159159

DESCRIPTION

G00002

Therapeutic agents for diabetes

TECHINICAL FIELD

The present invention provides therapeutic agents for diabetes comprising a 2-(N-cyanoimino)thiazolidin-4-one derivative or a solvate or a pharmaceutically acceptable salt thereof as an active ingredient.

BACKGROUND ART

Diabetes, recently mentioned as a representative example of life-style related diseases, is a disease that shows an acute symptom due to the remarkably high blood sugar or ketoacidosis, or various chronic, general metabolic abnormalities arising from a prolonged high blood sugar status or a decrease in glucose tolerance. The crisis of the diabetes has congenital genetic factors and acquired environmental factors such as eating habits and exercise levels. Both of them are mutually influenced, thus resulting in various types of diabetic crisis and various types of disease progress.

The pathogenic causes are insulin productive disorders, secretion disorders or reductions in activities and sensitivities of the secreted insulin. The diabetes is largely grouped into the following two types: insulin-dependent diabetes mellitus (also known as Type 1 diabetes) and non-insulin-dependent diabetes mellitus (also known as Type 2 diabetes). It is the latter insulin-nondependent diabetes a trend of which is a remarkable increase in a number of patients, and furthermore has a lot of of diabetes.

The hyperlipidemia is mentioned as one of the life-style-related diseases as much as so for diabetes. The hyperlipidemia means status in which levels of lipids in plasma are increased over normal ranges. The lipids in the plasma are triglycerides, cholesterol, phospholipids, and free fatty acids. All conditions in which any one type of these lipids or multiple types have increased are designated as hyperlipidemia. Almost all lipids in the blood exist as lipoproteins combined with proteins. The free fatty acids in the blood are combined with albumin or lipoproteins; these complexes are also included in the concept of the lipoproteins in the present invention.

Diabetes has been recognized since ancient times, and diagnostic and therapeutic methods have been investigated for many years. As the oral hypoglycemic agents, sulfonylureas (for example, tolbutamide, chlorpropamide and glibenclamide), biguanides (for example, metformin and buformin) and α-glucosidase inhibitors (for example, acarbose and voglibose) can be listed. In addition, recently the agents for insulin-resistance amelioration (for example, troglitazone, rosiglitazone and pioglitazone) have been developed and marketed. Thus,

currently there are various types of therapeutic agents, however, still the patient number has been continuously increasing. Thus, the development of more efficient agents is anticipated.

Currently targets of diabetes therapies and controls are said to inhibit pathogenesis and progress of vascular complications that lead to serious problems, and to allow the diabetes patients have longevity and curability equivalent to normal subjects. Many diabetes patients tend to develop microangiopathy and macroangiopathy that are frequently associated with hypertriglyceridemia and hypercholesterolemia, risk factors of complications. However, because of pathogenic differences between diabetes, hypertriglyceridemia and hypercholesterolemia, different agents have been applied for the respective therapies.

For example, as a first choice for hypertriglyceridemia, dextran sulflate sodium, nicotinic acid derivatives or fibrates have been selected, and among them, bezafibrate has been well known. For hypercholesterolemia, HMG-CoA reductase inhibitors, referred as statins, such as pravastatin and simvastatin have been widely in clinical usage. Generally, when only a cholesterol level is high, HMG-CoA reductase inhibitors are used. However, the combined administration of HMG-CoA reductase inhibitors with fibrates or nicotinic acids gives rise to an increased risk of rhabdomyolysis.

It has been already known that dioxothiazolidine derivatives act for lowering blood sugar to some degree. 5-(Benzyl)thiazolidine-2,4-dione, reported 1971 by Taylor et al; AL-321 (Chemical name: 5-[4-(2-methyl-2-phenypropoxy)benzyl]thiazolidine-2,4-dione, Chem. Pharm. Bull., 30, 3580 (1980)) reported 1982 by Sohda et al; ciglitazone, which obtained as a result of a optimization of AL-321; troglitazone, rosiglitazone, and pioglitazone, which are chosen for clinical development from a large number of thiazolidine derivatives synthesized in many enterprises through design and structure-activity relationship analysis of ciglitazone analogue; for example. Any of AL-321, ciglitazone, troglitazone, rosiglitazone and pioglitazone has a 5-(benzyl)thiazolidine-2,4-dione moiety, a common structural unit. And recently troglitazone, rosiglitazone and pioglitazone were marketed as antidiabetic agents.

However, within a few months after troglitazone on market, adverse effects of severe hepatic symptoms, including death cases, were reported, thereby, monotherapy with this agent was considered to generate a high risk rather than antidiabetic effects. Thus, combined administration of three agents; troglitazone, sulfonylureas and biguanides, has been regarded desirable. When rosiglitazone or pioglitazone is administered, periodical blood tests to monitor liver function are required similar to the case of troglitazone. Developments of antidiabetic agents more excellent in efficacy and safety have been anticipated.

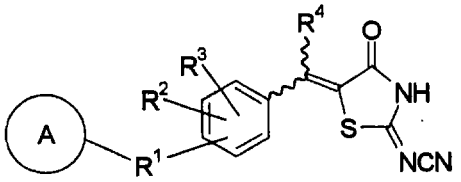
DISCLOSURE OF INVENTION

In Japanese Patent Application No. 1998-232216, the present inventor shows that novel 2-(N-cyanoimino)thiazolidin-4-one derivatives possess activities to improvement of the

hyperlipidemia such as hypertriglyceridemia and hypercholesterolemia. By conducting intensive research, 2-(N-cyanoimino)thiazolidin-4-one derivatives were found to have blood sugar lowering effects as much as troglitazone in diabetes model animals, despite its structural difference from 5-(benzyl)thiazolidine-2,4-dione, the structure of which has been regarded desirable. Thus the present invention was successfully established.

In summary, the compounds of the present invention act for improving hyperlipidemia as well as diabetes, and these traits prevent from the two big risk factors of vascular disease, diabetes and hyperlipidemia simultaneously. This means that said compounds act synergically from both aspects of the diabetes and hyperlipidemia, for improvement in complications such as microangiopathy and macroangiopathy. The said compounds can be excellent therapeutic agents for diabetes extremely suit aims of the diabetes control and therapy "prevention of pathogenesis and progression of vascular complications that evoke serious states".

This invention provides therapeutic agents for diabetes comprising a 2-(N-cyanoimino)thiazolidine-4-one derivative represented by formula I or a solvate or a pharmaceutically acceptable salt thereof as an active ingredient:



I

wherein ring A represents a benzene ring, a condensed ring or a heterocyclic ring, each of which may be substituted by one or more substituents selected from a straight or branched C_1 - C_4 alkyl group, a haloalkyl group, a halogen atom or $-OR^5$;

R^1 represents a single bond, an oxygen atom, a sulfur atom, a methyne group, a straight or branched C_1 - C_4 alkylene or alkenylene group optionally substituted by a phenyl group, R^6-X, X-R^6, X-R^6-X, R^6-X-R^6, -C(=O)-NR^7- or -NR^7-C(=O)-;

R^2 and R^3 are the same or different and each represents a hydrogen atom, a C_1 - C_4 alkyl group, $-OR^8$ or a halogen atom;

R^4 represents a hydrogen atom or a C_1 - C_4 alkyl group;

R^5 represents a hydrogen atom or a C_1 - C_4 alkyl group;

R^6 represents a straight or branched C_1 - C_4 alkylene or alkenylene group;

R^7 represents a hydrogen atom or a C_1 - C_4 alkyl group;

R^8 represents a hydrogen atom, a C_1 - C_4 alkyl group or an aralkyl group;

X represents an oxygen atom or a sulfur atom;

the configuration of the exocyclic methylene group at 5-position of the thiazolidine

ring includes both E- and Z-configuration.

The term therapeutic agents for diabetes of the present invention means the agents administered to diabetes-prone subjects, that is, prophylactic agents as well as the agents for treatment of diabetes patients.

"Salts" refers to low toxic salts derived from sodium, potassium, ammonia or organic amines, for instance.

"C_1 - C_4 alkyl group" refers to methyl, ethyl, n-propyl, iso-propyl, n-butyl or tert-butyl, for instance.

"C_1 - C_4 alkoxy group" refers to methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy or tert-butoxy, for instance.

"halogen atom" refers to generally fluorine atom, chlorine atom, bromine atom, or iodine atom. More preferably it is fluorine atom or chlorine atom.

"ring A" refers to a benzene ring, a benzodioxole ring, a benzofuran ring, a benzothiazole, a fluorene ring, an indan ring, an indoline ring or a pyridine ring, connecting with R^1 at any position, for instance.

The compounds of the present invention can be obtained in accordance with the method described in Japanese Patent Application No. 1998-232216, for instance. There are geometric isomers for these compounds, however, in solution, reversible isomerization of the exocyclic methylene group at 5-position of the thiazolidine ring occurs very easily by the action of light or heat.

