



[Document Name] Specification

[Title of Invention] Novel Triazine Derivative And Pharmaceutical Composition
Comprising The Same

[Technical Field]

[0001]

The invention relates to P2X receptor, specifically to a compound useful for the treatment of diseases or conditions associated with a P2X₃ receptor, specifically to a P2X₃ and/or P2X_{2/3} receptor, and a pharmaceutical composition comprising such compound.

[Background Art]

[0002]

ATP (adenosine triphosphate) is known to serve as a source of energy in cells and a substrate of phosphorylation, as well as an extracellular messenger. It is known that ATP is released from a cell by various stimulation such as cellular injury, inflammation, nociceptive stimulus, reduced blood oxygen level, and also known to be released together with another messenger from a primary sensory nerve terminal. ATP thus released mediates various extracellular signal transductions through an ATP receptor (Non-Patent Document 4, Non-Patent Document 5).

[0003]

ATP receptor is categorized into ionotropic P2X family and G protein-coupled P2Y family. For P2X family, seven subtypes have been reported, and a member of this family forms a homo-trimeric structure or a hetero-trimeric structure together with another member of this subtype and functions as a non-specific cation channel (Non-Patent Document 6).

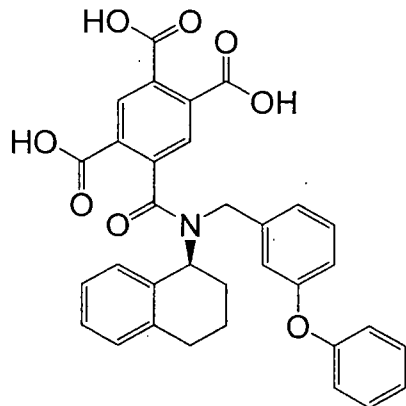
[0004]

ATP is known to cause pain, and studies with P2X₃ knockout and knockdown methodologies have shown that P2X₃ receptor mediates transmission of chronic pain. P2X₃ receptors are expressed in a specific manner on peripheral sensory nerve to form a homo-complex or hetero-complex with P2X₂ (P2X_{2/3}) (Non-Patent Document 1).

[0005]

Later, the compound A-317491 was reported as a specific antagonist to P2X₃ and P2X_{2/3} receptors. A-317491 is tri-substituted-N-[(1S)-1,2,3,4-tetrahydro-1-naphthalenyl]benzamide derivative represented by the formula:

[Chemical Formula 1]



(Patent Document 1). It was reported to exhibit an antagonist activity to P2X₃ and P2X_{2/3} receptors and analgesic action in neuropathic pain model and inflammatory pain model (Non-Patent Document 7). This indicates that pain sensation is transmitted via P2X₃ or P2X_{2/3} receptor and that a P2X₃ or P2X_{2/3} receptor antagonist



is useful as an analgesic. Also, compounds that exhibit P2X₃ or P2X_{2/3} receptor antagonizing effect are described in Patent Documents 2-7.

[0006]

Additionally, it was recently reported that vesical reflex was strongly reduced in P2X₃ knockout mouse (Non-Patent Document 2), suggesting that a P2X₃ antagonist is useful in the treatment of diseases caused by overactive bladder.

[0007]

Patent document 8, 9, 10 and 11 discloses that the compounds having similar chemical structures to the compound of the invention, however, does not disclose that the compounds having an analgesic effect and a P2X₃ or P2X_{2/3} receptor antagonizing effect. Non-Patent documents 8 disclose that the compounds having similar chemical structures to the compound of the invention and an analgesic effect, however, does not disclose that the compound having a P2X₃ or P2X_{2/3} receptor antagonizing effect.

[0008]

[Patent Document 1]WO02/094767

[Patent Document 2]WO2005/095359

[Patent Document 3]US20070037974

[Patent Document 4]US20070049758

[Patent Document 5]US20070049610

[Patent Document 6]US20070049609

[Patent Document 7]US20070049534

[Patent Document 8]JP12-072757

[Patent Document 9]WO2006/104713

[Patent Document 10]WO2006/104715

[Patent Document 11]WO2006/102112

[Non-Patent Document 1] Neuroscientist 11 (2005) 345-356

[Non-Patent Document 2] J. Physiol. 567.2 (2005) 621-639

[Non-Patent Document 3] Expert Opin. Ther. Patens (2006) 16(8) 113-1127

[Non-Patent Document 4] J. Physiol. (2003), 554(2), 301-308

[Non-Patent Document 5] J. Physiology (2003), 553(3), 683-694

[Non-Patent Document 6] Pflugers Arch Eur J physiol (2006), 452, 513-537

[Non-Patent Document 7] PNAS (2002), 99(26), 17179-17184

[Non-Patent Document 8] J. Med. Chem. (2008), 51(23), 7635-7639

[Disclosure of Invention]

[Problems to be Resolved by the Invention]

[0009]

The present invention provides a novel P2X₃ and/or P2X_{2/3} receptor antagonist.

[Means of Solving the Problems]

[0010]

During studies to solve the problems described above, the inventors have discovered novel compounds that bind specifically to P2X₃ and/or P2X_{2/3} receptor and exhibit an antagonizing effect, and thus, achieved the inventions described bellow.

[Effect of the Invention]

[0011]

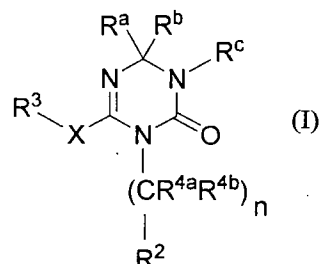
The compound of the invention has antagonizing effect on P2X₃ and/or P2X_{2/3} receptor and is useful in the treatment of diseases or conditions associated with a P2X₃ and/or P2X_{2/3} receptor, such as chronic pain, overactive bladder, etc.

[Mode for carrying out the Invention]

[0012]

(1) A compound represented by the formula (I):

[Chemical Formula 2]



wherein

R^a, R^b and R^c are,

(a) R^a and R^b are taken together =Z;

=Z is =O, =S or =N-R⁶;

R⁶ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^c is a group represented by R^{1c};

R^{1c} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

(b) R^b and R^c are taken together to form a bond;

R^a is a group represented by -Y-R^{1a};

R^{1a} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

-Y- is -O-, -S-, -N(R⁷)- or -C(R^{8a}R^{8b})-;

R⁷ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, or R⁷ and R^{1a} are taken together to form a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

R^{8a} and R^{8b} are each independently hydrogen, halogen, or substituted or unsubstituted alkyl;

n is an integer of 0 to 4;

R² is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or

unsubstituted heteroaryl;

R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are each independently hydrogen, substituted or unsubstituted alkyl, or R^{4a} and R^{4b} are taken together oxo;

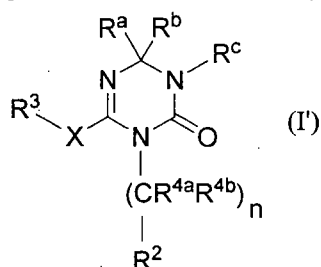
-X- is -O-, -S- or -N(R^5)-;

R^5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted acyl;

provided that R^3 is not cyclohexyl substituted with guanidyl when -X- is -NH-, or its pharmaceutically acceptable salt, or a solvate thereof.

(1') A compound represented by the formula (I'):

[Chemical Formula 3]



wherein

R^a , R^b and R^c are,

(a) R^a and R^b are taken together =Z; and R^c is R^{1c} ; or

(b) R^b and R^c are taken together to form a bond; and R^a is -Y- R^{1a} ;

R^{1a} and R^{1c} are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is an integer of 0 to 4;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are each independently hydrogen, substituted or unsubstituted alkyl;

-X- is -O-, -S- or -N(R^5)-;

R^5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted acyl;

when R^a , R^b and R^c are (a);

$=Z$ is $=O$, $=S$ or $=N \cdot R^6$;

R^6 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

when R^a , R^b and R^c are (b),

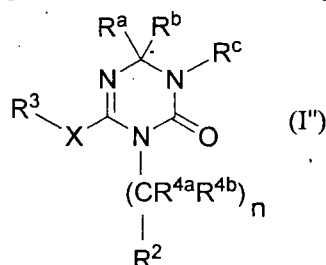
$-Y-$ is $-O-$, $-S-$ or $-N(R^7)-$;

R^7 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted acyl;

provided that R^3 is not cyclohexyl substituted with guanidyl when $-X-$ is $-NH-$, or its pharmaceutically acceptable salt, or a solvate thereof.

(1'') A compound represented by the formula (I''):

[Chemical Formula 4]



wherein

R^a , R^b and R^c are,

(a) R^a and R^b are taken together $=Z$; and R^c is R^{1c} ; or

(b) R^b and R^c are taken together to form a bond; and R^a is $-Y-R^{1a}$;

R^{1a} and R^{1c} are each independently hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted acyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are each independently hydrogen, or substituted or unsubstituted lower alkyl;

$-X-$ is $-O-$, $-S-$ or $-N(R^5)-$;

R^5 is hydrogen, or substituted or unsubstituted lower alkyl, or substituted or unsubstituted acyl;

when R^a , R^b and R^c are (a);

$=Z$ is $=O$, $=S$ or $=N \cdot R^6$;

R^6 is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is an integer of 1 to 3;

when R^a , R^b and R^c are (b);

R^3 is substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-Y- is -O-, -S- or -N(R^7)-;

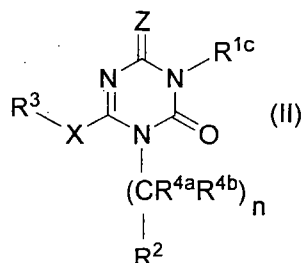
R^7 is hydrogen, substituted or unsubstituted lower alkyl, or substituted or unsubstituted acyl;

n is an integer of 0 to 3,

or its pharmaceutically acceptable salt, or a solvate thereof.

(2) The compound according to (1), wherein the compound is represented by the formula (II):

[Chemical Formula 5]



wherein

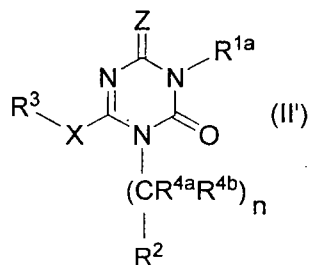
R^{1c} , R^{4a} , R^{4b} , -X- and =Z are as defined in (1);

n is an integer of 1 to 4;

R^2 and R^3 are each independently substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(2') The compound according to (1'), wherein the compound is represented by the formula (II'):

[Chemical Formula 6]



wherein

R^{1c} , R^{4a} , R^{4b} , -X- and =Z are as defined in (1);

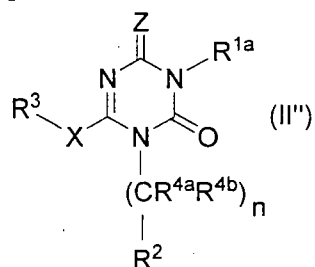
n is an integer of 1 to 4;

R^2 and R^3 are each independently substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(2'') The compound according to (1''), wherein the compound is represented by

the formula (II''):

[Chemical Formula 7]



wherein

R^{1a} , R^2 , R^3 , R^{4a} , R^{4b} , $-X-$, $=Z$ and n are as defined in (1''), or its pharmaceutically acceptable salt, or a solvate thereof.

(3) The compound according to the above (1) or (2), wherein $-X-$ is $-N(R^5)-$ wherein R^5 is as defined in the above (1), or its pharmaceutically acceptable salt, or a solvate thereof.

(3') The compound according to the above (2'), wherein $-X-$ is $-N(R^5)-$ wherein R^5 is as defined in the above (1'), or its pharmaceutically acceptable salt, or a solvate thereof.

(3'') The compound according to the above (2''), wherein $-X-$ is $-N(R^5)-$ wherein R^5 is as defined in the above (1''), or its pharmaceutically acceptable salt, or a solvate thereof.

(4) The compound according to any one of the above (1) to (3), wherein R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(4') The compound according to any one of the above (2') or (3'), wherein R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

(4'') The compound according to any one of the above (2'') or (3''), wherein R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

(5) The compound according to any one of the above (1) to (4), wherein $=Z$ is $=O$, or its pharmaceutically acceptable salt, or a solvate thereof.

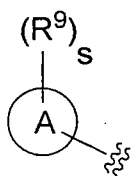
(6) The compound according to any one of the above (1) to (5), wherein R^{1c} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, hydroxy, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted

cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclic ring-oxy-carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(6') The compound according to any one of the above (2') to (4'), wherein R^{1c} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, hydroxy, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclic ring-oxy-carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(6'') The compound according to any one of the above (2'') to (4''), wherein R^{1a} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or two or more substituent selected from halogen, hydroxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted benzoyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted lower alkylcarbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(7) The compound according to any one of the above (1) to (6), wherein R^3 is a group represented by the formula:
[Chemical Formula 8]



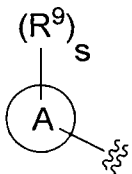
wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3; and

R⁹ is each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt, or a solvate thereof.

(7') The compound according to any one of the above (2') to (4') or (6'), wherein R³ is a group represented by the formula:

[Chemical Formula 9]



wherein ring A is aryl or heteroaryl;

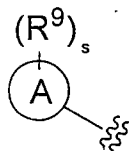
s is an integer of 0 to 3;

R⁹ is each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its

pharmaceutically acceptable salt, or a solvate thereof.

(7'') The compound according to any one of the above (2'') to (4'') or (6''), wherein R^3 is a group represented by the formula:

[Chemical Formula 10]



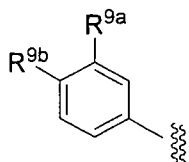
wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3;

R^9 is each independently halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkenyloxy, substituted or unsubstituted lower alkynyl, substituted or unsubstituted alkynyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted lower alkylcarbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, nitrile, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenyloxy, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt, or a solvate thereof.

(8) The compound according to any one of the above (1) to (7), wherein R^3 is a group represented by the formula:

[Chemical Formula 11]

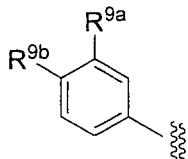


wherein R^{9a} and R^{9b} are each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy,

substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt, or a solvate thereof.

(8') The compound according to any one of the above (2') to (4'), (6') or (7'), wherein R^3 is a group represented by the formula:

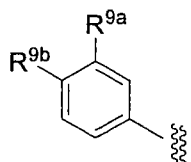
[Chemical Formula 12]



wherein R^{9a} and R^{9b} are each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt, or a solvate thereof.

(8'') The compound according to any one of the above (2'') to (4''), (6'') or (7''), wherein R^3 is a group represented by the formula:

[Chemical Formula 13]

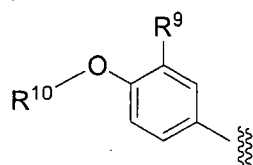


wherein R^{9a} and R^{9b} are each independently halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkenyloxy, substituted or unsubstituted lower alkynyl, substituted or unsubstituted alkynyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted lower alkylcarbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, nitrile, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenyloxy, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryl, or substituted or unsubstituted heteroaryloxy, or its

pharmaceutically acceptable salt, or a solvate thereof.

(9) The compound according to any one of the above (1) to (8), wherein R^3 is a group represented by the formula:

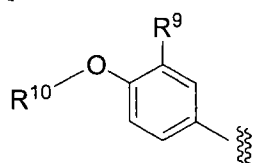
[Chemical Formula 14]



wherein R^9 is as defined in the above (7); and R^{10} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(9') The compound according to any one of the above (2') to (4') or (6') to (8'), wherein R^3 is a group represented by the formula:

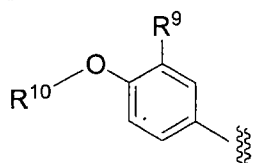
[Chemical Formula 15]



wherein R^9 is as defined in the above (7'); and R^{10} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(9'') The compound according to any one of the above (2'') to (4'') or (6'') to (8''), R^3 is a group represented by the formula:

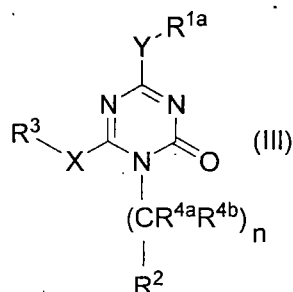
[Chemical Formula 16]



wherein R^9 is as defined in the above (7''); and R^{10} is substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(10) The compound according to the above (1), wherein the compound is represented by the formula (III):

[Chemical Formula 17]



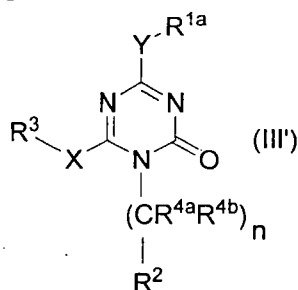
wherein R^{1a} , R^{4a} , R^{4b} , -X- and -Y- are as defined in the above (1);

n is an integer of 1 to 4; and

R^2 and R^3 are each independently substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(10') The compound according to the above (1'), wherein the compound is represented by the formula (III'):

[Chemical Formula 18]

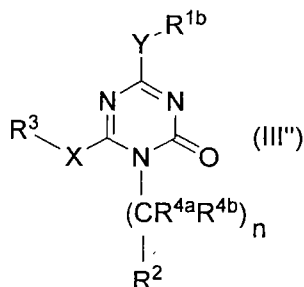


wherein R^{1a} , R^{4a} , R^{4b} , -X-, -Y- and n are as defined in the above (1');

R^2 and R^3 are each independently substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(10'') The compound according to the above (1''), wherein the compound is represented by the formula (III''):

[Chemical Formula 19]



wherein R^{1b} , R^2 , R^3 , R^{4a} , R^{4b} , -X-, -Y- and n are as defined in the above (1''), or its pharmaceutically acceptable salt, or a solvate thereof.

(11) The compound according to the above (1) or (10), wherein -X- is -N(R^5)- wherein R^5 is as defined in the above (1), or its pharmaceutically acceptable salt, or a solvate thereof.

(11') The compound according to the above (10'), wherein -X- is -N(R⁵)- wherein R⁵ is as defined in the above (1'), or its pharmaceutically acceptable salt, or a solvate thereof.

(11'') The compound according to the above (10'), wherein -X- is -N(R⁵)- wherein R⁵ is as defined in the above (1''), or its pharmaceutically acceptable salt, or a solvate thereof.

(12) The compound according to any one of the above (1), (10) or (11), wherein R² is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(12') The compound according to the above (10') or (11'), wherein R² is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

(12'') The compound according to the above (10') or (11'), wherein R² is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, and n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

(13) The compound according to any one of the above (1) or (10) to (12), wherein -Y- is -O-, or its pharmaceutically acceptable salt, or a solvate thereof.

(13') The compound according to the above (10') or (11'), wherein -Y- is -O-, or its pharmaceutically acceptable salt, or a solvate thereof.

(13'') The compound according to the above (10'') or (11''), wherein -Y- is -O-, or its pharmaceutically acceptable salt, or a solvate thereof.

(14) The compound according to any one of the above (1) or (10) to (13), wherein R^{1a} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, hydroxy, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclic ring-oxy-carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl), or its pharmaceutically acceptable salt, or a solvate thereof.

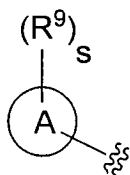
(14') The compound according to any one of the above (10') to (13'), wherein

R^{1a} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, hydroxy, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclic ring-oxy-carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl), or its pharmaceutically acceptable salt, or a solvate thereof.

(14'') The compound according to any one of the above (10'') to (13''), wherein R^{1b} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or two or more substituent selected from halogen, hydroxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted benzoyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted lower alkylcarbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

(15) The compound according to any one of the above (1) or (10) to (14), wherein R^3 is a group represented by the formula:

[Chemical Formula 20]



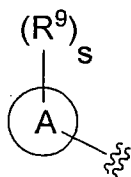
wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3; and

R^9 is as defined in the above (7), or its pharmaceutically acceptable salt, or a solvate thereof.

(15') The compound according to any one of the above (10') to (14'), wherein R^3 is a group represented by the formula:

[Chemical Formula 21]



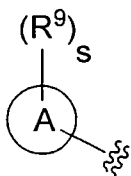
wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3; and

R⁹ is as defined in the above (7'), or its pharmaceutically acceptable salt, or a solvate thereof.

(15'') The compound according to any one of the above (10'') to (13''), wherein R³ is a group represented by the formula:

[Chemical Formula 22]



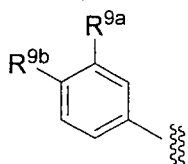
wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3; and

R⁹ is as defined in the above (7''), or its pharmaceutically acceptable salt, or a solvate thereof.

(16) The compound according to any one of the above (1) or (10) to (15), wherein R³ is a group represented by the formula:

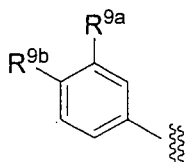
[Chemical Formula 23]



wherein R^{9a} and R^{9b} are as defined in the above (8), or its pharmaceutically acceptable salt, or a solvate thereof.

(16') The compound according to any one of the above (10') to (15'), wherein R³ is a group represented by the formula:

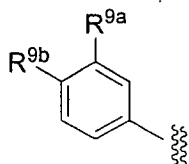
[Chemical Formula 24]



wherein R^{9a} and R^{9b} are as defined in the above (8'), or its pharmaceutically acceptable salt, or a solvate thereof.

(16'') The compound according to any one of the above (10'') to (15''), wherein R³ is a group represented by the formula:

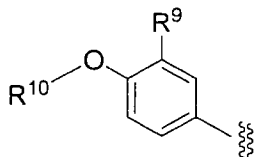
[Chemical Formula 25]



wherein R^{9a} and R^{9b} are as defined in the above (8''), or its pharmaceutically acceptable salt, or a solvate thereof.

(17) The compound according to any one of the above (1) or (10) to (16), wherein R³ is a group represented by the formula:

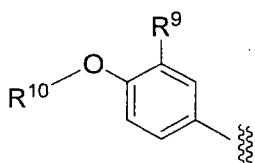
[Chemical Formula 26]



wherein R⁹ is as defined in the above (7); and R¹⁰ is as defined in the above (9), or its pharmaceutically acceptable salt, or a solvate thereof.

(17') The compound according to any one of the above (10') to (16'), wherein R³ is a group represented by the formula:

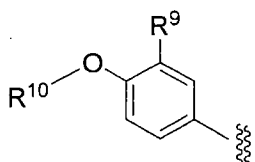
[Chemical Formula 27]



wherein R⁹ is as defined in the above (7'); and R¹⁰ is as defined in the above (9'), or its pharmaceutically acceptable salt, or a solvate thereof.

(17'') The compound according to any one of the above (10'') to (16''), wherein R³ is a group represented by the formula:

[Chemical Formula 28]



wherein R⁹ is as defined in the above (7''); and R¹⁰ is as defined in the above (9''), or its pharmaceutically acceptable salt, or a solvate thereof.

(18) A pharmaceutical composition comprising the compound according to any one of the above (1) to (17), or its pharmaceutically acceptable salt, or a solvate thereof.

(18') A pharmaceutical composition comprising the compound according to any one of the above (1') to (4') or (6') to (17'), or its pharmaceutically acceptable salt, or a solvate thereof.

(18'') A pharmaceutical composition comprising the compound according to any one of the above (1'') to (4'') or (6'') to (17''), or its pharmaceutically acceptable salt, or a solvate thereof.

(19) The pharmaceutical composition according to the above (18), wherein the composition is for a P2X₃ and/or P2X_{2/3} receptor antagonist.

(19') The pharmaceutical composition according to the above (18'), wherein the composition is for a P2X₃ and/or P2X_{2/3} receptor antagonist.

(19'') The pharmaceutical composition according to the above (18''), wherein the composition is for a P2X₃ and/or P2X_{2/3} receptor antagonist.

(20) A method for treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor characterized by administration of the compound according to any one of the above (1) to (17), or its pharmaceutically acceptable salt, or a solvate thereof.

(20') A method for preventing and/or treating a disease related to P2X₃ and/or P2X_{2/3} receptor characterized by administration of the compound according to any one of the above (1') to (4') or (6') to (17'), or its pharmaceutically acceptable salt, or a solvate thereof.

(20'') A method for preventing and/or treating a disease related to P2X₃ and/or P2X_{2/3} receptor characterized by administration of the compound according to any one of the above (1') to (4') or (6') to (17'), or its pharmaceutically acceptable salt, or a solvate thereof.

(21) Use of the compound of any one of the above (1) to (17), or its pharmaceutically acceptable salt, or a solvate thereof in the manufacturing of an agent for treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor.

(21') Use of the compound of any one of the above (1') to (4') or (6') to (17'), or its pharmaceutically acceptable salt, or a solvate thereof in the manufacturing of an agent for treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor.

(21'') Use of the compound of any one of the above (1'') to (4'') or (6'') to (17''), or its pharmaceutically acceptable salt, or a solvate thereof in the manufacturing of an agent for treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor.

(22) A compound according to any one of the above (1) to (17), or its pharmaceutically acceptable salt, or a solvate thereof for use in a method for treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor.

[0013]

As used throughout the specification, the following terms have the following meaning unless specifically indicated.

[0014]

The term "halogen" means fluorine, chlorine, bromine and iodine.

[0015]

The halogen moiety in said "lower haloalkyl", "lower haloalkyloxy", "haloalkyl" and "haloalkyloxy" is as defined above for "halogen".

[0016]

The term "alkyl" includes a straight or branched chain monovalent hydrocarbon group containing from 1 to 15, preferably from 1 to 10 more preferably from 1 to 6 carbons. For example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, isooctyl, n-nonyl, n-decyl, n-undecanyl, dodecanyl, tridecanyl, etc. are exemplified.

[0017]

The term "lower alkyl" includes a straight or branched chain monovalent hydrocarbon group containing from 1 to 6, preferably from 1 to 3 carbons. For example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, isohexyl, etc. are exemplified.

[0018]

The lower alkyl moiety in said "lower haloalkyl", "lower alkylamino", "lower alkylimino", "lower alkylsulfonyl", "lower alkylsulfamoyl" and "lower alkylcarbamoyl" is as defined above for "lower alkyl".

[0019]

The alkyl moiety in said "haloalkyl", "alkylamino", "alkylimino", "alkylsulfonyl", "alkylsulfamoyl", "alkylcarbamoyl", "arylalkyl" and "arylalkylamino" is as defined above for "alkyl".

[0020]

The term "lower alkyloxy" includes an alkyloxy group wherein the lower alkyl moiety is as defined above for "lower alkyl". For example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, etc. are exemplified.

The alkyl moiety in said "alkyloxy" is as defined above for "alkyl".

[0021]

The lower alkyloxy moiety in said "lower haloalkyloxy" and "lower alkyloxyimino" is as defined above for "lower alkyloxy".

[0022]

The term "lower alkylthio" includes, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, etc.

The alkyl moiety in said "alkylthio" is as defined above for "alkyl".

[0023]

The term "lower alkyloxycarbonyl" includes, for example, methyloxycarbonyl, ethyloxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, tert-butyloxycarbonyl, n-pentyloxycarbonyl, etc.

The alkyloxy moiety in said "alkyloxycarbonyl" is as defined above for "alkyloxy".

[0024]

The term "lower alkylcarbamoyl" includes mono- or di-lower alkylcarbamoyl. For example, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, n-butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, etc. are exemplified.

The alkyl moiety in said "alkylcarbamoyl" is as defined above for "alkyl".

[0025]

The term "alkenyl" includes a straight or branched chain alkenyl containing from 2 to 15 carbons, preferably containing from 2 to 10 carbons, more preferably containing from 2 to 6 carbons having one or more double bonds at any position. For

example, vinyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, etc. are exemplified.
[0026]

The term "lower alkenyl" includes a straight or branched chain alkenyl containing from 2 to 6 carbons, preferably containing from 2 to 3 carbons having one or more double bonds at any position. For example, vinyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, etc. are exemplified.
[0027]

The lower alkenyl moiety of "lower alkenyloxy" and "lower alkenyloxycarbonyl" is as defined above for "lower alkenyl".

The alkenyl moiety of "alkenyloxy" and "alkenyloxycarbonyl" is as defined above for "alkenyl".
[0028]

The term "alkynyl" includes a straight or branched chain alkynyl containing from 2 to 15 carbons, preferably containing from 2 to 10 carbons, more preferably containing from 2 to 6 carbons. For example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc. are exemplified. They have one or more triple bonds at any position, and optionally, have a double bond.
[0029]

The term "lower alkynyl" includes a straight or branched chain alkynyl containing from 2 to 6 carbons, preferably containing from 2 to 3 carbons. For example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, etc. are exemplified. They have one or more triple bonds at any position, and optionally, have a double bond.
[0030]

The lower alkynyl moiety of "lower alkynyloxy" and "lower alkynyloxycarbonyl" is as defined above for "lower alkynyl".

The alkynyl moiety of "alkynyloxy" and "alkynyloxycarbonyl" is as defined above for "alkynyl".
[0031]

The term "acyl" includes a group of the formula $R-C(=O)-$, wherein R is, for example, "lower alkyl", "alkyl", "lower alkenyl", "alkenyl", "lower alkynyl", "alkynyl" as defined above or "aryl", "a heterocyclic group", "cycloalkyl", "cycloalkenyl", "arylalkyl" or "heteroarylalkyl" as defined below.
[0032]

The acyl moiety of "acylamino" and "acylimino" is as defined above for "acyl".
[0033]

The term "cycloalkane" includes a monocyclic or polycyclic saturated cyclic carbocyclic ring containing from 3 to 10 carbons. Monocyclic cycloalkane includes, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, etc. Polycyclic cycloalkane includes norbornane, tetrahydronaphthalene, etc.
[0034]

The term "cycloalkyl" includes a monovalent group derived from "cycloalkane" as defined above. Monocyclic cycloalkyl includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, etc. Polycyclic cycloalkyl includes norbornanyl, tetrahydronaphthalene-5-yl, tetrahydronaphthalene-6-yl, etc.

Preferable "cycloalkyl" for R² is cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

[0035]

The cycloalkyl moiety of "cycloalkyloxycarbonyl" is as defined above for "cycloalkyl".

[0036]

The term "cycloalkane-diyl" includes a divalent group derived from "cycloalkane" as defined above. Monocyclic cycloalkane-diyl includes, for example, cyclopropane-diyl, cyclobutane-diyl, cyclopentane-diyl, cyclohexane-diyl, cycloheptane-diyl, cyclooctane-diyl, cyclonone-diyl, cyclodecane-diyl, etc. Polycyclic cycloalkane-diyl includes norbornane-diyl, etc.

[0037]

The term "cycloalkene" includes a non-aromatic monocyclic or polycyclic ring of 3 to 10 carbons containing at least one carbon-carbon double bond. Monocyclic cycloalkene includes, for example, cyclopentene, cyclohexene, etc. Polycyclic cycloalkene includes norborne, indene, etc.

[0038]

The term "cycloalkenyl" includes a monovalent group derived from "cycloalkene" as defined above. Monocyclic cycloalkenyl includes cyclopentenyl, cyclohexenyl, etc. Polycyclic cycloalkenyl includes norbornyl, indene-1-yl, indene-2-yl, indene-3-yl, etc.

[0039]

The cycloalkenyl moiety of "cycloalkenyloxycarbonyl" is as defined above for "cycloalkenyl".

[0040]

The term "cycloalkene-diyl" includes a divalent group derived from "cycloalkene" as defined above. Monocyclic cycloalkene-diyl includes cyclopentene-diyl, cyclohexene-diyl, etc. Polycyclic cycloalkene-diyl includes norbornene-diyl, etc.

[0041]

The term "aromatic carbocyclic ring" includes an aromatic hydrocarbocyclic ring which is monocyclic or fused-cyclic. For example, benzene ring, naphthalene ring, anthracene ring, phenanthrene ring, etc. are exemplified.

[0042]

The term "aryl" includes a monovalent group derived from "aromatic carbocyclic ring" as defined above. For example, phenyl, 1-naphthyl, 2-naphthyl, anthryl, phenanthryl, etc. are exemplified.

[0043]

The aryl moiety of "aryloxycarbonyl" is as defined above for "aryl".

[0044]

The term "aromatic carbocyclic ring-diyl" includes a divalent group derived from "aromatic carbocyclic ring" as defined above. For example, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthalene etc.

[0045]

The term "heterocyclic ring" includes an aromatic or a non-aromatic monocyclic or fused-cyclic ring, which includes a five- to seven-membered ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring; a fused ring consisting of two or more said five- to seven-membered rings; or a fused ring consisting of said five- to seven-membered ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring fused to one or more "aromatic

carbocyclic ring", "cycloalkane " or "cycloalkene" as defined above.

For example, a non-aromatic heterocyclic ring such as pyrroline, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran, dihydropyridine, dihydropyridazine, dioxane, oxathiolane, thiane, tetrahydrofuran, tetrahydropyran, tetrahydrothiazole, tetrahydroisothiazole, etc.;

a monocyclic aromatic heterocyclic ring such as pyrrole, pyrazine, pyrazole, tetrazole, furan, thiophene, pyridine, imidazole, triazole, tetrazole, triazine, pyridazine, pyrimidine, isoxazole, thiazole, isothiazole, thiadiazole, oxazole, oxadiazole, etc; and

a fused heterocyclic ring such as indole, isoindole, indazole, indolizine, indoline, isoindoline, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, naphthyridine, quinoxaline, purine, pteridine, benzopyrane, benzimidazole, benzisoxazole, benzoxazole, benzoxadiazole, benzisothiazole, benzothiazole, benzothiadiazole, benzofuran, isobenzofuran, benzothiophene, benzotriazole, imidazopyridine, triazolopyridine, imidazothiazole, pyrazinopyridazine, benzimidazole, benzodioxane, tetrahydroquinoline, tetrahydrobenzothiophene, etc. are exemplified.

[0046]

The term "heterocyclic group" includes a monovalent group derived from "heterocyclic ring" as defined above. For example, non-aromatic heterocyclic groups such as pyrrolinyl, pyrrolidino, pyrrolidinyl, imidazolynyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidino, piperidyl, piperadino, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, tetrahydropyranyl, dihydropyridyl, dihydropyridazinyl, dihydropyrazinyl, dioxanyl, oxathiolanyl, thianyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazolynyl, tetrahydroisothiazolynyl, etc.;

monocyclic aromatic heterocyclic groups such as pyrrolyl, pyrazinyl, pyrazolyl, tetrazolyl, furyl, thienyl, pyridyl, imidazolyl, triazolyl, tetrazolyl, triazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl and oxadiazolyl, etc; and

fused heterocyclic groups such as indolyl, isoindolyl, indazolyl, indolizinyl, indolinyl, isoindolinyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzopyranyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, benzimidazolynyl, benzodioxanyl, tetrahydroquinoline, tetrahydrobenzothienyl, etc. are exemplified.

[0047]

The term "heterocyclic ring-diyl" includes a divalent group derived from "heterocyclic ring" as defined above. For example, non-aromatic heterocyclic ring-diyl such as pyrrolin-diyl, pyrrolidin-diyl, imidazolidin-diyl, pyrazolin-diyl, pyrazolidin-diyl, piperidin-diyl, piperazine-diyl, morpholin-diyl, thiomorpholin-diyl, tetrahydropyran-diyl, dihydropyridine-diyl, dihydropyridazin-diyl, dihydropyrazin-diyl, dioxan-diyl, oxathiolan-diyl, thian-diyl, tetrahydrofuran-diyl, tetrahydropyran-diyl, tetrahydrothiazol-diyl, tetrahydroisothiazol-diyl, etc.;

a monocyclic aromatic heterocyclic ring-diyl such as pyrrole-diyl, pyrazine-diyl, pyrazole-diyl, tetrazole-diyl, furan-diyl, thiophene-diyl, pyridine-diyl, imidazole-diyl, triazole-diyl, tetrazole-diyl, triazine-diyl, pyridazine-diyl, pyrimidine-diyl, pyrazine-

diyl, isoxazole-diyl, thiazole-diyl, isothiazole-diyl, thiadiazole-diyl, oxazole-diyl, oxadiazole-diyl, etc; and

a fused heterocyclic ring-diyl such as indole-diyl, isoindole-diyl, indazole-diyl, indolizine-diyl, indoline-diyl, isoindoline-diyl, quinoline-diyl, isoquinoline-diyl, cinnoline-diyl, phthalazine-diyl, quinazoline-diyl, naphthyridine-diyl, quinoxaline-diyl, purine-diyl, pteridine-diyl, benzopyrane-diyl, benzimidazole-diyl, benzisoxazole-diyl, benzoxazole-diyl, benzoxadiazole-diyl, benzisothiazole-diyl, benzothiazole-diyl, benzothiadiazone-diyl, benzofuran-diyl, isobenzofuran-diyl, benzothiophene-diyl, benzotriazole-diyl, imidazopyridine-diyl, triazolopyridine-diyl, imidazothiazole-diyl, pyrazinopyridazine-diyl, benzimidazole-diyl, benzodioxane-diyl, tetrahydroquinoline-diyl, tetrahydrobenzothiophene-diyl, etc. are exemplified.

[0048]

The term "non-aromatic carbocyclic ring" includes "cycloalkane" as defined above, "cycloalkene" as defined above a fused ring consisting of "aromatic carbocyclic ring" as defined above fused to "cycloalkane" as defined above, and a fused ring consisting of "aromatic carbocyclic ring" as defined above fused to "cycloalkene" as defined above. As a fused ring, indene, etc are exemplified.

[0049]

The term "aromatic heterocyclic ring" includes aromatic rings of "heterocyclic ring" as defined above. "Aromatic heterocyclic ring" includes a five- to seven-membered aromatic ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring; a fused aromatic ring consisting of two or more said rings; and a fused ring consisting of a five- to seven-membered aromatic ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring fused to one or more "aromatic carbocyclic ring" as defined above.

For example, a monocyclic aromatic heterocyclic ring such as pyrazine, pyrazole, tetrazole, furan, thiophene, pyridine, imidazole, triazole, triazine, pyridazine, pyrimidine, pyrazine, isoxazole, thiazole, isothiazole, thiadiazole, oxazole, oxadiazole, etc; and

a fused aromatic heterocyclic ring such as indole, isoindole, indazole, indolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, naphthyridine, quinoxaline, purine, pteridine, benzimidazole, benzisoxazole, benzoxazole, benzoxadiazole, benzisothiazole, benzothiazole, benzothiadiazone, benzofuran, isobenzofuran, benzothiophene, benzotriazole, imidazopyridine, triazolopyridine, imidazothiazole, pyrazinopyridazine, benzimidazole, etc. are exemplified.

[0050]

The term "heteroaryl" includes a monovalent group derived from "aromatic heterocyclic ring" as defined above. "Heteroaryl" includes a five- to seven-membered aromatic group having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring; a fused aromatic group comprising two or more said rings; and a fused ring comprising a five- to seven-membered aromatic group having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring fused to one or more "aromatic carbocyclic ring" as defined above.

For example, monocyclic aromatic heterocyclic groups such as pyrrolyl, pyrazinyl, pyrazolyl, indolyl, tetrazolyl, furyl, thienyl, pyridyl, imidazolyl, triazolyl, tetrazolyl, triazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, etc; and

fused heterocyclic aromatic groups such as isoindolyl, indazolyl, indolizinyll,

isoindolynyl, quinolyl, isoquinolyl, cinnolynyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, benzimidazolynyl, etc. are exemplified.

[0051]

The heteroaryl moiety of "heteroaryloxycarbonyl" is as defined above for "heteroaryl".

[0052]

The term "non-aromatic heterocyclic ring" includes non-aromatic rings of "heterocyclic ring" as defined above. "Non-aromatic heterocyclic ring" includes, a five- to seven-membered non-aromatic ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring; a fused non-aromatic ring consisting of two or more said rings; a fused ring consisting of a five- to seven-membered aromatic ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring fused to one or more "cycloalkane" as defined above or "cycloalkene" as defined above; or a fused ring consisting of a five- to seven-membered non-aromatic heterocyclic ring having at least one nitrogen atom, oxygen atom, and/or sulphur atom in the ring fused to one or more "aromatic carbocyclic ring" as defined above or "non-aromatic carbocyclic ring" as defined above

For example, non-aromatic heterocyclic ring such as pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, tetrahydropyran, dihydropyridine, dihydropyridazine, dihydropyrazine, dioxane, oxathiolane, thiane, tetrahydrofuran, tetrahydropyran, tetrahydrothiazolin, tetrahydroisothiazole, etc.;

a fused non-aromatic heterocyclic ring such as indoline, isoindoline, benzopyrane, benzodioxane, tetrahydroquinoline, benzo[d] oxazole-2(3H)-one, tetrahydrobenzothiophene, etc. are exemplified.

[0053]

The term "non-aromatic heterocyclic group" includes a monovalent group derived from "non-aromatic heterocyclic ring" as defined above. For example, non-aromatic mono heterocyclic groups such as pyrrolinyl, pyrrolidino, pyrrolidinyl, imidazolynyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidino, piperidyl, piperidino, piperazinyl, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, tetrahydropyranyl, dihydropyridyl, dihydropyridazinyl, dihydropyrazinyl, dioxanyl, oxathiolanyl, thianyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazolinyl, tetrahydroisothiazolinyl, etc.; and fused heterocyclic groups such as benzodioxanyl, tetrahydroquinoline, tetrahydrobenzothienyl, etc. are exemplified.

[0054]

The term "nitrogen-containing non-aromatic heterocyclic group" includes a monovalent group derived from a four- to seven-membered aromatic group or a fused aromatic ring consisting of two or more said rings which includes at least one nitrogen atom in the ring and optionally includes one or more atoms selected from an oxygen atom and/or a sulphur atom at any position in the ring.

For example, pyrrolinyl, pyrrolidino, pyrrolidinyl, piperidino, piperidyl, piperadino, piperazinyl, morpholinyl, morpholino, thiomorpholino etc. are exemplified.

[0055]

The non-aromatic heterocyclic ring moiety of "non-aromatic heterocyclic ring-oxy-carbonyl" is as defined above for "non-aromatic heterocyclic ring".
[0056]

Substituents for "substituted lower alkyl", "substituted alkyl", "substituted lower alkenyl", "lower alkenyl", "substituted lower alkynyl", "substituted alkynyl", "substituted lower alkyloxy", "substituted alkyloxy", "substituted lower alkenyloxy", "substituted alkenyloxy", "substituted lower alkynyloxy", "substituted alkynyloxy", "substituted lower alkylthio", "substituted alkylthio", "substituted lower alkenylthio", "substituted alkenylthio", "substituted lower alkynylthio", "substituted alkynylthio", "substituted lower alkyloxycarbonyl", "substituted alkyloxycarbonyl", "substituted lower alkenyloxycarbonyl", "substituted alkenyloxycarbonyl", "substituted lower alkynyloxycarbonyl", "substituted alkynyloxycarbonyl", "substituted lower alkylcarbamoyl" and "substituted alkylcarbamoyl" include, but are not limited to, one or more same or different substituents selected from the group comprising: hydroxy, carboxy, halogen (F, Cl, Br, I), lower haloalkyloxy (e.g., CF₃O), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), lower alkyloxy (e.g., methoxy, ethoxy, propoxy, butoxy, etc.), lower alkenyloxy (e.g., vinyloxy, allyloxy, etc.), lower alkyloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), nitro, nitroso, amino, lower alkylamino (e.g., methylamino, ethylamino, dimethylamino, etc.), acylamino (e.g., acetylamino, benzoylamino, etc.), arylalkylamino (e.g., benzylamino, tritylamino), hydroxyamino, imino, hydroxyimino, lower alkylimino (e.g., methylimino, ethylimino, dimethylimino, etc.), lower alkyloxyimino (e.g., methoxyimino, ethoxyimino, etc.), acylimino (e.g., acetylmino, benzoylimino, etc.), azido, aryl (e.g., phenyl, etc.), arylalkyl (e.g., benzyl, phenylethyl, etc.), arylalkyloxy (e.g., benzyloxy), a non-aromatic heterocyclic group (e.g., pyrrolinyl, piperidyl, piperadino, pyrrolidino, pyrrolidinyl, morpholinyl, morpholino, etc.), heteroaryl (e.g., furyl, thienyl, pyridyl, isoxazolyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, tetrazolyl, indolyl, benzofuryl, etc.), heteroarylalkyl (e.g., pyridylmethyl, pyridylethyl, etc.), cyano, isocyano, isocyanato, thiocyanato, isothiocyanato, mercapto, lower alkylthio (e.g., methylthio, etc.), lower alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl), carbamoyl, lower alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, etc.), sulfamoyl, lower alkylsulfamoyl, acyl (e.g., formyl, acetyl, etc.), formyloxy, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfino, sulfo, hydrazino, azido, ureido, amidino, guanidino, phthalimido, tri-lower alkylsilyl (e.g., trimethylsilyl, etc.), or oxo.

Substituents for "substituted alkyl" and "substituted lower alkyl" of R^{1c} are exemplified as follows: cyano; halogen; hydroxy; carboxy; unsubstituted lower alkyloxy; lower alkyloxy substituted with one or more substituents selected from Substituent Group B (Substituent Group B: cycloalkyl, cycloalkenyl, a non-aromatic heterocyclic group, aryl, and heteroaryl); unsubstituted lower alkyloxycarbonyl; lower alkyloxycarbonyl substituted with one or more substituents selected from Substituent Group B; unsubstituted carbamoyl; carbamoyl substituted with one or more substituents selected from Substituent Group C (Substituent Group C: unsubstituted lower alkyl, hydroxyalkyl, dihydroxyalkyl, carboxyalkyl, lower alkyloxyalkyl, unsubstituted cycloalkylalkyl, lower alkyloxycarbonylalkyl, carboxycycloalkylalkyl and lower alkyloxycarbonylalkyl); unsubstituted amino; amino substituted with one or more substituents selected from Substituent Group D (Substituent Group D: lower alkyl, acyl, unsubstituted carbamoyl, lower alkylcarbamoyl, lower hydroxyalkylcarbamoyl, and lower carboxyalkylcarbamoyl); unsubstituted cycloalkyl;

cycloalkyl substituted with one or more substituents selected from Substituent Group E(Substituent Group E: lower hydroxyalkyl, carboxy, and lower alkyloxycarbonyl); a non-aromatic heterocyclic group; unsubstituted aryl; and aryl substituted with one or more substituents selected from Substituent Group F(Substituent Group F: halogen, lower alkyl, and lower alkyloxy).

Substituents for "substituted alkyl" and "substituted lower alkyl" of R^{1c} are exemplified as follows: cyano; halogen; hydroxy; carboxy; methoxy; methoxy substituted with tetrahydrofuryl or morpholino; lower alkyloxycarbonyl; unsubstituted carbamoyl; carbamoyl substituted with one or more substituents selected from Substituent Group G(Substituent Group G: methyl, ethyl, hydroxymethyl, hydroxyethyl, carboxymethyl, carboxyethyl, methoxyoxymethyl, dihydroxyisopropyl, carboxyisopropyl, and carboxycyclopropyl); methoxycarbonyl; ethoxycarbonyl; phenylmethylcarbonyl; cycloalkyl substituted with one or more substituents selected from Substituent Group H(Substituent Group H: hydroxymethyl, carboxy, methoxycarbonyl and ethoxycarbonyl); lower alkylcarbamoyl substituted with one or more substituents selected from Substituent Group I(Substituent Group I: amino, alkyl, acylcarbamoyl, lower alkylcarbamoyl, and hydroxy); unsubstituted phenyl; and phenyl substituted with one or more substituents selected from Substituent Group J(Substituent Group J: halogen, lower alkyl, and lower alkyloxy).

Substituents for "substituted alkyl" and "substituted lower alkyl" of R^{1a} are exemplified as follows: cyano; halogen; hydroxy; carboxy; unsubstituted lower alkyloxy; lower alkyloxy substituted with one or more substituents selected from Substituent Group B(Substituent Group B: cycloalkyl, cycloalkenyl, a non-aromatic heterocyclic group, aryl, and heteroaryl); unsubstituted lower alkyloxycarbonyl; lower alkyloxycarbonyl substituted with one or more substituents selected from Substituent Group B; unsubstituted carbamoyl; carbamoyl substituted with one or more substituents selected from Substituent Group C(Substituent Group C: unsubstituted lower alkyl, hydroxyalkyl, dihydroxyalkyl, carboxyalkyl, lower alkyloxyalkyl, unsubstituted cycloalkylalkyl, lower alkyloxycarbonylalkyl, carboxycycloalkylalkyl and lower alkyloxycarbonylalkyl); unsubstituted amino; amino substituted with one or more substituents selected from Substituent Group D(Substituent Group D: lower alkyl, acyl, unsubstituted carbamoyl, lower alkylcarbamoyl, lower hydroxyalkylcarbamoyl, and lower carboxyalkylcarbamoyl); unsubstituted cycloalkyl; cycloalkyl substituted with one or more substituents selected from Substituent Group E(Substituent Group E: lower hydroxyalkyl, carboxy, and lower alkyloxycarbonyl); a non-aromatic heterocyclic group; unsubstituted aryl; and aryl substituted with one or more substituents selected from Substituent Group F(Substituent Group F: halogen, lower alkyl, and lower alkyloxy).

Substituents for "substituted alkyl" and "substituted lower alkyl" of R^{1a} are exemplified as follows: cyano; halogen; hydroxy; carboxy; methoxy; methoxy substituted with tetrahydrofuryl or morpholino; lower alkyloxycarbonyl; unsubstituted carbamoyl; carbamoyl substituted with one or more substituents selected from Substituent Group G(Substituent Group G: methyl, ethyl, hydroxymethyl, hydroxyethyl, carboxymethyl, carboxyethyl, methoxyoxymethyl, dihydroxyisopropyl, carboxyisopropyl, and carboxycyclopropyl); methoxycarbonyl; ethoxycarbonyl; phenylmethylcarbonyl; cycloalkyl substituted with one or more substituents selected from Substituent Group H(Substituent Group H: hydroxymethyl, carboxy, methoxycarbonyl and ethoxycarbonyl); lower alkylcarbamoyl substituted with one or more substituents selected from Substituent Group I(Substituent Group

amino, alkyl, acylcarbamoyl, lower alkylcarbamoyl, and hydroxy); unsubstituted phenyl; and phenyl substituted with one or more substituents selected from Substituent Group J (Substituent Group J: halogen, lower alkyl, and lower alkyloxy).
[0057]

A substituent for "substituted acyl" is selected from the group comprising: substituents for "substituted lower alkyl" as defined above, substituents for "lower alkyl" as defined above, substituents for "lower alkenyl" as defined above, and substituents for "lower alkynyl" as defined above. Especially, when R of acyl ($R-C(=O)-$) is "cycloalkyl", "cycloalkenyl", "a non-aromatic heterocyclic group", "aryl" or "heteroaryl", a substituent for each ring is lower alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl, etc.), lower haloalkyl (e.g., CF_3 , CH_2CF_3 , CH_2CCl_3 , etc.), lower alkenyl, lower alkynyl (e.g., ethynyl), lower alkyloxy (e.g., methoxy, ethoxy, isopropoxy), or halogen (e.g., F, Cl, etc.), etc.

[0058]

For example, a substituent for "substituted carbamoyl" or "substituted sulfamoyl" is, but is not limited to, one or more same or different substituents selected from the group comprising: hydroxy, carboxy, halogen (F, Cl, Br, I), lower alkyl (e.g., methyl, ethyl), lower alkenyl (e.g., vinyl), lower alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), lower alkyloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), amino, lower alkylamino (e.g., methylamino, ethylamino, dimethylamino, etc.), acylamino (e.g., acetylamino, benzoylamino, etc.), arylalkylamino (e.g., benzylamino, tritylamino), hydroxyamino, aryl (e.g., phenyl, etc.), cyano, isocyano, isocyanato, thiocyanato, isothiocyanato or acyl (e.g., formyl, acetyl, etc.).

[0059]

For example, a substituent for "substituted amino" is, but is not limited to, one or more same or different substituents selected from the group comprising: lower alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl, etc.), lower haloalkyl (e.g., CF_3 , CH_2CF_3 , CH_2CCl_3 , etc.), lower hydroxyalkyl (e.g., hydroxyethyl, $-C(CH_3)_2CH_2OH$, etc.), lower alkenyl (e.g., vinyl), lower alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), lower alkyloxy (e.g., methoxy, ethoxy, propoxy, butoxy, etc.), lower haloalkyloxy (e.g., CF_3O), lower alkenyloxy (e.g., vinyloxy, allyloxy, etc.), lower alkyloxycarbonyl (tert-butyloxycarbonyl, etc.), amino, lower alkylamino (e.g., methylamino, ethylamino, dimethylamino, etc.), acylamino (e.g., acetylamino, benzoylamino, etc.), arylalkylamino (e.g., benzylamino, tritylamino), hydroxyamino, imino, hydroxyimino, lower alkylimino (e.g., methylimino, ethylimino, dimethylimino, etc.), lower alkyloxyimino (e.g., methoxyimino, ethoxyimino, etc.), acyl imino (e.g., acetylimino, benzoylimino, etc.), aryl (e.g., phenyl, etc.), arylalkyl (e.g., benzyl, etc.), aryloxy (e.g., phenoxy, etc.), a non-aromatic heterocyclic group (e.g., pyrrolinyl, pyrrolidino, piperidino, piperidyl, piperadino, piperazinyl, morpholinyl, morpholino, etc.), heteroaryl (e.g., pyridyl, thienyl, thiazolyl, furyl, etc.), heteroarylalkyl (e.g., pyridylmethyl, thienylmethyl, thiazolylmethyl, furylmethyl, etc.), non-aromatic heterocyclic ring-oxy (piperadinooxy, piperidinooxy, etc.), heteroaryloxy (pyridyl oxy, etc.), hydroxy, halogen (F, Cl, Br, I), cyano or acyl (e.g., formyl, acetyl, etc.).

[0060]

For example, a substituent for "substituted cycloalkyl", "substituted cycloalkenyl", "substituted aryl", "a substituted heterocyclic group", "substituted heteroaryl", "substituted arylalkyl", "substituted heteroarylalkyl", "a substituted non-

aromatic heterocyclic group" or "a substituted nitrogen-containing non-aromatic heterocyclic group" is, but is not limited to, one or more same or different substituents selected from the group comprising: lower alkyl(e.g., methyl, ethyl, isopropyl, tert-butyl, etc.), lower haloalkyl(e.g., CF_3 , CH_2CF_3 , CH_2CCl_3 , etc.), lower haloalkyloxy(e.g., CF_3O , CHCF_2O , etc.), lower alkenyl(e.g., vinyl), lower alkynyl(e.g., ethynyl), cycloalkyl(e.g., cyclopropyl), cycloalkenyl(e.g., cyclopropenyl), lower alkyloxy(e.g., methoxy, ethoxy, propoxy, butoxy, etc.), lower alkenyloxy(e.g., vinyloxy, allyloxy, etc.), lower alkyloxycarbonyl(e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), nitro, nitroso, amino, lower alkylamino(e.g., methylamino, ethylamino, dimethylamino, etc.), acylamino(e.g., acetylamino, benzoylamino, etc.), arylalkylamino(e.g., benzylamino, tritylamino), hydroxyamino, imino, hydroxyimino, lower alkylimino(e.g., methylimino, ethylimino, dimethylimino, etc.), lower alkyloxyimino(e.g., methoxyimino, ethoxyimino, etc.), acyl imino(e.g., acetylimino, benzoylimino, etc.), azido, aryl(e.g., phenyl, etc.), arylalkyl(e.g., benzyl, etc.), aryloxy(e.g., phenoxy, etc.), arylalkyloxy(e.g., benzyloxy, etc.), a non-aromatic heterocyclic group(e.g., pyrrolinyl, pyrrolidino, piperidino, piperidyl, piperadino, piperazinyl, morpholinyl, morpholino, etc.), heteroaryl(e.g., pyridyl, thienyl, thiazolyl, furyl, etc.), heteroarylalkyl(e.g., pyridylmethyl, thienylmethyl, thiazolylmethyl, furylmethyl, etc.), non-aromatic heterocyclic ring-oxy(piperadinooxy, piperidinooxy, etc.), heteroaryloxy(pyridyl oxy, etc.), cyano, isocyano, isocyanato, thiocyanato, isothiocyanato, mercapto, lower alkylthio(e.g., methylthio, etc.), lower alkylsulfonyl(e.g., methanesulfonyl, ethanesulfonyl), substituted or unsubstituted carbamoyl(e.g., carbamoyl, N-methyl-N-methoxycarbamoyl, etc.), substituted or unsubstituted lower alkylcarbamoyl(e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, trifluoromethylcarbamoyl, trifluoroethylcarbamoyl, etc.), sulfamoyl, lower alkylsulfamoyl, hydroxy, carboxy, halogen(F, Cl, Br, I), acyl(e.g., formyl, acetyl, etc.), formyl oxy, thio formyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfinio, sulfo, hydrazino, azido, ureido, amidino, guanidino, or phthalimido and oxo.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^{1c} are exemplified as follows: halogen, lower alkyl, lower haloalkyl, lower alkyloxy, cyano, nitro, lower alkylamino, etc.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^{1c} are exemplified as follows: methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, methoxy, methylamino, dimethylamino, amino, Cl, F, cyano, etc.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^{1a} are exemplified as follows: halogen, lower alkyl, lower haloalkyl, lower alkyloxy, cyano, nitro, lower alkylamino, etc.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^{1a} are exemplified as follows: methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, methoxy, methylamino, dimethylamino, amino, Cl, F, cyano, etc.

Substituents for "a substituted nitrogen-containing non-aromatic heterocyclic group" wherein the ring is formed by R^7 and R^{1a} include oxo.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted

heteroaryl" of R^2 are exemplified as follows: lower alkyl substituted with halogen, unsubstituted lower alkyl, unsubstituted lower alkenyl, unsubstituted lower alkynyl, unsubstituted lower alkyloxy, unsubstituted lower alkylthio, unsubstituted lower alkylamino, halogen, etc.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^2 are exemplified as follows: lower alkyl, lower trifluoroalkyl, lower alkyloxy, lower alkylamino, nitro, cyano, halogen, etc.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^2 are exemplified as follows: methyl, tert-butyl, trifluoromethyl, methoxy, dimethylamino, nitro, cyano, Cl and F, etc.

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^3 are exemplified as follows: halogen, hydroxy, nitro, cyano, carboxy, lower alkyl, lower alkyl substituted with halogen, lower alkyl substituted with amino substituted with lower alkyl, unsubstituted lower alkyloxy, lower alkyloxy substituted with one or more substituents selected from Substituent Group A (Substituent Group A: cyano, lower alkyloxy, and lower alkyloxycarbonyl), cycloalkyloxy, non-aromatic heterocyclic ring-oxy, aryloxy, heteroaryloxy, trifluoromethyl lower alkyloxy, lower difluoroalkyloxy, lower alkylthio, carboxy, lower alkyloxycarbonyl, lower alkylcarbonyl, non-aromatic heterocyclic ring-carbonyl, lower hydroxyalkylcarbonyl, cycloalkylcarbonyl, cycloalkenylcarbonyl, arylcarbonyl, non-aromatic heterocyclic ring carbonyl, heteroarylcarbonyl, lower alkylamino, lower alkylsulfonylamino, lower alkylsulfonyl, trifluoroalkylsulfonyl, sulfamoyl, lower alkylsulfamoyl, lower alkylsulfinoyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, a non-aromatic heterocyclic group, etc.

