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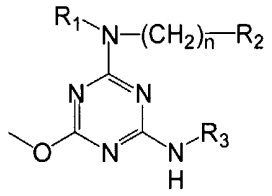
(54) Title: METHOXY-1,3,5-TRIAZINE DERIVATIVES AS ANTIVIRAL AGENTS

(57) Abstract: Methoxy-1,3,5-triazine derivatives and their pharmaceutically acceptable salts are described in which the derivatives have excellent inhibitory effects on proliferation of hepatitis B virus(HBV) and hepatitis C virus(HCV) so that they can be easily used as an effective ingredient against viruses. In addition, the process for preparing the derivatives is also described.

METHOXY-1,3,5-TRIAZINE DERIVATIVES AS ANTIVIRAL AGENTS

TECHNICAL FIELD

The present invention relates to methoxy-1,3,5-triazine derivatives and their pharmaceutical composition. More specifically, the present invention relates to methoxy-1,3,5-triazine derivatives and their pharmaceutically acceptable salts represented below in formula 1, which have excellent inhibitory effects on proliferation of hepatitis B virus(HBV) and hepatitis C virus(HCV). The present invention also includes the process for preparing compounds of formula 1 and their pharmaceutical composition as effective ingredients against viruses.



(I)

wherein,

R_1 is H or C_1-C_3 alkyl group,

R_2 is H; hydroxy; straight or branched C_1-C_4 alkyl group; straight or branched C_1-C_3 alkoxy group; C_1-C_3 hydroxyalkyl group; C_2-C_6 dialkylamino group; C_3-C_6 cycloalkyl group; lactam; saturated or unsaturated a 5 or 6 membered heterocyclic compounds containing 1 to 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted with straight or branched C_1~C_3 alkyl group;

bicyclo compounds containing 1 to 2 heteroatoms selected from N, O and S;

or R_1 and R_2 are joined to form a 5 or 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted with hydroxy, straight or branched C_1-C_4 alkyl group, C_1-C_3 hydroxyalkyl group, carbamoyl, C_1-C_3 alkylcarbamoyl, C_1-C_3 alkoxycarbonyl group, aryl group, or arylcarbonyl group,

n is an integer of 0 to 4,

R_3 is 5-indazolyl or 6-indazolyl group.

In the case that R_2 has the chiral carbon, the compound of formula 1 is the stereoisomer of (R) or (S) and the present invention contains both their stereoisomers and racemic compounds.

BACKGROUND OF THE INVENTION

Hepatitis B virus (HBV; referred as "HBV" hereinafter) causes acute or chronic hepatitis, which may progress to liver cirrhosis and liver cancer. It is estimated that three hundred million people are infected with HBV in the world (Tiollais & Buendia, *Sci. Am.*, 264, 48, 1991). There have been many studies on the molecular biological characteristics of HBV and its relationship to liver diseases in order to find ways to prevent and treat hepatitis B. Various vaccines and diagnostic drugs have

been developed and much effort is being focused on research to find effective anti-hepatitis B agent.

HBV genome consists of genes for polymerase (P), surface protein (pre-S1, pre-S2 and S), core protein (pre-C and C), and X protein. Of these proteins expressed from HBV genes, polymerase, surface protein, and core protein are structural proteins and X protein has a regulatory function.

The gene for HBV polymerase occupies about 80% of the whole virus genome and produces a protein of 94kD size with 845 amino acids, which has several functions in the replication of virus genome. This polypeptide includes sequences responsible for activities of protein primer, RNA dependent DNA polymerase, DNA dependent DNA polymerase, and RNase H. Kaplan and his coworkers first discovered reverse transcriptase activities of polymerase, which led to many studies on replicating mechanism of HBV.

HBV enters liver when antigenic protein on virion surface is recognized by hepatic cell-specific receptor. Inside the liver cell, DNAs are synthesized by the action of HBV polymerase, attached to short chain to form complete double helix for HBV genome. Complete double helical DNA genome of HBV produces pre-genomic mRNA and mRNAs of core protein, surface protein, and regulatory protein by the action of RNA polymerase. Using these mRNAs, virus proteins are synthesized. Polymerase has an important function in the

production of virus genome, forming a structure called replicasome with core protein and pre-genomic mRNA. This process is called encapsidation. Polymerase has repeated units of glutamic acid at the 3'-end with high affinity for nucleic acids, which is responsible for facile encapsidation. When replicasome is formed, (-) DNA strand is synthesized by reverse transcribing action of HBV polymerase and (+) DNA strand is made by the action of DNA dependent DNA polymerase and the (+)DNA strand produces pre-genomic mRNAs. The whole process is repeated until the pool of more than 200 to 300 genomes is maintained (Tiollais and Buendia, *Scientific American*, 264: 48-54, 1991).

Recently, nucleoside compounds such as lamivudine and famvir have been reported to be useful inhibitors of HBV proliferation, although they have been originally developed as therapeutics for the treatment of acquired immune deficiency syndrome (AIDS; referred as "AIDS" hereinafter) and herpes zoster infection (Gerin, J. L, *Hepatology*, 14: 198-199, 1991; Lok, A. S. P., *J. Viral Hepatitis*, 1: 105-124, 1994; Dienstag, J. L. *et al.*, *New England Journal of Medicine*, 333: 1657-1661, 1995). However, these nucleoside compounds are considered a poor choice for treatment of hepatitis B because of their high cost and side effects such as toxicity, appearance of resistant virus and recurrence of the disease after stopping treatment. Effort to find

therapeutics for hepatitis B among non-nucleoside compounds has been continued and antiviral effects against HBV have been reported for quinolone compounds (EP 563732, EP 563734), iridoides compounds (KR 94-1886), and terephthalic amide derivatives (KR 96-72384, KR 97-36589, KR 99-5100). In spite of much effort, however, effective drugs for hepatitis B have not been developed yet and therapeutic method mainly depends on symptomatic treatments.

Hepatitis C virus(referred as "HCV" hereinafter) is a virus that belongs to the flaviviridae having a membrane. HCV genome is single stranded (+)-RNA of 9.5 kb in length and express polyprotein consisting of 3010 amino acids. The HCV polyprotein is cleaved co- and posttranslationally by cellular and viral protease to yield 3 structural proteins and 6 nonstructural proteins.

5'- and 3'-terminus of the HCV genome contain untranslated regions(UTR), which have highly conserved nucleotide sequence of all most genotype. Recently, it is known that 5'-UTR is a 330~341 nucleotide sequence and 3'-UTR includes 98 nucleotides at the back of poly A, termed to X region which might be played a role of RNA replication and translation of virus. Amino end part of HCV genome produces structural proteins(Core, E1 and E2) and the other part produces non-structural proteins. The core is the main structural component of the viral capsid and the envelope

protein consists of E1 and E2. These proteins are cleaved by signal peptidase in endoplasmic reticulum. Serin-type protease NS3 and cofactor NS4A cleaves nonstructural proteins. NS5B protein is a RNA-dependant RNA polymerase. This protein plays an important role in the regulation of HCV replication.

It is reported that an infection by HCV is generated from a blood transfusion and community-acquired infection. Approximately 70% of HCV infected individuals will develop chronic hepatitis, of which 20% will progress to severe chronic liver disease within 5 years. Such higher progression rate, rarely in RNA virus, shows that HCV is a major cause of generating liver cancer. Mechanism studies of the continuous infection of HCV have not been reported. HCV test is therefore carried out in all blood and the infection opportunity by the blood transfusion is remarkably decreased. But, HCV infection presents a major public health problem worldwide because the community-acquired HCV infection hasn't regulated yet.

From the viewpoint of retrospective studies, HCV infection distributes worldwide and 1.5 - 2% of the world's population is infected. Compared to HBV, HCV infection is generally developed into chronic hepatitis and has a high probability of progression to liver cirrhosis and liver cancer. Because hepatitis C virus belongs to completely

different family, it cannot be inhibited using HBV vaccine. The treatment of α-interferon has been tried, but its antiviral effect depends on the genotypes of HCV and the shown effect is also weak.

