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(54) Title: PYRAZOLOPYRIMIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE

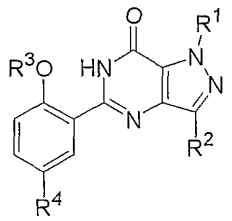
(57) Abstract: This invention relates to a series of pyrazolopyrimidinone derivatives, having an excellent inhibiting activity against cyclic guanosine 3',5'- monophosphate specific phosphodiesterase (cGMP specific PDE; PDE V), process for their preparation, intermediates in their preparation, their uses as therapeutic agents, and pharmaceutical compositions containing them.

PYRAZOLOPYRIMIDINONE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a series of pyrazolopyrimidinone derivatives represented in the formula (**1**), having an excellent inhibiting activity against cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE; PDE V), process for their preparation, intermediates in their preparation, their uses as therapeutic agents, and pharmaceutical compositions containing them,



(1)

wherein R^1 is H; C_1-C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3-C_6 cycloalkyl;

R^2 is H; C_1-C_6 alkyl optionally substituted with OH, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, one or more fluoro substituents; C_3-C_6 cycloalkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl, or with one or more fluoro substitutents; C_2-C_6 alkenyl; C_2-C_6 alkynyl; or C_3-C_6 cycloalkyl;

R^4 is $SO_2NR^5R^6$ or $NHCOR^7$;

R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino or piperazinyl group wherein said

group is substituted with R^8;

R^7 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl or with one or more fluoro substitutents; C_3-C_7 cycloalkyl;

R^8 is CO_2H; (C_1-C_4 alkyl)CO_2H; $PO(OR^9)(OR^{10})$; or (C_1-C_4 alkyl)$PO(OR^9)(OR^{10})$; and

R^9 and R^{10} are each independently H, or C_1-C_4 alkyl.

European patent applications EP-A-0463756 and EP-A-0526004 disclose certain pyrazolo[4,3-*d*]pyrimidin-7-ones as cGMP PDE inhibitors, useful in the treatment of cardiovascular disorders such as angina, hypertension and heart failure. International application WO 94/28902 discloses their use for the treatment of impotence. None of the compounds of this invention are specifically disclosed.

SUMMARY OF THE INVENTION

The compounds of this invention are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE; PDE V) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of impotence (male erectile dysfunction), sexual dysfunction in female, and various cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

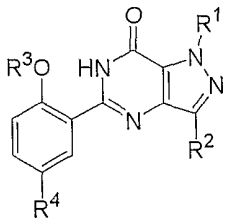
As a consequence of the selective PDE V inhibition exhibited by compounds of this invention, cGMP levels are elevated, which in turn can give rise to beneficial vasodilatory, anti-vasospastic, anti-platelet, anti-neutrophil, natriuretic and diuretic activities as well as potentiation of the effects of endothelium-derived relaxing factor (EDRF), nitrovasodilators,

atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP) and endothelium-dependent relaxing agents such as bradykinin, acetylcholine and 5-HT_1.

The compounds of this invention therefore have utility in the treatment of a number of disorders, including impotence, sexual dysfunction in female, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility (e.g. irritable bowel syndrome).

Detailed Description of the Invention

Thus, according to a first aspect, this invention provides compounds of the formula (**1**) and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof,



(1)

wherein R^1, R^2, R^3, and R^4 are the same as previously defined.

In the above definition, unless otherwise indicated, alkyl groups having three or more carbon atoms may be straight or branched chain. In

addition, alkenyl or alkynyl groups having four or more carbon atoms, or alkoxy groups having three carbon atoms, may be straight or branched chain.

Compounds of the formula (**1**) may contain one or more asymmetric centers and thus can exist as enantiomers or diastereomers. It is to be understood that the invention includes both mixtures and separate individual isomers of compounds of the formula (**1**). Furthermore certain compounds of the formula (**1**) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

Compounds of the formula (**1**) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers thereof.

Also included in the invention are radiolabelled derivatives of compounds of formula (**1**) which are suitable for biological studies.

Compounds of the formula (**1**) wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a piperazinyl group may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, citric, fumaric, lactic, maleic, succinic and tartaric acids.

Compounds of the formula (**1**) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

A preferred group of compounds of the formula (**1**) is that

wherein

R^1 is H; methyl; or ethyl;

R^2 is C_1-C_4 alkyl;

R^3 is ethyl; *n*-propyl; or allyl;

R^4 is $SO_2NR^5R^6$; or $NHCOR^7$;

R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino or piperazinyl group wherein said group is substituted with R^8;

R^7 is isopropyl; or cyclohexyl;

R^8 is CO_2H; (C_1-C_2 alkyl)CO_2H; $PO(OR^9)(OR^{10})$; or (C_1-C_2 alkyl)$PO(OR^9)(OR^{10})$; and

R^9 and R^{10} are each independently H, methyl, or ethyl.

A particularly preferred group of compounds of the formula (1) is that wherein,

R^1 is methyl;

R^2 is *n*-propyl;

R^3 is ethyl; or *n*-propyl;

R^4 is $SO_2NR^5R^6$; or $NHCOR^7$;

R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino or piperazinyl group wherein said group is substituted with R^8;

R^7 is cyclohexyl;

R^8 is CO_2H; (C_1-C_2 alkyl)CO_2H; $PO(OR^9)(OR^{10})$; or (C_1-C_2 alkyl)$PO(OR^9)(OR^{10})$; and

R^9 and R^{10} are each independently H, methyl, or ethyl.

Especially preferred individual compounds of the invention include:

5-(5-(4-(hydroxycarbonyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(hydroxycarbonylmethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(hydroxycarbonylmethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(2-hydroxycarbonylethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(2-hydroxycarbonylethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(hydroxycarbonylmethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(hydroxycarbonylmethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(2-hydroxycarbonylethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(2-hydroxycarbonylethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(ethylphosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(ethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(methylphosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(methylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(ethylphosphonomethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(ethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

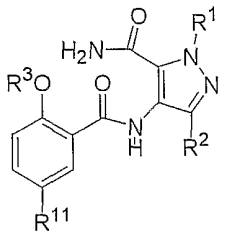
5-(2-ethoxy-5-(4-(methylphosphonomethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(methylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-cyclohexanecarbonylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

In another aspect, this invention provides three different processes for the preparation of compounds of the formula (**1**) or pharmaceutically

acceptable salts thereof. Compounds of the formula (**1**) may be prepared in accordance with the following "method A" by a cyclization reaction of the formula (**2**):



(**2**)

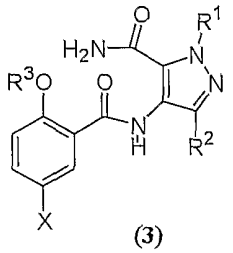
wherein R^1, R^2, and R^3 are as previously defined, and R^{11} is a group R^4 as hereinbefore defined or a precursor to a group R^4 thereof.

A cyclization reaction is generally carried out by heating at an elevated temperature, for example 50-150℃, in the presence of an acid or a base in a suitable solvent such as an aqueous C_1-C_4 alkanol, water, a halogenated hydrocarbon, or acetonitrile. Thus, for example, the cyclization may be affected by the treatment of a compound of the formula (**2**) with an inorganic base such as sodium hydroxide or potassium carbonate, optionally in the presence of hydrogen peroxide, in an ethanol-water medium at reflux temperature.

In an alternative cyclization procedure, compounds of the formula (**1**) may be obtained by treatment of (**2**) with polyphosphoric acid at or near 140 °C for 6-18 hours. Examples of R^{11} being a precursor to a group R^4 are when R^8 is a carboxylic acid or mono-alkyl phosphonate (R^8 is as previously defined). Ester group of the formula (**2**) can be converted to the corresponding carboxylic acid (R^8 = CO_2H or (C_1-C_4 alkyl)CO_2H) or mono-alkyl phosphonate (R^8 = $PO(OR^9)(OR^{10})$ or (C_1-C_4 alkyl)$PO(OR^9)(OR^{10})$ wherein R^9 or R^{10} = H) under the basic cyclization condition.

Compounds of the formula (**2**) may be prepared by reacting a

compound of the formula (3) with a compound of the formula (4):



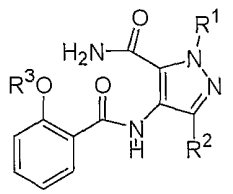
(3)

(4)

wherein R^1, R^2, R^3, R^5 and R^6 are as previously defined, and X represents sulfonyl halide, preferably halide being a chlorine atom.

The reaction is generally carried out at 0 °C to room temperature for 1-24 hours in a suitable solvent such as a C_1-C_3 alkanol, DMF, or water using an excess amount of (4) or in the presence of an organic tertiary amine, preferably triethylamine, to scavenge the acid by-product.

Compounds of the formula (3) may be prepared from compounds of the formula (5):



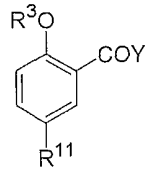
(5)

wherein R^1, R^2, and R^3 are as previously defined.

This reaction is performed by applying known methods for the introduction of a sulfonyl halide group into an aromatic ring, for example, when halide represents a chlorine atom, by the action of chlorosulfonic acid at 0 °C to room temperature for 3-24 hours without any solvent. The starting materials of the formula (5) are readily obtainable by the method known per se in the art (EP-A-0463756; *Bioorganic & Medicinal Chemistry Letters* **1996**, *6*, 1819-1824).

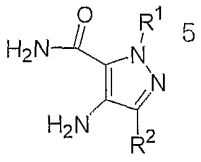
Compounds of the formula (1) may be prepared in accordance with the

second "method B" by a cyclization reaction of the same precursor (2), where the formula (2) can be obtained from compounds of the formula (6) and (7):



Y = OH or halide

(6)



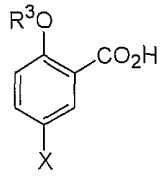
(7)

wherein R^1, R^2, and R^3 are as previously defined, and R^{11} is a group R^4 as hereinbefore defined or a precursor to a group R^4 thereof, and Y represents a hydroxyl group or a halogen atom, preferably a chlorine atom.

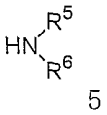
The reaction is generally carried out by first converting a carboxylic acid of the formula (6) (Y = OH) to the corresponding acyl chloride using excess amounts of well-known reagents in the literature, preferably thionyl chloride or oxalyl chloride, in the presence of an inert solvent such as dichloromethane or benzene, at room temperature to reflux temperature. The coupling reaction with a compound of the formula (7) is generally affected by using an excess of the resulting acyl chloride (6) (Y = Cl) in the presence of an excess of an organic tertiary amine such as triethylamine to act as scavenger for the acid by-product (HY), optionally in the presence of a catalyst such as 4-dimethylaminopyridine (DMAP), in an inert anhydrous solvent such as dichloromethane at 0 °C to room temperature for 2-6 hours. The starting materials of the formula (7) are readily obtainable by the method known per se in the art (EP-A-0463756; *Bioorganic & Medicinal Chemistry Letters* **1996**, *6*, 1819-1824).

Compounds of the formula (6) (wherein Y = OH) may be prepared by

reacting compounds of the formula (8) with a compound of the general formula (4):



(8)

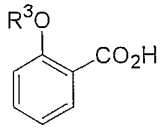


(4)

wherein R^3, R^5 and R^6 are as previously defined, and X represents sulfonyl halide, preferably halide being a chlorine atom.

The reaction is generally carried out at 0 °C to room temperature for 1-24 hours in a suitable solvent such as a C_1-C_3 alkanol, DMF, or water using an excess amount of (4) or in the presence of an organic tertiary amine, preferably triethylamine to scavenge the acid by-product.

Compounds of the formula (8) may be prepared from compounds of the formula (9):

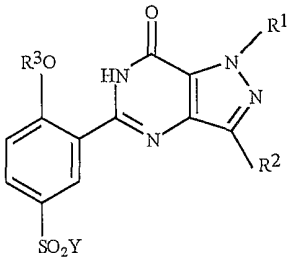


(9)

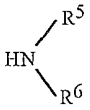
wherein R^3 is as previously defined.

This reaction is preformed by applying known methods for the introduction of a sulfonyl halide group into an aromatic ring, for example, when halide represents a chlorine atom, by the action of chlorosulfonic acid at 0 °C to room temperature for 3-24 hours without any solvent. The starting materials of the formula (9) are known compounds, which are either commercially available or readily obtainable by conventional synthetic procedures.

Compounds of the formula (**1**) may be prepared in accordance with the second "method B" from compounds of the formula (**10**) and compounds of the formula (**4**):



(**10**)

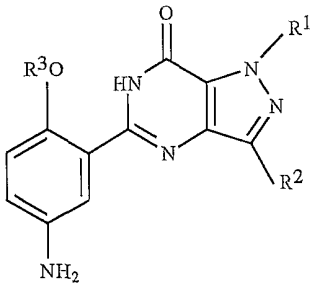


(**4**)

wherein R^1, R^2, R^3, R^5, and R^6 are as previously defined; and Y represents a halogen atom, preferably a chlorine atom.

The reaction of compounds of the formula (**10**) with a compound of the formula (**4**) is generally carried out at 0 °C to room temperature for 1-24 hours in a suitable solvent such as a C_1-C_3 alkanol, DMF, or water using an excess amount of (**4**) or in the presence of an organic tertiary amine, preferably triethylamine to scavenge the acid by-product.

Compounds of the formula (**1**) may be prepared in accordance with the third "method c" from compounds of the formula (**11**):

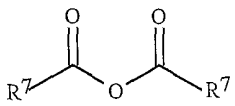


(**11**)

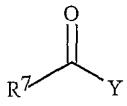
wherein R^1, R^2 and R^3 are as previously defined.

This reaction is conveniently carried out at 0 °C to room temperature for 1-24 hours in an inert anhydrous solvent such as dichloromethane or THF

using the compound of the formula (**11**) and an excess amount of the compound (**12**) or (**13**), in the presence of an organic tertiary amine, preferably triethylamine to scavenge the acid by-product,



(**12**)

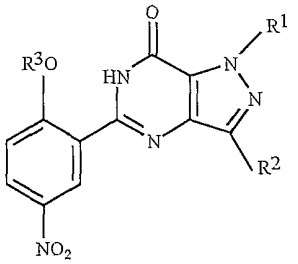


(**13**)

wherein R^7 is as previously defined; and Y represents a halogen atom, preferably a chlorine atom.

The carboxylic acid anhydride of the formula (**12**) and the acyl halide of the formula (**13**) are either commercially available or readily obtainable by conventional synthetic procedures.

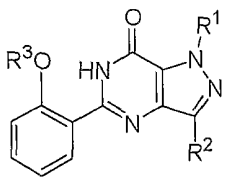
The amines of the formula (**11**) can be readily obtained by reduction of the corresponding nitro compounds of the formula (**14**) using well-known methods such as catalytic hydrogenation in an alcoholic solvent, or tin(II) chloride reduction, and so on,



(**14**)

wherein R^1, R^2, and R^3 are as previously defined.

Compounds of the formula (**10**) may be prepared from compounds of the formula (**15**):



(**15**)

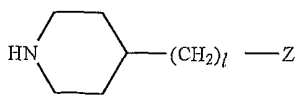
wherein R^1, R^2, and R^3 are as previously defined.