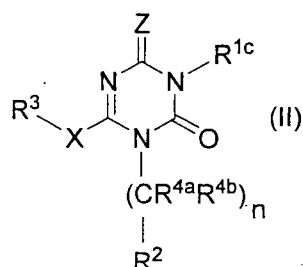
Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "a substituted non-aromatic heterocyclic group", "substituted aryl" and "substituted heteroaryl" of R^3 are exemplified as follows: halogen, nitro, cyano, hydroxy, carboxy, methyl, isopropyl, n-butyl, isobutyl, t-butyl, trifluoromethyl, methoxy, ethoxy, isopropoxy, cyano methoxy, methoxyethoxy, ethoxycarbonylmethoxy, cyclopentenoxy, phenoxy, trifluoromethoxy, difluoromethoxy, piperazinyl, methylthio, propylthio, t-butylcarbonyl, morpholino carbonyl, piperidinocarbonyl, morpholino ethylcarbonyl, methoxycarbonyl, methylcarbonyl, dimethylcarbonyl, hydroxyethylcarbonyl, isopropylcarbonyl, cyclopropylcarbonyl, phenylcarbonyl, sulfamoyl, trifluoromethylsulfonyl, propylsulfinoyl, methylamino, dimethylamino, ethylamino, diethylamino, methylsulfonylamino, isoxazolyl, furyl, morpholino, tetrahydro-2H-pyran, piperidine, etc.

[0061]

Embodiments of the compound of the present invention are described below.

Embodiments of the compound represented by (II-A) to (II-L) in the below in the formula (II):

[Chemical Formula 29]

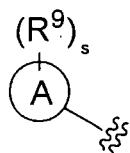


are as follows.

(II-A): The compound represented by the formula (II),
wherein R^{1c} , R^{4a} , R^{4b} , R^5 and $=Z$ are as defined in the above (1);
 R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 X is $-N(R^5)-$; and
 n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.
[0062]

(II-B): The compound represented by the formula (II),
wherein R^{1c} , R^{4a} , R^{4b} , and R^5 are as defined in the above (1);
 R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 X is $-N(R^5)-$;
 $=Z$ is $=O$; and
 n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.
[0063]

(II-C): The compound represented by the formula (II),
wherein R^{4a} , R^{4b} , and R^5 are as defined in the above (1);
 R^{1c} and R^2 are each independently substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^3 is a group represented by the formula:
[Chemical Formula 30]



wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3;

R^9 is each independently halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkenyloxy, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkynyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted lower alkylcarbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, nitrile, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenyloxy, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryl,

substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryl or substituted or unsubstituted heteroaryloxy;

-X- is -N(R⁵)-;

=Z is =O; and

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[0064]

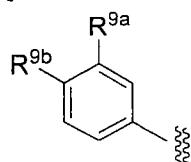
(II-D): The compound represented by the formula (II),

wherein R^{1c} is substituted lower alkyl;

R² is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R³ is a group represented by the formula:

[Chemical Formula 31]



wherein R^{9a} and R^{9b} are as defined in the above (8);

both of R^{4a} and R^{4b} are hydrogen;

-X- is -NH-; and

=Z is =O;

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[0065]

(II-E): The compound represented by the formula (II),

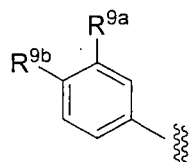
wherein R^{1c} is lower alkyl substituted with one or more substituents selected from Substituent Group L(cyano, halogen, hydroxy, carboxy, unsubstituted lower alkyloxy, lower alkyloxy substituted with cycloalkyl, lower alkyloxy substituted with cycloalkenyl, lower alkyloxy substituted with a non-aromatic heterocyclic group, lower alkyloxy substituted with non-aryl, unsubstituted lower alkyloxy, lower alkyloxy substituted with heteroaryl, lower alkyloxycarbonyl, lower alkyloxycarbonyl substituted with cycloalkyl, lower alkyloxycarbonyl substituted with cycloalkenyl, lower alkyloxycarbonyl substituted with a non-aromatic heterocyclic group, lower alkyloxycarbonyl substituted with non-aryl, lower alkyloxycarbonyl substituted with heteroaryl, lower alkyloxycarbonylcarbonyl, unsubstituted carbamoyl, lower alkylcarbamoyl, lower alkylcarbamoyl substituted with hydroxy, lower alkylcarbamoyl substituted with carboxy, lower alkylcarbamoyl substituted with lower alkyloxy, lower alkylcarbamoyl substituted with unsubstituted cycloalkyl, and lower alkylcarbamoyl substituted with carboxycycloalkyl, unsubstituted amino, lower alkyl, acyl, unsubstituted carbamoyl, lower alkylcarbamoyl, lower alkylcarbamoyl substituted with hydroxy, and lower alkylcarbamoyl substituted with carboxy, amino substituted with lower alkyl, amino substituted with acyl, amino substituted with unsubstituted carbamoyl, amino substituted with lower alkylcarbamoyl, amino substituted with lower hydroxyalkylcarbamoyl, amino substituted with lower carboxyalkylcarbamoyl, a non-aromatic heterocyclic ring substituted with lower hydroxyalkyl, a non-aromatic heterocyclic ring substituted with carboxy, a non-aromatic heterocyclic ring substituted with lower alkyloxycarbonyl, a non-aromatic heterocyclic ring substituted with lower hydroxyalkyl, a non-aromatic heterocyclic ring substituted with carboxy, a non-aromatic heterocyclic ring substituted with lower alkyloxycarbonyl, halogen and lower alkyloxy);

R² is aryl substituted with one or more substituents selected from Substituent Group

S(Substituent Group S: lower alkyl, lower alkyloxy, trifluoromethyl, dimethylamino, nitro, cyano, and halogen), or heteroaryl substituted with one or more substituents selected from Substituent Group S;

R³ is a group represented by the formula:

[Chemical Formula 32]



wherein R^{9a} and R^{9b} are each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkyloxy, substituted or unsubstituted lower alkenyloxy, substituted or unsubstituted lower alkynyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted a non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy;

both of R^{4a} and R^{4b} are hydrogen;

-X- is -NH-;

=Z is =O; and

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[0066]

(II-F): The compound represented by the formula (II),

wherein =Z is =O;

R^{1c} is substituted alkyl;

R² is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

n is 1;

R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen; and

-X- is -NH-, or its pharmaceutically acceptable salt, or a solvate thereof.

[0067]

(II-G): The compound represented by the formula (II),

wherein =Z is =O;

R^{1c} is substituted alkyl;

R² is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 1;

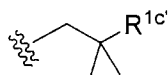
R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen; and

-X- is -NH-, or its pharmaceutically acceptable salt, or a solvate thereof.

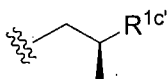
[0068]

(II-H): The compound represented by the formula (II),
 wherein =Z is =O;
 R^2 is substituted or unsubstituted aryl;
 n is 1;
 R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^{4a} and R^{4b} are hydrogen;
 $-X-$ is $-NH-$; and
 R^{1c} is a group represented by the formula:
 [Chemical Formula 33]



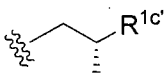
wherein R^{1c} is carboxy or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.
 [0069]

(II-I): The compound represented by the formula (II),
 wherein =Z is =O;
 R^2 is substituted or unsubstituted aryl;
 n is 1;
 R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^{4a} and R^{4b} are hydrogen;
 $-X-$ is $-NH-$; and
 R^{1c} is a group represented by the formula:
 [Chemical Formula 34]



wherein R^{1c} is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.
 [0070]

(II-J): The compound represented by the formula (II),
 wherein =Z is =O;
 R^2 is substituted or unsubstituted aryl;
 n is 1;
 R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^{4a} and R^{4b} are hydrogen;
 $-X-$ is $-NH-$; and
 R^{1c} is a group represented by the formula:
 [Chemical Formula 35]



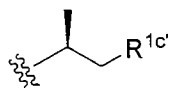
wherein R^{1c} is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.
 [0071]

(II-K): The compound represented by the formula (II),
 wherein =Z is =O;
 R^2 is substituted or unsubstituted aryl;
 n is 1;
 R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^{4a} and R^{4b} are hydrogen;

-X- is -NH-; and

R^{1c} is a group represented by the formula:

[Chemical Formula 36]



wherein R^{1c} is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0072]

(II-L): The compound represented by the formula (II),
wherein =Z is =O;

R² is substituted or unsubstituted aryl;

n is 1;

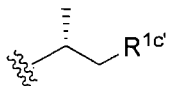
R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen;

-X- is -NH-; and

R^{1c} is a group represented by the formula:

[Chemical Formula 37]

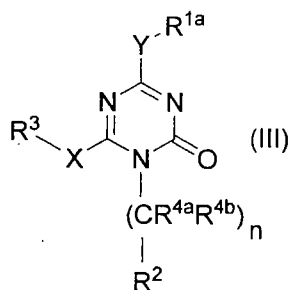


wherein R^{1c} is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0073]

Embodiments of the compound represented by (III-A) to (III-I) in the below in the formula (III):

[Chemical Formula 38]



are as follows.

(III-A): The compound represented by the formula (III),
wherein R^{1a}, R^{4a}, R^{4b}, R⁵ and -Y- are as defined in the above (1);

R² is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-X- is -N(R⁵)-; and

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[0074]

(III-B): The compound represented by the formula (III),
wherein R^{1a}, R^{4a}, R^{4b} and R⁵ are as defined in the above (1);

R² is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-X- is -N(R⁵)-;

-Y- is -O-; and

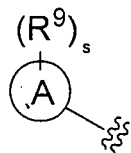
n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[0075]

(III-C): The compound represented by the formula (III),
wherein R^{1a} and R^2 are each independently substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is a group represented by the formula:

[Chemical Formula 39]



wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3;

R^9 is each independently halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkenyloxy, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkynyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted lower alkylcarbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, nitrile, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted a non-aromatic heterocyclic group, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryl or substituted or unsubstituted heteroaryloxy;

-X- is -N(R^5)-;

-Y- is -O-; and

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

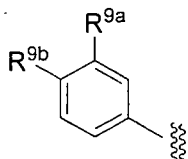
[0076]

(III-D): The compound represented by the formula (III),
wherein R^{1a} is substituted lower alkyl;

R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is a group represented by the formula:

[Chemical Formula 40]



wherein R^{9a} and R^{9b} are as defined in the above (8);

both of R^{4a} and R^{4b} are hydrogen;

-X- is -NH-;

-Y- is -O-; and

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

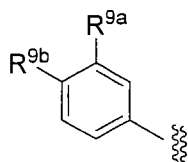
[0077]

(III-E): The compound represented by the formula (III),
wherein R^{1a} is lower alkyl substituted with one or more substituents selected from Substituent Group L;

R² is aryl substituted with one or more substituents selected from Substituent Group L, or heteroaryl substituted with one or more substituents selected from Substituent Group S;

R³ is a group represented by the formula:

[Chemical Formula 41]



wherein R^{9a} and R^{9b} are each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted lower alkyloxy, substituted or unsubstituted lower alkenyloxy, substituted or unsubstituted lower alkynyloxy, substituted or unsubstituted lower alkylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted lower alkyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted a non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy;

both of R^{4a} and R^{4b} are hydrogen;

-X- is -NH-;

-Y- is -O-; and

n is 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[0078]

(III-F): The compound represented by the formula (III),

wherein -Y- is -O- or -N(R⁷)-;

R⁷ is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted acyl;

R^{1a} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl;

R² is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

n is 1;

R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen; and

-X- is -NH-, or its pharmaceutically acceptable salt, or a solvate thereof.

[0079]

(III-G): The compound represented by the formula (III),

wherein -Y- is -O- or -N(R⁷)-;

R⁷ is hydrogen, or substituted or unsubstituted alkyl;

R^{1a} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl;

R² is substituted or unsubstituted aryl;

n is 1;

R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen; and

-X- is -NH-, or its pharmaceutically acceptable salt, or a solvate thereof.

[0080]

(III-H): The compound represented by the formula (III),

wherein -Y- is -N(R⁷)-;

R⁷ and R^{1a} are taken together a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

R² is substituted or unsubstituted aryl;

n is 1;

R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen; and

-X- is -NH-, or its pharmaceutically acceptable salt, or a solvate thereof.

[0081]

(III-I): The compound represented by the formula (III),

wherein -Y- is -O- or -N(R⁷)-;

R⁷ is hydrogen, or substituted or unsubstituted alkyl;

R² is substituted or unsubstituted aryl;

n is 1;

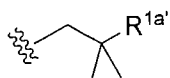
R³ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen;

-X- is -NH-; and

R^{1a} is a group represented by the formula:

[Chemical Formula 42]



wherein R^{1a'} is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0082]

(III-J): The compound represented by the formula (III),

wherein -Y- is -O- or -N(R⁷)-;

R⁷ is hydrogen, or substituted or unsubstituted alkyl;

R² is substituted or unsubstituted aryl;

n is 1;

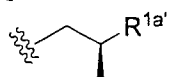
R³ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen;

-X- is -NH-; and

R^{1a} is a group represented by the formula:

[Chemical Formula 43]



wherein R^{1a'} is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0083]

(III-K): The compound represented by the formula (III),

wherein -Y- is -O- or -N(R⁷)-;

R⁷ is hydrogen, or substituted or unsubstituted alkyl;

R^2 is substituted or unsubstituted aryl;

n is 1;

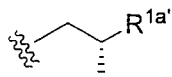
R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen;

$-X-$ is $-NH-$; and

R^{1a} is a group represented by the formula:

[Chemical Formula 44]



wherein $R^{1a'}$ is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0084]

(III-L): The compound represented by the formula (III),

wherein $-Y-$ is $-O-$ or $-N(R^7)-$;

R^7 is hydrogen, or substituted or unsubstituted alkyl;

R^2 is substituted or unsubstituted aryl;

n is 1;

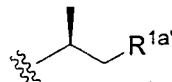
R^3 is substituted or unsubstituted aryl;

R^{4a} and R^{4b} are hydrogen;

$-X-$ is $-NH-$; and

R^{1a} is a group represented by the formula:

[Chemical Formula 45]



wherein $R^{1a'}$ is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0085]

(III-M): The compound represented by the formula (III),

wherein $-Y-$ is $-O-$ or $-N(R^7)-$;

R^7 is hydrogen, or substituted or unsubstituted alkyl;

R^2 is substituted or unsubstituted aryl;

n is 1;

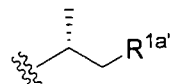
R^3 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are hydrogen;

$-X-$ is $-NH-$; and

R^{1a} is a group represented by the formula:

[Chemical Formula 46]



wherein $R^{1a'}$ is carboxy, or substituted or unsubstituted alkyloxycarbonyl, or its pharmaceutically acceptable salt, or a solvate thereof.

[0086]

General procedures for the synthesis of the compound of the invention are described bellow. Starting materials and reaction reagents used in such synthesis are commercially available or can be prepared according to methods well known in the art using compounds commercially available.

[0087]

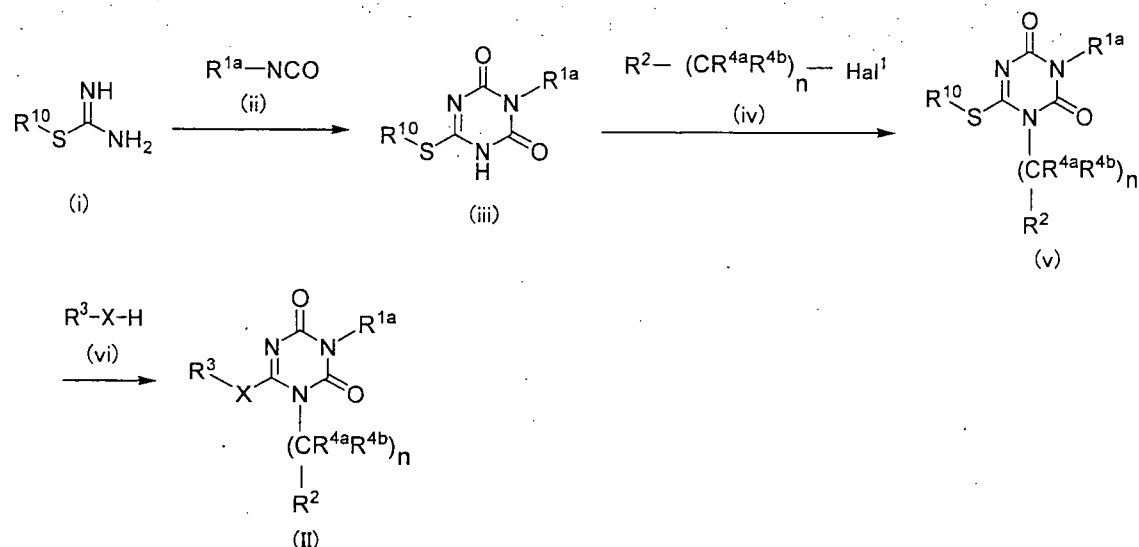
The compound of the present invention represented by the general formula (I),

(II) and (III) is able to be prepared in accordance with the synthetic methods as described bellow.

[0088]

[Method A]

[Chemical Formula 47]



wherein, R¹⁰ is lower alkyl; Hal¹ is halogen; all other variables are as defined above.

[Process 1]

Compound (i) or a salt thereof such as hydrochloride salt or hydrobromide salt is reacted with isocyanate (ii) in a solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N,N-dimethylimidazolidinone or dimethylsulfoxide, in the presence of a base such as DBU, triethylamine or pyridine, at temperature of -20°C to 50°C, preferably ice-cooling. Then, the obtained reaction mixture is reacted with a condensing agent such as 1,1'-carbonyldiimidazole, and a base such as DBU, triethylamine or pyridine, at temperature of -20°C to 50°C, preferably ice-cooling to give compound (iii).

[Process 2]

Compound (v) may be prepared by the reaction of compound (iii) and compound (iv) in a solvent such as acetonitrile, acetone, DMF or DMSO, in the presence of a base such as potassium carbonate or sodium carbonate, at temperature of 50°C to reflux temperature, preferably reflux temperature.

[Process 3]

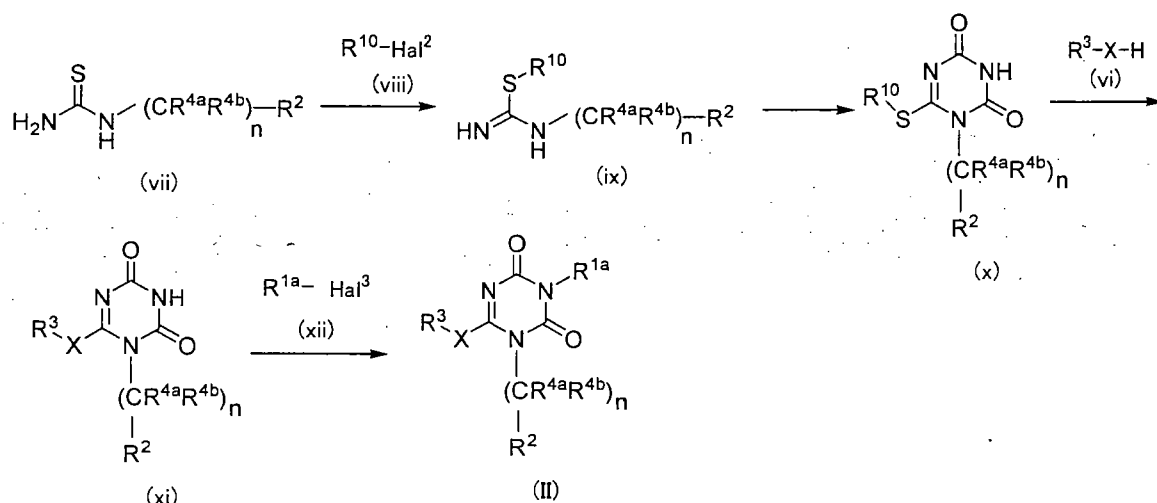
The compound represented by the general formula (II) may be prepared by the reaction of compound (v) and copound (vi) in a solvent such as NMP, DMF or DMSO, or without solvent, at temperature of 150°C to 250°C, preferably 200°C to 230°C, under microwave radiation. Also this compound may be prepared by the reaction of compound (v) and compound (vi) in a solvent such as t-butanol, in the presence of an acid such as acetic acid, at temperature of 60°C to 150°C, preferably 80°C to 120°C.

The chiral compound (II) may be prepared by using chiral isocyanate (ii).

[0089]

[Method B]

[Chemical Formula 48]



wherein, Hal^2 and Hal^3 are halogen; all other variables are as defined above.

[Process 1]

Compound (ix) may be prepared by the reaction of compound (vii) and alkylating reagent (viii) in a solvent such as methanol or ethanol at temperature of -40°C to 30°C , preferably ice-cooling.

[Process 2]

Compound (x) may be prepared by the reaction of compound (ix) and isocyanate such as N-chlorocarbonylisocyanate in a solvent such as dichloromethane, chloroform or 1,2-dichloroethane, in the presence of a base such as triethylamine or N,N-diisopropylamine, at temperature of -20°C to 30°C , preferably ice-cooling.

[Process 3]

Compound (xi) may be prepared by the reaction of compound (x) and compound (vi) in a solvent such as t-butanol, iso-propanol, ethanol or acetonitrile, in the presence of an acid such as acetic acid, formic acid or methanesulfonic acid, at reflux temperature.

[Process 4]

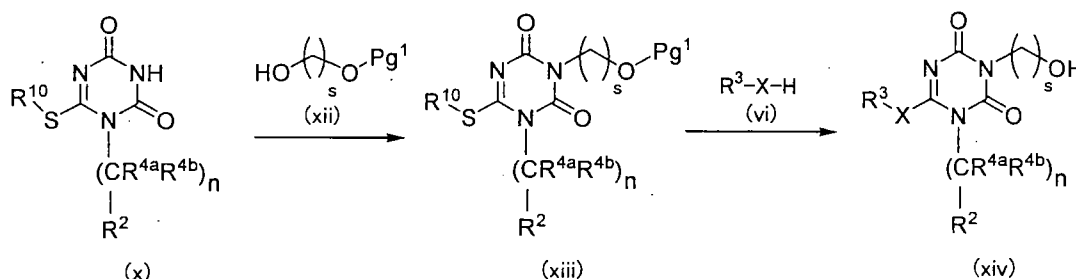
The compound represented by the general formula (II) may be prepared by the reaction of compound (xi) and compound (xii) in a solvent such as DMF or NMP, in the presence of a base such as potassium t-butoxide or sodium hydride, at temperature of 40°C to 100°C , preferably 50°C to 70°C .

The chiral compound (II) may be prepared by using chiral compound (xii).

[0090]

[Method C]

[Chemical Formula 49]



wherein, Pg^1 is an appropriate hydroxy protecting group; s is an integer of 1 to 4; all other variables are as defined above.

[Process 1]

The mixture of compound (x) obtained by Method B and alcohol (xii) such as 2-(tetrahydro-2H-pyran-2-yloxy)ethanol, where the other hydroxy group is protected, in a solvent such as THF or dioxane, is reacted with triphenylphosphine or the like and diethyl azodicarboxylate or the like to give compound (xiii).

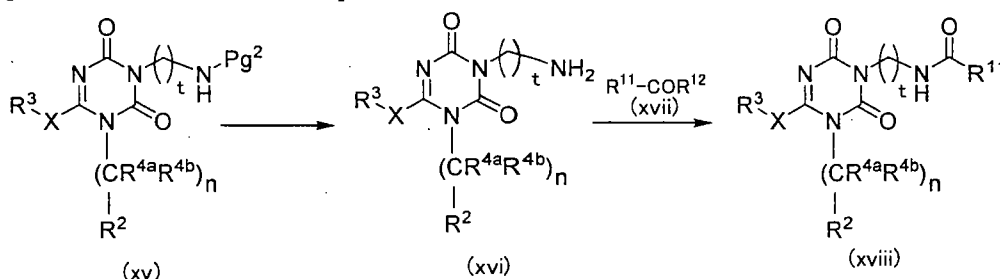
[Process 2]

Compound (xiv) may be prepared by the reaction of compound (xiii) and compound (vi) in the presence of an acid such as formic acid or acetic acid, at reflux temperature.

[0091]

[Method D]

[Chemical Formula 50]



wherein, Pg² is an appropriate amino protecting group; R¹¹ is substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl alkyl, substituted or unsubstituted heteroaryl alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted acyl, substituted or unsubstituted a non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R¹² is hydroxy or halogen; t is an integer of 1 to 4; all other variables are as defined above.

[Process 1]

Compound (xv) obtained by Method A or B is reacted with an acid such as a solution of hydrochloric acid in dioxane, a solution of hydrochloric acid in methanol, a solution of hydrochloric acid in ethyl acetate, or trifluoroacetic acid to give compound (xvi).

[Process 2]

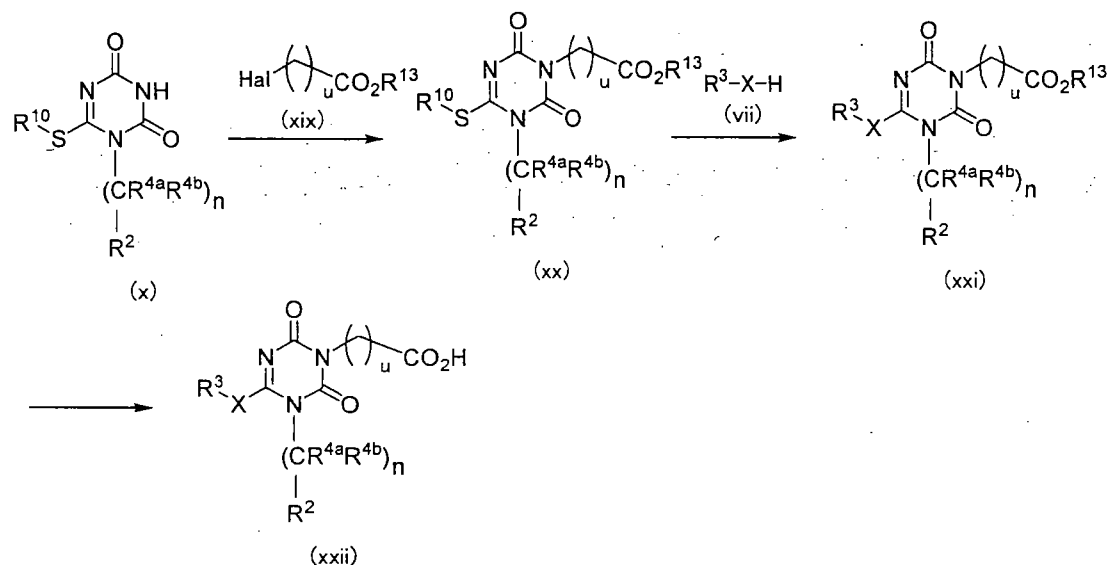
Compound (xviii) may be prepared by a reaction of compound (xvi) and an acid halide compound (xvii) wherein R¹² is halogen, in the presence of a base such as triethylamine or diisopropylethylamine in a solvent such as THF or dioxane. Dimethylaminopyridine may be added, if necessary.

Also, compound (xvi) is reacted with carboxylic acid (xvii) wherein R¹² is hydroxy, in a solvent such as THF or DMF, in the presence of a condensing agent such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and a base such as triethylamine or diisopropylethylamine, and 1-hydroxybenzotriazole to give compound (xviii).

[0092]

[Method E]

[Chemical Formula 51]



wherein, R^{13} is substituted or unsubstituted lower alkyl; u is an integer of 1 to 4; all other variables are as defined above.

[Process 1]

Compound (xx) may be prepared by the reaction of compound (x) obtained by Method B and compound (xix) in a solvent such as DMF, NMP or THF, in the presence of a base such as DBU, potassium *t*-butoxide or sodium hydride at temperature of 0°C to 80°C , preferably 30°C to 50°C .

[Process 2]

Compound (xxi) may be prepared by the reaction of compound (xx) and compound (vii) in a solvent such as *t*-butanol, isopropanol, ethanol or acetonitrile, in the presence of an acid such as formic acid, acetic acid or metanesulfonic acid at reflux temperature.

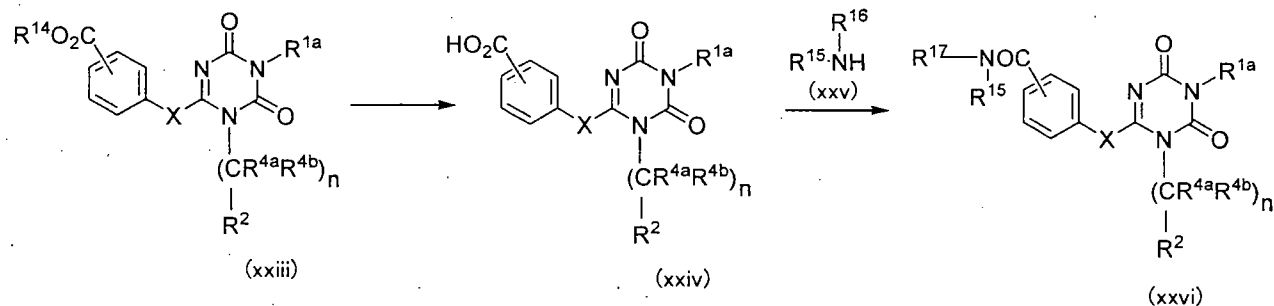
[Process 3]

Compound (xxii) may be prepared by the reaction of compound (xxi) and a reagent such as aqueous lithium hydroxide, aqueous sodium hydroxide or aqueous potassium hydroxide, in a solvent such as methanol, ethanol or a mixed solvent thereof with THF, dioxane, and the like.

[0093]

[Method F]

[Chemical Formula 52]



wherein, R^{14} is substituted or unsubstituted lower alkyl; R^{15} and R^{16} are each independently substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl alkyl, substituted or unsubstituted heteroaryl alkyl, substituted or

unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted acyl, substituted or unsubstituted a non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; u is an integer of 1 to 4; all other variables are as defined above.

[Process 1]

Compound (xxiv) may be prepared by the reaction of compound (xxiii) obtained by Method A or B and aqueous lithium hydroxide, aqueous sodium hydroxide or aqueous potassium hydroxide, in a solvent such as methanol, ethanol or a mixed thereof solvent with THF, dioxane and the like.

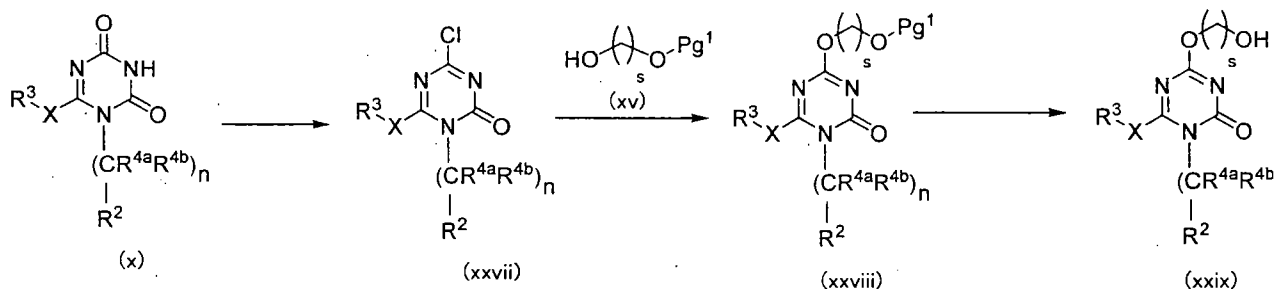
[Process 2]

Compound (xxiv) is reacted with compound (xxv) in a solvent such as THF, DMF or NMP, in the presence of a condensing agent such as 1-hydroxybenzotriazole, HOAt, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HATU or PyBOP, and a base such as triethylamine or diisopropylethylamine to give compound (xxvi).

[0094]

[Method G]

[Chemical Formula 52]



wherein, Pg¹ is an appropriate hydroxy protecting group; all other variables are as defined above.

[Process 1]

Compound (xxvii) may be prepared by the reaction of compound (x) obtained by Method B and a halogenating agent such as phosphorous oxychloride or phosphorous oxybromide, without solvent or in a solvent such as toluene or tetrahydrofuran at temperature of 0°C to 100°C, preferably 40°C to 60°C.

[Process 2]

To a mixture of alcohol (xv) such as 2-(tetrahydro-2H-pyran-2-yloxy)ethanol, where the other hydroxy group is protected, in a solvent such as THF, dioxane or DMF, is added a base, such as sodium hydride or potassium t-butoxide, and the resulting mixture is reacted with compound (xxvii) to give compound (xxviii).

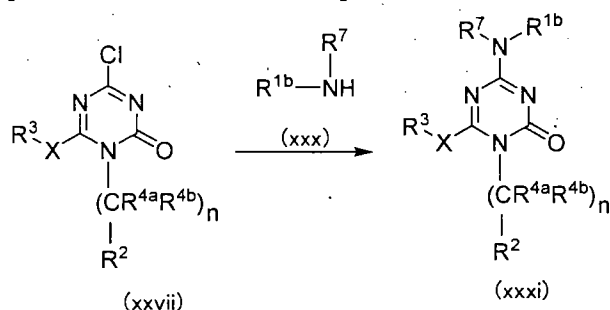
[Process 3]

Compound (xxix) may be prepared by the reaction of compound (xxviii) and an acid such as hydrochloric acid, p-toluenesulfonic acid or a hydrate thereof, or p-toluenesulfonic acid pyridinium salt, in a solvent such as methanol.

[0095]

[Method H]

[Chemical Formula 54]



wherein, R^7 is substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl alkyl, substituted or unsubstituted heteroaryl alkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted lower alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted acyl, substituted or unsubstituted a non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; all other variables are as defined above.

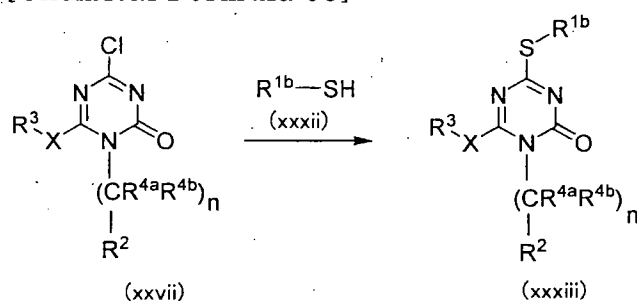
[Process 1]

Compound (xxxi) may be prepared by the reaction of compound (xxvii) obtained by Method G and compound (xxx) in a solvent such as THF or dioxane.

[0096]

[Method I]

[Chemical Formula 55]



wherein all variables are as defined above.

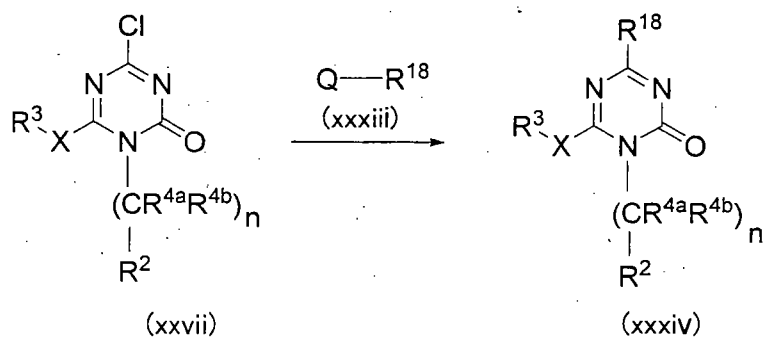
[Process 1]

Compound (xxvii) obtained by Method G in a solvent such as THF or dioxane, in the presence of a base such as sodium hydride is reacted with compound (xxxii) to give compound (xxxiii).

[0097]

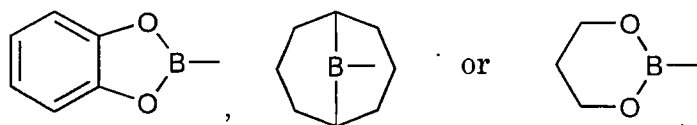
[Method J]

[Chemical Formula 56]



wherein, R^{18} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl; Q is dihydroxyborane, dialkoxyborane or dialkylborane,

[Chemical Formula 57]



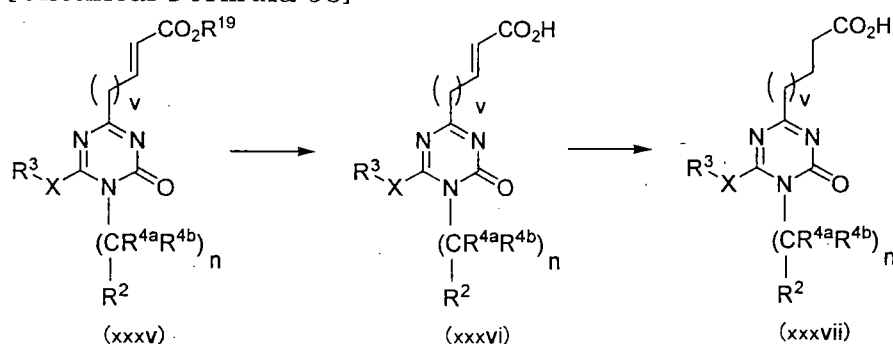
and all other variants are as defined above.

Compound (xxxiv) may be prepared by the reaction of compound (xxvii) obtained by Method G and compound (xxxiii) in a solvent such as THF or dioxane, in the presence a palladium catalyst and an aqueous potassium carbonate, aqueous cesium carbonate or aqueous sodium carbonate, at temperature of 50°C to reflux temperature, preferably reflux temperature or 120°C to 200°C , preferably 130°C to 150°C under microwave radiation.

[0098]

[Method K]

[Chemical Formula 58]



wherein, R^{19} is substituted or unsubstituted alkyl; v is an integer of 0 to 4; all other variables are as defined above.

A mixture of compound (xxxv) in a mixed solvent is hydrolyzed with a base such as sodium hydroxide or lithium hydroxide to give compound (xxxvi). In the above step, ethers such as dioxane, THF or DME, alcohols such as ethanol or methanol, DMF, DMA, DMSO or NMP is mixed with water as a mixed solvent. The room temperature is preferable. When the progress of the reaction is slow, the reaction temperature may be raised further.

[0099]

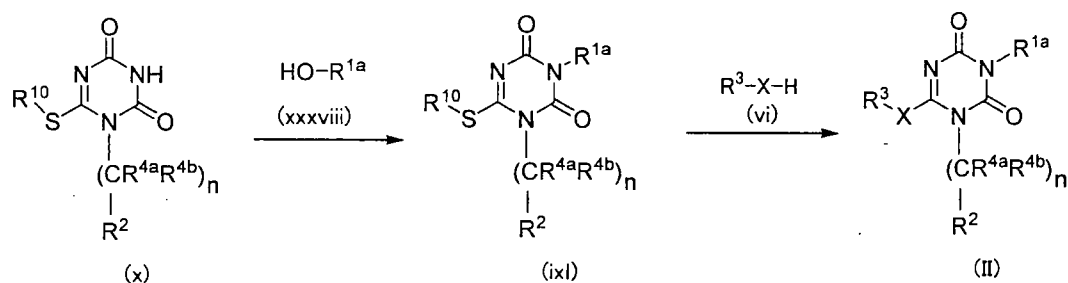
[Process 2]

Compound (xxxvi) is solved in an alcohol such as methanol or ethanol, and the solution is applied for a catalytic reduction by using a hydrogenation reactor (e.g., H-Cube (10%Pt-C, H₂ = 1 atm)) or a metallic catalyst such as palladium-carbon, platinum oxide or chlorotris(triphenylphosphine)rhodium(I) to give compound (xxxvii).

[0100]

[Method L]

[Chemical Formula 59]



wherein the variables are as defined above.

[Process 1]

The mixture of compound (x) obtained by Method B and alcohol (xxxviii) in a solvent such as THF or dioxane, is reacted with triphenylphosphine or the like and diethyl azodicarboxylate or the like to give compound (ixl).

[Process 2]

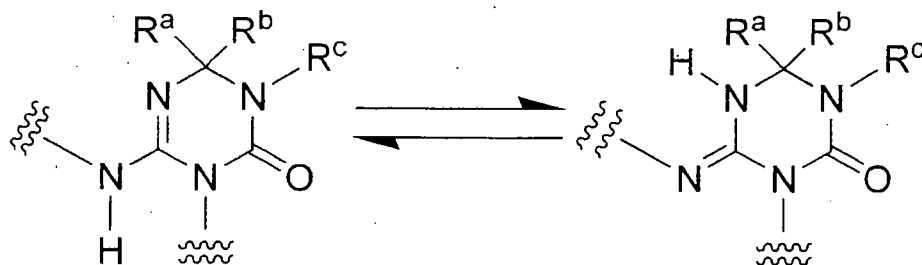
Compound (II) may be prepared by the reaction of compound (ixl) and compound (vi) in the presence of an acid such as formic acid or acetic acid at reflux temperature.

The chiral compound (II) may be prepared by using chiral alcohol (xxxviii).

[0101]

The compound (I) of the invention includes but is not limited to all possible isomers and racemates. For example, the compound (I) of the invention includes tautomers represented by formula:

[Chemical Formula 60]



[0102]

In addition, one or more hydrogen, carbon or other atoms of a compound of Formula (I) can be replaced by an isotope of the hydrogen, carbon or other atoms. Compounds of Formula (I) include all radiolabeled forms of compounds of Formula (I).

"radiolabeled," "radiolabeled form", and the like of a compound of Formula I, each of which is encompassed by the invention, is useful as a research and/or diagnostic tool in metabolism pharmacokinetic studies and in binding assays.

[0103]

Examples of isotopes that can be incorporated into a compound of Formula (I) of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine; such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Radiolabeled compounds of the invention can be prepared by methods known in the art. For example, tritiated compounds of Formula (I) can be prepared by introducing tritium into the particular compound of Formula (I), for example, by catalytic dehalogenation with tritium. This method may include reacting a suitably halogen-substituted precursor of a compound of Formula (I) with tritium gas in the presence of a suitable catalyst, for example, Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in Filer, "The Preparation and Characterization of Tritiated Neurochemicals," Chapter 6, pp. 155-192 in *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)* (1987). ^{14}C -labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

[0104]

Also, the compounds of the invention represented above by the general formula (I) or pharmaceutically acceptable salts thereof can be prepared in a form of hydrate or solvate thereof by published methods. Preferable solvate includes solvates with acetone, 2-butanol, 2-propanol, ethanol, ethyl acetate, tetrahydrofuran, diethylether, etc. For example, such solvate includes hydrate or solvate (For example, with ethanol, etc.) which has non-toxicity and solubility.

[0105]

The compound of the invention represented above by the general formula (I) has an antagonizing action on P2X_3 and/or $\text{P2X}_{2/3}$ receptor, and therefore, is useful as a therapeutic agent for diseases associated with a P2X_3 and/or $\text{P2X}_{2/3}$ receptor. Since P2X_3 and/or $\text{P2X}_{2/3}$ receptor is believed to associate with pain and diseases in urinary system (Nature 407, 26, 1011-1015 (2000), Nature, Vol.407, No.26, 1015-1017 (2000), Non-Patent Document 1, Non-Patent Document 2, etc.), the compound of the invention is useful in the treatment of, alleviation of symptoms or prevention of diseases, such as for example, pain associated with rheumatoid arthritis, pain associated with osteoarthritis, headache, migraine, orofacial pain, toothache, glossagra, pain associated with temporomandibular arthrosis, trigeminal neuralgia, shoulder pain, pain associated with hernia of intervertebral disk, pain associated with cervical spondylosis deformans, pain associated with spinal canal stenosis, pain associated with thoracic outlet syndrome, pain associated with traumatic brachial plexus injury syndrome, pain associated with shoulder-hand syndrome, pain associated with whiplash injury, chest pain, abdominal pain, colic pain, pain associated with cholelithiasis, pain associated with pancreatitis, pain associated with urinary calculosis, pain associated with irritable bowel syndrome, lumbar backache, sciatica, pain associated with bone fracture, pain associated with osteoporosis, joint pain, pain associated with gout, pain associated with cauda equina syndrome, pain associated with ankylosing spondylitis, sore muscle, pain associated with painful spasm, pain associated with myofascial pain syndrome, pain associated with fibromyalgia syndrome, pain associated with arteriosclerosis obliterans, pain associated with Buerger's disease, pain associated with Raynaud's phenomenon, pain

associated with zoster, causalgic pain, pain associated with entrapment neuropathy, pain associated with carpal canal syndrome, pain associated with diabetes, pain associated with Guillain-Barre syndrome, pain associated with Hansen's disease, pain associated with drug therapy, pain associated with radiation therapy, pain associated with cord injury, pain associated with syringomyelia, pain associated with stroke, thalamic pain, pain associated with deafferentation, sympathetically-maintained pain, pain associated with ABC syndrome, pain associated with multiple sclerosis, pain associated with skin disease, cancer pain, postoperative pain, pain associated with injury, pain associated with gangrene, pain associated with somatoform disorder, pain associated with somatization disorder, pain associated with depression, pain associated with Parkinson's disease, knee joint pain, pain associated with arthritis, neuropathic pain such as menstrual pain, intermenstrual pain, labor pain, etc., inflammatory pain, nociceptive pain, psychogenic pain, and overactive bladder, incontinence, pollakiuria, urinary urgency, cystatrophia, prostatic hypertrophy, prostatitis, prostate pain, detrusor hyperreflexia, dysuria, nervous pollakiuria, chronic prostatitis, chronic cystitis, etc.

[0106]

The compound of the invention can be a drug with reduced side-effect such as effect on motor function because it has a high affinity for ATP receptor, especially P2X₃ receptor, and also has high subtype selectivity and high selectivity for other receptors. Also, the compound of the invention is advantageous because of its high stability and high oral absorptivity, good bioavailability, low clearance, long half-life, prolonged duration of action, and/or low activity of hepatic enzyme inhibition, etc.

[0107]

In another embodiment, the invention provides a pharmaceutical composition comprising an effective amount of the compound of the invention, in combination with a pharmaceutically acceptable carrier

[0108]

For use of the compound of the invention as a medicament, a pharmaceutical composition can be prepared according to conventional methods, using pharmaceutically acceptable carriers well known in the art, such as excipients, binders, disintegrants, lubricants, colourants, flavors, surfactants, etc.

[0109]

For the pharmaceutical composition of the invention to be administered in the treatment of mammals including human, an appropriate unit dosage form may be selected depending on the purpose of the treatment and the route of administration. Specifically, such unit dosage form includes oral formulations such as tablet, coated tablet, powder, granule, capsule, liquid, pill, suspension, emulsion, etc., and parenteral formulations such as injectable solution, suppository, ointment, patch, aerosol, etc. Such unit dosage form can be formulated according to methods well known in the art.

[0110]

The amount of the compound in a formulation can be varied depending on its dosage form, route for administration, dosing regimen, etc.

[0111]

Means for administration of the pharmaceutical composition may be selected depending on dosage form, age, sex, body weight, severity of the disease, and other factors, etc., and route for administration can be selected from various routes such as oral, subcutaneous, transdermal, rectal, intranasal, buccal, etc.

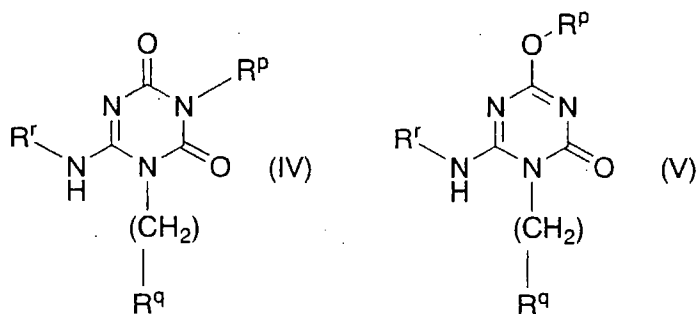
[0112]

Dose of the compound of the invention in a pharmaceutical composition of the invention can be determined depending on the choice of route for administration, age, sex, body weight, severity of the disease, the compound to be administered, and other factors, etc., and can be generally from 0.05 to 1000 mg/kg/day, preferably from 0.1 to 10 mg/kg/day, for oral administration to adults. For parenteral administration, dose can be varied widely depending on its route but generally from 0.005 to 100 mg/kg/day, preferably from 0.01 to 1 mg/kg/day. Such pharmaceutical composition of the invention may be administered once a day or in several times at a divided dosage in a day.

[0113]

Embodiments of the compound of the invention include compounds represented by the general formula (IV) and the general formula (V):

[Chemical Formula 61]



wherein each substituent is as shown below:

[0114]

[Table1]

	Rp		Rp
Rp1	Et	Rp23	propargyl
Rp2	Pr	Rp24	H ₂ N(CH ₂) ₂
Rp3	i-Pr	Rp25	Me ₂ N(CH ₂) ₂
Rp4	Bu	Rp26	AcHN(CH ₂) ₂
Rp5	t-Bu	Rp27	(morpholino)methyl
Rp6	c-PrCH ₂	Rp28	2-(morpholino)ethyl
Rp7	HO(CH ₂) ₂	Rp29	(piperidino)methyl
Rp8	HO(CH ₂) ₃	Rp30	2-(piperidino)ethyl
Rp9	(HOCH ₂) ₂ CH	Rp31	HOCOC(Me) ₂ CH ₂
Rp10	(HOCH ₂) ₂ CHCH ₂	Rp32	(1-hydroxycarbonyl-c-propyl) methyl
Rp11	(HOCH ₂) ₂ C(Me)CH ₂	Rp33	HOCOC(CH ₂) ₃
Rp12	EtOCOCH ₂	Rp34	HOCOC(Me) ₂ (CH ₂) ₂
Rp13	EtOCO(CH ₂) ₂	Rp35	H ₂ NCOCH ₂
Rp14	EtOCOCF ₂ CH ₂	Rp36	MeNHCOCH ₂
Rp15	HOCOCH ₂	Rp37	HOCH ₂ NHCOCH ₂
Rp16	HOCO(CH ₂) ₂	Rp38	HOCOCH ₂ NHCOCH ₂
Rp17	HOCOCF ₂ CH ₂	Rp39	HOCOCH(Me)CH ₂
Rp18	Ph-CH ₂	Rp40	HOCOCH ₂ CH(Me)
Rp19	3-pyridylmethyl	Rp41	(2-HOCO)PhCH ₂
Rp20	NCCH ₂	Rp42	(3-HOCO)PhCH ₂
Rp21	NC(CH ₂) ₂	Rp43	(4-HOCO)PhCH ₂
Rp22	allyl		

[Table2]

	Rq
Rq1	Ph
Rq2	4-Me-Ph
Rq3	4-MeO-Ph
Rq4	4-F-Ph
Rq5	4-Cl-Ph
Rq6	4-Br-Ph
Rq7	3,4-Cl ₂ -Ph
Rq8	5-Cl-2-pyridyl
Rq9	6-Cl-3-pyridyl
Rq10	c-hexyl
Rq11	3-F-4-Cl-Ph
Rq12	c-heptyl

[Table3]

	Rr
Rr1	3-Br-Ph
Rr2	3-CF ₃ -Ph
Rr3	4-EtO-Ph
Rr4	4-i-PrO-Ph
Rr5	4-PhO-Ph
Rr6	4-CHF ₂ O-Ph
Rr7	3-F-4-MeO-Ph
Rr8	3-F-4-EtO-Ph
Rr9	3-F-4-PrO-Ph
Rr10	3-F-4-i-PrO-Ph
Rr11	3-F-4-CHF ₂ O-Ph
Rr12	3-Cl-4-MeO-Ph
Rr13	3-Cl-4-EtO-Ph
Rr14	3-Cl-4-PrO-Ph
Rr15	3-Cl-4-i-PrO-Ph
Rr16	3-Cl-4-CHF ₂ O-Ph
Rr17	3-Me-4-EtO-Ph
Rr18	3-Me-4-PrO-Ph
Rr19	3-Me-4-i-PrO-Ph
Rr20	2-Me-benzofuran-5-yl
Rr21	3-MeS
Rr22	3,4-Cl ₂

In the above Tables, Ac indicates acetyl, Ms indicates mesyl, Me indicates methyl, Et indicates ethyl, Pr indicates propyl, i-Pr indicates isopropyl, Bu indicates n-butyl, t-Bu indicates tert-butyl, c-Pr indicates cyclopropyl, cBu indicates cyclobutyl, cPent indicates cyclopentyl, cHex indicates cyclohexyl and Ph indicates phenyl

[0115]

The compounds represented by the following (R_p, R_q, R_r) which show the combination of R^p, R^q and R^r are exemplified:

(R_p, R_q, R_r)=(Rp1, Rq1, Rr1), (Rp1, Rq1, Rr2), (Rp1, Rq1, Rr3), (Rp1, Rq1, Rr4), (Rp1, Rq1, Rr5), (Rp1, Rq1, Rr6), (Rp1, Rq1, Rr7), (Rp1, Rq1, Rr8), (Rp1, Rq1, Rr9), (Rp1, Rq1, Rr10), (Rp1, Rq1, Rr11), (Rp1, Rq1, Rr12), (Rp1, Rq1, Rr13), (Rp1, Rq1, Rr14), (Rp1, Rq1, Rr15), (Rp1, Rq1, Rr16), (Rp1, Rq1, Rr17), (Rp1, Rq1, Rr18), (Rp1, Rq1, Rr19), (Rp1, Rq1, Rr20), (Rp1, Rq1, Rr21), (Rp1, Rq1, Rr22), (Rp1, Rq2, Rr1), (Rp1, Rq2, Rr2), (Rp1, Rq2, Rr3), (Rp1, Rq2, Rr4), (Rp1, Rq2, Rr5), (Rp1, Rq2, Rr6), (Rp1, Rq2, Rr7), (Rp1, Rq2, Rr8), (Rp1, Rq2, Rr9), (Rp1, Rq2, Rr10), (Rp1, Rq2, Rr11), (Rp1, Rq2, Rr12), (Rp1, Rq2, Rr13), (Rp1, Rq2, Rr14), (Rp1, Rq2, Rr15), (Rp1, Rq2, Rr16), (Rp1, Rq2, Rr17), (Rp1, Rq2, Rr18), (Rp1, Rq2, Rr19), (Rp1, Rq2, Rr20), (Rp1, Rq2, Rr21), (Rp1, Rq2, Rr22), (Rp1, Rq3, Rr1), (Rp1, Rq3, Rr2), (Rp1, Rq3, Rr3), (Rp1, Rq3, Rr4), (Rp1, Rq3, Rr5), (Rp1, Rq3, Rr6), (Rp1, Rq3, Rr7), (Rp1, Rq3, Rr8), (Rp1, Rq3, Rr9), (Rp1, Rq3, Rr10), (Rp1, Rq3, Rr11), (Rp1, Rq3, Rr12), (Rp1, Rq3, Rr13), (Rp1, Rq3, Rr14), (Rp1, Rq3, Rr15), (Rp1, Rq3, Rr16), (Rp1, Rq3, Rr17), (Rp1, Rq3, Rr18), (Rp1, Rq3, Rr19), (Rp1, Rq3, Rr20), (Rp1, Rq3, Rr21), (Rp1, Rq3, Rr22), (Rp1, Rq4, Rr1), (Rp1, Rq4, Rr2), (Rp1, Rq4, Rr3), (Rp1, Rq4, Rr4), (Rp1, Rq

