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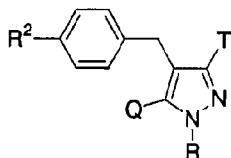
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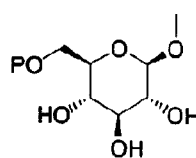
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(54) Title: GLUCOPYRANOSYLOXYPYRAZOLE DERIVATIVES AND USE THEREOF IN MEDICINES

(54) 発明の名称: グルコピラノシルオキシピラゾール誘導体及びその医薬用途



(I)



(II)

(57) Abstract: Glucopyranosyloxypyrazole derivatives represented by the general formula (I) or pharmacologically acceptable salts thereof, which exhibit human SGLT2 inhibiting activity, are improved in peroral absorbability, and are useful as preventive or therapeutic drugs for diseases due to hyperglycemia, e.g., diabetes, complications of diabetes, and obesity; and use of the compounds or the salts in medicines: (I) wherein R is hydrogen, lower alkyl, or a prodrug-constituting group; one of Q and T is a group of the general formula (II); (II) (wherein P is hydrogen or a prodrug-constituting group), and the other is lower alkyl or halogenated lower alkyl; and R<sup>2</sup> is hydrogen, lower alkyl, lower alkoxy, lower alkylthio, halogenated lower alkyl, or halogeno, with the proviso that when R is hydrogen or lower alkyl, P is not hydrogen.

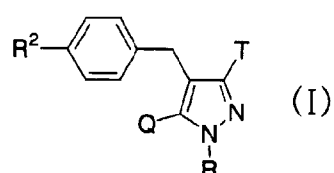
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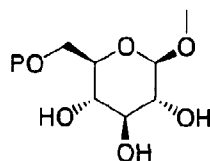


(57) 要約:

本発明は、ヒト SGLT 2 活性阻害作用を発現し、経口吸収性が改善された、糖尿病、糖尿病性合併症、肥満症等の高血糖症に起因する疾患の予防又は治療薬として有用な、一般式



〔式中の R は水素原子、低級アルキル基またはプロドラッグを構成する基であり、Q および T はどちらか一方が一般式



(式中の P は水素原子またはプロドラッグを構成する基である) で表される基であり、他方が低級アルキル基またはハロ低級アルキル基であり、R<sup>2</sup> は水素原子、低級アルキル基、低級アルコキシ基、低級アルキルチオ基、ハロ低級アルキル基またはハロゲン原子であり、但し、R が水素原子または低級アルキル基の場合、P は水素原子ではない〕で表されるグルコピラノシルオキシピラゾール誘導体及びその薬理学的に許容される塩、及びその医薬用途を提供するものである。

# VERIFICATION OF TRANSLATION

RE: INTERNATIONAL APPLICATION NO. PCT/JP01/11348

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am the translator of Patent Application No. PCT/JP01/11348

and I state that the following is a true translation to the  
best of my knowledge and belief.

(Signature of Translator) -----

*Kazuhiro Miyazawa*  
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(Dated) -----

*June 12, 2003*

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## DESCRIPTION

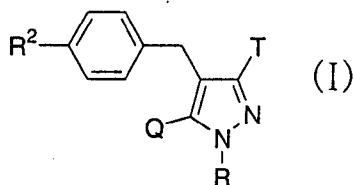
GLUCOPYRANOSYLOXYPYRAZOLE DERIVATIVES  
AND USE THEREOF IN MEDICINES

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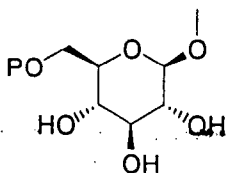
## Technical Field

The present invention relates to glucopyranosyloxy-  
pyrazole derivatives or pharmaceutically acceptable salts  
thereof which are useful as medicaments and pharmaceutical uses  
10 thereof.

More particularly, the present invention relates to  
glucopyranosyloxy-pyrazole derivatives represented by the  
general formula:



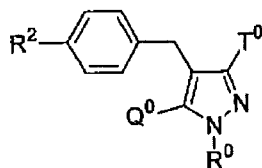
15 wherein R represents a hydrogen atom, a lower alkyl group or  
a group forming a prodrug; one of Q and T represents a group  
represented by the general formula:



(wherein P represents a hydrogen atom or a group forming a prodrug),  
20 while the other represents a lower alkyl group or a halo(lower  
alkyl) group; R<sup>2</sup> represents a hydrogen atom, a lower alkyl group,

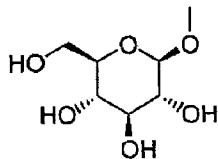
- 2 -

a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or pharmaceutically acceptable salts thereof, excluding 4'-((4'-methylthiophenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-carbomethoxy- $\beta$ -D-glucopyranosyl)-1H-pyrazole and 4'-((4'-ethylphenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-carbomethoxy- $\beta$ -D-glucopyranosyl)-1H-pyrazole which are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications or obesity, of which glucopyranosyloxypyrazole derivatives, which have an inhibitory activity in human SGLT2, represented by the general formula:



(II)

wherein  $R^0$  represents a hydrogen atom or a lower alkyl group; one of  $Q^0$  and  $T^0$  represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo(lower alkyl) group; and  $R^2$  represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, are active forms, and to pharmaceutical uses thereof.

#### Background Art

Diabetes is one of lifestyle-related diseases with the background of change of eating habit and lack of exercise. Hence, diet and exercise therapies are performed in patients with diabetes. Furthermore, when its sufficient control and continuous performance are difficult, drug treatment is simultaneously performed. Now, biguanides, sulfonylureas and insulin sensitivity enhancers have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglycemia, respectively. In a case of using insulin sensitivity enhancers, adverse effects such as edema occasionally are observed, and it is also concerned for advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.

In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 ( $\text{Na}^+$ /glucose cotransporter 2) is present in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose at the kidney, subsequently promotes excreting excess glucose though the urine, and normalizes blood glucose level. Therefore,

fast development of antidiabetic agents, which have a potent inhibitory activity in human SGLT2 and have a new mechanism, has been desired. Also, since such agents promote the excretion of excess glucose through the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventing or alleviating effect on obesity and a urinating effect. Furthermore, the agents are considered to be useful for various related diseases which occur accompanying the progress of diabetes or obesity due to hyperglycemia.

As compounds having pyrazole moiety, it is described that WAY-123783 increased an amount of excreted glucose in normal mice. However, its effects in human are not described at all (J. Med. Chem., Vol. 39, pp. 3920-3928 (1996)).

#### Disclosure of the Invention

The present inventors have studied earnestly to find compounds having an inhibitory activity in human SGLT2. As a result, it was found that compounds represented by the above general formula (I) are converted into glucopyranosyloxy-pyrazole derivatives represented by the above general formula (II) as their active forms *in vivo*, and show an excellent inhibitory activity in human SGLT2 as mentioned below, thereby forming the basis of the present invention.

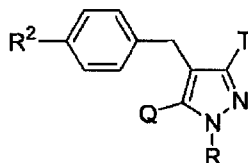
The present invention is to provide the following glucopyranosyloxypyrazole derivatives or pharmaceutically acceptable salts thereof, which exert an inhibitory activity in human SGLT2 *in vivo* and show an excellent hypoglycemic effect



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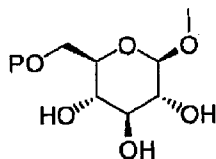
by excreting excess glucose in the urine through preventing the reabsorption of glucose at the kidney, and to provide pharmaceutical uses thereof.

This is, the present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:



(I)

wherein R represents a hydrogen atom, a lower alkyl group or a group forming a prodrug; one of Q and T represents a group represented by the general formula:



(wherein P represents a hydrogen atom or a group forming a prodrug), while the other represents a lower alkyl group or a halo(lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof; excluding 4'-((4'-methylthiophenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-carbomethoxy-β-D-glucopyranosyl)-1H-pyrazole and 4'-((4'-ethylphenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-carbomethoxy-β-D-glucopyranosyl)-1H-pyrazole.

Also, the present invention relates to a pharmaceutical composition, a human SGLT2 inhibitor and an agent for the prevention or treatment of a disease associated with

hyperglycemia, which comprise as an active ingredient a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

5       The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable  
10 salt thereof.

      The present invention relates to a use of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the  
15 prevention or treatment of a disease associated with hyperglycemia.

      Furthermore, the present invention relates to a pharmaceutical combination which comprises (A) a glucopyranosyloxypyrazole derivative represented by the above  
20 general formula (I) or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor  
25 kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor,

a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase  
 inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic  
 gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase  
 kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like  
 5 peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin,  
 an amylin analogue, an amylin agonist, an aldose reductase  
 inhibitor, an advanced glycation endproducts formation  
 inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid  
 receptor antagonist, a sodium channel antagonist, a transcript  
 10 factor NF- $\kappa$ B inhibitor, a lipid peroxidase inhibitor, an  
 N-acetylated- $\alpha$ -linked-acid-  
 dipeptidase inhibitor, insulin-like growth factor-I,  
 platelet-derived growth factor, a platelet-derived growth  
 factor analogue, epidermal growth factor, nerve growth factor,  
 15 a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin,  
 EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-  
 glutarylcoenzyme A reductase inhibitor, a fibric acid derivative,  
 a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol  
 acyltransferase inhibitor, probcol, a thyroid hormone receptor  
 20 agonist, a cholesterol absorption inhibitor, a lipase inhibitor,  
 a microsomal triglyceride transfer protein inhibitor, a  
 lipoxigenase inhibitor, a carnitine palmitoyl-transferase  
 inhibitor, a squalene synthase inhibitor, a low-density  
 lipoprotein receptor enhancer, a nicotinic acid derivative, a  
 25 bile acid sequestrant, a sodium/bile acid cotransporter  
 inhibitor, a cholesterol ester transfer protein inhibitor, an  
 appetite suppressant, an angiotensin-converting enzyme

inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, in combination with (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase

inhibitor, an advanced glycation endproducts formation  
 inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid  
 receptor antagonist, a sodium channel antagonist, a transcript  
 factor NF- $\kappa$ B inhibitor, a lipid peroxidase inhibitor, an  
 5 N-acetylated- $\alpha$ -linked-acid-  
 dipeptidase inhibitor, insulin-like growth factor-I,  
 platelet-derived growth factor, a platelet-derived growth  
 factor analogue, epidermal growth factor, nerve growth factor,  
 a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin,  
 10 EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-  
 glutaryl coenzyme A reductase inhibitor, a fibric acid derivative,  
 a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol  
 acyltransferase inhibitor, probcol, a thyroid hormone receptor  
 agonist, a cholesterol absorption inhibitor, a lipase inhibitor,  
 15 a microsomal triglyceride transfer protein inhibitor, a  
 lipoxygenase inhibitor, a carnitine palmitoyl-transferase  
 inhibitor, a squalene synthase inhibitor, a low-density  
 lipoprotein receptor enhancer, a nicotinic acid derivative, a  
 bile acid sequestrant, a sodium/bile acid cotransporter  
 20 inhibitor, a cholesterol ester transfer protein inhibitor, an  
 appetite suppressant, an angiotensin-converting enzyme  
 inhibitor, a neutral endopeptidase inhibitor, an angiotensin  
 II receptor antagonist, an endothelin-converting enzyme  
 inhibitor, an endothelin receptor antagonist, a diuretic agent,  
 25 a calcium antagonist, a vasodilating antihypertensive agent,  
 a sympathetic blocking agent, a centrally acting  
 antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an

antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

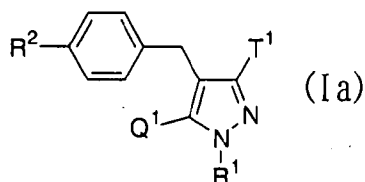
The present invention relates to a use of (A) a glucopyranosyloxypyrazole derivative represented by the above  
 5 general formula (I) or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor  
 10 kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic  
 15 gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation  
 20 inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid peroxidase inhibitor, an N-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I,  
 25 platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin,

EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

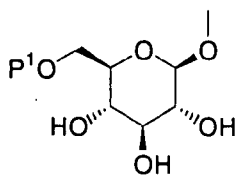
In the present invention, the term "prodrug" means a compound which is converted into a glucopyranosyloxypyrazole derivative represented by the above general formula (II) as an active form thereof *in vivo*. As examples of groups forming prodrugs, in cases of such groups located at a hydroxy group,

a hydroxy-protective group used generally as a prodrug such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group and a lower alkoxy-substituted (lower alkoxy-carbonyl) group are illustrated, and in cases of such groups located at a nitrogen atom, an amino-protective group used generally as a prodrug such as a lower acyl group, a lower alkoxy-carbonyl group, a lower acyloxymethyl group and a lower alkoxy-carbonyloxymethyl group are illustrated.

As the glucopyranosyloxypyrazole derivatives represented by the above general formula (I), for example, compounds represented by the general formula:



wherein R<sup>1</sup> represents a hydrogen atom, a lower alkyl group, a lower acyl group, a lower alkoxy-carbonyl group, a lower acyloxymethyl group or a lower alkoxy-carbonyloxymethyl group; one of Q<sup>1</sup> and T<sup>1</sup> represents a group represented by the general formula:



(wherein P<sup>1</sup> represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower



alkoxycarbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group, while the other represents a lower alkyl group or a halo(lower alkyl) group;  $R^2$  represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that  $P^1$  does not represent a hydrogen atom when  $R^1$  represents a hydrogen atom or a lower alkyl group, are illustrated:

In the present invention, the term "lower alkyl group" means a straight-chained or branched alkyl group having 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a hexyl group or the like; the term "lower alkoxy group" means a straight-chained or branched alkoxy group having 1 to 6 carbon atoms such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, an isopentyloxy group, a neopentyloxy group, a tert-pentyloxy group, a hexyloxy group or the like; and the term "lower alkylthio group" means a straight-chained or branched alkylthio group having 1 to 6 carbon atoms such as a methylthio group, an ethylthio group, a propylthio group, an isopropylthio group, a butylthio group, an isobutylthio group, a sec-butylthio group, a tert-butylthio group, a pentylthio group, an isopentylthio group, a neopentylthio group, a tert-pentylthio group, a hexylthio group

or the like. The term "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom; and the term "halo(lower alkyl) group" means the above lower alkyl group substituted by different or same 1 to 3 halogen atoms as defined

5 above. The term "lower acyl group" means a straight-chained, branched or cyclic acyl group having 2 to 7 carbon atoms such as an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a pivaloyl group, a hexanoyl group and a cyclohexylcarbonyl group; and the term "lower alkoxy-

10 substituted (lower acyl) group means the above lower acyl group substituted by the above lower alkoxy group. The term "lower alkoxy carbonyl group" means a straight-chained, branched or cyclic alkoxy carbonyl group having 2 to 7 carbon atoms such as a methoxy carbonyl group, an ethoxy carbonyl group, an

15 isopropoxy carbonyl group, an isobutyloxy carbonyl group and a cyclohexyloxy carbonyl group; the term "lower alkoxy carbonyl-substituted (lower acyl) group means the above lower acyl group substituted by the above lower alkoxy carbonyl group such as a 3-(ethoxy carbonyl)propionyl group; and the term "lower

20 alkoxy-substituted (lower alkoxy carbonyl) group means the above lower alkoxy carbonyl group substituted by the above alkoxy group such as a 2-methoxyethoxy carbonyl group. Furthermore, the term "lower acyloxy methyl group" means a hydroxymethyl group

O-substituted by the above lower acyl group; and the term "lower

25 alkoxy carbonyloxy methyl group" means a hydroxymethyl group O-substituted by the above lower alkoxy carbonyl group.

In the substituent R, a hydrogen atom or a straight-chained

or branched alkyl group having 1 to 3 carbon atoms are preferable; a hydrogen atom, an ethyl group, a propyl group or an isopropyl group are more preferable; and an isopropyl group is most preferable because of metabolic stability in human liver S9 fraction. In the substituent R<sup>2</sup>, a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms, or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms are preferable; and an ethyl group, an ethoxy group, an isopropoxy group, a methoxy group or a methylthio group are more preferable. In the substituents Q and T, it is preferable that the substituent Q is a lower alkyl group or a halo(lower alkyl) group. Among them, a lower alkyl group is preferable; a straight-chained or branched alkyl group having 1 to 3 carbon atoms is more preferable; and a methyl group is most preferable. In the substituent P, a lower acyl group and a lower alkoxy carbonyl group are preferable; a lower alkoxy carbonyl group is more preferable; and a straight-chained or branched alkoxy carbonyl group having 2 to 5 carbon atoms is most preferable. Concretely, a methoxycarbonyl group, an ethoxycarbonyl group, an isopropoxycarbonyl group or an isobutoxycarbonyl group are preferable.

