US 20020132809A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0132809 A1**

Oku et al. (43) **Pub. Date: Sep. 19, 2002**

(54) **HETEROCYCLIC CARBOXAMIDE DERIVATIVES AS INHIBITORS OF NITRIC OXIDE PRODUCTION**

(75) Inventors: **Teruo Oku**, Tokyo (JP); **Ichiro Shima**, Ibaraki (JP); **Takehiko Ohkawa**, Ibaraki (JP); **Kazuhiko Ohne**, Ibaraki (JP); **Tatsuya Zenko**, Tokyo (JP); **Kousei Yoshihara**, Ibaraki (JP); **Hiroyuki Setoi**, Ibaraki (JP)

Correspondence Address:
OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT PC
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202 (US)

(73) Assignee: **Fujisawa Pharmaceutical Co. Ltd.**, Osaka-shi (JP)

(21) Appl. No.: **10/080,663**

(22) Filed: **Feb. 25, 2002**

Related U.S. Application Data

(63) Continuation of application No. 09/673,660, filed as 371 of international application No. PCT/JP99/02231, filed on Apr. 26, 1999.

(30) **Foreign Application Priority Data**

May 4, 1998 (AU) ..... PP 3324
Jun. 10, 1998 (AU) ..... PP 4014

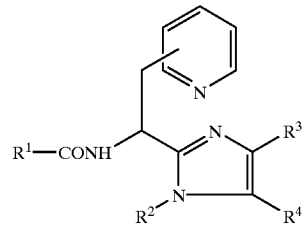
Publication Classification

(51) **Int. Cl.**[7] **C07D 413/14**; C07D 417/14; A61K 31/5377; A61K 31/4439

(52) **U.S. Cl.** **514/235.8**; 514/340; 514/341; 514/338; 544/124; 546/270.4; 546/273.4

(57) **ABSTRACT**

(I)



wherein each symbol is as defined in the specification, and pharmaceutically acceptable salts thereof. The compound (I) of the present invention and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO), and are useful for prevention and/or treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock, diabetes, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease, cerebral infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosus, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, dermatitis, hepatitis, liver cirrhosis, multiple sclerosis, pancreatitis, atherosclerosis, and the like in human being and animals.

HETEROCYCLIC CARBOXAMIDE DERIVATIVES AS INHIBITORS OF NITRIC OXIDE PRODUCTION

TECHNICAL FIELD

[0001] This invention relates to new amide compounds and pharmaceutically acceptable salts thereof which are useful as medicament.

BACKGROUND ART

[0002] Some peptide compounds have been known as described in, for example, EP 0 394 989 A2.

DISCLOSURE OF INVENTION

[0003] This invention relates to new amide compounds.

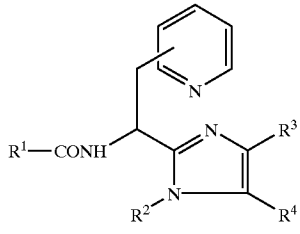
[0004] One object of this invention is to provide the new and useful amide compounds and pharmaceutically acceptable salts thereof that possess a strong inhibitory activity on the production of nitric oxide (NO).

[0005] Another object of this invention is to provide a process for the preparation of the amide compounds and salts thereof.

[0006] A further object of this invention is to provide a pharmaceutical composition comprising said amide compound or a pharmaceutically acceptable salt thereof.

[0007] Still further object of this invention is to provide a use of said amide compounds or pharmaceutically acceptable salts thereof as a medicament for prophylactic and therapeutic treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock (e.g., septic shock, etc.), diabetes (e.g., insulin-dependent diabetes mellitus, etc.), diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease (e.g., ulcerative colitis, chronic colitis, etc.), cerebral infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosus, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, dermatitis, hepatitis, liver cirrhosis, multiple sclerosis, pancreatitis, atherosclerosis, and the like in human being and animals. Further, they are useful for treatment of erectile dysfunction, male sexual dysfunction or female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

[0008] The object amide compounds of the present invention are novel and can be represented by the following general formula (I):



(I)

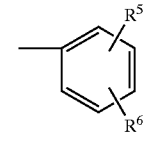
[0009] wherein

[0010] R^1 is (a) indolyl, (b) benzothienyl having suitable substituent(s) selected from the group consisting of nitro and halogen, (c) benzothiazolyl having halogen, (d) furopyridyl which may have nitro or (e) benzofuranyl which may have suitable substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, nitro, cyano, acyl and trihalo (lower) alkyl,

[0011] R^2 is lower alkyl,

[0012] R^3 is hydrogen or lower alkyl, and

[0013] R^4 is thienyl or a group of the formula:



[0014] wherein

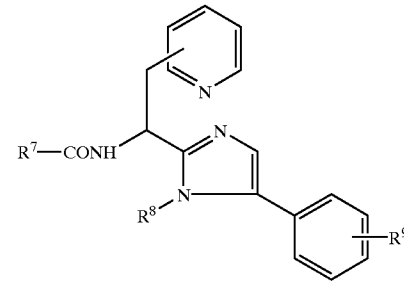
[0015] R^5 is hydrogen or halogen, and

[0016] R^6 is (a) imidazolyl which may have lower alkyl, (b) benzimidazolyl, (c) pyridyl, (d) pyrrolyl, (e) morpholinyl, (f) thienyl, (g) furyl, (h) phenyl, (j) thiazolyl, (k) halogen or (l) nitro,

[0017] provided that (i) R^3 is lower alkyl or R^6 is benzimidazolyl or imidazolyl having lower alkyl when R^1 is indolyl, and (ii) R^6 is benzimidazolyl or imidazolyl having lower alkyl when R^1 is benzofuranyl.

[0018] The present invention also provides novel amide compounds represented by the following general formula (II):

(II)



[0019] wherein

[0020] R^7 is indolyl, benzofuranyl, benzothienyl or benzothiazolyl,

[0021] R^8 is lower alkyl, and

[0022] R^9 is imidazolyl or nitro,

[0023] provided that (i) R^8 is not methyl when R^7 is indolyl, and (ii) R^9 is nitro when R^7 is benzofuranyl.

[0024] Suitable pharmaceutically acceptable salts of the object compounds (I) and (II) are conventional non-toxic salts and include, for example, 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'-dibenzylethylene-diamine 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, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); and a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, gultamic acid, etc.).

[0025] 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.

[0026] The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

[0027] Suitable "halogen" includes, for example, fluorine, bromine, chlorine and iodine.

[0028] Suitable "lower alkyl" includes straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, in which more preferred one is C_1-C_4 alkyl.

[0029] Suitable "lower alkoxy" includes straight or branched one having 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, in which more preferred one is C_1-C_4 alkoxy.

[0030] Suitable "acyl" includes, aliphatic acyl group such as lower alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, etc.).

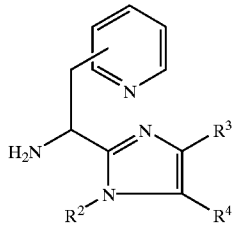
[0031] Suitable "trihalo(lower)alkyl" includes, for example, trifluoromethyl, trichloromethyl and tribromomethyl, in which preferred one is trifluoromethyl.

[0032] The term "morpholinyl" includes 2-morpholinyl, 3-morpholinyl and 4-morpholinyl (i.e. morpholino).

[0033] The object compounds (I) and (II) of the present invention can be prepared by the following processes.

[0034] Process (1)

(III)

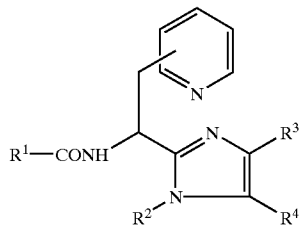


[0035] or its reactive derivative at the amino group, or a salt thereof

R^1—COOH (IV)

[0036] or its reactive derivative at the carboxy group, or a salt thereof→

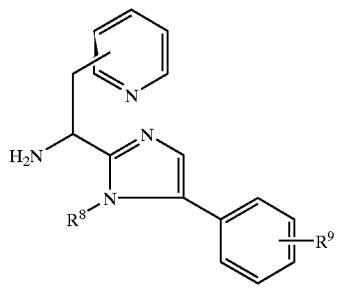
(I)



[0037] or a salt thereof

[0038] Process (2)

(V)

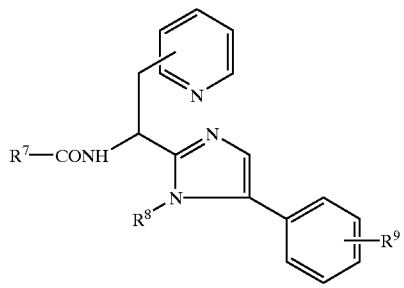


[0039] or its reactive derivative at the amino group, or a salt thereof

R^7—COOH (VI)

[0040] or its reactive derivative at the carboxy group, or a salt thereof→

(II)



[0041] or a salt thereof

[0042] wherein R^1, R^2, R^3, R^4, R^7, R^8 and R^9 are each as defined above.

[0043] The starting compounds can be prepared by the method of Preparation mentioned below or by a process known in the art for preparing their structually analogous compounds.

[0044] The processes for preparing the object compound are explained in detail in the following.

[0045] Process (1)

[0046] The compound (I) or a salt thereof can be prepared by reacting the compound (III) or its reactive derivative at the amino group, or a salt thereof with the compound (IV) or its reactive derivative at the carboxy group, or a salt thereof.

[0047] Suitable reactive derivative of the compound (III) includes Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (III) with phosphorus trichloride or phosgene.

[0048] Suitable reactive derivative of the compound (IV) includes an acid halide, an acid anhydride and an activated ester. The suitable example may be an acid chloride; an 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, alkanesulfonic 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, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); or an ester with an 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.). These reactive derivatives can optionally be selected from them according to the kind of the compound (IV) to be used.

[0049] 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 affect the reaction, or the mixture thereof.

[0050] When the compound (IV) 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 agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide; N,N-carbonyl-bis-(2-methylimidazole); pentamethylene-ketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

[0051] The reaction may also be carried out in the presence 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.

[0052] The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

[0053] Process (2)

[0054] The compound (II) or a salt thereof can be prepared by reacting the compound (V) or its reactive derivative at the amino group, or a salt thereof with the compound (VI) or its reactive derivative at the carboxy group, or a salt thereof.

[0055] This reaction can be carried out in a similar manner to the reaction in 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).

[0056] Suitable salts of the starting compounds and their reactive derivatives in Processes (1) and (2) can be referred to the ones as exemplified for the compounds (I) and (II).

[0057] The compounds obtained by the above process can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

[0058] It is to be noted that the compounds (I) and (II) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixtures thereof are included within the scope of this invention.

[0059] The object compounds (I) and (II) and pharmaceutically acceptable salts thereof include solvates [e.g., enclosure compounds (e.g., hydrate, etc.)].

[0060] The object compounds (I) and (II) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO).

[0061] Accordingly, the object compounds (I) and (II) and pharmaceutically acceptable salts thereof are expected to possess a nitric oxide synthase (NOS)-inhibitory activity or a NOS-production inhibitory activity.

[0062] Accordingly, they are useful for prevention and/or treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock (e.g., septic shock, etc.), diabetes (e.g., insulin-dependent diabetes mellitus, etc.), diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease (e.g., ulcerative colitis, chronic colitis, etc.), cerebral

infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosus, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, dermatitis, hepatitis, liver cirrhosis, multiple sclerosis, pancreatitis, atherosclerosis, and the like. Further, they are useful for treatment of erectile dysfunction, male sexual dysfunction or female sexual dysfunction including orgasmic dysfunction related to clitoral disturbances.

[0063] In order to illustrate the usefulness of the object compounds (I) and (II), the pharmacological test result of the representative compound of the compounds (I) and (II) is shown in the following.

[0064] Test Compounds

[0065] Compound (a): (1S)-(5-chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0066] Compound (b): (1S)-N-[1-[5-(4-biphenylyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-bromobenzo[b]furan-2-yl)formamide

[0067] Compound (c): (1S)-(benzo[b]thiophen-2-yl)-N-[1-[5-[4-(1-imidazolyl) -phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0068] Compound (d): (1S)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl](5-nitrobenzo[b]thiophen-2-yl)formamide

[0069] Compound (e): (1S)-N-[1-[1-ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(4-pyridyl)ethyl](indol-2-yl)formamide

[0070] Compound (f): (1S)-(5-methoxybenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0071] Compound (g): (1S)-(benzothiazol-2-yl)-N-[1-[5-[4-(1-imidazolyl) -phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0072] Test 1: Assay for Inhibitory Activity on the Production of Nitric Oxide

[0073] The murine macrophage cell line RAW264.7 (American Type Culture Collection, No. TIB71) was used in this study. RAW264.7 cells were grown on F75 plastic culture flasks at 37° C., 5% in Dulbecco's modified Eagle's medium (DMEM) supplemented with L-glutamine, penicillin, streptomycin and 10% heat-inactivated fetal bovine serum. They were removed from culture flasks by rubber cell scraper and were centrifuged and resuspended in DMEM without phenol red. They were plated in 96-well microtiter plates (10^5 cells per well) and allowed to adhere over 2 hours. The test samples were added and the cells were preincubated for 1 hour. Thereafter the cells were activated with both of lipopolysaccharide (LPS) (1 μg/ml) and interferon γ (INF γ) (3 u/ml) for 18-24 hours. An equal volume of Griess reagent (1% sulfanilamide/0.1% N-naphthylethylenediamine dihydrochloride/2.5% H_3PO_4) was added and the cells were incubated at room temperature for 10 minutes. The absorbance was read at 570 nm using microplate reader and $NO_2^-$was measured using $NaNO_2$ as a standard.

[0074] Test result

TABLE 1

Test compound (10^{-5} M)	Inhibition (%)
(a)	100
(b)	100
(c)	100
(d)	100
(e)	100
(f)	100
(g)	100

[0075] Test 2: Protective Effect of the Compound (a) Combined with FK 506 on Rat Cardiac Allograft

[0076] Method :

[0077] Experiments were performed on male Lewis and ACI rats weighing 175-200 g. Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and underwent allogeneic (Lewis donor to ACI recipient) heterotopic intra-abdominal cardiac transplantation. Experimental groups were divided into single-drug group and combined-drug group. Single-drug dose of FK506, which was prepared in a manner similar to that disclosed in EP-0184162, was 0.32 mg/kg. Combined-drug dose was FK506 (0.32 mg/kg)+the compound (a) (10 mg/kg). The grafted hearts were monitored by daily palpation where complete rejection was defined as the cessation of palpable contractile activity. Each drug was suspended in a solution of 0.5% methylcellulose, and administered by daily gastric intubation in a volume of 5 ml/kg of body weight for 14 days.

[0078] Test result:

[0079] The combination of the compound (a) and an immunosuppressive agent (FK506) was examined to determine whether it could improve rat cardiac allograft survival.

[0080] Graft survival is shown in the following table 2.

TABLE 2

Protective effect of the compound (a) combined with FK506 on rat cardiac allograft

Test compound(s)	n	MST (day)
FK506 (0.32 mg/kg)	6	10
Compound (a) (10 mg/kg) + FK506 (0.32 mg/kg)	9	>30

MST: Median Survival Time

[0081] The combination of the compound (a) and FK506 dramatically prolonged the graft survival.

[0082] The above experimental data indicate that the activity and/or efficacy of an immunosuppressant in rejection of transplantation can be remarkably and synergistically increased by administering compound (a) in combination, which has a strong inhibitory activity on the production of nitric oxide.

[0083] For therapeutic administration, the object compounds (I) and (II) of the present invention and pharmaceu-

tically acceptable salts thereof are used in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee, suppository or ointment, or in a liquid form such as solution, suspension or emulsion for injection, intravenous drip, ingestion, eye drop, 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.

[0084] The effective ingredient may usually be administered in 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, body weight and conditions of the patient or administering method.

[0085] The following Preparations and Example are given for the purpose of illustrating the present invention in detail.

[0086] Preparation 1

1-(4-Morpholinophenyl)ethan-1-one

[0087] A mixture of 1-(4-fluorophenyl)ethan-1-one (100 g), morpholine (126 ml) and potassium carbonate (95 g) in N,N-dimethylformamide (DMF) (1 L) was heated at 150° C. (bath temperature) for 48 hours. TLC showed the exhaust of the starting material. The reaction mixture was poured into water (2 L), and the precipitate was collected and washed with water. Then, the residue was dissolved in ethyl acetate, dried over magnesium sulfate, and filtered. After removal of the solvent, 1-(4-morpholinophenyl)ethan-1-one (81.5 g) was obtained as a yellow-brown powder.

[0088] ^{1}H-NMR (DMSO-d_6) δ2.46(3H,s), 3.30(4H,dd, J=4 Hz,J=5 Hz), 3.72(4H,dd,J=4 Hz,J=5 Hz), 6.98(2H,d,J=9 Hz), 7.83(2H,d,J=9 Hz)

[0089] Preparation 2

2-Bromo-1-(4-morpholinophenyl)ethan-1-one

[0090] To a solution of 1-(4-morpholinophenyl)ethan-1-one (170 g) in 48% HBr (340 ml) was added Br_2 (43 ml) in 48% HBr (60 ml) dropwise at 65-75° C. during the period of 0.5 hour. The mixture was stirred at 65° C. for an additional 1 hour. The reaction mixture was cooled to 10° C. and the resulting precipitate was collected by filtration. The resulting solid (HBr salt) was basified with saturated aqueous sodium hydrogencarbonate solution carefully, and extracted with chloroform (500 ml). The organic layer was dried over magnesium sulfate, and filtered. After removal of the solvent, 2-bromo-1-(4-morpholinophenyl)ethan-1-one (200 g) was obtained as a greenish yellow powder. Further purification was not attempted.

[0091] ^{1}H-NMR (DMSO-d_6) δ3.30-3.34(4H,dd,J=4 Hz,J=5 Hz), 3.34-3.43(4H,m), 6.99(2H,d,J=9 Hz), 7.86(2H, d,J=9 Hz)

[0092] Preparation 3

2-[2-(4-Morpholinophenyl)-2-oxoethyl]isoindoline-1,3-dione

[0093] A mixture of 2-bromo-1-(4-morpholinophenyl)ethan-1-one (200 g) and potassium phthalimide (137 g) in DMF (1500 ml) was stirred at 90° C. for 1 hour. After cooling to 10° C., the precipitate was collected, and washed with cold-DMF (150 ml) and water (250 ml×2), successively. 2-[2-(4-Morpholinophenyl)-2-oxoethyl]isoindoline-1,3-dione (186 g) was obtained as a pale yellow wet solid. This compound was used for next step without further dry-up or purification.

[0094] ^{1}H-NMR (DMSO-d_6) δ3.34(4H,dd,J=4 Hz,J=5 Hz), 3.72(4H,dd,J=4 Hz,J=5 Hz), 5.10(2H,s), 7.04(2H,d,J=9 Hz), 7.86-7.97(6H,m)

[0095] Preparation 4

2-Amino-1-(4-morpholinophenyl)ethan-1-one dihydrochloride

[0096] A slurry of 2-[2-(4-morpholinophenyl)-2-oxoethyl] isoindoline-1,3-dione (185 g) in concentrated hydrochloric acid (1900 ml) was heated under reflux for 8 hours. As a result, the slurry gradually dissolved and a clear pale yellow solution was obtained. After removal of the solvent in vacuo, the residual oily solid was triturated with methanol (400 ml), and the resulting precipitate was collected by filtration, and washed with methanol (100 ml) to give 2-amino-1-(4-morpholinophenyl)ethan-1-one dihydrochloride (125 g) as a white powder.

[0097] ^{1}H-NMR (DMSO-d_6) δ3.35(4H,dd,J=4 Hz,J=5 Hz), 3.73(4H,dd,J=4 Hz,J=5 Hz), 4.45(2H,d,J=4.5 Hz), 7.03(2H,d,J=9 Hz), 7.87(2H,d,J=9 Hz)

[0098] Preparation 5

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-(4-morpholinophenyl)-2-oxoethyl]-3-(2-pyridyl)propionamide

[0099] To a solution of 2-amino-1-(4-morpholinophenyl)ethan-1-one dihydrochloride (3.71g), (2S)-2-(tert-butoxycarbonylamino)-3-(2-pyridyl)propanoic acid (5.73 g) and diphenylphosphoryl azide (3.48 g) in N,N-dimethylformamide (70 ml) was added dropwise N,N-diisopropylethylamine (4.41 ml) at 0° C. and the mixture was stirred for 20 minutes. The mixture was heated to ambient temperature and stirred for 8 hours. The resulting mixture was diluted with ethyl acetate (200 ml) and washed successively with water, saturated aqueous sodium hydrogencarbonate solution and brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residual solid was triturated with ethyl acetate-diisopropyl ether (1:2) to give (2S)-2-(tert-butoxycarbonylamino)-N-[2-(4-morpholinophenyl)-2-oxoethyl]-3-(2-pyridyl)propionamide (2.06 g) as off-white crystals.

