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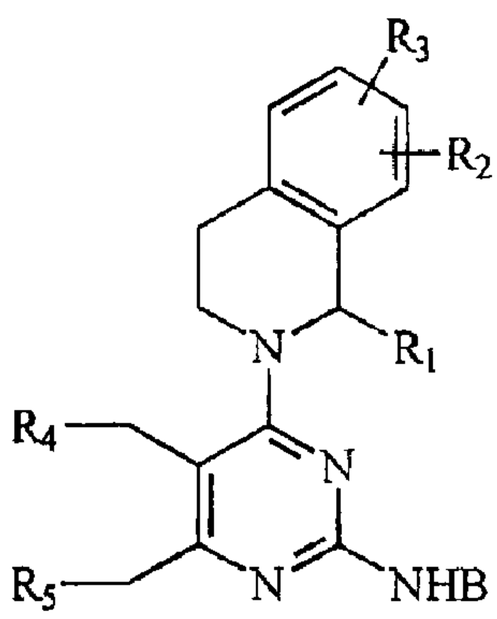
(54) Title: NOVEL PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF



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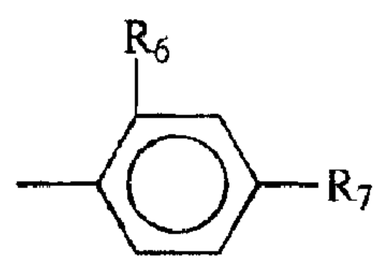

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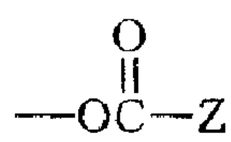

(III)

(57) Abrégé/Abstract:
The present invention relates to novel pyrimidine derivatives of formula (I) or pharmaceutically acceptable salts thereof which possess an excellent anti-secretory activity, pharmaceutical compositions containing the same as an active ingredient, their novel intermediates, and processes for the preparation thereof wherein: when A is piperidin-1-yl or -NH-B, wherein B is C_3-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_7 cycloalkyl, C_1-C_3 alkoxyethyl, phenylethyl which may be substituted or unsubstituted, 3-trifluoromethylphenylmethyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl, R_1 is hydrogen or methyl; and R_2, R_3, R_4 and R_5 are hydrogen; or when A is a group of formula (II); when R_1 is hydroxymethyl or C_1-C_3 alkoxymethyl, R_2, R_3, R_4, R_5 and R_6 are hydrogen; and R_7 is hydrogen or halogen; or when R_1 is hydrogen or methyl, R_7 is hydrogen or halogen; and one or two of R_2, R_3, R_4, R_5 and R_6 is hydroxy, methoxy, or a group of formula (III) wherein Z is C_1-C_4 alkyl, substituted or unsubstituted C_1-C_4 alkenyl, cyloalkyl, benzyloxyalkyl, alkoxycarbonylalkyl, morpholinomethyl, piperidinomethyl, 4-substituted-piperazinomethyl, substituted or unsubstituted phenyl, naphthyl, substituted or unsubstituted benzyl, thiophen-2-yl-methyl, 1-substituted-pyrrolidin-2-yl or -CHR_8NHR_9, wherein R_8 is hydrogen, methyl, isopropyl, benzyl, benzyloxymethyl, methylthioethyl, benzyloxycarbonylmethyl, carbamoylmethyl, carbamoylethyl, or 1-benzylimidazol-4-ylmethyl and R_9 is hydrogen or t-butoxycarbonyl; and the others are hydrogen or methyl.

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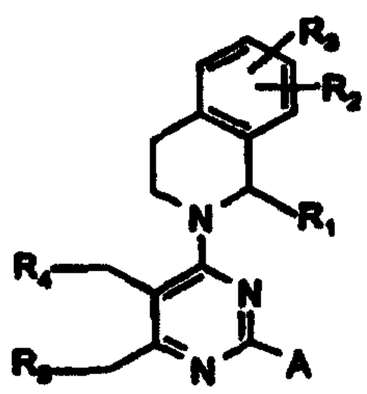

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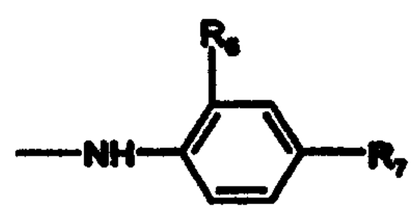

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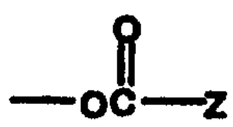


(III)

(57) Abstract

The present invention relates to novel pyrimidine derivatives of formula (I) or pharmaceutically acceptable salts thereof which possess an excellent anti–secretory activity, pharmaceutical compositions containing the same as an active ingredient, their novel intermediates, and processes for the preparation thereof wherein: when A is piperidin–1–yl or –NH–B, wherein B is C_3–C_4 alkyl, C_3–C_4 alkenyl, C_3–C_7 cycloalkyl, C_1–C_3 alkoxyethyl, phenylethyl which may be substituted or unsubstituted, 3–trifluoromethylphenylmethyl, 1–naphthylmethyl, 4–methylthiazol–2–yl or 4–phenylthiazol–2–yl, R_1 is hydrogen or methyl; and R_2, R_3, R_4 and R_5 are hydrogen; or when A is a group of formula (II); when R_1 is hydroxymethyl or C_1–C_3 alkoxymethyl, R_2, R_3, R_4, R_5 and R_6 are hydrogen; and R_7 is hydrogen or halogen; or when R_1 is hydrogen or methyl, R_7 is hydrogen or halogen; and one or two of R_2, R_3, R_4, R_5 and R_6 is hydroxy, methoxy, or a group of formula (III) wherein Z is C_1–C_4 alkyl, substituted or unsubstituted C_1–C_4 alkenyl, cyloalkyl, benzyloxyalkyl, alkoxycarbonylalkyl, morpholinomethyl, piperidinomethyl, 4–substituted–piperazinomethyl, substituted or unsubstituted phenyl, naphthyl, substituted or unsubstituted benzyl, thiophen–2–yl–methyl, 1–substituted–pyrrolidin–2–yl or $-CHR_8NHR_9$, wherein R_8 is hydrogen, methyl, isopropyl, benzyl, benzyloxymethyl, methylthioethyl, benzyloxycarbonylmethyl, carbamoylmethyl, carbamoylethyl, or 1–benzylimidazol–4–ylmethyl and R_9 is hydrogen or t–butoxycarbonyl; and the others are hydrogen or methyl.

WO 98/43968 PCT/KR98/00058

NOVEL PYRIMIDINE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Field of the Invention

The present invention relates to novel pyrimidine derivatives or pharmaceutically acceptable salts thereof which possess an excellent anti-secretory activity, pharmaceutical compositions containing same as an active ingredient, their novel intermediates, and processes for the preparation thereof.

Background of the Invention

For the treatment of peptic ulcer disease, various drugs such as antacid, anticholinergic agent, H_2-receptor antagonist and proton pump inhibitor have been used. The advent of omeprazole useful as a proton pump inhibitor has rekindled research activities in this field.

However, it has been pointed out that the proton pump inhibition by omeprazole is irreversible, which may induce side effects. Accordingly, various attempts to develop a reversible proton pump inhibitor are being actively made. For example, European Patent Nos. 322133 and 404322 disclose quinazoline derivatives, European Patent No. 259174 describes quinoline derivatives, and WO 91/18887 offers pyrimidine derivatives, as a reversible proton pump inhibitor. Further, the present inventors have also reported quinazoline derivatives in WO 94/14795 and pyrimidine derivatives in WO 96/05177.

Summary of the Invention

The present inventors have carried out extensive research to develop a reversible proton pump inhibitor with improved efficacy, and as a result have discovered that pyrimidine derivatives having a substituted tetrahydroisoquinoline group at 4-position of the pyrimidine nucleus or substituents at the 2-, 5-, or

6-position of the pyrimidine nucleus exhibit excellent proton pump inhibition effects and possess the ability to attain a reversible proton pump inhibition.

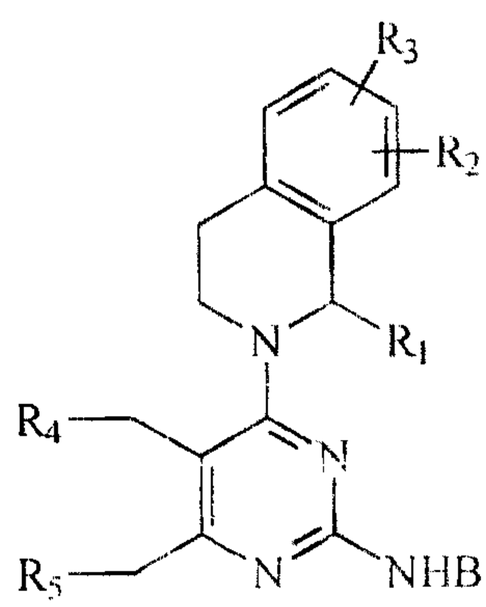
Accordingly, it is a primary object of the present invention to provide novel pyrimidine derivatives having a substituted tetrahydroisoquinoline group at 4-position of the pyrimidine nucleus or substituents at the 2-, 5-, or 6-position of the pyrimidine nucleus, or pharmaceutically acceptable salts thereof.

It is another object of the present invention to provide processes for preparing said compounds.

It is a further object of the present invention to provide pharmaceutical compositions for treating peptic ulcer containing the same as active ingredients.

It is still another object of the invention to provide novel intermediate compounds useful for the preparation of the novel pyrimidine derivatives.

In accordance with one aspect of the present invention, there are provided novel pyrimidine derivatives of formula (I) or pharmaceutically acceptable salts thereof :

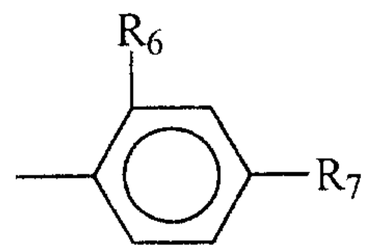


(I)

wherein

when B is C_3-C_7 cycloalkyl; C_1-C_3 alkoxyethyl; 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl;
R_1 is hydrogen or methyl; and
R_2, R_3, R_4 and R_5 are hydrogen: or

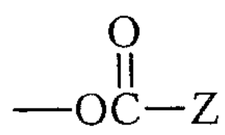
when B is a group of formula (II):



(II)

when R_1 is hydroxymethyl or C_1-C_3 **alkoxymethyl;**
R_2, R_3, R_4, R_5 and R_6 are hydrogen; and
R_7 is hydrogen or halogen; or

when R_1 is hydrogen or methyl;
R_7 is hydrogen or halogen; and
one or two of R_2, R_3, R_4, R_5 and R_6 is hydroxy, methoxy, or a group of formula (III)



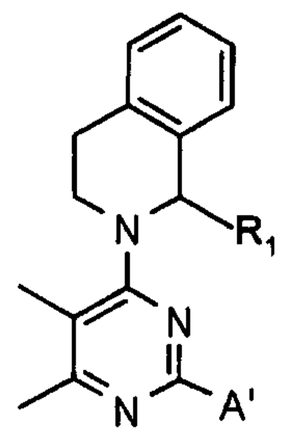
(III)

wherein Z is C_1-C_4 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl; morpholinomethyl; piperidinomethyl; phenyl; naphthyl; thiophen-2-yl-methyl; or $-CHR_8NHR_9$, wherein R_8 is hydrogen, methyl, isopropyl, benzyl, benzyloxymethyl, methylthioethyl, benzyloxycarbonylmethyl, carbamoylmethyl, carbamoylethyl, or 1-benzylimidazol-4-ylmethyl and R_9 is hydrogen or t-butoxycarbonyl, and the others are hydrogen or methyl, or

a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

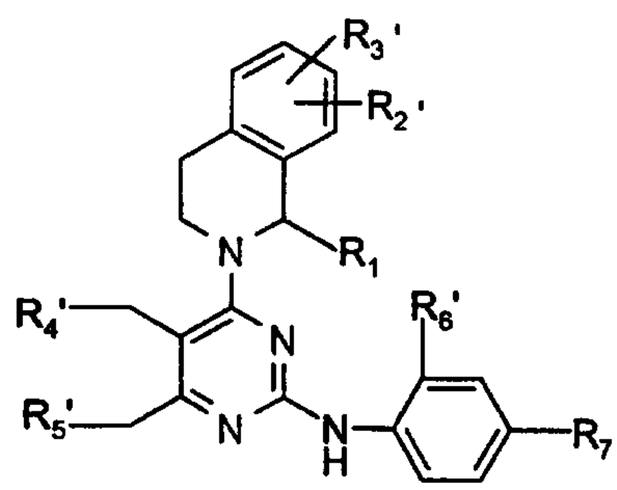
Among the compounds of formula (I), preferred are the compounds of the following formula (I-1) :



(I-1)

wherein R_1 is hydrogen or methyl ; and A' is piperidin-1-yl or -NH-B, wherein B is C_3-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_7 cycloalkyl, C_1-C_3 alkoxyethyl, phenylethyl which may be substituted or unsubstituted, 3-trifluoromethyl phenylmethyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl.

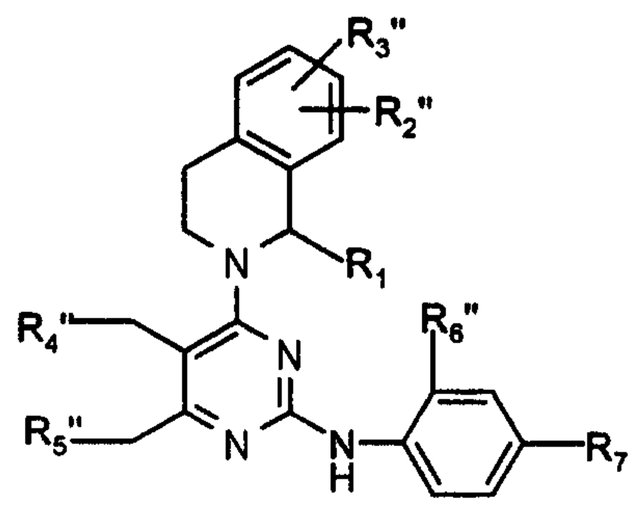
Among the compounds of the formula (I), also preferred compounds are the compounds of the following formula (I-2) :



(I-2)

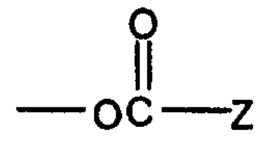
wherein R_1 is hydrogen or methyl ; R_7 is hydrogen or halogen ; one or two of R_2' , R_3' , R_4' , R_5' and R_6' is hydroxy or methoxy and the others are hydrogen or methyl.

Similarly preferred compounds are those of the following formula (I-3) :



(I-3)

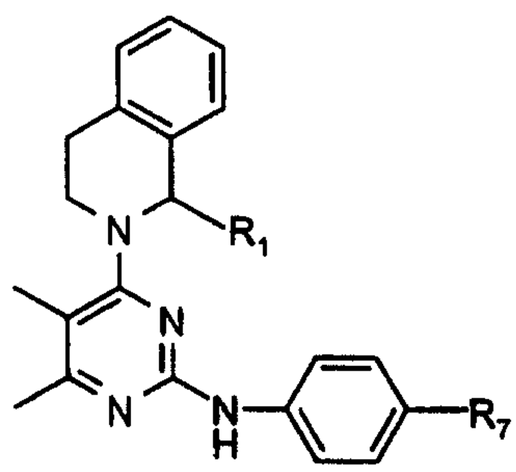
wherein R_1 is hydrogen or methyl ; R_7 is hydrogen or halogen ; one or two of R_2'' , R_3'' , R_4'' , R_5'' and R_6'' is a group of formula (III) :



(III)

wherein Z is C_1-C_4 alkyl, substituted or unsbstituted C_1-C_4 alkenyl, C_3-C_6 cycloalkyl, benzyloxyalkyl, alkoxycarbonylalkyl, morpholinomethyl, piperidinomethyl, 4-substituted-piperazinomethyl, substituted or unsubstituted phenyl, naphthyl, substituted or unsubstituted benzyl, thiophen-2-yl-methyl, 1-substituted-pyrrolidin-2-yl or $-CHR_8NHR_9$, wherein R_8 is hydrogen, methyl, isopropyl, benzyl, benzyloxymethyl, methylthioethyl, benzyloxycarbonylmethyl, carbamoylmethyl, carbamoylethyl, or 1-benzyl imdazol-4-ylmethyl and R_9 is hydrogen or t-butoxycarbonyl ; and the others are hydrogen or methyl.

Similarly preferred compounds are those of the following formula (I-4) :



(I-4)

wherein R_1 is hydroxymethyl or C_1-C_3 alkoxymethyl ; and R_7 is hydrogen or

halogen.

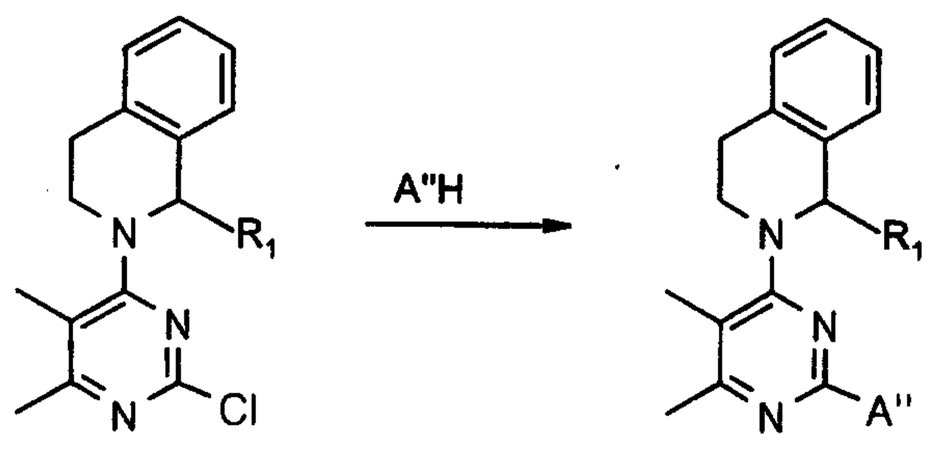
The pyrimidine derivatives of formula (I) in the present invention may exist in the form of an optical isomer, (R) or (S), or a mixture thereof. Both types of the isomeric compounds are found to exhibit excellent anti-secretory activity.

The compounds of the formula (I-1), (I-2), (I-3), and (I-4) may be prepared in accordance with the following methods.

Method for preparation of the formula (I-1)

The compound of formula (I-1a) may be prepared by reacting the compound (IV) with A"H in accordance with Scheme 1 described below.