This reaction is performed by applying known methods for the introduction of a sulfonyl halide group into an aromatic ring, for example, when halide represents a chlorine atom, by the action of chlorosulfonic acid at 0 °C to room temperature for 3-24 hours without any solvent.

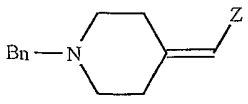
The nitro compounds of the formula (**14**) may be also prepared from compounds of the formula (**15**) by using known methods for the nitration of an aromatic ring, and the reaction is generally carried out using sodium nitrite or fuming nitric acid under a strongly acidic medium such as concentrated sulfuric acid or trifluoroacetic acid, preferably nitric acid and trifluoroacetic acid, at -10 °C to room temperature for 1-24 hours. The starting materials of the formula (**15**) are readily obtainable by the method known per se in the art (EP-A-0463756; *Bioorganic & Medicinal Chemistry Letters* **1996**, *6*, 1819-1824).

The amines of the formula (**4**), when not commercially available, can be prepared by conventional synthetic procedures, in accordance with literature precedent, from readily accessible starting materials using standard reagents and reaction conditions.

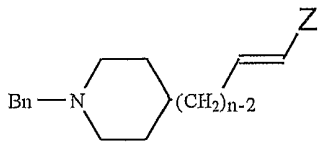
Certain compounds of the formula (**4a**), wherein R^5 and R^6 taken together with the nitrogen atom to which they are attached form a piperidino group substituted with R^8 (R^8 is as previously defined), can be synthesized efficiently from the compounds of the formula (**16**) or (**17**):



(4a)



(16)

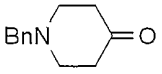


(17)

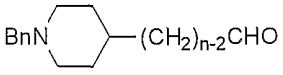
wherein *l* is 0, 1, 2, 3, or 4; n is 2, 3, or 4; Z is a group CO_2R or $PO(OR)_2$; and R is a group R^9, or R^{10} as hereinbefore defined or a precursor to a group H, R^9, or R^{10} thereof, wherein R^9 and R^{10} are as previously defined.

Examples of R being a precursor to a group H, R^9, or R^{10} are when R^8 is a carboxylic acid, phosphonic acid, or mono-alkyl phosphonate (R^8 is as previously defined). Ester group of the formula (**4a**) may be converted to the corresponding carboxylic acid, phosphonic acid, or mono-alkyl phosphonate under the basic or acidic condition. Removal of benzyl group and reduction of the double bond in the compounds of the formula (**16**) or (**17**) can be performed simultaneously under a hydrogenation condition using a catalytic amount of palladium on carbon in an alcoholic solvent such as methanol or ethanol, at room temperature to afford the corresponding compounds of the formula (**4a**).

The α,β-unsaturated compounds of the formula (**16**) and (**17**) may be prepared from the reaction of an appropriate carbonyl compound of the formula (**18**) or (**19**) with (carboalkoxymethylene) triphenylphosphorane (**20**) or tetraalkyl methylenediphosphonate (**21**):



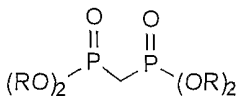
(18)



(19)
n = 2–4

$Ph_3P{=}CHCO_2R$

(20)

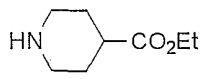


(21)

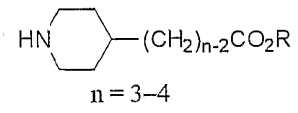
wherein R is as previously defined.

The olefination of 1-benzyl-4-piperidone (**18**) or aldehyde compounds of the formula (**19**) was generally carried out using (carboalkoxymethylene) triphenylphosphorane (**20**) in an anhydrous aprotic solvent such as acetonitrile at room temperature to 100 °C, or tetraalkyl methylenediphosphonate (**21**) in an anhydrous hydrocarbon solvent such as toluene at 0 °C to room temperature in the presence of an appropriate base, preferably sodium hydride. Reagents for the olefination, (**20**) and (**21**), are either commercially available or readily accessible by conventional synthetic procedures in accordance with literature precedents.

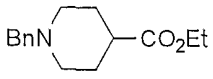
The aldehyde compound (**19**) can be prepared either from ethyl isonipecotate (**22**) or compounds of the formula (**23**) using a two-step procedure, which consists of N-benzylation and the conversion of ester group to aldehyde functionality. Benzylation of ethyl isonipecotate (**22**) or compounds of the formula (**23**) is conveniently carried out using benzyl halide, preferably halide being a bromine atom, in an anhydrous aprotic solvent such as acetonitrile at room temperature in the presence of an organic tertiary amine, preferably triethylamine to scavenge the acid by-product, to afford the corresponding compounds of the formula (**24**) or (**25**).



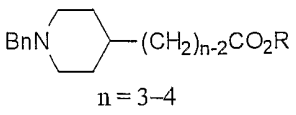
(**22**)



(**23**)



(**24**)

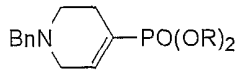


(**25**)

wherein R is as previously defined.

The ester compounds of the formula (**24**) and (**25**) can be efficiently converted to the corresponding aldehydes of the formula (**19**) by using a reducing reagent, preferably diisobutylaluminum hydride (DIBAL-H), at low temperature, for example, -78 °C, in an anhydrous aprotic solvent such as dichloromethane.

A compound of the formula (**4**) (wherein Z is $PO(OR)_2$ and n = 0) may be prepared from the compound of the formula (**26**):

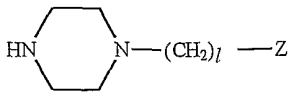


(**26**)

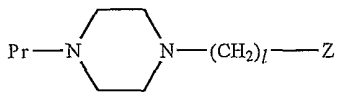
wherein R is as previously defined.

The compound of the formula (**26**) is readily obtainable by the method known per se in the art (*Tetrahedron Letters* **1989**, *40*, 5393-5396). Removal of benzyl group and reduction of the double bond are carried out simultaneously under a hydrogenation condition using a catalytic amount of palladium on carbon in an alcoholic solvent such as methanol or ethanol, at room temperature.

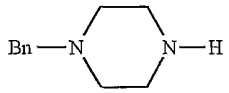
Certain compounds of the formula (**4b**), wherein R^5 and R^6 taken together with the nitrogen atom to which they are attached form a piperazinyl group substituted with R^8 (R^8 is as previously defined), can be synthesized readily from the compounds of the formula (**27**):



(**4b**)



(**27**)



(28)

wherein *l* is 0, 1, 2, 3, or 4; n is 2, 3, or 4; Z is a group CO_2R or $PO(OR)_2$; and R is as previously defined; and P represents an appropriate protecting group, for example, benzyl or benzyloxycarbonyl (Cbz).

Ester group of the formula (**4b**) may be converted to the corresponding carboxylic acid, phosphonic acid, or mono-alkyl phosphonate under the basic or acidic condition. Removal of benzyl or benzyloxycarbonyl (Cbz) group in the compounds of the formula (**27**) can be performed under a hydrogenation condition using a catalytic amount of palladium on carbon in an alcoholic solvent such as methanol or ethanol, at room temperature to afford the corresponding compound of the formula (**4b**). The starting materials of the formula (**27**) (wherein Z is $PO(OR)_2$) are readily obtainable by the method known per se in the art (JP 61-176579; *Heterocycles* **1981**, *16*, 1205-1242). Another starting compounds of the formula (**27**) (wherein Z is CO_2R) can be prepared from 1-benzylpiperazine (**28**) either by the reaction of conjugate addition with ethyl acrylate or direct N-alkylation with an appropriate alkyl halide containing an ester group.

The resulting compounds of this invention represented by the formula (**1**)-(**6**), (**8**), (**11**), and (**12**) can be separated and purified by appropriate conventional methods such as column chromatography and recrystallization.

Compounds of the invention may be administered by any suitable route, for example by oral, buccal, sub-lingual, rectal, vaginal, nasal, topical or

parenteral (including intravenous, intramuscular, subcutaneous and intracoronary) administration.

For administration to man in the curative or prophylactic treatment of the disorders identified above, oral, buccal or sub-lingual dosages of a compound of formula (1) will generally be in the range of from 0.1-400 mg daily for an average adult patient (70 Kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.05-200 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for parenteral administration will typically be within the range of from 0.01-100 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be the most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

For human use, a compound of the formula (1) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agent (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of

apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and caprylic/capric glycerides). A compound may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of the formula (1), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier thereof.

The invention also provides a compound of the formula (1), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for use in the treatment of impotence, sexual dysfunction in female, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility (e.g. irritable bowel syndrome).

The invention further provides the use of a compound of the formula (1), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of impotence, sexual dysfunction in female, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary

hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility (e.g. irritable bowel syndrome).

In a further aspect, the invention provides a method of treating or preventing impotence, sexual dysfunction in female, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility (e.g. irritable bowel syndrome), in a mammal (including a human being), which comprises administering to said mammal a therapeutically effective amount of a compound of formula (1), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity.

The invention also includes any novel intermediates of formulae (2) and (6) disclosed herein.

The present invention is further illustrated in the following Preparative Examples and Examples, which should not be taken to limit the scope of the invention.

Preparative Example 1

Preparation of 1-benzyl-4-(2-diethylphosphonovinyl)piperidine (a compound of the formula (17) wherein n = 2, Z = $PO(OEt)_2$)

To a cooled solution of ethyl 1-benzylisonipecotate (**24**) (0.36 g, 1.40 mmol) in CH_2Cl_2 (4 mL) at -78 °C under nitrogen atmosphere was added slowly 1.0 M solution of diisobutylaluminum hydride in toluene (1.5 mL, 1.50 mmol), and stirring was continued for 15 min at -78 °C. The reaction was quenched with saturated NH_4Cl aqueous solution (20 mL) at -78 °C, and then the mixture was warmed to room temperature immediately. The resulting white precipitate was removed by filtering through a Celite pad, and the filtrate was extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to afford the crude aldehyde product as a yellowish liquid, which was used for the next step without further purification.

To a suspension of NaH (95%, 42 mg, 1.64 mmol) in toluene (5 mL) was added tetraethyl methylenediphosphonate (0.41 g, 1.64 mmol) at room temperature, and stirring was continued for 15 min at room temperature. The crude aldehyde in toluene (2 mL) was added to the reaction mixture, and stirring was continued for 2 h at room temperature. The reaction was quenched with H_2O (10 mL), and then extracted with EtOAc (2 x 20 mL). The organic layers were combined, dried (Na_2SO_4), and filtered. The filtrate was evaporated to dryness under vacuum to afford yellowish oil. The crude product was purified by MPLC on silica gel (gradient elution: 2/1 EtOAc/hexanes followed by 4/1 EtOAc/hexanes) to afford the titled compound (0.38 g, 75%) as pale yellow oil.

IR (neat) 1629 (C=C), 1247 (P=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.315 (t, J = 7.2 Hz, 3 H, $PO(OCH_2CH_3)_2$), 1.316 (t, J

= 7.2 Hz, 3 H, PO(OCH_2CH_3)$_2$), 1.42-1.56 (m, 2 H, 2 CH_{ax}), 1.60-1.77 (m, 2 H, 2 CH_{eq}), 2.00 (td, *J* = 11.7 Hz, 2.1 Hz, 2 H, 2 NCH_{ax}), 2.06-2.17 (m, 1 H, CH), 2.86-2.94 (m, 2 H, 2 NCH_{eq}), 3.50 (s, 2 H, NCH_2Ph), 4.01-4.11 (m, 4 H, PO(OCH_2CH_3)$_2$), 5.61 (ddd, *J* = 20.6 Hz, 17.3 Hz, 1.5 Hz, 1 H, HC=C*H*PO), 6.75 (ddd, *J* = 22.5 Hz, 17.3 Hz, 6.3 Hz, 1 H, *H*C=CHPO), 7.22-7.34 (m, 5 H, ArH);

MS (FAB) *m/z* 338 (MH^+).

Preparative Example 2

Preparation of 4-(2-diethylphosphonoethyl)piperidine (a compound of the formula (4) wherein n = 2, Z = PO(OEt)$_2$)

A solution of 1-benzyl-4-(2-diethylphosphonovinyl)piperidine (0.38 g, 1.13 mmol) in MeOH (14 mL) was stirred for 16 h at room temperature in hydrogen atmosphere (a balloon) in the presence of 10% Pd/C (0.14 g). The mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness in vacuo to give yellow oil. The crude oily product was purified by MPLC on silica gel (gradient elution: 10% MeOH in $CHCl_3$ followed by 30% MeOH in $CHCl_3$) to afford the titled compound (0.23 g, 83%) as pale yellow oil.

IR (neat) 3390 (NH), 1199 (P=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.32 (t, *J* = 7.2 Hz, 6 H, PO(OCH_2CH_3)$_2$), 1.64-1.98 (m, 9 H, 4 CH_2 and CH), 2.82-2.98 (m, 2 H, 2 NCH_{ax}), 3.50 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 4.05-4.16 (m, 4 H, PO(OCH_2CH_3)$_2$);

MS (FAB) *m/z* 250 (MH^+).

Preparative Example 3 "Method A"

Preparation of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5- carboxamide (a compound of the formula (3) wherein X = SO_2Cl, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$)

To a stirred and cooled chlorosulfonic acid (30 mL) in an ice bath under nitrogen atmosphere was added portionwise 4-(2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (15.01 g, 45.40 mmol), and the reaction mixture was warmed to room temperature gradually after the addition. The resulting mixture was stirred at room temperature for 2 h and was diluted with $CHCl_3$ (500 mL). Water (100 mL) was carefully added to the cooled mixture in an ice bath, and the organic layer was separated. The aqueous layer was extracted further with $CHCl_3$ (2 x 100 mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure to give the desired sulfonyl chloride as an off-white solid. The crude product was solidified by dissolving in CH_2Cl_2 (20 mL) and adding it to hexane (800 mL) to afford the titled compound (16.02 g, 82%) as white solid. Analytically pure compound was obtained by crystallization from $CHCl_3$/hexanes.

mp 158-159 °C;

IR (neat) 3350, 3190 (NH), 1665, 1641 (C=O), 1176 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 0.95 (t, J = 7.4 Hz, 3 H, $CH_2CH_2CH_3$), 1.60-1.72 (m, 2 H, $CH_2CH_2CH_3$), 1.62 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 2.54 (dd, J = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 4.06 (s, 3 H, NCH_3), 4.46 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 5.71 (br s, 1 H, $CONH_2$), 7.26 (d, J = 9.0 Hz, 1 H, H-3'), 7.61 (br s, 1 H, $CONH_2$), 8.19 (dd,

J = 9.0 Hz, 2.7 Hz, 1 H, H-4'), 8.95 (d, J = 2.7 Hz, 1 H, H-6'), 9.19 (br s, 1 H, NH);

MS (FAB) m/z 429 (MH^+).

