D E S C R I P T I O N

PYRAZOLE DERIVATIVES USEFUL AS COX-I INHIBITORS

Technical Field

This invention relates to pyrazole compounds having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

Background Art

The presence of two cyclooxygenase isoenzymes, cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) is known (Proc. Nat. Acad. Sci. USA 88, 2692-2696 (1991)).

Traditional non steroidal anti-inflammatory compounds (NSAIDs) have inhibiting activities of both COX-I and COX-II (J. Biol. Chem., 268, 6610-6614 (1993), etc). The therapeutic use thereof involves undesired effects on the gastrointestinal tract, such as bleeding, erosions, gastric and intestinal ulcers, etc.

It was reported that selective inhibition of COX-II shows anti-inflammatory and analgesic activities comparable with conventional NSAIDs but with a lower incidence of some gastrointestinal undesired effects (Pro. Nat. Acad. Sci. USA, 91, 3228-3232(1994)). Accordingly, various selective COX-II inhibitors have been prepared. However, it was reported that those "selective COX-II inhibitor" show some side-effects on kidney and/or insufficient efficacy on acute pains.

Further, some compounds such as SC-560, mofezolac, etc, which have certain selective inhibiting activity against COX-I. WO98/57910 shows some compounds having such activity. However, their selectivity of inhibiting COX -I does not seem to be enough to use them as a clinically

acceptable and satisfactory analgesic agent due to their gastrointestinal disorders.

WO02/055502 shows some pyridine derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. Further, WO03/040110 shows some triazole derivatives having cyclooxygenase inhibiting activity, particularly cyclooxygenase-I inhibiting activity. And WO99/51580 shows some triazole derivatives having an inhibiting activity of cytokine production.

Disclosure of Invention

This invention relates to pyrazole compounds, which have pharmacological activity such as cyclooxygenase (hereinafter described as COX) inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

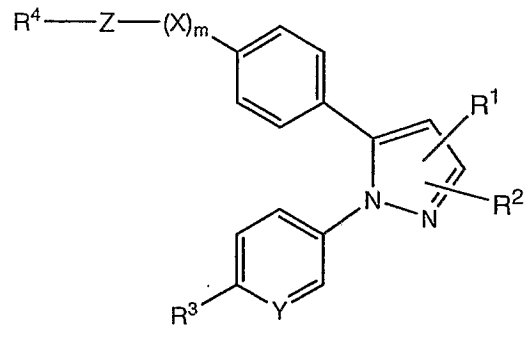
Accordingly, one object of this invention is to provide the pyrazole compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a process for production of the pyrazole compounds.

A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the pyrazole compounds.

Still further object of this invention is to provide a use of the pyrazole compounds for manufacturing a medicament for treating or preventing various diseases.

The new pyrazole compounds of this invention can be represented by the following general formula (I):



(I)

wherein R^1 is hydrogen or lower alkyl;

R^2 is lower alkyl optionally substituted with halogen, hydroxy, lower alkoxyimino or lower alkoxy; lower alkenyl; cycloalkyl; cyano; lower alkanoyl; cycloalkylcarbonyl; N,N-di(lower)alkylcarbamoyl; carbamoyl; N-lower alkoxy-N-lower alkylcarbamoyl; amino; di(lower)alkylamino; lower alkoxycarbonylamino; N,N-di(lower)alkylcarbamoylamino; N-(N,N-di(lower)alkylcarbamoyl)-N-lower alkylamino; halogen; hydroxy; carboxy; lower alkoxycarbonyl; aroyl; heterocycliccarbonyl; heterocyclic group; lower alkylsulfonyl; lower alkoxy optionally substituted with lower alkoxy, N,N-di(lower)alkylcarbamoyl or halogen; cycloalkyloxy; lower alkylthio; or lower alkylsufinyl;

R^3 is lower alkyl optionally substituted with amino, carbamoylamino or lower alkylsulfonylamino; halogen; cyano; hydroxy; lower alkanoyloxy; lower alkylenedioxy; lower alkoxy optionally substituted with aryl, hydroxy, cyano, amino, lower alkoxycarbonylamino, lower alkylsulfonylamino or carbamoylamino;

nitro; amino; hetrocyclic group; lower alkylthio; lower alkylsulfinyl; or lower alkylsufonyl;

R^4 is hydrogen; cyano; amino optionally substituted with phthaloyl or lower alkyl; aryl; heterocyclic group; lower alkoxy; hydroxy; lower alkylsulfonyloxy; lower alkanoyloxy; lower alkyl substituted with tritylamino and lower alkoxycarbonyl, amino and lower alkoxycarbonyl, amino and carboxy, amino and carbamoyl, or amino and hydroxy; N-lower alkoxycarbonyl-N-lower alkylamino; lower alkanoyl optionally substituted with halogen; carboxy; lower alkylsulfonyl; sulfo; lower alkylsilyloxy; lower alkoxycarbonyl; sulfamoyl optionally substituted with lower alkyl; carbamoyl optionally substituted with lower alkyl; lower alkylthio; lower alkylsulfinyl; carbamoyloxy; thioureido; or a group of the formula:

$$R^5\text{-}G\text{-}J\text{-}$$

in which G is $-CO-$ or $-SO_2-$;

J is $-N(R^6)-$

(wherein R^6 is hydrogen or lower alkyl); and

R^5 is amino optionally substituted with lower alkoxycarbonyl or lower alkyl; lower alkyl optionally substituted with hydroxy, lower alkoxycarbonylamino, lower alkanoyloxy, amino or halogen; lower alkoxy; hydrogen; heterocyclic group; or aryl;

X is O, S, SO or SO_2;

Y is CH or N;

Z is lower alkylene or lower alkenylene; and

m is 0 or 1;

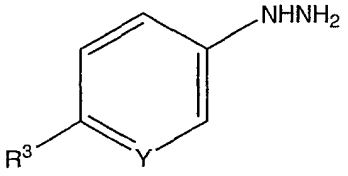
provided that when R^4 is hydrogen;

then R^3 is lower alkyl substituted with amino, carbamoylamino or lower alkylsulfonylamino; or lower alkoxy substituted with aryl, hydroxy, cyano, amino, lower alkoxycarbonylamino, lower alkylsulfonylamino or carbamoylamino;

or salts thereof.

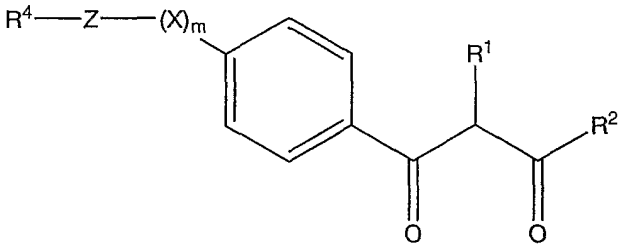
The object compound (I) of the present invention can be prepared by the following processes.

Process (1)

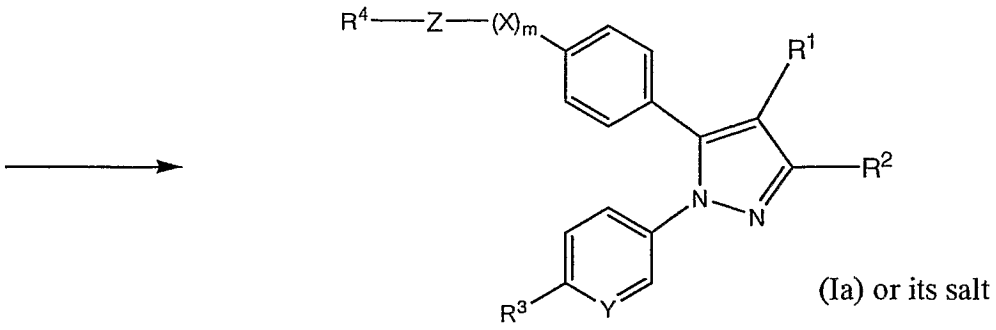


(II) or its salt

+

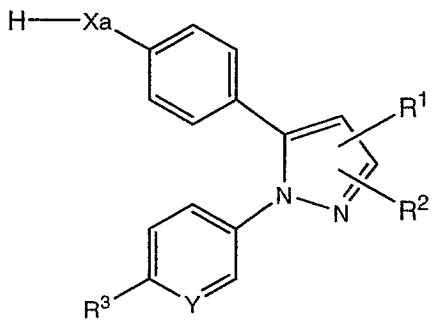


(III) or its salt



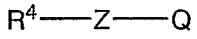
(Ia) or its salt

Process (2)

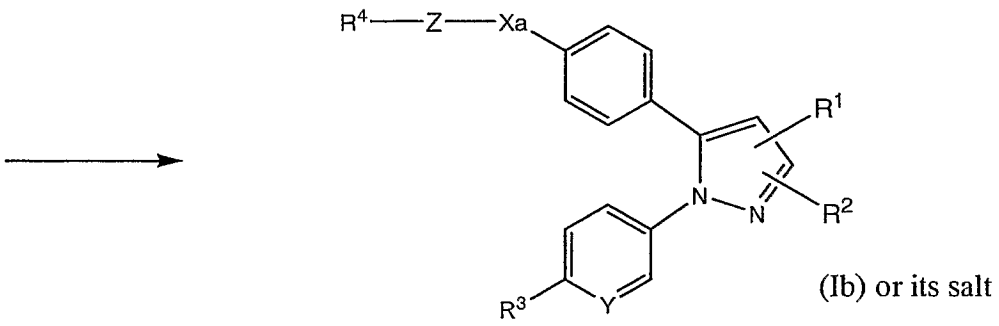


(IV) or its salt

+



(V) or its salt



(Ib) or its salt

In the above processes, R^1, R^2, R^3, R^4, X, Y, Z and m are each as defined above,

Xa is O or S, and

Q is hyroxy or an acid residue.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both

mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

So, the "lower alkyl" and lower alkyl moiety in the terms "lower alkylthio", "lower aklylsufinyl", "lower alkylsulfonyl" and "lower alkylsulfonylamino" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isoamyl, hexyl, and the like, and it is preferably (C_1-C_4)alkyl, more preferably (C_1-C_2)alkyl, most preferably methyl.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and it is preferably a fluorine atom or a chlorine atom, more preferably a chlorine atom.

The "lower alkyl substituted with halogen" means a monovalent group in which the above lower alkyl is substituted by one or more (more preferably 1 to 5, most

preferably 1 to 3) above halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, and it is preferably (C_1-C_4)alkyl substituted with halogen, more preferably (C_1-C_2)alkyl substituted with halogen, more preferably (C_1-C_2)alkyl substituted with fluorine, more preferably methyl substituted with fluorine, most preferably difluoromethyl or trifluoromethyl.

The "lower alkyl substituted with hydroxy" means a monovalent group in which the above lower alkyl is substituted by a OH group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 2-hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxyhexyl, or the like, and it is preferably (C_1-C_4)alkyl substituted with hydroxy, more preferably (C_1-C_3)alkyl substituted with hydroxy.

The "lower alkenyl" means a straight or branched chain aliphatic hydrocarbon having more than one double bond between two carbon atom, such as ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, and the like, and it is preferably (C_2-C_4)alkenyl, more preferably (C_2-C_3)alkenyl.

The "lower alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably (C_1-C_4)alkoxy, more preferably (C_1-C_2)alkoxy, most preferably methoxy.

The "cycloalkyl" and cycloalky moiety in the terms "cycloalkylcarbonyl" and "cycloalkyloxy" means C_3-C_{10}

cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like, and it is preferably C_3-C_6 cycloalkyl, more preferably C_3-C_5 cycloalkyl, most preferably cyclopropyl or cyclopentyl.

The "di(lower)alkylamino" means a amino group substituted by the same or different above (lower)alkyl groups, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, dipentylamino, dihexylamino, ethylmethylamino, methylpropylamino, butylmethylamino, ethylpropylamino, butylethylamino, or the like, and it is preferably [di(C_1-C_4)alkyl]amino, more preferably [di(C_1-C_4)alkyl]amino, most preferably dimethylamino.

The "lower alkoxycarbonyl" and lower alkoxycarbonyl moiety in the term "lower alkoxycarbonylamino" means a -CO_2-[(lower)alkyl] group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, and the like, and it is preferably [(C1-C4)alkoxy]carbonyl, more preferably ethoxycarbonyl or tert-butoxycarbonyl.

The "lower alkanoyl" means carbonyl group which is substituted by hydrogen or the above (lower)alkyl groups, such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, or the like, and it is preferably (C_1-C_5)alkanoyl, more preferably (C_2-C_3)alkanoyl, most preferably acetyl.

The "cycloalkylcarbonyl" means a carbonyl group substituted with cycloalkyl group mentioned above, such as cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl, norbornylcarbonyl,

adamantylcarbonyl, and the like, and it is preferably [(C_3-C_6)cycloalkyl]carbonyl, more preferably [(C_3-C_5)cycloalkyl]carbonyl, most preferably cyclopropylcarbonyl.

The "N,N-di(lower)alkylcarbamoyl" and N,N-di(lower)alkylcarbamoyl moiety in the term "N,N-di(lower)alkylcarbamoylamino" means a carbamonyl group substituted with the same or different lower alkyl groups mentioned above, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dipentylcarbamoyl, dihexylcarbamoyl, ethylmethylcarbamoyl, methylpropylcarbamoyl, butylmethylcarbamoyl, ethylpropylcarbamoyl, butylethylcarbamoyl, and the like, and it is preferably [di(C_1-C_4)alkyl]carbamoyl, more preferably [di(C_1-C_2)alkyl]carbamoyl, most preferably dimethycarbamoyl or ethylmethylcarbamoyl.

The "lower alkoxy substituted with halogen" means a monovalent group in which the above lower alkoxy is substituted by one or more (more preferably 1 to 5, most preferably 1 to 3) above halogen atom(s), such as fluoromethoxy, chloromethoxy, difluoromethoxy, dichloromethoxy, dibromomethoxy, trifluoromethoxy, trichloromethoxy, fluoroethoxy, chloroethoxy, 2,2-difluoroethoxy, 2,2-dichloroethoxy, 2,2,2-trifluoroethoxy, 2,2,2-trichloroethoxy, 2,2,3,3,3-pentafluoroethoxy, fluoropropoxy, fluorobutoxy, fluorohexyloxy, or the like, and it is preferably (C_1-C_4)alkoxy substituted with halogen, more preferably (C_1-C_2)alkoxy substituted with halogen, more preferably (C_1-C_2)alkoxy substituted with fluorine, more preferably ethoxy substituted with fluorine, most preferably

2,2-difluoroethoxy.

The "lower alkyl substituted with amino" means a monovalent group in which the above lower alkyl is substituted by a amino group, such as aminomethyl, 2-aminoethyl, aminopropyl, 1-aminoisopropyl, 2-aminoisopropyl, aminobutyl, aminoisobutyl, amino-tert-butyl, aminohexyl, or the like, and it is preferably (C_1-C_4)alkyl substituted with amino, more preferably (C_1-C_2)alkyl substituted with amino.

The "lower alkyl substituted with carbamoylamino" means a monovalent group in which the above (lower)alkyl is substituted by a carbamoylamino group (urea group), such as carbamoylaminomethyl, 2-(carbamoylamino)ethyl, carbamoylaminopropyl, 1-(carbamoylamino)isopropyl, 2-(carbamoylamino)isopropyl, carbamoylaminobutyl, carbamoylaminoisobutyl, carbamoylamino-tert-butyl, carbamoylaminohexyl, or the like, and it is preferably (C_1-C_4)alkyl substituted with carbamoylamino, more preferably (C_1-C_2)alkyl substituted with carbamoylamino.

The "aryl" and ar moiety in the term "aroyl" means an aromatic hydrocarbon group, such as phenyl, naphtyl, indenyl, or the like, and it is preferably (C_6-C_{10})aryl, more preferably phenyl.

The "aroyl" means a carbonyl group substituted with aryl group mentioned above, such as benzoyl, naphthoyl, or the like, and it is preferably benzoyol.

The "lower alkanoyloxy" means a monovalent group in which oxygen atom is substituted with lower alkanoyl group mentioned above, such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, or the like, and it is preferably [(C_1-C_4)alkanoyl]oxy, more preferably [(C_1-C_2)alkanoyl]oxy, most preferably acetoxy.

The "lower alkylene" means a straight or branched chain aliphatic hydrocarbon divalent group, such as methylene, ethylene, 1-methylethylene, 2-methylethylene, propylene, methylpropylene, butylene, pentylene, hexylene, and the like, and it is preferably (C_1-C_4)alkylene, more preferably (C_1-C_2)alkylene.

The "lower alkylenedioxy" means -O-[(lower)alkylene]-O- group. That is, in this case, R^3 is divalent group and is also substituted at the next carbon atom. This group may be exemplified by methylenedioxy, ethylenedioxy, methylethylenedioxy, propylenedioxy, and the like, and it is preferably [(C_1-C_4)alkylene]dioxy, more preferably [(C_1-C_2)alkylene]dioxy, most preferably methylenedioxy.

The "lower alkoxy substituted with aryl" means a monovalent group in which the above lower alkoxy is substituted by aryl group mentioned above.

The "lower alkoxy substituted with hydroxy" means a monovalent group in which the above lower alkoxy is substituted by hydroxy.

The "lower alkoxy substituted with cyano" means a monovalent group in which the above (lower)alkoxy is substituted by a cyano group, such as cyanomethoxy, cyanoethoxy, cyanopropoxy, cyanobutoxy, and the like, and it is preferably (C1-C4)alkoxy substituted with cyano, more preferably (C1-C2)alkoxy substituted with cyano, most preferably cyanomethoxy.

The "lower alkoxy substituted with amino" means a monovalent group in which the above lower alkoxy is substituted with amino.

The "lower alkoxy substituted with lower alkoxycarbonylamino means a lower alkoxy substituted with amino group mentioned above substituted with lower

alkoxycarbonyl group mentioned above.

The "lower alkoxy substituted with lower alkylsulfonylamino means a monovalent group in which the above lower alkoxy is substituted with lower alkylsulfonylamino group mentioned above.

The "lower alkoxy substituted with carbamoylamino" means a monovalent group in which the above lower alkoxy is substituted by a (carbamoyl)amino (urea) group, such as [(carbamoyl)amino]methoxy, [(carbamoyl)amino]ethoxy, [(carbamoyl)amino]propoxy, [(carbamoyl)amino]cyanobutoxy, and the like, and it is preferably (C1-C4)alkoxy substituted with [(carbamoyl)amino], more preferably (C_1-C_2)alkoxy substituted with [(carbamoyl)amino], most preferably carbamoylaminomethoxy.

The "lower alkokycarbonylamino" means an amino group substituted with lower alkokycarbonyl group mentioned above.

The "lower alkylsulfonylamino means a sulfonylamino group substituted with lower alkyl group mentioned above.

Suitable "heterocyclic group" may be one containing at least one hetero atom selected from nitrogen, sulfur and oxygen atom, and may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group, and preferable heterocyclic group may be N-containing heterocyclic group such as unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl [e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.], tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.;
saturated 3 to 7-membered heteromonocyclic group

containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, homopiperazinyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, imidazopyridyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g. tetrazolo[1,5-b]pyridazinyl, etc.], quioxalinyl, etc.;
unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.;
saturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, 1H-tetrahydropyranyl, tetrahydrofuranyl, etc.;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms, for example, thienyl, etc.;
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.], oxazolinyl [e.g. 2-oxazolinyl, etc.], etc.;
saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzofurazanyl, benzoxazolyl, benzoxadiazolyl, etc.];
unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.], etc.;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g. thiazolidinyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g. benzothiazolyl, benzothiadiazolyl, etc.];
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms [e.g. benzofuranyl, benzodioxolyl, chromanyl, etc.] and the like.

Said "heterocyclic group" may be substituted with lower alkyl as exemplified above or oxo, in which preferable one is pieridyl, pyrrolyl , 3-metyl-1,2,4-oxadiazol-5-yl, isoindole-1,3-dione-2-yl or 1-methyl-1H-imidazolyl.

The heterocyclic moiety in the term "heterocycliccarbonyl" means heterocyclic group mentioned above and, it is preferably piperidyl.

The "lower alkylsulfonyloxy" means a sulfonyloxy group substituted with lower alkyl group mentioned above.

The "lower alkanoyl substituted with halogen" means a lower alkanoyl group mentioned above substituted with halogen mentioned above, such as trifluoroacetyl, and the like.

The "lower alkylsilyloxy" means silyloxy group substituted by the same or different above (lower)alkyl groups, such as trimethylsilyloxy, triethylsilyloxy, tert-butyldimethylsilyloxy, or the like, and it is preferably tert-butyldimethylsilyloxy.

The "acid residue" means halogen (e.g. fluoro, chloro, bromo, iodo), arenesulfonyloxy (e.g. benzenesulfonyloxy, tosyloxy, etc.), alkanesulfonyloxy (e.g. mesyloxy, ethanesulfonyloxy, etc.), and the like.

Preferred compound (I) is one having hydrogen for R^1; lower alkyl optionally substituted with halogen;

cycloalkyl; halogen; or lower alkoxy optionally substituted with halogen for R^2; lower alkoxy for R^3; R^5-G-J-(wherein -CO- or -SO_2- for G, -NH- for J, amino or lower alkyl for R^5) for R^4; O for X; CH or N for Y; lower alkylene for Z; and 0 or 1 for m.

Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

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

Process (1)

The object compound (Ia) or its salt can be prepared by reacting a compound (II) or its salt with a compound (III) or its salt in the acidic condition, for example, by using acetic acid.

Suitable salts of the compounds (Ia) and (III) may be the same as those exemplified for the compound (I).

Suitable salt of the compound (II) may be acid addition salt exemplified for the compound (I).

The reaction is carried out in a conventional solvent

such as water, an alcohol (e.g. methanol, ethanol, propanol, isopropanol, etc.), tetrahydrofuran, dioxane, etc. or a mixture of thereof.

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

According to the starting material, the heterocyclic ring is formed but not to form pyrazole ring. In this case, the dehydration process is need to form pyrazole ring.

The hydration process is carried out under the higher temperature.

Process (2)

The object compound (Ib) or its salt can be prepared by reacting a compound (IV) or its salt with a compound (V) or its salt.

Suitable salts of the compounds (Ia), (IV) and (V) may be the same as those exemplified for the compound (I).

When the compound (V) having halogen for Q is used in this reaction, the reaction is preferably carried out in the presence of a base such as alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydride or hydroxide or carbonate or bicarbonate thereof.

When the compound (V) having hydroxy for Q is used in this reaction, the reaction is preferably carried out in the presence of diethyl azodicarboxylate and triphenylphosphine.

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

The reaction temperature is not critical and the

reaction can be carried out under cooling to heating.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the com pounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hrs after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
23	3.2	> 1.5
28	3.2	> 1.5
61	3.2	> 1.5
181	3.2	>= 1.5
240	3.2	>= 1.5
248	3.2	>= 1.5
250	3.2	>= 1.5
254	3.2	>= 1.5
267	3.2	>= 1.5

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method :

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500 μl Aliquots of human whole blood were immediately incubated with 2 μl of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37℃ to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5 μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4℃ to obtain serum. A 100 μl aliquot of serum was mixed with 400 μl methanol for protein precipitation. The

supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for TXB_2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of thromboxane B_2(TXB_2) production relative to control incubations containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl aliquots of human whole blood were incubated with either 2μl dimethyl sulfoxide vehicle or 2μl of a test compound at final concentrations for 15 min at 37℃. This was followed by incubation of the blood with 10μl of 5mg/ml lipopolysaccharide for 24hrs at 37℃ for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000Xg for 5 min at 4℃ to obtain plasma. A 100μl aliquot of plasma was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000Xg for 5min at 4℃ and was assayed for prostaglandin E_2 (PGE_2) using a radioimmunoassay kit after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

For a test compound, the results were expressed as percent inhibition of PGE_2 production relative to control incubations containing dimethyl sulfoxide vehicle. The

data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
23	< 0.01	> 0.1
28	< 0.01	> 0.1
61	< 0.01	> 0.1
181	< 0.01	> 0.1
240	< 0.01	> 0.1
248	< 0.01	> 0.1
250	< 0.01	> 0.1
254	< 0.01	> 0.1
267	< 0.01	> 0.1

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

[C] Inhibiting activity on aggregation of platelet

(i) Methods

Preparation of platelet-rich plasma

Blood from healthy human volunteers was collected into plastic vessels containing 3.8% sodium citrate (1/10 volume). The subject had no taken any compounds for at least 7days prior to blood collection. Platelet-rich plasma was obtained from the supernatant fraction of blood

after centrifugation at 1200rpm. for 10min. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 3000rpm for 10min.

Measurement of platelet aggregation

Platelet aggregation was measured according to the turbidimetric method with an aggregometer (Hema Tracer). In the cuvette, platelet-rich plasma was pre-incubated for 2min at 37℃ after the addition of compounds or vehicle. In order to quantify the inhibitory effects of each compound, the maximum increase in light transmission was determined from the aggregation curve for 7min after the addition of agonist. We used collagen as agonist of platelet aggregation in this study. The final concentration of collagen was 0.5μg/mL. The effect of each compound was expressed as percentage inhibition agonist-induced platelet aggregation compared with vehicle treatment. Data are presented as the mean ± S.E.M. for six experiments. The IC_{50} value was obtained by linear regression, and is expressed as the compound concentration required to produce 50% inhibition of agonist-induced platelet aggregation in comparison to vehicle treatment.

It appeared, from the above-mentioned Test Result, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against platelet aggregation. Therefore, the compound (I) or pharmaceutically acceptable salts thereof are useful for preventing or treating disorders induced by platelet aggregation, such as thrombosis.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as

gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc.

As shown above, the object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, scapulohumeral periarthritis, cervical syndrome, etc.]; lumbago; inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.]; inflammatory eye condition [e.g. conjunctivitis, etc.]; lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.]; condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varioloid, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.]; gingivitis; menorrhalgia; inflammation, pain and tumescence after operation or injury [pain after odontectomy, etc.] ; pyrexia, pain and other

conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The object compound (I) and a salt thereof can be used for prophylactic and therapeutic treatment of arterial thrombosis, arterial sclerosis, ischemic heart diseases [e.g. angina pectoris (e.g. stable angina pectoris, unstable angina pectoris including imminent infarction, etc.), myocardial infarction (e.g. acute myocardial infarction, etc.), coronary thrombosis, etc.], ischemic brain diseases [e.g. cerebral infarction (e.g. acute cerebral thrombosis, etc.), cerebral thrombosis (e.g. cerebral embolism, etc.), transient cerebral ischemia (e.g. transient ischemic attack, etc.), cerebrovascular spasm after cerebral hemorrhage (e.g. cerebrovascular spasm after subarachnoid hemorrhage, etc.), etc.], pulmonary vascular diseases (e.g. pulmonary thrombosis, pulmonary embolism etc.), peripheral circulatory disorder [e.g. arteriosclerosis obliterans, thromboangiitis obliterans (i.e. Buerger's disease), Raynaud's disease, complication of diabetes mellitus (e.g. diabetic angiopathy, diabetic neuropathy, etc.), phiebothrombosis (e.g. deep vein thrombosis, etc.), etc.], complication of tumors (e.g.

compression thrombosis), abortion [e.g. placental thrombosis, etc.], restenosis and reocclusion [e.g. restenosis and/or reocclusion after percutaneous transluminal coronary angioplasty (PTCA), restenosis and reocclusion after the administration of thrombolytic drug (e.g. tissue plasminogen activator (TPA), etc.)], thrombus formation in case of vascular surgery, valve replacement, extracorporeal circulation [e.g. surgery (e.g. open heart surgery, pump-oxygenator, etc.) hemodialysis, etc.] or transplantation, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia, essential thrombocytosis, inflammation (e.g. nephritis, etc.), immune diseases, atrophic thrombosis, creeping thrombosis, dilation thrombosis, jumping thrombosis, mural thrombosis, etc..

The object compound (I) and a salt thereof can be used for the adjuvant therapy with thrombolytic drug (e.g. TPA, etc.) or anticoagulant (e.g. heparin, etc.).

And, the compound (I) is also useful for inhibition of thrombosis during extra corporeal circulation such as dialysis.

Particularly, the following diseases are exemplified: pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis, etc; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury; etc..

And on the commercial package comprising the pharmaceutical composition mentioned above, the matter, which states above mentioned effects, may be written.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present

invention can be used in a form of pharmaceutical preparation containing said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

For therapeutic purpose, the analgesic agent of the present invention can be used in a form of pharmaceutical preparation suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like.

Particularly, the analgesic agent of this invention is useful for treating or preventing acute or chronic pains associated with acute or chronic inflammations in human beings or animals by using administered systemically or topically.

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

In the above and subsequent description of the present specification, the following abbreviations and acronyms mean ones as shown in the following table.

Abbreviations and Acronyms	Full Name
AcOEt or EtOAc	ethyl acetate
AcOH	acetic acid
BuOH, t-BuOH, etc.	butanol, t-butyl alcohol, etc.
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Et3N	triethylamine
EtOH	ethanol
IPE	diisopropyl ether
MeOH	methanol
PrOH, i-PrOH or IPA, etc.	propanol, isopropyl alcohol, etc.
TFA	trifluoroacetic acid
THF	tetrahydrofuran
EDCI or WSCD	1-ethyl-3-[3'-(dimethylamino)propyl]carbodiimide
HOBt or HOBT	1-hydroxybenztriazole
Pd/C	palladium on carbon
MCBA or mCPBA or mcpba	3-Chloroperoxybenzoic acid
deg	°C=degree centigrade
min	minute(s)
hr or h	hour(s)
conc.	concentrated
aq	aqueous (ex. aq NaHCO3 solution)

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

Example 1-1

(1E)-1-[4-(Methoxymethoxy)phenyl]-4-methyl-1-penten-3-one

1M Sodium hydroxide aqueous solution (5.4ml) was added to a solution of 4-mehoxymethoxybenzaldehyde (4.52g) and 3-methyl-2-butanone (4.69g) in ethanol (27ml), and the mixture was stirred at room temperature overnight.

The mixture partitioned between ethyl acetate and water. The organic layer was washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography eluted with 10% ethyl acetate/n-hexane to give the title compound (4.03g, 63.2%) as an oil.

1H NMR ($CDCl_3$) : δ 1.18(6H, d, J=6.7Hz), 2.92(1H, m), 3.48(3H, s), 5.21(2H, s), 6.71(1H, d, J=16.0Hz), 7.05(2H, d, J=8.8Hz), 7.51(2H, d, J=8.8Hz), 7.58(1H, d, J=16.0Hz).
MS (ESI+) : m/z 257 (M+Na).

Example 1-2

(1S,2R)- and (1R,2S)-1,2-epoxy-1-[4-(methoxymethoxy)-phenyl]-4-methyl-3-pentanone

30% H_2O_2 (1.7ml) and 3M sodium hydroxide aqueous solution (1.7ml) was added to a solution of (1E)-1-[4-(methoxymethoxy)phenyl]-4-methyl-1-penten-3-one obtained by Example 1-1 (2.00g) in ethanol:acetone=3:1

(34ml). The mixture was stirred at room temperature overnight.

The mixture was concentrated in vacuo, and partitioned between ethyl acetate and water. The organic layer was washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give the target compound (2.03g, 95%) as an oil.

1H NMR (DMSO-d6) : δ 1.05(6H, d, J=6.9Hz), 2.85(1H, m), 3.36(3H, s), 3.93(1H, d, J=1.9Hz), 4.00(1H, d, J=1.9Hz), 5.20(2H, s), 7.03(2H, d, J=8.6Hz), 7.30(2H, d, J=8.6Hz).
MS (ESI) : m/z 273 (M+Na).

Example 1-3

4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenol

A mixture of (1S,2R)- and (1R,2S)-1,2-epoxy-1-[4-(methoxymeth-oxy)phenyl]-4-methyl-3-pentanone obtained by Example 1-2 (2.10g) and 4-methoxyphenylhydrazine hydrochloride (1.76g) in ethanol:acetic acid=20:1 (20ml) was stirred at 60℃ for 3hrs.

The mixture was concentrated in vacuo. To the residue was added ethyl acetate and 1M hydrochloric acid. The whole mixture was treated with activated carbon, and was filtered through a celite pad. The filtrate was partitioned. The organic layer was washed successively with 1M hydrochloric acid, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid were collected and washed with ethyl acetate to give the target compound (322.2mg, 12.5%) as a white powder.

1H NMR ($CDCl_3$) : δ 1.33(6H, d, J=7.0Hz), 3.07(1H, m), 3.80(3H, s), 5.18(1H, s), 6.26(1H, s), 6.72(2H, d, J=8.8Hz), 6.83(2H, d, J=9.0Hz), 7.08(2H, d, J=8.8Hz), 7.20(2H, d, J=9.0Hz).

MS (ESI+) : m/z 309 (M+H).

Example 2

tert-Butyl 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethylcarbamate

Diethylazodicarboxylate (259mg) was added to a mixture of 4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 1-3 (305mg), 2-t-butoxycarbonylaminoethanol (479mg), and triphenylphosphine (390mg) in tetrahydrofuran (3ml). After stirring at room temperature for 7hrs, diethylazodicarboxylate (17mg) and triphenylphosphine (26mg) was added to the reaction mixture.

After stirring at room temperature for 1hr, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 30% ethyl acetate/n-hexane to give the target compound (396mg, 88.5%) as a solid.

1H NMR ($CDCl_3$) : δ 1.34(6H, d, J=7.0Hz), 1.45(9H, s), 3.07(1H, m), 3.48-3.57(2H, m), 3.80(3H, s), 3.97-4.03(2H, m), 4.97(1H, br-s), 6.26(1H, s), 6.76-6.87(4H, m), 7.14(2H, d, J=8.9Hz), 7.20(2H, d, J=9.0 Hz).

Example 3

2-{4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethanamine hydrochloride

4M Hydrochloric acid/dioxane (2ml) was added to a solution of tert-butyl 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethylcarbamate obtained by Example 2 (382mg) in dichloromethane (3ml) at 0℃.

After stirring at room temperature for 1hr, the reaction mixture was concentrated in vacuo. The residue was crystallized from a mixture of isopropanol and ethyl acetate to give the target compound (311mg, 94.7%) as a powder.

1H NMR (DMSO-d6) : δ 1.27(6H, d, J=6.9Hz), 2.95(1H, m), 3.14-3.22(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 6.41(1H, s), 6.93(4H, d, J=8.9Hz), 7.16(4H, d, J=8.9Hz), 8.22(2H, br-s).
MS (ESI+) : m/z 352 (M+H).

Example 4

N-(2-{4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}-ethyl)methanesulfonamide

Methanesulfonyl chloride (32.2mg) was added to a solution of 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 3 (90.9mg) and triethylamine (71.1mg) in dichloromethane (2ml). The mixture was stirred at room temperature for 2hrs.

The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and a mixture of 1M hydrochloric acid and brine. The aqueous layer was reextracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution,

and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from a mixture of ethyl acetate and isopropylether to give the target compound (78.0mg, 77.5%) as a white powder.

MP : 162-163℃.

1H NMR (DMSO-d6) : δ 1.26(6H, d, J=6.9Hz), 2.94(3H, s), 2.94(1H, m), 3.25-3.39(2H, m), 3.76(3H, s), 3.98-4.04(2H, m), 6.40(1H, s), 6.90(2H, d, J=8.8Hz), 6.93(2H, d, J=8.9Hz), 7.13(2H, d, J=8.8Hz), 7.15(2H, d, J=8.9Hz), 7.27(1H, s).

IR (KBr) : 3122, 2966, 2897, 2871, 1614, 1514cm^{-1}.

Example 5

N-(2-{4-[3-Isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

Trimethylsilylisocyanate (41.4mg) was added to a solution of 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 3 (93.0mg) and triethylamine (72.8mg) in dichloromethane (3ml) and the mixture wasstirred at room temperature for 3hrs. Trimethylsilylisocyanate (8.3mg) was added and the mixture was stirred at room temperature for 1.5hrs. Trimethylsilylisocyanate (13.8 mg) and triethylamine (12.1mg) was added and the mixture was stirred at room temperature for 1.5hrs.

The mixture was concentrated in vacuo, and the residue was partitioned between chloroform and a mixture of 1M hydrochloric acid and brine. The aqueous layer was extracted with chloroform. The combined organic layer was washed with saturated aqueous sodium bicarbonate solution

and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 10% methanol/chloroform. The separated silica gel was extracted with 10% methanol/chloroform and the solvent was evaporated in vacuo. The residue was crystallized from a mixture of ethyl acetate and isopropylether to give the target compound (85.7mg, 90.6%) as a white powder.

MP : 100-104℃.

1H NMR (DMSO-d6) : δ 1.26(6H, d, J=6.9Hz), 2.94(1H, m), 3.27-3.36(2H, m), 3.76(3H, s), 3.89-3.96(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.6Hz), 6.39(1H, s), 6.89(2H, d, J=8.7Hz), 6.93(2H, d, J=8.9Hz), 7.12(2H, d, J=8.7Hz), 7.15(2H, d, J=8.9Hz).

IR (KBr) : 3371, 3190, 2964, 2873, 1738, 1684, 1639, 1614, 1543, 1512cm^{-1}.

MS (ESI+) : m/z 395 (M+H).

Example 6

tert-Butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

tert-Butyl 2-{4-[3-ethoxycarbonyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate (1.37g) in tetrahydrofuran (10ml) was added dropwise to 0.93M solution of methyl magnesium bromide in tetrahydrofuran (16ml) at 24-27℃ with cooling in a waterbath.

After stirring at room temperature for 1hr, the mixture was poured into a mixture of saturated aqueous ammonium chloride solution and ice. The mixture was extracted with

ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 70% ethyl acetate/n-hexane to give the target compound (1.17g, 88%) as an amorphous powder.

MS (ESI+) : m/z 468(M+H)

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 1.65(6H, s), 2.78(1H, s), 3.48-3.57(2H, m), 3.81(3H, s), 3.97-4.03(2H, m), 4.97(1H, br), 6.36(1H, s), 6.78-6.89(4H, m), 7.13(2H, d, J=8.7Hz), 7.21(2H, d, J=8.9Hz).

Example 7

tert-Butyl 2-{4-[3-isopropenyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

Methanesulfonyl chloride (367mg) and triethylamine (649mg) were added successively to a solution of tert-butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 6 (1.0g) and N,N-dimethylformamide (91.5mg) in dichloromethane (10ml) and the mixture was stirred at room temperature for 2hrs. Additional methanesulfonyl chloride and triethylamine were added until all starting material was consumed with stirring at the same temperature.

The reaction mixture was partitioned between ethyl acetate and 1M hydrochloric acid, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue

was purified by silica gel column chromatography eluted with 30% ethyl acetate/n-hexane to give the target compound (900mg, 93.6%) as an amorphous powder.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 2.21(3H, s), 3.48-3.57(2H, m), 3.81(3H, s), 3.97-4.03(2H, m), 4.98(1H, br-s), 5.12(1H, br-s), 5.59(1H, br-s), 6.56(1H, s), 6.77-6.87(4H, m), 7.14(2H, d, J=8.7Hz), 7.22(2H, d, J=8.9Hz).
MS (ESI+) : m/z 450 (M+H).

Example 8

tert-Butyl 2-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

A mixture of 10% Pd-C 50% wet (65mg) and tert-butyl 2-{4-[3-isopropenyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 7 (645mg) in tetrahydrofuran (2ml) and methanol (4ml) was hydrogenated under H_2 1atm at room temperature for 3hrs.

The catalyst was removed by filtration. The filtrate and combined washings were concentrated in vacuo. The residue was crystallized from a mixture of ethyl acetate and isopropyl ether to give the target compound (370mg, 57.1%) as a white powder.

1H NMR ($CDCl_3$) : δ 1.34(6H, d, J=7.0Hz), 1.45(9H, s), 3.07(1H, m), 3.48-3.57(2H, m), 3.80(3H, s), 3.97-4.03(2H, m), 4.97(1H, br-s), 6.26(1H, s), 6.76-6.87(4H, m), 7.14(2H, d, J=8.9Hz), 7.20(2H, d, J=9.0Hz).
MS (ESI+) : m/z 452 (M+H).

Example 9

tert-Butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl-carbamate

The title compound (624.4mg, 42.9%) was prepared as an amorphous powder from tert-butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate in a similar manner to that of Example 6.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 1.65(6H, s), 3.49-3.57(3H, m), 3.93(3H, s), 3.98-4.04(2H, m), 4.98(1H, br), 6.39(1H, s), 6.72(1H, d, J=8.8Hz), 6.83(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.54(1H, dd, J=2.8, 8.8Hz), 8.07(1H, d, J=2.8Hz).
MS(ESI+) : 469 (M+H).

Example 10

tert-Butyl 2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (495mg, 85.7%) was prepared as an oil from tert-butyl 2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}-ethylcarbamate obtained by Example 9 in a similar manner to that of Example 7.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 2.20(3H, s), 3.49-3.57(2H, m), 3.92(3H, s), 3.98-4.04(2H, m), 4.99(1H, br-s), 5.15(1H, br-s), 5.60(1H, br-s), 6.58(1H, s), 6.72(1H, d, J=8.8Hz), 6.83(2H, d, J=8.7Hz), 7.15(2H, d, J=8.7Hz), 7.55(1H, dd, J=2.6, 8.8Hz), 8.09(1H, d, J=2.6Hz).

MS (ESI+) : m/z 451 (M+H).

Example 11

tert-Butyl 2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (220mg, quant.) was prepared as an amorphous powder from tert-butyl 2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}-ethylcarbamate obtained by Example 10 in a similar manner to that of Example 8.

1H NMR ($CDCl_3$) : δ 1.34(6H, d, J=6.8Hz), 1.45(9H, s), 3.07(1H, m), 3.48-3.57(2H, m), 3.92(3H, s), 3.98-4.04(2H, m), 4.98(1H, br), 6.28(1H, s), 6.71(1H, d, J=8.9Hz), 6.82(2H, d, J=8.9Hz), 7.14(2H, d, J=8.9Hz), 7.56(1H, dd, J=2.6, 8.9Hz), 8.05(1H, d, J=2.6Hz).
MS (ESI+) : m/z 453 (M+H).

Example 12

2-{4-[3-Isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride

The title compound (257mg, quant.) was prepared as an amorphous powder from tert-butyl 2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl-carbamate obtained by Example 11 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 1.27(6H, d, J=6.9Hz), 2.96(1H, m), 3.15-3.23(2H, m), 3.85(3H, s), 4.15-4.21(2H, m), 6.47(1H, s), 6.86(1H, d, J=8.8Hz), 6.97(2H, d, J=8.8Hz), 7.20(2H,

d, J=8.8Hz), 7.62(1H, dd, J=2.7, 8.8Hz), 8.01(1H, d, J=2.7Hz), 8.19(2H, s).

MS (ESI+) : m/z 353 (M+H).

Example 13

N-(2-{4-[3-Isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (49.9mg, 51.6%) was prepared as a white powder from 2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine obtained by Example 12 in a similar manner to that of Example 5.

MP : 106-107℃.

1H NMR (DMSO-d6) : δ 1.27(6H, d, J=6.9Hz), 2.96(1H, m), 3.27-3.36
(2H, m), 3.85(3H, s), 3.94(2H, t, J=5.5Hz), 5.52(2H, s), 6.15(1H, t, J=5.6Hz), 6.45(1H, s), 6.85(1H, d, J=8.8Hz), 6.93(2H, d, J=8.7Hz), 7.16(2H, d, J=8.7Hz), 7.60(1H, dd, J=2.6, 8.8Hz), 8.02(1H, d, J=2.6Hz).

IR (KBr) : 3400, 3390, 3379, 3352, 2960, 1657, 1608, 1547, 1512,
1500cm^{-1}.

MS (ESI+) : m/z 396 (M+H).

Example 14-1

5-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine

Sodium (3.19g) was added portionwise to ethanol (160ml). After all sodium was dissolved, 4-methoxyphenylhydrazine hydrochloride (14.5g) was added in one portion to the

solution. The mixture was stirred at room temperature for 10min. To this mixture was added 3-(4-benzyloxyphenyl)acrylonitrile (16.3g) in one portion, and the mixture was refluxed for 3days.

Insoluble matter was filtered off, and the filtrate was concentrated in vacuo. Ethyl acetate and water were added to the residue and the mixture was stirred at room temperature for 1hr. Precipitates were collected and washed successively with water, ethyl acetate, and air dried to give the target compound (12.57g, 48.6%) as a powder.

1H NMR (DMSO-d6) : δ 2.49(1H, dd, J=8.3, 16.1Hz), 3.29(1H, dd, J=10.2, 16.1Hz), 3.60(3H, s), 4.69(1H, dd, J=8.3, 10.2Hz), 5.06(2H, s), 5.62(2H, s), 6.65(4H, s), 6.97(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz), 7.31-7.48(5H, m).
MS : (ESI+) : m/z 374 (M+H).

Example 14-2

5-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine

MnO_2 (3.5g) was added to a solution of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine obtained by Example 14-1 (12.54g) in N,N-dimethylformamide (65ml) and the mixture was stirred at 60℃ for 2hrs. MnO_2 (5.3g) was added and the mixture was stirred at 60℃ for 1hr.

The mixture was filtered through a celite pad and the pad was washed with N,N-dimethylformamide. To the filtrate were added ethyl acetate and water, and the mixture was stirred at room temperature for 1hr. Precipitates were collected and washed with water and air dried. The obtained

powder was suspended in hot isopropylether cooled with stirring, collected and washed with isopropylether to give the target compound (11.70g, 93.8%) as a powder.

1H NMR (DMSO-d6) : δ 3.74(3H, s), 4.84(2H, s), 5.08(2H, s), 5.73(1H, s), 6.87(2H, d, J=9.0Hz), 6.96(2H, d, J=9.0Hz), 7.03-7.13(4H, m), 7.34-7.47(5H, m).
MS (ESI+) : m/z 372 (M+H).

Example 15

5-[4-(Benzyloxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazol-3-amine

37% Aqueous formamide solution (6ml) and sodium cyanoborohydride (1.39g) were added successively to a solution of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine obtained by Example 14-2 (2.75g) in methanol 30ml. The reaction mixture was stirred at room temperature for 3days, occasionally adding 37% aqueous formamide solution and sodium cyanoborohydride appropriate amount to consume all starting material.

The reaction mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate/chloroform to give the target compound (0.88g, 29.8%) as an oil.

1H NMR (DMSO-d6) : δ 2.81(6H, s), 3.75(3H, s), 5.08(2H, s), 6.03(1H, s), 6.90(2H, d, J=8.9Hz), 6.97(2H, d, J=8.8Hz),

7.06-7.16(4H, m), 7.32-7.46(5H, m).
MS (ESI+) : m/z 400 (M+H).

Example 16

4-[3-(Dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

A mixture of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazol-3-amine obtained by Example 15 (0.83g) and 10% Pd-C 50% wet (160mg) in acetic acid (8ml) was hydrogenated under H_2 1atm at room temperature for 10hrs.

The catalyst was removed by filtration. The filtrate and combined washings were concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate/chloroform and was crystallized from a mixture of isopropylether and ethyl acetate to give the target compound (455mg, 70.8%) as a white powder.

1H NMR (DMSO-d6) : δ 2.80(6H, s), 3.74(3H, s), 5.96(1H, s), 6.69(2H, d, J=8.5Hz), 6.89(2H, d, J=9.0Hz), 7.01(2H, d, J=8.5Hz), 7.09(2H, d, J=9.0Hz), 9.64(1H, s).
MS (ESI+) : m/z 310 (M+H).

Example 17

tert-Butyl 2-{4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (477.1mg, 99.7%) was prepared as an oil from 4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 16 in a

similar manner to that of Example 2.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 2.93(6H, s), 3.48-3.54(2H, m), 3.79(3H, s), 3.97-4.03(2H, m), 4.97(1H, br), 5.85(1H, s), 6.79(2H, d, J=8.7Hz), 6.81(2H, d, J=9.0Hz), 7.10-7.27(4H, m).

Example 18

5-[4-(2-Aminoethoxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazol-3-amine hydrochloride

The title compound (454mg, quant.) was prepared as an amorphous from tert-butyl 2-{4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl-carbamate obtained by Example 17 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 2.83(6H, s), 3.16-3.25(2H, m), 3.75(3H, s), 4.13-4.18(2H, m), 6.06(1H, s), 6.91(2H, d, J=9.0Hz), 6.94(2H, d, J=8.8Hz), 7.12(2H, d, J=9.0Hz), 7.17(2H, d, J=8.8Hz), 8.05(2H, br-s).
MS (ESI+) : m/z 353 (M+H).

Example 19

N-(2-{4-[3-(Dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (116mg, 55.7%) was prepared as an amorphous from 5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-N,N-dimethyl-1H-pyrazol-3-amine hydrochloride obtained by Example 18 in a similar manner to that of Example 75 described later.

1H NMR (DMSO-d6) : δ 2.81(6H, s), 3.29-3.34(2H, m), 3.74(3H, s), 3.92(2H, t, J=5.6Hz), 5.53(2H, s), 6.03(1H, s), 6.15(1H, t, J=5.6Hz), 6.88-6.92(4H, m), 7.04-7.14(4H, m).

IR (neat) : 3344, 3330, 3321, 1658, 1651, 1643, 1612, 1579, 1564, 1554, 1529, 1514cm^{-1}.

MS (ESI+) : m/z 396 (M+H).

Example 20-1

5-[4-(Methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine

The title compound (4.0g, 57.8%) was prepared as a powder from 3-(4-methoxymethoxyphenyl)acrylonitrile in a similar manner to that of Example 14-1.

1H NMR (DMSO-d6) : δ 2.49(1H, dd, J=8.3, 16.1Hz), 3.30(1H, dd, J=10.3, 16.1Hz), 3.36(3H, s), 3.59(3H, s), 4.70(1H, dd, J=8.3, 10.3Hz), 5.16(2H, s), 5.62(2H, s), 6.65(4H, s), 6.97(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz).

MS (ESI+) : m/z 328 (M+H).

Example 20-2

5-[4-(Methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine

The title compound (4.80g, quant.) was prepared as an oil from 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-amine obtained by Example 20-1 in a similar manner to that of Example 14-2.

1H NMR (DMSO-d6) : δ 3.36(3H, s), 3.74(3H, s), 4.85(2H, s), 5.18(2H, s), 5.74(1H, s), 6.88(2H, d, J=9.0Hz), 6.96 (2H, d, J=8.8Hz), 7.02-7.13(4H, m).

MS (ESI+) : m/z 326 (M+H).

Example 21

3-Chloro-5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazole

A mixture of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-amine obtained by Example 20-2 (3.79g), lithium chloride (2.47g), and copper(II) chloride (3.13g) in acetonitrile (60ml) was stirred at room temperature for 10min. To this mixture was added isoamyl nitrite (2.73g), and the mixture was stirred at room temperature for 1hr.

The mixture was partitioned between ethyl acetate and saturated aqueous ammonium chloride solution. The organic layer was washed with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 30% ethyl acetate/n-hexane. The solvent was evaporated in vacuo. The residue was crystallized from a mixture of isopropyl ether and ethyl acetate to give the target compound (2.38g, 59.3%) as a white powder.

1H NMR ($CDCl_3$) : δ 3.48(3H, s), 3.82(3H, s), 5.17(2H, s), 6.36(1H, s), 6.85(2H, d, J=9.0Hz), 6.95(2H, d, J=8.9Hz), 7.12(2H, d, J=8.9Hz), 7.20(2H, d, J=9.0Hz).

MS (ESI+) : m/z 345(M+H).

Example 22

4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

To a solution of 3-chloro-5-[4-(methoxymethoxy)-phenyl]-1-(4-methoxyphenyl)-1H-pyrazole obtained by Example 21 (2.35g) in tetrahydrofuran (10ml) and methanol (10ml) was added 36% hydrochloric acid (0.34ml). The reaction mixture was stirred at room temperature for 1hr, at 50℃ for 1.5hrs, and at 60℃ for 1.5hrs.

The mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue solid was collected and washed with a mixture of isopropylether and n-hexane to give the target compound (1.99g, 97.1%) as a white powder.

1H NMR (DMSO-d6) : δ 3.78(3H, s), 6.62(1H, s), 6.71(2H, d, J=8.7Hz), 6.96(2H, d, J=9.0Hz), 7.03(2H, d, J=8.7Hz), 7.19(2H, d, J=9.0Hz), 9.80(1H, s).

200MHz 1H NMR ($CDCl_3$) : δ 3.82(3H, s), 5.24(1H, s), 6.35(1H, s), 6.75(2H, d, J=8.6Hz), 6.84(2H, d, J=9.0Hz), 7.07(2H, d, J=8.6Hz), 7.18(2H, d, J=9.0Hz).

MS (ESI+) : m/z 301 (M+H).

Example 23

2-{4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethanol

Sodium hydride 60% dispersion in mineral oil (31.1mg) was added to a solution of 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 22 (180mg) in

N,N-dimethylformamide (2ml) under cooling in an ice bath. The reaction mixture was stirred at room temperature for 1hr. To the reaction mixture was added a solution of 2-bromoethyl tert-butyl(dimethyl)silyl ether (258mg) in N,N-dimethylformamide (2ml).

After stirring at room temperature overnight, the mixture was poured into ice water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in ethanol (3.6ml). To this solution was added 36% aqueous hydrochloric acid (0.3ml). After stirring at room temperature for 3 hrs, the mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 70% ethyl acetate/n-hexane. The separate silica gel was extracted with 10% methanol/chloroform and the solvent was evaporated in vacuo. The residue was crystallized from a mixture of isopropylether and ethyl acetate to give the target compound (136.4mg, 66.1%) as a white powder.

MP : 114.7-115.5℃.

1H NMR (DMSO-d6) : δ 3.64-3.73(2H, m), 3.77(3H, s), 3.97(2H, t, J=4.9Hz), 4.86(1H, t, J=5.4Hz), 6.68(1H, s), 6.91(2H, d, J=8.9Hz), 6.96(2H, d, J=8.9Hz), 7.15(2H, d, J=8.9Hz), 7.20(2H, d, J=8.9Hz).

IR(KBr) : 3521, 1610, 1518cm^{-1}.

MS (ESI+) : m/z 345 (M+H).

Example 24

tert-Butyl 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (329.5mg, 22.3%) was prepared as an amorphous from 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 22 in a similar manner to that of Example 73 described later.

1H NMR ($CDCl_3$) : δ 1.45(9H, s), 3.48-3.57(2H, m), 3.81(3H, s), 4.00(2H, t, J=5.1Hz), 4.96(1H, br), 6.35(1H, s), 6.81(2H, d, J=8.8Hz), 6.84(2H, d, J=8.9Hz), 7.12(2H, d, J=8.8Hz), 7.18(2H, d, J=8.9Hz).

MS (ESI+) : m/z 444 (M+H).

Example 25

tert-Butyl 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (1.31g, 97.8%) was prepared from 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 22 in a similar manner to that of Example 2.

MS (ESI+) : m/z 444 (M+H).

Example 26

2-{4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethanamine hydrochloride

The title compound (605.2mg, 85.4%) was prepared as

a white powder from tert-butyl 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 25 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 3.14-3.23(2H, m), 3.78(3H, s), 4.14-4.20(2H, m), 6.70(1H, s), 6.96(2H, d, J=8.8Hz), 6.97(2H, d, J=8.9Hz), 7.19(2H, d, J=8.8Hz), 7.21(2H, d, J=8.9Hz), 8.19(2H, br-s).

MS (ESI+) : m/z 344 (M+H).

Example 27

N-(2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)methanesulfonamide

The title compound (137.8mg, 82.8%) was prepared as a white powder from 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 26 in a similar manner to that of Example 4.

MP : 117-119℃.

1H NMR (DMSO-d6) : δ 2.94(3H, s), 3.27-3.34(2H, m), 3.76(3H, s), 4.02(2H, t, J=5.5Hz), 6.69(1H, s), 6.90-7.01(4H, m), 7.14-7.25(4H, m), 7.28(1H, t, J=5.7Hz).

IR (KBr) : 1612, 1516cm^{-1}.

MS (ESI+) : m/z 422(M+H).

Example 28

N-(2-{4-[3-Chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)urea

The title compound (174.6mg, 85.8%) was prepared as a white powder from 2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 26 in a similar manner to that of Example 75 described later.

MP : 144.8-145.4℃.

1H NMR (DMSO-d6) : δ 3.27-3.34(2H, m), 3.77(3H, s), 3.93(2H, t, J=5.5Hz), 5.52(2H, s), 6.15(1H, t, J=5.7Hz), 6.68(1H, s), 6.92(2H, d, J=9.0Hz), 6.97(2H, d, J=9.0Hz), 7.15(2H, d, J=9.0Hz), 7.20(2H, d, J=9.0Hz).

IR (ATR) : 3423, 3402, 3203, 3143, 3010, 2976, 2943, 2885, 1651, 1610, 1583, 1516cm^{-1}.

MS (ESI+) : m/z 387 (M+H).

Example 29-1

5-[4-(Methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-4,5-dihydro-1H-pyrazol-3-amine

The title compound (1.63g, 41.2%) was prepared as a powder from 3-(4-methoxymethoxyphenyl)acrylonitrile and 2-methoxy-5-pyridinylhydrazine dihydrochloride in a similar manner to that of Example 14-1.

H NMR (DMSO-d6) : δ 2.48-2.60(1H, dd, overlapping), 3.23-3.34(1H, dd, overlapping), 3.36(3H, s), 3.68(3H, s), 4.75(1H, dd, J=8.6, 10.0Hz), 5.16(2H, s), 5.77(2H, s), 6.56(1H, d, J=8.8Hz), 6.98(2H, d, J=8.6Hz), 7.15(1H, dd, J=2.8, 8.8Hz), 7.27(2H, d, J=8.6Hz), 7.49(1H, d, J=2.8Hz).

MS (ESI+) : m/z 329 (M+H).

Example 29-2

5-[4-(Methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-amine

The title compound (1.77g, quant.) was prepared as an oil from 5-[4-(methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-4,5-dihydro-1H-pyrazol-3-amine obtained by Example 29-1 in a similar manner to that of Example 14-2.

1H NMR (DMSO-d6) : δ 3.37(3H, s), 3.83(3H, s), 4.97(2H, s), 5.19(2H, s), 5.78(1H, s), 6.81(1H, d, J=8.9Hz), 6.99(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.51(1H, dd, J=2.7, 8.9Hz), 7.92(1H, d, J=2.7Hz).
MS (ESI+) : m/z 327 (M+H).

Example 30

5-{3-Chloro-5-[4-(methoxymethoxy)phenyl]-1H-pyrazol-1-yl}-2-methoxypyridine

The title compound (981.7mg, 57.9%) was prepared as a powder from 5-[4-(methoxymethoxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-amine obtained by Example 29-2 in a similar manner to that of Example 21.

1H NMR ($CDCl_3$) : δ 3.48(3H, s), 3.93(3H, s), 5.18(2H, s), 6.39(1H, s), 6.74(1H, d, J=8.8Hz), 6.99(2H, d, J=8.8Hz), 7.13(2H, d, J=8.8Hz), 7.55(1H, dd, J=2.7, 8.8Hz), 8.05 (1H, d, J=2.7Hz).
MS (ESI+) : m/z 346 (M+H).

Example 31

4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]-

phenol

The title compound (2.15g, 80.5%) was prepared as a white powder from 5-{3-chloro-5-[4-(methoxymethoxy)-phenyl]-1H-pyrazol-1-yl}-2-methoxypyridine obtained by Example 30 in a similar manner to that of Example 22.

1H NMR (DMSO-d6) : δ 3.87(3H, s), 6.68(1H, s), 6.74(2H, d, J=8.6Hz), 6.89(1H, d, J=8.8Hz), 7.07(2H, d, J=8.6Hz), 7.65(1H, dd, J=2.7, 8.8Hz), 8.09(1H, d, J=2.7Hz), 9.86 (1H, br-s).
MS (ESI+) : m/z 302 (M+H).

Example 32

2-{4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

The title compound (140.9mg, 86%) was prepared as a white powder from 4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 31 in a similar manner to that of Example 23.

MP : 136.5-138.2℃.
1H NMR (DMSO-d6) : δ 3.65-3.74(2H, m), 3.87(3H, s), 3.98(2H, t, J=4.9Hz), 4.87(1H, t, J=5.5Hz), 6.74(1H, s), 6.86-6.98(3H, m), 7.19(2H, d, J=8.8Hz), 7.67(1H, dd, J=2.8, 8.8Hz), 8.10(1H, d, J=2.8Hz).
IR (KBr) : 3369, 2960, 1610, 1502cm^{-1}.
MS (ESI+) : m/z 346 (M+H).

Example 33

tert-Butyl 2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-

pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (964mg, 93.4%) was prepared as a white solid from 4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 31 in a similar manner to that of Example 2.

1H NMR (DMSO-d6) : δ 1.37(9H, s), 3.22-3.33(2H, m), 3.87(3H, s), 3.95(2H, t, J=5.7Hz), 6.74(1H, s), 6.86-7.04(4H, m), 7.19(2H, d, J=8.7Hz), 7.67(1H, dd, J=2.7, 8.8Hz), 8.11(1H, d, J=2.7Hz).
MS (ESI+) : m/z 445 (M+H).

Example 34

2-{4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}-ethanamine dihydrochloride

The title compound (842mg, 98.6%) was prepared as an amorphous from tert-butyl 2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 33 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 3.15-3.24(2H, m), 3.87(3H, s), 4.19(2H, t, J=4.9Hz), 6.76(1H, s), 6.90(1H, d, J=8.8Hz), 6.99(2H, d, J=8.8Hz), 7.23(2H, d, J=8.8Hz), 7.68(1H, d, J=2.7, 8.8Hz), 8.10(1H, d,
J=2.7Hz), 8.20(2H, br-s).
MS (ESI+) : m/z 345 (M+H).

Example 35

N-(2-{4-[3-Chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-

5-yl]phenoxy}ethyl)urea

The title compound (119.5mg, 62.4%) was prepared as a white powder from 2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride obtained by Example 34 in a similar manner to that of Example 75 described later.

MP : 155.6-157.9℃.

1H NMR (DMSO-d6) : δ 3.27-3.34(2H, m), 3.87(3H, s), 3.94(2H, t, J=5.5Hz), 5.53(2H, s), 6.15(1H, t, J=5.5Hz), 6.75(1H, s), 6.89(1H, d, J=8.8Hz), 6.95(2H, d, J=8.8Hz), 7.19(2H, d, J=8.8Hz), 7.66(1H, dd, J=2.7, 8.8Hz), 8.11(1H, d, J=2.7Hz).

IR (KBr) : 3425, 3415, 3319, 1657, 1610, 1591, 1581, 1574, 1500cm^{-1}.

Example 36

5-[4-(Benzyloxy)phenyl]-3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazole

A mixture of 5-[4-(benzyloxy)phenyl]-3-hydroxy-1-(4-methoxyphenyl)-1H-pyrazol (2.4g), 2-iodopropane (5.48g), and potassium carbonate (2.67g) in N,N-dimethylformamide (10ml) was stirred at 100℃ for 3hrs.

The reaction mixture was poured into ice water and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate/n-hexane and the solvent was evaporated in vacuo. The residue was

recrystallized from a mixture of ethyl acetate and n-hexane to give the target compound (2.14g, 80.1%) as a white powder.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 3.76(3H, s), 4.75(1H, m), 5.08(2H, s), 6.00(1H, s), 6.92(2H, d, J=9.0Hz), 6.97(2H, d, J=8.9Hz), 7.10-7.16(4H, m), 7.34-7.43(5H, m).
MS (ESI+) : m/z 415 (M+H).

Example 37

4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenol

To a solution of ammonium formate (954mg) in water (2ml) were added ethanol (10ml), a solution of 5-[4-(benzyl-oxy)phenyl]-3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazole obtained by Example 36 (2.09g) in tetrahydrofuran (10ml), and 10% palladium on carbon 50% wet (200mg) successively. The mixture was refluxed for 1hr.

The catalyst was removed by filtration and washed with ethyl acetate. The filtrate and combined washings were concentrated in vacuo. Ethyl acetate and water were added to the residue. Precipitates were collected and washed with water and ethyl acetate to give the first crop of the target compound (419mg) as a white powder. The filtrate was partitioned, and the organic layer was saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue crystals were collected and washed with isopropylether to give the second crop of the target compound (1.19g, 72.5%) as a white powder.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.2Hz), 3.75(3H, s), 4.75(1H, m), 5.93(1H, s), 6.70(2H, d, J=8.6Hz), 6.91(2H,

d, J=9.0Hz), 7.01(2H, d, J=8.6Hz), 7.11(2H, d, J=9.0Hz), 9.70(1H, s).

MS (ESI+) : m/z 325(M+H).

Example 38

2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol

The title compound (147.3mg, 88.2%) was prepared as an oil from 4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 37 in a similar manner to that of Example 23.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.2Hz), 2.02(1H, t, J=5.8Hz), 3.79(3H, s), 3.94-4.00(2H, m), 4.04-4.10(2H, m), 4.87(1H, m), 5.85(1H, s), 6.81(2H, d, J=9.0Hz), 6.82(2H, d, J=8.9Hz), 7.10-7.21(4H, m).

IR (neat) : 3400, 3369, 2974, 2933, 1612, 1514cm^{-1}.

MS (ESI+) : m/z 369 (M+H).

Example 39

tert-Butyl 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (520mg, 72.2%) was prepared as a white powder from 4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol obtained by Example 37 in a similar manner to that of Example 2.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.2Hz), 1.37(9H, s), 3.22-3.31(2H, m), 3.75(3H, s), 3.90-3.97(2H, m), 4.76(1H, m), 5.99(1H, s), 6.86-6.96(4H, m), 7.01(1H, t, J=5.6Hz),

7.09-7.15(4H, m).

MS (ESI+) : m/z 467 (M+H).

Example 40

2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride

The title compound (557mg, quant.) was prepared as an amorphous from tert-butyl 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 39 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 3.12-3.28(2H, m), 3.76(3H, s), 4.00-4.18(2H, m), 4.76(1H, m), 6.01(1H, s), 6.92(2H, d, J=9.0Hz), 6.94(2H, d, J=8.7Hz), 7.10-7.19(4H, m), 8.06(2H, br-s).

MS (ESI+) : m/z 368 (M+H).

Example 41

N-(2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (125mg, 79.8%) was prepared as a white powder from 2-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 40 in a similar manner to that of Example 4.

MP : 167.9-168.0℃.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 2.94(3H, s), 3.27-3.36

(2H, m), 3.75(3H, s), 3.98-4.05(2H, m), 4.76(1H, m), 6.0 0(1H, s), 6.88-6.94(4H, m), 7.12(2H, d, J=9.0Hz), 7.14(2 H, d, J=8.9Hz), 7.29(1H, t, J=5.8Hz).

IR (KBr) : 3132, 2979, 2939, 1612, 1556, 1518cm^{-1}.

MS (ESI+) : m/z 446 (M+H).

Example 42

N-(2-{4-[3-Isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (76.3mg, 50.1%) was prepared as a white powder from 2-{4-[3-isopropoxy-1-(4-methoxy-phenyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 40 in a similar manner to that of Example 75 described later.

MP : 139-140℃.

1H NMR (DMSO-d6) : δ 1.31(6H, d, J=6.1Hz), 3.27-3.35(2H, m), 3.75(3H, s), 3.89-3.96(2H, m), 4.76(1H, m), 5.53(2H, s), 6.00(1H, s), 6.15(1H, t, J=5.7Hz), 6.90(2H, d, J=8. 9Hz), 6.92(2H, d, J=9.0Hz),
7.08-7.15(4H, m).

IR (KBr) : 3388, 3350, 3332, 1658, 1612, 1579, 1562, 1554, 1518cm^{-1}.

MS (ESI+) : m/z 411 (M+H).

Example 43

5-[4-(Benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-ol

To a solution of 3-(4-benzyloxyphenyl)propiolic acid (1g) and 1-hydroxybenzotriazole hydrate (643mg) in

N-methylpyrrolidone (10ml) was added WSCD·HCl (912mg) and the mixture was stirred at room temperature for 10min. In another flask, diisopropylethylamine (2.31g) was added to a suspension of 5-hydrazino-2-methoxypyridine dihydrochloride (1.26g) in N-methylpyrrolidone (4ml) and stirred at room temperature until all 5-hydrazino-2-methoxypyridine dihydrochloride was dissolved. Thus obtained hydrazine solution was added to the reaction flask and the mixture was stirred at room temperature for 1.5hrs.

The mixture was partitioned between ethyl acetate and 0.1M hydrochloric acid, and the aqueous layer was reextracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in dichloroethane (15ml) and tetrakis(triphenylphosphine)palladium(0) (45.8mg) was added. The mixture was refluxed for 1hr and then concentrated in vacuo. The residue was crystallized from ethyl acetate to give the target compound (739mg, 49.9%) as a powder.

1H NMR (DMSO-d6) : δ 3.84(3H, s), 5.10(2H, s), 5.87(1H, s), 6.83(1H, d, J=8.7Hz), 7.00(2H, d, J=8.7Hz), 7.16(2H, d, J=8.7Hz), 7.29-7.48(5H, m), 7.54(1H, dd, J=2.6, 8.7Hz), 7.97(1H, d, J=2.6Hz), 10.13(1H, s).
MS (ESI+) : m/z (M+H).

Example 44

5-{5-[4-(Benzyloxy)phenyl]-3-isopropoxy-1H-pyrazol-1-yl}-2-methoxypyridine

The title compound (1.33g, quant.) was prepared as a powder from 5-[4-(benzyloxy)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-ol obtained by Example 43 in a similar manner to that of Example 36.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.2Hz), 3.92(3H, s), 4.86(1H, m), 5.05(2H, s), 5.87(1H, s), 6.69(1H, d, J=8.8Hz), 6.91(2H, d, J=8.8Hz), 7.15(2H, d, J=8.8Hz), 7.35-7.43(5H, m), 7.51(1H, dd, J=2.7, 8.8Hz), 8.04(1H, d, J=2.7Hz).
MS (ESI+) : m/z 416 (M+H).

Example 45

4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

The title compound (442.5mg, 54.9%) was prepared as a powder from 5-{5-[4-(benzyloxy)phenyl]-3-isopropoxy-1H-pyrazol-1-yl}-2-methoxypyridine obtained by Example 44 in a similar manner to that of Example 37.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.2Hz), 3.91(3H, s), 4.84(1H, m), 5.80(1H, s), 5.87(1H, s), 6.71(1H, d, J=8.8Hz), 6.75(2H, d, J=8.6Hz), 7.08(2H, d, J=8.6Hz), 7.55(1H, dd, J=2.7, 8.8Hz), 8.00(1H, d, J=2.7Hz).
MS (ESI+) : m/z 326 (M+H).

Example 46

2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

The title compound (94.6mg, 52.2%) was prepared as a white powder from 4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 45 in a similar manner to that of Example 23.

MP : 74-75℃.

1H NMR ($CDCl_3$) : δ 1.40(6H, d, J=6.1Hz), 1.99(1H, t, J=6.1Hz), 3.91(3H, s), 3.94-4.00(2H, m), 4.05-4.11(2H, m), 4.86(1H, m), 5.88(1H, s), 6.69(1H, d, J=8.7Hz), 6.85(2H, d, J=8.7Hz), 7.15(2H, d, J=8.7Hz), 7.51(1H, dd, J=2.7, 8.7Hz), 8.03(1H, d, J=2.7Hz).

IR (KBr) : 3350, 1612, 1512, 1500cm^{-1}.

MS (ESI+) : m/z 370 (M+H).

Example 47

tert-Butyl 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (515.3mg, 87.6%) was prepared as a powder from 4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol obtained by Example 45 in a similar manner to that of Example 2.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.2Hz), 1.37(9H, s), 3.22-3.34(2H, m), 3.84(3H, s), 3.92(2H, t, J=5.7Hz), 4.77(1H, m), 6.06(1H, s), 6.84(1H, d, J=8.8Hz), 6.91(2H, d, J=8.8Hz), 7.01(1H, t, J=5.5Hz), 7.16(2H, d, J=8.8Hz), 7.58(1H, dd, J=2.7, 8.8Hz), 7.99(1H, d, J=2.7Hz).

Example 48

2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride

The title compound (531mg, quant.) was prepared as an amorphous from tert-butyl 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl-carbamate obtained by Example 47 in a similar manner to that of Example 3.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.1Hz), 3.15-3.24(2H, m), 3.84(3H, s), 4.19(2H, t, J=4.9Hz), 4.77(1H, m), 6.07(1H, s), 6.85(1H, d, J=8.8Hz), 6.97(2H, d, J=8.8Hz), 7.21(2H, d, J=8.8Hz), 7.60(1H, dd, J=2.7, 8.8Hz), 7.99(1H, d, J=2.7Hz), 8.22(2H, br-s).
MS (ESI+) : m/z 369 (M+H).

Example 49

N-(2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (81.4mg, 60.2%) was prepared as a white powder from 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride obtained by Example 48 in a similar manner to that of Example 75 described later.

MP : 120℃.
1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.2Hz), 3.27-3.36(2H, m), 3.84(3H, s), 3.94(2H, t, J=5.5Hz), 4.77(1H, m), 5.52(2H, s), 6.06(1H, s), 6.15(1H, t, J=5.6Hz), 6.84(1H, d, J=8.8Hz), 6.93(2H, d, J=8.8Hz), 7.17(2H, d, J=8.8Hz), 7.58(1H, dd, J=2.7, 8.8Hz), 7.99(1H, d, J=2.7Hz).
IR (KBr) : 3400, 3330, 1658, 1612, 1514, 1500cm^{-1}.
MS (ESI+) : m/z 412 (M+H).

Example 50

N-(2-{4-[3-Isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (94.4mg, 58.4%) was prepared from 2-{4-[3-isopropoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanamine dihydrochloride obtained by Example 48 in a similar manner to that of Example 4.

MP : 121.0-121.6℃.

1H NMR (DMSO-d6) : δ 1.32(6H, d, J=6.1Hz), 2.94(3H, s), 3.29-3.34(2H, m), 3.84(3H, s), 4.00-4.06(2H, m), 4.77(1H, m), 6.06(1H, s), 6.85(1H, d, J=8.7Hz), 6.94(2H, d, J=8.8Hz), 7.18(2H, d, J=8.8Hz), 7.28(1H, br-s), 7.58(1H, dd, J=2.7, 8.7Hz), 7.99(1H, d, J=2.7Hz).

IR (KBr) : 3242, 1612, 1514, 1502cm^{-1}.

MS (ESI+) : m/z 447 (M+H).

Example 51

2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate

To a solution of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanol (2.72 g) and triethylamine (1.55ml) in dichloromethane (30ml) was added dropwise methanesulfonyl chloride (0.86ml) under ice-cooling. The reaction mixture was allowed to warm to room temperature and stirred for 1hr.

The reaction mixture was quenched with water. The organic layer was separated and washed with 1N hydrochloric

acid and water, dried over sodium sulfate, filtered and evaporated under reduced pressure to give the target compound (3.25g, 98.5%).

1 HNMR ($CDCl_3$) : δ 2.929(3H, s), 3.072(2H, t, J=6.7Hz), 4.427(2H, t, J=6.7Hz), 6.739(1H,), 7.175(2H, d, J=8.4Hz), 7.234(2H, d, J=8.4Hz), 7.253(2H, d, J=8.9Hz), 7.344 (2H, d, J=8.8Hz).

MS (ESI+): m/z 467 (M+Na).

Example 52

2-(2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione

A mixture of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate obtained by Example 51 (3.2g) and Potassium phthalimide (1.6g) was stirred at 80℃ for 5hrs.

After cooling, the mixture was diluted with water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (twice). The combined organic layer was washed with water (twice) and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give the target compound (1.55g, 43.5%) as a powder.

1H NMR ($CDCl_3$) : δ 1.59(3H, s), 3.02(2H, t, J=7.3Hz), 3.94(2H, t, J=7.3Hz), 6.71(1H, s), 7.11(2H, d, J=8.2Hz), 7.21(2H, d, J=7.6Hz), 7.24(2H, d, J=8.4Hz), 7.32(2H, d, J=8.9Hz), 7.70-7.86(4H, m).

MS (ESI+) : m/z 518 (M+Na).

Example 53

2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine

A mixture of 2-(2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione obtained by Example 52 (1.5g) and hydrazine (2.93ml) in acetonitrile (30ml) was stirred at 60℃ for 5hrs.

After cooling, the mixture was filtered and washed with acetonitrile. The filtrate was evaporated under reduced pressure to give the target compound (1.1g, quant.) as an oil.

1H NMR ($CDCl_3$): δ 3.09(2H, dd, J=5.6Hz, 9.3Hz), 3.24(2H, dd, J=5.6Hz, 8.6Hz), 5.47(2H, s), 6.69(1H, s), 7.12(1H, d, J=8.2Hz), 7.21(1H, d, J=8.2Hz), 7.22(1H, d, J=8.9Hz), 7.32(1H, d, J=8.9Hz).

MS (ESI+) : m/z 366 (M+1).

Example 54

N-(2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)methanesulfonamide

To a solution of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine obtained by Example 53 (400mg) and triethylamine (0.46ml) in dichloromethane (20ml) was added dropwise methanesulfonyl chloride (0.25ml) at room temperature.

After stirring for 1hr, the reaction mixture was quenched with 1N hydrochloric acid. The aqueous layer was separated and extracted twice with chloroform. The

combined organic layer was washed with 1N hydrochloric acid, sodium hydrogencarbonate solution, water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (chloroform/methanol=4:1) to give the target compound (166mg, 34.2%) as an oil.

1H NMR ($CDCl_3$): δ 2.899(3H, s), 2.904(2H, t, J=6.9Hz), 3.417(2H, dt, J=6.7 ,6.8Hz), 4.272(1H, t, J=6.1Hz), 6.737 (1H, s), 7.178(2H, d, J=8.4Hz), 7.21(2H, d, J=8.4Hz), 7.255(2H, d, J=8.8Hz), 7.35(2H, d, J=8.8Hz).
IR (Film) : 3346, 1657, 1597, 1552, 1496, 1471, 1236, 1163, 1136, 1092, 978, 835, 756 cm^{-1}.
MS (ESI-) : 442 (M-1).

Example 55

N-(2-{4-[1-(4-Chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)urea

To a solution of 2-{4-[1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine obtained by Example 53 (300mg) and triethylamine (0.57ml) in dichloromethane (10ml) was added dropwise trimethylsilyl isocyanate (0.555ml) at room temperature.

After stirring overnight, the reaction mixture was quenched with 1N hydrochloric acid. Aqueous layer was separated and extracted twice with chloroform. The combined organic layer was washed with 1N hydrochloric acid, sodium hydrogencarbonate solution, water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel

(chloroform/methanol=4:1) to give the target compound (205mg, 61.1%) as an amorphous.

1H NMR ($CDCl_3$): δ 2.83(2H, t, J=7Hz), 3.43(2H, dt, J=6.6 Hz, 6.8Hz), 4.41(2H, s), 4.61(1H, t, J=5.4Hz), 6.72(1H, s), 7.16(4H, s), 7.25(2H, d, J=8.8Hz), 7.34(2H, d, J=8.8 Hz).

IR (Film): 3346, 1657, 1597, 1552, 1496, 1471, 1448, 1375, 1271, 1236, 1163, 1136, 1092, 978, 835, 756 cm^{-1}.

MS (ESI+) : m/z 431 (M+Na).

Example 56

4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile

A mixture of 4-(4,4,4-trifluoro-3-oxobutanoyl)-benzonitrile (1.0g), 4-methoxyphenylhydrazine hydrochloride (760mg), and sodium acetate (357mg) in acetic acid (10ml) was stirred at 80℃ for 4hrs.

After cooling, the reaction mixture was poured into water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. Combined organic layers were washed with saturated sodium hydrogencarbonate solution (twice), water and brine, dried over sodium sulfate, and evaporated under reduced pressure to give crude product. The crude product was column chromatographed on silica gel (50ml, n-hexane:ethyl acetate=5:1-4:1) and triturate with petroleum ether to give the target compound (553mg, 38.8%).

1H NMR ($CDCl_3$) : δ 3.84(3H, s), 6.82(1H, s), 6.9(2H, d, J=9Hz), 7.2(2H, d, J=9Hz), 7.33(2H, d, J=8.6Hz), 7.62(2H, d, J=8.6Hz).

IR (Film) : 2229, 1610, 1512, 1468, 1240, 1161, 1132, 839 cm^{-1}.

MS (ESI+) : m/z 366 (M+Na).

Example 57

4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl-amine hydrochloride

A mixture of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile obtained by Example 56 (430mg), Pd/C (100mg) and 1N hydrochloric acid (1.3ml) in methanol (43ml) was stirred under Hydrogen atmosphere for 5hrs.

The reaction mixture was filtered with paper filter, and filtrate was evaporated. After dissolving in methanol, the solution was filtered with membrane filter. The filtrate was evaporated to give the target compound (450mg, 93.6%) as crystals.

1H NMR ($CDCl_3$) : δ 3.79(3H, s), 4.04(2H, br-s), 6.69(1H, s), 6.85(2H, d, J=8.9Hz), 7.13(2H, d, J=8.9Hz), 7.24(2H, d, J=9Hz), 7.42(2H, d, J=9Hz).

IR (Film) : 2964, 1512, 1468, 1238, 1161, 1130, 976, 837 cm^{-1}.

MS (ESI+) : m/z 331 (M-Cl-NH_3).

Example 58

N-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

To a solution of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine

hydrochloride obtained by Example 57 (100mg) and triethylamine (0.073ml) in chloroform (10ml) was added dropwise methanesulfonyl chloride (0.04ml) at room temperature.

After stirring for 1hr, the reaction mixture was partitioned between chloroform and water. The organic layer was washed with water, sodium bicarbonate solution, brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give the target compound (90mg, 81.2%) as an oil.

1H NMR ($CDCl_3$) : δ 2.93(3H, s), 3.82(3H, s), 4.32(2H, d, J=6.2Hz), 4.71(1H, t, J=6.2Hz), 6.73(1H, s), 6.86(2H, d, J=9Hz), 7.21(2H, d, J=9Hz), 7.21(2H, d, J=8.3Hz), 7.31 (2H, d, J=8.3Hz).
IR (Film) : 3282, 1514, 1321, 1240, 1151, 974, 837cm^{-1}.
MASS (ESI+) : m/z 426 (M+1).

Example 59

4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzonitrile

The title compound (4.5g, 20.6%) was prepared from 4-(4,4-difluoro-3-oxobutanoyl)benzonitrile in a similar manner to that of Example 56.

1H NMR ($CDCl_3$) : δ 3.84(3H, s), 6.77(1H, t, J=54.9Hz), 6.8(1H, s), 6.9(2H, d, J=9Hz), 7.19(2H, d, J=9Hz), 7.33(2H, d, J=8.6Hz), 7.61(2H, d, J=8.6Hz).
MS (ESI+) : m/z 348 (M+Na).

Example 60

1-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride

The title compound (510mg, 45.4%) was prepared from 4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzonitrile obtained by Example 59 in a similar manner to that of Example 57.

1H NMR (DMSO-d6) : δ 3.35(3H, s), 3.79(2H, s), 7.1(1H, t, J=54.5Hz), 6.95(1H, s), 6.99(2H, d, J=8.8Hz), 7.26(2H, d, J=8.8Hz), 7.3(2H, d, J=8.3Hz), 7.49(2H, d, J=8.3Hz).
MS (ESI-): m/z 365 (M-HCl).

Example 61

N-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

The title compound (146mg, 65.5%) was prepared from 1-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride obtained by Example 60 in a similar manner to that of Example 58.