Scheme 1



(IV) (I-1a)

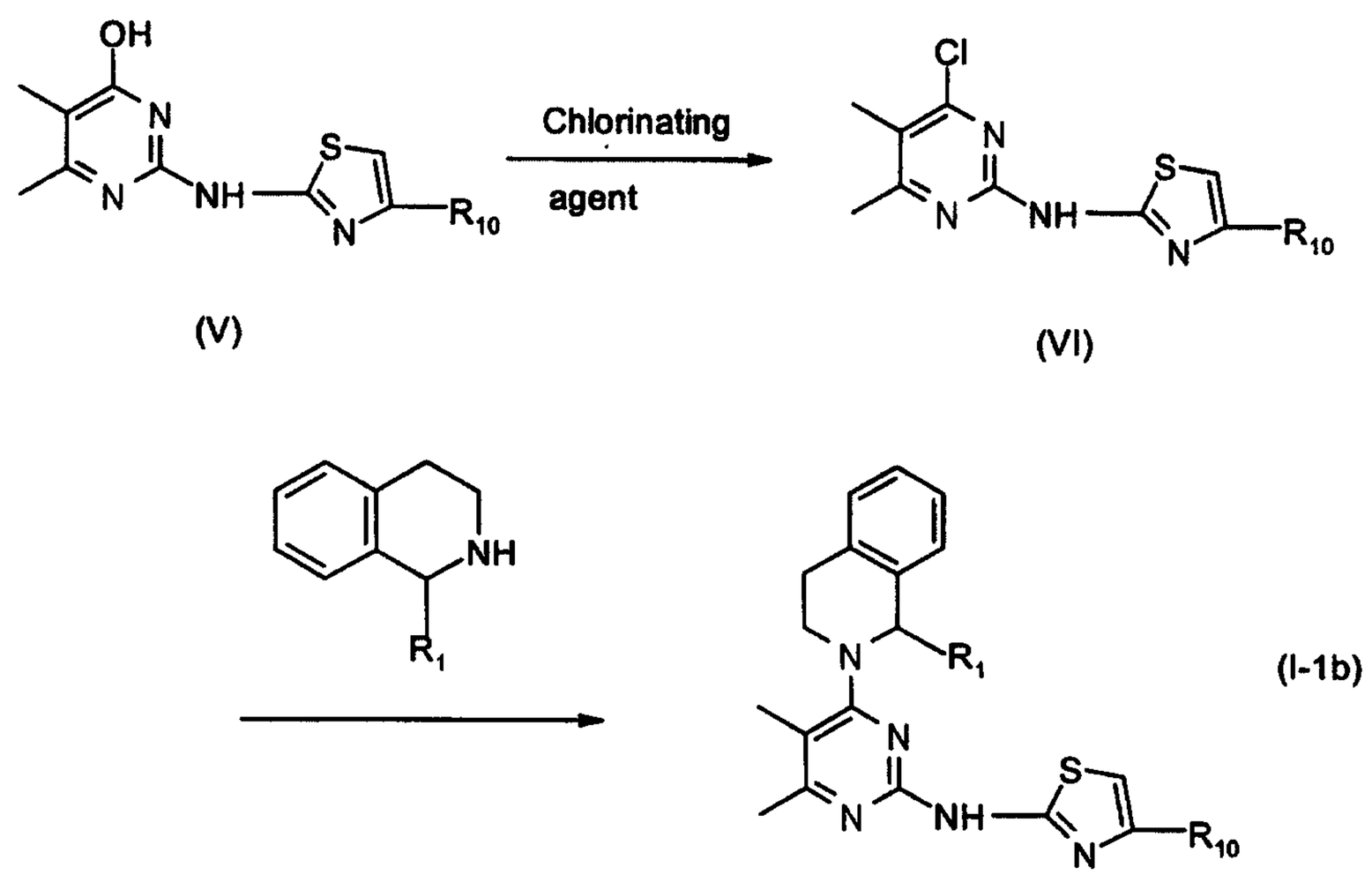
wherein R_1 is hydrogen or methyl ; and A" is piperidin-1-yl or -NH-B, wherein B is C_3-C_4 alkyl, C_3-C_4 alkenyl, C_3-C_7 cycloalkyl, C_1-C_3 alkoxyethyl, phenylethyl which may be substituted or unsubstituted, 3-trifluoromethylphenyl-methyl, or 1-naphthylmethyl.

In the process of Scheme 1, the compound of formula (IV) may be prepared by the same method as described in WO96/05177. The compound of A"H is commercially available (for example, from Aldrich Co. in U.S.A.).

As shown in Scheme 1, the pyrimidine compounds (IV) are reacted with A"H in the presence of an appropriate solvent and a base for 2 to 5 hours to give the compounds of formula (I-1a). Suitable solvents for this reaction may include dimethylformamide, p-dioxane, dimethylsulfoxide, and propyleneglycol. Suitable base for this reaction may include triethylamine, N,N-dimethylaniline, and pyridine. The reaction temperature preferably ranges from 80℃ to 140℃.

The compound of formula (I-1b) may be prepared by a process which comprises : chlorinating the compound of formula (V) to give a compound of formula (VI) ; and reacting the compound of formula (VI) with 1-R_1-1,2,3,4-tetrahydroisoquinoline in accordance with Scheme 2 described below.

Scheme 2



wherein R_1 is hydrogen or methyl ; and R_{10} is methyl or phenyl.

In the process of Scheme 2, the compound of formula (V) may be

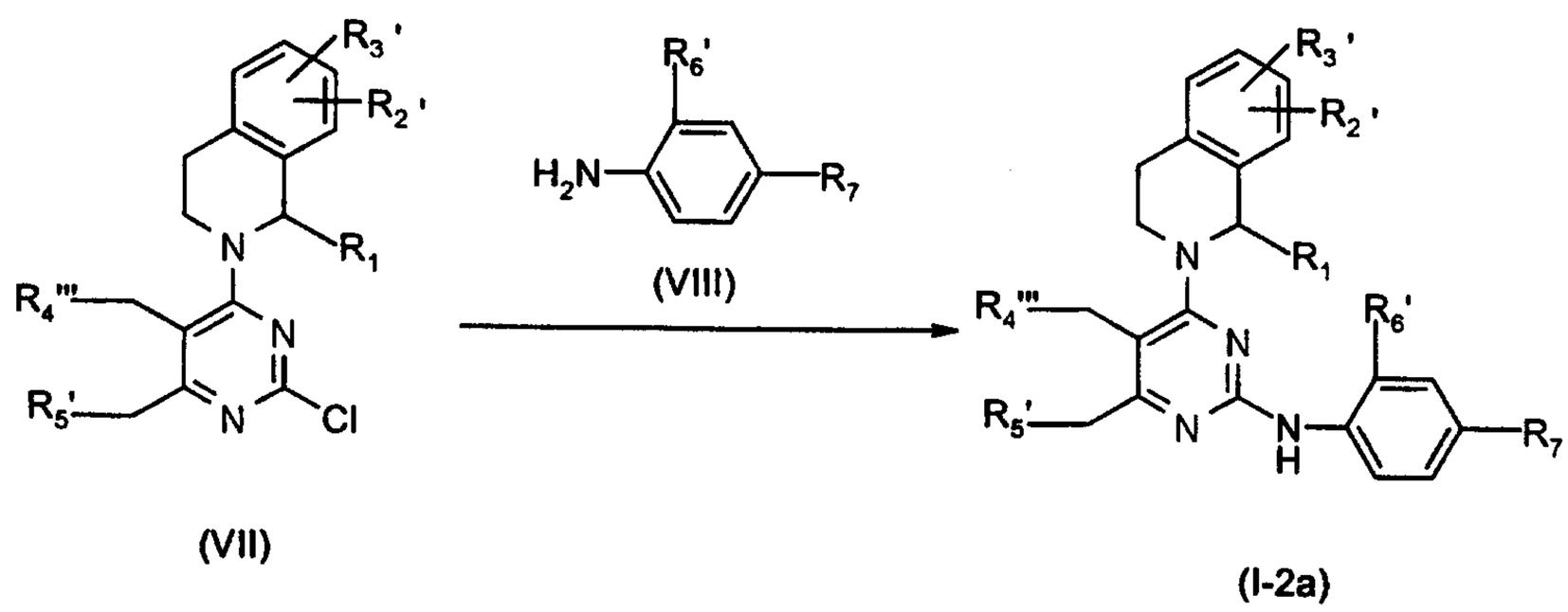
prepared by using a known process [see, e.g., J. Med. Chem., 33, 543, (1990) ; and J. Heterocyclic. Chem., 28, 231 (1991)].

The compound of formula (V) is chlorinated with chlorinating agent, e.g. phosphorous oxychloride, to give a compound of formula (VI). And then the compound of formula (VI) is reacted with 1-R_1-1,2,3,4-tetrahydroisoquinoline to give compounds of formula (I-1b).

Method for preparation of the formula (I-2)

The compound of formula (I-2a) may be prepared by reacting the compound (VII) with a compound of formula (VIII) in accordance with Scheme 3 described below.

Scheme 3

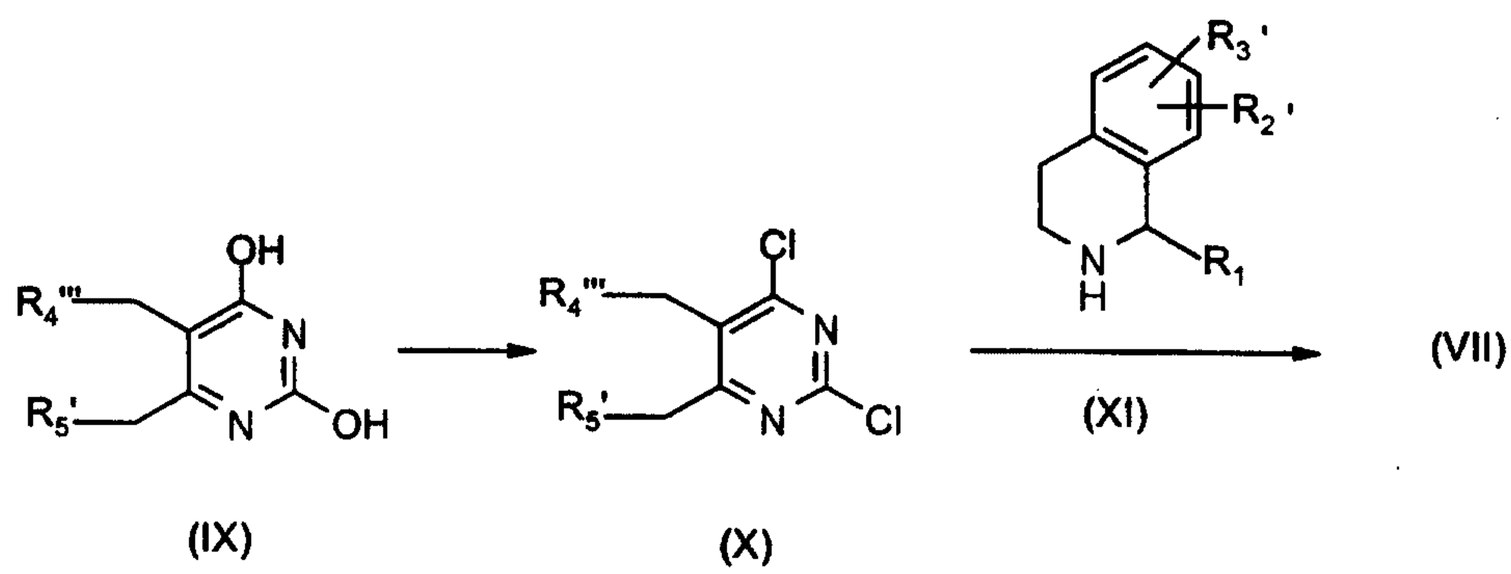


wherein R_1 , R_2' , R_3' , R_5' , R_6' and R_7 are the same as defined in formula (I-2) ; and R_4''' is hydrogen or methyl.

In Scheme 3, the reaction may be accomplished under same conditions, e.g., solvent, base, reaction time, and temperature, as those of Scheme 1. And also, a compound of formula (I-2a) wherein R_5' is hydroxy may be prepared by the demethylation of the corresponding compound of formula (I-2a) wherein R_5' is methoxy.

In the process of Scheme 3, the compound of formula (VII) may be prepared in accordance with Scheme 4.

Scheme 4



wherein R_1 , R_2' , R_3' , R_4''' and R_5' are the same as defined in the above.

In the process of Scheme 4, the compounds of formula (IX) and (XI) may be prepared by using a known process [see, e.g., J. Heterocyclic. Chem., 28, 231 (1991) ; Org. Synth., Coll. Vol., IV, 638, (1990) ; and European Patent No. 230,871].

The compound of formula (IX) is chlorinated with chlorinating agent, e.g. phosphorous oxychloride, to give a compound of formula (X). And then the compound of formula (X) is reacted with a compound of formula (XI) to give compounds of formula (VII). In the process of Scheme 4, the compound of formula (VII) wherein R_5' is hydroxy is prepared by the demethylation of the corresponding compound of formula (VII) wherein R_5' is methoxy.

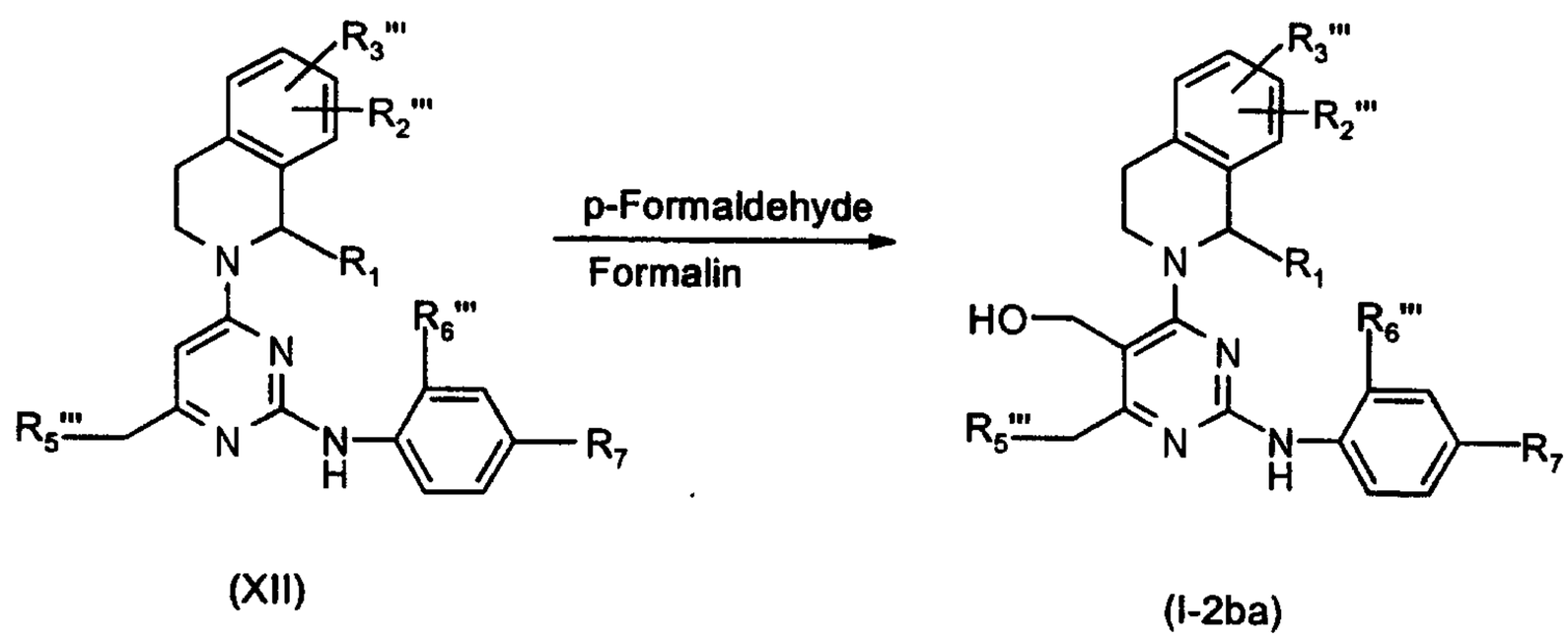
As shown in Scheme 4, the pyrimidine compounds (X) are reacted with a compound of formula (XI) in the presence of an appropriate solvent and a base for 1 to 24 hours to give the compounds of formula (VII). Suitable solvents for this reaction may include dichloromethane, acetone, acetonitrile, and dimethylformamide. Suitable base for this reaction may include

triethylamine, N,N-dimethylaniline, and pyridine. The reaction temperature preferably ranges from room temperature to 100℃.

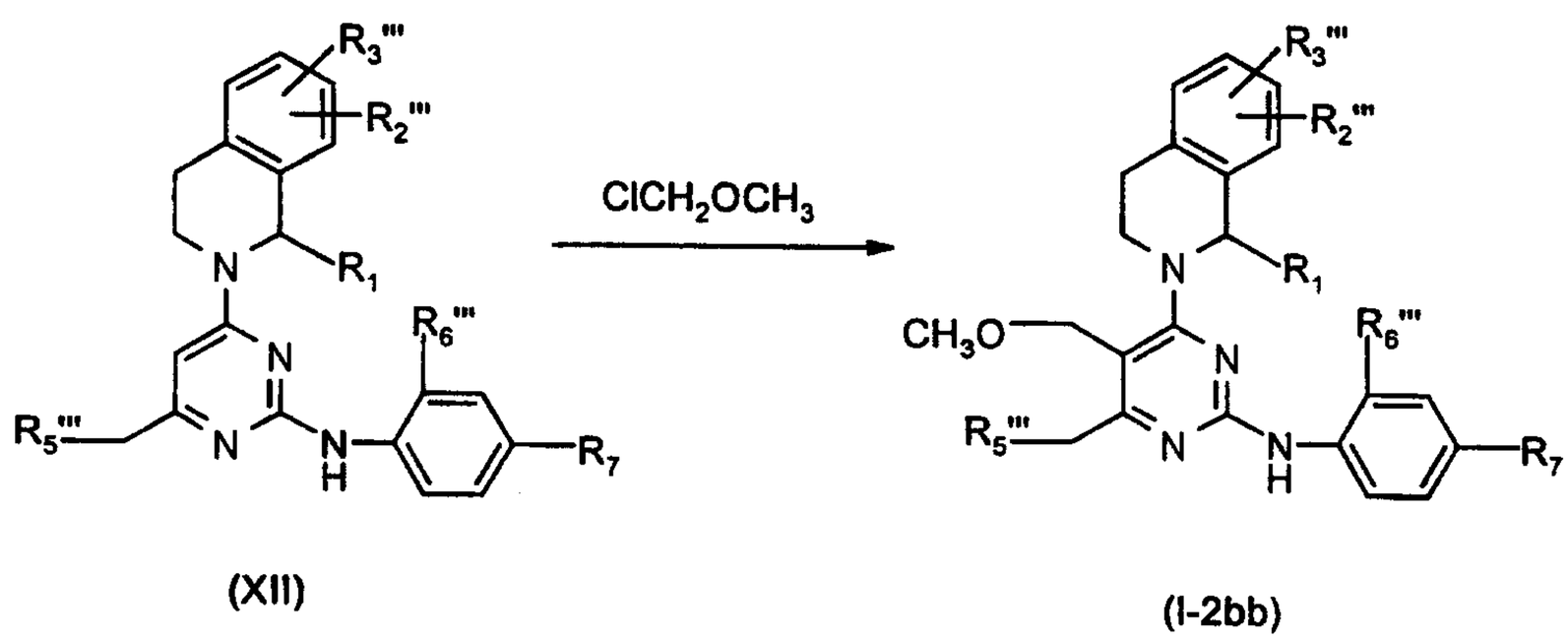
The compounds of formula (VII) prepared as above are novel and useful as intermidiates for the preparation of the pyrimidine compounds of formula (I-2a). Therefore, the present invention encompasses, within its scope, the novel compounds of formula (VII) and process for the preparation thereof.

The compound of formula (I-2b) may be prepared from the compound of formula (XII) in accordance with Scheme 5-1 and 5-2 described below.

Scheme 5-1



Scheme 5-2



wherein R_1 and R_7 are the same as defined in formula (I-2) ; R_2''' , R_3''' , R_5'''

and R_6''' are hydrogen or methyl, or one of R_2''' , R_3''' , R_5''' and R_6''' is hydroxy or methoxy.

