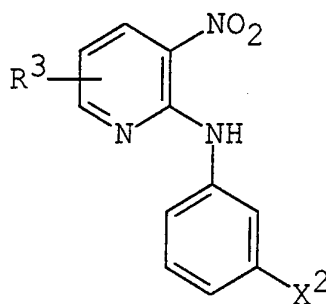
or a salt thereof

reduction



(V)

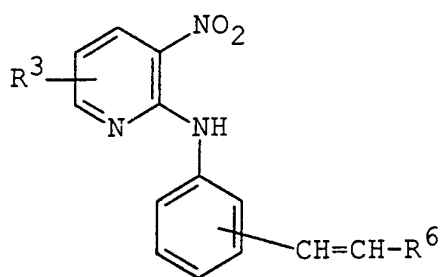
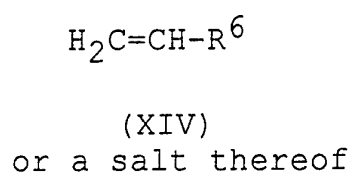
or a salt thereof

Process (D)

(XIII)

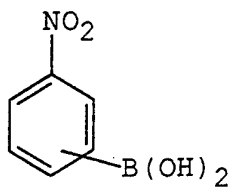
or a salt thereof

- 12 -



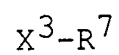
(VIa)
or a salt thereof

Process (E)



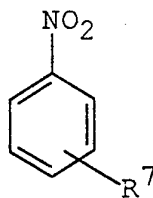
(XV)
or a salt thereof

- 13 -



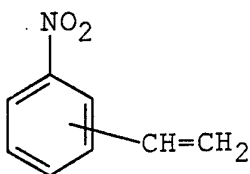
(XVI)

or a salt thereof



(XIIa)

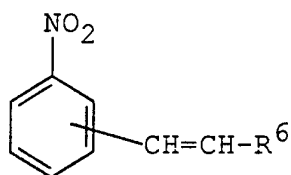
or a salt thereof

Process (F)

(XVII)

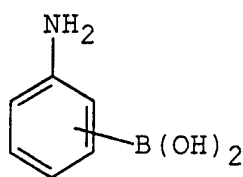
- 14 -

X^4-R^6
(XVIII)
or a salt thereof



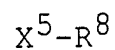
(XIIb)
or a salt thereof

Process (G)



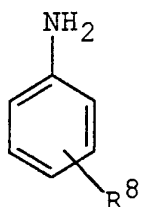
(XIX)
or a salt thereof

- 15 -



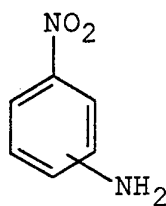
(XX)

or a salt thereof



(Va)

or a salt thereof

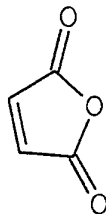
Process (H)

(XIIf)

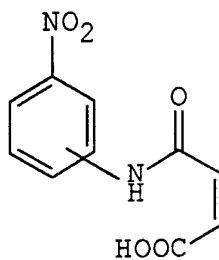
or a salt thereof

- 16 -

①



(XXI)



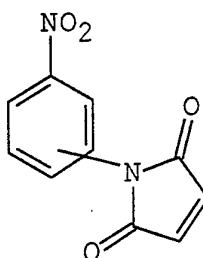
(XXII)

or a salt thereof

②

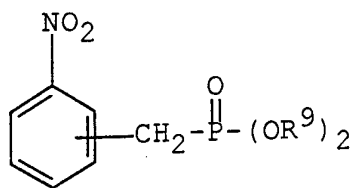
dehydration

- 17 -

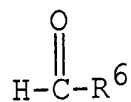


(XXIII)
or a salt thereof

Process (I)



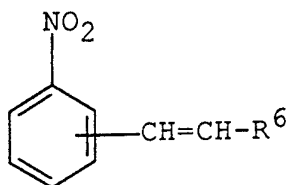
(XXIV)
or a salt thereof



(XXV)
or a salt thereof



- 18 -



(XIIb)
or a salt thereof

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

R^6 is heterocyclic group which may have 1 to 3
halogen,

R^7 is aryl,

R^8 is aryl having acylamino,

R^9 is lower alkyl, and

X^1 , X^2 , X^3 , X^4 and X^5 are each a leaving group.

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'-dibenzylethylenediamine salt, etc.);
an inorganic acid addition salt (e.g., hydrochloride,
hydrobromide, sulfate, phosphate, etc.);
an organic carboxylic or sulfonic acid addition salt
(e.g., formate, acetate, trifluoroacetate, maleate,
tartrate, fumarate, methanesulfonate, benzenesulfonate,

- 19 -

toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

5 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.

10

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

15 The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "ar(lower)alkyl", halo(lower)alkyl, "protected carboxy(lower)alkyl", "acyl(lower)alkyl", "heterocyclic(lower)alkyl" and "heterocyclicoxycarbonyl-(lower)alkyl" may include straight or branched one having 20 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 C₁-C₄ alkyl.

25 Suitable "lower alkenyl" may include vinyl, 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, methylvinyl, ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, 30 in which more preferable example may be C₂-C₄ alkenyl.

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

- 20 -

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

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

10 Suitable "cyclo(lower)alkyl" may include cyclopentyl, cyclohexyl and the like.

Suitable "cyclo(lower)alkenyl" may include cyclohexenyl, cyclohexadienyl and the like.

15 Suitable "aryl" and "aryl moiety" in the terms "ar(lower)alkyl", "arylthio", "aminoaryl" and "acylaminoaryl" may include phenyl, naphthyl and the like.

Suitable "halogen" and "halogen moiety" in the term "halo(lower)alkyl" may include fluorine, bromine, chlorine and iodine.

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

Suitable "acid residue" may include halogen as exemplified above, acyloxy and the like.

25 Suitable "halide" may include fluoride, bromide, chloride and the like.

30 Suitable "protected carboxy" and "protected carboxy moiety" in the term "protected carboxy(lower)alkyl" may include esterified carboxy and the like. 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.,

35

- 21 -

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-mesyloethyl ester, etc.); lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, t-butoxycarbonyloxymethyl ester, 1-(or 2)-methoxycarbonyloxyethyl ester, 1-(or 2)-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)alkyl(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,

- 22 -

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
5 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;
10 lower alkylthioester (e.g. methylthioester, ethylthioester, etc.) and the like.

Suitable "hydroxy protective group" in the term "protected hydroxy" may include acyl, mono(or di or tri)phenyl(lower)alkyl which may have one or more suitable
15 substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.), trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, t-butyl dimethylsilyl, etc.), etc.], tetrahydropyranyl and the like.

Suitable "N-protective group" may include acyl or a
20 conventional protecting group such as mono (or di or tri)aryl(lower)alkyl, for example, mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, trityl, etc.) or the like.

Suitable "protected amino" may include acylamino or
25 an amino group substituted by a conventional protecting group such as mono (or di or tri)aryl(lower)alkyl, for example, mono(or di or tri)phenyl(lower)alkyl (e.g., benzyl, trityl, etc.) or the like.

Suitable "acyl" and "acyl moiety" in the terms
30 "acylamino", "acyloxy" and "acyl(lower)alkyl" may include carbamoyl, thiocarbamoyl, 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.

- 23 -

Suitable example of said acyl may be illustrated as follows :

Carbamoyl; Thiocarbamoyl;

Aliphatic acyl such as lower or higher alkanoyl (e.g.,

5 formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl,
10 etc.);

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 or higher alkoxycarbonyl (e.g., methoxycarbonyl, 15 ethoxycarbonyl, isopropoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, 20 ethoxysulfonyl, etc.);

lower alkadienoyl (e.g., heptadienoyl, hexadienoyl, etc.);

cyclo(lower)alkylcarbonyl (e.g., cyclopropylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.);

cyclo(lower)alkylidene(lower)alkanoyl (e.g., 25 cycloheptylideneacetyl, cycloheptylidenepropanoyl, cyclohexylideneacetyl, cyclohexylidenepropanoyl, etc.);

cyclo(lower)alkyloxycarbonyl (e.g., cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, etc.);

lower alkylglyoxyloyl (e.g., methylglyoxyloyl, 30 ethylglyoxyloyl, propylglyoxyloyl, etc.);

lower alkoxyglyoxyloyl (e.g., methoxyglyoxyloyl, ethoxyglyoxyloyl, propoxyglyoxyloyl, etc.);

or the like;

Aromatic acyl such as

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

- 24 -

- 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.];
- 5 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.];
- 10 ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), etc.]; aryloxycarbonyl (e.g., phenoxy carbonyl, naphthyloxycarbonyl, etc.);
- 15 aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.); arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.);
- 20 arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); ar(lower)alkylsulfonyl [e.g., phenyl(lower)alkylsulfonyl (e.g., benzylsulfonyl, phenylethylsulfonyl, etc.), naphthyl(lower)alkylsulfonyl (e.g., naphthylmethylsulfonyl, naphthylethylsulfonyl, etc.), etc.]; or the like;
- 25 Heterocyclic acyl such as heterocycliccarbonyl; heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);
- 30 heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.); heterocyclicglyoxyloyl; heterocyclicoxycarbonyl; or the like;
- 35 in which suitable "heterocyclic moiety" in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl",

- 25 -

heterocyclic(lower)alkenoyl", heterocyclicoxycarbonyl and "heterocyclicglyoxyloyl" as mentioned above means, in more detail, saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom
5 such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4
10 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, 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.,
15 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

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.;

20 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,
25 benzopyrimidinyl (e.g., benzo[b]pyrimidinyl, etc.), etc.;

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.),
30 etc.;

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,
35 morpholinyl, syndnonyl, etc.;

- 26 -

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

5 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.;

10 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.;

15 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiynyl, dihydrodithionyl, etc.;

20 unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

 unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

25 unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s), for example, benzodioxolyl (e.g. methylenedioxyphenyl, etc.), benzofuryl, etc.;

 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.;

30 unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl (e.g., benzo[b]thienyl, etc.), benzodithiynyl, etc.;

 unsaturated condensed heterocyclic group containing

35

- 27 -

an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s) such as lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkylthio wherein lower alkyl moiety is as exemplified above, cyclo(lower)alkyl as exemplified above, cyclo(lower)alkenyl as exemplified above, cyclo(lower)alkyloxy wherein cyclo(lower)alkyl moiety is as exemplified above, halogen as exemplified above, amino, protected amino as exemplified above, hydroxy, protected hydroxy as exemplified above, cyano, nitro, carboxy, protected carboxy as exemplified above, sulfo, sulfamoyl, imino, oxo, amino(lower)alkyl wherein lower alkyl moiety is as exemplified above, carbamoyloxy, mono(or di or tri)-halo(lower)alkyl wherein halogen moiety and lower alkyl moiety are each as exemplified above, hydroxy(lower)alkyl wherein lower alkyl moiety is as exemplified above, heterocyclic group as exemplified above, heterocyclicoxy wherein heterocyclic moiety is as exemplified above, heterocyclicamino which may have nitro wherein heterocyclic moiety is as exemplified above, aryl which may have suitable substituent(s) wherein aryl moiety is as exemplified above, arylsulfonyl wherein aryl moiety is as exemplified above, ar(lower)alkyl wherein aryl moiety and lower alkyl moiety are each as exemplified above, protected carboxy(lower)alkenyl wherein protected carboxy moiety and lower alkenyl moiety are each as exemplified above, acyl as exemplified above, acylamino wherein acyl moiety is as exemplified above, or the like.

Suitable "heterocyclic group" and "heterocyclic moiety" in the terms "heterocyclic(lower)alkyl" and "heterocyclicoxycarbonyl(lower)alkyl" can be referred to the ones as mentioned above.

- 28 -

Suitable "substituent" in the term "ar(lower)alkyl which may have suitable substituent(s)" may include lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkenyl as exemplified above, lower alkynyl as exemplified above, mono(or di or tri)halo(lower)alkyl wherein halogen moiety and lower alkyl moiety are each as exemplified above, cyclo(lower)alkyl as exemplified above, cyclo(lower)alkenyl as exemplified above, halogen as exemplified above, carboxy, protected carboxy as exemplified above, hydroxy, protected hydroxy as exemplified above, aryl as exemplified above, ar(lower)alkyl wherein aryl moiety and lower alkyl moiety are each as exemplified above, carboxy(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected carboxy(lower)alkyl wherein protected carboxy moiety and lower alkyl moiety are each as exemplified above, nitro, amino, protected amino as exemplified above, di(lower)alkylamino wherein lower alkyl moiety is as exemplified above, amino(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected amino(lower)alkyl wherein protected amino moiety and lower alkyl moiety are each as exemplified above, hydroxy(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected hydroxy(lower)alkyl wherein protected hydroxy moiety and lower alkyl moiety are each as exemplified above, acyl as exemplified above, cyano, sulfo, sulfamoyl, carbamoyloxy, mercapto, lower alkylthio wherein lower alkyl moiety is as exemplified above, imino, and the like.

Suitable "substituent" in the term "aryl which may have suitable substituent(s)" may include lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkenyl as exemplified above, lower alkynyl as exemplified above, mono(or di or tri)halo(lower)alkyl wherein halogen moiety and lower alkyl moiety are each as

- 29 -

exemplified above, cyclo(lower)alkyl as exemplified above, cyclo(lower)alkenyl as exemplified above, halogen as exemplified above, cyclo(lower)alkyloxy wherein cyclo(lower)alkyl moiety is as exemplified above, carboxy, 5 protected carboxy as exemplified above, hydroxy, protected hydroxy as exemplified above, aryl as exemplified above, ar(lower)alkyl wherein aryl moiety and lower alkyl moiety are each as exemplified above, carboxy(lower)alkyl wherein lower alkyl moiety as exemplified above, protected 10 carboxy(lower)alkyl wherein protected carboxy moiety and lower alkyl moiety are each as exemplified above, nitro, amino, protected amino as exemplified above, acylamino wherein acyl moiety is as exemplified above, di(lower)alkylamino wherein lower alkyl moiety is as 15 exemplified above, amino(lower)alkyl wherein lower alkyl moiety is as exemplified above, protected amino(lower)alkyl wherein protected amino moiety and lower alkyl moiety are each as exemplified above, hydroxy(lower)alkyl wherein lower alkyl moiety is as 20 exemplified above, protected hydroxy(lower)alkyl wherein protected hydroxy moiety and lower alkyl moiety are each as exemplified above, acyl as exemplified above, cyano, sulfo, sulfamoyl, carbamoyloxy, mercapto, lower alkylthio wherein lower alkyl moiety is as exemplified above, lower 25 alkylamino wherein lower alkyl moiety is as exemplified above, N-acyl-N-lower alkylamino wherein acyl moiety and lower alkyl moiety are each as exemplified above, acyl(lower)alkyl wherein acyl moiety and lower alkyl moiety are each as exemplified above, ar(lower)alkenyl 30 which may have 1 to 3 halogen wherein aryl moiety, lower alkenyl moiety and halogen moiety are each as exemplified above, acyl(lower)alkenyl wherein acyl moiety, and lower alkenyl moiety are each as exemplified above, protected carboxy(lower)alkenyl wherein protected carboxy moiety and 35 lower alkenyl moiety are each as exemplified above,

- 30 -

cyano(lower)alkenyl wherein lower alkenyl moiety is as exemplified above, heterocyclicoxy which may have 1 to 3 aryl wherein heterocyclic moiety and aryl moiety are each as exemplified above, imino, [heterocyclicamino which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and aryl] wherein heterocyclic moiety, lower alkyl moiety and aryl moiety are each as exemplified above;

[aryl which may have 1 to 3 substituent(s) selected from the group consisting of carboxy(lower)alkenyl, protected carboxy(lower)alkenyl, aryl, lower alkoxy, cyclo(lower)alkyloxy, halogen, carboxy, protected carboxy, amino, acylamino, diacylamino and acyl] wherein aryl moiety, lower alkenyl moiety, protected carboxy moiety, lower alkoxy moiety, cyclo(lower)alkyl moiety, halogen moiety and acyl moiety are each as exemplified above; heterocyclic(lower)alkenyl which may have 1 to 3 halogen wherein heterocyclic moiety, lower alkenyl moiety and halogen moiety are each as exemplified above;

[heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of halogen, cyano, carboxy, protected carboxy, oxo, acyl, amino, protected amino and heterocyclic group] wherein heterocyclic moiety, halogen moiety, protected carboxy moiety, acyl moiety and protected amino moiety are each as exemplified above; and the like.

Suitable "substituent" in the term "heterocyclic(lower)alkyl which may have suitable substituent(s)" may include lower alkyl as exemplified above, lower alkoxy as exemplified above, lower alkenyl as exemplified above, lower alkynyl as exemplified above, mono(or di or tri)halo(lower)alkyl wherein halogen moiety and lower alkyl moiety are each as exemplified above, cyclo(lower)alkyl as exemplified above, cyclo(lower)alkenyl as exemplified above, halogen as

- 31 -

exemplified above, carboxy, protected carboxy as
exemplified above, hydroxy, protected hydroxy as
exemplified above, aryl as exemplified above,
ar(lower)alkyl wherein aryl moiety and lower alkyl moiety
5 are each as exemplified above, carboxy(lower)alkyl wherein
lower alkyl moiety as exemplified above, protected
carboxy(lower)alkyl wherein protected carboxy moiety and
lower alkyl moiety are each as exemplified above, nitro,
amino, protected amino as exemplified above,
10 di(lower)alkylamino wherein lower alkyl moiety is as
exemplified above, amino(lower)alkyl wherein lower alkyl
moiety is as exemplified above, protected
amino(lower)alkyl wherein protected amino moiety and lower
alkyl moiety are each as exemplified above,
15 hydroxy(lower)alkyl wherein lower alkyl moiety is as
exemplified above, protected hydroxy(lower)alkyl wherein
protected hydroxy moiety and lower alkyl moiety are each
as exemplified above, acyl as exemplified above, cyano,
sulfo, sulfamoyl, carbamoyloxy, mercapto, lower alkylthio
20 wherein lower alkyl moiety is as exemplified above, imino,
and the like.

The processes for preparing the object and the
starting compounds are explained in detail in the
25 following.

Process (1)

The compound (I) or a salt thereof can be prepared by
reacting the compound (II) or a salt thereof with the
30 compound (III) or a salt thereof.

This reaction is usually carried out in a solvent
such as water, alcohol (e.g., methanol, ethanol, etc.),
benzene, N,N-dimethylformamide, tetrahydrofuran, toluene,
methylene chloride, ethylene dichloride, chloroform,
35 diethyl ether or any other solvent which does not

- 32 -

adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

5 Process (2)

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or its reactive derivative at the amino group or a salt thereof to acylation reaction.

10 Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula :



15 (wherein R^{10} is acyl)

or its reactive derivative or a salt thereof.

20 Suitable reactive derivative at the amino group of the compound (Ia) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (Ia) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (Ia) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like;

25 a derivative formed by the reaction of the compound (Ia) with phosphorus trichloride or phosgene, and the like.

30 Suitable reactive derivative of the compound (VII) may include an acid halide, an acid anhydride, an activated ester, isocyanate, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfuric

35

- 33 -

acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl $[(CH_3)_2N^+=CH-]$ ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); substituted or unsubstituted aryl isocyanate; substituted or unsubstituted aryl isothiocyanate, and the like. These reactive derivatives can optionally be selected from them accordingly to the kind of the compound (VII) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (VII) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing

- 34 -

agent such as N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-
5 dimethylaminopropyl)carbodiimide; N,N-carbonyl-bis(2-
methylimidazole); pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine; ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl
polyphosphate; phosphorous oxychloride (phosphoryl
10 chloride); phosphorous trichloride; thionyl chloride;
oxalyl chloride; triphenylphosphite;
2-ethyl-7-hydroxybenzisoazolium salt;
2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-
molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-
15 1H-benzotriazole; so-called Vilsmeier reagent prepared by
the reaction of N,N-dimethylformamide with thionyl
chloride, phosgene, phosphorous oxychloride, etc.; or the
like.

The reaction may also be carried out in the presence
20 of an organic or inorganic base such as an alkali metal
bicarbonate, tri(lower)alkylamine, pyridine,
N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine,
or the like.

The reaction temperature is not critical, and the
25 reaction is usually carried out under cooling to heating.

Process (3)

The compound (Ia) or a salt thereof can be prepared
by subjecting the compound (Ib) or a salt thereof to
30 deacylation reaction.

Suitable method of this deacylation reaction may
include conventional one such as hydrolysis, reduction and
the like.

35 (i) For Hydrolysis :

- 35 -

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g., sodium, potassium, etc.], an alkaline earth metal [e.g., magnesium, calcium, etc.], the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine [e.g., trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], and an inorganic acid [e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g., trichloroacetic acid, trifluoroacetic acid, etc.], or the like is preferably carried out in the presence of cation trapping agents [e.g., anisole, phenol, etc.].

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl, alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing reagent to be used in chemical reduction are hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride,

- 36 -

sodium cyanoborohydride, etc.), or a combination of a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic acid or an inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g., platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, Ullman iron, etc.), and the like.

The reduction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

35 Process (4)

- 37 -

The compound (Ic) or a salt thereof can be prepared by subjecting the compound (XI) or a salt thereof to halogenation reaction.

This halogenation is usually carried out by using a conventional halogenating agent such as halogen (e.g., chlorine, bromine, etc.), phosphorus trihalide (e.g., phosphorus tribromide, phosphorus trichloride, etc.), phosphorus pentahalide (e.g., phosphorus pentachloride, phosphorus pentabromide, etc.), phosphorus oxychloride (e.g., phosphoryl trichloride, phosphoryl monochloride, etc.), thionyl halide (e.g., thionyl chloride, thionyl bromide, etc.), oxalyl halide (e.g., oxalyl chloride, oxalyl bromide, etc.), N-halosuccinimide (e.g. N-bromosuccinimide, N-chlorosuccinimide, etc.) and the like.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), benzene, dioxane, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

25 Process (5)-(1)

The compound (IX) or a salt thereof can be prepared by reacting the compound (Id) or a salt thereof with the compound (VIII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

35 The reaction temperature is not critical and the

- 38 -

reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g. zinc chloride, zinc bromide, etc.), etc.] and the like.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process (5) - (2)

The compound (Ie) or a salt thereof can be prepared by subjecting the compound (IX) or a salt thereof to elimination reaction of N-protective group.

This reaction can be carried out in a similar manner to that of the aforementioned Process (3), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to

- 39 -

those of the Process (3).

Process (A) - (1)

5 The compound (VI) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

10 This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating.

15 When the starting compound is in liquid, it can be also used as a solvent.

Process (A) - (2)

20 The compound (II) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

25 Suitable reducing reagent to be used in chemical reduction are hydrides (e.g., hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.) or a combination of a metal (e.g., tin, zinc, iron, etc.) or metallic compound (e.g., chromium chloride, chromium acetate, etc.) and an organic
30 acid or an inorganic acid (e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g.,
35 platinum plate, spongy platinum, platinum black, colloidal

- 40 -

platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g., reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g., reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g., reduced iron, Raney iron, etc.), copper catalysts (e.g., reduced copper, Raney copper, Ullman copper, etc.) and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g., methanol, ethanol, propanol, etc.), tetrahydrofuran, dioxane, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (B)

The compound (XI) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (X) or a salt thereof.

This reaction can be carried out in a similar manner to that of the aforementioned Process (1), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (1).

Process (C)

The compound (V) or a salt thereof can be prepared by subjecting the compound (XII) or a salt thereof to reduction reaction.

This reaction can be carried out in a similar manner to that of the aforementioned Process (A) - (2), and therefore the reagents to be used and the reaction

- 41 -

conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (A) - (2).

5 The present invention includes, within the scope of the invention, the case that a maleimidophenyl group is transformed into a succinimidophenyl group during the reaction.

Process (D)

10 The compound (VIa) or a salt thereof can be prepared by reacting the compound (XIII) or a salt thereof with the compound (XIV) or a salt thereof.

The reaction can be carried out in the manner disclosed in Preparation 51 or similar manners thereto.

15

Process (E)

The compound (XIIa) or a salt thereof can be prepared by reacting the compound (XV) or a salt thereof with the compound (XVI) or a salt thereof.

20 The reaction can be carried out in the manner disclosed in Preparation 41 or similar manners thereto.

Process (F)

25 The compound (XIIb) or a salt thereof can be prepared by reacting the compound (XVII) with the compound (XVIII) or a salt thereof.

The reaction can be carried out in the manner disclosed in Preparation 38 or similar manners thereto.

30 Process (G)

The compound (Va) or a salt thereof can be prepared by reacting the compound (XIX) or a salt thereof with the compound (XX) or a salt thereof.

35 The reaction can be carried out in the manner disclosed in Preparation 4, 61, 62 or 63, or similar

- 42 -

manners thereto.

Process (H) - ①

5 The compound (XXII) or a salt thereof can be prepared by reacting the compound (XIIf) or a salt thereof with the compound (XXI).

The reaction can be carried out in the manner disclosed in Preparation 77 or similar manners thereto.

10 Process (H) - ②

The compound (XXIII) or a salt thereof can be prepared by subjecting the compound (XXII) or a salt thereof to dehydration reaction.

15 The reaction can be carried out in the manner disclosed in Preparation 78 or similar manners thereto.

Process (I)

20 The compound (XIIf) or a salt thereof can be prepared by reacting the compound (XXIV) or a salt thereof with the compound (XXV) or a salt thereof.

The reaction can be carried out in the manner disclosed in Preparation 42 or similar manners thereto.

25 Suitable salts of the object and the starting compounds in Processes (1)-(5) and (A)-(I) can be referred to the ones as exemplified for the compound (I).

30 The new pyridopyrazine 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).

35 That is, the pyridopyrazine 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).

- 43 -

Accordingly, the new pyridopyrazine 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, etc.), osteoporosis, rejection by transplantation, asthma, eosinophilia, cystic fibrosis, hepatitis, pancreatitis, nephritis, endotoxin shock, specific autoimmune diseases [e.g., ankylosing spondylitis, autoimmune hematological disorders (e.g., hemolytic anaemia, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenia, etc.), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, atopic dermatitis, psoriasis, 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.], cancer cachexia, AIDS cachexia, thrombosis, and the like.

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

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

1. Test method :

Harvested U937 was freezed in -80°C and throwed to

- 44 -

destroy the cell body. The pellet of destroyed cell was washed by Phosphate-buffered saline (PBS).

The washed cell pellet was homogenized with Dounce homogenizer (20 strokes) in homogenizing buffer (0.5 % deoxycholate [DOC], 5 mM 2-mercaptoethanol, 1 μ M leupeptin, 100 μ M PMSF, 20 μ M p-tosyl-L-lysine-chloromethyl ketone [TLCK] in PBS). The homogenate was centrifuged at 100,000 g x 90 minutes (4°C) and the supernatant containing PDE IV activity was dialyzed against dialysis buffer, which was the same component as homogenizing buffer without DOC. The dialyzed supernatant of homogenate was stored in freezer (-80°C) as PDE IV enzyme preparation.

Enzyme preparation was diluted in assay buffer (10 mM Tris-HCl, 5 mM MgCl, 1 mM 2-Mercaptoethanol [pH 8.0]). In advance the rate of dilution was chosen every new lot of homogenizing preparation. For blank, a part of the enzyme preparation was boiled for 10 minutes.

Test compounds were dissolved in dimethylsulfoxide (DMSO) at a concentration of 4×10^{-2} [M] (final conc. 1×10^{-5} M), then serial dilutions were made in DMSO to achieve desired concentrations. The diluted compounds of each concentration were further diluted 1:500 in assay buffer (0.2% DMSO). Final DMSO concentration in assay tube was 0.025%.

In duplicate, the followings were added to a glass tube, in order, at 0°C (all concentrations are given as final concentrations in assay tube).

50 μ l compound or assay buffer for control or blank
50 μ l 8×10^{-5} [M] CI-930 (final 10 μ M) : (CI-930 is PDE III inhibitor)
200 μ l enzyme preparation or boiled enzyme preparation for blank.

35

- 45 -

The reaction tube was preincubated in a water bath (30°C) for 5 minutes, then 100 µl [³H]-cAMP (37.0 MBq/ml [³H]-cAMP : 4 µM cold cAMP = 1:800) was added thereto. After 15 minutes, 2.5 units/ml alkaline phosphatase was added to the reaction mixture and the reaction was continued for 15 minutes. Dowex 1 x 8 gel was added to the reaction mixture and was vortexed well. The mixture was centrifuged at 1000 rpm x 5 minutes, and then 500 µl of the supernatant was added to 10 ml scintillation fluid in appropriate vial, vortexed, and counted for [³H].

The inhibitory activity was calculated according to the following equation :

$$\% \text{ Inhibition} = 100 - \frac{\text{avg.cpm}[\text{test compound}] - \text{avg.cpm}[\text{blank(boiled enzyme)}]}{\text{avg.cpm}[\text{control(no compound)}] - \text{avg.cpm}[\text{blank(boiled enzyme)}]} \times 100$$

2. Test compound :

(a) 4-[3-[3-(1-Naphthyl)ureido]phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

3. Test result :

Test compound	IC ₅₀ (M)
(a)	3.1 x 10 ⁻⁸

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

1. Test method :

- 46 -

Blood was drawn from healthy volunteers with heparin. The mononuclear cell (MNC) fraction was obtained by gradient centrifugation (1800 rpm, 15 minutes), diluted with the same volume of RPMI-1640 culture medium, over
5 Ficoll-Paque (Pharmacia LKB Biotechnology). MNC were washed twice with RPMI-1640. Then, MNC were resuspended in RPMI-1640 culture medium supplemented with 2 mM L-glutamine and 1% fetal bovine serum. MNC were incubated at 37°C for 16 hours in 96-well micro culture plate at a
10 concentration of 3×10^{-5} cells/well with or without 1 µg/ml lipopolysaccharide (LPS) (from E. coli) and various amounts of test compound. At the end of incubation, the supernatant was obtained and its TNF-α active was measured by enzyme-linked immunosorbent assay (ELISA). ELISA was
15 performed with TNF-α ELISA kit (Otsuka Pharmaceutical Co., Ltd.).

2. Test compound :

20 (a) 4-[3-[3-(1-Naphthyl)ureido]phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

3. Test result :

25

Test compound	IC ₅₀ (M)
(a)	5.6×10^{-8}

For therapeutic administration, the object compounds
30 (I) of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is
35 suitable for oral, parenteral or external administration.

- 47 -

The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution, suspension or emulsion for injection, ingestion, eye drops, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered with a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

Preferred embodiments of the object compound (I) are as follows.

R^1 is phenyl which may have 1 to 3 (more preferably one or two; most preferably one) suitable substituent(s) (more preferably nitro); phenyl(lower)alkyl which may have 1 to 3 (more preferably one or two; most preferably one) suitable substituent(s) [more preferably substituent selected from the group consisting of nitro, amino, protected amino (more preferably acylamino), hydroxy and protected hydroxy (more preferably acyloxy; most preferably lower alkanoyloxy)]; halo(lower)alkyl; protected carboxy(lower)alkyl (more preferably esterified carboxy(lower)alkyl; most preferably lower alkoxycarbonyl(lower)alkyl); carbamoyl(lower)alkyl which may have one or two suitable substituent(s) [more preferably substituent selected from the group consisting of lower alkyl and heterocyclic group (more preferably pyrrolidinyl)];

- 48 -

heterocyclicoxycarbonyl(lower)alkyl (more preferably pyrrolidinylloxycarbonyl(lower)alkyl) which may have 1 to 3 (more preferably one or two) suitable substituent(s) (more preferably oxo);

5 heterocycliccarbonyl(lower)alkyl (more preferably pyrrolidinylcarbonyl(lower)alkyl or piperazinylcarbonyl(lower)alkyl) which may have 1 to 3 (more preferably one or two; most preferably one) substituent(s) selected from the group consisting of

10 protected carboxy (more preferably esterified carboxy; most preferably lower alkoxy carbonyl) and lower alkyl; indolyl; or indolyl(lower)alkyl, pyridyl(lower)alkyl, imidazolyl(lower)alkyl, morpholinyl(lower)alkyl or triazolyl(lower)alkyl,

15 each of which may have 1 to 3 (more preferably one or two; most preferably one) suitable substituent(s) [more preferably substituent selected from the group consisting of lower alkyl, N-oxide and aryl (more preferably phenyl)];

20 R^2 is phenyl or naphthyl, each of which may have 1 to 3 (more preferably one or two) suitable substituent(s) (more preferably substituent selected from the group consisting of lower alkyl; halogen; mono(or di or tri)halo(lower)alkyl (more preferably

25 trihalo(lower)alkyl); hydroxy; protected hydroxy (more preferably acyloxy; most preferably lower alkanoyloxy); carboxy; protected carboxy (more preferably esterified carboxy; most preferably lower alkoxy carbonyl or phenyl(lower)alkoxy carbonyl);

30 carboxy(lower)alkyl; protected carboxy(lower)alkyl (more preferably esterified carboxy(lower)alkyl; most preferably lower alkoxy carbonyl(lower)alkyl); lower alkoxy; cyano; nitro; amino; acylamino [more preferably lower alkanoylamino; aryloxycarbonylamino

35 (more preferably phenyl(lower)alkoxy carbonylamino);

- 49 -

lower alkoxycarbonylamino; lower alkoxyglyoxyloyl;
cyclo(lower)alkylcarbonylamino;
cyclo(lower)alkyloxycarbonylamino;
cyclo(lower)alkylidene(lower)alkanoylamino;
5 aroylamino (more preferably benzoylamino or
naphthoylamino) which may have 1 to 3 (more
preferably one or two) substituent(s) selected from
the group consisting of lower alkyl, halogen, lower
alkoxy, carboxy, protected carboxy (more preferably
10 esterified carboxy; most preferably lower
alkoxycarbonyl), nitro, hydroxy, protected hydroxy
(more preferably acyloxy; most preferably lower
alkanoyloxy), mono(or di or tri)halo(lower)alkyl
(more preferably trihalo(lower)alkyl),
15 cyclo(lower)alkyloxy, aryl (more preferably phenyl),
carboxy(lower)alkenyl, protected
carboxy(lower)alkenyl (more preferably esterified
carboxy(lower)alkenyl; most preferably lower
alkoxycarbonyl(lower)alkenyl), amino, protected amino
20 (more preferably aroylamino; most preferably
benzoylamino), heterocyclicoxy (more preferably
pyrimidinyloxy), and heterocyclicamino (more
preferably pyridylamino) which may have nitro;
arylsulfonylamino (more preferably
25 phenylsulfonylamino) which may have one or two
halogen; ar(lower)alkylsulfonylamino (more preferably
phenyl(lower)alkylsulfonylamino);
cyclo(lower)alkylcarbonylamino;
[mono(or di)ar(lower)alkanoyl]amino (more preferably
30 [mono(or di)phenyl(lower)alkanoyl]amino or
[naphthyl(lower)alkanoyl]amino);
lower alkadienoylamino; heterocycliccarbonylamino
(more preferably furylcarbonylamino,
pyridylcarbonylamino, thienylcarbonylamino,
35 indolylcarbonylamino, indolinylcarbonylamino,

- 50 -

quinolylcarbonylamino,
tetrahydroquinolylcarbonylamino,
benzofurylcarbonylamino, benzothienylcarbonylamino,
methylenedioxybenzoylamino or
5 morpholinylcarbonylamino) which may have 1 to 3 (more preferably one or two) substituent(s) selected from the group consisting of lower alkyl and halogen; ar(lower)alkenoylamino (more preferably phenyl(lower)alkenoylamino) which may have 1 to 3
10 (more preferably one or two; most preferably one) substituent(s) selected from the group consisting of lower alkyl, halogen, carboxy, protected carboxy (more preferably esterified carboxy; most preferably lower alkoxycarbonyl) and nitro;
15 heterocyclic(lower)alkenoylamino (more preferably pyridyl(lower)alkenoylamino); carbamoylamino which may have one or two substituent(s) selected from the group consisting of lower alkyl; aryl (more preferably phenyl or naphthyl) which may have 1 to 3
20 (more preferably one or two) substituent(s) selected from the group consisting of nitro, amino, protected amino (more preferably acylamino), lower alkoxy, lower alkylthio, lower alkyl, aryl (more preferably phenyl), carboxy, protected carboxy (more preferably esterified carboxy; most preferably lower
25 alkoxycarbonyl), di(lower)alkylamino, mono(cr di or tri)halo(lower)alkyl (more preferably trihalo(lower)alkyl) and halogen; arylsulfonyl (more preferably phenylsulfonyl); ar(lower)alkyl (more
30 preferably phenyl(lower)alkyl); cyclo(lower)alkyl; and heterocyclic group (more preferably thiazolyl, pyridyl, quinolyl or morpholinyl); or thiocarbamoylamino which may have one or two (more preferably one) substituent(s) selected from the
35 group consisting of aryl (more preferably phenyl or

- 51 -

naphthyl) and acyl (more preferably aroyl; most preferably benzoyl)]; lower alkylamino; N-acyl-N-lower alkylamino [more preferably N-lower alkanoyl-N-lower alkylamino, N-aroyl-N-lower alkylamino (more preferably N-benzoyl-N-lower alkylamino), N-arylcarbamoyl-N-lower alkylamino (more preferably N-phenylcarbamoyl-N-lower alkylamino) or N-protected carboxyar(lower)alkenoyl-N-lower alkylamino (more preferably N-[esterified carboxyphenyl](lower)-alkenoyl-N-lower alkylamino; most preferably N-[lower alkoxycarbonylphenyl](lower)alkenoyl-N-lower alkylamino)]; heterocyclicamino (more preferably thiazolylamino or pyrimidinylamino) which may have 1 to 3 (more preferably one or two; most preferably one) substituent(s) selected from the group consisting of lower alkyl and aryl (more preferably phenyl); acyl [more preferably lower alkanoyl, carbamoyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and aryl (more preferably phenyl) which may have one or two halogen, aroyl (more preferably benzoyl) which may have lower alkoxy or heterocycliccarbonyl (more preferably morpholinylcarbonyl or indoliziny carbonyl)]; acyl(lower)alkyl [more preferably carbamoyl(lower)alkyl which may have one or two (more preferably one) aryl (more preferably phenyl or naphthyl)]; aryl (more preferably phenyl or naphthyl) which may have 1 to 3 (more preferably one or two) substituent(s) selected from the group consisting of carboxy(lower)alkenyl, protected carboxy(lower)alkenyl (more preferably esterified carboxy(lower)alkenyl; most preferably lower alkoxycarbonyl(lower)alkenyl), aryl (more preferably phenyl), lower alkoxy, cyclo(lower)alkyloxy, halogen, carboxy, protected carboxy (more preferably

- 52 -

esterified carboxy; most preferably lower
alkoxycarbonyl), amino, acylamino [more preferably
lower alkanoylamino, aroylamino (more preferably
benzoylamino) which may have protected carboxy (more
5 preferably esterified carboxy) or carboxy, lower
alkylsulfonylamino, mono(or di or tri)halo(lower)-
alkanoylamino (more preferably trihalo(lower)-
alkanoylamino), lower alkoxycarbonylamino,
aryloxycarbonylamino (more preferably
10 phenoxycarbonylamino), carboxy(lower)alkanoylamino,
protected carboxy(lower)alkanoylamino (more
preferably esterified carboxy(lower)alkanoylamino;
most preferably lower alkoxycarbonyl(lower)-
alkanoylamino), carboxy(lower)alkenoylamino,
15 protected carboxy(lower)alkenoylamino (more
preferably esterified carboxy(lower)alkenoylamino;
most preferably lower alkoxycarbonyl(lower)-
alkenoylamino), cyclo(lower)alkylcarbonylamino, lower
alkylglyoxyloylamino, arylsulfonylamino (more
20 preferably phenylsulfonylamino) which may have one or
two halogen, ar(lower)alkenoylamino (more preferably
phenyl(lower)alkenoylamino) which may have protected
carboxy (more preferably esterified carboxy) or
carboxy, heterocyclic(lower)alkenoylamino (more
25 preferably pyridyl(lower)alkenoylamino),
heterocycliccarbonylamino (more preferably
quinoxalinyllcarbonylamino or
benzothienylcarbonylamino), carbamoylamino which may
have one or two substituent(s) selected from the
30 group consisting of lower alkyl and aryl (more
preferably phenyl)], diacylamino (more preferably
bis(lower alkylsulfonyl)amino) and acyl (more
preferably carbamoyl which may have one or two
substituent(s) selected from the group consisting of
35 lower alkyl and aryl (more preferably phenyl or

- 53 -

naphthyl); ar(lower)alkyl (more preferably phenyl(lower)alkyl or naphthyl(lower)alkyl); ar(lower)alkenyl (more preferably phenyl(lower)alkenyl or naphthyl(lower)alkenyl) which
5 may have 1 to 3 (more preferably one or two) halogen; acyl(lower)alkenyl (more preferably aroyl(lower)-alkenyl; most preferably benzoyl(lower)alkenyl); protected carboxy(lower)alkenyl (more preferably esterified carboxy(lower)alkenyl; most preferably
10 lower alkoxycarbonyl(lower)alkenyl); cyano(lower)alkenyl; heterocyclic(lower)alkenyl (more preferably pyridyl(lower)alkenyl which may have 1 to 3 (more preferably one or two; most preferably one) halogen, pyrimidinyl(lower)alkenyl or
15 quinolyl(lower)alkenyl); heterocyclic group (more preferably pyridyl, thienyl, pyrrolyl, pyrrolidinyl, indolyl, quinolyl, isoquinolyl, imidazolyl, thiazolyl, benzothiazolyl or triazolyl) which may have 1 to 3 (more preferably one or two)
20 substituent(s) selected from the group consisting of halogen, cyano, carboxy, protected carboxy (more preferably esterified carboxy; most preferably lower alkoxycarbonyl), oxo, acyl (more preferably lower alkanoyl), amino, protected amino (more preferably acylamino) and heterocyclic group (more preferably
25 pyridyl); and heterocyclicoxy (more preferably pyrimidinyl)oxy) which may have 1 to 3 (more preferably one or two; most preferably one) aryl (more preferably phenyl)}, or pyridyl,
30 R^3 is hydrogen, lower alkoxy or arylthio (more preferably phenylthio).

More preferred embodiments of the object compound (I) are as follows.

- 54 -

R¹ is phenyl, nitrophenyl, phenyl(lower)alkyl,
nitrophenyl(lower)alkyl, aminophenyl(lower)alkyl,
hydroxyphenyl(lower)alkyl, lower
alkanoyloxyphenyl(lower)alkyl, halo(lower)alkyl,
5 lower alkoxy carbonyl(lower)alkyl,
[pyrrolidinyl carbamoyl](lower)alkyl,
[N,N-di(lower)alkyl carbamoyl](lower)alkyl,
pyrrolidinyl carbonyl(lower)alkyl,
[dioxopyrrolidinyl oxy carbonyl](lower)alkyl, [lower
10 alkoxy carbonyl pyrrolidinyl carbonyl](lower)alkyl,
[lower alkyl piperazinyl carbonyl](lower)alkyl,
indolyl, indolyl(lower)alkyl, pyridyl(lower)alkyl
which may have N-oxide, imidazolyl(lower)alkyl which
may have lower alkyl or phenyl, or
15 morpholinyl(lower)alkyl,
R² is phenyl, lower alkyl phenyl, halophenyl,
trihalo(lower)alkyl phenyl, hydroxyphenyl, lower
alkanoyloxyphenyl, carboxyphenyl, lower
alkoxy carbonyl phenyl, [phenyl(lower)alkoxy carbonyl]-
20 phenyl, [carboxy(lower)alkyl]phenyl,
[lower alkoxy carbonyl(lower)alkyl]phenyl, lower
alkoxyphenyl, cyanophenyl, nitrophenyl, aminophenyl,
[lower alkanoylamino]phenyl, [phenoxy carbonylamino]-
phenyl, [lower alkoxy carbonylamino]phenyl,
25 [lower alkoxy glyoxyloxy lamino]phenyl,
[cyclo(lower)alkyl oxy carbonylamino]phenyl,
[cyclo(lower)alkyl carbonylamino]phenyl,
[cyclo(lower)alkylidene(lower)alkanoylamino]phenyl,
[benzoylamino]phenyl, [mono(or di)(lower alkyl)-
30 benzoylamino]phenyl, [mono(or di)halobenzoylamino]-
phenyl, [di(lower alkoxy)benzoylamino]phenyl,
[bis(lower alkoxy carbonyl)benzoylamino]phenyl,
[mono(or di)nitrobenzoylamino]phenyl,
[hydroxybenzoylamino]phenyl,
35 [lower alkanoyloxybenzoylamino]phenyl,

- 55 -

[bis[trihalo(lower)alkyl]benzoylamino]phenyl, phenyl
having benzoylamino substituted with lower
alkoxycarbonyl and nitro, phenyl having benzoylamino
substituted with lower alkoxy and
5 cyclo(lower)alkyloxy, [phenylbenzoylamino]phenyl,
[[lower alkoxycarbonyl(lower)alkenyl]benzoylamino]-
phenyl, [[benzoylamino]benzoylamino]phenyl,
[pyrimidinyloxybenzoylamino]phenyl,
[[nitropyridylamino]benzoylamino]phenyl,
10 [naphthoylamino]phenyl, [hydroxynaphthoylamino]-
phenyl, [[lower alkanoyloxynaphthoyl]amino]phenyl,
[[lower alkoxycarbonylnaphthoyl]amino]phenyl,
[phenylsulfonylamino]phenyl,
[dihalophenylsulfonylamino]phenyl,
15 [phenyl(lower)alkylsulfonylamino]phenyl,
[cyclo(lower)alkylcarbonylamino]phenyl,
[mono(or di)phenyl(lower)alkanoylamino]phenyl,
[naphthyl(lower)alkanoylamino]phenyl, [lower
alkadienoylamino]phenyl, [furylcarbonylamino]phenyl,
20 [pyridylcarbonylamino]phenyl,
[dihalopyridylcarbonylamino]phenyl,
[thienylcarbonylamino]phenyl,
[indolinylcarbonylamino]phenyl,
[quinolylcarbonylamino]phenyl,
25 [tetrahydroquinolylcarbonylamino]phenyl,
[benzofurylcarbonylamino]phenyl,
[lower alkylindolylcarbonylamino]phenyl,
[benzothienylcarbonylamino]phenyl,
[methylenedioxybenzoylamino]phenyl,
30 [morpholinylcarbonylamino]phenyl,
[phenyl(lower)alkenoylamino]phenyl, [[lower
alkylphenyl(lower)alkenoyl]amino]phenyl, [[mono(or
di)halophenyl(lower)alkenoyl]amino]phenyl, [[lower
alkoxycarbonylphenyl(lower)alkenoyl]amino]phenyl,
35 [[nitrophenyl(lower)alkenoyl]amino]phenyl,

- 56 -

[pyridyl(lower)alkenoylamino]phenyl, ureidophenyl,
[lower alkylureido]phenyl, [phenylureido]phenyl,
[[aminophenyl]ureido]phenyl,
[[halophenylureido]phenyl,
5 [[nitrophenyl]ureido]phenyl,
[[lower alkoxyphenyl]ureido]phenyl,
[[lower alkylthiophenyl]ureido]phenyl,
[[mono(or di)(lower alkyl)phenyl]ureido]phenyl,
[biphenylureido]phenyl,
10 [[carboxyphenyl]ureido]phenyl,
[[lower alkoxyphenyl]ureido]phenyl,
[[di(lower)alkylaminophenyl]ureido]phenyl,
[[trihalo(lower)alkylphenyl]ureido]phenyl,
[[dihalophenyl]ureido]phenyl, [naphthylureido]phenyl,
15 [phenylsulfonylureido]phenyl,
[phenyl(lower)alkylureido]phenyl,
[cyclo(lower)alkylureido]phenyl,
[thiazolylureido]phenyl, [pyridylureido]phenyl,
[quinolylureido]phenyl, [morpholinylureido]phenyl,
20 [N-phenyl-N-lower alkylureido]phenyl,
[phenyl(thioureido)]phenyl,
[naphthyl(thioureido)]phenyl,
[benzoyl(thioureido)]phenyl, [lower
alkylamino]phenyl, [N-lower alkanoyl-N-lower
25 alkylamino]phenyl, [N-benzoyl-N-lower
alkylamino]phenyl, [N-phenylcarbamoyl-N-lower
alkylamino]phenyl, [N-lower alkoxyphenyl-
(lower)alkenoyl-N-lower alkylamino]phenyl, [lower
alkylthiazolylamino]phenyl, [phenylthiazolylamino]-
30 phenyl, [pyrimidinylamino]phenyl, lower
alkanoylphenyl, carbamoylphenyl, [lower
alkylcarbamoyl]phenyl, [phenylcarbamoyl]phenyl,
[dihalophenylcarbamoyl]phenyl, [N-dihalophenyl-N-
lower alkylcarbamoyl]phenyl, benzoylphenyl, [lower
35 alkoxybenzoyl]phenyl, morpholinylcarbonylphenyl,

- 57 -

indolizinyldicarbonylphenyl,
[phenylcarbonyl(lower)alkyl]phenyl,
[naphthylcarbonyl(lower)alkyl]phenyl, phenylphenyl,
[[lower alkoxydicarbonyl(lower)alkenyl]phenyl]phenyl,,
5 biphenylylphenyl, phenyl having phenyl substituted
with lower alkoxy and cyclo(lower)alkyloxy,
[halophenyl]phenyl, [carboxyphenyl]phenyl, [lower
alkoxydicarbonylphenyl]phenyl, [aminophenyl]phenyl,
[[lower alkanoylamino]phenyl]phenyl,
10 [[benzoylamino]phenyl]phenyl,
[[carboxybenzoylamino]phenyl]phenyl, [[mono(or
bis)(lower alkylsulfonyl)amino]phenyl]phenyl,
[[trihalo(lower)alkanoylamino]phenyl]phenyl,
[[lower alkoxydicarbonylamino]phenyl]phenyl,
15 [[phenoxydicarbonylamino]phenyl]phenyl,
[[carboxy(lower)alkanoylamino]phenyl]phenyl, [[lower
alkoxydicarbonyl(lower)alkanoylamino]phenyl]phenyl,
[[lower alkoxydicarbonyl(lower)alkenoylamino]phenyl]-
phenyl, [[cyclo(lower)alkyldicarbonylamino]phenyl]-
20 phenyl, [[lower alkylglyoxyloylamino]phenyl]phenyl,
[[dihalophenylsulfonylamino]phenyl]phenyl,
[[phenyl(lower)alkenoylamino]phenyl]phenyl,
phenylphenyl substituted with (lower)alkenoylamino
having phenyl and carboxy,
25 [[pyridyl(lower)alkenoylamino]phenyl]phenyl,
[[quinoxalinyldicarbonylamino]phenyl]phenyl,
[[benzothienyldicarbonylamino]phenyl]phenyl,
[[lower alkylcarbonylamino]phenyl]phenyl,
[[phenylcarbonylamino]phenyl]phenyl,
30 [[naphthylcarbonyl]phenyl]phenyl, naphthylphenyl,
[lower alkoxyphenyl]phenyl,
[phenyl(lower)alkyl]phenyl,
[naphthyl(lower)alkyl]phenyl,
[phenyl(lower)alkenyl]phenyl,
35 [dihalophenyl(lower)alkenyl]phenyl,

- 58 -

- [naphthyl(lower)alkenyl]phenyl,
[benzoyl(lower)alkenyl]phenyl,
[lower alkoxy carbonyl(lower)alkenyl]phenyl,
[cyano(lower)alkenyl]phenyl,
5 [pyridyl(lower)alkenyl]phenyl,
[(halopyridyl)(lower)alkenyl]phenyl,
[pyrimidinyl(lower)alkenyl]phenyl,
[quinolyl(lower)alkenyl]phenyl, pyridylphenyl,
thienylphenyl, halothienylphenyl, pyrrolylphenyl,
10 [dihalopyrrolyl]phenyl, [cyanopyrrolyl]phenyl,
[lower alkoxy carbonylpyrrolyl]phenyl,
[dioxopyrrolidinyl]phenyl, indolylphenyl,
[lower alkoxy carbonylindolyl]phenyl,
[lower alkanoylindolyl]phenyl, quinolylphenyl,
15 isoquinolylphenyl, imidazolylphenyl,
[aminothiazolyl]phenyl, [pyridylthiazolyl]phenyl,
benzothiazolylphenyl, triazolylphenyl,
pyrimidinylloxyphenyl, [phenylpyrimidinylloxy]phenyl,
phenyl having halogen and amino, phenyl having
20 halogen and (halophenyl)ureido, phenyl having halogen
and (lower alkoxyphenyl)ureido, phenyl having halogen
and lower alkanoylamino, bis(lower
alkoxy carbonyl)phenyl, phenyl having lower
alkoxy carbonyl and amino, phenyl having lower
25 alkoxy carbonyl and lower alkanoylamino, phenyl having
lower alkoxy carbonyl and naphthoylamino, phenyl
having halogen and naphthoylamino, phenyl having
cyclo(lower)alkyloxy and lower alkoxy, naphthyl or
pyridyl, and
30 R^3 is hydrogen, lower alkoxy or phenylthio.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

- 59 -

Preparation 1

A mixture of 2-chloro-3-nitropyridine (1.59 g) and m-toluidine (1.07 g) was heated at 100°C for 20 minutes. The mixture was cooled and dissolved in ethyl acetate.

5 The organic solution was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography (hexane - ethyl acetate, 4:1) to afford 3-nitro-2-[(m-tolyl)aminol]pyridine (834 mg) as an orange solid.

10 NMR (CDCl₃, δ) : 2.49 (3H, s), 6.83 (1H, dd, J=5Hz, 8Hz), 7.02 (1H, d, J=8Hz), 7.29 (1H, t, J=8Hz), 7.4-7.5 (2H, m), 8.45-8.6 (2H, m), 10.08 (1H, br s)

15 Preparation 2

The following compounds were obtained according to a similar manner to that of Preparation 1.

