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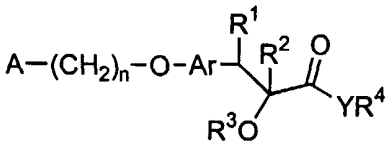
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(54) Title: ARYL SUBSTITUTED ALKYLCARBOXYLIC ACIDS AS HYPOCHOLESTEROLEMIC AGENTS



(I)

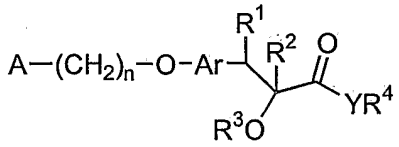
(57) Abstract: The present invention relates to novel antiobesity and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel b-aryl-a-oxysubstituted alkylcarboxylic acids of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.

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ARYL SUBSTITUTED ALKYLCARBOXYLIC ACIDS AS HYPOCHOLESTEROLEMIC AGENTS

Field of the Invention

The present invention relates to novel antiobesity and hypocholesterolemic compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them. More particularly, the present invention relates to novel β-aryl-α-oxysubstituted alkylcarboxylic acids of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutically acceptable compositions containing them.



(I)

The present invention also relates to a process for the preparation of the above said novel compounds, their analogs, their derivatives, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

The present invention also relates to novel intermediates, processes for their preparation and their use in the preparation of compounds of formula (I).

The compounds of the present invention lower plasma glucose, triglycerides, lower total cholesterol (TC) and increase high density lipoprotein (HDL) and decrease low density lipoprotein (LDL), which have a beneficial effect on coronary heart disease and atherosclerosis.

The compounds of general formula (I) are useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as

atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of hyperglycemia, hyperlipidemia, hypercholesterolemia, lowering of atherogenic lipoproteins, VLDL (very low density lipoprotein) and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis and nephropathy. The compounds of general formula (I) are also useful for the treatment and/or prophylaxis of type 2 diabetes, leptin resistance, atherosclerosis, impaired glucose tolerance, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, retinopathy, xanthoma, eating disorders, inflammation and for the treatment of cancer. The compounds of the present invention are also useful in the treatment and/or prophylaxis of the above said diseases in combination/concomittant with one or more HMG CoA reductase inhibitors, hypolipidemic/hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol and probucol.

Background of the Invention

Atherosclerosis and other peripheral vascular diseases are the major causes effecting the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and hyperlipidemia and development of effective therapeutic strategies.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in the general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD, particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as Low density lipoprotein (LDL), intermediate density lipoprotein (IDL), High density lipoprotein (HDL) and partially as Very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlationship between CAD and atherosclerosis with serum HDL-cholesterol concentrations. (Stampfer *et al., N. Engl. J. Med.,* **325** (1991), 373-381) and the risk of CAD increases with increasing levels of LDL and VLDL.

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al.,* (*Br. Med. J.,* **282** (1981), 1741 - 1744) have shown that increase in HDL-particles may decrease the number of sites of stenosis in coronary arteries of human, and high level of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al.,* (*Arteriosclerosis* **6** (1986) 434 - 441) have shown by *in vitro* experiment that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer it to liver (Macikinnon *et al., J. Biol. chem.* **261** (1986), 2548 - 2552). Therefore, agents that increase HDL cholesterol would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

Obesity is a disease highly prevalent in affluent societies and in the developing world and is a major cause of morbidity and mortality. It is a state of excess body fat accumulation. The causes of obesity are unclear. It is believed to be of genetic origin or promoted by an interaction between the genotype and environment. Irrespective of the cause, the result is fat deposition due to imbalance between the energy intake versus energy expenditure. Dieting, exercise and appetite suppression have been a part of obesity treatment. There is a need for efficient therapy to fight this disease since it may lead to coronary heart disease, diabetes, stroke, hyperlipidemia, gout, osteoarthritis, reduced fertility and many other psychological and social problems.

Diabetes and insulin resistance is yet another disease which severely effects the quality of a large population in the world. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably rises and develops into diabetes. Among the developed countries, diabetes mellitus is a common problem and is associated with a variety of abnormalities including obesity, hypertension, hyperlipidemia (J. Clin. Invest., (1985) 75 : 809 - 817; N. Engl. J. Med. (1987) 317: 350-357; J. Clin. Endocrinol. Metab., (1988) 66 : 580 - 583; J. Clin. Invest., (1975) 68 : 957 - 969) and other renal complications (See Patent Application No. WO 95/21608). It is now increasingly being recognized that insulin resistance and relative hyperinsulinemia have a contributory role in obesity, hypertension, atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

Hyperlipidemia is the primary cause for cardiovascular (CVD) and other peripheral vascular diseases. High risk of CVD is related to the higher LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) seen in hyperlipidemia. Patients having glucose intolerance/insulin resistance in addition to hyperlipidemia have higher risk of CVD. Numerous studies in the past have shown that lowering of plasma triglycerides and total cholesterol, in particular LDL and VLDL and increasing HDL cholesterol help in preventing cardiovascular diseases.

Peroxisome proliferator activated receptors (PPAR) are members of the nuclear receptor super family. The gamma (γ) isoform of PPAR (PPARγ) has been implicated in regulating differentiation of adipocytes (Endocrinology, (1994) 135: 798-800) and energy homeostasis (Cell, (1995) 83: 803-812), whereas the alpha (α) isoform of PPAR (PPARα) mediates fatty acid oxidation (Trend. Endocrin. Metab., (1993) 4: 291-296) thereby resulting in reduction of circulating free fatty acid in plasma (Current Biol. (1995) 5: 618 –621). PPARα agonists have been found useful for the treatment of obesity (WO 97/36579). It has been recently disclosed that there exists synergism for the molecules, which are agonists for both PPARα and PPARγ and suggested to be useful for the treatment of syndrome X (WO 97/25042). Similar synergism between the insulin sensitizer (PPARγ agonist) and HMG CoA reductase inhibitor has been observed which may be useful for the treatment of atherosclerosis and xanthoma (EP 0 753 298).

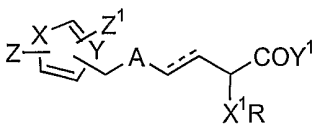
It is known that PPARγ plays an important role in adipocyte differentiation (Cell, (1996) 87, 377-389). Ligand activation of PPAR is sufficient to cause complete terminal differentiation (Cell, (1994) 79, 1147-1156) including cell cycle withdrawal. PPARγ is consistently expressed in certain cells and activation of this nuclear receptor with PPARγ agonists would stimulate the terminal differentiation of adipocyte precursors and cause morphological and molecular changes characteristics of a more differentiated,

less malignant state (Molecular Cell, (1998), 465-470; Carcinogenesis, (1998), 1949-53; Proc. Natl. Acad. Sci., (1997) 94, 237-241) and inhibition of expression of prostate cancer tissue (Cancer Research (1998) 58:3344-3352). This would be useful in the treatment of certain types of cancer, which express PPARγ and could lead to a quite nontoxic chemotherapy.

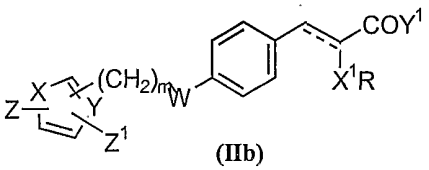
Leptin resistance is a condition wherein the target cells are unable to respond to leptin signal. This may give rise to obesity due to excess food intake and reduced energy expenditure and cause impaired glucose tolerance, type 2 diabetes, cardiovascular diseases and such other interrelated complications. Kallen *et al* (Proc. Natl. Acad. Sci. (1996) 93, 5793-5796) have reported that insulin sensitizers which perhaps due to the PPAR agonist expression and therefore lower plasma leptin concentrations. However, it has been recently disclosed that compounds having insulin sensitizing property also possess leptin sensitization activity. They lower the circulating plasma leptin concentrations by improving the target cell response to leptin (WO/98/02159).

A few β-aryl-α-hydroxy propionic acids, their derivatives and their analogs have been reported to be useful in the treatment of hyperglycemia and hypercholesterolemia. Some of such compounds described in the prior art are outlined below:

i) U.S. Pat. 5,306,726, WO 91/19702 discloses several 3-aryl-2-hydroxypropionic acid derivatives of general formulas (IIa) and (IIb) as hypolipidemic and hypoglycemic agents.

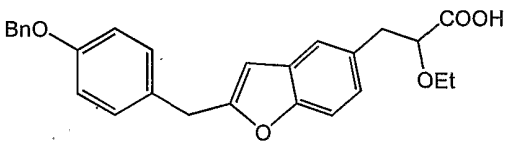


(IIa)

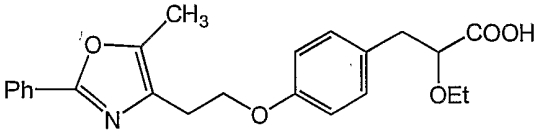


(IIb)

Examples of these compounds are shown in formulas (IIc) and (IId)

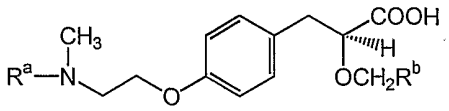


(IIc)



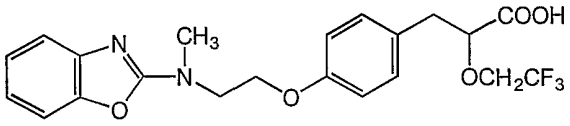
(IId)

ii) International Patent Applications, WO 95/03038 and WO 96/04260 disclose compounds of formula (IIe)



(IIe)

wherein R^a represents 2- benzoxazolyl or 2-pyridyl and R^b represent CF_3, CH_2OCH_3 or CH_3. A typical example is (*S*)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino] ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid (IIf).

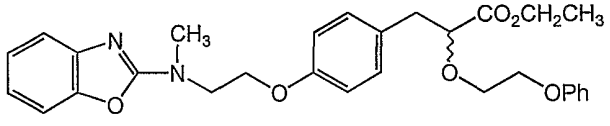


(IIf)

iii) International Patent Application Nos. WO 94/13650, WO 94/01420 and WO 95/17394 disclose the compounds of general formula (IIg)

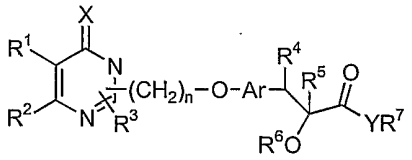
$$A^1—X—(CH_2)_n—O—A^2—A^3—Y.\ R^2 \qquad \text{(IIg)}$$

wherein A^1 represents aromatic heterocycle, A^2 represents substituted benzene ring and A^3 represents a moiety of formula $(CH_2)_m$-CH-(OR^1), wherein R^1 represents alkyl groups, m is an integer; X represents substituted or unsubstituted N; Y represents C=O or C=S; R^2 represents OR^3 where R^3 may be alkyl, aralkyl, or aryl group; n represents an integer in the range of 2-6. An example of these compounds is shown in formula (IIh)



(IIh)

iv) International publication No. WO 99/08501 discloses compounds of general formula (IIi)

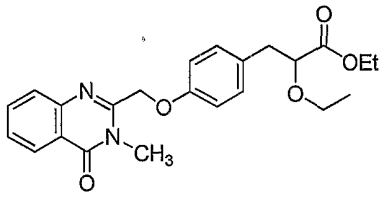


(IIi)

where X represents O or S ; the groups R^1, R^2 and group R^3 when attached to the carbon atom, may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^1, R^2 along with the adjacent atoms to which they are attached may also form a 5-6 membered substituted or unsubstituted cyclic structure containing carbon atoms with one or more double bonds, which may optionally contain one or more heteroatoms selected from oxygen, nitrogen and sulfur; R^3 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, alkylamino, arylamino, aralkylamino, aminoalkyl, aryloxy, aralkoxy, heteroaryloxy, heteroaralkoxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; the linking group represented by -$(CH_2)_n$-O- may be attached either through nitrogen atom or through carbon atom where n is an integer ranging from 1 – 4; Ar represents an optionally

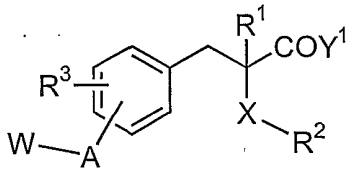
substituted divalent single or fused aromatic or heterocyclic group; R^4 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, optionally substituted aralkyl group or forms a bond together with the adjacent group R^5; R^5 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, optionally substituted aralkyl or R^5 forms a bond together with R^4; R^6 may be hydrogen, optionally substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups, with a provision that R^6 does not represent hydrogen when R^7 represents hydrogen or lower alkyl group; R^7 may be hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl groups; Y represents oxygen or NR^8, where R^8 represents hydrogen, alkyl, aryl, hydroxyalkyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R^7 and R^8 together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen.

An example of these compounds is shown in formula (IIj)



(IIj)

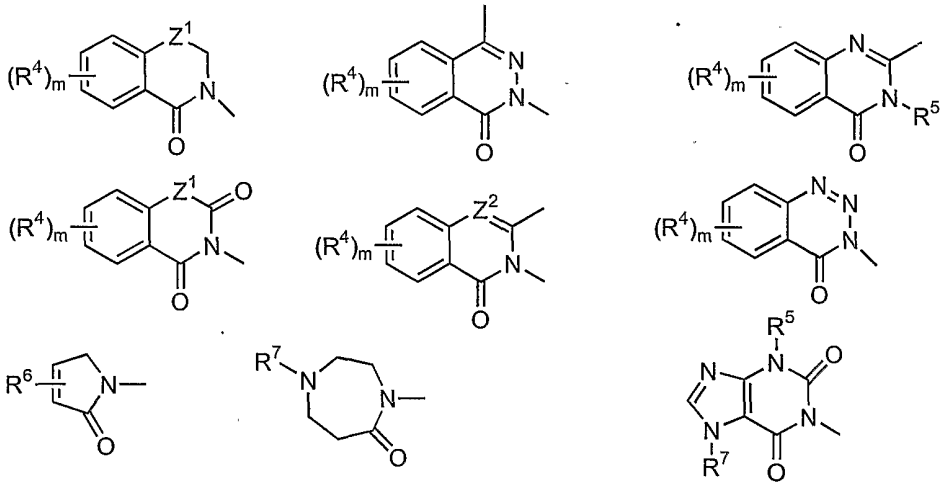
v) European publication No. EP 0903343 discloses compounds of general formula (IIk)



(IIk)

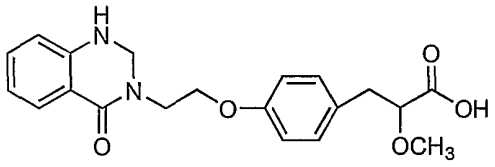
where A is an alkylene, alkyleneoxy or alkylenecarbonyl, X is O, S, NH or CH_2; Y^1 is an amino, hydroxylamino, hydroxyalkylamino, monoalkylamino,

dialkylamino, cyclic amino, hydroxy or lower alkoxy group; R^1 is a hydrogen atom, lower alkyl, hydroxyalkyl group, alkoxyalkyl, halogenalkyl or COY^2, where Y^2 is amino, hydroxyamino, hydroxyalkylamino, monoalkylamino, dialkylamino, cyclic amino, hydroxy or lower alkoxy group; R^2 is lower alkyl, hydroxyalkyl, alkoxyalkyl or halogenalkyl group, COY^2or a phenyl, pyridyl or aralkyl which may be substituted and R^3 is a hydrogen or halogen, alkyl, alkoxy, halogenalkyl, amino, hydroxy or acyl groups or a salt thereof; W is a monocyclic or cyclic lactam ring selected from the following groups which may be substituted :



wherein R^4 is a hydrogen, halogen, alkyl, alkoxy, halogenalkyl, amino, hydroxy, cyano, carbonyl, acyl, nitro, carboxy or sulfonamide, phenyl or benzyl which may be substituted; R^5 is a hydrogen, alkyl, aryl, aralkyl or pyridyl which may be substituted; R^6 is hydrogen or lower alkyl group R^7 is a lower alkyl, phenyl or aralkyl groups; Z^1 is O, S, CH_2 or NR^5, Z^2 is N or CH and m is an integer of 1 to 4.

An example of these compounds is shown in formula (III)



(III)

Summary of the Invention

With an objective to develop novel compounds for lowering cholesterol and reducing body weight with beneficial effects in the treatment and/or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetes complications thereof, for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism and for the treatment of hypertension, with better efficacy, potency and lower toxicity, we focused our research to develop new compounds effective in the treatment of the above mentioned diseases. Effort in this direction has led to compounds having general formula (I).

The main objective of the present invention is therefore, to provide novel β-aryl-α-oxysubstituted alkylcarboxylic acids, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them, or their mixtures.

Another objective of the present invention is to provide novel β-aryl-α-oxysubstituted alkylcarboxylic acids, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures which may have agonist activity against PPARα and/or PPARγ, and optionally inhibit HMG CoA reductase, in addition to having agonist activity against PPARα and/or PPARγ.

Another objective of the present invention is to provide novel β-aryl-α-oxysubstituted alkylcarboxylic acids, their derivatives, their analogs, their

tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and pharmaceutical compositions containing them or their mixtures having enhanced activities, without toxic effect or with reduced toxic effect.

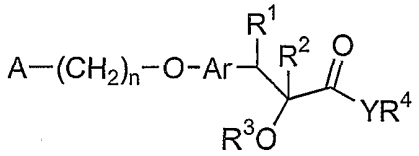
Yet another objective of the present invention is a process for the preparation of novel β-aryl-α-oxysubstituted alkylcarboxylic acids of formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts and their pharmaceutically acceptable solvates.

Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their analogs, their derivatives, their tautomers, their stereoisomers, their polymorphs, their salts, solvates or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

Another objective of the present invention is to provide novel intermediates, a process for their preparation and their use in the preparation of β-aryl-α-oxysubstituted alkyl carboxylic acids of formula (I), their derivatives, their analogs, their tautomers, their stereoisomers, their polymorphs, their salts and their pharmaceutically acceptable solvates.

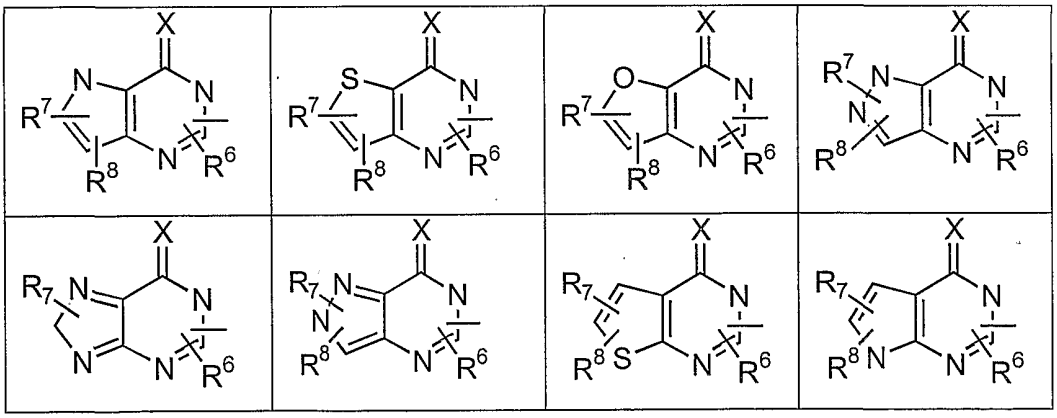
Detailed Description of the Invention

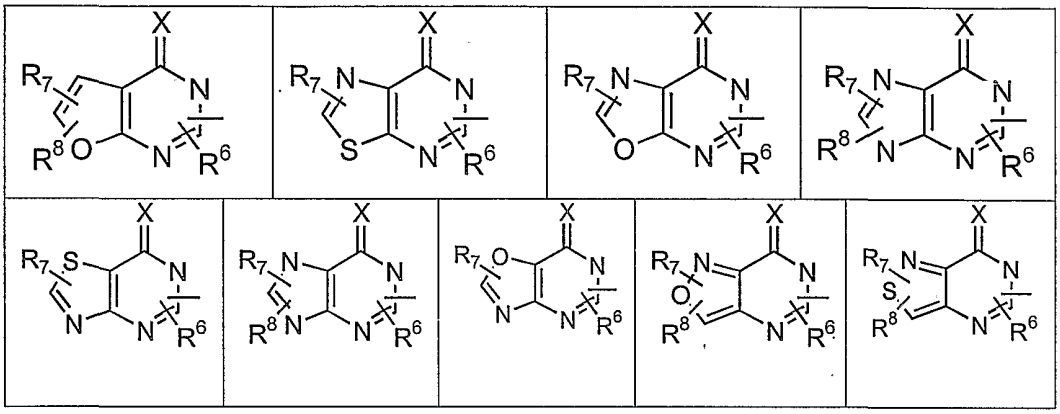
β-aryl α-oxysubstituted propionic acids, their derivatives and their analogs of the present invention have the general formula (I)



(I)

where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen or NR^5, where R^5 represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl, aralkyl, hydroxyalkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl, heteroaryl or heteroaralkyl groups; R^4 and R^5 together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, a nitrogen atom and which may optionally contain one or more additional heteroatoms selected from oxygen, sulfur or nitrogen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :





where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl,

heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups.

Suitable groups represented R^1 may be selected from hydrogen, hydroxy, halogen atom such as fluorine, chlorine, bromine or iodine; lower alkyl groups such as methyl, ethyl, propyl and the like; (C_1-C_3)alkoxy such as methoxy, ethoxy, propoxy and the like; substituted or unsubstituted aralkyl such as benzyl, phenethyl and the like or R^1 together with R^2 represent a bond. When the aralkyl group is substituted, the substituents may be selected from hydroxy, halogen atom, nitro or amino groups.

Suitable groups represented R^2 may be selected from hydrogen, hydroxy, halogen atom such as fluorine, chlorine, bromine, iodine; lower alkyl groups such as methyl, ethyl, propyl and the like; (C_1-C_3)alkoxy such as methoxy, ethoxy, propoxy and the like; linear or branched (C_2-C_{10})alkanoyl group such as acetyl, propanoyl, butanoyl, pentanoyl and the like; aroyl such as benzoyl, substituted benzoyl and the like; aralkanoyl groups such as phenylacetyl, phenylpropanoyl and the like; substituted or unsubstituted aralkyl such as benzyl, phenethyl and the like or R^2 together with R^1 forms a bond. The substituents may be selected from hydroxy, halogen, nitro, amino groups.

It is preferred that R^1 and R^2 represent hydrogen atom or R^1 and R^2 together represent a bond.