1H NMR ($CDCl_3$) : δ 2.90(3H, s), 3.82(3H, s), 4.31(2H, d, J=6.2Hz), 4.73(1H, t, J=6.2Hz), 6.72(1H, s), 6.77(1H, t, J=55Hz), 6.86(2H, d, J=9Hz), 7.19(2H, d, J=9Hz), 7.22(2H, d, J=8.4Hz), 7.30(2H, d, J=8.4Hz).
IR (film) : 3143, 1518, 1508, 1452, 1325, 1244, 1151, 1074, 1022,
972, 843, 793 cm^{-1}.
MS (ESI-) : m/z 406 (M-1).

Example 62

N-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}urea

To a solution of 1-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride obtained by Example 60 (100mg) in dichloromethane (1ml) was added dropwise triethylamine (0.163ml) and trimethylsilyl isocyanate (0.11ml) at room temperature.

The mixture was stirred at room temperature overnight and quenched by adding saturated sodium hydrogencarbonate solution (0.5ml). The mixture was filtered by Chemelute. The elution was evaporated and purified by preparative thin layer chromatography (0.5mm, 10% methanol/chloroform) to give solid. The solid was added ethyl acetate and n-hexane, and the precipitate was collected by filtration to give the target compound(160mg, 62.9%).

1H NMR ($CDCl_3$) : δ 3.82(3H, s), 4.35(2H, d, J=6Hz), 4.46(2H, br-s), 4.99(1H, t, J=6Hz), 6.69(1H, s), 6.76(1H, t, J=55.1Hz), 6.86(2H, d, J=9Hz), 7.14-7.21(6H, m).
MS (ESI+) : m/z 395 (M+Na).
IR (film) : 1657, 1608, 1593, 1550, 15120, 1510, 1467, 1338, 1252, 1171, 1088, 1030, 837, 796cm^{-1}.

Example 63

4-[1-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile

The title compound (942mg, 86.8%) was prepared from 4-(4,4,4-trifluoro-3-oxobutanoyl)benzonitrile in a similar manner to that of Example 56.

1H NMR ($CDCl_3$) : δ 2.39(3H, s), 6.82(1H, s), 7.15(2H, d, J=8.9Hz), 7.21(2H, d, J=8.8Hz), 7.33(2H, d, J=8.3Hz), 7.62(2H, d, J=8.3Hz).

MS (ESI+): m/z 328 (M+1).

Example 64

1-{4-[1-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride

The title compound (414mg, 92.1%) was prepared from 4-[1-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile obtained by Example 63 in a similar manner to that of Example 57.

1H NMR (DMSO-d6) : δ 2.35(3H, d, J=4.2Hz), 3.35(2H, s), 7.17(1H, s), 7.17-7.29(4H, m), 7.32(2H, d, J=8.1Hz), 7.51(2H, d, J=8.2Hz).

MS (ESI+): m/z 332 (M+1).

Example 65

N-{4-[1-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}urea

The title compound (81mg, 31.8%) was prepared from 1-{4-[1-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}methanamine hydrochloride obtained by Example 64 in a similar manner to that of Example 62.

1H NMR ($CDCl_3$) : δ 2.36(3H, s), 4.35(2H, d, J=5.9Hz), 4.50(2H, br-s), 5.02(1H, t, J=5.5Hz), 6.71(1H, s), 7.16(4H, s), 7.20(4H, d, J=5.7Hz).

IR (film) : 3344, 1658, 1600, 1552, 1518, 1236, 1159, 1134cm^{-1}.

MS (ESI+) : m/z 397 (M+Na).

Example 66

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile

The title compound (1.05g, 73.8%) was prepared from 4-methyl-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene in a similar manner to that of Example 69 described later.

MP : 125.0-125.5℃.

1H NMR (CDCl3) : δ 2.39(3H, s), 6.74(1H, s), 7.10(2H, d, J=8.1Hz), 7.19(2H, d, J=8.2Hz), 7.45(2H, d, J=8.7Hz), 7.65(2H, d, J=8.7Hz).

MASS (ESI+) : m/z 350 (M+Na).

Example 67

1-{4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}methanamine hydrochloride

The title compound (830mg, 92.3%) was prepared from 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1- yl]benzonitrile obtained by Example 66 in a similar manner to that of Example 70 described later.

1H NMR (DMSO-d6) : δ 2.30(3H, d, J=2.3Hz), 4.07(2H, s), 7.15(1H, s), 7.15(2H, d, J=9.0Hz), 7.21(2H, d, J=8.9Hz), 7.39(2H, d, J=8.5Hz), 7.58(2H, d, J=8.5Hz).

MS (ESI+) : m/z 332 (M+1).

Example 68

N-{4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}urea

The title compound (65mg, 31.9%) was prepared from 1-{4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}methanamine hydrochloride obtained by Example 67 in a similar manner to that of Example 72 described later.

1H NMR ($CDCl_3$) : δ 2.34(3H, s), 4.34(2H, d, J=5.8Hz), 4.56(2H, br-s), 5.23(1H, t, J=5.8Hz), 6.71(1H, s), 7.07(2H, d, J=8.7Hz), 7.13(2H, d, J=8.7Hz), 7.24(4H, s).
IR (film) : 3344, 1658, 1604, 1552, 1234, 1159, 1134cm^{-1}.
MS (ESI+) : 397 (M+Na).

Example 69

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile

A mixture of 4-methoxy-1-(4,4,4-trifluoro-3-oxobutanoyl)benzene (1.0g), 4-methoxyphenylhydrazine hydrochloride (758mg) and sodium acetate (367mg) in acetic acid (5ml) was stirred overnight at room temperature.

After then, the reaction mixture was poured into water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. Combined organic layers were washed with water, saturated sodium hydrogencarbonate (twice) and brine, dried over sodium sulfate, and evaporated under reduced pressure to give crude product. The crude product

was column chromatographed on silica gel (50ml, n-hexane:ethyl acetate=10:1-5:1) to give the target compound (930mg, 66.7%).

1H NMR ($CDCl_3$) : δ 3.84(3H, s), 6.72(1H, s), 6.9(2H, d, J=8.9Hz), 7.14(2H, d, J=8.9Hz), 7.46(2H, d, J=8.7Hz), 7.66(2H, d, J=8.7Hz).
MS (ESI+) : m/z 366 (M+Na).

Example 70

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine hydrochloride

A mixture of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile obtained by Example 69 (400mg) and 50% wet pd/C (400mg) in ethanol (10ml) and 1N hydrochloric acid (1.2ml) was stirred under hydrogen atmosphere for 8hrs.

The mixture was filtered and filtrate was evaporated under reduced pressure. The residue was washed with isopropyl ether to give the target compound (400mg, 89.4%) as a powder.

1H NMR ($CDCl_3$) : δ 3.36(s, 3H), 3.76(d, J=2.4, 2Hz), 6.94(d, J=8.7, 2Hz), 7.12(s, 1H), 7.23(d, J=8.7, 2Hz), 7.39(d, J=8.4, 2Hz), 7.59(d, J=8.4, 2Hz).
MS (ESI+) : m/z 348 (M+1).

Example 71

N-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}methanesulfonamide

To a solution of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine hydrochloride obtained by Example 70 (150mg) and triethylamine (0.1ml) in dichloromethane (10ml) was added dropwise methanesulfonyl chloride (0.06ml) under ice cooling.

After stirring for 1hr, the reaction mixture was quenched and partitioned between chloroform and water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water, 1N hydrochloric acid, saturated sodium hydrogencarbonate solution and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was chromatographed by high performanced thin layer chromatography to give the target compound (67mg, 40.3%).

1H NMR ($CDCl_3$) : δ 2.91(3H, s), 3.82(s, 3H), 4.35(2H, d, J=6.1Hz), 4.69(1H, t, J=6.1Hz), 6.69(1H, s), 6.84(2H, d, J=8.6Hz), 7.13(2H, d, J=8.6Hz), 7.32(2H, d, J=9Hz), 7.37(2H, d, J=9Hz).

IR (film) : 3207, 1479, 1456, 1323, 1252, 1234, 1146, 1122, 984, 968, 962, 841, 802cm^{-1}.

MS (ESI+) : m/z 448 (M+Na).

Example 72

N-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzyl}urea

To a solution of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine hydrochloride obtained by Example 70 (150mg) in water (8ml) and ethanol (4ml) was added sodium cyanate (100mg)

under ice cooling.

After stirring for 3hrs, the reaction mixture was partitioned between chloroform and water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was chromatographed by high performanced thin layer chromatography to give the target compound (105mg, 69%).

1H NMR ($CDCl_3$) : δ 3.80(3H, s), 4.35(2H, d, J=5.9Hz), 4.53(2H, br-s), 5.171(1H, t, J=5.7Hz), 6.68(1H, s), 6.84(2H, d, J=8.7Hz), 7.12(2H, d, J=8.7Hz), 7.25(4H, s).
MS (ESI+) : m/z 413 (M+Na).

Example 73

tert-Butyl 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

To solution of 4-[1-(4-methoxyphenyl)-3-trifluoromethyl-1H-pyrazol-5-yl]phenol (500g) in N,N-dimethylformamide (1.5L) was added sodium hydride (dispersion in mineral oil, 77.8g) over 25min under ice cooling. The mixture was warmed to room temperature over 10min and then stirred at room temperature for 30min. A solution of 2-tert-butoxycabonylaminoethyl bromide (469 g) (prepared by reacting di-ter-butyl dicarbonate with 2-bromoethylamine hydrobromide) reaction in N,N-dimethylformamide (300ml) was added to the mixture over 10min at 25-28℃, and the whole mixture was stirred at 60℃ for 6hrs.

After allowed to stand overnight, the mixture was poured

into a mixture of water (4.5L) and toluene (3L). The organic layer was separated, and the aqueous layer was extracted with toluene (1.5L). The combined organic layers were washed with water (1.5L×3) and brine (1.5L), dried over magnesium sulfate, filtered and evaporated to give the oil (1.02kg). The oil was purified with silica gel column chromatography [5L, n-hexane (10L), 50% ethyl acetate/n-hexane (30L)] to give the target compound (680g, 95%) as a pale yellow oil.

MP : 104.7-105.1℃.

1HNMR ($CDCl_3$) : δ 1.45(3H, s), 3.53(2H, dt, J=4Hz), 3.82 (3H, s),
4.01(2H, t, J=4Hz), 6.67(1H, s), 6.83(2H, d, J=8Hz), 6.8 7(2H, d, J=8Hz), 7.13(2H, d, J=8Hz), 7.23(2H, d, J=8Hz).

Example 74

2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride

To a solution of hydrogen chloride in ethyl acetate (4N, 1.0L) was added powdered tert-Butyl 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-phenoxy}ethylcarbamate obtained by Example 73 (500g) at 5℃ over 20min.

After stirring at the same temperature for 30min and then at room temperature for 1hr, the mixture was evaporated to give oil (543.12g). The oil was dissolved in toluene (1.5L). And then, n-hexane (200ml) and the target compound (as seeds for crystallization) were added to the solution. The mixture was stirred at room temperature overnight. And the precipitate was filtered, washed with toluene (500ml

×2) and isopropylether (650ml), and dried to give the target compound (420.5g, 97%) as a white powder.

MP : 166.8-168.0℃.

1HNMR (DMSO-d6) : δ 3.185(2H, t, J=5Hz), 3.8(3H, s), 4.215(2H, t, J=5Hz), 6.96-7.05(4H, m), 7.1(1H, s), 7.22-7.33(4H, m).

Example 75

N-(2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine hydrochloride obtained by Example 74 (400g) and sodium acetate (159g) was dissolved in a mixture of N,N-dimethylformamide (1.4L) and water (0.52L) at 50℃. A solution of potassium cyanate (157g) in water (520ml) was added dropwise to the solution over 15min at 38-40℃. The whole solution was stirred at 50℃ for 2hrs.

The solution was filtered and washed with N,N-dimethylformamide (0.68L) at the same temperature. The filtrate was cooled to room temperature, and then water (0.4L) and the target compound (A04 type crystal) was added as seeds for crystallization to the filtrate, and the mixture was stirred at room temperature for 30min. Then water (2.76L) was added dropwise to the mixture over 30min, and the mixture was stirred at room temperature for 30min. The precipitate was filtered, washed with water (0.8L×3), and dried under reduced pressure at 45℃ overnight to give the target compound (A04 type crystals, 442.01g) as a white powder.

1HNMR ($CDCl_3$) : δ 3.555(2H, dt, J=5, 6Hz), 3.81(3H, s), 3.995(2H, t, J=5Hz), 4.67(2H, s), 5.37(1H, t, J=6Hz), 6.66(1H, br-s), 6.79(2H, d, J=8Hz), 6.845(2H, d, J=6Hz), 7.11(2H, d, J=8Hz), 7.19(2H, d, J=8Hz).

1HNMR (DMSO-d6) : δ 3.28-3.36(2H, m), 3.79(3H, s), 3.945(2H, t, J=5Hz), 5.54(2H, br-s), 6.165(1H, t, J=5Hz), 6.92-7.08(5H, m), 7.2(2H, d, J=8Hz), 7.28(2H, d, J=8Hz).

Example 76

2-Hydroxy-N-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}acetamide

To a solution of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride obtained by Example 57 (46.5mg) in dichloromethane (1.5ml) was added diisopropylethylamine (135μL) and acetoxyacetylchloride (41.6μL) at 0℃.

After stirring at room temperature for 3hrs, the mixture was quenched with water. The whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and evaporated to give oil (67mg). The oil was dissolved in methanol (1.5ml). Potassium carbonate (55mg) was added to the solution. After stirring at room temperature for 3hrs, the mixture was filtered and evaporated to give oil which was purified with preparative thin layer chromatography (0.5mm×2, 10% methanol/chloroform) to give colorless oil (42.5mg). The oil was crystallized from a mixture of ethyl acetate, diisopropylether, and n-hexane with stirring at room temperature. The precipitate was filtered and dried to give the target compound (33.9mg, 64.8%) as a white powder.

1HNMR ($CDCl_3$) : δ 2.32(1H, t, J=5.2Hz), 3.83(3H, s), 4.20(2H, d, J=5.2Hz), 4.51(2H, d, J=6.1Hz), 6.72(1H, s), 6.87(2H, d, J=8.9Hz), 7.16-7.24(6H, m).

MS (ESI+) : 428.2(M+Na).

Example 77

2-Hydroxy-N-(2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)ethanesulfonamide

To a solution of 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine hydrochloride and triethylamine in chloroform was added methanesulfonyl chloride at room temperature.

After stirring for 1hr, the reaction mixture was poured into water and chloroform. The aqueous layer was separated and extracted with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel and crystallized to give the target compound (27.7mg, 23.5%).

1HNMR ($CDCl_3$) : δ 2.78-2.91(2H, m), 3.16(2H, t, J=5.1Hz), 3.32-3.43(2H, m), 3.82(3H, s), 3.96(2H, t, J=5.1Hz), 4.65(1H, t, J=6.2Hz), 6.72(1H, s), 6.87(2H, d, J=9.0Hz), 7.12-7.27(6H, m).

MS(LC, ESI+), 470.21(MH+), 511.17(MHMeCN).

Example 78-1

tert-Butyl 2-(4-acetylphenoxy)ethylcarbamate

To a solution of 4-hydroxyacetophenone (10g) and

2-tert-butoxycarbonylaminoethylbromide (24.7g) in N,N-dimethylformamide (50 ml) was added potassium iodide (12.2g) and potassium carbonate (15.2g).

After stirring at 50℃ overnight, the mixture was quenched with water and extracted with ethyl acetate (3 times). The combined organic layers were washed with 1N sodium hydroxide aqueous solution (2 times) and brine, dried over magnesium sulfate, and evaporated to give oil. The oil was purified with silica gel column chromatography [500ml, 20% ethyl acetate/n-hexane (1000ml), 30% ethyl acetate/n-hexane (1000ml)] to give the target compound (19.89g, 96.9%) as a white solid.

1HNMR($CDCl_3$) : δ 1.46(9H, s), 2.56(3H, s), 3.52-3.60(2H, m), 4.09(2H, t, J=5.1Hz), 6.93(2H, d, J=8.9Hz), 7.93(2H, d, J=8.9Hz).
MS (ESI+) : 280.09(MH+).

Example 78-2

tert-Butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)-phenoxy]ethylcarbamate

A mixture of tert-butyl 2-(4-acetylphenoxy)ethyl-carbamate obtained by Example 78-1 (15g), trifluoroacetic acid (8.95ml), and sodium ethoxide (8.77g) in ethanol (45ml) was stirred at 70℃ for 2.5hrs.

The mixture was poured into a mixture of aqueous hydrogen chloride solution (1N) and ethyl acetate. The whole mixture was extracted with ethyl acetate (2 times). The organic layer was separated, washed with saturated sodium hydrogencarbonate and brine, dried over magnesium sulfate, and evaporated to give oil (25g). The oil was purified with

silica gel column chromatography [500ml, 30% ethyl acetate/n-hexane (1000ml)] to give oil. The oil was dissolved in ethyl acetate (5ml) under heating by water bath. n-Hexane (100ml) was added to the solution, and the solution was cooled to room temperature over 30min under stirring. And n-hexane (100ml) was added to the mixture. The precipitate was filtered and dried to give the target compound (15.956g, 79.2%) as an orange powder.

1HNMR ($CDCl_3$) : δ 3.40-3.70(2H, m), 4.00-4.20(2H, m), 5.00(1H, br-s), 6.50(1H, s), 6.98(2H, d, J=8.6Hz), 7.93(2H, d, J=8.6Hz).

Example 78-3

tert-Butyl 2-{4-[1-(4-methoxyphenyl)-3-(trifluoro-methyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

To a suspension of 4-methoxyaniline (100mg) in a mixture of acetic acid (2ml) and concentrated hydrogen chloride (0.4ml) was added dropwise a solution of sodium nitrite (61.6mg) in water (0.1ml) over 5min at 3℃, and the mixture was stirred at 3℃ for 1hr. To the mixture was added dropwise a solution of tin chloride (641mg) in concentrated hydrogen chloride (0.3ml) at 0℃ over 10min, and then the mixture was stirred at 0℃ for 1hr. Acetic acid (5ml) was added dropwise to the mixture at between -20 and -10℃ over 2min, and then the mixture was quenched with a solution of sodium hydroxide (336mg) in water (2.24ml) at -10℃ over 2min and warmed to room temperature to give a solution containing 4-methoxyphenylhydrazine hydrochloride.

A solution of tert-butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)-phenoxy]ethylcarbamate obtained by Example

78-2 (305mg) was added to the former solution at -10℃, and then the mixture was stirred at room temperature for 3hrs. The mixture was poured into a mixture of saturated sodium hydrogen carbonate aqueous solution (150ml) and ethyl acetate (100ml), and adjusted pH to basic by sodium hydrogencarbonate powder.

The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50ml×2). The combined organic layers were washed with saturated sodium hydrogen carbonate aqueous solution and brine, dried over magnesium sulfate, filtered, and evaporated to give oil (450 mg). The oil was purified with silica gel column chromatography [35 ml, 15% ethyl acetate/n-hexane (800 ml)] to give an oil. (343.2mg, 88.5%). The oil was dissolved in isopropylether (2ml), and then n-hexane (6ml) was added to the solution. The whole mixture was stirred at room temperature for 1hr. And then the precipitate was filtered, washed with n-hexane (10ml), and dried under reduced pressure for 2hrs to give the target compound (280.6 mg, 72.4%) as a white powder.

1HNMR ($CDCl_3$) data was identical to authentic sample.
1HNMR ($CDCl_3$) : δ 1.45(3H, s), 3.53(2H, dt, J=4.4Hz), 3.82(3H, s), 4.01(2H, t, J=4Hz), 6.67(1H, s), 6.83(2H, d, J=8Hz), 6.87(2H, d, J=8Hz), 7.13(2H, d, J=8Hz), 7.23(2H, d, J=8Hz).

Example 79-1

1-[4-(Benzyloxy)phenyl]hydrazine hydrochloride

To the suspension of 4-benzyloxyaniline (10g) in concentrated hydrogen chloride (100ml) was added dropwise

a solution of sodium nitrite (3.2g) in water (10ml) over 10min at between -15 and -10℃, and then the mixture was stirred at 3℃ for 1hr. To the mixture was added dropwise a solution of tin chloride (33.5g) in concentrated hydrogen chloride (80ml) at between -20 and -10℃ over 30min, and then the mixture stirred at 0℃ for 1hr.

After cooling to -20℃, the precipitate was filtered, washed with water (25ml), ethanol (25ml) and ether (50ml), and dried to give the target compound (10.637g, 100%) as a pale brown powder.

NMR(DMSO-d6) : δ 5.05(2H, s), 6.93-7.03(4H, m), 7.46-7.28(4H, m).

Example 79-2

2-{4-[1-(4-Benzyloxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxyl}ethanamine hydrochloride

The title compound (12.9g, 87.5%) was prepared from 1-[4-(benzyloxy)phenyl]hydrazine hydrochloride obtained by Example 79-1 and tert-butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)phenoxy]ethylcarbamate obtained by Example 78-2 in a similar manner to that of Example 78-3.

1HNMR (DMSO-d6) : δ 3.10-3.30(2H, m), 4.19(2H, t, J=6.3Hz), 5.14(2H, s), 6.98(2H, d, J=8.7Hz), 7.09(1H, s), 7.09(2H, d, J=8.9Hz), 7.49-7.22(9H, m).

Example 80

N-(2-{4-[1-[4-(Benzyloxy)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (10.57g, 84.3%) was prepared from 2-{4-[1-(4-benzyloxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxyl}-ethanamine hydrochloride obtained by Example 79-2 in a similar manner to that of Example 75.

1HNMR ($CDCl_3$) : δ 3.57(2H, td, J=5.7, 5.0Hz), 4.01(2H, t, J=5.0Hz), 4.57(1H, br-s), 5.06(2H, s), 5.20(1H, t, J=5.7Hz), 6.66(1H, s), 6.80(2H, d, J=8.7Hz), 6.93(2H, d, J=9.0Hz), 7.12(2H, d, J=8.7Hz), 7.21(2H, d, J=9.0Hz), 7.35-7.42(5H, m).

Example 81

N-(2-{4-[1-(4-Hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)urea

To a solution of N-(2-{4-[1-[4-(benzyloxy)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea obtained by Example 80 (10.33g) in methanol (100ml) was added palladium on carbon (10% wet, 2g), and the mixture was stirred vigorously at room temperature under hydrogen atmosphere for 3hrs. The whole mixture was filtered and evaporated to give oil (8.23g). The oil was purified with silica gel column chromatography [250ml, 3% methanol/chloroform (500ml), 5% methanol/chloroform (500ml), and 10% methanol/chloroform (500ml)] to give the target compound (8.07g, 95.4%) as an oil.

1HNMR (DMSO-d6) : δ 3.28-3.33(2H, m), 3.94(2H, t, J=5.5 Hz), 5.52(2H, br-s), 6.14(1H, br-t, J=5.7Hz), 6.80(2H, d, J=8.7Hz), 6.93(2H, d, J=8.9Hz), 7.05(1H, s), 7.14(2H, d, J=8.7Hz), 7.19(2H, d, J=8.9Hz).

MS (ESI+) : 407.10(MH+).

Example 82

4-[5-(4-{2-[(Aminocarbonyl)amino]ethoxy}phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl acetate

To a mixture of N-(2-{4-[1-(4-hydroxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea obtained by Example 81 (148.5mg) in dichloromethane (1.5 ml) was added pyridine (163μL) and acetic anhydride (45μL), and the mixture was stirred at room temperature for 1hr and stirred under reflux for 3hrs.

After evaporation, the mixture was purified with preparative thin layer chromatography (1.0mm, 10% methanol/chloroform) to give oil. The oil was crystallized from a mixture of dichloromethane and isopropylether at room temperature to give the target compound (138.6mg, 84.6%) as a white powder.

1HNMR ($CDCl_3$) : δ 2.30(3H, s), 3.59(2H, td, J=5.5, 4.9Hz), 4.04(2H, t, J=4.9Hz), 4.51(2H, br-s), 5.22(1H, br-t, J=5.5Hz), 6.69(1H, s), 6.84(2H, d, J=8.7Hz), 7.10(2H, d, J=8.8Hz), 7.14(2H, d, J=8.7Hz), 7.31(2H, d, J=8.9Hz).
MS(LC, ESI+) : 449.24(MH^+), (ESI-) 492.5($M-H+HCO_2^-$).

Example 83-1

1-(1,3-Benzodioxol-5-yl)hydrazine hydrochloride

The title compound (1.811g, quant.) was prepared from 3,4-(methylenedioxy)aniline in a similar manner to that of Example 79-1.

1HNMR (DMSO-d6) : δ 5.94(2H, s), 6.53(1H, dd, J=2.2 8.2 Hz), 6.80(1H, s), 6.83(1H, d, J=8.2Hz).
MS(LS, ESI+): 153.9(MH+) 193.99(MH+CH_3CN).

Example 83-2

tert-Butyl 2-{4-[1-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate

The title compound (371.3mg, 56.7%) was prepared from tert-butyl 2-[4-(4,4,4-trifluoro-3-oxobutanoyl)-phenoxy]ethylcarbamate obtained by Example 78-2 and 1-(1,3-benzodioxol-5-yl)hydrazine hydrochloride obtained by Example 83-1 in a similar manner to that of Example 78-3.

NMR ($CDCl_3$) MA12.048 : δ 1.75(9H, s), 3.45-3.60(2H, m), 4.02(2H, t, J=5.1Hz), 6.02(2H, s), 6.66-6.88(1H, m), 7.16(2H, d, J=8.8Hz).
MS(LC, ESI+) : 492.22 (MH+), 533.26 (MHMeCN+).

Example 84

2-{4-[1-(1,3-Benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine

The title compound (181.2mg, 61.5%) was prepared from tert-butyl 2-{4-[1-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethylcarbamate obtained by Example 83-2 in a similar manner to that of Example 74.

1HNMR ($CDCl_3$) : δ 1.75(9H, s), 3.45-3.60(2H, m), 4.02(2H, t, J=5.1Hz), 6.02(2H, s), 6.66-6.88(1H, m), 7.16(2H, d,

J=8.8Hz).

MS (LC, ESI+) : 392.09(MH+), 433.16(MHMeCN+).

Example 85

N-(2-{4-[1-(1,3-Benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

The title compound (181.2mg, 90.1%) was prepared from 2-{4-[1-(1,3-benzodioxol-5-yl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanamine obtained by Example 84 in a similar manner to that of Example 75.

1HNMR ($CDCl_3$) : δ 3.6(2H, td, J=5.0, 5.0Hz), 4.045(2H, t, J=5Hz), 4.5(2H, br-s), 5.095(1H, br-t, J=5Hz), 6.01(2H, s), 6.66(1H, s), 6.75-6.86(3H, m), 6.84(2H, d, J=8Hz), 7.16(2H, d, J=8Hz).

MS (LC, ESI+) : 435.08(MH+).

Example 86

tert-Butyl 2-({4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}amino)-2-oxoethylcarbamate

A mixture of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride obtained by Example 57, N-tert-butoxycarbonyl-glycine, WSCD and 1-hydroxybenzotriazole hydrate in triethylamine and dichloromethane was stirred at room temperature.

After stirring for 15hrs, the reaction mixture was poured onto water and chloroform. The aqueous layer was separated and extracted with chloroform. The combined

organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel and crystallized to give the target compound (93.5mg, 88.9%).

1HNMR ($CDCl_3$) : δ 1.43(9H, s), 3.82(3H, s), 3.82-3.85(2H, m), 4.475(2H, d, J=6Hz), 6.71(1H, s), 6.87(2H, d, J=8Hz), 7.14-7.26(6H, m).
MS (ESI+) : 505(MH+).

Example 87

2-Amino-N-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}acetamide hydrochloride

The title compound (62.3mg, 82.9%) was prepared from tert-butyl 2-({4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}amino)-2-oxoethylcarbamate obtained by Example 86 in a similar manner to that of Example 74.

1HNMR (DMSO-d6) : δ 3.61(2H, s), 3.79(3H, s), 4.345(2H, d, J=6Hz), 7.005(2H, d, J=10Hz), 7.15(1H, s), 7.22-7.32 (6H, m), 8.09(2H, br-s), 8.93(1H, br-t, J=6Hz).
MS (ESI+) : 405.33 (free, MH+).

Example 88

N-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}acetamide

To a solution of 4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzylamine hydrochloride

obtained by Example 57 and triethylamine in dichloromethane was added dropwise acetyl chloride at 0℃.

After stirring at room temperature for 1hr, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (3 times). The combined organic layers were washed with 1N hydrochloric acid, water, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with silica gel column chromatography (eluted with 50% ethyl acetate/n-hexane) to give oil. The oil was crystallized from a mixture of ethyl acetate and n-hexane at 50℃ to give the target compound (52.2mg, 69.3%) as a solid.

1HNMR ($CDCl_3$) : δ 2.04(3H, s), 3.83(3H, s), 4.435(2H, d, J=6Hz), 6.71(1H, s), 6.87(2H, d, J=8Hz), 7.15-7.26(6H, m).
IR (KBr) : 1647cm^{-1}.
MS (ESI+) : 412.1(M+Na).

Example 89

N-(2-{4-[1-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]-phenyl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide

The title compound (72mg, 70.8%) was prepared from 2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine hydrochloride in a similar manner to that of Example 77.

1HNMR ($CDCl_3$) : δ 2.83(2H, t, J=8Hz), 3.26(2H, dt, J=6Hz), 3.75(3H, s), 3.83(3H, s), 5.005(1H, t, J=6Hz), 6.7(1H, s), 6.88(2H, d, J=8Hz), 7.13(4H, s), 7.22(2H, d, J=8Hz), 7.45-7.47(2H, m).

MS (ESI+) : 528.1 (MNa+).

Example 90

N-((1R)-2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}-1-methylethyl)urea

To a solution of (1R)-2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}-1-methylethanamine hydrochloride in dichloromethane was added triethylamine and trimethylsilyl isocyanate at 0℃.

After stirring for 5hrs, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give oil, which was purified with preparative thin layer chromatography (1mm, ethyl acetate) to give oil. The oil was crystallized from a mixture of isopropyl ether, ethyl acetate, and n-hexane to give the target compound as a white solid (22.8mg, 88.1%).

1HNMR ($CDCl_3$) : δ 1.29(3H, d, J=8Hz), 3.82(3H, s), 3.87-3.94(2H, m), 4.07-4.19(1H, m), 4.51(2H, s), 4.87(1H, d, J=8Hz), 6.67(1H, s), 6.8-6.89(4H, m), 7.12(2H, d, J=8Hz), 7.215(2H, d, J=10Hz).

MS (ESI+) : 435.3 (MH+), 476.3(MH+MeCN).

Example 91

N-(2-{4-[1-(6-Methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

The title compound (130mg, 71.8%) was prepared from 2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-

pyrazol-5-yl]phenoxy}ethanamine dihydrochloride in a similar manner to that of Example 77.

1HNMR ($CDCl_3$) : δ 3.03(3H, s), 3.555(2H, dt, J=5, 5Hz), 3.94(3H, s), 4.115(2H, t, J=5Hz), 4.785(1H, br-t, J=5Hz), 6.71(1H, s), 6.76(1H, d, J=8Hz), 6.85(2H, d, J=8Hz), 7.16(2H, d, J=8Hz), 7.555(2H, dd, J=8, 2Hz), 8.085(1H, d, J=2Hz).

MS (ESI+) : 479.1 (M+Na)+.

Example 92

4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol

A mixture of 4-methoxy-1-(4,4,4-trifluoro-3-oxo-butanoyl)benzene (5.0g) and p-hydroxyphenyl hydrazine hydrochloride (3.59g) in acetic acid (30ml) was stirred at room temperature.

After stirring for 15hrs, toluene and water was added. The aqueous layer was separated and extracted twice with toluene. The combined organic layer was washed with water (twice) and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel to give the target compound (4.88g, 71.9%) as crystals.

1H NMR ($CDCl_3$) : δ 3.80(3H, s), 6.68(1H, s), 6.72(2H, d, J=8.8Hz), 6.83(2H, d, J=8.8Hz), 7.12(2H, d, J=8.8Hz), 7.13(2H, d, J=8.8Hz).

MS (ESI+) : m/z 357 (M+Na).

Example 93

2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanol

A suspension of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol obtained by Example 92 (500mg), potassium carbonate (1.24g), potassium iodide (1.49g), and 2-chloro-1-ethanol (0.60ml) was stirred at 80℃ for 5hrs.

After cooling, the reaction mixture was poured into water. The mixture was extracted twice with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel to give the target compound (545mg, 96.4%).

1H NMR ($CDCl_3$) : δ 2.03(1H, t, J=5.8Hz), 3.81(3H, s), 3.94-4.01(2H, m), 4.09(2H, dd, J=3.5 ,4.6Hz), 4.52(3H, s), 6.68(1H, s), 6.84(2H, d, J=8.9Hz), 6.89(2H, d, J=9Hz), 7.13(2H, d, J=8.9Hz), 7.24(2H, d, J=9Hz).
MASS (ESI+) : m/z 401 (M+Na).

Example 94

{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}acetonitrile

A suspension of 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol obtained by Example 92 (2.0g), potassium carbonate (992mg), potassium iodide (993mg), and chloroacetonitrile (0.57ml) was stirred at 80℃ for 4hrs.

After cooling, the reaction mixture was poured into water. The mixture was extracted twice with ethyl acetate,

washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel to give the target compound (1.75g, 78.3%) as an oil.

1H NMR ($CDCl_3$) : δ 3.81(3H, s), 4.79(2H, s), 6.69(1H, s), 6.86(2H, d, J=8.8Hz), 6.96(2H, d, J=9Hz), 7.14(2H, d, J=8.8Hz), 7.31(2H, d, J=9Hz).
MS (APCI+) : m/z 374 (M+1).

Example 95

tert-Butyl 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethylcarbamate

The title compound (420mg, 21%) was prepared from 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenol obtained by Example 92 in a similar manner to that of Example 73.

1H NMR ($CDCl_3$) : δ 1.46(9H, s), 3.501-3.58(2H, m), 4.02(2H, t, J=5.1Hz), 4.99(1H, br-s), 6.67(1H, s), 6.84(2H, d, J=8.9Hz), 6.85(2H, d, J=9Hz), 7.13(2H, d, J=8.9Hz), 7.23(2H, d, J=9Hz).
MS (ESI+) : m/z 500 (M+Na).

Example 96

2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanamine hydrochloride

The title compound (0.35g, 96.2%) was prepared from tert-butyl 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethylcarbamate obtained

by Example 95 in a similar manner to that of Example 74.

1H NMR ($CDCl_3$+CD_3OD) : δ 3.2-3.5(4H, m), 3.81(3H, s), 4.2-4.35(2H, m), 6.70(1H, s), 6.84(2H, d, J=8.6Hz), 6.95(2H, d, J=8.6Hz), 7.13(2H, d, J=8.6Hz), 7.25(2H, d, J=8.6Hz).

MS (ESI+) : m/z 378 (M-Cl).

Example 97

N-(2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethyl)methanesulfonamide

To a solution of 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanamine hydrochloride obtained by Example 96 (100mg) in dichloromethane (5ml) and triethylamine (0.1ml) was added dropwise methanesulfonyl chloride (38μl) at room temperature.

After stirring for 2hrs, the reaction mixture was partitioned between chloroform and water. The aqueous layer was extracted with chloroform. The combined organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The residue was purified with high performanced thin layer chromatography to give the target compound (35mg, 31.8%) as crystals.

1H NMR ($CDCl_3$) : δ 3.03(3H, s), 3.56(2H, dt, J=5 ,5.7Hz), 3.81(3H, s), 4.11(2H, t, J=5Hz), 4.82(1H, t, J=5.7Hz), 6.68(1H, s), 6.85(2H, d, J=7.9Hz), 6.85(2H, d, J=8.7Hz), 7.13(2H, d, J=8.7Hz), 7.24(2H, d, J=7.9Hz).

MS (ESI+) : m/z 478 (M+Na).

Example 98

N-(2-{4-[5-(4-Methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-phenoxy}ethyl)urea

To a solution of 2-{4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenoxy}ethanamine hydrochloride obtained by Example 96 (200mg) in water (10ml) and ethanol (5ml) was added sodium cyanate (314mg) at room temperature.

After stirring for 15hrs, the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatography by high performanced thin layer chromatography (chloroform:methanol=8:1) to give the target compound (0.148g, 72.8%).

1H NMR ($CDCl_3$) : δ 3.60(2H, dt, J=5.6, 5.0Hz), 3.81(3H, s), 4.04(2H, t, J=5.0Hz), 4.50(2H, br-s), 5.12(1H, t, J=5.6Hz), 6.68(1H, s), 6.84(2H, d, J=8.8Hz), 6.85(2H, d, J=8.9Hz), 7.13(2H, d, J=8.8Hz), 7.22(2H, d, J=8.9Hz).
MS (ESI+) : m/z 443 (M+Na).

Example 99

N-(2-{4-[3-(Difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl)-2-hydroxyethanesulfonamide

To a solution of 2-(2-{4-[1-(4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione in acetonitrile was added

hydrazine monohydrate.

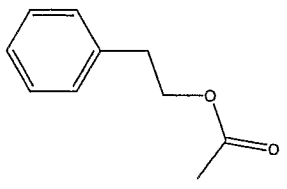
After stirring at 60℃ overnight, the mixture was filtered. And the filtrate was evaporated to give 2-{4-[1-(4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanamine as an orange oil.

To a solution of the oil and triethylamine in chloroform was added 2-hydroxyethanesulfonyl chloride at room temperature.

After stirring for 1hr, the reaction mixture was poured onto water and chloroform. The aqueous layer was separated and extracted with chloroform. The combined organic layer was washed with water and brine, dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel and crystalized to give the target compound (220mg, 76.1%).

1H NMR ($CDCl_3$) : δ 2.875(2H, t, J=7Hz), 2.91-3.19(2H, m), 3.395(2H, dt, J=6Hz), 3.83(3H, s), 3.985(2H, t, J=5Hz), 4.44(1H, br-t, J=6Hz), 6.7(1H, s), 6.765(1H, t, J=55Hz), 6.875(2H, d, J=10Hz), 7.12(6H, s).
MS (ESI+) : 452.19(MH+).

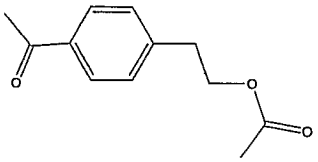
Preparation 1



I

To a suspension of AlCl3 (45.9g) was added dropwise acetyl chloride (13.4ml) (About 5°C), and then I (25.7g) mentioned above under ice-cooling(5-10°C). After stirring for 8 hours, the reaction

mixture was poured onto ice-water. The organic layer was separated and washed with water (twice) and 1NHCl, sat.NaHCO3 and brine, dried over MgSO4, filtered and evaporated under reduced pressure to give crude product. The product was distilled under reduced pressure to give 105.8g (84%) of the following compound (P0001)



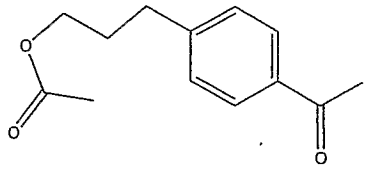
(P0001)

TLC Check: Ninhydrin/UV

b.p. 1> 91-117 °C /0.7mmHg. E111271-1 12.6g

2> 117 °C /0.7mmHg. E111271-2 105.8g

Preparation 2



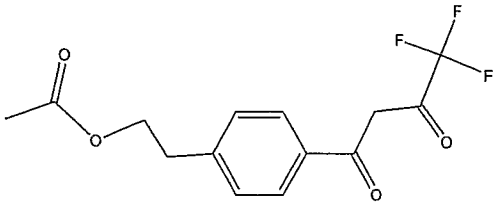
(P0002)

The above compound P0002 was prepared in a similar manner to that of P0001.

Mass (API-ES positive) : 243 (M+Na)+

200MHz 1H NMR (CDCl3, d) : 1.91-2.05(2H, m), 2.06(3H, s), 2.59(3H, s), 2.76(2H, t, J=7.7 Hz), 4.09(2H, t, J=6.5 Hz), 7.28(2H, d, J=8.2 Hz), 7.90(2H, d, J=8.2 Hz)

Preparation 3



(P0003)

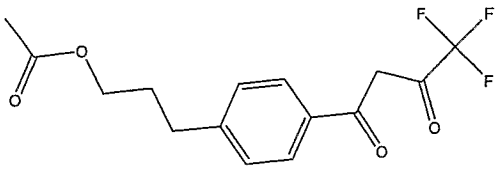
60% Sodium hydride 427mg was added to a solution of the compound P0001 (2g) and ethyl trifluoroacetate 2.6ml in DMF 10ml portionwise (in three portions) under ice bath cooling. The reaction mixture was stirred at same temperature for 45minutes. Then ice bath was replaced to water bath. The temperature of reaction mixture was raised to 24.5℃, then slowly fall down to 22℃ over 1hour. The mixture was stirred at r.t. for 1hour, then poured into a mixture of 1M HCl 12ml and ice 40ml. The whole mixture was extracted with AcOEt 20ml. The organic layer was washed with H2O 30ml, saturated aqueous sodium chloride solution, dried over magnesium sulfate, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with toluene. Obtained crystals were washed with chilled n-hexane 10ml and petroleum ether 5ml by decantation to give a compound P0003 as white crystals.

mp. 87-88°C

Mass (API-ES negative) : 301(M-H)+

200MHz 1H NMR (DMSO-d6, d) : 3.00(2H, t, J=6.7 Hz), 4.27(2H, t, J=6.7 Hz), 6.99(1H, s), 7.48(2H, d, J=8.3 Hz), 8.08(2H, d, J=8.3 Hz)

Preparation 4



(P0004)

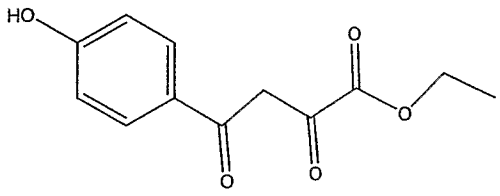
P0004 was prepared in a similar manner to that of P0003 as shown in Preparation 3.

Mass (API-ES negative) : 315 (M-H)+

NMR JA24.112

200MHz 1H NMR (CDCl3, d) : 1.92-2.06(2H, m), 2.06(3H, s), 2.74-2.82(2H,m), 4.10(2H,t, J=6.5Hz), 6.55(1H,s), 7.33(2H, d, J=8.3 Hz), 7.89(2H, d, J=8.3 Hz)

Preparation 5



(P0005)

P0005 was prepared in a similar manner to that of P0003 as shown in Preparation 3.

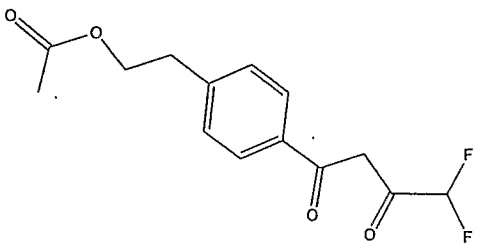
yellow crystals

Mass (API-ES positive) : 259 (M+Na)+

400MHz 1H NMR (CDCl3, d) :

1.41(3H, t, J=7.1 Hz), 4.40(2H, q, J=7.1 Hz), 6.93(2H, d, J=8.9 Hz), 7.02(1H, s), 7.96(2H, d, J=8.9 Hz)

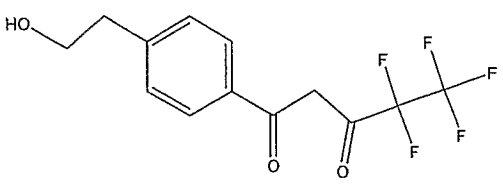
Preparation 6



(P0006)

P0006 was obtained according to a similar manner to that of P0003. (PREPARATION 3)

Preparation 7



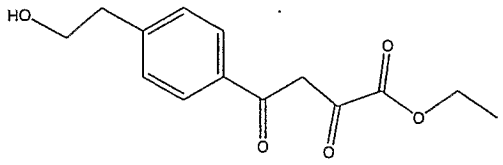
(P0007)

60% Sodium hydride 233mg was added to a solution of P0001 1g and ethyl pentafluoropropionate 0.93ml in three portions under ice bath cooling. The reaction mixture was stirred at 24-27°C with cooling in a water bath for several hours, then poured into a mixture of ice and 1M HCl 50ml. The whole mixture was extracted with AcOEt twice. The combined organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give P0007 1.94g as an oil.

Mass (API-ES negative) : 309 (M-H)+

200MHz 1H NMR (CDCl3, d) : 2.90-3.05(2H, m), 3.85-4.00(2H, m), 6.62(1H, s), 7.39(2H, d, J=8.3 Hz), 7.92(2H, d, J=8.3 Hz)

Preparation 8



(P0008)

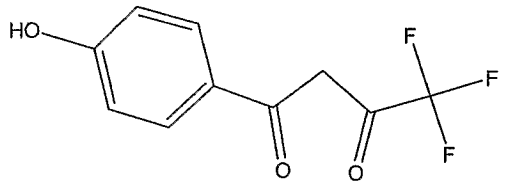
20% solution of sodium ethoxide in EtOH 18ml was added dropwise to a solution of P0001 (4.00g) and diethyl oxalate 5.95g in DMF 12ml at 4-6°C. After stirring at same temperature for 1hour, the reaction mixture was poured into a mixture of ice-water 100ml and conc.HCl 5ml, and extracted with AcOEt. The organic layer was washed successively with 1M HCl, H2O, and saturated aqueous sodium chloride solution, dried over

magnesium sulfate, treated with activated carbon, then filtered through a SiO2(20ml) pad. The pad was washed with AcOEt. The filtrate and combined washings were concentrated in vacuo to give P0008 (6.05g) as an oil.

Mass (API-ES positive) : 287(M+Na)+, (API-ES negative) 263(M-H)+

200MHz 1H NMR (CDCl3, d) : 1.42(3H, t, J=7.1Hz), 2.96(2H, t, J=6.5 Hz), 3.93(2H, t, J=6.5 Hz), 4.40(2H, q, J=7.1Hz), 7.06(1H, s), 7.38(2H, d, J=8.3 Hz), 7.96(2H, d, J=8.3Hz)

Preparation 9



(P0009)

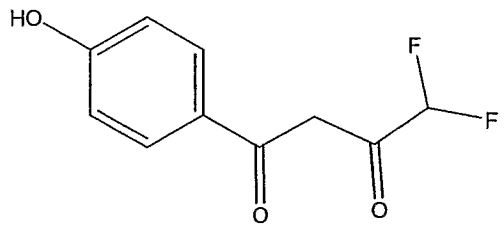
To a solution of 4-Hydroxybenzophenone (160 g), Ethyl trifluoroacetate (182 ml), and ethanol (11 ml) in N,N-dimethylformamide (670 ml) was added portionwise sodium hydride (suspension in mineral oil, 103 g) over 15 minutes at 0 ~ 35°C. The mixture was stirring at room temperature for 2 hours, and then at 35 ~ 40°C for 3 hours.
The mixture was poured into a mixture of ice and concentrated hydrogen chloride (320 ml) (aqueous layer total 4L) and diisopropyl ether (2 L). The aqueous layer was separated and extracted with diisopropyl ether (500 ml x 2). The combined organic layers were washed with water (500 ml x 4) and brine, dried over magnesium sulfate, and evaporated to give 415 g of solid. The solid was dissolved in diisopropyl ether (200 ml) at 65°C. The solution was added dropwise hexane (1.5 L) under stirring at room temperature.

After stirring at room temperature for 1 hour, The suspension was filtered and dried under reduced pressure to give solid (first crop, 109.53 g, 40%). The mother liquid evaporated and similarly treated diisopropyl ether (20 ml) and hexane (250 ml) to give second crop (71.11 g, 26%). P0009 (first corp and second corp total, 66.2%).

NMR(CDCl3); 5.65(1H, brs), 6.50(1H, s), 6.94(2H, d, J=8.8 Hz), 7.91(2H, d, J=8.8 Hz).

MS(ESI+), 255.1(M+Na)+.

Preparation 10



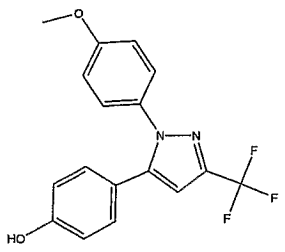
(P0010)

This compound was obtained according to a similar manner to that of P0009 (S0203744) as a powder (56.195 g, 102%).

NMR(CDCl3); 6.01(1H, t, J=54 Hz), 6.49(1H, s), 6.92(2H, d, J=8.8 Hz), 7.90(2H, d, J=8.8 Hz).

MS(ESI-), 213.3(M-H)+

Preparation 11



(P0011)

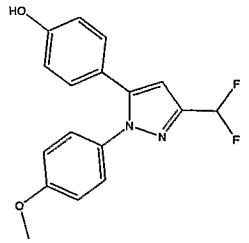
A mixture of P0009 (100 g), 4-Methoxyphenylhydrazine hydrochloride (82.4 g), and sodium acetate (42.6 g) in acetic

acid (550 ml) was stirring at 70℃ for 3 hours. After cooling to room temperature, the mixture was poured into water (4 L) and stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (250 ml x 3) and Hex(500 ml x 2)、and dried at room temperature overnight to give powder (157.86 g). The powder was purified by recrystallization from ethyl acetate and hexane to give P0011 as a powder 121.34G (77%).

NMR(CDCl3); 3.82(3H, s), 5.08(1H, brs), 6.67(1H, s), 6.77(2H, d, J=8.6 Hz), 6.87(2H, d, J=9.0 Hz), 7.09(2H, d, J=8.6 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+); 357.1(M+Na)+.

Preparation 12



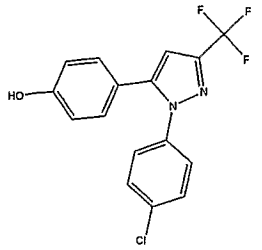
(P0012)

This compound was obtained according to a similar manner to that of P0011 as a solid (3.2028 g, 72%).

NMR(DMSO-d6); 3.88(3H, s), 6.74(2H, d, J=8.6 Hz), 6.82(1H, s), 6.90(1H, d, J=8.6 Hz), 7.10(2H, d, J=8.6 Hz), 7.09(1H, t, J=55 Hz), 7.68(1H, dd, J=8.6, 2.7 Hz), 8.12(1H, d, J=2.7 Hz).

MS(ESI+); 316.1(M-H)+, 633.3(2M-H).

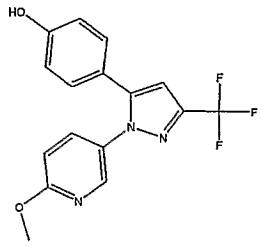
Preparation 13



(P0013)

This compound was obtained according to a similar manner to that of P0011.

Preparation 14



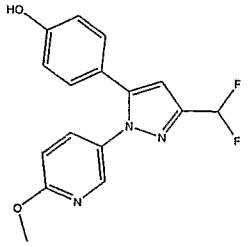
(P0014)

To a solution of 4-methoxyphenylhydrazine hydrochloride (3.43 g) in water (7.7 ml) was added a solution of P0009 in acetic acid (50 ml). The mixture was then allowed to stand at room temperature overnight. The mixture was poured into water (500 ml) and stirred at room temperature for 1 hour. The precipitate was filtered, washed with water (100 ml), and dried at room temperature to give P0014 as a brown solid (3.26 g, 90%).

NMR(DMSO-d6); 3.88(3H, s), 6.75(2H, d, J=8.6 Hz), 6.92(1H, d, J=8.5 Hz), 7.06-7.15(3H, m), 7.73(1H, dd, J=8.5, 2.8 Hz), 8.16(1H, d, J=2.8 Hz), 9.86(1H, s, OH).

MS(ESI-); 334.1(M-H)+, 669.2(2M-1)+.

Preparation 15



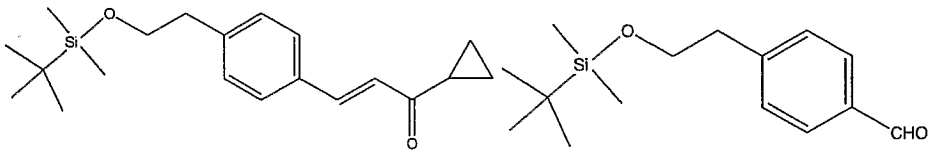
(P0015)

This compound was obtained according to a similar manner to that of P0014 as a pale brown powder (13.58 g, 91.7%).

NMR(DMSO-d6); 3.94(3H, s), 6.67(1H, s), 6.75(1H, t, J=55 Hz), 6.73-6.80(3H, m), 7.09(2H, d, J=8.6 Hz), 7.57(1H, dd, J=8.6, 2.6 Hz), 8.07(1H, d, J=2.6 Hz).

MS(ESI-); 316.1(M-H), 633.3(2M-H).

Preparation 16



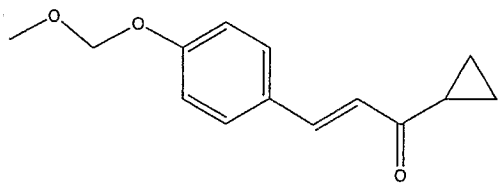
(P0016) (P0016-1)

1M NaOH 1ml was added to a solution of P0016-1 (reported in WO9427973) 1.31g and in EtOH 5ml and the mixture was stirred at amibient temperature overnight. The mixture partitioned between AcOEt and H2O. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane to give P0016 (900mg) as an oil.

Mass (ESI+) : 331 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : -0.05(6H, s), 0.82(9H, s), 0.94(4H, d, J=6.0 Hz), 2.38-2.52(1H, m), 2.78(2H, t, J=6.6 Hz), 3.79(2H, t, J=6.6 Hz), 7.01(1H, d, J=16.2 Hz), 7.29(2H, d, J=8.1 Hz), 7.65(2H, d, J=8.1 Hz), 7.65(1H, d, J=16.2 Hz)

Preparation 17



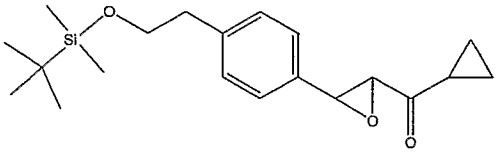
(P0017)

P0017 6.41g was prepared in a similar manner to that of P0016.

Mass (API-ES positive) : 255 (M+Na)+

200MHz 1H NMR (CDCl3, d) : 0.90-1.01(2H, m), 1.11-1.20(2H, m), 2.22(1H, m), 3.49(3H, s), 5.21(2H, s), 6.78(1H, d, J=16.0 Hz), 7.05(2H, d, J=8.7 Hz), 7.52(2H, d, J=8.7 Hz), 7.58(1H, d, J=16.0 Hz)

Preparation 18



(P0018)

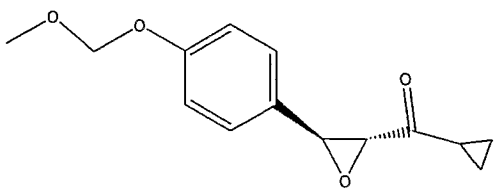
30% H2O2 0.64ml and 3M NaOH 0.64ml was added to a 0.25M solution of P0016 1.03g in EtOH:acetone=3:1. The mixture was stirred at ambient temperature overnight. The mixture was concentrated in vacuo, and partitioned between AcOEt and H2O. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give P0018 (792mg) as an oil.

Mass (ESI+) : 347 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

-0.05(6H, s), 0.82(9H, s), 0.92-1.04(4H, m), 2.24(1H, m), 2.75(2H, t, J=6.7 Hz), 3.76(2H, t, J=6.7 Hz), 3.86(1H, d, J=1.9 Hz), 4.19(1H, d, J=1.9 Hz), 7.24(2H, d, J=8.4 Hz), 7.30(2H, d, J=8.4 Hz)

Preparation 19



(P0019)

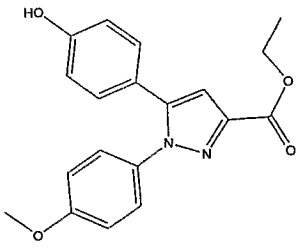
P0019 1.082g was prepared from P0017 1.0g in a similar manner to that of P0018.

Mass (API-ES positive) : 271(M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 0.90-1.04(4H, m), 2.24(1H, m), 3.37(3H, s), 3.88(1H, d, J=1.9 Hz), 4.17(1H, d, J=1.9 Hz), 5.20(2H, s), 7.03(2H, d, J=8.7 Hz), 7.32(2H, d, J=8.7 Hz)

200MHz 1H NMR (CDCl3, d) : 0.90-1.07(2H, m), 1.12-1.26(2H, m), 2.18(1H, m), 3.48(3H, s), 3.58(1H, d, J=1.9 Hz), 4.05(1H, d, J=1.9 Hz), 5.18(2H, s), 7.04(2H, d, J=8.7 Hz), 7.23(2H, d, J=8.7 Hz)

Preparation 20



(P0020)

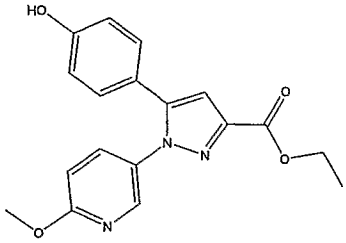
P0005 17.00g was dissolved in warm EtOH 68ml and AcOH 170ml at 70°C. To this solution was added P0005, suspended in H2O 20ml, in one portion. The mixture was stirred at 70°C for 1.5hours and then poured into a mixture of ice 500ml and conc.HCl 10ml. Diisopropyl ether 100ml was added and the mixture was stirred at ambient temperature for 20minutes. The precipitates were collected and washed successively with 1M HCl, H2O, and diisopropylether. This was air dried

overnight to give P0020 21.28g was a pale yellow powder.

Mass (ESI+) : 339 (M+H)+

400MHz 1H NMR (CDCl3, d) : 1.41(3H, t, J=7.1 Hz), 3.82(3H, s), 4.44(2H, q, J=7.1 Hz), 6.76(2H, d, J=8.7 Hz), 6.85(2H, d, J=9.0 Hz), 6.96(1H, s), 7.08(2H, d, J=8.7 Hz), 7.24(2H, d, J=9.0 Hz)

Preparation 21



(P0021)

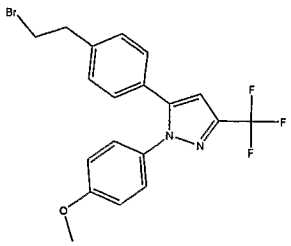
P0021 was prepared from P0005 in a similar manner to that of P0020.

white powder

Mass (ESI+) : 340 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.88(3H, s), 4.32(2H, q, J=7.1 Hz), 6.74(2H, d, J=8.6 Hz), 6.92(1H, d, J=8.8 Hz), 7.00(1H, s), 7.09(2H, d, J=8.6 Hz), 7.71(1H, dd, J=8.8,2.7 Hz), 8.13(1H, d, J=2.7 Hz), 9.82(1H, s)

Preparation 22



(P0022)

A solution of triphenylphosphine 831mg in THF 5ml was added dropwise to a solution of E0118 521.8mg and carbon

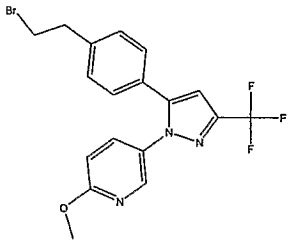
tetrabromide 1.15g in THF 5ml at ambient temperature. The reacion mixture was stirred at ambient temperaturer for 1hour. Carbon tetrabromide 573mg and triphenylphosphine 415mg were added in one portion and stirred for further 1hour. Unsoluble matter was filtered off and washed with THF. The filtrate and combined washings were concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 5%, then 25% to give P0022 647.2mg as pale yellow wax.

mp.60-70°C

Mass (API-ES positive) : 425,427 (M+H)+ , 447,449(M+Na)+

200MHz 1H NMR (CDCl3, d) : 3.12-3.19(2H, m), 3.52-3.60(2H, m), 3.82(3H, s), 6.72(1H, s), 6.87(2H, d, J=9.0 Hz), 7.16-7.30(6H, m)

Preparation 23



(P0023)

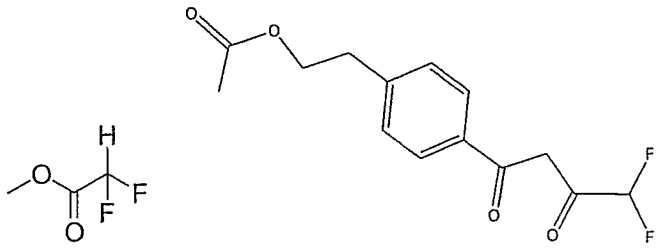
P0023 was prepared in a similar manner to that of P0022.

colorless oil

Mass (API-ES positive) : 448,450 (M+Na)+

400MHz 1H NMR (DMSO-d6, d) : 3.14(2H, t, J=7.2 Hz), 3.74(2H, t, J=7.2 Hz), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.20(1H, s), 7.27(2H, d, J=8.4 Hz), 7.32(2H, d, J=8.4 Hz), 7.76(1H, dd, J=2.7,8.8 Hz), 8.19(1H, d, J=2.7 Hz),

Preparation 24



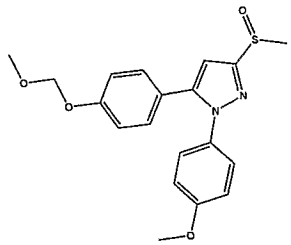
(P0024-0)

(P0024)

To a solution of P0001 (20.0g) and P0024-0 (53.4g) in DMF (200ml) was added portionwise NaH (4.27g) under ice-cooling. The reaction mixture was warmed at room temperature and the temperature was kept under 40°C. After stirring for 5 hours, the reaction mixture was poured onto ice-cooled dilHCl and extracted twise with ethylacetate. The combined organic layer was washed with water (twice) and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (500ml, Hex:EtOAc) to give 12.12g of P0024 as crystal.

mp: 52.6-53.6°C

Example 100



(E0100)

To a solution of 4-hydroxybenzophenone (4.16g) and chloromethyl methyl ether (2.46g) in N,N-dimethylacetoamide (15ml) was added portionwise sodium hydride (suspension in mineral oil (60%), 1.22g) over 15 minutes at 0 °C. The mixture was stirred for 30 minutes at ambient temperature. To the reaction mixture was added

2-propanole (0.5ml) , carbon disulfide (2.56g) and portionwise sodium hydride (suspension in mineral oil (60%), 2.50g) over 15 minutes at 25°C. The mixture was stirred at ambient temperature for 1.5 hours, diluted with toluene (20ml) and poured into a mixture of ice and concentrated hydrogen chloride (8 ml) (aqueous layer total 68ml). The resultant mixture was extracted with ethyl acetate , washed with brine, dried over magnesium sulfate, and evaporated. To the mixture of the resultant residue and sodium hydrogen carbonate (13g) in ethyl acetate (30ml) and water (20ml) was added portionwise the solution of iodine (3.88g) and sodium iodide (8.0g) in water at 0°C. To the mixture was added portionwise 4-Methoxyphenylhydrazine hydrochloride (3.80g) at 0°C under nitrogen. The mixture was stirred at ambient temperature for 3 hours and the organic layer was seperated, washed with water and brine, dried over magnesium sulfate, and evaporated. To the solution of the residue in ethyl acetate (30ml) was added methyl iodide (4.0ml) and triethylamine (10ml) at 0°C. The mixture was stirred for 30 minutes at ambient temperature, washed with water and aqueous potassium carbonate, dried over magnesium sulfate, and evaporated. The residue was column chromatographed on silica gel (80g) , eluting with a mixture of ethyl acetate and toluene (1:20) to give 7.56g of 5-[4-(methoxymethoxy)-phenyl]-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole.

To the solution of methyl sulfide (7.56g) in dichloromethane (30 ml) was added a solution of m-chloroperbenzoic acid (80%, 4.4g) in dichloromethane (15ml) at 0°C, and the mixture was stirred at 0°C for 1 hour. The mixture was washed with aqueous potassium carbonate , dried over magnesium sulfate, and evaporated. The residue was column chromatographed on silica gel (80g) , eluting with

ethyl acetate to give 5.43g of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfinyl)-1H-pyrazole (E0100).

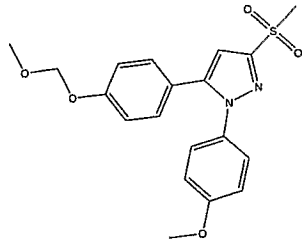
mp.136.9-137.3°C

Mass;373(M+1)

IR(KBr);1054cm-1

NMR(CDCl3,δ);3.00(H, s), 3.48(H, s), 3.83(H, s), 5.17(H, s), 6.88(H, d, J=9.0 Hz), 6.92(H, s), 6.97(H, d, J=8.8 Hz), 7.14(H, d, J=8.8 Hz), 7.22(H, d, J=9.0 Hz),

Example 101



(E0101)

To the solution of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfinyl)-1H-pyrazole (7.56g) in dichloromethane (20 ml) was added m-chloroperbenzoic acid (60%,3.76g) at 0°C, and the mixture was stirred at 0°C for 3 hour. The mixture was washed with aqueous sodium hydrogen carbonate , dried over magnesium sulfate, and evaporated. The residue was purified by recrystallization with toluene to give 5.07g of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole(E0101).

mp.128.0-128.1°C

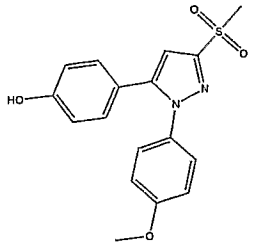
Mass;389(M+1)

IR(KBr);1300cm-1

NMR(CDCl3,δ);3.29(3H, s), 3.48(3H, s), 3.83(3H, s), 5.17(2H, s), 6.88(2H, d, J=9.0 Hz), 6.93(1H, s), 6.98(2H, d, J=8.8

Hz), 7.13(2H, d, J=8.8 Hz), 7.24(2H, d, J=9.0 Hz),

Preparation 25



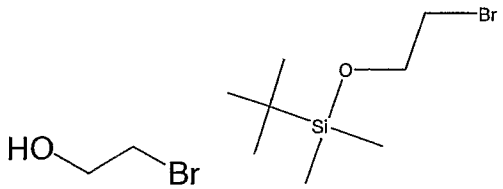
(P0024)

To the solution of 5-[4-(methoxymethoxy)phenyl]-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazole (0.93g) in a mixture of tetrahydrofuran (10ml) and isopropyl alcohol (5ml) was added hydrogen chloride aqueous solution (20%,8ml) at ambient temperature. The solution was stirred for 3 hours, extracted with ethyl acetate , washed with brine, dried over magnesium sulfate, and evaporated to give 0.82g of 4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazol-5-yl]phenol (P0025).

Mass;345(M+1)

NMR(DMSO-d6,δ);3.32(3H, s), 3.79(3H, s), 6.73(2H, d, J=8.6 Hz), 7.01(2H, d, J=8.9 Hz), 7.05(1H, s), 7.08(2H, d, J=8.6 Hz), 7.27(2H, d, J=8.9 Hz), 9.84(1H, s),

Preparation 26



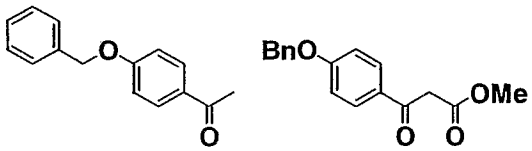
(P0026-0) (P0026)

To a solution of P0026-0 (5.0g) and imidazole (3.3g) in DMF (40ml) was added portionwise TBDMSCl (6.69g) at room

temperature. After stirring overnight, water and hexane was added. The aqueous layer was separated and extracted twice with hexane. The combined organic layer was washed with water (twice) and brine, dried over MgSO4, filtered and evaporated under reduced pressure to give 9.49g (98.3%) of P0026.

IR (film): 2952.5, 2935.1, 1467.6, 1255.4, 1124.3, 1097.3, 838.9, 777.2 cm-1.

Preparation 27



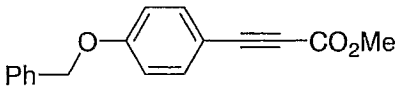
(P0027-0) (P0027)

To a solution of P0027-0 (10g) and dimethylcarbonate 5.97g in DMF was added sodium methoxide 4.77g. The mixture was stirred at ambient temperature for 2hours. The mixture was poured into water with 8 ml of conc. HCl, and extracted with AcOEt. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give orange solid. Which was recrystallized from MeOH to give P0027 as white crystals.

NMR (200 MHz, CDCl3) 3.75(3H, s), 3.96(2H, s), 5.14(2H, s), 7.02(2H, d, J=8.9 Hz), 7.34-7.45(5H, m), 7.93(2H, d, J=8.9 Hz)

Mass ESI 285(M+H)+ (file platform 7366-1)

Preparation 28



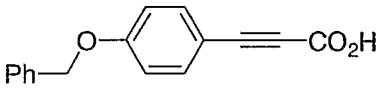
(P0028)

To a solution of triphenylphosphin oxide 294mg in 1,2-dichloroethane 3ml was added trifluoromethanesulfonic anhydride 198mg dropwise under cooling in an ice bath. The mixture was stirred at same temperature for 15minutes, when white precipitates were came out. To this mixture was added P0027 (300mg) in 1,2-dichloroethane 2ml dropwise, followed by addition of Et3N 214mg. The mixture was refluxed for 2hours. The mixture was allowed to cool to ambient temperature and was washed with H2O, sat.aq NaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 5%, and 10%. The residue was crystallized from IPE to give P0028 (166mg) as a white powder.

Mass (ESI+) : 289 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 3.76(3H, s), 5.18(2H, s), 7.11(2H, d, J=8.8 Hz), 7.33-7.48(5H, m), 7.62(2H, d, J=8.8 Hz)

Preparation 29



(P0029)

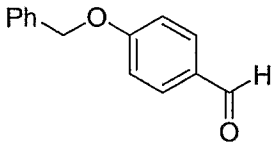
Solid KOH 124mg was dissolved in EtOH 5ml at 50°C. To this solution was added P0028 (196mg). After stirring at same temperature for 2hours, the reaction mixture was allowed to cool to ambient temperature. The mixture was partitioned between 1M HCl and CHCl3. The aqueous layer was reextracted with CHCl3. The combined organic layers were dried over MgSO4, evaporated in vacuo. The residual crystals were collected and washed with IPE to give 1st crop of P0029 (87mg) as a white powder. The mother liqour was concentrated in vacuo

and the residual crystals were collected and washed with n-hexane to give 2nd crop of P0029 (39mg) as a slightly reddish powder.

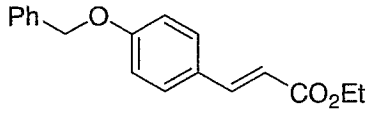
Mass (ESI-) : 251 (M-H)+

200MHz 1H NMR (CDCl3, d) : 5.10(3H, s), 6.97(2H, d, J=8.9 Hz), 7.34-7.43(5H, m), 7.56(2H, d, J=8.9 Hz)

Preparation 30



(P0030-0)

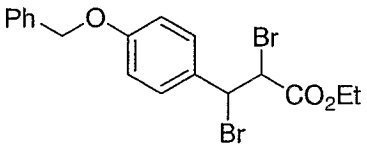


(P0030)

To a solution of P0030-0 (2g) and triethylphosphonoacetate 2.32g in DMF 20ml was added 60% NaH 490mg in two portions with cooling on ice bath. The mixture was stirred at same temperature for 1hour, and then poured into ice water containing NH4Cl. The mixture was stirred for a while, and white precipitates were collected and washed with water and 10% aqueous IPA to give P0030.

200MHz 1H NMR (CDCl3, d) : 1.33(3H, t, J=7.2 Hz), 4.25(2H, q, J=7.2 Hz), 5.10(2H, s), 6.31(1H, d, J=16.0 Hz), 6.97(2H, d, J=8.7 Hz), 7.32-7.50(7H, m), 7.64(1H, d, J=16.0 Hz)

Preparation 31

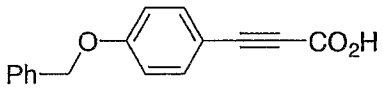


(P0031)

To a solution of P0030 (2.79g) in CH2Cl2 28ml was added bromine 1.66g dropwise under ice bath cooling. The mixture was stirred at same temperature for 30minutes. The reaction mixture was poured into 5% aqueous solution of Na2S2O3, and partitioned. The organic layer was washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residual crystals were collected and washed with n-hexane to give P0031 (3.07g) as a pale yellow powder.

200MHz 1H NMR (CDCl3, d) : 1.38(3H, t, J=7.2 Hz), 4.35(2H, q, J=7.2 Hz), 4.81(1H, d, J=11.8 Hz), 5.07(2H, s), 5.35(1H, d, J=11.8 Hz), 6.98(2H, d, J=8.7 Hz), 7.34(2H, d, J=8.7 Hz), 7.32-7.45(5H, m)

Preparation 32

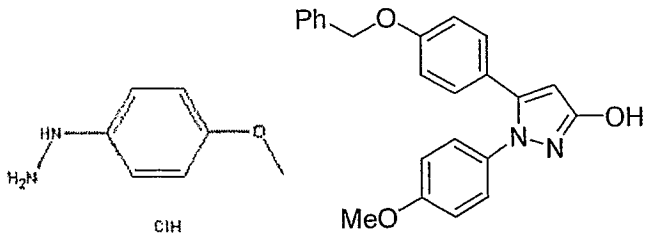


(P0032)

85% solid KOH 1.73g was dissolved in 95% aqueous EtOH 20ml at 50°C. P0031 (3.05g) was added in one portion and the mixture was refluxed for 9hours. To this mixture was added a solution of 85% KOH 0.32g dissolved in 95% aqueous EtOH 10ml and refluxed for 5hours. The mixture was cooled in an ice bath, precipitates were collected and washed with EtOH. The crystals were suspended in AcOEt and H2O, cooled in an ice bath, acidified by 3M HCl and 1M HCl. The mixture was partitioned and the organic layer was washed with H2O, dried over MgSO4, concentrated in vacuo. The residual solid was collected and washed with IPE-n-hexane to give P0032 (0.67g) as a white powder.

200MHz 1H NMR (CDCl3, d) : 5.10(3H, s), 6.97(2H, d, J=8.9 Hz), 7.34-7.43(5H, m), 7.56(2H, d, J=8.9 Hz)

Example 102



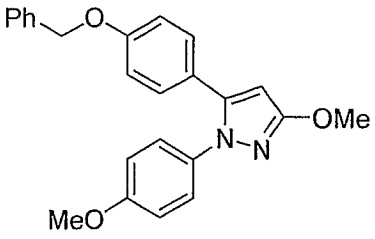
(E0102-0) (E0102)

To a solution of P0032(99.9mg) and HOBT 64.2mg in N-methylpyrrolidone 1ml was added WSCD·HCl 91.1mg and the mixture was stirred at ambient temperature for 20minutes. In another flask, diisopropylethylamine 76.8mg was added to a suspension of E0102-0 (83.0mg) in N-methylpyrrolidone 1ml and stirred at ambient temperature until all E0102-0 was dissolved. The solution of E0102-0 was added to the reaction flask and the mixture was stirred at ambient temperature for 1hour. The mixture was partitioned between AcOEt and H2O, washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, and concentrated in vacuo.The residue was dissolved in CH2Cl2 3ml, and stirred at ambient temperature for 24hours. The mixture was concentrated in vacuo. The residual crystals were suspended in hot AcOEt, cooled with stirring, collected and washed with AcOEt to give E0102 (90.9mg) as a white powder.

Mass (ESI+) : 373 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.75(3H, s), 5.08(2H, s), 5.81(1H, s), 6.90(2H, d, J=9.0 Hz), 6.96(2H, d, J=9.0 Hz), 7.10(2H, d, J=9.0 Hz), 7.12(2H, d, J=9.0 Hz), 7.32-7.47(5H, m), 10.00(1H, s)

Example 103



(E0103)

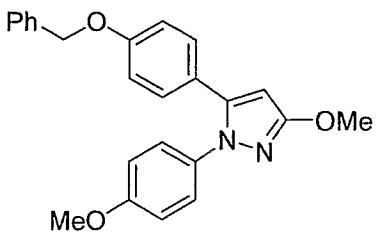
To a suspension of E0102 (20.9mg) and K2CO3 23.3mg in DMSO 0.5ml was added dimethylsulfate 10.6mg and the mixture was stirred at ambient temperature for 1hour. The mixture was partitioned between AcOEt and H2O, and the organic layer was washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by preparative thin layer chromatography developed with AcOEt / n-hexane = 25%. The obtained crystals were crystallized from IPE to give E0103 (12.0mg) as white crystals.

Mass (ESI+) : 387 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.76(3H, s), 3.83(3H, s), 5.08(2H, s), 6.04(1H, s), 6.92(2H, d, J=9.0 Hz), 6.97(2H, d, J=9.0 Hz), 7.11-7.17(4H, m), 7.30-7.50(5H, m)

200MHz 1H NMR (CDCl3, d) : 3.80(3H, s), 3.97(3H, s), 5.04(2H, s), 5.88(1H, s), 6.82(2H, d, J=9.0 Hz), 6.88(2H, d, J=8.9 Hz), 7.11-7.21(4H, m), 7.34-7.43(5H, m)

Example 104



(E0104)

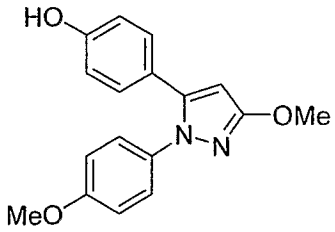
To suspension of E0102 (818mg) and K2CO3 911mg in DMF 6ml was added dimethylcarbonate 0.56ml. The mixture was

stirred at 120°C for 2hours. Additional dimethylcarbonate 1ml was added and stirred at 120°C for 8hours. The mixture was partitioned between AcOEt and H2O, and the aq layer was reextracted with AcOEt. The combined organic layers were washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30%. The residue was crystallized from AcOEt 2.5ml and n-hexane 5ml to give E0104 (583mg) as white crystals.

200MHz 1H NMR (DMSO-d6, d) : 3.76(3H, s), 3.83(3H, s), 5.08(2H, s), 6.04(1H, s), 6.92(2H, d, J=9.0 Hz), 6.97(2H, d, J=9.0 Hz), 7.11-7.17(4H, m), 7.30-7.50(5H, m)

200MHz 1H NMR (CDCl3, d) : 3.80(3H, s), 3.97(3H, s), 5.04(2H, s), 5.88(1H, s), 6.82(2H, d, J=9.0 Hz), 6.88(2H, d, J=8.9 Hz), 7.11-7.21(4H, m), 7.34-7.43(5H, m)

Preparation 33



(P0033)

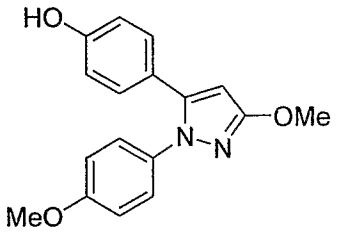
A mixture of 10% Pd-C 50% wet 50mg and E0104 (261mg) in AcOEt 2ml and MeOH 2ml was hydrogenated under H2 1atm at ambient temperature for 1day. The additional 10% Pd-C 50% wet 50mg was added and the mixture was hydrogenated under H2 3.5atm at ambient temperature for 3hours. The catalyst was filtered off and the filtrate and combined washings were concentrated in vacuo. The residue was dissolved in AcOEt, dried over MgSO4, and concentrated in vacuo. The residue was crystallized from AcOEt-n-hexane to give P0033 (146mg) as

a white powder.

Mass (ESI+) : 297 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.75(3H, s), 3.83(3H, s), 5.98(1H, s), 6.70(2H, d, J=8.6 Hz), 6.91(2H, d, J=8.9 Hz), 7.01(2H, d, J=8.6 Hz), 7.12(2H, d, J=8.9 Hz), 9.69(1H, s)

Preparation 34

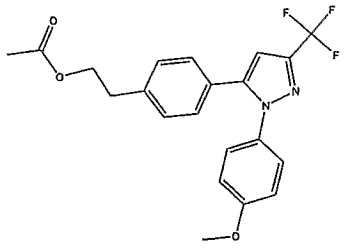


(P0034)

To a solution of ammmonium formate 455mg in H2O 1ml was added EtOH 6ml, E0104 (558mg), THF 1ml, and 10% Pd-C 50% wet 60mg successively. The mixture was refluxed for 1hour. The catalyst was removed by filtration. The filtrate and combined washings were concentrated in vacuo. The residue was partitioned between AcOEt and H2O, and the organic layer was washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residual crystals were recrystallized from AcOEt 3ml and n-hexane 3ml to give P0034 (335mg) as white crystals.

Mass (ESI+) : 297 (M+H)+

Example 105

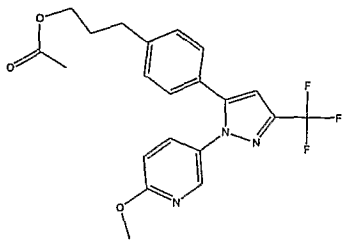


(E0105)

A mixture of P0003 (2.9g) and 4-methoxyphenylhydrazine (1.68g) in acetic acid (30ml) was stirred at room temperature for 15 hours. After addition of water, the mixture was extracted twice with toluene. The combined organic layer was washed with water (twice), sat.NaHCO3, water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc = 8:1-4:1) to give 2.2g (57%) of E0105 as an oil.

IR (film): 1737.6, 1511.9, 1240.0, 1159.0, 1130.1 cm-1.

Example 106



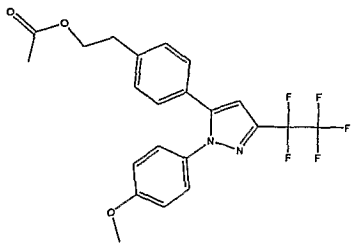
(E0106)

E0106 was prepared from P0004 in a similar manner to that of E0105.

Mass (ESI+) : 420 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.79-1.94(2H, m), 1.98(3H, s), 2.60-2.68(2H, m), 3.88(3H, s), 3.98(2H, t, J=6.5Hz), 6.92(1H, d, J=8.9 Hz), 7.18(1H, s), 7.24(4H, s), 7.75(1H, dd, J=2.7,8.9 Hz), 8.48(1H, d, J=2.7 Hz)

Example 107



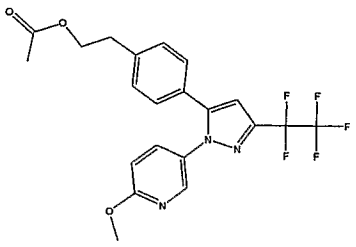
(E0107)

E0107 (175.7mg) was prepared from P0007 (590mg) and 4-methoxyphenylhydrazine hydrochloride (332mg) in a similar manner to that of E0105.

Mass (ESI+) : 455 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.88(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.15(1H, s), 7.17-7.30(6H, m)

Example 108



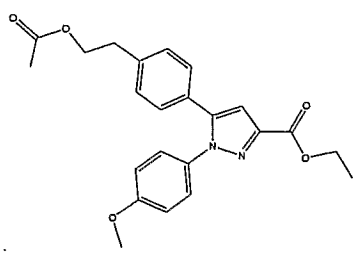
(E0108)

E0108 was prepared from P0007 in a similar manner to that of E0105.

Mass (API-ES positive) : 456 (M+H)+ , 478 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.89(2H, t, J=6.8 Hz), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 6.92(1H, d, J=8.8 Hz), 7.15-7.35(4H, m), 7.21(1H, s), 7.76(1H, dd, J=2.7,8.8 Hz), 8.17(1H, d, J=2.7 Hz)

Example 109



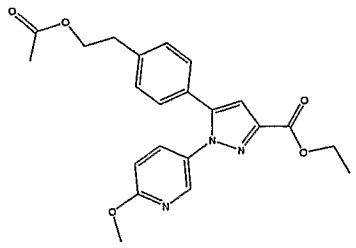
(E0109)

E0109 was prepared in a similar manner to that of E0105.