[0100] ESI-MS: 469(M+H)

[0101] ^{1}H-NMR (300MHz,$CDCl_3$) δ1.46(9H,s), 3.20-3.38(6H,m), 3.82-3.88(4H,m), 4.60(2H,d,J=5 Hz), 4.64-4.74(1H,br), 6.37-6.45(1H,br), 6.86(2H,d,J=9 Hz), 7.14(1H, dd,J=5,8 Hz), 7.21(1H,d,J=8 Hz), 7.59(1H,t,J=8 Hz), 7.82-7.90(3H,m), 8.56(1H,d,J=5 Hz)

[0102] Preparation 6

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0103] To a solution of (2S)-2-(tert-butoxycarbonylamino)-N-[2-(4-morpholinophenyl)-2-oxoethyl]-3-(2-py-

ridyl)propionamide (2.0 g) in acetic acid (4.0 ml) and xylene (60 ml) was added methylamine (40% in water, 4.0 ml) and the mixture was refluxed for 3 hours in a round-bottomed flask equipped with a Dean-Stark apparatus. The mixture was cooled to ambient temperature and a mixture of acetic acid (4.0 ml) and methylamine (40% in water, 4.0 ml) was added to the solution. The solution was refluxed for 2 hours and cooled to ambient temperature. The solution was extracted with 1N hydrochloric acid (100 ml) and the aqueous layer was washed with ethyl acetate (50 ml). The aqueous layer was basified with saturated aqueous sodium hydrogencarbonate solution and extracted with ethyl acetate (100 ml). The organic layer was washed successively with aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give (1S)-(tert-butoxy)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]-formamide (1.45 g) as yellow crystals.

[0104] ESI-MS: 464(M+H)

[0105] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.37(9H,s), 3.17-3.23(4H,m), 3.40(3H,s), 3.41-3.47(2H,m), 3.83-3.92(4H,m), 5.33-5.47(2H,m), 6.93(1H,s), 6.94(2H,d,J=9 Hz), 7.08-7.16(2H,m), 7.21(2H,d,J=9 Hz), 7.56(1H,t,J=8 Hz), 8.55(1H,d,J=5 Hz)

[0106] Preparation 7

(1S)-1-[1-Methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0107] To a solution of (1S)-(tert-butoxy)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (1.43 g) in dichloromethane (25 ml) was added trifluoroacetic acid (5.0 ml) at 0° C. and the mixture was stirred at ambient temperature for 2.5 hours. The resulting mixture was concentrated in vacuo and the residue was dissolved in water (20 ml). The aqueous layer was basified with saturated aqueous sodium hydrogencarbonate solution and extracted with chloroform (80 ml). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was triturated with ethyl acetate-diisopropyl ether (1:2) to give (1S)-1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethylamine (1.02 g) as yellow crystals.

[0108] ESI-MS: 364(M+H)

[0109] ^{1}H-NMR (300MHz,$CDCl_3$) δ3.17-3.23(4H,m), 3.27-3.47(2H,m), 3.49(3H,s), 3.84-3.91(4H,m), 4.58(1H,dd, J=5,8 Hz), 6.95(2H,d,J=9 Hz), 6.97(1H,s), 7.11-7.18(2H,m), 7.23(2H,d,J=9 Hz), 7.59(1H,t,J=8 Hz), 8.58(1H,d,J=5 Hz)

[0110] Preparation 8

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-(4-biphenylyl)-2-oxoethyl]-3-(2-pyridyl)propionamide

[0111] The title compound was obtained in substantially the same manner as in Preparation 5.

[0112] mp 129-132° C.

[0113] MS: 460(M+1)

[0114] ^{1}H-NMR (DMSO-d_6) δ: 1.29(9H,s), 2.90-3.11(1H,m), 3.17-3.23(1H,m), 4.47-4.55(1H,m), 4.56-4.78(2H,m), 7.09(1H,d,J=8 Hz), 7.20(1H,t,J=8 Hz), 7.30(1H,d,J=8 Hz), 7.40-7.58(3H,m), 7.70(1H,t,J=8 Hz), 7.78(2H,d,J=8 Hz), 7.85(2H,d,J=8 Hz), 8.09(2H,d,J=8 Hz), 8.21(1H,t,J=6 Hz), 8.50(1H,d,J=4 Hz)

[0115] Preparation 9

(1S)-(tert-Butoxy)-N-[1-[5-(4-biphenylyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0116] The title compound was obtained from the compound of Preparation 8 in substantially the same manner as in Preparation 6.

[0117] solid

[0118] MS: 455(M+1)

[0119] ^{1}H-NMR (DMSO-d_6) δ: 1.30(9H,s), 3.20-3.30(1H,m), 3.33-3.47(1H,m), 3.59(3H,s), 5.30(1H,q,J=8 Hz), 7.00(1H,s), 7.15-7.30(3H,m), 7.33-7.58(4H,m), 7.61-7.80(4H,m), 7.82(1H,d,J=8 Hz), 8.09(1H,d,J=8 Hz), 8.50(1H,d,J=4 Hz)

[0120] Preparation 10

(1S)-1-[5-(4-Biphenylyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)-ethylamine

[0121] The title compound was obtained from the compound of Preparation 9 in substantially the same manner as in Preparation 7.

[0122] oil

[0123] MS: 355(M+1)

[0124] ^{1}H-NMR (DMSO-d_6) δ: 3.10-3.20(1H,m), 3.28-3.38(1H,m), 3.60(3H,s), 4.48(1H,t,J=8 Hz), 6.99(1H,s), 7.18-7.30(2H,m), 7.36-7.59(4H,m), 7.60-7.80(6H,m), 8.51(1H,d,J=2 Hz)

[0125] Preparation 11

2-Bromo-1-[4-(1-imidazolyl)phenyl]ethan-1-one hydrobromide

[0126] To a solution of 1-[4-(1-imidazolyl)phenyl]ethan-1-one (50.25 g) in acetic acid (400 ml) was added 30% hydrogen bromide/acetic acid (d 1.35, 80 ml). Bromine (40.9 g) was added dropwise to the mixture for 20 minutes while the temperature of the reaction mixture was maintained between 20-25° C. After the addition was complete, the mixture was heated at 50° C. for 1 hour and allowed to cool to room temperature. The mixture was diluted with diisopropyl ether (400 ml) and the product was filtered and washed with diisopropyl ether. Recrystallization from methanol (750 ml) gave 2-bromo-1-[4-(1-imidazolyl)phenyl]ethan-1-one hydrobromide as a white powder (68.83 g).

[0127] MS(ESI)m/z: 265,267(free, M+H)$^+$

[0128] ^{1}H-NMR (DMSO-d_6,300 MHz) δ: 5.01(2H,s), 7.94(1H,s), 8.02(2H,d,J=8 Hz), 8.24(2H,d,J=8 Hz), 8.41(1H,s), 9.89(1H,s)

[0129] Preparation 12

2-Azido-1-[4-(1-imidazolyl)phenyl]ethan-1-one

[0130] To a suspension of 2-bromo-1-[4-(1-imidazolyl)phenyl]ethan-1-one hydrobromide (48.7 g) in N,N-dimethylformamide (500 ml) was added sodium azide (9.15

g) at 5° C. The mixture was stirred at the same temperature for 30 minutes, then at room temperature for 1 hour. The mixture was poured into diluted sodium hydrogencarbonate solution (1.6 L) and extracted three times with ethyl acetate. The extract was washed twice with brine and dried over magnesium sulfate. Evaporation of the solvent gave 2-azido-1-[4-(1-imidazolyl)-phenyl]ethan-1-one as a white solid (18.9 g).

[0131] MS(ESI)m/z: 228(M+H)$^+$

[0132] ^{1}H-NMR (DMSO-d_6,300 MHz) δ: 4.92(2H,s), 7.16(1H,s), 7.88(2H,d,J=8 Hz), 7.92(1H,s), 8.07(2H,d,J=8 Hz), 8.46(1H,s)

[0133] Preparation 13

2-Amino-1-[4-(1-imidazolyl)phenyl]ethan-1-one dihydrochloride

[0134] A solution of 2-azido-1-[4-(1-imidazolyl)phenyl] ethan-1-one (18.9 g) in a mixture of 2N hydrochloric acid (90 ml) and methanol (90 ml) was hydrogenated (3 atm) over 10% palladium on carbon (1.9 g) at room temperature for 3 hours. After the catalyst was filtered off, the filtrate was concentrated to give a white powder. The white powder was collected by filtration, washed with methanol and dried in vacuo to give 2-amino-1-[4-(1-imidazolyl)phenyl]ethan-1-one dihydrochloride (16.0 g).

[0135] MS(ESI)m/z: 202(free,M+H)$^+$

[0136] ^{1}H-NMR (DMSO-d_6,300 MHz) δ: 4.67(2H,q,J=5 Hz), 7.89(1H,s), 8.08(2H,d,J=8 Hz), 8.27(2H,d,J=8 Hz), 8.41(1H,s), 8.52(3H,br s), 9.78(1H,s)

[0137] Preparation 14

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(1-imidazolyl)phenyl]-2-oxoethyl]-3-(2-pyridyl)propionamide

[0138] The title compound was obtained from the compound of Preparation 13 in substantially the same manner as in Preparation 5.

[0139] oil

[0140] MS: 450(M+1)

[0141] ^{1}H-NMR ($CDCl_3$) δ1.42(9H,s), 3.20-3.30(1H,m), 3.31-3.42(1H,m), 4.62-4.73(1H,m), 4.70(2H,d,J=6 Hz), 6.42(1H,br s), 7.15(1H,t,J=6 Hz), 7.21(1H,d,J=6 Hz), 7.23(1H,s), 7.33(1H,s), 7.50(2H,d,J=8 Hz), 7.60(1H,t,J=8 Hz), 7.97(1H,s), 8.00(1H,br s), 8.08(2H,d,J=8 Hz), 8.57(1H, d,J=8 Hz)

[0142] Preparation 15

(1S)-(tert-Butoxy)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0143] The title compound was obtained from the compound of Preparation 14 in substantially the same manner as in Preparation 6.

[0144] amorphous solid

[0145] MS: 445(M+1)

[0146] ^{1}H-NMR ($CDCl_3$) δ1.38(9H,s), 3.39-3.52(2H,m), 3.49(3H,s), 5.38-5.52(1H,m), 5.49(1H,br s), 7.01(1H,s), 7.12(2H,d,J=8 Hz), 7.22(2H,d,J=8 Hz), 7.30(1H,s), 7.38-7.50(3H,m), 7.57(1H,t,J=8 Hz), 7.90(1H,s), 8.53(1H,d,J=2 Hz)

[0147] Preparation 16

(1S)-1-[5-[4-(1-Imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethylamine tetrahydrochloride

[0148] The title compound was obtained from the compound of Preparation 15 in substantially the same manner as in Preparation 26.

[0149] mp 253-256° C.

[0150] ^{1}H-NMR (DMSO-d_6) δ: 3.80-4.03(2H,m), 3.88(3H,s), 5.54(1H,t,J=6 Hz), 7.65(1H,t,J=5 Hz), 7.69-7.85(4H,m), 7.98-8.08(3H,m), 8.16(1H,t,J=8 Hz), 8.40(1H, s), 8.69(1H,d,J=5 Hz)

[0151] Preparation 17

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-(4-nitrophenyl)-2-oxoethyl]-3-(2-pyridyl)propionamide

[0152] The title compound was obtained in substantially the same manner as in Preparation 5.

[0153] MS(ESI)m/z: 429(M+H)$^+$

[0154] ^{1}H-NMR ($CDCl_3$,300 MHz) δ1.46(9H,s), 3.20-3.43(2H,m), 4.62-4.78(3H,m), 6.43(1H,br d,J=8 Hz), 7.12-7.27(2H,m), 7.56-7.67(1H,m), 8.04(1H,br s), 8.10(2H,d,J=8 Hz), 8.32(2H,d,J=8 Hz), 8.54(1H,d,J=5 Hz)

[0155] Preparation 18

(1S)-(tert-Butoxy)-N-[l-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0156] The title compound was obtained from the compound of Preparation 17 in substantially the same manner as in Preparation 6.

[0157] MS(ESI)m/z: 424(M+H)$^+$

[0158] ^{1}H-NMR ($CDCl_3$,300 MHz) δ1.38(9H,s), 3.38-3.50(2H,m), 3.53(3H,s), 5.37-5.51(1H,m), 5.54(1H,br d,J=8 Hz), 7.05-7.20(3H,m), 7.46(2H,d,J=8 Hz), 7.55(1H,t,J=8 Hz), 8.27(2H,d,J=8 Hz), 8.52(1H,d,J=5 Hz)

[0159] Preparation 19

(1S)-1-[1-Methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)-ethylamine

[0160] The title compound was obtained from the compound of Preparation 18 in substantially the same manner as in Preparation 26.

[0161] MS(ESI)m/z: 324(M+H)$^+$

[0162] ^{1}H-NMR ($CDCl_3$,300 MHz) δ3.27-3.50(2H,m), 3.61(3H,s), 4.62(1H,dd,J=8 and 6 Hz), 7.11-7.22(3H,m), 7.50(2H,d,J=8 Hz), 7.61(1H,t,J=7 Hz), 8.29(2H,d,J=8 Hz), 8.58(1H,d,J=5 Hz)

[0163] Preparation 20

(1 S) -N-[1-[5-(4-Aminophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-chlorobenzo[b]furan-2-yl)formamide

[0164] To a solution of (1S)-(5-chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (425 mg) in ethanol (10 ml) were added iron powder (473 mg) and acetic acid (508 mg) and the mixture was refluxed for 4 hours. The reaction mixture was filtered through a bed of Celite and the filtrate was concentrated in vacuo. The residue was diluted with a mixture of ethyl acetate and saturated aqueous sodium hydrogencarbonate solution and the mixture was filtered through a bed of Celite again. The organic layer was separated and washed with water and brine. The organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (3% methanol in chloroform) to give (1S)-N-[1-[5-(4-aminophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-chlorobenzo[b]furan-2-yl)formamide (230 mg).

[0165] MS(ES+): 472(M+H)

[0166] ^{1}H-NMR (300 MHz, $CDCl_3$) δ3.46(3H,s), 3.54-3.62(2H,m), 5.92(1H,m), 6.63-6.73(2H,m), 6.94(1H,s), 7.02-7.15(5H,m), 7.30-7.63(6H,m), 7.68-7.77(1H,m), 8.53(1H,m)

[0167] Preparation 21

2-[2-(4-Fluorophenyl)-2-oxoethyl]isoindoline-1,3-dione

[0168] A mixture of 2-bromo-1-(4-fluorophenyl)ethan-1-one (40 g) and potassium phthalimide (35.8 g) in 1,4-dioxane (300 ml) was refluxed for 6 hours. After cooling, the precipitated salt was filtered off and the filtrate was concentrated in vacuo. The crystalline residue was washed with diisopropyl ether to give 2-[2-(4-fluorophenyl)-2-oxoethyl] isoindoline-1,3-dione (49 g) as light yellow crystals.

[0169] mp 140-144° C.

[0170] MS(m/z): 282(M^+-H),146(bp)

[0171] ^{1}H-NMR ($CDCl_3$) δ5.10(2H,s), 7.21(2H,t,J=7.5 Hz), 7.77-7.80(2H,m), 7.89-7.93(2H,m), 8.03-8.09(2H,m)

[0172] Preparation 22

2-[2-[4-(2-Methylimidazol-1-yl)phenyl]-2-oxoethyl] isoindoline-1,3-dione

[0173] To a suspension of sodium hydride (424 mg) in DMF (20 ml) was added 2-methylimidazole (1.28 g) portionwise at 0° C. under stirring. After stirring at 0° C. for 0.5 hour, 2-[2-(4-fluorophenyl)-2-oxoethyl]isoindoline-1,3-dione (2.0 g) was added and the mixture was stirred at 60° C. for 4 hours. After cooling, the solvent was distilled away. The residue was diluted with ethyl acetate. The precipitated crystals were collected by suction filtration. The collected crystals were washed with a small amount of water and diethyl ether and dried to give 2-[2-[4-(2-methylimidazol-1-yl)-phenyl]-2-oxoethyl]isoindoline-1,3-dione (894 mg) as orange crystals.

[0174] mp 310-315° C.(decomposition)

[0175] MS(m/z): 346(M^++H,bp)

[0176] ^{1}H-NMR ($CDCl_3$) δ2.45(3H,s), 5.18(2H,s), 7.09(2H,d,J=4 Hz), 7.48(2H,d,J=8 Hz), 7.78-7.81(2H,m), 7.77-7.96(2H,m), 8.16(2H,d,J=8 Hz)

[0177] Preparation 23

2-Amino-1-[4-(2-methylimidazol-1-yl)phenyl]ethan-1-one dihydrochloride

[0178] 2-[2-[4-(2-Methylimidazol-1-yl)phenyl]-2-oxoethyl]isoindoline-1,3-dione (884 mg) was added to 37% hydrochloric acid (9 ml) and refluxed for 8 hours. After cooling, water was distilled away and the residue was washed with a small amount of methanol (2 ml) to give 2-amino-1-[4-(2-methylimidazol-1-yl)phenyl]ethan-1-one dihydrochloride (345 mg) as colorless crystals.

[0179] mp 320° C.(decomposition)

[0180] MS(m/z): 216(M^++H),148(bp)

[0181] ^{1}H-NMR (DMSO-d_6) δ2.60(3H,s), 4.68(2H,s), 7.81(1H,d,J=4 Hz), 7.89(2H,d,J=8 Hz), 7.97(1H,d,J=4 Hz), 8.28(2H,d,J=8 Hz), 8.59(2H,br.s)

[0182] Preparation 24

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(2-methylimidazol-1-yl)-phenyl]-2-oxoethyl]-3-(2-pyridyl-)propionamide

[0183] To a solution of (2S)-2-(tert-butoxycarbonylamino)-3-(2-pyridyl)-propanoic acid (648 mg) in DMF (5 ml) were added diphenylphosphoryl azide (0.55 ml) and 2-amino-1-[4-(2-methylimidazol-1-yl)phenyl]ethan-1-one dihydrochloride (701 mg) at 5° C. under stirring. Diisopropylethylamine (1.4 ml) was added dropwise at 5° C. The reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogencarbonate solution. The aqueous layer was extracted with ethyl acetate for another 2 times. The combined organic layers were washed with 1N hydrochloric acid. The aqueous layer was basified with saturated aqueous sodium hydrogencarbonate solution to pH 3, treated with charcoal, filtered and washed with water. The filtrate was basified with saturated aqueous sodium hydrogencarbonate solution and 1N aqueous sodium hydroxide solution to pH 8 and extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with a mixture of methanol and chloroform (1:20) to give (2S)-2-(tert-butoxycarbonylamino)-N-[2-[4-(2-methylimidazol-1-yl)phenyl]-2-oxoethyl]-3-(2-pyridyl)propionamide (340 mg) as a brown oil.

[0184] MS(m/z): 464(M^++H,bp)

[0185] ^{1}H-NMR ($CDCl_3$) δ1.61(9H,s), 2.42(3H,s), 3.24-3.42(3H,m), 4.72(2H,d,J=5 Hz), 7.06(2H,d,J=7.5 Hz), 7.15-7.24(2H,m), 7.43(2H,d,J=8 Hz), 7.63(1H,t,J=8 Hz), 8.03(2H,s) 8.09(2H,d,J=8 Hz), 8.58(1H,d,J=5 Hz)

[0186] Preparation 25

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(2-methylimidazol-1-yl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0187] To a solution of (2S)-2-(tert-butoxycarbonylamino)-N-[2-[4-(2-methylimidazol-1-yl)phenyl]-2-oxoet-

hyl]-3-(2-pyridyl)-propionamide (340 mg) in xylene (3.2 ml) were added acetic acid (0.32 ml) and methylamine (40% in water) (0.32 ml) under stirring and refluxed azeotropically for 3 hours. After cooling, the solvent was distilled away. The residue was diluted with saturated aqueous sodium hydrogencarbonate solution and extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with a mixture of methanol and chloroform (1:20) to give (1S)-(tert-butoxy)-N-[1-[1-methyl-5-[4-(2-methylimidazol-1-yl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (250 mg) as a brown oil.