BEST MODE FOR CARRYING OUT THE INVENTION

Particularly preferred compounds represented by formula I are as follows;

2-(N-Cyanoimino)-5-[(E)-4-styrylbenzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(α-methylstyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(benzyloxymethyl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(β-methylstyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(3-phenylpropoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(4-chlorophenoxy)benzylidene]thiazolidine-4-one;

2-(N-Cyanoimino)-5-(4-phenylthiobenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(2-fluorostyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(2,5-dimethylphenoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5- (4-phenethyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(2-phenylpropoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(3-phenethyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(benzyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(5-chlorobenzofuran-2-yl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-4-(4-methoxystyryl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5- (3-phenoxybenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(1,3-benzodioxole-5-ylmethoxy)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(4-methylbenzyloxy)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(4-chlorobenzyloxy)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[3-methoxy-(E)-4-styrylbenzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5- (2-phenethyloxybenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5- (4-phenoxybenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5-[3-(benzyloxy)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(benzylthio)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5- (4-phenethylbenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-[2-(4-chlorophenyl)ethoxy]benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[1-[(E)-4-(4-methoxystyryl)phenyl]ethylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5- (4-benzyloxy-2,5-dimethylbenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-3-styrylbenzylidene]thiazolidin-4-one.

The compounds of the present invention and pharmaceutically acceptable salts thereof can be orally or parenterally administered either alone or generally in the form of appropriate pharmaceutical compositions such as tablets, powders, granules, capsules, syrups, or injections comprised of pharmaceutically acceptable carriers, diluents, solubilizers, or other pharmaceutical additives. Oral administration is preferred. preferably by oral administration are especially preferred Among these preparations, oral administration preparations are particularly preferable.

The dosage will depend on the condition, age, body weight, and other factors of each patient or efficacy of an active ingredient. Generally, when the compound of the present invention is orally administered, the daily dose of the present invention preferably ranges from 10 to 2000 mg, more preferably from 100 to 1000 mg for adult, and is administered once or in several divided doses a day.

EXAMPLE 1

2-(N-Cyanoimino)-5-[(E)-4-stylylbenzylidene]thiazolidin-4-one (compound 1)

A mixture of 4.48g (0.025mol) of 2-(N-cyanoimino)thiazolidin-4-one potassium salt, 5.47g (0.026mol) of *trans*-4-stilbencarboxaldehyde and 2.02g (0.026mol) of ammonium acetate in 100 mL of ethanol was heated for 2 hours under reflux. After cooling, ether was added to the reaction mixture and the precipitated potassium salt of the title compound was collected by filtration. To the rapidly stirring suspension of the salt in 50 mL of acetone, 5

mL of conc. hydrochloric acid was added dropwise and then 250 mL of water was added. The precipitate was collected and dried under reduced pressure to yield the title compound as yellow crystals. The yield was 88% (7.32 g, 0.022mol).

mp: > 265 °C (dec.) (ethanol-DMF)

EI-MS: 331(M^+), 236, 202, 179

IR (KBr, cm^{-1}): 3015, 2920, 2740, 2185, 1725, 1580, 1505, 1490, 1340, 1290, 1170, 580, 540, 500

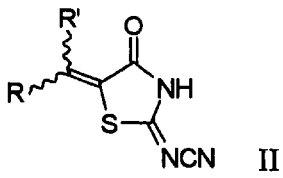
^{1}H NMR (DMSO-*d6*, ppm): δ = 5.80-7.00 (1H, br), 7.20-8.10 (11H, m), 7.86 (1H, s)

Elemental analysis for $C_{19}H_{13}N_3OS$(331.399):

Calcd. : H 3.95, C 68.86, N 12.68 (%) ;

Found : H 4.15, C 68.94, N 12.40 (%)

In the same manner, the compounds 2 to 61 shown in Table 1 to 6 were prepared. Their structural formulas, yields, and physical properties are shown in Table 1 to 6. R and R' used in these tables represent R and R' in the formula II respectively.



II

Abbreviations used and notes in Table 1 to 6 are as follows:

Ex.	Example
mp	melting point
recryst solv	recrystallization solvent
El-MS	electron impact ionization mass spectroscopy
IR	infrared spectroscopy
EA	elemental analysis
^{1}H NMR	proton nuclear magnetic resonance spectra
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
m	multiplet
br	broad
J	coupling constant

*1: After heating for 10 minutes at 130°C without solvent, the soluble part of reaction mixture in chloroform is chromatographed on a silica gel column.

*2: n-Butanol was used as solvent.

*3: E = ethanol, DMF = N,N-dimethylformamide, I = isopropanol, A = acetone, M = methanol, EA = ethyl acetate, H = hexane

*4: Solvent; 10% Pyridine-*d5* / DMSO-*d6*

Table 1.

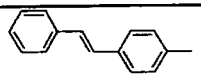
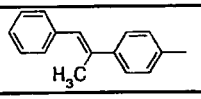
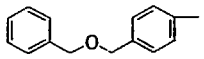
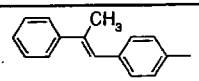
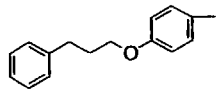
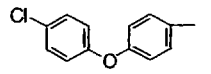
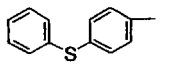
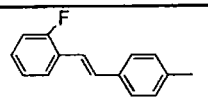
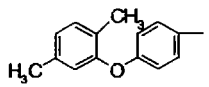
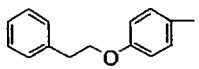
Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr, cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcd. / Found
1	yellow crystals	88		H	265 (dec) (E/DMF)	331(M^+), 236, 202, 179	3015, 2920, 2740, 2185, 1725, 1580, 1505, 1490, 1340, 1290, 1170, 580, 540, 500	5.80-7.00(1H,br), 7.20-8.10(11H,m), 7.86(1H,s)	$C_{19}H_{13}N_3OS$ (331.399)	H 3.95, C 68.86, N 12.68 H 4.15, C 68.94, N 12.40
2	orange-yellow crystals	84		H	226-227.5 (E/DMF)	345(M^+), 258, 243, 162	3150, 3080, 2925, 2210, 1724, 1580, 1360, 1348, 1180, 742, 700, 588, 525	2.27(3H,br), 3.50-4.40(1H,br), 7.08(1H,br), 7.20-7.55(5H,m), 7.60-7.80(4H,m), 7.88(1H,s)	$C_{20}H_{15}N_3OS$ (345.426)	H 4.38, C 69.54, N 12.16 H 4.59, C 69.51, N 11.99
3	pale yellow crystals	90		H	170.5-171.5 (E/DMF)	349(M^+), 320, 258, 243, 230, 162, 147, 135, 115, 103, 91, 79, 77	3200, 3110, 2200, 1740, 1600, 1350, 1307, 1250, 1200, 1190, 1146, 830, 755, 562, 540	3.86(1H,br), 4.57(2H,s), 4.62(2H,s), 7.37(5H,s), 7.60(4H,s), 7.87(1H,s)	$C_{19}H_{15}N_3O_2S$ (349.414)	H 4.33, C 65.31, N 12.03 H 4.64, C 65.54, N 11.70
4	yellow needles	66		H	236.5-237.5 (E/DMF)	345(M^+), 320, 249, 233, 205	2950, 2200, 1717, 1598, 1360, 1293, 1248, 1202, 1181, 763, 721, 700, 582, 542, 520	2.28(3H,s), 6.05(1H,br), 6.81(1H,s), 7.20-7.80(9H,m),7.84(1H,s)	$C_{20}H_{15}N_3OS$ (345.426)	H 4.38, C 69.54, N 12.16 H 4.65, C 69.62, N 11.76
5	yellow crystals	78		H	212.5-213 (dec) (E/DMF)	363(M^+), 272, 268, 245, 176, 150, 121, 91, 65	3110, 3050, 2925, 2780, 2190, 1690, 1585, 1555, 1500, 1490, 1350, 1260, 1245, 1205, 1170, 1110, 820, 720, 535	1.50-2.37(2H,m), 2.37-2.91(2H,m), 4.01(2H,t,J=6Hz), 7.05(2H,d,J=8.5Hz), 7.22(5H,s), 7.54(2H,d,J=8.5Hz), 7.76(1H,s)	$C_{20}H_{17}N_3O_2S$ (363.441)	H 4.71, C 66.10, N 11.56 H 4.85, C 66.05, N 11.53
6	orange-yellow needles	69		H	225-226.5 (dec) (E/DMF)	355(M^+), 262, 260, 149	3160, 3075, 2945, 2770, 2200, 1720, 1590, 1580, 1500, 1480, 1355, 1290, 1245, 1205, 1190, 1170, 1090, 1010, 830, 545, 490	6.40-8.00(1H,br), 7.13 (4H,dd,J=8.5Hz,9Hz), 7.49(2H,d,J=9Hz), 7.67 (2H,d,J=8.5Hz), 7.84(1H,s)	$C_{17}H_{10}ClN_3O_2S$ (355.805)	H 2.83, C 57.39, N 11.81 H 3.13, C 57.44, N 11.54
7	orange crystals	76		H	204.5-205.5 (dec) (E/DMF)	337(M^+), 242, 200, 197, 165	3125, 3040, 2930, 2750, 2200, 1730, 1700, 1615, 1600, 1580, 1545, 1490, 1470, 1405, 1355, 1320, 1300, 1185, 1080, 755, 715, 700	4.30-5.40(1H,br), 7.21(2H,d,J=9Hz), 7.40(5H,s), 7.50(2H,d,J=9Hz), 7.71(1H,s)	$C_{17}H_{11}N_3OS_2$ (337.427)	H 3.29, C 60.51, N 12.45 H 3.57, C 60.27, N 12.38
8	yellow crystals	91		H	271-272 (E/DMF)	349(M^+), 254	3050, 2960, 2800, 2200, 1700, 1580, 1357, 1296, 1211, 1177, 754, 550	3.93(1H,br), 7.20-7.84(10H,m), 7.87(1H,s)	$C_{19}H_{12}FN_3OS$ (349.388)	H 3.46, C 65.32, N 12.03 H 3.73, C 65.53, N 11.78
9	orange-yellow plates	62		H	196-197.5 (E)	349(M^+), 254, 121, 149, 134, 221, 105, 79	3050, 2950, 2770, 2190, 1735, 1705, 1590, 1500, 1425, 1350, 1290, 1250, 1235, 1195, 1165, 1110, 830, 725	2.09, 2.27(each 3H,s), 6.30-8.50(1H, br), 6.85(1H,s), 6.99(1H,d,J=7Hz,2H, d,J=8.5Hz), 7.24(1H,d, J=7Hz3-H), 7.62(1H,d,J=8.5Hz), 7.82(1H,s)	$C_{19}H_{15}N_3O_2S$ (349.414)	H 4.33, C 65.31, N 12.03 H 4.50, C 64.91, N 11.66
10	pale yellow crystals	78		H	193-194 (dec) (I/DMF)	349(M^+), 150, 105, 79	3050, 2920, 2750, 2175, 1725, 1580, 1505, 1495, 1345, 1305, 1290, 1255, 1020, 535	3.08(2H,t,J=7Hz), 4.30(2H,t,J=7Hz), 6.30-8.30(1H,br), 7.12(2H,d,J=8Hz), 7.33(5H,s), 7.60(2H,d,J=8Hz), 7.82(1H,s)	$C_{19}H_{15}N_3O_2S$ (349.414)	H 4.33, C 65.31, N 12.03 H 4.45, C 65.27, N 11.93

