DESCRIPTION

WATER-SOLUBLE PHENYLPYRIDAZINE DERIVATIVES AND MEDICINES CONTAINING THE SAME

TECHNICAL FIELD

This invention relates to water-soluble phenylpyridazine derivatives, which exhibit excellent inhibitory activity against interleukin-1β production, have high water solubility and oral absorbability, and are useful for the prevention and treatment of immune system diseases, inflammatory diseases, and ischemic diseases, for example, and also to medicines containing them as active ingredients therein.

BACKGROUND ART

In many diseases, for example, rheumatism, arthritis, osteoporosis, inflammatory colitis, immune deficiency syndrome, ichorrhemia, hepatitis, nephritis, ischemic diseases, insulin-dependent diabetes mellitus, arterial sclerosis, Parkinson's disease, Alzheimer's disease, and leukemia, stimulation of interleukin-1β production, an inflammatory cytokine, is observed. This interleukin-1β serves to induce synthesis of an enzyme which is considered to take part in inflammation - like collagenase and PLA2 - and, when intra-articularly injected to animals, causes

multiarticular damage highly resembling rheumatoid arthritis. In a healthy body, on the other hand, the activity of interleukin-1β is controlled by interleukin-1 receptor, soluble interleukin-1 receptor and interleukin-1 receptor antagonist.

From research conducted using recombinant versions of these bioactivity-inhibiting substances, anti-interleukin-1β antibodies and anti-receptor antibodies against various disease models and also from research performed using knockout mice, interleukin-1β has been found to play an important role in the body, leading to an increasing potential of substances having interleukin-1β inhibitory activity as therapeutics for such diseases.

For example, immunosuppressors and steroids, which are used for the treatment of rheumatism, have been reported to inhibit production of interleukin-1β. Among compounds currently under development, KE298, a benzoylpropionic acid derivative [The Japanese Society of Inflammation (11th), 1990], for example, has been reported to exhibit inhibitory activity against interleukin-1β production although it is an immunoregulator. Inhibitory activity against interleukin-1β production is also observed on a group of compounds which are called "COX-2 selective inhibitors", for example, nimesulide as a phenoxysulfonanilide derivative (DE 2333643), T-614 as a phenoxybenzopyran derivative (US Patent 4,954,518), and

tenidap (oxyindole derivative) as a dual inhibitor (COX-1/5-LO).

However, interleukin-1β production inhibitory activity is not the primary action or effect of any of these compounds so the inhibitory activity against interleukin-1β production is less than the primary action thereof.

More recently, increased synthetic research has been conducted emphasizing inhibitory activity against interleukin-1β production. Production inhibitors can be classified into (1) a group of compounds which inhibit the transfer process of an inflammatory signal to a cell nucleus and (2) another group of compounds which inhibit the enzyme ICE that functions in the processing of a precursor of interleukin-1β. Known examples of compounds presumed to have the former action (1) include SB203580 [Japanese Language Laid-Open (Kohyo) Publication (PCT) No. HEI 7-503017], FR167653 (Eur. J. Pharm., **327**, 169-175, 1997), E-5090 (EP 376288), CGP47969A (Gastroenterology, **109**, 812-828, 1995), hydroxyindole derivatives (Eur. J. Med. Chem. **31**, 187-198, 1996), and triarylpyrrole derivatives (WO 9705878), while known examples of compounds presumed to have the latter action (2) include VE-13,045 which is a peptide compound (Cytokine, **8**(5), 377-386, 1996).

None of these compounds, however, exhibit sufficient inhibitory activity against interleukin-1β production.

On the other hand, it is known that 5,6-diphenyl-pyridazine derivatives exhibit analgesic and anti-inflammatory action (Eur. J. Med. Chem., 14, 53-60, 1979). Further, 6-phenylpyridazinones have been reported to be useful as cardio-active compounds (US Patent 4,404,203). Nothing has been reported, however, with respect to inhibitory activity of these pyridazine compounds against interleukin-1β production.

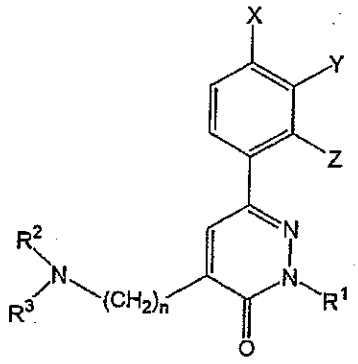
The present inventors previously reported in WO 99/44995 that high inhibitory activity against interleukin-1β production was observed on phenylpyridazine derivatives. Recently, certain phenylpyridazine compounds having inhibitory activity against interleukin-1β production have been reported (JP 7-69894 A, WO 98/41511, WO 99/10331, WO 99/10332, WO 99/25697, WO 00/50408). These reported compounds, however, are different in chemical structure from the compounds of the present invention.

DISCLOSURE OF THE INVENTION

The compounds disclosed in WO 99/44995 exhibit strong inhibitory activity against interleukin-1β production. However, the water solubility of these compounds is so low that their formulation into pharmaceutical preparations, such as tablets, was practically impossible. In the course of a further investigation, the present inventors discovered that the introduction of a substituted or unsubstituted aminoalkyl

group to the 4-position of 6-phenylpyridazine-3-one affords a compound useful as a preventive or therapeutic for immune system diseases, inflammatory diseases, and ischemic diseases, for example, due to its significantly improved water solubility, good oral absorbability and excellent inhibitory activity against interleukin-1β production, leading to the completion of the present invention.

Thus, in one aspect of the present invention, there is provided a pheylpyridazine compound represented by the following formula (1):



(1)

wherein:

R^1 represents a substituted or unsubstituted alkyl group or a substituted or unsubstituted alkenyl group;

R^2 and R^3 each independently represents a hydrogen atom or an alkyl, hydroxyalkyl, dihydroxyalkyl or alkynyl group, or R^2 and R^3 may be fused together with the adjacent nitrogen atom to form a substituted or unsubstituted, nitrogen-containing, saturated heterocyclic group;

X, Y and Z each independently represents a hydrogen or halogen atom, a substituted or unsubstituted alkyl, alkoxy, alkylthio, alkylsulfinyl or alkylsulfonyl group, or a substituted or unsubstituted aryl group; and

n stands for a number of from 1 to 5;

with the proviso that R^2 and R^3 are not hydrogen atoms or the same C_1-C_3 alkyl groups at the same time when R^1 is a benzyl group or a C_1-C_3 alkyl group; or a salt thereof.

In another aspect of the present invention, there is also provided a medicine comprising the phenylpyridazine compound (1) or the salt thereof as an active ingredient.

In yet a further aspect of the present invention, there is also provided a pharmaceutical composition comprising the phenylpyridazine compound (1) or the salt thereof and a pharmacologically acceptable carrier.

In still a further aspect of the present invention, there is also provided use of the phenylpyridazine compound (1) or

the salt thereof for the production of a medicine.

In a yet further aspect of the present invention, there is also provided a method for treating a disease caused by stimulation of interleukin-1β production, which comprises administering the phenylpyridazine compound (1) or the salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphic representation of the oral absorbability of a compound according to the present invention (Example 83) and a comparative compound 3;

FIG. 2 is graphic representations of the oral absorbability of another compound according to the present invention (Example 23);

FIG. 3 is graphic representations of the oral absorbability of a further compound according to the present invention (Example 25);

FIG. 4 is graphic representations of the oral absorbability of a still further compound according to the present invention (Example 143).

BEST MODES FOR CARRYING OUT THE INVENTION

In the above formula (1), the alkyl moieties in the alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkylthio, alkylsulfinyl and alkylsulfonyl groups represent those having

1 to 12 carbon atoms, more preferably 1 to 7 carbon atoms. These alkyl moieties may include linear, branched and cyclic alkyl groups as well as alkyl groups having cyclic structures, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

In the above formula (1), the alkyl group represented by R^1 has preferably 1 to 12 carbon atoms, more preferably 1 to 7 carbon atoms, notably 4 to 7 carbon atoms. Illustrative of such alkyl groups are linear, branched and cyclic alkyl groups as well as alkyl groups having cyclic structures. Preferred examples can include methyl, ethyl, propyl, isobutyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl, with methyl, ethyl, isobutyl, cyclopropylmethyl and cyclopentylmethyl being particularly preferred.

The alkenyl group represented by R^1 preferably has 2 to 12 carbon atoms, with 2 to 7 carbon atoms being particularly preferred. Illustrative of such alkenyl groups are linear and branched alkenyl groups, specifically vinyl, propenyl, butenyl and pentenyl.

Illustrative of group(s) which the alkyl or alkenyl group represented by R^1 may contain as substituent(s) are substituted

or unsubstituted aryl groups and substituted or unsubstituted heteroaryl groups. Examples of the aryl groups include aryl groups having 6 to 14 carbon atoms, specifically phenyl and naphthyl, with phenyl being particularly preferred. Examples of the heteroaryl groups, on the other hand, include 5- or 6-membered heteroaryl groups having 1 to 3 nitrogen atoms, specifically pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl and pyridazinyl, with pyridyl being particularly preferred.

These aryl or heteroaryl groups may contain 1 to 3 substituents such as halogen atoms, alkyl groups or alkoxy groups. Examples of the halogen atoms include fluorine, chlorine, bromine and iodine, with fluorine and chlorine being particularly preferred. These alkyl and alkoxy groups preferably have 1 to 12 carbon atoms, with 1 to 7 carbon atoms being particularly preferred.

The alkyl, hydroxyalkyl and dihydroxyalkyl groups represented by R^2 and R^3 preferably have 1 to 12 carbon atoms, with 1 to 7 carbon atoms being particularly preferred. These groups may preferably be linear or branched. Specific examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, dihydroxypropyl and dihydroxybutyl.

The alkynyl groups represented by R^2 and R^3 preferably have 3 to 12 carbon atoms, with 3 to 7 carbon atoms being

particularly preferred. Illustrative is propargyl (2-propynyl).

Illustrative of the nitrogen-containing, saturated heterocyclic group which may be formed as a result of fusing R^2 and R^3 with the adjacent nitrogen atom are 5- to 7-membered saturated heterocyclic groups, specifically pyrrolidinyl, piperidino, piperazinyl, homopiperazinyl and morpholino, with piperazinyl, piperidino and morpholino being particularly preferred.

Illustrative of group(s) which these heterocyclic groups may contain as substituent(s) are halogen atoms, alkyl groups, alkoxycarbonyl groups and aralkyl groups. Examples of the halogen atoms include fluorine, chlorine, bromine and iodine. The alkyl groups can contain 1 to 12 carbon atoms, preferably 1 to 7 carbon atoms. Illustrative of the alkoxycarbonyl groups are C_1-C_{12} alkyloxycarbonyl groups, with C_1-C_7 alkyloxycarbonyl groups being preferred. Illustrative of the aralkyl groups are phenyl(C_1-C_7 alkyl) groups, with benzyl being particularly preferred.

Illustrative of the halogen atoms represented by X, Y and Z are fluorine, chlorine, bromine, and iodine. The alkyl groups can contain 1 to 12 carbon atoms, with 1 to 7 carbon atoms being particularly preferred. Among these alkyl groups, linear or branched ones are particularly preferred. Illustrative of group(s) which the alkyl group may contain as substituent(s)

are halogen atoms and alkoxy groups. The alkoxy, alkylthio, alkylsulfinyl and alkylsulfonyl groups can contain 1 to 12 carbon atoms, with 1 to 7 carbon atoms being particularly preferred. Among these alkoxy, alkylthio, alkylsulfinyl and alkylsulfonyl groups, linear or branched ones are particularly preferred. Specific examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylthio, ethylthio, propylthio, isopropylthio, butylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, and butylsulfonyl. Illustrative of the aryl group are aryl groups having 6 to 14 carbon atoms, specifically phenyl and naphthyl, with phenyl being particularly preferred. Illustrative of group(s) which the aryl group may contain as substituent(s) are halogen atoms, alkyl groups, and alkoxy groups.

n stands for a number of from 1 to 5, with 1 to 3 being more preferred, and with 1 or 3 being particularly preferred.

When R^1 is a benzyl group or a C_1-C_3 alkyl group, R^2 and R^3 are not hydrogen atoms or the same C_1-C_3 alkyl groups at the same time.

In the formula (1), particularly preferred as R^1 are isobutyl, cyclopropylmethyl, cyclopentylmethyl, cinnamyl, halogenocinnamyl, benzyl, halogenobenzyl, dihalogenobenzyl, and (halogenophenyl)propyl. Preferred as R^2 and R^3 are hydrogen,

C_{1-7} alkyl, C_{1-7} hydroxyalkyl, and propargyl. Preferred as the heterocyclic group formed by R^2 and R^3 are piperazinyl, piperidino, pyrrolidinyl and morpholino, each of which may optionally be substituted by one or more C_{1-7} alkyl or benzyl groups. Preferred as X are methyl, methoxy, methylthio, and halogens. Preferred as Y are hydrogen, methyl and halogens. Preferred as Z is hydrogen. Preferred as n are 1 and 3.

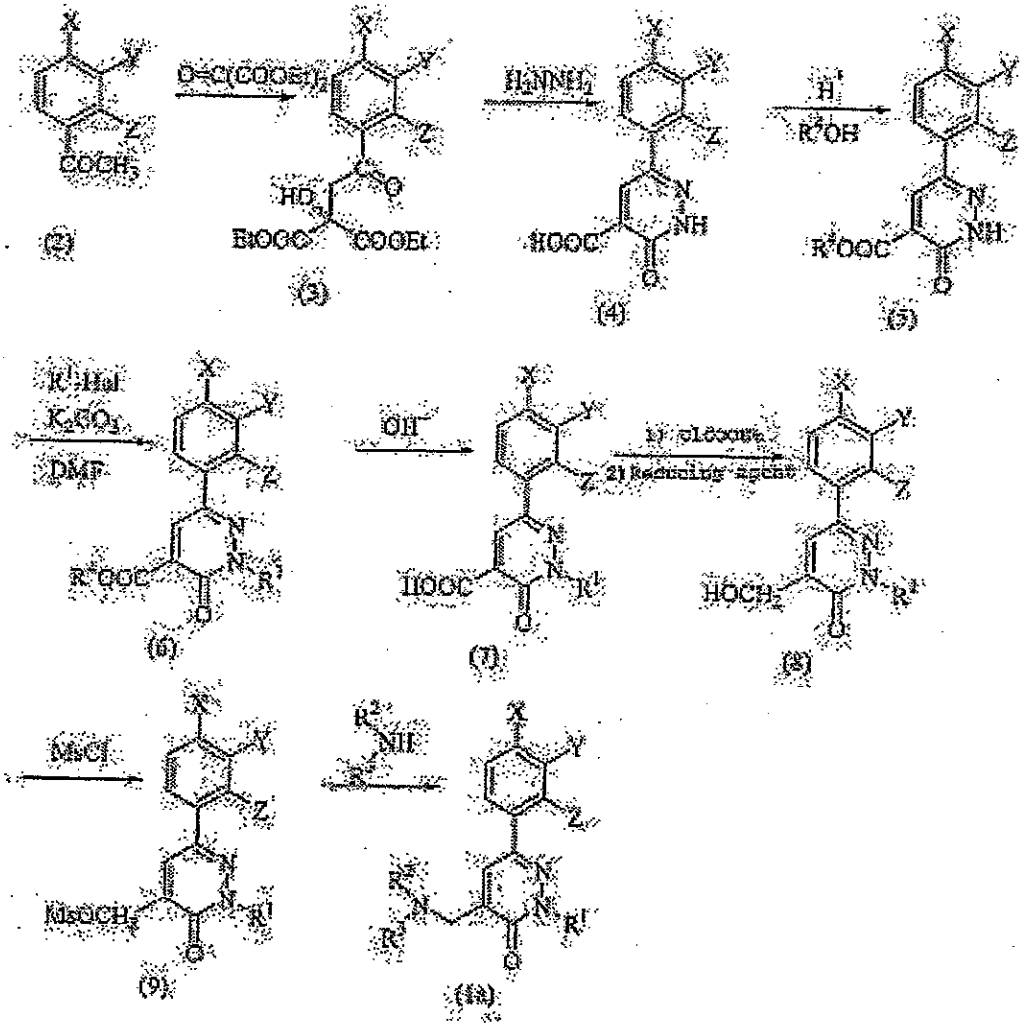
As the salt of the compound (1) of the present invention, an acid addition salt is preferred. Examples of the acid addition salt include inorganic acid salts, such as the hydrochloride, sulfate, nitrate and phosphate, and organic acid salts, such as the methanesulfonate, maleate, fumarate, citrate and oxalate.

Further, the compound according to the present invention may exist in the form of solvates and a keto-enol tautomer. Such solvates and tautomer are encompassed by the present invention. Illustrative of solvates are those formed as a result of addition of solvents used upon production, for example, water and alcohols. No particular limitation is imposed on the solvents insofar as they do not adversely affect the inhibitory activity or the like of the compound according to the present invention against interleukin-1β production. As a solvate, the hydrate is preferred.

The phenylpyridazine compound (1) according to the present invention can be prepared, for example, by the

following preparation processes (a) to (d).

(a) Preparation process of compounds having the formula (1) in which n=1



wherein R^4 represents an alkyl group, Hal represents a halogen atom, Ms represents a methanesulfonyl group, and R^1, R^2, R^3, X, Y and Z have the same meanings as described above.

A description will hereinafter be made about the individual reaction steps.

In the steps from an acetophenone (2) to a compound (5), the acetophenone (2) and diethyl ketomalonate are heated under stirring to yield a compound (3). Hydrazine is caused to act on the compound to carry out a ring-closing reaction, and the reaction product is then treated with an alkali, for example, sodium hydroxide or the like to afford a compound (4). The compound (4) is next reacted with an alcohol such as methanol to give the compound (5).

R^1-Hal is reacted to the compound (5) in the presence of an alkali such as potassium carbonate to provide a compound (6). The compound (6) is hydrolyzed into a compound (7). After ethyl chlorocarbonate is caused to act on the compound (7) to convert it into an acid anhydride, the acid anhydride is reduced with a reducing agent such as sodium borohydride to afford a compound (8). A reaction of methanesulfonyl chloride with the compound (8) in the presence of a base such as triethylamine provides a compound (9), a key intermediate in this reaction scheme.

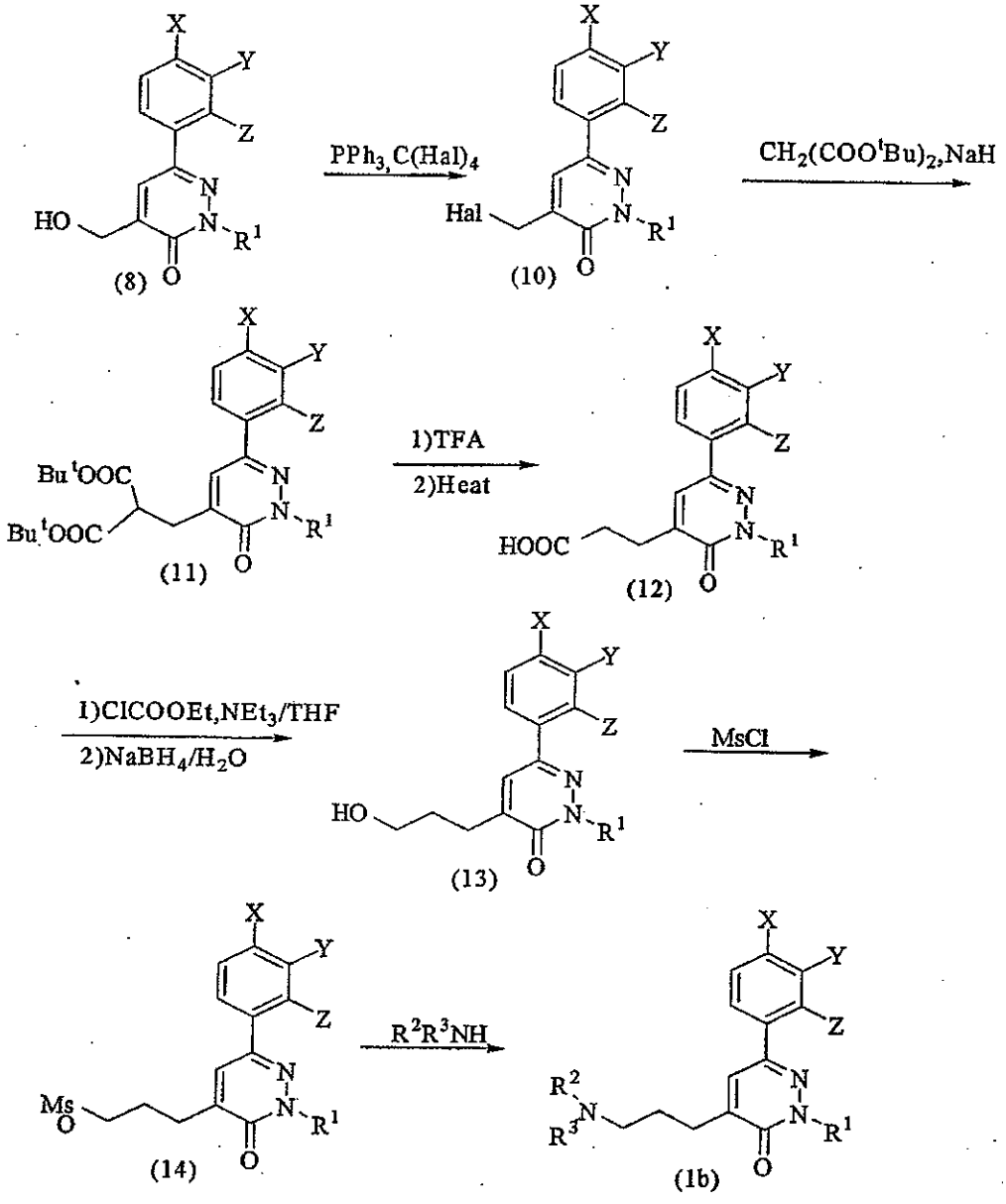
A reaction of a desired amine ($R^2(R^3)NH$) with the compound (9) yields the target compound (1a). It is preferred to carry out this reaction, for example, in a polar solvent such as dimethylformamide in the presence or absence of an alkali such as potassium carbonate. Incidentally, if an amino group is contained in the group R^2 or R^3 in the amine, a reaction may be carried out using a raw material protected with an appropriate protecting group, for example, an alkoxycarbonyl

group, followed by the removal of the protecting group.

To obtain a compound (1a) in which R^2 and R^3 are hydrogen atoms, potassium phthalimide is reacted with the compound (9), and the reaction product is reacted further with hydrazine or the like.

A compound (1a) in which X, Y and/or Z is a methylsulfinyl group or a methylsulfonyl group can be obtained by oxidizing a corresponding compound, in which X, Y and/or Z is a methylthio group, with a peracid, for example, perbenzoic acid. This methylsulfination or methylsulfonation may be carried out at the stage of the intermediate (9).

(b) Preparation process of compounds having the formula (1) in which n=3



wherein Hal, Ms, R^1, R^2, R^3, X, Y and Z have the same meanings as defined above.

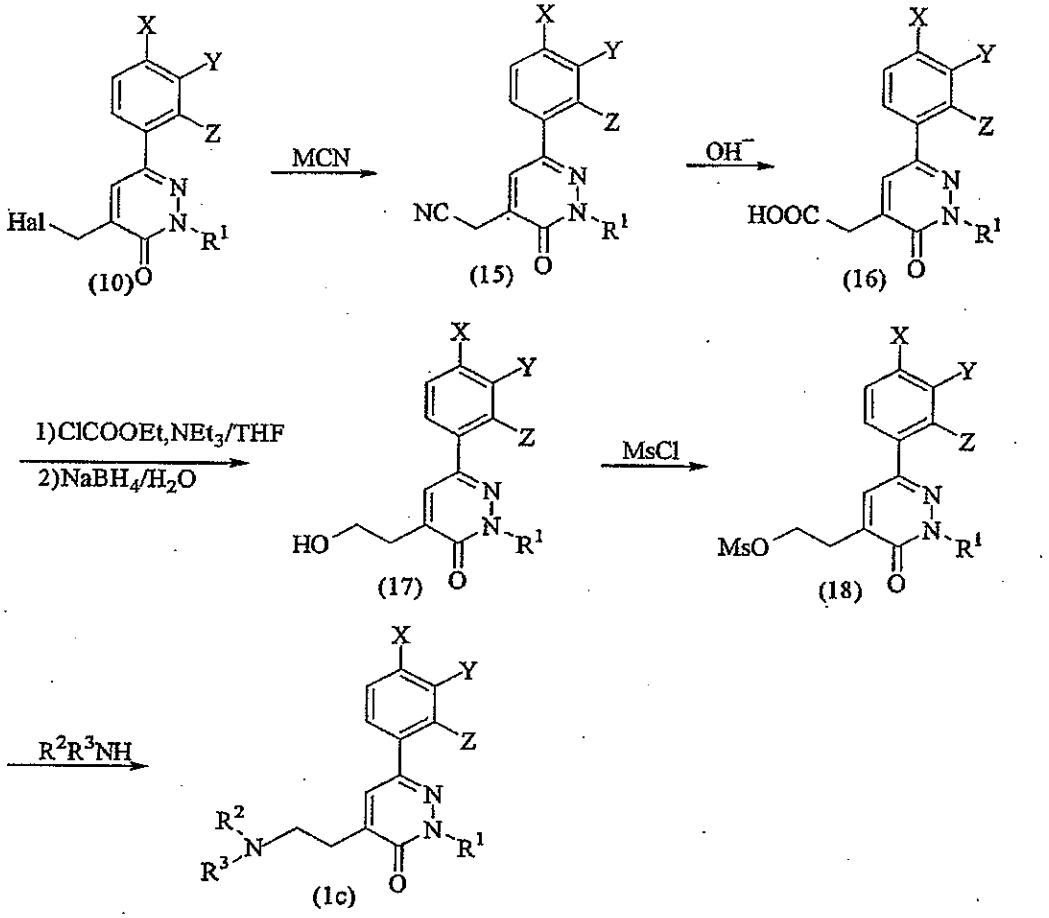
According to the preparation process (b), a carbon tetrahalide such as carbon tetrabromide is firstly reacted with the compound (8) in the presence of triphenylphosphine to

obtain a halide (10), with which a malonate is then reacted in the presence of sodium hydride to yield a compound (11). An acid such as trifluoroacetic acid is reacted with the compound (11) to convert it into a dicarboxylic acid, followed by heating to yield a compound (12). Ethyl chlorocarbonate is caused to act on the compound (12) to convert it into an acid anhydride, which is then reduced with a reducing agent such as sodium borohydride to yield a compound (13). Methanesulfonyl chloride is reacted with the compound (13) in the presence of a base such as triethylamine to yield a compound (14), a key intermediate in the process according to the present invention.

A target compound (1b) can be obtained by reacting a corresponding amine (R^2R^3NH) with the compound (14). This reaction may preferably be conducted, for example, in the presence or absence of an alkali such as potassium carbonate in a polar solvent such as dimethylformamide. When an amino group is contained in the group R^2 or R^3 of the amine, a reaction may be conducted using a raw material in which the amino group has been protected with an appropriate protecting group (for example, an alkoxycarbonyl group), followed by deprotection of the protecting group.

To yield a compound (1b) in which R^2 and R^3 are both hydrogen atoms, the compound can be obtained by reacting potassium phthalimide with the compound (14) and then reacting hydrazine or the like.

(c) Preparation process of compounds having the formula (1) in which n=2



wherein M represents a metal atom, and Hal, Ms, R^1, R^2, R^3, X, Y and Z have the same meanings as defined above.

According to the preparation process (c), a cyanide such as sodium cyanide is reacted with a halide (10) to convert it into a nitrile derivative (15), which is then hydrolyzed to yield a compound (16). From the compound (16), a target compound (1c) can be obtained via an alcohol derivative (17) and a mesyloxy derivative (18) by a similar procedure as in the

preparation of compounds each of which contains three methylene groups.

(d) Preparation process of compounds having the formula (1) in which n=4 or 5

These compounds can be obtained by combining the synthesis processes (b) and (c).

The salt of the compound (1) according to the present invention can be obtained by causing an organic acid or inorganic acid to act in a manner known *per se* in the art.

The compound (1) according to the present invention can be isolated and purified by subjecting it to purification procedures commonly employed in organic synthesis chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, various chromatographic procedures, and/or the like. Each intermediate can be subjected to the subsequent reaction without bothering to purify it. The compound (1) may be provided as a solvate with a solvent such as a reaction solvent or recrystallization solvent, especially as the hydrate.

The compound (1) according to the present invention is excellent in water solubility, is also good in oral absorbability and has inhibitory activity against interleukin-1β production, and therefore, is useful as a preventive or therapeutic for immune system diseases, inflammatory diseases, ischemic diseases, osteoporosis,

ichoremia and the like. Examples of ischemic diseases include ischemic heart diseases, ischemic encephalopathy, ischemic nephritis, and ischemic hepatitis.

The pharmaceutical composition of the present invention contains the compound (1) or the salt thereof as an active ingredient. Using the active ingredient alone or together with a pharmacologically acceptable carrier such as a solubilizer, excipient, binder or extender, it can be formed into pharmaceutical preparation forms such as tablets, capsules, granules, powders, injections and suppositories. These pharmaceutical preparations can be produced by known methods. For example, oral preparations can be produced by suitably formulating the compound (1) or the salt in combination with solubilizers such as tragacanth gum, gum arabic, sucrose esters, lecithin, olive oil, soybean oil and PEG400; excipients such as starch, mannitol and lactose; binders such as carboxy-methylcellulose sodium and hydroxypropylcellulose; disintegrators such as crystalline cellulose and carboxy-methylcellulose calcium; lubricants such as talc and magnesium stearate; anticaking agents such as light anhydrous silicic acid. The pharmaceutical composition according to the present invention is administered orally or parenterally.

The administered dosage of the pharmaceutical composition according to the present invention varies depending on the body weight, age, sex, conditions and the like

of each patient. In general, however, it is preferred to administer to an adult in an amount of about 0.01 to 1,000 mg, preferably 0.1 to 100 mg, of the present pharmaceutical composition in terms of the compound (1) per day in 1 to 3 portions.

EXAMPLES

The present invention will now be further described by reference to the following Examples. The Examples are provided solely for purposes of illustration and are not intended to be limitative.

Example 1

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

1) Preparation of 4-(1-hydroxyethyl)-2-fluorotoluene

To an ice-cold solution of 3-fluoro-4-methylbenzaldehyde (50 mg, 0.36 mmol) in THF (0.5 mL) was added dropwise a 0.93 M solution (0.47 mL) of methylmagnesium bromide (0.44 mmol) in THF. The temperature of the reaction mixture was allowed to rise back to room temperature, at which the reaction mixture was stirred for 1 hour. Then, 2 mol/L hydrochloric acid was added, and the mixture was extracted with ethyl acetate. The extract was

washed with brine and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to yield title compound as a pale yellow oil (55.8 mg, quantitative).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.46(3H, d, J=6.4 Hz), 2.26(3H, d, J=1.8 Hz), 4.85(1H, q, J=6.4 Hz), 6.99-7.06(2H, m), 7.14(1H, dd, J=7.8, 7.8 Hz).

2) Preparation of 3'-fluoro-4'-methylacetophenone

To a solution of 4-(1-hydroxyethyl)-2-fluorotoluene (55.8 mg, 0.36 mmol) in methylene chloride (1 mL) were added molecular sieve 4A (56.0 mg) and PCC 94.0 mg (0.43 mmol), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield the title compound as a pale yellow oil (47.5 mg, 86.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.32(3H, d, J=1.8 Hz), 2.56(3H, s), 7.26(1H, dd, J=7.6, 7.6 Hz), 7.56(1H, dd, J=1.6, 10.4 Hz), 7.62(1H, dd, J=1.6, 7.8 Hz).

3) Preparation of ethyl 2-ethoxycarbonyl-4-(3-fluoro-4-methylphenyl)-2-hydroxy-4-oxobutanoate

A mixture of 3'-fluoro-4'-methylacetophenone (4.92 g, 32.3 mmol) and diethyl ketomalonate (6.19 g, 35.6 mmol) was

stirred at 120℃ for 48 hours. The temperature of the reaction mixture was allowed to drop back to room temperature, and the mixture was purified by column chromatography on silica gel [silica gel 100 g, chloroform/ethyl acetate (10/1)] to yield the title compound as yellow crystals (8.41 g, 79.3%).

Melting point: 68.7-69.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30(6H, t, J=7.1 Hz), 2.34(3H, s), 3.78(2H, s), 4.25(1H, s), 4.31(4H, q, J=7.1 Hz), 7.29(1H, dd, J=7.6 Hz), 7.59(1H, d, J=10.2 Hz), 7.65(1H, dd, J=1.5, 7.8 Hz).