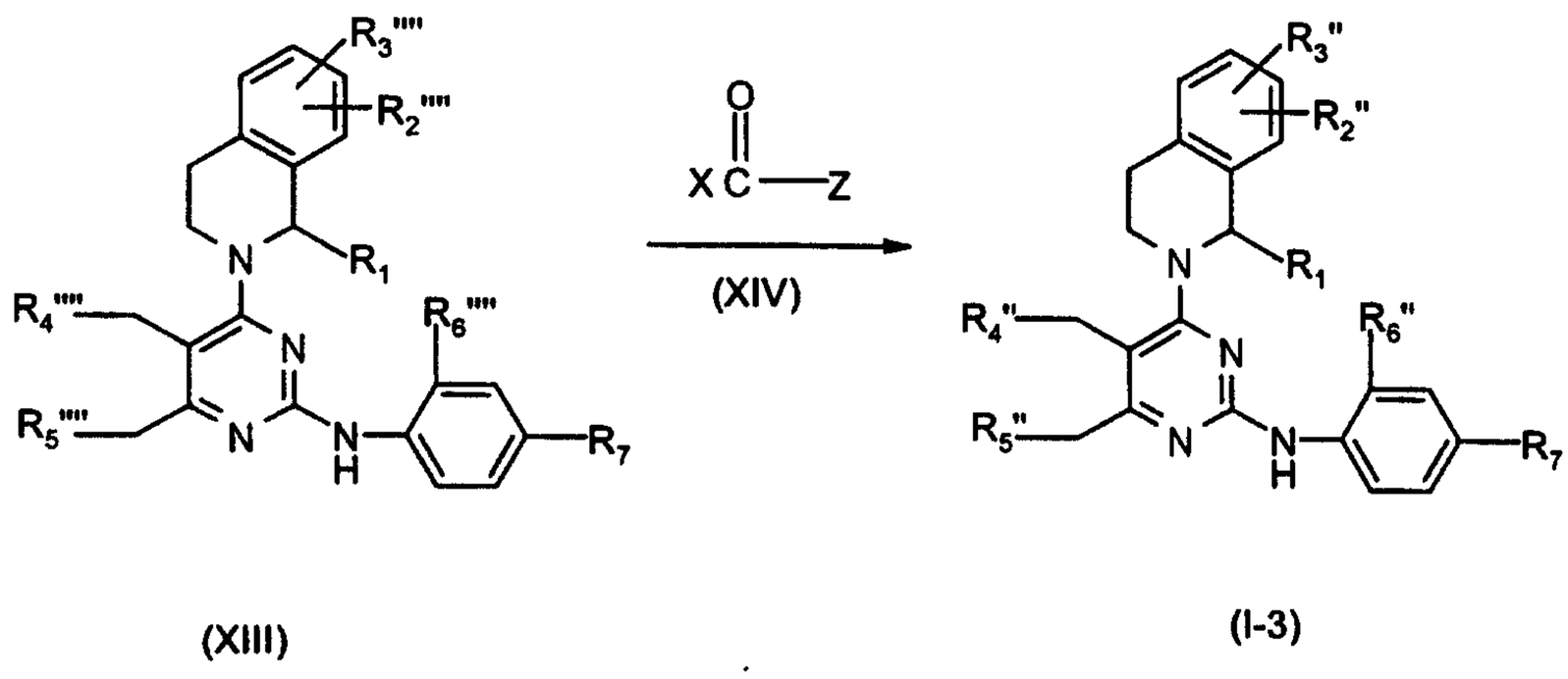
The compound of formula (XII) may be prepared by the same method as described in WO96/05177 or WO97/42186.

As shown in Scheme 5-1, the pyrimidine compound (XII) is reacted with p-formaldehyde in formalin solution for 24 hours to give the compounds of formula (I-2ba). The reaction temperature preferably ranges from 20℃ to 150℃. And also, in Scheme 5-2, the pyrimidine compound (XII) is reacted with chloromethyl methyl ether in a sealed tube to give the compounds of formula (I-2bb).

Method for preparation of the formula (I-3)

The compound of formula (I-3) may be prepared by reacting the compound (XIII) with a compound of formula (XIV) in accordance with Scheme 6 described below.

Scheme 6



wherein R_1 , R_2'' , R_3'' , R_4'' , R_5'' , R_6'' , R_7 and Z are the same as defined in formula (I-3); one or two of R_2'''' , R_3'''' , R_4'''' , R_5'''' and R_6'''' is hydroxy

and the others are hydrogen ; and X is halogen or hydroxy.

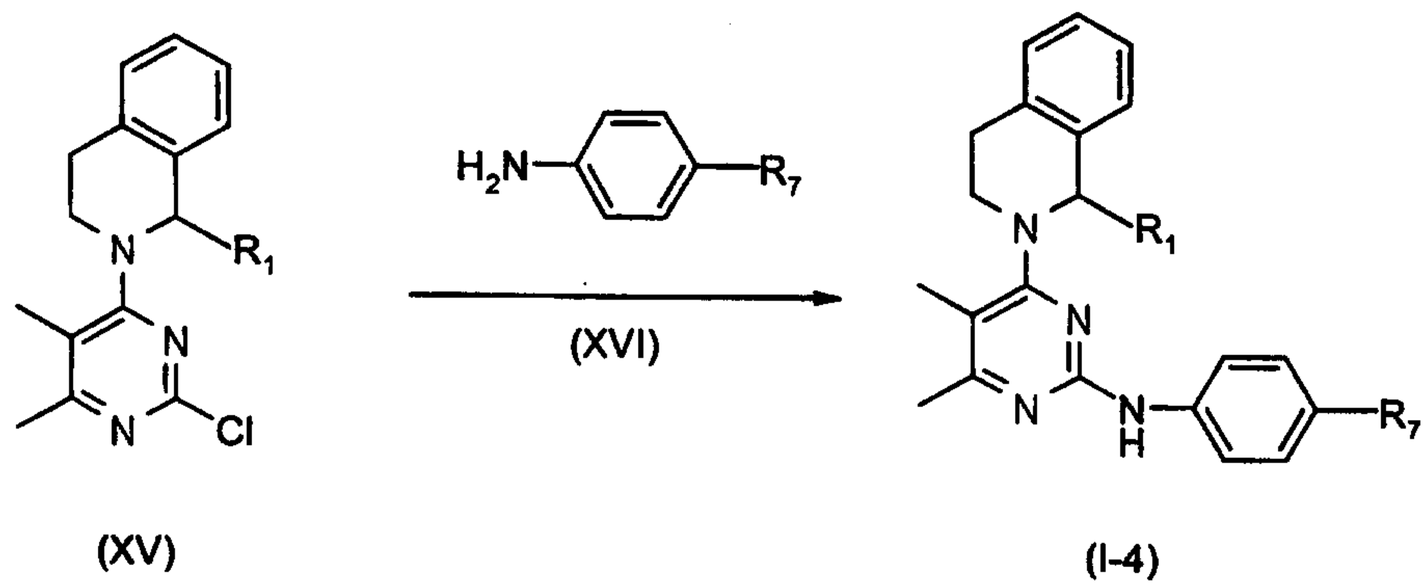
When X is halogen in Scheme 6, the pyrimidine compounds (XIII) are reacted with a compound of formula (XIV) in the presence of an appropriate solvent and a base for 3 to 24 hours to give the compounds of formula (I-3). Suitable solvents for this reaction may include dimethylformamide and dichloromethane. Suitable base for this reaction may include triethylamine and pyridine. The reaction temperature preferably ranges from 0℃ to 50℃.

When X is hydroxy in Scheme 6, the pyrimidine compounds (XIII) are reacted with a compound of formula (XIV) in the presence of an appropriate solvent and a coupling agent for 3 to 24 hours to give the compounds of formula (I-3). Suitable solvents for this reaction may include dimethylformamide and dichloromethane. Suitable coupling agents for this reaction may include 1-hydroxybenzotriazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and triethylamine. The reaction temperature preferably ranges from 0℃ to 50℃.

Method for preparation of the formula (I-4)

The compound of formula (I-4) may be prepared by reacting the compound (XV) with a compound of formula (XVI) in accordance with Scheme 7 described below.

Scheme 7



wherein R_1 is hydroxymethyl or C_1-C_3 alkoxymethyl ; and R_7 is hydrogen or halogen.

In Scheme 7, the reaction may be accomplished under same conditions, e.g., solvent, base, reaction time, and temperature, as those of Scheme 1.

The compounds of the present invention may be administered, either orally or intraperitoneally, in an effective amount ranging from 0.1 to 500 mg/kg, preferably from 1.0 to 100 mg/kg, into a subject patient per day.

The present invention further includes, within its scope, pharmaceutically acceptable salts of the compounds of formula (I). The non-toxic salts which fall within the scope of the present invention may include inorganic acid salts such as hydrochloride, sulfate, phosphate and nitrate, and organic acid salts such as tartrate, fumarate, citrate, mesylate and acetate.

The pharmaceutically acceptable salts may be prepared in accordance with a known method, e.g., by reacting the compounds of formula (I) with the acids mentioned above in the presence of a solvent, e.g., ethyl alcohol, dichloromethane, ethyl acetate and diethyl ether.

The present invention also includes within its scope pharmaceutical compositions comprising one or more of the inventive compounds as an acitive ingredient, in association with a pharmaceutically acceptable carrier, excipient and/or other additives, if necessary. The active ingredient present in the composition may range from 0.1 % to 99.9 % by weight thereof.

The following Examples are given for the purpose of illustration only, and are not intended to limit the scope of the invention. 2-Chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine and 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine were prepared by the same

method as described in WO96/05177.

Preparation 1 : Substituted 1,2,3,4-tetrahydroisoquinoline

Preparation 1-1 : 1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline

Step 1 : N-(3-methoxyphenylethyl)acetamide

3-methoxyphenethylamine(50g, 0.33mol) was dissolved in a soultion of water(130ml), dichloromethane(210ml) and sodium hydroxide(17.6g). Acetyl chloride(25.9ml, 0.36mol) was added dropwise at a room temperature to the mixture solution, which was then stirred for 1 hour. The separated dichloromethane layer was dried over anhydrous magnesium sulfate and then concentrated under a reduced pressure to give 63.6g of the titled compound.

Step 2 : 6-methoxy-1-methyl-3,4-dihydroisoquinoline

A mixture soultion of polyphosphoric acid (61.4ml, 0.66mol) and phosphorouspentoxide(28.0g, 0.2mol) was heated to 90°C. N-(3-methoxyphenyl-ethyl)acetamide (63.6g, 0.33mol) was added to the mixture solution and then stirred for 2 hours at 110°C. The reaction mixture was poured into ice water, adjusted to alkali with potassium hydroxide, and then extracted with ethyl ether. The extract was dried over anhydrous magnesium sulfate and concentrated under a reduces pressure. The resulting residue was purified by a silica gel column chromatography, using a solution of methanol and dichloromethane (1:20) as a eluent, to give 54.0g of the titled compound.

Step 3 : 6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline

6-methoxy-1-methyl-3,4-dihydroisoquinoline (54.0g, 0.31mmol) was added to a suspension of sodium borohydride(5.8g, 138 mmol) in ethanol. The mixture solution was stirred for 1 hour at a room temperature, cooled to below

5°C, acidified with diluted hydrochloric acid, adjusted to alkali with sodium hydroxide solution, and then extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated under a reduced pressure to give 45.4g of the titled compound.

Preparation 1-2 : 7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline

Step 1 : N-(4-acetoxyphenylethyl)acetamide

The mixture solution of 4-hydroxyphenethylamine(6.86g, 50mmol), triethylamine(13.9ml, 0.1mol) and dichloromethane(50ml) was cooled to 0°C. Acetylchloride(7.1ml, 0.1mol) was added dropwise to the mixture solution, which was then stirred for 2 hours at a room temperature, washed with 4N-hydrochloric acid, dried over anhydrous magnesium sulfate, and then concentrated to give 8.6g of the titled compound.

Step 2 : N-(4-hydroxyphenylethyl)acetamide

A solution of sodium hydroxide(2.3g, 58mmol) in water(20ml) was cooled to 0°C. A solution of N-(4-acetoxyphenylethyl)acetamide(6.4g, 29mmol) in methanol(40ml) was added dropwise to the soultion, stirred for 10 minutes, adjusted to pH 1 with hydrochloric acid, and then extracted 3 times with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated. The resulting oily residue was solidified with ethyl ether, filtered, and dried to give 4.4g of the titled compound.

Step 3 : N-(4-methoxyphenylethyl)acetamide

Potassium carbonate (3.5g, 25.5mol) and iodomethane(2.0ml, 31.9mmol) was added to a solution of N-(4-hydroxyphenylethyl)acetamide (4.4g, 24.6mmol) in ethanol(2.4ml), which was then refluxed for 12 hours. The resulting solid was filtered and washed with ethanol. The filtrate was concentrated to give

oily residue, which was diluted with ethyl acetate and washed with water. The separated organic layer was concentrated and the resulting solid was suspended in ethylether, filtered, and dried to give 2.9g of the titled compound.

Step 4 : 7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline

The same procedures as in Step 2 and 3 of Preparation 1-1 were repeated using N-(4-methoxyphenylethyl)acetamide (2.9g, 14.9mmol) to afford 0.96g of the titled compound.

Preparation 1-3 : 5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline

The same procedures as in Preparation 1-1 were repeated using 2-methoxyphenethylamine(5ml, 34.16mmol) to afford 6.45g of the titled compound.

Preparation 1-4. 5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline

The same procedures as in Preparation 1-1 were repeated using 4,5-dimethoxyphenethylamine(5.0g, 27.6mmol) to afford 2.65g of the titled compound.

Preparation 1-5. 1-methoxymethyl-1,2,3,4-tetrahydroisoquinoline

Step 1 : Preparation of methoxyacetic acid

A mixture solution of methoxyacetonitrile(10g, 0.14mole) and conc. hydrochloric acid was stirred for 30 minutes, then refluxed for another 30 minutes, cooled to room temperature, diluted with water, extracted with diethyl ether. The ether solution was separated, dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford 8.3g of titled compound.

Step 2 : Preparation of N-phenylethylmethoxyacetamide

Phenethylamine(11.6ml, 92.1mmol) was added dropwise to a solution of dicyclohexylcarbodiimide(19g, 92.1mmol), methoxyacetic acid(8.3g, 92.1mmol) in dichloromethane(50ml) at room temperature. After addition was completed, the reaction mixture was stirred for 1 hour at room temperature and the resulting solid was filtered. The filtrate was washed with aqueous hydrochloric acid solution, and the organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure to afford 8.15g of the titled compound.

Step 3 : Preparation of 1-methoxymethyl-1,2,3,4-tetrahydroisoquinoline

The same procedures as in Step 2 and 3 of Preparation 1-1 were repeated using N-phenylethylmethoxyacetamide(8.1g, 41.9mmol) to afford 2.6g of the titled compound.

Preparation 2 : 2,4-dichloro-6-methoxymethyl-5-methylpyrimidine

Step 1 : Ethyl 2-methyl-3-oxo-4-methoxybutyrate

Zinc(18.1ml, 275mmol), methoxyacetonitrile(13.7ml, 185mmol), benzene (180ml) and a catalytic amount of mercuric chloride were heated to reflux. A solution of ethyl 2-bromopropionate(35.9ml, 275mmol) in benzene(30ml) was added dropwise, then reflux continued for further a hour, and cooled to a room temperature. 10% Aqueous sulfuric acid solution (325ml) was added, and the organic layer was separated. The aqueous layer was further extracted with ethyl ether and the combined organic layers washed with water and aqueous sodium bicarbonate solution, then dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 29.3g of the titled compound.

Step 2 : 2-amino-4-hydroxy-6-methoxymethyl-5-methylpyrimidine

Ethyl 2-methyl-3-oxo-4-methoxybutyrate(10.5g, 60mmol) was added slowly to a suspension of sodium methoxide (6.5g, 120mmol) in dimethylformamide(10ml) while maintaining the reaction temperature under 20°C. A solution of guanidine(5.7g, 60mmol) in ethanol was added to a reaction mixture, which was then refluxed for 5 hours, cooled to a room temperature, and neutralized with conc. sulfuric acid. The resulting solid was filtered and dried to give 2.7g of the titled compound.

Step 3 : 2,4-dihydroxy-6-methoxymethyl-5-methylpyrimidine

2-amino-4-hydroxy-6-methoxymethyl-5-methylpyrimidine (2.7g, 16mmol) was added to 20% aqueous hydrochloric acid solution (7ml), and heated to 70°C. A solution of sodium nitrite (2.3g, 33.3mmol) in water was added dropwise to a reaction mixture while maintaining the reaction temperature under 70°C. The reaction mixture was cooled to a room temperature. The resulting solid was filtered and dried to give 1.5 g of the titled compound.

Step 4 : 2,4-dichloro-6-methoxymethyl-5-methylpyrimidine

A mixture solution of 2,4-dihydroxy-6-methoxymethyl-5-methyl pyrimidine (1.5g, 8.8mmol), phosphorous oxychloride(7ml) and N,N-dimethyl-aniline(0.9ml) was refluxed for 3 hours, cooled to a room temperature, and then poured into ice water. The aqueous layer was extracted with dichloromethane. The resulting organic layer was dried, concentrated, and purified by a silica gel column chromatography to give 1.3g of the titled compound.

Preparation 3. 4-morpholineacetic acid hydrochloride

Step 1 : ethyl 4-morpholineacetate

Morpholine(1.65ml, 18.9mmol) was added dropwise to a soultion of

ethyl bromoacetate(1ml, 9.0mmol) in benzene (9ml). The reaction mixture was stirred for 2 hours at a room temperature, diluted with ethyl ether, and washed with saturated NaCl solution. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under a reduced pressure to give 1.11 g of the titled compound as an oil. (Yield 71.2 %)

NMR($CDCl_3$): 1.3(t, 3H), 2.6(t, 4H), 3.2(s, 2H), 3.8(t, 4H), 4.2(q, 2H).

Step 2 : 4-Morpholineacetic acid hydrochloride

Ethyl 4-morpholinoacetate (1.1g, 6.3mmol) was added to 3M hydrochloric acid solution (35ml), refluxed for 2 hours, stirred for 1 day at a room temperature, and then concentrated under a reduced pressure. The resulting residue was dissolved in methanol and reconcentrated. The resulting solid was suspended in ethylether, filtered and dried under a reduced pressure to give 1.05g of the titled compound. (Yield 91.7 %)

NMR (DMSO-d6): 3.3(s, 4H), 3.9(s, 4H), 4.2(s, 2H).

Preparation 4. 4-benzylpiperazineacetic acid dihydrochloride

Step 1 : ethyl 4-benzylpiperazineacetate

4-Benzylpiperazine(3.3ml, 18.9mmol) was added to a solution of ethyl bromoacetate(1ml, 9.0mmol) in benzene(9ml), which was then stirred for 2 hours at a room temperature, diluted with ethyl ether, and washed with saturated NaCl solution. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 2.38 g of the titled compound. (Yield 100 %).

NMR($CDCl_3$): 1.3(t, 3H), 2.6(t, 8H), 3.2(s, 2H), 3.6(s, 2H), 4.2(q, 2H), 7.3(m, 5H).

Step 2 : 4-benzylpiperazineacetic acid dihydrochloride

Ethyl 4-benzylpiperazineacetate (2.38g, 9.0mmol) was added to 3M hydrochloric acid solution(12ml), refluxed for 2 hours, stirred for 1 day at a room temperature, and then concentrated under reduced pressure. The resulting residue was dissolved in methanol and reconcentrated. The resulting solid was suspended in ethyl ether, filtered and dried under a reduced pressure to give 2.14g of the titled compound. (Yield 77.4 %)

NMR(D2O): 3.3(s, 8H), 3.7(s, 2H), 4.0(s, 2H), 7.1(s, 5H).

Preparation 5. 1-piperidineacetic acid hydrochloride

Step 1 : ethyl 1-piperidineacetate

Piperidine(1.87ml, 18.9mmol) was added dropwise to a solution of ethyl bromoacetate(1ml, 9.0mmol) in benzene(9ml), stirred for 2 hours at a room temperature, diluted with ethyl ether, washed with saturated NaCl solution. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under a reduced pressure to give 1.26g of the titled compound. (Yield 81.8 %)

NMR($CDCl_3$): 1.3(t, 3H), 1.5(m, 2H), 1.7(m, 4H), 2.5(t, 4H), 3.2(s, 2H), 4.2(q, 2H).

Step 2 : 1-piperidineacetic acid hydrochloride

Ethyl 1-piperidineacetate (1.26g, 7.4mmol) was added to 3M hydrochloric acid solution (12ml), which was then refluxed for 2 hours, stirred for 1 day at a room temperature, then concentrated under a reduced pressure. The resulting residue was dissolved in methanol and reconcentrated. The

resulting solid was suspended in ethyl ether, filtered and dried under a reduced pressure to give 0.87g of the titled compound. (Yield 65.3 %).

NMR(D2O): 1.0(m, 2H), 1.4(m, 4H), 2.5(m, 2H), 3.1(m, 2H), 3.5(s, 2H).

Example 1.

5,6-dimethyl-2-(propylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Propylamine(0.44g, 5.4mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a mixture solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide(10ml). The reaction mixture was stirred for 5 hours at 130 °C, cooled to a room temperature, diluted with dichloromethane, and then washed with aqueous sodium hydroxide and water. The separated organic layer was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and then purified by column chromatography to give free base form of the titled compound. Ethyl ether saturated with hydrochloric acid was added to a mixture solution of the free base form of the titled compound in ethyl ether. The resulting solid was filtered and dried to obtain 490mg of the titled compound.

Yield : 81.8 %

M.P. : 157 - 160 °C

^{1}H-NMR(CDCl3) : δ 1.0(t, 3H), 1.7(m, 2H), 2.1(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.4(q, 2H), 3.9(t, 2H), 4.8(s, 2H), 7.2(m, 4H), 7.9(s, 1H), 13.8(s, 1H).