Suitable groups represented by R^3 may be selected from hydrogen, substituted or unsubstituted, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl,

pentyl, hexyl, octyl and the like; substituted or unsubstituted, linear or branched(C_2-C_{16})alkanoyl group such as acetyl, propanoyl, butanoyl, octanoyl, decanoyl and the like; aroyl such as benzoyl, substituted benzoyl and the like; (C_3-C_7)cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, the cycloalkyl group may be substituted; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; aralkyl such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; (C_1-C_6)alkoxy(C_1-C_6)alkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxypropyl and the like, the alkoxyalkyl group may be substituted; (C_1-C_6)alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like, which may be substituted; aryloxycarbonyl such as phenoxycarbonyl, naphthyloxycarbonyl and the like, which may be substituted; (C_1-C_6)alkylaminocarbonyl such as methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl and the like, which may be substituted; arylaminocarbonyl such as PhNHCO, naphthylaminocarbonyl and the like, which may be substituted. The substituents may be selected from halogen, hydroxy or nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkanoyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives.

Suitable groups represented by R^4 may be selected from hydrogen, substituted or unsubstituted, linear or branched (C_1-C_{16})alkyl, preferably (C_1-C_{12})alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, pentyl, hexyl, octyl and the like; (C_3-C_7)cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; aralkyl group such as benzyl, phenethyl and the like, the aralkyl group may be substituted; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted. The substituents on R^4 may be selected from the same group of R^7 and R^8.

Suitable Y represents oxygen or NR^5.

Suitable groups represented by R^5 may be selected from hydrogen, substituted or unsubstituted, linear or branched (C_1-C_{16})alkyl, especially, (C_1-C_{12})alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; hydroxy(C_1-C_6)alkyl, which may be substituted; substituted or unsubstituted, linear or branched(C_2-C_6)alkanoyl group such as acetyl, propanoyl, butanoyl and the like; aralkyl group such as benzyl, phenethyl and the like, the aralkyl groups may be substituted; aroyl such as benzoyl, substituted benzoyl and the like; aralkanoyl groups such as phenylacetyl, phenylpropanoyl and the like, which may be substituted; heterocyclyl group such as aziridinyl, pyrrolidinyl, piperidinyl, and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl,

oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted. The substituents may be selected from halogen, hydroxy, amino, nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, aryl, aralkyl group.

Suitable ring structures formed by R^4 and R^5 together may be selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolinyl, diazolinyl and the like.

Suitable substituents on the cyclic structure formed by R^4 and R^5 taken together may be selected from halogen, hydroxy, alkyl, oxo, aralkyl and the like.

Suitable n is an integer ranging from 1 to 4, preferably n represents an integer of 1 or 2.

Suitable groups represented by Ar include substituted or unsubstituted groups selected from divalent phenylene, naphthylene, pyridyl, quinolinyl, benzofuryl, dihydrobenzofuryl, benzopyranyl, indolyl, indolinyl, azaindolyl, azaindolinyl, pyrazolyl, benzothiazolyl, benzoxazolyl and the like. The substituents on the group represented by Ar may be selected from optionally halogenated substituted or unsubstituted linear or branched (C_1-C_6)alkyl, optionally halogenated (C_1-C_3)alkoxy, halogen, alkanoyl, amino, acylamino, thio or carboxylic or sulfonic acids and their derivatives.

It is preferred that Ar represents substituted or unsubstituted divalent phenylene, naphthylene, benzofuryl, indolyl, indolinyl, quinolinyl, azaindolyl, azaindolinyl, benzothiazolyl or benzoxazolyl.

It is more preferred that Ar is represented by divalent phenylene or naphthylene, which may be substituted or unsubstituted by methyl, halomethyl, methoxy or halomethoxy groups.

Suitable groups represented by R^6 when attached to carbon atom may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, or iodine; hydroxy, cyano, nitro, formyl; substituted or unsubstituted (C_1-

C_{12})alkyl group, especially, linear or branched (C_1-C_{10})alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like; cyclo(C_3-C_6)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; (C_1-C_6)alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, the alkoxy group may be substituted; cyclo(C_3-C_6)alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; aryloxy group such as phenoxy, naphthyloxy and the like, the aryloxy group may be substituted; aralkyl such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy and heteroaralkoxy, wherein heteroaryl and heteroaralkyl moieties are as defined earlier and may be substituted; alkanoyl group such as acetyl, propionyl and the like, the alkanoyl group may be substituted; aroyl such as benzoyl, substituted benzoyl and the like; alkanoyloxy group such as OOCMe, OOCEt, OOCPh and the like which may be substituted; hydroxy(C_1-C_6)alkyl, which may be substituted; amino; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$,

which may be substituted; mono(C_1-C_6)alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13} and the like, which may be substituted; (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$and the like, which may be substituted; arylamino group such as HNC_6H_5, $NCH_3(C_6H_5)$, $NHC_6H_4CH_3$, NHC_6H_4-Hal and the like, which may be substituted; aralkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; amino(C_1-C_6)alkyl, which may be substituted; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and the like, which may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, naphthyloxycarbonyl and the like, which may be substituted; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, the alkoxyalkyl groups may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; thio(C_1-C_6)alkyl, which may be substituted; (C_1-C_6)alkylthio, which may be substituted; alkoxycarbonylamino group such as $NHCOOC_2H_5$, $NHCOOCH_3$ and the like, which may be substituted; aryloxycarbonylamino group such as $NHCOOC_6H_5$, $N(CH_3)COOC_6H_5$, $N(C_2H_5)COOC_6H_5$, $NHCOOC_6H_4CH_3$, $NHCOOC_6H_4OCH_3$ and the like, which may be substituted; aralkoxycarbonylamino group such as $NHCOOCH_2C_6H_5$, $NHCOOCH_2CH_2C_6H_5$, $N(CH_3)COOCH_2C_6H_5$, $N(C_2H_5)COOCH_2C_6H_5$, $NHCOOCH_2C_6H_4CH_3$, $NHCOOCH_2C_6H_4OCH_3$ and the like, which may be substituted; carboxylic acid or its derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, or esters such as $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$ and the like, the carboxylic acid derivatives may be substituted; sulfonic acid or its derivatives such as

SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like, or esters such as $COOCH_3$, $COOC_2H_5$, $COOC_3H_7$ and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by R^6 attached to carbon atom are substituted, the substituents may be selected from halogen, hydroxy, nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkanoyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives or sulfonic acid or its derivatives.

It is preferred that the substituents on R^6 represents halogen atom such as fluorine, chlorine, bromine, hydroxy group, optionally halogenated groups selected from alkyl group such as methyl, ethyl, isopropyl, n-propyl, n-butyl; cycloalkyl group such as cyclopropyl; aryl group such as phenyl; aralkyl group such as benzyl; (C_1-C_3)alkoxy, benzyloxy, alkanoyl or alkanoyloxy groups.

Suitable groups represented by R^6 when attached to nitrogen atom may be selected from hydrogen, hydroxy, formyl; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_6)alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl and the like; cyclo(C_3-C_6)alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; (C_1-C_6)alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, the alkoxy group may be substituted; cyclo(C_3-C_6)alkoxy group such as cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like, the cycloalkoxy group may be substituted; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; aryloxy group such as phenoxy, naphthyloxy and the like, the aryloxy group

may be substituted; aralkyl such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, naphthylmethyl and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; heteroaryloxy and heteroaralkoxy, wherein heteroaryl and heteroaralkyl moieties are as defined earlier and may be substituted; alkanoyl group such as acetyl, propionyl and the like, the alkanoyl group may be substituted; aroyl such as benzoyl, substituted benzoyl and the like; alkanoyloxy group such as OOCMe, OOCEt, OOCPh and the like which may be substituted; hydroxy(C_1-C_6)alkyl, which may be substituted; amino; acylamino groups such as $NHCOCH_3$, $NHCOC_2H_5$, $NHCOC_3H_7$, $NHCOC_6H_5$, which may be substituted; mono(C_1-C_6)alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13} and the like, which may be substituted; (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$and the like, which may be substituted; arylamino group such as HNC_6H_5, $NCH_3(C_6H_5)$, $NHC_6H_4CH_3$, NHC_6H_4-Hal and the like, which may be substituted; aralkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; amino(C_1-C_6)alkyl, which may be substituted; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl and the like, which may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, naphthyloxycarbonyl and the like, which may be substituted;

aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl and the like, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, the alkoxyalkyl groups may be substituted; aryloxyalkyl group such as $C_6H_5OCH_2$, $C_6H_5OCH_2CH_2$, naphthyloxymethyl and the like, which may be substituted; aralkoxyalkyl group such as $C_6H_5CH_2OCH_2$, $C_6H_5CH_2OCH_2CH_2$ and the like, which may be substituted; thio(C_1-C_6)alkyl, which may be substituted; (C_1-C_6)alkylthio, which may be substituted; carboxylic acid or its derivatives such as amides, like $CONH_2$, CONHMe, $CONMe_2$, CONHEt, $CONEt_2$, CONHPh and the like, the carboxylic acid derivatives may be substituted; sulfonic acid or its derivatives such as SO_2NH_2, SO_2NHMe, SO_2NMe_2, SO_2NHCF_3 and the like, the sulfonic acid derivatives may be substituted.

When the groups represented by R^6 attached to nitrogen are substituted, preferred substituents may be selected from halogen such as fluorine, chlorine; hydroxy, alkanoyl, alkanoyloxy, amino groups.

Suitable groups represented by R^7 and R^8 when attached to carbon atom may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, or iodine; hydroxy, cyano, nitro, formyl; substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_{10})alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like; (C_1-C_6)alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, the alkoxy group may be substituted; aryl group such as phenyl, naphthyl and the like, the aryl group may be substituted; aryloxy group such as phenoxy and the like, the aryloxy group may be substituted; aralkyl such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$, and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as

benzyloxy, phenethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; hydroxy(C_1-C_6)alkyl, which may be substituted; amino; mono(C_1-C_6)alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13} and the like, which may be substituted; (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$and the like, which may be substituted; arylamino group such as HNC_6H_5, $NCH_3(C_6H_5)$, $NHC_6H_4CH_3$, NHC_6H_4-Hal and the like, which may be substituted; aralkylamino group such as $C_6H_5CH_2NH$, $C_6H_5CH_2CH_2NH$, $C_6H_5CH_2NCH_3$ and the like, which may be substituted; amino(C_1-C_6)alkyl, which may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, the alkoxyalkyl groups may be substituted; thio(C_1-C_6)alkyl, which may be substituted; (C_1-C_6)alkylthio, which may be substituted.

When the groups represented by R^7 and R^8 attached to carbon atom are substituted, the substituent may be selected from halogen, hydroxy, nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, arylamino, aminoalkyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or sulfonic acid.

It is preferred that the substituent on R^7 and R^8 represent halogen atom such as fluorine, chlorine or bromine; hydroxy group, optionally halogenated groups selected from alkyl group such as methyl, ethyl, isopropyl, n-propyl, n-

butyl and the like; cycloalkyl group such as cyclopropyl; aryl group such as phenyl; aralkyl group such as benzyl; (C_1-C_3)alkoxy or benzyloxy groups.

Suitable groups represented by R^7 and R^8 when attached to nitrogen atom may be selected from hydrogen, hydroxy, substituted or unsubstituted (C_1-C_{12})alkyl group, especially, linear or branched (C_1-C_{10})alkyl group, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like; (C_1-C_6)alkoxy such as methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like, the alkoxy group may be substituted; aryl group such as phenyl and the like, the aryl group may be substituted; aryloxy group such as phenoxy and the like, the aryloxy group may be substituted; aralkyl such as benzyl, phenethyl, $C_6H_5CH_2CH_2CH_2$ and the like, the aralkyl group may be substituted and the substituted aralkyl is a group such as $CH_3C_6H_4CH_2$, Hal-$C_6H_4CH_2$, $CH_3OC_6H_4CH_2$, $CH_3OC_6H_4CH_2CH_2$ and the like; aralkoxy group such as benzyloxy, phenethyloxy, phenylpropyloxy and the like, the aralkoxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl and the like, the heterocyclyl group may be substituted; heteroaryl group such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, benzopyranyl, benzofuranyl and the like, the heteroaryl group may be substituted; heteroaralkyl group such as furanmethyl, pyridinemethyl, oxazolemethyl, oxazolethyl and the like, the heteroaralkyl group may be substituted; hydroxy(C_1-C_6)alkyl, which may be substituted; amino; mono(C_1-C_6)alkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13} and the like, which may be substituted; (C_1-C_6)dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$and the like, which may be substituted; arylamino group such as HNC_6H_5, $NCH_3(C_6H_5)$, $NHC_6H_4CH_3$, NHC_6H_4-Hal and the like, which may be substituted.

When the groups represented by R^7 and R^8 attached to nitrogen are substituted, preferred substituents may be selected from halogen atom such as fluorine, chlorine; hydroxy, alkyl, alkanoyl, alkanoyloxy, amino groups.

When R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 or Ar are substituted, the substituents are as defined above.

The compounds of formula (I) where R^3 represents hydrogen atom and R^4 represents hydrogen or lower alkyl groups have been described in our US patent Nos. 5,885,997 and 5,985,884.

Pharmaceutically acceptable salts forming part of this invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as diethanolamine, choline and the like; chiral bases like alkylphenylamine, phenyl glycinol and the like, salts of natural amino acids such as lysine, arginine, guanidine, methionine, alanine, valine and the like; unnatural amino acids such as D-isomers or substituted amino acids; ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Particularly useful compounds according to the present invention includes:

(±) Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(+) Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(-) Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(±) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its salts ;

(+) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its salts ;

(-) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its salts ;

(±) Ethyl 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(+) Ethyl 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(-) Ethyl 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(±) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(+) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(-) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts ;

(±) Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(+) Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(-) Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(±) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(+) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(-) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(±) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(+) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(-) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(±) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(+) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(-) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(+) Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo

[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(-) Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(+) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(-) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(±) Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(+) Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(-) Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;
(+) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(-) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(±) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;
(+) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(-) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(±) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;
(+) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;
(-) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(±) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(+) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(-) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

(±) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(+) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(-) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

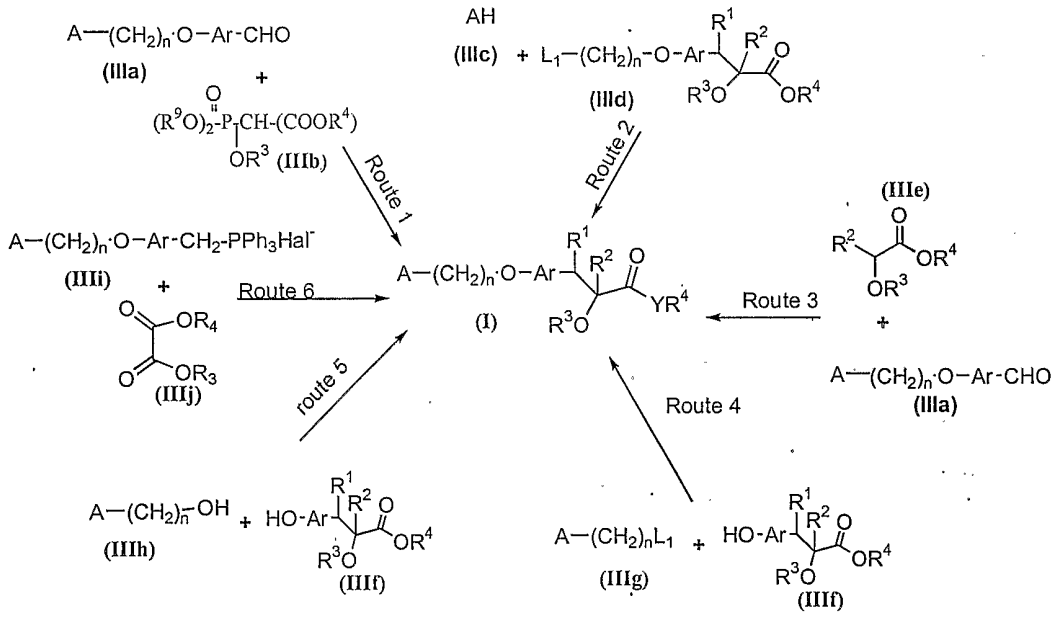
(±) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;
(+) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(-) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

[2R, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide and

[2S, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide.

According to a feature of the present invention, the compound of general formula (I) where R^1 and R^2 together represent a bond, Y represent oxygen atom R^3, R^4, A, n and Ar are as defined earlier, can be prepared by any of the following routes shown in Scheme-I below.



Scheme - I

Route (1) : The reaction of a compound of the general formula (IIIa) where A, Ar and n are as defined earlier with a compound of formula (IIIb) where R^9

represents (C_1-C_6)alkyl and all other symbols are as defined earlier to yield compound of general formula (I) where all symbols are as defined above may be carried out in the presence of a base such as alkali metal hydrides like NaH or KH; organolithiums such as CH_3Li, BuLi and the like; alkoxides such as NaOMe, NaOEt, K^+BuO^- and the like or mixtures thereof. The reaction may be carried out in the presence of solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78 °C to 50 °C, preferably at a temperature in the range of -10 °C to 30 °C. The reaction is more effective under anhydrous conditions. The compound of general formula (IIIb) may be prepared by Arbuzov reaction.

Alternatively, the compound of formula (I) may be prepared by reacting the compound of formula (IIIa) where all symbols are as defined earlier with Wittig reagents such as $HalPh_3P^+CH\text{-}(OR^3)CO_2R^4$ under similar reaction conditions as described above.

Route (2) : The reaction of a compound of general formula (IIIc) where A is as defined earlier with a compound of general formula (IIId) where L^1 is a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom; R^1, R^2 together represent a bond and all other symbols are as defined earlier to produce a compound of general formula (I) where all symbols are as defined above may be carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide or potassium hydroxide; alkali metal carbonates such as sodium carbonate or potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride;

organometallic bases like n-butyl lithium; alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIc), preferably the amount of base ranges from 1 to 3 equivalents. Phase transfer catalysts such as tetraalkylammonium halide or hydroxide may be added. Additives such as alkali metal halides such as LiBr may be added. The reaction may be carried out at a temperature in the range of 0 °C to 150 °C, preferably at a temperature in the range of 15 °C to 100 °C. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.25 to 24 hours.

Route (3) : The reaction of a compound of the general formula (IIIa) where all symbols are as defined earlier, with a compound of formula (IIIe) where R^2 represents hydrogen atom and all other symbols are as defined earlier may be carried out in the presence of a base. The nature of the base is not critical. Any base normally employed for aldol condensation reaction may be employed; bases like metal hydride such as NaH, KH, metal alkoxides such as NaOMe, t-BuO^-K^+, NaOEt, metal amides such as $LiNH_2$, $LiN(ipr)_2$ may be used. Aprotic solvents such as THF, ether, dioxane may be used. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, or He and the reaction is more effective under anhydrous conditions. Temperature in the range of -80 °C to 35 °C may be used. The β-hydroxy product initially produced may be dehydrated under conventional dehydration conditions such as treating with pTSA in solvents such as benzene or toluene. The nature of solvent and dehydrating agent is not critical. Temperature in the range of 20 °C to reflux temperature of the solvent used may be employed, preferably at reflux temperature of the solvent by continuous removal of water using a Dean Stark water separator.

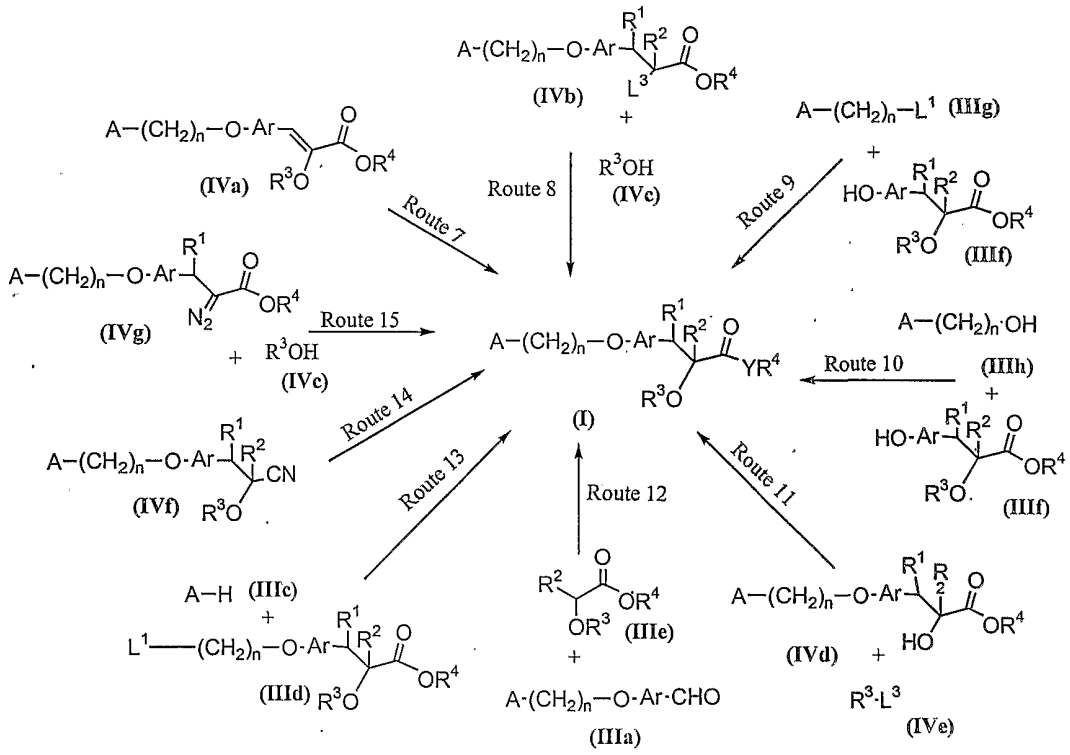
Route (4) : The reaction of compound of formula (IIIg) where A and n are as defined earlier and L^1 represents a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom with compound of formula (IIIf) where R^1 and R^2 together represent a bond and all other symbols are as defined earlier to produce a compound of the formula (I) defined above may be carried out in the presence of aprotic solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. Acetone may be used as solvent when Na_2CO_3 or K_2CO_3 is used as a base. The reaction temperature may range from 0 °C - 120 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours. The compound of formula (IIIf) can be prepared according to known procedure by a Wittig Horner reaction between the hydroxy protected aryl aldehyde such as benzyloxyaryl aldehyde and compound of formula (IIIb), followed by deprotection.