(1) 3-Nitro-2-[(pyridin-3-yl)aminol]pyridine

20 NMR (CDCl₃, δ) : 6.93 (1H, dd, J=5Hz, 8Hz), 7.35 (1H, dd, J=5Hz, 8Hz), 8.17 (1H, dt, J=8Hz, 1.5Hz), 8.42 (1H, dd, J=1.5Hz, 5Hz), 8.45-8.6 (2H, m), 8.87 (1H, d, J=3Hz), 10.10 (1H, s)

25 (2) 3-Nitro-2-[(pyridin-2-yl)aminol]pyridine

NMR (CDCl₃, δ) : 6.96 (1H, dd, J=5Hz, 8Hz), 7.05 (1H, m), 7.23 (1H, dt, J=1.5Hz, 8Hz), 8.3-8.65 (4H, m)

30 (3) 2-(1-Naphthyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 6.82 (1H, dd, J=1.5Hz, 8Hz), 7.45-7.65 (3H, m), 7.79 (1H, d, J=8Hz), 7.85-8.1 (4H, m), 8.41 (1H, dd, J=1.5Hz, 5Hz), 8.48 (1H, dd, J=1.5Hz, 8Hz)

- 60 -

(4) 2-(3-Ethoxycarbonylphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 1.42 (3H, t, J=7Hz), 4.41 (2H, q, J=7Hz), 6.89 (1H, dd, J=5Hz, 8Hz), 7.48 (1H, t, J=8Hz), 7.8-8.0 (2H, m), 8.28 (1H, s), 8.45-8.6 (2H, m), 10.17 (1H, br s)

5

(5) 2-(4-Methoxycarbonylphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 3.93 (3H, s), 6.96 (1H, dd, J=5Hz, 8Hz), 7.82 (2H, d, J=9Hz), 8.08 (2H, d, J=9Hz), 8.5-8.6 (2H, m)

10

(6) 2-(4-Methoxycarbonylmethylphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 3.64 (2H, s), 3.71 (3H, s), 6.83 (1H, dd, J=5Hz, 8Hz), 7.32 (2H, d, J=9Hz), 7.62 (2H, d, J=9Hz), 8.45-8.6 (2H, m), 10.11 (1H, br s)

15

(7) 2-(3-Methoxycarbonylmethylphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 3.68 (2H, s), 3.72 (3H, s), 6.85 (1H, dd, J=5Hz, 8Hz), 7.11 (1H, d, J=8Hz), 7.37 (1H, t, J=8Hz), 7.60 (2H, d, J=8Hz), 8.45-8.6 (2H, m), 10.12 (1H, br s)

20

25

(8) 2-(4-Acetylphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 2.61 (3H, s), 6.95 (1H, dd, J=5Hz, 8Hz), 7.83 (2H, d, J=9Hz), 8.00 (2H, d, J=9Hz), 8.5-8.6 (2H, m)

30

(9) 2-(3-Acetylphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 2.65 (3H, s), 6.90 (1H, dd, J=5Hz, 8Hz), 7.50 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 7.90 (1H, dd, J=1.5Hz, 8Hz), 8.25 (1H, s), 8.45-8.6 (2H, m), 10.19 (1H, br s)

35

- 61 -

(10) 2-(3-Fluorophenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 6.8-6.95 (2H, m), 7.25-7.4 (2H, m),
7.73 (1H, m), 8.5-8.6 (2H, m), 10.19 (1H, br s)

5 (11) 2-(3-Hydroxyphenyl)amino-3-nitropyridine

NMR (DMSO-d₆, δ) : 6.55 (1H, m), 6.95-7.25 (4H, m),
8.5-8.6 (2H, m), 9.48 (1H, s), 9.88 (1H, s)

10 (12) 2-(4-Methoxyphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 3.83 (3H, s), 6.78 (1H, dd, J=5Hz,
8Hz), 6.95 (2H, d, J=9Hz), 7.48 (2H, d, J=9Hz),
8.45 (1H, dd, J=1.5Hz, 5Hz), 8.51 (1H, dd,
J=1.5Hz, 8Hz), 9.97 (1H, br s)

15 (13) 2-(3-Methoxyphenyl)amino-3-nitropyridine

NMR (CDCl₃, δ) : 3.85 (3H, s), 6.74 (1H, m), 6.87
(1H, dd, J=5Hz, 8Hz), 7.18 (1H, m), 7.25-7.4
(2H, m), 8.45-8.6 (2H, m), 10.13 (1H, br s)

20 Preparation 3

A mixture of 3-nitro-2-[(m-tolyl)amino]pyridine (825 mg) and 10% palladium carbon (0.3 g) in ethanol (15 ml) and 1,4-dioxane (15 ml) was stirred under hydrogen (3 atm) at room temperature for 30 minutes. The catalyst was
25 removed and the solvent was evaporated. The solids were collected and washed with isopropyl ether to give 3-amino-2-[(m-tolyl)amino]pyridine (660 mg).

NMR (CDCl₃, δ) : 3.15 (2H, br s), 6.18 (1H, br s),
6.77 (1H, dd, J=5Hz, 8Hz), 6.95-7.3 (5H, m),
30 7.83 (1H, dd, J=1.5Hz, 5Hz)

Preparation 4

The following compounds were obtained according to a similar manner to that of Preparation 3.

- 62 -

(1) 3-Amino-2-[(pyridin-3-yl)amino]pyridine

5 NMR (DMSO-d₆, δ) : 5.12 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=1.5Hz, 8Hz), 7.24 (1H, dd, J=5Hz, 8Hz), 7.50 (1H, dd, J=1.5Hz, 5Hz), 7.95 (1H, s), 8.0-8.15 (2H, m), 8.76 (1H, d, J=3Hz)

(2) 3-Amino-2-[(pyridin-2-yl)amino]pyridine

10 NMR (DMSO-d₆, δ) : 5.23 (2H, s), 6.74 (1H, dd, J=5Hz, 8Hz), 6.83 (1H, m), 6.98 (1H, dd, J=1.5Hz, 8Hz), 7.5-7.7 (2H, m), 8.00 (1H, d, J=8Hz), 8.18 (1H, m), 8.39 (1H, s)

(3) 3-Amino-2-[(1-naphthyl)amino]pyridine

15 NMR (DMSO-d₆, δ) : 5.12 (2H, s), 6.64 (1H, dd, J=5Hz, 8Hz), 6.98 (1H, dd, J=1.5Hz, 8Hz), 7.35-7.65 (6H, m), 7.76 (1H, s), 7.90 (1H, m), 8.05 (1H, m)

20 (4) 2-(3-Acetamidophenyl)amino-3-aminopyridine

NMR (DMSO-d₆, δ) : 2.03 (3H, s), 5.09 (2H, s), 6.63 (1H, dd, J=5Hz, 8Hz), 6.89 (1H, dd, J=1.5Hz, 8Hz), 7.0-7.25 (2H, m), 7.33 (1H, m), 7.49 (1H, dd, J=1.5Hz, 5Hz), 7.71 (1H, s), 7.87 (1H, s), 25 9.80 (1H, s)

(5) 3-Amino-2-[(3-ethoxycarbonylphenyl)amino]pyridine

30 NMR (DMSO-d₆, δ) : 1.33 (3H, t, J=7Hz), 4.31 (2H, q, J=7Hz), 5.12 (2H, s), 6.68 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=1.5Hz, 8Hz), 7.3-7.5 (2H, m), 7.52 (1H, dd, J=1.5Hz, 5Hz), 7.95-8.1 (2H, m), 8.17 (1H, s)

(6) 3-Amino-2-[(4-methoxycarbonylphenyl)amino]pyridine

35 NMR (DMSO-d₆, δ) : 3.86 (3H, s), 5.19 (2H, s), 6.74

- 63 -

(1H, dd, J=5Hz, 8Hz), 6.98 (1H, dd, J=1.5Hz, 8Hz), 7.58 (1H, dd, J=1.5Hz, 5Hz), 7.70 (2H, d, J=9Hz), 7.83 (2H, d, J=9Hz), 8.28 (1H, s)

- 5 (7) 3-Amino-2-[(4-methoxycarbonylmethylphenyl)amino]-pyridine
NMR (DMSO-d₆, δ) : 3.58 (2H, s), 3.61 (3H, s), 5.07 (2H, s), 6.61 (1H, dd, J=5Hz, 8Hz), 6.89 (1H, dd, J=1.5Hz, 8Hz), 7.11 (2H, d, J=9Hz), 7.49
10 (1H, dd, J=1.5Hz, 5Hz), 7.57 (2H, d, J=9Hz), 7.70 (1H, s)
- (8) 3-Amino-2-[(3-methoxycarbonylmethylphenyl)amino]-pyridine
15 NMR (CDCl₃, δ) : 3.41 (2H, br s), 3.61 (2H, s), 3.69 (3H, s), 6.21 (1H, br s), 6.78 (1H, dd, J=5Hz, 8Hz), 6.87 (1H, m), 7.01 (1H, dd, J=1.5Hz, 8Hz), 7.15-7.3 (3H, m), 7.85 (1H, dd, J=1.5Hz, 5Hz)
- 20 (9) 2-(4-Acetylphenyl)amino-3-aminopyridine
NMR (DMSO-d₆, δ) : 2.49 (3H, s), 5.19 (2H, s), 6.75 (1H, dd, J=5Hz, 8Hz), 6.98 (1H, dd, J=1.5Hz, 8Hz), 7.57 (1H, dd, J=1.5Hz, 5Hz), 7.69 (2H, d, J=9Hz), 7.86 (2H, d, J=9Hz), 8.27 (1H, s)
25
- (10) 2-(3-Acetylphenyl)amino-3-aminopyridine
NMR (DMSO-d₆, δ) : 2.57 (3H, s), 5.11 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=1.5Hz, 8Hz), 7.2-7.55 (3H, m), 7.95-8.05 (2H, m), 8.13
30 (1H, s)
- (11) 3-Amino-2-[(3-fluorophenyl)amino]pyridine
NMR (DMSO-d₆, δ) : 5.11 (2H, s), 6.55-6.75 (2H, m), 6.93 (1H, dd, J=1.5Hz, 8Hz), 7.15-7.35 (2H, m),
35 7.54 (1H, dd, J=1.5Hz, 5Hz), 7.72 (1H, dt,

- 64 -

J=13Hz, 1.5Hz), 7.98 (1H, s)

(12) 3-Amino-2-[(3-hydroxyphenyl)amino]pyridine

5 NMR (DMSO-d₆, δ) : 5.12 (2H, br s), 6.27 (1H, m),
6.61 (1H, dd, J=1.5Hz, 8Hz), 6.85-7.05 (3H, m),
7.71 (1H, s), 7.49 (1H, dd, J=1.5Hz, 5Hz), 7.63
(1H, s), 9.12 (1H, s)

(13) 3-Amino-2-[(4-methoxyphenyl)amino]pyridine

10 NMR (CDCl₃, δ) : 3.07 (2H, br s), 3.79 (3H, s), 6.19
(1H, br s), 6.70 (1H, dd, J=5Hz, 8Hz), 6.87 (2H,
d, J=9Hz), 7.23 (2H, d, J=9Hz), 7.78 (1H, dd,
J=1.5Hz, 5Hz)

15 (14) 3-Amino-2-[(3-methoxyphenyl)amino]pyridine

NMR (CDCl₃, δ) : 3.42 (2H, br s), 3.79 (3H, s), 6.21
(1H, s), 6.51 (1H, m), 6.75-6.85 (2H, m), 6.92
(1H, m), 7.02 (1H, dd, J=1.5Hz, 8Hz), 7.18 (1H,
t, J=8Hz), 7.85 (1H, dd, J=1.5Hz, 5Hz)

20

Preparation 5

A mixture of 2-chloro-3-nitropyridine (6.12 g), 3'-
aminoacetanilide (5.80 g) and potassium carbonate (5.34 g)
in toluene (50 ml) was refluxed for 5 hours. The mixture
25 was cooled, and the solids were collected and washed with
water, ethanol and isopropyl ether successively to give
2-(3-acetamidophenyl)amino-3-nitropyridine (5.88 g) as an
orange solid.

30 NMR (DMSO-d₆, δ) : 2.06 (3H, s), 6.99 (1H, dd,
J=5Hz, 8Hz), 7.2-7.4 (3H, m), 7.91 (1H, s),
8.5-8.6 (2H, m), 9.93 (1H, s), 9.99 (1H, s)

Preparation 6

To a mixture of ethyl 3-aminobenzoate (996 mg) and
35 triethylamine (0.85 ml) in dichloromethane (10 ml) was

- 65 -

added benzoyl chloride (0.70 ml). The mixture was stirred at room temperature for 15 minutes, poured into a mixture of ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give ethyl 3-benzoylaminobenzoate (1.36 g).

NMR (DMSO-d₆, 300MHz, δ) : 1.33 (3H, t, J=7Hz), 4.33 (2H, q, J=7Hz), 7.45-7.75 (5H, m), 7.98 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz)

Preparation 7

To a suspension of sodium hydride (60% in oil, 5.19 g) in N,N-dimethylformamide (30 ml) was added a solution of 3'-nitroacetanilide (214 mg) in N,N-dimethylformamide (30 ml) at 0°C. The mixture was stirred at room temperature for 30 minutes, then iodomethane (3.59 ml) was added. After 30 minutes, 1N hydrochloric acid was poured into the mixture and extracted with ethyl acetate. The organic solution was washed with water and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give N-methyl-3'-nitroacetanilide (4.64 g).

NMR (DMSO-d₆, 200MHz, δ) : 1.92 (3H, s), 3.25 (3H, s), 7.65-7.9 (2H, m), 8.1-8.3 (2H, m)

Preparation 8

A mixture of ammonium thiocyanate (2.79 g) and benzoyl chloride (3.86 ml) in acetone (30 ml) was refluxed for 5 minutes. Then a solution of 3'-aminoacetanilide (5.00 g) in acetone (40 ml) was added thereto. The mixture was poured into water, and the resulting precipitate was separated by filtration. The crystals were heated at 50°C for 3 hours with 1N sodium hydroxide (150 ml) solution. The mixture was poured into a mixture

- 66 -

of ethyl acetate and water, and the resulting precipitate was collected and washed with ethyl acetate and water to give N-(3-acetylaminophenyl)thiourea (4.22 g).

5 NMR (DMSO-d₆, 300MHz, δ) : 2.03 (3H, s), 7.12 (1H, d, J=8Hz), 7.22 (1H, t, J=8Hz), 7.33 (1H, d, J=8Hz), 7.62 (1H, s), 9.68 (1H, s), 9.95 (1H, s)

Preparation 9

10 A mixture of 3-nitroaniline (6.14 g), 2-chloropyrimidine (4.85 g) and potassium carbonate (6.15 g) in dimethylsulfoxide (50 ml) was heated at 170°C for 5 hours. The mixture was cooled and poured into a mixture of ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and concentrated.
15 The resulting solid was collected and washed with isopropyl ether to give 2-(3-nitrophenylamino)pyrimidine (1.92 g).

20 NMR (DMSO-d₆, 300MHz, δ) : 6.97 (1H, t, J=5Hz), 7.57 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 8.58 (2H, d, J=5Hz), 8.85 (1H, s)

Preparation 10

25 A mixture of 3-nitrophenol (6.85 g), 2-chloropyrimidine (5.13 g) and potassium carbonate (6.81 g) in dimethylsulfoxide (50 ml) was heated at 150°C for 30 minutes. The mixture was cooled and poured into a mixture of ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The resulting solid was collected and washed with
30 isopropyl ether to give 2-(3-nitrophenoxy)pyrimidine (7.41 g).

NMR (DMSO-d₆, 300MHz, δ) : 7.35 (1H, t, J=5Hz), 7.7-7.8 (2H, m), 8.1-8.2 (2H, m), 8.69 (2H, d, J=5Hz)

- 67 -

Preparation 11

A mixture of methyl 3-hydroxybenzoate (3.4 g), 2-chloropyrimidine (2.29 g) and potassium carbonate (3.04 g) in dimethylsulfoxide (30 ml) was stirred at 150°C for 1 hour. The mixture was poured into a mixture of ethyl acetate and water. The organic phase was washed with water and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give methyl 3-(pyrimidine-2-yl)oxybenzoate (3.66 g).

NMR (CDCl₃, 300MHz, δ) : 3.92 (3H, s), 7.07 (1H, t, J=5Hz), 7.41 (1H, m), 7.52 (1H, t, J=8Hz), 7.88 (1H, t, J=1.5Hz), 7.96 (1H, d, J=8Hz), 8.58 (2H, d, J=5Hz)

Preparation 12

The following compound was obtained according to similar manners to those of Preparations 10 and 11.

2- (3-Nitrophenoxy)-4-phenylpyrimidine

NMR (DMSO-d₆, 300MHz, δ) : 7.5-7.65 (3H, m), 7.75-7.9 (2H, m), 7.93 (1H, d, J=5Hz), 8.1-8.25 (4H, m), 8.73 (1H, d, J=5Hz)

Preparation 13

To a solution of iodobenzene (3.53 ml) in ether (10 ml) was added n-butyllithium (1.6M in hexane, 20 ml), and the mixture was stirred at room temperature for 20 minutes. The above solution was added to a solution of 2-chloropyrimidine (3.52 g) in ether (90 ml) at -30°C. The mixture was stirred at -30°C for 30 minutes and then at 0°C for 30 minutes, quenched with a solution of acetic acid (1.83 ml) and water (0.31 ml) in tetrahydrofuran (6 ml), and treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (7.26 g) in tetrahydrofuran (30 ml). The mixture

- 68 -

was stirred at 0°C for 5 minutes, cooled to 0°C, treated with a cold aqueous solution of sodium hydroxide (3M, 9.2 ml), and stirred at 0°C for 5 minutes. The organic phase was separated, washed with water and brine, dried over magnesium sulfate, concentrated and subjected to silica gel column chromatography (hexane - ethyl acetate, 7:3) to afford 2-chloro-4-phenylpyrimidine (3.39 g) as a solid.

NMR (DMSO-d₆, 300MHz, δ) : 7.55-7.7 (3H, m),
8.15-8.25 (3H, m), 8.83 (1H, d, J=5Hz)

10

Preparation 14

A mixture of 2-bromo-3'-nitroacetophenone (12.2 g) and thiourea (3.81 g) in ethanol (100 ml) was stirred at room temperature for 15 minutes. The reaction mixture was poured into a mixture of ethyl acetate and an aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-amino-4-(3-nitrophenyl)thiazole (10.21 g).

20

NMR (DMSO-d₆, 300MHz, δ) : 7.24 (2H, s), 7.36 (1H, s), 7.67 (1H, t, J=8Hz), 8.10 (1H, dt, J=8Hz, 1.5Hz), 8.24 (1H, dt, J=8Hz, 1.5Hz), 8.62 (1H, t, J=1.5Hz)

25

Preparation 15

A mixture of 2-bromo-3'-nitroacetophenone (3.66 g) and 3-thiocarbamoylpyridine (2.07 g) in ethanol (40 ml) was refluxed for 1 hour. The reaction mixture was poured into a mixture of ethyl acetate and an aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 4-(3-nitrophenyl)-2-(pyridin-3-yl)thiazole (2.91 g).

35

- 69 -

NMR (DMSO-d₆, 300MHz, δ) : 7.55 (1H, m), 7.78 (1H, t, J=8Hz), 8.22 (1H, d, J=8Hz), 8.41 (1H, m), 8.50 (1H, d, J=8Hz), 8.59 (1H, s), 8.70 (1H, dd, J=1.5Hz, 5Hz), 8.83 (1H, s), 9.22 (1H, d, J=1.5Hz)

Preparation 16

A mixture of 2-bromo-3'-nitroacetophenone (4.88 g) and formamide (50 ml) was stirred at 185°C for 2 hours. The reaction mixture was poured into a mixture of ethyl acetate and an aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with ethyl acetate to give 4-(3-nitrophenyl)imidazole (2.32 g).

NMR (DMSO-d₆, 300MHz, δ) : 7.63 (1H, t, J=8Hz), 7.78 (1H, s), 7.90 (1H, s), 8.02 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz), 8.58 (1H, s), 12.36 (1H, br s)

Preparation 17

A mixture of 3-nitrobenzoyl chloride (3.71 g), anisole (2.0 ml) and aluminum chloride (2.67 g) in dichloromethane (50 ml) was refluxed for 1 hour. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with ethyl acetate to give 1-(3-nitrobenzoyl)-4-methoxybenzene (955 mg).

NMR (DMSO-d₆, 300MHz, δ) : 3.88 (3H, s), 7.12 (2H, d, J=8Hz), 7.75-7.9 (3H, m), 8.12 (1H, d, J=8Hz), 8.39 (1H, s), 8.48 (1H, m)

Preparation 18

A mixture of 3-nitrobenzoyl chloride (4.50 g) and

- 70 -

indolizine (2.84 g) in dichloromethane (30 ml) was stirred at room temperature for 30 minutes. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with ethyl acetate to give 3-(3-nitrobenzoyl)indolizine (4.51 g).

NMR (DMSO- d_6 , 300MHz, δ) : 6.74 (1H, d, J=5Hz), 7.18 (1H, m), 7.35-7.45 (2H, m), 7.8-7.9 (2H, m), 8.09 (1H, d, J=8Hz), 8.4-8.5 (2H, m), 9.85 (1H, d, J=7Hz)

Preparation 19

To a suspension of sodium hydride (60% in oil, 1.48 g) in N,N-dimethylformamide (40 ml) was added a solution of diethyl benzylphosphonate (7.69 g) in N,N-dimethylformamide (40 ml) at 0°C. The mixture was stirred at room temperature for 30 minutes, then a solution of 3-nitrobenzaldehyde (5.09 g) was added thereto. After stirring at 50°C for 1 hour, the mixture was poured into dilute hydrochloric acid, and extracted with ethyl acetate 3 times. The combined organic solution was washed with water and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give (E)-3-nitrostilbene (3.97 g).

NMR (CDCl₃, 300MHz, δ) : 7.1-7.6 (8H, m), 7.80 (1H, d, J=8Hz), 8.10 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, s)

Preparation 20

The following compounds were obtained according to a similar manner to that of Preparation 19.

(1) 2-((E)-3-Nitrostyryl)naphthalene

- 71 -

NMR (CDCl₃, 300MHz, δ) : 7.25 (1H, d, J=16Hz), 7.35-7.6 (4H, m), 7.7-7.95 (6H, m), 8.10 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, s)

5 (2) (E)-3-Nitrostyryl phenyl ketone

NMR (CDCl₃, 300MHz, δ) : 7.5-7.7 (5H, m), 7.86 (1H, d, J=16Hz), 7.93 (1H, d, J=8Hz), 8.06 (2H, d, J=8Hz), 8.28 (1H, dd, J=1.5Hz, 8Hz), 8.52 (1H, s)

10

(3) (E)-3-(3-Nitrophenyl)propenonitrile

NMR (CDCl₃, 300MHz, δ) : 6.07 (1H, d, J=16Hz), 7.48 (1H, d, J=16Hz), 7.64 (1H, t, J=8Hz), 7.78 (1H, d, J=8Hz), 8.25-8.4 (2H, m)

15

(4) (E)-Methyl 3-(3-nitrophenyl)propenoate

NMR (CDCl₃, 300MHz, δ) : 3.84 (3H, s), 6.57 (1H, d, J=16Hz), 7.59 (1H, t, J=8Hz), 7.73 (1H, d, J=16Hz), 7.83 (1H, d, J=8Hz), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, t, J=1.5Hz)

20

Preparation 21

A mixture of N-methyl-3'-nitroacetanilide (5.13 g) and 10% palladium carbon (0.6 g) in methanol (50 ml) and 1,4-dioxane (50 ml) and stirred under hydrogen (3 atm) at room temperature for 2 hours. The catalyst was removed by filtration and the solvent was evaporated. The resultant solid was collected and washed with isopropyl ether to give 3'-amino-N-methylacetanilide (4.06 g).

30 NMR (DMSO-d₆, 200MHz, δ) : 1.78 (3H, s), 3.08 (3H, s), 5.28 (2H, s), 6.35-6.6 (3H, m), 7.05 (1H, t, J=8Hz)

Preparation 22

35 The following compounds were obtained according to a

- 72 -

similar manner to that of Preparation 21.

(1) 3-(Pyrimidin-2-yl)aminoaniline

5 NMR (DMSO-d₆, 300MHz, δ) : 4.96 (2H, s), 6.28 (1H, m), 6.78 (1H, m), 6.8-6.95 (2H, m), 7.05 (1H, s), 8.42 (2H, d, J=5Hz), 9.28 (1H, s)

(2) 3-(Pyrimidin-2-yl)oxyaniline

10 NMR (DMSO-d₆, 300MHz, δ) : 5.23 (2H, s), 6.2-6.35 (2H, m), 6.43 (1H, d, J=8Hz), 7.02 (1H, t, J=8Hz), 7.23 (1H, t, J=5Hz), 8.62 (2H, d, J=5Hz)

(3) 3-(4-Phenylpyrimidin-2-yl)oxyaniline

15 NMR (DMSO-d₆, 300MHz, δ) : 5.27 (2H, s), 6.3-6.5 (3H, m), 7.07 (1H, t, J=8Hz), 7.45-7.65 (3H, m), 7.82 (1H, d, J=5Hz), 8.05-8.2 (2H, m), 8.67 (1H, d, J=5Hz)

Preparation 23

20 A mixture of (E)-3-nitrostilbene (3.63 g), hydrochloric acid (35 %, 10 ml) and iron powder (3.6 g) in ethanol (30 ml) was refluxed for 1 hour. The mixture was poured into aqueous sodium bicarbonate solution and extracted with ethyl acetate twice. The combined organic
25 solution was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give (E)-3-aminostilbene (2.05 g).

30 NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.49 (1H, d, J=8Hz), 6.7-6.85 (2H, m), 7.0-7.15 (3H, m), 7.2-7.45 (3H, m), 7.58 (2H, d, J=8Hz)

Preparation 24

35 The following compounds were obtained according to a similar manner to that of Preparation 23.

- 73 -

(1) 2-Amino-4-(3-aminophenyl)thiazole

NMR (DMSO-d₆, 300MHz, δ) : 5.02 (2H, s), 6.45 (1H, m), 6.76 (1H, s), 6.9-7.05 (5H, m)

5 (2) 3-[2-(Pyridin-3-yl)thiazol-4-yl]aniline

NMR (DMSO-d₆, 300MHz, δ) : 5.20 (2H, s), 6.58 (1H, d, J=8Hz), 7.05-7.2 (2H, m), 7.30 (1H, s), 7.58 (1H, m), 8.05 (1H, s), 8.35 (1H, d, J=8Hz), 8.68 (1H, d, J=5Hz), 9.19 (1H, d, J=1.5Hz)

10

(3) 3-(Imidazol-4-yl)aniline

NMR (DMSO-d₆, 300MHz, δ) : 4.96 (2H, s), 6.38 (1H, d, J=8Hz), 6.85-7.1 (3H, m), 7.40 (1H, s), 7.64 (1H, s), 12.04 (1H, br s)

15

(4) 3-Amino-4'-methoxybenzophenone

NMR (DMSO-d₆, 300MHz, δ) : 3.84 (3H, s), 5.37 (2H, s), 6.75-6.85 (2H, m), 6.89 (1H, t, J=1.5Hz), 7.07 (2H, dt, J=8Hz, 1.5Hz), 7.16 (1H, t, J=8Hz), 7.72 (2H, dt, J=8Hz, 1.5Hz)

20

(5) 3-(3-Indolizinylylcarbonyl)aniline

NMR (DMSO-d₆, 300MHz, δ) : 5.32 (2H, s), 6.65 (1H, d, J=5Hz), 6.75 (1H, m), 7.86 (1H, d, J=8Hz), 6.97 (1H, s), 7.05-7.2 (2H, m), 7.25-7.4 (2H, m), 7.77 (1H, d, J=8Hz), 9.81 (1H, d, J=7Hz)

25

(6) 3-[(E)-2-(2-Naphthyl)vinyl]aniline

NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.50 (1H, d, J=8Hz), 6.75-6.85 (2H, m), 7.03 (1H, t, J=8Hz), 7.23 (2H, s), 7.4-7.55 (2H, m), 7.8-7.95 (4H, m), 7.98 (1H, s)

30

(7) (E)-3-Aminostyryl phenyl ketone

NMR (DMSO-d₆, 300MHz, δ) : 5.21 (2H, s), 6.68 (1H,

35

- 74 -

d, J=8Hz), 6.95-7.15 (3H, m), 7.5-7.8 (5H, m),
8.10 (2H, d, J=8Hz)

(8) (E)-3-(3-Aminophenyl)propenenitrile

5 NMR (DMSO-d₆, 300MHz, δ) : 5.26 (2H, s), 6.23 (1H,
d, J=16Hz), 6.64 (1H, d, J=8Hz), 6.73 (1H, s),
6.79 (1H, d, J=8Hz), 7.08 (1H, t, J=8Hz), 7.48
(1H, d, J=16Hz)

10 (9) (E)-Methyl 3-(3-aminophenyl)propenoate

NMR (DMSO-d₆, 300MHz, δ) : 3.72 (3H, s), 5.19 (2H,
s), 6.41 (1H, d, J=16Hz), 6.64 (1H, dd, J=1.5Hz,
8Hz), 6.75-6.85 (2H, m), 7.06 (1H, t, J=8Hz),
7.48 (1H, d, J=16Hz)

15

Preparation 25

A mixture of N-(3-acetylaminophenyl)thiourea (0.84 g)
and 2-bromoacetophenone (0.84 g) in ethanol (10 ml) was
refluxed for 15 minutes. After evaporation of the
20 solvent, 3N hydrochloric acid was added thereto and the
mixture was refluxed for 30 minutes. The mixture was made
basic with sodium bicarbonate and extracted with ethyl
acetate. The organic solution was washed with water and
brine, dried over magnesium sulfate and concentrated. The
25 residue was crystallized from ethanol to give 3-(4-
phenylthiazol-2-yl)aminoaniline (0.88 g).

NMR (DMSO-d₆, 300MHz, δ) : 5.11 (2H, s), 6.20 (1H,
d, J=8Hz), 6.82 (1H, m), 6.9-7.0 (2H, m), 7.25-
7.35 (2H, m), 7.42 (2H, t, J=8Hz), 7.93 (2H, d,
30 J=8Hz)

Preparation 26

The following compound was obtained according to a
similar manner to that of Preparation 25.

35

- 75 -

3-(4-Methylthiazol-2-yl)aminoaniline

NMR (DMSO-d₆, 300MHz, δ) : 2.19 (3H, s), 5.02 (2H, s), 6.15 (1H, d, J=8Hz), 6.37 (1H, s), 6.65-6.8 (2H, m), 6.90 (1H, t, J=8Hz), 9.73 (1H, s)

5

Preparation 27

A mixture of 2-chloro-3-nitropyridine (1.96 g) and 3'-amino-N-methylacetanilide (2.03 g) in toluene (20 ml) was refluxed for 7 hours. The mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-[3-(N-methylacetamido)phenylamino]-3-nitropyridine (872 mg).

10

15

NMR (DMSO-d₆, 200MHz, δ) : 1.85 (3H, s), 3.18 (3H, s), 7.0-7.15 (2H, m), 7.42 (1H, t, J=8Hz), 7.66 (2H, m), 8.5-8.6 (2H, m), 10.01 (1H, s)

20 Preparation 28

A mixture of 2-chloro-3-nitropyridine (2.27 g), 3-chloroaniline (1.5 ml) and potassium carbonate (2.2 g) in 1,4-dioxane (30 ml) was refluxed for 20 hours. The insoluble materials were removed by filtration and the filtrate was concentrated. Silica gel column chromatography (chloroform-methanol, 50:1) afforded 2-(3-chlorophenylamino)-3-nitropyridine (404 mg) as an orange solid.

25

30

NMR (CDCl₃, 300MHz, δ) : 6.90 (1H, dd, J=5Hz, 8Hz), 7.15 (1H, dt, J=8Hz, 1.5Hz), 7.31 (1H, t, J=8Hz), 7.45 (1H, dt, J=8Hz, 1.5Hz), 7.88 (1H, t, J=1.5Hz), 8.5-8.6 (2H, m), 10.14 (1H, s)

Preparation 29

35

The following compounds were obtained according to

- 76 -

similar manners to those of Preparations 1, 5 and 28.

(1) 2-(3-Cyanophenylamino)-3-nitropyridine

5 NMR (CDCl₃, 300MHz, δ) : 6.97 (1H, dd, J=5Hz, 8Hz),
7.4-7.55 (2H, m), 7.7-7.8 (1H, m), 8.32 (1H, s),
8.5-8.65 (2H, m), 10.22 (1H, s)

(2) 2-(3-Biphenylylamino)-3-nitropyridine

10 NMR (CDCl₃, 300MHz, δ) : 6.85 (1H, dd, J=5Hz, 8Hz),
7.2-7.5 (5H, m), 7.55-7.7 (3H, m), 7.86 (1H, t,
J=1.5Hz), 8.45-8.6 (2H, m), 10.19 (1H, s)

(3) 3-Nitro-2-[3-(4-phenylthiazol-2-yl)aminophenylamino]-
pyridine

15 NMR (DMSO-d₆, 300MHz, δ) : 7.05 (1H, dd, J=5Hz,
8Hz), 7.21 (1H, d, J=8Hz), 7.25-7.5 (6H, m),
7.92 (2H, d, J=8Hz), 8.37 (1H, s), 8.5-8.6 (2H,
m)

20 (4) 3-Nitro-2-[3-(4-methylthiazol-2-yl)aminophenylamino]-
pyridine

25 NMR (DMSO-d₆, 300MHz, δ) : 2.22 (3H, s), 6.45 (1H,
s), 6.99 (1H, dd, J=5Hz, 8Hz), 7.17 (1H, d,
J=8Hz), 7.27 (1H, t, J=8Hz), 7.41 (1H, d,
J=8Hz), 8.01 (1H, s), 8.5-8.6 (2H, m)

(5) 3-Nitro-2-[3-(pyrimidin-2-yl)aminophenylamino]-
pyridine

30 NMR (DMSO-d₆, 300MHz, δ) : 6.84 (1H, t, J=5Hz), 6.98
(1H, m), 7.2-7.3 (2H, m), 7.54 (1H, m), 8.05
(1H, s), 8.45-8.55 (4H, m), 9.67 (1H, s)

(6) 3-Nitro-2-[3-(pyrimidin-2-yl)oxyphenylamino]pyridine

35 NMR (DMSO-d₆, 300MHz, δ) : 6.9-7.5 (2H, m), 7.28
(1H, t, J=5Hz), 7.41 (1H, t, J=8Hz), 7.53 (1H,

- 77 -

d, J=8Hz), 7.66 (1H, t, J=1.5Hz), 8.5-8.6 (2H, m), 8.66 (2H, d, J=5Hz)

(7) 3-Nitro-2-[3-[(4-phenylpyrimidin-2-yl)oxy]-phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 6.95-7.1 (2H, m), 7.43 (1H, t, J=8Hz), 7.5-7.65 (4H, m), 7.74 (1H, t, J=1.5Hz), 7.87 (1H, d, J=5Hz), 8.1-8.2 (2H, m), 8.45-8.6 (2H, m), 8.69 (1H, d, J=5Hz)

(8) 2-[3-(2-Aminothiazol-4-yl)phenylamino]-3-nitropyridine

NMR (DMSO-d₆, 300MHz, δ) : 6.9-7.1 (4H, m), 7.36 (1H, t, J=8Hz), 7.55-7.65 (2H, m), 7.98 (1H, s), 8.5-8.6 (2H, m), 9.99 (1H, s)

(9) 3-Nitro-2-[3-[2-(pyridin-3-yl)thiazol-4-yl]phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 7.01 (1H, m), 7.48 (1H, t, J=8Hz), 7.57 (1H, m), 7.74 (1H, d, J=8Hz), 7.84 (1H, d, J=8Hz), 8.29 (1H, s), 8.39 (1H, dd, J=1.5Hz, 8Hz), 8.5-8.6 (2H, m), 8.69 (1H, d, J=5Hz), 9.22 (1H, s), 10.05 (1H, s)

(10) 2-[3-(Imidazol-4-yl)phenylamino]-3-nitropyridine

NMR (DMSO-d₆, 300MHz, δ) : 6.98 (1H, dd, J=5Hz, 8Hz), 7.3-7.75 (4H, m), 7.99 (1H, s), 8.5-8.6 (2H, m), 9.99 (1H, s), 12.18 (1H, br s)

(11) 2-[3-(4-Methoxybenzoyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 3.91 (3H, s), 6.88 (1H, dd, J=5Hz, 8Hz), 6.98 (2H, dt, J=8Hz, 1.5Hz), 7.45-7.6 (2H, m), 7.8-7.95 (3H, m), 8.09 (1H, s), 8.50 (1H, d, J=5Hz), 8.55 (1H, d, J=8Hz), 10.20 (1H, s)

- 78 -

(12) 2-[3-(3-Indolizinylicarbonyl)phenylamino]-3-nitropyridine

5 NMR (CDCl₃, 300MHz, δ) : 6.55 (1H, d, J=5Hz), 6.86 (1H, dd, J=5Hz, 8Hz), 6.96 (1H, t, J=8Hz), 7.22 (1H, t, J=8Hz), 7.45-7.65 (4H, m), 7.79 (1H, d, J=8Hz), 8.17 (1H, s), 8.5-8.6 (2H, m), 9.98 (1H, d, J=7Hz), 10.22 (1H, s)

(13) 3-Nitro-2-[(E)-3-styrylphenylamino]pyridine

10 NMR (CDCl₃, 300MHz, δ) : 6.85 (1H, dd, J=5Hz, 8Hz), 7.13 (2H, s), 7.20-7.45 (5H, m), 7.5-7.65 (3H, m), 7.78 (1H, s), 8.5-8.6 (2H, m), 10.16 (1H, s)

(14) 2-[3-[(E)-2-(2-Naphthyl)vinyl]phenylamino]-3-nitropyridine

15 NMR (DMSO-d₆, 300MHz, δ) : 7.00 (1H, dd, J=5Hz, 8Hz), 7.35-7.55 (6H, m), 7.63 (1H, d, J=8Hz), 7.85-7.95 (5H, m), 8.02 (1H, s), 8.5-8.6 (2H, m), 10.02 (1H, s)

(15) 2-[3-((E)-2-Benzoylvinyl)phenylamino]-3-nitropyridine

20 NMR (DMSO-d₆, 300MHz, δ) : 7.10 (1H, dd, J=5Hz, 8Hz), 7.5-7.95 (7H, m), 8.03 (1H, d, J=16Hz), 8.15-8.3 (3H, m), 8.6-8.7 (2H, m), 10.12 (1H, s)

(16) 2-[3-((E)-2-Cyanovinyl)phenylamino]-3-nitropyridine

25 NMR (CDCl₃, 300MHz, δ) : 5.93 (1H, d, J=16Hz), 6.91 (1H, dd, J=5Hz, 8Hz), 7.35-7.5 (2H, m), 7.67 (1H, dd, J=1.5Hz, 8Hz), 7.91 (1H, t, J=1.5Hz), 30 8.45-8.6 (2H, m), 10.18 (1H, s)

(17) 2-[3-((E)-2-Methoxycarbonylvinyl)phenylamino]-3-nitropyridine

35 NMR (CDCl₃, 300MHz, δ) : 3.82 (3H, s), 6.48 (1H, d, J=16Hz), 6.89 (1H, dd, J=5Hz, 8Hz), 7.33 (1H, d,

- 79 -

J=8Hz), 7.41 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 7.72 (1H, d, J=16Hz), 8.5-8.6 (2H, m), 10.16 (1H, s)

5 Preparation 30

A mixture of 3-amino-2-chloropyridine (2.57 g) and 3-nitroaniline (2.76 g) was heated at 200°C for 1 hour. The mixture was cooled and partitioned between aqueous sodium bicarbonate solution and chloroform. The organic layer
10 was washed with brine, dried over magnesium sulfate, concentrated and subjected to silica gel column chromatography (chloroform-methanol, 40:1) to afford 3-amino-2-(3-nitrophenylamino)pyridine (141 mg) as an orange solid.

15 NMR (DMSO-d₆, 200MHz, δ) : 5.18 (2H, s), 6.74 (1H, dd, J=5Hz, 8Hz), 6.99 (1H, dd, J=1.5Hz, 8Hz), 7.45-7.7 (3H, m), 8.02 (1H, m), 8.33 (1H, s), 8.66 (1H, t, J=1.5Hz)

20 Preparation 31

A mixture of 3-nitro-2-((E)-3-styrylphenylamino)-pyridine (1.03 g) and 10% palladium on carbon (0.3 g) in methanol (20 ml) and 1,4-dioxane (20 ml) was stirred under hydrogen (3 atm) at room temperature for 1.5 hours. The
25 catalyst was removed by filtration and the solvent was evaporated. The resulting solid was collected and washed with isopropyl ether to give 3-amino-2-(3-phenethylphenylamino)pyridine (835 mg).

30 NMR (DMSO-d₆, 300MHz, δ) : 2.8-2.95 (4H, m), 5.05 (2H, s), 6.61 (1H, dd, J=5Hz, 8Hz), 6.72 (1H, d, J=8Hz), 6.89 (1H, d, J=8Hz), 7.1-7.35 (6H, m), 7.43 (1H, s), 7.50 (1H, d, J=5Hz), 7.55 (1H, dd, J=1.5Hz, 8Hz), 7.67 (1H, s)

- 80 -

Preparation 32

The following compounds were obtained according to similar manners to those of Preparations 3 and 31.

5 (1) 2-(3-Acetamidophenylamino)-3-amino-6-ethoxypyridine
NMR (DMSO-d₆, δ) : 1.35 (3H, t, J=7Hz), 2.02 (3H, s), 4.35 (2H, q, J=7Hz), 6.29 (1H, d, J=7Hz), 6.82 (1H, m), 6.90 (1H, d, J=7Hz), 7.05 (1H, dd, J=8Hz, 8Hz), 7.20 (1H, m), 7.75 (1H, s), 8.35
10 (1H, s), 9.71 (1H, s)

(2) 3-Amino-2-[3-[2-(2-naphthyl)ethyl]phenylamino]-pyridine
NMR (DMSO-d₆, 300MHz, δ) : 2.9-3.1 (4H, m), 5.07
15 (2H, s), 6.61 (1H, dd, J=5Hz, 8Hz), 6.76 (1H, d, J=8Hz), 6.89 (1H, dd, J=1.5Hz, 8Hz), 7.12 (1H, t, J=8Hz), 7.4-7.6 (6H, m), 7.68 (1H, s), 7.75 (1H, s), 7.8-7.9 (3H, m)

20 Preparation 33

A mixture of 2-(3-chlorophenylamino)-3-nitropyridine (394 mg), hydrochloric acid (35% 1.3 ml) and iron powder (0.44 g) in ethanol (5 ml) was refluxed for 15 minutes. The mixture was poured into aqueous sodium bicarbonate
25 solution and extracted with ethyl acetate twice. The combined organic solution was washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-amino-
30 2-(3-chlorophenylamino)pyridine (281 mg).

NMR (DMSO-d₆, 200MHz, δ) : 5.12 (2H, s), 6.68 (1H, dd, J=5Hz, 8Hz), 6.8-7.0 (2H, m), 7.23 (1H, t, J=8Hz), 7.45-7.6 (2H, m), 7.89 (1H, t, J=2Hz), 7.96 (1H, s)

Preparation 34

The following compounds were obtained according to a similar manner to that of Preparation 33.

- 5 (1) 3-Amino-2-(3-cyanophenylamino)pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.13 (2H, s), 6.71 (1H, dd, J=5Hz, 8Hz), 6.97 (1H, dd, J=1.5Hz, 8Hz), 7.25 (1H, d, J=8Hz), 7.42 (1H, t, J=8Hz), 7.57 (1H, dd, J=1.5Hz, 5Hz), 7.82 (1H, dd, J=1.5Hz, 8Hz), 8.13 (1H, s), 8.18 (1H, t, J=1.5Hz)
- 10 (2) 3-Amino-2-(3-biphenylamino)pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.6-6.7 (1H, m), 6.92 (1H, dt, J=8Hz, 1.5Hz), 7.12 (1H, d, J=8Hz), 7.25-7.4 (2H, m), 7.45-7.6 (3H, m), 7.63 (2H, d, J=8Hz), 7.69 (1H, d, J=8Hz), 7.83 (1H, s), 7.89 (1H, s)
- 15 (3) 3-Amino-2-[3-(2-aminothiazol-4-yl)phenylamino]pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.08 (2H, s), 6.61 (1H, dd, J=5Hz, 8Hz), 6.8-6.9 (2H, m), 6.98 (2H, s), 7.15-7.3 (2H, m), 7.49 (1H, m), 7.65 (1H, d, J=8Hz), 7.76 (1H, s), 7.91 (1H, s)
- 20 (4) 3-Amino-2-[3-[2-(pyridin-3-yl)thiazol-4-yl]phenylamino]pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.12 (2H, s), 6.65 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, d, J=8Hz), 7.33 (1H, t, J=8Hz), 7.45-7.6 (3H, m), 7.82 (1H, dd, J=1.5Hz, 8Hz), 7.89 (1H, s), 8.14 (1H, s), 8.22 (1H, s), 8.38 (1H, m), 8.69 (1H, d, J=5Hz), 9.22 (1H, d, J=1.5Hz)
- 25 (5) 3-Amino-2-[3-(imidazol-4-yl)phenylamino]pyridine
- 30
- 35

- 82 -

NMR (DMSO-d₆, δ, 300MHz, δ) : 5.07 (2H, s), 6.61 (1H, dd, J=5Hz, 8Hz), 6.90 (1H, d, J=8Hz), 7.15-7.25 (2H, m), 7.4-7.8 (5H, m), 7.94 (1H, s), 12.18 (1H, br s)

5

(6) 3-Amino-2-[3-(4-methoxybenzoyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 3.87 (3H, s), 5.09 (2H, s), 6.65 (1H, dd, J=5Hz, 8Hz), 6.91 (1H, d, J=8Hz), 7.05-7.2 (3H, m), 7.38 (1H, t, J=8Hz), 7.49 (1H, m), 7.80 (2H, dt, J=8Hz, 1.5Hz), 7.9-8.05 (3H, m)

10

(7) 3-Amino-2-[3-(3-indolizinylylcarbonyl)phenylamino]-pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.60-6.75 (2H, m), 6.94 (1H, d, J=8Hz), 7.11 (1H, m), 7.22 (1H, d, J=8Hz), 7.25-7.45 (2H, m), 7.5-7.55 (2H, m), 7.75-7.85 (2H, m), 8.00 (1H, s), 8.08 (1H, s), 9.86 (1H, d, J=7Hz)

15

20

(8) 3-Amino-2-((E)-3-styrylphenylamino)pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.07 (2H, s), 6.63 (1H, dd, J=5Hz, 8Hz), 6.90 (1H, d, J=8Hz), 7.05-7.4 (7H, m), 7.5-7.65 (4H, m), 7.78 (2H, d, J=8Hz)

25

(9) 3-Amino-2-[3-((E)-2-(2-naphthyl)vinyl)phenylamino]-pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, d, J=8Hz), 7.17 (1H, d, J=8Hz), 7.2-7.65 (7H, m), 7.81 (1H, s), 7.85-8.0 (5H, m), 8.02 (1H, s)

30

(10) 3-Amino-2-[3-((E)-2-benzoylvinyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.94 (1H, dd, J=1.5Hz, 8Hz),

35

- 83 -

7.34 (1H, t, J=8Hz), 7.42 (1H, d, J=8Hz),
7.5-7.9 (8H, m), 7.98 (1H, s), 8.12 (2H, dd,
J=1.5Hz, 8Hz)

- 5 (11) 3-Amino-2-[3-((E)-2-cyanovinyl)phenylamino]pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.32 (1H,
d, J=16Hz), 6.67 (1H, dd, J=5Hz, 8Hz), 6.92 (1H,
dd, J=1.5Hz, 8Hz), 7.17 (1H, d, J=8Hz), 7.30
(1H, t, J=8Hz), 7.5-7.95 (5H, m)

10.

- (12) 3-Amino-2-[3-((E)-2-methoxycarbonylvinyl)-
phenylamino]pyridine
NMR (DMSO-d₆, 300MHz, δ) : 3.73 (3H, s), 5.08 (2H,
s), 6.49 (1H, d, J=16Hz), 6.66 (1H, dd, J=5Hz,
15 8Hz), 6.93 (1H, d, J=8Hz), 7.15-7.35 (2H, m),
7.5-7.75 (3H, m), 7.85 (1H, s), 7.90 (1H, s)

- (13) 3-Amino-2-[3-(N-methylacetamido)phenylamino]pyridine
NMR (DMSO-d₆, 200MHz, δ) : 1.83 (3H, s), 3.16 (3H,
20 s), 5.09 (2H, s), 6.65 (1H, dd, J=5Hz, 8Hz),
6.77 (1H, d, J=8Hz), 6.92 (1H, dd, J=1.5Hz,
8Hz), 7.28 (1H, t, J=8Hz), 7.5-7.65 (3H, m),
7.90 (1H, s)

- 25 (14) 3-Amino-2-[3-(4-phenylthiazol-2-yl)aminophenylamino]-
pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.67 (1H,
dd, J=5Hz, 8Hz), 6.92 (1H, m), 7.0-7.55 (6H, m),
7.53 (1H, d, J=5Hz), 7.73 (1H, s), 7.91 (2H, d,
30 J=8Hz), 8.19 (1H, s)

- (15) 3-Amino-2-[3-(4-methylthiazol-2-yl)aminophenylamino]-
pyridine
NMR (DMSO-d₆, 300MHz, δ) : 2.21 (3H, s), 5.09 (2H,
35 s), 6.39 (1H, s), 6.62 (1H, dd, J=5Hz, 8Hz),

- 84 -

6.89 (1H, d, J=8Hz), 7.05-7.3 (3H, m), 7.49 (1H, d, J=5Hz), 7.68 (1H, s), 7.89 (1H, s)

5 (16) 3-Amino-2-[3-(pyrimidin-2-yl)aminophenylamino]-pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.08 (2H, s), 6.60 (1H, dd, J=5Hz, 8Hz), 6.79 (1H, d, J=5Hz), 6.88 (1H, d, J=8Hz), 7.10 (1H, t, J=8Hz), 7.22 (1H, m), 7.30 (1H, m), 7.48 (1H, d, J=5Hz), 7.66 (1H, s), 10 7.92 (1H, t, J=1.5Hz), 8.45 (2H, d, J=5Hz), 9.47 (1H, s)

(17) 3-Amino-2-[3-(pyrimidin-2-yl)oxyphenylamino]pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.6-6.7 (2H, m), 6.91 (1H, d, J=8Hz), 7.2-7.3 (2H, m), 15 7.4-7.55 (2H, m), 7.60 (1H, s), 7.89 (1H, s), 8.65 (2H, d, J=5Hz)

(18) 3-Amino-2-[3-(4-phenylpyrimidin-2-yl)oxyphenylamino]pyridine
NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.63 (1H, dd, J=5Hz, 8Hz), 6.72 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 7.30 (1H, t, J=8Hz), 7.45-7.6 (5H, m), 7.69 (1H, s), 7.84 (1H, d, J=5Hz), 7.91 (1H, s), 25 s), 8.1-8.2 (2H, m), 8.68 (1H, d, J=5Hz)

Preparation 35

4N Aqueous solution of sodium hydroxide (2 ml) was added to a solution of ethyl 3-(benzoylamino)benzoate (695 mg) in ethanol (5 ml) and 1,4-dioxane (5 ml). After 30 stirred at 50°C for 1 hour, the mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with dilute hydrochloric acid and brine, dried over magnesium sulfate and concentrated 35 to give 3-(benzoylamino)benzoic acid (595 mg) as solid.

- 85 -

NMR (DMSO-d₆, 300MHz, δ) : 7.45-7.75 (5H, m), 7.99 (2H, d, J=8Hz), 8.05 (1H, d, J=8Hz), 8.44 (1H, s)

5 Preparation 36

The following compound was obtained according to a similar manner to that of Preparation 35.

3-(Pyrimidin-2-yl)oxybenzoic acid

10 NMR (DMSO-d₆, 300MHz, δ) : 7.30 (1H, t, J=5Hz), 7.48 (1H, d, J=8Hz), 7.58 (1H, t, J=8Hz), 7.69 (1H, s), 7.84 (1H, d, J=8Hz), 8.67 (2H, d, J=5Hz)

Preparation 37

15 4N Aqueous solution of sodium hydroxide (1 ml) was added to a solution of ethyl 3-[(3-nitropyridin-2-yl)amino]benzoate (322 mg) in ethanol (2 ml) and 1,4-dioxane (2 ml). After stirred at room temperature for 1 hour, the mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase
20 was washed with water and brine, dried over magnesium sulfate and concentrated to give 3-[(3-nitropyridin-2-yl)amino]benzoic acid (263 mg) as solid.

25 NMR (DMSO-d₆, 300MHz, δ) : 7.03 (1H, dd, J=5Hz, 8Hz), 7.49 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.88 (1H, d, J=8Hz), 8.26 (1H, s), 8.5-8.6 (2H, m), 10.03 (1H, s)

Preparation 38

30 A mixture of 3-nitrostyrene (4.6 ml), 3-bromopyridine (2.6 ml), palladium(II) acetate (0.20 g), tetrabutylammonium chloride (8.4 g) and sodium bicarbonate (6.3 g) in N,N-dimethylformamide (40 ml) was stirred at 110°C for 3 hours. Then the mixture was poured into
35 aqueous sodium bicarbonate and extracted with ethyl

- 86 -

acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-[(E)-2-(3-nitrophenyl)vinyl]pyridine (5.34 g).

NMR (CDCl₃, 300MHz, δ) : 7.21 (2H, s), 7.33 (1H, dd, J=5Hz, 8Hz), 7.57 (1H, t, J=8Hz), 7.8-7.9 (2H, m), 8.13 (1H, dd, J=2Hz, 8Hz), 8.38 (1H, t, J=2Hz), 8.55 (1H, d, J=5Hz), 8.78 (1H, d, J=2Hz)

10

Preparation 39

The following compound was obtained according to a similar manner to that of Preparation 38.