4,Rr5),(Rp1,Rq4,Rr6),(Rp1,Rq4,Rr7),(Rp1,Rq4,Rr8),(Rp1,Rq4,Rr9),(Rp1,Rq4,Rr10),(Rp1,Rq4,Rr11),(Rp1,Rq4,Rr12),(Rp1,Rq4,Rr13),(Rp1,Rq4,Rr14),(Rp1,Rq4,Rr15),(Rp1,Rq4,Rr16),(Rp1,Rq4,Rr17),(Rp1,Rq4,Rr18),(Rp1,Rq4,Rr19),(Rp1,Rq4,Rr20),(Rp1,Rq4,Rr21),(Rp1,Rq4,Rr22),(Rp1,Rq5,Rr1),(Rp1,Rq5,Rr2),(Rp1,Rq5,Rr3),(Rp1,Rq5,Rr4),(Rp1,Rq5,Rr5),(Rp1,Rq5,Rr6),(Rp1,Rq5,Rr7),(Rp1,Rq5,Rr8),(Rp1,Rq5,Rr9),(Rp1,Rq5,Rr10),(Rp1,Rq5,Rr11),(Rp1,Rq5,Rr12),(Rp1,Rq5,Rr13),(Rp1,Rq5,Rr14),(Rp1,Rq5,Rr15),(Rp1,Rq5,Rr16),(Rp1,Rq5,Rr17),(Rp1,Rq5,Rr18),(Rp1,Rq5,Rr19),(Rp1,Rq5,Rr20),(Rp1,Rq5,Rr21),(Rp1,Rq5,Rr22),(Rp1,Rq6,Rr1),(Rp1,Rq6,Rr2),(Rp1,Rq6,Rr3),(Rp1,Rq6,Rr4),(Rp1,Rq6,Rr5),(Rp1,Rq6,Rr6),(Rp1,Rq6,Rr7),(Rp1,Rq6,Rr8),(Rp1,Rq6,Rr9),(Rp1,Rq6,Rr10),(Rp1,Rq6,Rr11),(Rp1,Rq6,Rr12),(Rp1,Rq6,Rr13),(Rp1,Rq6,Rr14),(Rp1,Rq6,Rr15),(Rp1,Rq6,Rr16),(Rp1,Rq6,Rr17),(Rp1,Rq6,Rr18),(Rp1,Rq6,Rr19),(Rp1,Rq6,Rr20),(Rp1,Rq6,Rr21),(Rp1,Rq6,Rr22),(Rp1,Rq7,Rr1),(Rp1,Rq7,Rr2),(Rp1,Rq7,Rr3),(Rp1,Rq7,Rr4),(Rp1,Rq7,Rr5),(Rp1,Rq7,Rr6),(Rp1,Rq7,Rr7),(Rp1,Rq7,Rr8),(Rp1,Rq7,Rr9),(Rp1,Rq7,Rr10),(Rp1,Rq7,Rr11),(Rp1,Rq7,Rr12),(Rp1,Rq7,Rr13),(Rp1,Rq7,Rr14),(Rp1,Rq7,Rr15),(Rp1,Rq7,Rr16),(Rp1,Rq7,Rr17),(Rp1,Rq7,Rr18),(Rp1,Rq7,Rr19),(Rp1,Rq7,Rr20),(Rp1,Rq7,Rr21),(Rp1,Rq7,Rr22),(Rp1,Rq8,Rr1),(Rp1,Rq8,Rr2),(Rp1,Rq8,Rr3),(Rp1,Rq8,Rr4),(Rp1,Rq8,Rr5),(Rp1,Rq8,Rr6),(Rp1,Rq8,Rr7),(Rp1,Rq8,Rr8),(Rp1,Rq8,Rr9),(Rp1,Rq8,Rr10),(Rp1,Rq8,Rr11),(Rp1,Rq8,Rr12),(Rp1,Rq8,Rr13),(Rp1,Rq8,Rr14),(Rp1,Rq8,Rr15),(Rp1,Rq8,Rr16),(Rp1,Rq8,Rr17),(Rp1,Rq8,Rr18),(Rp1,Rq8,Rr19),(Rp1,Rq8,Rr20),(Rp1,Rq8,Rr21),(Rp1,Rq8,Rr22),(Rp1,Rq9,Rr1),(Rp1,Rq9,Rr2),(Rp1,Rq9,Rr3),(Rp1,Rq9,Rr4),(Rp1,Rq9,Rr5),(Rp1,Rq9,Rr6),(Rp1,Rq9,Rr7),(Rp1,Rq9,Rr8),(Rp1,Rq9,Rr9),(Rp1,Rq9,Rr10),(Rp1,Rq9,Rr11),(Rp1,Rq9,Rr12),(Rp1,Rq9,Rr13),(Rp1,Rq9,Rr14),(Rp1,Rq9,Rr15),(Rp1,Rq9,Rr16),(Rp1,Rq9,Rr17),(Rp1,Rq9,Rr18),(Rp1,Rq9,Rr19),(Rp1,Rq9,Rr20),(Rp1,Rq9,Rr21),(Rp1,Rq9,Rr22),(Rp1,Rq10,Rr1),(Rp1,Rq10,Rr2),(Rp1,Rq10,Rr3),(Rp1,Rq10,Rr4),(Rp1,Rq10,Rr5),(Rp1,Rq10,Rr6),(Rp1,Rq10,Rr7),(Rp1,Rq10,Rr8),(Rp1,Rq10,Rr9),(Rp1,Rq10,Rr10),(Rp1,Rq10,Rr11),(Rp1,Rq10,Rr12),(Rp1,Rq10,Rr13),(Rp1,Rq10,Rr14),(Rp1,Rq10,Rr15),(Rp1,Rq10,Rr16),(Rp1,Rq10,Rr17),(Rp1,Rq10,Rr18),(Rp1,Rq10,Rr19),(Rp1,Rq10,Rr20),(Rp1,Rq10,Rr21),(Rp1,Rq10,Rr22),(Rp1,Rq11,Rr1),(Rp1,Rq11,Rr2),(Rp1,Rq11,Rr3),(Rp1,Rq11,Rr4),(Rp1,Rq11,Rr5),(Rp1,Rq11,Rr6),(Rp1,Rq11,Rr7),(Rp1,Rq11,Rr8),(Rp1,Rq11,Rr9),(Rp1,Rq11,Rr10),(Rp1,Rq11,Rr11),(Rp1,Rq11,Rr12),(Rp1,Rq11,Rr13),(Rp1,Rq11,Rr14),(Rp1,Rq11,Rr15),(Rp1,Rq11,Rr16),(Rp1,Rq11,Rr17),(Rp1,Rq11,Rr18),(Rp1,Rq11,Rr19),(Rp1,Rq11,Rr20),(Rp1,Rq11,Rr21),(Rp1,Rq11,Rr22),(Rp1,Rq12,Rr1),(Rp1,Rq12,Rr2),(Rp1,Rq12,Rr3),(Rp1,Rq12,Rr4),(Rp1,Rq12,Rr5),(Rp1,Rq12,Rr6),(Rp1,Rq12,Rr7),(Rp1,Rq12,Rr8),(Rp1,Rq12,Rr9),(Rp1,Rq12,Rr10),(Rp1,Rq12,Rr11),(Rp1,Rq12,Rr12),(Rp1,Rq12,Rr13),(Rp1,Rq12,Rr14),(Rp1,Rq12,Rr15),(Rp1,Rq12,Rr16),(Rp1,Rq12,Rr17),(Rp1,Rq12,Rr18),(Rp1,Rq12,Rr19),(Rp1,Rq12,Rr20),(Rp1,Rq12,Rr21),(Rp1,Rq12,Rr22),(Rp2,Rq1,Rr1),(Rp2,Rq1,Rr2),(Rp2,Rq1,Rr3),(Rp2,Rq1,Rr4),(Rp2,Rq1,Rr5),(Rp2,Rq1,Rr6),(Rp2,Rq1,Rr7),(Rp2,Rq1,Rr8),(Rp2,Rq1,Rr9),(Rp2,Rq1,Rr10),(Rp2,Rq1,Rr11),(Rp2,Rq1,Rr12),(Rp2,Rq1,Rr13),(Rp2,Rq1,Rr14),(Rp2,Rq1,Rr15),(Rp2,Rq1,Rr16),(Rp2,Rq1,Rr17),(Rp2,Rq1,Rr18),(Rp2,Rq1,Rr19),(Rp2,Rq1,Rr20),(Rp2,Rq1,Rr21),(Rp2,Rq1,Rr22),(Rp2,Rq2,Rr1),(Rp2,Rq2,Rr2),(Rp2,Rq2,Rr3),(Rp2,Rq2,Rr4),(Rp2,Rq2,Rr5),(Rp2,Rq2,Rr6),(Rp2,Rq2,Rr7),(Rp2,Rq2,Rr8),(Rp2,Rq2,Rr9),(Rp2,Rq2,Rr10),(Rp2,Rq2,Rr11),(Rp2,Rq2,Rr12),(Rp2,Rq2,Rr13),(Rp2,Rq2,Rr14),(Rp2,Rq2,Rr15),(Rp2,Rq2,Rr16),(Rp2,Rq2,Rr17),(Rp2,Rq2,Rr18),(Rp2,Rq2,Rr19),(Rp2,Rq2,Rr20),(Rp2,Rq2,Rr21),(Rp2,Rq2,Rr22),(Rp2,Rq3,Rr1),(Rp2,Rq3,Rr2),(Rp2,Rq3,Rr3),(Rp2,Rq3,Rr4),(Rp2,Rq3,Rr5),(Rp2,Rq3,Rr6),(Rp2,Rq3,Rr7),(Rp2,Rq3,Rr8),(Rp2,Rq3,Rr9),(Rp2,Rq3,Rr10),(Rp2,Rq3,Rr11),(Rp2,Rq3,Rr12),(Rp2,Rq3,Rr13),(Rp2,Rq3,Rr14),(Rp2,Rq3,Rr15),(Rp2,Rq3,Rr16),(Rp2,Rq3,Rr17),(Rp2,Rq3,Rr18),(Rp2,Rq3,Rr19),(Rp2,Rq3,Rr20),(Rp2,Rq3,Rr21),(Rp2,Rq3,Rr22),(Rp2,Rq4,Rr1),(Rp2,Rq4,Rr2),(Rp2,Rq4,Rr3),(Rp2,Rq4,Rr4),(Rp2,Rq4,

(Rp3,Rq4,Rr6),(Rp3,Rq4,Rr7),(Rp3,Rq4,Rr8),(Rp3,Rq4,Rr9),(Rp3,Rq4,Rr10),(Rp3,Rq4,Rr11),(Rp3,Rq4,Rr12),(Rp3,Rq4,Rr13),(Rp3,Rq4,Rr14),(Rp3,Rq4,Rr15),(Rp3,Rq4,Rr16),
 (Rp3,Rq4,Rr17),(Rp3,Rq4,Rr18),(Rp3,Rq4,Rr19),(Rp3,Rq4,Rr20),(Rp3,Rq4,Rr21),(Rp3,Rq4,Rr22),(Rp3,Rq5,Rr1),(Rp3,Rq5,Rr2),(Rp3,Rq5,Rr3),(Rp3,Rq5,Rr4),(Rp3,Rq5,Rr5),
 (Rp3,Rq5,Rr6),(Rp3,Rq5,Rr7),(Rp3,Rq5,Rr8),(Rp3,Rq5,Rr9),(Rp3,Rq5,Rr10),(Rp3,Rq5,Rr11),(Rp3,Rq5,Rr12),(Rp3,Rq5,Rr13),(Rp3,Rq5,Rr14),(Rp3,Rq5,Rr15),(Rp3,Rq5,Rr16),
 (Rp3,Rq5,Rr17),(Rp3,Rq5,Rr18),(Rp3,Rq5,Rr19),(Rp3,Rq5,Rr20),(Rp3,Rq5,Rr21),(Rp3,Rq5,Rr22),(Rp3,Rq6,Rr1),(Rp3,Rq6,Rr2),(Rp3,Rq6,Rr3),(Rp3,Rq6,Rr4),(Rp3,Rq6,Rr5),
 (Rp3,Rq6,Rr6),(Rp3,Rq6,Rr7),(Rp3,Rq6,Rr8),(Rp3,Rq6,Rr9),(Rp3,Rq6,Rr10),(Rp3,Rq6,Rr11),(Rp3,Rq6,Rr12),(Rp3,Rq6,Rr13),(Rp3,Rq6,Rr14),(Rp3,Rq6,Rr15),(Rp3,Rq6,Rr16),
 (Rp3,Rq6,Rr17),(Rp3,Rq6,Rr18),(Rp3,Rq6,Rr19),(Rp3,Rq6,Rr20),(Rp3,Rq6,Rr21),(Rp3,Rq6,Rr22),(Rp3,Rq7,Rr1),(Rp3,Rq7,Rr2),(Rp3,Rq7,Rr3),(Rp3,Rq7,Rr4),(Rp3,Rq7,Rr5),
 (Rp3,Rq7,Rr6),(Rp3,Rq7,Rr7),(Rp3,Rq7,Rr8),(Rp3,Rq7,Rr9),(Rp3,Rq7,Rr10),(Rp3,Rq7,Rr11),(Rp3,Rq7,Rr12),(Rp3,Rq7,Rr13),(Rp3,Rq7,Rr14),(Rp3,Rq7,Rr15),(Rp3,Rq7,Rr16),
 (Rp3,Rq7,Rr17),(Rp3,Rq7,Rr18),(Rp3,Rq7,Rr19),(Rp3,Rq7,Rr20),(Rp3,Rq7,Rr21),(Rp3,Rq7,Rr22),(Rp3,Rq8,Rr1),(Rp3,Rq8,Rr2),(Rp3,Rq8,Rr3),(Rp3,Rq8,Rr4),(Rp3,Rq8,Rr5),
 (Rp3,Rq8,Rr6),(Rp3,Rq8,Rr7),(Rp3,Rq8,Rr8),(Rp3,Rq8,Rr9),(Rp3,Rq8,Rr10),(Rp3,Rq8,Rr11),(Rp3,Rq8,Rr12),(Rp3,Rq8,Rr13),(Rp3,Rq8,Rr14),(Rp3,Rq8,Rr15),(Rp3,Rq8,Rr16),
 (Rp3,Rq8,Rr17),(Rp3,Rq8,Rr18),(Rp3,Rq8,Rr19),(Rp3,Rq8,Rr20),(Rp3,Rq8,Rr21),(Rp3,Rq8,Rr22),(Rp3,Rq9,Rr1),(Rp3,Rq9,Rr2),(Rp3,Rq9,Rr3),(Rp3,Rq9,Rr4),(Rp3,Rq9,Rr5),
 (Rp3,Rq9,Rr6),(Rp3,Rq9,Rr7),(Rp3,Rq9,Rr8),(Rp3,Rq9,Rr9),(Rp3,Rq9,Rr10),(Rp3,Rq9,Rr11),(Rp3,Rq9,Rr12),(Rp3,Rq9,Rr13),(Rp3,Rq9,Rr14),(Rp3,Rq9,Rr15),(Rp3,Rq9,Rr16),
 (Rp3,Rq9,Rr17),(Rp3,Rq9,Rr18),(Rp3,Rq9,Rr19),(Rp3,Rq9,Rr20),(Rp3,Rq9,Rr21),(Rp3,Rq9,Rr22),(Rp3,Rq10,Rr1),(Rp3,Rq10,Rr2),(Rp3,Rq10,Rr3),(Rp3,Rq10,Rr4),(Rp3,Rq10,Rr5),
 (Rp3,Rq10,Rr6),(Rp3,Rq10,Rr7),(Rp3,Rq10,Rr8),(Rp3,Rq10,Rr9),(Rp3,Rq10,Rr10),(Rp3,Rq10,Rr11),(Rp3,Rq10,Rr12),(Rp3,Rq10,Rr13),(Rp3,Rq10,Rr14),(Rp3,Rq10,Rr15),
 (Rp3,Rq10,Rr16),(Rp3,Rq10,Rr17),(Rp3,Rq10,Rr18),(Rp3,Rq10,Rr19),(Rp3,Rq10,Rr20),(Rp3,Rq10,Rr21),(Rp3,Rq10,Rr22),(Rp3,Rq11,Rr1),(Rp3,Rq11,Rr2),(Rp3,Rq11,Rr3),
 (Rp3,Rq11,Rr4),(Rp3,Rq11,Rr5),(Rp3,Rq11,Rr6),(Rp3,Rq11,Rr7),(Rp3,Rq11,Rr8),(Rp3,Rq11,Rr9),(Rp3,Rq11,Rr10),(Rp3,Rq11,Rr11),(Rp3,Rq11,Rr12),(Rp3,Rq11,Rr13),(Rp3,Rq11,Rr14),
 (Rp3,Rq11,Rr15),(Rp3,Rq11,Rr16),(Rp3,Rq11,Rr17),(Rp3,Rq11,Rr18),(Rp3,Rq11,Rr19),(Rp3,Rq11,Rr20),(Rp3,Rq11,Rr21),(Rp3,Rq11,Rr22),(Rp3,Rq12,Rr1),(Rp3,Rq12,Rr2),
 (Rp3,Rq12,Rr3),(Rp3,Rq12,Rr4),(Rp3,Rq12,Rr5),(Rp3,Rq12,Rr6),(Rp3,Rq12,Rr7),(Rp3,Rq12,Rr8),(Rp3,Rq12,Rr9),(Rp3,Rq12,Rr10),(Rp3,Rq12,Rr11),(Rp3,Rq12,Rr12),
 (Rp3,Rq12,Rr13),(Rp3,Rq12,Rr14),(Rp3,Rq12,Rr15),(Rp3,Rq12,Rr16),(Rp3,Rq12,Rr17),(Rp3,Rq12,Rr18),(Rp3,Rq12,Rr19),(Rp3,Rq12,Rr20),(Rp3,Rq12,Rr21),(Rp3,Rq12,Rr22),
 (Rp4,Rq1,Rr1),(Rp4,Rq1,Rr2),(Rp4,Rq1,Rr3),(Rp4,Rq1,Rr4),(Rp4,Rq1,Rr5),(Rp4,Rq1,Rr6),(Rp4,Rq1,Rr7),(Rp4,Rq1,Rr8),(Rp4,Rq1,Rr9),(Rp4,Rq1,Rr10),(Rp4,Rq1,Rr11),
 (Rp4,Rq1,Rr12),(Rp4,Rq1,Rr13),(Rp4,Rq1,Rr14),(Rp4,Rq1,Rr15),(Rp4,Rq1,Rr16),(Rp4,Rq1,Rr17),(Rp4,Rq1,Rr18),(Rp4,Rq1,Rr19),(Rp4,Rq1,Rr20),(Rp4,Rq1,Rr21),(Rp4,Rq1,Rr22),
 (Rp4,Rq2,Rr1),(Rp4,Rq2,Rr2),(Rp4,Rq2,Rr3),(Rp4,Rq2,Rr4),(Rp4,Rq2,Rr5),(Rp4,Rq2,Rr6),(Rp4,Rq2,Rr7),(Rp4,Rq2,Rr8),(Rp4,Rq2,Rr9),(Rp4,Rq2,Rr10),(Rp4,Rq2,Rr11),
 (Rp4,Rq2,Rr12),(Rp4,Rq2,Rr13),(Rp4,Rq2,Rr14),(Rp4,Rq2,Rr15),(Rp4,Rq2,Rr16),(Rp4,Rq2,Rr17),(Rp4,Rq2,Rr18),(Rp4,Rq2,Rr19),(Rp4,Rq2,Rr20),(Rp4,Rq2,Rr21),(Rp4,Rq2,Rr22),
 (Rp4,Rq3,Rr1),(Rp4,Rq3,Rr2),(Rp4,Rq3,Rr3),(Rp4,Rq3,Rr4),(Rp4,Rq3,Rr5),(Rp4,Rq3,Rr6),(Rp4,Rq3,Rr7),(Rp4,Rq3,Rr8),(Rp4,Rq3,Rr9),(Rp4,Rq3,Rr10),(Rp4,Rq3,Rr11),
 (Rp4,Rq3,Rr12),(Rp4,Rq3,Rr13),(Rp4,Rq3,Rr14),(Rp4,Rq3,Rr15),(Rp4,Rq3,Rr16),(Rp4,Rq3,Rr17),(Rp4,Rq3,Rr18),(Rp4,Rq3,Rr19),(Rp4,Rq3,Rr20),(Rp4,Rq3,Rr21),(Rp4,Rq3,Rr22),
 (Rp4,Rq4,Rr1),(Rp4,Rq4,Rr2),(Rp4,Rq4,Rr3),(Rp4,Rq4,Rr4),(Rp4,Rq4,Rr5),(Rp4,

Rq4,Rr6),(Rp4,Rq4,Rr7),(Rp4,Rq4,Rr8),(Rp4,Rq4,Rr9),(Rp4,Rq4,Rr10),(Rp4,Rq4,Rr11),
 (Rp4,Rq4,Rr12),(Rp4,Rq4,Rr13),(Rp4,Rq4,Rr14),(Rp4,Rq4,Rr15),(Rp4,Rq4,Rr16),(Rp4,
 Rq4,Rr17),(Rp4,Rq4,Rr18),(Rp4,Rq4,Rr19),(Rp4,Rq4,Rr20),(Rp4,Rq4,Rr21),(Rp4,Rq4,
 Rr22),(Rp4,Rq5,Rr1),(Rp4,Rq5,Rr2),(Rp4,Rq5,Rr3),(Rp4,Rq5,Rr4),(Rp4,Rq5,Rr5),(Rp4,
 Rq5,Rr6),(Rp4,Rq5,Rr7),(Rp4,Rq5,Rr8),(Rp4,Rq5,Rr9),(Rp4,Rq5,Rr10),(Rp4,Rq5,Rr11),
 (Rp4,Rq5,Rr12),(Rp4,Rq5,Rr13),(Rp4,Rq5,Rr14),(Rp4,Rq5,Rr15),(Rp4,Rq5,Rr16),(Rp4,
 Rq5,Rr17),(Rp4,Rq5,Rr18),(Rp4,Rq5,Rr19),(Rp4,Rq5,Rr20),(Rp4,Rq5,Rr21),(Rp4,Rq5,
 Rr22),(Rp4,Rq6,Rr1),(Rp4,Rq6,Rr2),(Rp4,Rq6,Rr3),(Rp4,Rq6,Rr4),(Rp4,Rq6,Rr5),(Rp4,
 Rq6,Rr6),(Rp4,Rq6,Rr7),(Rp4,Rq6,Rr8),(Rp4,Rq6,Rr9),(Rp4,Rq6,Rr10),(Rp4,Rq6,Rr11),
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[illegible]

[illegible]

[illegible]

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[illegible]

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[illegible]

[illegible]

[illegible]

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 6,Rr14),(Rp37,Rq6,Rr15),(Rp37,Rq6,Rr16),(Rp37,Rq6,Rr17),(Rp37,Rq6,Rr18),(Rp37,R
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 7),(Rp37,Rq7,Rr8),(Rp37,Rq7,Rr9),(Rp37,Rq7,Rr10),(Rp37,Rq7,Rr11),(Rp37,Rq7,Rr12)
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),(Rp37,Rq7,Rr18),(Rp37,Rq7,Rr19),(Rp37,Rq7,Rr20),(Rp37,Rq7,Rr21),(Rp37,Rq7,Rr2
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 9),(Rp37,Rq9,Rr10),(Rp37,Rq9,Rr11),(Rp37,Rq9,Rr12),(Rp37,Rq9,Rr13),(Rp37,Rq9,Rr
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 ,Rr7),(Rp37,Rq10,Rr8),(Rp37,Rq10,Rr9),(Rp37,Rq10,Rr10),(Rp37,Rq10,Rr11),(Rp37,R
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 11,Rr4),(Rp37,Rq11,Rr5),(Rp37,Rq11,Rr6),(Rp37,Rq11,Rr7),(Rp37,Rq11,Rr8),(Rp37,R
 q11,Rr9),(Rp37,Rq11,Rr10),(Rp37,Rq11,Rr11),(Rp37,Rq11,Rr12),(Rp37,Rq11,Rr13),(R
 p37,Rq11,Rr14),(Rp37,Rq11,Rr15),(Rp37,Rq11,Rr16),(Rp37,Rq11,Rr17),(Rp37,Rq11,R
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 ,Rq12,Rr6),(Rp37,Rq12,Rr7),(Rp37,Rq12,Rr8),(Rp37,Rq12,Rr9),(Rp37,Rq12,Rr10),(Rp
 37,Rq12,Rr11),(Rp37,Rq12,Rr12),(Rp37,Rq12,Rr13),(Rp37,Rq12,Rr14),(Rp37,Rq12,Rr
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 Rq1,Rr3),(Rp38,Rq1,Rr4),(Rp38,Rq1,Rr5),(Rp38,Rq1,Rr6),(Rp38,Rq1,Rr7),(Rp38,Rq1,
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[0116]

Following examples illustrate the present invention in more detail, however, the present invention is not limited to these examples. The meaning of each abbreviation is as follows.

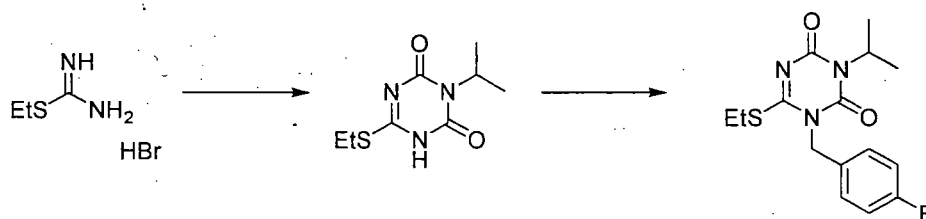
Me: methyl
 Et: ethyl
 Bu: butyl
 Ac: acetyl
 TMS: tetramethylsilane
 TMS-Cl: trimethylsilyl chloride
 DMSO: dimethyl sulfoxide
 DMF: dimethylformamide
 THF: tetrahydrofuran
 DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
 NMP: N-methyl-2-pyrrolidone
 HOAt: 1-hydroxy-7-azabenzotriazole
 HATU: 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate
 PyBOP: benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate
 rt: room temperature

[0117]

Example 1

Preparation of 6-(ethylthio)-1-(4-fluorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 62]



To a mixture of S-ethylthiourea hydrobromide (14.8 g, 80 mmol) and DMF (75 mL) were added isopropylisocyanate (8.2 mL, 84 mmol) and DBU (12.6 mL, 84 mmol) under ice-cooling, and the resulting mixture was stirred under ice-cooling for 6 hours.

1,1'-carbonyldiimidazole (15.57 g, 96 mmol) and DBU (18.0 mL, 120 mmol) were added to the reaction mixture under ice-cooling, and the resulting mixture was stirred for 2 hours. Then, 2 mol/L hydrochloric acid (240 mL) was added to the reaction mixture under ice-cooling for about 50 minutes, and the precipitated solid was collected by filtration. The resulting solid was dissolved in ethyl acetate, and the mixture was dried over anhydrous magnesium sulphate and then concentrated in vacuo to give 6-(ethylthio)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (12.29 g, yield: 71%) as light brown solid.

¹H-NMR (δ ppm TMS / DMSO-d₆): 1.27 (6H, t, J=7.2 Hz), 1.33 (6H, d, J=6.9 Hz), 3.05 (2H, q, J=7.2 Hz), 4.81 (1H, sept, J=6.9 Hz).

To a mixture of 6-(ethylthio)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (4.09 g, 19 mmol), potassium carbonate (7.88 g, 57 mmol) and acetonitrile (80 mL) was added 4-fluorobenzyl bromide (3.55 mL, 28.5 mmol), and the resulting mixture was stirred at reflux for 1.5 hours. Then, ice-water (20 mL) was poured into the reaction mixture, and the resulting mixture was extracted with ethyl acetate (10 mL). The extract was dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The aimed compound was triturated with ethyl acetate and hexane to give 6-(ethylthio)-1-(4-fluorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (5.96 g, yield: 97%) as colorless solid.

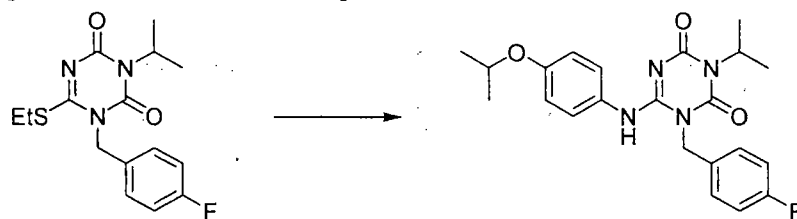
¹H-NMR (δ ppm TMS / CDCl₃): 1.37 (3H, t, J=7.5 Hz), 1.47 (6H, d, J=6.9 Hz), 3.21 (2H, q, J=7.5 Hz), 5.02 (1H, sept, J=6.9), 5.06 (2H, s), 7.01-7.07 (2H, m), 7.31-7.36 (2H, m).

[0118]

Example 2

Preparation of 1-(4-fluorobenzyl)-6-(4-isopropoxyphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 63]



A mixture of 6-(ethylthio)-1-(4-fluorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.323 g, 1 mmol), 4-isopropoxyaniline (0.907 g, 6 mmol) and 1-methyl-2-pyrrolidone (1 mL) was heated at 230°C for 30 min under microwave radiation. Then, water (10 mL) was poured into the reaction mixture, and the

resulting mixture was extracted with ethyl acetate (10 mL). The extract was dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The aimed compound was triturated with ethyl acetate and hexane to give 1-(4-fluorobenzyl)-6-(4-isopropoxyphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.21 g, yield: 51%) as colorless solid.

Melting point: 176-177°C

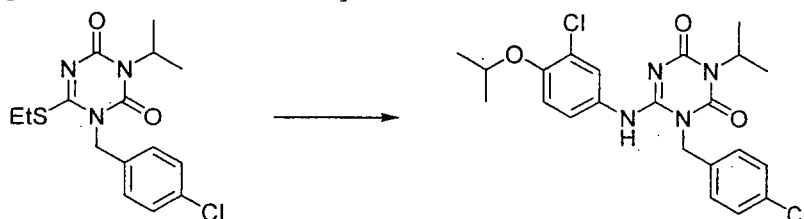
¹H-NMR (8 ppm TMS / CDCl₃): 1.34 (6H, d, J=6.0 Hz), 1.44 (6H, d, J=6.9 Hz), 4.49 (1H, sept, J=6.0 Hz), 4.96 (1H, sept, J=6.9 Hz), 5.18 (2H, s), 6.75-7.06 (6H, m), 7.53-7.57 (2H, m).

[0119]

Example 3

Preparation of 6-(3-chloro-4-isopropoxyphenylamino)-1-(4-chlorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 64]



A mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.60 g, 1.78 mmol), 3-chloro-4-isopropoxyaniline (0.99 g, 5.3 mmol) and acetic acid (10 mL) was heated at 90°C for 6 hours. Then, the reaction mixture was poured into saturated sodium hydrogen carbonate solution (10 mL), and the resulting mixture was extracted with ethyl acetate (10 mL). The extract was washed with saturated sodium hydrogen carbonate solution (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The aimed compound was triturated with diethyl ether and hexane to give 6-(3-chloro-4-isopropoxyphenylamino)-1-(4-chlorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.605 g, yield: 73%) as colorless solid.

Melting point: 167°C

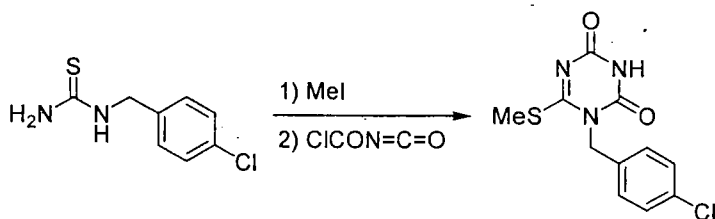
¹H-NMR (8 ppm TMS / DMSO-d₆): 1.28 (6H, d, J=6.0 Hz), 1.34 (6H, d, J=6.9 Hz), 4.62 (1H, m), 4.83 (1H, sept, J=6.9 Hz), 5.18 (2H, brs), 7.12-7.15 (2H, m), 7.34-7.37 (3H, m), 7.43 (2H, d, J=8.7 Hz), 9.23 (1H, brs).

[0120]

Example 4

Preparation of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 65]



To a mixture of 1-(4-chlorobenzyl)thiourea (11.19 g, 55.8 mmol) and methanol (50 mL) was added methyl iodide (4.18 mL, 66.9 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 5 hours. Then, the reaction mixture was concentrated in vacuo. To the resulting residue were added dichloromethane (60 mL) and N,N-diisopropylethylamine (29.2 mL, 167 mmol), and then a solution of N-(chlorocarbonyl) isocyanate (4.94 mL, 61.4 mmol) in dichloromethane (20 mL) was added to the resulting mixture under ice-cooling gradually. The resulting mixture was stirred at room temperature for 1 hour. Then, the precipitated solid was collected by filtration. The obtained solid was washed with a small amount of dichloromethane and dried under reduced pressure to give 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione (9.19 g, yield: 58%) as colorless solid.

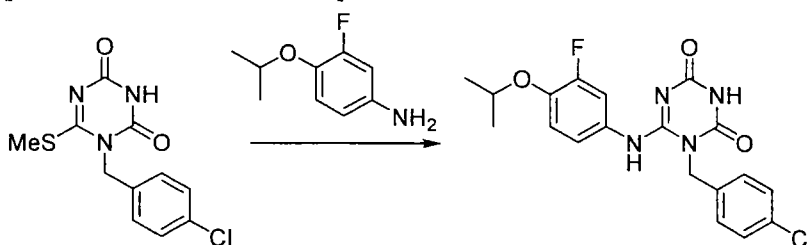
¹H-NMR (δ ppm TMS / DMSO-d₆): 2.46 (3H, s), 5.04 (2H, s), 7.31-7.43 (4H, m), 11.60 (1H, brs).

[0121]

Example 5

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 66]



A mixture of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione (4.21 g, 14.8 mmol), 3-fluoro-4-isopropoxyaniline (3.77 g, 22.3 mmol), t-butanol (84 mL) and acetic acid (17 mL) was heated at reflux for 8 hours. Then, the reaction mixture was poured into saturated sodium hydrogen carbonate solution (30 mL), and the resulting mixture was extracted with ethyl acetate (10 mL). The extract was washed with saturated sodium hydrogen carbonate solution (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The aimed compound was triturated with diisopropyl ether to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione (4.54 g, yield: 76%) as colorless solid.

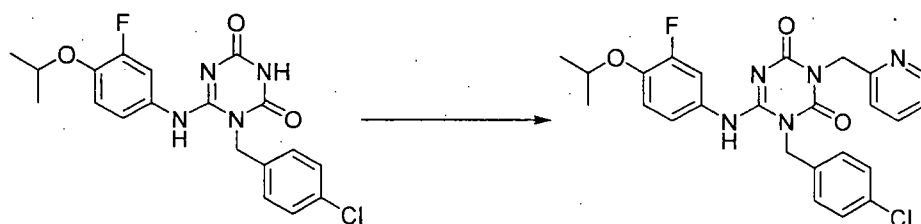
¹H-NMR (δ ppm TMS / CDCl₃): 1.36 (6H, d, J=6.1 Hz), 4.49 (1H, sept, J=6.1 Hz), 5.14 (2H, s), 6.47 (1H, m), 6.59 (1H, m), 6.97 (1H, m), 7.30 (2H, d, J=8.5 Hz), 7.47 (2H, d, J=8.5 Hz), 8.06 (1H, brs).

[0122]

Example 6

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-pyridylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 67]



To a mixture of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione (0.15 g, 0.37 mmol) and DMF (3 mL) was added potassium *t*-butoxide (0.9 mg, 0.82 mmol), and the resulting mixture was stirred at room temperature for 5 minutes. To the mixture was added 2-(bromomethyl)pyridine hydrobromide (0.103 g, 0.41 mmol), and the resulting mixture was stirred at 60 °C for 2 hours. Then, water (20 mL) was poured into the mixture, and the resulting mixture was extracted with ethyl acetate (20 mL×2). The extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The aimed compound was triturated with hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-pyridylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.69 g, yield: 37%) as colorless solid.

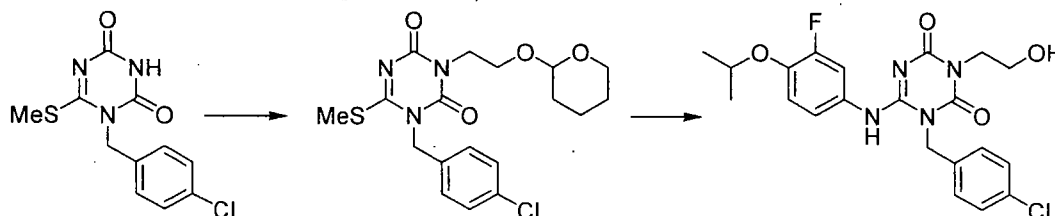
¹H-NMR (δ ppm TMS / CDCl₃): 1.36 (2H, d, *J*=6.2 Hz), 4.47 (1H, sept, *J*=6.2 Hz), 5.15 (2H, s), 5.19 (2H, s), 6.51 (1H, m), 6.62 (1H, m), 6.97 (1H, m), 7.17-7.48 (7H, m), 7.65 (1H, m), 8.53 (1H, m).

[0123]

Example 7

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxyethyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 68]



To a mixture of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione (0.28 g, 1 mmol), 2-(tetrahydro-2H-pyran-2-yloxy)ethanol (0.15 g, 1.00 mmol), triphenylphosphine (0.53 g, 2 mmol) and THF (5 mL) was gradually added diisopropylazocarboxylate (0.23 mL, 1.2 mmol) dropwise under ice-cooling, and the resulting mixture was stirred at room temperature for 3 hours. The mixture was poured into water (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL×2). The extract was washed with brine (20 mL), dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane) to give 1-(4-chlorobenzyl)-6-(methylthio)-3-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]-1,3,5-triazine-2,4(1H,3H)-dione (0.32 g, yield: 78%) as colorless amorphous.

¹H-NMR (δ ppm TMS / CDCl₃): 1.42-1.83 (6H, m), 2.58 (3H, s), 3.47 (1H, m), 3.74-4.32 (5H, m), 4.63 (1H, m), 5.10 (2H, s), 7.28-7.33 (4H, m).

A mixture of 1-(4-chlorobenzyl)-6-(methylthio)-3-[2-(tetrahydro-2H-pyran-2-

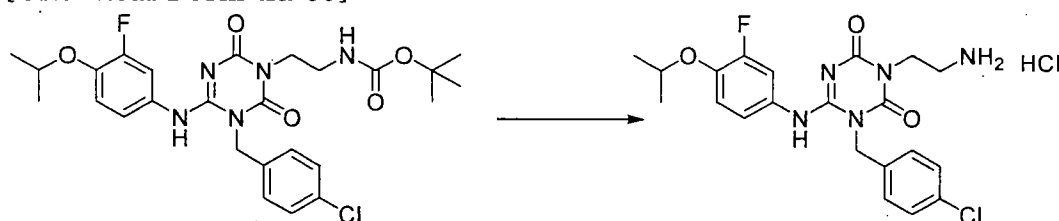
loxy)ethyl]-1,3,5-triazine-2,4(1H,3H)-dione (0.32 g, 0.78 mmol), 3-fluoro-4-isopropoxyaniline (0.40 g, 2.4 mmol) and acetic acid (3 mL) was heated at 10 °C for 3 hours. Then, the reaction mixture was poured into saturated sodium hydrogen carbonate solution (10 mL), and the resulting mixture was extracted with chloroform (10 mL×2). The extract was dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (methanol/chloroform). The aimed compound was triturated with diisopropyl ether and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxyethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.12 g, yield: 33%) as colorless solid.

[0124]

Example 8

Preparation of 3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione hydrochloride

[Chemical Formula 69]



To 3-(2-*t*-butoxycarbonylaminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione (0.44 g, 0.8 mmol) was added 4mol/L solution of hydrochloric acid in dioxane (5mL) under ice-cooling, and the resulting mixture was stirred at room temperature for 1 hour. Then, the precipitated solid was collected by filtration. The resulting solid was washed with diethyl ether, dried under reduced pressure to give 3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione hydrochloride (0.31 g, yield: 81%) as colorless solid.

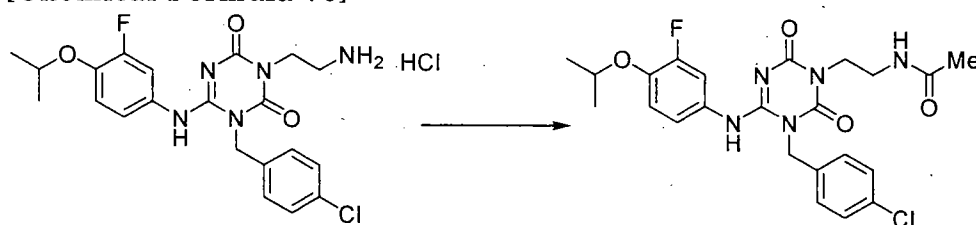
¹H-NMR (δ ppm TMS / DMSO-*d*₆): 1.27 (6H, d, *J*=5.9 Hz), 3.01 (2H, m), 3.98 (2H, m), 4.57 (1H, sept, *J*=5.9 Hz), 5.27 (2H, brs), 6.98-7.17 (3H, m), 7.42 (3H, s), 7.87 (2H, brs).

[0125]

Example 9

Preparation of 3-(2-acetylaminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 70]



To a mixture of 3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione hydrochloride (0.104 g, 0.22

mmol), triethylamine (0.74 mL, 0.54 mmol), dimethylaminopyridine (0.26 g, 0.22 mmol) and THF (2 mL) was added acetyl chloride (0.23 mL, 0.32 mmol) dropwise under ice-cooling, and the resulting mixture was stirred at room temperature for 30 minutes. Water (20 mL) was poured into the reaction mixture, and the resulting mixture was extracted with ethyl acetate (10 mL×2). The extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The aimed compound was triturated with diisopropyl ether and hexane to give 3-(2-acetylaminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione (0.104 g, yield: 99%) as colorless solid.

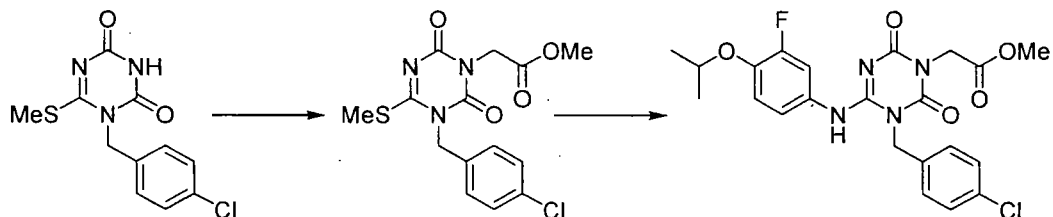
¹H-NMR (δ ppm TMS / CDCl₃): 1.37 (6H, d, J=6.1 Hz), 1.86 (3H, s), 3.51 (2H, m), 4.0 (2H, m), 4.47 (1H, sept, J=6.1 Hz), 5.16 (2H, s), 5.83 (1H, m), 6.51 (1H, m), 6.60 (1H, m), 6.97 (1H, m), 7.27-7.51 (5H, m).

[0126]

Example 10

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methoxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 71]



To a mixture of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione (0.28 g, 1 mmol) and THF (3 mL) was added DBU (0.166 mL, 1.1 mmol), and the resulting mixture was stirred at room temperature for 5 minutes. Bromomethyl acetate (0.104 mL, 1.1 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature for 3 hours. Water (20 mL) was poured into the mixture, and the precipitated solid was collected by filtration. The resulting solid was dried and purified on a silica gel column chromatography (ethyl acetate/hexane) to give 1-(4-chlorobenzyl)-3-(methoxycarbonylmethyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione (0.25 g, yield: 69%) as colorless solid.

¹H-NMR (δ ppm TMS / CDCl₃): 2.59 (3H, s), 3.78 (3H, s), 4.69 (2H, s), 5.13 (2H, s), 7.27-7.35 (4H, m).

A mixture of 1-(4-chlorobenzyl)-3-(methoxycarbonylmethyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dione (0.24 g, 0.68 mmol), 3-fluoro-4-isopropoxyaniline (0.17 mg, 1.03 mmol), t-butanol (4.8 mL) and acetic acid (0.4 mL) was heated at reflux for 32 hours. Then, the mixture was poured into saturated sodium hydrogen carbonate solution (20 mL), and the resulting mixture was extracted with ethyl acetate (10 mL).

The extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The resulting aimed compound was triturated with diisopropyl ether to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methoxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione

(0.31 g, yield: 95%) as colorless amorphous.

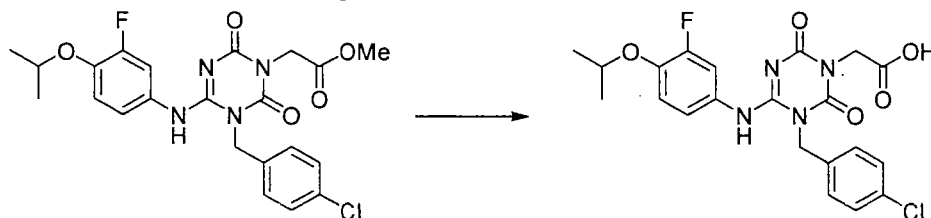
¹H-NMR (δ ppm TMS / CDCl₃): 1.37 (6H, d, J=5.9 Hz), 3.78 (3H, s), 4.47 (1H, sept, J=5.9 Hz), 4.58 (2H, s), 5.17 (2H, s), 6.50 (1H, m), 6.60 (1H, m), 6.97 (1H, m), 7.28-7.47 (5H, m).

[0127]

Example 11

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(hydroxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 72]



To a mixture of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methoxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.30 g, 0.63 mmol), methanol (3 mL) and THF (3 mL) was added 1mol/L lithium hydroxide (3.8 mL) under ice-cooling, and the resulting mixture was stirred at room temperature for 1 hour. Then, the mixture was treated with 2mol/L hydrochloric acid to pH2 or less. The mixture was poured into brine (20 mL), and the resulting mixture was extracted with chloroform (10 mL×3). The extract was dried over anhydrous sodium sulphate and concentrated in vacuo. The resulting residue was triturated with diethyl ether and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(hydroxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.28 g, yield: 97%) as colorless solid.

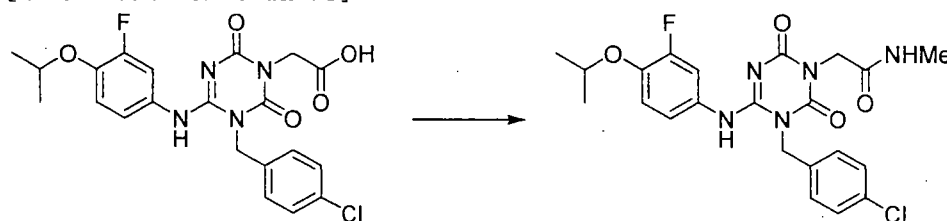
¹H-NMR (δ ppm TMS / CDCl₃): 1.36 (6H, d, J=6.1 Hz), 4.47 (1H, sept, J=6.1 Hz), 4.62 (2H, s), 5.18 (2H, s), 6.51 (1H, m), 6.60 (1H, m), 6.96 (1H, m), 7.30 (2H, d, J=8.7 Hz), 7.45 (2H, d, J=8.7 Hz), 7.64 (1H, brs).

[0128]

Example 12

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methylcarbamoylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 73]



To a mixture of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(hydroxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.83 g, 0.19 mmol) and DMF (2 mL) were added methylamine hydrochloride (0.15 g, 0.21 mmol), 1-hydroxybenzotriazole hydrate (0.3 g, 0.2 mmol), 4-dimethylaminopyridine (0.02 g, 0.2 mmol), 1-ethyl-3-(3-dimethylanimopropyl)carbodiimide hydrochloride (0.38 g, 0.2

mmol) and triethylamine (0.3 mL, 0.21 mmol), and the resulting mixture was stirred at 60 °C for 4 hours. Then, the mixture was poured into water (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL). The extract was washed with brine (10 mL), dried over anhydrous sodium sulphate and concentrated in vacuo.

The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane) and the aimed compound was triturated with diisopropyl ether to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methylcarbamoylmethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.76 g, yield: 89%) as colorless solid.

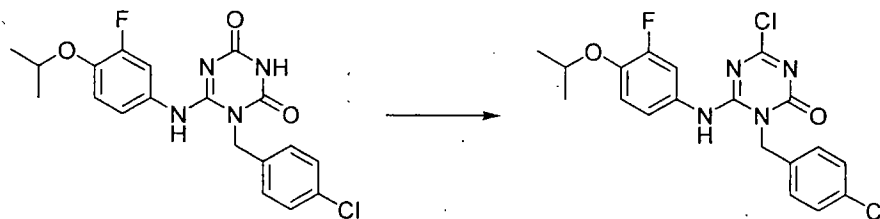
¹H-NMR (δ ppm TMS / CDCl₃): 1.37 (6H, d, J=6.1 Hz), 2.85 (3H, d, J=4.9 Hz), 4.37 (2H, s), 4.46 (1H, sept, J=6.1 Hz), 5.15 (2H, s), 5.78 (1H, d, J=4.7 Hz), 6.46 (1H, m), 6.57 (1H, m), 6.95 (1H, m), 7.27-7.46 (4H, m), 7.99 (1H, ms).

[0129]

Example 13

Preparation of 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one

[Chemical Formula 74]



To 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dione (0.486 g, 1.2 mmol) was added phosphorous oxychloride (2.24 mL, 24 mmol), and the resulting mixture was stirred at 50 °C for 2 hours. Then, the mixture was concentrated in vacuo. The resulting residue was dissolved in ethyl acetate (30 mL), washed with saturated sodium hydrogen carbonate solution (10 mL) and brine (10 mL), dried over anhydrous sodium sulphate and concentrated in vacuo to give crude 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.57 g) as colorless solid.

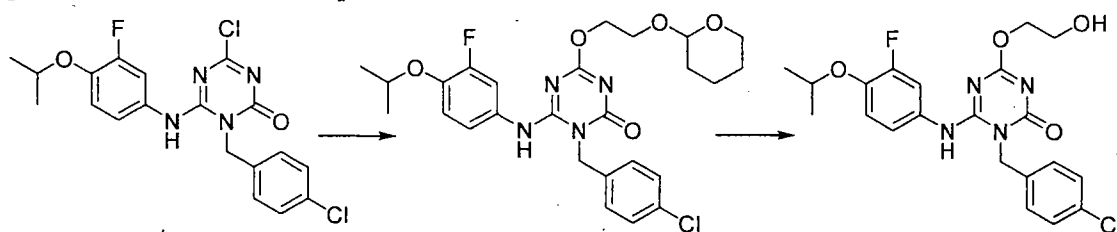
¹H-NMR (δ ppm TMS / CDCl₃): 1.35 (6H, d, J=6.3 Hz), 4.51 (1H, sept, J=6.3 Hz), 5.28 (2H, s), 6.72 (1H, brs), 6.80 (1H, m), 6.91 (1H, m), 7.08 (1H, m), 7.30 (2H, d, J=8.4 Hz), 7.44 (2H, d, J=8.4 Hz).

[0130]

Example 14

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-4-(2-hydroxyethoxy)-1,3,5-triazine-2(1H)-one

[Chemical Formula 75]



To a mixture of 2-(tetrahydro-2H-pyran-2-yloxy)ethanol (0.17 mL, about 1.25 mmol) and THF (5.6 mL) was added 60% sodium hydride (0.5 g, 1.25 mmol), and the resulting mixture was stirred at room temperature for 10 minutes. A solution of crude 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.224 g, about 0.5 mmol) in THF (5.6 mL) was added to the mixture under ice-cooling, and the resulting mixture was stirred at room temperature for 5 hours. Then, half-saturated ammonium chloride aqueous solution (50 mL) was poured into the mixture and the resulting mixture was extracted with ethyl acetate (50 mL). The extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane) and the aimed compound was triturated with hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-4-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]-1,3,5-triazine-2(1H)-one (0.166 g, yield: 62%) as colorless oil.

To a mixture of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-4-[2-(tetrahydro-2H-pyran-2-yloxy)ethoxy]-1,3,5-triazine-2(1H)-one (0.15 g, 0.28 mmol) and methanol (1.5 mL) was added p-toluenesulfonic acid hydrate (0.8 g, 0.4 mmol), and the resulting mixture was stirred at room temperature for 2 hours. Then, the mixture was poured into half-saturated sodium hydrogen carbonate solution (10 mL) and the resulting mixture was extracted with ethyl acetate (20 mL). The extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (methanol/chloroform) and the aimed compound was triturated with hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-4-(2-hydroxyethoxy)-1,3,5-triazine-2(1H)-one (0.104 g, yield: 83%) as colorless solid.

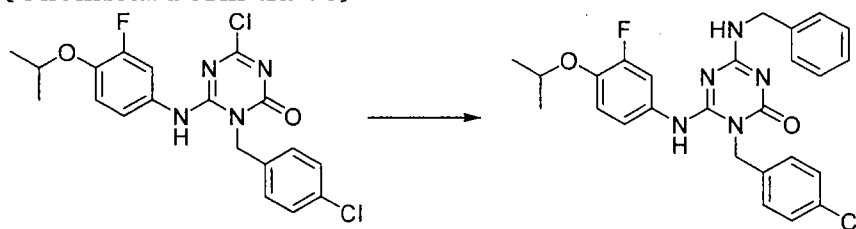
¹H-NMR (δ ppm TMS / CDCl₃): 1.34 (6H, d, J=6.1 Hz), 2.53 (1H, brs), 3.91 (2H, brs), 4.44-4.52 (3H, m), 5.30 (2H, s), 6.60 (1H, brs), 6.75-7.10 (3H, m), 7.27-7.43 (4H, m).

[0131]

Example 15

Preparation of 4-benzylamino-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one

[Chemical Formula 76]



To a mixture of crude 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.19 g, about 0.4 mmol) and THF (4.7 mL) was added benzylamine (0.108 mL, 1 mmol), and the resulting mixture was stirred at room temperature for 6 hours. Water (10 mL) and ethyl acetate (10 mL) were poured into the mixture and the precipitated solid was collected by filtration. The obtained solid was washed with ethyl acetate, dried under reduced pressure to give 4-benzylamino-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-

triazine-2(1H)-one (0.102 g, yield: 52%) as colorless solid.

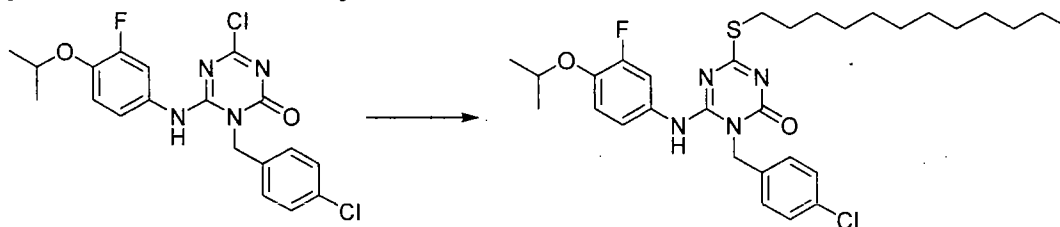
¹H-NMR (δ ppm TMS / DMSO-d₆): 1.25 (6H, d, J=5.7 Hz), 4.28 (1H, m), 4.41 (1H, m), 4.54 (1H, sept, J=5.7 Hz), 5.22 (2H, m), 7.08-7.52 (8H, m), 7.90 (1H, brs), 8.94 (1H, brs).

[0132]

Example 16

Preparation of 1-(4-chlorobenzyl)-4-(dodecylthio)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one

[Chemical Formula 77]



To a mixture of 1-dodecanethiol (0.24 mL, 1.0 mmol) and THF (4.8 mL) was added 60% sodium hydride (0.45 g, 1.0 mmol), and the resulting mixture was stirred at room temperature for 10 minutes. A solution of crude 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.19 g, about 0.4 mmol) in THF (2 mL) was added to the reaction mixture under ice-cooling.

After the reaction mixture was stirred at 50°C for 5 hours, half-saturated ammonium chloride aqueous solution (50 mL) was poured into the mixture and the resulting mixture was extracted with ethyl acetate (50 mL). The extract was washed with brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane) and the aimed compound was triturated with hexane to give 1-(4-chlorobenzyl)-4-(dodecylthio)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.92 g, yield: 39%) as colorless oil.

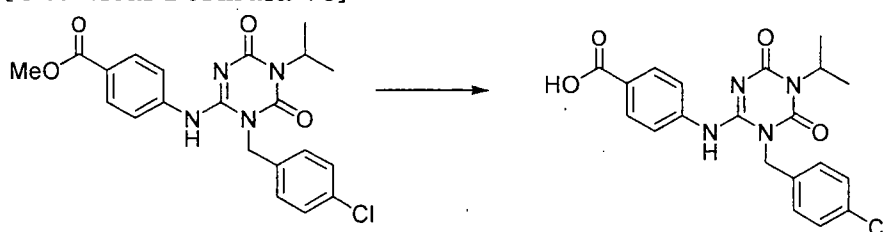
¹H-NMR (δ ppm TMS / CDCl₃): 0.89 (3H, t, J=6.9 Hz), 1.27 (14H, s), 1.34 (6H, d, J=6 Hz), 1.50-1.70 (6H, m), 3.02 (2H, t, J=7.5 Hz), 4.48 (1H, sept, J=6 Hz), 5.26 (2H, s), 6.52 (1H, brs), 6.75 (1H, m), 6.88 (1H, m), 7.10 (1H, m), 7.28-7.50 (4H, m).

[0133]

Example 17

Preparation of 1-(4-chlorobenzyl)-6-(4-hydroxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 78]



To a mixture of 1-(4-chlorobenzyl)-6-(4-methoxycarbonylphenylamino)-3-

isopropyl-1,3,5-triazine-2,4(1H,3h)-dione (0.70 g, 1.63 mmol), methanol (4 mL) and THF (4 mL) was added 2mol/L lithium hydroxide (4.9 mL) under ice-cooling, and the resulting mixture was stirred at room temperature for 8 hours. The mixture was poured into water (50 mL) and the resulting mixture was treated with 2mol/L hydrochloric acid to pH3 or less. The resulting mixture was extracted with ethyl acetate (50 mL×2). The extract was washed with brine (50 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The obtained solid was washed with diethyl ether to give 1-(4-chlorobenzyl)-6-(4-hydroxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.60 g, yield: 89%) as colorless solid.

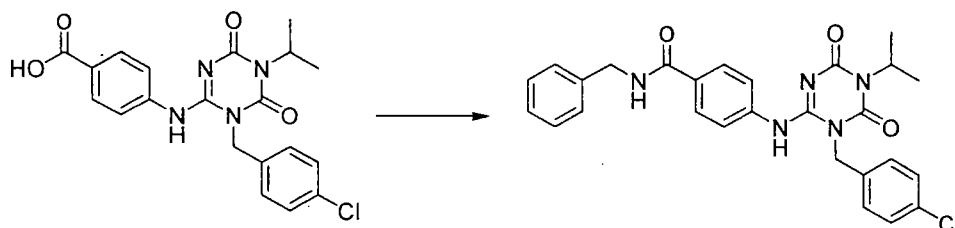
¹H-NMR (δ ppm TMS / CDCl₃): 1.46 (6H, d, J=6.9 Hz), 4.98 (1H, sept, J=6.9 Hz), 5.19 (2H, s), 6.90 (2H, d, J=8.1 Hz), 7.31 (2H, d, J=8.7 Hz), 7.50 (2H, d, J=8.7 Hz), 7.90 (2H, d, J=8.1 Hz).

[0134]

Example 18

Preparation of 1-(4-chlorobenzyl)-6-[4-(N-benzylcarbamoyl)phenylamino]-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 79]



To a mixture of 1-(4-chlorobenzyl)-6-(4-hydroxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3h)-dione (08 g, 0.19 mmol) and THF (2 mL) were added benzylamine (023 mL, 0.21 mmol), 1-hydroxybenzotriazole (03 g, 0.21 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (041 g, 0.2 mmol) and triethylamine (03 mL, 0.21 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours. The mixture was poured into water (30 mL) and the resulting mixture was extracted with ethyl acetate (30 mL). The extract was washed with brine (30 mL), dried over anhydrous sodium sulphate and concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane) and the aimed compound was triturated with diethyl ether to give 1-(4-chlorobenzyl)-6-[4-(N-benzylcarbamoyl)phenylamino]-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (07 g, yield: 72%) as colorless solid.

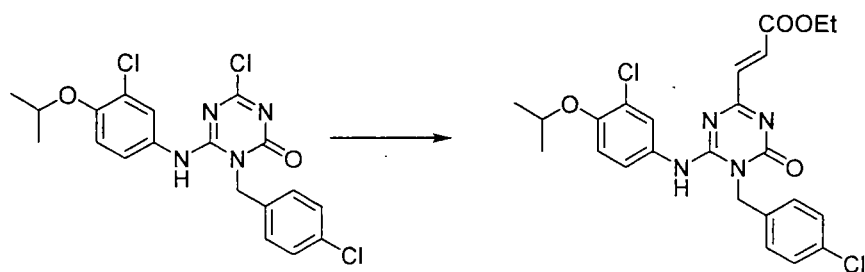
¹H-NMR (δ ppm TMS / CDCl₃): 1.43 (6H, d, J=6.9 Hz), 4.67 (2H, d, J=4.0 Hz), 4.96 (1H, sept, J=6.9 Hz), 5.18 (2H, s), 6.34 (1H, m), 6.88 (2H, d, J=8.4 Hz), 7.17 (1H, brs), 7.29-7.34 (6H, m), 7.50 (2H, d, J=8.4 Hz), 7.80 (2H, d, J=8.4 Hz).

[0135]

Example 19

Preparation of 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-4-hydroxycarbonyl-1,3,5-triazine-2(1H)-one

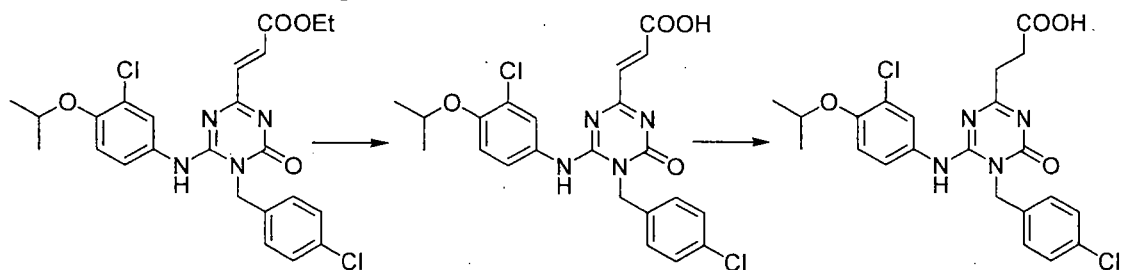
[Chemical Formula 80]



A mixture of 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.15 g, 0.34 mmol), 1,1'-bis(di-*t*-butylphosphinoferrocene)palladium(II) dichloride (22.23 mg, 0.34 mmol), and THF (3 mL) was placed in a flask under nitrogen. To the mixture were added (*E*)-ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)acrylate (0.63 g, 0.49 mmol) and 2 mol/L potassium carbonate (0.682 mL, 1.364 mmol), and the resulting mixture was heated at reflux for 7 hours. Then, the mixture was poured into water (30 mL) and the resulting mixture was extracted with chloroform (30 mL). The extract was dried over anhydrous sodium sulphate and concentrated in vacuo. The resulting residue was purified on a high performance liquid chromatography (0.3% HCO₂H H₂O/MeCN 50-80%) to give 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-ethoxycarbonyl-1,3,5-triazine-2(1H)-one (0.5 g, yield: 30%) as pale orange oil.

¹H-NMR (δ ppm TMS / DMSO-*d*₆): 1.20-1.28 (9H, m), 4.17-4.22 (2H, m), 4.54 (1H, brs), 5.10 (2H, brs), 7.40 (8H, brs), 8.14 (1H, s), 9.77 (1H, s).

[Chemical Formula 81]



To a mixture of 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-ethoxycarbonyl-1,3,5-triazine-2(1H)-one (0.5 g, 0.1 mmol), THF (1 mL), EtOH (1 mL) and water (0.3 mL) was added lithium hydroxide hydrate (12.5 mg, 0.3 mmol), and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was purified on a high performance liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-4-hydroxycarbonyl-1,3,5-triazine-2(1H)-one (27 mg, yield: 57%) as pale orange oil.