Route (5) : The reaction of compound of general formula (IIIh) where A and n are as defined earlier with a compound of general formula (IIIf) where R^1 and R^2 together represent a bond and all other symbols are as defined earlier may be carried out using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/dialkylazadicarboxylate such as PPh_3 / DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME, CH_2Cl_2, $CHCl_3$, toluene, acetonitrile, carbon tetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably

0.25 to 1 equivalents. The reaction temperature may be in the range of 0 °C to 100 °C, preferably at a temperature in the range of 20 °C to 80 °C. The duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route 6 : The reaction of a compound of formula (IIIi) where all symbols are as defined earlier with a compound of formula (IIIj) where $R^3 = R^4$ and are as defined earlier excluding hydrogen, to produce a compound of the formula (I) where R^1 and R^2 together represent a bond may be carried out neat in the presence of a base such as alkali metal hydrides like NaH, KH or organolithiums like CH_3Li, BuLi and the like or alkoxides such as NaOMe, NaOEt, t-BuO^-K^+ and the like or mixtures thereof. The reaction may be carried out in the presence of aprotic solvents such as THF, dioxane, DMF, DMSO, DME and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78 °C to 100 °C, preferably at a temperature in the range of -10 °C to 50 °C.

In yet another embodiment of the present invention, the compound of the general formula (I) where R^1 represents hydrogen atom, hydroxy, alkoxy, halogen, lower alkyl, substituted or unsubstituted aralkyl group; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl; R^3, R^4, n Ar and A are as defined earlier and Y represents oxygen atom can be prepared by one or more of the processes shown in Scheme-II below.



Scheme - II

Route 7 : The reduction of compound of the formula (IVa) which represents a compound of formula (I) where R^1 and R^2 together represent a bond and Y represent oxygen atom and all other symbols are as defined earlier, obtained as described earlier(Scheme-I), to yield a compound of the general formula (I) where R^1 and R^2 each represent hydrogen atom and all symbols are as defined earlier, may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate, alcohol such as methanol, ethanol and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5 - 10 % Pd/C and the amount of catalyst used may range from 5 - 100 % w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium in alcohol or sodium amalgam in alcohol, preferably methanol. The hydrogenation may be carried out in the

presence of metal catalysts containing chiral ligands to obtain a compound of formula (I) in optically active form. The metal catalyst may contain Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines such as optically pure enantiomers of 2,3-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenyl phenylphosphino)ethane, 2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane and the like. Any suitable chiral catalyst may be employed which would give required optical purity of the product (I) (Ref : Principles of Asymmetric Synthesis, Tetrahedron Series Vol 14, pp311-316, Ed. Baldwin J. E.).

Route 8 : The reaction of compound of formula (IVb) where R^4 is as defined earlier excluding hydrogen all other symbols are as defined earlier and L^3 is a leaving group such as halogen atom with an alcohol of general formula (IVc), where R^3 is as defined earlier excluding hydrogen to produce a compound of the formula (I) defined earlier may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe, NaOEt, t-BuO^-K^+ or NaH or mixtures thereof. Phase transfer catalysts such as tetraalkylammonium halides or hydroxides may be employed. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 100 °C. The duration of the reaction may range from 1 to 12 hours, preferably from 2 to 6 hours. The compound of general formula (IVb) where R^4 represents hydrogen or lower alkyl group and its preparation has been disclosed in our US patent Nos. 5,885,997 and 5,985,884.

Route 9 : The reaction of compound of formula (IIIg) defined earlier with compound of formula (IIIf) where all symbols are as defined earlier to produce a compound of the formula (I) defined above, may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 NaH and the like or mixtures thereof. Acetone may be used as a solvent when K_2CO_3 or Na_2CO_3 is used as a base. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 80 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours. The compound of formula (IIIf) may be prepared by Wittig Horner reaction between the protected hydroxyaryl aldehyde and compound of formula (IIIb) followed by reduction of the double bond and deprotection. Alternatively, the compound of formula (IIIf) may be prepared by following a procedure disclosed in WO 94/01420.

Route 10 : The reaction of compound of general formula (IIIh) defined earlier with a compound of general formula (IIIf) where all symbols are as defined above may be carried out using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/dialkylazadicarboxylate such as PPh_3 / DEAD and the like. The reaction may be carried out in the presence of solvents such as THF, DME, CH_2Cl_2, $CHCl_3$, toluene, acetonitrile, carbon tetrachloride and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of DMAP, HOBT and they may be used in the range of 0.05 to 2 equivalents, preferably 0.25 to 1 equivalents. The reaction temperature may be in the range of 0 °C to 100 °C, preferably at a temperature in the range of 20 °C to 80 °C. The

duration of the reaction may range from 0.5 to 24 hours, preferably from 6 to 12 hours.

Route 11 : The reaction of compound of formula (IVd) which represents a compound of formula (I) where all symbols are as defined above with a compound of formula (IVe) where R^3 is as defined earlier excluding hydrogen and L^3 is a halogen atom may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as KOH, NaOH, NaOMe, t-BuO^-K^+, NaH and the like. Phase transfer catalyst such as tetraalkylammonium halides or hydroxides may be employed. The reaction temperature may range from 20 °C to 150 °C, preferably at a temperature in the range of 30 °C to 100 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 6 hours.

The compound of formula (IVd) where R^4 represents hydrogen or lower alkyl group and its preparation has been described in our US patent Nos. 5,885,997 and 5,985,884. The compound of formula (IVd) represents a compound of formula (I) where R^6 represents hydrogen atom and all other symbols are as defined earlier.

Route 12 : The reaction of a compound of the general formula (IIIa) as defined above with a compound of formula (IIIe) where R^2 represents hydrogen atom and all other symbols are as defined earlier may be carried out under conventional conditions. The base is not critical. Any base normally employed for aldol condensation reaction may be employed, metal hydride such as NaH or KH; metal alkoxides such as NaOMe, t-BuO^-K^+ or NaOEt; metal amides such as $LiNH_2$, $LiN(iPr)_2$. Aprotic solvent such as THF may be used. Inert atmosphere may be employed such as argon and the reaction is more effective

under anhydrous conditions. Temperature in the range of -80 °C to 25 °C may be used. The β-hydroxy aldol product may be dehydroxylated using conventional methods, conveniently by ionic hydrogenation technique such as by treating with a trialkyl silane in the presence of an acid such as trifluoroacetic acid. Solvent such as CH_2Cl_2 may be used. Favorably, reaction proceeds at 25 °C. Higher temperature may be employed if the reaction is slow.

Route 13 : The reaction of a compound of general formula (IIIc) where all symbols are as defined earlier with a compound of general formula (IIId) where L^1 is a leaving group such as halogen atom, p-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, preferably a halogen atom and all other symbols are as defined earlier to produce a compound of general formula (I) where all symbols are as defined above may be carried out in the presence of solvents such as DMSO, DMF, DME, THF, dioxane, ether and the like or a combination thereof. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar, He and the like. The reaction may be effected in the presence of a base such as alkalis like sodium hydroxide, potassium hydroxide; alkali metal carbonates like sodium carbonate or potassium carbonate; alkali metal hydrides such as sodium hydride or potassium hydride; organometallic bases like n-butyl lithium; alkali metal amides like sodamide or mixtures thereof. The amount of base may range from 1 to 5 equivalents, based on the amount of the compound of formula (IIIc), preferably the amount of base ranges from 1 to 3 equivalents. Additives such as alkali metal halides such as LiBr may be added. The reaction may be carried out at a temperature in the range of 0 °C to 150 °C, preferably at a temperature in the range of 15 °C to 100 °C. The duration of the reaction may range from 0.25 to 48 hours, preferably from 0.25 to 24 hours.

Route 14 : The conversion of compound of formula (IVf) where all symbols are as defined earlier to a compound of formula (I) may be carried out either in the presence of base or acid and the selection of base or acid is not critical. Any base normally used for hydrolysis of nitrile to acid may be employed, metal hydroxides such as NaOH or KOH in an aqueous solvent or any acid normally used for hydrolysis of nitrile to ester may be employed such as dry HCl in an excess of alcohol such as methanol, ethanol, propanol etc. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent used, preferably at a temperature in the range of 25 °C to reflux temperature of the solvent used. The duration of the reaction may range from 0.25 to 48 hrs.

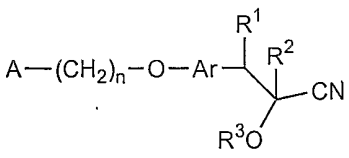
Route 15 : The reaction of a compound of formula (IVg) where R^4 is as defined earlier excluding hydrogen and all symbols are as defined earlier with a compound of formula (IVc) where R^3 is as defined earlier excluding hydrogen to produce a compound of formula (I) (by a rhodium carbenoid mediated insertion reaction) may be carried out in the presence of rhodium (II) salts such as rhodium (II) acetate. The reaction may be carried out in the presence of solvents such as benzene, toluene, dioxane, ether, THF and the like or a combination thereof or when practicable in the presence of R^6OH as solvent at any temperature providing a convenient rate of formation of the required product, generally at an elevated temperature, such as reflux temperature of the solvent. The inert atmosphere may be maintained by using inert gases such as N_2, Ar, He and the like. The duration of the reaction may be range from 0.5 to 24 h, preferably from 0.5 to 6 h.

The compound of general formula (I) where R^4 represents hydrogen atom may be prepared by hydrolysing using conventional methods, a

compound of formula (I) where R^4 represents all groups defined earlier except hydrogen. The hydrolysis may be carried out in the presence of a base such as Na_2CO_3 and a suitable solvent such as methanol, ethanol, water and the like or mixtures thereof. The reaction may be carried out at a temperature in the range of 20-120 °C, preferably at 25-30 °C. The reaction time may range from 2 to 48 h, preferably from 4 to 12 h.

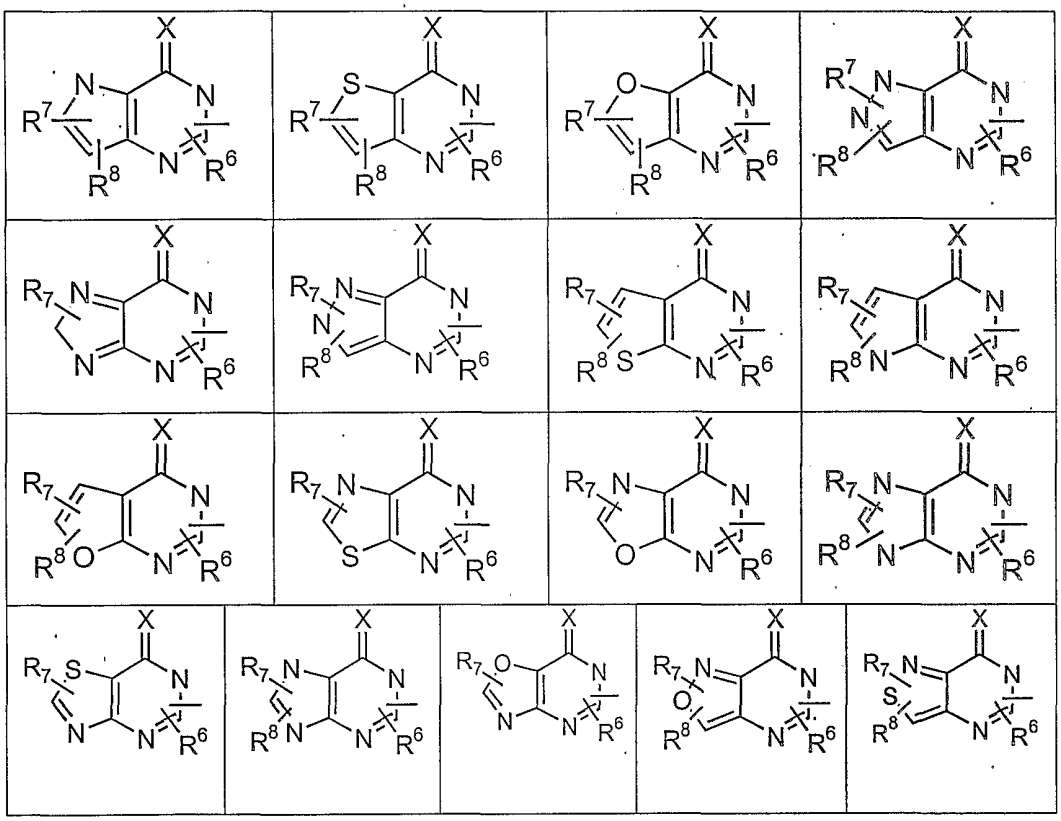
The compound of general formula (I) where Y represents oxygen and R^4 is as defined earlier may be converted to compound of formula (I), where Y represents NR^5 by reaction with appropriate amines. Suitably the compound of formula (I) where YR^4 represents OH may be converted to acid halide, preferably YR^4 = halogen, by reacting with appropriate reagents such as oxalyl chloride, thionyl chloride and the like, followed by treatment with amines; Alternatively, mixed anhydrides may be prepared from compound of formula (I) where YR^4 represents OH and all other symbols are as defined earlier by treating with acid halides such acetyl chloride, acetyl bromide, pivaloyl chloride, dichlorobenzoyl chloride and the like. The reaction may be carried out in the presence of suitable base such as pyridine, triethylamine, diisopropyl ethylamine and the like. Solvents such as halogenated hydrocarbons like $CHCl_3$, CH_2Cl_2, hydrocarbons such as benzene, toluene, xylene and the like may be used. The reaction may be carried out at a temperature in the range of -40 °C to 40 °C, preferably 0 °C to 20 °C. The acid halide or mixed anhydride thus prepared may further be treated with appropriate amines.

In another embodiment of the present invention there is provided the novel intermediates of formula (IVf)



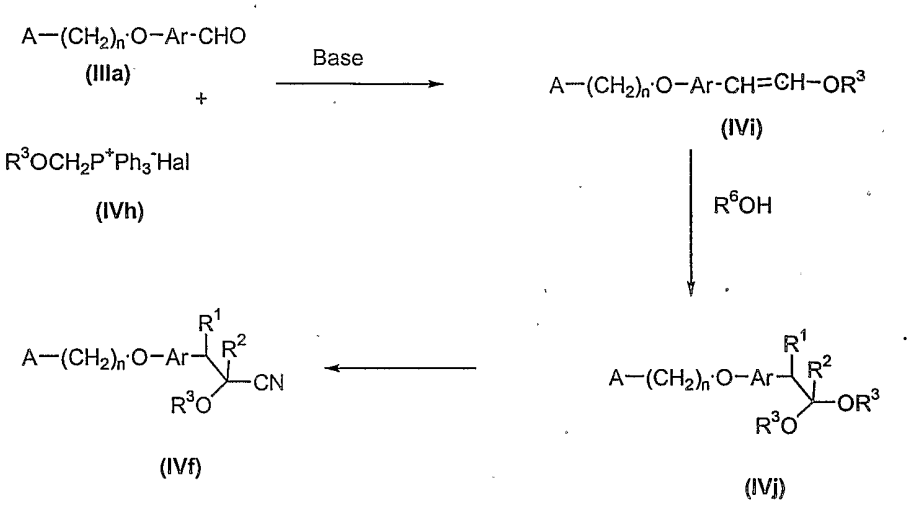
(IVf)

where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or

unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups and a process for its preparation and its use in the preparation of β-aryl-α-oxysubstituted alkylcarboxylic acids is provided (Scheme-III).



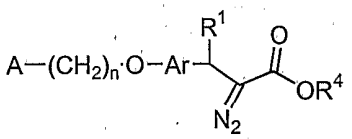
Scheme III

The reaction of a compound of formula (IIIa) where all symbols are as defined earlier with a compound of formula (IVh) where R^3 is as defined earlier excluding hydrogen and Hal represent a halogen atom such as Cl, Br, I to produce a compound of formula (IVi) where all symbols are defined earlier and R^3 is as defined earlier excluding hydrogen may be carried out under conventional conditions in the presence of a base. The base is not critical. Any base normally employed for Wittig reaction may be employed, metal hydride such as NaH, KH, metal alkoxides such as NaOMe, K^tBuO^-, NaOEt, metal amides such as $LiNH_2$, $LiN(iPr)_2$. Aprotic solvent such as THF, DMSO, dioxane, DME and the like may be used. Mixture of solvents may be used. HMPA may be used as cosolvent. Inert atmosphere may be employed such as argon and the reaction is more effective under anhydrous conditions. Temperature in the range of -80 °C to 100 °C may be used.

The compound of formula (IVi) where all symbols are as defined earlier and R^3 is as defined earlier excluding hydrogen may be converted to a compound of formula (IVj) where all symbols are as defined earlier, by treating with an alcohol under anhydrous conditions in the presence of a strong anhydrous acid such as p-toluenesulfonic acid.

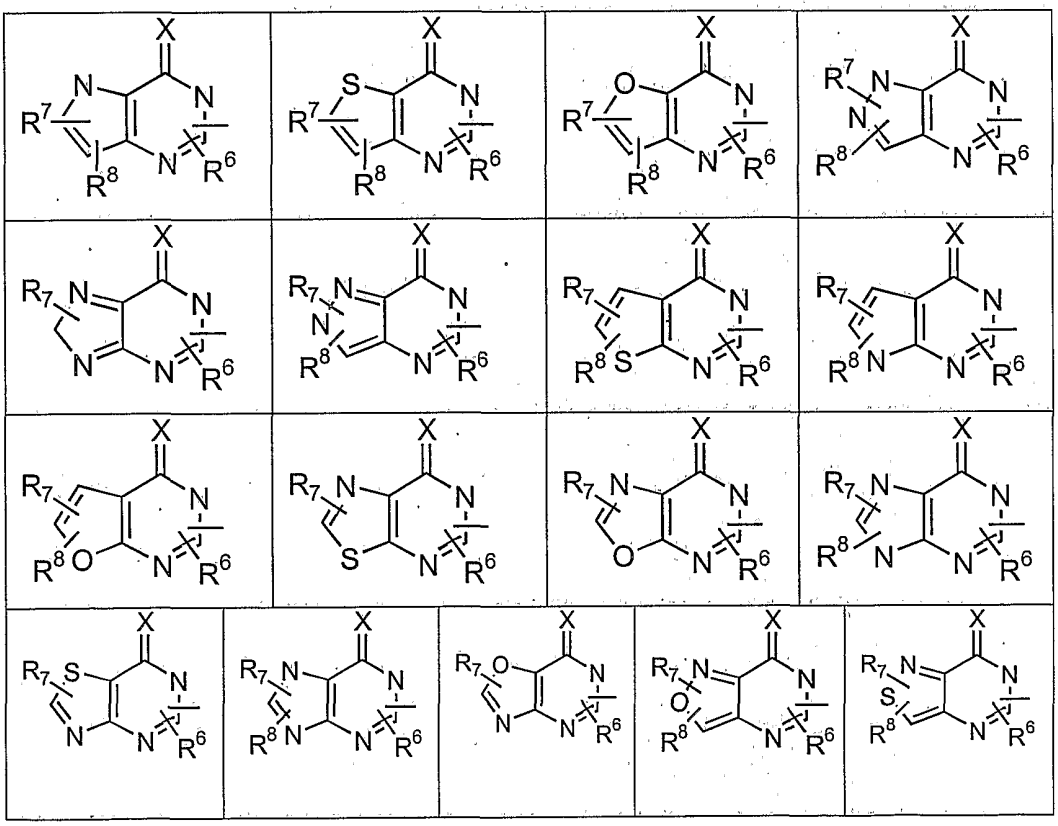
The compound of formula (IVj) defined above upon treatment with trialkylsilyl cyanide such as trimethylsilyl cyanide produces a compound of formula (IVf) where all symbols are as defined earlier.

In still another embodiment of the present invention there is provided the novel intermediates of formula (IVg)



(IVg)

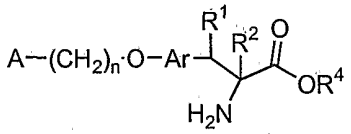
where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups and a

process for its preparation and its use in the preparation of β-aryl-α-oxysubstituted alkylcarboxylic acids is provided.

The compound of formula (IVg) where all other symbols are as defined earlier may be prepared by reacting a compound of formula (IVk)

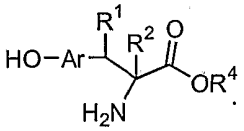


(IVk)

where R^2 is hydrogen atom and all other symbols are as defined earlier, with an appropriate diazotizing agent.

The diazotization reaction may be under conventional conditions. A suitable diazotizing agent is an alkyl nitrile, such as iso-amyl nitrile. The reaction may be carried out in presence of solvents such as THF, dioxane, ether, benzene and the like or a combination thereof. Temperature in the range of –50 °C to 80 °C may be used. The reaction may be carried out in an inert atmosphere which may be maintained by using inert gases such as N_2, Ar or He. The duration of the reaction may range from 1 to 24 h, preferably, 1 to 12 h.

The compound of formula (IVk) may also be prepared by a reaction between (IIIh) where all symbols are as defined earlier and a compound of formula (IVl)



(IVl)

where R^2 is hydrogen atom and all other symbols are as defined earlier.

The reaction of compound of formula (IIIh) where all symbols are as defined earlier and a compound of formula (IVl) where all symbols are as defined earlier may be carried out in the presence of solvents such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be

carried out in an inert atmosphere which is maintained by using inert gases such as N_2, Ar or He. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH or mixtures thereof. Acetone may be used as a solvent when K_2CO_3 or Na_2CO_3 is used as a base. The reaction temperature may range from 20 °C - 120 °C, preferably at a temperature in the range of 30 °C - 80 °C. The duration of the reaction may range from 1 to 24 hours, preferably from 2 to 12 hours.

