Translation of Japanese Description into English.

DESCRIPTION

150150

G00001

Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives

TECHINICAL FIELD

The invention relates to novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or pharmaceutically acceptable salts or solvates thereof, which have excellent activities in a lowering blood triglyceride level and a cholesterol level, and are useful for prevention from and/or treatment of hyperlipidemia and related complications.

BACKGROUND ART

Many epidemiological studies have shown that hypercholesterolemia is a risk factor for coronary heart disease (CHD). Recently, hypertriglycemia is confirmed to be an independent risk factor for CHD. (J Jpn Atheroscler Soc, 25 (1 · 2), 1-34 (1997) -- Guideline for Diagnosis and Treatment of Hyperlipidemias in Adults).

For the therapy of hypertriglycemia, dextran sulfate sodium, nicotinic acid derivatives, fibric acid derivatives (fibrates) have been used as the first choice. In particular bezafibrate is known to have more potent cholesterol lowering property as well as triglyceride lowering property than the earlier fibrates. And for hypercholesterolemia, HMG-CoA reductase inhibitors (e.g. pravastatin, simvastatin, etc., known as statins) are generally provided for clinical use.

When blood cholesterol level alone is elevated, HMG-CoA reductase inhibitors are employed. However, when both levels of blood cholesterol and triglyceride are elevated or the effect of hypolipidemic agent is not sufficient, some lipid lowering drugs are combined.

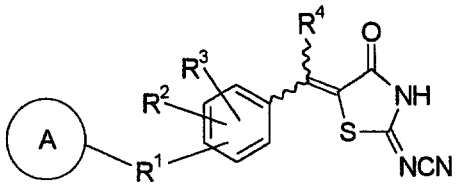
Thus, an aim of the present invention is to provide a novel class of potent hypolipidemic agents, which reduce more effectively a blood triglyceride level or both levels of blood triglycerides and cholesterol.

Some antidiabetic agents that are partially analogous to the compounds of the present invention have been found and developed, for example, troglitazone and pioglitazone. However, they are thiazolidin-2,4-dione derivatives, and according to the conference abstract of the 28th Meeting of the Japan Atherosclerosis Society, Osaka, June, 1996, No.024, pioglitazone did not change total cholesterol and triglyceride levels in hyperlipidemic rabbits. Therefore, from a view of chemical and biological properties, the compounds of the present invention are considered to be different from those antidiabetic compounds.

DISCLOSURE OF INVENTION

This invention provides prophylactic or therapeutic agents for hyperlipidemia and

related complications comprising novel 2-(N-cyanoimino)thiazolidin-4-one derivatives represented by formula I or a pharmaceutically acceptable salt or solvate thereof as active ingredients:



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 present inventors have carried out various investigations to solve the above problem and found that the novel 2-(N-cyanoimino)thiazolidin-4-one derivatives represented by formula I have excellent blood triglyceride lowering and cholesterol lowering activities. Thus the present invention was successfully established.

BEST MODE FOR CARRYINFG OUT THE INVENTION

"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.

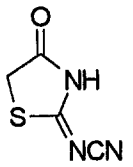
Particularly preferred compounds represented by formula I are as follows:

2-(N-Cyanoimino)-5-[(E)-4-stylylbenzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-4-(a-methylstylyl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(benzyloxymethyl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-4-(b-methylstylyl)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-fluorostylyl)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-methoxystylyl)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-stylylbenzylidene]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-methoxystylyl)phenyl]ethylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-(4-benzyloxy-2,5-dimethylbenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-3-stylylbenzylidene]thiazolidin-4-one;

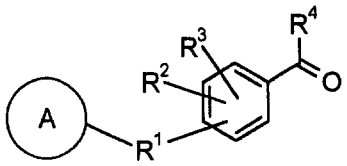
The compounds of the present invention are novel compounds not described in any

literature and can be prepared by the following methods as the example.

A 2-(N-cyanoimino)thiazolidin-4-one represented by formula II or the salts thereof are reacted with an aldehyde or ketone represented by formula III



II



III

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 reaction can be carried out in a suitable solvent such as ethanol, acetonitrile, 1,4-dioxane, N,N-dimethylformamide, dimethyl sulfoxide, pyridine, toluene, and xylene, alternatively without employing a solvent, in the presence of ammonium acetate at a temperature ranged from ambient temperature to 200°C, preferably from 70°C to 150°C, for a period of time between 10 minutes to 10 hours, usually 20 minutes to 5 hours.

There are geometric isomers for the present compounds, however, in solution, reversible isomerization of C5-double bond of thiazolidine occurs very easily by the action of light or heat.

The compounds of the present invention have excellent activities in lowering blood triglyceride and cholesterol levels and are pharmaceutically useful as therapeutic agents for prevention and/or treatment of hyperlipidemia and related complications.