[0188] MS(m/z): 459(M^++H,bp)

[0189] ^{1}H-NMR ($CDCl_3$) δ1.38(9H,s), 2.40(3H,s), 3.45(1H,d,J=6 Hz), 3.53(3H,s), 5.44(2H,br.s), 7.05(2H,d,J=7.5 Hz), 7.08(1H,s), 7.12(2H,d,J=7.5 Hz), 7.38(4H,AB,J=8 Hz,J=8 Hz), 7.54-7.60(1H,m), 8.55(2H,d,J=6 Hz)

[0190] Preparation 26

(1S)-1-[1-Methyl-5-[4-(2-methylimidazol-1-yl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0191] To a solution of (1S)-(tert-butoxy)-N-[1-[1-methyl-5-[4-(2-methylimidazol-1-yl)phenyl]imidazol-2-yl]-2-(2-pyridyl)-ethyl]formamide (242 mg) in methanol (1 ml) was added 4N hydrogen chloride in ethyl acetate (1.2 ml) at room temperature under stirring.

[0192] The resulting mixture was stirred at room temperature for 5 hours. After evaporation of the solvent, the residue was basified with 1N aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with a mixture of methanol and chloroform (1:5~1:1) to give (1S)-1-[1-methyl-5-[4-(2-methylimidazol-1-yl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethylamine (143 mg) as a yellow oil.

[0193] MS(m/z): 359(M^++H,bp)

[0194] ^{1}H-NMR ($CDCl_3$) δ2.42(3H,s), 3.31-3.48(2H,m), 3.44(3H,s), 4.68(1H,dd,J=8 Hz,J=7 Hz),7.08(2H,d,J=7 Hz), 7.10(1H,s), 7.16-7.20(2H,m),7.40(4H,AB,J=8 Hz,J=8 Hz), 7.62(1H,t,J=7 Hz), 8.60(1H,d,J=7 Hz)

[0195] Preparation 27

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-(4-bromophenyl)-2-oxoethyl]-3-(2-pyridyl)propionamide

[0196] The title compound was obtained in substantially the same manner as in Preparation 5.

[0197] MS(ESI)m/z: 462,464$(M+H)^+$

[0198] ^{1}H-NMR ($CDCl_3$,300 MHz) δ1.44(9H,s), 3.18-3.43(2H,m), 4.58-4.75(1H,m), 4.64(2H,d,J=5 Hz), 6.42(1H, br d,J=8 Hz), 7.10-7.23(2H,m), 7.53-7.65(1H,m), 7.61(2H, d,J=8 Hz), 7.79(2H,d,J=8 Hz), 7.92(1H,br s), 8.53(1H,d,J=5 Hz)

[0199] Preparation 28

(1S)-(tert-Butoxy)-N-[1-[5-(4-bromophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0200] The title compound was obtained from the compound of Preparation 27 in substantially the same manner as in Preparation 6.

[0201] MS(ESI)m/z: 457,459$(M+H)^+$

[0202] ^{1}H-NMR ($CDCl_{3,300}$ MHz) δ1.37(9H,s), 3.33-3.52(2H,m), 3.42(3H,s), 5.31-5.52(2H,m), 6.99(1H,s), 7.05-7.15(2H,m), 7.18(2H,d,J=8 Hz), 7.48-7.61(1H,m), 7.53(2H, d,J=8 Hz), 8.53(1H,d,J=5 Hz)

[0203] Preparation 29

(1S)-(tert-Butoxy)-N-[1-[5-[4-(2-furyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0204] A mixture of 2-(tributylstannyl)furan(264 mg), (1S)-(tert-butoxy)-N-[1-[5-(4-bromophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]-formamide (260 mg), tetrakis(triphenylphosphine) palladium (66 mg) and anhydrous lithium chloride (72 mg) in toluene (10 ml) was heated at 100° C. for 2 hours. The cooled mixture was filtered through a bed of Celite and concentrated in vacuo. The residue was purified by silica gel column chromatography (3% methanol in chloroform) to give (1S)-(tert-butoxy)-N-[1-[5-[4-(2-furyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (218 mg) as a white powder.

[0205] mp 131-135° C.

[0206] MS(ES+): 445(M+H)

[0207] ^{1}H-NMR (300 MHz, $CDCl_3$) δ1.37(9H,s), 3.41-3.51(5H,m), 5.35-5.48(2H,m), 6.48(1H,m), 6.68(1H,m), 7.02(1H,s), 7.07-7.16(2H,m), 7.32(2H,d,J=8 Hz), 7.48(1H, s), 7.55(1H,dd,J=8 Hz,J=8 Hz), 7.70(2H,d,J=8 Hz), 8.54(1H,m)

[0208] Preparation 30

(1S)-1-[5-[4-(2-Furyl)phenyl]-1methylimidazol-2-yl]-2-(2-pyridyl)ethylamine

[0209] The title compound was obtained from the compound of Preparation 29 in substantially the same manner as in Preparation 26.

[0210] MS(ES+): 345(M+H)

[0211] ^{1}H-NMR (300 MHz, $CDCl_3$) δ1.73(2H,d,J=7 Hz), 3.33(1H,m), 3.45(1H,m), 3.54(3H,s), 4.59(1H,m), 6.48(1H, m), 6.68(1H,m), 7.06(1H,s), 7.10-7.21(2H,m), 7.35(2H,d, J=8 Hz), 7.49(1H,m), 7.60(1H,m), 7.72(2H,d,J=8 Hz), 8.58(1H,d,J=6 Hz)

[0212] Preparation 31

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(2-thienyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0213] The title compound was obtained from the compound of Preparation 28 in substantially the same manner as in Preparation 29.

[0214] MS(ES+): 461(M+H)

[0215] ^{1}H-NMR (300 MHz, $CDCl_3$) δ1.37(9H,s), 3.38-3.51(m,5H), 5.32-5.51(m,2H), 7.02(12H,d), 7.06-7.20(4H, m), 7.27-7.37(2H,m), 7.49-7.60(3H,m), 7.65(1H,d,J=8 Hz), 8.54(1H,m)

[0216] Preparation 32

(1S)-1-[1-Methyl-5-[4-(2-thienyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0217] The title compound was obtained from the compound of Preparation 31 in substantially the same manner as in Preparation 26.

[0218] MS(ES+): 361(M+H)

[0219] ^{1}H-NMR (300 MHz, $CDCl_3$) δ1.78(2H,br), 3.26-3.38(1H,m), 3.38-3.50(1H,m), 3.52 and 3.56(s,Total 3H), 4.54-4.65(1H,m), 7.00-7.22(5H,m), 7.28-7.38(2H,m), 7.51-7.70(4H,m), 8.58(1H,m)

[0220] Preparation 33

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(2-thiazolyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0221] The title compound was obtained from the compound of Preparation 28 and 2-(trimethylstannyl)thiazole in substantially the same manner as in Preparation 29.

[0222] MS(ES+): 462(M+H)

[0223] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.37(9H,s), 3.41-3.67(5H,m), 5.42-5.54(1H,m), 5.61-5.72(1H,m), 7.09(1H,s), 7.10-7.18(2H,m), 7.34-7.42(3H,m), 7.56(1H,dd,J=8 Hz,J=8 Hz), 7.89(1H,d,J=4 Hz), 8.02(2H,d,J=8 Hz), 8.52(1H,m)

[0224] Preparation 34

(1S)-1-[1-Methyl-5-[4-(2-thiazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0225] The title compound was obtained from the compound of Preparation 33 in substantially the same manner as in Preparation 26.

[0226] MS(ES+): 362(M+H)

[0227] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.74(2H,br), 3.34(1H,dd,J=15 Hz,J=8 Hz), 3.46(1H,dd,J=15 Hz,J=6 Hz), 3.55(3H,s), 4.60(1H,br), 7.04-7.21(3H,m), 7.35(1H,d,J=5 Hz), 7.40(2H,d,J=8 Hz), 7.60(1H,m), 7.89(1H,d,J=5 Hz), 8.03(2H,d,J=8 Hz), 8.58(1H,d,J=6 Hz)

[0228] Preparation 35

1-(3-Fluoro-4-morpholinophenyl)ethan-1-one

[0229] A mixture of 1-(3,4-difluorophenyl)ethan-1-one (3 g), morpholine (3.4 ml) and potassium carbonate (2.5 g) in DMF (30 ml) was heated at 150° C. (bath temperature) for 48 hours. TLC showed the exhaust of the starting material. The reaction mixture was poured into water (60 ml), and the precipitate was collected and washed with water. Then, the residue was dissolved in ethyl acetate, dried over magnesium sulfate, and filtered. After removal of the solvent, 1-(3-fluoro-4-morpholinophenyl)ethan-1-one (3.04 g) was obtained as a yellow-brown powder.

[0230] ^{1}H-NMR (DMSO-d_6) δ3.14(4H,dd,J=4 Hz,J=5 Hz), 3.33(3H,s), 3.73(4H,dd,J=4 Hz,J=5 Hz), 7.10(2H,dd,J=9 Hz), 7.66(2H,dd,J=15 Hz,J=1.5 Hz), 7.73(2H,dd,J=9 Hz,J=1.5 Hz)

[0231] Preparation 36

2-Bromo-1-(3-fluoro-4-morpholinophenyl)ethan-1-one

[0232] To a solution of 1-(3-fluoro-4-morpholinophenyl)ethan-1-one (3.0 g) in 48% HBr (5 ml) was added Br2 (0.7 ml) in 48% HBr (2 ml) dropwise at 65-70° C. during the period of 0.5 hour. The mixture was stirred at 65° C. for an additional 1 hour. The reaction mixture was cooled to 10° C. and basified with saturated aqueous sodium hydrogencarbonate solution carefully, and extracted with ethyl acetate (50 ml). The organic layer was dried over magnesium sulfate, and filtered. After removal of the solvent, 2-bromo-1-(3-fluoro-4-morpholinophenyl)ethan-1one (3.7 g) was obtained as a brown solid.

[0233] Preparation 37

2-[2-(3-Fluoro-4-morpholinophenyl)-2-oxoethyl]isoindoline-1,3-dione

[0234] A mixture of 2-bromo-1-(3-fluoro-4-morpholinophenyl)ethan-1-one (3.7 g) and potassium phthalimide (2.38 g) in DMF (30 ml) was stirred at 90° C. for 1 hour. After cooling to 10° C., the precipitate was collected and washed with cold-DMF (10 ml) and water (25×2), successively. 2-[2-(3-Fluoro-4-morpholinophenyl)-2-oxoethyl]-isoindoline-1,3-dione (2.95 g) was obtained as a pale yellow wet solid. This compound was used for next step without further dry-up or purification.

[0235] Preparation 38

2-Amino-1-(3-fluoro-4-morpholinophenyl)ethan-1-one dihydrochloride

[0236] A slurry of 2-[2-(3-fluoro-4-morpholinophenyl)-2-oxoethyl]-isoindoline-1,3-dione (2.9 g) in concentrated hydrochloric acid (30 ml) was heated under reflux for 8 hours. As a result, the slurry gradually dissolved and a clear pale yellow solution was obtained. After removal of the solvent in vacuo, the residual oily solid was triturated with methanol (10 ml), collected by filtration, and washed with methanol to give 2-amino-1-(3-fluoro-4-morpholinophenyl)ethan-1-one dihydrochloride (1.64 g) as a white powder.

[0237] ^{1}H-NMR (DMSO-d_6) δ3.20(4H,dd,J=4 Hz,J=5 Hz), 3.73(4H,dd,J=4 Hz,J=5 Hz), 4.50(2H,s), 7.15(2H,dd,J=9 Hz), 7.71-7.83(3H,m)

[0238] Preparation 39

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-(3-fluoro-4-morpholinophenyl)-2-oxoethyl]-3-(2-pyridyl)propionamide

[0239] The title compound was obtained from the compound of Preparation 38 in substantially the same manner as in Preparation 5.

[0240] MS: 487(ES+)

[0241] Preparation 40

(1S)-(tert-Butoxy)-N-[1-[5-(3-fluoro-4-morpholinophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0242] The title compound was obtained from the compound of Preparation 39 in substantially the same manner as in Preparation 6.

[0243] Preparation 41

(1S)-1-[5-(3-Fluoro-4-morpholinophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethylamine

[0244] The title compound was obtained from the compound of Preparation 40 in substantially the same manner as in Preparation 26.

[0245] Preparation 42

2-Bromo-1-(2-thienyl)ethan-1-one

[0246] To a stirred solution of 2-acetylthiophene (3 g) in dichloromethane (50 ml) and methanol (20 ml) was added tetrabutylammonium tribromide (12.6 g) at room temperature. The reaction mixture was stirred at room temperature for 12 hours. After evaporation of the solvent, the residue was taken up in ether, washed with 5% aqueous sodium thiosulfate and water, dried over magnesium sulfate and concentrated in vacuo to give 2-bromo-1-(2-thienyl)ethan-1-one (4.53 g) as a yellow oil.

[0247] ^{1}H-NMR ($CDCl_3$) δ4.36(2H,s), 7.18(1H,dd,J=5 Hz,J=4 Hz), 7.73(1H,d,J=5 Hz), 7.81(1H,d,J=4 Hz)

[0248] Preparation 43

2-Azido-1-(2-thienyl)ethan-1-one

[0249] To a solution of 2-bromo-1-(2-thienyl)ethan-1-one (9.5 g) in DMF (50 ml) was added sodium azide (3.01 g) at 0° C. under stirring. The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexane (1:10) to give 2-azido-1-(2-thienyl)-ethan-1one (1.88 g) as a brown oil.

[0250] ^{1}H-NMR ($CDCl_3$) δ4.46(2H,s), 7.16-7.19(1H,m), 7.71-7.75(2H,m)

[0251] Preparation 44

2-Amino-1-(2-thienyl)ethan-1-one hydrochloride

[0252] A mixture of 2-azido-1-(2-thienyl)ethan-1-one (2.57 g) and hydrochloric acid (2.8 ml) in a mixture of methanol (35 ml), tetrahydrofuran (35 ml) and water (35 ml) was hydrogenated over 10% palladium carbon (420 mg) under 2 atm of hydrogen for 5 hours at room temperature. The catalyst was filtered off through Celite pad. After evaporation of the filtrate, the resulting residue was washed with diisopropyl ether to give 2-amino-1-(2-thienyl)ethan-1-one hydrochloride (2.51 g) as green crystals.

[0253] MS(m/z): 142(M^++H,bp)

[0254] ^{1}H-NMR (DMSO-d_6) δ4.52(2H,s), 7.32-7.35(1H,m), 8.11(1H,d,J=5 Hz), 8.17(1H,d,J=5 Hz), 8.37(2H,br.s)

[0255] Preparation 45

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-oxo-2-(2-thienyl)ethyl]-3-(2-pyridyl)propionamide

[0256] The title compound was obtained from the compound of Preparation 44 in substantially the same manner as in Preparation 5.

[0257] MS(m/z): 390(M^++H,bp)

[0258] ^{1}H-NMR ($CDCl_3$) δ1.46(9H,s), 3.21-3.40(2H,m), 4.62(2H,d,J=7 Hz), 4.65-4.70(1H,m), 6.40(1H,d,J=7 Hz), 7.13-7.22(3H,m), 7.59(1H,ddd,J=7 Hz,J=7 Hz,J=2 Hz), 7.68(1H,dd,J=7 Hz,J=2 Hz), 7.75(1H,dd,J=7 Hz,J=2 Hz), 7.91(1H,br.s), 8.54(1H,d,J=7 Hz)

[0259] Preparation 46

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-(2-thienyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0260] The title compound was obtained from the compound of Preparation 45 in substantially the same manner as in Preparation 6.

[0261] MS(m/z): 385(M^++H,bp)

[0262] ^{1}H-NMR ($CDCl_3$) δ1.37(9H,s), 3.43(2H,d,J=7 Hz), 3.47(3H,s), 5.36-5.48(2H,m), 6.99(1H,d,J=3 Hz), 7.14-7.17(4H,m), 7.35(1H,d,J=7 Hz), 7.56(1H,t,J=7 Hz), 8.53(1H,d,J=3 Hz)

[0263] Preparation 47

(1S)-1-[1-Methyl-5-(2-thienyl)imidazol-2-yl]-2-(2-pyridyl)-ethylamine

[0264] The title compound was obtained from the compound of Preparation 46 in substantially the same manner as in Preparation 26.

[0265] MS(m/z): 285(M^++H,bp)

[0266] ^{1}H-NMR ($CDCl_3$) δ3.36(2H,dddd,J=15 Hz,J=14 Hz,J=8 Hz,J=7 Hz), 3.56(3H,s), 4.58(1H,dd,J=8 Hz,J=7 Hz), 7.03(1H,d,J=3 Hz), 7.08-7.17(4H,m), 7.34(1H,dd,J=7 Hz,J=3 Hz), 7.59(1H,ddd,J=8 Hz,J=8 Hz,J=3 Hz), 8.57(1H,d,J=7 Hz)

[0267] Preparation 48

2-Bromo-1-(2,4-dichlorophenyl)ethan-1-one

[0268] To a solution of 2,4-dichloroacetophenone (5 g) and hydrochloric acid (0.1 ml) in acetic acid (50 ml) was added dropwise a solution of bromine (1.36 ml) in acetic acid (9 ml) at 15° C. under stirring. The reaction mixture was stirred at room temperature for 6 hours. After evaporation of the solvent, the residue was taken up in ethyl acetate and washed with saturated aqueous sodium hydrogencarbonate solution, 5% aqueous sodium thiosulfate and brine, dried over magnesium sulfate and concentrated in vacuo to give 2-bromo-1-(2,4-dichlorophenyl)ethan-1-one (7.09 g) as a light yellow oil.

[0269] MS(m/z): 269,271(M^++H),235(bp)

[0270] ^{1}H-NMR ($CDCl_3$) δ4.50(2H,s), 7.37(1H,dd,J=8 Hz,J=2 Hz), 7.48(1H,d,J=2 Hz), 7.55(1H,d,J=8 Hz)

[0271] Preparation 49

2-Azido-1-(2,4-dichlorophenyl)ethan-1-one

[0272] The title compound was obtained from the compound of Preparation 48 in substantially the same manner as in Preparation 43.

[0273] ^{1}H-NMR ($CDCl_3$) δ4.51(2H,s),7.37(1H,dd,J=8 Hz,J=2 Hz), 7.48(1H,d,J=2 Hz),7.60(1H,d,J=8 Hz)

[0274] Preparation 50

2-Amino-1-(2,4-dichlorophenyl)ethan-1-one hydrochloride

[0275] The title compound was obtained from the compound of Preparation 49 in substantially the same manner as in Preparation 44.

[0276] MS(m/z);204(M^++H),85(bp)

[0277] ^{1}H-NMR (DMSO-d_6) δ4.51(2H,d,J=7 Hz), 7.64(1H,dd,J=8 Hz,J=3 Hz), 7.84(1H,d,J=3 Hz), 8.00(1H,d, J=8 Hz), 8.45(2H,br.s)

[0278] Preparation 51

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-(2,4-dichlorophenyl)-2-oxoethyl]-3-(2-pyridyl)propionamide

[0279] The title compound was obtained from the compound of Preparation 50 in substantially the same manner as in Preparation 5.

[0280] MS(m/z): 452,454(M^+,bp)

[0281] ^{1}H-NMR ($CDCl_3$) δ1.46(9H,s), 3.16-3.35(2H,m), 4.26(2H,d,J=7 Hz), 4.60-4.69(1H,m), 6.19(1H,br.s), 7.12-7.22(2H,m), 7.30(1H,dd,J=8 Hz,J=2 Hz), 7.43(1H,d,J=2 Hz), 7.56(1H,d,J=8 Hz), 7.62(1H,ddd,J=8 Hz,J=8 Hz,J=2 Hz), 8.00(1H,br.s), 8.52(1H,d,J=7 Hz)

[0282] Preparation 52

(1S)-(tert-Butoxy)-N-[1-[5-(2,4-dichlorophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0283] The title compound was obtained from the compound of Preparation 51 in substantially the same manner as in Preparation 6.

