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(54) Title: Piperazine Derivatives and Process for the Preparation Thereof

(57) Abstract

The present invention relates to novel compound having strong antitumor activities of general formula (I), wherein R₁ and R₂ are independently hydrogen, substituted or unsubstituted C₁-C₄ alkyl, substituted or unsubstituted C₇-C₁₀ cycloalkyl, substituted or unsubstituted C₂-C₄ unsaturated alkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₁-C₄ alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C₁-C₄ lower ester, C₁-C₄ lower thioether, thiol, substituted or unsubstituted carboxyl, epoxide, substituted or unsubstituted C₁-C₄ lower thioalkoxy; or R₁ and R₂ are fused to form C₃-C₄ saturated or unsaturated chain; R₃, R₄, R₅, R₆, and R₇, are independently hydrogen, halogen, hydroxy, nitro, C₁-C₄ lower ester, C₁-C₄ lower alkoxy, substituted or unsubstituted C₃-C₇ cycloalkyl, C₁-C₄ lower alkoxy, C₁-C₄ lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted arylalkoxy, substituted or unsubstituted lower alkylamine, or lower alkyl substituted or unsubstituted carbamate; or among R₃, R₄, R₅, R₆, and R₇, two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylen; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or -NR₄⁺ (wherein, R₄ is the same with the above-mentioned R₃); Z is hydroxy, C₁-C₄ lower alkoxy, C₁-C₄ lower thioalkoxy, substituted or unsubstituted aryl, C₁-C₄ lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; A is nitrogen or -CH⁺⁺⁻, its pharmaceutically acceptable acid addition salts and process for the preparation thereof.
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TT  Trinidad and Tobago
UA  Ukraine
UG  Uganda
US  United States of America
UZ  Uzbekistan
VN  Viet Nam
YU  Yugoslavia
ZW  Zimbabwe
Piperazine derivatives and process for the preparation thereof

The present invention relates to new piperazine derivatives of the general formula (I)

![Chemical Structure](image)

(I)

wherein R₁ and R₂ are independently hydrogen, substituted or unsubstituted C₁⁻C₈ alkyl, substituted or unsubstituted C₃⁻C₆ cycloalkyl, substituted or unsubstituted C₂⁻C₈ unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted C₁⁻C₄ alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, C₁⁻C₄ lower ester, C₁⁻C₄ lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted C₁⁻C₄ lower thioalkoxy; or R₁ and R₂ are fused to form C₃⁻C₄ saturated or unsaturated chain; R₃, R₄, R₅, R₆ and R₇ are independently hydrogen, halogen, hydroxy, nitro, C₁⁻C₄ lower ester, C₁⁻C₄ lower alkyl, C₁⁻C₄ lower thioalkyl, substituted or unsubstituted C₃⁻C₆ cycloalkyl, C₁⁻C₄ lower alkoxy, C₁⁻C₄ lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower aryalkoxy, substituted or unsubstituted lower alkenyl, or lower alkyl substituted or unsubstituted carbamate; or among R₃, R₄, R₅, R₆ and R₇, two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; X is oxygen, sulfur, or substituted or unsubstituted imino; Y is bonded at the 3-position or 4-position of the aromatic ring part wherein Y is oxygen or -NR₈⁻ (wherein, R₈ is the same with the above-mentioned R₃); Z is hydroxy, C₁⁻C₄ lower alkoxy, C₁⁻C₄ lower thioalkoxy, substituted or unsubstituted arylalkoxy, C₁⁻C₄ lower alkenyl, substituted or unsubstituted cycloalkyl containing 1⁻5 nitrogen atoms; A is nitrogen or -CH⁻; its pharmaceutically acceptable acid addition
salts and process for the preparation thereof.

In the above definitions, C₁–C₈ alkyl means straight or branched alkyl group such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl, iso-pentyl, hexyl, heptyl, octyl, 2-methylpentyl or the like.

C₁–C₄ lower alkyl means methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl.

Substituted or unsubstituted C₃–C₆ cycloalkyl means substituted or unsubstituted cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, substituted cyclopropyl, substituted cyclopentyl, substituted cyclohexyl or the like.

C₁–C₄ lower ester means a carboxyl group esterified by a lower alkyl group.

C₁–C₄ lower alkoxy means methoxy, ethoxy, propoxy, isopropanoxy, butyroxy, isobutyroxy, tert-butyroxy group or the like.

C₁–C₄ lower thioalkoxy means methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, tert-butylthio group or the like.

C₁–C₄ lower alkylamino means methylamino, ethylamino, propylamino, butylamino group or the like.

Aryloxy means phenoxy, substituted phenoxy, naphthoxy or substituted naphthoxy or the like.

Cycloamino group containing 1–5 nitrogen atoms means pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, piperazinyl or the like.

The present inventors had studied for a long time to find compounds having intensive antitumor activity. As the results, now we have finally found out the facts that the present compounds of the general formula(I) and acid addition salts thereof have not only prominent antitumor activities but very low toxicities.

Accordingly, the one object of the present invention is to provide the novel compounds of the general formula(I) and acid addition salts thereof having not only prominent antitumor activities but very low toxicities.

The other object of the present invention is to provide a process for
the preparation of the compounds of general formula (I) and acid addition salts thereof.

The compounds of the present invention can be mixed with pharmaceutically acceptable vehicles by a known method to give pharmaceutical compositions and the pharmaceutical compositions can be used to prevent or treat with various kinds of tumors of human beings or mammals.

Therefore, another object of the present invention is to provide pharmaceutical compositions containing the compounds of the general formula (I) or acid addition salts thereof as active ingredients.

Acids which can be reacted with the compounds of the general formula (I) to form acid addition salts are pharmaceutically acceptable inorganic or organic acids; for example, inorganic acids such as hydrochloric acid, bromic acid, sulfuric acid, phosphoric acid, nitric acid; organic acids such as formic acid, acetic acid, propionic acid, succinic acid, citric acid, maleic acid, malonic acid, glycolic acid, lactic acid; amino acids such as glycine, alanine, valine, leucine, isoleucine, serine, cysteine, cystine, asparagin acid, glutamic acid, lysine, arginine, tyrosine, proline; sulfonic acids such as methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, toluene sulfonic acid; or the like.

Vehicles which can be used in the preparation of pharmaceutical compositions containing the compounds of the general formula (I) as active ingredients are sweetening agent, binding agent, dissolving agent, aids for dissolution, wetting agent, emulsifying agent, isotonic agent, adsorbent, degrading agent, antioxidant, antiseptics, lubricating agent, filler, perfume or the like; such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine, silica, talc, stearic acid, stearin, magnesium stearate, calcium stearate, magnesium aluminum silicate, starch, gelatine, tragacanth gum, glycine, silica, alginic acid, sodium alginate, methyl cellulose, sodium carboxy methyl cellulose, agar, water, ethanol, polyethyleneglycol, polyvinyl pyrrolidone, sodium chloride, potassium chloride, orange essence, strawberry essence, vanilla aroma or the like.

Daily dosage of the compound of the general formula (I) may be varied depending on age, sex of patient and the degree of disease. Daily dosage is 1.0mg to 5,000mg may be administered one to several times.
The compounds of the general formula (I) according to the present invention may be prepared by the following scheme I.

**Scheme I**

![Diagram](image)

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, A, X, Y and Z are as defined above, and Lie is a leaving group such as halogen atom, sulfonyl or the like.

The above process comprises reacting a compound of the general formula (a) with a -C(=X)- group-providing agent in organic solvent to obtain a compound of the general formula (b) and successively reacting the compound of the general formula (b) with a compound of the general formula (c) to give the compound of the general formula (I).

The used -C(=X)-group-providing agent preferably be selected from 1,1-carbonyldimidazole, 1,1-carbonylthiodimidazole, phosgene, thiophosgene, carbonyldiphenoxide, phenylchloroformate or the like.

The reaction may be carried out in conventional organic solvent such as, for example, tetrahydrofuran, dichloromethane, chloroform,
acetonitrile.
And also the reaction is preferably carried out in the presence of
coupling agent such as conventional inorganic or organic base. Such
conventional inorganic or organic base used in the reaction means
sodium hydride, potassium hydride, sodium hydroxide, potassium
hydroxide, sodium carbonate, potassium carbonate, cesium carbonate,
sodium bicarbonate, potassium bicarbonate, triethylamine, pyridine, DBU
or the like, and 1-1.5 equivalent, preferably 1-1.1 equivalent thereof
may be used.
The reaction may be carried out between 3°C and boiling point of the
solvent used, preferably at 50°C -100°C for 5 - 48 hours, preferably for
10 - 24 hours.
-C(=X)-group-providing agent may be used in an amount of 1 - 1.5
equivalent, preferably 1-1.1 equivalent to the starting compound.
A compound of the general formula(I) wherein Y is -NR₆₋ may be
prepared by the following scheme II

Scheme II.

![Diagram](image-url)
wherein, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, A, X and Z are as defined above.

A compound of the general formula (Ib) above may be prepared effectively by introducing R₈ providing agent into a compound of the general formula (Ia).

R₈ providing agent preferably used in the above reaction is C₁-C₈ lower alkylhalogen, C₁-C₈ lower alkyl sulfonate, substituted or unsubstituted C₃-C₈ cycloalkylhalogen, arylhalogen, substituted or unsubstituted C₃-C₈ cycloalkyl sulfonate, arylsulfonate, or the like.

C₁-C₈ lower alkylhalogen means methylchloride, methylbromide, methyliodide, ethylchloride, ethylbromide, ethyliodide, propylchloride, propylbromide, propyliodide, butylchloride, butylbromide, butyliodide, pentylchloride, pentylbromide, pentyliodide, ethylbromacetate, or the like.

C₁-C₈ lower alkyl sulfonate means methylsulfonate, ethylsulfonate, propylsulfonate, butylsulfonate, pentylsulfonate, or the like.

Substituted or unsubstituted C₃-C₈ cycloalkylhalogen cyclopropylchloride, cyclopropylbromide, cyclopropyliodide, cyclobutylnchloride, cyclobutylbromide, cyclobutyliodide, cyclopentylchloride, cyclopentylbromide, cyclopentyliodide, cyclohexylchloride, cyclohexylbromide, cyclohexyliodide, cyclopropyl methylchloride, cyclopropyl methylbromide, cyclopropyl methyliodide, cyclobutyl methylvchloride, cyclobutyl methylbromide, cyclobutyl methylidide, cyclopentyl methylchloride, cyclopentyl methylbromide, cyclopentyl methyliodide, cyclohexyl methylchloride, cyclohexyl methylbromide, cyclohexyl methylidide, or the like.

Arylhalogen means benzylchloride, benzylbromide, benzyliodide, benzoylchloride, benzoylbromide, benzozyliodide, toluylchloride, toluylbromide, toluylidide, or the like.

Substituted or unsubstituted C₃-C₈ cycloalkyl sulfonate means cyclopropyl sulfonate, cyclobutyl sulfonate, cyclopentyl sulfonate.
cyclohexyl sulfonate, methylcyclopentyl sulfonate, methylcyclobutyl sulfonate, methylcyclopentyl sulfonate, methylcyclohexyl sulfonate, or the like.

Arylsulfonate means benzyl sulfonate, benzoyle sulfonate, tolyl sulfonate, or the like.

More particularly, a compound of the general formula (1a) may be reacted with an alkylating agent or arylation agent in a solvent at the temperature of 25-80°C, for 30 minutes - 20 hours to give the object compound of the general formula (lb).

An alkylating agent or arylation agent may be used in amount of 1.0 - 1.5 equivalent.

Conventional organic solvent such as for example tetrahydrofuran, dichloromethane, acetonitrile, dimethylformamide may be used in the above reaction.

In the above reactions, if any acid material is formed, any basic material may be preferably added as scavenger in order to eliminate the acid material from the reaction phase. Such basic material may be alkali metal hydroxide, alkali earth metal hydroxide, alkali metal oxide, alkali earth metal oxide, alkali metal carbonate, alkali earth metal carbonate, alkali metal hydrogen carbonate, alkali earth metal hydrogen carbonate such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, calcium oxide, potassium carbonate, sodium carbonate, calcium carbonate, magnesium carbonate, magnesium bicarbonate, sodium bicarbonate, calcium bicarbonate or the like, or organic amines.

The compound of the general formula (a) is described in prior art (J. Med. Chem., 1992, 35, 3784, 3792) or may be prepared in a similar method to the art.

Hereinafter the present invention will be described in more details with reference to following examples but it is not intended to limit the scope
of the invention thereinto.

Compounds of the general formula(I) and formula(Ib) are prepared in following examples according to the above-mentioned process.

wherein $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $A$, $X$, $Y$, $Z$ are the same above.
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Example 1

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

a) Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate:

3-Amino-5,6-dimethyl-2-methoxypyridine(1.52g, 0.01mol) and phenylchloroformate(1.56g, 0.01mol) were dissolved in dichloromethane and was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:6) to obtain the titled compound.

yield: 92 %

$^1$H-NMR(CDC$_3$) $\delta$ : 2.18(3H,s), 2.36(3H,s), 4.00(3H,s), 7.31(5H,m), 8.07(1H,s)

b) 1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate(136mg, 0.5mmol) and 1-(2-methylthiophenyl)piperazine(104mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(76mg, 0.5mmol) was added. The mixture was stirred at room temperature for 2 hours and concentrated under the reduced pressure to remove tetrahydrofuran. The concentrate was purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield: 59%

m.p. : 167-169°C

$^1$H NMR(CDC$_3$) $\delta$ : 2.21(3H,s), 2.43(6H,s), 3.06(4H,t), 3.68(4H,t), 4.09(3H,s), 6.89(1H,s), 7.06(1H,m), 7.14(3H,s), 8.26(1H,s)

Example 2

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-isopropenylphenyl)piperazine:

Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield: 62 %
m.p. : 139–140°C
$^1$H NMR (CDCl$_3$) δ : 2.20 (3H, s), 2.21 (6H, s), 3.10 (4H, t), 3.64 (4H, t), 3.84 (3H, s), 5.07 (1H, s), 5.13 (1H, s), 6.64 (1H, s), 6.98 (1H, s), 7.04 (3H, dd), 7.18 (1H, d), 7.91 (1H, s)

Example 3
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperaazine:
Phenyl N-[(5,6-dimethyl-2-methoxypyridin-3-yl)carbamate and
1-(2,3,5,6-tetramethylphenyl)piperazone were reacted by the same way with the example 1 to obtain the titled compound.
yield : 71%
m.p. : 190–192°C
$^1$H NMR (CDCl$_3$) δ : 2.21 (15H, s), 2.42 (3H, s), 3.17 (4H, t), 3.61 (4H, t), 4.08 (3H, s), 6.84 (1H, s), 6.89 (1H, s), 8.26 (1H, s)

Example 4
1-[(5-Ethyl-6-methyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl)piperazone:
Phenyl N-[(5-ethyl-6-methyl-2-methoxypyridin-3-yl)carbamate and
1-(2-methylthiophenyl)piperazone were reacted by the same way with the example 1 to obtain the titled compound.
yield : 56%
m.p. : 160–161°C
$^1$H NMR (CDCl$_3$) δ : 1.19 (3H, t), 2.43 (3H, s), 2.50 (3H, s), 2.58 (2H, q), 3.07 (4H, t), 3.69 (4H, t), 4.15 (3H, s), 6.93 (1H, s), 7.06 (1H, m), 7.14 (3H, m), 8.35 (1H, s)
Mass (EI) m/z : Calcd for C$_{21}$H$_{28}$N$_4$O$_2$ 400.1932, found 400.1925

Example 5
1-[(5-Ethyl-6-methyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-isopropenylphenyl)piperazone:
Phenyl N-[(5-ethyl-6-methyl-2-methoxypyridin-3-yl)carbamate and
1-(2-isopropenylphenyl)piperazone were reacted by the same way with the example 1 to obtain the titled compound.
yield : 51%
m.p. : 185–187°C

\[ ^1H \text{ NMR (CDCl}_3 \delta ] : 1.18(3H, t), 2.21(3H, s), 2.42(3H, s), 2.56(2H, q), 3.08(4H, t), 3.62(4H, t), 4.03(3H, s), 5.08(1H, s), 5.13(1H, s), 6.90(1H, s), 7.02(3H, m), 7.18(1H, d), 8.25(1H, s) \]

Example 6

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:
Phenyl N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 69%
m.p. : 176–177°C

\[ ^1H \text{ NMR (CDCl}_3 \delta ] : 1.19(3H, t), 2.21(12H, s), 2.44(3H, s), 2.57(2H, q), 3.17(4H, t), 3.62(4H, t), 4.06(3H, s), 6.84(1H, s), 6.92(1H, s), 8.30(1H, s) \]

Example 7

1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-thiophenyl)piperazine:
Phenyl N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-(3-thiophenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 63%
m.p. : 108–110°C

\[ ^1H \text{ NMR (CDCl}_3 \delta ] : 1.17(3H, t), 2.37(3H, s), 2.49(2H, q), 3.28(4H, t), 3.60(4H, t), 3.98(3H, s), 6.87(4H, m), 6.98(1H, s), 8.18(1H, s) \]

Example 8

1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 67%
m.p. : 82–84°C

\[ ^1H \text{ NMR (CDCl}_3 \delta ] : 0.94(3H, t), 1.58(2H, m), 2.37(3H, s), 2.49(2H, q), 3.94(4H, q), 5.60(1H, d), 6.84(4H, m), 7.18(1H, s), 8.18(1H, d) \]
3.25(4H,t), 3.66(4H,t), 3.78(6H,s), 3.99(3H,s), 6.07(3H,m), 6.88(1H,s),
8.16(1H,s)
Mass(EI) m/z : Calcd for C_{28}H_{38}N_{4}O_{4} 428.2423, found 428.2447

5 Example 9
1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethylphenyl)piperazine
Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 64%
m.p. : 145-146°C
\(^1\)H NMR(CDC\(_3\)) \(\delta\) : 0.95(3H,t), 1.59(2H,m), 2.29(6H,s), 2.41(3H,s),
2.49(2H,q), 3.24(4H,t), 3.67(4H,t), 3.98(3H,s), 6.59(3H,m), 6.89(1H,s),
8.17(1H,s)
Mass(EI) m/z : Calcd for C_{38}H_{48}N_{4}O_{4} 428.2423, found 428.2385

Example 10
1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-
difluorophenyl)piperazine:
Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(3,5-difluorophenyl)piperazine were reacted by the same way with the
example 1 to obtain the titled compound.
yield : 57%
m.p. : 121-123°C
\(^1\)H NMR(CDC\(_3\)) \(\delta\) : 0.95(3H,t), 1.59(2H,m), 2.38(3H,s), 2.50(2H,q),
3.29(3H,t), 3.66(3H,t), 4.00(3H,s), 6.28(1H,m), 6.36(2H,d), 6.87(1H,s),
8.17(1H,s)

30 Example 11
1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-(2-
methoxyphenyl)piperazine:
Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)carbamate and
1-(2-methoxyphenyl)piperazine were reacted by the same way with the
example 1 to obtain the titled compound.
yield : 71%
m.p. : 109-110°C

$^1$H NMR (CDCl₃) δ : 0.95 (3H, t), 1.59 (2H, m), 2.37 (3H, s), 2.49 (2H, q),
3.12 (4H, t), 3.70 (4H, t), 3.89 (3H, s), 3.97 (3H, s), 6.91 (4H, m), 6.95 (1H, s),
8.19 (1H, s)

Example 12
1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine:
Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 65%
m.p. : 115-116°C
$^1$H NMR (CDCl₃) δ : 1.21 (3H, t), 2.21 (3H, s), 2.65 (2H, q), 3.27 (4H, t),
3.64 (4H, t), 3.79 (6H, s), 3.98 (3H, s), 6.09 (3H, m), 6.86 (1H, s), 8.12 (1H, s)
Mass (EI) m/z : Calcd for C₂₂H₂₃N₄O₄ 414.2267, found 414.2240