It is appreciated that in any of the above mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The pharmaceutically acceptable salts are prepared by reacting the compounds of formula (I) wherever applicable with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, tromethamine, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) where YR^4 represents OH may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

Various polymorphs of compounds of general formula (I) and (IIIm) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for crystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment and / or prophylaxis diseases such as hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of familial hypercholesterolemia, hypertriglyceridemia, lowering of atherogenic lipoproteins, VLDL and LDL. The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy. The compounds of general formula (I) are also useful for the treatment / prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and for the treatment of cancer. The compounds of the present inventions are useful in the treatment and / or prophylaxis of the above said diseases in combination / concomittant with one or more HMG CoA reductase inhibitors, hypolipidemic / hypolipoproteinemic agents such as fibric acid derivatives, nicotinic acid, cholestyramine, colestipol, probucol. The compounds of the present invention in combination with HMG CoA reductase inhibitors, hypolipidemic / hypolipoproteinemic agents can be administered together or

within such a period to act synergistically. The HMG CoA reductase inhibitors may be selected from those used for the treatment or prevention of hyperlipidemia such as lovastatin, provastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin and their analogs thereof. Suitable fibric acid derivative may be gemfibrozil, clofibrate, fenofibrate, ciprofibrate, benzafibrate and their analogs thereof.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavourants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The compound of the formula (I) as defined above are clinically administered to mammals, including man, via either oral or parenteral routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. By either route, the dosage is in the range of about 0.01 to about 100 mg / kg body weight of the subject per day or preferably about 0.01 to about 30 mg / kg body weight per day administered singly or as a divided dose. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

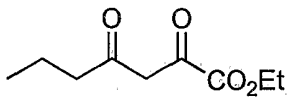
Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in the amounts sufficient to

provide the desired dosage in the range as described above. Thus, for oral administration, the compounds can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the compounds can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically acceptable acid addition salts or salts with base of the compounds. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Preparation 1

Ethyl 2,4-dioxoheptanoate



Sodium (11.5 g, 500 mmol) was added to ethanol (130 mL) in portions at room temperature with vigorous stirring. After sodium got dissolved, the solution was cooled to 0 °C. Methyl propyl ketone (53.0 mL, 500 mmol) was added dropwise and the stirring was continued for further 15 – 20 min. Diethyl oxalate (68.0 mL, 500 mmol) was added dropwise to the resulting solution at 0 °C and the stirring was continued for another 15 min at 0 °C. The reaction mixture was then allowed to attain room temperature and the stirring was

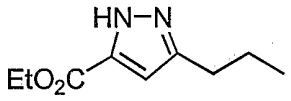
continued for further 12 h at this temperature. The reaction mixture was then kept in refrigerator for 24 h. The solvent was removed under vacuum at room temperature. The resulting residue was diluted with dil. hydrochloric acid on an ice bath and extracted the aqueous layer with diethyl ether (4 x 50 mL). The combined ether extracts were washed with water, brine, dried (Na_2SO_4) and concentrated under vacuum. The crude mass was chromatographed on silica gel using 3 % ethyl acetate in pet. ether as eluent to yield the title compound (60.0 g, 64.5 %).

^{1}H NMR ($CDCl_3$) : δ 14.45 (broad s, D_2O exchangeable, 1H), 6.33 (s, 1H), 4.32 (q, J = 7.10 Hz, 2H), 2.44 (t, J = 7.40 Hz, 2H), 1.72 – 1.57 (m, 2H), 1.35 (t, J = 7.30 Hz, 3H), 0.94 (t, J = 7.40 Hz, 3H).

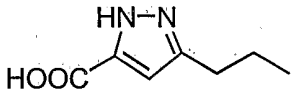
Preparation 2

Ethyl 3-propyl-1H-5-pyrazole carboxylate (2A)

3-Propyl-1H-5-pyrazole carboxylic acid (2B)



2A



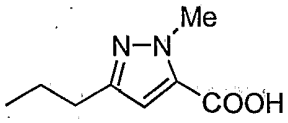
2B

To a stirred mixture of ethyl 2,4-dioxoheptanoate (28.0 g, 150 mmol) obtained in preparation 1, acetic acid (225 mL) and methoxy ethanol (225 mL), hydrazine hydrochloride (31.6 g, 300 mmol) was added and heated to 105 °C for 3 h. Acetic acid and methoxy ethanol were removed under vacuum at 90 °C. The residue was taken in water and extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated to obtain solids suspended in liquid. The solids were filtered and washed with pet. ether to yield the title compound **2B** (5.0 g, 21.6 %). The solvent was evaporated from the filtrate to yield **2A** (16.0 g, 58.4 %) as liquid.

2A ^{1}H NMR (2A) ($CDCl_3$) : δ 6.57 (s, 1H), 4.34 (q, J = 7.10 Hz, 2H), 2.65 (t, J = 7.50 Hz, 2H), 1.71 – 1.59 (m, 2H), 1.33 (t, J = 7.20 Hz, 3H), 0.92 (t, J = 7.30 Hz, 3H).

Preparation 3

1-Methyl-3-propyl-1H-5-pyrazole carboxylic acid

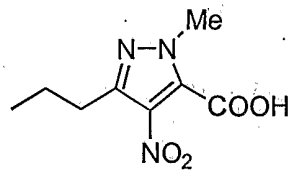


Dimethyl sulfate (6.0 g, 48.35 mmol) was added to the pyrazole ester obtained in preparation 2 (16.0 g, 88 mmol) and the reaction mixture was heated at 160 °C for 2 h. The reaction mixture was cooled to ~ 90 °C and 5N sodium hydroxide solution (64 mL) was added and the reaction mixture was stirred at 80 – 90 °C for 30 min. The reaction mixture was cooled in an ice bath and was acidified to pH 4 with 2N hydrochloric acid resulting precipitation of the product. The precipitate was filtered, washed with cold water and dried under vacuum to yield the title compound (12.0 g, 81 %).

^{1}H NMR ($CDCl_3$) : δ 6.70 (s, 1H), 4.14 (s, 3H), 2.64 (t, J = 7.60 Hz, 2H), 1.72 – 1.61 (m, 2H), 0.95 (t, J = 7.30 Hz, 3H).

Preparation 4

1-Methyl-4-nitro-3-propyl-1H-5-pyrazole carboxylic acid



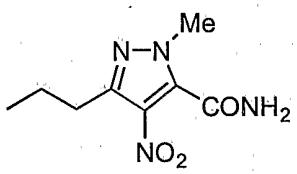
Nitrating agent was prepared by adding 90 % nitric acid (7.18 mL) to concentrated sulphuric acid (13.8 mL) at 75-78 °C. 1-Methyl-3-propyl-1H-5-pyrazole carboxylic acid (11.5 g, 68.4 mmol) obtained in preparation 3, was added to the nitrating agent portion wise with stirring so that the temperature

is maintained at ~ 85 °C. After the complete addition, the mixture was heated at 100 °C for 2 h. The reaction mixture was cooled and poured into crushed ice. The suspension was filtered cold (10 °C) and the solids were washed with ice cold brine and dried to yield the title compound (5.0 g, 34 %).

^{1}H NMR ($CDCl_3$) : δ 6.90 (broad s, D_2O exchangeable, 1H), 4.20 (s, 3H), 2.90 (t, J = 7.60 Hz, 2H), 1.79-1.64 (m, 2H), 1.02 (t, J = 7.40 Hz, 3H).

Preparation 5

1-Methyl-4-nitro-3-propyl-1H-5-pyrazole carboxamide

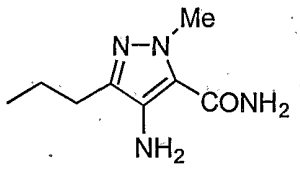


Thionyl chloride (7.2 mL, 98 mmol) was added to 1-methyl-4-nitro-3-propyl-1H-5-pyrazole carboxylic acid obtained in preparation 4 (3.3 g, 15.5 mmol) and refluxed for 3.5 h. The excess thionyl chloride was removed from the reaction mixture under vacuum and the residue was taken in dry acetone (20 mL). Ammonia gas was passed through this solution till pH reached 8-9. The precipitate formed was filtered. The filtrate was concentrated and then dissolved in ethyl acetate. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated to yield the title compound as a fluffy material (3.1 g, 94 %).

^{1}H NMR ($CDCl_3$) : δ 7.50 (broad s, D_2O exchangeable, 1H), 6.08 (broad s, D_2O exchangeable, 1H), 4.05 (s, 3H), 2.86 (t, J = 7.70 Hz, 2H), 1.75-1.60 (m, 2H), 0.98 (t, J = 7.30 Hz, 3H).

Preparation 6

4-Amino-1-methyl-3-propyl-1H-5-pyrazole carboxamide

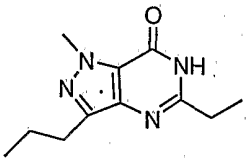


To a solution of 1-methyl-4-nitro-3-propyl-1H-5-pyrazole carboxamide obtained in preparation 5 (3.2 g, 15.0 mmol) in methanol (30 mL), Raney nickel (450 mg) was added and hydrogenated by passing hydrogen gas at 50 psi for 10 h. The reaction mixture was filtered through celite bed and washed with methanol. The filtrate and washings were combined, concentrated, purified by silica gel column chromatography using ethyl acetate-pet. ether (1 : 1) as eluent to yield the title compound (2.0 g, 73 %).

^{1}H NMR ($CDCl_3$) : δ 7.05 (broad s, D_2O exchangeable, 2H), 4.07 (s, 3H), 2.75 (broad s, D_2O exchangeable, 2H), 2.51 (t, J = 7.60 Hz, 2H), 1.69 – 1.50 (m, 2H), 0.95 (t, J = 7.30 Hz, 3H).

Preparation 7

5-Ethyl-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one



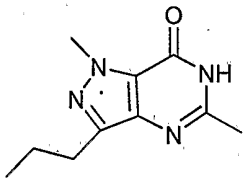
To 4-amino-1-methyl-3-propyl-1H-5-pyrazole carboxamide obtained in preparation 6 (1.3 g, 7.1 mmol) in xylene (10.5 mL), propionic acid (10.5 mL) was added and cooled in ice bath. Triethyl amine (2.2 mL, 15.7 mmol) was added to the reaction mixture and stirred for 15 min. Propionyl chloride was added and stirred at the same temperature for 30 min. The reaction mixture was refluxed for 36 h and the solvent was removed under vacuum. The resulting residue was diluted with water and extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and concentrated. The crude compound was purified by silica gel

column chromatography using 30 % ethyl acetate in pet. ether as eluent to yield the title compound (560 mg, 36 %).

^{1}H NMR ($CDCl_3$) : δ 11.1 (broad s, D_2O exchangeable, 1H), 4.23 (s, 3H), 2.89 – 2.69 (m, 4H), 1.85 –1.71 (m, 2H), 1.37 (t, J = 7.50 Hz, 3H), 0.98 (t, J = 7.40 Hz, 3H).

Preparation 8

1,5-Dimethyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one

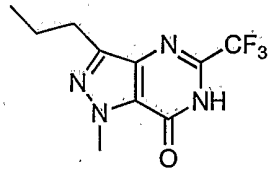


The title compound (360 mg, 36 %) was obtained as fluffy solid from 4-amino-1-methyl-3-propyl-1H-5-pyrazole carboxamide (950 mg, 5.2 mmol) obtained in preparation 6, acetyl chloride (450 mg, 5.74 mmol), triethyl amine (1.15 g, 11.48 mmol) and acetic acid (7.5 mL) by refluxing in xylene (7.5 mL) for 72 h following a similar procedure as described in preparation 7.

^{1}H NMR ($CDCl_3$) : δ 11.18 (broad s, D_2O exchangeable, 1H), 4.23 (s, 3H), 2.84 (t, J = 7.60 Hz, 2H), 2.51 (s, 3H), 1.84 –1.75 (m, 2H), 0.98 (t, J = 7.30 Hz, 3H).

Preparation 9

1-Methyl-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one



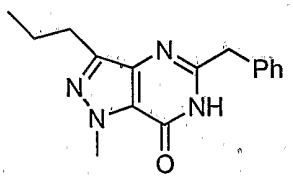
The title compound (275 mg, 96.2 %) was obtained as fluffy solid from 4-amino-1-methyl-3-propyl-1H-5-pyrazole carboxamide (200 mg, 1.09 mmol)

obtained in preparation 6, trifluoroacetic anhydride (0.17 mL, 1.2 mmol) and propionic acid (2.5 mL) by refluxing in xylene (2.5 mL) for 24 h following a similar procedure as described in preparation 7, mp 198.5 - 200.5 °C.

^{1}H NMR ($CDCl_3$) : δ 11.40 (broad s, D_2O exchangeable, 1H), 4.29 (s, 3H), 2.91 (t, J = 7.60 Hz, 2H), 1.92 –1.72 (m, 2H), 1.00 (t, J = 7.30 Hz, 3H).

Preparation 10

5-Benzyl-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one

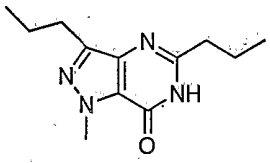


The title compound (115 mg, 37 %) was obtained as a fluffy solid from 4-amino-1-methyl-3-propyl-1H-5-pyrazole carboxamide (200 mg, 1.09 mmol) obtained in preparation 6, phenylacetyl chloride (0.159 mL, 1.2 mmol), triethylamine (0.336 mL, 2.40 mmol) and propionic acid (2.5 mL) by refluxing in xylene (2.5 mL) for 36 h following a similar procedure as described in preparation 7, mp 174-179 °C.

^{1}H NMR ($CDCl_3$) : δ 7.32 - 7.26 (m, 5H), 4.21 (s, 3H), 4.04 (s, 2H), 2.89 (t, J = 7.50 Hz, 2H), 1.90 –1.75 (m, 2H), 1.02 (t, J = 7.30 Hz, 3H).

Preparation 11

3,5-Dipropyl-1-methyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one



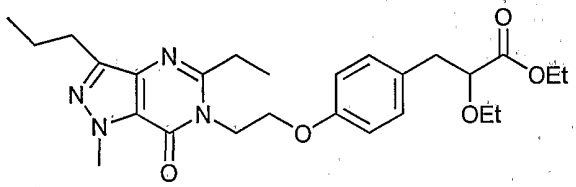
The title compound (550 mg, 71.3 %) was obtained as a fluffy solid from 4-amino-1-methyl-3-propyl-1H-5-pyrazole carboxamide (600 mg, 3.3 mmol)

obtained in preparation 6, butyryl chloride (0.38 mL, 3.62 mmol), triethyl amine (1 mL, 7.25 mmol) and propionic acid (4 mL) by refluxing in xylene (4 mL) for 48 h following a similar procedure as described in preparation 7, mp 180-182 °C.

^{1}H NMR ($CDCl_3$) : δ 11.00 (broad s, D_2O exchangeable, 1H), 4.22 (s, 3H), 2.84 (t, J = 7.60 Hz, 2H), 2.68 (t, J = ~7.80 Hz, 2H), 1.92 –1.65 (m, 4H), 1.01 (t, J = 7.20 Hz, 3H), 0.97 (t, J = 7.30 Hz, 3H).

Example 1

Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate

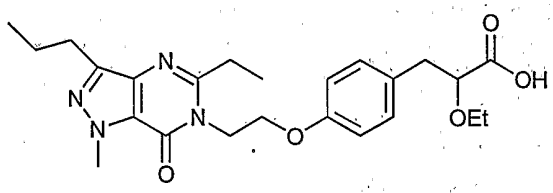


A mixture of 5-ethyl-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (100 mg, 0.454 mmol) obtained in preparation 7 and anhydrous K_2CO_3 (188 mg, 1.36 mmol) in dry *N,N*-dimethylformamide (2 mL) was stirred under argon atmosphere for 30 min at room temperature. Ethyl 3-[4-(2-bromoethoxy)phenyl]-2-ethoxypropanoate (188 mg, 0.545 mmol) prepared as disclosed in US patent application 09/012,585 taken in dry *N,N*-dimethylformamide (2 mL) was added. The reaction mixture was stirred at room temperature for 8 h, diluted with water and extracted with ethyl acetate (3 X 10 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4) and evaporated to dryness. The title compound (150 mg, 68 %) was obtained by purifying over silica gel column using 20 % ethyl acetate in pet. ether as eluent, mp 112 °C.

^{1}H NMR ($CDCl_3$) : δ 7.10 (d, J = 8.60 Hz, 2H), 6.76 (d, J = 8.40 Hz, 2H), 4.49 (t, J = 5.20 Hz, 2H), 4.29 – 4.10 (m, 7H), 3.93 (t, J = ~ 7.00 Hz, 1H), 3.65 – 3.20 (m, 2H), 3.09 – 2.81 (m, 6H), 1.93 – 1.75 (m, 2H), 1.38 (t, J = 7.30 Hz, 3H), 1.26 – 1.11 (m, 6H), 0.99 (t, J = 7.30 Hz, 3H).

Example 2

2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid

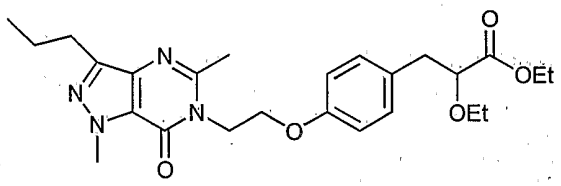


To a solution of ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate (95 mg, 0.196 mmol) obtained in example 1 in methanol (10 mL) sodium carbonate (104 mg, 0.98 mmol) in water (10 mL) was added and stirred at room temperature for 12 h. Methanol was removed from the reaction mixture under vacuum and the resulting aqueous layer was extracted with ethyl acetate. The aqueous layer was acidified with 2N hydrochloric acid at low temperature. The solids were filtered and washed with cold water, dried under vacuum overnight to yield the title compound (60 mg, 67 %), mp 171 °C.

^{1}H NMR ($CDCl_3$) : δ 7.13 (d, J = 8.40 Hz, 2H), 6.77 (d, J = 8.60 Hz, 2H), 4.50 (t, J= 5.00 Hz, 2H), 4.29 – 4.22 (m, 5H), 4.01 (t, J = 3.70 Hz, 1H), 3.69 – 3.35 (m, 2H), 3.10-2.94 (m, 4H), 2.84 (t, J = 7.50 Hz, 2H), 1.90 – 1.78 (m, 2H), 1.38 (t, J = 7.30 Hz, 3H), 1.16 (t, J = 7.00 Hz, 3H), 0.97 (t, J = 7.40 Hz, 3H).

Example 3

Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate

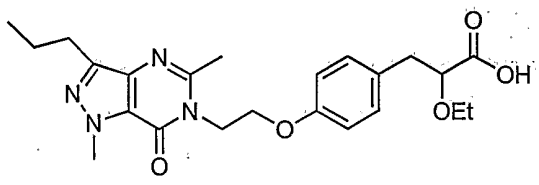


The title compound (200 mg, 58.4 %) was obtained as a white solid by condensing 1,5-dimethyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (150 mg, 0.728 mmol) obtained in preparation 8, with ethyl 3-[4-(2-bromoethoxy)phenyl]-2-ethoxypropanoate (502 mg, 1.45 mmol) prepared as disclosed in US patent application 09/012,585 taken in dry *N,N*-dimethylformamide (3 mL) in the presence of anhydrous K_2CO_3 (300 mg, 2.18 mmol) for 24 h at room temperature following a similar procedure as described in example 1, mp 120 °C.

^{1}H NMR ($CDCl_3$) : δ 7.10 (d, J = 8.40 Hz, 2H), 6.75 (d, J = 8.60 Hz, 2H), 4.47 (t, J= 5.00 Hz, 2H), 4.30 – 4.08 (m, 7H), 3.92 (t, J = 6.40 Hz, 1H), 3.65 – 3.50 (m, 1H), 3.39 – 3.25 (m, 1H), 2.91 (d, J = 6.30 Hz, 2H), 2.82 (t, J = 7.70 Hz, 2H), 2.75 (s, 3H), 1.90 – 1.70 (m, 2H), 1.20 (t, J = 7.30 Hz, 3H), 1.12 (t, J = 7.20 Hz, 3H), 0.98 (t, J = 7.30 Hz, 3H).

Example 4

3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid

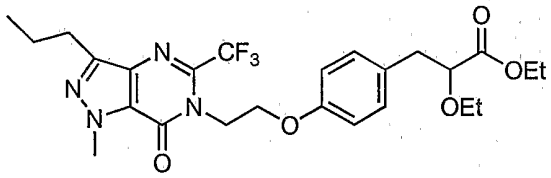


The title compound (74 mg, 78 %) was obtained as a white solid from ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]
phenyl]-2-ethoxypropanoate (134 mg, 0.258 mmol) obtained in example 3 by hydrolyzing in methanol-water (1 : 1, 20 mL) using sodium carbonate (112 mg, 1.06 mmol) at room temperature for 24 h following a similar procedure as described in example 2, mp 172 °C.

^{1}H NMR ($CDCl_3$) : δ 7.13 (d, J = 8.30 Hz, 2H), 6.78 (d, J = 8.30 Hz, 2H), 4.48 (t, J = 4.60 Hz, 2H), 4.35 – 4.15 (m, 5H), 4.10 - 3.97 (m, 1H), 3.56 – 3.38 (m, 2H), 3.12 – 2.90 (m, 2H), 2.83 (t, J = 7.80 Hz, 2H), 2.76 (s, 3H), 1.89 – 1.71 (m, 2H), 1.16 (t, J = 7.00 Hz, 3H), 0.98 (t, J = 7.30 Hz, 3H).

Example 5

Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate



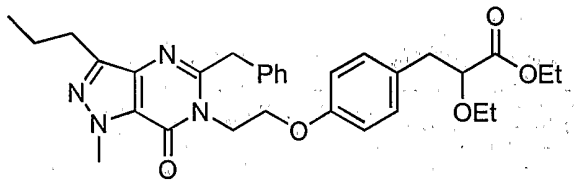
The title compound (145 mg, 36 %) was obtained by condensing 1-methyl-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (200 mg, 0.77 mmol) obtained in preparation 9, with ethyl 3-[4-(2-bromoethoxy)phenyl]-2-ethoxypropanoate (510 mg, 1.48 mmol) prepared as disclosed in US patent application 09/012,585 taken in dry *N,N*-dimethylformamide (4 mL) in the presence of anhydrous K_2CO_3 (318 mg, 2.30 mmol) for 48 h at room temperature following a similar procedure as described in example 1.

^{1}H NMR ($CDCl_3$) : δ 7.15 (d, J = 8.50 Hz, 2H), 6.84 (d, J = 8.50 Hz, 2H), 4.96 (t, J = ~4.70 Hz, 2H), 4.38 (t, J = 4.50 Hz, 2H), 4.24-4.07 (m, 5H), 3.95 (t, J =

6.50 Hz, 1H), 3.62-3.25 (m, 2H), 3.01 – 2.86 (m, 4H), 1.89-1.72 (m, 2H), 1.21 (t, J = 7.00 Hz, 3H), 1.14 (t, J = 6.80 Hz, 3H), 0.98 (t, J = 7.30 Hz, 3H).

Example 6

Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate

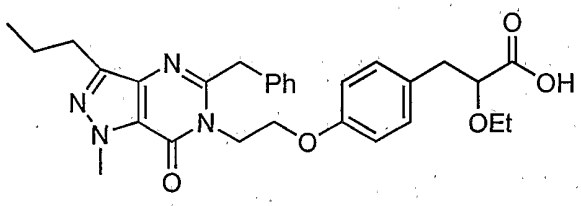


The title compound (110 mg, 56.8 %) was obtained as a liquid from 5-benzyl-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (100 mg, 0.354 mmol) obtained in preparation 10, ethyl 3-[4-(2-bromoethoxy)phenyl]-2-ethoxypropanoate (159 mg, 0.46 mmol) prepared as disclosed in US patent application 09/012,585 and anhydrous K_2CO_3 (146 mg, 1.06 mmol) in *N,N*-dimethylformamide (2 mL) by following a similar procedure as described in example 1.