Mass (ESI+) 409(M+H)+, 431(M+Na)+

NMR: SE20.059 200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 4.32(2H, q, J=7.1 Hz), 6.99(2H, d, J=9.0 Hz), 7.08(1H, s), 7.16-7.28(6H, m)

Example 110



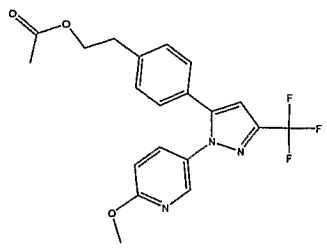
(E0110)

E0110 was prepared in a similar manner to that of E0105.

Mass (ESI+) : 410 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.32(3H, t, J=7.1 Hz), 1.96(3H, s), 2.89(2H, t, J=6.8 Hz), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 4.33(2H, q, J=7.1 Hz), 6.92(1H, d, J=8.8 Hz), 7.12(1H, s), 7.19-7.32(4H, m), 7.73(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 111



(E0111)

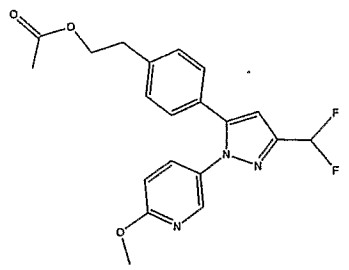
E0111 was prepared in a similar manner to that of E0105.

Mass (API-ES positive) : 406(M+H)+ , 428(M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.89(2H, t, J=6.7 Hz), 3.88(3H, s), 4.21(2H, t, J=6.7 Hz), 6.92(1H, d, J=8.8

Hz), 7.20(1H, s), 7.24(2H, d, J=8.7 Hz), 7.30(2H, d, J=8.7 Hz), 7.76(1H, dd, J=2.7, 8.8 Hz), 8.18(1H, d, J=2.7 Hz)

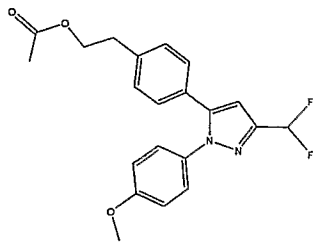
Example 112



(E0112)

E0112 was obtained according to a similar manner to that of E0105.

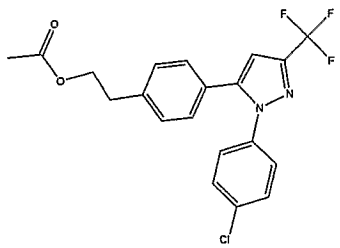
Example 113



(E0113)

E0113 was obtained according to a similar manner to that of E0105.

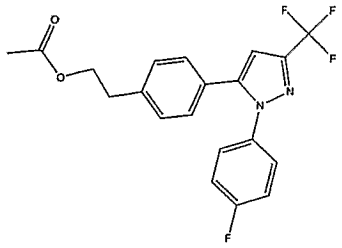
Example 114



(E0114)

E0114 was obtained according to a similar manner to that of E0105.

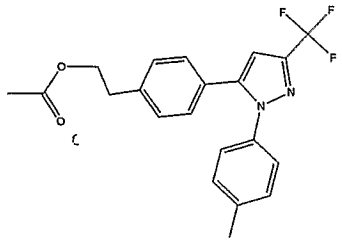
Example 115



(E0115)

E0115 was obtained according to a similar manner to that of E0105.

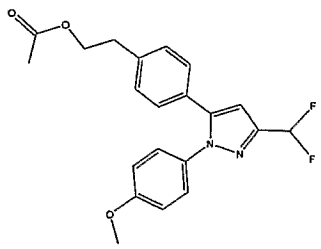
Example 116



(E0116)

E0116 was obtained according to a similar manner to that of E0105.

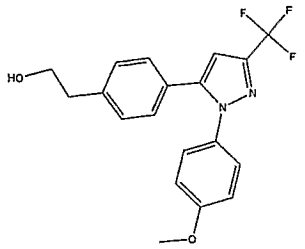
Example 117



(E0117)

E0117 was obtained according to a similar manner to that of E0105.

Example 118



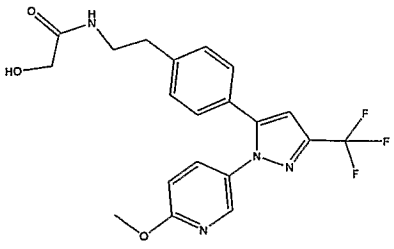
(E0118)

A mixture of E0105 (2.0g) and 1N NaOH (15ml) in THF (40ml) was stirred at room temperature for 5 hours. After the reaction was completed, the mixture was neutralized with 1N HCl (15ml), extracted twice with ethylacetate, washed with 1N HCl, sat.NaHCO3, and brine, dried over NA2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (H/EA = 2:1-1:1) to give 1.14g (64%) of E0118 as a crystal.

mp: 103-104°C

IR (film): 3396.0, 1513.9, 1467.6, 1238.1, 1160.9, 1132.0 cm-1.

Example 119



(E0119)

E0119 was prepared from E0217 in a similar manner to that of E0118.

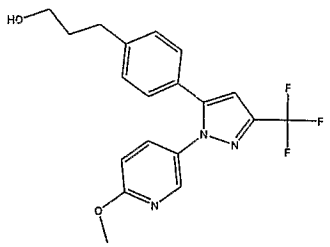
IR (neat) : 3359, 3332, 3325, 1658, 1651, 1624, 1614, 1545, 1533, 1500cm-1

Mass (ESI+) : 421 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71-2.79(2H, m), 3.28-3.39(2H, m), 3.76(2H, brs), 3.88(3H, s), 5.47(1H, br), 6.92(1H, d,

J=8.9 Hz), 7.18(1H, s), 7.24(4H, s), 7.74(1H, dd, J=2.7, 8.9 Hz), 7.80(1H, t, J=5.9 Hz), 8.19(1H, d, J=2.7 Hz)

Example 120



(E0120)

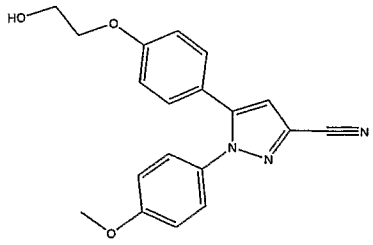
E0120 was prepared from E0002 in a similar manner to that of E0118.

IR (neat) : 3433, 3423, 3398, 3367, 2945, 1612, 1500cm-1

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.62-1.77(2H, m), 2.57-3.65(2H, m), 3.34-3.44(2H, m), 3.88(3H, s), 4.48(1H, t, J=5.1 Hz), 6.92(1H, d, J=8.9 Hz), 7.17(1H, s), 7.23(4H, s), 7.76(1H, dd, J=8.9,2.8 Hz), 8.18(1H, d, J=2.8 Hz)

Example 121



(E0121)

E0121 was prepared from E0268 in a similar manner to that of E0118.

white powder

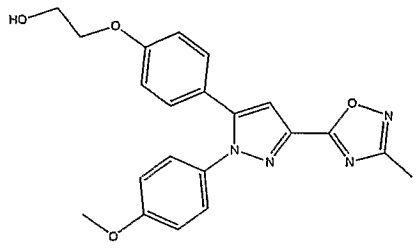
mp. 91-92°C

IR (KBr) : 3491, 3471, 3437, 2941, 2239, 1610, 1508cm-1

Mass (ESI+) : 336 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.79(3H, s), 3.95-4.05(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.16(2H, d, J=8.8 Hz), 7.28(2H, d, J=9.0 Hz), 7.32(1H, s)

Example 122



(E0122)

E0122 was prepared from E0353 in a similar manner to that of E0118.

white powder

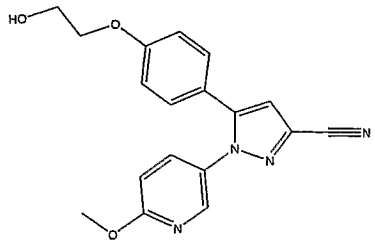
mp. 158-159°C

IR (KBr) : 3399, 2955, 1707, 1693, 1647, 1614, 1566, 1547, 1529, 1512cm-1

Mass (ESI+) : 393 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.44(3H, s), 3.66-3.74(2H, m), 3.80(3H, s), 3.96-4.02(2H, m), 4.88(1H, t, J=5.4 Hz), 6.94(2H, d, J=8.7 Hz), 7.02(2H, d, J=8.9 Hz), 7.22(2H, d, J=8.7 Hz), 7.26(1H, s), 7.31(2H, d, J=8.9 Hz)

Example 123



(E0123)

E0123 was prepared from E0358 in a similar manner to that

of E0118.

white powder

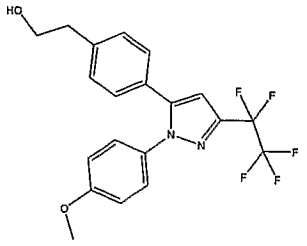
mp. 105-107°C

IR (KBr) : 3529, 3437, 2956, 1610, 1570, 1547, 1529cm-1

Mass (ESI+) : 337 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.3 Hz), 6.93(1H, d, J=8.8 Hz), 6.96(2H, d, J=8.7 Hz), 7.21(2H, d, J=8.7 Hz), 7.35(1H, s), 7.73(1H, dd, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

Example 124



(E0124)

E0124 was prepared from E0107 in a similar manner to that of E0118.

white powder

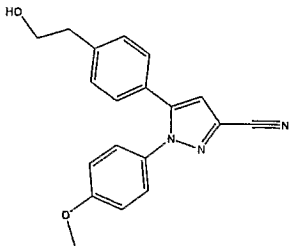
mp. 97-98°C

IR (KBr) : 3427, 2960, 1608, 1516cm-1

Mass (ESI+) : 413 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71(2H, t, J=6.9 Hz), 3.54-3.65(2H, m), 3.79(3H, s), 4.64(1H, t, J=5.1 Hz), 7.00(2H, d, J=9.0 Hz), 7.12(1H, s), 7.15-7.33(4H, m), 7.29(2H, d, J=9.0 Hz)

Example 125



(E0125)

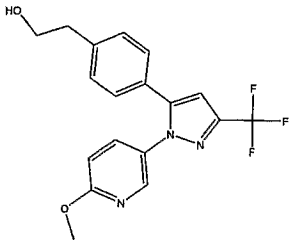
E0125 was prepared in a similar manner to that of E0118.

IR (neat) : 3435, 3425, 3406, 3398, 3367, 1691, 1658, 1647, 1614, 1547, 1512cm-1

Mass (ESI+) : 320 (M+H)+ , 361(M+CH3CN+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71(2H, t, J=6.8 Hz), 3.54-3.64(2H,m), 3.79(3H,s), 4.64(1H,t,J=5.2Hz), 7.00(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.3 Hz), 7.23(2H, d, J=8.3 Hz), 7.29(2H, d, J=8.9 Hz), 7.34(1H, s)

Example 126



(E0126)

E0126 was prepared from E0111 in a similar manner to that of E0118.

white powder

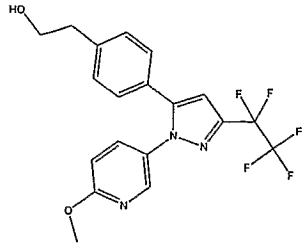
mp. 89-92°C

IR (KBr) : 3481, 2947, 1608, 1496cm-1

Mass (ESI+) : 364 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.8 Hz), 3.55-3.65(2H,m), 3.88(3H,s), 4.65(1H,t,J=5.2Hz), 6.92(1H, d, J=8.8 Hz), 7.16(1H, s), 7.19-7.28(4H, m), 7.77(1H, dd, J=2.6,8.8 Hz), 8.19(1H, d, J=2.6 Hz)

Example 127



(E0127)

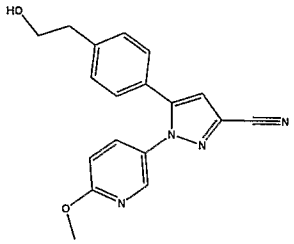
E0127 was prepared from E0108 in a similar manner to that of E0118.

IR (neat) : 3400, 2951, 1610, 1502cm-1

Mass (API-ES positive) : 414 (M+H)+ , 436 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.9 Hz), 3.51-3.65(2H,m), 3.88(3H, s), 4.65(1H, t, J=5.1Hz), 6.93(1H, d, J=8.8 Hz), 7.15-7.35(4H, m), 7.18(1H, s), 7.77(1H, dd, J=2.7,8.8 Hz), 8.18(1H, d, J=2.7 Hz)

Example 128



(E0128)

E0128 104.4mg was prepared in a similar manner to that of E0118.

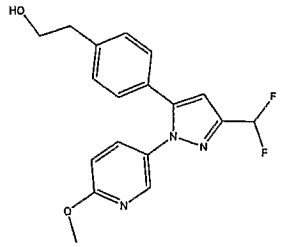
IR (neat) : 3433, 3423, 3398, 2947, 2873, 2243, 1608cm-1

Mass (ESI+) : 321 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.8 Hz), 3.55-3.65(2H,m), 3.88(3H, s), 4.65(1H, t, J=5.1Hz), 6.93(1H, d, J=8.8 Hz), 7.19(2H, d, J=8.4 Hz), 7.26(2H, d, J=8.4 Hz), 7.38(1H, s), 7.76(1H, dd, J=2.7,8.8 Hz), 8.21(1H, d, J=2.7

Hz)

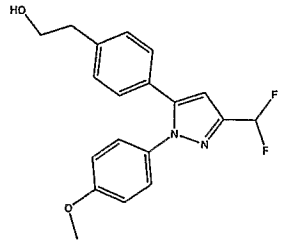
Example 129



(E0129)

E0129 was obtained according to a similar manner to that of E0118.

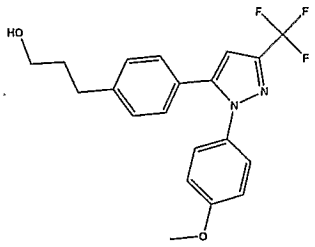
Example 130



(E0130)

E0130 was obtained according to a similar manner to that of E0118.

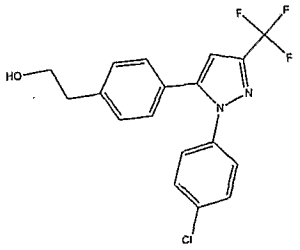
Example 131



(E0131)

E0131 was obtained according to a similar manner to that of E0118.

Example 132

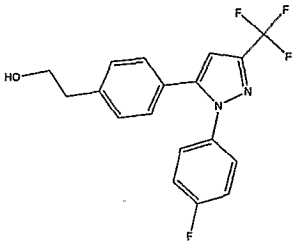


(E0132)

E0132 was obtained according to a similar manner to that of E0118.

IR (film): 3392.2, 1494.6, 1236.2, 1160.9, 1133.9, 1095.4, 975.8, 833.1 cm-1.

Example 133



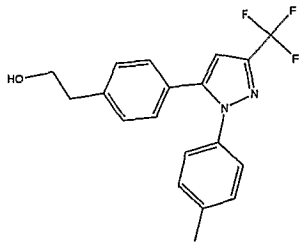
(E0133)

E0133 was obtained according to a similar manner to that of E0118.

IR (film): 3374.8, 1511.9, 1471.4, 1274.7, 1232.3, 1160.9, 1133.9, 977.7, 842.7, 811.9 cm-1.

mp: 82-83 °C

Example 134

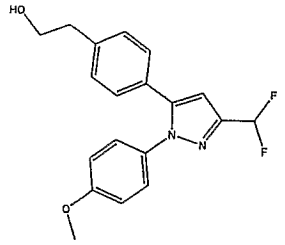


(E0134)

E0134 was obtained according to a similar manner to that of E0118.

IR (film): 3386.4, 1511.9, 1471.4, 1236.2, 1159.0, 1132.0, 1047.2, 975.8, 817.7 cm-1.

Example 135

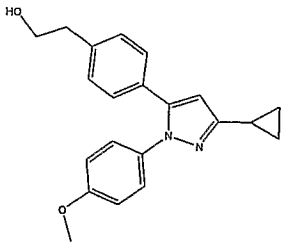


(E0135)

E0135 was obtained according to a similar manner to that of E0118.

IR (film): 3399.9, 1610.3, 1513.9, 1459.9, 1251.6, 1172.5, 1083.8, 1033.7, 836.9, 802.2 cm-1. (FS7081)

Example 136



(E0136)

P0018 (277mg) and 4-methoxyphenylhydrazine hydrochloride (209mg) in EtOH:AcOH=20:1 6ml was refluxed for 2hours. The mixture was partitioned between AcOEt and H2O. The organic layer was washed successively with 1M HCl, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane =

30%, 40%, 50%. Thepure fraction was collected and concentrated in vacuo. The residue was crystallized from AcOEt / n-hexane to give E0136 (95.6mg) as a white powder.

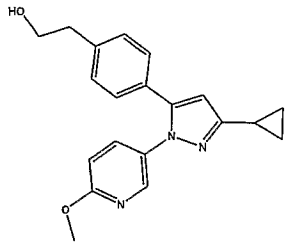
mp. 111-112°C

IR (KBr) : 3325, 2931, 1707, 1693, 1685, 1658, 1647, 1564, 1549, 1514cm-1

Mass (ESI+) : 335 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.86-0.96(2H, m), 1.93(1H, m), 2.69(2H, t, J=6.9 Hz), 3.53-3.64(2H, m), 3.76(3H, s), 4.64(1H, t, J=5.2 Hz), 6.28(1H, s), 6.92(2H, d, J=9.0 Hz), 7.05-7.19(6H, m)

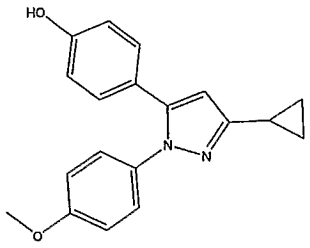
Example 137



(E0137)

E0137 was prepared from P0018 498.5mg in a similar manner to that of E0136.

Preparation 34



(P0034)

P0034 was prepared in a similar manner to that of E0137.

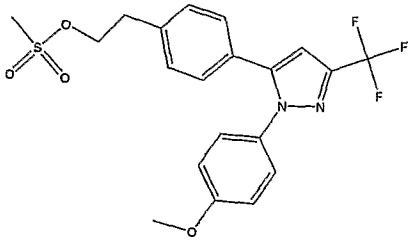
white powder

Mass (ESI+) : 306 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

0.67-0.76(2H, m), 0.84-0.94(2H, m), 1.91(1H, m), 3.76(3H, s), 6.18(1H, s), 6.68(2H, d, J=8.7 Hz), 6.91(2H, d, J=9.0 Hz), 6.98(2H, d, J=8.7 Hz), 7.12(2H, d, J=9.0 Hz), 9.63(1H, s)

Example 138

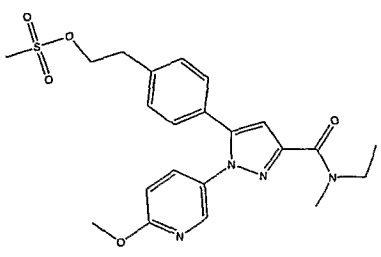


(E0138)

To a solution of E0118 (1.0g) and Et3N (0.6ml) in CH2Cl2 (20ml) was added dropwise methanesulfonyl chloride (0.26ml) under ice-cooling. After stirring for 1 hour, the reaction mixture was quenched with water and extracted with CHCl3. The organic layer was washed with water, dried over Na2SO4, filtered and evaporated to give 1.2g (99%) of crude E0138 as an off-white solid.

IR (film): 1513.9, 1469.5, 1351.9, 1240.0, 1166.7, 1130.1, 971.9, 835.0, 804.2cm-1.

Example 139



(E0139)

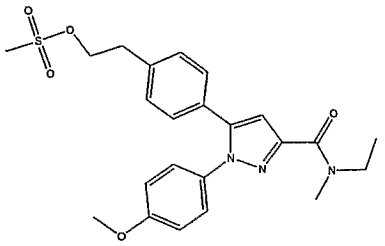
E0139 was prepared in a similar manner to that of E00138.

Mass (ESI+) : 459 (M+H)+

200MHz 1H NMR (DMSO-d6, d)

1.09-1.23(3H, m), 2.98,3.29(3H, s), 3.01(2H, t, J=6.6 Hz), 3.09(3H, s), 3.43-3.77(2H, m), 3.87(3H, s), 4.42(2H, t, J=6.6 Hz), 6.88-6.92(2H, m), 7.25(2H, d, J=8.3 Hz), 7.33(2H, d, J=8.3 Hz), 7.65-7.73(1H, m), 8.15(1H, d, J=2.6 Hz)

Example 140



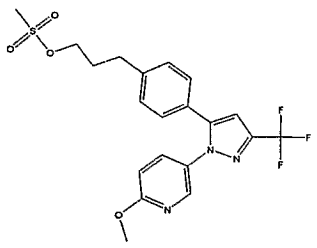
(E0140)

E0140 was prepared in a similar manner to that of E0138.

Mass (APCI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.05-1.25(3H, m), 2.96-3.03(2H, m), 2.98,3.29(3H, s), 3.08(3H, s), 3.40-3.85(2H, m), 3.78(3H, s), 4.42(2H, t, J=6.6 Hz), 6.86,6.88(1H, s), 6.98(2H, d, J=8.9 Hz), 7.18-7.32(6H, m)

Example 141



(E0141)

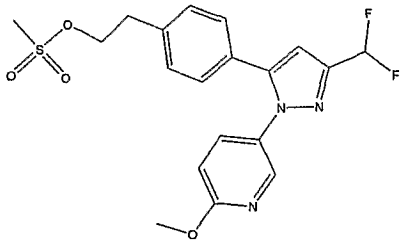
E0141 was prepared in a similar manner to that of E0138.

Mass (ESI+) : 456 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.89-2.04(2H, m), 2.52-2.73(2H, m), 3.16(3H, s), 3.88(3H, s), 4.19(2H, t, J=6.3 Hz), 6.92(1H, d, J=8.9 Hz), 7.18(1H, s), 7.21-7.31(4H, m), 7.76(1H, dd,

J=2.6,8.9 Hz), 8.19(1H, d, J=2.6 Hz)

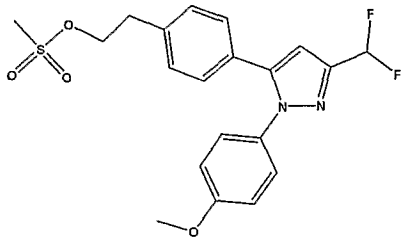
Example 142



(E0142)

E0142 was obtained according to a similar manner to that of E0138.

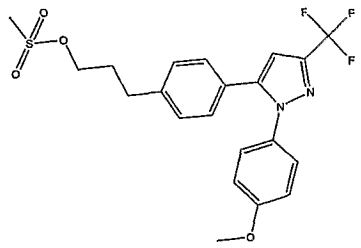
Example 143



(E0143)

E0143 was obtained according to a similar manner to that of E0138.

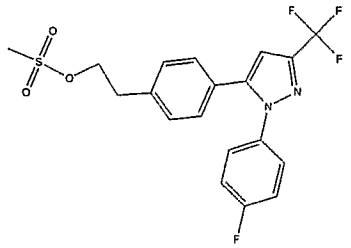
Example 144



(E0144)

This compound was obtained according to a similar manner to that of E0138.

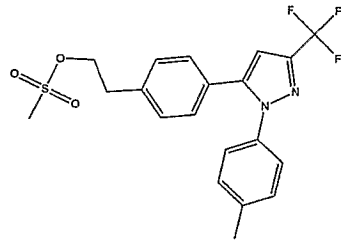
Example 145



(E0145)

This compound was obtained according to a similar manner to that of E0138.

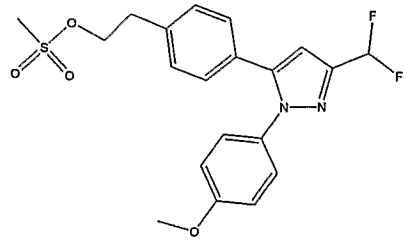
Example 146



(E0146)

This compound was obtained according to a similar manner to that of E0138.

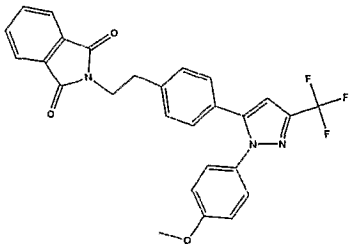
Example 147



(E0147)

This compound was obtained according to a similar manner to that of E0138.

Example 148

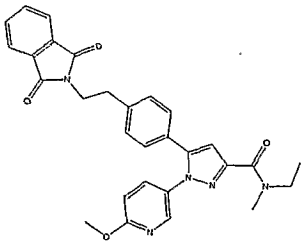


(E0148)

A mixture of E0138 (900mg) and potassium phthalimide (454mg) in DMF (18ml) was stirred at 60oC for 3.0 hours. After addition of water, the reaction mixture was extracted with EtOAc and washed twice with water and with brine. The organic layer was dried over Na2SO4 , filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) to give 930mg (93%) of E0148 as a powder.

IR (film): 1772.3, 1712.5, 1240.0, 1160.9, 1130.1cm-1.

Example 149



(E0149)

E0149 was prepared from E0139 in a similar manner to that of E0148.

amorphous powder

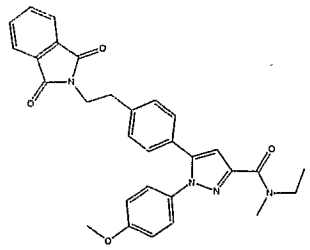
Mass (ESI+) : 510 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.08-1.22(3H, m), 2.89-2.98(2H, m), 2.98,3.27(3H, s), 3.48,3.70(2H, q, J=7.1,6.9 Hz), 3.82(2H, t, J=7.3 Hz), 3.88(3H, s), 6.83-6.88(2H, m), 7.23(2H, d, J=8.7Hz), 7.18(2H, d, J=8.7 Hz), 7.53-7.63(1H, m), 7.79-7.89(4H, m), 8.15(1H,

d, J=2.6 Hz)

Example 150



(E0150)

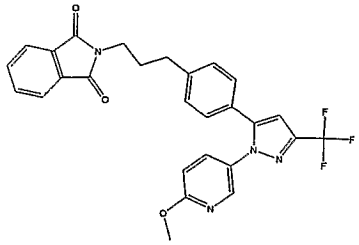
E0150 was prepared from E0140 in a similar manner to that of E0148.

amorphous powder

Mass (ESI+) : 509 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.12,1.18(3H, t, J=7.0,7.1 Hz), 2.92(2H, t, J=7.0 Hz), 2.97,3.28(3H, s), 3.47,3.71(2H, q, J=7.1,7.0 Hz), 3.78(3H, s), 3.81(2H, t, J=7.0 Hz), 6.82,6.84(1H, s), 6.94(2H, d, J=9.0 Hz), 7.11-7.20(6H, m), 7.79-7.89(4H, m)

Example 151



(E0151)

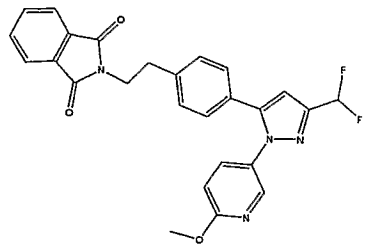
E0151 was prepared from E0038 in a similar manner to that of E0148.

Mass (ESI+) : 507 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.82-1.97(2H, m), 2.59-2.67(2H, m), 3.60(2H, t, J=7.0 Hz), 3.88(3H, s), 6.91(1H, d, J=8.8 Hz), 7.14(1H, s), 7.20(2H, d, J=8.5 Hz), 7.26(2H, d, J=8.5

Hz), 7.73(1H, dd, J=8.8,2.8 Hz), 7.78-7.89(4H, m), 8.17(1H, d, J=2.8 Hz)

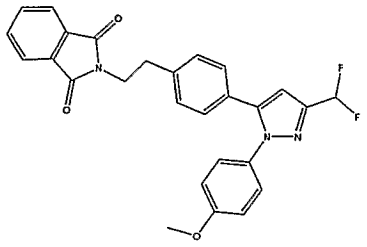
Example 152



(E0152)

This compound was obtained according to a similar manner to that of E0148.

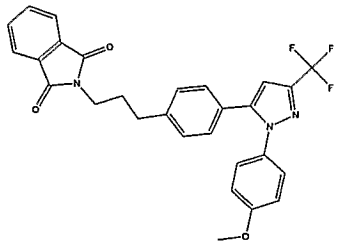
Example 153



(E0153)

This compound was obtained according to a similar manner to that of E0148.

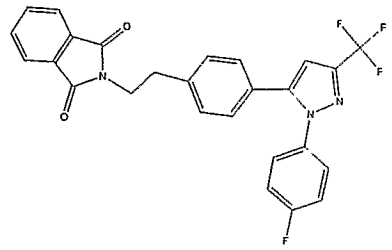
Example 154



(E0154)

This compound was obtained according to a similar manner to that of E0148.

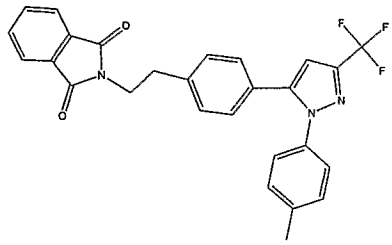
Example 155



(E0155)

This compound was obtained according to a similar manner to that of E0148.

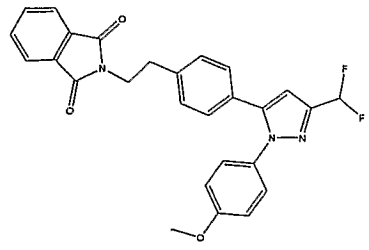
Example 156



(E0156)

This compound was obtained according to a similar manner to that of E0148.

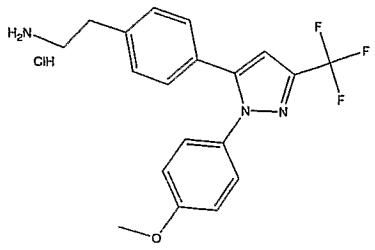
Example 157



(E0157)

This compound was obtained according to a similar manner to that of E0148.

Example 158

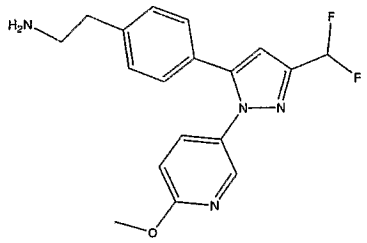


(E0158)

To a solution of E0148 (800mg) in CH3CN (10ml) was added hydrazine hydroxide (87ul) at room temperature. After stirring for 1 hour, the reaction mixture was filtered and evaporated. After addition of dichloromethane, the mixture was stirred for an hour, filtered and evaporated. The residue was treated with 4NHCl/EtOAc to give 518mg (80%) of E0158.

IR (Film); 3403.74, 1610.27, 1511.92, 1467.56, 1238.08, 1160.94, 1130.08, 1027.87, 975.80, 836.96, 806.10cm-1.

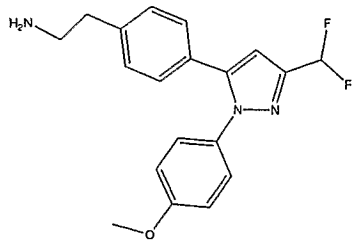
Example 159



(E0159)

This compound was obtained according to a similar manner to that of E0158.

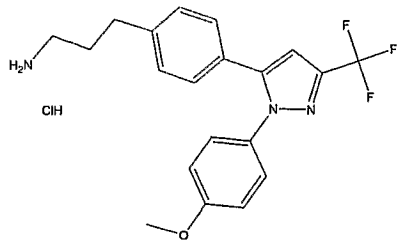
Example 160



(E0160)

This compound was obtained according to a similar manner to that of E0158.

Example 161

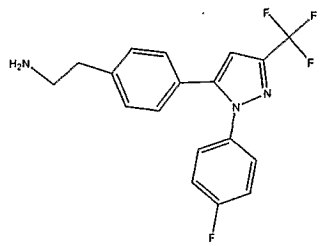


(E0161)

This compound was obtained according to a similar manner to that of E00158.

IR (film): 3428.8, 1511.9, 1467.6, 1238.1, 1160.9, 1132.0cm-1.

Example 162

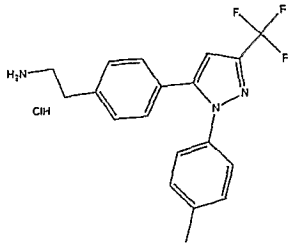


(E0162)

This compound was obtained according to a similar manner to that of E0158.

IR (film): 3371.0, 1511.9, 1471.4, 1272.8, 1230.4, 1160.9, 1133.9, 975.8, 842.7, 810.0cm-1.

Example 163



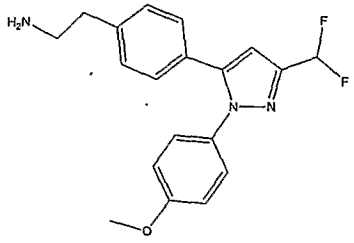
(E0163)

This compound was obtained according to a similar manner to that of E0158.

mp: 163.1-165.1°C

IR (film): 2973.7, 1511.9, 1471.4, 1236.2, 1159.0, 1133.9cm-1.

Example 164

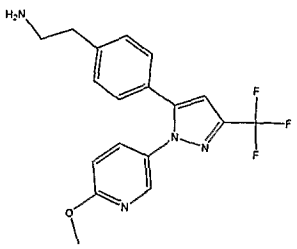


(E0164)

This compound was obtained according to a similar manner to that of E0158.

IR(film): 3369.0, 1604.5, 1513.9, 1459.9, 1251.6, 1172.5, 1083.8, 1029.8,837.0, 800.3 cm-1.

Example 165

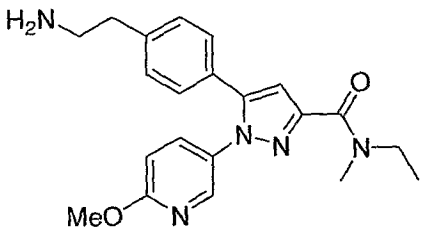


(E0165)

To a solution of E0395 (1.08 g) in acetonitril (15 ml) was

added hydrazine monohydrate (0.53 ml). After stirring at 60°C overnight, the mixture was filtered. And the filtrate was evaporated to give E0165 as an orange oil (814 mg, 102%).
NMR(CDCl3), 2.76(2H, t, J=6.5 Hz), 2.98(2H, t, J=6.5 Hz), 3.94(3H, s), 6.73(1H, s), 6.76(1H, d, J=8.9 Hz), 7.22-7.12(4H, m), 7.57(1H, dd, J=8.9, 2.7 Hz), 8.09(1H, d, J=2.7 Hz).
MS(ESI+);363.3(MH+).

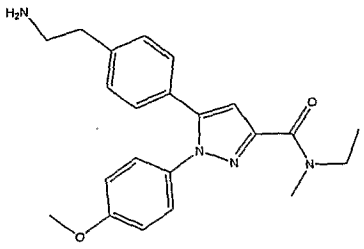
Example 166



(E0166)

E0166 was prepared from E0046 in a similar manner to that of E0165.
Mass (ESI+) : 380 (M+H)+
200MHz 1H NMR (DMSO-d6, d) :
1.91-1.23(3H, m), 2.59-2.79(4H, m), 2.98,3.28(3H, s), 3.48,3.71(2H, q, J=7.2,7.0 Hz), 3.87(3H, s), 6.86-6.93(2H, m), 7.16-7.26(4H, m), 7.64-7.73(1H, m), 8.15(1H, d, J=2.5 Hz)

Example 167



(E0167)

E0167 was prepared from E0150 in a similar manner to that

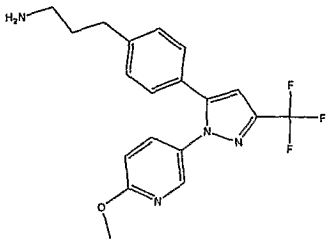
of E0165.

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.08-1.22(3H, m), 2.57-2.78(4H, m), 2.97,3.29(3H, s), 3.48,3.72(2H, q, J=7.2,7.0 Hz), 3.78(3H, s), 6.83,6.85(1H, s), 6.98(2H, d, J=8.9 Hz), 7.06-7.26(6H, m)

Example 168



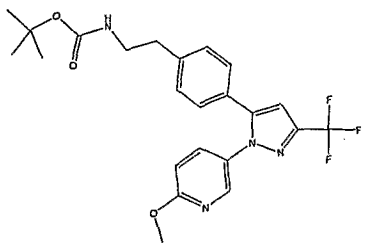
(E0168)

E0168 was prepared from E0048 in a similar manner to that of E0165.

Mass (ESI+) : 377 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.54-1.69(2H, m), 2.49-2.64(4H, m), 3.88(3H, s), 6.92(1H, d, J=8.7 Hz), 7.17(1H, s), 7.22(4H, s), 7.75(1H, dd, J=8.7,2.6 Hz), 8.18(1H, d, J=2.6 Hz)

Example 169



(E0169)

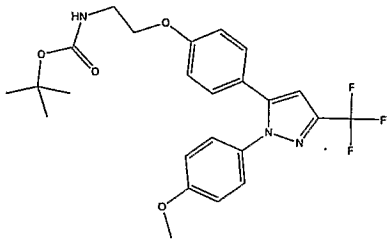
To a solution of E0165 (180 mg) in tetrahydrofuran (2 ml) was added triethylamine (0.242 ml) and t-butoxycarbonyl anhydride (325 mg) at room temperature. After stirring at room temperature overnight, the mixture was quenched with

water and extracted with ethyl acetate (x3). The organic layer was washed with hydrogen chloride aqueous solution (1N), saturated sodium hydrogen carbonate aqueous solution, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO2 25 ml, 20% ethyl acetate/hexane) to give E0169 as an oil (224 mg , 97.5%).

NMR(CDCl3); 1.35(9H, s), 2.69(2H, t, J=7.7 Hz), 3.09-3.19(2H, m), 3.88(3H, s), 6.91(1H, d, J=8.8 Hz), 7.17(1H, s), 7.18-7.27(4H, m), 7.75(1H, dd, J=8.8, 2.7 Hz), 8.19(1H, d, J=2.7 Hz).

MS(ESI+); 485.2(M+Na).

Example 170



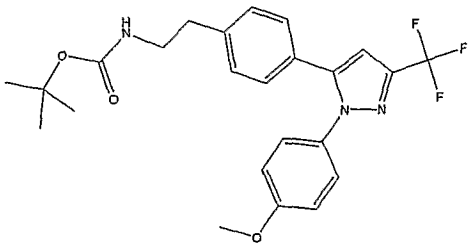
(E0170)

This compound was obtained according to a similar manner to that of E0169.

NMR(CDCl3), 1.45(9H, s), 3.49-3.57(2H, m), 3.82(3H, s), 4.01(2H, t, J=5.1 Hz), 6.67(1H, s), 6.82(2H, d, J=8.7 Hz), 6.87(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).

MS(ESI+), 500.2(M+Na).

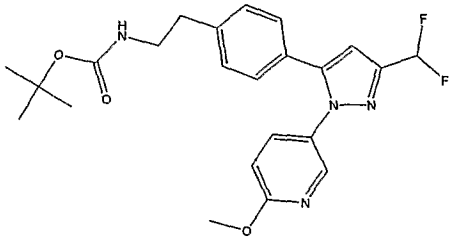
Example 171



(E0171)

A mixture of E0158 (650mg) , Boc2O (428mg) and 1NNaOH (3.3ml) in THF (20ml) was stirred at room temperature for 15 hours. Water and EtOAc was added and the aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with sat NaHCO3, water and brine, dried over NA2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc) to give 700mg (93%) of E0171 as an oil.

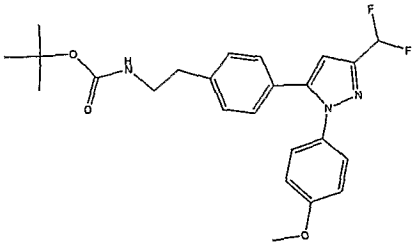
Example 172



(E0172)

This compound was obtained according to a similar manner to that of E0171.

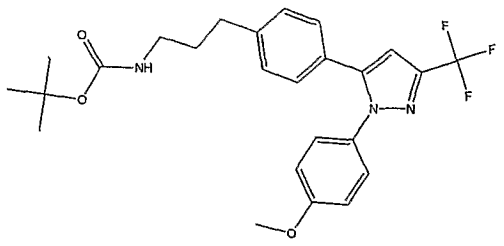
Example 173



(E0173)

This compound was obtained according to a similar manner to that of E0171.

Example 174

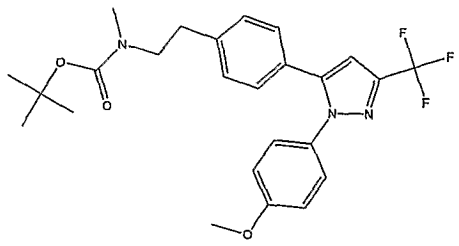


(E0174)

This compound was obtained according to a similar manner to that of E0171.

IR (film): 1702.8, 1513.9, 1241.9, 1164.8, 1132.0cm-1.

Example 175

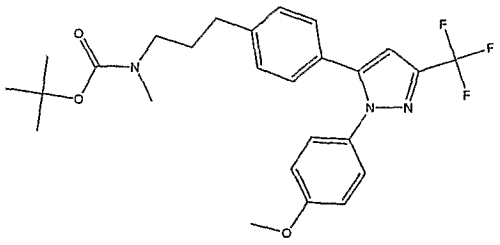


(E0175)

To a solution of E0171 (200mg) and MeI (0.14ml) in THF (20ml) was added portionwise NaH (35mg) at room temperature. Then the reaction mixture was heated at 70oC for 1 hour. Almost no reaction.

MeI (0.3ml) and NaH (40mg) was added, and DMF was added. The mixture was stirred at 70°C for 12 hours, and then cooled, quenched with water. The aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated. The residue was column chromatographed on silica gel to give 151mg (73%) of E0175 as an oil.

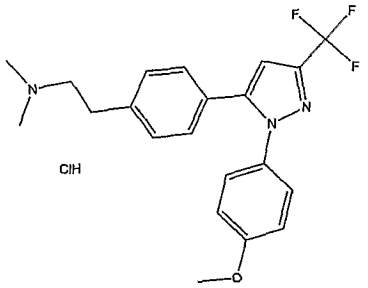
Example 176



(E0176)

This compound was obtained according to a similar manner to that of E0175.

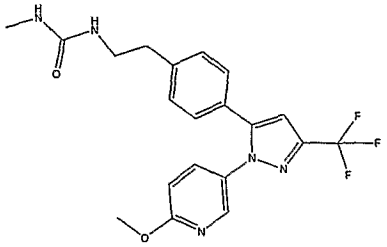
Example 177



(E0177)

To a mixture of E0158 (150mg) and HCHO (46ul) in Et3N (53ul) and CH3CN (5ml) was added portionwise NaBH(OAc)2 (240mg) at room temperature. After stirring for 15 hours, the mixture was quenched with water and extracted three times with EtOAc. The combined organic layer was washed with water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (CHCl3/MeOH) and treated with 4NHCl/dioxane to give 108mg (70%) of E0177.

Example 178



(E0178)

Methylisocyanate 36.2mg was added to a solution of E0165 (199.3mg) and triethylamine 48.6mg in CH2Cl2 2ml under ice bath cooling. The reaction mixture was stirred at same temperature for 1hour and concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was recrstallized from AcOEt-n-hexane. Obtained powder was dissolved in CHCl3 and further purified by preparative thin layer silica gel chromatography developed by MeOH / CHCl3 = 10%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo. The residual solid was collected and washed with diisopropyl ether to give E0178 (101.3mg) as a white powder.

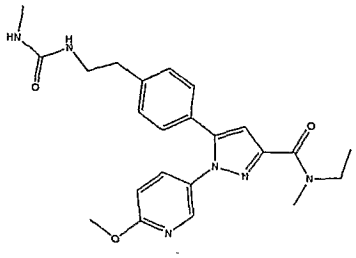
mp. 149°C

IR (KBr) : 3348, 2947, 2885, 1626, 1583, 1529, 1500cm-1

Mass (ESI+) : 420 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.49-2.53(3H, overlapping), 2.64-2.72(2H, m), 3.15-3.26(2H, m), 3.88(3H, s), 5.72(1H, q, J=4.5 Hz), 5.89(1H, t, J=5.7 Hz), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.24(4H, s), 7.76(1H, dd, J=2.7, 8.8 Hz), 8.19(1H, d, J=2.7 Hz)

Example 179



(E0179)

E0179 80.7mg was prepared from E0166 in a similar manner to that of E0178.

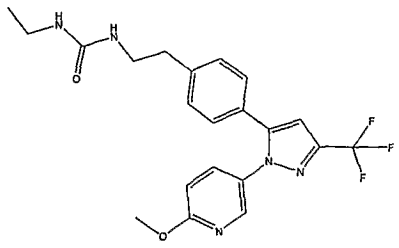
amorphous powder

IR (neat) : 3350, 2950, 2930, 1707, 1691, 1674, 1645, 1641, 1622, 1614, 1566, 1549, 1533, 1510cm-1

Mass (ESI+) : 437 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.09-1.23(3H, m), 2.49-2.54(3H, overlapping), 2.67(2H, t, J=7.2 Hz), 2.98,3.28(3H, s), 3.15-3.28(2H, m), 3.48,3.71(2H, q, J=6.8,6.9 Hz), 3.88(3H, s), 5.73(1H, q, J=4.6 Hz), 5.90(1H, t, J=5.6 Hz), 6.86-6.93(2H, m), 7.22(4H, s), 7.64-7.73(1H, m), 8.15(1H, d, J=2.6 Hz)

Example 180



(E0180)

E0180 was prepared from E0294 in a similar manner to that of E0178.

white powder

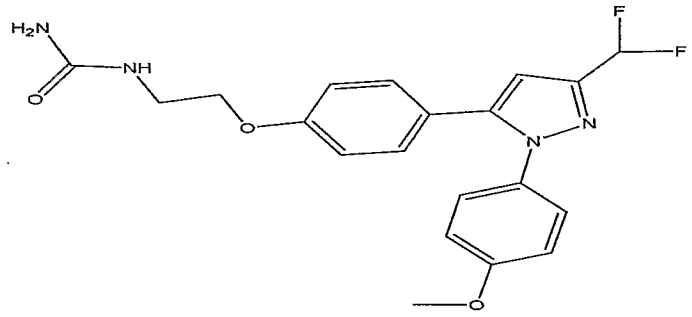
mp. 155-157°C

IR (KBr) : 3336, 2968, 1707, 1693, 1674, 1621, 1576, 1533cm-1

Mass (ESI+) : (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.96(3H, t, J=7.1 Hz), 2.64-2.72(2H, m), 2.91-3.05(2H, m), 3.15-3.26(2H, m), 3.88(3H, s), 5.76-5.84(2H, m), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.24(4H, s), 7.76(1H, dd, J=8.8,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 181

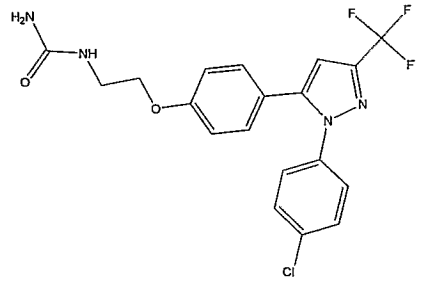


(E0181)

This compound was obtained according to a similar manner to that of E0178.

IR (film) : 3343.9, 1658.5, 1608.3, 1513.9, 1457.9, 1249.6, 1029.8, 836.9 cm-1.

Example 182



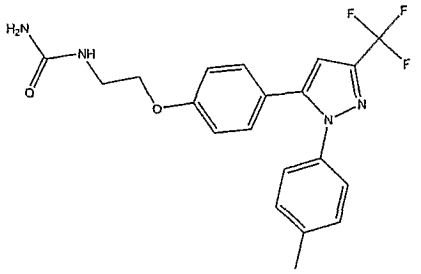
(E0182)

This compound was obtained according to a similar manner to that of E0178.

IR (Film) : 1659.0, 1608.8, 1554.8, 1485.4, 1470.0, 1240.4, 1165.1, 1134.3, 1097.6, 835.3cm-1.

Example 183

SUBSTITUTE SHEET(RULE26)

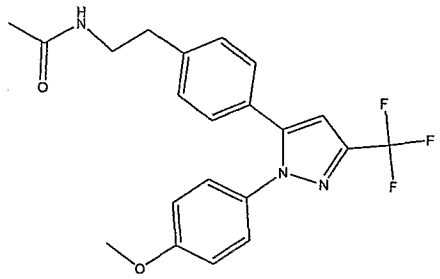


(E0183)

This compound was obtained according to a similar manner to that of E0178.

IR (film): 3249.8, 1658.5, 1608.3, 1554.3, 1469.5, 1240.0, 1164.8, 1133.9, 1097.3, 975.8, 835.0 cm-1.

Example 184



(E0184)

AcCl 23.3mg was added to E0158 (107.4mg) and triethylamine 68.3mg in CH2Cl2 2ml with cooling in an ice bath. After stirring at same temperature for 1hour, the reaction mixture was concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid were collected and washed with diisopropyl ether to give E0184 (84mg) as a white powder.

mp. 79-80°C

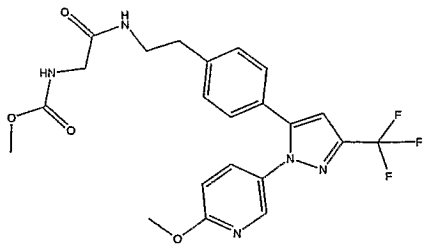
IR (KBr) : 3307, 3221, 3093, 2964, 1689, 1639, 1554, 1514cm-1

Mass (ESI+) : 404 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.76(3H, s), 2.65-2.73(2H, m),

3.18-3.31(2H,m), 3.79(3H,s), 6.99(2H,d,J=8.9Hz), 7.12(1H, s), 7.20(4H, s), 7.28(2H, d, J=8.9 Hz), 7.92(1H, t, J=5.4 Hz)

Example 185



(E0185)

E0185 (143.4mg) was prepared from E0232 (155.3mg), methyl chloroformate 35.8mg, and triethylamine 105mg in a similar manner to that of E0184.

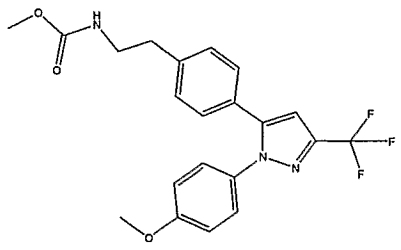
amorphous powder

IR (neat) : 3319, 2954, 1718, 1711, 1668, 1660, 1612, 1545, 1533, 1500cm-1

Mass (ESI+) : 178 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.75(2H, m), 3.22-3.33(2H, m), 3.50-3.60(2H, overlapping), 3.53(3H, s), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.18(1H, s), 7.24(4H, s), 7.28(1H, t, J=6 Hz), 7.75(1H, dd, J=2.7,8.8 Hz), 7.94(1H, t, J=5.6 Hz), 8.19(1H, d, J=2.7 Hz)

Example 186



(E0186)

E0186 (59.3mg) was prepared from E0158 (96.2mg), methyl

chloroformate 25.1mg and triethylamine 61.2mg in a similar manner to that of E0184.

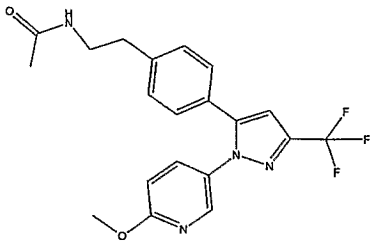
mp. 78-80°C

IR (KBr) : 3352, 1739, 1695, 1658, 1647, 1549, 1514cm-1

Mass (ESI+) : 420 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.66-2.74(2H, m), 3.14-3.25(2H, m), 3.49(3H, s), 3.79(3H, s), 6.99(2H, d, J=8.9Hz), 7.12(1H, s), 7.12-7.32(1H, m), 7.20(4H, s), 7.28(2H, d, J=8.9 Hz)

Example 187



(E0187)

E0187 (63.4mg) was prepared from E0165 (113.6mg), acetyl chloride 29.5mg, and triethylamine 41.2mg in a similar manner to that of E0184.

white powder

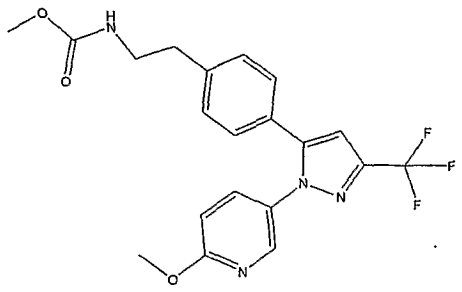
mp.97-98°C

IR (KBr) : 3311, 2956, 1674, 1641, 1543, 1500cm-1

Mass (ESI+) : 405 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.76(3H, s), 2.66-2.74(2H, m), 3.19-3.30(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8Hz), 7.18(1H, s), 7.24(4H, s), 7.75(1H, dd, J=8.8,2.6 Hz), 7.92(1H, t, J=5.3 Hz), 8.19(1H, d, J=2.6 Hz)

Example 188



(E0188)

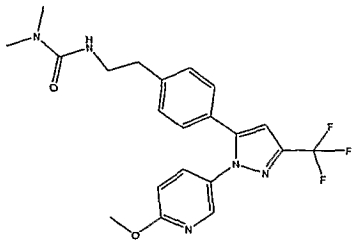
E0188 was prepared from E0165 in a similar manner to that of E0184 .

IR (neat) : 3338, 3020, 2951, 1716, 1610, 1527, 1500cm-1

Mass (ESI+) : 421 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.75(2H, m), 3.14-3.25(2H, m), 3.49(3H, s), 3.88(3H, s), 6.92(1H, d, J=8.9 Hz), 7.15-7.35(5H, m), 7.18(1H, s), 7.75(1H, dd, J=2.7,8.9 Hz), 8.19(1H, d, J=2.7 Hz)

Example 189



(E0189)

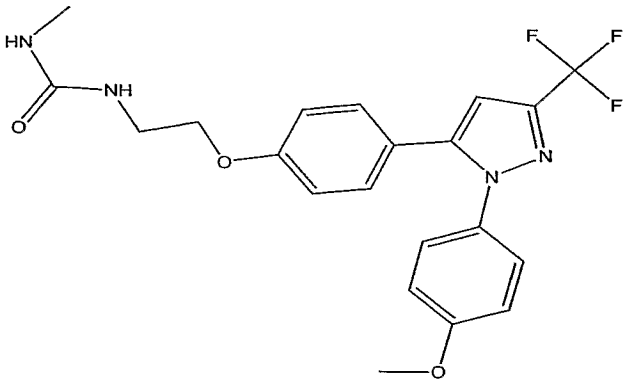
E0189 was prepared from E0294 in a similar manner to that of E0184.

IR (neat) : 3352, 2939, 1691, 1639, 1533, 1500cm-1

Mass (ESI+) : 434 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.74(2H, m), 2.74(6H, s), 3.15-3.26(2H, m), 3.88(3H, s), 6.34(1H, t, J=5.4 Hz), 6.92(1H, d, J=8.9 Hz), 7.17(1H, s), 7.23(4H, s), 7.75(1H, dd, J=8.9,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 190



(E0190)

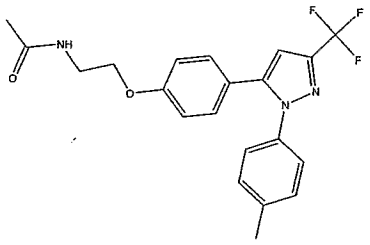
This compound was obtained according to a similar manner to that of E0189.

NMR(CDCl3); 2.78(3H, d, J=5.0 Hz), 3.56-3.64(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.1 Hz), 4.2-4.4(1H, m, NH), 4.6-4.9(1H, m, NH), 6.67(1H, s), 6.80-6.91(4H, m), 7.13(2H, d, J=8.8 Hz), 7.22(2H, d, J=9.0 Hz).

MS(ESI+).457.1(M+Na).

IR(NBr), 1627.6cm-1

Example 191



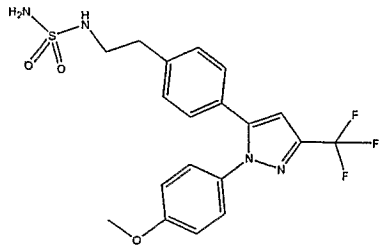
(E0191)

This compound was obtained according to a similar manner to that of E0184.

IR (film): 3299.6, 1658.5, 1550.5, 1515.8, 1467.6, 1240.0, 1164.8, 1132.0, 975.8, 829.2, 755.9 cm-1.

Example 192

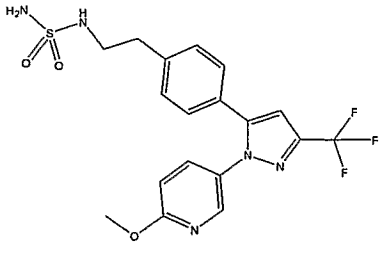
SUBSTITUTE SHEET(RULE26)



(E0192)

E0158 (250mg) was suspended in AcOEt 5ml and was partitioned between AcOEt and saturated aqueous sodium bicarbonate solution. The organic layer was washed with aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in dimethoxyethane 5ml, sulfamide 181mg was added and refluxed for 2days. The reacion mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography eluted with MeOH / CHCl3 = 1%, 2%, then 3%. Obtained amorphous powder was crystallized from EtOH-diisopropyl ehter to give E0192 153mg as a white powder.
mp. 127-128°C
IR (KBr) : 3357, 1707, 1693, 1647, 1564, 1549, 1529, 1514cm-1
Mass (ESI+) : 441 (M+H)+
400MHz 1H NMR (DMSO-d6, d) : 2.76-2.80(2H, m), 3.06-3.11(2H, m), 3.79(3H, s), 6.53(2H, s), 6.53-6.61(1H, broad), 7.00(2H, d, J=8.9 Hz), 7.12(1H, s), 7.21(2H, d, J=8.5 Hz), 7.24(2H, d, J=8.5 Hz), 7.29(2H, d, J=8.9 Hz)

Example 193



(E0193)

E0193 was prepared from E0294 in a similar manner to that of E0192.

white powder

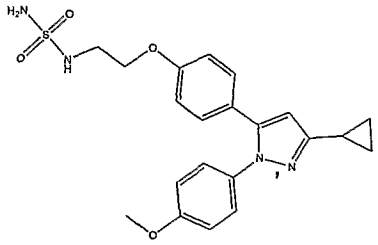
mp.114-115°C

IR (KBr) : 3489, 3469, 3458, 3435, 3425, 3398, 3363, 3280, 1647, 1500cm-1

Mass (ESI+) : 442 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.75-2.83(2H, m), 3.00-3.20(2H, m), 3.88(3H, s), 6.45-6.67(3H, m), 6.92(1H, d, J=8.7 Hz), 7.18(1H, s), 7.21-7.31(4H, m), 7.76(1H, dd, J=2.6,8.7 Hz), 8.19(1H, d, J=2.6 Hz)

Example 194



(E0194)

E0194 was prepared from E0322 in a similar manner to that of E0192.

white powder

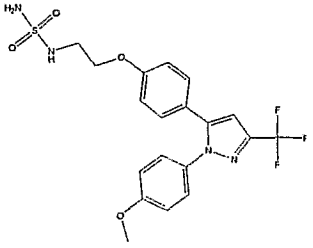
mp. 142-143°C

IR (KBr) : 3415, 3323, 3111, 3093, 3010, 2962, 1614, 1516cm-1

Mass (ESI+) : 429 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.68-0.76(2H, m), 0.85-0.95(2H, m), 1.92(1H, m), 3.15-3.31(2H, m), 3.76(3H, s), 4.00-4.07(2H, m), 6.25(1H, 1), 6.60(2H, brs), 6.72(1H, brs), 6.86-6.96(4H, m), 7.10(2H, d, J=8.7 Hz), 7.13(2H, d, J=8.9 Hz)

Example 195



(E0195)

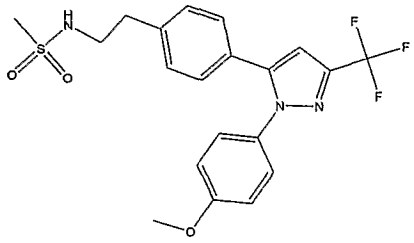
This compound was obtained according to a similar manner to that of E0192.

NMR(CDCl3), 3.50-3.59(2H, m), 3.82(3H, s), 4.14(2H, t, J=4.9 Hz), 6.68(1H, s), 6.80-6.90(4H, m), 7.15(2H, d, J=8.8 Hz), 7.22(2H, d, J=9.0 Hz).

IR(KBr); 1612, 1552cm-1.

MS(ESI+), 479.1(M+Na).

Example 196

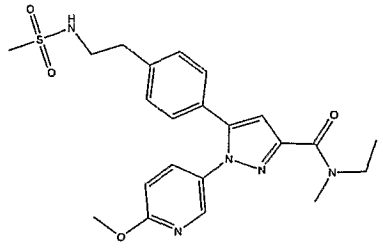


(E0196)

To a solution of E0158 (100mg) and Et3N (53ul) in CHCl3 (10ml) was added MsCl (29ul) at room temperature. After stirring for 1 hour, the reaction mixture was poured onto water and CHCl3. The aqueous layer was separated and extracted with CHCl3. The combined organic layer was washed with water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) and crystalized to give 75mg (68%) of E0196 as a powder.

IR (film): 3284.2, 1513.9, 1319.1, 1240.0, 1151.3, 973.9cm-1.

Example 197



(E0197)

E0197 was prepared from E0166 in a similar manner to that of E0196.

mp.137-138°C

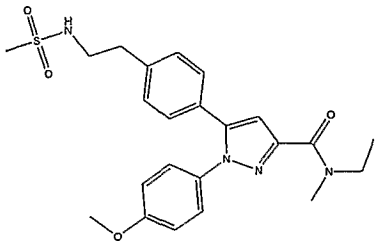
IR (KBr) : 3222, 1691, 1684, 1658, 1645, 1610, 1566, 1547, 1531cm-1

Mass (ESI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d)

1.09-1.22(3H, m), 2.73-2.81(2H, m), 2.80(3H, s), 2.98,3.28(3H, s), 3.09-3.30(2H, m), 3.48,3.71(2H, q, J=7.0,6.8Hz), 3.87(3H, s), 6.88-6.93(2H, m), 7.10(1H, brs), 7.22(2H, d, J=8.5Hz), 7.28(2H, d, J=8.5Hz), 7.64-7.73(1H, m), 8.15(1H, d, J=2.5 Hz)

Example 198



(E0198)

E0198 was prepared from E0167 in a similar manner to that of E0196.

mp.162-163°C

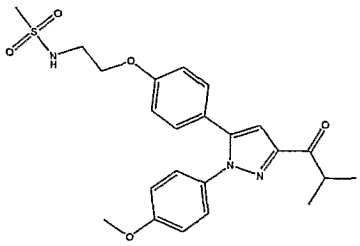
IR (KBr) : 3224, 1610, 1547, 1512cm-1

Mass (ESI+) : 457 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.08-1.22(3H, m), 2.76(2H, t, J=7.2 Hz), 2.80(3H, s), 2.98,3.29(3H, s), 3.12-3.23(2H, m), 3.48,3.73(2H, q, J=7.2,6.9 Hz), 3.78(3H, s), 6.84,6.87(1H, s), 6.98(2H, d, J=9.0 Hz), 7.09(1H, t, J=5.7 Hz), 7.16-7.26(6H, m)

Example 199



(E0199)

E0199 was prepared from E0234 in a similar manner to that of E0196.

white powder,

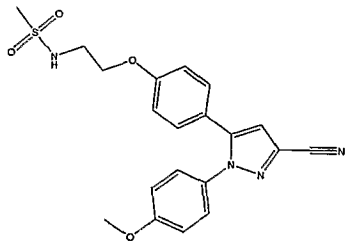
mp. 155°C

IR (KBr) : 3265, 2974, 2937, 1682, 1612, 1512cm-1

Mass (ESI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.8 Hz), 2.94(3H, s), 3.27-3.36(2H, m), 3.68(1H, m), 3.79(3H, s), 4.03(2H, t, J=5.5 Hz), 6.93(2H, d, J=8.8 Hz), 6.98(1H, s), 7.00(2H, d, J=8.9 Hz), 7.19(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz), 7.17-7.30(1H, overlapping)

Example 200



(E0200)

E0200 was prepared from E0235 in a similar manner to that of E0196.

white powder

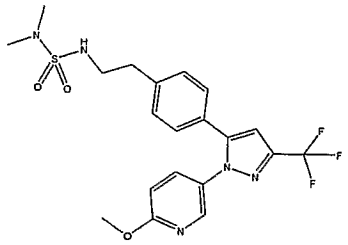
mp. 149-153°C

IR (KBr) : 3321, 1693, 1658, 1647, 1610, 1547, 1510cm-1

Mass (ESI+) : 413 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.93(3H, s), 3.27-3.35(2H, m), 3.79(3H, s), 4.03(2H, t, J=5.5 Hz), 6.95(2H, d, J=8.7 Hz), 7.01(2H, d, J=9.0 Hz), 7.18(2H, d, J=8.7 Hz), 7.28(2H, d, J=9.0 Hz), 7.31(1H, s), 7.15-7.31(1H, overlapping)

Example 201



(E0201)

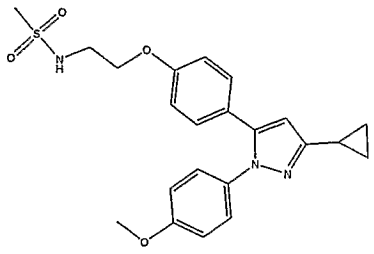
E0201 was prepared from E0294 in a similar manner to that of E0196.

IR (neat) : 3298, 2952, 2885, 1612, 1566, 1547, 1529cm-1

Mass (ESI+) : 470 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.56(6H, s), 2.71-2.79(2H, m), 3.07-3.17(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.7Hz), 7.18(1H, s), 7.19-7.30(5H, m), 7.77(1H, dd, J=8.7,2.6 Hz), 8.18(1H, d, J=2.6 Hz)

Example 202



(E0202)

E0202 was prepared from E0322 in a similar manner to that of E0196.

white powder

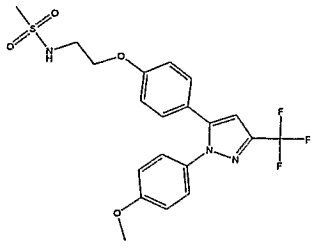
mp. 166-168°C

IR (KBr) : 3093, 2964, 2873, 2854, 1614, 1516cm-1

Mass (ESI+) : 428 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.68-0.76(2H, m), 0.85-0.95(2H, m), 1.92(1H, m), 2.93(3H, s), 3.27-3.36(2H, m), 3.76(3H, s), 3.98-4.04(2H, m), 6.25(1H, s), 6.90(2H, d, J=8.7 Hz), 6.92(2H, d, J=8.9 Hz), 7.11(2H, d, J=8.7 Hz), 7.13(2H, d, J=8.9 Hz), 7.27(1H, t, J=5.8 Hz)

Example 203



(E0203)

This compound was obtained according to a similar manner to that of E00196.

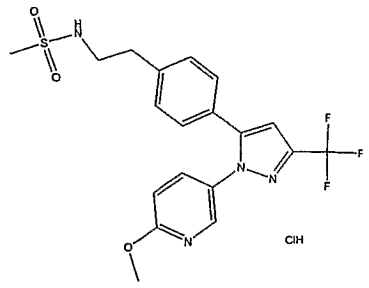
MS(ESI+); 454.1(MH+).

IR(KBr); 1612.2, 1515.8cm-1.

NMR(CDCl3), 3.03(3H, s), 3.51-3.59(2H, m), 3.82(3H, s), 4.10(2H, t, J=4.9 Hz), 6.68(1H, s), 6.82(1H, d, J=8.7 Hz), 6.88(1H, d, J=8.9 Hz), 7.15(1H, d, J=8.7 Hz), 7.22(1H, d,

J=8.9 Hz).

Example 204



(E0204)

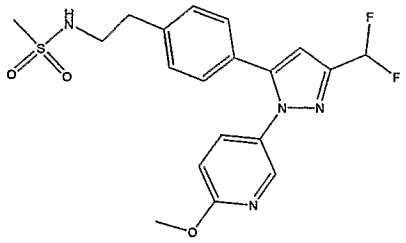
This compound was obtained according to a similar manner to that of E0196.

NMR(DMSO-d6); 2.80(3H, s), 2.73-2.84(2H, m), 3.13-3.22(2H, m), 3.88(3H, s), 6.92(1H, d, J=9.0 Hz), 7.08-7.13(1H, m), 7.19(1H, s), 7.22-7.33(4H, m), 7.76(1H, dd, J=9.0, 2.6 Hz), 8.19(1H, d, J=2.6 Hz).

MS(ESI+),463.1(M+Na).

IR(KBr), 3136, 1614, 1554, 1144cm-1.

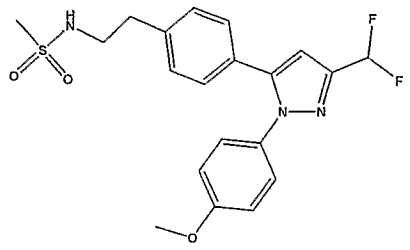
Example 205



(E0205)

This compound was obtained according to a similar manner to that of E0196.

Example 206



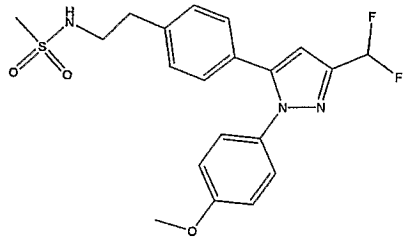
(E0206)

This compound was obtained according to a similar manner to that of E0196.

mp: 134.2-134.5°C

IR (film): 3284.2, 1610.3, 1513.9, 1457.9, 1321.0, 1251.6, 1151.3, 1083.8, 1031.7, 838.9, 802.2, 757.9 cm-1.

Example 207

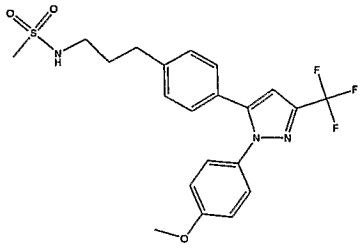


(E0207)

This compound was obtained according to a similar manner to that of E00196.

IR (film): 3286.11, 1606.41, 1513.85, 1457.92, 1319.07, 1251.58, 1153.22, 1081.87, 1029.80, 836.955 cm-1.

Example 208



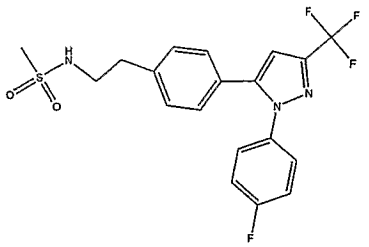
(E0208)

This compound was obtained according to a similar manner

to that of E0196.

IR(film): 3284.2, 1513.9, 1317.1, 1240.0, 1153.2cm-1.

Example 209

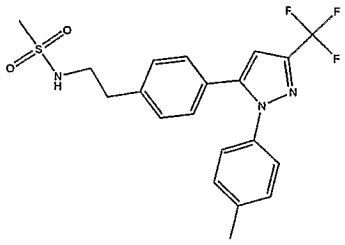


(E0209)

This compound was obtained according to a similar manner to that of E0196.

IR (film): 3286.1, 1511.9, 1321.0, 1230.4, 1155.2, 975.8, 842.7, 756.0cm-1.

Example 210

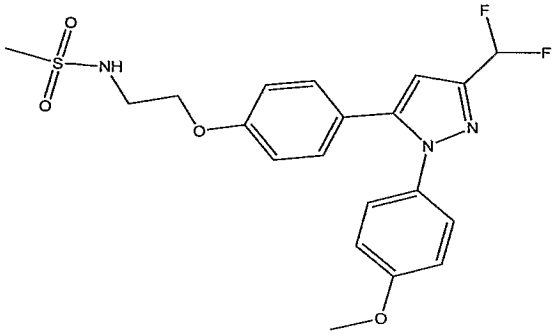


(E0210)

This compound was obtained according to a similar manner to that of E0196.

IR (film): 3284.2, 1511.9, 1469.5, 1321.0, 1236.2, 1153.2, 975.8, 821.5, 756.0cm-1.

Example 211

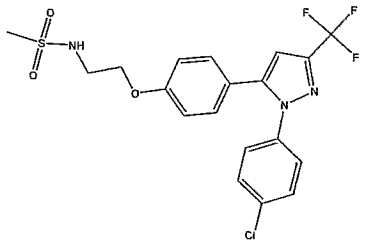


(E0211)

This compound was obtained according to a similar manner to that of E0196.

IR (film): 3289.9, 1612.2, 1513.9, 1322.9, 1251.6, 1155.1, 1085.7, 1029.8, 975.8, 836.9, 796.4 cm-1.

Example 212

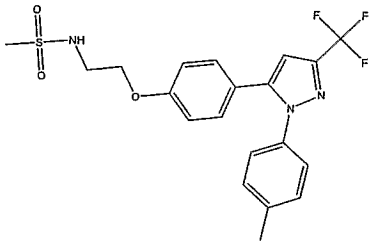


(E0212)

This compound was obtained according to a similar manner to that of E0196.

IR (film): 3266.8, 1612.2, 1469.5, 1321.0, 1240.0, 1153.2, 1097.3, 975.8, 835.0 cm-1.

Example 213



(E0213)

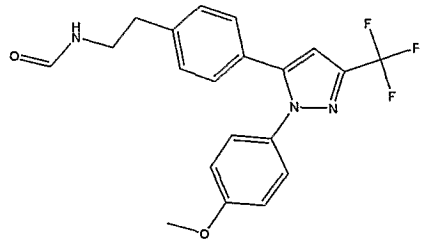
This compound was obtained according to a similar manner

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to that of E0196.

IR (film): 3288.0, 1612.2, 1322.9, 1240.0, 1153.2, 975.8, 946.9 cm-1.

Example 214

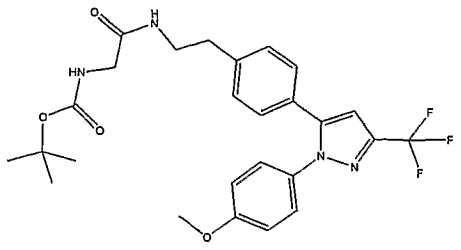


(E0214)

A mixture of E0158 (180mg), formic acid (38ul), and WSCD (155mg) in Et3N (0.3ml) and THF (5ml) was stirred at room temperature for 1 hour. After addition of water and EtOAc, the aqueous layer was separated and extracted twice with EtOAc. The combined organic layer was washed with 1NHCl, sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc=2:1) to give 136mg (70%) of E0214 as a powder.

IR (film): 1670.1, 1513.9, 1238.1, 1160.9, 1130.1cm-1.

Example 215

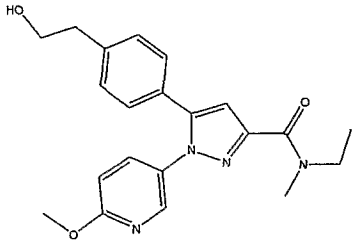


(E0215)

A mixture of E0158 (250mg), BocGly (132mg), WSCD (127mg) and HOBt (110mg) in Et3N (114ul) and CH2Cl2 (30ml) was stirred at room temperature. After stirring for 15 hour, the reaction

mixture was poured onto water and CHCl3. The aqueous layer was separated and extracted with CHCl3. The combined organic layer was washed with water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) and crystalized to give 325mg (99%) of E0215 as an oil.

Example 216



(E0216)

E0216 was prepared in a similar manner to that of E0215.

oil

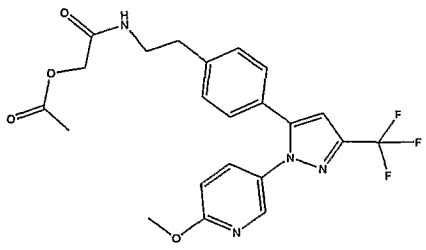
IR (neat) : 3431, 3421, 3404, 3400, 2939, 1614, 1570, 1547cm-1

Mass (ESI+) : 381(M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.09-1.23(3H, m), 2.72(2H, t, J=6.9 Hz), 2.98,3.29(3H, s), 3.42-3.77(4H, m), 3.88(3H, s), 6.86-6.93(2H, m), 7.19(2H, d, J=8.5 Hz), 7.24(2H, d, J=8.5 Hz), 7.65-7.74(1H, m), 8.15(1H, d, J=2.6 Hz)

Example 217



(E0217)

E0217 was prepared from E0294 and acetoxyacetic acid in a

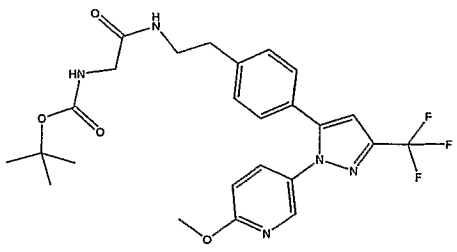
similar manner to that of E0215.

oil

Mass (ESI+) : 463(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.07(3H, s), 2.69-2.77(2H, m), 3.24-3.33(2H, m), 3.88(3H, s), 4.40(2H, s), 6.92(1H, d, J=8.7 Hz), 7.18(1H, s), 7.24(4H, s), 7.75(1H, dd, J=2.7,8.7 Hz), 8.10(1H, t, J=5.6 Hz), 8.19(1H, d, J=2.7 Hz)

Example 218



(E0218)

E0218 was prepared from E0294 and N-tert-butoxycarbonyl glycine in a similar manner to that of E0215 using N-methylmorpholine 55.8mg instead of triehtylamine.

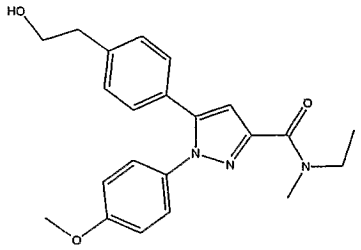
amorphous powder

IR (neat) : 3315, 1707, 1693, 1684, 1676, 1658, 1649, 1624, 1614, 1564, 1547, 1533, 1510, 1500cm-1

Mass (ESI+) : 520 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 2.67-2.75(2H, m), 3.22-3.33(2H, m), 3.47(2H, d, J=6.0 Hz), 3.88(3H, s), 6.80-7.00(1H, overlapping), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.24(4H, s), 7.75(1H, dd, J=8.8,2.7 Hz), 7.86(1H, t, J=5.6 Hz), 8.19(1H, d, J=2.7 Hz)

Example 219



(E0219)

E0219 was prepared in a similar manner to that of E0215.

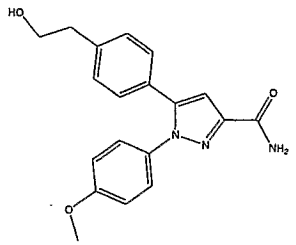
oil

IR (KBr) : 3329, 3313, 3303, 1620, 1564, 1547, 1512 cm-1

Mass (ESI+) : 380 (M+H)+

200MHz 1H NMR (DMSO-d6, d): 1.08-1.22(3H, m), 2.71(2H, t, J=6.9 Hz), 2.97,3.29(3H, s), 3.42-3.78(4H, m), 3.78(3H, s), 4.65(1H, t, J=5.1 Hz), 6.82,6.85(1H, s), 6.98(2H, d, J=8.9 Hz), 7.12-7.27(6H, m)

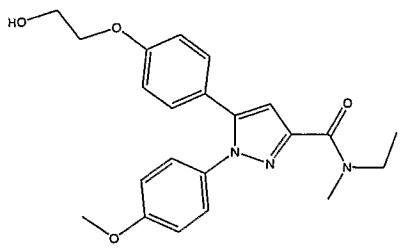
Example 220



(E0220)

E0220 was prepared in a similar manner to that of E0215.

Example 221



(E0221)

E0221 was prepared in a similar manner to that of E0215.

white powder

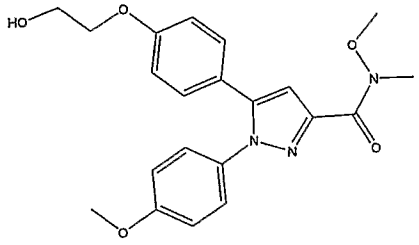
mp. 95-101°C

IR (KBr) : 3421, 1693, 1647, 1603, 1566, 1549, 1516cm-1

Mass (ESI+) : 396 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.42-3.74(4H, m), 3.78(3H, s), 3.95-4.00(2H, m), 4.86(1H, t, J=5.4 Hz), 6.78,6.81(1H, s), 6.91(2H, d, J=8.8 Hz), 6.98(2H, d, J=8.8 Hz), 7.16(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.8 Hz)

Example 222



(E0222)

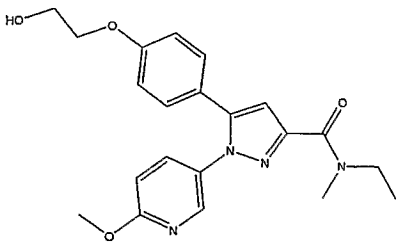
E0222 was prepared in a similar manner to that of E0215.

white powder

Mass (ESI+) : 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.38(3H, s), 3.65-3.74(2H, m), 3.77(3H, s), 3.78(3H, s), 3.95-4.01(2H, m), 4.87(1H, t, J=5.4 Hz), 6.89(1H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, s, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz)

Example 223



(E0223)

E0223 was prepared in a similar manner to that of E0215.

white powder

mp. 110-111°C

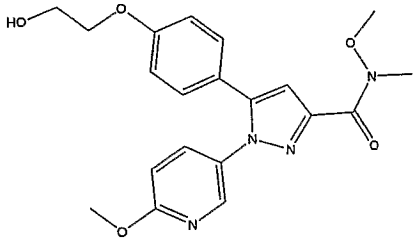
IR (KBr) : 3425, 2979, 2945, 1606, 1570, 1549cm-1

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.09-1.23(3H, m), 2.98,3.28(3H, s), 3.42-3.73(4H, m), 3.87(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.3 Hz), 6.82-6.97(4H, m), 7.21(2H, d, J=8.7 Hz), 7.63-7.72(1H, m), 8.14(1H, d, J=2.6 Hz)

Example 224



(E0224)

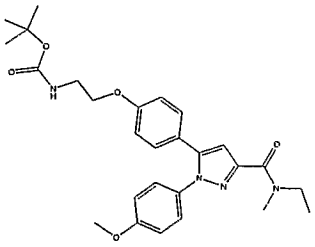
E0224 was prepared in a similar manner to that of E0215.

white powder

Mass (ESI+) : 399 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.37(3H, s), 3.66-3.74(2H, m), 3.77(3H, s), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.5 Hz), 6.88-6.97(4H, m), 7.21(2H, d, J=8.7 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 225



(E0225)

E0225 was prepared in a similar manner to that of E0215.