Example 13
1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylethylphenyl)piperazine:
Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and
1-(3,5-dimethylethylphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 61%
m.p. : 135-136°C
$^1$H NMR (CDCl₃) δ : 1.22 (3H, t), 2.21 (3H, s), 2.29 (6H, s), 2.65 (2H, q),
3.24 (4H, t), 3.66 (4H, t), 3.98 (3H, s), 6.59 (3H, m), 6.87 (1H, s), 8.12 (1H, s)
Mass (EI) m/z : Calcd for C₂₂H₃₀N₄O₂ 382.2368, found 382.2376

Example 14
1-[(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:
Phenyl N-(6-ethyl-2-methoxy-5-methylpyridin-3-yl)carbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the
example 1 to obtain the titled compound.
yield : 56%
m.p. : 168–170°C
¹H NMR(CDCl₃) δ : 1.21(3H,t), 2.20(2H,s), 2.63(2H,t), 3.28(4H,t), 3.68(4H,t),
3.98(3H,s), 6.41(1H,d), 6.55(1H,d), 6.84(1H,m), 6.87(1H,s), 7.13(1H,t),
8.10(1H,s)
Mass(El) m/z : Calcd for C₂₆H₂₆N₄O₃ 370.2004, found 370.1992

Example 15
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine:
Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 57%
m.p. : 121–122°C
¹H NMR(CDCl₃) δ : 0.96(3H,t), 1.67(2H,m), 2.21(3H,s), 2.58(2H,t),
3.26(4H,t), 3.68(4H,t), 3.79(6H,s), 3.97(3H,s), 6.14(3H,m), 6.89(1H,s),
8.11(1H,s)
Mass(El) m/z : Calcd for C₂₆H₂₆N₄O₄ 428.2423, found 428.2423

Example 16
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-di-
methylphenyl)piperazine:
Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 54%
m.p. : 138–139°C
¹H NMR(CDCl₃) δ : 0.96(3H,t), 1.72(2H,m), 2.21(6H,s), 2.30(3H,s),
2.59(2H,t), 3.28(4H,t), 3.76(4H,t), 3.97(3H,s), 6.70(3H,m), 6.87(1H,s),
8.11(1H,s)
Mass(El) m/z : Calcd for C₂₈H₂₈N₄O₂ 396.2525, found 396.2432

Example 17
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3-
hydroxyphenyl)piperazine:
Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)carbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 52%

m.p. : 153-155°C

$^1$H NMR (CDCl$_3$) $\delta$ : 0.95(3H,t), 1.69(2H,m), 2.19(3H,s), 2.59(2H,t), 3.22(4H,t), 3.68(4H,t), 3.97(3H,s), 6.42(1H,d), 6.52(1H,d), 6.87(1H,s), 7.12(1H,t), 8.09(1H,s)

Mass (EI) m/z : Calcd for C$_{21}$H$_{28}$N$_4$O$_3$ 384.2161, found 384.2153

Example 18

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 59%

m.p. : 143-144°C

$^1$H NMR (CDCl$_3$) $\delta$ : 2.10(2H,m), 2.87(4H,m), 3.12(4H,t), 3.70(4H,t), 3.78(6H,s), 4.00(3H,s), 6.08(3H,m), 6.90(1H,s), 8.24(1H,s)

Example 19

1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 55%

m.p. : 183-185°C

$^1$H NMR (CDCl$_3$) $\delta$ : 2.08(2H,m), 2.28(6H,s), 2.87(4H,m), 3.22(4H,t), 3.67(4H,t), 4.00(3H,s), 6.57(3H,m), 6.89(1H,s), 8.24(1H,s)

Example 20

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinoline-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 54%
m.p. : 161-163°C

$^1$H NMR(CDC$_3$) $\delta$: 1.75(2H,m), 1.84(2H,m), 2.67(2H,t), 2.73(2H,t),
3.27(4H,t), 3.71(4H,t), 3.79(6H,s), 3.97(3H,s), 6.10(3H,m), 6.90(1H,s),
8.07(1H,s)

Example 21

1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 51%
m.p. : 143-144°C

$^1$H NMR(CDC$_3$) $\delta$: 1.75(2H,m), 1.84(2H,m), 2.30(6H,s), 2.68(2H,t),
2.72(2H,t), 3.26(4H,t), 3.67(4H,t), 3.97(3H,s), 6.61(3H,m), 6.91(1H,s),
8.07(1H,s)

Example 22

1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate(200mg, 0.7mmol) and 1-(3,5-dimethylphenyl)piperazine(154mg, 0.7mmol) were dissolved in anhydrous tetrahydrofuran and DBU(106mg) was added thereto. The mixture was stirred at room temperature for 2 hours and concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography( ethylacetate : hexane = 1 : 2 ) to obtain the titled compound.

yield : 50%
m.p. : 192-193°C

$^1$H NMR(CDC$_3$) $\delta$: 2.21(3H,s), 2.29(6H,s), 2.36(3H,s), 3.33(4H,t),
3.96(3H,s), 4.09(4H,t), 6.57(3H,m), 7.33(1H,s), 8.11(1H,s)

Mass(EI) m/z : Calcd for C$_{29}$H$_{36}$N$_4$O$_5$S$_1$ 384.1983, found 384.1992
Example 23
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:
Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and
1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield: 47%
m.p.: 60-62°C
$^1$H NMR(CDC$_3$) $\delta$: 2.21(3H,s), 2.36(3H,s), 3.39(4H,t), 3.96(3H,s),
4.10(3H,t), 6.29(3H,m), 7.33(1H,s), 8.14(1H,s)

Example 24
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:
Phenyl N-(5,6-dimethyl-2-methoxypyridin-3-yl)thiocarbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield: 43%
m.p.: 185-186°C
$^1$H NMR(CDC$_3$) $\delta$: 2.14(3H,s), 2.36(3H,s), 3.25(4H,t), 3.89(3H,s),
4.09(4H,t), 6.30(1H,d), 6.36(2H,m), 7.03(1H,t), 7.48(1H,s), 8.56(1H,s)

Example 25
1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(2-methoxy-6-methyl-5-propylpyridin-3-yl)thiocarbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield: 55%
m.p.: 143-144°C
$^1$H NMR(CDC$_3$) $\delta$: 0.93(3H,t), 1.66(2H,m), 2.17(3H,s), 2.65(2H,t),
3.38(4H,t), 3.79(6H,s), 3.98(3H,s), 4.15(4H,t), 6.11(3H,m), 7.43(1H,s),
8.25(1H,s)

Example 26
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5
-dimethoxyphenyl)piperazine:
Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 22 to obtain the titled compound.
yield : 52%

m.p. : 183-184°C
'\textsuperscript{1}H NMR(CDC\textsubscript{5}) \delta : 0.98(3H,t), 1.72(2H,m), 2.17(3H,s), 2.62(2H,t),
3.39(4H,t), 3.79(6H,s), 3.96(3H,s), 4.19(4H,t), 6.15(3H,m),
7.42(1H,s), 8.08(1H,s)

Mass(El) m/z : Calcd for C\textsubscript{23}H\textsubscript{28}N\textsubscript{4}O\textsubscript{5}S\textsubscript{1} 444.2195, found 444.2171

Example 27
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3,5
-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 22 to obtain the titled compound.
yield : 49%

m.p. : 195-197°C

'\textsuperscript{1}H NMR(CDC\textsubscript{5}) \delta : 0.98(3H,t), 1.73(2H,m), 2.18(6H,s), 2.34(3H,s),
2.62(2H,t), 3.47(4H,t), 3.96(3H,s), 4.01(4H,t), 6.59(3H,m), 7.02(1H,s),
7.99(1H,s)

Mass(El) m/z : Calcd for C\textsubscript{23}H\textsubscript{28}N\textsubscript{4}O\textsubscript{5}S\textsubscript{1} 412.2296, found 412.2266

Example 28
1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminothiocarbonyl]-4-(3-
hydroxyphenyl)piperazine:
Phenyl N-(2-methoxy-5-methyl-6-propylpyridin-3-yl)thiocarbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the
example 22 to obtain the titled compound.
yield : 48%

m.p. : 160-162°C

'\textsuperscript{1}H NMR(CDC\textsubscript{5}) \delta : 0.98(3H,t), 1.72(2H,m), 2.22(3H,s), 2.61(3H,t),
3.31(4H,t), 3.95(3H,s), 4.10(4H,t), 6.45(3H,m), 7.12(1H,t), 7.41(1H,s),
8.08(1H,s)

Mass(El) m/z : Calcd for C\textsubscript{21}H\textsubscript{28}N\textsubscript{4}O\textsubscript{5}S\textsubscript{1} 400.1932, found 400.1969
Example 29
1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield : 55%
m.p. : 169-170°C

1H NMR(CDCl3) δ: 2.10(2H,m), 2.89(4H,m), 3.30(4H,t), 3.77(6H,s), 3.98(3H,s), 4.20(4H,t), 6.05(3H,m), 7.37(1H,s), 8.25(1H,s)

Example 30
1-[N-(2-Methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl) thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield : 53%
m.p. : 159-161°C

1H NMR(CDCl3) δ: 2.09(2H,m), 2.28(6H,s), 2.87(4H,m), 3.67(4H,t), 4.00(3H,s), 4.21(4H,t), 6.57(3H,m), 6.93(3H,m), 8.24(1H,s)

Example 31
1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)thiocarbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 22 to obtain the titled compound.
yield : 56%
m.p. : 160-161°C

1H NMR(CDCl3) δ: 1.77(2H,m), 1.83(2H,m), 2.70(2H,t), 2.76(2H,t), 3.38(4H,t), 3.79(6H,s), 3.96(3H,s), 4.16(4H,t), 6.12(3H,m), 7.45(1H,s), 8.03(1H,s)

Example 32
1-[(2-Methoxy-5,6,7,8-tetrahydroquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(2-methoxy-5,6,7,8-tetrahydroquinolin-3-yl)thiocarbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 22 to obtain the titled compound.
yield : 54%
m.p. : 200-201°C
$^1$H NMR (CDCl$_3$) $\delta$: 1.77 (2H, m), 1.84 (2H, m), 2.34 (6H, s), 2.71 (3H, t),
2.75 (3H, t), 3.47 (4H, t), 3.97 (3H, s), 4.42 (4H, t), 6.35 (3H, m), 6.91 (1H, s),
7.91 (1H, s)

Example 33
1-[(5,6-Dimethyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(5,6-dimethyl-2-methylaminopyridin-3-yl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 53%
m.p. : 150-151°C
$^1$H NMR (CDCl$_3$) $\delta$: 2.29 (3H, s), 2.48 (3H, s), 3.29 (4H, t), 3.45 (3H, s),
3.77 (6H, s), 3.79 (4H, t), 6.10 (3H, m), 7.40 (1H, s)

Example 34
1-[(5,6-Dimethyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(5,6-dimethyl-2-methylaminopyridin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 1 to obtain the titled compound.
yield : 52%
m.p. : 160-162°C
$^1$H NMR (CDCl$_3$) $\delta$: 2.30 (9H, s), 2.48 (3H, s), 3.31 (4H, t), 3.46 (3H, s),
3.78 (4H, t), 6.60 (3H, m), 7.41 (1H, s)

Example 35
1-[(5-Ethyl-6-methyl-2-methylaminopyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(5-ethyl-6-methyl-2-methylaminopyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 56%

m.p. : 143-145°C

$^1$H NMR (CDCl$_3$) δ : 1.22 (3H, t), 2.28 (6H, s), 2.52 (3H, s), 2.72 (2H, q), 3.29 (4H, t), 3.45 (3H, s), 3.78 (4H, t), 6.59 (3H, m), 7.41 (1H, s)

Example 36

1-[(2-Methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 49%

m.p. : 148-150°C

$^1$H NMR (CDCl$_3$) δ : 2.09 (2H, m), 2.95 (4H, m), 3.30 (4H, t), 3.47 (3H, s), 3.77 (4H, t), 3.80 (6H, s), 6.10 (3H, m), 7.49 (1H, s)

Example 37

1-[(2-Methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methylamino-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.

yield : 48%

m.p. : 185-187°C

$^1$H NMR (CDCl$_3$) δ : 2.14 (2H, m), 2.29 (6H, s), 2.95 (4H, m), 3.32 (4H, t), 3.47 (3H, s), 3.79 (4H, t), 6.59 (3H, m), 7.48 (1H, s)

Example 38

1-(5,6-Dimethyl-2-(4′-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[5,6-dimethyl-2-(4′-t-butoxycarbonylpiperazinyl)pyridin-3-yl]carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield: 58%
m.p.: 74–75°C
$^1$H NMR (CDCl₃) δ: 1.46 (9H, s), 2.20 (3H, s), 2.21 (3H, s), 2.90 (4H, t), 3.20 (4H, t), 3.55 (4H, t), 3.65 (4H, t), 3.98 (3H, s), 6.02 (3H, m), 8.20 (1H, s)

Example 39
1-(5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-[5,6-dimethyl-2-(4'-butoxycarbonylpiperazinyl)pyridin-3-yl]carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield: 56%
m.p.: 155–156°C
$^1$H NMR (CDCl₃) δ: 1.48 (9H, s), 2.22 (3H, s), 2.29 (6H, s), 2.35 (3H, s), 2.95 (4H, t), 3.25 (4H, t), 3.57 (4H, t), 3.67 (4H, t), 6.59 (3H, m), 8.21 (1H, s)

Example 40
1-(5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-[5-ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield: 52%
m.p.: 119–120°C
$^1$H NMR (CDCl₃) δ: 1.25 (3H, t), 1.48 (9H, s), 2.38 (3H, s), 2.51 (2H, q), 2.96 (4H, t), 3.27 (4H, t), 3.58 (8H, m), 3.78 (6H, s), 6.08 (3H, m), 8.24 (1H, s)

Example 41
1-(5-Ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-[5-ethyl-6-methyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 1 to obtain the titled compound.
yield: 50%
m.p. : 126-128°C

$^1$H NMR (CDCl$_3$) $\delta$ : 1.20(3H, t), 1.49(9H, s), 2.29(6H, s), 2.39(3H, s),
2.52(2H, q), 2.98(4H, t), 3.23(4H, t), 3.59(8H, m), 6.59(3H, m), 7.58(1H, s),
8.26(1H, s)

Example 42

1-[(5,6-Dimethyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine(0.218g, 0.4mmol) was dissolved in dichloromethane : nitromethane = 2 : 1(10ml) and anisole(0.26g, 2.4mmol) and aluminum chloride(0.3g, 2.4mmol) were added slowly thereto. The mixture was stirred at room temperature for 20min. Distilled water(50ml) was added into the mixture and the mixture was made basic with saturated NaHCO$_3$ and extracted with dichloromethane and then concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography(methanol : dichloromethane = 8:1) to obtain the titled compound.

yield : 89%

m.p. : oil phase

$^1$H NMR (CDCl$_3$) $\delta$ : 2.21(3H, s), 2.35(3H, s), 3.02(4H, t), 3.34(4H, t),
3.59(4H, t), 3.62(4H, t), 3.78(6H, s), 6.08(3H, m), 8.18(1H, s)

Example 43

1-[(5,6-Dimethyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5,6-Dimethyl-2-(4'-t-butoxycarbonylpiperazinyl)pyridin-3-yl]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 85%

m.p. : 103-105°C

$^1$H NMR (CDCl$_3$) $\delta$ : 2.16(3H, s), 2.24(6H, s), 2.40(3H, s), 3.30(4H, t),
3.44(4H, t), 3.50(4H, t), 3.81(4H, t), 6.95(3H, m), 7.72(1H, s)

Example 44
1-[(5-Ethyl-6-methyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Ethyl-6-methyl-2-(4′-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 88%
m.p. : 68-70°C
$^1$H NMR(CDC$_3$) $\delta$: 1.20(3H,t), 2.40(3H,s), 2.52(2H,q), 2.75(4H,t), 3.32(4H,t), 3.70(8H,m), 3.78(6H,s), 6.09(3H,m), 7.68(1H,s), 8.23(1H,s)

Example 45
1-[(5-Ethyl-6-methyl-2-piperazinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(5-Ethyl-6-methyl-2-(4′-t-butoxycarbonylpiperazinyl)pyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 42 to obtain the titled compound.

yield : 85%
m.p. : 100-102°C
$^1$H NMR(CDC$_3$) $\delta$: 1.20(3H,t), 2.28(6H,s), 2.39(3H,s), 2.65(2H,q), 2.76(4H,t), 3.00(4H,t), 3.23(4H,t), 3.70(4H,t), 6.58(3H,m), 7.66(1H,s), 8.24(1H,s)

Example 46
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate(200mg, 0.67mmol) and 1-[(3,5-dimethoxyphenyl)piperazine(150mg, 0.67mmol) were dissolved in anhydrous tetrahydrofuran(15ml) and DBU(100mg, 0.67mmol) was added. The mixture was stirred at room temperature for 2 hrs and concentrated under the reduced pressure to remove tetrahydrofuran. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 83%
m.p. : 149-151°C
$^1$H NMR(CDC$_3$) $\delta$: 2.57(3H,s), 2.65(3H,s), 3.28(4H,t, J=4.65Hz), 3.70(4H,t,
J=4.65Hz), 3.79(6H,s), 4.06(3H,s), 6.09(1H,s), 6.14(2H,d), 6.94(1H,s), 8.87(1H,s)

Example 47
5 1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-[(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 82%
m.p. : 66-69°C
$^1$H NMR(CDCls) δ : 2.31(6H,s), 2.57(3H,s), 2.65(3H,s), 3.08(4H,t), 3.30(4H,t), 4.10(3H,s), 6.71(2H,d), 6.94(1H,s), 8.89(1H,s)

Example 48
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-[(3,5-difluorophenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 77%
m.p. : 180-181°C
$^1$H NMR(CDCls) δ : 2.57(3H,s), 2.65(3H,s), 3.33(4H,t,J=5.0Hz), 3.74(4H,t, J=5.0Hz), 4.07(3H,s), 6.37(1H,s), 6.46(2H,d), 6.93(1H,s), 8.85(1H,s)

Example 49
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and 1-[(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.

yield : 81%
m.p. : oil phase
$^1$H NMR(CDCls) δ : 2.57(3H,s), 2.65(3H,s), 3.34(4H,t), 3.78(4H,t), 4.04(3H,s), 6.93(3H,m), 8.80(1H,s)
Example 50
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:
Pheny N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and
1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.
yield : 81%
m.p. : 173-174°C
'H NMR(CDCl₃) δ : 2.29(6H,s), 2.58(3H,s), 2.65(3H,s), 2.98(4H,t), 3.70(4H,t), 4.06(3H,s), 6.91(1H,d), 6.97(1H,s), 7.10(1H,t), 8.89(1H,s)

Example 51
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and
1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.
yield : 79%
m.p. : 153-154°C
'H NMR(CDCl₃) δ : 2.58(3H,s), 2.65(3H,s), 3.15(4H,t), 3.73(4H,t), 3.90(3H,s), 4.06(3H,s), 6.91(1H,d), 6.96(1H,d), 6.97(1H,s), 7.10(1H,t), 8.89(1H,s)

Example 52
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:
Pheny N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)carbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 46 to obtain the titled compound.
yield : 76%
m.p. : oil phase
'H NMR(CDCl₃) δ : 2.60(3H,s), 2.72(3H,s), 3.34(4H,t), 3.79(4H,t), 3.98(3H,s), 6.45(3H,m), 6.98(1H,m), 8.97(1H,s)

Example 53
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5...
-dimethoxyphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 22 to obtain the titled compound.

yield: 77%
m.p.: 167-169°C
\(^1\)H NMR(CDC\(_3\)) \(\delta: 2.58(3\text{H}, s), 2.68(3\text{H}, s), 3.47(4\text{H}, t), 3.81(6\text{H}, s), 4.05(3\text{H}, s), 4.36(4\text{H}, t), 6.42(3\text{H}, m), 7.49(1\text{H}, s), 9.05(1\text{H}, s)\)