^{1}H NMR ($CDCl_3$) : δ 7.31-7.12 (m, 7H), 6.78 (d, J = 8.50 Hz, 2H), 4.46 (s, 2H), 4.33 (t, J = 4.80 Hz, 2H), 4.23-4.09 (m, 7H), 3.94 (t, J = 6.60 Hz, 1H), 3.63-3.28 (m, 2H), 2.99 – 2.80 (m, 4H), 1.90-1.76 (m, 2H), 1.23 (t, J = 7.10 Hz, 3H), 1.14 (t, J = 7.10 Hz, 3H), 1.01 (t, J = 7.30 Hz, 3H).

Example 7

3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid

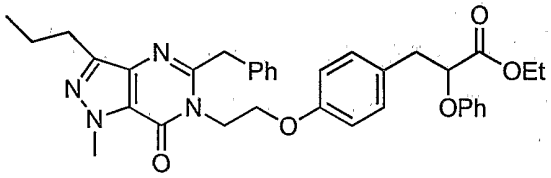


The title compound (37 mg, 46 %) was obtained as solid from ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]
-2-ethoxypropanoate (85 mg, 0.156 mmol) obtained in example 6 by hydrolyzing in methanol-water (1 : 1, 5 mL) using sodium carbonate (81 mg, 0.587 mmol) at room temperature for 17 h by following a similar procedure as described in example 2, mp 149-151 °C.

^{1}H NMR ($CDCl_3$) : δ 7.32 – 7.13 (m, 7H), 6.79 (d, J = 6.50 Hz, 2H), 4.47 (s, 2H), 4.34 (t, J = 4.90 Hz, 2H), 4.24-4.19 (m, 5H), 4.05 (dd, J = 4.40 and 7.10 Hz, 1H), 3.63-3.37 (m, 2H), 3.13 – 2.85 (m, 4H), 1.89-1.72 (m, 2H), 1.18 (t, J = 7.00 Hz, 3H), 1.02 (t, J = 7.30 Hz, 3H).

Example 8

Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate

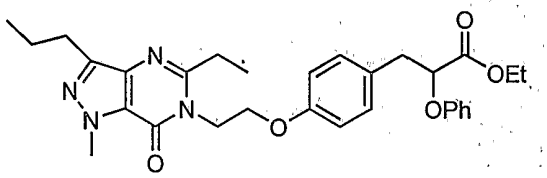


The title compound (180 mg, 85.4 %) was obtained as a liquid from 5-benzyl-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (100 mg, 0.35 mmol) obtained in preparation 10, ethyl 3-[4-(2-bromoethoxy)phenyl]-2-phenoxypropanoate (278 mg, 0.70 mmol) and anhydrous K_2CO_3 (145 mg, 1.05 mmol) as a base by following a similar procedure described in example 1.

^{1}H NMR ($CDCl_3$) : δ 7.30-7.15 (m, 9H), 6.93 – 6.75 (m, 5H), 4.72 (t, J = 6.50 Hz, 1H), 4.46 (s, 2H), 4.33 – 4.10 (m, 9H), 3.17 (d, J = 6.60 Hz, 2H), 2.88 (t, J = 7.50 Hz, 2H), 1.90-1.75 (m, 2H), 1.19 (t, J = 7.10 Hz, 3H), 1.01 (t, J = 7.30 Hz, 3H).

Example 9

Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate

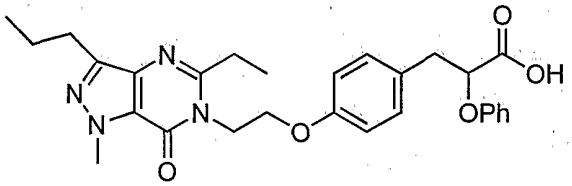


The title compound (450 mg, 74.5 %) was obtained as a solid from 5-ethyl-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (250 mg, 1.136 mmol) obtained in preparation 7, ethyl 3-[4-(2-bromoethoxy)phenyl]-2-phenoxypropanoate (670 mg, 1.70 mmol) and anhydrous K_2CO_3 (470 mg, 3.40 mmol) as a base by following a similar procedure as described in example 1, mp 84-86 °C.

^{1}H NMR ($CDCl_3$) : δ 7.22-7.17 (m, 4H), 6.97 – 6.76 (m, 5H), 4.71 (t, J = 6.50 Hz, 1H), 4.49 (t, J = 5.10 Hz, 2H), 4.28-4.10 (m, 7H), 3.16 (d, J = 6.60 Hz, 2H), 3.04 (q, J = 7.30 Hz, 2H), 2.85 (t, J = ~7.60 Hz, 2H), 1.90 – 1.73 (m, 2H), 1.38 (t, J = 7.30 Hz, 3H), 1.18 (t, J = 7.10 Hz, 3H), 0.99 (t, J = 7.30 Hz, 3H).

Example 10

3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid



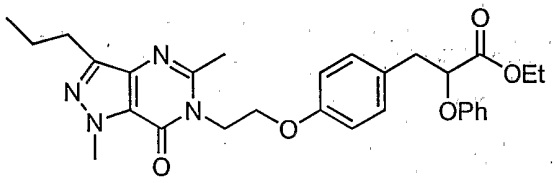
The title compound (246 mg, 78 %) was obtained as a solid from ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]

-2-phenoxypropanoate (330 mg, 0.620 mmol) obtained in example 9 and sodium carbonate (328 mg, 3.10 mmol) as a base in methanol-water (1 : 1) by following a similar procedure as described in example 2, mp 148-150 °C.

^{1}H NMR ($CDCl_3$) : δ 7.21 (broad s, 4H), 6.98 – 6.70 (m, 5H), 4.77 (broad s, 1H), 4.47 – 4.20 (m, 7H), 3.20 – 2.79 (m, 6H), 1.84-1.73 (m, 2H), 1.36 (t, J = 7.00 Hz, 3H), 0.97 (t, J = 7.20 Hz, 3H).

Example 11

Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate

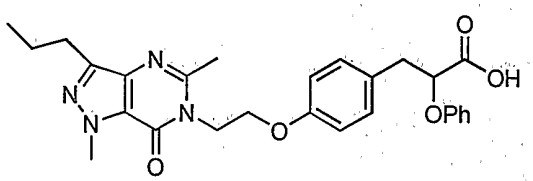


The title compound (250 mg, 69.4 %) was obtained as a white solid from 1,5-dimethyl-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (150 mg, 0.694 mmol) obtained in preparation 8, ethyl 3-[4-(2-bromoethoxy)phenyl]-2-phenoxypropanoate (546 mg, 1.39 mmol) and anhydrous K_2CO_3 (192 mg, 1.39 mmol) as a base by following a similar procedure as described in example 1, mp 128 - 132 °C.

^{1}H NMR ($CDCl_3$) : δ 7.20 (d, J = 7.30 Hz, 4H), 6.95 – 6.75 (m, 5H), 4.71 (t, J= 6.50 Hz, 1H), 4.48 (t, J = 4.70 Hz, 2H), 4.29 – 4.11 (m, 7H), 3.16 (d, J = 6.60 Hz, 2H), 2.84 (t, J = 7.20 Hz, 2H), 2.76 (s, 3H), 1.90 – 1.71 (m, 2H), 1.19 (t, J = 7.10 Hz, 3H), 0.99 (t, J = 7.30 Hz, 3H).

Example 12

3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid



The title compound (100 mg, 75.5 %) was obtained as a white solid from ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]

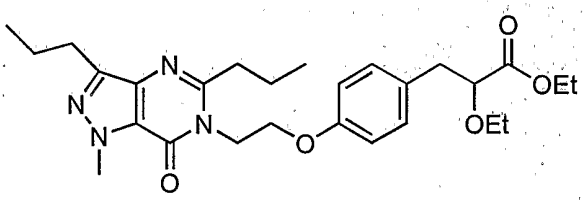
phenyl]-2-phenoxypropanoate (150 mg, 0.270 mmol) obtained in example 11 and sodium carbonate (143 mg, 1.35 mmol) as a base in methanol-water (5 : 1, 12 mL) by following a similar procedure as described in example 2, mp 172-174 °C.

^{1}H NMR ($CDCl_3$) : δ 7.20 – 7.15 (m, 4H), 6.96 – 6.72 (m, 5H), 4.75 (t, J = 5.80 Hz, 1H), 4.50 – 4.40 (m, 2H), 4.24 (t, J = ~5.00 Hz, 2H), 4.18 (s, 3H), 3.17 (d, J = 5.60 Hz, 2H), 2.80 (t, J = 7.50 Hz, 2H), 2.72 (s, 3H), 1.83 - 1.67 (m, 2H), 0.96 (t, J = 7.30 Hz, 3H).

Example 13

Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]

pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate



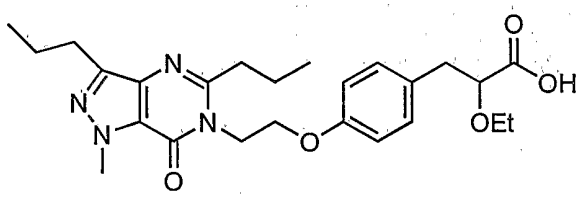
The title compound (240 mg, 57.1 %) was obtained as a white solid by treating 3,5-dipropyl-1-methyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (200 mg, 0.855 mmol) obtained in preparation 11, with ethyl 3-[4-(2-bromoethoxy)phenyl]-2-ethoxypropanoate (737mg, 2.14 mmol) prepared as disclosed in US patent application 09/012,585 taken in dry *N,N*-dimethylformamide (4 mL) in the presence of anhydrous K_2CO_3 (360 mg, 2.56

mmol) as a base for 48 h at room temperature by following a similar procedure as described in example 1, mp 110 - 114 °C.

^{1}H NMR ($CDCl_3$) : δ 7.12 (d, J = 8.50 Hz, 2H), 6.75 (d, J = 8.50 Hz, 2H), 4.48 (t, J= 5.10 Hz, 2H), 4.28 – 4.13 (m, 4H), 4.21 (s, 3H), 3.92 (t, J = 6.40 Hz, 1H), 3.65 – 3.22 (m, 2H), 3.00 – 2.79 (m, 6H), 1.95 – 1.70 (m, 2H), 1.21 (t, J = 7.20 Hz, 3H), 1.13 (t, J = 6.90 Hz, 3H), 1.06 (t, J = 7.20 Hz, 3H), 0.98 (t, J = 7.30 Hz, 3H).

Example 14

3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid



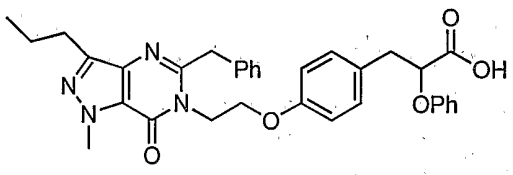
The title compound (75 mg, 66.2 %) was obtained as a white solid from ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy] phenyl]-2-ethoxypropanoate (120 mg, 0.241 mmol) obtained in example 13 and sodium carbonate (128 mg, 1.20 mmol) as a base in methanol-water (5 : 1, 12 mL) reacting for 48 h at room temperature by following a similar procedure as described in example 2, mp 160-161 °C.

^{1}H NMR ($CDCl_3$) : δ 7.13 (d, J = 8.30 Hz, 2H), 6.78 (d, J = 8.30 Hz, 2H), 4.49 (t, J= ~5.10 Hz, 2H), 4.29 – 4.22 (m, 5H), 4.10 – 3.98 (m, 1H), 3.65 – 3.40 (m, 2H), 3.12 – 2.80 (m, 4H), 1.95 – 1.75 (m, 4H), 1.17 (t, J = ~ 7.00 Hz, 3H), 1.07 (t, J = 7.50 Hz, 3H), 0.99 (t, J = 7.50 Hz, 3H).

Example 15

3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]

pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid



The title compound (65 mg, 52.3 %) was obtained as a solid from ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]

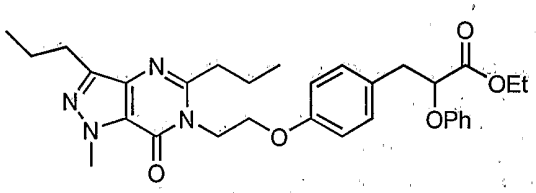
phenyl]-2-phenoxypropanoate (130 mg, 0.219 mmol) obtained in example 8 and sodium carbonate (116 mg, 1.09 mmol) in methanol-water (1 : 1) by following a similar procedure as described in example 2, mp 68-72 °C.

^{1}H NMR ($CDCl_3$) : δ 7.29-7.18 (m, 9H), 7.03-6.76 (m, 5H), 4.82 (t, J= ~6.50 Hz, 1H), 4.45 (s, 2H), 4.36 – 4.10 (m, 7H), 3.22 (d, J = 5.90 Hz, 2H), 2.88 (t, J = 7.80 Hz, 2H), 1.90 – 1.75 (m, 2H), 1.00 (t, J = 7.30 Hz, 3H).

Example 16

Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]

pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate



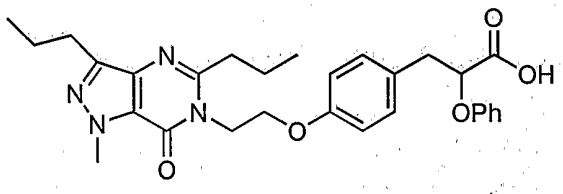
The title compound (296 mg, 63.5 %) was obtained as a white solid from 1-methyl-3,5-dipropyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-7-one (200 mg, 0.855 mmol) obtained in preparation 11, ethyl 3-[4-(2-bromoethoxy)phenyl]-2-phenoxypropanoate (1.16 g, 2.95 mmol) and K_2CO_3

(0.59 g, 4.27 mmol) in dry *N,N*-dimethylformamide (7 mL) by following a similar procedure described in example 1, mp 82 °C.

^{1}H NMR ($CDCl_3$) : δ 7.21-7.17 (m, 4H), 6.92 – 6.75 (m, 5H), 4.70 (t, J = ~ 5.60 Hz, 1H), 4.48 (t, J = 5.00 Hz, 2H), 4.28 – 4.11 (m, 7H), 3.15 (d, J = 6.30 Hz, 2H), 2.97 (t, J = 7.70 Hz, 2H), 2.84 (t, J = 7.30 Hz, 2H), 1.95-1.75 (m, 4H), 1.18 (t, J = 7.10 Hz, 3H), 1.06 (t, J = 7.30 Hz, 3H), 0.98 (t, J = 7.40 Hz, 3H).

Example 17

3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid

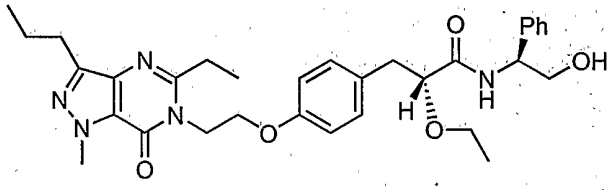


The title compound (207 mg, 88 %) was obtained as a white solid from ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy] phenyl]-2-ethoxypropanoate (246 mg, 0.450 mmol) obtained in example 16 and sodium carbonate (239 mg, 2.25 mmol) in methanol-water (10 : 1, 33 mL) by following a similar procedure as described in example 2, mp 159-163 °C.

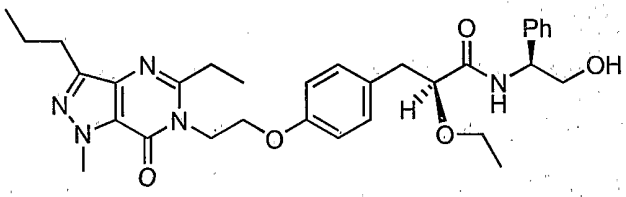
^{1}H NMR ($CDCl_3$) : δ 7.24-7.16 (m, 4H), 6.92 – 6.73 (m, 5H), 4.74 (t, J= ~5.60 Hz, 1H), 4.46 (t, J = ~4.60 Hz, 2H), 4.27 – 4.18 (m, 2H), 4.19 (s, 3H), 3.16 (d, J = 5.10 Hz, 2H), 2.95 (t, J = 7.30 Hz, 2H), 2.82 (t, J = 7.50 Hz, 2H), 1.95 – 1.72 (m, 4H), 1.04 (t, J = 7.30 Hz, 3H), 0.97 (t, J = 7.50 Hz, 3H).

Example 18

[2R, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl) propanamide (18 A)



[2S, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl) propanamide (18 B)



To a cold solution of S(+)-2-phenylglycinol (390 mg, 2.85 mmol) in dry dichloromethane (10 mL), triethyl amine (0.79 mL, 5.70 mmol) was added dropwise and stirred for 15 min at 0 °C. In a separate arrangement to a solution of 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy] phenyl]-2-ethoxypropanoic acid (1.3 g, 2.85 mmol) obtained in example 2 in dry dichloromethane (10 mL) at 0 °C triethyl amine (0.99 mL, 7.12 mmol) was added and stirred for 15 min. To this solution pivaloyl chloride (0.386 mL, 3.136 mmol) was added dropwise and stirred for 30 min at °C. This mixture was added to the phenylglycinol mixture dropwise at 0 °C and stirred for 1 h at that temperature. The reaction mixture was stirred overnight at room temperature. The organic phase was washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by silica gel column chromatography using 60 % ethyl acetate in pet ether – 100 % ethyl acetate as

an eluent to afford a diastereomer tentatively assigned as [2R, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide **(18 A)** (500 mg, 30.5 %), mp 138-139 °C followed by [2S, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)

propanamide **(18 B)** (400 mg, 24.4 %), mp 182-183 °C.

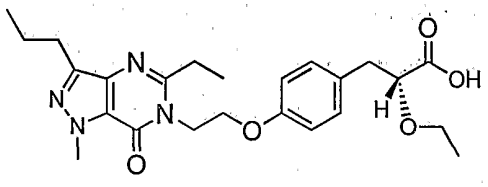
18A : $[\alpha]^{25}_{D}$ = +20.2° (C = 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ : 7.32 - 7.27 (m, 4H), 7.16 (d, J = 8.50 Hz, 2H), 7.00 (d, J = 7.30 Hz, 1H), 6.80(d, J = 8.30 Hz, 2H), 5.05 – 4.89 (m, 1H), 4.51 (t, J = 5.00 Hz, 2H), 4.28 (t, J = 4.80 Hz, 2H), 4.22 (s, 3H), 3.95 (dd, J = 3.90 and 2.20 Hz, 1H), 3.67 – 3.62 (m, 2H), 3.48 (q, J = ~ 7.20 Hz, 2H), 3.12 – 2.92 (m, 4H), 2.86 (t, J = 7.50 Hz, 2H), 1.91 – 1.75 (m, 2H), 1.39 (t, J = 7.30 Hz, 3H), 1.13 (t, J = 6.90 Hz, 3H), 1.00 (t, J = 7.30 Hz, 3H).

18B : $[\alpha]^{25}_{D}$ = -12.6° (C= 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ : 7.23 - 7.01 (m, 7H), 6.68 (d, J = 8.50 Hz, 2H), 5.06 – 4.90 (m, 1H), 4.51 (t, J = 5.00 Hz, 2H), 4.27 – 4.22 (m, 5H), 3.96 (dd, J = ~4.00 and 2.90 Hz, 1H), 3.84 (d, J = 4.20 Hz, 2H), 3.60 – 3.45 (m, 2H), 3.13 – 2.75 (m, 6H), 1.91-1.78 (m, 2H), 1.39 (t, J = 7.30 Hz, 3H), 1.13 (t, J = 7.00 Hz, 3H), 1.00 (t, J = 7.30 Hz, 3H).

Example 19

(+) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo

[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid

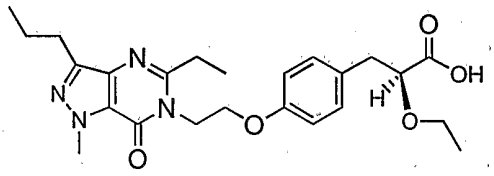


[2R, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (300 mg, 0.52 mmol) obtained in example **18A** was taken in a mixture of dioxane (1.4 mL), water (1.4 mL) and 1M sulfuric acid (1.36 mL) at room temperature and stirred under reflux for 34 h. Water and dioxane were removed under vacuum. The residue was taken in water and extracted with ethyl acetate and the ethyl acetate layer was washed with water, dried (Na_2SO_4) and evaporated to dryness to yield the crude compound. The crude compound was purified by column chromatography using 50 % ethyl acetate in pet. ether as an eluent to afford the title compound. (120 mg, 50.6 %) mp 144-145 °C.

$[\alpha]^{25}_D$ = 17.2° (c = 0.5, CH_3OH); ^1H NMR ($CDCl_3$) : δ 7.12 (d, J = 8.50 Hz, 2H), 6.76 (d, J = 8.50 Hz, 2H), 4.49 (t, J = 5.00 Hz, 2H), 4.28 – 4.21 (m, 5H), 4.01 (dd, J = 4.50 and 2.90 Hz, 1H), 3.65-3.33 (m, 2H), 3.12 – 2.90 (m, 4H), 2.84 (t, J = 7.50 Hz, 2H), 1.90 –1.74 (m, 2H), 1.37 (t, J = 7.30 Hz, 3H), 1.15 (t, J = 7.10 Hz, 3H), 0.98 (t, J = 7.30 Hz, 3H).

Example 20

(-) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid



The title compound (69 mg, 48.3 %) was obtained by hydrolyzing [2S, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide (180 mg, 0.31 mmol) obtained in example **18 B**

using dioxane (1.1 mL), water (1.10 mL) and 1M sulfuric acid (1.00 mL) following a similar procedure described in example 19, mp 134-136 °C. $[\alpha]^{25}_{D}$ = -17.6° (c = 0.5, CH_3OH); ^1H NMR ($CDCl_3$) : δ 7.13 (d, J = 8.50 Hz, 2H), 6.77 (d, J = 8.50 Hz, 2H), 4.50 (t, J = 5.10 Hz, 2H), 4.29 – 4.22 (m, 5H), 4.02 (dd, J = 4.40 and 2.90 Hz, 1H), 3.63-3.38 (m, 2H), 3.10 – 2.94 (m, 4H), 2.85 (t, J = 7.40 Hz, 2H), 1.86 –1.75 (m, 2H), 1.38 (t, J = 7.30 Hz, 3H), 1.16 (t, J = 7.10 Hz, 3H), 0.99 (t, J = 7.30 Hz, 3H).

