

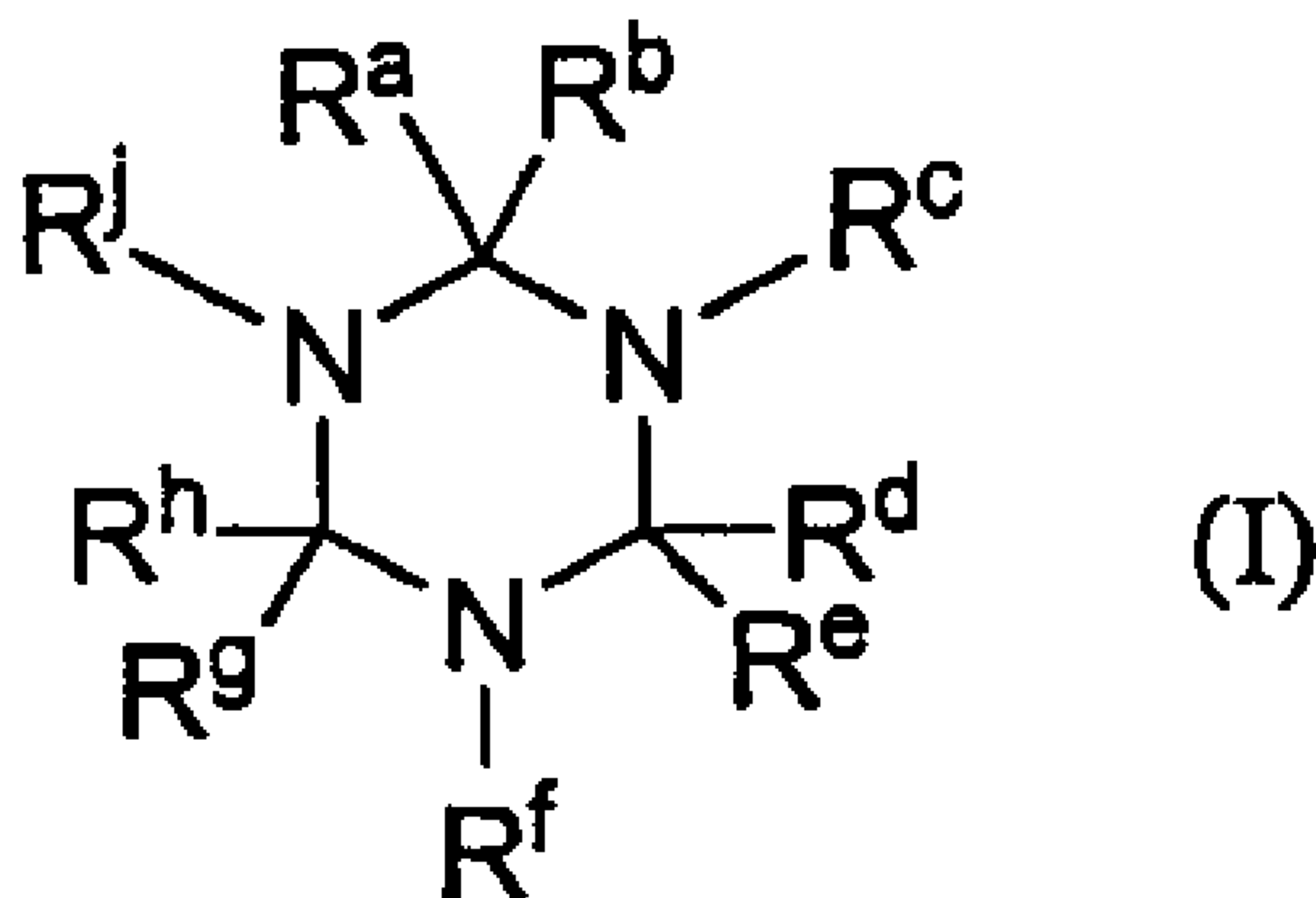


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(54) Titre : DERIVE DE TRIAZINE ET COMPOSITION PHARMACEUTIQUE PRESENTANT UNE ACTIVITE
ANALGESIQUE A TENEUR EN DERIVE DE TRIAZINE
(54) Title: TRIAZINE DERIVATIVE AND PHARMACEUTICAL COMPOUND THAT CONTAINS SAME AND EXHIBITS
ANALGESIC ACTIVITY



(57) Abrégé/Abstract:

Disclosed is a novel compound that acts as an antagonist for P2X₃ and/or P2X_{2/3} receptors. Also disclosed is a pharmaceutical composition that exhibits analgesic activity or acts to ameliorate urinary problems, said composition containing: a compound

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(57) Abrégé(suite)/Abstract(continued):

represented by formula (I), a pharmacologically permitted salt thereof, or a solvate of either. In the formula, R^h and R^j together form a bond; R^a and R^b, and/or R^d and R^e, together form an oxo or the like; R^c represents hydrogen, a substituted or unsubstituted alkyl, or the like; -R^f represents -(CR^{4a}R^{4b})_n-R²; R^{4a} and R^{4b} represent hydrogen, a substituted or unsubstituted alkyl, or the like; R² represents a substituted or unsubstituted cycloalkyl or the like; n represents an integer from 1 to 4; -R^g represents -X-R³; -X- represents -O-, -S-, or the like; and R³ represents a substituted or unsubstituted cycloalkyl or the like.

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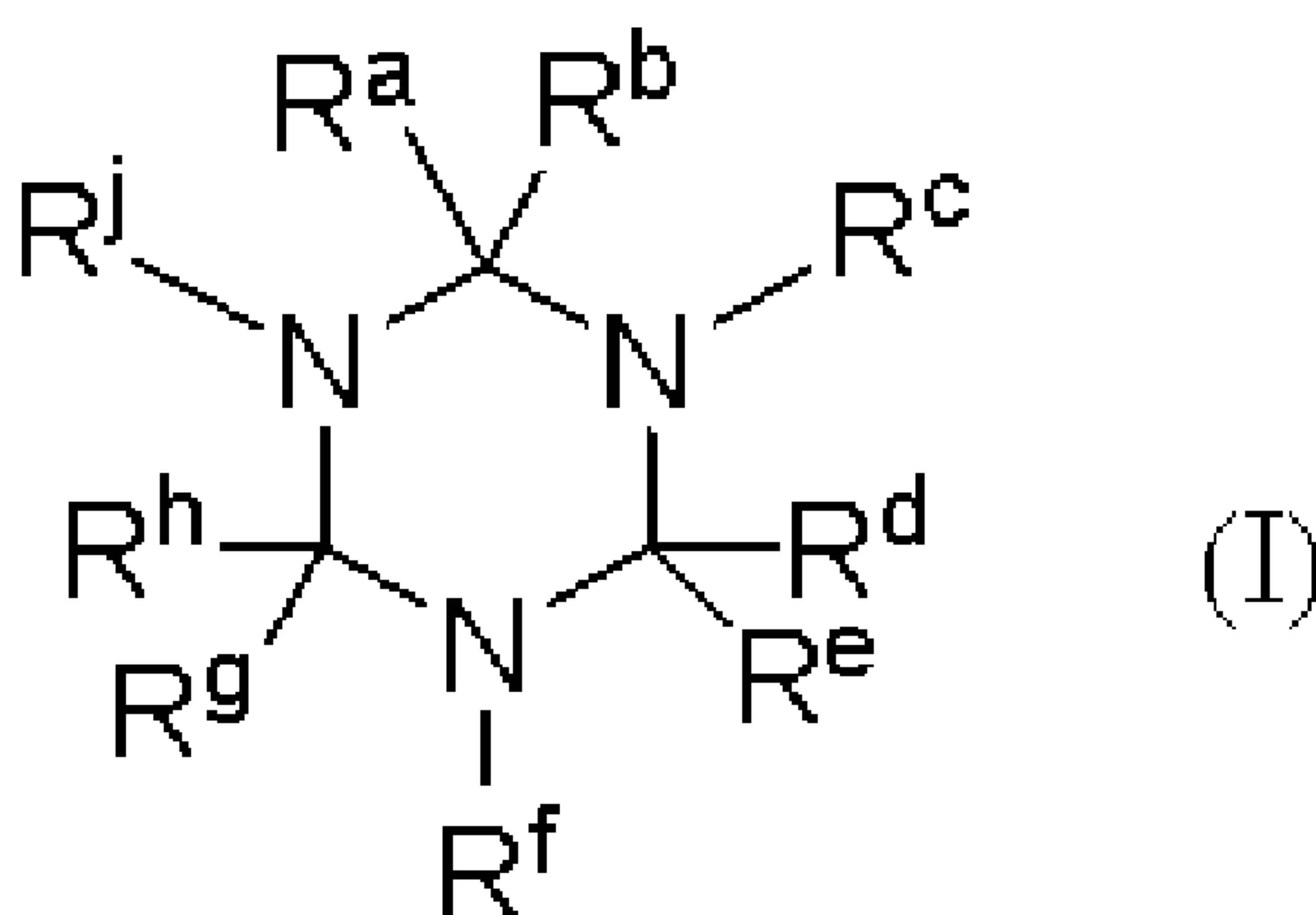
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[続葉有]