Example 54
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-
dimethylphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 22 to obtain the titled compound.

yield: 75%
m.p.: 176-177°C
\(^1\)H NMR(CDC\(_3\)) \(\delta: 2.34(6\text{H}, s), 2.58(3\text{H}, s), 2.68(3\text{H}, s), 3.48(4\text{H}, t), 4.06(3\text{H}, s), 4.43(4\text{H}, t), 7.05(3\text{H}, m), 7.52(1\text{H}, s), 9.04(1\text{H}, s)\)

Example 55
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3-
hydroxyphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)thiocarbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the
example 22 to obtain the titled compound.

yield: 71%
m.p.: 114-115°C
\(^1\)H NMR(CDC\(_3\)) \(\delta: 2.56(3\text{H}, s), 2.75(3\text{H}, s), 3.68(4\text{H}, t), 4.05(3\text{H}, s), 4.45(4\text{H}, t), 7.30(4\text{H}, m), 9.03(1\text{H}, s)\)

Mass(El) m/z: Calcd for C\(_{22}\)H\(_{26}\)N\(_4\)O\(_5\)S: 458.1987, found 458.2527

Example 56
1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]
-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine (100mg, 0.23mmol) was dissolved in anhydrous ethanol (15ml) and NaBH₄ (8.66mg) was added. The reaction solution was stirred at room temperature for 2 hours. The mixture was concentrated under the reduced pressure to remove ethanol and purified by column chromatography (ethylacetate : hexane = 2:1) to obtain the titled compound.

yield: 97%
m.p.: 124-126°C

1H NMR(CDC₃) δ: 1.48(3H,d), 2.42(3H,s), 3.27(4H,t), 3.69(4H,t), 3.79(6H,s), 3.99(3H,s), 5.03(1H,q), 6.09(1H,s), 6.15(2H,d), 6.90(1H,s), 8.46(1H,s)

Mass(EI) m/z: Calcd for C₂₂H₂₆N₄O₅ 430.2216, found 430.2265

Example 57

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield: 95%
m.p.: 153-154°C

1H NMR(CDC₃) δ: 1.48(3H,d), 2.30(6H,s), 2.42(3H,s), 3.26(4H,t), 3.68(4H,t), 3.99(3H,s), 5.05(1H,q), 6.71(2H,d), 6.96(1H,s), 8.46(1H,s)

Mass(EI) m/z: Calcd for C₂₂H₂₆N₄O₃ 398.2317, found 398.2343

Example 58

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield: 96%
m.p.: 100-102°C

1H NMR(CDC₃) δ: 1.47(3H,d), 1.59(3H,s), 2.25(3H,s), 2.28(3H,s), 2.43(3H,s), 2.93(4H,t), 3.66(4H,t), 3.99(3H,s), 5.05(1H,q), 6.93(3H,m), 7.11(1H,m), 8.48(1H,s)
Example 59
1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}
-4-(3,5-difluorophenyl)piperazine:

5 1-{[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-
  difluorophenyl)piperazine was reacted by the same way with the
example 56 to obtain the titled compound.
yield : 97%
m.p. : 184-186°C

1 H NMR(CDCls) δ : 1.48(3H,d), 2.50(3H,s), 3.30(4H,t), 3.70(4H,t),
4.11(3H,s), 5.06(1H,q), 6.33(1H,s), 6.42(2H,d), 6.92(1H,s), 8.54(1H,s)

Example 60
1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}

15 -4-(3,5-dichlorophenyl)piperazine:
1-{[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(3,5-
dichlorophenyl)piperazine was reacted by the same way with the
example 56 to obtain the titled compound.
yield : 95%
m.p. : 197-200°C

1 H NMR(CDCls) δ : 1.46(3H,d), 2.41(3H,s), 3.28(4H,t), 3.66(4H,t),
3.96(3H,s), 5.20(1H,q), 7.02(3H,m), 8.42(1H,s)

Example 61
25 1-{[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}
-4-(2-methoxyphenyl)piperazine:
1-{[5-Acetyl-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl}-4-(2-
methoxyphenyl)piperazine was reacted by the same way with the
example 56 to obtain the titled compound.

30 yield : 97%
m.p. : 88-90°C

1 H NMR(CDCls) δ : 1.47(3H,d), 2.42(3H,s), 3.11(4H,t), 3.70(4H,t),
3.89(3H,s), 3.99(3H,s), 5.03(1H,q), 6.89(3H,m), 6.94(1H,s), 7.05(1H,m),
8.48(1H,s)

Example 62
1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield: 87%
m.p.: 194-196°C

$^1$H NMR (CDCl$_3$) δ: 1.47 (3H, d), 2.41 (3H, s), 3.27 (4H, t), 3.79 (4H, t), 3.98 (3H, s), 5.04 (1H, q), 6.57 (3H, m), 6.90 (1H, s), 7.13 (1H, t), 8.41 (1H, s)

Example 63

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield: 89%
m.p.: 189-190°C

$^1$H NMR (CDCl$_3$) δ: 1.47 (3H, d), 2.43 (3H, s), 3.35 (4H, t), 3.78 (6H, s), 3.97 (3H, s), 4.09 (4H, t), 5.05 (1H, q), 6.07 (3H, m), 7.35 (1H, s), 8.42 (1H, s)

Example 64

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 56 to obtain the titled compound.

yield: 88%
m.p.: 170-172°C

$^1$H NMR (CDCl$_3$) δ: 1.46 (3H, d), 2.29 (6H, s), 2.43 (3H, s), 3.43 (4H, t), 3.97 (3H, s), 4.10 (4H, t), 5.06 (1H, q), 6.60 (3H, m), 7.37 (1H, s), 8.40 (1H, s)

Example 65

1-[(5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine (214 mg, 0.50 mmol) was dissolved in tetrahydrofuran (10 ml) and \( \text{CH}_3\text{MgBr} \) (0.50 ml, 1.50 mmol) was added slowly. The mixture solution was refluxed for 15 hrs and concentrated under the reduced pressure to remove the solvent and extracted with ethylacetate, dried and filtered. The resultant was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

**yield**: 84%

**m.p.**: 146-148°C

1. H NMR (CDCl₃) \( \delta \): 1.64 (6H, s), 2.64 (3H, s), 3.25 (4H, t), 3.67 (4H, t), 3.78 (6H, s), 3.99 (3H, s), 6.07 (3H, m), 6.86 (1H, s), 8.47 (1H, s)

**Example 66**

1-((5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl)]aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine:

1-((5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 65 to obtain the titled compound.

**yield**: 81%

**m.p.**: oil phase

1. H NMR (CDCl₃) \( \delta \): 1.64 (6H, s), 2.29 (6H, s), 2.65 (3H, s), 3.24 (4H, t), 3.67 (4H, t), 3.99 (3H, s), 6.59 (3H, m), 7.05 (1H, s), 8.48 (1H, s)

**Example 67**

1-((5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-((5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine (214 mg, 0.50 mmol) was dissolved in tetrahydrofuran (10 ml) and \( \text{C}_7\text{H}_8\text{MgBr} \) (0.50 mg, 1.50 mmol) was added slowly. The mixture solution was refluxed for 15 hours and concentrated under the reduced pressure to remove the solvent and extracted with ethylacetate, dried and filtered. The resultant was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

**yield**: 76%

**m.p.**: 127-129°C
$^1$H NMR (CDCl$_3$) $\delta$: 0.83 (3H, t), 1.63 (3H, s), 1.94 (2H, m), 2.61 (3H, s), 3.26 (4H, t), 3.68 (4H, t), 3.79 (6H, s), 3.99 (3H, s), 6.08 (3H, m), 6.86 (1H, s), 8.44 (1H, s)

5 Example 68
1-[(5-(1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 67 to obtain the titled compound.
yield: 74%
m.p.: 164-165°C
$^1$H NMR (CDCl$_3$) $\delta$: 0.83 (3H, t), 1.60 (3H, s), 1.95 (2H, m), 2.29 (6H, s), 2.61 (3H, s), 3.23 (4H, t), 3.67 (4H, t), 3.99 (3H, s), 6.59 (3H, m), 6.87 (1H, s), 8.45 (1H, s)

Example 69
1-[[4-(3,5-Dimethoxyphenyl)piperazino]carbonyl]amino)-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate:
20 Triphenylphosphin(e(262mg, 1.0mmol) was dissolved in tetrahydrofuran(15ml) and diethyl azodicarboxylate(157μl, 1.0mmol) was added and then the mixture was stirred at 0°C for 30min.
1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(213mg, 0.5mmol) and thioacetic acid(72μl, 1.0mmol) were dissolved in tetrahydrofuran and was added into the above solution. The mixture solution was stirred at 0°C for 1hour and at room temperature for 1hour and then was concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.
yield: 62%
m.p.: oil phase
$^1$H NMR (CDCl$_3$) $\delta$: 1.55 (3H, d), 2.20 (3H, s), 2.39 (3H, s), 3.15 (4H, t), 3.57 (4H, t), 3.69 (6H, s), 3.90 (3H, s), 4.74 (1H, q), 6.01 (3H, m), 6.89 (1H, s), 8.33 (1H, s)
Example 70
1-[(4-(3,5-Dimethylphenyl)piperazinocarbonyl)amino]-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate:
1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 69 to obtain the titled compound.
yield : 60%
m.p. : oil phase
$^1$H NMR (CDCl$_3$) $\delta$: 1.60 (3H, d), 2.26 (6H, s), 2.52 (3H, s), 3.20 (4H, t),
3.64 (4H, t), 3.96 (3H, s), 4.80 (1H, q), 6.56 (3H, m), 6.91 (1H, s), 8.38 (1H, s)

Example 71
1-[(2-Methoxy-6-methyl-5-(1-sulfanylmethyl)]aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-([(4-(3,5-Dimethoxyphenyl)piperazinocarbonyl)amino]-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate(180mg, 0.37mmol) was dissolved in tetrahydrofuran(15ml) and LiAlH$_4$(15mg, 0.4mmol) was added and then the mixture was stirred at 0°C for 20min. 2N-HCl was added the above solution. The mixture was concentrated under the reduced pressure to remove the solvent and extracted with dichloromethane, dried and filtered. The resultant was concentrated under the reduced pressure and purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.
yield : 88%
m.p. : oil phase
$^1$H NMR (CDCl$_3$) $\delta$: 1.42 (3H, d), 2.39 (3H, s), 3.25 (4H, t), 3.66 (4H, t),
3.76 (6H, s), 3.96 (3H, s), 5.02 (1H, q), 6.17 (3H, m), 6.87 (1H, s), 8.41 (1H, s)

Example 72
1-[(2-Methoxy-6-methyl-5-(1-sulfanylmethyl)]aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(5-([(4-(3,5-Dimethylphenyl)piperazinocarbonyl)amino]-6-methoxy-2-methylpyridin-3-yl]ethyl ethanthioate was reacted by the same way with the example 71 to obtain the titled compound.
yield : 87%
m.p. : oil phase
- 45 -

$^1$H NMR (CDCl$_3$) $\delta$: 1.43 (3H, d), 2.28 (6H, s), 2.40 (3H, s), 3.25 (4H, t), 3.72 (4H, t), 5.03 (1H, q), 6.64 (3H, m), 6.88 (1H, s), 8.42 (1H, s)

Example 73

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was dissolved in chloroform (15 ml) and pyridinium p-toluensulfonate (60 mg, 0.23 mmol) was added and then the mixture solution was refluxed 16 hours. The above solution was concentrated under the reduced pressure to remove chloroform and purified by column chromatography to obtain the titled compound.

yield: 93%
m.p.: 140-141°C

$^1$H NMR (CDCl$_3$) $\delta$: 2.43 (3H, s), 3.27 (4H, t), 3.69 (4H, t), 3.79 (6H, s), 4.00 (3H, s), 5.25 (1H, d), 5.65 (1H, d), 6.08 (1H, s), 6.13 (2H, d), 6.82 (1H, d), 6.91 (1H, s), 8.53 (1H, s)

Mass (EI) m/z: Calcd for C$_{22}$H$_{28}$N$_4$O$_4$ 412.2110, found 412.2119

Example 74

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield: 94%
m.p.: 131-132°C

$^1$H NMR (CDCl$_3$) $\delta$: 1.57 (3H, s), 2.31 (6H, s), 2.43 (1H, s), 3.25 (4H, t), 3.68 (4H, t), 4.00 (3H, s), 5.25 (1H, d), 5.65 (1H, d), 6.60 (3H, m), 6.82 (1H, dd), 6.92 (1H, s), 8.53 (1H, s)

Mass (EI) m/z: Calcd for C$_{22}$H$_{28}$N$_4$O$_2$ 380.2212, found 380.2236

Example 75

1-[(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

1-[(5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]
-4- (3,5-difluorophenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield : 93%
m.p. : 160-161°C

1H NMR (CDCl₃) δ : 2.44(3H,s), 3.30(4H,t,J=5.5Hz), 3.68(4H,t,J=5.5Hz), 4.01(3H,s), 5.26(1H,d), 5.65(1H,d), 6.30(1H,s), 6.39(2H,d), 6.81(1H,dd), 8.53(1H,s)

Mass (EI) m/z : Calcd for C₂₂H₂₇N₄O₄ 412.2110, found 412.2102

Example 76
1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

- [(5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 73 to obtain the titled compound.

yield : 96%
m.p. : 83-85°C

1H NMR (CDCl₃) δ : 2.01(3H,s), 2.38(3H,s), 3.25(4H,t), 3.66(4H,t), 3.78(6H,s), 3.99(3H,s), 4.86(1H,s), 5.30(1H,s), 6.11(3H,m), 6.90(1H,s), 8.18(1H,s)

Example 77
1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with example 73 to obtain the titled compound.

yield : 93%
m.p. : 140-142°C

1H NMR (CDCl₃) δ : 2.01(3H,s), 2.29(6H,s), 2.28(3H,s), 3.23(4H,t), 3.66(4H,t), 3.99(3H,s), 4.86(1H,s), 5.18(1H,s), 6.59(3H,m), 6.91(1H,s), 8.18(1H,s)

Example 78
Ethyl 2-[1-[(4-(3,5-dimethoxyphenyl)piperazino)carbonyl]amino]-6-methoxy-2-methylpyridin-3-yl]ethoxyacetate:
1-[[5-(1-Hydroxy)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (0.5mmol) was dissolved in dimethylformamide (15ml) and NaH (18.5mg, 0.5mmol) was added and then the mixture solution was stirred at room temperature for 15min.

Ethylbromoacetate (83.5mg, 0.5mmol) was added into the above mixture and stirred at room temperature for 3 hours. The mixture was concentrated under the reduced pressure to remove the solvent and purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield: 89%
m.p.: oil phase

$^1$H NMR (CDCl₃) δ: 1.25 (3H, t), 1.34 (3H, d), 2.42 (3H, s), 3.00 (4H, t), 3.29 (4H, t), 3.74 (6H, s), 3.97 (3H, s), 4.16 (4H, s), 4.53 (1H, q), 6.03 (3H, m), 7.58 (1H, s)

Example 79

4-[[1-[[4-(3,5-Dimethoxyphenyl)piperazino]carbonyl]amino]-6-methoxy-2-methylpyridin-3-yl]ethoxy]-4-oxobutanoic acid:

1-[[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl] -4-(3,5-dimethoxyphenyl)piperazine (107mg, 0.25mmol) and dimethylaminopyridine (3mg, 0.025mmol) were dissolved in pyridine and anhydrous succinic acid (50mg, 0.5mmol) was added. The mixture was stirred at room temperature for 5 hrs. Distilled water was added into the above mixture. The above solution was extracted with CH₂Cl₂ and the organic phase washed with 1N-HCl and then concentrated under the reduced pressure to remove the solvent. The concentrate was purified by column chromatography (dichloromethane : methanol = 20:1) to obtain the titled compound.

yield: 78%
m.p.: 158-160°C

$^1$H NMR (CDCl₃) δ: 1.42 (3H, d), 2.43 (3H, s), 2.61 (4H, m), 3.24 (4H, t), 3.66 (4H, t), 3.76 (6H, s), 3.95 (3H, s), 5.94 (1H, q), 6.04 (3H, m), 6.89 (1H, s), 8.13 (1H, s)

Example 80

4-[[1-[[4-(3,5-Dimethylphenyl)piperazino]carbonyl]amino]-6-methoxy-
2-methylpyridin-3-yl\(\text{ethoxy})\)-4-oxobutanoic acid:

\[1-[(5-(1\text{-hydroxyethyl})-2\text{-methoxy-6-methylpyridin-3-yl})\text{aminocarbonyl}]\]

\[-4-(3,5\text{-dimethylphenyl})\text{piperazine} \] was reacted by the same way with
the example 79 to obtain the titled compound.

yield: 76%
m.p.: 138-140°C

\(^1\text{H} \text{NMR (CDCl}_3\text{)} \delta: 1.43(3\text{H,d}), 2.27(6\text{H,s}), 2.55(3\text{H,s}), 2.65(4\text{H,m}),
3.24(4\text{H,t}), 3.69(4\text{H,t}), 3.95(3\text{H,s}), 5.95(1\text{H,q}), 6.60(3\text{H,m}), 6.88(1\text{H,s}),
8.11(1\text{H,s})\]

Example 81

1-[(2-Methoxyquinolin-3-yl)\text{aminocarbonyl}]\-4-(3,5\text{-dimethoxyphenyl})
piperazine:

a) Phenyl N-(2-methoxyquinolin-3-yl)\text{carbamate}:

3-Amino-2-methoxyquinoline\(4\text{g}, 23\text{mmol}\) and phenyl
chloroformate\(4.04\text{g}, 25\text{mmol}\) were dissolved in dichloromethane and
stirred at room temperature for 2 hours. The above mixture was
concentrated under the reduced pressure to remove dichloromethane and
purified by column chromatography\(\text{hexane : ether = 8:1}\) to obtain the
titled compound.

yield: 75%
m.p.: oil phase

\(^1\text{H} \text{NMR (CDCl}_3\text{)} \delta: 4.01(3\text{H,s}), 7.30(5\text{H,s}), 7.41(1\text{H,t}), 7.70(1\text{H,d}),
7.71(1\text{H,d}), 8.71(1\text{H,s})\]

b) 1-[(2-Methoxyquinolin-3-yl)\text{aminocarbonyl}]\-4-(3,5\text{-dimethoxyphenyl})
piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)\text{carbamate}(148mg, 0.5mmol) and
1-(3,5-dimethoxyphenyl)piperazine\(112\text{mg}, 0.5\text{mmol}\) were dissolved in
anhydrous tetrahydrofuran and DBU\(117\text{mg}, 0.75\text{mmol}\) was added. The
solution was stirred at room temperature for 2 hours. The mixture was
concentrated under the reduced pressure to remove tetrahydrofuran and
purified by column chromatography\(\text{hexane : ether = 5:1}\) to obtain the
titled compound.

yield: 81%
m.p. : 200–201°C
$^1$H NMR (CDCl$_3$): $\delta$ 3.31(4H,t,J=5.0Hz), 3.74(4H,t), 3.79(6H,s), 4.17(3H,s), 6.09(1H,s), 6.17(2H,s), 7.35(1H,t), 7.49(1H,t), 7.71(1H,d), 7.78(1H,d), 8.78(1H,s)

Mass(EI) m/z : Calcd for C$_{25}$H$_{28}$N$_4$O$_4$ 422.1954, found 422.1952

Example 82
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 79%

m.p. : 143–145°C
$^1$H NMR (CDCl$_3$): $\delta$ 2.30(6H,s), 3.29(4H,t), 3.80(4H,t), 4.18(3H,s), 6.62(3H,m), 7.36(1H,t), 7.49(1H,t), 7.71(1H,d), 7.78(1H,d), 8.79(1H,s)