As the compounds of the present invention,  
 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxy-  
 carbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,  
 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,

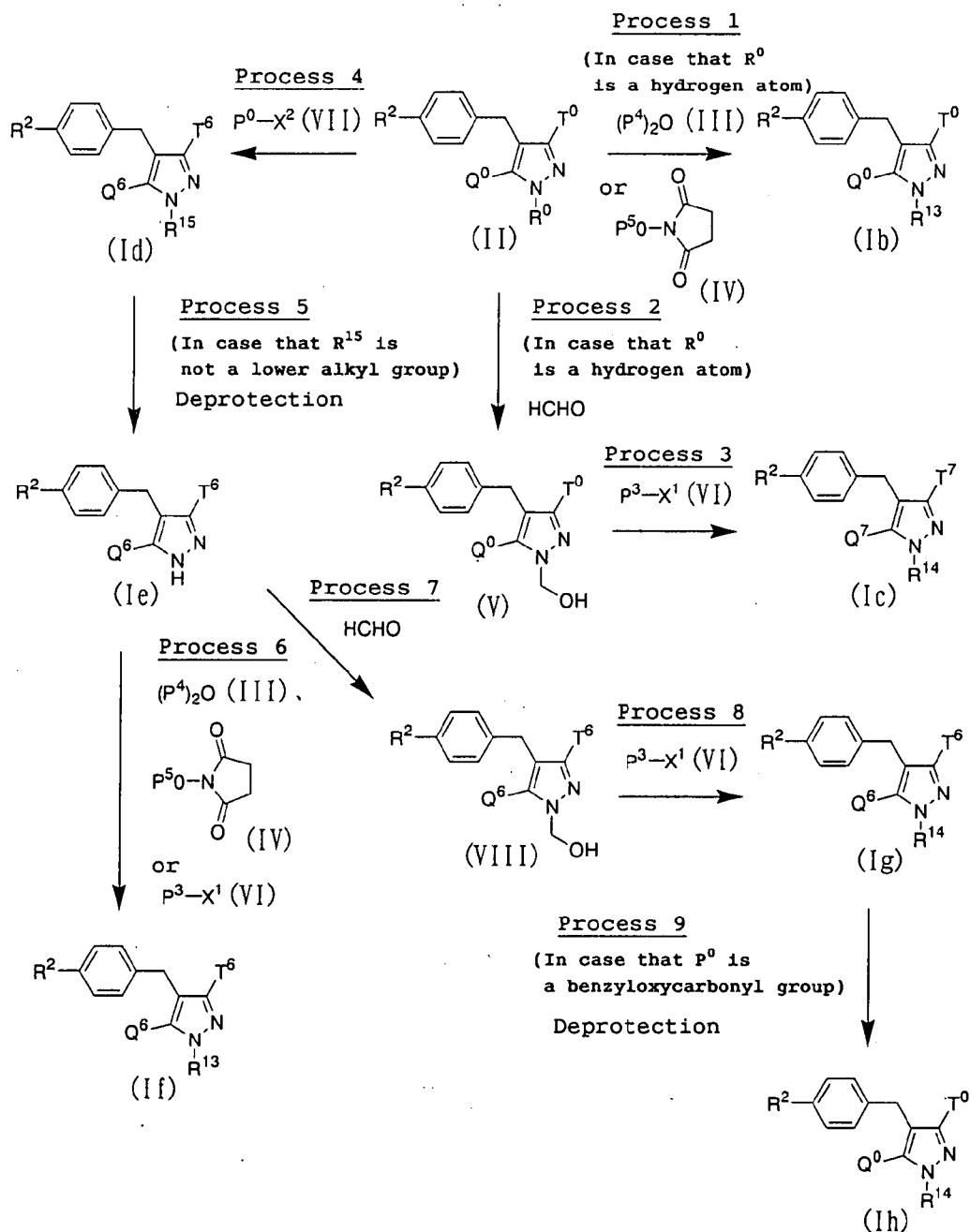
- 3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 5 4-[(4-ethylphenyl)methyl]-1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,
- 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethylphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethylphenyl)methyl]-3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 10 4-[(4-ethylphenyl)methyl]-3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,
- 15 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethoxyphenyl)methyl]-3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethoxyphenyl)methyl]-3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 20 1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,
- 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,
- 25 3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,
- 3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-iso-

propyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,  
1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-  
5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-  
5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-  
isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-  
isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole  
and the like, including their pharmaceutically acceptable  
salts are preferable;  
4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-  
methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,  
3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,  
3-(6-O-isopropoxyphenyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,  
3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole and  
the like, including their pharmaceutically acceptable  
salts are more preferable; and  
3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole and  
the like, including their pharmaceutically acceptable  
salts are most preferable.

The compounds represented by the above general  
formula (I) of the present invention can be prepared by  
introducing hydroxyl- and/or amino-protective groups  
capable of using generally as a prodrug into a hydroxyl  
group and/or a nitrogen atom of a  
glucopyranosyloxypyrazole derivative represented by

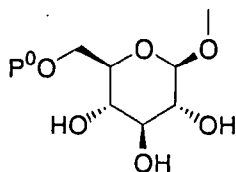
the above general formula (II) in usual way.

For example, the compounds of the present invention can be prepared using a glucopyranosyloxypyrazole derivative represented by the above general formula (II) according to the  
5 following procedure or analogous procedures thereof:

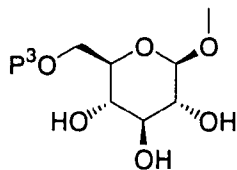


Wherein P<sup>0</sup> represents a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group, a lower alkoxy-substituted (lower alkoxycarbonyl) group or a benzyloxycarbonyl group; P<sup>3</sup> represents a lower acyl group or a lower alkoxycarbonyl group;

$P^4$  represents a lower acyl group;  $P^5$  represents a lower  
 alkoxy carbonyl group;  $R^{13}$  represents a lower acyl group or a  
 lower alkoxy carbonyl group;  $R^{14}$  represents a lower acyloxymethyl  
 group or a lower alkoxy carbonyloxymethyl group;  $R^{15}$  represents  
 5 an amino-protective group such as a lower alkyl group, a lower  
 acyl group, a lower alkoxy-substituted (lower acyl) group, a  
 lower alkoxy carbonyl-substituted (lower acyl) group, a lower  
 alkoxy carbonyl group, a lower alkoxy-substituted (lower  
 alkoxy carbonyl) group or a benzyloxycarbonyl group; one of  $Q^6$   
 10 and  $T^6$  represents a group represented by the general formula:



(wherein  $P^0$  has the same meaning as defined above), while the  
 other represents a lower alkyl group or a halo(lower alkyl) group;  
 one of  $Q^7$  and  $T^7$  represents a group represented by the general  
 15 formula:



(wherein  $P^3$  has the same meaning as defined above), while the  
 other represents a lower alkyl group or a halo(lower alkyl) group;  
 $X^1$  and  $X^2$  represent a leaving group such as a bromine atom or  
 20 a chlorine atom; and  $R^0$ ,  $R^2$ ,  $Q^0$  and  $T^0$  have the same meanings  
 as defined above.

Process 1



A prodrug represented by the above general formula (Ib) can be prepared by protecting the nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) with an aliphatic acid anhydride represented by the above general formula (III) in an aliphatic acid such as acetic acid at usually 0°C to reflux temperature for usually 30 minutes to 1 day, or alternatively, by protecting the nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) with a succinimide derivative represented by the above general formula (IV) in an inert solvent such as tetrahydrofuran at usually room temperature to reflux temperature for usually 1 hour to 1 day. The reaction time can be appropriately varied based on a used starting material, solvent and reaction temperature.

#### 15 Process 2

A compound represented by the above general formula (V) can be prepared by introducing a hydroxymethyl group into the nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) using formaldehyde in a various solvent. As the solvent used in the reaction, water, methanol, ethanol, tetrahydrofuran, dichloromethane, ethyl acetate, *N,N*-dimethylformamide, acetonitrile, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

#### 25 Process 3

A prodrug represented by the above general formula (Ic) can be prepared by protecting the hydroxymethyl group of a compound represented by the above general formula (V) with a reagent for protecting represented by the above general formula (VI) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

#### Process 4

A prodrug represented by the above general formula (Id) or an analogous compound thereof can be prepared by protecting the hydroxymethyl group, or the nitrogen atom and the hydroxymethyl group of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) with a reagent for protecting represented by the above general formula (VII) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without

any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and  
5 the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

#### Process 5

10 A prodrug represented by the above general formula (Ie) or an analogous compound thereof can be prepared by subjecting a compound represented by the above general formula (Id) to deacylation in the presence of a weak base such as sodium hydrogen carbonate, sodium carbonate or potassium carbonate in an  
15 alcoholic solvent such as methanol or ethanol. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 15 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

#### Process 6

20 A prodrug represented by the above general formula (If) or an analogous compound thereof can be prepared by protecting the nitrogen atom of a compound represented by the above general formula (Ie) with an aliphatic acid anhydride represented by the above general formula (III) in an aliphatic acid such as  
25 acetic acid at usually 0°C to reflux temperature for usually 30 minutes to 1 day, alternatively, with a succinimide derivative represented by the above general formula (IV) in an inert solvent

such as tetrahydrofuran at usually room temperature to reflux temperature for 1 hour to 1 day, and further alternatively, with a reagent for protecting represented by the above general formula (VI) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent such as dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol or a mixed solvent thereof, or without any solvent at usually -40°C to reflux temperature for 30 minutes to 2 days. The reaction time can be appropriately varied based on a used starting material, solvent and reaction temperature.

#### Process 7

A compound represented by the above general formula (VIII) can be prepared by introducing a hydroxymethyl group into the nitrogen atom of a compound represented by the above general formula (Ie) using formaldehyde in a various solvent. As the solvent used in the reaction, water, methanol, ethanol, tetrahydrofuran, dichloromethane, ethyl acetate, *N,N*-dimethylformamide, acetonitrile, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

#### Process 8

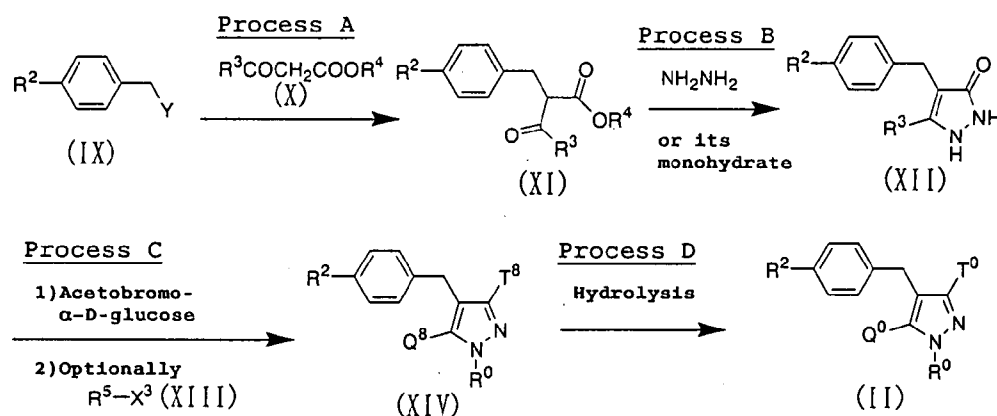
A prodrug represented by the above general formula (Ig) or an analogous compound thereof can be prepared by protecting the hydroxymethyl group of a compound represented by the above general formula (VIII) with a reagent for protecting represented by the above general formula (VI) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropylether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on a used starting material, solvent and reaction temperature.

#### Process 9

A prodrug represented by the above general formula (Ih) can be prepared by subjecting a compound represented by the above general formula (Ig) to deprotection by catalytic hydrogenation in the presence of a palladium catalyst such as palladium carbon in an inert solvent. As the inert solvent used in the reaction, methanol, ethanol, tetrahydrofuran, ethyl acetate, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based

on a used starting material, solvent and reaction temperature.

For example, the compounds represented by the above general formula (II) which are used as starting materials in the aforementioned production process can be prepared according to the following procedure:



wherein  $X^3$  and Y represent a leaving group such as a halogen atom, a mesyloxy group or a tosyloxy group;  $R^3$  represents a lower alkyl group or a halo(lower alkyl) group;  $R^4$  represents a methyl group or an ethyl group;  $R^5$  represents a lower alkyl group; one of  $Q^8$  and  $T^8$  represents a 2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy group, while the other represents a lower alkyl group or a halo(lower alkyl) group; and  $R^0$ ,  $R^2$ ,  $Q^0$  and  $T^0$  have the same meanings as defined above.

#### 15 Process A

A compound represented by the above general formula (XI) can be prepared by condensing a benzyl derivative represented by the above general formula (IX) with a ketoacetate represented by the above general formula (X) in the presence of a base such as sodium hydride or potassium *tert*-butoxide in an inert solvent.

As the inert solvent used in the reaction, 1,2-dimethoxyethane, tetrahydrofuran, *N,N*-dimethylformamide, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

#### Process B

A pyrazolone derivative represented by the above general formula (XII) can be prepared by condensing a compound represented by the above general formula (XI) with hydrazine or hydrazine monohydrate in an inert solvent. As the inert solvent used in the reaction, toluene, tetrahydrofuran, chloroform, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature. The obtained pyrazolone derivative represented by the above general formula (XII) can be also used in process C after converting into a salt thereof in usual way.

#### Process C

In case of pyrazolone derivatives represented by the above general formula (XII) wherein  $R^3$  is a lower alkyl group, a corresponding compound represented by the above general formula (XIV) can be prepared by subjecting a corresponding pyrazolone derivative represented by the above general formula (XII) to

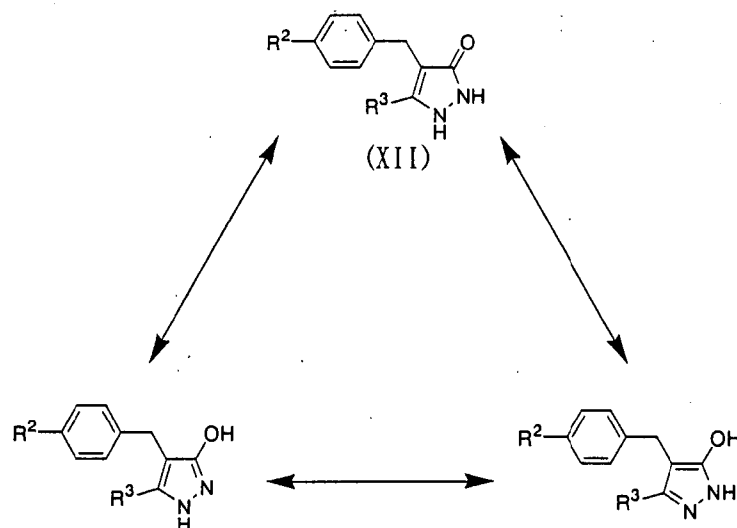
glycosidation using acetobromo- $\alpha$ -D-glucose in the presence of a base such as silver carbonate in an inert solvent, and subjecting the resulting compound to *N*-alkylation using an alkylating agent represented by the above general formula (XIII) in the presence  
5 of a base such as potassium carbonate in an inert solvent as occasion demands. As the solvent used in the glycosidation reaction, tetrahydrofuran and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to  
10 1 day, varying based on a used starting material, solvent and reaction temperature. As the solvent used in the *N*-alkylation reaction, acetonitrile, *N,N*-dimethylformamide, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to  
15 reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

In case of pyrazolone derivatives represented by the above general formula (XII) wherein  $R^3$  is a halo(lower alkyl) group,  
20 a corresponding compound represented by the above general formula (XIV) can be prepared by subjecting a corresponding pyrazolone derivative represented by the above general formula (XII) to glycosidation using acetobromo- $\alpha$ -D-glucose in the presence of a base such as potassium carbonate in an inert solvent, and  
25 subjecting the resulting compound to *N*-alkylation using an alkylating agent represented by the above general formula (XIII) in the presence of a base such as potassium carbonate in an inert



solvent as occasion demands. As the solvent used in the glycosidation reaction, acetonitrile, tetrahydrofuran and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature. As the solvent used in the *N*-alkylation reaction, acetonitrile, *N,N*-dimethylformamide, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on a used starting material, solvent and reaction temperature.

In the compound represented by the above general formula (XII) as starting materials, there are the following three tautomers, varying based on the change of reaction conditions:



wherein  $R^2$  and  $R^3$  have the same meanings as defined above.

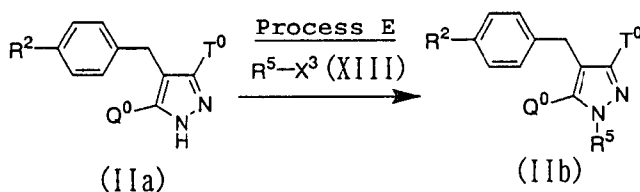
The obtained compounds represented by the above general

formula (XIV) can be also used in process D after converting into a salt thereof in usual way.

#### Process D

A glucopyranosyloxypyrazole represented by the above  
 5 general formula (II) can be prepared by subjecting a compound represented by the above general formula (XIV) to hydrolysis. As the solvent used in the reaction, methanol, ethanol, tetrahydrofuran, water, a mixed solvent thereof and the like can be illustrated, and as the base used, sodium hydroxide, sodium  
 10 ethoxide and the like can be illustrated. The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 30 minutes to 6 hours, varying based on a used starting material, solvent and reaction temperature.

15 Of the compounds represented by the above general formula (II) which are also used as starting materials in the aforementioned production process, compounds wherein the substituent  $R^0$  is a lower alkyl group can be also prepared according to the following procedure:



20

wherein  $R^2$ ,  $R^5$ ,  $Q^0$ ,  $T^0$  and  $X^3$  have the same meanings as defined above.

#### Process E

A compound represented by the above general formula (IIb)

can be prepared by subjecting a compound represented by the above general formula (IIa) to *N*-alkylation using an *N*-alkylating agent represented by the above general formula (XIII) in the presence of a base such as potassium carbonate or cesium carbonate, and  
5 occasionally a catalytic amount of sodium iodide in an inert solvent. As the inert solvent used in the reaction, *N,N*-dimethylformamide, 1,2-dimethoxyethane, dimethyl sulfoxide, tetrahydrofuran, ethanol, a mixed solvent thereof and the like can be illustrated. The reaction temperature is  
10 usually from room temperature to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature.

The compounds represented by the above general formula (I) of the present invention obtained by the above production  
15 processes can be isolated and purified by conventional separation means such as fractional recrystallization, purification using chromatography, solvent extraction and solid phase extraction.

The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention can be  
20 converted into their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, acid addition salts with organic acids such as  
25 formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic

acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, glutamic acid, aspartic acid, adipic acid, oleic acid, stearic acid and the like, and salts with inorganic bases such as a sodium salt, a potassium salt, a calcium salt, a magnesium salt and the like.

The prodrugs represented by the above general formula (I) of the present invention include their solvates with pharmaceutically acceptable solvents such as ethanol and water.

Of the compounds represented by the above general formula (I) of the present invention, there are two optical isomers, *R*-isomer and *S*-isomer, in each compound having an asymmetric carbon atom excluding the glucopyranosyloxy moiety. In the present invention, either of *R*-isomer or *S*-isomer can be employed, and a mixture of both isomers can be also employed.

The prodrugs represented by the above general formula (I) of the present invention are converted into glucopyranosyloxy pyrazole derivatives represented by the above general formula (II) as their active forms *in vivo*, and show an excellent inhibitory activity in human SGLT2. On the other hand, since WAY-123783 has an extremely weak inhibitory activity in human SGLT2, it can not be expected that it exerts an enough effect as a human SGLT2 inhibitor. In addition, the prodrugs represented by the above general formula (I) of the present invention have an improved oral absorption, and pharmaceutical compositions comprising as an active ingredient the prodrug have a highly usefulness as oral formulations. Therefore, the prodrugs of the present invention are extremely useful as agents

for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications (e.g., retinopathy, neuropathy, nephropathy, ulcer, macroangiopathy), obesity, hyperinsulinemia, glucose metabolism disorder,  
 5 hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia, gout or the like.

Furthermore, the compounds of the present invention can be suitably used in combination with at least one member selected  
 10 from drugs other than SGLT2 inhibitors. Examples of the drugs which can be used in combination with the compounds of the present invention include an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an  
 15 insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor,  
 20 a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts  
 25 formation inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid

peroxidase inhibitor, an *N*-acetylated- $\alpha$ -linked-acid-  
 dipeptidase inhibitor, insulin-like growth factor-I,  
 platelet-derived growth factor (PDGF), a platelet-derived  
 growth factor (PDGF) analogue (e.g., PDGF-AA, PDGF-BB, PDGF-AB),  
 5 epidermal growth factor (EGF), nerve growth factor, a carnitine  
 derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761,  
 bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl  
 coenzyme A reductase inhibitor, a fibric acid derivative, a  
 $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol  
 10 acyltransferase inhibitor, probcol, a thyroid hormone receptor  
 agonist, a cholesterol absorption inhibitor, a lipase inhibitor,  
 a microsomal triglyceride transfer protein inhibitor, a  
 lipoxygenase inhibitor, a carnitine palmitoyltransferase  
 inhibitor, a squalene synthase inhibitor, a low-density  
 15 lipoprotein receptor enhancer, a nicotinic acid derivative, a  
 bile acid sequestrant, a sodium/bile acid cotransporter  
 inhibitor, a cholesterol ester transfer protein inhibitor, an  
 appetite suppressant, an angiotensin-converting enzyme  
 inhibitor, a neutral endopeptidase inhibitor, an angiotensin  
 20 II receptor antagonist, an endothelin-converting enzyme  
 inhibitor, an endothelin receptor antagonist, a diuretic agent,  
 a calcium antagonist, a vasodilating antihypertensive agent,  
 a sympathetic blocking agent, a centrally acting  
 antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an  
 25 antiplatelets agent, a uric acid synthesis inhibitor, a  
 uricosuric agent and a urinary alkalinizer.