(54) Title: TRIAZINE DERIVATIVE AND PHARMACEUTICAL COMPOUND THAT CONTAINS SAME AND EXHIBITS ANALGESIC ACTIVITY

(54) 発明の名称: トリアジン誘導体およびそれを含有する鎮痛作用を有する医薬組成物



(57) **Abstract:** Disclosed is a novel compound that acts as an antagonist for P2X₃ and/or P2X_{2/3} receptors. Also disclosed is a pharmaceutical composition that exhibits analgesic activity or acts to ameliorate urinary problems, said composition containing: a compound represented by formula (I), a pharmacologically permitted salt thereof, or a solvate of either. In the formula, R^h and Rⁱ together form a bond; R^a and R^b, and/or R^d and R^e, together form an oxo or the like; R^c represents hydrogen, a substituted or unsubstituted alkyl, or the like; -R^f represents -(CR^{4a}R^{4b})_n-R²; R^{4a} and R^{4b} represent hydrogen, a substituted or unsubstituted alkyl, or the like; R² represents a substituted or unsubstituted cycloalkyl or the like; *n* represents an integer from 1 to 4; -R^g represents -X-R³; -X- represents -O-, -S-, or the like; and R³ represents a substituted or unsubstituted cycloalkyl or the like.

(57) 要約:

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新規な P_2X_3 および／または $P_2X_{2/3}$ 受容体拮抗作用を有する化合物を提供する。 式 (I) : 化 1 [式中、 R^h および R^i は、一緒になって結合を形成し； R^a と R^b および／または R^d と R^e は、一緒になって、オキソ等； R^c は、水素、置換もしくは非置換のアルキル等； 等； $-R^f$ は、 $-(CR^{4a}R^{4b})_n-R^2$ ； R^{4a} および R^{4b} は、水素、置換もしくは非置換のアルキル等； R^2 は、置換もしくは非置換のシクロアルキル等； n は 1～4 の整数； $-R^g$ は、 $-X-R^3$ ； $-X-$ は、 $-O-$ 、 $-S-$ 等； R^3 は、置換もしくは非置換のシクロアルキル等] で示される化合物もしくはその製薬上許容される塩またはそれらの溶媒和物を含む、鎮痛作用または排尿障害改善作用を有する医薬組成物。

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 386

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 386

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NOM DU FICHER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

[Document Name] Specification

[Title of Invention] TRIAZINE DERIVATIVE AND PHARMACEUTICAL COMPOUND THAT CONTAINS SAME AND EXHIBITS ANALGESIC ACTIVITY

[Technical field]

[0001]

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

[Background Art]

[0002]

Adenosine triphosphate (ATP) 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).

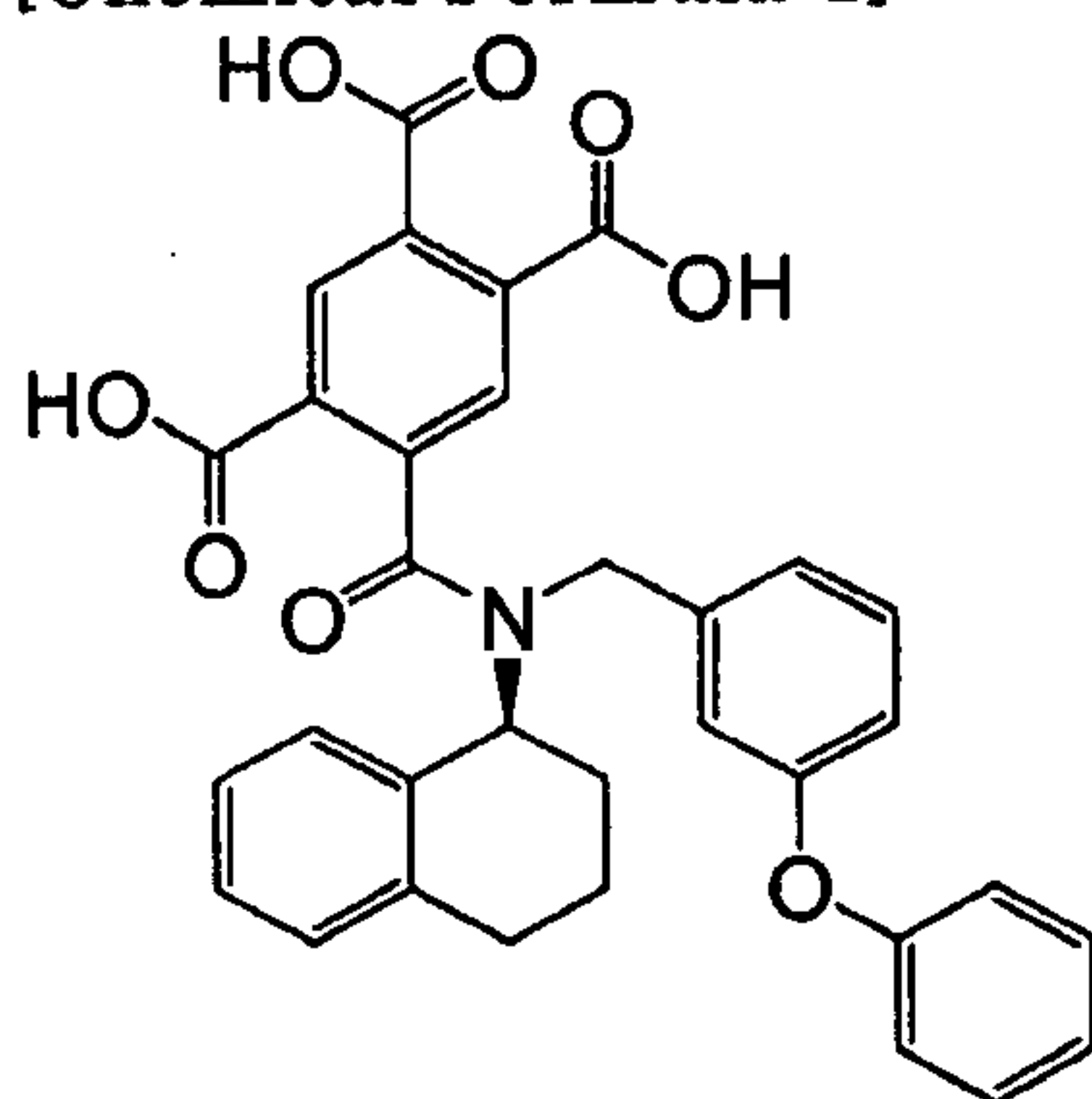
[0004]

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 compound having a P2X₃ or P2X_{2/3}

receptor antagonistic effect is useful as an analgesic. Also, compounds that exhibit P2X₃ or P2X_{2/3} receptor antagonistic 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 compound having P2X₃ antagonistic effect is useful in the treatment of diseases caused by overactive bladder.