Mass(EI) m/z : Calcd for C$_{31}$H$_{28}$N$_4$O$_2$ 390.2055, found 390.2066

Example 83
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 83%

m.p. : 174–175°C
$^1$H NMR (CDCl$_3$): $\delta$ 2.20(3H,s), 2.39(3H,s), 3.28(4H,t), 3.69(4H,t), 3.93(3H,s), 5.98(1H,s), 6.30(1H,t), 6.37(1H,s), 6.39(1H,s), 6.63(1H,s)

Example 84
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 78%
Example 85

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine;
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1- (3,5-dichlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 56%

m.p. : 156-158°C

1H NMR (CDCl3): δ 3.33(4H,t), 3.73(4H,t), 4.21(3H,s) 6.79(1H,s),
6.83(1H,d), 6.93(1H,t), 7.26(1H,t), 7.38(1H,t), 7.52(1H,t), 7.71(1H,d),
7.83(1H,d)

Mass (EI) m/z : Calcd for C21H20N4O2Cl, 430.0963, found 430.0977

Example 86

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine;
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and

1-(2-fluorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 81%

m.p. : 156-158°C

1H NMR (CDCl3): δ 3.18(4H,t), 3.74(4H,t), 4.18(3H,s), 6.99(2H,q),
7.07(2H,m), 7.35(2H,m), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d)

Example 87

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine;
Phenyl N-(2-methoxyquinoline-3-yl)carbamate and

1-(2-chlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield : 78%

m.p. : 79-80°C

1H NMR (CDCl3): δ 3.32(4H,t), 3.74(4H,t), 4.20(3H,s), 6.82(2H,q),
Example 88
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-chlorophenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-chlorophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield: 73%
m.p. : 97-98°C

$^1$H NMR (CDCl$_3$): δ 3.31(4H,t), 3.73(4H,t), 4.18(3H,s), 6.82(1H,d), 6.87(1H,d), 6.92(1H,s), 7.21(1H,t), 7.32(1H,s), 7.37(1H,t), 7.51(1H,t), 7.70(1H,d), 7.78(1H,d), 8.80(1H,s)

Example 89
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-hydroxyphenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield: 75%
m.p. : 190-191°C

$^1$H NMR (CDCl$_3$): δ 3.33(4H,t), 3.80(4H,t), 4.19(3H,s), 6.47(1H,s), 6.62(2H,s), 7.16(1H,t), 7.32(1H,s), 7.37(1H,t), 7.51(1H,t), 7.72(1H,d), 7.78(1H,d), 8.78(1H,s)

Example 90
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield: 88%
m.p. : 159-161°C

$^1$H NMR (CDCl$_3$): δ 3.28(4H,t), 3.71(4H,t), 3.81(3H,s), 4.18(3H,s), 6.52(2H,s), 6.62(1H,s), 7.23(1H,t), 7.31-7.53(3H,m), 7.72(2H,m), 8.81(1H,s)
Example 91
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl) piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield: 78%
m.p.: 147-149°C
\[^{1}\text{H} \text{NMR (CDCl\textsubscript{3})}: \delta 2.44(3H,s), 3.07(4H,t), 3.75(4H,t), 4.18(3H,s),
7.13(3H,m), 7.18(1H,d), 7.39(2H,m), 7.70(3H,m), 8.81(1H,s)\]  

Example 92
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl) piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-isopropoxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield: 93%
m.p.: 111-113°C
\[^{1}\text{H} \text{NMR (CDCl\textsubscript{3})}: \delta 1.34(6H,d), 3.30(4H,t), 3.74(4H,t), 4.18(3H,s),
4.55(1H,m), 6.49(2H,s), 7.05(1H,s), 7.20(1H,t), 7.32(1H,s), 7.37(1H,t),
7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)\]  

Example 93
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-cyclopropylmethoxy phenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(3-cyclopropylmethoxyphenyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.
yield: 90%
m.p.: 146-147°C
\[^{1}\text{H} \text{NMR (CDCl\textsubscript{3})}: \delta 0.36(2H,t), 0.65(2H,m), 1.28(1H,m), 3.31(4H,t),
3.75(4H,t), 3.80(2H,d), 4.18(3H,s), 6.50(1H,s), 6.60(2H,s), 7.19(1H,t),
7.32(1H,s), 7.37(1H,t), 7.50(1H,t), 7.70(1H,d), 7.77(1H,d), 8.79(1H,s)\]  

Example 94
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way
with the example 81 to obtain the titled compound.
yield: 76%
m.p.: 115-116°C
$^1$H NMR (CDCl$_3$): δ 2.30(3H,s), 3.14(4H,t), 3.75(4H,t), 3.87(3H,s),
4.18(3H,s), 6.79(2H,m), 6.84(1H,d), 7.35(2H,m), 7.50(1H,t), 7.72(1H,d),
7.77(1H,d), 8.82(1H,s)

Example 95
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-phenylphenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(2-methoxy-5-phenylphenyl)piperazine were reacted by the same way
with the example 81 to obtain the titled compound.
yield: 77%
m.p.: 122-123°C
$^1$H NMR (CDCl$_3$): δ 3.38(4H,t) 3.86(4H,t), 3.97(3H,s), 4.18(3H,s),
7.05(2H,m), 7.34-7.45(6H,m), 7.50(1H,t), 7.56(2H,d), 7.71(2H,d),
7.78(2H,d), 8.88(1H,s)

Example 96
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)carbamate and
1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way
with the example 81 to obtain the titled compound.
yield: 82%
m.p.: 128-130°C
$^1$H NMR (CDCl$_3$): δ 2.30(3H,s), 3.37(4H,t), 3.84(4H,t), 3.78(3H,s),
3.97(3H,s), 7.05(2H,m), 7.13(1H,d), 7.38(3H,m), 7.62(1H,d), 7.80(1H,s),
8.88(1H,s)

Example 97
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine: Phenyl N-(2-methoxyquinolin-3-yl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 81 to obtain the titled compound.

yield: 68%

m.p.: 158-160˚C

$^1$H NMR (CDCl$_3$): δ 3.22(4H, t), 3.86(4H, t), 4.20(3H, s), 7.13(1H, d), 7.38(2H, m), 7.43(1H, t), 7.53(3H, m), 7.62(1H, d), 7.72(1H, d), 7.80(1H, d), 7.86(1H, d), 8.24(1H, d), 8.84(1H, s)

Example 98

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)

piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and sodium hydride(6.0mg, 0.25mmol) was added and the solution was stirred at room temperature for 15 min. Iodomethane(35mg, 0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography(ethylacetate : hexane = 1:2) to obtain the titled compound.

yield: 93%

m.p.: 88-89˚C

$^1$H NMR (CDCl$_3$): δ 2.93(4H, t), 3.17(3H, s), 3.34(4H, t), 3.72(6H, s), 4.15(3H, t), 5.95(2H, s), 5.98(1H, s), 7.40(1H, t), 7.61(2H, m), 7.73(1H, s), 7.84(1H, d)

Mass(El) m/z: Calcd for C$_{24}$H$_{28}$N$_4$O$_4$ 436.2110, found 436.2105

Example 99

1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)

piperazine(106mg, 0.25mmol) was dissolved in dimethylformamide(15ml) and was sodium hydride(6.0mg, 0.25mmol) was added and the solution was stirred at room temperature for 15 min. Iodoethane(35mg,
0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 91%
m.p. : 118-120°C

$^1$H NMR (CDCl₃): δ 1.16(3H,t), 2.89(4H,t), 3.30(4H,t), 3.63(2H,m), 3.71(6H,s), 4.13(3H,s), 5.93(2H,s), 5.98(1H,s), 7.41(1H,t), 7.60(1H,t), 7.66(1H,d), 7.71(1H,s), 7.84(1H,d)

MassEI m/z: Calcd for C$_{26}$H$_{32}$N$_4$O$_4$ 450.2227, found 450.2206

Example 100

1-[N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)phenyl:

1-[N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine (106mg, 0.25mmol) was dissolved in dimethylformamide (15ml) and sodium hydride (6.0mg, 0.25mmol) was added and the reaction solution was stirred at room temperature for 15 min.

2-Propyl iodide (42mg, 0.25mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove the dimethylformamide. The concentrate was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 87%
m.p. : 123-125°C

$^1$H NMR (CDCl₃): δ 1.21(6H,d), 2.79(4H,t), 3.29(4H,t), 3.70(6H,s), 4.08(3H,s), 4.41(1H,m), 5.90(2H,s), 5.96(1H,s), 7.43(1H,t), 7.63(1H,t), 7.69(1H,d), 7.75(1H,s), 7.83(1H,d)

Example 101

1-[N-Cyclopropylmethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-Cyclopropylmethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine (106mg, 0.25mmol) was dissolved in dimethylformamide (15ml) and sodium hydride (6.2mg, 0.26mmol) was added and the solution was
stirred at room temperature for 15 min. Bromomethylcyclopropane (22mg, 0.26mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield: 78%
m.p.: 118-120°C

$	extsuperscript{1}$H NMR (CDCl$_3$): δ 0.41(2H,m), 0.85(2H,m), 1.28(1H,m), 2.88(4H,t), 3.24(4H,t), 3.42(2H,d), 3.71(6H,s), 4.13(3H,s), 5.94(3H,s), 7.44(1H,d), 7.62(1H,d), 7.78(3H,m)

Example 102

1-[N-Benzyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (114mg, 0.27mmol) was dissolved in dimethylformamide (15ml) and sodium hydride (6.6mg, 0.27mmol) was added and the solution was stirred at room temperature for 15 min. Benzyl bromide (46mg, 0.27mmol) was added to the above solution. The mixture was stirred at room temperature for 16 hours and concentrated under the reduced pressure to remove dimethylformamide. The concentrate was purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield: 90%
m.p.: oil phase

$	extsuperscript{1}$H NMR (CDCl$_3$): δ 2.92(4H,t), 3.39(4H,t), 3.72(6H,s), 4.13(3H,s), 4.79(2H,s), 6.01(3H,m), 7.21(1H,m), 7.25(2H,m), 7.33(3H,m), 7.51(1H,s), 7.57(2H,m), 7.81(2H,d)

Example 103

1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl) piperazine was reacted by the same way with the example 98 to obtain the titled compound.
yield : 92%
m.p. : 142–143°C

1H NMR (CDCl₃): δ 2.27(6H,d), 2.90(4H,t), 3.17(3H,s), 3.34(4H,t),
4.15(3H,s), 6.41(2H,s), 6.49(1H,s), 7.40(1H,t), 7.63(1H,t), 7.65(1H,d),
7.73(1H,s), 7.84(1H,d)

Mass(El) m/z : Calcd for C₉₂Hₘ₉N₈O₂ 404.2212, found 404.2225

Example 104
1-[(N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethyl
phenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine was reacted by the same way with the example 99 to obtain
the titled compound.

yield : 89%
m.p. : 84–86°C

1H NMR (CDCl₃): δ 1.16(3H,t), 2.21(6H,s), 2.87(4H,t), 3.30(4H,t),
3.64(2H,q), 4.13(3H,t), 6.40(2H,s), 6.48(1H,s), 7.40(1H,t), 7.62(1H,t),
7.66(1H,d), 7.71(1H,s), 7.84(1H,d)

Example 105
1-[(N-Isopropyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-
dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine was reacted by the same way with the example 100 to
obtain the titled compound.

yield : 84%
m.p. : 114–115°C

1H NMR (CDCl₃): δ 1.21(6H,d), 2.20(6H,s), 2.77(4H,t), 3.28(4H,t),
4.08(3H,s), 4.39(1H,m), 6.37(2H,s), 6.46(1H,s), 7.41(1H,t), 7.63(1H,t),
7.69(1H,d), 7.75(1H,s), 7.83(1H,d)

Example 106
1-[(N-Benzyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-
dimethylphenyl)piperazine:

1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine was reacted by the same way with the example 102 to
obtain the titled compound.
yield : 90%
m.p. : oil phase
\(^1^H\) NMR (CDCl\(_3\)) : \(\delta\) 2.24(6H, s), 2.87(4H, t), 3.31(4H, t), 4.13(3H, s),
4.80(2H, s), 6.42(3H, s), 7.49(1H, t), 7.62(2H, m), 7.72(2H, m)

Example 107
1-[N-(2-Methoxyquinolin-3-yl)-N-methylaminocarbonyl]-4-(3-isopropoxyphenyl)piperazine:
1-[N-(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine was reacted by the same way with the example 98 to obtain the titled compound.
yield : 92%
m.p. : oil phase
\(^1^H\) NMR (CDCl\(_3\)) : \(\delta\) 1.28(6H, d), 2.97(4H, t), 3.18(3H, s), 3.37(4H, t),
4.14(3H, s), 4.49(1H, m), 6.41(3H, m), 7.13(1H, m), 7.40(1H, t), 7.62(1H, t),
7.66(1H, d), 7.74(1H, s), 7.84(1H, d)

Example 108
1-[N-Ethyl-N-(2-methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine:
1-[N-(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3-isopropoxyphenyl)piperazine was reacted by the same way with the example 99 to obtain the titled compound.
yield : 87%
m.p. : oil phase
\(^1^H\) NMR (CDCl\(_3\)) : \(\delta\) 1.16(3H, t), 1.34(6H, d), 2.89(4H, t), 3.30(4H, t),
3.63(2H, m), 4.13(3H, s), 4.55(1H, m), 6.49(2H, s), 7.05(1H, s), 7.20(1H, t),
7.32(1H, s), 7.37(1H, t), 7.50(1H, t), 7.70(1H, d), 7.77(1H, d), 8.80(1H, s)

Example 109
1-[((2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate(56mg, 0.5mmol) and
1-(3,5-dimethoxyphenyl)piperazine(111mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added. The
reaction solution was stirred at room temperature for 2 hours. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and concentrated was purified by column chromatography (Hexane : ether = 5:1) to obtain the titled compound.

yield: 76%
m.p.: 171-172°C

$^1$H NMR (CDCl$_3$): δ 3.41(4H,t), 3.81(6H,s), 4.17(3H,s), 4.21(4H,t), 6.12(1H,s), 6.20(1H,d), 7.38(1H,t), 7.54(1H,t), 7.74(1H,d), 7.81(1H,d), 8.96(1H,s)

Example 110
1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl $N$-[(2-methoxyquinolin-3-yl)thiocarbamate and

1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield: 79%
m.p.: 170-171°C

$^1$H NMR (CDCl$_3$): δ 2.30(6H,s), 3.38(4H,t), 4.09(3H,s), 4.17(4H,t), 6.63(3H,m), 7.38(1H,t), 7.54(1H,t), 7.72(1H,d), 7.81(1H,d), 8.96(1H,s)

Example 111
1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl $N$-[(2-methoxyquinolin-3-yl)thiocarbamate and

1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield: 78%
m.p.: 140-142°C

$^1$H NMR (CDCl$_3$): δ 3.44(4H,t), 4.20(4H,t), 4.25(3H,s), 6.33(2H,m), 6.45(1H,d), 7.41(1H,t), 7.56(1H,m), 7.72(1H,m), 7.97(1H,m), 8.96(1H,s)

Example 112
1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:

Phenyl $N$-[(2-methoxyquinolin-3-yl)thiocarbamate and
1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield: 62%
m.p.: 181-183°C

$^1$H NMR (CDCl$_3$): δ 3.44(4H,t), 4.20(4H,t), 4.26(3H,s), 6.77(1H,s), 6.88(2H,t), 7.41(1H,t), 7.59(1H,t), 7.70(2H,m), 8.01(1H,t), 8.11(1H,s), 8.93(1H,s)

Example 113

1-[(2-Methoxyquinolin-3-yl)aminothiocarbonyl]-4-(3-methoxyphenyl)piperazine:

Phenyl N-(2-methoxyquinolin-3-yl)thiocarbamate and 1-(3-methoxyphenyl)piperazine were reacted by the same way with the example 109 to obtain the titled compound.

yield: 81%
m.p.: oil phase

$^1$H NMR (CDCl$_3$): δ 3.17(4H,t), 3.89(3H,s), 4.17(4H,t), 6.90(4H,m), 7.34(1H,t), 7.48(1H,t), 7.70(1H,d), 7.77(1H,d), 8.80(1H,s)

Example 114

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

a) Phenyl N-(2-methylquinolin-3-yl)carbamate:

3-aminoo-2-methylquinoline (4g, 25mmol) and phenyl chloroformate (4.04g, 25mmol) were dissolved in methylene chloride and then was stirred at room temperature for 2 hrs. The mixture solution was concentrated under the reduced pressure to remove methylene chloride and purified by column chromatography (ethylacetate : hexane = 1:10) to obtain the titled compound.

yield: 88%

$^1$H NMR (CDCl$_3$): δ 2.77(3H,s), 7.30-7.53(9H,m), 8.67(1H,s)

b) 1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(2-methylquinolin-3-yl)carbamate (140mg, 0.5mmol) and
1-(3,5-dimethoxyphenyl)piperazine (112 mg, 0.5 mmol) were dissolved in
tetrahydrofuran and DBU (117 mg, 0.75 mmol) was added and then the
mixture was stirred at room temperature for 2 hrs. The above solution
was concentrated under the reduced pressure to remove tetrahydrofuran
and purified by column chromatography (ethylacetate : hexane = 1:2) to
obtain the titled compound.

yield: 84%
m.p.: 199–200°C

¹H NMR (CDCl₃): δ 2.81 (3H, s), 3.30 (4H, t), 3.76 (4H, t), 3.80 (6H, s),
6.08 (1H, s), 6.12 (2H, d), 7.48 (1H, t), 7.62 (1H, t), 7.71 (1H, d), 8.03 (1H, d),
8.59 (1H, s)

Example 115
1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)
piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and
1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 114 to obtain the titled compound.

yield: 86%
m.p.: 230–232°C

¹H NMR (CDCl₃): δ 2.31 (6H, s), 2.82 (3H, s), 3.29 (4H, t), 3.76 (4H, t),
6.60 (3H, s), 7.49 (1H, t), 7.63 (1H, t), 7.73 (1H, d), 8.05 (1H, d), 8.61 (1H, s)

Example 116
1-[(2-methylquinolin-3-yl)aminocarbonyl]-4-(2,3-dimethylphenyl)
piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and
1-(2,3-dimethylphenyl)piperazine were reacted by the same way with
the example 114 to obtain the titled compound.

yield: 81%
m.p.: 169–170°C

¹H NMR (CDCl₃): δ 2.28 (6H, d), 2.84 (3H, s), 3.00 (4H, t), 3.76 (4H, t),
6.94 (2H, m), 7.11 (1H, t), 7.49 (1H, t), 7.63 (1H, t), 7.72 (1H, d),
8.07 (1H, d), 8.64 (1H, s)
Example 117
1-[(2-Methoxyquinolin-3-yl)aminocarbonyl]-4-(3,5-difluorophenyl) piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 81%
m.p. : 238-240°C

$^1$H NMR (CDCl₃): δ 2.81(3H,t), 3.34(4H,t), 3.77(4H,t), 6.32(1H,t), 6.39(2H,d), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.03(1H,d), 8.58(1H,s)

Example 118
1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(3,5-dichlorophenyl) piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 65%
m.p. : 247-249°C

$^1$H NMR (CDCl₃): δ 2.79(3H,s), 3.33(4H,t), 3.75(4H,t), 6.78(2H,s), 6.87(1H,s), 7.49(1H,t), 7.63(1H,t), 7.72(1H,d), 8.56(1H,s)

Example 119
1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl) piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and

1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.

yield : 83%
m.p. : 135-136°C

$^1$H NMR (CDCl₃): δ 2.82(3H,s), 3.18(4H,t), 3.79(4H,t), 3.91(3H,s), 6.88(1H,d), 6.97(2H,s), 7.07(1H,m), 7.48(1H,t), 7.62(1H,t), 7.72(1H,d), 8.04(1H,d), 8.63(1H,s)