IR(KBr) cm^{-1}: 3485, 1740, 1684, 1253, 856, 577.

4) Preparation of 4-carboxy-6-(3-fluoro-4-methylphenyl)-2H-pyridazin-3-one

To a solution of ethyl 2-ethoxycarbonyl-4-(3-fluoro-4-methylphenyl)-2-hydroxy-4-oxobutanoate (8.41 g, 25.8 mmol) in isopropanol (100 mL) was added hydrazine monohydrate (2.84 g, 56.8 mmol), and the mixture was heated under stirring at 100℃ for 6 hours. Then, 2 mol/L sodium hydroxide was added, and the mixture was stirred further at the same temperature for 4 hours. The reaction mixture was ice-cooled, and concentrated hydrochloric acid was added to acidify the system. The precipitate was collected by filtration, thoroughly washed with water and dried to yield the

title compound as a slightly yellow crystalline powder (5.67 g, 87.7%).

Melting point: 281.3-282.0℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.28(3H, d, J=1.0 Hz), 7.41(1H, dd, J=8.1, 8.1 Hz), 7.67-7.73(2H, m), 8.49(1H, s), 14.09(1H, br).

IR(KBr) cm^{-1}: 1736, 1641, 1441, 1125, 926, 806.

5) Preparation of 6-(3-fluoro-4-methylphenyl)-4-methoxy-carbonyl-2H-pyridazin-3-one

To an ice-cold suspension of 4-carboxy-6-(3-fluoro-4-methyl-phenyl)-2H-pyridazin-3-one (5.50 g, 22.2 mmol) in methanol (100 mL) was added dropwise thionyl chloride (2.72 g, 24.4 mmol), and the mixture was stirred at 80℃ for 8 hours. The temperature of the reaction mixture was allowed to drop back to room temperature, and the solvent was distilled off under reduced pressure. Water was added to the ice-cold residue. The precipitate was collected by filtration, washed with water and dried to yield the title compound as pale yellow fine-needles (5.43 g, 92.7%).

Melting point: 206.0-207.3℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, d, J=1.7 Hz), 4.00(3H, s), 7.29(1H, dd, J=7.9, 7.9

Hz), 7.46-7.53(2H, m), 8.32(1H, s), 11.61(1H, s).

IR(KBr) cm^{-1}: 1715, 1671, 1266, 1177, 1091, 812.

6) Preparation of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one

To a solution of 6-(3-fluoro-4-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one (5.28 g, 20.0 mmol) in N,N-dimethylformamide (40 mL) were added potassium carbonate (5.53 g, 40.0 mmol) and isobutyl bromide (3.29 g, 24.0 mmol), and the mixture was stirred at 80℃ for 1 hour. The temperature of the reaction mixture was allowed to drop back to room temperature. A saturated aqueous solution of sodium hydrogencarbonate was added, and the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel [silica gel 100 g, chloroform/methanol (100/1→50/1)) to yield the title compound as an orange oil (5.41 g, 84.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.32-2.42(1H, m), 2.33(3H, s), 3.98(3H, s), 4.12(2H, d, J=7.4 Hz), 7.28(1H, dd, J=7.8, 7.8 Hz), 7.46(1H, dd, J=1.6, 7.8 Hz), 7.50(1H, dd, J=1.6, 10.7 Hz), 8.21(1H, s).

7) Preparation of

4-carboxy-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

To a suspension of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one (5.27 g, 16.6 mmol) in methanol (50 mL) was added a 2 mol/L aqueous sodium hydroxide (50 mL), and the mixture was stirred at 60℃ for 15 minutes. The temperature of the reaction mixture was allowed to drop back to room temperature, and then, water was added. After the system was acidified with concentrated hydrochloric acid, the mixture was extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized from chloroform-hexane to yield the title compound as colorless fine-needles (4.73 g, 93.8%).

Melting point: 159.0-159.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.02(6H, d, J=6.7 Hz), 2.33-2.42(1H, m), 2.35(3H, d, J=1.6 Hz), 4.21(2H, d, J=7.4 Hz), 7.32(1H, dd, J=7.8, 7.8 Hz), 7.52(1H, dd, J=1.8, 8.0 Hz), 7.55(1H, dd, J=1.8, 10.6 Hz), 8.63(1H, s), 14.13(1H, s).

IR(KBr) cm^{-1}: 2960, 1742, 1633, 1574, 1425, 1101, 820.

8) Preparation of

6-(3-fluoro-4-methylphenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one

To a solution of 4-carboxy-6-(3-fluoro-4-methyl-phenyl)-2-isobutyl-2H-pyridazin-3-one (4.53 g, 14.9 mmol) in THF (40 mL) was added triethylamine (1.66 g, 16.4 mmol). To the ice-cooled mixture was added dropwise a solution of ethyl chlorocarbonate (1.78 g, 16.4 mmol) in THF (5 mL), and the mixture was stirred for 30 minutes. Triethylamine hydrochloride was filtered off. A solution of sodium borohydride (564 mg, 14.9 mmol) in water (1 mL) was added to the filtrate, and then, the mixture was stirred at room temperature for 10 minutes. Thereafter, 2 mol/L hydrochloric acid was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel [silica gel 300 g, chloroform/methanol (100/1→50/1)) to yield the title compound as a colorless crystalline powder (1.08 g, 25.0%).

Melting point: 147.3-147.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.29-2.39(1H, m), 2.32(3H, d, J=1.8 Hz), 3.05(1H, t, J=6.0 Hz), 4.08(2H, d, J=7.4 Hz), 4.71(2H, dd,

J=1.2, 6.0 Hz), 7.26(1H, dd, J=7.8 Hz), 7.46(1H, dd, J=7.8, 7.8Hz), 7.50(1H, dd, J=1.8, 10.8 Hz), 7.65(1H, s).

IR(KBr) cm^{-1}: 3330, 1644, 1596, 1514, 1226, 1087, 824.

9) Preparation of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

To an ice-cold solution of 6-(3-fluoro-4-methyl-phenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one (1.08 g, 3.73 mmol) in methylene chloride (20 mL) were added triethylamine (491 mg, 4.85 mmol) and methanesulfonyl chloride (513 mg, 4.48 mmol), and the mixture was stirred for 1 hour. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture, and then, the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized from chloroform-hexane to yield the title compound as a colorless crystalline powder (964 mg, 70.4%).

Melting point: 142.7-143.4℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.30-2.34(1H, m), 2.33(3H, d, J=1.8 Hz), 3.17(3H, s), 4.08(2H, d, J=7.4 Hz), 5.27(2H, d, J=1.4 Hz), 7.27(1H, dd, J=7.8, 7.8 Hz), 7.45(1H, dd, J=1.8, 8.0 Hz),

7.50(1H, dd, J=1.8, 10.9 Hz), 7.76(1H, t, J=1.4 Hz).
IR(KBr) cm^{-1}: 3435, 2964, 1658, 1610, 1354, 1165, 875.

10) Preparation of
4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

To a solution of
6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one (100 mg, 0.27 mmol) in acetonitrile (1 mL) were added potassium carbonate (56.3 mg, 0.41 mmol) and tert-butyl 1-piperazine-carboxylate (60.7 mg, 0.33 mmol), and the mixture was stirred at 80℃ for 2 hours. The temperature of the reaction mixture was allowed to drop back to room temperature, and then, water was added. The mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol (40/1)] to yield the title compound as a yellow oil (115 mg, 92.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:
0.98(6H, d, J=3.4 Hz), 1.47(9H, s), 2.28-2.40(1H, m), 2.33(3H, s), 2.52(4H, t, J=4.7 Hz), 3.51(4H, t, J=4.7 Hz), 3.58(2H, s), 4.07(2H, d, 4.1 Hz), 7.27(1H, dd, J=7.6, 7.6 Hz), 7.44-7.52(2H,

m), 7.77(1H, s).

Example 2

Preparation of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

To a solution of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one (115 mg, 0.25 mmol) in ethyl acetate (2 mL) was added a 4 mol/L solution (2 mL) of hydrochloric acid in ethyl acetate, and the mixture was stirred at 50℃ for 1 hour. The temperature of the reaction mixture was allowed to drop back to room temperature, and then, diethyl ether was added. The precipitate was collected to yield the title compound as a colorless crystalline powder (81.1 mg, 75.0%).

Melting point: 186.2-195.0℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.22-2.33(1H, m), 2.29(3H, d, J=2.0 Hz), 3.15(4H, br), 3.32(4H, t, J=5.2 Hz), 3.93(2H, s), 4.02(2H, d, J=7.1 Hz), 7.40(1H, dd, J= 8.1, 8.1 Hz), 7.59-7.66(2H, m), 8.21(1H, s).

IR(KBr) cm^{-1}: 1656, 1610, 1425, 1306, 956.

Mass m/z: 358(M^+)

Example 3

Preparation of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 93.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.28-2.40(1H, m), 2.33(6H, s), 2.52(4H, br), 2.62(4H, br), 3.58(2H, s), 4.07(2H, d, J=7.4 Hz), 7.27(1H, dd, J=7.9, 7.9 Hz), 7.46-7.52(2H, m), 7.75(1H, d, J=1.0 Hz).

Example 4

Preparation of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

To a solution of 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one (94.4 mg, 0.25 mmol) in methanol (1 mL) was added dropwise at room temperature under stirring a 4 mol/L solution (0.15 mL) of hydrochloric acid in ethyl acetate. The solvent was distilled off under reduced pressure. The residue was recrystallized from

methanol-diethyl ether to yield the title compound as a colorless crystalline powder (71.9 mg, 63.7%).

Melting point: 248.5-252.0℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.29(3H, d, J=1.8 Hz), 2.22-2.33(1H, m), 2.77(3H, s), 3.18(4H, br), 3.38(4H, br), 3.91(2H, s), 4.02(2H, d, J=7.0 Hz), 7.40(1H, dd, J=8.0, 8.0 Hz), 7.59-7.65(2H, m), 8.16(1H, s).

IR(KBr) cm^{-1}: 1653, 1609, 1451, 1425, 951.

Mass m/z: 372(M^+)

Example 5

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 84.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.96(6H, d, J=6.6 Hz), 2.27-2.38(1H, m), 2.30(3H, s), 2.70(4H, t, J=5.0 Hz), 3.66(4H, t, J=5.2 Hz), 3.69(2H, s), 4.06(2H, d, J=7.2 Hz), 7.23(1H, dd, J=7.9, 7.9 Hz), 7.46-7.52(2H, m), 7.79(1H, s).

Example 6

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 85.9%).

Melting point: 159.7-160.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.6 Hz), 2.20-2.34(1H, m), 2.30(3H, d, J=1.7 Hz), 3.35(4H, t, J=5.1 Hz), 3.84(4H, t, J=5.1 Hz), 4.05(2H, d, J=7.0 Hz), 4.45(2H, s), 7.42(1H, dd, J=8.2, 8.2 Hz), 7.62-7.68(2H, m), 8.47(1H, s).

IR(KBr) cm^{-1}: 1663, 1613, 1427, 1087, 1052, 821.

Mass m/z: 359(M^+-H_2O)

Example 7

Preparation of 4-dimethylaminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

To 6-(3-fluoro-4-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one (100 mg, 0.27 mmol) was

added a 40% aqueous dimethylamine (1 mL), and the mixture was stirred at 80℃ for 2 hours. The temperature of the reaction mixture was allowed to drop back to room temperature, and then, water was added. The mixture was extracted with chloroform. The extract was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel [chloroform/methanol (40/1)] to yield the title compound as a yellow oil (69.7 mg, 80.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.23-2.41(1H, m), 2.31(3H, s), 2.35(6H, s), 3.50(2H, d, J=1.2 Hz), 4.08(2H, d, J=7.4 Hz), 7.26(1H, dd, J=7.9, 7.9 Hz), 7.47-7.54(2H, m), 7.76(1H, d, J=1.4 Hz).

Example 8

Preparation of 4-dimethylaminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethyl-aminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 85.4%).

Melting point: 246.5-248.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.6 Hz), 2.23-2.34(1H, m), 2.30(3H, s), 2.81(6H, s), 4.05(2H, d, J=7.0 Hz), 4.27(2H, s), 7.41(1H, dd, J=8.0, 8.0 Hz), 7.22-7.68(2H, m), 8.52(1H, s).

IR(KBr) cm^{-1}: 1648, 1607, 1422, 1227, 1110, 1051.

Mass m/z: 317(M^+)

Example 9

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

1) Preparation of 4-carboxy-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-cyclo-propylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methoxy-carbonyl-2H-pyridazin-3-one was reacted to yield the title compound as yellow crystals (yield: 98.9%).

Melting point: 169.1-170.7℃

^1H NMR(400MHz, $CDCl_3$)δ:

0.50-0.67(4H, m), 1.40-1.50(1H, m), 3.97(3H, s), 4.23(2H, d, J=7.3 Hz), 7.07(1H, dd, J=8.5, 8.5 Hz), 7.57(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.85(1H, dd, J=2.2, 12.2 Hz), 8.63(1H, s), 14.20(1H, s).

IR(KBr) cm^{-1} : 1761, 1629, 1521, 1476, 1461.

Mass m/z: 318 (M^+).

2) Preparation of

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow fine-needles (yield: 21.3%).

Melting point: 119.4-122.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.60(4H, m), 1.36-1.47(1H, m), 3.12(1H, t, J=6.0 Hz), 3.95(3H, s), 4.10(2H, d, J=7.3 Hz), 4.72(2H, dd, J=1.2, 5.9 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.51(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.62(1H, dd, J=2.2, 12.4 Hz), 7.65(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 3431. 1652, 1604, 1524.

Mass m/z: 304(M^+).

3) Preparation of

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 80.4%).

Melting point: 156.9-158.4℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.61(4H, m), 1.36-1.46(1H, m), 3.18(3H, s), 3.95(3H, s), 4.10(2H, d, J=7.3 Hz), 5.28(2H, d, J=1.2 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.51(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.62(1H, dd, J=2.2, 12.2 Hz), 7.76(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 1656, 1612, 1523, 1358, 1177.

Mass m/z: 382(M^+).

4) Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methylaminomethyl-2H-pyridazin-3-one

A solution of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one (160 mg, 0.42 mmol) in 30% methylamine/ethanol (5 mL) was stirred at 80℃ for 4 hours in a sealed tube. The solvent was distilled off under reduced pressure, and the residue was purified by preparative thin-layer chromatography on silica gel [developing solvent: chloroform/methanol (10/1)] to yield title compound as a slightly yellow oil (87 mg, 65.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.59(4H, m), 1.36-1.47(1H, m), 1.85(1H, br), 2.52(3H, s), 3.80(2H, d, J=1.2 Hz), 3.95(3H, s), 4.10(2H, d, J=7.3 Hz), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.52(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.62(1H, dd, J=2.2, 12.4 Hz), 7.66(1H, t, J=1.2 Hz).

Mass m/z: 317(M^+).

Example 10

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methylaminomethyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-methylaminomethyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 93.8%).

Melting point: 220.8-224.3℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.44-0.54(4H, m), 1.29-1.40(1H, m), 2.66(3H, s), 3.91(3H, s), 4.05(2H, d, J=7.3 Hz), 4.12(2H, s), 7.33(1H, dd, J=8.5, 8.5 Hz), 7.70-7.79(2H, m), 8.39 (1H, s).

IR(KBr) cm^{-1}: 1645, 1599, 1521, 1437.

Example 11

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield:

73.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.59(4H, m), 1.36-1.47(1H, m), 2.33(3H, s), 2.52(4H, br), 2.62(4H, br), 3.80(2H, d, J=1.2 Hz), 3.58(2H, d, J=1.0 Hz), 3.95(3H, s), 4.09(2H, d, J=7.3 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.53(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.61(1H, dd, J=2.2, 12.4 Hz), 7.74(1H, t, J=1.2 Hz).

IR(Neat) cm^{-1}: 1652, 1608, 1520, 1456, 1440.

Mass m/z: 386 (M^+).

Example 12

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow needles (yield: 81.0%).

Melting point: 237.4-238.4℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.47-0.58(4H, m), 1.31-1.41(1H, m), 2.33(3H, s), 2.52(4H, br), 2.62(4H, br), 2.90-3.85(10H, m), 3.91(3H, s), 4.03(2H, d, J=7.3 Hz), 7.30(1H, dd, J=8.5, 8.5 Hz), 7.70-7.78(2H, m),

8.28(1H, brs).

IR(KBr) cm^{-1}: 1653, 1608, 1523, 1438.

Example 13

Preparation of 2-cyclopropylmethyl-4-dimethylamino-methyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow oil (yield: 88.1%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.45-0.59(4H, m), 1.37-1.48(1H, m), 2.36(6H, s), 3.51(2H, s), 3.95(3H, s), 4.10(2H, d, J=7.3 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.53-7.57(1H, m), 7.64(1H, dd, J=2.2, 12.7 Hz), 7.75(1H, s).

IR(Neat) cm^{-1}: 1652, 1608, 1523, 1456, 1438.

Mass m/z: 331(M^+).

Example 14

Preparation of 2-cyclopropylmethyl-4-dimethylamino-methyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 89.0%).

Melting point: 233.6-235.0℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.41-0.54(4H, m), 1.27-1.37 (1H, m), 2.83(6H, s), 3.92(3H, s), 4.06(2H, d, J=7.3 Hz), 4.30(2H, s), 7.33(1H, dd, J=8.8, 8.8 Hz), 7.69-7.77(2H, m), 8.51(1H, s).

IR(KBr) cm^{-1}: 1648, 1584, 1522, 1439.

Example 15

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(2-hydroxyethyl)aminomethyl-2H-pyridazin-3-one

Following the procedure of Example 9(4), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 2-aminoethanol were reacted to yield the title compound as a yellow oil (yield: 72.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.59(4H, m), 1.36-1.47(1H, m), 2.86(2H, t, J=5.1 Hz), 3.73(2H, t, J=5.1 Hz), 3.84(2H, d, J=1.0 Hz), 3.94(3H, s), 4.10(2H, d, J=7.3 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.50-7.54(1H, m), 7.62(1H, dd, J=2.2, 12.7 Hz), 7.67(1H, s).

IR(Neat) cm^{-1}: 3411, 1651, 1605, 1523, 1439.

Mass m/z: 347 (M^+).

Example 16

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(2-hydroxyethyl)aminomethyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-N-(2-hydroxyethyl)-aminomethyl-2H-pyridazin-3-one was reacted to yield the title compound as pale brown needles (yield: 79.2%).

Melting point: 166.8-169.3℃ (dec.)

^1H NMR(400MHz, $CDCl_3$)δ:

0.40-0.54(4H, m), 1.27-1.37(1H, m), 3.13(2H, br), 3.28(2H, br), 3.74(3H, s), 4.05(2H, d, J=7.1 Hz), 4.18(2H, s), 5.31(1H, br), 7.33(1H, dd, J=8.8, 8.8 Hz), 7.69-7.79(2H, m), 8.40(1H, s).

IR(KBr) cm^{-1}: 3334, 1654, 1616, 1604, 1523, 1441.

Example 17

Preparation of 4-(4-benzyl-1-piperazinyl)methyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10),

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-benzylpiperazine were reacted to yield the title compound as a yellow oil (yield: 97.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.58(4H, m), 1.36-1.46(1H, m), 2.56(4H, br), 2.62(4H, br), 3.56(2H, s), 3.58(2H, d, J=1.0 Hz), 3.95(3H, s), 4.09(2H, d, J=7.1 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.23-7.36(5H, m), 7.50-7.55(1H, m), 7.61(1H, dd, J=2.2, 12.7 Hz), 7.75(1H, s).

IR(Neat) cm^{-1}: 1652, 1608, 1522, 1438, 1289, 1237.

Mass m/z: 462(M^+).

Example 18

Preparation of 4-(4-benzyl-1-piperazinyl)methyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 4-(4-benzyl-1-piperazinyl)methyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow prisms (yield: 85.7%).

Melting point: 253.0-257.9℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.41-0.55(4H, m), 1.27-1.38(1H, m), 3.06-3.49(10H, br), 3.56(2H, s), 3.91(3H, s), 4.02(2H, d, J=7.3 Hz), 4.39(2H, brs), 7.30(1H, dd, J=8.5, 8.5 Hz), 7.44-7.48(3H, m), 7.59-7.64(2H, m), 7.69-7.77(2H, m) , 8.30(1H, brs).

IR(KBr) cm^{-1}: 1656, 1616, 1523, 1439, 1292, 1271.

Example 19

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a pale brown oil (yield: 98.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.59(4H, m), 1.47(9H, s), 1.38-1.46(1H, m), 2.53(4H, t, J=4.9 Hz), 3.51(4H, t, J=4.9 Hz), 3.58(2H, d, J=1.2 Hz), 3.95(3H, s), 4.10(2H, d, J=7.3 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.51(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.61(1H, dd, J=2.2, 12.7 Hz), 7.76(1H, s).

IR(Neat) cm^{-1}: 1698, 1653, 1609, 1523, 1438, 1427.

Mass m/z: 472 (M^+).

Example 20

Preparation of

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

4-(4-tert-Butoxycarbonyl-1-piperazinyl)methyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazine-3-one (220 mg, 0.47 mmol) was dissolved in ice-cold trifluoroacetic acid (2 mL), and at the same temperature, the mixture was stirred for 15 minutes. Water (10 mL) was added to the reaction mixture. The mixture was alkalinized with potassium carbonate and extracted twice with chloroform (20 mL). The extracts were washed with brine (20 mL) and dried over anhydrous sodium sulfate. The solvent was distilled off. The residue was recrystallized from chloroform-hexane to yield the title compound as pale yellow prisms (120 mg, 69.2%).

Melting point: 111.5-118.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.59(4H, m), 1.36-1.47(1H, m), 2.55(4H, br), 2.96(4H, t, J=4.9 Hz), 3.56(2H, d, J=1.5 Hz), 3.95(3H, s), 4.09(2H, d, J=7.3 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.53(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.62(1H, dd, J=2.2, 12.7 Hz), 7.76(1H, t, J=1.5 Hz).

IR(KBr) cm^{-1}: 3328, 1648, 1605, 1520, 1437.

Mass m/z: 372(M^+).

Example 21

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)-methyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow prisms (yield: 94.5%).

Melting point: 139.1-142.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.42-0.56(4H, m), 1.29-1.39(1H, m), 3.40(4H, br), 3.70(4H, br), 3.91(3H, s), 4.16(2H, d, J=7.3 Hz), 4.16(2H, brs), 7.31(1H, dd, J=8.5, 8.5 Hz), 7.71-7.73(2H, m), 8.41(1H, brs).

IR(KBr) cm^{-1}: 3435, 1660, 1610, 1526, 1440, 1291.

Example 22

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were

reacted to yield the title compound as a pale brown oil (yield: 83.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.43-0.58(4H, m), 1.35-1.46(1H, m), 2.71(4H, t, J=4.9 Hz), 3.67(4H, t, J=4.9 Hz), 3.71(2H, s), 3.85(2H, br), 3.94(3H, s), 4.10(2H, d, J=7.3 Hz), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.51-7.56(1H, m), 7.61(1H, dd, J=2.2, 12.4 Hz), 7.73(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 3616, 3476, 3275, 1648, 1601, 1529.

Mass m/z: 391(M^+).

Example 23

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow prisms (yield: 75.9%).

Melting point: 175.2-176.8℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.42-0.55(4H, m), 1.28-1.39(1H, m), 3.36(4H, br), 3.82(4H, br), 3.92(3H, s), 4.06(2H, d, J=7.3 Hz), 4.49(2H, brs), 7.33(1H, dd, J=8.5, 8.5 Hz), 7.71-7.79(2H, m), 8.47(1H, brs).

IR(KBr) cm^{-1}: 3162, 1652, 1604, 1531.

Example 24

Preparation of 4-aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

1) Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-phthalimidomethyl-2H-pyridazin-3-one

To a solution of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one (220 mg, 0.57 mmol) in N,N-dimethylformamide (5 mL) was added potassium phthalimide (160 mg, 0.87 mmol), and the mixture was stirred at 80℃ for 2 hours. Water (30 mL) was added to the reaction mixture. After stirring under cooling over ice water, precipitated crystals were collected by filtration, dried in air, and recrystallized from chloroform-hexane to yield the title compound as colorless needles (202 mg, 81.0%).

Melting point: 241.7-243.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.59(4H, m), 1.37-1.47(1H, m), 3.90(3H, s), 4.10(2H, d, J=7.1 Hz), 4.91 (2H, d, J=1.2 Hz), 6.95(1H, dd, J=8.5, 8.5 Hz), 7.29(1H, t, J=1.2 Hz), 7.38(1H, ddd, J=1.2, 2.2, 8.5 Hz), 7.48(1H, dd, J=2.2, 12.4 Hz), 7.76-7.81(2H, m),

7.90-7.95(2H, m).

IR(KBr) cm^{-1}: 1712, 1653, 1614, 1524.

Mass m/z: 433(M^+).

2) Preparation of

4-aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

To a solution of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxypheyl)-4-phthalimidomethyl-2H-pyridazin-3-one (190 mg, 0.43 mmol) in methanol (5 mL) was added hydrazine monohydrate (110 mg, 2.20 mmol), and the mixture was heated under reflux for 2 hours. Methanol was distilled off, and chloroform (20 mL) was added to the residue. The mixture was successively washed with water (10 mL) and brine (10 mL) in this order, and was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel [developing solvent: chloroform/10% w/v solution of methanol in ammonia (20/1)] to yield the title compound as yellow crystals (130 mg, 97.8 %).

^1H NMR(400MHz, $CDCl_3$)δ:

0.45-0.59(4H, m), 1.37-1.47(1H, m), 1.51(2H, br), 3.89(2H, d, J=1.2 Hz), 3.95(3H, s), 4.11(2H, d, J=7.1 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.53(1H, ddd, J=1.2, 2.4, 8.5 Hz), 7.63(1H, dd, J=2.2, 12.7 Hz), 7.68(1H, s).

IR(KBr) cm^{-1}: 3393, 1651, 1606, 1523, 1438, 1293.

Mass m/z: 303(M^+).

Example 25

Preparation of

4-aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow needles (81.0%).

Melting point: 188.2-194.2℃ (dec.)

^1H NMR(400MHz, DMSO-d_6)δ:

0.42-0.55(4H, m), 1.29 -1.39(1H, m), 3.92(3H, s), 4.01(2H, s), 4.06(2H, d, J=7.1 Hz), 7.34(1H, dd, J=8.5, 8.5 Hz), 7.71-7.78(2H, m), 8.31(1H, s).

IR(KBr) cm^{-1}: 3507, 3440, 1644, 1581, 1522, 1438.

Example 26

Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and tert-butyl

1-piperazine-carboxylate were reacted to yield the title compound as a yellow oil (yield: 94.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 1.46(9H, s), 2.27-2.40(1H, m), 2.52(4H, t, J=5.2 Hz), 3.50(4H, t, J=5.2 Hz), 3.57(2H, s), 3.95(3H, s), 4.06(2H, d, J=7.4 Hz), 7.03(1H, dd, J=8.6, 8.6 Hz), 7.51(1H, dd, J=1.2, 8.4 Hz), 7.60(1H, dd, J=2.2, 12.5 Hz), 7.75(1H, s).

Example 27

Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-fluoro-4-methoxy-phenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 58.5%).

Melting point: 163.0-177.0℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.22-2.33(1H, m), 3.17(4H, br), 3.33(4H, t, J=5.3 Hz), 3.92(3H, s), 3.96(2H, s), 4.01(2H, d, J=7.1 Hz), 7.27(1H, dd, J=8.9, 8.9 Hz), 7.67-7.72(2H, m), 8.22(1H, s).

IR(KBr) cm^{-1}: 1656, 1608, 1522, 1440, 1291, 1113.

Mass m/z: 374(M^+)

Example 28

Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 80.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.28-2.40(1H, m), 2.34(3H, s), 2.55(4H, br), 2.63(4H, br), 3.58(2H, d, J=1.4 Hz), 3.95(3H, s), 4.06(2H, d, J=7.4 Hz), 7.04(1H, dd, J=8.6, 8.6 Hz), 7.53(1H, dd, J=1.2, 8.6 Hz), 7.61(1H, dd, J=2.2, 12.5 Hz), 7.73(1H, s).

Example 29

Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield:

73.3%).

Melting point: 236.9-237.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.21-2.32(1H, m), 2.77(3H, s), 3.14(4H, br), 3.36(4H, br), 3.87(2H, s), 3.91(3H, s), 4.00(2H, d, J=7.1 Hz), 7.26(1H, dd, J=8.5, 8.5 Hz), 7.66-7.71(2H, m), 8.12(1H, s).

IR(KBr) cm^{-1}: 1655, 1606, 1524, 1440, 1291, 1113, 1022.

Mass m/z: 388(M^+)

Example 30

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 87.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.96(6H, d, J=6.8 Hz), 2.27-2.39(1H, m), 2.71(4H, t, J=5.0 Hz), 3.67(4H, t, J=5.0 Hz), 3.70(2H, s), 3.93(3H, s), 4.07(2H, d, J=7.4 Hz), 7.01(1H, dd, J=8.6, 8.6 Hz), 7.53(1H, dd, J=1.4, 8.4 Hz), 7.61(1H, dd, J=2.2, 12.5 Hz), 7.72(1H, s).

Example 31

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless flakes (yield: 89.0%).

Melting point: 129.8-133.1℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.23-2.34(1H, m), 3.34(4H, t, J=5.1 Hz), 3.83(4H, t, J=5.2 Hz), 3.92(3H, s), 4.03(2H, d, J=7.0 Hz), 4.44(2H, s), 7.29(1H, dd, J=8.7, 8.7 Hz), 7.69-7.75(2H, m), 8.46(1H, s).

IR(KBr) cm^{-1}: 1652, 1601, 1525, 1440, 1277.

Mass m/z: 362(M^+-CH_2OH)

Example 32

Preparation of

4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 7, 6-3-(fluoro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and

dimethylamine were reacted to yield the title compound as a yellow oil (yield: 88.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.30-2.40(1H, m), 2.36(6H, s), 3.50(2H, s), 3.93(3H, s), 4.07(2H, d, J=7.2 Hz), 7.02(1H, dd, J=8.6, 8.6 Hz), 7.55(1H, d, J=8.6 Hz), 7.63(1H, dd, J=2.1, 12.5 Hz), 7.75(1H, s).

Example 33

Preparation of 4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethyl-aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 81.0%).

Melting point: 212.4-212.8℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.23-2.33(1H, m), 2.81(6H, s), 3.92(3H, s), 4.04(2H, s, J=7.1 Hz), 4.27(2H, s), 7.29(1H, dd, J=8.1, 8.1 Hz), 7.70-7.75(2H, m), 8.51(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1522, 1439, 1292, 1112.

Mass m/z: 333(M^+)

Example 34

Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one

1) Preparation of

4-methoxycarbonyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(5), 4-carboxy-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow crystals (yield: 98.9%).

Melting point: 202.5-206.2℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

4.01(3H, s), 7.45-7.54(3H, m), 7.78-7.85(2H, m), 8.38(1H, s), 11.86(1H, br).

IR(KBr) cm^{-1}: 1717, 1670, 1443, 1259.

Mass m/z: 230(M^+).

2) Preparation of 2-isobutyl-4-methoxycarbonyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 4-methoxycarbonyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 94.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.00(6H, d, J=6.6 Hz), 2.33-2.44(1H, m), 3.98(3H, s), 4.14(2H, d, J=7.4 Hz), 7.42-7.51(3H, m), 7.79-7.83(2H, m), 8.27(1H, s).

3) Preparation of

4-carboxy-2-isobutyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-isobutyl-4-methoxycarbonyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 82.5%).

Melting point: 120.5-121.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.03(6H, d, J=6.6 Hz), 2.34-2.45(1H, m), 4.23(2H, d, J=7.4 Hz), 7.49-7.54(3H, m), 7.84-7.89(2H, m), 8.69(1H, s), 14.20(1H, s).

IR(KBr) cm^{-1}: 3448, 2956, 1741, 1636, 1418, 1116.

Mass m/z: 272(M^+)

4) Preparation of

4-hydroxymethyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-isobutyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 22.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 3.67(1H, br), 4.08(2H, d, J=7.4 Hz), 4.72(2H, d, J=3.9 Hz), 7.39-7.49(3H, m), 7.76(1H, t, J=1.4 Hz), 7.79-7.84(2H, m).

5) Preparation of 2-isobutyl-4-methanesulfonyloxymethyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 4-hydroxymethyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 68.4%).