Patent Documents 8, 9, 10 and 11 disclose compounds having similar structure to the compounds of the present invention but they do not disclose analgesic effect and P2X₃ or P2X_{2/3} receptor antagonistic effect. Non-Patent Document 8 discloses compounds having similar structure to the compounds of the present invention and having analgesic effect, but it does not disclose P2X₃ or P2X_{2/3} receptor antagonistic effect. Patent Document 12 discloses compounds having P2X₃ receptor antagonistic effect but the structures are different with those of the compounds of the present invention. Patent Document 13 discloses compounds having P2X₃ or P2X_{2/3} receptor antagonistic effect with a triazine structure but in case that a ring corresponding to ring B of the present application is a cyclopentane ring, a benzene ring, a tetrahydropyran ring or a piperazine ring, then the ring is unsubstituted, and therefore, the structures are different with those of the present invention.

Patent Document 14 discloses compounds having a pyrazolyl-substituted triazine ring but the structures are different with those of the compound of the formula (XII) of the present invention. Patent Document 14 does not disclose a process for converting a pyrazolyl group on a triazine ring into an anilino group by using a pyrazolyl group as a leaving group.

Non-Patent Documents 9, 10, 11 and 12 disclose a process for converting a pyrazolyl group to an anilino group by using a pyrazolyl group as a leaving group, but do not disclose a process for converting a pyrazolyl group on a triazine ring into an anilino group.

[Prior Art]

[Patent Document]

[0007]

[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] JP12-072757A
 [Patent Document 9] WO2006/104713
 [Patent Document 10] WO2006/104715
 [Patent Document 11] WO2006/102112
 [Patent Document 12] WO2010/051188
 [Patent Document 13] WO2010/092966
 [Patent Document 14] EP547461A

[Non-patent Document]

[0008]

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

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

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

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

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

[Non-Patent Document 6] Pflungers Arch Eur J physiol (2006), p.452, 513-

537

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

[Non-Patent Document 8] Journal of Medicinal Chemistry (2008), 51(23),
p.7635-7639

[Non-Patent Document 9] J. Org. Chem. (1992), 57, p.2497-2502

[Non-Patent Document 10] Tetrahedron Lett. (2007), 48, p.2357-2359

[Non-Patent Document 11] Tetrahedron Lett. (2002), 43, p.1401-1403

[Non-Patent Document 12] Bioorganic & Medicinal Chemistry Letters (2010),
20(23), p.6895-6898

[Summary of the invention]

[Problems to be solved by the Invention]

[0009]

The present invention provides a novel compound having a P2X₃ and/or P2X_{2/3} receptor antagonistic effect. It also provides a pharmaceutical composition having a P2X₃ and/or P2X_{2/3} receptor antagonistic effect and having an analgesic effect or an improving effect of urination disorder. Furthermore, it provides methods of producing the above-mentioned compound or pharmaceutical composition and important intermediates for the producing methods.

[Means for Solving the Problem]

[0010]

Through their extensive research to solve the aforementioned problems, the inventors have found novel compounds that bind specifically to P2X₃ and/or P2X_{2/3} receptor and exhibit an antagonistic effect, and novel compounds that bind specifically to P2X₃ and/or P2X_{2/3} receptor. Additionally, they have discovered pharmaceutical compositions that have P2X₃ and/or P2X_{2/3} antagonistic effect and having an analgesic effect or an improving effect of urination disorder. Furthermore, they have found methods for producing the above-mentioned compound or pharmaceutical composition and important intermediates for the producing methods.

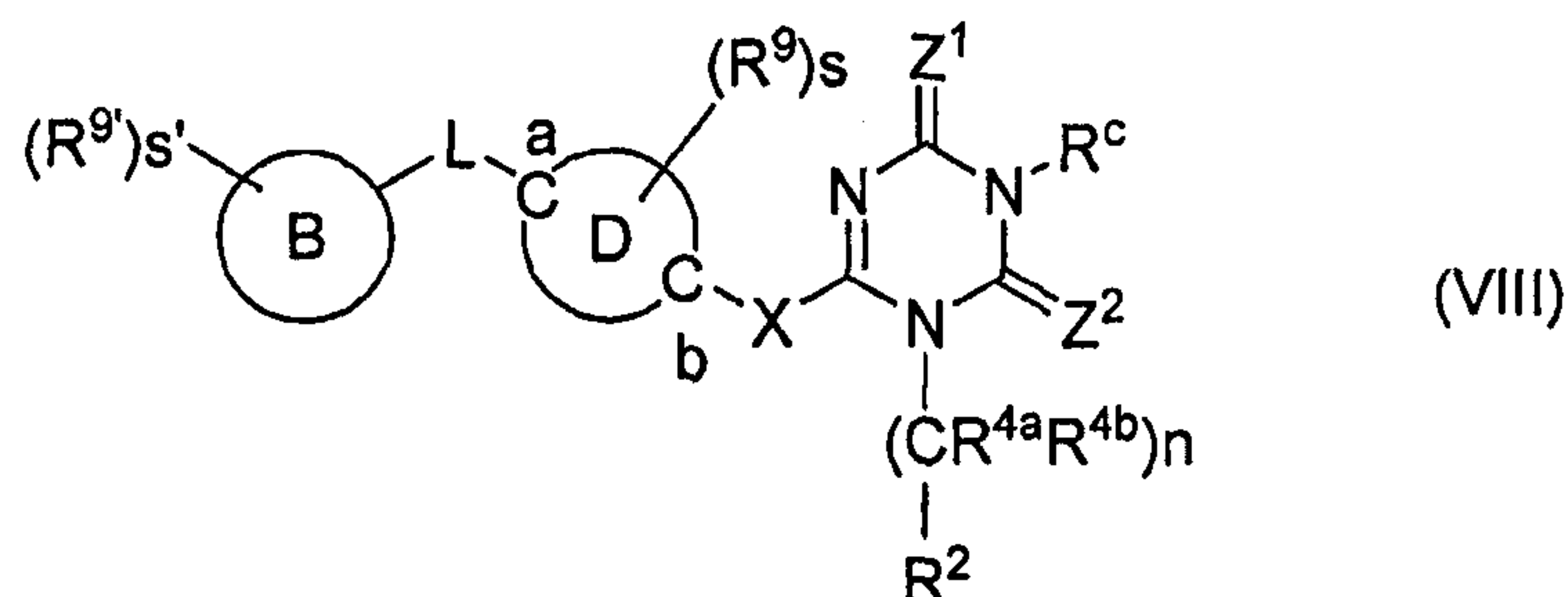
The compounds and pharmaceutical compositions encompassed by the present invention produced excellent results of P2X₃ receptor inhibitory effect, P2X₃ receptor inhibitory effect in the presence of rat serum albumin (hereinafter referred to as RSA) and the like. The compounds encompassed by the present invention or the pharmaceutical compositions encompassed by the present invention also produced excellent results in CYP enzyme inhibition assay, FAT assay, solubility assay, metabolic stability assay, hERG inhibitory activity assay, bioavailability assay and/or protein binding assay and the like. The compounds encompassed by the present invention or the pharmaceutical composition encompassed by the present invention showed potent analgesic effect or improving effect of urination disorder.