Preparative Example 4

Preparation of 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (3) wherein X = SO_2Cl, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$)

The titled compound was prepared as described in Preparative Example 3 by using 4-(2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 83%

mp 140-141 °C (CH_2Cl_2/hexanes);

IR (neat) 3469, 3286 (NH), 1683, 1651 (C=O), 1177 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.11 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.59-1.72 (m, 2 H, $CH_2CH_2CH_3$), 1.94-2.06 (m, 2 H, $OCH_2CH_2CH_3$), 2.52 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 4.06 (s, 3 H, NCH_3), 4.34 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 5.68 (br s, 1 H, $CONH_2$), 7.27 (d, J = 9.0 Hz, 1 H, H-3'), 7.56 (br s, 1 H, $CONH_2$), 8.19 (dd, J = 9.0 Hz, 2.7 Hz, 1 H, H-4'), 8.96 (d, J = 2.7 Hz, 1 H, H-6'), 9.19 (br s, 1 H, NH);

MS (FAB) m/z 443 (MH^+).

Preparative Example 5

Preparation of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(hydroxycarbonyl)piperidinyl)

A mixture of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (2.11 g, 6.39 mmol) and isonicopetic acid (1.97 g, 15.25 mmol) in anhydrous EtOH (130 mL) was stirred at room temperature under nitrogen atmosphere for 18 h. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting residue was purified by MPLC on silica gel (gradient elution: 5% MeOH in $CHCl_3$, 10% MeOH in $CHCl_3$, followed by 30% MeOH in $CHCl_3$) to afford the titled compound (2.50 g, 97%) as a white solid. Analytically pure compound was obtained by crystallization from MeOH/$CHCl_3$/hexanes.

mp 247 °C dec;

IR (neat) 3345, 3160 (NH, CO_2H), 1706, 1656, 1640 (C=O), 1156 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.42 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.51-1.65 (m, 4 H, 2 CH_{ax} and $CH_2CH_2CH_3$), 1.84-1.94 (m, 2 H, 2 CH_{eq}), 2.17-2.27 (m, 1 H, $CHCO_2$), 2.36-2.52 (m, 4 H, 2 NCH_{ax} and $CH_2CH_2CH_3$), 3.40-3.52 (m, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.30 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.34 (br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.81 (br s, 1 H, $CONH_2$), 7.84 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.88 (d, J = 2.4 Hz, 1 H, H-6'), 9.61 (br s, 1 H, NH);

MS (FAB) m/z 522 (MH^+).

Preparative Example 6

Preparation of 4-(5-(4-(hydroxycarbonyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(hydroxycarbonyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 5 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 99%

mp 171-172 °C (MeOH/$CHCl_3$);

IR (neat) 3346, 3183, 3075 (NH, CO_2H), 1673, 1641 (C=O), 1167 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.51-1.65 (m, 4 H, 2 CH_{ax} and $CH_2CH_2CH_3$), 1.76-1.85 (m, 4 H, 2 CH_{eq} and $OCH_2CH_2CH_3$), 2.00-2.02 (m, 1 H, $CHCO_2$), 2.41-2.52 (m, 4 H, 2 NCH_{ax} and $CH_2CH_2CH_3$), 3.38-3.43 (m, 2 H, 2 NCH_{eq}), 3.91 (s, 3 H, NCH_3), 4.19 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.40 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.44 (br s, 1 H, $CONH_2$), 7.83 (dd, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.81-7.87 (m, 2 H, $CONH_2$ and H-6'), 9.67 (br s, 1 H, NH);

MS (FAB) *m/z* 536 (MH^+).

Preparative Example 7

Preparation of 4-(2-ethoxy-5-(4-

(ethoxycarbonylmethyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(ethoxycarbonylmethyl)piperidinyl)

A mixture of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (0.65 g, 1.51 mmol), 4-(ethoxycarbonylmethyl)piperidine (0.31 g, 1.81 mmol) and triethylamine (0.63 mL, 4.53 mmol) in anhydrous EtOH (25 mL) was stirred at room temperature under nitrogen atmosphere for 2 h. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting residue was purified by MPLC on silica gel using 2% MeOH in $CHCl_3$ to afford the titled compound (0.79 g, 93%) as a white solid. Analytically pure compound was obtained by crystallization from EtOAc/hexanes.

mp 177-178 °C;

IR (neat) 3357, 3180, 3075 (NH), 1733, 1670, 1640 (C=O), 1168 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.15 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.16-1.29 (m, 2 H, 2 CH_{ax}), 1.42 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.53-1.65 (m, 3 H, CH and $CH_2CH_2CH_3$), 1.71 (br d, J = 12.6 Hz, 2 H, 2 CH_{eq}), 2.18-2.26 (m, 2 H, 2 NCH_{ax}), 2.21 (d, J = 6.6 Hz, 2 H, CH_2CO_2), 2.46 (dd, J = 7.8 Hz, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.02 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.30 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.33 (br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.87 (br s, 1 H, $CONH_2$), 7.88 (d, J = 2.4 Hz, 1 H, H-6'), 9.60 (br s, 1 H,

NH);

MS (FAB) *m/z* 564 (MH^+).

Preparative Example 8

Preparation of 4-(5-(4-(ethoxycarbonylmethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(ethoxycarbonylmethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 95%

mp 171-172 °C (EtOAc/hexanes);

IR (neat) 3348, 3182, 3074 (NH), 1741, 1670, 1641 (C=O), 1168 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.15 (t, *J* = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.17-1.29 (m, 2 H, 2 CH_{ax}), 1.52-1.65 (m, 3 H, CH and $CH_2CH_2CH_3$), 1.71 (br d, *J* = 12.3 Hz, 2 H, 2 CH_{eq}), 1.78-1.88 (m, 2 H, $OCH_2CH_2CH_3$), 2.17-2.27 (m, 2 H, 2 NCH_{ax}), 2.22 (d, *J* = 6.6 Hz, 2 H, CH_2CO_2), 2.46 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, *J* = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.02 (q, *J* = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.20 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.33 (br s, 1 H, $CONH_2$), 7.41 (d, *J* = 8.7

Hz, 1 H, H-3'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (br s, 1 H, $CONH_2$), 7.87 (d, J = 2.4 Hz, 1 H, H-6'), 9.57 (br s, 1 H, NH);

MS (FAB) m/z 578 (MH^+).

Preparative Example 9

Preparation of 4-(2-ethoxy-5-(4-(2-ethoxycarbonylethyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(2-ethoxycarbonylethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(2-ethoxycarbonylethyl)piperidine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 90%

mp 174-175 °C (EtOAc/hexanes);

IR (neat) 3358, 3202, 3180 (NH), 1730, 1668, 1640 (C=O), 1170 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.09-1.21 (m, 3 H, CH and 2 CH_{ax}), 1.15 (t, J = 6.9 Hz, 3 H, $CO_2CH_2CH_3$), 1.39-1.47 (m, 2 H, $CHCH_2CH_2$), 1.42 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.52-1.65 (m, 2 H, $CH_2CH_2CH_3$), 1.70 (br d, J = 9.3 Hz, 2 H, 2 CH_{eq}), 2.16 (br t, J = 10.5 Hz, 2 H, 2 NCH_{ax}), 2.25 (t, J = 7.5 Hz, 2 H, CH_2CO_2), 2.46 (dd, J = 8.1 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.01 (q, J = 6.9 Hz, 2 H, $CO_2CH_2CH_3$), 4.30 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.33

(br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.84 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.87 (br s, 1 H, $CONH_2$), 7.88 (d, J = 2.4 Hz, 1 H, H-6'), 9.60 (br s, 1 H, NH);

MS (FAB) *m/z* 578 (MH^+).

Preparative Example 10

Preparation of 4-(5-(4-(2-ethoxycarbonylethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-ethoxycarbonylethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(2-ethoxycarbonylethyl)piperidine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 91%

mp 170-171 °C (EtOAc/hexanes);

IR (neat) 3349, 3208, 3077 (NH), 1731, 1669, 1640 (C=O), 1166 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.97 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.15 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.10-1.20 (m, 3 H, CH and 2 CH_{ax}), 1.39-1.47 (m, 2 H, $CHCH_2CH_2$), 1.52-1.62 (m, 2 H, $CH_2CH_2CH_3$), 1.65-1.72 (m, 2 H, 2 CH_{eq}), 1.75-1.86 (m, 2 H, $OCH_2CH_2CH_3$), 2.17 (br t, J = 10.5 Hz, 2 H, 2 NCH_{ax}), 2.26 (t, J = 7.5 Hz, 2 H, CH_2CO_2), 2.45 (t, J =

7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.02 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.19 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 7.33 (br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.81-7.86 (m, 3 H, H-4', H-6', and $CONH_2$), 9.57 (br s, 1 H, NH);

MS (FAB) m/z 592 (MH^+).

Preparative Example 11

Preparation of 4-(2-ethoxy-5-(4-(3-ethoxycarbonylpropyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(3-ethoxycarbonylpropyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(3-ethoxycarbonylpropyl)piperidine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 76%

mp 168-168.5 °C (MeOH/Et_2O);

IR (neat) 3365, 3179, 3074 (NH), 1733, 1670, 1639 (C=O), 1167 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.15 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.06-1.18 (m, 5 H, $CHCH_2CH_2$ and 2 CH_{ax}), 1.40-1.51 (m, 2 H, $CHCH_2CH_2$), 1.42 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.52-1.62 (m, 2 H, $CH_2CH_2CH_3$), 1.70 (br d, J = 9.9 Hz, 2 H, 2 CH_{eq}), 2.18 (br t, J = 10.8 Hz, 2 H, 2 NCH_{ax}), 2.23 (t, J = 7.2 Hz, 2 H, CH_2CO_2), 2.46 (dd, J = 8.1 Hz, 7.2 Hz, 2 H,

$CH_2CH_2CH_3$), 3.61 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.02 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.30 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.33 (br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (br s, 1 H, $CONH_2$), 7.84 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.88 (d, J = 2.4 Hz, 1 H, H-6'), 9.60 (br s, 1 H, NH);

MS (FAB) *m/z* 592 (MH^+).

Preparative Example 12

Preparation of 4-(5-(4-(3-ethoxycarbonylpropyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(3-ethoxycarbonylpropyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(3-ethoxycarbonylpropyl)piperidine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 75%

mp 153-154.5 °C ($MeOH/Et_2O$);

IR (neat) 3350, 3184, 3074 (NH), 1735, 1668, 1640 (C=O), 1167 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.12-1.21 (m, 5 H, $CHCH_2CH_2$ and 2 CH_{ax}), 1.15 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$),

1.43-1.52 (m, 2 H, $CHCH_2CH_2$), 1.52-1.65 (m, 2 H, $CH_2CH_2CH_3$), 1.70 (br d, J = 10.2 Hz, 2 H, 2 CH_{eq}), 1.76-1.88 (m, 2 H, $OCH_2CH_2CH_3$), 2.19 (br t, J = 11.1 Hz, 2 H, 2 NCH_{ax}), 2.23 (t, J = 7.2 Hz, 2 H, CH_2CO_2), 2.45 (dd, J = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.92 (s, 3 H, NCH_3), 4.02 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.20 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.33 (br s, 1 H, $CONH_2$), 7.42 (d, J = 8.7 Hz, 1 H, H-3'), 7.80 (br s, 1 H, $CONH_2$), 7.83 (dd, J = 8.7 Hz, 2.7 Hz, 1 H, H-4'), 7.87 (d, J = 2.7 Hz, 1 H, H-6'), 9.57 (br s, 1 H, NH);

MS (FAB) *m/z* 606 (MH^+).

Preparative Example 13

Preparation of 4-(2-ethoxy-5-(4-(ethoxycarbonylmethyl)piperazinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(ethoxycarbonylmethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(ethoxycarbonylmethyl)piperazine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 68%

mp 178-178.5 °C ($CHCl_3$/EtOAc/hexanes);

IR (neat) 3359, 3182 (NH), 1747, 1674, 1640 (C=O), 1169 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.16 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.42 (t, J = 6.9 Hz, 3 H,

OCH_2CH_3), 1.53-1.65 (m, 2 H, $CH_2CH_2CH_3$), 2.46 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.60 (br s, 4 H, 2 NCH_2), 2.88 (br s, 4 H, 2 NCH_2), 3.24 (s, 2 H, NCH_2CO_2), 3.92 (s, 3 H, NCH_3), 4.05 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.31 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.31 (br s, 1 H, $CONH_2$), 7.43 (d, J = 8.7 Hz, 1 H, H-3'), 7.78-7.90 (m, 3 H, H-4', H-6', and $CONH_2$), 9.64 (br s, 1 H, NH);

MS (FAB) m/z 565 (MH^+).

Preparative Example 14

Preparation of 4-(5-(4-(ethoxycarbonylmethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(ethoxycarbonylmethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperazine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 61%

mp 130 °C dec (EtOAc/hexanes);

IR (neat) 3345, 3186 (NH), 1739, 1671, 1642 (C=O), 1171 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.16 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.53-1.65 (m, 2 H, $CH_2CH_2CH_3$), 1.76-1.88 (m, 2 H, $OCH_2CH_2CH_3$), 2.46 (t, J = 7.5 Hz, 2 H,

$CH_2CH_2CH_3$), 2.59 (br s, 4 H, 2 NCH_2), 2.89 (br s, 4 H, 2 NCH_2), 3.23 (s, 2 H, NCH_2CO_2), 3.92 (s, 3 H, NCH_3), 4.05 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.22 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 7.32 (br s, 1 H, $CONH_2$), 7.43 (d, J = 9.6 Hz, 1 H, H-3'), 7.78-7.84 (m, 3 H, H-4', H-6', and $CONH_2$), 9.62 (br s, 1 H, NH);

MS (FAB) m/z 579 (MH^+).

Preparative Example 15

Preparation of 4-(2-ethoxy-5-(4-(2-ethoxycarbonylethyl)piperazinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(2-ethoxycarbonylethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(2-ethoxycarbonylethyl)piperazine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 95%

mp 160.5-161 °C (EtOAc/hexanes);

IR (neat) 3365, 3191 (NH), 1726, 1673, 1643 (C=O), 1169 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 0.96 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.22 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.60 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.60-1.72 (m, 2 H, $CH_2CH_2CH_3$), 2.42 (t, J = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.52-2.57 (m, 6 H, 3 NCH_2), 2.69 (t, J = 7.2 Hz, 2 H, CH_2CO_2), 3.05 (br s, 4 H, 2 NCH_2), 4.07 (s, 3 H, NCH_3), 4.10 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$), 4.40 (q, J = 7.2 Hz, 2 H, OCH_2CH_3),

5.62 (br s, 1 H, $CONH_2$), 7.17 (d, J = 9.0 Hz, 1 H, H-3'), 7.69 (br s, 1 H, $CONH_2$), 7.91 (dd, J = 9.0 Hz, 2.4 Hz, 1 H, H-4'), 8.63 (d, J = 2.4 Hz, 1 H, H-6'), 9.28 (br s, 1 H, NH);

MS (FAB) *m/z* 579 (MH^+).