Since HCV was discovered in 1987, there has been attempted a lot of research, but remarkably effective drug hasn't yet developed. α-Interferon is the unique choice for the treatment so far, but it has confirmed that the its medical care rate is less than 30%, HCV is recurred after cessation of its treatment and several interferon-resistant mutant virus generates. So far, there aren't specific antiviral agents with proliferation inhibitory activity against HCV.

Therefore, we, inventors of the present invention, tried to develop therapeutics to treat hepatitis B with little chance of toxicity, side effects, and development of resistant viral strains. We found the compounds with excellent antiviral effect against HBV; synthesized novel methoxy-1,3,5-triazine derivatives represented in formula 1 and completed the invention by showing their dramatic inhibitory effect on proliferation of HCV as well as of HBV.

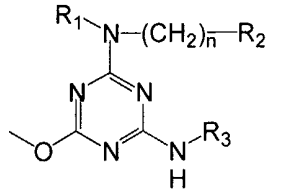
SUMMARY OF THE INVENTION

It is an objective of this invention to provide methoxy-1,3,5-triazine derivatives, their pharmaceutically acceptable salts, and the process for preparing them.

It is a further objective of this invention to provide a pharmaceutical composition containing derivatives stated above with cost effectiveness and little chance of side effects, as a therapeutic agent as well as a preventive agent for hepatitis B and hepatitis C.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methoxy-1,3,5-triazine derivatives represented by following formula 1 and their pharmaceutically acceptable salts:



(I)

wherein,

R_1 is H or C_1-C_3 alkyl group,

R_2 is H; hydroxy; straight or branched C_1-C_4 alkyl group; straight or branched C_1-C_3 alkoxy group; C_1-C_3 hydroxyalkyl group; C_2-C_6 dialkylamino group; C_3-C_6 cycloalkyl group; lactam; saturated or unsaturated a 5 or 6 membered heterocyclic compounds containing 1 to 2 heteroatoms

selected from N, O and S, which is unsubstituted or substituted with straight or branched C_1~C_3 alkyl group; bicyclo compounds containing 1 to 2 heteroatoms selected from N, O and S;

or R_1 and R_2 are joined to form a 5 or 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted with hydroxy, straight or branched C_1-C_4 alkyl group, C_1-C_3 hydroxyalkyl group, carbamoyl, C_1-C_3 alkylcarbamoyl, C_1-C_3 alkoxycarbonyl group, aryl group, or arylcarbonyl group,

n is an integer of 0 to 4,

R_3 is 5-indazolyl or 6-indazolyl group.

In the case that R_2 has the chiral carbon, the compound of formula 1 is the stereoisomer of (R) or (S) and the present invention contains both their stereoisomers and racemic compounds.

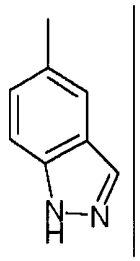
More preferably, wherein,

R_1 is hydrogen atom,

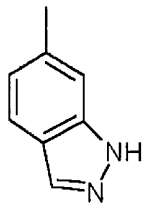
R_2 is hydroxy, methyl, ethyl, isopropyl, cyclopropyl, morpholinyl, piperazinyl, pyrrolyl, indolyl, pyridinyl, pyrrolidinyl, imidazolyl, piperidinyl or isonicotinyl group,

n is an integer between 0 and 3.

In the present invention, 5-indazoly and 6-indazolyl group represent below in formula 2 and formula 3.



(II)



(III)

More preferable compounds in accordance with the present invention are as follows;

1) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-morpholino ethyl)amino-1,3,5-triazine;
2) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-morpholino ethyl)amino-1,3,5-triazine;
3) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-methylamino-1,3,5-triazine;
4) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-methylamino-1,3,5-triazine;
5) 2-(1*H*-5-indazolyl)amino-4-isopropylamino-6-methoxy-1,3,5-triazine;
6) 2-(1*H*-6-indazolyl)amino-4-isopropylamino-6-methoxy-1,3,5-triazine;
7) 2-cyclopropylamino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;
8) 2-cyclopropylamino-4-(1*H*-6-indazolyl)amino-6-methoxy-

1,3,5-triazine;

9) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-methoxy ethyl)amino-1,3,5-triazine;

10) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-methoxy ethyl)amino-1,3,5-triazine;

11) 2-(2-hydroxyethyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

12) 2-(2-hydroxyethyl)amino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

13) 2-(2-dimethylaminoethyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

14) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-morpholinoamino-1,3,5-triazine;

15) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-morpholinoamino-1,3,5-triazine;

16) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino amino-1,3,5-triazine;

17) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino amino-1,3,5-triazine;

18) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-(2-pyridyl)ethyl) amino-1,3,5-triazine;

19) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-(2-pyridyl)ethyl) amino-1,3,5-triazine;

20) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(3-(2-oxo-pyrrolidino)propyl)amino-1,3,5-triazine;

21) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(3-(2-oxo-pyrrolidino)propyl)amino-1,3,5-triazine;

22) 2-(1*H*-5-indazolyl)amino-4-(2-(1*H*-3-indolyl)ethyl)amino-6-methoxy-1,3,5-triazine;

23) 2-(1*H*-6-indazolyl)amino-4-(2-(1*H*-3-indolyl)ethyl)amino-6-methoxy-1,3,5-triazine;

24) 2-(3-(1*H*-1-imidazolyl)propyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

25) 2-(3-(1*H*-1-imidazolyl)propyl)amino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

26) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-morpholino-1,3,5-triazine;

27) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-morpholino-1,3,5-triazine;

28) 2-(1*H*-1-imidazolyl)-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

29) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-pyrrolidino-1,3,5-triazine;

30) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-pyrrolidino-1,3,5-triazine;

31) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-((2*S*)-methoxy carbonyl)pyrrolidino-1,3,5-triazine;

32) 2-(4-hydroxy)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

33) 2-(4-hydroxy)piperidino-4-(1*H*-6-indazolyl)amino-6-

methoxy-1,3,5-triazine;

34) 2-(4-amido)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

35) 2-(4-amido)piperidino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

36) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-*N*-methylamido) piperidino-1,3,5-triazine;

37) 2-(4-ethoxycarbonyl)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

38) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino-1,3,5-triazine;

39) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino-1,3,5-triazine;

40) 2-(4-(2-hydroxyethyl))piperazino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

41) 2-(4-(2-hydroxyethyl))piperazino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

42) 2-(4-ethoxycarbonyl)piperazino-4-(1*H*-5-indazolyl)amino-6-methoxyl-1,3,5-triazine;

43) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-(*N*-methylamido methyl))piperazino-1,3,5-triazine;

44) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-(*N*-methylamido methyl))piperazino-1,3,5-triazine;

45) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-nicotinoyl) piperazino-1,3,5-triazine;

46) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-nicotinoyl) piperazino-1,3,5-triazine;

47) 2-(4-(5-ethoxycarbonyl-2-methylthio-1,3-pyrimidinyl)) piperazino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

48) 2-(4-(5-ethoxycarbonyl-2-methylthio-1,3-pyrimidinyl)) piperazino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

49) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(3-morpholinopropyl) amino-1,3,5-triazine; and

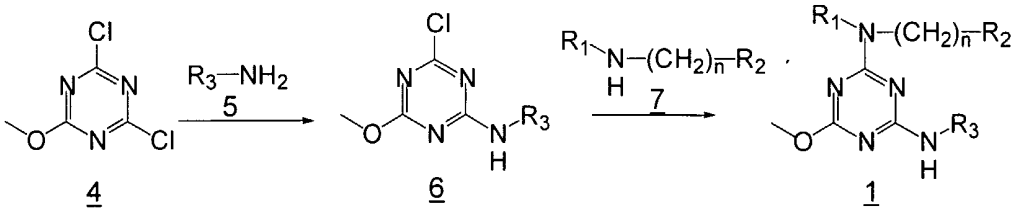
50) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(3-morpholinopropyl) amino-1,3,5-triazine.