The obtained intermediate was dissolved in methanol (3 mL), the resulting solution was conducted a catalytic reduction by using H-Cube (10%Pt-C, H₂ = 1 atm).

The reaction mixture was purified on a high performance liquid chromatography (0.3% HCO₂H H₂O/MeCN 50-80%) to give 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-4-hydroxycarbonyl-1,3,5-triazine-2(1H)-one (2.3 mg, yield: 8.5%) as colorless oil.

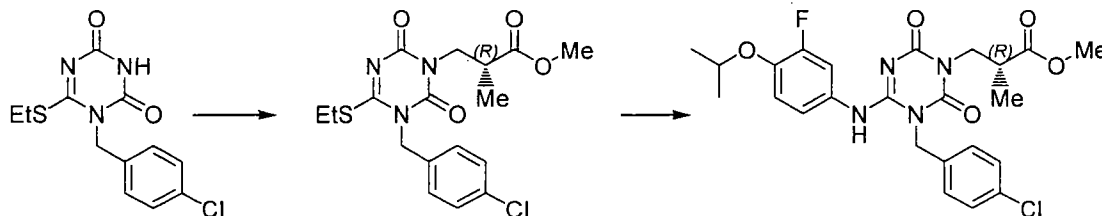
¹H-NMR (δ ppm TMS / CDCl₃): 1.36 (6H, d, *J*=5.7 Hz), 2.22 (1H, t, *J*=7.8 Hz), 2.74 (3H, brs), 4.48 (1H, sept, *J*=5.7 Hz), 5.18 (2H, s), 6.88 (2H, s), 7.13 (1H, s), 7.30 (2H, d, *J*=8.4 Hz), 7.45 (2H, d, *J*=8.4 Hz).

[0136]

Example 20

Preparation of (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 82]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dione (1.0 g, 3.4 mmol), di-2-methoxyethyl azocarboxylate (1.02 g, 4.4 mmol), triphenylphosphine (1.15 g, 4.4 mmol) and dioxane (8 mL) was gradually added methyl (R)-(-)-3-hydroxyisobutyrate (0.52 g, 4.4 mmol), and the resulting mixture was stirred at room temperature for 1 hour. Water (20 mL) was poured into the mixture, and the resulting mixture was extracted with ethyl acetate (20 mL×2). The extract was washed with brine (20 mL), dried over anhydrous magnesium sulfate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane) to give (R)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.98 g, yield: 74%) as colorless amorphous.

¹H-NMR (δ ppm TMS / CDCl₃): 1.19 (3H, d, J=5.7 Hz), 1.37 (3H, t, J=7.1 Hz), 2.96 (1H, m), 3.12 (2H, q, J=7.1 Hz), 3.60 (3H, s), 3.98 (1H, m), 4.21 (1H, m), 5.08 (2H, s), 7.29-7.34 (4H, m).

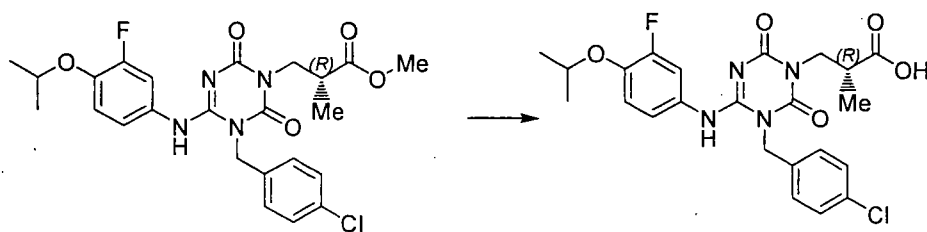
A mixture of (R)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.32 g, 0.8 mmol), 3-fluoro-4-isopropoxyaniline (0.20 g, 1.2 mmol), acetic acid (0.72 g, 12 mmol) and t-butanol (6 mL) was heated at reflux over night. Then, the mixture was poured into saturated sodium hydrogen carbonate solution (40 mL), and the resulting mixture was extracted with ethyl acetate (40 mL×2). The extract was washed with 2mol/L hydrochloric acid (20 mL×2), dried over anhydrous sodium sulphate, and then concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The obtained compound was triturated with diethyl ether to give (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.29 g, yield: 71%) as lilac powder.

[0137]

Example 21

Preparation of (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 83]



To a mixture of (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-methoxycarbonylisopropyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.26 g, 0.5 mmol) and dioxane (4 mL) was added 1mol/L lithium hydroxide (1.6 mL), and the resulting mixture was stirred at 50 °C for 6 hours. Then, water (50 mL) was poured into the mixture. The resulting mixture was treated with 2mol/L hydrochloric acid to about pH3. The precipitated solid was collected by filtration and the obtained solid was dried under reduced pressure at 40 °C for 2 hours to give (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.21 g, yield: 84%) as colorless solid.

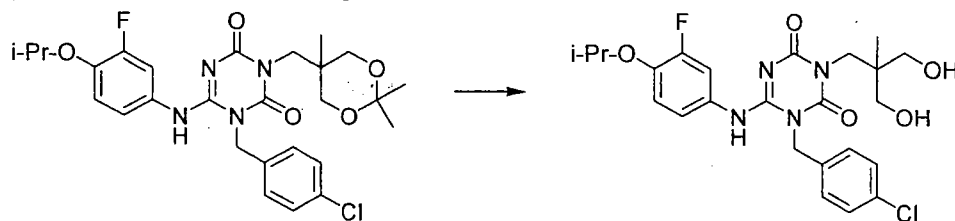
¹H-NMR (δ ppm TMS / CDCl₃): 1.19 (3H, d, J=5.7 Hz), 1.34 (6H, d, J=5.7 Hz), 2.91 (1H, m), 3.89 (1H, m), 4.11 (1H, m), 4.44 (1H, sept, J=5.7 Hz), 5.16 (2H, s), 6.47-6.60 (2H, m), 6.93 (1H, m), 7.28-7.44 (4H, m), 7.94 (1H, brs).

[0138]

Example 22

Preparation of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-[2,2-di(hydroxymethyl)propyl]-1,3,5-triazine-2,4(1H,3H)-dione

[Chemical Formula 84]



To a mixture of 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2,2,5-trimethyl-1,3-dioxane-5-yl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (7.9 g, 14.44 mmol) and methanol (160 mL) was added p-toluenesulfonic acid monohydrate (5.49 g, 28.9 mmol), and the resulting mixture was stirred at room temperature for 1 hour. Then, the mixture was poured into saturated sodium hydrogen carbonate solution (20 mL) and the resulting mixture was extracted with ethyl acetate (30 mL×2). The extract was washed with brine (30 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified on a silica gel column chromatography (ethyl acetate/hexane). The obtained compound was triturated with water. The precipitated solid was collected by filtration and the obtained solid was dried under reduced pressure at 70 °C for 6 hours to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-[2,2-di(hydroxymethyl)propyl]-1,3,5-triazine-2,4(1H,3H)-dione (5.12 g, yield: 70%) as white powder.

¹H-NMR (δ ppm TMS / CDCl₃): 1.37 (6H, d, J=6.0 Hz), 3.26-3.46 (6H, m), 3.99 (2H, s), 4.48 (1H, sept, J=6.0 Hz), 5.19 (2H, s), 6.49-6.64 (2H, m), 6.99 (1H, m), 7.30-7.51 (5H, m).

Elemental analysis

Calculated value $C_{24}H_{28}ClFN_4O_5 \cdot 1/3H_2O$,

C: 56.19, H: 5.63, Cl: 6.91, F: 3.70, N: 10.92

Water: 1.18%

Measured value C: 56.33, H: 5.60, Cl: 6.79, F: 3.58, N: 11.06

Karl Fischer moisture measurement: 1.02%

[0139]

The following compounds were synthesized in a manner similar to those described in the general procedures and Examples. The chemical structure of the compounds and the physical properties of them are described below.

(Method of identification for the compound)

LC/MS data of the compounds were measured under any one of the following 3 conditions (Method A, B and C), and a retention time and $[M+H]^+$ are shown.

[0140]

(Method 1)

Column: Luna C18(2) (5 μ m, i.d. 4.6x50mm) (Phenomenex)

Flow rate: 3 mL/min

UV detection wavelength: 254nm

Mobile phase: [A] is 0.1% formic acid-containing aqueous solution, and [B] is 0.1% formic acid-containing acetonitrile solution

Gradient: Linear gradient of 10% to 10% solvent [B] for 3 minutes was performed, and 10% solvent [B] was maintained for 1 minute.

(Method 2)

Column: Xbridge C18(5 μ m, i.d. 4.6x50mm) (Waters)

Flow rate: 3 mL/min

UV detection wavelength: 254nm

Mobile phase: [A] is 0.1% formic acid-containing aqueous solution, and [B] is 0.1% formic acid-containing acetonitrile solution

Gradient: Linear gradient of 10% to 10% solvent [B] for 3 minutes was performed, and 10% solvent [B] was maintained for 1 minute.

(Method 3)

Column: Shim-pack XR-ODS (2.2 μ m, i.d. 50x3.0mm) (Shimadzu)

Flow rate: 1.6 mL/min

UV detection wavelength: 254nm

Mobile phase: [A] is 0.1% formic acid-containing aqueous solution, and [B] is 0.1% formic acid-containing acetonitrile solution

Gradient: Linear gradient of 10% to 10% solvent [B] for 3 minutes was performed, and 10% solvent [B] was maintained for 1 minute.

(Method 4)

Column: Develosil RPAq, (50x4.5mm)

Flow rate: 1.5 mL/min

UV detection wavelength: 254nm

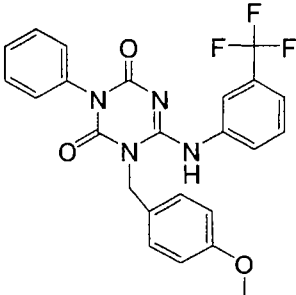
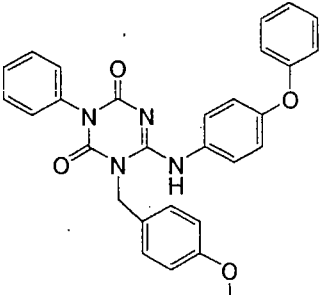
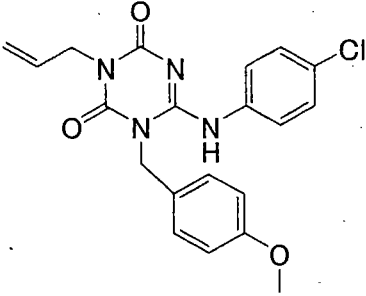
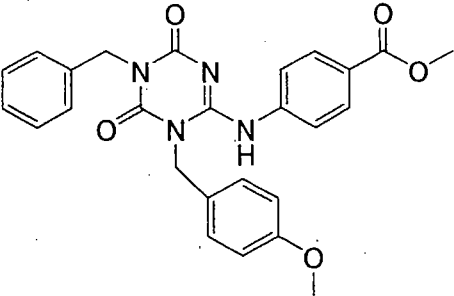
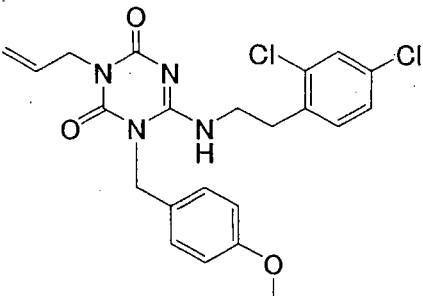
Mobile phase: [A] is 0.1% formic acid-containing aqueous solution, and [B] is 0.1% formic acid-containing acetonitrile solution

Gradient: 60% solvent [B] was maintained for 0.5 minute, linear gradient of

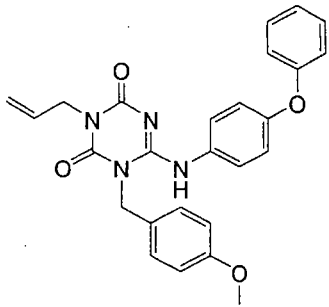
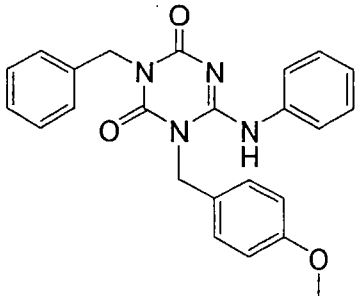
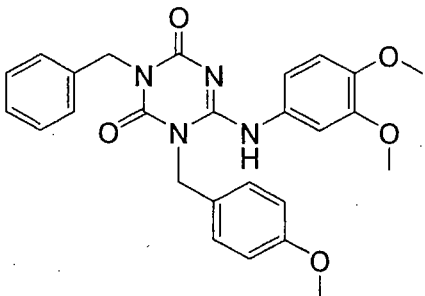
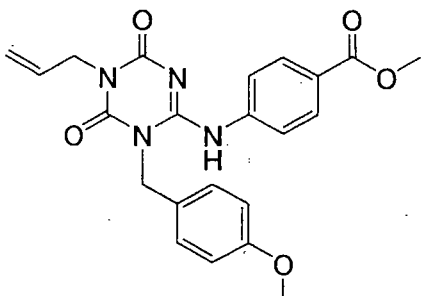
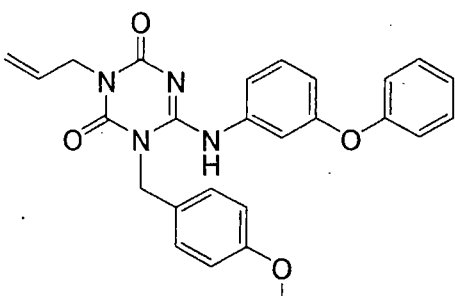
60% to 10% solvent [B] for 4.5 minutes was performed, and 10% solvent [B] was maintained for 1.0 minute.

[0141]

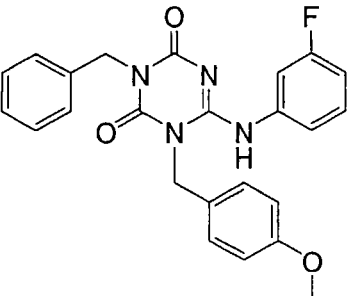
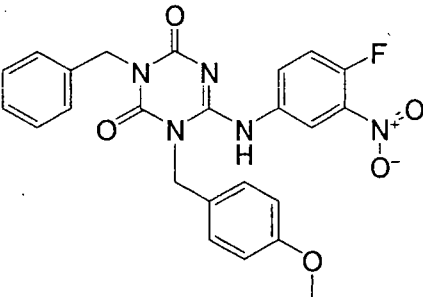
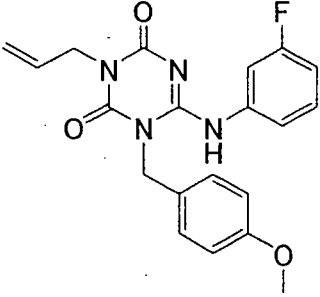
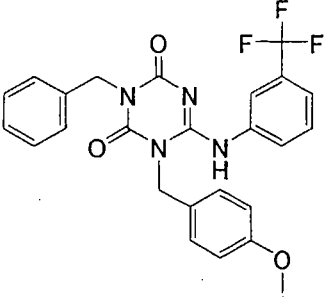
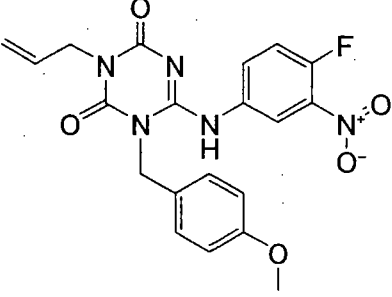
[Table 4]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-001	469	2.46	3
	I-002	493	2.49	3
	I-003	399	2.31	3
	I-004	473	2.47	3
	I-005	461	2.37	3

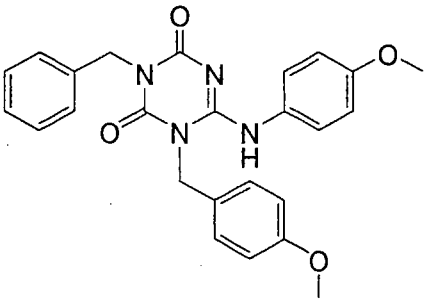
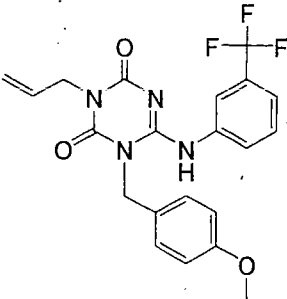
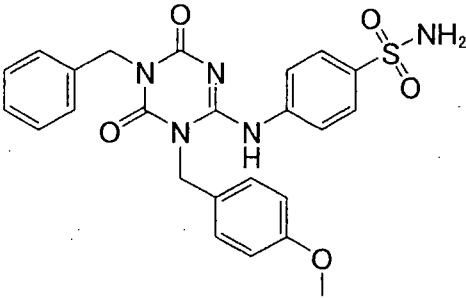
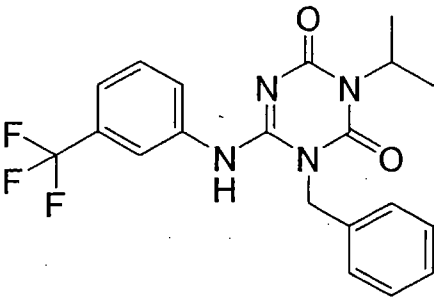
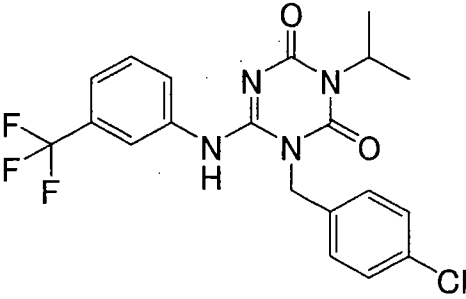
[Table 5]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-006	457	2.48	3
	I-007	415	2.34	3
	I-008	475	2.22	3
	I-009	423	2.23	3
	I-010	457	2.48	3

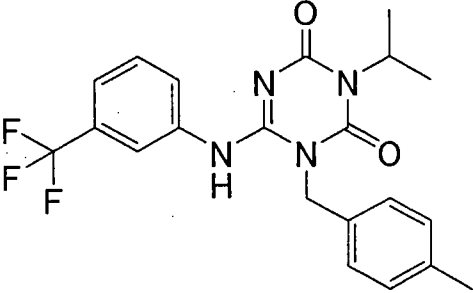
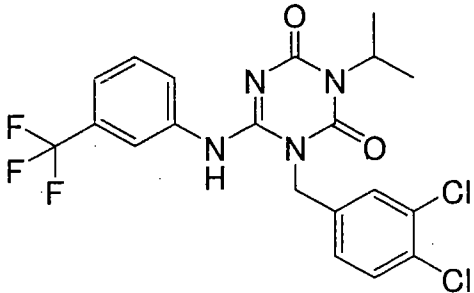
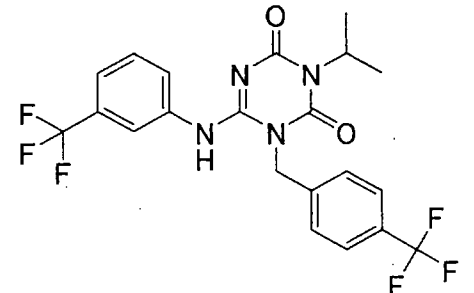
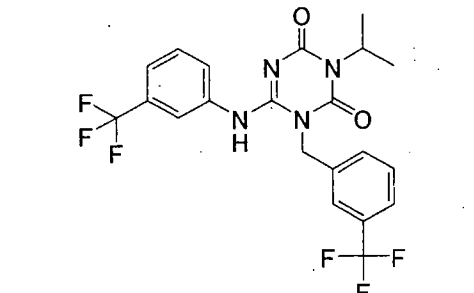
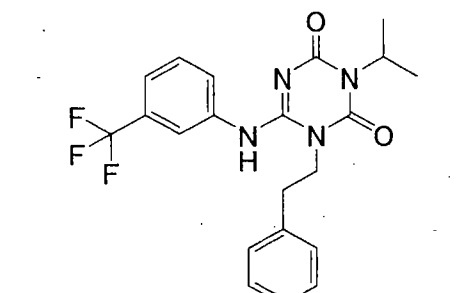
[Table 6]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-011	433	2.47	3
	I-012	478	2.51	3
	I-013	383	2.23	3
	I-014	483	2.65	3
	I-015	428	2.29	3

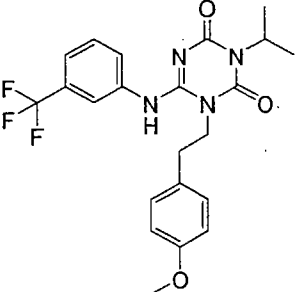
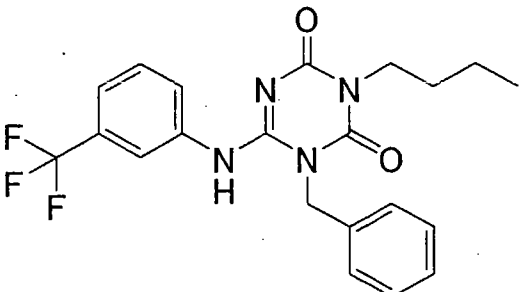
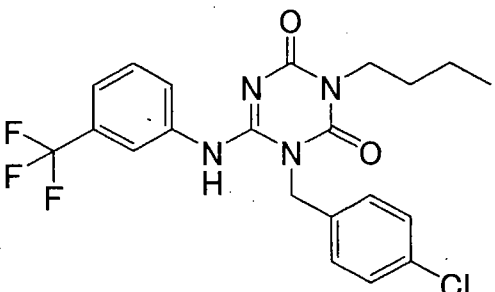
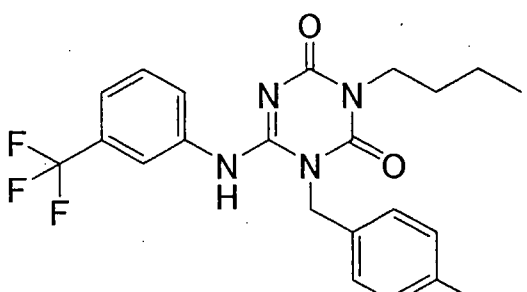
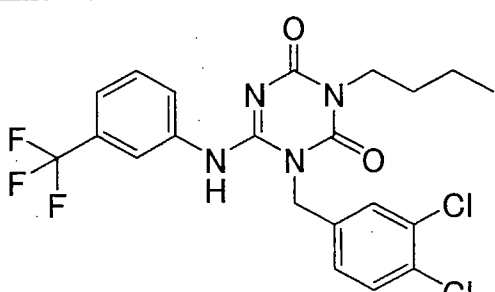
[Table 7]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-016	445	2.29	3
	I-017	433	2.45	3
	I-018	494	2.09	3
	I-019	405	2.16	4
	I-020	439	3.88	4

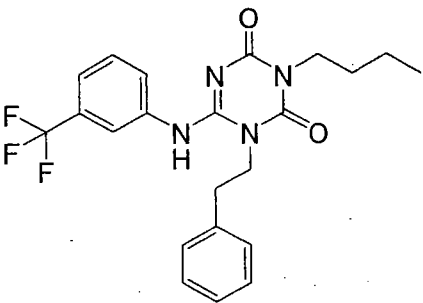
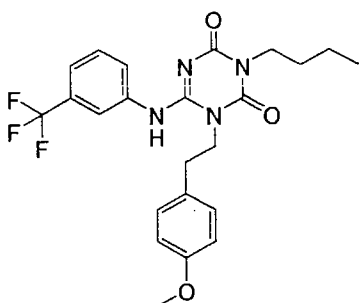
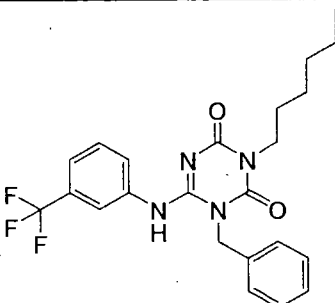
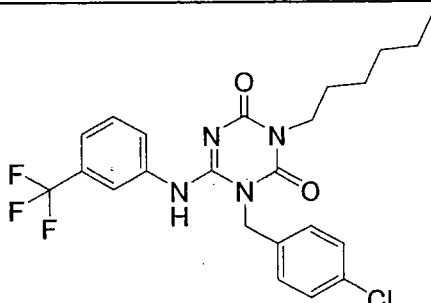
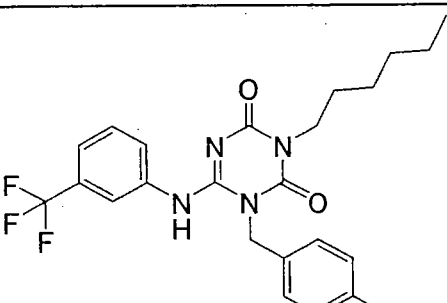
[Table 8]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-021	419	3.63	4
	I-022	474	4.43	4
	I-023	473	3.91	4
	I-024	473	3.93	4
	I-025	419	3.33	4

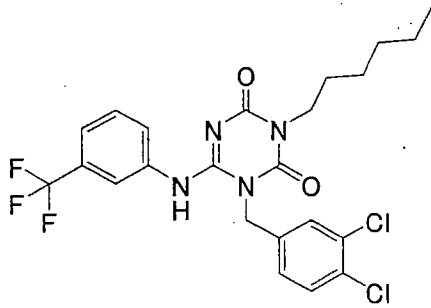
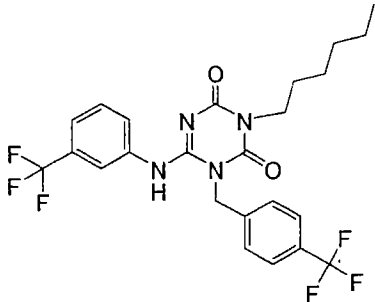
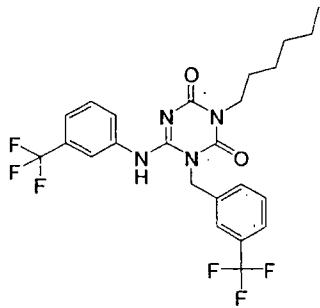
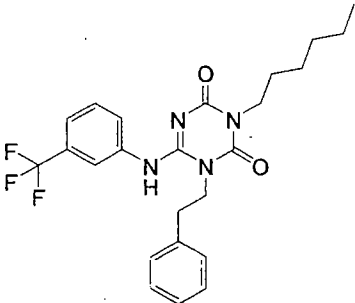
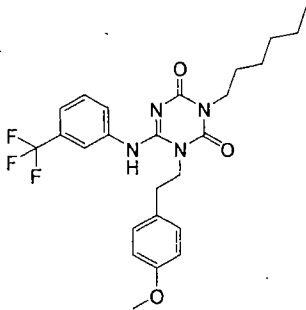
[Table 9]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-026	449	3.16	4
	I-027	419	2.46	4
	I-028	453	3.27	4
	I-029	433	2.95	4
	I-030	488	3.94	4

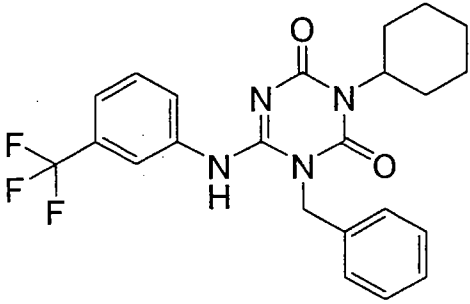
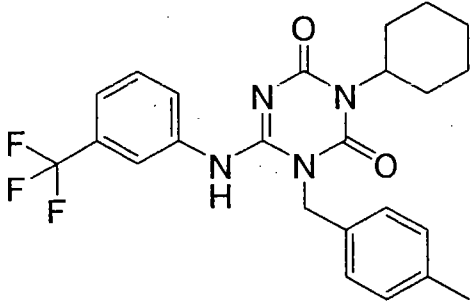
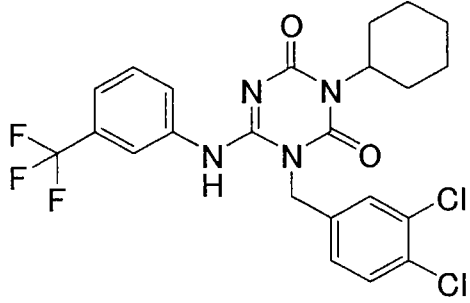
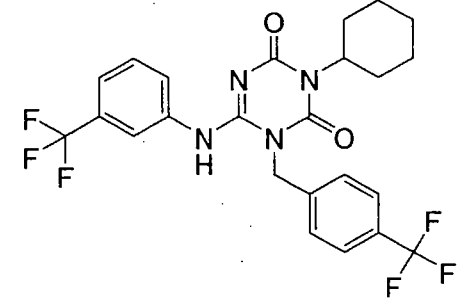
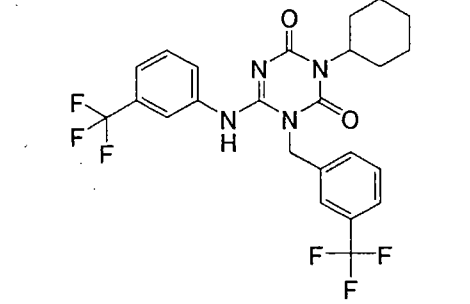
[Table 10]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-031	433	2.61	4
	I-032	463	2.39	4
	I-033	447	4.31	4
	I-034	481	4.86	4
	I-035	461	4.68	4

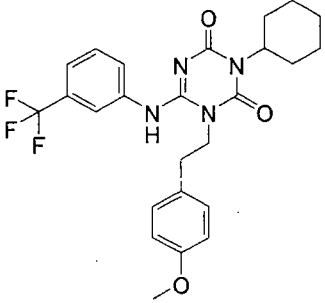
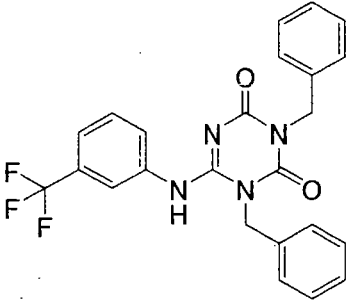
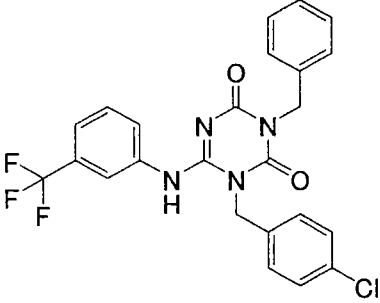
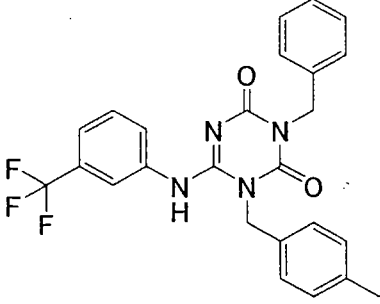
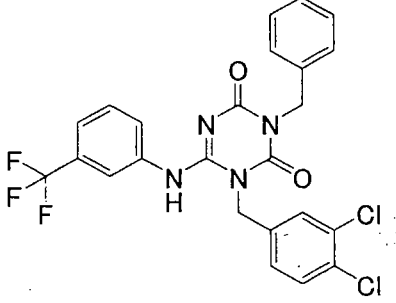
[Table 11]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-036	516	3.73	4
	I-037	515	4.80	4
	I-038	515	4.83	4
	I-039	461	3.67	4
	I-040	491	3.47	4

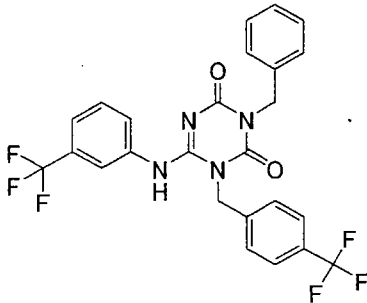
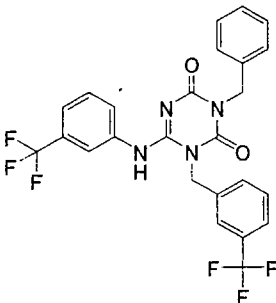
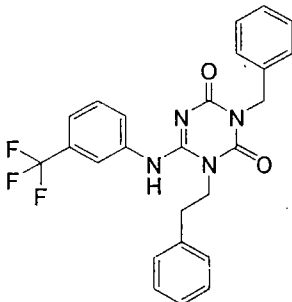
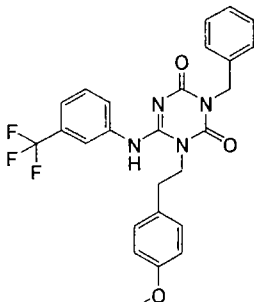
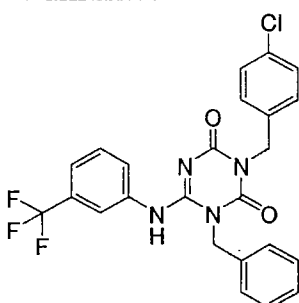
[Table 12]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-041	445	4.09	4
	I-042	459	4.45	4
	I-043	514	3.51	4
	I-044	513	4.62	4
	I-045	513	4.65	4

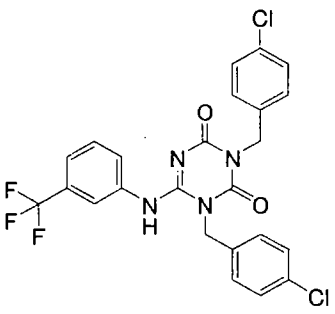
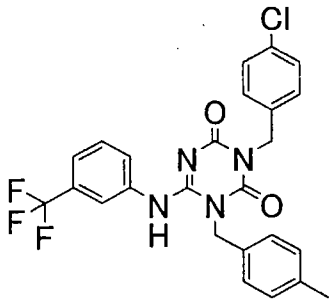
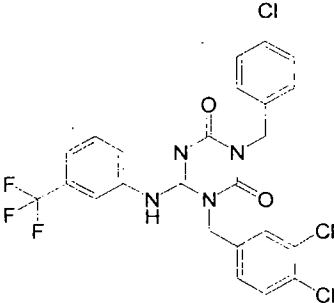
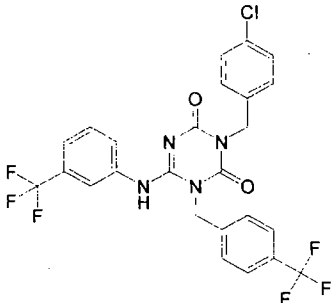
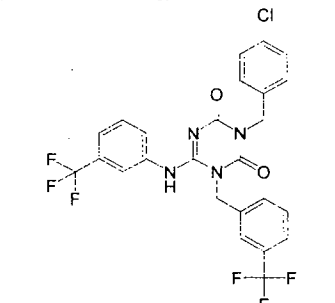
[Table 13]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-046	489	3.17	4
	I-047	453	3.46	4
	I-048	487	4.09	4
	I-049	467	3.83	4
	I-050	522	4.56	4

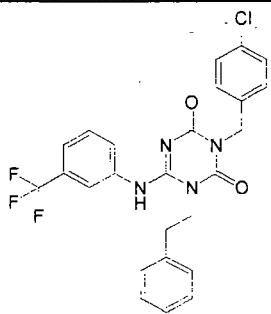
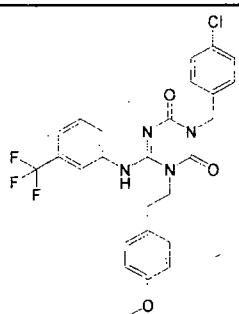
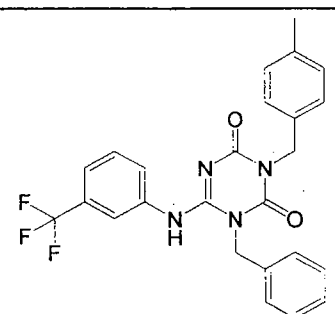
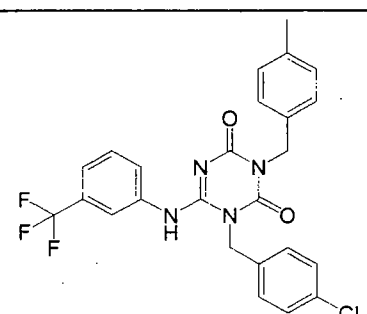
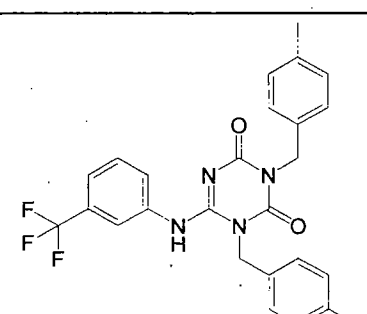
[Table 14]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-051	521	4.09	4
	I-052	521	4.12	4
	I-053	467	3.57	4
	I-054	497	3.42	4
	I-055	487	3.90	4

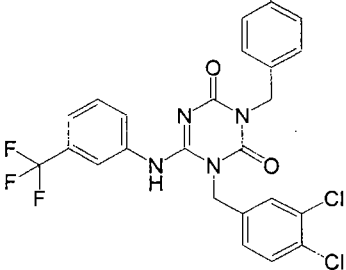
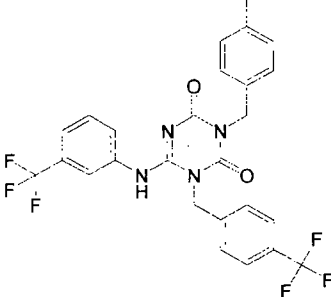
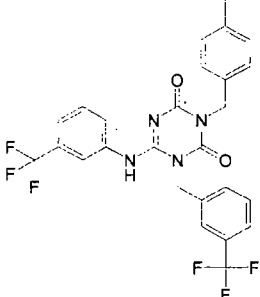
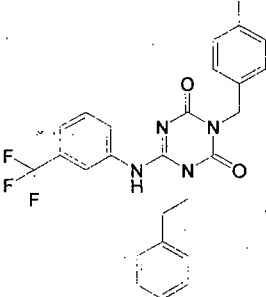
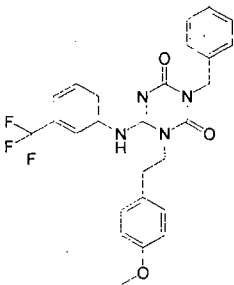
[Table 15]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-056	522	4.49	4
	I-057	501	4.26	4
	I-058	556	4.94	4
	I-059	555	4.45	4
	I-060	555	4.50	4

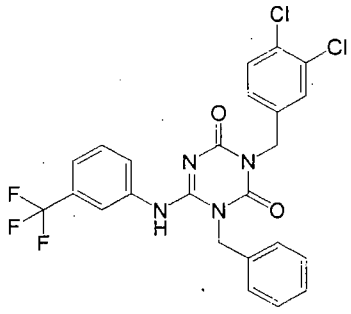
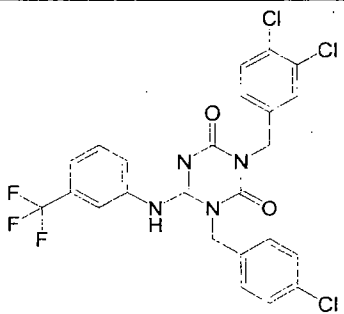
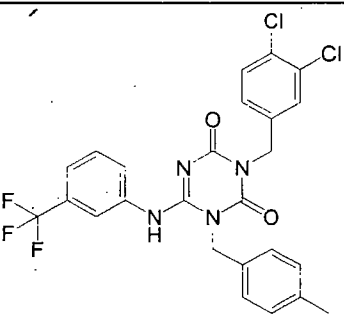
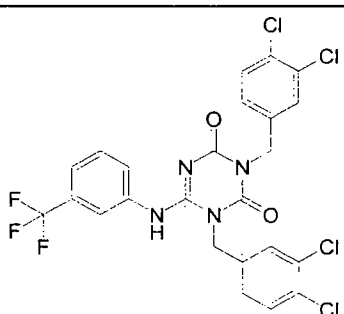
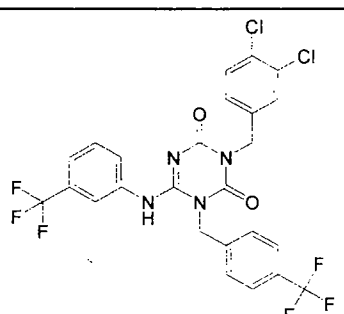
[Table 16]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-061	501	3.99	4
	I-062	531	3.86	4
	I-063	467	2.81	4
	I-064	501	2.40	4
	I-065	481	3.32	4

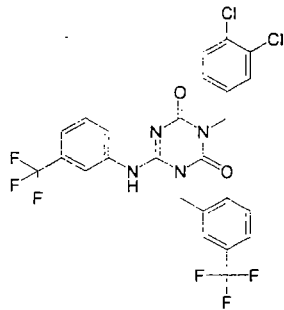
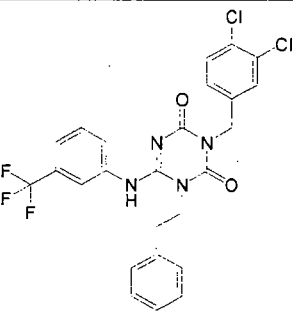
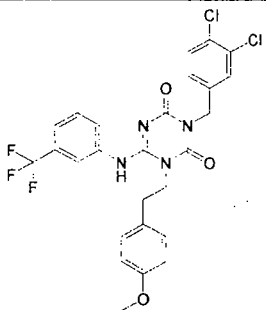
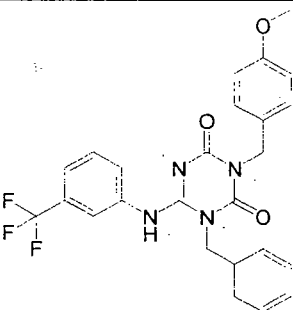
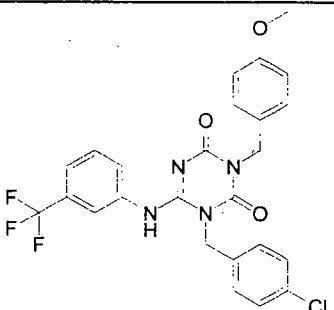
[Table 17]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-066	534	4.30	4
	I-067	535	3.60	4
	I-068	535	3.60	4
	I-069	481	3.91	4
	I-070	511	2.76	4

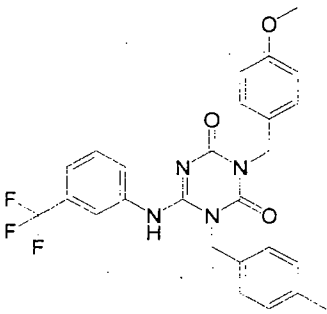
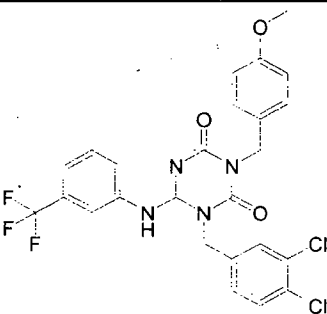
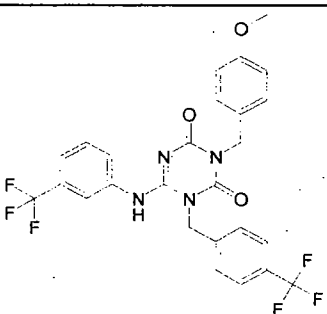
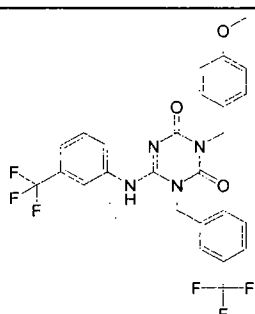
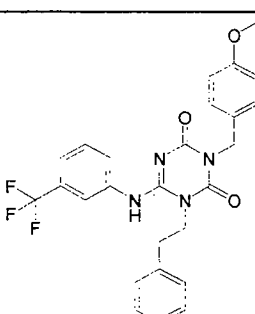
[Table 18]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-071	522	3.43	4
	I-072	556	4.12	4
	I-073	536	3.86	4
	I-074	591	4.68	4
	I-075	590	4.07	4

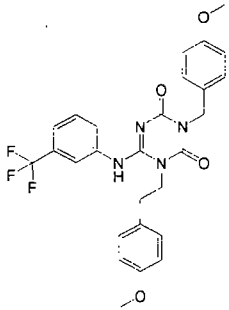
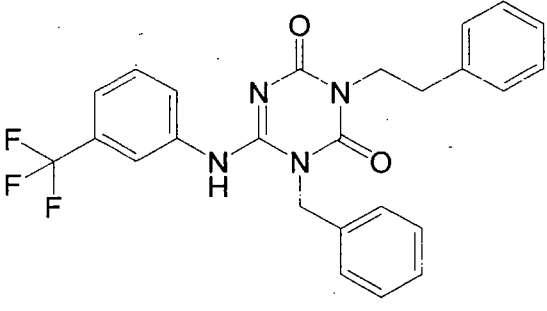
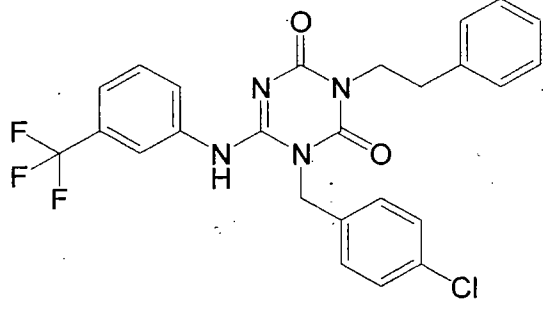
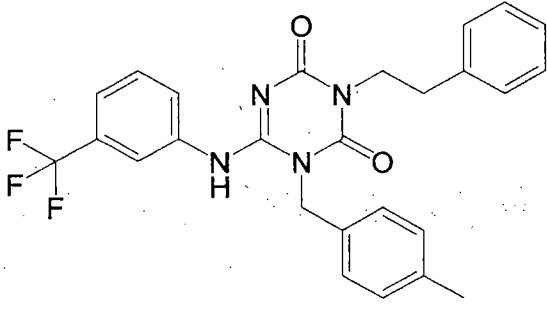
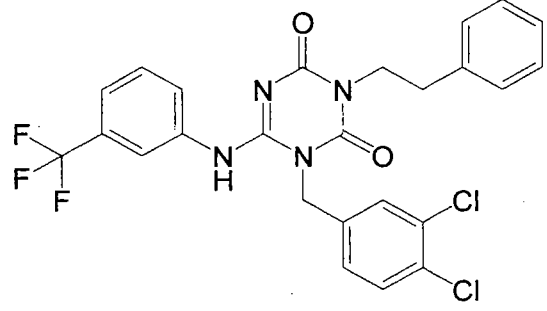
[Table 19]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-076	590	4.11	4
	I-077	536	3.55	4
	I-078	566	3.49	4
	I-079	483	2.38	4
	I-080	517	3.21	4

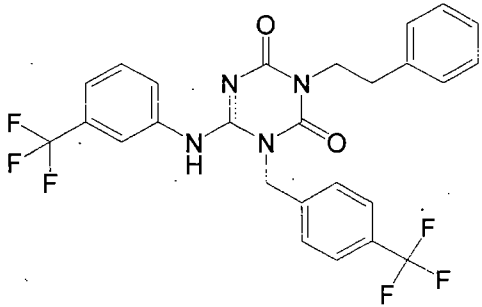
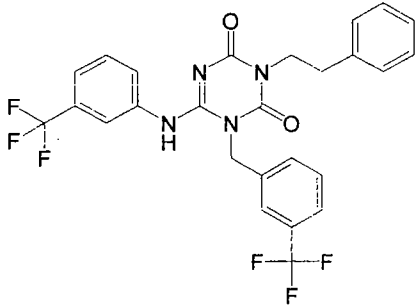
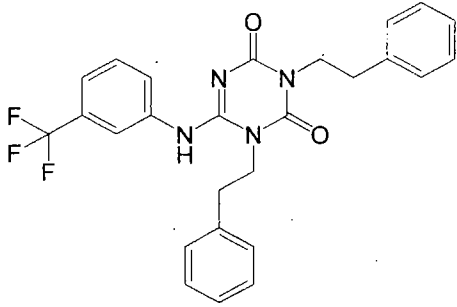
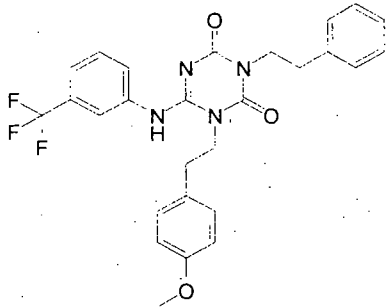
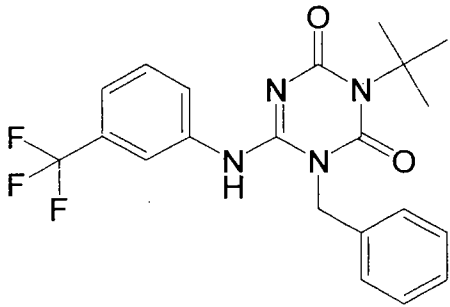
[Table 20]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-081	497	2.85	4
	I-082	552	3.85	4
	I-083	551	3.22	4
	I-084	551	3.23	4
	I-085	497	2.48	4

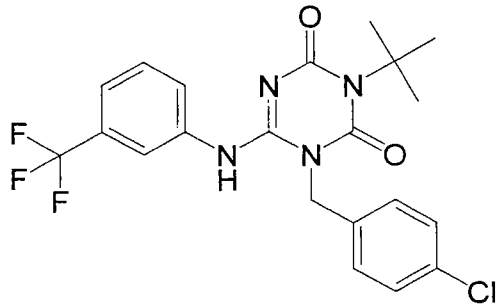
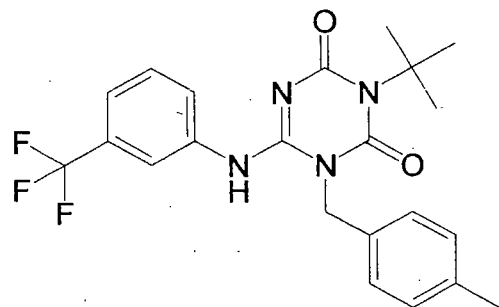
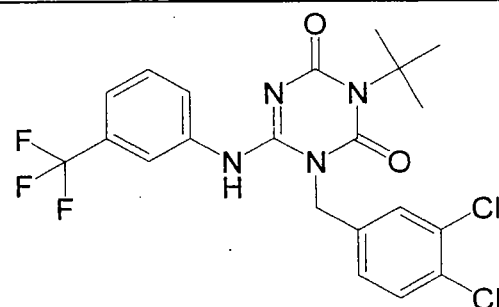
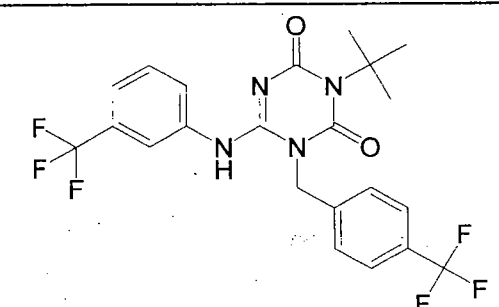
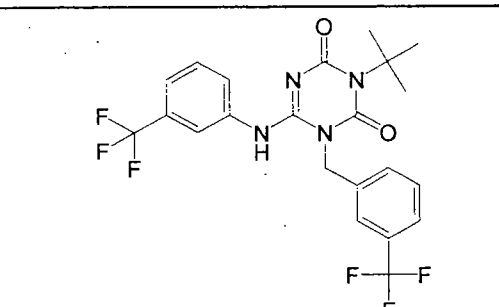
[Table 21]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-086	527	2.29	4
	I-087	467	2.75	4
	I-088	501	3.54	4
	I-089	481	3.19	4
	I-090	536	4.15	4

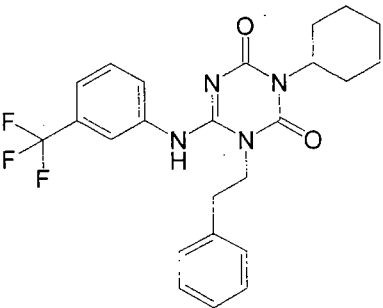
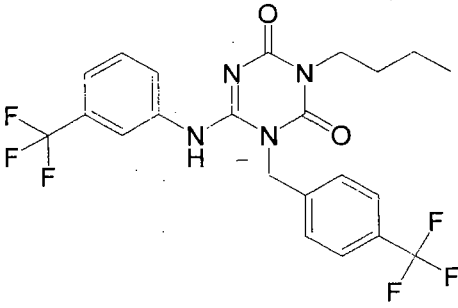
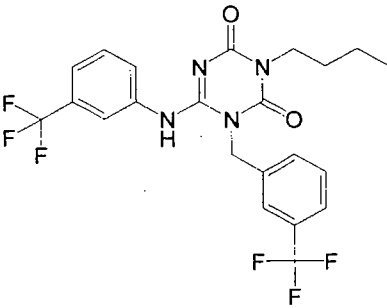
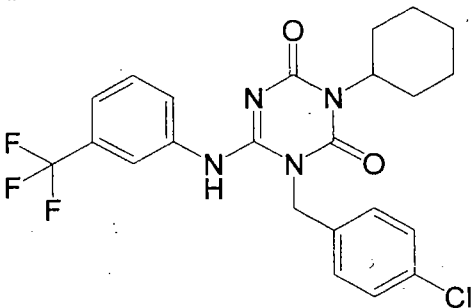
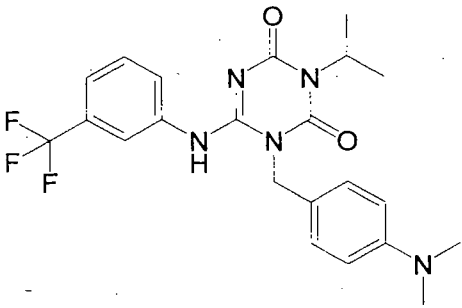
[Table 22]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-091	535	3.49	4
	I-092	535	3.57	4
	I-093	481	3.03	4
	I-094	511	2.79	4
	I-095	419	3.58	4

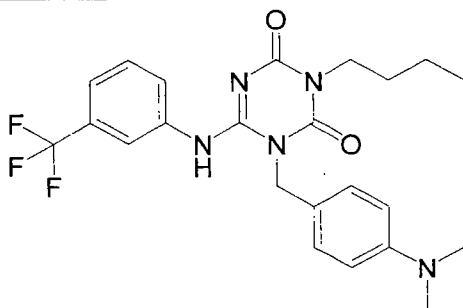
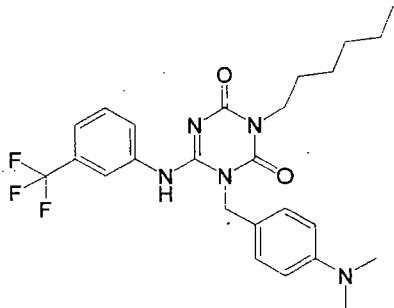
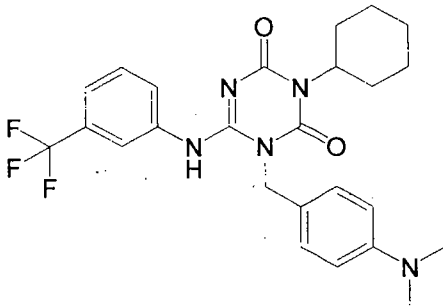
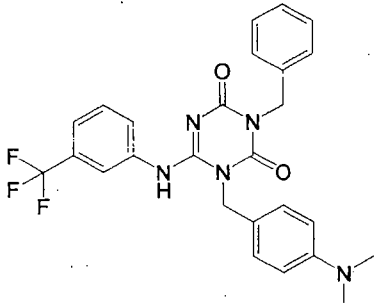
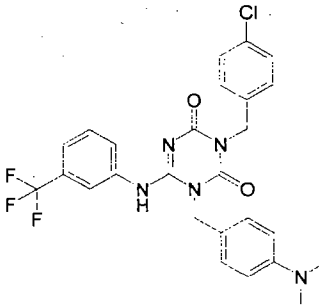
[Table 23]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-096	453	4.22	4
	I-097	433	4.21	4
	I-098	488	4.03	4
	I-099	487	3.38	4
	I-100	487	4.24	4

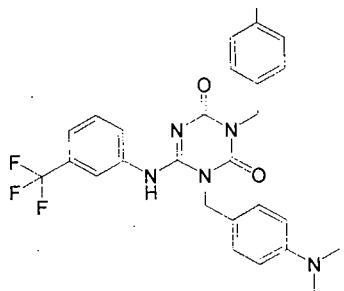
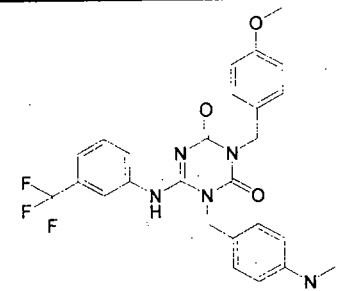
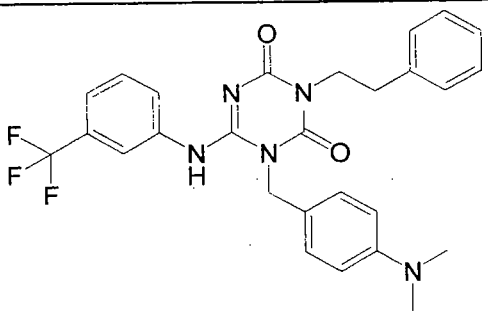
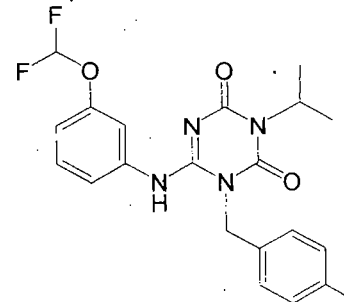
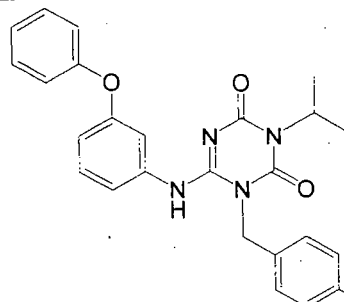
[Table 24]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-101	459	3.38	4
	I-102	487	4.16	4
	I-103	487	4.18	4
	I-104	479	4.69	4
	I-105	448	3.38	4

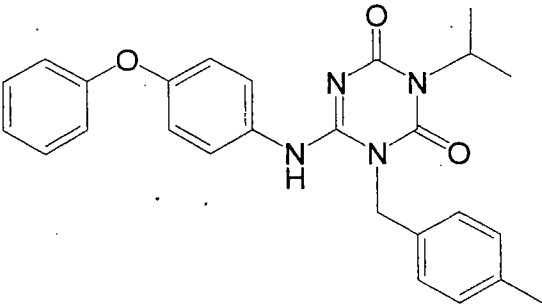
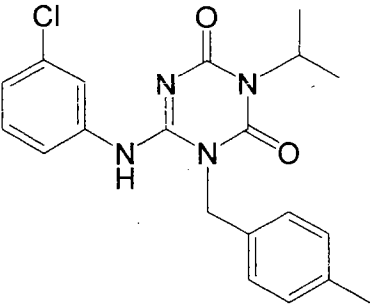
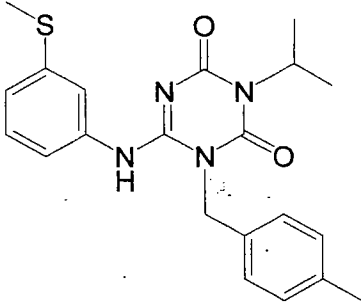
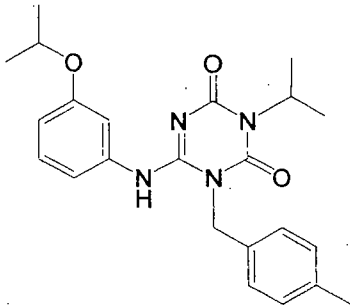
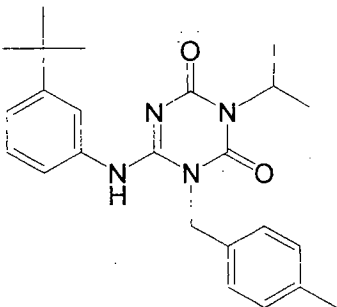
[Table 25]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-106	462	3.59	4
	I-107	490	4.05	4
	I-108	488	3.85	4
	I-109	496	3.66	4
	I-110	530	3.97	4