Example 120
1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-fluorophenyl)piperazine:
Phenyl N-\((2\text{-methylquinolin-3-yl})\)carbamate and 1-(2-fluorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.  
yield : 84%  
m.p. : 201-203°C  
$^1$H NMR (CDCl$_3$): δ 2.84(3H,s), 3.20(4H,t), 3.80(4H,t), 6.99(2H,m), 7.07(2H,m), 7.49(1H,t), 7.62(1H,t), 7.71(1H,d), 8.04(1H,d), 8.62(1H,s)  

Example 121

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-chlorophenyl)piperazine: Phenyl N-\((2\text{-methylquinolin-3-yl})\)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.  
yield : 72%  
m.p. : 180-181°C  
$^1$H NMR (CDCl$_3$): δ 2.83(3H,s), 3.16(4H,t), 3.80(4H,t), 7.04(3H,m), 7.40(1H,d), 7.49(1H,t), 7.63(1H,t), 7.71(1H,d), 8.05(1H,d), 8.62(1H,s)  

Example 122

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methylthiophenyl) piperazine: Phenyl N-\((2\text{-methylquinolin-3-yl})\)carbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.  
yield : 76%  
m.p. : 165-166°C  
$^1$H NMR (CDCl$_3$): δ 2.45(3H,s), 2.85(3H,s), 3.11(4H,t), 3.79(4H,t), 7.05(1H,m), 7.15(3H,d), 7.49(1H,t), 7.63(1H,t), 7.69(1H,d), 8.07(1H,d), 8.62(1H,s)  

Example 123

1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(2-methoxy-5-methyl phenyl)piperazine: Phenyl N-\((2\text{-methylquinolin-3-yl})\)carbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 114 to obtain the titled compound.
yield: 80%
m.p.: oil phase
$^1$H NMR (CDCl$_3$): $\delta$ 2.30(3H,s), 2.72(3H,s), 3.17(4H,t), 3.70(4H,t), 3.87(3H,s), 6.77(1H,s), 6.82(2H,s), 7.73(4H,m), 8.60(1H,s)

Example 124
1-[(2-Methylquinolin-3-yl)aminocarbonyl]-4-(1-naphthyl)piperazine:
Phenyl N-(2-methylquinolin-3-yl)carbamate and
1-(1-naphthyl)piperazine were reacted by the same way with the
example 114 to obtain the titled compound.
yield: 64%
m.p.: 220-222°C
$^1$H NMR (CDCl$_3$): $\delta$ 2.83(3H,s), 3.23(4H,t), 3.80(4H,t), 6.91(1H,s), 7.12(1H,d), 7.44(1H,d), 7.50(3H,m), 7.61(2H,m), 7.73(1H,d), 7.86(1H,d), 8.05(1H,d), 8.23(1H,d), 8.64(1H,s)

Example 125
1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:

a) Phenyl N-(2-methylquinolin-3-yl)thiocarbamate:
3-Amino-2-methylquinoline(4g, 25mmol) and phenyl chlorothionoformate(4.32g, 25mmol) were dissolved in methylene chloride and then was stirred at room temperature for 2 hours. The mixture solution was concentrated under reduced pressure to remove methylene chloride and purified by column chromatography(ethylacetate : hexane = 1 : 2) to obtain the titled compound.
yield: 78%
$^1$H NMR (CDCl$_3$): $\delta$ 2.77(3H,s), 7.09-7.90(9H,m), 9.14(1H,s)

b)
1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl) piperazine:
Phenyl N-(2-methylquinolin-3-yl)thiocarbamate(147mg, 0.5mmol) and
1-(3,5-dimethoxyphenyl)piperazine(112mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU(117mg, 0.75mmol) was added and
then the mixture was stirred at room temperature for 2 hrs. The above solution was concentrated under the reduced pressure to remove tetrahydrofuran and purified by column chromatography (ethylacetate : hexane = 1 : 2) to obtain the titled compound.

yield: 86%
m.p.: 211-212°C

$^1$H NMR (CDCl₃): $\delta$ 2.81(3H,s), 3.35(4H,t), 3.79(6H,s), 4.14(4H,t), 6.07(3H,s), 7.49(2H,t), 7.68(2H,m), 8.01(1H,s), 8.07(1H,d)

Example 126
1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(2-methylquinolin-3-yl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 125 to obtain the titled compound.
yield: 81%
m.p.: 196-197°C

$^1$H NMR (CDCl₃): $\delta$ 2.27(6H,s), 2.81(3H,s), 3.31(4H,t), 4.11(4H,t), 6.53(2H,s), 6.58(1H,s), 7.48(2H,t), 7.67(2H,m), 7.96(1H,s), 8.04(1H,d)

Example 127
1-[(2-Methylquinolin-3-yl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:
Phenyl N-(2-methylquinolin-3-yl)thiocarbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 125 to obtain the titled compound.
yield: 74%
m.p.: 211-213°C

$^1$H NMR (CDCl₃): $\delta$ 2.85(3H,s), 3.43(4H,t), 4.22(4H,t), 6.33(2H,m), 7.49(1H,t), 7.64(1H,d), 7.72(1H,t), 8.16(2H,m)

Example 128
1-[(2-(Pyridin-2-yl)quinolin-4-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-[2-(pyridin-3-yl)quinolin-4-yl]carbamate (171mg, 0.5mmol) and 1-(3,5-dimethoxyphenyl)piperazine (111mg, 0.5mmol) were dissolved in
anhydrous tetrahydrofuran and DBU (117 mg, 0.75 mmol) was added and
then the mixture was stirred at room temperature for 2 hrs. The above
solution was concentrated under the reduced pressure to remove
tetrahydrofuran and purified by column chromatography
(dichloromethane : methanol = 20:1) to obtain the titled compound.
yield: 73%  
m.p.: 97–98°C
$^1$H NMR (CDCl$_3$): $\delta$ 3.34 (4H, t), 3.79 (6H, s), 3.90 (4H, t), 6.07 (1H, s),
6.12 (2H, s), 7.43 (1H, t), 7.50 (1H, t), 7.68 (1H, t), 7.93 (1H, t), 8.26 (1H, d),
8.59 (1H, d), 8.80 (1H, d), 8.98 (1H, s)
Mass (EI) m/z: Calcd for C$_{31}$H$_{27}$N$_5$O$_3$ 517.2113, found 517.3244

Example 129
1-[(2-(Pyridin-3-yl)quinolin-4-yl)aminocarbonyl]-4-(3,5-
dimethoxyphenyl)piperazine:
Phenyl N-[2-pyridin-3-yl]quinolin-4-yl]carbamate (171 mg, 0.5 mmol) and
1-(3,5-dimethoxyphenyl)piperazine (111 mg, 0.5 mmol) were dissolved in
anhydrous tetrahydrofuran and DBU (117 mg, 0.75 mmol) was added and
then the mixture was stirred at room temperature for 2 hours. The
above solution was concentrated under the reduced pressure to remove
tetrahydrofuran and purified by column chromatography
(dichloromethane : methanol = 20:1) to obtain the titled compound.
yield: 67%  
m.p.: 95–96°C
$^1$H NMR (CDCl$_3$): $\delta$ 3.36 (4H, t), 3.87 (6H, s), 3.90 (4H, t), 6.08 (1H, s),
6.12 (2H, s), 7.50 (1H, t), 7.71 (1H, t), 7.93 (1H, t), 8.25 (1H, d), 8.53 (1H, d),
8.67 (1H, s), 8.73 (1H, d), 9.35 (1H, s)

Example 130
1-[(2-Thien-2-yl)quinolin-4-yl]aminocarbonyl]-4-(3,5-dimethoxyphenyl)
piperazine:  
Phenyl N-[2-(thien-2-yl)quinolin-4-yl]carbamate (173 mg, 0.5 mmol) and
1-(3,5-dimethoxyphenyl)piperazine (111 mg, 0.5 mmol) were dissolved in
anhydrous tetrahydrofuran and DBU (117 mg, 0.75 mmol) was added. The
resulting mixture was stirred at room temperature for 2 hours,
concentrated under the reduced pressure to remove tetrahydrofuran and
purified by column chromatography (ethyl acetate : hexane = 1:1) to obtain the titled compound.

yield: 61%

m.p. : oil phase

$^1$H NMR (CDCl$_3$): $\delta$ 3.37(4H,t), 3.59(6H,s), 3.97(4H,t), 7.01(3H,m), 7.49(1H,t), 7.69(1H,t), 7.93(1H,t), 8.20(1H,d), 8.52(1H,d), 8.64(1H,s), 8.71(1H,d), 9.35(1H,s)

Example 131

1-[(2-(Pyridin-3-yl)quinolin-4-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-[2-(pyridin-3-yl)quinolin-4-yl]carbamate (171mg, 0.5mmol) and 1-(3,5-dimethylphenyl)piperazine (95mg, 0.5mmol) were dissolved in anhydrous tetrahydrofuran and DBU (117mg, 0.75mmol) was added. The resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove tetrahydrofuran, and purified by column chromatography (ethylacetate : hexane = 1:1) to obtain the titled compound.

yield: 64%

m.p. : 211-213°C

$^1$H NMR (CDCl$_3$): $\delta$ 2.31(6H,s), 3.32(4H,t), 3.85(4H,t), 6.61(3H,s), 7.47(1H,t), 7.55(1H,t), 7.72(1H,t), 7.86(1H,t), 8.25(1H,d), 8.53(1H,d), 8.66(1H,s), 8.72(1H,d), 9.37(1H,s)

Example 132

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[((5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (100mg, 0.25mmol) was dissolved in dimethylformamide (15ml) and thereto sodium hydride (6.0mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 15 min and thereto iodomethane (35mg, 0.25mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure to remove dimethylformamide, and purified by column chromatography (ethyl acetate : hexane = 1:2) to obtain the titled compound.
yield: 94%
m.p.: oil phase

$^1$H NMR (CDCl₃) δ: 2.17 (3H, s), 2.38 (3H, s), 2.92 (4H, t), 3.04 (3H, s),
3.29 (4H, t), 3.74 (6H, s), 3.96 (3H, s), 6.00 (3H, m), 7.08 (1H, s)

Example 133
1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (100mg, 0.25mmol) was dissolved in
dimethylformamide (15ml) and thereto sodium hydride (6.0mg, 0.25mmol)
was added, followed by stirring at room temperature for 15 min and
then iodoethane (39.2mg, 0.25mmol) was added. The resulting mixture
was stirred at room temperature for 16 hrs, concentrated under the
reduced pressure to remove dimethylformamide, and purified by column
chromatography (ethylacetate: hexane=1:2) to obtain the titled compound.
yield: 86%
m.p.: oil phase

$^1$H NMR (CDCl₃) δ: 1.08 (3H, t), 2.04 (3H, s), 2.38 (3H, s), 2.90 (4H, t),
3.26 (4H, t), 3.52 (2H, q), 3.74 (6H, s), 5.99 (3H, m), 7.06 (1H, s)

Example 134
1-[N-Isopropyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (100mg, 0.25mmol) was dissolved in
dimethylformamide (15ml) and thereto sodium hydride (6.0mg, 0.25mmol)
was added, followed by stirring at room temperature for 15 min, and
then 2-iodopropane (42mg, 0.25mmol) was added. The resulting mixture
was stirred at room temperature for 16 hrs, concentrated under the
reduced pressure to remove dimethylformamide, purified by column
chromatography (ethylacetate: hexane=1:2) to obtain the titled compound.
yield: 78%
m.p.: oil phase

$^1$H NMR (CDCl₃) δ: 1.13 (6H, d), 2.19 (3H, s), 2.38 (3H, s), 2.82 (4H, t),
3.26 (4H, t), 3.74 (6H, s), 3.89 (3H, s), 4.27 (1H, m), 6.06 (1H, s), 6.10 (2H, d).
7.07(1H, s), 8.14(1H, s)
Mass (EI) m/z: Calcd for C_{26}H_{34}N_{4}O_{4} 442.2580, found 442.2538

Example 135

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 97%

m.p. : oil phase

\( ^1H \) NMR(CDCl\textsubscript{3}) \( \delta \) : 2.15(6H, s), 2.23(3H, s), 2.37(3H, s), 2.89(4H, t), 3.04(3H, s), 3.30(4H, t), 3.97(3H, s), 6.46(3H, m), 7.08(1H, s)

Example 136

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 94%

m.p. : 131-132°C

\( ^1H \) NMR(CDCl\textsubscript{3}) \( \delta \) : 2.16(3H, s), 2.38(3H, s), 2.80(4H, t), 3.05(3H, s), 3.35(4H, t), 3.82(3H, s), 3.97(3H, s), 6.83(4H, m), 7.08(1H, s)

Example 137

1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:

1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

yield : 87%

m.p. : 112-113°C

\( ^1H \) NMR(CDCl\textsubscript{3}) \( \delta \) : 1.08(3H, t), 2.16(3H, s), 2.38(3H, s), 2.77(4H, t), 3.31(4H, t), 3.58(2H, q), 3.81(3H, s), 3.96(3H, s), 6.88(4H, m), 7.06(1H, s)
Example 138
1-[N-Benzyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine (100mg, 0.27mmol) was dissolved in dimethylformamide (15ml) and thereto sodium hydride (6.5mg, 0.27mmol) was added, followed by stirring at room temperature for 1hr, and successively benzyl bromide (46.2mg, 0.27mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure and purified by column chromatography (ethylacetate : hexane = 1: 2) to obtain the titled compound.
yield : 93%
m.p. : oil phase

1H NMR (CDCl3) δ : 2.08 (3H, s), 2.35 (3H, s), 2.85 (4H, t), 3.32 (4H, t), 3.81 (3H, s), 3.96 (3H, s), 4.76 (2H, s), 6.96 (4H, m), 7.41 (5H, m)

Example 139
1-[N-Cyclopropylmethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine:
1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine (100mg, 0.26mmol) was dissolved in dimethylformamide (15ml) and thereto sodium hydride (6.2mg, 0.26mmol) was added, followed by stirring at room temperature for 15 min, and successively bromomethylcyclopropane (21.8mg, 0.26mmol) was added. The resulting mixture was stirred at room temperature for 16 hrs, concentrated under the reduced pressure and purified by column chromatography (ethylacetate : hexane = 1: 2) to obtain the titled compound.
yield : 78%
m.p. : oil phase

1H NMR (CDCl3) δ : 0.34 (2H, m), 0.49 (2H, m), 1.35 (1H, m), 2.85 (4H, t), 3.28 (4H, t), 3.40 (2H, s), 3.89 (3H, s), 3.97 (3H, s), 6.97 (4H, m), 7.11 (1H, s)

Example 140
1-[N-(5,6-Dimethyl-2-methoxypyridin-3-yl)-N-methylaminocarbonyl]-4-
(5-methoxy-2-methylphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 74%
m.p. : 91-93°C
$^1$H NMR(CDCls) δ : 2.15(3H,s), 2.18(3H,s), 2.39(3H,s), 2.67(4H,t), 3.05(3H,s), 3.30(4H,t), 3.75(3H,s), 3.97(3H,s), 6.48(3H,m), 7.10(1H,s)

Example 141
1-[N-Ethyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

yield : 94%
m.p. : oil phase
$^1$H NMR(CDCls) δ : 1.09(3H,t), 2.15(3H,s), 2.18(3H,s), 2.39(3H,s), 2.60(4H,t), 3.27(4H,t), 3.59(2H,q), 3.75(3H,s), 3.96(3H,s), 6.45(3H,m), 7.08(1H,s)

Example 142
1-[N-Benzyl-N-(5,6-dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:
1-[(5,6-Dimethyl-2-methoxypyridin-3-yl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine was reacted by the same way with the example 138 to obtain the titled compound.

yield : 97%
m.p. : oil phase
$^1$H NMR(CDCls) δ : 1.25(3H,t), 2.08(3H,s), 2.14(3H,s), 2.35(3H,s), 2.60(4H,t), 3.32(4H,t), 3.74(3H,s), 3.95(3H,s), 4.66(2H,s), 6.44(4H,m), 6.96(5H,m), 7.12(1H,s)

Example 143
1-[N-(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 87%
m.p. : 78-79°C
1H NMR(CDCl3) δ : 1.14(3H,t), 2.41(3H,s), 2.52(2H,q), 2.91(4H,t), 3.02(3H,s), 3.28(4H,t), 3.74(6H,s), 3.98(3H,s), 5.98(3H,m), 7.11(1H,s)
Mass(El) m/z : Calcd for C23H32N4O4 428.2423, found 428.2434

Example 144
1-[N-(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.
yield : 84%
m.p. : 86-87°C
1H NMR(CDCl3) δ : 1.14(3H,t), 2.23(6H,s), 2.45(3H,s), 2.58(2H,q), 2.87(4H,t), 3.05(3H,s), 3.30(4H,t), 3.98(3H,s), 6.46(3H,m), 7.11(1H,s)
Mass(El) m/z : Calcd for C23H32N4O4 396.2525, found 396.2575

Example 145
1-[N-Ethyl-N-(5-ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl] -4-(3,5-dimethylphenyl)piperazine:
1-[(5-Ethyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.
yield : 86%
m.p. : 84-85°C
1H NMR(CDCl3) δ : 1.13(6H,m), 2.23(6H,s), 2.41(3H,s), 2.58(2H,q), 2.85(4H,t), 3.26(4H,t), 3.46(2H,q), 3.96(3H,s), 6.45(3H,m), 7.08(1H,s)

Example 146
1-[N-(2-Methoxy-6-methyl-5-propylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(2-Methoxy-6-methyl-5-propylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 89%
m.p. : oil phase

1H NMR(CDCl3) δ : 1.01(3H,t), 1.78(2H,m), 2.21(3H,s), 2.78(2H,t), 3.78(6H,s), 3.86(4H,t), 3.99(3H,s), 4.00(3H,s), 4.22(4H,t), 6.01(3H,m), 7.02(1H,s)

Example 147

1-[N-(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[{(6-Ethyl-2-methoxy-5-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 85%
m.p. : oil phase

1H NMR(CDCl3) δ : 2.21(3H,t), 2.21(3H,s), 2.45(2H,q), 3.21(4H,t), 3.40(3H,s), 3.67(4H,t), 3.77(6H,s), 4.01(3H,s), 6.07(3H,m), 6.96(1H,s), 8.07(1H,s)

Example 148

1-[N-(2-Methoxy-5-methyl-6-propylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(2-Methoxy-5-methyl-6-propylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 86%
m.p. : 106-107°C

1H NMR(CDCl3) δ : 0.98(3H,t), 1.73(2H,q), 2.18(3H,s), 2.63(2H,t), 2.92(4H,t), 3.05(3H,s), 3.29(4H,t), 3.74(6H,s), 3.96(3H,s), 6.00(3H,m), 7.11(1H,s)

Mass(EI) m/z : Calcd for C24H34N4O4 442.2580, found 442.2543

Example 149

1-[N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

Yield: 89%

m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 2.50 (3H, s), 2.70 (3H, s), 2.97 (4H, t), 3.09 (3H, s), 3.33 (4H, t), 3.75 (6H, s), 4.06 (3H, s), 6.03 (3H, m), 7.72 (1H, s)

Mass (EI) m/z: Calcd for C$_{32}$H$_{30}$N$_4$O$_5$ 442.2216, 442.2229

Example 150

1-[(N-Ethyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 133 to obtain the titled compound.