The compounds of the present invention and pharmaceutically acceptable salts thereof can be orally or parenterally administered either alone or preferably 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.

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 400 mg for adult, and is administered once or in several divided doses a day.

The invention is illustrated by the following examples.

EXAMPLE 1

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

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. hydrogen chloride 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.

The structural formula, yield, and the physical property of the compound are shown in Table 1.

EXAMPLE 2 TO EXAMPLE 61

In substantially the same manner as in Example 1, the compounds shown in Table 1 were obtained.

Their structural formulas, yields, and physical properties are shown in Table 1.

Abbreviations used in Table 1 are defined 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

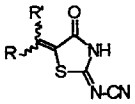
*1: After heating for 10 minutes at 130°C without solvent, the soluble part of reaction mixture in chloroform is chromatographed on a silica gel column.

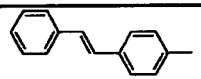
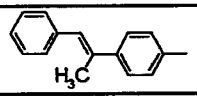
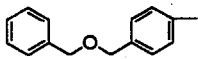
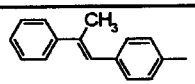
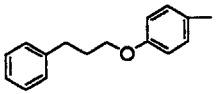
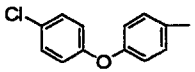
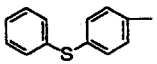
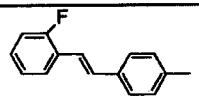
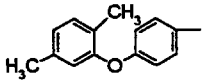
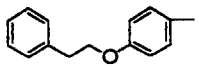
*2: n-Butanol was used as solvent.

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

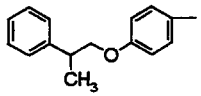
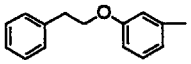
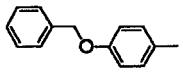
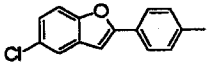
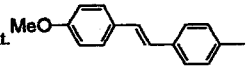
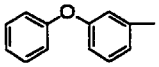
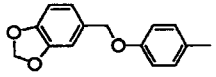
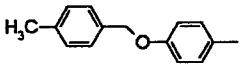
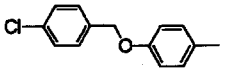
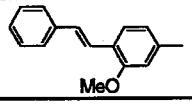
*4: Solvent; 10% Pyridine-*d5* / DMSO-*d6*

Table 1. 2-(N-Cyanoimino)thiazolidin-4-ones

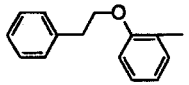
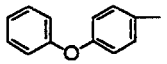
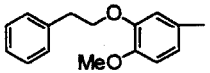
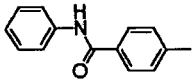
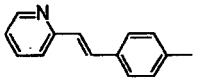
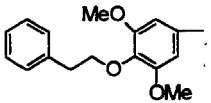
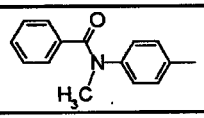
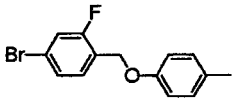
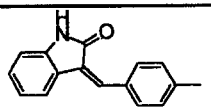
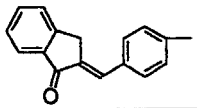


Ex. No.	Description	Yield (%)	R	R'	mp(°C) (recryst solv *3)	EI-MS(m/z)	IR(KBr, cm^{-1})	^{1}H-NMR(DMSO-d6, δ:ppm)	Molecular formula (Molecular weight)	EA(%) Calcld. / Found
1	yellow crystals	88		H	265 (dec) (E-DMF)	331(M^+), 236, 202, 179	3015, 2920, 2740, 2185, 1725, 1580, 1505, 1490, 1340, 1290, 1170, 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

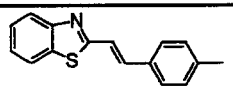
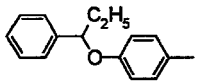
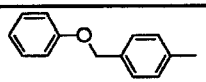
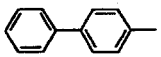
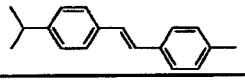
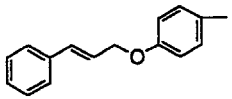
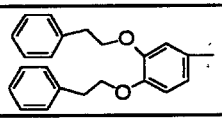
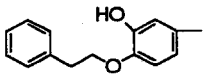
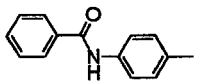
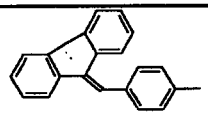
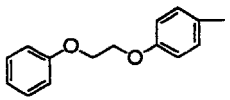
(Continued)

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(%) Calcld. / 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	$C_{20}H_{15}N_3O_2S \cdot 1/2H_2O$ (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