15 5-[(E)-2-(3-Nitrophenyl)vinyl]pyrimidine

NMR (DMSO-d₆, 300MHz, δ) : 7.51 (1H, d, J=16Hz), 7.7-7.8 (2H, m), 8.09 (1H, d, J=8Hz), 8.18 (1H, dd, J=2Hz, 8Hz), 8.47 (1H, s), 9.10 (3H, m)

20 Preparation 40

A mixture of 1-iodo-3-nitrobenzene (7.47 g), 2-vinylpyridine (4.73 g), palladium(II) acetate (0.20 g), tetrabutylammonium chloride (8.34 g) and sodium bicarbonate (6.3 g) in N,N-dimethylformamide (50 ml) was stirred at 110°C for 5 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-[(E)-2-(3-nitrophenyl)vinyl]pyridine (3.37 g).

30 NMR (CDCl₃, 300MHz, δ) : 7.15-7.3 (2H, m), 7.41 (1H, d, J=8Hz), 7.54 (1H, t, J=8Hz), 7.65-7.75 (2H, m), 8.13 (1H, dd, J=2Hz, 8Hz), 8.43 (1H, s), 8.64 (1H, d, J=5Hz)

35

- 87 -

Preparation 41

To a solution of 2-bromonaphthalene (5.0 g) and tetrakis(triphenylphosphine)palladium(0) (0.56 g) in toluene (50 ml) was added a solution of dihydroxy(3-nitrophenyl)borane (4.44 g) in methanol and 2M sodium carbonate solution in water (12 ml). The resulting mixture was stirred at 80°C for 4 hours and extracted with ethyl acetate. After evaporation of the solvent, the crude residue was crystallized from hexane to give 3-(2-naphthyl)-1-nitrobenzene (5.4 g).

NMR (CDCl₃, δ) : 7.54 (2H, m), 7.65 (1H, t, J=8Hz), 7.75 (1H, d, J=8Hz), 7.91 (2H, m), 7.98 (1H, d, J=8Hz), 8.05 (1H, dd, J=9Hz, 2Hz), 8.11 (1H, s), 8.23 (1H, dd, J=8Hz, 2Hz), 8.59 (1H, s)

Preparation 42

To a suspension of sodium hydride (60% in oil, 0.75 g) in N,N-dimethylformamide (20 ml) was added a solution of diethyl 3-nitrobenzylphosphonate (4.40 g) in N,N-dimethylformamide (20 ml). The mixture was stirred at room temperature for 15 minutes, then a solution of 4-quinolinecarbaldehyde (2.81 g) in N,N-dimethylformamide (20 ml) was added thereto. After stirring at 50°C for 30 minutes, the mixture was poured into aqueous sodium bicarbonate, and extracted with ethyl acetate twice. The combined organic solution was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (chloroform-methanol (50:1)) to give 4-[(E)-2-(3-nitrophenyl)vinyl]quinoline (1.57 g) as a solid.

NMR (DMSO-d₆, 300MHz, δ) : 7.65-7.85 (4H, m), 7.89 (1H, d, J=5Hz), 8.07 (1H, d, J=8Hz), 8.21 (1H, dd, J=2Hz, 8Hz), 8.3-8.4 (2H, m), 8.62 (1H, d, J=8Hz), 8.70 (1H, t, J=2Hz), 8.94 (1H, d, J=5Hz)

- 88 -

Preparation 43

The following compound was obtained according to a similar manner to that of Preparation 42.

5 2-[(E)-2-(3-Nitrophenyl)vinyl]quinoline
NMR (DMSO-d₆, 300MHz, δ) : 7.60 (1H, t, J=8Hz),
7.65-7.85 (3H, m), 7.9-8.05 (4H, m), 8.15-8.3
(2H, m), 8.41 (1H, d, J=8Hz), 8.57 (1H, t,
J=2Hz)

10

Preparation 44

A mixture of 3-[(E)-2-(3-nitrophenyl)vinyl]pyridine (3.64 g), iron powder (3.6 g) and hydrochloric acid (35%, 11 ml) in ethanol (30 ml) was stirred at 80°C for 4 hours.

15 Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and
20 washed with isopropyl ether to give 3-[(E)-2-(3-aminophenyl)vinyl]pyridine (1.25 g).

NMR (DMSO-d₆, 300MHz, δ) : 5.12 (2H, s), 6.52 (1H, dd, J=2Hz, 8Hz), 6.75-6.85 (2H, m), 7.0-7.15 (2H, m), 7.23 (1H, d, J=16Hz), 7.39 (1H, m),
25 8.02 (1H, m), 8.45 (1H, d, J=5Hz), 8.75 (1H, d, J=2Hz)

Preparation 45

A mixture of 3-(2-naphthyl)-1-nitrobenzene (5.4 g),
30 iron (3.63 g) and acetic acid (13.0 g) in ethanol (50 ml) was stirred under reflux for 3 hours. The reaction mixture was diluted with chloroform, filtered and treated with saturated sodium bicarbonate solution. The chloroform layer was separated, dried, evaporated and
35 chromatographed on silica gel to give 3-(2-

- 89 -

naphthyl)aniline (5.2 g).

NMR (CDCl₃, δ) : 3.75 (2H, br s), 6.70 (1H, dd, J=8Hz, 2Hz), 7.03 (1H, s), 7.12 (1H, d, J=8Hz), 7.27 (1H, dd, J=8Hz, 8Hz), 7.47 (2H, m), 7.70 (1H, dd, J=8Hz, 2Hz), 7.87 (3H, m), 8.01 (1H, s)

Preparation 46

The following compounds were obtained according to a similar manner to that of Preparation 3, 21, 23, 44 or 45.

(1) 2-[(E)-2-(3-Aminophenyl)vinyl]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.12 (2H, s), 6.53 (1H, dd, J=2Hz, 8Hz), 6.75-6.85 (2H, m), 7.0-7.15 (2H, m), 7.23 (1H, dd, J=5Hz, 8Hz), 7.45-7.6 (2H, m), 7.78 (1H, t, J=8Hz), 8.56 (1H, d, J=5Hz)

(2) 5-[(E)-2-(3-Aminophenyl)vinyl]pyrimidine

NMR (DMSO-d₆, 300MHz, δ) : 5.17 (2H, s), 6.55 (1H, dd, J=2Hz, 8Hz), 6.79 (2H, m), 7.0-7.1 (2H, m), 7.39 (1H, d, J=16Hz), 9.03 (3H, m)

(3) 4-[(E)-2-(3-Aminophenyl)vinyl]quinoline

NMR (DMSO-d₆, 300MHz, δ) : 5.15 (2H, s), 6.60 (1H, dd, J=2Hz, 8Hz), 6.95-7.05 (2H, m), 7.11 (1H, t, J=8Hz), 7.45 (1H, d, J=16Hz), 7.67 (1H, t, J=8Hz), 7.75-7.95 (3H, m), 8.05 (1H, d, J=8Hz), 8.44 (1H, d, J=8Hz), 8.88 (1H, d, J=5Hz)

(4) 2-[(E)-2-(3-Aminophenyl)vinyl]quinoline

NMR (DMSO-d₆, 300MHz, δ) : 5.18 (2H, s), 6.59 (1H, d, J=8Hz), 6.85-6.95 (2H, m), 7.10 (1H, t, J=8Hz), 7.31 (1H, d, J=16Hz), 7.56 (1H, t, J=8Hz), 7.65-7.8 (2H, m), 7.85-8.0 (3H, m), 8.33 (1H, d, J=8Hz)

- 90 -

(5) 3-(3-Biphenylyl)aniline

NMR (CDCl₃, δ) : 3.74 (2H, s), 6.69 (1H, dd, J=8Hz,
2Hz), 6.95 (1H, t, J=2Hz), 7.02 (1H, d, J=8Hz),
7.24 (1H, m), 7.35 (1H, m), 7.4-7.6 (5H, m),
7.64 (2H, m), 7.79 (1H, s)

5

Preparation 47

A mixture of 2-chloro-3-nitropyridine (1.15 g),
3-[(E)-2-(3-aminophenyl)vinyl]pyridine (1.23 g) and
10 potassium carbonate (1.1 g) in 1,4-dioxane (15 ml) was
stirred under reflux for 22 hours. After cooling,
insoluble materials were removed by filtration and the
filtrate was concentrated. The residue was
chromatographed on silica gel column (2% methanol in
15 chloroform) to give 3-nitro-2-[3-[(E)-2-(3-pyridyl)vinyl]-
phenylamino]pyridine (510 mg) as an orange solid.

NMR (DMSO-d₆, 300MHz, δ) : 7.02 (1H, m), 7.3-7.5
(5H, m), 7.65 (1H, m), 7.89 (1H, s), 8.08 (1H,
d, J=8Hz), 8.48 (1H, d, J=5Hz), 8.5-8.6 (2H, m),
20 8.80 (1H, d, J=2Hz)

Preparation 48

A mixture of 3-(2-naphthyl)aniline (5.0 g), 2-chloro-
3-nitropyridine (3.62 g) and potassium carbonate (6.31 g)
25 in dioxane (50 ml) was stirred under reflux for 6 days.
The reaction mixture was extracted with chloroform and
evaporated. Crude residue was chromatographed on silica
gel to give 2-[3-(2-naphthyl)phenylamino]-3-nitropyridine
as an orange crystal (5.23 g).

30 NMR (DMSO-d₆, δ) : 7.02 (1H, dd, J=8Hz, 5Hz), 7.55
(4H, m), 7.75 (1H, m), 7.85-8.1 (5H, m), 8.26
(1H, s), 8.55 (2H, m)

Preparation 49

35 A mixture of 2-chloro-3-nitropyridine (8.5 g), 3-

- 91 -

iodoaniline (12.5 g) and potassium carbonate (9.0 g) in 1,4-dioxane (100 ml) was stirred under reflux for 20 hours. After cooling, insoluble materials were removed by filtration and the filtrate was concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-(3-iodophenylamino)-3-nitropyridine (3.88 g) as an orange solid.

NMR (CDCl₃, 300MHz, δ) : 6.89 (1H, dd, J=5Hz, 8Hz), 7.11 (1H, t, J=8Hz), 7.50 (1H, d, J=8Hz), 7.60 (1H, dd, J=2, 8Hz), 8.12 (1H, s), 8.45-8.6 (2H, m)

Preparation 50

The following compounds were obtained according to a similar manner to that of Preparation 1, 5, 27, 28, 47, 48 or 49.

(1) 3-Nitro-2-[3-[(E)-2-(2-pyridyl)vinyl]phenylamino]-pyridine

NMR (CDCl₃, 300MHz, δ) : 6.87 (1H, dd, J=2Hz, 8Hz), 7.4-7.8 (7H, m), 7.98 (1H, s), 8.05-8.2 (2H, m), 8.5-8.6 (2H, m)

(2) 3-Nitro-2-[3-[(E)-2-(5-pyrimidinyl)vinyl]phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 7.02 (1H, dd, J=5Hz, 8Hz), 7.28 (1H, d, J=16Hz), 7.49-7.5 (2H, m), 7.58 (1H, d, J=16Hz), 7.68 (1H, m), 7.90 (1H, s), 8.5-8.6 (2H, m), 9.0-9.1 (3H, m)

(3) 3-Nitro-2-[3-[(E)-2-(4-quinolyl)vinyl]phenylamino]-pyridine

NMR (DMSO-d₆, 300MHz, δ) : 7.02 (1H, dd, J=5, 8Hz), 7.47 (1H, t, J=8Hz), 7.55-7.85 (6H, m), 7.89 (1H, d, J=5Hz), 8.05-8.2 (6H, m), 8.5-8.6 (3H,

- 92 -

m), 8.90 (1H, d, J=5Hz)

(4) 3-Nitro-2-[3-[(E)-2-(2-quinolyl)vinyl]phenylamino]-pyridine

5 NMR (DMSO-d₆, 300MHz, δ) : 7.03 (1H, dd, J=5, 8Hz),
7.4-7.6 (4H, m), 7.7-8.05 (7H, m), 8.37 (1H, d,
J=8Hz), 8.55-8.6 (2H, m)

(5) 2-[3-(2-Cyanopyrrol-1-yl)phenylamino]-3-nitropyridine

10 NMR (DMSO-d₆, δ) : 6.46 (1H, m), 7.06 (1H, m), 7.25
(1H, m), 7.31 (1H, m), 7.56 (1H, m), 7.78 (1H,
m), 8.03 (1H, m), 8.56 (2H, m)

(6) 2-[3-(Benzothiazol-2-yl)phenylamino]-3-nitropyridine

15 NMR (DMSO-d₆, δ) : 7.06 (1H, dd, J=8Hz, 4Hz), 7.50
(1H, dd, J=8Hz, 8Hz), 7.57 (2H, dd, J=8Hz, 8Hz),
7.88 (2H, m), 8.09 (1H, d, J=8Hz), 8.18 (1H, d,
J=8Hz), 8.46 (1H, m), 8.57 (2H, m)

20 (7) 2-(3-Benzoylphenylamino)-3-nitropyridine

NMR (CDCl₃, δ) : 6.88 (1H, dd, J=8Hz, 5Hz), 7.51
(3H, m), 7.60 (2H, m), 7.88 (3H, m), 8.14 (1H,
m), 8.49 (1H, dd, J=5Hz, 2Hz), 8.55 (1H, dd,
J=8Hz, 2Hz)

25

(8) 2-(3-Trifluoromethylphenylamino)-3-nitropyridine

NMR (DMSO-d₆, δ) : 7.05 (1H, dd, J=8Hz, 4Hz), 7.45
(1H, d, J=8Hz), 7.60 (1H, dd, J=8Hz, 8Hz), 7.92
(1H, d, J=8Hz), 8.12 (1H, s), 8.53 (2H, m)

30

(9) 2-[3-(Indol-1-yl)phenylamino]-3-nitropyridine

NMR (CDCl₃, δ) : 6.70 (1H, d, J=3Hz), 6.89 (1H, dd,
J=8Hz, 4Hz), 7.17 (1H, m), 7.21 (1H, m), 7.30
(1H, m), 7.39 (1H, d, J=3Hz), 7.50 (2H, m), 7.72
35 (2H, m), 8.10 (1H, m), 8.50 (1H, m), 8.55 (1H,

- 93 -

m)

(10) 2-(3-Carboxyphenylamino)-3-nitropyridine

5 NMR (DMSO-d₆, δ) : 7.03 (1H, dd, J=8Hz, 5Hz), 7.50
(1H, dd, J=8Hz, 8Hz), 7.71 (1H, m), 7.88 (1H,
m), 8.25 (1H, m), 8.55 (2H, m)

(11) 2-[(5-Acetamido-2-fluorophenyl)amino]-3-nitropyridine

10 NMR (CDCl₃, δ) : 2.15 (3H, s), 6.92 (1H, dd, J=8Hz,
.5Hz), 7.11 (1H, dd, J=8Hz, 8Hz), 7.35 (1H, m),
8.55 (3H, m)

(12) 2-[3-(1-Naphthyl)phenylamino]-3-nitropyridine

15 NMR (CDCl₃, δ) : 6.83 (1H, dd, J=8Hz, 5Hz), 7.31
(1H, d, J=7Hz), 7.4-7.55 (5H, m), 7.74 (1H, dd,
J=8Hz, 2Hz), 7.79 (1H, m), 7.90 (2H, m), 8.00
(1H, d, J=8Hz), 8.47 (1H, m), 8.53 (1H, d,
J=8Hz)

20 (13) 2-[3-(3-Biphenyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, δ) : 6.86 (1H, dd, J=8Hz, 6Hz), 7.39
(1H, m), 7.4-7.7 (11H, m), 7.83 (1H, s), 7.89
(1H, s), 8.50 (2H, m)

25 Preparation 51

A mixture of 2-(3-iodophenylamino)-3-nitropyridine
(3.86 g), 4-vinylpyridine (1.78 g), palladium(II) acetate
(80 mg), tetrabutylammonium chloride (3.14 g) and sodium
bicarbonate (2.4 g) in N,N-dimethylformamide (20 ml) was
30 stirred at 110°C for 22 hours. Then the mixture was
poured into aqueous sodium bicarbonate and extracted with
ethyl acetate twice. The combined organic phase was
washed with aqueous sodium bicarbonate and brine, dried
over magnesium sulfate and concentrated. The residue was
35 chromatographed on silica gel column (chloroform-methanol

- 94 -

(50:1)) to give 3-nitro-2-[3-[(E)-2-(4-pyridyl)vinyl]-phenylamino]pyridine (1.41 g) as an orange solid.

NMR (CDCl₃, 300MHz, δ) : 6.88 (1H, dd, J=5Hz, 8Hz),
7.07 (1H, d, J=16Hz), 7.3-7.5 (5H, m), 7.62 (1H,
5 d, J=8Hz), 7.85 (1H, s), 8.5-8.65 (4H, m)

Preparation 52

A mixture of 3-nitro-2-[3-[(E)-2-(3-pyridyl)vinyl]-phenylamino]pyridine (493 mg), iron powder (0.35 g) and
10 hydrochloric acid (35%, 1 ml) in methanol (5 ml) was stirred under reflux for 4 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried
15 over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-amino-2-[3-[(E)-2-(3-pyridyl)vinyl]phenylamino]-pyridine (291 mg).

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.66 (1H,
20 dd, J=5Hz, 8Hz), 6.92 (1H, d, J=8Hz), 7.1-7.45 (5H, m), 7.54 (1H, d, J=5Hz), 7.62 (1H, d, J=8Hz), 7.80 (2H, d, J=8Hz), 8.08 (1H, d, J=8Hz), 8.47 (1H, d, J=5Hz), 8.79 (1H, d, J=2Hz)

25 Preparation 53

A mixture of 3-nitro-2-[3-[(E)-2-(4-pyridyl)vinyl]-phenylamino]pyridine (1.38 g), iron powder (1.0 g) and hydrochloric acid (35%, 3.0 ml) in ethanol (10 ml) was stirred at 80°C for 2 hours. Then the mixture was poured
30 into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (8% methanol in chloroform) to give
35 3-amino-2-[3-[(E)-2-(4-pyridyl)vinyl]phenylamino]pyridine

- 95 -

(1.14 g) as powder.

NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.65 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, d, J=8Hz), 7.1-7.2 (2H, m), 7.28 (1H, t, J=8Hz), 7.45-7.7 (5H, m), 7.82 (1H, s), 7.88 (1H, s), 8.54 (2H, d, J=5Hz)

Preparation 54

A mixture of 2-[3-(2-naphthyl)phenylamino]-3-nitropyridine (3.0 g), iron (2.46 g) and acetic acid (5.28 g) in ethanol (14 ml) was stirred under reflux for 6 hours. The reaction mixture was diluted with chloroform, filtered and treated with saturated sodium bicarbonate solution. The chloroform layer was separated, dried, evaporated and chromatographed on silica gel to give 2-[3-(2-naphthyl)phenylamino]-3-aminopyridine (1.2 g, 43.9%).

NMR (CDCl₃, δ) : 5.10 (2H, s), 6.65 (1H, dd, J=8Hz, 6Hz), 6.94 (1H, dd, J=8Hz, 2Hz), 7.28 (1H, m), 7.37 (1H, dd, J=8Hz, 8Hz), 7.53 (3H, m), 7.77 (1H, m), 7.81 (1H, d, J=8Hz), 7.90 (1H, s), 7.95 (1H, m), 8.00 (3H, m), 8.16 (1H, s)

Preparation 55

The following compounds were obtained according to a similar manner to that of Preparation 3, 31, 33, 52, 53 or 54.

(1) 3-Amino-2-[3-[(E)-2-(2-pyridyl)vinyl]phenylamino]-pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.66 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, d, J=8Hz), 7.1-7.3 (4H, m), 7.55-7.7 (4H, m), 7.75-7.85 (2H, m), 7.90 (1H, s), 8.59 (1H, d, J=5Hz)

(2) 3-Amino-2-[3-[(E)-2-(5-pyrimidinyl)vinyl]phenylamino]pyridine

- 96 -

5 NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.66 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, d, J=8Hz), 7.1-7.2 (2H, m), 7.29 (1H, t, J=8Hz), 7.45-7.55 (2H, m), 7.62 (1H, d, J=8Hz), 7.83 (2H, d, J=8Hz), 9.0-9.1 (1H, m)

(3) 3-Amino-2-[3-[(E)-2-(2-quinolyl)vinyl]phenylamino]-pyridine

10 NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.68 (1H, dd, J=5Hz, 8Hz), 6.95 (1H, d, J=8Hz), 7.2-7.45 (3H, m), 7.5-7.6 (2H, m), 7.65 (1H, d, J=8Hz), 7.7-8.05 (7H, m), 8.36 (1H, d, J=8Hz)

15 (4) 3-Amino-2-[3-[(E)-2-(4-quinolyl)vinyl]phenylamino]-pyridine

20 NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.94 (1H, d, J=8Hz), 7.3-7.45 (2H, m), 7.5-7.6 (2H, m), 7.65-8.1 (8H, m), 8.48 (1H, d, J=8Hz), 8.89 (1H, d, J=5Hz)

(5) 2-[3-(Benzothiazol-2-yl)phenylamino]-3-aminopyridine

25 NMR (DMSO-d₆, δ) : 5.15 (2H, s), 6.70 (1H, dd, J=8Hz, 5Hz), 6.97 (1H, dd, J=8Hz, 2Hz), 7.4-7.5 (2H, m), 7.56 (3H, m), 7.96 (1H, dd, J=8Hz, 2Hz), 8.08 (2H, m), 8.16 (1H, d, J=8Hz), 8.40 (1H, m)

(6) 2-[3-(3-Acetylmethylindol-1-yl)phenylamino]-3-aminopyridine

30 NMR (CDCl₃, δ) : 2.57 (3H, s), 3.49 (2H, br s), 6.49 (1H, s), 6.80 (1H, dd, J=8Hz, 5Hz), 7.05 (2H, m), 7.30 (4H, m), 7.45 (1H, dd, J=9Hz, 8Hz), 7.61 (1H, m), 7.68 (1H, m), 7.87 (1H, m), 7.95 (1H, s), 8.44 (1H, m)

(7) 2-[3-(2-Cyanopyrrol-1-yl)phenylamino]-3-aminopyridine

35 NMR (DMSO-d₆, δ) : 5.13 (2H, s), 6.43 (1H, m), 6.67

- 97 -

(1H, m), 6.95 (2H, m), 7.20 (1H, m), 7.40 (1H, dd, J=8Hz, 8Hz), 7.48 (1H, m), 7.52 (1H, m), 7.66 (1H, m), 7.98 (1H, m), 8.10 (1H, s)

5 (8) 2-(3-Benzoylphenylamino)-3-aminopyridine

NMR (CDCl₃, δ) : 3.45 (2H, br s), 6.37 (1H, s), 6.79 (1H, dd, J=8Hz, 5Hz), 7.02 (1H, dd, J=8Hz, 2Hz), 7.38 (2H, m), 7.49 (2H, m), 7.60 (2H, m), 7.69 (1H, m), 7.84 (3H, m)

10

(9) 2-(3-Trifluoromethylphenylamino)-3-aminopyridine

NMR (CDCl₃, δ) : 3.41 (2H, br s), 6.38 (1H, br s), 6.82 (1H, dd, J=8Hz, 5Hz), 7.05 (1H, dd, J=8Hz, 2Hz), 7.18 (1H, d, J=8Hz), 7.37 (1H, dd, J=8Hz, 8Hz), 7.49 (1H, d, J=8Hz), 7.55 (1H, br s), 7.85 (1H, dd, J=5Hz, 2Hz)

15

(10) 2-(3-Methoxycarbonylphenylamino)-3-aminopyridine

NMR (DMSO-d₆, δ) : 3.83 (3H, s), 5.30 (2H, br s), 6.68 (1H, dd, J=8Hz, 6Hz), 6.95 (1H, d, J=8Hz), 7.37 (1H, dd, J=8Hz, 8Hz), 7.44 (1H, d, J=8Hz), 7.51 (1H, d, J=6Hz), 7.99 (1H, d, J=8Hz), 8.09 (1H, s), 8.18 (1H, s)

20

25 (11) 2-[(5-Acetamido-2-fluorophenyl)amino]-3-aminopyridine

NMR (CDCl₃, δ) : 2.09 (3H, s), 6.80 (1H, dd, J=8Hz, 5Hz), 7.00 (1H, dd, J=8Hz, 8Hz), 7.05 (1H, dd, J=8Hz, 2Hz), 7.22 (1H, m), 7.72 (2H, m)

30 (12) 2-[3-(1-Indolyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.43 (2H, br s), 6.35 (1H, s), 6.67 (1H, m), 6.80 (1H, m), 7.05 (2H, m), 7.20 (3H, m), 7.38 (2H, m), 7.55 (1H, s), 7.69 (1H, dd, J=8Hz, 8Hz), 7.83 (1H, d, J=3Hz)

35

- 98 -

(13) 2-[3-(1-Naphthyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.40 (2H, br s), 6.29 (1H, s), 6.75
(1H, dd, J=8Hz, 6Hz), 6.97 (1H, d, J=8Hz), 7.08
(1H, m), 7.30 (1H, s), 7.35-7.55 (6H, m), 7.85
(3H, m), 8.01 (1H, d, J=8Hz)

(14) 2-[3-(3-Biphenylyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.45 (2H, br s), 6.30 (1H, s),
6.80 (1H, dd, J=8Hz, 6Hz), 7.03 (1H, d, J=8Hz),
7.2-7.7 (12H, m), 7.80 (1H, m), 7.87 (1H, m)

Preparation 56

A mixture of 2-[3-(indol-1-yl)phenylamino]-3-nitropyridine (1.0 g), acetic anhydride (0.46 g), and aluminum chloride (1.21 g) in dry methylene chloride (10 ml) was stirred at room temperature for 3 hours. The reaction mixture was treated with 1N sodium hydroxide solution and precipitated brown crystals were collected, washed with water and dried to give 2-[3-(3-acety lindol-1-yl)phenylamino]-3-nitropyridine (1.17 g).

NMR (DMSO-d₆, δ) : 2.54 (3H, s), 7.06 (1H, dd, J=8Hz, 6Hz), 7.33 (2H, m), 7.45 (1H, m), 7.63 (1H, dd, J=8Hz, 8Hz), 7.73 (1H, m), 7.78 (1H, m), 8.09 (1H, m), 8.32 (1H, m), 8.57 (1H, m), 8.66 (1H, s)

Preparation 57

The following compounds were obtained according to a similar manner to that of Preparation 41.

(1) 3-(1-Naphthyl)-1-nitrobenzene

NMR (CDCl₃, δ) : 7.4-7.6 (4H, m), 7.68 (1H, t, J=8Hz), 7.77 (1H, d, J=8Hz), 7.83 (1H, dd, J=8Hz, 2Hz), 7.93 (2H, m), 8.30 (1H, dd, J=8Hz, 2Hz), 8.39 (1H, m)

- 99 -

(2) 3-(3-Biphenylyl)-1-nitrobenzene

NMR (CDCl₃, δ) : 7.35-7.75 (9H, m), 7.82 (1H, s),
7.98 (1H, d, J=8Hz), 8.23 (1H, dd, J=8Hz, 2Hz),
8.50 (1H, m)

5

Preparation 58

To a solution of 2-methyl-4-(3-aminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (7.4 g) and triethylamine (5.72 ml) in dioxane was added 3,5-dichlorobenzoyl chloride (6.14 g) in dropwise. The mixture was stirred for 3 hours at room temperature. The reaction mixture was quenched by water and extracted with ethyl acetate (100 ml). The crude product was purified by chromatography to obtain 2-methyl-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (4.4 g).

15

NMR (CDCl₃, 300MHz, δ) : 9.09 (1H, br s), 8.38 (1H, m), 8.19 (1H, d, J=7Hz), 7.80 (1H, s), 7.68 (2H, s), 7.52 (1H, d, J=6Hz), 7.39 (1H, s), 7.35-7.23 (2H, m), 6.54 (1H, d, J=6Hz), 2.73 (3H, s)

20

Preparation 59

A mixture of 3-nitrophenylhydrazine hydrochloride (8.77 g) and 1,3,5-triazine (2.50 g) in ethanol (40 ml) was stirred under reflux for 4 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (hexane - ethyl acetate, 3:7) to give 1-(3-nitrophenyl)-1H-1,2,4-triazole (2.89 g) as a solid.

25

30

NMR (CDCl₃, 300MHz, δ) : 7.74 (1H, t, J=8Hz), 8.10 (1H, dt, J=8Hz, 2Hz), 8.18 (1H, s), 8.28 (1H, dt, J=8Hz, 2Hz), 8.60 (1H, t, J=2Hz), 8.70 (1H, s)

35

- 100 -

Preparation 60

To a solution of morpholine (5.0 ml) in dichloromethane (50 ml) was added 3-nitrobenzoyl chloride (5.05 g). The mixture was stirred at room temperature for 15 minutes, then poured into a mixture of ethyl acetate and water. The organic phase was separated, washed with dilute hydrochloric acid, sodium bicarbonate and brine, dried over magnesium sulfate and concentrated to give 4-(3-nitrophenylcarbonyl)morpholine (6.46 g).

10 NMR (CDCl₃, 300MHz, δ) : 3.3-4.0 (8H, m), 7.65 (1H, t, J=8Hz), 7.78 (1H, dt, J=8Hz, 2Hz), 8.30 (2H, m)

Preparation 61

15 To a mixture of 4-bromopyridine hydrochloride (5.25 g) and tetrakis(triphenylphosphine)palladium(0) (0.93 g) in toluene (50 ml) was added 3M aqueous solution of sodium bicarbonate (27 ml) and a solution of dihydroxy(3-nitrophenyl)borane (5.0 g) in methanol (12 ml). The mixture was stirred at 80°C for 1 hour and cooled. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (1%-2% methanol in chloroform) to give 4-(3-nitrophenyl)pyridine (3.46 g).

20 NMR (CDCl₃, 300MHz, δ) : 7.57 (2H, dd, J=2Hz, 5Hz), 7.70 (1H, t, J=8Hz), 7.98 (1H, dt, J=8Hz, 2Hz), 8.32 (1H, m), 8.51 (1H, t, J=2Hz), 8.76 (2H, d, J=5Hz)

30

Preparation 62

To a mixture of 2-bromopyridine (1.91 ml) and tetrakis(triphenylphosphine)palladium(0) (0.46 g) in 1,2-dimethoxyethane (40 ml) was added 2M aqueous solution

35

- 101 -

of sodium bicarbonate (20 ml) and a solution of dihydroxy(3-nitrophenyl)borane (3.67 g) in methanol (10 ml). The mixture was stirred at 80°C for 2.5 hours and cooled. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (hexane - ethyl acetate (3:1)) to give 2-(3-nitrophenyl)pyridine (1.35 g).

NMR (CDCl₃, 300MHz, δ) : 7.32 (1H, m), 7.65 (1H, t, J=8Hz), 7.83 (2H, m), 8.27 (1H, m), 8.38 (1H, d, J=8Hz), 8.73 (1H, m), 8.87 (1H, t, J=2Hz)

15 Preparation 63

To a mixture of 3-bromopyridine (2.6 ml) and tetrakis(triphenylphosphine)palladium(0) (0.93 g) in toluene (50 ml) was added 2M aqueous solution of sodium bicarbonate (27 ml) and a solution of dihydroxy(3-nitrophenyl)borane (5.0 g) in methanol (12 ml). The mixture was stirred at 80°C for 6 hours and cooled. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel (hexane - ethyl acetate (3:7)) to give 3-(3-nitrophenyl)pyridine (3.57 g).

NMR (CDCl₃, 300MHz, δ) : 7.46 (1H, dd, J=5Hz, 8Hz), 7.69 (1H, t, J=8Hz), 7.9-8.0 (2H, m), 8.28 (1H, dt, J=8Hz, 2Hz), 8.47 (1H, t, J=2Hz), 8.70 (1H, dd, J=2Hz, 5Hz), 8.90 (1H, d, J=2Hz)

Preparation 64

The following compounds were obtained according to a similar manner to that of Preparation 41, 61, 62 or 63.

- 102 -

(1) 2-(3-Nitrophenyl)thiophene

NMR (CDCl₃, 300MHz, δ) : 7.13 (1H, dd, J=4Hz, 5Hz),
7.39 (1H, dd, J=1Hz, 5Hz), 7.45 (1H, dd, J=1Hz,
4Hz), 7.55 (1H, t, J=8Hz), 7.91 (1H, m), 8.12
5 (1H, dt, J=8Hz, 2Hz), 8.47 (1H, t, J=2Hz)

(2) 2-Chloro-5-(3-nitrophenyl)thiophene

NMR (CDCl₃, 300MHz, δ) : 6.97 (1H, d, J=4Hz), 7.21
(1H, d, J=4Hz), 7.57 (1H, t, J=8Hz), 7.80 (1H,
10 dt, J=8Hz, 2Hz), 8.14 (1H, dt, J=8Hz, 2Hz), 8.37
(1H, t, J=2Hz)

(3) 3-(3-Nitrophenyl)thiophene

NMR (CDCl₃, 300MHz, δ) : 7.45-7.5 (2H, m), 7.58 (1H,
15 m), 7.92 (1H, dt, J=8Hz, 2Hz), 8.14 (1H, dt,
J=8Hz, 2Hz), 8.45 (1H, t, J=2Hz)

(4) 1-(2-Fluorophenyl)-3-nitrobenzene

NMR (CDCl₃, 300MHz, δ) : 7.15-7.3 (2H, m), 7.35-7.55
20 (2H, m), 7.63 (1H, t, J=8Hz), 7.90 (1H, d,
J=8Hz), 8.25 (1H, d, J=8Hz), 8.43 (1H, s)

(5) Methyl 4-(3-nitrophenyl)benzoate

NMR (CDCl₃, 300MHz, δ) : 3.98 (3H, s), 7.6-7.75 (3H,
25 m), 7.97 (1H, dt, J=8Hz, 2Hz), 8.18 (2H, dt,
J=8Hz, 2Hz), 8.27 (1H, dt, J=8Hz, 2Hz), 8.49
(1H, t, J=2Hz)

(6) 4-(3-Nitrophenyl)acetanilide

NMR (DMSO-d₆, 300MHz, δ) : 2.09 (3H, s), 7.8-7.9
30 (5H, m), 8.1-8.2 (2H, m), 8.40 (1H, s)

(7) 3-(6-Methoxy-2-naphthyl)aniline

NMR (DMSO-d₆, δ) : 3.89 (3H, s), 5.16 (2H, s), 6.56
35 (1H, m), 6.90 (1H, m), 6.96 (1H, m), 7.12 (1H,

- 103 -

d, J=8Hz), 7.18 (1H, dd, J=8Hz, 2Hz), 7.33 (1H, m), 7.69 (1H, m), 7.88 (2H, m), 8.00 (1H, m)

(8) 3-(3-Quinolyl)aniline

5 NMR (CDCl₃, δ) : 3.85 (2H, s), 6.75 (1H, dd, J=8Hz, 2Hz), 7.00 (1H, m), 7.10 (1H, d, J=8Hz), 7.30 (1H, dd, J=8Hz, 8Hz), 7.55 (1H, dd, J=8Hz, 8Hz), 7.72 (1H, dd, J=8Hz, 8Hz), 7.85 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz), 8.25 (1H, d, J=2Hz), 9.15
10 (1H, s)

(9) 3-(3-Cyclopentyloxy-4-methoxyphenyl)aniline

NMR (CDCl₃, δ) : 1.60 (2H, m), 1.8-2.0 (8H, m), 3.71 (2H, s), 3.87 (3H, s), 4.84 (1H, m), 6.64 (1H, m), 6.85 (1H, m), 6.92 (2H, m), 7.09 (2H, m),
15 7.20 (1H, m)

(10) 3-(3-Methoxycarbonylphenyl)aniline

NMR (CDCl₃, δ) : 3.92 (3H, s), 6.68 (1H, dd, J=8Hz, 3Hz), 6.93 (1H, s), 7.00 (1H, dd, J=8Hz, 2Hz),
20 7.24 (1H, dd, J=8Hz, 3Hz), 7.47 (1H, dd, J=8Hz, 8Hz), 7.73 (1H, dd, J=8Hz, 2Hz), 7.99 (1H, dd, J=8Hz, 2Hz), 8.24 (1H, dd, J=2Hz, 2Hz)

MASS (m/z) : 228 (M+1)

25

(11) Methyl (E)-3-(3-aminophenyl)cinnamate

NMR (CDCl₃, δ) : 3.77 (2H, br s), 3.81 (3H, s), 6.50 (1H, d, J=15Hz), 6.70 (1H, dd, J=8Hz, 2Hz), 6.90 (1H, d, J=2Hz), 6.98 (1H, d, J=8Hz), 7.24 (1H, dd, J=8Hz, 8Hz), 7.43 (1H, dd, J=8Hz, 8Hz), 7.50 (1H, m), 7.58 (1H, m), 7.70 (1H, m), 7.75 (1H, d, J=15Hz)

30

(12) 3-(4-Isoquinolyl)aniline

35 NMR (CDCl₃, δ) : 3.80 (2H, s), 6.80 (2H, m), 6.90

- 104 -

(1H, d, J=8Hz), 7.30 (1H, dd, J=8Hz, 8Hz), 7.63
(2H, m), 8.00 (2H, m), 8.78 (1H, s), 9.23 (1H,
s)

5 (13) 3-(3-Acetamidophenyl)aniline

NMR (DMSO-d₆, δ) : 2.05 (3H, s), 5.17 (2H, s), 6.54
(1H, m), 6.70 (1H, m), 6.80 (1H, m), 7.10 (1H,
dd, J=8Hz, 8Hz), 7.20 (1H, m), 7.32 (1H, dd,
J=8Hz, 8Hz), 7.50 (1H, m), 7.82 (1H, m)

10 MASS (m/z) : 227 (M+1)

Preparation 65

A mixture of 4-(3-nitrophenyl)acetanilide (4.25 g)
and 10% palladium on carbon (0.8 g) in ethanol (50 ml) and
15 1,4-dioxane (50 ml) was stirred under hydrogen (3 atm) at
room temperature for 3 hours. The catalyst was removed by
filtration and the solvent was evaporated. The resulting
solid was collected and washed with isopropyl ether to
give 4-(3-aminophenyl)acetanilide (3.40 g).

20 NMR (DMSO-d₆, 300MHz, δ) : 2.05 (3H, s), 5.11 (2H,
s), 6.52 (1H, d, J=8Hz), 6.74 (1H, d, J=8Hz),
6.81 (1H, s), 7.07 (1H, t, J=8Hz), 7.49 (2H, d,
J=8Hz), 7.63 (2H, d, J=8Hz)

25 Preparation 66

A mixture of methyl 4-(3-nitrophenyl)benzoate (8.37
g), iron powder (7.5 g) and hydrochloric acid (35%, 22
ml) in methanol (60 ml) was stirred under reflux for 3
hours. Then the mixture was poured into aqueous sodium
30 bicarbonate and extracted with ethyl acetate twice. The
combined organic phase was washed with aqueous sodium
bicarbonate and brine, dried over magnesium sulfate and
concentrated. The resultant solid was collected and
washed with isopropyl ether to give methyl 4-(3-
35 aminophenyl)benzoate (5.33 g).

- 105 -

NMR (DMSO-d₆, 300MHz, δ) : 3.88 (3H, s), 5.22 (2H, s), 6.62 (1H, dt, J=8Hz, 2Hz), 6.84 (1H, dt, J=8Hz, 2Hz), 6.90 (1H, t, J=2Hz), 7.13 (1H, t, J=8Hz), 7.70 (2H, dt, J=8Hz, 2Hz), 8.01 (2H, dt, J=8Hz, 2Hz)

Preparation 67

The following compounds were obtained according to a similar manner to that of Preparation 3, 21, 23, 44, 45, 65 or 66.

(1) 4-(3-Aminophenylcarbonyl)morpholine

NMR (DMSO-d₆, 300MHz, δ) : 3.2-3.7 (8H, m), 5.23 (2H, s), 6.47 (1H, dt, J=8Hz, 2Hz), 6.54 (1H, t, J=2Hz), 6.60 (1H, dt, J=8Hz, 2Hz), 7.06 (1H, t, J=8Hz)

(2) 3-(2-Fluorophenyl)aniline

NMR (DMSO-d₆, 300MHz, δ) : 5.18 (2H, s), 6.5-6.7 (2H, m), 6.72 (1H, m), 7.10 (1H, t, J=8Hz), 7.2-7.5 (4H, m)

(3) 1-(3-Aminophenyl)-1H-1,2,4-triazole

NMR (DMSO-d₆, δ) : 5.48 (2H, s), 6.59 (1H, m), 6.93 (1H, m), 7.03 (1H, t, J=2Hz), 7.17 (1H, t, J=8Hz), 8.18 (1H, s), 9.14 (1H, s)

(4) 3-(3-Aminophenyl)thiophene

NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.50 (1H, dd, J=2Hz, 8Hz), 6.8-6.9 (2H, m), 7.05 (1H, t, J=8Hz), 7.40 (1H, dd, J=2Hz, 5Hz), 7.60 (1H, m), 7.65 (1H, t, J=2Hz)

(5) 2-(3-Aminophenyl)-5-chlorothiophene

NMR (DMSO-d₆, 300MHz, δ) : 5.24 (2H, s), 6.53 (1H,

- 106 -

dd, $J=2\text{Hz}$, 5Hz), 6.7-6.75 (2H, m), 7.0-7.15 (2H, m), 7.21 (1H, d, $J=4\text{Hz}$)

(6) 2-(3-Aminophenyl)thiophene

5 NMR (DMSO- d_6 , 300MHz, δ) : 5.20 (2H, s), 6.50 (1H, m), 6.75-6.85 (2H, m), 7.0-7.15 (2H, m), 7.33 (1H, dd, $J=1\text{Hz}$, 4Hz), 7.47 (1H, dd, $J=1\text{Hz}$, 5Hz)

(7) 4-(3-Aminophenyl)pyridine

10 NMR (DMSO- d_6 , 300MHz, δ) : 5.27 (2H, s), 6.67 (1H, dd, $J=2\text{Hz}$, 8Hz), 6.85-6.95 (2H, m), 7.15 (1H, t, $J=8\text{Hz}$), 7.57 (2H, dd, $J=2\text{Hz}$, 5Hz), 8.59 (2H, d, $J=5\text{Hz}$)

15 (8) 3-(3-Aminophenyl)pyridine

NMR (DMSO- d_6 , 300MHz, δ) : 5.23 (2H, s), 6.62 (1H, m), 6.8-6.9 (2H, m), 7.13 (1H, t, $J=8\text{Hz}$), 7.45 (1H, dd, $J=5\text{Hz}$, 8Hz), 7.94 (1H, dt, $J=8\text{Hz}$, 2Hz), 8.53 (1H, d, $J=5\text{Hz}$), 8.78 (1H, d, $J=2\text{Hz}$)

20

(9) 2-(3-Aminophenyl)pyridine

NMR (DMSO- d_6 , 300MHz, δ) : 5.19 (2H, s), 6.62 (1H, m), 7.05-7.2 (2H, m), 7.25-7.35 (2H, m), 7.75-7.85 (2H, m), 8.61 (1H, m)

25

(10) 3-(Benzoylamino)aniline

NMR (DMSO- d_6 , 300MHz, δ) : 5.07 (2H, s), 6.34 (1H, d, $J=8\text{Hz}$), 6.86 (1H, d, $J=8\text{Hz}$), 6.97 (1H, t, $J=8\text{Hz}$), 7.14 (1H, s), 7.5-7.6 (3H, m), 7.95 (2H, d, $J=8\text{Hz}$), 9.97 (1H, s)

30

(11) Methyl 1-(3-aminophenyl)indole-5-carboxylate

NMR (CDCl₃, δ) : 3.86 (2H, s), 3.92 (3H, s), 6.70 (2H, m), 6.77 (1H, m), 6.85 (1H, d, $J=8\text{Hz}$), 7.27 (1H, d, $J=8\text{Hz}$), 7.35 (1H, d, $J=3\text{Hz}$), 7.57 (1H,

35

- 107 -

d, J=8Hz), 7.90 (1H, d, J=8Hz), 8.42 (1H, s)

(12) 3-(3-Aminophenylcarbamoyl)quinoline

5 NMR (DMSO-d₆, 300MHz, δ) : 5.14 (2H, s), 6.37 (1H, d, J=8Hz), 6.9-7.05 (2H, m), 7.15 (1H, s), 7.72 (1H, t, J=8Hz), 7.90 (1H, t, J=8Hz), 8.1-8.2 (2H, m), 8.92 (1H, s), 9.33 (1H, d, J=2Hz)

(13) 3-[(E)-2-(3,5-Dichlorophenyl)vinyl]aniline

10 NMR (DMSO-d₆, 300MHz, δ) : 5.13 (2H, s), 6.53 (1H, d, J=8Hz), 6.78 (2H, m), 7.0-7.1 (2H, m), 7.31 (1H, d, J=16Hz), 7.46 (1H, s), 7.69 (2H, s)

(14) 3-Amino-N-(3,5-dichlorophenyl)benzamide

15 NMR (DMSO-d₆, 300MHz, δ) : 5.37 (2H, s), 7.0-7.1 (2H, m), 7.17 (1H, t, J=8Hz), 7.30 (1H, s), 7.89 (1H, d, J=2Hz)

(15) 3-Amino-N-methyl-N-(3,5-dichlorophenyl)benzamide

20 NMR (DMSO-d₆, 300MHz, δ) : 3.32 (3H, s), 5.20 (2H, s), 6.33 (1H, d, J=8Hz), 6.51 (1H, dd, J=2Hz, 8Hz), 6.59 (1H, s), 6.90 (1H, t, J=8Hz), 7.29 (2H, s), 7.40 (1H, s)

25 Preparation 68

A mixture of 2-chloro-3-nitropyridine (3.20 g), methyl 3,5-diaminobenzoate (3.20 g) and potassium carbonate (4.0 g) in 1,4-dioxane (60 ml) was stirred under reflux for 4 hours. After cooling, insoluble materials
30 were removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel column (5% methanol in chloroform) to give 2-(3-amino-5-methoxycarbonylphenylamino)-3-nitropyridine (1.12 g).

35 NMR (DMSO-d₆, 300MHz, δ) : 3.81 (3H, s), 5.48 (2H, s), 6.95-7.0 (2H, m), 7.12 (1H, m), 7.39 (1H,

- 108 -

s), 8.5-8.55 (2H, m), 9.86 (1H, s)

Preparation 69

A mixture of 2-chloro-3-nitropyridine (1.15 g), 2-(3-aminophenyl)pyridine (1.12 g) and potassium carbonate (1.36 g) in diglyme (15 ml) was stirred at 150°C for 3 hours. After cooling, insoluble materials were removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel column (hexane - ethyl acetate, 1:1) to give 3-nitro-2-[3-(2-pyridyl)-phenylamino]pyridine (1.68 g)

NMR (CDCl₃, 300MHz, δ) : 6.85 (1H, dd, J=5Hz, 8Hz), 7.2-7.3 (1H, m), 7.50 (1H, t, J=8Hz), 7.75-7.85 (4H, m), 8.23 (2H, m), 8.5-8.6 (1H, m), 8.70 (1H, d, J=5Hz)

Preparation 70

The following compounds were obtained according to a similar manner to that of Preparation 1, 5, 27, 28, 47, 48, 49, 68 or 69.

(1) 2-[3,5-Bis(methoxycarbonyl)phenylamino]-3-nitropyridine

NMR (DMSO-d₆, 300MHz, δ) : 3.92 (6H, s), 7.09 (1H, dd, J=5Hz, 8Hz), 8.22 (1H, m), 8.5-8.6 (4H, m)

(2) 2-[3-(Morpholinocarbonyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 3.5-3.9 (8H, m), 6.90 (1H, dd, J=5Hz, 8Hz), 7.10 (1H, dt, J=8Hz, 2Hz), 7.44 (1H, t, J=8Hz), 7.68 (1H, dt, J=8Hz, 2Hz), 7.89 (1H, t, J=2Hz), 8.49 (1H, dd, J=2Hz, 5Hz), 8.56 (1H, dd, J=2Hz, 8Hz)

(3) 2-[3-(4-Acetylaminophenyl)phenylamino]-3-nitropyridine

- 109 -

NMR (CDCl₃, 300MHz, δ) : 2.21 (3H, s), 6.86 (1H, dd, J=5Hz, 8Hz), 7.3-7.5 (3H, m), 7.55-7.65 (5H, m), 7.84 (1H, s), 8.45-8.6 (2H, m)

- 5 (4) 2-[3-(4-Methoxycarbonylphenyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 3.96 (3H, s), 6.87 (1H, dd, J=5Hz, 8Hz), 7.4-7.55 (2H, m), 7.70 (3H, m), 7.92 (1H, t, J=2Hz), 8.13 (2H, dt, J=8Hz, 2Hz), 8.5-8.6 (2H, m)

10

- (5) 2-[3-(2-Fluorophenyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 6.86 (1H, dd, J=5Hz, 8Hz), 7.1-7.5 (6H, m), 7.70 (1H, d, J=8Hz), 7.82 (1H, d, J=2Hz), 7.5-7.6 (2H, m)

15

- (6) 1-[3-[(3-Nitropyridin-2-yl)amino]phenyl]-1H-1,2,4-triazole

NMR (CDCl₃, 300MHz, δ) : 6.93 (1H, dd, J=5Hz, 8Hz), 7.4-7.55 (2H, m), 7.61 (1H, dt, J=8Hz, 2Hz), 8.13 (1H, s), 8.30 (1H, t, J=2Hz), 8.55-8.65 (3H, m)

20

- (7) 3-Nitro-2-[3-(3-thienyl)phenylamino]pyridine

NMR (CDCl₃, 300MHz, δ) : 6.86 (1H, dd, J=5Hz, 8Hz), 7.5-7.55 (5H, m), 7.61 (1H, m), 7.88 (1H, s), 8.5-8.6 (2H, m)

25

- (8) 2-[3-(5-Chloro-2-thienyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 6.85-6.95 (2H, m), 7.12 (1H, d, J=4Hz), 7.32 (1H, dt, J=8Hz, 2Hz), 7.40 (1H, t, J=8Hz), 7.58 (1H, m), 7.87 (1H, t, J=2Hz), 8.5-8.6 (2H, m)

30

- 35 (9) 3-Nitro-2-[3-(2-thienyl)phenylamino]pyridine

- 110 -

NMR (CDCl₃, 300MHz, δ) : 6.86 (1H, dd, J=5Hz, 8Hz),
7.10 (1H, dd, J=4Hz, 5Hz), 7.3-7.45 (4H, m),
7.60 (1H, m), 7.90 (1H, t, J=2Hz), 8.5-8.6 (2H,
m)

5

(10) 3-Nitro-2-[3-(4-pyridyl)phenylamino]pyridine

NMR (CDCl₃, 300MHz, δ) : 6.89 (1H, dd, J=5Hz, 8Hz),
7.4-7.6 (4H, m), 7.72 (1H, dt, J=8Hz, 2Hz), 7.99
(1H, t, J=2Hz), 8.5-8.6 (2H, m), 8.69 (2H, d,
J=5Hz)

10

(11) 3-Nitro-2-[3-(3-pyridyl)phenylamino]pyridine

NMR (CDCl₃, 300MHz, δ) : 6.89 (1H, dd, J=5Hz, 8Hz),
7.35-7.45 (2H, m), 7.52 (1H, t, J=8Hz), 7.68
(1H, dt, J=8Hz, 2Hz), 7.9-8.0 (2H, m), 8.5-8.6
(2H, m), 8.62 (1H, dd, J=2Hz, 5Hz), 8.90 (1H, d,
J=2Hz)

15

(12) 2-[3-(Benzoylamino)phenylamino]-3-nitropyridine

NMR (DMSO-d₆, 300MHz, δ) : 7.01 (1H, dd, J=5Hz,
8Hz), 7.35 (1H, t, J=8Hz), 7.44 (1H, d, J=8Hz),
7.5-7.65 (4H, m), 7.98 (2H, d, J=8Hz), 8.11 (1H,
s), 8.5-8.6 (2H, m), 9.99 (1H, s), 10.31 (1H, s)

20

(13) 2-[3-(6-Methoxy-2-naphthyl)phenylamino]-3-nitropyridine

NMR (DMSO-d₆, δ) : 3.90 (3H, s), 7.01 (1H, m), 7.20
(1H, m), 7.37 (1H, m), 7.50 (1H, dd, J=8Hz,
8Hz), 7.57 (1H, m), 7.73 (1H, m), 7.84 (1H, m),
7.93 (2H, m), 8.04 (1H, m), 8.18 (1H, s), 8.56
(2H, m)

25

30

(14) 3-Nitro-2-(3-succinimidophenylamino)pyridine

NMR (CDCl₃, 300MHz, δ) : 8.56-8.47 (2H, m), 7.79
(1H, s), 7.67 (1H, d, J=9Hz), 7.48 (1H, t,

35

- 111 -

J=9Hz), 7.10 (1H, d, J=9Hz), 6.91-6.84 (1H, m),
2.91 (4H, s)

5 (15) 2-[3-(5-Methoxycarbonylindol-1-yl)phenylamino]-3-nitropyridine

NMR (CDCl₃, δ) : 3.94 (3H, s), 6.78 (1H, d, J=3Hz),
6.91 (1H, dd, J=8Hz, 5Hz), 7.28 (1H, m), 7.45
(1H, d, J=3Hz), 7.52 (2H, m), 7.72 (1H, d,
J=8Hz), 7.95 (1H, d, J=8Hz), 8.16 (1H, m), 8.45
10 (1H, s), 8.55 (2H, m)

(16) 2-[3-(3-Quinolyl)phenylamino]-3-nitropyridine

NMR (CDCl₃, δ) : 6.89 (1H, dd, J=8Hz, 3Hz),
7.55 (3H, m), 7.70 (2H, m), 7.92 (1H, d, J=8Hz),
15 8.07 (1H, s), 8.14 (1H, d, J=8Hz), 8.34 (1H, d,
J=3Hz), 8.52 (1H, m), 8.57 (1H, m), 9.21 (1H, d,
J=3Hz)

20 (17) 2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)phenylamino]-3-nitropyridine

NMR (DMSO-d₆, δ) : 1.59 (2H, m), 1.74 (4H, m), 1.90
(2H, m), 3.79 (3H, s), 4.92 (1H, m), 7.00 (1H,
dd, J=8Hz, 5Hz), 7.04 (1H, d, J=8Hz), 7.20 (2H,
m), 7.41 (2H, m), 7.63 (1H, m), 7.88 (1H, s),
25 8.53 (2H, m)

(18) 2-[3-(3-Methoxycarbonylphenyl)phenylamino]-3-nitropyridine

mp : 179-181°C

30 NMR (CDCl₃, δ) : 3.95 (3H, s), 6.87 (1H, dd, J=8Hz,
5Hz), 7.50 (3H, m), 7.70 (1H, m), 7.82 (1H, m),
7.89 (1H, m), 8.04 (1H, m), 8.30 (1H, m), 8.52
(2H, m)

35 (19) 2-[3-[(E)-3-Methoxycarbonylvinylphenyl]phenylamino]-

- 112 -

3-nitropyridine

5 NMR (DMSO-d₆, δ) : 3.74 (3H, s), 6.80 (1H, d, J=16Hz), 7.03 (1H, dd, J=8Hz, 5Hz), 7.52 (3H, m), 7.76 (4H, m), 7.98 (1H, m), 8.07 (1H, m), 8.55 (2H, m)

(20) 2-[3-(4-Isoquinolyl)phenylamino]-3-nitropyridine

10 NMR (DMSO-d₆, δ) : 7.01 (1H, m), 7.33 (1H, dd, J=8Hz, 2Hz), 7.57 (1H, dd, J=8Hz, 8Hz), 7.7-7.9 (4H, m), 8.03 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.54 (3H, m), 9.36 (1H, s)

(21) 2-[3-(3-Acetamidophenyl)phenylamino]-3-nitropyridine

15 NMR (CDCl₃, δ) : 2.20 (3H, s), 6.83 (1H, dd, J=8Hz, 5Hz), 7.3-7.4 (4H, m), 7.45 (1H, dd, J=8Hz, 8Hz), 7.52 (1H, m), 7.67 (1H, m), 7.75 (1H, s), 7.83 (1H, m), 8.52 (2H, m)

(22) 3-[3-[(3-Nitropyridin-2-yl)amino]phenylcarbamoyl]-quinoline

20 NMR (DMSO-d₆, 300MHz, δ) : 7.02 (1H, dd, J=5Hz, 8Hz), 7.35-7.5 (2H, m), 7.62 (1H, d, J=8Hz), 7.74 (1H, t, J=8Hz), 7.91 (1H, t, J=8Hz), 8.1-8.2 (3H, m), 8.55-8.6 (2H, m), 8.99 (1H, s), 9.38 (1H, d, J=2Hz)

25

(23) 2-[3-[(E)-2-(3,5-Dichlorophenyl)vinyl]phenylamino]-3-nitropyridine

30 NMR (CDCl₃, 300MHz, δ) : 6.68 (1H, dd, J=5Hz, 8Hz), 6.99 (1H, d, J=16Hz), 7.13 (1H, d, J=16Hz), 7.27 (1H, m), 7.32 (1H, d, J=8Hz), 7.35-7.45 (3H, m), 7.59 (1H, d, J=8Hz), 7.83 (1H, s), 8.5-8.6 (2H, m)

35 (24) 2-[3-(3,5-Dichlorophenylcarbamoyl)phenylamino]-3-

- 113 -

nitropyridine

NMR (DMSO-d₆, 300MHz, δ) : 7.04 (1H, dd, J=5Hz, 8Hz), 7.23 (1H, s), 7.55 (1H, t, J=8Hz), 7.72 (1H, d, J=8Hz), 7.9-8.0 (3H, m), 8.20 (1H, s), 8.5-8.6 (2H, m)

(25) 2-[3-[N-Methyl-N-(3,5-dichlorophenyl)carbamoyl]-phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 3.49 (3H, s), 6.88 (1H, dd, J=5Hz, 8Hz), 7.0-7.2 (4H, m), 7.28 (1H, t, J=8Hz), 7.56 (1H, dd, J=2Hz, 8Hz), 7.94 (1H, s), 7.45-7.55 (2H, m)

(26) 2-(3-Carboxyphenylamino)-3-nitropyridine

NMR (DMSO-d₆, δ) : 7.03 (1H, dd, J=8Hz, 5Hz), 7.50 (1H, dd, J=8Hz, 8Hz), 7.71 (1H, m), 7.88 (1H, m), 8.25 (1H, m), 8.55 (2H, m)

(27) 6-Phenylthio-2-[3-(3-phenylureidophenyl)]-3-nitropyridine

NMR (DMSO-d₆, δ) : 6.60 (1H, d, J=8Hz), 7.00 (3H, m), 7.10 (1H, m), 7.29 (2H, m), 7.4-7.7 (8H, m), 8.38 (1H, d, J=8Hz), 8.67 (2H, m)

25 Preparation 71

A mixture of 2-(3-acetylamino-5-methoxycarbonylphenylamino)-3-nitropyridine (1.20 g) and 10% palladium on carbon (0.25 g) in methanol (15 ml) and 1,4-dioxane (15 ml) was stirred under hydrogen (3 atm) at room temperature for 3 hours. The catalyst was removed by filtration and the solvent was evaporated. The resulting solid was collected and washed with isopropyl ether to give 2-(3-acetylamino-5-methoxycarbonylphenylamino)-3-aminopyridine (1.10 g).