The compounds represented by formula 1 of the present invention may be utilized in the form of salts and the acid addition salts prepared by adding pharmaceutically acceptable free acids are useful. Compounds of formula 1 may be changed to the corresponding acid addition salts according to the general practices in this field. Both inorganic and organic acids may be used as free acids in this case. Among inorganic acids, hydrochloric acid, hydrobromic acid, sulfuric acid, or phosphoric acid may be used. Among organic acids, citric acid, acetic acid, lactic acid, tartaric acid, maleic acid, fumaric acid, formic acid, propionic acid, oxalic acid, trifluoroacetic acid, benzoic

acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, 4-toluenesulfonic acid, galacturonic acid, embonic acid, glutamic acid or aspartic acid may be used.

The present invention also provides a process for preparing methoxy-1,3,5-triazine derivatives of formula 1, represented by scheme 1 as follows:

scheme 1



4 6 1

(wherein, R_1, R_2, R_3 and n are as defined in formula 1.)

The process for preparing in the present invention comprises the following steps of:

1) reacting 2,4-dichloro-6-methoxy-1,3,5-triazine (4) with 5-aminoindazole or 6-aminoindazole (5) in the presence of a base in order to prepare 2-chloro-6-methoxy-1,3,5-triazine derivatives substituted with aminoindazole (6) (step 1); and

2) reacting thus obtained compound (6) with amine compound (7) in the presence of a base in order to prepare methoxy-1,3,5-triazine derivatives (1) (step 2).

Chemical reagents used as starting and reaction materials in the scheme 1, namely, 2,4-dichloro-6-methoxytriazine(4), 5-aminoindazole, 6-aminoindazole (5) and amine compounds (7), are commercially available and may be purchased or can be easily done by one with general knowledge in the technical field.

A detail description will be stepwise given of the method for preparing of methoxy-1,3,5-triazine derivatives of the present invention.

In the step 1, 2-chloro-6-methoxy-1,3,5-triazine derivatives (6) was prepared by reaction of the 2,4-dichloro-6-methoxy-1,3,5-triazine (4) with 5-aminoindazole or 6-aminoindazole in the presence of the base at the proper conditions(temperature and solvent).

In the step 1, it is preferably used tertiary organic base having weak basicity such as triethylamine, *N,N*-diisopropylethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine, *N,N*-dimethylaniline, 2,6-lutidine, pyridine.

The reaction temperature is preferably 0~10 ℃.

For a solvent, a single or a mixture of solvents selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran, methanol, ethanol is preferable.

In the step 2, compounds of the formula 1 is prepared by reacting 2-chloro-6-methoxy-1,3,5-triazine obtained by step 1 with amine compound at the proper conditions(solvent, temperature).

The amine compound (5) in the step 2 is also used to introduce R_1, R_2 substituents into the desired compound of formula 1 and an appropriate amine compound should be selected depending on the substituent desired. For example, These amine compounds (7) are methyamine, ethylamine, isopropylamine, cyclopropylamine, ethanolamine, propanolamine, morpholine and piperazine, etc. It is advisable to use the amine compound (7) a bit excess to increase the yield.

The base using in step 2 is the same one of the step 1 and tertiary organic base is preferred.

And, the reaction solvent is single or mixed solvent selected from the type of alcohol (as methanol, ethanol, isopropanol, etc), acetonitrile, chloroform and methylene chloride, etc.

The reaction temperature may be changed by the class of the amine compound (7) and is preferably 0~10 ℃.

Furthermore, the present invention provides the pharmaceutical compositions of therapeutics containing methoxy-1,3,5-triazine derivatives and their

pharmaceutically acceptable salts of formula 1 as effective ingredients to prevent and treat hepatitis B.

The present invention also provides the pharmaceutical compositions of therapeutics containing methoxy-1,3,5-triazine derivatives and their pharmaceutically acceptable salts of formula 1 as effective ingredients to prevent and treat hepatitis C.

Compounds of formula 1 may be taken orally as well as through other routes in clinical uses; for example, it may be administered intravenously, subcutaneously, intraperitoneally, locally and in the form of general drugs. For clinical use of drugs with the pharmaceutical compositions of the present invention, compounds of formula 1 may be mixed with pharmaceutically acceptable excipients and made into various pharmaceutically acceptable forms; for example, tablets, capsules, trochese, solutions, suspensions for oral administration; injection solutions, suspensions, and dried powder to be mixed with distilled water for the formulation of instant injection solution.

Effective dosage for compound of formula 1 is generally 10~500 mg/kg, preferably 50~300 mg/kg for adults, which may be divided into several doses, preferably into 1~6 doses per day if deemed appropriate by a doctor or a pharmacist.

Hereinafter the present invention describes in more detail.

However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

EXAMPLE

<Preparation example 1>: preparation of 2-chloro-4-(1H-5-indazolyl)amino-6-methoxy-1,3,5-triazine

To the methanol solution 70 ml of 5-aminoindazole 1.8g was added triethylamine 1.72ml , the solution was cooled down to 5℃ and then 2,4-dichloro-6-methoxy-1,3,5-triazine 1.8g was slowly added. The solid was precipitated, stirred for 1 hour, filtered under the reduced pressure and washed with methanol 20ml. The desired compound(2.35g, 76%) was obtained by drying of the solid product at 40~50℃ *in vacuo.*

m.p. : >280 ℃

^{1}H-NMR (DMSO-d_6), ppm : 3.93(3H, s), 7.46-7.56(2H, m), 7.55-8.11(2H. m), 10.54-10.67(1H, m), 13.05(1H, brs)

<Preparation example 2>: preparation of 2-chloro-4-(1H-6-indazolyl)amino-6-methoxy-1,3,5-triazine

To the solution of 5-aminoindazole 1.8g in methanol 70 ml was added triethylamine 1.72ml , the solution was cooled

down to 5℃ and then 2,4-dichloro-6-methoxy-1,3,5-triazine 1.8g was slowly added. The solid was precipitated, stirred for 1 hour, filtered under the reduced pressure and washed with methanol 20ml. The desired compound(2.32g, 75%) was obtained by drying of the solid product at 40~50℃ *in vacuo*.

m.p. : >280 ℃

^{1}H-NMR (DMSO-d_6), ppm : 3.99(3H, s), 7.28(1H, d), 7.68(1H, d), 8.00(1H, s), 8.18(1H, s), 10.71-10.84(1H, m), 13.00(1H, s)

<Example 1>: preparation of 2-(1*H*-5-indazolylamino)-4-methoxy-6-(2-morpholinoethyl)amino-1,3,5-triazine

To the solution of 2-chloro-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine o.3g obtained by preparation example 1 in methanol 30 ml were added triethylamine 0.23 ml and 4-(2-aminoethyl)morpholine 0.17 ml. The solution was refluxed 5 hours and then the solution was evaporated in vacuo, The residue was diluted with H_2O 20 ml. The solution was extracted with dichloromethane 30 ml. The organic layer was separated, concentrated under reduced pressure and stirred 1 hour in methanol 5 ml. The solid was precipitated, filtered and washed methanol. The desired compound(0.31g, 78%) was obtained by drying of the solid product at 40~50℃ *in vacuo*.

m.p. : 203~207 ℃

^{1}H-NMR (DMSO-d_6), ppm : 2.44(6H, m), 3.51(2H, m), 3.54(4H, m),

3.79(3H, m), 7.43(1H, m), 7.54(1H, m), 7.95(1H, s), 8.15(1H, s), 9.49(1H, m), 12.91(1H, m)

<Example 2>: preparation of 2-(1*H*-6-indazolylamino)-4-methoxy-6-(2-morpholinoethyl)amino-1,3,5-triazine

To the solution of 2-chloro-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine o.3g obtained by preparation example 2 in methanol 30 ml were added triethylamine 0.23 ml and 4-(2-aminoethyl)morpholine 0.17 ml, the solution was refluxed 2 hours and then the solution was cooled down at room temperature and added water, stirring for 3 hours. The solid was precipitated, filtered and washed water. The desired compound(0.30g, 75%) was obtained by drying of the solid product at 40~50℃ *in vacuo*.

m.p. : 246~247 ℃

^{1}H-NMR (DMSO-d_6), ppm : 2.40(6H, m), 3.53(6H, m), 3.83(3H, m), 7.36(1H, m), 7.61(1H, m), 7.93(1H, s), 8.20(1H, m), 9.67(1H, m), 12.86(1H, m)

The example 3-example 50 were prepared according to the synthetic method of example 1 and 2. The table 1 showed melting point, yield, nomenclature, staring material(6) and amines(7) of compound 3-50. the table 2 is showed ^{1}H-NMR result of compound 3-50.