Example 2.

5,6-dimethyl-2-(3-allylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After allylamine(0.20ml, 2.7mmol) and triethylamine(0.38 ml, 2.7

mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 170mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 28.5 %

M.P. : 192 - 194 °C

^{1}H-NMR(CDCl3) : δ 2.2(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.9(t, 2H), 4.1(t, 2H), 4.8(s, 2H), 5.3(q, 2H), 5.9(m, 1H), 7.2(m, 4H), 8.0(s, 1H), 14.0(s, 1H).

Example 3.

5,6-dimethyl-2-butylamino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After butylamine(0.53 ml, 5.4 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydro-isoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 300mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 48.0 %

M.P. : 110 - 113°C

^{1}H-NMR(CDCl3) : δ 1.0(t, 3H), 1.4(m, 2H), 1.6(m, 2H), 2.1(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.5(q, 2H), 3.9(t, 2H), 4.8(s, 2H), 7.2(m, 4H), 7.9(s, 1H), 13.8(s, 1H).

Example 4.

5,6-dimethyl-2-isobutylamino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After isobutylamine(0.27 ml, 2.7 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetra-

hydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 180mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 28.8 %
M.P. : 169 - 172 °C
^{1}H-NMR(CDCl3) : δ 1.0(d, 6H), 1.9(m, 1H), 2.1(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.3(d, 2H), 3.9(t, 2H), 4.8(s, 2H), 7.2(m, 4H), 8.0(s, 1H), 13.9(s, 1H).

Example 5.
5,6-dimethyl-2-(2-methoxyethylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After methoxyethylamine(0.23 ml, 2.7 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 470mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 74.8 %
M.P. : 145 - 150 °C
^{1}H-NMR(CDCl3) : δ 2.1(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.4(s, 3H), 3.6(m, 4H), 3.9(t, 2H), 4.8(s, 2H), 7.2(m, 4H), 7.9(s, 1H), 14.0(s, 1H).

Example 6.
5,6-dimethyl-2-phenylethylamino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After phenethylamine(0.34 ml, 2.7 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 600mg of the titled compound was obtained in accordance with the same procedure as

in Example 1.

Yield : 84.4 %

M.P. : 150 - 154°C

^{1}H-NMR(CDCl3) : δ 2.1(s, 3H), 2.4(s, 3H), 2.9(t, 2H), 3.1(t, 2H), 3.7(q, 2H), 3.9(t, 2H), 4.8(s, 2H), 7.2(m, 9H), 8.1(s, 1H).

Example 7.

5,6-dimethyl-2-(1-naphthylmethyl)amino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 1-naphthylmethylamine(0.40 ml, 2.7 mmol) and triethylamine (0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 680mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 87.7 %

M.P. : 194 - 197 °C

^{1}H-NMR(CDCl3) : δ 2.1(s, 3H), 2.4(s, 3H), 2.9(t, 2H), 3.8(t, 2H), 4.6(s, 2H), 5.1(d, 2H), 7.0(m, 1H), 7.2(m, 3H), 7.5(m, 4H), 7.8(d, 1H), 7.9(d, 1H), 8.2(d, 1H), 8.5(s, 1H), 14.1(s, 1H).

Example 8.

5,6-dimethyl-2-(cyclohexylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After cyclohexylamine(0.31ml, 2.7mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 340mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 70.0 %

M.P. : 173 - 177 °C

^{1}H-NMR(CDCl3) : δ 1.4(m, 6H), 1.8(m, 2H), 1.9(m, 2H), 2.2(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.9(t, 3H), 4.8(s, 2H), 7.2(m, 4H), 7.9(d, 1H), 13.7(s, 1H).

Example 9.

5,6-dimethyl-2-(cyclopentylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After cyclopentylamine(0.27 ml, 2.7 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 270mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 41.8 %

M.P. : 148 - 153°C

^{1}H-NMR(CDCl3) : δ 1.6(m, 4H), 1.8(m, 2H), 2.0(m, 2H), 2.1(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.9(t, 2H), 4.2(q, 1H), 4.8(s, 2H), 7.2(m, 4H), 8.0(d, 1H), 13.7(s, 1H).

Example 10.

5,6-dimethyl-2-(piperidin-1-yl)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After piperidine(0.27 ml, 2.7 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.8mmol) in dimethylformamide, 260mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 40.2 %

M.P. : 77 - 82°C

^{1}H-NMR(CDCl3) : δ 1.7(s, 6H), 2.2(s, 3H), 2.7(s, 3H), 3.1(t, 2H), 3.9(t, 2H), 4.1(s, 4H), 4.8(s, 2H), 7.2(m, 4H), 12.9(bs, 1H).

Example 11.

5,6-dimethyl-2-propylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After propylamine(0.43 ml, 5.22 mmol) and triethylamine(0.36ml, 2.59mmol) were added to a solution of 5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-chloropyrimidine(0.5g, 1.74mmol) in dimethylformamide, 530mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 63.0 %

M.P. : 162 - 164 °C

^{1}H-NMR(CDCl3) : δ 1.0(t, 3H), 1.7(q, 5H), 2.2(s, 3H), 2.4(s, 3H), 2.9(m, 1H), 3.1-3.7(m, 5H), 4.3(m, 1H), 5.4(q, 1H), 7.2(m, 4H), 7.9(s, 1H), 13.8(s, 1H).

Example 12.

5,6-dimethyl-2-(3-allylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After allylamine(0.40 ml, 5.22 mmol) and triethylamine(0.36ml, 2.59mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.74mmol) in dimethylformamide, 510mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 85.0 %

M.P. : 192 - 194 °C

^{1}H-NMR(CDCl3) : δ 1.7(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 4.6(s, 2H), 4.3(m, 1H), 5.1-5.5(m, 3H), 4.8(s, 2H), 5.9(m, 1H), 7.2(m, 4H), 8.0(s, 1H), 13.9(s, 1H).

Example 13.

5,6-dimethyl-2-butylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After butylamine(0.52 ml, 5.22 mmol) and triethylamine(0.36ml, 2.59mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 430mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 68.5 %

M.P. : 105 - 107°C

^{1}H-NMR(CDCl3) : δ 1.0(t, 3H), 1.4-1.7(m, 4H), 1.7(d, 3H), 2.1(s, 3H), 2.4(s, 3H), 2.9(m, 1H), 3.2-3.7(m, 4H), 4.3(m, 1H), 5.4(q, qH), 7.3(m, 4H), 7.8(s, 1H), 13.8(s, 1H).

Example 14.

5,6-dimethyl-2-isobutylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After isobutylamine(0.26 ml, 2.58 mmol) and triethylamine(0.36 ml, 2.59mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.74mmol) in dimethylformamide, 133mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 20.0%

M.P. : 93 - 95°C

^{1}H-NMR(CDCl3) : δ 0.9(d, 6H), 1.5(d, 3H), 1.9(m, 1H), 2.1(s, 3H), 2.3(s, 3H),

2.8(m, 1H), 3.1(t, 2H), 3.2(m, 1H), 3.5(m, 2H), 4.0(m, 1H), 5.1(q, 1H), 7.2(m, 4H).

Example 15.

5,6-dimethyl-2-(2-methoxyethylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 2-methoxyethylamine(0.23 ml, 2.7 mmol) and triethylamine(0.38 ml, 2.7 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 320mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 50.7 %

M.P. : 64 - 67°C

^{1}H-NMR(CDCl3) : δ 1.6(d, 3H), 2.1(s, 3H), 2.4(s, 3H), 2.9(m, 1H), 3.3(m, 1H), 3.4(s, 3H), 3.6(m, 5H), 4.3(m, 1H), 5.4(q, 1H), 7.2(m, 4H), 7.8(s, 1H), 13.8(s, 1H).

Example 16.

5,6-dimethyl-2-phenylethylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 2-phenethylamine(0.33 ml, 2.61 mmol) and triethylamine(0.36 ml, 2.59 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 500mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 70.2 %

M.P. : 124 - 127°C

^{1}H-NMR(CDCl3) : δ 1.7(d, 3H), 2.1(s, 3H), 2.4(s, 3H), 3.0(m, 3H), 3.3(m,

1H), 3.7(m, 3H), 4.3(m, 1H), 5.4(q, 1H), 7.2(m, 9H), 8.0(s, 1H), 13.8(s, 1H).

Example 17.

5,6-dimethyl-2-(1-naphthylmethyl)amino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 1-naphthylmethylamine(0.38 ml, 2.61 mmol) and triethylamine (0.36 ml, 2.59 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 630mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 81.4 %

M.P. : 179 - 182 °C

^{1}H-NMR(CDCl3) : δ 1.4(d, 3H), 2.1(s, 3H), 2.4(s, 3H), 2.7(m, 1H), 3.0(m, 1H), 3.4(m, 1H), 4.1(m, 1H), 5.1(m, 3H), 6.8(d, 1H), 7.1(m, 3H), 7.5(m, 4H), 7.8(d, 1H), 7.9(d, 1H), 8.1(d, 1H), 8.5(s, 1H), 14.0(s, 1H).

Example 18.

5,6-dimethyl-2-(3-trifluoromethylphenylmethyl)amino-4-(1-methyl-1,2,3,4-tetrahydro isoquinolin-2-yl)pyrimidine hydrochloride

After 3-trifluoromethylbenzylamine(0.30 ml, 2.61 mmol) and triethyl amine(0.36 ml, 2.59 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 630mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 78.2 %

M.P. : 190 - 192 °C

^{1}H-NMR(CDCl3) : δ 1.5(d, 3H), 2.1(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 4.2(m, 1H), 4.6(d, 2H), 5.2(q, 1H), 7.1(m, 4H), 7.6(m, 4H),

8.6(s, 1H), 14.0(s, 1H).

Example 19.

5,6-dimethyl-2-(cyclopentylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After cyclopentylamine(0.26 ml, 2.61 mmol) and triethylamine(0.36 ml, 2.59 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 550mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 84.8 %

M.P. : 150 - 153°C

^{1}H-NMR(CDCl3) : δ 1.6(d, 6H), 1.7-2.0(m, 5H), 2.1(s, 3H), 2.4(s, 3H), 2.9(m, 1H), 3.1(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.2(m, 2H), 5.4(q, 1H), 7.2(m, 4H), 8.0(d, 1H), 13.6(s, 1H).

Example 20.

5,6-dimethyl-2-(cyclohexylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After cyclohexylamine(0.30 ml, 2.61 mmol) and triethylamine(0.36 ml, 2.59 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5 g, 1.74 mmol) in dimethylformamide, 550mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 81.7 %

M.P. : 140 - 144°C

^{1}H-NMR(CDCl3) : δ 1.4(m, 5H), 1.6(d, 3H), 2.0(m, 5H), 2.2(s, 3H), 2.4(s, 3H), 2.9(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 3.9(bs, 1H), 4.3(m, 1H), 5.4(q, 1H),

7.2(m, 4H), 7.8(d, 1H), 13.6(s, 1H).

Example 21.

5,6-dimethyl-2-(piperidin-1-yl)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After piperidine(0.26 ml, 2.61 mmol) and triethylamine(0.36 ml, 2.59 mmol) were added to a solution of 2-chloro-5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.74mmol) in dimethylformamide, 490mg of the titled compound was obtained in accordance with the same procedure as in Example 1.

Yield : 75.5 %

M.P. : 103 - 107°C

^{1}H-NMR(CDCl3) : δ 1.6(d, 3H), 1.7(s, 6H), 2.1(s, 3H), 2.7(s, 3H), 2.9(m, 1H), 3.2(m, 1H), 3.5(m, 1H), 4.0(s, 4H), 4.3(m, 1H), 5.4(q, 1H), 7.2(m, 4H), 13.2(s, 1H).

Example 22.

5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 2-guanyl-4-methylthiazole hydrochloride

After refluxing a solution of 2-aminothiourea(11.08 g, 93.77 mmol) in ethanol(85 ml), chloroacetone(8.2 ml, 103.15mmol) was added dropwise to the solution. The reaction mixture was stirred for 4 hours, and then stand for 1 day, while maintaining the temperature under 10℃. The resulting solid was filtered, washed with ethyl ether, and then dried under a reduced pressure to give 11.7g of the titled compound. (Yield : 64.7 %)

Step 2 : 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-hydroxypyrimidine

A mixture solution of ethyl 2-methylacetoacetate(0.7 ml, 5.19 mmol), sodium methoxide (0.56 g, 10.38 mmol), 2-guanyl-4-methylthiazole (1.0 g, 5.19 mmol), and methanol(13 ml) was refluxed and then stirred for 3 hours. The reaction mixture was cooled to a room temperature and then adjusted to pH 7 with hydrochloric acid. The resulting solid was filtered, washed with water and methanol, and then dried under a reduced pressure to give 0.98 g of the titled compound. (Yield : 32 %)

Step 3 : 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-chloropyrimidine

The mixture solution of 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-hydroxypyrimidine (1.15 g, 4.78 mmol), phosphorus oxychloride(7ml), and dimethylformamide(5ml) was heated to 70°C for 30 minutes, cooled to a room temperature and then poured into ice water. The aqueous layer was extracted with dichloromethane, washed with 1N sodium hydroxide solution, and then washed with water. The separated organic layer was concentrated and the residual oil was suspended in a mixture solution of ethyl ether and hexane. The resulting solid was filtered and dried to give 0.42 g of the titled compound. (Yield : 33.9 %)

Step 4 : 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

A soultion of 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-chloropyrimidine (0.41 g, 1.6 mmol), 1-methyl-1,2,3,4-tetrahydroisoquinoline(0.47 ml, 3.2 mmol) and dimethylformamide(2 ml) was heated to 120°C for 6 hours, diluted with dichloromethane, and then washed with water. The separated organic layer was dried over anhydrous magnesium sulfate and concentrated. The resulting residue was purified by silica gel column chromatography, using a solution of ethylacetate and hexane (1:2) as a eluent. After evaporating of the solvent, the residual oil was dissolved in a solution of ethyl ether and

ethyl acetate and treated with ethylether saturated with hydrochloric acid. The resulting solid was filtered and dried to give 0.5g of the titled compound.

Yield : 78 %

M.P. : 183 - 185°C

^{1}H-NMR(DMSO-d6) : δ 1.6(d, 3H), 2.2(s, 3H), 2.3(s, 3H), 2.4(s, 3H), 2.9(m, 1H), 3.2(m, 1H), 3.7(m, 1H), 4.4(m, 1H), 5.6(m, 1H), 6.7(s, 1H), 7.2(m, 4H), 7.4(m, 1H), 8.0(bs, 1H), 12.8(bs, 1H).

Example 23

5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Step 4 of Example 22 were repeated using 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-chloropyrimidine(0.85 g, 3.34 mmol), 1,2,3,4-tetrahydroisoquinoline(0.42 ml, 3.34 mmol) and dimethylformamide(5ml) to afford 140 mg of the titled compound.

Yield : 10.8%

M.P. : 257 - 262°C

^{1}H-NMR(DMSO-d6) : δ 2.2(s, 3H), 2.3(s, 3H), 2.4(s, 3H), 3.1(s, 2H), 4.0(s, 2H), 6.7(s, 1H), 5.6(m, 1H), 7.2(d, 4H).

Example 24.

5,6-dimethyl-2-(4-phenylthiazol-2-yl)amino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 2-guanyl-4-phenylthiazole hydrobromide

The same procedures as in Step 1 of Example 22 were repeated using 2-aminothiourea(20 g, 169.26 mmol), 2-bromoacetophenone(35.38 g, 1.05 eq.) and ethanol(170ml) to afford 49.9g of the titled compound. (Yield : 98.5 %)

Step 2 : 5,6-dimethyl-2-(4-phenylthiazol-2-yl)amino-4-hydroxypyrimidine

The same procedures as in Step 2 of Example 22 were repeated using 2-guanyl-4-phenylthiazole hydrobromide(30.5 g, 101.94 mmol) and ethyl 2-methylacetoacetate(14.4 ml, 101.94 mmol) to afford 5.6g of the titled compound. (Yield: 18.4 %)

Step 3 : 5,6-dimethyl-2-(4-phenylthiazol-2-yl)amino-4-chloropyrimidine

The same procedures as in Step 3 of Example 22 were repeated using 5,6-dimethyl-2-(4-phenylthiazol-2-yl)amino-4-hydroxypyrimidine (5.6 g, 18.77 mmol) and phosphorus oxychloride(7ml) to afford 3.0g of the titled compound. (Yield : 50 %)

Step 4 : 5,6-dimethyl-2-(4-phenylthiazol-2-yl)amino-4-(1,2,3,4-tetrahydroiso-quinolin-2-yl)pyrimidine hydrochloride

A mixture solution of 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-chloropyrimidine (0.36g, 1.14mmol), 1,2,3,4-tetrahydroisoquinoline(0.16ml, 1.25 mmol), triethylamine(0.16 ml, 1.25mmol) and propyleneglycol(1.1 ml) was heated to 140°C, stirred for 5 hours, diluted with dichloromethane, and then washed with water. The separated organic layer was dried over anhydrous magnesium sulfate and concentrated. The resulting residue was purified by a silica gel column chromatography using a soluton of ethyl acetate and hexane (1:3) as a eluent. After evaporating of the solvent, the residual oil was dissolved in a solution of ethyl ether and ethyl acetate and treated with ethylether saturated with hydrochloric acid. The resulting solid was filtered and dried to give 0.18g of the titled compound.

Yield : 35 %

M.P. : 283 - 285°C

^{1}H-NMR(DMSO-d6) : δ 2.2(s, 3H), 2.4(s, 3H), 3.1(t, 2H), 3.7(t, 2H), 4.7(s, 2H), 7.0(s, 1H), 7.3(m, 7H), 7.9(d, 2H).

Example 25.

6-methoxymethyl-5-methyl-2-(2-methylphenylamino)-4-(1,2,3,4-tetrahydroisoquinoli n-2-yl)pyrimidine hydrochloride

Step 1 : 6-methoxymethyl-5-methyl-2-chloro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

1,2,3,4-tetrahydroisoquinoline(0.9ml, 6.9mmol) was added dropwise to a solution of 2,4-dichloro-6-methoxymethyl-5-methylpyrimidine(1.3g, 6.3mmol) and triethylamine(0.96ml, 6.9mmol) in dimethylformamide and stirred for 5 hours at a room temperature. The reaction mixture was diluted with dichloromethane and washed with water and aqueous sodium hydroxide solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under a reduced pressure. The resulting residue was purified by a silica gel column chromatography to give 1.8g of the titled compound. (Yield : 94.0 %)

Step 2 : 6-methoxymethyl-5-methyl-2-(2-methylphenylamino)-4-(1,2,3,4-tetrahydro isoquinolin-2-yl)pyrimidine hydrochloride

o-Toluidine(0.48 ml, 4.5 mmol) and triethylamine were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine (0.9g, 3mmol) in dimethylformamide(5ml) and stirred for 5 hours at 130°C. The reaction mixture was cooled to a room temperature, diluted with dichloromethane, and washed with aqueous sodium hydroxide and water. The organic layer was dried over anhydrous magnesium sulfate, concentrated, and the residual oil was purified by column chromatography. The purified compound was dissolved in ethyl ether. Ethyl ether saturated with hydrochloric acid was added to a mixture solution. The resulting solid was filtered and dried to give 400mg of the titled compound.

Yield : 32.5 %

M.P. : 178 - 183°C

^{1}H-NMR(CDCl3) : δ 2.2(s, 3H), 2.4(s, 3H), 2.9(m, 2H), 3.6(s, 3H), 3.9(m, 2H), 4.5(s, 2H), 4.8(s, 2H), 7.0-7.1(m, 7H), 7.6(m, 1H), 10.2(s, 1H), 14.1(s, 1H).

Example 26.

6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.43 ml, 4.5 mmol) and triethylamine(0.63ml, 4.5mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.9g, 3mmol) in dimethylformamide(5ml), 190mg of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 15 %

M.P. : 226 - 237°C

^{1}H-NMR(CDCl3) : δ 2.2(s, 3H), 3.1(m, 2H), 3.6(s, 3H), 3.9(m, 2H), 4.5(s, 2H), 4.8(s, 2H), 7.0-7.3(m, 6H), 7.6(m, 2H), 11.2(s, 1H), 13.5(s, 1H).

Example 27.