The compounds of the present invention lowered random blood sugar level, triglyceride, total cholesterol, LDL, VLDL and increased HDL. This was demonstrated by *in vitro* as well as *in vivo* animal experiments.

Demonstration of Efficacy of Compounds :

A) ***In vitro*** **:**

a) Determination of hPPARα activity :

Ligand binding domain of hPPARα was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPARα was measured using Packard Luclite kit (Packard, USA) in Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Superfect Transfection Reagent Handbook. February 1997. Qiagen, Germany).

b) Determination of hPPARγ activity :

Ligand binding domain of hPPARγ1 was fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using lipofectamine (Gibco BRL, USA) as transfecting reagent HEK-293 cells were transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound was added at 1 μM concentration after 48 hrs of transfection and incubated overnight. Luciferase activity as a function of drug binding/activation capacity of PPARγ1 was measured using Packard Luclite kit (Packard, USA) in Packard Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Guide to Eukaryotic Transfections with Cationic Lipid Reagents. Life Technologies, GIBCO BRL, USA).

PPARα and PPARγ activity

Example No	Concentration	PPARα	Concentration	PPARγ
Example 1	50 μM	5.00	1 μM	11.0
Example 3	50 μM	6.9	1 μM	19.0
Example 4	50 μM	8.32	1 μM	14.6

c) **Determination of HMG CoA reductase inhibition activity** : Liver microsome bound reductase was prepared from 2% cholestyramine fed rats at mid-dark cycle. Spectrophotometric assays were carried out in 100 mM KH_2PO_4, 4 mM DTT, 0.2 mM NADPH, 0.3 mM HMG CoA and 125 μg of liver microsomal enzyme. Total reaction mixture volume was kept as 1 ml. Reaction was started by addition of HMG CoA. Reaction mixture was incubated at 37 °C for 30 min and decrease in absorbance at 340 nm was recorded. Reaction mixture without substrate was used as blank (Goldstein, J. L and Brown, M. S. Progress in understanding the LDL receptor and HMG CoA reductase, two membrane proteins that regulate the plasma cholesterol. J.

Lipid Res. 1984, 25: 1450 – 1461). The test compounds inhibited the HMG CoA reductase enzyme.

B) ***<u>In vivo</u>*** **:**

a) **<u>Efficacy in genetic models</u> :**

Mutation in colonies of laboratory animals and different sensitivities to dietary regimens have made the development of animal models with non-insulin dependent diabetes and hyperlipidemia associated with obesity and insulin resistance possible. Genetic models such as db/db and ob/ob (Diabetes, (1982) 31(1) : 1- 6) mice and zucker fa/fa rats have been developed by the various laboratories for understanding the pathophysiology of disease and testing the efficacy of new antidiabetic compounds (Diabetes, (1983) 32: 830-838 ; Annu. Rep. Sankyo Res. Lab. (1994). 46 : 1-57). The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory, US, are obese, hyperglycemic, hyperinsulinemic and insulin resistant (J. Clin. Invest., (1990) 85 : 962-967), whereas heterozygous are lean and normoglycemic. In db/db model, mouse progressively develops insulinopenia with age, a feature commonly observed in late stages of human type II diabetes when blood sugar levels are insufficiently controlled. The state of pancreas and its course vary according to the models. Since this model resembles that of type II diabetes mellitus, the compounds of the present invention were tested for blood sugar and triglycerides lowering activities.

Male C57BL/KsJ-db/db mice of 8 to 14 weeks age, having body weight range of 35 to 60 grams, bred at Dr. Reddy's Research Foundation (DRF) animal house, were used in the experiment. The mice were provided with standard feed (National Institute of Nutrition (NIN), Hyderabad, India) and acidified water, ad libitum. The animals having more than 350 mg / dl blood sugar were used for testing. The number of animals in each group was 4.

Test compounds were suspended on 0.25 % carboxymethyl cellulose and administered to test group at a dose of 0.001 mg to 30 mg / kg through oral gavage daily for 6 days. The control group received vehicle (dose 10 ml / kg). On 6th day the blood samples were collected one hour after administration of test compounds / vehicle for assessing the biological activity.

The random blood sugar and triglyceride levels were measured by collecting blood (100 µl) through orbital sinus, using heparinised capillary in tubes containing EDTA which was centrifuged to obtain plasma. The plasma glucose and triglyceride levels were measured spectrometrically, by glucose oxidase and glycerol-3-PO_4 oxidase/peroxidase enzyme (Dr. Reddy's Lab. Diagnostic Division Kits, Hyderabad, India) methods respectively.

The blood sugar and triglycerides lowering activities of the test compound was calculated according to the formula.

No adverse effects were observed for any of the mentioned compounds of invention in the above test.

BLOOD GLUCOSE LOWERING ACTIVITY IN DB/DB MICE

Compound	Dose (mg / kg)	Reduction in Blood Glucose Level (%)	Triglyceride Lowering (%)
Example 3	3 mg	58	23
Example 4	3 mg	42	17
Example 10	3 mg	33	35

The ob/ob mice were obtained at 5 weeks of age from Bomholtgard, Denmark and were used at 8 weeks of age. Zucker fa/fa fatty rats were obtained from IffaCredo, France at 10 weeks of age and were used at 13 weeks of age. The animals were maintained under 12 hour light and dark cycle at 25 $\pm$ 1 °C. Animals were given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum* (Fujiwara, T., Yoshioka, S., Yoshioka, T.,

Ushiyama, I and Horikoshi, H. Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats. Diabetes. 1988. 37 : 1549 – 1558).

The test compounds were administered at 0.1 to 30 mg/kg/day dose for 9 days. The control animals received the vehicle (0.25 % carboxymethylcellulose, dose 10 ml/kg) through oral gavage.

The blood samples were collected in fed state 1 hour after drug administration on 0 and 9 day of treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride, glucose, free fatty acid, total cholesterol and insulin estimations. Measurement of plasma triglyceride, glucose, total cholesterol were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division kits, Hyderabad, India). The plasma free fatty acid was measured using a commercial kit form Boehringer Mannheim, Germany. The plasma insulin was measured using a RIA kit (BARC, India). The reduction of various parameters examined are calculated according to the formula.

In ob/ob mice oral glucose tolerance test was performed after 9 days treatment. Mice were fasted for 5 hrs and challenged with 3 gm/kg of glucose orally. The blood samples were collected at 0, 15, 30, 60 and 120 min for estimation of plasma glucose levels.

The experimental results from the db/db mice, ob/ob mice, Zucker fa/fa rats suggest that the novel compounds of the present invention also possess therapeutic utility as a prophylactic or regular treatment for diabetes, obesity, cardiovascular disorders such as hypertension, hyperlipidaemia and other diseases; as it is known from the literature that such diseases are interrelated to each other.

Blood glucose level and triglycerides are also lowered at doses greater than 10 mg/kg. Normally, the quantum of reduction is dose dependent and plateaus at certain dose.

b) <u>Cholesterol lowering activity in hypercholesterolemic rat models</u> :

Male Sprague Dawley rats (NIN stock) were bred in DRF animal house. Animals were maintained under 12 hour light and dark cycle at 25 ± 1 ^{0}C. Rats of 180 - 200 gram body weight range were used for the experiment. Animals were made hypercholesterolemic by feeding 2% cholesterol and 1% sodium cholate mixed with standard laboratory chow [National Institute of Nutrition (NIN), Hyderabad, India] for 6 days. Throughout the experimental period the animals were maintained on the same diet (Petit, D., Bonnefis, M. T., Rey, C and Infante, R. Effects of ciprofibrate on liver lipids and lipoprotein synthesis in normo- and hyperlipidemic rats. Atherosclerosis. 1988. 74 : 215 – 225).

The test compounds were administered orally at a dose 0.1 to 30 mg/kg/day for 3 days. Control group was treated with vehicle alone (0.25 % Carboxymethylcellulose; dose 10 ml/kg).

The blood samples were collected in fed state 1 hour after drug administration on 0 and 3 day of compound treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for total cholesterol, HDL and triglyceride estimations. Measurement of plasma triglyceride, total cholesterol and HDL were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). LDL and VLDL cholesterol were calculated from the data obtained for total cholesterol, HDL and triglyceride. The reduction of various parameters examined are calculated according to the formula.

CHOLESTEROL LOWERING ACTIVITY IN MALE SPRAGUE DAWLEY RAT MODELS

Compound	Dose mg/kg	Triglyceride (%)↓	Total Cholesterol (%)↓	HDL ↑ (%)	LDL (%)↓	VLDL (%)↓
Example 2	3 mg	70	60	164	72	71

c) **Plasma triglyceride and total cholesterol lowering activity in Swiss albino mice:**

Male Swiss albino mice (SAM) and male Guinea pigs were obtained from NIN and housed in DRF animal house. All these animals were maintained under 12 hour light and dark cycle at 25 ± 1 ^{0}C. Animals were given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum*. SAM of 20 - 25 g body weight range and Guinea pigs of 500 - 700 g body weight range were used (Oliver, P., Plancke, M. O., Marzin, D., Clavey, V., Sauzieres, J and Fruchart, J. C. Effects of fenofibrate, gemfibrozil and nicotinic acid on plasma lipoprotein levels in normal and hyperlipidemic mice. Atherosclerosis. 1988. 70 : 107 – 114).

The test compounds were administered orally to Swiss albino mice at 0.3 to 30 mg/kg/day dose for 6 days. Control mice were treated with vehicle (0.25% Carboxymethylcellulose; dose 10 ml/kg). The test compounds were administered orally to Guinea pigs at 0.3 to 30 mg/kg/day dose for 6 days. Control animals were treated with vehicle (0.25% Carboxymethylcellulose; dose 5 ml/kg).

The blood samples were collected in fed state 1 hour after drug administration on 0 and 6 day of treatment. The blood was collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride and total cholesterol (Wieland, O. Methods of Enzymatic analysis. Bergermeyer, H. O.,

Ed., 1963. 211 - 214; Trinder, P. Ann. Clin. Biochem. 1969. 6 : 24 – 27). Measurement of plasma triglyceride, total cholesterol and HDL were done using commercial kits (Dr. Reddy's Diagnostic Division, Hyderabad, India).

TRIGLYCERIDE LOWERING ACTIVITY IN SWISS ALBINO MICE

Compound	Dose (mg / kg)	Triglyceride (%)↓
Example 1	3 mg	45
Example 3	3 mg	61
Example 4	3 mg	66
Example 13	3 mg	25

Formulae for calculation :

1. Percent reduction in Blood sugar / triglycerides / total cholesterol were calculated according to the formula :

$$\text{Percent reduction (\%)} = \left[1 - \frac{TT / OT}{TC / OC}\right] \times 100$$

OC = Zero day control group value

OT = Zero day treated group value

TC = Test day control group value

TT = Test day treated group value

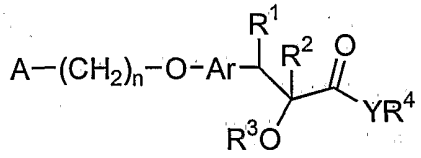
2. LDL and VLDL cholesterol levels were calculated according to the formula :

$$\text{LDL cholesterol in mg/dl} = [\text{Total cholesterol} - \text{HDL cholesterol} - \frac{\text{Triglyceride}}{5}] \text{ mg/dl}$$

VLDL cholesterol in mg/dl = [Total cholesterol - HDL cholesterol - LDL cholesterol] mg/dl.

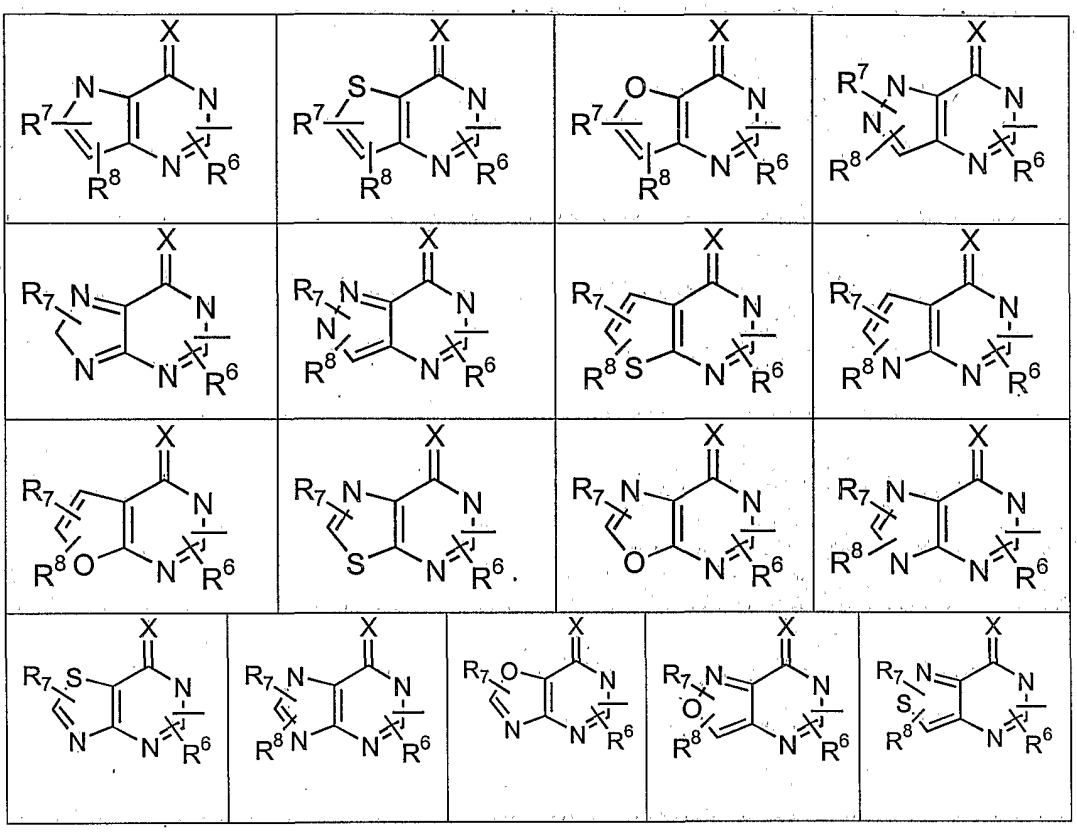
Claims :

1. A compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen or NR^5, where R^5 represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl, aralkyl, hydroxyalkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl, heteroaryl or heteroaralkyl groups; R^4 and R^5 together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, a nitrogen atom and which may optionally contain one or more additional heteroatoms selected from oxygen, sulfur or nitrogen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy,

heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups.

2. A compound of formula (I) according to claim 1, wherein the groups represented by R^3 are substituted, the substituents may be selected from halogen, hydroxy or nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkanoyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, aryloxy, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives.

3. A compound of formula (I) according to claim 1, wherein the groups represented by R^6 when attached to carbon atom are substituted, the substituents may be selected from halogen, hydroxy, nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkanoyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, arylamino, aminoalkyl, alkoxycarbonyl, alkylamino, alkoxyalkyl, alkylthio,

thioalkyl groups, carboxylic acid or its derivatives or sulfonic acid or its derivatives.

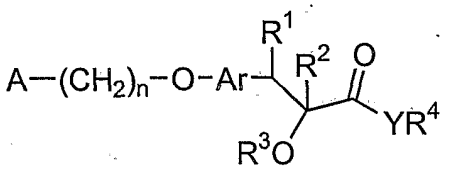
4. A compound of formula (I) according to claim 1, wherein Ar represents substituted or unsubstituted divalent phenylene, naphthylene, pyridyl, quinolinyl, benzofuryl, dihydrobenzofuryl, benzopyranyl, indolyl, indolinyl, azaindolyl, azaindolinyl, pyrazolyl, benzothiazolyl or benzoxazolyl groups.

5. A compound of formula (I) according to claim 1, wherein the groups represented by R^6 when attached to nitrogen are substituted, preferred substituents may be selected from halogen, hydroxy, alkanoyl, alkanoyloxy, amino groups.

6. A compound of formula (I) according to claim 1, wherein the groups represented by R^7 and R^8 attached to carbon atom are substituted, the substituent may be selected from halogen, hydroxy, nitro or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, aralkoxyalkyl, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, arylamino, aminoalkyl, alkylamino, alkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or sulfonic acid.

7. A compound of formula (I) according to claim 1, wherein the groups represented by R^7 and R^8 when attached to nitrogen are substituted, preferred substituents may be selected from halogen such as fluorine, chlorine; hydroxy, alkyl, alkanoyl, alkanoyloxy or amino groups.

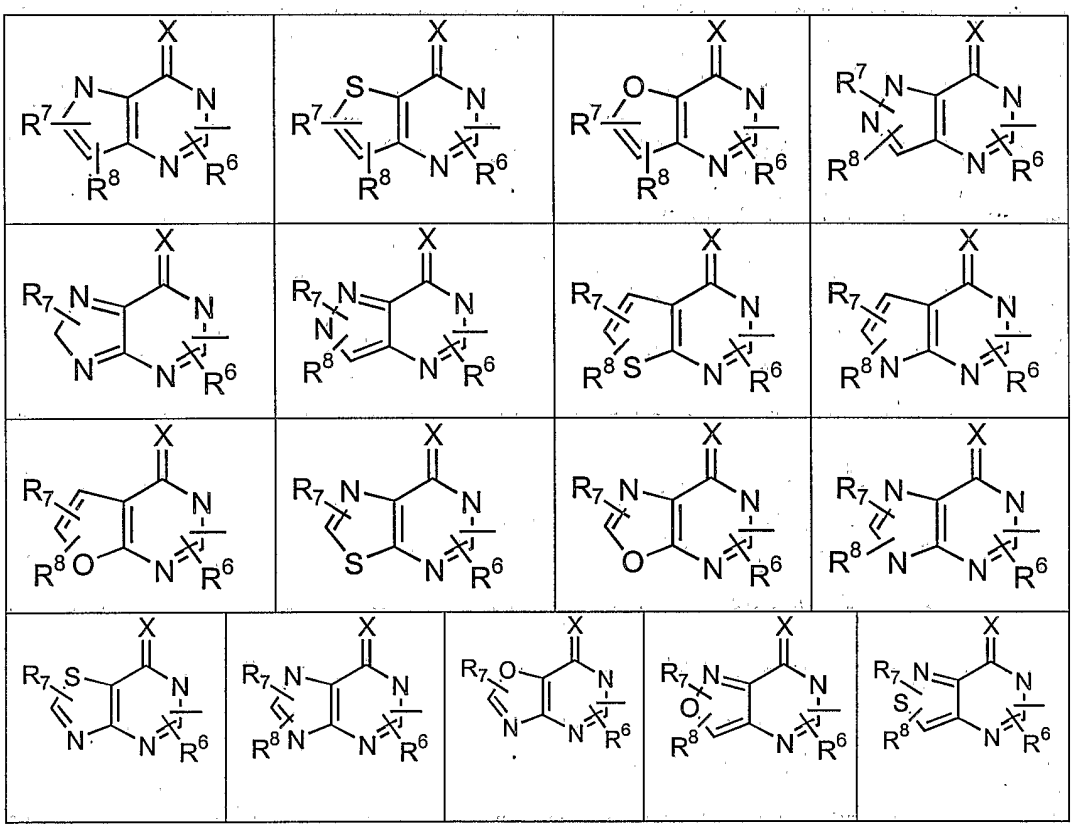
8. A process for the preparation of compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 forms a bond together with the adjacent group R^2; R^3 may be hydrogen atom or substituted or unsubstituted groups selected

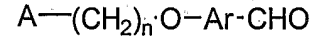
from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl,

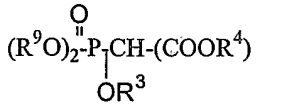
heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, which comprises :

a) reacting a compound of formula (IIIa)



$$A—(CH_2)_n\text{-}O—Ar\text{-}CHO \quad \text{(IIIa)}$$

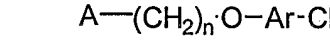
where all symbols are as defined above with a compound of formula (IIIb)



$$(R^9O)_2\text{-}P(=O)\text{-}CH(OR^3)\text{-}(COOR^4) \quad \textbf{(IIIb)}$$

where R^9 represents (C_1-C_6)alkyl and all other symbols are as defined above, to yield the compound of general formula (I) where all symbols are as defined above;

b) reacting the compound of formula (IIIa)



$$A—(CH_2)_n-O-Ar-CHO \quad (IIIa)$$

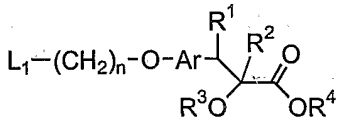
where all symbols are as defined above with Wittig reagent to yield a compound of formula (I) where all symbols are as defined above;

(c) reacting a compound of formula (IIIc)



$$A-H \quad \textbf{(IIIc)}$$

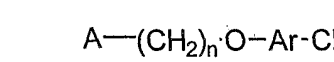
where A is as defined above with a compound of formula (IIId)



$$L_1-(CH_2)_n-O-Ar-C(R^1)(R^2)-C(=O)-C(R^3O)(OR^4) \quad \textbf{(IIId)}$$

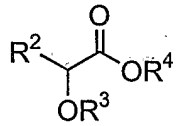
where R^1, R^2 together represent a bond and all other symbols are as defined above and L^1 is a leaving group to produce a compound of general formula (I) defined above;

d) reacting a compound of formula (IIIa)



$$A—(CH_2)_n-O-Ar-CHO \quad (IIIa)$$

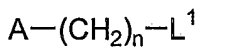
where all symbols are as defined above, with compound of formula (IIIe)



$$R^2-C(=O)-C(OR^3)-OR^4 \quad \textbf{(IIIe)}$$

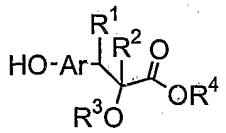
where R^2 represents hydrogen atom and all other symbols are as defined above to produce a compound of the formula (I) defined above;

e) reacting a compound of formula (IIIg)



$$A-(CH_2)_n-L^1 \quad \textbf{(IIIg)}$$

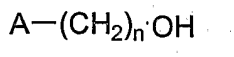
where A and n are as defined above and L^1 represents a leaving group, with compound of formula (IIIf)



(IIIf)

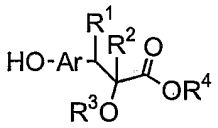
where R^1 and R^2 together represent a bond and all other symbols are as defined above to produce a compound of the formula (I) defined above;

f) reacting a compound of formula (IIIh)



(IIIh)

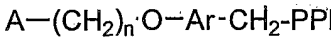
where A and n symbols are as defined above with a compound of general formula (IIIf)



(IIIf)

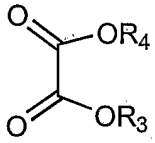
where R^1 and R^2 together represent a bond and all other symbols are as defined above to produce a compound of formula (I) defined above;

g) reacting a compound of formula (IIIi)



(IIIi)

where Hal represents halogen and A, Ar and n are as defined above with a compound of formula (IIIj)

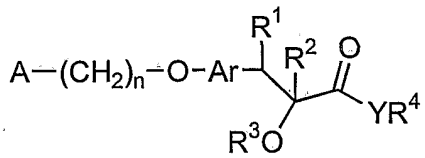


(IIIj)

where $R^3 = R^4$ and are as defined above excluding hydrogen to produce a compound of the formula (I);

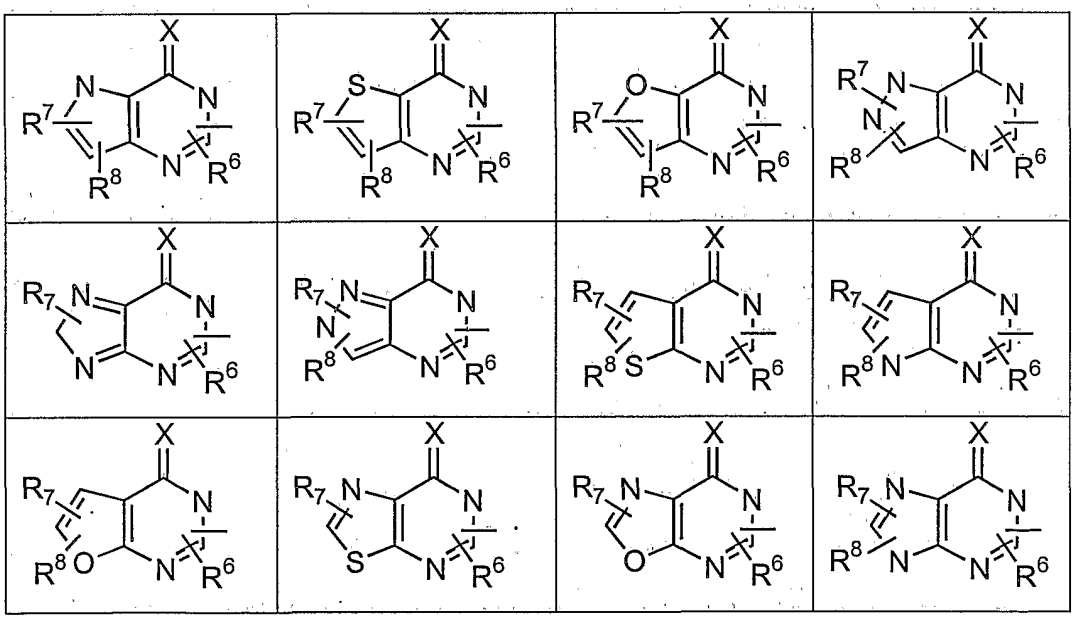
h) converting the compounds of formula (I) obtained in any of the processes described above into pharmaceutically acceptable salts or pharmaceutically acceptable solvates by conventional methods.