Preparative Example 16

Preparation of 4-(5-(4-(2-ethoxycarbonylethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-ethoxycarbonylethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(2-ethoxycarbonylethyl)piperazine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 90%

mp 177-177.5 °C (EtOAc/hexanes);

IR (neat) 3422, 3190 (NH), 1723, 1670, 1643 (C=O), 1170 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 0.95 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.10 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.22 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.60-1.72 (m, 2 H, $CH_2CH_2CH_3$), 1.91-2.03 (m, 2 H, $OCH_2CH_2CH_3$), 2.42 (t, J = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.51-2.57 (m, 6 H, 3 NCH_2), 2.69 (t, J = 7.2 Hz, 2 H, CH_2CO_2), 3.05 (br s, 4 H, 2 NCH_2), 4.07 (s, 3 H, NCH_3), 4.10 (q, J = 7.2 Hz, 2 H, $CO_2CH_2CH_3$),

4.28 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 5.60 (br s, 1 H, $CONH_2$), 7.18 (d, J = 9.0 Hz, 1 H, H-3'), 7.64 (br s, 1 H, $CONH_2$), 7.91 (dd, J = 9.0 Hz, 2.4 Hz, 1 H, H-4'), 8.63 (d, J = 2.4 Hz, 1 H, H-6'), 9.27 (br s, 1 H, NH);

MS (FAB) *m/z* 593 (MH^+).

Preparative Example 17

Preparation of 4-(5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(diethylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(diethylphosphonomethyl)piperidine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 82%

mp 192-193.5 °C (MeOH/Et_2O);

IR (neat) 3351, 3181 (NH), 1668, 1639 (C=O), 1280 (P=O), 1165 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.19 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.20-1.36 (m, 2 H, 2 CH_{ax}), 1.42 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.52-1.73 (m, 5 H, CH, $CH_2CH_2CH_3$ and CH_2PO), 1.86 (br d, J = 11.1 Hz, 2 H, 2 CH_{eq}), 2.23 (br t, J = 11.1 Hz, 2 H, 2 NCH_{ax}), 2.46 (dd, J = 7.8 Hz, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.59 (br d, J = 11.7 Hz, 2 H, 2 NCH_{eq}), 3.87-4.00 (m, 4 H, $PO(OCH_2CH_3)_2$), 3.92 (s, 3 H, NCH_3), 4.30 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.32 (br s, 1 H, $CONH_2$), 7.41 (d, J

= 9.0 Hz, 1 H, H-3'), 7.83 (dd, J = 9.0 Hz, 2.4 Hz, 1 H, H-4'), 7.85 (br s, 1 H, $CONH_2$), 7.88 (d, J = 2.4 Hz, 1 H, H-6'), 9.60 (br s, 1 H, NH);

MS (FAB) m/z 628 (MH^+).

Preparative Example 18

Preparation of 4-(5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(diethylphosphonomethyl)piperidine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 97%

mp 205-207 °C (EtOAc/hexanes):

IR (neat) 3344, 3182 (NH), 1669, 1640 (C=O), 1249 (P=O), 1166 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.19 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.24-1.36 (m, 2 H, 2 CH_{ax}), 1.52-1.71 (m, 5 H, CH, $CH_2CH_2CH_3$ and CH_2PO), 1.77-1.91 (m, 4 H, 2 CH_{eq} and $OCH_2CH_2CH_3$), 2.17-2.29 (m, 2 H, 2 NCH_{ax}), 2.45 (t, J = 7.8 Hz, 2 H, $CH_2CH_2CH_3$), 3.59 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.89-4.00 (m, 4 H, $PO(OCH_2CH_3)_2$), 3.91 (s, 3 H, NCH_3), 4.19 (t, J = 6.3 Hz,

2 H, $OCH_2CH_2CH_3$), 7.33 (br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.85 (br s, 1 H, $CONH_2$), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 9.58 (br s, 1 H, NH);

MS (FAB) *m/z* 642 (MH^+).

Preparative Example 19

Preparation of 4-(5-(4-(2-diethylphosphonoethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-diethylphosphonoethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(2-diethylphosphonoethyl)piperidine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 75%

mp 131-134 °C (EtOAc/hexanes);

IR (neat) 3348, 3183 (NH), 1671, 1639 (C=O), 1244 (P=O), 1167 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.20 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.12-1.20 (m, 3 H, $CHCH_2CH_2$), 1.31-1.41 (m, 2 H, 2 CH_{ax}), 1.52-1.66 (m, 2 H, $CH_2CH_2CH_3$), 1.62-1.79 (m, 4 H, 2 CH_{eq} and CH_2PO), 1.76-1.88 (m, 2 H, $OCH_2CH_2CH_3$), 2.16 (br t, J = 11.7 Hz, 2 H, 2 NCH_{ax}), 2.45 (dd, J = 7.8 Hz, 7.5 Hz, 2 H,

$CH_2CH_2CH_3$), 3.61 (br d, J = 11.7 Hz, 2 H, 2 NCH_{eq}), 3.88-4.01 (m, 4 H, $PO(OCH_2CH_3)_2$), 3.92 (s, 3 H, NCH_3), 4.19 (t, J = 6.5 Hz, 2 H, $OCH_2CH_2CH_3$), 7.33 (br s, 1 H, $CONH_2$), 7.41 (d, J = 8.7 Hz, 1 H, H-3'), 7.81 (br s, 1 H, $CONH_2$), 7.84 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.87 (d, J = 2.4 Hz, 1 H, H-6'), 9.58 (br s, 1 H, NH);

MS (FAB) *m/z* 656 (MH^+).

Preparative Example 20

Preparation of 4-(5-(4-(dimethylphosphonomethyl)piperazinylsulfonyl)-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(dimethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(dimethylphosphonomethyl)piperazine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 87%

mp 214 °C dec (EtOAc/hexanes);

IR (neat) 3322, 3184 (NH), 1677, 1638 (C=O), 1252 (P=O), 1165 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.42 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.53-1.65 (m, 2 H, $CH_2CH_2CH_3$), 2.46 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.64 (br s, 4 H, 2 NCH_2), 2.85 (d, J = 11.1 Hz, 2 H, CH_2PO), 2.87 (br s, 4 H, 2 NCH_2), 3.59 (d, J = 10.5 Hz, 6 H, $PO(OCH_3)_2$), 3.92 (s, 3 H, NCH_3), 4.31 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.32 (br s, 1 H, $CONH_2$), 7.43 (d, J = 8.7 Hz, 1 H, H-3'), 7.83-

7.86 (m, 3 H, H-4', H-6', and $CONH_2$), 9.64 (br s, 1 H, NH);

MS (FAB) *m/z* 601 (MH^+).

Preparative Example 21

Preparation of 4-(5-(4-(dimethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(dimethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(dimethylphosphonomethyl)piperazine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 88%

mp 176.5-177 °C (EtOAc/hexanes);

IR (neat) 3318, 3187 (NH), 1678, 1637 (C=O), 1257 (P=O), 1170 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, *J* = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.53-1.63 (m, 2 H, $CH_2CH_2CH_3$), 1.76-1.88 (m, 2 H, $OCH_2CH_2CH_3$), 2.46 (dd, *J* = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.65 (br s, 4 H, 2 NCH_2), 2.85 (d, *J* = 11.4 Hz, 2 H, CH_2PO), 2.87 (br s, 4 H, 2 NCH_2), 3.60 (d, *J* = 10.8 Hz, 6 H, $PO(OCH_3)_2$), 3.92 (s, 3 H, NCH_3), 4.20 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.32 (br s, 1 H, $CONH_2$), 7.43 (d, *J* = 9.3 Hz, 1

H, H-3'), 7.79-7.84 (m, 3 H, H-4', H-6', and $CONH_2$), 9.61 (br s, 1 H, NH);

MS (FAB) *m/z* 615 (MH^+).

Preparative Example 22

Preparation of 4-(5-(4-(diethylphosphonomethyl)piperazinylsulfonyl)-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(diethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(diethylphosphonomethyl)piperazine in place of 4-(ethoxycarbonylmethyl)piperidine.

yield: 87%

mp 191 °C dec (EtOAc/hexanes);

IR (neat) 3351, 3183 (NH), 1673, 1640 (C=O), 1279 (P=O), 1168 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.89 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.18 (t, *J* = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.42 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.53-1.65 (m, 2 H, $CH_2CH_2CH_3$), 2.46 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.65 (br s, 4 H, 2 NCH_2), 2.80 (d, *J* = 11.4 Hz, 2 H, CH_2PO), 2.89 (br s, 4 H, 2 NCH_2), 3.91-4.01 (m, 4 H, $PO(OCH_2CH_3)_2$), 3.92 (s, 3 H, NCH_3), 4.31 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 7.31 (br s, 1 H, $CONH_2$), 7.43 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.82-7.86 (m, 3 H, H-4', H-6', and $CONH_2$), 9.64 (br s, 1 H, NH);

MS (FAB) *m/z* 629 (MH^+).

Preparative Example 23

Preparation of 4-(5-(4-(diethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Preparative Example 7 by using 4-(5-chlorosulfonyl-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(diethylphosphonomethyl)piperazine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 85%

mp 170-170.5 °C (EtOAc/hexanes);

IR (neat) 3325, 3189 (NH), 1678, 1639 (C=O), 1256 (P=O), 1170 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.90 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.99 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.19 (t, J = 6.9 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.15-1.63 (m, 2 H, $CH_2CH_2CH_3$), 1.78-1.87 (m, 2 H, $OCH_2CH_2CH_3$), 2.46 (dd, J = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 2.66 (br s, 4 H, 2 NCH_2), 2.81 (d, J = 11.1 Hz, 2 H, CH_2PO), 2.90 (br s, 4 H, 2 NCH_2), 3.90-4.03 (m, 4 H, $PO(OCH_2CH_3)_2$), 3.92 (s, 3 H, NCH_3), 4.21 (t, J = 6.9 Hz, 2 H, $OCH_2CH_2CH_3$), 7.32 (br s, 1 H, $CONH_2$), 7.44 (d, J = 9.3 Hz, 1 H, H-3'), 7.79-7.84 (m, 3 H, H-4', H-6', and $CONH_2$), 9.62 (br s, 1 H, NH);

MS (FAB) m/z 643 (MH^+).

Preparative Example 24 "Method B"

Preparation of 5-chlorosulfonyl-2-*n*-propoxybenzoic acid (a compound of the formula (8) wherein R^3 = $CH_2CH_2CH_3$; X = SO_2Cl)

The titled compound was prepared as described in Preparative Example 3 by using 2-*n*-propoxybenzoic acid in place of 4-(2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 79%

mp 113-114 °C (CH_2Cl_2/hexanes);

IR (neat) 3402, 3079 (CO_2H), 1705, 1685 (C=O), 1168 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.14 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.94-2.06 (m, 2 H, $OCH_2CH_2CH_3$), 4.31 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.23 (d, *J* = 9.0 Hz, 1 H, H-3), 8.19 (dd, *J* = 9.0 Hz, 2.7 Hz, 1 H, H-4), 8.80 (d, *J* = 2.7 Hz, 1 H, H-6), 11.50 (br s, 1 H, CO_2H);

MS (FAB) *m/z* 279 (MH^+).

Preparative Example 25

Preparation of 5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxybenzoic acid (a compound of the formula (6) wherein R^{11} = $SO_2NR^5R^6$, R^3 = $CH_2CH_2CH_3$, Y = OH; NR^5R^6 is 4-(diethylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Preparative Example 7 by using 5-chlorosulfonyl-2-*n*-propoxybenzoic acid and 4-(diethylphosphonomethyl)piperidine in place of 4-(5-chlorosulfonyl-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide and 4-(ethoxycarbonylmethyl)piperidine.

yield: 86%

mp 135-136 °C (EtOAc/hexanes);

IR (neat) 3350 (CO_2H), 1701 (C=O), 1203 (P=O), 1164 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.13 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.30 (t, *J* = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.38-1.48 (m, 2 H, 2 CH_{ax}), 1.64-1.72 (m, 3 H, $CHCH_2PO$), 1.90-2.04 (m, 4 H, $OCH_2CH_2CH_3$ and 2 CH_{eq}), 2.30 (td, *J* = 12.0 Hz, 2.4 Hz, 2 H, 2 NCH_{ax}), 3.76 (br d, *J* = 12.0 Hz, 2 H, 2 NCH_{eq}), 4.01-4.13 (m, 4 H, $PO(OCH_2CH_3)_2$), 4.27 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 7.15 (d, *J* = 8.7 Hz, 1 H, H-3), 7.91 (dd, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4), 8.48 (d, *J* = 2.4 Hz, 1 H, H-6);

MS (FAB) *m/z* 478 (MH^+).

Preparative Example 26

Preparation of 4-(5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (a compound of the formula (2) wherein R^{11} = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphonomethyl)piperidinyl)

A solution of 5-(4-(diethylphosphonomethyl)piperidinylsulfonyl-2-*n*-propoxybenzoic acid (90 mg, 0.19 mmol) in thionyl chloride (2 mL) was refluxed under nitrogen atmosphere for 3 h, and the excess thionyl chloride was removed under reduced pressure. The resulting acid chloride in CH_2Cl_2 (1.5 mL) was added slowly to the cooled mixture of 4-amino-1-methyl-3-*n*-propylpyrazole-5-carboxamide (30 mg, 0.16 mmol), DMAP (2 mg, 0.02 mmol) and triethylamine (34 μL, 0.25 mmol) in CH_2Cl_2 (1.5 mL) in an ice bath, and the reaction mixture was stirred in an ice bath for 2 h. The reaction was quenched with 1 N HCl solution (1 mL), and it was extracted

with 5% MeOH in $CHCl_3$ (3 x 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution once followed by brine. The organic layer was dried ($MgSO_4$), filtered, and was evaporated to dryness in vacuo to afford an off-white solid. The crude product was purified by MPLC on silica gel using 5% MeOH in $CHCl_3$ to afford the titled compound (126 mg, 88%) as a white solid.

Spectroscopic data are identical to those reported in Preparative Example 18.

Preparative Example 27 " Method C"

Preparation of 1-methyl-5-(5-nitro-2-*n*-propoxyphenyl)-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (11) wherein $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_2CH_3$, $X = NO_2$)

To a stirred solution of 1-methyl-5-(2-*n*-propoxyphenyl)-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (2.20 g, 6.70 mmol) in trifluoroacetic acid (18 mL) was added slowly concentrated HNO_3 (3.3 mL) at -10 °C, and the mixture was stirred at room temperature for 2h. The reaction mixture was poured carefully into ice (150 g) and was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layer was concentrated in vacuo, and the resulting yellow residue was purified by MPLC on silica gel (gradient elution: 1/6 EtOAc in hexanes, 1/3 EtOAc in hexanes, followed by 1/1 EtOAc in $CHCl_3$) to afford the titled compound (2.29 g, 91%) as a pale yellow solid. Analytically pure compound was obtained by crystallization from EtOAc/hexanes.

mp 199-199.5 °C;

IR (neat) 3319 (NH), 1699 (C=O), 1343 (NO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.05 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.20 (t, J = 7.5

Hz, 3 H, $OCH_2CH_2CH_3$), 1.82-1.94 (m, 2 H, $CH_2CH_2CH_3$), 2.01-2.13 (m, 2 H, $OCH_2CH_2CH_3$), 2.96 (dd, J = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 4.28 (s, 3 H, NCH_3), 4.31 (t, J = 7.5 Hz, 2 H, $OCH_2CH_2CH_3$), 7.16 (d, J = 9.3 Hz, 1 H, H-3'), 8.33 (dd, J = 9.3 Hz, 3.0 Hz, 1 H, H-4'), 9.34 (d, J = 3.0 Hz, 1 H, H-6'), 10.80 (br s, 1 H, NH);

MS (FAB) *m/z* 372 (MH^+).