In case of uses of the compound of the present invention

in combination with the above one or more drugs, the present invention includes either dosage forms of simultaneous administration as a single preparation or separated preparations in way of same or different administration route, and  
5 administration at different dosage intervals as separated preparations in way of same or different administration route. A pharmaceutical combination comprising the compound of the present invention and the above one or more drugs includes both dosage forms as a single preparation and separated preparations  
10 for combination as mentioned above.

The compounds of the present invention can obtain more advantageous effects than additive effects in the prevention or treatment of the above diseases when using suitably in combination with the above drugs. Also, the administration dose  
15 can be decreased in comparison with administration of either drug alone, or adverse effects of coadministered drugs other than SGLT2 inhibitors can be avoided or declined.

Concrete compounds as the above drugs used for combination and preferable diseases to be treated are exemplified as follows.  
20 However, the present invention is not limited thereto, and for example, the concrete compounds include their free compounds, and their or other pharmaceutically acceptable salts.

As insulin sensitivity enhancers, peroxisome proliferator-activated receptor- $\gamma$  agonists such as  
25 troglitazone, pioglitazone hydrochloride, rosiglitazone maleate, sodium darglitazone, GI-262570, isaglitazone, LG-100641, NC-2100, T-174, DRF-2189, CLX-0921, CS-011, GW-1929,

ciglitazone, sodium englitazone and NIP-221, peroxisome proliferator-activated receptor- $\alpha$  agonists such as GW-9578 and BM-170744, peroxisome proliferator-activated receptor- $\alpha/\gamma$  agonists such as GW-409544, KRP-297, NN-622, 5 CLX-0940, LR-90, SB-219994, DRF-4158 and DRF-MDX8, retinoid X receptor agonists such as ALRT-268, AGN-4204, MX-6054, AGN-194204, LG-100754 and bexarotene, and other insulin sensitivity enhancers such as reglixane, ONO-5816, MBX-102, CRE-1625, FK-614, CLX-0901, CRE-1633, NN-2344, BM-13125, 10 BM-501050, HQL-975, CLX-0900, MBX-668, MBX-675, S-15261, GW-544, AZ-242, LY-510929, AR-H049020 and GW-501516 are illustrated. Insulin sensitivity enhancers are used preferably for diabetes, diabetic complications, obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, 15 hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for diabetes, hyper-insulinemia or glucose metabolism disorder because of improving the disturbance of insulin signal transduction in peripheral tissues and enhancing glucose uptake into the tissues 20 from the blood, leading to lowering of blood glucose level.

As glucose absorption inhibitors,  $\alpha$ -glucosidase inhibitors such as acarbose, voglibose, miglitol, CKD-711, emiglitate, MDL-25,637, camiglibose and MDL-73,945, and  $\alpha$ -amylase inhibitors such as AZM-127 are illustrated. Glucose 25 absorption inhibitors are used preferably for diabetes, diabetic complications, obesity, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism



disorder because of inhibiting the gastrointestinal enzymatic digestion of carbohydrates contained in foods, and inhibiting or delaying the absorption of glucose into the body.

As biguanides, phenformin, buformin hydrochloride,  
 5 metformin hydrochloride or the like are illustrated.  
 Biguanides are used preferably for diabetes, diabetic complications, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes, hyperinsulinemia or glucose metabolism disorder because of lowering blood glucose  
 10 level by inhibitory effects on hepatic gluconeogenesis, accelerating effects on anaerobic glycolysis in tissues or improving effects on insulin resistance in peripheral tissues.

As insulin secretion enhancers, tolbutamide, chlor-propamide, tolazamide, acetohexamide, glyclopyramide,  
 15 glyburide (glibenclamide), gliclazide, 1-butyl-3-metanilyl-urea, carbutamide, glibornuride, glipizide, gliquidone, glisoxapide, glybuthiazol, glybuzole, glyhexamide, sodium glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride, nateglinide, mitiglinide calcium hydrate,  
 20 repaglinide or the like are illustrated. Insulin secretion enhancers are used preferably for diabetes, diabetic complications or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder because of lowering blood glucose level by acting on pancreatic  $\beta$ -cells  
 25 and enhancing the insulin secretion.

As insulin preparations, human insulin, human insulin analogues, animal-deprived insulin or the like are illustrated.

Insulin preparations are used preferably for diabetes, diabetic complications or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder.

As glucagon receptor antagonists, BAY-27-9955,  
5 NNC-92-1687 or the like are illustrated; as insulin receptor kinase stimulants, TER-17411, L-783281, KRX-613 or the like are illustrated; as tripeptidyl peptidase II inhibitors, UCL-1397 or the like are illustrated; as dipeptidyl peptidase IV inhibitors, NVP-DPP728A, TSL-225, P-32/98 or the like are  
10 illustrated; as protein tyrosine phosphatase 1B inhibitors, PTP-112, OC-86839, PNU-177496 or the like are illustrated; as glycogen phosphorylase inhibitors, NN-4201, CP-368296 or the like are illustrated; as fructose-bisphosphatase inhibitors, R-132917 or the like are illustrated; as pyruvate dehydrogenase  
15 inhibitors, AZD-7545 or the like are illustrated; as hepatic gluconeogenesis inhibitors, FR-225659 or the like are illustrated; as glucagon-like peptide-1 analogues, exendin-4, CJC-1131 or the like are illustrated; as glucagon-like peptide 1 agonists; AZM-134, LY-315902 or the like are illustrated; and  
20 as amylin, amylin analogues or amylin agonists, pramlintide acetate or the like are illustrated. These drugs, glucose-6-phosphatase inhibitors, D-chiroinsitol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1 are used preferably for diabetes, diabetic complications,  
25 hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder.

As aldose reductase inhibitors, ascorbyl gamolenate,

tolrestat, epalrestat, ADN-138, BAL-ARI8, ZD-5522, ADN-311, GP-1447, IDD-598, fidarestat, sorbinil, ponalrestat, risarestat, zenarestat, minalrestat, methosorbinil, AL-1567, imirestat, M-16209, TAT, AD-5467, zopolrestat, AS-3201, NZ-314, SG-210, JTT-811, lindolrestat or the like are illustrated. Aldose reductase inhibitors are preferably used for diabetic complications because of inhibiting aldose reductase and lowering excessive intracellular accumulation of sorbitol in accelerated polyol pathway which are in continuous hyperglycemic condition in the tissues in diabetic complications.

As advanced glycation endproducts formation inhibitors, pyridoxamine, OPB-9195, ALT-946, ALT-711, pimagedine hydrochloride or the like are illustrated. Advanced glycation endproducts formation inhibitors are preferably used for diabetic complications because of inhibiting formation of advanced glycation endproducts which are accelerated in continuous hyperglycemic condition in diabetes and declining of cellular damage.

As protein kinase C inhibitors, LY-333531, midostaurin or the like are illustrated. Protein kinase C inhibitors are preferably used for diabetic complications because of inhibiting of protein kinase C activity which is accelerated in continuous hyperglycemic condition in diabetes.

As  $\gamma$ -aminobutyric acid receptor antagonists, topiramate or the like are illustrated; as sodium channel antagonists, mexiletine hydrochloride, oxcarbazepine or the like are illustrated; as transcrit factor NF- $\kappa$ B inhibitors, dextrilipotam

or the like are illustrated; as lipid peroxidase inhibitors, tirilazad mesylate or the like are illustrated; as N-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitors, GPI-5693 or the like are illustrated; and as carnitine derivatives, 5 carnitine, levacecarnine hydrochloride, levocarnitine chloride, levocarnitine, ST-261 or the like are illustrated. These drugs, insulin-like growth factor-I, platelet-derived growth factor, platelet derived growth factor analogues, epidermal growth factor, nerve growth factor, uridine, 5-hydroxy-1-methyl- 10 hidantoin, EGB-761, bimoclomol, sulodexide and Y-128 are preferably used for diabetic complications.

As hydroxymethylglutaryl coenzyme A reductase inhibitors, sodium cerivastatin, sodium pravastatin, lovastatin, simvastatin, sodium fluvastatin, atorvastatin calcium hydrate, 15 SC-45355, SQ-33600, CP-83101, BB-476, L-669262, S-2468, DMP-565, U-20685, BAY-x-2678, BAY-10-2987, calcium pitavastatin, calcium rosuvastatin, colestolone, dalvastatin, acitemate, mevastatin, crilvastatin, BMS-180431, BMV-21950, glenvastatin, carvastatin, BMV-22089, bervastatin or the like are illustrated. 20 Hydroxymethylglutaryl coenzyme A reductase inhibitors are used preferably for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypercholesterolemia or atherosclerosis because of lowering 25 blood cholesterol level by inhibiting hydroxymethylglutaryl coenzyme A reductase.

As fibric acid derivatives, bezafibrate, beclobate,

binifibrate, ciprofibrate, clinofibrate, clofibrate, aluminum clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, AHL-157 or the like are illustrated. Fibric acid derivatives are used preferably for hyper-insulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypertriglyceridemia or atherosclerosis because of activating hepatic lipoprotein lipase and enhancing fatty acid oxidation, leading to lowering of blood triglyceride level.

As  $\beta_3$ -adrenoceptor agonists, BRL-28410, SR-58611A, ICI-198157, ZD-2079, BMS-194449, BRL-37344, CP-331679, CP-114271, L-750355, BMS-187413, SR-59062A, BMS-210285, LY-377604, SWR-0342SA, AZ-40140, SB-226552, D-7114, BRL-35135, FR-149175, BRL-26830A, CL-316243, AJ-9677, GW-427353, N-5984, GW-2696 or the like are illustrated.  $\beta_3$ -Adrenoceptor agonists are used preferably for obesity, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder, and more preferably for obesity or hyperinsulinemia because of stimulating  $\beta_3$ -adrenoceptor in adipose tissue and enhancing the fatty acid oxidation, leading to induction of energy expenditure.

As acyl-coenzyme A cholesterol acyltransferase inhibitors, NTE-122, MCC-147, PD-132301-2, DUP-129, U-73482, U-76807, RP-70676, P-06139, CP-113818, RP-73163, FR-129169, FY-038, EAB-309, KY-455, LS-3115, FR-145237, T-2591, J-104127,

R-755, FCE-28654, YIC-C8-434, avasimibe, CI-976, RP-64477, F-1394, eldacimibe, CS-505, CL-283546, YM-17E, lecimibide, 447C88, YM-750, E-5324, KW-3033, HL-004, eflucimibe or the like are illustrated. Acyl-coenzyme A cholesterol acyltransferase inhibitors are used preferably for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder, and more preferably for hyperlipidemia or hypercholesterolemia because of lowering blood cholesterol level by inhibiting acyl-coenzyme A cholesterol acyltransferase.

As thyroid hormone receptor agonists, sodium liothyronine, sodium levothyroxine, KB-2611 or the like are illustrated; as cholesterol absorption inhibitors, ezetimibe, SCH-48461 or the like are illustrated; as lipase inhibitors, orlistat, ATL-962, AZM-131, RED-103004 or the like are illustrated; as carnitine palmitoyltransferase inhibitors, etomoxir or the like are illustrated; as squalene synthase inhibitors, SDZ-268-198, BMS-188494, A-87049, RPR-101821, ZD-9720, RPR-107393, ER-27856 or the like are illustrated; as nicotinic acid derivatives, nicotinic acid, nicotinamide, nicomol, niceritrol, acipimox, nicorandil or the like are illustrated; as bile acid sequestrants, colestyramine, colestilan, colesevelam hydrochloride, GT-102-279 or the like are illustrated; as sodium/bile acid cotransporter inhibitors, 264W94, S-8921, SD-5613 or the like are illustrated; and as cholesterol ester transfer protein inhibitors, PNU-107368E, SC-795, JTT-705, CP-529414 or the like are illustrated. These drugs, probcol, microsomal triglyceride transfer protein inhibitors, lipoxigenase inhibitors and

low-density lipoprotein receptor enhancers are preferably used for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder.

As appetite suppressants, monoamine reuptake inhibitors, serotonin reuptake inhibitors, serotonin releasing stimulants, serotonin agonists (especially 5HT<sub>2C</sub>-agonists), noradrenaline reuptake inhibitors, noradrenaline releasing stimulants,  $\alpha_1$ -adrenoceptor agonists,  $\beta_2$ -adrenoceptor agonists, dopamine agonists, cannabinoid receptor antagonists,  $\gamma$ -aminobutyric acid receptor antagonists, H<sub>3</sub>-histamine antagonists, L-histidine, leptin, leptin analogues, leptin receptor agonists, melanocortin receptor agonists (especially, MC3-R agonists, MC4-R agonists),  $\alpha$ -melanocyte stimulating hormone, cocaine-and amphetamine-regulated transcript, mahogany protein, enterostatin agonists, calcitonin, calcitonin-gene-related peptide, bombesin, cholecystokinin agonists (especially CCK-A agonists), corticotropin-releasing hormone, corticotrophin-releasing hormone analogues, corticotropin-releasing hormone agonists, urocortin, somatostatin, somatostatin analogues, somatostatin receptor agonists, pituitary adenylate cyclase-activating peptide, brain-derived neurotrophic factor, ciliary neurotrophic factor, thyrotropin-releasing hormone, neurotensin, sauvagine, neuropeptide Y antagonists, opioid peptide antagonists, galanin antagonists, melanin-concentrating hormone antagonists, agouti-related protein inhibitors and orexin receptor antagonists are illustrated. Concretely, as monoamine reuptake inhibitors, mazindol or the

like are illustrated; as serotonin reuptake inhibitors, dexfenfluramine hydrochloride, fenfluramine, sibutramine hydrochloride, fluvoxamine maleate, sertraline hydrochloride or the like are illustrated; as serotonin agonists, inotriptan, 5 (+)-norfenfluramine or the like are illustrated; as noradrenaline reuptake inhibitors, bupropion, GW-320659 or the like are illustrated; as noradrenaline releasing stimulants, rolipram, YM-992 or the like are illustrated; as  $\beta_2$ -adrenoceptor agonists, amphetamine, dextroamphetamine, phentermine, 10 benzphetamine, methamphetamine, phendimetrazine, phenmetrazine, diethylpropion, phenylpropanolamine, clobenzorex or the like are illustrated; as dopamine agonists, ER-230, doprexin, bromocriptine mesylate or the like are illustrated; as cannabinoid receptor antagonists, rimonabant 15 or the like are illustrated; as  $\gamma$ -aminobutyric acid receptor antagonists, topiramate or the like are illustrated; as  $H_3$ -histamine antagonists, GT-2394 or the like are illustrated; as leptin, leptin analogues or leptin receptor agonists, LY-355101 or the like are illustrated; as cholecystokinin 20 agonists (especially CCK-A agonists), SR-146131, SSR-125180, BP-3.200, A-71623, FPL-15849, GI-248573, GW-7178, GI-181771, GW-7854, A-71378 or the like are illustrated; and as neuropeptide Y antagonists, SR-120819-A, PD-160170, NGD-95-1, BIBP-3226, 1229-U-91, CGP-71683, BIBO-3304, CP-671906-01, J-115814 or the 25 like are illustrated. Appetite suppressants are used preferably for diabetes, diabetic complications, obesity, glucose metabolism disorder, hyperlipidemia, hyper-



cholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia or gout, and more preferably for obesity because of stimulating or inhibiting the activities of  
5 intracerebral monoamines or bioactive peptides in central appetite regulatory system and suppressing the appetite, leading to reduction of energy intake.

As angiotensin-converting enzyme inhibitors, captopril, enalapril maleate, alacepril, delapril hydrochloride, ramipril,  
10 lisinopril, imidapril hydrochloride, benazepril hydrochloride, ceronapril monohydrate, cilazapril, sodium fosinopril, perindopril erbumine, calcium moveltipril, quinapril hydrochloride, spirapril hydrochloride, temocapril hydrochloride, trandolapril, calcium zofenopril, moexipril hydrochloride,  
15 rentiapril or the like are illustrated. Angiotensin-converting enzyme inhibitors are preferably used for diabetic complications or hypertension.

As neutral endopeptidase inhibitors, omapatrilat, MDL-100240, fasidotril, sampatrilat, GW-660511X, mixanpril,  
20 SA-7060, E-4030, SLV-306, ecadotril or the like are illustrated. Neutral endopeptidase inhibitors are preferably used for diabetic complications or hypertension.

As angiotensin II receptor antagonists, candesartan cilexetil, candesartan cilexetil/hydrochlorothiazide,  
25 potassium losartan, eprosartan mesylate, valsartan, telmisartan, irbesartan, EXP-3174, L-158809, EXP-3312, olmesartan, tasosartan, KT-3-671, GA-0113, RU-64276, EMD-90423,

BR-9701 or the like are illustrated. Angiotensin II receptor antagonists are preferably used for diabetic complications or hypertension.

As endothelin-converting enzyme inhibitors, CGS-31447,  
 5 CGS-35066, SM-19712 or the like are illustrated; as endothelin receptor antagonists, L-749805, TBC-3214, BMS-182874, BQ-610, TA-0201, SB-215355, PD-180988, sodium sitaxsentan, BMS-193884, darusentan, TBC-3711, bosentan, sodium tezosentan, J-104132, YM-598, S-0139, SB-234551, RPR-118031A, ATZ-1993, RO-61-1790,  
 10 ABT-546, enlasentan, BMS-207940 or the like are illustrated. These drugs are preferably used for diabetic complications or hypertension, and more preferably for hypertension.

As diuretic agents, chlorthalidone, metolazone, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide,  
 15 hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, indapamide, tripamide, mefruside, azosemide, etacrynic acid, torasemide, piretanide, furosemide, bumetanide, meticrane, potassium canrenoate, spironolactone, triamterene, aminophylline, cicletanine hydrochloride, LLU- $\alpha$ , PNU-80873A,  
 20 isosorbide, D-mannitol, D-sorbitol, fructose, glycerin, acetazolamide, methazolamide, FR-179544, OPC-31260, lixivaptan, conivaptan hydrochloride or the like are illustrated. Diuretic drugs are preferably used for diabetic complications, hypertension, congestive heart failure or edema, and more  
 25 preferably for hypertension, congestive heart failure or edema because of reducing blood pressure or improving edema by increasing urinary excretion.