Melting point: 129.7℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.30-2.41(1H, m), 3.17(3H, s), 4.10(2H, d, J=7.2 Hz), 5.28(2H, d, J=1.2 Hz), 7.43-7.52(3H, m), 7.79-7.82(3H, m).

IR(KBr) cm^{-1}: 3442, 2963, 1658, 1611, 1355, 1165, 872.

Mass m/z: 336(M^+)

6) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxy-6-phenyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted in N,N-dimethylformamide as a solvent to yield the title compound as a yellow oil (yield: 83.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 1.47(9H, s), 2.53(4H, t, J=4.9 Hz),

3.50(4H, t, J=4.9 Hz), 3.59(2H, d, J=1.0 Hz), 4.09(2H, d, J=7.2 Hz), 7.40-7.50(3H, m), 7.80-7.84(3H, m).

Example 35

Preparation of 2-isobutyl-6-phenyl-4-(1-piperazinyl)-methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as a white solid (yield: 67.9%).

Melting point: 154.3-159.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.94(6H, d, J=6.8 Hz), 2.20-2.32(1H, m), 2.86(4H, br), 3.21(4H, br), 3.71(2H, s), 4.01(2H, d, J=7.2 Hz), 7.42-7.53(3H, m), 7.84-7.89(2H, m), 7.96(1H, s).

IR(KBr) cm^{-1}: 1656, 1610, 1445, 694.

Mass m/z: 326(M^+)

Example 36

Preparation of 2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-phenyl-2H-pyridazin

-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 77.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.30-2.40(1H, m), 2.34(3H, s), 2.55(4H, br), 2.64(4H, br), 3.59(2H, d, J=1.4 Hz), 4.08(2H, d, J=7.2 Hz), 7.40-7.50(3H, m), 7.78-7.84(3H, m).

Example 37

Preparation of

2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-phenyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 66.3%).

Melting point: 243.8-244.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.22-2.34(1H, m), 2.76(3H, s), 3.01(4H, br), 3.30(4H, br), 3.77(2H, s), 4.02(2H, d, J=7.2 Hz), 7.43-7.53(3H, m), 7.85-7.89(2H, m), 8.02(1H, s).

IR(KBr) cm^{-1}: 2960, 1653, 1610, 1446.

Mass m/z: 340(M^+)

Example 38

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-phenyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 38.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 2.79(4H, br), 3.70(4H, br), 3.80(2H, s), 4.09(2H, d, J=7.4 Hz), 7.39-7.48(3H, m), 7.81-7.87(3H, m).

Example 39

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless flakes (yield: 68.4%).

Melting point: 131.6-132.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.6 Hz), 2.25-2.35(1H, m), 3.35(4H, t, J=5.1 Hz), 3.84(4H, t, J=5.4 Hz), 4.06(2H, d, J=7.1 Hz), 4.47(2H, s), 7.45-7.54(3H, m), 7.90-7.94(2H, m), 8.48(1H, s).

IR(KBr) cm^{-1}: 1655, 1610, 1421, 1053.

Mass m/z: 314 (M^+-CH_2OH)

Example 40

Preparation of

4-dimethylaminomethyl-2-isobutyl-6-phenyl-

2H-pyridazin-3-one

Following the procedure of Example 7, 2-isobutyl-4-methanesulfonyloxymethyl-6-phenyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow oil (yield: 81.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.32-2.41(1H, m), 2.35(6H, s), 3.51(2H, d, J=1.2 Hz), 4.09(2H, d, J=7.2 Hz), 7.38-7.48(3H, m), 7.80-7.87(3H, m).

Example 41

Preparation of

4-dimethylaminomethyl-2-isobutyl-6-phenyl-

2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethyl-aminomethyl-2-isobutyl-6-phenyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow flakes (yield: 71.5%).

Melting point: 221.7-222.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.8 Hz), 2.24-2.35(1H, m), 2.82(6H, s), 4.06(2H, d, J=7.1 Hz), 4.29(2H, s), 7.44-7.54(3H, m), 7.90-7.94(2H, m), 8.54(1H, s).

IR(KBr) cm^{-1}: 1648, 1610, 1460, 1052.

Mass m/z: 285(M^+)

Example 42

Preparation of 4-(4-benzyl-1-piperazinyl)methyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

1) Preparation of 2-isobutyl-4-methoxycarbonyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(6), 4-methoxy-carbonyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 91.6%).

Melting point: 67.0-70.1℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.32-2.43(1H, m), 2.41(3H, s), 3.98(3H, s), 4.13(2H, d, J= 7.3 Hz), 7.28(2H, d, J=8.3 Hz), 7.70(2H, d, J=8.3 Hz), 8.24(1H, s).

IR(KBr) cm^{-1}: 1718, 1663, 1605.

Mass m/z: 300(M^+).

2) Preparation of

4-carboxy-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-isobutyl-4-methoxycarbonyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 86.7%).

Melting point: 162.1-165.4℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.02(6H, d, J=6.8 Hz), 2.34-2.44(1H, m), 2.47(3H, s), 4.21(2H, d, J=7.3 Hz), 7.31(2H, d, J=8.3 Hz), 7.75(2H, d, J=8.3 Hz), 8.66(1H, s), 14.26(1H, s).

IR(KBr) cm^{-1}: 1740, 1633, 1571, 1425.

Mass m/z: 286(M^+).

3) Preparation of

4-hydroxymethyl-2-isobutyl-6-(4-methyl-phenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 46.0%).

Melting point: 121.9-123.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.30-2.40(1H, m), 2.40(3H, s), 3.22(1H, br), 4.08(2H, d, J=7.3 Hz), 4.71(2H, s), 7.27(2H, d, J=8.3 Hz), 7.77(1H, s), 7.70(2H, d, J=8.3 Hz).

IR(KBr) cm^{-1}: 3334, 1645, 1596, 1522.

Mass m/z: 272(M^+).

4) Preparation of

2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(9), 4-hydroxy-methyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 87.4%).

Melting point: 132.0-135.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.29-2.39(1H, m), 2.41(3H, s), 3.17(3H, s), 4.08(2H, d, J=7.6 Hz), 5.27(2H, t, J=1.5 Hz), 7.27(2H, d, J=8.3 Hz), 7.72(2H, d, J=8.3 Hz), 7.79(1H, t, J=1.5 Hz).

IR(KBr) cm^{-1}: 1656, 1609, 1355, 1166.

Mass m/z: 350(M^+).

5) Preparation of

4-(4-benzyl-1-piperazinyl)methyl-2-isobutyl-6-(4-

methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and 1-benzylpiperazine were reacted to yield the title compound as a pale yellow oil (yield: 97.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.8 Hz), 2.29-2.39(1H, m), 2.41(3H, s), 2.55(4H, br), 2.61(4H, br), 3.54(2H, s), 3.57(2H, d, J=1.5 Hz), 4.07(2H, d, J=7.3 Hz), 7.22-7.36(7H, m), 7.70(2H, d, J=8.3 Hz), 7.77(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1657, 1652, 1518, 1455.

Mass m/z: 430(M^+).

Example 43

Preparation of 4-(4-benzyl-1-piperazinyl)methyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 4-(4-benzyl-1-piperazinyl)methyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 91.8%).

Melting point: 253.5-260.1℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.92(6H, d, J=6.6 Hz), 2.18-2.28 (1H, m), 2.34(3H, s), 3.43(10H, br), 3.99(2H, d, J= 7.3 Hz), 4.36(2H, brs),

7.22(2H, d, J=8.1 Hz), 7.43-7.49(3H, m), 7.58-7.65(2H, m), 7.78(2H, d, J=8.1 Hz), 8.30(1H, brs).

IR(KBr) cm^{-1}: 1660, 1617, 1452.

Example 44

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a slightly yellow oil (yield: 96.6%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.38-2.41(1H, m), 2.35(6H, s), 2.40(3H, s), 3.50(2H, d, J=1.5 Hz), 4.08(2H, d, J=7.3 Hz), 7.26(2H, d, J=8.1 Hz), 7.73(2H, d, J=8.1 Hz), 7.78(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1652, 1609, 1518, 1455.

Mass m/z: 299(M^+).

Example 45

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4,

4-dimethyl-aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 91.8%).

Melting point: 237.6-239.6℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.19-2.30(1H, m), 2.37(3H, s), 2.81(6H, s), 4.02(2H, d, J=7.0 Hz), 4.30(2H, s), 7.34(2H, d, J=8.1 Hz), 7.81(2H, d, J=8.1 Hz), 8.46(1H, s).

IR(KBr) cm^{-1}: 1648, 1605, 1460, 1421.

Example 46

Preparation of 4-diethylaminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 9(4), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and diethylamine were reacted to yield the title compound as a pale yellow oil (yield: 95.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.07(6H, t, J=7.1 Hz), 2.30-2.42(1H, m), 2.40(3H, s), 2.60(4H, q, J=7.1 Hz), 3.60(2H, d, J=1.5 Hz), 4.08(2H, d, J=7.3 Hz), 7.26(2H, d, J=8.1 Hz), 7.73(2H, d, J=8.1 Hz), 7.89(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1652, 1609, 1518, 1465, 1455.

Mass m/z: 327(M^+).

Example 47

Preparation of 4-diethylaminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-diethyl-aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 93.8%).

Melting point: 203.9-207.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 1.27(6H, t, J=7.2 Hz), 2.20-2.30(1H, m), 2.37(3H, s), 3.09-3.24(4H, m), 4.03(2H, d, J=7.1 Hz), 4.28(2H, d, J=5.4 Hz), 7.34(2H, d, J=8.1 Hz), 7.82(2H, d, J=8.1 Hz), 8.55(1H, s).

IR(KBr) cm^{-1}: 1652, 1610, 1523, 1481, 1468.

Example 48

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a pale yellow oil (yield: 95.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.6 Hz), 2.28-2.41(1H, m), 2.40(3H, s), 2.71(4H, t, J=5.0 Hz), 3.66(4H, t, J=5.0 Hz), 3.70(2H, s), 3.78(2H, br), 4.09(2H, d, J=7.6 Hz), 7.26(2H, d, J=8.1 Hz), 7.68(1H, s), 7.70(2H, d, J=8.1 Hz).

IR(Neat) cm^{-1}: 3392, 1645, 1600, 1520.

Mass m/z: 341(M^+-H_2O).

Example 49

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 86.4%).

Melting point: 158.9-161.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.19-2.30(1H, m), 2.37(3H, s), 3.27-3.46(4H, m), 3.77-3.85(4H, m), 4.02(2H, d, J=7.3 Hz), 4.50(2H, brs), 5.35(2H, br), 7.34(2H, d, J=8.1 Hz), 7.81(2H, d, J=8.1 Hz), 8.46(1H, s).

IR(KBr) cm^{-1}: 3292, 1664, 1615, 1423.

Example 50

Preparation of

4-aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

1) Preparation of

2-isobutyl-6-(4-methylphenyl)-4-phthalimidomethyl-2H-pyridazin-3-one

Following the procedure of Example 24(1), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 98.2%).

Melting point: 221.6-223.8℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.27-2.41(1H, m), 2.36(3H, s), 4.08(2H, d, J=7.3 Hz), 4.91 (2H, d, J=1.5 Hz), 7.20(2H, d, J=8.1 Hz), 7.32(1H, t, J=1.5 Hz), 7.56(2H, d, J=8.1 Hz), 7.75-7.80(2H, m), 7.89-7.94(2H, m).

IR(KBr) cm^{-1}: 1767, 1721, 1655, 1616.

Mass m/z: 401(M^+).

2) Preparation of

4-aminomethyl-2-isobutyl-6-(4-methyl-phenyl)-2H-pyridazin-3-one

Following the procedure of Example 24(2), 2-isobutyl-6-(4-methylphenyl)-4-phthalimidomethyl-2H-

pyridazin-3-one was reacted to yield the title compound as colorless prisms (yield: 98.1%).

Melting point: 74.9-77.9℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.9 Hz), 1.68(2H, br), 2.28-2.42(1H, m), 2.40(3H, s), 3.87(2H, d, J=1.2 Hz), 4.07 (2H, d, J=7.3 Hz), 7.26(2H, d, J=8.0 Hz), 7.69(1H, t, J=1.5 Hz), 7.71(2H, d, J=8.0 Hz).

IR(KBr) cm^{-1}: 3363, 3289, 1648, 1604, 1519.

Mass m/z: 271(M^+).

Example 51

Preparation of 4-aminomethyl-2-isobutyl-6-(4-methyl-phenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow prisms (yield: 93.1%).

Melting point: 207.4-209.4℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.6 Hz), 2.19-2.30(1H, m), 2.37(3H, s), 4.01(2H, d, J=7.1 Hz), 4.02 (2H, s), 7.34(2H, d, J=8.1 Hz), 7.80(2H, d, J=8.1 Hz), 8.26(1H, s).

IR(KBr) cm^{-1}: 1655, 1616, 1520, 1467.

Example 52

Preparation of

4-(1,3-dihydroxypropan-2-yl)amino-methyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and 2-amino-1,3-propanediol were reacted to yield the title compound as colorless needles (yield: 83.7%).

Melting point: 134.1-135.2℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.6 Hz), 2.29-2.39(1H, m), 2.40(3H, s), 2.60(3H, br), 2.82-2.87(1H, m), 3.64(2H, dd, J=5.6, 11.2 Hz), 3.80 (2H, dd, J=4.5, 11.2 Hz), 3.86(2H, d, J=1.0 Hz), 4.07(2H, d, J=7.3 Hz), 7.26(2H, d, J=8.1 Hz), 7.71(2H, d, J=8.1 Hz), 7.74(1H, s).

IR(KBr) cm^{-1}: 3408, 3293, 1641, 1592, 1520.

Mass m/z: 345(M^+).

Example 53

Preparation of

4-(1,3-dihydroxypropan-2-yl)amino-methyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N-(1,3-dihydroxypropan-2-yl)aminomethyl-2-isobutyl-6-(4-

methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 95.7%).

Melting point: 191.2-193.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.6 Hz), 2.19-2.30(1H, m), 2.37(3H, s), 3.29(1H, br), 3.60-3.78(4H, m), 4.02(2H, d, J=7.1 Hz), 4.29(2H, s), 5.40(2H, brs), 7.34(2H, d, J=8.1 Hz), 7.81(2H, d, J=8.1 Hz), 8.38(1H, s).

IR(KBr) cm^{-1}: 3392, 1652, 1610.

Example 54

Preparation of 2-isobutyl-4-methylaminomethyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 9(4), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and methylamine were reacted to yield the title compound as a slightly yellow oil (yield: 94.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 1.87(1H, br), 2.29-2.42(1H, m), 2.40(3H, s), 2.50(3H, s), 3.76(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 7.26(2H, d, J=8.1 Hz), 7.67(1H, t, J=1.2 Hz), 7.71(2H, d, J=8.1 Hz).

IR(Neat) cm^{-1}: 3317, 1652, 1607.

Mass m/z: 285(M^+).

Example 55

Preparation of 2-isobutyl-4-methylaminomethyl-6-(4-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-isobutyl-4-methylaminomethyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 97.5%).

Melting point: 198.3-201.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.20-2.31(1H, m), 2.37(3H, s), 2.65(3H, s), 4.02(2H, d, J=7.3 Hz), 4.12(2H, s), 7.34(2H, d, J=8.1 Hz), 7.80(2H, d, J=8.1 Hz), 8.35(1H, s).

IR(KBr) cm^{-1}: 3085, 1652, 1612.

Example 56

Preparation of 4-(2-hydroxyethyl)aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 9(4), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-methylphenyl)-2H-pyridazin-3-one and 2-aminoethanol were reacted to yield the title compound as a slightly yellow oil (yield: 80.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.20-2.38(3H, m), 2.39(3H, s), 2.84(2H, t, J=5.1 Hz), 3.72(2H, t, J=5.1 Hz), 3.82(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 7.26(2H, d, J=8.1 Hz), 7.68(1H, s), 7.70(2H, d, J=8.1 Hz).

IR(Neat) cm^{-1}: 3429, 1652, 1601, 1519.

Mass m/z: 315(M^+).

Example 57

Preparation of 4-(2-hydroxyethyl)aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N-(2-hydroxyethyl)aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 93.4%).

Melting point: 190.8-191.9℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.20-2.31(1H, m), 2.37(3H, s), 3.12(2H, t, J=5.4 Hz), 3.70-3.76(2H, m), 4.02(2H, d, J=7.3 Hz), 4.18(2H, s), 5.30(1H, br), 7.34(2H, d, J=8.3 Hz), 7.81(2H, d, J=8.3 Hz), 8.36(1H, s).

IR(KBr) cm^{-1}: 3491, 1652, 1611.

Example 58

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-(4-trifluoromethyl-phenyl)-2H-pyridazin-3-one

1) Preparation of ethyl 2-ethoxycarbonyl-2-hydroxy-4-(4-trifluoromethylphenyl)-4-oxo-butanoate

Following the procedure of Example 1(3), 4'-(trifluoromethyl)acetophenone was reacted to yield the title compound as pale yellow crystals (yield: 80.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30(6H, t, J=7.1 Hz), 3.85(2H, s), 4.22(1H, s), 4.31(4H, q, J=7.1 Hz), 7.76(2H, d, J=8.6 Hz), 8.07(2H, d, J=8.6 Hz).

IR(KBr) cm^{-1}: 3446, 1750, 1727, 1691.

Mass m/z: 343(M^+-H_2O).

2) Preparation of 4-carboxy-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(4), ethyl 2-ethoxycarbonyl-2-hydroxy-4-(4-trifluoromethylphenyl)-4-oxobutanoate was reacted to yield the title compound as a pale brown crystalline powder (yield: 91.4%).

3) Preparation of

4-methoxycarbonyl-6-(4-trifluoromethyl-phenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(5), 4-carboxy-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow crystalline powder (yield: 88.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

4.02(3H, s), 7.75(2H, d, J=8.2 Hz), 7.95(2H, d, J=8.2 Hz), 8.39(1H, s), 11.69(1H, br).

IR(KBr) cm^{-1}: 3218, 3140, 3097, 1720, 1678, 1326.

Mass m/z: 298(M^+).

4) Preparation of 2-isobutyl-4-methoxycarbonyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(6), 4-methoxy-carbonyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as yellow crystals (yield: 82.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.00(6H, d, J=6.6 Hz), 2.32-2.43(1H, m), 3.99(3H, s), 4.15(2H, d, J=7.2 Hz), 7.74(2H, d, J=8.4 Hz), 7.93(2H, d, J=8.4 Hz), 8.12(1H, s).

IR(Neat) cm^{-1}: 2961, 1746, 1670, 1327, 1115, 1068.

Mass m/z: 354(M^+).

5) Preparation of

4-carboxy-2-isobutyl-6-(4-trifluoro-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-isobutyl-4-methoxycarbonyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 91.6%).

Melting point: 184.4-185.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.03(6H, d, J=6.6 Hz), 2.34-2.45(1H, m), 4.25(2H, d, J=7.2 Hz), 7.78(2H, d, J=8.2 Hz), 7.99(2H, d, J=8.2 Hz), 8.70(1H, s), 14.02(1H, s).

IR(KBr) cm^{-1}: 3447, 1739, 1631, 1570, 1330, 1174, 1114, 1070, 847.

Mass m/z: 340(M^+)

6) Preparation of

4-hydroxymethyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 28.1%).

Melting point: 145.8-146.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.30-2.41(1H, m), 2.96(1H, t, J=5.9 Hz), 4.11(2H, d, J=7.4 Hz), 4.74(2H, dd, J=1.4, 5.8 Hz), 7.70-7.74(3H, m), 7.94(2H, d, J=8.2 Hz).

IR(KBr) cm^{-1}: 3339, 1646, 1596, 1328, 1131, 1070, 848.

7) Preparation of

2-isobutyl-4-methanesulfonyloxymethyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(9), 4-hydroxy-methyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 89.9%).

Melting Point: 122.9—123.8℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 3.18(3H, s), 4.11(2H, d, J=7.2 Hz), 5.29(2H, d, J=1.4 Hz), 7.73(2H, d, J=8.2 Hz), 7.83(1H, t, J=1.4 Hz), 7.93(2H, d, J=8.2 Hz).

IR(KBr) cm^{-1}: 3447, 1659, 1613, 1359, 1329, 1169, 1123, 1071, 846.

Mass m/z: 404(M^+)

8) Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10),

2-isobutyl-4-methanesulfonyloxymethyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 83.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 1.47(9H, s), 2.29-2.41(1H, m), 2.53(4H, t, J=4.9 Hz), 3.51(4H, t, J=4.8 Hz), 3.60(2H, s), 4.10(2H, d, J=7.4 Hz), 7.72(2H, d, J=8.2 Hz), 7.84(1H, s), 7.94(2H, d, J=8.2 Hz).

Example 59

Preparation of 2-isobutyl-4-(1-piperazinyl)methyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 95.0%).

Melting point: 210.8-212.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.6 Hz), 2.22-2.35(1H, m), 3.12(4H, br), 3.30(4H, t, J=5.2 Hz), 3.92(2H, s), 4.05(2H, d, J=7.1 Hz), 7.84(2H,

d, J=8.3 Hz), 8.11(2H, d, J=8.1 Hz), 8.25(1H, s).

IR(KBr) cm^{-1}: 1656, 1608, 1328, 1125, 1069.

Mass m/z: 394(M^+)

Example 60

Preparation of

2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 81.1%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.30-2.41(1H, m), 2.33(3H, s), 2.53(4H, br), 2.63(4H, br), 3.60(2H, s), 4.10(2H, d, J=7.2 Hz), 7.72(2H, d, J=8.2 Hz), 7.83(1H, s), 7.94(2H, d, J=8.2 Hz).

Example 61

Preparation of

2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-6-(4-

trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless flakes (yield: 88.6%).

Melting point: 249.9-252.8℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.22-2.35(1H, m), 2.77(3H, s), 3.14(4H, br), 3.35(4H, br), 3.88(2H, s), 4.05(2H, d, J=7.2 Hz), 7.84(2H, d, J=8.2 Hz), 8.10(2H, d, J=8.0 Hz), 8.19(1H, s).

IR(KBr) cm^{-1}: 2966, 1653, 1610, 1328, 1125, 1069.

Mass m/z: 408(M^+)

Example 62

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 79.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 2.72(4H, br), 3.67(4H, t, J=4.2 Hz), 3.72(2H, s), 4.10(2H, d, J=7.4 Hz), 7.70(2H, d, J=7.6 Hz), 7.82(1H, s), 7.94(2H, d, J=8.2 Hz).

Example 63

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-(4-trifluoromethyl-phenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 58.2%).

Melting point: 134.9-135.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.97(6H, d, J=6.6 Hz), 2.25-2.36(1H, m), 3.34(4H, br), 3.83(4H, t, J=5.1 Hz), 4.07(2H, d, J=7.0 Hz), 4.46(2H, s), 7.86(2H, d, J=8.2 Hz), 8.13(2H, d, J=8.2 Hz), 8.55(1H, s).

IR(KBr) cm^{-1}: 1653, 1605, 1319, 1125, 1069.

Mass m/z: 395(M^+-H_2O)

Example 64

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-isobutyl-4-methanesulfonyloxymethyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 80.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.31-2.40(1H, m), 2.36(6H, s), 3.51(2H, d, J=1.2 Hz), 4.10(2H, d, J=7.4 Hz), 7.71(2H, d, J=8.4 Hz), 7.83(1H, t, J=1.4 Hz), 7.97(2H, d, J=8.2 Hz).

Example 65

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethylaminomethyl-2-isobutyl-6-(4-trifluoromethylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow flakes (yield: 93.0%).

Melting point: 242.2-242.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.97(6H, d, J=6.6 Hz), 2.25-2.36(1H, m), 2.83(6H, s), 4.07(2H, d, J=7.3 Hz), 4.30(2H, s), 7.86(2H, d, J=8.3 Hz), 8.14(2H, d, J=8.0 Hz), 8.61(1H, s).

IR(KBr) cm^{-1}: 2963, 1646, 1606, 1321, 1115, 1069.

Mass m/z: 353(M^+)

Example 66

Preparation of

6-(4-biphenylyl)-4-(4-tert-butoxy-carbonyl-1-

piperazinyl)methyl-2-isobutyl-2H-pyridazin-3-one

1) Preparation of ethyl

4-(4-biphenylyl)-2-ethoxycarbonyl-2-hydroxy-4-oxobutanoate

Following the procedure of Example 1(3), 4-acetyl-biphenyl was reacted to yield the title compound as colorless flakes (yield: 83.3%).

Melting point: 88.0-88.3℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.31(6H, t, J=7.1 Hz), 3.87(2H, s), 4.32(4H, q, 7.1 Hz), 7.41(1H, tt, J=1.4, 7.2 Hz), 7.48(2H, dd, J=7.2, 7.2 Hz), 7.63(2H, d, J=7.0 Hz), 7.70(2H, d, J=8.6 Hz), 8.04(2H, d, J=8.6 Hz).

IR(KBr) cm^{-1}: 3449, 1736, 1680, 1604, 1301, 1244, 1204, 763.

2) Preparation of

6-(4-biphenylyl)-4-carboxy-2H-pyridazin-3-one

Following the procedure of Example 1(4), ethyl 4-(4-biphenylyl)-2-ethoxycarbonyl-2-hydroxy-4-oxobutanoate was reacted to yield the title compound as a yellow crystalline powder (yield: 90.2%).

Melting point: 299.7-300.8℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

7.40(1H, t, J=7.4 Hz), 7.49(2H, dd, J=7.4, 7.4 Hz), 7.74(2H, d, J=7.2 Hz), 7.82(2H, d, J=8.4 Hz), 8.03(2H, d, J=8.4 Hz),

8.54(1H, s).

IR(KBr) cm^{-1}: 1753, 1652, 1590, 1446, 1201, 768.

3) Preparation of

6-(4-biphenylyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(5), 6-(4-biphenylyl)-4-carboxy-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 90.4%).

Melting point: 277.0-277.9℃ (dec.)

^1H NMR(400MHz, $CDCl_3$)δ:

4.01(3H, s), 7.39-7.45(3H, m), 7.64(2H, d, J=7.2 Hz), 7.72(2H, d, J=8.2 Hz), 7.89(2H, d, J=8.0 Hz), 8.42(1H, s), 10.7(1H, s).

IR(KBr) cm^{-1}: 2954, 1727, 1671, 1594, 1265, 1098, 768.

4) Preparation of

6-(4-biphenylyl)-2-isobutyl-4-methoxy-carbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(4-biphenylyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as yellow crystals (yield: 62.7%).

Melting point: 186.2-195.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.01(6H, d, J=6.8 Hz), 2.34-2.45(1H, m), 3.99(3H, s), 4.16(2H, d, J=7.4 Hz), 7.39(1H, tt, J=1.4, 7.4 Hz), 7.48(2H, dd, J=7.2, 7.2 Hz), 7.64(2H, d, J=7.0 Hz), 7.71(2H, d, J=8.6 Hz), 7.89(2H, d, J=8.6 Hz), 8.31(1H, s).

5) Preparation of 6-(4-biphenylyl)-4-carboxy-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(7), 6-(4-biphenylyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 79.2%).

Melting point: 156.9-157.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.04(6H, d, J=6.6 Hz), 2.36-2.46(1H, m) 4.24(2H, d, J=7.4 Hz), 7.41(1H, t, J=7.4 Hz), 7.49(2H, dd, J=7.4, 7.4 Hz), 7.65(2H, d, J=7.0 Hz), 7.74(2H, d, J=8.4 Hz), 7.95(2H, d, J=8.4 Hz), 8.73(1H, s), 14.22(1H, s).

IR(KBr) cm^{-1}: 2963, 1749, 1631, 1565, 1470, 735.

6) Preparation of 6-(4-biphenylyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(8),

6-(4-biphenylyl)-4-carboxy-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a while solid (yield: 15.6%).

Melting point: 146.4-147.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.01(6H, d, J=6.8 Hz), 2.32-2.43(1H, m), 3.13(1H, t, J=6.2 Hz), 4.11(2H, d, J=7.4 Hz), 4.74(2H, dd, J=1.2, 6.2 Hz), 7.39(1H, t, J=7.3 Hz), 7.48(2H, dd, J=7.4, 7.4 Hz), 7.64(2H, d, J=7.0 Hz), 7.70(2H, d, J=8.6 Hz), 7.74(1H, t, J=1.2 Hz), 7.90(2H, d, J=8.6 Hz).

IR(KBr) cm^{-1}: 3431, 2961, 1647, 1596, 1077, 769.

7) Preparation of 6-(4-biphenylyl)-2-isobutyl-4-methane-sulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 6-(4-biphenylyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 79.3%).

Melting point: 121.3-122.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.01(6H, d, J=6.8 Hz), 2.33-2.42(1H, m), 3.18(3H, s), 4.12(2H, d, J=7.4 Hz), 5.30(2H, d, J=1.2 Hz), 7.39(1H, t, J=7.4 Hz), 7.48(2H, dd, J=7.6 Hz), 7.64(2H, d, J=7.4 Hz), 7.71(2H, d,

J=8.4 Hz), 7.85-7.91(3H, m).

IR(KBr) cm^{-1}: 2964, 1658, 1610, 1354, 1165, 874, 529.

8) Preparation of

6-(4-biphenylyl)-4-(4-tert-butoxy-carbonyl-1-piperazinyl)methyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(4-biphenylyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-pipeazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 87.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.00(6H, d, J=6.6 Hz), 1.47(9H, s), 2.30-2.43(1H, m), 2.54(4H, t, J=4.9 Hz), 3.51(4H, t, J=4.9 Hz), 3.60(2H, d, J=1.4 Hz), 4.10(2H, d, J=7.4 Hz), 7.38(1H, tt, J=1.4, 7.2 Hz), 7.47(2H, dd, J=7.4, 7.4 Hz), 7.64(2H, d, J=7.0 Hz), 7.70(2H, d, J=8.6 Hz), 7.85-7.92(3H, m).

Example 67

Preparation of

6-(4-biphenylyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 6-(4-biphenylyl)-4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the

title compound as a colorless crystalline powder (yield: 51.5%).

Melting point: 226.8-228.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.97(6H, d, J=6.8 Hz), 2.25-2.36(1H, m), 3.19(4H, br), 3.34(4H, t, J=5.1 Hz), 3.98(2H, s), 4.05(2H, d, J=7.1 Hz), 7.39(1H, t, J=7.3 Hz), 7.49(2H, dd, J=7.7, 7.7 Hz), 7.71(2H, d, J=7.8 Hz), 7.79(2H, d, J=8.3 Hz), 7.99(2H, d, J=8.3 Hz), 8.29(1H, s).

IR(KBr) cm^{-1}: 1653, 1604, 1446, 771.

Mass m/z: 402(M^+)

Example 68

Preparation of 6-(4-biphenylyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(4-biphenylyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 68.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.00(6H, d, J=6.6 Hz), 2.30-2.43(1H, m), 2.34(3H, s), 2.55(4H, br), 2.65(4H, br), 3.61(2H, d, J=1.2 Hz), 4.10(2H, d, J=7.2 Hz), 7.38(1H, t, J=7.3 Hz), 7.47(2H, dd, J=7.5, 7.5 Hz), 7.64(2H, d, J=7.2 Hz), 7.70(2H, d, J=8.4 Hz), 7.84(1H,

s), 7.90(2H, d, J=8.4 Hz).

Example 69

Preparation of

6-(4-biphenylyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(4-biphenylyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 69.9%).

Melting point: 262.2-263.6℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.97(6H, d, J=6.6 Hz), 2.26-2.35(1H, m), 2.77(3H, s), 3.10(4H, br), 3.34(4H, br), 3.85(2H, s), 4.04(2H, d, J=7.1 Hz), 7.39(1H, t, J=7.6 Hz), 7.49(2H, dd, J=8.0, 8.0 Hz), 7.71(2H, d, J=8.0 Hz), 7.78(2H, d, J=8.3 Hz), 7.89(2H, d, J=8.3 Hz), 8.13(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1465, 1050.

Mass m/z: 416(M^+)

Example 70

Preparation of

6-(4-biphenylyl)-4-N,N-bis(2-hydroxy-ethyl) aminomethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10),

6-(4-biphenylyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 62.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.30-2.43(1H, m), 2.73(4H, t, J=4.8 Hz), 3.67(4H, t, J=4.8 Hz), 3.73(2H, s), 4.12(2H, d, J=7.4 Hz), 7.38(1H, t, J=7.2 Hz), 7.47(2H, dd, J=7.2, 7.2 Hz), 7.63(2H, d, J=7.4 Hz), 7.68(2H, d, J=8.2 Hz), 7.79(1H, s), 7.89(2H, d, J=8.2 Hz).