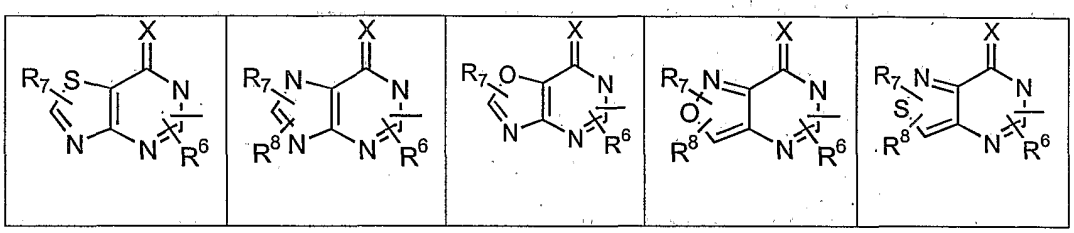
9. A process for the preparation of compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl group; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :

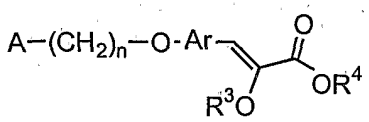




where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent

hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, which comprises :

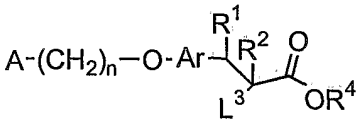
a) reducing methods a compound of formula (IVa)



(IVa)

which represents a compound of formula (I) where R^1 and R^2 together represent a bond and Y represent oxygen atom and all other symbols are as defined above, to yield a compound of the general formula (I) where R^1 and R^2 each represent hydrogen atom and all other symbols are as defined above;

b) reacting a compound of formula (IVb)



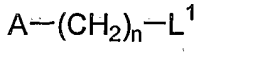
(IVb)

where R^4 is as defined above excluding hydrogen, L^3 is a leaving group and all other symbols are as defined above and with an alcohol of general formula (IVc),

$$R^3OH \qquad \text{(IVc)}$$

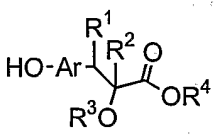
where R^3 represents substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkanoyl, aroyl, heterocyclyl, heteroaryl, heteroaralkyl groups to produce a compound of the formula (I) defined above;

c) reacting a compound of formula (IIIg)



(IIIg)

where L^1 is a leaving group and A, n are as defined above with a compound of formula (IIIf)



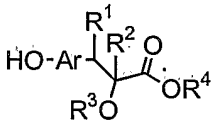
(IIIf)

where all symbols are as defined above to produce a compound of the formula (I) defined above;

d) reacting a compound of formula (IIIh)

$$A-(CH_2)_n-OH \qquad \textbf{(IIIh)}$$

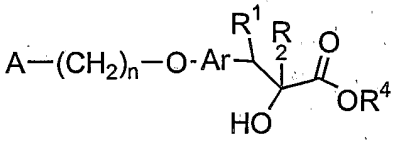
where A and n are as defined above with a compound of general formula (IIIf)



(IIIf)

where all symbols are as defined above to produce a compound of the formula (I) defined above;

e) reacting a compound of formula (IVd)



(IVd)

which represents a compound of formula (I) where R^3 represent hydrogen atom and all symbols are as defined above with a compound of formula (IVe)

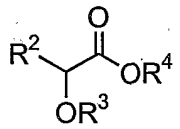
$$R^3\text{-}L^3 \qquad \text{(IVe)}$$

where R^3 represents substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkanoyl, aroyl, heterocyclyl, heteroaryl, heteroaralkyl groups and L^3 is a halogen atom to produce a compound of formula (I) defined above;

f) reacting a compound of the formula (IIIa)

$$A-(CH_2)_n\text{-}O-Ar\text{-}CHO \qquad \text{(IIIa)}$$

where all symbols are as defined above with a compound of formula (IIIe)



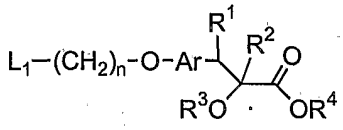
(IIIe)

where R^2 is hydrogen and all other symbols are as defined above to yield a compound of formula (I) as defined above after dehydroxylation;

g) reacting a compound of general formula (IIIc)

$$A-H \qquad \text{(IIIc)}$$

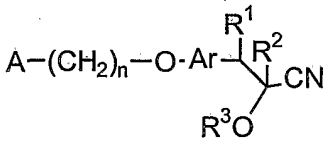
where A is as defined above with a compound of formula (IIId)



(IIId)

where L^1 is a leaving group, and all other symbols are as defined above to produce a compound of general formula (I) defined above;

h) converting a compound of formula (IVf)

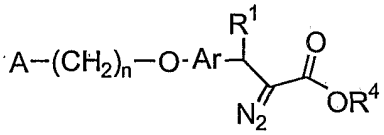


(IVf)

where all symbols are as defined above to a compound of formula (I) defined above;

i) reacting a compound of formula (IVg) where R^4 is as defined above excluding

hydrogen and all other symbols as defined above



(IVg)

with a compound of formula (IVc)

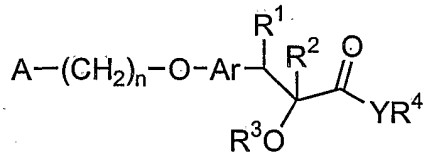
$$R^3OH \qquad \text{(IVc)}$$

where R^3 represents substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl,

alkylaminocarbonyl, arylaminocarbonyl, alkanoyl, aroyl, heterocyclyl, heteroaryl, heteroaralkyl groups to produce a compound of formula (I);

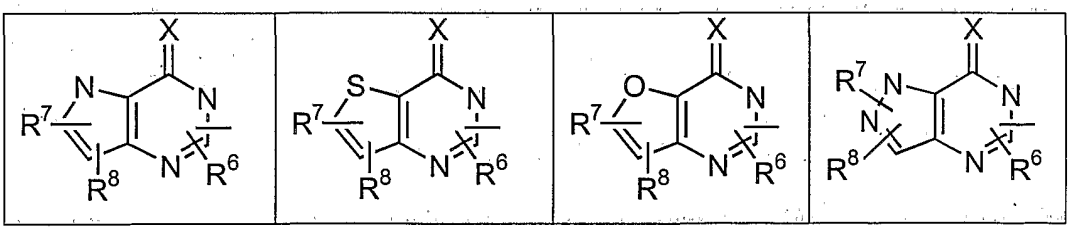
j) converting the compounds of formula (I) obtained in any of the processes described above into pharmaceutically acceptable salts or pharmaceutically acceptable solvates by conventional methods.

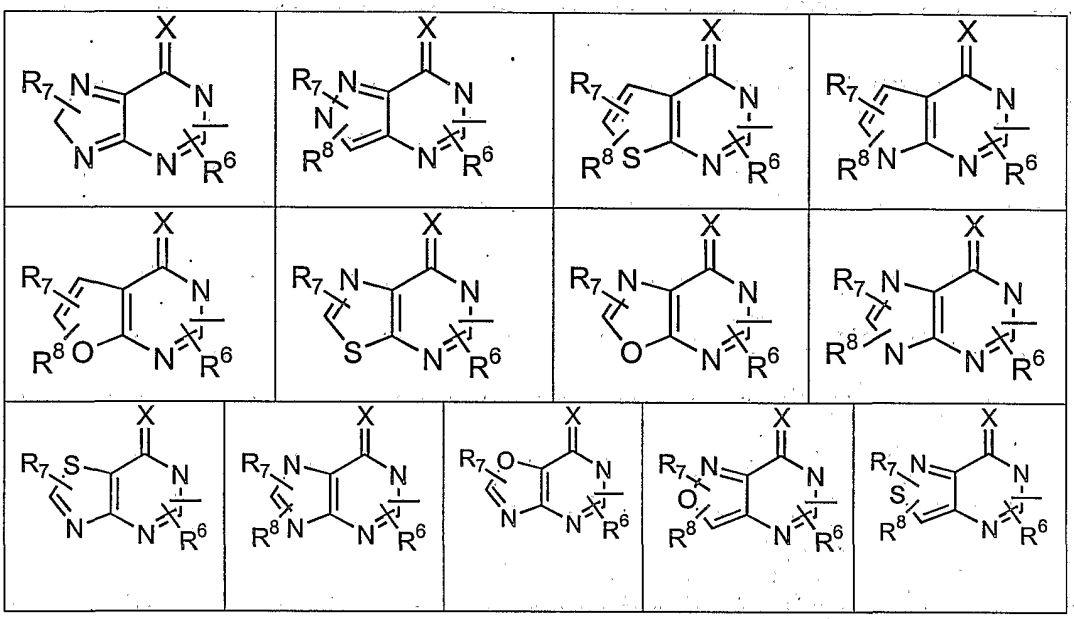
10. A process for the preparation of compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :

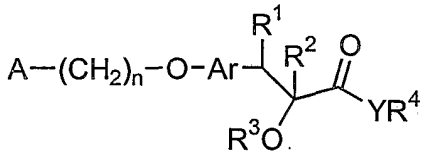




where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its

derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, which comprises : hydrolysing a compound of formula (I) described in any of the claim 8, where R^4 represents substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl groups and all other symbols are as defined earlier by conventional methods.

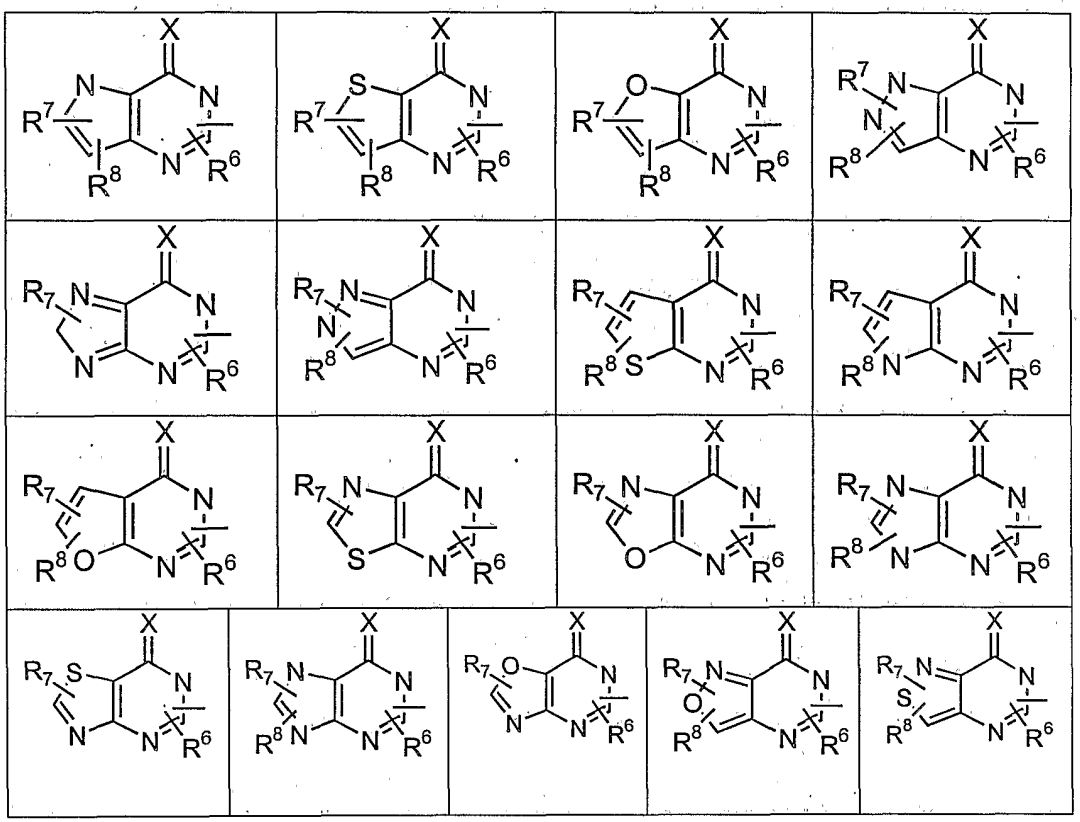
11. A process for the preparation of compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does

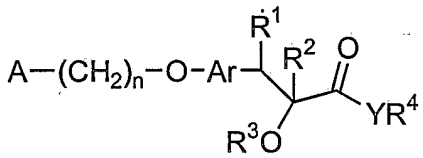
not represent hydrogen when R^4 represents hydrogen; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its

derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, which comprises : hydrolysing a compound of formula (I) described in any of the claim 9, where R^4 represents substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl groups and all other symbols are as defined earlier by conventional methods.

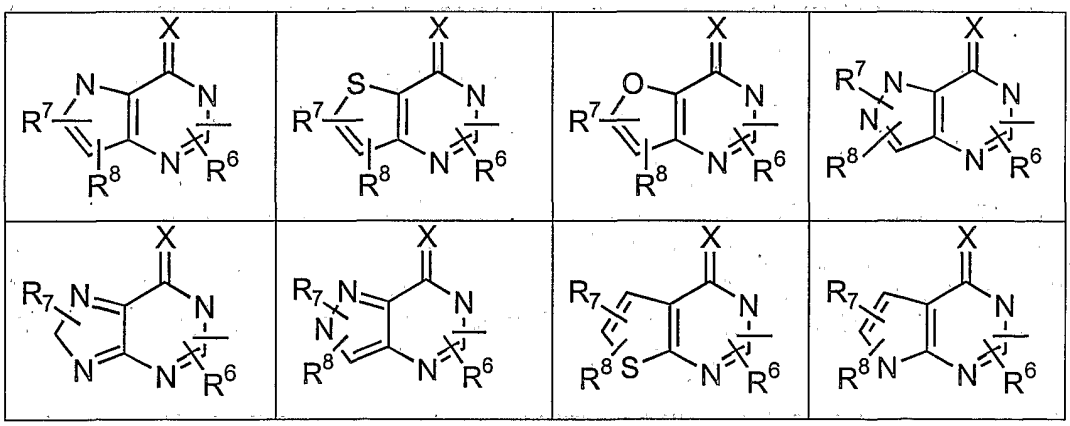
12. A process for the preparation of compound of formula (I)

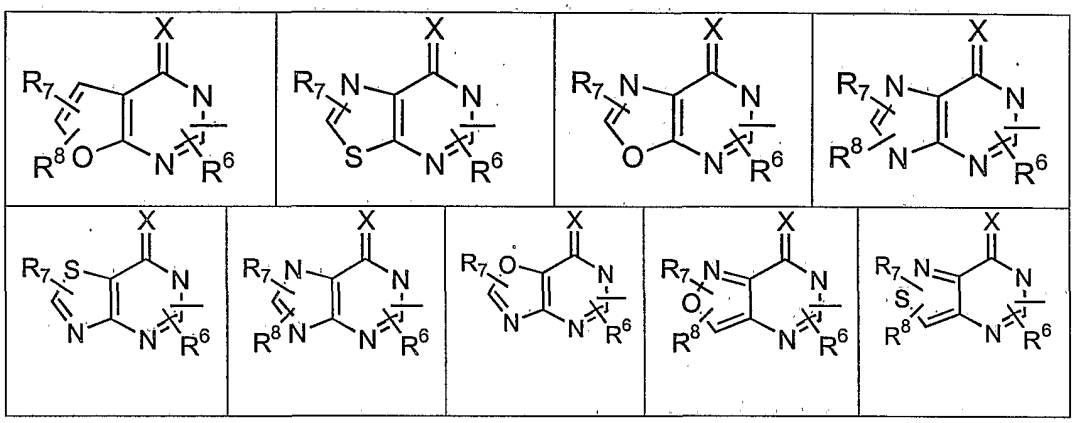


(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy,

lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents NR^5, where R^5 represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl, aralkyl, hydroxyalkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl, heteroaryl or heteroaralkyl groups; R^4 and R^5 together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, a nitrogen atom and which may optionally contain one or more additional heteroatoms selected from oxygen, sulfur or nitrogen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :





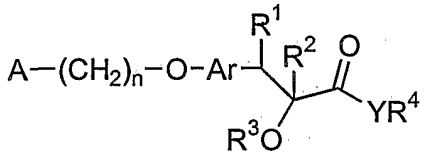
where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl,

heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, which comprises :

a) reacting a compound of formula (I) where all symbols are as defined above and Y represent oxygen or YR^4 represents a halogen atom or $COYR^4$ represents a mixed anhydride group with appropriate amines of the formula NHR^4R^5, where R^4 and R^5 are as defined earlier and if desired;

b) converting the compounds of formula (I) obtained above into pharmaceutically acceptable salts or pharmaceutically acceptable solvates by conventional methods.

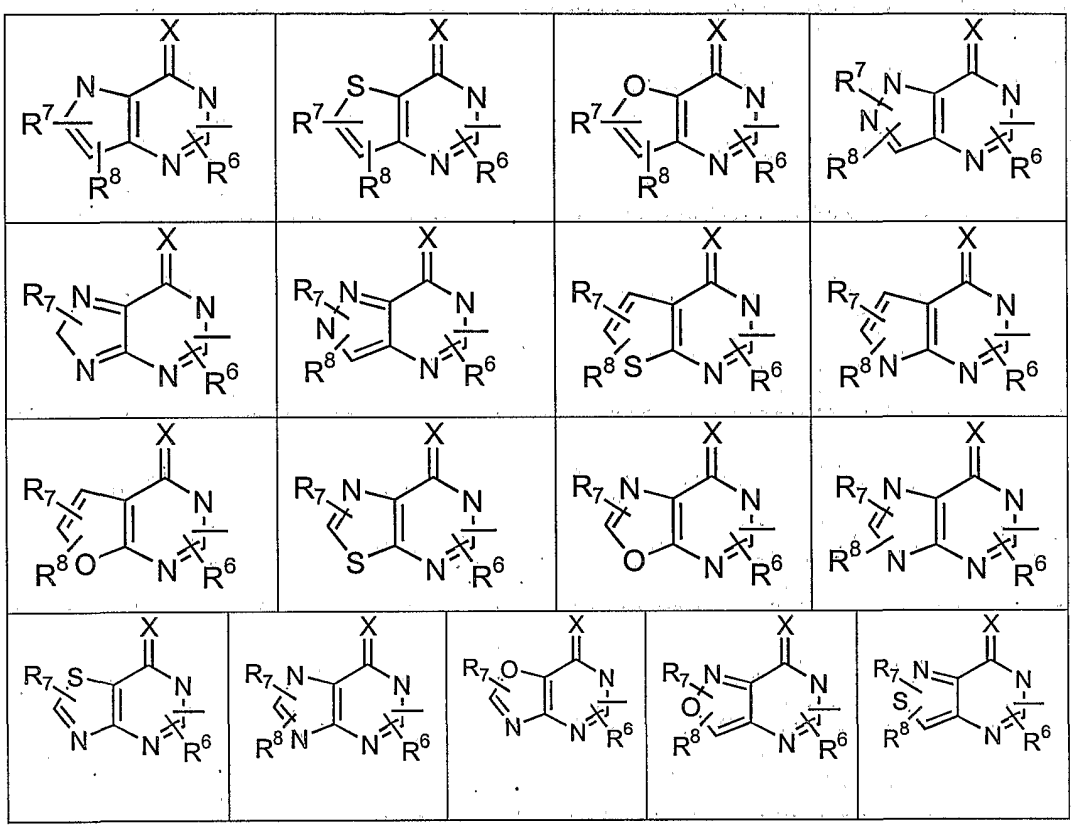
13. A compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 forms a bond together with the adjacent group R^2; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted

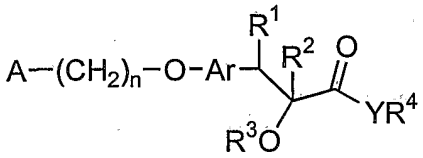
or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted

groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, prepared according to the process of claim 8.