As calcium antagonists, aranidipine, efonidipine hydrochloride, nicardipine hydrochloride, barnidipine hydrochloride, benidipine hydrochloride, manidipine hydrochloride, cilnidipine, nisoldipine, nitrendipine, 5 nifedipine, nilvadipine, felodipine, amlodipine besilate, pranidipine, lercanidipine hydrochloride, isradipine, elgodipine, azelnidipine, lacidipine, vatanidipine hydrochloride, lemlidipine, diltiazem hydrochloride, clentiazem maleate, verapamil hydrochloride, S-verapamil, 10 fasudil hydrochloride, bepridil hydrochloride, gallopamil hydrochloride or the like are illustrated; as vasodilating antihypertensive agents, indapamide, todralazine hydrochloride, hydralazine hydrochloride, cadralazine, budralazine or the like are illustrated; as sympathetic blocking agents, amosulalol 15 hydrochloride, terazosin hydrochloride, bunazosin hydrochloride, prazosin hydrochloride, doxazosin mesylate, propranolol hydrochloride, atenolol, metoprolol tartrate, carvedilol, nipradilol, celiprolol hydrochloride, nebivolol, betaxolol hydrochloride, pindolol, tertatolol hydrochloride, 20 bevantolol hydrochloride, timolol maleate, carteolol hydrochloride, bisoprolol hemifumarate, bopindolol malonate, nipradilol, penbutolol sulfate, acebutolol hydrochloride, tilisolol hydrochloride, nadolol, urapidil, indoramin or the like are illustrated; as centrally acting antihypertensive 25 agents, reserpine or the like are illustrated; and as  $\alpha_2$ -adrenoceptor agonists, clonidine hydrochloride, methyldopa, CHF-1035, guanabenz acetate, guanfacine

hydrochloride, moxonidine, lofexidine, talipexole hydrochloride or the like are illustrated. These drugs are preferably used for hypertension.

As antiplatelets agents, ticlopidine hydrochloride, 5 dipyridamole, cilostazol, ethyl icosapentate, sarpogrelate hydrochloride, dilazep dihydrochloride, trapidil, beraprost sodium, aspirin or the like are illustrated. Antiplatelets agents are preferably used for atherosclerosis or congestive heart failure.

10 As uric acid synthesis inhibitors, allopurinol, oxypurinol or the like are illustrated; as uricosuric agents, benzbromarone, probenecid or the like are illustrated; and as urinary alkalizers, sodium hydrogen carbonate, potassium citrate, sodium citrate or the like are illustrated. These drugs 15 are preferably used for hyperuricemia or gout.

In case of use in combination with drugs other than SGLT2 inhibitors, for example, in the use for diabetes, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a 20 biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6- 25 phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3

inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1  
analogue, a glucagon-like peptide-1 agonist, amylin, an amylin  
analogue, an amylin agonist and an appetite suppressant is  
preferable; the combination with at least one member of the group  
5 consisting of an insulin sensitivity enhancer, a glucose  
absorption inhibitor, a biguanide, an insulin secretion enhancer,  
an insulin preparation, a glucagon receptor antagonist, an  
insulin receptor kinase stimulant, a tripeptidyl peptidase II  
inhibitor, a dipeptidyl peptidase IV inhibitor, a protein  
10 tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase  
inhibitor, a glucose-6-phosphatase inhibitor, a fructose-  
biphosphatase inhibitor, a pyruvate dehydrogenase inhibitor,  
a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen  
synthase kinase-3 inhibitor, glucagon-like peptide-1, a  
15 glucagon-like peptide-1 analogue, a glucagon-like peptide-1  
agonist, amylin, an amylin analogue and an amylin agonist is  
more preferable; and the combination with at least one member  
of the group consisting of an insulin sensitivity enhancer, a  
glucose absorption inhibitor, a biguanide, an insulin secretion  
20 enhancer and an insulin preparation is most preferable.  
Similarly, in the use for diabetic complications, the combination  
with at least one member of the group consisting of an insulin  
sensitivity enhancer, a glucose absorption inhibitor, a  
biguanide, an insulin secretion enhancer, an insulin preparation,  
25 a glucagon receptor antagonist, an insulin receptor kinase  
stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl  
peptidase IV inhibitor, a protein tyrosine phosphatase-1B

inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, glycogen synthase kinase-3

5 inhibitors, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid antagonist, a sodium

10 channel antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a

15 carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimoclomol, sulodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a

20 diuretic agent is preferable; and the combination with at least one member of the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist is more preferable. Furthermore, in the use for

25 obesity, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer,

an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a  $\beta_3$ -adrenoceptor agonist and an appetite suppressant is preferable; and the combination with at least one member of the group consisting of a  $\beta_3$ -adrenoceptor agonist and an appetite suppressant is more preferable.

When the pharmaceutical compositions of the present invention are employed in the practical treatment, various dosage forms are used depending on their uses. As examples of the dosage forms, powders, granules, fine granules, dry sirups, tablets, capsules, injections, solutions, ointments, suppositories, poultices and the like are illustrated, which are orally or parenterally administered.

These pharmaceutical compositions can be prepared by admixing with or by diluting and dissolving an appropriate pharmaceutical additive such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents, dissolving aids and the like, and formulating

the mixture in accordance with conventional. In case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, they can be prepared by formulating each active ingredient together or individually.

5        When the pharmaceutical compositions of the present invention are employed in the practical treatment, the dosage of a compound represented by the above general formula (I) or a pharmaceutically acceptable salt thereof as the active ingredient is appropriately decided depending on the age, sex,  
10   body weight and degree of symptoms and treatment of each patient, which is approximately within the range of from 0.1 to 1,000mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 300mg per day per adult human in the case of parenteral administration, and  
15   the daily dose can be divided into one to several doses per day and administered suitably. Also, in case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, the dosage of the compound of the present invention can be decreased appropriately and  
20   occasionally depending on the dosage of the drugs other than SGLT2 inhibitors.

      The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test  
25   Examples. However, the present invention is not limited thereto.



## Reference Example 1

1,2-Dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one

To a solution of 4-isopropoxybenzylalcohol (0.34g) in tetrahydrofuran (6mL) were added triethylamine (0.28mL) and methanesulfonyl chloride (0.16mL), and the mixture was stirred at room temperature for 30 minutes. The resulting insoluble material was removed by filtration. The obtained solution of 4-isopropoxybenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 81mg) and methyl acetoacetate (0.20mL) in 1,2-dimethoxyethane (10mL), and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (5mL). Anhydrous hydrazine (0.19mL) was added to the solution, and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one (95mg).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.22 (6H, d, J=6.0Hz), 1.99 (3H, s), 3.45 (2H, s), 4.40-4.60 (1H, m), 6.65-6.80 (2H, m), 6.95-7.10 (2H, m)

## Reference Example 2

1,2-Dihydro-5-methyl-4-[(4-propylphenyl)methyl]-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-propylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

0.75-0.95 (3H, m), 1.45-1.65 (2H, m), 1.99 (3H, s), 2.40-2.55 (2H, m), 3.32 (2H, s), 6.95-7.10 (4H, m)

10

## Reference Example 3

1,2-Dihydro-4-[(4-isobutylphenyl)methyl]-5-methyl-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-isobutylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

0.83 (6H, d, J=6.6Hz), 1.70-1.85 (1H, m), 1.99 (3H, s), 2.30-2.45 (2H, m), 3.50 (2H, s), 6.90-7.10 (4H, m)

20

## Reference Example 4

1,2-Dihydro-5-methyl-4-[(4-propoxyphenyl)methyl]-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-propoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

0.95 (3H, t, J=7.4Hz), 1.60-1.75 (2H, m), 1.98 (3H, s), 3.46 (2H, s), 3.75-3.90 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

5 Reference Example 5

4-[(4-Ethoxyphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-ethoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.20-1.35 (3H, m), 1.98 (3H, s), 3.46 (2H, s), 3.85-4.05 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

15 Reference Example 6

1,2-Dihydro-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-trifluoromethylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

2.02 (3H, s), 3.64 (2H, s), 7.30-7.45 (2H, m), 7.55-7.70 (2H, m)

25 Reference Example 7

4-[(4-tert-Butylphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-*tert*-butylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

5 1.24 (9H, s), 2.01 (3H, s), 3.49 (2H, s), 7.00-7.15 (2H, m),  
7.15-7.30 (2H, m)

#### Reference Example 8

4-[(4-Butoxyphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-  
10 3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-butoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

15 0.91 (3H, t, J=7.4Hz), 1.30-1.50 (2H, m), 1.55-1.75 (2H, m),  
1.98 (3H, s), 3.46 (2H, s), 3.80-3.95 (2H, m), 6.70-6.85 (2H, m),  
6.95-7.10 (2H, m)

#### Reference Example 9

20 1,2-Dihydro-5-methyl-4-[(4-methylthiophenyl)methyl]-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-(methylthio)benzyl alcohol instead of 4-isopropoxybenzyl alcohol.

25 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.99 (3H, s), 2.42 (3H, s), 3.50 (2H, s), 7.05-7.20 (4H, m)

## Reference Example 10

5-Ethyl-1,2-dihydro-4-[(4-methylthiophenyl)methyl]-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-(methylthio)benzyl alcohol instead of 4-isopropoxybenzyl alcohol and using methyl 3-oxopentanoate instead of methyl acetoacetate.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.02 (3H, t, J=7.6Hz), 2.39 (2H, q, J=7.6Hz), 2.42 (3H, s), 3.51  
10 (2H, s), 7.05-7.20 (4H, m)

## Reference Example 11

1,2-Dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3H-pyrazol-3-one

15 To a suspension of sodium hydride (60%, 40mg) in 1,2-dimethoxyethane (1mL) were added methyl acetoacetate (0.11mL), 4-isopropylbenzyl chloride (0.17g) and a catalytic amount of sodium iodide, and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated  
20 aqueous sodium hydrogen carbonate solution, and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (1mL). Anhydrous hydrazine (0.094mL) was added to  
25 the solution, and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent:

dichloromethane/methanol = 10/1) to give 1,2-dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3H-pyrazol-3-one (0.12g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.16 (6H, d, J=6.9Hz), 2.01 (3H, s), 2.70-2.90 (1H, m), 3.49  
5 (2H, s), 6.95-7.20 (4H, m)

#### Reference Example 12

4-[(4-Ethylphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

10        The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-ethylbenzyl chloride instead of 4-isopropylbenzyl chloride.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.13 (3H, t, J=7.6Hz), 2.00 (3H, s), 2.45-2.60 (2H, m), 3.49  
15 (2H, s), 7.00-7.15 (4H, m)

#### Reference Example 13

1,2-Dihydro-5-methyl-4-[(4-methylphenyl)methyl]-3H-pyrazol-3-one

20        The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-methylbenzyl bromide instead of 4-isopropylbenzyl chloride.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.98 (3H, s), 2.23 (3H, s), 3.48 (2H, s), 6.95-7.10 (4H, m)  
25

#### Reference Example 14

4-Benzyl-1,2-dihydro-5-trifluoromethyl-3H-pyrazol-3-one

The title compound was prepared in a similar manner to that described in Reference Example 11 using ethyl trifluoroacetoacetate instead of methyl acetoacetate and using benzyl bromide instead of 4-isopropylbenzyl chloride.

5 <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

3.73 (2H, s), 7.05-7.35 (5H, m), 12.50-13.10 (1H, brs)

#### Reference Example 15

1,2-Dihydro-4-[(4-methoxyphenyl)methyl]-5-methyl-3H-pyrazol  
10 -3-one

The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-methoxybenzyl bromide instead of 4-isopropylbenzyl chloride.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

15 1.99 (3H, s), 3.47 (2H, s), 3.69 (3H, s), 6.75-6.85 (2H, m),  
7.00-7.10 (2H, m), 8.70-11.70 (2H, br)

#### Reference Example 16

4-Benzyl-1,2-dihydro-5-methyl-3H-pyrazol-3-one

20 The title compound was prepared in a similar manner to that described in Reference Example 11 using benzyl bromide instead of 4-isopropylbenzyl chloride.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

2.00 (3H, s), 3.54 (2H, s), 7.05-7.30 (5H, s)

25

#### Reference Example 17

4-[(4-Isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-

acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole

To a suspension of 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3H-pyrazol-3-one (46mg), acetobromo- $\alpha$ -D-glucose (99mg) and 4A molecular sieves in tetrahydrofuran (3mL) was added silver carbonate (66mg), and the mixture was stirred under shading the light at 65°C overnight. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran). Further purification by preparative thin layer chromatography on silica gel (developing solvent: ethyl acetate/hexane = 2/1) afforded 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole (42mg).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

1.25-1.35 (6H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.80-3.90 (1H, m), 4.13 (1H, dd,  $J=2.3, 12.4\text{Hz}$ ), 4.31 (1H, dd,  $J=4.0, 12.4\text{Hz}$ ), 4.40-4.55 (1H, m), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.05 (2H, m).

## 20 Reference Example 18

5-Methyl-4-[(4-propylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-propylphenyl)methyl]-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.



<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

0.91 (3H, t, J=7.3Hz), 1.50-1.65 (2H, m), 1.86 (3H, s), 2.01  
 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.45-2.55  
 (2H, m), 3.55 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90  
 5 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.30 (1H, dd, J=3.9, 12.4Hz),  
 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 7.00-7.20 (4H, m)

#### Reference Example 19

4-[(4-Isobutylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-  
 10 acetyl-β-D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to  
 that described in Reference Example 17 using 1,2-dihydro-4-  
 [(4-isobutylphenyl)methyl]-5-methyl-3H-pyrazol-3-one  
 instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-  
 15 methyl-3H-pyrazol-3-one.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

0.87 (6H, d, J=6.6Hz), 1.70-1.85 (1H, m), 1.87 (3H, s), 2.01  
 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.40 (2H,  
 d, J=7.2Hz), 3.56 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz),  
 20 3.80-3.90 (1H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd,  
 J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.95-7.10  
 (4H, m)

#### Reference Example 20

25 5-Methyl-4-[(4-propoxyphenyl)methyl]-3-(2,3,4,6-tetra-O-  
 acetyl-β-D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to

that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-propoxyphenyl)methyl]-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one

5  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

1.01 (3H, t,  $J=7.4\text{Hz}$ ), 1.70-1.85 (2H, m), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.53 (1H, d,  $J=15.7\text{Hz}$ ), 3.59 (1H, d,  $J=15.7\text{Hz}$ ), 3.80-3.95 (3H, m), 4.14 (1H, dd,  $J=2.3, 12.4\text{Hz}$ ), 4.31 (1H, dd,  $J=4.0, 12.4\text{Hz}$ ), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m).

#### Reference Example 21

4-[(4-Ethoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-ethoxyphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

1.38 (3H, t,  $J=7.0\text{Hz}$ ), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.53 (1H, d,  $J=15.8\text{Hz}$ ), 3.59 (1H, d,  $J=15.8\text{Hz}$ ), 3.80-3.90 (1H, m), 3.98 (2H, q,  $J=7.0\text{Hz}$ ), 4.13 (1H, dd,  $J=2.3, 12.4\text{Hz}$ ), 4.31 (1H, dd,  $J=4.0, 12.4$ ), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

## Reference Example 22

5-Methyl-3-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyloxy)-  
4-[(4-trifluoromethylphenyl)methyl]-1*H*-pyrazole

5        The title compound was prepared in a similar manner to  
that described in Reference Example 17 using 1,2-dihydro-5-  
methyl-4-[(4-trifluoromethylphenyl)methyl]-3*H*-pyrazol-3-one  
instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-  
methyl-3*H*-pyrazol-3-one.

10         $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.14  
(3H, s), 3.65 (1H, d,  $J=15.9\text{Hz}$ ), 3.71 (1H, d,  $J=15.9\text{Hz}$ ), 3.80-3.90  
(1H, m), 4.14 (1H, dd,  $J=2.4, 12.4\text{Hz}$ ), 4.31 (1H, dd,  $J=4.0, 12.4\text{Hz}$ ),  
5.15-5.40 (3H, m), 5.55-5.65 (1H, m), 7.20-7.30 (2H, m),  
15    7.45-7.55 (2H, m)

## Reference Example 23

4-[(4-*tert*-Butylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-  
acetyl- $\beta$ -D-glucopyranosyloxy)-1*H*-pyrazole

20        The title compound was prepared in a similar manner to  
that described in Reference Example 17 using 4-[(4-*tert*-butyl-  
phenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one  
instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-  
methyl-3*H*-pyrazol-3-one.

25         $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

1.27 (9H, s), 1.84 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06  
(3H, s), 2.14 (3H, s), 3.56 (1H, d,  $J=15.8\text{Hz}$ ), 3.64 (1H, d,

J=15.8Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 7.00-7.10 (2H, m), 7.20-7.30 (2H, m)

5 Reference Example 24

4-[(4-Butoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-butoxyphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one  
10 instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

0.96 (3H, t, J=7.4Hz), 1.40-1.55 (2H, m), 1.65-1.80 (2H, m),  
15 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.52 (1H, d, J=15.8Hz), 3.59 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 3.91 (2H, t, J=6.5Hz), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

20

Reference Example 25

5-Methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-methylthiophenyl)methyl]-3H-pyrazol-3-one  
25 instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-

methyl-3*H*-pyrazol-3-one.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.07 (3H, s), 2.12  
(3H, s), 2.44 (3H, s), 3.50-3.65 (2H, m), 3.80-3.90 (1H, m),  
5 4.13 (1H, dd, J=2.4, 12.4Hz), 4.31 (1H, dd, J=4.1, 12.4Hz),  
5.15-5.30 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20  
(2H, m), 8.65-8.85 (1H, brs)

#### Reference Example 26

10 5-Ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-  
acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

The title compound was prepared in a similar manner to  
that described in Reference Example 17 using 5-ethyl-1,2-  
dihydro-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one  
15 instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-  
methyl-3*H*-pyrazol-3-one.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.13 (3H, t, J=7.6Hz), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H,  
s), 2.06 (3H, s), 2.44 (3H, s), 2.45-2.55 (2H, m), 3.50-3.70  
20 (2H, m), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd,  
J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10  
(2H, m), 7.10-7.20 (2H, m), 8.80-9.20 (1H, brs)

#### Reference Example 27

25 4-[(4-Isopropylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-  
acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

The title compound was prepared in a similar manner to

that described in Reference Example 17 using 1,2-dihydro-4-  
 [(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one  
 instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-  
 methyl-3*H*-pyrazol-3-one.