Example 71

Preparation of 6-(4-biphenylyl)-4-N,N-bis(2-hydroxy-ethyl) aminomethyl-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(4-biphenylyl)-4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 63.9%).

Melting point: 218.3-218.6℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.98(6H, d, J=6.8 Hz), 2.26-2.37(1H, m), 3.36(4H, t, J=5.1 Hz), 3.85(4H, t, J=5.1 Hz), 4.08(2H, d, J=7.3 Hz), 4.48(2H, s), 7.40(1H, tt, J=1.2, 7.3 Hz), 7.49(2H, dd, J=7.3 Hz), 7.72(2H, dd, J=1.2, 7.3 Hz), 7.81(2H, d, J=8.3 Hz), 8.01(2H,

d, J=8.3 Hz), 8.52(1H, s).

IR(KBr) cm^{-1}: 1654, 1607, 1053, 847, 769.

m/z(EI): 403(M^+-H_2O)

Example 72

Preparation of 6-(4-biphenylyl)-4-dimethylamino-methyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 7, 6-(4-biphenylyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 87.7%).

^1H NMR(400MHz, $CDCl_3$)δ:

1.00(6H, d, J=6.6 Hz), 2.36(6H, s), 2.29-2.43(1H, m), 3.52(2H, d, J=1.0 Hz), 4.10(2H, d, J=7.2 Hz), 7.37(1H, t, J=7.4 Hz), 7.46(2H, dd, J=7.4, 7.4 Hz), 7.63(2H, d, J=7.2 Hz), 7.68(2H, d, J=8.4 Hz), 7.85(1H, s), 7.92(2H, d, J=8.4 Hz).

Example 73

Preparation of 6-(4-biphenylyl)-4-dimethylamino-methyl-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(4-biphenylyl)-4-dimethylaminomethyl-2-isobutyl-2H-

pyridazin-3-one was reacted to yield the title compound as colorless flakes (yield: 58.2%).

Melting point: 243.9-244.1℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.98(6H, d, J=6.6 Hz), 2.26-2.37(1H, m), 2.83(6H, s), 4.03(2H, d, J=7.1 Hz), 4.30(2H, s), 7.39(1H, tt, J=1.2, 7.3 Hz), 7.49(2H, dd, J=7.3, 7.3 Hz), 7.72(2H, dd, J=1.2, 7.1 Hz), 7.81(2H, d, J=8.8 Hz), 8.02(2H, d, J=8.6 Hz), 8.57(1H, s).

IR(KBr) cm^{-1}: 1647, 1604, 1460, 1409, 1052.

Mass m/z: 361(M^+)

Example 74

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-chloro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and tert-butyl 1-piperazine-carboxylate were reacted to yield the title compound as a yellow oil (yield: 89.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.47(9H, s), 2.27-2.40(1H, m), 2.52(4H, t, J=4.9 Hz), 3.50(4H, t, J=5.0 Hz), 3.57(2H, d, J=1.4 Hz), 3.96(3H, s), 4.07(2H, d, J=7.2 Hz), 7.00(1H, d,

J=8.6 Hz), 7.66(1H, dd, J=2.4, 8.6 Hz), 7.74(1H, t, J=1.3 Hz), 7.86(1H, d, J=2.4 Hz).

Example 75

Preparation of 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-chloro-4-methoxy-phenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a white solid (yield: 70.2%).

Melting point: 203.6-204.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.6 Hz), 2.20-2.34(1H, m), 3.14(4H, br), 3.31(4H, t, J=5.2 Hz), 3.93(5H, s), 4.01(2H, d, J=7.0 Hz), 7.26(1H, d, J=8.8 Hz), 7.84(1H, dd, J=2.4, 8.6 Hz), 7.91(1H, d, J=2.4 Hz), 8.19(1H, s).

IR(KBr) cm^{-1} : 1654, 1608, 1507, 1289, 1065.

Mass m/z: 390(M^+), 392(M^+).

Example 76

Preparation of 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10),

6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 76.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.28-2.40(1H, m), 2.33(3H, s), 2.53(4H, br), 2.63(4H, br), 3.58(2H, d, J=1.2 Hz), 3.96(3H, s), 4.06(2H, d, J=7.2 Hz), 7.01(1H, d, J=8.6 Hz), 7.67(1H, dd, J=2.2, 8.6 Hz), 7.72(1H, s), 7.86(1H, d, J=2.2 Hz).

Example 77

Preparation of 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 67.5%).

Melting point: 235.8-236.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.25-2.32(1H, m), 2.77(3H, s), 3.15(4H, br), 3.36(4H, br), 3.88(2H, s), 3.93(3H, s), 4.01(2H, d, J=7.0 Hz), 7.26(1H, d, J=8.6 Hz), 7.83(1H, dd,

J=2.2, 8.6 Hz), 7.91(1H, d, J=2.2 Hz), 8.12(1H, s).

IR(KBr) cm^{-1}: 1653, 1608, 1507, 1289, 1064.

Mass m/z: 404(M^+), 406(M^+).

Example 78

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-chloro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 79.6%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.96(6H, d, J=6.6 Hz), 2.28-2.39(1H, m), 2.71(4H, t, J=4.9 Hz), 3.66(4H, t, J=4.9 Hz), 3.70(2H, s), 3.94(3H, s), 4.07(2H, d, J=7.4 Hz), 6.98(1H, d, J=8.8 Hz), 7.68(1H, dd, J=1.8, 8.7 Hz), 7.72(1H, s), 7.85(1H, d, J=2.1 Hz).

Example 79

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-chloro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4,

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-chloro-4-methoxyphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 60.1%).

Melting point: 153.0-153.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.6 Hz), 2.23-2.34(1H, m), 3.34(4H, t, J=5.1 Hz), 3.83(4H, t, J=5.1 Hz), 3.94(3H, s), 4.04(2H, d, J=7.1 Hz), 4.44(2H, s), 7.28(1H, d, J=8.8 Hz), 7.85(1H, dd, J=2.4, 8.6 Hz), 7.94(1H, d, J=2.4 Hz), 8.45(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1508, 1421, 1293, 1062.

Mass m/z: 391(M^+-H_2O)

Example 80

Preparation of 6-(3-chloro-4-methoxyphenyl)-4-dimethylaminomethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 7, 6-(3-chloro-4-methoxyphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 84.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.31-2.39(1H, m), 2.35(6H, s), 3.50(2H, s), 3.95(3H, s), 4.07(2H, d, J=7.2 Hz), 6.99(1H, d, J=8.6 Hz), 7.70(1H, dd, J=1.4, 8.6 Hz), 7.88(1H, d, J=1.4

Hz).

Example 81

Preparation of 6-(3-chloro-4-methoxyphenyl)-4-dimethylaminomethyl-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(3-chloro-4-methoxyphenyl)-4-dimethylaminomethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a white solid (yield: 69.4%).

Melting point: 213.6-214.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.22-2.34(1H, m), 2.81(6H, s), 3.94(3H, s), 4.04(2H, d, J=7.1Hz), 4.27(2H, s), 7.28(1H, d, J=8.8 Hz), 7.87(1H, dd, J=2.2, 8.8 Hz), 7.95(1H, d, J=2.2 Hz), 8.53(1H, s).

IR(KBr) cm^{-1}: 1652, 1608, 1508, 1289, 1064.

Mass m/z: 349(M^+), 351(M^+).

Example 82

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of ethyl 2-ethoxycarbonyl-4-(4-fluoro-3-methylphenyl)-2-hydroxy-

4-oxobutanoate

Following the procedure of Example 1(3), 5-acetyl-2-fluorotoluene was reacted to yield the title compound as pale yellow prisms (yield: 95.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30(6H, t, J=7.1 Hz), 2.33(3H, d, J=1.7 Hz), 3.79(2H, s), 4.29(1H, s), 4.31(4H, q, J=7.1 Hz), 7.08(1H, dd, J=8.8, 8.8 Hz), 7.78-7.85(2H, m).

2) Preparation of 4-carboxy-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(4), ethyl 2-ethoxycarbonyl-4-(4-fluoro-3-methylphenyl)-2-hydroxy-4-oxo-butanoate was reacted to yield the title compound as a pale yellow crystalline powder (yield: 88.9%).

Melting point: 213.6-214.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.51(3H, d, J=1.7 Hz), 7.26(1H, dd, J=9.1, 9.1 Hz), 7.77-7.81(1H, m), 7.89(1H, d, J=7.3 Hz), 8.49(1H, s), 13.99(1H, br).

3) Preparation of 6-(4-fluoro-3-methylphenyl)-4-methoxy-carbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(5), 4-carboxy-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

was reacted to yield the title compound as a pale yellow crystalline powder (yield: 76.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.35(3H, d, J=2.0 Hz), 3.99(3H, s), 7.10(1H, dd, J=8.9, 8.9 Hz), 7.58-7.62(1H, m), 7.60(1H, d, J=7.3 Hz), 8.31(1H, s).

4) Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(4-fluoro-3-methylphenyl)-2-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow prisms (yield: 86.3%).

Melting point: 71.4-73.8℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.31-2.42(1H, m), 2.35(3H, d, J=2.0 Hz), 3.98(3H, s), 4.12(2H, d, J=7.3 Hz), 7.10(1H, dd, J=8.8, 8.8 Hz), 7.57-7.65(2H, m), 8.21(1H, s).

5) Preparation of 4-carboxy-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(7), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow needles (yield: 90.0%).

Melting point: 129.3-132.1℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.02(6H, d, J=6.8 Hz), 2.33-2.44(1H, m), 2.37(3H, d, J=2.0 Hz), 4.21(2H, d, J=7.3 Hz), 7.13(1H, dd, J=8.8, 8.8 Hz), 7.64-7.71(2H, m), 8.63(1H, s).

IR(KBr) cm^{-1}: 1742, 1636, 1537, 1422.

Mass m/z: 304(M^+).

6) Preparation of 6-(4-fluoro-3-methylphenyl)-4-hydroxy-methyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 24.7%).

Melting point: 107.4-110.4℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 2.35(3H, d, J=1.7 Hz), 3.14(1H, t, J=5.9 Hz), 4.08(2H, d, J=7.6 Hz), 4.71(2H, d, J=5.9 Hz), 7.08 (1H, dd, J=8.8, 8.8 Hz), 7.56-7.65(3H, m).

IR(KBr) cm^{-1}: 3401, 1658, 1648, 1618, 1602, 1501.

Mass m/z: 290(M^+).

7) Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 91.4%).

Melting point: 114.6-117.1℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.29-2.40(1H, m), 2.36(3H, s), 3.17(3H, s), 4.08(2H, d, J=7.6 Hz), 5.27(2H, d, J=1.5 Hz), 7.09 (1H, dd, J=8.9, 8.9 Hz), 7.56-7.69(2H, m), 7.75(1H, t, J=1.5 Hz).

IR(KBr) cm^{-1}: 1656, 1611, 1505, 1354, 1166.

Mass m/z: 368(M^+).

8) Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a slightly yellow oil (yield: 79.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.27-2.40(1H, m), 2.32(3H, s), 2.36(3H, d, J=2.0 Hz), 2.51(4H, br), 2.62(4H, br), 3.58(2H, d, J=1.5 Hz), 4.07(2H, d, J=7.3 Hz), 7.09 (1H, dd, J=8.8, 8.8 Hz), 7.58(1H, ddd, J=2.0, 4.9, 8.8 Hz), 7.64(1H, dd,

J=2.0, 7.3 Hz), 7.73(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1652, 1609, 1503.

Mass m/z: 372(M^+).

Example 83

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless prisms (yield: 95.9%).

Melting point: 234.8-237.4℃ (dec.)

^1H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.8 Hz), 2.19-2.30(1H, m), 2.32(3H, d, J=2.0 Hz), 2.81(3H, s), 2.89-3.62(10H, brm), 4.00(2H, d, J=7.3 Hz), 7.29(1H, dd, J=9.0, 9.0 Hz), 7.72-7.78(1H, m), 7.83(1H, dd, J=2.4, 7.6 Hz), 8.31(1H, brs).

IR(KBr) cm^{-1}: 1660, 1609, 1504.

Example 84

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methylaminomethyl-2H-pyridazin-3-one

Following the procedure of Example 9(4),

6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow oil (yield: 96.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.65(1H, br), 2.29-2.42(1H, m), 2.34(3H, d, J=1.7 Hz), 2.51(3H, s), 3.77(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 7.07(1H, dd, J=8.8, 8.8 Hz), 7.54-7.63(2H, m), 7.64(1H, t, J=1.2 Hz).

IR(Neat) cm^{-1}: 3306, 1653, 1605, 1507.

Mass m/z: 303(M^+).

Example 85

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methylaminomethyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methylaminomethyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless prisms (yield: 86.6%).

Melting point: 196.8-199.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.8 Hz), 2.19-2.31(1H, m), 2.32(3H, s), 2.65(3H, s), 4.02(2H, d, J=7.3 Hz), 4.12(2H, s), 7.31(1H, dd, J=8.5, 8.5 Hz), 7.72-7.78(1H, m), 7.80-7.85(1H, m), 8.32(1H, s).

IR(KBr) cm^{-1}: 2722, 1652, 1615, 1505.

Example 86

Preparation of 4-(4-benzyl-1-piperazinyl)methyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and 1-benzylpiperazine were reacted to yield the title compound as a pale yellow oil (yield: 98.6%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.8 Hz), 2.29-2.39 (1H, m), 2.36(3H, d, J=1.7 Hz), 2.55(4H, br), 2.61(4H, br), 3.55(2H, s), 3.57(2H, d, J=1.2 Hz), 4.06(2H, d, J=7.6 Hz), 7.09(1H, dd, J=8.9, 8.9 Hz), 7.23-7.34(5H, m), 7.51(1H, ddd, J=2.4, 4.8, 8.9 Hz), 7.63(1H, dd, J=2.4, 7.2 Hz), 7.72(1H, s).

IR(Neat) cm^{-1} : 1652, 1608, 1505.

Mass m/z: 448(M^+).

Example 87

Preparation of 4-(4-benzyl-1-piperazinyl)methyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 4-(4-benzyl-1-piperazinyl)methyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 95.3%).

Melting point: 259.1-263.1℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.6 Hz), 2.17-2.29(1H, m), 2.32(3H, s), 2.55(4H, br), 3.23-3.56(8H, brm), 4.00(2H, d, J=7.3 Hz), 4.11(2H, brs), 4.38(2H, brs), 7.29(1H, dd, J=9.0, 9.0 Hz), 7.43-7.48(3H, m), 7.59-7.65(2H, m), 7.72-7.77(1H, m), 7.79-7.84(1H, m), 8.35(1H, brs).

IR(KBr) cm^{-1}: 1660, 1618, 1612, 1453.

Example 88

Preparation of 4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 7, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a slightly yellow oil (yield: 96.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.28-2.39(1H, m), 2.35(3H, d, J=2.2 Hz), 2.56(6H, s), 3.50(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 7.07(1H, dd, J=8.9, 8.9 Hz), 7.59-7.67(2H, m), 7.74(1H,

t, J=1.2 Hz).

IR(Neat) cm^{-1}: 1652, 1608, 1506.

Mass m/z: 317(M^+).

Example 89

Preparation of 4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethyl-aminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 97.2%).

Melting point: 208.5-213.0℃

^1H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.19-2.30(1H, m), 2.32(3H, s), 2.81(6H, s), 4.03(2H, d, J=7.0 Hz), 4.30(2H, s), 7.30(1H, dd, J=9.0, 9.0 Hz), 7.74-7.80(1H, m), 7.85(1H, m), 8.51(1H, s).

IR(KBr) cm^{-1}: 1648, 1608, 1507.

Example 90

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10),

6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a slightly yellow oil (yield: 91.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.8 Hz), 2.27-2.40(1H, m), 2.34(3H, d, J=2.0 Hz), 2.70(4H, t, J=5.0 Hz), 3.66(4H, d, J=5.0 Hz), 3.69(2H, s), 3.91(2H, br), 4.07(2H, d, J=7.6 Hz), 7.07(1H, dd, J=8.9, 8.9 Hz), 7.60(1H, ddd, J=2.2, 5.1, 8.9 Hz), 7.64(1H, dd, J=2.2, 7.3 Hz), 7.71(1H, s).

IR(Neat) cm^{-1}: 3391, 1654, 1371, 1505.

Mass m/z: 359(M^+-H_2O).

Example 91

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 92.4%).

Melting point: 155.1-157.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.20-2.31(1H, m), 2.32(3H, d, J=1.2 Hz), 3.35(4H, br, overlapped with H2O), 3.82(4H, br), 4.02(2H, d, J=7.3 Hz), 4.50(2H, s), 5.37(2H, br), 7.30(1H, dd, J=9.0, 9.0 Hz), 7.78(1H, ddd, J=2.0, 4.9, 9.0 Hz), 7.85(1H, dd, J=2.0, 7.3 Hz), 7.71(1H, s).

IR(KBr) cm^{-1}: 3281, 1655, 1606.

Example 92

Preparation of

6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(piperidino) methyl-2H-pyridazin-3-one

6-(4-Fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one (80 mg, 0.22 mmol) and piperidine (55 mg, 0.65 mmol) were dissolved in ethanol (0.5 mL), and the mixture was heated at 80℃ for 1 hour under stirring. The solvent was distilled off. The residue was purified by preparative thin-layer chromatography on silica gel [developing solvent: chloroform/methanol (10/1)] to yield the title compound as a slightly yellow oil (73 mg, 94.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.9 Hz), 1.45-1.53(2H, m), 1.61- 1.68(4H, m), 2.28-2.41(1H, m), 2.36(3H, d, J=2.0 Hz), 2.47-2.53(4H, m), 3.52(2H, d, J=1.5 Hz), 4.07(2H, d, J=7.3 Hz), 7.08(1H, dd,

J=8.9, 8.9 Hz), 7.59(1H, ddd, J=1.7, 4.9, 8.9 Hz), 7.65(1H, dd, J=1.7, 7.3 Hz), 7.76(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1652, 1616, 1506.

Mass m/z: 357(M^+).

Example 93

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(piperidino)methyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(piperidino)methyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow prisms (yield: 90.7%).

^1H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 1.34-1.47(1H, m), 1.64-1.73(1H, m), 1.74- 1.83(4H, m), 2.20-2.30(1H, m), 2.32(3H, s), 2.95-3.02(2H, m), 3.36-3.45(1H, m), 4.02(2H, d, J=7.3 Hz), 4.25(2H, d, J=5.1 Hz), 7.30(1H, dd, J=9.0, 9.0 Hz), 7.75-7.80(1H, m), 7.83-7.87(1H, m), 8.59(1H, s).

IR(KBr) cm^{-1}: 2532, 1652, 1616, 1505, 1433.

Example 94

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(morpholino)methyl-2H-pyridazin-3-one

Following the procedure of Example 92, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and morpholine were reacted to yield the title compound as a slightly yellow oil (yield: 97.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.28-2.41(1H, m), 2.36(3H, d, J=2.0 Hz), 2.58(4H, t, J=4.6 Hz), 3.57(2H, d, J=1.2 Hz), 3.78(4H, t, J=4.6 Hz), 4.07(2H, d, J=7.3 Hz), 7.09(1H, dd, J=8.8, 8.8 Hz), 7.58(1H, ddd, J=2.0, 4.9, 8.8 Hz), 7.64(1H, dd, J=2.0, 7.3 Hz), 7.75(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1659, 1606, 1503.

Mass m/z: 359(M^+).

Example 95

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(morpholino)methyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(morpholino)methyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless prisms (yield: 92.4%).

Melting point: 215.4-216.6℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.19-2.30(1H, m), 2.32(3H, s),

3.21(2H, br), 3.79-3.98(6H, m), 4.02(2H, d, J=7.3 Hz), 4.33(2H, brs), 7.30(1H, dd, J=9.0, 9.0 Hz), 7.74-7.79(1H, m), 7.81-7.86(1H, m), 8.56(1H, brs).

IR(KBr) cm^{-1}: 2392, 1647, 1607.

Example 96

Preparation of 4-aminomethyl-6-(4-fluoro-3-methyl-phenyl)-2-isobutyl-2H-pyridazin-3-one

1) Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-phthalimidomethyl-2H-pyridazin-3-one

Following the procedure of Example 24(1), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 93.7%).

Melting point: 181.2-187.2℃

^1H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 2.30(3H, s), 4.07(2H, d, J=7.3 Hz), 4.91 (2H, s), 7.01(1H, dd, J=9.0, 9.0 Hz), 7.31(1H, s), 7.41-7.46(1H, m), 7.50-7.53(1H, m), 7.76-7.81(2H, m), 7.90-7.95(2H, m).

IR(KBr) cm^{-1}: 1720, 1656, 1619, 1611.

Mass m/z: 419(M^+).

2) Preparation of

4-aminomethyl-6-(4-fluoro-3-methyl-phenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 24(2), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-phthalimidomethyl-2H-pyridazin-3-one was reacted to yield the title compound as a slightly yellow oil (yield: 99.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.64(2H, br), 2.30-2.40(1H, m), 2.35(3H, d, J=2.0 Hz), 3.89(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 7.07(1H, dd, J=8.8, 8.8 Hz), 7.60(1H, ddd, J=2.1, 4.9, 8.8 Hz), 7.64(1H, dd, J=2.1, 7.4 Hz), 7.67(1H, t, J=1.2 Hz).

IR(Neat) cm^{-1}: 3372, 3301, 1655, 1605, 1504.

Mass m/z: 289(M^+).

Example 97

Preparation of 4-aminomethyl-6-(4-fluoro-3-methyl-phenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 79.8%).

Melting point: 217.5-220.5℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.6 Hz), 2.20-2.30(1H, m), 2.32(3H, d, J=1.7 Hz), 4.01(2H, d, J=2.2 Hz), 4.02(2H, d, J=7.3 Hz), 7.31(1H, dd, J=9.0, 9.0 Hz), 7.75(1H, ddd, J=2.1, 4.9, 9.0 Hz), 7.83(1H, dd, J=2.1, 7.4 Hz), 8.28(1H, s).

IR(KBr) cm^{-1}: 2960, 2927, 2872, 1656, 1614, 1507.

Example 98

Preparation of 4-diethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 9(4), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethylamine were reacted to yield the title compound as a slightly yellow oil (yield: 94.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.07(6H, t, J=7.1 Hz), 2.30-2.41(1H, m), 2.35(3H, d, J=1.5 Hz), 2.61(4H, q, J=7.1 Hz), 3.60(2H, d, J=1.7 Hz), 4.08(2H, d, J=7.5 Hz), 7.08(1H, dd, J=8.9, 8.9 Hz), 7.60(1H, ddd, J=2.2, 4.9, 8.9 Hz), 7.65(1H, dd, J=2.2, 7.3 Hz), 7.85(1H, t, J=1.5 Hz).

IR(Neat) cm^{-1}: 1652, 1609, 1506.

Mass m/z: 345(M^+).

Example 99

Preparation of

4-diethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-diethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 70.1%).

Melting point: 154.3-157.3℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.92(6H, d, J=6.8 Hz), 1.29(6H, t, J=7.2 Hz), 2.20-2.30(1H, m), 2.32(3H, d, J=1.2 Hz), 3.09-3.25(4H, m), 4.03(2H, d, J=7.3 Hz), 4.28(2H, d, J=5.6 Hz), 7.30(1H, dd, J=9.0, 9.0 Hz), 7.80(1H, ddd, J=2.0, 4.9, 9.0 Hz), 7.87(1H, dd, J=2.0, 7.3 Hz), 7.85(1H, t, J=1.5 Hz).

IR(KBr) cm^{-1}: 2559, 2491, 1652, 1613, 1507.

Example 100

Preparation of

4-(4-tert-butoxycarbonyl-1-pierazinyl)methyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-methanesulfonyloxy-methyl-2H-pyridazin-3-one and tert-butyl 1-piperazine-carboxylate were reacted to yield the title compound as a slightly yellow oil (yield: 97.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 1.46(9H, s), 2.28-2.40(1H, m), 2.36(3H, d, J=1.7 Hz), 3.50(4H, t, J=4.9 Hz), 3.58(2H, d, J=1.0 Hz), 4.08(2H, d, J=7.3 Hz), 7.09(1H, dd, J=8.9, 8.9 Hz), 7.58(1H, ddd, J=2.0, 4.9, 8.9 Hz), 7.63(1H, dd, J=2.0, 7.3 Hz), 7.75(1H, s).

IR(Neat) cm^{-1}: 1695, 1652, 1608, 1506.

Example 101

Preparation of 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-pierazinyl)methyl-6-(4-fluoro-3-methyl-phenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow oil (yield: quantitative).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz),1.47(1H, br), 2.28-2.40(1H, m), 2.36(3H, d, J=1.7 Hz), 2.56(4H, t, J=4.9 Hz), 2.97(4H, t, J=4.9 Hz), 3.56(2H, d, J=1.4 Hz), 4.07(2H, d, J=7.3 Hz), 7.09(1H, dd, J=8.8, 8.8 Hz), 7.58(1H, ddd, J=2.0, 4.9, 8.8 Hz), 7.64(1H, dd, J=2.0, 7.3 Hz), 7.75(1H, t, J=1.4 Hz).

Example 102

Preparation of

6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(1-piperazinyl) methyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow prisms (yield: 87.2%).

Melting point: 154.9-158.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.19-2.30(1H, m), 2.32(3H, d, J=1.7 Hz), 3.04(4H, br), 3.71(4H, br), 4.01(2H, d, J=7.3 Hz), 7.28(1H, dd, J=8.8, 8.8 Hz), 7.76(1H, ddd, J=2.0, 4.9, 8.8 Hz), 7.83(1H, dd, J=2.0, 7.3 Hz), 8.40(1H, brs).

IR(KBr) cm^{-1}: 1659, 1610, 1504, 1422.

Example 103

Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

1) Preparation of ethyl

4-(3,4-difluorophenyl)-2-ethoxy-carbonyl-2-hydroxy-4-oxobutanoate

Following the procedure of Example 1(3), 3',4'-difluoroacetophenone was reacted to yield the title compound as a pale yellow oil (yield: 81.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30(6H, t, J=7.1 Hz), 3.78(2H, s), 4.22(1H, s), 4.31(4H, q, J=7.1 Hz), 7.24-7.30(1H, m), 7.73-7.82(2H, m).

IR(Neat) cm^{-1}: 3483, 1740, 1695, 1612.

Mass m/z: 312(M^+-H_2O).

2) Preparation of

4-carboxy-6-(3,4-difluorophenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(4), ethyl 4-(3,4-difluorophenyl)-2-ethoxycarbonyl-2-hydroxy-4-oxo-butanoate was reacted to yield the title compound as a pale yellow crystalline powder (yield: 88.9%).

3) Preparation of

4-methoxycarbonyl-6-(3,4-difluorophenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(5), 4-carboxy-6-(3,4-difluorophenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 85.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

4.01(3H, s), 7.25-7.32(1H, m), 7.53-7.57(1H, m), 7.67-7.73(1H, m), 8.31(1H, s), 11.70(1H, br).

IR(KBr) cm^{-1}: 3223, 3159, 1722, 1676, 1659.

Mass m/z: 266(M^+).

4) Preparation of

6-(3,4-difluorophenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3,4-difluorophenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: quantitative).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.30-2.41(1H, m), 3.98(3H, s), 4.13(2H, d, J=7.2 Hz), 7.23-7.30(1H, m), 7.49-7.55(1H, m), 7.68(1H, ddd, J=2.2, 7.6, 11.1 Hz), 8.20(1H, s).

5) Preparation of

4-carboxy-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(7), 6-(3,4-difluorophenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine needles (yield: 91.4%).

Melting point: 163.4-163.7℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.02(6H, d, J=6.6 Hz), 2.33-2.43(1H, m), 4.22(2H, d, J=7.4 Hz), 7.27-7.35(1H, m), 7.56-7.62(1H, m), 7.74(1H, ddd, J=2.4, 7.6,

11.2 Hz), 8.62(1H, s), 14.05(1H, s).

IR(KBr) cm^{-1}: 3436, 1737, 1635, 1522, 1434, 1276, 1102, 806.

Mass m/z: 308(M^+)

6) Preparation of 6-(3,4-difluorophenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 25.0%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.29-2.39(1H, m), 2.96(1H, t, J=5.9 Hz), 4.08(2H, d, J=7.4 Hz), 4.72(2H, dd, J=1.2, 5.8 Hz), 7.22-7.28(1H, m), 7.51-7.55(1H, m), 7.64-7.71(2H, m).

7) Preparation of 6-(3,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 6-(3,4-difluorophenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless fine-needles (yield: 81.4%).

Melting point: 113.3-113.4℃

^1H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.27-2.40(1H, m), 3.18(3H, s), 4.08(2H, d, J=7.4 Hz), 5.28(2H, d, J=1.6 Hz), 7.23-7.30(1H, m), 7.50-7.54(1H, m), 7.68(1H, ddd, J=2.2, 7.6, 11.1 Hz), 7.75(1H, t, J=1.4 Hz).

IR(KBr) cm^{-1}: 3447, 1656, 1613, 1522, 1354, 1167, 1049, 877.

Mass m/z: 372(M^+)

8) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 85.5%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 1.47(9H, s), 2.28-2.38(1H, m), 2.52(4H, t, J=4.7 Hz), 3.51(4H, t, J=4.7 Hz), 3.58(2H, s), 4.07(2H, d, J=7.2 Hz), 7.21-7.29(1H, m), 7.50-7.55(1H, m), 7.64-7.71(1H, m), 7.76(1H, d, J=1.0 Hz).

Example 104

Preparation of 6-(3,4-difluorophenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2,

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a white solid (yield: 72.5%).

Melting point: 182.5-186.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.22-2.33(1H, m), 3.11(4H, br), 3.30(4H, t, J=5.1 Hz), 3.90(2H, s), 4.02(2H, d, J=7.1 Hz), 7.52(1H, ddd, J=8.6, 8.6, 10.5 Hz), 7.73-7.78(1H, m), 7.90(1H, ddd, J=2.2, 8.0, 11.7 Hz), 8.20(1H, s).

IR(KBr) cm^{-1}: 1656, 1609, 1522, 1436, 1276, 1112.

Mass m/z: 362(M^+)

Example 105

Preparation of 6-(3,4-difluorophenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 79.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.28-2.39(1H, m), 2.34(3H, s), 2.55(4H, br), 2.63(4H, br), 3.58(2H, s), 4.07(2H, d, J=7.2 Hz),

7.22-7.29(1H,m), 7.50-7.57(1H,m), 7.64-7.72(1H,m), 7.74(1H, s).

Example 106

Preparation of 6-(3,4-difluorophenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(3,4-difluorophenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 70.3%).

Melting point: 242.5-243.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.22-2.33(1H, m), 2.77(3H, s), 3.11(4H, br), 3.34(4H, br), 3.84(2H, s), 4.02(2H, d, J=7.1 Hz), 7.52(1H, ddd, J=8.6, 8.6, 10.5 Hz), 7.72-7.77(1H, m), 7.89(1H, ddd, J=2.2, 7.9, 11.7 Hz), 8.12(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1522, 1435, 1278.

Mass m/z: 376(M^+)

Example 107

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10),

6-(3,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 75.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.6 Hz), 2.25-2.38(1H, m), 2.70(4H, br), 3.64-3.70(6H, m), 4.06(2H, d, J=7.4 Hz), 7.15-7.25(1H, m), 7.54-7.58(1H, m), 7.67-7.73(1H, m), 7.88(1H, s).

Example 108

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a white solid (yield: 70.3%).

Melting point: 127.5-128.3℃

^{1}H NMR(400MHz, $DMSO_6$)δ:

0.95(6H, d, J=6.8 Hz), 2.23-2.34(1H, m), 3.35(4H, t, J=5.1 Hz), 3.84(4H, t, J=5.1 Hz), 4.05(2H, d, J=7.1 Hz), 4.45(2H, s), 7.54(1H, ddd, J=8.6, 8.6, 10.5 Hz), 7.76-7.81(1H, m), 7.93(1H, ddd, J=2.2, 7.8, 12.0 Hz), 8.53(1H, s).

IR(KBr) cm^{-1}: 1653, 1604, 1521, 1437, 1275.

Mass m/z: 363(M^+-H_2O)

Example 109

Preparation of 6-(3,4-difluorophenyl)-4-dimethylaminomethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 7, 6-(3,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 85.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.29-2.40(1H, m), 2.35(6H, s), 3.50(2H, s), 4.07(2H, d, J=7.4Hz), 7.20-7.30(1H, m), 7.53-7.60(1H, m), 7.67-7.73(1H, m), 7.74(1H, s).