Preparative Example 28

Preparation of 5-(5-amino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (12) wherein $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_2CH_3$, $X = NH_2$)

A mixture of 1-methyl-5-(5-nitro-2-*n*-propoxyphenyl)-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (2.29 g, 6.17 mmol) and 10% Pd/C (0.20 g) in THF (70 mL) and EtOH (70 mL) was purged with hydrogen gas three times and stirred vigorously under hydrogen atmosphere (a balloon) at room temperature for 3 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness under reduced pressure. The resulting yellow residue was purified by MPLC on silica gel (gradient elution: 1/4 EtOAc in hexanes, 1/2 EtOAc in hexanes, followed by 1/1 EtOAc in $CHCl_3$) to afford the titled compound (2.08 g, 99%) as a pale yellow solid. Analytically pure compound was obtained by crystallization from EtOAc/hexanes.

mp 110-110.5 °C;

IR (neat) 3422, 3349, 3279 (NH), 1694 (C=O) cm^{-1};

^{1}H NMR ($CDCl_3$/TMS) δ 1.04 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.14 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.81-1.92 (m, 2 H, $CH_2CH_2CH_3$), 1.90-2.01 (m, 2 H, $OCH_2CH_2CH_3$), 2.93 (dd, *J* = 7.8 Hz, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 4.08 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 6.79 (dd, *J* = 8.7 Hz, 3.0 Hz, 1 H, H-4'), 6.89 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.83 (d, *J* = 3.0 Hz, 1 H, H-6'), 11.30 (br s, 1 H, NH);

MS (FAB) *m/z* 342 (MH^+).

Example 1 " Method A"

Preparation of 5-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(hydroxycarbonyl)piperidinyl)

A suspension of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide (2.50 g, 4.79 mmol) in 1 N NaOH aqueous solution (34 mL, 34.00 mmol) and EtOH (17 mL) was heated at 90 °C under nitrogen atmosphere for 17h. The reaction mixture was cooled and was acidified to about pH 2-3 with 2N aqueous HCl solution. The resulting solution was extracted with 10% MeOH in $CHCl_3$ (3 x 20 mL), and the combined extracts were washed once with brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness in vacuo to afford an off-white solid. The crude product was purified by MPLC on silica gel (gradient elution: 7% MeOH in $CHCl_3$, 10% MeOH in $CHCl_3$, followed by

30% MeOH in $CHCl_3$) to afford the titled compound (1.65 g, 68%) as a white solid. Analytically pure compound was obtained by crystallization from MeOH/$CHCl_3$/hexanes.

mp 203-204.5 °C;

IR (neat) 3294, 3101 (NH, CO_2H), 1706, 1684 (C=O), 1164 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.33 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.53-1.63 (m, 2 H, 2 CH_{ax}), 1.64-1.80 (m, 2 H, $CH_2CH_2CH_3$), 1.81-1.89 (m, 2 H, 2 CH_{eq}), 2.16-2.23 (m, 1 H, $CHCO_2$), 2.47 (br t, J = 9.0 Hz, 2 H, 2 NCH_{ax}), 2.78 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.43 (br d, J = 11.7 Hz, 2 H, 2 NCH_{eq}), 4.16 (s, 3 H, NCH_3), 4.22 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.36 (d, J = 8.7 Hz, 1 H, H-3'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.87 (d, J = 2.1 Hz, 1 H, H-6'), 12.20 (br s, 1 H, NH);

MS (FAB) m/z 504 (MH^+).

The titled compound can be also prepared in 79% yield as described in Example 27 by using 5-(5-chlorosulfonyl-2-ethoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one and excess amount of isonicopetic acid (3 equiv) in place of 5-(5-chlorosulfonyl-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 4-(diethylphosphono)piperidine, and triethylamine.

Example 2

Preparation of 5-(5-(4-(hydroxycarbonyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 =

$SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(hydroxycarbonyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(hydroxycarbonyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 91%

mp 222-223 °C (EtOAc/hexanes);

IR (neat) 3312 (CO_2H), 1707 (C=O), 1162 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.53-1.67 (m, 2 H, 2 CH_{ax}), 1.69-1.80 (m, 4 H, 2 $CH_2CH_2CH_3$), 1.85-1.95 (m, 2 H, 2 CH_{eq}), 2.19-2.29 (m, 1 H, $CHCO_2$), 2.24-2.45 (m, 2 H, 2 NCH_{ax}), 2.78 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.46 (br d, *J* = 11.7 Hz, 2 H, 2 NCH_{eq}), 4.11 (t, *J* = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.83 (dd, *J* = 9.0 Hz, 2.1 Hz, 1 H, H-4'), 7.87 (d, *J* = 2.1 Hz, 1 H, H-6'), 12.18 (br s, 1 H, NH);

MS (FAB) *m/z* 518 (MH^+).

Example 3

Preparation of 5-(2-ethoxy-5-(4-(hydroxycarbonylmethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(hydroxycarbonylmethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(2-ethoxy-5-(4-(ethoxycarbonylmethyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 84%

mp 219-220 °C ($CHCl_3/Et_2O$);

IR (neat) 3306, 3123 (NH, CO_2H), 1729, 1674 (C=O), 1163 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.14-1.27 (m, 2 H, 2 CH_{ax}), 1.33 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.51-1.65 (m, 1 H, CH), 1.68-1.80 (m, 4 H, 2 CH_{eq} and $CH_2CH_2CH_3$), 2.12 (d, *J* = 6.9 Hz, 2 H, CH_2CO_2), 2.26 (br t, *J* = 12.0 Hz, 2 H, 2 NCH_{ax}), 2.78 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, *J* = 12.0 Hz, 2 H, 2 NCH_{eq}), 4.16 (s, 3 H, NCH_3), 4.21 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 7.36 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.82 (dd, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, *J* = 2.4 Hz, 1 H, H-6'), 12.18 (br s, 1 H, NH);

MS (FAB) *m/z* 518 (MH^+).

Example 4

Preparation of 5-(5-(4-(hydroxycarbonylmethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(hydroxycarbonylmethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using

4-(5-(4-(ethoxycarbonylmethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 66%

mp 179-180 °C (EtOAc/hexanes);

IR (neat) 3286, 3079 (NH, CO_2H), 1729, 1705 (C=O), 1167 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.15-1.27 (m, 2 H, 2 CH_{ax}), 1.53-1.65 (m, 1 H, CH), 1.66-1.80 (m, 6 H, 2 CH_{eq} and 2 $CH_2CH_2CH_3$), 2.11 (d, J = 6.9 Hz, 2 H, CH_2CO_2), 2.27-2.31 (m, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 4.11 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 12.18 (br s, 1 H, NH);

MS (FAB) m/z 532 (MH^+).

Example 5

Preparation of 5-(2-ethoxy-5-(4-(2-hydroxycarbonylethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(2-hydroxycarbonylethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(2-ethoxy-5-(4-(2-ethoxycarbonylethyl)piperidinylsulfonyl)benzamido)-1-

methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 93%

mp 208-209 °C ($CHCl_3/Et_2O$);

IR (neat) 3294, 3103 (NH, CO_2H), 1706, 1689 (C=O), 1164 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.05-1.25 (m, 3 H, CH and 2 CH_{ax}), 1.33 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.36-1.47 (m, 2 H, $CHCH_2CH_2$), 1.62-1.81 (m, 4 H, 2 CH_{eq} and $CH_2CH_2CH_3$), 2.12-2.29 (m, 4 H, 2 NCH_{ax} and CH_2CO_2), 2.78 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 4.16 (s, 3 H, NCH_3), 4.20 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.36 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.85 (d, J = 2.4 Hz, 1 H, H-6'), 11.97 (br s, 1 H, CO_2H), 12.19 (br s, 1 H, NH);

MS (FAB) *m/z* 532 (MH^+).

Example 6

Preparation of 5-(5-(4-(2-hydroxycarbonylethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-hydroxycarbonylethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(2-ethoxycarbonylethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place

of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 87%

mp 181-182 °C (EtOAc/hexanes);

IR (neat) 3314, 3052 (NH, CO_2H), 1702 (C=O), 1163 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.10-1.25 (m, 3 H, CH and 2 CH_{ax}), 1.36-1.45 (m, 2 H, $CHCH_2CH_2$), 1.68-1.78 (m, 6 H, 2 CH_{eq} and 2 $CH_2CH_2CH_3$), 2.12-2.25 (m, 4 H, 2 NCH_{ax} and CH_2CO_2), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 4.11 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.36 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 12.10 (br s, 1 H, NH);

MS (FAB) m/z 546 (MH^+).

Example 7

Preparation of 5-(2-ethoxy-5-(4-(3-hydroxycarbonylpropyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(3-hydroxycarbonylpropyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(2-ethoxy-5-(4-(3-ethoxycarbonylpropyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-

propylpyrazole-5-carboxamide.

yield: 91%

mp 215.5-216.5 °C (MeOH/$CHCl_3$/Et_2O);

IR (neat) 3293 (NH, CO_2H), 1705 (C=O), 1164 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 1.06-1.20 (m, 5 H, $CHCH_2CH_2$ and 2 CH_{ax}), 1.33 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.40-1.50 (m, 2 H, $CHCH_2CH_2$), 1.68-1.80 (m, 4 H, 2 CH_{eq} and $CH_2CH_2CH_3$), 2.14 (t, J = 7.2 Hz, 2 H, CH_2CO_2), 2.22 (br t, J = 11.1 Hz, 2 H, 2 NCH_{ax}), 2.78 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.62 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 4.16 (s, 3 H, NCH_3), 4.21 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 7.36 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 12.12 (br s, 1 H, NH);

MS (FAB) m/z 546 (MH^+).

Example 8

Preparation of 5-(5-(4-(3-hydroxycarbonylpropyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(3-hydroxycarbonylpropyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(3-ethoxycarbonylpropyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 71%

mp 183.5-184.5 °C (MeOH/$CHCl_3$/Et_2O);

IR (neat) 3290 (NH, CO_2H), 1732, 1706 (C=O), 1165 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.07-1.20 (m, 5 H, $CHCH_2CH_2$ and 2 CH_{ax}), 1.41-1.52 (m, 2 H, $CHCH_2CH_2$), 1.68-1.78 (m, 6 H, 2 CH_{eq} and 2 $CH_2CH_2CH_3$), 2.15 (t, J = 7.5 Hz, 2 H, CH_2CO_2), 2.22 (br t, J = 10.5 Hz, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.62 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 4.11 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, J = 9.0 Hz, 1 H, H-3'), 7.82 (dd, J = 9.0 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 11.92 (br s, 1 H, CO_2H), 12.16 (br s, 1 H, NH);

MS (FAB) m/z 560 (MH^+).

Example 9

Preparation of 5-(2-ethoxy-5-(4-(hydroxycarbonylmethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(hydroxycarbonylmethyl) piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(2-ethoxy-5-(4-(ethoxycarbonylmethyl)piperazinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-

propylpyrazole-5-carboxamide.

yield: 83%

mp 212 °C dec ($CHCl_3/Et_2O$);

IR (neat) 3311 (NH, CO_2H), 1735, 1701 (C=O), 1169 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.35 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.69-1.81 (m, 2 H, $CH_2CH_2CH_3$), 2.78 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.20-3.60 (m, 10 H, 5 NCH_2), 4.17 (s, 3 H, NCH_3), 4.23 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.43 (d, J = 9.0 Hz, 1 H, H-3'), 7.86-7.92 (m, 2 H, H-4' and H-6'), 12.30 (br s, 1 H, NH);

MS (FAB) m/z 519 (MH^+).

Example 10

Preparation of 5-(5-(4-(hydroxycarbonylmethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(hydroxycarbonylmethyl)piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(ethoxycarbonylmethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 87%

mp 189 °C dec ($CHCl_3/Et_2O$);

IR (neat) 3317 (NH, CO_2H), 1733, 1701 (C=O), 1169 (SO_2) cm^{-1};

^{1}H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.65-1.82 (m, 4 H, 2 $CH_2CH_2CH_3$), 2.78 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.18-3.75 (m, 10 H, 5 NCH_2), 4.13 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.17 (s, 3 H, NCH_3), 7.44 (d, J = 8.7 Hz, 1 H, H-3'), 7.88 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.91 (d, J = 2.4 Hz, 1 H, H-6'), 12.26 (br s, 1 H, NH);

MS (FAB) m/z 533 (MH^+).

Example 11

Preparation of 5-(2-ethoxy-5-(4-(2-hydroxycarbonylethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = CH_2CH_3; NR^5R^6 is 4-(2-hydroxycarbonylethyl) piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(2-ethoxy-5-(4-(2-ethoxycarbonylethyl)piperazinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 74%

mp 236 °C dec ($CHCl_3$/MeOH/hexanes);

IR (neat) 3318, 3068 (NH, CO_2H), 1730, 1693 (C=O), 1161 (SO_2) cm^{-1};

^{1}H NMR (DMSO-d_6) δ 0.95 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.34 (t, J = 6.9 Hz, 3H, OCH_2CH_3), 1.69-1.81 (m, 2 H, $CH_2CH_2CH_3$), 2.75-2.81 (m, 4 H, $CH_2CH_2CH_3$ and CH_2CO_2), 3.09-3.90 (m, 10 H, 5 NCH_2), 4.17 (s, 3 H, NCH_3), 4.22 (q, J = 6.9

Hz, 2 H, OCH_2CH_3), 7.42 (d, J = 8.7 Hz, 1 H, H-3'), 7.88-7.93 (m, 2 H, H-4' and H-6'), 12.28 (br s, 1 H, NH);

MS (FAB) m/z 533 (MH^+).

Example 12

Preparation of 5-(5-(4-(2-hydroxycarbonylethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-hydroxycarbonylethyl)piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(2-ethoxycarbonylethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 79%

mp 220 °C dec ($CHCl_3$/MeOH/hexanes);

IR (neat) 3315, 3061 (NH, CO_2H), 1728, 1693 (C=O), 1161 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.66-1.80 (m, 4 H, 2 $CH_2CH_2CH_3$), 2.70-2.82 (m, 4 H, $CH_2CH_2CH_3$ and CH_2CO_2), 3.10-3.90 (m, 10 H, 5 NCH_2), 4.13 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.17 (s, 3 H, NCH_3), 7.42 (d, J = 8.7 Hz, 1 H, H-3'), 7.87-7.93 (m, 2 H, H-4' and H-6'), 12.26 (br s, 1 H, NH);

MS (FAB) m/z 547 (MH^+).