5 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.20 (6H, d, J=6.9Hz), 1.85 (3H, s), 2.01 (3H, s), 2.03 (3H,  
 s), 2.06 (3H, s), 2.13 (3H, s), 2.75-2.90 (1H, m), 3.56 (1H,  
 d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m),  
 4.05-4.20 (1H, m), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H,  
 10 m), 5.50-5.60 (1H, m), 7.00-7.15 (4H, m), 8.70-9.30 (1H, brs)

#### Reference Example 28

4-[(4-Methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-  
 D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

15 To a solution of 1,2-dihydro-4-[(4-methylthiophenyl)-  
 methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one (2.0g) in  
 acetonitrile (100mL) were added acetobromo-α-D-glucose (3.1g)  
 and potassium carbonate (1.1g), and the mixture was stirred at  
 room temperature overnight. Water was added to the reaction  
 20 mixture, and the resulting mixture was extracted with ethyl  
 acetate. The organic layer was washed with a saturated aqueous  
 sodium hydrogen carbonate solution and brine and dried over  
 anhydrous magnesium sulfate. The solvent was removed under  
 reduced pressure, and the residue was purified by column  
 25 chromatography on silica gel (eluent: hexane/ethyl acetate =  
 1/1) to give 4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-  
*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazo

le (2.0g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.91 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.45  
(3H, s), 3.73 (2H, s), 3.75-3.90 (1H, m), 4.15-4.35 (2H, m),  
5 5.15-5.65 (4H, m), 7.00-7.20 (4H, m)

#### Reference Example 29

4-Benzyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-  
5-trifluoromethyl-1H-pyrazole

10 The title compound was prepared in a similar manner to  
that described in Reference Example 28 using 4-benzyl-1,2-  
dihydro-5-trifluoromethyl-3H-pyrazol-3-one instead of  
1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-  
1-3H-pyrazol-3-one.

15 <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 3.70-3.90  
(3H, m), 4.15-4.30 (2H, m), 5.10-5.50 (4H, m), 7.10-7.30 (5H,  
m)

#### 20 Reference Example 30

4-[(4-Methoxyphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl-β-D-  
glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

The title compound was prepared in a similar manner to  
that described in Reference Example 28 using 1,2-dihydro-4-  
25 [(4-methoxyphenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-  
one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-  
trifluoromethyl-3H-pyrazol-3-one.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.93 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.65-3.75 (2H, m), 3.77 (3H, s), 3.75-3.90 (1H, m), 4.15-4.35 (2H, m), 5.10-5.45 (4H, m), 6.75-6.85 (2H, m), 7.00-7.15 (2H, m)

5

Reference Example 31

4-[(4-Methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-4-[(4-methoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.89 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.76 (3H, s), 3.80-3.90 (1H, m), 4.11 (1H, dd, J=2.2, 12.4Hz), 4.30 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.85 (2H, m), 7.00-7.10 (2H, m)

20

Reference Example 32

4-Benzyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-benzyl-1,2-dihydro-5-methyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one.



<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.11  
(3H, s), 3.59 (1H, d, J=15.8Hz), 3.66 (1H, d, J=15.8Hz), 3.80-3.90  
(1H, m), 4.11 (1H, dd, J=2.3, 12.4Hz), 4.30 (1H, dd, J=4.0, 12.4Hz),  
5 5.15-5.30 (3H, m), 5.50-5.65 (1H, m), 7.05-7.30 (5H, m),  
8.75-9.55 (1H, brs)

### Reference Example 33

4-[(4-Methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-  
10 O-acetyl-β-D-glucopyranosyloxy)pyrazole

A suspension of 4-[(4-methoxyphenyl)methyl]-5-methyl-3-  
(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole  
(18mg), potassium carbonate (14mg) and iodomethane (4.7mg) in  
acetonitrile (2mL) was stirred at 75°C overnight. The reaction  
15 mixture was filtered through celite®, and the solvent of the  
filtrate was removed under reduced pressure. The residue was  
purified by preparative thin layer chromatography on silica gel  
(developing solvent: benzene/acetone = 2/1) to give  
4-[(4-methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-  
20 O-acetyl-β-D-glucopyranosyloxy)pyrazole (4mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.90 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.07  
(3H, s), 3.45-3.60 (2H, m), 3.60 (3H, s), 3.76 (3H, s), 3.80-3.90  
(1H, m), 4.13 (1H, dd, J=2.4, 12.4Hz), 4.29 (1H, dd, J=4.1, 12.4Hz),  
25 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m),  
7.00-7.10 (2H, m)

## Reference Example 34

1-Methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole

A suspension of 4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole (30mg), potassium carbonate (8.0mg) and iodomethane (8.2mg) in tetrahydrofuran (1mL) was stirred at 75°C overnight. The reaction mixture was filtered through celite®, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (developing solvent: dichloromethane/ethyl acetate = 5/1) to give 1-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole (13mg).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  ppm:

1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.44 (3H, s), 3.65-3.95 (6H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.29 (1H, dd, J=4.3, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 7.00-7.20 (4H, m)

20

## Reference Example 35

1-Ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 34 using iodoethane instead of iodomethane.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  ppm:

1.40 (3H, t, J=7.2Hz), 1.90 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 3.72 (2H, s), 3.80-3.90 (1H, m), 4.05-4.20 (3H, m), 4.27 (1H, dd, J=4.5, 12.4Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m)

#### Reference Example 36

4-[(4-Methylthiophenyl)methyl]-1-propyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 34 using 1-iodopropane instead of iodomethane.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

0.92 (3H, t, J=7.4Hz), 1.75-1.90 (2H, m), 1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 3.72 (2H, s), 3.80-3.90 (1H, m), 3.90-4.05 (2H, m), 4.12 (1H, dd, J=2.3, 12.4Hz), 4.27 (1H, dd, J=4.5, 12.4Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m)

#### Reference Example 37

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole

To a solution of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole (61mg) in ethanol (3mL) was added 1 mol/L aqueous sodium hydroxide solution (0.53mL), and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced

pressure, and the residue was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol) to give 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-1H-pyrazole (39mg).

5  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.26 (6H, d,  $J=5.9\text{Hz}$ ), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 4.45-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

#### 10 Reference Example 38

3-( $\beta$ -D-Glucopyranosyloxy)-5-methyl-4-[(4-propylphenyl)-methyl]-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-propylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

20 0.91 (3H, t,  $J=7.5\text{Hz}$ ), 1.50-1.65 (2H, m), 2.05 (3H, s), 2.45-2.60 (2H, m), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.83 (1H, d,  $J=11.9\text{Hz}$ ), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

#### Example 39

25 3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-isobutylphenyl)methyl]-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to

that described in Reference Example 37 using 4-[(4-isobutyl-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

0.87 (6H, d, J=6.6Hz), 1.70-1.90 (1H, m), 2.04 (3H, s), 2.41 (2H, d, J=7.1Hz), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.15 (4H, m)

10

Reference Example 40

3-( $\beta$ -D-Glucopyranosyloxy)-5-methyl-4-[(4-propoxyphenyl)methyl]-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-propoxyphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

1.02 (3H, t, J=7.4Hz), 1.65-1.80 (2H, m), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (3H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Reference Example 41

4-[(4-Ethoxyphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-ethoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

1.34 (3H, t, J=7.0Hz), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (1H, m), 3.97 (2H, q, J=7.0Hz), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

#### Reference Example 42

3-( $\beta$ -D-Glucopyranosyloxy)-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-trifluoromethylphenyl)methyl]-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

2.08 (3H, s), 3.20-3.40 (4H, m), 3.67 (1H, dd, J=5.0, 11.9Hz), 3.75-3.90 (3H, m), 5.00-5.10 (1H, m), 7.30-7.45 (2H, m), 7.45-7.60 (2H, m)

#### Reference Example 43

4-[(4-tert-Butylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-

methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-tert-butylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ ppm:

1.28 (9H, s), 2.06 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 7.05-7.15 (2H, m), 7.20-7.30 (2H, m)

Reference Example 44

4-[(4-Butoxyphenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-butoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD) δ ppm:

0.97 (3H, t, J=7.4Hz), 1.40-1.55 (2H, m), 1.65-1.80 (2H, m), 2.05 (3H, s), 3.30-3.45 (4H, m), 3.60-3.75 (3H, m), 3.83 (1H, d, J=12.0Hz), 3.91 (2H, t, J=6.4Hz), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Reference Example 45

3-( $\beta$ -D-Glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)-methyl]-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-

5 [(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

10 2.06 (3H, s), 2.42 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.05-7.20 (4H, m)

#### Reference Example 46

5-Ethyl-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-methylthiophenyl)-methyl]-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.06 (3H, t,  $J=7.6\text{Hz}$ ), 2.42 (3H, s), 2.47 (2H, q,  $J=7.6\text{Hz}$ ),  
3.25-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m),  
25 5.00-5.10 (1H, m), 7.10-7.20 (4H, m)

#### Reference Example 47



3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-isopropylphenyl)methyl]-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-isopropylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

10 1.20 (6H, d,  $J=6.9\text{Hz}$ ), 2.05 (3H, s), 2.75-2.90 (1H, m), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

#### Reference Example 48

15 3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

20 2.42 (3H, s), 3.25-3.50 (4H, m), 3.69 (1H, dd,  $J=4.9, 12.0\text{Hz}$ ),  
25 3.75-3.90 (3H, m), 4.90-5.10 (1H, m), 7.10-7.20 (4H, m)

#### Reference Example 49

4-Benzyl-3-( $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-benzyl-3-

5 (2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

10 3.25-3.45 (4H, m), 3.67 (1H, dd,  $J=5.3, 12.0\text{Hz}$ ), 3.80-3.95 (3H, m), 4.97 (1H, d,  $J=7.4\text{Hz}$ ), 7.05-7.25 (5H, m)

Reference Example 50

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-  
15 trifluoromethyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methoxyphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of

20 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

3.25-3.45 (4H, m), 3.67 (1H, d,  $J=5.4, 12.1\text{Hz}$ ), 3.73 (3H, s),  
3.75-3.90 (3H, m), 4.90-5.00 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15  
25 (2H, m)

Reference Example 51

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

2.04 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.73 (3H, s), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 6.75-6.85 (2H, m), 7.05-7.15 (2H, m)

#### Reference Example 52

4-Benzyl-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-benzyl-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 7.05-7.25 (5H, m)

25

#### Reference Example 53

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-1,5-

dimethylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

2.06 (3H, s), 3.25-3.45 (4H, m), 3.55-3.70 (6H, m), 3.73 (3H, s), 3.75-3.90 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.05-7.15 (2H, m)

Reference Example 54

3-( $\beta$ -D-Glucopyranosyloxy)-1-methyl-4-[(4-methylthiophenyl)methyl]-5-trifluoromethylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 1-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

2.42 (3H, s), 3.30-3.50 (4H, m), 3.69 (1H, dd,  $J=4.7, 12.0\text{Hz}$ ), 3.75-3.90 (6H, m), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Reference Example 55

1-Ethyl-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-methylthiophenyl)-

methyl]-5-trifluoromethylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 1-ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.38 (3H, t,  $J=7.1\text{Hz}$ ), 2.42 (3H, s), 3.30-3.50 (4H, m), 3.60-3.75 (1H, m), 3.75-3.90 (3H, m), 4.14 (2H, q,  $J=7.1\text{Hz}$ ), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Reference Example 56

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methylthiophenyl)methyl]-1-propyl-5-trifluoromethylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methylthiophenyl)methyl]-1-propyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

0.90 (3H, t,  $J=7.4\text{Hz}$ ), 1.75-1.90 (2H, m), 2.42 (3H, s), 3.30-3.50 (4H, m), 3.69 (1H, dd,  $J=4.9, 12.0\text{Hz}$ ), 3.75-3.90 (3H, m), 4.00-4.10 (2H, m), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Reference Example 57

3-( $\beta$ -D-Glucopyranosyloxy)-5-methyl-4-[(4-methylphenyl)-methyl]-1*H*-pyrazole

5-Methyl-4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyloxy)-1*H*-pyrazole was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-methylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyloxy)-1*H*-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

2.04 (3H, s), 2.26 (3H, s), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.15 (4H, m)

#### Reference Example 58

4-[(4-Ethylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

4-[(4-Ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyloxy)-1*H*-pyrazole was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-ethylphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference

Example 37 using 4-[(4-ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

5  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.18 (3H, t,  $J=7.6\text{Hz}$ ), 2.04 (3H, s), 2.57 (2H, q,  $J=7.6\text{Hz}$ ), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.20 (4H, m)

10 Reference Example 59

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methylphenyl)methyl]-5-trifluoromethyl-1H-pyrazole

4-[(4-Methylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was

15 prepared in a similar manner to that described in Reference Example 28 using 1,2-dihydro-4-[(4-methylphenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner

20 to that described in Reference Example 37 using 4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

25  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

2.25 (3H, s), 3.20-3.45 (4H, m), 3.55-3.70 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 6.90-7.15 (4H, m)

## Reference Example 60

4-[(4-Ethylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

5            4-[(4-Ethylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference Example 28 using 4-[(4-ethylphenyl)methyl]-1,2-dihydro-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-  
10 [(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-ethylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of  
15 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.18 (3H, t,  $J=7.6\text{Hz}$ ), 2.50-2.60 (2H, m), 3.15-3.40 (4H, m),  
3.55-3.65 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m),  
20 6.95-7.15 (4H, m)

## Reference Example 61

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-isopropylphenyl)methyl]-5-trifluoromethyl-1H-pyrazole

25            4-[(4-Isopropylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference



Example 28 using 1,2-dihydro-4-[(4-isopropylphenyl)-methyl]-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-isopropylphenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

10  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.20 (6H, d,  $J=6.9\text{Hz}$ ), 2.75-2.85 (1H, m), 3.15-3.40 (4H, m), 3.55-3.65 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 7.00-7.15 (4H, m)

15 Reference Example 62

4-[(4-Chlorophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

4-[(4-Chlorophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference Example 28 using 4-[(4-chlorophenyl)methyl]-1,2-dihydro-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-chlorophenyl)methyl]-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of

4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

3.20-3.40 (4H, m), 3.55-3.70 (1H, m), 3.75-3.90 (3H, m),  
5 4.80-4.95 (1H, m), 7.10-7.25 (4H, m)

#### Reference Example 63

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1-propylpyrazole

10 To a suspension of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole (50mg) and cesium carbonate (0.20g) in *N,N*-dimethylformamide (1mL) was added 1-iodopropane (0.036mL) at 50°C, and the mixture was stirred overnight. Water was added to the reaction mixture, and the  
15 resulting mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol). The resulting semi-purified material was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 8/1) to give 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxy-  
20 phenyl)methyl]-5-methyl-1-propylpyrazole (28mg).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

0.87 (3H, t,  $J=7.4\text{Hz}$ ), 1.26 (6H, d,  $J=6.0\text{Hz}$ ), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.95 (3H, m), 4.40-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m),  
25 7.00-7.10 (2H, m)

#### Reference Example 64

1-Ethyl-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropylphenyl)-methyl]-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using iodoethane instead of 1-iodopropane.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.26 (6H, d,  $J=6.0\text{Hz}$ ), 1.29 (3H, t,  $J=7.2\text{Hz}$ ), 2.08 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 3.96 (2H, q,  $J=7.2\text{Hz}$ ), 4.40-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

#### Reference Example 65

1-Ethyl-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)-methyl]-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1H-pyrazole instead of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole and using iodoethane instead of 1-iodopropane.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.29 (3H, t,  $J=7.1\text{Hz}$ ), 2.07 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (6H, m), 3.82 (1H, dd,  $J=2.0, 12.0\text{Hz}$ ), 3.90-4.05 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

#### Reference Example 66

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-

## methyl-1-propylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1H-pyrazole instead of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

0.87 (3H, t, J=7.5Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.35-3.45 (4H, m), 3.60-3.75 (3H, m), 3.73 (3H, s), 3.75-3.85 (1H, m), 3.85-3.95 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

## Reference Example 67

1-Ethyl-4-[(4-ethoxyphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethoxyphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole and using iodoethane instead of 1-iodopropane.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

1.28 (3H, t, J=7.4Hz), 1.34 (3H, t, J=7.2Hz), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.85 (1H, m), 3.90-4.00 (4H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

## Reference Example 68

4-[(4-Ethoxyphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1-propylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethoxyphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

0.87 (3H, t,  $J=7.6\text{Hz}$ ), 1.34 (3H, t,  $J=7.1\text{Hz}$ ), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.81 (1H, dd,  $J=2.1, 12.1\text{Hz}$ ), 3.85-4.05 (4H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

## 15 Reference Example 69

1-Ethyl-4-[(4-ethylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole and using iodoethane instead of 1-iodopropane.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.17 (3H, t,  $J=7.6\text{Hz}$ ), 1.28 (3H, t,  $J=7.2\text{Hz}$ ), 2.06 (3H, s), 2.56 (2H, q,  $J=7.6\text{Hz}$ ), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.85 (1H, m), 3.90-4.00 (2H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H,

m)

Reference Example 70

4-[(4-Ethylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-  
5 methyl-1-propylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethylphenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole.  
10

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

0.87 (3H, t, J=7.4Hz), 1.17 (3H, t, J=7.6Hz), 1.65-1.80 (2H, m), 2.06 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.60-3.95 (6H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)  
15

Reference Example 71

1-Butyl-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 1-bromobutane instead of 1-iodopropane.  
20

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

0.92 (3H, t, J=7.4Hz), 1.20-1.40 (8H, m), 1.60-1.75 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.81 (1H, dd, J=2.1, 12.0Hz), 3.91 (2H, t, J=7.2Hz), 4.45-4.55 (1H, m),  
25 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

## Reference Example 72

3-( $\beta$ -D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Reference Example 63 using 2-bromopropane instead of 1-iodopropane.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.26 (6H, d,  $J=6.0\text{Hz}$ ), 1.30-1.40 (6H, m), 2.08 (3H, s), 3.15-3.45 (4H, m), 3.55-3.75 (3H, m), 3.78 (1H, dd,  $J=2.3, 12.0\text{Hz}$ ), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

## Reference Example 73

4-[(4-Ethylthiophenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

To a solution of 4-ethylthiobenzyl alcohol (8.3g) and triethylamine (6.9mL) in tetrahydrofuran (200mL) was added methanesulfonyl chloride (3.8mL) at  $0^\circ\text{C}$ , and the mixture was stirred for 1 hour. Insoluble material was removed by filtration. The obtained solution of 4-ethylthiobenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 2.2g) and methyl acetoacetate (5.3mL) in 1,2-dimethoxyethane (200mL), and the mixture was stirred at  $80^\circ\text{C}$  overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was

removed under reduced pressure. To a solution of the residue in toluene (150mL) was added hydrazine monohydrate (7.2mL), and the mixture was stirred at 80°C for 1 hour. The reaction mixture was cooled to 0°C and stirred for additional 1 hour. The resulting precipitates were collected by filtration and washed with water and hexane to give 4-[(4-ethylthiophenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one (1.5g).