NMR (DMSO-d₆, 300MHz, δ) : 2.05 (3H, s), 3.82 (3H,

- 114 -

s), 5.12 (2H, s), 6.68 (1H, dd, J=5Hz, 8Hz),
6.92 (1H, d, J=8Hz), 7.52 (1H, d, J=5Hz), 7.78
(1H, t, J=2Hz), 7.90 (1H, m), 8.00 (1H, s), 8.21
(1H, s)

5

Preparation 72

The following compounds were obtained according to a similar manner to that of Preparation 3, 31, 33, 52, 53, 54 or 71.

10

- (1) 2-[3-(4-Acetylaminophenyl)phenylamino]-3-aminopyridine

NMR (DMSO-d₆, 300MHz, δ) : 2.07 (3H, s), 5.09 (2H, s), 6.63 (1H, dd, J=5Hz, 8Hz), 6.91 (1H, dd, J=2Hz, 8Hz), 7.10 (1H, d, J=8Hz), 7.29 (1H, t, J=8Hz), 7.5-7.6 (3H, m), 7.65-7.7 (3H, m), 7.82 (2H, d, J=8Hz)

15

- (2) 3-Amino-2-[3-(2-pyridyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.12 (2H, s), 6.64 (1H, m), 6.92 (1H, d, J=8Hz), 7.3-7.4 (2H, m), 7.53 (2H, d, J=8Hz), 7.85-7.95 (4H, m), 8.27 (1H, s), 8.67 (1H, d, J=5Hz)

20

- (3) 3-Amino-2-[3-(3-pyridyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.64 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=2Hz, 8Hz), 7.18 (1H, dd, J=2Hz, 8Hz), 7.35 (1H, t, J=8Hz), 7.45-7.55 (2H, m), 7.72 (1H, dd, J=2Hz, 8Hz), 7.85-7.95 (2H, m), 8.01 (1H, dt, J=8Hz, 2Hz), 8.57 (1H, dd, J=2Hz, 5Hz), 8.83 (1H, d, J=2Hz)

30

- (4) 3-Amino-2-[3-(4-pyridyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=2Hz, 8Hz), 7.25

35

- 115 -

(1H, d, J=8Hz), 7.38 (1H, t, J=8Hz), 7.53 (1H, dd, J=2Hz, 5Hz), 7.64 (2H, d, J=5Hz), 7.78 (1H, d, J=8Hz), 7.91 (1H, s), 8.02 (1H, s), 8.63 (2H, d, J=5Hz)

5

(5) 3-Amino-2-[3-(2-thienyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.66 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=2Hz, 8Hz), 7.1-7.2 (2H, m), 7.27 (1H, t, J=8Hz), 7.42 (1H, dd, J=2Hz, 5Hz), 7.5-7.55 (2H, m), 7.66 (1H, d, J=8Hz), 7.86 (1H, s), 7.91 (1H, t, J=2Hz)

10

(6) 3-Amino-2-[3-(5-chloro-2-thienyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.93 (1H, dd, J=2Hz, 8Hz), 7.1-7.2 (2H, m), 7.25-7.35 (2H, m), 7.54 (1H, dd, J=2Hz, 5Hz), 7.65 (1H, dd, J=2Hz, 8Hz), 7.89 (1H, d, J=2Hz)

15

(7) 3-Amino-2-[3-(3-thienyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.08 (2H, s), 6.63 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, dd, J=2Hz, 8Hz), 7.18 (1H, d, J=8Hz), 7.27 (1H, t, J=8Hz), 7.47 (1H, dd, J=2Hz, 5Hz), 7.53 (1H, dd, J=2Hz, 5Hz), 7.63 (2H, m), 7.73 (1H, m), 7.79 (1H, s), 7.90 (1H, t, J=2Hz)

20

(8) 1-[3-[(3-Aminopyridin-2-yl)amino]phenyl]-1H-1,2,4-triazole

NMR (DMSO-d₆, 300MHz, δ) : 5.13 (2H, s), 6.69 (1H, dd, J=5Hz, 8Hz), 6.96 (1H, dd, J=2Hz, 8Hz), 7.30 (1H, m), 7.39 (1H, t, J=8Hz), 7.55 (1H, dd, J=2Hz, 5Hz), 7.68 (1H, dt, J=8Hz, 2Hz), 8.07 (1H, s), 8.19 (1H, t, J=2Hz), 8.22 (1H, s), 9.21 (1H, s)

35

- 116 -

(9) 3-Amino-2-[3-(2-fluorophenyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.64 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, dd, J=2Hz, 8Hz), 7.01 (1H, d, J=8Hz), 7.25-7.55 (6H, m), 7.72 (1H, dt, J=8Hz, 2Hz), 7.80 (1H, d, J=2Hz), 7.87 (1H, s)

5

(10) 3-Amino-2-[3-(4-methoxycarbonylphenyl)phenylamino]-pyridine

NMR (DMSO-d₆, 300MHz, δ) : 3.89 (3H, s), 5.10 (2H, s), 6.67 (1H, dd, J=5Hz, 8Hz), 6.94 (1H, dd, J=2Hz, 8Hz), 7.20 (1H, d, J=8Hz), 7.37 (1H, t, J=8Hz), 7.53 (1H, dd, J=2Hz, 5Hz), 7.79 (3H, m), 7.91 (1H, s), 7.98 (1H, t, J=2Hz), 8.07 (2H, d, J=8Hz)

10

15

(11) 3-Amino-2-[3-(morpholinocarbonyl)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 3.3-3.7 (8H, m), 5.09 (2H, s), 6.65 (1H, dd, J=5Hz, 8Hz), 6.86 (1H, dt, J=8Hz, 2Hz), 6.92 (1H, dd, J=2Hz, 8Hz), 7.29 (1H, t, J=8Hz), 7.51 (1H, dd, J=2Hz, 5Hz), 7.65 (1H, dt, J=8Hz, 2Hz), 7.73 (1H, t, J=2Hz), 7.90 (1H, s)

20

(12) 3-Amino-2-[3,5-bis(methoxycarbonyl)phenylamino]-pyridine

25

NMR (DMSO-d₆, 300MHz, δ) : 3.88 (6H, s), 5.13 (2H, s), 6.71 (1H, dd, J=5Hz, 8Hz), 6.97 (1H, d, J=8Hz), 7.55 (1H, d, J=5Hz), 7.96 (1H, s), 8.29 (1H, s), 8.52 (1H, s)

30

(13) 3-Amino-2-[3-methoxycarbonyl-5-(2-naphthoylamino)phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 3.89 (3H, s), 5.18 (2H, s), 6.70 (1H, dd, J=5, 8Hz), 6.96 (1H, d, J=8Hz), 7.57 (1H, m), 7.6-7.7 (2H, m), 7.95-8.15

35

- 117 -

(7H, m), 8.50 (1H, s), 8.63 (1H, s)

(14) 3-Amino-2-[3-(benzoylamino)phenylamino]pyridine

5 NMR (DMSO-d₆, 300MHz, δ) : 5.11 (2H, s), 6.64 (1H, m), 6.91 (1H, d, J=8Hz), 7.15-7.3 (2H, m), 7.4-7.65 (5H, m), 7.79 (1H, s), 7.98 (2H, d, J=8Hz), 8.08 (1H, s)

10 (15) 2-[3-(6-Methoxy-2-naphthyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.45 (2H, br s), 3.93 (3H, s), 6.30 (1H, s), 6.80 (1H, dd, J=8Hz, 5Hz), 7.04 (1H, m), 7.16 (2H, m), 7.30 (2H, m), 7.39 (1H, m), 7.54 (1H, m), 7.71 (1H, m), 7.79 (2H, m), 7.87 (1H, m), 7.98 (1H, s)

15

(16) 2-[3-(5-Methoxycarbonylindol-1-yl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.48 (2H, s), 3.93 (3H, s), 6.42 (1H, s), 6.73 (1H, m), 6.81 (1H, m), 7.05 (2H, m), 7.21 (1H, m), 7.42 (1H, m), 7.61 (1H, m), 7.70 (1H, m), 7.88 (1H, m), 7.91 (1H, m), 8.42 (1H, m)

20

25 (17) 2-[3-(3-Quinolylyl)phenylamino]-3-aminopyridine

NMR (DMSO-d₆, δ) : 5.12 (2H, s), 6.67 (1H, dd, J=8Hz, 5Hz), 6.95 (1H, d, J=8Hz), 7.34 (1H, d, J=8Hz), 7.42 (1H, dd, J=8Hz, 8Hz), 7.55 (1H, d, J=5Hz), 7.67 (1H, dd, J=8Hz, 8Hz), 7.80 (2H, m), 7.95 (1H, s), 8.09 (2H, m), 8.59 (1H, m), 9.21 (1H, d, J=3Hz)

30

(18) 2-[3-(3-Cyclopentyloxy-4-methoxyphenyl)phenylamino]-3-aminopyridine

35 NMR (CDCl₃, δ) : 1.62 (2H, m), 1.85 (2H, m), 1.94

- 118 -

(4H, m), 3.45 (2H, m), 3.87 (3H, s), 4.85 (1H, m), 6.27 (1H, s), 6.79 (1H, dd, J=8Hz, 5Hz), 6.92 (1H, d, J=8Hz), 7.03 (1H, d, J=8Hz), 7.13 (3H, m), 7.23 (1H, m), 7.34 (1H, dd, J=8Hz, 8Hz), 7.42 (1H, m), 7.85 (1H, d, J=5Hz)

(19) 2-[3-(3-Methoxycarbonylphenyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.47 (2H, s), 3.94 (3H, s), 6.32 (1H, s), 6.79 (1H, dd, J=8Hz, 5Hz), 7.03 (1H, d, J=8Hz), 7.22 (1H, m), 7.35 (2H, m), 7.49 (2H, m), 7.79 (1H, d, J=8Hz), 7.85 (1H, m), 8.00 (1H, d, J=8Hz), 8.28 (1H, s)

(20) 2-[3-[3-[(E)-2-Methoxycarbonylvinyl]phenyl]phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.45 (2H, br s), 3.81 (3H, s), 6.30 (1H, s), 6.50 (1H, d, J=16Hz), 6.81 (1H, m), 7.05 (1H, m), 7.17 (1H, m), 7.30 (1H, m), 7.36 (1H, m), 7.48 (2H, m), 7.60 (1H, m), 7.72 (1H, s), 7.75 (1H, d, J=16Hz), 7.87 (1H, d, J=3Hz)

(21) 2-[3-(4-Isoquinolyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 3.50 (2H, br s), 6.40 (1H, s), 6.80 (1H, m), 7.03 (1H, m), 7.10 (1H, m), 7.44 (3H, m), 7.66 (2H, m), 7.85 (1H, m), 8.05 (2H, m), 8.52 (1H, s), 9.22 (1H, s)

(22) 2-[3-(3-Acetamidophenyl)phenylamino]-3-aminopyridine

NMR (CDCl₃, δ) : 2.13 (3H, s), 3.50 (2H, br s), 6.33 (1H, s), 6.77 (1H, dd, J=8Hz, 5Hz), 7.00 (1H, d, J=8Hz), 7.12 (1H, dd, J=8Hz, 2Hz), 7.2-7.4 (5H, m), 7.50 (1H, m), 7.55 (1H, m), 7.61 (1H, s), 7.82 (1H, d, J=5Hz)

- 119 -

(23) 2-(3-Iodophenylamino)-3-aminopyridine

NMR (DMSO-d₆, δ) : 5.06 (2H, s), 6.66 (1H, m),
6.92 (1H, m), 7.00 (1H, dd, J=8Hz, 8Hz), 7.15
(1H, m), 7.51 (1H, m), 7.61 (1H, m), 7.83 (1H,
s), 8.08 (1H, s)

5

(24) 3-[3-[(3-Aminopyridin-2-yl)amino]phenylcarbamoyl]-quinoline

NMR (DMSO-d₆, 300MHz, δ) : 5.12 (2H, s), 6.65 (1H,
dd, J=5Hz, 8Hz), 6.92 (1H, d, J=8Hz), 7.2-7.35
(2H, m), 7.45 (1H, d, J=8Hz), 7.52 (1H, d,
J=5Hz), 7.73 (1H, t, J=8Hz), 7.81 (1H, s), 7.90
(1H, t, J=8Hz), 8.1-8.2 (3H, m), 8.97 (1H, d,
J=2Hz), 9.37 (1H, s)

10

15

(25) 3-Amino-2-[3-[(E)-2-(3,5-dichlorophenyl)vinyl]-phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.09 (2H, s), 6.64 (1H,
dd, J=5Hz, 8Hz), 6.92 (1H, d, J=8Hz), 7.1-7.2
(2H, m), 7.28 (1H, t, J=8Hz), 7.4-7.6 (4H, m),
7.72 (2H, s), 7.80 (1H, s), 7.84 (1H, s)

20

(26) 3-Amino-2-[3-[N-methyl-N-(3,5-dichlorophenyl)-carbamoyl]phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 3.37 (3H, s), 5.08 (2H,
s), 6.63 (1H, dd, J=5Hz, 8Hz), 6.73 (1H, d,
J=8Hz), 6.90 (1H, d, J=8Hz), 7.13 (1H, t,
J=8Hz), 7.3-7.45 (3H, m), 7.5-7.6 (2H, m), 7.83
(2H, m)

25

30

(27) 6-Phenylthio-2-[3-(3-phenylureido)phenylamino]-3-aminopyridine

NMR (DMSO-d₆, δ) : 4.50 (2H, br s), 6.5-7.6 (10H,
m), 8.30 (1H, m), 8.95 (2H, m)

35

- 120 -

(28) 2-(3-Phenylsulfonylamino)phenylamino)-3-aminopyridine

NMR (DMSO-d₆, δ) : 5.07 (2H, s), 6.55 (1H, m), 6.61 (1H, m), 6.89 (1H, m), 7.02 (1H, dd, J=8Hz, 8Hz), 7.25 (2H, m), 7.55 (5H, m), 7.82 (2H, m)

5

(29) 2-(3-Methoxycarbonylphenylamino)-3-aminopyridine

NMR (DMSO-d₆, δ) : 3.83 (3H, s), 5.30 (2H, br s), 6.68 (1H, dd, J=8Hz, 6Hz), 6.95 (1H, d, J=8Hz), 7.37 (1H, dd, J=8Hz, 8Hz), 7.44 (1H, d, J=8Hz), 7.51 (1H, d, J=6Hz), 7.99 (1H, d, J=8Hz), 8.09 (1H, s), 8.18 (1H, s)

10

Preparation 73

To a mixture of 2-(3-amino-5-

15 methoxycarbonylphenylamino)-3-nitropyridine (550 mg) and triethylamine (0.3 ml) in 1,4-dioxane (10 ml) was added 2-naphthoyl chloride (0.40 g). The mixture was stirred at room temperature for 15 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. 20 The organic phase containing orange solid was washed with water twice and the solid was collected to give 2-[3-methoxycarbonyl-5-(2-naphthoylamino)phenylamino]-3-nitropyridine (730 mg).

25 NMR (DMSO-d₆, 300MHz, δ) : 3.90 (3H, s), 7.05 (1H, dd, J=5Hz, 8Hz), 7.6-7.7 (2H, m), 8.0-8.15 (5H, m), 8.29 (1H, t, J=2Hz), 8.47 (1H, m), 8.55-8.6 (2H, m), 8.64 (1H, s)

Preparation 74

30 To a mixture of 2-[3-amino-5-methoxycarbonylphenylamino]-3-nitropyridine (1.10 g), triethylamine (0.6 ml) and 4-dimethylaminopyridine (14 mg) in 1,4-dioxane (15 ml) was added acetic anhydride (0.40 ml). The mixture was stirred at room temperature for 20 35 hours, then poured into a mixture of ethyl acetate and

- 121 -

aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-(3-acetylamino-5-methoxycarbonylphenylamino)-3-nitropyridine (1.21 g).

NMR (CDCl₃, 300MHz, δ) : 2.21 (3H, s), 3.93 (3H, s), 6.89 (1H, dd, J=5, 8Hz), 7.49 (1H, s), 7.79 (1H, s), 8.01 (1H, s), 8.41 (1H, s), 8.5-8.6 (2H, m)

Preparation 75

To a mixture of 3-nitroaniline (5.95 g) and triethylamine (6.0 ml) in dichloromethane (40 ml) was added dropwise a solution of benzoyl chloride (5.0 ml) in dichloromethane (20 ml). The mixture was stirred at room temperature for 15 minutes, then poured into a mixture of ethyl acetate and water. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 1-benzoylamino-3-nitrobenzene (9.05 g).

NMR (CDCl₃, 300MHz, δ) : 7.45-7.65 (4H, m), 7.90 (2H, d, J=8Hz), 8.01 (1H, d, J=8Hz), 8.05-8.2 (2H, m), 8.50 (1H, s)

Preparation 76

The solution of 3-nitro-2-(3-succinimidophenylamino)-pyridine (3.47 g) was hydrogenated with palladium on carbon (0.5 g) at 3 atm for 5 hours. The mixture was filtrated and evaporated to give 3-amino-2-(3-succinimidophenylamino)pyridine (2.89 g).

NMR (DMSO-d₆, 300MHz, δ) : 8.00 (1H, s), 7.64 (1H, dd, J=8Hz, 1Hz), 7.56 (1H, d, J=1Hz), 7.50 (1H, d, J=3Hz), 7.31 (1H, t, J=8Hz), 6.92 (1H, d, J=7Hz), 6.70 (1H, d, J=7Hz), 6.66 (1H, dd,

- 122 -

J=8Hz, 3Hz), 5.23 (2H, br s), 2.69 (4H, s)

Preparation 77

The following compound was synthesized from 3-nitroaniline and maleic anhydride according to a similar manner to that described in Organic Synthesis Collective Volume 5 pp944.

(Z)-3-(3-Nitrophenylcarbamoyl)acrylic acid

10 NMR (DMSO-d₆, 300MHz, δ) : 6.34 (1H, d, J=10Hz),
6.50 (1H, d, J=10Hz), 7.63 (1H, t, J=8Hz), 7.92
(1H, d, J=8Hz), 7.95 (1H, d, J=8Hz), 8.65 (1H,
s)

MASS (FAB) (m/e) : 235

15

Preparation 78

The following compound was synthesized from (Z)-3-(3-nitrophenylcarbamoyl)acrylic acid according to a similar manner to that described in Organic Synthesis Collective
20 Volume 5 pp944.

N-(3-Nitrophenyl)maleimide

NMR (DMSO-d₆, 300MHz, δ) : 7.26 (2H, s), 7.77-7.88
(2H, m), 8.22-8.31 (2H, m)

25

Preparation 79

To a solution of N-(3-nitrophenyl)maleimide (26.3 g) in methanol-dioxane (1:1) was added suspension of palladium on carbon (2 g) in water. The reaction mixture
30 was hydrogenated for 4 hours at 3 atm. (White crystal was precipitated.) The mixture was added 1N hydrochloric acid (ca. 300 ml) to dissolve the crude product. The mixture was filtrated and evaporated. Obtained residue was dissolved in water and basified by aqueous sodium
35 hydrogencarbonate. Precipitate was collected by suction

- 123 -

to give N-(3-aminophenyl)succinimide (12.6 g).

NMR (DMSO-d₆, 300MHz, δ) : 2.72 (4H, s), 5.25 (2H, s), 6.33 (1H, d, J=7Hz), 6.39 (1H, d, J=1Hz), 6.58 (1H, dd, J=7Hz, 1Hz), 7.07 (1H, t, J=9Hz)

5 MASS (FAB) (m/e) : 191 (M+1)

Preparation 80

A mixture of ethyl 4-hydroxy-3-methoxybenzoate (7.17 g), cyclopentyl bromide (4.7 ml) and potassium carbonate
10 (7.6 g) in N,N-dimethylformamide (70 ml) was stirred at 80°C for 3 hours. Then the mixture was poured into water and extracted with ethyl acetate twice. The combined organic solution was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was
15 chromatographed on silica gel column (hexane - ethyl acetate, 4:1) to give ethyl 4-cyclopentyloxy-3-methoxybenzoate (8.58 g) as an oil.

NMR (CDCl₃, 300MHz, δ) : 1.39 (3H, t, J=7Hz), 1.55-2.10 (8H, m), 3.90 (3H, s), 4.36 (2H, q, J=7Hz), 4.83 (1H, m), 6.88 (1H, d, J=8Hz), 7.54
20 (1H, d, J=2Hz), 7.65 (1H, dd, J=2Hz, 8Hz)

Preparation 81

A mixture of ethyl 4-cyclopentyloxy-3-methoxybenzoate
25 (1.06 g) and 4N aqueous sodium hydroxide (4 ml) in ethanol (8 ml) and 1,4-dioxane (8 ml) was stirred at 80°C for 3 hours. Then the mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The organic solution was washed with dilute hydrochloric acid
30 and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 4-cyclopentyloxy-3-methoxybenzoic acid (730 mg).

NMR (CDCl₃, 300MHz, δ) : 1.55-2.10 (8H, m), 3.90
35 (3H, s), 4.87 (1H, m), 6.91 (1H, d, J=8Hz),

- 124 -

7.60 (1H, d, J=2Hz), 7.74 (1H, dd, J=2Hz, 8Hz)

Preparation 82

To a solution of 3-quinolinecarboxylic acid (2.50 g) in dichloromethane (50 ml) was added oxalyl chloride (2.6 ml) and three drops of N,N-dimethylformamide. After stirring at room temperature for 30 minutes, the mixture was concentrated and the residual solid was added to a mixture of 3-nitroaniline (1.60 g) and triethylamine (4.0 ml) in dichloromethane (40 ml). After stirring at room temperature for 15 minutes, the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate three times. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-(3-nitrophenylcarbonyl)quinoline (2.98 g).

NMR (DMSO-d₆, 300MHz, δ) : 7.7-7.8 (2H, m), 7.93 (1H, t, J=8Hz), 8.02 (1H, dd, J=2Hz, 8Hz), 8.15-8.3 (3H, m), 8.84 (1H, m), 9.02 (1H, d, J=2Hz), 9.40 (1H, s)

Preparation 83

A mixture of 3-nitrostyrene (4.6 ml), 1,3-dichloro-5-iodobenzene (7.8 g), palladium(II) acetate (0.20 g), tetrabutylammonium chloride (8.4 g) and sodium bicarbonate (6.3 g) in N,N-dimethylformamide (40 ml) was stirred at 110°C for 4 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 1,3-dichloro-5-[(E)-2-(3-nitrophenyl)vinyl]benzene (7.93 g).

NMR (DMSO-d₆, 300MHz, δ) : 7.4-7.55 (2H, m),

- 125 -

7.6-7.75 (4H, m), 8.05 (1H, d, J=8Hz), 8.15 (1H, dd, J=2Hz, 8Hz), 8.43 (1H, t, J=2Hz)

Preparation 84

5 To a mixture of 3,5-dichloroaniline (8.1 g) and triethylamine (7.0 ml) in chloroform (100 ml) was added dropwise a solution of 3-nitrobenzoyl chloride (9.3 g) in chloroform (50 ml). The mixture was stirred at room temperature for 1 hour, then poured into aqueous sodium bicarbonate. The resultant precipitate was collected and washed with chloroform and water to give 3-nitro-N-(3,5-dichlorophenyl)benzamide (12.50 g).

10 NMR (DMSO-d₆, 300MHz, δ) : 7.38 (1H, s), 7.8-7.9 (3H, m), 8.39 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.80 (1H, s)

Preparation 85

A mixture of 2-[3-(3,5-dichlorophenylcarbamoyl)-phenylamino]-3-nitropyridine (565 mg) and iron powder (0.4 g) in acetic acid (5 ml) and 1,4-dioxane (5 ml) was stirred at 80°C for 3 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-amino-2-[3-(3,5-dichlorophenylcarbamoyl)phenylamino]pyridine (284 mg).

25 NMR (DMSO-d₆, 300MHz, δ) : 5.12 (2H, s), 6.68 (1H, m), 6.93 (1H, d, J=8Hz), 7.3-7.6 (4H, m), 7.9-8.1 (5H, m)

Preparation 86

To a suspension of sodium hydride (60% in oil, 1.1 g) in N,N-dimethylformamide (20 ml) was added dropwise a

- 126 -

solution of 3-nitro-N-(3,5-dichlorophenyl)benzamide (5.89 g) in N,N-dimethylformamide (40 ml). The mixture was stirred at room temperature for 1 hour, then iodomethane (3 ml) was added thereto. After stirring at room
5 temperature for 1 hour, dilute hydrochloric acid was added to the mixture and extracted with ethyl acetate twice. The combined organic solution was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was solidified with isopropyl ether to give
10 3-nitro-N-methyl-N-(3,5-dichlorophenyl)benzamide (4.62 g).
NMR (CDCl₃, 300MHz, δ) : 3.49 (3H, s), 7.00 (2H, s),
7.21 (1H, m), 7.48 (1H, t, J=8Hz), 7.63 (1H, d,
J=8Hz), 8.15-8.25 (2H, m)

15 Preparation 87

A mixture of 3-amino-2-(3-biphenylamino)pyridine (157 mg) and 4-methyl-2-oxopentanoic acid (94 mg) in ethanol (3 ml) was stirred under reflux for 2 hours. The mixture was cooled and then poured into a mixture of ethyl
20 acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (hexane - ethyl acetate, 3:1) to give 4-(3-biphenyl)-2-isobutyl-3-
25 oxo-3,4-dihydropyrido[2,3-b]pyrazine (47 mg).

NMR (CDCl₃, 300MHz, δ) : 1.07 (6H, d, J=7Hz), 2.39
(1H, m), 2.90 (2H, d, J=7Hz), 7.25-7.5 (6H, m),
7.6-7.8 (4H, m), 8.20 (1H, d, J=8Hz), 8.43 (1H,
d, J=5Hz)

30

Preparation 88

The following compounds were obtained according to a similar manner to that of Preparation 87.

35 (1) 4-(3-Iodophenyl)-2-methyl-3-oxo-3,4-

- 127 -

dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 2.48 (3H, s), 7.38 (3H, s), 7.78 (1H, s), 7.75 (1H, m), 8.20 (1H, m), 8.36 (1H, m)

5

(2) 2-Methyl-4-(3-succinimidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 2.79 (4H, s), 3.31 (3H, s), 7.30 (1H, s), 7.36-7.45 (3H, m), 7.65 (1H, t, J=8Hz), 8.22 (1H, d, J=7Hz), 8.37 (1H, d, J=5Hz)

10

(3) 2-Isobutyl-4-[3-(2-naphthoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 1.04 (6H, d, J=7Hz), 2.38 (1H, m), 2.89 (2H, d, J=7Hz), 6.85 (1H, dt, J=8Hz, 2Hz), 7.29 (1H, dd, J=5Hz, 8Hz), 7.45-7.60 (3H, m), 7.72 (1H, dd, J=2Hz, 8Hz), 7.8-7.9 (5H, m), 8.18 (1H, dd, J=2Hz, 8Hz), 8.32 (1H, s), 8.40 (1H, dd, J=2Hz, 5Hz), 8.52 (1H, s)

15

20

(4) 2-Methyl-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 2.49 (3H, s), 3.86 (3H, s), 7.39 (1H, dd, J=4Hz, 7Hz), 7.67 (1H, d, J=7Hz), 7.72 (1H, dd, J=6Hz, 7Hz), 7.97 (1H, s), 8.08 (1H, d, J=7Hz), 8.22 (1H, d, J=6Hz), 8.35 (1H, d, J=4Hz)

25

(5) 4-(3-Biphenyllyl)-2-(1-methylpropyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 1.00 (3H, t, J=7Hz), 1.34 (3H, d, J=7Hz), 1.65 (1H, m), 1.98 (1H, m), 3.50 (1H, m), 7.25-7.45 (5H, m), 7.52 (1H, s), 7.6-7.7 (3H, m), 7.76 (1H, dd, J=2Hz, 8Hz), 8.20

35

- 128 -

(1H, dd, J=2Hz, 8Hz), 8.42 (1H, d, J=5Hz)

(6) 2-Isobutyl-4-[3-(1H-1,2,4-triazol-1-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (CDCl₃, 300MHz, δ) : 1.07 (6H, d, J=7Hz), 2.38 (1H, m), 2.90 (2H, d, J=7Hz), 7.3-7.4 (2H, m), 7.7-7.8 (2H, m), 7.86 (1H, dd, J=2Hz, 8Hz), 8.10 (1H, s), 8.40 (1H, dd, J=2Hz, 5Hz), 8.60 (1H, s)

10 (7) 2-Methyl-4-[3-(1-naphthyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 196-198°C

NMR (CDCl₃, δ) : 2.68 (3H, s), 7.30 (1H, dd, J=8Hz, 6Hz), 7.38 (1H, m), 7.4-7.55 (5H, m), 7.70 (2H, m), 7.88 (2H, m), 8.09 (1H, m), 8.15 (1H, d, J=8Hz), 8.47 (1H, d, J=6Hz)

15

(8) 2-Methyl-4-(3-biphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (CDCl₃, 300MHz, δ) : 2.68 (3H, s), 7.25-7.50 (6H, m), 7.59-7.68 (3H, m), 7.50 (1H, dd, J=8Hz, 3Hz), 8.16 (1H, dd, J=8Hz, 3Hz), 8.41 (1H, dd, J=7Hz, 3Hz)

25 (9) 2-Methyl-4-(3-acetamidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 2.04 (3H, s), 2.49 (3H, s), 6.98 (1H, d, J=7Hz), 7.39 (1H, dd, J=5Hz, 7Hz), 7.44 (1H, dd, J=7Hz, 7Hz), 7.57 (1H, d, J=7Hz), 7.65 (1H, s), 8.21 (1H, d, J=7Hz), 8.47 (1H, d, J=5Hz)

30

Preparation 89

A mixture of 3-amino-2-[(3-cyclopentyloxy-4-methoxyphenyl)amino]pyridine (180 mg) and 2-oxosuccinic

35

- 129 -

acid (90 mg) in ethanol (4 ml) was stirred under reflux for 1.5 hours. The mixture was cooled and then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was washed with ethanol to give 4-(3-cyclopentyloxy-4-methoxyphenyl)-2-methyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (100 mg).

NMR (CDCl₃, 300MHz, δ) : 1.5-1.65 (2H, m), 1.75-2.0 (6H, m), 2.67 (3H, s), 3.91 (3H, s), 4.73 (1H, m), 6.77 (1H, d, J=2Hz), 6.82 (1H, dd, J=2Hz, 8Hz), 7.04 (1H, d, J=8Hz), 7.29 (1H, m), 8.15 (1H, d, J=8Hz), 8.46 (1H, d, J=5Hz)

15 Preparation 90

The suspension of 2-methyl-4-(3-acetamidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (8.6 g) in 3N hydrochloric acid (50 ml) was refluxed for an hour. The mixture was made basic by sodium bicarbonate (15 g) to obtain 2-methyl-4-(3-aminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (7.4 g) in yellow powder.

NMR (CDCl₃, 300MHz, δ) : 2.64 (3H, s), 3.80 (2H, br s), 6.57 (1H, d, J=3Hz), 6.63 (1H, d, J=7Hz), 6.81 (1H, dd, J=7Hz, 3Hz), 7.25-7.30 (2H, m), 7.35 (1H, dd, J=7Hz, 7Hz), 8.13 (1H, d, J=7Hz), 8.44 (1H, m)

Preparation 91

The following compound was obtained according to a similar manner to that of Preparation 73 or 74.

2-(3-Phenylsulfonylamino)phenylamino)-3-nitropyridine

NMR (DMSO-d₆, δ) : 6.83 (1H, m), 7.00 (1H, dd, J=8Hz, 4Hz), 7.20 (2H, m), 7.58 (4H, m), 7.82 (2H, m), 8.50 (2H, m), 9.87 (1H, s)

- 130 -

Preparation 92

A mixture of 2-methoxy-5-nitrophenol (4.86 g), cyclopentyl bromide (3.4 ml) and potassium carbonate (4.8 g) in N,N-dimethylformamide (50 ml) was stirred at 50°C for 3 hours. Then the mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-cyclopentyloxy-4-methoxy-1-nitrobenzene (5.05 g).

NMR (CDCl₃, 300MHz, δ) : 1.6-2.1 (8H, m), 3.94 (3H, s), 4.86 (1H, m), 6.90 (1H, d, J=8Hz), 7.75 (1H, d, J=2Hz), 7.90 (1H, dd, J=2Hz, 8Hz)

Preparation 93

A mixture of 3-cyclopentyloxy-4-methoxy-1-nitrobenzene (5.02 g), iron powder (4.8 g) and hydrochloric acid (35%, 15 ml) in ethanol (40 ml) was stirred under reflux for 3 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated to give 3-cyclopentyloxy-4-methoxyaniline (2.60 g) as an oil.

NMR (DMSO-d₆, 300MHz, δ) : 1.5-1.9 (8H, m), 3.59 (3H, s), 4.55-4.7 (3H, m), 6.05 (1H, m), 6.23 (1H, d, J=2Hz), 6.61 (1H, d, J=8Hz)

Preparation 94

A mixture of 2-chloro-3-nitropyridine (2.17 g), 3-cyclopentyloxy-4-methoxyaniline (2.58 g) and potassium carbonate (2.6 g) in 1,4-dioxane (30 ml) was stirred under reflux for 20 hours. After cooling, insoluble materials were removed by filtration and the filtrate was

- 131 -

concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-[(3-cyclopentyloxy-4-methoxyphenyl)amino]-3-nitropyridine (1.35 g) as an orange solid.

5 NMR (CDCl₃, 300MHz, δ) : 1.55-1.7 (2H, m), 1.8-2.0 (6H m), 3.86 (3H, s), 4.79 (1H, m), 6.79 (1H, dd, J=5Hz, 8Hz), 6.89 (1H, d, J=8Hz), 7.09 (1H, m), 7.19 (1H, m), 8.46 (1H, d, J=5Hz), 8.52 (1H, dd, J=2Hz, 8Hz)

10

Preparation 95

A mixture of 2-[(3-cyclopentyloxy-4-methoxyphenyl)-amino]-3-nitropyridine (1.30 g) and 10% palladium on carbon (0.3 g) in ethanol (20 ml) and 1,4-dioxane (20 ml) was stirred under hydrogen (3 atm) at room temperature for 1 hours. The catalyst was removed by filtration and the solvent was evaporated. The resulting solid was collected and washed with isopropyl ether to give 3-amino-2-[(3-cyclopentyloxy-4-methoxyphenyl)amino]pyridine (992 mg).

20 NMR (DMSO-d₆, 300MHz, δ) : 1.5-1.95 (8H, m), 3.69 (3H, s), 4.70 (1H, m), 6.58 (1H, dd, J=5Hz, 8Hz), 6.8-6.9 (2H, m), 7.15 (1H, m), 7.31 (1H, d, J=2Hz), 7.42 (1H, d, J=5Hz), 7.70 (1H, s)

25 Preparation 96

To a mixture of 3-nitroaniline (2.07 g) and triethylamine (2.3 ml) in 1,4-dioxane (40 ml) was added 2-naphthoyl chloride (3.00 g) and the mixture was stirred at room temperature for 30 minutes. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate three times. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give N-(3-nitrophenyl)-2-naphthalenecarboxamide (3.02 g).

35

- 132 -

NMR (DMSO-d₆, 300MHz, δ) : 7.6-7.75 (3H, m),
7.95-8.15 (5H, m), 8.28 (1H, dt, J=8Hz, 2Hz),
8.65 (1H, s), 8.87 (1H, t, J=2Hz)

5 Preparation 97

A mixture of N-(3-nitrophenyl)-2-naphthalenecarboxamide (2.94 g), iron powder (3.0 g) and hydrochloric acid (35%, 9 ml) in ethanol (30 ml) was stirred at 80°C for 2 hours. Then the mixture was poured
10 into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give N-(3-
15 aminophenyl)-2-naphthalenecarboxamide (2.17 g).

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.34 (1H, dt, J=8Hz, 2Hz), 6.91 (1H, dt, J=8Hz, 2Hz), 6.99 (1H, t, J=8Hz), 7.17 (1H, t, J=2Hz), 7.6-7.7 (2H, m), 7.95-8.1 (4H, m), 8.55 (1H, s)

20

Preparation 98

A mixture of 2-chloro-3-nitropyridine (0.87 g), N-(3-aminophenyl)-2-naphthalenecarboxamide (1.31 g) and potassium carbonate (1.0 g) in 1,4-dioxane (20 ml) was
25 stirred under reflux for 20 hours. After cooling, insoluble materials were removed by filtration and the filtrate was concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-[3-(2-naphthoylamino)phenylamino]-3-nitropyridine (961 mg) as an
30 orange solid.

NMR (DMSO-d₆, 300MHz, δ) : 7.02 (1H, dd, J=5Hz, 8Hz), 7.39 (1H, t, J=8Hz), 7.47 (1H, d, J=8Hz), 7.6-7.7 (3H, m), 8.0-8.2 (5H, m), 8.55-8.65 (3H, m)

35

- 133 -

Preparation 99

A mixture of 2-[3-(2-naphthoylamino)phenylamino]-3-nitropyridine (948 mg), iron powder (0.55 g) and hydrochloric acid (35%, 2 ml) in ethanol (8 ml) was stirred at 80°C for 30 minutes. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-amino-2-[3-(2-naphthoylamino)phenylamino]pyridine (682 mg).

NMR (DMSO-d₆, 300MHz, δ) : 5.11 (2H, s), 6.64 (1H, dd, J=5Hz, 8Hz), 6.92 (1H, dd, J=2Hz, 8Hz), 7.2-7.3 (2H, m), 7.45 (1H, dt, J=8Hz, 2Hz), 7.52 (1H, dd, J=2Hz, 5Hz), 7.6-7.7 (2H, m), 7.80 (1H, s), 8.0-8.15 (5H, m), 8.60 (1H, s)

Preparation 100

The following compound was obtained by subjecting 2-(3-carboxyphenylamino)-3-aminopyridine to methyl esterification in the conventional manner.

2-(3-Methoxycarbonylphenylamino)-3-aminopyridine

NMR (CDCl₃, δ) : 3.95 (3H, s), 6.89 (1H, dd, J=8Hz, 5Hz), 7.49 (1H, dd, J=8Hz, 8Hz), 7.86 (1H, m), 7.92 (1H, m), 8.30 (1H, m), 8.53 (1H, m)

Preparation 101

A mixture of 3-nitrostyrene (3.98 g), 3,5-dichloropyridine (3.70 g), palladium(II) acetate (0.20 g), tetrabutylammonium chloride (7.0 g) and sodium bicarbonate (5.3 g) in N,N-dimethylformamide (35 ml) was stirred at 135°C for 2 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl

- 134 -

acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-chloro-5-[(E)-2-(3-nitrophenyl)vinyl]pyridine (3.01 g).

NMR (CDCl₃, 300MHz, δ) : 7.1-7.3 (2H, m), 7.59 (1H, t, J=8Hz), 7.8-7.9 (2H, m), 8.18 (1H, m), 8.40 (1H, t, J=2Hz), 8.51 (1H, d, J=2Hz), 8.63 (1H, s)

Preparation 102

A mixture of 3-chloro-5-[(E)-2-(3-nitrophenyl)vinyl]pyridine (2.99 g), iron powder (2.6 g) and hydrochloric acid (35%, 8 ml) in methanol (50 ml) was stirred at 60°C for 3 hours. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 3-[(E)-2-(3-aminophenyl)vinyl]-5-chloropyridine (1.33 g).

NMR (DMSO-d₆, 300MHz, δ) : 5.13 (2H, s), 6.54 (1H, d, J=8Hz), 6.79 (2H, m), 7.0-7.15 (2H, m), 7.37 (1H, d, J=16Hz), 8.21 (1H, s), 8.47 (1H, d, J=2Hz), 8.70 (1H, s)

Preparation 103

The following compound was obtained according to a similar manner to that of Preparation 1, 5, 27, 28, 47, 48, 49, 68 or 69.

2-[3-[(E)-2-(5-Chloropyridin-3-yl)vinyl]phenylamino]-3-nitropyridine

NMR (CDCl₃, 300MHz, δ) : 6.88 (1H, dd, J=5Hz, 8Hz), 7.06 (1H, d, J=16Hz), 7.20 (1H, d, J=16Hz),

- 135 -

7.3-7.45 (2H, m), 7.61 (1H, d, J=8Hz), 7.85 (2H, m), 8.47 (1H, s), 8.5-8.6 (3H, m)

Preparation 104

5 The following compound was obtained according to a similar manner to that of Preparation 3, 31, 33, 52, 53, 54 or 71.

10 3-Amino-2-[3-[(E)-2-(5-chloropyridin-3-yl)vinyl]phenylamino]pyridine

NMR (DMSO-d₆, 300MHz, δ) : 5.10 (2H, s), 6.64 (1H, dd, J=5Hz, 8Hz), 6.91 (1H, d, J=8Hz), 7.1-7.3 (3H, m), 7.4-7.65 (3H, m), 7.75-7.9 (2H, m), 8.27 (1H, s), 8.48 (1H, s), 8.73 (1H, s)

15

20

25

30

35

- 136 -

Example 1

A mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (150 mg) and 1-naphthyl isocyanate (94 mg) in dry dioxane (3 ml) was stirred at room temperature for 3 hours. The precipitates were collected and washed with isopropyl ether to give 4-[3-[3-(1-naphthyl)ureido]phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 4.23 (2H, s), 6.95 (1H, m), 7.15-7.7 (13H, m), 7.95 (2H, t, J=7Hz), 8.11 (1H, d, J=8Hz), 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz), 8.83 (1H, s), 9.25 (1H, s)

Example 2

A mixture of 3-amino-2-[(m-tolyl)amino]pyridine (299 mg) and phenylpyruvic acid (246 mg) in ethanol (5 ml) was refluxed for 2 hours. The mixture was cooled and the precipitates were collected and washed with ethanol to give 2-benzyl-3-oxo-4-(m-tolyl)-3,4-dihydropyrido[2,3-b]pyrazine (264 mg).

NMR (CDCl₃, δ) : 2.42 (3H, s), 4.31 (2H, s), 7.05 (2H, d, J=8Hz), 7.2-7.55 (8H, m), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz)

Example 3

The following compounds were obtained according to a similar manner to that of Example 2.

(1) 2-Benzyl-3-oxo-4-(pyridin-3-yl)-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 4.32 (2H, s), 7.15-7.4 (4H, m), 7.45-7.6 (3H, m), 7.68 (1H, dt, J=3Hz, 1.5Hz), 8.21 (1H, dd, J=1.5Hz, 8Hz), 8.37 (1H, dd, J=1.5Hz, 5Hz), 8.57 (1H, d, J=1.5Hz), 8.73 (1H, dd, J=1.5Hz, 5Hz)

- 137 -

- (2) 2-Benzyl-3-oxo-4-(pyridin-2-yl)-3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (CDCl₃, δ) : 4.30 (2H, s), 7.2-7.55 (8H, m),
7.97 (1H, dt, J=1.5Hz, 8Hz), 8.19 (1H, dd,
J=1.5Hz, 8Hz), 8.36 (1H, dd, J=1.5Hz, 5Hz), 8.75
(1H, m)

- (3) 2-Benzyl-4-(1-naphthyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

10 NMR (CDCl₃, δ) : 4.36 (2H, d, J=5Hz), 7.1-7.55 (10H,
m), 7.64 (1H, t, J=8Hz), 7.9-8.1 (2H, m), 8.15-
8.35 (2H, m)

- (4) 4-(3-Acetamidophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

15 NMR (DMSO-d₆, δ) : 2.05 (3H, s), 4.21 (2H, s), 6.99
(1H, dt, J=8Hz, 1Hz), 7.15-7.5 (7H, m), 7.58
(2H, d, J=8Hz), 8.23 (1H, dd, J=1.5Hz, 8Hz),
8.38 (1H, dd, J=1.5Hz, 5Hz), 10.13 (1H, s)

- (5) 2-Benzyl-4-(3-ethoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (CDCl₃, δ) : 1.37 (3H, t, J=7Hz), 4.25-4.45 (4H,
m), 7.15-7.55 (7H, m), 7.65 (1H, t, J=8Hz), 7.95
25 (1H, s), 8.20 (2H, dd, J=1.5Hz, 8Hz), 8.38 (1H,
dd, J=1.5Hz, 5Hz)

- (6) 2-Benzyl-4-(4-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

30 NMR (CDCl₃, δ) : 3.96 (3H, s), 4.31 (2H, s), 7.2-
7.55 (8H, m), 8.15-8.3 (3H, m), 8.38 (1H, dd,
J=1.5Hz, 5Hz)

- (7) 2-Benzyl-4-(4-methoxycarbonylmethylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

35

- 138 -

NMR (CDCl₃, δ) : 3.70 (2H, s), 3.72 (3H, s), 4.30 (2H, s), 7.15-7.4 (6H, m), 7.48 (4H, m), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz)

5

- (8) 2-Benzyl-4-(3-methoxycarbonylmethylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 3.69 (5H, s), 4.31 (2H, s), 7.15-7.6 (10H, m), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz)

10

- (9) 4-(4-Acetylphenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 2.67 (3H, s), 4.32 (2H, s), 7.2-7.55 (8H, m), 8.1-8.25 (3H, m), 8.38 (1H, dd, J=1.5Hz, 5Hz)

15

- (10) 4-(3-Acetylphenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 2.61 (3H, s), 4.32 (2H, s), 7.2-7.35 (4H, m), 7.45-7.55 (3H, m), 7.68 (1H, t, J=8Hz), 7.86 (1H, s), 8.09 (1H, dt, J=8Hz, 1.5Hz), 8.20 (1H, dd, J=1.5Hz, 8Hz), 8.37 (1H, dd, J=1.5Hz, 5Hz)

20

25

- (11) 2-Benzyl-4-(3-fluorophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 4.31 (2H, s), 6.95-7.1 (2H, m), 7.15-7.4 (5H, m), 7.45-7.65 (3H, m), 8.20 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz)

30

- (12) 2-Benzyl-4-(3-hydroxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 4.21 (2H, s), 6.72 (2H, d, J=8Hz), 6.88 (1H, m), 7.2-7.45 (6H, m), 8.22

35

- 139 -

(1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.71 (1H, s)

(13) 2-Benzyl-4-(4-methoxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 3.87 (3H, s), 4.31 (2H, s), 7.0-7.4 (8H, m), 7.51 (2H, d, J=8Hz), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz)

(14) 2-Benzyl-4-(3-methoxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 3.81 (3H, s), 4.31 (2H, s), 6.75-6.9 (2H, m), 7.05 (1H, m), 7.2-7.55 (7H, m), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.42 (1H, dd, J=1.5Hz, 5Hz)

Example 4

A mixture of 2-benzyl-4-(3-hydroxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (135 mg), acetic anhydride (84 mg), triethylamine (83 mg) and 4-dimethylaminopyridine (5 mg) in dichloromethane (2 ml) was stirred at room temperature for 1 hour. The mixture was poured into ethyl acetate and washed with water and brine, dried over magnesium sulfate and concentrated. The solids were collected and washed with isopropyl ether to give 4-(3-acetoxyphenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (90 mg).

NMR (CDCl₃, δ) : 2.28 (3H, s), 4.30 (2H, s), 7.05-7.35 (7H, m), 7.45-7.6 (3H, m), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz)

Example 5

1N aqueous solution of sodium hydroxide (2 ml) was added to a solution of 2-benzyl-4-(3-methoxycarbonylmethylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (213

- 140 -

mg) in methanol (4 ml) and 1,4-dioxane (2 ml). After stirred at room temperature for 1 hour, the mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate and concentrated to give 2-benzyl-4-(3-carboxymethylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (163 mg) as powder.

NMR (DMSO-d₆, δ) : 3.64 (2H, s), 4.21 (2H, s), 7.15-7.65 (10H, m), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz)

Example 6

The following compounds were obtained according to a similar manner to that of Example 5.

(1) 2-Benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 4.22 (2H, s), 7.15-7.75 (8H, m), 7.92 (1H, s), 8.05 (1H, dt, J=8Hz, 1.5Hz), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz)

(2) 2-Benzyl-4-(4-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 4.22 (2H, s), 7.2-7.6 (8H, m), 8.10 (2H, d, J=9Hz), 8.26 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz)

(3) 2-Benzyl-4-(4-carboxymethylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 3.68 (2H, s), 4.21 (2H, s), 7.15-7.5 (10H, m), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz)

Example 7

- 141 -

A mixture of 2-benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (143 mg), ethylamine hydrochloride (39 mg), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (92 mg) and triethylamine (49 mg) in dichloromethane (2 ml) and N,N-dimethylformamide (1 ml) was stirred at room temperature for 3 hours. The mixture was poured into ethyl acetate and washed with water and brine, dried over magnesium sulfate and concentrated. The residue was subjected to preparative thin layer chromatography (hexane - ethyl acetate, 1:4) to afford 2-benzyl-4-(3-ethylcarbamoylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (16 mg) as powder.