<Table 1>

	Compound's name			
	Preparation example (compd.6)	amine compound(7)	yield(%)	m.p.(°C)
3	2-(1*H*-5-indazolyl)amino-4-methoxy-6-methylamino-1,3,5-triazine			
	1	methylamine	85	224-225
4	2-(1*H*-6-indazolyl)amino-4-methoxy-6-methylamino-1,3,5-triazine			
	2	methylamine	87	253-255
5	2-(1*H*-5-indazolyl)amino-4-isopropylamino-6-methoxy-1,3,5-triazine			
	1	isopropylamine	92	120-122
6	2-(1*H*-6-indazolyl)amino-4-isopropylamino-6-methoxy-1,3,5-triazine			
	2	isopropylamine	88	215-216
7	2-cyclopropylamino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	cycloprpoylamine	79	220-221
8	2-cyclopropylamino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	cyclopropylamine	87	230-232
9	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-methoxyethyl)amino-1,3,5-triazine			
	1	2-methoxyethylamine	71	212-215
10	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-methoxyethyl)amino-1,3,5-triazine			
	2	2-methoxyethylamine	79	174-177
11	2-(2-hydroxyethyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	ethanolamine	86	219-220
12	2-(2-hydroxyethyl)amino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	ethanolamine	81	145-150
13	2-(2-dimethylaminoethyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	*N*,*N*-dimethylethylene diamine	71	194-195
14	2-(1*H*-5-indazolyl)amino-4-methoxy-6-morpholinoamino-1,3,5-triazine			
	1	*N*-aminomorpholine	69	253-255
15	2-(1*H*-6-indazolyl)amino-4-methoxy-6-morpholinoamino-1,3,5-triazine			
	2	*N*-amionmorpholine	74	255-256
16	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-methyl)piperazinoamino-1,3,5-triazine			
	1	1-amino-4-methylpiperazine	76	222-230
17	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-methyl)piperazinoamino-1,3,5-triazine			
	2	1-amino-4-methylpiperazine	71	165-168
18	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-(2-pyridyl)ethyl)amino-1,3,5-triazine			
	1	2-(2-aminoethyl)pyridine	65	214-216
19	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-(2-pyridyl)ethyl)amino-1,3,5-triazine			
	2	2-(2-aminoethyl)pyridine	68	206-208
20	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(3-(2-oxo-pyrrolidino)propyl)amino-1,3,5-triazine			

	1	1-(3-aminopropyl)-2-pyrrolidinone	72	103-106
21	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(3-(2-oxo-pyrrolidino)propyl)amino-1,3,5-triazine			
	2	1-(3-aminopropyl)-2-pyrrolidinone	70	208-210
22	2-(1*H*-5-indazolyl)amino-4-(2-(1*H*-3-indolyl)ethyl)amino-6-methoxy-1,3,5-triazine			
	1	tryptamine	66	150-151
23	2-(1*H*-6-indazolyl)amino-4-(2-(1*H*-3-indolyl)ethyl)amino-6-methoxy-1,3,5-triazine			
	2	tryptamine	60	207-209
24	2-(3-(1*H*-1-imidazolyl)propyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	1-(3-aminopropyl)imidazole	82	140-142
25	2-(3-(1*H*-1-imidazolyl)propyl)amino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	1-(3-aminopropyl)imidazole	83	179-180
26	2-(1*H*-5-indazolyl)amino-4-methoxy-6-morpholino-1,3,5-triazine			
	1	morpholine	77	253-254
27	2-(1*H*-6-indazolyl)amino-4-methoxy-6-morpholino-1,3,5-triazine			
	2	morpholine	71	283-284
28	2-(1*H*-1-imidazolyl)-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	imidazole	70	>280
29	2-(1*H*-5-indazolyl)amino-4-methoxy-6-pyrrolidino-1,3,5-triazine			
	1	pyrrolidine	68	270-271
30	2-(1*H*-6-indazolyl)amino-4-methoxy-6-pyrrolidino-1,3,5-triazine			
	2	pyrrolidine	80	286-288
31	2-(1*H*-6-indazolyl)amino-4-methoxy-6-((2*S*)-methoxycarbonyl)pyrrolidino-1,3,5-triazine			
	2	L-proline methyl ester	74	236-237
32	2-(4-hydroxy)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	4-hydroxypiperidine	73	275-276
33	2-(4-hydroxy)piperidino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	4-hydroxypiperidine	71	271-272
34	2-(4-amido)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	isonipecotate	66	270-272
35	2-(4-amido)piperidino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	isonipecotate	65	>280
36	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-*N*-methylamido)piperidino-1,3,5-triazine			
	1	piperidine-4-carboxyl methylamide	66	264-267
37	2-(4-ethoxycarbonyl)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	ethyl isonipecotate	65	216-218
38	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino-1,3,5-triazine			
	1	*N*-methylpiperazine	73	246-247

39	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino-1,3,5-triazine			
	2	*N*-methylpiperazine	76	246-248
40	2-(4-(2-hydroxyethyl))piperazino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	1-(2-hydroxyethyl)piperazine	80	231-233
41	2-(4-(2-hydroxyethyl))piperazino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	1-(2-hydroxyethyl)piperazine	79	241-243
42	2-(4-ethoxycarbonyl)piperazino-4-(1*H*-5-indazolyl)amino-6-methoxyl-1,3,5-triazine			
	1	1-ethylpiperazinecarboxylate	73	232-237
43	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-(*N*-methylamidomethyl))piperazino-1,3,5-triazine			
	1	*N*-1-methyl-2-piperazine-1-yl-acetamine	68	255-257
44	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-(*N*-methylamidomethyl))piperazino-1,3,5-triazine			
	2	*N*-1-methyl-2-piperazine-1-yl-acetamine	70	260-262
45	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-nicotinoyl)piperazino-1,3,5-triazine			
	1	piperazine-1-yl-pyridine-3-yl-methanone	74	218-222
46	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-nicotinoyl)piperazino-1,3,5-triazine			
	2	piperazine-1-yl-pyridine-3-yl-methanone	68	228-229
47	2-(4-(5-ethoxycarbonyl-2-methylthio-1,3-pyrimidinyl))piperazino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine			
	1	2-methylthio-4-piperazine-1-yl-pyrimidine-5-carboxylacid ethyl ester	63	158-160
48	2-(4-(5-ethoxycarbonyl-2-methylthio-1,3-pyrimidinyl))piperazino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine			
	2	2-methylthio-4-piperazine-1-yl-pyrimidine-5-carboxylacid ethyl ester	66	133-135
49	2-(1*H*-5-indazolyl)amino-4-methoxy-6-(3-morpholinopropyl)amino-1,3,5-triazine			
	1	4-(3-aminopropyl)morpholine	73	195-197
50	2-(1*H*-6-indazolyl)amino-4-methoxy-6-(3-morpholinopropyl)amino-1,3,5-triazine			
	2	4-(3-aminopropyl)morpholine	80	208-209