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm:

1.19 (3H, t, J=7.3Hz), 2.00 (3H, s), 2.90 (2H, q, J=7.3Hz), 3.51 (2H, s), 7.05-7.15 (2H, m), 7.15-7.25 (2H, m)

#### Reference Example 74

4-[(4-Ethylthiophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole

To a suspension of 4-[(4-ethylthiophenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one (1.6g) and acetobromo-α-D-glucose (2.9g) in tetrahydrofuran (30mL) was added silver carbonate (2.1g), and the mixture was stirred under shading the light at 60°C overnight. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran) and further column chromatography on silica gel (eluent: hexane/ethyl acetate =1/3) to give 4-[(4-ethylthiophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole (1.4g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm:

1.28 (3H, t, J=7.4Hz), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 2.89 (2H, q, J=7.4Hz), 3.56 (1H,



d,  $J=15.9\text{Hz}$ ), 3.62 (1H, d,  $J=15.9\text{Hz}$ ), 3.80-3.90 (1H, m), 4.13 (1H, dd,  $J=2.3, 12.6\text{Hz}$ ), 4.31 (1H, dd,  $J=3.9, 12.6\text{Hz}$ ), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.15-7.25 (2H, m), 8.79 (1H, brs)

5

#### Reference Example 75

4-[(4-Ethylthiophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole

To a solution of 4-[(4-ethylthiophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyloxy)-1H-pyrazole (1.3g) in methanol (10mL) was added sodium methoxide (28% methanol solution, 0.13mL), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 5/1) to give 4-[(4-ethylthiophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole (0.87g).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:  
1.24 (3H, t,  $J=7.3\text{Hz}$ ), 2.06 (3H, s), 2.88 (2H, q,  $J=7.3\text{Hz}$ ), 3.30-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.10-7.30 (4H, m)

#### Reference Example 76

1-(Benzyloxycarbonyl)-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole

To a solution of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-iso-

propoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (1.3g) in tetrahydrofuran (30mL) was added *N*-(benzyloxycarbonyloxy)-succinimide (1.6g), and the mixture was heated under reflux overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/ methanol = 10/1) to give 1-(benzyloxycarbonyl)-3-( $\beta$ -D-glucopyranosyloxy) -4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole (1.3g).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  ppm:

1.27 (6H, d, *J*=6.3Hz), 2.35 (3H, s), 3.45-3.70 (6H, m), 3.76 (1H, dd, *J*=4.5, 12.0Hz), 3.85 (1H, dd, *J*=2.8, 12.0Hz), 4.40-4.50 (1H, m), 5.30-5.40 (2H, m), 5.48 (1H, d, *J*=8.0Hz), 6.70-6.80 (2H, m), 6.95-7.05 (2H, m), 7.25-7.50 (5H, m)

#### 15 Reference Example 77

1-(Benzyloxycarbonyl)-3-(6-*O*-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole

To a solution of 1-(benzyloxycarbonyl)-3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole (0.20g) in 2,4,6-trimethylpyridine (4mL) was added ethyl chloroformate (0.092mL), and the mixture was stirred at room temperature for 1 day. To the reaction mixture were added water and citric acid monohydrate, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was

purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1-(benzyloxy-carbonyl)-3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole (0.17g).

5  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.19 (3H, t,  $J=7.1\text{Hz}$ ), 1.26 (6H, d,  $J=6.0\text{Hz}$ ), 2.36 (3H, s),  
3.30-3.50 (3H, m), 3.50-3.75 (3H, m), 4.10 (2H, q,  $J=7.1\text{Hz}$ ),  
4.25-4.35 (1H, m), 4.35-4.45 (1H, m), 4.45-4.60 (1H, m),  
5.35-5.45 (2H, m), 5.45-5.60 (1H, m), 6.70-6.85 (2H, m),  
10 7.00-7.15 (2H, m), 7.30-7.55 (5H, m)

#### Reference Example 78

1-(Benzyloxycarbonyl)-4-[(4-isopropoxyphenyl)methyl]-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole

15 The title compound was prepared in a similar manner to that described in Reference Example 77 using methyl chloroformate instead of ethyl chloroformate.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm:

1.30 (6H, d,  $J=6.4\text{Hz}$ ), 2.43 (3H, s), 3.45-3.70 (6H, m), 3.78  
20 (3H, s), 4.39 (1H, dd,  $J=2.2, 11.8\text{Hz}$ ), 4.40-4.55 (2H, m), 5.38  
(2H, s), 5.40-5.50 (1H, m), 6.70-6.85 (2H, m), 7.00-7.10 (2H, m),  
7.30-7.50 (5H, m)

#### Example 1

25 3-(6-O-Ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

To a solution of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-iso-

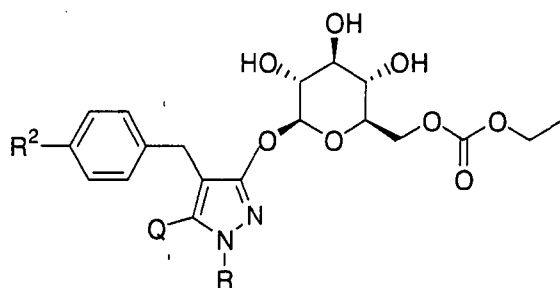
propoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole (0.10g) in 2,4,6-trimethylpyridine (1mL) was added ethyl chloroformate (0.072g), and the mixture was stirred at room temperature overnight. To the reaction mixture were added citric acid monohydrate (3.3g) and water, and the resulting mixture was purified by ODS solid phase extraction (washing solvent: distilled water, eluent: methanol). Further purification by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) and recrystallization (recrystallization solvent: ethyl acetate/hexane = 1/3) afforded 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole (0.084g).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.23 (3H, t,  $J=7.0\text{Hz}$ ), 1.26 (6H, d,  $J=5.8\text{Hz}$ ), 1.30-1.40 (6H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 4.12 (2H, q,  $J=7.0\text{Hz}$ ), 4.21 (1H, dd,  $J=5.4, 11.6\text{Hz}$ ), 4.34 (1H, dd,  $J=1.7, 11.6\text{Hz}$ ), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

## 20 Examples 2-14

The compounds listed in Table 1 were prepared from the corresponding starting material in a similar manner to that described in Example 1.



[Table 1]

Example	R	R <sup>2</sup>	Q
2	Methyl	Methoxy	Methyl
3	Methyl	Methylthio	Trifluoromethyl
4	Ethyl	Methylthio	Trifluoromethyl
5	Propyl	Methylthio	Trifluoromethyl
6	Propyl	Isopropoxy	Methyl
7	Ethyl	Isopropoxy	Methyl
8	Ethyl	Methoxy	Methyl
9	Propyl	Methoxy	Methyl
10	Ethyl	Ethoxy	Methyl
11	Propyl	Ethoxy	Methyl
12	Ethyl	Ethyl	Methyl
13	Propyl	Ethyl	Methyl
14	Butyl	Isopropoxy	Methyl

## Example 15

- 5 4-[(4-Isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxy-carbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Example 1 using methyl chloroformate instead of ethyl chloroformate.

- 10 <sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

1.26 (6H, d, J=6.1Hz), 1.30-1.40 (6H, m), 2.07 (3H, s), 3.25-3.45

(4H, m), 3.60-3.70 (2H, m), 3.71 (3H, s), 4.22 (1H, dd, J=5.2, 11.7Hz), 4.35 (1H, dd, J=2.1, 11.7Hz), 4.35-4.45 (1H, m), 4.45-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

5

#### Example 16

3-(6-O-Isobutyloxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Example 1 using isobutyl chloroformate instead of ethyl chloroformate.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

0.90 (6H, d, J=6.7Hz), 1.26 (6H, d, J=5.9Hz), 1.30-1.40 (6H, m), 1.80-2.00 (1H, m), 2.07 (3H, s), 3.25-3.50 (4H, m), 3.60-3.70 (2H, m), 3.80-3.90 (2H, m), 4.21 (1H, dd, J=5.2, 11.5Hz), 4.36 (1H, dd, J=1.8, 11.5Hz), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

#### Example 17

4-[(4-Isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(6-O-propionyl- $\beta$ -D-glucopyranosyloxy)pyrazole

To a solution of 3-( $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole (0.10g) in 2,4,6-trimethylpyridine (1mL) was added propionyl chloride (0.072g) at 0°C, and the mixture was stirred for 5 hours. To the reaction mixture were added citric acid monohydrate (3.3g) and water, and the resulting mixture was purified by ODS solid

phase extraction (washing solvent: distilled water, eluent: methanol). Further purification by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) afforded 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(6-O-propionyl- $\beta$ -D-glucopyranosyloxy)pyrazole (0.074g)

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.05 (3H, t,  $J=7.5\text{Hz}$ ), 1.26 (6H, d,  $J=5.9\text{Hz}$ ), 1.30-1.40 (6H, m), 2.07 (3H, s), 2.27 (2H, q,  $J=7.5\text{Hz}$ ), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 4.18 (1H, dd,  $J=5.6, 11.8\text{Hz}$ ), 4.30 (1H, dd,  $J=2.2, 11.8\text{Hz}$ ), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

#### Example 18

3-(6-O-Acetyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Example 17 using acetyl chloride instead of propionyl chloride.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.26 (6H, d,  $J=6.4\text{Hz}$ ), 1.30-1.40 (6H, m), 1.98 (3H, s), 2.08 (3H, s), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 4.16 (1H, dd,  $J=5.6, 11.8\text{Hz}$ ), 4.29 (1H, dd,  $J=2.0, 11.8\text{Hz}$ ), 4.35-4.55 (2H, m), 5.00-5.10 (1H, m), 6.70-7.80 (2H, m), 7.00-7.10 (2H, m)

#### Example 19

3-(6-O-Butyryl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

The title compound was prepared in a similar manner to that described in Example 17 using butyryl chloride instead of propionyl chloride.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

5 0.88 (3H, t,  $J=7.4\text{Hz}$ ), 1.26 (6H, d,  $J=6.0\text{Hz}$ ), 1.30-1.40 (6H, m), 1.50-1.65 (2H, m), 2.07 (3H, s), 2.15-2.30 (2H, m), 3.25-3.50 (4H, m), 3.60-3.70 (2H, m), 4.17 (1H, dd,  $J=5.7, 11.9\text{Hz}$ ), 4.31 (1H, dd,  $J=2.0, 11.9\text{Hz}$ ), 4.30-4.55 (2H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

10

#### Example 20

4-[(4-Isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(6-O-pivaloyl- $\beta$ -D-glucopyranosyloxy)pyrazole

15 The title compound was prepared in a similar manner to that described in Example 17 using pivaloyl chloride instead of propionyl chloride.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.10 (9H, s), 1.26 (6H, d,  $J=6.1\text{Hz}$ ), 1.30-1.40 (6H, m), 2.06 (3H, s), 3.30-3.45 (4H, m), 3.60-3.70 (2H, m), 4.16 (1H, dd,  $J=5.8, 11.7\text{Hz}$ ), 4.30 (1H, dd,  $J=2.0, 11.7\text{Hz}$ ), 4.30-4.55 (2H, m), 5.05-5.15 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

20

#### Example 21

1-Ethoxycarbonyl-3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole

25

To a solution of 4-[(4-ethylthiophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole (0.03g) in 2,4,6-tri-



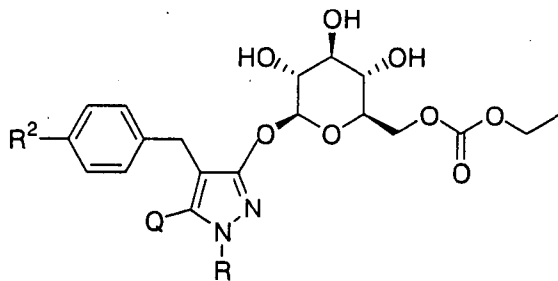
methylpyridine (0.5mL) was added ethyl chloroformate (0.021mL),  
 and the mixture was stirred at room temperature overnight. To  
 the reaction mixture was added 10% aqueous citric acid solution,  
 and the resulting mixture was extracted with ethyl acetate. The  
 5 organic layer was dried over anhydrous magnesium sulfate, and  
 the solvent was removed under reduced pressure. The residue  
 was purified by preparative thin layer chromatography on silica  
 gel (eluent: dichloromethane/ methanol = 10/1) to give  
 1-ethoxycarbonyl-3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyl-  
 10 oxy)-4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole  
 (0.023g).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.15-1.30 (6H, m), 1.39 (3H, t,  $J=7.1\text{Hz}$ ), 2.37 (3H, s), 2.87  
 (2H, q,  $J=7.3\text{Hz}$ ), 3.35-3.50 (3H, m), 3.60-3.80 (3H, m), 4.12  
 15 (2H, q,  $J=7.1\text{Hz}$ ), 4.29 (1H, dd,  $J=5.3, 11.9\text{Hz}$ ), 4.35-4.50 (3H,  
 m), 5.50-5.60 (1H, m), 7.10-7.25 (4H, m)

#### Examples 22-43

The compounds listed in Table 2 were prepared from the  
 20 corresponding starting material in a similar manner to that  
 described in Example 21.



[Table 2]

Example	R	R <sup>2</sup>	Q
22	Ethoxycarbonyl	Isopropoxy	Methyl
23	Ethoxycarbonyl	Propyl	Methyl
24	Ethoxycarbonyl	Isobutyl	Methyl
25	Ethoxycarbonyl	Propoxy	Methyl
26	Ethoxycarbonyl	Ethoxy	Methyl
27	Ethoxycarbonyl	Trifluoromethyl	Methyl
28	Ethoxycarbonyl	tert-Butyl	Methyl
29	Ethoxycarbonyl	Butoxy	Methyl
30	Ethoxycarbonyl	Methylthio	Methyl
31	Ethoxycarbonyl	Methylthio	Ethyl
32	Ethoxycarbonyl	Isopropyl	Methyl
33	Ethoxycarbonyl	Methylthio	Trifluoromethyl
34	Ethoxycarbonyl	Hydrogen	Trifluoromethyl
35	Ethoxycarbonyl	Methoxy	Trifluoromethyl
36	Ethoxycarbonyl	Methoxy	Methyl
37	Ethoxycarbonyl	Hydrogen	Methyl
38	Ethoxycarbonyl	Methyl	Methyl
39	Ethoxycarbonyl	Ethyl	Methyl
40	Ethoxycarbonyl	Methyl	Trifluoromethyl
41	Ethoxycarbonyl	Ethyl	Trifluoromethyl
42	Ethoxycarbonyl	Isopropyl	Trifluoromethyl
43	Ethoxycarbonyl	Chlorine	Trifluoromethyl

## Example 44

3-(6-O-Ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-(ethoxy-  
 5 carbonyloxymethyl)-4-[(4-methylthiophenyl)methyl]-5-methyl-  
 pyrazole

To a solution of 3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-4-  
 [(4-methylthiophenyl)methyl]-1H-pyrazole (0.11g) in water

(0.5mL) and ethanol (0.1mL) was added formaldehyde (37% aqueous solution, 0.068mL), and the mixture was stirred at 40°C for 3 days. To the reaction mixture were added tetrahydrofuran and anhydrous magnesium sulfate, and the resulting insoluble material was removed by filtration. The solvent of the filtrate was removed under reduced pressure. The residue was dissolved in 2,4,6-trimethylpyridine (1mL). Ethyl chloroformate (0.099g) was added to the solution, and the mixture was stirred at room temperature overnight. To the reaction mixture were added citric acid monohydrate (4g) and water, and the resulting mixture was purified by ODS solid phase extraction (washing solvent: 10% aqueous citric acid solution, distilled water, eluent: methanol). Further purification by column chromatography on silica gel (eluent: dichloromethane/methanol = 15/1) afforded 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-(ethoxycarbonyloxymethyl)-4-[(4-methylthiophenyl)methyl]-5-methylpyrazole (0.058g).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.23 (3H, t,  $J=7.1\text{Hz}$ ), 1.26 (3H, t,  $J=7.1\text{Hz}$ ), 2.18 (3H, s), 2.42 (3H, s), 3.30-3.45 (3H, m), 3.50-3.60 (1H, m), 3.63 (1H, d,  $J=16.0\text{Hz}$ ), 3.70 (1H, d,  $J=16.0\text{Hz}$ ), 4.13 (2H, q,  $J=7.1\text{Hz}$ ), 4.18 (2H, q,  $J=7.1\text{Hz}$ ), 4.28 (1H, dd,  $J=4.8, 11.7\text{Hz}$ ), 4.39 (1H, dd,  $J=2.0, 11.7\text{Hz}$ ), 5.25-5.35 (1H, m), 5.80-5.95 (2H, m), 7.10-7.20 (4H, m)

25

#### Example 45

1-Acetyl-4-[(4-ethylthiophenyl)methyl]-3-( $\beta$ -D-glucosyl)-

pyranosyloxy)-5-methylpyrazole

To a solution of 4-[(4-ethylthiophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole (0.41g) in tetrahydrofuran (10mL) were added acetic acid (0.11mL) and acetic anhydride (0.18mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and diethyl ether was added to the residue. The resulting precipitated crystal was collected by filtration to give 1-acetyl-4-[(4-ethylthiophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole (0.36g).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.24 (3H, t,  $J=7.3\text{Hz}$ ), 2.43 (3H, s), 2.54 (3H, s), 2.89 (2H, q,  $J=7.3\text{Hz}$ ), 3.30-3.50 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (1H, m), 5.45-5.55 (1H, m), 7.10-7.30 (4H, m)

#### Example 46

1-Acetyl-3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole

To a solution of 1-acetyl-4-[(4-ethylthiophenyl)methyl]-3-( $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole (0.03g) in 2,4,6-trimethylpyridine (0.5mL) was added ethyl chloroformate (0.012mL), and the mixture was stirred at room temperature overnight. To the reaction mixture was added 10% aqueous citric acid solution (5mL), and the resulting mixture was stirred at room temperature overnight. The resulting precipitate were collected by filtration and washed with 10% aqueous citric acid solution and water to give 1-acetyl-3-(6-O-

ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethylthio-phenyl)methyl]-5-methylpyrazole (0.020g).