Table 2.

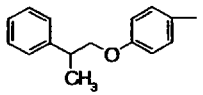
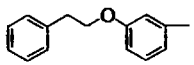
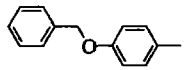
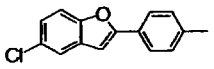
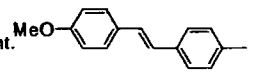
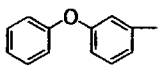
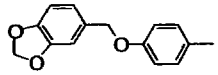
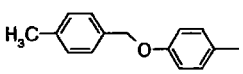
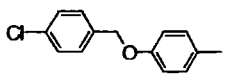
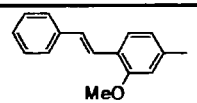
Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr. cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcd. / Found
11	pale yellow crystals	66		H	190-191 (E/DMF)	363(M^+), 244, 210, 149	2940, 2210, 1730, 1600, 1517, 1360, 1268, 1180, 1019, 777; 742, 706, 561, 548	1.34(3H,d,J=6.6Hz), 3.00-3.50(1H, m), 4.17(2H,d,J=6.6Hz), 5.10(1H ,br), 7.09(2H,d,J=9Hz), 7.31(5H, s), 7.58(2H,d,J=9Hz), 7.80(1H,s)	$C_{20}H_{17}N_3O_2S$ (363.441)	H 4.71, C 66.10, N 11.56 H 4.76, C 65.76, N 11.57
12	pale yellow crystals	80		H	172-173 (dec) (E/DMF)	349(M^+), 150, 105	3050, 3020, 2930, 2775, 2220, 1720, 1620, 1600, 1490, 1350, 1290, 1220, 1060, 1030, 990, 780, 750, 730, 700, 525	3.05(2H,t,J=7Hz), 4.24 (2H,t,J=7Hz), 6.85-7.60(9H,m), 7.82(1H,s)	$C_{19}H_{15}N_3O_2S$ (349.414)	H 4.33, C 65.31, N 12.03 H 4.53, C 65.64, N 11.96
13	yellow brown crystals	60		H	230-231 (dec) (E/DMF)	335(M^+), 149, 121, 91	3130, 3070, 2960, 2790, 2215, 1710, 1600, 1590, 1510, 1365, 1260, 1240, 1210, 1180, 985, 840, 765, 730, 595, 510	3.80-4.90(1H,br), 5.19(2H,s), 7.18(2H,d,J=9Hz), 7.42(5H,s), 7.60(2H,d,J=9Hz), 7.81(1H,s)	$C_{18}H_{13}N_3O_2S$ (335.387)	H 3.90, C 64.46, N 12.53 H 4.20, C 64.52, N 12.20
14	yellow needles	56		H	265 (dec) (DMF)	379(M^+), 286, 284	3050, 2930, 2750, 2195, 1715, 1595, 1495, 1445, 1415, 1350, 1330, 1290, 1260, 1240, 1165, 1060, 1035, 800, 720, 560, 540	7.33(1H,dd,J=9Hz,2.5Hz), 7.46-7.83(6H,m), 8.03(2H,d,J=8Hz)	$C_{19}H_{10}ClN_3O_2S$ (379.827)	H 2.65, C 60.09, N 11.06 H 3.06, C 60.51, N 10.91
15	yellow crystals	quant.		H	161-162 (E/DMF)	361(M^+), 266, 251, 234, 221, 189, 179, 165, 133, 105, 89, 77	3050, 2940, 2750, 2210, 1728, 1583, 1512, 1328, 1292, 1244, 1176, 1022, 969, 839, 800, 707, 633, 560, 542	3.81(3H,s), 6.87-7.90(11H,m) *4	$C_{20}H_{15}N_3O_2S$ · $1/2H_2O$ (370.433)	H 4.35, C 64.85, N 11.34 H 4.23, C 64.87, N 11.29
16	Light-brown crystals	93		H	202.5-203.5 (E/DMF)	321(M^+), 226, 197, 165	3025, 2920, 2750, 2200, 1733, 1630, 1600, 1485, 1340, 1286, 1260, 1220, 754, 720, 525	5.18(1H,br), 7.00-7.68(9H,m), 7.86(1H,s)	$C_{17}H_{11}N_3O_2S$ (321.36)	H 3.45, C 63.54, N 13.08 H 3.72, C 63.61, N 12.80
17	yellow crystals	95		H	217-218 (dec) (E/DMF)	379(M^+), 245, 150, 135, 105, 77	3050, 2950, 2775, 2200, 1700, 1585, 1510, 1445, 1355, 1300, 1255, 1215, 1175, 1040, 1020, 985, 930, 830, 810, 730, 550	3.60-4.70(1H,br), 5.05(2H,s), 5.95(2H,s.), 6.80-7.05(3H,m), 7.13(2H,d,J=9Hz), 7.58 (2H,d,J=9Hz), 7.68(1H,s)	$C_{19}H_{13}N_3O_4S$ (379.396)	H 3.45, C 60.15, N 11.08 H 3.74, C 59.82, N 10.96
18	light-orange crystals	84		H	248.5-249.5 (dec) (E/DMF)	349(M^+), 150, 105	3030, 2930, 2770, 2225, 2200, 1715, 1600, 1590, 1505, 1355, 1290, 1260, 1240, 1190, 1170, 990, 835, 800, 725, 555, 540, 480	2.31(3H,s), 4.60-6.20(1H,br), 5.13(2H,s), 7.00-7.47(6H,m), 7.60(2H,d,J=9Hz), 7.80(1H,s)	$C_{19}H_{15}N_3O_2S$ (349.414)	H 4.33, C 65.31, N 12.03 H 4.52, C 65.40, N 11.78
19	orange crystals	54		H	220-221 (dec) (E/DMF)	369(M^+), 149, 127, 125, 105	3050, 2930, 2780, 2225, 1720, 1620, 1610, 1595, 1510, 1360, 1290, 1260, 1245, 1200, 1175, 1000, 850, 840, 820, 720, 540, 510	3.90-5.00(1H,br), 5.20(2H,s), 7.19(2H,d,J=9Hz), 7.48(4H,s), 7.63(2H,d,J=9Hz), 7.82(1H,s)	$C_{18}H_{12}ClN_3O_2S$ (369.832)	H 3.27, C 58.46, N 11.36 H 3.52, C 58.65, N 11.09
20	red crystals	89		H	250.5 (dec) (E/DMF)	361(M^+), 262, 234, 223, 206	3030, 2950, 2203, 1744, 1593, 1516, 1360, 1330, 1279, 1161, 1043, 970, 839, 763, 698, 637, 604, 555, 520	3.92(3H,s), 4.22(1H,br), 7.09-7.99(10H,m), 7.85(1H,s)	$C_{20}H_{15}N_3O_2S$ (361.425)	H 4.18, C 66.47, N 11.63 H 4.35, C 66.71, N 11.35

Table 3.