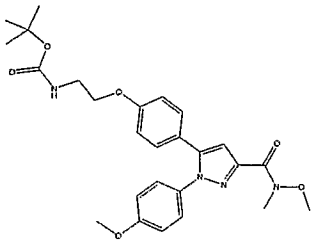
white powder

Mass (ESI+) : 495(M+H)+

400MHz 1H NMR (DMSO-d6, d) :

1.12,1.18(3H, t, J=7.0 Hz), 1.37(9H, s), 2.97,3.29(3H, s), 3.24-3.28(2H, m), 3.48,3.45(2H, q, J=7.0 Hz), 3.78(3H, s), 3.95(2H, t, J=5.7 Hz), 6.78,6.81(1H, s), 6.91(2H, d, J=8.8 Hz), 6.98(2H, d, J=8.8 Hz), 7.00(1H, overlapping), 7.16(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.9 Hz)

Example 226



(E0226)

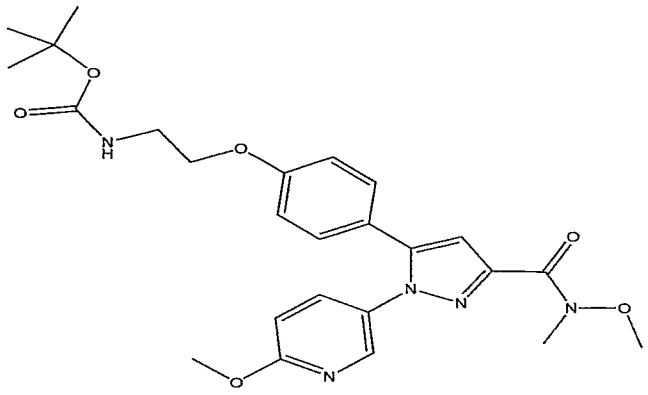
E0226 was prepared in a similar manner to that of E0215.

white powder

Mass (ESI+) : 497 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.25-3.29(2H, m), 3.37(3H, brs), 3.76(3H, s), 3.78(3H, s), 3.95(2H, t, J=5.7 Hz), 6.88(1H, s), 6.91(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 6.97-7.00(1H, br), 7.17(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz)

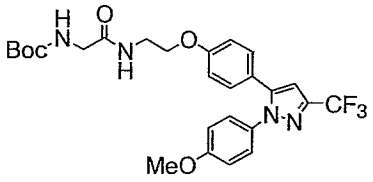
Example 227



(E0227)

E0227 was prepared in a similar manner to that of E0215.
white powder
Mass (ESI+) : 498 (M+H)+
200MHz 1H NMR (DMSO-d6, d) :
1.37(9H, s), 3.22-3.33(2H, m), 3.37(3H, s), 3.77(3H, s), 3.88(3H, s), 3.93-3.99(2H, m), 6.88-7.05(5H, m), 7.22(2H, d, J=8.6 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 228

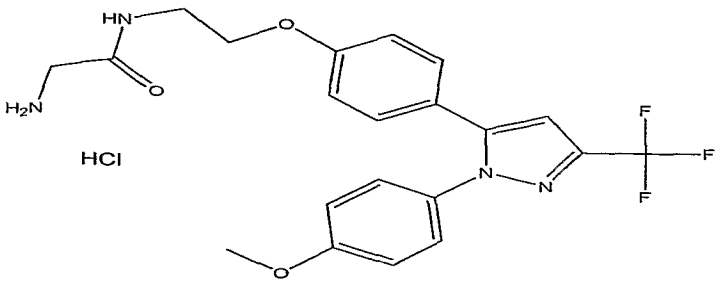


(E0228)

This compound was obtained according to a similar manner to that of E0215 as an oil (371.9 mg, 96%).
NMR(CDCl3); 1.43(9H, s), 3.65-3.73(2H, m), 3.79-3.82(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.2 Hz), 6.67(1H, s), 6.79-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).
MS(ESI+); 557.2(M+Na).

Example 229

SUBSTITUTE SHEET(RULE26)



(E0229)

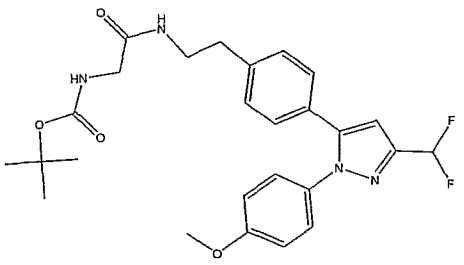
This compound was obtained according to a similar manner to that of E0289 as a white powder.

NMR(DMSO-d6),3.49-3.63(4H, m), 3.79(3H, s), 4.03(2H, t, J=4.8 Hz), 6.92-7.08(5H, m), 7.21(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz).

MS(ESI-), 433.2(M-H).

IR(KBr); 1683cm-1

Example 230

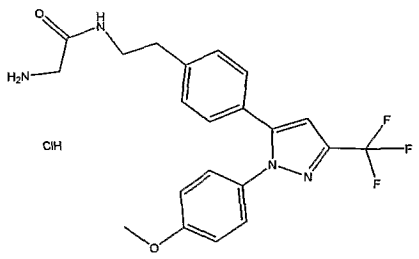


(E0230)

This compound was obtained according to a similar manner to that of E0215.

IR (film): 3320.82, 1706.69, 1668.12, 1515.77, 1249.65, 1168.65, 1031.73 cm-1.

Example 231



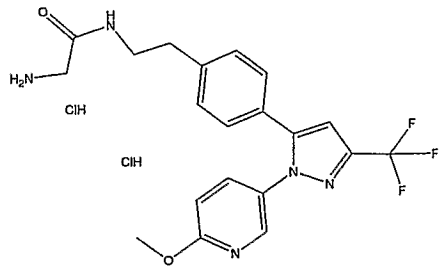
SUBSTITUTE SHEET(RULE26)

(E0231)

A mixture of E0215 (300mg) and 4NHCl in dioxane (5.8ml) was stirred at room temperature for 1.0 hour. After then, the reaction mixture was evaporated under reduced pressure to give 260mg (99%) of E0231 as an amorphous.

IR(film): 3226.3, 1679.7, 1513.9, 1251.6, 1083.8, 1029.8, 837.0cm-1.

Example 232



(E0232)

E0232 was prepared in a similar manner to that of E0231.

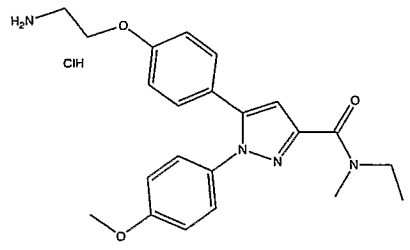
white powder

IR (KBr) : 3458, 3435, 3404, 3244, 3078, 3026, 1671, 1614, 1579, 1566, 1554, 1500cm-1

Mass (ESI+) : 420 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71-2.79(2H, m), 3.30-3.41(2H, m), 3.44-3.54(2H, m), 3.88(3H, s), 6.93(1H, d, J=8.7 Hz), 7.22(1H, s), 7.22-7.33(4H, m), 7.77(1H, dd, J=2.7,8.7 Hz), 8.10(2H, br), 8.19(1H, d, J=2.7 Hz), 8.55(1H, t, J=5.4 Hz)

Example 233



(E0233)

E0233 was prepared in a similar manner to that of E0231.

white powder

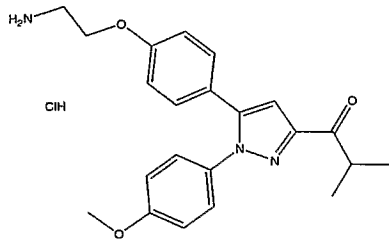
mp. 207-209°C

IR (KBr) : 2966, 2933, 2871, 2750, 1606, 1566, 1549, 1512cm-1

Mass (ESI+) : 395 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.17-3.22(2H, m), 3.40-3.80(2H, m), 3.78(3H, s), 4.14-4.20(2H, m), 6.80,6.83(1H, s), 6.94-7.01(4H, m), 7.18-7.26(4H, m), 8.13(2H, brs)

Example 234



(E0234)

E0234 was prepared in a similar manner to that of E0231.

white powder

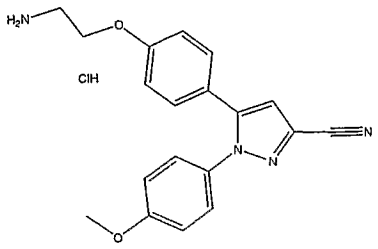
mp. 129-142°C

IR (KBr) : 3471, 3437, 2968, 2933, 1674, 1639, 1631, 1612, 1545, 1512cm-1

Mass (ESI+) : 380 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 3.16-3.22(2H, m), 3.68(1H, m), 3.79(3H, s), 4.15-4.20(2H, m), 6.94-7.05(5H, m), 7.22(2H, d, J=8.8 Hz), 7.29(2H, d, J=8.9 Hz), 8.15(2H, brs)

Example 235



(E0235)

E0235 was prepared and in a similar manner to that of E0231.

white powder

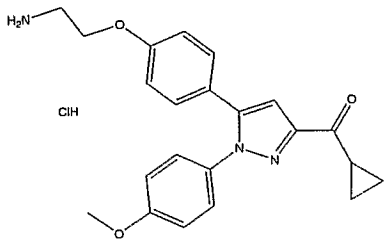
mp. 186-189°C

IR (KBr) : 3209, 3136, 2968, 2873, 1647, 1610, 1547, 1512cm-1

Mass (ESI+) : 335 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.19(2H, t, J=4.9 Hz), 3.79(3H, s), 4.18(2H, t, J=4.9 Hz), 6.96-7.05(4H, m), 7.21(2H, d, J=8.8 Hz), 7.29(2H, d, J=9.0 Hz), 7.32(1H, s), 8.16(2H, brs)

Example 236



(E0236)

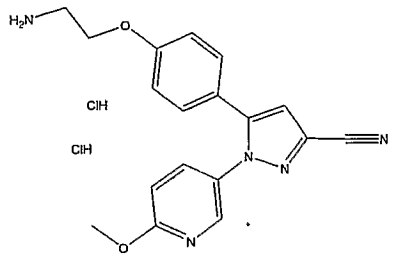
E0236 was prepared in a similar manner to that of E0231.

white powder

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.1 Hz), 3.04(1H, m), 3.14-3.22(2H, m), 3.80(3H, s), 4.15-4.21(2H, m), 6.93-7.05(5H, m), 7.23(2H, d, J=8.6 Hz), 7.31(2H, d, J=8.9 Hz), 8.15(2H, brs)

Example 237



(E0237)

E0237 was prepared in a similar manner to that of E0231.

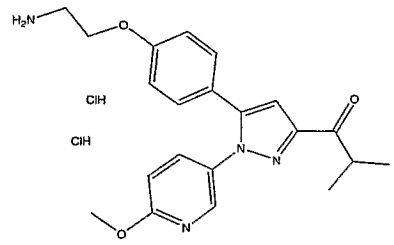
amorphous powder

IR (KBr) : 3433, 3425, 3404, 3043, 3028, 3022, 2962, 1658, 1612cm-1

Mass (ESI+) : 336 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.15-3.24(2H, m), 3.88(3H, s), 4.16-4.22(2H, m), 6.94(1H, d, J=8.8 Hz), 7.01(2H, d, J=8.7 Hz), 7.25(2H, d, J=8.7 Hz), 7.36(1H, s), 7.75(1H, dd, J=2.6,8.8 Hz), 8.10-8.30(2H, br), 8.20(1H, d, J=2.6 Hz)

Example 238



(E0238)

E0238 was prepared in a similar manner to that of E0231.

white powder

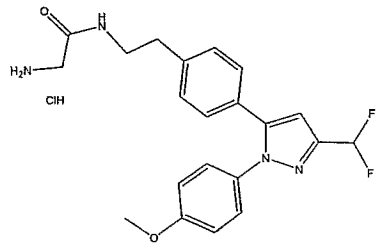
mp. 156-161°C

IR (KBr) : 2970, 1676, 1647, 1612, 1550, 1500cm-1

Mass (ESI+) : 381 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.15-3.24(2H, m), 3.68(1H, m), 3.88(3H, s), 4.16-4.22(2H, m), 6.91-7.06(4H, m), 7.26(2H, d, J=8.7 Hz), 7.75(1H, dd, J=2.7,8.9 Hz), 8.18(1H, d, J=2.7 Hz), 8.22(2H, brs)

Example 239

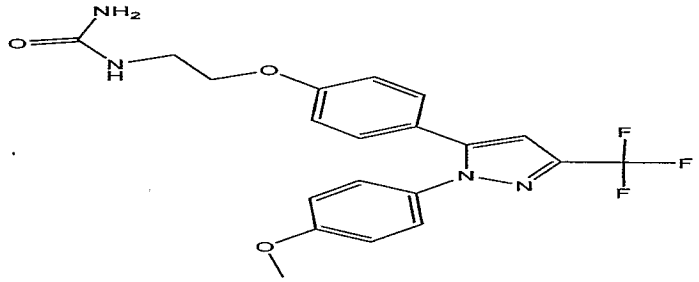


(E0239)

This compound was obtained according to a similar manner to that of E0231.

IR (film): 3220.5, 1679.7, 1513.9, 1461.8, 1251.6, 1081.9, 1029.8, 837.0, 800.3 cm-1.

Example 240



(E0240)

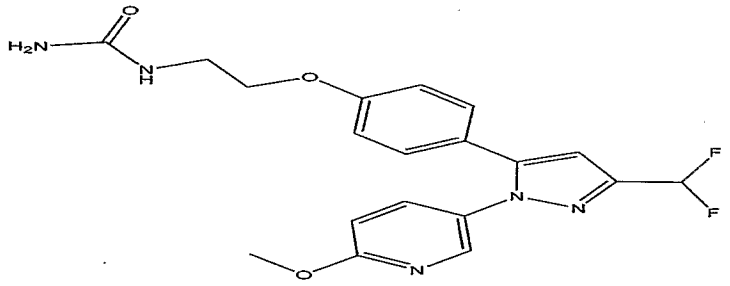
To a solution of E0267 (75.2 mg) in dichloromethane (1 ml) was added triethylamine (30.4 ml) and trimethylsilyl isocyanate (36.9 ml) at 0°C. After stirring for 5 hours, the mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give oil, which was purified with preparative TLC (1 mm, ethyl acetate) to give oil. The oil was crystallized from a mixture of isopropyl ether, ethyl acetate, and hexane to give E0240 as a white solid (39.1 mg, 51.2%).

NMR(DMSO-d6); 3.27-3.32(2H, m), 3.79(3H, s), 3.94(2H, t, J=5.6 Hz), 5.52(2H, brs, NH2), 6.15(1H, t, J=5.6 Hz, NH), 6.94(2H, d, J=8.8 Hz), 7.00(2H, d, J=8.9 Hz), 7.07(1H, s), 7.20(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz).

MS(ESI+); 443.2(M+Na).

IR(KBr), 1685.5, 1656.6cm-1.

Example 241



(E0241)

E0241 was prepared from E0194 in a similar manner to that of E0240.

white powder

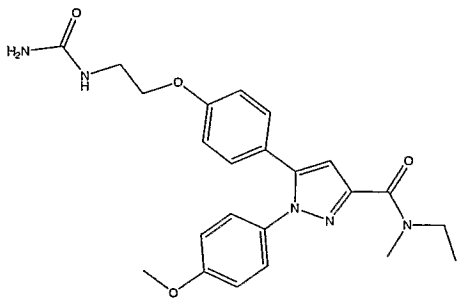
mp. 139-140°C

IR (KBr) : 3458, 3342, 1691, 1647, 1604, 1572, 1529cm-1

Mass (ESI+) : 404 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.28-3.36(2H, m), 3.87(3H, s), 3.92-3.98(2H, m), 5.52(2H, brs), 6.15(1H, t, J=5.5 Hz), 6.88-6.98(4H, m), 7.10(1H, t, J=54.4 Hz), 7.22(2H, d, J=8.7 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 242



(E0242)

E0242 was prepared in a similar manner to that of E0240.

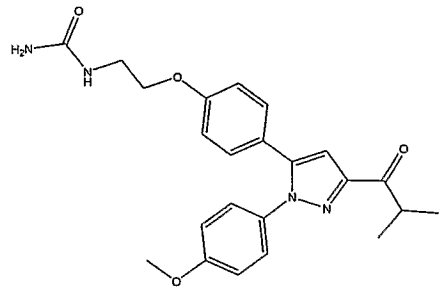
white powdermp. 108-113°C

IR (KBr) : 3492, 3435, 3425, 3359, 3298, 1647, 1614, 1564, 1549, 1512cm-1

Mass (ESI+) : 438 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.08-1.22(3H, m), 2.97,3.29(3H, s), 3.20-3.85(4H, m), 3.78(3H, s), 3.94(2H, t, J=5.5 Hz), 5.53(2H, s), 6.15(1H, t, J=5.6Hz), 6.79,6.81(1H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.23(2H, d, J=8.9 Hz)

Example 243



(E0243)

E0243 was prepared from E0234 in a similar manner to that of E0240.

white powder

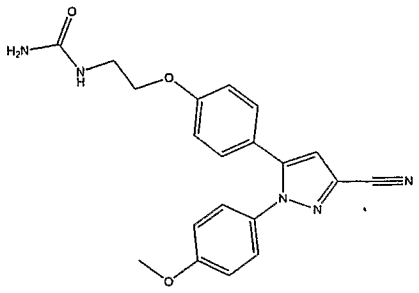
mp. 144-145°C

IR (KBr) : 3435, 3369, 3176, 2970, 1674, 1612, 1547, 1514cm-1

Mass (ESI+) : 423 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 3.27-3.36(2H, m), 3.68(1H, m), 3.79(3H, s), 3.90-3.97(2H, m), 5.53(2H, s), 6.15(1H, t, J=5.6 Hz), 6.92(2H, d, J=8.7 Hz), 6.98(1H, s), 7.00(2H, d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 244



(E0244)

E0244 was prepared from E0235 in a similar manner to that of E0240.

white powder

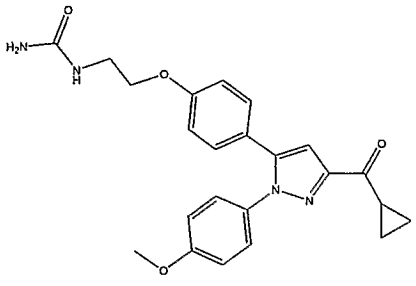
mp. 187-190°C

IR (KBr) : 3379, 3201, 1649, 1614, 1579, 1527, 1506cm-1

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.27-3.34(2H, m), 3.79(3H, s), 3.94(2H, t, J=5.5 Hz), 5.52(2H, brs), 6.14(1H, t, J=5.6 Hz), 6.94(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.17(2H, d, J=8.8 Hz), 7.24-7.31(3H, m)

Example 245



(E0245)

E0245 was prepared in a similar manner to that of E0240.

white powder

mp. 136-137°C

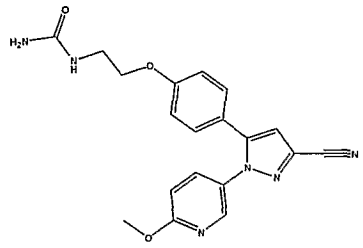
IR (KBr) : 3433, 3342, 3221, 1658, 1612, 1581, 1549, 1512cm-1

Mass (ESI+) : 421 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 3.03(1H,

m), 3.27-3.36(2H, m), 3.80(3H, s), 3.90-3.97(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.6 Hz), 6.93(2H, d, J=8.8 Hz), 6.97(1H, s), 7.01(2H, d, J=8.9 Hz), 7.19(2H, d, J=8.8 Hz), 7.30(2H, d, J=8.9 Hz)

Example 246



(E0246)

E0246 was prepared in a similar manner to that of E0240.

white powder

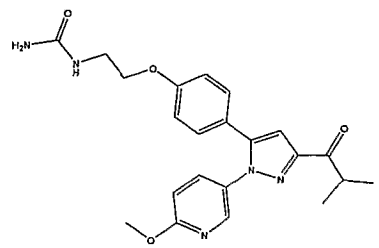
mp. 173-176°C

IR (KBr) : 3473, 3334, 1630, 1624, 1601, 1583cm-1

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.27-3.36(2H, m), 3.88(3H, s), 3.92-3.98(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.7 Hz), 6.93(1H, d, J=8.8 Hz), 6.97(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.8 Hz), 7.35(1H, s), 7.73(1H, dd, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

Example 247



(E0247)

E0247 was prepared in a similar manner to that of E0240.

white powder

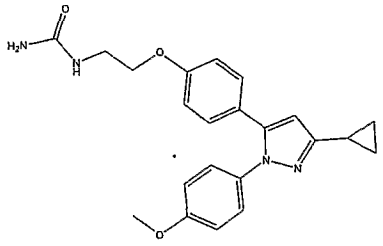
mp. 145-147°C

IR (KBr) : 3367, 3174, 2972, 1689, 1674, 1610, 1566, 1502cm-1

Mass (ESI+) : 424 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.28-3.37(2H, m), 3.68(1H, m), 3.88(3H, s), 3.92-3.98(2H, m), 5.52(2H, s), 6.15(1H, t, J=5.6 Hz), 6.93(1H, d, J=8.7 Hz), 6.95(2H, d, J=8.8 Hz), 7.02(1H, s), 7.22(2H, d, J=8.8 Hz), 7.73(1H, dd, J=2.7,8.7 Hz), 8.19(1H, d, J=2.7 Hz)]

Example 248



(E0248)

E0248 was prepared in a similar manner to that of E0240.

white powder

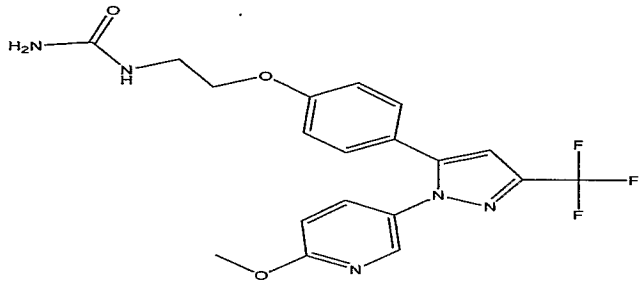
mp. 150.8-151.0°C

IR (KBr) : 3496, 3361, 3294, 1705, 1674, 1647, 1603, 1581, 1568, 1554, 1516cm-1

Mass (ESI+) : 393 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.71-0.77(2H, m), 0.85-0.92(2H, m), 1.92(1H, m), 3.27-3.37(2H, m), 3.76(3H, s), 3.92(2H, t, J=5.5 Hz), 5.51(2H, s), 6.14(1H, t, J=5.5 Hz), 6.24(1H, s), 6.86-6.96(4H, m), 7.07-7.15(4H, m)

Example 249



(E0249)

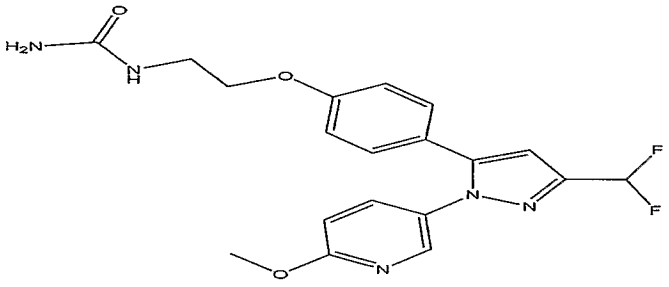
This compound was obtained according to a similar manner to that of E0240 as an amorphous.

NMR(CDCl3), 3.56-3.64(2H, m), 3.94(3H, s), 4.04(2H, t, J=4.9 Hz), 4.50(2H, brs, NH2), 6.69(1H, s), 6.76(1H, d, J=8.8 Hz), 6.84(2H, d, J=8.8 Hz), 7.12(2H, d, J=8.8 Hz), 7.58(1H, dd, J=8.8, 2.8 Hz), 8.05(1H, d, J=2.8 Hz).

MS(ESI+), 444.1 (M+Na)+. IR(KBr); 1650.8, 1608.3cm-1.

LCMS(ESI+), 422.27(MH+).

Example 250



(E0250)

This compound was obtained according to a similar manner to that of E0240 as a white powder.

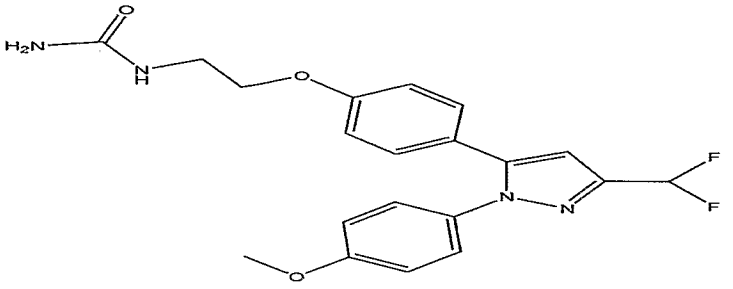
NMR(CDCl3), 3.55-3.63(2H, m), 3.93(3H, s), 4.04(2H, t, J=5.1 Hz), 4.55(2H, brs, NH2), 5.23(1H, brt, J=5.4 Hz, NH), 6.67(1H, s), 6.75(1H, t, J=55 Hz), 6.75(1H, d, J=8.4 Hz), 6.88(2H, d, J=8.8 Hz), 7.13(2H, d, J=8.8 Hz), 7.56(1H, d, J=8.4, 2.9 Hz), 8.04(1H, d, J=2.9 Hz).

LCMS(ESI+), 404.39(MH+).

IR(KBr) 1649cm-1

MP, 141.5 - 142.1°C.

Example 251



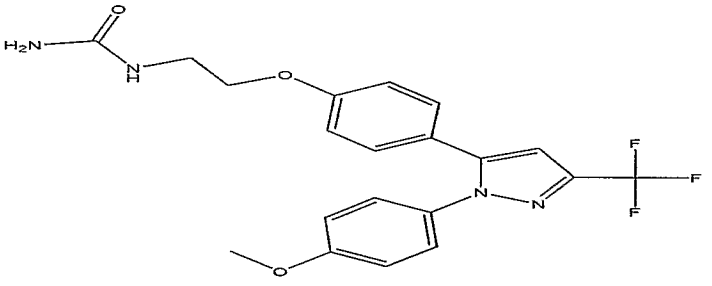
(E0251)

This compound was obtained according to a similar manner to that of E0240 as a powder.

NMR(CDCl3), 3.56-3.64(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.0 Hz), 4.42(2H, brs), 6.65(1H, s), 6.76(1H, t, J=55 Hz), 6.79-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.20(2H, d, J=9.0 Hz).

MS(ESI+), 425(M+Na)+.

Example 252



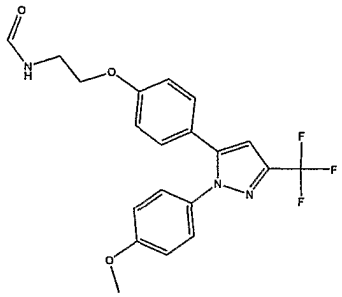
(E0252)

To a solution of E0267 (15.3 g) in ethanol (75 ml) and hydrogen chloride aqueous solution (1N, 220 ml) was added dropwise a solution of sodium cyanate (14.4 g) in water (300 ml) at 45°C over 5 minutes. After stirring at 45°C for 4 hours, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to give powder. The powder was crystallized from ethyl acetate and hexane at

room temperature ~ 70°C to give E0252 as a powder (12.628 g, 81.2%).

The physical data of this compound was identical to previously obtained authentic sample.

Example 253



(E0253)

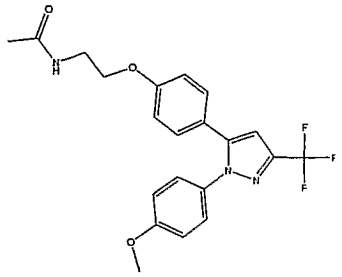
To a solution of E0267 (200 mg) in methanol (1 ml) was added sodium methoxide methanol solution (5.2M, 0.1 ml) at room temperature. After stirring for 20 minutes, the mixture was evaporated to give residue. To the residue was added tetrahydrofuran, and the mixture was filtered and evaporated to give oil. The oil was dissolved in ethyl formate (2 ml) and stirred at room temperature overnight. The mixture was evaporated and purified with preparative TLC (1 mm, 50% ethyl acetate/hexane) to give oil, which was crystallized from isopropyl ether, ethyl acetate, and hexane to give E0253 as a white powder (162.8 mg, 83%).

NMR(CDCl3), 3.68-3.76(2H, m), 3.82(3H, s), 4.06(2H, t, J=5.0 Hz), 6.68(1H, s), 6.80-6.89(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz), 8.22(1H, s).

MS(ESI+), 428.2(M+Na).

IR(KBr), 1660.4, 1614.1cm-1.

Example 254



(E0254)

To a solution of E0267 (800 mg) and triethylamine (0.7 ml) in dichloromethane (9 ml) was added dropwise acetyl chloride (0.18 ml) at 0°C. After stirring at room temperature for 1 hour, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (x3). The combined organic layers were washed with hydrogen chloride aqueous solution (1N), water, and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO2 100 ml, eluted with 50% ethyl acetate/hexane) to give oil. The oil was crystallized from a mixture of ethyl acetate and hexane at 50°C to give E0254 as a solid (768.6 mg, 94.8%).

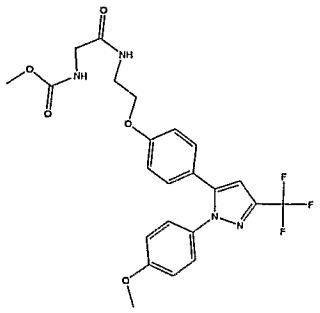
NMR(CDCl3). 2.01(3H, s), 3.62-3.70(2H, m), 3.82(3H, s), 4.03(2H, t, J=5.0 Hz), 6.67(1H, s), 6.80-6.91(4H, m), 7.14(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).

MP; 109.8 - 110.2°C

IR(KBr), 1649cm-1.

MS(ESI+).442.1(M+Na).

Example 255



(E0255)

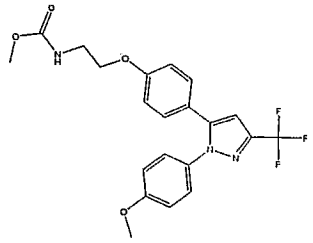
This compound was obtained according to a similar manner to that of E0254 as an oil.

NMR(CDCl3), 3.69(3H, s), 3.65-3.73(2H, m), 3.82(3H, s), 3.86(2H, d, J=5.9 Hz), 4.04(2H, t, J=5.1 Hz), 6.67(1H, s), 6.80-6.89(4H, m), 7.14(2H, d, J=8.5 Hz), 7.22(2H, d, J=8.9 Hz),

MS(ESI+).515.2(M+Na).

IR(KBr, 20727-10), 1722.1, 1710.6, 1673.9cm-1.

Example 256



(E0256)

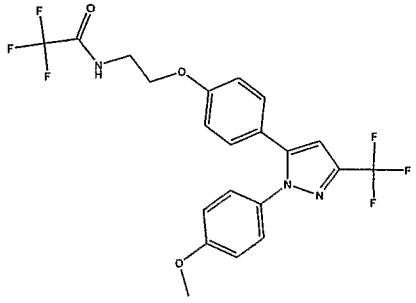
This compound was obtained according to a similar manner to that of E0254 as an oil (82 mg, 78%).

MS(ESI+).458.2(M+Na).

IR(Neat), 1699cm-1.

NMR(CDCl3); 3.54-3.62(2H, m), 3.69(3H, s), 3.82(3H, s), 4.02(2H, t), 6.67(1H, s), 6.80-6.89(4H, m), 7.13(2H, d, J=8.9 Hz), 7.22(2H, d, J=9.0 Hz).

Example 257



(E0257)

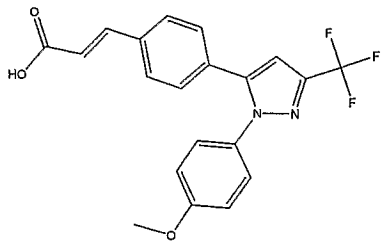
To a solution of E0275 (97.5 mg) and pyridine (0.14 ml) in dichloromethane (1 ml) was added trifluoroacetic anhydride (60.6 ml) at 0°C. After stirring at room temperature overnight, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution (0.5 ml), filtered with chemelute1001 (Varian), and purified with preparative TLC (1 mm, 50% ethyl acetate/hexane) to give E0257 as a solid (92.5 mg, 76%).

MS(ESI+), 496.1(M+Na).

IR(KBr), 1705cm-1.

NMR(CDCl3),3.75-3.87(2H, m), 3.82(3H, s), 4.10(4.8H, t), 6.68(1H, s), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.8 Hz), 7.22(2H, d, J=8.9 Hz).

Example 258

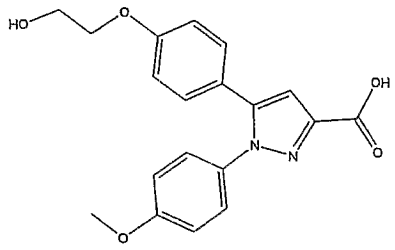


(E0258)

To a solution of E0327 (400mg) in THF (5ml) was added dropwise 1N NaOH (2.5ml) at room temperature. The mixture was stirred overnight, and then quenched with 1N HCl and CHCl3. The organic layer was separated and water layer was extracted twice with CHCl3. The combined organic layer was washed with water and brine, dried over Na2SO4, and evaporated under reduced pressure. The residue was washed with IPE to give 273mg (70.7%) of E0258.

IR (film): 2971.8, 1683.6, 1629.6, 1515.8, 1315.2, 1230.4, 1159.0, 1132.0, 977.7, 835.0cm-1.

Example 259



(E0259)

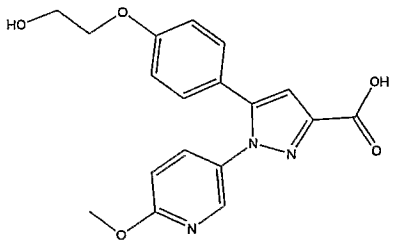
E0259 was prepared in a similar manner to that of E0258.

white powder

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.63-3.78(2H, m), 3.79(3H, s), 3.95-4.00(2H, m), 4.86(1H, brs), 6.91(2H, d, J=8.7 Hz), 6.95(1H, s), 6.99(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.24(2H, d, J=8.9 Hz), 12.88(1H, brs)

Example 260



(E0260)

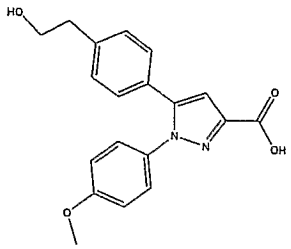
E0260 was prepared in a similar manner to that of E0258.

white powder

Mass (ESI+) : 356 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.69-3.79(2H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, br), 6.89-7.00(4H, m), 7.20(2H, d, J=8.8 Hz), 7.70(1H, dd, J=2.6,8.8 Hz), 8.14(1H, d, J=2.6 Hz), 12.97(1H, br)

Example 261



(E0261)

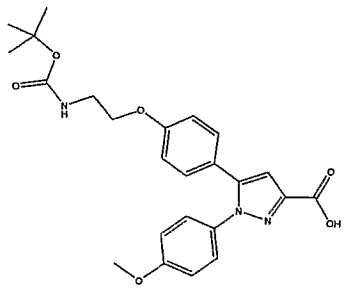
E0261 was prepared from E0109 in a similar manner to that of E0258.

white powder

Mass (ESI+) : 339(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.70(2H, t, J=6.9 Hz), 3.59(2H, t, J=6.9 Hz), 3.79(3H, s), 4.64(1H, brs), 6.96-7.03(3H, m), 7.12-7.28(6H, m), 12.90(1H, br)

Example 262



(E0262)

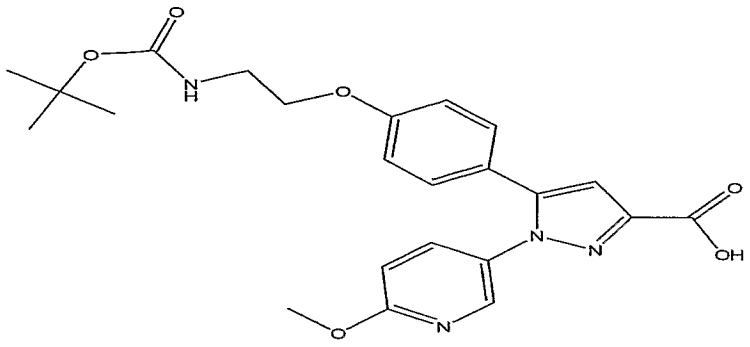
E0262 was prepared in a similar manner to that of E0258.

white powder

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.79(3H, s), 3.91-3.98(2H, m), 6.90(2H, d, J=8.7 Hz), 6.90-7.03(1H, overlapping), 6.95(1H, s), 6.99(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.24(2H, d, J=8.9 Hz)

Example 263



(E0263)

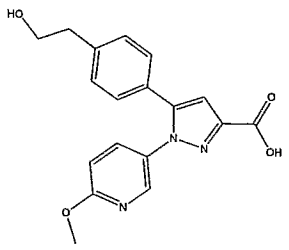
E0263 was prepared in a similar manner to that of E0258.

amorphous powder

Mass (ESI+) : 455 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.88(3H, s), 3.93-3.98(2H, m), 6.89-7.05(5H, m), 7.20(2H, d, J=8.7 Hz), 7.70(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz), 12.98(1H, br)

Example 264



(E0264)

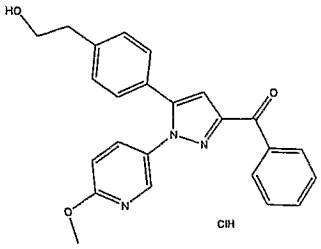
E0264 was prepared from E0006 in a similar manner to that of E0258.

white powder

Mass (ESI+) : 340 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.71(2H, t, J=6.9 Hz), 3.56-3.64(2H, m), 3.88(3H, s), 4.64(1H, br), 6.92(1H, d, J=8.8 Hz), 7.03(1H, s), 7.16-7.28(4H, m), 7.72(1H, dd, J=8.8,2.7 Hz), 8.15(1H, d, J=2.7 Hz), 12.94(1H, br)

Example 265



(E0265)

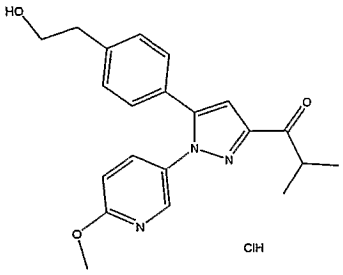
4M HCl/AcOEt 0.4ml was added to a solution of E0378 (73mg) in AcOEt 1ml. The mixture was concentrated and dried in vacuo to give E0265 68.4mg as an amorphous powder.

IR (neat) : 3440, 2960, 1739, 1707, 1691, 1674, 1647, 1624, 1614, 1566, 1549, 1533, 1500cm-1

Mass (ESI+) : 400 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.73(2H, t, J=6.9 Hz), 3.62(2H, t, J=6.9 Hz), 3.89(3H, s), 6.94(1H, d, J=8.8 Hz), 7.19-7.32(5H, m), 7.52-7.70(3H, m), 7.80(1H, dd, J=8.8,2.7 Hz), 8.22-8.28(3H, m)

Example 266



(E0266)

E0266 was prepared in a similar manner to that of E0265.

oil

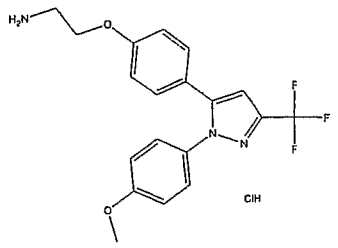
IR (neat) : 3435, 2966, 2935, 1678, 1662, 1649, 1612, 1581, 1566, 1547, 1533, 1500cm-1

Mass (ESI+) : 366 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 2.72(2H, t, J=6.9 Hz), 3.54-3.75(3H, m), 3.89(3H, s), 6.93(1H, d, J=8.8 Hz), 7.05(1H, s), 7.13-7.35(4H, m), 7.76(1H, dd,

J=2.7,8.8 Hz), 8.19(1H, d, J=2.7 Hz)

Example 267



(E0267)

To a solution of E0275 (765 mg) in ethyl acetate (1.9 ml) was added a solution of hydrogen chloride in ethyl acetate (4N, 0.56 ml). The mixture was evaporated to give oil, which was crystallized from diisopropyl ether and ethyl acetate at 65°C to give E0267 as a solid (766.8 mg, 91.4%).

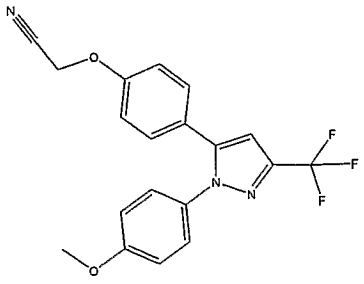
NMR(CDCl3), 3.30(2H, t, J=5.0 Hz), 3.79(3H, s), 4.18(2H, t, J=5.0 Hz), 6.62(1H, s), 6.83-6.88(4H, m), 7.10(2H, d, J=8.8 Hz), 7.18(2H, d, J=8.8 Hz).

NMR(DMSO-d6), 3.19(2H, brs), 3.79(3H, s), 4.18(2H, t, J=5.0 Hz), 6.96-7.01(4H, m), 7.08(1H, s), 7.23-7.29(4H, m).

MS(ESI+), 378.3(MH+, free).

IR(KBr, 20727-2), 1612.2, 1513.9cm-1.

Example 268



(E0268)

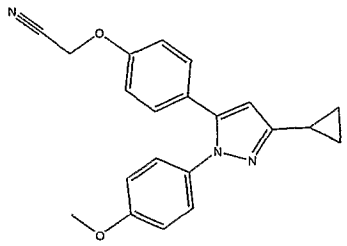
A mixture of P0011 (30 g), chloroacetonitrile (8.52 ml), potassium iodide (4.47 g), and potassium carbonate (14.9 g) in acetone (150 ml) was stirring under reflux at 80°C

for 2.5 hours. After cooling to room temperature, the mixture was quenched with water (600 ml) and extracted with ethyl acetate (300 ml x 2, 150 ml). The combined organic layers were washed with brine (300 ml), dried over magnesium sulfate, and evaporated to give solid (36.34 g). The solid was recrysallized from diisopropyl ether (60 ml) and hexane (200 ml) at room temperature to give E0268 as a powder (31.5 g, 94%).

NMR(CDCl3), 3.83(3H, s), 4.78(2H, s), 6.70(1H, s), 6.86-6.97(4H, m), 7.18-7.24(4H, m).

IR(KBr), 2051.9cm-1.

Example 269



(E0269)

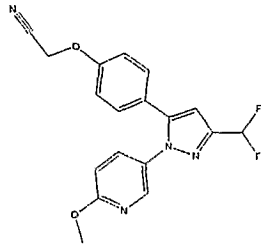
E0269 was obtained according to a similar manner to that of E0268.

white powder

Mass (ESI+) : 346(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.86-0.96(2H, m), 1.92(1H, m), 3.76(3H, s), 5.16(2H, s), 6.30(1H, s), 6.93(2H, d, J=9.0 Hz), 7.02(2H, d, J=8.8 Hz), 7.10-7.21(4H, m)

Example 270



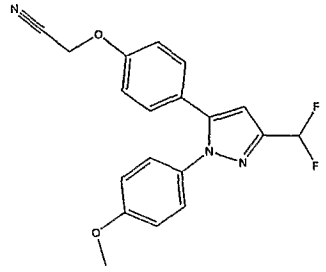
(E0270)

This compound was obtained according to a similar manner to that of E0268 as a powder.

NMR(CDCl3), 3.95(3H, s), 4.78(2H, s), 6.71(1H, s), 6.76(1H, t, J=55 Hz), 6.76(1H, d, J=8.4 Hz), 6.96(2H, d, J=8.9 Hz), 7.23(2H, d, J=8.9 Hz), 7.53(1H, dd, J=8.4, 2.6 Hz), 8.08(1H, d, J=2.6 Hz).

MS(ESI+),379(M+Na).

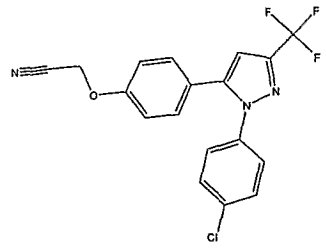
Example 271



(E0271)

This compound was obtained according to a similar manner to that of E0268.

Example 272



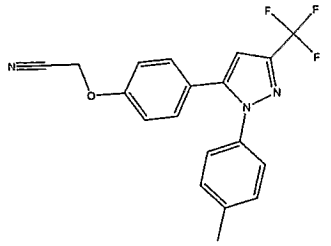
(E0272)

This compound was obtained according to a similar manner

to that of E0268.

IR (film): 1612.2, 1482.9, 1234.2, 1162.8, 1132.0, 1095.3, 973.8, 835.0 cm-1.

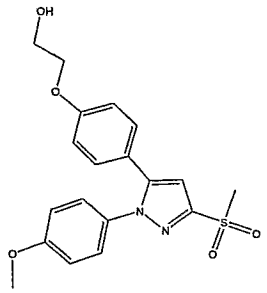
Example 273



(E0273)

This compound was obtained according to a similar manner to that of E0268.

Example 274



(E0274)

This compound was obtained according to a similar manner to that of E0268.

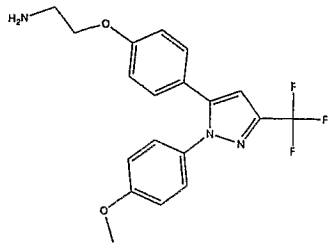
mp.96-99°C

Mass;389(M+1)

NMR(CDCl3,δ);

1.98(1H, t, J=6.1 Hz), 3.29(3H, s), 3.83(3H, s), 3.93-4.01(2H, m), 4.06-4.11(2H, m), 6.86(2H, d, J=8.8 Hz), 6.88(2H, d, J=9.0 Hz), 6.93(1H, s), 7.14(2H, d, J=8.8 Hz), 7.23(2H, d, J=9.0 Hz)

Example 275



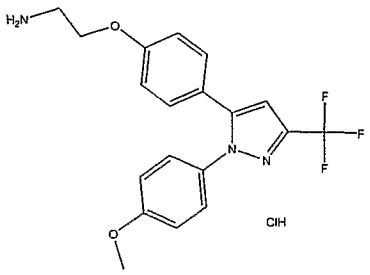
(E0275)

To a suspension of lithium aluminum hydride (250 mg) in ether (14 ml) was added E0268 (1.38 g) in ether (5 ml) and tetrahydrofuran (1 ml) under ice-bath. The mixture was stirred at room temperature for 1 hour. Lithium aluminum hydride (50 mg) was added to the mixture under ice-bath., and then the mixture was stirred at room temperature for 1 hour. The mixture was quenched with water (0.3 ml), sodium hydroxide aqueous solution (15%, 0.3 ml), and water (0.9 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with ether. The filtrate was evaporated to give 1.307 g of oil. The oil purified with column chromatography (SiO2, 100 ml, eluted with 20% methanol / chloroform (500 ml)) to give E0275 as an oil (1.156 g, 82.9%).

NMR(CDCl3), 3.09(2H, t, J=5.1 Hz), 3.82(3H, s), 3.99(2H, t, J=5.1 Hz), 6.67(1H, s), 6.82-6.89(4H, m), 7.14(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+), 378(MH+).

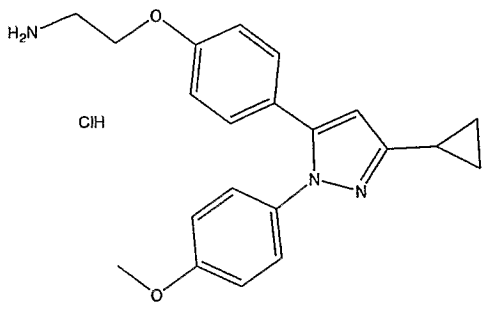
Example 276



(E0276)

To a solution of E0268 (27.43 g) in tetrahydrofuran (270 ml) was added borane methylsulfide complex (10M, 15 ml) at room temperature. The mixture was stirred at room temperature overnight. Then borane methylsulfide complex (7.5 ml) was added to the mixture. After stirring at room temperature overnight, the mixture was quenched with methanol (100 ml) and evaporated under reduced pressure to give oil. The oil was dissolved in a mixture of tetrahydrofuran (150 ml) and hydrochloric acid (6N, 100 ml), and then stirred at 40 ~ 50°C for 1 hour. To the mixture was added dropwise aqueous sodium hydroxide solution (30%, 80 ml), and then sodium hydrogen carbonate, and sodium chloride. The mixture was extracted with ethyl acetate (x4). The organic layer was evaporated to give oil (31.86 g), which was purified with column chromatography (SiO2, 1 L, eluted with 20% methanol/dichloromethane and concentrated ammonia/methanol/chloroform (0.025:1:4)) to give oil. A solution of hydrogen chloride in ethyl acetate (4N, 22 ml) was added to the solution of the oil in ethyl acetate (50 ml), and the mixture was evaporated to give E0276 as an amorphous (22.87 g, 69.4%).

Example 277



(E0277)

E0277 was prepared in a similar manner to that of E0276.

white powder

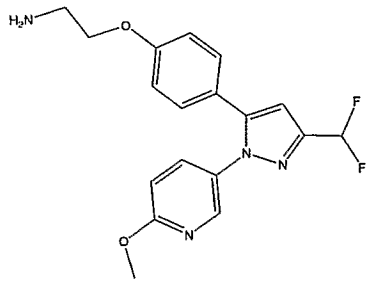
mp. 229-231°C

IR (KBr) : 3084, 2960, 2885, 2800, 2731, 2563, 2519, 2482, 1606, 1576, 1516cm-1

Mass (ESI+) : 350 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.84-0.96(2H, m), 1.93(1H, m), 3.14-3.22(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 6.26(1H, s), 6.94(4H, d, J=8.8 Hz), 7.14(4H, d, J=8.8 Hz), 8.21(2H, brs)

Example 278



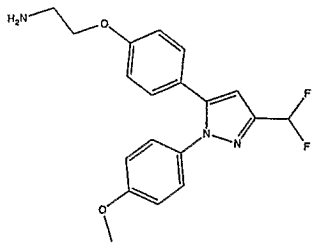
(E0278)

This compound was obtained according to a similar manner to that of E0276 without formation of hydrogen chloride salt (oil).

NMR(CDCl3), 3.09(2H, t, J=5.2 Hz), 3.94(3H, s), 3.99(2H, t, J=5.2 Hz), 6.77(1H, t, J=54.9 Hz), 6.67(1H, s), 6.74(2H, d, J=7.5 Hz), 6.87(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.7 Hz),

7.55(1H, dd, J=8.9, 2.8 Hz), 8.09(1H, d, J=2.8 Hz).
MS(ESI+), 361(MH+).

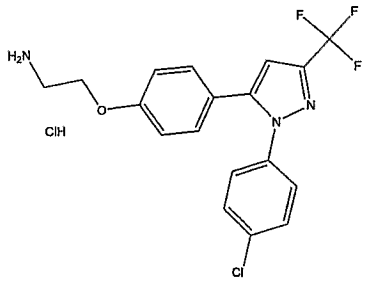
Example 279



(E0279)

This compound was obtained according to a similar manner to that of E0276.

Example 280

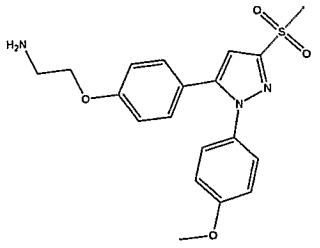


(E0280)

This compound was obtained according to a similar manner to that of E0276.

IR (film): 3423.0, 1612.2, 1469.5, 1240.0, 1164.8, 1132.0, 1095.4, 975.8, 836.9 cm-1.

Example 281



(E0281)

This compound was obtained according to a similar manner to that of E0276.

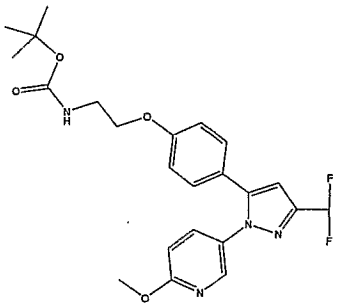
mp.104-106°C

Mass;388(M+1)

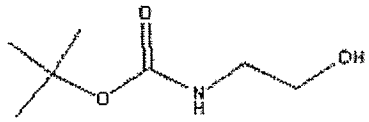
IR(KBr);1310cm-1

NMR(CDCl3,δ);3.09(2H, t, J=5.1 Hz), 3.29(3H, s), 3.83(3H, s), 3.99(2H, t, J=5.1 Hz), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=8.9 Hz), 6.93(1H, s), 7.13(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz),

Example 282



(E0282)



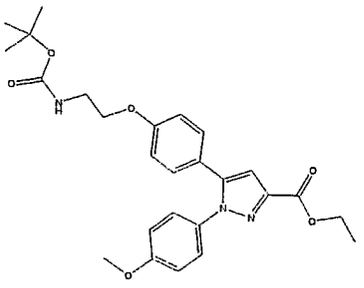
(P0015-1)

Diethylazodicarboxylate 82.3mg was added to a solution of P0015 (100mg), P0015-1 (152mg), and triphenylphosphine 124mg in THF 2ml. After stirring at ambient temperature for 5 hours, Thereaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / CHCl3 = 5% viscous oil to give E0282.

Mass (ESI+) : 461 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.33(2H, m), 3.87(3H, s), 3.93-3.99(2H, m), 6.88-7.04(5H, m), 7.10(1H, t, J=54.4 Hz), 7.21(2H, d, J=8.7 Hz), 7.69(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 283



(E0283)

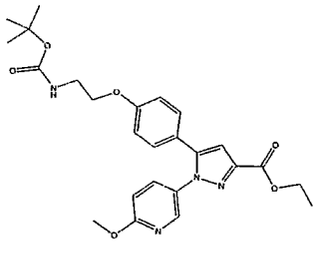
E0283 was prepared from P0020 in a similar manner to that of E0282.

white powder

Mass (ESI+) : 482 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 1.37(9H, s), 3.22-3.32(2H, m), 3.79(3H, s), 3.91-3.98(2H, m), 4.32(2H, q, J=7.1 Hz), 6.90(2H, d, J=8.7 Hz),6.95-7.06(1H, overlapping), 6.99(2H, d, J=8.9 Hz), 7.01(1H, s), 7.17(2H, d, J=8.7 Hz), 7.25(2H, d, J=8.9 Hz)

Example 284



(E0284)

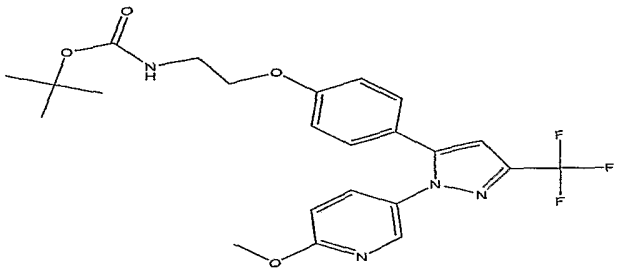
E0284 was prepared in a similar manner to that of E0282.

white powder

Mass (ESI+) : 483 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 1.37(9H, s), 3.22-3.33(2H, m), 3.88(3H, s), 3.96(2H, t, J=5.7 Hz), 4.33(2H, q, J=7.1 Hz), 6.89-7.05(1H, overlapping), 6.92(1H, d, J=8.9 Hz), 6.93(2H, d, J=8.7 Hz), 7.05(1H, s), 7.21(2H, d, J=8.7 Hz), 7.72(1H, dd, J=2.7,8.9 Hz), 8.15(1H, d, J=2.7 Hz)

Example 285



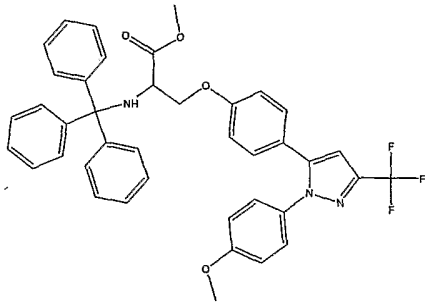
(E0285)

This compound was obtained according to a similar manner to that of E0282 as an oil.

NMR(CDCl3), 1.45(9H, s), 3.50-3.58(2H, m), 3.94(3H, s), 4.02(2H, t, J=5.1 Hz), 6.70(1H, s), 6.75(1H, d, J=8.4 Hz), 6.85(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.9 Hz), 7.56(1H, dd, J=8.4, 2.9 Hz), 8.08(1H, d, J=2.9 Hz).

MS(ESI+), 501.2(M+Na).

Example 286



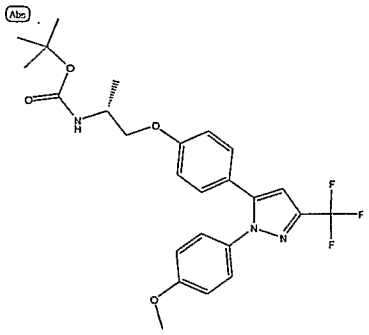
(E0286)

This compound was obtained according to a similar manner to that of E0282 as a powder.

NMR(CDCl3), 2.89(1H, d, J=10.4 Hz, NH), 3.23(3H, s), 3.67-3.78(1H, m), 3.81(3H, s), 3.99(1H, dd, J=9.2, 6.4 Hz), 4.22(1H, dd, J=9.2, 5.0 Hz), 6.67(1H, s), 6.81(2H, d, J=8.9 Hz), 6.86(2H, d, J=6.0 Hz), 7.10-7.29(13H, m), 7.49-7.54(6H, m).

MS(ESI+), 678.4(MH+).

Example 287



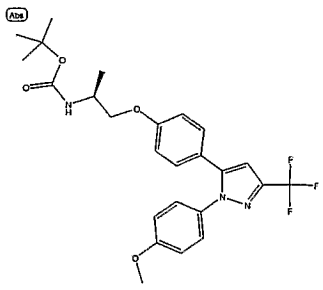
(E0287)

This compound was obtained according to a similar manner to that of E0282 as an oil.

NMR(CDCl3), 1.28(3H, d, J=6.6 Hz), 1.45(9H, s), 3.82(3H, s), 3.92(2H, d, J=4.1 Hz), 3.90-4.14(1H, m), 6.67(1H, s), 6.84(2H, d, J=8.9 Hz), 6.86(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+), 514.2(M+Na).

Example 288



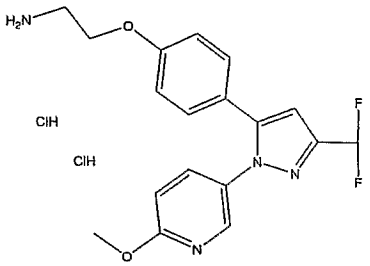
(E0288)

This compound was obtained according to a similar manner to that of E0282 as an oil.

NMR(CDCl3), 1.28(3H, d, J=6.6 Hz), 1.45(9H, s), 3.82(3H, s), 3.92(2H, d, J=4.1 Hz), 3.90-4.14(1H, m), 6.67(1H, s), 6.84(2H, d, J=8.9 Hz), 6.86(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.9 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+), 514.2(M+Na).

Example 289



(E0289)

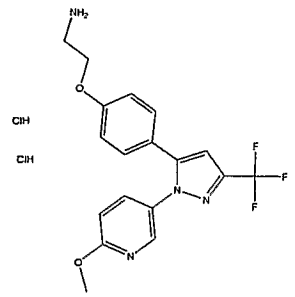
4M HCl/AcOEt 1ml was added to a solution of E0282 (129mg) in AcOEt 1ml, and the mixture was stirred at ambient temperature for 1hour. The supernatant was removed by decantation. The residual oily solid was washed with AcOEt 1ml by decantation. To the residue was added acetone 2ml, and oily residual solid became white powder on stirring. This was stirred at ambient temperature for 20minutes. The precipitates were collected and washed with acetone to give E0289 (91.4mg) as a white powder.

IR (neat) : 2964, 1705, 1668, 1660, 1614, 1581, 1566, 1531, 1512cm-1

Mass (ESI+) : 361 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.11-3.23(2H, m), 3.87(3H, s), 4.12-4.28(2H, m), 6.90-7.02(4H, m), 7.11(1H, t, J=54.3 Hz), 7.26(2H, d, J=8.6 Hz), 7.71(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz), 8.24(2H, brs)

Example 290



(E0290)

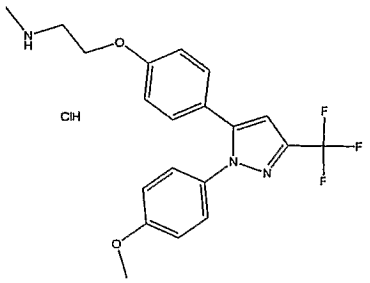
This compound was obtained according to a similar manner to that of E0289 as a white powder.

NMR(DMSO-d6), 3.17-3.21(2H, m), 3.95(3H, s), 4.19(2H, t, J=5.0 Hz), 6.93(1H, d, J=8.8 Hz), 7.00(2H, d, J=8.8 Hz), 7.15(1H, s), 7.28(2H, d, J=8.8 Hz), 7.76(1H, dd, J=8.8, 2.6 Hz), 8.18(1H, d, J=2.6 Hz).

MS(ESI+), 379.1(MH+).

IR(KBr), 1612.2cm-1.

Example 291



(E0291)

This compound was obtained according to a similar manner to that of E0289 as a white powder.

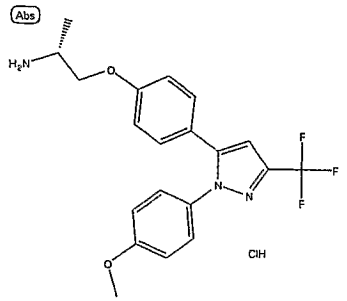
NMR(DMSO-d6), 2.60(3H, s), 3.28-3.33(2H, m), 3.79(3H, s), 4.25(2H, t, J=4.7 Hz), 7.04-6.96(4H, m), 7.09(1H, s), 7.22-7.31(4H, m).

MS(ESI-), 426.2 (M+Cl)+.

IR(KBr); 1610.2, 1515.8cm-1.

MP; 189 - 189.2°C.

Example 292



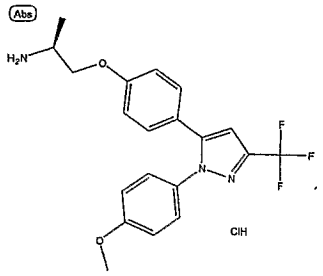
(E0292)

This compound was obtained according to a similar manner to that of E0289 as a white amorphous.

NMR(DEMSO-d6),1.04(3H, d, J=6.0 Hz), 3.5-3.7(1H, m), 3.79(3H, s), 3.98(1H, dd, J=10.1, 6.9 Hz), 4.11(1H, dd, J=10.1, 6.5Hz), 6.96-7.04(4H, m), 7.09(1H, s), 7.22-7.31(4H, m).

MS(ESI+), 392.2(MH+).

Example 293



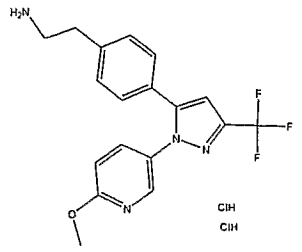
(E0293)

This compound was obtained according to a similar manner to that of E0289 as a white amorphous.

NMR(DEMSO-d6),1.04(3H, d, J=6.0 Hz), 3.5-3.7(1H, m), 3.79(3H, s), 3.98(1H, dd, J=10.1, 6.9 Hz), 4.11(1H, dd, J=10.1, 6.5Hz), 6.96-7.04(4H, m), 7.09(1H, s), 7.22-7.31(4H, m).

MS(ESI+), 392.2(MH+). IR(Neat) 1612.2cm-1.

Example 294



(E0294)

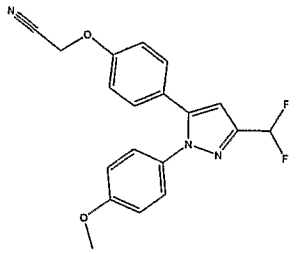
This compound was obtained according to a similar manner to that of E0289 as a white powder.

NMR(DMSO-d6); 2.84-3.20(4H, m), 3.88(3H, s), 6.93(1H, d, J=8.9Hz), 7.19(1H, s), 7.30-7.36(4H, m), 7.86(1H, dd, J=8.9, 2.7 Hz), 8.19(1H, d, J=2.7 Hz).

MS(ESI+); 363.3(MH+).

IR(KBr); 1612.2, 1500.3cm-1.

Example 295



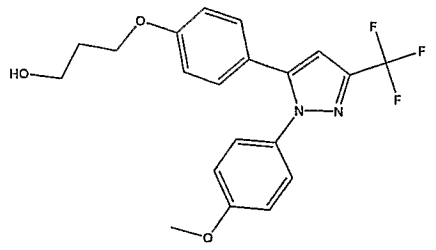
(E0295)

A mixture of P0012 (0.5 g), chloroacetonitrile (0.2 ml), potassium iodide (525 mg), and potassium carbonate (437 mg) in N,N-dimethylformamide (6 ml) was stirring at 75°C for 6 hours. After cooling to room temperature, the mixture was quenched with water, and extracted with ethyl acetate (x3). The combined organic layers were washed with water (x3) and brine, dried over magnesium sulfate, and evaporated to give E0295 as a solid (631.6 mg, 112%).

NMR(CDCl3), 3.83(3H, s), 4.77(2H, s), 6.69(1H, s), 6.76(1H, t, J=55 Hz), 6.96-6.86(4H, m), 7.18-7.24(4H, m).

MS(ESI+), 378.1(M+Na).

Example 296



(E0296)

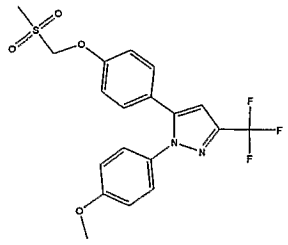
This compound was obtained according to a similar manner to that of E0295 as an oil.

NMR(CDCl3); 1.63(1H, t, J=5.2 Hz), 1.99-2.11(2H, m), 3.82(3H, s), 3.82-3.91(2H, m), 4.12(2H, t, J=6.0 Hz), 6.67(1H, s), 6.84(2H, d, J=8.8 Hz), 6.87(2H, d, J=8.9 Hz), 7.13(2H, d, J=8.8 Hz), 7.32(2H, d, J=8.9 Hz).

IR(Neat); 1612, 1514cm-1.

MS(ESI+); 393.1(MH+), 415.1(M+Na).

Example 297



(E0297)

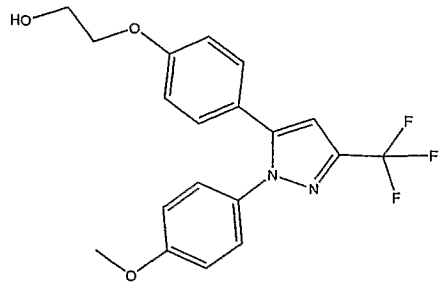
This compound was obtained according to a similar manner to that of E0205 as an oil.

NMR(CDCl3); 3.03(3H, s), 3.83(3H, s), 4.97(2H, s), 6.70(1H, s), 6.88(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.8 Hz), 7.17-7.26(4H, m).

IR(KBr); 1612.2, 1513.9 cm-1.

MS(ESI+), 449.1(M+Na).

Example 298



(E0298)

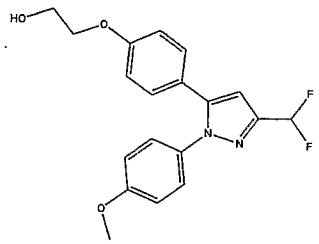
This compound was obtained according to a similar manner to that of E0295 as a white solid.

NMR(DMSO-d6), 3.65-3.73(2H, m), 3.79(3H, s), 3.98(2H, t, J=4.7 Hz), 4.87(1H, t, J=5.4 Hz), 6.93(2H, d, J=8.7 Hz), 7.00(2H, d, J=8.9 Hz), 7.07(1H, s), 7.19(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz).

MS(ESI+), 401.2(M+Na).

IR(KBr); 1610.3, 1511.9cm-1.

Example 299



(E0299)

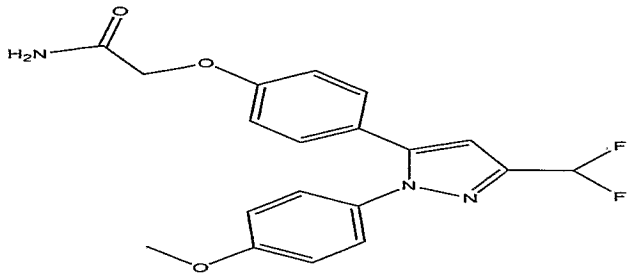
This compound was obtained according to a similar manner to that of E0295 as a white solid.

NMR(CDCl3), 2.01(1H, t, J=6.1 Hz), 3.82(3H, s), 3.93-4.10(4H, m), 6.66(1H, s), 6.76(1H, t, J=55.1 Hz), 6.85(2H, d, J=8.7 Hz), 6.87(2H, d, J=9.0 Hz), 7.15(2H, d, J=8.7 Hz), 7.21(2H, d, J=9.0 Hz).

MS(ESI+); 383.2(M+Na).

IR(KBr); 1610.3, 1513.9, 1454.1cm-1.

Example 300



(E0300)

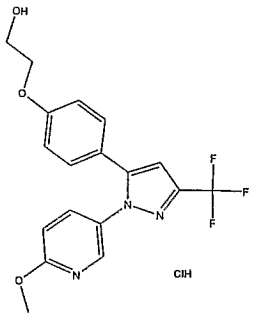
This compound was obtained according to a similar manner to that of E0295 as a white powder.

NMR(DMSO-d6); 3.78(3H, s), 4.43(2H, s), 6.80-7.53(12H, m, NH2),

MS(ESI+);396.3(M+Na)+.

IR(KBr); 1681.6, 1606.4cm-1.

Example 301



(E0301)

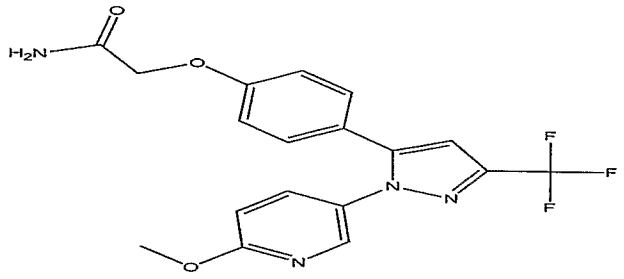
Alkylation of this compound was achieved by a similar manner to that of E0295 to give salt free compound as an oil. Hydrogen chloride salt formation was achieved successively by a similar manner to that of E0172 to give E0301 as a white powder (498.7 mg, 49.6%).

NMR(DMSO-d6), 3.69(2H, t, J=5.0 Hz), 3.88(3H, s), 3.99(2H, t, J=5.0 Hz), 6.92(1H, d, J=8.7 Hz), 6.96(2H, d, J=8.8 Hz), 7.13(1H, s), 7.23(2H, d, J=8.8 Hz), 7.53(1H, dd, J=8.7, 2.9 Hz), 8.18(1H, d, J=2.9 Hz).

MS(ESI+), 402.1(M+Na)+, (Free).

IR(Neat), 1614, 1552cm-1.

Example 302



(E0302)

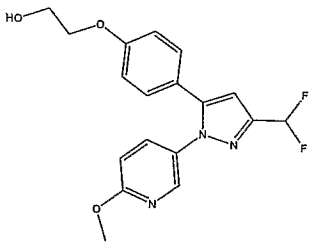
This compound was obtained according to a similar manner to that of E0295 as a white solid.

NMR(CDCl3); 3.88(3H, s), 4.45(2H, s), 6.92(1H, d, J=8.9 Hz), 6.96(2H, d, J=8.8 Hz), 7.14(1H, s), 7.26(2H, d, J=8.8 Hz), 7.41(1H, brs, NH2), 7.56(1H, brs, NH2), 7.76(1H, dd, J=8.9, 2.5 Hz), 8.18(1H, d, J=2.5 Hz).

MS(ESI+); 415.1(M+Na).

IR(KBr); 1693.2, 1608.3cm-1.

Example 303



(E0303)

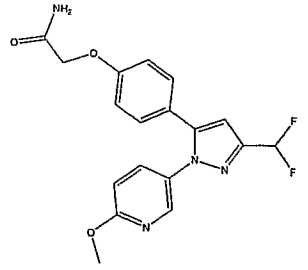
This compound was obtained according to a similar manner to that of E0295 as an oil.

NMR(CDCl3); 3.94(3H, s), 3.94-4.14(4H, m), 6.68(1H, s), 6.74(1H, d, J=8.7 Hz), 6.86(1H, t, J=55.0 Hz), 6.88(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.9 Hz), 7.53(1H, dd, J=2.6, 8.7 Hz), 8.08(1H, d, J=2.6 Hz).

MS(ESI+); 384.2(M+Na).

IR(KBr), 1805.1, 1612.2cm-1.

Example 304



(E0304)

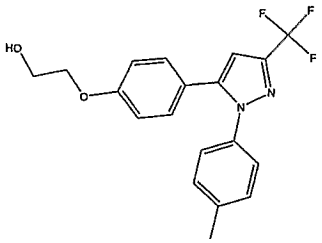
This compound was obtained according to a similar manner to that of E0295 as a white powder.

NMR(DMSO-d6); 3.88(3H, s), 4.44(2H, s), 6.98-9.89(4H, m), 7.10(1H, t, J=54.3 Hz), 7.24(2H, d, J=8.8 Hz), 7.39(1H, brs, NH2), 7.54(1H, brs, NH2), 7.70(1H, dd, J=8.9, 2.8 Hz), 8.14(1H, d, J=2.8 Hz).

MS(ESI-); 373 (M-H)+.

IR(KBr); 1662.3, 1610.3cm-1.

Example 305

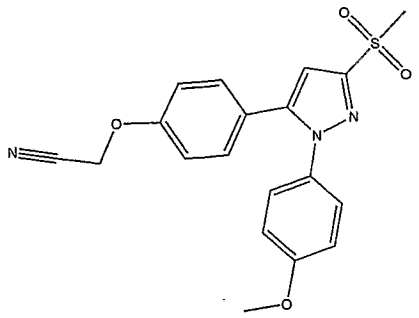


(E0305)

This compound was obtained according to a similar manner to that of E0298.

IR (film): 3388.3, 1494.6, 1236.2, 1160.9, 1133.9, 1095.4, 975.8, 833.1 cm-1.

Example 306

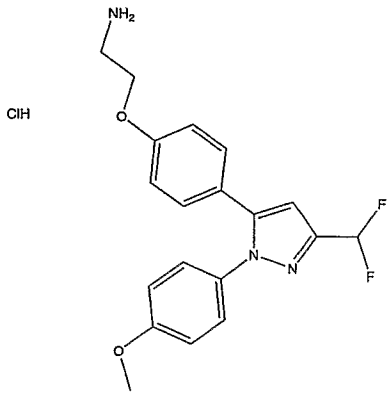


(E0306)

This compound was obtained according to a similar manner to that of E0295.

Mass;384(M+1)

Example 307



(E0307)

To a suspension of lithium aluminum hydride (250 mg) in ether (5 ml) was added E0295 (630 mg) in tetrahydrofuran (1 ml) under ice-bath. After stirring at room temperature for 1 hour. the mixture was quenched with water (0.125 ml), sodium hydroxide aqueous solution (15%, 0.125 ml), and water (0.375 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with ether. The filtrate was evaporated to give 0.5 g of oil. The oil was purified with column chromatography (SiO2, 50 ml, eluted with methanol / dichloromethane / concentrated ammonia water

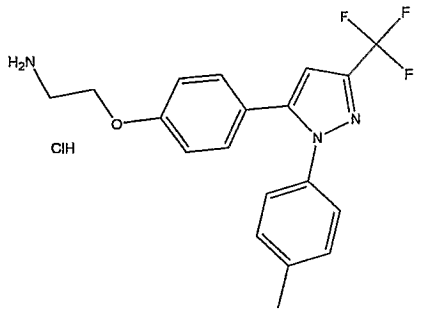
(1/10/0.05)) to give oil (300 mg). The oil was dissolved in ethyl acetate and added a solution of hydrogen chloride in ethyl acetate (4N, 1.6 ml). The mixture was evaporated to give oil, which was crystallized from methanol and diisopropyl ether to give E0307 as a powder (300 mg, 42.7%).

NMR(DMSO-d6), 3.20(2H, t, J=4.9 Hz), 3.78(3H, s), 4.16(2H, t, J=4.9 Hz), 6.85(1H, s), 6.94-7.01(4H, m), 7.08(1H, t, J=54.6 Hz), 7.20-7.26(4H, m).

MS(ESI+), 360.3(MH+, free).

IR(KBr, 20727-7), 1612, 1513.9 cm-1.

Example 308

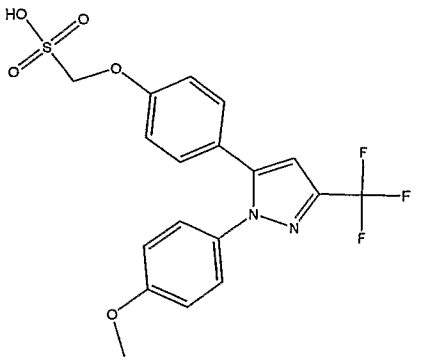


(E0308)

This compound was obtained according to a similar manner to that of E0307.

IR (film): 3401.8, 1610.3, 1511.9, 1469.5, 1240.0, 1162.9, 1130.1, 975.8, 827.3 cm-1.

Example 309



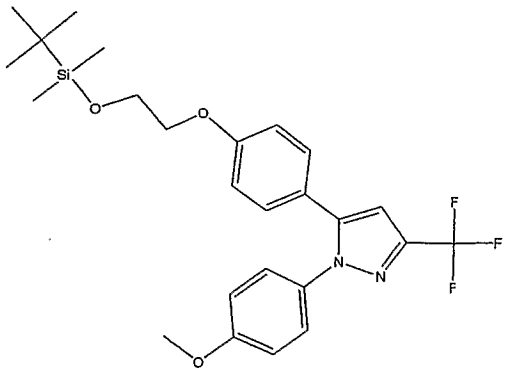
(E0309)

A mixture of P0011 (200 mg), Chloromethylsulfonic acid sodium salt (274 mg), potassium iodide (298 mg), and potassium carbonate (248 mg) in 1-methyl-2-pyrrolidinone (2 ml) was stirring at 150°C overnight. After cooling to room temperature, the mixture was poured into a mixture of aqueous hydrogen chloride solution (1 N), brine, and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate (x3). The combined organic layers were dried over magnesium sulfate, and evaporated under reduced pressure to give oil. The oil was purified with column chromatography (SiO2 100 ml, eluted with 15% methanol / dichloromethane) to give E0309 as a brown amorphous (154.3 mg, 60%)

MS(ESI-); 427.1(M-H).

NMR(DMSO-d6), 3.79(3H, s), 4.52(2H, s), 7.00(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.9 Hz), 7.07(1H, s), 7.18(2H, d, J=9.0 Hz), 7.27(2H, d, J=8.9 Hz).

Example 310

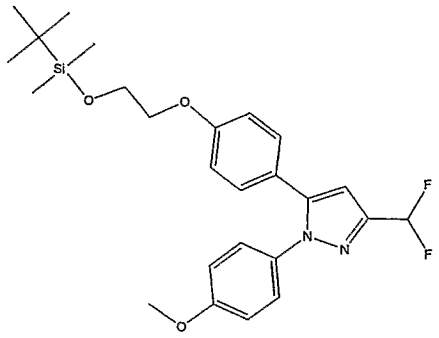


(E0310)

To a solution of P0011 (1.0g) in DMF (10ml) under water cooling was added portionwise NaH (60%in Oil, 144mg) and stirred for 1 hour. After then, III (787mg) was added and the reaction mixture was stirred at 50oC for 5 hours. The mixture was quenched with water and extracted twice with

EtOAc. The organic layer was washed three times with water and once with brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) to give 803mg (55%) of E0310 as a oil.

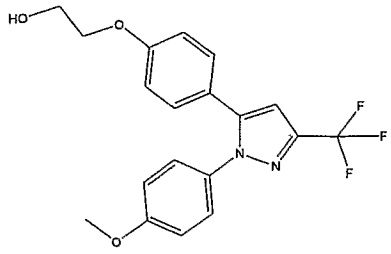
Example 311



(E0311)

This compound was obtained according to a similar manner to that of E0310.

Example 312

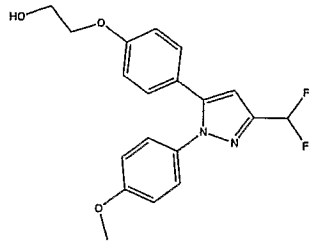


(E0312)

The mixture of E0310 (800mg) and cHCl (100ul) in EtOH (10ml) was stirred at room temperature for 3 hours. After addition of aqueous sodium bicarbonate, the mixture was evaporated, and extracted twice with EtOAc. The organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue (710mg) was column chromatographed on silica gel (50ml) to give 570mg (93%) of E0312.

IR (film): 3409.5, 1612.2, 1513.9, 1467.6, 1243.9, 1162.9, 1130.1, 835.0, 835.0 cm-1.

Example 313



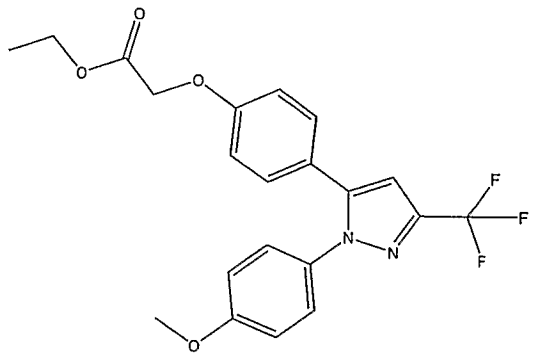
(E0313)

This compound was obtained according to a similar manner to that of E0312.

mp: 122.3-122.5°C

IR (film): 3399.9, 1612.2, 1513.9, 1456.0, 1251.6, 1174.4, 1083.8, 1033.7, 836.9, 800.3 cm-1.

Example 314



(E0314)

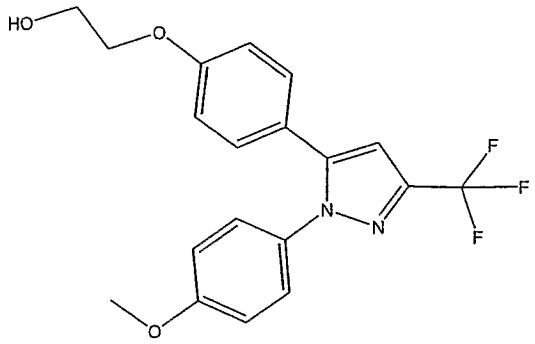
60% Sodium hydride 39.7mg was added to a solution of P0011 (255mg) in DMF 1.5ml. The mixture was stirred at ambient temperature for 1hour. To this was added ethyl bromoacetate 153mg. The reaction mixture was stirred at ambient temperature for 1hour, and then quenched by adding saturated ammonium chloride solution, and whole mixture was extracted

with AcOEt. The organic layer was washed with H2O, aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30% to give E0314 (217mg) as an oil.

Mass (ESI+) 421(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.94(3H, t, J=7.1 Hz), 3.79(3H, s), 4.15(2H, q, J=7.1 Hz), 4.79(2H, s), 6.92(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.09(1H, s), 7.20(2H, d, J=8.8 Hz), 7.28(2H, d, J=8.9 Hz)

Example 315



(E0315)

1M solution of diisobutylaluminum hydride in toluene 0.5ml was added dropwise to a solution of E0314 (98mg) in THF 3ml at -50°C. The mixture was stirred at -50°C for 1hour, then at 5°C for 1hour. Additional 1M solution of diisobutylaluminum hydride in toluene 0.5ml was added dropwise. After stirring at 5°C for one more hour, the reaction was quenched by adding 10% aqueous potassium sodium tartaric acid salt, and the mixture was filtered through a celite pad. The filtrate was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by

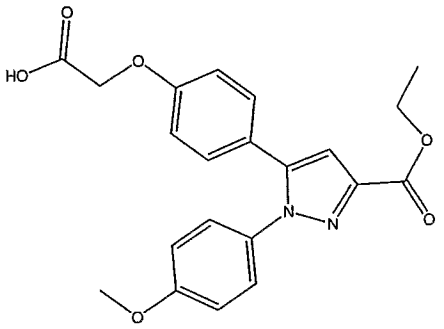
preparative thin layer silica gel chromatography developed by AcOEt / n-hexane = 60%. The separated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give E0315 (54.5mg) as an oil, which became solid on standing.