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.20 (3H, t,  $J=7.2\text{Hz}$ ), 1.24 (3H, t,  $J=7.4\text{Hz}$ ), 2.41 (3H, s), 2.55  
 5 (3H, s), 2.88 (2H, q,  $J=7.4\text{Hz}$ ), 3.30-3.40 (1H, m), 3.40-3.50  
 (2H, m), 3.50-3.65 (1H, m), 3.65 (1H, d,  $J=15.8\text{Hz}$ ), 3.72 (1H,  
 d,  $J=15.8\text{Hz}$ ), 4.05-4.15 (2H, m), 4.27 (1H, dd,  $J=6.3, 11.7\text{Hz}$ ),  
 4.42 (1H, dd,  $J=2.0, 11.7\text{Hz}$ ), 5.40-5.55 (1H, m), 7.10-7.30 (4H,  
 m)

10

#### Example 47

3-(6-O-Ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methyl-1H-pyrazole

To a solution of 1-(benzyloxycarbonyl)-3-(6-O-ethoxy-  
 15 carbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-  
 methyl]-5-methylpyrazole (0.17g) in tetrahydrofuran (4mL) was  
 added 10% palladium-carbon powder, and the mixture was stirred  
 under hydrogen atmosphere at room temperature for 3 hours. The  
 resulting insoluble material was removed by filtration, and the  
 20 solvent of the filtrate was removed under reduced pressure. The  
 residue was purified by column chromatography on silica gel  
 (eluent: dichloromethane/methanol = 10/1) to give 3-(6-O-  
 ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxy-  
 phenyl)methyl]-5-methyl-1H-pyrazole (0.10g).

25  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  ppm:

1.23 (3H, t,  $J=7.1\text{Hz}$ ), 1.26 (6H, d,  $J=6.0\text{Hz}$ ), 2.04 (3H, s),  
 3.30-3.55 (4H, m), 3.61 (1H, d,  $J=15.9\text{Hz}$ ), 3.67 (1H, d,  $J=15.9\text{Hz}$ ),

4.12 (2H, q, J=7.1Hz), 4.27 (1H, dd, J=4.9, 11.7Hz), 4.38 (1H, dd, J=2.0, 11.7Hz), 4.45-4.60 (1H, m), 5.10-5.20 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

## 5 Example 48

4-[(4-Isopropoxyphenyl)methyl]-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methyl-1H-pyrazole

The title compound was prepared in a similar manner to that described in Example 47 using 1-(benzyloxycarbonyl)-4-  
 10 [(4-isopropoxyphenyl)methyl]-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole instead of 1-(benzyloxycarbonyl)-3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  ppm:

15 1.26 (6H, d, J=5.9Hz), 2.04 (3H, s), 3.30-3.55 (4H, m), 3.61 (1H, d, J=15.9Hz), 3.67 (1H, d, J=15.9Hz), 3.72 (3H, s), 4.28 (1H, dd, J=5.2, 11.7Hz), 4.39 (1H, dd, J=1.8, 11.7Hz), 4.45-4.55 (1H, m), 5.05-5.15 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

20

## Test Example 1

Assay for inhibitory effect on human SGLT2 activity

1) Construction of the plasmid vector expressing human SGLT2

Preparation of the cDNA library for PCR amplification was  
 25 performed by reverse transcription of a total RNA deprived from human kidney (Ori gene) with oligo dT as the primer, using SUPERScript Preamplification System (Gibco-BRL: LIFE

TECHNOLOGIES). The DNA fragment coding for human SGLT2 was amplified by the PCR reaction, in which the human kidney cDNA library described above was used as the template and the following oligo nucleotides 0702F and 0712R, presented as sequence number 1 and 2 respectively, were used as the primers. The amplified DNA fragment was ligated into pCR-Blunt (Invitrogen), a vector for cloning, according to standard method of the kit. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformants was performed on the LB agar medium containing 50 µg/mL of kanamycin. After plasmid DNA was extracted and purified from the one of the transformants, amplifying of the DNA fragment coding for human SGLT2 was performed by the PCR reaction, in which the following oligo nucleotides 0714F and 0715R, presented as sequence number 3 and 4 respectively, were used as the primers. The amplified DNA fragment was digested with restriction enzymes, Xho I and Hind III, and then purified with Wizard Purification System (Promega). This purified DNA fragment was inserted at into the corresponding restriction sites of pcDNA3.1 (-) Myc/His - B (Invitrogen), a vector for expressing of fusion protein. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformant was performed on the LB agar medium containing 100 µg/mL of ampicillin. After plasmid DNA was extracted and purified from this transformant, the base sequence of the DNA fragment inserted at the multi-cloning sites of the vector pcDNA3.1 (-) Myc/His - B was analyzed. This clone had a single base substitution (ATC which codes for the

isoleucine-433 was substituted by GTC) compared with the human SGLT2 reported by Wells et al (Am. J. Physiol., Vol. 263, pp. 459-465 (1992)). Sequentially, a clone in which valine is substituted for isoleucine-433 was obtained. This plasmid  
 5 vector expressing human SGLT2 in which the peptide presented as sequence number 5 is fused to the carboxyl terminal alanine residue was designated KL29.

Sequence Number 1 ATGGAGGAGCACACAGAGGC

10 Sequence Number 2 GGCATAGAAGCCCCAGAGGA

Sequence Number 3 AACCTCGAGATGGAGGAGCACACAGAGGC

Sequence Number 4 AACAAAGCTTGGCATAGAAGCCCCAGAGGA

Sequence Number 5 KLGPEQKLISEEDLNSAVDHHHHHH

15 2) Preparation of the cells expressing transiently human SGLT2

KL29, the plasmid coding human SGLT2, was transfected into COS-7 cells (RIKEN CELL BANK RCB0539) by electroporation. Electroporation was performed with GENE PULSER II (Bio-Rad Laboratories) under the condition: 0.290 kV, 975  $\mu$ F,  $2 \times 10^6$   
 20 cells of COS-7 cell and 20  $\mu$ g of KL29 in 500  $\mu$ L of OPTI-MEM I medium (Gibco-BRL: LIFE TECHNOLOGIES) in the 0.4 cm type cuvette. After the gene transfer, the cells were harvested by centrifugation and resuspended with OPTI-MEM I medium (1mL/cuvette). To each well in 96-wells plate, 125  $\mu$ L of this  
 25 cell suspension was added. After overnight culture at 37 °C under 5 % CO<sub>2</sub>, 125  $\mu$ L of DMEM medium which is containing 10 % of fetal bovine serum (Sanko Jyunyaku), 100 units/mL sodium penicillin



G (Gibco-BRL: LIFE TECHNOLOGIES), 100 µg/mL streptomycin sulfate (Gibco-BRL: LIFE TECHNOLOGIES) was added to each well. These cells were cultured until the next day and then they were used for the measurement of the inhibitory activity against the uptake  
5 of methyl- $\alpha$ -D-glucopyranoside.

### 3) Measurement of the inhibitory activity against the uptake of methyl- $\alpha$ -D-glucopyranoside

After a test compounds was dissolved in dimethyl sulfoxide  
10 and diluted with the uptake buffer (a pH 7.4 buffer containing 140 mM sodium chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 5 mM methyl- $\alpha$ -D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane), each  
15 diluent was used as test sample for measurement of the inhibitory activity. After removal of the medium of the COS-7 cells expressing transiently human SGLT2, to each well 200 µL of the pretreatment buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM  
20 magnesium chloride, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)-aminomethane) was added, and the cells were incubated at 37°C for 10 minutes. After the pretreatment buffer was removed, 200 µL of the same buffer was added again, and the cells were incubated  
25 at 37 °C for 10 minutes. The buffer for measurement was prepared by adding of 7 µL of methyl- $\alpha$ -D-(U-14C)glucopyranoside (Amersham Pharmacia Biotech) to 525 µL of the prepared test sample. For

the control, the buffer for measurement without test compound was prepared. For estimate of the basal uptake in the absence of test compound and sodium, the buffer for measurement of the basal uptake, which contains 140 mM choline chloride in place of sodium chloride, was prepared similarly. After the pretreatment buffer was removed, 75  $\mu$ L of the each buffer for measurement was added to each well, the cells were incubated at 37 °C for 2 hours. After the buffer for measurement was removed, 200  $\mu$ L of the washing buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM methyl- $\alpha$ -D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane) was added to each well and immediately removed. After two additional washing, the cells were solubilized by addition of 75  $\mu$ L of 0.2 mol/L sodium hydroxide to each well. After the cell lysates were transferred to the PicoPlate (Packard) and 150  $\mu$ L of MicroScint-40 (Packard) was added to each well, the radioactivity was measured with microplate scintillation counter TopCount (Packard). The difference in uptake was obtained as 100 % value by subtracting the radioactivity in the basal uptake from that in control and then the concentrations at which 50 % of uptake were inhibited (IC<sub>50</sub>) were calculated from the concentration-inhibition curve by least square method. The results are shown in the following Table 3.

[Table 3]

Test compound	IC <sub>50</sub> value (nM)
Reference Example 37	181
Reference Example 38	441
Reference Example 39	346
Reference Example 40	702
Reference Example 41	185
Reference Example 45	84
Reference Example 46	509
Reference Example 47	441
Reference Example 48	679
Reference Example 50	415
Reference Example 51	383
Reference Example 54	835
Reference Example 57	280
Reference Example 58	190
Reference Example 60	634
Reference Example 72	369
WAY-123783	>100000

## Test Example 2

### Assay for oral absorbability

- 1) Preparation of the samples for measurement of the drug  
5 concentration after intravenous injection to the tail vein

As experimental animal, overnight fasted SD rats (CLEA JAPAN, INC., male, 5 weeks of age, 140-170g) were used. Sixty mg of a test compound was dissolved by adding of 1.8 mL of ethanol, 7.2 mL of polyethylene glycol 400 and 9 mL of saline, and then

3.3 mg/mL solution was prepared. The body weights of rats were measured and the solution of the test compound was intravenously injected to the tail vein of unanesthetized rats at the dose of 3 mL/kg (10 mg/kg). The intravenous injection to the tail  
5 was performed with 26 G injection needle and 1 mL syringe. The sampling times for collection of blood were 2, 5, 10, 20, 30, 60 and 120 minutes after the intravenous injection to the tail. The blood was centrifuged and the plasma was used as the sample for measurement of the drug concentration in plasma.

10

2) Preparation of the samples for measurement of the drug concentration after oral administration

As experimental animal, overnight fasted SD rats (CLEA JAPAN, INC., male, 5 weeks of age, 140-170g) were used. A test  
15 compound was suspended or dissolved in 0.5 % sodium carboxymethylcellulose solution at the concentration of 1 mg/mL of active form. When homogenous suspension was not obtained in this condition, the test compound was dissolved in ethanol at the concentration of 100 mg/mL of active form and then  
20 suspension was obtained by adding this solution to 99 times volumes of 0.5 % sodium carboxymethylcellulose solution. After the body weights of rats were measured, the liquid containing test compound described above was orally administered at the dose of 10 mL/kg (10 mg/kg as active form). The oral  
25 administration was performed with gastric tube for rat and 2.5 mL syringe. The sampling times for collection of blood were 15, 30, 60, 120 and 240 minutes after the oral administration.

The blood was centrifuged and the plasma was used as the sample for measurement of the drug concentration in plasma.

### 3) Measurement of drug concentration

#### 5 Method A

To 0.1 mL of the plasma obtained in 1) and 2), described above, an adequate amount of an adequate internal standard material was added according to usual method and then deproteinization was performed by adding of 1 mL of methanol.

10 After centrifugation, the methanol phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 300  $\mu$ L of the mobile phase and 30  $\mu$ L aliquot of the solution was injected into HPLC. The drug concentration in plasma was measured by HPLC method under the condition as follows. To 0.1  
15 mL of the blank plasma an adequate internal standard and various concentrations of corresponding active form of the compound were adequately added according to usual method, similar operating described above was done and then the standard curve was prepared.

20 Column: Develosil ODS-UG-5 (4.6 x 250 mm)

Mobile phase: acetonitrile / 10 mM phosphate buffer (pH 3.0)  
= 22: 78 (v/v)

Column temperature: 50 °C

Flow rate: 1.0 mL/minute

25 Wavelength for measurement: UV 232 nm

#### Method B

To 50  $\mu$ L of the plasma obtained in 1) and 2) described above, an adequate amount of an adequate internal standard material was added according to usual method and 100  $\mu$ L of distilled water was added, and then extraction was performed by adding of 1 mL of diethyl ether. After centrifugation, the diethyl ether phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 200  $\mu$ L of the mobile phase and 10  $\mu$ L aliquot of the solution was injected into LC-MS/MS. The drug concentration in plasma was measured by LC-MS/MS method under the condition as follows. To 50  $\mu$ L of the blank plasma an adequate internal standard and various concentrations of corresponding active form of compound were adequately added according to usual method, similar operating described above was done and then the standard curve was prepared

15

LC

Column: Symmetry C<sub>8</sub> (2.1 x 20 mm)

Mobile phase: acetonitrile / 0.1 % acetic acid solution = 65:35 (v/v)

20 Column temperature: 40 °C

Flow rate: 0.2 mL/minute

MS/MS

25 Ionization method: ESI (Turbo Ion Spray), positive ion detection mode

Ion spray voltage: 5000 V

Heater gas temperature: 450 °C

Collision energy: 17.5 V

Multiplier voltage: 2300 V

Flow rate of turbo ion spray gas: 7000 mL/min

Nebulizer gas: 11 BIT

5 Curtain gas: 11 BIT

Collision gas: 4 BIT

Each area under the plasma concentration-time curve by intravenous injection to the tail vein and oral administration of test compound was estimated with WinNonlin Standard made by Pharsight Corporation from the plasma concentrations at each time obtained from method A and B and then the bioavailability (%) was calculated based on the following formula. The results are shown in the following Table 4.

15

Bioavailability(%) =

(Area under the Plasma Concentration - Time Curve by Oral Administration / Area under the Plasma Concentration - Time Curve by Intravenous Injection to the Tail Vein) x 100

20

25

[Table 4]

Test compound	Method	Bioavailability(%)
Example 1	B	27
Example 15	B	27
Example 16	B	32
Example 47	A	15
Example 48	A	11
Reference Example 37	A	0

## Test Example 3

Assay for the facilitatory effect on urinary glucose excretion

5        As experimental animal, overnight fasted SD rats (Japan SLC. Inc., male, 7 weeks of age, 202-221g) were used. A Test compound was suspended in 0.5 % sodium carboxymethylcellulose solution at the concentration of 2 mg/mL. When homogenous suspension was not obtained in this condition, the test compound

10       was dissolved in ethanol at the concentration of 200 mg/mL of active form and then 2 mg/mL suspension was obtained by adding this solution to 99 times volumes of 0.5 % sodium

carboxymethylcellulose solution. A part of this suspension was diluted with 0.5 % sodium carboxymethylcellulose solution and

15       then 0.6 and 0.2 mg/mL suspensions were prepared. After the body weights of rats were measured, the test suspension was orally administered at the dose of 5 mL/kg (1, 3 and 10 mg/kg). For control, just only 0.5 % sodium carboxymethylcellulose solution was orally administered at the dose of 5 mL/kg. Immediately

20       after this oral administration, 400 g/L glucose solution was



orally administered at the dose of 5 mL/kg (2 g/kg). The oral administration was performed with gastric tube for rat and 2.5 mL syringe. The head count in one group was 3. Collection of urine was performed in metabolic cage after the glucose administration was finished. The sampling time for collection of urine was 24 hours after the glucose administration. After collection of urine was finished, the urine volume was recorded and the urinary glucose concentration was measured. The glucose concentration was measured with a kit for laboratory test: Glucose B-Test WAKO (Wako Pure Chemical Industries, Ltd.). The amount of urinary glucose excretion in 24 hours per 200 g of body weight was calculated from urine volume, urinary glucose concentration and body weight. The results are shown in the following Table 5.

15

[Table 5]

Test compound	Dose (mg/kg)	Amount of Urinary Glucose Excretion (mg/24 hours·200g body weight)
Example 1	1	1.6
	3	28.3
	10	127.5
Example 15	1	1.7
	3	36.8
	10	167.3

Tset Example 4

Acute toxicity test

After 4 week old male ICR mice (Japan SLC. Inc., 20 - 25 g, 5 animals in each group) were fasted for 4 hours, the suspension (200 mg/mL) prepared by adding of 0.5 % sodium carboxymethyl-cellulose solution to the test compound was orally administered at the dose of 10 mL/kg (2000 mg/kg). Observation was performed until 24 hours after the administration. The results are shown in the following Table 6.

[Table 6]

Test compound	Death number
Example 48	0 / 5

## 10 Industrial Applicability

The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention or pharmaceutically acceptable salts thereof have an improved oral absorption. In addition, they show an excellent hypoglycemic effect by excreting excess glucose into the urine through preventing the reabsorption of glucose at the kidney because they are converted into glucopyranosyloxypyrazole derivatives represented by the above general formula (II) as their active forms *in vivo* and exhibit a potent inhibitory activity in human SGLT2. Therefore, the present invention can provide agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications, obesity or the like, which are also suitable as oral formulations.

25 [SEQUENCE LISTING FREE TEXT]

- Sequence Number 1: Synthetic DNA primer  
Sequence Number 2: Synthetic DNA primer  
Sequence Number 3: Synthetic DNA primer  
Sequence Number 4: Synthetic DNA primer  
5 Sequence Number 5: Peptide fused to the carbonyl terminal  
alanine residue of human SGLT2

10 In the claims which follow and in the preceding  
description of the invention, except where the context  
requires otherwise due to express language or necessary  
implication, the word "comprise" or variations such as  
"comprises" or "comprising" is used in an inclusive sense,  
i.e. to specify the presence of the stated features but  
not to preclude the presence or addition of further  
15 features in various embodiments of the invention.

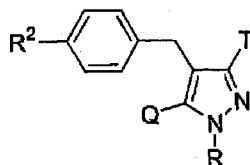
It is to be understood that, if any prior art publication  
is referred to herein, such reference does not constitute  
an admission that the publication forms a part of the  
20 common general knowledge in the art, in Australia or any  
other country.

2002225356 20 Feb 2008

- 120 -

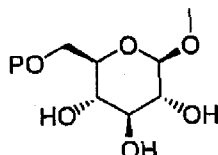
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A glucopyranosyloxypyrazole derivative represented by the general formula:



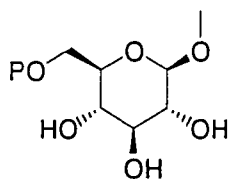
5

wherein R represents a hydrogen atom, a lower alkyl group or a group forming a prodrug; one of Q and T represents a group represented by the general formula:



- 10 (wherein P represents a hydrogen atom or a group forming a prodrug), while the other represents a lower alkyl group or a halo(lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that P does not represent a  
 15 hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof; excluding 4'-((4'-methylthiophenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-carbomethoxy-β-D-glucopyranosyl)-1H-pyrazole and 4'-((4'-  
 20 ethylphenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-carbomethoxy-β-D-glucopyranosyl)-1H-pyrazole.

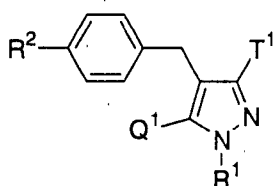
2. A glucopyranosyloxypyrazole derivative as claimed in  
 25 claim 1 wherein T represents a group represented by the general formula:



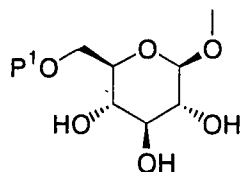
(wherein P represents a hydrogen atom or a group forming a prodrug); and Q represents a lower alkyl group or a halo(lower alkyl) group, or a pharmaceutically acceptable salt thereof.