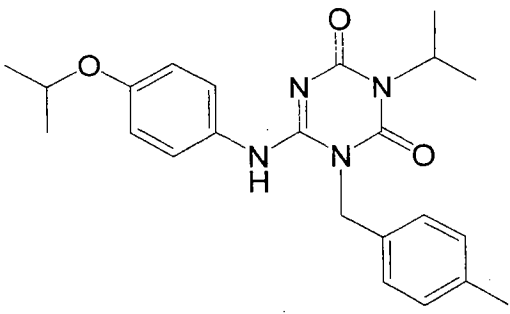
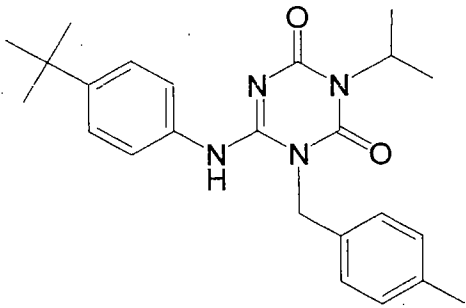
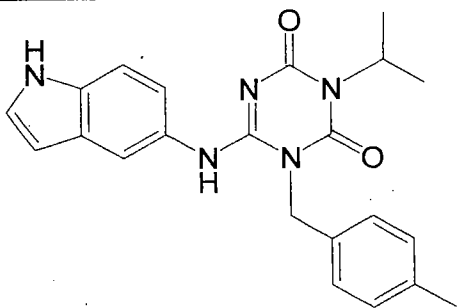
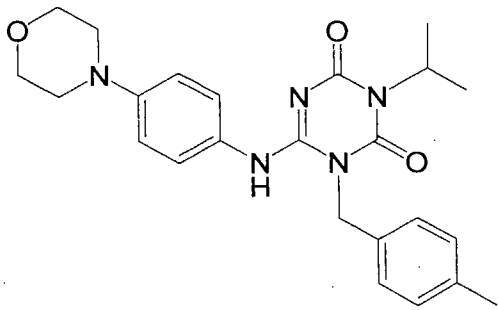
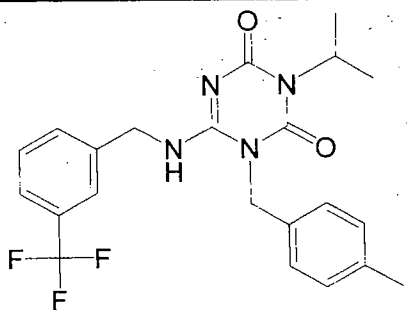
[Table 26]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-111	510	3.84	4
	I-112	526	3.67	4
	I-113	510	3.77	4
	I-114	417	2.44	1
	I-115	443	2.67	1

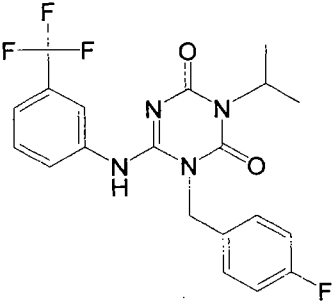
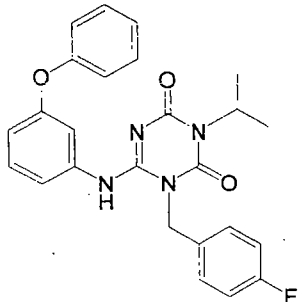
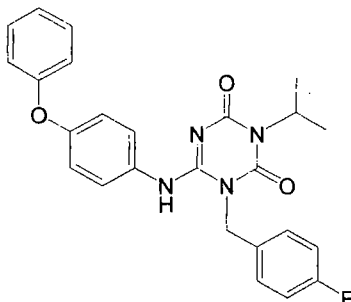
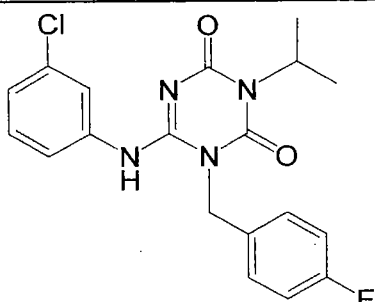
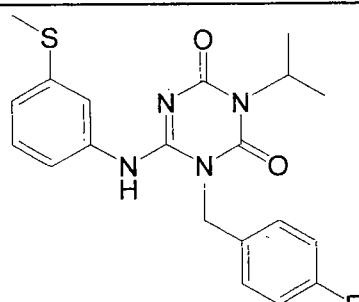
[Table 27]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-116	443	2.59	1
	I-117	385	2.52	1
	I-118	397	2.44	1
	I-119	409	2.52	1
	I-120	407	2.70	1

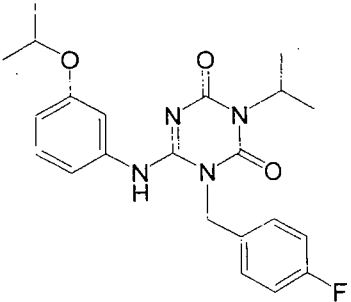
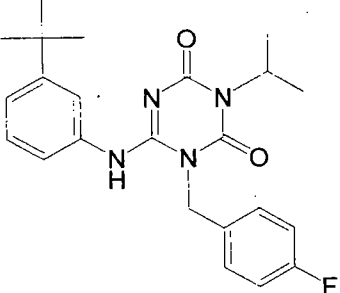
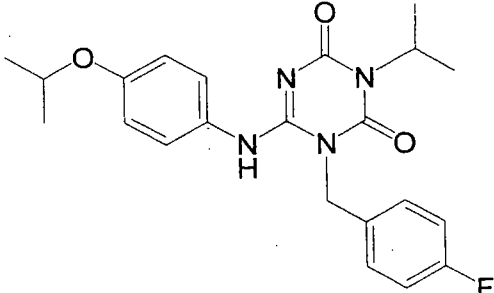
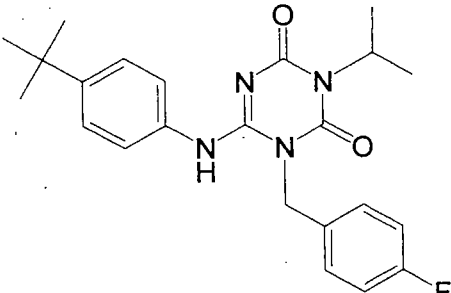
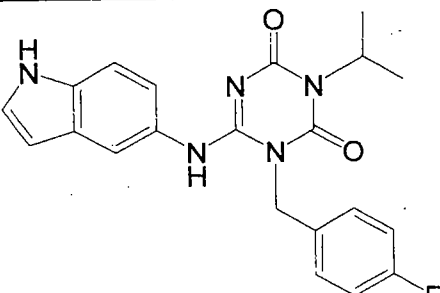
[Table 28]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-121	409	2.40	1
	I-122	407	2.68	1
	I-123	390	2.05	1
	I-124	436	2.04	1
	I-125	433	2.31	1

[Table 29]

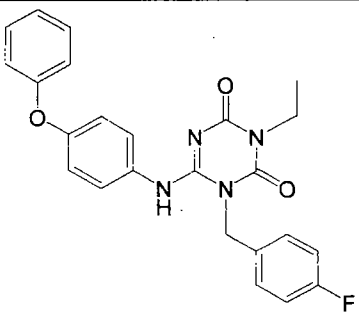
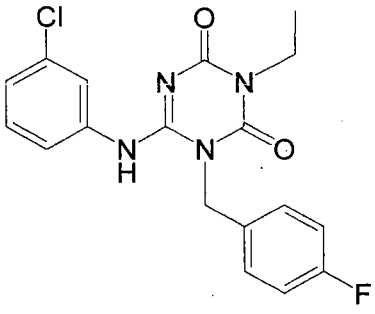
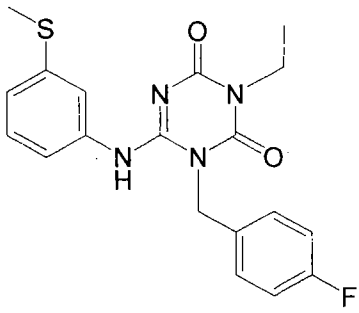
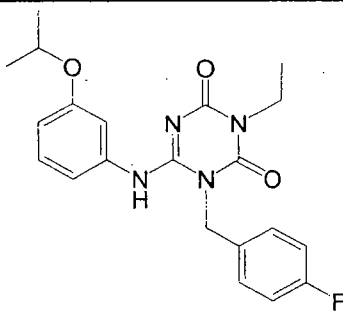
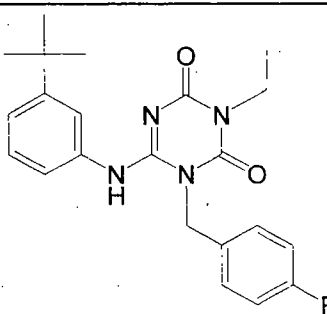
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-126	423	2.51	1
	I-127	447	2.60	1
	I-128	447	2.52	1
	I-129	389	2.44	1
	I-130	401	2.36	1

[Table 30]

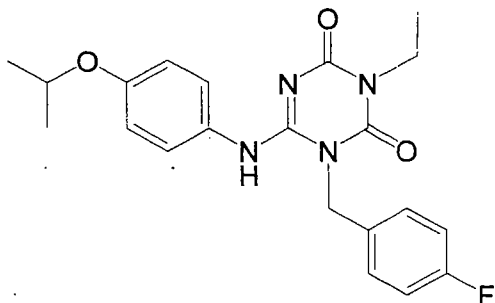
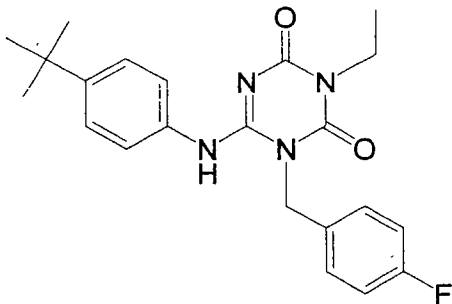
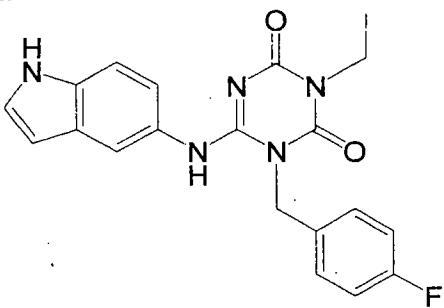
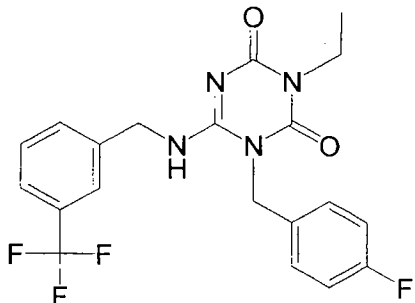
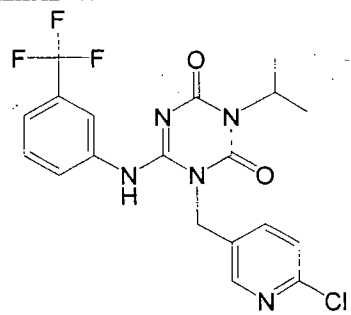
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-131	413	2.44	1
	I-132	411	2.60	1
	I-133	413	2.31	1
	I-134	411	2.58	1
	I-135	394	1.96	1

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-136	440	1.93	1
	I-137	437	2.18	1
	I-138	409	2.35	1
	I-139	407	2.18	1
	I-140	433	2.44	1

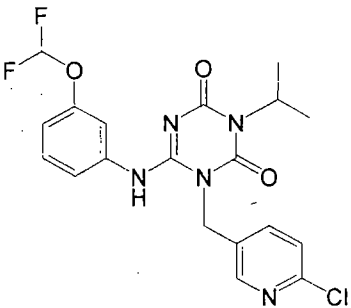
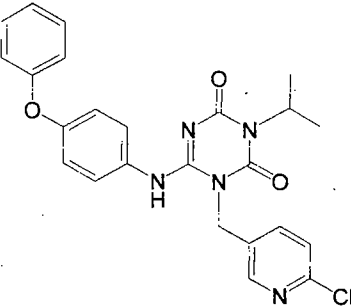
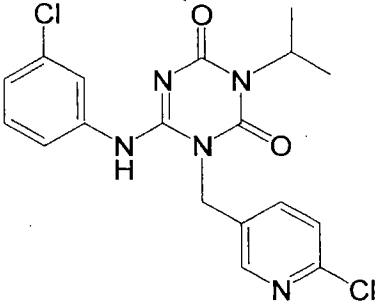
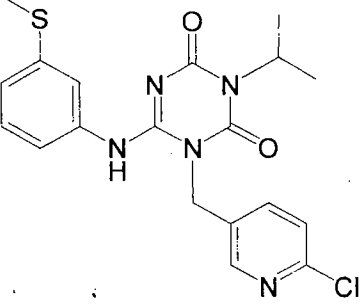
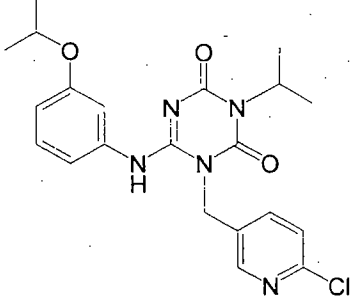
[Table 32]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-141	433	2.37	1
	I-142	374	2.26	1
	I-143	387	2.17	1
	I-144	399	2.27	1
	I-145	397	2.45	1

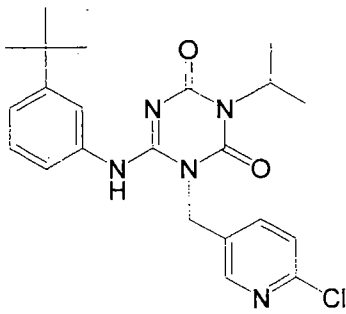
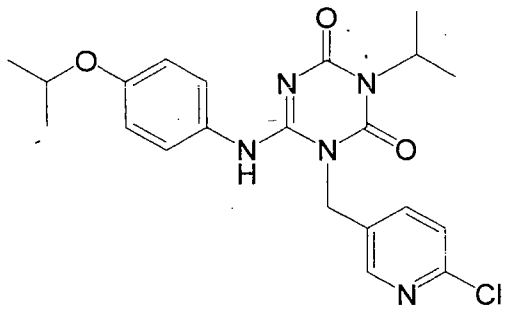
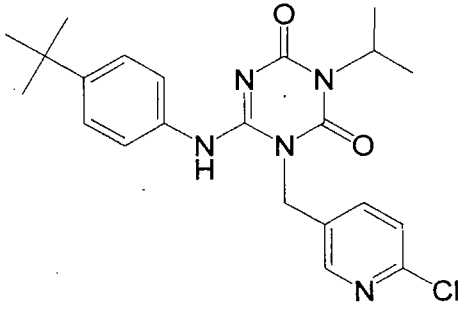
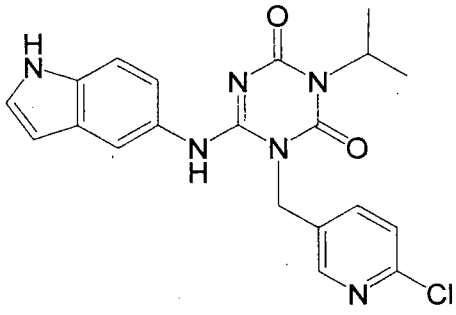
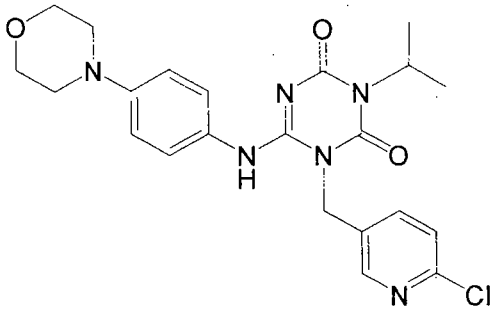
[Table 33]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-146	399	2.13	1
	I-147	397	2.42	1
	I-148	380	1.78	1
	I-149	423	2.04	1
	I-150	440	2.40	1

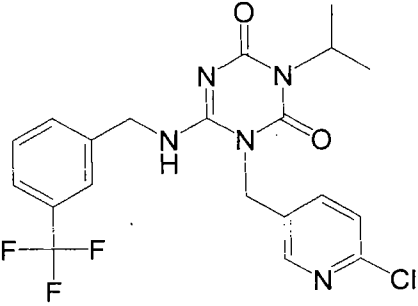
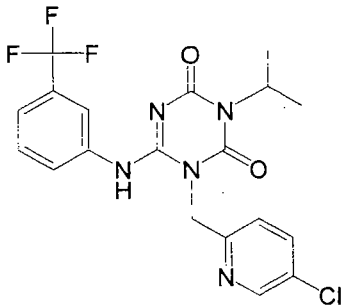
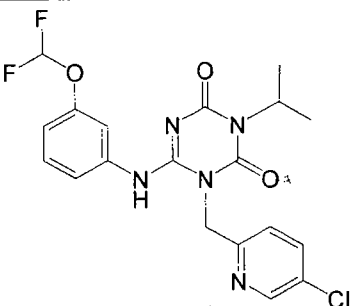
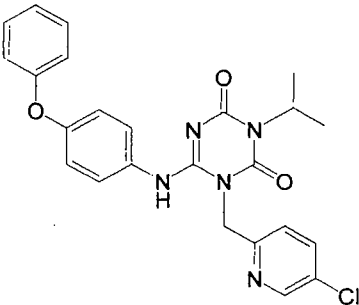
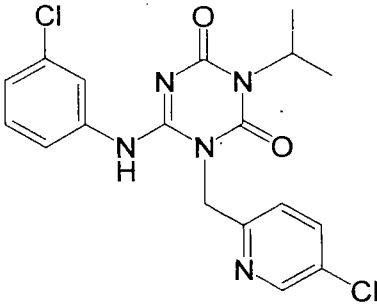
[Table 34]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-151	438	2.24	1
	I-152	464	2.44	1
	I-153	407	2.30	1
	I-154	418	2.25	1
	I-155	430	2.34	1

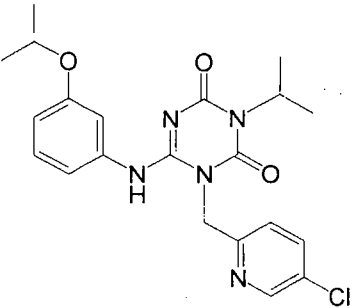
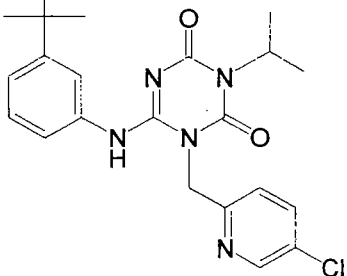
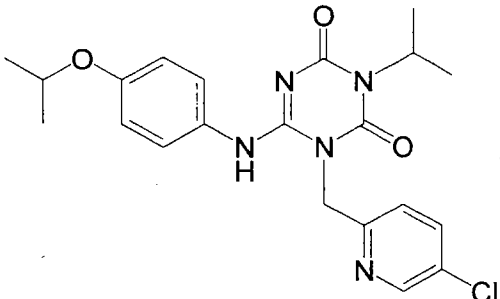
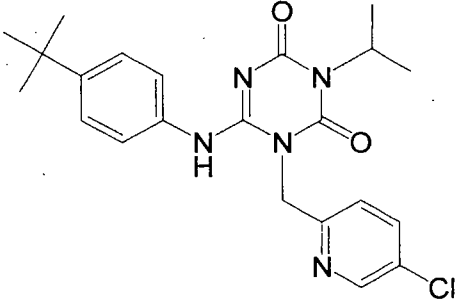
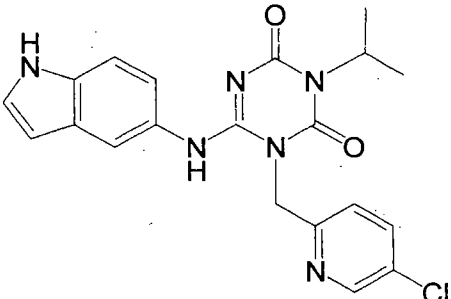
[Table 35]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-156	428	2.53	1
	I-157	430	2.21	1
	I-158	428	2.51	1
	I-159	411	1.83	1
	I-160	457	1.77	1

[Table 36]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-161	454	2.04	1
	I-162	440	2.40	1
	I-163	438	2.24	1
	I-164	464	2.48	1
	I-165	407	2.31	1

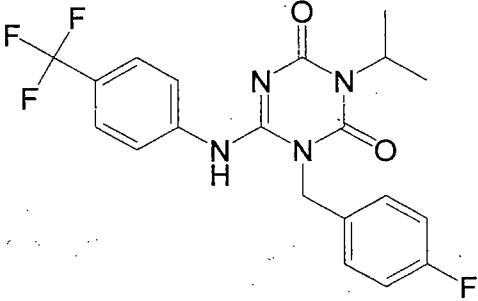
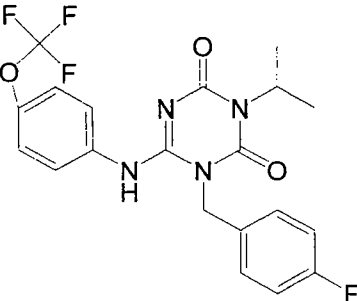
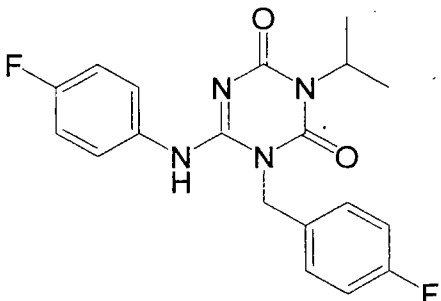
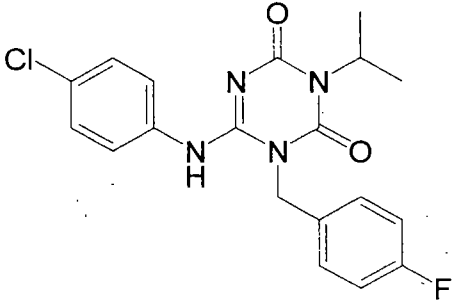
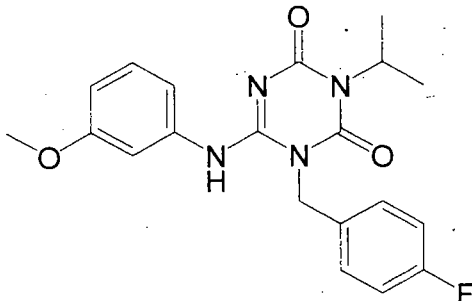
[Table 37]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-166	430	2.38	1
	I-167	428	2.58	1
	I-168	430	2.31	1
	I-169	430	2.60	1
	I-170	411	1.94	1

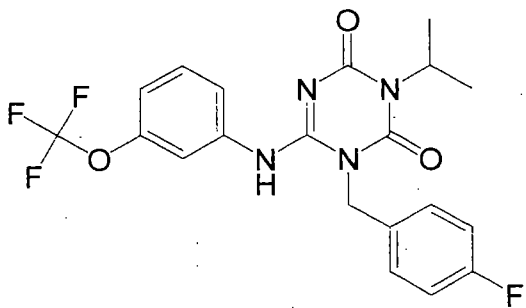
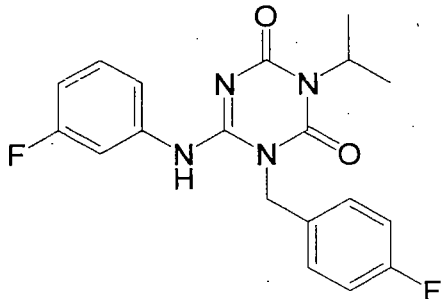
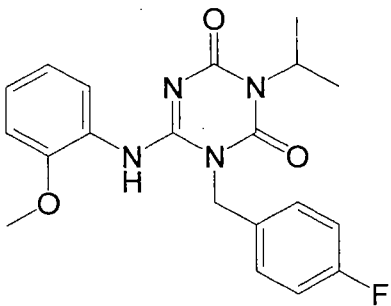
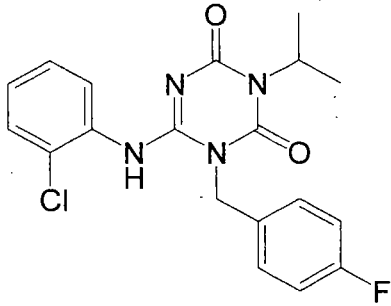
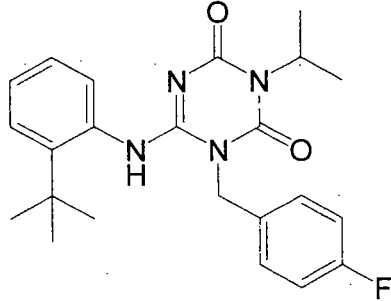
[Table 38]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-171	457	1.92	1
	I-172	454	2.20	1
	I-173	438	2.30	3
	I-174	421	2.38	3
	I-175	385	2.20	3

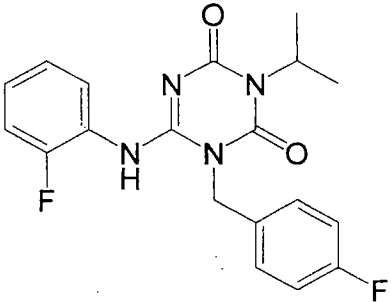
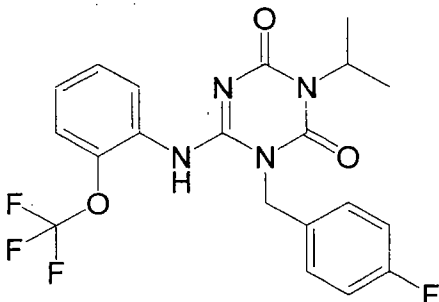
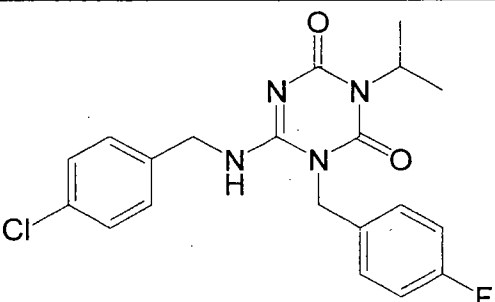
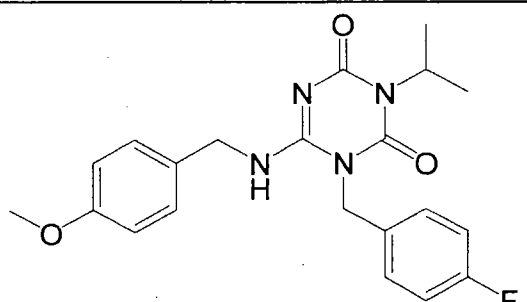
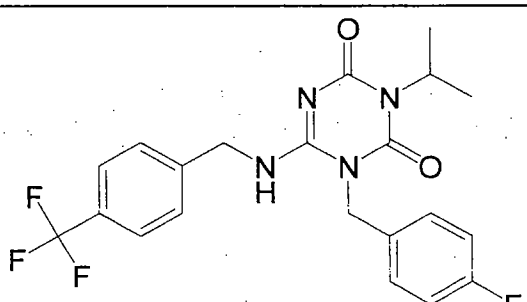
[Table 39]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-176	423	2.70	3
	I-177	439	2.70	3
	I-178	373	2.30	3
	I-179	389	2.50	3
	I-180	385	2.40	3

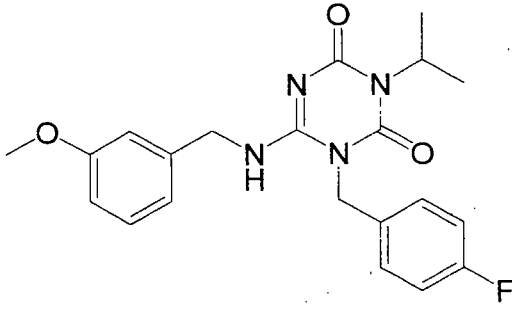
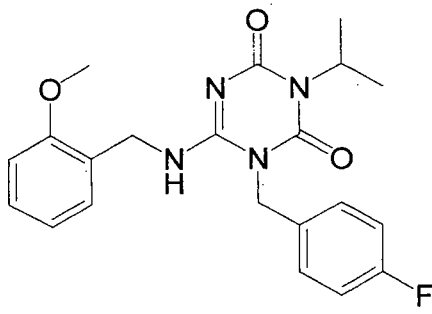
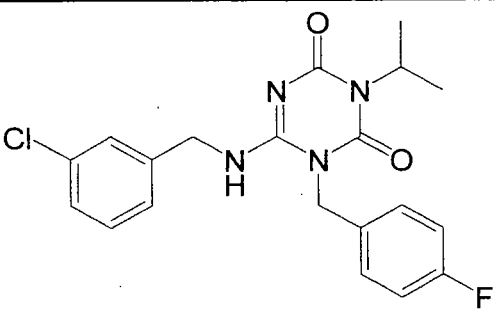
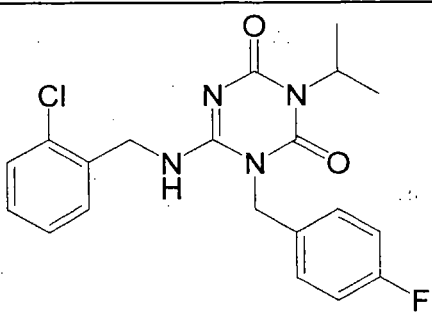
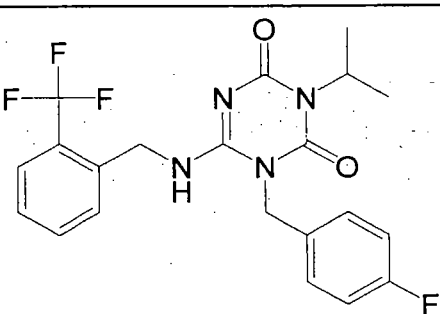
[Table 40]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-181	439	2.70	3
	I-182	373	2.40	3
	I-183	385	2.30	3
	I-184	389	2.60	3
	I-185	411	2.90	3

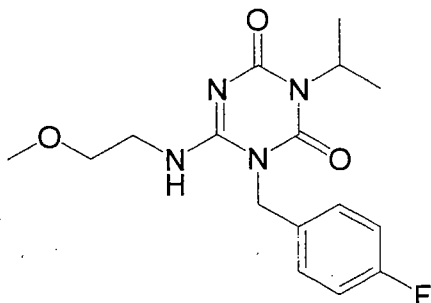
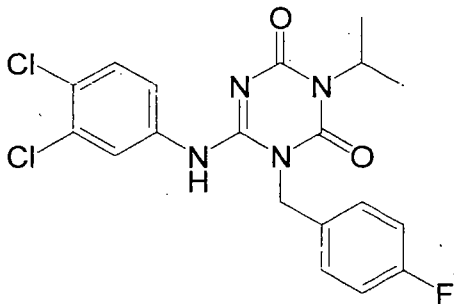
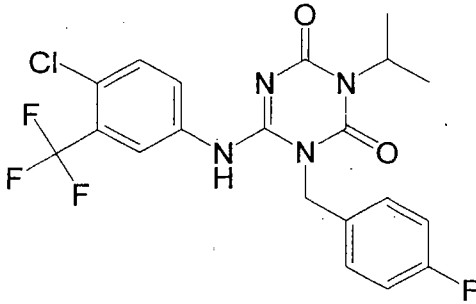
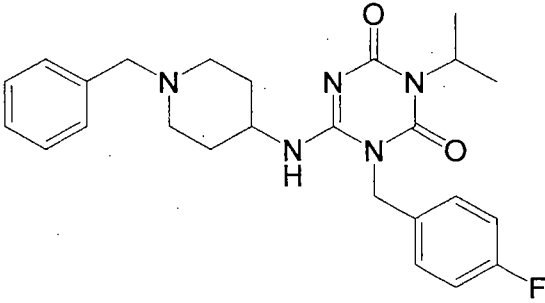
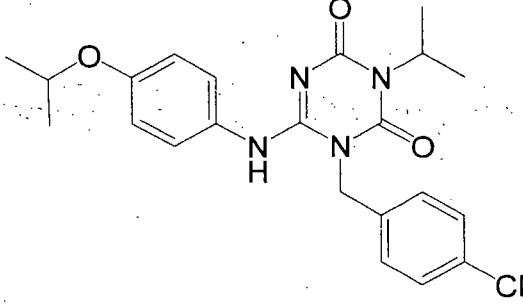
[Table 41]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-186	373	2.40	3
	I-187	439	2.70	3
	I-188	403	1.20	3
	I-189	399	1.20	3
	I-190	437	2.10	3

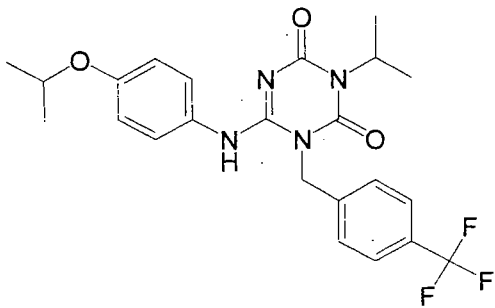
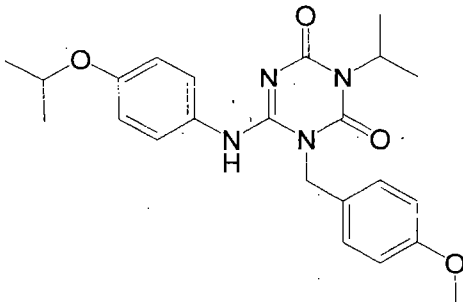
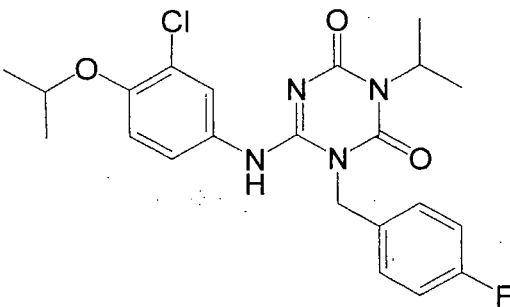
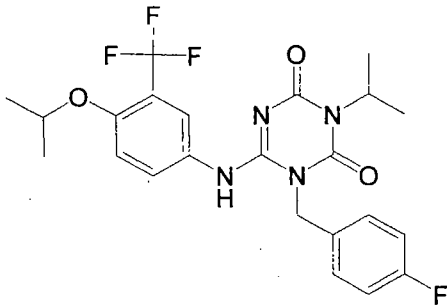
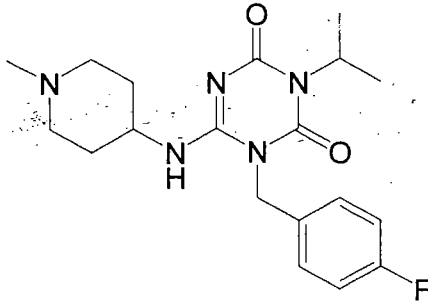
[Table 42]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-191	399	1.90	3
	I-192	399	1.90	3
	I-193	403	2.20	3
	I-194	403	2.20	3
	I-195	437	2.30	3

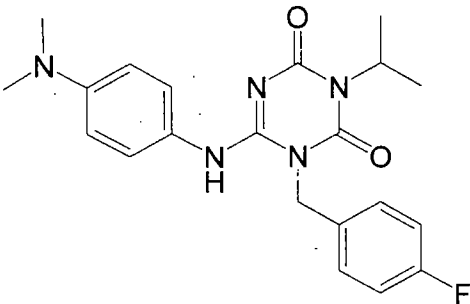
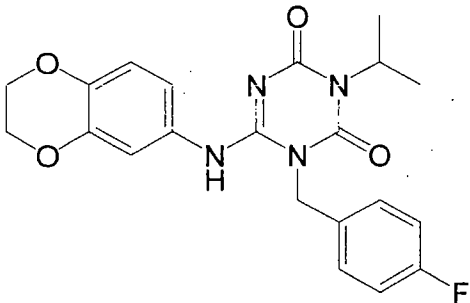
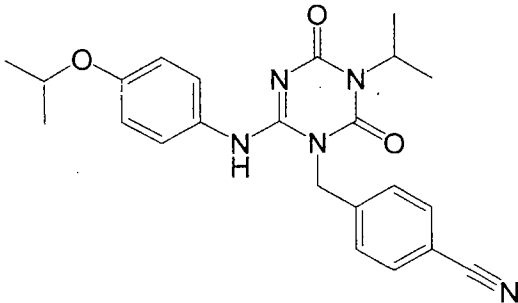
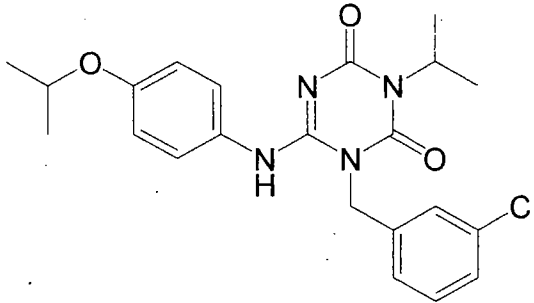
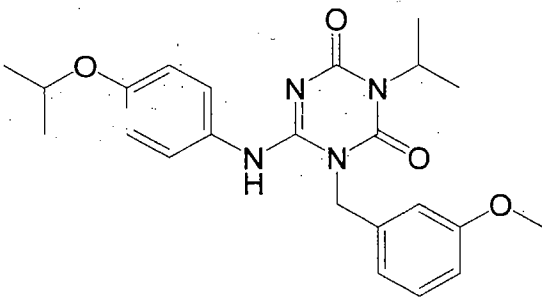
[Table 43]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-196	337	1.70	3
	I-197	424	2.80	3
	I-198	457	2.80	3
	I-199	452	1.40	3
	I-200	429	2.60	3

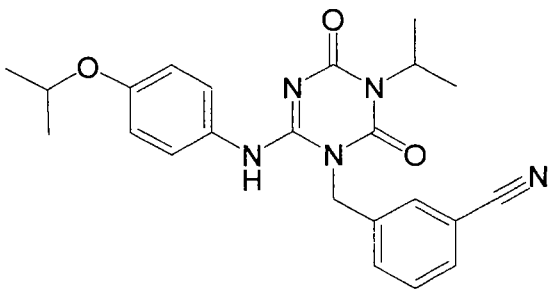
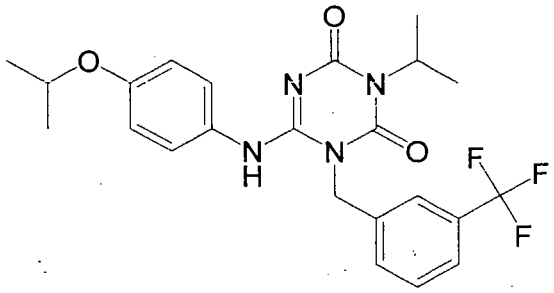
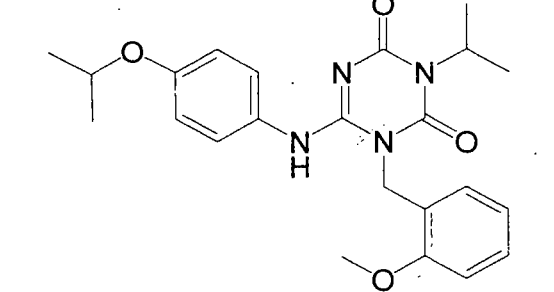
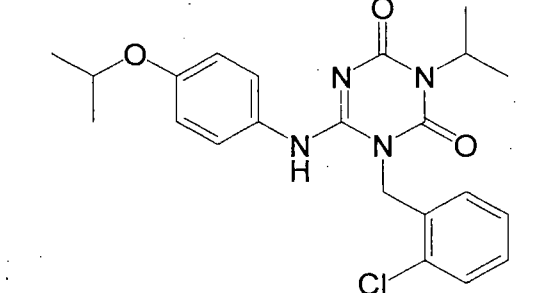
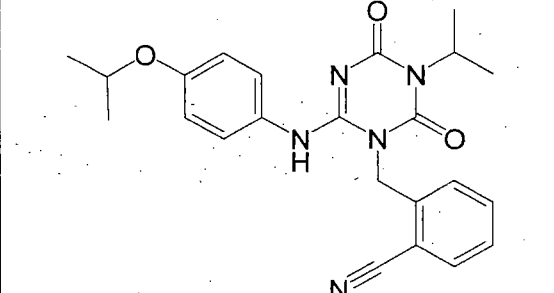
[Table 44]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-201	463	2.70	3
	I-202	425	2.40	3
	I-203	447	2.70	3
	I-204	481	2.80	3
	I-205	376	1.20	3

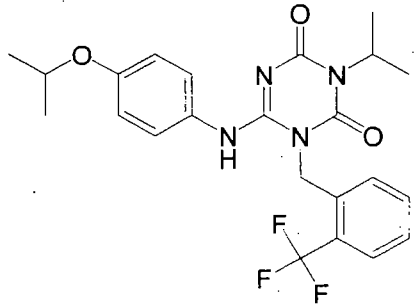
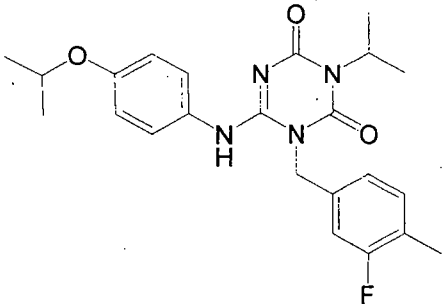
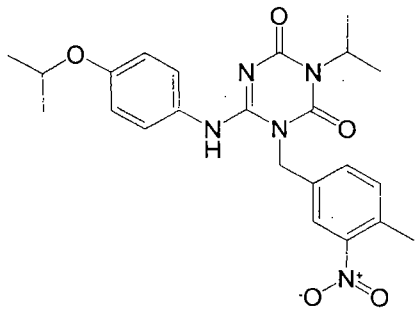
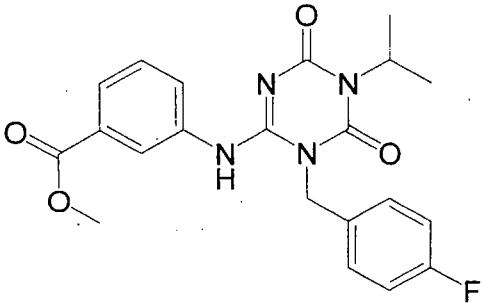
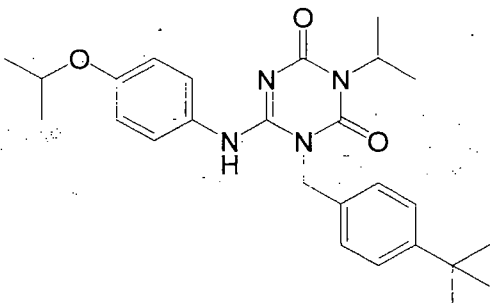
[Table 45]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-206	398	1.80	3
	I-207	413	2.20	3
	I-208	420	2.30	3
	I-209	429	2.60	3
	I-210	425	2.40	3

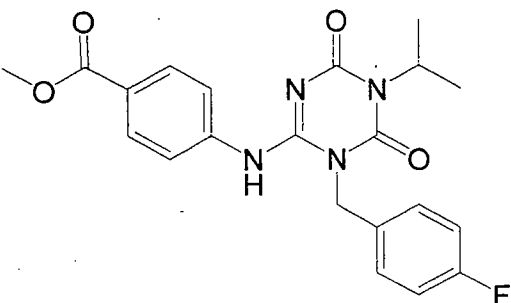
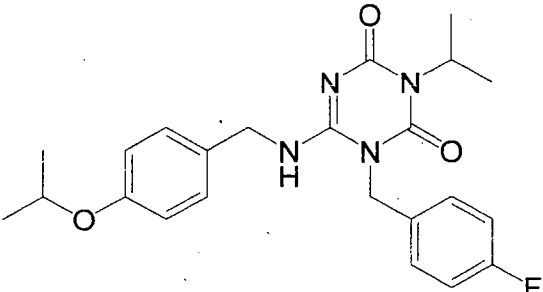
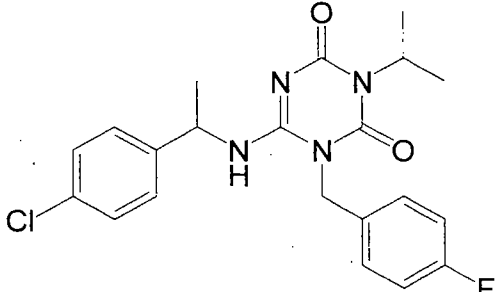
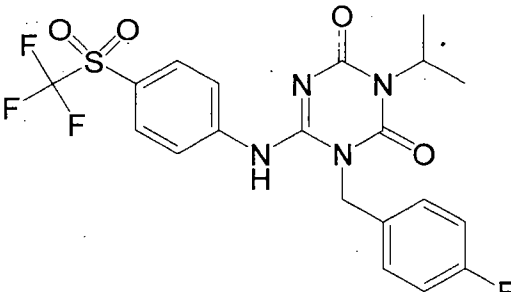
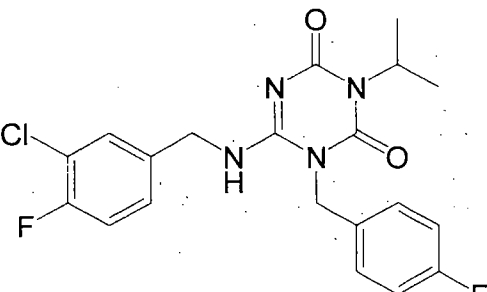
[Table 46]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-211	420	2.40	3
	I-212	463	2.70	3
	I-213	425	2.40	3
	I-214	429	2.60	3
	I-215	420	2.40	3

[Table 47]

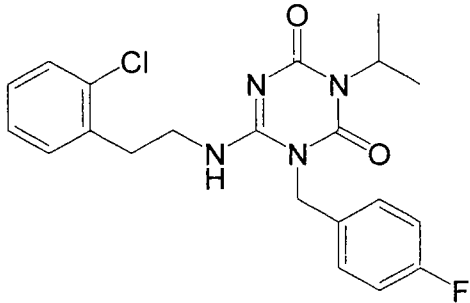
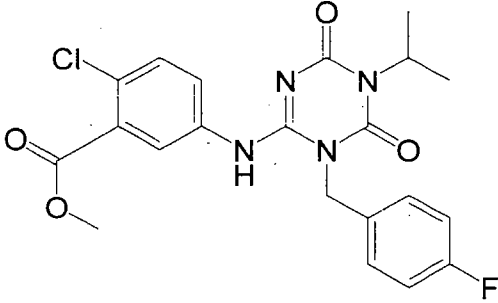
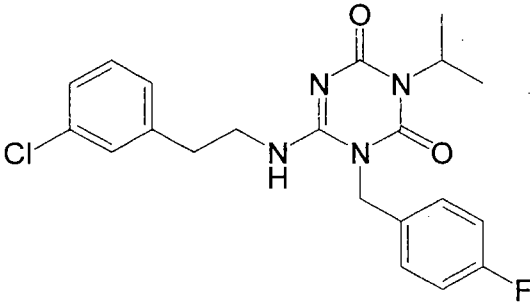
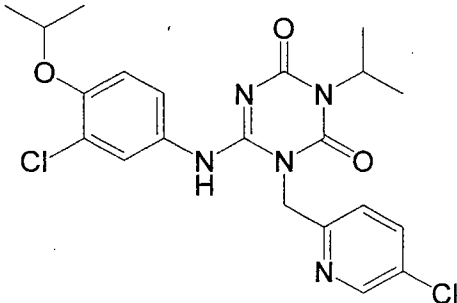
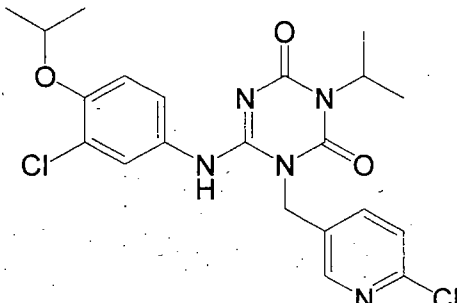
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-216	463	2.70	3
	I-217	427	2.60	3
	I-218	454	2.50	3
	I-219	413	2.40	3
	I-220	451	2.90	3

[Table 48]

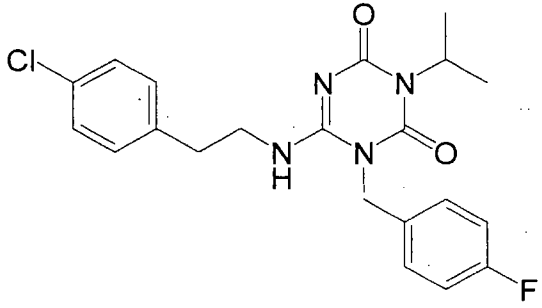
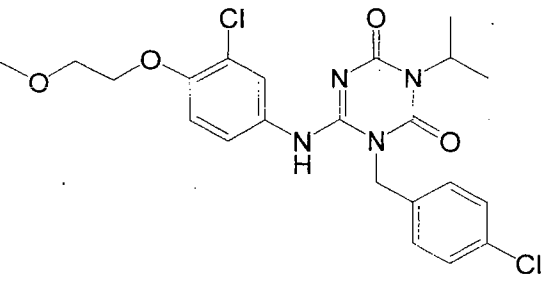
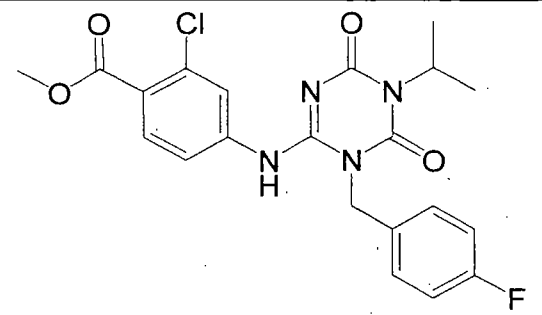
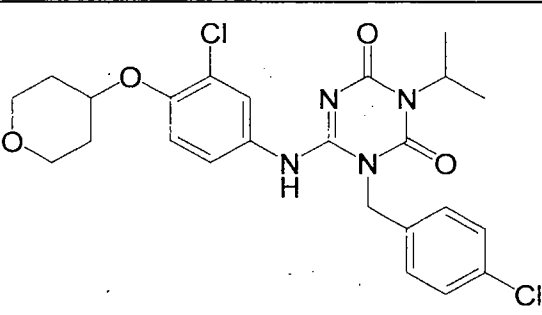
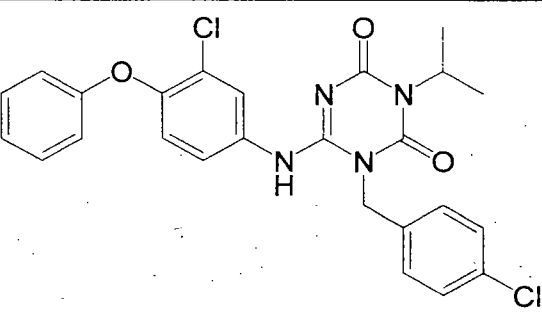
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-221	413	2.40	3
	I-222	427	2.40	3
	I-223	417	2.40	3
	I-224	487	2.70	3
	I-225	421	2.30	3

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-226	414	2.60	3
	I-227	438	2.50	3
	I-228	463	2.90	3
	I-229	437	2.40	3
	I-230	475	2.60	3

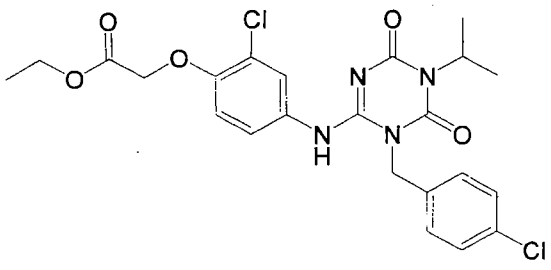
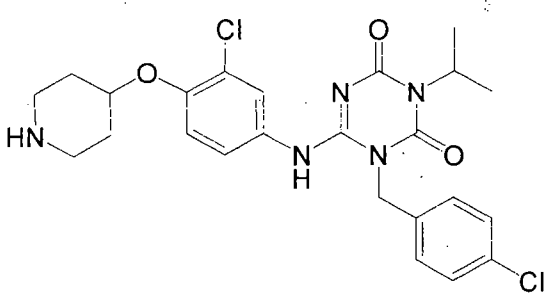
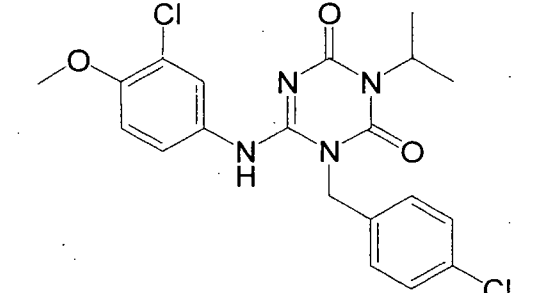
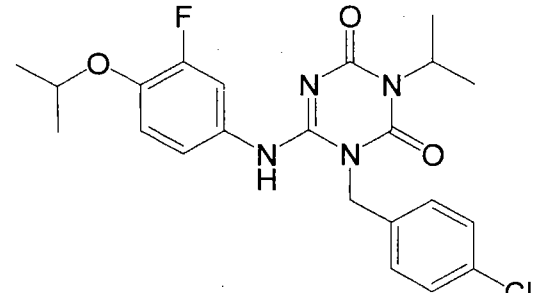
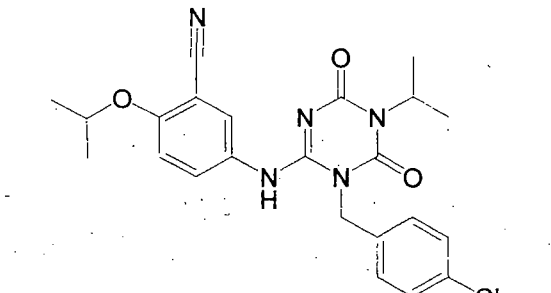
[Table 50]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-231	417	2.40	3
	I-232	447	2.40	3
	I-233	417	2.40	3
	I-234	465	2.60	3
	I-235	464	2.60	3

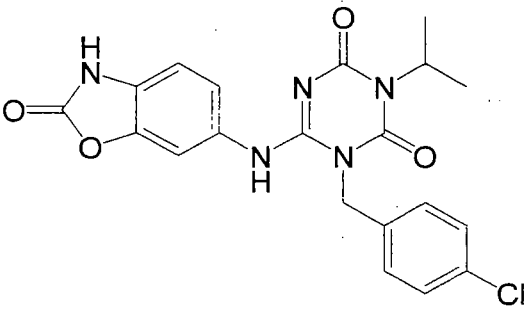
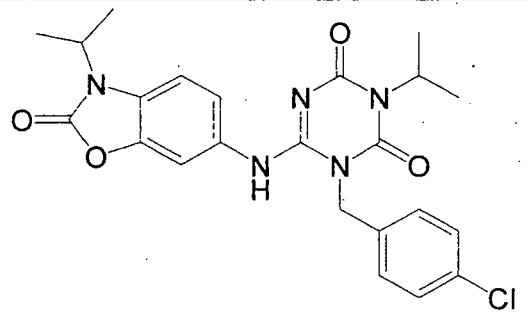
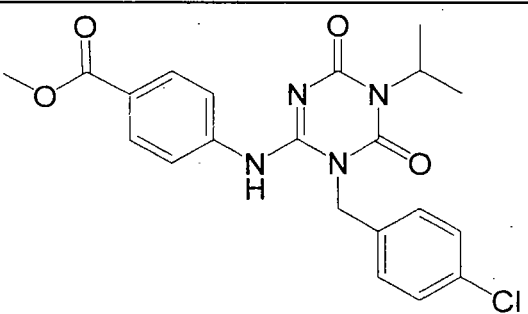
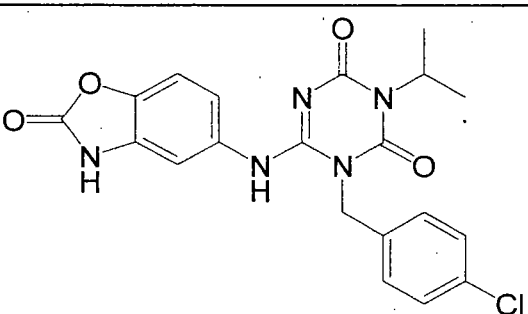
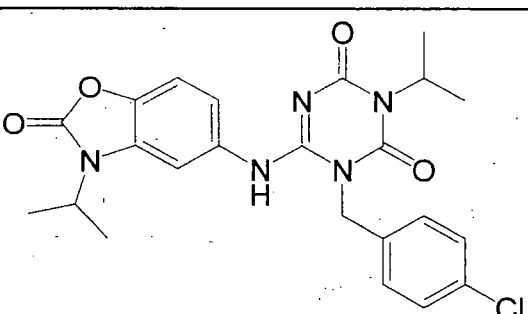
[Table 51]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-236	417	2.40	3
	I-237	479	2.60	3
	I-238	447	2.70	3
	I-239	505	2.70	3
	I-240	497	3.10	3

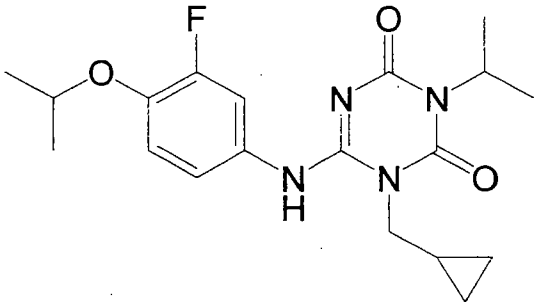
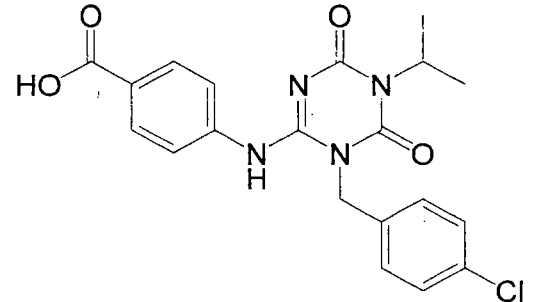
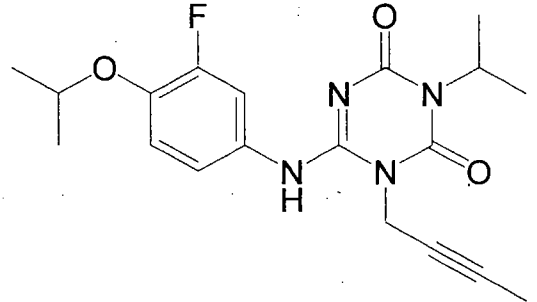
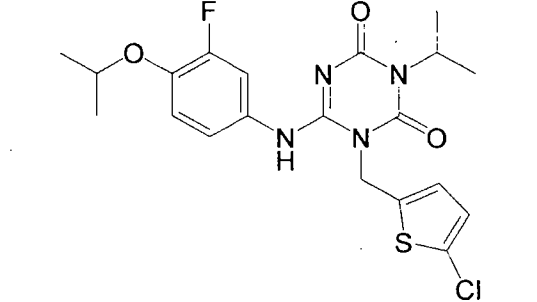
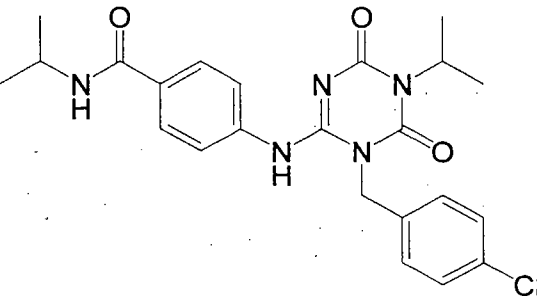
[Table 52]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-241	507	2.70	3
	I-242	505	1.60	3
	I-243	435	2.60	3
	I-244	447	2.80	3
	I-245	454	2.70	3