This invention relates to

[0011]

(1) A compound of the formula (VIII):

[Chemical Formula 2]



wherein

Z^1 and Z^2 are each independently an oxygen atom, a sulfur atom or $=N-R^x$;
 R^x is a hydrogen atom, 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 hydrogen atom, 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;
 R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo;

n is an integer of 1 to 4;

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;

$-X-$ is $-O-$, $-S-$, $-N(R^5)-$ or $-(CR^{5a}R^{5b})-$;

$-L-$ is $-O-$, $-S-$, $-N(R^{5'})-$ or $-(CR^{5a'}R^{5b'})-$;

R^5 and $R^{5'}$ are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted acyl;

R^{5a} , R^{5b} , $R^{5a'}$ and $R^{5b'}$ are each independently a hydrogen atom, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy or substituted or unsubstituted alkenyloxy;

ring D is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring;

carbon atom a and carbon atom b are carbon atoms which constitute ring D;

ring B is an aromatic carbocyclic ring, a non-aromatic carbocyclic ring, an aromatic heterocyclic ring or a non-aromatic heterocyclic ring;

s and s' are each independently an integer of 0 to 3; and

R^9 and $R^{9'}$ are each independently halogen, hydroxy, carboxy, 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, 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 sulfonyl, substituted sulfinyl, 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 heterocyclyloxy, substituted or unsubstituted aryloxy or substituted or unsubstituted heteroaryloxy;

provided that s' is an integer of 1 to 3 when ring B is a cyclopentane ring, a benzene ring, a tetrahydropyran ring or a piperidine ring, or its pharmaceutically acceptable salt or a solvate thereof.

[0012]

(2) The compound according to the above (1), wherein $\cdot L \cdot$ is $\cdot O \cdot$, or its pharmaceutically acceptable salt or a solvate thereof.

(3) The compound according to the above (1) or (2), wherein ring B is an aromatic heterocyclic ring, or its pharmaceutically acceptable salt or a solvate thereof.

(4) The compound according to any one of the above (1) to (3), wherein ring B is a thiazole ring, an isothiazole ring, an oxazole ring, an isoxazole ring, a pyrazole ring, an imidazole ring, a triazole ring, a furan ring, a thiophene ring, a thiadiazole ring, an oxadiazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, a triazine ring or a benzoxazole ring, or its pharmaceutically acceptable salt or a solvate thereof.

(5) The compound according to any one of the above (1) to (4), wherein ring B is a thiazole ring, an isothiazole ring, an oxazole ring, an isoxazole ring, a thiadiazole ring, an oxadiazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring, or its pharmaceutically acceptable salt or a solvate thereof.

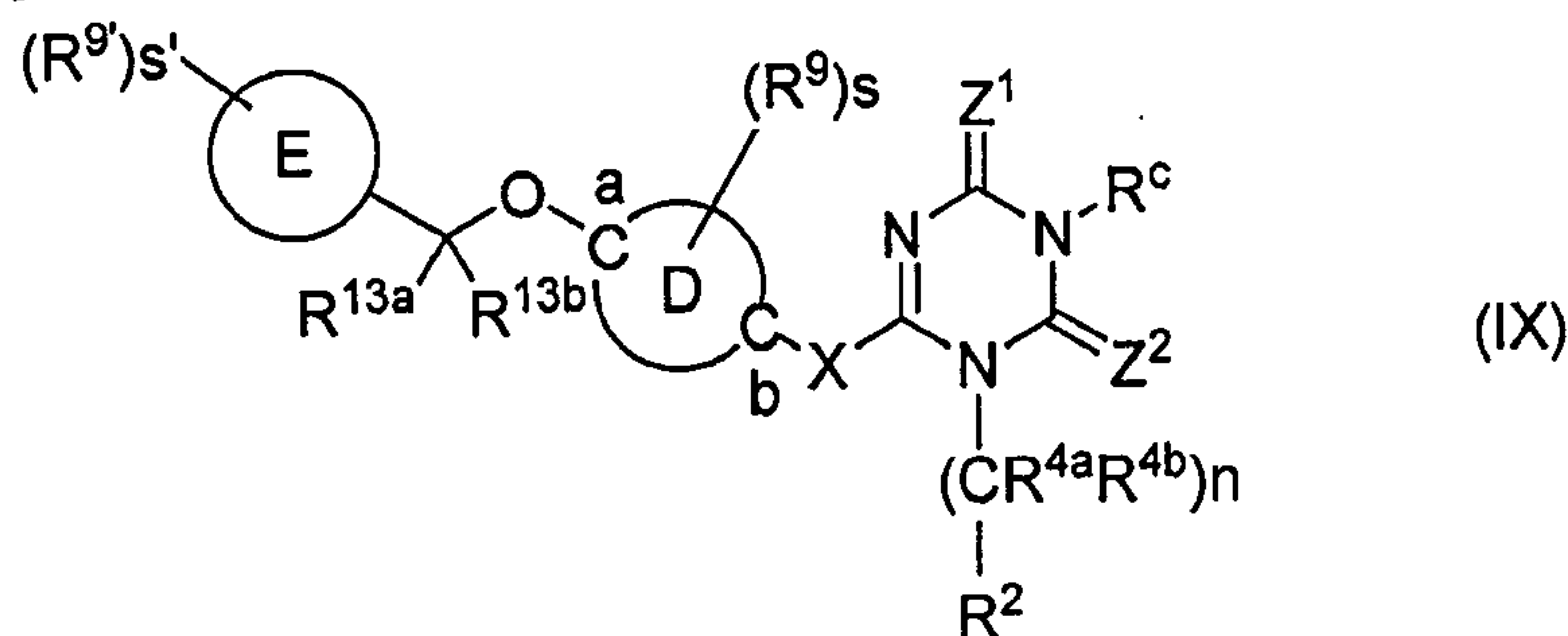
(6) The compound according to any one of the above (1) to (5), wherein s' is an integer of 1 to 2, and at least one of R^9 is hydroxy, carboxy, cyano, substituted alkyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted amino, substituted or unsubstituted sulfamoyl, substituted sulfonyl or substituted sulfinyl, or its pharmaceutically acceptable salt or a solvate thereof.

(7) The compound according to any one of the above (1) to (6), wherein s' is 1, and R^9 is carboxy or substituted or unsubstituted carbamoyl, or its pharmaceutically acceptable salt or a solvate thereof.