<Table 2>

example	NMR solvent	^{1}H-NMR data(ppm)
3	$CD_3OD+CDCl_3$	2.89(3H, m), 3.48(3H, m), 7.45(1H, brs), 7.93(1H, s), 8.07(1H, m)
4	$CD_3OD+CDCl_3$	2.90(3H, m), 3.91(3H, m), 7.15(1H, d), 7.59(1H, m), 7.89(1H, s), 8.24(1H, m)
5	DMSO-d_6	1.02(6H, m), 3.58(1H, m), 3.89(3H, m), 7.41-7.58(3H, m), 7.95-8.24(2H, m), 9.28-9.43(1H, m), 12.95(1H, m)
6	DMSO-d_6	3.34(2H, m), 3.51(2H, m), 3.82(3H, m), 4.68(1H, m), 7.41-7.59(3H, m), 7.95(1H, s), 8.17(1H, m), 9.15-9.47(1H, m), 12.90(1H, s)
7	DMSO-d_6	0.53(2H, m), 0.65(2H, m), 2.76(1H, m), 3.82(3H, m), 7.43(1H, m), 7.56(1H, m), 7.96(1H, s), 8.33(1H, m), 9.55(1H, m), 12.89(1H, s)
8	DMSO-d_6	0.54(2H, m), 0.81(2H, m), 2.80(1H, m), 3.81(3H, s), 7.25(1H, m), 7.56(1H, m), 8.04(1H, s), 8.48(1H. m), 9.72(1H, m), 12.85(1H, m)
9	$CD_3OD+CDCl_3$	3.28(3H, s), 3.48(4H, m), 3.82-3.89(3H, m), 7.38-7.45(2H, m), 7.87-7.99(2H, m)
10	DMSO-d_6	3.25(3H, m), 3.44-3.49(4H, m), 3.82-3.93(3H, m), 7.29-7.59(3H, m), 7.90(1H, d), 8.09-8.22(1H, m), 9.54-9.67(1H, m), 12.80-12.85(1H, m)
11	$CD_3OD+CDCl_3$	3.40(2H, m), 3.52(2H, m), 3.81(2H, m), 7.37(2H, m), 7.87(1H, s), 8.00(1H, s)
12	DMSO-d_6	3.42(2H, m), 3.50-3.57(2H, m), 3.83-3.86(3H, m), 4.67-4.71(1H, m), 7.29-7.39(2H, m), 7.58(1H, d), 7.91(1H, s), 8.10-8.24(1H, m), 9.52-9.65(1H, m), 12.79-12.83(1H, m)
13	DMSO-d_6	2.16(6H, s), 2.32-2.42(2H, m0, 3.34-3.40(2H, m), 3.79-3.82(3H, m), 7.10-7.41(1H, brs), 7.41-7.43(1H, m), 7.51-7.58(1H, m), 7.92-7.96(1H, m), 8.22(1H, brs), 9.35-9.50(1H, m), 12.92(1H, s)
14	DMSO-d_6	2.83(4H, m), 3.66(4H, m), 3.81(3H, s), 7.42(1H, d), 7.59(1H, brs), 7.95(1H, s), 8.20(1H, m), 8.66(1H, m), 9.65(1H, m), 12.91(1H, m)
15	DMSO-d_6	2.81(4H, m), 3.68(4H, m), 3.84(3H, s), 7.38(1H, m), 7.58(1H, d), 7.91(1H, s), 8.33(1H, brs), 9.80(1H, brs), 12.85(1H, brs)
16	DMSO-d_6	2.18(3H, m), 2.41(4H, m), 2.82(4H, m), 3.80(3H, s), 7.41(1H, d), 7.58(1H, m), 7.94(1H, m), 8.19(1H, m), 8.77(1H, m), 9.61(1H, m), 12.91(1H, m)
17	DMSO-d_6	2.18(3H, s), 2.41(4H, m), 2.81(4H, m), 3.84(3H, s), 7.37(1H, m), 7.58(1H, d), 7.91(1H, m), 8.21(1H, m)
18	DMSO-d_6	3.01(2H, m), 3.61(2H, m), 3.79(3H, m), 7.20(2H, m), 7.41(1H, d), 7.56(1H, m), 7.69(1H, m), 7.95(1H, s), 8.20(1H, brs),

		8.49(1H, m), 9.50(1H, m), 12.90(1H, s)
19	DMSO-d_6	3.10(2H, m), 3.77(2H, m), 3.89(3H, m), 7.29(1H, m), 7.35(1H, m), 7.44(1H, brs), 7.64(1H, m), 7.78(1H, m), 7.99(1H, s), 8.15(1H, m), 8.27(1H, m), 8.55(1H, s), 9.73(1H, m), 12.90(1H, m)
20	DMSO-d_6	1.68-1.94(4H, m), 2.19-2.23(2H, m), 3.33-3.39(6H, m), 3.81-3.83(3H, m), 7.41-7.59(3H, m), 7.97-8.02(1H, m), 8.19(1H, s), 9.35-9.49(1H, m), 12.91(1H, s)
21	DMSO-d_6	1.75-1.86(4H, m), 2.18-2.22(2H, m), 3.33-3.35(6H, m), 3.82-3.86(3H, m), 7.26(1H, d), 7.59(1H, d), 7.91(1H, s), 8.33(1H, m), 9.52-9.67(1H, m), 12.80-12.89(1H, m)
22	DMSO-d_6	2.92-2.99(2H, m), 3.53-3.64(2H, m), 3.80-3.84(3H, m), 6.95-6.99(2H, m), 7.03-7.59(4H, m), 7.95(1H, s), 8.20(1H, s), 10.79(1H, m), 12.88(1H, m)
23	DMSO-d_6	2.97-3.00(2H, m), 3.54-3.65(2H, m), 3.82-3.87(3H, m), 6.88-7.07(2H, m), 7.17(1H, d), 7.30-7.36(2H, m), 7.50-7.60(2H, m), 7.91(1H, s), 8.09-8.19(1H, m), 10.80(1H, s), 12.80(1H, m)
24	DMSO-d_6	1.92-1.99(2H, m), 3.22-3.25(2H, m), 3.80(3H, s), 4.13(2H, m), 6.87(1H, d), 7.19(1H, d), 7.42-7.65(4H, m), 7.96-7.99(1H, m), 8.14(1H, s), 9.36-9.51(1H, m), 12.93(1H, s)
25	DMSO-d_6	1.99(2H, m), 3.27(2H, m), 3.83(3H, s), 4.06(2H, m), 6.88(1H, s), 7.20-7.27(2H, m), 7.58-7.71(3H, m), 7.92(1H, s), 8.23(1H, m), 9.53-9.69(1H, m), 12.83(1H, s)
26	DMSO-d_6	3.62(4H, brs), 3.72(4H, brs), 3.83(3H, s), 7.42(1H, m), 7.54(1H, m), 7.98(1H, s), 8.06(1H, s), 9.56(1H, s), 12.93(1H, s)
27	DMSO-d_6	3.65(4H, brs), 3.76(4H, brs), 3.86(3H, s), 7.25(1H, m), 7.58(1H, m), 7.91(1H, s), 8.18(1H, s), 9.75(1H, s), 12.86(1H, s)
28	DMSO-d_6	4.02(3H, m), 7.17(1H, s), 7.32(1H, s), 7.68(1H, m), 7.88(1H, d), 7.98(1H, s), 8.25(1H, s), 8.55(1H, d), 10.63(1H, s), 12.97(1H, s)
29	DMSO-d_6	1.86-1.92(4H, m), 3.36-3.48(4H, m), 3.82(3H, s), 7.42(1H, d), 7.60(1H, d), 7.97(1H, s), 8.21(1H, s), 9.44(1H, s), 12.89(1H, s)
30	DMSO-d_6	1.92(4H, m), 3.47-3.58(4H, m), 3.85(3H, s), 7.28(1H, d), 7.58(1H, d), 7.89(1H, s), 8.33(1H, s), 9.63(1H, s), 12.83(1H, s)
31	DMSO-d_6	1.98-2.07(4H, m), 2.32(2H, m), 3.61(3H, s), 3.78(3H, s), 7.28(1H, d), 7.56-7.60(1H, m), 7.91(1H, s), 8.31(1H, s), 9.79(1H, s), 12.79-12.85(1H, m)
32	DMSO-d_6	1.31(2H, m), 1.76(2H, m), 3.3.(2H, m), 3.70(1H, m), 3.82(3H, s), 4.22(2H, brs), 4.76(1H, m), 7.43(1H, m), 7.54(1H, m), 7.94(1H, m), 8.08(1H, brs), 9.48(1H, s), 12.92(1H, s)