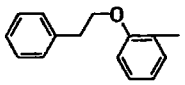
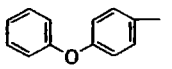
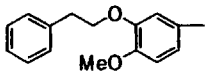
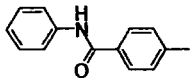
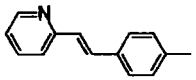
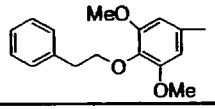
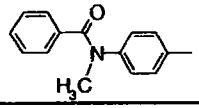
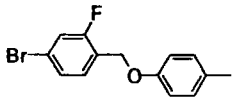
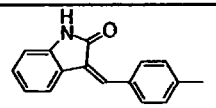
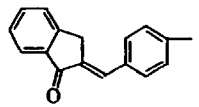
Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr, cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcd. / Found
21	yellow crystals	52		H	204-205.5 (dec) (E/DMF)	349(M^+), 178, 149, 105, 77	3010, 2910, 2760, 2200, 1725, 1620, 1610, 1590, 1480, 1445, 1345, 1290, 1280, 1230, 1180, 1150, 750, 720, 690, 520	3.05(2H,t,J=6.5Hz), 4.25(2H,t,J=6.5Hz), 6.85-7.60(9H,m), 8.01(1H,s)	$C_{19}H_{15}N_3O_2S$ (349.414)	H 4.33, C 65.31, N 12.03 H 4.48, C 65.34, N 12.09
22	pale yellow crystals	84		H	218-219 (dec) (E/DMF)	321(M^+), 226, 197, 149, 121, 77	3500-2700, 2200, 1730, 1580, 1505, 1490, 1360, 1295, 1260, 1200, 1170, 745, 530, 480	4.00-4.80(1H,br), 7.00-7.53(7H, m), 7.66(2H,d,J=9Hz), 7.84(1H,s)	$C_{17}H_{11}N_3O_2S$ (321.36)	H 3.45, C 63.53, N 13.08 H 3.79, C 63.69, N 12.93
23	orange-yellow crystals	84		H	195-195.5 (E/DMF)	379(M^+), 274, 180, 105, 79	3050, 2950, 2790, 2195, 1720, 1700, 1590, 1580, 1510, 1435, 1340, 1270, 1250, 1220, 1170, 1145, 1020, 720, 545, 485	3.06(2H,t,J=7Hz), 3.83(3H,s), 4.22(2H,t,J=7Hz), 6.95-7.50(8H,m), 7.77(1H,s)	$C_{20}H_{17}N_3O_3S$ (379.44)	H 4.52, C 63.31, N 11.07 H 4.73, C 63.64, N 11.00
24	pale yellow crystals	59		H	275 (dec) (E/DMF)	348(M^+), 256, 161, 133, 91	3050, 2950, 2770, 2190, 1735, 1650, 1595, 1530, 1500, 1440, 1345, 1320, 1295, 1240, 1180, 770, 720, 690, 585, 565, 540	4.15-5.40(2H,br), 6.95-7.62(3H,m), 7.62-8.30(7H,m)	$C_{18}H_{12}N_4O_2S$ (348.386)	H 3.47, C 62.06, N 16.08 H 3.71, C 62.11, N 15.92
25	yellow crystals	79		H	295-296 (dec) (DMF)	331[(M-1)$^+$], 236, 204, 158, 113, 79, 51	3050, 2925, 2900-2300, 2175, 1730, 1640, 1610, 1510, 1470, 1425, 1320, 1300, 1270, 1250, 1210, 1175, 980, 820, 600, 545	7.30-8.90(m)	$C_{18}H_{12}N_4OS \cdot 1/3H_2O$ (338.392)	H 3.77, C 63.89, N 16.56 H 4.03, C 63.70, N 16.32
26	yellow crystals	65		H	194-195 (E)	409(M^+), 305, 210, 105, 79	3050, 3025, 2940, 2830, 2760, 2195, 1730, 1700, 1600, 1500, 1450, 1420, 1320, 1240, 1185, 1155, 1130, 990, 730, 700, 560, 545, 530	2.97(2H,t,J=7Hz), 3.81(6H,s), 4.18(2H,t,J=7Hz), 6.90(2H,s), 7.10-7.40(5H,m), 7.80(1H,s)	$C_{21}H_{19}N_3O_4S$ (409.466)	H 4.68, C 61.60, N 10.26 H 4.75, C 61.64, N 10.19
27	orange plates	79		H	202.5-203.5 (dec) (E)	362(M^+), 105, 77	3050, 2935, 2755, 2195, 1730, 1600, 1515, 1350, 1300, 1290(sh), 1245, 1180, 1105, 720	3.42(3H,s), 5.50-6.40(1H,br), 7.28(1H,s), 7.30(2H,d,J=8Hz), 7.54(2H,d,J=8Hz), 7.78(1H,s)	$C_{19}H_{14}N_4O_2S \cdot 1/2C_2H_5OH$ (385.448)	H 4.45, C 62.32, N 14.54 H 4.56, C 62.19, N 14.16
28	light brown crystals	95		H	270-271 (E/DMF)	433[(M+2)$^+$], 431(M^+), 189, 187, 149, 107	3060, 2940, 2800, 2230, 1720, 1635, 1618, 1600, 1520, 1361, 1298, 1273, 1255, 1180, 1002, 897, 852, 840, 540	3.62(1H,br), 5.22(2H,s), 7.23(2H,d,J=9Hz), 7.42-7.78(5H,m), 7.83(1H,s)	$C_{18}H_{11}BrFN_3O_2S$ (432.273)	H 2.56, C 50.01, N 9.72 H 2.87, C 50.22, N 9.68
29	orange crystals	65		H	>300 (E/DMF)	372(M^+), 277	3320, 3050, 2940, 2750, 2190, 1720, 1690, 1640, 1590, 1465, 1380, 1345, 1330, 1290, 1245, 1190, 1100, 795, 760, 725, 600, 525		$C_{20}H_{12}N_4O_2S \cdot 1/2C_3H_7NO$ (408.956)	H 3.82, C 63.15, N 15.41 H 4.12, C 62.96, N 15.40
30	pale yellow crystals	68		H	>300 (DMF)	371(M^+), 276, 247, 213, 139, 114, 89	3050, 2930, 2770, 2190, 1730, 1690, 1610, 1590, 1505, 1415, 1345, 1325, 1290, 1265, 1240, 1195, 1180, 1090, 735, 720, 600, 540		$C_{21}H_{13}N_3O_2S$ (371.42)	H 3.53, C 67.91, N 11.31 H 3.88, C 68.11, N 11.12

Table 4.