[0013]

(8) A compound of the formula (IX):

[Chemical Formula 3]



wherein

Z^1 and Z^2 are each independently an oxygen atom, a sulfur atom or $=N-R^*$;

R^* is a hydrogen atom, 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 hydrogen atom, 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;

R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo;

n is an integer of 1 to 4;

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;

$-X-$ is $-O-$, $-S-$, $-N(R^5)-$ or $-(CR^{5a}R^{5b})-$;

R^5 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted acyl;

R^{5a} and R^{5b} are each independently a hydrogen atom, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy;

ring D is a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring;

carbon atom a and carbon atom b are carbon atoms which constitute ring D;

R^{13a} and R^{13b} are each independently a hydrogen atom, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy, or R^{13a} and R^{13b} attached to the same carbon atom are taken together to form oxo or thioxo;

ring E is a cycloalkane ring or a cycloalkene ring;

s and s' are each independently an integer of 0 to 3; and

R^9 and R^9 are each independently halogen, hydroxy, carboxy, 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, 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 sulfonyl, substituted sulfinyl, 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 heterocyclyloxy, substituted or unsubstituted aryloxy or substituted or unsubstituted heteroaryloxy;

or its pharmaceutically acceptable salt or a solvate thereof.

[0014]

(9) The compound according to the above (8), wherein R^{13a} and R^{13b} are both hydrogen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(10) The compound according to the above (8) or (9), wherein ring E is a cyclopropane ring, or its pharmaceutically acceptable salt or a solvate thereof.

(11) The compound according to any one of the above (1) to (10), wherein ring D is a benzene ring, or its pharmaceutically acceptable salt or a solvate thereof.

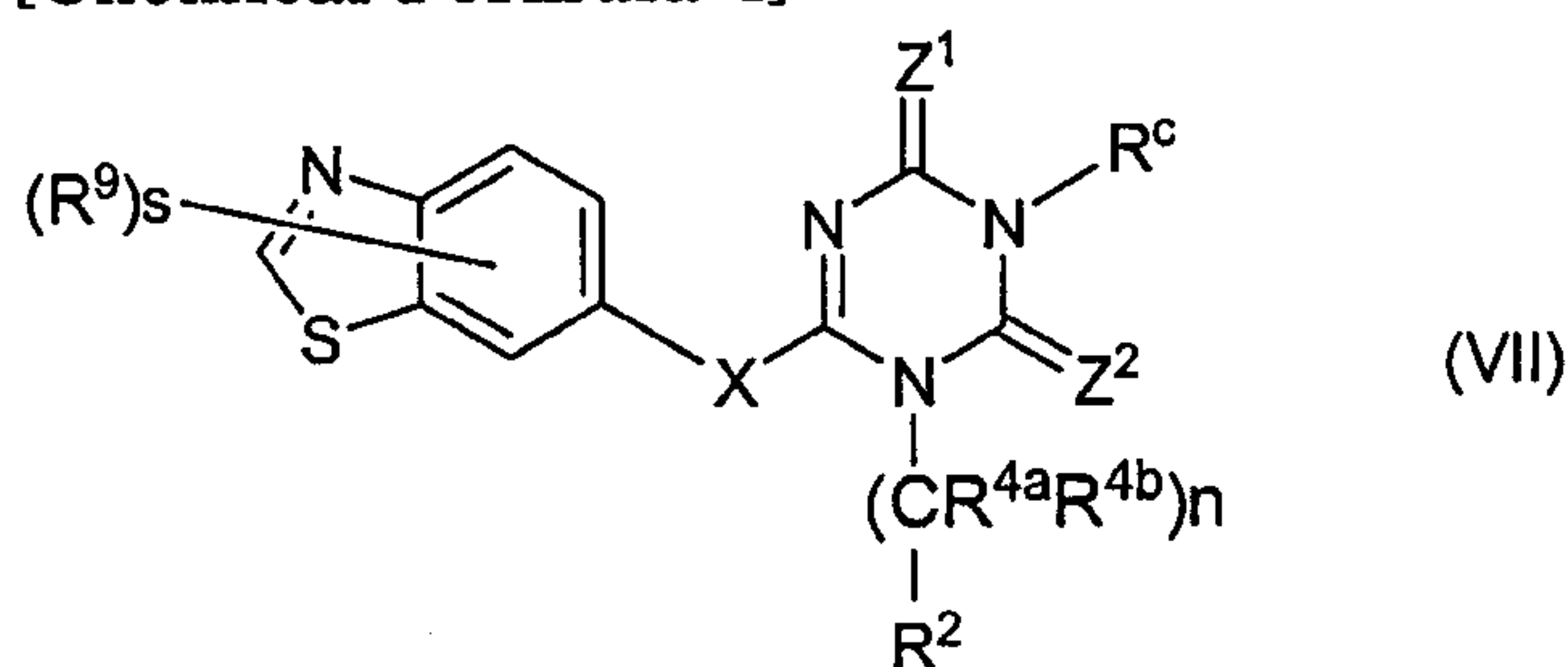
(12) The compound according to any one of the above (1) to (11), wherein carbon atom a is positioned on ring D in a 1,4 relationship with respect to carbon atom b, or its pharmaceutically acceptable salt or a solvate thereof.

(13) The compound according to any one of the above (1) to (12), wherein s and s' are each independently an integer of 0 to 2; and R^9 and $R^{9'}$ are each independently halogen, hydroxy, carboxy, 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, 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 sulfonyl or substituted sulfinyl, or its pharmaceutically acceptable salt or a solvate thereof.

[0015]

(14) A compound of the formula (VII):

[Chemical Formula 4]



wherein

Z¹ and Z² are each independently an oxygen atom, a sulfur atom or =N-R^x;

R^x is a hydrogen atom, 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 hydrogen atom, 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;

R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo;

n is an integer of 1 to 4;

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;

-X- is -O-, -S-, -N(R⁵)- or -(CR^{5a}R^{5b})-;

R⁵ is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted acyl;

R^{5a} and R^{5b} are each independently a hydrogen atom, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy;

s is an integer of 0 to 3; and

R⁹ is each independently halogen, hydroxy, carboxy, 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, 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 sulfonyl, substituted sulfinyl, 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 heterocyclyloxy, substituted or unsubstituted aryloxy or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof.

[0016]

(15) The compound according to the above (14), wherein s is an integer of 0 to 2; and R⁹ is each independently halogen, hydroxy, carboxy, 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, 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 sulfonyl or substituted sulfinyl, or its pharmaceutically acceptable salt or a solvate thereof.

(16) The compound according to any one of the above (1) to (15), wherein Z^1 and Z^2 are both oxygen atoms or both sulfur atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(17) The compound according to any one of the above (1) to (16), wherein Z^1 and Z^2 are both oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(18) The compound according to any one of the above (1) to (17), wherein R^c is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group A, unsubstituted alkynyl or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof.

[0017]

(19) The compound according to any one of the above (1) to (18), wherein R^c is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group B'' (Substituent Group B'': hydroxy, carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group B'', unsubstituted alkynyl or alkynyl substituted with one or more substituents selected from Substituent Group B'', or its pharmaceutically acceptable salt or a solvate thereof.

(20) The compound according to any one of the above (1) to (19), wherein R^c is unsubstituted alkyl, or its pharmaceutically acceptable salt or a solvate thereof.