33	DMSO-d_6	1.35(2H, brs), 1.79(2H, brs), 3.35(2H, brs), 3.75(1H, brs), 3.85(3H, s), 4.23(2H, brs), 4.79(1H, s), 7.25(1H, m), 7.58(1H, m), 7.91(1H, s), 8.21(1H, s), 9.67(1H, s), 12.87(1H, s)
34	DMSO-d_6	1.44(2H, m), 1.75(2H, m), 2.35(1H, m), 2.92(2H, brs), 3.79(3H, s), 4.59(2H, m), 6.83(1H, s), 7.30(1H, s), 7.43(1H, m), 7.54(1H, m), 7.95(1H, d), 8.08(1H, s), 10.67(1H, s), 13.06(1H, s)
35	DMSO-d_6	1.48(2H, brs), 1.79(2H, brs), 2.40(1H, brs), 2.95(2H, brs), 3.86(3H, s), 4.63(2H, brs), 6.82(1H, s), 7.24(2H, m), 7.58(1H, m), 7.91(1H, s), 8.19(1H, s), 9.69(1H, s), 12.87(1H, s)
36	DMSO-d_6	1.44(2H, m), 1.71(2H, m), 2.36(1H, m), 2.54(3H, d), 2.91(2H, m), 3.82(3H, s), 4.59(2H, m), 7.42(1H, m), 7.54(1H, m), 7.74(1H, d), 7.97(1H, s), 8.07(1H, s), 9.46(1H, s), 12.90(1H, s)
37	DMSO-d_6	1.15(3H, t), 1.44(2H, m), 1.87(2H, m), 2.50(1H, m), 3.06(2H, brs), 3.79(3H, s), 3.96(2H, m), 4.47(2H, m), 7.43(1H, m), 7.54(1H, m), 7.98(1H, s), 8.07(1H, s), 9.51(1H, s), 12.92(1H, s)
38	DMSO-d_6	2.19(3H, d), 2.33(4H, brs), 3.73(4H, brs), 3.82(3H, s), 7.42(1H, m), 7.54(1H, m), 7.98(1H, s), 8.06(1H, s), 9.48(1H, s), 12.90(1H, s)
39	DMSO-d_6	2.20(3H, s), 2.35(4H, brs), 3.77(4H, brs), 3.86(3H, s), 7.27(1H, brs), 7.58(1H, brs), 7.91(1H, s), 8.18(1H, s), 9.67(1H, s), 12.84(1H, s)
40	DMSO-d_6+TFA-d_1	3.10(2H, m), 3.18(2H, m), 3.43(2H, m), 3.55(2H, m), 3.73(2H, brs), 3.88(3H, m), 4.66(2H, brs), 7.51(2H, m), 7.99(1H, brs), 8.07(1H, s)
41	DMSO-d_6	2.49(6H, m), 3.52(2H, m), 3.76(4H, m), 3.86(3H, s), 4.47(1H, brs), 7.26(1H, d), 7.60(1H, d), 7.91(1H, s), 8.20(1H, s), 9.69(1H, brs), 12.86(1H, brs)
42	DMSO-d_6	1.17(3H, t), 3.44(4H, brs), 3.75(4H, brs), 3.84(3H, s), 4.03(2H, q), 7.43(1H, m), 7.54(1H, m), 8.00(1H, s), 8.08(1H, s), 9.58(1H, s), 12.92(1H, s)
43	DMSO-d_6	2.49-2.53(4H, m), 2.65(3H, d), 2.96(2H, s), 3.81-3.86(7H, m), 7.47(1H, d), 7.58(1H, d), 7.81(1H, m), 8.02(1H, s), 8.11(1H, s), 9.56(1H, s), 12.96(1H, s)
44	DMSO-d_6	2.48-2.49(4H, m), 2.62(3H, d), 2.95(2H, s), 3.80-3.86(7H, m), 7.24(1H, d), 7.59(1H, d), 7.80(1H, m), 7.91(1H, s), 8.22(1H, s), 9.72(1H, s), 12.86(1H, s)
45	DMSO-d_6	3.44(2H, m), 3.72-3.84(9H, m), 7.43-7.57(3H, m), 7.86-8.09(3H, m), 8.65-8.67(2H, m), 9.59(1H, s), 12.92(1H, s)

46	DMSO-d_6	3.46(2H, m), 3.87-4.04(9H, m), 7.25(1H, m), 7.48-7.61(2H, m), 7.88-7.90(2H, m), 8.25(1H, brs), 8.68(2H, s), 9.79(1H, s), 12.82(1H, brs)
47	DMSO-d_6	1.25(3H, s), 2.49(3H, s), 3.64(4H, m), 3.81-3.87(7H, m), 4.27(2H, q), 7.45(1H, d), 7.57(1H, d), 8.00(1H, s), 8.09(1H, s), 8.47(1H, s), 9.59(1H, s), 12.93(1H, s)
48	DMSO-d_6	1.28(3H, t), 2.49(3H, s), 3.63-3.68(4H, m), 3.87(7H, m), 4.27(2H, q), 7.26(1H, d), 7.59(1H, d), 7.91(1H, s), 8.22(1H, s), 8.47(1H, s), 9.77(1H, s), 12.85(1H, s)
49	DMSO-d_6	1.67(2H, m), 2.32(6H, m), 3.29(2H, m), 3.52(2H, m), 3.56(2H, m), 3.79(3H, s), 7.41(1H, m), 7.54(1H, m), 7.86(1H, s), 9.44(1H, m), 12.89(1H, m)
50	DMSO-d_6	1.69(2H, m), 2.32(6H, m), 3.33(2H, m), 3.58(4H, m), 3.84(3H, m), 7.32(1H, m), 7.57(1H, m), 7.91(1H, s), 8.24(1H, m), 9.64(1H, m), 12.86(1H, m)

<Preparation 1> Preparation of Injection solution

Injection solution containing effective ingredient 50mg was made in following method. The compound 5g of example 1, sodium chloride 0.6g and ascorbic acid 0.1g were solved in distilled water to be 100ml volume totally. This solution sterilized for 30 minutes at 60℃.

Constituents of the injection solution stated above is as follows.

The compound of example 1 ·····5g

Sodium chloride·····0.6g

Ascorbic acid·····0.1g

Water for injection ad.·····100ml

<Preparation 2> Preparation of tablet

Tablet containing effective ingredient 60mg was made in following method. The compound of example 1 was mixed with lactose 175.9g, starch 180g and colloidal silicic acid 32g. 10% gellatin solution was added to this mixture and the mixture was ground, filtered in 14 mesh and dried. Finally, starch 160g, talc 50g and stearic acid magnesium salts 5g were added to the mixture and tablet was formed.

Constituents of the tablet stated above is as follows.

The compound of example 1·····1000g

Lactose·····175.9g

Starch·····180g

Colloidal silicic acid·····32g

10% gellatin solution

Starch·····160g

Talc ·····50g

Stearic acid magnesium salts ·····5g

<Experiment 1> Inhibitory effect on the *in vitro* activities of HBV polymerase in reverse transcription

The following *in vitro* experiment was performed to determine the effect of the compounds of formula 1 on the activity of HBV polymerase during reverse transcription.

The present inventors submitted application for a patent concerning HBV polymerase genetically expressed in and

separated from *E.coli*, the process of their preparation, and the method to measure the enzyme activities (KR 94-3918, KR 96-33998). In the present experiments HBV polymerase was used which had been expressed in *E. coli* as stated above.

The method used in the present invention to measure *in vitro* reverse transcribing activities of HBV polymerase is as follows. Basic principles are the same as those for ELISA, nucleotides with biotin- or digoxigenin- group are included as substrates and anti-DIG antibodies attached to peroxidase enzyme recognize the polymerized substrates.