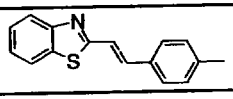
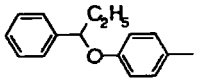
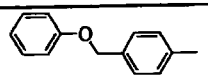
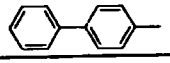
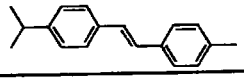
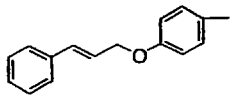
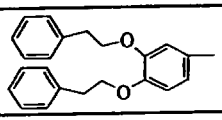
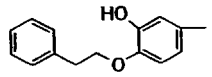
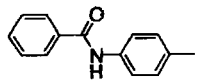
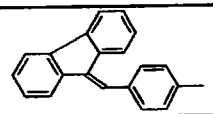
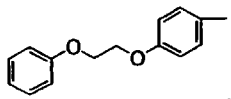
Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr, cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcd. / Found
31	yellow crystals	79		H	>300 (DMF)	388(M^+), 294, 292, 260, 249, 236, 163, 149, 77	3050, 3020, 2950, 2750, 2190, 1725, 1595, 1510, 1415, 1350, 1320, 1290, 1240, 1190, 1175, 760, 720, 565, 550	7.40-8.50(m)	$C_{20}H_{12}N_4OS_2 \cdot 1/3C_3H_7NO$ (412.84)	H 3.50, C 61.10, N 14.70 H 3.71, C 61.02, N 14.57
32	pale yellow crystals	70		H	144-145.5 (EA/H)	363(M^+), 244, 210, 149	2960, 2930, 2200, 1730, 1598, 1507, 1357, 1259, 1177, 1000, 978, 829, 705, 523	0.90(3H,t,J=7.2Hz), 1.61-2.10(2H, m), 4.40(1H,br), 5.35(1H,t,J=6.2 Hz), 7.05(2H,d,J=8.4Hz), 7.33(5H ,s), 7.50(2H,d,J=8.4Hz), 8.73(1H,s)	$C_{20}H_{17}N_3O_2S$ (363.441)	H 4.71, C 66.10, N 11.56 H 4.89, C 66.00, N 11.38
33	yellow crystals	94		H	238.5-240 (E/DMF)	335(M^+), 250, 240, 173, 147	3040, 2945, 2770, 2205, 1730, 1603, 1498, 1358, 1338, 1300, 1250, 1180, 810, 753, 514	5.19(2H,s), 5.53(1H,br), 6.94-7.53(5H,m), 7.63(4H,s), 7.86(1H.s)	$C_{18}H_{13}N_3O_2S$ (335.387)	H 3.91, C 64.46, N 12.53 H 4.07, C 64.44, N 12.17
34	yellow crystals	93		H	253.5-255 (E/DMF)	305(M^+), 210	3045, 2950, 2750, 2200, 1737, 1595, 1490, 1339, 1179, 770, 640, 560, 547	4.32(1H,br), 7.33-7.95(9H,m), 7.91(1H,s)	$C_{17}H_{11}N_3OS$ (305.361)	H 3.63, C 66.87, N 13.76 C 66.93, H 3.96, N 13.70
35	orange crystals	82		H	240 (dec) (E/A)	373(M^+), 358, 278, 263, 230, 202, 129, 91, 68	3020, 2955, 2760, 2200, 1730, 1585, 1510, 1340, 1295, 1245, 1190, 1170, 830, 555	1.20(6H,d,J=7Hz), 2.92(1H, septet), 3.60-4.50(1H,br), 7.15-7.90(11H,m)	$C_{22}H_{19}N_3OS$ (373.48)	H 5.13, C 70.75, N 11.25 H 5.29, C 70.81, N 11.21
36	pale yellow crystals	85		H	219.5-220.5 (dec) (E/DMF)	361(M^+), 150, 117, 91	3100, 3050, 2950, 2780, 2195, 1710, 1590, 1580, 1560, 1510, 1360, 1250, 1205, 1175, 1000, 970, 835, 730, 550	3.50-5.00(1H,br), 4.83(2H,d, J=5 Hz), 6.45-6.80(2H,m), 7.18(2H,d, J=9Hz), 6.90-7.80(5H,m), 7.63 (2H,d,J=9Hz,2,6-H), 7.82(1H,s)	$C_{20}H_{15}N_3O_2S$ (361.425)	H 4.19, C 66.50, N 11.63 H 4.40, C 66.46, N 11.41
37	yellow crystals	37		H	161.5-162.5 (E)	469(M^+), 364, 267, 105, 77	3050, 3005, 2930, 2750, 2190, 1720, 1590, 1500, 1460, 1345, 1300, 1270, 1250, 1210, 1165, 1135, 1010, 745, 715, 690	3.04(4H,t,J=6.5Hz), 4.00-4.45(4H,m), 6.90-7.60(13H,m), 7.78(1H,s)	$C_{27}H_{23}N_3O_3S$ (469.565)	H 4.94, C 69.06, N 8.95 H 5.09, C 69.02, N 8.64
38	orange-yellow crystals	73		H	189.5-190.5 (dec) (M)	365(M^+), 166, 105, 79	3050, 2930, 2770, 2200, 1720(sh), 1710, 1595, 1505, 1455, 1360, 1280, 1250, 1210, 1170, 1135, 1010, 720, 700, 510	3.09(2H,t,J=7Hz), 4.27(2H,t,J=7Hz), 6.90-7.55(8H,m), 7.71(1H,s)	$C_{19}H_{15}N_3O_3S$ (365.413)	H 4.14, C 62.45, N 11.50 H 4.30, C 62.16, N 11.13
39	orange-yellow crystals	57		H	297 (dec) (E/DMF)	348(M^+), 197, 148, 105	3060, 2950, 2930, 2770, 2195, 1720, 1705, 1655, 1590, 1510, 1485, 1415, 1350, 1320, 1295, 1240, 1185, 710, 630, 610, 535	7.40-8.20(m)	$C_{18}H_{12}N_4O_2S$ (348.386)	H 3.47, C 62.06, N 16.08 H 3.74, C 62.12, N 15.86
40	orange crystals	55		H	257-259 (dec) (E/DMF)	405(M^+), 310, 253, 165	3050, 2950, 2760, 2200, 1715, 1595, 1445, 1350, 1290, 1240, 1190, 1170, 775, 730, 610, 540	3.50-4.35(1H,br), 6.95-8.15(14H,m)	$C_{25}H_{15}N_3OS \cdot C_2H_5OH$ (451.55)	H 4.69, C 71.82, N 9.31 H 4.80, C 72.12, N 9.18
41	yellow crystals	80		H	225-226.5 (dec) (E/DMF)	365(M^+), 270, 245, 176, 150, 121, 93, 77	3120, 3060, 2945, 2780, 2190, 1710, 1600, 1505, 1485, 1450, 1360, 1260, 1250, 1230, 1200, 1170, 1065, 955, 830, 760, 725, 540	4.37(4H,br), 6.80-7.47(7H,m), 7.47-7.75(3H,m) *4	$C_{19}H_{15}N_3O_3S$ (365.413)	H 4.14, C 62.45, N 11.50 H 4.32, C 62.39, N 11.44

Table 5.

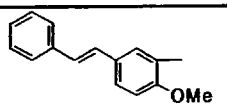
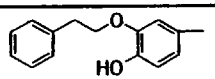
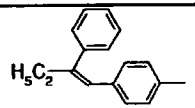
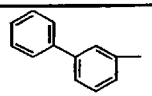
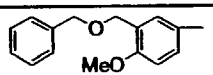
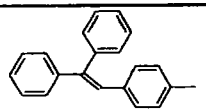
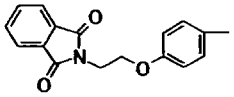
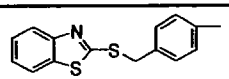
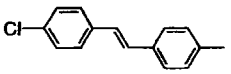
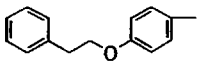
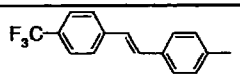
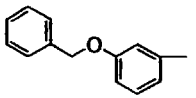
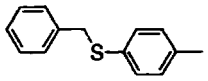
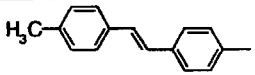
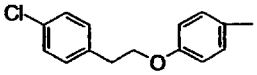
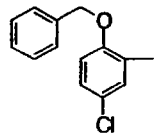
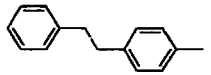
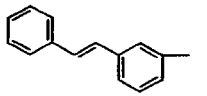
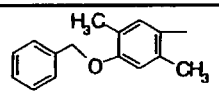
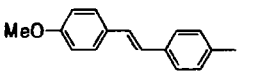
Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr, cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcd. / Found
42	orange crystals	76		H	273-275 (dec) (E/DMF)	361(M^+), 189, 177, 165, 147	3045, 2975, 2210, 1710, 1600, 1512, 1365, 1282, 1252, 1219, 1199, 1036, 970, 823, 730, 540	3.93(3H,s), 5.25(1H,br), 7.11-7.92(10H,m), 7.93(1H,s)	$C_{20}H_{15}N_3O_2S$ (361.425)	H 4.18, C 66.47, N 11.63 H 4.44, C 66.43, N 11.27
43	yellow crystals	76		H	206-207 (dec) (E)	365(M^+), 166, 105, 79	3050, 2940, 2760, 2195, 1705, 1570, 1510, 1350, 1300, 1285, 1220, 1190, 1125, 720, 695	3.10(2H,t,J=7Hz), 4.27(2H,t,J=7Hz), 6.90-7.60(8H,m), 7.79(1H,s)	$C_{19}H_{15}N_3O_3S$ (365.413)	H 4.14, C 62.45, N 11.50 H 4.28, C 62.26, N 11.33
44	brown crystals	49		H	198-200 (E/DMF)	359(M^+), 344, 330, 283, 264, 249, 216, 188, 147, 129, 116, 114, 91	3050, 2955, 2760, 2200, 1733, 1597, 1350, 1297, 1223, 1190, 700	1.01(3H,t,J=7Hz), 2.52(2H,m), 4.19(1H,br), 6.54(1H,s), 6.92-7.69(9H,m), 7.73(1H,s)	$C_{21}H_{17}N_3OS$ (359.453)	H 4.77, C 70.17, N 11.69 H 4.96, C 70.15, N 11.52
45	yellow crystals	85		H	242-243 (E/DMF)	305(M^+), 304, 210, 165	3130, 3060, 2980, 2200, 1703, 1604, 1594, 1353, 1240, 760, 720, 700, 542	5.43(1H,br), 7.38-7.93(9H,m), 7.96(1H,s)	$C_{17}H_{11}N_3OS$ (305.361)	H 3.63, C 66.87, N 13.76 H 3.99, C 66.96, N 13.49
46	reddish brown crystals	55		H	183.5-185 (E/DMF)	379(M^+), 289, 273, 244, 178, 147, 91	3080, 2955, 2205, 1735, 1597, 1502, 1363, 1274, 1205, 1140, 1110, 1037, 742, 560, 493	3.87(3H,s), 4.56(2H,s), 4.62(2H,s), 7.04-7.71(8H,m), 7.80(1H,s)	$C_{20}H_{17}N_3O_3S$ (379.44)	H 4.52, C 63.31, N 11.07 H 4.64, C 63.20, N 10.79
47	yellow crystals	62		H	238-239 (E/DMF)	407(M^+), 312, 235, 203	3050, 2200, 1736, 1600, 1500, 1343, 1330, 1297, 1188, 772, 707, 640, 616, 550	4.55(1H,br), 6.89-7.60(15H,m), 7.77(1H,s)	$C_{25}H_{17}N_3OS$ (407.497)	H 4.20, C 73.69, N 10.31 H 4.47, C 73.83, N 10.00
48	pale yellow crystals	71		H	235-236 (dec) (E/DMF)	418(M^+), 174, 130, 78	3050, 2950, 2760, 2195, 1770, 1710, 1590, 1510, 1390, 1350, 1250, 1170, 1120, 720	3.90-4.50(4H,m), 7.04(2H,d,J=8.5Hz), 7.53(2H,d,J=8.5Hz), 7.60(1H,s), 7.88(4H,s) *4	$C_{21}H_{14}N_4O_4S$ (418.433)	H 3.37, C 60.28, N 13.39 H 3.62, C 60.27, N 13.10
49	pale yellow crystals	70		H	200-201.5 (E/DMF)	408(M^+), 375, 280, 242, 147, 91	3060, 2930, 2750, 2190, 1730, 1640, 1600, 1455, 1430, 1350, 1295, 1245, 1195, 1180, 1000, 760, 715, 545	4.71(2H,s), 7.18-7.80(8H,m), 7.80-8.10(2H,m) *4	$C_{19}H_{12}N_4OS_3 \cdot 2/3C_3H_7NO$ (457.26)	H 3.67, C 55.16, N 14.30 H 3.75, C 55.46, N 14.00
50	yellow crystals	79		H	>300 (DMF)	365(M^+), 272, 270, 234, 202, 178	3040, 2930, 2760, 2220, 1736, 1617, 1590, 1357, 1298, 1181, 1094, 838, 734, 538	3.92(1H,br), 7.20-7.87(10H,m), 7.83(1H,s)	$C_{19}H_{12}ClN_3OS$ (365.844)	H 3.31, C 62.38, N 11.49 H 3.53, C 62.48, N 11.46
51	yellow amorphous	18 *1		Me	69-71	363(M^+), 164	3070, 2950, 2200, 1722, 1600, 1515, 1342, 1250, 1178, 1020, 836, 754, 700, 540	2.67(3H,s), 3.06(2H,t,J=6Hz), 3.86(1H,br), 4.28(2H,t,J=6Hz), 7.06(2H,d,J=9Hz), 7.30(5H,s), 7.46(2H,d,J=9Hz)	$C_{20}H_{17}N_3O_2S \cdot 1/4H_2O$ (367.945)	H 4.79, C 65.29, N 11.42 H 4.86, C 65.47, N 11.02
52	yellow crystals	91		H	275-280 (dec) (E/DMF)	399(M^+), 304, 259, 227	3050, 2940, 2770, 2220, 1740, 1620, 1600, 1323, 1300, 1180, 1121, 1070, 838, 727, 526	4.40(1H,br), 7.45(2H,s), 7.50-7.90(8H,m), 7.83(1H,s)	$C_{20}H_{12}F_3N_3OS$ (399.393)	H 3.03, C 60.15, N 10.52 H 3.25, C 60.28, N 10.63