IR (KBr) : 3431, 2931, 1612, 1564, 1549, 1512cm-1

Mass (ESI+) : 379 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 3.67-3.72(2H, m), 3.79(3H, s), 3.84-3.99(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(2H, d, J=8.7 Hz), 7.00(2H, d, J=8.9 Hz), 7.10(1H, s), 7.19(2H, d, J=8.7 Hz), 7.27(2H, d, J=8.9 Hz)

Example 316



(E0316)

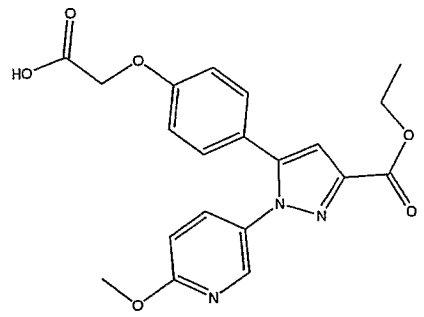
60% Sodium hydride 52mg was added to a solution of P0020 (200mg) in DMF 2ml under ice bath cooling. The mixture was stirred at same temperature for 30minutes. To this was added bromoacetic acid 90.3mg. The reaction mixture was stirred at ambient temperature for 2hours, and then quenched by adding s1M HCl 3ml. H2O 3ml and diisopropyl ether 2ml were added and the mixture was stirred in an ice bath for 30minutes. The precipitates were collected and washed with H2O and diisopropyl ether to give E0316 (231.2mg) as a white powder

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.79(3H, s), 4.32(2H, q, J=7.1 Hz), 4.68(2H, s), 6.88(2H, d, J=8.8

Hz), 7.00(2H, d, J=8.9 Hz), 7.02(1H, s), 7.18(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.9 Hz), 13.05(1H, brs)

Example 317



(E0317)

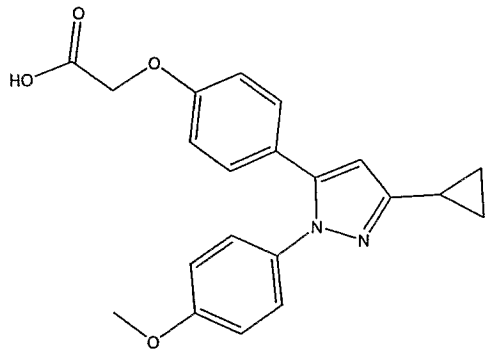
E0317 was prepared in a similar manner to that of E0316.

white powder

Mass (ESI+) : 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.88(3H, s), 4.33(2H, q, J=7.1 Hz), 4.70(2H, s), 6.92(2H, d, J=8.8 Hz), 6.89-7.00(1H, m), 7.06(1H, s), 7.22(2H, d, J=8.8 Hz), 7.73(1H, dd, J=2.8,8.8 Hz), 8.15(1H, d, J=2.8 Hz), 13.04(1H, brs)

Example 318



(E0318)

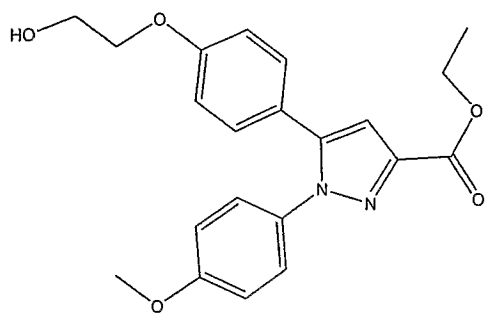
E0318 was obtained according to a similar manner to that of E0316.

oil

Mass (ESI+) : 365 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.70-0.93(4H, m), 1.70-2.00(1H, m), 3.76(3H, s), 4.66(2H, s), 6.25(1H, s), 6.85(2H, d, J=8.9 Hz), 6.92(2H, d, J=9.0 Hz), 7.06-7.16(4H, m), 13.00(1H, brs)

Example 319



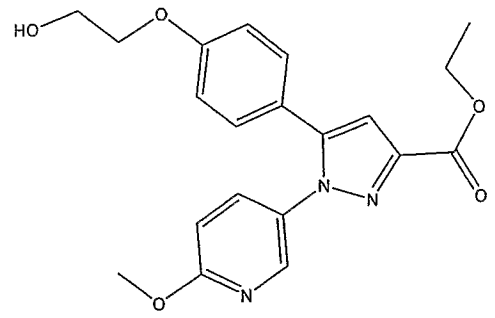
(E0319)

To a suspension of sodium borohydride 19.1mg in THF 2ml was added boron trifluoride diethyl etherate 89.5mg dropwise under ice bath cooling 2.5eq. The mixture was stirred at same temperature for 30minutes. E0316 (100mg) was added in one portion and the mixture was stirred at ambient temperature for 5hours. 1M HCl 5ml was added and the mixture was stirred at ambient temperature for 30minutes. The mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give E0319 (68.9mg) as a white powder.

Mass (ESI+) : 383 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.65-3.73(2H, m), 3.79(3H, s), 3.94-4.00(2H, m), 4.32(2H, q, J=7.1 Hz), 4.87(1H, t, J=5.5 Hz), 6.91(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.01(1H, s), 7.17(2H, d, J=8.8 Hz), 7.25(2H, d, J=8.9 Hz)

Example 320



(E0320)

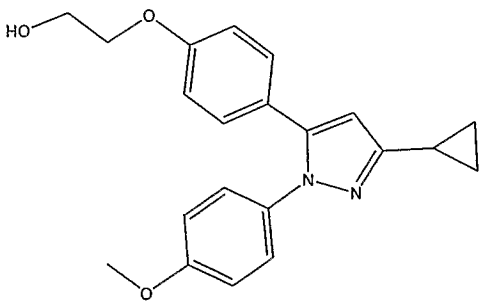
E0320 was prepared in a similar manner to that of E0319.

white powder

Mass (ESI+) : 384 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.31(3H, t, J=7.1 Hz), 3.65-3.74(2H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.33(2H, q, J=7.1 Hz), 4.87(1H, t, J=5.4 Hz), 6.89-6.96(3H, m), 7.05(1H, s), 7.21(2H, d, J=8.7 Hz), 7.72(1H, dd, J=2.7,8.8 Hz), 8.14(1H, d, J=2.7 Hz)

Example 321



(E0321)

E0321 was prepared in a similar manner to that of E0319.

white powder

mp. 142-144°C

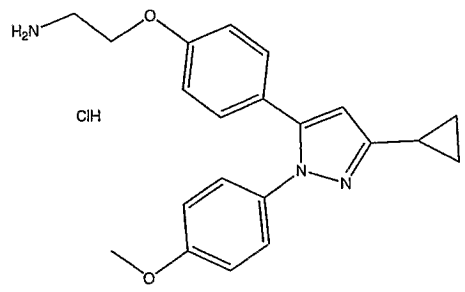
IR (KBr) : 3246, 2924, 1612, 1566, 1547, 1516cm-1

Mass (ESI+) : 351 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.68-0.77(2H, m), 0.85-0.95(2H,

m), 1.92(1H, m), 3.64-3.73(2H, m), 3.76(3H, s), 3.96(2H, t, J=4.9 Hz), 4.85(1H, t, J=5.5 Hz), 6.24(1H, s), 6.85-6.96(4H, m), 7.05-7.17(4H, m)

Example 322



(E0322)

E0322 was prepared in a similar manner to that of E0319.

white powder

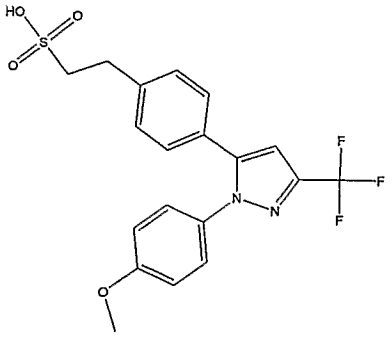
mp. 228-231°C

IR (KBr) : 3082, 2958, 2885, 2802, 2733, 2480, 1606, 1572, 1512cm-1

Mass (ESI+) : 350 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.69-0.77(2H, m), 0.83-0.96(2H, m), 1.93(1H, m), 3.14-3.22(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 6.27(1H, s), 6.93(4H, d, J=8.8 Hz), 7.14(4H, d, J=8.8 Hz), 8.24(2H, brs)

Example 323



(E0323)

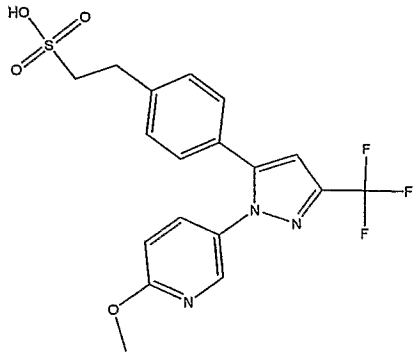
A solution of sodium sulfite 84.2mg in H2O 1ml was added

to a solution of P0022 (258.1mg) in EtOH 3ml and stirred at 70°C for 2hours. At which time, white precipitates were appeared and H2O 1ml was added to dissolve the precipitates. The mixture was stirred at 80°C overnight to give a clear solution. This was stirred at 80°C further for 28hours. The reaction mixture was acidified by 1M HCl 0.7ml, concentrated and dried under vacuo. The residue was dissolved in CHCl3, dried over magnesium sulfate, all of unsoluble matter was filtered off, and concentrated in vacuo to give E0323 (245mg) as an amorphous powder.

Mass (API-ES negative) 425(M-H)+

200MHz 1H NMR (DMSO-d6, d) : 2.61-2.69(2H, m), 2.78-2.91(2H, m), 3.79(3H, s), 7.00(2H, d, J=8.9 Hz), 7.12(1H, s), 7.17(2H, d, J=8.6 Hz), 7.22(2H, d, J=8.6 Hz), 7.29(2H, d, J=8.9 Hz)

Example 324



(E0324)

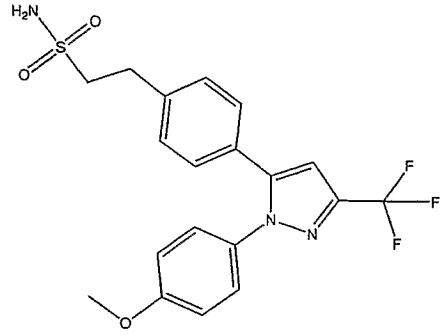
E0324 was prepared from P0023 in a similar manner to that of E0323.

amorphous powder

Mass (API-ES negative) : 426 (M-H)+

200MHz 1H NMR (DMSO-d6, d) : 2.61-2.69(2H, m), 2.83-2.92(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.17(1H, s), 7.23(4H, s), 7.75(1H, dd, J=8.8,2.7 Hz), 8.20(1H, d, J=2.7 Hz)

Example 325



(E0325)

DMF 41mg was added to a solution of E0319 (239mg) in thionyl chloride 0.6ml and the mixture was stirred at 50°C for 30minutes. The reaction mixture was concentrated in vacuo. To the residue was added toluene 3ml, and concentrated in vacuo. The residue was dissolved in THF 10ml and was added dropwise to a solution of 28% aqoueous ammonium hydroxide solution 0.5ml and tetrabutylammonium hydrogensulfate 19mg in THF 4ml under ice bath cooling. After stirring at ambient temperature for 30minutes, the reaction mixture was partitioned between AcOEt and aqueous sodium chloride solution. The organic layer was washed with aqueous sodium chloride solution, dried over magnesium sulfate. The residue was purified by silica gel column chromatography eluted with MeOH / CHCl3 = 2%, 5%. Pure fraction was collected and concentrated in vacuo. The residual solid was recrystallized from EtOH-diisopropyl ether to give E0325 (72.6mg) as a white powder.

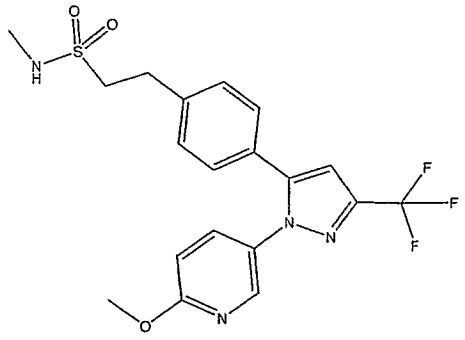
mp. 131-132°C

IR (KBr) : 3354, 3184, 3126, 1707, 1693, 1676, 1647, 1564, 1549, 1516cm-1

Mass (ESI+) : 426 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.95-3.04(2H, m), 3.21-3.30(2H, m), 3.79(3H, s), 6.87(2H, s), 7.00(2H, d, J=8.9Hz), 7.14(1H, s), 7.23-7.33(6H, m)

Example 326



(E0326)

E0326 was prepared in a similar manner to that of E0325.

white powder

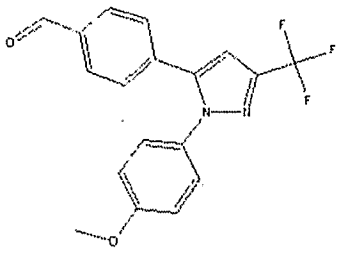
mp. 139-140°C

IR (KBr) : 3230, 3132, 1610, 1568, 1527, 1500cm-1

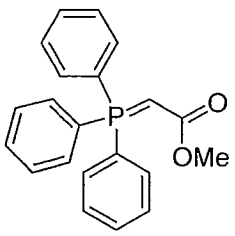
Mass (ESI+) : 441 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.58(3H, s), 2.90-3.00(2H, m), 3.25-3.33(2H, m), 3.88(3H, s), 6.93(1H, d, J=8.9Hz), 6.97(1H, brs), 7.19(1H, s), 7.26(2H, d, J=8.3 Hz), 7.34(2H, d, J=8.3 Hz), 7.77(1H, dd, J=8.9,2.8 Hz), 8.19(1H, d, J=2.8 Hz)

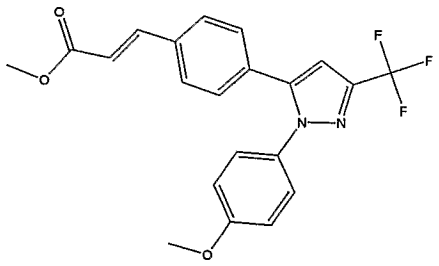
Example 327



(E0327-0)



(E0327-1)

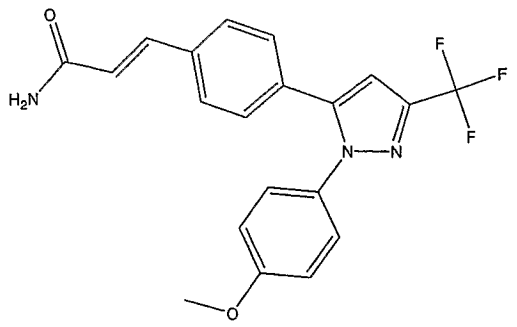


(E0327)

A mixture of E0327-0 (800mg) and E0327-1 , methyl (triphenylphosphoranylidene)- acetate (850mg) in toluene (10ml) was stirred under reflux condition for 5 hrs. The mixture was evaporated under reduced pressure and column chromatographed on silica gel (50ml, Hex:EtOAc=5:1) to give 795mg(85.5%) of E0327.

IR (film): 1718.3, 1637.3, 1513.9, 1241.9, 1166.7, 1132.0, 977.7, 837.0cm-1

Example 328

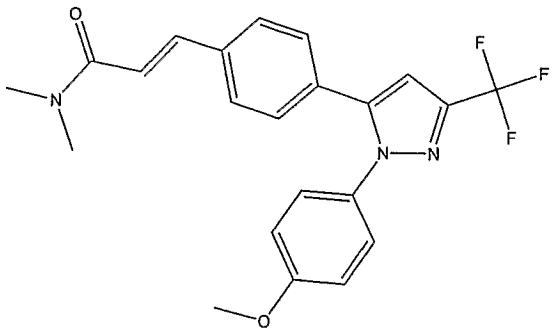


(E0328)

To a suspension of E0258 (180mg) in toluene (5ml) was adde thionylchloride (0.17ml) at room temperature. The reaction mixture was stirred at 100°C for 5 hours until the mixture become clear solution. After then, the mixture was evaporated under reduced pressure. (become solid) THF was added, and then aqueous NH3 (37%) was added. The mixture was stirred for 1 hour, and quenched with water, and extracted twice with EtOAc. The combined organic layer was washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure to give 170mg (95%) of E0328 as a powder.

IR (KBr): 3347.8, 1671.9, 1606.4, 1513.9, 1467.6, 1388.5, 1236.2, 1164.8, 1132.0, 979.7, 837.0cm-1.

Example 329



(E0329)

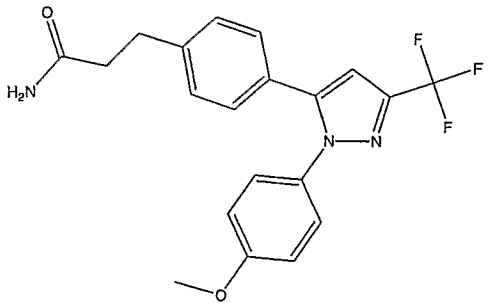
T a suspension of E0258 (200mg) in toluene (4ml) was added thionylchloride (0.19ml) at room temperature. The reaction mixture was stirred at 10°C for 5 hours until the mixture become clear solution. After then, the mixture was evaporated under reduced pressure. (become solid) THF was added, and then Me2NH (116mg) was added. The mixture was stirred for 1 hour, and quenched with water, and extracted twice with EtOAc. The combined organic layer was washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure to give 45mg (21%) of E0329 as a powder.

Filtrate (58mg).

mp: 118-120°C

IR (film): 1650.8, 1608.3, 1511.9, 1469.5, 1240.0, 1159.0, 1133.9cm-1.

Example 330

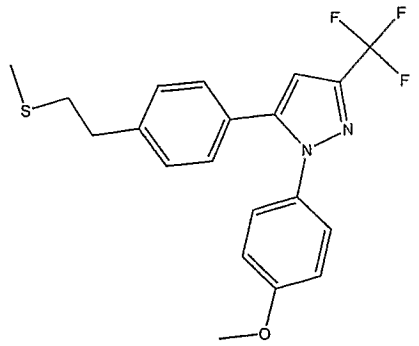


(E0330)

A mixture of E0328 (125mg) and Pd/C (100mg) in EtOH (10m) was stirred under H2 atmosphere for 3.0 hours. After filtration, a filtrate was evaporated under reduced pressure. The residue was dissolved in EtOH and filtered with syringe driven filter, and evaporated to give 85mg of E0330.

IR (KBr): 3342.0, 1670.0, 1511.9, 1240.0, 1160.9, 1130.1cm-1.

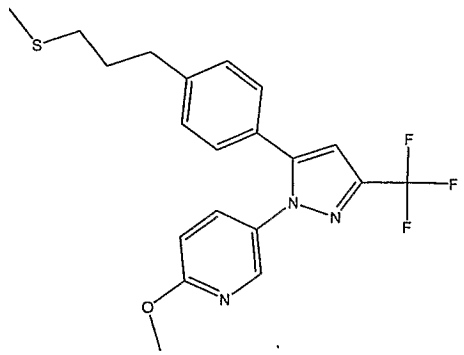
Example 331



(E0331)

A mixture of E0138 (300mg) and MeSNa (72mg) in DMF (6ml) was heated at 70°C for 5 hours. After cooling, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was separated and extracted with EtOAc. The combined organic layer was washed with water (twice) and brine, dried over Na2SO4, filtered and evaporated. The residue was column chromatographed on silica gel to give 270mg (quant) of E0331.

Example 332



(E0332)

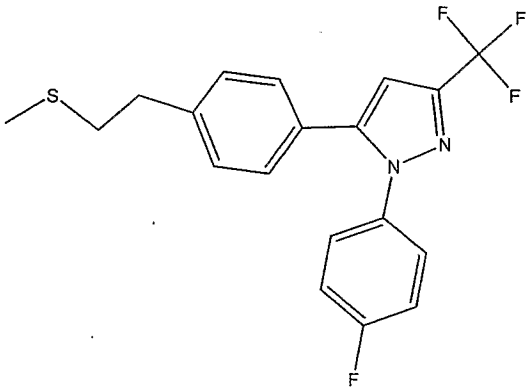
E0332 was prepared from E0141 in a similar manner to that of E0331.

oil

Mass (ESI+) : 408 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.73-1.89(2H, m), 2.03(3H, s), 2.40-2.52(2H, m), 2.62-2.70(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.18(1H, s), 7.24(4H, s), 7.76(1H, dd, J=8.8,2.7 Hz), 8.18(1H, d, J=2.7 Hz)

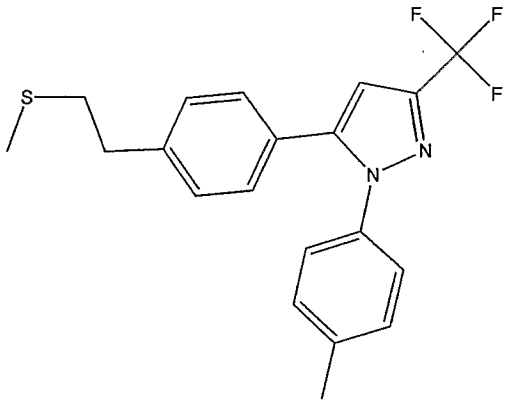
Example 333



(E0333)

This compound was obtained according to a similar manner to that of E0331.

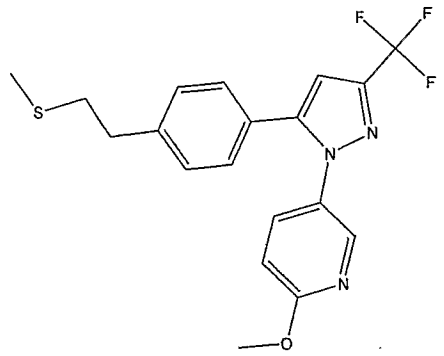
Example 334



(E0334)

This compound was obtained according to a similar manner to that of E0331.

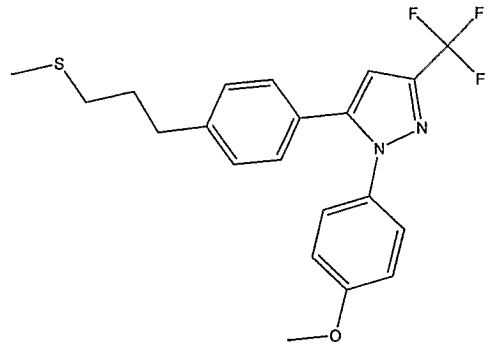
Example 335



(E0335)

This compound was obtained according to a similar manner to that of E0331

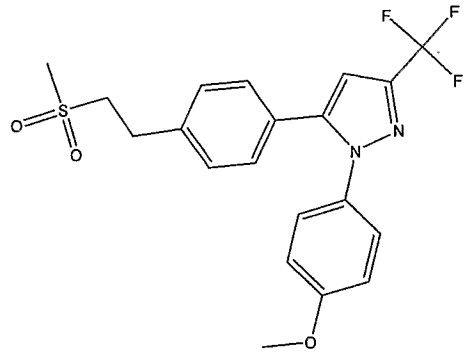
Example 336



(E0336)

This compound was obtained according to a similar manner to that of E0331.

Example 337



(E0337)

A mixture of E0331 (250mg) and mcpba (165mg) in CH2Cl2 was stirred under ice-cooling for 1 hour, and then mcpba (55mg) was added. After stirring for 1 hour under ice cooling, the reaction mixture was partitioned between CHCl3 and sat.NaHCO3. The organic layer was separated , washed with sat.NaHCO3, water and brine, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc) to give 141mg (52%) of E0337.

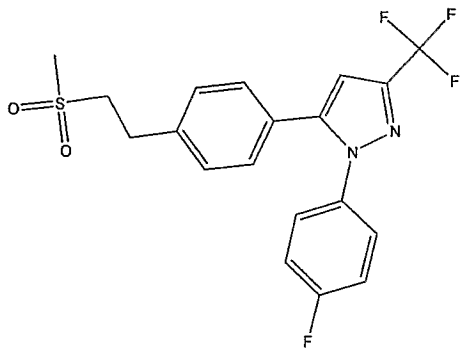
IR (film): 1511.9, 1303.6, 1240.0, 1130.1cm-1.

Oxide: FR267958

NMR (CDCl3): 2.599(s, 3H), 2.85-3.21(m, 4H), 3.828(s, 3H), 6.721(s, 1H), 6.872(d,J=9.0Hz,2H), 7.141(s, 4H), 7.179(d,J=9.0Hz, 2H).

MS: (M+Na)+ 431.1 (M110092-2)

Example 338

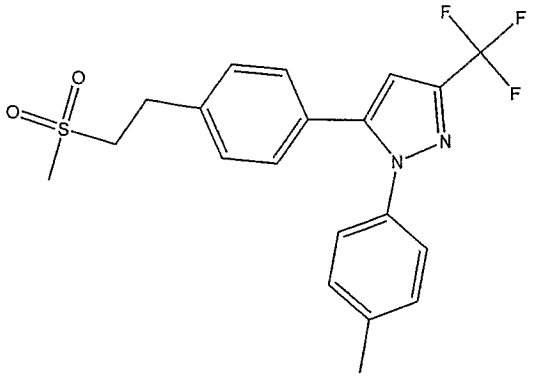


(E0338)

This compound was obtained according to a similar manner to that of E0337.

IR (film): 1511.9, 1469.5, 1311.4, 1282.4, 1236.2, 1126.2, 973.9, 823.5, 759.8 cm-1.

Example 339

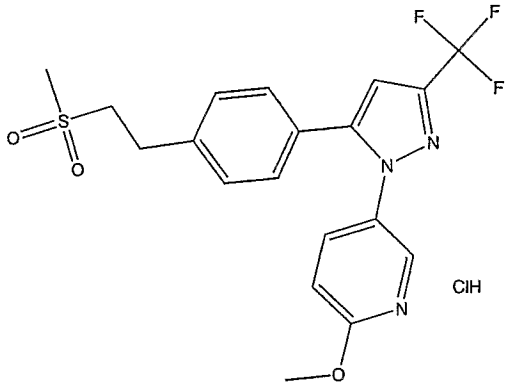


(E0339)

This compound was obtained according to a similar manner to that of E0337.

IR (film): 1511.9, 1469.5, 1311.4, 1282.4, 1236.2, 1128.2, 973.9, 823.5, 759.8cm-1.

Example 340



(E0340)

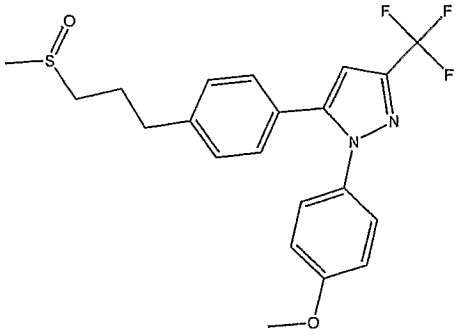
This compound was obtained according to a similar manner to that of E0337.

IR(film): 1673.9, 1616.1, 1498.4, 1477.2, 1467.6, 1390.4, 1307.5, 1290.1, 1240.0, 1160.9, 1132.0, 971.9, 756.0cm-1.

NMR (CDCl3): 2.76-2.94(m, 4H), 3.927(s, 3H), 3.943(s, 3H), 6.728(s, 1H), 6.752(d, J=8.9Hz, 1H), 7.12-7.26(m, 4H), 7.46-7.59(m, 1H), 8.04-8.10(m, 1H).

MASS (M+Na)+445.1 (FR267958-N)

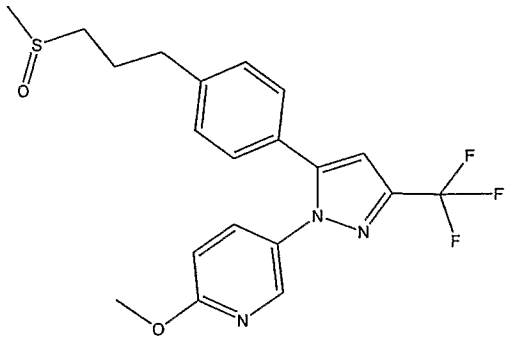
Example 341



(E0341)

To a solution of E0336 (450mg) in dichloromethane (45ml) was added MCPBA (306mg) at room temperature. After stirring for 1 hour, the reaction mixture was washed with sat.NaHCO3 (twice) and water, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) to give 470mg of E0341 as an oil.

Example 342



(E0342)

E0342 was prepared in a similar manner to that of E0341. white powder.

mp. 92-93°C

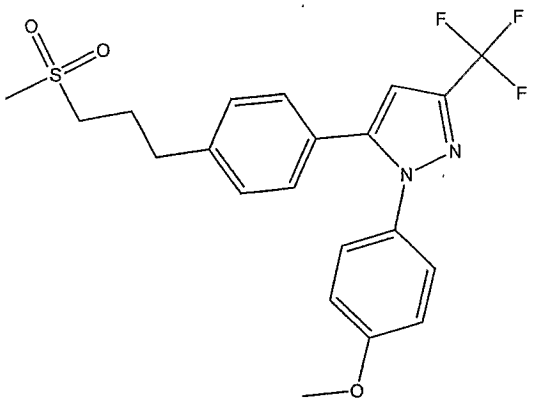
IR (KBr) : 3080, 2952, 1612, 1566, 1547, 1529, 1500cm-1

Mass (ESI+) : 424 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.87-2.00(2H, m), 2.51(3H, s), 2.56-2.78(4H, m), 3.88(3H, s), 6.92(1H, d, J=8.9Hz), 7.19(1H, s), 7.21-7.31(4H, m), 7.76(1H, dd, J=2.7,8.9 Hz), 8.19(1H,

d, J=2.7 Hz)

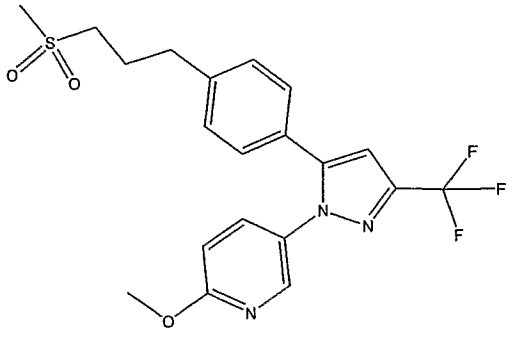
Example 343



(E0343)

To a solution of E0336 (450mg) in dichloromethane (45ml) was added MCPBA (306mg) at room temperature. After stirring for 1 hour, the reaction mixture was washed with sat.NaHCO3 (twice) and water, dried over Na2SO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (50ml) and recrystalized from EtOH to give 168mg (44%) of E0343.

Example 344



(E0344)

3-Chloroperoxybenzoic acid (407mg) was added to a solution of E0342 (666.3mg) in CH2Cl2 6ml under ice bath cooling. The reaction mixture was stirred at ambient temperature for 1hour. The mixture was diluted with CHCl3, washed with 1M

NaOH, 5% aqueous sodium thiosulfate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from AcOEt-n-hexane to give E0344 (565.2mg) as a white powder.

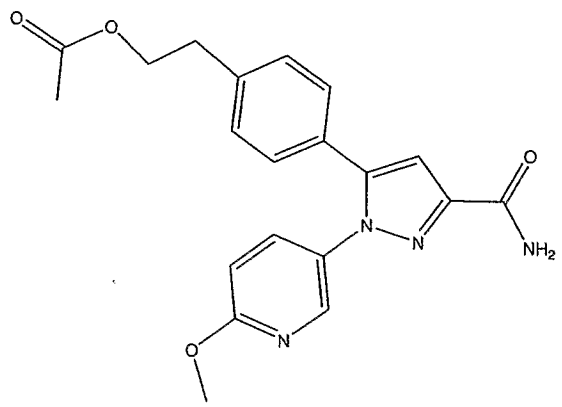
mp. 121-122°C

IR (KBr) : 3120, 2954, 1707, 1693, 1647, 1612, 1566, 1547, 1529, 1500cm-1

Mass (ESI+) : 440 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.93-2.06(2H, m), 2.67-2.75(2H, m), 2.96(3H, s), 3.04-3.13(2H, m), 3.88(3H, s), 6.92(1H, d, J=8.8 Hz), 7.19(1H, s), 7.19-7.31(4H, m), 7.76(1H, dd, J=8.8,2.8 Hz), 8.19(1H, d, J=2.8 Hz)

Example 345



(E0345)

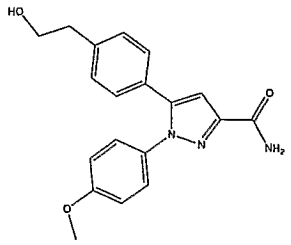
Oxalylchloride 286mg was added to a suspension of E0363 (0.43g) in CH2Cl2 3ml under ice bath cooling. DMF 1drop was added and the mixture was stirred at same temperature for 1hour, and then concentrated in vacuo. To the residue, was added toluene and concentrated in vacuo. The residue was dissolved in THF 5ml and was added to a solution of aqueous ammoniumhydroxide solution 5ml with under ice bath cooling. The mixture was stirred at same temperature for 1hour,

diluted with AcOEt, washed successively with 1M HCl, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane= 60%. The pure fraction was collected and concentrated in vacuo and the residue was crystallized from diisopropylether to give E0345 (287.8mg) as a white powder.

Mass (ESI+) : 381 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.97(3H, s), 2.89(2H, t, J=6.8 Hz), 3.87(3H, s), 4.21(2H, t, J=6.8 Hz), 6.91(1H, d, J=8.8 Hz), 6.98(1H, s), 7.22(2H, d, J=8.4 Hz), 7.28(2H, d, J=8.4 Hz), 7.38(1H, brs), 7.63-7.75(1H, brs), 7.72(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 346



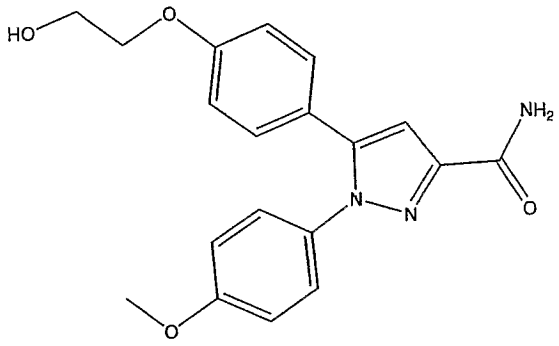
(E0346)

A mixture of E0109 (449.1mg) and sodium methoxide 238mg in formamide 5ml was heated at 70°C for 5hours. The mixture was allowed to cool to ambient temperature, and was partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with CHCl3, then MeOH / CHCl3 = 2%, 5% to give E0346 (235.7mg) as a white powder.

Mass (ESI+) : 338(M+H)+

400MHz 1H NMR (DMSO-d6, d) : 2.70(2H, t, J=6.9 Hz), 3.56-3.62(2H, m), 3.79(3H, s), 4.65(1H, t, J=5.1 Hz), 6.92(1H, s), 6.99(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.3 Hz), 7.20(2H, d, J=8.3 Hz), 7.27(2H, d, J=8.9 Hz), 7.33(1H, s), 7.64(1H, s)

Example 347



(E0347)

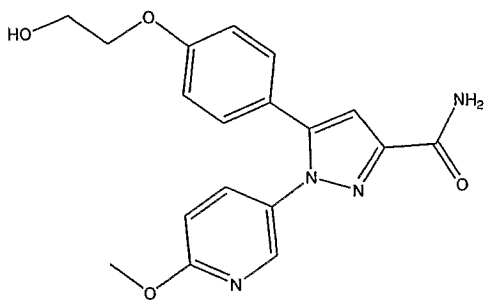
E0347 was prepared in a similar manner to that of E0346.

white powder

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.78(3H, s), 3.94-4.00(2H, m), 4.86(1H, t, J=5.5 Hz), 6.88(1H, s), 6.91(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.9 Hz), 7.32(1H, s), 7.63(1H, s)

Example 348



(E0348)

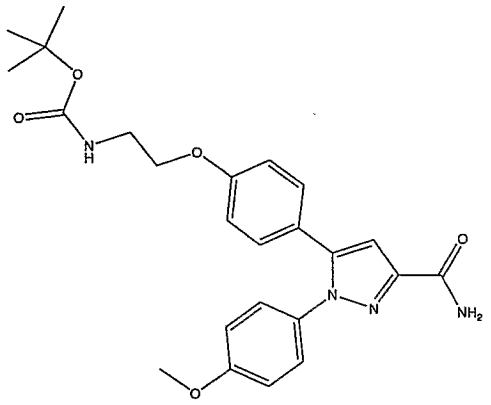
E0348 was prepared in a similar manner to that of E0346.

white powder

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.65-3.74(2H, m), 3.87(3H, s), 3.96-4.05(2H, m), 4.87(1H, t, J=5.5 Hz), 6.88-6.97(4H, m), 7.20(2H, d, J=8.7 Hz), 7.37(1H, brs), 7.67-7.73(1H, brs, overlapping), 7.71(1H, dd, J=2.6,8.8 Hz), 8.16(1H, d, J=2.6 Hz)

Example 349



(E0349)

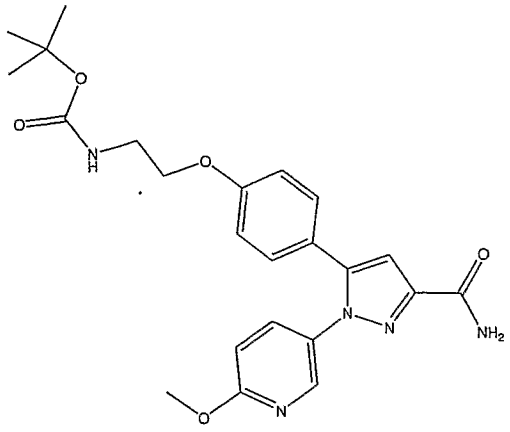
E0349 was prepared in a similar manner to that of E0346.

white powder

Mass (ESI+) : 453 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.24-3.29(2H, m), 3.78(3H, s), 3.94(2H, t, J=5.8 Hz), 6.88(1H, s), 6.90(2H, d, J=8.8 Hz), 6.99(2H, d, J=9.0 Hz), 6.97-7.00(1H, br), 7.16(2H, d, J=8.8 Hz), 7.25(2H, d, J=9.0 Hz), 7.32(1H, brs), 7.62(1H, brs)

Example 350



(E0350)

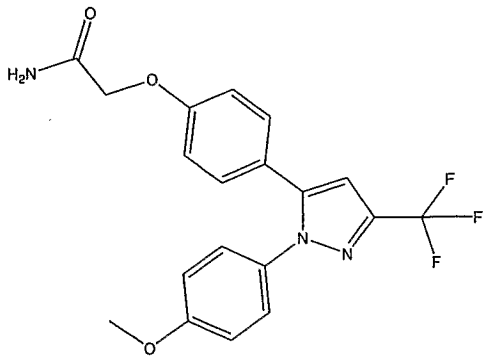
E0350 was prepared in a similar manner to that of E0346.

white powder

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.33(2H, m), 3.88(3H, s), 3.93-3.99(2H, m), 6.88-7.10(4H, m), 6.91(1H, s), 7.20(2H, d, J=8.7 Hz), 7.36(1H, brs), 7.68(1H, brs), 7.71(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 351



(E0351)

E0351 was prepared in a similar manner to that of E0346.

mp. 168-169°C

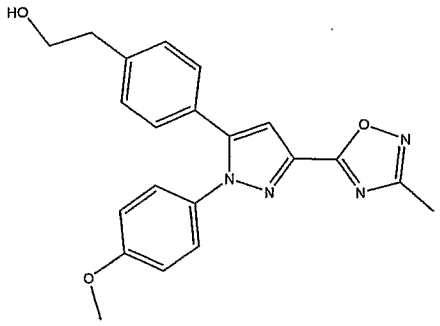
IR (KBr) : 3381, 3192, 1705, 1695, 1674, 1643, 1614, 1564, 1549, 1516cm-1

Mass (ESI+) : 392 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 3.79(3H, s), 4.43(2H, s), 6.93(2H,

d, J=8.9 Hz), 7.00(2H, d, J=9.0 Hz), 7.08(1H, s), 7.21(2H, d, J=8.9 Hz), 7.28(2H, d, J=9.0 Hz), 7.40(1H, brs), 7.54(1H, brs)

Example 352

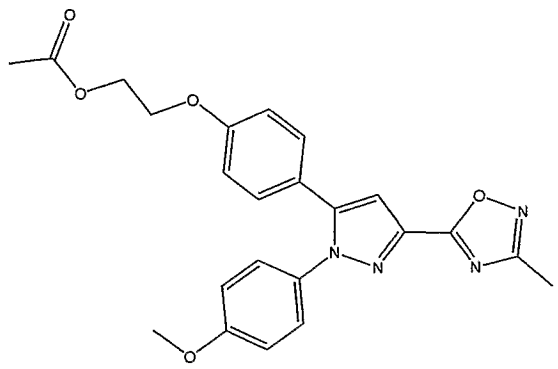


(E0352)

A mixture of E0346 (433.5mg) and N,N-dimethylacetamide dimethyl acetal 856mg in toluene 5ml was heated at 100°C for 40minutes. The reaction mixture was concentrated in vacuo. To the residue was added toluene and concentrated in vacuo. The residue was dissolved in toluene 5ml, hydroxylamine hydrochloride 893mg and AcOH 3ml was added and the mixture was heated at 100°C for 1hour. The mixture was cooled to ambient temperature, and partitioned between AcOEt and H2O, The organic layer was washed with H2O, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40%, 60%, 80%. The pure fraction was collected and concentrated in vacuo. The residue was crystallized from AcOEt / n-hexane to give E0352 (203mg) as a white powder.
mp. 148-150°C
IR (KBr) : 3431, 3425, 3406, 1614, 1547, 1510cm-1
Mass (ESI+) : 377 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.44(3H, s), 2.72(2H, t, J=6.9

Hz), 3.55-3.65(2H, m), 3.80(3H, s), 4.66(1H, t, J=5.1 Hz), 7.02(2H, d, J=8.9 Hz), 7.20(2H, d, J=9.0 Hz), 7.24(2H, d, J=9.0 Hz), 7.28-7.36(3H, m)

Example 353



(E0353)

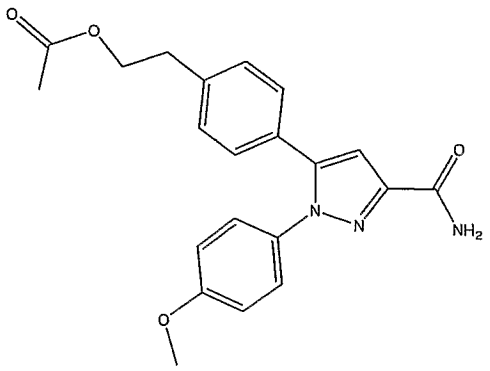
E0353 was prepared in a similar manner to that of E0352.

oil

Mass (ESI+) : 435 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.03(3H, s), 2.44(3H, s), 3.80(3H, s), 4.17-4.22(2H, m), 4.25-4.35(2H, m), 6.97(2H, d, J=8.7 Hz), 7.02(2H, d, J=9.0 Hz), 7.23(2H, d, J=8.7 Hz), 7.27(1H, s), 7.31(2H, d, J=9.0 Hz)

Example 354



(E0354)

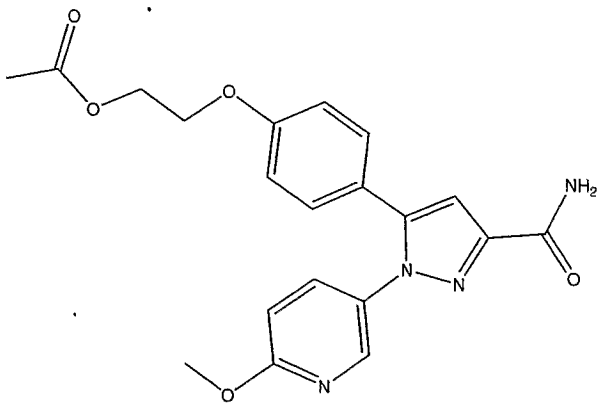
Acetic anhydride 124mg was added to a solution of E0346 (102.6mg) and pyridine 241mg in CH2Cl2 1ml. The reaction

mixture was stirred at ambient temperature for 1hour. Acetic anhydride 62mg and pyridine 1ml was added and stirred at ambient overnight. Acetic anhydride 62mg was added and stirred at ambient for 4hours. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid was collected and washed with diisopropyl ether to give E0354 (76.3mg) as a white powder.

Mass (ESI+) : 380 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 3.78(3H, s), 4.20(2H, t, J=6.8 Hz), 6.94(1H, s), 6.98(2H, d, J=8.9 Hz), 7.15-7.30(6H, m), 7.33(1H, s), 7.64(1H, s)

Example 355



(E0355)

E0355 was prepared in a similar manner to that of E0354.

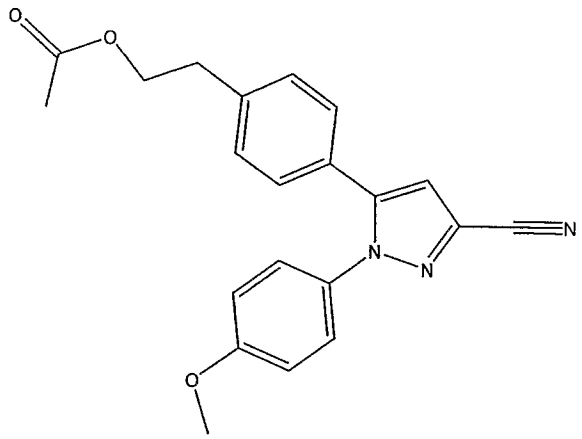
white powder

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.03(3H, s), 3.87(3H, s), 4.16-4.21(2H, m), 4.29-4.34(2H, m), 6.88-6.98(4H, m), 7.21(2H, d, J=8.7 Hz), 7.37(1H, brs), 7.68-7.70(1H,

brs,overlapping), 7.71(1H, dd, J=2.7,8.8 Hz), 8.16(1H, d, J=2.7 Hz)

Example 356



(E0356)

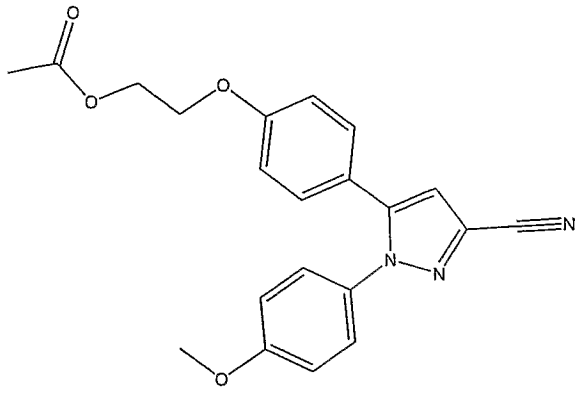
Phosphorus oxychloride 40.4mg was added to DMF 0.5ml under ice bath cooling. After stirring at same temperature for 5minutes, E0354 (50mg) was added in one portion. The reaction mixture was stirred at same temperature for 1hour, and quenched by adding aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give E0356 (45.0mg) as an oil.

Mass (ESI+) : 403 (M+CH3CN+H)+

Mass (API-ES positive) : 362 (M+H)+ , 384 (M+Na)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.88(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 7.00(2H, d, J=8.9 Hz), 7.15-7.31(6H, m), 7.36(1H, s)

Example 357



(E0357)

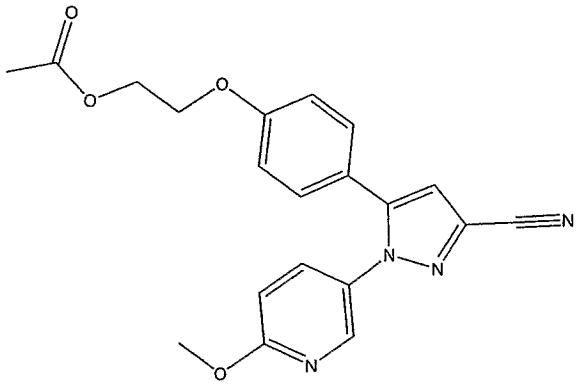
E0357 was prepared in a similar manner to that of E0356.

oil

Mass (ESI+) : 378 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.02(3H, s), 3.79(3H, s), 4.15-4.21(2H, m), 4.29-4.34(2H, m), 6.93-7.04(4H, m), 7.18(2H, d, J=8.8 Hz), 7.24-7.31(3H, m)

Example 358



(E0358)

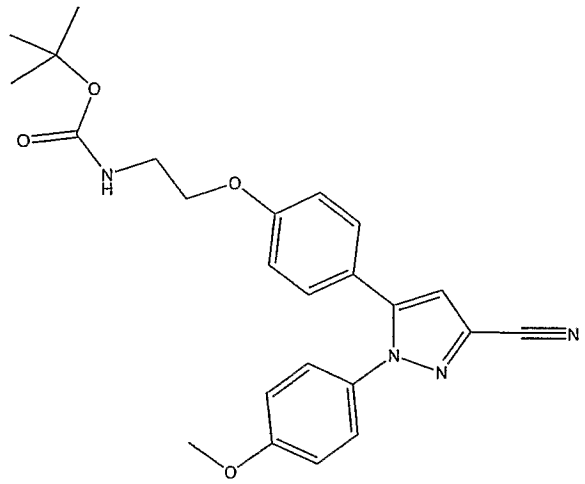
E0358 was prepared in a similar manner to that of E0356.

oil

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.02(3H, s), 3.88(3H, s), 4.17-4.21(2H, m), 4.29-4.34(2H, m), 6.90-7.03(3H, m), 7.22(2H, d, J=8.8 Hz), 7.36(1H, s), 7.74(1H, dd, J=2.7,8.9 Hz), 8.20(1H, d, J=2.7 Hz)

Example 359



(E0359)

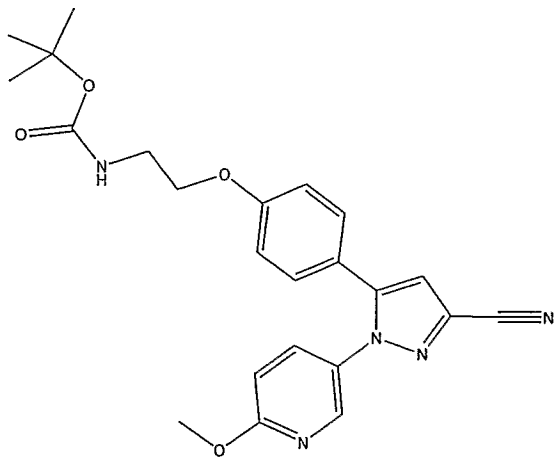
E0359 was prepared in a similar manner to that of E0356.

amorphous powder

Mass (ESI+) : 435 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :1.37(9H, s), 3.22-3.32(2H, m), 3.79(3H, s), 3.92-3.98(2H, m), 6.90-7.08(1H, br,overlapping), 6.92(2H, d, J=8.8 Hz), 7.00(2H, d, J=9.0 Hz), 7.16(2H, d, J=8.8 Hz), 7.28(2H, d, J=9.0 Hz), 7.30(1H, s)

Example 360



(E0360)

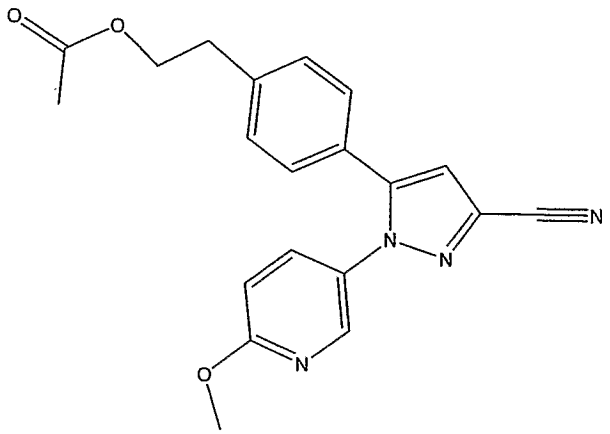
E0360 was prepared in a similar manner to that of E0356.

white powder

Mass (ESI+) : 436 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.88(3H, s), 3.93-3.99(2H, m), 6.90-7.01(1H, overlapping), 6.92(1H, d, J=8.8 Hz), 6.95(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.8 Hz), 7.34(1H, s), 7.73(1H, d, J=2.7,8.8 Hz), 8.20(1H, d, J=2.7 Hz)

Example 361



(E0361)

E0361 was prepared from E0345 in a similar manner to that of E0356.

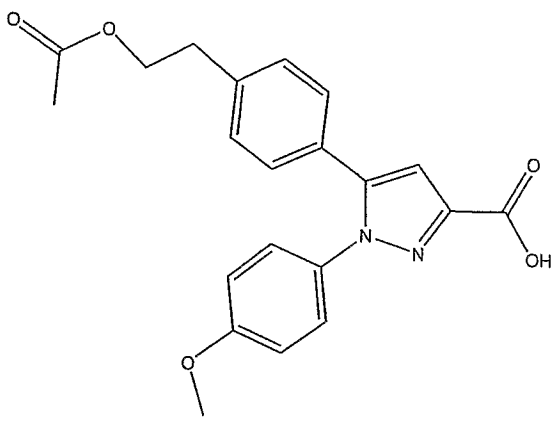
oil

Mass (ESI+) : 363 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

1.96(3H, s), 2.89(2H, t, J=6.8 Hz), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 6.92(1H, d, J=8.8 Hz), 7.22(2H, d, J=8.3 Hz), 7.30(2H, d, J=8.3 Hz), 7.41(1H, s), 7.75(1H, dd, J=8.8,2.7 Hz), 8.20(1H, d, J=2.7 Hz)

Example 362



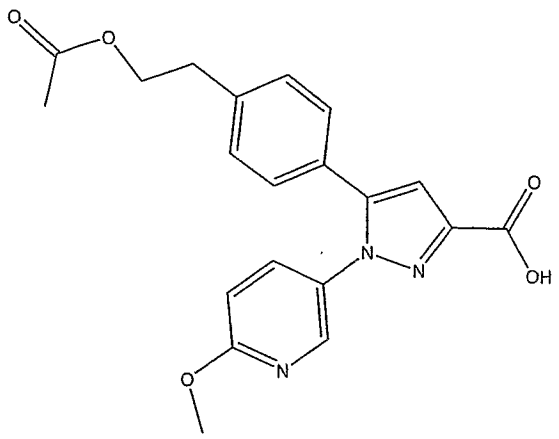
(E0362)

A solution of acetyl chloride 0.28ml in was added to a solution of E0261 (441.6mg) in CH2Cl2 4ml and pyridine 2ml under ice bath cooling. The reaction mixture was stirred at ambient temperature for 1hour. Acetyl chloride 0.14ml was added and stirred at ambient temperature for 1hour. The reaction was quenched by adding aqueous sodium bicarbonate solution and the mixture was stirred at ambient temperature overnight. The mixture was acidified to pH 2 by 6M HCl and extracted with ethyl acetate. The organic layer was washed with H2O and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give E0362 (405.3mg) as a white powder.

Mass (ESI+) : 381(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 3.79(3H, s), 4.20(2H, t, J=6.8 Hz), 6.96-7.02(3H, m), 7.15-7.27(6H, m), 12.91(1H, br)

Example 363



(E0363)

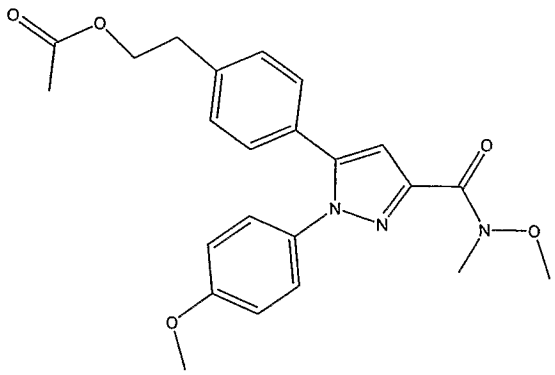
E0363 was prepared in a similar manner to that of E0362.

oil

Mass (ESI+) : 382 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.04(3H, s), 2.94(2H, t, J=7.0 Hz), 3.95(3H, s), 4.29(2H, t, J=7.0 Hz), 6.76(1H, d, J=8.8 Hz), 7.08(1H, s), 7.04-7.35(4H, m), 7.59(1H, dd, J=2.7,8.8 Hz), 8.12(1H, d, J=2.7 Hz)

Example 364



(E0364)

Oxalyl chloride 264mg was added to a suspension of E0362 (395mg) in CH2Cl2 5ml under ice bath cooling. DMF 1drop was added and the mixture was stirred at ambient temperature for 1hour.

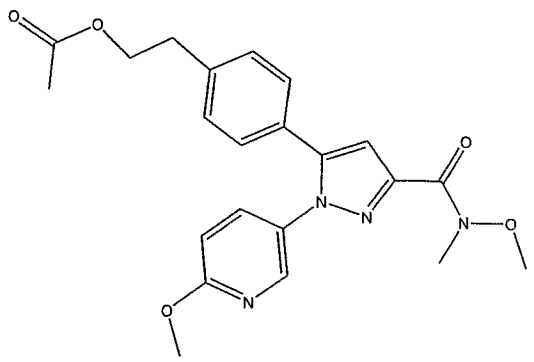
The mixture was concentrated in vacuo. To the residue was added toluene, and concentrated in vacuo. The residue was

dissolved in CH2Cl2 30ml, cooled in an ice bath, N,O-dimethylhydroxylamine hydrochloride 203mg and triethylamine 525mg were added and the mixture was stirred at ambient temperature overnight. The mixture was diluted with AcOEt, washed successively with 1M HCl, aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with CHCl3, then AcOEt / CHCl3= 10%, 20% to give E0364 (418.4mg) as an oil.

Mass (ESI+) : 424 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.97(3H, s), 2.88(2H, t, J=6.8 Hz), 3.38(3H, s), 3.77(3H, s), 3.78(3H, s), 4.20(2H, t, J=6.8 Hz), 6.94-7.03(3H, m), 7.16-7.27(6H, m)

Example 365



(E0365)

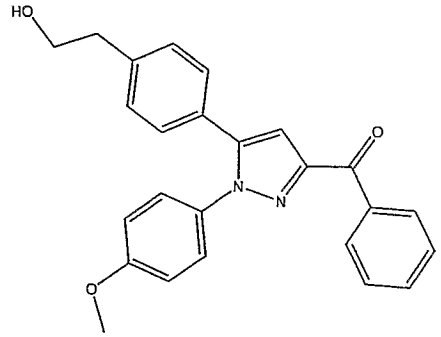
E0365 was prepared from E0363 and N,O-dimethylhydroxylamine hydrochloride in a similar manner to that of E0364.

oil

Mass (ESI+) : 425 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.97(3H, s), 2.89(2H, t, J=6.8 Hz), 3.37(3H, s), 3.77(3H, s), 3.88(3H, s), 4.21(2H, t, J=6.8 Hz), 6.91(1H, d, J=8.8 Hz), 6.98(1H, s), 7.20-7.33(4H, m), 7.70(1H, dd, J=2.8,8.8 Hz), 8.15(1H, d, J=2.8 Hz)

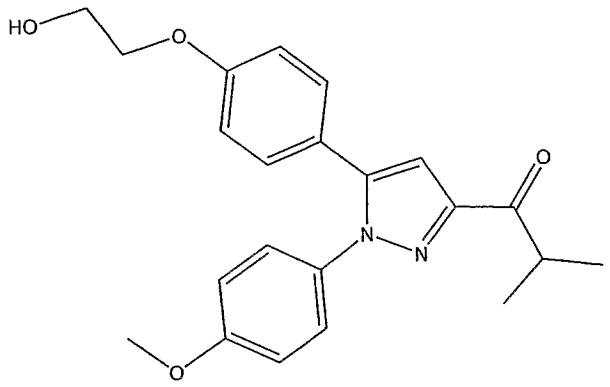
Example 366



(E0366)

To a solution of 1.0M phenylmagnesium bromide in THF 3.4ml was added a solution of E0364 (106.5mg) in THF 2ml under ice bath cooling. After stirring at same temperature for 1hour, the mixture was poured into sat.aqNH4Cl, and extracted with AcOEt. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30%, 40%, 50% to give E0366 (107mg)as an oil.
IR (neat) : 3469, 3435, 3425, 3406, 3398, 3369, 2937, 1647, 1606, 1512cm-1
Mass (ESI+) : 399 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.72(2H, t, J=6.9 Hz), 3.56-3.66(2H, m), 3.80(3H, s), 4.65(1H, t, J=5.1Hz), 7.02(2H, d, J=8.9 Hz), 7.20(1H, s), 7.22(4H, s), 7.34(2H, d, J=8.9 Hz), 7.52-7.68(3H, m), 8.25(2H, d, J=8.5 Hz)

Example 367



(E0367)

E0367 was prepared in a similar manner to that of E0366.

white powder

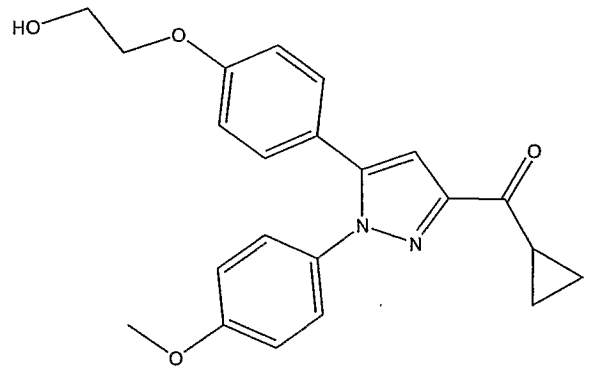
mp. 95-96°C

IR (KBr) : 3498, 3476, 2966, 1678, 1649, 1612, 1547, 1512cm-1

Mass (ESI+) : 381 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.8 Hz), 3.61-3.75(3H, m), 3.79(3H, s), 3.95-4.00(2H, m), 4.87(1H, t, J=5.3 Hz), 6.91(2H, d, J=8.7 Hz), 6.98(1H, s), 7.00(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 368



(E0368)

E0368 was prepared in a similar manner to that of E0366.

white powder

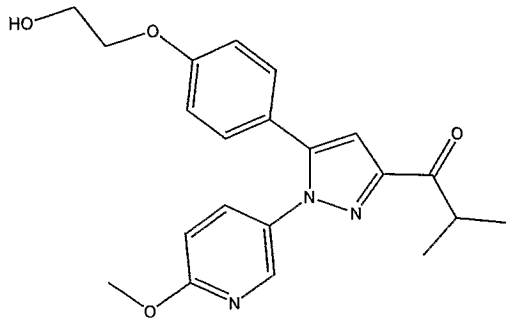
mp.132-133 °C

IR (KBr) : 3390, 3334, 3288, 1707, 1670, 1612, 1564, 1549, 1512cm-1

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 3.03(1H, m), 3.65-3.73(2H, m), 3.80(3H, s), 3.95-4.00(2H, m), 4.87(1H, t, J=5.4 Hz), 6.92(2H, d, J=8.7 Hz), 6.96(1H, s), 7.01(2H, d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.31(2H, d, J=8.9 Hz)

Example 369



(E0369)

E0369 was prepared in a similar manner to that of E0366.

white powder

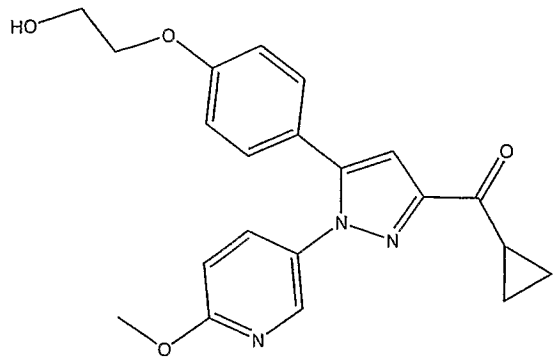
mp. 108-109°C

IR (KBr) : 3440, 2966, 1678, 1610, 1566, 1549, 1533, 1502cm-1

Mass (ESI+) : 382 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 3.64-3.74(3H, m), 3.88(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(1H, d, J=8.9 Hz), 6.94(2H, d, J=8.7 Hz), 7.02(1H, s), 7.21(2H, d, J=8.7 Hz), 7.74(1H, dd, J=2.7,8.9 Hz), 8.18(1H, d, J=2.7 Hz)

Example 370



(E0370)

E0370 was prepared in a similar manner to that of E0368.

white powder

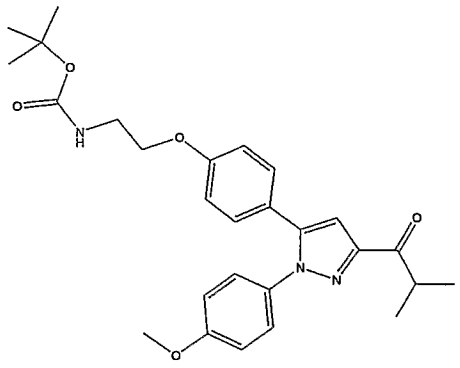
mp. 104-106°C

IR (KBr) : 3367, 2947, 1668, 1610, 1566, 1549, 1531cm-1

Mass (ESI+) : 380 (M+H)+

2500MHz 1H NMR (DMSO-d6, d) : 1.05(4H, d, J=6.2 Hz), 3.04(1H, m), 3.65-3.73(2H, m), 3.89(3H, s), 3.96-4.02(2H, m), 4.87(1H, t, J=5.4 Hz), 6.93(1H, d, J=8.8 Hz), 6.95(2H, d, J=8.8 Hz), 7.06(1H, s), 7.22(2H, d, J=8.8 Hz), 7.76(1H, dd, J=2.6,8.8 Hz), 8.21(1H, d, J=2.6 Hz)

Example 371



(E0371)

E0371 was prepared in a similar manner to that of E0366.

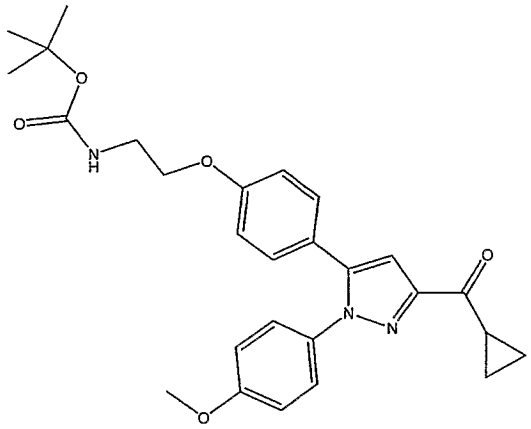
white powder

Mass (ESI+) : 480 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.15(6H, d, J=6.9 Hz), 1.37(9H,

s), 3.25-3.33(2H, m), 3.68(1H, m), 3.79(3H, s), 3.91-3.98(2H, m), 6.90(2H, d, J=8.7 Hz), 6.90-7.05(1H, overlapping), 6.97(1H, s), 7.00(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz)

Example 372



(E0372)

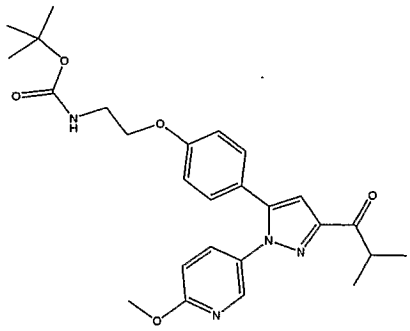
E0372 was prepared in a similar manner to that of E0368.

white powder

Mass (ESI+) : 477 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.04(4H, d, J=6.2 Hz), 1.37(9H, s), 3.04(1H, m), 3.22-3.33(2H, m), 3.80(3H, s), 3.95(2H, t, J=5.7 Hz), 6.88-7.03(1H, overlapping), 6.91(2H, d, J=8.7 Hz), 6.97(1H, s), 7.01(2H, d, J=8.9 Hz), 7.18(2H, d, J=8.7 Hz), 7.31(2H, d, J=8.9 Hz)

Example 373



(E0373)

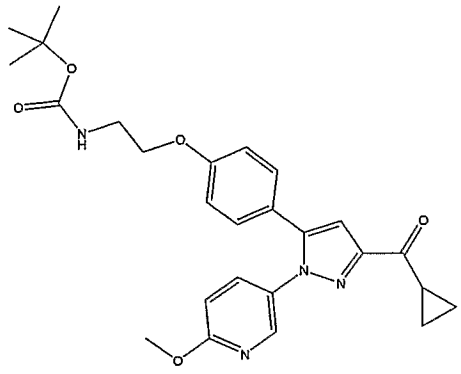
E0373 was prepared in a similar manner to that of E0366.

white powder

Mass (ESI+) : 481 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 1.37(9H, s), 3.22-3.32(2H, m), 3.68(1H, m), 3.88(3H, s), 3.93-3.99(2H, m), 6.90-7.02(5H, m), 7.22(2H, d, J=8.7 Hz), 7.73(1H, dd, J=2.7,8.8 Hz), 8.18(1H, d, J=2.7 Hz)

Example 374



(E0374)

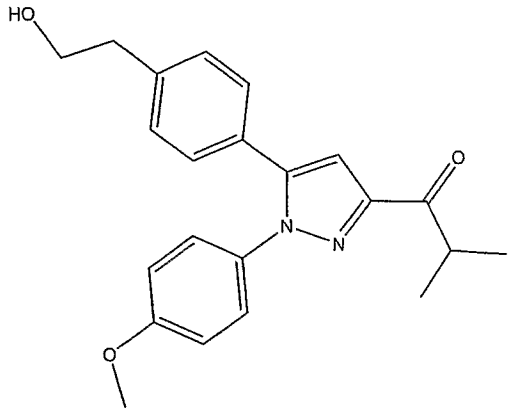
E0374 was prepared in a similar manner to that of E0368.

white powder

Mass (ESI+) : 479 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.05(4H, d, J=6.2 Hz), 1.37(9H, s), 3.04(1H, m), 3.23-3.33(2H, m), 3.89(3H, s), 3.93-3.99(2H, m), 6.89-7.08(5H, m), 7.22(2H, d, J=8.7 Hz), 7.76(1H, dd, J=2.7,8.8 Hz), 8.21(1H, d, J=2.7 Hz)

Example 375



(E0375)

E0375 was prepared from E0364 in a similar manner to that of E0366.

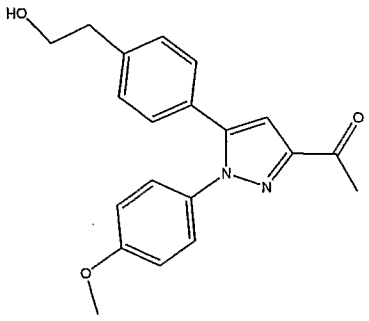
oil

IR (neat) : 3487, 3469, 3435, 3408, 3398, 3369, 2966, 2933, 1678, 1512cm-1

Mass (ESI+) : 365 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.19(6H, d, J=7.9 Hz), 2.70(2H, t, J=6.9 Hz), 3.54-3.75(3H, m), 3.79(3H, s), 4.64(1H, t, J=5.1 Hz), 7.00(2H, d, J=8.9 Hz), 7.02(1H, s), 7.16(2H, d, J=8.6 Hz), 7.21(2H, d, J=8.6 Hz), 7.29(2H, d, J=8.9 Hz)

Example 376



(E0376)

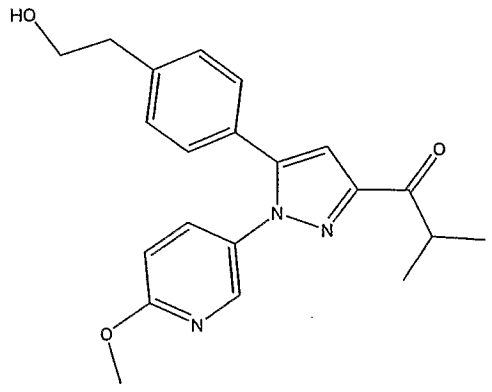
To a solution of 1.0M methylmagnesium bromide in diethyl ether 2.8ml was added a solution of E0364 (237.6mg) in THF 4ml dropwise under ice bath cooling. After stirring at same temperature for 30minues the mixture was poured into

sat.aqNH4Cl, and extracted with AcOEt. The organic layer was washed successively with a mixture of 1M HCl and saturated aqueous sodium chloride solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo.The residue was dissolved in THF1ml, 1M NaOH 0.4ml was added and the mixture was stirred at ambient temperature for several hours. The mixture was neutralized with 1M HCl 0.4ml, and partitioned between AcOEt and saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 50% to give E0376 (139.1mg) as a white powder.

Mass (ESI+) : 337 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.54(3H, s), 2.70(2H, t, J=6.9 Hz), 3.55-3.64(2H, m), 3.80(3H, s), 4.65(1H, t, J=5.1 Hz), 7.00(2H, d, J=8.9 Hz), 7.01(1H, s), 7.15(2H, d, J=8.5 Hz), 7.21(2H, d, J=8.5 Hz), 7.29(2H, d, J=8.9 Hz)

Example 377



(E0377)

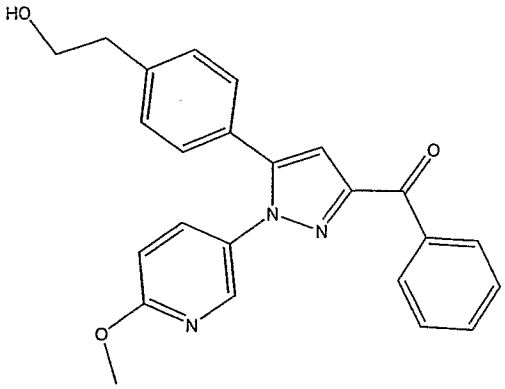
E0377 was prepared in a similar manner to that of E0376.

oil

Mass (ESI+) : 366 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.16(6H, d, J=6.9 Hz), 2.72(2H, t, J=6.9 Hz), 3.55-3.75(3H, m), 3.88(3H, s), 4.65(1H, t, J=5.1 Hz), 6.93(1H, d, J=8.8 Hz), 7.05(1H, s), 7.17-7.29(4H, m), 7.76(1H, dd, J=8.8,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

Example 378



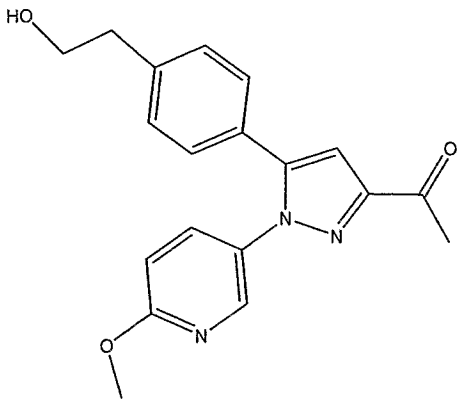
(E0378)

E0378 was prepared in a similar manner to that of E0376.

oil

200MHz 1H NMR (DMSO-d6, d) : 2.73(2H, t, J=6.9 Hz), 3.57-3.66(2H, m), 3.89(3H, s), 4.66(1H, t, J=5.0 Hz), 6.94(1H, d, J=8.8 Hz), 7.23(1H, s), 7.15-7.35(4H, m), 7.52-7.72(3H, m), 7.80(1H, dd, J=2.7,8.8 Hz), 8.23-8.32(3H, m)

Example 379



(E0379)

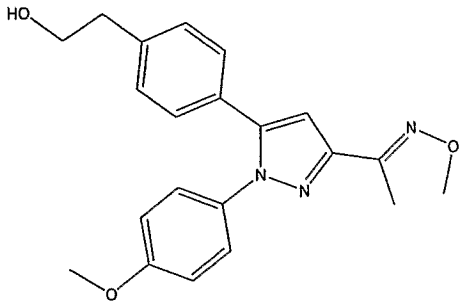
E0379 was prepared in a similar manner to that of E0376.

white powder

Mass (ESI+) : 338 (M+H)+

00MHz 1H NMR (DMSO-d6, d) : 2.55(3H, s), 2.71(2H, t, J=6.9 Hz), 3.55-3.65(2H, m), 3.89(3H, s), 4.65(1H, t, J=5.1 Hz), 6.93(1H, d, J=8.8 Hz), 7.05(1H, s), 7.19(2H, d, J=8.6 Hz), 7.24(2H, d, J=8.6 Hz), 7.75(1H, dd, J=2.7,8.8 Hz), 8.19(1H, d, J=2.7 Hz)

Example 380



(E0380)

A mixture of E0376 (127mg), O-methylhydroxylamine hydrochloride 47.3mg and pyridine in EtOH 3ml was heated at 60°C for 1hour. The mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40%. The pure fraction was collected and concentrated in vacuo. The residue was crystallized from diisopropyl ether to give E0380 (103.2mg) as a white powder.

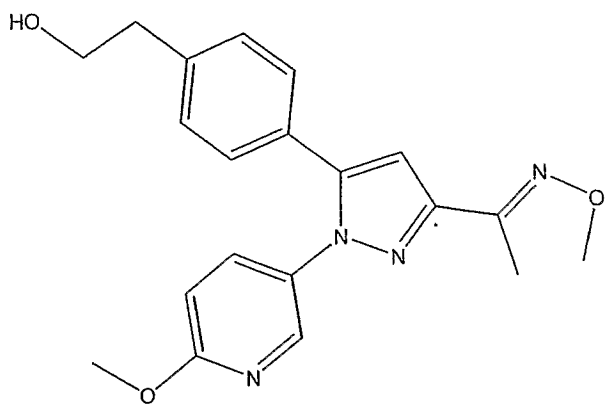
mp. 82-86°C

IR (KBr) : 3359, 3269, 3246, 2939, 1549, 1512cm-1

Mass (ESI+) : 366(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.20(3H, s), 2.70(2H, t, J=6.9 Hz), 3.54-3.65(2H, m), 3.78(3H, s), 3.92(3H, s), 4.65(1H, t, J=5.0 Hz), 6.77(1H, s), 6.97(2H, d, J=8.9 Hz), 7.12-7.26(6H, m)

Example 381



(E0381)

E0381 was prepared in a similar manner to that of E0380.

white powder

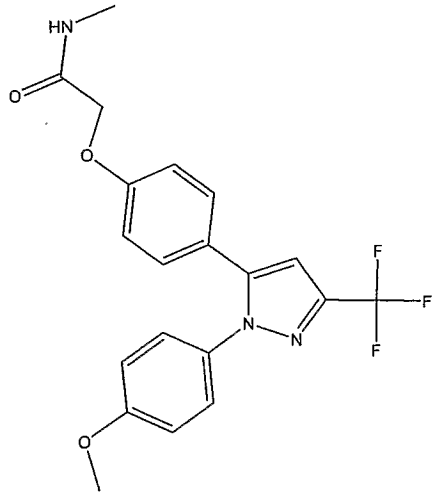
mp.94-95°C

IR (KBr) : 3469, 3433, 3423, 3404, 3400, 3371, 1647, 1549cm-1

Mass (ESI+) : 267(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.20(3H, s), 2.71(2H, t, J=6.8 Hz), 3.55-3.65(2H, m), 3.87(3H, s), 3.92(3H, s), 4.65(1H, t, J=5.0 Hz), 6.81(1H, s), 6.90(1H, d, J=8.8 Hz), 7.18(2H, d, J=8.7 Hz), 7.23(2H, d, J=8.7 Hz), 7.69(1H, dd, J=8.8,2.7 Hz), 8.11(1H, d, J=2.7 Hz)

Example 382



(E0382)

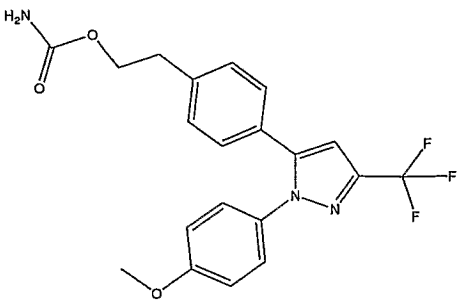
To a solution of E0314 (100 mg) in methanol (21 ml) was added a solution of methyl amine in methanol (40%, 92 ml). After stirring at room temperature overnight, the mixture was evaporated to give oil, which was purified with preparative TLC (1 mm, 60% ethyl acetate / hexane) to give E0382 as an oil (97 mg, 100%).

NMR(CDCl3), 2.92(3H, d, J=5.0 Hz), 3.83(3H, s), 4.49(2H, s), 6.69(1H, s), 6.82-6.91(4H, m), 7.14-7.24(4H, m).

MS(ESI+); 428.2(M+Na).

IR(Neat, 20727-11), 1693.2cm-1.

Example 383



(E0383)

Trichloroacetyl isocyanate 62.4mg was added to a solution of E0118 100mg in CH2Cl2 2ml under ice bath cooling. After stirring at ambient temperature for 3hours, the reaction mixture was concentrated in vacuo. The residue was dissolved in THF 1ml, MeOH 1ml, and H2O 1ml. Potassium carbonate 153mg was added to the reaction mixture, and stirred at ambient temperature overnight. The reaction mixture was partitioned between AcOEt and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual solid was recrystallized from AcOEt-n-hexane to give E0383 84.1mg as a white powder.

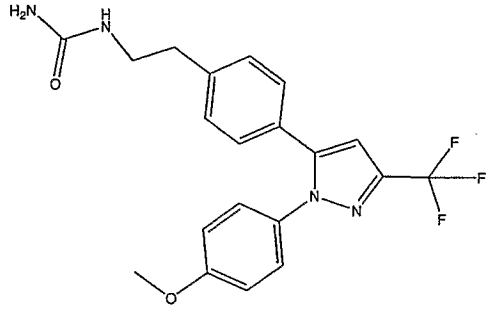
mp. 169-170°C

IR (KBr) : 3435, 3332, 3263, 3209, 1684, 1610, 1516cm-1

Mass (ESI+) : 406 (M+H)+

400MHz 1H NMR (DMSO-d6, d) : 2.84(2H, t, J=6.8 Hz), 3.79(3H, s), 4.10(2H, t, J=6.8 Hz), 6.30-6.70(2H, br), 7.00(2H, d, J=9.0 Hz), 7.14(1H, s), 7.21(2H, d, J=8.4 Hz), 7.26(2H, d, J=8.4 Hz), 7.29(2H, d, J=9.0 Hz)

Example 384



(E0384)

Trimethylsilyl isocyanate 42.7mg was added to a solution of E0158 98.2mg and triethylamine 30mg in CH2Cl2 1ml under ice bath cooling. The reaction mixture was stirred at same temperature for 1hour and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by MeOH / CHCl3 = 10%. The separated silica gel was extracted with 10% MeOH/CHCl3, filtered, and the solvent was evaporated in vacuo. The residue was crystallized from ethylacetate-diisopropyl ehter to give E0384 (59.7mg) as a white powder.

mp.157-158°C

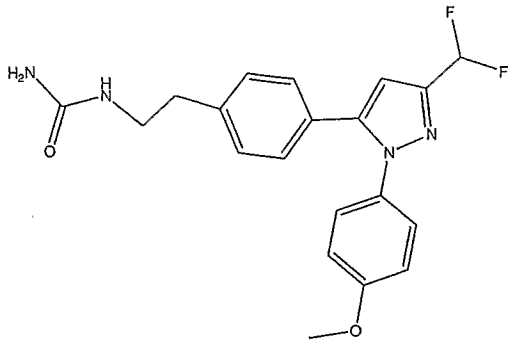
IR (KBr) : 3406, 3357, 3330, 3209, 1704, 1662, 1614, 1529, 1520cm-1

Mass (ESI+) : 405 (M+H)+

200MHz 1H NMR (DMSO-d6, d) NO06.067: 2.62-2.70(2H, m), 3.13-3.24(2H, m), 3.79(3H, s), 5.42(2H, s), 5.93(1H, t, J=5.4 Hz), 7.00(2H, d, J=8.8 Hz), 7.12(1H, s), 7.21(4H, s), 7.29(2H,

d, J=8.8 Hz)

Example 385

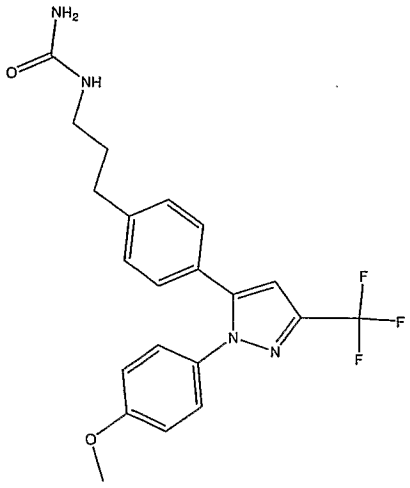


(E0385)

This compound was obtained according to a similar manner to that of E0384.