6-methoxymethyl-5-methyl-2-(4-fluoro-2-methylphenylamino)-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 2-methyl-4-fluoroaniline(0.51 g, 4.5 mmol) and triethylamine (0.63ml, 4.5mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.9g, 3mmol) in dimethylformamide(5ml), 750mg of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 60 %

M.P. : 157 - 159°C

^{1}H-NMR(CDCl3) : δ 2.2(s, 3H), 2.4(s, 3H), 2.9(m, 2H), 3.6(s, 3H), 3.8(m, 2H), 4.5(s, 2H), 4.8(s, 2H), 6.8-7.3(m, 6H), 7.5(m, 1H), 10.2(s, 1H), 14.0(s, 1H).

Example 28.

6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

The same procedures as in Step 1 of Example 25 were repeated using 2,4-dichloro-6-methoxymethyl-5-methylpyrimidine(1.3g, 6.3mmol) and 1-methyl-1,2,3,4-tetrahydroisoquinoline(1.02g, 6.93mmol) to afford 1.2g of the titled compound. (Yield : 60 %)

Step 2 : 6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.43 ml, 4.5 mmol) and triethylamine(0.63ml, 4.5mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine (0.96 g, 3 mmol) in dimethylformamide(5ml), 600mg of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 47 %

M.P. : 228 - 233°C

^{1}H-NMR(CDCl3) : δ 1.6(d 3H), 2.2(s, 3H), 2.9(d, 1H), 3.1(m, 1H), 3.5-3.7(s+m, 4H), 4.3(bd, 2H), 4.5(dd, 2H), 5.4(q, 1H), 6.9-7.3(m, 6H), 7.6(m, 2H), 11.2(s, 1H), 13.3(bs, 1H).

Example 29.

6-methoxymethyl-5-methyl-2-(2-methyl-4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 2-methyl-4-fluoroaniline(0.62 ml, 4.5 mmol) and triethylamine (0.63ml, 4.5mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.96 g, 3 mmol) in dimethylformamide(5ml), 600mg of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 47 %

M.P. : 175 - 177°C

^{1}H-NMR(CDCl3) : δ 1.5(d 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(d, 1H), 3.1(m, 1H), 3.4-3.7(s+m, 4H), 4.3(m, 1H), 4.5(s, 2H), 5.4(qq, 1H), 6.8-7.6(m, 7H), 10.0(ss, 1H), 13.9(ss, 1H).

Example 30.

6-methoxymethyl-5-methyl-2-(2-methylphenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After o-toluidine(0.32 ml, 3.0 mmol) and triethylamine(0.63ml, 4.5mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.96 g, 3 mmol) in dimethylformamide(5ml), 250mg of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 20 %

M.P. : 247 - 250°C

^{1}H-NMR(CDCl3) : δ 1.5(d 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(d, 1H), 3.1(m, 1H), 3.5-3.7(s+m, 4H), 4.3(bd, 1H), 4.5(s, 2H), 5.3(q, 1H), 7.0-7.3(m, 7H), 7.6(d, 1H), 10.2(s, 1H), 13.9(bs, 1H).

Example 31.

6-methoxymethyl-5-methyl-2-phenylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After aniline (2.41ml, 26.4mmol) and triethylamine(3.68ml, 26.4mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(7g, 22mmol) in dimethylformamide (20ml), 4.1g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 45 %

M.P. : 208 - 212°C

^{1}H-NMR(CDCl3) : δ 1.6(d, 3H), 2.2(s, 3H), 2.8(d, 1H), 3.1-3.3(m, 1H), 3.4-3.7(s+m, 4H), 4.35(bd, 1H), 4.50(dd, 2H), 5.45(q, 1H), 6.80-7.50(m, 7H), 7.65(d, 2H), 11.10(s, 1H), 13.50(bs, 1H).

Example 32.

6-hydroxymethyl-5-methyl-2-phenylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

A solution of 6-methoxymethyl-5-methyl-2-phenylamino-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(4.0g, 9.7mmol) in dichloromethane (50ml) was cooled under 0°C. Boron tribromide (1M-dichloromethane solution, 38.8ml, 38.8mmol) was added dropwise to the solution. The reaction mixture was stirred for 30 minutes at 0°C and poured into ice water. The separated dichloromethane layer was washed with aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, concentrated under a reduced pressure. Ethyl ether was added to the resulting residue to give a solid, which was then dissolved in ethanol and treated with ethyl ether saturated with hydrochloric acid to give 2.3g of the titled compound.

Yield : 59.5 %

M.P. : 193 - 198°C

^{1}H-NMR(DMSO-d6) : δ 1.6(d 3H), 2.2(s, 3H), 2.9(d, 1H), 3.1(m, 1H), 3.0-3.2(m, 1H), 4.3(bd, 1H), 4.6(q, 2H), 5.5(q, 1H), 7.0-7.4(m, 5H), 7.4(t, 2H), 7.6(d, 2H).

Example 33.

6-hydroxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydrois oquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydrois oquinolin-2-yl)pyrimidine(0.25 g, 0.58 mmol) and borone tribromide(1M-dichloro methane solution, 2.5 ml, 2.5 mmol) to afford 0.1g of the titled compound.

Yield : 29 %

M.P. : 223 - 226°C

^{1}H-NMR(DMSO-d6) : δ 1.6(d, 3H), 2.2(s, 3H), 2.9(d, 1H), 3.0-3.2(m, 1H), 3.6-3.8(t, 1H), 4.3(bd, 1H), 4.7(q, 2H), 5.5(q, 1H), 7.0-7.4(m, 6H), 7.5-7.7(m, 2H).

Example 34.

6-hydroxymethyl-5-methyl-2-(2-methylphenylamino)-4-(1-methyl-1,2,3,4-tetrahydroi soquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 6-methoxymethyl-5-methyl-2-(2-methylphenylamino)-4-(1-methyl-1,2,3,4-tetrahydroi soquinolin-2-yl)pyrimidine(9.7 g, 22.1 mmol) and borone tribromide(1M-dichloromethane solution, 88.4 ml, 88.4 mmol) to afford 4.7g of the titled compound.

Yield : 54.7 %

M.P. : 225 - 227°C

^{1}H-NMR(DMSO-d6) : δ 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.8(bd, 1H), 3.0(m, 1H), 3.5(m, 1H), 4.2(m, 1H), 4.6(q, 2H), 5.3(q, 1H), 7.1(s, 5H), 7.3(d, 2H), 7.7(d, 1H), 10.0(s, 1H), 12.3(s, 1H).

Example 35.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 5,6-dimethyl-2-chloro-4-(6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After 1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline(1.3g, 7.3mmol) and triethylamine(1.0ml, 7.3mmol) were added to a suspension of 5,6-dimethyl-2,4-dichloropyrimidine(1.2g, 6.64mmol) in dimethylformamide, the reaction mixture was stirred for 3 hours at 85 ℃. The reaction mixture was cooled to a room temperature and diluted with ethyl acetate. The organic layer was washed with water and aqueous sodium hydroxide, dried over anhydrous magnesium sulfate, concentrated under a reduced pressure, and then purified by a silica gel column chromatography to give 1.7g of the titled compound. (Yield : 78.5 %)

Step 2 : 5,6-dimethyl-2-(4-fluorophenylamino)-4-(6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.72 ml, 7.5 mmol) and triethylamine(1.0ml, 7.3mmol) were added to a solution of 5,6-dimethyl-2-chloro-4-(6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(1.6g, 5.0mmol) in dimethylformamide(10ml), 1.26g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 60 %

M.P. : 190 - 192°C

^{1}H-NMR(DMSO-d6) : δ 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.6(s, 3H), 2.9(bd, 1H), 3.1(m, 1H), 3.6(m, 1H), 4.2(dd, 1H), 5.4(q, 1H), 7.2-7.3(m, 6H), 7.5-7.7(dd, 2H), 10.2(s, 1H), 12.9(s, 1H).

Example 36.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride(1.2 g, 2.8 mmol) and borone tribromide (1M-dichloromethane solution, 11.2ml, 11.2mmol) to afford 179mg of the titled compound.

Yield : 15.4 %

M.P. : 147 - 150°C

^{1}H-NMR(CDCl3) : δ 1.5(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.0(m,1H), 3.5(m, 1H), 4.2(m, 1H), 5.2(q, 1H), 6.8(m, 5H), 7.4(m, 2H), 10.0(s, 1H), 13.8(s, 1H).

Example 37.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 5,6-dimethyl-2-chloro-4-(7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After 1-methyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline (0.9g, 5.1mmol) and triethylamine(0.7ml, 5.1mmol) were added to a suspension of 5,6-dimethyl-2,4-dichloropyrimidine(0.8g, 4.64mmol) in dimethylformamide, 1.0g of the titled compound was obtained in accordance with the same procedure as in Step 1

of Example 35. (Yield : 70.3 %)

Step 2 : 5,6-dimethyl-2-(4-fluorophenylamino)-4-(7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.32 ml, 3.3mmol) and triethylamine(0.46ml, 3.3mmol) were added to a solution of 5,6-dimethyl-2-chloro-4-(7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.7g, 2.2 mmol) in dimethylformamide(5ml), 0.55g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 58.6 %

M.P. : 122 - 125°C

^{1}H-NMR(CDCl3) : δ 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.1(m,1H), 3.5(m, 1H), 3.8(s, 3H), 4.2(m, 1H), 5.4(q, 1H), 6.6(s, 1H), 6.8(d, 1H), 7.0(m, 3H), 7.5(m, 2H), 10.2(s, 1H), 14.0(s, 1H).

Example 38.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(7-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride(0.55g, 1.3mmol) and borone tribromide (1M-dichloromethane solution, 5.2ml, 5.2mmol) to afford 166mg of the titled compound.

Yield : 30.8 %

M.P. : 157 - 160°C

^{1}H-NMR(DMSO-d6) : δ 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.0(m,1H), 3.5(m, 1H), 4.2(m, 1H), 5.4(q, 1H), 6.6(s, 1H), 6.7(d, 1H), 7.0(d, 1H), 7.1(t, 2H), 7.5(m, 2H), 9.0(s, 1H), 10.2(s, 1H), 14.0(s, 1H).

Example 39.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 5,6-dimethyl-2-chloro-4-(5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After 1-methyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline(0.9g, 5.1mmol) and triethylamine(0.7ml, 5.1mmol) were added to a suspension of 5,6-dimethyl-2,4-dichloropyrimidine(0.8g, 4.64mmol) in dimethylformamide, 1.0g of the titled compound was obtained in accordance with the same procedure as in Step 1 of Example 35. (Yield : 70.3 %)

Step 2 : 5,6-dimethyl-2-(4-fluorophenylamino)-4-(5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.32 ml, 3.3mmol) and triethylamine(0.46ml, 3.3mmol) were added to a solution of 5,6-dimethyl-2-chloro-4-(5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.7g, 2.2 mmol) in dimethylformamide(5ml), 0.55g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 58.6 %

M.P. : 122 - 125°C

^{1}H-NMR(CDCl3) : δ 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.1(m,1H), 3.5(m, 1H), 3.8(s, 3H), 4.2(m, 1H), 5.4(q, 1H), 6.6(s, 1H), 6.8(d, 1H), 7.0(m, 3H), 7.5(m, 2H), 10.2(s, 1H), 14.0(s, 1H).

Example 40.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-5-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(5-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride(0.55g, 1.3mmol) and borone tribromide (1M-dichloromethane solution, 5.2ml, 5.2mmol) to afford 166mg of the titled compound.

Yield : 30.8 %

M.P. : 157 - 160°C

^{1}H-NMR(DMSO-d6) : δ 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.0(m,1H), 3.5(m, 1H), 4.2(m, 1H), 5.4(q, 1H), 6.6(s, 1H), 6.7(d, 1H), 7.0(d, 1H), 7.1(t, 2H), 7.5(m, 2H), 9.0(s, 1H), 10.2(s, 1H), 14.0(s, 1H).

Example 41.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 5,6-dimethyl-2-chloro-4-(1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline(1.6g, 4.98 mmol) and triethylamine(0.7ml, 4.98mmol) were added to a suspension of 5,6-dimethyl-2,4-dichloropyrimidine(0.8g, 4.53mmol) in dimethylformamide, 1.1g of the titled compound was obtained in accordance with the same procedure as in Step 1 of Example 35. (Yield : 76 %)

Step 2 : 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

4-fluoroaniline(0.46ml, 4.70mmol) and triethylamine(0.66ml, 4.70mmol) were added to a solution of 5,6-dimethyl-2-chloro-4-(1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(1.0g, 3.13mmol) in dimethylform-

amide(5ml) and then stirred for 3 hours at 120°C. The reaction mixture was cooled to a room temperature and diluted with dichloromethane. Aqueous sodium hydroxide solution was added to the reaction mixture, which was then stirred. The dichloromethane layer was dried over anhydrous magnesium sulfate, concentrated under a reduced pressure. The resulting residue was purified by a silica gel column chromatography and dissolved in ethanol. Ethyl ether saturated with hydrochloric acid was added to the solution. The resulting solid was filtered and dried to give 530mg of the titled compound.

Yield : 39.3 %

M.P. : 198 - 201°C

^{1}H-NMR(DMSO-d6) : δ 1.1(d, 2H), 1.3(d, 1H), 2.0(d, 3H), 2.4(s, 3H), 3.8(d, 1H), 4.0(m, 1H), 4.2(d, 2H), 5.2(q, 1H), 7.3(t, 3H), 7.6(q, 3H), 10.5(s, 1H).

Example 42.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 5,6-dimethyl-2-chloro-4-(5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After 5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline(1.0g, 4.82 mmol) and triethylamine (0.67ml, 4.82mmol) were added to a suspension of 5,6-dimethyl-2,4-dichloropyrimidine(0.71g, 4.02mmol) in dimethylformamide, 1.02g of the titled compound was obtained in accordance with the same procedure as in Step 1 of Example 35. (Yield : 72.8 %)

Step 2 : 5,6-dimethyl-2-(4-fluorophenylamino)-4-(5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.40 ml, 4.13mmol) and triethylamine(0.58ml, 4.13mmol) were added to a solution of 5,6-dimethyl-2-chloro-4-(5,8-dimethoxy-

1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine (1.0g, 2.87 mmol) in dimethylformamide(5ml), 0.67g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25. (Yield : 51.2 %)

M.P. : 251 - 253°C

NMR($CDCl_3$) : 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.8(m, 2H), 3.5(m, 2H), 3.8(d, 6H), 4.0(m, 1H), 5.2(q, 1H), 6.6(s, 2H), 7.0(t, 2H), 7.5(q, 2H)

Example 43.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(5,8-dihydroxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(5,8-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride(0.6g, 1.3mmol) and borone tribromide(1M-dichloromethane solution, 5.2ml, 5.2mmol) to afford 124mg of the titled compound.

Yield : 48.1 %

M.P. : 275 - 278°C

^{1}H-NMR(DMSO-d6+TFA) : δ 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 2H), 3.6(m, 1H), 4.3(d, 1H), 5.6(s, 1H), 6.6(s, 2H), 7.2(t, 2H), 7.7(q, 2H).

Example 44.

6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

Step 1 : 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

After 1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline(1.2g, 6.8mmol)

and triethylamine(0.96ml, 6.9mmol) were added to a suspension of 2,4-dichloro-6-methoxymethyl-5-methylpyrimidine(1.3g, 6.3mmol) in dimethylformamide, 2.0g of the titled compound was obtained in accordance with the same procedure as in Step 1 of Example 35. (Yield : 73.6 %)

Step 2 : 6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

After 4-fluoroaniline(0.32 ml, 3.3mmol) and triethylamine(0.46ml, 3.3mmol) were added to a solution of 6-methoxymethyl-5-methyl-2-chloro-4-(1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine (1.0g, 2.3 mmol) in dimethylformamide(5ml), 0.56g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25.

Yield : 53.4 %
^{1}H-NMR(CDCl3) : 1.5(d, 3H), 2.2(s, 1H), 2.7(m, 1H), 3.1(m, 1H), 3.5(s, 3H), 3.8(s, 3H), 4.0(m, 1H), 4.4(s, 2H), 5.1(q, 1H), 6.6(m, 1H), 6.8(m, 1H), 6.9(m, 3H), 7.5(m, 2H).

Example 45.
6-hydroxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride

The same procedures as in Example 32 were repeated using 6-methoxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine hydrochloride(0.5g, 1.1mmol) and boron tribromide(1M-dichloromethane solution, 4.4ml, 4.42mmol) to afford 210mg of the titled compound.

Yield : 44.5 %
M.P. : 181 - 184°C
^{1}H-NMR(DMSO-d6) : δ 1.5(d, 3H), 2.1(s, 3H), 2.6(d, 1H), 2.8-3.1(m, 1H),

3.0(m,1H), 3.5(m, 1H), 3.9(m, 1H), 4.4(d, 2H), 4.9-5.1(m, 2H), 6.6(m, 2H), 6.8-7.1(m, 3H), 7.6-7.9(m, 2H), 9.2(s, 2H).

Example 46.

5-hydroxymethyl-6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluorophenylamino)-pyrimidine

Step 1 : 6-methyl-4-hydroxy-2-(4-fluorophenylamino)pyrimidine

A mixture solution of ethyl acetoacetate(3.8ml, 30.3mmol), 4-fluorophenylguanidine carbonate(5g, 26.3mmol), and dimethylformamide(5ml) was refluxed for 2 hours and cooled to a room temperature. Ethyl ether was added to the reaction mixture and the resulting solid was filtered, washed with ethyl ether, and concentrated under a reduced pressure to give 1.74g of the titled compound. (Yield 30%)

Step 2 : 6-methyl-4-chloro-2-(4-fluorophenylamino)pyrimidine

A reaction mixture of 6-methyl-4-hydroxy-2-(4-fluorophenylamino)-pyrimidine (1.74g, 7.93mmol) and phosphorus oxychloride was stirred for 1 hour at a room temperature and then dissolved in dichloromethane. Water was added dropwise to the reaction mixture and stirred for 30 minutes. The separated organic layer was washed with 2N NaOH solution, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure to give 1.57g of the titled compound. (Yield 83.5%)

NMR (CDCl3): 2.4(s, 3H), 6.6(s, 1H), 7.0(m, 3H), 7.6(m, 2H)

Step 3 : 6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin)-2-(4-fluorophenyl-amino)pyrimidine

A reaction mixture of 6-methyl-4-chloro-2-(4-fluorophenylamino)

pyrimidine(1.4g, 5.89mmol), 1-methyl-1,2,3,4-tetrahydroisoquinolin(1.12g, 7.66 mmol), triethylamine(1.06ml, 7.66mmol), and propylene glycol(19ml) was stirred for 2 hours at 120℃, cooled to a room temperature, diluted with dichloromethane, and washed with water. The separated organic layer was dried over anhydrous sodium sulfate, concentrated under a reduced pressure and the residual oil was purified by a silica gel column chromatography (ethylacetate / n-hexane = 1/1) to give 1.98g of the titled compound. (Yield 96.4%)

NMR (CDCl3): 1.5(d, 3H), 2.3(s, 3H), 2.9(m, 2H), 3.5(m, 1H), 4.2(m, 1H), 5.4(br, 1H), 6.0(s, 1H), 6.8(s, 1H), 7.0(m, 2H), 7.2(m, 4H), 7.5(m, 2H)

Step 4 : 5-hydroxymethyl-6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluorophenylamino)pyrimidine

A mixture solution of 6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin)-2-(4-fluorophenylamino)pyrimidine(1.3g, 3.73mmol), formaline(37%, 30ml) and p-formaldehyde (20g) was stirred for 1 day at 80℃, extracted with dichloromethane, and then washed with aqueous 1N-NaOH solution and water. The separated organic layer was concentrated under a reduced pressure and the residual oil was purified by a silica gel column chromatography (ethylacetate / n-hexane = 1/1) to give 0.17g of the titled compound. (Yield 12%)

NMR (CDCl3): 1.6(d, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.2(m, 1H), 4.6(q, 2H), 5.4(q, 1H), 6.9(m, 2H), 7.2(m, 4H), 7.5(m, 2H)

Example 47.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methoxymethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine

Step 1 : 5,6-dimethyl-2-chloro-4-(1-methoxymethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine

After 1-methoxymethyl-1,2,3,4-tetrahydroisoquinolin(0.5g, 2.82mmol) and triethylamine(0.4ml, 2.82mmol) were added to a suspension of 5,6-dimethyl-2,4-dichloropyrimidine(0.48g, 2.68mmol) in dimethylformamide (5ml), 0.5g of the titled compound was obtained in accordance with the same procedure as in Step 1 of Example 35.