NMR (CDCl₃, δ) : 1.22 (3H, t, J=7Hz), 3.48 (2H, m), 4.30 (2H, s), 6.14 (1H, br s), 7.2-7.45 (5H, m), 7.48 (2H, d, J=7Hz), 7.6-7.7 (2H, m), 7.90 (1H, d, J=8Hz), 8.19 (1H, d, J=8Hz), 8.37 (1H, m)

Example 8

The following compound was obtained according to a similar manner to that of Example 7.

2-Benzyl-4-(3-methylcarbamoylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 2.98 (3H, d, J=7Hz), 4.31 (2H, s), 6.22 (1H, br s), 7.2-7.55 (8H, m), 7.6-7.8 (2H, m), 7.88 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.37 (1H, m)

Example 9

A mixture of 2-benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (50 mg), 1-iodopropane (48 mg) and potassium carbonate (58 mg) in N,N-dimethylformamide (1 ml) was stirred at room temperature for 2 hours. The mixture was poured into ethyl acetate

- 142 -

and washed with water and brine, dried over magnesium sulfate and concentrated. The residue was subjected to preparative thin layer chromatography (hexane - ethyl acetate, 1:1) to afford 2-benzyl-3-oxo-4-(3-propyloxycarbonylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine (18 mg) as powder.

NMR (CDCl₃, δ) : 0.99 (3H, t, J=7Hz), 1.77 (2H, m), 4.2-4.35 (4H, m), 7.15-7.55 (7H, m), 7.66 (1H, t, J=8Hz), 7.95 (1H, s), 8.19 (2H, dt, J=1.5Hz, 8Hz), 8.38 (1H, dt, J=1.5Hz, 5Hz)

Example 10

A mixture of 2-benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (166 mg), diphenylphosphoryl azide (128 mg) and triethylamine (47 mg) in ethanol (3 ml) was refluxed for 4 hours. The mixture was poured into ethyl acetate and washed with water and brine, dried over magnesium sulfate and concentrated. The residue was subjected to silica gel column chromatography (hexane - ethyl acetate, 1:1) to afford 2-benzyl-4-(3-ethoxycarbonylamino-phenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (35 mg) as powder.

NMR (CDCl₃, δ) : 1.27 (3H, t, J=7Hz), 4.18 (2H, q, J=7Hz), 4.30 (2H, s), 6.82 (1H, s), 6.94 (1H, dt, J=8Hz, 1.5Hz), 7.15-7.55 (9H, m), 8.18 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz)

Example 11

A mixture of 4-(3-acetamidophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (6.03 g) in 3N hydrochloric acid (150 ml) was refluxed for 1 hour. Sodium bicarbonate was added thereto until the mixture was alkaline. The mixture was extracted with ethyl acetate and the organic solution was washed with water and brine, dried over magnesium sulfate and concentrated to give the

- 143 -

solids. The solids were collected and washed with ethanol to give 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (5.05 g).

5 NMR (DMSO-d₆, δ) : 4.20 (2H, s), 5.27 (2H, s), 6.39 (2H, d, J=8Hz), 6.66 (1H, d, J=8Hz), 7.1-7.45 (7H, m), 8.22 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz)

Example 12

10 The following compounds were obtained according to a similar manner to that of Example 1.

(1) 4-[3-(3-Ethylureido)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

15 NMR (DMSO-d₆, δ) : 1.03 (3H, t, J=7Hz), 3.08 (2H, m), 4.20 (2H, s), 6.16 (1H, t, J=6Hz), 6.82 (1H, m), 7.2-7.45 (9H, m), 8.22 (1H, d, J=8Hz), 8.38 (1H, d, J=5Hz), 8.60 (1H, s)

20 (2) 4-[3-(3-Phenylureido)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 4.22 (2H, s), 6.9-7.0 (2H, m), 7.2-7.55 (13H, m), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 8.72 (1H, s), 8.87 (1H, s)

25

Example 13

To a solution of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (200 mg) in acetic acid (2 ml) and water (2 ml) was added solution of potassium cyanate (99 mg) in water (1 ml). The mixture was stirred at room temperature for 2 hours and concentrated. The residue was dissolved in ethyl acetate and washed with an aqueous sodium bicarbonate solution, and brine, dried over magnesium sulfate and concentrated. The residue was

30

35

- 144 -

subjected to silica gel column chromatography (4% methanol in chloroform) to afford 2-benzyl-3-oxo-4-(3-ureidophenyl)-3,4-dihydropyrido[2,3-b]pyrazine (78 mg) as solid.

5 NMR (DMSO-d₆, δ) : 4.21 (2H, s), 5.92 (2H, s), 6.84 (1H, m), 7.15-7.5 (9H, m), 8.22 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz), 8.72 (1H, s)

10 Example 14

A mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (150 mg), phenylisothiocyanate (79 mg) in 1,4-dioxane (2 ml) was stirred at 80°C for 4 hours. The precipitates were collected and washed with isopropyl ether to give 2-benzyl-3-oxo-4-[3-(3-(phenylthioureido)phenyl)]-3,4-dihydropyrido[2,3-b]pyrazine (113 mg).

15 NMR (DMSO-d₆, δ) : 4.22 (2H, s), 7.05-7.55 (14H, m), 7.74 (1H, d, J=8Hz), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz), 9.86 (1H, s), 9.93 (1H, s)

Example 15

25 The following compounds were obtained according to a similar manner to that of Example 1.

(1) 2-Benzyl-3-oxo-4-[3-(3-phenylsulfonylureido)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

30 NMR (DMSO-d₆, 200MHz, δ) : 4.19 (2H, s), 6.98 (1H, m), 7.15-7.5 (9H, m), 7.55-7.75 (3H, m), 7.95 (2H, dd, J=1.5Hz, 8Hz), 8.21 (1H, dd, J=1.5Hz, 8Hz), 8.36 (1H, m), 9.09 (1H, s)

(2) 2-Benzyl-3-oxo-4-[3-(3-benzylureido)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

35

- 145 -

NMR (DMSO-d₆, 200MHz, δ) : 4.21 (2H, s), 4.28 (1H, d, J=6Hz), 6.70 (1H, t, J=6Hz), 6.85 (1H, m), 7.15-7.5 (14H, m), 8.22 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz), 8.78 (1H, s)

5

- (3) 2-Benzyl-3-oxo-4-[3-[3-(4-nitrophenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.99 (1H, m), 7.2-7.6 (9H, m), 7.68 (2H, d, J=9Hz), 8.15-8.3 (3H, m), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.23 (1H, s), 9.50 (1H, s)

10

- (4) 2-Benzyl-3-oxo-4-[3-[3-(3-nitrophenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 4.23 (2H, s), 6.98 (1H, m), 7.2-7.9 (12H, m), 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 8.58 (1H, t, J=1.5Hz), 9.07 (1H, s), 9.30 (1H, s)

15

- (5) 2-Benzyl-3-oxo-4-[3-[3-(2-nitrophenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.99 (1H, m), 7.15-7.6 (11H, m), 7.68 (1H, dt, J=1.5Hz, 8Hz), 8.09 (1H, dd, J=1.5Hz, 8Hz), 8.2-8.3 (2H, m), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.63 (1H, s), 10.05 (1H, s)

20

- (6) 2-Benzyl-3-oxo-4-[3-[3-(4-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 3.71 (3H, s), 4.22 (2H, s), 6.8-6.95 (3H, m), 7.2-7.6 (11H, m), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 8.52 (1H, s), 8.78 (1H, s)

30

- (7) 2-Benzyl-3-oxo-4-[3-[3-(3-methoxyphenyl)-

35

- 146 -

ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 3.71 (3H, s), 4.22 (2H, s), 6.55 (1H, dd, J=1.5Hz, 8Hz), 6.85-7.00 (2H, m), 7.1-7.5 (10H, m), 7.55 (1H, s), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 8Hz), 8.73 (1H, s), 8.86 (1H, s)

5

(8) 2-Benzyl-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

10 NMR (DMSO-d₆, 200MHz, δ) : 3.88 (3H, s), 4.22 (2H, s), 6.8-7.1 (4H, m), 7.2-7.6 (1H, m), 8.08 (1H, dd, J=1.5Hz, 8Hz), 8.2-8.3 (2H, m), 8.39 (1H, dd, J=1.5Hz, 5Hz), 9.51 (1H, s)

15 (9) 2-Benzyl-3-oxo-4-[3-[3-(3-methylthiophenyl)ureido]-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (DMSO-d₆, 300MHz, δ) : 2.44 (3H, s), 4.22 (2H, s), 6.8-7.0 (2H, m), 7.1-7.6 (12H, m), 8.23 (1H, d), 8.40 (1H, d, J=5Hz), 8.78 (1H, s), 8.89 (1H, s)

(10) 2-Benzyl-3-oxo-4-[3-[3-(4-trifluoromethylphenyl)-ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

25 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.97 (1H, m), 7.2-7.7 (13H, m), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.01 (1H, s), 9.17 (1H, s)

(11) 2-Benzyl-3-oxo-4-[3-[3-(3,4-dichlorophenyl)ureido]-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

30 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.97 (1H, m), 7.2-7.6 (11H, m), 7.88 (1H, d, J=3Hz), 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.03 (1H, s), 9.07 (1H, s)

35

- 147 -

(12) 2-Benzyl-3-oxo-4-[3-(3-phenyl-1-methylureido)phenyl]-
3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 3.34 (3H, s), 4.22 (2H,
s), 6.98 (1H, t, J=8Hz), 7.15-7.65 (14H, m),
5 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.32 (1H, s), 8.41
(1H, dd, J=1.5Hz, 5Hz)

Example 16

The following compounds were obtained according to a
10 similar manner to that of Example 2.

(1) 2-(4-Nitrophenyl)-3-oxo-4-phenyl-3,4-
dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 7.38-7.63 (6H, m),
15 8.35-8.54 (6H, m)

(2) 2-Benzyl-3-oxo-4-[3-(N-methylacetamido)phenyl]-3,4-
dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 1.88 (3H, s), 3.20 (3H,
20 s), 4.22 (2H, s), 7.15-7.65 (10H, m), 8.24 (1H,
dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz)

(3) 2-(3-Indolyl)-3-oxo-4-phenyl-3,4-dihydropyrido-
[2,3-b]pyrazine

25 NMR (DMSO-d₆, 200MHz, δ) : 6.62 (1H, dd, J=7Hz,
9Hz), 6.82 (1H, d, J=7Hz), 6.88 (1H, dd, J=1Hz,
9Hz), 7.16-7.34 (3H, m), 7.34-7.75 (6H, m), 8.32
(1H, m), 8.90 (1H, m)

30 (4) 2-(3-Indolylmethyl)-3-oxo-4-phenyl-3,4-
dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 4.31 (2H, s), 7.12-6.93
(2H, m), 7.27 (1H, d, J=1Hz), 7.28-7.40 (4H, m),
35 7.45-7.61 (3H, m), 7.67 (1H, d, J=10Hz), 8.22
(1H, dd, J=1Hz, 10Hz), 8.36 (1H, dd, J=1Hz, 5Hz)

- 148 -

- (5) 2-Phenethyl-3-oxo-4-phenyl-3,4-dihydropyrido[2,3-b]-pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 3.05-3.23 (4H, m), 7.15-7.60 (11H, m), 8.28 (1H, dd, J=1Hz, 8Hz), 8.39 (1H, dd, J=1Hz, 5Hz)

5

- (6) 2-(3-Phenylpropyl)-3-oxo-4-phenyl-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 2.21 (2H, quint, J=7Hz), 2.82 (2H, t, J=7Hz), 3.06 (2H, t, J=7Hz), 7.15-7.35 (8H, m), 7.49-7.63 (3H, m), 8.16 (1H, d, J=7Hz), 8.41 (1H, dd, J=1Hz, 7Hz)

10

- (7) 2-(2-Nitrobenzyl)-3-oxo-4-phenyl-3,4-dihydropyrido[2,3-b]pyrazine

15

NMR (DMSO-d₆, 200MHz, δ) : 4.63 (2H, s), 7.28-7.40 (3H, m), 7.48-7.80 (6H, m), 8.01 (1H, dd, J=1Hz, 10Hz), 8.12 (1H, dd, J=1Hz, 10Hz), 8.38 (1H, dd, J=1Hz, 5Hz)

20

- (8) 2-Benzyl-3-oxo-4-phenyl-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 200MHz, δ) : 4.31 (2H, s), 7.20-7.38 (6H, m), 7.42-7.62 (5H, m), 8.18 (1H, dd, J=1Hz, 8Hz), 8.40 (1H, dd, J=1Hz, 5Hz)

25

- (9) 2-Benzyl-3-oxo-4-(3-methoxycarbonylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 200MHz, δ) : 3.90 (3H, s), 4.32 (2H, s), 4.22-7.37 (4H, m), 7.45-7.53 (3H, m), 7.66 (1H, dd, J=9Hz, 9Hz), 7.95 (1H, dd, J=1Hz, 1Hz), 8.16-8.22 (2H, m), 8.38 (1H, dd, J=1Hz, 5Hz)

30

- (10) 2-(4-Hydroxybenzyl)-3-oxo-4-(3-methoxycarbonylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine

35

- 149 -

- 5 NMR (DMSO-d₆, 200MHz, δ) : 3.87 (3H, s), 3.90 (2H, s), 6.70 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 7.39 (1H, dd, J=5Hz, 9Hz), 7.75-7.61 (2H, m), 7.98 (1H, m), 8.08 (1H, m), 8.24 (1H, dd, J=1Hz, 9Hz), 8.37 (1H, dd, J=1Hz, 5Hz), 9.27 (1H, br s)
- (11) 3-Oxo-2-phenyl-4-[3-[3-(2-methoxyphenyl)-ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
10 NMR (DMSO-d₆, δ) : 3.87 (3H, s), 6.9-7.1 (4H, m), 7.3 (2H, m), 7.4-7.6 (6H, m), 7.65 (1H, s), 8.1 (1H, m), 8.3 (2H, m), 8.4 (1H, m), 9.55 (1H, s)
- (12) 2-(2-Carboxyethyl)-3-oxo-4-[3-[3-(2-methoxyphenyl)-ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
15 mp : 143-153°C (dec.)
NMR (DMSO-d₆, δ) : 2.78 (2H, t, J=7Hz), 3.11 (2H, t, J=7Hz), 3.88 (3H, s), 6.8-7.05 (4H, m), 7.45 (3H, m), 7.59 (1H, s), 8.10 (1H, d, J=7Hz), 8.25 (1H, d, J=7Hz), 8.29 (1H, s), 8.40 (1H, d, J=3Hz), 9.53 (1H, s)
20
- (13) 2-(4-Hydroxyphenylmethyl)-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
25 mp : 220-221°C
NMR (DMSO-d₆, δ) : 3.88 (3H, s), 4.10 (2H, s), 6.70 (2H, d, J=8Hz), 6.8-7.1 (4H, m), 7.18 (2H, d, J=8Hz), 7.43 (3H, m), 7.55 (1H, s), 8.08 (1H, d, J=7Hz), 8.25 (2H, m), 8.40 (1H, m), 9.26 (1H, s), 9.50 (1H, s)
30
- (14) 2-(2-Nitrophenylmethyl)-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
35 mp : 200-208°C (dec.)

- 150 -

NMR (DMSO-d₆, δ) : 3.90 (3H, s), 4.63 (2H, s), 6.8-7.1 (4H, m), 7.3-7.5 (3H, m), 7.6-7.7 (4H, m), 8.02 (1H, d, J=7Hz), 8.10 (2H, m), 8.30 (1H, s), 8.40 (1H, m), 9.55 (1H, s)

5

(15) 4-(3-Acetamidophenyl)-2-(2-carboxyethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 264-269°C (dec.)

10 NMR (DMSO-d₆, δ) : 2.05 (3H, s), 3.77 (2H, t, J=7Hz), 3.09 (2H, t, J=7Hz), 7.00 (1H, d, J=7Hz), 7.4 (3H, m), 7.60 (1H, d, J=7Hz), 7.64 (1H, s), 8.21 (1H, d, J=7Hz), 8.38 (1H, d, J=3Hz)

15 (16) 4-(3-Acetamidophenyl)-2-benzyl-6-ethoxy-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 212-214°C

20 NMR (DMSO-d₆, δ) : 1.25 (3H, t, J=7Hz), 2.08 (3H, s), 4.15 (5H, m), 6.70 (1H, d, J=8Hz), 7.05 (3H, m), 7.20 (3H, m), 7.47 (1H, dd, J=8Hz, 8Hz), 7.61 (1H, m), 7.75 (1H, s), 7.98 (1H, d, J=8Hz)

(17) 2-Benzyl-3-oxo-4-[3-((E)-2-methoxycarbonylvinyl)-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

25 NMR (CDCl₃, 300MHz, δ) : 3.78 (3H, s), 4.31 (2H, s), 6.43 (1H, d, J=16Hz), 7.2-7.35 (5H, m), 7.42 (1H, s), 7.50 (2H, d, J=8Hz), 7.55-7.75 (3H, m), 8.19 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz)

30

(18) 2-Benzyl-3-oxo-4-[3-((E)-2-cyanovinyl)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

d, NMR (CDCl₃, 300MHz, δ) : 4.30 (2H, s), 6.88 (1H, J=16Hz), 7.2-7.65 (11H, m), 8.20 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz)

35

- 151 -

- (19) 4-[3-((E)-2-Benzoylvinyl)phenyl]-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.35 (5H, m), 7.45-7.65 (8H, m), 7.77 (1H, d, J=8Hz), 7.82 (1H, d, J=16Hz), 7.98 (2H, dd, J=1.5Hz, 8Hz), 8.20 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz)
- (20) 2-Benzyl-3-oxo-4-[3-[2-(2-naphthyl)ethyl]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 2.95-3.15 (4H, m), 4.12 (2H, s), 7.17 (1H, d, J=8Hz), 7.2-7.5 (12H, m), 7.76 (3H, m), 8.23 (1H, d, J=8Hz), 8.38 (1H, d, J=5Hz)
- (21) 2-Benzyl-4-[3-[(E)-2-(2-naphthyl)vinyl]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.24 (2H, s), 7.2-7.6 (12H, m), 7.67 (1H, s), 7.75 (1H, d, J=8Hz), 7.85-7.95 (4H, m), 7.99 (1H, s), 8.27 (1H, dd, J=1.5Hz, 8Hz), 8.42 (1H, dd, J=1.5Hz, 5Hz)
- (22) 2-Benzyl-3-oxo-4-(3-phenethylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.1-7.5 (15H, m), 8.23 (1H, d, J=8Hz), 8.39 (1H, d, J=5Hz)
- (23) 2-Benzyl-3-oxo-4-((E)-3-styrylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.2-7.45 (12H, m), 7.5-7.65 (4H, m), 7.68 (1H, dd, J=1Hz, 8Hz), 8.25 (1H, d, J=8Hz), 8.39 (1H, d, J=5Hz)
- (24) 2-Benzyl-3-oxo-4-[3-(3-indolizinylicarbonyl)phenyl]-

- 152 -

3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.35 (2H, s), 6.54 (1H, d, J=5Hz), 6.95 (1H, m), 7.15-7.35 (5H, m), 7.45-7.6 (5H, m), 7.65-7.75 (2H, m), 7.97 (1H, d, J=8Hz), 8.19 (1H, d, J=8Hz), 8.42 (1H, d, J=5Hz), 9.96 (1H, d, J=7Hz)

5

(25) 2-Benzyl-3-oxo-4-[3-(4-methoxybenzoyl)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

10 NMR (CDCl₃, 300MHz, δ) : 3.98 (3H, s), 4.41 (2H, s), 7.05 (2H, d, J=8Hz), 7.3-7.45 (4H, m), 7.55-7.65 (3H, m), 7.75-7.85 (2H, m), 7.95-8.05 (3H, m), 8.28 (1H, d, J=8Hz), 8.49 (1H, d, J=5Hz)

15 (26) 2-Benzyl-3-oxo-4-[3-(imidazol-4-yl)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.12 (1H, d, J=8Hz), 7.15-7.8 (10H, m), 7.88 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 8.38 (1H, d, J=5Hz), 12.19 (1H, br s)

20

(27) 2-Benzyl-3-oxo-4-[3-[2-(pyridin-3-yl)thiazol-4-yl]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

25 NMR (DMSO-d₆, 300MHz, δ) : 4.23 (2H, s), 7.2-7.45 (7H, m), 7.55 (1H, dd, J=5Hz, 8Hz), 7.66 (1H, t, J=8Hz), 8.07 (1H, t, J=1.5Hz), 8.18 (1H, d, J=8Hz), 8.26 (1H, d, J=8Hz), 8.3-8.4 (3H, m), 8.68 (1H, d, J=5Hz), 9.20 (1H, d, J=1.5Hz)

30 (28) 4-[3-(2-Aminothiazol-4-yl)phenyl]-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.04 (3H, s), 7.2-7.45 (7H, m), 7.52 (1H, t, J=8Hz), 7.72 (1H, s), 7.89 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.38 (1H, d, J=5Hz)

35

- 153 -

- (29) 2-Benzyl-3-oxo-4-[3-(4-phenylpyrimidin-2-yl)oxy-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.21 (2H, s), 7.15-7.65 (13H, m), 7.87 (1H, d, J=5Hz), 8.13 (2H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.44 (1H, d, J=5Hz), 8.72 (1H, d, J=5Hz)
- (30) 2-Benzyl-3-oxo-4-[3-(pyrimidin-2-yl)oxyphenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.21 (2H, s), 7.15-7.5 (10H, m), 7.58 (1H, t, J=8Hz), 8.23 (1H, d, J=8Hz), 8.42 (1H, d, J=5Hz), 8.67 (2H, d, J=5Hz)
- (31) 2-Benzyl-3-oxo-4-[3-(pyrimidin-2-yl)aminophenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.23 (2H, s), 6.8-6.95 (2H, m), 7.2-7.5 (7H, m), 7.77 (1H, s), 7.83 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.47 (2H, d, J=5Hz), 9.84 (1H, s)
- (32) 2-Benzyl-3-oxo-4-[3-(4-methylthiazol-2-yl)aminophenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 2.17 (3H, s), 4.21 (2H, s), 6.46 (1H, s), 6.86 (1H, d, J=8Hz), 7.2-7.5 (8H, m), 7.75 (1H, m), 8.23 (1H, d, J=8Hz), 8.39 (1H, d, J=5Hz)
- (33) 2-Benzyl-3-oxo-4-[3-(4-phenylthiazol-2-yl)aminophenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.23 (2H, s), 6.94 (1H, d, J=8Hz), 7.2-7.6 (12H, m), 7.83 (2H, d, J=8Hz), 7.94 (1H, d, J=8Hz), 8.26 (1H, d, J=8Hz), 8.42 (1H, d, J=5Hz)
- (34) 2-Benzyl-3-oxo-4-(3-biphenyl)-3,4-dihydropyrido-

- 154 -

[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.33 (2H, s), 7.2-7.8 (15H, m), 8.20 (1H, dd, J=1.5Hz, 8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz)

5

(35) 2-Benzyl-3-oxo-4-(3-cyanophenyl)-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.30 (2H, s), 7.2-7.35 (4H, m), 7.45-7.85 (6H, m), 8.21 (1H, dd, J=1.5Hz, 8Hz), 8.37 (1H, dd, J=1.5Hz, 5Hz)

10

(36) 2-Benzyl-3-oxo-4-(3-chlorophenyl)-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.12 (1H, d, J=8Hz), 7.2-7.75 (8H, m), 7.88 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.38 (1H, d, J=5Hz)

15

(37) 2-Benzyl-3-oxo-4-(3-nitrophenyl)-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.4 (4H, m), 7.48 (2H, d, J=7Hz), 7.64 (1H, d, J=8Hz), 7.76 (1H, t, J=8Hz), 8.2-8.3 (1H, m), 8.35-8.45 (1H, m)

20

25 Example 17

The following compound was obtained according to a similar manner to that of Example 11.

2-Benzyl-3-oxo-4-(3-methylaminophenyl)-3,4-dihydropyrido[2,3-b]pyrazine

30

NMR (DMSO-d₆, 200MHz, δ) : 2.67 (3H, d, J=5Hz), 4.21 (2H, s), 5.85 (1H, q, J=5Hz), 6.4-6.5 (2H, m), 6.62 (1H, d, J=8Hz), 7.15-7.45 (7H, m), 8.22 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz)

35

- 155 -

Example 18

The following compounds were obtained according to a similar manner to that of Example 14.

- 5 (1) 2-Benzyl-3-oxo-4-[3-[3-benzoyl(thioureido)]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 4.23 (2H, s), 7.2-7.8 (13H, m), 7.9-8.05 (3H, m), 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.42 (1H, dd, J=1.5Hz, 5Hz)

10

- (2) 2-Benzyl-3-oxo-4-[3-[3-(1-naphthyl)(thioureido)]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 4.21 (2H, s), 7.05-7.55 (13H, m), 7.75-8.05 (4H, m), 8.23 (1H, dd,

- 15 J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz), 9.90 (1H, s), 9.97 (1H, s)

Example 19

A mixture of 1-naphthylacetic acid (82 mg), oxalyl chloride (0.02 ml) and catalytic amount of N,N-dimethylformamide in dichloromethane (2 ml) was stirred at room temperature for 30 minutes. The above solution was added to a mixture of 4-(3-aminophenyl)-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine (131 mg) and triethylamine (0.085 ml) in dichloromethane (2 ml). The mixture was stirred at room temperature for 30 minutes, then poured into a mixture of ethyl acetate and water. The organic phase was washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated. The residue was crystallized with ethanol to give 2-benzyl-3-oxo-4-[3-[(1-naphthyl)-acetylaminophenyl]-3,4-dihydropyrido[2,3-b]pyrazine (123 mg).

35 NMR (DMSO-d₆, 200MHz, δ) : 4.16 (2H, s), 4.19 (2H, s), 7.01 (1H, d, J=8Hz), 7.2-7.7 (13H, m),

- 156 -

7.8-8.0 (2H, m), 8.12 (1H, m), 8.21 (1H, dd, J=1.5Hz, 8Hz), 8.37 (1H, dd, J=1.5Hz, 5Hz)

Example 20

5 To a mixture of 4-(3-aminophenyl)-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine (150 mg), benzylsulfonyl chloride (96 mg) and pyridine (0.04 ml) in 1,4-dioxane (3 ml) was stirred at 80°C for 2 hours. The mixture was poured into a mixture of ethyl acetate and water. The organic phase was washed with water and brine, dried over magnesium sulfate, concentrated, and subjected to silica gel column chromatography (hexane - ethyl acetate 1:1) to afford 4-(3-benzylsulfonylaminophenyl)-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine (49 mg) as a solid.

15 NMR (DMSO-d₆, 300MHz, δ) : 4.23 (2H, s), 4.51 (2H, s), 7.0-7.7 (15H, m), 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz)

Example 21

20 To a mixture of 4-(3-aminophenyl)-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine (131 mg) and triethylamine (0.067 ml) in dichloromethane (3 ml) was added benzoyl chloride (0.056 ml). The mixture was stirred at room temperature for 30 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The residue was crystallized from isopropyl ether to give 4-(3-benzoylaminophenyl)-3-oxo-2-benzyl-3,4-dihydropyrido-

25 [2,3-b]pyrazine (110 mg).

30 NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.08 (1H, d, J=8Hz), 7.2-7.65 (10H, m), 7.75-7.85 (2H, m), 7.96 (2H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.40 (1H, m)

- 157 -

Example 22

The following compounds were obtained according to similar manners to those of Examples 19, 20 and 21.

- 5 (1) 2-Benzyl-3-oxo-4-[(3-cinnamoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 6.85 (1H, d, J=16Hz), 7.05 (1H, d, J=8Hz), 7.2-7.8 (15H, m), 8.25 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz)
- 10 (2) 2-Benzyl-3-oxo-4-[3-(4-isobutylcinnamoylamino)-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 0.88 (6H, d, J=7Hz), 1.86 (1H, m), 2.48 (2H, d, J=7Hz), 4.22 (2H, s), 6.78 (1H, d, J=16Hz), 7.03 (1H, d, J=8Hz), 7.2-7.6 (12H, m), 7.7-7.8 (2H, m), 8.25 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz)
- 15 (3) 2-Benzyl-3-oxo-4-[3-(3,4-dimethoxybenzoylamino)-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 3.83 (6H, s), 4.22 (2H, s), 7.0-7.1 (2H, m), 7.2-7.55 (8H, m), 7.62 (1H, d, J=8Hz), 7.72 (1H, s), 8.87 (1H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz)
- 20 (4) 2-Benzyl-3-oxo-4-[3-(diphenylacetylaminophenyl)-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.20 (2H, s), 5.18 (1H, s), 7.02 (1H, d, J=8Hz), 7.2-7.5 (17H, m), 7.62 (1H, d, J=8Hz), 7.69 (1H, t, J=1.5Hz), 8.22 (1H, d, J=8Hz), 8.36 (1H, d, J=5Hz)
- 25 (5) 2-Benzyl-3-oxo-4-[3-((E)-3-phenyl-2-methylpropenoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 2.10 (3H, s), 4.22 (2H,
- 30
- 35

- 158 -

s), 7.05 (1H, d, J=8Hz), 7.2-7.55 (12H, m), 7.7-7.8 (3H, m), 8.25 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz)

- 5 (6) 2-Benzyl-3-oxo-4-[3-(3,4-dichlorobenzoylamino)-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.11 (1H, d, J=8Hz), 7.2-7.45 (6H, m), 7.54 (1H, t, J=8Hz), 7.75-7.85 (3H, m), 7.92 (1H, dd, J=1.5Hz, 8Hz), 8.2-8.3 (2H, m), 8.40 (1H, d, J=5Hz)

10

- 15 (7) 2-Benzyl-3-oxo-4-[3-(cyclohexylideneacetyl-amino)-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 1.45-1.7 (6H, m), 2.1-2.25 (2H, m), 2.75-2.9 (2H, m), 4.22 (2H, s), 5.81 (1H, s), 6.98 (1H, d, J=8Hz), 7.15-7.5 (7H, m), 7.59 (1H, d, J=8Hz), 7.71 (1H, t, J=1.5Hz), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz), 10.07 (1H, s)

20

- (8) 2-Benzyl-3-oxo-4-[3-(3,4-methylenedioxybenzoylamino)-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.30 (2H, s), 6.01 (2H, s), 6.78 (1H, d, J=8Hz), 6.86 (1H, d, J=8Hz), 7.1-7.35 (5H, m), 7.4-7.5 (3H, m), 7.6-7.7 (2H, m), 8.15-8.25 (2H, m), 8.40 (1H, m)

25

- 30 (9) 2-Benzyl-3-oxo-4-[3-(2-thienylcarbonylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.06 (1H, d, J=8Hz), 7.15-7.45 (7H, m), 7.54 (1H, t, J=8Hz), 7.68 (1H, m), 7.75-7.9 (2H, m), 8.04 (1H, t, J=1.5Hz), 8.25 (1H, d, J=8Hz), 8.40 (1H,

35

- 159 -

d, J=5Hz), 10.42 (1H, s)

- (10) 2-Benzyl-3-oxo-4-[3-(2,4-hexadienoylamino)phenyl]-
3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (CDCl₃, 300MHz, δ) : 1.81 (3H, d, J=6Hz), 4.32
(2H, s), 5.60 (1H, d, J=16Hz), 5.95-6.1 (2H, m),
6.83 (1H, d, J=8Hz), 7.1-7.55 (10H, m),
8.22 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd,
J=1.5Hz, 5Hz)

10

- (11) 4-[3-[3-(Benzoylamino)benzoylamino]phenyl]-3-oxo-2-
benzyl-3,4-dihydropyrido[2,3-b]pyrazine

15 NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.08 (1H,
dt, J=8Hz, 1.5Hz), 7.2-7.65 (11H, m), 7.69 (1H,
dt, J=8Hz, 1.5Hz), 7.8-7.9 (2H, m), 7.95-8.05
(3H, m), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.31 (1H,
t, J=1.5Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz)

- (12) 2-Benzyl-3-oxo-4-[3-[3-[(pyrimidin-2-yl)oxy]-
benzoylamino]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (CDCl₃, 300MHz, δ) : 4.24 (2H, s), 6.78 (1H, d,
J=8Hz), 6.98 (1H, t, J=5Hz), 7.0-7.1 (1H, m),
7.17 (2H, t, J=8Hz), 7.25-7.5 (7H, m), 7.6-7.7
(2H, m), 7.77 (1H, d, J=8Hz), 8.19 (1H, d,
25 J=8Hz), 8.41 (1H, m), 8.45-8.55 (3H, m)

- (13) 2-Benzyl-3-oxo-4-[3-[3-[(3-nitropyridin-2-yl)amino]-
benzoylamino]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

30 NMR (CDCl₃, 300MHz, δ) : 4.28 (2H, s), 6.8-6.9 (2H,
m), 7.05-7.8 (13H, m), 8.15-8.25 (2H, m), 8.35-
8.55 (3H, m), 10.14 (1H, s)

- (14) 2-Benzyl-3-oxo-4-[3-(4-biphenyllylcarbonylamino)-
phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

35 NMR (DMSO-d₆, 300MHz, δ) : 4.23 (2H, s), 7.08 (1H,

- 160 -

d, J=8Hz), 7.2-7.6 (10H, m), 7.77 (2H, d, J=8Hz), 7.8-7.9 (4H, m), 8.07 (2H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz)

- 5 (15) 2-Benzyl-3-oxo-4-(3-cyclohexylcarbonylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 1.1-1.5 (5H, m), 1.6-1.9 (5H, m), 2.32 (1H, m), 4.21 (2H, s), 6.98 (1H, d, J=8Hz), 7.2-7.5 (7H, m), 7.59 (1H, d, J=8Hz), 7.67 (1H, t, J=1.5Hz), 8.23 (1H, d, J=8Hz), 8.38 (1H, m)

10

- (16) 2-Benzyl-3-oxo-4-[3-(3-phenylpropionylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

15 NMR (DMSO-d₆, 300MHz, δ) : 2.64 (2H, t, J=7Hz), 2.89 (2H, t, J=7Hz), 4.20 (2H, s), 6.98 (1H, d, J=8Hz), 7.1-7.7 (14H, m), 8.23 (1H, d, J=8Hz), 8.38 (1H, d, J=5Hz)

- 20 (17) 2-Benzyl-3-oxo-4-[3-(4-propylbenzoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 0.90 (3H, t, J=7Hz), 1.62 (2H, m), 2.62 (2H, t, J=7Hz), 4.22 (2H, s), 7.07 (1H, d, J=8Hz), 7.2-7.6 (9H, m), 7.75-7.9 (4H, m), 8.25 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz)

25

- (18) 2-Benzyl-3-oxo-4-[3-(4-chlorobenzoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

30 NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.08 (1H, d, J=8Hz), 7.2-7.45 (6H, m), 7.52 (1H, t, J=8Hz), 7.62 (2H, d, J=8Hz), 7.75-7.85 (2H, m), 7.98 (2H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 8.39 (1H, d, J=5Hz)

- 35 (19) 2-Benzyl-3-oxo-4-[3-(3-nitrobenzoylamino)phenyl]-3,4-

- 161 -

dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.13 (1H, d, J=8Hz), 7.2-7.45 (7H, m), 7.57 (1H, t, J=8Hz), 7.75-7.9 (3H, m), 8.27 (1H, d, J=8Hz), 8.35-8.5 (3H, m), 8.80 (1H, s)

5

(20) 2-Benzyl-3-oxo-4-[3-(4-nitrobenzoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.12 (1H, d, J=8Hz), 7.2-7.45 (6H, m), 7.55 (1H, t, J=8Hz), 8.35-8.45 (2H, m), 8.18 (2H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.35-8.45 (3H, m)

10

(21) 2-Benzyl-3-oxo-4-[3-(2-naphthoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.24 (2H, s), 7.11 (1H, d, J=8Hz), 7.2-7.75 (9H, m), 7.8-8.2 (6H, m), 8.27 (1H, d, J=8Hz), 8.42 (1H, d, J=5Hz), 8.60 (1H, s)

15

20

(22) 2-Benzyl-3-oxo-4-[3-(1-naphthoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.24 (2H, s), 7.11 (1H, d, J=8Hz), 7.2-7.7 (10H, m), 7.75-7.85 (2H, m), 7.92 (1H, s), 8.0-8.3 (4H, m), 8.43 (1H, d, J=5Hz)

25

(23) 2-Benzyl-3-oxo-4-(3-isonicotinoylamino)phenyl)-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.12 (1H, d, J=8Hz), 7.2-7.45 (6H, m), 7.55 (1H, t, J=8Hz), 7.75-7.9 (4H, m), 8.25 (1H, d, J=8Hz), 8.40 (1H, m), 8.78 (2H, d, J=5Hz)

30

35 (24) 2-Benzyl-3-oxo-4-(3-nicotinoylamino)phenyl)-3,4-

- 162 -

dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.11 (1H, d, J=8Hz), 7.2-7.6 (8H, m), 7.75-7.9 (2H, m), 8.2-8.35 (2H, m), 8.40 (1H, d, J=5Hz), 8.77 (1H, d, J=5Hz), 9.10 (1H, s)

5

(25) 2-Benzyl-3-oxo-4-[3-(N-methyl-N-benzoylamino)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 3.52 (3H, s), 4.28 (2H, s), 6.98 (1H, t, J=1.5Hz), 7.06 (1H, dd, J=1.5Hz, 8Hz), 7.1-7.5 (13H, m), 8.15 (1H, dd, J=1.5Hz, 8Hz), 8.27 (1H, dd, J=1.5Hz, 5Hz)

10

Example 23

15 To a stirred solution of 4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3-oxo-2-(2-carboxyethyl)-3,4-dihydropyrido[2,3-b]pyrazine (2.30 g) and N-hydroxysuccinimide (1.15 g) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (1.20 g) and the
20 resulting mixture was stirred for 24 hours. The reaction mixture was concentrated, diluted with ethyl acetate, washed with a saturated sodium bicarbonate solution, water and brine, and dried over magnesium sulfate. After
25 evaporation of the solvent, the residue was triturated with ether to give 4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3-oxo-2-[2-succinimidooxycarbonyl]ethyl)-3,4-dihydropyrido[2,3-b]pyrazine (2.35 g) as a solid.

mp : 235-237°C

NMR (DMSO-d₆, δ) : 1.79 (2H, m), 1.94 (2H, m), 2.78 (2H, t, J=7Hz), 3.12 (2H, t, J=7Hz), 3.30 (2H, t, J=7Hz), 3.54 (2H, t, J=7Hz), 3.88 (3H, s), 6.8-7.05 (4H, m), 7.4 (3H, m), 7.58 (1H, s), 8.09 (1H, d, J=7Hz), 8.20 (1H, d, J=7Hz), 8.29 (1H, s), 8.40 (1H, m), 9.53 (1H, s)

30

35

- 163 -

Example 24

To a solution of 2-[2-succinimidooxycarbonyl]ethyl]-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (0.28 g) in dioxane was added a solution of dimethylamine hydrochloride (81 mg) in water and triethylamine (101 mg). The mixture was stirred for 18 hours, diluted with ethyl acetate, washed with water. After removal of the solvents, crude residue was crystallized from ethanol to give 2-[2-(N,N-dimethylcarbamoyl)ethyl]-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine.

mp : 242-245°C

NMR (DMSO-d₆, δ) : 2.85 (3H, s), 2.87 (2H, m), 3.06 (3H, s), 3.10 (2H, m), 3.88 (3H, s), 6.8-7.05 (4H, m), 7.40 (3H, m), 7.58 (1H, s), 8.09 (1H, d, J=7Hz), 8.22 (1H, d, J=7Hz), 8.28 (1H, s), 8.39 (1H, m), 9.53 (1H, s)

Example 25

The following compound was obtained according to a similar manner to that of Example 24.

4-[3-[3-(2-Methoxyphenyl)ureido]phenyl]-3-oxo-2-[2-(1-pyrrolidinylcarbamoyl)ethyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, δ) : 0.98 (1H, m), 1.28 (2H, m), 1.57 (1H, m), 2.00 (1H, m), 2.39 (2H, m), 2.75 (3H, m), 3.25 (1H, m), 3.45 (1H, m), 3.88 (3H, s), 6.75 (1H, m), 6.90 (3H, m), 7.02 (1H, d, J=7Hz), 7.18 (1H, m, J=7Hz), 7.29 (1H, m), 7.40 (1H, dd, J=7Hz, 7Hz), 7.50 (2H, m), 7.60 (1H, m), 8.08 (1H, d, J=7Hz), 8.23 (1H, s), 9.46 (1H, s)

Example 26

A mixture of 2-benzyl-3-oxo-4-(3-carboxyphenyl)-3,4-

- 164 -

dihydropyrido[2,3-b]pyrazine (357 mg), triethylamine (0.14 ml) and diphenylphosphoryl azide (0.216 ml) in benzene (5 ml) was refluxed for 15 minutes. 3-Aminopyridine (113 mg) was then added to the mixture and the reflux was continued for 5 hours. The reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with methanol to give 2-benzyl-3-oxo-4-[3-[3-(3-pyridyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine (168 mg).

NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.96 (1H, m), 7.2-7.6 (10H, m), 7.92 (1H, m), 8.15-8.3 (2H, m), 8.41 (1H, dd, J=1.5Hz, 5Hz), 8.60 (1H, d, J=1.5Hz), 8.91 (1H, s), 9.02 (1H, s)

Example 27

A mixture of 2-benzyl-3-oxo-4-(3-carboxyphenyl)-3,4-dihydropyrido[2,3-b]pyrazine (214 mg), triethylamine (0.084 ml) and diphenylphosphoryl azide (0.129 ml) in toluene (4 ml) was refluxed for 30 minutes. 2-Aminopyridine (113 mg) was then added to the mixture and reflux was continued for 1 hour. The reaction mixture was poured into a mixture of ethyl acetate and water. The organic phase was separated, washed with brine, dried over magnesium sulfate, concentrated and subjected to silica gel column chromatography (hexane - ethyl acetate, 1:3) to afford 2-benzyl-3-oxo-4-[3-[3-(2-pyridyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine (48 mg) as a solid.

NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.95-7.05 (2H, m), 7.2-7.8 (12H, m), 8.2-8.3 (2H, m), 8.41 (1H, dd, J=1.5Hz, 5Hz), 9.56 (1H, s)

Example 28

The following compounds were obtained according to

- 165 -

similar manners to those of Example 26 and 27.

- (1) 2-Benzyl-3-oxo-4-[3-[3-(4-pyridyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.98 (1H, m), 7.2-7.6 (11H, m), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.3-8.45 (3H, m), 9.09 (1H, s) 9.18 (1H, s)

- 10 (2) 2-Benzyl-3-oxo-4-[3-(3-phenyl-3-methylureido)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 3.27 (3H, s), 4.20 (2H, s), 6.90 (1H, d, J=8Hz), 7.15-7.45 (13H, m), 7.57 (1H, d, J=8Hz), 8.23 (1H, dd, J=1.5Hz, 8Hz),
15 8.32 (1H, s), 8.40 (1H, dd, J=1.5Hz, 5Hz)

- (3) 2-Benzyl-3-oxo-4-[3-[3-(o-tolyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 2.25 (3H, s), 4.22 (2H, s), 6.85-7.0 (2H, m), 7.05-7.5 (11H, m), 7.55 (1H, s), 7.78 (1H, d, J=8Hz), 7.98 (1H, s), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.21 (1H, s)

- 25 (4) 2-Benzyl-3-oxo-4-[3-[3-(2,6-xylyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 2.20 (6H, s), 4.21 (2H, s), 6.88 (1H, dt, J=8Hz, 1.5Hz), 7.06 (3H, s), 7.15-7.55 (9H, m), 7.79 (1H, s), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 8.96 (1H, s)

- (5) 2-Benzyl-3-oxo-4-[3-[3-(2-biphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

35 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.90 (1H,

- 166 -

m), 7.1-7.6 (17H, m), 7.72 (1H, s), 7.88 (1H, d, J=8Hz), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.22 (1H, s)

5 (6) 2-Benzyl-3-oxo-4-[3-[3-(2-methoxycarbonylphenyl)-ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 200MHz, δ) : 3.90 (3H, s), 4.22 (2H, s), 6.97 (1H, d, J=8Hz), 7.08 (1H, t, J=8Hz), 7.2-7.65 (9H, m), 7.95 (1H, dd, J=1.5Hz, 8Hz),
10 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.32 (1H, d, J=8Hz), 8.41 (1H, dd, J=1.5Hz, 5Hz), 10.08 (2H, s)

(7) 2-Benzyl-3-oxo-4-[3-[3-(2-thiazolyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
15 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 7.00 (1H, m), 7.11 (1H, d, J=4Hz), 7.2-7.5 (10H, m), 7.59 (1H, s), 8.24 (1H, dd, J=1.5Hz, 8Hz), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.17 (1H, s)

20 (8) 2-Benzyl-3-oxo-4-[3-(3-cyclohexylureido)phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 200MHz, δ) : 1.05-1.9 (10H, m), 3.3-3.55 (1H, m), 4.22 (2H, s), 6.14 (1H, d, J=8Hz),
25 6.82 (1H, m), 7.2-7.5 (9H, m), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.39 (1H, dd, J=1.5Hz, 5Hz), 8.49 (1H, s)

(9) 2-Benzyl-3-oxo-4-[3-(indolin-1-yl)carbonylamino-phenyl]-3,4-dihydropyrido[2,3-b]pyrazine
30 NMR (DMSO-d₆, 300MHz, δ) : 3.17 (2H, d, J=8Hz), 4.12 (2H, d, J=8Hz), 4.22 (2H, s), 6.85-7.75 (13H, m), 7.84 (1H, d, J=8Hz), 8.25 (1H, d, J=8Hz), 8.41 (1H, m), 8.71 (1H, s)

35

- 167 -

(10) 2-Benzyl-3-oxo-4-[3-(1,2,3,4-tetrahydroquinolin-1-yl)carbonylamino]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (DMSO-d₆, 300MHz, δ) : 1.89 (2H, m), 2.73 (2H, t, J=7Hz), 3.70 (2H, t, J=7Hz), 4.21 (2H, s), 6.9-7.6 (14H, m), 8.23 (1H, d, J=8Hz), 8.40 (1H, m), 9.05 (1H, s)

(11) 2-Benzyl-3-oxo-4-[3-[3-(2-carboxyphenyl)ureido]-phenyl]-[3,4-dihydropyrido[2,3-b]pyrazine

10 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.75-6.95 (2H, m), 7.15-7.65 (9H, m), 7.98 (1H, dd, J=1.5Hz, 8Hz), 8.1-8.3 (2H, m), 8.40 (1H, dd, J=1.5Hz, 5Hz), 9.68 (1H, s)

15 (12) 2-Benzyl-3-oxo-4-[3-[3-[4-(N,N-dimethylamino)phenyl]-ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (DMSO-d₆, 300MHz, δ) : 2.82 (6H, s), 4.21 (2H, s), 6.67 (2H, d, J=8Hz), 6.88 (1H, d, J=5Hz), 7.2-7.45 (11H, m), 7.50 (1H, s), 8.23 (1H, d, J=8Hz), 8.33 (1H, s), 8.39 (1H, d, J=5Hz), 8.69 (1H, s)

Example 29

25 A mixture of 2-benzyl-3-oxo-4-(3-carboxymethylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine (250 mg), oxalyl chloride (0.07 ml) and catalytic amount of N,N-dimethylformamide in dichloromethane (3 ml) was stirred at 0°C for 10 minutes. The above solution was

30 added to a mixture of aniline (0.065 ml) and triethylamine (0.135 ml) in dichloromethane (3 ml). The mixture was stirred at room temperature for 2 hours, then poured into a mixture of ethyl acetate and water. The organic phase was washed with aqueous sodium bicarbonate and brine,

35 dried over magnesium sulfate and concentrated. The

- 168 -

resultant solid was collected and washed with methanol to give 2-benzyl-3-oxo-4-(3-anilinocarbonylmethyl)-3,4-dihydropyrido[2,3-b]pyrazine (112 mg).

5 NMR (DMSO-d₆, 200MHz, δ) : 3.71 (2H, s), 4.21 (2H, s), 7.0-7.65 (13H, m), 7.87 (2H, d, J=8Hz), 8.23 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz), 10.21 (1H, s)

10 Example 30

The following compound was obtained according to a similar manner to that of Example 29.

15 4-[3-(1-Naphthyl)carbamoylmethylphenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 200MHz, δ) : 3.89 (2H, s), 4.22 (2H, s), 7.1-7.8 (15H, m), 7.9-8.1 (2H, m), 8.25 (1H, dd, J=1.5Hz, 8Hz), 8.38 (1H, dd, J=1.5Hz, 5Hz), 10.18 (1H, s)

20

Example 31

A mixture of 2-benzyl-3-oxo-4-(3-carboxyphenyl)-3,4-dihydropyrido[2,3-b]pyrazine (186 mg) and 1,1'-carbonyldiimidazole (130 mg) in tetrahydrofuran (4 ml) was stirred at room temperature for 3 hours. Aniline (0.075 ml) was then added to the mixture and stirring was continued for 24 hours. The reaction mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate solution. The organic phase was washed with
30 brine, dried over magnesium sulfate, concentrated, and subjected to silica gel column chromatography (chloroform - methanol, 40:1) to afford 2-benzyl-3-oxo-4-(3-anilinocarbonylphenyl)-3,4-dihydropyrido[2,3-b]pyrazine (103 mg) as a solid.

35 NMR (DMSO-d₆, 300MHz, δ) : 4.23 (2H, s), 7.10 (1H,

- 169 -

t, J=8Hz), 7.2-7.45 (8H, m), 7.60 (1H, d, J=8Hz), 7.65-7.8 (3H, m), 7.93 (1H, t, J=1.5Hz), 8.10 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz), 8.39 (1H, m)

5

Example 32

A mixture of 2-quinolinecarboxylic acid (520 mg) and 1,1'-carbonyldiimidazole (243 mg) in tetrahydrofuran (5 ml) was stirred at room temperature for 1.5 hours.

10 A solution of 4-(3-aminophenyl)-3-oxo-2-benzyl-3,4-dihydropyrido[2,3-b]pyrazine (493 mg) in 1,4-dioxane (5 ml) was added to the mixture and stirring was continued for 5 days. The reaction mixture was poured into a mixture of ethyl acetate and an aqueous sodium bicarbonate
15 solution. The organic phase was washed with brine, dried over magnesium sulfate, concentrated, and subjected to silica gel column chromatography (hexane - ethyl acetate, 1:1) to afford 2-benzyl-3-oxo-4-[3-(quinolin-2-yl)carbonylaminophenyl]-3,4-dihydropyrido[2,3-b]pyrazine
20 (87 mg) as a solid.

NMR (DMSO-d₆, 300MHz, δ) : 4.24 (2H, s), 7.14 (1H, d, J=8Hz), 7.2-7.45 (6H, m), 7.57 (1H, t, J=8Hz), 7.76 (1H, t, J=8Hz), 7.85-8.15 (4H, m), 8.2-8.3 (3H, m), 8.42 (1H, d, J=5Hz), 8.63 (1H, d, J=8Hz), 10.93 (1H, s)
25

Example 33

To a suspension of 2-(2-carboxyethyl)-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine (0.15 g) in ethanol (9 ml) was added conc. sulfonic acid (0.9 ml) and the mixture was refluxed for 30
30 minutes. After cooling, the reaction mixture was neutralized and ethanol was evaporated. Crystalline materials formed were collected, washed with water and
35 dried to give 2-(2-ethoxycarbonylethyl)-3-oxo-4-[3-[3-(2-

- 170 -

methoxyphenyl)-

ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine (0.12 g).

mp : 175°C

5 NMR (DMSO-d₆, δ) : 1.20 (3H, t, J=7Hz), 2.82 (2H, t, J=7Hz), 3.15 (2H, t, J=7Hz), 3.89 (3H, s), 4.10 (2H, q, J=7Hz), 6.8-7.05 (4H, m), 7.4 (3H, m), 7.60 (1H, s), 8.10 (1H, d, J=7Hz), 8.20 (1H, d, J=7Hz), 8.30 (1H, s), 8.40 (1H, m), 9.52 (1H, s)

10 Example 34

The following compounds were obtained according to a similar manner to that of Example 33.

15 (1) 4-[3-[3-(2-Methoxyphenyl)ureido]phenyl]-3-oxo-2-(2-propyloxycarbonyl)ethyl)-3,4-dihydropyrido[2,3-b]pyrazine

mp : 161-163°C

20 NMR (DMSO-d₆, δ) : 0.88 (3H, t, J=7Hz), 1.60 (2H, m), 2.84 (2H, t, J=7Hz), 3.13 (2H, t, J=7Hz), 3.88 (3H, s), 4.01 (2H, t, J=7Hz), 6.8-7.05 (4H, m), 7.4 (3H, m), 7.58 (1H, s), 8.09 (1H, d, J=7Hz), 8.18 (1H, d, J=7Hz), 8.28 (1H, s), 8.40 (1H, d, J=3Hz), 9.52 (1H, s)

25 (2) 2-(2-Methoxycarbonyl)ethyl)-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine

mp : 194-196°C

30 NMR (DMSO-d₆, δ) : 2.86 (2H, t, J=7Hz), 3.15 (2H, t, J=7Hz), 3.65 (3H, s), 3.89 (3H, s), 6.85-7.1 (4H, m), 7.45 (3H, m), 7.60 (1H, s), 8.10 (1H, d, J=7Hz), 8.21 (1H, d, J=7Hz), 8.29 (1H, s), 8.40 (1H, d, J=3Hz), 9.52 (1H, s)

35 Example 35

- 171 -

To a stirred suspension of 2-(2-carboxyethyl)-3-oxo-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3,4-dihydropyrido[2,3-b]pyrazine (115 mg) and 1-hydroxybenzotriazole (40 mg) in dry dioxane (10 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (47 mg) and N-methylpiperazine (30 mg). The mixture was stirred at room temperature for 4 hours, diluted with ethyl acetate, washed with water. After evaporation of the solvents, crude residue was crystallized from ethanol to give 4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-2-[2-(4-methylpiperazin-1-yl)carbonylethyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine.

mp : 195-197°C

NMR (DMSO-d₆, δ) : 2.20 (3H, s), 2.24 (2H, m), 2.36 (2H, m), 2.85 (2H, t, J=7Hz), 3.12 (2H, t, J=7Hz), 3.48 (2H, m), 3.55 (2H, m), 3.88 (3H, s), 6.8-7.05 (4H, m), 7.4 (3H, m), 7.60 (1H, s), 8.10 (1H, d, J=7Hz), 8.21 (1H, d, J=7Hz), 8.28 (1H, s), 8.40 (1H, m), 9.53 (1H, s)

Example 36

The following compound was obtained according to a similar manner to that of Example 35.