Example 13

Preparation of 5-(2-ethoxy-5-(4-(ethylphosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(ethylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 82%

mp 211.5-213 °C (MeOH/H_2O);

IR (neat) 3291 (NH), 1687 (C=O), 1274 (P=O), 1162 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.17 (t, *J* = 6.9 Hz, 3 H, $PO(OCH_2CH_3)$), 1.22-1.31 (m, 2 H, 2 CH_{ax}), 1.33 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.48-1.60 (m, 3 H, CH and CH_2PO), 1.68-1.80 (m, 2 H, $CH_2CH_2CH_3$), 1.86 (br d, *J* = 11.4 Hz, 2 H, 2 CH_{eq}), 2.26 (br t, *J* = 11.4 Hz, 2 H, 2 NCH_{ax}), 2.78 (t, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 3.59 (br d, *J* = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.82-3.92 (m, 2 H, $PO(OCH_2CH_3)$), 4.16 (s, 3 H, NCH_3), 4.21 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 7.36 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.82 (dd, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.85 (d, *J* = 2.4 Hz, 1 H, H-6'), 12.19 (br s, 1 H, NH);

MS (FAB) *m/z* 582 (MH^+).

Example 14

Preparation of 5-(5-(4-(ethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(ethylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 80%

mp 194-195 °C ($MeOH/H_2O$);

IR (neat) 3325 (NH), 1697 (C=O), 1240 (P=O), 1162 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.94 (t, *J* = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.03 (t, *J* = 6.9 Hz, 3 H, $PO(OCH_2CH_3)$), 1.10-1.25 (m, 4 H, 2 CH_{ax} and CH_2PO), 1.35-1.50 (m, 1 H, CH), 1.65-1.79 (m, 2 H, $CH_2CH_2CH_3$), 1.87 (br d, *J* = 11.7 Hz, 2 H, 2 CH_{eq}), 2.30 (br t, *J* = 10.8 Hz, 2 H, 2 NCH_{ax}), 2.76 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.51 (br d, *J* = 11.4 Hz, 2 H, 2 NCH_{eq}), 3.55-3.65 (m, 2 H, $PO(OCH_2CH_3)$), 4.10 (t, *J* = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.35 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.79-7.83 (m, 2 H, H-4' and H-6'), 12.31 (br s, 1 H, NH);

MS (FAB) *m/z* 596 (MH^+).

Example 15

Preparation of 5-(5-(4-(2-(ethylphosphonoethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-ethylphosphonoethyl)piperidinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(2-diethylphosphonoethyl)piperidinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 85%

mp 255 °C dec (EtOAc/$CHCl_3$);

IR (neat) 3321 (NH), 1702 (C=O), 1248 (P=O), 1166 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.91 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.93 (t, *J* = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.06 (t, *J* = 6.9 Hz, 3 H, $PO(OCH_2CH_3)$), 1.01-1.18 (m, 3 H, $CHCH_2CH_2$), 1.22-1.40 (m, 4 H, 2 CH_{ax} and CH_2PO), 1.62-1.78 (m, 6 H, 2 $CH_2CH_2CH_3$ and 2 CH_{eq}), 2.12-2.27 (m, 2 H, 2 NCH_{ax}), 2.75 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.61 (br d, *J* = 9.0 Hz, 2 H, 2 NCH_{eq}), 3.66-3.76 (m, 2 H, $PO(OCH_2CH_3)$), 4.08 (t, *J* = 6.0 Hz, 2 H, $OCH_2CH_2CH_3$), 4.15 (s, 3 H, NCH_3), 7.33 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.81 (dd, *J* = 9.0 Hz, 2.1 Hz, 1 H, H-4'), 7.86 (d, *J* = 2.1 Hz, 1 H,H-6'), 12.21 (br s, 1 H, NH);

MS (FAB) *m/z* 610 (MH^+).

Example 16

Preparation of 5-(2-ethoxy-5-(4-(ethylphosphonomethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(ethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(diethylphosphonomethyl)piperazinylsulfonyl)-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 79%

mp 234 °C dec ($CHCl_3/Et_2O$);

IR (neat) 3328, 3326 (NH), 1695 (C=O), 1207 (P=O), 1168 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.09 (t, *J* = 7.2 Hz, 3 H, $PO(OCH_2CH_3)$), 1.31 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.69-1.77 (m, 2 H, $CH_2CH_2CH_3$), 2.77 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.92-3.10 (m, 4 H, 2 NCH_2), 3.35 (br s, 6 H, 2 NCH_2 and CH_2PO), 3.70-3.76 (m, 2 H, $PO(OCH_2CH_3)$), 4.16 (s, 3 H, NCH_3), 4.20 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 7.38 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.79-7.86 (m, 2 H, H-4' and H-6');

MS (FAB) *m/z* 583 (MH^+).

Example 17

Preparation of 5-(5-(4-(ethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-

propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(ethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(diethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 82%

mp 237 °C dec (MeOH);

IR (neat) 3376, 3038 (NH), 1697 (C=O), 1210 (P=O), 1169 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.90 (t, J = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.92 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.08 (t, J = 7.2 Hz, 3 H, $PO(OCH_2CH_3)$), 1.64-1.76 (m, 4 H, $CH_2CH_2CH_3$ and $OCH_2CH_2CH_3$), 2.76 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.91 (br d, J = 12.0 Hz, CH_2PO), 3.11 (br s, 8 H, 4 NCH_2), 3.66-3.75 (m, 2 H, $PO(OCH_2CH_3)$), 4.08 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, J = 8.7 Hz, 1 H, H-3'), 7.75 (d, J = 2.4 Hz, 1 H, H-6'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 12.79 (br s, 1 H, NH);

MS (FAB) m/z 597 (MH^+).

The titled compound can be also prepared in 85% yield as described in Example 36 by using 5-(5-(4-(diethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-

methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one in place of 5-(5-(4-(diethylphosphono)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one .

Example 18

Preparation of 5-(2-ethoxy-5-(4-(methylphosphonomethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(methylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(dimethylphosphonomethyl)piperazinylsulfonyl)-2-ethoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 79%

mp 192 °C dec ($CHCl_3/Et_2O$);

IR (neat) 3326 (NH), 1700 (C=O), 1210 (P=O), 1170 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.28 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.68-1.77 (m, 2 H, $CH_2CH_2CH_3$), 2.76 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.99 (d, *J* = 12.3 Hz, CH_2PO), 3.18 (br s, 8 H, 4 NCH_2), 3.33 (d, *J* = 10.8 Hz, 3 H, $PO(OCH_3)$), 4.16 (s, 3 H, NCH_3), 4.19 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 7.37 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.74 (d, *J* = 2.4 Hz, 1 H, H-6'), 7.83 (dd, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 12.83 (br s, 1 H, NH);

MS (FAB) *m/z* 569 (MH^+).

Example 19

Preparation of 5-(5-(4-(methylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(methylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Example 1 by using 4-(5-(4-(dimethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxybenzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide in place of 4-(2-ethoxy-5-(4-(hydroxycarbonyl)piperidinylsulfonyl)benzamido)-1-methyl-3-*n*-propylpyrazole-5-carboxamide.

yield: 77%

mp 235 °C dec ($CHCl_3$/MeOH/Et_2O);

IR (neat) 3327 (NH), 1695 (C=O), 1216 (P=O), 1170 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.90 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.93 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.60-1.79 (m, 4 H, 2 $CH_2CH_2CH_3$), 2.76 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.00 (d, *J* = 11.4 Hz, CH_2PO), 3.19 (br s, 8 H, 4 NCH_2), 3.33 (d, *J* = 10.5 Hz, 3 H, $PO(OCH_3)$), 4.09 (t, *J* = 6.0 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.74 (d, *J* = 2.1 Hz, 1 H, H-6'), 7.83 (dd, *J* = 9.0 Hz, 2.1 Hz, 1 H, H-4'), 12.87 (br s, 1 H, NH);

MS (FAB) *m/z* 583 (MH^+).

Example 20

Preparation of 5-(2-ethoxy-5-(4-(methylphosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein $R^4 = SO_2NR^5R^6$, $R^1 = CH_3$, $R^2 = CH_2CH_2CH_3$, $R^3 = CH_2CH_3$; NR^5R^6 is 4-(methylphosphonomethyl)piperidinyl)

A suspension of 5-(2-ethoxy-5-(4-(phosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (0.15 g, 0.27 mmol) in trimethyl orthoformate (0.4 mL) was heated at 110 °C for 1h under nitrogen atmosphere, and a clear solution was obtained. The reaction mixture was evaporated to dryness in vacuo and was purified by MPLC on silica gel (gradient elution: 10% MeOH in $CHCl_3$ followed by 20% MeOH in $CHCl_3$) to afford the titled compound (0.082 g, 54%) as a white solid. Analytically pure compound was obtained by crystallization from MeOH/$CHCl_3$/Et_2O.

mp 222 °C dec;

IR (neat) 3281 (NH), 1689 (C=O), 1273 (P=O), 1165 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.23-1.34 (m, 2 H, 2 CH_{ax}), 1.33 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.46-1.62 (m, 3 H, $CHCH_2PO$), 1.68-1.80 (m, 2 H, $CH_2CH_2CH_3$), 1.86 (br d, J = 12.3 Hz, 2 H, 2 CH_{eq}), 2.25 (br t, J = 11.4 Hz, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.48 (d, J = 10.8 Hz, 3 H, OCH_3), 3.58 (br d, J = 11.1 Hz, 2 H, 2 NCH_{eq}), 4.16 (s, 3 H, NCH_3), 4.21 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 7.36 (d, J = 8.7 Hz, 1 H, H-3'), 7.83 (d, J = 8.7 Hz, 1 H, H-4'), 7.85 (s, 1 H, H-6'), 12.20 (br s, 1 H, NH);

MS (FAB) *m/z* 568 (MH^+).

Example 21

Preparation of 5-(5-(4-(methylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(methylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Example 20 by using 5-(5-(4-(phosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one in place of 5-(2-ethoxy-5-(4-(phosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one.

yield: 48%

mp 186.5-187.5 °C (MeOH/$CHCl_3$/Et_2O);

IR (neat) 3321, 3079 (NH), 1701 (C=O), 1238 (P=O), 1163 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.91 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.93 (t, *J* = 7.2 Hz, 3 H, $OCH_2CH_2CH_3$), 1.10-1.60 (m, 5 H, $CHCH_2PO$ and 2 CH_{ax}) 1.65-1.77 (m, 4 H, 2 $CH_2CH_2CH_3$), 1.85-1.95 (m, 2 H, 2 CH_{eq}), 2.13-2.24 (m, 2 H, 2 NCH_{ax}), 2.74 (dd, *J* = 7.8 Hz, *J* = 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 3.29 (br d, *J* = 10.5 Hz, 3 H, OCH_3), 3.47-3.58 (m, 2 H, 2 NCH_{eq}), 4.09 (t, *J* = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.15 (s, 3 H, NCH_3), 7.35 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.78 (d, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.82 (d, *J* = 2.4 Hz, 1 H, H-6'), 12.28 (br s, 1 H, NH);

MS (FAB) *m/z* 582 (MH^+).

Example 22 "Method C"

Preparation of 5-(5-acetylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $NHCOR^7$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; R^7 = CH_3)

To a stirred solution of 5-(5-amino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo-[4,3-*d*]pyrimidin-7-one (0.32 g, 0.92 mmol) and triethylamine (0.33 mL, 2.34 mmol) in CH_2Cl_2 (4 mL) was added acetic anhydride (0.17 mL, 1.76 mmol), and the mixture was stirred at room temperature for 1h. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting yellow residue was purified by MPLC on silica gel (gradient elution: 2% MeOH in $CHCl_3$ followed by 5% MeOH in $CHCl_3$) to afford the titled compound (0.35 g, 99%) as a white solid. Analytically pure compound was obtained by crystallization from EtOAc/hexanes.

mp 233-233.5 °C;

IR (neat) 3310, 3285 (NH), 1703, 1661 (C=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.03 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.16 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.80-1.92 (m, 2 H, $CH_2CH_2CH_3$), 1.93-2.05 (m, 2 H, $OCH_2CH_2CH_3$), 2.21 (s, 3 H, CH_3CO), 2.92 (dd, *J* = 8.1 Hz, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 4.16 (t, *J* = 6.5 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 7.02 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.35 (br s, 1 H, CONH), 8.01 (dd, *J* =

9.0 Hz, 3.0 Hz, 1 H, H-4'), 8.20 (d, *J* = 3.0 Hz, 1 H, H-6'), 11.20 (br s, 1 H, 6-NH);

MS (FAB) *m/z* 384 (MH^+).

Example 23

Preparation of 5-(5-propionylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $NHCOR^7$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; R^7 = CH_2CH_3)

The titled compound was prepared as described in Example 22 by using propionic anhydride in place of acetic anhydride.

yield: 99%

mp 212 -213 °C (EtOAc/hexanes):

IR (neat) 3314, 3288 (NH), 1705, 1659 (C=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.03 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.16 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.28 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2CO), 1.80-1.92 (m, 2 H, $CH_2CH_2CH_3$), 1.93-2.05 (m, 2 H, $OCH_2CH_2CH_3$), 2.43 (q, *J* = 7.5 Hz, 2 H, CH_3CH_2CO), 2.92 (dd, *J* = 7.8 Hz, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 4.16 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 7.02 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.34 (br s, 1 H, CONH), 8.07 (dd, *J* = 9.0 Hz, 2.7 Hz, 1 H, H-4'), 8.18 (d, *J* = 2.7 Hz, 1 H, H-6'), 11.20 (br s, 1 H, 6-NH);

MS (FAB) *m/z* 398 (MH^+).

Example 24

Preparation of 5-(5-butyrylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $NHCOR^7$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; R^7 = $CH_2CH_2CH_3$)

The titled compound was prepared as described in Example 22 by using butyric anhydride in place of acetic anhydride.

yield: 99%

mp 207-207.5 °C (EtOAc/hexanes);

IR (neat) 3317, 3291 (NH), 1704, 1656 (C=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.03 (t, *J* = 7.5 Hz, 6 H, $CH_2CH_2CH_3$ and $CH_3CH_2CH_2CO$), 1.16 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.73-1.93 (m, 4 H, $CH_2CH_2CH_3$ and $CH_3CH_2CH_2CO$), 1.93-2.05 (m, 2 H, $OCH_2CH_2CH_3$), 2.37 (t, *J* = 7.5 Hz, 2 H, $CH_3CH_2CH_2CO$), 2.92 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 4.16 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 7.02 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.29 (br s, 1 H, CONH), 8.07 (dd, *J* = 9.0 Hz, 3.0 Hz, 1 H, H-4'), 8.18 (d, *J* = 3.0 Hz, 1 H, H-6'), 11.20 (br s, 1 H, 6-NH);

MS (FAB) *m/z* 412 (MH^+).