Yield: 87%

m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 1.09 (3H, t), 2.49 (3H, s), 2.70 (3H, s), 3.00 (4H, t), 3.32 (4H, t), 3.77 (6H, s), 4.01 (3H, s), 4.09 (2H, q), 5.98 (3H, m), 7.76 (1H, s)

Example 151

1-[(N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

Yield: 88%

m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 2.24 (6H, s), 2.50 (3H, s), 2.70 (3H, s), 2.93 (4H, t), 3.09 (3H, s), 3.28 (4H, t), 4.06 (3H, s), 6.46 (3H, m), 7.73 (1H, s)

Example 152

1-[(N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:

1-[(N-(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (0.47 mmol) was dissolved in
anhydrous ethanol (15ml) and thereto sodium borohydride (17.3mg) was added, then followed by stirring at room temperature for 2 hrs. The resulting mixture was concentrated under the reduced pressure to remove ethanol and purified by column chromatography (ethyl acetate : hexane = 2:1) to obtain the titled compound.

yield: 97%
m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 1.14 (3H, d), 2.44 (3H, s), 2.93 (4H, t), 3.06 (3H, s), 3.30 (4H, t), 3.74 (6H, s), 3.98 (3H, s), 5.03 (1H, q), 6.02 (3H, m), 7.50 (1H, s)

Example 153
1-(N-Ethyl-N-[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine;
1-[N-Ethyl-N-(5-cetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl] -4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 152 to obtain the titled compound.
yield: 96%
m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 1.09 (3H, t), 1.41 (3H, d), 2.44 (3H, s), 2.91 (4H, t), 3.27 (4H, t), 3.54 (1H, q), 3.74 (6H, s), 3.96 (3H, s), 5.03 (1H, q), 6.02 (3H, m), 8.46 (1H, s)

Example 154
1-(N-[5-(1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl)-4-(3,5-dimethylphenyl)piperazine;
1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 152 to obtain the titled compound.
yield: 97%
m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 1.41 (3H, d), 2.24 (6H, s), 2.44 (3H, s), 2.91 (4H, t), 3.06 (3H, s), 3.26 (4H, t), 3.99 (3H, s), 5.03 (1H, q), 6.49 (3H, m), 7.50 (1H, s)

Example 155
1-(N-[5-(1-Hydroxy-1-methylethyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:
1-[N-Methyl-N-(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine (221mg, 0.5mmol) was dissolved in tetrahydrofuran (10ml) and thereto methyl magnesium bromide (0.50ml, 1.50mmol). The resulting mixture was refluxed for 15 hrs, concentrated under the reduced pressure to remove used solvent, extracted with ethylacetate, filtered to dryness, and purified by column chromatography (ethylacetate : hexane =1:2) to obtain the titled compound.

yield: 92%

m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 1.59 (6H, s), 2.66 (3H, s), 2.93 (4H, t), 3.06 (3H, s), 3.30 (4H, t), 3.74 (6H, s), 3.99 (3H, s), 6.03 (3H, m), 7.45 (1H, s)

Example 156

1-[[N-[5- (1-Hydroxy-1-methylpropyl)-2-methoxy-6-methylpyridin-3-yl]-N-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-Methyl-N- (5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine (213mg, 0.5mmol) was dissolved in tetrahydrofuran (10ml) and thereto methyl magnesium bromide (0.50ml, 1.50mmol) was added slowly, then refluxed for 15 hrs. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with ethylacetate, filtered to dryness, and purified by column chromatography (ethylacetate : hexane =1:2) to obtain the titled compound.

yield: 88%

m.p.: oil phase

$^1$H NMR (CDCl$_3$) $\delta$: 0.79 (3H, t), 1.58 (3H, s), 1.85 (2H, q), 2.61 (3H, s), 2.99 (4H, t), 3.07 (3H, s), 3.30 (4H, t), 3.76 (6H, s), 6.12 (3H, m), 7.47 (1H, s)

Example 157

1-[N-[2-Methoxy-5- (1-methoxyethyl)-6-methylpyridin-3-yl]-N-methyl aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[N-[5- (1-Hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

t: 95%
m.p. : 117-119°C

$^1$H NMR(CDCl₃) δ : 1.34(3H,t), 2.43(3H,s), 2.94(4H,t), 3.06(3H,s),
3.18(3H,s), 3.30(4H,t), 3.74(6H,s), 3.99(3H,s), 4.44(1H,q), 6.02(3H,m),
7.37(1H,s)

Example 158
1-[N-(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)-N-methylamino
carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[((2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the
example 132 to obtain the titled compound.
yield : 94%
m.p. : oil phase
$^1$H NMR(CDCl₃) δ : 2.46(3H,s), 2.93(4H,t), 3.07(3H,s), 3.30(4H,t),
3.73(6H,s), 3.99(3H,s), 5.25(1H,d), 5.48(1H,d), 6.01(3H,m), 6.78(1H,s),
7.43(1H,s)

Example 159
1-[N-(2-Methoxy-6-methyl-5-vinylpyridin-3-yl)-N-methylamino
carbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[((2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the
example 132 to obtain the titled compound.
yield : 89%
m.p. : oil phase
$^1$H NMR(CDCl₃) δ : 2.24(6H,s), 2.43(3H,s), 2.90(4H,t), 3.04(3H,s),
3.27(4H,t), 3.99(3H,s), 5.23(1H,d), 5.45(1H,d), 6.05(3H,m), 6.77(1H,s),
7.40(1H,s)

Example 160
1-[N-Ethyl-N-(2-methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-
4-(3,5-dimethoxyphenyl)piperazine:
1-[((2-Methoxy-6-methyl-5-vinylpyridin-3-yl)aminocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the
example 133 to obtain the titled compound.
yield : 92%
m.p. : oil phase

\[ ^1\text{H} \text{NMR (CDCl}_3\text{)} \delta : 1.09(3\text{H},t), 2.43(3\text{H},s), 2.94(4\text{H},t), 3.28(4\text{H},t), 3.77(6\text{H},s), 4.01(3\text{H},s), 4.11(2\text{H},q), 5.25(1\text{H},d), 5.49(1\text{H},d), 5.98(3\text{H},m), 6.77(1\text{H},s), 7.44(1\text{H},s) \]

5 Example 161
1-[N-(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 92%

m.p. : oil phase

\[ ^1\text{H} \text{NMR (CDCl}_3\text{)} \delta : 1.98(3\text{H},s), 2.43(3\text{H},s), 2.92(4\text{H},t), 3.06(3\text{H},s), 3.29(4\text{H},t), 3.74(6\text{H},s), 3.99(3\text{H},s), 4.84(1\text{H},s), 5.30(1\text{H},s), 6.01(3\text{H},m), 7.10(1\text{H},s) \]

15 Example 162
1-[N-(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)-N-methylamino carbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(5-Isopropenyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 132 to obtain the titled compound.

yield : 91%

m.p. : oil phase

\[ ^1\text{H} \text{NMR (CDCl}_3\text{)} \delta : 1.98(3\text{H},s), 2.24(6\text{H},s), 2.43(3\text{H},s), 2.90(4\text{H},t), 3.06(3\text{H},s), 3.28(4\text{H},t), 4.00(3\text{H},s), 4.84(1\text{H},s), 5.19(1\text{H},s), 6.46(3\text{H},m), 7.10(1\text{H},s) \]

25 Example 163
Ethyl 2-((4-(3,5-dimethoxyphenyl)piperazin0)carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonat:

1-[(5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(200mg, 0.5mmol) was dissolved in dimethylformamide(15ml) and thereto sodium hydride(18.5mg, 0.5mmol) was added, then followed by stirring at room temperature for 15 min.
and ethylbromoacetate (83.5mg, 0.5mmol) was added. The resulting mixture was stirred at room temperature for 3 hrs, concentrated under the reduced pressure to remove the used solvent, and purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 84%
m.p. : oil phase
1H NMR (CDCl₃) δ : 1.26 (3H, t), 2.51 (3H, s), 2.69 (3H, s), 3.04 (4H, t), 3.43 (4H, t), 3.75 (6H, s), 4.05 (3H, s), 4.15 (2H, q), 4.19 (2H, s), 6.08 (3H, s), 7.96 (1H, s)

Example 164
Ethyl 2-((4-(3,5-dimethylphenyl)piperazino)carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate:

1-((5-Acetyl-2-methoxy-6-methylpyridin-3-yl)aminocarbonyl)-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 163 to obtain the titled compound.

yield : 80%
m.p. : oil phase
1H NMR (CDCl₃) δ : 1.25 (3H, t), 2.56 (3H, s), 2.69 (3H, s), 3.00 (4H, t), 3.29 (4H, t), 3.78 (6H, s), 4.06 (3H, s), 4.18 (2H, s), 5.90 (3H, m), 7.98 (1H, s)

Example 165
2-((4-(3,5-Dimethoxyphenyl)piperazino)carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetic acid:

Ethyl (4-(3,5-dimethoxyphenyl)piperazino)carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate (200mg, 0.38mmol) was dissolved in mixed solvent of dioxane : distilled water = 4:1 (15ml), and lithium hydroxide hydrate (48.1mg, 1.14mmol) was added, then followed by stirring at room temperature for 3 hrs. The resulting mixture was made acidic with 1N-HCl, extracted with ethylacetate, filtered to dryness, concentrated under the reduced pressure and purified by column chromatography (ethylacetate : hexane = 1:2) to obtain the titled compound.

yield : 94%
m.p. : 135-137°C
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) : 2.52 (3H, s), 2.69 (3H, s), 3.11 (4H, t), 3.49 (4H, t), 3.74 (6H, s), 4.05 (3H, s), 4.24 (2H, s), 6.15 (3H, m), 7.83 (1H, s)

Example 166

Ethyl 2-\(((4-(3,5-dimethoxyphenyl)piperazino)carbonyl)\[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:

Ethyl 2-\(((4-(3,5-dimethoxyphenyl)piperazino)carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 152 to obtain the titled compound.

yield : 97%
m.p. : 125–127°C
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) : 1.26 (3H, t), 1.42 (3H, d), 2.44 (3H, s), 3.04 (4H, t), 3.31 (4H, t), 3.75 (6H, s), 3.97 (3H, s), 4.16 (2H, q), 4.19 (2H, s), 6.15 (3H, m), 7.69 (1H, s)

Example 167

Ethyl 2-\(((4-(3,5-dimethoxyphenyl)piperazino)carbonyl)\[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:

Ethyl 2-\(((4-(3,5-dimethoxyphenyl)piperazino)carbonyl)(5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 164 to obtain the titled compound.

yield : 92%
m.p. : oil phase
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) : 1.41 (3H, d), 2.44 (3H, s), 2.98 (4H, t), 3.36 (4H, t), 3.74 (6H, s), 3.98 (3H, s), 4.40 (2H, s), 5.00 (1H, q), 6.08 (3H, m), 7.69 (1H, s)

Example 168

Ethyl 2-\(((4-(3,5-dimethylphenyl)piperazino)carbonyl)\[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate:

Ethyl 2-\(((4-(3,5-dimethylphenyl)piperazino)carbonyl)(5-acetyl-2-methoxy-6-methylpyridin-3-yl)amino)acetate was reacted by the same way with the example 152 to obtain the titled compound.

yield : 94%
m.p. : 68–70°C
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) : 1.13 (3H, t), 1.47 (3H, d), 2.33 (6H, s), 2.44 (3H, s),
Example 169

5

2-\{[(3)-(3,5-Dimethylphenyl)piperazino]carbonyl\}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetic acid:

Ethyl 2-\{[(3)-(3,5-dimethylphenyl)piperazino]carbonyl\}[5-(1-hydroxyethyl)-2-methoxy-6-methylpyridin-3-yl]amino)acetate was reacted by the same way with the example 165 to obtain the titled compound.

yield : 92%
m.p. : 114-116°C

1H NMR(CDCl₃) δ : 1.40(3H,d), 2.23(6H,s), 2.40(3H,s), 2.91(4H,t), 3.21(4H,t), 3.98(3H,s), 4.06(2H,s), 4.90(1H,q), 6.50(3H,m), 6.51(1H,s)

Example 170

1-\{[(3)-(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-phenylpiperazine

a) 3,4-Dimethyl anisole:

To 3,4-dimethylphenol(19.3g, 0.16mol), methanol(150ml) and KOH(9.65g, 0.25mol) were added and then refluxed for 2hrs. Methyl iodide(36.5g, 0.25mol) was added thereto, refluxed for 3 hours and then followed by addition of water(150ml). The resulting mixture was extracted with ethylacetate and purified by column chromatography to obtain the titled compound.

yield : 81%

1H NMR(500MHz, CDCl₃) : δ 2.20(3H,s), 2.24(3H,s), 3.77(3H,s), 6.71(2H,m), 6.97(1H,s)

b) 4,5-Dimethyl-2-nitroanisole:

Trifluoroacetic acid(250ml) was added into 3,4-dimethylanisole(17.1g, 0.13mol), successively sodium nitrite(16.6g, 0.24mol) was added slowly in water bath, and stirred at room temperature for 14 hrs. After trifluoroacetic acid was removed and water was added thereto, the resulting mixture was extracted with ether, and purified by column chromatography to obtain the titled compound.

yield : 55%

1H NMR(500MHz, CDCl₃) : δ 2.25(3H,s), 2.32(3H,s), 3.94(3H,s)
6.85(1H,s), 7.70(1H,s) 
c) 4,5-Dimethyl-2-methoxyaniline: 
Tetrahydrofuran(100ml) and ethanol(40ml) were added into 
4,5-dimethyl-2-nitroanisole(7.80g, 0.043mol) and then added 10% 
Pd/activated carbon(0.57g) slowly, hydrogenated for 5 hrs. The reaction 
was completed by the same way with the above and the resulting 
product was purified by column chromatography to obtain the titled 
compound. 
yield : 82%

10  
$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.23(3H,s), 2.27(3H,s), 3.90(3H,s), 
6.80(1H,s), 7.68(1H,s) 
d) Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate: 
To 4,5-dimethyl-2-methoxyaniline(4.50g, 0.03mol), methylene 
chloride(100ml) was added and phenyl chloroformate(4.80g, 0.03mol) was 
added slowly. The resulting solution was stirred for 2 hrs and thereto 
water(150ml) was added, and extracted with methylene chloride and 
purified by column chromatography to obtain the titled compound. 
yield : 98% 
$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.24(3H,s), 2.27(3H,s), 3.89(3H,s), 
6.85(1H,s), 7.20(5H,m), 7.90(1H,s) 
e) 1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-phenylpiperazine: 
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate(5.422g, 0.02mol) and 
1-phenylpiperazine(3.44g, 0.02mol) were dissolved in 
tetrahydrofuran(10ml). After DBU(3.04g, 0.02mol) was added, the 
resulting solution was stirred at room temperature for 2 hrs, 
concentrated and purified by column chromatography to obtain the 
titled compound. 
yield : 85% 
m.p.: 143-144°C 
$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.21(3H,s), 3.25(4H,t), 3.67(4H,t), 
3.85(3H,s), 6.64(1H,s), 6.94(3H,m), 6.99(1H,s), 7.29(1H,t), 7.91(1H,s) 

Example 171 
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine: 
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and
1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 85%
m.p.: 119-120°C

$^1$H NMR (500 MHz, CDCl$_3$): δ 2.20 (3H, s), 2.21 (3H, s), 3.27 (4H, t), 3.70 (4H, t), 3.79 (6H, s), 3.85 (3H, s), 6.17 (2H, m), 6.65 (1H, s), 6.98 (1H, s), 7.90 (1H, s)
Mass (EI) m/z: Calcld for C$_{22}$H$_{28}$N$_{3}$O$_{4}$ 399.2158, found 399.2168

Example 172

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

Phenyl N-[(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 88%
m.p.: 177-178°C
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.20 (3H, s), 2.21 (3H, s), 2.29 (6H, s), 3.23 (4H, t), 3.66 (4H, t), 3.85 (3H, s), 6.58 (2H, m), 6.65 (1H, s), 6.99 (1H, s), 7.92 (1H, s)

Mass (EI) m/z: Calcld for C$_{22}$H$_{28}$N$_{3}$O$_{2}$ 367.2259, found 367.2290

Example 173

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2,3-dimethylphenyl)piperazine:

Phenyl N-[(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2,3-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield: 95%
m.p.: 140-142°C
$^1$H NMR (500 MHz, CDCl$_3$): δ 2.21 (3H, s), 2.22 (3H, s), 2.27 (3H, s), 2.29 (3H, s), 2.95 (4H, t), 3.67 (4H, t), 3.85 (3H, s), 6.65 (1H, s), 7.01 (3H, m), 7.93 (1H, s)

Example 174

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2,3,5,6-tetramethylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2,3,5,6-tetramethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield : 93%

m.p. : oil phase

$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(9H,s), 2.21(9H,s), 3.17(4H,t), 3.63(4H,t), 3.84(3H,s), 6.64(1H,s), 6.84(1H,s), 7.95(1H,s)

Example 175

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarboxyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 170 to obtain the tilted compound.

yield : 89%

m.p. : 102-103°C

$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.22(3H,s), 3.29(4H,t), 3.68(4H,t), 3.85(3H,s), 6.65(1H,s), 6.97(3H,m), 7.89(1H,s)

Example 176

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarboxyl]-4-(2-chlorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-chlorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield : 90%

m.p. : 176-177°C

$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.21(3H,s), 2.22(3H,s), 3.10(4H,t,J=5.0Hz), 3.69(4H,t,J=5.0Hz), 3.85(3H,s), 6.65(1H,s), 7.02(2H,m), 7.24(1H,m), 7.39(1H,d,J=4.0Hz), 7.92(1H,s)

Example 177

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarboxyl]-4-(3-chlorophenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-chlorophenyl)piperazine were reacted by the same way with the
example 170 to obtain the titled compound.

yield : 84%
m.p. : 75–76°C

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.20 (3H, s), 2.22 (3H, s), 3.27 (4H, t, J=5.0 Hz), 3.68 (4H, t, J=5.0 Hz), 3.85 (3H, s), 6.65 (1H, s), 6.90 (3H, m), 7.21 (1H, t), 7.90 (1H, s)

Mass (EI) m/z : Calcld for C$_{20}$H$_{24}$N$_3$O$_2$Cl$_i$ 373.1557, found 373.1590

**Example 178**

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-hydroxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-hydroxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.

yield : 87%
m.p. : 197–199°C

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.20 (3H, s), 2.21 (3H, s), 2.98 (4H, t), 3.72 (4H, t), 3.84 (3H, s), 6.65 (1H, s), 6.89 (1H, t), 7.00 (2H, m), 7.13 (2H, m), 7.89 (1H, s)

**Example 179**

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-hydroxyphenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-hydroxyphenyl) were reacted by the same way with the example 170 to obtain the titled compound.

yield : 88%
m.p. : 177–178°C

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.19 (3H, s), 2.21 (3H, s), 3.24 (4H, t), 3.68 (4H, t), 3.85 (3H, s), 6.41 (3H, m), 6.65 (1H, s), 6.98 (1H, s), 7.13 (1H, t), 7.88 (1H, s)

**Example 180**

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-thiophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-thiophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 79%
m.p.: 108-110°C
$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.21(3H,s), 3.26(4H,t), 3.65(4H,t), 3.84(3H,s), 6.64(1H,s), 6.97(4H,m), 7.05(1H,s), 7.89(1H,s)

Example 181

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-acetoxyphenyl)piperazine: Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-acetoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 84%
m.p.: 129-131°C
$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.21(3H,s), 2.32(3H,s), 3.05(4H,t), 3.63(4H,t), 3.85(3H,s), 6.64(1H,s), 6.99(1H,s), 7.04(1H,m), 7.17(2H,m), 7.22(1H,m), 7.90(1H,s)

Example 182

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3-acetoxyphenyl)piperazine: Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(3-acetoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 87%
m.p.: 154-156°C
$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.21(3H,s), 2.29(3H,s), 3.27(4H,t), 3.68(4H,t), 3.85(3H,s), 6.64(1H,s), 6.66(2H,m), 6.82(1H,m), 6.98(1H,s), 7.90(1H,s)

Example 183

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxyphenyl)piperazine: Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 90%
m.p.: 144-145°C

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.20(3H,s), 2.22(3H,s), 2.26(3H,s), 2.95(4H,t, J=5.0Hz), 3.65(4H,t,J=5.0Hz), 3.78(3H,s), 3.85(3H,s), 6.59(1H,s), 6.65(1H,s), 7.00(1H,s), 7.11(1H,s), 7.93(1H,s)

Example 184
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(5-methoxy-2-methylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(5-methoxy-2-methylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 88%
m.p.: 140-141°C