4-[3-[3-(2-Methoxyphenyl)ureido]phenyl]-3-oxo-2-[2-[(2S)-2-methoxycarbonylpyrrolidin-1-yl]carbonylethyl]-3,4-dihydropyrido[2,3-b]pyrazine

mp : 209-212°C

NMR (DMSO-d₆, δ) : 1.86 (1H, m), 1.97 (1H, m), 2.18 (1H, m), 2.83 (1H, m), 3.10 (2H, m), 3.58 (3H, s), 3.18 (2H, m), 3.87 (3H, s), 4.31 (1H, m), 6.8-7.05 (4H, m), 7.42 (3H, m), 7.59 (1H, s), 8.08 (1H, d, J=7Hz), 8.23 (1H, d, J=7Hz), 8.28 (1H, s), 8.39 (1H, m), 9.53 (1H, s)

- 172 -

Example 37

The mixture of 2-(2-nitrobenzyl)-3-oxo-4-phenyl-3,4-dihydropyrido[2,3-b]pyrazine (1.39 g), iron (2.17 g) and acetic acid (1.16 g) in ethanol (15 ml) was refluxed for 3 hours. The reaction mixture was cooled and filtered. To the filtrate was added saturated sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was dried and evaporated. The crude product was purified by silica column chromatography to obtain 2-(2-aminobenzyl)-3-oxo-4-phenyl-3,4-dihydropyrido[2,3-b]pyrazine (120 mg).

NMR (CDCl₃, 200MHz, δ) : 4.21 (2H, s), 4.21 (2H, br s), 6.64 (1H, dd, J=1Hz, 7Hz), 6.73 (1H, dd, J=1Hz, 7Hz), 7.04 (1H, ddd, J=1Hz, 7Hz and 7Hz), 7.18-7.35 (3H, m), 7.35-7.60 (4H, m), 8.14 (1H, dd, J=1Hz, 10Hz), 8.37 (1H, dd, J=1Hz, 5Hz)

Example 38

To a mixture of 4-(3-aminophenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (180 mg) and triethylamine (0.10 ml) in 1,4-dioxane (4 ml) was added 3,5-dichlorobenzoylchloride (126 mg). The mixture was stirred at room temperature for 10 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (ethyl acetate) and crystallized from ethanol to give 4-[3-(3,5-dichlorobenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (163 mg).

NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.12 (1H, d, J=8Hz), 7.3-7.45 (2H, m), 7.56 (1H, t, J=8Hz), 7.75-7.85 (3H, m), 7.88 (1H, t, J=2Hz), (2H, d, J=2Hz), 8.21 (1H, dd, J=2, 8Hz),

- 173 -

8.41 (1H, d, J=5Hz), 8.48 (1H, d, J=5Hz), 8.60
(1H, d, J=2Hz)

Example 39

5 To a mixture of 4-(3-aminophenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (480 mg) and triethylamine (0.23 ml) in dichloromethane (7 ml) was added 2-naphthoyl chloride (291 mg). The mixture was stirred at room temperature for 20 minutes, then poured
10 into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from ethanol to give 4-[3-(2-naphthoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (280
15 mg).

NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 6.91 (1H, d, J=8Hz), 7.2-7.35 (2H, m), 7.45-7.6 (3H, m), 7.72 (1H, dd, J=2, 8Hz), 7.75-7.9 (6H, m), 8.18 (1H, d),
20 8.31 (1H, s), 8.4-8.5 (3H, m), 8.71 (1H, m)

Example 40

To a solution of 4-(3-aminophenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (329
25 mg) in chloroform (5 ml) was added 3,5-dichlorobenzoylchloride (220 mg). The mixture was stirred at room temperature for 15 minutes and concentrated. The residue was crystallized from methanol to give 4-[3-(3,5-dichlorobenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-
30 3,4-dihydropyrido[2,3-b]pyrazine-hydrochloride (370 mg).

NMR (DMSO-d₆, 300MHz, δ) : 4.49 (2H, s), 7.11 (1H, d, J=8Hz), 7.40 (1H, dd, J=5, 8Hz), 7.57 (1H, t, J=8Hz), 7.80 (1H, d, J=8Hz), 7.89 (2H, m), 8.0-8.05 (3H, m), 8.17 (1H, dd, J=2, 5Hz),
35 8.42 (1H, d, J=5Hz), 8.53 (1H, d, J=8Hz), 8.83

- 174 -

(1H, d, J=5Hz), 8.92 (1H, s)

Example 41

5 The following compounds were obtained according to a similar manner to that of Example 19, 20, 21, 38, 39 or 40.

(1) 4-[3-(2-Chlorobenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
10 NMR (CDCl₃, 300MHz, δ) : 4.30 (2H, s), 7.04 (1H, d, J=8Hz), 7.2-7.45 (5H, m), 7.5-7.65 (2H, m), 7.70 (1H, dd, J=2, 8Hz), 7.75-7.9 (2H, m), 8.15-8.25 (2H, m), 8.42 (1H, d, J=5Hz), 8.48 (1H, d, J=5Hz), 8.70 (1H, s)

15

(2) 4-[3-(3-Bromobenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.80 (1H, d, J=8Hz), 7.19 (1H, dd, J=5Hz, 8Hz), 7.25-7.35 (2H, m), 7.41 (1H, t, J=8Hz), 7.60 (1H, d, J=8Hz), 7.65-7.8 (4H, m), 7.90 (1H, t, J=2Hz), 8.20 (1H, d, J=8Hz), 8.4-8.45 (2H, m), 8.49 (1H, s), 8.70 (1H, d, J=2Hz)

20

(3) 4-[3-[3-(2-Pyrimidinylloxy)benzoylamino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.25 (2H, s), 7.10 (1H, d, J=8Hz), 7.3-7.65 (6H, m), 7.75-7.9 (5H, m), 8.21 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.47 (1H, m), 8.60 (1H, s), 8.68 (2H, d, J=5Hz)

30

(4) 4-[3-[4-[(E)-2-Methoxycarbonylvinyl]benzoylamino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

35

- 175 -

NMR (CDCl₃, 300MHz, δ) : 3.80 (3H, s), 4.30 (2H, s),
6.48 (1H, d, J=16Hz), 6.89 (1H, d, J=8Hz), 7.2-
7.35 (2H, m), 7.4-7.55 (3H, m), 7.6-7.7 (2H, m),
7.75-7.85 (4H, m), 8.18 (1H, d, J=8Hz), 8.34
5 (1H, s), 8.41 (1H, dd, J=2, 5Hz), 8.48 (1H, d,
J=5Hz), 8.72 (1H, d, J=2Hz)

(5) 4-[3-[(E)-Cinnamoylamino]phenyl]-2-(3-pyridylmethyl)-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

10 NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.38 (1H, d,
J=16Hz), 6.90 (1H, d, J=8Hz), 7.2-7.45 (8H, m),
7.5-7.7 (3H, m), 8.20 (1H, d, J=8Hz), 8.35 (1H,
d, J=8Hz), 8.4-8.5 (2H, m), 8.73 (1H, s)

15 (6) 4-[3-[(E)-3-(2-Chlorophenyl)propenoylamino]phenyl]-2-
(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.38 (1H, d,
J=16Hz), 7.15-7.5 (8H, m), 7.75 (1H, s), 7.83
20 (1H, d, J=8Hz), 7.98 (1H, d, J=16Hz), 8.21 (1H,
d, J=8Hz), 8.4-8.5 (3H, m), 8.72 (1H, s)

(7) 4-[3-[(E)-3-(2,6-Dichlorophenyl)propenoylamino]-
phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-
25 [2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.49 (1H, d,
J=16Hz), 6.91 (1H, d, J=8Hz), 7.1-7.2 (2H, m),
7.25-7.45 (5H, m), 7.7-7.85 (3H, m), 8.21 (1H,
d, J=8Hz), 8.4-8.5 (2H, m), 8.71 (1H, s), 8.80
30 (1H, s)

(8) 4-[3-[(E)-3-(4-Methoxycarbonylphenyl)propenoylamino]-
phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-
[2,3-b]pyrazine

35 NMR (CDCl₃, 300MHz, δ) : 3.90 (3H, s), 4.32 (2H, s),

- 176 -

5 6.43 (1H, d, J=16Hz), 6.89 (1H, d, J=8Hz),
 7.2-7.5 (5H, m), 7.55-7.7 (3H, m), 7.82 (1H, d,
 J=8Hz), 7.97 (2H, d, J=8Hz), 8.21 (1H, dd,
 J=2Hz, 8Hz), 7.4-7.5 (3H, m), 8.74 (1H, d,
 J=2Hz)

10 (9) 4-[3-(3,4-Methylenedioxybenzoylamino)phenyl]-2-(3-
 pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
 NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 6.02 (2H, s),
 6.79 (1H, d, J=8Hz), 6.93 (1H, d, J=8Hz), 7.2-
 7.35 (4H, m), 7.48 (1H, t, J=8Hz), 7.60 (1H, d,
 J=8Hz), 7.75-7.85 (2H, m), 8.10 (1H, s), 8.17
 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.48 (1H,
 d, J=5Hz), 8.71 (1H, s)

15

 (10) 4-[3-[(Benzofuran-2-yl)carbonylamino]phenyl]-2-(3-
 pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
 NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.05 (1H, d,
 J=8Hz), 7.2-7.6 (7H, m), 7.69 (1H, d, J=8Hz),
20 7.75-7.85 (3H, m), 8.19 (1H, d, J=8Hz), 8.43
 (1H, m), 8.5-8.6 (2H, m), 8.72 (1H, s)

 (11) 4-[3-[(1-Methylindol-2-yl)carbonylamino]phenyl]-2-(3-
 pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
25 NMR (CDCl₃, 300MHz, δ) : 4.03 (3H, s), 4.31 (2H, s),
 6.95-7.05 (2H, m), 7.1-7.4 (5H, m), 7.54 (1H, t,
 J=8Hz), 7.61 (2H, d, J=8Hz), 7.8-7.85 (2H, m),
 8.19 (1H, d, J=8Hz), 8.23 (1H, s), 8.43 (1H, d,
 J=5Hz), 8.49 (1H, d, J=5Hz), 8.72 (1H, s)

30

 (12) 4-[3-[(Benzo[b]thiophen-2-yl)carbonylamino]phenyl]-2-
 (3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
 pyrazine
 NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 6.92 (1H, d,
35 J=8Hz), 7.2-7.55 (5H, m), 7.65 (1H, d, J=8Hz),

- 177 -

7.7-7.9 (4H, m), 8.18 (1H, d, J=8Hz), 8.32 (1H, s), 8.4-8.55 (2H, m), 8.73 (1H, s)

(13) 4-[3-[(6-Methoxycarbonyl-2-naphthoyl)amino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.00 (3H, s), 4.22 (2H, s), 6.93 (1H, d, J=8Hz), 7.2-7.35 (2H, m), 7.51 (1H, t, J=8Hz), 7.7-8.0 (2H, m), 8.11 (1H, d, J=8Hz), 8.19 (1H, d, J=8Hz), 8.32 (1H, s), 8.4-8.55 (3H, m), 8.60 (1H, s), 8.72 (1H, s)

(14) 4-[3-[(6-Acetoxy-2-naphthoyl)amino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 2.35 (3H, s), 4.28 (2H, s), 7.11 (1H, d, J=8Hz), 7.3-7.5 (3H, m), 7.57 (1H, t, J=8Hz), 7.75-7.9 (4H, m), 8.14 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.42 (1H, d, J=5Hz), 8.48 (1H, d, J=5Hz), 8.6-8.65 (2H, m)

20

(15) 4-[3-[(3-Methoxycarbonyl-5-nitrobenzoyl)amino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 3.98 (3H, s), 4.28 (2H, s), 7.17 (1H, dd, J=2Hz, 8Hz), 7.3-7.45 (2H, m), 7.59 (1H, t, J=8Hz), 7.75-7.85 (2H, m), 7.89 (1H, d, J=8Hz), 8.21 (1H, d, J=8Hz), 8.4-8.5 (2H, m), 8.60 (1H, d, J=2Hz), 8.78 (1H, s), 8.92 (1H, s), 9.05 (1H, s)

30

(16) 4-[3-(3,5-Dinitrobenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 6.70 (1H, d, J=8Hz), 6.93 (1H, dd, J=5Hz, 8Hz), 7.25-7.35 (2H, m), 7.43 (1H, dd, J=5Hz, 8Hz), 7.67 (1H, d,

35

- 178 -

J=8Hz), 8.0-8.1 (2H, m), 8.32 (1H, d, J=8Hz),
8.50 (2H, m), 8.99 (2H, d, J=2Hz), 9.07 (1H, t,
J=2Hz), 9.63 (1H, s)

5 (17) 4-[3-(3,5-Dimethoxybenzoylamino)phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 3.80 (6H, s), 4.27 (2H,
s), 6.71 (1H, m), 7.10 (3H, m), 7.3-7.45 (2H,
m), 7.53 (1H, t, J=8Hz), 7.75-7.9 (3H, m), 8.21
10 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.47 (1H,
d, J=5Hz), 8.59 (1H, s)

(18) 4-[3-(3,5-Dibromobenzoylamino)phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
15 pyrazine·hydrochloride
NMR (DMSO-d₆, 300MHz, δ) : 4.49 (2H, s), 7.11 (2H,
d, J=8Hz), 7.41 (1H, dd, J=5Hz, 8Hz), 7.57 (1H,
t, J=8Hz), 7.80 (1H, d, J=8Hz), 7.89 (1H, s),
8.0-8.2 (5H, m), 8.42 (1H, d, J=5Hz), 8.55 (1H,
20 d, J=8Hz), 8.83 (1H, d, J=5Hz), 8.93 (1H, d,
J=2Hz)

(19) 4-[3-[3,5-Bis(trifluoromethyl)benzoylamino]phenyl]-2-
(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
25 pyrazine·hydrochloride
NMR (DMSO-d₆, 300MHz, δ) : 4.49 (2H, s), 7.13 (1H,
d), 7.42 (1H, dd, J=5Hz, 8Hz), 7.60 (1H, t,
J=8Hz), 7.8-7.9 (2H, m), 8.01 (1H, dd, J=5Hz,
8Hz), 8.18 (1H, d, J=8Hz), 8.39 (1H, s), 8.43
30 (1H, d, J=5Hz), 8.53 (1H, dd, J=2Hz, 8Hz), 8.62
(2H, s), 8.83 (1H, d, J=5Hz), 8.83 (1H, s)

(20) 4-[2-Fluoro-5-(2-naphthoylamino)phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
35 mp : 264-268°C

- 179 -

NMR (CDCl_3 - CD_3OD = 1:1, δ) : 4.37 (2H, s), 7.3-7.45 (3H, m), 7.6 (3H, m), 7.85-8.05 (7H, m), 8.25 (1H, d, $J=8\text{Hz}$), 8.45 (3H, m), 8.64 (1H, s)

5 (21) 2-Benzyl-4-(3-cyclohexylcarbonylaminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR ($\text{DMSO}-d_6$, 300MHz, δ) : 1.1-1.5 (5H, m), 1.6-1.9 (5H, m), 2.33 (1H, m), 4.21 (2H, s), 6.98 (1H, d, $J=8\text{Hz}$), 7.2-7.5 (7H, m), 7.59 (1H, d, $J=8\text{Hz}$),
10 7.68 (1H, s), 8.23 (1H, d, $J=8\text{Hz}$), 8.39 (1H, m)

Example 42

A mixture of 3-amino-2-[3-[(E)-2-(4-pyridyl)vinyl]-phenylamino]pyridine (575 mg) and 3-(3-pyridyl)pyruvic
15 acid (0.37 g) in ethanol (10 ml) was stirred under reflux for 1.5 hours. After evaporation of the solvent, the residue was chromatographed on silica gel column (chloroform-methanol, 9:1) and crystallized from ethanol to give 2-(3-pyridylmethyl)-4-[3-[(E)-2-(4-
20 pyridyl)vinyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine (395 mg).

NMR ($\text{DMSO}-d_6$, 300MHz, δ) : 4.28 (2H, s), 7.25-7.45 (4H, m), 7.5-7.7 (7H, m), 7.78 (2H, m), 8.23 (1H, dd, $J=2\text{Hz}$, 5Hz), 8.41 (1H, m), 8.48 (1H, d, $J=5\text{Hz}$),
25 8.55 (2H, d, $J=5\text{Hz}$), 8.60 (1H, d, $J=2\text{Hz}$)

Example 43

A mixture of 2-[3-(2-naphthyl)phenylamino]-3-aminopyridine and 3-(3-pyridyl)pyruvic acid in ethanol was
30 stirred under reflux for 40 hours. After evaporation of the solvent, crude residue was chromatographed on silica gel to give 4-[3-(2-naphthyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine. Crystallization from ether and recrystallization with methanol afforded
35 colorless crystals.

- 180 -

mp : 155-156°C

NMR (CDCl₃, δ) : 4.34 (2H, s), 7.30 (3H, m), 7.48
(2H, m), 7.62 (1H, s), 7.71 (1H, dd, J=8Hz,
8Hz), 7.74 (1H, dd, J=8Hz, 2Hz), 7.88 (4H, m),
8.08 (1H, s), 8.19 (1H, d, J=8Hz), 8.45 (1H, d,
J=5Hz), 8.51 (1H, d, J=4Hz), 8.75 (1H, s)

MASS (m/z) : 441 (M+1)

Example 44

10 A mixture of 2-(3-acetamidophenylamino)-3-aminopyridine (1.0 g) and 3-(3-pyridyl)pyruvic acid (0.82 g) in ethanol (50 ml) was stirred under reflux for 6 hours. After evaporation of the solvent, crude residue was chromatographed on silica gel and crystallized from ethyl acetate to give 4-(3-acetamidophenyl)-2-(3-pyridyl-methyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (1.04 g).

15 NMR (CDCl₃, δ) : 2.00 (3H, s), 4.31 (2H, s), 6.95 (1H, m), 7.25 (1H, dd, J=8Hz, 5Hz), 7.33 (1H, dd, J=8Hz, 5Hz), 7.45 (2H, m), 7.60 (1H, s),
20 7.81 (1H, m), 7.98 (1H, s), 8.20 (1H, dd, J=8Hz, 1Hz), 8.44 (1H, dd, J=5Hz, 1Hz), 8.48 (1H, m), 8.72 (1H, s)

MASS (m/z) : 372 (M+1)

25 Example 45

The following compounds were obtained according to a similar manner to that of Example 2, 42, 43 or 44.

30 (1) 2-(3-Pyridylmethyl)-4-[3-[(E)-2-(2-quinolyl)vinyl]-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.29 (2H, s), 7.3-7.65 (6H, m), 7.7-8.0 (8H, m), 8.23 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.4-8.5 (2H, m), 8.61 (1H, d)

35

- 181 -

- (2) 2-(3-Pyridylmethyl)-4-[3-[(E)-2-(4-quinolyl)vinyl]-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.30 (2H, s), 7.3-7.45 (3H, m), 7.6-7.95 (8H, m), 8.04 (1H, d, J=8Hz), 8.13 (1H, d, J=16Hz), 8.25 (1H, d, J=8Hz), 8.4-8.55 (3H, m), 8.61 (1H, s), 8.90 (1H, d, J=5Hz)

5

- (3) 2-(3-Pyridylmethyl)-4-[3-[(E)-2-(5-pyrimidinyl)-vinyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.28 (2H, s), 7.25-7.45 (4H, m), 7.55-7.65 (3H, m), 7.7-7.85 (2H, m), 8.22 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.48 (1H, m), 8.60 (1H, d, J=2Hz), 9.05 (2H, s), 9.08 (1H, s)

10

15

- (4) 2-(3-Pyridylmethyl)-4-[3-[(E)-2-(2-pyridyl)vinyl]-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.25-7.85 (12H, m), 8.23 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.48 (1H, d, J=5Hz), 8.55-8.65 (2H, m)

20

- (5) 2-(3-Pyridylmethyl)-4-[3-[(E)-2-(3-pyridyl)vinyl]-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.28 (2H, s), 7.25-7.8 (10H, m), 8.05 (1H, d, J=8Hz), 8.22 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.48 (2H, m), 8.60 (1H, s), 8.77 (1H, s)

25

- (6) 2-Benzyl-4-[3-[3-(2-methoxyphenyl)ureido]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 238-239°C

NMR (DMSO-d₆, δ) : 6.46 (1H, m), 7.06 (1H, m), 7.25 (1H, m), 7.31 (1H, m), 7.56 (1H, m), 7.78 (1H, m), 8.03 (1H, m), 8.56 (2H, m)

30

35

- 182 -

- (7) 2-Benzyl-4-[3-(2-cyanopyrrol-1-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 165-166°C
NMR (DMSO-d₆, δ) : 4.22 (2H, s), 6.46 (1H, m),
5 7.2-7.45 (7H, m), 7.52 (2H, m), 7.65-7.8 (3H, m), 8.26 (1H, m), 8.42 (1H, m)
MASS (m/z) : 404 (M+1)
- (8) 2-Benzyl-4-[3-(benzothiazol-2-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
10 mp : 197-198°C
NMR (DMSO-d₆, δ) : 4.23 (2H, s), 7.2-7.6 (9H, m), 7.77 (1H, dd, J=8Hz, 8Hz), 8.05 (1H, d, J=8Hz), 8.15-8.3 (4H, m), 8.40 (1H, m)
- (9) 2-Benzyl-4-(3-benzoylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
15 mp : 154-155°C
NMR (CDCl₃, δ) : 4.30 (2H, s), 7.2-7.35 (4H, m),
20 7.45-7.6 (6H, m), 7.70 (1H, dd, J=8Hz, 8Hz), 7.74 (1H, m), 7.85 (2H, m), 7.96 (1H, m), 8.20 (1H, dd, J=8Hz, 2Hz), 8.40 (1H, dd, J=5Hz, 2Hz)
- (10) 2-Benzyl-4-(3-trifluoromethylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
25 mp : 125-127°C
NMR (CDCl₃, δ) : 4.30 (2H, s), 7.2-7.35 (4H, m),
30 7.48 (3H, m), 7.55 (1H, s), 7.68 (1H, s), 7.75 (1H, m), 8.20 (1H, dd, J=8Hz, 2Hz), 8.38 (1H, dd, J=5Hz, 2Hz)
- (11) 2-Benzyl-4-[3-(3-acetyllindol-1-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
35 mp : 157-159°C
NMR (DMSO-d₆, δ) : 2.50 (3H, s), 4.35 (2H, s), 7.10

- 183 -

(2H, m), 7.22 (3H, m), 7.32 (3H, m), 7.50 (1H, m), 7.61 (1H, m), 7.75-7.90 (3H, m), 8.12 (1H, m), 8.29 (2H, m), 8.60 (1H, s)

5 (12) 4-(3-Methoxycarbonylphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 208-210°C

NMR (CDCl₃, δ) : 3.91 (3H, s), 4.32 (2H, s), 7.28 (2H, m), 7.49 (1H, m), 7.68 (1H, dd, J=8Hz, 8Hz), 7.81 (1H, m), 7.97 (1H, m), 8.20 (1H, m), 8.40 (1H, m), 8.50 (1H, m), 8.72 (1H, m)

(13) 4-[3-(1-Pyrrolyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

15 mp : 128-130°C

NMR (CDCl₃, δ) : 4.27 (2H, s), 6.36 (2H, m), 7.03 (2H, m), 7.12 (1H, m), 7.18 (1H, dd, J=8Hz, 5Hz), 7.25 (1H, m), 7.30 (1H, dd, J=8Hz, 5Hz), 7.50 (1H, m), 7.56 (1H, m), 7.60 (1H, dd, J=8Hz, 8Hz), 8.10 (1H, dd, J=8Hz, 1Hz), 8.31 (1H, m), 8.35 (1H, dd, J=5Hz, 1Hz), 8.46 (1H, m)

(14) 4-(3-Trifluoromethylphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

25 mp : 88-90°C

NMR (CDCl₃, δ) : 4.22 (2H, m), 7.18 (1H, m), 7.30 (1H, m), 7.48 (3H, m), 7.69 (1H, m), 7.80 (1H, m), 8.27 (1H, m), 8.35 (1H, m), 8.47 (1H, m)

30 (15) 4-(5-Acetamido-2-fluorophenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 212-214°C

NMR (DMSO-d₆, δ) : 2.03 (3H, s), 4.27 (2H, s), 7.40 (3H, m), 7.61 (1H, m), 7.79 (2H, m), 8.23 (1H, dd, J=8Hz, 2Hz), 8.43 (1H, dd, J=5Hz, 2Hz), 8.47

- 184 -

(1H, m), 8.59 (1H, m)

(16) 4-(3-Benzoylphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

5 mp : 142-143°C

NMR (CDCl₃, δ) : 4.26 (2H, s), 7.17 (1H, dd, J=8Hz, 5Hz), 7.30 (1H, dd, J=8Hz, 5Hz), 7.50 (4H, m), 7.60 (1H, m), 7.68 (1H, dd, J=8Hz, 8Hz), 7.75 (1H, m), 7.80 (2H, m), 7.96 (1H, m), 8.10 (1H, dd, J=8Hz, 2Hz), 8.29 (1H, m), 8.35 (1H, dd, J=5Hz, 2Hz), 8.44 (1H, m)

10

(17) 4-[3-(3-Acetylmethylindol-1-yl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

15 mp : 153-156°C

NMR (CDCl₃, δ) : 2.56 (3H, s), 4.33 (2H, s), 7.25-7.45 (5H, m), 7.50 (1H, m), 7.60 (1H, m), 7.70 (1H, m), 7.80 (2H, m), 8.00 (1H, s), 8.20 (1H, d, J=8Hz), 8.45 (2H, m), 8.51 (1H, m), 8.73 (1H, m)

20

(18) 4-[3-(1-Indolyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 166-168°C

NMR (DMSO-d₆, δ) : 4.28 (2H, s), 6.73 (1H, d, J=3Hz), 7.1-7.25 (2H, m), 7.3-7.45 (3H, m), 7.6-7.8 (7H, m), 8.22 (1H, dd, J=8Hz, 2Hz), 8.46 (2H, m), 8.60 (1H, br s)

25

30 (19) 4-[3-(1-Naphthyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 162-165°C

NMR (CDCl₃, δ) : 4.31 (2H, s), 7.2-7.6 (8H, m), 7.70 (2H, m), 7.85 (3H, m), 8.07 (1H, d, J=8Hz), 8.17 (1H, d, J=8Hz), 8.50 (2H, m), 8.72 (1H, s)

35

- 185 -

(20) 4-[3-(3-Biphenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-
3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 4.32 (2H, s), 7.2-7.7 (12H, m),
7.80 (3H, m), 8.18 (1H, m), 8.44 (1H, m), 8.50
5 (1H, m), 8.72 (1H, m)

Example 46

A solution of 4-(3-acetamidophenyl)-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (0.9
10 g) in 4N hydrochloric acid (22 ml) was stirred under
reflux for 90 minutes, and cooled. The reaction mixture
was neutralized with solid sodium bicarbonate and
precipitated white crystals were collected, washed with
water and dried to give 4-(3-aminophenyl)-2-(3-
15 pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
(0.73 g).

mp : 168-170°C

NMR (CDCl₃, δ) : 3.81 (2H, s), 4.30 (2H, s), 6.53
(1H, m), 6.62 (1H, dd, J=8Hz, 2Hz), 6.80 (1H,
20 dd, J=8Hz, 2Hz), 7.27 (2H, m), 7.35 (1H, dd,
J=8Hz, 8Hz), 7.83 (1H, m), 8.17 (1H, dd, J=8Hz,
1Hz), 8.48 (1H, m), 8.50 (1H, m), 8.72 (1H, m)

Example 47

25 The following compound was obtained according to a
similar manner to that of Example 11 or 46.

4-(5-Amino-2-fluorophenyl)-2-(3-pyridylmethyl)-3-oxo-
3,4-dihydropyrido[2,3-b]pyrazine

30 mp : 177-179°C

NMR (DMSO-d₆, δ) : 4.26 (2H, s), 5.18 (2H, s), 6.53
(1H, dd, J=7Hz, 4Hz), 6.68 (1H, m), 7.08 (1H,
dd, J=8Hz, 8Hz), 7.36 (1H, dd, J=8Hz, 5Hz), 7.42
(1H, dd, J=8Hz, 5Hz), 7.77 (1H, m), 8.21 (1H,
35 dd, J=8Hz, 2Hz), 8.47 (2H, m), 8.59 (1H, m)

- 186 -

Example 48

Treatment of 4-[3-(2-naphthoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (3.84 g) with methanolic hydrogen chloride afforded 4-[3-(2-naphthoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine·hydrochloride (2.80 g) as pale yellow solid.

NMR (DMSO-d₆, 300MHz, δ) : 4.50 (2H, s), 7.10 (1H, d, J=8Hz), 7.42 (1H, dd, J=5Hz, 8Hz), 7.55-7.7 (3H, m), 7.88 (1H, d, J=8Hz), 7.95-8.15 (7H, m), 8.45 (1H, m), 8.56 (1H, d, J=8Hz), 8.62 (1H, s), 8.83 (1H, d, J=5Hz), 8.95 (1H, s)

Example 49

The following compound was obtained according to a similar manner to that of Example 48.

4-[3-(3-Biphenylyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine·hydrochloride

mp : 202-205°C

NMR (DMSO-d₆, δ) : 4.53 (2H, s), 7.35 (1H, dd, J=8Hz, 6Hz), 7.40 (1H, d, J=8Hz), 7.49 (2H, m), 7.62 (2H, d, J=8Hz), 7.75 (5H, m), 7.92 (1H, dd, J=8Hz, 6Hz), 8.00 (2H, m), 8.07 (1H, m), 8.11 (1H, d, J=8Hz), 8.29 (1H, d, J=6Hz), 8.40 (1H, d, J=8Hz), 8.78 (1H, d, J=6Hz), 8.82 (1H, s)

Example 50

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 4-[2-Fluoro-5-[3-(2-fluorophenyl)ureido]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 146-149°C

NMR (DMSO-d₆, δ) : 4.28 (2H, s), 7.01 (1H, m), 7.11

- 187 -

(1H, m), 7.22 (1H, dd, J=13Hz, 8Hz), 7.36 (2H, m), 7.44 (1H, m), 7.50 (1H, m), 7.70 (1H, m), 7.79 (1H, d, J=8Hz), 8.09 (1H, dd, J=8Hz, 8Hz), 8.23 (1H, d, J=8Hz), 8.44 (2H, m), 8.58 (2H, m), 9.26 (1H, s)

(2) 4-[2-Fluoro-5-[3-(2-methoxyphenyl)ureido]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine

mp : 152-155°C

NMR (DMSO-d₆, δ) : 3.87 (3H, s), 4.28 (2H, s), 6.87 (1H, m), 6.94 (1H, m), 7.02 (1H, m), 7.3-7.44 (4H, m), 8.09 (1H, m), 8.23 (2H, m), 8.45 (2H, m), 8.60 (1H, s), 9.53 (1H, s)

(3) 4-[3-[3-(2-Nitrophenyl)ureido]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 188-189°C

NMR (DMSO-d₆, δ) : 4.25 (2H, s), 6.98 (1H, m), 7.20 (1H, dd, J=8Hz, 8Hz), 7.37 (2H, m), 7.48 (2H, m), 7.57 (1H, s), 7.69 (1H, dd, J=8Hz, 8Hz), 7.78 (1H, m), 8.08 (1H, dd, J=8Hz, 1Hz), 8.19 (1H, dd, J=8Hz, 1Hz), 8.24 (1H, d, J=8Hz), 8.40 (1H, dd, J=5Hz, 1Hz), 8.45 (1H, dd, J=5Hz, 1Hz), 8.59 (1H, d, J=1Hz), 9.61 (1H, s)

(4) 4-[3-[3-(2-Methoxyphenyl)ureido]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 163-169°C

NMR (CDCl₃, δ) : 3.45 (3H, s), 4.38 (2H, s), 6.77 (2H, m), 6.92 (2H, m), 7.02 (1H, m), 7.16 (1H, s), 7.23 (1H, m), 7.30 (1H, m), 7.37 (1H, dd, J=8Hz, 5Hz), 7.66 (1H, s), 7.87 (1H, m), 7.94 (1H, s), 8.09 (1H, dd, J=8Hz, 3Hz), 8.25 (1H, dd, J=8Hz, 1Hz), 8.49 (2H, m), 8.76 (1H, m)

- 188 -

Example 51

A mixture of 3-amino-2-[3-(3-pyridyl)phenylamino]pyridine (150 mg) and 3-phenylpyruvic acid (113 mg) in ethanol (4 ml) was stirred under reflux for 2 hours. The mixture was cooled and then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from ethanol to give 2-benzyl-4-[3-(3-pyridyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (127 mg).

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.4 (6H, m), 7.45-7.55 (3H, m), 7.65-7.8 (2H, m), 7.89 (1H, dt, J=8Hz, 2Hz), 8.21 (1H, dd, J=2Hz, 8Hz), 8.41 (1H, dd, J=2Hz, 5Hz), 8.59 (1H, dd, J=2Hz, 5Hz), 8.87 (1H, s, J=2Hz)

Example 52

A mixture of 2-[3-acetylamino-5-methoxycarbonylphenylamino]-3-aminopyridine (1.07 g) and 3-(3-pyridyl)pyruvic acid (0.65 g) in methanol (15 ml) was stirred under reflux for 5 hours. The precipitate was collected and washed with methanol to give 4-(3-acetylamino-5-methoxycarbonylphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (1.08 g).

NMR (DMSO-d₆, 300MHz, δ) : 2.09 (3H, s), 3.87 (3H, s), 4.24 (2H, s), 7.8-7.95 (2H, m), 7.63 (1H, s), 7.78 (1H, d, J=8Hz), 7.90 (1H, s), 8.20 (1H, d, J=8Hz), 8.26 (1H, s), 8.38 (1H, d, J=5Hz), 8.47 (1H, m), 8.59 (1H, s)

Example 53

A mixture of 3-amino-2-[3-methoxycarbonyl-5-(2-naphthoylamino)phenylamino]pyridine (180 mg) and 3-phenylpyruvic acid (86 mg) in methanol (4 ml) was stirred

- 189 -

under reflux for 4 hours. The precipitate was collected and washed with methanol to give 2-benzyl-4-[3-methoxycarbonyl-5-(2-naphthoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (169 mg).

5 NMR (CDCl₃, 300MHz, δ) : 3.81 (3H, s), 4.32 (2H, s),
7.15-7.35 (4H, m), 7.45-7.65 (5H, m), 7.8-7.9
(4H, m), 8.15-8.3 (3H, m), 8.33 (1H, s), 8.39
(1H, d, J=5Hz), 8.56 (1H, s)

10 Example 54

The following compounds were obtained according to a similar manner to that of Example 2, 42, 43, 44, 51, 52 or 53.

15 (1) 4-[3-[(E)-2-Phenylvinyl]phenyl]-2-(3-pyridylmethyl)-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.1-7.7 (13H,
m), 7.93 (1H, d, J=8Hz), 8.20 (1H, dd, J=2Hz,
8Hz), 8.45 (1H, dd, J=2Hz, 5Hz), 8.52 (1H, dd,
20 J=2, 5Hz), 8.72 (1H, s)

(2) 4-[3-[(E)-2-(2-Naphthyl)vinyl]phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.33 (2H, s), 7.1-7.35 (5H,
25 m), 7.4-7.5 (3H, m), 7.59 (1H, t, J=8Hz), 7.70
(2H, m), 7.75-7.9 (5H, m), 8.20 (1H, d, J=8Hz),
8.45 (1H, d, J=5Hz), 8.52 (1H, dd, J=2Hz, 5Hz),
8.73 (1H, s)

30 (3) 2-Benzyl-4-[3-(2-pyridyl)phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 7.2-7.35 (6H,
m), 7.50 (2H, d, J=8Hz), 7.6-7.8 (3H, m), 7.94
(1H, m), 8.1-8.25 (2H, m), 8.40 (1H, m), 8.65
35 (1H, d, J=5Hz)

- 190 -

- (4) 2-(3-Pyridylmethyl)-4-[3-(2-pyridyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 7.2-7.35 (4H, m), 7.65-7.85 (4H, m), 7.97 (1H, t, J=2Hz), 8.17 (2H, m), 8.41 (1H, dd, J=2Hz, 5Hz), 8.50 (1H, dd, J=2Hz, 5Hz), 8.67 (1H, m), 8.73 (1H, d, J=2Hz)

5

- (5) 2-(3-Pyridylmethyl)-4-[3-(3-pyridyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

10

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.4 (4H, m), 7.50 (1H, t, J=2Hz), 7.65-7.8 (2H, m), 7.83 (1H, dt, J=8Hz, 2Hz), 7.90 (1H, dt, J=8Hz, 2Hz), 8.20 (1H, dd, J=2Hz, 8Hz), 8.43 (1H, dd, J=2Hz, 5Hz), 8.52 (1H, dd, J=2Hz, 5Hz), 8.60 (1H, dd, J=2Hz, 5Hz), 8.73 (1H, d, J=2Hz), 8.88 (1H, d, J=2Hz)

15

- (6) 2-Benzyl-4-[3-(4-pyridyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

20

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.4 (5H, m), 7.45-7.55 (5H, m), 7.70 (1H, t, J=8Hz), 7.78 (1H, dt, J=8Hz, 2Hz), 8.21 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz), 8.65 (2H, dd, J=2Hz, 5Hz)

25

- (7) 2-Benzyl-4-[3-(2-thienyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.07 (1H, m), 7.15-7.35 (7H, m), 7.45-7.6 (4H, m), 7.73 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.41 (1H, m)

30

- (8) 2-(3-Pyridylmethyl)-4-[3-(2-thienyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

35

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.07 (1H, dd,

- 191 -

- J=5Hz, 8Hz), 7.18 (1H, m), 7.2-7.35 (4H, m),
7.49 (1H, t, J=2Hz), 7.59 (1H, t, J=8Hz), 7.75
(1H, dt, J=8Hz, 2Hz), 7.82 (1H, dt, J=8Hz, 2Hz),
8.19 (1H, dd, J=2Hz, 8Hz), 8.43 (1H, dd, J=2Hz,
5Hz), 8.51 (1H, dd, J=2Hz, 5Hz), 8.73 (1H, d,
J=2Hz)
- (9) 4-[3-(5-Chloro-2-thienyl)phenyl]-2-benzyl-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.88 (1H, d,
J=4Hz), 7.08 (1H, d, J=4Hz), 7.15-7.4 (6H, m),
7.45-7.65 (4H, m), 8.20 (1H, dd, J=2Hz, 8Hz),
8.40 (1H, m)
- (10) 4-[3-(5-Chloro-2-thienyl)phenyl]-2-(3-pyridylmethyl)-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.89 (1H, d,
J=4Hz), 7.09 (1H, d, J=4Hz), 7.15-7.45 (4H, m),
7.55-7.7 (2H, m), 7.83 (1H, dd, J=2Hz, 8Hz),
8.20 (1H, dd, J=2Hz, 8Hz), 8.43 (1H, dd, J=2Hz,
5Hz), 8.52 (1H, dd, J=2Hz, 5Hz), 8.73 (1H, s)
- (11) 2-Benzyl-4-[3-(3-thienyl)phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 7.15-7.4 (7H,
m), 7.45-7.55 (4H, m), 7.59 (1H, t, J=8Hz)
- (12) 2-(3-Pyridylmethyl)-4-[3-(3-thienyl)phenyl]-3-oxo-
3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 7.15-7.4 (5H,
m), 7.46 (2H, m), 7.60 (1H, t, J=8Hz), 7.73 (1H,
d, J=8Hz), 7.82 (1H, dt, J=8Hz, 2Hz), 8.18 (1H,
dd, J=2Hz, 8Hz), 8.42 (1H, dd, J=2Hz, 5Hz), 8.51
(1H, dd, J=2Hz, 5Hz), 8.72 (1H, s)

- 192 -

- (13) 2-Benzyl-4-[3-(1H-1,2,4-triazol-1-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 7.2-7.5 (7H, m), 7.74 (1H, t, J=8Hz), 7.95 (1H, t, J=2Hz), 8.02 (1H, dt, J=8Hz, 2Hz), 8.27 (2H, m), 8.40 (1H, dd, J=2Hz, 5Hz), 9.30 (1H, s)
- (14) 2-(3-Pyridylmethyl)-4-[3-(1H-1,2,4-triazol-1-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.35-7.5 (3H, m), 7.7-7.8 (2H, m), 7.96 (1H, t, J=2Hz), 8.03 (1H, dt, J=8Hz, 2Hz), 8.2-8.3 (2H, m), 8.41 (1H, dd, J=2Hz, 5Hz), 8.47 (1H, dd, J=2Hz, 5Hz), 8.60 (1H, d, J=2Hz), 9.31 (1H, s)
- (15) 2-Benzyl-4-[3-(2-fluorophenyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.1-7.35 (8H, m), 7.45-7.55 (4H, m), 7.6-7.75 (2H, m), 8.19 (1H, dd, J=2Hz, 8Hz), 8.42 (1H, dd, J=2Hz, 5Hz)
- (16) 4-[3-(2-Fluorophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.1-7.35 (6H, m), 7.45-7.55 (2H, m), 7.66 (1H, t, J=8Hz), 7.72 (1H, m), 7.83 (1H, dt, J=8Hz, 2Hz), 8.18 (1H, dd, J=2Hz, 8Hz), 8.44 (1H, dd, J=2Hz, 5Hz), 8.51 (1H, dd, J=2Hz, 5Hz), 8.72 (1H, d, J=2Hz)
- (17) 2-Benzyl-4-[3-(4-methoxycarbonylphenyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 3.94 (3H, s), 4.33 (2H, s), 7.2-7.35 (5H, m), 7.51 (2H, m), 7.65-7.7 (3H, m), 7.77 (1H, dt, J=8Hz, 2Hz), 8.10 (2H, dt, J=8Hz, 2Hz), 8.21 (1H, dd, J=2Hz, 8Hz), 8.41

- 193 -

(1H, dd, J=2Hz, 5Hz)

(18) 4-[3-(4-Acetylamino-phenyl)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (CDCl₃, 300MHz, δ) : 2.10 (3H, s), 4.33 (2H, s),
7.2-7.35 (5H, m), 7.4-7.7 (10H, m), 8.22 (1H,
dd, J=2Hz, 8Hz), 8.42 (1H, dd, J=2Hz, 5Hz)

(19) 4-[3-(4-Acetylamino-phenyl)phenyl]-2-(3-

10 pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 2.13 (3H, s), 4.33 (2H, s),
7.2-7.35 (3H, m), 7.4-7.7 (8H, m), 7.83 (1H, d,
J=8Hz), 8.20 (1H, d, J=8Hz), 8.45 (1H, m), 8.51
(1H, m), 8.73 (1H, s)

15

(20) 2-Benzyl-4-(3-morpholinocarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 3.3-3.7 (8H, m), 4.22
(2H, s), 7.2-7.65 (10H, m), 8.24 (1H, dd, J=2Hz,
20 8Hz), 8.39 (1H, dd, J=2Hz, 5Hz)

(21) 2-Benzyl-4-[3,5-bis(methoxycarbonyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

25 NMR (CDCl₃, 300MHz, δ) : 3.93 (6H, s), 4.31 (2H, s),
7.2-7.35 (4H, m), 7.48 (2H, d, J=8Hz), 8.14 (2H,
s), 8.20 (1H, d, J=8Hz), 8.34 (1H, m), 8.81 (1H,
s)

(22) 4-[3,5-Bis(methoxycarbonyl)phenyl]-2-(3-

30 pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 3.94 (6H, s), 4.31 (2H, s),
7.2-7.35 (2H, m), 7.80 (1H, d, J=8Hz), 8.15-8.25
(3H, m), 8.38 (1H, d, J=5Hz), 8.52 (1H, d,
J=5Hz), 8.72 (1H, s), 8.83 (1H, t, J=2Hz)

35

- 194 -

(23) 4-[3-Methoxycarbonyl-5-(2-naphthoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine

5 NMR (DMSO-d₆, 300MHz, δ) : 3.90 (3H, s), 4.28 (2H, s), 7.8-7.95 (2H, m), 7.6-7.7 (2H, m), 7.75 (1H, d, J=2Hz), 7.79 (1H, d, J=8Hz), 8.0-8.15 (4H, m), 8.2-8.25 (2H, m), 8.40 (1H, d, J=5Hz), 8.48 (1H, d, J=5Hz), 8.57 (1H, t, J=2Hz), 8.61 (1H, d, J=2Hz), 8.65 (1H, s)

10

(24) 4-[3-(6-Methoxy-2-naphthyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 228-231°C

15 NMR (DMSO-d₆, δ) : 3.89 (3H, s), 4.29 (2H, s), 7.20 (1H, m), 7.38 (4H, m), 7.67 (1H, dd, J=8Hz, 8Hz), 7.82 (3H, m), 7.91 (3H, m), 8.20 (2H, m), 8.42 (1H, m), 8.47 (1H, m), 8.61 (1H, m)

(25) 4-[3-(5-Methoxycarbonylindol-1-yl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
20 mp : 193-197°C

25 NMR (DMSO-d₆, δ) : 3.86 (3H, s), 4.27 (2H, s), 6.90 (1H, d, J=3Hz), 7.35 (1H, m), 7.43 (1H, m), 7.47 (1H, m), 7.69 (1H, d, J=8Hz), 7.75-7.85 (6H, m), 8.23 (1H, d, J=8Hz), 8.38 (1H, s), 8.47 (1H, m), 8.61 (1H, m)

(26) 4-[3-(3-Quinolyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
30 mp : 237°C

35 NMR (DMSO-d₆, δ) : 4.28 (2H, s), 7.37 (1H, dd, J=8Hz, 5Hz), 7.42 (1H, dd, J=8Hz, 5Hz), 7.47 (1H, d, J=8Hz), 7.65 (1H, dd, J=8Hz, 8Hz), 7.75 (1H, m), 7.79 (2H, m), 7.97 (1H, m), 8.05 (3H, m), 8.24 (1H, m), 8.43 (1H, m), 8.48 (1H, m),

- 195 -

8.62 (1H, m), 8.71 (1H, d, J=3Hz), 9.28 (1H, s)

(27) 4-[3-(3-Cyclopentyloxy-4-methoxyphenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 109-111°C

5 NMR (CDCl₃, δ) : 1.60 (2H, m), 1.85 (2H, m), 1.90 (4H, m), 3.87 (3H, s), 4.33 (2H, s), 4.82 (1H, m), 6.91 (1H, d, J=8Hz), 7.13 (2H, m), 7.20 (1H, m), 7.27 (1H, m), 7.31 (1H, m), 7.41 (1H, m),
10 7.63 (1H, dd, J=8Hz, 8Hz), 7.69 (1H, m), 7.84 (1H, m), 8.19 (1H, m), 8.45 (1H, d, J=5Hz), 8.51 (1H, m), 8.74 (1H, m)

(28) 4-[3-(3-Methoxycarbonylphenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 179-181°C

NMR (CDCl₃, δ) : 3.92 (3H, s), 4.32 (2H, s), 7.30 (3H, m), 7.52 (2H, m), 7.69 (1H, dd, J=8Hz, 8Hz), 7.80 (3H, m), 8.03 (1H, d, J=8Hz), 8.19 (1H, d, J=8Hz), 8.30 (1H, s), 8.44 (1H, m), 8.51 (1H, m), 8.74 (1H, m)

MASS (m/z) : 449 (M+1)

(29) 4-[3-[(E)-2-Methoxycarbonylvinyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 180-181°C

25 NMR (DMSO-d₆, δ) : 3.71 (3H, s), 4.27 (2H, s), 6.77 (1H, d, J=16Hz), 7.40 (3H, m), 7.53 (1H, dd, J=8Hz, 8Hz), 7.66 (1H, dd, J=8Hz, 8Hz), 7.7-7.85 (5H, m), 7.92 (1H, d, J=8Hz), 8.07 (1H, s), 8.22 (1H, d, J=8Hz), 8.41 (1H, m), 8.48 (1H, m), 8.61 (1H, m)

(30) 4-[3-(4-Isoquinolyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
35

- 196 -

mp : 157-163°C

NMR (CDCl₃, δ) : 4.33 (2H, s), 7.23 (1H, m), 7.32 (1H, m), 7.40 (1H, m), 7.45 (1H, m), 7.60-7.85 (5H, m), 8.04 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.50 (2H, m), 8.58 (1H, s), 8.73 (1H, m), 9.25 (1H, s)

(31) 4-[3-(3-Acetamidophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 188-194°C

NMR (CDCl₃, δ) : 2.13 (3H, s), 4.32 (2H, s), 7.2-7.35 (5H, m), 7.45 (2H, m), 7.55 (1H, s), 7.62 (1H, dd, J=8Hz, 8Hz), 7.70 (2H, m), 7.82 (1H, m), 8.18 (1H, d, J=8Hz), 8.41 (1H, m), 8.49 (1H, d, J=5Hz), 8.73 (1H, s)

MASS (m/z) : 448 (M+1)

Example 55

A mixture of 2-benzyl-4-[3-(4-methoxycarbonylphenyl)-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (150 mg) and lithium bromide (0.30 g) in N,N-dimethylformamide (3 ml) was stirred under reflux for 4 hours. The mixture was cooled and poured into dilute hydrochloric acid with stirring. The resultant precipitate was collected and washed with water to give 2-benzyl-4-[3-(4-carboxyphenyl)-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (119 mg).

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.35 (5H, m), 7.5-7.6 (3H, m), 7.65-7.85 (4H, m), 8.14 (2H, d, J=8Hz), 8.22 (1H, dd, J=2Hz, 8Hz), 8.42 (1H, dd, J=2Hz, 5Hz)

Example 56

A suspension of 4-[3-(4-acetylamino-phenyl)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (963 mg) in 3N hydrochloric acid (25 ml) was stirred under reflux for

- 197 -

3 hours. Then the mixture was poured into ice-water and
alkalinized with sodium bicarbonate. The resultant solid
was collected and washed with water to give 4-[3-(4-
aminophenyl)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido-
5 [2,3-b]pyrazine (577 mg).

NMR (DMSO-d₆, 300MHz, δ) : 4.32 (2H, s), 5.28 (2H,
s), 6.63 (2H, d, J=8Hz), 7.15-7.45 (9H, m), 7.52
(2H, m), 7.67 (1H, d, J=8Hz), 8.23 (1H, dd,
J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz)

10

Example 57

To a mixture of 4-[3-(4-aminophenyl)phenyl]-2-benzyl-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (94 mg) and
triethylamine (0.04 ml) in dichloromethane (3 ml) was
15 added methanesulfonyl chloride (0.04 ml). The mixture was
stirred at room temperature for 30 minutes, then poured
into a mixture of ethyl acetate and aqueous sodium
bicarbonate. The organic phase was separated, washed with
aqueous sodium bicarbonate and brine, dried over magnesium
20 sulfate and concentrated. The residue was chromatographed
on silica gel column (35% ethyl acetate in hexane) and
crystallized from ethanol to give 2-benzyl-4-[3-(4-
methylsulfonylamino)phenyl]phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine (53 mg).

25 NMR (CDCl₃, 300MHz, δ) : 3.00 (3H, s), 4.33 (2H, s),
6.77 (1H, s), 7.2-7.35 (7H, m), 7.42 (1H, m),
7.45-7.55 (4H, m), 7.6-7.7 (2H, m), 8.21 (1H,
dd, J=2Hz, 8Hz), 8.41 (1H, dd, J=2Hz, 5Hz)

30 Example 58

To a mixture of 4-[3-(4-aminophenyl)phenyl]-2-benzyl-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (95 mg) and
triethylamine (0.05 ml) in dichloromethane (3 ml) was
added benzoyl chloride (0.03 ml). The mixture was stirred
35 at room temperature for 20 minutes, then poured into a

- 198 -

mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from
5 methanol to give 4-[3-(4-benzoylamino-phenyl)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (73 mg).

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.1-7.35 (5H, m), 7.4-7.75 (12H, m), 7.85 (2H, d, J=8Hz), 7.99 (1H, d), 8.20 (1H, d, J=8Hz), 8.41 (1H, m)

10

Example 59

A mixture of 2-benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (339 mg), diphenylphosphoryl azide (0.21 ml) and triethylamine (0.14 ml) in benzene (5
15 ml) was stirred under reflux for 30 minutes. Then 4-aminomorpholine (0.11 ml) was added to the mixture and reflux was continued additional 3 hours. The mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with
20 aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (3% methanol in chloroform) to give 2-benzyl-4-[3-(3-morpholinoureido)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (138 mg).

25 NMR (CDCl₃, 300MHz, δ) : 2.65 (2H, br s), 3.0 (2H, br s), 3.65 (2H, br s), 3.9 (2H, br s), 4.31 (2H, s), 5.48 (1H, s), 6.93 (1H, dt, J=8Hz, 2Hz), 7.2-7.35 (4H, m), 7.40 (1H, t, J=2Hz), 7.45-7.55 (3H, m), 7.71 (1H, dd, J=2Hz, 8Hz),
30 8.19 (2H, dt, J=8Hz, 2Hz), 7.40 (1H, dd, J=2Hz, 5Hz)

Example 60

A mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (339 mg), triethylamine (0.18
35

- 199 -

ml), 4-dimethylaminopyridine (5 mg) and morpholinocarbonyl chloride (0.15 ml) in 1,4-dioxane (4 ml) was stirred at 80°C for 2 hours. Then the mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate.