Table 6.

Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr, cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcd. / Found
53	pale yellow crystals	94		H	201-202.5 (E/DMF)	335(M^+), 245, 177, 149, 121	3030, 2920, 2770, 2210, 2200, 1720, 1630, 1612, 1491, 1424, 1357, 1300, 1226, 1023, 786, 740, 723, 525	5.18(2H,s), 5.70(1H,br), 7.02-7.65(9H,m), 7.80(1H,s)	$C_{18}H_{13}N_3O_2S$ (335.387)	H 3.91, C 64.46, N 12.53 H 4.09, C 64.35, N 12.37
54	yellow crystals	73		H	282-283 (E/DMF)	351(M^+), 260, 165, 121, 91, 65	3060, 2960, 2790, 2200, 1700, 1592, 1577, 1541, 1494, 1408, 1358, 1300, 1254, 1192, 1089, 832, 814, 723, 589, 570, 554, 525, 437	3.60(1H,br), 4.32(2H,s), 7.15-7.58(9H,m), 7.77(1H,s)	$C_{18}H_{13}N_3OS_2$ (351.454)	H 3.73, C 61.52, N 11.96 H 3.97, C 61.53, N 12.04
55	yellow crystals	86		H	>300 (E/DMF)	345(M^+), 251, 178	3090, 2200, 1720, 1589, 1519, 1352, 1300, 1178, 978, 826, 730, 550	2.32(3H,s), 5.13(1H,s), 7.10-7.73(11H,m)*4	$C_{20}H_{15}N_3OS$ (345.426)	H 4.38, C 69.54, N 12.16 H 4.66, C 70.12, N 11.48
56	orange crystals	69		H	206.5-208.5 (E/DMF)	383(M^+), 244, 149, 139	3060, 2950, 2760, 2180, 1727, 1587, 1510, 1262, 1179, 1018, 826, 797, 723, 540	3.08(2H,t,J=6.8Hz), 4.30(2H,t,J=6.8Hz), 4.30(1H,br), 7.13(2H,d,J=9Hz), 7.38(4H,s), 7.62(2H,d,J=9Hz), 7.83(1H,s)	$C_{19}H_{14}ClN_3O_2S$ (383.859)	H 3.68, C 59.45, N 10.95 H 3.87, C 59.67, N 10.65
57	yellow crystals	79		H	190-191 (E)	369(M^+), 185, 183, 91	3175, 3100, 3080, 3040, 2950, 2770, 2200, 1740, 1593, 1585, 1487, 1460, 1350, 1294, 1252, 1220, 1179, 1027, 935, 750, 742, 721, 550	3.80-5.80(1H,br), 5.26(2H,s), 7.10-7.70(8H,m), 7.91(1H,s)	$C_{18}H_{12}ClN_3O_2S$ (369.832)	H 3.27, C 58.46, N 11.36 H 3.49, C 58.35, N 10.98
58	pale yellow crystals	64		H	212-214 (E/DMF)	333(M^+), 242, 147, 91	3110, 3060, 3030, 2960, 2775, 2200, 1505, 1600, 1588, 1352, 1299, 1251, 1198, 1175, 760, 728, 700	2.92(4H,s), 7.00-7.70(9H,m), 7.82(1H,s)	$C_{19}H_{15}N_3OS$ (333.415)	H 4.53, C 68.45, N 12.60 H 4.72, C 68.70, N 12.37
59	yellow crystals	45		H	247-248 (E/DMF)	331(M^+), 236, 203, 147, 103	3120, 3078, 3055, 3024, 2966, 2790, 2200, 1729, 1705, 1609, 1590, 1355, 1314, 1294, 1265, 1245, 1225, 1200, 1165, 960, 788, 755, 720, 689, 528	5.30-6.40(1H,br), 7.10-8.00(12H,m)	$C_{19}H_{13}N_3OS$ (331.399)	H 3.95, C 68.86, N 12.68 H 4.24, C 68.90, N 12.27
60	orange-yellow crystals	80		H	227-228 (dec) (E/A)	363(M^+), 177, 91	3060, 3040, 2950, 2775, 2195, 1730, 1685, 1590, 1505, 1310, 1270, 1230, 1095, 995, 730	2.22, 2.39(each 3H,s), 5.19(2H,s), 7.07(1H,s), 7.19(1H,s), 7.23-7.65(5H,m), 7.86(1H,s)	$C_{20}H_{17}N_3O_2S$ (363.441)	H 4.71, C 66.10, N 11.56 H 4.97, C 66.34, N 11.34
61	yellow brown crystals	83 *2		Me	203-204 (E/DMF)	375(M^+), 280, 266, 250, 232, 221, 210, 166	3060, 3020, 2930, 2827, 2765, 2189, 1716, 1592, 1519, 1334, 1250, 1216, 1173, 1027, 968, 833, 563, 539	2.71(3H,s), 3.78(3H,s), 6.75-7.85(10H,m)	$C_{21}H_{17}N_3O_2S \cdot 1/3H_2O$ (381.457)	H 4.67, C 66.12, N 11.02 H 4.92, C 66.22, N 10.80

EXAMPLE 2

2-(N-Cyanoimino)-5-[(E)-4-stylylbenzylidene]thiazolidin-4-one potassium salt: potassium salt of the compound 1

The crude product (18.98g) was recrystallized from 65% isopropanol to yield the title compound as yellow powder (10.87g) (compound 62).

mp: > 300 °C (60% Isopropanol)

IR (KBr, cm^{-1}): 3025, 2180, 1650, 1590, 1490, 1420, 1340, 1290, 1205, 1180, 960, 820, 745, 540

NMR (DMSO-*d6*, ppm): δ = 7.25-7.55 (6H, m), 7.55-7.85(6H, m)

EXAMPLE 3

2-(N-Cyanoimino)-5-[(E)-4-stylylbenzylidene]thiazolidin-4-one sodium salt: sodium salt of the compound 1

100g (0.3mol) of compound 1 was dissolved in DMF. To a stirred solution of compound 1, 12.6g (0.3mol) of sodium hydroxide in 50mL of water, and then activated charcoal was added. The activated charcoal was filtered off and the filtrate was concentrated under reduced pressure. The crude product was collected by filtration, washed with methanol and ether, and recrystallized from isopropanol/2-butanol/water to yield the title compound as yellow powder (69.9g) (compound 63).

mp: > 300 °C (Isopropanol/2-butanol/water)

IR (KBr, cm^{-1}): 3025, 2180, 1650, 1585, 1495, 1420, 1340, 1280, 1205, 1180, 960, 815, 745, 540

NMR (DMSO-*d6*, ppm): δ = 7.25-7.52 (6H, m), 7.52-7.85(6H, m)

EXAMPLE 4

Blood sugar lowering actions in genetically diabetic mice:

Genetically diabetic db/db mice(C57BL/ksJ Jcl-dbm db/db mice) older than 8 weeks were grouped depend on their blood sugar levels of the prior measurements in order to divide groups with almost equal mean value of the sugar level. The respective groups of db/db mice were designates as the following groups : the group given the compound of the present invention, the group of troglitazone, and the group given no administrating group.