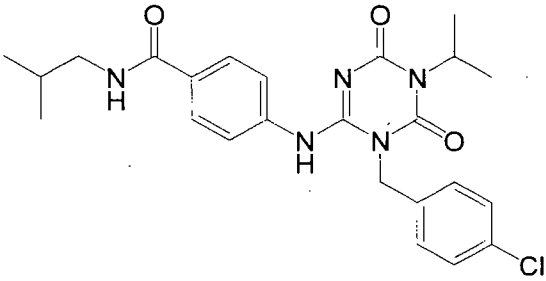
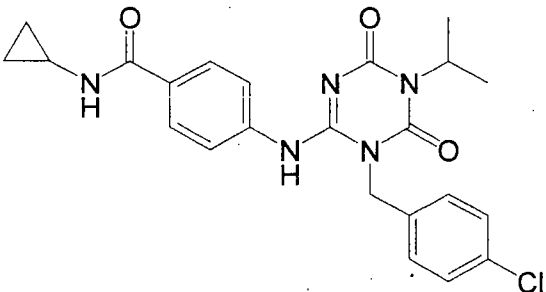
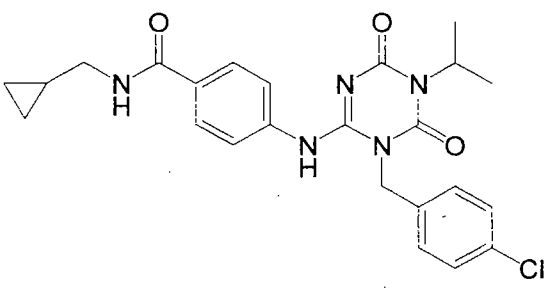
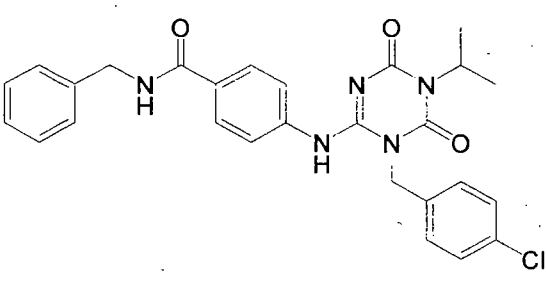
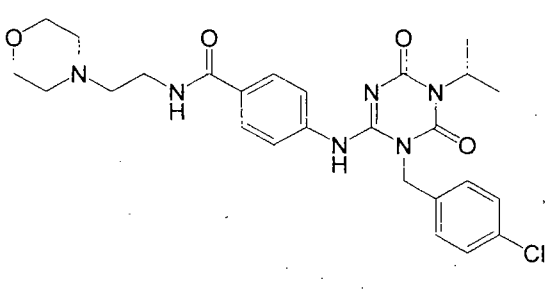
[Table 53]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-246	428	2.20	3
	I-247	470	2.50	3
	I-248	429	2.60	3
	I-249	428	2.20	3
	I-250	470	2.60	3

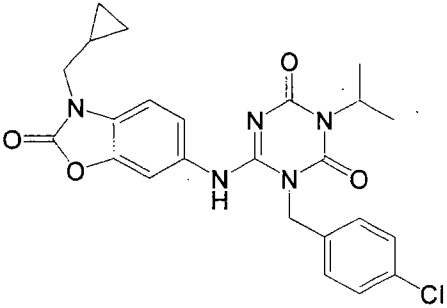
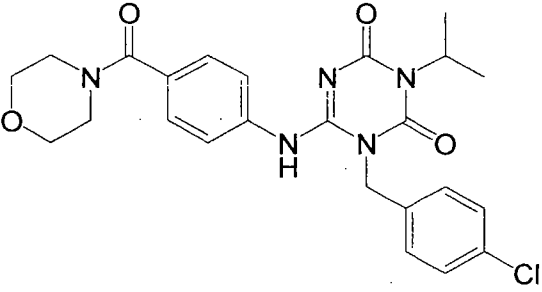
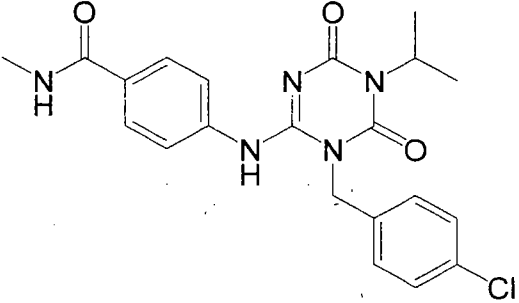
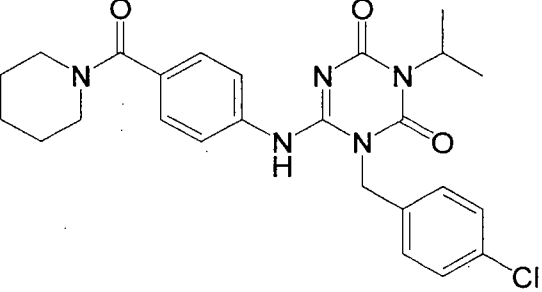
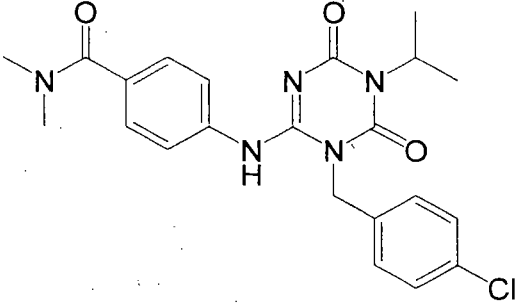
[Table 54]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-251	377	2.40	3
	I-252	415	2.30	3
	I-253	375	2.30	3
	I-254	453	2.90	3
	I-255	456	2.40	3

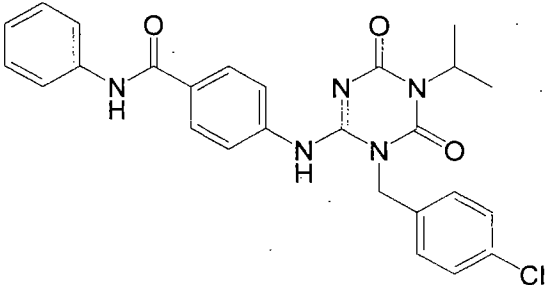
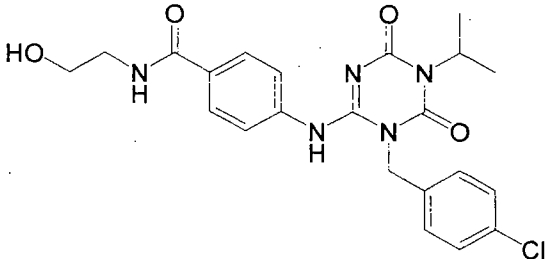
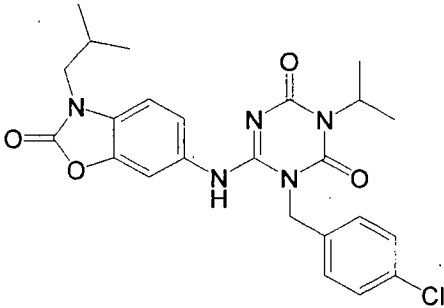
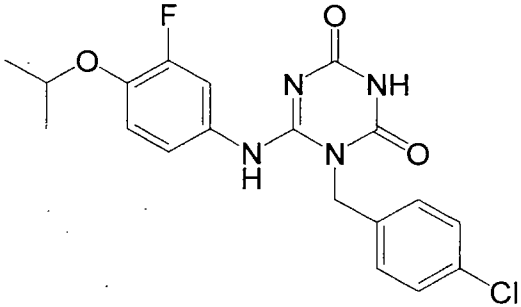
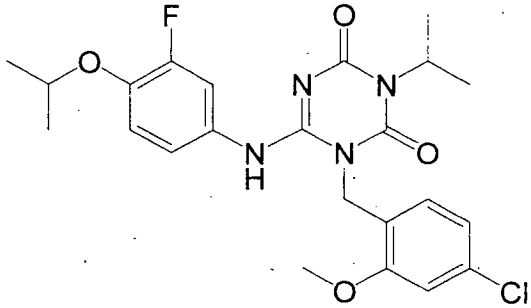
[Table 55]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-256	470	2.50	3
	I-257	454	2.20	3
	I-258	468	2.40	3
	I-259	504	2.50	3
	I-260	528	1.50	3

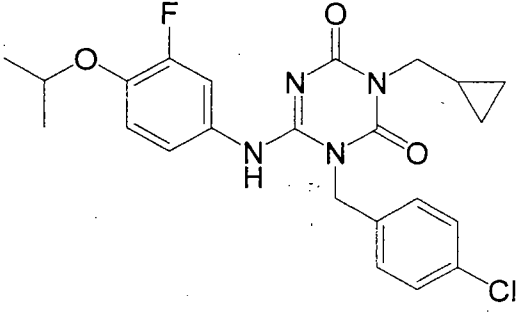
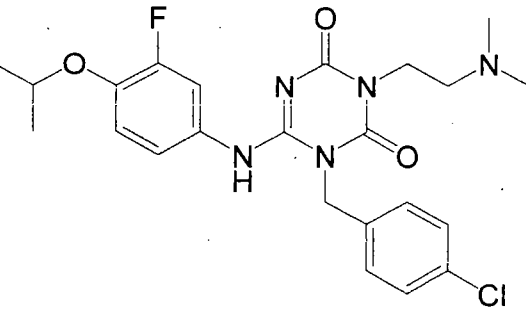
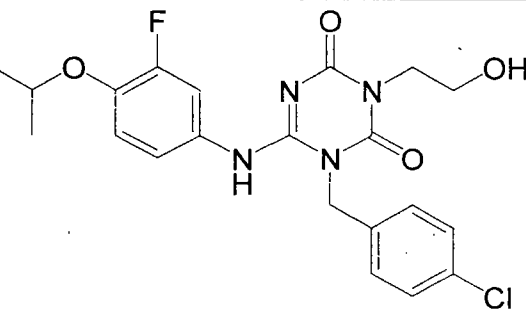
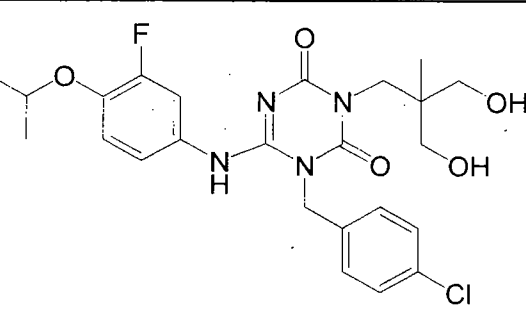
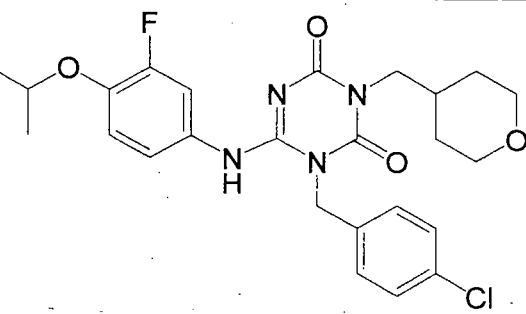
[Table 56]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-261	482	2.60	3
	I-262	484	2.20	3
	I-263	428	2.10	3
	I-264	482	2.50	3
	I-265	442	2.30	3

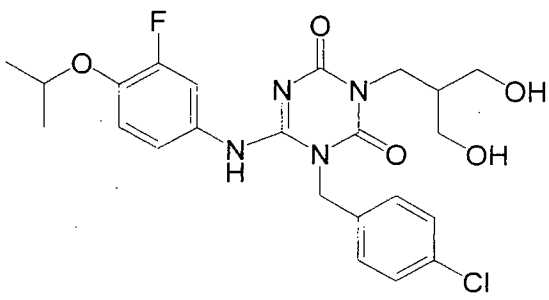
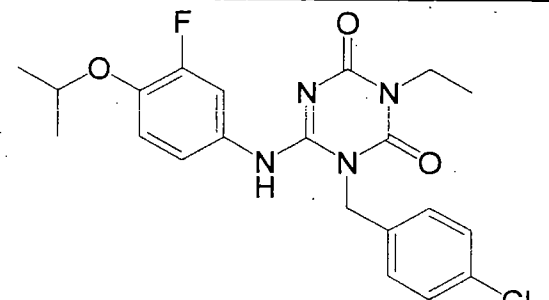
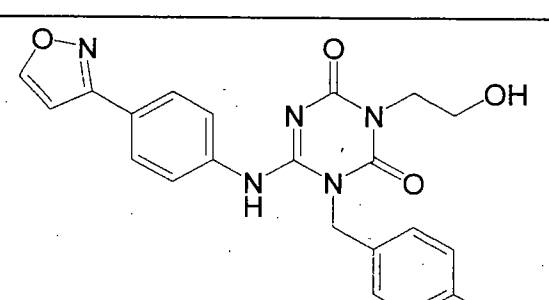
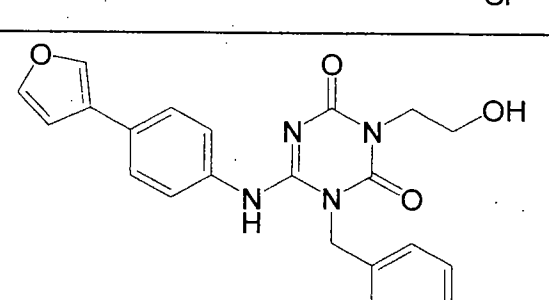
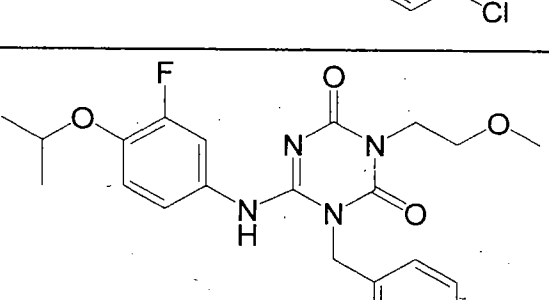
[Table 57]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-266	490	2.60	3
	I-267	458	2.00	3
	I-268	484	2.60	3
	I-269	405	2.03	1
	I-270	477	2.42	1

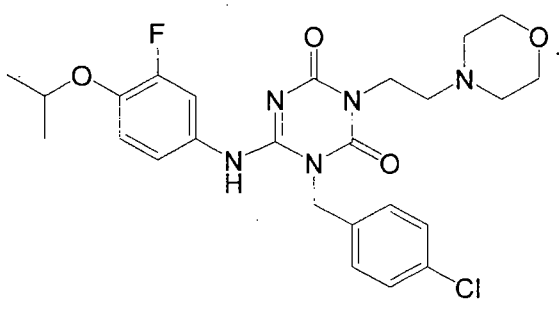
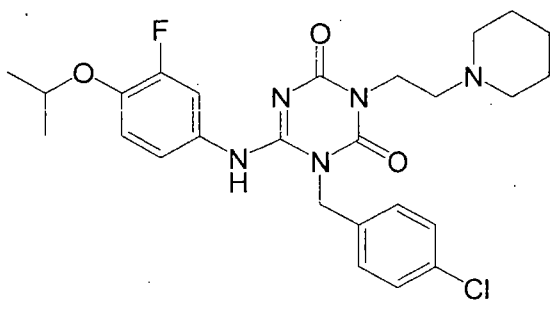
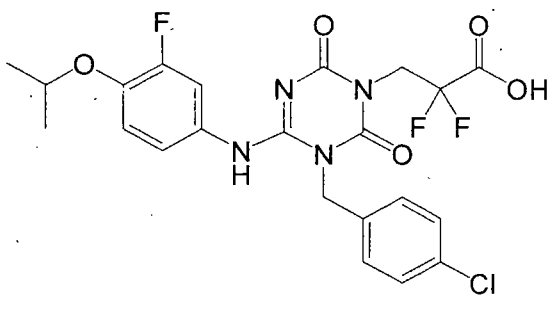
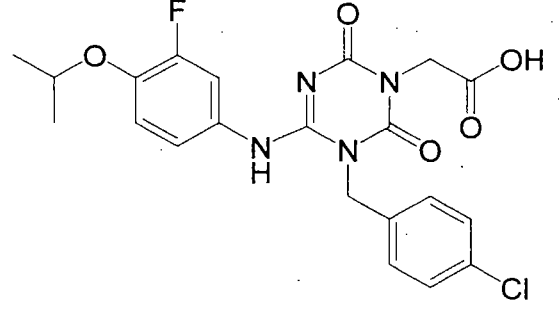
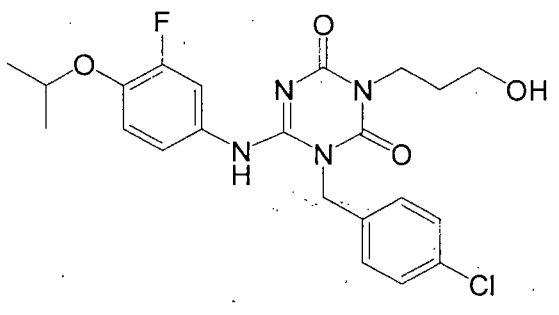
[Table 58]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-271	459	2.49	1
	I-272	476	1.44	1
	I-273	449	1.96	1
	I-274	507	1.98	1
	I-275	503	2.27	1

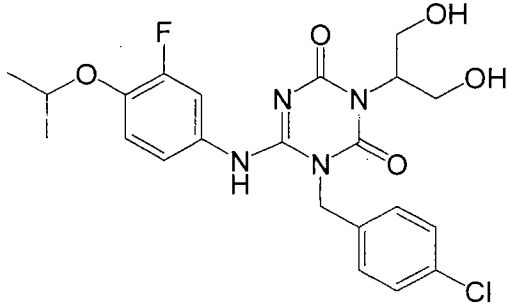
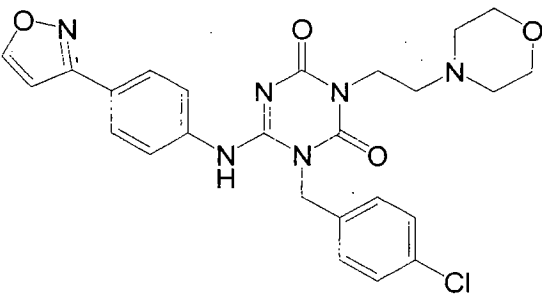
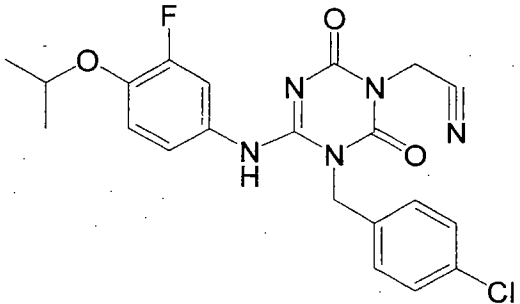
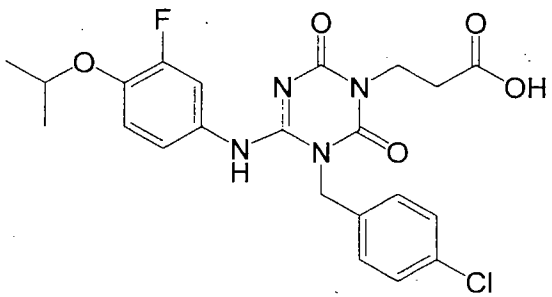
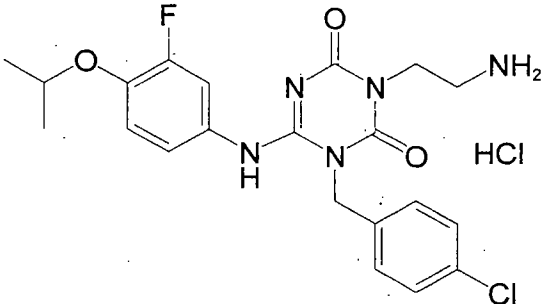
[Table 59]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-276	493	1.85	1
	I-277	433	2.34	1
	I-278	440	1.70	1
	I-279	439	1.90	1
	I-280	463	2.21	1

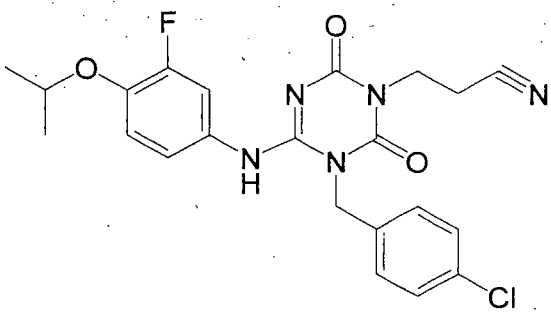
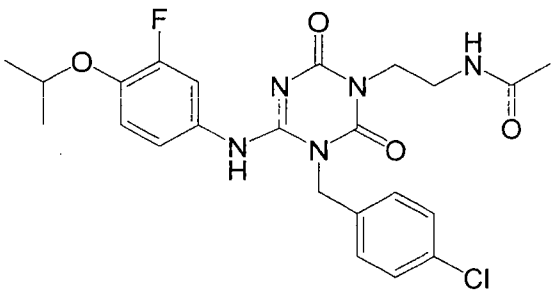
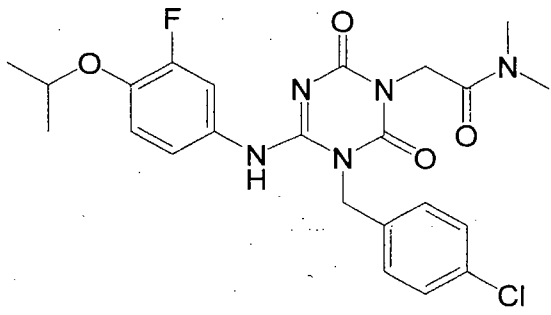
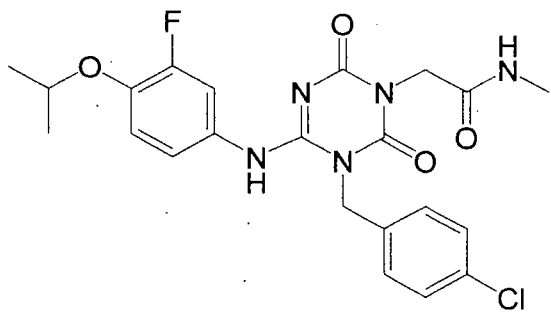
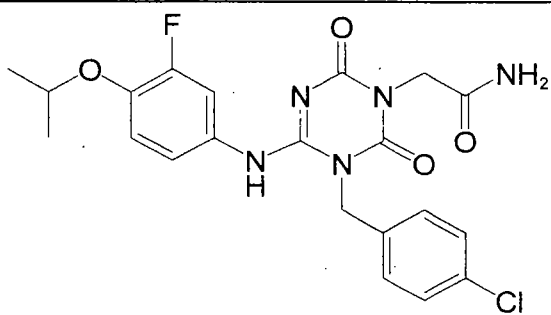
[Table 60]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-281	518	1.47	1
	I-282	516	1.50	1
	I-283	513	1.82	1
	I-284	463	1.96	1
	I-285	463	2.00	1

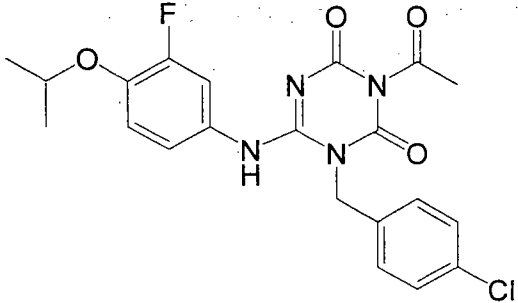
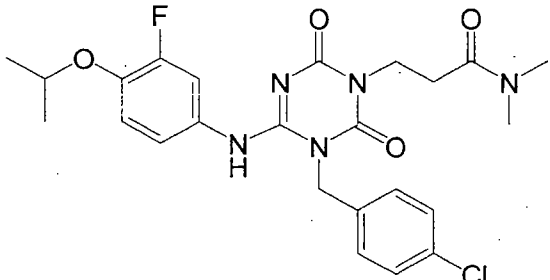
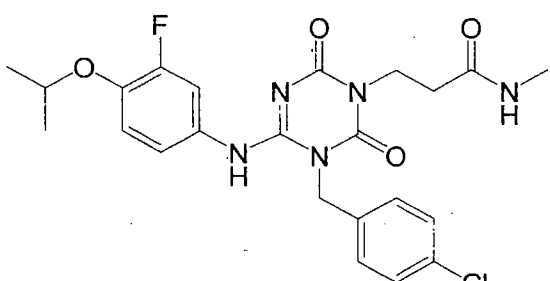
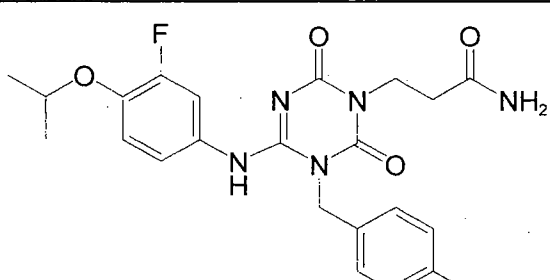
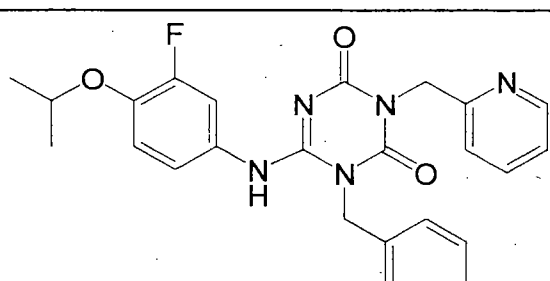
[Table 61]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-286	479	1.80	1
	I-287	509	1.30	1
	I-288	444	2.15	1
	I-289	477	2.00	1
	I-290	448	1.40	1

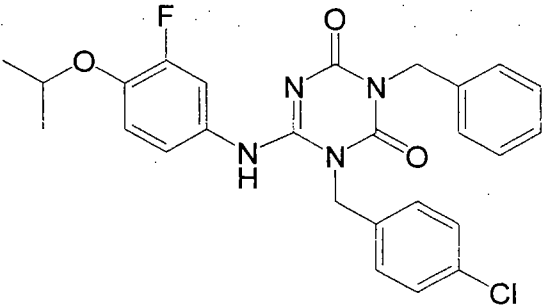
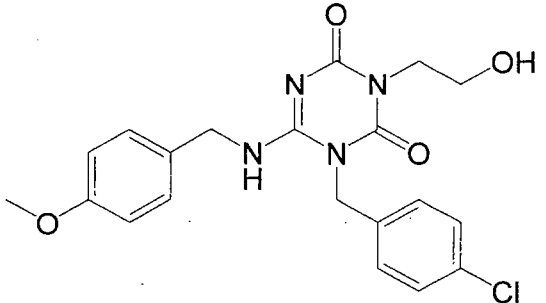
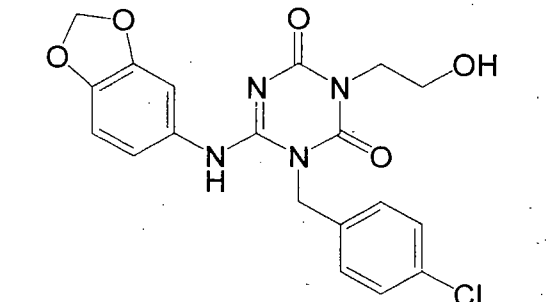
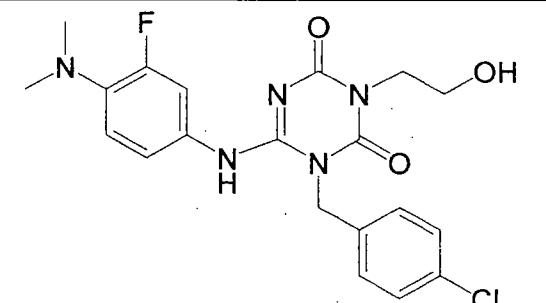
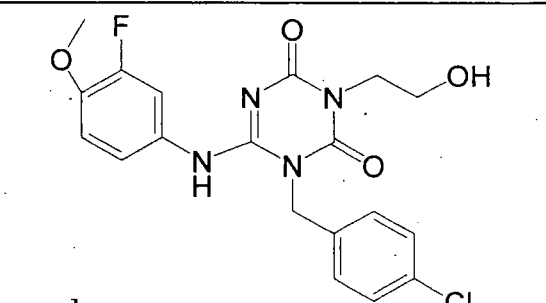
[Table 62]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-291	458	2.15	1
	I-292	489	1.90	1
	I-293	490	2.00	1
	I-294	476	1.91	1
	I-295	462	1.85	1

[Table 63]

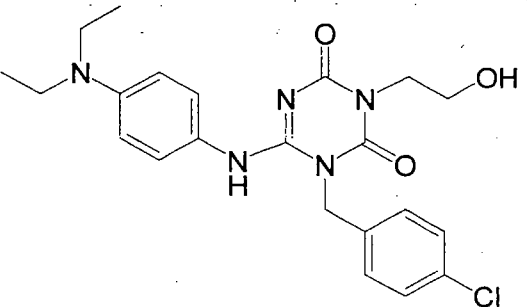
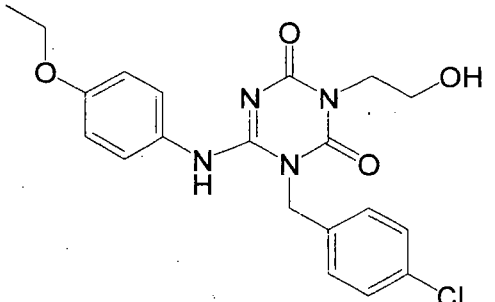
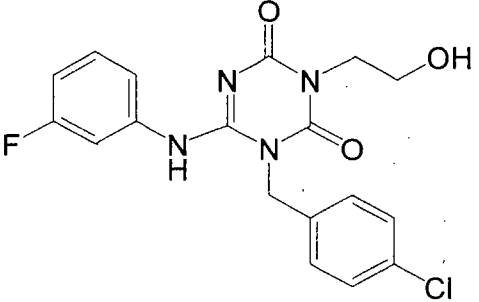
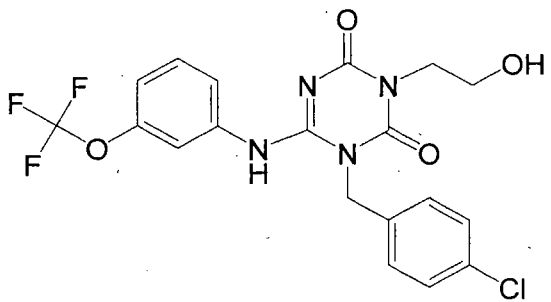
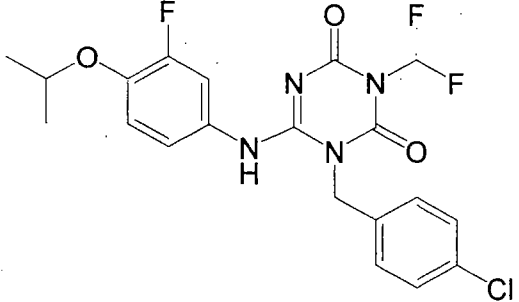
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-296	447	2.18	1
	I-297	504	2.04	1
	I-298	490	1.90	1
	I-299	476	1.86	1
	I-300	496	2.06	1

[Table 64]

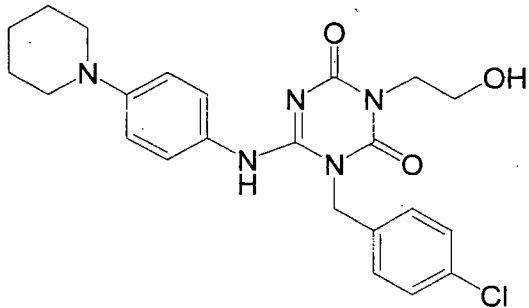
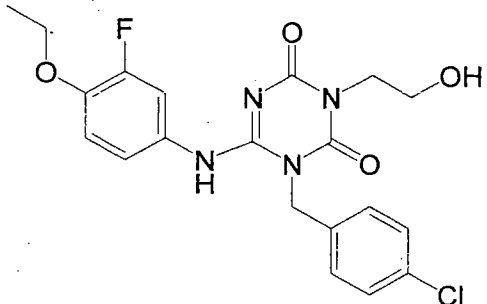
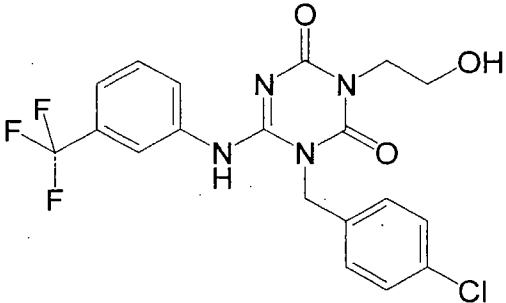
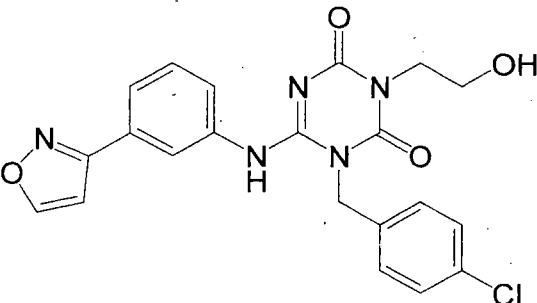
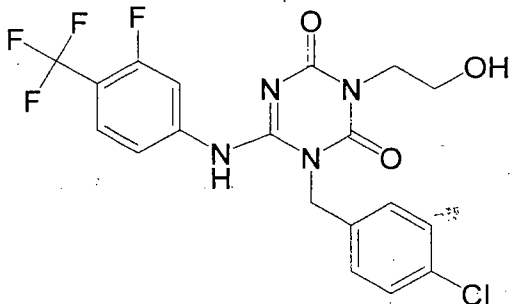
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-301	495	2.53	1
	I-302	417	1.50	1
	I-303	417	1.60	1
	I-304	434	1.50	1
	I-305	421	1.69	1

[0142]

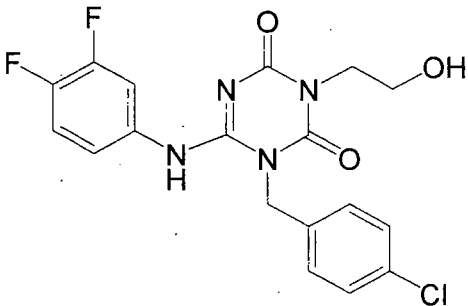
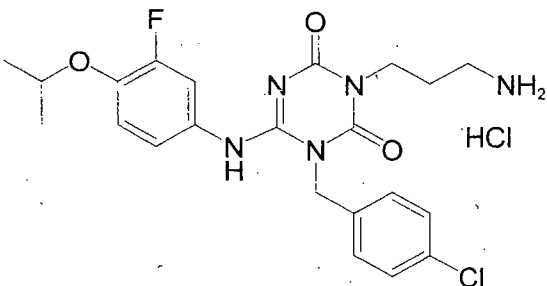
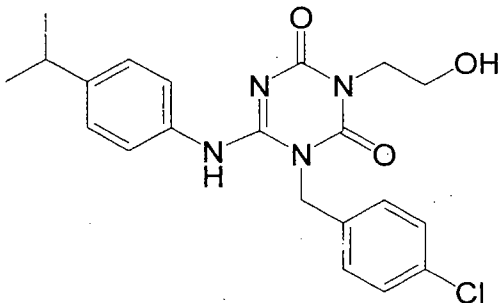
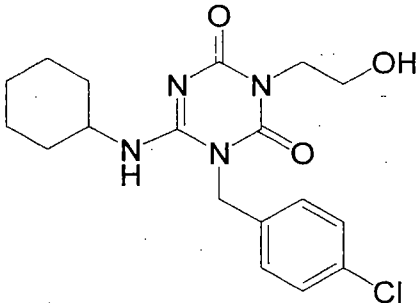
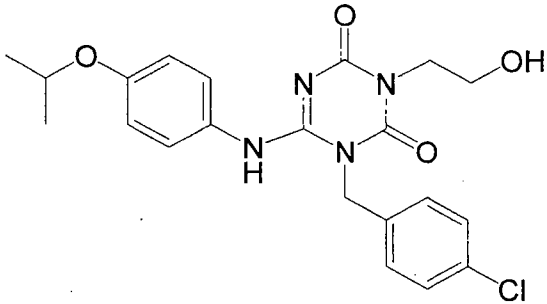
[Table 65]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-306	444	1.11	1
	I-307	417	1.72	1
	I-308	391	1.80	1
	I-309	457	2.09	1
	I-310	455	2.21	1

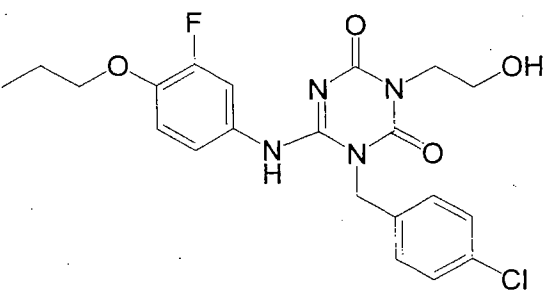
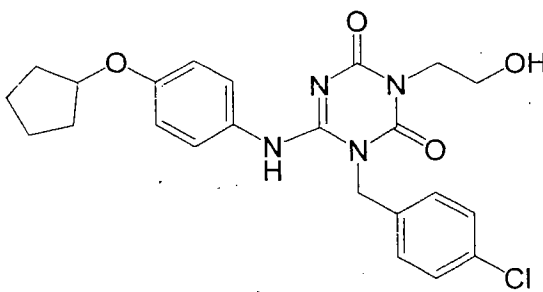
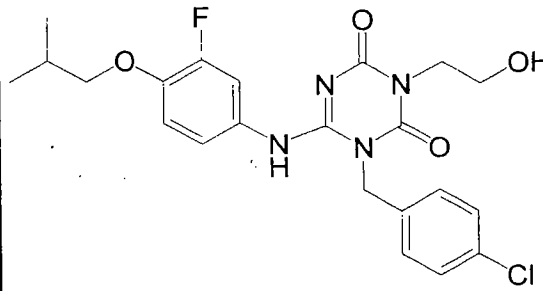
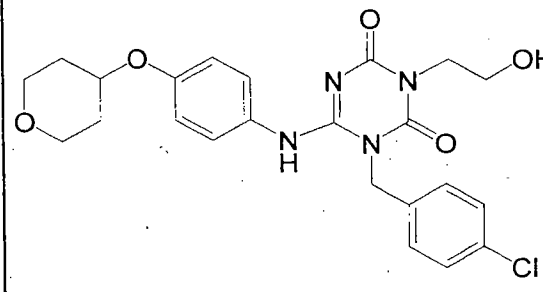
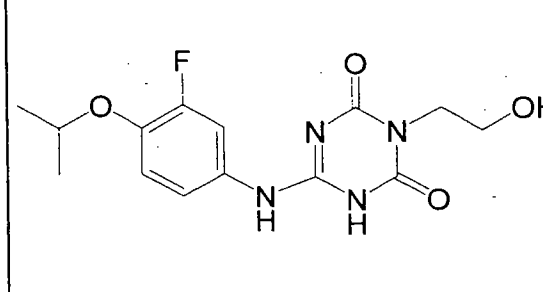
[Table 66]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-311	456	1.14	1
	I-312	435	1.83	1
	I-313	441	2.00	2
	I-314	440	1.70	2
	I-315	459	2.09	2

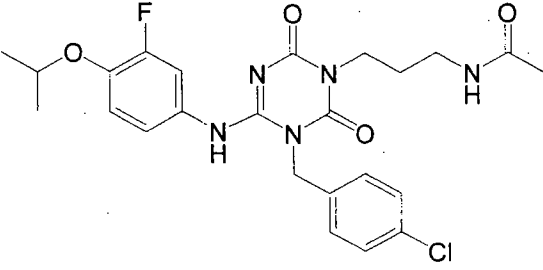
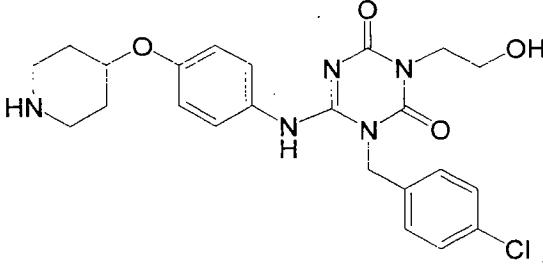
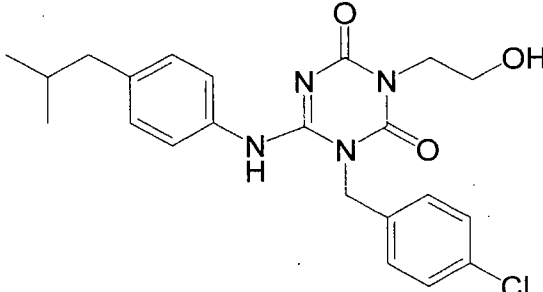
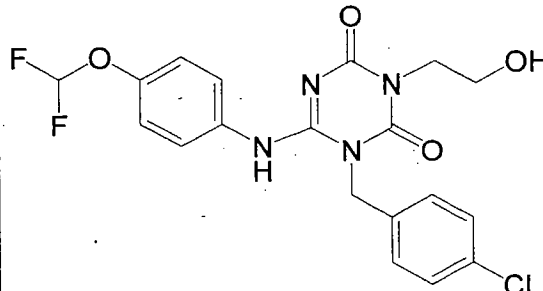
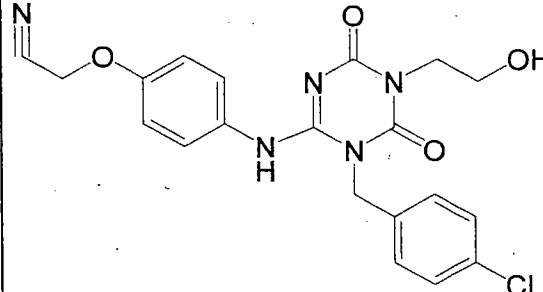
[Table 67]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-316	409	1.84	2
	I-317	462	1.40	2
	I-318	415	2.01	2
	I-319	379	1.68	2
	I-320	431	1.83	2

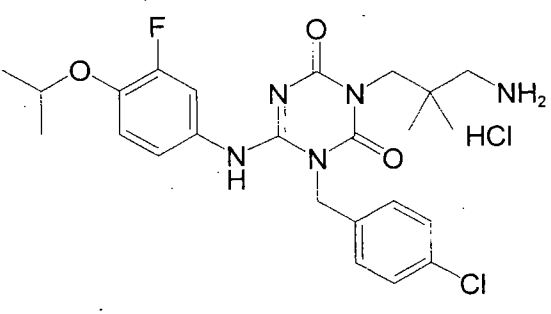
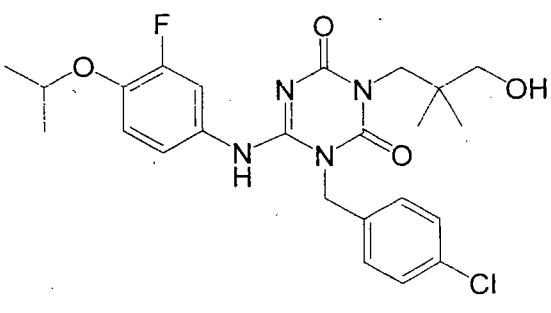
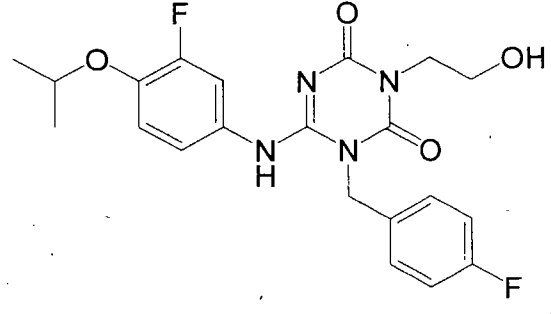
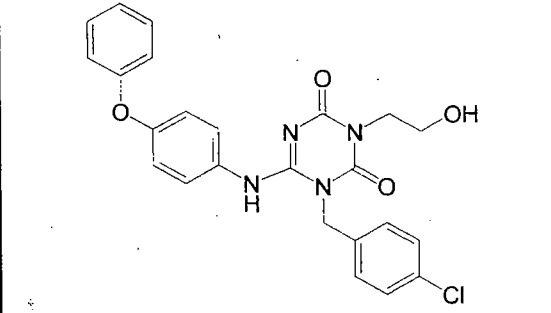
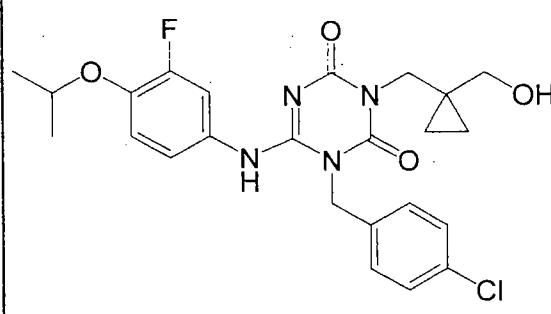
[Table 68]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-321	449	1.99	2
	I-322	457	2.03	2
	I-323	463	2.16	2
	I-324	473	1.61	2
	I-325	325	1.10	2

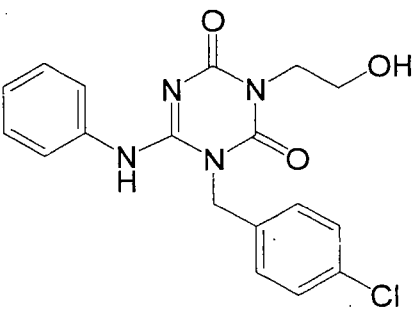
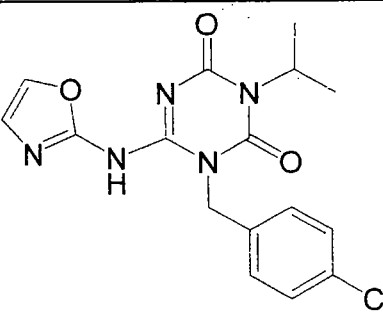
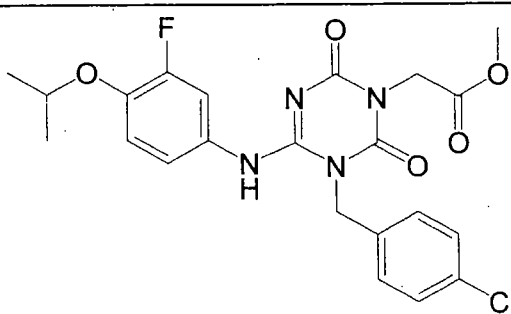
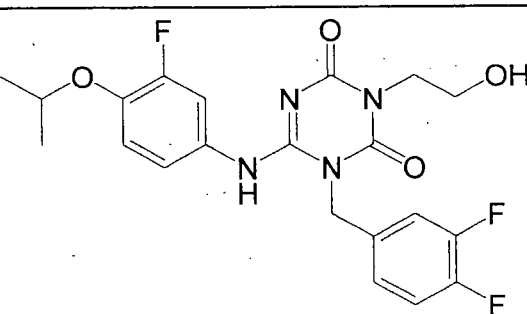
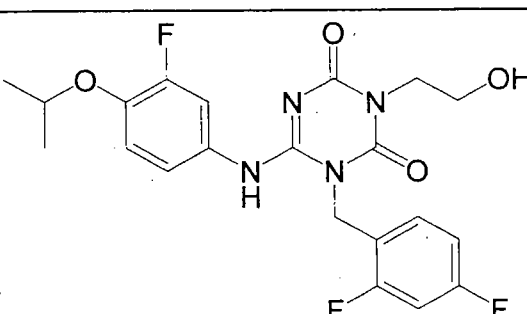
[Table 69]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-326	504	1.93	2
	I-327	472	1.03	2
	I-328	429	2.15	2
	I-329	439	1.80	2
	I-330	428	1.56	2

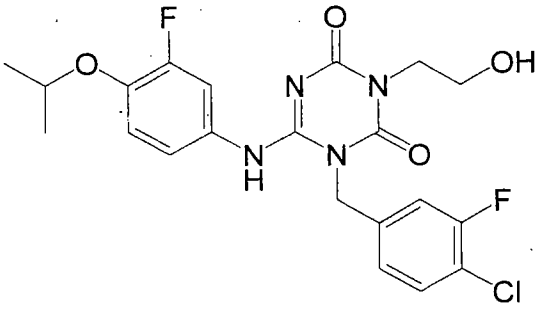
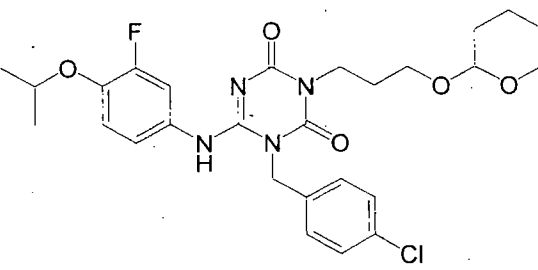
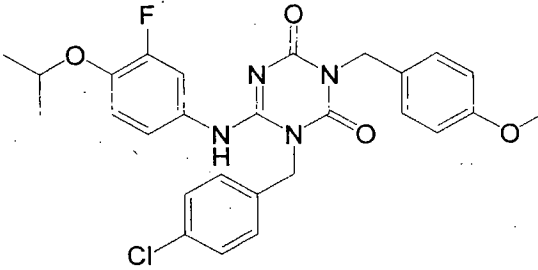
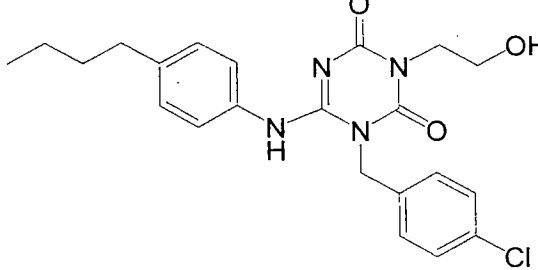
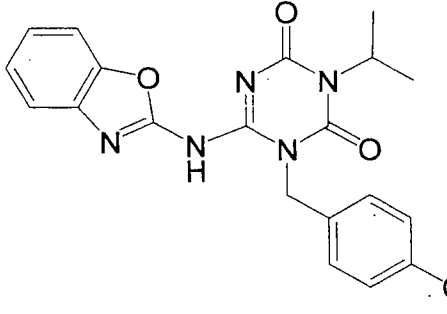
[Table 70]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-331	490	1.49	2
	I-332	491	2.26	2
	I-333	433	1.80	2
	I-334	465	2.35	3
	I-335	489	2.19	2

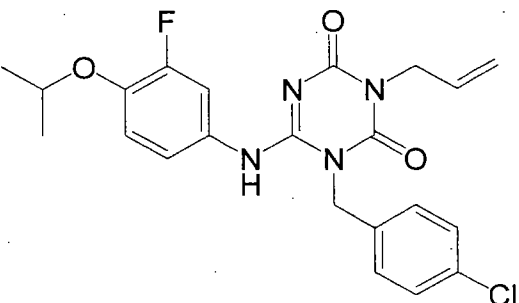
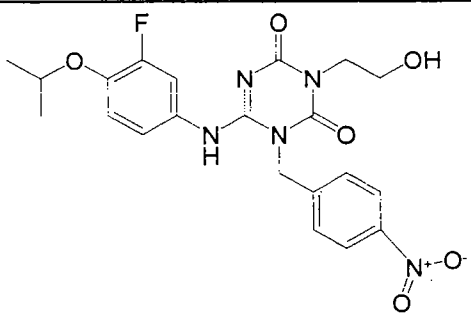
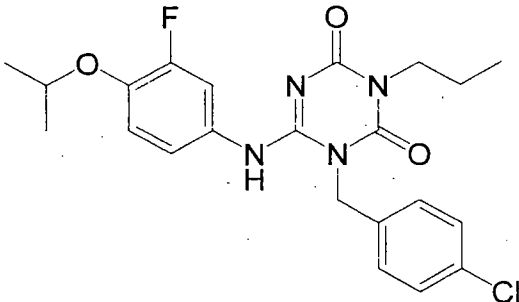
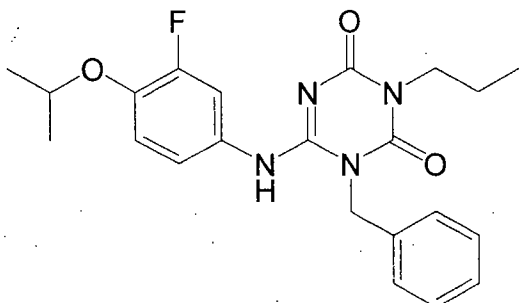
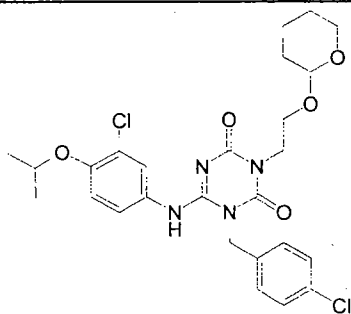
[Table 71]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-336	373	1.61	2
	I-337	362	2.39	2
	I-338	477	2.45	3
	I-339	451	1.88	2
	I-340	451	1.84	2

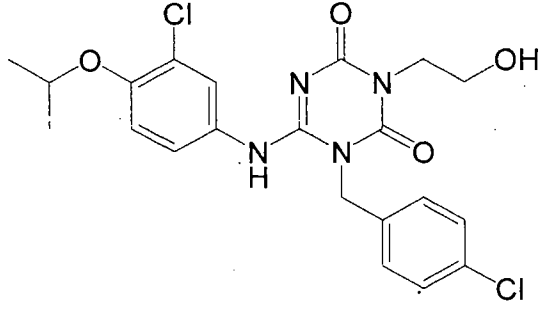
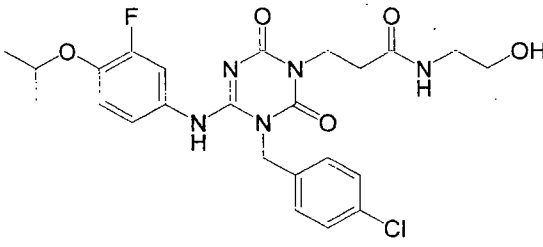
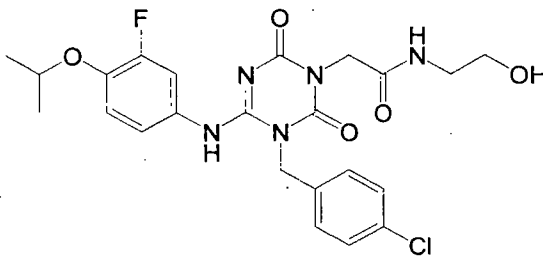
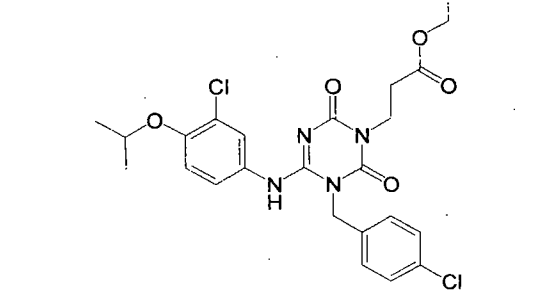
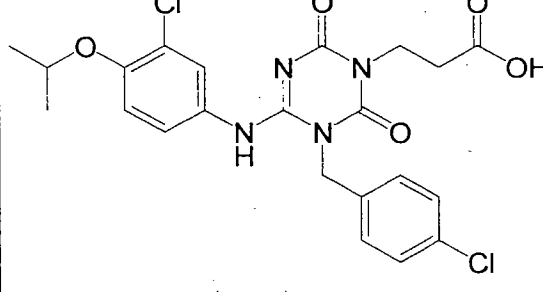
[Table 72]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-341	467	2.01	2
	I-342	548	2.81	3
	I-343	525	2.50	2
	I-344	429	2.48	3
	I-345	412	2.74	2

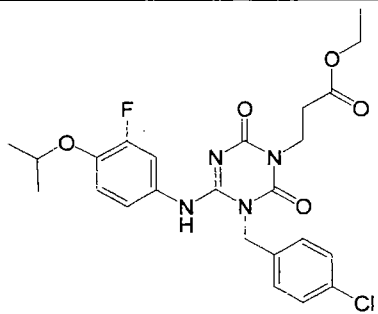
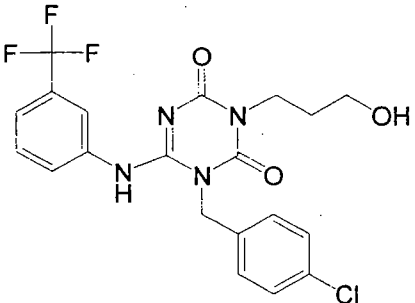
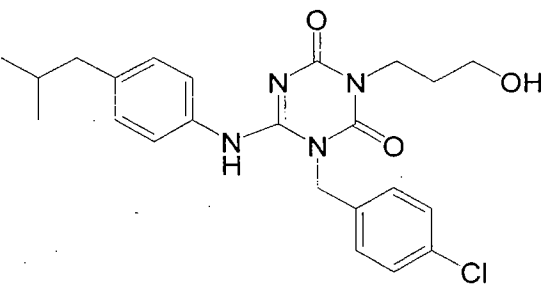
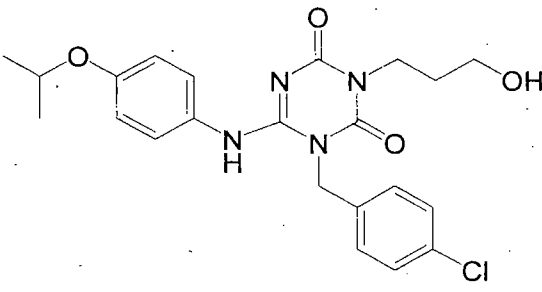
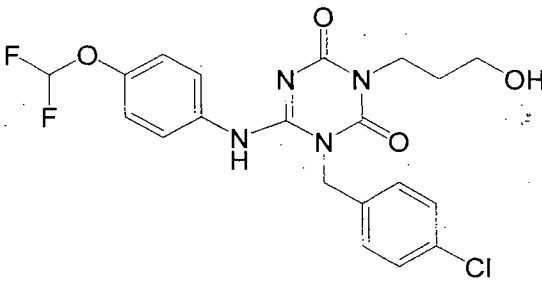
[Table 73]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-346	445	2.34	2
	I-347	460	1.78	2
	I-348	447	2.45	2
	I-349	413	2.20	2
	I-350	549	2.55	2