5 The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (ethyl acetate) to give 2-benzyl-4-[3-(morpholinocarbonylamino)phenyl]-3-oxo-3,4-

10 dihydropyrido[2,3-b]pyrazine (242 mg).

NMR (DMSO-d₆, 300MHz, δ) : 3.42 (4H, m), 3.60 (4H, m), 4.21 (2H, s), 6.90 (1H, d, J=8Hz), 7.2-7.45 (8H, m), 7.55 (1H, d, J=8Hz), 8.23 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz), 8.72

15 (1H, s)

Example 61

A mixture of 4-(3-acetylamino-5-methoxycarbonylphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-

20 dihydropyrido[2,3-b]pyrazine (847 mg) and hydrochloric acid (35%, 1 ml) in methanol (10 ml) was stirred under reflux for 2 hours. After cooling, the resultant precipitate was collected and washed with methanol to give

4-(3-amino-5-methoxycarbonylphenyl)-2-(3-pyridylmethyl)-3-

25 oxo-3,4-dihydropyrido[2,3-b]pyrazine dihydrochloride (612 mg).

NMR (CD₃OD, 300MHz, δ) : 3.96 (3H, s), 4.59 (2H, s), 7.42 (1H, dd, J=5Hz, 8Hz), 7.67 (1H, s), 8.02 (1H, s), 8.1-8.2 (3H, m), 8.38 (1H, d, J=5Hz),

30 8.73 (1H, d, J=8Hz), 8.82 (1H, d, J=5Hz), 8.99 (1H, s)

Example 62

To a mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-

35 dihydropyrido[2,3-b]pyrazine (150 mg) and triethylamine

- 200 -

(0.1 ml) in dichloromethane (4 ml) was added 2-furoyl chloride (0.05 ml). The mixture was stirred at room temperature for 20 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from ethanol to give 2-benzyl-4-[3-(2-furoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (145 mg).

10 NMR (CDCl₃, 300MHz, δ) : 6.52 (1H, m), 7.00 (1H, d, J=8Hz), 7.15-7.35 (5H, m), 7.45-7.6 (4H, m), 7.7-7.8 (2H, m), 8.15-8.25 (2H, m), 8.41 (1H, m)

Example 63

15 To a mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (150 mg) and triethylamine (0.16 ml) in dichloromethane (3 ml) was added 3-[(E)-3-pyridyl]acryloyl chloride·hydrochloride (140 mg). The mixture was stirred at room temperature for 30 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from methanol to give 2-benzyl-4-[3-[(E)-3-(3-pyridyl)acryloylamino]phenyl]-3-oxo-3,4-dihydropyrido-

20

25 [2,3-b]pyrazine (138 mg).

NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.35 (1H, d, J=16Hz), 6.84 (1H, d, J=8Hz), 7.05 (1H, t, J=8Hz), 7.15-7.6 (9H, m), 7.71 (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz), 8.43 (1H, d, J=5Hz), 8.53 (1H, d, J=5Hz), 8.62 (1H, s), 8.69 (1H, s)

30

Example 64

To a mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (150 mg) and triethylamine

35

- 201 -

(0.1 ml) in dichloromethane (4 ml) was added methoxyglyoxyloyl chloride (0.05 ml). The mixture was stirred at room temperature for 20 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with methanol to give 2-benzyl-4-[3-(methoxyglyoxyloylamino)phenyl]-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine (163 mg).

NMR (DMSO-d₆, 300MHz, δ) : 3.86 (3H, s), 4.21 (2H, s), 7.13 (1H, d, J=8Hz), 7.2-7.45 (6H, m), 7.53 (1H, t, J=8Hz), 7.75-7.85 (2H, m), 8.24 (2H, d, J=8Hz), 8.39 (1H, d, J=5Hz)

Example 65

To a mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (192 mg) and triethylamine (0.12 ml) in 1,4-dioxane (4 ml) was added isopropyl chloroformate (0.10 ml). The mixture was stirred at room temperature for 30 minutes, then poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with methanol to give 2-benzyl-4-(3-isopropoxycarbonylamino)phenyl)-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine (167 mg).

NMR (DMSO-d₆, 300MHz, δ) : 1.23 (6H, d, J=8Hz), 4.21 (2H, s), 4.87 (1H, m), 6.93 (1H, dt, J=8Hz, 2Hz), 7.2-7.5 (9H, m), 8.23 (1H, dd, J=2Hz, 8Hz), 8.39 (1H, dd, J=2Hz, 5Hz), 9.77 (1H, s)

Example 66

The following compounds were obtained according to a

- 202 -

similar manner to that of Example 19, 20, 21, 38, 39, 40, 60, 62, 63, 64 or 65.

(1) 4-[3-(4-Acetoxybenzoylamino)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

5 NMR (CDCl₃, 300MHz, δ) : 2.30 (3H, s), 4.30 (2H, s), 6.83 (1H, m), 7.08 (2H, d, J=8Hz), 7.1-7.35 (4H, m), 7.4-7.5 (3H, m), 7.61 (1H, s), 7.70 (1H, d, J=8Hz), 7.79 (2H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.27 (1H, s), 8.40 (1H, m)

(2) 4-[3-[3,5-Bis(methoxycarbonyl)benzoylamino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine hydrochloride

15 NMR (DMSO-d₆, 300MHz, δ) : 3.95 (6H, s), 4.49 (2H, s), 7.13 (1H, d, J=8Hz), 7.42 (1H, dd, J=5Hz, 8Hz), 7.59 (1H, t, J=8Hz), 7.8-7.9 (2H, m), 8.01 (1H, dd, J=5Hz, 8Hz), 8.19 (1H, d, J=8Hz), 8.44 (1H, t, J=2Hz), 8.52 (1H, d, J=8Hz), 8.64 (1H, d, J=2Hz), 8.75-8.85 (3H, m), 8.93 (1H, s)

(3) 4-[3-(3,5-Diethoxybenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

25 NMR (DMSO-d₆, 300MHz, δ) : 1.33 (6H, t, J=7Hz), 4.09 (4H, q, J=7Hz), 4.27 (2H, s), 6.69 (1H, d, J=2Hz), 7.05-7.1 (3H, m), 7.3-7.45 (3H, m), 7.53 (1H, t, J=8Hz), 7.75-7.85 (3H, m), 8.21 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.47 (1H, d, J=5Hz), 8.60 (1H, s)

(4) 4-[3-(3,5-Diisopropoxybenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

35 NMR (DMSO-d₆, 300MHz, δ) : 1.29 (12H, d, J=7Hz), 4.28 (2H, s), 4.69 (2H, m), 6.66 (1H, t, J=2Hz), 7.0-7.1 (3H, m), 7.35-7.45 (2H, m), 7.52 (1H, t,

- 203 -

J=8Hz), 7.75-7.85 (3H, m), 8.21 (1H, d, J=8Hz),
8.41 (1H, m), 8.48 (1H, d, J=5Hz), 8.60 (1H, d,
J=2Hz)

- 5 (5) 4-[3-(3,5-Di-tert-butylbenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine·hydrochloride

NMR (DMSO-d₆, 300MHz, δ) : 1.32 (18H, s), 4.49 (2H, s), 7.09 (1H, d, J=8Hz), 7.42 (1H, dd, J=5Hz, 8Hz), 7.5-7.65 (2H, m), 7.77 (2H, s), 7.8-7.9 (2H, m), 8.01 (1H, dd, J=5Hz, 8Hz), 8.18 (1H, d, J=8Hz), 8.44 (1H, m), 8.52 (1H, d, J=8Hz), 8.83 (1H, d, J=5Hz), 8.92 (1H, s)

- 15 (6) 4-[3-[(2,6-Dichloropyridin-4-ylcarbonylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine·hydrochloride

NMR (DMSO-d₆, 300MHz, δ) : 4.48 (2H, s), 7.14 (1H, d, J=8Hz), 7.41 (1H, dd, J=5Hz, 8Hz), 7.60 (1H, t, J=8Hz), 7.80 (1H, d, J=8Hz), 7.79 (1H, s), 8.0-8.1 (3H, m), 8.18 (1H, d, J=8Hz), 8.42 (1H, d, J=5Hz), 8.52 (1H, d, J=8Hz), 8.82 (1H, d, J=5Hz), 8.92 (1H, s)

- 25 (7) 2-Benzyl-4-[3-[(E)-3-(4-pyridyl)acryloylamino]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.0-7.1 (2H, m), 7.35-7.45 (2H, m), 7.5-7.6 (4H, m), 7.7-7.8 (3H, m), 8.21 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.48 (1H, d, J=5Hz), 8.60 (1H, d, J=2Hz), 8.65 (2H, d, J=5Hz)

- (8) 4-[3-(3,4-Dichlorobenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

35 NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.79 (1H, d,

- 204 -

J=8Hz), 7.17 (1H, dd, J=5Hz, 8Hz), 7.3-7.5 (3H, m), 7.6-7.7 (3H, m), 7.88 (1H, d, J=2Hz), 8.22 (1H, d, J=8Hz), 8.35-8.45 (2H, m), 8.62 (1H, s), 8.69 (1H, s)

5

(9) 4-[3-(3,5-Dimethylbenzoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 2.36 (6H, s), 4.31 (2H, s), 7.01 (1H, d, J=8Hz), 7.18 (1H, s), 7.2-7.35 (2H, m), 7.41 (2H, s), 7.55 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 7.75-7.85 (2H, m), 7.99 (1H, s), 8.19 (1H, d, J=8Hz), 8.4-8.5 (2H, m), 8.72 (1H, s)

10

Example 67

15 A mixture of 3-amino-2-(3-biphenylamino)pyridine (196 mg) and 3-(4-hydroxyphenyl)pyruvic acid (162 mg) in ethanol (5 ml) was stirred under reflux for 2 hours. The mixture was cooled and then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase
20 was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from methanol to give 4-(3-biphenyl)-2-(4-hydroxybenzyl)-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine (186 mg).

25 NMR (DMSO-d₆, 300MHz, δ) : 4.11 (2H, s), 6.70 (2H, dt, J=8Hz, 2Hz), 7.18 (2H, d, J=8Hz), 7.3-7.5 (5H, m), 7.6-7.75 (4H, m), 7.81 (1H, d, J=8Hz), 8.26 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 9.26 (1H, s)

30

Example 68

The following compounds were obtained according to a similar manner to that of Example 2, 42, 43, 44, 51, 52, 53 or 67.

35

- 205 -

- (1) 4-(3-Biphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 7.2-7.5 (7H, m), 7.6-7.7 (3H, m), 7.75 (1H, dt, J=8Hz, 2Hz),
5 7.83 (1H, dt, 8Hz, 2Hz), 8.19 (1H, dd, J=2Hz, 8Hz), 8.44 (1H, dd, J=2Hz, 5Hz), 8.51 (1H, dd, J=2Hz, 5Hz), 8.73 (1H, d, J=2Hz)
- (2) 4-[3-(3-Indolizinylicarbonyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
10 NMR (DMSO-d₆, 300MHz, δ) : 4.28 (2H, s), 6.71 (1H, d, J=5Hz), 7.13 (1H, dt, J=2Hz, 8Hz), 7.3-7.5 (4H, m), 7.61 (1H, m), 7.7-7.85 (4H, m), 7.90 (1H, dt, J=8Hz, 2Hz), 8.22 (1H, dd, J=2Hz, 8Hz),
15 8.45 (2H, m), 8.60 (1H, d, J=2Hz), 9.87 (1H, d, J=8Hz)
- (3) 4-(3-Benzoylamino-phenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
20 NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.09 (1H, d, J=8Hz), 7.35-7.45 (2H, m), 7.5-7.65 (4H, m), 7.75-7.9 (3H, m), 7.96 (2H, d, J=8Hz), 8.21 (1H, dd, J=2Hz, 8Hz), 8.42 (1H, dd, J=2Hz, 5Hz), 8.48 (1H, dd, J=2Hz, 8Hz), 8.60 (1H, d, J=2Hz)
25
- (4) 4-(3-Biphenyl)-2-phenyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 7.3-7.8 (13H, m), 8.30 (1H, dd, J=2Hz, 8Hz), 8.40 (2H, m), 8.48 (1H, dd, J=2Hz, 5Hz)
30
- (5) 2-(3-Pyridylmethyl)-4-[3-[(quinolin-3-yl)-carbonylamino]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
35 NMR (DMSO-d₆, 300MHz, δ) : 4.29 (2H, s), 7.14 (1H,

- 206 -

d, J=8Hz), 7.35-7.45 (2H, m), 7.59 (1H, t, J=8Hz), 7.7-7.95 (5H, m), 8.1-8.25 (3H, m), 8.4-8.5 (2H, m), 8.61 (1H, s), 8.98 (1H, d, J=2Hz), 9.37 (1H, d, J=2Hz)

5

(6) 4-[3-(N-Methyl-N-acetylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 3.20 (3H, s), 4.27 (2H, s), 7.3-7.5 (4H, m), 7.61 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.21 (1H, m), 8.40 (1H, d, J=5Hz), 8.47 (1H, d, J=5Hz), 8.60 (1H, s)

10

(7) 4-[3-[(E)-2-(3,5-Dichlorophenyl)vinyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.32 (2H, s), 6.97 (1H, d, J=16Hz), 7.1-7.4 (8H, m), 7.55-7.65 (2H, m), 7.83 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.43 (1H, m), 8.52 (1H, m), 8.73 (1H, s)

15

(8) 2-(3-Pyridylmethyl)-4-[3-(3,5-dichlorophenylcarbamoyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.3-7.45 (3H, m), 7.64 (1H, d, J=8Hz), 7.7-7.85 (2H, m), 7.9-8.0 (3H, m), 8.10 (1H, d, J=8Hz), 8.23 (1H, d, J=8Hz), 8.4-8.5 (2H, m), 8.60 (1H, s)

25

(9) 2-(3-Pyridylmethyl)-4-[3-[N-methyl-N-(3,5-dichlorophenyl)carbamoyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 3.45 (3H, s), 4.48 (2H, s), 6.99 (2H, s), 7.18 (1H, m), 7.2-7.3 (3H, m), 7.45-7.55 (2H, m), 7.80 (1H, dd, J=2Hz, 8Hz), 8.13 (1H, m), 8.32 (1H, m), 8.51 (1H, m), 8.70 (1H, d, J=2Hz)

30

35

- 207 -

- (10) 2-Benzyl-4-[3-[(E)-2-(4-pyridyl)vinyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 7.01 (1H, d, J=16Hz), 7.2-7.35 (8H, m), 7.4-7.7 (5H, m), 8.20 (1H, m), 8.40 (1H, d, J=5Hz), 8.58 (2H, d, J=5Hz)
5
- (11) 2-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (CDCl₃, 300MHz, δ) : 1.5-1.65 (2H, m), 1.75-2.0 (6H, m), 3.89 (3H, s), 4.31 (2H, s), 4.70 (1H, m), 6.72 (1H, d, J=2Hz), 6.79 (1H, dd, J=2Hz), 7.01 (1H, d, J=8Hz), 7.2-7.32 (4H, m), 7.50 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.43 (1H, d, J=5Hz)
10
15
- (12) 4-[3-[3-(2-Methoxyphenyl)ureido]phenyl]-2-phenyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
NMR (DMSO-d₆, δ) : 3.88 (3H, s), 6.55 (1H, m), 6.95 (5H, m), 7.25 (2H, m), 7.50 (5H, m), 8.30 (4H, m), 9.55 (1H, s)
20
- (13) 2-Benzyl-4-(3-phenylsulfonylaminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 199-211°C
NMR (DMSO-d₆, δ) : 4.20 (2H, s), 6.98 (1H, d, J=8Hz), 7.13 (2H, m), 7.30 (7H, m), 7.55 (2H, m), 7.62 (1H, m), 7.79 (2H, m), 8.20 (1H, d, J=8Hz), 8.35 (1H, m)
25
30
- (14) 2-Benzyl-6-phenylthio-4-[3-(3-phenylureido)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 183-185°C
NMR (DMSO-d₆, δ) : 4.20 (2H, s), 6.9-7.05 (19H, m),
35

- 208 -

7.62 (1H, s), 7.98 (1H, d, J=8Hz), 8.80 (1H, s),
8.93 (1H, s)

(15) 2-Benzyl-4-[3-(pyrrol-1-yl)phenyl]-3-oxo-3,4-
5 dihydropyrido[2,3-b]pyrazine
mp : 169-170°C

(16) 2-(4-Hydroxybenzyl)-4-[3-(pyrrol-1-yl)phenyl]-3-oxo-
3,4-dihydropyrido[2,3-b]pyrazine
10 mp : 263°C
NMR (DMSO-d₆, δ) : 4.08 (2H, s), 6.26 (2H, m), 6.70
(2H, d, J=8Hz), 7.18 (2H, d, J=8Hz), 7.21 (1H,
m), 7.40 (3H, m), 7.61 (1H, dd, J=8Hz, 8Hz),
7.67 (1H, m), 7.73 (1H, m), 8.26 (1H, dd, J=8Hz,
15 2Hz), 8.40 (1H, dd, J=5Hz, 2Hz), 9.25 (1H, s)

(17) 2-Benzyl-4-[3-(2-methoxycarbonylpyrrol-1-yl)phenyl]-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 190-191°C
20 NMR (DMSO-d₆, δ) : 3.72 (3H, s), 4.23 (2H, s), 6.65
(1H, m), 7.24 (1H, m), 7.3-7.45 (6H, m), 7.50
(1H, m), 7.67 (1H, dd, J=8Hz, 8Hz), 7.85 (2H,
m), 8.03 (1H, m), 8.27 (1H, m), 8.41 (1H, m)

25 Example 69

To a mixture of 4-(3-biphenyl)-2-(4-hydroxybenzyl)-
3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (76 mg),
triethylamine (0.05 ml) and 4-dimethylaminopyridine (3 mg)
in 1,4-dioxane (2 ml) was added acetic anhydride (0.035
30 ml). The mixture was stirred at room temperature for 1
hour, then poured into a mixture of ethyl acetate and
aqueous sodium bicarbonate. The organic phase was
separated, washed with aqueous sodium bicarbonate and
brine, dried over magnesium sulfate and concentrated to
35 give 2-(4-acetoxybenzyl)-4-(3-biphenyl)-3-oxo-3,4-

- 209 -

dihydropyrido[2,3-b]pyrazine (58 mg).

NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 7.03 (2H, d, J=8Hz), 7.25-7.8 (12H, m), 8.20 (1H, d, J=8Hz), 8.43 (1H, d, J=5Hz)

5

Example 70

A mixture of cyclopentanol (0.08 ml) and triphosgene (87 mg) in 1,2-dichloroethane (2 ml) was stirred at room temperature for 20 hours. Then the mixture was added to a mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (193 mg) and triethylamine (0.25 ml) in 1,4-dioxane (3 ml). The mixture was stirred at room temperature for 1 hour, then poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The combined organic phase was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (chloroform-methanol, 40:1) to give 2-benzyl-4-(3-cyclopentyloxy carbonylaminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (41 mg).

20

NMR (CDCl₃, 300MHz, δ) : 1.55-1.95 (8H, m), 4.31 (2H, s), 5.17 (1H, m), 6.73 (1H, s), 6.94 (1H, m), 7.2-7.5 (8H, m), 8.19 (1H, dd, J=2Hz, 8Hz), 8.42 (1H, dd, J=2Hz, 5Hz)

25

Example 71

To a mixture of 4-[3-(4-acetoxybenzoylamino)phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (147 mg) in methanol (3 ml) and 1,4-dioxane (3 ml) was added a solution of potassium carbonate (83 mg) in water (0.5 ml). The mixture was stirred at room temperature for 1.5 hours, then poured into a mixture of ethyl acetate and water. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The residue was crystallized from ethanol to give 2-benzyl-4-[3-(4-

35

- 210 -

hydroxybenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (53 mg).

NMR (DMSO-d₆, 300MHz, δ) : 4.22 (2H, s), 6.87 (2H, d, J=8Hz), 7.04 (1H, m), 7.2-7.45 (7H, m), 7.50 (1H, t, J=8Hz), 7.75-7.9 (4H, m), 8.23 (1H, m), 8.40 (1H, d, J=5Hz)

Example 72

The following compound was obtained by reacting 4-[3-(3-aminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine with methyl isocyanate according to a similar manner to that of Example 1.

4-[3-[3-(3-Methylureido)phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 248-252°C

NMR (DMSO-d₆, δ) : 2.63 (3H, d, J=6Hz), 4.28 (2H, s), 6.01 (1H, q, J=6Hz), 7.20 (1H, d, J=8Hz), 7.3-7.43 (5H, m), 7.60 (1H, m), 7.64 (1H, d, J=8Hz), 7.76 (3H, m), 8.20 (1H, m), 8.41 (1H, d, J=5Hz), 8.47 (1H, m), 8.59 (1H, s), 8.62 (1H, s)

Example 73

The following compound was obtained by reacting 4-[3-(3-aminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine with ethylisocyanate according to a similar manner to that of Example 1.

4-[3-[3-(3-Ethylureido)phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 257-258°C

NMR (DMSO-d₆, δ) : 1.04 (3H, t, J=7Hz), 3.08 (2H, m), 4.26 (2H, s), 6.11 (1H, t, J=7Hz), 7.20 (1H, m), 7.3-7.43 (5H, m), 7.61 (1H, m), 7.64 (1H, d, J=8Hz), 7.75 (3H, m), 8.20 (1H, m), 8.40 (1H, d,

- 211 -

J=5Hz), 8.46 (1H, d, J=5Hz), 8.53 (1H, s), 8.60 (1H, s)

Example 74

5 The following compound was obtained by reacting 4-[3-(3-aminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine with phenylisocyanate according to a similar manner to that of Example 1.

10 4-[3-[3-(3-Phenylureido)phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 234°C

NMR (DMSO-d₆, δ) : 4.28 (2H, s), 6.97 (1H, dd, J=8Hz, 8Hz), 7.28 (3H, m), 7.40 (7H, m), 7.66 (2H, m), 7.80 (3H, m), 8.20 (1H, m), 8.40 (1H, m), 8.47 (1H, m), 8.60 (1H, s), 8.70 (1H, s), 8.80 (1H, s)

Example 75

20 The following compound was obtained according to a similar manner to that of Example 56.

4-[3-(3-Aminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

25 mp : 202-204°C

NMR (CDCl₃, δ) : 3.73 (2H, s), 4.32 (2H, s), 6.15 (1H, m), 6.90 (1H, m), 6.98 (1H, d, J=8Hz), 7.25 (4H, m), 7.44 (1H, s), 7.62 (1H, dd, J=8Hz, 8Hz), 7.70 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.43 (1H, d, J=5Hz), 8.50 (1H, m), 8.72 (1H, s)

Example 76

35 The following compounds were obtained according to a similar manner to that of Example 57 or 58.

- 212 -

(1) 4-[3-[3-N,N-Bis(methylsulfonyl)amino]phenyl]phenyl]-
2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
pyrazine

mp : 240-246°C

5 NMR (DMSO-d₆, δ) : 3.55 (6H, s), 4.28 (2H, s), 7.40
(3H, m), 7.53 (1H, m), 7.60 (1H, dd, J=8Hz,
8Hz), 7.69 (1H, dd, J=8Hz, 8Hz), 7.79 (3H, m),
7.85 (1H, m), 7.90 (1H, m), 8.23 (1H, d, J=8Hz),
8.41 (1H, m), 8.48 (1H, m), 8.60 (1H, m)

10

(2) 4-[3-[3-(2-Naphthoylamino)phenyl]phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 202-210°C

15 NMR (DMSO-d₆, δ) : 4.28 (2H, s), 7.38 (3H, m), 7.46
(2H, m), 7.65 (4H, m), 7.80 (2H, m), 7.90 (1H,
m), 8.05 (4H, m), 8.16 (1H, s), 8.22 (1H, d,
J=8Hz), 8.44 (2H, m), 8.60 (2H, s)

20 (3) 4-[3-[3-[(Benzo[b]thiophen-2-yl)carbonylamino]-
phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine

mp : 216-218°C

25 NMR (DMSO-d₆, δ) : 4.27 (2H, s), 7.40 (3H, m), 7.48
(4H, m), 7.69 (2H, m), 7.81 (3H, m), 8.01 (1H,
m), 8.07 (1H, d, J=8Hz), 8.12 (1H, s), 8.22 (1H,
d, J=8Hz), 8.37 (1H, s), 8.41 (1H, d, J=4Hz),
8.48 (1H, d, J=4Hz), 8.60 (1H, s)

30 (4) 4-[3-[3-(2-Quinoxalinylylcarbonylamino)phenyl]phenyl]-
2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
pyrazine

mp : 206-209°C

35 NMR (DMSO-d₆, δ) : 4.26 (2H, s), 7.40 (3H, m), 7.52
(2H, m), 7.68 (1H, m), 7.72 (1H, m), 7.80 (1H,
m), 7.85 (1H, m), 8.02 (3H, m), 8.22 (2H, m),

- 213 -

8.30 (2H, m), 8.42 (1H, m), 8.46 (1H, m), 8.60
(1H, s), 9.57 (1H, s)

5 (5) 4-[3-(3-Propionylaminophenyl)phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
pyrazine

mp : 223-224°C

10 NMR (DMSO-d₆, δ) : 1.08 (3H, t, J=7Hz), 2.31 (2H, q,
J=7Hz), 4.26 (2H, s), 7.35 (5H, m), 7.62 (3H,
m), 7.76 (2H, m), 7.95 (1H, s), 8.20 (1H, m),
8.41 (1H, m), 8.47 (1H, m), 8.59 (1H, s)

15 (6) 4-[3-[3-[(E)-3-(4-Pyridyl)acryloylamino]phenyl]-
phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-
[2,3-b]pyrazine

mp : 185-191°C

20 NMR (DMSO-d₆, δ) : 4.27 (2H, s), 7.03 (1H, d,
J=16Hz), 7.40 (5H, m), 7.57 (3H, m), 7.75 (5H,
m), 8.01 (1H, s), 8.21 (1H, m), 8.41 (1H, m),
8.47 (1H, m), 8.62 (3H, m)

Example 77

25 The following compounds were obtained according to
similar manners to those of Example 57 or 58, and Example
48.

30 (1) 4-[3-[3-(3,5-Dichlorophenylsulfonylamino)phenyl]-
phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-
[2,3-b]pyrazine·hydrochloride

mp : 185-195°C

NMR (DMSO-d₆, δ) : 4.48 (2H, s), 7.10 (1H, m), 7.40
(4H, m), 7.50 (2H, m), 7.6-7.8 (5H, m), 7.98
(1H, m), 8.18 (1H, m), 8.42 (1H, m), 8.50 (1H,
m), 8.81 (1H, m), 8.90 (1H, s)

35

- 214 -

(2) 4-[3-(3-Benzoylamino-phenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine-hydrochloride

mp : ~210°C (dec.)

5 NMR (DMSO-d₆, δ) : 4.47 (2H, s), 7.35-7.75 (10H, m),
7.80 (2H, m), 7.97 (3H, m), 8.18 (2H, m), 8.45
(2H, m), 8.80 (1H, d, J=5Hz), 8.90 (1H, s)

MASS : 510 (M+1)

10 (3) 4-[3-[3-[(E)-3-Ethoxycarbonylacryloylamino]phenyl]-phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine

mp : 130-160°C (dec.)

15 NMR (DMSO-d₆, δ) : 1.25 (3H, t, J=7Hz), 4.21 (2H, q,
J=7Hz), 4.49 (2H, s), 6.70 (1H, d, J=14Hz), 7.24
(1H, d, J=14Hz), 7.35-7.5 (4H, m), 7.62 (2H, m),
7.69 (1H, dd, J=8Hz, 8Hz), 7.78 (1H, m), 8.00
(1H, m), 8.10 (1H, s), 8.17 (1H, d, J=8Hz), 8.43
(1H, d, J=5Hz), 8.51 (1H, m), 8.82 (1H, m), 8.92
20 (1H, s)

(4) 4-[3-(3-Ethoxycarbonylamino-phenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine-hydrochloride

25 mp : 168-183°C

NMR (DMSO-d₆, δ) : 1.23 (3H, t, J=7Hz), 4.12 (2H, q,
J=7Hz), 4.45 (2H, s), 7.28 (1H, m), 7.40 (4H,
m), 7.58 (1H, m), 7.66 (1H, dd, J=8Hz, 8Hz),
7.74 (1H, m), 7.84 (1H, m), 7.96 (1H, dd, J=8Hz,
30 6Hz), 8.17 (1H, d, J=8Hz), 8.42 (1H, m),
8.47 (1H, m), 8.79 (1H, m), 8.89 (1H, s), 9.72
(1H, s)

35 (5) 4-[3-[3-(Cyclopropylcarbonylamino)phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-

- 215 -

pyrazine·hydrochloride

mp : 265-274°C

NMR (DMSO-d₆, δ) : 0.77 (4H, d, J=7Hz), 1.83 (1H, m), 4.48 (2H, s), 7.3-7.45 (4H, m), 7.55 (1H, m), 7.60 (1H, m), 7.68 (1H, dd, J=8Hz, 8Hz), 7.75 (1H, m), 8.00 (2H, m), 8.18 (1H, d, J=8Hz), 8.43 (1H, m), 8.51 (1H, m), 8.83 (1H, m), 8.92 (1H, s)

10 (6) 4-[3-(3-Pyruvoylaminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine·hydrochloride

mp : 202-206°C (dec.)

15 NMR (DMSO-d₆, δ) : 3.84 (3H, s), 4.48 (2H, s), 7.38 (1H, dd, J=8Hz, 2Hz), 7.41 (1H, dd, J=8Hz, 5Hz), 7.48 (2H, m), 7.63 (1H, m), 7.70 (1H, dd, J=8Hz, 8Hz), 7.79 (2H, m), 8.00 (1H, dd, J=8Hz, 5Hz), 8.10 (1H, s), 8.18 (1H, dd, J=8Hz, 2Hz), 8.44 (1H, d, J=5Hz), 8.49 (1H, dd, J=8Hz, 2Hz), 8.82 (1H, d, J=5Hz), 8.91 (1H, s)

25 (7) 4-[3-[3-(3-Ethoxycarbonylpropanoylamino)phenyl]-phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine·hydrochloride

mp : 104-158°C (dec.)

30 NMR (DMSO-d₆, δ) : 1.17 (3H, t, J=7Hz), 2.59 (4H, m), 4.03 (2H, q, J=7Hz), 4.48 (2H, s), 7.3-7.43 (4H, m), 7.53 (1H, m), 7.60 (1H, m), 7.68 (1H, dd, J=8Hz, 8Hz), 7.75 (1H, m), 7.96 (1H, m), 8.00 (1H, m), 8.19 (1H, m), 8.43 (1H, m), 8.47 (1H, m), 8.80 (1H, m), 8.90 (1H, s)

35 (8) 4-[3-(3-Phenoxycarbonylaminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine·hydrochloride

- 216 -

mp : 188-197°C

NMR (DMSO-d₆, δ) : 4.47 (2H, s), 7.2-7.3 (3H, m),
7.3-7.5 (7H, m), 7.60 (1H, s), 7.68 (1H, dd,
J=8Hz, 8Hz), 7.78 (1H, m), 7.91 (1H, m), 7.98
(1H, m), 8.17 (1H, m), 8.43 (1H, m), 8.47 (1H,
m), 8.80 (1H, m), 8.90 (1H, s)

5

(9) 4-[3-[(E)-3-Cinnamoylamino]phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
pyrazine hydrochloride

10

mp : 181-191°C

NMR (DMSO-d₆, δ) : 4.50 (2H, s), 6.90 (1H, d,
J=16Hz), 7.43 (7H, m), 7.56 (1H, m), 7.62 (3H,
m), 7.70 (2H, m), 7.79 (1H, m), 8.00 (1H, dd,
J=8Hz, 5Hz), 8.12 (1H, m), 8.19 (1H, d, J=8Hz),
8.45 (1H, m), 8.50 (1H, m), 8.82 (1H, d, J=5Hz),
8.92 (1H, s)

15

(10) 4-[3-(3,5-Difluorobenzoylamino)phenyl]-2-(3-
pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

20

NMR (CDCl₃, 300MHz, δ) : 4.31 (2H, s), 6.85 (1H, d,
J=8Hz), 6.9-7.0 (1H, m), 7.21 (1H, dd, J=5Hz,
8Hz), 7.3-7.5 (4H, m), 7.62 (1H, d, J=8Hz), 7.71
(1H, s), 7.79 (1H, d, J=8Hz), 8.20 (1H, d,
J=8Hz), 8.42 (2H, m), 8.57 (1H, s), 8.70 (1H, s)

25

(11) 4-[3-[(E)-3-(4-Nitrophenyl)propenoylamino]phenyl]-2-
(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
pyrazine

30

NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.0-7.1
(2H, m), 7.35-7.45 (2H, m), 7.53 (1H, t, J=8Hz),
7.65-7.8 (4H, m), 7.90 (2H, d, J=8Hz), 8.21 (1H,
d, J=8Hz), 8.30 (2H, d, J=8Hz), 8.40 (1H, d,
J=5Hz), 8.48 (1H, d, J=5Hz), 8.60 (1H, d, J=2Hz)

35

- 217 -

(12) 4-[3-(3,5-Dichlorophenylsulfonylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine·hydrochloride

mp : 228-238°C

5 NMR (DMSO-d₆, δ) : 4.40 (2H, s), 6.80 (1H, m), 7.08 (1H, m), 7.17 (1H, m), 7.23 (1H, m), 7.40 (3H, m), 7.74 (1H, m), 7.88 (1H, m), 7.99 (1H, m), 8.05 (1H, m), 8.38 (2H, m), 8.75 (1H, m), 8.84 (1H, m)

10

(13) 4-(3-Phenoxycarbonylamino)phenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 227-232°C

15 NMR (DMSO-d₆, δ) : 4.45 (2H, s), 7.01 (1H, m), 7.22 (3H, m), 7.40 (3H, m), 7.53 (3H, m), 8.00 (1H, m), 8.13 (1H, m), 8.41 (1H, m), 8.51 (1H, m), 8.82 (1H, m), 8.90 (1H, m)

Example 78

20 The solution of 2-methyl-4-(3-succinimidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (18.4 g), N-bromosuccinimide (12.7 g) and benzoylperoxide (1.6 g) were refluxed for 4 hours. The mixture was evaporated and purified by chromatography (chloroform) to obtain

25 2-bromomethyl-4-(3-succinimidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (15.6 g) as yellow crystals.

NMR (CDCl₃, 300MHz, δ) : 2.89 (4H, s), 4.67 (2H, s), 7.33 (1H, dd, J=7Hz, 4Hz), 7.36 (1H, dd, J=7Hz, 1Hz), 7.43 (1H, t, J=1Hz), 7.59 (1H, dd, J=7Hz, 1Hz), 7.69 (1H, t, J=7Hz), 8.22 (1H, d, J=7Hz), 8.48 (1H, d, J=4Hz)

30

MASS (FAB) (m/e) : 413, 415

Example 79

35 To a solution of 2-bromomethyl-3-succinimidophenyl-3-

- 218 -

oxo-3,4-dihydropyrido[2,3-b]pyrazine (990 mg) in acetonitrile (10 ml) was added 1-acetylimidazole (528 mg). The solution was refluxed for an hour. The mixture was evaporated. The residue was dissolved in 4N-hydrochloric acid (15 ml), and the solution was heated at 110°C for 2 hours. The solution was evaporated. To the residue was added triethylamine (5 ml) and methanol (10 ml). The mixture was evaporated. The residue was purified by column chromatography to obtain 2-(1-imidazolylmethyl)-4-(3-aminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (410 mg) as yellow powder.

NMR (DMSO-d₆, 300MHz, δ) : 5.32 (2H, br s), 5.44 (2H, s), 6.38-6.46 (2H, m), 6.68 (1H, d, J=7Hz), 6.95 (1H, s), 7.18 (1H, dd, J=7Hz, 7Hz), 7.22 (1H, s), 7.35-7.41 (1H, m), 7.72 (1H, s), 8.13 (1H, d, J=7Hz), 8.43 (1H, d, J=5Hz)

MASS (FAB) (m/e) : 319

Example 80

The solution of 2-(1-imidazolylmethyl)-4-(3-aminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (1.07 g), 2-naphthoyl chloride (705 mg) and triethylamine (0.94 ml) in dioxane-dimethyl sulfoxide (10 ml) (2:1) was stirred for 18 hours. To the mixture was added water. The mixture was extracted by ethyl acetate (100 ml) and organic layer was dried by magnesium sulfate and evaporated. The crude product was chromatographed to obtain 2-(1-imidazolylmethyl)-4-[3-(2-naphthoylamino)-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (360 mg) as yellow powder.

NMR (DMSO-d₆, 300MHz, δ) : 5.47 (2H, s), 6.96 (1H, s), 7.11 (1H, d, J=7Hz), 7.24 (1H, s), 7.38-7.43 (1H, m), 7.55-7.69 (3H, m), 7.72 (1H, s), 7.88 (1H, d, J=7Hz), 7.94 (1H, s), 7.96-8.11 (4H, m), 8.19 (1H, d, J=7Hz), 8.45 (1H, m), 8.59 (1H, s)

- 219 -

Example 81

A solution of 4-[3-(3-aminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (100 mg) and phthalic anhydride (48 mg) in dioxane (3 ml) was stirred overnight at room temperature. The reaction mixture was diluted with water, and precipitated crystals were collected to give 4-[3-[3-(2-carboxybenzoylamino)-phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (110 mg).

10 mp : 150°C (dec.)

NMR (DMSO-d₆, δ) : 4.26 (2H, s), 7.40 (5H, m), 7.55 (2H, m), 7.65 (4H, m), 7.75 (2H, m), 7.88 (1H, d, J=8Hz), 8.05 (1H, s), 8.20 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.46 (1H, br s), 8.60 (1H, br s)

15

MASS : 554 (M+1)

Example 82

The following compounds were obtained according to a similar manner to that of Example 81.

20

(1) 4-[3-[3-(3-Carboxypropanoylamino)phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
mp : 193-199°C

25

NMR (DMSO-d₆, δ) : 2.55 (4H, m), 4.27 (2H, s), 7.40 (5H, m), 7.55 (1H, m), 7.64 (2H, m), 7.77 (2H, m), 7.94 (1H, m), 8.21 (1H, m), 8.40 (1H, m), 8.45 (1H, m), 8.60 (1H, s)

30

(2) 4-[3-[3-[(Z)-3-Carboxy-3-phenylacryloylamino]-phenyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 189-198°C (dec.)

35

NMR (DMSO-d₆, δ) : 4.25 (2H, s), 6.43 (1H, s), 7.40 (8H, m), 7.65 (5H, m), 7.78 (2H, m), 8.01 (1H,

- 220 -

m), 8.20 (1H, m), 8.40 (1H, m), 8.47 (1H, m),
8.60 (1H, m)

Example 83

5 To a solution of 4-[3-(3-aminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (200 mg) in dioxane (6 ml) was added trifluoroacetic anhydride (48 mg) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water
10 and sodium bicarbonate solution and precipitated crystals were collected to give 4-[3-(3-trifluoroacetylaminophenyl)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (0.25 g).

mp : 138-144°C

15 NMR (DMSO-d₆, δ) : 4.25 (2H, s), 7.39 (3H, m), 7.53 (2H, m), 7.69 (3H, m), 7.80 (2H, m), 7.97 (1H, m), 8.21 (1H, m), 8.40 (1H, m), 8.47 (1H, m),
8.60 (1H, m)

MASS : 502 (M+1)

20

Example 84

To a solution of 4-cyclopentyloxy-3-methoxybenzoic acid (118 mg) in dichloromethane (2 ml) was added oxalyl chloride (0.09 ml) and 1 drop of N,N-dimethylformamide.
25 After stirring at room temperature for 30 minutes, the mixture was concentrated and the residue was dissolved in dichloromethane (2 ml). The above solution was added to a mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (137 mg) and triethylamine
30 (0.105 ml) in dichloromethane (3 ml). The mixture was stirred at room temperature for 30 minutes, then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium
35 sulfate and concentrated. The residue was crystallized

- 221 -

from methanol to give 2-benzyl-4-[3-(4-cyclopentyloxy-3-methoxybenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (139 mg).

5 NMR (CDCl₃, 300MHz, δ) : 1.5-2.0 (8H, m), 3.84 (3H, s), 4.30 (2H, s), 4.78 (1H, m), 6.74 (1H, d, J=8Hz), 6.88 (1H, d, J=8Hz), 7.15-7.3 (4H, m), 7.35-7.5 (4H, m), 7.62 (1H, t, J=2Hz), 7.71 (1H, d, J=8Hz), 8.12 (1H, s), 8.19 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz)

10

Example 85

A mixture of 4-[3-(6-acetoxy-2-naphthoylamino)-phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (840 mg) in 3N hydrochloric acid (25 ml) 15 was stirred at room temperature for 2 hours. Then the mixture was concentrated and poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and 20 concentrated. The residue was crystallized from ethanol to give 4-[3-(6-hydroxy-2-naphthoylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (127 mg).

25 NMR (DMSO-d₆, 300MHz, δ) : 4.28 (2H, s), 7.10 (1H, d, J=8Hz), 7.20 (2H, m), 7.35-7.45 (2H, m), 7.55 (1H, t, J=8Hz), 7.75-8.0 (6H, m), 8.22 (1H, d, J=8Hz), 8.4-8.55 (3H, m), 8.62 (1H, s)

Example 86

30 A solution of 4-[3-(N-methyl-N-acetylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (2.02 g) in 3N hydrochloric acid (20 ml) was stirred under reflux for 2 hours. Then the mixture was poured into ice-water and alkalized with sodium bicarbonate. The 35 resultant solid was collected and washed with water and

- 222 -

recrystallized from ethanol to give 4-[3-(methylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (1.06 g).

5 NMR (DMSO-d₆, 300MHz, δ) : 2.67 (3H, d, J=6Hz), 4.24 (2H, s), 5.86 (1H, m), 6.43 (2H, m), 6.64 (1H, d, J=8Hz), 7.22 (1H, t, J=8Hz), 7.38 (2H, m), 7.78 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.4-8.5 (2H, m), 8.60 (1H, s)

10 Example 87

To a solution of 4-[3-(methylamino)phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (200 mg) in chloroform (5 ml) was added 3-[(E)-4-methoxycarbonylphenyl]propenoyl chloride (137 mg). The mixture was stirred at room temperature for 15 minutes and concentrated. The residue was crystallized from methanol to give 4-[3-[N-methyl-N-[(E)-4-methoxycarbonylcinnamoyl]-amino]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-

15 [2,3-b]pyrazine hydrochloride (114 mg).

20 NMR (CDCl₃, 300MHz, δ) : 3.50 (3H, s), 3.92 (3H, s), 4.49 (2H, s), 6.72 (1H, d, J=16Hz), 7.17 (1H, t, J=2Hz), 7.25-7.4 (2H, m), 7.4-7.55 (3H, m), 7.65-7.75 (2H, m), 7.88 (1H, dd, J=5Hz, 8Hz), 7.99 (2H, d, J=8Hz), 8.18 (1H, m), 8.37 (1H, m), 8.49 (1H, d, J=8Hz), 8.68 (1H, d, J=5Hz), 8.87 (1H, s)

25

Example 88

The following compounds were obtained according to a similar manner to that of Example 79.

30

(1) 4-[3-(1-Naphthyl)phenyl]-2-(1-imidazolylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 180-185°C

35 NMR (CDCl₃, δ) : 5.41 (2H, s), 7.10 (1H, s), 7.15

- 223 -

(1H, s), 7.35 (2H, m), 7.50 (5H, m), 7.72 (3H, m), 7.90 (2H, m), 8.07 (1H, m), 8.19 (1H, d, J=8Hz), 8.53 (1H, m)

MASS : 430 (M+1)

5

(2) 2-(1-Imidazolylmethyl)-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, 300MHz, δ) : 5.41 (2H, s), 6.84 (1H, d, J=7Hz), 7.00 (1H, s), 7.09 (1H, s), 7.34 (1H, dd, J=7Hz, 5Hz), 7.40-7.47 (2H, m), 7.64-7.74 (5H, m), 8.17 (1H, d, J=7Hz), 8.45 (1H, m), 8.90 (1H, s)

10

(3) 2-(1-Imidazolylmethyl)-4-(3-biphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

15

NMR (CDCl₃, 300MHz, δ) : 5.40 (2H, s), 7.10 (1H, s), 7.14 (1H, s), 7.20-7.50 (5H, m), 7.57-7.78 (6H, m), 8.17 (1H, dd, J=8Hz, 3Hz), 8.47 (1H, m)

20 Example 89

The following compound was synthesized from 1-amino-1H-1,3,5-triazole and 2-bromomethyl-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine according to a similar manner to that disclosed in Journal of Organic Chemistry 54, 731 (1989).

25

2-(1-1H-1,2,4-Triazolylmethyl)-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (DMSO-d₆, 300MHz, δ) : 3.88 (3H, s), 5.66 (2H, s), 7.41 (1H, dd, J=8Hz, 7Hz), 7.68 (1H, d, J=9Hz), 7.73 (1H, dd, J=9Hz, 9Hz), 8.01 (1H, s), 8.05 (1H, s), 8.10 (1H, d, J=8Hz), 8.17 (1H, d, J=8Hz), 8.42 (1H, d, J=7Hz), 8.63 (1H, s)

30

35

- 224 -

Example 90

The following compound was synthesized from 1-amino-1H-1,3,4-triazole and 2-bromomethyl-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine according to a similar manner to that disclosed in Journal of Organic Chemistry 54, 731 (1989).

2-(1-1H-1,2,4-Triazolylmethyl)-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

10 NMR (DMSO-d₆, 300MHz, δ) : 3.88 (3H, s), 5.66 (2H, s), 7.41 (1H, dd, J=8Hz, 7Hz), 7.68 (1H, d, J=9Hz), 7.73 (1H, dd, J=9Hz, 9Hz), 8.01 (1H, s), 8.05 (1H, s), 8.10 (1H, d, J=8Hz), 8.17 (1H, d, J=8Hz), 8.42 (1H, d, J=7Hz), 8.63 (1H, s)

15

Example 91

The following compound was obtained according to a similar manner to that of Example 78.

20 2-Bromomethyl-4-[3-(1-naphthyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

NMR (CDCl₃, δ) : 4.70 (2H, s), 7.35 (1H, dd, J=8Hz, 6Hz), 7.41 (1H, m), 7.45-7.55 (5H, m), 7.70 (2H, m), 7.90 (2H, m), 8.07 (1H, m), 8.23 (1H, m), 8.54 (1H, d, J=6Hz)

25

Example 92

The following compound was obtained according to a similar manner to that of Example 35.

30

2-[2-(Pyrrolidinylcarbonyl)ethyl]-4-[3-[3-(2-methoxycarbonylphenyl)ureido]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 235-237°C

35 NMR (DMSO-d₆, δ) : 1.80 (2H, m), 1.94 (2H, m), 2.77

- 225 -

5 (2H, t, J=7Hz), 3.10 (2H, t, J=7Hz), 3.30 (2H, t, J=7Hz), 3.53 (2H, t, J=7Hz), 3.87 (3H, s), 6.8-7.05 (4H, m), 7.40 (3H, m), 7.59 (1H, m), 8.08 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.29 (1H, s), 8.38 (1H, m), 9.51 (1H, s)

Example 93

The following compounds were obtained according to a similar manner to that of Example 26, 27 or 59.

10

(1) 2-Benzyl-4-[3-[3-(2-biphenyl)ureido]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

15 NMR (DMSO-d₆, 200MHz, δ) : 4.21 (2H, s), 6.90 (1H, m), 7.1-7.6 (17H, m), 7.72 (1H, s), 7.89 (1H, d, J=8Hz), 8.23 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz), 9.21 (1H, s)

(2) 2-Benzyl-4-[3-[3-(5-quinolyl)ureido]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (DMSO-d₆, 200MHz, δ) : 4.22 (2H, s), 6.97 (1H, d, J=8Hz), 7.2-7.7 (10H, m), 7.82 (1H, d, J=8Hz), 7.96 (1H, d, J=6Hz), 8.24 (2H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.59 (1H, d, J=6Hz), 8.98 (1H, s), 9.30 (1H, m)

25

Example 94

To a solution of 2-benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (41 mg) in dichloromethane (2 ml) was added oxalyl chloride (0.02 ml) and 1 drop of N,N-dimethylformamide. After stirring at room temperature for 15 minutes, ammonia solution (28%, 1 ml) was added to the mixture and stirred at room temperature for 15 minutes. The mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate.

35 The organic phase was separated, washed with aqueous

- 226 -

sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-benzyl-4-(3-carbamoylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (139 mg).

NMR (DMSO-d₆, 200MHz, δ) : 4.21 (2H, s), 7.15-7.7 (9H, m), 7.82 (1H, s), 7.95-8.1 (2H, m), 8.25 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz)

10 Example 95

A mixture of 2-benzyl-4-(3-carboxyphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (200 mg), benzyl bromide (144 mg) and potassium carbonate (155 mg) in N,N-dimethylformamide (2 ml) was stirred at room temperature for 1 hour. Then the mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The resultant solid was collected and washed with isopropyl ether to give 2-benzyl-4-(3-benzyloxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (206 mg).

NMR (CDCl₃, 200MHz, δ) : 4.30 (2H, s), 5.37 (2H, s), 7.2-7.5 (12H, m), 7.66 (1H, t, J=8Hz), 7.98 (1H, t, J=2Hz), 8.21 (2H, dt, J=2Hz, 8Hz), 8.38 (1H, dd, J=2Hz, 5Hz)

Example 96

A mixture of 4-(3-aminophenyl)-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (105 mg), propionic anhydride (0.045 ml), pyridine (0.029 ml) and 4-dimethylaminopyridine (1 mg) in dichloromethane (2 ml) was stirred at room temperature for 2 hours. Then the mixture was poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated,

- 227 -

washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from ethanol to give 2-benzyl-4-(3-propionylaminophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]-pyrazine (90 mg)

NMR (DMSO-d₆, 300MHz, δ) : 1.07 (3H, t, J=7Hz), 2.32 (2H, q, J=7Hz), 4.21 (2H, s), 6.99 (1H, d, J=8Hz), 7.2-7.5 (7H, m), 7.55-7.65 (2H, m), 8.23 (1H, d, J=8Hz), 8.39 (1H, m)

Example 97

A mixture of 2-benzyl-4-[3-[3-(2-nitrophenyl)ureido]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (120 mg) and 10% palladium on carbon (40 mg) in methanol (2 ml) and 1,4-dioxane (2 ml) was stirred under hydrogen (3 atm) at room temperature for 4 hours. The catalyst was removed by filtration and the solvent was evaporated. The residue was crystallized from methanol to give 4-[3-[3-(2-aminophenyl)ureido]phenyl]-2-benzyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (97 mg).

NMR (DMSO-d₆, 200MHz, δ) : 4.21 (2H, s), 4.80 (2H, s), 6.57 (1H, dt, J=2Hz, 8Hz), 6.7-6.95 (3H, m), 7.2-7.55 (10H, m), 7.79 (1H, s), 8.24 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz), 8.96 (1H, s)

Example 98

A mixture of 3-amino-2-(3-biphenylamino)pyridine (196 mg) and 3-(2-nitrophenyl)pyruvic acid (188 mg) in ethanol (5 ml) was stirred under reflux for 1 hour. The mixture was cooled and then poured into a mixture of ethyl acetate and aqueous sodium bicarbonate. The organic phase was separated, washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was crystallized from methanol to give 4-(3-

- 228 -

biphenyl)-2-(2-nitrobenzyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (140 mg).

5 NMR (CDCl₃, 300MHz, δ) : 4.80 (2H, s), 7.22 (1H, dd, J=5Hz, 8Hz), 7.3-7.55 (7H, m), 7.6-7.7 (4H, m), 7.78 (1H, dt, J=8Hz, 2Hz), 7.99 (1H, dd, J=2Hz, 8Hz), 8.14 (1H, dd, J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz)

Example 99

10 A mixture of 4-(3-methoxycarbonylphenyl)-2-methyl-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (5.02 g), N-bromosuccinimide (4.0 g) and benzoyl peroxide (0.50 g) in chloroform (60 ml) was stirred under reflux for 2 hours. The mixture was concentrated and chromatographed
15 on silica gel column (1% methanol in chloroform) to give 2-bromomethyl-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (4.75 g).

20 NMR (CDCl₃, 300MHz, δ) : 3.91 (3H, s), 4.19 (2H, s), 7.37 (1H, dd, J=5Hz, 8Hz), 7.53 (1H, m), 7.69 (1H, t, J=8Hz), 8.01 (1H, s), 8.2-8.3 (2H, m), 8.46 (1H, d, J=5Hz)

Example 100

25 A mixture of 2-bromomethyl-4-(3-methoxycarbonylphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (1.22 g) and 2-methylimidazole (1.35 g) in N,N-dimethylformamide (10 ml) was stirred at 80°C for 1 hour. Then the mixture was poured into aqueous sodium bicarbonate and extracted with ethyl acetate twice. The
30 combined organic solution was washed with aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel column (5% methanol in chloroform) to give 4-(3-methoxycarbonylphenyl)-2-[(2-methylimidazol-1-yl)methyl]-
35 3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (154 mg).