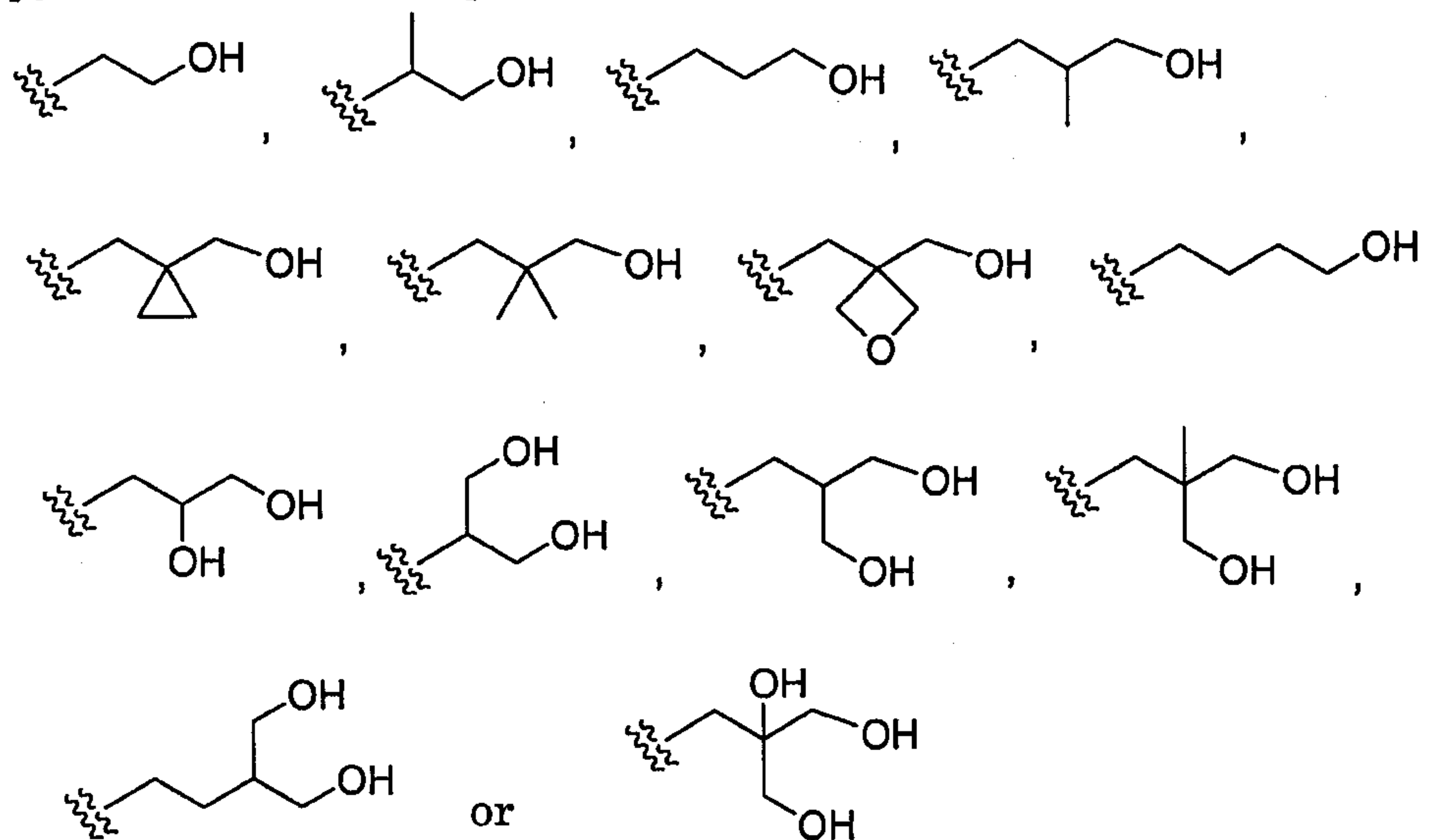
(21) The compound according to any one of the above (1) to (19), wherein R^c is $-(CR^{11a}R^{11b})_m-OH$; R^{11a} and R^{11b} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, or R^{11a} and R^{11b} together with the carbon atom to which they are attached form a substituted or unsubstituted cycloalkane ring, a substituted or unsubstituted cycloalkene ring, or a substituted or unsubstituted non-aromatic heterocyclic ring; and m is an integer of 2 to 4, or its pharmaceutically acceptable salt or a solvate thereof.

(22) The compound according to any one of the above (1) to (19) and (21), wherein R^c is $-(CR^{11a}R^{11b})_m-OH$; R^{11a} is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl; R^{11b} is $-(CR^{12a}R^{12b})_u-OH$; R^{12a} and R^{12b} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl; u is an integer of 0 to 2; and m is an integer of 2 to 4, or its pharmaceutically acceptable salt or a solvate thereof.

[0018]

(23) The compound according to any one of the above (1) to (19), (21) and (22), wherein R^c is a group of the formula:

[Chemical Formula 5]



or its pharmaceutically acceptable salt or a solvate thereof.

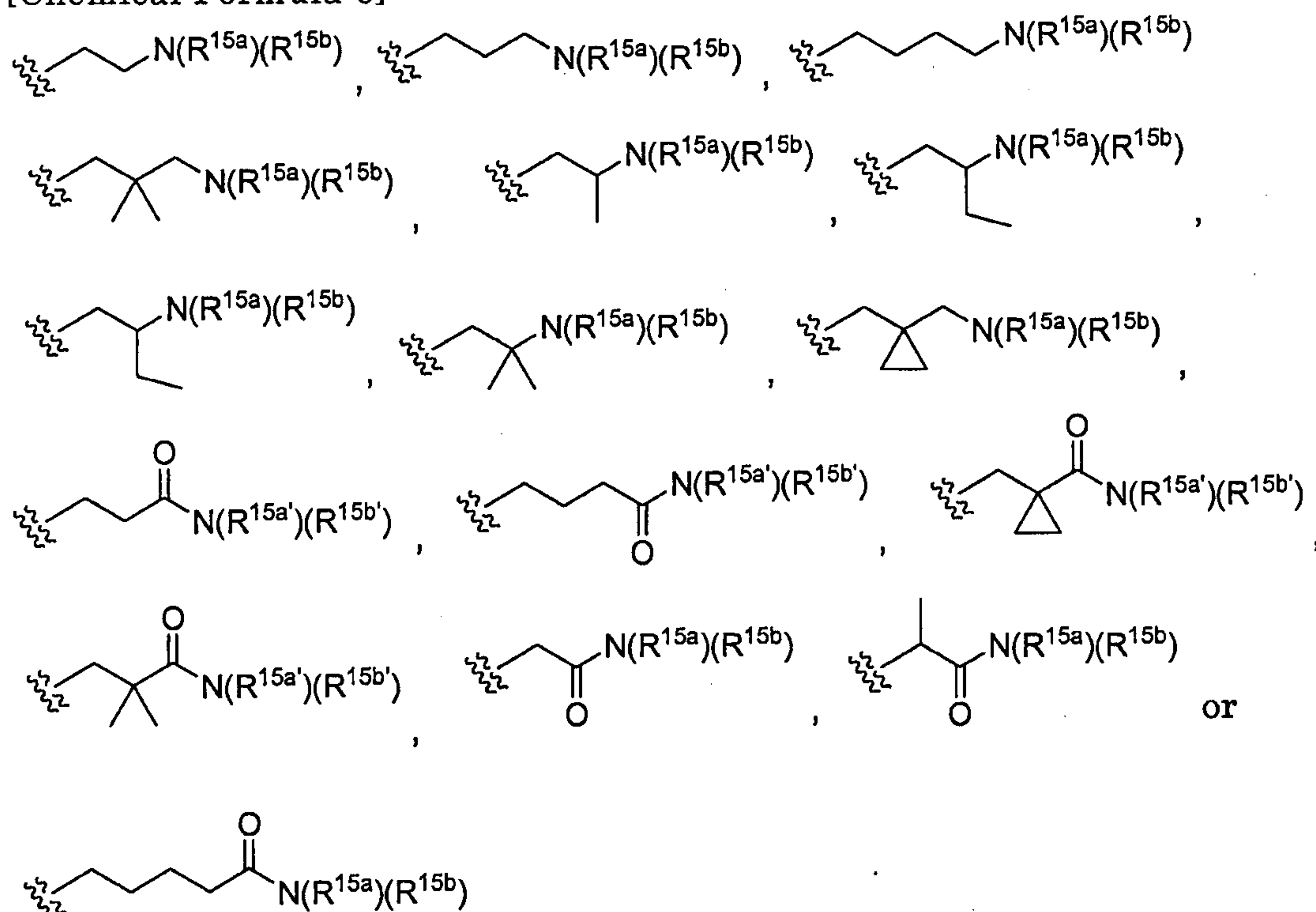
(24) The compound according to any one of the above (1) to (19), wherein R^c is $-(CR^{14a}R^{14b})_t-N(R^{15a})(R^{15b})$; R^{14a} and R^{14b} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, or R^{14a} and R^{14b} together with the carbon atom to which they are attached form a substituted or unsubstituted cycloalkane ring, a substituted or unsubstituted cycloalkene ring, or a substituted or unsubstituted non-aromatic heterocyclic ring; t is an integer of 2 to 4; and R^{15a} and R^{15b} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted acyl, substituted sulfonyl or substituted sulfinyl; or $-(CR^{14a'}R^{14b'})_{t'}-C(=O)N(R^{15a'})(R^{15b'})$; $R^{14a'}$ and $R^{14b'}$ are each independently a hydrogen

atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl or $R^{14a'}$ and $R^{14b'}$ together with the carbon atom to which they are attached form a substituted or unsubstituted cycloalkane ring, a substituted or unsubstituted cycloalkene ring, or a substituted or unsubstituted non-aromatic heterocyclic ring; t' is an integer of 1 to 4; and $R^{15a'}$ and $R^{15b'}$ are each independently a hydrogen atom, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted acyl, substituted sulfonyl or substituted sulfinyl, or its pharmaceutically acceptable salt or a solvate thereof.

[0019]

(25) The compound according to any one of the above (1) to (19), and (24), wherein R^c is a group of the formula:

[Chemical Formula 6]



wherein R^{15a} , R^{15b} , $R^{15a'}$ and $R^{15b'}$ are as defined in the above (24), or its pharmaceutically acceptable salt or a solvate thereof.

(26) The compound according to any one of the above (1) to (25), wherein n is 1, or its pharmaceutically acceptable salt or a solvate thereof.

(27) The compound according to any one of the above (1) to (26), wherein R^{4a} and R^{4b} are both hydrogen atoms, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo, or its pharmaceutically acceptable salt or a solvate thereof.

(28) The compound according to any one of the above (1) to (27), wherein n is 1, and R^{4a} and R^{4b} are both hydrogen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(29) The compound according to any one of the above (1) to (28), wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a

solvate thereof.

[0020]

(30) The compound according to any one of the above (1) to (29), wherein R^2 is cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl), aryl optionally substituted with one or more substituents selected from Substituent Group C, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

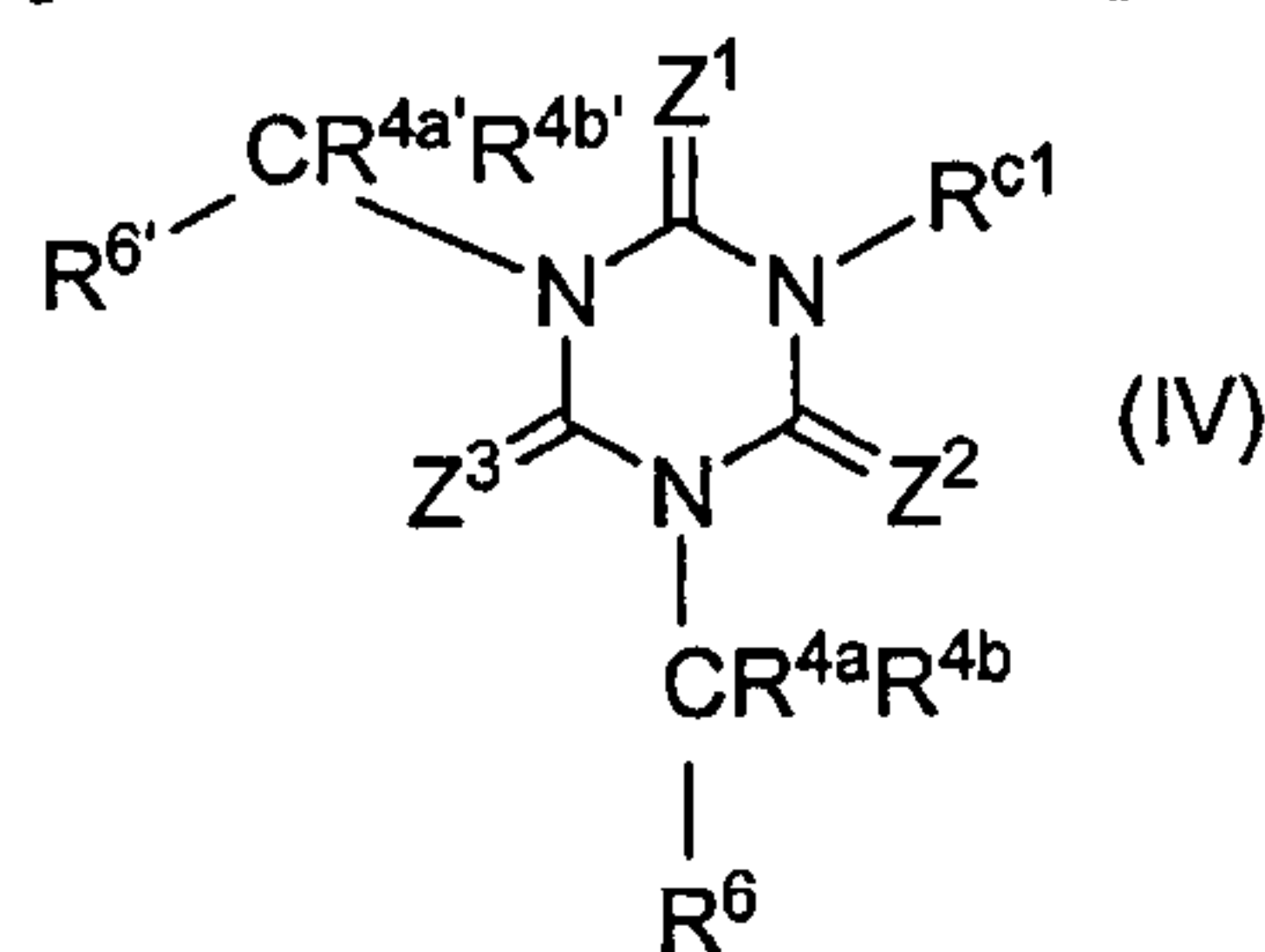
(31) The compound according to any one of the above (1) to (30), wherein $-X-$ is $-N(R^5)-$, and R^5 is as defined in the above (1), or its pharmaceutically acceptable salt or a solvate thereof.

(32) The compound according to any one of the above (1) to (31), wherein $-X-$ is $-NH-$, or its pharmaceutically acceptable salt or a solvate thereof.