[0284] MS(m/z): 447,449(M^+,bp)

[0285] ^{1}H-NMR ($CDCl_3$) δ1.39(9H,s), 3.21(3H,s), 3.43(2H,t,J=7 Hz), 5.38(1H,q,J=7 Hz), 7.05-7.14(4H,m), 7.20(1H,d,J=8 Hz), 7.27(1H,ddd,J=8 Hz,J=8 Hz,J=2 Hz), 7.45-7.55(2H,m), 8.51 (1H,d,J=6 Hz)

[0286] Preparation 53

(1S)-1-[5-(2,4-Dichlorophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethylamine

[0287] The title compound was obtained from the compound of Preparation 52 in substantially the same manner as in Preparation 26.

[0288] MS(m/z): 347,349(M^+,bp)

[0289] ^{1}H-NMR ($CDCl_3$) δ3.29(3H,s), 3.33-3.48(2H,m), 4.58(1H,t,J=7 Hz), 6.98(1H,s), 7.09(1H,d,J=7.5 Hz), 7.13(1H,t,J=7.5 Hz), 7.21(1H,d,J=7.5 Hz), 7.30(1H,ddd,J=7.5 Hz,J=7.5 Hz,J=2 Hz), 7.49(1H,d,J=2 Hz), 7.57(1H,ddd, J=7 Hz,J=7 Hz,J=2 Hz), 8.55(1H,d,J=7 Hz)

[0290] Preparation 54

1-[4-(Iminomethoxymethyl)phenyl]ethan-1-one hydrochloride

[0291] To a solution of 4-cyanoacetophenone (8.0 g) in methanol (80 ml) was added a solution of sodium methoxide (298 mg) in methanol (5 ml) and the mixture was stirred at 60° C. for 1 hour. The reaction mixture was cooled and 5N ethanolic hydrogen chloride (5 ml) was added thereto. The precipitated sodium chloride was filtered off and the mother liquid was evaporated. The crystalline residue was triturated and washed with diethyl ether (100 ml) to give 1-[4-(iminomethoxymethyl)-phenyl]ethan-1-one hydrochloride (2.7 g) as white crystals.

[0292] mp 105-145° C.

[0293] ^{1}H-NMR (DMSO-d_6) δ2.62(3H,s), 2.64(3H,s), 8.02(2H,d,J=8 Hz), 8.13(2H,d,J=8 Hz)

[0294] Preparation 55

1-[4-[(2,2-Diethoxyethylamino)iminomethyl]phenyl] ethan-1-one hydrochloride

[0295] A mixture of 1-[4-(iminomethoxymethyl)phenyl] ethan-1-one hydrochloride (3.3 g), aminoacetaldehyde diethyl acetal (2.03 g) and ethanol (33 ml) was refluxed for 4 hours. The solvent was distilled away and the crystalline residue was triturated and washed with diethyl ether (50 ml) to give 1-[4-[(2,2-diethoxyethylamino)-iminomethyl]phenyl]ethan-1-one hydrochloride (2.3 g) as white crystals.

[0296] mp 143-146° C.

[0297] ^{1}H-NMR (DMSO-d_6) δ1.15(6H,t,J=6 Hz), 2.65(3H,s), 3.50-3.64(4H,m), 3.64-3.78(2H,m),4.82(1H,t, J=6 Hz), 7.88(2H,d,J=8 Hz), 8.13(2H,d,J=8 Hz)

[0298] Preparation 56

1-[4-(2-Imidazolyl)phenyl]ethan-1-one

[0299] A solution of 1-[4-[(2,2-diethoxyethylamino)iminomethyl]phenyl]-ethan-1-one hydrochloride (2.3 g) in 6N hydrochloric acid (23 ml) was stirred for 15 hours at ambient temperature and then 3 hours at 100° C. The reaction mixture was evaporated. The crystalline residue was washed with ethanol (20 ml). The obtained salt was partitioned between chloroform (100 ml) and saturated aqueous sodium hydrogencarbonate solution (100 ml). The organic layer was separated, dried over sodium sulfate (20 g) and evaporated. The crystalline residue was triturated and washed with ethyl acetate (5 ml) to give 1-[4-(2-imidazolyl)phenyl]ethan-1-one (300 mg) as white crystals. mp 213-216° C.

[0300] ESI-MS: 185(M−1)

[0301] ^{1}H-NMR (DMSO-d_6) δ2.60(3H,s), 7.10-7.40(2H, br), 8.00-8.12(4H,m)

[0302] Preparation 57

1-[4-(1-Methylimidazol-2-yl)phenyl]ethan-1-one

[0303] To a suspension of sodium hydride (709 mg) in tetrahydrofuran (100 ml) was added 1-[4-(2-imidazolyl)phenyl]ethan-1-one (5.0 g) at 5° C. and the mixture was stirred for 1 hour at ambient temperature. The reaction mixture was cooled to −78° C. and methyl iodide (4 g) was added dropwise. The mixture was warmed to ambient temperature and stirred for 15 hours. The reaction mixture was evaporated and the residue was partitioned between ethyl acetate (100 ml) and water (50 ml). The organic layer was dried over sodium sulfate (20 g) and evaporated. The crystalline resi-

due was triturated and washed with diisopropyl ether (20 ml) to give 1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one (3.98 g) as white crystals.

[0304] mp 88-93° C.

[0305] ESI-MS: 201(M+1)

[0306] ^{1}H-NMR ($CDCl_3$) δ2.67(3H,s), 3.82(3H,s), 7.03(1H,s), 7.18(1H,s), 7.78(2H,d,J=8 Hz), 8.05(2H,d,J=8 Hz)

[0307] Preparation 58

2-Bromo-1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one hydrobromide

[0308] To a solution of 1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one (1.0 g) in acetic acid (10 ml) was added 30% hydrogen bromide in acetic acid (2 ml) at 5° C. and the mixture was stirred for 10 minutes. To the mixture was added bromine (0.24 ml) and the mixture was stirred for 1 hour at ambient temperature. The reaction mixture was diluted with diisopropyl ether (20 ml) and the precipitate was collected by filtration and washed with diisopropyl ether (10 ml). The obtained solid was recrystallized from methanol (10 ml) to give 2-bromo-1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one hydrobromide (1.2 g) as pale brown crystals.

[0309] mp 202-206° C.

[0310] ESI-MS: 278(M+1)

[0311] ^{1}H-NMR (DMSO-d_6) δ3.91(3H,s), 5.05(2H,s), 7.88(1H,s), 7.91(1H,s), 8.00(2H,d,J=8 Hz), 8.25(2H,d,J=8 Hz)

[0312] Preparation 59

2-Azido-1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one

[0313] To a solution of 2-bromo-1-[4-(1-methylimidazol-2-yl)phenyl]-ethan-1-one hydrobromide (1.13 g) in DMF (11 ml) was added sodium azide (224 mg) at 5° C. and the mixture was stirred for 1 hour at ambient temperature. To the reaction mixture was added water (20 ml) and the precipitate was collected by filtration and washed with water. The solid was air-dried to give 2-azido-1-[4-(1-methylimidazol-2-yl)-phenyl]ethan-1one (700 mg) as a pale brown solid.

[0314] mp >250° C.

[0315] ESI-MS: 242(M+1)

[0316] ^{1}H-NMR ($CDCl_3$) δ3.83(3H,s), 4.60(2H,s), 7.04(1H,s), 7.19(1H,s), 7.82(2H,d,J=8 Hz), 8.01(2H,d,J=8 Hz)

[0317] Preparation 60

2-Amino-1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one dihydrochloride

[0318] A mixture of 2-azido-1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one (920 mg), palladium on carbon (90 mg), methanol (10 ml), water (5 ml) and concentrated hydrochloric acid (1 ml) was stirred under hydrogen (3 atm) at ambient temperature for 4 hours. The reaction mixture was filtered and the filtrate was evaporated. The crystalline residue was triturated and washed with methanol (5 ml) to give 2-amino-1-[4-(1-methylimidazol-2-yl)phenyl]ethan-1-one dihydrochloride (500 mg) as white crystals.

[0319] mp>250° C.

[0320] ESI-MS: 216(M+1)

[0321] ^{1}H-NMR (DMSO-d_6) δ3.92(3H,s), 4.70(2H,d,J=6 Hz), 7.83(1H,s), 7.90(1H,s), 8.05(2H,d,J=8 Hz), 8.26(2H,d, J=8 Hz), 8.55(2H,br.s)

[0322] Preparation 61

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(1-methylimidazol-2-yl)phenyl]-2-oxoethyl]-3-(2-pyridyl-)propionamide

[0323] The title compound was obtained from the compound of Preparation 60 in substantially the same manner as in Preparation 5.

[0324] mp 120-124° C.

[0325] ESI-MS: 464(M+1)

[0326] ^{1}H-NMR ($CDCl_3$) δ1.47(9H,s), 3.20-3.45(2H,m), 3.82(3H,s), 4.63-4.75(3H,m), 6.45(1H,br.s), 7.02(1H,s), 7.12-7.19(2H,m), 7.23(1H,d,J=8 Hz), 7.59(2H,d,J=8 Hz), 7.80(2H,d,J=8 Hz), 7.95(1H,br.s), 8.03(2H,d,J=8 Hz), 8.57(1H,d,J=4 Hz)

[0327] Preparation 62

(1S)-(tert-Butoxy)-N-[1-[5-[4-(1-methylimidazol-2-yl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0328] The title compound was obtained from the compound of Preparation 61 in substantially the same manner as in Preparation 6.

[0329] mp 160-163° C.

[0330] ESI-MS: 459(M+1)

[0331] ^{1}H-NMR ($CDCl_3$) δ1.38(9H,s), 3.40-3.53(5H,m), 3.80(3H,s), 5.35-5.52(2H,m), 7.00(1H,s), 7.05(1H,s), 7.08-7.18(3H,m), 7.39(2H,d,J=8 Hz), 7.55(1H,t,J=8 Hz), 7.70(2H,d,J=8 Hz), 8.55(1H,d,J=4 Hz)

[0332] Preparation 63

(1S)-1-[5-[4-(1-Methylimidazol-2-yl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethylamine tetrahydrochloride

[0333] The title compound was obtained from the compound of Preparation 62 in substantially the same manner as in Preparation 26.

[0334] mp>250° C.

[0335] ^{1}H-NMR (DMSO-d_6) δ3.85(3H,s), 3.93(3H,s), 5.48(1H,br.s), 7.60(1H,t,J=5 Hz), 7.65(1H,s), 7.68(1H,d,J=8 Hz), 7.78(2H,d,J=8 Hz), 7.86(1H,s), 7.91(1H,s), 8.00(2H,d, J=8 Hz), 8.13(1H,t,J=8 Hz), 8.68(1H,d,J=5 Hz)

[0336] Preparation 64

2-Bromo-1-(4-fluorophenyl)propan-1-one

[0337] To an ice-cooled solution of 1-(4-fluorophenyl-)propan-1-one (10 g) in diethyl ether (200 ml) was added bromine (10.4 g) dropwise and the mixture was stirred for 30

minutes. The reaction mixture was washed with water (100 ml), aqueous sodium hydrogencarbonate solution (100 ml), aqueous sodium thiosulfate solution (100 ml) and brine (50 ml), dried over sodium sulfate and evaporated to give 2-bromo-1-(4-fluorophenyl)propan-1-one (18 g).

[0338] oil

[0339] ESI-MS: 232(M+1)

[0340] ^{1}H-NMR ($CDCl_3$) δ1.91(3H,d,J=6 Hz), 5.25(1H, q,J=6 Hz), 7.10-7.20(2H,m), 8.04-8.12(2H,m)

[0341] Preparation 65

2-[2-(4-Fluorophenyl)-1-methyl-2-oxoethyl]isoindoline-1,3-dione

[0342] The title compound was obtained from the compound of Preparation 64 in substantially the same manner as in Preparation 21.

[0343] ESI-MS: 298(M+1)

[0344] ^{1}H-NMR ($CDCl_3$) 6 1.72(3H,d,J=6 Hz), 5.63(1H, q,J=6 Hz), 7.01-7.13(2H,m), 7.68-7.90(6H,m)

[0345] Preparation 66

2-[2-[4-(1-Imidazolyl)phenyl]-1-methyl-2-oxoethyl] isoindoline-1,3-dione

[0346] The title compound was obtained from the compound of Preparation 65 in substantially the same manner as in Preparation 22.

[0347] ESI-MS: 346(M+1)

[0348] ^{1}H-NMR ($CDCl_3$) δ1.74(3H,d,J=6 Hz), 5.66(1H, q,J=6 Hz), 7.21(1H,s), 7.30(1H,s), 7.43(2H,d,J=8 Hz), 7.69-7.75(2H,m), 7.80-7.86(2H,m), 7.88(1H,s), 7.95(2H,d,J=8 Hz)

[0349] Preparation 67

2-Amino-1-[4-(1-imidazolyl)phenyl]propan-1-one dihydrochloride

[0350] The title compound was obtained from the compound of Preparation 66 in substantially the same manner as in Preparation 23.

[0351] ESI-MS: 216(M+1)

[0352] ^{1}H-NMR (DMSO-d_6) δ1.45(3H,d,J=6 Hz), 5.15-5.30(1H,m), 7.91(1H,s), 8.09(2H,d,J=8 Hz), 8.33(2H,d,J=8 Hz), 8.42(1H,s), 8.61(2H,s), 9.80(1H,s)

[0353] Preparation 68

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(1-imidazolyl)phenyl]-1-methyl-2-oxoethyl]-3-(2-pyridyl-)propionamide

[0354] The title compound was obtained from the compound of Preparation 67 in substantially the same manner as in Preparation 5.

[0355] amorphous solid

[0356] ESI-MS: 464(M+1)

[0357] ^{1}H-NMR ($CDCl_3$) δ1.25(3×2/5H,d,J=6 Hz), 1.37(3×3/5H,d,J=6 Hz), 1.45(9H,s), 3.15-3.45(2H,m), 5.47(1H,q,J=6 Hz), 7.07-7.24(2H,m), 7.36(1H,s), 7.45-7.83(4H,m), 7.95(1H,s), 8.08(2H,d,J=8 Hz), 8.48(1×2/5H, d,J=4 Hz), 8.54(1×3/5H,d,J=4 Hz)

[0358] Preparation 69

(1S)-(tert-Butoxy)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1,4-dimethylimidazol-2-yl]-2-(2-pyridyl)ethyl] formamide

[0359] The title compound was obtained from the compound of Preparation 68 in substantially the same manner as in Preparation 6.

[0360] amorphous solid

[0361] ESI-MS: 459(M+1)

[0362] ^{1}H-NMR ($CDCl_{13}$) δ1.36(9H,s), 2.20(3H,s), 3.35(3H,s), 3.43(2H,d,J=6 Hz), 3.47(2H,d,J=8 Hz), 5.30-5.55(2H,m), 7.08-7.18(2H,m), 7.24(1H,s), 7.30-7.37(3H, m), 7.55(2H,d,J=8 Hz), 7.80(1H,d,J=8 Hz), 7.90(1H,s), 8.57(1H,d,J=4 Hz)

[0363] Preparation 70

(1S)-1-[5-[4-(1-Imidazolyl)phenyl]-1,4-dimethylimidazol-2-yl]-2-(2-pyridyl)ethylamine tetrahydrochloride

[0364] The title compound was obtained from the compound of Preparation 69 in substantially the same manner as in Preparation 26.

[0365] ESI-MS: 359(M+1)

[0366] ^{1}H-NMR (DMSO-d_6) δ2.26(3H,s), 3.81(3H,s), 3.90-4.10(2H,m), 5.60(1H,t,J=6 Hz), 7.63(1H,t,J=8 Hz), 7.70-7.80(2H,m), 8.00(2H,s), 8.07(2H,d,J=8 Hz), 8.16(1H, t,J=8 Hz), 8.44(1H,s), 8.69(1H,d,J=4 Hz)

[0367] Preparation 71

(1S)-(tert-Butoxy)-N-[1[-1-ethyl-5-[4-(1-imidazolyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl] formamide

[0368] The title compound was obtained from the compound of Preparation 14 in substantially the same manner as in Preparation 6.

[0369] oil

[0370] MS: 459(M+1)

[0371] ^{1}H-NMR ($CDCl_3$) δ1.18(3H,t,J=8 Hz), 1.40(9H,s), 3.42-3.52(1H,m), 3.53-3.70(1H,m), 3.95-4.12(2H,m), 5.50(1H,q,J=8 Hz), 5.70(1H,br s), 7.08(1H,s), 7.10-7.20(2H,m), 7.21-7.30(2H,m), 7.31(1H,s), 7.40-7.51(3H, m), 7.58(1H,t,J=8 Hz), 7.90(1H,s), 8.52(1H,d,J=2 Hz)

[0372] Preparation 72

(1S)-1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0373] The title compound was obtained from the compound of Preparation 71 in substantially the same manner as in Preparation 7.

[0374] oil

[0375] MS: 359(M+1)

[0376] ^{1}H-NMR ($CDCl_3$) δ1.20(3H,t,J=8 Hz), 3.35-3.60(2H,m), 3.90-4.17(2H,m), 4.62-4.72(1H,m), 7.03(1H,s), 7.18(2H,d,J=8 Hz), 7.23(2H,d,J=8 Hz), 7.31(1H,s), 7.40-7.50(2H,m), 7.61(1H,t,J=8 Hz), 7.89-7.92(2H,m), 8.59(1H,d,J=2 Hz)

[0377] Preparation 73

(1S)-(tert-Butoxy)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0378] The title compound was obtained from the compound of Preparation 14 in substantially the same manner as in Preparation 6.

[0379] MS(ESI)m/z: 473(M+H)$^+$

[0380] ^{1}H-NMR ($CDCl_3$,300 MHz) δ: 0.76(3H,t,J=7 Hz), 1.38(9H,s), 1.40-1.60(2H,m), 3.48-3.80(2H,m), 3.88-4.08(2H,m), 5.40-5.60(2H,m), 7.02-7.65(10H,m), 7.92(1H,s), 8.52(1H,d,J=5 Hz)

[0381] Preparation 74

(1S)-1-[5-[4-(1-Imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethylamine

[0382] The title compound was obtained from the compound of Preparation 73 in substantially the same manner as in Preparation 26.

[0383] MS(ESI)m/z: 373(M+H)$^+$

[0384] ^{1} H-NMR ($CDCl_3$,300 MHz) δ: 0.78(3H,t,J=7 Hz), 1.36-1.72(2H,m), 3.42-3.74(2H,m), 3.85-4.24(2H,m), 4.81-5.02(1H,m), 7.08(1H,s), 7.15-7.72(9H,m), 7.93(1H,s), 8.55(1H,d,J=5 Hz)

[0385] Preparation 75

2-[2-[4-(1-Benzimidazolyl)phenyl]-2-oxoethyl]isoindoline-1,3-dione

[0386] The title compound was obtained from the compound of Preparation 21 in substantially the same manner as in Preparation 22.

[0387] mp 290-295° C. (decomposition)

[0388] MS(m/z): 382(M$^+$+H), 119(bp)

[0389] ^{1}H-NMR ($CDCl_3$) δ5.20(2H,s), 7.38-7.43(2H,m), 7.61-7.66(1H,m), 7.73(2H,d,J=8 Hz), 7.77-7.82(2H,m), 7.89-7.95(3H,m), 8.24(3H,t,J=7 Hz)

[0390] Preparation 76

2-Amino-1-[4-(1-benzimidazolyl)phenyl]ethan-1-one dihydrochloride

[0391] The title compound was obtained from the compound of Preparation 75 in substantially the same manner as in Preparation 23.