Step 2 : 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methoxymethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine

After 4-fluoroaniline(0.15ml, 1.57mmol) and triethylamine(0.21ml, 1.53mmol) were added to a solution of 5,6-dimethyl-2-chloro-4-(1-methoxymethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.5g, 1.57mmol) in dimethylformamide(5ml), 0.4g of the titled compound was obtained in accordance with the same procedure as in Step 2 of Example 25(Yield : 63.7%).

M.P. : 193 - 195°C

NMR (DMSO-d6): 2.2(s, 3H), 2.3(s, 3H), 2.8-3.2(m, 2H), 3.4(s, 3H), 3.6-4.0(m, 3H), 4.3(bd, 1H), 5.5(bs, 1H), 7.0-7.5(m, 6H), 7.5-7.8(m, 2H), 9.6(s, 1H)

Example 48.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-hydroxymethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine

The same procedures as in Example 32 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methoxymethyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-pyrimidine(0.4g, 1.0mmol) and boron tribromide(1M-dichloromethane solution, 4.0ml, 4.0mmol) to afford 150mg of the titled compound.

Yield : 36 %

M.P. : 198 - 200°C

^{1}H-NMR(DMSO-d6) : δ 2.2(s, 3H), 2.4(s, 3H), 2.8-3.2(m, 2H), 3.6-4.0(m,

3H), 4.3(bd, 1H), 5.5(bs, 1H), 7.0-7.4(m, 6H), 7.4-7.7(m, 2H), 10.4(s, 1H).

Example 49.

5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluoro-2-hydroxyphenylamino)pyrimidine

Step 1 : 4-fluoro-2-methoxynitrobenzene

Potassium carbonate(14.5g, 105.1mol) and iodomethane(7.1ml, 114.6 mmol) were added to a solution of 2-nitro-5-fluorophenol(15g, 95.5mmol) in ethanol (100 ml), which was then refluxed for 12 hours. The resulting solid was filtered, washed with ethanol, and concentrated. The resulting oily residue was diluted with ethyl acetate and washed with water. The separated organic layer was concentrated and the residual oil was purified by column chromatography(ethylacetate / hexane = 1/3) to give 1.65g of the titled compound. (Yield 9.7%).

NMR ($CDCl_3$): 4.0 (s, 3H), 6.8 (m, 2H), 8.0 (m, 1H).

Step 2 : 4-fluoro-2-methoxy-aniline

Paladium/carbon(Pd/C, 5%, 0.5 g) was added to a solution of 4-fluoro-2-methoxynitrobenzene (1.65g, 9.6mmol) in ethanol, which was then stirred for 1 hour under 30psi of hydrogen pressure. The reaction mixture was filtered to remove paladium/carbon, and concentrated to give 1.35g of the titled compound. (Yield 100 %)

NMR ($CDCl_3$): 3.8 (s, 3H), 6.5 (m, 3H).

Step 3 : 5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluoro-2-methoxyphenylamino)pyrimidine

A reaction mixture of 4-fluoro-2-methoxy-aniline(0.155g, 1.10 mmol), 5,6-dimethyl-2-chloro-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(0.241g, 0.84mmol), triethylamine(0.15ml, 1.1mmol) and propyleneglycol (2ml) was heated to 140℃ for 5 hours, cooled to a room temperature, diluted with dichloromethane(10ml), and then washed with water. The separated organic layer was concentrated and the residual oil was purified by column chromatography(ethylacetate / N-hexane = 1/1) to give 0.247g of the titled compound. (Yield 75.2%)

NMR ($CDCl_3$): 1.5 (d, 3H), 2.2 (s, 3H), 2.4 (s, 3H), 2.8 (m, 1H), 3.2 (m, 1H), 3.5 (m, 1H), 3.8 (s, 3H), 4.0 (m, 1H), 5.0 (q, 1H), 6.6 (m, 6H), 7.0 (d, 1H).

Step 4 : 5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluoro-2-hydroxyphenylamino)pyrimidine

Boron tribromide (1M dichloromethane solution, 1.9ml, 1.9mmol) was added dropwise to a solution of 5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluoro-2-methoxyphenylamino)pyrimidine(0.247g, 0.63mmol) in dichloromethane(2ml) at 0°C, stirred for 1 hour, and poured into ice water. The separated organic layer was concentrated and the residual oil was purified by column chromatography (dichloromethane / methanol = 10/1) to give 57mg of the titled compound. (Yield 24%)

NMR ($CDCl_3$): 1.5 (d, 3H), 2.2 (s, 3H), 2.3 (s, 3H), 2.7 (m, 1H), 3.1 (m, 1H), 3.5 (m, 1H), 3.9 (m, 1H), 5.0 (q, 1H), 6.6 (m, 6H), 7.0 (d, 1H).

Example 50.

5-methyl-6-acetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

Acetyl chloride (2.71 μl, 39.6 μmol) and triethylamine(20 μl, 142.6 μ

mol) were added to a suspension of 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine (10mg, 26.4 μmol) in dichloromethane(1ml) and stirred for 1 day at a room temperature. The reaction mixture was purified with a silica gel column chromatography (ethylacetate / n-hexane = 1/ 1) to give 12mg of the titled compound.

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 6H), 2.8(m, 1H), 3.2(m, 1H), 4.0(m, 1H), 5.0(s, 2H), 5.2(q, 1H), 6.9(m, 3H), 7.2(m, 4H), 7.5(m, 2H)

Example 51-74

The same procedures as in Example 50 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(10mg, 26.4 μmol), correspondent acylchloride(39.6 μmol) and triethylamine(20 μl, 142.6 μmol) to give the following titled compound.

Example 51.

5-methyl-6-ethylcarbonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.2(t, 3H), 1.5(d, 3H), 2.2(s, 3H), 2.4(q, 2H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.0(s, 2H), 5.1(q, 1H), 6.8(s, 1H), 6.9(t, 2H), 7.2(m, 4H), 7.5(m, 2H)

Example 52.

5-methyl-6-isopropylcarbonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.1(d, 6H), 1.6(d, 3H), 2.2(s, 3H), 2.7(m, 2H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.1(m, 2H), 7.0(m, 3H), 7.2(m, 4H), 7.5(m, 2H)

Example 53.

5-methyl-6-butylcarbonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 0.9(t, 3H), 1.4(m, 3H), 1.6(m, 4H), 2.2(s, 3H), 2.4(t, 2H), 2.8(m, 1H), 3.2(m, 2H), 3.6(m, 1H), 4.0(m, 1H), 5.1(m, 3H), 6.9(m, 3H), 7.2(m, 4H), 7.5(m, 2H)

Example 54.

5-methyl-6-cyclopropylcarbonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 0.9(m, 2H), 1.1(m, 2H), 1.5(d, 3H), 1.7(m, 1H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.0(s, 3H), 5.1(q, 1H), 6.8(s, 1H), 6.9(t, 2H), 7.2(m, 4H), 7.5(m, 2H)

Example 55.

5-methyl-6-cyclobutylcarbonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(m, 3H), 2.2(s, 3H), 2.3(m, 3H), 2.8(m, 1H), 3.2(m, 2H), 3.5(m, 1H), 3.9(m, 1H), 5.0(s, 2H), 5.1(q, 1H), 6.8(s, 1H), 6.9(t, 2H), 7.1(m, 4H), 7.5(m, 2H)

Example 56.

5-methyl-6-cyclohexylcarbonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.3(m, 2H), 1.4(m, 2H), 1.5(d, 3H), 1.6(m, 2H), 1.9(m, 2H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.0(m, 2H), 5.1(q, 1H), 6.8(s, 1H), 6.9(m, 2H), 7.1(m, 4H), 7.5(m, 2H)

Example 57.

5-methyl-6-{(2-ethoxycarbonylethyl)carbonyloxymethyl}-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.2(t, 3H), 1.5(d, 3H), 2.2(s, 3H), 2.7(m, 5H), 3.2(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 4.2(q, 2H), 5.1(m, 3H), 7.0(m, 3H), 7.2(m, 4H), 7.5(m, 2H)

Example 58.

5-methyl-6-benzoyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 5.3(s, 2H), 6.8(t, 2H), 7.1(m, 4H), 7.5(m, 6H), 8.2(d, 2H)

Example 59.

5-methyl-6-(4-methylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.5(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 5.3(s, 2H), 6.8(t, 2H), 7.2(m, 5H), 7.5(m, 2H), 8.0(m, 3H)

Example 60.

5-methyl-6-(4-propylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.0(m, 3H), 1.6(d, 3H), 1.7(m, 2H), 2.2(s, 3H), 2.7(m, 2H), 2.8(m, 1H), 3.2(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 5.3(s, 2H), 6.8(t, 2H), 7.2(m, 6H), 7.5(m, 2H), 8.0(m, 3H)

Example 61.

5-methyl-6-(4-pentylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 0.9(m, 5H), 1.3(m, 4H), 1.6(d, 3H), 2.2(s, 3H), 2.6(m, 3H), 3.2(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 5.3(s, 2H), 6.8(t, 2H), 7.2(m, 6H), 7.5(m, 2H), 8.0(m, 3H)

Example 62.

5-methyl-6-(3-fluorobenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 5.3(s, 2H), 6.8(t, 2H), 7.2(m, 6H), 7.5(m, 2H), 7.9(m, 2H)

Example 63.

5-methyl-6-(3-trifluoromethylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 5.4(s, 2H), 6.8(m, 3H), 7.2(m, 4H), 7.5(m, 2H), 7.6(t, 1H), 7.8(d, 1H), 8.4(m, 2H)

Example 64.

5-methyl-6-(2,3-difluorobenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.1(q, 1H), 5.3(s, 2H), 6.8(s, 3H), 7.1(m, 5H), 7.4(m, 3H), 7.8(m. 1H)

Example 65.

5-methyl-6-(2-chlorobenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR(CDCl3): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.1(q, 1H), 5.3(s, 2H), 6.8(m, 3H), 7.2(m, 5H), 7.6(m, 4H), 7.9(d, 1H)

Example 66.

5-methyl-6-(3-methoxyphenyl)acetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.6(m, 1H), 3.7(s, 2H), 3.8(s, 3H), 3.9(m, 1H), 5.1(m, 3H), 6.8(m, 7H), 7.2(m, 4H), 7.5(m, 2H)

Example 67.

5-methyl-6-(4-methoxyphenyl)acetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.5(m, 1H), 3.6(s, 2H), 3.7(s, 3H), 3.9(m, 1H), 5.1(m, 3H), 5.3(s, 2H), 6.8(s, 1H), 6.9(m, 4H), 7.2(m, 6H), 7.5(m, 2H)

Example 68.

5-methyl-6-(4-nitrobenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.1(q, 1H), 5.3(s, 2H), 6.9(m, 3H), 7.2(m, 4H), 7.5(m, 2H), 8.3(s, 4H)

Example 69.

5-methyl-6-(3-cyanobenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.1(q, 1H), 5.3(s, 2H), 6.8(m, 3H), 7.1(m, 4H), 7.4(m, 2H), 7.6(t, 2H), 7.9(d, 1H), 8.4(m, 2H)

Example 70.

5-methyl-6-(1-naphthoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.1(q, 1H), 5.4(s, 2H), 6.8(m, 3H), 7.1(m, 4H), 7.5(m, 5H), 7.9(d, 1H), 8.0(d, 1H), 8.3(d, 1H), 9.0(d, 1H)

Example 71.

5-methyl-6-benzyloxyacetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 4.2(s, 2H), 4.6(s, 2H), 5.1(m, 3H), 6.8(s, 1H), 7.0(t, 2H), 7.2(m, 4H), 7.4(m, 7H)

Example 72.

5-methyl-6-cinnamoyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.2(m, 3H), 6.6(d, 1H), 6.9(m, 3H), 7.1(m, 4H), 7.5(m, 7H), 7.8(d, 1H)

Example 73.

5-methyl-6-crotonyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 1.9(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 2H), 3.5(m, 1H), 4.0(m, 1H), 5.1(m, 3H), 6.0(m, 1H), 6.9(m, 3H), 7.1(m, 4H), 7.5(m, 2H)

Example 74.

5-methyl-6-(thiophen-2-yl-acetoxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 3H), 5.1(m, 3H), 6.7(s, 1H), 7.0(m, 4H), 7.2(m, 5H), 7.5(m, 2H)

Example 75-113

The same procedures as in Example 50 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(10mg, 26.4 μmol), correspondent acylchloride(39.6 μmol) and triethylamine(20 μl, 142.6 μmol) to give the following titled compound.

Example 75.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.4(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H)

Example 76.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-ethylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.2(t, 3H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.6(q, 2H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 77.
5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-isopropylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine.

NMR($CDCl_3$): 1.3(d, 6H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.8(m, 2H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H)

Example 78.
5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-butylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 0.9(m, 3H), 1.5(m, 5H), 1.7(m, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.5(t, 2H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H)

Example 79.
5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-cyclopropylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$):1.0(m, 2H), 1.1(m, 2H), 1.5(d, 3H), 1.8(m, 1H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 80.
5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-cyclobutylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 20.(m, 4H), 2.1(s, 3H), 2.3(s, 5H), 2.7(m, 1H),

3.1(m, 1H), 3.5(m, 2H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 81.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-cyclohexylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.2(m, 9H), 1.5(d, 3H), 1.6(m, 1H), 2.1(s, 3H), 2.3(s, 3H), 2.5(m, 1H). 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 82.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2-ethoxycarbonylethyl)carbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine.

NMR($CDCl_3$): 1.3(t, 3H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 2.9(m, 2H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.1(q, 2H), 5.1(q, 1H), 7.0(m, 5H), 7.1(m, 1H), 7.5(m, 2H)

Example 83.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-benzoyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.6(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.0(m, 1H), 5.2(q, 1H), 7.0(m, 4H), 7.2(m, 1H), 7.5(m, 5H), 8.0(s, 1H), 8.2(d, 2H)

Example 84.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-methylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.4(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 8H), 7.5(m, 2H), 8.1(d, 2H)

Example 85.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-ethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.3(t, 3H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 7H), 7.3(m, 1H), 7.5(m, 2H), 8.1(d, 2H)

Example 86.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-propylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.0(t, 3H), 1.5(d, 3H), 1.8(m, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.3 (m, 1H), 7.5(m, 3H), 8.1(d, 2H)

Example 87.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-t-butylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.3(s, 9H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 4H), 8.1(m, 2H)

Example 88.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-pentylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 0.9(m, 5H), 1.3(m, 4H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.3(m, 2H), 7.5(m, 2H), 8.1(m, 2H)

Example 89.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 5H), 8.1(d, 1H)

Example 90.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 5H), 7.1(m, 1H), 7.5(m, 4H), 8.1(d, 2H)

Example 91.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 4H), 8.1(m, 2H)

Example 92.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4-dichloro-5-fluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H), 7.6(d, 2H), 7.8(d, 2H)

Example 93.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4,6-trichlorobenzoyloxy)-1,2

,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 7H), 7.5(m, 3H)

Example 94.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-fluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 5H), 7.2(m, 1H), 7.3(m, 1H), 7.5(m, 3H), 8.0(m, 2H)

Example 95.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine.

NMR ($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 7H), 7.6(m, 3H), 7.9(m, 1H)

Example 96.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,6-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 8H), 7.5(m, 3H)

Example 97.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H),

3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 8H), 7.5(m, 2H), 8.1(m, 1H)

Example 98.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3,4-trifluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 7H), 7.5(m, 2H), 7.9(m, 1H)

Example 99.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3,6-trifluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 7H), 7.5(m, 3H)

Example 100.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4,5-trifluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 7H), 7.5(m, 2H), 8.0(m, 1H)

Example 101.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-trifluoromethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H), 7.6(m, 1H), 7.9(m, 1H), 8.4(m, 2H)

Example 102.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-trifluoromethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.3(m, 2H), 7.5(m, 2H), 8.2(m, 2H)

Example 103.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3,4,5-tetrafluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H), 7.7(m, 1H)

Example 104.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 6H), 5.1(q, 1H), 7.0(m, 9H), 7.3(m, 1H), 7.5(m, 2H)

Example 105.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine.

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 6H), 5.1(q, 1H), 7.0(m, 9H), 7.3(m, 1H), 7.5(m, 2H)

Example 106.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-butoxybenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.0(m, 3H), 1.2(m, 2H), 1.5(d, 3H), 1.7(m, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.1(t, 2H), 5.1(q, 1H), 7.0(m, 8H), 7.5(m, 2H), 8.1(m, 2H)

Example 107.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-nitrobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H), 8.4(m, 4H)

Example 108.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-cyanobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H), 7.6(d, 1H), 7.9(d, 1H), 8.4(m, 2H)

Example 109.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(1-naphthoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 5H), 7.9(d, 1H), 8.1(d, 1H), 8.5(d, 1H), 9.0(d, 1H)

Example 110.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-cinnamoyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H),

3.5(m, 1H), 3.9(,m, 1H), 5.1(q, 1H), 6.6(d, 1H), 6.9(m, 6H), 7.5(m, 6H), 7.8(d, 1H)

Example 111.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-crotonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.0(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.0(d, 1H), 6.9(m, 5H), 7.2(m, 2H), 7.5(m, 2H)

Example 112.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(thiophen-2-yl-acetoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 4.1(s, 2H), 5.1(q, 1H), 6.9(m, 9H), 7.5(m, 2H)

Example 113.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-benzyloxyacetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 4.3(s, 2H), 4.6(d, 1H), 4.7(s, 2H), 5.1(q, 1H), 6.9(m, 4H), 7.1(m, 2H), 7.4(m, 7H)

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The same procedures as in Example 50 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(10mg, 26.4 μmol), correspondent acylchloride(39.6 μmol) and triethylamine(20 μl, 142.6 μmol) to give the following titled compound.

Example 114.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 6H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 5H), 7.1(m, 1H), 7.5(m, 2H)

Example 115.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-ethylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.2(t, 3H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.6(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 116.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-isopropylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.3(m, 6H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 2H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 6H), 7.5(m, 2H)

Example 117.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-butylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR ($CDCl_3$): 1.0(m, 3H), 1.5(m, 5H), 1.7(m, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.6(t, 2H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 4H), 7.1(m, 1H), 7.5(m, 2H)

Example 118.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-cyclopropylcarbonyloxy-1,2,3,4

-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.0(m, 2H), 1.2(m, 2H), 1.5(d, 3H), 1.8(m, 1H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 119.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-cyclobutylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.0(m, 2H), 2.1(s, 3H), 2.3(m, 7H), 2.7(m, 1H), 3.1(m, 1H), 3.4(m, 2H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 120.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-cyclohexylcarbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.3(m, 6H), 1.5(d, 3H), 1.7(m, 4H), 2.1(s, 3H), 2.3(s, 3H), 2.6(m, 1H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 5H), 7.5(m, 2H), 7.8(s, 1H)

Example 121.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(2-ethoxycarbonylethyl)carbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.2(t, 3H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 2.9(m, 2H), 3.1(m, 1H), 3.5(m, 1H), 3.9(,m, 1H), 4.2(q, 2H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H)

Example 122.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-benzoyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 5H), 7.2(d, 1H), 7.5(m, 5H), 8.2(d, 2H)

Example 123.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-methylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.5(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.1(m, 1H), 7.3(m, 1H), 7.4(m, 2H), 8.1(m, 2H)

Example 124.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-propylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.0(t, 3H), 1.5(d, 3H), 1.7(m, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 5H), 7.1(m, 1H), 7.3(m, 2H), 7.5(m, 2H), 8.1(m, 2H)

Example 125.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-pentylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 0.9(t, 3H), 1.3(m, 6H), 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.2(m, 1H), 7.3(m, 1H), 7.5(m, 2H), 8.1(m, 2H)

Example 126.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(2-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 5H), 8.0(d, 1H)

Example 127.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-fluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 4H), 7.9(d, 1H), 8.0(d, 1H)

Example 128.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-trifluoromethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 7.0(m, 5H), 7.2(t, 1H), 7.5(m, 2H), 7.7(t, 1H), 7.9(d, 1H), 8.4(d, 1H), 8.5(s, 1H)

Example 129.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(2,3-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 4H), 7.9(t, 1H)

Example 130.
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H),

3.5(m, 1H), 3.8(m, 6H), 5.1(q, 1H), 6.9(m, 10H), 7.5(m, 2H)

Example 131.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.8(m, 6H), 5.1(q, 1H), 6.9(m, 10H), 7.5(m, 2H)

Example 132.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-nitrobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 2H), 8.4(s, 4H)

Example 133.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-cyanobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 5H), 7.2(d, 2H), 7.4(m, 2H), 7.7(t, 1H), 7.9(d, 1H), 8.4(m, 2H)

Example 134.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(1-naphthoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.9(m, 6H), 7.5(m, 5H), 7.9(d, 1H), 8.1(d, 1H), 8.5(d, 1H), 9.0(d, 1H)

Example 135.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-cinnamoyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.6(d, 1H), 6.9(m, 5H), 7.1(d, 1H), 7.4(m, 4H), 7.6(m, 2H), 7.9(d, 1H)

Example 136.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-crotonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.0(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 5.1(q, 1H), 6.0(d, 1H), 6.9(m, 4H), 7.1(m, 2H), 7.5(m, 2H)

Example 137.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(thiophen-2-yl-acetoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.1(s, 2H), 5.1(q, 1H), 6.9(m, 9H), 7.5(m, 2H)

Example 138.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-benzyloxyacetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(d, 2H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.4(s, 2H), 4.6(d, 1H), 4.7(s, 2H), 5.1(q, 1H), 6.9(m, 2H), 7.1(m, 3H), 7.4(m, 8H)

Example 139.