Example 25

Preparation of 5-(5-isobutyrylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $NHCOR^7$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 =

$CH_2CH_2CH_3$; $R^7 = CH(CH_3)_2$)

The titled compound was prepared as described in Example 22 by using isobutyric anhydride in place of acetic anhydride.

yield: 99%

mp 223-223.5 °C (EtOAc/hexanes);

IR (neat) 3314 (NH), 1703, 1661 (C=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.04 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.16 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.29 (d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.81-1.91 (m, 2 H, $CH_2CH_2CH_3$), 1.91-2.05 (m, 2 H, $OCH_2CH_2CH_3$), 2.55 (septet, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 2.93 (dd, *J* = 7.8 Hz, 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 4.17 (t, *J* = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 7.03 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.28 (br s, 1 H, CONH), 8.11 (dd, *J* = 9.0 Hz, 2.7 Hz, 1 H, H-4'), 8.16 (d, *J* = 2.7 Hz, 1 H, H-6'), 11.20 (br s, 1 H, 6-NH);

MS (FAB) *m/z* 412 (MH^+).

Example 26

Preparation of 5-(5-cyclohexanecarbonylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $NHCOR^7$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; R^7 = cyclohexyl)

The titled compound was prepared as described in Example 22 by using cyclohexanecarbonyl chloride in place of acetic anhydride.

yield: 99%

mp 213-214 °C (EtOAc/hexanes);

IR (neat) 3314, 3290 (NH), 1703, 1657 (C=O) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.03 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.16 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.24-1.40 (m, 3 H, c-Hex), 1.50-1.59 (m, 2 H, c-Hex), 1.70-1.76 (m, 1 H, c-Hex), 1.81-1.93 (m, 4 H, $CH_2CH_2CH_3$ and c-Hex), 1.93-2.05 (m, 4 H, $OCH_2CH_2CH_3$ and c-Hex), 2.44 (tt, *J* = 15.0 Hz, 3.3 Hz, 1 H, CHCO), 2.93 (dd, *J* = 8.1 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 4.16 (t, *J* = 6.5 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 7.02 (d, *J* = 9.0 Hz, 1 H, H-3'), 7.27 (br s, 1 H, CONH), 8.11 (dd, *J* = 9.0 Hz, 3.0 Hz, 1 H, H-4'), 8.16 (d, *J* = 3.0 Hz, 1 H, H-6'), 11.20 (br s, 1 H, 6-NH);

MS (FAB) *m/z* 452 (MH^+).

Example 27 "Method C"

Preparation of 5-(5-(4-(diethylphosphono)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphono)piperidinyl)

To a mixture of 5-(5-chlorosulfonyl-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (0.50 g, 1.18 mmol) and 4-(diethylphosphono)piperidine (0.31 g, 1.41 mmol) in anhydrous EtOH (25 mL) was added triethylamine (0.49 mL, 3.53 mmol), and the mixture was stirred at room temperature under nitrogen atmosphere for 2h. The reaction mixture was evaporated to dryness under reduced pressure,

and the resulting oily residue was purified by MPLC on silica gel (gradient elution: 1% MeOH in $CHCl_3$ followed by 3% MeOH in $CHCl_3$) to afford the titled compound (0.58 g, 80%) as a white solid. Analytically pure compound was obtained by crystallization from EtOAc/hexanes.

yield: 80%

mp 141-142 °C;

IR (neat) 3315 (NH), 1693 (C=O), 1255 (P=O), 1166 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, *J* = 7.2 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.19 (t, *J* = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.40-1.60 (m, 2 H, 2 CH_{ax}), 1.67-1.80 (m, 4 H, 2 $CH_2CH_2CH_3$), 1.78-1.90 (m, 3 H, 2 CH_{eq} and CHPO), 2.33 (br t, *J* = 11.2 Hz, 2 H, 2 NCH_{ax}), 2.78 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.63-3.74 (m, 2 H, 2 NCH_{eq}), 3.91-4.01 (m, 4 H, $PO(OCH_2CH_3)_2$), 4.11 (t, *J* = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.38 (d, *J* = 8.7 Hz, 1 H, H-3'), 7.82 (dd, *J* = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.88 (d, *J* = 2.4 Hz, 1 H, H-6'), 12.16 (br s, 1 H, NH);

MS (FAB) *m/z* 610 (MH^+).

Example 28

Preparation of 5-(5-(4-(diethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphonomethyl)piperidinyl)

The titled compound was prepared as described in Example 27 by using

4-(diethylphosphonomethyl)piperidine in place of 4-(diethylphosphono)piperidine.

yield: 94%

mp 115-117 °C (EtOAc/hexanes);

IR (neat) 3547, 3309 (NH), 1687 (C=O), 1238 (P=O), 1165 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.94 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.95 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.19 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.24-1.34 (m, 2 H, 2 CH_{ax}), 1.43-1.62 (m, 1 H, CH), 1.65-1.80 (m, 6 H, 2 $CH_2CH_2CH_3$ and CH_2PO), 1.81-1.90 (m, 2 H, 2 CH_{eq}), 2.22-2.33 (m, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.60 (br d, J = 11.7 Hz, 2 H, 2 NCH_{eq}), 3.88-4.00 (m, 4 H, $PO(OCH_2CH_3)_2$), 4.11 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 12.15 (br s, 1 H, NH);

MS (FAB) m/z 624 (MH^+).

Example 29

Preparation of 5-(5-(4-(diethylphosphono)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphono)piperazinyl)

The titled compound was prepared as described in Example 27 by using 4-(diethylphosphono)piperazine in place of 4-(diethylphosphono)piperidine.

yield: 75%

mp 180-181 °C (EtOAc/hexanes);

IR (neat) 3303 (NH), 1699 (C=O), 1248 (P=O), 1168 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.14 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.66-1.80 (m, 4 H, 2 $CH_2CH_2CH_3$), 2.73-2.84 (m, 4 H, 4 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.13-3.29 (m, 4 H, 4 NCH_{eq}), 3.78-3.91 (m, 4 H, $PO(OCH_2CH_3)_2$), 4.12 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.39 (d, J = 8.7 Hz, 1 H, H-3'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.86 (d, J = 2.4 Hz, 1 H, H-6'), 12.19 (br s, 1 H, NH);

MS (FAB) m/z 611 (MH^+).

Example 30

Preparation of 5-(5-(4-(diethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(diethylphosphonomethyl)piperazinyl)

The titled compound was prepared as described in Example 27 by using 4-(diethyl-phosphonomethyl)piperazine in place of 4-(diethylphosphono)piperidine.

yield: 75%

mp 147-148 °C (EtOAc/hexanes);

IR (neat) 3310 (NH), 1702 (C=O), 1272 (P=O), 1168 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.03 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.20 (t, J = 7.5

Hz, 3 H, $OCH_2CH_2CH_3$), 1.28 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.80-1.93 (m, 2 H, $CH_2CH_2CH_3$), 1.99-2.11 (m, 2 H, $OCH_2CH_2CH_3$), 2.74-2.78 (m, 6 H, 4 NCH_{ax} and CH_2PO), 2.93 (dd, J = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 3.07-3.15 (m, 4 H, 4 NCH_{eq}), 4.03-4.13 (m, 4 H, $PO(OCH_2CH_3)_2$), 4.27 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.28 (s, 3 H, NCH_3), 7.16 (d, J = 8.7 Hz, 1 H, H-3'), 7.83 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 8.83 (d, J = 2.4 Hz, 1 H, H-6'), 10.85 (br s, 1 H, NH);

MS (FAB) m/z 625 (MH^+).

Example 31

Preparation of 5-(5-(4-(2-diethylphosphonoethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-diethylphosphonoethyl)piperazinyl)

The titled compound was prepared as described in Example 27 by using 4-(2-diethylphosphonoethyl)piperazine in place of 4-(diethylphosphono)piperidine.

yield: 85%

mp 122-124 °C (EtOAc/hexanes);

IR (neat) 3318 (NH), 1701 (C=O), 1274 (P=O), 1165 (SO_2) cm^{-1};

^1H NMR ($CDCl_3$/TMS) δ 1.03 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 1.19 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.28 (t, J = 7.2 Hz, 6 H, $PO(OCH_2CH_3)_2$), 1.80-1.89 (m, 2 H, $CH_2CH_2CH_3$), 1.89-1.94 (m, 2 H, CH_2PO), 1.99-2.11 (m, 2 H,

$OCH_2CH_2CH_3$), 2.56 (dd, J = 4.8 Hz, 4.5 Hz, 4 H, 4 NCH_{ax}), 2.61-2.70 (m, 2 H, NCH_2), 2.93 (dd, J = 7.8 Hz, 7.2 Hz, 2 H, $CH_2CH_2CH_3$), 3.10 (br s, 4 H, 4 NCH_{eq}), 4.00-4.12 (m, 4 H, $PO(OCH_2CH_3)_2$), 4.27 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.27 (s, 3 H, NCH_3), 7.16 (d, J = 8.7 Hz, 1 H, H-3'), 7.82 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 8.81 (d, J = 2.4 Hz, 1 H, H-6'), 10.87 (br s, 1 H, NH);

MS (FAB) *m/z* 639 (MH^+).

Example 32 "Method C"

Preparation of 5-(5-(4-phosphonopiperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-phosphonopiperidinyl)

To a mixture of 4-phosphonopiperidine (0.09 g, 0.45 mmol) and triethylamine (0.30 mL, 1.86 mmol) in H_2O (2 mL) at room temperature was added slowly 5-(5-chlorosulfonyl-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (0.16 g, 0.37 mmol) in anhydrous DMF (4 mL), and the mixture was stirred for 12 h at room temperature. The reaction mixture was acidified to pH 2-3 using 1 N HCl aqueous solution and evaporated to dryness under reduced pressure. The resulting residue was purified by column chromatography on C_{18} reversed-phase silica gel (gradient elution: 1/3 MeOH in H_2O followed by 1/1 MeOH in H_2O) to afford the titled compound (0.19 g, 91%) as a white solid. Analytically pure compound was obtained by crystallization from

CH_2Cl_2/hexanes.

mp 155-156 °C;

IR (neat) 3335 (NH), 1703 (C=O), 1333 (P=O), 1163 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.18-1.31 (m, 1 H, CHPO), 1.35-1.55 (m, 2 H, 2 CH_{ax}), 1.68-1.79 (m, 6 H, 2 $CH_2CH_2CH_3$ and 2 CH_{eq}), 2.20 (br t, J = 10.8 Hz, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.64 (br d, J = 8.7 Hz, 2 H, 2 NCH_{eq}), 4.10 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.35 (d, J = 8.7 Hz, 1 H, H-3'), 7.81 (dd, J = 8.7 Hz, 2.4 Hz, 1 H, H-4'), 7.85 (d, J = 2.4 Hz, 1 H, H-6'), 12.10 (br s, 1 H, NH);

MS (FAB) m/z 554 (MH^+).

Example 33

Preparation of 5-(5-(4-phosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(phosphonomethyl)piperidinyl)

The titled compound was prepared as described in Example 32 by using 4-(phosphonomethyl)piperidine in place of 4-phosphonopiperidine.

yield: 58%

mp 230-231 °C (MeOH/H_2O);

IR (neat) 3313 (NH), 1707 (C=O), 1240 (P=O), 1165 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 3 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.15-1.32 (m, 2 H, 2 CH_{ax}),

1.42-1.60 (m, 3 H, $CHCH_2PO$), 1.68-1.77 (m, 4 H, 2 $CH_2CH_2CH_3$), 1.84-1.95 (m, 2 H, 2 CH_{eq}), 2.10-2.30 (m, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.58 (br d, J = 11.4 Hz, 2 H, 2 NCH_{eq}), 4.11 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.37 (d, J = 8.7 Hz, 1 H, H-3'), 7.81-7.86 (m, 2 H, H-4' and H-6'), 12.15 (br s, 1 H, NH);

MS (FAB) m/z 568 (MH^+).

Example 34

Preparation of 5-(5-(4-phosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(phosphonomethyl)piperazinyl)

The titled compound was prepared as described in Example 32 by using 4-(phosphonomethyl)piperazine in place of 4-phosphonopiperidine.

yield: 63%

mp 224 °C dec (MeOH);

IR (neat) 3321 (NH), 1706 (C=O), 1275 (P=O), 1170 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7.5 Hz, 6 H, $CH_2CH_2CH_3$ and $OCH_2CH_2CH_3$), 1.65-1.79 (m, 4 H, 2 $CH_2CH_2CH_3$), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.91 (br d, J = 12.0 Hz, 2 H, NCH_2PO), 3.07 (br s, 8 H, 4 NCH_2), 4.11 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.39 (d, J = 9.6 Hz, 1 H, H-3'), 7.83-7.86 (m, 2 H, H-4' and H-6'), 12.53 (br s, 1 H, NH);

MS (FAB) *m/z* 569 (MH^+).

Example 35

Preparation of 5-(5-(4-(2-phosphonoethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-phosphonoethyl)piperazinyl)

The titled compound was prepared as described in Example 32 by using 4-(2-phosphonoethyl)piperazine in place of 4-phosphonopiperidine.

yield: 61%

mp 138 °C dec (CH_2Cl_2/Et_2O);

IR (neat) 3326 (NH), 1699 (C=O), 1274 (P=O), 1166 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, *J* = 7.5 Hz, 6 H, $CH_2CH_2CH_3$ and $OCH_2CH_2CH_3$), 1.62-1.79 (m, 6 H, CH_2PO and 2 $CH_2CH_2CH_3$), 2.67-2.82 (m, 6 H, NCH_2 and 4 NCH_{ax}), 2.77 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.01 (br s, 4 H, 4 NCH_{eq}), 4.10 (t, *J* = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.38 (d, *J* = 9.3 Hz, 1 H, H-3'), 7.82-7.85 (m, 2 H, H-4' and H-6'), 12.48 (br s, 1 H, NH);

MS (FAB) *m/z* 583 (MH^+).

Example 36 "Hydrolysis"

Preparation of 5-(5-(4-(ethylphosphono)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 =

$SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(ethylphosphono)piperidinyl)

A mixture of 5-(5-(4-(diethylphosphono)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (0.156 g, 0.26 mmol) and 2.5 N NaOH aqueous solution (4 mL) in EtOH (8 mL) was refluxed for 2-3 h, and was cooled to room temperature. The reaction mixture was acidified to pH 4 using 1 N HCl aqueous solution and evaporated to dryness under reduced pressure. The resulting residue was purified by MPLC on silica gel (gradient elution: 20% MeOH in $CHCl_3$ followed by 30% MeOH in $CHCl_3$) to afford the titled compound (0.105 g, 71%) as a white solid. Analytically pure compound was obtained by crystallization from MeOH/H_2O.

mp 190-191 °C;

IR (neat) 3309 (NH), 1700 (C=O), 1233 (P=O), 1163 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, J = 7.2 Hz, 6 H, $CH_2CH_2CH_3$ and $OCH_2CH_2CH_3$), 1.03 (t, J = 6.9 Hz, 3 H, $PO(OCH_2CH_3)$), 1.06-1.24 (m, 1 H, CHPO), 1.35-1.51 (m, 2 H, 2 CH_{ax}), 1.64-1.80 (m, 6 H, 2 CH_{eq} and 2 $CH_2CH_2CH_3$), 2.19 (br t, J = 10.8 Hz, 2 H, 2 NCH_{ax}), 2.77 (t, J = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 3.57-3.67 (m, 4 H, 2 NCH_{eq} and $PO(OCH_2CH_3)$), 4.10 (t, J = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.35 (d, J = 8.4 Hz, 1 H, H-3'), 7.80 (dd, J = 8.4 Hz, 2.4 Hz, 1 H, H-4'), 7.83 (d, J = 2.4 Hz, 1 H, H-6'), 12.37 (br s, 1 H, NH);

MS (FAB) *m/z* 582 (MH^+).