[0392] mp 295-300° C. (decomposition)

[0393] MS(m/z): 252(M$^+$+H),85(bp)

[0394] ^{1}H-NMR (DMSO-d6) δ4.69(2H,d,J=7 Hz), 7.52-7.58(2H,m), 7.80-7.85(1H,m), 7.91-7.96(1H,m), 8.04(2H,d,J=8 Hz), 8.32(2H,d,J=8 Hz), 8.58(2H,s), 9.49(1H,s)

[0395] Preparation 77

(2S)-N-[2-[4-(1-Benzimidazolyl)phenyl]-2-oxoethyl]-2-(tert-butoxycarbonylamino)-3-(2-pyridyl)propionamide

[0396] The title compound was obtained from the compound of Preparation 76 in substantially the same manner as in Preparation 5.

[0397] MS(m/z): 500(M$^+$+H,bp)

[0398] ^{1}H-NMR ($CDCl_3$) δ1.49(9H,s), 3.24-3.50(3H,m), 4.77(2H,d,J=7 Hz), 7.15-7.24(2H,m), 7.37-7.40(3H,m), 7.59-7.63(2H,m), 7.66-7.70(3H,m), 7.89-7.93(1H,m), 8.02(1H,s), 8.14-8.19(2H,m),8.58(1H,d,J=7 Hz)

[0399] Preparation 78

(1S)-N-[1-[5-[4-(1-Benzimidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](tert-butoxy)formamide

[0400] The title compound was obtained from the compound of Preparation 77 in substantially the same manner as in Preparation 6.

[0401] MS(m/z): 495(M$^+$+H,bp)

[0402] ^{1}H-NMR ($CDCl_3$) δ1.40(9H,s), 3.49(2H,d,J=7 Hz), 3.57(3H,s), 5.45-5.50(2H,m), 7.10(1H,s), 7.15(2H,d,J=7.5 Hz), 7.36-7.40(2H,m), 7.51-7.60(6H,m), 7.89-7.93(1H,m), 8.17(1H,s), 8.58(1H,d,J=7 Hz)

[0403] Preparation 79

(1S)-1-[5-[4-(1-Benzimidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethylamine

[0404] The title compound was obtained from the compound of Preparation 78 in substantially the same manner as in Preparation 26.

[0405] MS(m/z): 395(M$^+$+H,bp)

[0406] ^{1}H-NMR ($CDCl_3$) δ3.32-3.52(2H,m), 3.62(3H,s), 4.64(1H,dd,J=8 Hz,J=5 Hz), 7.14-7.20(2H,m), 7.27(1H,s), 7.33-7.40(2H,m), 7.50-7.69(6H,m), 7.89-7.95(1H,m), 8.18(1H,s), 8.61(1H,d,J=7 Hz)

[0407] Preparation 80

2-[2-[4-(2-Ethylimidazol-1-yl)phenyl]-2-oxoethyl]isoindoline-1,3-dione

[0408] The title compound was obtained from the compound of Preparation 21 in substantially the same manner as in Preparation 22.

[0409] MS(ES+): 360(M+H)

[0410] ^{1}H-NMR (300 MHz,CDCl3) δ1.31(3H,t,J=7 Hz), 2.74(2H,q,J=7 Hz), 5.17(2H,s), 7.06(1H,s), 7.11(1H,s), 7.49(2H,d,J=8 Hz), 7.74-7.83(2H,m), 7.89-7.98(2H,m), 8.17(2H,d,J=8 Hz)

[0411] Preparation 81

2-Amino-1-[4-(2-ethylimidazol-1-yl)phenyl]ethan-1-one dihydrochloride

[0412] The title compound was obtained from the compound of Preparation 80 in substantially the same manner as in Preparation 23.

[0413] MS(ES+): 230(M+H)

[0414] ^{1}H-NMR (300 MHz,DMSO-d6) δ1.22(3H,t,J=7 Hz), 2.93(2H,q,J=7 Hz), 4.62-4.74(2H,m), 7.85(1H,s), 7.90(2H,d,J=8 Hz), 7.98(1H,s), 8.29(2H,d,J=8 Hz), 8.66(2H,br)

[0415] Preparation 82

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(2-ethylimidazol-1-yl)-phenyl]-2-oxoethyl]-3-(2-pyridyl-)propionamide

[0416] The title compound was obtained from the compound of Preparation 81 in substantially the same manner as in Preparation 5.

[0417] MS(ES+): 478(M+H)

[0418] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.28(3H,t,J=7 Hz), 1.47(9H,s), 2.71(2H,q,J=7 Hz), 3.27(1H,m), 3.39(1H,m), 4.65-4.77(3H,m), 6.46(1H,m), 7.02(1H,s), 7.10(1H,s), 7.16(1H,m), 7.22(1H,d,J=8 Hz), 7.42(2H,d,J=8 Hz), 7.61(1H,m), 8.01(1H,br), 8.07(2H,d,J=8 Hz), 8.56(1H,d,J=5 Hz)

[0419] Preparation 83

(1S)-(tert-Butoxy)-N-[1-[5-[4-(2-ethylimidazol-1-yl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0420] The title compound was obtained from the compound of Preparation 82 in substantially the same manner as in Preparation 6.

[0421] MS(ES+): 473(M+H)

[0422] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.28(3H,t,J=7 Hz), 1.38(9H,s), 2.70(2H,q,J=7 Hz), 3.46(2H,d,J=8 Hz), 3.52(3H,s), 5.35-5.65(2H,m), 7.01(1H,s), 7.03-7.18(4H,m), 7.34(2H,d,J=8 Hz), 7.42(2H,d,J=8 Hz), 7.57(1H,m), 8.56(1H,m)

[0423] Preparation 84

(1S)-1-[5-[4-(2-Ethylimidazol-1-yl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethylamine

[0424] The title compound was obtained from the compound of Preparation 83 in substantially the same manner as in Preparation 26.

[0425] MS(ES+): 373(M+H)

[0426] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.29(3H,t,J=7 Hz), 1.94(2H,br), 2.71(2H,q,J=7 Hz), 3.34(1H,m), 3.47(1H,m), 3.60(3H,s), 4.62(1H,m), 7.14-7.21(4H,m), 7.34(2H,d,J=8 Hz), 7.43(2H,d,J=8 Hz), 7.60(1H,dd,J=8 Hz,J=8 Hz), 8.59(1H,m)

[0427] Preparation 85

1-[4-(3-Pyridyl)phenyl]ethan-1-one

[0428] A mixture of diethyl(3-pyridyl)borane (1.66 g), 4-bromo-acetophenone (3.37 g), powdered potassium hydroxide (1.9 g), tetrabutylammonium bromide (1.82 g) and tetrakis(triphenylphosphine)-palladium (1.3 g) in tetrahydrofuran (45ml) was refluxed under nitrogen for 1.5 hours. After removal of the solvent, the catalyst was removed and washed with ethyl acetate. The filtrate was washed with saturated aqueous sodium hydrogencarbonate solution and brine, and dried over sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography with ethyl acetate-hexane (1:1) as an eluent to give 1-[4-(3-pyridyl)phenyl]ethan-1-one (2.0 g) as crystals.

[0429] MS(ES+): 198(M+H)

[0430] ^{1}H-NMR (300 MHz,$CDCl_3$) δ2.68(3H,s), 7.41(1H,m), 7.69(2H,d,J=8 Hz), 7.93(1H,m), 8.08(2H,d,J=8 Hz), 8.65(1H,m), 8.89(1H,m)

[0431] Preparation 86

2-Bromo-1-[4-(3-pyridyl)phenyl]ethan-1-one hydrobromide

[0432] The title compound was obtained from the compound of Preparation 85 in substantially the same manner as in Preparation 58.

[0433] MS(ES+): 357(M+H)

[0434] ^{1}H-NMR (300 MHz,DMSO-d_6) δ5.02(2H,s), 8.02-8.13(3H,m), 8.17(2H,d,J=8 Hz), 8.85(1H,m), 8.91(1H,m), 9.30(1H,s)

[0435] Preparation 87

2-Azido-1-[4-(3-pyridyl)phenyl]ethan-1-one

[0436] The title compound was obtained from the compound of Preparation 86 in substantially the same manner as in Preparation 59.

[0437] MS(ES+): 239(M+H)

[0438] ^{1}H-NMR (300MHz,$CDCl_3$) δ4.61(2H,s), 7.42(1H,m), 7.73(2H,d,J=8 Hz), 7.93(1H,m), 8.04(2H,d,J=8 Hz), 8.66(1H,m), 8.89(1H,m)

[0439] Preparation 88

2-Amino-1-[4-(3-pyridyl)phenyl]ethan-1-one dihydrochloride

[0440] The title compound was obtained from the compound of Preparation 87 in substantially the same manner as in Preparation 60.

[0441] MS(ES+): 213(M(free)+H)

[0442] ^{1}H-NMR (300 MHz,DMSO-d6) δ4.60-4.76(2H,m), 7.99(1H,m), 8.11(2H,d,J=8 Hz), 8.19(2H,d,J=8 Hz), 8.52(2H,br), 8.75(1H,d,J=8 Hz), 8.88(1H,d,J=5 Hz), 9.28(1H,m)

[0443] Preparation 89

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(3-pyridyl)phenyl]-2-oxoethyl]-3-(2-pyridyl)propionamide

[0444] The title compound was obtained from the compound of Preparation 88 in substantially the same manner as in Preparation 5.

[0445] MS(ES+): 461(M+H)

[0446] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.48(9H,s), 3.18-3.48(2H,m), 4.60-4.81(3H,m), 6.45(1H,m), 7.10-7.31(2H,m), 7.40(1H,m), 7.59(1H,m), 7.68(2H,d,J=8 Hz), 7.86-8.14(4H,m), 8.57(1H,d,J=5 Hz), 8.65(1H,m), 8.88(1H,m)

[0447] Preparation 90

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(3-pyridyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0448] The title compound was obtained from the compound of Preparation 89 in substantially the same manner as in Preparation 6.

[0449] MS(ES+): 456(M+H)

[0450] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.38(9H,s), 3.40-3.56(5H,m), 5.35-5.56(2H,m), 7.06(1H,s), 7.07-7.19(2H,m), 7.34-7.48(3H,m), 7.56(1H,dd,J=8 Hz,J=8 Hz), 7.63(2H,d,J=8 Hz), 7.91(1H,m), 8.54(1H,m), 8.62(1H,m), 8.87(1H,m)

[0451] Preparation 91

(1S)-1-[1-Methyl-5-[4-(3-pyridyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0452] The title compound was obtained from the compound of Preparation 90 in substantially the same manner as in Preparation 26.

[0453] MS(ES+): 356(M+H)

[0454] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.85(2H,br.s), 3.34(1H,m), 3.46(1H,m), 3.58(3H,s), 4.62(1H,m), 7.10(1H,s), 7.12-7.22(2H,m), 7.34-7.53(3H,m),7.55-7.74(3H,m), 7.90(1H,m), 8.52-8.69(2H,m), 8.88(1H,s)

[0455] Preparation 92

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(2-pyridyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0456] (1S)-(tert-Butoxy)-N-[1-[5-(4-bromophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (200 mg), 2-pyridyl trifluoromethane-sulfonate (99 mg), tetrakis(triphenylphosphine)palladium (25 mg) and anhydrous lithium chloride (55 mg) were mixed under nitrogen. Hexamethylditin (143 mg) and anhydrous 1,4-dioxane (10 ml) were added successively, and the mixture was refluxed for 23 hours. The cooled mixture was poured into a mixture of saturated aqueous potassium fluoride (25 ml) and ethyl acetate, and the mixture was vigorously stirred for 2 hours. The two phase mixture was filtered through a bed of Celite and the separated organic layer was extracted with 1N hydrochloric acid (10 ml×2). The aqueous layer was basified (pH 9) with sodium hydrogencarbonate and extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated in vacuo to give (1S)-(tert-butoxy)-N-[1-[1-methyl-5-[4-(2-pyridyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (220 mg) as a yellow amorphous solid.

[0457] MS(ES+): 456(M+H)

[0458] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.36(9H,s), 3.39-3.54(5H,m), 5.42(1H,m), 5.52(1H,m), 7.02-7.86(10H,m), 8.05(1H,d,J=8 Hz), 8.55(1H,m), 8.71(1H,m)

[0459] Preparation 93

(1S)-1-[1-Methyl-5-[4-(2-pyridyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0460] The title compound was obtained from the compound of Preparation 92 in substantially the same manner as in Preparation 26.

[0461] MS(ES+): 356(M+H)

[0462] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.76(2H,br), 3.24-3.69(5H,m), 4.60(1H,br), 6.96-8.15(11H,m), 8.58(1H,m), 8.70(1H,m)

[0463] Preparation 94

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(4-pyridyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0464] A mixture of trimethyl(4-pyridyl)stannane (222 mg), (1S)-(tert-butoxy)-N-[1-[5-(4-bromophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)-ethyl]formamide (350 mg), bis(triphenylphosphine)palladium chloride (53.7 mg) and anhydrous lithium chloride (55 mg) in 1,4-dioxane (10 ml) was refluxed for 24 hours. The cooled mixture was poured into a mixture of saturated aqueous potassium fluoride solution (25 ml) and ethyl acetate, and the mixture was vigorously stirred for 2 hours. The two phase mixture was filtered through a bed of Celite and the separated organic layer was extracted with 1N hydrochloric acid (10 ml×2). The aqueous layer was basified (pH 9) with sodium hydrogencarbonate and extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (3% methanol in chloroform) to give (1S)-(tert-butoxy)-N-[1-[1-methyl-5-[4-(4-pyridyl)-phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide (135 mg).

[0465] MS(ES+): 456(M+H)

[0466] ^{1}H-NMR (300MHz,$CDCl_3$) δ1.37(9H,s), 3.37-3.56(5H,m), 5.34-5.58(2H,m), 7.07(1H,s), 7.09-7.23(2H,m), 7.43(2H,d,J=8 Hz), 7.48-7.63(3H,m), 7.70(2H,d,J=8 Hz), 8.55(1H,m), 8.68(2H,d,J=8 Hz)

[0467] Preparation 95

(1S)-1-[1-Methyl-5-[4-(4-pyridyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0468] The title compound was obtained from the compound of Preparation 94 in substantially the same manner as in Preparation 26.

[0469] MS(ES+): 356(M+H)

[0470] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.93(2H,s), 3.35(1H,m), 3.46(1H,m), 3.59(3H,s), 4.63(1H,m), 7.06-7.23(3H,m), 7.39-7.76(7H,m), 8.59(1H,m), 8.68(2H,d,J=7 Hz)

[0471] Preparation 96

(1S)-(tert-Butoxy)-N-[1-[1-methyl-5-[4-(5-thiazolyl)phenyl]-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0472] The title compound was obtained from the compound of Preparation 28 and 5-(trimethylstannyl)thiazole in substantially the same manner as in Preparation 29.

[0473] MS(ES+): 462(M+H)

[0474] ^{1}H-NMR (300 MHz,$CDCl_3$)δ1.39(9H,s), 3.40-3.66(5H,m), 7.07(1H,s), 7.10-7.18(2H,m), 7.35(2H,d,J=8 Hz), 7.57(1H,m), 7.65(2H,d,J=8 Hz), 8.13(1H,s), 8.52(1H,m), 8.80(1H,s)

[0475] Preparation 97

(1S)-1-[1-Methyl-5-[4-(5-thiazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethylamine

[0476] The title compound was obtained from the compound of Preparation 96 in substantially the same manner as in Preparation 26.

[0477] MS(ES+): 362(M+H)

[0478] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.75(2H,br), 3.33(1H,m), 3.46(1H,m), 3.58(3H,s), 4.51(1H,br), 7.08(1H,s), 7.12-7.21(2H,m), 7.38(2H,d,J=8 Hz), 7.56-7.68(3H,m), 8.12(1H,s), 8.59(1H,m), 8.78(1H,s)

[0479] Preparation 98

(2S)-2-(tert-Butoxycarbonylamino)-N-[2-[4-(1-imidazolyl)phenyl]-2-oxoethyl]-3-(4-pyridyl)propionamide

[0480] The title compound was obtained from the compound of Preparation 13 in substantially the same manner as in Preparation 5.

[0481] amorphous solid

[0482] ESI-MS: 450(M+1)

[0483] ^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 3.00-3.37(2H,m), 4.58(1H,br s), 4.65-4.85(2H,m), 5.08(1H,d,J=6 Hz), 7.07(1H,br s), 7.18(2H,d,J=8 Hz), 7.38(1H,s), 7.55(2H,d,J=8 Hz), 7.98(1H,s), 8.10(2H,d,J=8 Hz), 8.55(2H,d,J=8 Hz)

[0484] Preparation 99

(1S)-(tert-Butoxy)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(4-pyridyl)ethyl]formamide

[0485] The title compound was obtained from the compound of Preparation 98 in substantially the same manner as in Preparation 6.

[0486] MS(m/z): 473(M^++H,bp)

[0487] ^{1}H-NMR ($CDCl_3$) δ0.94(3H,t,J=7 Hz), 1.40(9H,s), 3.19-3.25(2H,m), 3.31-3.50(2H,m), 5.12(1H,d,J=8 Hz), 5.28(1H,d,J=8 Hz), 7.07(1H,s), 7.10-7.18(2H,m), 7.32(1H,s), 7.37-7.50(4H,m), 7.91(2H,s), 8.45-8.60(3H,m)

[0488] Preparation 100

(1S)-1-[5-[4-(1-Imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(4-pyridyl)ethylamine

[0489] The title compound was obtained from the compound of Preparation 99 in substantially the same manner as in Preparation 26.

[0490] MS(m/z): 346(M^++H,bp)

[0491] ^{1}H-NMR ($CDCl_3$) δ0.69(3H,t,J=7 Hz), 1.30-1.50(2H,m), 3.23-3.42(2H,m), 3.55-3.65(1H,m), 3.75-3.84(1H,m), 4.28(1H,t,J=7 Hz), 7.10(3H,t,J=3 Hz), 7.25(1H,s), 7.33(1H,s), 7.45(4H,dd,J=7 Hz,7 Hz), 7.93(1H,s), 8.53(2H,d,J=3 Hz)

[0492] Preparation 101

(1S)-(tert-Butoxy)-N-[1-[1-ethyl-5-[4-(1-imidazolyl)phenyl]-imidazol-2-yl]-2-(4-pyridyl)ethyl]formamide

[0493] The title compound was obtained from the compound of Preparation 98 in substantially the same manner as in Preparation 6.

[0494] MS(m/z): 459(M^++H), 42(bp)

[0495] ^{1}H-NMR ($CDCl_3$) δ1.00(3H,t,J=7 Hz), 1.41(9H,s), 3.22-3.39(3H,m), 5.12(1H,d,J=8 Hz), 5.30(1H,d,J=8 Hz), 7.08(1H,s), 7.10-7.18(3H,m), 7.34(1H,s), 7.40-7.49(4H,m), 7.89-7.92(2H,m), 8.49-8.55(3H,m)

[0496] Preparation 102

(1S)-1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(4-pyridyl)ethylamine

[0497] The title compound was obtained from the compound of Preparation 101 in substantially the same manner as in Preparation 26.

[0498] MS(m/z): 359(M^++H,bp)

[0499] ^{1}H-NMR ($CDCl_3$) δ1.09(3H,t,J=7 Hz), 3.15-3.22(1H,m), 3.29-3.40(1H,m), 3.70-3.80(1H,m), 3.89-3.97(1H,m), 4.18(1H,d,J=7 Hz), 7.09(1H,s), 7.10(2H,d,J=7.5 Hz), 7.25(1H,s), 7.33(1H,d,J=3 Hz), 7.42-7.49(4H,m), 7.91(1H,d,J=3 Hz), 8.52(2H,d,J=7.5 Hz)

[0500] Preparation 103

(1S) -1-[5-(4-Bromophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)-ethylamine

[0501] The title compound was obtained from the compound of Preparation 28 in substantially the same manner as in Preparation 26.