For the compounds of the present invention, two doses : 75mg/kg and 150mg/kg, and for troglitazone, a dose of 150mg/kg were individually given to the mice as a forced oral administration once daily for 14 days successively. These agents were suspended in 3.0%

Arabic gum solution for administration. To the control group, only the same volume of 3.0% Arabic gum solution was administered. On the next day of the final administration, each mouse was bred for sampling. The blood samples were subject to serum separation. The glucose level in the serum of each group was measured. Then, a reduction rate in a glucose level (%) compared to the control group was calculated with mean value of each group according to the equation below. As a result, it was demonstrated that the compounds of the present invention have the activity to reduce blood sugar levels more effectively than troglitazone (Table 7).

$$\text{Equation : Reduction rate (\%)} = \left\{ 1 - \frac{\text{(mean measured level in each treated group)}}{\text{(mean measured level in control group)}} \right\} \times 100$$

Table 7. Blood sugar lowering effects in genetically diabetic mice

Compound No.	Dose	Reduction in Blood Glucose (%)
1	75 mg/kg	31
	150 mg/kg	37
3	75 mg/kg	24
	150 mg/kg	49
22	75 mg/kg	16
	150 mg/kg	34
63	75 mg/kg	32
troglitazone	150 mg/kg	18

EXAMPLE 5

Differentiation-inducing actions on adipose cells

The cloned cell line 3T3-L1 of the preadipocyte cells at the 9 – 20th generation were used. The cell suspension at a concentration of 2 x 10^4 cells/ml was added 500μl/well in a 24 well microplate. Then, the microplates were cultured at 37°C in the atmosphere of 5% CO_2 for 4 days with D-MEM containing 5% inactivated fetal calf serum (hereinafter abbreviated as "FCS D-MEM"). Next, the following procedures were conducted.

(1) To test compound of this invention, 500μl/well of the following solutions was added to each well:

1) test compound -containing medium (T-MEM) in which the test compound in a stock solution (30mM in DMSO) was diluted with FCS D-MEM containing 0.1μM dexamethazone and 100ng/ml insulin (hereinafter abbreviated as DEX-Ins-FCS D-MEM); 2) FCS-D-MEM; 3) DEX-Ins-FCS D-MEM; 4) 0.1% DMSO-containing DEX-Ins-FCS

D-MEM for me control wells.

(2)After above additions done, the culture plates were incubated at 37°C in 5% CO_2 for 3 days. Then, the same operations as in the procedure (1) were repeated for exchange of the culture medium. the culture plates were incubated at 37°C in 5% CO_2 for further 3 days.

(3)After incubation, the culture medium was removed from the culture plates. Then, the FCS D-MEM was added to the FCS D-MEM–wells, and next the medium prepared for containing 100ng/ml of insulin with the FCS D-MEM(hereinafter abbreviated as "Ins-FCS D-MEM") was added at 500μl/well to the T-MEM wells and DEX-Ins-FCS D-MEM wells. All culture plates were incubated for 4 days.

(4)After incubation, the culture medium was removed. For cell fixation, 500μl/well of 10% formalin in neutral buffer was added, and left at the room temperature for approximately 20 minutes or longer. Then the formalin solution was removed, and 60% 2-propanol solution was added at 500μl/well, then quickly removed, the oil red-O staining solution was added at 250μl/well. The culture plates were sealed with plate seals, and left at room temperature for 30 minutes or longer. After incubation, the staining solution was removed, and the 60% 2-propanol solution was added at 500μl/well, and quickly removed. The cells were rinsed with water a few times, and then water drops were flipped away. A cell-lysis buffer was added at 500μl/well, and the culture plates were sealed with plate seals, and left at 37°C for 1 hour to extract the pigments. Next, 300μl/well of the extract solution was transferred at a 96 well micro-plates, and then the absorbance of each extract was measured at wavelength of 490nm.

The absorbance ratios of the respective test compounds-groups to the control group, the mean absorbance of which was designated as 1.0, are shown in Table 8. Based on the judgement that the absorbance higher than that of the control group indicates a greater differentiation-inducing activity of the test compound, the compounds of the present invention were determined to have the activity to induce differentiation of preadipocytes to adipocytes, resulting in elevating insulin sensitivity of organs. Thereby, this activity would confer the efficacy in the therapy of diabetes.

Table 8. Activities to induce differentiation of preadipocytes to adipocytes

Compound No.	Absorbance Ratio	Compound No.	Absorbance Ratio
1	1.46	16	1.18
2	1.57	19	1.51
3	1.48	21	2.02
4	2.62	22	1.73
5	1.87	26	1.09
7	1.93	34	1.40
8	1.95	42	2.01
10	2.12	44	1.83
12	1.74	45	1.14
13	2.51	47	1.24
Control	1.00		

EXAMPLE 6

Antihyperlipidemic activities in genetically diabetic mice

In the same way as described in EXAMPLE 4, db/db mice were grouped in the manner by which the respective groups had almost equivalent mean blood sugar levels. The compounds 1, 3, 13, 21 and 22 of the present invention, suspended in 3.0% Arabic gum solution, were orally administrated, with a dose of 150mg/kg, once daily for successive 14 days. The control group of mice were given the vehicle solution onby. On the next day of the final administration, each mouse was bled for sampling. The blood was subjected for serum separation, and then subjected to measurements of β-lipoproteins, free fatty acids, and triglycerides. The reduction rate (%) of each measurement compared to treat of the control group was calculated by the equation indicated in EXAMPLE 4. As a result, it was demonstrated that the compounds of the present invention reduced β-lipoproteins, free fatty acids, and triglycerides in the genetically diabetic mice. (Table 9).

Table 9. Antihyperlipidemic activities in genetically diabetic mice

Compound No.	Reduction Rate (%)		
	β-lipoproteins	Free Fatty Acids	Triglycerides
1	51	39	69
3	65	58	85
13	65	38	70
21	38	25	41
22	56	41	65

At a dose of 150 mg/kg p.o.

EXAMPLE 7

Hypotriglyceridemic activity in fructose-induced hyperlipidemic rats

The compounds were tested for a hypotriglyceridemic activity in fructose-induced hyperlipidemic rats in accordance with the method described in Nippon Yakurigaku Zasshi, 92 (3), 175-180 (1988). Sprague Dawley rats were grouped by the ranking method of body weight. Then, instead of drinking water, rats were given 75% fructose aqueous ad libitum for one week, thereby, resulting in the state of hypertriglyceridemia. The compounds of the present invention, suspended in 3% Arabic gum aqueous solution, and a dose of 30mg/kg was orally administrated once daily for 7 days during the fructose-loading period. The control group of rats were given 3% Arabic gum aqueous solution only. Two hours later of the final administration, the rats were bled from the abdominal aorta to measure serum triglycerides and total cholesterol. The results obtained are shown in Table 10. The reduction rate (%) of each measurement compared to the control groups was calculated according to the equation indicated in EXAMPLE 4. These results have demonstrated that the compounds of the present invention have the activity to lower serum triglycerides in hyperlipidemic rats.

Table 10. The hypotriglyceridemic activity in fructose induced hyperlipidemic rats

Compound No.	Reduction in Serum Triglyceride (%)	Compound No.	Reduction in Serum Triglyceride (%)
1	47	20	54
2	67	21	48
3	64	22	65
4	42	26	46
6	84	28	36
7	60	32	47
8	47	34	71
9	49	37	41
10	39	39	57
11	62	40	42
12	59	43	67
13	55	45	43
14	36	47	69
15	47	49	39
16	54	51	67
17	37	52	44
19	38		

At a dose of 30 mg/kg p.o.