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.20(3H,s), 2.22(3H,s), 2.26(3H,s), 2.95(4H,t, J=5.0Hz), 3.65(4H,t,J=5.0Hz), 3.78(3H,s), 3.85(3H,s), 6.59(1H,s), 6.65(1H,s), 7.00(1H,s), 7.11(1H,s), 7.93(1H,s)

Example 185
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 80%
m.p.: 107-108°C

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 2.20(3H,s), 2.21(3H,s), 2.29(3H,s), 3.10(4H,t, J=5.0Hz), 3.69(4H,t,J=5.0Hz), 3.85(3H,s), 3.86(3H,s), 6.55(1H,s), 6.79(2H,m), 7.01(1H,s), 9.94(1H,s)

Example 186
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-methoxy-5-phenylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and

1-(2-methoxy-5-phenylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 91%
m.p.: 139–140°C
^1^H NMR(500MHz, CDCl₃): δ 2.21(3H,s), 2.22(3H,s), 3.20(4H,t), 3.74(4H,t), 3.85(3H,s), 3.94(3H,s), 6.65(1H,s), 7.02(2H,m), 7.32(2H,m), 7.42(2H,t), 7.55(2H,d), 7.93(1H,s)

Example 187
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(2-isopropenylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 80%
m.p.: 134–135°C
^1^H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.21(6H,s), 3.10(4H,t), 3.64(4H,t), 3.85(3H,s), 5.08(1H,s), 5.14(1H,s), 6.64(1H,s), 7.05(3H,m), 7.70(1H,m), 7.92(1H,s)

Example 188
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(1-naphthyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 92%
m.p.: 160–162°C
^1^H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.24(3H,s), 3.31(4H,t,J=5.0Hz), 3.83(3H,s), 4.04(4H,t), 6.39(2H,m), 6.69(1H,s), 7.13(1H,t), 7.30(1H,s), 7.46(1H,s)

Example 189
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(1-anthranyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)carbamate and 1-(1-anthranyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 94%
m.p.: 74-75°C

$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.22(3H,s), 3.24(4H,t), 3.70(4H,t), 3.86(3H,s), 6.70(1H,s), 7.05(3H,m), 7.45(5H,m), 8.00(2H,m)

5 Example 190

1-[$N$-(4,5-Dimethyl-2-methoxyphenyl)-$N$-methylaminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (0.2g, 0.5mmole) was dissolved in dimethylformamide (15ml), sodium hydride (12mg, 0.5mmole) was added thereto slowly, and then the resulting mixture was stirred at room temperature for 15 min, then followed by addition of iodomethane (71mg, 0.5mmole) and subsequently at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.

yield: 92%
m.p.: 86-88°C

$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.21(3H,s), 2.24(3H,s), 2.92(4H,t), 3.06(3H,s), 3.31(4H,t), 3.75(6H,s), 3.83(3H,s), 6.00(3H,m), 6.71(1H,s), 6.83(1H,s)

Mass (EI) m/z : Calcd for C$_{23}$H$_{23}$N$_3$O$_4$ 413.2314, found 413.2293

20 Example 191

1-[$N$-(4,5-Dimethyl-2-methoxyphenyl)-$N$-methylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 190 to obtain the titled compound.

yield: 90%
m.p.: 137-138°C

$^1$H NMR(500MHz, CDCl$_3$): $\delta$ 2.15(3H,s), 2.24(9H,s), 2.88(4H,t), 3.06(3H,s), 3.29(4H,t), 3.83(3H,s), 6.45(3H,m), 6.71(1H,s), 6.83(1H,s)

Mass (EI) m/z : Calcd for C$_{23}$H$_{23}$N$_3$O$_2$ 381.2416, 381.2436
Example 192
1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-methylaminocarbonyl]-4-(3,5-difluorophenyl)piperazine:
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 190 to obtain the titled compound.
yield: 87%
m.p.: 98-100°C
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.16(3H,s), 2.25(3H,s), 2.92(4H,t),
3.06(3H,s), 3.29(4H,t), 3.83(3H,s), 6.23(3H,m), 6.72(1H,s), 6.83(1H,s)

Example 193
1-[N-Ethyl-N-(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine (0.2g, 0.5mmole) was dissolved in dimethylformamide (15ml), and thereto sodium hydride (12mg, 0.5mmole) was added slowly. The resulting mixture was stirred at room temperature for 15 min. After iodoethane (78mg, 0.5mmol) was added, the resulting mixture was stirred at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.
yield: 89%
m.p.: oil phase
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 1.09(3H,t), 2.16(3H,s), 2.24(3H,s), 2.75(4H,t),
3.28(4H,t), 3.52(2H,q), 3.75(6H,s), 3.81(3H,s), 5.98(3H,m), 6.70(1H,s), 6.80(1H,s)

Example 194
1-[N-(4,5-Dimethyl-2-methoxyphenyl)-N-ethylaminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine was reacted by the same way with the example 193 to obtain the titled compound.
yield: 93%
m.p.: 80–82°C

$^1$H NMR (500 MHz, CDCl₃): $\delta$ 1.21 (3H, t), 2.15 (3H, s), 2.23 (9H, s), 2.90 (4H, t), 3.25 (4H, t), 3.59 (2H, q), 3.81 (3H, s), 6.45 (3H, m), 6.69 (1H, s), 6.81 (1H, s)

Example 195

1-[(4,5-Dimethyl-2-methoxyphenyl)-N-ethylaminocarbonyl]-4-(3,5-difluorophenyl)piperazine;

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine was reacted by the same way with the example 193 to obtain the titled compound.

yield: 87%

m.p.: oil phase

$^1$H NMR (500 MHz, CDCl₃): $\delta$ 1.09 (3H, t), 2.16 (3H, s), 2.25 (3H, s), 2.90 (4H, t), 3.27 (4H, t), 3.52 (2H, q), 3.81 (3H, s), 6.24 (3H, m), 6.70 (1H, s), 6.81 (1H, s)

Example 196

1-[(N-Isopropyl-N-(4,5-dimethyl-2-methoxyphenyl)aminocarbonyl)-4-(3,5-difluorophenyl)piperazine:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine (0.2g, 0.52mmole) was dissolved in dimethylformamide (15ml) and thereto sodium hydride (12.48mg, 0.52mmole) was slowly added. The resulting mixture was stirred at room temperature for 15 min. After 2-iodopropane (87.88mg, 0.52mmole) was added thereto, the resulting mixture was stirred at room temperature for 16 hours. The resulting mixture was concentrated under the reduced pressure to remove the used solvent, extracted with methylene chloride, dried, filtered and purified by column chromatography to obtain the titled compound.

yield: 84%

m.p.: oil phase

$^1$H NMR (500 MHz, CDCl₃): $\delta$ 1.10 (3H, s), 1.26 (3H, s), 2.20 (3H, s), 2.25 (3H, s), 2.86 (4H, t), 3.26 (4H, t), 3.77 (3H, s), 4.25 (1H, m), 6.17 (3H, m), 6.68 (1H, s), 6.82 (1H, s)

Example 197

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
(a) Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate:
To 3,4-dimethyl-2-methoxylaniline (4.50g, 0.03mol), methylene chloride (100ml) was added and then phenyl chlorothionoformate (5.16g, 0.03mol) was added slowly. The resulting mixture was stirred for 2 hours, and thereto water (150ml) was added. The resulting mixture was extracted with methylene chloride and purified by column chromatography to obtain the titled compound.
yield: 92% 
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.21(3H,s), 2.25(3H,s), 3.85(3H,s), 6.80(1H,s), 6.93(5H,m), 7.31(1H,s)

(b) 1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate (0.2g, 0.7mmol) and 1-(3,5-dimethoxyphenyl)piperazine (0.16g, 0.7mmol) were dissolved in tetrahydrofuran (10ml) and thereto DBU (0.11g, 0.7mmole) was added, followed by stirring at room temperature for 2 hours. The resulting product was concentrated and purified by chromatography to obtain the titled compound.
yield: 84%
m.p.: 128-129°C 
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.24(3H,s), 2.32(6H,s), 3.37(4H,t), 3.83(3H,s), 4.08(4H,t), 6.69(3H,m), 7.39(1H,m), 7.47(1H,s)
Mass (EI) m/z: Calcd for C$_{22}$H$_{28}$N$_3$O$_5$S$_1$ 415.1929, found 415.1912

Example 198
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 90%
m.p.: 164-165°C 
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.20(3H,s), 2.24(3H,s), 2.32(6H,s), 3.37(4H,t), 3.83(3H,s), 4.08(4H,t), 6.69(3H,m), 7.39(1H,m), 7.47(1H,s)
Mass (EI) m/z: Calcd for C$_{22}$H$_{28}$N$_3$O$_5$S$_1$ 383.2031, found 383.2086
Example 199
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2,3-dimethylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(2,3-dimethylphenyl)piperazine were reacted by the same way with
the example 197 to obtain the titled compound.
yield: 89%
m.p.: 151–152°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.21(3H,s), 2.24(3H,s), 2.29(6H,s),
3.03(4H,t), 3.83(3H,s), 4.10(4H,t), 6.69(1H,s), 6.97(2H,m), 7.11(1H,t)

Example 200
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-difluorophenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(3,5-difluorophenyl)piperazine were reacted by the same way with the
example 197 to obtain the titled compound.
yield: 92%
m.p.: 167–168°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.20(3H,s), 2.24(3H,s), 2.27(3H,s),
2.32(3H,s), 3.39(4H,t,J=5.0Hz), 3.83(3H,s), 4.14(4H,t), 6.70(1H,s),
6.80(2H,m), 7.36(1H,s), 7.44(1H,s)

Example 201
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3,5-dichlorophenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the
example 197 to obtain the titled compound.
yield: 85%
m.p.: 188–189°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.20(3H,s), 2.24(3H,s), 3.35(4H,t,J=5.0Hz),
3.83(3H,s), 4.04(4H,t,J=5.0Hz), 6.70(2H,m), 6.83(1H,s), 7.30(1H,s),
7.48(1H,s)
Mass(EI) m/z : Calcd for C$_{20}$H$_{24}$N$_3$O$_2$Cl: 423.0938, 423.0956
Example 202
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-fluorophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(2-fluorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 87%
m.p.: 139-140°C
^1H NMR(500MHz, CDCl3): δ 2.21(3H,s), 2.24(3H,s), 3.40(4H,t),
3.83(3H,s), 4.25(4H,t), 6.70(1H,s), 7.13(3H,m), 7.37(2H,m)

Example 203
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-chlorophenyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(2-chlorophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 85%
m.p.: 115-116°C
^1H NMR(500MHz, CDCl3): δ 2.21(3H,s), 2.24(3H,s), 3.18(4H,t),
3.83(3H,s), 4.09(4H,t), 6.69(1H,s), 7.05(2H,m), 7.33(1H,s), 7.41(2H,m)

Example 204
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-methoxyphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and
1-(2-methoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 90%
m.p.: oil phase
^1H NMR(500MHz, CDCl3): δ 2.20(3H,s), 2.23(3H,s), 3.14(4H,t,J=5.0Hz),
3.82(3H,s), 3.88(3H,s), 4.06(4H,t,J=5.0Hz), 6.69(1H,s), 6.94(3H,m),
7.30(1H,s), 7.40(1H,s)

Example 205
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-
(2-methylthiophenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methylthiophenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 93%
m.p.: 136-137°C

$^1$H NMR(500MHz, CDCl₃): δ 2.20(3H,s), 2.26(3H,s), 2.45(3H,s), 3.33(4H,t), 3.82(3H,s), 4.39(4H,t), 6.74(1H,s), 7.16(3H,m), 7.47(2H,m)

Example 206

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(3-hydroxyphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(3-hydroxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 77%
m.p.: Decomposed(200°C)

$^1$H NMR(500MHz, CDCl₃): δ 2.17(3H,s), 2.23(3H,s), 3.31(4H,t), 3.82(3H,s), 4.03(3H,t), 6.37(2H,m), 6.47(1H,d), 6.69(1H,s), 7.13(1H,t), 7.45(1H,s)

Example 207

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-phenoxyphenyl)piperazine:

Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-phenoxyphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.

yield: 86%
m.p.: oil phase

$^1$H NMR(500MHz, CDCl₃): δ 2.17(3H,s), 2.24(3H,s), 3.19(4H,t), 3.80(3H,s), 3.85(4H,t), 6.66(1H,s), 6.91(2H,m), 6.98(1H,m), 7.05(3H,m), 7.13(1H,m), 7.23(1H,m), 7.31(2H,m), 7.36(1H,s)

Example 208

1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-isopropenylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-isopropenylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 75%
m.p.: 157–158°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.20(3H,s), 2.21(3H,s), 2.24(3H,s), 3.19(4H,t), 3.82(3H,s), 4.05(4H,t), 5.07(1H,s), 5.16(1H,s), 6.69(1H,s), 7.11(3H,m), 7.33(1H,s), 7.45(1H,s)

Example 209
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(2-methoxy-5-methylphenyl)piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(2-methoxy-5-methylphenyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 87%
m.p.: oil phase
$^1$H NMR(500MHz, CDCl$_3$): δ 2.20(3H,s), 2.23(3H,s), 2.29(3H,s), 3.13(4H,t), 3.83(3H,s), 3.85(3H,s), 4.05(4H,t), 6.69(1H,s), 6.83(2H,m), 7.30(1H,s), 7.40(1H,s)

Example 210
1-[(4,5-Dimethyl-2-methoxyphenyl)aminothiocarbonyl]-4-(1-naphthyl) piperazine:
Phenyl N-(4,5-dimethyl-2-methoxyphenyl)thiocarbamate and 1-(1-naphthyl)piperazine were reacted by the same way with the example 197 to obtain the titled compound.
yield: 87%
m.p.: 139–140°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.23(3H,s), 2.24(3H,s), 3.21(4H,t), 3.84(3H,s), 4.09(4H,t), 6.70(1H,s), 7.10(1H,d), 7.48(5H,m), 7.85(1H,m), 8.22(1H,d)

Example 211
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dimethoxyphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 91%
m.p.: 103-105°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.54(3H,s), 2.59(3H,s), 3.27(4H,t), 3.70(4H,t), 3.79(6H,s), 3.94(3H,s), 6.13(3H,m), 6.70(1H,s), 7.05(1H,s), 8.72(1H,s)

Example 212

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dimethylphenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 88%
m.p.: 140-142°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.30(3H,s), 2.54(3H,s), 2.59(3H,s), 3.26(4H,t), 3.70(4H,t), 3.97(3H,s), 6.61(3H,m), 6.70(1H,s), 7.06(1H,s), 8.72(1H,s)

Example 213

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dichloro-phenyl)piperazine:
Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 170 to obtain the titled compound.
yield: 78%
m.p.: 170-172°C
$^1$H NMR(500MHz, CDCl$_3$): δ 2.54(3H,s), 2.59(3H,s), 3.32(4H,t), 3.74(4H,t), 3.94(3H,s), 6.69(1H,s), 6.86(3H,m), 7.04(1H,s), 8.69(1H,s)

Example 214

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.47mmol) was dissolved in
anhydrous ethanol(15ml), and sodium borohydride(17mg) was added thereto, and then the resulting mixture was stirred at room temperature for 2 hours, concentrated under the reduced pressure to remove ethanol, and purified by column chromatography(ethylacetate:hexane = 1:2) to obtain the titled compound.

yield: 96%
m.p.: 152–154°C

$^1$H NMR(500MHz, CDCl3): $\delta$ 1.41(3H,d), 2.32(3H,s), 3.27(4H,t), 3.71(4H,t), 3.79(6H,s), 3.87(3H,s), 5.04(1H,q), 6.10(3H,m), 6.63(1H,s), 7.01(1H,s), 8.22(1H,s)

Example 215

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethylphenyl)piperazine:

yield: 96%
m.p.: 140–142°C

$^1$H NMR(500MHz, CDCl3): $\delta$ 1.48(3H,d), 2.33(3H,s), 3.26(4H,t), 3.68(4H,t), 3.87(3H,s), 5.06(1H,q), 6.61(3H,m), 6.64(1H,s), 7.01(1H,s), 8.22(1H,s)

Example 216

1-[(2-Methoxy-4-methyl-5-vinylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine(0.2g, 0.47mmol) was dissolved in chloroform(15ml), pyridium p-toluenesulfonate(0.12g, 0.47mmol) was added thereto, and the resulting mixture was refluxed for 16 hours, and concentrated under the reduced pressure to remove chloroform and purified by column chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 84%
m.p.: 163–165°C

$^1$H NMR(500MHz, CDCl3): $\delta$ 2.31(3H,s), 3.23(4H,t), 3.58(4H,t), 3.77(6H,s),
3.87(3H,s), 5.20(1H,d), 5.62(1H,d), 6.59(3H,m), 6.63(1H,s), 6.88(1H,t),
6.99(1H,s), 8.32(1H,s)

Example 217

1-[(2-Methoxy-4-methyl-5-vinylphenyl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine:

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the
example 216 to obtain the titled compound.

yield: 82%
m.p.: 201-203°C

$^1$H NMR(500MHz, CDCl₃): $\delta$ 2.29(6H,s), 2.34(3H,s), 3.24(4H,t), 3.68(4H,t),
3.87(3H,s), 5.22(1H,d), 5.66(1H,d), 6.59(3H,m), 6.63(1H,s), 6.86(1H,t),
7.02(1H,s), 8.32(1H,s)

Example 218

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and

1-[(3,5-dimethoxyphenyl)piperazine were reacted by the same way with
the example 197 to obtain the titled compound.

yield: 82%
m.p.: 163-165°C

$^1$H NMR(500MHz, CDCl₃): $\delta$ 2.16(3H,s), 2.56(3H,s), 3.35(4H,t),
3.91(6H,s), 4.03(3H,s), 4.13(4H,t), 6.06(3H,m), 6.73(1H,s), 8.62(1H,s)

Example 219

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dimethylphenyl)piperazine:

Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and

1-(3,5-dimethylphenyl)piperazine were reacted by the same way with
the example 197 to obtain the titled compound.

yield: 79%
m.p.: 180-182°C

$^1$H NMR(500MHz, CDCl₃): $\delta$ 2.29(6H,s), 2.57(6H,s), 3.32(4H,t),
3.92(3H,s), 4.12(4H,t), 6.56(3H,m), 6.72(1H,s), 7.39(1H,s), 8.63(1H,s)
Example 220
1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dichlorophenyl)piperazine:

5 Phenyl N-(5-acetyl-2-methoxy-4-methylphenyl)thiocarbamate and
1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the
example 197 to obtain the titled compound.

yield: 79%
m.p.: 201-203°C

10 $^1$H NMR(500MHz, CDCl$_3$): δ 2.20(3H,s), 2.57(3H,s), 3.46(4H,t),
3.92(3H,s), 4.25(4H,t), 6.64(1H,s), 6.88(3H,m), 7.72(1H,s), 8.57(1H,s)

Example 221
1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine:

15 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dimethoxyphenyl)piperazine was reacted by the same way with the
example 214 to obtain the titled compound.

yield: 94%
m.p.: 146-148°C

20 $^1$H NMR(500MHz, CDCl$_3$): δ 1.44(3H,d), 2.32(3H,s), 3.35(4H,t),
3.78(6H,s), 3.84(3H,s), 4.11(4H,t), 5.06(1H,q), 6.13(3H,m), 6.66(1H,s),
7.41(1H,s), 7.77(1H,s)

Example 222
1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dimethylphenyl)piperazine:

25 1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the
example 214 to obtain the titled compound.

yield: 93%
m.p.: 150-152°C

30 $^1$H NMR(500MHz, CDCl$_3$): δ 1.44(3H,d), 2.29(6H,s), 2.33(3H,s),
3.30(4H,t), 3.84(3H,s), 4.07(4H,t), 5.06(1H,q), 6.61(3H,m), 6.66(1H,s),
7.38(1H,s), 7.79(1H,s)
Example 223

1-[(5-(1-Hydroxyethyl)-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dichlorophenyl)piperazine:

1-[(5-Acetyl-2-methoxy-4-methylphenyl)aminothiocarbonyl]-4-
(3,5-dichlorophenyl)piperazine was reacted by the same way with the
example 214 to obtain the titled compound.

yield: 77%
m.p.: 166-168°C

\[^1\text{H}\text{ NMR}(500\text{MHz, CDCl}_3): \delta 1.45(3H,d), 2.33(3H,s), 3.35(4H,t),\]
3.84(3H,s), 4.03(4H,t), 5.07(1H,q), 6.68(3H,m), 6.83(1H,s), 7.37(1H,s),
7.82(1H,s)

Example 224

Ethyl 2-[(4-(3,5-dimethoxyphenyl)piperazino)carbonyl]-2-methoxy-4,5-
dimethylanilinoacetate:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-(3,5-dimethoxy
phenyl)piperazine(0.2g, 0.5mmol) was dissolved in
dimethylformamide(15ml), sodium hydride(18.5mg, 0.5mmol) was added
thereto, and the resulting mixture was stirred at room temperature.