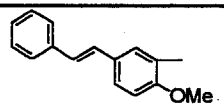
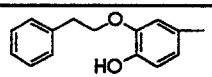
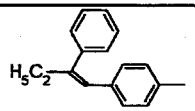
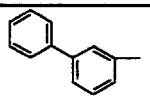
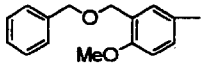
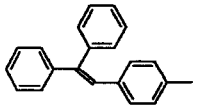
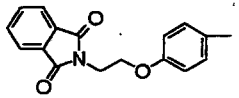
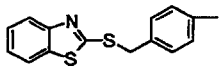
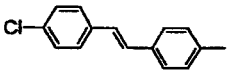
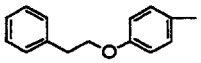
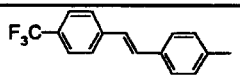
(Continued)

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(%) Calcld. / 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)	$C_{18}H_{12}N_4OS$ · 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)	$C_{19}H_{14}N_4O_2S$ · 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		$C_{20}H_{12}N_4O_2S$ · 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

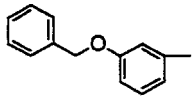
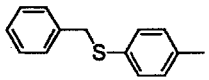
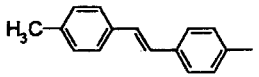
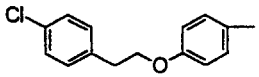
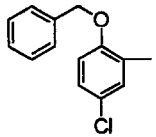
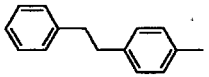
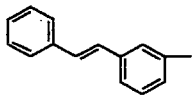
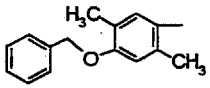
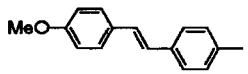
(Continued)

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(%) Calcld. / 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)	$C_{20}H_{12}N_4OS_2$ · 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)	$C_{25}H_{15}N_3OS$ · 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

(Continued)

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(%) Calcld. / 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

(Continued)

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(%) Calcld. / 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 62

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

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

mp: > 300 °C

IR (KBr, cm^{-1}): 3025, 2180, 1750, 1590, 1490, 1420, 1340, 1290, 1205, 1180, 960, 820, 745, 540

^{1}H-NMR (DMSO-*d6*, ppm): δ = 7.25-7.55 (6H, m), 7.55-7.85 (6H, m)

PHARMACOLOGICAL EXAMPLES

EXAMPLE 63

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 divided into experimental groups with a comparable mean body weight. 75% fructose solution as drinking water was given to the animals for 7 days, while normal water was given to the intact groups ad libitum. During the experimental period the test compounds suspended in 3% gum arabic were given to the test group orally once a day in a daily dose of 30 mg/kg. The vehicle solution was given to the control group and the intact group. After 2 hours from the final administration, blood was collected from the abdominal aorta under ether anesthesia, and levels of total cholesterol and triglyceride in the serum were measured. The results are shown in Table 2. The reduction rate (%) was calculated according to the following equation:

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

Above experimental model is well known as a model of hypertriglicemia. As shown in Table 2, the compounds of the present invention have a serum trigriceride reducing activity.

Table 2. The hypotriglyceridemic activity in fructose induced hyperlipidemic rats

Compound	Triglyceride (% Reduction)	Compound	Triglyceride (% Reduction)
Example 1	47	Example 20	54
Example 2	67	Example 21	48
Example 3	64	Example 22	65
Example 4	42	Example 26	46
Example 6	84	Example 28	36
Example 7	60	Example 32	47
Example 8	47	Example 34	71
Example 9	49	Example 37	41
Example 10	39	Example 39	57
Example 11	62	Example 40	42
Example 12	59	Example 43	67
Example 13	55	Example 45	43
Example 14	36	Example 47	69
Example 15	47	Example 49	39
Example 16	54	Example 51	67
Example 17	37	Example 52	44
Example 19	38		

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

Example 64

Lipid lowering effects in high cholesterol-fed hamsters

The compounds were tested for lipid lowering effects in high cholesterol-fed hamsters in accordance with the method described in Jpn Pharmacol Ther, 23 (suppl 4), s1047-1053 (1995). Male Syrian hamsters were fed the high cholesterol diet supplemented with 1% cholesterol and 10% coconut oil for 8 weeks. Before drug administration, blood was collected from the orbital venous plexus under ether anesthesia, and a serum total cholesterol level was measured. The animals were divided into groups so as to have a comparable mean total cholesterol level. The designated doses of the compound of Example 1 or Bezafibrate were administrated to test groups and the vehicle solution was given to the control group orally once a day for 7 days under the high cholesterol diet feeding. The intact group of animals were fed normal diet. After 4 hours of the final administration, blood was collected by cardiac puncture, and the total cholesterol and triglyceride levels in the serum were determined by the enzymatic method.