IR (film): 3343.9, 1656.6, 1604.5, 1550.5, 1515.8, 1457.9, 1342.2, 1251.6, 1029.8 cm-1.

Example 386

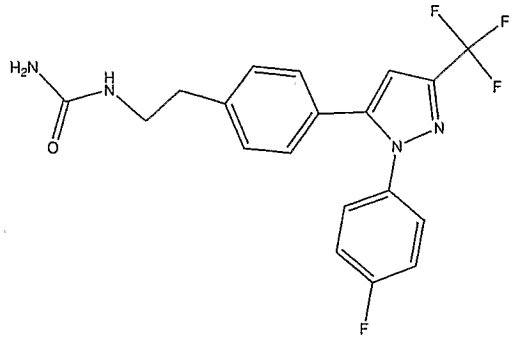


(E0386)

This compound was obtained according to a similar manner to that of E0384.

IR (film): 3345.9, 1654.6, 1604.5, 1556.3, 1513.9, 1465.6, 1240.0, 1160.9, 1132.0cm-1.

Example 387

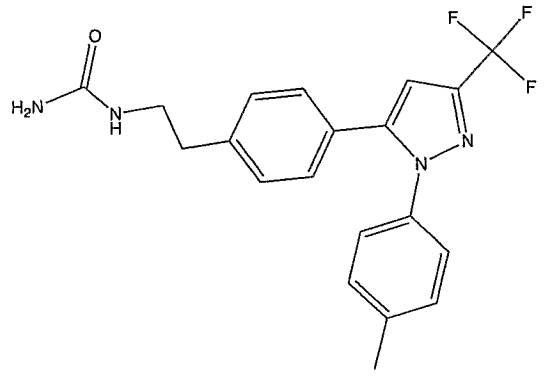


(E0387)

This compound was obtained according to a similar manner to that of E0384.

IR (film): 3345.9, 1658.5, 1602.6, 1552.4, 1236.2, 1159.0, 1133.9cm-1.

Example 388

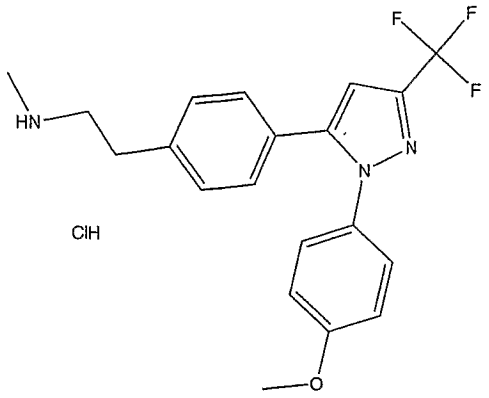


(E0388)

This compound was obtained according to a similar manner to that of E0384.

IR(film): 3345.9, 1658.5, 1602.6, 1552.4, 1517.7, 1236.2, 1159.0, 1133.9cm-1.

Example 389

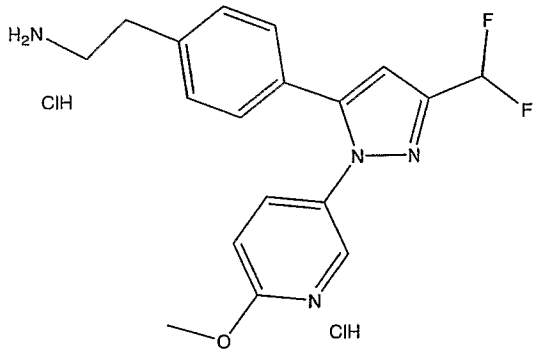


(E0389)

A mixture of E0175 (150mg) and 6ml of 4N HCl/dioxane was stirred at room temperature. After 2 hours, the reaction mixture was evaporated under reduced pressure to give 128mg (quant.) of E0389 as an oil.

IR(film): 3403.7, 1513.9, 1467.6, 1241.9, 1162.9, 1130.1cm-1.

Example 390

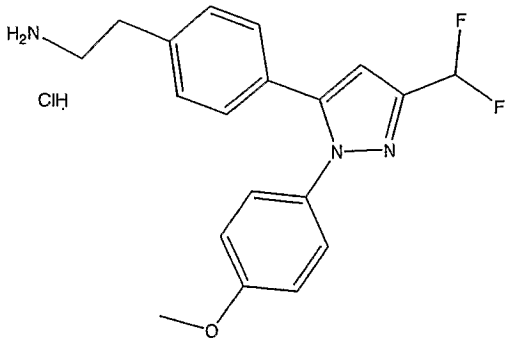


(E0390)

This compound was obtained according to a similar manner to that of E0389.

IR(film): 3428.8, 1662.34, 1612.2, 1500.4, 1461.8, 1390.4, 1292.1, 1166.7, 1087.7, 1029.8cm-1.

Example 391

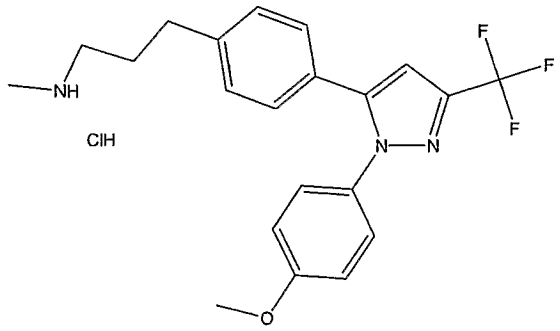


(E0391)

This compound was obtained according to a similar manner to that of E0389.

IR (film): 3403.74, 2965.98,1610.27, 1513.85, 1461.78, 1251.58, 1170.58, 1085.73, 1029.80, 836.955, 800.314 cm-1.

Example 392

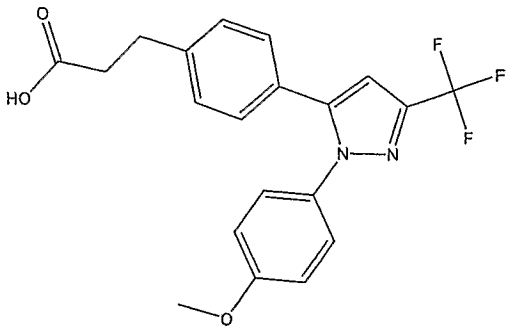


(E0392)

This compound was obtained according to a similar manner to that of E0389.

IR (film): 3432.7, 1511.9, 1467.6, 1240.0, 1160.9, 1130.1cm-1.

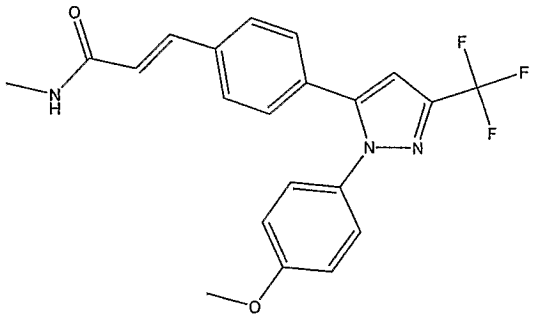
Example 393



(E0393)

A mixture of E0258 (100mg) and Pd/C (100mg) in EtOH (10m) was stirred under H2 atmosphere for 3.0 hours. After filtration, a filtrate was evaporated under reduced pressure. The resudue was dissolved in EtOH and filtered with syringe driven filter, and evaporated to give 93mg (93%) of E0393. IR (film):3019.9, 1704.8, 1513.9, 1303.6, 1238.1, 1133.9cm-1.

Example 394



(E0394)

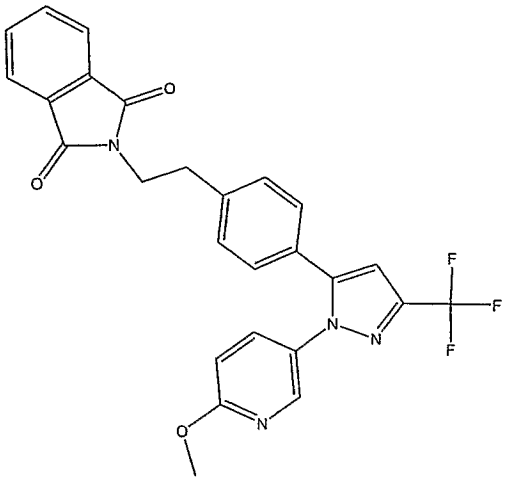
T a suspension of E0258 (200mg) in toluene (4ml) was added thionylchloride (0.19ml) at room temperature. The reaction mixture was stirred at 100°C for 5 hours until the mixture become clear solution. After then, the mixture was evaporated under reduced pressure. (become solid) THF was added, and then aqueous MeNH2 (37%) was added. The mixture was stirred for 1 hour, and quenched with water, and extracted twice with EtOAc. The combined organic layer was washed with sat.NaHCO3, water and brine, dried over

Na2SO4, filtered and evaporated under reduced pressure to give 63mg (31%) of E0394 as a powder.

mp: 155-157°C

IR(film) 3297.7, 1662.3, 1617.9, 1513.9, 1236.2, 1162.9, 1133.9cm-1

Example 395



(E0395)

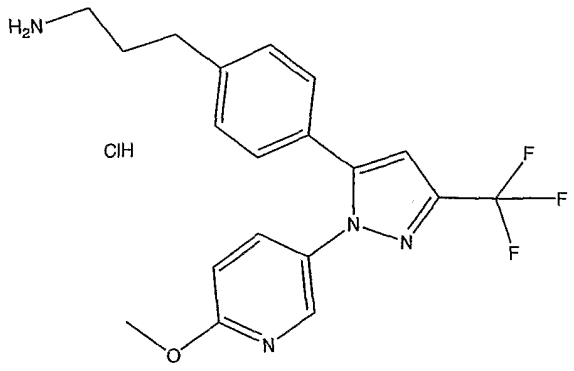
A suspension of E0399 (1.8 g) and potassium phtalimido (1.13 g) in N,N-dimethylformamide (6.6 ml) was stirred at 80°C for 3 hours. The mixture was added water (700 ml) and extracted with a mixture of ethyl acetate and hexane (2:1) (x4). The combined organic layers were washed with aqueous sodium hydroxide (1N) (x2) and brine, dried over magnesium sulfate, and evaporated to give oil, which was purified with column chromatography (SiO2 100 ml, eluted with 30% ethyl acetate/hexane) to give oil (1.83g, 91.1%). Ethanol (15 ml) was added to the oil, then the mixture was stirred at room temperature for 10 minutes. The precipitate was filtered, washed with ethanol (3 ml), and dried under reduced pressure to give E0395 as a white solid (1.16 g, 58%).

NMR(CDCl3), 3.00(2H, t, J=7.6 Hz), 3.93(2H, t, J=7.6 Hz), 3.94(3H, s), 6.73(1H, s), 6.73(1H, d, J=8.7 Hz), 7.13-7.26(4H,

m), 7.49(1H, dd, J=8.7, 2.5 Hz), 7.70-7.86(4H, m), 8.10(1H, d, J=2.5 Hz).

MS(ESI+), 515(M+Na).

Example 396



(E0396)

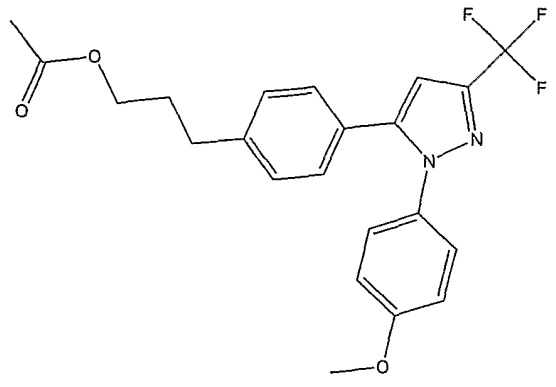
6M HCl 0.045ml was added to a solution of E0168 (101.5mg) in AcOEt 1ml and EtOH 1ml. The mixture was concentrated and dried in vacuo to give E0396 (94.8mg) as an amorphous powder.

IR (neat) : 3433, 3020, 2956, 1668, 1658, 1612, 1572, 1543, 1500cm-1

Mass (ESI+) : 377 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.76-1.92(2H, m), 2.52-2.81(4H, m), 3.88(3H, s), 6.93(1H, d, J=8.9 Hz), 7.19(1H, s), 7.26(4H, s), 7.76(1H, dd, J=8.9,2.7 Hz), 8.19(1H, d, J=2.7 Hz)

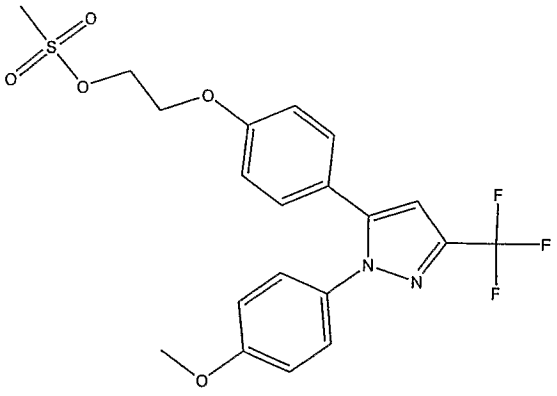
Example 397



(E0397)

To a mixture of P0002 (5.0g) and CF3COOEt (3.5ml) in DMF (30ml) was added NaH (1.1g) under ice-cooling. The reaction mixture was allowed to warm to room temperature, and stirred under 40oC for 1 hour. The reaction mixture was extracted twice with EtOAc. The organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue, sodium acetate (2.23g) and 4-methoxyphenylhydrazine (3.96g) in acetic acid (20ml) was stirred at room temperature for 15 hours. The mixture was extracted twice with ethyl acetate. The combined organic layer was washed with water (twice), sat.NaHCO3, water and brine, dried over MgSO4, filtered and evaporated under reduced pressure. The residue was column chromatographed on silica gel (Hex/EtOAc = 8:1-4:1) to give 2.58g (36%) of E0397 as an oil.

Example 398



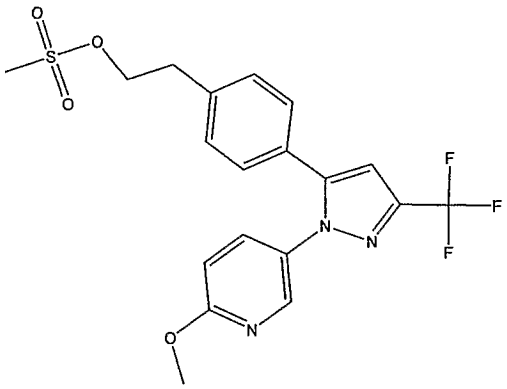
(E0398)

To a solution of E0312 (326.7 mg) in ethyl acetate (3 ml) was added methanesulfonyl chloride (86.9 ml) and triethylamine (0.181 ml) at 0°C. After stirring for 40 minutes at 0°C, the mixture was quenched with water and extracted with ethyl acetate (x3). The combined organic layers were washed with water and brine, dried over sodium

sulfate, and evaporated under reduced pressure to give E0398 as an oil (351.3 mg, 89%).

NMR(CDCl3); 3.09(3H, s), 3.82(3H, s), 4.22-4.26(2H, m), 4.52-4.59(2H, m), 6.68(1H, s), 6.75(2H, d, J=8.7 Hz), 6.87(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.22(2H, d, J=8.9 Hz).

Example 399



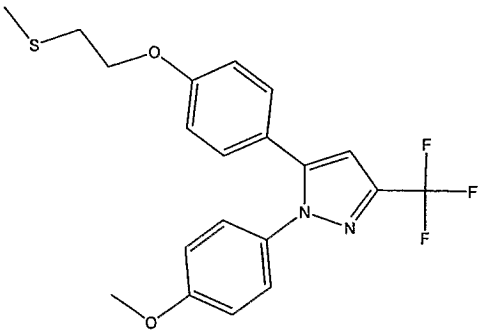
(E0399)

This compound was obtained according to a similar manner to that of E0398 as a pale yellow oil (1.82 g, 98.6%).

NMR(CDCl3), 2.91(3H, s), 3.07(2H, t, J=6.8 Hz), 3.94(3H, s), 4.43(2H, t, J=6.8 Hz), 6.75(1H, s), 6.78(1H, d, J=8.2 Hz), 7.17-7.26(4H, m), 7.58(1H, dd, J=9.0, 2.9 Hz), 8.05(1H, d, J=2.8 Hz).

MS(ESI+), 442.1(MH+), 464.0(M+Na).

Example 400

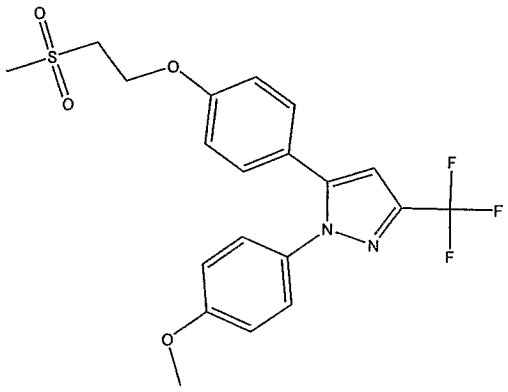


(E0400)

A suspension of E0398 (351.3 mg) and sodium thiomethoxide

(162 mg) in N,N-dimethylformamide (3 ml) was stirred at 60°C for 3.5 hours. The mixture was quenched with water and extracted with ethyl acetate (x3). The combined organic layers were washed with water and brine, dried over magnesium sulfate, and evaporated to give oil. The oil was purified with column chromatography (SiO2 50 ml, eluted with 10% ethyl acetate / hexane) to give E0400 as an oil (236.7 mg, 75.3%).
NMR(CDCl3); 2.24(3H, s), 2.88(2H, t, J=6.6 Hz), 3.82(3H, s), 4.15(2H, t, J=6.6 Hz), 6.67(1H, s), 6.83(2H, d, J=8.8 Hz), 6.88(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.8 Hz), 7.23(2H, d, J=9.0 Hz).
MS(ESI+);431(M+Na).

Example 401



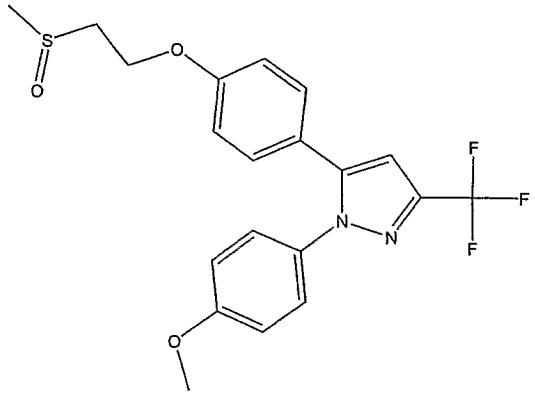
(E0401)

To a solution of E0400 (103.5 mg) in dichloromethane (1 ml) was added m-chloroperbenzoic acid (134 mg) at room temperature. After stirring at room temperature for 1 hour, the mixture was added saturated sodium hydrogen sulfate aqueous solution (0.5 ml) and sodium thiosulfate pentahydrate (100 mg), and stirred for 30 minutes at room temperature. The mixture was filtered by Chemelut 1001(Varian) and evaporated to give oil, which was purified with preparative TLC (1 mm, 50% ethyl acetate/hexane) to give E0401 as an amorphous (105.9 mg, 94.9%).

NMR(CDCl3);3.07(3H, s), 3.45(2H, t, J=5.3 Hz), 4.44(2H, t, J=5.3 Hz), 3.83(3H, s), 6.69(1H, s), 6.69-6.90(4H, m), 7.15-7.26(4H, m).

MS(ESI+); 463.1 (M+Na)+. IR(KBr, 20727-8), 1612.2, 1515.8cm-1.

Example 402



(E0402)

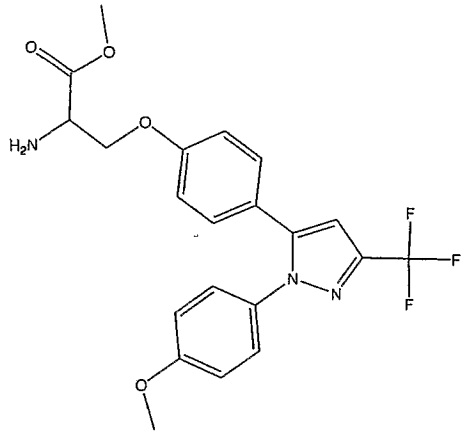
To a solution of E0400 (104.8 mg) in dichloromethane (1 ml) was added m-chloroperbenzoic acid (44.7 mg) at 0°C, and the mixture was stirred at 0°C for 1 hour. Then m-chloroperbenzoic acid (35 mg) was added to the mixture. After stirring at 0°C for 30 minutes, the mixture was quenched with saturated sodium hydrogen sulfate aqueous solution (0.5 ml) and sodium thiosulfate pentahydrate (100 mg), and stirred for 30 minutes at room temperature. The mixture was filtered by Chemelut 1001(Varian) and evaporated to give oil, which was purified with preparative TLC (1 mm, ethyl acetate) to give 2 fractions of E0401 (TLC upper) as an amorphous (40.7 mg, 37.4%) and E0402 (TLC lower) as a powder (60 mg, 55%).

NMR(CDCl3); 2.70(3H, s), 2.99-3.27(2H, m), 3.83(3H, s), 4.40-4.46(2H, m), 6.68(1H, s), 6.84-6.90(4H, m), 7.15(2H, d, J=8.7 Hz), 7.22(2H, d, J=9.0 Hz).

MS(ESI+); 447.1 (M+Na).

IR(KBr); 1612.2, 1513.9cm-1.

Example 403



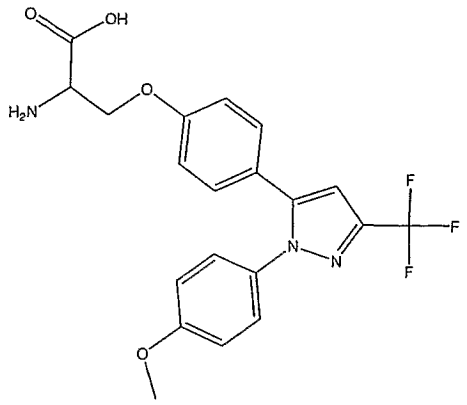
(E0403)

To a solution of E0286 (500 mg) in dichloromethane (1.5 ml) was added successively anisol (0.5 ml) and triflutoroacetic acid (1 ml). After stirring at room temperature for 2 hours, the mixture was quenched with saturated sodium hydrogen carbonate aqueous solution and extracted with ethyl acetate (x3). The organic layers were dried over magnesium sulfate and evaporated to give oil, which was purified with column chromatography (SiO2 50 ml, eluted with ethyl acetate) to give E0403 as an oil (302.5 mg, 94.2%).

NMR(CDCl3), 3.77(3H, s), 3.80(3H, s), 3.80-3.87(1H, m), 4.21-4.28(2H, m), 6.67(1H, s), 6.80-6.89(4H, m), 7.13(2H, d, J=8.7 Hz), 7.22(2H, d, J=8.9 Hz).

MS(ESI+), 436.1(MH+).

Example 404



(E0404)

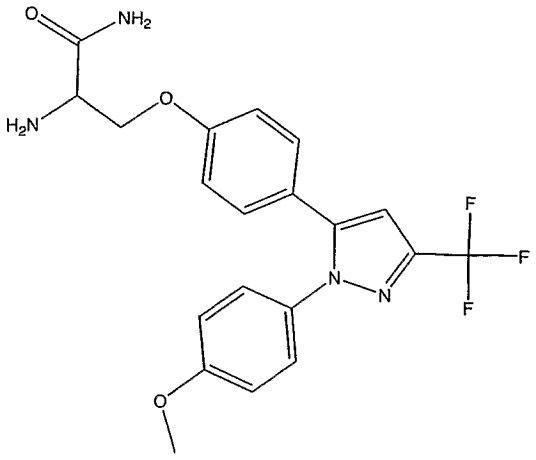
A solution of E0403 (104.6 mg) in methanol (3 ml) and sodium hydroxide aqueous solution (1N, 2 ml) was stirred at room temperature for 3 hours. The mixture was evaporated, and methanol was added to the residue and evaporated to give white powder, which was purified with preparative TLC (1 mm, 20%methanol/chloroform) to give E0404 as a powder (29.9 mg, 29.5%).

NMR(DMSO-d6), 3.50-3.54(1H, m), 3.79(3H, s), 4.13-4.30(2H, m), 6.91-7.07(5H, m), 7.21(2H, d, J=8.7 Hz), 7.27(2H, d, J=8.9 Hz).

MS(ESI-).420.4(M-H).

IR(KBr), 1641, 1616cm-1.

Example 405



(E0405)

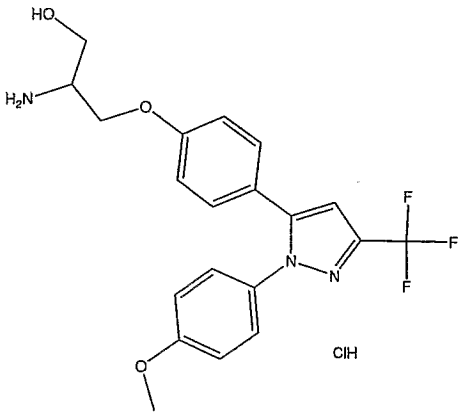
To a solution of E0403 (106.6 mg) in methanol (2 ml) was added concentrated ammonia solution (1 ml). After stirring at room temperature overnight, the mixture was evaporated to give solid, which was purified with preparative TLC (1 mm, 20%methanol/chloroform) to give E0405 as a solid (58.2 mg, 56.5%).

NMR(CDCl3), 3.75-3.82(1H, m), 3.82(3H, s), 4.15-4.29(2H, m), 6.67(1H, s), 6.83-6.91(4H, m), 7.14(2H, d, J=6.7 Hz), 7.22(2H, d, J=9.0 Hz).

MS(ESI+).421.4(MH+), 462.4(MHMeCN)+.

IR(KBr), 1658 cm-1.

Example 406



(E0406)

To a solution of E0403 (87.5 mg) in tetrahydrofuran (1 ml) was added lithium aluminum hydride (30.5 mg) at room temperature. After stirring at room temperature for 2 hours, the mixture was quenched with water (30 ml), sodium hydroxide aqueous solution (15%, 30 ml), and water (90 ml), and then stirred at room temperature for 30 minutes. Magnesium sulfate and celite was added to the mixture, then the suspension was filtered and washed with tetrahydrofuran.

The filtrate was evaporated to give oil, which was purified

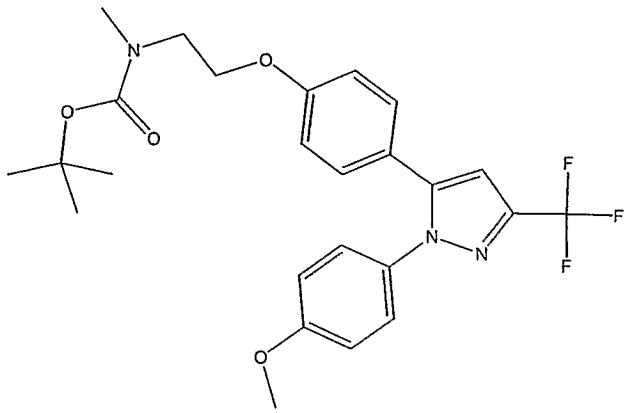
with preparative TLC (0.5 mm, 20%methanol/chloroform) to give oil.

To a solution of the oil in ethyl acetate was added a solution of hydrogen chloride in ethyl acetate (4N, 0.5 ml), and then the mixture was evaporated to give E0406 as an oil (43.5 mg, 49%).

NMR(CDCl3), 3.64-4.13(5H, m), 3.76(3H, s), 6.60(1H, s), 6.73-6.85(4H, m), 7.07(2H, d, J=8.5 Hz), 7.16(2H, d, J=8.9 Hz).

MS(ESI+), 408.1(MH+)(Free). IR(Neat, 20727-5), 1614.1cm-1.

Example 407



(E0407)

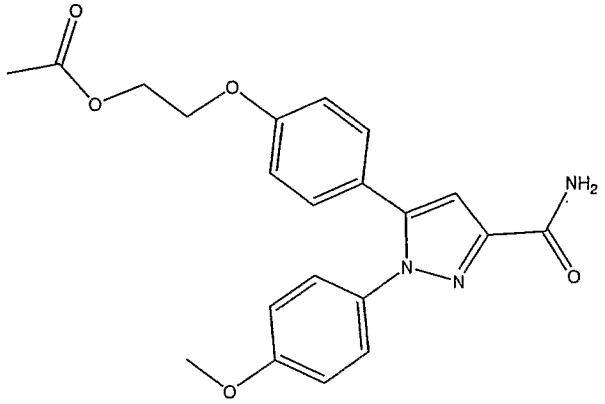
To a suspension of sodium hydride (34.8 mg) in terahydrofuran (2 ml) was added a solution of E0347 (208 mg) in tetrahydrofuran (1 ml) at 0□, and then the mixture was stirred at room temperature for 20 minutes. Then iodomethane (54.2 ml) was added to the mixture. After stirring at room temperature overnight, the mixture was quenched with water, extracted with ethyl acetate (x3). The combined organic layers were washed with water (x3) and brine, dried over magnesium sulfate, and evaporated under reduced pressure to give oil, which was purified with preparative TLC (1 mm, 30% ethyl acetate/hexane) to give E0407 as an oil (160 mg,

74.7%).

NMR(CDCl3), 1.45(9H, s), 2.97(3H, s), 3.59(2H, t, J=5.5 Hz), 3.82(3H, s), 4.0-4.15(2H, m), 6.67(1H, s), 6.80-6.91(4H, m), 7.13(2H, d, J=8.8 Hz), 7.23(2H, d, J=9.0 Hz).

MS(ESI+).514.2(M+Na).

Example 408



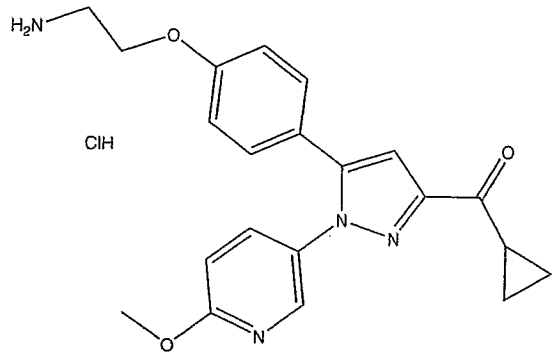
(E0408)

AcCl 0.31ml was added to a suspension of E0347 (1.29g) and Et3N 0.66ml in CH2Cl2 10ml under ice bath cooling. The mixture was stirred at ambient temperature for 2hours. AcCl 0.31ml and Et3N 0.66ml was added and stirred at ambient temperature for 3hours. To this mixture was added H2O and stirred at ambient temperature for a while. White precipitates were appeared, which was collected and washed with H2O and diisopropyl ether to give E0408 (879.3mg) as a white powder.

Mass (ESI+) : 396(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.03(3H, s), 3.78(3H, s), 4.15-4.19(2H, m), 4.29-4.33(2H, m), 6.89(1H, s), 6.93(2H, d, J=8.8 Hz), 6.98(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 7.26(2H, d, J=8.9 Hz), 7.32(1H, s), 7.63(1H, s)

Example 409



(E0409)

To a solution of E0374 (61.4mg) in CH2Cl2 2ml was added trimethylsilyl trifluoromethanesulfonate 85.6mg at 0°C, followed by an addition of triethylamine 39mg. The mixture was stirred at 0°C for 30minutes, and partitioned between AcOEt and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 28% NH3aq : MeOH : CHCl3 =1:10:100. The separated silica gel was extracted with 28% NH3aq : MeOH : CHCl3 =1:10:100 and the solvent was evaporated in vacuo. The residu was dried under vacuo and then dissolved in EtOH 3ml. To this solution was added 1M HCl 0.0892ml and concentrated in vacuo. The residue was dried under vacuo to give E0409 (37mg) as an amorphous powder.

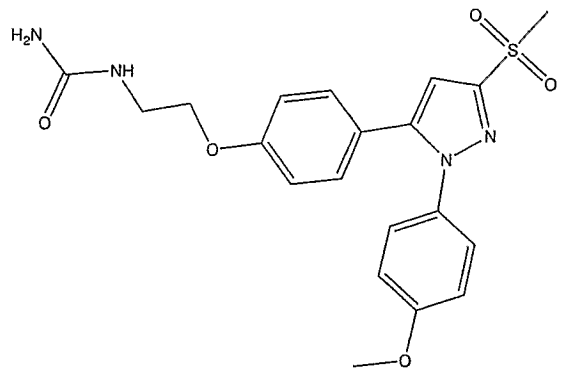
IR (KBr) : 2958, 1668, 1662, 1612, 1581, 1568, 1549, 1531, 1500cm-1

Mass (ESI+) : 379 (M+H)+

200MHz 1H NMR

1.05(4H, d, J=6.2Hz), 3.04(1H, m), 3.15-3.24(2H, m), 3.89(3H, s), 4.16-4.22(2H, m), 6.94(1H, d, J=8.8 Hz), 7.00(2H, d, J=8.7 Hz), 7.02(1H, s), 7.27(2H, d, J=8.7 Hz), 7.78(1H, dd, J=2.7,8.8 Hz), 8.14(2H, brs), 8.21(1H, d, J=2.7 Hz)

Example 410



(E0410)

To a solution of 2-{4-[1-(4-methoxyphenyl)-3-(methylsulfonyl)-1H-pyrazol-5-yl]phenoxy}ethanamine (133mg,0.342mmol) in methylene chloride(5ml) was added trimethylsilyl isocyanate (118mg,1.03mmol) and triethylamine(1.39mg,1.37mmol) at ambient temperature and stirred for two days. The reaction mixture was washed with water and brine, dried over magnesium sulfate, filtered and evaporated. Purification by column chromatography (silica gel, methylene chloride/methanol =20/1) followed by recrystallization from ethyl acetate gave 102 mg (69%) of E0410 as white crystals.

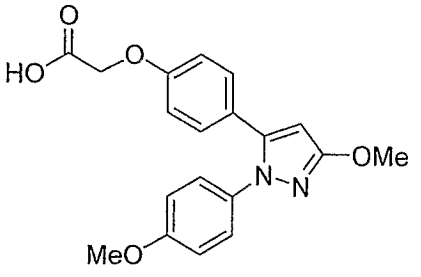
mp.165-167°C

Mass;431(M+1)

IR(KBr);1650,1310CM-1

NMR(DMSO-d6,δ); 3.32(2H, q, J=5.5 Hz), 3.33(3H, s), 3.79(3H, s), 3.94(2H, t, J=5.5 Hz), 5.52(2H, s), 6.14(1H, t, J=5.5 Hz), 6.94(2H, d, J=8.7 Hz), 7.01(2H, d, J=8.9 Hz), 7.11(1H, s), 7.20(2H, d, J=8.7 Hz), 7.28(2H, d, J=8.9 Hz),

Example 411



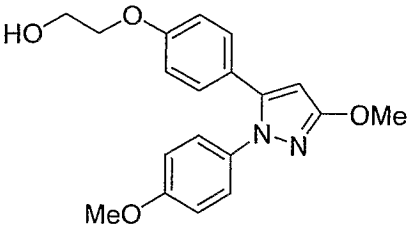
(E0411)

A solution of P0034 64mg in DMF 1ml was added 60% NaH 11.4mg at 4°C and the mixture was stirred at same temperature for 30minutes. To the mixture was added bromoacetic acid 33mg and the mixture was stirred at ambient temperature for 2hours. The reaction was quenched by adding 1M HCl 2ml, and the mixture was extracted with AcOEt. The organic layer was washed with H2O, sat.aqNaCl, dried over MgSO4, concentrated in vacuo to give E0411 (73mg) as crystals.

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.79(3H, s), 3.96(3H, s), 4.63(2H, s), 5.88(1H, s), 6.82(4H, d, J=9.0 Hz), 7.14(2H, d, J=9.0 Hz), 7.17(2H, d, J=9.0 Hz)

Example 412



(E0412)

Boron trifluoride diethyl etherate 137mg was added to a suspension of sodium borohydride 29.3mg in THF 3ml with cooling in an ice bath, and the mixture was stirred at same temperature for 30minutes. To the reaction mixture was added E0411 (137mg) in THF 3ml in one portion and the mixture was

stirred at ambient temperature for 4hours. The reacion was quenched by adding ice water containing 1M HCl 1ml, and the mixture was stirred at ambient temperature for 1hour. The mixture was extracted with AcOEt for 2 times, the combined organic layers were washed with sat.aqNaHCO3, sat.aqNaCl, dried over MgSO4, evaporated in vacuo. The residue was purified by preparative thin layer chromatography developed with AcOEt / n-hexane = 50%. The residue was crystallized from IPE to give E0412 (79.2mg) as a white powder.

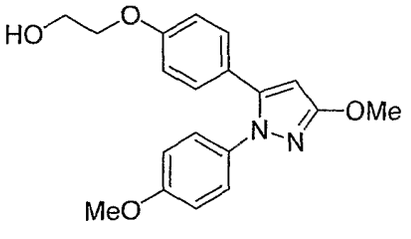
mp. 107-109°C

IR (KBr) : 3334, 2935, 1693, 1612, 1564, 1520cm-1

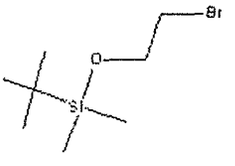
Mass (ESI+) : 341 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.02(1H, t, J=6.1 Hz), 3.80(3H, s), 3.91-3.99(2H, m), 3.97(3H, s), 4.04-4.09(2H, m), 5.88(1H, s), 6.82(4H, d, J=9.0 Hz), 7.14(2H, d, J=9.0 Hz), 7.17(2H, d, J=9.0 Hz)

Example 413



(E0413)

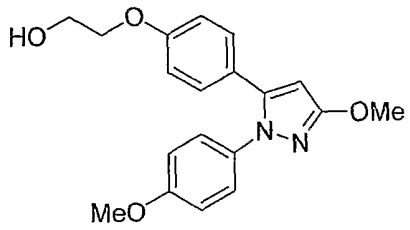


(E0413-0)

To a solution of P0034 (237mg) in DMF 2ml was added 60% NaH 41.6mg with cooling in an ice bath, and the mixture was stirred at ambient temperature for 1hour. To the mixture was added E0413-0 (287mg) in DMF 1ml and the mixture was stirred at ambient temperature for 13hours, and at 60 °C for 3hours. The reaction was quenched by adding sat.NH4Claq, and the mixture was extracted with AcOEt. The organic layer was washed with H2O, sat.aqNaCl, dried over MgSO4, concentrated

in vacuo. The residue was dissolved in EtOH 4ml, and conc.HCl 40μL was added. After stirring at ambient temperature for 2hours, the mixture was concentrated in vacuo. The residue was partitioned between AcOEt and sat.aqNaHCO3, and the organic layer was washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40%, 60%. The residue was crystallized from AcOEt 1ml and IPE 2ml. The obtained crystals were recrystallized from AcOEt 0.7ml and IPE 1.5ml to give E0413 (196.9mg) as white crystals.
mp. 114.9-116 (115) °C Mass (ESI+) : 341 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 3.65-3.73(2H, m), 3.75(3H, s), 3.83(3H, s), 3.94-3.99(2H, m), 4.86(1H, t, J=5.4Hz), 6.04(1H, s), 6.87-6.96(4H, m), 7.10-7.16(4H, m)

Example 414



(E0414)
To a solution of P0034 (100mg) in DMF 1ml was added 60% NaH 17.5mg with cooling in an ice bath. The mixture was stirred at ambient temperature for 1hour. The mixture was cooled to 0°C. To the mixture was added 2-bromoethyl acetate 113mg and the mixture was stirred at ambient temperature for 24hours. The reaction was quenched by adding sat.NH4Claq, and the mixture was extracted with AcOEt. The organic layer was washed with H2O, sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was dissolved in THF 0.9ml and MeOH 0.9ml. To this solution was added 1M NaOH 0.4ml.

The mixture was stirred at ambient temperature for 1hour. The mixture was partitioned between AcOEt and H2O, and the aqueous layer was reexracted with AcOEt. The combined organic layers were washed with sat.aqNaCl, dried over MgSO4, concentrated in vacuo. The residue was crystallized from AcOEt 0.3ml-IPE 0.9ml to give E0414 (82.4mg) as white crystals.

Mass (ESI+) : 341 (M+H)+

(continued to the next page)

Preparation 35

To a solution of N'-[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (1.19g) in EtOH (10ml) and THF (10ml) were added a solution of ammonium formate (509mg) in H2O (2ml) and 10% Pd-C 50% wet (150mg). The mixture was refluxed for 1hour. The catalyst was filtered off through a celite pad and the pad was washed with EtOH. The filtrate and combined washings were concentrated in vacuo. To the residue were added AcOEt and H2O. White precipitates were appeared and collected and washed with H2O and IPE successively to give N'-[5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (555mg) as a white powder.

Mass (ESI+) : 353 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.91(6H, s), 3.76(3H, s), 6.57(1H, s), 6.71(2H, d, J=8.6 Hz), 6.93(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.6 Hz), 7.14(2H, d, J=9.0 Hz), 8.99(1H, s), 9.68(1H, s)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 35.

Preparation 36

N-[5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N',N'-trimethylurea

white powder

Mass (ESI+) : 367 (M+H)+

200MHz 1H NMR (DMSO-d6, d) :

2.78(6H, s), 3.11(3H, s), 3.76(3H, s), 6.19(1H, s), 6.70(2H, d, J=8.6 Hz), 6.93(2H, d, J=9.0 Hz), 7.03(2H, d, J=8.6 Hz), 7.15(2H, d, J=9.0 Hz), 9.72(1H, s)

Preparation 37

4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

powder

Mass (ESI+) : 311(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.32(3H, t, J=7.0 Hz), 3.75(3H, s), 4.16(2H, q, J=7.0 Hz), 5.96(1H, s), 6.70(2H, d, J=8.6 Hz), 6.91(2H, d, J=8.9 Hz), 7.01(2H, d, J=8.6 Hz), 7.11(2H, d, J=8.9 Hz), 9.74(1H, brs)

Preparation 38

4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenol

white powder

Mass (ESI+) : 339 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.02(6H, d, J=6.6 Hz), 2.10(1H, m), 3.79(3H, s), 3.98(6.6H, d, J=2 Hz), 5.38(1H, s), 5.87(1H, s), 6.72(2H, d, J=8.6 Hz), 6.81(2H, d, J=9.0 Hz), 7.07(2H, d, J=8.6 Hz), 7.16(2H, d, J=9.0 Hz)

Preparation 39

4-[3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

white powder

Mass (ESI+) : 341 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.30(3H, s), 3.62-3.67(2H, m), 3.75(3H, s), 4.21-4.26(2H, m), 5.98(1H, s), 6.70(2H, d, J=8.6 Hz), 6.91(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.6 Hz), 7.12(2H, d, J=9.0 Hz), 9.69(1H, s)

Preparation 40

4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

white powder

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.13(3H, t, J=7.0 Hz), 3.49(2H, q, J=7.0 Hz), 3.65-3.71(2H, m), 3.75(3H, s), 4.20-4.25(2H, m), 5.99(1H, s), 6.70(2H, d, J=8.6 Hz), 6.91(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.6 Hz), 7.12(2H, d, J=9.0 Hz), 9.72(1H, s)

Preparation 41

2-{[5-(4-hydroxyphenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]oxy}-N,N-dimethylacetamide

white powder

Mass (ESI+) : 368 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.84(3H, s), 2.97(3H, s), 3.75(3H, s), 4.87(2H, s), 6.01(1H, s), 6.70(2H, d, J=8.6 Hz), 6.92(2H, d, J=9.0 Hz), 7.01(2H, d, J=8.6 Hz), 7.10(2H, d, J=9.0 Hz), 9.71(1H, s)

Preparation 42

4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 298 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.84(6H, s), 6.05(1H, s), 6.73(2H, d, J=8.6 Hz), 6.85(1H, d, J=8.8 Hz), 7.05(2H, d, J=8.6 Hz), 7.59(1H, dd, J=8.8,2.7 Hz), 7.98(1H, d, J=2.7 Hz), 9.77(1H, s)

Preparation 43

4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 312 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 3.84(3H, s), 4.18(2H, q, J=7.0 Hz), 6.03(1H, s), 6.73(2H, d, J=8.6 Hz), 6.84(1H, d, J=8.7 Hz), 7.05(2H, d, J=8.6 Hz), 7.57(1H, dd, J=2.6,8.7 Hz), 7.97(1H, d, J=2.6 Hz), 9.76(1H, s)

Preparation 44

4-[1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenol

MASS (ESI+): m/z = 371.2 (M+Na).

1HNMR (400MHz, CDCl3): 2.15 (3H, s), 3.78 (3H, s), 6.79 (2H, d, J = 8.9Hz), 6.8 (2H, d, J = 8.6Hz), 7.01 (2H, d, J = 8.6Hz), 7.13 (2H, d, J = 8.9Hz).

Preparation 45

4-[3-cyclopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

white powder

MS(ESI+) : m/z 308 (M+H)

1HNMR (200MHz, CDCl3): 0.76 - 0.85 (2H, m), 0.93 - 1.06 (2H, m), 1.97 - 2.08 (1H, m), 3.91 (3H, s), 6.08 (1H, s), 6.15 (1H, s), 6.68 - 6.76 (3H, m), 7.04 (2H, d, J = 8.6Hz), 7.56 (1H, dd, J = 2.7 ,6.2Hz), 8.02 (1H, d, J = 2.7Hz)

Preparation 46

4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 352 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 2.41 (8H, m), 3.84 (3H, s), 4.92 - 5 (1H, m), 6.01 (1H, s), 6.73 (2H, d, J = 8.6Hz),

6.84 (1H, d, J = 8.8Hz), 7.05 (2H, d, J = 8.6Hz), 7.57 (1H, dd, J = 2.7 ,8.8Hz), 7.97 (1H, d, J = 2.7Hz), 9.76 (1H, brs)

Preparation 47

4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 365 (M+H)

1HNMR (200MHz, DMSOd6): 3.76 (3H, s), 4.8 (1H, d, J = 9Hz), 4.89 (1H, d, J = 9Hz), 6.15 (1H, s), 6.71 (2H, d, J = 8.6Hz), 6.93 (2H, d, J = 8.9Hz), 7.03 (2H, d, J = 8.6Hz), 7.14 (2H, d, J = 8.9Hz), 9.74 (1H, brs)

Preparation 48

4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 347 (M+H)

1HNMR (200MHz, DMSOd6): 3.76 (3H, s), 4.43 (2H, dt, J = 3.5 ,14.9Hz), 6.08 (1H, s), 6.40 (1H, tt, J = 3.5, 54.6Hz), 6.71 (2H, d, J = 8.6Hz), 6.92 (2H, d, J = 9.0Hz), 7.02 (2H, d, J = 8.6Hz), 7.14 (2H, d, J = 9.0Hz)

Preparation 49

4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 366 (M+H)

1HNMR (200MHz, CDCl3): 3.92 (3H, s), 4.61 (1H, d, J = 8.5Hz), 4.69 (1H, d, J = 8.5Hz), 5.39 (1H, brs), 5.97 (1H, s), 6.72 (1H, d, J = 8.9Hz), 6.76 (2H, d, J = 8.5Hz),

7.09 (2H, d, J = 8.5Hz), 7.51 (1H, dd, J = 2.7 ,8.9Hz), 8.01 (1H, d, J = 2.7Hz)

Preparation 50

4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 348 (M+H)

1HNMR (200MHz, CDCl3): 3.92 (3H, s), 4.46 (2H, dt, J = 4.2 ,13.5Hz), 5.42 (1H, brs), 5.93 (1H, s), 6.16 (1H, tt, J = 4.2, 55.4Hz), 6.72 (1H, d, J = 8.7Hz), 6.76 (2H, d, J = 8.6Hz), 7.09 (2H, d, J = 8.6Hz), 7.51 (1H, dd, J = 2.7 ,8.7Hz), 8.01 (1H, d, J = 2.7Hz)

Preparation 51

4-[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 281 (M+H)

200MHz 1H NMR (DMSO-d6, d) : 2.00(3H, s), 3.74(3H, s), 6.74(2H, d, J=8.5 Hz), 6.88(2H, d, J=9.0 Hz), 6.96(2H, d, J=8.5 Hz), 7.09(2H, d, J=9.0 Hz), 7.53(1H, s), 9.66(1H, s)

Preparation 52

4-[1-(6-methoxy-3-pyridinyl)-4-methyl-1H-pyrazol-5-yl]phenol

white powder

MS (ESI+) : m/z 282 (M+H)

1HNMR (200MHz, DMSOd6): 2.01 (3H, s), 3.83 (3H, s), 6.75 - 6.85 (3H, m), 7.01 (2H, d, J = 8.6Hz), 7.53 (1H, dd, J = 2.7 ,8.8Hz), 7.6 (1H, s), 7.96 (1H, d, J = 2.7Hz), 9.73 (1H, brs)

Preparation 53

To a solution of 4'-benzyloxypropiophenone (6.0g) in THF (120ml) at -60 °C was added 38ml of 1N lithium bis(trimethylsilyl)amide (LiHMDS), and the mixture was stirred at under -60°C for 45mins. 1-(Trifluoroacetyl)-imidazole (3.4ml) was added and the mixture was stiired at -60°C for 1 hour and at 0°C for 30 min. The raction mixture was quenched with 0.5N HCl, the mixture was poured into EtOAc and water, and the EtOAc layer was separated, washed with brine, died over MgSO4, and concentrated to give 1-[4-(benzyloxy)phenyl]-4,4,4-trifluoro-2-methyl-1,3-butanedione.

MASS (ESI+): m/z = 359.2 (m+Na).

1HNMR (400MHz, CDCl3): 1.36 (1H, d, J = 7.2Hz), 1.52 (2H, d, J = 7Hz), 5.16 (2H, s), 7.02 - 7.08 (2H, m), 7.37 - 7.44 (5H, m), 7.92 - 7.98 (2H, m).

Preparation 54

To a mixture of 4-(methylthio)aniline (6.3g) and conc.HCl (45ml) was added dropwise NaNO2 (3.6g) in water (18ml) under ice-coling. After stirring for 30 min., SnClH2O (28.6g) in conc.HCl (24ml) was added under ice cooling over 1 hour. After stirring for 1 hour, filtrate, washed with conc.HCl and water, and dried to give 14.1g of [4-(methylthio)phenyl]hydrazine hydrochloride as a solid.

MASS (ESI+): m/z = 139.3 (M-NH2+1).

1HNMR (400MHz, DMSOd6): 2.42 (3H, s), 3.75 (2H, b.s), 6.97 (2H, d, J = 8.7Hz), 7.24 (2H, d, J = 8.7Hz), 10.24 (1H, b.s).

Preparation 55

A mixture of 4-hydroxypropiophenone (20g), benzyl chloride

(16.1ml), K2CO3 (12.9g) and KI (2.21g) in EtOH (80ml) and H2O (1ml) was stirred under reflux condition for 4 hours. The reaction mixture was cooled and filtered. Appeared crystal was dissovled with EtOAc and water. Organic layer was separated and washed with water and brine, dried over MgSO4 and filtered. Filtrate was evaporated under reduced pressure to give 30.0g (94%) of 1-[4-(benzyloxy)phenyl]-1-propanone as a crystal.

MASS (ESI+): m/z = 263.2 (M+Na).

1HNMR (400MHz, CDCl3): 1.21 (3H, t, J = 7.3Hz), 2.95 (2H, q, J = 7.3Hz), 5.13 (2H, s), 7 (2H, d, J = 8.9Hz), 7.34 - 7.45 (5H, m), 7.95 (2H, d, J = 8.9Hz).

Preparation 56

1M NaOH (4.8ml) was added to a solution of 4-benzyloxybenzaldehyde (5g) and cyclopropyl methyl ketone (3.96g) in EtOH (24ml) and the mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with H2O and EtOH. The mixture was stirred at ambient temperature for 20minutes. Pale yellow crystals were collected and washed with H2O and 50% aqueous EtOH to give (2E)-3-[4-(benzyloxy)phenyl]-1-cyclopropyl-2-propen-1-one (6.29g).

Pale yellow crystals

MS (ESI+) : m/z 301 (M+Na)

1HNMR (200MHz, CDCl3): 0.9 - 1.00 (2H, m), 1.11 - 1.19 (2H, m), 2.16 - 2.29 (1H, m), 5.11 (2H, s), 6.77 (1H, d, J = 16.1Hz), 6.99 (2H, d, J = 8.8Hz), 7.32 - 7.46 (4H, m), 7.52 (2H, d, J = 8.8Hz), 7.58 (2H, d, J = 16.1Hz)

Preparation 57

(2E)-3-[4-(Benzyloxy)phenyl]-1-cyclopropyl-2-propen-1-

one (6.25g) was suspended in EtOH (67.5ml), acetone (22.5ml). To this mixture was added hydrogen peroxide 30% aqueous solution (4.5ml), and 3M NaOH (4.5ml), and the mixture was stirred at ambient temperature for 1day. The mixture was diluted with H2O. White precipitates were collected and washed with H2O, and air dried to give {(2R,3S)-3-[4-(benzyloxy)phenyl]-2-oxiranyl}(cyclopropyl)methanone (6.27g).

powder

MS (ESI+) : m/z 317 (M+Na)

1HNMR (200MHz, DMSOd6): 0.96 - 1.07 (2H, m), 1.12 - 1.19 (2H, m), 2.11 - 2.22 (1H, m), 3.59 (1H, d, J = 1.8Hz), 4.04 (1H, d, J = 1.8Hz), 5.08 (2H, s), 6.97 (2H, d, J = 8.8Hz), 7.23 (2H, d, J = 8.8Hz), 7.35 - 7.43 (5H, m)

Preparation 58

To a solution of 4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5- yl]phenol (501mg) in CH2Cl2 (5ml) was added trifluoromethanesulfonic anhydride (300µl) and diisopropylethylamine (324µl) under ice-bath cooling. The mixture was stirred at same temperature for 2hours. Additional trifluoromethanesulfonic anhydride (57µl) and diisopropylethylamine (147µl) were added and stirring at same temperature was continued for 1hour. The mixture was washed with 1M HCl, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 20% to give 4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenyl trifluoromethanesulfonate (712.3mg) as an oil.

MS (ESI+) : m/z 429 (M+H)

1HNMR (200MHz, CDCl3): 3.81 (3H, s), 3.98 (3H, s), 5.97 (1H, s), 6.85 (2H, d, J = 9.0Hz), 7.11 - 7.32 (6H, m)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 58.

Preparation 59

4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenyl trifluoromethanesulfonate

oil

MS ESI+) : m/z 457 (M+H)

1HNMR (200MHz, CDCl3): 1.40 (6H, d, J = 6.1Hz), 3.81 (3H, s), 4.89 (1H, m), 5.94 (1H, s), 6.84 (2H, d, J = 9.0Hz), 7.14 (2H, d, J = 9.0Hz), 7.20 - 7.32 (4H, m)

Preparation 60

4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenyl trifluoromethanesulfonate

oil

MS (ESI+) : m/z 433 (M+H)

1HNMR (200MHz, CDCl3): 3.82 (3H, s), 6.46 (1H, s), 6.86 (2H, d, J = 9.0Hz), 7.17 (2H, d, J = 9.0Hz), 7.23 - 7.32 (4H, m)

Preparation 61

A mixture of 4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl trifluoromethanesulfonate (679mg), zinc cyanide (279mg), and tetrakis(triphenylphosphine)-palladium(0) (183mg) in DMF (4ml) was stirred at 85°C for 5hours. The reaction mixture was cooled to ambient temperature and AcOEt and H2O were added. Unsoluble matter was filtered off through a celite pad. The filtrate was

partitioned, and the organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 20%. The pure fractions were collected and concentrated in vacuo to give 4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzonitrile (326mg) as a powder.
mp.112-113°C
MS (ESI+) : m/z 306 (M+H), 328 (M+Na)
IR (KBr) : 2929, 2227, 1568, 1552, 1541, 1518cm-1
1HNMR (200MHz, CDCl3): 3.81 (3H, s), 3.98 (3H, s), 6.01 (1H, s), 6.85 (2H, d, J = 8.9Hz), 7.15 (2H, d, J = 8.9Hz), 7.30 (2H, d, J = 8.5Hz), 7.57 (2H, d, J = 8.5Hz)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 61.

Preparation 62

4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-benzonitrile
mp.96-97°C
MS (ESI+) : m/z 334 (M+H), 356 (M+Na)
1HNMR (200MHz, CDCl3): 1.40 (6H, d, J = 6.1Hz), 3.81 (3H, s), 4.89 (1H, m), 5.98 (1H, s), 6.84 (2H, d, J = 9.0Hz), 7.14 (2H, d, J = 9.0Hz), 7.30 (2H, d, J = 8.6Hz), 7.56 (2H, d, J = 8.6Hz)

Preparation 63

4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]benzonitrile
oil
MS (ESI+) : m/z 375 (M+H)

1HNMR (200MHz, CDCl3): 3.94 (3H, s), 4.62 (1H, d, J = 8.4Hz), 4.71 (1H, d, J = 8.4Hz), 6.12 (1H, s), 6.76 (1H, d, J = 8.7Hz), 7.33 (2H, d, J = 8.4Hz), 7.5 (1H, dd, J = 2.7 ,8.7Hz), 7.62 (2H, d, J = 8.4Hz), 7.97 (1H, d, J = 2.7Hz)

Preparation 64

4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-benzonitrile

powder

MS (ESI+) : m/z 310 (M+H), 332 (M+Na)

1HNMR (200MHz, CDCl3): 3.83 (3H, s), 6.50 (1H, s), 6.87 (2H, d, J = 9.0Hz), 7.16 (2H, d, J = 9.0Hz), 7.30 (2H, d, J = 8.5Hz), 7.60 (2H, d, J = 8.5Hz)

Preparation 65

4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]-benzonitrile

powder

MS (ESI+) : m/z 311 (M+H), 333 (M+Na)

1HNMR (200MHz, CDCl3): 3.94 (3H, s), 6.53 (1H, s), 6.78 (1H, d, J = 8.9Hz), 7.33 (2H, d, J = 8.4Hz), 7.54 (1H, dd, J = 2.7 ,8.9Hz), 7.64 (2H, d, J = 8.4Hz), 7.99 (1H, d, J = 2.7Hz)

Preparation 66

A solution of trifluoromethanesulfonic anhydride (207µl) in CH2Cl2 (1ml) was added to a solution of 4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenol (300mg) and pyridine (199µl) in CH2Cl2 (3ml) inder ice-bath cooling. The mixture was stirred at same temperature for 1hour. The reaction was quenched

by adding saturated aqueous ammonium chloride solution (5ml). The mixture was partitioned between AcOEt and 1M HCl. The mixture was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give 4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoro-ethoxy)-1H-pyrazol-5-yl]phenyl trifluoromethane-sulfonate (439mg) as an oil.

MS (ESI+) : m/z 498 (M+H)

1HNMR (200MHz, CDCl3): 3.94 (3H, s), 4.62 (1H, d, J = 8.4Hz), 4.71 (1H, d, J = 8.4Hz), 6.08 (1H, s), 6.74 (1H, d, J = 8.7Hz), 7.22 - 7.38 (4H, m), 7.47 (1H, dd, J = 2.7 ,8.7Hz), 8.01 (1H, d, J = 2.7Hz)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 66.

Preparation 67

4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]-phenyl trifluoromethanesulfonate

oil

MS (ESI+) : m/z 434 (M+H)

1HNMR (200MHz, CDCl3): 3.94 (3H, s), 6.49 (1H, s), 6.76 (1H, d, J = 8.9Hz), 7.23 - 7.34 (4H, m), 7.52 (1H, dd, J = 2.8 ,8.9Hz), 8.02 (1H, d, J = 2.8Hz)

Preparation 68

A solution of 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl benzyl ether (2.79g) and thioanisole (3.56g) in trifluoroacetic acid (25ml) was stirred at ambient temperature overnight. The mixture was concentrated in vacuo. The residue was recrystallized from AcOEt (15ml) and n-hexane

(12ml) to givr 1st crop of FR282117 (1.48g). The mother liqour was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30%. The pure fractions were collected and concentrated in vacuo. The residual crystals were collected and washed with IPE to give 2nd crop of 4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol(457.2mg) white powder

Mass (ESI+) : m/z 301 (M+H)

200MHz 1H NMR (DMSO-d6, d) : 3.78(3H, s), 6.62(1H, s), 6.71(2H, d, J=8.7 Hz), 6.96(2H, d, J=9.0 Hz), 7.03(2H, d, J=8.7 Hz), 7.19(2H, d, J=9.0 Hz), 9.80(1H, s)

The following compound(s) was(were) obtained in a similar manner to that of Preparation 68.

Preparation 69

4-[1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazol-5-yl]-phenol

powder

MS (ESI+) : m/z 313 (M+H)

1HNMR (200MHz, DMSOd6): 2.50 (3H, s), 3.77 (3H, s), 6.49 (1H, s), 6.70 (2H, d, J = 8.6Hz), 6.94 (2H, d, J = 9.0Hz), 7.02 (2H, d, J = 8.6Hz), 7.16 (2H, d, J = 9.0Hz), 9.71 (1H, brs)

The following compound(s) was(were) obtained in a similar manner to that of Example 596.

Preparation 70

4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-

pyrazol-5-yl]phenol

MASS (ESI+): m/z = 373.1 (M+Na).

1HNMR (400MHz, CDCl3): 2.49 (3H, s), 5.13 (1H, b.s), 6.67 (1H, s), 6.79 (2H, d, J = 8.7Hz), 7.1 (2H, d, J = 8.7Hz), 7.2 (2H, d, J = 9.1Hz), 7.23 (2H, d, J = 9.1Hz).

Preparation 71

4-{3-(difluoromethyl)-1-[4-(methylthio)phenyl]-1H-pyrazol-5-yl}phenol

MASS (ESI+) m/z = 355.1 (M+Na)

1HNMR (400MHz, CDCl3): 2.49 (3H, s), 5.17 (1H, b.s), 6.65 (1H, s), 6.76 (1H, t, J = 55Hz), 6.78 (2H, d, J = 8.7Hz), 7.1 (2H, d, J = 8.7Hz), 7.2 (4H, s).

Preparation 72

4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzonitrile

MASS (ESI+): m/z = 345.1, 367.1 (m+H, m+Na).

1HNMR (400MHz, CDCl3): 3.96 (3H, s), 6.8 (1H, d, J = 8.8Hz), 6.85 (1H, s), 7.36 (2H, d, J = 8.4Hz), 7.57 (1H, dd, J = 2.7 ,8.8Hz), 7.66 (2H, d, J = 8.4Hz), 8.04 (1H, d, J = 2.7Hz).

Preparation 73

4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzonitrile

MASS (ESI+): m/z = 327.1 (m+1).

1HNMR (400MHz, CDCl3): 3.95 (3H, s), 6.77 (1H, t, J = 54.8Hz), 6.79 (1H, d, J = 8.8Hz), 6.82 (1H, s), 7.36 (2H, d, J = 8.4Hz), 7.54 (1H, dd, J = 2.8 ,8.8Hz), 7.65 (2H, d, J = 8.4Hz), 8.04 (1H, d, J = 2.8Hz).

Example 415

4M HCl in dioxane (3ml) was added to a solution of tert-butyl (2-{4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)-carbamate (236mg) in CH2Cl2 (3ml). The reaction mixture was stirred at ambient temperature for 3hours. 2-Propanol (2ml) was added to dissolve unsoluble oil, and stirred at ambient temperature for 4hours. The mixture was concentrated in vacuo. The residue was suspended in CH2Cl2 (3ml). Methanesulfonyl chloride (127mg) was added and then Et3N was added to adjust pH of the rection mixture to neutral. After stirring for 1hour, the reaction mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate and water. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 50% AcOEt / n-hexane to give N-(2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methane-sulfonamide (118mg) as an oil.

1H NMR (CDCl3) δ 2.20(3H, s), 3.03(3H, s), 3.51-3.60(2H, m), 3.93(3H, s), 4.07-4.13(2H, m), 4.77(1H, t, J=6.0 Hz), 5.15(1H, brs), 5.60(1H, brs), 6.59(1H, s), 6.73(1H, d, J=8.9 Hz), 6.83(2H, d, J=8.8 Hz), 7.17(2H, d, J=8.8 Hz), 7.55(1H, dd, J=2.6,8.8 Hz), 8.09(1H, d, J=2.6 Hz)

Example 416

A mixture of 10% Pd-C 50% wet (20mg) and N-(2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide (118mg) in

THF (1ml) and MeOH (1ml) was hydrogenated under H2 1atm at ambient temperature for 1day.The catalyst was removed by filtration.The filtrate and combined washings were concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by AcOEt/n-hexane= 70%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo. The residue was recrystallized from AcOEt-IPE to give N-(2-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide (68.6mg) as white powder.

white powder :

mp. 96-97°C

IR (KBr) : 3269, 2970, 1612, 1512cm-1

MS (ESI+) : m/z 431 (M+H)

1H NMR (DMSO-d6) δ 1.27(6H, d, J=6.9 Hz), 2.88-2.99(1H, m), 2.92(3H, s), 3.92-3.35(2H, m), 3.85(3H, s), 3.99-4.06(2H, m), 6.46(1H, s), 6.88(1H, d, J=8.7 Hz), 6.94(2H, d, J=8.8 Hz), 7.17(2H, d, J=8.8 Hz), 7.28(1H, s), 7.60(1H, dd, J=2.7,8.7 Hz), 8.02(1H, d, J=2.7 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 416.

Example 417

tert-butyl {4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate

oil

MS (ESI+) : m/z 422 (M+H)

1HNMR (200MHz,): 1.34 (6H, d, J = 7.0Hz), 1.46 (9H, s), 3.08 (1H, m), 3.80 (3H, s), 4.30 (2H, d, J = 5.9Hz), 4.81 (1H, brs), 6.31 (1H, s), 6.83(2H, d, J = 9.0Hz),

7.15 - 7.26 (6H, m)

Example 418

tert-butyl {4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}carbamate

oil

MS (ESI+) : m/z 423 (M+H)

1HNMR (200MHz, CDCl3): 1.34 (6H, d, J = 7Hz), 1.46 (9H, s), 3.07 (1H, m), 3.92 (3H, s), 4.30 (2H, d, J = 6.0Hz), 4.84 (1H, brs), 6.33 (1H, s), 6.72 (1H, d, J = 8.8Hz), 7.15 - 7.26 (4H, m), 7.56 (1H, dd, J = 2.7 ,8.8Hz), 8.04 (1H, d, J = 2.7Hz)

Example 419

A 4M solution of HCl in dioxane (2ml) was added to a solution of ter-butyl (2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate (269.7mg) in CH2Cl2 (2ml). The reaction mixture was stirred at ambient temperature for 2hours, then, was concentrated in vacuo to give (2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride (259mg) as an amorphous powder.

MS (ESI+) : m/z 351 (M+H)

1H NMR (DMSO-d6) δ 2.10(3H, s), 3.15-3.23(2H, m), 3.86(3H, s), 4.16-4.24(2H, m), 5.15(1H, brs), 5.63(1H, brs), 6.85(1H, s), 6.86-7.00(3H, m), 7.18-7.25(2H, m), 7.66(1H, dd, J=2.8,8.7 Hz), 8.06(1H, d, J=2.8 Hz), 8.24(2H, brs)

The following compound(s) was(were) obtained in a similar manner to that of Example 419.

Example 420

(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)amine hydrochloride

white powder

Mass (ESI+) : 340 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.16-3.23(2H, m), 3.76(3H, s), 3.84(3H, s), 4.14-4.20(2H, m), 6.06(1H, s), 6.93(2H, d, J=8.9 Hz), 6.94(2H, d, J=8.7 Hz), 7.14(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 8.16(2H, brs)

Example 421

(2-{4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)amine hydrochloride

white powder

Mass (ESI+) : 354 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 3.14-3.23(2H, m), 3.76(3H, s), 4.12-4.23(4H, m), 6.04(1H, s), 6.92(2H, d, J=9.0 Hz), 6.94(2H, d, J=8.8 Hz), 7.12(2H, d, J=9.0 Hz), 7.16(2H, d, J=8.8 Hz), 8.24(2H, brs)

Example 422

(2-{4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

amorphous

Mass (ESI+) : 382 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.97(6H, d, J=6.7 Hz), 2.03(1H, m), 3.14-3.23(2H, m), 3.76(3H, s), 3.90(2H, d, J=6.6 Hz), 4.14-4.20(2H, m), 6.06(1H, s), 6.92(2H, d, J=9.0 Hz), 6.94(2H, d, J=8.8 Hz), 7.08-7.19(4H, m), 8.23(2H, brs)

Example 423

(2-{4-[3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

amorphous

Mass (ESI+) : 384 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.15-3.23(2H, m), 3.31(3H, s), 3.62-3.67(2H, m), 3.75(3H, s), 4.14-4.27(4H, m), 6.06(1H, s), 6.92(2H, d, J=8.9 Hz), 6.95(2H, d, J=8.8 Hz), 7.13(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.8 Hz), 8.20(2H, brs)

Example 424

(2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

amorphous

Mass (ESI+) : 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.13(3H, t, J=7.0 Hz), 3.15-3.24(2H, m), 3.50(2H, q, J=7.0 Hz), 3.66-3.71(2H, m), 3.76(3H, s), 4.13-4.27(4H, m), 6.07(1H, s), 6.93(2H, d, J=8.9 Hz), 6.95(2H, d, J=8.7 Hz), 7.13(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 8.13(2H, brs)

Example 425

(2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

amorphous

MS (ESI+) : m/z 341 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.16-3.23(2H, m), 3.84(3H, s), 3.85(3H, s), 4.16-4.21(2H, m), 6.12(1H, s), 6.86(1H, d, J=8.7 Hz), 6.98(2H, d, J=8.7 Hz), 7.21(2H, d, J=8.7 Hz), 7.62(1H, dd, J=2.5,8.7 Hz), 7.99(1H, d, J=2.5 Hz), 8.24(2H, brs)

Example 426

(2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

amorphous

MS (ESI+) : m/z 355 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 3.15-3.24(2H, m), 3.84(3H, s), 4.13-4.24(2H, m), 4.19(2H, q, J=7.0 Hz), 6.10(1H, s), 6.86(1H, d, J=8.9 Hz), 6.98(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.8 Hz), 7.60(1H, dd, J=2.7,8.9 Hz), 7.98(1H, d, J=2.7 Hz), 8.19(2H, brs)

Example 427

(2-{4-[1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

MASS (ESI+): m/z = 392.2 (M+H).

1HNMR (400MHz, DMSOd6): 2.09 (3H, s), 3.1 - 3.3 (2H, m), 3.36 (2H, b.s), 3.57 (3H, s), 4.20 (2H, t, J = 5Hz), 6.94 (2H, d, J = 8.9Hz), 7.01 (2H, d, J = 8.8Hz), 7.2 (2H, d, J = 8.9Hz), 7.21 (2H, d, J = 8.8Hz), 8.29 (2H, br.s).

Example 428

(2-{4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

MASS (ESI+): m/z = 394.1 (M(Free)+1, HCl salt).

1HNMR (200MHz, DMSOd6): 2.5 (3H, s), 3.15 - 3.25 (2H, m), 4.22 (2H, t, J = 5Hz), 7 (2H, d, J = 8.7Hz), 7.1 (1H, s), 7.26 (2H, d, J = 8.7Hz), 7.27 (2H, d, J = 9.8Hz), 7.33 (2H, d, J = 9.8Hz), 8.35 (2H, b.s).

Example 429

[2-(4-{3-(difluoromethyl)-1-[4-(methylthio)phenyl]-1H-pyrazol-5-yl}phenoxy)ethyl]amine hydrochloride

MASS (ESI-): m/z = 410.0 (M-1).

1HNMR (400MHz, DMSOd6): 2.49 (3H, s), 3.2 (2H, t, J =

5Hz), 4.19 (2H, t, J = 5Hz), 6.87 (1H, s), 6.99 (1H, d, J = 8.7Hz), 7.09 (1H, t, J = 53.5Hz), 7.24 (4H, d, J = 9.6Hz), 7.3 (2H, d, J = 8.7Hz), 8.17 (2H, b.s).

Example 430

(2-{4-[3-cyclopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

amorphous powder

MS (ESI+) : m/z 351 (M+H)

1HNMR (200MHz, DMSOd6): 0.70- 0.78 (2H, m), 0.86 - 1.02 (2H, m), 1.88 - 1.99 (1H, m), 3.10 - 3.20 (2H, m), 3.85 (3H, s), 4.15 - 4.21 (2H, m), 6.31 (1H, s), 6.86 (1H, d, J = 8.9Hz), 6.96 (2H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.8Hz), 7.60 (1H, dd, J = 2.7 ,8.9Hz), 8.00 (1H, d, J = 2.7Hz), 8.24 (2H, brs)

Example 431

(2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

amorphous powder

MS (ESI+) : m/z 421 (M+H)

1HNMR (200MHz, DMSOd6): 1.43 - 1.72 (6H, m), 3.14 - 3.24 (2H, m), 3.52 - 3.70 (2H, m), 3.77 - 3.95 (2H, m), 3.78 (3H, s), 4.15 - 4.20 (2H, m), 6.79 (1H, s), 6.96 (2H, d, J = 8.8Hz), 6.99 (2H, d, J = 8.9Hz), 7.21 (2H, d, J = 8.8Hz), 7.24 (2H, d, J = 8.9Hz), 8.14 (2H, brs)

Example 432

(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

amorphous powder

MS (ESI+) : m/z 422 (M+H)

1HNMR (200MHz, CDCl3): 1.42 - 1.75 (6H, m), 3.14 - 3.24 (2H, m), 3.52 - 3.70 (2H, m), 3.73 - 3.94 (2H, m), 3.87 (3H, s), 4.16 - 4.22 (2H, m), 6.83 (1H, s), 6.91 (1H, d, J = 8.9Hz), 6.99 (2H, d, J = 8.8Hz), 7.25 (2H, d, J = 8.8Hz), 7.69 (1H, dd, J = 2.7 ,8.9Hz), 8.14 (1H, d, J = 2.7Hz), 8.21 (2H, brs)

Example 433

5-[4-(2-aminoethoxy)phenyl]-N-ethyl-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide dihydrochloride

amorphous powder

Mass (ESI+) : m/z 396 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.23 (3H, m), 2.98, 3.29 (3H, s), 3.13 - 3.25 (2H, m), 3.43 - 3.78 (4H, m), 3.87 (3H, s), 4.16- 4.22 (2H, m), 6.84, 6.86 (1H, s), 6.91 (1H, d, J = 8.7Hz), 7 .00(2H, d, J = 8.7Hz), 7.25 (2H, d, J = 8.7Hz), 7.61 - 7.74 (1H, m), 8.13 - 8.20 (3H, m)

Example 434

(2-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

amorphous powder

MS (ESI+) : m/z 395 (M+H)

1HNMR (400MHz, DMSOd6): 1.57 - 1.91 (8H, m), 3.16 - 3.21 (2H, m), 3.84 (3H, s), 4.17 - 4.21 (2H, m), 4.95 - 5 (1H, m), 6.08 (1H, s), 6.85 (1H, d, J = 8.8Hz), 6.98 (2H, d, J = 8.8Hz), 7.2 (2H, d, J = 8.8Hz), 7.59 (1H, dd, J = 2.8 ,8.8Hz), 7.98 (1H, d, J = 2.8Hz), 8.24 (2H, brs)

Example 435

(2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

oil

MS (ESI+) : m/z 408 (M+H)

1HNMR (200MHz, DMSOd6): 3.13 - 3.24 (2H, m), 3.76 (3H, s), 4.15 - 4.21 (2H, m), 4.82 (1H, d, J = 9.0Hz), 4.91 (1H, d, J = 9.0Hz), 6.23 (1H, s), 6.92 - 6.99 (4H, m), 7.13 - 7.21 (4H, m), 8.20 (2H, brs)

Example 436

(2-{4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

amorphous powder

MS (ESI+) : m/z 390 (M+H)

1HNMR (200MHz, DMSOd6): 3.13 - 3.23 (2H, m), 3.76 (3H, s), 4.14 - 4.20 (2H, m), 4.44 (2H, dt, J = 3.5 ,14.9Hz), 6.16 (1H, s), 6.41 (1H, tt, J = 3.5, 54.6Hz), 6.94 (2H, d, J = 8.9Hz), 6.95 (2H, d, J = 8.9Hz), 7.16 (2H, d, J = 8.9Hz), 7.18 (2H, d, J = 8.9Hz), 8.17 (2H, brs)

Example 437

(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoro-ethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

amorphous powder

MS (ESI+) : m/z 409 (M+H)

1HNMR (200MHz, DMSOd6): 3.16 - 3.21 (2H, m), 3.85 (3H, s), 4.16 - 4.22 (2H, m), 4.83 (1H, d, J = 9.0Hz), 4.92 (1H, d, J = 9.0Hz), 6.29 (1H, s), 6.88 (1H, d, J = 8.8Hz), 6.99 (2H, d, J = 8.8Hz), 7.22 (2H, d, J = 8.8Hz), 7.63 (1H, dd, J = 2.7 ,8.8Hz), 8.03 (1H, d, J = 2.7Hz), 8.19 (2H, brs)

Example 438

(2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

powder

MS (ESI+) : m/z 391 (M+H)

1HNMR (200MHz, DMSOd6): 3.15 - 3.24 (2H, m), 3.85 (3H, s), 4.16 - 4.22 (2H, m), 4.46 (2H, dt, J = 3.5 ,14.9Hz), 6.22 (1H, s), 6.42 (1H, tt, J = 3.5, 54.5Hz), 6.87 (1H, d, J = 8.9Hz), 6.99 (2H, d, J = 8.7Hz), 7.22 (2H, d, J = 8.7Hz), 7.62 (1H, dd, J = 2.7 ,8.9Hz), 8.02 (1H, d, J = 2.7Hz), 8.20 (2H, brs)

Example 439

{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]benzyl}amine hydrochloride

amorphous powder

MS (ESI+) : m/z 391 (M+H)

1HNMR (200MHz, DMSOd6): 1.43 - 1.74 (6H, m), 3.51 - 3.72 (2H, m), 3.77 - 3.93 (2H, m), 3.79 (3H, s), 3.97 - 4.06 (2H, m), 6.90 (1H, s), 6.99 (2H, d, J = 8.9Hz), 7.26 (2H, d, J = 8.9Hz), 7.30 (2H, d, J = 8.2Hz), 7.46 (2H, d, J = 8.2Hz), 8.38 (2H, brs)

Example 440

5-[4-(aminomethyl)phenyl]-N-ethyl-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide hydrochloride

powder

MS (ESI+) : m/z 365 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.22 (3H, m), 2.98, 3.29 (3H, s), 3.35 - 3.80 (2H, m), 3.79 (3H, s), 3.97 - 4.08

(2H, m), 6.91, 6.93 (1H, s), 6.99 (2H, d, J = 8.9Hz), 7.26 (2H, d, J = 8.9Hz), 7.30 (2H, d, J = 8.3Hz), 7.46 (2H, d, J = 8.3Hz), 8.37 (2H, brs)

Example 441

{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-benzyl}amine hydrochloride

oil

MS (ESI+) : m/z 322 (M+H)

1HNMR (200MHz, DMSOd6): 1.27 (6H, d, J = 6.8Hz), 2.96 (1H, m), 3.77 (3H, s), 3.95 - 4.03 (2H, m), 6.51 (1H, s), 6.94 (2H, d, J = 8.9Hz), 7.17 (2H, d, J = 8.9Hz), 7.25 (2H, d, J = 8.2Hz), 7.45 (2H, d, J = 8.2Hz), 8.45 (2H, brs)

Example 442

1-[5-[4-(aminomethyl)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-2-methyl-1-propanone hydrochloride

amorphous powder

MS (ESI+) : m/z 350 (M+H)

1HNMR (200MHz, DMSOd6): 1.16 (6H, d, J = 6.9Hz), 3.68 (1H, m), 3.80 (3H, s), 4.01 (2H, s), 7.01 (2H, d, J = 8.9Hz), 7.10 (1H, s), 7.26 - 7.34 (4H, m), 7.46 (2H, d, J = 8.2Hz), 8.33 (2H, brs)

Example 443

{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]benzyl}amine dihydrochloride

oil

MS (ESI+) : m/z 392 (M+H)

1HNMR (200MHz, DMSO-d6): 1.45 - 1.73 (6H, m), 3.53 - 3.70 (2H, m), 3.70 - 3.98 (2H, m), 3.98 - 4.08 (2H, m), 6.92

(1H, d, J = 8.8Hz), 6.93 (1H, s), 7.32 - 7.55 (4H, m), 7.74 (1H, dd, J = 2.7 ,8.8Hz), 8.15 (1H, d, J = 2.7Hz), 8.38 (2H, brs)

Example 444

5-[4-(aminomethyl)phenyl]-N-ethyl-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide dihydrochloride

oil

MS (ESI+) : m/z 366 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.23 (3H, m), 2.98, 3.29 (3H, s), 3.43 - 3.77 (2H, m), 3.88 (3H, s), 3.97 - 4.06 (2H, m), 6.89 - 6.96 (2H, m), 7.32 - 7.80 (5H, m), 8.14 - 8.16 (1H, m), 8.52 (2H, brs)

Example 445

{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}amine dihydrochloride

amorphous powder

MS (ESI+) : m/z 323 (M+H)

1HNMR (200MHz, DMSOd6): 1.28 (6H, d, J = 6.9Hz), 2.86 - 3.05 (1H, m), 3.85 (3H, s), 3.96 - 4.06 (2H, m), 6.57 (1H, s), 6.88 (1H, d, J = 8.8Hz), 7.26 - 7.53 (4H, m), 7.66 (1H, dd, J = 2.7 ,8.8Hz), 8.02 (1H, d, J = 2.7Hz), 8.48 (2H, brs)

Example 446

1-[5-[4-(aminomethyl)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-3-yl]-2-methyl-1-propanone dihydrochloride

oil

MS (ESI+) : m/z 351 (M+H)

1HNMR (200MHz, DMSOd6): 1.17 (6H, d, J = 6.8Hz), 3.68

(1H, m), 3.89 (3H, s), 3.98 - 4.06 (2H, m), 6.95 (1H, d, J = 8.8Hz), 7.13 (1H, s), 7.36 (2H, d, J = 8.2Hz), 7.51 (2H, d, J = 8.2Hz), 7.80 (1H, dd, J = 2.7 ,8.8Hz), 8.19 (1H, d, J = 2.7Hz), 8.43 (2H, brs)

Example 447

(2-{4-[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-5-yl]-phenoxy}ethyl)amine hydrochloride

powder

MS (ESI+) : m/z 324 (M+H)

200MHz 1H NMR (DMSO-d6, d) : 2.02(3H, s), 3.17-3.26(2H, m), 3.74(3H, s), 4.13-4.19(2H, m), 6.89(2H, d, J=9.0Hz), 6.98(2H, d, J=8.7 Hz), 7.10(2H, d, J=8.9 Hz), 7.13(2H, d, J=8.7 Hz), 7.57(1H, s), 8.05(2H, brs)

Example 448

(2-{4-[1-(6-methoxy-3-pyridinyl)-4-methyl-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride

oil

MS(ESI+) : m/z 325 (M+H)

1HNMR (200MHz, DMSOd6): 2.03 (3H, s), 3.16 - 3.24 (2H, m), 3.83 (3H, s), 4.18 - 4.24 (2H, m), 6.84 (1H, d, J = 8.7Hz), 7.01 (2H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.8Hz), 7.56 (1H, dd, J = 2.7 ,8.7Hz), 7.64 (1H, s), 7.98 (1H, d, J = 2.7Hz), 8.28 (2H, brs)

Example 449

(2-{4-[1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride

amorphous powder

MS (ESI+) : m/z 356 (M+H)

1HNMR (200MHz, DMSOd6): 2.52 (3H, s), 3.14 - 3.23 (2H,

m), 3.77 (3H, s), 4.15 - 4.21 (2H, m), 6.57 (1H, s), 6.95 (4H, d, J = 8.9Hz), 7.17 (4H, d, J = 8.9Hz), 8.22 (2H, brs)

The following compound(s) was(were) obtained in a similar manner to that of Example 428.