5-methyl-6-(N-t-butoxycarbonyl-glycyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), N-t-butoxycarbonylglycine(27.8 mg, 0.158mmol) and triethylamine(23.9 μl, 0.171mmol) were added to a suspension of 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol) in anhydrous methylene chloride(1ml). The reaction mixture was stirred for 1 day at room temperature, washed with water. The separated organic layer was concentrated and the residual oil was purified by a silica gel column chromatography (dichloromethane / methanol = 20 / 1) to give the titled compound.

NMR($CDCl_3$): 1.4(s, 9H), 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 4.0(m, 3H), 5.1(s, 2H), 5.2(q, 1H), 6.9(m, 2H), 7.1(m, 5H), 7.4 (m, 2H).

Example 140-146

The same procedures as in Example 139 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine (50mg, 0.132mmol), 1-hydroxybenzotriazole (26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), correspondent N-t-butoxycarbonylamino acid (0.158mmol) and triethylamine (23.9 μl, 0.171mmol) to obtain the following titled compound.

Example 140.

5-methyl-6-(N-t-butoxycarbonyl-valyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 0.9(d, 3H), 1.0(d, 3H), 1.4(s, 9H), 1.5(d, 3H), 2.2(s, 3H), 2.3(m, 1H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 4.2(m, 1H), 5.1(m, 3H),

6.9(m, 2H), 7.1(m, 5H), 7.4(m, 2H).

Example 141.

5-methyl-6-(N-t-butoxycarbonyl-O-benzylseryloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.4(s, 9H), 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 4.0(m, 2H), 4.5(s, 2H), 4.6(m, 1H), 5.1(s, 3H), 5.5(d, 1H), 6.9(m, 2H), 7.1(m, 5H), 7.2(m, 5H), 7.4(m, 2H).

Example 142.

5-methyl-6-(N-t-butoxycarbonyl-methionyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.4(s, 9H), 1.5(d, 3H), 2.1(s, 3H), 2.2(s, 3H), 2.8(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 4.0(m, 1H), 4.6(m, 1H), 5.1(m, 3H), 6.9(m, 2H), 7.1(m, 5H), 7.4(m, 2H).

Example 143.

5-methyl-6-(N-t-butoxycarbonyl-O-benzyl-aspartyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.4(s, 9H), 1.5(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.1(m, 3H), 3.5(m, 1H), 4.0(m, 1H), 4.8(m, 1H), 5.1(s, 5H), 5.6(d, 1H), 6.9(m, 2H), 7.1(m, 5H), 7.3(m, 5H), 7.4(m, 2H).

Example 144.

5-methyl-6-(N-t-butoxycarbonyl-Im-benzyl-histidyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.4(s, 9H),1.5 (d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.1(m, 3H), 3.5(m, 1H), 4.0(m, 1H), 4.7(m, 1H), 4.9(s, 2H), 5.1(m, 3H), 6.0(d, 1H), 6.6(s,

1H), 6.9(m, 2H), 7.1(m, 5H), 7.3(m, 5H), 7.4(s, 1H), 7.5(m, 2H).

Example 145.

5-methyl-6-(N-t-butoxycarbonyl-phenylalanyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.4(s, 9H), 1.5(d, 3H), 2.1(s, 3H), 2.8(m, 1H), 3.1(m, 3H), 3.5(m, 1H), 4.0(m, 1H), 4.7(m, 1H), 5.1(m, 3H), 6.9(m, 2H), 7.2(m, 10H), 7.5(m, 2H).

Example 146.

5-methyl-6-(N-t-butoxycarbonyl-prolyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine

NMR($CDCl_3$): 1.4(m, 11H), 1.5(d, 3H), 2.0(m, 2H), 2.2(d, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 3H), 4.0(m, 1H), 4.4(m, 1H), 5.1(m, 3H), 6.8(s, 1H), 6.9(m, 2H), 7.1(m, 5H), 7.5(m, 2H).

Example 147-156

The same procedures as in Example 139 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), correspondent N-t-butoxycarbonylamino acid(0.158 mmol) and triethylamine (23.9 μl, 0.171mmol) to obtain the following titled compound.

Example 147.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonylglycyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5 (m, 12H), 2.1 (s, 3H), 2.3 (s, 3H), 2.7 (m, 1H), 3.1 (m,

1H), 3.5 (m, 1H), 3.9 (m, 1H), 4.1 (d, 2H), 5.1 (m, 2H), 6.9 (m, 4H), 7.1 (d, 1H), 7.4 (m, 2H).

Example 148.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-valyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.0 (m, 6H), 1.5 (m, 12H), 2.1 (s, 3H), 2.3 (s, 3H), 2.7 (m, 1H), 3.1 (m, 1H), 3.5 (m, 1H), 3.9 (m, 1H), 4.4 (m, 1H), 5.1 (m, 2H), 6.9 (m, 4H), 7.1 (d, 1H), 7.5 (m, 2H).

Example 149.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-O-benzyl-seryloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5 (m, 12H), 2.1 (s, 3H), 2.3 (s, 3H), 2.7 (m, 1H), 3.1 (m, 1H), 3.5 (m, 1H), 3.8 (m, 1H), 4.0 (m, 2H), 4.6 (m, 2H), 5.1 (q, 1H), 5.5 (d, 1H), 6.9 (m, 4H), 7.1 (d, 1H), 7.3 (m, 5H), 7.4 (m, 2H).

Example 150.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-methionyl oxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5 (m, 12H), 2.1 (m, 6H), 2.3 (s, 3H), 2.6 (m, 3H), 3.1 (m, 1H), 3.5 (m, 1H), 3.9 (m, 1H), 4.6 (m, 1H), 5.1 (m, 2H), 6.9 (m, 4H), 7.1 (d, 1H), 7.4 (m, 2H).

Example 151.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-O-benzyl-aspartyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5 (m, 12H), 2.1 (s, 3H), 2.3 (s, 3H), 2.7 (m, 1H), 3.1 (m,

3H), 3.5 (m, 1H), 3.9 (m, 1H), 4.8 (m, 1H), 5.1 (m, 3H), 5.6 (d, 1H), 6.9 (m, 4H), 7.1 (d, 1H), 7.3 (m, 5H), 7.5 (m, 2H).

Example 152.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-asparagin yloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5 (m, 12H), 2.1 (s, 3H), 2.3 (s, 3H), 2.7 (m, 1H), 3.0 (m, 3H), 3.5 (m, 1H), 4.1 (m, 1H), 4.3 (m, 1H), 5.1 (q, 1H), 6.0 (d, 1H), 6.6 (s, 1H), 6.7 (m, 1H), 6.9 (m, 3H), 7.4 (m, 2H).

Example 153.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-glutaminy loxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5 (m, 12H), 2.1 (m, 5H), 2.3 (s, 3H), 2.6 (m, 3H), 3.0 (m, 1H), 3.5 (m, 1H), 3.9 (m, 1H), 4.3 (m, 1H), 5.0 (q, 1H), 6.6 (m, 2H), 6.9 (m, 3H), 7.4 (m, 2H).

Example 154.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-Im-benzyl -histidyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 3H), 3.5(m, 1H), 3.9(m, 1H), 4.8(m, 1H), 5.0(m, 3H), 6.2(m, 1H), 6.8(m, 2H), 6.9(m, 4H), 7.1 (m, 1H), 7.3(m, 3H), 7.4(m, 3H).

Example 155.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-phenylala nyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.4(s, 9H), 1.5(m, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H),

3.1(m, 3H), 3.5(m, 1H), 3.9(m, 1H), 4.8(m, 1H), 5.1(m, 2H), 6.8(m, 2H), 7.0(m, 2H), 7.2(m, 6H), 7.5(m, 2H).

Example 156.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(N-t-butoxycarbonyl-prolyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.0(m, 4H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 3H), 3.9(m, 1H), 4.5(m, 1H), 5.1(q, 1H), 6.9(m, 4H), 7.1(m, 1H), 7.5(m, 2H).

Example 157 - 166.

The same procedures as in Example 139 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132 mmol), 1-hydroxybenzotriazole(26.8 mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (32.9mg, 0.171mmol), correspondent N-t-butoxycarbonylamino acid(0.158mmol), and triethylamine(23.9 μl, 0.171mmol) to obtain the following titled compound.

Example 157.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonylglycyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.2(d, 2H), 5.1(q, 1H), 5.2(t, 1H), 6.9(m, 4H), 7.1(d, 1H), 7.4(m, 2H).

Example 158.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-valyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.1(m, 6H), 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.5(m, 1H), 5.1(q, 1H), 5.2(t, 1H), 6.9(m, 4H), 7.1(d, 1H), 7.5(m, 2H).

Example 159.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-O-benzyl-seryloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 1H), 3.8(m, 2H), 4.1(m, 1H), 4.6(m, 2H), 4.7(m, 1H), 5.0(q, 1H), 5.5(d, 1H), 6.9(m, 5H), 7.3(m, 5H), 7.4(m, 2H).

Example 160.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-methionyl oxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(m, 6H), 2.3(s, 3H), 2.6(m, 3H), 3.1(m, 1H), 3.5(m, 1H), 3.9(m, 1H), 4.6(m, 1H), 5.1(m, 2H), 6.9(m, 4H), 7.1(d, 1H), 7.4(m, 2H).

Example 161.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-O-benzyl-aspartyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 3H), 3.5(m, 1H), 3.9(m, 1H), 4.8(m, 1H), 5.1(m, 3H), 5.6(d, 1H), 6.9(m, 5H), 7.3(m, 5H), 7.5(m, 2H).

Example 162.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-asparagin yloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.6(m, 1H), 3.0(m, 3H), 3.5(m, 1H), 4.1(m, 1H), 4.3(m, 1H), 5.1(q, 1H), 6.0(d, 1H), 6.6(s, 1H), 6.7(m, 1H), 6.9(m, 3H), 7.4(m, 2H).

Example 163.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-glutaminy loxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(m, 5H), 2.3(s, 3H), 2.6(m, 3H), 3.0(m, 1H), 3.5(m, 1H), 4.1(m, 2H), 5.1(q, 1H), 6.6(s, 1H), 6.7(d, 1H), 6.9(m, 3H), 7.5(m, 2H).

Example 164.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-Im-benzyl -histidyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 3H), 3.5(m, 1H), 3.9(m, 1H), 4.8(m, 1H), 5.0(m, 3H), 6.9(m, 8H), 7.3(m, 3H), 7.4(m, 3H).

Example 165.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-phenylala nyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.4(s, 9H), 1.5(m, 3H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.2(m, 2H), 3.5(m, 1H), 3.9(m, 1H), 4.8(m, 1H), 5.1(m, 2H), 6.6(m, 2H), 6.9(m, 2H), 7.2(m, 6H), 7.5(m, 2H).

Example 166.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(N-t-butoxycarbonyl-prolyloxy) -1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

NMR($CDCl_3$): 1.5(m, 12H), 2.0(m, 4H), 2.1(s, 3H), 2.3(s, 3H), 2.7(m, 1H), 3.1(m, 1H), 3.5(m, 3H), 3.9(m, 1H), 4.5(m, 1H), 5.1(q, 1H), 6.6(m, 1H), 6.9(m, 4H), 7.4(m, 2H).

Example 167.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-valyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (32.9mg, 0.171mmol), N-t-butyloxycarbonyl-valine (34.4mg, 0.158mmol), and triethylamine (23.9μl, 0.171mmol) were added to a suspension of 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol) in anhydrous methylene chloride (1ml). The reaction mixture was stirred for 1 day at room temperature and washed with water. The separated organic layer was concentrated and the residual oil was purified by a silica gel column chromatography (dichloromethane / methanol = 20 / 1). After evaporating of the solvent, the residual oil was dissolved in 3M hydrochloride-ethylacetate solution, stirred for 2 hours at room temperature and concentrated. The resulting white solid was suspended in ethyl ether and filtered to give the titled compound.

NMR(DMSO-d6): 1.0(m, 6H), 1.6(d, 3H), 2.2(s, 3H), 2.4(m, 4H), 2.9(m, 1H), 3.1(m, 1H), 3.6(m, 1H), 4.2(m, 2H), 5.4(m, 1H), 7.0(m, 2H), 7.3(m, 3H), 7.6(m, 2H), 8.8(m, 2H), 10.2(s, 1H)

Example 168.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-phenylalanyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procedures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198

mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (32.9mg, 0.171mmol), N-t-butyloxycarbonyl-phenylalanine(42.0mg, 0.158mmol), and triethylamine(23.9 μl, 0.171mmol) to afford the titled compound.

NMR(DMSO-d6): 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.2(d, 2H), 3.6(m, 1H), 4.2(m, 1H), 4.5(m, 1H), 5.4(m, 1H), 6.8(m, 2H), 7.3(m, 8H), 7.6(m, 2H), 9.0(m, 2H), 10.2(s, 1H)

Example. 169.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-valyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procedures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), N-t-butyloxycarbonyl-valine (34.4mg, 0.158mmol), and triethylamine (23.9 μl, 0.171mmol) to afford the titled compound.

NMR(DMSO-d6): 1.0(m, 6H), 1.6(d, 3H), 2.2(s, 3H), 2.4(m, 4H), 2.9(m, 1H), 3.1(m, 1H), 3.6(m, 1H), 4.2(m, 2H), 5.4(m, 1H), 7.0(m, 2H), 7.3(m, 3H), 7.6(m, 2H), 8.9(m, 2H), 10.3(s, 1H)

Example 170.

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-phenylalanyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procedures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (32.9mg, 0.171mmol), N-t-butyloxycarbonyl-phenylalanine (42.0mg, 0.158mmol), and triethylamine(23.9

μl, 0.171mmol) to afford the titled compound.

NMR(DMSO-d6): 1.5(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.2(d, 2H), 3.6(m, 1H), 4.2(m, 1H), 4.5(m, 1H), 5.3(m, 1H), 6.8(m, 2H), 7.3(m, 8H), 7.6(m, 2H), 9.0(m, 2H), 10.2(s, 1H)

Example 171.

5-methyl-6-valyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procedures as in Example 167 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (32.9mg, 0.171 mmol), N-t-butyloxycarbonyl-valine (34.4mg, 0.158mmol), and triethylamine(23.9 μl, 0.171mmol) to afford the titled compound.

NMR(DMSO-d6): 1.0(d, 6H), 1.6(d, 3H), 2.2(s, 3H), 2.3(m, 1H), 2.8(m, 1H), 3.2(m, 1H), 3.6(m, 1H), 4.2(m, 2H), 5.4(m, 3H), 7.2(m, 6H), 7.6(m, 2H), 8.8(m, 2H), 10.8(bs, 1H)

Example 172.

5-methyl-6-(phenylalanyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procedures as in Example 167 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (32.9mg, 0.171 mmol), N-t-butyloxycarbonyl-phenylalanine (42.0mg, 0.158mmol), and triethylamine(23.9 μl, 0.171mmol) to afford the titled compound.

NMR(DMSO-d6): 1.6(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.3(d, 2H), 3.6(m, 1H), 4.2(m, 1H), 4.6(m, 1H), 5.4(m, 3H), 7.2(m, 11H), 7.6(m, 2H), 8.8(m, 2H), 10.8(bs, 1H)

Example 173.
5-acetoxymethyl-6-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

Acetylchloride (2.71 μl, 39.6 μmol) and triethylamine (20 μl, 142.6 μmol) were added to a suspension of 5-hydroxymethyl-6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluorophenylamino)pyrimidine (10mg, 26.4 μmol) in dichloromethane(1ml) and stirred for 1 day at a room temperature. The reaction mixture was purified by a silica gel column chromatography (ethylacetate/n-hexane=1/1) to give the titled compound.

NMR ($CDCl_3$): 1.6(d, 3H), 2.2 (s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.6 (m, 1H), 4.2(m, 1H), 4.6 (q, 2H), 5.4(q, 1H), 6.9(m, 3H), 7.2(m, 4H), 7.5(m, 2H)

Example 174.
5-valyloxymethyl-6-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5-hydroxymethyl-6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluorophenylamino)pyrimidine (50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (32.9mg, 0.171 mmol), N-t-butyloxycarbonyl-valine (34.4mg, 0.158mmol), and triethylamine(23.9 μl, 0.171mmol) to afford the titled compound.

NMR (DMSO-d_6): 1.0 (d, 6H), 1.6 (d, 3H), 2.4 (s, 3H), 2.3 (m, 1H), 2.8 (m, 1H), 3.2 (m, 1H), 3.6 (m, 1H), 4.2 (m, 2H), 5.4 (m, 3H), 7.2 (m, 6H), 7.6

(m, 2H), 8.8 (m, 2H), 10.8(br, 1H)

Example 175.

5-methyl-6-(4-morpholineacetoxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 4-morpholineacetic acid hydrochloride(28.8mg, 0.158mmol), and triethylamine(46 μl, 0.330 mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 5H), 3.5(m, 1H), 3.8(s, 4H), 4.1(s, 2H), 4.2(m, 1H), 5.2(m, 3H), 7.0(m, 6H), 7.5(m, 2H), 11.0(s, 1H)

Example 176.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-morpholineacetoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 4-morpholineacetic acid hydrochloride (28.8mg, 0.158mmol), and triethylamine (46 μl, 0.330mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.7(m, 4H), 2.8(m, 1H), 3.2(m, 1H), 3.5(m, 3H), 3.8(m, 4H), 4.2(m, 1H), 5.3(m, 1H), 7.0(m, 5H), 7.5(m, 2H), 10.6(s, 1H), 14(bs, 1H).

Example 177

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-morpholineacetoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 4-morpholineacetic acid hydrochloride(28.8mg, 0.158mmol), and triethylamine(46 μl, 0.330 mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.0(s, 4H), 3.2(m, 1H), 3.5(m, 1H), 3.7(m, 4H), 3.9(m, 4H), 4.2(m, 1H), 5.3(m, 1H), 7.0(m, 5H), 7.5(m, 2H), 10.2(s, 1H)

Example 178.

5-methyl-6-(4-benzylpiperazine)acetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine trihydrochloride

The same procudures as in Example 167 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 4-benzylpiperazineacetic acid dihydrochloride (48.7mg, 0.158mmol), and triethylamine(64 μl, 0.462mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.3(m, 8H), 3.5(m, 1H), 4.0(s, 2H), 4.2(m, 3H), 5.2(m, 3H), 7.0(m, 7H), 7.5(m, 6H), 11.0(d, 1H).

Example 179.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-benzylpiperazine)acetoxy-1,

2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine trihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 4-benzylpiperazinoacetic acid dihydrochloride (48.7mg, 0.158mmol), and triethylamine(64 μl, 0.462mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.7(m, 9H), 3.1(m, 1H), 3.5(m, 3H), 3.6(s, 2H), 4.0(m, 1H), 5.2(m, 1H), 6.9(m, 5H), 7.3(m, 5H), 7.5(m, 2H), 8.9(bs, 1H).