[0502] MS(ESI)m/z: 357,359$(M+H)^+$

[0503] ^{1}H-NMR ($CDCl_3$,300 MHz) δ3.23-3.47(2H,m), 3.49(3H,s), 4.59(1H,t,J=7 Hz), 7.01(1H,s), 7.05-7.22(4H,m), 7.54(2H,d,J=8 Hz), 7.55-7.64(1H,m), 8.57(1H,d,J=5 Hz)

EXAMPLE 1

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholino-phenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0504] To a solution of (1S)-1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethylamine (120 mg), 5-chlorobenzo[b]furan-2-carboxylic acid (68.1 mg) and 1-hydroxybenzotriazole (49.1 mg) in N,N-dimethylformamide (2.0 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (69.6 mg). The mixture was stirred at ambient temperature for 2 hours and allowed to stand overnight. The resulting mixture was diluted with water (20 ml) and extracted with ethyl acetate (25 ml). The organic layer was extracted with 1N hydrochloric acid (15 ml) and the aqueous layer was basified with saturated aqueous sodium hydrogencarbonate solution, then extracted with ethyl acetate (20 ml). The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residual solid was treated with hot acetonitrile

(1.5 ml) and the mixture was cooled to ambient temperature. The solid was collected by filtration and washed with acetonitrile to give (1S)-(5-chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)-ethyl]formamide (89 mg) as off-white crystals.

[0505] mp 162-164° C.

[0506] ESI-MS: 542(M+)

[0507] ^{1}H-NMR (300MHz, DMSO-d6) δ3.11-3.17(4H, m), 3.42-3.60(2H,m), 3.53(3H,s), 3.70-3.77(4H,m), 5.83(1H,q,J=8 Hz), 6.88(1H,s), 6.99(2H,d,J=9 Hz), 7.18(1H,dd,J=5,8 Hz), 7.26(2H,d,J=9 Hz), 7.30(1H,d,J=8 Hz), 7.47(1H,d,J=8 Hz), 7.59(1H,s), 7.63(1H,d,J=8 Hz), 7.68(1H,d,J=8 Hz), 7.87(1H,s), 8.48(1H,d,J=5 Hz), 9.32(1H,d,J=8 Hz) $[\alpha]_D$=171.90 ($CHCl_3$, c=1.030%)

EXAMPLE 2

(1S)-(5-Bromobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0508] The title compound was obtained from the compound of Preparation 7 in substantially the same manner as in Example 1.

[0509] mp 173-174° C.

[0510] ESI-MS: 586.2(M+)

[0511] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.11-3.18(4H,m), 3.42-3.61(2H,m), 3.54(3H,s), 3.70-3.78(4H,m), 5.83(1H,q, J=8 Hz), 6.88(1H,s), 6.99(2H,d,J=9 Hz), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.26(2H,d,J=9 Hz), 7.30(1H,d,J=8 Hz), 7.57-7.68(4H,m), 8.02(1H,s), 8.48(1H,d,J=5 Hz), 9.32(1H,d,J=8 Hz)

EXAMPLE 3

(1S)-(5-Methoxybenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0512] The title compound was obtained from the compound of Preparation 7 in substantially the same manner as in Example 1.

[0513] mp 122-124° C.

[0514] ESI-MS: 538(M+H)

[0515] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.11-3.18(4H, m), 3.42-3.62(2H,m), 3.53(3H,s), 3.71-3.77(4H,m), 3.80(3H,s), 5.82(1H,q,J=8 Hz), 6.87(1H,s), 7.00(2H,d,J=9 Hz), 7.03(1H,d,J=8 Hz), 7.18(1H,dd,J=8 Hz), 7.26(2H,d,J=9 Hz), 7.27-7.33(2H,m), 7.52(1H,s), 7.53(1H,d,J=8 Hz), 7.65(1H,t,J=8 Hz), 8.49(1H,d,J=5 Hz), 9.17(1H,d,J=8 Hz)

EXAMPLE 4

(1S)-(5-Fluorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0516] The title compound was obtained from the compound of Preparation 7 in substantially the same manner as in Example 1.

[0517] mp 130-132° C.

[0518] ESI-MS: 526(M+H)

[0519] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.10-3.20(4H, m), 3.42-3.62(2H,m), 3.53(3H,s), 3.70-3.80(4H,m), 5.83(1H,q,J=8 Hz), 6.88(1H,s), 7.00(2H,d,J=9 Hz), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.23-7.38(4H,m), 7.57-7.73(4H,m), 8.49(1H,d,J=5 Hz), 9.29(1H,d,J=8 Hz)

EXAMPLE 5

(1S)-(5-Methylbenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0520] The title compound was obtained from the compound of Preparation 7 in substantially the same manner as in Example 1.

[0521] mp 125-127° C.

[0522] ESI-MS: 522(M+H)

[0523] ^{1}H-NMR (300 MHz,DMSO-d_6) δ2.40(3H,s), 3.11-3.18(4H,m), 3.48(1H,dd,J=15 Hz,J=8 Hz), 3.52-3.60(1H, m), 3.54(3H,s), 3.70-3.78(4H,m), 5.83(1H,q,J=8 Hz), 6.87(1H,s), 7.00(2H,d,J=9 Hz), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.23-7.32(4H,m), 7.49-7.56(3H,m), 7.56(1H,t,J=8 Hz), 8.48(1H,d,J=5 Hz), 9.17(1H,d,J=8 Hz)

EXAMPLE 6

(1S)-(5-Chlorobenzothiazol-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0524] The title compound was obtained from the compound of Preparation 7 in substantially the same manner as in Example 1.

[0525] mp 96-99° C.

[0526] MS(ES+): 559(M+)

[0527] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.18-3.21(4H,m), 3.50(3H,s), 3.56(2H,d,J=7 Hz), 3.85-3.86(4H,m), 5.93(1H, m), 6.93(2H,d,J=8 Hz), 6.98(1H,s), 7.09-7.15(2H,m), 7.20(2H,d,J=8 Hz), 7.45(1H,d,J=8 Hz), 7.53(1H,dd,J=8 Hz,J=8 Hz), 7.85(1H,d,J=8 Hz), 8.06(1H,s), 8.30(1H,d,J=8 Hz), 8.54(1H,d,J=5 Hz)

EXAMPLE 7

(1S)-(5-Chlorobenzo[b]thiophen-2-yl)-N-[1-[1-methyl-5-(4-morpholinophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0528] The title compound was obtained from the compound of Preparation 7 in substantially the same manner as in Example 1.

[0529] ESI-MS: 558.2(M+)

[0530] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.09-3.18(4H, m), 3.42-3.63(2H,m), 3.55(3H,s), 3.69-3.78(4H,m), 5.80(1H,q,J=8 Hz), 6.88(1H,s), 6.99(2H,d,J=9 Hz), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.25(2H,d,J=9 Hz), 7.31(1H,d, J=8 Hz), 7.47(1H,dd,J=8 Hz,J=2 Hz), 7.64(1H,t,J=8 Hz), 8.04(1H,d,J=8 Hz), 8.05(1H,s), 8.18(1H,s), 8.48(1H,d,J=5 Hz), 9.45(1H,d,J=8 Hz)

EXAMPLE 8

(1S)-N-[1-[5-(4-Biphenylyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)-ethyl](5-bromobenzo[b]furan-2-yl)formamide

[0531] The title compound was obtained from the compound of Preparation 10 in substantially the same manner as in Example 1.

[0532] mp 180.5-181.5° C.

[0533] MS(m/z): 577,579 (M^+),146(bp)

[0534] ^{1}H-NMR ($CDCl_3$) δ3.58(3H,s), 3.62(2H,d,J=7 Hz), 5.98(1H,q,J=7 Hz), 7.09(1H,s), 7.15(2H,d,J=7.5 Hz), 7.34-7.38(4H,m), 7.40-7.50(3H,m), 7.55(1H,d,J=7.5 Hz), 7.57-7.66(4H,m), 7.75(1H,d,J=7.5 Hz), 7.80(1H,s), 8.56(1H,d,J=7 Hz)

EXAMPLE 9

(1S)-N-[1-[5-(4-Biphenylyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)-ethyl](5-methoxybenzo[b]furan-2-yl)formamide

[0535] The title compound was obtained from the compound of Preparation 10 in substantially the same manner as in Example 1.

[0536] mp 150-152° C.

[0537] MS(m/z): 529(M^+,bp)

[0538] ^{1}H-NMR ($CDCl_3$) δ3.58(3H,s), 3.64(1H,d,J=7 Hz), 3.86(3Hs), 5.98(1H,q,J=7 Hz), 7.00-7.16(5H,m), 7.36-7.40(5H,m), 7.43-7.49(2H,m), 7.53-7.59(1H,m), 7.63(6H,t, J=7 Hz), 8.57(1H,d,J=7 Hz)

EXAMPLE 10

(1S)-N-[1-[5-(4-Biphenylyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)-ethyl](5-chlorobenzo[b]furan-2-yl)formamide

[0539] The title compound was obtained from the compound of Preparation 10 in substantially the same manner as in Example 1.

[0540] mp 171-174° C.

[0541] MS(m/z): 533(M^+,bp)

[0542] ^{1}H-NMR ($CDCl_3$) δ3.59(3H,s), 3.64(2H,d,J=7 Hz), 5.98(1H,q,J=7 Hz), 7.09(1H,s), 7.15(2H,d,J=7 Hz), 7.36-7.40(5H,m), 7.43-7.50(3H,m), 7.55-7.67(6H,m), 7.74(1H,d,J=7 Hz), 8.57(1H,d,J=7 Hz)

EXAMPLE 11

(1S)-(6-Chlorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0543] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0544] mp 165-169° C.

[0545] MS(m/z): 523(M^++H,bp)

[0546] ^{1}H-NMR ($CDCl_3$) δ3.60(3H,s), 3.64(2H,d,J=7 Hz), 5.98(1H,q,J=7 Hz), 7.09(1H,s), 7.13-7.18(2H,m), 7.24(1H,s), 7.30-7.32(2H,m), 7.40-7.48(5H,m), 7.53-7.60(3H,m), 7.75(1H,d,J=7 Hz), 7.90(1H,s), 8.57(1H,d,J=7 Hz)

EXAMPLE 12

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl] formamide

[0547] The title compound was obtained from the compound of Preparation 19 in substantially the same manner as in Example 1.

[0548] mp 199-201° C.

[0549] MS: 500(ES−)

[0550] ^{1}H-NMR (DMSO-d_6) δ3.50(1H,dd,J=15 Hz,J=7.5 Hz), 3.60(1H,dd,J=15 Hz,J=7.5 Hz), 3.70(3H,s), 5.88(1H, dd,J=15 Hz,J=7.5 Hz), 7.16-7.34(2H,m), 7.46-7.73(4H,m), 7.75(2H,d,J=9 Hz), 7.89(1H,m), 8.28(2H,d,J=9 Hz), 8.50(1H,d,J=6 Hz), 9.41(1H,d,J=9 Hz)

EXAMPLE 13

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(1-pyrrolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0551] A solution of (1S)-N-[1-[5-(4-aminophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-chlorobenzo[b]furan-2-yl)formamide (220 mg) and 2,5-dimethoxytetrahydrofuran (67.8 mg) in glacial acetic acid (1 ml) was heated at 95° C. for 2 hours. The acetic acid was removed by vacuum distillation, and the residue was diluted with ethyl acetate and washed with saturated aqueous sodium hydrogencarbonate solution and brine. The organic layer was dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (2% methanol in chloroform) to give (1S)-(5-chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(1-pyrrolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)-ethyl] formamide (111 mg) as a brown amorphous solid.

[0552] MS(ES+): 522(M+H)

[0553] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.54-3.68(5H,m), 5.99(1H,m), 6.36(2H,m), 7.04(1H,s), 7.08-7.18(4H,m), 7.30-7.40(4H,m), 7.40-7.48(3H,m), 7.56(1H,m), 7.61(1H, s), 7.91(1H,d,J=8 Hz), 8.56(1H,m)

EXAMPLE 14

(1S)-(Indol-2-yl)-N-[1-[1-methyl-5-[4-(2-methylimidazol-1-yl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0554] The title compound was obtained from the compound of Preparation 26 in substantially the same manner as in Example 1.

[0555] mp 207-211° C.

[0556] MS(m/z): 500(M^+−H,bp)

[0557] ^{1}H-NMR (DMSO-d_6) δ2.32(3H,s), 3.46-3.64(2H, m), 3.70(3H,s), 5.92(1H,q,J=7 Hz), 6.92(1H,s), 7.01(1H,t,

J=7.5 Hz), 7.10(1H,s), 7.14-7.21(2H,m), 7.27(1H,s), 7.33-7.40(3H,m), 7.50-7.69(7H,m), 8.49(1H,d,J=7 Hz), 9.07(1H, d,J=7.5 Hz)

EXAMPLE 15

(1S)-(Benzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(2-methylimidazol-1-yl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0558] The title compound was obtained from the compound of Preparation 26 in substantially the same manner as in Example 1.

[0559] mp 167-171° C.

[0560] MS(m/z): 503(M^++H,bp)

[0561] ^{1}H-NMR (DMSO-d_6) 6 2.41(3H,s), 3.60-3.65(5H, m), 5.99(1H,q,J=7 Hz), 7.04(2H,d,J=7 Hz), 7.10(1H,s), 7.12-7.19(2H,m), 7.29-7.45(7H,m), 7.51-7.60(2H,m), 7.66(1H,d,J=7.5 Hz), 7.71(1H,d,J=7.5 Hz), 8.56(1H,d,J=7 Hz)

EXAMPLE 16

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[5-[4-(2-furyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0562] The title compound was obtained from the compound of Preparation 30 in substantially the same manner as in Example 1.

[0563] mp 144-146° C.

[0564] MS(ES+): 523(M+H)

[0565] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.56(3H,s), 3.61(2H, d,J=8 Hz), 5.96(1H,dd,J=8 Hz,J=8 Hz), 6.49(1H,m), 6.69(1H,m), 7.06(1H,s), 7.09-7.17(2H,m), 7.27-7.40(4H, m), 7.41-7.51(2H,m), 7.55(1H,m), 7.62(1H,m), 7.66-7.76(3H,m), 8.55(1H,m)

EXAMPLE 17

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(2-thienyl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0566] The title compound was obtained from the compound of Preparation 32 in substantially the same manner as in Example 1.

[0567] mp 110-114° C.

[0568] MS(ES+): 539(M+)

[0569] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.50-3.66(5H,m), 5.88-6.02(1H,m), 7.00-7.19(5H,m), 7.27-7.47(5H,m), 7.49-7.59(2H,m), 7.59-7.68(2H,m), 7.71-7.80(1H,m), 8.51-8.58(1H,m)

EXAMPLE 18

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(2-thiazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0570] The title compound was obtained from the compound of Preparation 34 in substantially the same manner as in Example 1.

[0571] mp 144-146° C.

[0572] MS(ES+): 540(M+)

[0573] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.54-3.69(5H,m), 5.97(1H,dd,J=15 Hz,J=7 Hz), 7.06-7.18(3H,m), 7.31-7.48(6H,m), 7.50-7.66(2H,m), 7.74(1H,d,J=8 Hz), 7.89(1H, d,J=4 Hz), 8.00(2H,d,J=8 Hz), 8.55(1H,m)

EXAMPLE 19

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[5-(3-fluoro-4-morpholinophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0574] The title compound was obtained from the compound of Preparation 41 in substantially the same manner as in Example 1.

[0575] mp 134-135° C.

[0576] MS: 560(ES+)

[0577] ^{1}H-NMR (DMSO-d_6) δ3.00-3.06(4H,m), 3.37-3.55(2H,m), 3.58(3H,s), 3.70-3.77(4H,m), 5.78-5.86(1H, m), 6.96-7.88(10H,m), 8.48(1H,d,J=4.5 Hz), 9.33(1H,d,J=9 Hz)

EXAMPLE 20

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(2-thienyl)-imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0578] The title compound was obtained from the compound of Preparation 47 in substantially the same manner as in Example 1.

[0579] mp 70-74° C.

[0580] MS(m/z): 463(M^++H,bp)

[0581] ^{1}H-NMR ($CDCl_3$) δ3.56(3H,s), 3.58-3.60(2H,m), 5.95(1H,q,J=7.5 Hz), 7.00(1H,d,J=2 Hz), 7.05-7.14(4H,m), 7.33-7.39(3H,m), 7.42-7.45(1H,m), 7.55(1H,ddd,J=7 Hz,J=7 Hz,J=2 Hz), 7.62(1H,d,J=2 Hz), 7.76(1H,d,J=8 Hz), 8.54(1H,d,J=6 Hz)

EXAMPLE 21

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[5-(2,4-dichlorophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0582] The title compound was obtained from the compound of Preparation 53 in substantially the same manner as in Example 1.

[0583] mp 181-183° C.

[0584] MS(m/z): 525,527,529(M^+), 100(bp)

[0585] ^{1}H-NMR ($CDCl_3$) δ3.32(3H,s), 3.59(2H,ABX,J=15 Hz,J=15 Hz,J=7 Hz), 5.91(1H,q,J=7 Hz), 6.98(1H,s), 7.08-7.13(2H,m), 7.18(1H,d,J=7.5 Hz), 7.27-7.30(1H,m), 7.35-7.39(2H,m), 7.44-7.47(2H,m), 7.53(1H,ddd,J=7.5 Hz,J=7.5 Hz,J=2 Hz), 7.63(1H,d,J=2 Hz), 7.70(1H,d,J=7.5 Hz), 8.52(1H,d,J=5 Hz)

EXAMPLE 22

(1S)-(Indol-2-yl)-N-[1-[5-[4-(1-methylimidazol-2-yl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0586] The title compound was obtained from the compound of Preparation 63 in substantially the same manner as in Example 1.

[0587] mp 218-222° C.

[0588] ESI-MS(M+1): 502

[0589] ^{1}H-NMR (DMSO-d_6) δ3.45-3.65(2H,m), 3.70(3H, s), 3.77(3H,s), 5.91(1H,q,J=6 Hz), 7.00(1H,s), 7.03(1H,d, J=8 Hz), 7.10(1H,s), 7.13-7.20(2H,m), 7.24-7.29(2H,m), 7.30-7.40(2H,m), 7.53(2H,d,J=8 Hz), 7.57-7.67(2H,m), 7.78(2H,d,J=8 Hz), 8.50(1H,d,J=4 Hz), 9.07(1H,d,J=8 Hz)

EXAMPLE 23

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1,4-dimethylimidazol-2-yl]-2-(2-pyridyl)ethyl](indol-2-yl)formamide

[0590] The title compound was obtained from the compound of Preparation 70 in substantially the same manner as in Example 1.

[0591] mp 156-157° C.

[0592] ESI-MS(M+1): 502

[0593] ^{1}H-NMR ($CDCl_3$) δ2.20(3H,s), 3.48(3H,s), 3.64(2H,t,J=6 Hz), 6.00(1H,q,J=6 Hz), 7.03(1H,s), 7.08-7.18(3H,m), 7.23(1H,s), 7.28-7.42(5H,m), 7.48(2H,d,J=8 Hz), 7.52-7.60(2H,m), 7.66(1H,d,J=8 Hz), 7.81(1H,d,J=8 Hz), 7.92(1H,s), 8.55(1H,d,J=4 Hz), 9.52(1H,s)

EXAMPLE 24

(1S)-(5-Formylbenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0594] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0595] mp 194-197° C.

[0596] ESI-MS(M+1): 517

[0597] ^{1}H-NMR ($CDCl_3$) δ3.53-3.70(5H,m), 5.98(1H,q, J=6 Hz), 7.08(1H,s), 7.12-7.20(2H,m), 7.25(1H,s), 7.31(1H, s), 7.36-7.50(4H,m), 7.52-7.63(2H,m), 7.67(1H,d,J=8 Hz), 7.83(1H,d,J=8 Hz), 7.90(1H,s), 8.00(1H,dd,J=8 Hz,J=2 Hz), 8.22(1H,s), 8.56(1H,d,J=4 Hz)

EXAMPLE 25

(1S)-(5-Cyanobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0598] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0599] mp 174-176° C.

[0600] ESI-MS(M+1): 514

[0601] ^{1}H-NMR ($CDCl_3$) δ3.55-3.70(5H,m), 5.98(1H,q, J=6 Hz), 7.09(1H,s), 7.11-7.20(2H,m), 7.24(1H,s), 7.33(1H, s), 7.37-7.50(4H,m), 7.58(1H,dd,J=8 Hz,J=2 Hz), 7.63(1H, d,J=8 Hz), 7.72(1H,dd,J=8 Hz,J=2 Hz), 7.85-7.95(2H,m), 8.04(1H,s), 8.57(1H,d,J=4 Hz)

EXAMPLE 26

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl][]5-(trifluoromethyl-)benzo[b]furan-2-yl]formamide

[0602] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0603] mp 150-151° C.