Example 450

5-[4-(aminomethyl)phenyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carbonitrile hydrochloride

MASS (ESI+): m/z = 304.2 (M+1).

Example 451

To a solution of (2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride (126.4mg) and Et3N (125µl) in CH2Cl2 (2ml) was added methanesulfonyl chloride (34.7µl) under ice bath cooling. The mixture was stirred at ambient temperature for 1hour. Additional methanesulfonyl chloride (6.9µl) and Et3N (41.6µl) were added and the reaction mixture was stirred at ambient temperature for 30minutes. The mixture was concentrated in vacuo, and the residue was partitioned between AcOEt and 1M HCl. The aqueous layer was reextracted with AcOEt. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by AcOEt/n-hexane= 70%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo. The residue was crystallized from AcOEt-IPE to give N-(2-{4-[3-isopropenyl-1-(6-methoxy-

3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methane-sulfonamide (48.0mg) as white powder.

mp. 96-99°C

IR (KBr) : 3205, 3140, 1612, 1502cm-1

MS (ESI+) : m/z 429 (M+H)

1H NMR (CDCl3) δ 2.20(3H, s), 3.03(3H, s), 3.51-3.60(2H, m), 3.93(3H, s), 4.07-4.13(2H, m), 4.75(1H, t, J=5.8 Hz), 5.15(1H, brs), 5.60(1H, brs), 6.59(1H, s), 6.73(1H, d, J=8.9 Hz), 6.83(2H, d, J=8.8 Hz), 7.17(2H, d, J=8.8 Hz), 7.55(1H, dd, J=2.6,8.8 Hz), 8.09(1H, d, J=2.6 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 451.

Example 452

N-(2-{4-[3-{[(dimethylamino)carbonyl]amino}-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methane-sulfonamide

powder : mp. 166-167°C

IR (KBr) : 3309, 3188, 3182, 3174, 1657, 1651, 1643, 1568, 1514cm-1

Mass (ESI+) : 474 (M+H)+

200MHz 1H NMR (CDCl3, d) : 3.02(3H, s), 3.04(6H, s), 3.49-3.57(2H, m), 3.81(3H, s), 4.07(2H, t, J=5.0Hz), 4.84(1H, t, J=5.5 Hz), 6.78(2H, d, J=8.9 Hz), 6.85(2H, d, J=9.0 Hz), 6.85(1H, s), 7.05(1H, s), 7.15(2H, d, J=9.0 Hz), 7.18(2H, d, J=8.9 Hz)

Example 453

N-(2-{4-[3-[[(dimethylamino)carbonyl](methyl)amino]-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)-methanesulfonamide

amorphous

IR (neat) : 1658, 1649, 1641, 1631, 1620, 1612, 1518, 1502cm-1

Mass (ESI+) : 488 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.79(6H, s), 2.94(3H, s), 3.12(3H, s), 3.30-3.34(2H, m), 3.76(3H, s), 4.02(2H, t, J=5.4 Hz), 6.26(1H, s), 6.92(2H, d, J=8.7 Hz), 6.94(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.7 Hz), 7.16(2H, d, J=8.9 Hz), 7.29(1H, s)

Example 454

N-(2-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

white powder : mp. 112-114°C

IR (KBr) : 3280, 1612cm-1

Mass (ESI+) : 423 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.94(3H, s), 3.29-3.34(2H, m), 3.87(3H, s), 4.03(2H, t, J=5.4 Hz), 6.75(1H, s), 6.89(1H, d, J=8.8 Hz), 6.96(2H, d, J=8.7 Hz), 7.20(2H, d, J=8.7 Hz), 7.29(1H, brs), 7.67(1H, dd, J=2.7,8.8 Hz), 8.11(1H, d, J=2.7 Hz)

Example 455

N-(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp. 103-104°C

IR (KBr) : 3271, 1612, 1579, 1560, 1520, 1514cm-1

Mass (ESI+) : 418 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.94(3H, s), 3.28-3.33(2H, m), 3.76(3H, s), 3.83(3H, s), 3.98-4.05(2H, m), 6.05(1H, s), 6.88-6.96(4H, m), 7.09-7.17(4H, m), 7.27(1H, s)

Example 456

N-(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-

yl]phenoxy}ethyl)ethanesulfonamide

white powder : mp. 117.8-118.0°C

IR (KBr) : 3269, 1612, 1552, 1520cm-1

Mass (ESI+) : 432 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.18(3H, t, J=7.3 Hz), 3.04(2H, q, J=7.3 Hz), 3.26-3.34(2H, m), 3.75(3H, s), 3.83(3H, s), 3.96-4.03(2H, m), 6.05(1H, s), 6.91(2H, d, J=8.9 Hz), 6.92(2H, d, J=9.0 Hz), 7.09-7.17(4H, m), 7.32(1H, brs)

Example 457

N-(2-{4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)methanesulfonamide

white powder : mp. 146-147°C

IR (KBr) : 3130, 1612, 1518cm-1

Mass (ESI+) : 432 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 2.94(3H, s), 3.27-3.36(2H, m), 3.75(3H, s), 3.98-4.05(2H, m), 4.17(2H, q, J=7.0 Hz), 6.03(1H, s), 6.91(2H, d, J=8.8 Hz), 6.92(2H, d, J=9.0 Hz), 7.12(2H, d, J=9.0 Hz), 7.14(2H, d, J=8.8 Hz), 7.29(1H, t, J=5.8 Hz)

Example 458

N-(2-{4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

white powder : mp. 164.3-165.2°C

IR (KBr) : 3140, 2952, 2933, 2870, 1614, 1518cm-1

Mass (ESI+) : 460 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 0.97(6H, d, J=6.8 Hz), 2.03(1H, m), 2.94(3H, s), 3.27-3.36(2H, m), 3.75(3H, s), 3.90(2H, d, J=6.6 Hz), 3.99-4.05(2H, m), 6.05(1H, s), 6.88-6.96(4H, m), 7.12(2H, d, J=9.0 Hz), 7.14(2H, d, J=8.8 Hz), 7.28(1H, t, J=5.8 Hz)

Example 459

N-(2-{4-[3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

white powder : mp. 94.5-94.7°C

IR (KBr) : 3319, 2933, 2891, 1612, 1520cm-1

Mass (ESI+) : 462 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.94(3H, s), 3.29-3.35(2H, m), 3.30(3H, s), 3.62-3.67(2H, m), 3.75(3H, s), 3.98-4.05(2H, m), 4.22-4.27(2H, m), 6.05(1H, s), 6.89-6.95(4H, m), 7.10-7.17(4H, m), 7.28(1H, s)

Example 460

N-(2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

white powder : mp. 116.3-116.4°C

IR (KBr) : 3141, 2873, 1612, 1518cm-1

Mass (ESI+) : 476 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.13(3H, t, J=7.0 Hz), 2.94(3H, s), 3.28-3.40(2H, m), 3.49(2H, q, J=7.0 Hz), 3.66-3.71(2H, m), 3.75(3H, s), 3.98-4.05(2H, m), 4.21-4.26(2H, m), 6.06(1H, s), 6.89-6.95(4H, m), 7.09-7.17(4H, m), 7.29(1H, brs)

Example 461

N-(2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp. 116-117.5°C

IR (KBr) : 3126, 1614, 1520, 1500cm-1

MS (ESI+) : m/z 419 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.94(3H, s), 3.28-3.36(2H, m), 3.85(3H, s), 4.00-4.06(2H, m), 6.11(1H, s), 6.85(1H, d, J=8.9 Hz), 6.94(2H, d, J=8.8 Hz), 7.18(2H, d, J=8.8 Hz), 7.29(1H,

s), 7.60(1H, dd, J=2.6,8.9 Hz), 8.00(1H, d, J=2.6 Hz)

Example 462

N-(2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

white powder : mp. 122.0-122.6°C

IR (KBr) : 3242, 1614, 1518, 1502cm-1

MS (ESI+) : m/z 433 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 2.94(3H, s), 3.29-3.35(2H, m), 3.84(3H, s), 4.00-4.06(2H, m), 4.19(2H, q, J=7.0 Hz), 6.10(1H, s), 6.85(1H, d, J=8.8 Hz), 6.94(2H, d, J=8.7 Hz), 7.18(2H, d, J=8.7 Hz), 7.29(1H, brs), 7.59(1H, dd, J=2.7,8.8 Hz), 7.99(1H, d, J=2.7 Hz)

Example 463

N-(2-{4-[1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

MASS (ESI+): m/z = 492.1 (M+Na).

1HNMR (400MHz, CDCl3): 2.15 (3H, s), 3.03 (3H, s), 3.53 - 3.57 (2H, m),
3.79 (3H, s), 4.11 (2H, t, J = 5.0Hz), 4.78 (1H, t, J = 6.0Hz),
6.81 (2H, d, J = 9.0Hz), 6.86 (2H, d, J = 8.8Hz), 7.08 (2H, d, J = 8.8Hz),
7.13 (2H, d, J = 9.0Hz).

Example 464

N-[2-(4-{3-(difluoromethyl)-1-[4-(methylthio)phenyl]-1H-pyrazol-5-yl}phenoxy)ethyl]methanesulfonamide

mp: 122.7-122.8°C .

MASS (ESI+): m/z = 476.1 (M+Na).

1HNMR (400MHz, CDCl3): 2.49 (3H, s), 3.03 (3H, s), 3.55 (2H, dt, J = 4.9 ,6Hz), 4.1 (2H, t, J = 4.9Hz), 4.8 (1H, t, J = 6Hz), 6.66 (1H, s), 6.76 (1H, t, J = 55Hz), 6.83 (2H, d, J = 8.8Hz), 7.16 (2H, d, J = 8.8Hz), 7.22 (4H, s).

Example 465

N-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

Crystal. mp: 125-126°C

MASS (ESI+): 449.0 (M+Na).

1HNMR (400MHz, CDCl3): 2.91 (3H, s), 3.94 (3H, s), 4.34 (2H, d, J = 6.2Hz), 4.74 (1H, t, J = 6.2Hz), 6.74 (1H, s), 6.77 (1H, d, J = 8.8Hz), 7.24 (2H, d, J = 8.3Hz), 7.35 (2H, d, J = 8.3Hz), 7.58 (1H, dd, J = 2.7 ,8.8Hz), 8.03 (1H, d, J = 2.7Hz).

Example 466

N-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp: 125.7-126.1°C

MASS (ESI+): m/z = 431.0 (M+Na).

1HNMR (400MHz, CDCl3): 2.92 (3H, s), 3.94 (3H, s), 4.33 (2H, d, J = 6.1Hz), 4.73 (1H, b.s), 6.74 (1H, s), 6.77 (1H, t, J = 55Hz), 7.24 (2H, d, J = 8.8Hz), 7.25 (1H, d, J = 7.9Hz), 7.34 (2H, d, J = 7.9Hz), 7.55 (1H, dd, J = 2.3 ,8.8Hz), 8.03 (1H, d, J = 2.3Hz).

Example 467

N-(2-{4-[3-cyclopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp.95-97°C

MS (ESI+) : m/z 429 (M+H)

1HNMR (200MHz,): 0.70 - 0.78 (2H, m), 0.87 - 0.98 (2H, m), 1.87 - 1.99 (1H, m), 2.94 (3H, s), 3.20 - 3.52 (2H, m), 3.85 (3H, s), 3.99 - 4.05 (2H, m), 6.30 (1H, s), 6.85 (1H, d, J = 8.8Hz), 6.93 (2H, d, J = 8.7Hz), 7.15 (2H, d, J = 8.7Hz), 7.27 (1H, brs), 7.59 (1H, dd, J = 2.7 ,8.8Hz), 8.00 (1H, d, J = 2.7Hz)

Example 468

N-(2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp.149.1-150.3°C

Mass (ESI+) : 499 (M+H)

1HNMR (200MHz, DMSOd6): 1.43 - 1.74 (6H, m), 2.94 (3H, s), 3.25 - 3.39 (2H, m), 3.52 - 3.70 (2H, m), 3.77 - 3.92 (2H, m), 3.78 (3H, s), 3.99 - 4.06 (2H, m), 6.78 (1H, s), 6.93 (2H, d, J = 8.9Hz), 6.98 (2H, d, J = 8.9Hz), 7.18 (2H, d, J = 8.9Hz), 7.23 (2H, d, J = 8.9Hz), 7.27 (1H, brs)

Example 469

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methane-sulfonamide

mp.158.8-159.1°C

Mass (ESI+) : m/z 500 (M+H)

1HNMR (200MHz, DMSOd6): 1.43 - 1.74 (6H, m), 2.94 (3H, s), 3.22 - 3.40 (2H, m), 3.52 - 3.69 (2H, m), 3.75 - 3.91 (2H, m), 3.87 (3H, s), 4.00 - 4.07 (2H, m), 6.82 (1H, s), 6.90 (1H, d, J = 8.8Hz), 6.96 (2H, d, J = 8.8Hz), 7.22 (2H, d, J = 8.8Hz), 7.28 (1H, brs), 7.68 (1H, dd, J = 2.7 ,8.8Hz), 8.14 (1H, d, J = 2.7Hz)

Example 470

N-ethyl-1-(4-methoxyphenyl)-N-methyl-5-(4-{2-[(methylsulfonyl)amino]ethoxy}phenyl)-1H-pyrazole-3-carboxamide

mp.106.0-106.3°C

Mass (ESI+) : m/z 473 (M+H)

1HNMR (200MHz, DMSOd6): 1.08 - 1.22 (3H, m), 2.94 (3H, s), 2.97, 3.29 (3H, s), 3.28 - 3.35 (2H, m), 3.42 - 3.53, 3.67 - 3.79 (2H, m), 3.78 (3H, s), 3.99 - 4.06 (2H, m), 6.79, 6.81 (1H, s), 6.93 (2H, d, J = 8.9Hz), 6.98 (2H, d, J = 9Hz), 7.15 - 7.26 (4H, m), 7.28 (1H, brs)

Example 471

N-ethyl-1-(6-methoxy-3-pyridinyl)-N-methyl-5-(4-{2-[(methylsulfonyl)amino]ethoxy}phenyl)-1H-pyrazole-3-carboxamide

mp.110-111°C

Mass (ESI+) : m/z 474 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.23 (3H, m), 2.94 (3H, s), 2.98, 3.28 (3H, s), 3.28 - 3.36 (2H, m), 3.42 - 3.55, 3.66 - 3.78 (2H, m), 3.87 (3H, s), 4.01 - 4.07 (2H, m), 6.83, 6.85 (1H, s), 6.90 (1H, d, J = 9.0Hz), 6.96 (2H, d, J = 8.7Hz), 7.22 (2H, d, J = 8.7Hz), 7.28 (1H, brs), 7.61 - 7.75 (1H, m), 8.14 - 8.16 (1H, m)

Example 472

N-(2-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp. 155.6-155.8°C

MS (ESI+) : m/z 459 (M+H)

1HNMR (200MHz, DMSOd6): 1.16 (6H, d, J = 6.9Hz), 2.94 (3H, s), 3.25 - 3.40 (2H, m), 3.68 (1H, m), 3.88 (3H,

s), 4.01 - 4.07 (2H, m), 6.93 (1H, d, J = 8.7Hz), 6.96 (2H, d, J = 8.7Hz), 7.02 (1H, s), 7.23 (2H, d, J = 8.7Hz), 7.28 (1H, brs), 7.74 (1H, dd, J = 2.7 ,8.7Hz), 8.18 (1H, d, J = 2.7Hz)

Example 473

N-(2-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

oil

MS (ESI+) : m/z 473 (M+H)

1HNMR (200MHz, DMSOd6): 1.51 - 2.00 (8H, m), 2.94 (3H, s), 3.24 - 3.39 (2H, m), 3.84 (3H, s), 4 - 4.06 (2H, m), 4.98 (1H, m), 6.07 (1H, s), 6.84 (1H, d, J = 8.8Hz), 6.94 (2H, d, J = 8.8Hz), 7.18 (2H, d, J = 8.8Hz), 7.28 (1H, brs), 7.58 (1H, dd, J = 2.7 ,8.8Hz), 7.99 (1H, d, J = 2.7Hz)

Example 474

N-(2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp.131.3-131.4°C

MS (ESI+) : m/z 486 (M+H)

1HNMR (200MHz, DMSOd6): 2.94 (3H, s), 3.25 - 3.39 (2H, m), 3.76 (3H, s), 3.99 - 4.05 (2H, m), 4.81 (1H, d, J = 9.0Hz), 4.90 (1H, d, J = 9.0Hz), 6.22 (1H, s), 6.90 - 6.98 (4H, m), 7.11 - 7.18 (4H, m), 7.28 (1H, brs)

Example 475

N-(2-{4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp. 145.0-145.1°C

MS (ESI+) : m/z 468 (M+H)

1HNMR (200MHz, DMSOd6): 2.93 (3H, s), 3.28 - 3.34 (2H, m), 3.76 (3H, s), 3.99 - 4.05 (2H, m), 4.44 (2H, dt, J = 3.5 ,14.9Hz), 6.15 (1H, s), 6.41 (1H, tt, J = 3.5, 54.6Hz), 6.92 (2H, d, J = 9.0Hz), 6.93 (2H, d, J = 9.0Hz), 7.11 - 7.18 (4H, m), 7.27 (1H, brs)

Example 476

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

oil

MS (ESI+) : m/z 487 (M+H)

1HNMR (200MHz, DMSOd6): 2.94 (3H, s), 3.29 - 3.35 (2H, m), 3.85 (3H, s), 4.00 - 4.06 (2H, m), 4.83 (1H, d, J = 9.0Hz), 4.92 (1H, d, J = 9.0Hz), 6.28 (1H, s), 6.87 (1H, d, J = 8.8Hz), 6.95 (2H, d, J = 8.8Hz), 7.19 (2H, d, J = 8.8Hz), 7.28 (1H, brs), 7.61 (1H, dd, J = 2.7 ,8.9Hz), 8.03 (1H, d, J = 2.7Hz)

Example 477

N-(2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

solid

MS (ESI+) : m/z 469 (M+H)

1HNMR (200MHz, CDCl3): 3.03 (3H, s), 3.51 - 3.60 (2H, m), 3.92 (3H, s), 4.07 - 4.13 (2H, m), 4.46 (2H, dt, J = 4.2 ,13.4Hz), 4.76 (1H, t, J = 6Hz), 5.95 (1H, s), 6.17 (1H, tt, J = 4.2, 55.4Hz), 6.72 (1H, d, J = 8.8Hz), 6.83 (2H, d, J = 8.8Hz), 7.15 (2H, d, J = 8.8Hz), 7.49 (1H, dd, J = 2.8 ,8.8Hz), 8.01 (1H, d, J = 2.8Hz)

Example 478

N-(2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)-2-hydroxyethanesulfonamide

mp.139.1-139.4°C

MS (ESI+) : m/z 452 (M+H)

1HNMR (200MHz, DMSOd6): 3.18 - 3.35 (4H, m), 3.69 - 3.77 (2H, m), 3.78 (3H, s), 3.97 - 4.04 (2H, m), 4.90 (1H, t, J = 5.6Hz), 6.69 (1H, s), 6.90 - 7.01 (4H, m), 7.14 - 7.26 (5H, m)

Example 479

N-(2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

oil

Mass (ESI+) : m/z 439 (M+H)

1HNMR (200MHz, CDCl3): 3.03 (3H, s), 3.51 - 3.60 (2H, m), 3.94 (3H, s), 4.08 - 4.14 (2H, m), 4.75 (1H, t, J = 5.6Hz), 6.68 (1H, s), 6.75 (1H, d, J = 8.9Hz), 6.76 (1H, t, J = 55Hz), 6.85 (2H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.8Hz), 7.53 (1H, dd, J = 2.7 ,8.9Hz), 8.08 (1H, d, J = 2.7Hz)

Example 480

N-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.179.3-179.6°C

MS (ESI+) : m/z 469 (M+H)

1HNMR (200MHz, DMSOd6): 1.42 - 1.72 (6H, m), 2.85 (3H, s), 3.52 - 3.69 (2H, m), 3.75 - 3.92 (2H, m), 3.78 (3H, s), 4.15 (2H, s), 6.85 (1H, s), 6.98 (2H, d, J = 9Hz), 7.21 - 7.35 (6H, m), 7.58 (1H, brs)

Example 481

N-ethyl-1-(4-methoxyphenyl)-N-methyl-5-(4-{[(methyl-sulfonyl)amino]methyl}phenyl)-1H-pyrazole-3-carboxamide

mp.149.8-150.8°C

MS (ESI+) : m/z 443 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.21 (3H, m), 2.86 (3H, s), 2.98, 3.29 (3H, s), 3.40 - 3.78 (2H, m), 3.78 (3H, s), 4.13 - 4.17 (2H, m), 6.86, 6.88 (1H, s), 6.98 (2H, d, J = 9Hz), 7.21 - 7.35 (6H, m), 7.58 (1H, brs)

Example 482

N-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-benzyl}methanesulfonamide

mp.130.9-131.0°C

MS (ESI+) : m/z 400 (M+H)

1HNMR (200MHz, DMSOd6): 1.27 (6H, d, J = 6.9Hz), 2.84 (3H, s), 2.96 (1H, m), 3.76 (3H, s), 4.14 (2H, s), 6.47 (1H, s), 6.93 (2H, d, J = 8.9Hz), 7.11 - 7.21 (4H, m), 7.30 (2H, d, J = 8.2Hz), 7.56 (1H, brs)

Example 483

N-{4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.155.8-155.9°C

MS (ESI+) : m/z 428 (M+H)

1HNMR (200MHz,): 1.16 (6H, d, J = 6.9Hz), 2.86 (3H, s), 3.68 (1H, m), 3.79 (3H, s), 4.15 (2H, s), 7.00 (2H, d, J = 8.9Hz), 7.06 (1H, s), 7.22 - 7.35 (6H, m), 7.58 (1H, s)

Example 484

N-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-

carbonyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.182.6-182.9°C

MS (ESI+) : m/z 470 (M+H)

1HNMR (200MHz, DMSOd6): 1.42 - 1.72 (6H, m), 2.86 (3H, s), 3.53 - 3.69 (2H, m), 3.75 - 3.9 (2H, m), 3.87 (3H, s), 4.16 (2H, s), 6.89 (1H, s), 6.90 (1H, d, J = 8.8Hz), 7.28 (2H, d, J = 8.4Hz), 7.36 (2H, d, J = 8.4Hz), 7.59 (1H, s), 7.70 (1H, dd, J = 2.7 ,8.8Hz), 8.14 (1H, d, J = 2.7Hz)

Example 485

N-ethyl-1-(6-methoxy-3-pyridinyl)-N-methyl-5-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1H-pyrazole-3-carboxamide

white powder

MS (ESI+) : m/z 444 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.23 (3H, m), 2.86 (3H, s), 2.98, 3.29 (3H, s), 3.49, 3.72 (2H, q, J = 7.1Hz), 3.87 (3H, s), 4.16 (2H, s), 6.88 - 6.93 (2H, m), 7.28 (2H, d, J = 8.3Hz), 7.36 (2H, d, J = 8.3Hz), 7.56 (1H, brs), 7.65 - 7.74 (1H, m), 8.13 - 8.14 (1H, m)

Example 486

N-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

oil

MS (ESI+) : m/z 401 (M+H)

1HNMR (200MHz, CDCl3): 1.34 (6H, d, J = 6.9Hz), 2.86 (3H, s), 3.03 (1H, m), 3.90 (3H, s), 4.28 (2H, d, J = 6.1Hz), 5.19 (1H, t, J = 6.1Hz), 6.34 (1H, s), 6.72 (1H, d, J = 8.8Hz), 7.21 (2H, d, J = 8.2Hz), 7.29 (2H, d, J = 8.2Hz), 7.56 (1H, dd, J = 2.7 ,8.8Hz), 7.98 (1H, d, J = 2.7Hz)

Example 487

N-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.160.8-161.2°C

MS (ESI+) : m/z 429 (M+H)

1HNMR (200MHz, DMSOd6): 1.16 (6H, d, J = 6.8Hz), 2.86 (3H, s), 3.68 (1H, m), 3.88 (3H, s), 4.16 (2H, d, J = 5.5Hz), 6.93 (1H, d, J = 8.8Hz), 7.09 (1H, s), 7.29 (2H, d, J = 8.3Hz), 7.36 (2H, d, J = 8.3Hz), 7.59 (1H, t, J = 5.5Hz), 7.76 (1H, dd, J = 2.8 ,8.8Hz), 8.18 (1H, d, J = 2.7Hz)

Example 488

N-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.94.0-94.3°C

MS (ESI+) : m/z 388 (M+H)

1HNMR (200MHz, DMSOd6): 2.85 (3H, s), 3.76 (3H, s), 3.84 (3H, s), 4.14 (2H, s), 6.12 (1H, s), 6.92 (2H, d, J = 8.9Hz), 7.14 (2H, d, J = 8.9Hz), 7.20 (2H, d, J = 8.2Hz), 7.30 (2H, d, J = 8.2Hz), 7.57 (1H, s)

Example 489

N-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

amorphous

MS (ESI+) : m/z 416 (M+H)

1HNMR (200MHz, DMSOd6): 1.32 (6H, d, J = 6.1Hz), 2.85 (3H, s), 3.75 (3H, s), 4.14 (2H, s), 4.77 (1H, m), 6.07 (1H, s), 6.91 (2H, d, J = 8.9Hz), 7.13 (2H, d, J = 8.9Hz), 7.19 (2H, d, J = 8.2Hz), 7.30 (2H, d, J = 8.2Hz), 7.57

(1H, brs)

Example 490

N-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoro-ethoxy)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.130-131°C

Mass (ESI+) : 457 (M+H)

1HNMR (200MHz, CDCl3): 2.92 (3H, s), 3.93 (3H, s), 4.33 (2H, d, J = 6.0Hz), 4.54 - 4.71 (1H, m), 4.62 (1H, d, J = 8.4Hz), 4.70 (1H, d, J = 8.4Hz), 6.04 (1H, s), 6.73 (1H, d, J = 8.8Hz), 7.22 (2H, d, J = 8.3Hz), 7.33 (2H, d, J = 8.3Hz), 7.52 (1H, dd, J = 2.7 ,8.8Hz), 7.95 (1H, d, J = 2.7Hz)

Example 491

N-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

mp.68.3-69.3°C

Mass (ESI+) : 392 (M+H)

1HNMR (200MHz, DMSOd6): 2.85 (3H, s), 3.77 (3H, s), 4.14 (2H, s), 6.76 (1H, s), 6.96 (2H, d, J = 8.9Hz), 7.17 - 7.24 (4H, m), 7.32 (2H, d, J = 8.2Hz), 7.58 (1H, s)

Example 492

N-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide

oil

Mass (ESI+) : 393 (M+H)

1HNMR (200MHz, DMSOd6): 2.86 (3H, s), 3.86 (3H, s), 4.16 (2H, s), 6.82 (1H, s), 6.89 (1H, d, J = 8.8Hz), 7.26 (2H, d, J = 8.3Hz), 7.35 (2H, d, J = 8.3Hz), 7.59 (1H, brs), 7.69 (1H, dd, J = 2.7 ,8.8Hz), 8.1 (1H, d, J = 2.7Hz)

Example 493

N-(2-{4-[1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazol-5-yl]phenoxy}ethyl)methanesulfonamide

mp. 165.0-166.0°C

MS (ESI+) : m/z 434 (M+H)

1HNMR (200MHz, DMSOd6): 2.51 (3H, s), 2.94 (3H, s), 3.27 - 3.36 (2H, m), 3.77 (3H, s), 3.99 - 4.05 (2H, m), 6.56 (1H, s), 6.92 (2H, d, J = 8.8Hz), 6.95 (2H, d, J = 8.9Hz), 7.15 (2H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.9Hz), 7.27 (1H, t, J = 5.8Hz)

Example 494

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)benzenesulfonamide

amorphous powder

Mass (ESI+) : 503 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.64-2.72(2H, m), 2.91-3.02(2H, m), 3.88(3H, s), 6.91(1H, d, J=9.0 Hz), 7.03-7.21(5H, m), 7.56-7.80(7H, m), 8.18(1H, d, J=2.6 Hz)

Example 495

N-methoxy-1-(4-methoxyphenyl)-N-methyl-5-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)-1H-pyrazole-3-carboxamide

oil

Mass (ESI+) : m/z 459 (M+H)

1HNMR (200MHz, CDCl3): 2.84 - 2.91 (2H, m), 2.87 (3H, s), 3.35 - 3.46 (2H, m), 3.51 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 4.26 (1H, t, J = 6.2Hz), 6.86 (2H, d, J = 9.0Hz), 6.97 (1H, s), 7.12 - 7.29 (6H, m)

Example 496

N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-5-(4-{2-[(methylsulfonyl)amino]ethyl}phenyl)-1H-pyrazole-3-carboxamide

oil

Mass (ESI+) : m/z 460 (M+H)

1HNMR (200MHz, CDCl3): 2.80 - 2.93 (2H, m), 2.88 (3H, s), 3.36 - 3.47 (2H, m), 3.50 (3H, s), 3.85 (3H, s), 3.94 (3H, s), 4.28 (1H, t, J = 6.2Hz), 6.75 (1H, d, J = 8.8Hz), 6.98 (1H, s), 7.20 (4H, s), 7.56 (1H, dd, J = 2.7 ,8.8Hz), 8.10 (1H, d, J = 2.7Hz)

Example 497

Trimethylsilyl isocyanate (73.8µl) was addded to a solution of (2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine dihydrochloride (115.4mg) and Et3N (114µl) and the mixture was stirred at ambient temperature for 1.5 hours. The mixture was concentrated in vacuo and the residue was partitioned between AcOEt and 1M HCl. The aqueous layer was reextracted with AcOEt. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 10% MeOH/CHCl3. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo. The residue was crystallized from AcOEt-IPE to give N-(2-{4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea (40.1mg) as a white powder.

white powder : mp. 94-98°C

IR (KBr) : 3435, 3388, 3344, 3333, 1657, 1631, 1610, 1577, 1572, 1562, 1552, 1502cm-1

1H NMR (DMSO-d6) δ 2.10(3H, s), 3.28-3.27(2H, m), 3.86(3H, s), 3.91-3.97(2H, m), 5.15(1H, brs), 5.53(2H, s), 5.62(1H, brs), 6.16(1H, t, J=5.5 Hz), 6.84(1H, s), 6.88(1H, d, J=8.8 Hz), 6.95(2H, d, J=8.8 Hz), 7.19(2H, d, J=8.8 Hz), 7.64(1H, dd, J=2.7,8.8 Hz), 8.07(1H, d, J=2.7 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 497.

Example 498

N-(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp. 108-111°C

IR (KBr) : 3388, 3342, 1657, 1631, 1612, 1593, 1577, 1562, 1522cm-1

Mass (ESI+) : 383 (M+H)+

200MHz 1H NMR (CDCl3, d) : 3.54-3.62(2H, m), 3.79(3H, s), 3.96(3H, s), 3.98-4.04(2H, m), 4.44(2H, s), 5.03(1H, t, J=5.5 Hz), 5.88(1H, s), 6.78(2H, d, J=8.8 Hz), 6.82(2H, d, J=8.9 Hz), 7.12(2H, d, J=8.8 Hz), 7.16(2H, d, J=8.9 Hz)

Example 499

N-(2-{4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

white powder : mp. 154.2-154.4°C

IR (KBr) : 3398, 3332, 1658, 1631, 1612, 1566, 1518cm-1

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 3.27-3.34(2H, m), 3.75(3H, s), 3.89-3.96(2H, m), 4.17(2H, q, J=7.0 Hz), 5.53(2H, s), 6.03(1H, s), 6.15(1H, t, J=5.6

Hz), 6.90(2H, d, J=8.9 Hz), 6.92(2H, d, J=9.0 Hz), 7.10-7.15(4H, m)

Example 500

Imidazole (680mg) and t-butyldimethylsilyl chloride (903mg) was added successively to a solution of ethyl 5-[4-{2-(hydroxy)ethoxy}phenyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (1.91g) in DMF (15ml) under cooling in an ice bath. After stirring at ambient temperature for 2hours, the mixture was partitioned between AcOEt and H2O. The oreganic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over MgSO4, concentrated in vacuo. The residual crystals were collected and washed with n-hexane to give ethyl 5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)-phenyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (2.34g).

powder

mp. 86-87°C

MS (ESI+) : m/z 497 (M+H)

1H NMR (CDCl3) δ 0.09(6H, s), 0.90(9H, s), 1.42(3H, t, J=7.1 Hz), 3.82(3H, s), 3.94-3.97(2H, m), 4.01-4.04(2H, m), 4.44(2H, q, J=7.1 Hz), 6.83(2H, d, J=8.7 Hz), 6.85(2H, d, J=8.9 Hz), 6.96(1H, s), 7.11(2H, d, J=8.7 Hz), 7.24(2H, d, J=8.9 Hz)

Example 501

A solution of ethyl 5-[4-(2-{[tert-butyl(dimethyl)silyl]-oxy}ethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (0.3g) in THF (3ml) was added dropwise to a 1M solution of methylmagnesium bromide (3ml) at ambient temperature. The reaction mixture was stirred at ambient

temperature for 1hour, then was poured into a mixture of crushed ice and saturated aqueous ammonium chloride solution. The mixture was extracted with AcOEt. The oreganic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give 2-[5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}-ethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-2-propanol (0.27g) as an oil.

oil

MS (ESI+) : m/z 483 (M+H)

1H NMR (CDCl3) δ 0.09(6H, s), 0.90(9H, s), 1.65(6H, s), 3.81(3H, s), 3.94-3.97(2H, m), 4.01-4.04(2H, m), 6.35(1H, s), 6.82(2H, d, J=8.8 Hz), 6.85(2H, d, J=8.9 Hz), 7.12(2H, d, J=8.8 Hz), 7.21(2H, d, J=8.9 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 501.

Example 502

N-(2-{4-[3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

white powder : mp. 147-152°C

IR (KBr) : 3333, 3271, 2976, 1676, 1664, 1658, 1612, 1547, 1537, 1516, 1502cm-1

MS (ESI+) : m/z 411 (M+H)

1H NMR (DMSO-d6) δ 1.48(6H, s), 3.22-3.40(2H, m), 3.76(3H, s), 3.90-3.96(2H, m), 4.98(1H, s), 5.52(2H, s), 6.14(1H, t, J=5.6 Hz), 6.49(1H, s), 6.90(2H, d, J=8.7 Hz), 6.94(2H, d, J=8.8 Hz), 7.12(2H, d, J=8.7 Hz), 7.15(2H, d, J=8.8 Hz)

Example 503

tert-butyl {4-[3-(1-hydroxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate

powder

MS (ESI+) : m/z 438 (M+H)

1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 1.49 (6H, s), 3.76 (3H, s), 4.11 (2H, d, J = 6.1Hz), 5.01 (1H, s), 6.54 (1H, s), 6.94 (2H, d, J = 8.9Hz), 7.15 (2H, d, J = 8.9Hz), 7.17 (4H, brs), 7.4 (1H, t, J = 6.1Hz)

Example 504

tert-butyl {4-[3-(1-hydroxy-1-methylethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}-carbamate

powder

MS (ESI+) : m/z 439 (M+H)

1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 1.49 (6H, s), 3.85 (3H, s), 4.12 (2H, d, J = 6.1Hz), 5.05 (1H, s), 6.59 (1H, s), 6.86 (1H, d, J = 8.8Hz), 7.20 (4H, s), 7.40 (1H, t, J = 6.1Hz), 7.62 (1H, dd, J = 2.7 ,8.8Hz), 8.00 (1H, d, J = 2.7Hz)

Example 505

A solution of 2-[5-[4-(2-{[tert-butyl(dimethyl)silyl]-oxy}ethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-2-propanol (180mg) in DMF (2ml) was added dropwise to a suspension of sodium hydride 60% dispersion in mineral oil (17mg) in DMF (1ml) under cooling in an ice bath. After 10minutes, iodemethane (63.5mg) was added and the reaction mixture was stirred at same temperature for 1hour and at ambient temperature for 1hour. Additional iodomethane was added until all starting material was consumed. The reaction was quenched by adding saturated ammonium chloride. The

mixture was extracted with ethyl acetate. The organic layer was washed with H2O and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane, which polarity was gradually changed from 20% to 80%, to give 5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)phenyl]-3-(1-methoxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazole (32.2mg) as an oil.

Mass (ESI+) : 497 (M+H)

1H NMR (CDCl3) δ 0.09(6H, s), 0.90(9H, s), 1.58(3H, s), 1.63(3H, s), 3.22(3H, s), 3.81(3H, s), 3.93-4.04(4H, m), 6.42(1H, s), 6.82(2H, d, J=8.8 Hz), 6.84(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.8 Hz), 7.22(2H, d, J=9.0 Hz)

Example 506

A 1M solution of tetra-n-butylammonium fluoride in THF (0.24ml) was added to a solution of 5-[4-(2-{[tert-butyl-(dimethyl)silyl]oxy}ethoxy)phenyl]-3-(1-methoxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazole (98mg) in THF(2ml) under ice bath cooling. The reaction mixture was stirred at same temperature for 1hour. The mixture was partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 50% AcOEt / n-hexane. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give 2-{4-[3-(1-methoxy-1-methylethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol (66mg) as an oil.

IR (neat) : 3423, 3398, 3371, 2976, 2935, 1647, 1612, 1566,

1549, 1512cm-1

MS (ESI+) : m/z 383 (M+H)

1H NMR (CDCl3) δ 1.60(3H, s), 1.63(3H, s), 2.03(1H, t, J=6.1 Hz), 3.22(3H, s), 3.81(3H, s), 3.91-4.00(2H, m), 4.05-4.10(2H, m), 6.43(1H, s), 6.83(2H, d, J=8.9Hz), 6.84(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.9 Hz), 7.21(2H, d, J=8.9 Hz)

Example 507

A 4M solution of HCl in dioxane (2ml) was added to a solution of ethyl 5-(4-{2-[(tert-butoxycarbonyl)amino]ethoxy}-phenyl)-1-(4- methoxyphenyl)-1H-pyrazole-3-carboxylate (300mg) in CH2Cl2 (3ml) under coolingin an ice bath. After stirring at ambient temperature for 1hour, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH2Cl2 (3ml), Et3N (189mg) and trimethylsilyl isocyanate (108mg) were added, and the mixture was stirred at ambient temperature overnight. The stirring was continued for more 4hours, adding more trimethylsilyl isocyanate and Et3N to consume all starting material. The mixture was concentrated in vacuo and the residue was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residual crystals were suspended in hot ethyl acetate, cooled with stirring, collected and washed with ethyl acetate to give ethyl 5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (217mg) as a white powder.

MS (ESI+) : m/z 425 (M+H)

1H NMR (DMSO-d6) δ 1.31(3H, t, J=7.1 Hz), 3.27-3.36(2H, m), 3.79(3H, s), 3.90-3.96(2H, m), 4.32(2H, q, J=7.1Hz), 5.52(2H,

s), 6.14(1H, t, J=5.7 Hz), 6.92(2H, d, J=8.8 Hz), 6.99(2H, d, J=8.8 Hz), 7.01(1H, s), 7.17(2H, d, J=8.8 Hz), 7.25(2H, d, J=8.8 Hz)

Example 508

1M NaOH (5ml) was added to a solution of ethyl 5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (1.75g) in THF (15ml) and MeOH (10ml). The reaction mixture was stirred at ambient temperature and concentrated in vacuo. The residue was dissolved in H2O and acidified by 1M HCl. white precipitates were collected and washed successively with H2O and IPE to give 5-(4-{2-[(aminocarbonyl)amino]-ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylic acid (1.58g) as a white powder.
MS (ESI+) : m/z 397 (M+H)
1H NMR (DMSO-d6) δ 3.15-3.55(2H, m), 3.90-3.97(2H, m), 5.52(2H, s), 6.14(1H, t, J=5.7Hz), 6.89-7.03(5H, m), 7.17(2H, d, J=8.8 Hz), 7.24(2H, d, J=8.9 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 508.

Example 509

5-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylic acid
white powder
MS (ESI+) : m/z 424(M+H)
1HNMR (200MHz, DMSOd6): 1.38 (9H, s), 3.79 (3H, s), 4.11 (2H, d, J = 6.1Hz), 6.99 (2H, d, J = 8.9Hz), 7.01 (1H, s), 7.20 (4H, brs), 7.25 (2H, d, J = 8.9Hz), 7.41 (1H, t, J = 6.1Hz), 12.92 (1H, brs)

Example 510

5-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazole-3-carboxylic acid

powder

MS (ESI+) : m/z 425 (M+H)

1HNMR (200MHz, CDCl3): 1.46 (9H, s), 3.95 (3H, s), 4.33 (2H, d, J = 5.9Hz), 4.9 (1H, brs), 6.76 (1H, d, J = 8.8Hz), 7.07 (1H, s), 7.19 (2H, d, J = 8.4Hz), 7.27 (2H, d, J = 8.4Hz), 7.58 (1H, dd, J = 2.7 ,8.8Hz), 8.11 (1H, d, J = 2.7Hz)

Example 511

A mixture of 5-(4-{2-[(aminocarbonyl)amino]ethoxy}-phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylic acid (1.56g), diphenylphosphoryl azide (1.62g), and Et3N (597mg) in t-butanol (5ml) was refluxed for 3hours. The mixture was concentrated in vacuo, and the residue was partitioned between ethyl acetate and H2O. The combined organic layer was washed twice with 1M HCl. and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with ethyl acetate to give tert-butyl [5-(4-{2-[(aminocarbonyl)amino]-ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]carbamate (519mg) as an amorphous powder.

MS (ESI+) : m/z 468 (M+H)

1H NMR (DMSO-d6) δ 1.46(9H, s), 3.27-3.36(2H, m), 3.76(3H, s), 3.90-3.96(2H, m), 5.52(2H, s), 6.15(1H, t, J=5.6 Hz), 6.55(1H, s), 6.90(2H, d, J=8.9 Hz), 6.93(2H, d, J=8.9 Hz), 7.13(4H, d, J=8.9 Hz), 9.74(1H, s)

Example 512

A 4M solution of HCl in dioxane (3ml) was added to a solution of tert-butyl [5-(4-{2-[(aminocarbonyl)amino]ethoxy}-phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]carbamate (478mg) in CH2Cl2 (3ml). The reaction mixture was stirred at ambient temperature for 5hours and concentrated in vacuo. The residue was partitioned between CHCl3 and saturated aqueous sodium bicarbonate solution. The aq layer was reextrated with CHCl3. The combined organic layer was dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with CHCl3:MeOH:28% aqueous NH4OH=10:1:0.1 to give N-(2-{4-[3-amino-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea (244.6mg) as an amorphous powder.

MS (ESI+) : m/z 368 (M+H)

IR (neat) : 3400, 3388, 3342, 3330, 1658, 1651, 1643, 1612, 1579, 1562, 1554, 1520cm-1

1H NMR (DMSO-d6) δ 3.27-3.37(2H, m), 3.73(3H, s), 3.89-3.95(2H, m), 4.83(2H, s), 5.52(2H, s), 5.73(1H, s), 6.15(1H, t, J=5.5 Hz), 6.85-6.92(4H, m), 7.03-7.12(4H, m)

Example 513

37% aqueous solution of formaldehyde (0.23ml) and sodium cyanoborohydride (53mg) were added to a solution of N-(2-{4-[3-amino-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)urea (103.1mg) in MeOH (2ml). The reaction mixture was stirred at ambient temperature for 3hours. 37% aqueous solution of formaldehyde (0.23ml) and sodium cyanoborohydride (53mg) were added to the mixture and the reaction mixture was stirred at ambient temperature for 4days. The mixture was concentrated in vacuo, and the residue was

partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by CHCl3 : MeOH : 28%aqueous NH4OH= 100:10:1. The seaparated silica gel was extracted with same solvent and the solvent was evaporated in vacuo to give N-(2-{4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea (59.9mg) as an amorphous powder.

MS (ESI+) : m/z 396 (M+H)

1H NMR (DMSO-d6) δ 2.81(6H, s), 3.27-3.36(2H, m), 3.74(3H, s), 3.89-3.96(2H, m), 5.52(2H, s), 5.78(1H, s), 6.15(1H, t, J=5.7 Hz), 6.87-6.92(4H, m), 7.05-7.15(4H, m)

Example 514

To a solution of 4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol (98.7mg) in DMF (2ml) was added sodium hydride 60% dispersion in mineral oil (15.3mg). The mixture was stirred at ambient temperature for 1hour. To the reaction mixture was added (2-bromoethoxy)-tert-butyldimethylsilane (153mg) in DMF (1ml) dropwise and the mixture was stirred at ambient temperature overnight. The mixture was poured into ice water, extracted with AcOEt, washed with H2O and saturated aqueous sodium chloride solution. The aqueous layer was reextracted with AcOEt. The combined organic layers were dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in EtOH (2ml). To this solution was added concentrated hydrochloric acid (100μl) and the mixture was stirred at ambient temperature for 3hours. The mixture was concentrated in vacuo, and the residue was partitioned between AcOEt and saturated

aqueous sodium bicarbonate solution, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by AcOEt / n-hexane = 60%. The residual crystals were collected and washed with IPE to give 2-{4-[3-(dimethylamino)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol (97mg) as a white powder.
mp. 120-122°C
IR (KBr) : 3292, 2924, 1612, 1577, 1562, 1531, 1514cm-1
Mass (ESI+) : 354 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.81(6H, s), 3.66-3.72(2H, m), 3.74(3H, s), 3.94-4.00(2H, m), 4.86(1H, br), 6.02(1H, s), 6.86-6.94(4H, m), 7.10(2H, d, J=8.9 Hz), 7.12(2H, d, J=8.7 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 514.

Example 515
N-[5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N',N'-trimethylurea
oil
IR (neat) : 3410, 2931, 1658, 1649, 1641, 1631, 1612, 1518, 1502cm-1
Mass (ESI+) : 411 (M+H)+
200MHz 1H NMR (CDCl3, d) : 2.08(1H, t, J=5.9 Hz), 2.89(6H, s), 3.33(3H, s), 3.81(3H, s), 3.92-4.00(2H, m), 4.05-4.10(2H, m), 6.15(1H, s), 6.84(4H, d, J=9.1 Hz), 7.14(2H, d, J=9.1 Hz), 7.19(2H, d, J=9.1 Hz)

Example 516

2-{4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethanol

white powder : mp. 67.7-69.2°C

IR (ATR) : 3363, 2993, 2956, 2925, 2837, 1610, 1577, 1552, 1508cm-1

Mass (ESI+) : 355 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.42(3H, t, J=7.1 Hz), 2.01(1H, t, J=6.0 Hz), 3.79(3H, s), 3.92-4.00(2H, m), 4.04-4.10(2H, m), 4.29(2H, q, J=7.1 Hz), 5.87(1H, s), 6.77-6.85(4H, m), 7.14(2H, d, J=8.8 Hz), 7.17(2H, d, J=8.9 Hz)

Example 517

2-{4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethanol

oil

Mass (ESI+) : m/z 383 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.03(6H, d, J=6.8 Hz), 2.02(1H, t, J=6.1 Hz), 2.11(1H, m), 3.79(3H, s), 3.91-4.09(4H, m), 3.99(2H, d, J=6.8 Hz), 5.88(1H, s), 6.77-6.86(4H, m), 7.09-7.21(4H, m)

Example 518

2-{4-[3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol

oil

Mass (ESI+) : 385 (M+H)+

IR (neat) : 3400, 3390, 3369, 2935, 1612, 1517cm-1

200MHz 1H NMR (DMSO-d6, d) : 3.31(3H, s), 3.62-3.73(4H, m), 3.75(3H, s), 3.94-3.99(2H, m), 4.22-4.27(2H, m), 4.85(1H, t, J=5.5 Hz), 6.04(1H, s), 6.89(2H, d, J=8.8 Hz), 6.92(2H, d, J=8.9 Hz), 7.08-7.15(4H, m)

Example 519

2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol

oil

IR(neat) : 2972, 2933, 2873, 1612, 1554, 1518, 1510cm-1

Mass (ESI+) : 399 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.25(3H, t, J=7.0 Hz), 2.04(1H, t, J=6.1 Hz), 3.61(2H, q, J=7.0 Hz), 3.78-3.83(2H, m), 3.79(3H, s), 3.93-4.00(2H, m), 4.04-4.07(2H, m), 4.38-4.44(2H, m), 5.92(1H, s), 6.82(4H, d, J=8.8 Hz), 7.13(2H, d, J=8.8 Hz), 7.16(2H, d, J=8.8 Hz)

Example 520

2-{[5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]oxy}-N,N-dimethylacetamide

white powder : mp. 106.6-107.1°C

IR (KBr) : 3321, 2939, 1658, 1643, 1608, 1518cm-1

MS (ESI+) : m/z 412 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.84(3H, s), 2.97(3H, s), 3.65-3.73(2H, m), 3.75(3H, s), 3.94-4.00(2H, m), 4.87(1H, t, J=5.1 Hz), 4.87(2H, s), 6.07(1H, s), 6.90(2H, d, J=8.8 Hz), 6.92(2H, d, J=9.0 Hz), 7.11(2H, d, J=9.0 Hz), 7.12(2H, d, J=8.8 Hz)

Example 521

2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

white powder : mp.92.2-92.5°C

IR (KBr) : 3325, 1614, 1525, 1504cm-1

MS (ESI+) : m/z 342 (M+H)+

200MHz 1H NMR (CDCl3, d) : 2.01(1H, t, J=6.1 Hz), 3.92-4.10(4H, m), 3.92(3H, s), 3.97(3H, s), 5.91(1H, s), 6.70(1H, d, J=8.5

Hz), 6.85(2H, d, J=8.8 Hz), 7.15(2H, d, J=8.8 Hz), 7.52(1H, dd, J=2.5,8.5 Hz), 8.04(1H, d, J=2.5 Hz)

Example 522

2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

white powder : mp. 81-82°C

IR (KBr) : 3303, 3298, 1612, 1516cm-1

Mass (sample ID cox022145) (ESI+) : 356 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 3.65-3.74(2H, m), 3.84(3H, s), 3.95-4.01(2H, m), 4.19(2H, q, J=7.0 Hz), 4.87(1H, t, J=5.4 Hz), 6.09(1H, s), 6.85(1H, d, J=8.8 Hz), 6.93(2H, d, J=8.8 Hz), 7.16(2H, d, J=8.8 Hz), 7.58(1H, d, J=2.6,8.8 Hz), 7.99(1H, d, J=2.6 Hz)

Example 523

To a solution of 5-(hydroxyl)phenyl-1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazole (5.0g) and 2-bromoethoxy-tert-butyldimethylsilane (6.87g) in DMF (100ml) was added portionwise NaH (919mg, 50% in oil) at room temperature. The reacion mixture was stirred overnight. The reaction mixture was quenched with water. Aqueouslayer was extracted twice with EtOAc. Combined organic layer was washed twice with water, and brine. Dried, filtered and evaporated under reduced pressure to give 5.29g (73%) of 5-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}-ethoxy)phenyl]-1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazole.

MASS (ESI+): m/z = 507.1 (M+1), 529.0 (M+Na).

1HNMR (400MHz, CDCl3): .07 (3H, s), .09 (3H, s), .9 (9H, s), 2.15 (3H, s), 3.78 (3H, s), 3.62 - 4.13 (4H, m), 6.79 (2H, d, J = 8.5Hz), 6.88 (2H, d, J = 8.7Hz), 7.05 (2H,

d, J = 8.7Hz), 7.13 (2H, d, J = 8.5Hz).

Example 524

2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethanol

mp 50.7-51.7°C

Mass (ESI+) : 409 (M+H)+

1HNMR (200MHz, CDCl3): 1.99 (1H, t, J = 6.0Hz), 3.80 (3H, s), 3.92 - 4.00 (2H, m), 4.05 - 4.10 (2H, m), 4.62 (1H, d, J = 8.5Hz), 4.70 (1H, d, J = 8.5Hz), 5.95 (1H, s), 6.79 - 6.92 (4H, m), 7.07 - 7.18 (4H, m)

Example 525

2-{4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethanol

oil

Mass (ESI+) : 391 (M+H)

1HNMR (200MHz, CDCl3): 1.99 (1H, t, J = 6.1Hz), 3.80 (3H, s), 3.92 - 4.00 (2H, m), 4.05 - 4.09 (2H, m), 4.47 (2H, dt, J = 4.2 ,13.5Hz), 5.92 (1H, s), 6.17 (1H, tt, J = 4.2,55.5Hz), 6.79 - 6.87 (4H, m), 7.09 - 7.20 (4H, m)

Example 526

2-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethanol

mp. 91.2-91.3°C

Mass (sample ID cox031168) (ESI+) : 410 (M+H)+

1HNMR (200MHz, CDCl3): 1.99 (1H, t, J = 6.1Hz), 3.91 (3H, s), 3.92 - 4.01 (2H, m), 4.06 - 4.11 (2H, m), 4.61 (1H, d, J = 8.4Hz), 4.70 (1H, d, J = 8.4Hz), 5.98 (1H, s), 6.71 (1H, d, J = 8.8Hz), 6.86 (2H, d, J = 8.8Hz), 7.14 (2H, d, J = 8.8Hz), 7.48 (1H, dd, J = 2.7 ,8.8Hz), 8.02

(1H, d, J = 2.7Hz)

Example 527

2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethanol

oil

Mass (ESI+) : 392 (M+H)

1HNMR (200MHz, CDCl3): 3.92 (3H, s), 3.93 - 4.00 (2H, m), 4.06 - 4.11 (2H, m), 4.46 (2H, dt, J = 4.2 ,13.2Hz), 5.94 (1H, s), 6.17 (1H, tt, J = 4.2, 55.5Hz), 6.71 (1H, d, J = 9.0Hz), 6.86 (2H, d, J = 8.9Hz), 7.14 (2H, d, J = 8.9Hz), 7.48 (1H, dd, J = 2.7 , 9.0Hz), 8.02 (1H, d, J = 2.7Hz)

Example 528

Carbonyldiimidazole (1.26g) was added to a solution of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-3-amino-1H-pyrazole (2.4g) in 1-methyl-2-pyrrolidinone (22ml). After stirring at ambient temperature for 2hour, 2M solution of dimethylamine in THF (7.4ml) was added and th emixture was stirred ambient temperature for 2hour. The reaction mixture was partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane =80% to give N'-[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (2.35g) as amorphous powder.

Mass (ESI+) : 443 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.91(6H, s), 3.76(3H, s), 5.09(2H, s), 6.63(1H, s), 6.93(2H, d, J=9.0 Hz), 6.98(2H, d, J=9.0

Hz), 7.14(2H, d, J=9.0 Hz), 7.15(2H, d, J=9.0 Hz), 7.34-7.44(5H, m), 9.02(1H, s)

Example 529

A mixture of N'-[5-[4-(hydroxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (121.9mg), 2-(tert-butyl- dimethylsilyloxy)ethyl bromide (166mg), and K2CO3 (95.6mg) in DMF (1.5ml) was stirred at 75°C for 7hours. 2-(tert-butyldimethylsilyloxy)ethyl bromide (83mg) and KI (57.4mg) was added to the reaction mixture, and the mixture was stirred at 75°C overnight. The mixture was allowed to cool to ambient temperature, and was partitioned between ethyl acetate and H2O. The aqueous layer was reextracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 5% MeOH / CHCl3. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give N'-[5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (115mg) as an amorphous powder. 84.3mg of amorphous powder was crystallized from AcOEt-IPE to give N'-[5-[4-(2-hydroxyethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (79.5mg) as a white powder.

mp. 167.4-167.6°C

IR (KBr) : 3317, 1670, 1612, 1587, 1572, 1510cm-1

Mass (ESI+) : 397 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.91(6H, s), 3.65-3.74(2H, m), 3.76(3H, s), 3.94-4.00(2H, m), 4.87(1H, t, J=5.5Hz), 6.62(1H, s), 6.90(2H, d, J=8.7 Hz), 6.93(2H, d, J=8.9 Hz), 7.12(2H,

d, J=8.7 Hz), 7.15(2H, d, J=8.9 Hz), 9.02(1H, s)

Example 530

Diethylazodicarboxylate 308mg was added to a solution of N'-[5-[4-(hydroxy)-phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea 415mg, tert-butyl N-(2-hydroxyethyl)carbamate 380mg, and triphenylphosphine 463mg in THF 5ml. After stirring at ambient temperature for overnight, the reaction mixture was concentrated in vacuo. To a solution of the residue in CH2Cl2 5ml, was added 4M aolution of HCl in dioxane 5ml. After stirring at ambient temperature for 1.5hours, the reaction mixture was concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The aqueous layer was reextracted with AcOEt and concentrated in vacuo. The remained H2O was evaporated azeotropically with toluene to give N'-[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea hydrochloride 580mg as an amorphous powder.

Mass (ESI+) : 396 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.91(6H, s), 3.15-3.24(2H, m), 3.76(3H, s), 4.14-4.21(2H, m), 6.64(1H, s), 6.94(2H, d, J=8.9 Hz), 6.95(2H, d, J=8.7 Hz), 7.15(2H, d, J=8.9 Hz), 7.17(2H, d, J=8.7 Hz), 8.20(2H, brs), 9.04(1H, s)

The following compound(s) was(were) obtained in a similar manner to that of Example 530.

Example 531

N-[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N',N'-trimethylurea hydrochloride amorphous

Mass (ESI+) : 410(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.79(6H, s), 3.13(3H, s), 3.14-3.24(2H, m), 3.80(3H, s), 4.15-4.20(2H, m), 6.27(1H, s), 6.94(2H, d, J=8.6 Hz), 6.94(2H, d, J=8.9 Hz), 7.16(2H, d, J=8.9 Hz), 7.19(2H, d, J=8.6 Hz), 8.24(2H, brs)

Example 532

2-{[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]oxy}-N,N-dimethylacetamide hydrochloride amorphous

MS (ESI+) : m/z 411 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.84(3H, s), 2.97(3H, s), 3.14-3.24(2H, m), 3.76(3H, s), 4.14-4.20(2H, m), 4.88(2H, s), 6.09(1H, s), 6.93(2H, d, J=9.0 Hz), 6.95(2H, d, J=8.8 Hz), 7.07-7.29(4H, m), 8.21(2H, brs)

Example 533

A solution of potassium cyanate (64.9mg) in H2O (0.5ml) was added to a solution of N'-[5-[4-(2-aminoethoxy)phenyl]-1-(4-methoxy-phenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea hydrochloride (172.8mg) and sodium acetate (65.6mg) in a mixture of DMF (1.5ml) and H2O (0.5ml). The reaction mixture was stirred at ambient temperature overnight. The mixture was diluted with H2O, partitioned between AcOEt and H2O. The aqueous layer was reextracted with AcOEt. saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by 10% MeOH / CHCl3. The seaparated silica gel was extracted with 10% MeOH / CHCl3 and the solvent was evaporated in vacuo. The residue was crystallized from AcOEt-IPE to give N'-[5-(4-{2-[(aminocarbonyl)-

amino]ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N-dimethylurea (87.0mg) as a powder.
mp. 193-196°C
IR (KBr) : 3437, 3421, 1660, 1649, 1620, 1612, 1581, 1562, 1554, 1529, 1512cm-1
Mass (ESI+) : 439 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.91(6H, s), 3.27-3.34(2H, m), 3.76(3H, s), 3.93(2H, t, J=5.5 Hz), 5.53(2H, s), 6.16(1H, t, J=5.7 Hz), 6.62(1H, s), 6.91(2H, d, J=8.7 Hz), 6.93(2H, d, J=8.9 Hz), 7.13(2H, d, J=8.7 Hz), 7.15(2H, d, J=8.9 Hz), 9.02(1H, s)

The following compound(s) was(were) obtained in a similar manner to that of Example 533.

Example 534

N-[5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N',N'-trimethylurea
powder : mp. 158.6-159.0°C
IR (KBr) : 3433, 3369, 1687, 1658, 1643, 1612, 1514, 1500cm-1
Mass (ESI+) : 453 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 2.79(6H, s), 3.12(3H, s), 3.27-3.34(2H, m), 3.76(3H, s), 3.93(2H, t, J=5.5 Hz), 5.53(2H, s), 6.15(1H, t, J=5.6 Hz), 6.25(1H, s), 6.91(2H, d, J=8.7 Hz), 6.94(2H, d, J=8.9 Hz), 7.15(2H, d, J=8.7 Hz), 7.15(2H, d, J=8.9 Hz)

Example 535

N-(2-{4-[3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea
white powder : mp. 131-132°C
IR (KBr) : 3435, 3429, 3388, 3350, 1658, 1612, 1562, 1554,

1518cm-1

Mass (sample ID cox022116) (ESI+) : 427 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.28-3.38(2H, m), 3.30(3H, s), 3.62-3.68(2H, m), 3.75(3H, s), 3.89-3.96(2H, m), 4.21-4.27(2H, m), 5.53(2H, s), 6.05(1H, s), 6.15(1H, t, J=5.7 Hz), 6.91(2H, d, J=8.9 Hz), 6.92(2H, d, J=9.0 Hz), 7.10-7.15(4H, m)

Example 536

N-(2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

white powder : mp. 124.1-124.2°C

IR (KBr) : 3388, 3379, 3340, 1657, 1643, 1612, 1562, 1554, 1518cm-1

Mass (ESI+) : 441 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.13(3H, t, J=7.0 Hz), 3.27-3.36(2H, m), 3.49(2H, q, J=7.0 Hz), 3.66-3.71(2H, m), 3.75(3H, s), 3.89-3.96(2H, m), 4.21-4.26(2H, m), 5.53(2H, s), 6.06(1H, s), 6.15(1H, t, J=5.7 Hz), 6.91(2H, d, J=8.8 Hz), 6.92(2H, d, J=9.0 Hz), 7.10-7.15(4H, m)

Example 537

2-{[5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]oxy}-N,N-dimethyl-acetamide

white powder : mp.223-227°C

IR (KBr) : 3402, 3332, 3201, 3194, 2925, 1664, 1612, 1518, 1502cm-1

MS (ESI+) : m/z 454 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.84(3H, s), 2.97(3H, s), 3.27-3.35(2H, m), 3.75(3H, s), 3.89-3.96(2H, m), 4.87(2H, s), 5.53(2H, s), 6.07(1H, s), 6.15(1H, t, J=5.5 Hz), 6.91(2H,

d, J=8.9 Hz), 6.93(2H, d, J=9.0 Hz), 7.11(2H, d, J=9.0 Hz), 7.13(2H, d, J=8.9 Hz)

Example 538

N-(2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

white powder : mp. 192.6-192.7°C

IR (KBr) : 3390, 3352, 3311, 3305, 1657, 1610, 1583, 1568, 1525, 1502cm-1

MS (ESI+) : m/z 384 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.27-3.36(2H, m), 3.34(3H, s), 3.85(3H, s), 3.91-3.97(2H, m), 5.53(2H, s), 6.11(1H, s), 6.15(1H, t, J=5.7 Hz), 6.85(1H, d, J=8.7 Hz), 6.94(2H, d, J=8.8 Hz), 7.17(2H, d, J=8.8 Hz), 7.59(1H, dd, J=2.6,8.7 Hz), 8.00(1H, d, J=2.6 Hz)

Example 539

N-(2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

white powder : mp. 133-138°C

IR (KBr) : 3350, 1657, 1643, 1612, 1579, 1562, 1554, 1518, 1500cm-1; MS (ESI+) : m/z 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 3.28-3.35(2H, m), 3.84(3H, s), 3.91-3.97(2H, m), 4.19(2H, q, J=7.0 Hz), 5.53(2H, s), 6.09(1H, s), 6.16(1H, t, J=5.6 Hz), 6.85(1H, d, J=8.8 Hz), 6.94(2H, d, J=8.8 Hz), 7.17(2H, d, J=8.8 Hz), 7.58(1H, dd, J=2.7,8.8 Hz), 8.00(1H, d, J=2.7 Hz)

Example 540

N-(2-{4-[3-cyclopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp.94-96°C

MS (ESI+) : m/z 394 (M+H)

1HNMR (200MHz, DMSOd6): 0.72 - 0.78 (2H, m), 0.87 - 0.95 (2H, m), 1.87 - 2.01 (1H, m), 3.23 - 3.42 (2H, m), 3.85 (3H, s), 3.90 - 3.97 (2H, m), 5.52 (2H, s), 6.12 (1H, t, J = 5.6Hz), 6.30 (1H, s), 6.85 (1H, d, J = 8.8Hz), 6.92 (2H, d, J = 8.7Hz), 7.13 (2H, d, J = 8.7Hz), 7.58 (1H, dd, J = 2.7 ,8.8Hz), 8.01 (1H, d, J = 2.7Hz)

Example 541

N-(2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp.152.0-152.2°C

Mass (ESI+) : 464 (M+H)

1HNMR (200MHz, DMSOd6): 1.42 - 1.73 (6H, m), 3.27 - 3.36 (2H, m), 3.53 - 3.67 (2H, m), 3.73 - 3.96 (2H, m), 3.78 (3H, s), 3.90 - 3.97 (2H, m), 5.51 (2H, s), 6.14 (1H, t, J = 5.7Hz), 6.77 (1H, s), 6.92 (2H, d, J = 8.8Hz), 6.98 (2H, d, J = 9,0Hz), 7.17 (2H, d, J = 8.8Hz), 7.23 (2H, d, J = 9.0Hz)

Example 542

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp.164-167°C

Mass (ESI+) : 465 (M+H)

1HNMR (200MHz, DMSOd6): 1.42 - 1.73 (6H, m), 3.22 - 3.40 (2H, m), 3.52 - 3.70 (2H, m), 3.75 - 3.95 (2H, m), 3.87 (3H, s), 3.92 - 3.98 (2H, m), 5.52 (2H, s), 6.15 (1H, t, J = 5.6Hz), 6.81 (1H, s), 6.90 (1H, d, J = 8.9Hz), 6.95 (2H, d, J = 8.8Hz), 7.21 (2H, d, J = 8.8Hz), 7.67 (1H, dd, J = 2.7 ,8.9Hz), 8.14 (1H, d, J = 2.7Hz)

Example 543

5-(4-{2-[(aminocarbonyl)amino]ethoxy}phenyl)-N-ethyl-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide

mp.146.3-146.7°C

MS (ESI+) : m/z 439 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.23 (3H, m), 2.98, 3.28 (3H, s), 3.28 - 3.37 (2H, m), 3.40 - 3.53, 3.63 - 3.77 (2H, m), 3.87 (3H, s), 3.92 - 3.98 (2H, m), 5.52 (2H, s), 6.15 (1H, t, J = 5.5Hz), 6.82, 6.85 (1H, s), 6.90 (1H, d, J = 9.0Hz), 6.95 (2H, d, J = 8.7Hz), 7.21 (2H, d, J = 8.7Hz), 7.60 - 7.73 (1H, m), 8.14 - 8.16 (1H, m)

Example 544

N-(2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp.130-132°C

MS (ESI+) : m/z 451 (M+H)

1HNMR (200MHz, DMSOd6): 3.27 - 3.33 (2H, m), 3.76 (3H, s), 3.90 - 3.96 (2H, m), 4.81 (1H, d, J = 9.0Hz), 4.90 (1H, d, J = 9.0Hz), 5.52 (2H, s), 6.14 (1H, t, J = 5.6Hz), 6.21 (1H, s), 6.89 - 6.98 (4H, m), 7.12 - 7.18 (4H, m)

Example 545

N-(2-{4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp. 138.6-139.1°C

MS (ESI+) : m/z 432 (M+H)

1HNMR (200MHz, DMSOd6): 3.27 - 3.36 (2H, m), 3.76 (3H, s), 3.90 - 3.96 (2H, m), 4.44 (2H, dt, J = 3.5 ,14.9Hz), 5.52 (2H, s), 6.11 - 6.17 (1H, m), 6.15 (1H, s), 6.41

(1H, tt, J = 3.5, 54.6Hz), 6.91 (2H, d, J = 8.9Hz), 6.93 (2H, d, J = 8.9Hz), 7.14 (2H, d, J = 8.9Hz), 7.15 (2H, d, J = 8.9Hz)

Example 546

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp. 134.8-134.9°C

MS (ESI+) : m/z 452 (M+H)

1HNMR (200MHz,): 3.24 - 3.39 (2H, m), 3.85 (3H, s), 3.91 - 3.98 (2H, m), 4.83 (1H, d, J = 9Hz), 4.92 (1H, d, J = 9Hz), 5.52 (2H, s), 6.15 (1H, t, J = 5.6Hz), 6.27 (1H, s), 6.87 (1H, d, J = 8.8Hz), 6.95 (2H, d, J = 8.8Hz), 7.18 (2H, d, J = 8.8Hz), 7.61 (1H, dd, J = 2.7 ,8.8Hz), 8.04 (1H, d, J = 2.7Hz)

Example 547

N-(2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp.146.9-147.3°C

MS (ESI+) : m/z 434 (M+H)

1HNMR (200MHz, DMSOd6): 3.23 - 3.40 (2H, m), 3.85 (3H, s), 3.91 - 3.97 (2H, m), 4.45 (2H, dt, J = 3.5 ,14.9Hz), 5.52 (2H, s), 6.15 (1H, t, J = 5.7Hz), 6.21 (1H, s), 6.42 (1H, tt, J = 3.5, 54.6Hz), 6.86 (1H, d, J = 8.8Hz), 6.94 (2H, d, J = 8.8Hz), 6.94 (2H, d, J = 8.8Hz), 7.60 (1H, dd, J = 2.8 ,8.8Hz), 8.03 (1H, d, J = 2.8Hz)

Example 548

5-(4-{[(aminocarbonyl)amino]methyl}phenyl)-N-ethyl-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide

mp.184.7-185.1°C

MS (ESI+) : m/z 408 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.22 (3H, m), 2.98, 3.29 (3H, s), 3.41 - 3.78 (2H, m), 3.78 (3H, s), 4.16 (2H, d, J = 6.0Hz), 5.54 (2H, s), 6.44 (1H, t, J = 6Hz), 6.84, 6.86 (1H, s), 6.99 (2H, d, J = 8.9Hz), 7.2 - 7.27 (6H, m)

Example 549

N-{4-[3-isopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}urea

amorphous powder

MS (ESI+) : m/z 365 (M+H)

1HNMR (200MHz, DMSOd6): 1.27 (6H, d, J = 7.0Hz), 2.95 (1H, m), 3.76 (3H, s), 4.15 (2H, d, J = 6.0Hz), 5.53 (2H, s), 6.42 (1H, t, J = 6.0Hz), 6.44 (1H, s), 6.93 (2H, d, J = 8.9Hz), 7.11 - 7.22 (6H, m)

Example 550

N-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]benzyl}urea

mp.178.9-178.9°C

MS (ESI+) : m/z 435 (M+H)

1HNMR (400MHz, DMSOd6): 1.47 - 1.70 (6H, m), 3.55 - 3.66 (2H, m), 3.78 - 3.89 (2H, m), 3.87 (3H, s), 4.17 (2H, d, J = 6.0Hz), 5.55 (2H, s), 6.45 (1H, t, J = 6.0Hz), 6.86 (1H, s), 6.91 (1H, d, J = 8.8Hz), 7.24 (4H, s), 7.70 (1H, dd, J = 2.7 ,8.8Hz), 8.14 (1H, d, J = 2.7Hz)

Example 551

5-(4-{[(aminocarbonyl)amino]methyl}phenyl)-N-ethyl-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide

mp.172.6-172.8°C

MS (ESI+) : m/z 409 (M+H)

1HNMR (400MHz, DMSOd6): 1.13 , 1.19 (3H, t, J = 7.0Hz), 2.98, 3.29 (3H, s), 3.48, 3.72 (2H, q, J = 7.0Hz), 3.87 (3H, s), 4.18 (2H, d, J = 6.0Hz), 5.55 (2H, s), 4.45 (1H, t, J = 6.0Hz), 6.87 - 6.93 (2H, m), 7.24 (4H, s), 7.67 - 7.73 (1H, m), 8.14 - 8.16 (1H, m)

Example 552

N-{4-[3-isopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}urea

mp.139-144°C

MS (ESI+) : m/z 366 (M+H)

1HNMR (200MHz, DMSOd6): 1.27 (6H, d, J = 7.0Hz), 2.97 (1H, m), 3.85 (3H, s), 4.17 (2H, d, J = 6.0Hz), 5.53 (2H, s), 6.43 (1H, t, J = 6.0Hz), 6.5 0(1H, s), 6.86 (1H, d, J = 8.8Hz), 7.15 - 7.26 (4H, m), 7.62 (1H, dd, J = 2.8 ,8.8Hz), 8.02 (1H, d, J = 2.7Hz)

Example 553

N-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}urea

mp.157.0-157.3°C

MS (ESI+) : m/z 394 (M+H)

1HNMR (200MHz, DMSOd6): 1.16 (6H, d, J = 6.8Hz), 3.68 (1H, m), 3.88 (3H, s), 4.17 (2H, d, J = 6.0Hz), 5.54 (2H, s), 6.45 (1H, t, J = 6.0Hz), 6.93 (1H, d, J = 8.8Hz), 7.06 (1H, s), 7.25 (4H, s), 7.76 (1H, dd, J = 2.7 ,8.8Hz), 8.18 (1H, d, J = 2.7Hz)

Example 554

N-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-

yl]benzyl}urea

mp.206.0-260.9°C

MS (ESI+) : m/z 353 (M+H)

1HNMR (200MHz, DMSOd6): 3.76 (3H, s), 3.84 (3H, s), 4.15 (2H, d, J = 6.0Hz), 5.53 (2H, s), 6.09 (1H, s), 6.42 (1H, t, J = 6.0Hz), 6.93 (2H, d, J = 9Hz), 7.12 - 7.23 (6H, m)

Example 555

N-{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}urea

solid

MS (ESI+) : m/z 381 (M+H)

1HNMR (200MHz, DMSOd6): 1.31 (6H, d, J = 6.1Hz), 3.76 (3H, s), 4.15 (2H, d, J = 6.0Hz), 4.76 (1H, m), 5.53 (2H, s), 6.04 (1H, s), 6.43 (1H, t, J = 6.0Hz), 6.92 (2H, d, J = 8.9Hz), 7.10 - 7.22 (6H, m)

Example 556

N-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-benzyl}urea

mp.125.5-126.2°C

Mass (ESI+) : 357 (M+H)

1HNMR (200MHz, DMSOd6): 3.78 (3H, s), 4.15 (2H, d, J = 6.1Hz), 5.54 (2H, s), 6.43 (1H, t, J = 6.1Hz), 6.73 (1H, s), 6.97 (2H, d, J = 8.9Hz), 7.14 - 7.24 (6H, m)

Example 557

N-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}urea

mp.111-115°C

Mass (ESI+) : 358 (M+H)

1HNMR (200MHz, DMSOd6): 3.87 (3H, s), 4.17 (2H, d, J = 6.0Hz), 5.54 (2H, s), 6.44 (1H, t, J = 6.0Hz), 6.79 (1H, s), 6.89 (1H, d, J = .8Hz), 7.23 (4H, s), 7.69 (1H, dd, J = 2.7 ,8.8Hz), 8.11 (1H, d, J = 2.7Hz)

Example 558

N-(2-{4-[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-5-yl]-phenoxy}ethyl)urea

amorphous powder

MS (ESI+) : m/z 367 (M+H)

1HNMR (400MHz, DMSOd6): 2.02 (3H, s), 3.32 - 3.36 (2H, m), 3.74 (3H, s), 3.92 - 3.96 (2H, m), 5.51 (2H, s), 6.15 (1H, t, J = 5.6Hz), 6.89 (2H, d, J = 8.9Hz), 6.94 (2H, d, J = 8.8Hz), 7.08 (2H, d, J = 8.8Hz), 7.09 (2H, d, J = 8.9Hz), 7.55 (1H, s)

Example 559

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-4-methyl-1H-pyrazol-5-yl]phenoxy}ethyl)urea

powder

MS (ESI+) : m/z 368 (M+H)

1HNMR (400MHz, DMSOd6): 2.03 (3H, s), 3.31 - 3.36 (2H, m), 3.83 (3H, s), 3.94 - 3.98 (2H, m), 5.51 (2H, s), 6.15 (1H, t, J = 5.6Hz), 6.82 (1H, d, J = 8.8Hz), 6.97 (2H, d, J = 8.8Hz), 7.13 (2H, d, J = 8.8Hz), 7.53 (1H, dd, J = 2.7 ,8.8Hz), 7.62 (1H, s), 7.98 (1H, d, J = 2.7Hz)

Example 560

N-(2-{4-[1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp. 141.2-142.2°C

MS (ESI+) : m/z 399 (M+H)

1HNMR (200MHz, DMSOd6): 2.50 (3H, s), 3.27 - 3.36 (2H, m), 3.77 (3H, s), 3.90 - 3.96 (2H, m), 5.52 (2H, s), 6.14 (1H, t, J = 5.6Hz), 6.56 (1H, s), 6.91 (2H, d, J = 8.8Hz), 6.95 (2H, d, J = 8.8Hz), 7.14 (2H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.8Hz)

Example 561

N-(2-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl)urea

mp.205-206°C

MS (ESI+) : m/z 406 (M+H)

1HNMR (200MHz, DMSOd6): 2.64 - 2.72 (2H, m), 3.13 - 3.24 (2H, m), 3.88 (3H, s), 5.42 (2H, s), 5.95 (1H, t, J = 5.6Hz), 6.92 (1H, d, J = 8.9Hz), 7.17 (1H, s), 7.24 (4H, s), 7.75 (1H, dd, J = 2.8 ,8.9Hz), 8.19 (1H, d, J = 2.8Hz)

Example 562

5-(4-{2-[(aminocarbonyl)amino]ethyl}phenyl)-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide

oil

MS (ESI+) : m/z 243 (M+H)

1HNMR (200MHz, CDCl3): 2.75 - 2.82 (2H, m), 3.34 - 3.45 (2H, m), 3.51 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 4.46 (2H, s), 4.92 (1H, t, J = 5.5Hz), 6.84 (2H, d, J = 9.0Hz), 6.92 (1H, s), 7.11 (4H, s), 7.15 (2H, d, J = 9.0Hz)

Example 563

5-(4-{2-[(aminocarbonyl)amino]ethyl}phenyl)-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide

oil

MS (ESI+) : m/z 425 (M+H)

1HNMR (200MHz, CDCl3): 2.78 - 2.86 (2H, m), 3.39 - 3.49 (2H, m), 3.49 (3H, s), 3.85 (3H, s), 3.94 (3H, s), 4.39 (2H, s), 4.70 (1H, t, J = 5.8Hz), 6.75 (1H, d, J = 8.9Hz), 6.80 (1H, s), 7.12 - 7.23 (4H, m), 7.56 (1H, dd, J = 2.7 , 8.9Hz), 8.05 (1H, d, J = 2.7Hz)

Example 564

Sodium hydride 60% dispersion in mineral oil 93.1mg was added in one portion to a solution of N-[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N',N'-dimethylurea 1.43g in DMF 10ml under ice bath cooling. The reaction mixture was stirred at ambient temperature for 1hour. MeI 688mg was added the reaction mixture was stirred at ambient temperature overnight. The mixture was partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt-n-hexane=75%, 80% to give N-[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]-N,N',N'-trimethylurea 1.45g as an oil.

Mass (ESI+) : 457 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.79(6H, s), 3.12(3H, s), 3.77(3H, s), 5.09(2H, s), 6.25(1H, s), 6.91-7.00(4H, m), 7.14-7.19(4H, m), 7.32-7.46(5H, m)

Example 565

A mixture of N-(2-{4-[3-amino-1-(4-methoxyphenyl)-1H-pyrazol-5- yl]phenoxy}ethyl)urea 111mg, lithium chloride 64mg, and copper(II) chloride 81.2mg in acetonitrile 2ml was stirred at ambient temperature for 10minutes. To this mixture was added isoamyl nitrite 62.3mg,

and the mixture was stirred at ambient temperature for 3hours. The mixture was partitioned between ethyl acetate and saturated aqueous ammonium chloride solution. The organic layer was washed with saturated aqueous ammonium chloride solution, H2O, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by MeOH / CHCl3 = 10%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo. The residu was crystallized from AcOEt / IPE to give N-(2-{4-[3-chloro-1-(4-methoxyphenyl)-1H- pyrazol-5-yl]phenoxy}ethyl)urea 31.1mg as a white powder.

mp. 140-142°C

Mass (ESI+) : 386 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 3.27-3.34(2H, m), 3.77(3H, s), 3.93(2H, t, J=5.5 Hz), 5.52(2H, s), 6.15(1H, t, J=5.7 Hz), 6.68(1H, s), 6.92(2H, d, J=9.0 Hz), 6.97(2H, d, J=9.0 Hz), 7.15(2H, d, J=9.0 Hz), 7.20(2H, d, J=9.0 Hz)

Example 566

Diethyl azodicarboxylate (0.17ml) was added dropwise to a suspension of 3-methoxy-1-(4-methoxyphenyl)-5-(4-hydroxyphenyl)-1H-pyrazole (215.6mg), tert-butyl N-(2-hydroxyethyl)carbamate (352mg), and triphenylphosphine (286mg) in THF (3ml). The mixture was stirred at ambient temperature for 7hours. Triphenylphosphine (19.1mg) and diethyl azodicarboxylate (11.5µl) were added and the mixture stirred at ambient temperature overnight. The mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt/n-hexane=30% to give tert-butyl

(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate
(319mg) as an oil.
Mass (ESI+) : 440 (M+H)+
200MHz 1H NMR (CDCl3, d) : 1.45(9H, s), 3.47-3.56(2H, m), 3.80(3H, s), 3.96-4.03(2H, m), 3.97(3H, s), 4.96(1H, brs), 5.87(1H, s), 6.79(2H, d, J=8.8 Hz), 6.82(2H, d, J=8.9 Hz), 7.09-7.20(4H, m)

The following compound(s) was(were) obtained in a similar manner to that of Example 566.