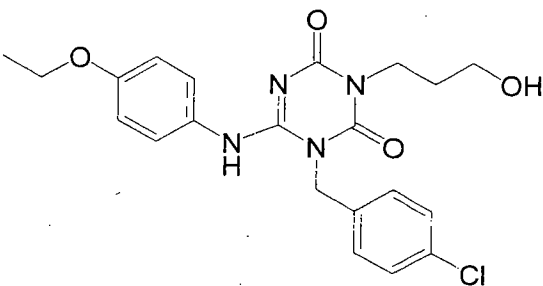
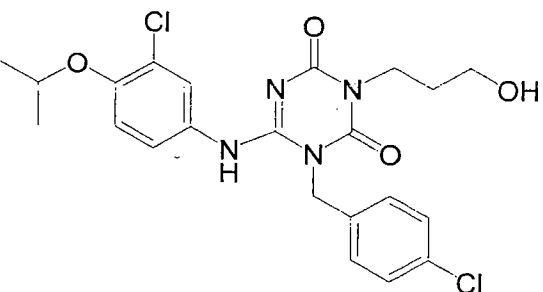
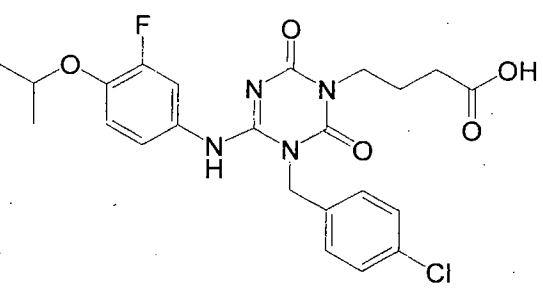
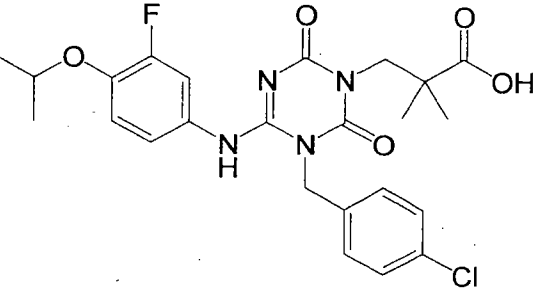
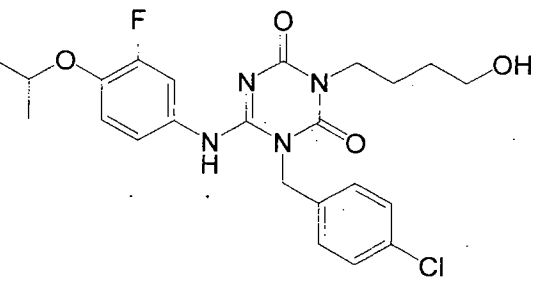
[Table 74]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-351	465	2.06	2
	I-352	520	1.78	2
	I-353	506	1.77	2
	I-354	521	2.47	2
	I-355	493	2.10	2

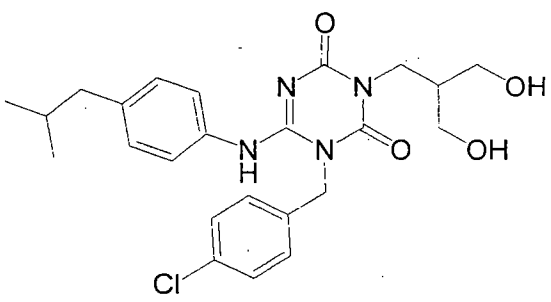
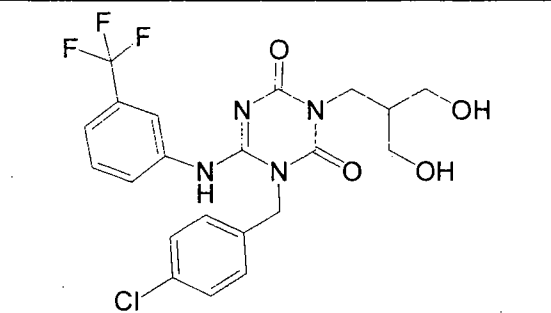
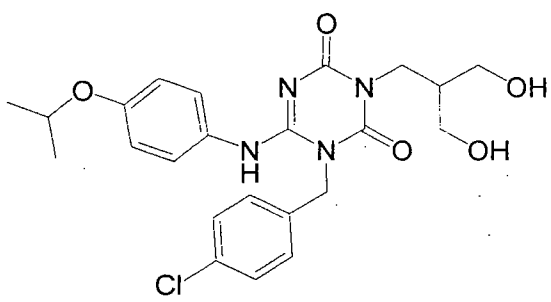
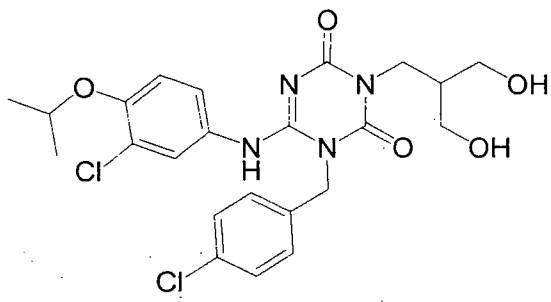
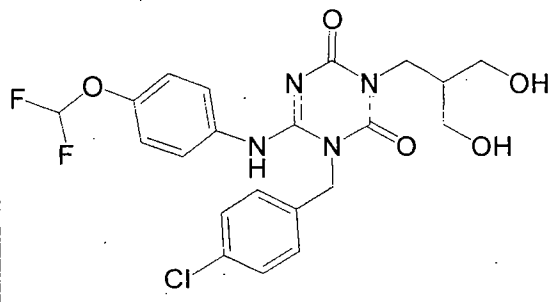
[Table 75]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-356	505	2.33	2
	I-357	455	2.07	2
	I-358	442	2.23	2
	I-359	445	1.85	2
	I-360	453	1.84	2

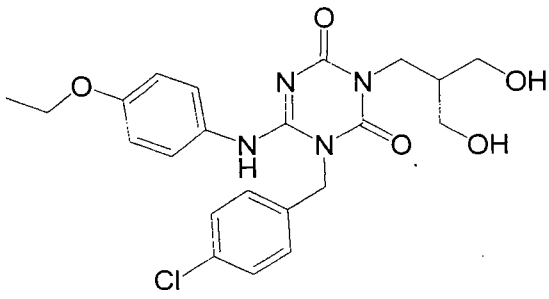
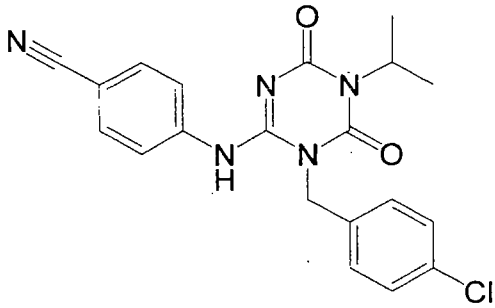
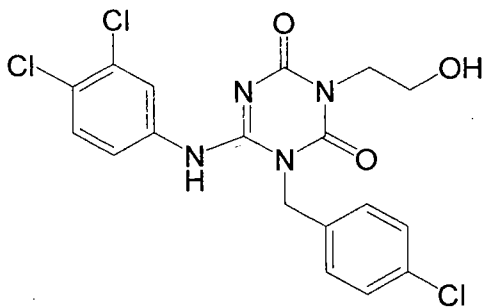
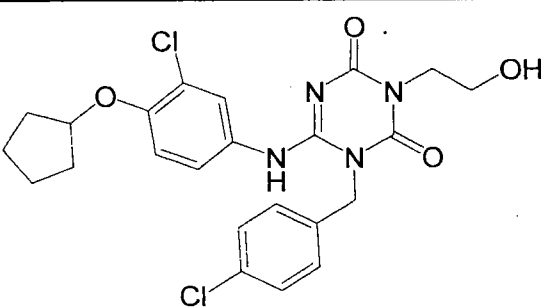
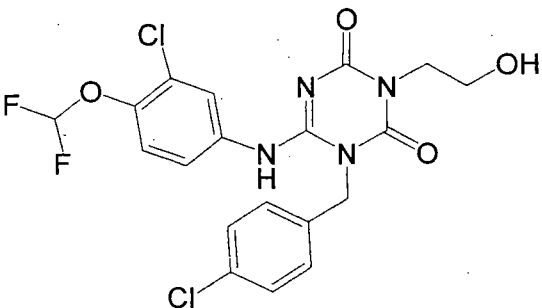
[Table 76]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-361	431	1.77	2
	I-362	479	2.12	2
	I-363	491	2.05	2
	I-364	505	2.12	2
	I-365	477	2.03	2

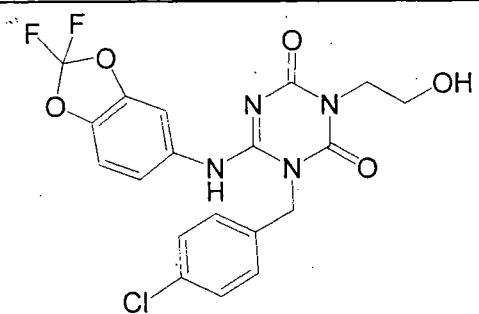
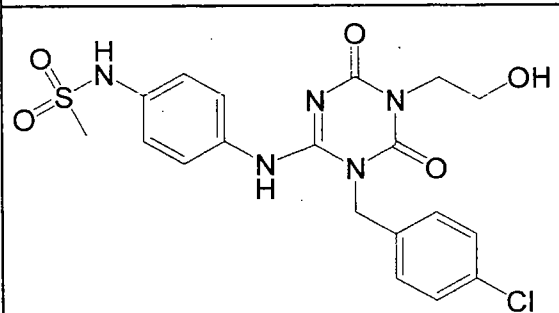
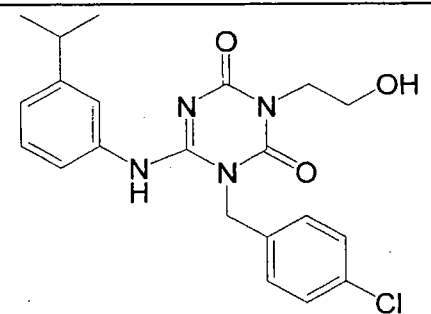
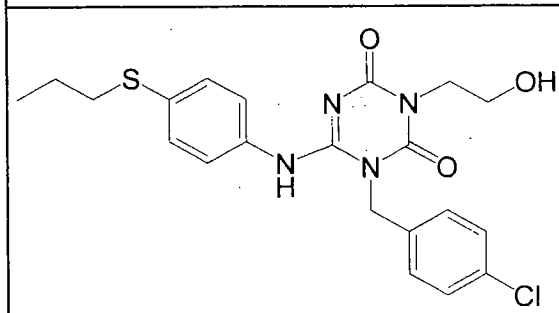
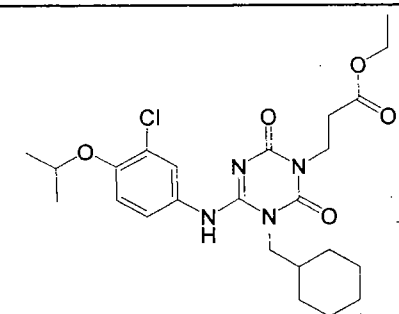
[Table 77]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-366	473	2.33	3
	I-367	485	2.17	3
	I-368	475	2.00	3
	I-369	510	2.24	3
	I-370	483	1.98	3

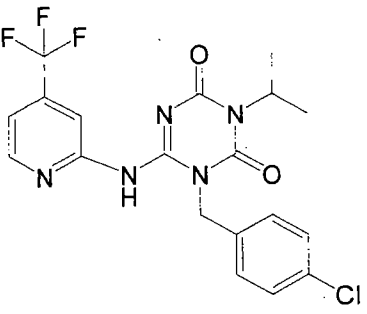
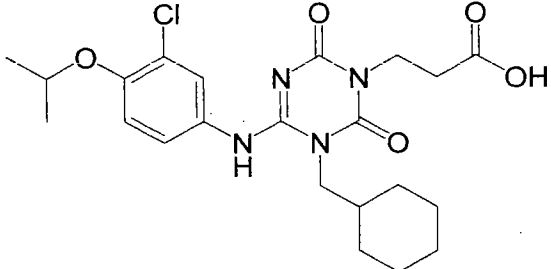
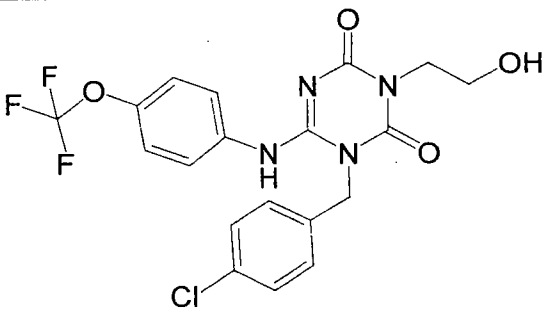
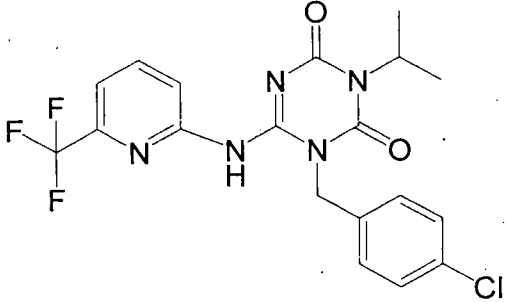
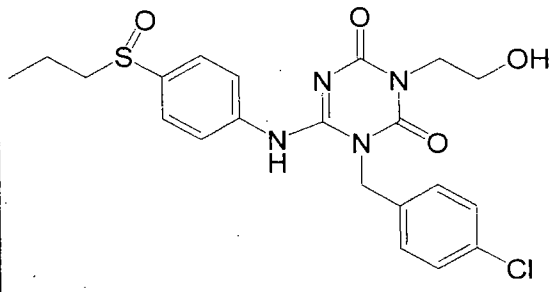
[Table 78]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-371	461	1.88	3
	I-372	396	2.27	2
	I-373	443	2.17	2
	I-374	491	2.28	2
	I-375	473	2.32	3

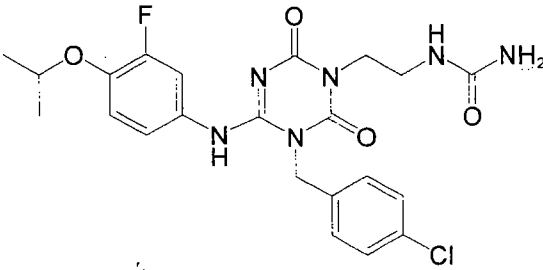
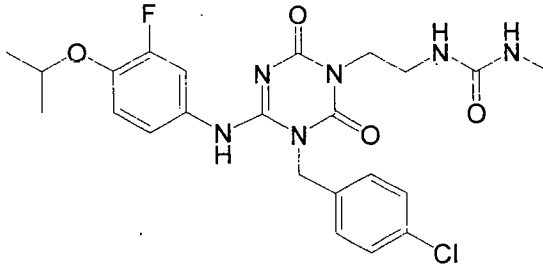
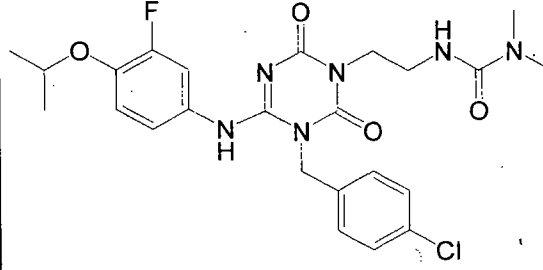
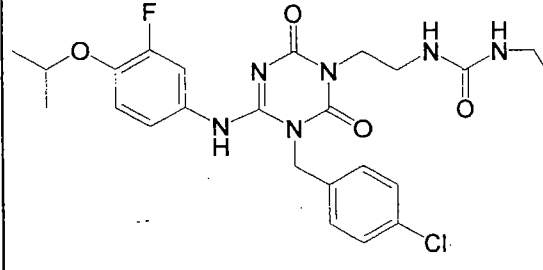
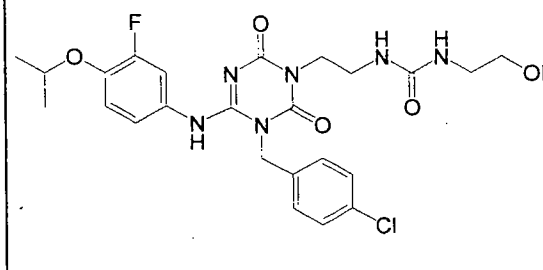
[Table 79]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-376	453	2.30	3
	I-377	446	1.41	2
	I-378	415	2.02	2
	I-379	447	2.11	2
	I-380	493	2.49	2

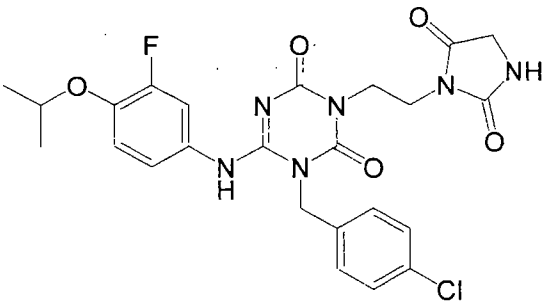
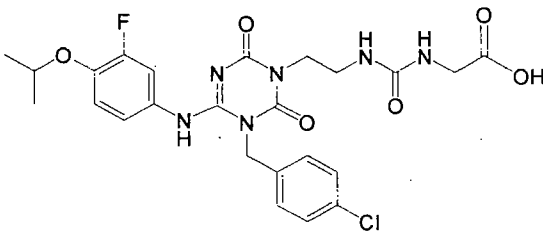
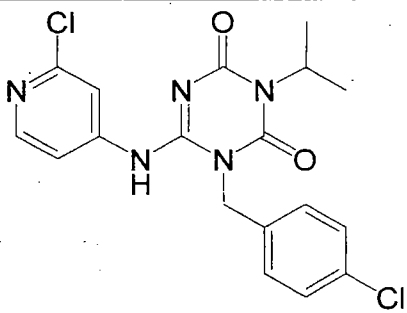
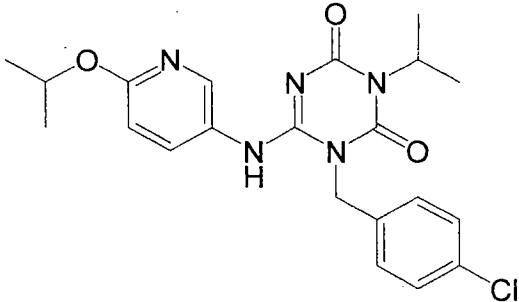
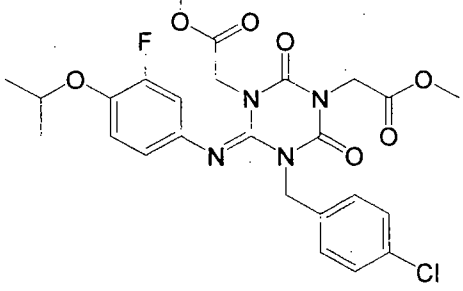
[Table 80]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-381	440	3.04	3
	I-382	465	2.09	2
	I-383	457	2.32	3
	I-384	440	2.77	2
	I-385	463	1.56	2

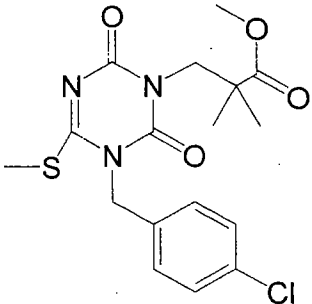
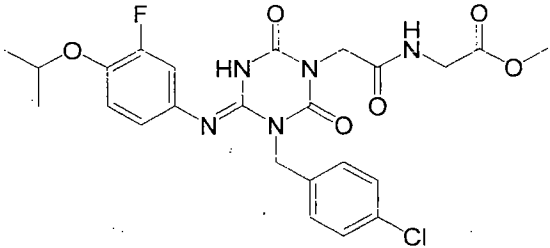
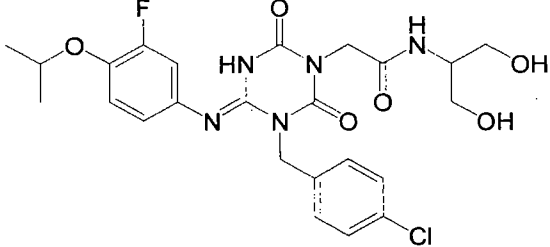
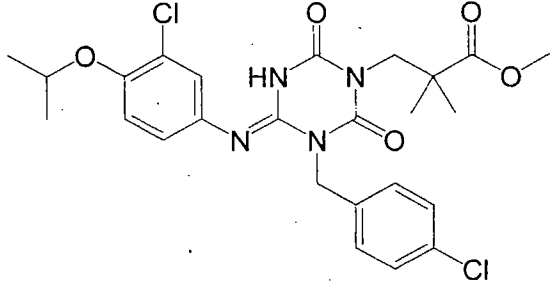
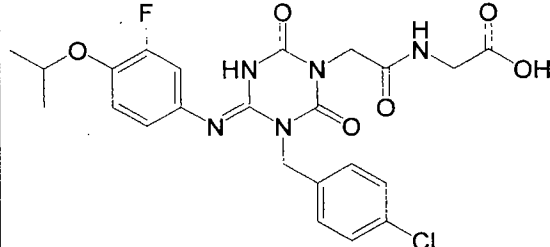
[Table 81]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-386	491	1.81	2
	I-387	505	1.86	2
	I-388	519	1.98	2
	I-389	519	1.94	2
	I-390	535	1.77	2

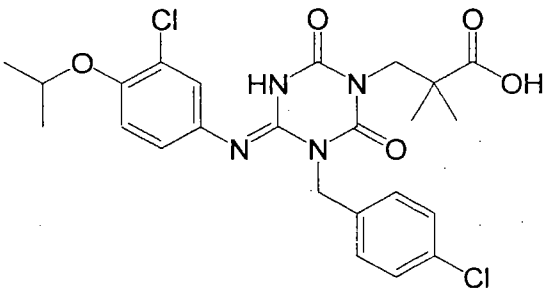
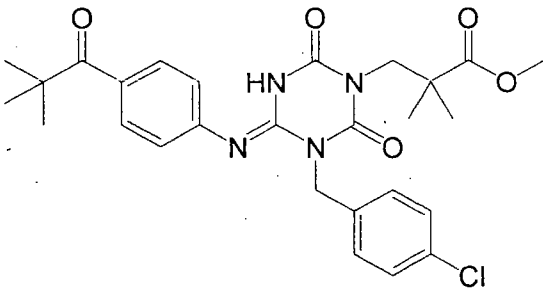
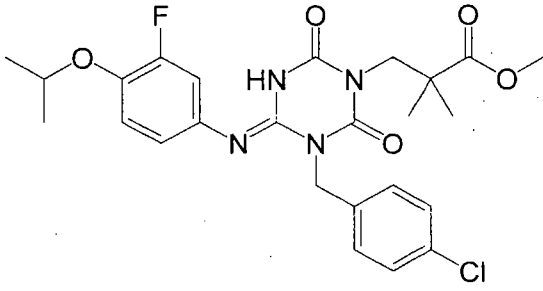
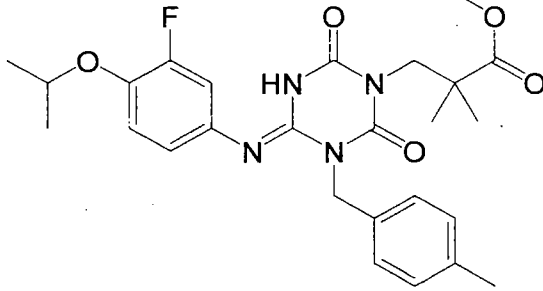
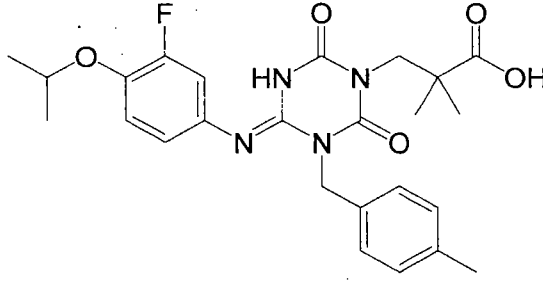
[Table 82]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-391	531	1.89	2
	I-392	549	1.77	2
	I-393	406	2.28	2
	I-394	430	2.30	2
	I-395	549	2.77	3

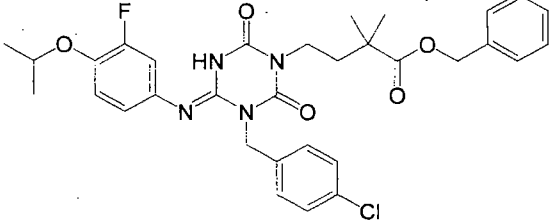
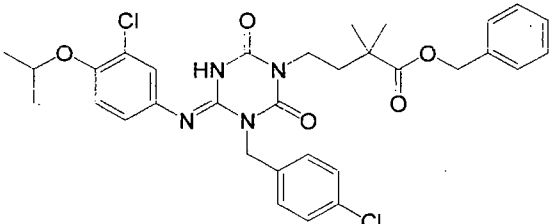
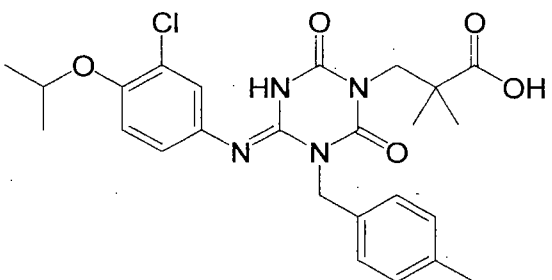
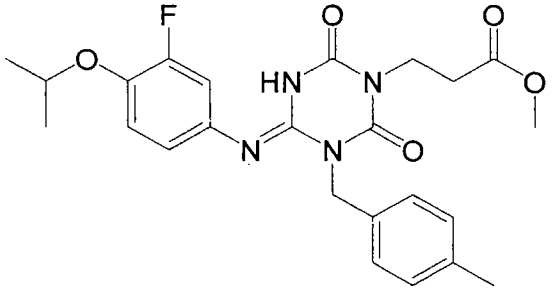
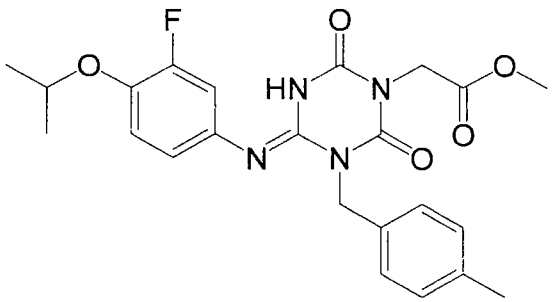
[Table 83]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-396	398	2.03	2
	I-397	534	1.94	2
	I-398	536	1.69	2
	I-399	535	2.51	2
	I-400	520	1.81	2

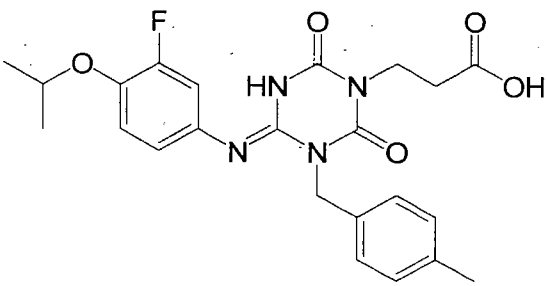
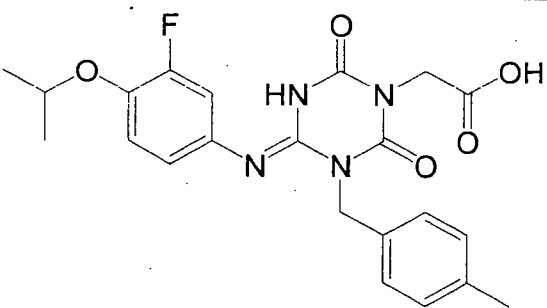
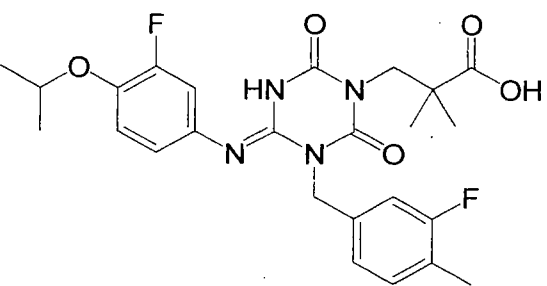
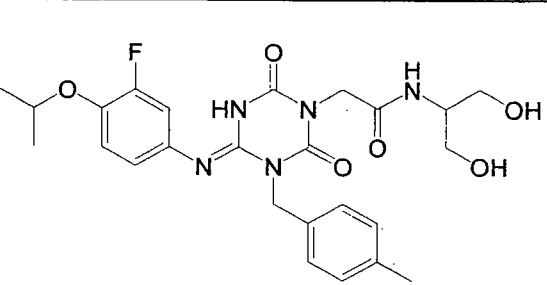
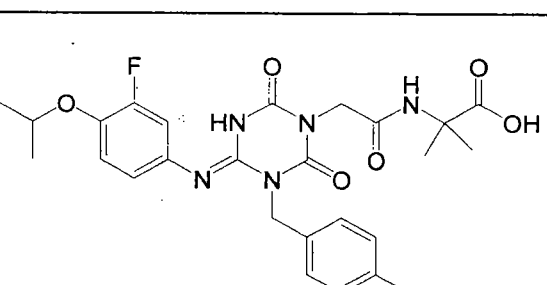
[Table 84]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-401	521	2.24	2
	I-402	527	2.49	2
	I-403	519	2.40	2
	I-404	499	2.32	2
	I-405	485	2.04	2

[Table 85]

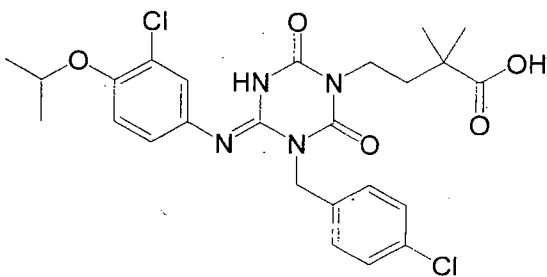
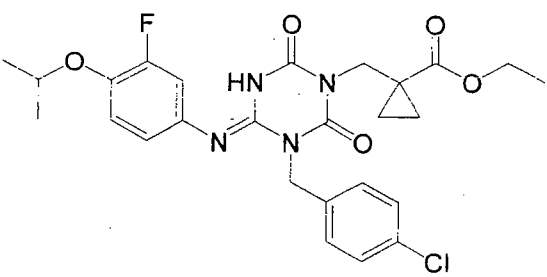
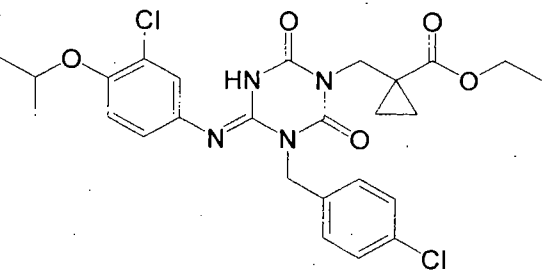
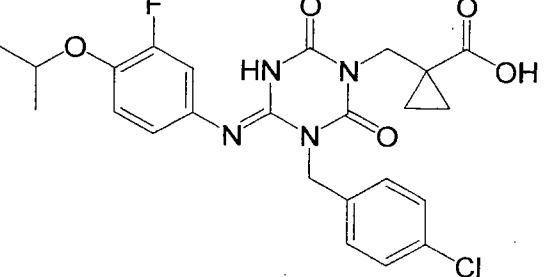
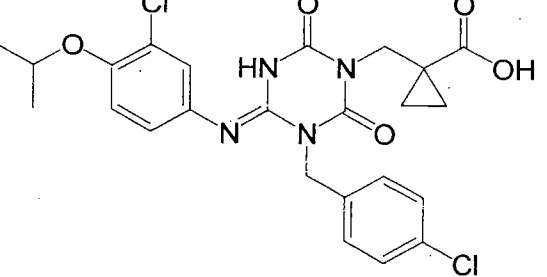
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-406	609	2.74	2
	I-407	625	2.84	2
	I-408	501	2.16	2
	I-409	471	2.13	2
	I-410	457	2.09	2

[Table 86]

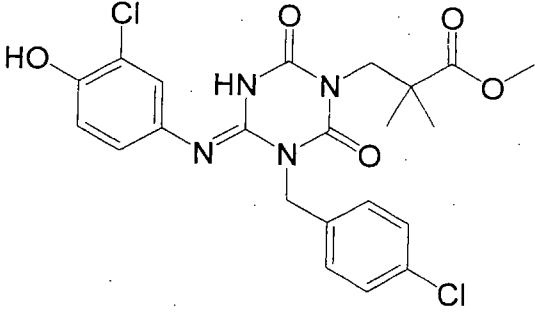
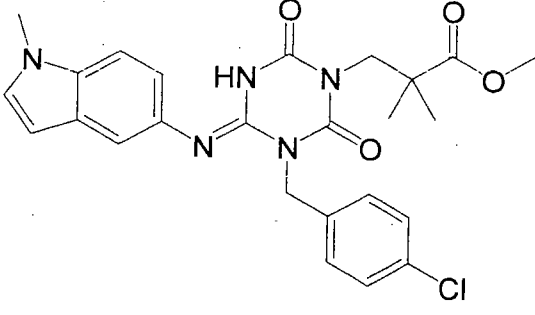
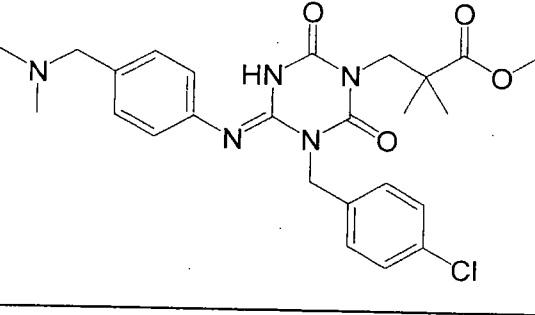
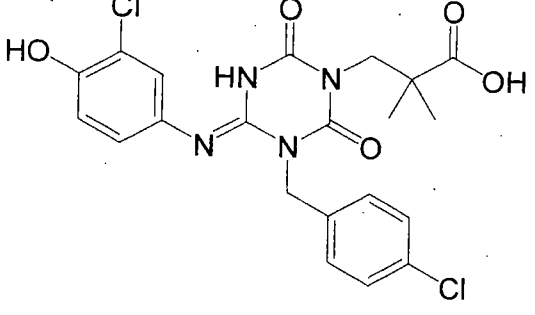
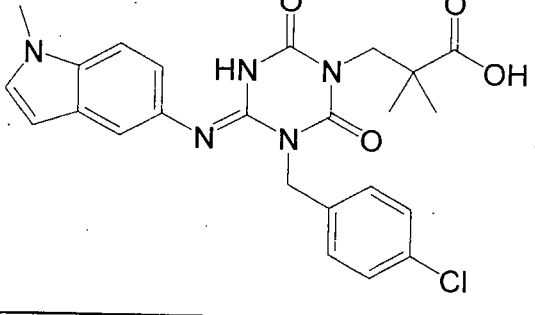
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-411	457	1.92	2
	I-412	443	1.87	2
	I-413	503	2.10	2
	I-414	516	1.63	2
	I-415	528	1.84	2

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-416	500	1.74	2
	I-417	514	1.78	2
	I-418	514	1.79	2
	I-419	526	1.78	2
	I-420	519	2.21	2

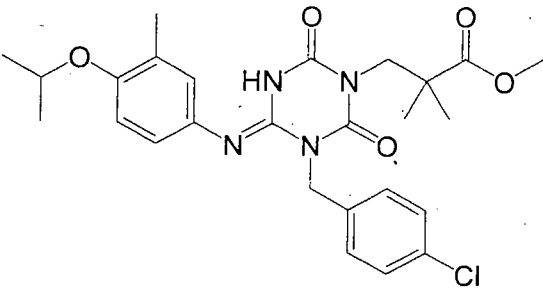
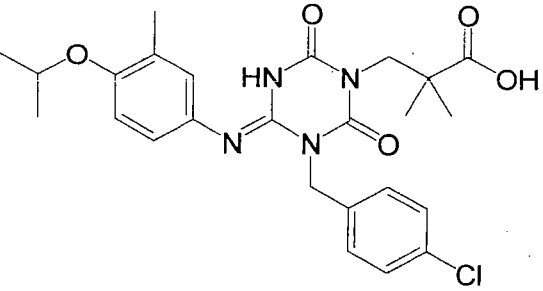
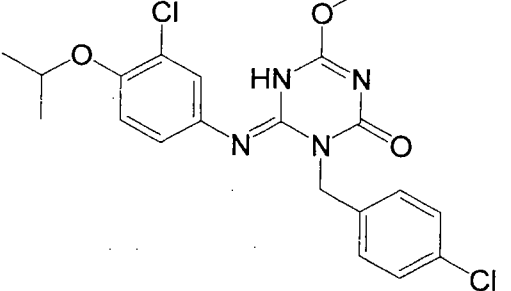
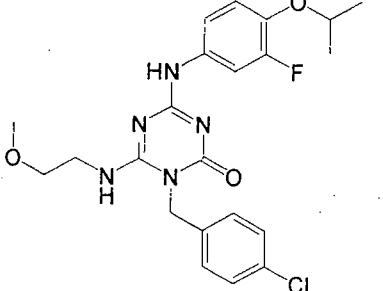
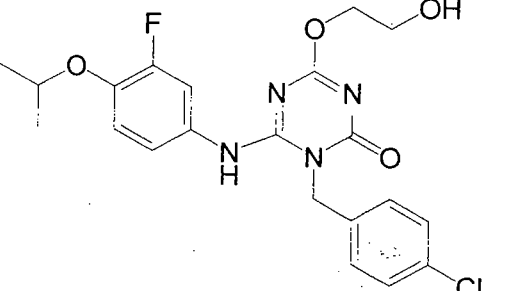
[Table 88]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-421	535	2.32	2
	I-422	531	2.45	2
	I-423	547	2.53	2
	I-424	503	2.09	2
	I-425	519	2.20	2

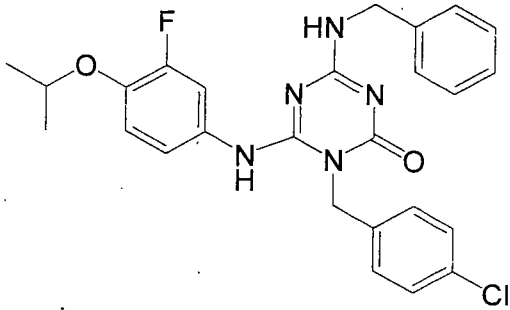
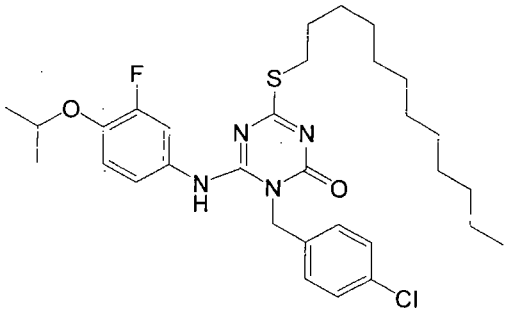
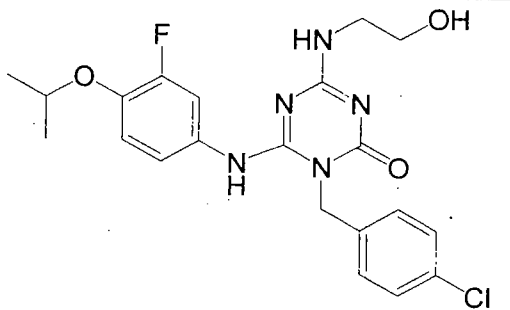
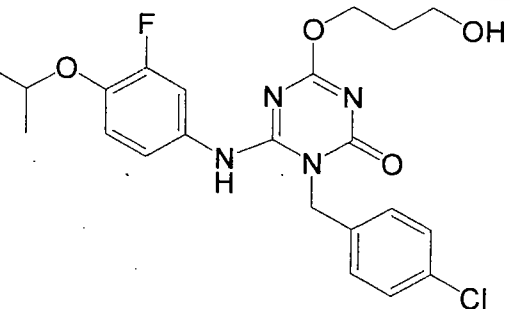
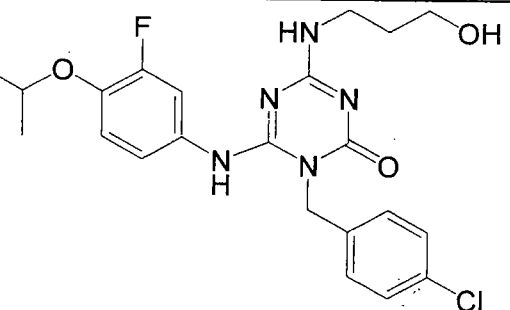
[Table 89]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-426	493	1.99	2
	I-427	496	2.12	2
	I-428	500	1.25	2
	I-429	479	1.72	2
	I-430	482	1.85	2

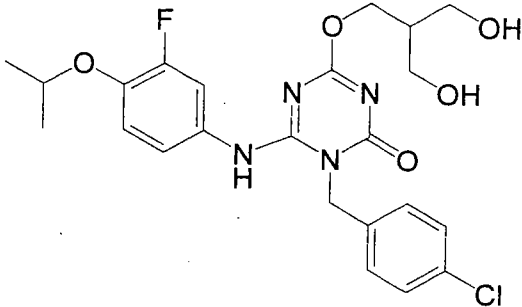
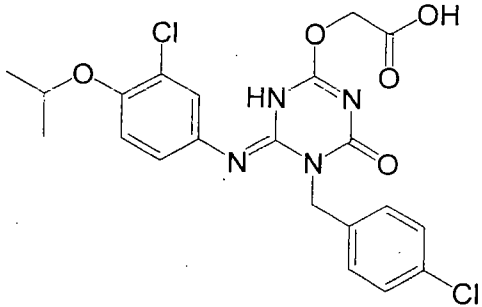
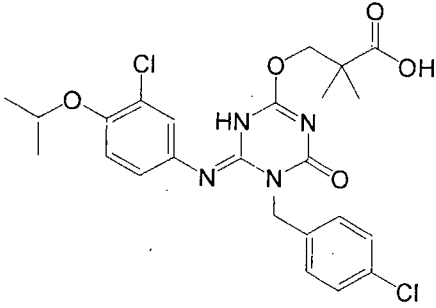
[Table 90]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-431	515	2.44	2
	I-432	501	2.15	2
	I-433	435	2.10	1
	II-001	462	1.79	1
	II-002	449	1.80	1

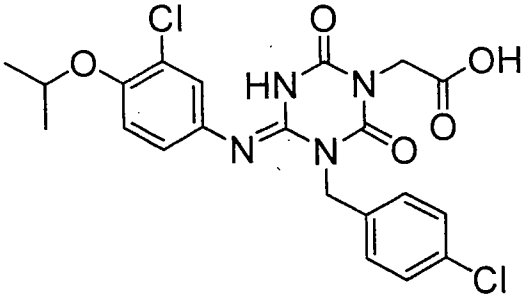
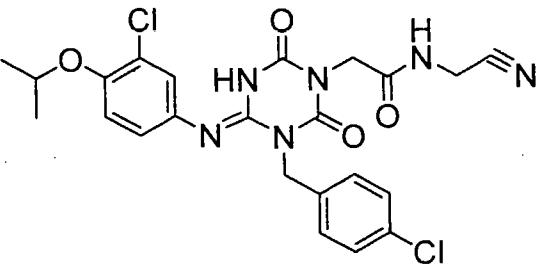
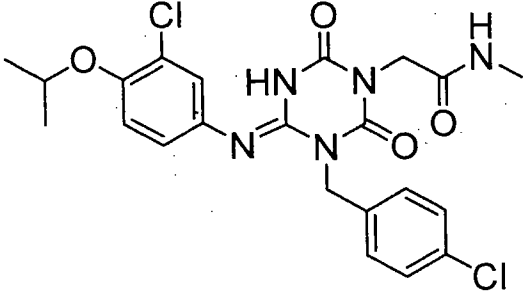
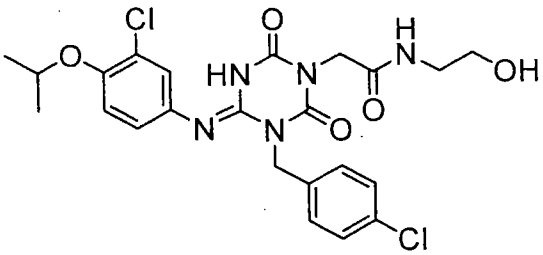
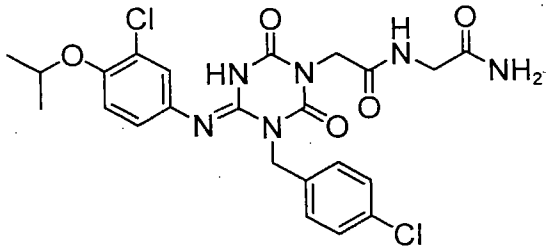
[Table 91]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	II-003	494	1.90	1
	II-004	590	3.40	1
	II-005	448	1.50	2
	II-006	464	1.80	2
	II-007	462	1.50	2

[Table 92]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	II-008	493	1.70	2
	II-009	479	1.88	1
	II-010	521	2.09	1

[Table 93]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-434	479	2.06	2
	I-435	517	2.21	3
	I-436	492	2.16	3
	I-437	522	2.03	3
	I-438	535	1.98	3

[Table 94]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-439	515	2.11	3
	I-440	533	1.87	3
	I-441	521	2.43	2
	I-442	487	2.23	2
	I-443	509	2.5	3

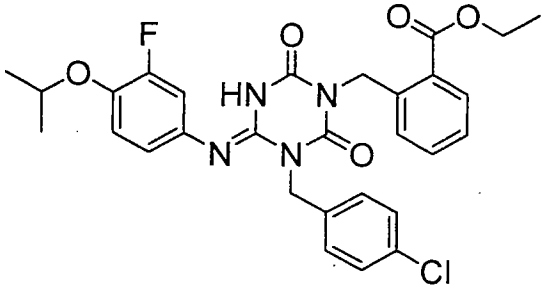
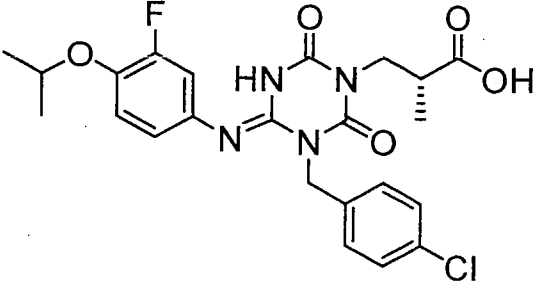
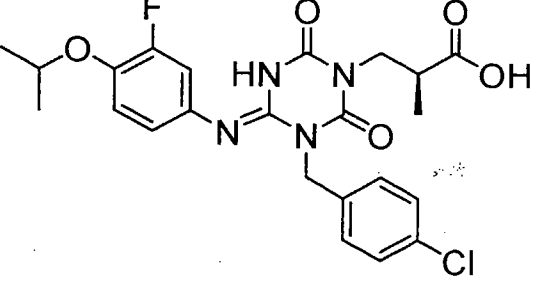
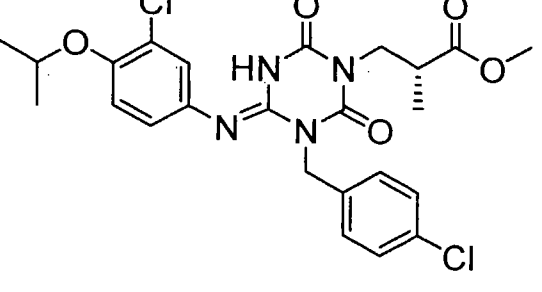
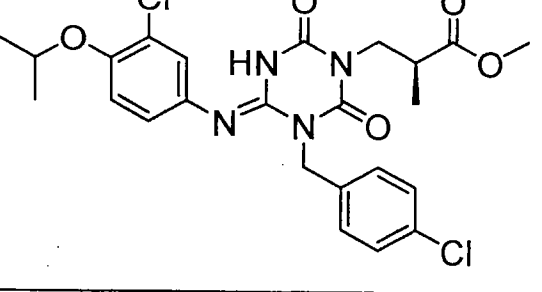
[Table 95]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-444	553	2.61	3
	I-445	539	2.33	3
	I-446	507	2.31	2
	I-447	473	2.1	2
	I-448	495	2.22	2

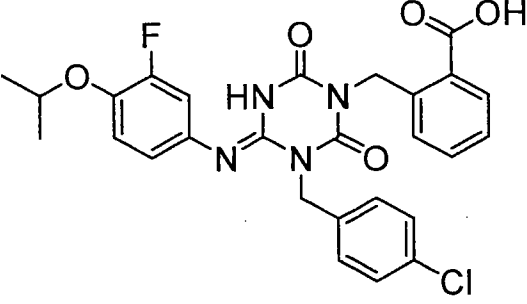
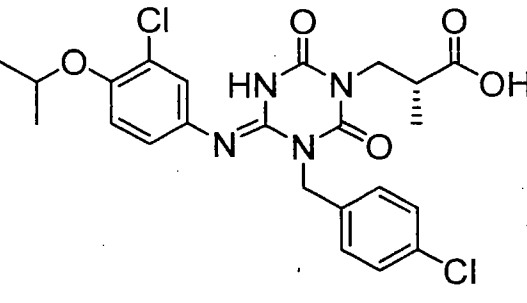
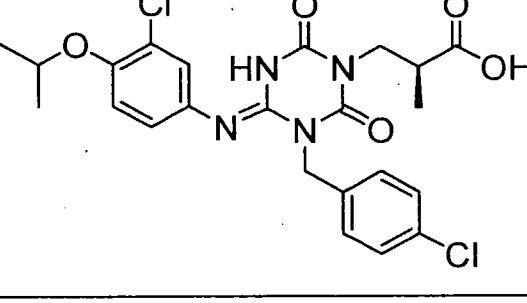
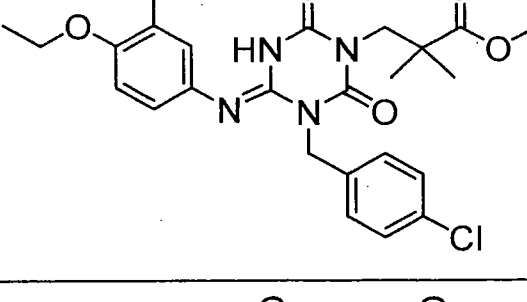
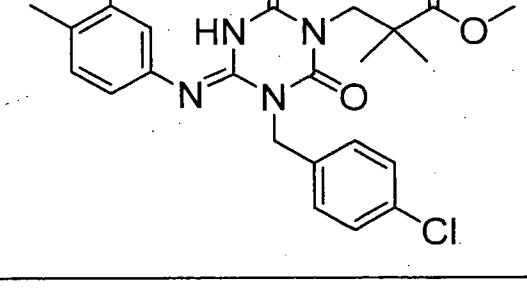
[Table 96]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-449	511	2.67	2
	I-450	553	2.63	3
	I-451	539	2.36	3
	I-452	505	2.29	2
	I-453	505	2.3	2

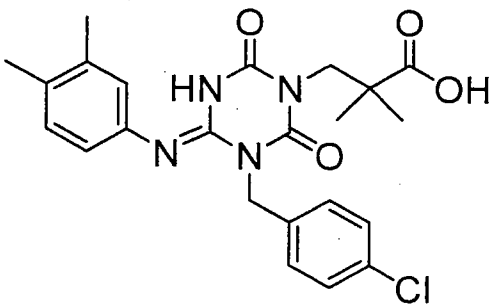
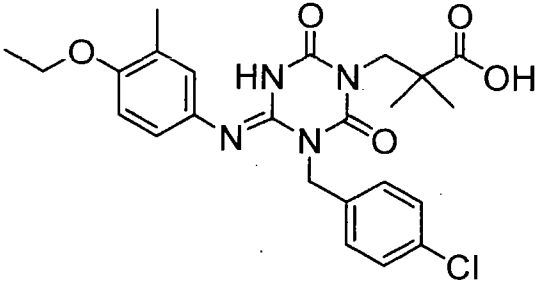
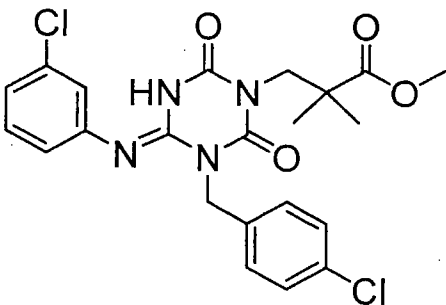
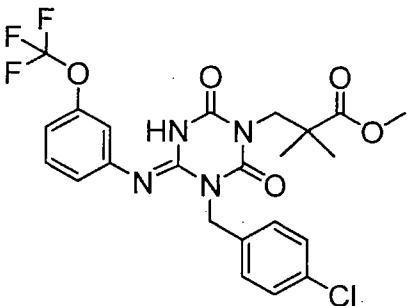
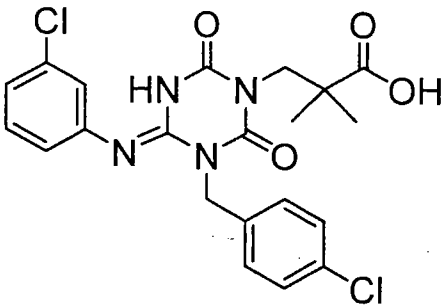
[Table 97]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-454	567	2.74	3
	I-455	491	2.22	3
	I-456	491	2.22	3
	I-457	521	2.41	2
	I-458	521	2.41	2

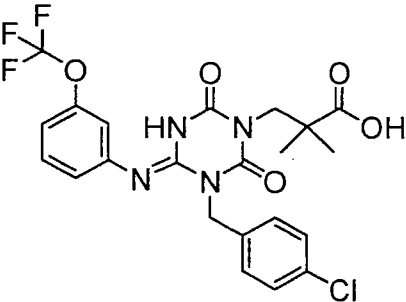
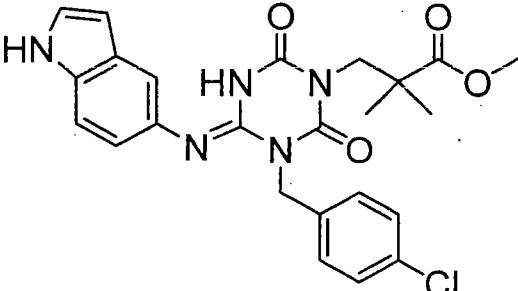
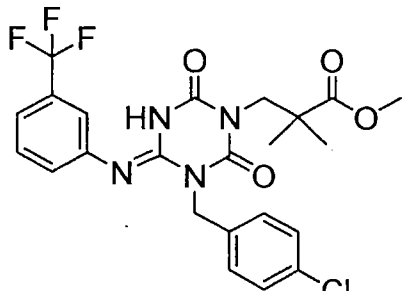
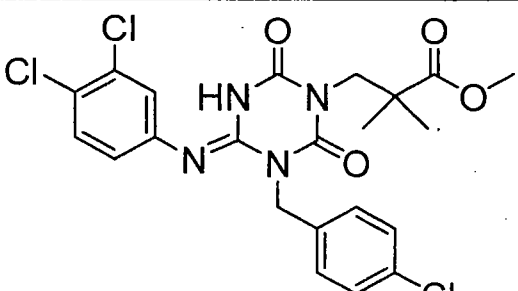
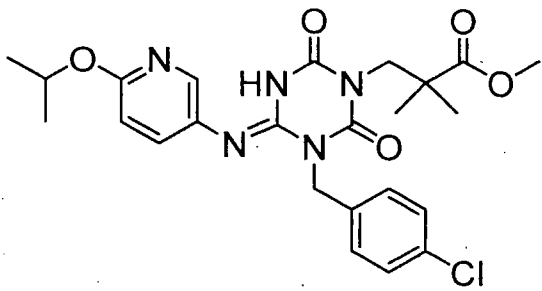
[Table 98]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-459	539	2.38	3
	I-460	507	2.34	3
	I-461	507	2.33	3
	I-462	501	2.33	2
	I-463	471	2.31	2

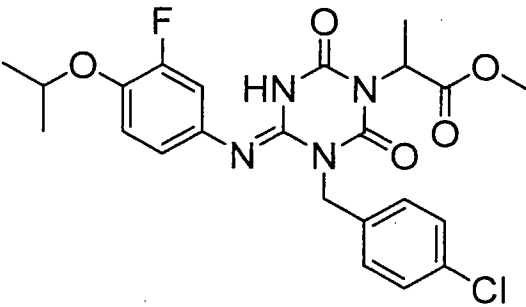
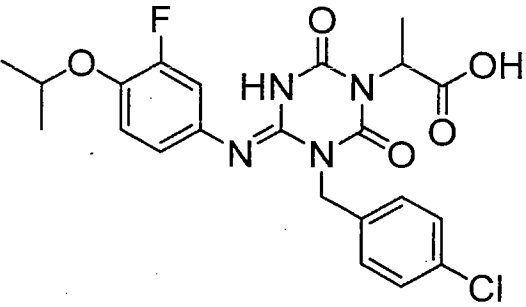
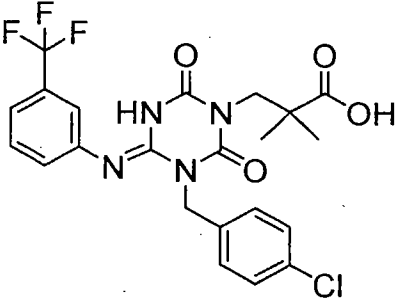
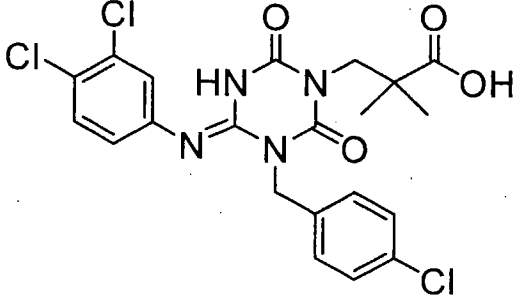
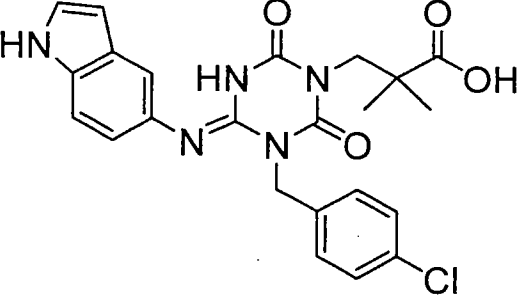
[Table 99]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-464	457	2.02	2
	I-465	487	2.06	2
	I-466	477	2.41	2
	I-467	527	2.5	2
	I-468	463	2.29	3

[Table 100]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-469	513	2.41	3
	I-470	482	2.15	3
	I-471	511	2.63	3
	I-472	512	2.75	3
	I-473	502	1.78	2