[0604] MS(m/z): 557(M^++H,bp)

[0605] ^{1}H-NMR ($CDCl_3$) δ3.60(3H,s), 3.62-3.65(3H,m), 5.99(1H,q,J=7 Hz), 7.10(1H,s), 7.16(2H,d,J=7 Hz), 7.24(1H,d,J=7 Hz), 7.31(1H,s), 7.40-7.50(5H,m), 7.55-7.65(3H,m), 7.88(1H,s), 7.98(1H,s), 8.56(1H,d,J=7 Hz)

EXAMPLE 27

(1S)-(Furo[2,3-b]pyridin-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0606] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0607] mp 108-110° C.

[0608] MS(m/z): 490(M^++H,bp)

[0609] ^{1}H-NMR ($CDCl_3$) δ3.60(3H,s), 3.61-6.35(2H,m), 6.00(1H,q,J=7 Hz), 7.09(1H,s), 7.10-7.19(2H,m), 7.23(1H, s), 7.28-7.33(2H,m), 7.40-7.47(5H,m), 7.57(1H,ddd,J=7 Hz,J=7 Hz,J=2 Hz), 7.80(1H,d,J=7 Hz), 7.90(1H,s), 8.03(1H,dd,J=7 Hz,J=2 Hz), 8.45(1H,dd,J=7 Hz,J=2 Hz), 8.56(1H,d,J=7 Hz)

EXAMPLE 28

(1S) -N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-nitrofuro[2,3-b]pyridin-2-yl)formamide

[0610] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1

[0611] mp 11 4-118° C.

[0612] MS(m/z): 535(M^++H,bp)

[0613] ^{1}H-NMR ($CDCl_3$) δ3.60(3H,s), 3.61-3.64(2H,m), 5.98(1H,q,J=7 Hz), 7.06(1H,s), 7.10-7.19(2H,m), 7.24(1H, s), 7.30(1H,s), 7.40-7.47(4H,m), 7.55-7.61(2H,m), 7.90(1H, s), 8.04(1H,d,J=7 Hz), 8.56(1H,d,J=3 Hz), 8.88(1H,d,J=3 Hz), 9.35(1H,d,J=3 Hz)

EXAMPLE 29

(1S)-N-[1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl][5-(trifluoromethyl-)benzo[b]furan-2-yl]formamide

[0614] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0615] mp 85-89° C.

[0616] MS(m/z): 569(M^+−H,bp)

[0617] ^{1}H-NMR ($CDCl_3$) δ1.18(3H,t,J=7 Hz), 3.55-3.68(2H,m), 3.92-4.04(iH,m), 4.09-4.20(1H,m), 5.99(1H,q, J=7 Hz), 7.08(1H,s), 7.12(1H,s), 7.22-7.28(3H,m), 7.30(1H, s), 7.40-7.48(4H,m), 7.53-7.72(4H,m), 7.90(1H,s), 7.97(1H, s), 8.56(1H,d,J-3 Hz)

EXAMPLE 30

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl][5-(trifluoromethyl-)benzo[b]furan-2-yl]formamide

[0618] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0619] mp 92-98° C.

[0620] MS(m/z): 585(M^++H,bp)

[0621] ^{1}H-NMR ($CDCl_3$) δ0.76(3H,t,J=7 Hz), 1.40-1.60(2H,m), 3.63(2H,d,J=7 Hz), 3.82-3.92(1H,m), 4.00-4.11(1H,m), 5.97(1H,q,J=7 Hz), 7.08(1H,s), 7.13-7.17(2H, m), 7.24(1H,s), 7.33(1H,s), 7.40-7.49(4H,m), 7.50(1H,s), 7.54-7.76(4H,m), 7.90(1H,s), 7.98(1H,s), 8.55-8.59(1H,m)

EXAMPLE 31

(1S)-N-[1-[5-[4-(1-Benzimidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](indol-2-yl)formamide

[0622] The title compound was obtained from the compound of Preparation 79 in substantially the same manner as in Example 1.

[0623] mp 233-237° C.

[0624] MS(m/z): 538(M^++H,bp)

[0625] ^{1}H-NMR (DMSO-d_6) δ3.58-3.71(2H,m), 3.65(3H, s), 6.04(1H,q,J=7.5 Hz), 7.00(1H,s), 7.12(1H,s), 7.14-7.19(3H,m), 7.29(1H,m), 7.35-7.43(3H,m), 7.50-7.60(6H, m), 7.68(1H,d,J=7.5 Hz), 7.81(1H,d,J=7.5H7.5 Hz), 7.88-7.91(1H,m), 8.15(1H,s), 8.58(1H,d,J=7 Hz), 9.45(1H,s)

EXAMPLE 32

(1S)-N-[1-[5-[4-(1-Benzimidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](benzo[b]furan-2-yl)formamide

[0626] The title compound was obtained from the compound of Preparation 79 in substantially the same manner as in Example 1.

[0627] mp 152-155° C.

[0628] MS(m/z): 539(M^++H),100(bp)

[0629] ^{1}H-NMR (DMSO-d_6) δ3.64(3H,s), 3.67(2H,d,J=7 Hz), 6.03(1H,q,J=7 Hz), 7.12(1H,s), 7.12-7.17(1H,m), 7.19(1H,d,J=7.5 Hz), 7.31(1H,d,J=7.5 Hz), 7.35-7.45(4H, m), 7.50-7.60(7H,m), 7.68(1H,d,J=7.5 Hz), 7.74(1H,d,J=7.5 Hz), 7.88-7.91(1H,m), 8.15(1H,s), 8.57(1H,d,J=7 Hz)

EXAMPLE 33

(1S)-N-[1-[5-[4-(2-Ethylimidazol-1-yl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](indol-2-yl)formamide

[0630] The title compound was obtained from the compound of Preparation 84 in substantially the same manner as in Example 1.

[0631] MS(ES+): 516(M^+H)

[0632] ^{1}H-NMR (300 MHz,$CDCl_3$) δ1.28(3H,t,J=7 Hz), 2.69(2H,q,J=7 Hz), 3.60(3H,s), 3.62-3.67(2H,m), 6.09(1H, m), 6.99(1H,s), 7.02-7.18(5H,m), 7.19-7.46(6H,m), 7.50(1H,m), 7.64(1H,d,J=8 Hz), 8.14(1H,d,J=8 Hz), 8.52(1H,m)

EXAMPLE 34

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(3-pyridyl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0633] The title compound was obtained from the compound of Preparation 91 in substantially the same manner as in Example 1.

[0634] mp 158-160° C.

[0635] MS(ES−): 532(M−H)

[0636] ^{1}H-NMR (300 MHz,$CDCl_3$) 6 3.53-3.70(5H,m), 5.97(1H,m), 7.04-7.19(3H,m), 7.31-7.50(6H,m), 7.52-7.69(4H,m), 7.75(1H,d,J=8 Hz), 7.89(1H,m), 8.54(1H,m), 8.61(1H,m), 8.88(1H,m)

EXAMPLE 35

(1S)-(5-Bromobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(3-pyridyl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0637] The title compound was obtained from the compound of Preparation 91 in substantially the same manner as in Example 1.

[0638] mp 168-171° C.

[0639] MS(ES+): 578(M^+H)

[0640] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.56-3.66(5H,m), 5.98(1H,m), 7.09(1H,s), 7.10-7.17(2H,m), 7.34-7.46(5H, m), 7.47-7.60(2H,m), 7.64(2H,d,J=8 Hz), 7.75(1H,d,J=8 Hz), 7.79(1H,s), 7.89(1H,m), 8.56(1H,m), 8.62(1H,m), 8.87(1H,m)

EXAMPLE 36

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(2-pyridyl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0641] The title compound was obtained from the compound of Preparation 93 in substantially the same manner as in Example 1.

[0642] mp 175-180° C.

[0643] MS(ES+): 534(M^+H) ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.51-3.70(5H,m), 5.91-6.04(1H,m), 7.06-7.20(3H,m), 7.32-7.50(5H,m), 7.52-7.84(5H,m), 8.04(2H,d,J=8 Hz), 8.57(1H,m), 8.70(1H,m)

EXAMPLE 37

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(4-pyridyl)-phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0644] The title compound was obtained from the compound of Preparation 95 in substantially the same manner as in Example 1.

[0645] mp 135-140° C.

[0646] MS(ES+): 534(M^+H)

[0647] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.57-3.66(5H,m), 5.98(1H,m), 7.06-7.18(3H,m), 7.33-7.47(5H,m), 7.49-7.73(5H,m), 7.78(1H,d,J=8 Hz), 8.56(1H,m), 8.68(2H,d,J=7 Hz)

EXAMPLE 38

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-[4-(5-thiazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0648] The title compound was obtained from the compound of Preparation 97 in substantially the same manner as in Example 1.

[0649] mp 165-167° C.

[0650] MS(ES+): 540(M^+H)

[0651] ^{1}H-NMR (300 MHz,$CDCl_3$) δ3.57(3H,s), 3.62(2H,m), 5.97(1H,m), 7.08(1H,s), 7.10-7.17(2H,m), 7.32-7.40(4H,m), 7.45(1H,d,J=9 Hz), 7.56(1H,m), 7.60-7.66(3H,m), 7.74(1H,d,J=9 Hz), 8.11(1H,s), 8.56(1H,m), 8.79(1H,s)

EXAMPLE 39

(1S)-N-[1-[1-Methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)-ethyl][5-(trifluoromethyl)benzo[b]furan-2-yl]formamide

[0652] The title compound was obtained from the compound of Preparation 19 in substantially the same manner as in Example 1.

[0653] mp 192-194° C.

[0654] MS: 536(ES+)

[0655] ^{1}H-NMR (DMSO-d_6) δ3.51(1H,dd,J=15 Hz,J=7.5 Hz), 3.61(1H,dd,J=15 Hz,J=7.5 Hz), 3.72(3H,s), 5.90(1H,dd,J=15 Hz,J=7.5 Hz), 7.16-7.35(2H,m), 7.53-7.90(6H,m), 8.25(1H,s), 8.28(2H,d,J=9 Hz), 8.50(1H,d,J=6 Hz), 9.50(1H,d,J=9 Hz)

EXAMPLE 40

(1S)-N-[1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl](5-formylbenzo[b]furan-2-yl)formamide

[0656] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0657] ESI-MS: 531(M+H)

[0658] ^{1}H-NMR (300 MHz,DMSO-d_6) δ1.08(3H,t,J=8 Hz), 3.52(1H,dd,J=15 Hz,J=8 Hz), 3.58(1H,dd,J=15 Hz,J=7 Hz), 4.06(1H,quintet,J=8 Hz), 4.10(1H,quintet,J=8 Hz), 5.90(1H,q,J=8 Hz), 7.04(1H,s), 7.13(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.33(1H,d,J=8 Hz), 7.55(2H,d,J=9 Hz), 7.66(1H,t,J=8 Hz), 7.73(2H,d,J=9 Hz), 7.78-7.88(3H,m), 7.98(1H,d,J=8 Hz), 8.32(1H,s), 8.39(1H,s), 8.50(1H,d,J=5 Hz), 9.48(1H,d,J=8 Hz)

EXAMPLE 41

(1S)-(5-Cyanobenzo[b]furan-2-yl)-N-[1-[1-ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0659] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0660] ESI-MS: 526(M−H)

[0661] ^{1}H-NMR (300MHz,DMSO-d_6) δ1.07(3H,t,J=8 Hz), 3.50(1H,dd,J=15 Hz,J=8 Hz), 3.58(1H,dd,J=15 Hz,J=7 Hz), 3.98-4.28(2H,m), 5.88(1H,q,J=8 Hz), 7.04(1H,s), 7.13(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.32(1H,d,J=8 Hz), 7.56(2H,d,J=9 Hz), 7.66(1H,t,J=8 Hz), 7.70-7.78(3H,m), 7.80(1H,s), 7.89(2H,s), 8.32(1H,s), 8.37(1H,s), 8.50(1H,d,J=5 Hz), 9.53(1H,d,J=8 Hz)

EXAMPLE 42

(1S)-(5-Formylbenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0662] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0663] ESI-MS: 545(M+H)

[0664] ^{1}H-NMR (300 MHz,DMSO-d_6) δ0.64(3H,t,J=8 Hz), 1.35-1.52(2H,m), 3.53(1H,dd,J=15 Hz,J=8 Hz), 3.61(1H,dd,J=15 Hz,J=7 Hz), 3.99(1H,quintet,J=8 Hz), 4.14(1H,quintet,J=8 Hz), 5.92(1H,q,J=8 Hz), 7.04(1H,s), 7.13(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.32(1H,d,J=8 Hz), 7.57(2H,d,J=9 Hz), 7.66(1H,t,J=8 Hz), 7.73(2H,d,J=9 Hz), 7.78-7.90(3H,m), 8.00(1H,d,J=8 Hz), 8.33(1H,s), 8.40(1H,s), 8.50(1H,d,J=5 Hz), 9.48(1H,d,J=8 Hz)

EXAMPLE 43

(1S)-(5-Cyanobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0665] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0666] ESI-MS: 540(M−H)

[0667] ^{1}H-NMR (300 MHz,DMSO-d_6) δ0.63(3H,t,J=8 Hz), 1.34-1.52(2H,m), 3.52(1H,dd,J=15 Hz,J=8 Hz), 3.60(1H,dd,J=15 Hz,J=7 Hz), 3.99(1H,quintet,J=8 Hz), 4.13(1H,quintet,J=8 Hz), 5.90(1H,q,J=8 Hz), 7.04(1H,s), 7.13(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.32(1H,d,J=8 Hz), 7.53(2H,d,J=9 Hz), 7.66(1H,t,J=8 Hz), 7.70-7.78(3H,m), 7.82(1H,s), 7.88(2H,s), 8.32(1H,s), 8.37(1H,s), 8.48(1H,d,J=5 Hz), 9.52(1H,d,J=8 Hz)

EXAMPLE 44

(1S)-(5-Bromobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0668] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0669] mp 93-99° C.

[0670] MS(m/z): 595,597(M^+,bp)

[0671] ^{1}H-NMR ($CDCl_3$) δ0.71(3H,t,J=7 Hz), 1.40-1.60(2H,m), 3.60(2H,d,J=7 Hz), 3.80-3.90(1H,m), 3.98-4.08(1H,m), 5.95(1H,q,J=7 Hz), 7.08(1H,s), 7.10-7.15(2H,m), 7.24(1H,s), 7.31(1H,s), 7.35-7.45(6H,m), 7.50-7.60(2H,m), 7.64(1H,d,J=7.5 Hz), 7.80(1H,d,J=3 Hz), 7.90(1H,s), 8.56(1H,d,J=3 Hz)

EXAMPLE 45

(1S)-(Benzo[b]thiophen-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0672] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0673] mp 190-193° C.

[0674] ESI-MS: 505(M+1)

[0675] ^{1}H-NMR ($CDCl_3$) δ3.50-3.70(5H,m), 5.91(1H,q,J=6 Hz), 7.06(1H,s) 7.10-7.22(2H,m), 7.24(1H,s), 7.32(1H,s), 7.35-7.50(5H,m), 7.59(1H,dt,J=8 Hz,2 Hz), 7.75(1H,d,J=8 Hz), 7.78-7.87(2H,m), 7.90(1H,s), 8.55(1H,d,J=4 Hz)

EXAMPLE 46

(1S)-(5-Bromobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0676] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0677] mp 197-199° C.

[0678] ESI-MS: 567(M+1)

[0679] ^{1}H-NMR ($CDCl_3$) δ3.58,3.62(2H,d,J=6 Hz), 5.98(1H,q,J=6 Hz), 7.08(1H,s), 7.12-7.18(2H,m), 7.24(1H,s), 7.32(1H,s), 7.37(1H,s), 7.38-7.49(5H,m), 7.51-7.63(2H,m), 7.75(2H,d,J=8 Hz), 7.80(1H,s), 7.90(1H,s), 8.56(1H,d,J=4 Hz)

EXAMPLE 47

(1S) -N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-nitrobenzo[b]thiophen-2-yl)formamide

[0680] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0681] mp 228-231° C.

[0682] ESI-MS: 550(M+1)

[0683] ^{1}H-NMR ($CDCl_3$) δ3.55-3.80(5H,m), 5.90(1H,q,J=8 Hz), 7.05(1H,s), 7.13-7.22(2H,m), 7.24(1H,s), 7.31(1H,s), 7.40-7.54(5H,m), 7.62(1H,dt,J=8 Hz,2 Hz), 7.85(1H,s), 7.87-8.00(2H,m), 8.25(1H,dd,J=8 Hz,2 Hz), 8.50-8.62(2H,m), 8.65(1H,d,J=2 Hz)

EXAMPLE 48

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0684] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0685] mp 173-175° C.

[0686] ESI-MS: 551(M+1)

[0687] ^{1}H-NMR ($CDCl_3$) 6 0.73(3H,t,J=6 Hz), 1.38-1.60(2H,m), 3.62(2H,d,J=6 Hz), 3.77-4.17(2H,m), 5.95(1H,q,J=6 Hz), 7.04(1H,s), 7.08-7.17(2H,m), 7.23(1H,s), 7.32(1H,s), 7.35-7.50(8H,m), 7.55(1H,dt,J=8 Hz,2 Hz), 7.60-7.67(2H,m), 7.95(1H,s), 8.56(1H,d,J=4 Hz)

EXAMPLE 49

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0688] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0689] mp 63-73° C.

[0690] ESI-MS: 523(M+1)

[0691] ^{1}H-NMR ($CDCl_3$) δ3.61(3H,s), 3.62-3.70(2H,m), 6.00(1H,q,J=8 Hz), 7.08(IH,s), 7.12-7.20(2H,m), 7.25(1H,s), 7.30(1H,s), 7.35-7.50(6H,m), 7.57(1H,t,J=8 Hz), 7.64(1H,s), 7.83(1H,d,J=8 Hz), 7.88(1H,s), 8.56(1H,d,J=4 Hz)

EXAMPLE 50

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-nitrobenzo[b]furan-2-yl)formamide

[0692] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0693] mp 221-223° C.

[0694] ESI-MS: 534(M+1)

[0695] ^{1}H-NMR ($CDCl_3$) δ3.60(3H,s), 3.61-3.66(2H,m), 5.99(1H,q,J=8 Hz), 7.08(1H,s), 7.10-7.20(2H,m), 7.24(1H,s), 7.32(1H,s), 7.35-7.50(4H,m), 7.57(1H,s), 7.58-7.68(2H,m), 7.85-7.94(2H,m), 8.36(1H,dd,J=8 Hz,2 Hz), 8.58(1H,d,J=6 Hz), 8.62(1H,d,J=3 Hz)

EXAMPLE 51

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-methoxybenzo[b]furan-2-yl)formamide

[0696] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0697] mp 151-153° C. ESI-MS: 519(M+1)

[0698] ^{1}H-NMR ($CDCl_3$) δ3.55-3.65(2H,m), 3.60(3H,s), 3.85(3H,s), 5.99(1H,q,J=8 Hz), 7.00-7.09(3H,m), 7.11-7.20(2H,m), 7.25(1H,s), 7.32(1H,s), 7.36-7.48(5H,m), 7.53-7.61(1H,m), 7.63(1H,d,J=8 Hz), 7.90(1H,s), 8.57(1H,d,J=6 Hz)

EXAMPLE 52

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(4-pyridyl)ethyl](indol-2-yl) formamide

[0699] The title compound was obtained from the compound of Preparation 100 in substantially the same manner as in Example 1.

[0700] mp 238-240° C.(decomposition)

[0701] MS(m/z): 516 (M^++H,bp)

[0702] ^{1}H-NMR ($CDCl_3$) δ0.65(3H,t,J=7 Hz), 1.26-1.43(2H,m), 3.42-3.50(2H,m), 3.54-3.67(1H,m), 3.78-3.90(1H,m), 5.70(1H,q,J=7 Hz), 7.01(1H,d,J=2 Hz), 7.09-7.11(3H,m), 7.16(1H,t,J=7 Hz), 7.24-7.33(3H,m), 7.38-7.48(5H,m), 7.68(1H,d,J=8 Hz), 7.91(1H,s), 8.03(1H,s), 8.47-8.50(2H,m), 9.43(1H,s)

EXAMPLE 53

(1S) -N-[1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(4-pyridyl)ethyl](indol-2-yl)formamide

[0703] The title compound was obtained from the compound of Preparation 102 in substantially the same manner as in Example 1.