Example 180.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{(1-methyl-7-(4-benzylpiperazine)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine trihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 4-benzylpiperazinoacetic acid dihydrochloride (48.7mg, 0.158mmol), and triethylamine(64 μl, 0.462mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 2.2(s, 3H), 2.4(s, 3H), 2.8(m, 9H), 3.1(m, 1H), 3.5(m, 3H), 3.8(s, 2H), 4.2(m, 1H), 5.2(m, 1H), 6.9(m, 5H), 7.4(m, 7H), 10.1(bs, 1H).

Example 181.

5-methyl-6-(1-piperidineacetoxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5-methyl-6-hydroxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), piperidineacetic acid hydrochloride (28.5mg, 0.158mmol), and triethylamine(46 μl, 0.330mmol) to afford the titled compound.

NMR($CDCl_3$): 1.6(d, 3H), 1.9(m, 6H), 2.2(s, 3H), 2.8(m, 1H), 3.1(m, 1H), 3.2(m, 4H), 3.5(m, 1H), 4.2(m, 3H), 5.2(m, 3H), 6.9(m, 2H), 7.2(m, 4H), 7.5(m, 2H), 10.2(bs, 1H).

Example 182.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(1-piperidineacetoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 1-piperidineacetic acid hydrochloride (28.5mg, 0.158mmol), and triethylamine(46 μl, 0.330mmol) to afford the titled compound.

NMR($CDCl_3$): 1.5(m, 9H), 2.2(s, 3H), 2.4(s, 3H), 2.6(m, 4H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 3H), 4.0(m, 1H), 5.2(m, 1H), 7.0(m, 5H), 7.5(m, 2H), 8.5(bs, 1H).

Example 183.

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(1-piperidinoacetoxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-7-hydroxy-1,2,3,4-tetrahydroisoq

uinolin-2-yl)pyrimidine(50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), 1-piperidineacetic acid hydrochloride(28.5mg, 0.158mmol), and triethylamine(46 μl, 0.330mmol) to afford the titled compound.

NMR($CDCl_3$): 1.5(m, 9H), 2.2(s, 3H), 2.4(s, 3H), 2.6(m, 4H), 2.8(m, 1H), 3.1(m, 1H), 3.5(m, 3H), 4.1(m, 1H), 5.2(m, 1H), 7.0(m, 5H), 7.5(m, 2H), 9.9 (bs, 1H).

Example 184.

5,6-dimethyl-2-(4-fluoro-2-valyloxyphenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procudures as in Example 167 were repeated using 5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluoro-2-hydroxyphenylamino)pyrimidine (50mg, 0.132mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol), N-t-butyloxycarbonyl-valine(34.4mg, 0.158mmol), and triethylamine(23.9 μl, 0.171 mmol) to afford the titled compound.

NMR (DMSO-d_6): 1.0 (m, 6H), 1.6 (d, 3H), 2.2 (s, 3H), 2.4 (m, 4H), 2.9 (m, 1H), 3.1 (m, 1H), 3.6 (m, 1H), 4.2 (m, 1H), 4.6 (m, 1H), 5.4 (m, 1H), 7.2 (m, 5H), 7.6 (m, 2H), 8.9 (m, 2H).

Example 185.

5,6-dimethyl-2-(4-fluoro-2-phenylalanyloxyphenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine dihydrochloride

The same procedures as in Example 167 were repeated using 5,6-dimethyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluoro-2-hydroxyphenylamino)pyrimidine (50 mg, 0.132 mmol), 1-hydroxybenzotriazole(26.8mg, 0.198mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide(32.9mg, 0.171mmol),

N-t-butyloxycarbonyl-phenylalanine(42.0mg, 0.158mmol), and triethylamine(23.9 μl, 0.171mmol) to afford the titled compound.

NMR (DMSO-d_6): 1.5 (d, 3H), 2.2 (s, 3H), 2.4 (s, 3H), 2.8 (m, 1H), 3.1 (m, 3H), 3.6 (m, 1H), 4.2 (m, 1H), 5.0 (m, 1H), 5.4 (m, 1H), 6.8 (m, 2H), 7.2 (m, 10H), 9.0 (m, 2H).

Example 186.

2-(4-Fluorophenylamino)-5-methoxymethyl-6-methyl-4-(1-methyl-1,2,3,4-tetrahydro isoquinoline-2-yl)pyrimidine hydrochloride

2-(4-Fluorophenylamino)-6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinoline-2-yl)pyrimidine (0.9g, 2.58mmol) was added to chloromethyl methyl ether (3ml) in a sealed tube. The mixture was stirred at 80°C for 1 day. After cooling to room temperature, ethyl ether was added to mixture. Resulting solid was removed by filtration. Filtrate was washed with aqueous 2N NaOH solution, dried over sodium sulfate, and concentrated under reduced pressure. Crude product was purified with a silica gel column chromatography (eluent: ethyl acetate : hexane = 1 : 3). Purified compound was treated with HCl solution in ethyl ether. Precipitated solid was isolated by filtration, washed with ethyl ether, and dried in vacuum. It gave 0.6mg of the titled compound.

Yield : 0.05%

NMR (CDCl3) : δ 1.6(d, 3H), 2.4(s, 3H), 2.8(m, 1H), 3.2(m, 1H), 3.5(s, 3H), 3.6(m, 1H), 4.2(m, 3H), 5.4(q, 1H), 6.9(m, 2H), 7.1(m, 4H), 7.5(m, 2H)

Test 1 : Inhibition of proton pump (H^+/K^+-ATPase activity)

A proton pump enzyme was prepared by the same method as in the Experiment 1-1 of WO 94/14795. Further, the inhibitory effect of proton pump activity was measured by the same method as in Experiment 1-2 of WO 94/14795.

Namely, the proton pump activity stimulated by Mg^{++} was used as a negative comparative group, and the activity stimulated by Mg^{++} and K^{+} was used as a positive comparative group. The comparative compound was omeprazole.

Test tubes were divided into 4 groups: Group 1 as negative comparative group(n=3), Group 2 as positive comparative group(n=3), Group 3(n=5x2) to be administered with the compound of the present invention and Group 4(n=5x2) to be administered with the comparative compound.

The inhibitory effects of Groups 3 and 4 on proton pump activity were measured by employing the compound prepared in Examples and omeprazole, respectively, each of which was dissolved in dimethylsulfoxide at 5 different concentrations.

To each of Groups 1, 2, 3 and 4 were added 100 μl of magnesium chloride(40mM) dissolved in 40mM Tris-HCl buffer(pH 6.0) and 100 μg of the enzyme source. The 50 μl of potassium chloride(50mM) and 50 μl of ammonium chloride(6mM) dissolved in 40mM Tris-HCl buffer(pH 6.0) were added to all groups except for group 1.

10 μl of dimethylsulfoxide was added to each of Groups 1 and 2; and to Group 3 was added 10 μl of dimethylsulfoxide solution prepared by dissolving compound of Example at 5 different concentration(n=5x2). To Group 4, 10 μl of the solution prepared by dissolving omeprazole in dimethylsulfoxide at 5 different concentration(37.6, 21.4, 12.2, 7.0 and 4.0 μM) was added(n=5x2). 40mM Tris-HCl buffer(pH=6.0) was added thereto so as to make the total volume 400 μl.

Thereafter, the test tube of each Group were placed at 37 °C for 30 minutes for the preincubation. 100 μl ATP solution (6.6mM) was added until

the reaction volume became 500 μl. After the reaction was carried out at 37 ° C for 30 minutes, 25% cold trichloroacetic acid was added to terminate the enzyme reaction. The released inorganic phosphate was measured by an automatic analyzer(Express 550, corning).

The difference between Group 1 and Group 2 represents the proton pump activity activated by K^+ only. The IC_{50}s of Group 3 and 4 were calculated from Litchfield-wilcoxon equation[see, e.g., J. Pharmacol. Exp. Ther., 96, 99(1949)]. The concentrations of the test compounds inhibiting 50% of the proton pump activity are represented as IC_{50} in Table 1.

Table 1.

Test compound	IC50 (uM)	Effect ratio
Example 2	7.85	1.4
Example 5	6.91	1.6
Example 14	2.15	5.2
Example 22	6.69	1.7
Example 23	0.43	25.8
Example 25	1.85	6.0
Example 26	2.60	4.3
Example 27	1.55	7.2
Example 28	1.74	6.4
Example 29	2.55	4.4
Example 31	2.56	4.3
Example 32	1.34	8.3
Example 34	0.43	25.8
Example 36	0.31	35.8
Example 43	0.18	61.7
Omeprazole	11.10	-

As shown in Table 1, the compounds of the present invention have an excellent proton pump inhibitory activity over omeprazole.

Test 2 : Inhibition of gastric secretion

In accordance with the method disclosed in Shay, H., et al., Gastroenterology 5 43-61(1945), Test 2 was carried out.

Sprague-Dawly rats having a body weight of 170±10g were divided into 3 groups(n=5) and deprived of food for 24 hours before the experiment with free access to water. Under ether anesthesia, the abdomen was incised, and the pylorus was ligated. As a comparative group, Group 1 was administered intraduodenally in a volume of 0.5ml/200g of 30% aqueous polyethylene glycol 400 solution. Groups 2 and 3 were administered intraduodenally with the compound of Example and omeprazole, respectively, each of which was suspended in 30% aqueous polyethylene glycol 400 solution at a concentration of 20mg/kg. After closing the abdominal cavity, the rats were placed for 5 hours and then killed by cervical dislocation. The stomach was extracted to obtain gastric juice.

Tne gastric juice was centrifuged at 1,000g to remove precipitates. The amount and acidity of the gastric juice were measured. Relative volumes, relative acid concentrations and relative acid outputs of the test compounds were calculated from equations(I), (II) and (III) and the results are shown in Table 2.

Relative volume = (the average amount of gastric juice of Group 1 - the average amount of gastric juice of Group 2) / (the average amount of gastric juice of Group 1 - the average amount of gastric juice of Group 3) --- (I)

Relative acid concerntration = (the average acidity of Group 1 - the

average acidity of Group 2) / (the average acidity of Group 1 - the average acidity of Group 3) --- (II)

Relative acid output = (the total amount of acid output of Group 1 - the total amount of acid output of Group 2) / (the total amount of acid output of Group 1 - the total amount of acid output of Group 3) --- (III)

The results are shown in Table 2.

Table 2.

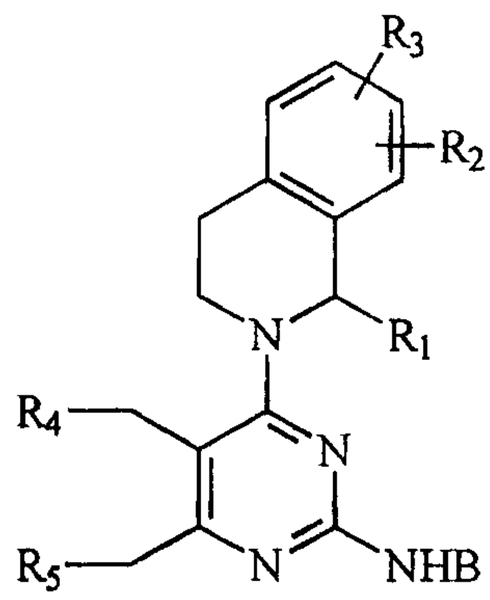
Test compound	Relative volume	Relative conc.	Relative Acid Output
Example 2	0.69	0.57	0.70
Example 5	0.45	0.18	0.43
Example 14	0.93	0.41	0.79
Example 22	0.59	0.46	0.62
Example 23	1.58	1.34	1.23
Example 25	1.00	0.52	0.86
Example 26	0.67	0.64	0.74
Example 27	0.99	0.68	0.90
Example 28	0.78	0.60	0.78
Example 29	0.78	0.81	0.88
Example 31	1.06	0.97	1.01
Example 32	0.84	0.47	0.77

Table 2. (continued)

Test compound	Relative volume	Relative conc.	Relative Acid Output
Example 34	0.81	0.45	0.78
Example 36	1.05	1.08	1.15
Example 50	1.01	0.77	0.98
Example 51	1.09	1.02	1.06
Example 52	0.86	0.88	0.96
Example 54	0.79	0.79	0.95
Example 74	1.57	1.02	1.25
Example 107	0.62	0.56	0.73
Example 139	1.01	0.75	1.01
Example 144	0.90	0.80	0.94
Example 171	1.46	1.42	1.33
Example 172	1.48	1.33	1.34
Example 175	0.87	0.30	0.79
Example 181	0.99	0.16	0.80

CLAIMS

1. Pyrimidine derivative of the following formula (I):

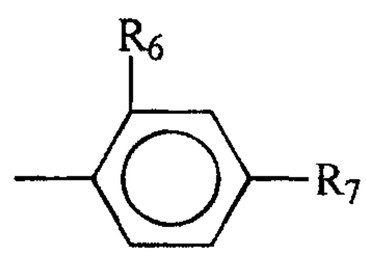


(I)

wherein

when B is C_3-C_7 cycloalkyl; C_1-C_3 alkoxyethyl; 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl;
R_1 is hydrogen or methyl; and
R_2, R_3, R_4 and R_5 are hydrogen; or

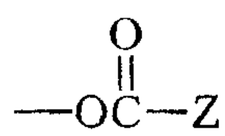
when B is a group of formula (II):



(II)

when R_1 is hydroxymethyl or C_1-C_3 alkoxymethyl;
R_2, R_3, R_4, R_5 and R_6 are hydrogen; and
R_7 is hydrogen or halogen; or

when R_1 is hydrogen or methyl;
R_7 is hydrogen or halogen; and
one or two of R_2, R_3, R_4, R_5 and R_6 is hydroxy, methoxy, or a group of formula (III)



(III) .

wherein Z is C_1-C_4 alkyl; C_2-C_4 alkenyl; C_3-C_6 cycloalkyl; morpholinomethyl; piperidinomethyl; phenyl; naphthyl; thiophen-2-yl-methyl; or -CHR_8NHR_9, wherein R_8 is hydrogen, methyl, isopropyl, benzyl, benzyloxymethyl, methylthioethyl, benzyloxycarbonylmethyl, carbamoylmethyl, carbamoylethyl, or 1-benzylimidazol-4-ylmethyl and R_9 is hydrogen or t-butoxycarbonyl, and the others are hydrogen or methyl, or

a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein B is C_3-C_7 cycloalkyl, C_1-C_3 alkoxyethyl, 1-naphthylmethyl, 4-methylthiazol-2-yl or 4-phenylthiazol-2-yl.

3. The compound of claim 1, wherein B is a group of formula (II); R_1 is hydrogen or methyl; and one or two of R_2, R_3, R_4, R_5 and R_6 are hydroxy or methoxy.

4. The compound of claim 1, wherein B is a group of formula (II); R_1 is hydrogen or methyl; and one or two of R_2, R_3, R_4, R_5 and R_6 are a group of formula (III).

5. The compound of claim 1, wherein B is a group of formula (II) and R_1 is hydroxymethyl or C_1-C_3 alkoxymethyl.

6. 6-hydroxymethyl-5-methyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine or a pharmaceutically acceptable salt thereof.

7. 5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine or a pharmaceutically acceptable salt thereof.

8. 5-hydroxymethyl-6-methyl-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-(4-fluorophenylamino)pyrimidine or a pharmaceutically acceptable salt thereof.

9. 5-methyl-6-(thiophen-2-yl-acetoxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine or a pharmaceutically acceptable salt thereof.

10. 5-methyl-6-valyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine or a pharmaceutically acceptable salt thereof.

11. 5-methyl-6-(phenylalanyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine or a pharmaceutically acceptable salt thereof.

12. 5,6-dimethyl-2-(4-methylthiazol-2-yl)amino-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine or a pharmaceutically acceptable salt thereof.

13. A compound selected from the group consisting of :

5-methyl-6-{(2-ethoxycarbonylethyl)carbonyloxymethyl}-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinoline-2-yl)pyrimidine;

5-methyl-6-(4-methylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

5-methyl-6-(4-propylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

5-methyl-6-(4-pentylbenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

5-methyl-6-(3-fluorobenzoyloxymethyl)-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

5-methyl-6-benzyloxyacetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

5-methyl-6-cinnamoyloxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2-ethoxycarbonylethyl)carbonyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-methylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-ethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-propylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-t-butylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-pentylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4-dichloro-5-fluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4,6-trichlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-fluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,6-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3,4-trifluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3,6-trifluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,4,5-trifluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-trifluoromethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-trifluoromethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(2,3,4,5-tetrafluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-butoxybenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-nitrobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(3-cyanobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-cinnamoyloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-6-benzyloxyacetoxy-1,2,3,4-tetra hydroisoquinolin-2-yl)pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(2-ethoxycarbonylethyl)carbon yloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-methylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-propylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-pentylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(2-chlorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-fluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-trifluoromethylbenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(2,3-difluorobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-methoxyphenyl)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-nitrobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(3-cyanobenzoyloxy)-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-cinnam yloxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine;

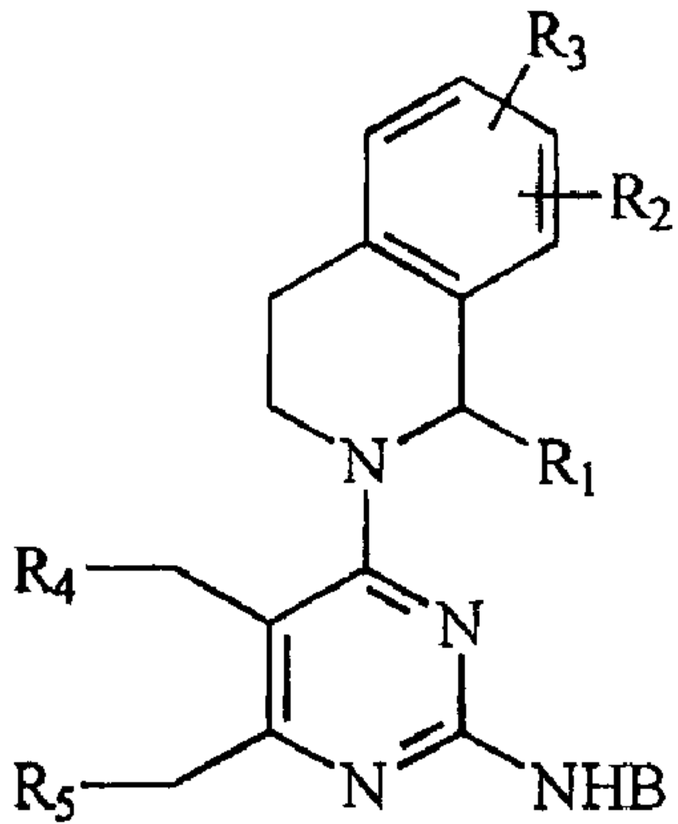
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-benzyloxyacetoxy-1,2,3,4-tetra hydroisoquinolin-2-yl}pyrimidine;

5-methyl-6-(4-benzylpiperazine)acetoxymethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl)pyrimidine;

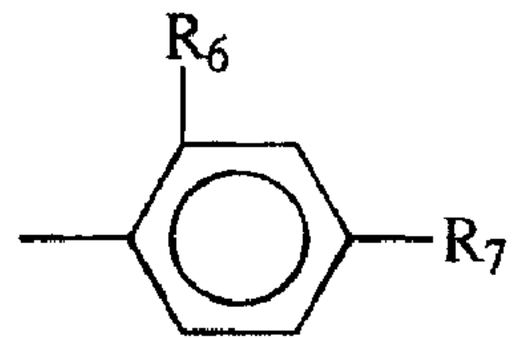
5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-6-(4-benzylpiperazine)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine; and

5,6-dimethyl-2-(4-fluorophenylamino)-4-{1-methyl-7-(4-benzylpiperazine)acetoxy-1,2,3,4-tetrahydroisoquinolin-2-yl}pyrimidine

or a pharmaceutically acceptable salt thereof.



(I)



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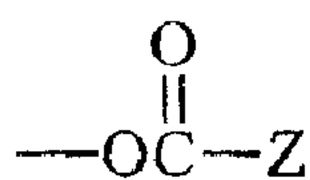

(III)