Example 37

Preparation of 5-(5-(4-(2-ethylphosphonoethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (a compound of the formula (1) wherein R^4 = $SO_2NR^5R^6$, R^1 = CH_3, R^2 = $CH_2CH_2CH_3$, R^3 = $CH_2CH_2CH_3$; NR^5R^6 is 4-(2-ethylphosphonoethyl)piperazinyl)

The titled compound was prepared as described in Example 36 by using 5-(5-(4-(2-diethylphosphonoethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one in place of 5-(5-(4-(diethylphosphono)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one .

yield: 91%

mp 155 °C dec (CH_2Cl_2/Et_2O);

IR (neat) 3324 (NH), 1699 (C=O), 1274 (P=O), 1166 (SO_2) cm^{-1};

^1H NMR (DMSO-d_6) δ 0.93 (t, *J* = 7.5 Hz, 6 H, $CH_2CH_2CH_3$ and $OCH_2CH_2CH_3$), 1.10 (t, *J* = 6.9 Hz, 3 H, $PO(OCH_2CH_3)$), 1.64-1.79 (m, 6 H, 2 $CH_2CH_2CH_3$ and CH_2PO), 2.60-2.79 (m, 6 H, NCH_2 and 4 NCH_{ax}), 2.76 (t, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_3$), 2.98 (br s, 4 H, 4 NCH_{eq}), 3.75 (br s, 2 H, $PO(OCH_2CH_3)$), 4.10 (t, *J* = 6.3 Hz, 2 H, $OCH_2CH_2CH_3$), 4.16 (s, 3 H, NCH_3), 7.38 (d, *J* = 9.3 Hz, 1 H, H-3'), 7.81-7.84 (m, 2 H, H-4' and H-6'), 12.35 (br s, 1 H, NH);

MS (FAB) *m/z* 611 (MH^+).

Example 38 : Production of tablets (Direct compression)

Composition	Amount (mg/tablet)
Active ingredient	5.0
Lactose	14.1
Crospovidone USNF	0.8
Magnesium Stearate	0.1
Total weight	20

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

Alternatively, the active ingredient and lactose were dissolved in water and freeze-dried. Then, the dried mixture was blended with the excipients and was compressed into tablets.

Example 39 : Production of tablets (Wet granulation)

composition	mg/tablet
Active ingredient	5.0
Polysorbate 80	0.3
Lactose	16.0
Starch	4.0
Colloidal Silicon Dioxide	2.7
Magnesium Stearate	2.0
Total weight	30

The active ingredient was sieved and blended with the lactose and starch. The polysorbate 80 was dissolved in purified water. Suitable

volumes of the polysorbate 80 solution were added and the powders were granulated. After drying, the granules were screened and blended with the colloidal silicon dioxide and magnesium stearate. The granules were then compressed into tablets.

Example 40 :Production of powder and encapsulated medicine

composition	mg/capsule
Active ingredient	5.0
Lactose	14.8
Polyvinyl pyrrolidone	10.0
Magnesium Stearate	0.2
Total weight	30

The active ingredient was sieved and blended with the excipients. The mix was filled into No. 5 hard gelatin capsules using suitable equipment.

Experimental Example 1 : *in vitro* Test

The PDE V activity and PDE III activity was determined using a method of Ballard et al (*J. Urol.*, **1998**, *159*, 2164-2171).

As a result, the compounds of Examples 2, 5, 6, 12, 13 and 14 showed an excellent inhibitory activity against PDE V with 0.02-0.5 nM of IC_{50}, while they did weak activity against PDE III with 0.5-15 μM of of IC_{50}. Therefore, the compounds of this invention have utility in a variety of therapeutic areas because they are potent and selective inhibitors of PDE V.

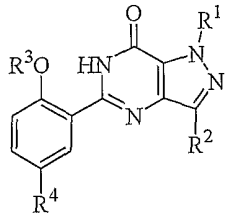
Experimental Example 2 : Safety Profile

Several compounds of the invention have been tested at doses of up to 10 mg/kg p. o. in rats with no untoward effects being observed, and up to 100 mg/kg p. o. in rats with no death being observed.

CLAIMS

What is claimed is :

1. A compound of the formula (1) and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof,



(1)

wherein

R^1 is H; C_1-C_3 alkyl optionally substituted with one or more fluoro substituents; or C_3-C_6 cycloalkyl;

R^2 is H; C_1-C_6 alkyl optionally substituted with OH, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, or with one or more fluoro substituents; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; or C_2-C_6 alkynyl;

R^3 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl or with one or more fluoro substituents; C_2-C_6 alkenyl; C_2-C_6 alkynyl; or C_3-C_6 cycloalkyl;

R^4 is $SO_2NR^5R^6$; or $NHCOR^7$;

R^5 and R^6 together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, or piperazinyl group wherein said group is substituted with R^8;

R^7 is C_1-C_6 alkyl optionally substituted with C_3-C_6 cycloalkyl or with one or more fluoro substituents; or C_3-C_7 cycloalkyl;

R^8 is CO_2H; (C_1-C_4 alkyl)CO_2H; $PO(OR^9)(OR^{10})$; or (C_1-C_4 alkyl)$PO(OR^9)(OR^{10})$; and

R^9 and R^{10} are each independently H or C_1-C_4 alkyl.

2. The compounds according to Claim 1, wherein R^1 is H; methyl; or ethyl; R^2 is C_1-C_4 alkyl; R^3 is ethyl; *n*-propyl; or allyl; R^4 is $SO_2NR^5R^6$; or $NHCOR^7$; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino or piperazinyl group wherein said group is substituted with R^8; R^7 is isopropyl; or cyclohexyl; R^8 is CO_2H; (C_1-C_2 alkyl)CO_2H; $PO(OR^9)(OR^{10})$; or (C_1-C_2 alkyl)$PO(OR^9)(OR^{10})$; R^9 and R^{10} are each independently H, methyl, or ethyl.

3. The compound according to Claim 2, wherein R^1 is methyl; R^2 is *n*-propyl; R^3 is ethyl; or *n*-propyl; R^4 is $SO_2NR^5R^6$; or $NHCOR^7$; R^5 and R^6 together with the nitrogen atom to which they are attached form a piperidino or piperazinyl group wherein said group is substituted with R^8; R^7 is cyclohexyl; R^8 is CO_2H; (C_1-C_2 alkyl)CO_2H; $PO(OR^9)(OR^{10})$; or (C_1-C_2 alkyl)$PO(OR^9)(OR^{10})$; R^9 and R^{10} are each independently H, methyl, or ethyl.

4. The compound according to Claim 3, wherein said compound is selected from:

5-(5-(4-(hydroxycarbonyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(hydroxycarbonylmethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(hydroxycarbonylmethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(2-hydroxycarbonylethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-

dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(2-hydroxycarbonylethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(hydroxycarbonylmethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(hydroxycarbonylmethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(2-hydroxycarbonylethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(2-hydroxycarbonylethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(ethylphosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(ethylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(methylphosphonomethyl)piperidinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(methylphosphonomethyl)piperidinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-

d]pyrimidin-7-one;

5-(2-ethoxy-5-(4-(ethylphosphonomethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(ethylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

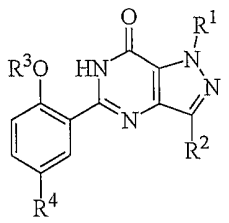
5-(2-ethoxy-5-(4-(methylphosphonomethyl)piperazinylsulfonyl)phenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-(4-(methylphosphonomethyl)piperazinylsulfonyl)-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one;

5-(5-cyclohexanecarbonylamino-2-*n*-propoxyphenyl)-1-methyl-3-*n*-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one; and

physiologically acceptable salts and solvates (e.g. hydrates) thereof.

5. A pharmaceutical composition for inhibiting PDE V comprising a compound of the formula (**1**) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier thereof,

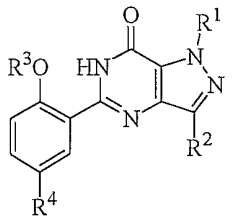


(1)

wherein R^1, R^2, R^3, and R^4 are as defined in claim 1.

6. The pharmaceutical composition according to Claim 5, wherein diseases relating to PDE V are impotence, sexual dysfunction in female, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility (e.g. irritable bowel syndrome).

7. A therapeutic agent to prevent or treat diseases by selective inhibiting activity against PDE V, which comprises a compound of the formula (**1**) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier thereof,



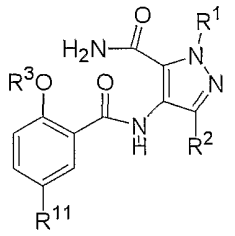
(**1**)

wherein R^1, R^2, R^3, and R^4 are as defined in claim 1.

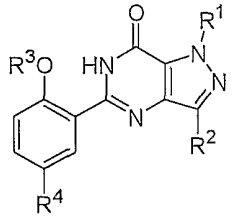
8. The therapeutic agent to prevent or treat diseases according to claim 7, wherein said diseases are impotence, sexual dysfunction in female, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g. post-percutaneous

transluminal coronary angioplasty), peripheral vascular disease, vascular disorders such as Raynaud's disease, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma and diseases characterized by disorders of gut motility (e.g. irritable bowel syndrome), in a mammal (including a human being).

9. A process for preparing a compound of the formula (**1**), and pharmaceutically acceptable salts thereof, which cyclizes a compound of the formula (**2**)



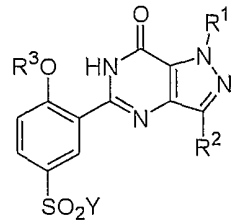
(2)



(1)

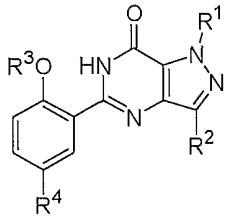
wherein R^1, R^2, and R^3 are as defined in Claim 1; and R^{11} is a group R^4 as defined in Claim1 or a precursor to a group R^4.

10. A process for preparing a compound of the formula (**1**), and pharmaceutically acceptable salts thereof, which comprises reacting a compound of the formula (**10**) with a compound of the formula (**4**),



(10)

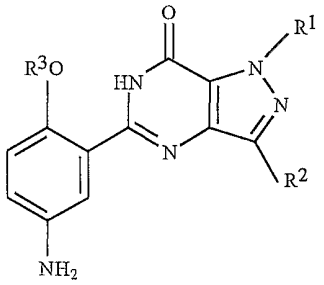
(4)



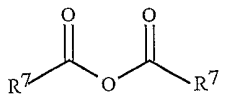
(1)

wherein R^1, R^2, R^3, R^4, $R^5$and R^6 are as defined in Claim 1; and Y represents a halogen atom.

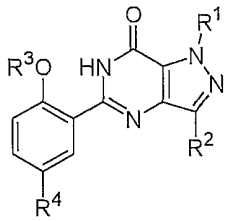
11. A process for preparing a compound of the formula (1), which comprises reacting a compound of the formula (11) with a compound of the formula (12),



(11)



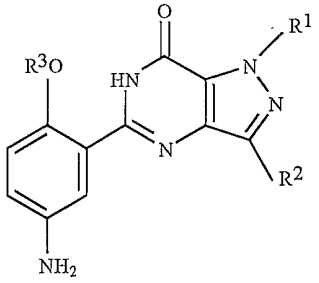
(12)



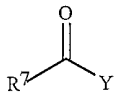
(1)

wherein R^1, R^2, R^3, R^4, and R^7 are as defined in Claim 1; and Y represents a halogen atom.

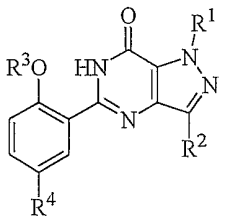
12. A process for preparing a compound of the formula (**1**), which which comprises reacting a compound of the formula (**11**) with a compound of the formula (**13**),



(**11**)



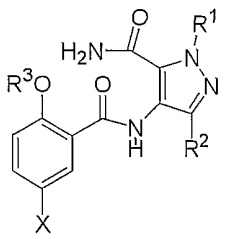
(**13**)



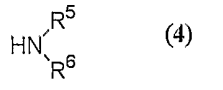
(**1**)

wherein R^1, R^2, R^3, R^4, and R^7 are as defined in Claim 1.

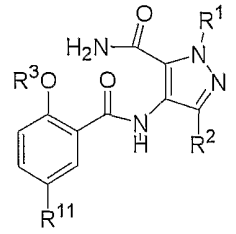
13. A process for preparing a compound of the formula (**2**), which comprises reacting a compound of the formula (**3**) with a compound of the formula (**4**),



(**3**)



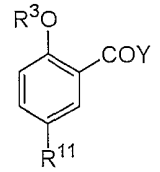
(4)



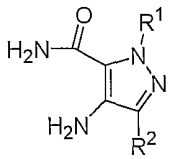
(2)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Claim 1; R^{11} is a group R^4 as defined in Claim1 or a precursor to a group R^4 thereof; and X represents sulfonyl halide.

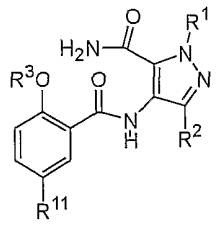
14. A process for preparing a compound of the formula (2), which comprises reacting a compound of the formula (6) with a compound of the formula (7),



(6)



(7)

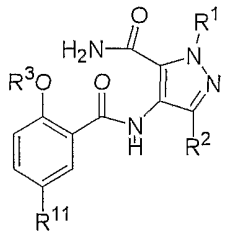


(2)

wherein R^1, R^2, and R^3 are as defined in Claim 1; R^{11} is a group R^4 as defined in Claim1 or a precursor to a group R^4 thereof; and Y represents a halide

atom.

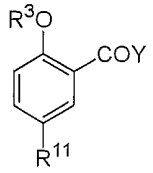
15. A compound of the formula (2):



(2)

wherein R^1, R^2, and R^3 are as claimed in Claim 1, and R^{11} is a group R^4 as claimed in Claim 1 or a precursor to a group R^4 thereof.

16. A compound of the formula (6):



(6)

wherein R^3 is as claimed in Claim 1, R^{11} is as claimed in Claim 10, and Y represents a hydroxyl group or a halogen atom.

INTERNATIONAL SEARCH REPORT

..ernational application No.
PCT/KR00/00480

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 487/04, A61K 31/505

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

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
IPC7 : C07D

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)
CAS On-Line (MARPAT)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/05661 A (PFIZER LIMITED) 17 March 1994, see page 10, compound no. IX	16
A	EP 995750 A (PFIZER LIMITED) 26 April 2000, see page 2:15 - page 5:12, page 6:40 - page 14:32	1-16
A	EP 463756 A (PFIZER LIMITED) 02 January 1992, cited in the application, see entire document	1-16
A	WO 94/28902 A (PFIZER LIMITED) 22 December 1994, cited in the application, see entire document	1-16
A	WO 98/49166 A (PFIZER LIMITED) 05 November 1998, cited in the application, see entire document	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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