[0704] mp 255-260° C.(decomposition)

[0705] MS(m/z): 502(M^++H,bp)

[0706] ^{1}H-NMR ($CDCl_3$-CD_3OD) δ1.02(3H,t,J=7 Hz), 3.43(2H,q,J=7 Hz), 3.78-3.86(1H,m), 4.03-4.13(1H,m), 5.68(1H,t,J=7 Hz), 7.09(1H,s), 7.14(1H,t,J=7 Hz), 7.17-7.21(3H,m), 7.29(1H,t,J=7 Hz), 7.36(1H,s), 7.41-7.51(5H,m), 7.68(1H,d,J=7 Hz), 7.94(1H,s), 8.43(2H,d,J=7 Hz)

EXAMPLE 54

(1S)-(5-Fluorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0707] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0708] mp 180-182° C.

[0709] MS(m/z): 507(M^++H,bp)

[0710] ^{1}H-NMR ($CDCl_3$) δ3.59(3H,s), 3.61-3.65(3H,m), 5.98(1H,q,J=7 Hz), 7.07(1H,s), 7.10-7.19(2H,m), 7.24(1H,s), 7.28-7.31(2H,m), 7.40-7.50(6H,m), 7.56(1H,t,J=7.5 Hz), 7.70(1H,d,J=7.5 Hz), 7.90(1H,s), 8.55(1H,d,J=7 Hz)

EXAMPLE 55

(1S)-N-[1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl](5-fluorobenzo[b]furan-2-yl)formamide

[0711] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0712] mp 80-84° C.

[0713] MS(m/z): 521(M^++H,bp)

[0714] ^{1}H-NMR ($CDCl_3$) δ1.16(3H,t,J=7 Hz), 3.63(2H,heptet,J=7 Hz), 3.91-4.05(1H,m), 4.08-4.20(1H,m), 5.99(1H,q,J=7 Hz), 7.06(1H,s), 7.12-7.19(3H,m), 7.22-7.28(3H,m), 7.30(1H,s), 7.40(1H,s), 7.42-7.48(4H,m), 7.52-7.64(2H,m), 7.90(1H,s), 8.55(1H,d,J=7 Hz)

EXAMPLE 56

(1S)-(5-Fluorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)-phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0715] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0716] mp 77-81° C.

[0717] MS(m/z): 535(M^++H,bp)

[0718] ^{1}H-NMR ($CDCl_3$) δ0.74(3H,t,J=7 Hz), 1.40-1.60(2H,m), 3.62(2H,d,J=7 Hz), 3.80-3.91(1H,m), 3.98-4.08(1H,m), 5.96(1H,q,J=7 Hz), 7.06(1H,s), 7.12-7.19(3H,m), 7.24(1H,s), 7.29-7.33(2H,m), 7.35-7.45(6H,m), 7.54-7.59(1H,m), 7.64(1H,d,J=7.5 Hz), 7.90(1H,s), 8.56(1H,d,J=3 Hz)

EXAMPLE 57

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-nitrobenzo[b]furan-2-yl)formamide

[0719] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0720] MS(ES+): 562(M+H)

[0721] ^{1}H-NMR (300 MHz,$CDCl_3$) δ0.75(3H,t,J=7 Hz), 1.36-1.66(2H,m), 3.61(2H,d,J=7 Hz), 3.78-3.95(1H,m), 3.96-4.13(1H,m), 5.96(1H,m), 7.04(1H,s), 7.10-7.20(2H,m), 7.23(1H,s), 7.31(1H,s), 7.35-7.51(4H,m), 7.51-7.70(3H,m), 7.84(1H,d,J=8 Hz), 7.90(1H,s), 8.35(1H,m), 8.52-8.69(2H,m)

EXAMPLE 58

(1S)-N-[1-[5-[4-(1-Imidazolyl)phenyl]-1-propylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-methoxybenzo[b]furan-2-yl)formamide

[0722] The title compound was obtained from the compound of Preparation 74 in substantially the same manner as in Example 1.

[0723] MS(ES+): 547(M+H)

[0724] ^{1}H-NMR (300 MHz,$CDCl_3$) δ0.73(3H,t,J=7 Hz), 1.38-1.60(2H,m), 3.54-3.71(2H,m), 3.77-3.95(4H,m), 3.97-4.12(1H,m), 5.96(1H,dd,J=8 Hz,8 Hz), 6.98-7.19(5H,m), 7.23(1H,s), 7.32(1H,s), 7.33-7.66(8H,m), 7.90(1H,s), 8.55(1H,m)

EXAMPLE 59

(1S)-N-[1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl](5-nitrobenzo[b]furan-2-yl)formamide trihydrochloride

[0725] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0726] mp 190-200° C.

[0727] MS: 548(ES+)

[0728] ^{1}H-NMR (DMSO-d_6) δ1.12(3H,m), 4.02(3H,s), 4.35(2H,m), 4.37(2H,m), 6.13(1H,m), 7.63-8.45(13H,m), 8.73(1H,s), 8.80(1H,s), 9.88(1H,s)

EXAMPLE 60

(1S)-N-[1-[1-Ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl)ethyl](5-methoxybenzo[b]furan-2-yl)formamide trihydrochloride

[0729] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0730] mp 190-195° C.

[0731] MS: 533(ES+)

[0732] ^{1}H-NMR (DMSO-d_6) 6 1.12(3H,m), 3.82(3H,s), 3.93(2H,m), 4.35(2H,m), 6.08(1H,m), 7.06(1H,m), 7.28(1H,s), 7.52-8.18(11H,m), 8.40(1H,s), 8.70(1H,br-s), 9.88(1H,s)

EXAMPLE 61

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1-[1-ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide trihydrochloride

[0733] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0734] mp 198-203° C.

[0735] MS: 537(ES+)

[0736] ^{1}H-NMR (DMSO-d_6) δ1.13(3H,m), 3.93(2H,m), 4.35(2H,m), 6.10(1H,br-s), 7.48-8.18(13H,m), 8.40(1H,s), 8.70(1H,s), 9.86(1H,s)

EXAMPLE 62

(1S)-(5-Methoxybenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0737] The title compound was obtained from the compound of Preparation 19 in substantially the same manner as in Example 1.

[0738] mp 210-211° C.

[0739] MS: 498(ES+)

[0740] ^{1}H-NMR (DMSO-d_6) δ3.50(1H,dd,J=15 Hz,J=7.5 Hz), 3.60(1H,dd,J=15 Hz,J=7.5 Hz), 3.70(3H,s), 3.79(3H,s), 5.88(1H,dd,J=15 Hz,J=7.5 Hz), 7.02-7.34(4H,m), 7.52-7.77(3H,m), 7.75(2H,d,J=9 Hz), 8.27(2H,d,J=9 Hz), 8.50(1H,d,J=6 Hz), 9.27(1H,d,J=9 Hz)

EXAMPLE 63

(1S)-(5-Fluorobenzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0741] The title compound was obtained from the compound of Preparation 19 in substantially the same manner as in Example 1.

[0742] mp 207-208° C.

[0743] MS: 486(ES+)

[0744] ^{1}H-NMR (DMSO-d_6) δ3.50(1H,dd,J=15 Hz,J=7.5 Hz), 3.60(1H,dd,J=15 Hz,J=7.5 Hz), 3.71(3H,s), 5.88(1H,dd,J=15 Hz,J=7.5 Hz), 7.16-7.35(3H,m), 7.57-7.72(4H,m), 7.75(2H,d,J=9 Hz), 8.28(2H,d,J=9 Hz), 8.49(1H,d,J=6 Hz), 9.38(1H,d,J=9 Hz)

EXAMPLE 64

(1S)-(Benzo[b]furan-2-yl)-N-[1-[1-methyl-5-(4-nitrophenyl)imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0745] The title compound was obtained from the compound of Preparation 19 in substantially the same manner as in Example 1.

[0746] mp 103-104° C.

[0747] MS: 466(ES−)

[0748] ^{1}H-NMR (DMSO-d_6) δ3.50(1H,dd,J=15 Hz,J=7.5 Hz), 3.60(1H,dd,J=15 Hz,J=7.5 Hz), 3.70(3H,s), 5.88(1H,dd,J=15 Hz,J=7.5 Hz), 7.16-7.50(4H,m), 7.60-7.69(3H,m), 7.75(2H,d,J=9 Hz), 7.77(1H,m), 8.27(2H,d,J=9 Hz), 8.50(1H,d,J=6 Hz), 9.32(1H,d,J=9 Hz)

EXAMPLE 65

(1S)-(Benzothiazol-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0749] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0750] ESI-MS: 506(M+H)

[0751] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.58(2H,d,J=8 Hz), 3.64(3H,s), 5.84(1H,q,J=8 Hz), 7.07(1H,s), 7.13(1H,s), 7.21(1H,dd,J=8 Hz,J=5 Hz), 7.30(1H,d,J=8 Hz), 7.54-7.69(5H,m), 7.74(2H,d,J=8 Hz), 7.81(1H,s), 8.17(1H,d,J=8 Hz), 8.22(1H,d,J=8 Hz), 8.32(1H,s), 8.52(1H,d,J=5 Hz), 9.56(1H,d,J=8 Hz)

EXAMPLE 66

(1S)-(5-Ethylbenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0752] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0753] ESI-MS: 517(M+H)

[0754] ^{1}H-NMR (300 MHz,DMSO-d_6) δ1.22(3H,t,J=8 Hz), 2.71(2H,q,J=8 Hz), 3.46-3.58(2H,m), 3.64(3H,s), 5.87(1H,q,J=8 Hz), 7.06(1H,s), 7.12(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.28-7.36(2H,m), 7.51-7.60(5H,m), 7.65(1H,t, J=8 Hz), 7.73(2H,d,J=9 Hz), 7.81(1H,s), 8.32(1H,s), 8.49(1H,d,J=5 Hz), 9.23(9.23(1H,d,J=8 Hz)

EXAMPLE 67

(1S)-(5-Bromobenzo[b]furan-2-yl)-N-[1-[1-ethyl-5-[4-(1-imidazolyl)phenyl]imidazol-2-yl]-2-(2-pyridyl-)ethyl]formamide

[0755] The title compound was obtained from the compound of Preparation 72 in substantially the same manner as in Example 1.

[0756] ESI-MS: 581(M+)

[0757] ^{1}H-NMR (300 MHz,DMSO-d_6) δ1.07(3H,t,J=8 Hz), 3.49(1H,dd,J=15 Hz,J=8 Hz), 3.57(1H,dd,J=15 Hz,7 Hz), 3.98-4.26(2H,m), 5.88(1H,q,J=8 Hz), 7.04(1H,s), 7.13(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.32(1H,d,J=8 Hz), 7.56(2H,d,J=9 Hz), 7.58-7.70(4H,m), 7.74(2H,d,J=8 Hz), 7.81(1H,s), 8.02(1H,s), 8.33(1H,s), 8.50(1H,d,J=5 Hz), 9.43(1H,d,J=8 Hz)

EXAMPLE 68

(1S)-(7-Chlorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0758] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0759] mp 182-184° C.

[0760] ESI-MS: 523(M+)

[0761] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.48-3.62(2H, m), 3.66(3H,s), 5.90(1H,q,J=8 Hz), 7.08(1H,s), 7.13(1H,s), 7.19(1H,dd,J=8 Hz,J=5 Hz), 7.31-7.38(2H,m), 7.54-7.61(3H,m), 7.67(1H,t,J=8 Hz), 7.72-7.78(4H,m), 7.81(1H, s), 8.32(1H,s), 8.51(1H,d,J=5 Hz), 9.44(1H,d,J=8 Hz)

EXAMPLE 69

(1S)-(4-Chlorobenzo[b]furan-2-yl)-N-[1-[5-[4-(1-imidazolyl)phenyl]-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0762] The title compound was obtained from the compound of Preparation 16 in substantially the same manner as in Example 1.

[0763] MS: 523(M+)

[0764] ^{1}H-NMR (300 MHz,DMSO-d_6) δ3.44-3.60(2H, m), 3.64(3H,s), 5.88(1H,q,J=8 Hz), 7.08(1H,s), 7.13(1H,s), 7.18(1H,dd,J=8 Hz,J=5 Hz), 7.34(1H,d,J=8 Hz), 7.44(1H,d, J=8 Hz), 7.48(1H,t,J=8 Hz), 7.57(2H,d,J=8 Hz), 7.63-7.78(5H,m), 7.82(1H,s), 8.32(1H,s), 8.50(1H,d,J=5 Hz), 9.40(1H,d,J=8 Hz)

EXAMPLE 70

(1S)-(5-Chlorobenzo[b]furan-2-yl)-N-[1[-1-methyl-5-[4-(2-methylimidazol-1-yl)phenyl] imidazol-2-yl]-2-(2-pyridyl)ethyl]formamide

[0765] The title compound was obtained from the compound of Preparation 26 in substantially the same manner as in Example 1.

[0766] mp 159-161° C.

[0767] MS(m/z): 537(M^++1,bp)

[0768] ^{1}H-NMR ($CDCl_3$) δ2.40(3H,s), 3.60(3H,s), 3.63(2H,d,J=7 Hz), 5.99(1H,q,J=7 Hz), 7.03(2H,d,J=7 Hz), 7.10(1H,s), 7.15(2H,d,J=7 Hz), 7.33-7.48(7H,m), 7.58(1H, ddd,J=7 Hz,J=7 Hz,J=2 Hz), 7.64(1H,J=2 Hz), 7.74(1H,d, J=7 Hz), 8.55(1H,d,J=5 Hz)

EXAMPLE 71

(1S)-N-[1-[5-(4-Bromophenyl)-1-methylimidazol-2-yl]-2-(2-pyridyl)ethyl](5-chlorobenzo[b]furan-2-yl)formamide

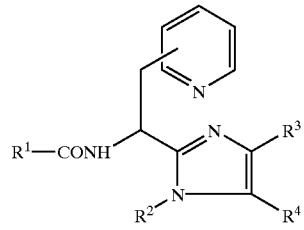
[0769] The title compound was obtained from the compound of Preparation in substantially the same manner as in Example 1.

[0770] mp 185-188° C.

[0771] ESI-MS(M+1): 536

[0772] ^{1}H-NMR ($CDCl_3$) δ3.53(3H,s), 3.60(2H,d,J=6 Hz), 5.95(1H,q,J=6 Hz), 7.03(1H,s), 7.10-7.20(4H,m), 7.33-7.60(7H,m), 7.63(1H,d,J=2 Hz), 7.77(1H,d,J=8 Hz), 8.50-8.57(1H,m)

1. A compound of the formula (I):


(I)

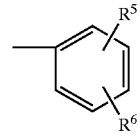
wherein

R is (a) indolyl, (b) benzothienyl having suitable substituent(s) selected from the group consisting of nitro and halogen, (c) benzothiazolyl having halogen, (d) furopyridyl which may have nitro or (e) benzofuranyl which may have suitable substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, nitro, cyano, acyl and trihalo(lower)alkyl,

R^2 is lower alkyl,

R^3 is hydrogen or lower alkyl, and

R^4 is thienyl or a group of the formula:



wherein

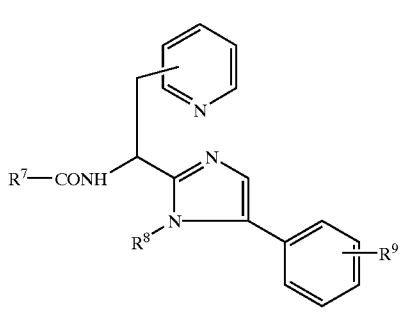
R^5 is hydrogen or halogen, and

R^6 is (a) imidazolyl which may have lower alkyl, (b) benzimidazolyl, (c) pyridyl, (d) pyrrolyl, (e) morpholinyl, (f) thienyl, (g) furyl, (h) phenyl, (j) thiazolyl, (k) halogen or (1) nitro,

provided that (i) R^3 is lower alkyl or R^6 is benzimidazolyl or imidazolyl having lower alkyl when R^1 is indolyl, and (ii) R^6 is benzimidazolyl or imidazolyl having lower alkyl when R^1 is benzofuranyl,

and a pharmaceutically acceptable salt thereof.

2. A compound of the formula (II):



(II)

wherein

R^7 is indolyl, benzofuranyl, benzothienyl or benzothiazolyl,

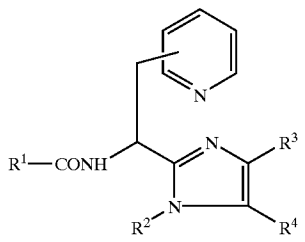
R^8 is lower alkyl, and

R^9 is imidazolyl or nitro,

provided that (i) R^8 is not methyl when R^7 is indolyl, and (ii) R^9 is nitro when R^7 is benzofuranyl,

and a pharmaceutically acceptable salt thereof.

3. A process for preparing a compound of the formula



(I)

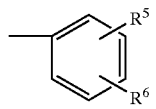
wherein

R^1 is (a) indolyl, (b) benzothienyl having suitable substituent(s) selected from the group consisting of nitro and halogen, (c) benzothiazolyl having halogen, (d) furopyridyl which may have nitro or (e) benzofuranyl which may have suitable substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, nitro, cyano, acyl and trihalo(lower)alkyl,

R^2 is lower alkyl,

R^3 is hydrogen or lower alkyl, and

R^4 is thienyl or a group of the formula:



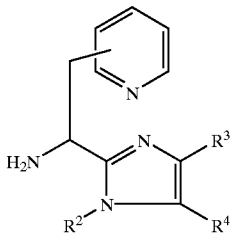
wherein

R^5 is hydrogen or halogen, and

R^6 is (a) imidazolyl which may have lower alkyl, (b) benzimidazolyl, (c) pyridyl, (d) pyrrolyl, (e) morpholinyl, (f) thienyl, (g) furyl, (h) phenyl, (j) thiazolyl, (k) halogen or (1) nitro,

provided that (i) R^3 is lower alkyl or R^6 is benzimidazolyl or imidazolyl having lower alkyl when R^1 is indolyl, and (ii) R^6 is benzimidazolyl or imidazolyl having lower alkyl when R^1 is benzofuranyl,

or a salt thereof, which comprises reacting a compound of the formula



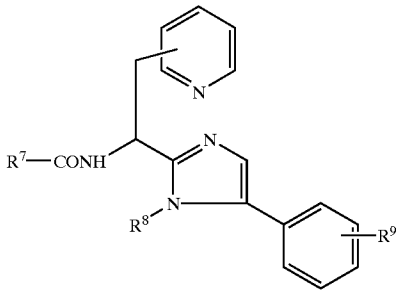
(III)

wherein R^2, R^3 and R^4 are each as defined above, or its reactive derivative at the amino group, or a salt thereof, with a compound of the formula

R^1—COOH (IV)

wherein R^1 is as defined above, or its reactive derivative at the carboxy group, or a salt thereof.

4. A process for preparing a compound of the formula



(II)

wherein

R^7 is indolyl, benzofuranyl, benzothienyl or benzothiazolyl,

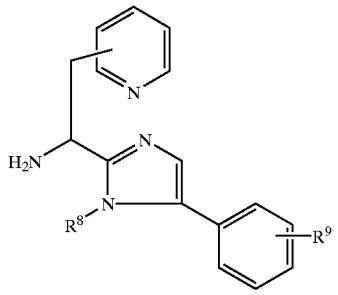
R^8 is lower alkyl, and

R^9 is imidazolyl or nitro,

provided that (i) R^8 is not methyl when R^7 is indolyl, and (ii) R^9 is nitro when R^7 is benzofuranyl,

or a salt thereof, which comprises reacting a compound of the formula

(V)



wherein R^8 and R^9 are each as defined above, or its reactive derivative at the amino group, or a salt thereof, with a compound of the formula

R^7—COOH (VI)

wherein R^7 is as defined above, or its reactive derivative at the carboxy group, or a salt thereof.

5. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising the compound of claim 2 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

7. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

8. Use of the compound of claim 2 or a pharmaceutically acceptable salt thereof as a medicament.

9. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament for prophylactic or therapeutic treatment of NO-mediated diseases.

10. Use of the compound of claim 2 or a pharmaceutically acceptable salt thereof as a medicament for prophylactic or therapeutic treatment of NO-mediated diseases.

* * * * *