Example 110

Preparation of 6-(3,4-difluorophenyl)-4-dimethyl-aminomethyl-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(3,4-difluorophenyl)-4-dimethylaminomethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow flakes (yield: 85.9%).

Melting point: 226.5-227.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.8 Hz), 2.23-2.34(1H, m), 2.81(6H, s), 4.05(2H, d, J=7.1 Hz), 4.28(2H, s), 7.54(ddd, J=8.7, 8.7, 10.5 Hz), 7.76-7.81(1H, m), 7.93(1H, ddd, J=2.2, 7.9, 12.0 Hz), 8.57(1H, s).

IR(KBr) cm^{-1}: 1648, 1607, 1525, 1437, 1288, 1112.

Mass m/z: 321(M^+)

Example 111

Preparation of 4-aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

1) Preparation of ethyl 4-(2,4-difluorophenyl)-2-ethoxy-carbonyl-2-hydroxy-4-oxobutanoate

Following the procedure of Example 1(3), 2',4'-difluoroacetophenone was reacted to yield the title compound as a pale yellow oil (yield: 76.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30(6H, t, J=7.1 Hz), 3.81(2H, d, J=3.4 Hz), 4.18(1H, s), 4.30(4H, q, J=7.1 Hz), 6.90(1H, ddd, J=2.4, 8.5, 10.0 Hz), 6.94-7.00(1H, m), 7.94(1H, ddd, J=6.6, 8.5, 8.5 Hz).

IR(Neat) cm^{-1}: 3491, 1743, 1692, 1612.

Mass m/z: 312(M^+-H_2O)

2) Preparation of

4-carboxy-6-(2,4-difluorophenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(4), ethyl 4-(2,4-difluorophenyl)-2-ethoxycarbonyl-2-hydroxy-4-oxo-butanoate was reacted to yield the title compound as a pale yellow crystalline powder (yield: 95.2%).

3) Preparation of

6-(2,4-difluorophenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(5), 4-carboxy-6-(2,4-difluorophenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 81.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.99(3H, s), 6.96(1H, ddd, J=2.4, 8.8, 10.1 Hz), 6.99-7.04(1H, m), 7.77(1H, ddd, J=6.3, 8.8, 8.8 Hz), 8.30(1H, d, J=2.0 Hz), 12.05(1H, br).

IR(KBr) cm^{-1}: 3217, 3148, 1721, 1673, 1611.

Mass m/z: 266(M^+).

4) Preparation of

6-(2,4-difluorophenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6),

6-(2,4-difluorophenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow oil (yield: 84.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.29-2.42(1H, m), 3.97(3H, s), 4.12(2H, d, J=7.3 Hz), 6.94(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.98-7.04(1H, m), 7.73(1H, ddd, J=6.3, 6.3, 8.8 Hz), 8.18(1H, d, J=2.0 Hz).

IR(Neat) cm^{-1}: 1755, 1748, 1668, 1620, 1506.

Mass m/z: 322(M^+).

5) Preparation of 4-carboxy-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(7), 6-(2,4-difluorophenyl)-2-isobutyl-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 92.7%).

Melting point: 126.5-128.2℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.02(6H, d, J=6.6 Hz), 2.31-2.43(1H, m), 4.22(2H, d, J=7.6 Hz), 6.96-7.07(2H, m), 7.74(1H, ddd, J=6.3, 6.3, 8.8 Hz), 8.61(1H, d, J=2.2 Hz), 14.02(1H, s).

IR(KBr) cm^{-1}: 1739, 1636, 1618, 1573, 1465.

Mass m/z: 308(M^+).

6) Preparation of

6-(2,4-difluorophenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow oil (yield: 45.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.27-2.40(1H, m), 3.15(1H, t, J=6.1 Hz), 4.08(2H, d, J=7.3 Hz), 4.69(2H, dd, J=1.2, 6.1 Hz), 6.93(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.96-7.02(1H, m), 7.61-7.63(1H, m), 7.72(1H, ddd, J=6.3, 6.3, 8.8 Hz).

IR(Neat) cm^{-1}: 3412, 1652, 1620, 1507.

Mass m/z: 294(M^+).

7) Preparation of 6-(2,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 6-(2,3-difluorophenyl)-4-hydroxymethyl-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 96.3%).

Melting point: 86.7-88.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.26-2.39(1H, m), 3.16(3H, s),

4.08(2H, d, J=7.3 Hz), 5.26(2H, d, J=1.2 Hz), 6.94(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.97-7.03(1H, m), 7.71(1H, ddd, J=6.3, 6.3, 8.8 Hz), 7.73-7.75(1H, m).

IR(KBr) cm^{-1}: 1659, 1612, 1508, 1359, 1166.

Mass m/z: 372(M^+).

8) Preparation of 6-(2,4-difluorophenyl)-2-isobutyl-4-phthalimidomethyl-2H-pyridazin-3-one

Following the procedure of Example 24(1), 6-(2,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 91.1%).

Melting point: 152.3-155.6℃

^1H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.28-2.39(1H, m), 4.07(2H, d, J=7.3 Hz), 4.89(2H, d, J=1.0 Hz), 6.83(1H, ddd, J=2.4, 8.8, 11.0 Hz), 6.91-6.97(1H, m), 7.27-7.31(1H, m), 7.66(1H, ddd, J=6.3, 6.3, 8.8 Hz), 7.74-7.80(2H, m), 7.86-7.94(2H, m).

IR(KBr) cm^{-1}: 1773, 1720, 1650, 1617, 1509, 1418, 1389.

Mass m/z: 423(M^+).

9) Preparation of 4-aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 24(2),

2-isobutyl-6-(2,4-difluorophenyl)-4-phthalimidomethyl-2H-pyridazin-3-one was reacted to yield the title compound as a slightly yellow oil (yield: 98.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.66(2H, br), 2.24-2.41(1H, m), 3.87(2H, s), 4.08(2H, d, J=7.3 Hz), 6.92(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.97-7.02(1H, m), 7.63(1H, t, J=1.1 Hz), 7.71(1H, ddd, J=6.3, 6.3, 8.8 Hz).

IR(Neat) cm^{-1}: 3381, 3307, 1652, 1611, 1508.

Mass m/z: 293(M^+).

Example 112

Preparation of 4-aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 94.9%).

Melting point: 161.4-163.9℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.8 Hz), 2.18-2.34(1H, m), 4.01(2H, s), 4.02(2H, d, J=7.3 Hz), 7.24-7.31(1H, m), 7.46(1H, ddd, J=2.4, 8.8, 11.5 Hz), 7.76(1H, ddd, J=6.3, 6.3, 8.8 Hz), 7.95(1H, s).

IR(KBr) cm^{-1}: 1652, 1616, 1597, 1509.

Example 113

Preparation of

6-(2,4-difluorophenyl)-4-dimethyl-aminomethyl-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 7, 6-(2,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a slightly yellow oil (yield: 94.1%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 2.27-2.38(1H, m), 2.34(6H, s), 3.49(2H, d, J=1.5 Hz), 4.07(2H, d, J=7.6 Hz), 6.92(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.95-7.01(1H, m), 7.70(1H, t, J=1.5 Hz), 7.71(1H, ddd, J=6.3, 6.3, 8.8 Hz).

IR(Neat) cm^{-1}: 1652, 1612, 1508.

Mass m/z: 321(M^+).

Example 114

Preparation of

6-(2,4-difluorophenyl)-4-dimethyl-aminomethyl-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 6-(2,4-difluorophenyl)-4-dimethylaminomethyl-2-isobutyl-2H-

pyridazin-3-one was reacted to yield the title compound as pale yellow prisms (yield: 89.8%).

Melting point: 170.1-173.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 2.18-2.29(1H, m), 2.80(6H, s), 4.03(2H, d, J=7.3 Hz), 4.30(2H, s), 7.25-7.31(1H, m), 7.45(1H, ddd, J=2.4, 8.8, 11.2 Hz), 7.81(1H, ddd, J=6.3, 6.3, 8.8 Hz). 8.15(1H, d, J=1.7 Hz),

IR(KBr) cm^{-1}: 1648, 1612, 1523, 1510.

Example 115

Preparation of 4-diethylaminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 9(4), 6-(2,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethylamine were reacted to yield the title compound as a pale yellow oil (yield: quantitative).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.06(6H, t, J=7.1 Hz), 2.27-2.39(1H, m), 2.59(4H, q, J=7.1 Hz), 3.59(2H, d, J=1.7 Hz), 4.07(2H, d, J=7.3 Hz), 6.92(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.95-7.01(1H, m), 7.72(1H, ddd, J=6.3, 6.3, 8.8 Hz), 7.83(1H, td, J=1.5, 2.9 Hz).

IR(Neat) cm^{-1}: 1656, 1613, 1508.

Mass m/z: 349(M^+).

Example 116

Preparation of

4-diethylaminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-diethylamino-methyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 80.9%).

Melting point: 128.9-131.7℃

^1H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.8 Hz), 1.28(6H, t, J=7.2 Hz), 2.18-2.29(1H, m), 3.10-3.23(4H, m), 4.03(2H, d, J=7.3 Hz), 4.29(2H, d, J=5.4 Hz), 7.28(1H, ddd, J=2.2, 8.8, 8.8 Hz), 7.45(1H, ddd, J=2.2, 8.8, 8.8 Hz), 7.81(1H, ddd, J=6.3, 8.8, 8.8 Hz), 8.24(1H, d, J=1.5 Hz).

Example 117

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(2,4-difluorophenyl)-2-isobutyl-4-

methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a slightly yellow oil (yield: 97.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.6 Hz), 2.26-2.40(1H, m), 2.70(4H, t, J=5.0 Hz), 3.65(4H, t, J=5.0 Hz), 3.70(2H, s), 4.09(2H, d, J=7.3 Hz), 6.92(1H, ddd, J=2.7, 8.8, 11.2 Hz), 6.97-7.03(1H, m), 7.63(1H, d, J=2.4 Hz), 7.75(1H, ddd, J=6.3, 6.3, 8.8 Hz).

IR(Neat) cm^{-1}: 3401, 1648, 1597, 1508.

Mass m/z: 363(M^+-H_2O).

Example 118

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow prisms (yield: 89.0%).

Melting point: 161.8-163.9℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.6 Hz), 2.18-2.29(1H, m), 3.27-3.40(4H, br, overlapped with H2O), 3.76-3.84(4H, m), 4.03(2H, d, J=7.3 Hz), 4.51(2H, brs), 5.34(2H, br), 7.24-7.31(1H, m),

7.41-7.48(1H, m), 7.76-7.84(1H, m), 8.15(1H, m).

IR(KBr) cm^{-1}: 3233, 3172, 1645, 1613, 1593, 1421.

Example 119

Preparation of

6-(2,4-difluorophenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(2,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a pale yellow oil (yield: 94.0%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.97(6H, d, J=6.6 Hz), 2.28-2.38(1H, m), 2.31(3H, s), 2.50(4H, br), 2.61(4H, br), 3.57(2H, d, J=1.5 Hz), 4.07(2H, d, J=7.3 Hz), 6.93(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.96-7.02(1H, m), 7.69-7.75(2H, m).

IR(Neat) cm^{-1}: 1655, 1616, 1596, 1508.

Mass m/z: 376(M^+).

Example 120

Preparation of

6-(2,4-difluorophenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4,

6-(2,4-difluorophenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 90.4%).

Melting point: 248.1-251.7℃ (dec.).

^{1}H NMR(400MHz, DMSO-d_6, 100℃)δ:

0.93(6H, d, J=6.8 Hz), 2.20-2.29(1H, m), 2.76(3H, s), 3.09(4H, br, overlapped with H_2O), 3.27(4H, br), 3.74(2H, s), 4.00(2H, d, J=7.1 Hz), 7.14-7.29(2H, m), 7.71-7.79(2H, m).

IR(KBr) cm^{-1}: 1652, 1612, 1514.

Example 121

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(2,4-difluorophenyl)-2-isobutyl-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a slightly yellow oil (yield: 97.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.47(9H, s), 2.28-2.39(1H, m), 2.52(4H, t, J=4.9 Hz), 3.49(4H, t, J=4.9 Hz), 3.57(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 6.93(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.96-7.02(1H, m), 7.69-7.75(2H, m).

IR(Neat) cm^{-1}: 1695, 1655, 1613, 1508, 1425.

Mass m/z: 462(M^+).

Example 122

Preparation of 6-(2,4-difluorophenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 20, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(2,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: quantitative).

^1H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.8 Hz), 1.81(1H, br), 2.27-2.39(1H, m), 2.50-2.56(4H, brm), 2.94(4H, t, J=4.8 Hz), 3.54(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.3 Hz), 6.93(1H, ddd, J=2.4, 8.8, 11.2 Hz), 6.94-7.02(1H, m), 7.69-7.76(2H, m).

IR(Neat) cm^{-1}: 3314, 1655, 1613, 1508.

Mass m/z: 362(M^+).

Example 123

Preparation of 6-(2,4-difluorophenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 6-(2,4-difluorophenyl)-2-isobutyl-4-(1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as

a slightly yellow crystalline powder (yield: 90.8%).

Melting point: 136.3-140.9℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.93(6H, d, J=6.6 Hz), 2.20-2.30(1H, m), 2.95(4H, t, J=5.0 Hz), 3.02(4H, t, J=5.0 Hz), 3.76(2H, s), 4.00(2H, d, J=7.3 Hz), 7.14-7.20(1H, m), 7.26(1H, ddd, J=2.7, 8.8, 11.2 Hz), 7.86(1H, ddd, J=6.6, 6.6, 8.8 Hz), 7.81(1H, s).

IR(KBr) cm^{-1}: 1656, 1616, 1597, 1509, 1426.

Example 124

Preparation of

2-benzyl-4-(4-tert-butoxycarbonyl-1-piperazinyl) methyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

1) Preparation of

2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and benzyl chloride were reacted to yield the title compound as yellow needles (yield: 71.0%).

Melting point: 109.0-110.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.35(3H, d, J=1.7 Hz), 3.96(3H, s), 5.44(2H, s), 7.10(1H, dd, J=8.8, 8.8 Hz), 7.28-7.37(3H, m), 7.52(2H, d, J=6.3 Hz), 7.57-7.64(2H, m), 8.21(1H, s).

IR(KBr) cm^{-1}: 1750, 1744, 1657, 1278, 1233, 1123.

Mass m/z: 352(M^+).

2) Preparation of

2-benzyl-4-carboxy-6-(4-fluoro-3-methyl-phenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 65.2%).

Melting point: 191.2-192.3℃

^1H NMR(400MHz, $CDCl_3$)δ:

2.37(3H, d, J=2.0 Hz), 5.52(2H, s), 7.13(1H, dd, J=8.8, 8.8 Hz), 7.33-7.41(3H, m), 7.48-7.52(2H, m), 7.64-7.70(2H, m), 8.62(1H, s), 14.01(1H, br).

IR(KBr) cm^{-1}: 1739, 1633, 1569, 1457, 1423, 1240.

Mass m/z: 338(M^+).

3) Preparation of

2-benzyl-6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 2-benzyl-4-carboxy-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 28.4%).

Melting point: 119.5-120.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.34(3H, d, J=1.7 Hz), 3.01(1H, t, J=5.9 Hz), 4.70(2H, dd, J=1.2, 5.9 Hz), 5.41(2H, s), 7.08 (1H, dd, J=8.8, 8.8 Hz), 7.27-7.37(3H, m), 7.48(1H, d, J=6.6 Hz), 7.57-7.65(2H, m) , 7.66(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 3330, 1657, 1643, 1611, 1597, 1506, 1239.

Mass m/z: 324(M^+).

4) Preparation of 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 98.9%).

Melting point: 147.6-148.3℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.35(3H, d, J=2.0 Hz), 3.15(3H, s), 5.26(2H, d, J =1.2 Hz), 5.41(2H, s), 7.09 (1H, dd, J=8.8, 8.8 Hz), 7.27-7.37(3H, m), 7.47(2H, d, J=6.6 Hz), 7.62(1H, d, J=7.3 Hz), 7.57-7.60(1H, m), 7.75(1H, s).

IR(KBr) cm^{-1}: 1656, 1617, 1507, 1355, 1168, 1033, 879.

Mass m/z: 402(M^+).

5) Preparation of

2-benzyl-4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 91.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.46(9H, s), 2.35(3H, d, J=1.8 Hz), 2.50(4H, t, J=4.9 Hz), 3.49(4H, t, J=4.9 Hz), 3.56(2H, d, J=1.4 Hz), 5.40(2H, s), 7.26-7.36(4H, m), 7.49(2H, d, J=6.6 Hz), 7.55-7.60(1H, m), 7.63(1H, dd, J=1.8, 7.2 Hz), 7.74(1H, s).

Example 125

Preparation of 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 2-benzyl-4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 60.9%).

Melting point: 162.7-180.7℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(3H, d, J=2.0 Hz), 3.09(4H, br), 3.28(4H, t, J=5.2 Hz), 3.89(2H, s), 5.36(2H, s), 7.21-7.40(6H, m), 7.70-7.76(1H, m), 7.79(1H, dd, J=1.7, 7.3 Hz), 8.16(1H, s).

IR(KBr) cm^{-1}: 1656, 1607, 1505, 1239, 1126, 700.

Mass m/z: 392(M^+)

Example 126

Preparation of 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 81.3%).

^1H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, s), 2.36(3H, d, J=1.8 Hz), 2.53(4H, br), 2.61(4H, br), 3.57(2H, d, J=1.4 Hz), 5.40(2H, s), 7.08(1H, t, J=8.9 Hz), 7.26-7.36(3H, m), 7.49(2H, d, J=6.8 Hz), 7.56-7.60(1H, m), 7.64(1H, dd, J=1.8, 7.2 Hz), 7.73(1H, s).

Example 127

Preparation of 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 78.6%).

Melting point: 240.0-242.5℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(3H, d, J=1.7 Hz), 2.76(3H, s), 3.10(4H, br), 3.33(4H, br), 3.84(2H, s), 5.36(2H, s), 7.21-7.39(6H, m), 7.69-7.74(1H, m), 7.78(1H, dd, J=2.1, 7.8 Hz), 8.09(1H, s).

IR(KBr) cm^{-1}: 1653, 1607, 1504, 1454, 1240, 1127.

Mass m/z: 406(M^+)

Example 128

Preparation of 2-benzyl-4-N,N-bis(2-hydroxyethyl)-aminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 87.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, s), 2.69(4H, t, J=4.9 Hz), 3.64(4H, t, J=5.0 Hz),

3.68(2H, s), 5.40(2H, s), 7.06(1H, t, J=8.9 Hz), 7.26-7.38(3H, m), 7.45(2H, d, J=7.0 Hz), 7.58-7.68(2H, m), 7.75(1H, s).

Example 129

Preparation of 2-benzyl-4-N,N-bis(2-hydroxyethyl)-aminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-benzyl-4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 75.9%).

Melting point: 161.7-163.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(2H, d, J=2.0 Hz), 3.34(4H, t, J=5.2 Hz), 3.83(4H, t, J=5.4 Hz), 4.47(2H, s), 5.39(2H, s), 7.23-7.40(6H, m), 7.73-7.77(1H, m), 7.82(1H, dd, J=1.7, 7.3 Hz), 8.47(1H, s).

IR(KBr) cm^{-1}: 1602, 1503, 1239, 1088.

Mass m/z: 393(M^+-H_2O)

Example 130

Preparation of 2-benzyl-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-benzyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow oil (yield: 92.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.34(9H, s), 3.49(2H, s), 5.40(2H, s), 7.06(1H, t, J=8.9 Hz), 7.25-7.35(3H, m), 7.49(2H, d, J=7.4 Hz), 7.58-7.67(2H, m), 7.75(1H, s).

Example 131

Preparation of 2-benzyl-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-benzyl-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as colorless flakes (yield: 72.6%).

Melting point: 225.3-226.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(3H, d, J=2.0 Hz), 2.81(6H, s), 4.28(2H, s), 5.39(2H, s), 7.21-7.41(6H, m), 7.73-7.78(1H, m), 7.83(1H, dd, J=2.2, 7.6 Hz), 8.52(1H, s).

IR(KBr) cm^{-1}: 1652, 1610, 1506, 1240, 1126, 702.

Mass m/z: 351(M^+)

Example 132

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

1) Preparation of 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and cinnamyl bromide were reacted to yield the title compound as pale yellow needles (yield: 58.7%).

Melting point: 95.9-96.7℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.35(3H, d, J=1.7 Hz), 3.99(3H, s), 5.04(2H, dd, J=1.2, 6.8 Hz), 6.45(1H, dt, J=15.9, 6.8 Hz), 6.75(1H, d, J=15.9 Hz), 7.10(1H, dd, J=8.9, 8.9 Hz), 7.20-7.33(3H, m), 7.39(2H, d, J=7.1 Hz), 7.58-7.66(2H, m), 8.23(1H, s).

IR(KBr) cm^{-1}: 1724, 1661, 1603, 1501, 1292, 1234, 1123.

Mass m/z: 378(M^+).

2) Preparation of 4-carboxy-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7),

2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow needles (yield: 85.1%).

Melting point: 142.8-143.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.36(3H, d, J=2.0 Hz), 5.12(2H, dd, J=1.2, 6.8 Hz), 6.42(1H, dt, J=15.9, 6.8 Hz), 6.80(1H, d, J=15.9 Hz), 7.13(1H, dd, J=8.8, 8.8 Hz), 7.22-7.36(3H, m), 7.40-7.43(2H, m), 7.65-7.72(2H, m), 8.64(1H, s), 14.04(1H, br).

IR(KBr) cm^{-1}: 3438, 3061, 2688, 1747, 1637, 1567, 1463, 1244.

Mass m/z: 364(M^+).

3) Preparation of 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 20.1%).

Melting point: 139.9-140.9℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.34(3H, d, J=1.5 Hz), 3.00(1H, br), 4.73(2H, s), 5.01(2H, d, J=6.6 Hz), 6.44(1H, dt, J=15.9, 6.6 Hz), 6.72(2H, d, J=15.9 Hz), 7.08(1H, dd, J=8.9, 8.9 Hz), 7.24(1H, t, J=7.3 Hz), 7.30(2H, dd, J=7.3, 7.3 Hz), 7.39(2H, d, J=7.3 Hz),

7.58-7.62(1H, m), 7.64(1H, d, J=7.3 Hz), 7.67(1H, s).
IR(KBr) cm^{-1}: 3393, 1655, 1648, 1602, 1505, 1451, 1238, 1077.
Mass m/z: 350(M^+).

4) Preparation of 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 91.9%).
Melting point: 78.4-80.5℃
^1H NMR(400MHz, $CDCl_3$)δ:
2.35(3H, d, J=2.0 Hz), 3.17(3H, s), 5.10(2H, dd, J=1.2, 6.8 Hz), 5.28(2H, d, J=1.2 Hz), 6.42(1H, dt, J=15.9, 6.8 Hz), 6.73(1H, d, J=15.9 Hz), 7.09(1H, dd, J=8.9, 8.9 Hz), 7.21-7.33(3H, m), 7.40(2H, d, J=8.8 Hz), 7.57-7.62(1H, m), 7.64(1H, d, J=8.8 Hz), 7.77(1H, t, J=1.3 Hz).
IR(KBr) cm^{-1}: 1663, 1612, 1508, 1355, 1241, 1167, 988, 958, 873.
Mass m/z: 428(M^+).

5) Preparation of
4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-

methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 86.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.47(9H, s), 2.35(3H, d, J=1.6 Hz), 2.52(4H, t, J=5.0 Hz), 3.51(4H, t, J=4.9 Hz), 3.59(2H, d, J=1.4 Hz), 5.00(2H, dd, J=1.0, 6.6 Hz), 6.45(1H, dt, J=15.8, 6.6 Hz), 6.72(1H, d, J=15.8 Hz), 7.08(1H, dd, J=8.9, 8.9 Hz), 7.22(1H, t, J=7.2 Hz), 7.29(2H, dd, J=7.0, 7.0 Hz), 7.38(2H, d, J=7.7 Hz), 7.56-7.61(1H, m), 7.65(1H, dd, J=1.8, 7.2 Hz), 7.77(1H, s).

Example 133

Preparation of 2-cinnamyl-6-(4-fluoro-3-methyl-phenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 96.0%).

Melting point: 171.1-187.1℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(3H, d, J=2.0 Hz), 3.21(4H, t, J=4.9 Hz), 3.34(4H, t, J=5.1 Hz), 3.99(2H, s), 4.95(2H, dd, J=1.3, 6.4 Hz), 6.45(1H,

dt, J=16.1, 6.3 Hz), 6.68(1H, d, J=16.1 Hz), 7.20-7.26(2H, m), 7.29-7.34(2H, m), 7.41-7.45(2H, m), 7.73-7.79(1H, m), 7.83(1H, dd, J=1.7, 7.3 Hz), 8.26(1H, s).

IR(KBr) cm^{-1}: 1656, 1605, 1505, 1239, 962.

Mass m/z: 418(M^+)

Example 134

Preparation of

2-cinnamyl-6-(4-fluoro-3-methyl-phenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 80.1%).

^1H NMR(400MHz, $CDCl_3$)δ:

2.32(3H, s), 2.35(3H, d, J=1.8 Hz), 2.51(4H, br), 2.62(4H, br), 3.59(2H, d, J=1.4 Hz), 4.99(2H, dd, J=1.1, 6.6 Hz), 6.45(1H, dt, J=15.8, 6.0 Hz), 6.72(1H, d, J=15.8 Hz), 7.08(1H, dd, J=8.9, 8.9 Hz), 7.22(1H, tt, J=1.6, 7.2 Hz), 7.29(2H, dd, J=7.2, 7.2 Hz), 7.39(2H, dd, J=1.4, 7.2 Hz), 7.56-7.61(1H, m), 7.65(1H, dd, J=1.8, 7.2 Hz), 7.75(1H, t, J=1.4 Hz).

Example 135

Preparation of

2-cinnamyl-6-(4-fluoro-3-methyl-phenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 66.3%).

Melting point: 236.1-237.1℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.32(3H, d, J=2.2 Hz), 2.76(3H, s), 3.08(4H, br), 3.32(4H, br), 3.83(2H, s), 4.94(2H, dd, J=1.2, 6.4 Hz), 6.45(1H, dt, J=16.1, 6.3 Hz), 6.67(1H, d, J=15.8 Hz), 7.19-7.26(2H, m), 7.29-7.34(2H,m), 7.41-7.44(2H,m), 7.71-7.76(1H,m), 7.81(1H, dd, J=2.2, 7.6 Hz), 8.07(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1505, 1239, 1129.

Mass m/z: 432(M^+)

Example 136

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and

diethanolamine were reacted to yield the title compound as a yellow oil (yield: 83.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.32(3H, s), 2.69(4H, t, J=4.9 Hz), 3.65(4H, d, J=4.9 Hz), 3.69(2H, s), 4.98(2H, d, J=6.6 Hz), 6.41(1H, dt, J=15.8, 6.5 Hz), 6.68(1H, d, J=15.8 Hz), 7.05(1H, dd, J=8.9, 8.9 Hz), 7.21(1H, t, J=7.2 Hz), 7.28(2H, dd, J=7.2, 7.2 Hz), 7.37(2H, d, J=7.6 Hz), 7.58-7.63(1H, m), 7.66(1H, dd, J=1.8, 7.2 Hz), 7.81(1H, s).

Example 137

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cinnamyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cinnamyl-6-(4-fluoro-3-methyl-phenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 63.2%).

Melting point: 112.5-113.2℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.32(3H, d, J=1.9 Hz), 3.35(4H, t, J=5.1 Hz), 3.84(4H, t, J=5.1 Hz), 4.46(2H, s), 4.98(2H, dd, J=1.5, 6.1 Hz), 6.45(1H,

dt, J=15.8, 6.1 Hz), 6.69(1H, d, J=16.0 Hz), 7.21-7.27(2H, m), 7.29-7.34(2H, m), 7.41-7.44(2H, m), 7.757.80(1H, m), 7.85(1H, dd, J=2.0, 7.3 Hz), 8.47(1H, s).

IR(KBr) cm^{-1}: 1652, 1604, 1505, 1241, 971.

Mass m/z: 419(M^+-H_2O)

Example 138

Preparation of

2-cinnamyl-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-cinnamyl-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow oil (yield: 90.9%).

^1H NMR(400MHz, $CDCl_3$)δ:

2.34(3H, d, J=2.0 Hz), 2.36(6H, s), 3.51(2H, d, J=1.4 Hz), 5.00(2H, dd, J=1.3, 6.8 Hz), 6.46(1H, dt, J=15.8, 6.6 Hz), 6.72(1H, d, J=15.8 Hz), 7.07(1H, dd, J=8.9, 8.9 Hz), 7.22(1H, tt, J=1.4, 7.2 Hz), 7.29(2H, dd, J=7.2, 7.2 Hz), 7.39(2H, dd, J=1.6, 7.0 Hz), 7.60-7.65(1H, m), 7.67(1H, dd, J=2.2, 7.2 Hz), 7.76(1H, s).

Example 139

Preparation of

2-cinnamyl-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-cinnamyl-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 81.1%).

Melting point: 183.6-184.5℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.32(3H, d, J=2.0 Hz), 2.83(6H, s), 4.29(2H, s), 4.98(2H, dd, J=1.3, 6.4 Hz), 6.46(1H, dt, J=16.1, 6.3 Hz), 6.69(1H, d, J=16.1 Hz), 7.22-7.27(2H, m), 7.29-7.35(2H, m), 7.41-7.44(2H, m), 7.76-7.81(1H, m), 7.86(1H, dd, J=2.2, 7.3 Hz), 8.50(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1505, 1240, 965.

Mass m/z: 377(M^+)

Example 140

Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

1) Preparation of 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6),

6-(3-fluoro-4-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and 4-chlorocinnamyl chloride were reacted to yield the title compound as yellow needles (yield: 71.7%).

Melting point: 137.8-138.8℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.35(3H, d, J=1.7 Hz), 3.99(3H, s), 5.03(2H, d, J=6.6 Hz), 6.43(1H, dt, J=15.6, 6.6 Hz), 6.70(1H, d, J=15.6 Hz), 7.10(1H, d, J=8.8 Hz), 7.27(2H, d, J=8.8 Hz), 7.31(2H, d, J=8.8 Hz), 7.58-7.63(1H, m), 7.64(1H, dd, J= 2.1, 7.0 Hz), 8.24(1H, s).

IR(KBr) cm^{-1}: 1724, 1709, 1667, 1506, 1291, 1236, 1126, 831.

Mass m/z: 412(M^+), 414(M^+).

2) Preparation of

4-carboxy-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-(4-chloro-cinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow crystalline powder (yield: 86.2%).

Melting point: 186.0-186.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.36(3H, d, J=2.0 Hz), 5.11(2H, dd, J=1.2, 6.8 Hz), 6.39(1H, dt, J=15.9, 6.8 Hz), 6.75(1H, d, J=15.6 Hz), 7.13(1H, dd, J=8.8, 8.8 Hz), 7.29(2H, d, J=8.5 Hz), 7.33(2H, d, J=8.5 Hz),

7.65-7.71(2H, m), 8.64(1H, s), 13.98(1H, br).

IR(KBr) cm^{-1}: 3471, 1738, 1631, 1566, 1490, 1467, 1403, 1242, 812, 802.

Mass m/z: 398(M^+), 400(M^+).

3) Preparation of 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly yellow needles (yield: 17.2%).

Melting point: 131.8-133.1℃

^1H NMR(400MHz, $CDCl_3$)δ:

2.34(3H, d, J=2.0 Hz), 4.73 (2H, d, J=1.2 Hz), 4.99(2H, dd, J=1.0, 6.6 Hz), 6.40(1H, dt, J=15.9, 6.6 Hz), 6.75(1H, d, J=15.9 Hz), 7.08(1H, dd, J=8.9, 8.9 Hz), 7.26(2H, d, J=8.8 Hz), 7.31(2H, d, J=8.8. Hz), 7.57-7.62(1H, m), 7.64(1H, dd, J=2.2, 7.3 Hz), 7.69(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 3359, 1653, 1598, 1506, 1492, 1240, 1091, 1076.

Mass m/z: 384(M^+), 386(M^+).

4) Preparation of 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as colorless needles (yield: 94.9%).

Melting point: 117.8-119.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.35(3H, d, J=2.0 Hz), 3.17(3H, s), 4.99(2H, dd, J=1.2, 6.6 Hz), 5.28(2H, d, J=1.2 Hz), 6.38(1H, dt, J=15.9, 6.6 Hz), 6.75(1H, d, J=15.9 Hz), 7.10(1H, dd, J=8.8, 8.8 Hz), 7.27(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5. Hz), 7.57-7.65(2H, m), 7.78(1H, t, J=1.3 Hz).