Then, ethyl bromoacetate(83.5mg, 0.5mmol) was added thereto and the
resulting mixture was stirred for 3 hours, concentrated under the
reduced pressure to remove the used solvent and purified by column
chromatography(ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 79%
m.p.: oil phase

\[^1\text{H}\text{ NMR}(500\text{MHz, CDCl}_3): \delta 1.36(3H,t), 2.15(3H,s), 2.23(3H,s), 2.91(4H,t),\]
3.22(4H,t), 3.82(6H,s), 4.12(3H,s), 4.18(2H,s), 5.98(3H,m), 6.69(1H,s),
7.03(1H,s)

Example 225

Ethyl 2-[(4-(3,5-dimethylphenyl)piperazino)carbonyl]-2-methoxy-4,5-
dimethylanilinoacetate:

1-[(4,5-Dimethyl-2-methoxyphenyl)aminocarbonyl]-4-
(3,5-dimethylphenyl)piperazine was reacted by the same way with the
example 224 to obtain the titled compound.

yield: 78%
m.p.: oil phase
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 1.26(3H,t), 1.56(6H,s), 2.17(3H,s), 2.24(3H,s), 3.32(4H,t), 3.52(4H,t), 3.82(3H,s), 4.15(2H,q), 4.18(2H,s), 6.70(3H,m), 6.94(1H,s), 7.46(1H,s)

Example 226

2-((4-(3,5-Dimethoxyphenyl)piperazino)carbonyl)-2-methoxy-4,5-dimethylaminilino)acetic acid:

Ethyl 2-((4-(3,5-dimethoxyphenyl)piperazino)carbonyl)-2-methoxy-4,5-dimethylaminilino)acetate (200mg, 0.41mmole) was dissolved in dioxanep; distilled water (4:1, 15ml), lithium hydroxide monohydrate (50.7mg, 1.23mmol) was added thereto, and then the resulting mixture was stirred at room temperature for 3 hours, acidified with 1N-hydrochloric acid, extracted with ethylacetate, filtered to dryness, concentrated under the reduced pressure to remove the used solvent, and purified by column chromatography (ethylacetate:hexane=1:2) to obtain the titled compound.

yield: 80%
m.p.: 188-189°C

$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.14(3H,s), 2.23(3H,s), 2.93(4H,t), 3.35(4H,t), 3.75(6H,s), 3.87(3H,s), 4.18(2H,s), 5.96(3H,m), 6.71(1H,s), 7.71(1H,s)

Example 227

2-((4-(3,5-Dimethylphenyl)piperazino)carbonyl)-2-methoxy-4,5-dimethylaminilino)acetic acid:

Ethyl 2-((4-(3,5-dimethylphenyl)piperazino)carbonyl)-2-methoxy-4,5-dimethylaminilino)acetate was reacted by the same way with the example 226 to obtain the titled compound.

yield: 78%
m.p.: 170-171°C

$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.13(3H,s), 2.24(9H,s), 2.91(4H,t), 3.35(4H,t), 3.83(3H,s), 4.18(2H,s), 6.45(3H,m), 6.70(2H,s), 6.80(1H,s)

Example 228

1-((2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl)-4-(3,5-dimethoxyphenyl)piperazine:
(a) 4,5-Dimethyl-2-nitrophenol:
To 3,4-dimethylphenol (12.1g, 0.1mol), trifluoroacetic acid (250ml) was added, and in water bath sodium nitrite (12.4g, 0.18mol) was added slowly. The resulting mixture was stirred at room temperature for 14 hours and concentrated under the reduced pressure to remove trifluoroacetic acid, followed by addition of water (150ml), extracted with ether and purified by column chromatography to obtain the titled compound.

yield: 80%
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.23 (3H, s), 2.29 (3H, s), 6.93 (1H, s), 7.84 (1H, s)

(b) 4,5-Dimethyl-2-hydroxyaniline:
To 4,5-dimethyl-2-nitrophenol (11.7g, 0.07mol), tetrahydrofuran (100ml) and ethanol (40ml) were added, and 10% palladium/activated carbon (0.57g) was added slowly, and then the mixture was hydrogenated for 5 hours. The reaction mixture was concentrated and chromatographed by the same way above to obtain the titled compound.

yield: 77%
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.11 (6H, s), 6.56 (2H, s)

(c) Phenyl N-(4,5-dimethyl-2-hydroxyphenyl)carbamate:
To 4,5-dimethyl-2-hydroxyaniline (6.80g, 0.05mole), methylene chloride (100ml) was added and then phenyl chloroformate (8.0g, 0.05mole) was added slowly. After stirring for 2 hours, addition of water (150ml), extraction with methylene chloride and column chromatography gave the titled compound.

yield: 92%
$^1$H NMR (500MHz, CDCl$_3$): $\delta$ 2.17 (6H, s), 6.74 (1H, s), 7.15 (5H, m), 7.31 (1H, s)

d) Phenyl N-[2-(t-butyldimethylsilyloxy)-4,5-dimethylphenyl]carbamate:
To a mixture of phenyl N-(4,5-dimethyl-2-hydroxyphenyl)carbamate (7.72g, 0.03mol) and imidazole (2.2g, 33mmol), methylene chloride (100ml) was added, and with stirring t-butyldimethylsilylchloride (5.0g, 33mmole)
was added. Then the mixture was stirred for 2 hours, and water (150 ml) was added thereto. The resulting mixture was extracted with methylene chloride, dried, concentrated under the reduced pressure and purified by column chromatography to obtain the titled compound.

yield: 83%

\[^{1}H\text{NMR}(500MHz,\text{CDCl}_3): \delta 0.27(6H,s), 0.98(9H,s), 2.17(6H,s), 7.12(5H,m), 7.30(2H,s)\]

(e) 1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[2-(t-butyldimethylsilyloxy)-4,5-dimethylphenyl]carbamate (0.17 g, 0.5 mmole) and 1-(3,5-dimethoxyphenyl)piperazine (0.13 g, 0.6 mmole) were dissolved in tetrahydrofuran (10 ml), and thereto with stirring DBU (0.09 g, 0.6 mmole) was added, and the resulting mixture was stirred for 2 hours, concentrated and chromatographed to obtain the titled compound.

yield: 87%
m.p.: 145–146°C

\[^{1}H\text{NMR}(500MHz,\text{CDCl}_3): \delta 2.14(3H,s), 2.18(3H,s), 3.26(4H,t), 3.67(4H,t), 3.79(6H,s), 6.07(3H,m), 6.40(3H,m), 6.67(1H,s), 6.82(1H,s), 8.87(1H,s)\]

Example 229

1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dimethoxyphenyl)piperazine:

Phenyl N-[2-hydroxy-4,5-dimethylphenyl]carbamate and 1-(3,5-dimethyl phenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 84%
m.p.: 160–162°C

\[^{1}H\text{NMR}(500MHz,\text{CDCl}_3): \delta 2.13(3H,s), 2.17(3H,s), 2.31(6H,s), 3.26(4H,t), 3.75(4H,t), 6.73(3H,m), 6.81(1H,s), 8.86(1H,s)\]

Example 230

1-[(2-Hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-difluorophenyl)piperazine:

Phenyl N-[2-hydroxy-4,5-dimethylphenyl]carbamate and
1-(3,5-difluorophenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 80%
m.p.: 152–154°C

$^1$H NMR (500MHz, CDCl₃): δ 2.17(3H,s), 2.20(3H,s), 3.30(4H,t), 3.70(4H,t), 6.40(3H,m), 6.70(1H,s), 6.82(1H,s), 6.98(1H,s)

Example 231
1-[(2-hydroxy-4,5-dimethylphenyl)aminocarbonyl]-4-(3,5-dichlorophenyl)piperazine:
Phenyl N-(2-hydroxy-4,5-dimethylphenyl)carbamate and 1-(3,5-dichlorophenyl)piperazine were reacted by the same way with the example 228 to obtain the titled compound.

yield: 77%
m.p.: oil phase

$^1$H NMR (500MHz, CDCl₃): δ 2.15(3H,s), 2.20(3H,s), 3.32(4H,t), 3.69(4H,t), 6.29(3H,m), 6.69(1H,s), 6.81(1H,s), 8.65(1H,s)
Antitumor activities of compounds of the present invention were tested in vitro against 5 kinds of human tumor cell lines and 2 kinds of leukemia tumor cell lines. The method and result of in vitro tests is as follows.

Experimental 1: In vitro antitumor effect against human tumor cell lines.

A. Tumor cell line: A549 (human non-small lung cell)
    SKOV-3 (human ovarian)
    HCT-15 (human colon)
    XF 498 (human CNS)
    SKMEL-2 (human melanoma)

B. SRB Assay Method.

a. Human solid tumor cell lines, A549(non-small lung cell), SKMEL-2(melanoma), HCT-15(colon), SKOV-3(ovarian), XF-498(CNS) were cultured at 37°C, in 5% CO₂ incubators using the RPMI 1640 media containing 10% FBS, while they were transfer-cultured successively once or twice per week. Cell cultures were dissolved in a solution of 0.25% trypsin and 3 mM CDTA PBS(−) and then cells were separated from media which the cells were stuck on.

b. 5×10³～2×10⁴ cells were added into each well of 96-well plate and cultured in 5% CO₂ incubator, at 37°C, for 24 hours.

c. Each sample drug was dissolved in a little DMSO and diluted with the used medium to a prescribed concentration for experiments, wherein the final concentration of DMSO was controlled below 0.5%.

d. Medium of each well cultured for 24 hours as above b. was removed by aspiration. Each 200 μl of drug samples prepared in c. was added into each well and the wells were cultured for 48 hours. Tz(time zero) plates were collected at the point of time drugs were added.
e. According to the SRB assay method, cell fixing with TCA, staining with 0.4% SRB solution, washing with 1% acetic acid and elution of dye with 10mM Tris solution were carried out on Tz plates and culture-ended plates, and then, OD values were measured at 520 nm.

C. Calculation of result

a. Time zero(Tz) value was determined with measuring the SRB protein value at the point of time drugs were added.

b. Control value(C) was determined with the OD value of an well untreated with drug.

c. Drug-treated test value(T) was determined with the OD value of drug-treated well.

d. Effects of drugs were estimated with growth stimulation, net growth inhibition, net killing etc. calculated from Tz, C and T.

e. If T ≥ Tz, cellular response function was calculated by 100x(T−Tz)/(C−Tz), and if T < Tz, by 100x(T−Tz)/Tz. The results are shown in the next table 1.

*REFERENCE


D. Results.

It was found that compounds of the present invention have the
superior antitumor activities than those of cisplatin, one control, and equal to or higher antitumor activities than those of adriamycin, another control, against human solid cancer cell lines.

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ED₅₀ = µg/ml
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Experimental 2.
In vitro antitumor effects against animal leukemia cells.

A. Materials:
Tumor cell lines: L1210(mouse leukemia cell)
P388 (mouse lymphoid neoplasma cell)

B. Method: Dye Exclusion Assay.
1) The concentrations of L1210 and P388 cells being cultured in RPMI 1640 media containing 10% FBS were regulated to $1 \times 10^6$ cells/ml.
2) Sample drugs of respective concentrations diluted in the ratio of log doses were added into cell media, and cultured at 37°C, for 48 hours, in 50% CO₂ incubator, and then viable cell number was measured by dye exclusion test using trypan blue.

3) The concentration of sample compounds showing 50% cell growth inhibition (IC₅₀) compared with the control were determined and listed in the table 2 below.

*REFERENCE*

C. Results
As the results of measurement of antitumor activities of compounds of the present invention against L1210 and P388 mouse cancer cells, it was found that the compounds tested have equal to or higher antitumor activities than those of the control drug, mitomycin C.
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35 Experimental 3.

* In vivo antitumor effects against mouse leukemia P388 cells.
A. Material of experiment
   BDF1 mice were used.
B. Method of experiment
   1) Leukemia P388 cells being transfer-cultured successively in
      DBA/2 mouse, were grafted into each mouse of a group comprising 8
      mice of 6 week old BDF1 mouse with the dose of $1 \times 10^6$ cells/0.1ml.

   2) Sample drugs were dissolved in PBS or suspended in 0.5%
      tween 80, and then injected into abdominal cavity of mouse at each
      prescribed concentration on days 1, 5, 9, respectively.

   3) With observation everyday, survival times of tested mice were
      measured. Antitumor activities was determined in such a manner that
      the increasing ratio (T/C%) of average survival days of drug-treated
      groups compared with the control group was calculated using the
      mean survival times of each tested groups.
      The results are shown at the next table 3.
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<th>Interval of administration</th>
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<td>T/C (%)</td>
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</table>
C. Result

Through in vivo experiments using P388 mouse cancer cells, significant antitumor effect of the compounds of examples were observed.

Experimental 4.

Acute toxicity test (LD$_{50}$) : Litchfield-Wilcoxon method.

6 weeks old ICR mice(male 30±2.0g) were fed freely with solid feed and water at room temperature, 23±1°C and at humidity 60±5%.
Sample drugs were injected into the abdominal cavities of mice, while each group comprises 6 mice. Observed during 14 days, external appearances and life or dead were recorded, and then, visible pathogenies were observed from dead animals by dissection. LD$_{50}$ value was calculated by Litchfield-wilcoxon method.
The results are shown at the next table 4.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg) (i.p)</th>
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<td>Cisplatin</td>
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</table>

As described above, it was found that the compounds of the present invention are more safer and have superior antitumor activities to cisplatin, and accordingly have solved the problems of drugs by the prior art such as restriction of dosage, toxicity, etc.
What is claimed:

1. A compound of the general formula (I)

\[
\begin{align*}
\text{R}_1 & \quad \text{Y} \quad \text{C} \quad \text{N} \quad \text{R}_5 \\
\text{R}_2 & \quad \text{Z} \quad \text{A} \\
\end{align*}
\]

wherein \( R_1 \) and \( R_2 \) are independently hydrogen, substituted or unsubstituted \( C_1-C_8 \) alkyl, substituted or unsubstituted \( C_3-C_6 \) cycloalkyl, substituted or unsubstituted \( C_2-C_8 \) unsaturated alkyl, ketone, substituted or unsubstituted aryl, substituted or unsubstituted \( C_1-C_4 \) alkoxy, substituted or unsubstituted arylhydroxy, substituted or unsubstituted amino, \( C_1-C_4 \) lower ester, \( C_1-C_4 \) lower thioester, thiol, substituted or unsubstituted carboxyl, epoxy, substituted or unsubstituted \( C_1-C_4 \) lower thioalkoxy; or \( R_1 \) and \( R_2 \) are fused to form \( C_3-C_4 \) saturated or unsaturated chain; \( R_3, R_4, R_5, R_6 \) and \( R_7 \) are independently hydrogen, halogen, hydroxy, nitro, \( C_1-C_4 \) lower ester, \( C_1-C_4 \) lower alkyl, \( C_1-C_4 \) lower thioalkyl, substituted or unsubstituted \( C_3-C_6 \) cycloalkyl, \( C_1-C_4 \) lower alkoxy, \( C_1-C_4 \) lower thioalkoxy, substituted or unsubstituted aryl, substituted or unsubstituted lower arylalkoxy, substituted or unsubstituted lower alkylamino, or lower alkyl substituted or unsubstituted carbamate; or among \( R_3, R_4, R_5, R_6 \) and \( R_7 \), two adjacent groups are bonded with each other to form 1,2-phenylene or 2,3-naphthylene; \( X \) is oxygen, sulfur, or substituted or unsubstituted imino; \( Y \) is bonded at the 3-position or 4-position of the aromatic ring part wherein \( Y \) is oxygen or \(-NR_8-\) (wherein, \( R_8 \) is the same with the above-mentioned \( R_3 \)); \( Z \) is hydroxy, \( C_1-C_4 \) lower alkoxy, \( C_1-C_4 \) lower thioalkoxy, substituted or unsubstituted aryloxy, \( C_1-C_4 \) lower alkylamino, substituted or unsubstituted cycloamino containing 1-5 nitrogen atoms; \( A \) is nitrogen or \(-CH=\); and pharmaceutically acceptable acid addition salts thereof.
2. A process for the preparation of compound of the general formula (I) or a pharmaceutically acceptable acid addition salt thereof comprising reacting a compound of the general formula (a) with a \(-\text{C}(=\text{X})-\) group-providing agent in the presence of organic solvent to obtain a compound of the general formula (b) and reacting the compound of the general formula (b) with a compound of the general formula (c).

\[
\begin{align*}
\text{(a)} & \quad \text{(b)} \\
\begin{array}{c}
R_1 \\
R_2 \\
R_3 \\
\end{array} & \quad \begin{array}{c}
R_1 \\
R_2 \\
R_3 \\
\end{array} \\
& \quad \begin{array}{c}
Y \quad H \\
X \quad Y \quad \text{Le} \\
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
\text{(c)} & \quad \text{(l)} \\
\begin{array}{c}
R_7 \\
R_8 \\
R_9 \\
R_4 \\
R_5 \\
R_6 \\
\end{array} & \quad \begin{array}{c}
R_1 \\
R_2 \\
R_3 \\
R_7 \\
R_8 \\
R_9 \\
\end{array} \\
\text{H} & \quad \text{Y} \\
N & \quad \text{N} \\
\end{align*}
\]

wherein, \(R_1, R_2, R_3, R_4, R_5, R_6, R_7, A, X, Y\) and \(Z\) are as defined above and \(\text{Le}\) is a leaving group.

3. A process for the preparation of compound of the general formula (Ib) by introducing \(R_8\) providing agent into a compound of the general formula (Ia).

\[
\begin{align*}
\text{(Ia)} \\
\text{(Ib)}
\end{align*}
\]

wherein, \(R_1, R_2, R_3, R_4, R_5, R_6, R_7, A, X\) and \(Z\) are as defined above.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC\(^6\): C 07 D 213/65, 213/68, 295/108, 295/13, 409/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC\(^6\): C 07 D 213/00, 295/00, 409/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT; Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>WO 96/21 648 A1 (SAMJIN PHARMACEUTICAL CO., LTD.) 18 July 1996 (18.07.96), claims 1, 2.</td>
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<td>US 5 461 047 A (HANSEN) 24 October 1995 (24.10.95), claims; example 43.</td>
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<td>EP 0 547 517 A1 (THOMAE) 23 June 1993 (23.06.93), claims.</td>
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☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance.
  "E" earlier document but published on or after the international filing date.
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
  "O" document referring to an oral disclosure, use, exhibition or other means.
  "P" document published prior to the international filing date but later than the priority date claimed.

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family.

Date of the actual completion of the international search
03 September 1997 (03.09.97)

Date of mailing of the international search report
05 September 1997 (05.09.97)

Name and mailing address of the ISA/ AT
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Kohlmarkt 8-10
A-1014 Vienna

Facsimile No. 1/53424/535

Authorized officer
Hammer

Telephone No. 1/53424/374

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