The results are shown in Table 3. The reduction rate (%) was calculated according to

the following equation:

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

The result indicates that the compound of Example 1 has potent reducing activities in serum cholesterol and triglyceride levels and it is more effective than bezafibrate.

Table 3. Effect of the compound of Example 1 and bezafibrate on serum lipid levels in high cholesterol-fed hamsters

Compound	Bezafibrate		Compound of Example 1	
Activity / Dose	Total cholesterol (% Reduction)*	Triglyceride (% Reduction)*	Total cholesterol (% Reduction)	Triglyceride (% Reduction)
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

*: A minus quantity represents the rate of increase.

EXAMPLE 65

Lipid lowering effects in high cholesterol-fed hamsters

The compounds of the present invention were evaluated for selecting more effective lipid lowering activities in the same manner described in Example 64 at a dose of 15 mg/kg p.o.. The results are shown in Table 4. The reduction rate (%) was calculated according to the following equation:

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

Table 4. Hypolipidemic effects in high cholesterol-fed hamsters

Compound	Total cholesterol (% Reduction)	Triglyceride (% Reduction)
Example 2	27	57
Example 3	16	17
Example 7	18	12
Example 9	15	15
Example 14	11	24
Example 15	32	61

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

EXAMPLE 66

Acute Toxicity

The single dose toxicity of the compound of Example 1 and Example 10 were evaluated after oral administration at a dose of 2000 mg/kg with each group comprising 3 mice. The animals were observed daily for 2 weeks after the administration. As a result, no deaths were observed.

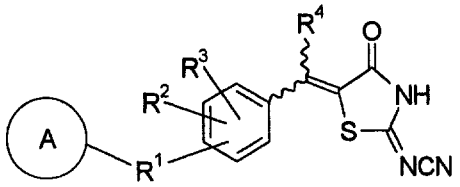
EXAMPLE 67

Mutagenicity test

The mutagenicity of the compound of Example 1 was examined by a reverse mutation test using *Salmonella typhimurium* TA100 and TA98 in the absence or presence of S9 mix. The compound of Example 1 did not increase the number of revertant colonies, and was not mutagenic in this test system.

CLAIMS

1. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives represented by formula I or a pharmaceutically acceptable salt or solvate thereof:



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.

2. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein ring A represents a benzene ring, a benzodioxole ring, a benzofuran ring, a benzothiazole, a fluorene ring, an indan ring, an indoline ring or a pyridine 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^5 represents a hydrogen atom or a C_1 - C_4 alkyl group.

3. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, 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.

4. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein R^1 represents a methyne group or a straight or branched C_1 - C_4 alkylene or alkenylene group optionally substituted by a phenyl group.

5. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein R^1 represents an oxygen atom or a sulfur atom.

6. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein R^1 represents a single bond.

7. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein R^1 represents R^6-X, X-R^6, X-R^6-X or R^6-X-R^6 ; R^6 represents a straight or branched C_1 - C_4 alkylene or alkenylene group; X represents an oxygen atom or a sulfur atom.

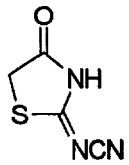
8. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein R^1 represents -C(=O)-NR^7- or -NR^7-C(=O)-; R^7 represents a hydrogen atom or a C_1 - C_4 alkyl group.

9. Novel 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein the compound of formula I is any one of the following:

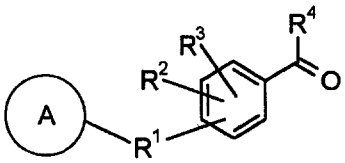
2-(N-Cyanoimino)-5-[(E)-4-stylylbenzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-4-(a-methylstylyl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(benzyloxymethyl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-4-(b-methylstylyl)benzylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-[4-(3-phenylpropoxy)benzylidene]thiazolidin-4-one;
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-fluorostylyl)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-methoxystylyl)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-stylylbenzylidene]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-methoxystylyl)phenyl]ethylidene]thiazolidin-4-one;
2-(N-Cyanoimino)-5-(4-benzyloxy-2,5-dimethylbenzylidene)thiazolidin-4-one;
2-(N-Cyanoimino)-5-[(E)-3-stylylbenzylidene]thiazolidin-4-one.

10. A process for preparing a 2-(N-cyanoimino)thiazolidin-4-one derivatives or a pharmaceutically acceptable salt or solvate thereof according to claim 1, which comprises reacting a compound represented by formula II, or salts thereof, with an aldehyde or ketone represented by formula III:



II



III

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.

11. A pharmaceutical composition for treating hyperlipidemia comprising novel 2-(N-cyanoimino)thiazolidin-4-one derivatives and/or a pharmaceutically acceptable salt and/or solvate thereof according to claim 1 – 10 as an active ingredient and a pharmaceutically acceptable carrier.