To the wells coated with streptavidin, 20 ㎕ of HBV polymerase, 20 ㎕ of reaction mixture (10 μM each of DIG-UTP and Biotin-UTP, 46 mM Tris-HCl, 266 mM KCl, 27.5 mM $MgCl_2$, 9.2 mM DTT substrate/primer hybrid), and 20 ㎕ of test compound(added to 1, 0.1, and 0.01 ㎍/㎖) were added and allowed to react at 22℃ for 15 hrs. During this reaction, HBV polymerase catalyzes DNA synthesis, and digoxigenin and biotin attached to nucleotides form bonds to streptavidin coated on the bottom of wells. When the reaction was done, each well was washed with 250 ㎕ of cleaning buffer (pH 7.0) for 30 seconds, which was repeated five times to remove remaining impurities. 200 ㎕ of anti-DIG-POD antibody was added to each well and allowed to react for 1 hr at 37℃, and the wells were washed with cleaning buffer to remove

impurities. 200 ㎕ of ABTS™, a substrate of peroxidase, was then added to each well and allowed to react at room temperature for 30 min. Absorbency was measured at 405 nm using ELISA reader.

The inhibitory effects in HBV polymerase activities for reverse transcription were calculated using the group without test compound as a control and the results are shown in Table 3 as follows.

<Table 3>

Inhibitory effect on the HBV polymerase activities in reverse transcription

compound	Inhibitory activity on HBV-RT (%)		
	1 ㎍/㎖	0.1 ㎍/㎖	0.01 ㎍/㎖
Example 1	73	41	30
Example 2	79	54	49
Example 3	56	33	12
Example 4	55	36	16
Example 5	77	63	36
Example 6	65	52	39
Example 7	43	20	12
Example 8	54	21	3
Example 9	73	56	52
Example 10	75	37	32
Example 11	55	34	22
Example 12	73	33	20
Example 13	40	41	31
Example 14	67	31	11
Example 15	72	44	27
Example 16	39	22	6
Example 17	54	12	2

Example 18	65	39	36
Example 19	48	27	20
Example 20	60	27	7
Example 21	43	30	16
Example 22	43	32	14
Example 23	49	26	20
Example 24	56	50	25
Example 25	58	41	30
Example 26	56	50	25
Example 27	58	41	30
Example 28	78	40	11
Example 29	67	23	10
Example 30	63	30	9
Example 31	58	20	0
Example 32	43	40	25
Example 33	48	37	12
Example 34	59	48	11
Example 36	32	18	2
Example 37	56	36	6
Example 38	69	42	32
Example 39	53	14	10
Example 40	55	26	12
Example 41	40	20	3
Example 42	43	23	2
Example 45	58	35	11
Example 46	46	23	10
Example 47	39	3	0
Example 48	53	17	4
Example 49	68	39	24
Example 50	83	56	51

<Experiment 2> Inhibitory effect on the *in vitro* HCV activity in RNA-dependant RNA-polymerase.

The following *in vitro* experiment was performed to

determine inhibitory effects of compounds of formula 1 on the activity in RNA-dependant RNA-polymerase.

To test in vitro for HCV activity in RNA-dependant RNA-polymerase, the following experiment was carried out.

First, 10 μl of HCV NS5B(RNA-polymerase) and 25 μl of reaction buffer solution [Tris·Cl (pH 7.5) 0.1 M, NaCl 0.1 M, $MgCl_2$ 0.01 M, KCl 0.2 M, EDTA 0.002 M, DTT 0.05 M] were added to a well coated with streptavidin. 10 ㎕ of reaction mixture containing poly A/UTP,as a RNA template-primer, DIG-UTP, biotin-UTP and UTP were added and subsequently test compounds prepared were also added at the final concentration of 10, 1 and 0.1 μg/ml. The mixture was allowed to react 22 ℃ for 1 hr. The inhibitory activity was measured in comparison with negative control without the test compounds. At this time, RNA was formed from RNA by the action of HCV polymerase, forming bonds with streptavidin coated on the bottom of wells due to dioxigenin and biotin attached to nucleotides. When the reaction was completed, each well was washed with 200 ㎕ of washing buffer (pH 7.0) for 30 sec. three times to remove remaining impurities. 200 ㎕ of anti-DIG-POD antibody was added to each well and allowed to react for 1 hr at 37℃, and the wells were washed with cleaning buffer to remove impurities. 200 ㎕ of ABTS™, a substrate for peroxidase(POD), was added to

each well, allowed to react at room temperature for 30 min., and absorbency at 405 nm was measured for each solution using ELISA reader.

The percentage of inhibitory effect in the activity of HCV RNA polymerase, was calculated using the negative control without the test compounds and the results are represented in Table 4 as follows.

<Table 4>

Inhibitory effect on the HCV proliferation

compound	Inhibitory activity on HCV-RNA polymerase(%)		
	10 ㎍/㎖	1 ㎍/㎖	0.1 ㎍/㎖
Example 1	33	11	0
Example 2	46	33	16
Example 3	55	30	10
Example 4	46	26	19
Example 5	70	56	38
Example 6	25	23	0
Example 7	59	38	12
Example 8	83	54	40
Example 9	90	61	46
Example 10	63	41	24
Example 11	52	37	10
Example 12	81	55	37
Example 13	46	37	5
Example 14	62	33	15
Example 15	60	32	10
Example 16	59	29	0
Example 17	69	43	30
Example 18	55	28	19
Example 19	66	13	0
Example 22	33	22	7

Example 23	52	39	6
Example 24	72	52	43
Example 25	66	41	30
Example 26	72	52	43
Example 27	66	41	30
Example 28	40	20	0
Example 29	75	40	20
Example 30	65	33	7
Example 31	42	10	0
Example 32	34	12	0
Example 33	57	32	10
Example 34	85	48	37
Example 36	45	33	0
Example 37	44	15	0
Example 38	45	26	12
Example 39	30	0	0
Example 40	68	45	22
Example 41	83	54	37
Example 42	44	15	0
Example 43	47	20	4
Example 44	32	11	2
Example 47	49	18	0
Example 48	36	11	0
Example 49	45	31	20
Example 50	84	53	40

<Experiment 4> Cytotoxicity test

To determine if compounds of formula 1 exhibit cytotoxicity, *in vitro* tests were carried out using HepG2 cells with MTT analysis method as generally known and the results are showed in Table 5 as follows.

<Table 5>

Cytotoxicities on the HepG2 cell

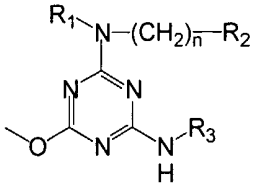
Compound	Cytotoxicities on the $HepG_2$ cell(IC_{50})
Example 2	>100
Example 12	>100
Example 34	>100
IC_{50} : 50% Inhibitory Concentration(㎍/㎖)	

As a result, the compounds used in the experiments have higher than 100 ㎍/㎖ for IC_{50} and are considered to have little cytotoxicity.

As described above, novel methoxy-1,3,5-triazine derivatives represented by formula 1 of the present invention have the dramatic inhibitory effect on proliferation of HBV and HCV with little side effect, and may be useful as therapeutic agents for prevention and treatment of hepatitis B and C. Moreover, it is expected that compounds of the present invention, being non-nucleosidic, do not have problems such as toxicity and early development of resistant virus strains observed by nucleoside substances. Furthermore, compounds of the present invention may be used together with nucleoside compounds since the former seem to act on allosteric binding pockets while the latter work in the domain of polymerase activities.