IR(KBr) cm^{-1}: 1663, 1619, 1506, 1492, 1346, 1240, 1172, 960, 830.

Mass m/z: 462(M^+), 464(M^+).

5) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methyl-phenyl)-2H-pyridazin-one

Following the procedure of Example 1(10), 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 87.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.47(9H, s), 2.35(3H, d, J=1.6 Hz), 2.52(4H, t, J=4.9 Hz), 3.50(4H, t, J=5.0 Hz), 3.59(2H, d, J=1.2 Hz), 4.99(2H, dd, J=1.0, 6.6 Hz), 6.42(1H, dt, J=15.8, 6.6 Hz), 6.67(1H, d, J=16.0 Hz), 7.09(1H, dd, J=8.9, 8.9 Hz), 7.25(2H, d, J=8.8 Hz), 7.31(2H, d, J=8.6 Hz), 7.55-7.61(1H, m), 7.64(1H, dd, J=2.0, 7.2 Hz), 7.77(1H, s).

Example 141

Preparation of 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a pale brown crystalline powder (yield: 84.7%).

Melting point: 186.7-197.0℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(3H, d, J=2.0 Hz), 3.15(4H, br), 3.31(4H, t, J=5.2 Hz), 3.94(2H, s), 4.95(2H, dd, J=1.3, 6.3 Hz), 6.47(1H, dt, J=15.9, 6.1 Hz), 6.66(1H, d, J=15.9 Hz), 7.22(1H, dd, J=9.0, 9.0 Hz), 7.34(2H, d, J=8.6 Hz), 7.45(2H, d, J=8.6 Hz), 7.73-7.78(1H, m), 7.82(1H,, dd, J=1.9, 7.6 Hz), 8.21(1H, s).

IR(KBr) cm^{-1}: 1656, 1606, 1240, 1090, 964.

Mass m/z: 452(M^+), 454(M^+).

Example 142

Preparation of

2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 71.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.32(3H, s), 2.35(3H, s), 2.51(4H, br), 2.62(4H, br), 3.59(2H, s), 4.99(2H, d, J=6.6 Hz), 6.42(1H, dt, J=15.8, 6.4 Hz), 6.66(1H, d, J=15.9 Hz), 7.09(1H, dd, J=8.9, 8.9 Hz), 7.24(2H, d, J=8.6 Hz), 7.30(2H, d, J=8.6 Hz), 7.56-7.62(1H, m), 7.65(1H, dd, J=1.8, 7.2 Hz), 7.76(1H, s).

Example 143

Preparation of

2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-(4-chloro-cinnamyl)-6-(4-fluoro-3-methylphenyl)-4-(4-

methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 80.4%).

Melting point: 229.7-243.3℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.31(3H, d, J=1.8 Hz), 2.76(3H, s), 3.09(4H, br), 3.33(4H, br), 3.83(2H, s), 4.94(2H, dd, J=1.2, 6.0 Hz), 6.42(1H, dt, J=16.0, 6.2 Hz), 6.65(1H, d, J=16.0 Hz), 7.22(1H, dd, J=9.1, 9.1 Hz), 7.34(2H, d, J=8.6 Hz), 7.45(2H, d, J=8.6 Hz), 7.71-7.76(1H, m), 7.80(1H, dd, J=2.2, 7.0 Hz), 8.08(1H, s).

IR(KBr) cm^{-1}: 1652, 1608, 1492, 1239, 1130.

Mass m/z: 466(M^+), 468(M^+).

Example 144

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 76.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, s), 2.70(4H, t, J=4.5 Hz), 3.66(4H, t, J=4.9 Hz), 3.70(2H, s), 4.98(2H, d, J=6.6 Hz), 6.36(1H, dt, J=15.8, 6.5 Hz), 6.63(1H, d, J=15.8 Hz), 7.06(1H, dd, J=8.6, 8.6 Hz), 7.24(2H, d, J=8.6 Hz), 7.30(2H, d, J=8.2 Hz), 7.58-7.63(1H, m), 7.65(1H, dd, J=1.8, 7.2 Hz), 7.78(1H, s).

Example 145

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 76.1%).

Melting point: 151.9-153.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.32(3H, d, J=1.7 Hz), 3.35(4H, t, J=5.1 Hz), 3.83(4H, t, J=5.4 Hz), 4.46(2H, s), 4.97(2H, dd, J=1.2, 6.1 Hz), 6.48(1H, dt, J=15.9, 6.2 Hz), 6.67(1H, d, J=15.9 Hz), 7.24(1H, dd, J=9.1, 9.1 Hz), 7.35(2H, d, J=8.8 Hz), 7.45(2H, d, J=8.6 Hz), 7.75-7.80(1H, m), 7.85(1H, dd, J=1.7, 7.9 Hz), 8.48(1H, s).

IR(KBr) cm^{-1}: 1652, 1604, 1492, 1240, 1090, 968.

Mass m/z: 440(M^+), 442(M^+).

Example 146

Preparation of

2-(4-chlorocinnamyl)-4-dimethylamino-methyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-(4-chloro-cinnamyl)-6-(4-fluoro-3-methylphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 84.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, d, J=1.6 Hz), 2.36(6H, s), 3.52(2H, d, J=1.2 Hz), 4.99(2H, dd, J=1.0, 6.6 Hz), 6.43(1H, dt, J=15.8, 6.6 Hz), 6.66(1H, d, J=15.8 Hz), 7.07(1H, dd, J=8.9, 8.9 Hz), 7.24(2H, d, J=8.6 Hz), 7.30(2H, d, J=8.6 Hz), 7.60-7.68(2H, m), 7.77(1H, s).

Example 147

Preparation of

2-(4-chlorocinnamyl)-4-dimethylamino-methyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-(4-chloro-cinnamyl)-4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield:

34.4%).

Melting point: 201.3-201.9℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

2.32(3H, d, J=1.7 Hz), 2.83(6H, s), 4.28(2H, s), 4.98(2H, dd, J=1.3, 6.1 Hz), 6.48(1H, dt, J=16.1, 6.1 Hz), 6.67(1H, d, J=16.1 Hz), 7.24(1H, dd, J=9.3, 9.3 Hz), 7.35(2H, d, J=8.6 Hz), 7.45(2H, d, J=8.6 Hz), 7.75-7.80(1H, m), 7.85(1H, dd, J=2.3, 7.6 Hz), 8.47(1H, s).

IR(KBr) cm^{-1}: 1652, 1608, 1491, 1239, 968.

Mass m/z: 411(M^+), 413(M^+).

Example 148

Preparation of 2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

1) Preparation of 4-carboxy-2-cyclopropylmethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-cyclopropylmethyl-4-methoxycarbonyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow crystalline powder (yield: 98.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.50-0.66(4H, m), 1.40-1.53(1H, m), 2.54(3H, s), 4.24(2H, d, J=7.4 Hz), 7.34(2H, d, J=8.6 Hz), 7.78(2H, d, J=8.6 Hz),

8.66(1H, s), 14.22(1H, s).

IR(KBr) cm^{-1}: 3430, 1752, 1631, 1472, 1452, 1403, 1093, 825.

Mass m/z: 316(M^+)

2) Preparation of 2-cyclopropylmethyl-4-hydroxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-cyclopropylmethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 22.6%).

^1H NMR(400MHz, $CDCl_3$)δ:

0.45-0.60(4H, m), 1.37-1.46(1H, m), 2.53(3H, s), 3.09(1H, t, J=6.1 Hz), 4.11(2H, d, J=7.2 Hz), 4.72(2H, d, J=6.0 Hz), 7.32(2H, d, J=8.6 Hz), 7.67(1H, s), 7.74(2H, d, J=8.6 Hz).

IR(KBr) cm^{-1}: 3393, 1657, 1602, 1514, 1095, 822.

Mass m/z: 302(M^+).

3) Preparation of 2-cyclopropylmethyl-4-methanesulfonyloxy-methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-cyclopropylmethyl-4-hydroxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow fine-needles (yield: 78.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-1.61(4H, m), 1.37-1.47(1H, m), 2.53(3H, s), 3.17(3H, s), 4.11(2H, d, J=7.2 Hz), 5.28(2H, s), 7.33(2H, d, J=8.4 Hz), 7.74(2H, d, J=8.4 Hz), 7.79(1H, s).

IR(KBr) cm^{-1}: 3446, 1652, 1607, 1359, 1178, 1024, 829.

Mass m/z: 380(M^+).

4) Preparation of 2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one and 1-methyl-piperazine were reacted to yield the title compound as a yellow oil (yield: 85.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.58(4H, m), 1.36-1.48(1H, m), 2.33(3H, s), 2.53(3H, s), 2.47-2.66(8H, m), 3.59(2H, s), 4.10(2H, d, J=7.3 Hz), 7.33(2H, d, J=8.3 Hz), 7.75(2H, d, J=8.3 Hz), 7.78(1H, s).

Example 149

Preparation of 2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 69.1%).

Melting point: 234.6-239.2℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.40-0.45(2H, m), 0.50-0.56(2H, m), 1.30-1.40(1H, m), 2.53(3H, s), 2.77(3H, s), 2.97(4H, br), 3.28(4H, br), 3.72(2H, s), 4.05(2H, d, J=7.1 Hz), 7.39(2H, d, J=8.6 Hz), 7.82(2H, d, J=8.3 Hz), 7.96(1H, s).

IR(KBr) cm^{-1}: 3438, 1651, 1606, 1402, 1095.

Mass m/z: 384(M^+).

Example 150

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropylmethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 78.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.59(4H, m), 1.36-1.45(1H, m), 2.53(3H, s), 2.73(4H,

br), 3.67(4H, t, J=4.9 Hz), 3.73(2H, s), 4.13(2H, d, J=7.3 Hz), 7.32(2H, d, J=8.3 Hz), 7.70(1H, s), 7.74(2H, d, J=8.3 Hz).

Example 151

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropylmethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropylmethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a slightly yellow solid (yield: 75.1%).

Melting point: 169.2-171.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.42-0.46(2H, m), 0.52-0.57(2H, m), 1.30-1.40(1H, m), 2.53(3H, s), 3.31(4H, br), 3.81(4H, t, J=5.3 Hz), 4.42(2H, s), 7.41(2H, d, J=8.8 Hz), 7.85(2H, d, J=9.0 Hz), 8.37(1H, s).

IR(KBr) cm^{-1}: 3242, 1652, 1604, 1420, 1094, 1059, 823.

Mass m/z: 358(M^+-CH_2OH).

Example 152

Preparation of

2-cyclopropylmethyl-4-dimethylamino-methyl-6-[4-

(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 7, 2-cyclopropyl-methyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 98.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.58(4H, m), 1.36-1.48(1H, m), 2.35(6H, s), 3.51(2H, s), 4.51(2H, d, J=7.3 Hz), 7.31(2H, d, J=8.3 Hz), 7.77(2H, d, J=7.8 Hz), 7.78(1H, s).

Example 153

Preparation of 2-cyclopropylmethyl-4-dimethylamino-methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-4-dimethylaminomethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 75.5%).

Melting point: 230.2-232.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.42 -0.46(2H, m), 0.52-0.58(2H, m), 1.31-1.40(1H, m), 2.53(3H, s), 2.82(6H, s), 4.09(2H, d, J=7.1 Hz), 4.25(2H, s), 7.41(2H, d, J=8.6 Hz), 7.84(2H, d, J=8.5 Hz), 8.34(1H, s).

IR(KBr) cm^{-1}: 3435, 1646, 1604, 1402, 1093, 829.

Mass m/z: 329(M^+).

Example 154

Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one

1) Preparation of

4-carboxy-2-isobutyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one

To a solution of 4-methoxycarbonyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one (8.00 g, 29.0 mmol) in N,N-dimethylformamide (80 mL) were added potassium carbonate (8.02 g, 58.0 mmol) and isobutyl bromide (4.76 g, 34.8 mmol), and the mixture was stirred at 80℃ for 2 hours. The temperature of the reaction mixture was allowed to drop back to room temperature, and a saturated aqueous solution of sodium hydrogencarbonate was added. The mixture was then extracted with ethyl acetate. The extract was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off. Following the procedure of Example 1(7), the residue was reacted to yield the title compound as a yellow solid [yield: 65.1% (2 steps)].

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.01(6H, d, J=6.6 Hz), 2.33-2.46(1H, m), 2.54(3H, s), 4.21(2H, d, J=7.4 Hz), 7.34(2H, d, J=8.4 Hz), 7.80(2H, d,

J=8.4 Hz), 8.68(1H, s), 12.72(1H, s).

Mass m/z: 318(M^+).

2) Preparation of 4-hydroxymethyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 35.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.27-2.39(1H, m), 2.53(3H, s), 4.08(2H, d, J=7.4 Hz), 4.71(2H, d, J=5.9 Hz), 7.26(2H, d, J=8.4 Hz), 7.66(1H, s), 7.73(2H, d, J=8.6 Hz).

3) Preparation of 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(9), 4-hydroxymethyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 73.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.28-2.40(1H, m), 2.53(3H, s), 3.17(3H, s), 4.08(2H, d, J=7.4 Hz), 5.27(2H, d, J=1.2 Hz),

7.32(2H, d, J=8.4 Hz), 7.73(2H, d, J=8.4 Hz), 7.75(1H, d, J=1.4 Hz).

Mass m/z: 382(M^+).

4) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-6-4-methanesulfonyloxymethyl-6-[4-(methylthio) phenyl]-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 88.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 1.47(9H, s), 2.28-2.40(1H, m), 2.50-2.55(4H, m), 2.53(3H, s), 3.50(4H, t, J=4.8 Hz), 3.58(2H, s), 4.07(2H, d, J=7.4 Hz), 7.32(2H, d, J=8.4 Hz), 7.73(2H, d, J=8.6 Hz), 7.78(1H, s).

Example 155

Preparation of 2-isobutyl-6-[4-(methylthio)phenyl]-4-(1-piperazinyl) methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to

yield the title compound as a yellow crystalline powder (yield: 70.5%).

Melting point: 248.5-253.7℃(dec.).

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.6 Hz), 2.21-2.33(1H, m), 2.52(3H, s), 3.10(4H, t, J=4.8 Hz), 3.30(4H, t, J=5.2 Hz), 3.90(2H, s), 4.01(2H, d, J=7.3 Hz), 7.39(2H, d, J=8.3 Hz), 7.83(2H, d, J=8.3 Hz), 8.15(1H, s).

IR(KBr) cm^{-1}: 2961, 2442, 1640, 1596, 1511, 1433, 1406, 1089, 912.

Mass m/z: 372(M^+).

Example 156

Preparation of 2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 68.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.29-2.39(1H, m), 2.32(3H, s), 2.51(4H, br), 2.53(3H, s), 2.62(4H, br), 3.58(2H, d, J=1.4 Hz), 4.07(2H, d, J=7.4 Hz), 7.33(2H, d, J=8.6 Hz), 7.74(2H, d, J=6.8 Hz), 7.76(1H, s).

Example 157

Preparation of 2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 86.4%).

Melting point: 242.6-243.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.21-2.33(1H, m), 2.52(3H, s), 2.76(3H, s), 3.09(4H, br), 3.33(4H, br), 3.83(2H, s), 4.01(2H, d, J=7.1 Hz), 7.39(2H, d, J=8.6 Hz), 7.82(2H, d, J=8.5 Hz), 8.07(1H, s).

IR(KBr) cm^{-1}: 3432, 2957, 2437, 1652, 1607, 1090, 953.

Mass m/z: 386(M^+).

Example 158

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10),

2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio) phenyl]-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 71.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.96(6H, d, J=6.6 Hz), 2.27-2.39(1H, m), 2.51(3H, s), 2.71(4H, t, J=5.1 Hz), 3.66(4H, t, J=5.1 Hz), 3.70(2H, s), 4.08(2H, d, J=7.2 Hz), 7.30(2H, d, J=8.6 Hz), 7.71-7.76(3H, m).

Example 159

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one oxalate

To a solution of 4-N,N-bis(2-hydroxyethyl)amino-methyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (69.7 mg, 0.18 mmol) in methanol (1 mL) was added at room temperature oxalic acid dihydrate (22.4 mg, 0.18 mmol). The solvent was distilled off. The residue was recrystallized from chloroform-diethyl ether to obtain the title compound as a white solid (59.5 mg, 69.4%).

Melting point: 116.4-118.1℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.94(6H, d, J=6.6 Hz), 2.20-2.33(1H, m), 2.52(3H, s), 2.91(4H, t, J=5.8 Hz), 3.61(4H, t, J=5.6 Hz), 3.94(2H, s), 4.01(2H, d, J=7.3 Hz), 7.39(2H, d, J=8.6 Hz), 7.81(2H, d,

J=8.6 Hz), 8.14(1H, s).

IR(KBr) cm^{-1}: 3344, 2927, 1659, 1611, 1402, 1049, 721.

Mass m/z: 360(M^+-CH_2OH).

Example 160

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylthio) phenyl]-2H-pyridazin-3-one

Following the procedure of Example 7, 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio) phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 73.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.29-2.41(1H, m), 2.36(6H, s), 2.52(3H, s), 3.52(2H, d, J=1.2 Hz), 4.07(2H, d, J=7.4 Hz), 7.31(2H, d, J=8.6 Hz), 7.77(2H, d, J=8.4 Hz), 7.79(1H, s).

Example 161

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylthio) phenyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethyl-aminomethyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 82.3%).

Melting point: 216.8-218.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.8 Hz), 2.23-2.36(1H, m), 2.53(3H, s), 2.82(6H, s), 4.05(2H, d, J=7.1 Hz), 4.27(2H, s), 7.41(2H, d, J=8.3 Hz), 7.84(2H, d, J=8.3 Hz), 8.42(1H, s).

IR(KBr) cm^{-1}: 3485, 1740, 1684, 1253, 856, 577.

Mass m/z: 331(M^+).

Example 162

Preparation of 2-isobutyl-6-[4-(methylthio)phenyl]-4-propargyl aminomethyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio) phenyl]-2H-pyridazin-3-one and propargylamine were reacted to yield the title compound as a yellow oil (yield: 52.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.26(1H, t, J=2.3 Hz), 2.29-2.40(1H, m), 2.52(3H, s), 3.51(2H, d, J=2.4 Hz), 3.90(2H, s), 4.07(2H, d, J=7.4 Hz), 7.31(2H, d, J=8.4 Hz), 7.70(1H, s), 7.73(2H, d, J=8.4 Hz).

Example 163

Preparation of 2-isobutyl-6-[4-(methylthio)phenyl]-4-propargylaminomethyl-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-isobutyl-6-[4-(methylthio)phenyl]-4-propargylaminomethyl-2H-pyridazin-3-one was reacted to yield the title compound as a white solid (yield: 73.6%).

Melting point: 197.5-198.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.6 Hz), 2.23-2.36(1H, m), 2.53(3H, s), 3.48(1H, t, J=2.4 Hz), 3.95(2H, d, J=2.4 Hz), 4.03(2H, d, J=7.1 Hz), 4.17(2H, s), 7.41(2H, d, J=8.3 Hz), 7.82(2H, d, J=8.6 Hz), 8.28(1H, s).

IR(KBr) cm^{-1}: 3447, 3207, 2958, 2122, 1651, 1607, 1441, 1093.

Mass m/z: 341(M^+).

Example 164

Preparation of 2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

1) Preparation of 2-cyclopropylmethyl-4-methanesulfonyloxy-methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

To a solution of 2-cyclopropylmethyl-4-methane-sulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (300 mg, 0.79 mmol) in methylene chloride (10 mL) was added dropwise at -20℃ a solution of 3-chloroperbenzoic acid (204 mg, 1.12 mmol) in

methylene chloride (2 mL), and at the same temperature, the mixture was stirred for 30 minutes. A 10% aqueous sodium hydrogensulfite was added to the reaction mixture, and then, the mixture was extracted with chloroform. The extract was successively washed with a saturated aqueous sodium hydrogencarbonate and brine, and was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was recrystallized from chloroform-hexane to yield the title compound as a colorless crystalline powder (139 mg, 44.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.48-0.63(4H, m), 1.37-1.46(1H, m), 2.77(3H, s), 3.18(3H, s), 4.14(2H, d, J=7.3 Hz), 5.30(2H, d, J=1.4 Hz), 7.76(2H, d, J=8.6 Hz), 7.84(1H, t, J=1.4 Hz), 7.98(2H, d, J=8.8 Hz).

Mass m/z: 396(M^+).

2) Preparation of 2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropyl-4-methanesulfonyloxymethyl-6-[4-(methyl-sulfinyl)phenyl]-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 60.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.46-0.60(4H, m), 1.37-1.49(1H, m), 2.34(3H, s), 2.54(4H, br), 2.64(4H, br), 2.78(3H, s), 3.61(2H, s), 4.13(2H, d, J=7.2 Hz), 7.75(2H, d, J=8.2 Hz), 7.84(1H, s), 7.99(2H, d, J=8.2 Hz).

Example 165

Preparation of 2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methyl-sulfinyl)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 64.3%).

Melting point: 80℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.41-0.57(4H, m), 1.30-1.41(1H, m), 2.76(3H, s), 2.77(3H, s), 3.01(4H, br), 3.31(4H, br), 3.77(2H, s), 4.08(2H, d, J=6.8 Hz), 7.80(2H, d, J=8.3 Hz), 8.05-8.09(3H, m).

IR(KBr) cm^{-1}: 3430, 3005, 1652, 1607, 1458, 1401, 1010, 838.

Mass m/z: 400(M^+).

Example 166

Preparation of

2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

1) Preparation of

2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 164(1), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 54.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.00(6H, d, J=6.8 Hz), 2.29-2.41(1H, m), 2.77(3H, s), 3.18(3H, s), 4.11(2H, d, J=7.3 Hz), 5.29(2H, d, J=1.5 Hz), 7.76(2H, d, J=8.8 Hz), 7.83(1H, t, J=1.2 Hz), 7.98(2H, d, J=8.6 Hz).

Mass m/z: 398(M^+).

2) Preparation of

2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 61.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.30-2.41(1H, m), 2.34(3H, s), 2.54(4H, br), 2.64(4H, br), 2.77(3H, s), 3.60(2H, s), 4.10(2H, d, J=7.4 Hz), 7.75(2H, d, J=8.2 Hz), 7.82(1H, s), 7.99(2H, d, J=8.2 Hz).

Example 167

Preparation of 2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfinyl)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 76.1%).

Melting point: 224.5-229.1℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.6 Hz), 2.22-2.35(1H, m), 2.76(3H, s), 2.77(3H, s), 3.14(4H, br), 3.35(4H, br), 3.87(2H, s), 4.04(2H, d, J=7.1 Hz), 7.80(2H, d, J=8.3 Hz), 8.07(2H, d, J=8.3 Hz), 8.18(1H, s).

IR(KBr) cm^{-1}: 3426, 2960, 1656, 1608, 1459, 1400, 1044, 1011.

Mass m/z: 402(M^+).

Example 168

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 7, 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 46.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.8 Hz), 2.30-2.43(1H, m), 2.38(6H, s), 2.76(3H, s), 3.54(2H, s), 4.10(2H, d, J=7.4 Hz), 7.74(2H, d, J=8.2 Hz), 7.87(1H, s), 8.02(2H, d, J=8.2 Hz).

Example 169

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylsulfinyl)phenyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylsulfinyl)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 77.4%).

Melting point: 204.2-206.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.97(6H, d, J=6.6 Hz), 2.24-2.36(1H, m), 2.78(3H, s), 2.83(6H, s), 4.07(2H, d, J=7.1 Hz), 4.28(2H, s), 7.82(2H,

d, J=8.3 Hz), 8.09(2H, d, J=8.3 Hz), 8.49(1H, s).
IR(KBr)cm^{-1}: 3438, 2961, 1652, 1607, 1467, 1400, 1047.
Mass m/z: 347(M^+).

Example 170

Preparation of
2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

1) Preparation of
2-cyclopropylmethyl-4-methanesulfonyloxy-methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

To a solution of 2-cyclopropylmethyl-4-methane-sulfonyloxymethyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one (226 mg, 0.59 mmol) in methylene chloride (10 mL) was added dropwise at -20℃ a solution of 3-chloroperbenzoic acid (410 mg, 2.38 mmol) in methylene chloride (2 mL), and at the same temperature, the mixture was stirred for 30 minutes. A 10% aqueous sodium hydrogensulfite was added to the reaction mixture, and then, the mixture was extracted with chloroform. The extract was successively washed with a saturated aqueous sodium hydrogencarbonate and brine, and was then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was recrystallized from chloroform-hexane to yield the title compound as a colorless

crystalline powder (209 mg, 85.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.46-0.63(4H, m), 1.37-1.46(1H, m), 3.10(3H, s), 3.18(3H, s), 4.20(2H, d, J=7.3 Hz), 5.31(2H, d, J=1.2 Hz), 7.86(1H, t, J=1.2 Hz), 8.02(2H, d, J=8.8 Hz), 8.06(2H, d, J=9.0 Hz).

Mass m/z: 412(M^+).

2) Preparation of

2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 80.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.46-0.61(4H, m), 1.38-1.48(1H, m), 2.34(3H, s), 2.54(4H, br), 2.64(4H, br), 3.10(3H, s), 3.61(2H, d, J=1.2 Hz), 4.13(2H, d, J=7.1 Hz), 7.85(1H, t, J=1.2 Hz), 8.03(2H, d, J=9.0 Hz), 8.05(2H, d, J=9.0 Hz).

Example 171

Preparation of

2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

dihydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methyl-sulfonyl)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 76.8%).

Melting point: 209.0-211.4℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.41-0.46(2H, m), 0.52-0.57(2H, m), 1.31-1.41(1H, m), 2.77(3H, s), 3.04(4H, br), 3.21(3H, s), 3.31(4H, br), 3.80(2H, s), 4.09(2H, d, J=7.1 Hz), 8.04(2H, d, J=8.3 Hz), 8.12(1H, s), 8.14(2H, d, J=8.3 Hz).

IR(KBr) cm^{-1}: 3434, 3012, 1652, 1596, 1458, 1402, 1302, 1150.

Mass m/z: 416(M^+).

Example 172

Preparation of 2-cyclopropylmethyl-4-dimethylamino-methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow oil (yield: 65.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.62(4H, m), 1.39-1.49(1H, m), 2.38(6H, s), 3.09(3H, s), 3.55(2H, s), 4.14(2H, d, J=7.2 Hz), 7.89(1H, s), 8.02(2H, d, J=8.4 Hz), 8.06(2H, d, J=8.6 Hz).

Example 173

Preparation of 2-cyclopropylmethyl-4-dimethylamino-methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 2-cyclopropyl-methyl-4-dimethylaminomethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 63.4%).

Melting point: 239.5-240.7℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.43-0.59(4H, m), 1.33-1.43(1H, m), 2.83(6H, s), 3.23(3H, s), 4.13(2H, d, J=7.1 Hz), 4.29(2H, s), 8.06(2H, d, J=7.8 Hz), 8.17(2H, d, J=8.3 Hz), 8.57(1H, s).

IR(KBr) cm^{-1}: 3447, 2674, 1646, 1608, 1596, 1306, 1150, 777.

Mass m/z: 361(M^+).

Example 174

Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-[4-(methyl-sulfonyl)phenyl]-2H-pyridazin-3-one

1) Preparation of 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 170(1), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 97.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.29-2.41(1H, m), 3.10(3H, s), 3.18(3H, s), 4.12(2H, d, J=7.3 Hz), 5.29(2H, d, J=1.2 Hz), 7.85(1H, t, J=1.4 Hz), 8.02(2H, d, J=8.8 Hz), 8.05(2H, d, J=8.8 Hz).

Mass m/z: 414(M^+).

2) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)-methyl-2-isobutyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 75.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 1.47(9H, s), 2.29-2.41(1H, m), 2.54(4H, br), 3.09(3H, s), 3.51(4H, br), 3.60(2H, s), 4.11(2H, d, J=7.2 Hz), 7.86(1H, s), 8.02(2H, d, J=8.8 Hz), 8.05(2H, d, J=8.8 Hz).

Example 175

Preparation of 2-isobutyl-6-[4-(methylsulfonyl)-phenyl]-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 2, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-isobutyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 88.2%).

Melting point: 222.4-224.2℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.96(6H, d, J=6.8 Hz), 2.22-2.35(1H, m), 3.06(4H, br), 3.21(3H, s), 3.28(4H, t, J=5.2 Hz), 3.87(2H, s), 4.05(2H, d, J=7.1 Hz), 8.04(2H, d, J=8.6 Hz), 8.14(2H, d, J=8.3 Hz), 8.22(1H, s).

IR(KBr) cm^{-1}: 3421, 2957, 1656, 1611, 1597, 1305, 1149, 961.

Mass m/z: 404(M^+).

Example 176

Preparation of
2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 88.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:
0.99(6H, d, J=6.8 Hz), 2.28-2.40(1H, m), 2.37(3H, s), 2.53(4H, br), 2.63(4H, br), 3.10(3H, s), 3.60(2H, s), 4.10(2H, d, J=7.3 Hz), 7.84(1H, s), 8.02(2H, d, J=9.0 Hz), 8.05(2H, d, J=8.8 Hz).

Example 177

Preparation of
2-isobutyl-4-(4-methyl-1-piperazinyl)-methyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylsulfonyl)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 62.0%).

Melting point: 224.5-228.0℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.95(6H, d, J=6.8 Hz), 2.23-2.35(1H, m), 2.76(3H, s), 3.08(4H, br), 3.21(3H, s), 3.32(4H, br), 3.83(2H, s), 4.05(2H, d, J=7.1 Hz), 8.04(2H, d, J=8.3 Hz), 8.13(2H, d, J=8.5 Hz), 8.15(1H, s).

IR(KBr) cm^{-1}: 3447, 2958, 1652, 1610, 1596, 1319, 1152, 955.

Mass m/z: 418(M^+).

Example 178

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-2-isobutyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 51.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.98(6H, d, J=6.6 Hz), 2.28-2.40(1H, m), 2.73(4H, t, J=4.8 Hz), 3.08(3H, s), 3.68(4H, t, J=4.9 Hz), 3.73(2H, s), 4.11(2H, d, J=7.4 Hz), 7.93(1H, s), 8.00(2H, d, J=8.6 Hz), 8.05(2H, d, J=8.8 Hz).

Mass m/z: 392(M^+-CH_2OH).

Example 179

Preparation of

4-dimethylaminomethyl-2-isobutyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one

Following the procedure of Example 7, 2-isobutyl-4-methanesulfonyloxymethyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 82.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.99(6H, d, J=6.6 Hz), 2.30-2.41(1H, m), 2.37(6H, s), 3.09(3H, s), 3.52(2H, s), 4.11(2H, d, J=7.2 Hz), 7.86(1H, s), 8.02(2H, d, J=8.8 Hz), 8.05(2H, d, J=8.8 Hz).

Example 180

Preparation of 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylsulfonyl)phenyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-dimethylaminomethyl-2-isobutyl-6-[4-(methylsulfonyl)-phenyl]-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 58.6%).

Melting point: 221.4-223.3℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.97(6H, d, J=6.6 Hz), 2.25-2.36(1H, m), 2.82(6H, s), 3.22(3H, s), 4.08(2H, d, J=7.3 Hz), 4.28(2H, s), 8.06(2H, d, J=8.3 Hz), 8.15(2H, d, J=8.5 Hz), 8.55(1H, s).

IR(KBr) cm^{-1}: 3447, 2963, 1653, 1609, 1597, 1307, 1152, 777.

Mass m/z: 363(M^+).

Example 181

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-pyrrolidinomethyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and pyrrolidine were reacted to yield the title compound as a yellow oil (yield: 75.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.61(4H, m), 1.42(1H, m), 1.85-2.00(4H, m), 2.70-3.00(4H, m), 3.83(2H, brs), 3.94 (3H, s), 4.10 (2H, d, J=7.3 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.60(1H, d, J=8.5 Hz), 7.65(1H, dd, J=8.5, 2.0 Hz), 8.00(1H, brs).

IR(Neat) cm^{-1}: 1652, 1608, 1523, 1438, 1286, 758.

Mass m/z: 357(M^+).

Example 182

Preparation of 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-

methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and cyclopentylmethyl bromide {J. Org. Chem., 36, 3103 (1971)} were reacted to yield the title compound as yellow needles (yield: 72.0%).

Melting point: 56-66℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30-1.45(2H, m), 1.53-1.65(2H, m), 1.65-1.80(4H, m), 2.57(1H, m), 3.95(3H, s), 3.98(3H, s), 4.24(2H, d, J=7.8 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.50(1H, d, J=8.8 Hz), 7.61(1H, d, J=10.2 Hz), 8.19(1H, s).