[Table 101]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-474	491	2.42	3
	I-475	477	2.18	3
	I-476	497	2.2	2
	I-477	499	2.31	2
	I-478	468	1.71	2

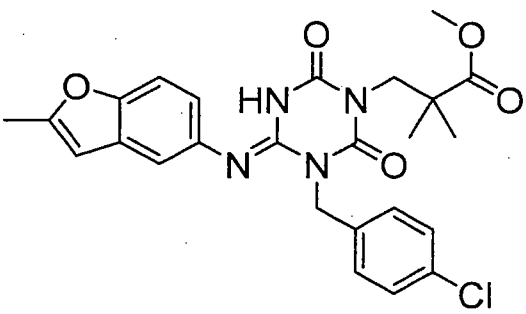
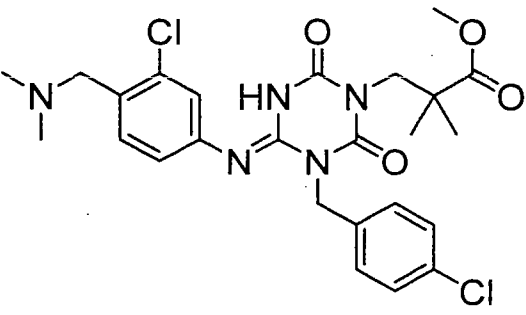
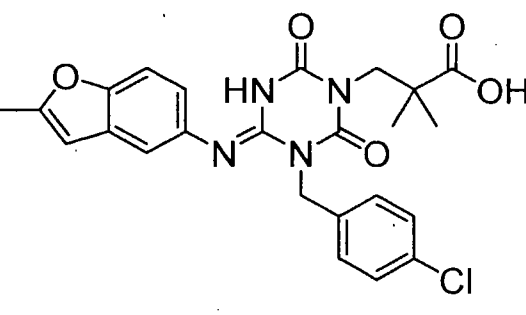
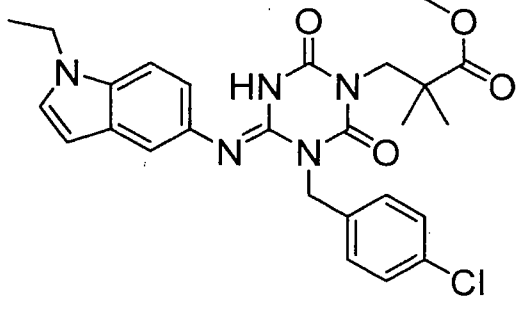
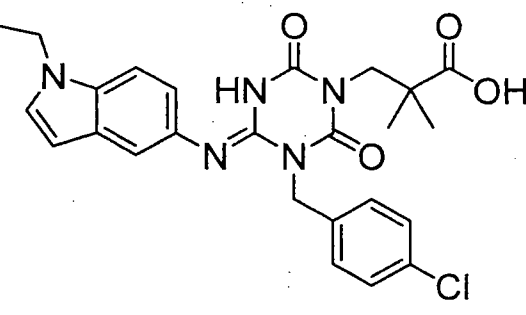
[Table 102]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-479	487	2.17	2
	I-480	473	2.06	2
	I-481	487	2.22	2
	I-482	488	1.53	2
	I-483	473	1.93	2

[Table 103]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-484	459	1.82	2
	I-485	473	1.98	2
	I-486	487	2.08	2
	I-487	493	2.03	2
	I-488	498	1.98	2

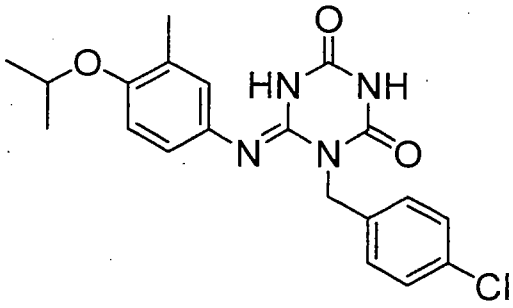
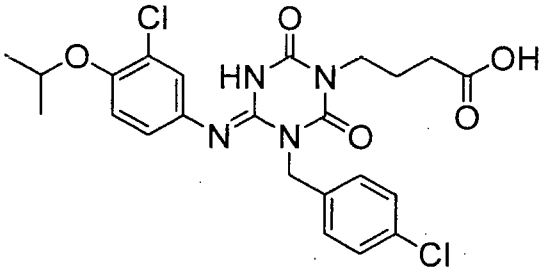
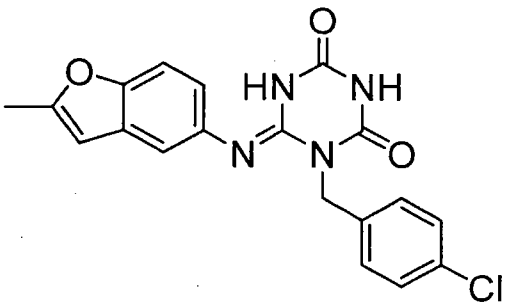
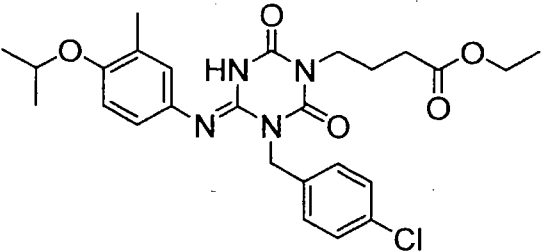
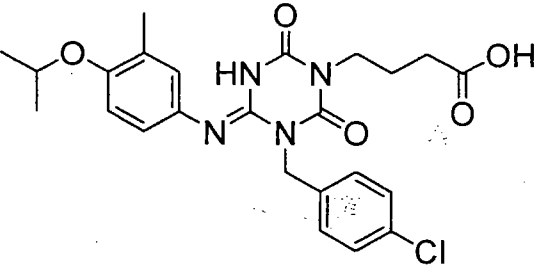
[Table 104]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-489	497	2.28	2
	I-490	534	1.62	2
	I-491	483	2	2
	I-492	510	2.23	2
	I-493	496	1.96	2

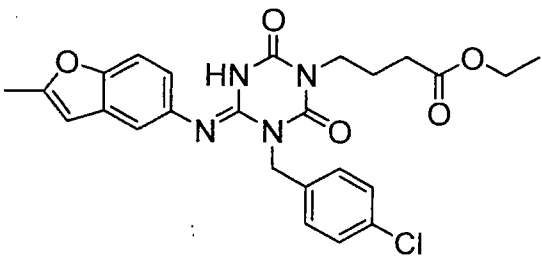
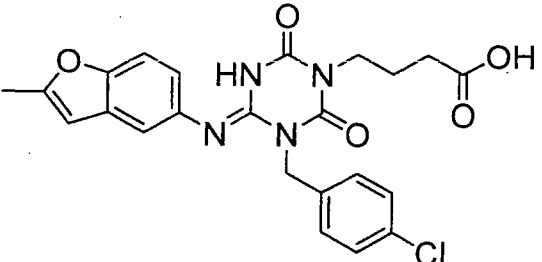
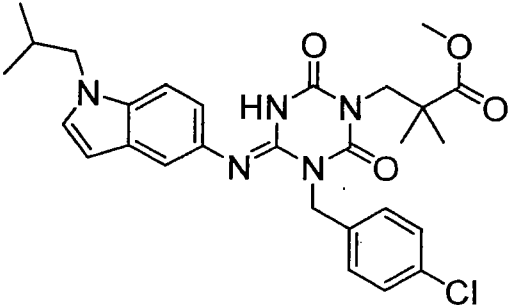
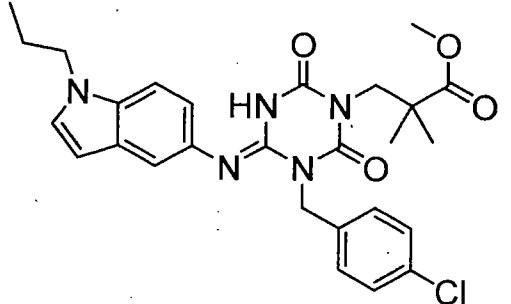
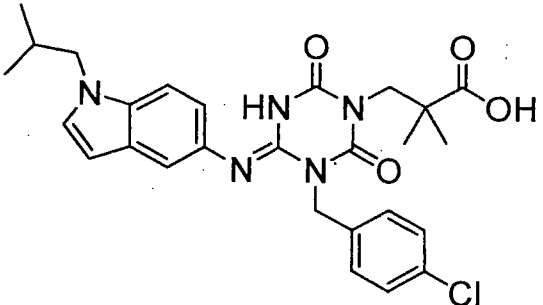
[Table 105]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-494	498	2.04	2
	I-495	520	1.43	2
	I-496	484	1.75	2
	I-497	484	1.74	2
	I-498	535	2.5	2

[Table 106]

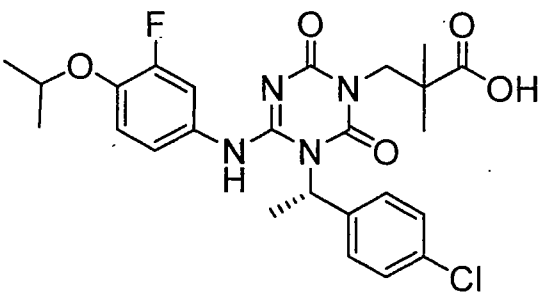
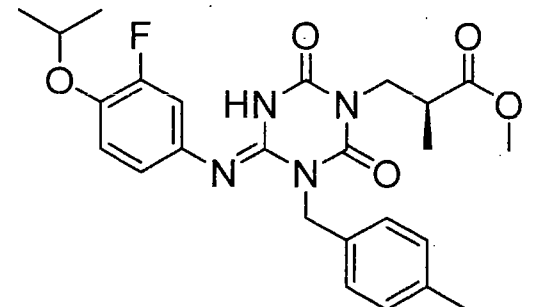
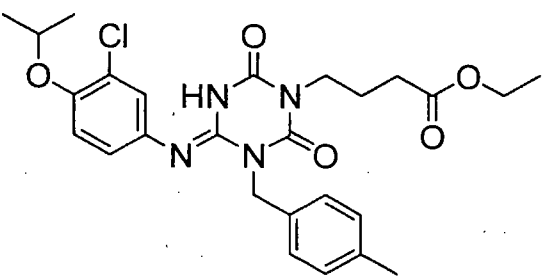
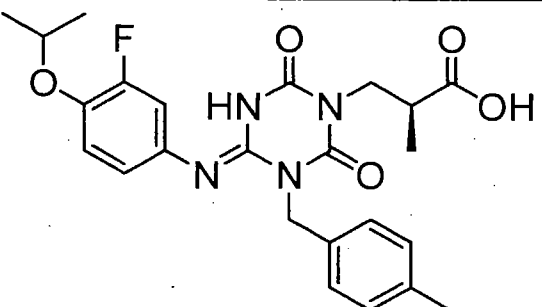
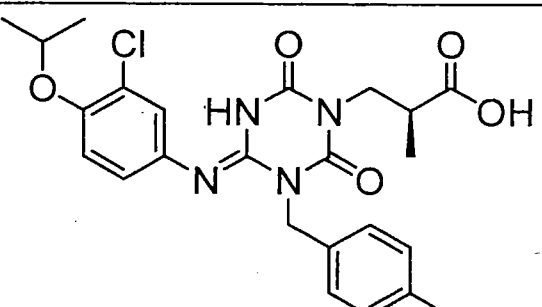
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-499	401	2.03	2
	I-500	507	2.13	2
	I-501	383	1.85	2
	I-502	515	2.41	2
	I-503	487	2.06	2

[Table 107]

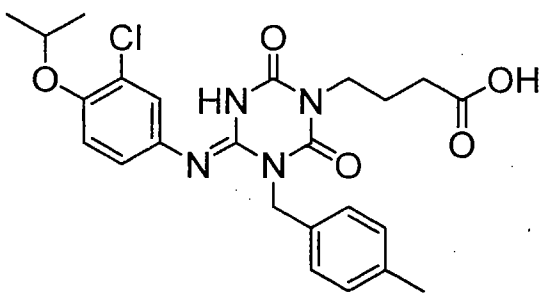
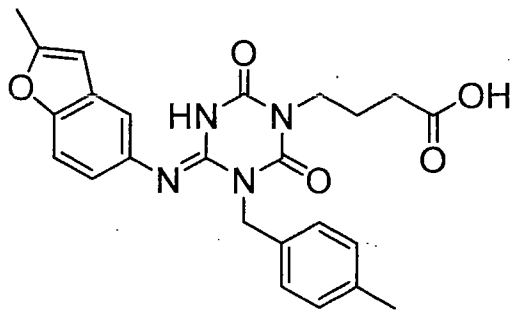
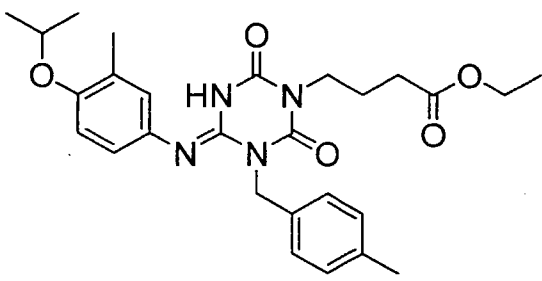
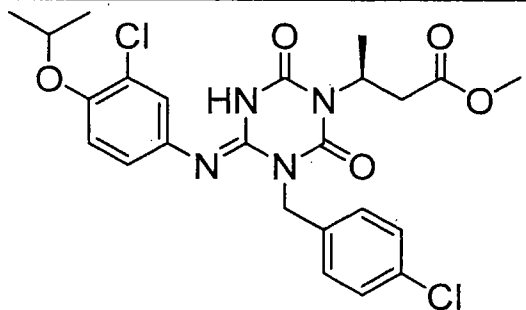
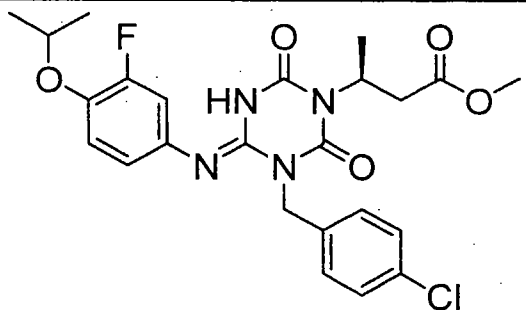
Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-504	497	2.25	2
	I-505	469	1.89	2
	I-506	538	2.44	2
	I-507	524	2.34	2
	I-508	524	2.17	2

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-509	510	2.07	2
	I-510	475	2.23	3
	I-511	441	2.67	3
	I-512	533	2.75	3
	I-513	533	2.75	3

[Table 109]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-514	519	2.5	3
	I-515	485	2.4	3
	I-516	516	2.62	3
	I-517	471	2.18	3
	I-518	487	2.28	3

[Table 110]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-519	487	2.25	3
	I-520	449	2	3
	I-521	495	2.55	3
	I-522	521	2.64	3
	I-523	505	2.53	3

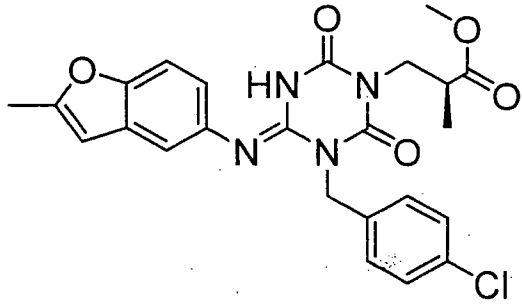
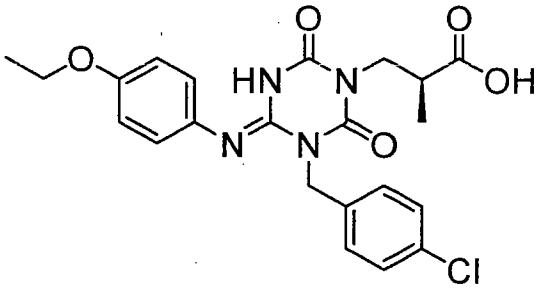
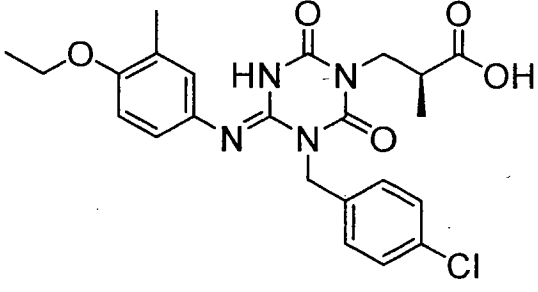
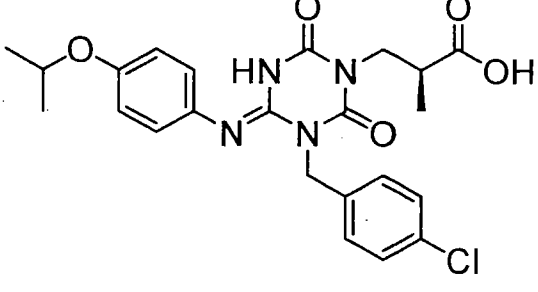
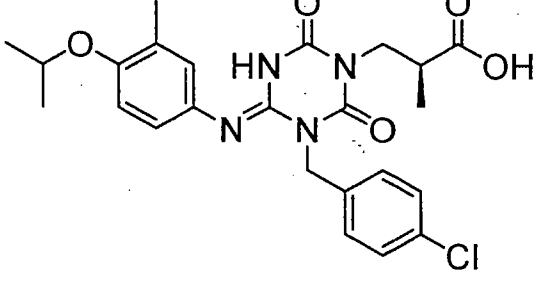
[Table 111]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-524	501	2.57	3
	I-525	467	2.2	3
	I-526	507	2.38	3
	I-527	491	2.26	3
	I-528	487	2.3	3

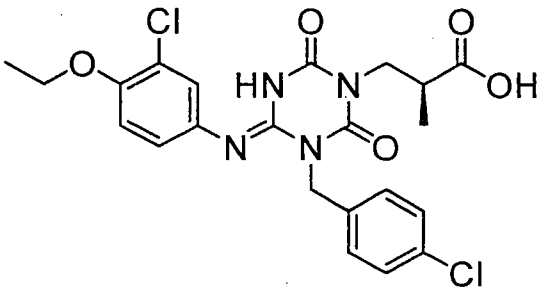
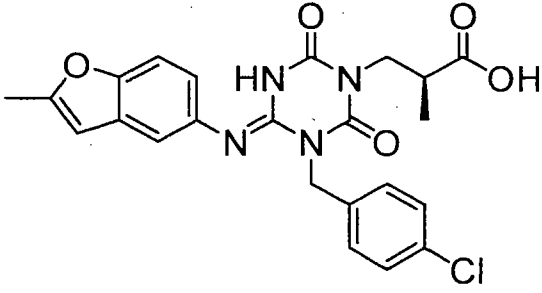
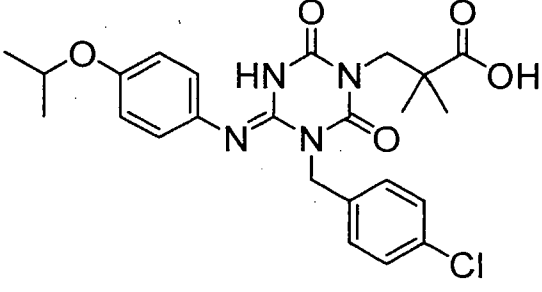
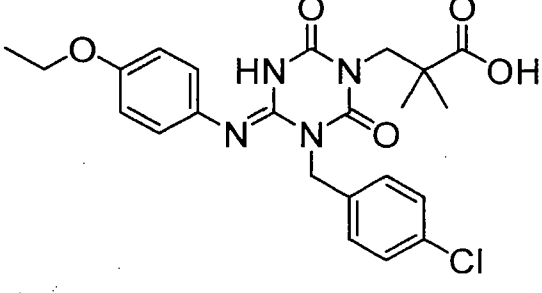
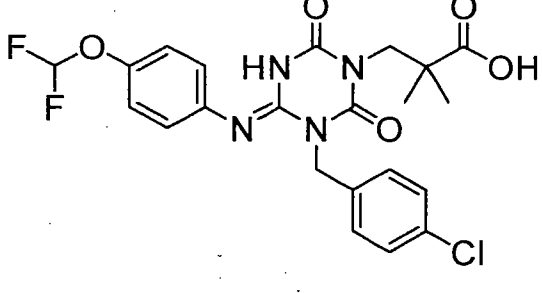
[Table 112]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-529	487	2.18	2
	I-530	473	2.07	2
	I-531	501	2.33	2
	I-532	487	2.23	2
	I-533	507	2.29	2

[Table 113]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-534	483	2.16	2
	I-535	459	1.82	2
	I-536	473	1.98	2
	I-537	473	1.91	2
	I-538	487	2.09	2

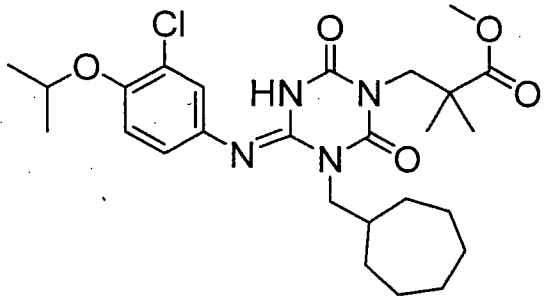
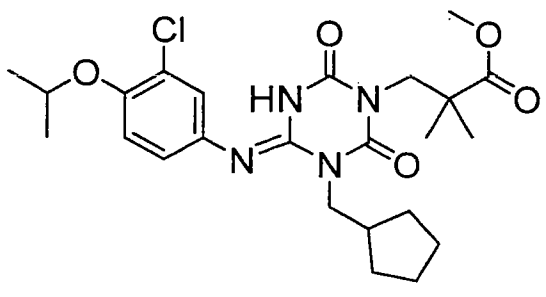
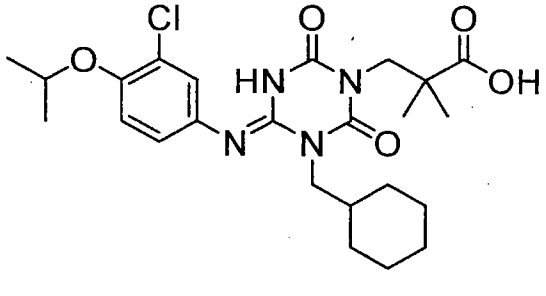
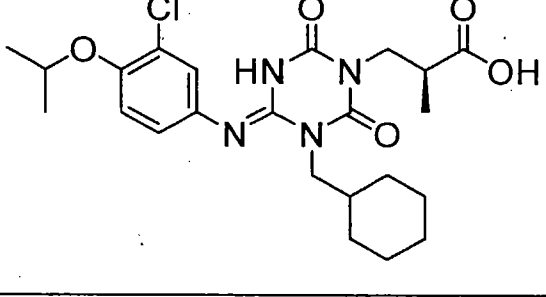
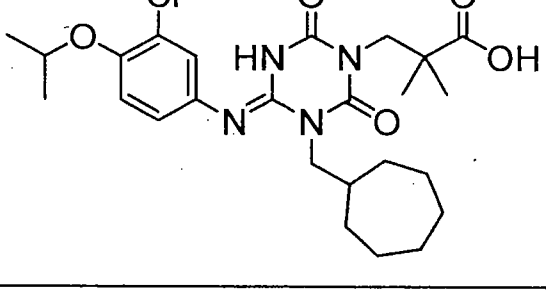
[Table 114]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-539	493	2.03	2
	I-540	469	1.91	2
	I-541	487	1.99	2
	I-542	473	1.9	2
	I-543	495	1.97	2

[Table 115]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-544	475	1.99	2
	I-545	533	2.41	2
	I-546	547	2.76	2
	I-547	507	2.53	2
	I-548	493	2.42	2

[Table 116]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-549	521	2.65	2
	I-550	493	2.43	2
	I-551	493	2.23	2
	I-552	479	2.16	2
	I-553	507	2.35	2

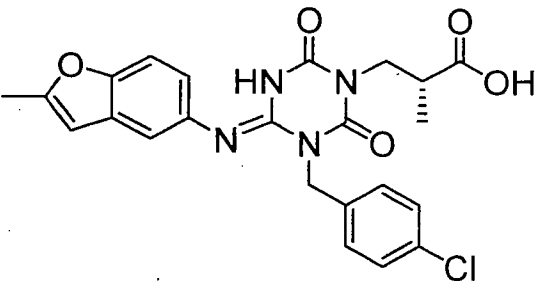
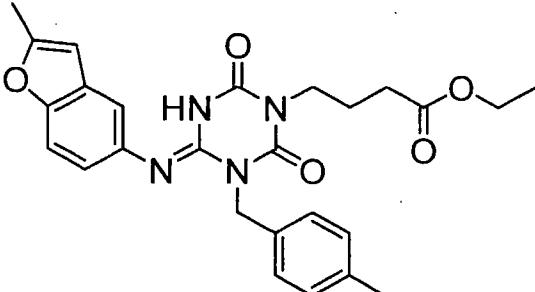
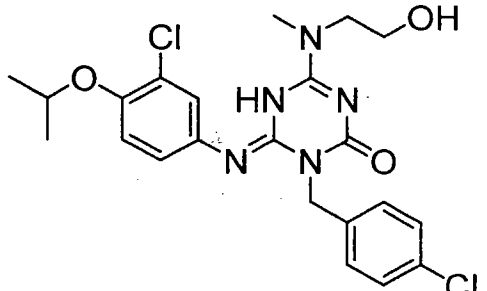
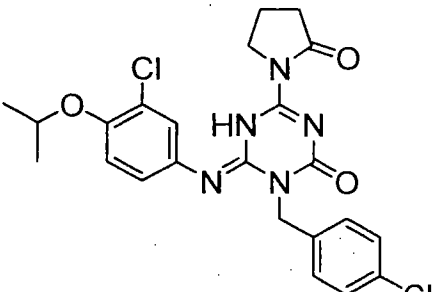
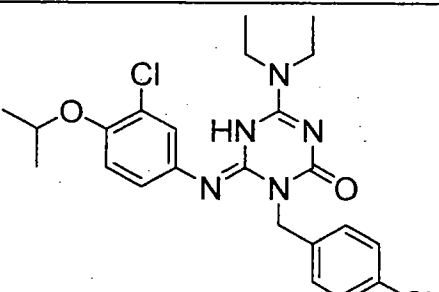
[Table 117]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-554	479	2.12	2
	I-555	473	2.37	2
	I-556	521	2.44	2
	I-557	501	2.37	2
	I-558	483	2.16	2

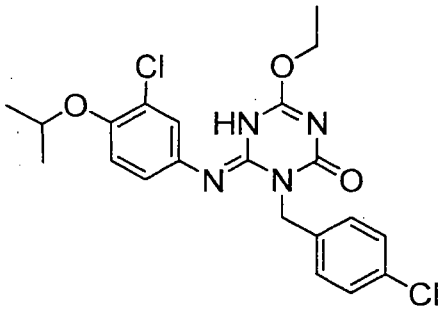
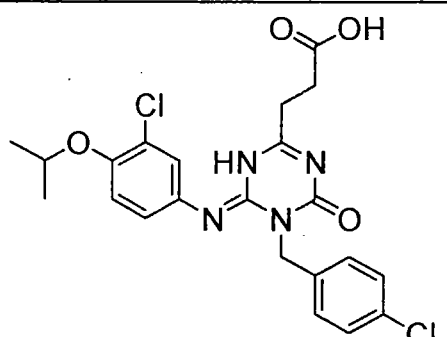
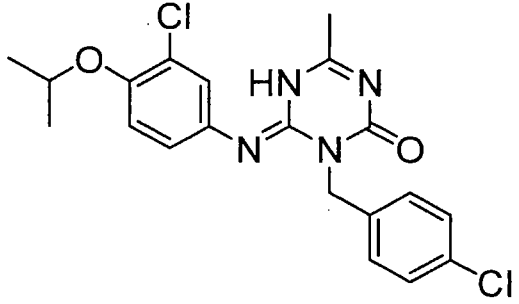
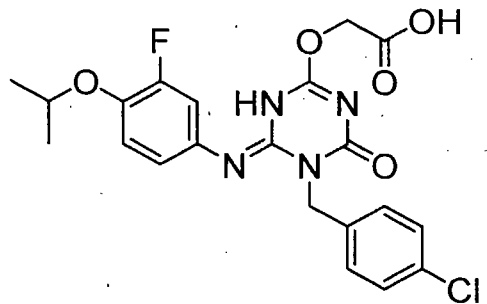
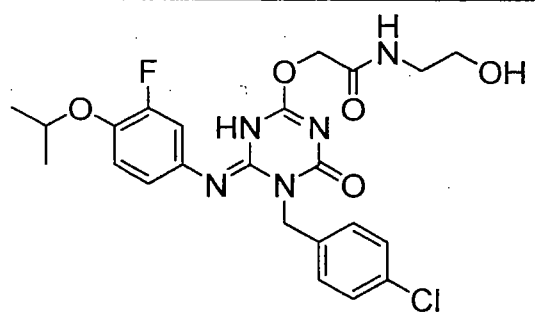
[Table 118]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-559	459	2.09	2
	I-560	505	2.34	2
	I-561	507	2.18	2
	I-562	491	2.28	3
	I-563	487	2.32	3

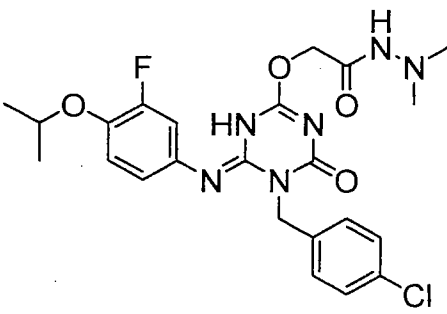
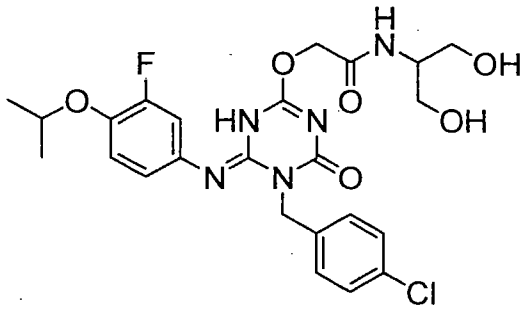
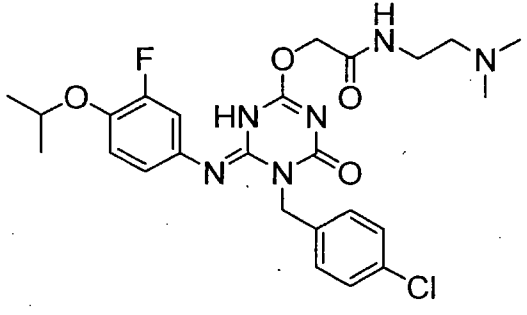
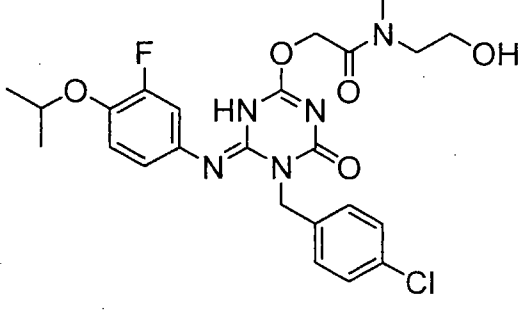
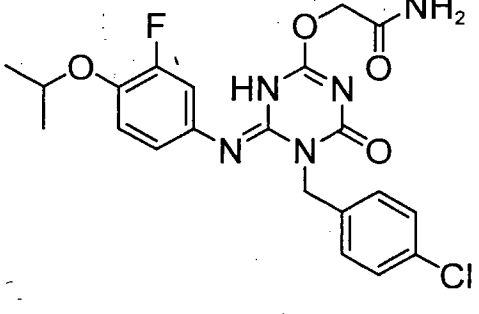
[Table 119]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	I-564	469	2.11	3
	I-565	477	2.41	3
	II-011	478	1.74	2
	II-012	488	2.44	2
	II-013	476	2.04	2

[Table 120]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	II-014	449	2.21	2
	II-015	477	2.07	2
	II-016	419	2.28	2
	II-017	463	1.78	2
	II-018	506	1.62	2

[Table 121]

Chemical Structure	Compound No.	[M+H]	Retention time (min)	Method
	II-019	505	1.72	2
	II-020	536	1.56	2
	II-021	533	1.4	2
	II-022	520	1.65	2
	II-023	462	1.66	2

[0143]

Test Examples

Stably expressing cell line (C6BU-1 cell transfected with human P2X₃ receptor gene (GenBank accession number Y07683)) was used. The cells were seeded in a 96-well microtiter plate at a concentration of 8000 cells/well and cultured in the medium (8.3% fetal bovine serum, 8.3% horse serum, 1% antibiotic and antifungal in DMEM) for one day at 37 °C under 5 % carbon dioxide atmosphere. The medium was replaced with 4 μ M Fluo-3-AM solution (pH7.5) containing 20 mM HEPES, 137 mM NaCl, 2.7 mM KCl, 0.9 mM MgCl₂, 5.0 mM CaCl₂, 5.6 mM D-glucose, 2.5 mM probenecid, 10% BSA, and 0.08% Pluronic F-127, and incubated at 37°C under 5% dioxide carbon atmosphere for one hour. The plate was washed with washing buffer (20 mM HEPES, 137 mM NaCl, 2.7 mM KCl, 0.9 mM MgCl₂, 5.0 mM CaCl₂, 5.6 mM D-glucose, 2.5mM probenecid, pH7.5), and each well was added with 40 μ L of this buffer. The plate was placed in High-Throughput Screening System FDSS 3000 (Hamamatsu Photonics K.K.). Measurement of fluorescence intensity by FDSS 3000 was started, and 40 μ L of DMSO solutions containing different concentrations of the test compound as prepared by dilution with dilution buffer (20 mM HEPES, 137 mM NaCl, 2.7 mM KCl, 0.9 mM MgCl₂, 5.0 mM CaCl₂, 5.6 mM D-glucose, 2.5 mM probenecid, 0.1% Pluronic F-127, pH7.5) were dispensed to each well through the built-in automatic dispenser. Five minutes after, 40 nM ATP solution (50 μ L) prepared by dilution with the dilution buffer was dispensed through the built-in automatic dispenser, and the measurement of fluorescence intensity was continued for 3 min. For each well, the specific maximum fluorescence intensity was calculated as the ratio of the maximum fluorescence intensity after addition of the ATP solution to the fluorescence intensity at the starting of the measurement. The 50% inhibitory concentration (IC₅₀) was calculated under the assumption that the specific maximum fluorescence intensity without test compound is 0% inhibition and that the specific maximum fluorescence intensity when the dilution buffer was added in place of ATP solution is 100% inhibition, to evaluate the inhibitory activity of the test compound. FDSS software (Hamamatsu Photonics K.K.) was used for calculation of the specific maximum fluorescence intensity. IC₅₀ was calculated using Microsoft™ Excel™ (Microsoft Corporation) and XLfit™ (ID Business Solutions Ltd.)

The results of the compounds of the invention are shown in the following tables.

[0144]

[Table122]

Compound No.	P2X3 IC50(μ M)	Compound No.	P2X3 IC50(μ M)	Compound No.	P2X3 IC50(μ M)	Compound No.	P2X3 IC50(μ M)
I-020	0.389	I-271	0.032	I-329	0.266	I-383	0.532
I-021	0.197	I-272	0.180	I-330	0.594	I-385	0.908
I-029	0.595	I-273	0.038	I-331	0.066	I-386	0.041
I-097	0.505	I-274	0.009	I-332	0.008	I-387	0.037
I-116	0.484	I-275	0.021	I-333	0.192	I-388	0.036
I-117	0.387	I-276	0.012	I-334	0.099	I-389	0.064
I-118	0.231	I-277	0.038	I-335	0.007	I-390	0.067
I-121	0.246	I-278	0.931	I-338	0.053	I-391	0.133
I-123	0.815	I-280	0.030	I-339	0.775	I-392	0.038
I-126	0.689	I-281	0.012	I-340	0.336	I-394	0.435
I-128	0.840	I-282	0.027	I-341	0.149	I-397	0.019
I-130	0.953	I-283	0.019	I-342	0.005	I-398	0.007
I-133	0.339	I-284	0.629	I-343	0.021	I-399	0.008
I-138	0.619	I-285	0.014	I-344	0.128	I-400	0.044
I-141	0.685	I-286	0.277	I-346	0.016	I-401	0.007
I-162	0.379	I-287	0.222	I-347	0.251	I-402	0.443
I-164	0.860	I-288	0.093	I-348	0.013	I-403	0.015
I-181	0.985	I-289	0.066	I-349	0.113	I-404	0.012
I-182	0.714	I-290	0.266	I-350	0.010	I-405	0.032
I-200	0.128	I-291	0.009	I-351	0.015	I-406	0.030
I-203	0.110	I-292	0.034	I-352	0.036	I-407	0.027
I-204	0.558	I-293	0.351	I-353	0.018	I-408	0.010
I-217	0.268	I-294	0.040	I-354	0.008	I-409	0.012
I-218	0.505	I-295	0.046	I-355	0.020	I-410	0.044
I-221	0.276	I-296	0.176	I-356	0.012	I-411	0.061
I-223	0.909	I-297	0.045	I-357	0.047	I-413	0.099
I-227	0.970	I-298	0.027	I-358	0.055	I-414	0.007
I-228	0.031	I-299	0.046	I-359	0.040	I-415	0.314
I-234	0.298	I-300	0.025	I-360	0.148	I-416	0.035
I-235	0.985	I-301	0.048	I-361	0.076	I-417	0.035
I-237	0.230	I-305	0.946	I-362	0.007	I-418	0.200
I-238	0.658	I-307	0.250	I-363	0.078	I-419	0.071
I-239	0.116	I-309	0.357	I-364	0.030	I-420	0.053
I-240	0.953	I-310	0.389	I-365	0.018	I-421	0.019
I-241	0.447	I-311	0.142	I-366	0.046	I-422	0.006
I-242	0.787	I-312	0.104	I-367	0.040	I-423	0.004
I-243	0.450	I-313	0.178	I-368	0.041	I-424	0.049
I-244	0.045	I-314	0.555	I-369	0.007	I-425	0.016
I-245	0.168	I-315	0.183	I-370	0.154	I-426	0.211
I-246	0.996	I-316	0.712	I-371	0.063	I-427	0.678
I-248	0.420	I-317	0.137	I-372	0.964	I-429	0.779
I-254	0.144	I-320	0.083	I-373	0.185	I-431	0.004
I-255	0.520	I-321	0.033	I-374	0.080	I-432	0.026
I-256	0.867	I-322	0.112	I-375	0.152	I-433	0.199
I-257	0.682	I-323	0.148	I-377	0.755	II-002	0.079
I-258	0.683	I-324	0.309	I-378	0.347	II-006	0.398
I-266	0.861	I-325	0.665	I-379	0.330	II-008	0.943
I-269	0.415	I-326	0.011	I-380	0.034	II-009	0.034
I-270	0.271	I-328	0.124	I-382	0.096	II-010	0.349

[Table123]

Compound No.	P2X3 IC50(μ M)	Compound No.	P2X3 IC50(μ M)	Compound No.	P2X3 IC50(μ M)	Compound No.	P2X3 IC50(μ M)
I-434	0.407	I-468	0.137	I-502	0.020	I-539	0.007
I-435	0.006	I-469	0.101	I-503	0.050	I-540	0.027
I-436	0.008	I-470	0.080	I-504	0.015	I-541	0.058
I-437	0.006	I-471	0.024	I-505	0.120	I-542	0.096
I-438	0.005	I-472	0.047	I-506	0.279	I-543	0.172
I-439	0.018	I-473	0.583	I-507	0.301	I-544	0.601
I-440	0.055	I-474	0.014	I-508	0.511	I-545	0.006
I-441	0.011	I-475	0.571	I-509	0.652	I-546	0.459
I-442	0.117	I-476	0.035	I-510	0.098	I-547	0.011
I-443	0.207	I-477	0.056	I-515	0.006	I-548	0.012
I-444	0.017	I-478	0.629	I-516	0.005	I-549	0.019
I-445	0.008	I-479	0.007	I-517	0.015	I-550	0.033
I-446	0.020	I-480	0.012	I-518	0.007	I-551	0.034
I-447	0.279	I-481	0.012	I-519	0.012	I-552	0.023
I-448	0.388	I-483	0.100	I-520	0.080	I-553	0.034
I-450	0.036	I-484	0.290	I-521	0.004	I-554	0.139
I-451	0.016	I-485	0.198	I-522	0.029	I-555	0.013
I-452	0.003	I-486	0.042	I-523	0.072	I-556	0.005
I-453	0.005	I-487	0.027	I-524	0.060	I-557	0.019
I-454	0.024	I-488	0.124	I-525	0.054	I-558	0.005
I-455	0.030	I-489	0.010	I-526	0.024	I-559	0.097
I-456	0.008	I-490	0.046	I-527	0.033	I-560	0.007
I-457	0.003	I-491	0.027	I-528	0.053	I-561	0.008
I-458	0.004	I-492	0.102	I-529	0.022	I-562	0.027
I-459	0.039	I-493	0.952	I-530	0.034	I-563	0.040
I-460	0.016	I-494	0.034	I-531	0.010	I-564	0.048
I-461	0.009	I-495	0.125	I-532	0.029	II-012	0.568
I-462	0.004	I-496	0.125	I-533	0.010	II-013	0.430
I-463	0.074	I-497	0.458	I-534	0.018	II-014	0.254
I-464	0.564	I-498	0.009	I-535	0.052	II-015	0.614
I-465	0.057	I-499	0.137	I-536	0.046		
I-466	0.037	I-500	0.013	I-537	0.019		
I-467	0.037	I-501	0.191	I-538	0.016		

[0145]

Test Examples2 CYP3A4 fluorescent MBI test

The CYP3A4 fluorescent MBI test is a test of investigating enhancement of CYP3A4 inhibition of a compound by a metabolism reaction, and the test was performed using, as CYP3A4 enzyme expressed in *Escherichia coli* and employing, as an index, a reaction in which 7-benzyloxytrifluoromethylchmarin (7-BFC) is debenzylated by the CYP3A4 enzyme to produce a metabolite, 7-hydroxytrifluoromethylchmarin (HFC) emitting fluorescent light.

[0146]

The reaction conditions were as follows: substrate, 5.6 μ mol/L 7-BFC; pre-reaction time, 0 or 30 minutes; reaction time, 15 minutes; reaction temperature, 25°C (room temperature); CYP3A4 content (expressed in *Escherichia coli*), at pre-reaction 62.5 pmol/mL, at reaction 6.25 pmol/mL (at 10-fold dilution); test drug concentration, 0.625, 1.25, 2.5, 5, 10, 20 μ mol/L (six points).

[0147]

An enzyme in a K-Pi buffer (pH 7.4) and a test drug solution as a pre-reaction solution were added to a 96-well plate at the composition of the pre-reaction, a part of

it was transferred to another 96-well plate so that it was 1/10 diluted by a substrate in a K-Pi buffer, NADPH as a co-factor was added to initiate a reaction as an index (without preincubation) and, after a predetermined time of a reaction, acetonitrile/0.5 mol/L Tris (trishydroxyaminomethane) = 4/1 was added to stop the reaction. In addition, NADPH was added to a remaining preincubation solution to initiate a preincubation (with preincubation) and, after a predetermined time of a preincubation, a part was transferred to another plate so that it was 1/10 diluted with a substrate and a K-Pi buffer to initiate a reaction as an index. After a predetermined time of a reaction, acetonitrile/0.5 mol/L Tris (trishydroxyaminomethane) = 4/1 was added to stop the reaction. For the plate on which each index reaction had been performed, a fluorescent value of 7-HFC which is a metabolite was measured with a fluorescent plate reader. (Ex = 420 nm, Em = 535 nm).

[0148]

Addition of only DMSO which is a solvent dissolving a drug to a reaction system was adopted as a control (100%), remaining activity (%) was calculated at each concentration of a test drug added as the solution, and IC₅₀ was calculated by reverse-presumption by a logistic model using a concentration and an inhibition rate. When a difference between IC₅₀ values is 5 µM or more, this was defined as (+) and, when the difference is 3 µM or less, this was defined as (-).

[0149]

Test Examples3 CYP inhibition test

Using commercially available pooled human hepatic microsome, and employing, as markers, 7-ethoxyresorufin O-deethylation (CYP1A2), tolbutamide methyl-hydroxylation (CYP2C9), mephenytoin 4'-hydroxylation (CYP2C19), dextromethorphan O-demethylation (CYP2D6), and terfenadine hydroxylation as typical substrate metabolism reactions of human main five CYP enzyme forms (CYP1A2, 2C9, 2C19, 2D6, 3A4), an inhibitory degree of each metabolite production amount by a test compound was assessed.

[0150]

The reaction conditions were as follows: substrate, 0.5 µmol/L ethoxyresorufin (CYP1A2), 100 µmol/L tolbutamide (CYP2C9), 50 µmol/L S-mephenytoin (CYP2C19), 5 µmol/L dextromethorphan (CYP2D6), 1 µmol/L terfenadine (CYP3A4); reaction time, 15 minutes; reaction temperature, 37°C; enzyme, pooled human hepatic microsome 0.2 mg protein/mL; test drug concentration, 1, 5, 10, 20 µmol/L (four points).

[0151]

Each five kinds of substrates, human hepatic microsome, or a test drug in 50 mM Hepes buffer as a reaction solution was added to a 96-well plate at the composition as described above, NADPH, as a cofactor was added to initiate metabolism reactions as markers and, after the incubation at 37°C for 15 minutes, a methanol/acetonitrile = 1/1 (v/v) solution was added to stop the reaction. After the centrifugation at 3000 rpm for 15 minutes, resorufin (CYP1A2 metabolite) in the supernatant was quantified by a fluorescent multilabel counter and tributamide hydroxide (CYP2CP metabolite), mephenytoin 4' hydroxide (CYP2C19 metabolite), dextromethorphan (CYP2D6 metabolite), and terfenadine alcohol (CYP3A4 metabolite) were quantified by LC/MS/MS.

[0152]

Addition of only DMSO being a solvent dissolving a drug to a reaction system was adopted as a control (100%), remaining activity (%) was calculated at each concentration of a test drug added as the solution and IC₅₀ was calculated by reverse

presumption by a logistic model using a concentration and an inhibition rate.
[0153]

Test Examples 4 FAT Test

20 μ L of freezing-stored rat typhoid bacillus (*Salmonella typhimurium* TA98 strain, TA100 strain) was inoculated on 10 mL of a liquid nutrient medium (2.5% Oxoid nutrient broth No.2), and this was cultured before shaking at 37°C for 10 hours. 9 mL of a bacterial solution of the TA98 strain was centrifuged (2000 $\times$ g, 10 minutes) to remove a culturing solution, the bacteria was suspended in 9 mL of a Micro F buffer (K_2HPO_4 : 3.5 g/L, KH_2PO_4 : 1 g/L, $(NH_4)_2SO_4$: 1 g/L, trisodium citrate dehydrate: 0.25 g/L, $MgSO_4 \cdot 7H_2O$: 0.1 g/L), the suspension was added to 110 mL of an Exposure medium (Micro F buffer containing Biotin: 8 μ g/mL, histidine: 0.2 μ g/mL, glucose: 8 mg/mL), and the TA100 strain was added to 120 mL of the Exposure medium relative to 3.16 mL of the bacterial solution to prepare a test bacterial solution. Each 12 μ L of a test substance DMSO solution (8 stage dilution from maximum dose 50 mg/mL at 2-fold ratio), DMSO as a negative control, 50 μ g/mL of 4-nitroquinoline-1-oxide DMSO solution for the TA98 strain, 0.25 μ g/mL of 2-(furyl)-3-(5-nitro-2-furyl)acrylamide DMSO solution for the TA100 strain under the non-metabolism activating condition, 40 μ g/mL of 2-aminoanthracene DMSO solution for the TA98 strain, 20 μ g/mL of 2-aminoanthracene DMSO solution for the TA100 strain under the metabolism activating condition as a positive control, and 588 μ L of the test bacterial solution (a mixed solution of 498 μ L of the test bacterial solution and 90 μ L of S9 mix under the metabolism activating condition) were mixed, and this was shaking-cultured at 37°C for 90 minutes. 460 μ L of the bacterial solution exposed to the test substance was mixed with 2300 μ L of an Indicator medium (Micro F buffer containing biotin: 8 μ g/mL, histidine: 0.2 μ g/mL, glucose: 8 mg/mL, Bromo Cresol Purple: 37.5 μ g/mL), each 50 μ L was dispensed into microplate 48 wells/dose, and this was subjected to stationary culturing at 37°C for 3 days. Since a well containing a bacterium which has obtained the proliferation ability by mutation of an amino acid (histidine) synthesizing enzyme gene turns from purple to yellow due to a pH change, the bacterium proliferation well which has turned to yellow in 48 wells per dose is counted, and was assessed by comparing with a negative control group.
[0154]

Test Examples 5 Solubility test

The solubility of a compound is determined under a condition in which 1% DMSO is added. 10 mM compound solution is prepared using DMSO, and then 6 μ L of the compound solution is added to 594 μ L of artificial intestinal juice in pH 6.8 (to 250 mL of 0.2 mol/L potassium dihydrogen phosphate reagent solution is added 118 mL of 0.2 mol/L NaOH reagent solution and water to provide a final volume of 1000 mL). After standing at 25 degrees Celsius for 16 hours, the mixed solution is filtrated with suction. The filtrate is diluted twice with methanol/water (1/1), and then a concentration in the filtration is measured with HPLC or LC/MS/MS by the absolute calibration method.
[0155]

Test Examples 6 Metabolism Stability Test

Using commercially available pooled human hepatic microsomes, a test compound was reacted for a constant time, a remaining rate was calculated by comparing a reacted sample and an unreacted sample, thereby, a degree of metabolism in liver was assessed.
[0156]

A reaction was performed (oxidative reaction) at 37°C for 0 minute or 30

minutes in the presence of 1 mmol/L NADPH in 0.2 mL of a buffer (50 mmol/L Tris-HCl pH 7.4, 150 mmol/L potassium chloride, 10 mmol/L magnesium chloride) containing 0.5 mg protein/mL of human liver microsomes. After the reaction, 50 μ L of the reaction solution was added to 100 μ L of a methanol/acetonitrile = 1/1 (v/v), mixed and centrifuged at 3000 rpm for 15 minutes. The test compound in the supernatant was quantified by LC/MS/MS, and a remaining amount of the test compound after the reaction was calculated, letting a compound amount at 0 minute reaction time to be 100%.

[0157]

Test Examples 7 hERG Test

For the purpose of assessing risk of an electrocardiogram QT interval prolongation, effects on delayed rectifier K⁺ current (I_{Kr}), which plays an important role in the ventricular repolarization process, was studied using HEK293 cells expressing human ether-a-go-go related gene (hERG) channel.

[0158]

After a cell was retained at a membrane potential of -80 mV by whole cell patch clamp method using an automated patch clamp system (PatchXpress 7000A, Axon Instruments Inc.), I_{Kr} induced by depolarization pulse stimulation at +40 mV for 2 seconds and, further, repolarization pulse stimulation at -50 mV for 2 seconds was recorded. After the generated current was stabilized, extracellular solution (NaCl: 135 mmol/L, KCl: 5.4 mmol/L, NaH₂PO₄: 0.3 mmol/L, CaCl₂ · 2H₂O: 1.8 mmol/L, MgCl₂ · 6H₂O: 1 mmol/L, glucose: 10 mmol/L, HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid): 10 mmol/L, pH=7.4) in which the test compound had been dissolved at an objective concentration was applied to the cell under the room temperature condition for 10 minutes. From the recording I_{Kr}, an absolute value of the tail peak current was measured based on the current value at the resting membrane potential using an analysis software (DataXpress ver.1, Molecular Devices Corporation). Further, the % inhibition relative to the tail peak current before application of the test substance was calculated, and compared with the vehicle-applied group (0.1% dimethyl sulfoxide solution) to assess influence of the test substance on I_{Kr}.

[0159]

Test Example 8 Metabolism Stability Test

Using a prepared frozen rat hepatocyte, a test compound is reacted for a constant time, a remaining rate is calculated by comparing a reacted sample and an unreacted sample, thereby, a degree of metabolism in liver is assessed.

[0160]

A reaction is performed at 37°C for 0, 1 or 2 hours in William's E medium containing rat frozen hepatocyte 1.0x10⁶ cells/mL. After the reaction, 50 μ L of the reaction solution is added to 100 μ L of a methanol/acetonitrile = 1/1 (v/v), mixed and centrifuged at 3000 rpm for 15 minutes. The test compound in the supernatant is quantified by LC/MS/MS, and a remaining amount of the test compound after the reaction is calculated, letting a compound amount at 0 minute reaction time to be 100%.

[0161]

As shown, the compounds of the invention showed inhibiting activity on P2X₃ receptor. Furthermore, as the compounds of the invention can be effective to P2X₃ subtype, the compounds also have inhibiting activity on P2X_{2/3} receptor, which comprises P2X₃ subtype.

[Industrial Applicability]

[0162]

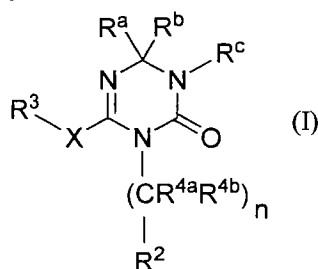
The compound of the invention has antagonizing effect on P2X₃ and/or P2X_{2/3} receptor and is useful in the treatment of diseases or conditions associated with a P2X₃ and/or P2X_{2/3} receptor, such as chronic pain, overactive bladder, etc.

[Document Name] Claims

[Claim 1]

A compound represented by the formula (I):

[Chemical Formula 1]



wherein

R^a , R^b and R^c are,

(a) R^a and R^b are taken together =Z;

=Z is =O, =S or =N- R^6 ;

R^6 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^c is a group represented by R^{1c} ;

R^{1c} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

(b) R^b and R^c are taken together to form a bond;

R^a is a group represented by -Y- R^{1a} ;

R^{1a} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

-Y- is -O-, -S-, -N(R^7)- or -C(R^{8a} R^{8b})-;

R^7 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted acyl, or R^7 and R^{1a} are taken together to form a substituted or unsubstituted nitrogen-containing non-aromatic heterocyclic group;

R^{8a} and R^{8b} are each independently hydrogen, halogen, or substituted or unsubstituted alkyl;

n is an integer of 0 to 4;

R^2 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-

aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a} and R^{4b} are each independently hydrogen, substituted or unsubstituted alkyl or R^{4a} and R^{4b} are taken together oxo;

$-X-$ is $-O-$, $-S-$ or $-N(R^5)-$;

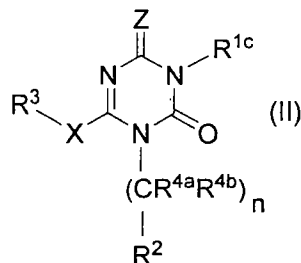
R^5 is hydrogen, substituted or unsubstituted alkyl, or substituted or unsubstituted acyl;

provided that R^3 is not cyclohexyl substituted with guanidyl when $-X-$ is $-NH-$, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 1]

The compound according to claim 1, wherein the compound is represented by the formula (II):

[Chemical Formula 2]



wherein

R^{1c} , R^{4a} , R^{4b} , $-X-$ and $=Z$ are as defined in claim 1;

n is an integer of 1 to 4;

R^2 and R^3 are each independently substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 2]

The compound according to claim 2, wherein $-X-$ is $-N(R^5)-$ wherein R^5 is as defined in claim 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 3]

The compound according to claim 2, wherein R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 4]

The compound according to claim 2, wherein $=Z$ is $=O$, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 5]

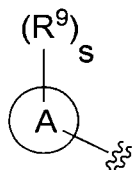
The compound according to claim 2, wherein R^{1c} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, hydroxy, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or

unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclic ring-oxy-carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl), or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 6]

The compound according to claim 2, wherein R^3 is a group represented by the formula:

[Chemical Formula 3]



wherein ring A is aryl or heteroaryl;

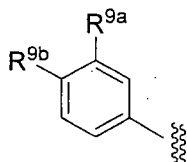
s is an integer of 0 to 3; and

R^9 is each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 7]

The compound according to claim 2, wherein R^3 is a group represented by the formula:

[Chemical Formula 4]



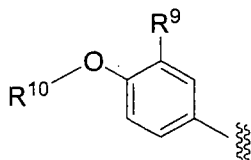
wherein R^{9a} and R^{9b} are each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or

unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclic ring-oxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 8]

The compound according to claim 2, wherein R^3 is a group represented by the formula:

[Chemical Formula 5]

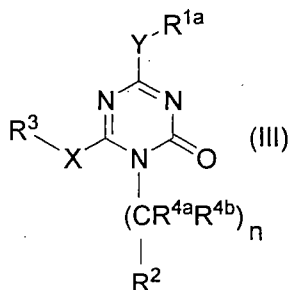


wherein R^9 is as defined in claim 7; and R^{10} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 9]

The compound according to claim 1, wherein the compound is represented by the formula (III):

[Chemical Formula 6]



wherein R^{1a} , R^{4a} , R^{4b} , -X- and -Y- are as defined in claim 1;

n is an integer of 1 to 4; and

R^2 and R^3 are each independently substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 10]

The compound according to claim 10, wherein -X- is -N(R^5)- wherein R^5 is as

defined in claim 1, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 1 1]

The compound according to claim 10, wherein R^2 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 1 2]

The compound according to claim 10, wherein -Y- is -O-, or its pharmaceutically acceptable salt, or a solvate thereof.

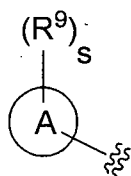
[Claim 1 3]

The compound according to claim 10, wherein R^{1a} is hydrogen; unsubstituted alkyl; or alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, hydroxy, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, carboxy, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclic ring-oxy-carbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, cyano, nitro, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl), or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 1 4]

The compound according to claim 10, wherein R^3 is a group represented by the formula:

[Chemical Formula 7]



wherein ring A is aryl or heteroaryl;

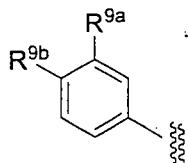
s is an integer of 0 to 3; and

R^9 is as defined in claim 7, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 1 5]

The compound according to claim 10, wherein R^3 is a group represented by the formula:

[Chemical Formula 8]

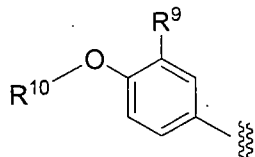


wherein R^{9a} and R^{9b} are as defined in claim 8, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 16]

The compound according to claim 10, wherein R^3 is a group represented by formula:

[Chemical Formula 9]



wherein R^9 is as defined in claim 7; and R^{10} is as defined in claim 9, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 17]

A pharmaceutical composition comprising the compound according to any one of claims 1 to 17, or its pharmaceutically acceptable salt, or a solvate thereof.

[Claim 18]

The pharmaceutical composition according to claim 18, wherein the composition is for a $P2X_3$ and/or $P2X_{2/3}$ receptor antagonist.

[Claim 19]

A compound according to any one of claims 1 to 17, or its pharmaceutically acceptable salt, or a solvate thereof for use in a method for treating and/or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor.

[Claim 20]

Use of the compound according to any one of claims 1 to 17, or its pharmaceutically acceptable salt, or a solvate thereof in the manufacturing of an agent for treating and/or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor.

[Claim 21]

A method for treating and/or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor characterized by administration of the compound according to any one of claims 1 to 17, or its pharmaceutically acceptable salt, or a solvate thereof.