5

3. A glucopyranosyloxypyrazole derivative as claimed in claim 1, represented by the general formula:



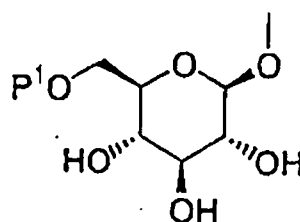
wherein  $R^1$  represents a hydrogen atom, a lower alkyl group, a lower acyl group, a lower alkoxy-carbonyl group, a lower acyloxymethyl group or a lower alkoxy-carbonyloxymethyl group; one of  $Q^1$  and  $T^1$  represents a group represented by the general formula:



15 (wherein  $P^1$  represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group), while the other represents a lower alkyl

group or a halo(lower alkyl) group;  $R^2$  represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that  $P^1$  does not  
 5 represent a hydrogen atom when  $R^1$  represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

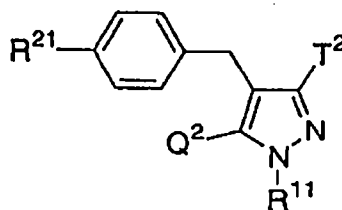
4. A glucopyranosyloxypyrazole derivatives as claimed in  
 10 claim 3 wherein  $T^1$  represents a group represented by the general formula:



(wherein  $P^1$  represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower  
 15 alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group or a lower alkoxy-substituted (lower alkoxycarbonyl) group); and  $Q^1$  represents a lower alkyl group or a halo(lower alkyl) group, or a pharmaceutically acceptable salt thereof.

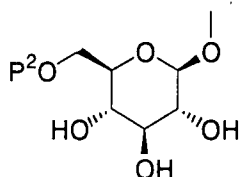
20

5. A glucopyranosyloxypyrazole derivatives as claimed in claim 3, represented by the general formula:



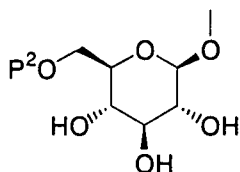
25

wherein  $R^{11}$  represents a hydrogen atom or a lower alkyl group; one of  $Q^2$  and  $T^2$  represents a group represented by the general formula:



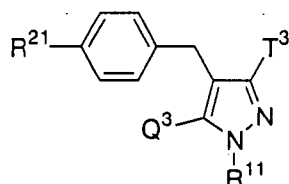
5 (wherein  $P^2$  represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group), while the other represents a lower alkyl group; and  $R^{21}$  represents  
10 a lower alkyl group, a lower alkoxy group or a lower alkylthio group, or a pharmaceutically acceptable salt thereof.

6. A glucopyranosyloxypyrazole derivative as claimed in claim 5 wherein  $T^2$  represents a group represented by the general  
15 formula:

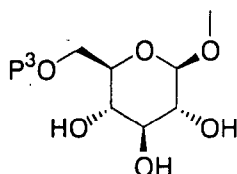


(wherein  $P^2$  represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group);  
20 and  $Q^2$  represents a lower alkyl group, or a pharmaceutically acceptable salt thereof.

7. A glucopyranosyloxypyrazole derivative as claimed in claim 5, represented by the general formula:

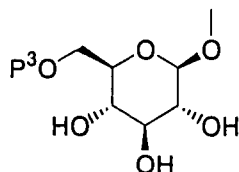


5 wherein  $R^{11}$  represents a hydrogen atom or a lower alkyl group; one of  $Q^3$  and  $T^3$  represents a group represented by the general formula:



(wherein  $P^3$  represents a lower acyl group or a lower  
10 alkoxy carbonyl group), while the other represents a lower alkyl group; and  $R^{21}$  represents a lower alkyl group, a lower alkoxy group or a lower alkylthio group, or a pharmaceutically acceptable salt thereof.

15 8. A glucopyranosyloxypyrazole derivative as claimed in claim 7 wherein  $T^3$  represents a group represented by the general formula:

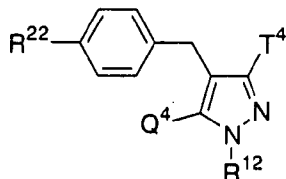


(wherein  $P^3$  represents a lower acyl group or a lower

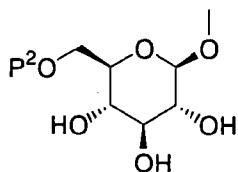


alkoxycarbonyl group); and  $Q^3$  represents a lower alkyl group, or a pharmaceutically acceptable salt thereof.

9. A glucopyranosyloxypyrazole derivative as claimed in claim 5, represented by the general formula:

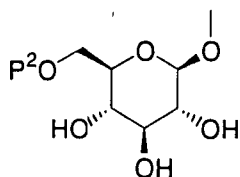


wherein  $R^{12}$  represents a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms; one of  $Q^4$  and  $T^4$  represents a group represented by the general formula:



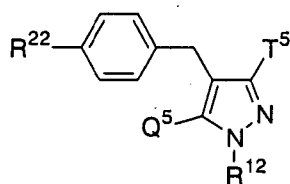
(wherein  $P^2$  represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group or a lower alkoxy-substituted (lower alkoxycarbonyl) group), while the other represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms; and  $R^{22}$  represents a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

10. A glucopyranosyloxypyrazole derivative as claimed in claim 9 wherein  $T^4$  represents a group represented by the general formula:

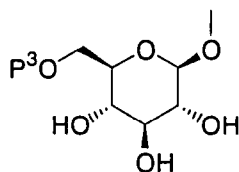


5 (wherein  $P^2$  represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group or a lower alkoxy-substituted (lower alkoxycarbonyl) group); and  $Q^4$  represents a straight-chained or branched alkyl group  
10 having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

11. A glucopyranosyloxypyrazole derivative as claimed in claim 9, represented by the general formula:

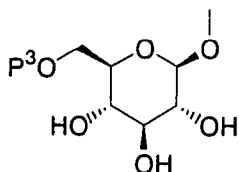


15 wherein  $R^{12}$  represents a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms; one of  $Q^5$  and  $T^5$  represents a group represented by the general formula:



(wherein  $P^3$  represents a lower acyl group or a lower alkoxy carbonyl group), while the other represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms; and  $R^{22}$  represents a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

12. A glucopyranosyloxypyrazole derivative as claimed in claim 11 wherein  $T^5$  represents a group represented by the general formula:



(wherein  $P^3$  represents a lower acyl group or a lower alkoxy carbonyl group); and  $Q^5$  represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

13. A glucopyranosyloxypyrazole derivative as claimed in claim 12, which is selected from the group consisting of 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole, 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,

- 3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 5 4-[(4-ethylphenyl)methyl]-1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,
- 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethylphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethylphenyl)methyl]-3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 10 4-[(4-ethylphenyl)methyl]-3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,
- 15 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-ethoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethoxyphenyl)methyl]-3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 4-[(4-ethoxyphenyl)methyl]-3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole,
- 20 1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,
- 3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,
- 25 3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,
- 3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,

propyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole,  
1-isopropyl-3-(6-O-methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-  
5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-isopropyl-  
5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-  
isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-1-  
isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole,  
and pharmaceutically acceptable salts thereof.

14. A glucopyranosyloxypyrazole derivative as claimed in  
claim 13, which is selected from the group consisting of  
4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-  
methoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-5-methylpyrazole,  
3-(6-O-ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,  
3-(6-O-isopropoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,  
3-(6-O-isobutoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,  
and pharmaceutically acceptable salts thereof.

15. 3-(6-O-Ethoxycarbonyl- $\beta$ -D-glucopyranosyloxy)-4-[(4-  
isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole or  
a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising as an active  
ingredient a glucopyranosyloxypyrazole derivative as  
claimed in any one of claims 1 to 15 or a pharmaceutically  
acceptable salt thereof.

17. A pharmaceutical composition as claimed in claim 16  
wherein the composition is a human SGLT2 inhibitor.

18. A pharmaceutical composition as claimed in claim 16  
or 17 wherein the composition is an agent for the

prevention or treatment of a disease associated with hyperglycemia.

19. A pharmaceutical composition as claimed in claim 18  
5 wherein the disease associated with hyperglycemia is selected from the group consisting of diabetes, diabetic complications, obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder,  
10 atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia and gout.

20. A pharmaceutical composition as claimed in claim 19  
15 wherein the disease associated with hyperglycemia is diabetes.

21. A pharmaceutical composition as claimed in claim 19  
20 wherein the disease associated with hyperglycemia is diabetic complications.

22. A pharmaceutical composition as claimed in claim 19  
wherein the disease associated with hyperglycemia is obesity.

23. A pharmaceutical composition as claimed in any one of  
25 claims 16 to 22 wherein the composition is an oral formulation.

24. A method for the prevention or treatment of a disease  
30 associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxypyrazole derivative as claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof.

25. A use of glucopyranosyloxypyrazole derivative as  
35 claimed in any one of claims 1 to 15 or a pharmaceutically

acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

- 5 26. A pharmaceutical combination which comprises (A) a glucopyranosyloxypyrazole derivative as claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3
- 10
- 15
- 20

inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1  
 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin  
 analogue, an amylin agonist, an aldose reductase inhibitor, an  
 advanced glycation endproducts formation inhibitor, a protein  
 5 kinase C inhibitor, a  $\gamma$ -aminobutyric acid receptor antagonist,  
 a sodium channel antagonist, a transcript factor NF- $\kappa$ B inhibitor,  
 a lipid peroxidase inhibitor, an *N*-acetylated- $\alpha$ -linked-acid-  
 dipeptidase inhibitor, insulin-like growth factor-I,  
 platelet-derived growth factor, a platelet-derived growth  
 10 factor analogue, epidermal growth factor, nerve growth factor,  
 a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin,  
 EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-  
 glutaryl coenzyme A reductase inhibitor, a fibric acid derivative,  
 a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol  
 15 acyltransferase inhibitor, probcol, a thyroid hormone receptor  
 agonist, a cholesterol absorption inhibitor, a lipase inhibitor,  
 a microsomal triglyceride transfer protein inhibitor, a  
 lipoxygenase inhibitor, a carnitine palmitoyl-transferase  
 inhibitor, a squalene synthase inhibitor, a low-density  
 20 lipoprotein receptor enhancer, a nicotinic acid derivative, a  
 bile acid sequestrant, a sodium/bile acid cotransporter  
 inhibitor, a cholesterol ester transfer protein inhibitor, an  
 appetite suppressant, an angiotensin-converting enzyme  
 inhibitor, a neutral endopeptidase inhibitor, an angiotensin  
 25 II receptor antagonist, an endothelin-converting enzyme  
 inhibitor, an endothelin receptor antagonist, a diuretic agent,  
 a calcium antagonist, a vasodilating antihypertensive agent,



a sympathetic blocking agent, a centrally acting antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

5

27. A pharmaceutical combination claimed in claim 26 for the prevention or treatment of a disease associated with hyperglycemia.

10 28. A pharmaceutical combination claimed in claim 27 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt  
15 thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipetidyl peptidase  
20 IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen  
25 synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist and an appetite suppressant, and the disease associated with hyperglycemia is diabetes.

30

29. A pharmaceutical combination claimed in claim 28 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt  
35 thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion

enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue and an amylin agonist.

30. A pharmaceutical combination claimed in claim 29 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer and an insulin preparation.

31. A pharmaceutical combination claimed in claim 27 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic glyconeogenesis inhibitor, D-chiroinsitol, a glycogen

synthase kinase-3 inhibitors, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation  
5 endproducts formation inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid antagonist, a sodium channel antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I,  
10 platelet-derived growth factor, a platelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimoclomol, sulodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral  
15 endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a diuretic agent, and the disease associated with hyperglycemia is diabetic complications.

20

32. A pharmaceutical combination claimed in claim 31 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt  
25 thereof is at least one member selected from the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist.

30

33. A pharmaceutical combination claimed in claim 27 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt  
35 thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion

enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a  $\beta_3$ -adrenoceptor agonist and an appetite suppressant, and the disease associated with hyperglycemia is obesity.

34. A pharmaceutical combination claimed in claim 33 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of a  $\beta_3$ -adrenoceptor agonist and an appetite suppressant.

35. A pharmaceutical combination claimed in claim 34 wherein the appetite suppressant is a drug selected from the group consisting of a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, a serotonin releasing stimulant, a serotonin agonist, a noradrenaline reuptake inhibitor, a noradrenaline releasing stimulant, an  $\alpha_1$ -adrenoceptor agonist, a  $\beta_2$ -adrenoceptor agonist, a dopamine agonist, a cannabinoid receptor antagonist, a  $\gamma$ -aminobutyric acid receptor antagonist, a  $H_3$ -histamine antagonist, L-histidine, leptin, a leptin analogue, a leptin receptor agonist, a melanocortin receptor agonist,  $\alpha$ -melanocyte stimulating hormone, cocaine-and amphetamine-regulated transcript, mahogany protein, an enterostatin agonist, calcitonin, calcitonin-gene-related peptide, bombesin, a cholecystokinin agonist, corticotrophin-

releasing hormone, a corticotrophin-releasing hormone  
analogue, a corticotrophin-releasing hormone agonist,  
urocortin, somatostatin, a somatostatin analogue, a  
somatostatin receptor agonist, pituitary adenylate  
5 cyclase-activating peptide, brain-derived neurotrophic  
factor, ciliary neurotrophic factor, thyrotropin-releasing  
hormone, neurotensin, sauvagine, a neuropeptide Y  
antagonist, an opioid peptide antagonist, a galanin  
antagonist, a melanin-concentrating hormone antagonist, an  
10 agouti-related protein inhibitor and an orexin receptor  
antagonist.

36. A method for the prevention or treatment of a disease  
associated with hyperglycemia, which comprises  
15 administering an effective amount of (A) a  
glucopyranosyloxypyrazole derivative claimed in any one of  
claims 1 to 15 or a pharmaceutically acceptable salt  
thereof, in combination with (B) at least one member  
selected from the group consisting of an insulin  
20 sensitivity enhancer, a glucose absorption inhibitor, a  
biguanide, an insulin secretion enhancer, an insulin  
preparation, a glucagon receptor antagonist, an insulin  
receptor kinase stimulant, a tripeptidyl peptidase II  
inhibitor, a dipeptidyl peptidase IV inhibitor, a protein  
25 tyrosine phosphatase-1B inhibitor, a glycogen  
phosphorylase inhibitor, a glucose-6-phosphatase  
inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate  
dehydrogenase inhibitor, a hepatic gluconeogenesis  
inhibitor, D-chiroinsitol, a glycogen synthase kinase-3  
30 inhibitor, glucagon-like peptide-1, a glucagon-like  
peptide-1 analogue, a glucagon-like peptide-1 agonist,

amylin, an amylin analogue and an amylin agonist, an  
aldose reductase inhibitor, an advanced glycation  
endproducts formation inhibitor, a protein kinase C  
inhibitor, a

5

$\gamma$ -aminobutyric acid receptor antagonist, a sodium channel  
 antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid  
 peroxidase inhibitor, an *N*-acetylated- $\alpha$ -linked-acid-  
 dipeptidase inhibitor, insulin-like growth factor-I,  
 5 platelet-derived growth factor, a platelet-derived growth  
 factor analogue, epidermal growth factor, nerve growth factor,  
 a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin,  
 EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-  
 glutaryl coenzyme A reductase inhibitor, a fibric acid derivative,  
 10 a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol  
 acyltransferase inhibitor, probcol, a thyroid hormone receptor  
 agonist, a cholesterol absorption inhibitor, a lipase inhibitor,  
 a microsomal triglyceride transfer protein inhibitor, a  
 lipoxygenase inhibitor, a carnitine palmitoyl-transferase  
 15 inhibitor, a squalene synthase inhibitor, a low-density  
 lipoprotein receptor enhancer, a nicotinic acid derivative, a  
 bile acid sequestrant, a sodium/bile acid cotransporter  
 inhibitor, a cholesterol ester transfer protein inhibitor, an  
 appetite suppressant, an angiotensin-converting enzyme  
 20 inhibitor, a neutral endopeptidase inhibitor, an angiotensin  
 II receptor antagonist, an endothelin-converting enzyme  
 inhibitor, an endothelin receptor antagonist, a diuretic agent,  
 a calcium antagonist, a vasodilating antihypertensive agent,  
 a sympathetic blocking agent, a centrally acting  
 25 antihypertensive agent, an  $\alpha_2$ -adrenoceptor agonist, an  
 antiplatelets agent, a uric acid synthesis inhibitor, a  
 uricosuric agent and a urinary alkalinizer.

37. A use of (A) a glucopyranosyloxypyrazole derivative claimed in any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin

5 sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein

10 tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic glycconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3

15 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a  $\gamma$ -aminobutyric acid receptor antagonist, a sodium channel

20 antagonist, a transcript factor NF- $\kappa$ B inhibitor, a lipid peroxidise inhibitor, an N-acetylated- $\alpha$ -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth

25 factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a  $\beta_3$ -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol,

30 a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a

35 squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter



2002225356 20 Feb 2008

- 141 -

inhibitor, a cholesterol ester transfer protein inhibitor,  
an appetite suppressant, an angiotensin-converting enzyme  
inhibitor, a neutral endopeptidase inhibitor, an  
angiotensin II receptor antagonist, an endothelin-  
5 converting enzyme inhibitor, an endothelin receptor  
antagonist, a diuretic agent, a sympathetic blocking  
agent, a centrally acting antihypertensive agent, an  $\alpha_2$ -  
adrenoceptor agonist, an antiplatelets agent, a uric acid  
synthesis inhibitor, a uricosuric agent and a urinary  
10 alkalinizer, for the manufacture of a pharmaceutical  
composition for the prevention or treatment of a disease  
associated with hyperglycemia.

38. A glucopyranosyloxypyrazole derivative excluding 4'-  
15 ((4'-methylthiophenyl)methyl)-5'-trifluoromethyl-3'-O-(6-  
O-carbomethoxy- $\beta$ -D-glucopyranosyl)-1H-pyrazole and 4'-  
((4'-ethylphenyl)methyl)-5'-trifluoromethyl-3'-O-(6-O-  
carbomethoxy- $\beta$ -D-glucopyranosyl)-1H-pyrazole, a  
pharmaceutical composition or combination comprising it,  
20 or a method or use involving it, substantially as herein  
described with reference to the accompanying examples.

1 / 2

## SEQUENCE LISTING

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<120> GLUCOPYRANOSYLOXYPIRAZOLE DERIVATIVES AND PHARMACEUTICAL USES THEREOF

<130> PCT-A0138

<150> JP 2000/403534

<151> 2000-12-28

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<400> 5

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1 5 10 15

Ala Val Asp His His His His His His  
20 25