EXAMPLE 8

Lipid lowering effects in high cholesterol-fed hamsters

According to the method described in Jpn Pharmacol Ther, 23 (suppl 4), s1047-1053 (1995), male syrian hamstars were fed for 3 weeks with 1% cholesterol 10% coconut oil (W/W) supplemented diet, and thereby, became to be hypercholesterolemia models. Prior to administration of the compounds, under ether anesthesia, the hamsters were bled from the orbital vein for measurement of serum total cholesterol. They were grouped in the manner by which the respective groups had almost equal serum total cholesterol levels. The normal group of hamsters were fed ordinary diet. Thereafter, the compound 1 and bezafibrate were orally administered once daily at doses of 15 (for only compound 1), 30, 60 and 120mg/kg for 7 days. Even during the treatment period, cholesterol loading was continued. Four hours later of the final administration, the hamsters were bled by cardiac puncture. The total cholesterol and triglycerides in the serum obtained were measured by the enzymatic method. The results are shown in Table 11 (the negative values mean elevation rates.)

These results demonstrate that the compounds of the present invention have the activity to lower serum cholesterol and triglycerides serums more efficiently than bezafibrate.

Table 11. Effect of the compound 1 and bezafibrate on serum lipid levels in high cholesterol-fed hamsters

Compound	Bezafibrate		Compound 1	
Activity	Reduction Rate (%)*			
Dose	Total cholesterol	Triglyceride	Total cholesterol	Triglyceride
15 mg/kg	-	-	26	60
30 mg/kg	-5	-21	25	62
60 mg/kg	-0	-18	29	69
120 mg/kg	20	16	41	80

*: The negative values mean elevation rate.

EXAMPLE 9

Lipid lowering effects in high cholesterol-fed hamsters

The actions of the compounds of the present invention at a dose of 15mg/kg were measured in the same method as described in EXAMPLE 8. The results are shown in Table 12.

Table 12. Hypolipidemic effects in high cholesterol-fed hamsters

Compound No.	Reduction Rate (%)	
	Total cholesterol	Triglyceride
2	27	57
3	16	17
7	18	12
9	15	15
14	11	24
15	32	61

At a dose of 15 mg/kg p.o.

EXAMPLE 10

Acute toxicity tests with single dosing in mice

The compounds (the compound 1 and 10) of the present invention were singly orally administered to each mouse at a dose of 2000mg/kg. Then, the mice were observed for 2 weeks. The result was that all 3 mice given the respective compounds survived.

EXAMPLE 11

Mutagenesis tests

In order to examine mutagenecity of the compound 1, the reverse mutation test was conducted with use of Salmonella typhimurium TA100 and TA98.

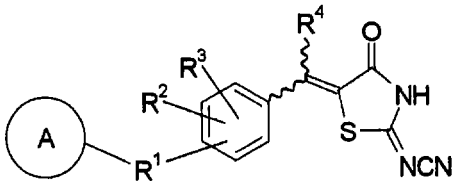
In the group of the compound 1 treatment, neither of the strains [in the direct method(-s9mix) and also in the metabolically activated method(+s9mix)] did not give rise to an increased number of reversely mutated colonies, therefore, the compound 1 was determined to be non-mutagenic.

INDUSTRIAL UTILIZATION

As mentioned above, 2-(N-cyanoimino)thiazolidin-4-one derivatives, solvates, and pharmaceutically acceptable salts thereof, provided by the present invention, are useful as therapeutic agents for diabetes, especially as therapeutic agents for the diabetes patients with accompanying complications related to hyperlipidemia such as hypertriglyceridemia and hypercholesterolemia.

CLAIMS

1. A pharmaceutical composition for the treatment of diabetes comprising a 2-(N-cyanoimino)thiazolidin-4-one derivative represented by formula I or a solvate or a pharmaceutically acceptable salt thereof as an active ingredient and a pharmaceutically acceptable carrier:



I

wherein ring A represents a benzene ring, a condensed ring, or a heterocyclic ring, each of which may be substituted by one or more substituents selected from a straight or branched C_1 - C_4 alkyl group, a haloalkyl group, a halogen atom or $-OR^5$,

R^1 represents a single bond, an oxygen atom, a sulfur atom, a methyne group, a straight or branched C_1 - C_4 alkylene or alkenylene group optionally substituted by a phenyl group, R^6-X, X-R^6, X-R^6-X, R^6-X-R^6, -C(=O)-NR^7- or -NR^7-C(=O)-,

R^2 and R^3 are the same or different and each represents a hydrogen atom, a C_1 - C_4 alkyl group, $-OR^8$ or a halogen atom,

R^4 represents a hydrogen atom or a C_1 - C_4 alkyl group,

R^5 represents a hydrogen atom or a C_1 - C_4 alkyl group,

R^6 represents a straight or branched C_1 - C_4 alkylene or alkenylene group,

R^7 represents a hydrogen atom or a C_1 - C_4 alkyl group,

R^8 represents a hydrogen atom, a C_1 - C_4 alkyl group or an aralkyl group,

X represents an oxygen atom or a sulfur atom,

the configuration of the exocyclic methylene group at 5-position of the thiazolidine ring includes both E- and Z-configuration.

2. A pharmaceutical composition for the treatment of diabetes comprising a 2-(N-cyanoimino)thiazolidin-4-one derivative according to claim 1 or a solvate or a pharmaceutically acceptable salt thereof as an active ingredient and a pharmaceutically acceptable carrier, wherein ring A represents a benzene ring which may be substituted by one or more substituents selected from a straight or branched C_1 - C_4 alkyl group, a haloalkyl group, a halogen atom or $-OR^5$; R^5 represents a hydrogen atom or a C_1 - C_4 alkyl group.

3. A pharmaceutical composition for the treatment of diabetes comprising a

2-(N-cyanoimino)thiazolidin-4-one derivative according to claim 1 as an active ingredient, which selected from:

2-(N-Cyanoimino)-5-[(E)-4-styrylbenzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(α-methylstyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(benzyloxymethyl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(β-methylstyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(3-phenylpropoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(4-chlorophenoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(4-phenylthiobenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(2-fluorostyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(2,5-dimethylphenoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(4-phenethyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(2-phenylpropoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(3-phenethyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-(4-benzyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(5-chlorobenzofuran-2-yl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-4-(4-methoxystyryl)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(3-phenoxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(1,3-benzodioxol-5-ylmethoxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(4-methylbenzyloxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(4-chlorobenzyloxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[3-methoxy-(E)-4-styrylbenzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(2-phenethyloxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-(4-phenoxybenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[3-(benzyloxy)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-(benzylthio)benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(4-phenethylbenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[4-[2-(4-chlorophenyl)ethoxy]benzylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-[1-[(E)-4-(4-methoxystyryl)phenyl]ethylidene]thiazolidin-4-one;

2-(N-Cyanoimino)-5-(4-benzyloxy-2,5-dimethylbenzylidene)thiazolidin-4-one;

2-(N-Cyanoimino)-5-[(E)-3-styrylbenzylidene]thiazolidin-4-one;

and a pharmaceutically acceptable carrier.

4. A pharmaceutical composition for the treatment of diabetes according to claim 1, wherein the 2-(N-cyanoimino)thiazolidin-4-one derivative is 2-(N-cyanoimino)-5-[(E)-4-styrylbenzylidene]thiazolidin-4-one.

5. A pharmaceutical composition for the treatment of diabetes according to claim 1, wherein the diabetes is non-insulin dependent diabetes mellitus.

6. A pharmaceutical composition for the treatment of diabetes according to claim 2, wherein the diabetes is non-insulin dependent diabetes mellitus.

7. A pharmaceutical composition for the treatment of diabetes according to claim 3, wherein the diabetes is non-insulin dependent diabetes mellitus.

8. A pharmaceutical composition for the treatment of diabetes according to claim 4, wherein the diabetes is non-insulin dependent diabetes mellitus.

9. A pharmaceutical composition for the treatment of diabetes according to claim 1, which is characterized by having hypolipidemic and hypoglycemic activity.

10. A pharmaceutical composition for the treatment of diabetes according to claim 2, which is characterized by having hypolipidemic and hypoglycemic activity.

11. A pharmaceutical composition for the treatment of diabetes according to claim 3, which is characterized by having hypolipidemic and hypoglycemic activity.

12. A pharmaceutical composition for the treatment of diabetes according to claim 4, which is characterized by having hypolipidemic and hypoglycemic activity.

13. A pharmaceutical composition for the treatment of diabetes according to any one of claims 9 to 12, wherein the hypolipidemic activity is hypotriglyceridemic activity.

14. A pharmaceutical composition for the treatment of diabetes according to any one of claims 9 to 12, wherein the hypolipidemic activity is hypocholesterolemic activity.

15. A pharmaceutical composition for the treatment of diabetes patients accompanied with hyperlipidemia according to any one of claims 1 to 12.

16. A pharmaceutical composition for the treatment of diabetes patients accompanied with hypertriglyceridemia according to any one of claims 1 to 12.

17. A pharmaceutical composition for the treatment of diabetes patients accompanied with

hypercholesterolemia according to any one of claims 1 to 12.

18. A pharmaceutical composition for the treatment of diabetes patients accompanied with vascular diseases caused by hyperlipidemia according to any one of claims 1 to 12.