2) Preparation of 4-carboxy-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 71.1%).

Melting point: 159-161℃

^{1}H NMR(400MHz, $CDCl_3$)δ::

1.33-1.45(2H, m), 1.58-1.65(2H, m), 1.68-1.82(4H, m), 2.57(1H, m), 3.97(3H, s), 4.32(2H, d, J=7.6 Hz), 7.06(1H, dd, J=8.5, 8.5 Hz), 7.56(1H, d, J=8.5 Hz), 7.68(1H, dd,

J=12.2, 2.0 Hz), 8.61(1H, s).

3) Preparation of

2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 47.3%).

Melting point: 130-133℃

^{1}H NMR(400MHz, $CDCl_3$)δ: :

1.30-1.42(2H, m), 1.50-1.62(2H, m), 1.62-1.80(4H, m), 2.54(1H, m), 3.95(3H, s), 4.19(2H, d, J=7.6 Hz), 4.71(2H, s), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.51(1H, d, J=8.5 Hz), 7.62(1H, dd, J=12.8 ,1.5 Hz), 7.63(1H, s).

4) Preparation of

2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 75.3%).

Melting point: 108-116℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.25-1.32(2H, m), 1.32-1.45(2H, m), 1.65-1.77(4H, m), 2.54(1H, m), 3.17(3H, s), 3.95(3H, s), 4.19(2H, d, J=7.6 Hz), 5.27(2H, s), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.50(1H, d, J=8.5 Hz), 7.62(1H, dd, J=12.2, 2.2 Hz), 7.74(1H, s).

5) Preparation of

2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 61.4%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.32-1.42(2H, m), 1.50-1.60(2H, m), 1.65-1.80(4H, m), 2.38, 2.40(each s, 3H in total), 2.54(1H, m), 2.60-2.75(8H, m), 3.59(2H, s), 3.95(3H, s), 4.18(2H, d, J=7.6 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.54(1H, d, J=8.5 Hz), 7.61(1H, dd, J=8.5, 2.2 Hz), 7.72(1H, s).

IR(Neat) cm^{-1}: 1652, 1608, 1523, 1439, 1286, 760.

Mass m/z: 414(M^+).

Example 183

Preparation of

2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale brown crystalline powder (yield: 59.6%).

Melting point: 234-236℃ (dec.)

^{1}H NMR(400MHz, DMSO-d_6)δ:

1.28-1.40(2H, m), 1.48-1.56(2H, m), 1.60-1.73(4H, m), 2.46(1H, m), 2.82(3H, s), 3.50-3.75(10H, m), 3.91(3H, s), 4.10(2H, d, J=7.6 Hz), 7.31(1H, dd, J=8.8, 8.8 Hz), 7.68-7.76(2H, m), 8.25(1H, s).

IR(KBr) cm^{-1}: 1652, 1606, 1523, 1439, 1292, 764.

Example 184

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 54.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30-1.45(2H, m), 1.50-1.62(2H, m), 1.62-1.80(4H, m), 2.53(1H, m), 2.75-2.90(4H, m), 3.70-3.75(4H, m), 3.80-3.85(2H, m), 3.94(3H, s), 4.20(2H, d, J=7.6 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.56(1H, d, J=8.5 Hz), 7.63(1H, dd, J=8.5, 2.0 Hz), 7.65(1H, m).

IR(Neat) cm^{-1}: 1648, 1598, 1523, 1439, 1267, 728.

Mass m/z: 383(M^+-$2H_2O$).

Example 185

Preparation of 2-cyclopentylmethyl-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow oil (yield: 63.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30-1.45(2H, m), 1.50-1.63(2H, m), 1.63-1.80(4H, m), 2.43(6H, s), 2.55(1H, m), 3.61(2H, s), 3.94(3H, s), 4.19(2H, d, J=7.6 Hz), 7.20(1H, d, J=8.5, 8.5 Hz), 7.58(1H, d, J=8.5 Hz), 7.65(1H, dd, J=8.5, 2.2 Hz), 7.91(1H, brs).

IR(Neat) cm^{-1}: 1652, 1608, 1523, 1438, 1288, 762.

Mass m/z: 359(M^+).

Example 186

Preparation of 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazi-3-one

Following the procedure of Example 1(10), 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 78.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.35-1.43(2H, m), 1.47(9H, s), 1.55-1.60(2H, m), 1.65-1.75(4H, m), 2.45-2.60 (5H, m), 3.45-3.55(4H, m), 3.95(3H, s), 4.18(2H, d, J=7.6 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.52(1H, m), 7.62(1H, d, J=12.4 Hz), 7.74(1H, m).

2) Preparation of 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 20, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-

cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 88.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.33-1.43(2H, m), 1.50-1.62(2H, m), 1.62-1.80(4H, m), 2.55(1H, m), 2.57-2.63(4H, m), 3.00-3.02(4H, m), 3.56(2H, brs), 3.95(3H,s), 4.18(2H, d, J=7.6 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.52(1H, d, J=8.5 Hz), 7.62(1H, dd, J=8.5, 2.2 Hz), 7.73(1H, s).

IR(Neat) cm^{-1}: 1652, 1608, 1523, 1439, 1287, 761.

Mass m/z: 400(M^+).

Example 187

Preparation of 4-aminomethyl-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 24(1), 2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield a crude product. Without purification, the crude product was reacted further in accordance with the procedure of Example 24(2) to yield the title compound as a yellow oil (yield: 53.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.30-1.45(2H, m), 1.50-1.63(2H, m), 1.63-1.80(4H, m),

2.54(1H, m), 3.91(2H, s), 3.93(3H, s), 4.17(2H, d, J=7.6 Hz), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.52(1H, d, J=8.5 Hz), 7.62(1H, dd, J=8.5, 2.2 Hz), 7.71(1H, brs).

IR(Neat) cm^{-1}: 3376, 1649, 1606, 1523, 1439, 1285, 761.

Mass m/z: 331(M^+).

Example 188

Preparation of 4-aminomethyl-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 59.0%).

Melting point: 193-196℃

^1H NMR(400MHz, DMSO-d_6)δ:

1.29-1.40(2H, m), 1.45-1.57(2H, m), 1.60-1.70(4H, m), 2.45(1H, m), 3.91(3H, s), 4.00(2H, s), 4.12(2H, d, J=7.6 Hz), 7.34(1H, dd, J=8.5, 8.5 Hz), 7.69-7.72(2H, m), 8.47(1H, brs).

IR(KBr) cm^{-1}: 3436, 1656, 1617, 1521, 1438, 1295, 763.

Example 189

Preparation of

2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of

2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and 4-fluorobenzyl chloride were reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 86.6%).

^{1}H NMR(400MHz,$CDCl_3$)δ:

3.95(3H, s), 3.97(3H, s), 5.39(2H, s), 7.00-7.06(3H, m), 7.48-7.63(4H, m), 8.19(1H, s).

2) Preparation of

4-carboxy-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 97.7%).

Melting point: 222-224℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.97(3H, s), 5.47(2H, s), 7.03-7.10(3H, m), 7.49-7.56(3H, m), 7.67(1H, dd, J=12.1, 2.2 Hz), 8.60(1H, s).

3) Preparation of 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 27.0%).

Melting point: 127-130℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.95(3H, s), 4.79(2H, d, J=1.5 Hz), 5.36(2H, s), 6.98-7.05(3H, m), 7.46-7.52 (3H, m), 7.61(1H, dd, J=12.2, 2.2 Hz), 7.65(1H, s).

4) Preparation of 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow powder (yield: 49.4%).

Melting point: 125-133℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.15(3H, s), 3.95(3H, s), 5.25(2H, d, J=1.2 Hz), 5.35(2H, s), 7.00-7.06(3H, m), 7.45-7.55(3H, m), 7.61(1H, dd, J=12.4, 2.2 Hz), 7.74(1H, s).

5) Preparation of

2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiprazine were reacted to yield the title compound as a slightly-brown crystalline powder (yield: 45.8%).

Melting point: 112-113℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.39(3H, s), 2.60-2.90(8H, m), 3.60(2H, s), 3.95(3H, s), 5.34(2H, s), 6.99-7.06(3H, m), 7.47-7.51(3H, m), 7.59(1H, dd, J=12.4, 2.0 Hz), 7.71(1H, s).

IR(KBr) cm^{-1}: 1651, 1608, 1518, 1439, 1289, 764.

Mass m/z: 440(M^+).

Example 190

Preparation of

4-dimethylaminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a

slightly-yellow crystalline powder (yield: 60.8%).

Melting point: 127-129℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.41(6H, s), 3.58(2H, s), 3.94(3H, s), 5.35(2H, s), 6.98-7.05(3H, m), 7.46-7.52(2H, m), 7.56(1H, d, J=8.8 Hz), 7.64(1H, dd, J=12.4, 2.2 Hz), 7.90(1H, brs).

IR(KBr) cm^{-1}: 1652, 1612, 1519, 1439, 1291, 763.

Mass m/z: 385(M^+).

Example 191

Preparation of 4-N,N-bis(2-hydroxyethyl)aminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 66.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.70-2.92(4H, m), 3.70-3.85(6H, m), 3.93(3H, s), 5.35(2H, s), 6.99-7.04(3H, m), 7.45-7.50(2H, m), 7.55(1H, d, J=8.3 Hz), 7.63(1H, dd, J=12.4, 2.0 Hz), 7.90(1H, m).

IR(Neat) cm^{-1}: 1652, 1606, 1520, 1435, 1281, 762.

Mass m/z: 385(M^+-CH_2OH).

Example 192

Preparation of 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 78.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.46(9H, s), 1.55-1.65(4H, m), 3.40-3.60(4H, m), 3.95(3H, s), 5.34(2H, s), 6.96-7.05(3H, m), 7.47-7.50(3H, m), 7.41(1H, d, J=12.4 Hz), 7.74(1H, brs).

2) Preparation of 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 20, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-

3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 63.4%).

Melting point: 142-143℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.50-2.60(4H, m), 2.96-3.02(4H, m), 3.54(2H, d, J=1.2 Hz), 3.95(3H, s), 5.34(2H, s), 6.98-7.06(3H, m), 7.46-7.53(3H, m), 7.61(1H, dd, J=12.5, 2.2 Hz), 7.74(1H, br.s).

IR(KBr) cm^{-1}: 1652, 1609, 1523, 1437, 1290, 762.

Mass m/z: 426(M^+).

Example 193

Preparation of 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one was reacted to yield the title compound as a colorless crystalline powder (yield: 76.9%).

Melting point: 153-156℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

3.30-3.75(10H, m), 3.90(3H, s), 5.33(2H, s), 7.15-7.21(2H, m), 7.30(1H, m), 7.43-7.49(2H, m), 7.69-7.78(3H, m).

IR(KBr) cm^{-1}: 1660, 1609, 1524, 1439, 1292, 766.

Example 194

Preparation of 4-aminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 24(1), 2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield a crude product. Without purification, the crude product was reacted further in accordance with the procedure of Example 24(2) to yield the title compound as a pale brown crystalline powder (yield: 50.4%).

Melting point: 145-149℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.92(3H, s), 3.94(2H, s), 5.31(2H, s), 6.95-7.03(3H, m), 7.40-7.52(3H, m), 7.60(1H, dd, J=12.5, 2.2 Hz), 7.75(1H, brs).

IR(KBr) cm^{-1}: 3391, 1648, 1606, 1519, 1437, 1292, 761.

Mass m/z: 357(M^+).

Example 195

Preparation of 4-aminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-

methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 72.5%).

Melting point: 210-214℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

3.91(3H, s), 4.01(2H, s), 5.35(2H, s), 7.16-7.21(2H, m), 7.34(1H, dd, J=8.8, 8.8 Hz), 7.45-7.49(2H, m), 7.68-7.78(2H, m), 8.29(1H, s).

IR(KBr) cm^{-1}: 3429, 1653, 1612, 1522, 1439, 1292, 764.

Example 196

Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and the mesylate derivative of 3-(4-fluorophenyl)-1-propanol {J. Med. Chem., 19, 461 (1976)} were reacted to yield the title compound as a yellow oil (yield: 90.1%). The mesylate derivative was prepared in accordance with the procedure of Example 1(9).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.16-2.26(2H, m), 2.71(2H, t, J=7.3 Hz), 3.95(3H, s),

3.98(3H, s), 4.32(2H, t, J=7.3 Hz), 6.93-7.06(3H, m), 7.14-7.18(2H, m), 7.49(1H, m), 7.60(1H, dd, J=13.2, 2.2 Hz), 8.17(1H, s).

2) Preparation of 4-carboxy-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 1(7), 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 89.2%).

Melting point: 185-187℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.20-2.30(2H, m), 2.74(2H, t, J= 7.3 Hz), 3.97(3H, s), 4.40(2H, t, J=7.3 Hz), 6.94-7.17(5H, m), 7.55(1H, d, J=8.5 Hz), 7.66(1H, dd, J=12.2, 2.2 Hz), 8.58(1H, s).

3) Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 37.0%).

Melting point: 130-133℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.15-2.22(2H, m), 2.71(2H, t, J=7.3 Hz), 3.95(3H, s), 4.27(2H, t, J=7.3 Hz), 4.70(2H, d, J=1.2 Hz), 6.93-7.06(3H, m), 7.14-7.18(2H, m), 7.50(1H, d, J=8.8 Hz), 7.61(1H, dd, J=12.7, 2.2 Hz), 7.63(1H, s).

4) Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow powder (yield: 92.3%).

Melting point: 112-116℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.15-2.25(2H, m), 2.71(2H, t, J=7.3 Hz), 3.17(3H, s), 3.95(3H, s), 4.27(2H, t, J=7.3 Hz), 5.25(2H, d, J=1.2 Hz), 6.93-7.05(3H, m), 7.14-7.18(2H, m), 7.49(1H, d, J=8.5 Hz), 7.61(1H, dd, J=13.4, 2.0 Hz), 7.72(1H, s).

5) Preparation of 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4

-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 79.3%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.15-2.25(2H, m), 2.41(3H, s), 2.60-2.75(10H, m), 3.58(2H, s), 3.75(3H, s), 4.27(2H, t, J=7.3 Hz), 6.92-7.06(3H, m), 7.14-7.18(2H, m), 7.51(1H, d, J=8.5 Hz), 7.60(1H, dd, J=12.4, 2.0 Hz), 7.69(1H, s).

IR(Neat) cm^{-1}: 1652, 1608, 1511, 1439, 1284, 758.

Mass m/z: 468(M^+).

Example 197

Preparation of 4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 7, 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a pale yellow crystalline powder (yield: 61.8%).

Melting point: 97-100℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.15-2.25(2H, m), 2.43(6H, s), 2.71(2H, t, J=7.3 Hz), 3.60(2H, s), 3.94(3H, s), 4.27(2H, t, J=7.3 Hz), 6.93-7.05(3H, m), 7.15-7.18(2H, m), 7.57(1H, d, J=8.5 Hz),

7.64(1H, dd, J=12.6, 2.2 Hz), 7.90(1H, brs).

IR(KBr) cm^{-1}: 1653, 1611, 1510, 1436, 1296, 763.

Mass m/z: 413(M^+).

Example 198

Preparation of

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 67.3%).

^1H NMR(400MHz, $CDCl_3$)δ:

2.14-2.22(2H, m), 2.70(2H, t, J=7.6 Hz), 2.75-2.95(4H, m), 3.70-3.80(6H, m), 3.94(3H, s), 4.28(2H, t, J=7.6 Hz), 6.93-7.05(3H, m), 7.15-7.18(2H, m), 7.56(1H, m), 7.63(1H, m), 7.85(1H, m).

IR(Neat) cm^{-1}: 1645, 1601, 1510, 1439, 1277, 763.

Mass m/z: 473(M^+).

Example 199

Preparation of

6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)

propyl]-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of

4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 72.6%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.40(9H, s), 2.07-2.16(2H, m), 2.40-2.50(4H, m), 2.63(2H, t, J=7.6 Hz), 3.36-3.46(4H, m) 3.48(2H, brs), 3.88(3H, s), 4.20(2H, t, J=7.6 Hz), 6.84-6.98(3H, m), 7.07-7.11(2H, m), 7.43(1H, d, J=8.1 Hz), 7.53(1H, d, J=12.4 Hz), 7.65(1H, brs).

2) Preparation of

6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-(1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 20, 4-(4-tert-butoxycarbonyl-1-piperazinyl)methyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 97.2%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.12-2.22(2H, m), 2.50-2.60(4H, m), 2.71(2H, t, J=7.3 Hz), 2.92-3.02(4H, m), 3.53(2H, s), 3.95(3H, s), 4.27(2H, t, J=7.3 Hz), 6.91-7.06(3H, m), 7.15-7.18(2H, m), 7.51(1H, d, J=8.8 Hz), 7.61(1H, dd, J=12.5, 2.2 Hz), 7.73(1H, s).

IR(Neat) cm^{-1}: 1650, 1607, 1510, 1439, 1275, 758.

Mass m/z: 454(M^+).

Example 200

Preparation of 4-aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 24(1), 6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to a crude product. Without purification, the crude product was reacted in accordance with the procedure of Example 24(2) to yield the title compound as a pale yellow crystalline powder (yield: 41.7%).

Melting point: 82-84℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.12-2.22(2H, m), 2.70(2H, t, J=7.6 Hz), 3.89(2H, s), 3.94(3H, s), 4.27(2H, t, J=7.6 Hz), 6.93-7.04(3H, m), 7.15-7.18(2H, m), 7.51(1H, d, J=7.3 Hz), 7.61(1H, dd, J=12.4, 2.0 Hz), 7.67(1H, s).

IR(KBr) cm^{-1}: 3366, 1651, 1605, 1509, 1436, 1273, 764.

Mass m/z: 385(M^+).

Example 201

Preparation of 4-aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 73.1%).

Melting point: 160-165℃

^1H NMR(400MHz, DMSO-d_6)δ:

2.05-2.15(2H,m), 2.66(2H, t, J=7.3 Hz), 3.92(3H, s), 3.99(2H, s), 4.19(2H, t, J=7.3 Hz), 7.05-7.12(2H, m), 7.23-7.30(2H, m), 7.34(1H,dd, J=8.8, 8.8 Hz), 7.66-7.76(2H, m), 8.25(1H,s).

IR(KBr) cm^{-1}: 3430, 1652, 1515, 1436, 1269, 763.

Example 202

Preparation of 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of

2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and 4-chlorobenzyl chloride were reacted to yield the title compound as yellow needles (yield: 97.6%).

Melting point: 170.5-171.1℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.95(3H, s), 3.99(3H, s), 5.38((2H, s), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.31(2H, d, J=8.5 Hz), 7.47(2H, d, J=8.5 Hz), 7.49(1H, m), 7.60(1H, dd, J=12.2, 2.2 Hz), 8.20(1H, s)

IR(KBr) cm^{-1}: 1723, 1670, 1526, 1271, 1128.

Mass m/z: 402(M+), 404((M$^+$).

2) Preparation of

4-carboxy-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a pale yellow crystalline powder (yield: 96.0%).

Melting point: 228.3-229.1℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.97(3H, s), 5.46(2H, s), 7.07(1H, dd, J=8.5, 8.5 Hz),

7.35(2H, d, J=8.3 Hz), 7.46(2H, d, J=8.3 Hz), 7.55(1H, d, J=8.4 Hz), 7.67(1H, dd, J=12.2, 2.2 Hz), 8.61(1H, s).

IR(KBr) cm^{-1}: 1745, 1635, 1456, 1447, 1431, 1298, 1273.

Mass m/z: 388(M^+), 390(M^+).

3) Preparation of

2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow needles (yield: 20.4%).

Melting point: 164.6-165.3℃

^1H NMR(400MHz, $CDCl_3$)δ:

3.94(3H, s), 4.69(2H, s), 5.34 (2H, s), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.30(2H, d, J=8.5 Hz), 7.42(2H, d, J=8.5 Hz), 7.50(1H, m), 7.63(1H, dd, J=12.4, 2.2 Hz), 7.67(1H, s).

IR(KBr) cm^{-1}: 3373, 1653, 1610, 1527, 1291, 1135.

Mass m/z: 374(M^+), 376(M^+).

4) Preparation of

2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-

hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow needles (yield: 81.6%).

Melting point: 156.5-157.4℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.15(3H, s), 3.95(3H, s), 5.22(2H, d, J=1.5 Hz), 5.35(2H, s), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.31(2H, d, J=8.5 Hz), 7.42(2H, d, J=8.5 Hz), 7.49(1H, m), 7.61(1H, dd, J=12.2, 2.2 Hz), 7.75(1H, s).

IR(KBr) cm^{-1}: 1658, 1616, 1358, 1183, 1017.

5) Preparation of 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as pale brown prisms (yield: 39.5%).

Melting point: 128.7-130.2℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, s), 2.52(4H, brs), 2.60(4H, brs), 3.55(2H, s), 3.95(3H, s), 5.34(2H, s), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.30(2H, d, J=8.5 Hz), 7.43(2H, d, J=8.5 Hz), 7.51(1H, m), 7.60(1H, dd, J=12.4, 2.0 Hz), 7.73(1H, s).

IR(KBr) cm^{-1}: 1652, 1607, 1524, 1516, 1438, 1288, 1135.

Example 203

Preparation of

2-(4-chlorobenzyl)-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 74.7%).

Melting point: 95.3-96.7℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(6H,s), 3.47(2H, d, J=1.2 Hz), 3.94(3H, s), 5.34(2H, s), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.30(2H, d, J=8.5 Hz), 7.44(2H, d, J=8.5 Hz), 7.53(1H, ddd, J=8.5, 2.0, 1.2 Hz), 7.62(1H, dd, J=12.4, 2.2 Hz), 7.74(1H, s).

IR(KBr) cm^{-1}: 1652, 1609, 1524, 1515, 1436, 1289, 1264, 1017.

Mass m/z: 401(M^+), 403(M^+).

Example 204

Preparation of

2-(4-chlorobenzyl)-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4,

2-(4-chlorobenzyl)-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 59.7%).

Melting point: 193.4-194.7℃

^{1}H NMR(400MHz, CD_3OD)δ:

2.96(6H, s), 3.94(3H, s), 4.33(2H, s), 5.43(2H, s), 7.22(1H, dd, J=8.5, 8.5 Hz), 7.36(2H, d, J=8.5 Hz), 7.46(2H, d, J=8.5 Hz), 7.67-7.72(2H, m), 8.20(1H, s).

IR(KBr) cm^{-1}: 1655, 1616, 1529, 1327, 1279.

Example 205

Preparation of 4-aminomethyl-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

1) Preparation of 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-phthalimidomethyl-2H-pyridazin-3-one

Following the procedure of Example 24(1), 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly-yellow needles (yield: 75.4%).

Melting point: 212.5-213.9℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.90(3H, s), 4.88(2H, d, J=0.73 Hz), 5.35(2H, s), 6.95(1H, dd, J=8.5, 8.5 Hz), 7.29(1H, s), 7.31(2H, d, J=8.5 Hz), 7.36(1H, m), 7.44(2H, d, J=8.5 Hz), 7.47(1H, dd, J=12.2, 2.0 Hz), 7.76-7.81(2H, m), 7.89-7.94(2H, m).

IR(KBr) cm^{-1}: 1773, 1713, 1651, 1610, 1522, 1439, 1419, 1393, 1300.

Mass m/z: 503(M^+), 505(M^+).

2) Preparation of 4-aminomethyl-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 24(2), 2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-phthalimidomethyl-2H-pyridazin-3-one was reacted to yield the title compound as slightly-yellow needles (yield: 48.8%).

Melting point: 128.5-131.4℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.88(2H, s), 3,94(3H, s), 5.34(2H, s), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.30(2H, d, J=8.5 Hz), 7.43(2H, d, J=8.5 Hz), 7.51(1H, ddd, J=8.5, 2.2, 1.2 Hz), 7.61(1H, dd, J=12.4, 2.2 Hz), 7.69(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 3392, 1615, 1604, 1520, 1434, 1292, 1133, 1018.

Mass m/z: 373(M^+), 375((M$^+$).

Example 206

Preparation of

4-aminomethyl-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-aminomethyl-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 66.0%).

Melting point: 202.0-205.5℃

^{1}H NMR(400MHz, CD_3OD)δ:

3.94(3H, s), 4.13(2H, s), 5.41(2H, s), 7.21(1H, dd, J=8.8, 8.8 Hz), 7.35(2H, d, J=8.5 Hz), 7.46(2H, d, J=8.5 Hz), 7.65-7.71(2H, m), 8.08(1H. s).

IR(KBr) cm^{-1}: 2940, 1655, 1616, 1526, 1439, 1292.

Example 207

Preparation of

2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of

2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin

-3-one and 3,4-difluorobenzyl bromide was reacted to yield the title compound as a yellow crystalline powder (yield: 92.1%).

Melting point: 144-148℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.96(3H, s), 3.97(3H, s), 5.35(2H, s), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.12(1H, m), 7.28(1H, m), 7.36(1H, m), 7.50(1H, m), 7.60(1H, dd, J=12.2, 1.5 Hz), 8.21(1H, s).

IR(KBr) cm^{-1}: 1756, 1656, 1609, 1518, 1439, 1239, 1293, 1278, 1204.

Mass m/z: 404(M^+).

2) Preparation of 4-carboxy-2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the title compound as a yellow crystalline powder (yield: 97.6%).

Melting point: 196.4-197.0℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.97(3H, s), 5.44(2H, s), 7.07(1H, dd, J=8.5, 8.5 Hz), 7.17(1H, m), 7.27(1H, m), 7.36(1H, ddd, J=8.1, 8.1, 2.2 Hz), 7.56(1H, m), 7.66(1H, dd, J=12.2, 2.2 Hz), 8.61(1H, s), 13.83(1H, s).

IR(KBr) cm^{-1}: 1757, 1636, 1567, 1518, 1463, 1440, 1284.

Mass m/z: 390(M^+).

3) Preparation of

2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as slightly-yellow neeldes (yield: 7.7%).

Melting point: 154.1-155.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.85(1H, t, J=5.6 Hz), 3.95(3H, s), 4.71(2H, d, J=5.6 Hz), 5.33(2H, s), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.12(1H, m), 7.23(1H, m), 7.31(1H, ddd, J=11.0, 7.6, 2.2 Hz), 7.51(1H, ddd, J=8.5, 2.2, 1.2 Hz), 7.61(1H, dd, J=12.4, 2.2 Hz), 7.68(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 3390, 1648, 1602, 1518, 1440, 1285, 1141.

Mass m/z: 376(M+).

4) Preparation of

2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the

title compound as slightly-yellow neeldes (yield: 91.5%).

Melting point: 145.6-146.6℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.16(3H, s), 3.96(3H, s), 5.26(2H, d, J=1.2 Hz), 5.32(2H, s), 7.04(1H, dd, J=8.5 8.5 Hz), 7.13(1H, m), 7.23(1H, m), 7.32(1H, m), 7.50(1H, m), 7.61(1H, dd, J=12.4, 2.2 Hz), 7.76(1H, t, J=1.2 Hz).

IR (KBr) cm^{-1}: 1656, 1612, 1522, 1440, 1352, 1277, 1163.

Mass m/z: 454(M^+).

5) Preparation of

2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as slightly-yellow neeldes (yield: 55.0%).

Melting point: 135.4-136.0℃

^{1}H NMR(400MHz, $CDCl_3$) δ :

2.33(3H, s), 2.51(4H, brs), 2.62(4H, brs), 3.56(2H, d, J=1.5 Hz), 3.95(3H, s), 5.31(2H, s), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.11(1H, m), 7.23(1H, m), 7.32(1H, ddd, J=11.0, 7.6, 2.0 Hz), 7.52(1H, ddd, J=8.5, 2.2, 1.2 Hz), 7.59(1H, dd, J=12.2, 2.2 Hz), 7.74(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 1652, 1608, 1522, 1437, 1291, 1273, 1139.

Mass m/z: 458(M^+).

Example 208

Preparation of

2-(3,4-difluorobenzyl)-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as slightly-yellow needles (yield: 77.1%).

Melting point: 129.9-130.4℃

^1H NMR(400MHz, $CDCl_3$)δ:

2.35(6H, s), 3.49(2H, s), 3.95(3H, s), 5.32(2H, s), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.11(1H, m), 7.24(1H, m), 7.32(1H, ddd, J=11.0, 7.6, 2.2 Hz), 7.54(1H, ddd, J=8.5, 2.2, 1.2 Hz), 7.62(1H, dd, J=12.4, 2.2 Hz), 7.77(1H, s).

IR(KBr) cm^{-1}: 1653, 1610, 1519, 1437, 1291, 1283, 1267, 1138, 1114.

Mass m/z: 403(M^+).

Example 209

Preparation of

2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-(

4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

1) Preparation of

2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one

Following the procedure of Example 1(6), 6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one and 4-chlorocinnamyl chloride were reacted to yield the title compound as a pale yellow crystalline powder (yield: 51.1%).

Melting point: 117-119℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.95(3H, s), 3.98(3H, s), 5.02(2H, dd, J=6.8, 1.2 Hz), 6.43(1H, dt, J=15.9, 6.8 Hz), 6.70(1H, d, J=15.9 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.25(2H, d, J=8.8 Hz), 7.31(2H, d, J=8.8 Hz), 7.50(1H, dt, J=8.5, 2.2 Hz), 7.62(1H, dd, J=12.2, 2.2 Hz), 8.22(1H,s).

IR(KBr) cm^{-1}: 1724, 1709, 1667, 1506, 1291, 1236, 1126, 831.

Mass m/z: 412(M^+), 414(M^+).

2) Preparation of

4-carboxy-2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(7), 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-methoxycarbonyl-2H-pyridazin-3-one was reacted to yield the

title compound as a pale yellow crystalline powder (yield: 98.2%).

Melting point: 217.2-218.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

3.97(3H, s), 5.10(2H, d, J=6.8 Hz), 6.39(1H, dt, J=15.9, 6.8 Hz), 6.75(1H, d, J=15.9 Hz), 7.06(1H, dd, J=8.5, 8.5 Hz), 7.30(2H, d, J=8.5 Hz), 7.34(2H, d, J=8.5 Hz), 7.57(1H, m), 7.69(1H, dd, J=12.2, 2.2 Hz), 8.63(1H, s), 13.99(1H, s).

IR(KBr) cm^{-1}: 3059, 1744, 1629, 1523, 1480, 1438, 1426, 1296, 1272.

Mass m/z: 414(M^+), 416(M^+).

3) Preparation of 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-carboxy-2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow crystals (yield: 17.0%).

Melting point: 158.2-160.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.95(1H, t, J=5.9 Hz), 3.94(3H, s), 4.73(2H, dd, J=5.9, 1.2 Hz), 4.98(2H, dd, J=6.6, 1.2 Hz), 6.40(1H, dt, J=15.9, 6.6 Hz), 6.67(1H, d, J=15.9 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.27(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 7.51(1H, ddd,

J=8.8, 2.2, 1.2 Hz), 7.63(1H, dd, J=12.4, 2.2 Hz), 7.67(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 3392, 1648, 1603, 1523, 1440, 1284, 1273, 1140.

Mass m/z: 400(M^+), 402(M^+).

4) Preparation of 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one was reacted to yield the title compound as pale yellow neeldes (yield: 90.7%).

Melting point: 135.8-136.4℃

^1H NMR(400MHz, $CDCl_3$)δ:

3.17(3H, s), 3.95(3H, s), 4.98(2H, dd, J=6.6, 0.98 Hz), 5.28(2H, d, J=1.5 Hz), 6.39(1H, dt, J=15.9, 6.6 Hz), 6.67(1H, d, J=15.9 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.27(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 7.50(1H, m), 7.62(1H, dd, J=12.2, 2.2 Hz), 7.77(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 1660, 1615, 1523, 1436, 1360, 1335, 1287, 1273, 1179.

Mass m/z: 478(M^+), 480(M^+).

5) Preparation of 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-

methyl-1-piperazinyl)methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as pale brown neeldes (yield: 66.3%).

Melting point: 123.9-125.5℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.33(3H, s), 2.52(4H, brs), 2.62(4H, brs), 3.58(2H, d, J=1.2 Hz), 3.95(3H, s), 4.98(2H, dd, J=6.8, 1.2 Hz), 6.41(1H, dt, J=15.9, 6.8 Hz), 6.66(1H, d, J=15.9 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.26(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 7.53 (1H, ddd, J=8.5, 2.0, 1.2 Hz), 7.62(1H, dd, J=12.4, 2.2 Hz), 7.75(1H, t, J=1.2 Hz).