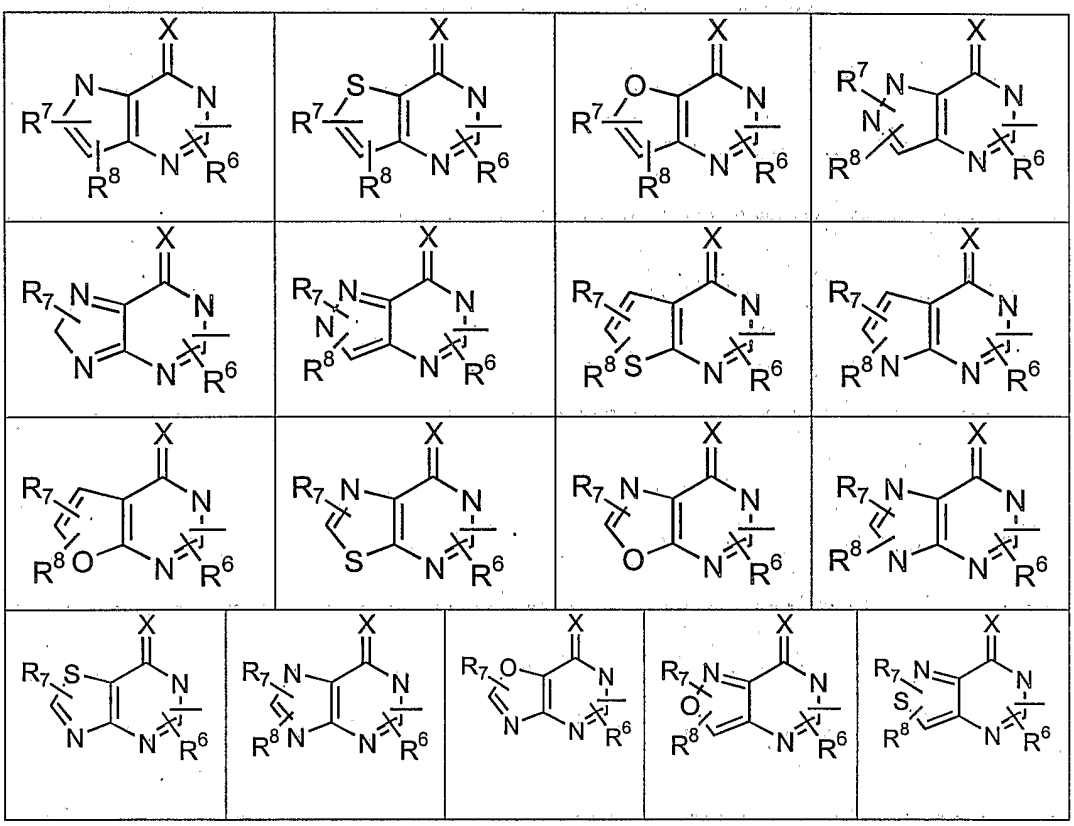
14. A compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl group; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl,

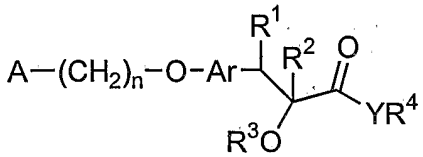
alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl,

amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, prepared according to the process of claim 9.

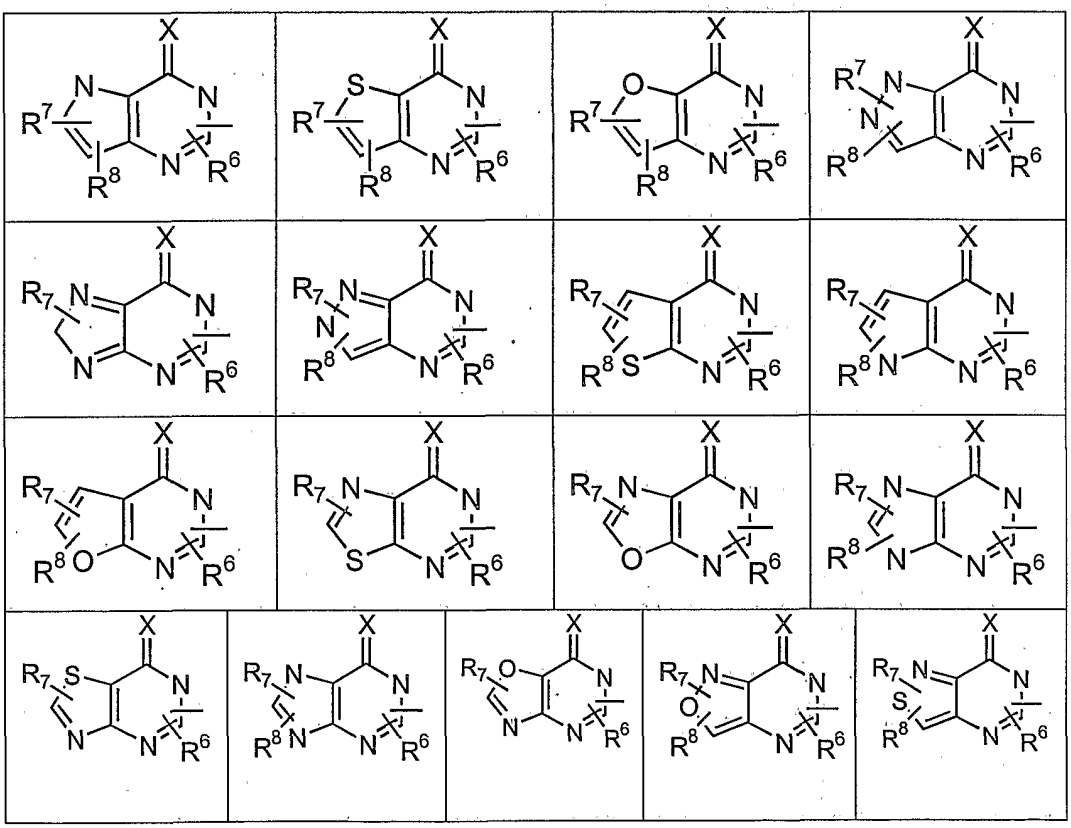
15. A compound of formula (I)



(I)

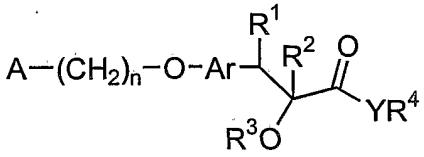
its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically

acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



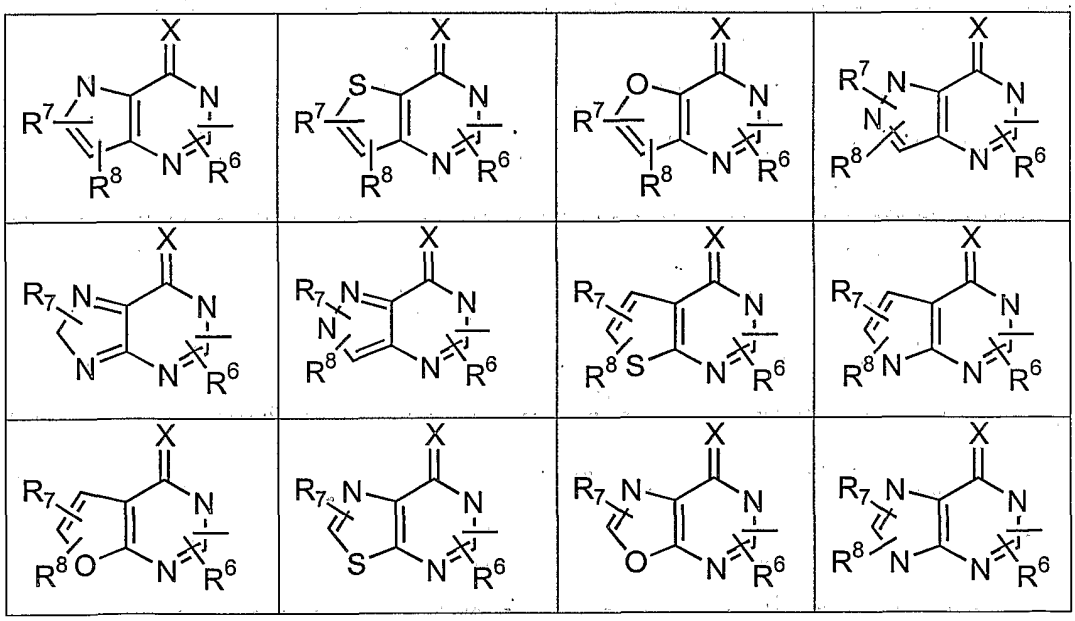
where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, groups prepared according to the process of claim 10.

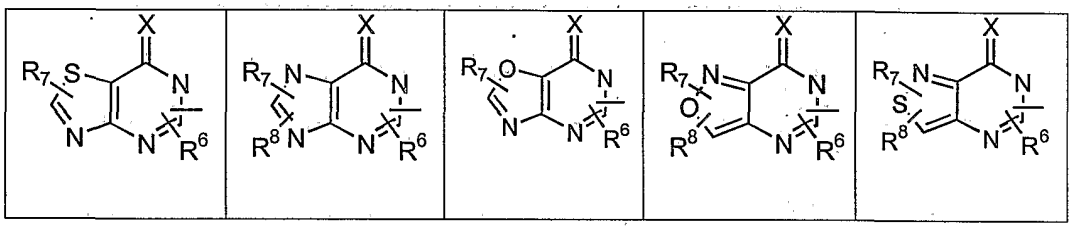
16. A compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen; Y represents oxygen; n is an integer ranging from 1- 4; Ar represents substituted or unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :

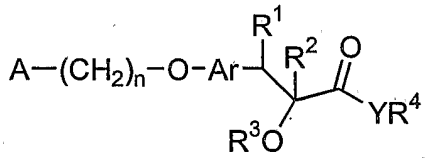




where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent

hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, prepared according to the process of claim 11.

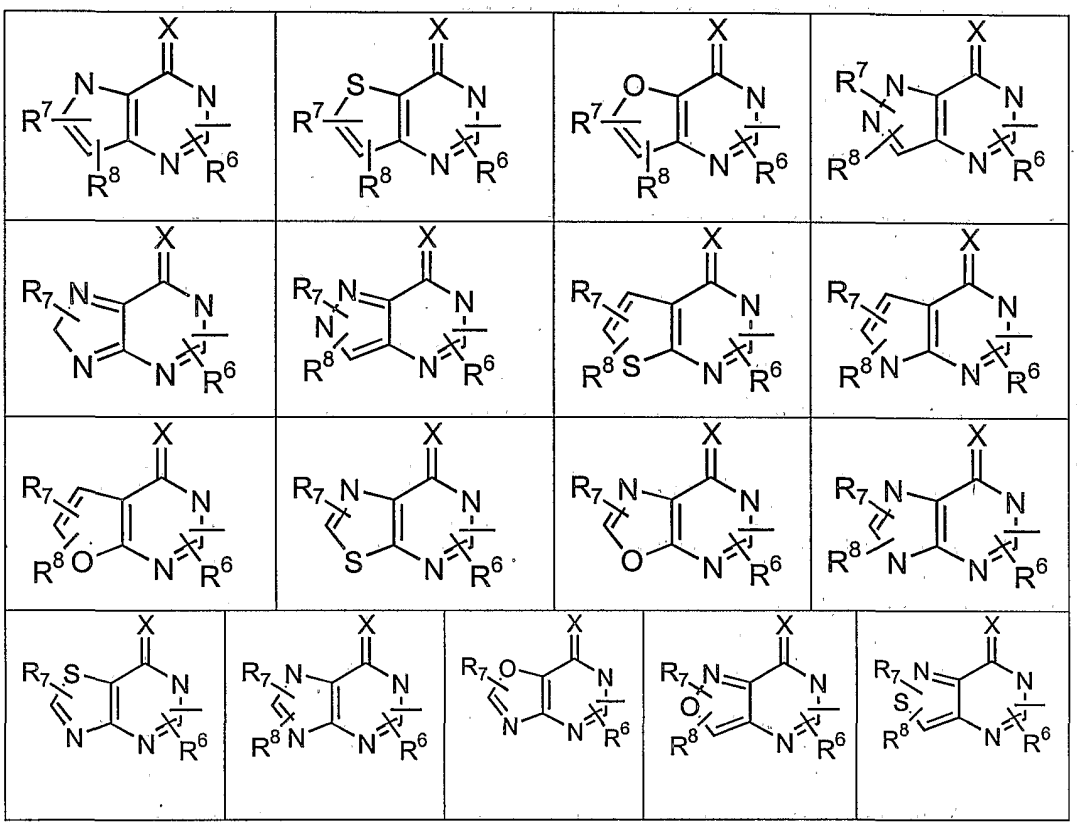
17. A compound of formula (I)



(I)

its derivatives, its analogs, its tautomeric forms, its stereoisomers, its polymorphs, its pharmaceutically acceptable salts, its pharmaceutically acceptable solvates, where R^1 represents hydrogen atom, halogen, hydroxy, lower alkyl, alkoxy, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^2; R^2 represents hydrogen, hydroxy, halogen, lower alkyl, alkoxy, alkanoyl, aroyl, aralkanoyl, substituted or unsubstituted aralkyl or R^2 forms a bond together with R^1; R^3 may be hydrogen atom or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, alkanoyl, aroyl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl groups, with a provision that R^3 does not represent hydrogen when R^4 represents hydrogen or lower alkyl group; R^4 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents NR^5, where R^5 represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl, aralkyl, hydroxyalkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl, heteroaryl or heteroaralkyl groups; R^4 and R^5 together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, a nitrogen atom and which may optionally contain one or more additional heteroatoms selected from oxygen, sulfur or nitrogen; n is an integer ranging from 1- 4; Ar represents substituted or

unsubstituted, divalent, single or fused, aromatic or heterocyclic group; A represents a cyclic structure given below :



where X represents O or S; R^6 when attached to the carbon atom represents hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^6 when attached to nitrogen atom represents hydrogen, hydroxy, formyl or substituted or unsubstituted

groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, aryloxy, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, alkanoyl, aroyl, alkanoyloxy, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid or its derivatives, or sulfonic acid or its derivatives; R^7 and R^8 when attached to carbon atom may be same or different and represent hydrogen, halogen, hydroxy, cyano, nitro, formyl or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, alkoxyalkyl, thioalkyl, alkylthio groups; R^7 and R^8 when attached to nitrogen may be same or different and represent hydrogen, hydroxy or substituted or unsubstituted groups selected from alkyl, alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, hydroxyalkyl, amino, monoalkylamino, dialkylamino, arylamino groups, prepared according to the process of claim 12.

18. A compound according to claim 1, which is selected from :

(±) Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(+) Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(-) Ethyl 2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(±) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its salts ;

(+) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its salts ;

(-) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its salts ;

(±) Ethyl 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(+) Ethyl 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(-) Ethyl 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(±) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(+) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(-) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts ;

(±) Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(+) Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(-) Ethyl 2-ethoxy-3-[4-[2-(1-methyl-7-oxo-3-propyl-5-trifluoromethyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoate ;

(±) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(+) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(-) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo

[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(±) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;
(+) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;
(-) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(±) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(+) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(-) Ethyl 3-[4-[2-(5-benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(+) Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;
(-) Ethyl 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(+) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;
(-) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(±) Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(+) Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(-) Ethyl 3-[4-[2-(1,5-dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(+) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

(-) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(±) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(+) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(-) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoate ;

(±) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(+) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(-) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its salts;

(±) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

(+) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

(-) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

(±) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(+) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(-) Ethyl 3-[4-[2-(3,5-dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoate ;

(±) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(+) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts ;

(-) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its salts;

[2R, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide and

[2S, N(1S)]-2-ethoxy-3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-y]ethoxy]phenyl]-N-(2-hydroxy-1-phenylethyl)propanamide.

19. A compound according to claim 1 wherein the pharmaceutically acceptable salt is selected from Li, Na, K, Ca, Mg, lysine, arginine, guanidine,

diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts.

20. A compound according to claim 18, which is selected from :

(±) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(-) 2-Ethoxy 3-[4-[2-(5-ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]propanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(-) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca,

Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(-) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo [4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(-) 3-[4-[2-(5-Ethyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(-) 3-[4-[2-(1,5-Dimethyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(-) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d] pyrimidin-6-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K,

Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

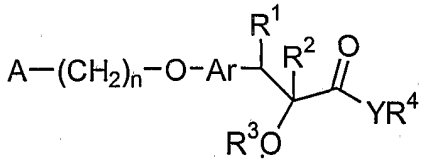
(-) 3-[4-[2-(5-Benzyl-1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(±) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts ;

(+) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts and

(-) 3-[4-[2-(3,5-Dipropyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-6-yl)ethoxy]phenyl]-2-phenoxypropanoic acid or its Li, Na, K, Ca, Mg, lysine, arginine, guanidine, diethanolamine, choline, ammonium, substituted ammonium salts or aluminium salts.

21. A pharmaceutical composition, which comprises a compound of formula (I)



(I)

as defined in claim 1 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

22. A pharmaceutical composition as claimed in claim 21, in the form of a tablet, capsule, powder, syrup, solution or suspension.

23. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a compound of formula (I) as defined in claim 1 or a pharmaceutical composition as claimed in claims 21 and 22 to a patient in need thereof.

24. A method according to claim 23, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.

25. A method for the treatment and / or prophylaxis of disorders related to Syndrome X, which comprises administering an effective amount of an agonist of PPARα and / or PPARγ of formula (I) to a patient in need thereof.

26. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an effective amount of a compound of formula (I) as defined in claim 1 to a patient in need thereof

27. A method according to claim 23 wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase

inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

28. A method according to claim 23, wherein a composition as defined in claim 21 is administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

29. A method according to claim 24, wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

30. A method according to claim 25, wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

31. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an effective amount of a compound of formula (I) as defined in claim 1 in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

32. A pharmaceutical composition which comprises a compound as claimed in claim 18 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

33. A pharmaceutical composition as claimed in claim 32, in the form of a tablet, capsule, powder, syrup, solution or suspension.

34. A pharmaceutical composition which comprises a compound as claimed in claim 20 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

35. A pharmaceutical composition as claimed in claim 34, in the form of a tablet, capsule, powder, syrup, solution or suspension.

36. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a compound of formula (I) as defined in claim 1 or a pharmaceutical composition as claimed in claim 18 to a patient in need thereof.

37. A method according to claim 36, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.

38. A method for the treatment and / or prophylaxis of disorders related to Syndrome X, which comprises administering an effective amount of an agonist of PPARα and / or PPARγ of formula (I) as claimed in claim 18 to a patient in need thereof.

39. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an

effective amount of a compound of formula (I) as defined in claim 18 to a patient in need thereof

40. A method according to claim 36 wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

41. A method according to claim 37, wherein a compound of formula (I) is administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

42. A method according to claim 38, wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

43. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an effective amount of a compound of formula (I) as defined in claim 18 in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

44. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a compound of

formula (I) as defined in claim 1 or a pharmaceutical composition as claimed in claim 20 to a patient in need thereof.

45. A method according to claim 44, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.

46. A method for the treatment and / or prophylaxis of disorders related to Syndrome X, which comprises administering an effective amount of an agonist of PPARα and / or PPARγ of formula (I) as claimed in claim 20 to a patient in need thereof.

47. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an effective amount of a compound of formula (I) as defined in claim 20 to a patient in need thereof

48. A method according to claim 44 wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

49. A method according to claim 45, wherein the compound of formula (I) is administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or

probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

50. A method according to claim 46, wherein a compound of formula (I) administered in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

51. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering an effective amount of a compound of formula (I) as defined in claim 20 in combination / concomittant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

52. Use of a compound of formula (I) as defined in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, impaired glucose tolerance, atherosclerosis, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

53. Use of a compound according to claim 53, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, coronary artery disease and other cardiovascular disorders; certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), dementia, diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic

dystrophy, pancreatitis, arteriosclerosis, xanthoma, eating disorders, cancer or as inflammatory agents

54. Use of a compound of formula (I) as defined in claim in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids or increasing HDL in the plasma.

55. Use of a compound of formula (I) as defined in claim in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 an agonist of PPARα and / or PPARγ of formula (I) to a patient in need thereof.

56. Use of a compound of formula (I) as defined in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, impaired glucose tolerance, atherosclerosis, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism to a patient in need thereof.

57. Use of a compound according to claim 56, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, coronary artery disease and other cardiovascular disorders; certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), dementia, diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic

dystrophy, pancreatitis, arteriosclerosis, xanthoma, eating disorders, cancer or as inflammatory agents.

58. Use of a compound of formula (I) as defined in claim in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids or increasing HDL in the plasma.

59. A medicine for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, impaired glucose tolerance, atherosclerosis, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a compound of formula (I) as defined in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22.

60. A medicine according to claim 59, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, coronary artery disease and other cardiovascular disorders; certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), dementia, diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma, eating disorders, cancer or as inflammatory agents.

61. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids or increasing HDL in the plasma comprising an effective amount of compound of formula (I) as defined in claim 1 or a

compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22.

62. A medicine for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, impaired glucose tolerance, atherosclerosis, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising a compound of formula (I) as defined in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

63. A medicine according to claim 62, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, coronary artery disease and other cardiovascular disorders; certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), dementia, diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma, eating disorders, cancer or as inflammatory agents.

64. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids or increasing HDL in the plasma, which comprises a compound of formula (I) claimed in claim 1 or a compound as claimed in claim 18 or 20 or a pharmaceutical composition as claimed in claims 21 and 22 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/IB 02/00342

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61P03/04

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 08501 A (REDDY RESEARCH FOUNDATION ;REDDY CHEMINOR INC (US)) 25 February 1999 (1999-02-25) cited in the application page 91 -page 96; claim 1 ---	1-64
X	EP 0 903 343 A (SSP CO., LTD., JAPAN) 24 March 1999 (1999-03-24) examples 1BL,1BO,1BP page 2, line 37 - line 38; claim 1; tables 17,18 -----	1-64

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2002	06/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seelmann, I

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Due to the terms "derivatives" and "analogs" the present claims relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Furthermore, support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) as defined in claim 1 without any derivatives or analogs.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int al Application No
PCT/IB 02/00342

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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