Example 567

tert-butyl (2-{4-[3-isobutoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate
white powder
Mass (ESI+) : 482 (M+H)+
200MHz 1H NMR (CDCl3, d) : 1.03(6H, d, J=6.7 Hz), 1.45(9H, s), 2.11(1H, m), 3.48-3.57(2H, m), 3.79(3H, s), 3.97-4.03(2H, m), 4.97(1H, br), 5.88(1H, s), 6.79(2H, d, J=8.7 Hz), 6.82(2H, d, J=8.9 Hz), 7.09-7.19(4H, m)

Example 568

tert-butyl (2-{4-[3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate
solid
Mass (ESI+) : 484 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 3.22-3.32(2H, m), 3.31(3H, s), 3.62-3.67(2H, m), 3.75(3H, s), 3.91-3.97(2H, m), 4.21-4.27(2H, m), 6.04(1H, s), 6.86-6.99(5H, m), 7.10-7.15(4H, m)

Example 569

tert-butyl (2-{4-[3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

Mass (ESI+) : 498 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.09-1.21(3H, overlapping), 1.37(9H, s), 3.25-3.34(2H, m), 3.66-3.71(2H, m), 3.75(3H, s), 3.90-4.15(4H, m), 4.21-4.26(2H, m), 6.06(1H, s), 6.86-6.96(4H, m), 7.01(1H, m), 7.12(4H, d, J=8.9 Hz),

Example 570

tert-butyl (2-{4-[3-methoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

powder

MS (ESI+) : m/z 441 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.45(9H, s), 3.48-3.57(2H, m), 3.92(3H, s), 3.97(3H, s), 3.98-4.03(2H, m), 4.99(1H, br), 5.90(1H, s), 6.70(1H, d, J=8.5 Hz), 6.82(2H, d, J=8.9 Hz), 7.14(2H, d, J=8.9 Hz), 7.52(1H, dd, J=2.5,8.5 Hz), 8.03(1H, d, J=2.5 Hz)

Example 571

tert-butyl (2-{4-[3-ethoxy-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

white powder

MS (ESI+) : m/z 455 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.33(3H, t, J=7.0 Hz), 1.37(9H, s), 3.22-3.33(2H, m), 3.84(3H, s), 3.92-3.98(2H, m), 4.19(2H, q), 6.08(1H, s), 6.85(1H, d, J=8.8 Hz), 6.92(2H, d, J=8.8 Hz), 7.02(1H, t, J=5.5 Hz), 7.16(2H, d, J=8.8 Hz), 7.58(1H, dd, J=2.7,8.8 Hz), 7.99(1H, d, J=2.7 Hz)

Example 572

tert-butyl [2-(4-{3-(difluoromethyl)-1-[4-(methylthio)phenyl]-1H-pyrazol-5-yl}phenoxy)ethyl]carbamate

MASS (ESI+): m/z = 498.2 (M+Na).

1HNMR (400MHz, CDCl3): 1.45 (9H, s), 2.49 (3H, s), 3.54 (2H, q, J = 5.1Hz), 4.02 (2H, t, J = 5.1Hz), 4.98 (1H, b.s), 6.66 (1H, s), 6.76 (1H, t, J = 55.1Hz), 6.84 (2H, d, J = 8.8Hz), 7.15 (2H, d, J = 8.8Hz), 7.2 (4H, s).

Example 573

tert-butyl (2-{4-[3-cyclopropyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

MS ESI+) : m/z 451 (M+H)

1HNMR (200MHz, CDCl3): 0.77 - 0.86 (2H, m), 0.93 - 1.04 (2H, m), 1.45 (9H, s), 1.96 - 2.09 (1H, m), 3.48 - 3.57 (2H, m), 3.92 (3H, s), 3.97 - 4.03 (2H, m), 4.97 (1H, brs), 6.10 (1H, s), 6.71 (1H, d, J = 8.8Hz), 6.81 (2H, d, J = 8.8Hz), 7.11 (2H, d, J = 8.8Hz), 7.53 (1H, dd, J = 2.7 ,8.8Hz), 8.03 (1H, d, J = 2.7Hz)

Example 574

tert-butyl (2-{4-[3-(cyclopentyloxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

MS (ESI+) : m/z 494 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 1.5 - 1.99 (8H, m), 3.48 - 3.57 (2H, m), 3.91 (3H, s), 3.98 - 4.04 (2H, m), 4.92 - 5.05 (2H, m), 5.88 (1H, s), 6.69 (1H, d, J = 8.9Hz), 6.82 (2H, d, J = 8.8Hz), 7.14 (2H, d, J = 8.8Hz), 7.52 (1H, dd, J = 2.7 ,8.9Hz), 8.02 (1H, d, J = 2.7Hz)

Example 575

tert-butyl (2-{4-[1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

MS (ESI+) : m/z 508 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 3.48 - 3.57 (2H, m), 3.81 (3H, s), 3.97 - 4.03 (2H, m), 4.62 (1H, d, J = 8.5Hz), 4.70 (1H, d, J = 8.5Hz), 4.95 (1H, brs), 5.95 (1H, s), 6.77 - 6.86 (4H, m), 7.08 - 7.18 (4H, m)

Example 576

tert-butyl (2-{4-[3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

MS (ESI+) : m/z 490 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 3.48 - 3.57 (2H, m), 3.80 (3H, s), 3.97 - 4.03 (2H, m), 4.46 (2H, dt, J = 4.3 ,13.4Hz), 4.96 (1H, brs), 5.91 (1H, s), 6.17 (1H, tt, J = 4.3, 55.5Hz), 6.77 - 6.88 (4H, m), 7.09 - 7.18 (4H, m)

Example 577

tert-butyl (2-{4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]phenoxy}ethyl)-carbamate

oil

MS (ESI+) : m/z 509 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 3.48 - 3.57 (2H, m), 3.92 (3H, s), 3.98 - 4.04 (2H, m), 4.61 (1H, d, J = 8.4Hz), 4.70 (1H, d, J = 8.4Hz), 4.96 (1H, brs), 5.97 (1H, s), 6.71 (1H, d, J = 8.8Hz), 6.83 (2H, d, J = 8.8Hz), 7.13 (2H, d, J = 8.8Hz), 7.48 (1H, dd, J = 2.7 ,8.8Hz),

8.02 (1H, d, J = 2.7Hz)

Example 578

tert-butyl (2-{4-[3-(2,2-difluoroethoxy)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}ethyl)-carbamate

solid

MS (ESI+) : m/z 513 (M+Na)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 3.48 - 3.57 (2H, m), 3.92 (3H, s), 3.98 - 4.04 (2H, m), 4.46 (2H, dt, J = 4.2 ,13.4Hz), 4.96 (1H, brs), 5.94 (1H, s), 6.16 (1H, tt, J = 4.2, 55.5Hz), 6.71 (1H, d, J = 8.8Hz), 6.83 (2H, d, J = 8.9Hz), 7.13 (2H, d, J = 8.9Hz), 7.48 (1H, dd, J = 2.7 ,8.8Hz), 8.02 (1H, d, J = 2.7Hz)

Example 579

tert-butyl (2-{4-[1-(4-methoxyphenyl)-4-methyl-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

MS (ESI+) : m/z 424 (M+H)

200MHz 1H NMR (DMSO-d6, d) : 1.37(9H, s), 2.01(3H, s), 3.23-3.33(2H, m), 3.74(3H, s), 3.92-3.98(2H, m), 6.86-6.95(4H, m), 7.05-7.12(4H, m), 7.55(1H, s)

Example 580

tert-butyl (2-{4-[1-(6-methoxy-3-pyridinyl)-4-methyl-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

MS (ESI+) : m/z 425 (M+H)

1HNMR (400MHz, CDCl3): 1.42 (9H, s), 2.09 (3H, s), 3.52 - 3.57 (2H, m), 3.91 (3H, s), 4.01 - 4.04 (2H, m), 4.98 (1H, brs), 6.68 (1H, d, J = 8.8Hz), 6.87 (2H, d, J =

8.8Hz), 7.08 (2H, d, J=8.8Hz), 7.48 (1H, dd, J=2.7,8.8Hz), 7.58 (1H, s), 8.00 (1H, d, J = 2.7Hz)

Example 581

tert-butyl (2-{4-[1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate

oil

Mass (ESI+) : m/z 456 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 2.58 (3H, s), 3.48 - 3.57 (2H, m), 3.81 (3H, s), 3.97 - 4.03 (2H, m), 4.96 (1H, m), 6.36 (1H, s), 6.77 - 6.86 (4H, m), 7.12 (2H, d, J = 8.9Hz), 7.2 (2H, d, J = 9.0Hz)

Example 582

To a solution of (2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride (150mg) and triethylamine (121mg) in CH2Cl2 (3ml) was added trifluoromethanesulfonic anhydride (113mg). The mixture was stirred at ambient temperature for 2hours. Additional triethylamine (92mg) was added and stirring at ambient temperature was continued for 4hours. The mixture was concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 50% to give 1,1,1-trifluoro-N-(2-{4-[3-methoxy-1-(4-methoxy-phenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)methane-sulfonamide (109mg) as an oil.

IR (neat) : 2960, 1612, 1522cm-1

Mass (ESI+) : 472 (M+H)+

200MHz 1H NMR (CDCl3, d) : 3.60-3.73(2H, m), 3.80(3H, s), 3.97(3H, s), 4.06-4.12(2H, m), 5.45(1H, brs), 5.89(1H, s), 6.70-6.87(4H, m), 7.15(2H, d, J=8.9 Hz), 7.17(2H, d, J=9.0 Hz)

Example 583

To a suspension of 5-[4-(benzyloxy)phenyl]-3-hydroxy-1-(4-methoxyphenyl)-1H-pyrazole 2.0g and K2CO3 2.23g in DMSO 20ml was added diethylsulfate 1.24g. After stirring at ambient temperature for 2hours, the reaction was quenched by adding 28% aqueous ammonium hydroxide solution and ice. The mixture was partitioned between AcOEt and H2O. The organic layer was washed with H2O and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 40% and the solvent was evaporated in vacuo. The reisual solid was recrystallized from IPE to give 5-[4-(benzyloxy)phenyl]-3-ethoxy-1-(4-methoxy-phenyl)-1H-pyrazole 1.44g as a powder.

Mass (ESI+) : 401(M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.32(3H, t, J=7.0 Hz), 3.76(3H, s), 4.17(2H, q, J=7.0 Hz), 5.08(2H, s), 6.03(1H, s), 6.92(2H, d, J=9.0 Hz), 6.97(2H, d, J=8.8 Hz), 7.09-7.16(4H, m), 7.32-7.46(5H, m)

The following compound(s) was(were) obtained in a similar manner to that of Example 583.

Example 584

5-{5-[4-(benzyloxy)phenyl]-3-ethoxy-1H-pyrazol-1-yl}-2-methoxypyridine

oil; MS (ESI+) : m/z 402 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.43(3H, t, J=7.1 Hz), 3.92(3H, s), 4.28(2H, q, J=7.1 Hz), 5.05(2H, s), 5.90(1H, s), 6.70(1H, d, J=8.7 Hz), 6.91(2H, d, J=8.8 Hz), 7.14(2H, d, J=8.8 Hz), 7.35-7.43(5H, m), 7.51(1H, dd, J=2.6,8.7 Hz), 8.04(1H, d, J=2.6 Hz)

Example 585

To a solution of 4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenol (515.5mg) in DMF (5ml) was added sodium hydride 60% dispersion in mineral oil (79.7mg) at 3°C. The mixture was stirred at ambient temperature for 40minutes. To the rection mixture was added a solution of tert-butyl (2-bromoethyl)carbamate(558mg) in DMF (2ml). The mixture was stirred at at 60°C for 24hours. The reaction mixture was poured into ice water and was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from AcOEt, collected and washed with IPE to give 1st crop of tert-butyl (2-{4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate (344mg) as a white powder. The mother liqour was concentrated in vacuo and purified by silica gel column chromatography eluted with AcOEt / CHCl3 = 10% to give 2nd crop of tert-butyl (2-{4-[3-ethoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate (218mg) as a powder.

Mass (ESI+) : 454 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.42(3H, t, J=7.1 Hz), 1.45(9H, s), 3.48-3.57(2H, m), 3.80(3H, s), 3.97-4.03(2H, m), 4.29(2H, q, J=7.1 Hz), 5.87(1H, s), 6.79(2H, d, J=9.0 Hz), 6.82(2H, d, J=8.9 Hz), 7.00-7.19(4H, m)

Example 586

A suspension of 5-[4-(benzyloxy)phenyl]-3-hydroxy-1-(4-methoxyphenyl)-1H-pyrazole (1.5g), 1-bromo-2-methylpropane (2.76g) and anhydrous potassium carbonate (1.67g) in DMF (10ml) was added stirred at 100°C for 1hour. The mixture was poured into ice water and extracted with AcOEt. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt n-hexane =30% to give 5-[4-(benzyloxy)phenyl]-3-isobutoxy-1-(4-methoxyphenyl)-1H-pyrazole (1.64g) as a solid.

powder

Mass (ESI+) : 429 (M+H)+

200MHz 1H NMR (CDCl3, d) : 1.03(6H, d, J=6.6 Hz), 2.11(1H, m), 3.80(3H, s), 3.99(2H, d, J=6.6Hz), 5.04(2H, s), 5.88(1H, s), 6.82(2H, d, J=9.0 Hz), 6.88(2H, d, J=8.8 Hz), 7.11-7.20(4H, m), 7.35-7.43(5H, m)

The following compound(s) was(were) obtained in a similar manner to that of Example 586.

Example 587

5-[4-(benzyloxy)phenyl]-3-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazole

powder

Mass (ESI+) : 431 (M+H)+

200MHz 1H NMR (CDCl3, d) : 3.46(3H, s), 3.73-3.80(2H, m), 3.79(3H, s), 4.39-4.44(2H, m), 5.04(2H, s), 5.91(1H, s), 6.83(2H, d, J=8.9 Hz), 6.87(2H, d, J=9.0 Hz), 7.10-7.20(4H,

m), 7.34-7.42(5H, m)

Example 588

5-[4-(benzyloxy)phenyl]-3-(2-ethoxyethoxy)-1-(4-methoxyphenyl)-1H-pyrazole

oil

Mass (ESI+) : 445 (M+H)+

400MHz 1H NMR (CDCl3, d) : 1.25(3H, t, J=7.0 Hz), 3.61(2H, q, J=7.0 Hz), 3.79-3.82(2H, m), 3.80(3H, s), 4.39-4.42(2H, m), 5.04(2H, s), 5.91(1H, s), 6.82(2H, d, J=8.9 Hz), 6.88(2H, d, J=8.7 Hz), 7.12(2H, d, J=8.7 Hz), 7.17(2H, d, J=8.9 Hz), 7.36-7.41(5H, m)

Example 589

2-{[5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-1H-pyrazol-3-yl]oxy}-N,N-dimethylacetamide

powder

Mass (ESI+) : 458 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.84(3H, s), 2.97(3H, s), 3.76(3H, s), 4.87(2H, s), 5.09(2H, s), 6.08(1H, s), 6.92(2H, d, J=9.0 Hz), 6.98(2H, d, J=8.8 Hz), 7.09-7.17(4H, m), 7.34-7.43(5H, m)

Example 590

5-[5-[4-(benzyloxy)phenyl]-3-(cyclopentyloxy)-1H-pyrazol-1-yl]-2-methoxypyridine

solid

MS (ESI+) : m/z 442 (M+H)

1HNMR (200MHz, CDCl3): 1.52 - 1.98 (8H, m), 3.92 (3H, s), 4.98 - 5.05 (1H, m), 5.05 (2H, s), 5.88 (1H, s), 6.69 (1H, d, J = 8.7Hz), 6.91 (2H, d, J = 8.8Hz), 7.15 (2H, d, J = 8.8Hz), 7.35 - 7.43 (5H, m), 7.52 (1H, dd, J =

2.7 ,8.7Hz), 8.04 (1H, d, J = 2.7Hz)

Example 591

5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazole

oil

MS (ESI+) : m/z 455 (M+H)

1HNMR (200MHz, DMSOd6): 3.76 (3H, s), 4.81 (1H, d, J = 9.0Hz), 4.90 (1H, d, J = 9.0Hz), 5.09 (2H, s), 6.21 (1H, s), 6.91 - 7.01 (4H, m), 7.13 - 7.19 (4H, m), 7.34 - 7.46 (5H, m)

Example 592

5-[4-(benzyloxy)phenyl]-3-(2,2-difluoroethoxy)-1-(4-methoxyphenyl)-1H-pyrazole

oil

MS (ESI+) : m/z 437 (M+H)

1HNMR (200MHz, CDCl3): 3.80 (3H, s), 4.46 (2H, dt, J = 4.2 ,13.5Hz), 5.04 (2H, s), 5.91 (1H, s), 6.17 (1H, tt, J = 4.2, 55.5Hz), 6.81 - 6.91 (4H, m), 7.10 - 7.19 (4H, m), 7.34 - 7.43 (5H, m)

Example 593

5-[5-[4-(benzyloxy)phenyl]-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl]-2-methoxypyridine

oil

Mass (ESI+) : 456 (M+H)

1HNMR (200MHz, CDCl3): 3.93 (3H, s), 4.61 (1H, d, J = 8.4Hz), 4.69 (1H, d, J = 8.4Hz), 5.05 (2H, s), 5.97 (1H, s), 6.71 (1H, d, J = 9Hz), 6.91 (2H, d, J = 8.9Hz), 7.14 (2H, d, J = 8.9Hz), 7.36 - 7.43 (5H, m), 7.48 (1H, dd, J = 2.7 ,9Hz), 8.04 (1H, d, J = 2.7Hz)

Example 594

5-[5-[4-(benzyloxy)phenyl]-3-(2,2-difluoroethoxy)-1H-pyrazol-1-yl]-2-methoxypyridine

oil

MS (ESI+) : m/z 438 (M+H)

1HNMR (200MHz, CDCl3): 3.93 (3H, s), 4.46 (2H, dt, J = 4.2 ,13.3Hz), 5.05 (2H, s), 5.94 (1H, s), 6.16 (1H, tt, J = 4.2, 55.4Hz), 6.71 (1H, d, J = 8.8Hz), 6.91 (2H, d, J = 8.8Hz), 7.14 (2H, d, J = 8.8Hz), 7.35 - 7.43 (5H, m), 7.48 (1H, dd, J = 2.8 ,8.8Hz), 8.04 (1H, d, J = 2.8Hz)

Example 595

A suspension of 5-{5-[4-(benzyloxy)phenyl]-3-hydroxy-1H-pyrazol-1-yl}-2-methoxypyridine (800mg), dimethyl carbonate (0.9ml) and potassium carbonate (888mg) in DMF (8ml) was stirred at 120°C for 5hours. The mixture was poured into ice water and extracted with AcOEt. The organic layer was washed with H2O, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane =30% to give 5-{5-[4-(benzyloxy)phenyl]-3-methoxy-1H-pyrazol-1-yl}-2-methoxy-pyridine (1.069g) as a solid.

powder

MS (ESI+) : m/z 388 (M+H)+

200MHz 1H NMR (CDCl3, d) : 3.92(3H, s), 3.97(3H, s), 5.05(2H, s), 5.90(1H, s), 6.71(1H, d, J=8.7 Hz), 6.91(2H, d, J=8.9 Hz), 7.14(2H, d, J=8.9 Hz), 7.35-7.43(5H, m), 7.52(1H, dd, J=2.6,8.7 Hz), 8.05(1H, d, J=2.6 Hz)

Example 596

A solution of 4,4,4-trifluoro-1-[4-(2-hydroxy-ethyl)phenyl]- 1,3-butanedione (670mg) and (4-nitrophenyl)hydrazine hydrochloride (439mg) in AcOH (5ml) and H2O (0.5ml) was stirred at ambient temperature overnight. The mixture was cocncentrated in vacuo, and the residue was partitioned between AcOEt and 1M HCl. The oreganic layer was washed with 1M HCl for two times, saturated aqueous sodium bicarbonate solution for three times, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 10% and 15% to give 2-{4-[1-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate (501mg) as an oil.
MS (ESI+) : m/z 420(M+H)+ , 442(M+Na)+
200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.91(2H, t, J=6.8 Hz), 4.22(2H, t, J=6.8 Hz), 7.22-7.37(5H, m), 7.61(2H, d, J=9.0 Hz), 8.30(2H, d, J=9.0 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 596.

Example 597

5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazole
MASS (ESI+): m/z = 439.1 (M+1), 461.2 (M+Na).
1HNMR (400MHz, CDCl3): 2.15 (3H, s), 3.79 (3H, s), 5.06 (2H, s), 6.8 (2H, d, J = 8.9Hz), 6.95 (2H, d, J = 8.7Hz), 7.07 (2H, d, J = 8.7Hz), 7.14 (2H, d, J = 8.9Hz), 7.342 - 7.44 (5H, m).

Example 598

2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate

MASS (ESI+): m/z = 346.1 (M-Ac+2), 388.1 (M+1).

1HNMR (400MHz, CDCl3): 2.04 (3H, s), 2.94 (2H, t, J = 7Hz), 3.94 (3H, s), 4.28 (2H, t, J = 7Hz), 6.72 (1H, s), 6.77 (1H, t, J = 55Hz), 6.75 (1H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.5Hz), 7.22 (2H, d, J = 8.5Hz), 7.54 (1H, dd, J = 3.9 ,8.8Hz), 8.08 (1H, d, J = 3.9Hz).

Example 599

To a solution of ammonium chloride 58.8mg in H2O 0.5ml was added iron powder 368mg and EtOH 2ml. The reaction mixture was warmed in oil bath, and a solution of 2-{4-[1-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate 460.7mg in EtOH 3ml was added. After being refluxed for 3hours, the reaction mixture was cooled to ambient temperature and unsoluble matter was removed by filtration. The filtrate was concentrated in vacuo. The residue was dissolved in AcOEt, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from IPE to give 2-{4-[1-(4-aminophenyl)-3-(trifluoro-methyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate 182.3mg as a powder.

MS (ESI+) : m/z 390 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 1.96(3H, s), 2.87(2H, t, J=6.8 Hz), 4.20(2H, t, J=6.8 Hz), 5.46(2H, s), 6.54(2H, d, J=8.7 Hz), 6.95(2H, d, J=8.7 Hz), 7.07(1H, s), 7.18-7.28(4H, m)

Example 600

A mixture of 2-{4-[1-(4-aminophenyl)-3-(trifluoro-

methyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate 165.6mg and 2,5-dimethoxytetrahydrofuran 112mg in AcOH 3ml was stirred at 50°C for 3hours. 2,5-Dimethoxytetrahydrofuran 0.22ml was added and the mixture was stirred at 50°C for 2hours. The mixture was partitioned between ethyl acetate and H2O. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by AcOEt / n-hexane = 20%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give 2-{4-[1-[4-(1H-pyrrol-1-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate 136.1mg as an oil.
MS (ESI+) : m/z 440 (M+H)+
200MHz 1H NMR (DMSO-d6, d) : 1.95(3H, s), 2.88(2H, t, J=6.8 Hz), 4.20(2H, t, J=6.8 Hz), 6.29(2H, t, J=2.0 Hz), 7.18(1H, s), 7.23-7.32(4H, m), 7.39-7.47(4H, m), 7.69(2H, d, J=8.8 Hz)

Example 601

1M NaOH (436µl) was added to a solution of 2-{4-[1-[4-(1H-pyrrol-1-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate (128mg) in THF (1.5ml) and MeOH (0.3ml) under ice bath cooling. The mixture was stirred at 0°C~ambient temperature for 2hours. The mixture was neutralized with 1M HCl (436µl), and was partitioned between AcOEt and H2O. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by AcOEt / n-hexane = 50%. The

seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give 2-{4-[1-[4-(1H-pyrrol-1-yl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenyl}ethanol (96.5mg) as an amorphous powder.

IR (KBr) : 3404, 2924, 2883, 1612, 1522cm-1

MS (ESI+) : m/z 398 (M+H)+

200MHz 1H NMR (DMSO-d6, d) : 2.67-2.75(2H, m), 3.55-3.65(2H, m), 4.64(1H, t, J=5.1 Hz), 6.30(2H, t, J=2.0 Hz), 7.16(1H, s), 7.19-7.28(4H, m), 7.40-7.48(4H, m), 7.70(2H, d, J=8.9 Hz)

Example 602

A mixture of 10% Pd-C 50% wet (100mg) and ethyl 5-(4-cyanophenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (1g) in THF (10ml), MeOH (5ml), and 1M HCl (2.9ml) was hydrogenated under H2 1atm at ambient temperature for 6.5hours. The catalyst was filtered off through a celite pad and the pad was washed with MeOH. The filtrate and combined washings were concentrated in vacuo. The residue was dissolved in EtOH and concentrated in vacuo. The residue was crystallized from AcOEt to give ethyl 5-[4-(aminomethyl)phenyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate hydrochloride (984mg) as a powder.

MS (ESI+) : m/z 352 (M+H)+

1H NMR (DMSO-d6) δ 1.32(3H, t, J=7.1 Hz), 3.80(3H, s), 4.01(2H, s), 4.33(2H, q, J=7.1 Hz), 7.00(2H, d, J=9.0 Hz), 7.14(1H, s), 7.28(2H, d, J=9.0 Hz), 7.31(2H, d, J=8.3 Hz), 7.47(2H, d, J=8.3 Hz), 8.30(2H, brs)

The following compound(s) was(were) obtained in a similar manner to that of Example 602.

Example 603

ethyl 5-[4-(aminomethyl)phenyl]-1-(6-methoxy-3-pyridinyl)-1H-pyrazole-3-carboxylate dihydrochloride

powder

MS (ESI+) : m/z 353 (M+H)

1HNMR (200MHz, DMSOd6): 1.32 (3H, t, J = 7.1Hz), 3.88 (3H, s), 3.97 - 4.06 (2H, m), 4.34 (2H, q, J = 7.1Hz), 6.94 (1H, d, J = 8.7Hz), 7.17 (1H, s), 7.35 (2H, d, J = 8.2Hz), 7.51 (2H, d, J = 8.2Hz), 7.78 (1H, dd, J = 2.7 ,8.7Hz), 8.15 (1H, d, J = 2.7Hz), 8.47 (2H, brs)

Example 604

{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-benzyl}amine hydrochloride

oil

MS (ESI+) : m/z 310 (M+H)

1HNMR (200MHz, DMSOd6): 3.76 (3H, s), 3.85 (3H, s), 3.91 - 4.26 (2H, m), 6.16 (1H, s), 6.93 (2H, d, J = 8.9Hz), 7.16 (2H, d, J = 8.9Hz), 7.26 (2H, d, J = 8.2Hz), 7.45 (2H, d, J = 8.2Hz), 8.41 (2H, brs)

Example 605

{4-[3-isopropoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}amine hydrochloride

powder

MS (ESI+) : m/z 338 (M+H)

1HNMR (200MHz, DMSOd6): 1.32 (6H, d, J = 6.2Hz), 3.76 (3H, s), 4.00 (2H, s), 4.77 (1H, m), 6.11 (1H, s), 6.93 (2H, d, J = 8.9Hz), 7.15 (2H, d, J = 8.9Hz), 7.25 (2H, d, J = 8.2Hz), 7.44 (2H, d, J = 8.2Hz), 8.31 (2H, brs)

Example 606

Et3N (326mg) and then a solution of di-tert-butyl dicarbonate (594mg) in CH2Cl2 (3ml) was added successively to a suspension of ethyl 5-[4-(aminomethyl)phenyl]-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate hydrochloride (960mg) in CH2Cl2 (9ml). After stirring at ambient temperature for 1hour, the reaction mixture was concentrated in vacuo. The residue was partitioned between ethyl acetate and 1M HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from AcOEt / n-hexane to give ethyl 5-(4-{[(tert-butoxy-carbonyl)amino]methyl}phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (1.045g) as a powder.
MS (ESI+) : m/z 452 (M+H)+
1H NMR (DMSO-d6) δ 1.31(3H, t, J=7.1 Hz), 1.38(9H, s), 3.79(3H, s), 4.11(2H, d, J=6.2 Hz), 4.32(2H, q, J=7.1 Hz), 6.99(2H, d, J=8.9 Hz), 7.07(1H, s), 7.20(4H, s), 7.26(2H, d, J=8.9 Hz), 7.40(1H, t, J=6.2 Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 606.

Example 607

ethyl 5-(4-{[(tert-butoxycarbonyl)amino]methyl}phenyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazole-3-carboxylate
powder
Mass (ESI+) : m/z 453 (M+H)
1HNMR (200MHz, DMSOd6): 1.32 (3H, t, J = 7.1Hz), 1.38 (9H, s), 3.88 (3H, s), 4.12 (2H, d, J = 6.1Hz), 4.33 (2H, q, J = 7.1Hz), 6.92 (1H, d, J = 8.9Hz), 7.10 (1H,

s), 7.19 - 7.28 (4H, m), 7.41 (1H, t, J = 6.0Hz), 7.74 (1H, dd, J = 2.7 ,8.9Hz), 8.14 (1H, d, J = 2.7Hz)

Example 608

A mixture of ethyl 5-(4-{[(tert-butoxycarbonyl)amino]-methyl}phenyl)-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (500mg) and sodium methoxide (239mg) in formamide 5ml was stirred at 70°C for 2hours. The mixture was cooled to ambient temperature and partitioned between AcOEt and brine. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo to give tert-butyl {4-[3-(aminocarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate (512mg) as an oil.

MS (ESI+) : m/z 423 (M+H)+

1H NMR (DMSO-d6) δ 1.38(9H, s), 3.78(3H, s), 4.11(2H, d, J=6.1 Hz), 6.93(1H, s), 6.98(2H, d, J=8.9 Hz), 7.19-7.43(8H, m), 7.64(1H, brs)

Example 609

Phosphorous oxychloride (0.22ml) was added to DMF (2ml) under ice bath cooling. To this solution was added a solution of tert-butyl {4-[3-(aminocarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate (499mg) in DMF (3ml) dropwise. The reaction mixture was stirred at 4°C for 1hour. Phosphorous oxychloride (0.15ml) was added and the reaction mixture was stirred at 4°C for 1hour. The reaction was quenched by adding saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by

preparative thin layer silica gel chromatography developed by AcOEt/n-hexane=40%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give tert-butyl {4-[3-cyano-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzylcarbamate (136mg) as an oil.
MS (ESI+) : m/z 427 (M+Na)+ , (ESI-) : m/z 403 (M-H)+
200MHz 1H NMR (CDCl3, d) : 1.46(9H, s), 3.83(3H, s), 4.32(2H, d, J=5.9 Hz), 4.75(1H, br), 6.83(1H, s), 6.87(2H, d, J=9.0 Hz), 7.11-7.26(6H, m)

Example 610

To a solution of 5-[4-(2-{[tert-butyl(dimethyl)-silyl]oxy}ethoxy)phenyl]-1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazole (5.2g) in EtOH (200ml) was added conc.HCl (20ml) at room temperature. After stirring for 2 hrs, the reaction mixture was partitioned between EtOAc and water. Organic layer was separated and washed with water, dried over MgSO4, filtered and evaporated. The residue was chromatographed on silica gel (Hex/EtOAc=2:1 -1:1) to give 2.05g (51%) of 2-{4-[1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethanol as a crystal.
MASS (ESI+): e/z = 415.1 (M+Na).
1HNMR (400MHz, CDCl3): 2.15 (3H, s), 1.99 (1H, t, J = 6.2Hz), 2.15 (3H, s), 3.95 - 4.00 (2H, m), 4.08 - 4.10 (2H, m), 6.80 (2H, d, J = 9Hz), 6.90 (2H, d, J = 8.8Hz), 7.08 (2H, d, J = 8.8Hz), 7.13 (2H, d, J = 9Hz).

Example 611

To solution of 4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5yl]phenol (5.0g) in DMF(20ml) was added NaH(0.75g) over 25min under ice cooling

(5~20°C)(gas), stir at 3°C for 10min. tert-Butyl N-(2-bromoethyl)carbamate (4.48g) in DMF(5ml) was added to the mixture over 10min stir at 60°C(bath 70°C) for 6h and allowed to stand for overnight.

The mixture was poured into water(50ml) and EtOAc(30ml), seperation and extracted with EtOAc(10ml). The organic layer was washed with water(25 x 3) and brine(25ml), dried MgSO4, evaporated. The residue was column chromatographed on silica gel (75ml, 15v/w, AcOEt/Hex(2:1-1:1) and evaporated to give 7.0g of tert-butyl (2-{4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate as an oil.

MASS (ESI+): m/z = 516.1 (M+Na).

1HNMR (400MHz, CDCl3): 1.45 (9H, s), 2.49 (3H, s), 3.49 - 3.58 (2H, m), 4.02 (2H, t, J = 10.2Hz), 4.97 (1H, b.s), 6.68 (1H, s), 6.84 (2H, d, J = 17.5Hz), 7.14 (2H, d, J = 17.5Hz), 7.21 (4H, s).

The following compound(s) was(were) obtained in a similar manner to that of Example 611.

Example 612

tert-butyl (2-{4-[1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)-carbamate

MASS (ESI+): m/z = 514.2 (M+Na).

1HNMR (400MHz, CDCl3): 1.45 (9H, s), 2.15 (3H, s), 3.52-3.56 (2H, m), 3.79 (3H, s), 4.02 (2H, t, J = 5.1Hz), 4.99 (1H, b.s), 6.80 (2H, d, J = 9.0Hz), 6.87 (2H, d, J = 8.8Hz), 7.07 (2H, d, J = 8.8Hz), 7.13 (H, d, J = 9.0Hz).

Example 613

To a suspension of (2-{4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride (7.5g) in H2O (150ml) and EtOH (75ml) was added NaOCN (2.27g) at room temperature. pH was ajusted to 6.3 with 1NHCl . The mixture was stirred for 5 hours under the condition of pH 6.0-7.0. The reaction mixture was extracted with EtOAc and washed with dil. NaCl (twice), dried over MgSO4, filtered and evaporated. The residue was column chromatographed on silica gel (CH2Cl2/MeOH) and evaporated. The residue was crytalized from IPE/EtOH. Recrystalized from EtOH/H2O (50ml-50ml Final) and dried to give 4.10g (54%) of N-(2-{4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea.

MASS (ESI+): m/z = 459.1 (m+Na)

1HNMR (400MHz, DMSOd6): 2.05 (3H, s), 3.33 (2H, q, J = 5.6Hz), 3.95 (2H, t, J = 5.6Hz), 5.54 (2H, b.s), 6.16 (1H, t, J = 5.6Hz), 6.96 (2H, d, J = 8.8Hz), 7.09 (1H, s), 7.22 (2H, d, J = 8.6Hz), 7.27 (2H, d, J = 8.7Hz), 7.32 (2H, d, J = 8.7Hz).

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(cm-1):3399.89, 3197.40, 1650.77, 1614.13, 1554.34, 1475.28, 1459.85,1442.49, 1232.29, 1160.94, 1126.22, 1087.66, 1049.09, 970.019, 827.312.

The following compound(s) was(were) obtained in a similar manner to that of Example 613.

Example 614

N-(2-{4-[1-(4-methoxyphenyl)-4-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea

mp: 150.5-151.1°C

MASS (ESI+): m/z = 457.2 (m+Na).

1HNMR (400MHz, CDCl3): 2.15 (3H, s), 3.6 (2H, dt, J = 5 ,5.4Hz), 3.78 (3H, s), 4.04 (2H, t, J = 5Hz), 4.5 (2H, b.s), 5.08 (1H, t, J = 5.4Hz), 6.8 (2H, d, J = 9Hz), 6.86 (2H, d, J = 8.8Hz), 7.07 (2H, d, J = 8.8Hz), 7.13 (2H, d, J = 9Hz).

Example 615

N-[2-(4-{3-(difluoromethyl)-1-[4-(methylthio)phenyl]-1H-pyrazol-5-yl}phenoxy)ethyl]urea

mp: 184.3-184.7°C

MASS (ESI+): m/z = 441.1 (M+Na).

1HNMR (400MHz, DMSOd6): 2.5 (3H, s), 3.33 (2H, dt, J = 5.6 ,6.3Hz), 3.95 (2H, t, J = 5.6Hz), 5.53 (2H, b.s), 6.15 (1H, t, J = 6.3Hz), 6.85 (1H, s), 6.95 (2H, d, J = 8.7Hz), 7.09 (1H, t, J = 54.1Hz), 7.2 (2H, d, J = 8.7Hz), 7.23 (2H, d, J = 8.7Hz), 7.3 (2H, d, J = 8.7Hz).

Example 616

N-(2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)urea

mp: 194-196 °C

MASS (ESI+): m/z = 410.2 (M+Na).

1HNMR (400MHz, DMSOd6): 2.68 (2H, t, J = 7.3Hz), 3.19 (2H, dt, J = 5.6 ,7.3Hz), 3.88 (3H, s), 5.42 (2H, b.s), 5.95 (1H, t, J = 5.6Hz), 6.91 (1H, d, J = 8.8Hz), 6.93 (1H, s), 7.11 (1H, t, J = 54.4Hz), 7.23 (4H, s), 7.7 (1H, dd, J = 2.8 ,8.8Hz), 8.15 (1H, d, J = 2.8Hz).

Example 617

N-{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-

5-yl]benzyl}urea

Crystal. mp: 147-149°C .

MASS (ESI+): m/z = 414.1 (M+Na).

1HNMR (400MHz, CDCl3): 3.93 (3H, s), 4.37 (2H, d, J = 6Hz), 4.52 (2H, b.s), 5.08 (1H, t, J = 6Hz), 6.73 (1H, s), 6.77 (1H, d, J = 8.8Hz), 7.18 (2H, d, J = 8.3Hz), 7.27 (2H, d, J = 8.3Hz), 7.59 (1H, dd, J = 2.7 ,8.8Hz), 8.03 (1H, d, J = 2.7Hz).

Example 618

N-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}urea

MASS (ESI+): m/z = 396.1 (m+Na).

1HNMR (400MHz, DMSOd6): 3.87 (3H, s), 4.17 (2H, d, J = 6Hz), 5.55 (2H, b.s), 6.45 (1H, t, J = 6Hz), 6.91 (1H, d, J = 8.8Hz), 6.94 (1H, s), 7.11 (1H, t, J = 53.2Hz), 7.27 (4H, s), 7.71 (1H, dd, J = 2.7 ,8.8Hz), 8.14 (1H, d, J = 2.7Hz).

Example 619

A mixture of N-(2-{4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea (250mg) and mCPBA (326mg) in CH2Cl2 (10ml)was stirred for 18 hrs. sat. NaHCO3 and CH2Cl2 was added. Aqueou layer was separated and extracted. The combined organic layer was washed with sat. NaHCO3 (twice), dried and evaporated to give 207mg (79.9%) of crude product. The crude product was column chromatographed by preparative TLC to give 207mg (80%) of N-(2-{4-[1-[4-(methylsulfinyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea as an amorphous.

MASS (ESI+): 475.1 (m+Na).

1HNMR (400MHz, DMSOd6): 2.79 (3H, s), 3.3 - 3.34 (2H, m), 3.95 (2H, t, J = 5.6Hz), 5.53 (2H, b.s), 6.15 (1H, t, J = 5.6Hz), 6.97 (2H, d, J = 8.8Hz), 7.16 (1H, s), 7.23 (2H, d, J = 8.8Hz), 7.55 (2H, d, J = 8.6Hz), 7.77 (2H, d, J = 8.6Hz).

Example 620

A mixture of N-(2-{4-[1-[4-(methylthio)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea (250mg) and mCPBA (326mg) in CH2Cl2 (10ml)was stirred for 18 hrs. sat. NaHCO3 and CH2Cl2 was added. Aqueou layer was separated and extracted. The combined organic layer was washed with sat. NaHCO3 (twice), dried and evaporated to give 207mg (79.9%) of crude product. The crude product was column chromatographed by preparative TLC to give 116mg (43%) of N-(2-{4-[1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea as a amorphous.

MASS (ESI+): m/z = 491.0 (m+Na).

1HNMR (400MHz, DMSOd6): 3.28 (3H, s), 3.28 - 3.34 (2H, m), 3.96 (2H, t, J = 5.4Hz), 5.54 (2H, b.s), 6.16 (1H, t, J = 5.4Hz), 6.99 (2H, d, J = 8.4Hz), 7.18 (1H, s), 7.25 (2H, d, J = 8.4Hz), 7.61 (2H, d, J = 8.4Hz), 8.01 (2H, d, J = 8.4Hz).

Example 621

To a solution of 2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl acetate (10g) in THF (120ml) and MeOH (30ml) was added 1NNaOH (60ml) at room temperature. The reaction mixture was stirred at the same temperature for 4 hrs, and then neutralized with 1NHCl (60ml), evaporated, and extracted twice with EtOAc. The

organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated to give crude product.

The residue was column chromatographed on silica gel and crystalized from IPE and filtered to give 3.0g of 2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethanol. The filtrate was evaporated and filtered to give 4.65g of second crystal.

MASS (ESI+): m/z = 368.2 (M+Na).

1HNMR (400MHz, CDCl3): 1.49 (1H, t, J = 5.8Hz), 2.87 (2H, t, J = 6.5Hz), 3.88 (2H, dt, J = 5.8 ,6.5Hz), 6.71 (1H, s), 6.76 (1H, t, J = 55Hz), 6.75 (1H, d, J = 8.8Hz), 7.17 (2H, d, J = 8.4Hz), 7.21 (2H, d, J = 8.4Hz), 7.55 (1H, dd, J = 2.8 ,8.8Hz), 8.08 (1H, d, J = 2.8Hz).

Example 622

To a solution of 2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethanol (7.4g) and Et3N(4.5ml) in CH2Cl2 (75ml) was added MsCl (2.5ml) under ice-cooling. After stirring for 1 hour, the reaction mixture was quenched with water, separated. The aqueous layer was extracted with CH2Cl2 and combined organic layer was washed with water and brine, dried over MgSO4, filtered and evaporated under reduced pressure to give 10.5g (quant) of 2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate as an oil.

MASS (ESI+): m/z = 446.1 (M+Na).

1HNMR (400MHz, CDCl3): 2.9 (3H, s), 3.06 (2H, t, J = 6.8Hz), 3.94 (3H, s), 4.42 (2H, t, J = 6.8Hz), 6.73 (1H, s), 6.76 (1H, d, J = 8.8Hz), 6.77 (1H, t, J = 55Hz), 7.19 (2H, d, J = 8.6Hz), 7.23 (2H, d, J = 8.6Hz), 7.55 (1H, dd, J = 2.6 ,8.8Hz), 8.04 (1H, d, J = 2.6Hz).

Example 623

A mixture of 2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate (7.4g) and Ph(CO)2NK (3.88g) in DMF (50ml) was stirred at 60°C for 8 hours. Added water. The organic layer was extracted twice with EtOAc. Aqueous layer was washed with water (twice) and brine, dried over MgSO4, filtered, and evaporated under reduced pressure. The residue was triturated with IPE, filtered and dried to give 7.65g of 2-(2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dione as a solid.

MASS (ESI+): 475.2 (M+1), 497.2 (M+Na).

1HNMR (400MHz, CDCl3): 3 (2H, t, J = 7.6Hz), 3.92 (2H, t, J = 7.6Hz), 3.95 (3H, s), 6.7 (1H, s), 6.73 (1H, d, J = 8.8Hz), 6.76 (1H, t, J = 55Hz), 7.14 (2H, d, J = 8.1Hz), 7.22 (2H, d, J=8.1Hz), 7.46 (1H, dd, J=2.7,8.8Hz), 7.71 - 7.73 (2H, m), 7.83 - 7.85 (2H, m), 8.1 (1H, d, J = 2.7Hz).

Example 624

A mixture of 2-(2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)-1H-isoindole-1,3(2H)-dion (5.0g) and NH2NH2 (2.8ml) in CH3CN (50ml) was stirred at 60°C for 8 hours. The reaction mixture was filtered. Filtrate was evaporated under reduced pressure. 4N HCl/Dioxane and then IPE was added. The product was triturated, filtered and died under reduced pressure to give 3.94g (90%) of (2-{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)amine dihydrochloride as a solid.

MASS (ESI+): m/z = 345.2 (M(free)+1).

1HNMR (400MHz, DMSOd6): 2.9 - 2.95 (2H, m), 3.01 - 3.06 (2H, m), 3.88 (3H, s), 6.92 (1H, d, J = 8.8Hz), 6.95 (1H, s), 7.13 (1H, t, J = 56.1Hz), 7.27 (2H, d, J = 8.4Hz), 7.3 (2H, d, J = 8.4Hz), 7.72 (1H, dd, J = 2.8 ,8.8Hz), 8.15 (1H, d, J = 2.8Hz).

The following compound(s) was(were) obtained in a similar manner to that of Example 602.

Example 625

{4-[1-(6-methoxy-3-pyridinyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]benzyl}amine dihydrochloride

MASS (ESI+): m/z = 332.2 (M-NH2), 349.1 (M+H).

1HNMR (400MHz, DMSOd6): 3.88 (3H, s), 6.94 (1H, d, J = 9.6Hz), 7.25 (1H, s), 7.37 (2H, d, J = 8Hz), 7.53 (2H, d, J = 8Hz), 7.8 (1H, dd, J = 2.9 ,9.6Hz), 8.45 (1H, d, J = 2.8Hz).

Example 626

{4-[3-(difluoromethyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]-benzyl}amine hydrochloride

MASS (ESI+): m/z = 314.2 (M-NH2), 331.1 (M+1).

1HNMR (400MHz, DMSOd6): 3.88 (3H, s), 6.93 (1H, d, J = 8.8Hz), 7.00 (1H, s), 7.14 (1H, t, J = 54Hz), 7.35 (2H, d, J = 8.2Hz), 7.53 (2H, d, J = 8.2Hz), 7.75 (1H, dd, J = 2.7 ,8.8Hz), 8.15 (1H, d, J = 2.7Hz).

Example 627

To a solution of 5-hydrazino-2-methoxypyridine dihydrochloride (4.78g) and Et3N (7.01g) in EtOH (50ml) was added {(2R,3S)-3-[4-(benzyloxy)phenyl]-2-oxiranyl}-(cyclopropyl)methanone (5.10g) and refluxed for 9hours.

THs mixture was concentrated in vacuo. To the residue were added AcOEt and 1MHCl, and unsoluble matter was filtered off through a celit pad. The filtrate was partitioned, and the organic lauer was washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in CH2Cl2 (50ml). To this solution were added Et3N (5.26g) and methanesulfonyl chloride (2.98g) successively under ice-bath cooling. The mixture was stirred at ambient temperature for 2hours. The mixture was washed with 1M HCl, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 20% to give 5-{5-[4-(benzyloxy)phenyl]-3-cyclopropyl-1H-pyrazol-1-yl}-2-methoxypyridine (4.20g) as a solid.

MS (ESI+) : m/z 398 (M+H)

1HNMR (200MHz, DMSOd6): 0.69 - 0.78 (2H, m), 0.87 - 0.97 (2H, m), 1.89 - 1.99 (1H, m), 3.85 (3H, s), 5.09 (2H, s), 6.30 (1H, s), 6.85 (1H, d, J = 8.8Hz), 6.99 (2H, d, J = 8.8Hz), 7.15 (2H, d, J = 8.8Hz), 7.34 - 7.46 (5H, m), 7.60 (1H, dd, J = 2.7 ,8.8Hz), 8.01 (1H, d, J = 2.7Hz)

Example 628

To a mixture of tert-butyl (2-{4-[1-(4-methoxyphenyl)-3-carboxy-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate (313.9mg), piperidine (88.4mg), and 1-hydroxybenzotriazole (140mg) in DMF 3ml was added water soluble carbodiimide hydrochloride (199mg) under ice-bath cooling. The mixture was stirred at ambient temperature overnight, then was partitioned between AcOEt and H2O. The organic layer was

separated, washed with 1M HCl, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 70%. The residu was crystallized from IPE to give tert-butyl 2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)carbamate (332.5mg) as a white powder.

MS (ESI+) : m/z 521 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 1.53 - 1.79 (6H, m), 3.48 - 3.57 (2H, m), 3.67 - 3.81 (2H, m), 3.82 (3H, s), 3.88 - 4.02 (2H, m), 3.98 - 4.04 (2H, m), 4.96 (1H, brs), 6.77 (1H, s), 6.81 (2H, d, J = 8.8Hz), 6.86 (2H, d, J = 9.0Hz), 7.15 (2H, d, J = 8.8Hz), 7.21 (2H, d, J = 9.0Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 628.

Example 629

tert-butyl (2-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]phenoxy}ethyl)-carbamate

powder

MS (ESI+) : m/z 522 (M+H)

1HNMR (200MHz, CDCl3): 1.45 (9H, s), 1.54 - 1.78 (6H, m), 3.49 - 3.57 (2H, m), 3.69 - 3.82 (2H, m), 3.86 - 3.99 (2H, m), 3.94 (3H, s), 3.99 - 4.05 (2H, m), 4.96 (1H, s), 6.73 (1H, d, J = 8.8Hz), 6.79 (1H, s), 6.84 (2H, d, J = 8.8Hz), 7.16 (2H, d, J = 8.8Hz), 7.50 (1H, dd, J = 2.7 ,8.8Hz), 8.12 (1H, d, J = 2.7Hz)

Example 630

tert-butyl (2-{4-[3-{[ethyl(methyl)amino]carbonyl}-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenoxy}-ethyl)carbamate

powder

Mass (ESI+) : m/z 496 (M+H)

1HNMR (200MHz, DMSOd6): 1.08 - 1.22 (3H, m), 1.37 (9H, s), 2.98, 3.29 (3H, s), 3.23 - 3.32 (2H, m), 3.42 - 3.53, 3.63 - 3.75 (2H, m), 3.87 (3H, s), 3.93- 4.00 (2H, m), 6.82, 6.84 (1H, s), 6.87 - 7.00 (4H, m), 7.21 (2H, d, J = 8.6Hz), 7.61 - 7.72 (1H, m), 8.13 - 8.15 (1H, m)

Example 631

2-{4-[1-(4-methoxyphenyl)-3-(1-piperidinylcarbonyl)-1H-pyrazol-5-yl]phenoxy}ethanol

mp.121.9-123.8°C

Mass (ESI+) : m/z 422 (M+H)

1HNMR (200MHz, DMSOd6): 1.42 - 1.74 (6H, m), 3.53 - 3.70 (2H, m), 3.65 - 3.73 (2H, m), 3.70 - 3.92 (2H, m), 3.78 (3H, s), 3.95 - 4.00 (2H, m), 4.86 (1H, t, J = 5.4Hz), 6.77 (1H, s), 6.91 (2H, d, J = 8.8Hz), 6.98 (2H, d, J = 8.9Hz), 7.16 (2H, d, J = 8.8Hz), 7.23 (2H, d, J = 8.9Hz)

Example 632

2-{4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]phenoxy}ethanol

mp.123.4-124.0°C

Mass (ESI+) : m/z 423 (M+H)

1HNMR (200MHz, DMSOd6): 1.45 - 1.74 (6H, m), 3.50 - 3.69 (2H, m), 3.65 - 3.74 (2H, m), 3.71 - 3.90 (2H, m), 3.87 (3H, s), 3.96 - 4.02 (2H, m), 4.86 (1H, t, J = 5.4Hz),

6.81 (1H, s), 6.90 (1H, d, J = 8.7Hz), 6.94 (2H, d, J = 8.6Hz), 7.20 (2H, d, J = 8.6Hz), 7.68 (1H, dd, J = 2.7 ,8.7Hz), 8.14 (1H, d, J = 2.7Hz)

Example 633

tert-butyl {4-[1-(4-methoxyphenyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]benzyl}carbamate

amorphous powderr

MS (ESI+) : m/z 491 (M+H)

1HNMR (200MHz, CDCl3): 1.46 (9H, s), 1.55 - 1.8 (6H, m), 3.68 - 3.82 (2H, m), 3.82 (3H, s), 3.97 - 4.00 (2H, m), 4.31 (2H, d, J = 6.0Hz), 4.84 (1H, brs), 6.82 (1H, s), 6.86 (2H, d, J = 9Hz), 7.15 - 7.25 (6H, m)

Example 634

tert-butyl {4-[3-{[ethyl(methyl)amino]carbonyl}-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate

amorphous powder

MS (ESI+) : m/z 465 (M+H)

1HNMR (200MHz, CDCl3): 1.20 - 1.31 (3H, m), 1.46 (9H, s), 3.11, 3.40 (3H, s), 3.61, 3.85 (2H, q, J = 7.1Hz), 3.82 (3H, s), 4.31 (2H, d, J = 5.8Hz), 4.86 (1H, brs), 6.81 - 6.90 (3H, m), 7.16 - 7.25 (6H, m)

Example 635

tert-butyl {4-[3-{[methoxy(methyl)amino]carbonyl}-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate

solid

MS (ESI+) : m/z 467 (M+H)

1HNMR (200MHz, CDCl3): 1.46 (9H, s), 3.51 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 4.31 (2H, d, J = 5.9Hz), 4.87 (1H, brs), 6.86 (2H, d, J = 9.0Hz), 6.96 (1H, s), 7.15

- 7.26 (6H, m)

Example 636

tert-butyl {4-[1-(6-methoxy-3-pyridinyl)-3-(1-piperidinyl-carbonyl)-1H-pyrazol-5-yl]benzyl}carbamate

oil

MS (ESI+) : m/z 492 (M+H)

1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 1.46 - 1.75 (6H, m), 3.52 - 3.69 (2H, m), 3.75 - 3.93 (2H, m), 3.87 (3H, s), 4.13 (2H, d, J = 6.1Hz), 6.86 (1H, s), 6.90 (1H, d, J = 8.9Hz), 7.19 - 7.28 (4H, m), 7.41 (1H, t, J = 6.1Hz), 7.70 (1H, dd, J = 2.7 ,8.9Hz), 8.13 (1H, d, J = 2.7Hz)

Example 637

tert-butyl {4-[3-{[ethyl(methyl)amino]carbonyl}-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}-carbamate

oil

MS (ESI+) : m/z 466 (M+H)

1HNMR (200MHz, DMSOd6): 1.09 - 1.22 (3H, m), 1.39 (9H, s), 2.98,3.28 (3H, s), 3.73 - 3.77 (2H, m), 3.87 (3H, s), 4.13 (2H, d, J = 6.0Hz), 6.87 - 6.93 (2H, m), 7.18 - 7.30 (4H, m), 7.41 (1H, t, J = 6.0Hz), 7.65 - 7.74 (1H, m), 8.14 (1H, d, J = 2.6Hz)

Example 638

tert-butyl {4-[3-{[methoxy(methyl)amino]carbonyl}-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}carbamate

powder

MS (ESI+) : m/z 468 (M+H)

1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 3.37 (3H, s), 3.77

(3H, s), 3.87 (3H, s), 4.13 (2H, d, J = 6.1Hz), 6.91 (1H, d, J = 8.8Hz), 6.97 (1H, s), 7.25 (4H, s), 7.42 (1H, t, J = 6.1Hz), 7.71 (1H, dd, J = 2.7 ,8.8Hz), 8.15 (1H, d, J = 2.7Hz)

Example 639

5-[4-(2-hydroxyethyl)phenyl]-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide

oil

MS (ESI+) : m/z 382 (M+H)

1HNMR (200MHz, CDCl3): 1.44 (1H, t, J = 5.8Hz), 2.83 - 2.90 (2H, m), 3.51 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 3.84 - 3.89 (2H, m), 6.86 (2H, d, J = 9.0Hz), 6.96 (1H, s), 7.13 - 7.26 (6H, m)

Example 640

5-[4-(2-hydroxyethyl)phenyl]-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide

oil

Mass (ESI+) : m/z 383 (M+H)

1HNMR (200MHz, CDCl3): 2.84 - 2.91 (2H, m), 3.51 (3H, s), 3.85 (3H, s), 3.81 - 3.92 (2H, m), 3.95 (3H, s), 6.74 (1H, d, J = 8.6Hz), 6.97 (1H, s), 7.20 (4H, s), 7.55 (1H, dd, J = 2.8 ,8.6Hz), 8.13 (1H, d, J = 2.8Hz)

Example 641

To a solution of tert-butyl{4-[3-(1-hydroxy-1-methyl-ethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}-carbamate (1.1g) and Et3N (1.02g) was added methanesulfonyl chloride (576mg). The mixture was stirred at ambient temperature overnight. The mixture was concentrated in vacuo. The residue was partitioned between AcOEt and 1M HCl. The

organic layer was separated, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 25%. The pure fraction was collected and concentrated in vacuo to give tert-butyl {4-[3-isopropenyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate (857mg) as a solid.

MS (ESI+) : m/z 420 (M+H)

1HNMR (200MHz,): 1.46 (9H, s), 2.21(3H, s), 3.81 (3H, s), 4.30 (2H, d, J = 5.9Hz), 4.84 (1H, brs), 5.13 (1H, brs), 5.60 (1H, brs), 6.60 (1H, s), 6.84 (2H, d, J = 8.9Hz), 7.18 - 7.26 (6H, m)

The following compound(s) was(were) obtained in a similar manner to that of Example 641.

Example 642

tert-butyl {4-[3-isopropenyl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}carbamate

oil

MS (ESI+) : m/z 421 (M+H)

1HNMR (200MHz, DMSOd6): 1.39 (9H, s), 2.10 (3H, s), 3.86 (3H, s), 4.12 (2H, d, J = 6.2Hz), 5.15 (1H, brs), 5.63 (1H, brs), 6.88 (1H, s), 6.88 (1H, d, J = 8.8Hz), 7.22 (4H, s), 7.40 (1H, t, J = 6.2Hz), 7.67 (1H, dd, J = 2.7 ,8.8Hz), 8.06 (1H, d, J = 2.7Hz)

Example 643

A 0.76M solution of isopropylmagnesium bromide in THF (8.5ml) was added dropwise to a solution of tert-butyl

{4-[3-{[methoxy(methyl)amino]carbonyl}-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate (1g) in THF (10ml) at 10-15°C. The mixture was stirred at ambient temperature for 4hours. The reaction mixture was poured into a mixture of 1M HCl and ice. The mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 20%, 25%, then 10% MeOH/CHCl3. The combined pure fraction was concentrated in vacuo to give tert-butyl {4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}carbamate (318mg) as an amorphous powder.
MS (ESI+) : m/z 450 (M+H)
1HNMR (200MHz, CDCl3): 1.25 (6H, d, J = 6.8Hz), 1.46 (9H, s), 3.72 - 3.87 (1H, m), 3.83 (3H, s), 4.31 (2H, d, J = 5.9Hz), 4.75 - 4.93 (1H, m), 6.88 (2H, d, J = 9Hz), 6.98 (1H, s), 7.14 - 7.27 (6H, m)

The following compound(s) was(were) obtained in a similar manner to that of Example 643.

Example 644

tert-butyl {4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]benzyl}carbamate
oil
MS (ESI+) : m/z 451 (M+H)
1HNMR (200MHz, DMSOd6): 1.16 (6H, d, J = 6.8Hz), 1.38 (9H, s), 3.68 (1H, m), 3.88 (3H, s), 4.13 (2H, d, J = 6.1Hz), 6.92 (1H, d, J = 8.8Hz), 7.07 (1H, s), 7.19 - 7.29 (4H, m), 7.41 (1H, t, J = 6.1Hz), 7.75 (1H, dd,

J = 2.7 ,8.8Hz), 8.17 (1H, d, J = 2.7Hz)

Example 645

To a solution of 4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]benzonitrile (197mg) in THF (2ml) was added lithium aluminum hydride (30mg) under ice-bath cooling. The mixture was stirred at same temperature for 1hour and then at ambient temperature for 2hours. The reaction was quenched by adding 5% aqueous solution of potassium sodium tartaric acid (ca.0.5ml). The mixture was diluted with AcOEt, dried over MgSO4, and filtered through a celite pad. The filtrate was concentrated in vacuo to give {4-[1-(6-methoxy-3-pyridinyl)-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl]benzyl}amine (200mg) as an oil.

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

1HNMR (200MHz, DMSOd6): 3.75 (2H, s), 3.85 (3H, s), 4.84 (1H, d, J = 9Hz), 4.93 (1H, d, J = 9Hz), 6.32 (1H, s), 6.87 (1H, d, J = 8.9Hz), 7.19 (2H, d, J = 8.2Hz), 7.33 (2H, d, J = 8.2Hz), 7.64 (1H, dd, J = 2.7 ,8.9Hz), 8.03 (1H, d, J = 2.7Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 645.

Example 646

1-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenyl}methanamine

oil

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

1HNMR (200MHz, DMSOd6): 3.69 (2H, s), 3.78 (3H, s), 6.72 (1H, s), 6.96 (2H, d, J = 9Hz), 7.16 (2H, d, J = 8.2Hz), 7.22 (2H, d, J = 9Hz), 7.3 (2H, d, J = 8.2Hz)

Example 647

1-{4-[3-chloro-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}methanamine

powder

MS (ESI+) : m/z 315 (M+H)

1HNMR (200MHz, DMSOd6): 3.70 (2H, s), 3.86 (3H, s), 6.78 (1H, s), 6.89 (1H, d, J = 8.7Hz), 7.20 (2H, d, J = 8.3Hz), 7.33 (2H, d, J = 8.3Hz), 7.69 (1H, dd, J = 2.7 ,8.7Hz), 8.10 (1H, d, J = 2.7Hz)

Example 648

A mixture of 5-[4-(benzyloxy)phenyl]-3-amino-1-(4-methoxyphenyl)-1H-pyrazole (4.0g), lithium chloride (2.28g), and copper(II) chloride (2.90g) in acetonitrile (50ml) was stirred at ambient temperature for 10minutes. To this mixture was added isoamyl nitrite (2.52g), and the mixture was stirred at ambient temperature for 1.5hours. To the reaction mixture was added a mixture of ethyl acetate and saturated aqueous ammonium chloride solution. The mixture was stirred at ambient temperature for a while, and partitioned. The aqueous layer was reextracted with ethyl acetate. The combined organic layers were washed with saturated aqueous ammonium chloride solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with 20% AcOEt / n-hexane. The pure fractions were collected and concentrated in vacuo to give 5-[4-(benzyloxy)phenyl]-3-chloro-1-(4-methoxyphenyl)-1H-pyrazole (2.81g) as a solid.

MS ESI+) : m/z 391 (M+H)

1HNMR (200MHz, CDCl3): 3.81 (3H, s), 5.05 (2H, s), 6.35 (1H, s), 6.84 (2H, d, J = 9Hz), 6.89 (2H, d, J = 8.9Hz), 7.12 (2H, d, J = 8.9Hz), 7.19 (2H, d, J = 9Hz), 7.34 - 7.43 (5H, m)

Example 649

A solution of 4-benzyloxypropiophenone (5g) in N,N-dimethylformamide dimethyl acetal (20ml) was refluxed for 24hours. The mixture was concentrated in vacuo. The residue was dissolved in toluene and concentrated in vacuo. This was repeated one more time. The residue was dissolved in EtOH. To this solution was added 4-methoxyphenylhydrazine hydrochloride (3.63g), and the mixture was refluxed for 3hours. The reaction mixture was cooled to ambient temperature and partitioned between AcOEt and 1MHCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 30% to give 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-4-methyl-1H-pyrazole (5.31g) as a powder.
MS (ESI+) : m/z 371(M+H)
200MHz 1H NMR (CDCl3, d) : 2.10(3H, s), 3.79(3H, s), 5.06(2H, s), 6.80(2H, d, J=8.9 Hz), 6.94(2H, d, J=8.8 Hz), 7.09(2H, d, J=8.8 Hz), 7.14(2H, d, J=8.9 Hz), 7.31-7.48(5H, m), 7.55(2H, s)

The following compound(s) was(were) obtained in a similar manner to that of Example 649.

Example 650

5-{5-[4-(benzyloxy)phenyl]-4-methyl-1H-pyrazol-1-yl}-2-methoxypyridine

powder

MS (ESI+) : m/z 372 (M+H)

200MHz 1H NMR (CDCl3, d) : 2.10(3H, s), 3.91(3H, s), 5.06(2H, s), 6.68(1H, d, J=8.8 Hz), 6.96(2H, d, J=8.7 Hz), 7.09(2H, d, J=8.7 Hz), 7.36-7.52(6H, m), 7.59(1H, s), 8.02(1H, d, J=2.7 Hz)

Example 651

A solution of t-butyl nitrite (1.14ml) in CHCl3 (3ml) was added dropwise to a solution of 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-3-amino-1H-pyrazole (1.5g) and dimethyldisulfide (1.15ml) in CHCl3 (10ml). After all of t-butyl nitrite solution was added, the tempearature of reaction mixture began to rise and reached to reflux. After the reflux ceased, the mixture was stirred at ambient temperature for 1hour. The mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 25% to give 5-[4-(benzyloxy)phenyl]-1-(4-methoxyphenyl)-3-(methylthio)-1H-pyrazole (635.2mg) as an oil.

Mass (ESI+) : m/z 403 (M+H)

1HNMR (200MHz, CDCl3): 2.58 (3H, s), 3.81 (3H, s), 5.04 (2H, s), 6.36 (1H, s), 6.81 - 6.91 (4H, m), 7.13 (2H, d, J = 8.7Hz), 7.20(2H, d, J = 9Hz), 7.34 - 7.43 (5H, m)

Example 652

A mixture of 3-cyano-1-(4-methoxyphenyl)-5-[4-(aminometyl)phenyl]-1H-pyrazole (90mg) , trimethylsilylisocyanate (152mg) and Et3N (0.18ml) in

CH2Cl2 (5ml) was stirred at room temperature.
After stirring for 5 hours(checked by TLC), water and CHCl3 was added. The organic layer was separated. Aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine. Dried over MgSO4, filtered and evaporated under reduced pressure to give 48mg (52%) of N-{4-[3-cyano-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}urea.
MASS (ESI+): m/z = 370.1 (M+Na).
1HNMR (200MHz, CDCl3): 3.83 (H, s), 4.38 (2H, d, J = 6Hz), 4.42 (2H, b.s), 4.902 - (1H, m), 6.82 (1H, s), 6.87 (2H, d, J = 9Hz), 7.15 (2H, d, J = 8.3Hz), 7.19 (2H, d, J = 9Hz), 7.26 (2H, d, J = 8.3Hz).

Example 653

To a mixture of (2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)amine hydrochloride (150mg) in CHCl3 (2ml) and saturated aqueous sodium bicarbonate solution (1ml) was added thiophosgene (68.8mg) under ice-bath cooling. The mixture was stirred at ambient temperature for 5hours. To the mixture was added 28% aqueous ammonium hydroxide (1ml) and the mixture was stirred at ambient temperature overnight. To the mixture were added 28% aqueous ammonium hydroxide (1ml) and MeOH (1ml) and the mixture was stirred at r.t. for 7hours. The reaction mixture was partitioned between AcOEt and H2O. The organic layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from ACOEt-IPE. The obtained powder was recrystallized from AcOEt-n-hexane to give N-(2-{4-[3-methoxy-1-(4-methoxyphenyl)-1H-pyrazol-5-

yl]phenoxy}ethyl)thiourea (116mg) as a powder.

mp. 141.6-142.3°C

MS (ESI+) : m/z 399 (M+H)

1HNMR (200MHz, DMSOd6): 3.61 - 3.89 (2H, m), 3.75 (3H, s), 3.83 (3H, s), 3.98 - 4.12 (2H, m), 6.04 (1H, s), 6.92 (4H, d, J = 8.9Hz), 7.09 (2H, brs), 7.13 (4H, d, J = 8.9Hz), 7.77 (1H, t, J = 5.2Hz)

Example 654

A solution of methanesulfonyl chloride (328mg) in CH2Cl2 (2ml) was added to a solution of 5-[4-(2-hydroxyethyl)-phenyl]-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide (840mg) and Et3N (334mg) in CH2Cl2 (10ml) under ice bath cooling. The mixture was stirred at sametemperature for 1hour. The mixture was diluted with CHCl3 and washed with 1M HCl, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with AcOEt / n-hexane = 80%, 90%. The pure fractions were collected and concentrated in vacuo to give 2-{4-[3-{[methoxy(methyl)amino]carbonyl}-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate (1.01g) as an oil.

Mass (ESI+) : m/z 460 (M+H)

1HNMR (200MHz, CDCl3): 2.89 (3H, s), 3.05 (2H, t, J = 6.8Hz), 3.51 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 4.41 (2H, t, J = 6.8Hz), 6.86 (2H, d, J = 9.0Hz), 6.97 (1H, s), 7.18 - 7.26 (6H, m)

The following compound(s) was(were) obtained in a similar manner to that of Example 654.

Example 655

2-{4-[3-{[methoxy(methyl)amino]carbonyl}-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate

oil

Mass (ESI+) : m/z 461 (M+H)

1HNMR (200MHz, CDCl3): 2.91 (3H, s), 3.06 (2H, t, J = 6.8Hz), 3.50 (3H, s), 3.85 (3H, s), 3.94 (3H, s), 4.43 (2H, t, J = 6.8Hz), 6.74 (1H, d, J = 8.8Hz), 6.99 (1H, s), 7.32 (4H, s), 7.55 (1H, dd, J = 2.7 ,8.8Hz), 8.09 (1H, d, J = 2.7Hz)

Example 656

A mixture of 2-{4-[3-{[methoxy(methyl)amino]-carbonyl}-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl methanesulfonate (1.02g), 15-crown-5 (489mg), sodium azide (722mg) in hexamethylphosphoric triamide (6ml) was stirred at 55°C for 1hour. The mixture was poured into ice water, and the mixture was extracted with AcOEt. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in MeOH (6ml). To this solution was added a solution of 6M HCl (0.37ml) in MeOH (2ml) and 10% palladium on carbon (50%wet) (200mg). The mixture was hydrogenated under H2 1atm at ambient temperature for 2hours. The catalyst was removed by filtration. The filtrate was concentrated in vacuo to give 5-[4-(2-aminoethyl)phenyl]-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide hydrochloride (0.93g) as an oil.

Mass (ESI+) : m/z 381 (M+H)

1HNMR (200MHz, DMSOd6): 2.79 - 3.16 (4H, m), 3.38 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 6.95 (1H, s), 6.99 (2H, d, J = 9.0Hz), 7.15 - 7.36 (6H, m), 8.00 (2H, brs)

The following compound(s) was(were) obtained in a similar manner to that of Example 656.

Example 657

5-[4-(2-aminoethyl)phenyl]-N-methoxy-1-(6-methoxy-3-pyridinyl)-N-methyl-1H-pyrazole-3-carboxamide hydrochloride

oil

Mass (ESI+) : m/z 382 (M+H)

1HNMR (200MHz, DMSOd6): 2.80 - 3.15 (4H, m), 3.38 (3H, s), 3.77 (3H, s), 3.88 (3H, s), 6.92 (1H, d, J = 8.8Hz), 6.98 (1H, s), 7.22 - 7.36 (4H, m), 7.72 (1H, dd, J = 2.7, 8.8Hz), 8.02 (2H, brs), 8.17 (1H, d, J = 2.7Hz)

Example 658

To a 0.76M solution of isopropylmagnesium bromide in THF (2.0ml) was added a solution of 5-(4-{2-[(aminocarbonyl)-amino]ethyl}phenyl)-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide (130mg) in THF (2ml) dropwise at at 4°C. The mixture was stirred at ambient temperature overnight. Additional 0.76M solution of isopropylmagnesium bromide in THF (2.0ml) was added and the mixture was stirred at 50°C for 5hours. The reaction mixture was cooled to ambient temperature and was quenched by adding saturated aqueous ammonium chloride solution. The mixture was extracted with AcOEt. The oreganic layer was washed with 1M HCl, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, dried over

magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by MeOH/CHC3 10%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give N-(2-{4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl)urea (30mg) as amorphous powder.

MS (ESI+) : m/z 407 (M+H)

1HNMR (200MHz, CDCl3): 1.25 (6H, d, J = 6.8Hz), 2.77 - 2.85 (2H, m), 3.37 - 3.48 (2H, m), 3.72 - 3.87 (1H, m), 3.83 (3H, s), 4.32 (2H, s), 4.57 (1H, t, J = 4.9Hz), 6.89 (2H, d, J = 8.9Hz), 6.96 (1H, s), 7.14 (4H, s), 7.24 (2H, d, J = 8.9Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 658.

Example 659

N-(2-{4-[3-isobutyryl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl)methanesulfonamide

oil

MS (ESI+) : m/z 442

1HNMR (200MHz, CDCl3): 1.26 (6H, d, J = 6.9Hz), 2.84 - 2.91 (2H, m), 2.87 (3H, s), 3.35 - 3.46 (2H, m), 3.73 - 3.87 (1H, m), 3.84 (3H, s), 4.21 (1H, t, J = 6.1Hz), 6.89 (2H, d, J = 9.0Hz), 6.99 (1H, s), 7.13 - 7.29 (6H, m)

Example 660

N-(2-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)urea

oil

MS (ESI+) : m/z 408 (M+H)

1HNMR (200MHz, CDCl3): 1.26 (6H, d, J = 6.9Hz), 2.79 - 2.87 (2H, m), 3.39 - 3.50 (2H, m), 3.77 - (1H, m), 3.95 (3H, s), 4.35 (2H, s), 4.57 (1H, t, J = 5.4Hz), 6.78 (1H, d, J = 8.9Hz), 6.98 (1H, s), 7.17 (4H, s), 7.60 (1H, dd, J = 2.7 ,8.9Hz), 8.07 (1H, d, J = 2.7Hz)

Example 661

N-(2-{4-[3-isobutyryl-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)methanesulfonamide

oil

MS (ESI+) : m/z 443 (M+H)

1HNMR (200MHz, CDCl3): 1.26 (6H, d, J = 6.8Hz), 2.85 - 2.93 (2H, m), 2.88 (3H, s), 3.36 - 3.47 (2H, m), 3.77 (3H, m), 3.95 (3H, s), 4.24 (1H, t, J = 6.2Hz), 6.78 (1H, d, J = 8.8Hz), 7.00 (1H, s), 7.19 (4H, s), 7.57 (1H, dd, J = 2.7 ,8.8Hz), 8.11 (1H, d, J = 2.7Hz)

Example 662

To a solution of cyclopropylmagnesium bromide, which was prepared from cyclopropyl bromide (257mg) and magnesium (57mg) in THF (1ml) as usual method, was added a solution of 5-(4-{2-[(aminocarbonyl)-amino]ethyl}phenyl)-N-methoxy-1-(4-methoxyphenyl)-N-methyl-1H-pyrazole-3-carboxamide (90mg) in THF (3ml) dropwise at ambient temperature. The mixture was stirred at 50°C for 5hours. The reaction mixture was cooled to ambient temperature and was quenched by adding saturated aqueous ammonium chloride solution. The mixture was extracted with AcOEt. The oreganic layer was washed with 1M HCl, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated

in vacuo. The residue was purified by preparative thin layer silica gel chromatography developed by MeOH/CHC3 10%. The seaparated silica gel was extracted with 10% MeOH/CHCl3 and the solvent was evaporated in vacuo to give N-(2-{4-[3-(cyclopropylcarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl)urea (23mg) as a powder.

Mass (ESI+) : m/z 405 (M+H)

1HNMR (200MHz, CDCl3): 0.99 - 1.09 (2H, m), 1.22 - 1.30 (2H, m), 2.77 - 2.84 (2H, m), 3.13 (1H, m), 3.37 - 3.48 (2H, m), 3.84 (3H, s), 4.33 (2H, s), 4.59 (1H, t, J = 5.4Hz), 6.89 (2H, d, J = 8.9Hz), 6.96 (1H, s), 7.14 (4H, s), 7.26 (2H, d, J = 8.9Hz)

The following compound(s) was(were) obtained in a similar manner to that of Example 662.

Example 663

N-(2-{4-[3-(cyclopropylcarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenyl}ethyl)methanesulfonamide

oil

MS (ESI+) : m/z 440 (M+H

1HNMR (200MHz, CDCl3): 0.99 - 1.09 (2H, m), 1.22 - 1.31 .(2H, m), 2.80 - 2.91 (2H, m), 2.87 (3H, s), 3.14 (1H, m), 3.35 - 3.46 (2H, m), 3.84 (1H, s), 4.22 (1H, t, J = 5.7Hz), 6.90 (2H, d, J = 9.0Hz), 6.99 (1H, s), 7.12 (4H, s), 7.27 (2H, d, J = 9.0Hz)

Example 664

N-(2-{4-[3-(cyclopropylcarbonyl)-1-(6-methoxy-3-pyridinyl)-1H-pyrazol-5-yl]phenyl}ethyl)methanesulfonamide

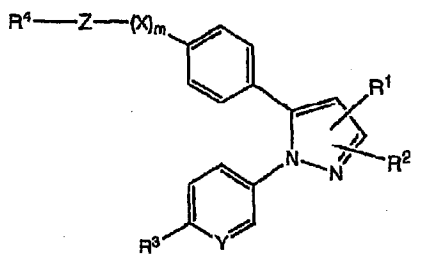
oil

Mass (ESI+) : m/z 441 (M+H)

1HNMR (200MHz, CDCl3): 1.03 - 1.11 (2H, m), 1.24 - 1.32 (2H, m), 2.85 - 2.93 (2H, m), 2.88 (3H, s), 3.11 (1H, m), 3.36 - 3.47 (2H, m), 3.96 (3H, s), 4.22 (1H, t, J = 6.0Hz), 6.78 (1H, d, J = 8.9Hz), 7.00(1H, s), 7.20 (4H, s), 7.60 (1H, dd, J = 2.7 ,8.9Hz), 8.13 (1H, d, J = 2.7Hz)

CLAIMS

1. A compound of the formula (I):



(I)

wherein R^1 is hydrogen or lower alkyl;

R^2 is lower alkyl optionally substituted with halogen, hydroxy, lower alkoxyimino or lower alkoxy; lower alkenyl; cycloalkyl; cyano; lower alkanoyl; cycloalkylcarbonyl; N,N-di(lower)alkylcarbamoyl; carbamoyl; N-lower alkoxy-N-lower alkylcarbamoyl; amino; di(lower)alkylamino; lower alkoxycarbonylamino; N,N-di(lower)alkylcarbamoylamino; N-(N,N-di(lower)alkylcarbamoyl)-N-lower alkylamino; halogen; hydroxy; carboxy; lower alkoxycarbonyl; aroyl; lower alkylsulfonyl; lower alkoxy optionally substituted with lower alkoxy, N,N-di(lower)alkylcarbamoyl or halogen; cycloalkyloxy; lower alkylthio; or lower alkylsufinyl;

R^3 is lower alkyl optionally substituted with amino, carbamoylamino or lower alkylsulfonylamino; halogen; cyano; hydroxy; lower alkanoyloxy; lower alkylenedioxy; lower alkoxy optionally

substituted with aryl, hydroxyl, cyano, amino, lower alkoxycarbonylamino, lower alkylsulfonylamino or carbamoylamino; nitro; amino; lower alkylthio, lower alkylsulfinyl; or lower alkylsulfonyl;

R^4 is a group of the formula:-

R^5-G-J-

in which G is -CO-;

J is $-N(R^6)-$

(wherein R^6 is hydrogen or lower alkyl); and

R^5 is amino optionally substituted with lower alkoxycarbonyl or lower alkyl, lower alkyl optionally substituted with hydroxy, lower alkoxycarbonylamino, lower alkanoyloxy, amino or halogen; lower alkoxy; hydrogen; or aryl;

X is O,S,SO or SO_2

Y is CH;

Z is lower alkylene or lower alkenylene; and

m is 0 or 1;

or a salt thereof.

2. The compound of Claim 1, wherein

R^1 is hydrogen;

R^2 is lower alkyl optionally substituted with halogen, hydroxy, lower alkyoxyimino or lower alkoxy, cycloalkyl; halogen; lower alkoxy optionally substituted with halogen; or lower alkylthio;

R^3 is lower alkoxy optionally substituted with aryl, hydroxy, cyano, amino, lower alkoxyxcarbonylamino, lower alkylsulfonylamino or carbamoylamino;

X is O or S; and

Z is lower alkylene.

3. The compound of Claim 2, wherein

R^2 is lower alkyl optionally substituted with halogen, cycloalkyl; halogen; or lower alkoxy optionally substituted with halogen;

R^3 is lower alkoxy;

J is -NH- and

R^5 is amino or lower alkyl;and

X is O

4. The compound of claim 3, which is

N-(2-{4-[3-chloro-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]-phenoxy}ethyl)urea,

N-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}methanesulfonamide,

N-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]benzyl}urea,

N-(2-{4-[3-(difluoromethyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea,

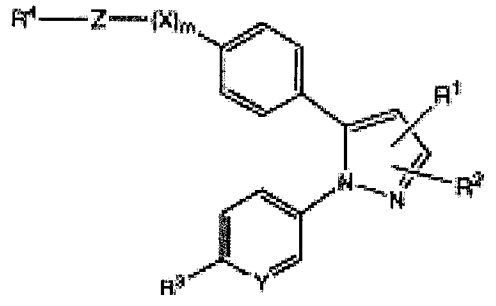
N-(2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea,

N-(2-{4-[3-cyclopropyl-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]phenoxy}ethyl)urea, or

N-(2-{4-[1-(4-methoxyphenyl)-3-trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl)acetamide.

5. The compound of Claim 4, which is N-(2-{4-[1-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]phenoxy}ethyl}urea.

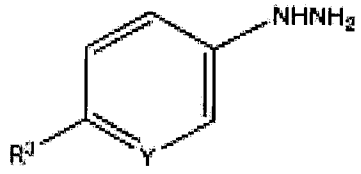
6. A process of preparing a compound of the formula:



(I)

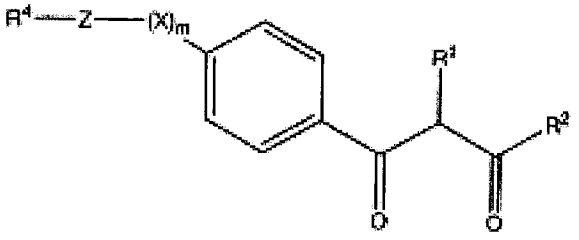
wherein R^1, R^2, R^3, R^4, R^5, G, J, R^6, X, Y, Z and m are defined in Claim 1 or salts thereof,
which comprises,

1) reacting a compound of the formula :



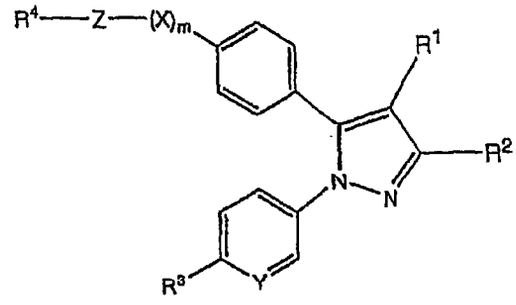
(II)

or its salts with a compound of the formula:



(III)

or its salt in the acidic condition to provide a compound of the formula:



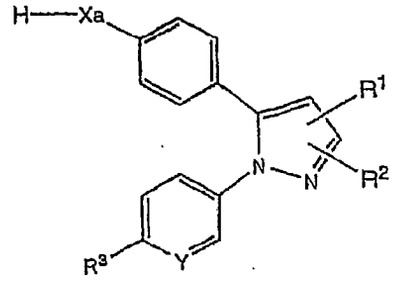
(Ia)

or its salt, in the above formulas,

R^1, R^2, R^3, R^4, X, Y, Z and m are each as defined above,

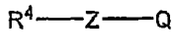
or

2) reacting a compound of the formula:



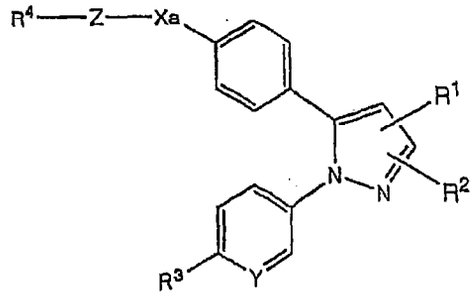
(IV)

or its salt with a compound (V) of the formula:



(V)

or its salt to provide a compound of the formula:



(Ib)

or its salt, in the above formulas:

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

Xa is O or S, and

Q is hydroxy or an acid residue.

7. A pharmaceutical composition comprising the compound of Claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.

8. A compound of Claim 1 for use as a medicament.

9. Use of the compound of Claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases in human beings or animals.

10. The analgesic agent comprising the compound of Claim 1, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations without causing gastrointestinal disorders.

11. The analgesic agent of Claim 10, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, or juvenile arthritis; lumbago; cervico-omo-brachial syndrome ; scapulohumeral periarthritis; pain and tumescence after operation or injury without causing gastrointestinal disorders.

12. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 and a written matter associated therewith, wherein the written matter states that the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegerative diseases.