WHAT IS CLAIMED IS;

1. A compound of formula 1 or its pharmaceutically acceptable salt:



(I)

wherein,

R_1 is H or C_1-C_3 alkyl group,

R_2 is H; hydroxy; straight or branched C_1-C_4 alkyl group; straight or branched C_1-C_3 alkoxy group; C_1-C_3 hydroxyalkyl group; C_2-C_6 dialkylamino group; C_3-C_6 cycloalkyl group; lactam; saturated or unsaturated a 5 or 6 membered heterocyclic compounds containing 1 to 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted with straight or branched C_1~C_3 alkyl group; bicyclo compounds containing 1 to 2 heteroatoms selected from N, O and S;

or R_1 and R_2 are joined to form a 5 or 6 membered heterocyclic ring containing 1 to 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted with hydroxy, straight or branched C_1-C_4 alkyl group, C_1-C_3 hydroxyalkyl group, carbamoyl, C_1-C_3 alkylcarbamoyl, C_1-C_3 alkoxycarbonyl group, aryl group, or arylcarbonyl group;

n is an integer of 0 to 4;

R_3 is 5-indazolyl or 6-indazolyl group;

in the case that R_2 has the chiral carbon, the compound of formula 1 is the stereoisomer of (R) or (S) and the present invention contains both their stereoisomers and racemic compounds.

2. The compound of claim 1, wherein R_1 is hydrogen atom;

R_2 is hydroxy, methyl, ethyl, isopropyl, cyclopropyl, morpholinyl, piperazinyl, pyrrolyl, indolyl, pyridinyl, pyrrolidinyl, imidazolyl, piperidinyl or isonicotinyl group; and n is an integer of 0 to 3.

3. The compound of claim 1, which is selected from the group consisting of:

1) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-morpholino ethyl)amino-1,3,5-triazine;
2) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-morpholino ethyl)amino-1,3,5-triazine;
3) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-methylamino-1,3,5-triazine;
4) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-methylamino-1,3,5-triazine;
5) 2-(1*H*-5-indazolyl)amino-4-isopropylamino-6-methoxy-1,3,5-triazine;
6) 2-(1*H*-6-indazolyl)amino-4-isopropylamino-6-methoxy-1,3,5-

triazine;

7) 2-cyclopropylamino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

8) 2-cyclopropylamino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

9) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-methoxy ethyl)amino-1,3,5-triazine;

10) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-methoxy ethyl)amino-1,3,5-triazine;

11) 2-(2-hydroxyethyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

12) 2-(2-hydroxyethyl)amino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

13) 2-(2-dimethylaminoethyl)amino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

14) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-morpholinoamino-1,3,5-triazine;

15) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-morpholinoamino-1,3,5-triazine;

16) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino amino-1,3,5-triazine;

17) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino amino-1,3,5-triazine;

18) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(2-(2-pyridyl)ethyl) amino-1,3,5-triazine;

19) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(2-(2-pyridyl)ethyl) amino-1,3,5-triazine;

20) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(3-(2-oxo-pyrrolidino)propyl)amino-1,3,5-triazine;

21) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(3-(2-oxo-pyrrolidino)propyl)amino-1,3,5-triazine;

22) 2-(1*H*-5-indazolyl)amino-4-(2-(1*H*-3-indolyl)ethyl)amino-6-methoxy-1,3,5-triazine;

23) 2-(1*H*-6-indazolyl)amino-4-(2-(1*H*-3-indolyl)ethyl)amino-6-methoxy-1,3,5-triazine;

24) 2-(3-(1*H*-1-imidazolyl)propyl)amino-4-(1*H*-5-indazolyl) amino-6-methoxy-1,3,5-triazine;

25) 2-(3-(1*H*-1-imidazolyl)propyl)amino-4-(1*H*-6-indazolyl) amino-6-methoxy-1,3,5-triazine;

26) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-morpholino-1,3,5-triazine;

27) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-morpholino-1,3,5-triazine;

28) 2-(1*H*-1-imidazolyl)-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

29) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-pyrrolidino-1,3,5-triazine;

30) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-pyrrolidino-1,3,5-triazine;

31) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-((2*S*)-methoxy

carbonyl)pyrrolidino-1,3,5-triazine;

32) 2-(4-hydroxy)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

33) 2-(4-hydroxy)piperidino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

34) 2-(4-amido)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

35) 2-(4-amido)piperidino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

36) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-*N*-methylamido) piperidino-1,3,5-triazine;

37) 2-(4-ethoxycarbonyl)piperidino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

38) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino-1,3,5-triazine;

39) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-methyl)piperazino-1,3,5-triazine;

40) 2-(4-(2-hydroxyethyl))piperazino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

41) 2-(4-(2-hydroxyethyl))piperazino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

42) 2-(4-ethoxycarbonyl)piperazino-4-(1*H*-5-indazolyl)amino-6-methoxyl-1,3,5-triazine;

43) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-(*N*-methylamido methyl))piperazino-1,3,5-triazine;

44) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-(*N*-methylamido methyl))piperazino-1,3,5-triazine;

45) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(4-nicotinoyl) piperazino-1,3,5-triazine;

46) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(4-nicotinoyl) piperazino-1,3,5-triazine;

47) 2-(4-(5-ethoxycarbonyl-2-methylthio-1,3-pyrimidinyl)) piperazino-4-(1*H*-5-indazolyl)amino-6-methoxy-1,3,5-triazine;

48) 2-(4-(5-ethoxycarbonyl-2-methylthio-1,3-pyrimidinyl)) piperazino-4-(1*H*-6-indazolyl)amino-6-methoxy-1,3,5-triazine;

49) 2-(1*H*-5-indazolyl)amino-4-methoxy-6-(3-morpholinopropyl) amino-1,3,5-triazine; and

50) 2-(1*H*-6-indazolyl)amino-4-methoxy-6-(3-morpholinopropyl) amino-1,3,5-triazine.

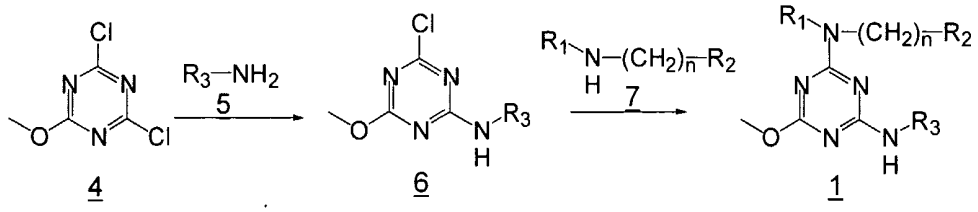
4. A process for preparing the compound of claim 1, which comprises:

1) reacting 2,4-dichloro-6-methoxy-1,3,5-triazine (4) with 5-aminoindazole or 6-aminoindazole (5) in the presence of a base in order to prepare 2-chloro-6-methoxy-1,3,5-triazine derivative substituted with aminoindazole (6); and

2) reacting thus obtained compound (6) with amine

compound (7) in the presence of a base in order to prepare the compound of claim 1:

Scheme 1



(wherein, R_1, R_2, R_3 and n are as defined in formula 1.)

5. A pharmaceutical composition for treating or preventing hepatitis B, which comprises the compound of claim 1 or its pharmaceutically acceptable salt as an effective ingredient.

6. A pharmaceutical composition for treating or preventing hepatitis C, which comprises the compound of claim 1 or its pharmaceutically acceptable salt as an effective ingredient.

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/KR02/00565

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 401/02, C07D 401/14, A61K 31/53, C07D 251/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D, A61K

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

Electronic data base consulted during the internatational search (name of data base and, where practicable, search terms used)

CA(STN), MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,962,453 A (Nippon Shinyaku Co. Ltd.) 5 Oct. 1999 abstract, claims	1-6
A	Br. J. Pharmacol. Chemother., 1966, 27(3), 486-490 "Aspects of the Metabolism of Triazine Derivatives Active in Experimentally Induced Virus Infections", CRESSERI, ANGEL et al. abstract	1-6
A, P	Biooragnic & Medicinal Chemistry Letters, 3 Sept. 2001, 11(17), 2229 - 2234 "Evolution of Anti-HIV Drug Candidates Part 2 : Diaryltriazine (DATA) Analogues", LUDOVICI, D. W. et al. abstract	1-6
A, P	WO 0147897 A1 (Pharmacopeia, Bristo-Myers Squibb) 5 July 2001 abstract, claims	1-6

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

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

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