IR(KBr) cm^{-1}: 1647, 1606, 1522, 1439, 1282, 1270.

Mass m/z: 482(M^+), 484(M^+).

Example 210

Preparation of 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-[4-(2-hydroxyethyl)-1-piperazinyl]methyl-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-methanesulfonyloxymethyl-2H-pyridazin-3-one and

1-piperazineethanol were reacted to yield the title compound as slightly-yellow needles (yield: 65.1%).

Melting point: 133.1-134.9℃

^{1}H NMR(400MHz, $CDCl_3$)δ:

2.57-2.62(11H, m), 3.58(2H, d, J=1.2 Hz), 3.63(2H, t, J=5.4 Hz), 3.94(3H, s), 4.97(2H, d, J=6.6 Hz), 6.41(1H, dt, J=15.9, 6.6 Hz), 6.67(1H, d, J=15.9 Hz), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.26(2H, d, J=8.5 Hz), 7.32(2H, d, J=8.5 Hz), 7.53(1H, m), 7.61(1H, dd, J=12.4, 2.2 Hz), 7.75(1H, s).

IR(KBr) cm^{-1}: 3451, 1647, 1605, 1523, 1438, 1285, 1274, 1137.

Mass m/z: 478(M^+), 480(M^+).

Example 211

Preparation of

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(4-methyl-1-piperazinyl)propyl]-2H-pyridazin-3-one

1) Preparation of

4-bromomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

2-Cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-hydroxymethyl-2H-pyridazin-3-one (185 mg, 0.61 mmol), carbon tetrabromide (404 mg, 1.2 mmol) and pyridine (48 mg, 0.61 mmol) were dissolved in tetrahydrofuran (3 mL), and under ice-cold stirring, a solution of triphenylphosphine (319 mg, 1.2 mmol) in tetrahydrofuran (3 mL) was added. Under ice cooling, the

mixture was stirred for 1 hour, and further stirred overnight at room temperature. Insoluble materials were filtered off, the solvent was distilled off under reduced pressure, and the residue was isolated and purified by column chromatography on silica gel (hexane/ethyl acetate=2/1) to yield the title compound as a yellow powder (yield: 155 mg, 69.5%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.60(4H, m), 1.58(1H, m), 3.95(3H, s), 4.12(2H, d, J=7.3 Hz), 4.49(2H, s), 7.03(1H, dd, J=8.5, 8.5 Hz), 7.50(1H, m), 7.60(1H, dd, J=13.4, 2.2 Hz), 7.77(1H, s).

2) Preparation of

2-cyclopropylmethyl-4-[2,2-di(tert-butoxycarbonyl)ethyl]-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

After 55% sodium hydride (322 mg, 7.38 mmol) was added to a solution of di-tert-butyl malonate (970 mg, 4.48 mmol) in N,N-dimethylformamide (10 mL), 4-bromomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one (1.8 g, 4.90 mmol) was added under ice-cold stirring. The reaction mixture was stirred at room temperature for 1 hour, poured into water, and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The residue was isolated and purified by chromatography on silica gel (hexane/ethyl acetate=3/1) to

yield the title compound as a yellow powder (yield: 1.39 mg, 61.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.50(2H, m), 0.50-0.58(2H, m), 1.41(18H, s), 1.56(1H, m), 3.12(2H, d, J=7.8 Hz), 3.87(1H, t, J=7.8 Hz), 3.94(3H, s), 4.09(2H, d, J=7.8 Hz), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.43(1H, d, J=8.5 Hz), 7.50(1H, s), 7.57(1H, dd, J=12.4, 2.2 Hz).

3) Preparation of 4-(2-carboxyethyl)-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Trifluoroacetic acid (21 mL) was added to 2-cyclopropylmethyl-4-[2,2-di(tert-butoxycarbonyl)ethyl]-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one (1.39 g, 2.77 mmol), and the mixture was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and toluene was added further, followed by azeotropic boiling. The residue was heated at 190 to 200℃ for 30 minutes under a nitrogen atmosphere to yield the title compound as a pale brown powder (yield: 907 mg, 94.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.45-0.50(2H, m), 0.50-0.60(2H, m), 1.41(1H, m), 2.80(2H, t, J=7.1 Hz), 2.97(2H, t, J=7.1 Hz), 3.94(3H, s), 4.10(2H, d, J=7.3 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.47(1H, d, J=8.5

Hz), 7.55(1H, s), 7.59(1H, dd, J=12.4, 2.2 Hz).

4) Preparation of

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-hydroxypropyl)-2H-pyridazin-3-one

Following the procedure of Example 1(8), 4-(2-carboxyethyl)-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a brown oil (yield: 82.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.52(2H, m), 0.52-0.60(2H, m), 1.42(1H, m), 1.88-1.94(2H, m), 2.81(2H, t, J=6.1 Hz), 3.63(2H, t, J=5.9 Hz), 3.95(3H, s), 4.12(2H, d, J=7.3 Hz), 7.02(1H, dd, J= 8.5, 8.5 Hz), 7.50(1H, m), 7.52(1H, s), 7.60(1H, dd, J=12.4, 2.2 Hz).

5) Preparation of

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-methanesulfonyloxypropyl)-2H-pyridazin-3-one

Following the procedure of Example 1(9), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-hydroxypropyl)-2H-pyridazin-3-one was reacted to yield the title compound as a pale brown powder (yield: 82.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.51(2H, m), 0.51-0.60(2H, m), 1.41(1H, m),

2.13-2.21(2H, m), 2.80(2H, t, J=7.1 Hz), 3.04(3H, s), 3.94(3H, s), 4.09(2H, d, J=7.3 Hz), 4.31(2H, t, J=6.1 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.49(1H, d, J=8.5 Hz), 7.53(1H, s), 7.61(1H, dd, J=12.4, 2.2 Hz).

6) Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(4-methyl-1-piperazinyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-methanesulfonyloxypropyl)-2H-pyridazin-3-one and 1-methylpiperazine were reacted to yield the title compound as a yellow oil (yield: 62.0%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.50(2H, m), 0.50-0.60(2H, m), 1.41(1H, m), 1.90-2.00(2H, m), 2.45(3H, s), 2.50-3.00(12H, m), 3.94(3H, s), 4.08(2H, d, J=7.3 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.48(1H, s), 7.50(1H, d, J=8.5 Hz), 7.70(1H, dd, J=12.3, 2.0 Hz).

IR(Neat) cm^{-1}: 1648, 1607, 1524, 1286, 1122, 1022, 755.

Mass m/z: 414(M^+).

Example 212

Preparation of 2-cyclopropylmethyl-4-(3-dimethylaminopropyl)-6-(3-

fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 7, 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-methanesulfonyloxypropyl)-2H-pyridazin-3-one and dimethylamine were reacted to yield the title compound as a yellow powder (yield: 64.7%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.50(2H, m), 0.53-0.60(2H, m), 1.40(1H, m), 2.24-2.35(2H, m), 2.75-2.80(2H, m), 2.79(6H, s), 3.03(2H, t, J=7.3 Hz), 3.94(3H, s), 4.08(2H, d, J=7.1 Hz), 7.04(1H, dd, J=8.5, 8.5 Hz), 7.57(1H, d, J=8.5 Hz), 7.65(1H, dd, J=12.4, 2.2 Hz), 7.72(1H, s).

IR(Neat) cm^{-1}: 1649, 1608, 1524, 1288, 1122, 1022, 761.

Mass m/z: 359(M^+).

Example 213

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(1-piperazinyl)propyl]-2H-pyridazin-3-one

1) Preparation of 2-cyclopropylmethyl-4-[3-(4-tert-butoxycarbonyl-1-piperazinyl)propyl]-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-

methanesulfonyloxypropyl)-2H-pyridazin-3-one and tert-butyl 1-piperazinecarboxylate were reacted to yield the title compound as a yellow oil (yield: 76.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.50(2H, m), 0.52-0.60(2H, m), 1.44(1H, m), 1.46(9H, s), 2.00-2.40(2H, m), 2.50-2.80(6H, m), 3.50-3.75(6H, m), 3.94(3H, s), 4.08(2H, d, J=7.1 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.47-7.65(3H, m).

2) Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(1-piperazinyl)propyl]-2H-pyridazin-3-one

Following the procedure of Example 20, 2-cyclopropylmethyl-4-[3-(4-tert-butoxycarbonyl-1-piperazinyl)propyl]-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a yellow oil (yield: 78.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.43-0.50(2H, m), 0.50-0.59(2H, m), 1.42(1H, m), 1.82-1.92(2H, m), 2.40-2.50(6H, m), 2.68(2H, t, J=7.6 Hz), 2.93-2.95(4H, m), 3.94(3H, s), 4.08(2H, d, J=7.3 Hz), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.45(1H, s), 7.48(1H, d, J=8.5 Hz), 7.59(1H, dd, J=11.4, 2.0 Hz).

IR(Neat) cm^{-1}: 1648, 1607, 1523, 1288, 1122, 1023, 760.

Mass m/z: 400(M^+).

Example 214

Preparation of 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(1-piperazinyl)propyl]-2H-pyridazin-3-one dihydrochloride

Following the procedure of Example 4, 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(1-piperazinyl)propyl]-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 83.1%).

Melting point: 174-178℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.39-0.45(2H, m), 0.45-0.55(2H, m), 1.32(1H, m), 2.00-2.25(2H, m), 2.62-2.66 (2H, m), 3.20-3.85(10H, m), 3.90(3H, s), 4.01(2H, d, J=7.1 Hz), 7.28(1H, dd, J=8.8, 8.8 Hz), 7.72-7.80(2H, m), 7.96(1H, s).

IR(KBr) cm^{-1}: 1647, 1604, 1523, 1297, 1123, 1020, 762.

Example 215

Preparation of 4-[3-[N,N-bis(2-hydroxyethyl)amino]propyl]-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 1(10),

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-methanesulfonyloxypropyl)-2H-pyridazin-3-one and diethanolamine were reacted to yield the title compound as a yellow oil (yield: 13.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.50(2H, m), 0.50-0.60(2H, m), 1.41(1H, m), 2.10-2.20(2H, m), 2.76(2H, t, J=7.3 Hz), 3.00-3.15(6H, m), 3.87-3.92(4H, m), 3.94(3H, s), 4.08(2H, d, J=7.3 Hz), 7.02(1H, dd, J=8.5, 8.5 Hz), 7.53(1H, d, J=8.5 Hz), 7.60(1H, s), 7.62(1H, dd, J=12.4, 2.2 Hz).

IR(Neat) cm^{-1}: 1645, 1602, 1524, 1288, 1123, 1024, 756.

Mass m/z: 400(M^+-CH_2OH).

Example 216

Preparation of 4-(3-aminopropyl)-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one

Following the procedure of Example 24(1), 2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(3-methanesulfonyloxypropyl)-2H-pyridazin-3-one was reacted to yield a crude product. Without purification, the crude product was reacted further in accordance with the procedure of Example 24(2) to yield the title compound as a yellow oil (yield: 67.8%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

0.44-0.50(2H, m), 0.50-0.60(2H, m), 1.41(1H, m), 1.84-1.96(2H, m), 2.67-2.80(4H, m), 2.87(2H, t, J=6.1 Hz), 3.94(3H, s), 4.08(2H, d, J=7.3 Hz), 7.01(1H, dd, J=8.5, 8.5 Hz), 7.49(1H, d, J=8.5 Hz), 7.50(1H, s), 7.59(1H, dd, J=12.4, 2.2 Hz).

IR(Neat) cm^{-1}: 3370, 1648, 1606, 1523, 1289, 1122, 1023, 760.

Mass m/z: 331(M^+).

Example 217

Preparation of 4-(3-aminopropyl)-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one hydrochloride

Following the procedure of Example 4, 4-(3-aminopropyl)-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one was reacted to yield the title compound as a slightly-yellow crystalline powder (yield: 70.6%).

Melting point: 183-185℃

^{1}H NMR(400MHz, DMSO-d_6)δ:

0.40-0.45(2H, m), 0.45-0.55(2H, m), 1.32(1H, m), 1.88-1.93(2H, m), 2.64(2H, t, J=7.3 Hz), 2.78-2.88(2H, m), 3.90(3H, s), 4.00(2H, d, J=7.3 Hz), 7.28(1H, dd, J=8.5, 8.5 Hz), 7.70-7.78(2H, m), 7.96(1H, s).

IR(KBr) cm^{-1}: 3437, 1648, 1608, 1526, 1273, 1122, 1021, 762.

Referential Example

Preparation of 3-(2,6-dichlorophenyl)-1-propanol methanesulfonate

1) Preparation of ethyl 2,6-dichlorocinnamate

To a solution of 2,6-dichlorobenzaldehyde (350 mg, 2.0 mmol) and triethyl phosphonoacetate (448 mg, 2.6 mmol) in THF (5 mL), potassium tert-butoxide (291 mg, 2.6 mmol) was added under ice cooling, and at the same temperature, the mixture was stirred for 2 hours. A saturated aqueous solution of ammonium chloride was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. Further, the residue was purified by chromatography on a silica gel column (hexane/ethyl acetate=50/1) to yield the title compound as a colorless syrupy substance (yield: 65.1%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.35(3H, t, J=7.2 Hz), 4.30(2H, q, J=7.2 Hz), 6.59(1H, d, J=16.4 Hz), 7.19(1H, t, J=8.0 Hz), 7.36(2H, t, J=8.0 Hz), 7.79(1H, d, J=16.4 Hz).

2) Preparation of 3-(2,6-dichlorophenyl)-1-propanol

Lithium aluminum hydride (98.8 mg, 2.60 mmol) was added to THF (5 mL), and under ice-cold strring, a solution of ethyl 2,6-dichlorocinnamate (319 mg, 1.30 mmol) in THF (5 mL) was

added dropwise. The mixture was then stirred at room temperature for 30 minutes. A small amount of a saturated aqueous solution of ammonium chloride was added to the reaction mixture, followed by drying over anhydrous magnesium sulfate. Subsequent to filtration through Celite, the mixture was concentrated under reduced pressure and further, purified by chromatography on a silica gel column (hexane/ethyl acetate=10/1) to yield the title compound as a pale yellow syrupy substance (yield: 46.9%).

^{1}H NMR(400MHz, $CDCl_3$)δ:

1.83-1.93(2H, m), 3.02(2H, t, J=7.8 Hz), 3.73(2H, t, J=6.3 Hz), 7.09(1H, t, J=8.3 Hz), 7.27(2H, d, J=8.3 Hz).

3) Preparation of 3-(2,6-dichlorophenyl)-1-propanol methanesulfonate

To a solution of 3-(2,6-dichlorophenyl)-1-propanol (125 mg, 0.61 mmol) and triethylamine (123 mg, 1.22 mmol) in methylene chloride (3 mL), methanesulfonyl chloride (105 mg, 0.915 mmol) was added under ice cooling, followed by stirring at room temperature for 2 hours. Brine was added to the reaction mixture. The organic layer was allowed to separate, was collected, and was then dried over anhydrous sodium sulfate. Subsequent to concentration under reduced pressure, the residue was purified by chromatography on a silica gel column (hexane/ethyl acetate=10/1) to yield the title compound as a

pale yellow syrupy substance (yield: quantitative).

^{1}H NMR(400MHz, $CDCl_3$)δ:

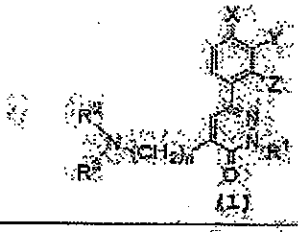
2.02-2.12(2H, m), 3.00-3.10(5H, m), 4.32(2H, t, J=6.3 Hz), 7.10(1H, t, J=8.3 Hz), 7.28(2H, d, J=8.3 Hz).

Experiment 1

Inhibitory Activity against Interleukin-1β Production

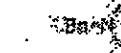
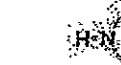
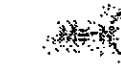
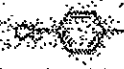
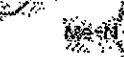
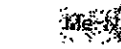
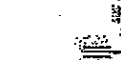
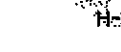
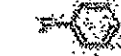
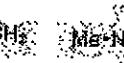
HL-60 cells were cultured for 4 days until confluence on RPMI 1640 medium with 10% fetal bovine serum (FBS) added thereto. The medium was centrifuged. The supernatant was discarded, and the cells were then suspended at 1 x 10^6 cells/mL on RPMI 1640 medium with 3% FBS, and lipopolysaccharide was added to give a final concentration of 10 μg/mL. The culture was inoculated at 1 mL/well to a 24-well plate. A sample compound was added at 1 μL/well, followed by culturing for 3 days. Three days later, the amount of interleukin-1β in each culture was determined by ELISA. Each IC_{50} value was determined by a comparison in yield with a control to which no test sample was added. Results on some representative compounds are shown in Table 1.

Table 1



(I)

Cyp-CH$_2$: Cyclopropylmethyl

Example No.	X	Y	Z	n	R^1	R^{2}R^{3}N-	Salt	Tie-1B production inhibitting activity IC50 (uM)
6	MeO	F	H	1	iso-Bu	Me_2N-	HCl	3.41
14	MeO	F	H	1	Cyp-CH$_2$	Me_2N-	HCl	1.61
18	MeO	F	H	1	Cyp-CH$_2$		2HCl	5.49
21	MeO	F	H	1	Cyp-CH$_2$		2HCl	1.01
23	MeO	F	H	1	Cyp-CH$_2$	$(HOCH_2CH_2)_2N$-	HCl	0.33
35	MeO	F	H	1	Cyp-CH$_2$	H_2N-	HCl	2.74
45	MeO	H	H	1	iso-Bu	Me_2N-	HCl	6.21
47	MeO	H	H	1	iso-Bu	Et_2N-	HCl	7.29
49	MeO	H	H	1	iso-Bu	$(HOCH_2CH_2)_2N$-	HCl	3.33
83	F	Me	H	1	iso-Bu		2HCl	0.27
89	F	Me	H	1	iso-Bu	Me_2N-	HCl	5.58
108	F	F	H	1	sec-Bu	$(HOCH_2CH_2)_2N$-	HCl	3.16
119	F	Me	H	1			2HCl	0.35
149	MeS	H	H	1	Cyp-CH$_2$		2HCl	3.63
153	MeS	H	H	1	Cyp-CH$_2$	Me_2N-	HCl	0.38
161	MeS	H	H	1	iso-Bu	Me_2N-	HCl	2.78
163	MeS	H	H	1	iso-Bu		HCl	2.78
215	MeO	F	H	2	Cyp-CH$_2$		free	0.21
216	MeO	H	H	2	Cyp-CH$_2$	H_2N-	free	1.14
189	MeO	H	H	1			free	0.67
191	MeO	F	H	1			free	0.64

Experiment 2 (Water Solubility Test)

Testing method

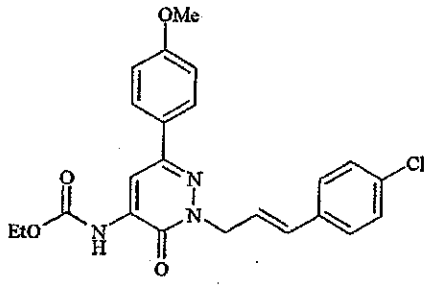
Each sample compound was weighed in the amount shown in Table 3, to which purified water was added in 0.05 mL aliquots. The solubility (%) of the compound was determined based on the amount of water required for its dissolution.

Results

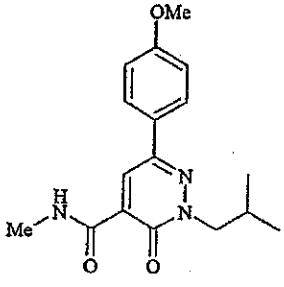
As is shown in Table 2, the compounds of the present invention showed water solubility significantly improved over the comparative compounds.

Table 2

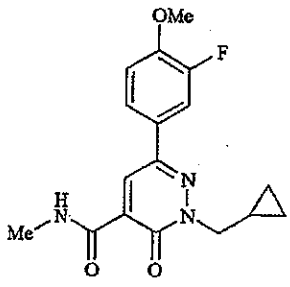
Example No.	Weighed amount (mg)	Amount of added water (mL)	Solubility (%)
14	2.048	0.25	0.8
18	1.048	0.1	1
21	10.47	0.05	>20
23	10.82	0.1	10
25	1.025	0.25	0.4
45	10.37	0.25	4
47	10.47	0.05	>20
89	10.57	0.05	>20
108	9.75	0.045	>20
149	3.09	0.03	>10
153	2.95	0.6	0.5
188	2.008	2.5	0.08
193	5.032	0.1	5
195	5.072	2.2	0.2
206	2.042	3.5	0.06
214	5.061	0.05	10
217	5.061	0.05	10
Comparative Compound 1	0.677	100 (insoluble)	<0.001
Comparative Compound 2	0.742	100 (insoluble)	<0.001
Comparative Compound 3	0.740	100 (insoluble)	<0.001
Comparative Compound 4	0.95	100 (insoluble)	<0.001



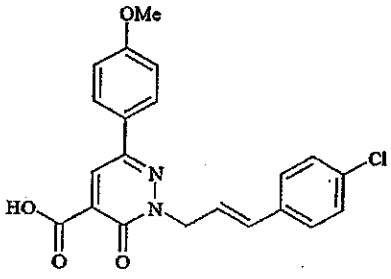
Comp.comp'd 1



Comp.comp'd 2



Comp.comp'd 3



Comp.comp'd 4

Experiment 3 (Oral Absorbability Test on Rats)

The compound of Example 83 and the comparative compound 3 were suspended at 2 mg/mL with a 0.5% MC solution in mortars, respectively, and were orally administered to male SD rats at 10 mg/5 mL/kg. Upon elapsed time of 0.25, 0.5, 1, 2, 4, 6 and 8 hours after the administration, blood samples were collected and then centrifuged to provide plasma samples. The plasma levels of the respective compounds were determined by HPLC. As is shown in FIG. 1, no substantial absorption was observed on the comparative compound 3, but good absorption was observed on the compound of Example 83 equipped with increased water solubility. The compound of Example 83 is, therefore, useful

as an orally dosable medicine.

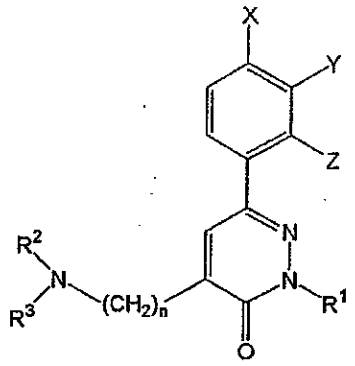
Experiment 4 (Oral Absorbability Test on Rats and/or Mice)

In a similar manner as in Experiment 3, test compounds of Examples 23, 25, 143, 193, 245, 246, 247, 248 and 249 were orally administered to mice and/or rats to test their oral absorbability. As is shown in FIGS. 2 to 6, good absorbability was observed on all of these test compounds so that they are useful as orally dosable medicines.

Having described the present invention, it will now be apparent to one of ordinary skill in the art that many changes and modifications may be made to the above-described embodiments without departing from the spirit and the scope of the present invention.

CLAIMS

1. A phenylpyridazine derivative having the formula (1):



(I)

wherein:

R^1 is optionally substituted alkyl, or optionally substituted alkenyl;

R^2 and R^3 each independently represents hydrogen or an alkyl, hydroxyalkyl, dihydroxyalkyl or alkynyl, or R^2 and R^3 are fused together with the adjacent nitrogen atom to form an optionally substituted, nitrogen-containing, saturated heterocyclic group;

X, Y and Z each independently represents hydrogen or halogen, optionally substituted alkyl, alkoxy, alkylthio, alkylsulfinyl or alkylsulfonyl, or optionally substituted aryl; and

n stands for a number of from 1 to 5;

with the proviso that R^2 and R^3 are not hydrogen or the same C_1-C_3 alkyl groups at the same time when R^1 is a benzyl group or a C_1-C_3 alkyl group; or a salt thereof

2. The compound of Claim 1, wherein R^1 is optionally

substituted alkyl having 1 to 7 carbon atoms or optionally substituted alkenyl having 2 to 7 carbon atoms.

3. The compound of Claim 2, wherein one or more substituents on said alkyl or alkenyl group represented by R^1 are each independently an aryl group having 6 to about 14 carbon atoms or a 5- or 6-membered heteroaryl group having 1 to 3 nitrogen atoms; and said aryl or heteroaryl group are each optionally substituted by 1 to 3 substituents selected from the group consisting of halogen, alkyl groups and alkoxy.

4. The compound of Claim 1, wherein R^2 and R^3 each independently represents hydrogen, alkyl, hydroxyalkyl, dihydroxyalkyl or alkynyl; or R^2 and R^3 are fused together with the adjacent nitrogen atom to form a 5- to 7-membered, nitrogen-containing, saturated heterocyclic group, said heterocyclic group being optionally substituted with one or more halogen atoms, or alkyl, alkoxycarbonyl, aralkyl or hydroxyalkyl groups.

5. The compound of Claim 1, wherein X, Y and Z each independently are hydrogen, halogen, alkyl which is optionally substituted by one or more halogen atoms or alkoxy, an alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, or C_6-C_{14} aryl groups which are optionally substituted by one or more of halogen, alkyl or alkoxy.

6. The compound of Claim 1, wherein R^1 is isobutyl, cyclopropylmethyl, cyclopentylmethyl, cinnamyl, halogenocinnamyl, benzyl, halogenobenzyl or dihalogenobenzyl

or (halogenophenyl)propyl; R^2 and R^3 are each independently hydrogen, C_{1-7} alkyl, C_{1-7} hydroxyalkyl or propargyl; said heterocyclic group formed by R^2 and R^3 is piperazinyl, piperidino or morpholino which is optionally substituted by C_{1-7} alkyl, benzyl or hydroxyalkyl; X is methyl, methoxy, methylthio or halogen; Y is hydrogen, methyl or halogen; Z is hydrogen; and n is 1 or 3.

7. The compound of Claim 1, which comprises

4-dimethylaminomethyl-6-(3-fluoro-4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one,

2-cyclopropylmethyl-4-dimethylamino-methyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-benzyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

2-cyclopropyl-methyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)-methyl-2H-pyridazin-3-one,

4-N,N-bis(2-hydroxyethyl)amino-methyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

4-aminomethyl-2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

4-dimethyl-aminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one,

4-diethylaminomethyl-2-isobutyl-6-(4-methylphenyl)-2H-pyridazin-3-one,

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(4-methylphenyl)-2-isobutyl-2H-pyridazin-3-one,

6-(4-fluoro-3-methylphenyl)-2-isobutyl-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

4-dimethylaminomethyl-6-(4-fluoro-3-methylphenyl)-2-isobutyl-2H-pyridazin-3-one,

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3,4-difluorophenyl)-2-isobutyl-2H-pyridazin-3-one,

2-(4-chlorocinnamyl)-6-(4-fluoro-3-methylphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

2-cyclopropylmethyl-4-(4-methyl-1-piperazinyl)methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one,

4-N,N-bis(2-hydroxyethyl)aminomethyl-2-cyclopropyl-methyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one,

2-cyclopropylmethyl-4-dimethylaminomethyl-6-[4-(methylthio)-phenyl]-2H-pyridazin-3-one,

2-isobutyl-6-[4-(methylthio)-phenyl]-4-propargylaminomethyl-2H-pyridazin-3-one,

4-dimethylaminomethyl-2-isobutyl-6-[4-(methylthio)phenyl]-2H-pyridazin-3-one,

2-(4-chlorobenzyl)-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

2-cyclopentylmethyl-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-(1-piper

azinyl)methyl-2H-pyridazin-3-one,

4-aminomethyl-2-cyclopentylmethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

4-dimethylaminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(1-piperazinyl)methyl-2H-pyridazin-3-one,

4-aminomethyl-2-(4-fluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

4-aminomethyl-2-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

2-(3,4-difluorobenzyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

2-(3,4-difluorobenzyl)-4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2H-pyridazin-3-one,

6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-(4-methyl-1-piperazinyl)methyl-2H-pyridazin-3-one,

4-dimethylaminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one,

4-N,N-bis(2-hydroxyethyl)aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-2H-pyridazin-3-one,

6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluorophenyl)propyl]-4-(1-piperazinyl)methyl-2H-pyridazin-3-one,

4-aminomethyl-6-(3-fluoro-4-methoxyphenyl)-2-[3-(4-fluoroph
enyl)propyl]-2H-pyridazin-3-one,
2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-[4-(2-h
ydroxyethyl)-1-piperazinyl]methyl-2H-pyridazin-3-one,
2-(4-chlorocinnamyl)-6-(3-fluoro-4-methoxyphenyl)-4-(4-meth
yl-1-piperazinyl)methyl-2H-pyridazin-3-one,
2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(4-me
thyl-1-piperazinyl)propyl]-2H-pyridazin-3-one,
2-cyclopropylmethyl-4-(3-dimethylaminopropyl)-6-(3-fluoro-4
-methoxyphenyl)-2H-pyridazin-3-one,
2-cyclopropylmethyl-6-(3-fluoro-4-methoxyphenyl)-4-[3-(1-pi
perazinyl)propyl]-2H-pyridazin-3-one, or
4-(3-aminopropyl)-2-cyclopropylmethyl-6-(3-fluoro-4-methoxy
phenyl)-2H-pyridazin-3-one.

8. A medicine comprising as an active ingredient the compound of any one of claims 1-7 or a salt thereof.

9. The medicine of claim 8, which is a preventive or therapeutic for a disease caused by stimulation of interleukin-1β production.

10. The medicine of claim 8, which is a preventive or therapeutic for immune system diseases, inflammatory diseases, ischemic diseases, osteoporosis, or ichorrhemia.

11. The medicine of claim 8, which is a preventive or therapeutic for rheumatism, arthritis or inflammatory colitis.

12. An interleukin-1β production inhibitor comprising as

an active ingredient the compound of any one of claims 1-7 or a salt thereof.

13. A pharmaceutical composition comprising the compound of any one of claims 1-7 or a salt thereof and a pharmacologically acceptable carrier.

14. The pharmaceutical composition of claim 13, which is a pharmaceutical composition for the prevention or treatment of a disease caused by stimulation of interleukin-1β production.

15. The pharmaceutical composition of claim 13, which is a pharmaceutical composition for the prevention or treatment of immune system diseases, inflammatory diseases, ischemic diseases, osteoporosis, or ichorrhemia.

16. The pharmaceutical composition of claim 13, which is a pharmaceutical composition for the prevention or treatment of rheumatism, arthritis or inflammatory colitis.

17. Use of the compound of any one of claims 1-7 or a salt thereof for the production of a medicine.

18. The use of claim 17, wherein said medicine is a preventive or therapeutic for a disease caused by stimulation of interleukin-1β production.

19. The use of claim 17, wherein said medicine is a preventive or therapeutic for immune system diseases, inflammatory diseases, ischemic diseases, osteoporosis, or ichorrhemia.

20. The use of claim 17, wherein said medicine is a preventive or therapeutic for rheumatism, arthritis or inflammatory colitis.

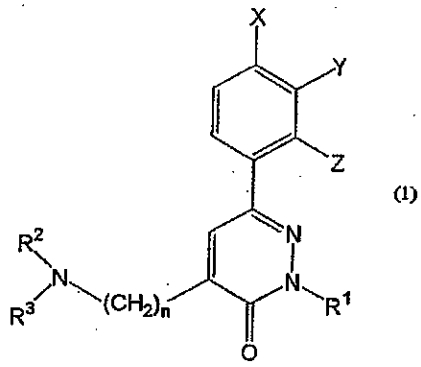
21. A method for treating a disease caused by stimulation of interleukin-1β production, which comprises administering the compound of any one of Claims 1-7 or a salt thereof.

22. A method for treating immune system diseases, inflammatory diseases, ischemic diseases, osteoporosis or ichorrhemia, which comprises administering the compound of any one of Claims 1-7 or a salt thereof.

23. The method of claim 22, wherein rheumatism, arthritis or inflammatory colitis is treated.

ABSTRACT OF THE DISCLOSURE

Compounds having the formula (1):



(1)

wherein R^1 represents an alkyl or alkenyl group, R^2 and R^3 each independently represents a hydrogen atom or an alkyl, hydroxyalkyl, dihydroxyalkyl or alkynyl group, or R^2 and R^3 may be fused together with the adjacent nitrogen atom to form a substituted or unsubstituted, nitrogen-containing, saturated heterocyclic group, X, Y and Z each independently represents a hydrogen atom, an alkyl group, a halogen atom or the like, and n stands for an integer of from 1 to 5; and also to pharmaceutical compositions containing them. These compounds have inhibitory activity against IL-1β production, high water solubility and good oral absorbability.