- 229 -

NMR (CDCl₃, 300MHz, δ) : 2.49 (3H, s), 3.91 (3H, s),
5.32 (2H, s), 6.96 (1H, s), 7.02 (1H, s), 7.33
(1H, dd, J=5Hz, 8Hz), 7.50 (1H, d, J=8Hz), 7.69
(1H, t, J=8Hz), 7.99 (1H, s), 8.15-8.25 (2H, m),
8.44 (1H, d, J=5Hz)

Example 101

A mixture of 3-amino-2-[(3-biphenyl)amino]pyridine
(350 mg) and 2-ketoglutaric acid (235 mg) in ethanol (5
ml) was stirred under reflux for 1 hour. After
evaporation of the solvent, the residue was
chromatographed on silica gel column (2.5%-3% methanol in
chloroform) to give 4-(3-biphenyl)-2-(2-carboxyethyl)-3-
oxo-3,4-dihydropyrido[2,3-b]pyrazine (222 mg).

NMR (DMSO-d₆, 300MHz, δ) : 2.78 (2H, t, J=7Hz), 3.12
(2H, t, J=7Hz), 7.3-7.5 (5H, m), 7.6-7.75 (4H,
m), 7.81 (1H, m), 8.23 (1H, dd, J=2Hz, 8Hz),
8.40 (1H, dd, J=2Hz, 5Hz)

Example 102

A mixture of 4-(3-biphenyl)-2-(2-carboxyethyl)-3-
oxo-3,4-dihydropyrido[2,3-b]pyrazine (80 mg), iodomethane
(0.04 ml) and potassium carbonate (90 mg) in N,N-
dimethylformamide (2 ml) was stirred at room temperature
for 1 hour. Then the mixture was poured into a mixture of
ethyl acetate and aqueous sodium bicarbonate. The organic
phase was separated, washed with aqueous sodium
bicarbonate and brine, dried over magnesium sulfate and
concentrated. The residue was crystallized from methanol
to give 4-(3-biphenyl)-2-(2-methoxycarbonyl)ethyl)-3-oxo-
3,4-dihydropyrido[2,3-b]pyrazine (71 mg).

NMR (DMSO-d₆, 300MHz, δ) : 2.86 (2H, t, J=7Hz), 3.17
(2H, t, J=7Hz), 3.63 (3H, s), 7.3-7.5 (5H, m),
7.6-7.75 (4H, m), 7.82 (1H, m), 8.22 (1H, dd,
J=2Hz, 8Hz), 8.40 (1H, dd, J=2Hz, 5Hz)

- 230 -

Example 103

A mixture of 4-(3-methoxycarbonylphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (0.29 g) and 4N hydrochloric acid (18 ml) was stirred
5 under reflux for 2 hours. After evaporation of the solvent, crude residue was chromatographed on silica gel (29 g, chloroform-methanol 9:1 as eluent) and crystallized from methanol to afford 4-(3-carboxyphenyl)-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]-
10 pyrazine hydrochloride as colorless crystal (0.29 g).

mp : 260-265°C

NMR (DMSO-d₆, δ) : 4.25 (2H, s), 7.39 (2H, m),
7.61 (1H, m), 7.69 (1H, dd, J=8Hz, 8Hz), 7.78
(1H, m), 7.94 (1H, s), 8.05 (1H, m), 8.20 (1H,
15 d, J=8Hz), 8.38 (1H, m), 8.48 (1H, m), 8.60 (1H,
m)

Example 104

To a solution of 2-(bromomethyl)-4-(3-succinimidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine
20 (420 mg) in acetonitrile (4 ml) was added 1-acetylimidazole (179 mg). The solution was refluxed for an hour. The mixture was evaporated. The residue was dissolved in water, and to the solution was added sodium
25 carbonate. The mixture was extracted by ethyl acetate. The organic layer was evaporated. The residue was purified by column chromatography to obtain 2-(1-imidazolylmethyl)-4-(3-succinimidophenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (105 mg) as yellow powder.

30 NMR (DMSO-d₆, 300MHz, δ) : 2.79 (4H, s), 5.44 (2H, s), 6.94 (1H, s), 7.22 (1H, s), 7.32-7.46 (4H, m), 7.68 (1H, d, J=8Hz), 7.72 (1H, s), 8.16 (1H, d, J=8Hz), 8.42 (1H, d, J=7Hz)

MASS (FAB) (m/e) : 401

35

- 231 -

Example 105

The mixture of 2-(3-pyridylmethyl)-4-(3-biphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (100 mg) and m-chloroperbenzoic acid (44.2 mg) in methylene chloride (10 ml) was stirred for 3 hours at 0°C. The mixture was washed with aqueous sodium hydrogencarbonate and extracted by chloroform (50 ml). The organic layer was evaporated and chromatographed to obtain 2-[(3-pyridyl-N-oxide)-methyl]-4-(3-biphenyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (25 mg).

NMR (CDCl₃, 300MHz, δ) : 4.28 (2H, s), 7.20-7.48 (8H, m), 7.59-7.68 (3H, m), 7.74 (1H, d, J=9Hz), 8.12 (1H, d, J=8Hz), 8.18 (1H, dd, J=8Hz, 3Hz), 8.36 (1H, s), 8.45 (1H, dd, J=7Hz, 3Hz)

MASS (FAB) (m/e) : 407

Example 106

To a solution of 2-(3-pyridylmethyl)-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (200 mg) in methylene chloride (50 ml) was added m-chloroperbenzoic acid (96.1 mg) at 0°C. The mixture was stirred for 2 hours at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 5 hours. A 10% solution of sodium sulfate (20 ml) was added to the reaction mixture. The mixture was extracted by chloroform. The organic layer was dried and evaporated. The crude mixture was purified by chromatography to obtain 2-[(3-pyridyl-N-oxide)methyl]-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine as yellow crystals.

NMR (DMSO-d₆, 300MHz, δ) : 4.21 (2H, s), 7.12 (1H, d, J=7Hz), 7.34-7.44 (3H, m), 7.56 (1H, dd, J=7Hz, 7Hz), 7.77-7.86 (2H, m), 7.88 (1H, m), 7.98 (1H, s), 7.99 (1H, s), 8.14 (1H, d, J=7Hz), 8.24 (1H, d, J=7Hz), 8.26 (1H, s), 8.41 (1H, d,

- 232 -

J=5Hz)

MASS (FAB) (m/e) : 518, 520

Example 107

5 The mixture of 2-methyl-4-(3-biphenyl-1-yl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (17 g), N-bromosuccinimide (10.6 g) and 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile (167 mg) in benzene (200 ml) was refluxed for 2 hours. The mixture was washed with water and evaporated. The crude products was purified by column chromatography to obtain 2-bromomethyl-4-(3-biphenyl-1-yl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (5 g).

10 NMR (CDCl₃, 300MHz, δ) : 4.70 (2H, s), 7.28-7.52 (6H, m), 7.59-7.69 (3H, m), 7.50 (1H, dd, J=8Hz, 3Hz), 8.23 (1H, dd, J=8Hz, 3Hz), 8.48 (1H, dd, J=7Hz, 3Hz)

Example 108

20 To a solution of 2-bromomethyl-4-(3-biphenyl-1-yl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (200 mg) in acetonitrile was added triethylamine (0.14 ml) and morpholine (0.089 ml). The reaction mixture was stirred for 5 hours at 60°C. The mixture was poured into water and extracted by ethyl acetate. The organic layer was evaporated. The crude product was purified by chromatography (SiO₂) to obtain 2-(1-morpholinomethyl)-4-(3-biphenyl-1-yl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (110 mg) as yellow powder.

25 NMR (CDCl₃, 300MHz, δ) : 2.77 (4H, s), 3.82 (4H, s), 3.91 (2H, s), 7.23-7.78 (10H, m), 8.28 (1H, d, J=8Hz), 8.44 (1H, m)

Example 109

35 The mixture of 2-methyl-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido-

- 233 -

[2,3-b]pyrazine (4.4 g), N-bromosuccinimide (2.39 g) and benzoylperoxide in chloroform (40 ml) was refluxed for 3 hours. The mixture was washed with water and extracted by chloroform (80 ml), and evaporated. The crude product was
5 purified by chromatography to obtain 2-bromomethyl-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine (1.4 g).

NMR (CDCl₃, 300MHz, δ) : 4.69 (2H, s), 6.93 (1H, d, J=6Hz), 7.35 (1H, dd, J=7Hz, 5Hz), 7.43-7.50
10 (2H, m), 7.62 (1H, m), 7.74 (1H, d, J=7Hz), 7.99 (1H, s), 8.12 (1H, s), 8.24 (1H, d, J=7Hz), 8.37 (1H, s), 8.49 (1H, d, J=5Hz)

Example 110

15 The solution of 2-bromomethyl-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine (105 mg) and 2-methylimidazole (171 mg) in N,N-dimethylformamide (10 ml) was stirred for 3 hours at 70°C and 1 hour at 80°C. The mixture was poured into
20 aqueous sodium hydrogencarbonate and extracted by ethyl acetate (100 ml). The organic layer was evaporated and chromatographed to obtain 2-[(2-methylimidazol-1-yl)-methyl]-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (50 mg) in brown powder form.

25 NMR (CDCl₃, 300MHz, δ) : 2.47 (3H, s), 5.37 (2H, s), 6.82 (1H, d, J=6Hz), 6.91 (1H, s), 6.99 (1H, s), 7.34 (1H, dd, J=7Hz, 5Hz), 7.41-7.48 (2H, m), 7.56 (1H, d, J=7Hz), 7.69-7.71 (2H, m), 7.87 (1H, s), 8.18 (1H, d, J=7Hz), 8.46 (1H, d, J=4Hz), 8.88 (1H, s)
30

Example 111

The solution of 2-bromomethyl-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido-
35 [2,3-b]pyrazine (285 mg) and 2-phenylimidazole (734 mg) in

- 234 -

N,N-dimethylformamide (30 ml) was stirred for 3 hours at 80°C. The mixture was poured into aqueous sodium hydrogencarbonate (150 ml) and extracted by ethyl acetate (150 mg). The organic layer was evaporated and
5 chromatographed to obtain 2-[(2-phenylimidazol-1-yl)methyl]-4-[3-(3,5-dichlorobenzoylamino)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine (52 mg) in brown powder form.

10 NMR (CDCl₃, 300MHz, δ) : 5.53 (2H, s), 6.82 (1H, d, J=7Hz), 7.10 (1H, s), 7.17 (1H, s), 7.28-7.55 (7H, m), 7.59-7.66 (4H, m), 7.72 (1H, m), 8.17 (1H, dd, J=7Hz, 3Hz), 8.44-8.50 (2H, m)

Example 112

15 The following compound was obtained according to a similar manner to that of 2, 42, 43, 44, 51, 53 or 67.

4-[3-[(E)-2-(5-Chloropyridin-3-yl)vinyl]phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

20 NMR (DMSO-d₆, 300MHz, δ) : 4.27 (2H, s), 7.25-7.45 (4H, m), 7.5-7.65 (3H, m), 7.71 (1H, d, J=8Hz), 7.79 (1H, d, J=8Hz), 8.22 (2H, m), 8.35-8.5 (3H, m), 8.60 (1H, s), 8.70 (1H, s)

25 Example 113

The following compound was obtained by reacting 2-benzyl-4-[3-(1-pyrrolyl)phenyl]-3-oxo-3,4-dihydropyrido-[2,3-b]pyrazine with N-bromosuccinimide in a conventional
30 manner.

2-Benzyl-4-[3-(2,5-dibromopyrrol-1-yl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine

mp : 90°C (dec.)

35 NMR (DMSO-d₆, δ) : 4.22 (2H, s), 6.46 (2H, s), 7.23 (1H, m), 7.3-7.5 (7H, m), 7.55 (1H, m), 7.72

- 235 -

(1H, dd, J=8Hz, 8Hz), 8.23 (1H, m), 8.41 (1H, m)

MASS : 537 (M⁺)Example 114

5 The following compounds can be obtained according to
a similar manner to that of Example 57 or 58.

10 (1) 4-[3-[3-[(E)-3-(3-Pyridyl)acryloylamino]phenyl]-
phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-
[2,3-b]pyrazine

15 (2) 4-[3-[3-[(E)-3-(2-Pyridyl)acryloylamino]phenyl]-
phenyl]-2-(3-pyridylmethyl)-3-oxo-3,4-dihydropyrido-
[2,3-b]pyrazine

20

25

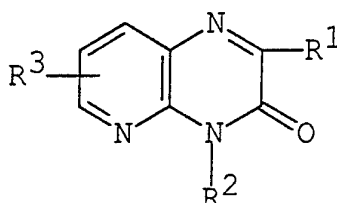
30

35

- 236 -

C L A I M S

1. A compound of the formula :



wherein

R^1 is aryl which may have suitable substituent(s),
 ar(lower)alkyl which may have suitable
 substituent(s), halo(lower)alkyl, protected
 carboxy(lower)alkyl, acyl(lower)alkyl, heterocyclic
 group or heterocyclic(lower)alkyl which may have
 suitable substituent(s),

R^2 is aryl which may have suitable substituent(s) or
 heterocyclic group, and

R^3 is hydrogen, lower alkoxy or arylthio,
 and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is phenyl which may have 1 to 3 suitable
 substituent(s); phenyl(lower)alkyl which may have 1
 to 3 suitable substituent(s); halo(lower)alkyl;
 protected carboxy(lower)alkyl; carbamoyl(lower)alkyl
 which may have one or two suitable substituent(s);
 heterocyclicoxycarbonyl(lower)alkyl which may have 1
 to 3 suitable substituent(s);
 heterocycliccarbonyl(lower)alkyl which may have 1 to
 3 substituent(s) selected from the group consisting
 of protected carboxy and lower alkyl; indolyl; or

- 237 -

indolyl(lower)alkyl, pyridyl(lower)alkyl,
imidazolyl(lower)alkyl, morpholinyl(lower)alkyl or
triazolyl(lower)alkyl, each of which may have 1 to 3
suitable substituent(s);

- 5 R^2 is phenyl or naphthyl, each of which may have 1 to 3
suitable substituent(s), or pyridyl, and
 R^3 is hydrogen, lower alkoxy or phenylthio.

3. A compound of claim 2, wherein

- 10 R^1 is phenyl which may have one or two nitro;
phenyl(lower)alkyl which may have one or two
substituent(s) selected from the group consisting of
nitro, amino, protected amino, hydroxy and protected
hydroxy; halo(lower)alkyl; esterified
15 carboxy(lower)alkyl; carbamoyl(lower)alkyl which may
have one or two substituent(s) selected from the
group consisting of lower alkyl and heterocyclic
group; pyrrolidinylloxycarbonyl(lower)alkyl which may
have one or two oxo; pyrrolidinylcarbonyl(lower)alkyl
20 or piperazinylcarbonyl(lower)alkyl, each of which may
have one or two substituent(s) selected from the
group consisting of esterified carboxy and lower
alkyl; indolyl; or indolyl(lower)alkyl,
pyridyl(lower)alkyl, imidazolyl(lower)alkyl,
25 morpholinyl(lower)alkyl or triazolyl(lower)alkyl,
each of which may have one or two substituent(s)
selected from the group consisting of lower alkyl,
N-oxide and aryl;
- R^2 is phenyl or naphthyl, each of which may have one or
30 two substituent(s) selected from the group consisting
of lower alkyl; halogen; mono(or di or
tri)halo(lower)alkyl; hydroxy; protected hydroxy;
carboxy; protected carboxy; carboxy(lower)alkyl;
protected carboxy(lower)alkyl; lower alkoxy; cyano;
35 nitro; amino; acylamino; lower alkylamino; N-acyl-N-

- 238 -

lower alkylamino; heterocyclicamino which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and aryl; acyl; acyl(lower)alkyl; aryl which may have 1 to 3 substituent(s) selected from the group consisting of carboxy(lower)alkenyl, protected carboxy(lower)alkenyl, aryl, lower alkoxy, cyclo(lower)alkyloxy, halogen, carboxy, protected carboxy, amino, acylamino, diacylamino and acyl; ar(lower)alkyl; ar(lower)alkenyl which may have 1 to 3 halogen; acyl(lower)alkenyl; protected carboxy(lower)alkenyl; cyano(lower)alkenyl; heterocyclic(lower)alkenyl which may have 1 to 3 halogen; heterocyclic group which may have 1 to 3 substituent(s) selected from the group consisting of halogen, cyano, carboxy, protected carboxy, oxo, acyl, amino, protected amino and heterocyclic group; and heterocyclicoxy which may have 1 to 3 aryl, or pyridyl.

20

4. A compound of claim 3, wherein

R¹ is phenyl which may have nitro; phenyl(lower)alkyl which may have nitro, amino, acylamino, hydroxy or acyloxy; halo(lower)alkyl; lower alkoxycarbonyl(lower)alkyl; carbamoyl(lower)alkyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and pyrrolidinyl; pyrrolidinylloxycarbonyl(lower)alkyl which may have one or two oxo; pyrrolidinylcarbonyl(lower)alkyl or piperazinylcarbonyl(lower)alkyl, each of which may have lower alkoxycarbonyl or lower alkyl; indolyl; or indolyl(lower)alkyl, pyridyl(lower)alkyl, imidazolyl(lower)alkyl, morpholinyl(lower)alkyl or

35

- 239 -

triazolyl(lower)alkyl, each of which may have lower alkyl, N-oxide or phenyl;

R^2 is phenyl or naphthyl, each of which may have one or two substituent(s) selected from the group consisting of lower alkyl; halogen; trihalo(lower)alkyl; hydroxy; acyloxy; carboxy; esterified carboxy; carboxy(lower)alkyl; esterified carboxy(lower)alkyl; lower alkoxy; cyano; nitro; amino; lower alkanoylamino; aryloxy-carbonylamino; lower alkoxy-carbonylamino; lower alkoxyglyoxyloyl; cyclo(lower)alkyl-carbonylamino; cyclo(lower)alkyloxy-carbonylamino; cyclo(lower)alkylidene(lower)alkanoylamino; aroylamino which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, halogen, lower alkoxy, carboxy, protected carboxy, nitro, hydroxy, protected hydroxy, mono(or di or tri)halo(lower)alkyl, cyclo(lower)alkyloxy, aryl, carboxy(lower)alkenyl, protected carboxy(lower)alkenyl, amino, protected amino, heterocycloxy, and heterocyclicamino which may have nitro; arylsulfonylamino which may have one or two halogen; ar(lower)alkylsulfonylamino; cyclo(lower)alkyl-carbonylamino; [mono(or di)ar(lower)alkanoyl]amino; lower alkadienoylamino; heterocycliccarbonylamino which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and halogen; ar(lower)alkenoylamino which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, halogen, carboxy, protected carboxy and nitro; heterocyclic(lower)alkenoylamino; carbamoylamino which may have one or two substituent(s) selected from the group consisting of lower alkyl; [aryl which may have 1 to 3 substituent(s) selected from the

- 240 -

group consisting of nitro, amino, protected amino, lower alkoxy, lower alkylthio, lower alkyl, aryl, carboxy, protected carboxy, di(lower)alkylamino, mono(or di or tri)halo(lower)alkyl and halogen]; arylsulfonyl; ar(lower)alkyl; cyclo(lower)alkyl; and heterocyclic group; thiocarbamoylamino which may have one or two substituent(s) selected from the group consisting of aryl and acyl; lower alkylamino; N-lower alkanoyl-N-lower alkylamino; N-aroyle-N-lower alkylamino; N-arylcarbonyl-N-lower alkylamino; N-protected carboxyl(lower)alkenyl-N-lower alkylamino; thiazolylamino or pyrimidinylamino, each of which may have one or two substituent(s) selected from the group consisting of lower alkyl and phenyl; lower alkanoyl; carbonyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and aryl which may have one or two halogen; aroyle which may have lower alkoxy or heterocycliccarbonyl; carbonyl(lower)alkyl which may have one or two aryl; phenyl or naphthyl, each of which may have one or two substituent(s) selected from the group consisting of carboxyl(lower)alkenyl, esterified carboxyl(lower)alkenyl, phenyl, lower alkoxy, cyclo(lower)alkyloxy, halogen, carboxy, esterified carboxy, amino, lower alkanoylamino, aroyleamino which may have protected carboxy or carboxy, lower alkylsulfonylamino, mono(or di or tri)halo(lower)alkanoylamino, lower alkoxycarbonylamino, aryloxy carbonylamino, carboxyl(lower)alkanoylamino, protected carboxyl(lower)alkanoylamino, carboxyl(lower)alkenoylamino, protected carboxyl(lower)alkenoylamino, cyclo(lower)alkylcarbonylamino, lower alkylglyoxyloyleamino, arylsulfonylamino which may

- 241 -

have one or two halogen, ar(lower)alkenoylamino which may have protected carboxy or carboxy, heterocyclic(lower)alkenoylamino, heterocycliccarbonylamino, carbamoylamino which may have one or two substituent(s) selected from the group consisting of lower alkyl and aryl, bis(lower alkylsulfonyl)amino, and carbamoyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and aryl; phenyl(lower)alkyl; naphthyl(lower)alkyl; phenyl(lower)alkenyl or naphthyl(lower)alkenyl, each of which may have one or two halogen; aroyl(lower)alkenyl; esterified carboxy(lower)alkenyl; cyano(lower)alkenyl; pyridyl(lower)alkenyl which may have one or two halogen; pyrimidinyl(lower)alkenyl; quinolyl(lower)alkenyl; pyridyl, thienyl, pyrrolyl, pyrrolidinyl, indolyl, quinolyl, isoquinolyl, imidazolyl, thiazolyl, benzothiazolyl or triazolyl, each of which may have one or two substituent(s) selected from the group consisting of halogen, cyano, carboxy, esterified carboxy, oxo, lower alkanoyl, amino, acylamino and pyridyl; and pyrimidinylloxy which may have one or two phenyl; or pyridyl.

25

5. A compound of claim 4, wherein

R¹ is phenyl which may have nitro; phenyl(lower)alkyl which may have nitro, amino, acylamino, hydroxy or lower alkanoyloxy; halo(lower)alkyl; lower alkoxy carbonyl(lower)alkyl; carbamoyl(lower)alkyl which may have one or two substituent(s) selected from the group consisting of lower alkyl and pyrrolidinyl; pyrrolidinylloxycarbonyl(lower)alkyl which may have two oxo; pyrrolidinylcarbonyl(lower)alkyl which may have lower

- 242 -

alkoxycarbonyl; piperazinylcarbonyl(lower)alkyl which
may have lower alkyl; indolyl; indolyl(lower)alkyl;
pyridyl(lower)alkyl which may have N-oxide;
imidazolyl(lower)alkyl which may have lower alkyl or
5 phenyl; morpholinyl(lower)alkyl; or
triazolyl(lower)alkyl;

R^2 is phenyl or naphthyl, each of which may have one or
two substituent(s) selected from the group consisting
of lower alkyl; halogen; trihalo(lower)alkyl;
10 hydroxy; lower alkanoyloxy; carboxy; lower
alkoxycarbonyl; phenyl(lower)alkoxycarbonyl;
carboxy(lower)alkyl; lower
alkoxycarbonyl(lower)alkyl; lower alkoxy; cyano;
nitro; amino; lower alkanoylamino;
15 phenoxycarbonylamino; lower alkoxycarbonylamino;
lower alkoxyglyoxyloyl;
cyclo(lower)alkylcarbonylamino;
cyclo(lower)alkyloxycarbonylamino;
cyclo(lower)alkylidene(lower)alkanoylamino;
20 benzoylamino or naphthoylamino, each of which may
have one or two substituent(s) selected from the
group consisting of lower alkyl, halogen, lower
alkoxy, carboxy, esterified carboxy, nitro, hydroxy,
acyloxy, trihalo(lower)alkyl, cyclo(lower)alkyloxy,
25 phenyl, carboxy(lower)alkenyl, esterified
carboxy(lower)alkenyl, amino, aroylamino,
pyrimidinyloxy, and pyridylamino which may have
nitro; phenylsulfonylamino which may have one or two
halogen; phenyl(lower)alkylsulfonylamino;
30 cyclo(lower)alkylcarbonylamino; [mono(or
di)phenyl(lower)alkanoyl]amino;
[naphthyl(lower)alkanoyl]amino; lower
alkadienoylamino; furylcarbonylamino,
pyridylcarbonylamino, thienylcarbonylamino,
35 indolylcarbonylamino, indolinylcarbonylamino,

- 243 -

quinolylcarbonylamino,
tetrahydroquinolylcarbonylamino,
benzofurylcarbonylamino, benzothienylcarbonylamino,
methylenedioxybenzoylamino or
5 morpholinylcarbonylamino, each of which may have one
or two substituent(s) selected from the group
consisting of lower alkyl and halogen;
phenyl(lower)alkenoylamino which may have one or two
substituent(s) selected from the group consisting of
10 lower alkyl, halogen, carboxy, esterified carboxy and
nitro; pyridyl(lower)alkenoylamino; carbamoylamino
which may have one or two substituent(s) selected
from the group consisting of lower alkyl; [phenyl or
naphthyl, each of which may have one or two
15 substituent(s) selected from the group consisting of
nitro, amino, acylamino, lower alkoxy, lower
alkylthio, lower alkyl, phenyl, carboxy, esterified
carboxy, di(lower)alkylamino, trihalo(lower)alkyl and
halogen]; phenylsulfonyl; phenyl(lower)alkyl;
20 cyclo(lower)alkyl; thiazolyl; pyridyl; quinolyl; and
morpholinyl; thiocarbamoylamino which may have
phenyl, naphthyl or aroyl; lower alkylamino; N-lower
alkanoyl-N-lower alkylamino; N-benzoyl-N-lower
alkylamino; N-phenylcarbamoyl-N-lower alkylamino;
25 N-[esterified carboxyphenyl](lower)alkenoyl-N-lower
alkylamino; thiazolylamino or pyrimidinylamino each
of which may have lower alkyl or phenyl; lower
alkanoyl; carbamoyl which may have lower alkyl, or
phenyl which may have one or two halogen; benzoyl
30 which may have lower alkoxy; morpholinylcarbonyl;
indolizinyllcarbonyl; carbamoyl(lower)alkyl which may
have phenyl or naphthyl; phenyl or naphthyl, each of
which may have one or two substituent(s) selected
from the group consisting of carboxy(lower)alkenyl,
35 lower alkoxycarbonyl(lower)alkenyl, phenyl, lower

- 244 -

alkoxy, cyclo(lower)alkyloxy, halogen, carboxy, lower
alkoxycarbonyl, amino, lower alkanoylamino,
benzoylamino which may have esterified carboxy or
carboxy, lower alkylsulfonylamino,
5 trihalo(lower)alkanoylamino, lower
alkoxycarbonylamino, phenoxycarbonylamino,
carboxy(lower)alkanoylamino, esterified
carboxy(lower)alkanoylamino,
carboxy(lower)alkenoylamino, esterified
10 carboxy(lower)alkenoylamino,
cyclo(lower)alkylcarbonylamino, lower
alkylglyoxyloylamino, phenylsulfonylamino which may
have one or two halogen, phenyl(lower)alkenoylamino
which may have esterified carboxy or carboxy,
15 pyridyl(lower)alkenoylamino,
quinoxalinyllcarbonylamino, benzothienylcarbonylamino,
carbamoylamino which may have one or two
substituent(s) selected from the group consisting of
lower alkyl and phenyl, bis(lower
20 alkylsulfonyl)amino, and carbamoyl which may have one
or two substituent(s) selected from the group
consisting of lower alkyl, phenyl and naphthyl;
phenyl(lower)alkyl; naphthyl(lower)alkyl;
phenyl(lower)alkenyl or naphthyl(lower)alkenyl, each
25 of which may have one or two halogen;
benzoyl(lower)alkenyl; lower
alkoxycarbonyl(lower)alkenyl; cyano(lower)alkenyl;
pyridyl(lower)alkenyl which may have halogen;
pyrimidinyl(lower)alkenyl; quinolyl(lower)alkenyl;
30 pyridyl, thienyl, pyrrolyl, pyrrolidinyl, indolyl,
quinolyl, isoquinolyl, imidazolyl, thiazolyl,
benzothiazolyl or triazolyl which may have one or two
substituent(s) selected from the group consisting of
halogen, cyano, carboxy, lower alkoxycarbonyl, oxo,
35 lower alkanoyl, amino, acylamino and pyridyl; and

- 245 -

pyrimidinyloxy which may have phenyl; or pyridyl.

6. A compound of claim 5, wherein

R¹ is phenyl, nitrophenyl, phenyl(lower)alkyl,

5 nitrophenyl(lower)alkyl, aminophenyl(lower)alkyl,
hydroxyphenyl(lower)alkyl, lower
alkanoyloxyphenyl(lower)alkyl, halo(lower)alkyl,
lower alkoxycarbonyl(lower)alkyl,
[pyrrolidinylcarbamoyl](lower)alkyl, [N,N-
10 di(lower)alkylcarbamoyl](lower)alkyl,
pyrrolidinylcarbonyl(lower)alkyl,
[dioxopyrrolidinylloxycarbonyl](lower)alkyl, [lower
alkoxycarbonylpyrrolidinylcarbonyl](lower)alkyl,
[lower alkylpiperazinylcarbonyl](lower)alkyl,
15 indolyl, indolyl(lower)alkyl, pyridyl(lower)alkyl
which may have N-oxide, imidazolyl(lower)alkyl which
may have lower alkyl or phenyl, or
morpholinyl(lower)alkyl,

R² is phenyl or naphthyl, each of which may have one or
20 two substituent(s) selected from the group consisting
of lower alkyl; halogen; trihalo(lower)alkyl;
hydroxy; lower alkanoyloxy; carboxy; lower
alkoxycarbonyl; phenyl(lower)alkoxycarbonyl;
carboxy(lower)alkyl; lower
25 alkoxycarbonyl(lower)alkyl; lower alkoxy; cyano;
nitro; amino; lower alkanoylamino;
phenoxycarbonylamino; lower alkoxycarbonylamino;
lower alkoxyglyoxyloyl;
cyclo(lower)alkylcarbonylamino;
30 cyclo(lower)alkyloxycarbonylamino;
cyclo(lower)alkylidene(lower)alkanoylamino;
benzoylamino which may have one or two substituent(s)
selected from the group consisting of lower alkyl,
halogen, lower alkoxy, carboxy, lower alkoxycarbonyl,
35 nitro, hydroxy, lower alkanoyloxy,

- 246 -

trihalo(lower)alkyl, cyclo(lower)alkyloxy, phenyl,
carboxy(lower)alkenyl, lower
alkoxycarbonyl(lower)alkenyl, amino, benzoylamino,
pyrimidinyloxy, and pyridylamino which may have
5 nitro; phenylsulfonylamino which may have one or two
halogen; naphthoylamino which may have hydroxy, lower
alkanoyloxy or lower alkoxycarbonyl;
phenyl(lower)alkylsulfonylamino;
cyclo(lower)alkylcarbonylamino;
10 [mono(or di)phenyl(lower)alkanoyl]amino;
[naphthyl(lower)alkanoyl]amino;
lower alkadienoylamino; furylcarbonylamino;
pyridylcarbonylamino which may have one or two
halogen; thienylcarbonylamino; indolylcarbonylamino
15 which may have lower alkyl; indolinylcarbonylamino;
quinolylcarbonylamino;
tetrahydroquinolylcarbonylamino;
benzofurylcarbonylamino; benzothienylcarbonylamino;
methylenedioxybenzoylamino; morpholinylcarbonylamino;
20 phenyl(lower)alkenylamino which may have lower alkyl,
halogen, carboxy, lower alkoxycarbonyl or nitro;
pyridyl(lower)alkenoylamino; carbamoylamino which may
have one or two substituent(s) selected from the
group consisting of lower alkyl; [phenyl which may
25 have one or two substituent(s) selected from the
group consisting of nitro, amino, acylamino, lower
alkoxy, lower alkylthio, lower alkyl, phenyl,
carboxy, lower alkoxycarbonyl, di(lower)alkylamino,
trihalo(lower)alkyl; naphthyl and halogen];
30 phenylsulfonyl; phenyl(lower)alkyl;
cyclo(lower)alkyl; thiazolyl; pyridyl; quinolyl; and
morpholinyl; thiocarbamoylamino which may have
phenyl, naphthyl, or benzoyl; lower alkylamino;
N-lower alkanoyl-N-lower alkylamino; N-benzoyl-N-
35 lower alkylamino; N-phenylcarbamoyl-N-lower

- 247 -

alkylamino; N-[lower alkoxy carbonyl phenyl] (lower)-
alkenoyl-N-lower alkylamino; thiazolylamino which may
have lower alkyl or phenyl; pyrimidinylamino;
lower alkanoyl; carbamoyl which may have lower alkyl
or phenyl which may have one or two halogen; benzoyl
which may have lower alkoxy; morpholinyl carbonyl;
indoliziny carbonyl; carbamoyl (lower) alkyl which may
have phenyl or naphthyl; phenyl which may have one or
two substituent(s) selected from the group consisting
of carboxy (lower) alkenyl, lower
alkoxy carbonyl (lower) alkenyl, phenyl, lower alkoxy,
cyclo (lower) alkyloxy, halogen, carboxy, lower
alkoxy carbonyl, amino, lower alkanoylamino,
benzoylamino which may have esterified carboxy or
carboxy, lower alkyl sulfonylamino,
trihalo (lower) alkanoylamino, lower
alkoxy carbonylamino, phenoxy carbonylamino,
carboxy (lower) alkanoylamino, lower
alkoxy carbonyl (lower) alkanoylamino,
carboxy (lower) alkenoylamino, lower
alkoxy carbonyl (lower) alkenoylamino,
cyclo (lower) alkyl carbamoylamino, lower
alkyl glyoxyloylamino, phenyl sulfonylamino which may
have one or two halogen, phenyl (lower) alkenoylamino
which may have esterified carboxy or carboxy,
pyridyl (lower) alkenoylamino,
quinoxaliny carbonylamino, benzothienyl carbonylamino,
carbamoylamino which may have one or two
substituent(s) selected from the group consisting of
lower alkyl and phenyl, bis (lower
alkyl sulfonyl) amino, carbamoyl which may have one or
two substituent(s) selected from the group consisting
of lower alkyl, phenyl and naphthyl;
phenyl (lower) alkyl; naphthyl (lower) alkyl;
phenyl (lower) alkenyl which may have two halogen;

- 248 -

naphthyl(lower)alkenyl; benzoyl(lower)alkenyl; lower
alkoxycarbonyl(lower)alkenyl; cyano(lower)alkenyl;
pyridyl(lower)alkenyl which may have halogen;
pyrimidinyl(lower)alkenyl; quinolyl(lower)alkenyl;
5 pyridyl; thienyl which may have halogen; pyrrolyl
which may have one or two substituent(s) selected
from the group consisting of halogen, cyano and lower
alkoxycarbonyl; pyrrolidinyl which may have oxo;
indolyl which may have lower alkoxycarbonyl or lower
10 alkanoyl; quinolyl; isoquinolyl; imidazolyl;
thiazolyl which may have amino, acylamino or pyridyl;
benzothiazolyl; triazolyl; and pyrimidinyloxy which
may have phenyl; or pyridyl.

15 7. A compound of claim 6, wherein
 R^2 is phenyl, lower alkylphenyl, halophenyl,
trihalo(lower)alkylphenyl, hydroxyphenyl, lower
alkanoyloxyphenyl, carboxyphenyl, lower
alkoxycarbonylphenyl,
20 [phenyl(lower)alkoxycarbonyl]phenyl,
[carboxy(lower)alkyl]phenyl, [lower
alkoxycarbonyl(lower)alkyl]phenyl, lower
alkoxyphenyl, cyanophenyl, nitrophenyl, aminophenyl,
[lower alkanoylamino]phenyl,
25 [phenoxycarbonylamino]phenyl,
[lower alkoxycarbonylamino]phenyl,
[lower alkoxyglyoxyloylamino]phenyl,
[cyclo(lower)alkyloxycarbonylamino]phenyl,
[cyclo(lower)alkylcarbonylamino]phenyl,
30 [cyclo(lower)alkylidene(lower)alkanoylamino]phenyl,
[benzoylamino]phenyl,
[mono(or di)(lower alkyl)benzoylamino]phenyl,
[mono(or di)halobenzoylamino]phenyl,
[di(lower alkoxy)benzoylamino]phenyl,
35 [bis(lower alkoxycarbonyl)benzoylamino]phenyl,

- 249 -

[mono(or di)nitrobenzoylamino]phenyl,
[hydroxybenzoylamino]phenyl,
[lower alkanoyloxybenzoylamino]phenyl,
[bis(trihalo(lower)alkyl)benzoylamino]phenyl, phenyl
5 having benzoylamino substituted with lower
alkoxycarbonyl and nitro, phenyl having benzoylamino
substituted with lower alkoxy and
cyclo(lower)alkyloxy, [phenylbenzoylamino]phenyl,
[[lower alkoxycarbonyl(lower)alkenyl]benzoylamino]-
10 phenyl, [[benzoylamino]benzoylamino]phenyl,
[pyrimidinyloxybenzoylamino]phenyl,
[[nitropyridylamino]benzoylamino]phenyl,
[naphthoylamino]phenyl,
[hydroxynaphthoylamino]phenyl,
15 [[lower alkanoyloxynaphthoyl]amino]phenyl,
[[lower alkoxycarbonylnaphthoyl]amino]phenyl,
[phenylsulfonylamino]phenyl,
[dihalophenylsulfonylamino]phenyl,
[phenyl(lower)alkylsulfonylamino]phenyl,
20 [cyclo(lower)alkylcarbonylamino]phenyl,
[mono(or di)phenyl(lower)alkanoylamino]phenyl,
[naphthyl(lower)alkanoylamino]phenyl, [lower
alkadienoylamino]phenyl, [furylcarbonylamino]phenyl,
[pyridylcarbonylamino]phenyl,
25 [dihalopyridylcarbonylamino]phenyl,
[thienylcarbonylamino]phenyl,
[indolinylcarbonylamino]phenyl,
[quinolylcarbonylamino]phenyl,
[tetrahydroquinolylcarbonylamino]phenyl,
30 [benzofurylcarbonylamino]phenyl,
[lower alkylindolylcarbonylamino]phenyl,
[benzothienylcarbonylamino]phenyl,
[methylenedioxybenzoylamino]phenyl,
[morpholinylcarbonylamino]phenyl,
35 [phenyl(lower)alkenoylamino]phenyl,

- 250 -

[[lower alkylphenyl(lower)alkenoyl]amino]phenyl,
[[mono(or di)halophenyl(lower)alkenoyl]amino]phenyl,
[[lower alkoxycarbonylphenyl(lower)alkenoyl]amino]-
phenyl, [[nitrophenyl(lower)alkenoyl]amino]phenyl,
5 [pyridyl(lower)alkenoylamino]phenyl, ureidophenyl,
[lower alkylureido]phenyl, [phenylureido]phenyl,
[[aminophenyl]ureido]phenyl,
[[halophenyl]ureido]phenyl,
[[nitrophenyl]ureido]phenyl,
10 [[lower alkoxyphenyl]ureido]phenyl,
[[lower alkylthiophenyl]ureido]phenyl,
[[mono(or di)(lower alkyl)phenyl]ureido]phenyl,
[biphenylureido]phenyl,
[[carboxyphenyl]ureido]phenyl,
15 [[lower alkoxycarbonylphenyl]ureido]phenyl,
[[di(lower)alkylaminophenyl]ureido]phenyl,
[[trihalo(lower)alkylphenyl]ureido]phenyl,
[[dihalophenyl]ureido]phenyl, [naphthylureido]phenyl,
[phenylsulfonylureido]phenyl,
20 [phenyl(lower)alkylureido]phenyl,
[cyclo(lower)alkylureido]phenyl,
[thiazolylureido]phenyl, [pyridylureido]phenyl,
[quinolylureido]phenyl, [morpholinylureido]phenyl,
[N-phenyl-N-lower alkylureido]phenyl,
25 [phenyl(thioureido)]phenyl,
[naphthyl(thioureido)]phenyl,
[benzoyl(thioureido)]phenyl,
[lower alkylamino]phenyl,
[N-lower alkanoyl-N-lower alkylamino]phenyl,
30 [N-benzoyl-N-lower alkylamino]phenyl,
[N-phenylcarbamoyl-N-lower alkylamino]phenyl,
[N-lower alkoxycarbonylphenyl(lower)alkenoyl-N-lower
alkylamino]phenyl, [lower alkylthiazolylamino]phenyl,
[phenylthiazolylamino]phenyl,
35 [pyrimidinylamino]phenyl, lower alkanoylphenyl,

- 251 -

carbamoylphenyl, [lower alkylcarbamoyl]phenyl,
[phenylcarbamoyl]phenyl,
[dihalophenylcarbamoyl]phenyl, [N-dihalophenyl-N-
lower alkylcarbamoyl]phenyl, benzoylphenyl, [lower
5 alkoxybenzoyl]phenyl, morpholinylcarbonylphenyl,
indolizinyllcarbonylphenyl,
[phenylcarbamoyl(lower)alkyl]phenyl,
[naphthylcarbamoyl(lower)alkyl]phenyl, phenylphenyl,
[[lower alkoxy carbonyl(lower)alkenyl]phenyl]phenyl,
10 biphenylphenyl, phenyl having phenyl substituted
with lower alkoxy and cyclo(lower)alkyloxy,
[halophenyl]phenyl, [carboxyphenyl]phenyl, [lower
alkoxy carbonylphenyl]phenyl, [aminophenyl]phenyl,
[[lower alkanoylamino]phenyl]phenyl,
15 [[benzoylamino]phenyl]phenyl,
[[carboxybenzoylamino]phenyl]phenyl,
[[mono(or bis)(lower alkylsulfonyl)amino]phenyl]-
phenyl, [[trihalo(lower)alkanoylamino]phenyl]phenyl,
[[lower alkoxy carbonylamino]phenyl]phenyl,
20 [[phenoxy carbonylamino]phenyl]phenyl,
[[carboxy(lower)alkanoylamino]phenyl]phenyl,
[[lower alkoxy carbonyl(lower)alkanoylamino]phenyl]-
phenyl, [[lower alkoxy carbonyl(lower)alkenoylamino]-
phenyl]phenyl, [[cyclo(lower)alkylcarbonylamino]-
25 phenyl]phenyl, [[lower alkylglyoxyloylamino]-
phenyl]phenyl, [[dihalophenylsulfonylamino]-
phenyl]phenyl, [[phenyl(lower)alkenoyl-
amino]phenyl]phenyl, phenylphenyl substituted with
(lower)alkenoylamino having phenyl and carboxy,
30 [[pyridyl(lower)alkenoylamino]phenyl]phenyl,
[[[halopyridyl(lower)alkenoyl]amino]phenyl]phenyl,
[[quinoxalinyllcarbonylamino]phenyl]phenyl,
[[benzothienylcarbonylamino]phenyl]phenyl,
[[lower alkylcarbamoylamino]phenyl]phenyl,
35 [[phenylcarbamoylamino]phenyl]phenyl,

- 252 -

[[naphthylcarbamoyl]phenyl]phenyl, naphthylphenyl,
[lower alkoxyphenyl]phenyl,
[phenyl(lower)alkyl]phenyl,
[naphthyl(lower)alkyl]phenyl,
5 [phenyl(lower)alkenyl]phenyl,
[dihalophenyl(lower)alkenyl]phenyl,
[naphthyl(lower)alkenyl]phenyl,
[benzoyl(lower)alkenyl]phenyl,
[lower alkoxyphenyl(lower)alkenyl]phenyl,
10 [cyano(lower)alkenyl]phenyl,
[pyridyl(lower)alkenyl]phenyl,
[pyrimidinyl(lower)alkenyl]phenyl,
[quinolyl(lower)alkenyl]phenyl, pyridylphenyl,
thienylphenyl, [halothienyl]phenyl, pyrrolylphenyl,
15 [dihalopyrrolyl]phenyl, [cyanopyrrolyl]phenyl,
[lower alkoxyphenylpyrrolyl]phenyl,
[dioxopyrrolidinyl]phenyl, indolylphenyl,
[lower alkoxyphenylindolyl]phenyl,
[lower alkanoylindolyl]phenyl, quinolylphenyl,
20 isoquinolylphenyl, imidazolylphenyl,
[aminothiazolyl]phenyl, [pyridylthiazolyl]phenyl,
benzothiazolylphenyl, triazolylphenyl,
pyrimidinylphenyl, [phenylpyrimidinyl]phenyl,
phenyl having halogen and amino, phenyl having
25 halogen and (halophenyl)ureido, phenyl having halogen
and (lower alkoxyphenyl)ureido, phenyl having halogen
and lower alkanoylamino, bis(lower
alkoxyphenyl)phenyl, phenyl having lower
alkoxyphenyl and amino, phenyl having lower
30 alkoxyphenyl and lower alkanoylamino, phenyl having
lower alkoxyphenyl and naphthoylamino, phenyl
having halogen and naphthoylamino, phenyl having
cyclo(lower)alkyloxy and lower alkoxy, naphthyl or
pyridyl.

35

- 253 -

8. A compound of claim 7, wherein
R¹ is pyridyl(lower)alkyl,
R² is [(dihalobenzoyl)amino]phenyl, [bis(lower
alkoxycarbonyl)benzoylamino]phenyl,
5 (naphthoylamino)phenyl,
[(lower alkanoyloxynaphthoyl)amino]phenyl,
[pyridyl(lower)alkenyl]phenyl,
[[halopyridyl](lower)alkenyl]phenyl,
[quinolyl(lower)alkenyl]phenyl, naphthylphenyl or
10 [[[pyridyl(lower)alkenoyl]amino]phenyl]phenyl and
R³ is hydrogen.
9. A compound of claim 8, which is selected from the
group consisting of
15 (1) 2-(3-pyridylmethyl)-4-[3-(3,5-
dibromobenzoylamino)phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine, or its
hydrochloride,
(2) 2-(3-pyridylmethyl)-4-[3-(3,5-
20 dichlorobenzoylamino)phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine, or its
hydrochloride,
(3) 2-(3-pyridylmethyl)-4-[3-[3,5-
bis(methoxycarbonyl)benzoylamino]phenyl]-3-oxo-
25 3,4-dihydropyrido[2,3-b]pyrazine, or its
hydrochloride,
(4) 2-(3-pyridylmethyl)-4-[3-[(E)-2-(4-
quinolyl)vinyl]phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine,
30 (5) 2-(3-pyridylmethyl)-4-[3-(2-
naphthoylamino)phenyl]-3-oxo-3,4-
dihydropyrido[2,3-b]pyrazine, or its
hydrochloride,
(6) 2-(3-pyridylmethyl)-4-[3-[(6-acetoxy-2-
35 naphthoyl)amino]phenyl]-3-oxo-3,4-

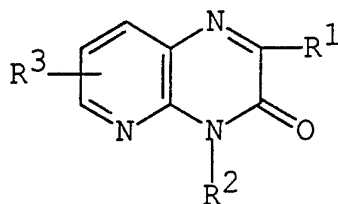
- 254 -

- dihydropyrido[2,3-b]pyrazine,
- (7) 2-(3-pyridylmethyl)-4-[3-[(E)-2-(3-pyridyl)vinyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine,
- 5 (8) 2-(3-pyridylmethyl)-4-[3-[(E)-2-(4-pyridyl)vinyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine,
- (9) 2-(3-pyridylmethyl)-4-[3-[(E)-2-(5-chloropyridin-3-yl)vinyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine,
- 10 (10) 2-(3-pyridylmethyl)-4-[3-(2-naphthyl)phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine and
- (11) 2-(3-pyridylmethyl)-4-[3-[3-[(E)-3-(4-pyridyl)acryloylamino]phenyl]phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine.
- 15

10. A compound of claim 7, wherein
 R^1 is imidazolyl(lower)alkyl,
 R^2 is (naphthoylamino)phenyl, and
 R^3 is hydrogen.
- 20

11. A compound of claim 10, which is
 2-(1-imidazolylmethyl)-4-[3-(2-naphthoylamino)-phenyl]-3-oxo-3,4-dihydropyrido[2,3-b]pyrazine.
- 25

12. A process for preparing a compound of the formula :
- 30



35

- 255 -

wherein

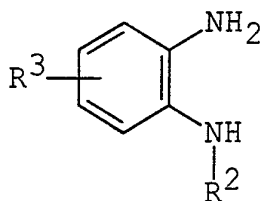
R¹ is aryl which may have suitable substituent(s),
ar(lower)alkyl which may have suitable
substituent(s), halo(lower)alkyl, protected
5 carboxy(lower)alkyl, acyl(lower)alkyl, heterocyclic
group or heterocyclic(lower)alkyl which may have
suitable substituent(s),

R² is aryl which may have suitable substituent(s) or
heterocyclic group, and

10 R³ is hydrogen, lower alkoxy or arylthio,
or a salt thereof,
which comprises

(1) reacting a compound of the formula :

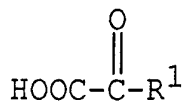
15



20

wherein R² and R³ are each as defined above,
or a salt thereof with a compound of the formula :

25

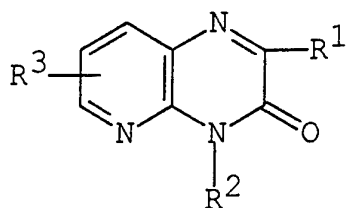


30

wherein R¹ is as defined above,
or a salt thereof to give a compound of the formula :

35

- 256 -

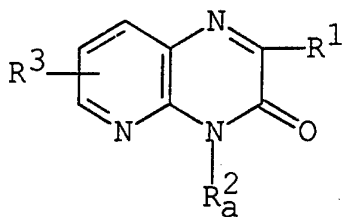


5

10 wherein R¹, R² and R³ are each as defined above,
or a salt thereof, or

(2) subjecting a compound of the formula :

15



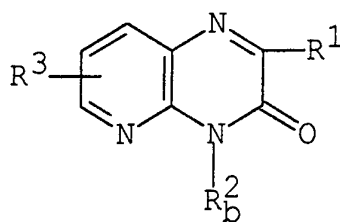
20

25 wherein R¹ and R³ are each as defined above, and
R_a² is aryl having amino or aryl having
aminoaryl,
or its reactive derivative at the amino group,
or a salt thereof to acylation reaction to give a
compound of the formula :

30

35

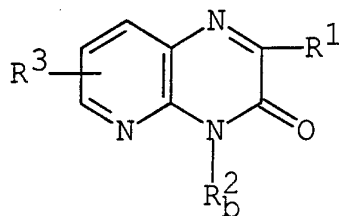
- 257 -



5

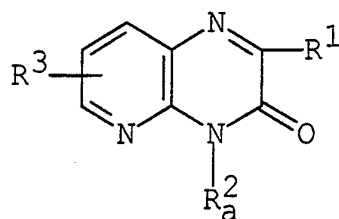
10 wherein R^1 and R^3 are each as defined above and
 R_b^2 is aryl having acylamino or aryl having
 acylaminoaryl,
 or a salt thereof, or

15 (3) subjecting a compound of the formula :



20

25 wherein R^1 , R_b^2 and R^3 are each as defined above,
 or a salt thereof to deacylation to give a compound
 of the formula :



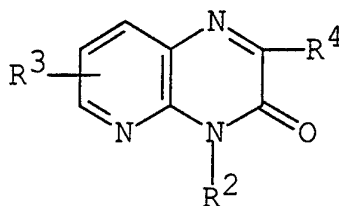
30

35

- 258 -

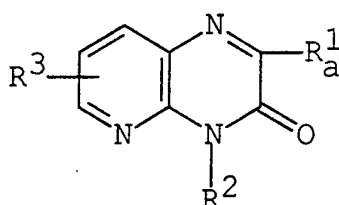
wherein R^1 , R_a^2 and R^3 are each as defined above,
or a salt thereof, or

(4) subjecting a compound of the formula :



wherein R^2 and R^3 are each as defined above, and
 R^4 is lower alkyl,

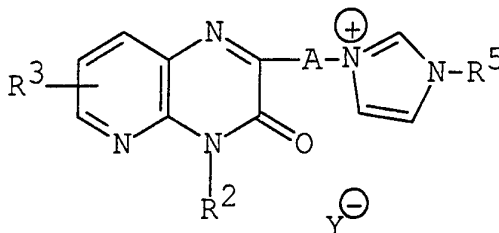
or a salt thereof to halogenation to give a compound
of the formula :



wherein R^2 and R^3 are each as defined above, and
 R_a^1 is halo(lower)alkyl,
or a salt thereof, or

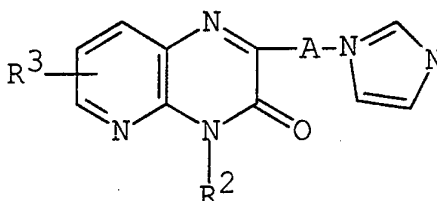
(5) subjecting a compound of the formula :

- 259 -



wherein R² and R³ are each as defined above,
 R⁵ is N-protective group,
 A is lower alkylene, and
 Y⁻ is halide,

or a salt thereof to elimination of N-protective group to give a compound of the formula :



wherein R², R³ and A are each as defined above,
 or a salt thereof.

13. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

- 260 -

14. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as an inhibitor on the production of phosphodiesterase IV (PDE-IV) and an inhibitor on the production of tumor necrosis factor (TNF).

5

15. A method for the prophylactic or therapeutic treatment of phosphodiesterase IV (PDE-IV) and tumor necrosis factor (TNF) mediated diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salts thereof to human or animals.

10

16. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

15

20

25

30

35

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/JP 95/01366

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/495 //(C07D471/04,241:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 008 864 (FISONS) 19 March 1980 cited in the application see page 6, line 20 - page 7, line 19; claims 1,8; examples 27,37 --- -/--	1,13

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

21 September 1995

Date of mailing of the international search report

- 5. 10. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

Internat 1 Application No

PCT/JP 95/01366

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 83, no. 9, 1975 Columbus, Ohio, US; abstract no. 71860e, S. HAYASHI ET AL. 'Antispasmodic action of 1-diethylaminoethyl-3-(p-methoxybenzyl)-2- quinaxolone (P 201-1) and its inhibitory effect on cyclic 3',5'-nucleotide phosphodiesterase activity' page 63; see abstract & CHEM.PHARM.BULL., vol. 23, no. 4, 1975 pages 810-816, -----	1,13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 95/01366

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

PCT/JP 95/01366

Form PCT/ISA/210 (patent family annex) (July 1992)