[0021]

(33) A compound of the formula (IV):

[Chemical Formula 7]



wherein

Z^1 , Z^2 and Z^3 are each independently an oxygen atom or a sulfur atom;

R^{c1} is unsubstituted alkyl, unsubstituted alkynyl, alkyl substituted with one or more substituents selected from Substituent Group B (Substituent Group B: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, and nitro), alkenyl substituted with one or more substituents selected from Substituent Group B, alkynyl substituted with one or more substituents selected from Substituent Group B;

R^{4a} is a hydrogen atom or substituted or unsubstituted alkyl;

R^{4b} is a hydrogen atom;

R⁶ is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

R^{4a'} is a hydrogen atom or substituted or unsubstituted alkyl;

R^{4b'} is a hydrogen atom; and

R^{6'} is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; provided that

1) a compound wherein R^{c1} is ethyl substituted with substituted or unsubstituted amino, or propyl substituted with substituted or unsubstituted amino, and R⁶ and R^{6'} are both substituted or unsubstituted phenyl, and

2) a compound wherein R^{c1} is unsubstituted oxirane, substituted or unsubstituted phenyl, or alkyl substituted with unsubstituted acetyl, are excluded,

or its pharmaceutically acceptable salt or a solvate thereof.

(34) The compound according to the above (33), wherein Z¹, Z² and Z³ are oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(35) The compound according to the above (33) or (34), wherein R⁶ is cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl), aryl optionally substituted with one or more substituents selected from Substituent Group C, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

(36) The compound according to any one of the above (33) to (35), wherein R^{6'} is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof.

[0022]

(37) A pharmaceutical composition comprising the compound according to any one of the above (1) to (36), or its pharmaceutically acceptable salt, or a solvate thereof.

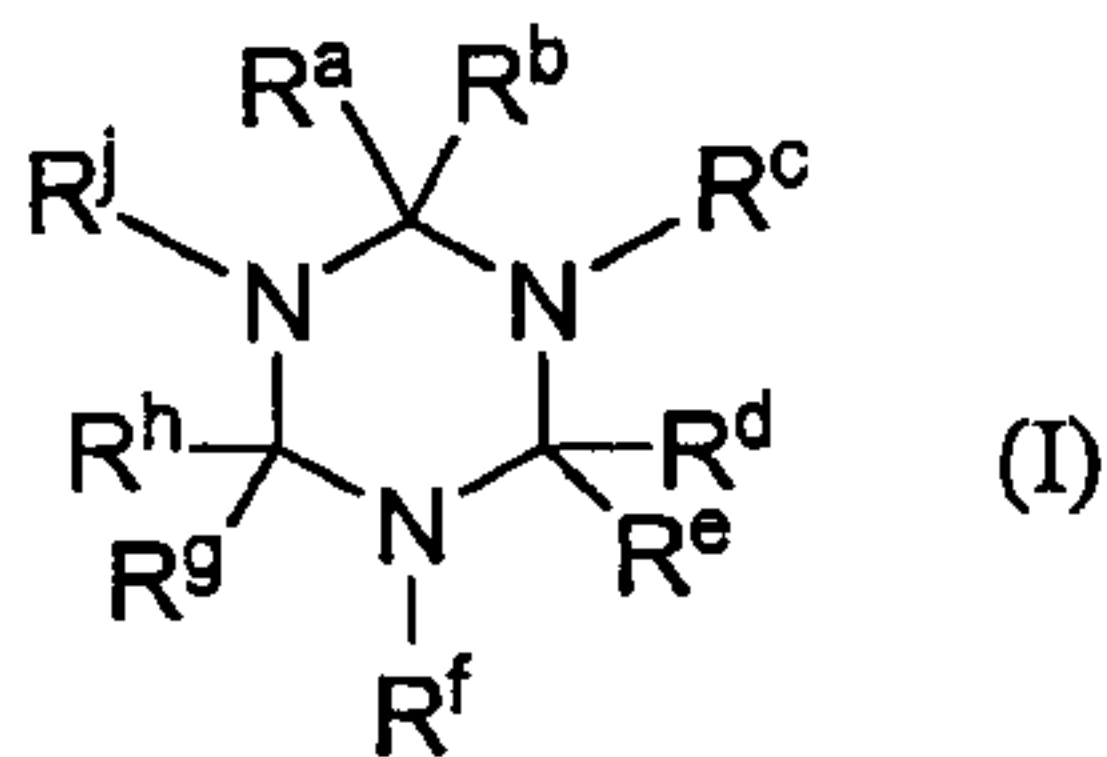
(38) The pharmaceutical composition according to the above (37), wherein the composition has a P2X₃ and/or P2X_{2/3} receptor antagonistic effect.

(39) A compound according to any one of the above (1) to (36), 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.

(40) A method for treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor comprising administering the compound according to any one of the above (1) to (36), or its pharmaceutically acceptable salt, or a solvate thereof.

(41) A pharmaceutical composition having an analgesic effect or an improving effect of urination disorder comprising a compound of the formula (I):

[Chemical Formula 8]



wherein

(i)

 R^h and R^j are taken together to form a bond; R^a and R^b and/or R^d and R^e are taken together to form oxo, thioxo or $=N-R^x$; R^x is a hydrogen atom, 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 hydrogen atom, 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; $-R^f$ is $-(CR^{4a}R^{4b})_n-R^2$; R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo; n is an integer of 1 to 4; 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; $-R^g$ is $-X-R^3$; $-X-$ is $-O-$, $-S-$, $-N(R^5)-$ or $-(CR^{5a}R^{5b})-$; R^3 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^5 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted acyl; and R^{5a} and R^{5b} are each independently a hydrogen atom, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy; or

[0024]

(ii)

 R^h and R^j are taken together to form a bond; R^a is a group of $-Y-R^{1a}$; R^{1a} is a hydrogen atom, 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 a hydrogen atom, substituted or unsubstituted alkyl, or substituted or unsubstituted acyl;

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

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

R^d and R^e are taken together to form oxo or thioxo; and

R^f and R^g are as defined in the above (i); or

[0025]

(iii)

R^a and R^b , R^d and R^e , and/or R^g and R^h are taken together to form oxo or thioxo;

R^c is unsubstituted alkyl, unsubstituted alkynyl, alkyl substituted with one or more substituents selected from Substituent Group B (Substituent Group B: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, and nitro), alkenyl substituted with one or more substituents selected from Substituent Group B, or alkynyl substituted with one or more substituents selected from Substituent Group B;

R^f is $-(CR^{4a}R^{4b})-R^6$;

R^j is $-(CR^{4a'}R^{4b'})-R^{6'}$;

R^6 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

$R^{6'}$ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

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

[0026]

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

R^a is a group of $-Y-R^{1a}$;

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

R^{1a} is a hydrogen atom, 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; R^c is a hydrogen atom, 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; R^d and R^e are taken together to form oxo, thioxo or $=N-R^x$;

R^x is a hydrogen atom, 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;

$-R^f$ is $-(CR^{4a}R^{4b})_n-R^2$;

R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo;

n is an integer of 1 to 4;

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^g and R^h are taken together to form $=N-R^3$; and

R^3 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, provided that

1) a compound wherein, in (i), $-X-$ is $-NH-$, and R^3 is cyclohexyl substituted with guanidyl, and

2) a compound wherein, in (ii), R^a is substituted phenyl, R^d and R^e are taken together to form thioxo, R^{4a} and R^{4b} are taken together to form oxo, and R^3 is unsubstituted cyclohexyl,

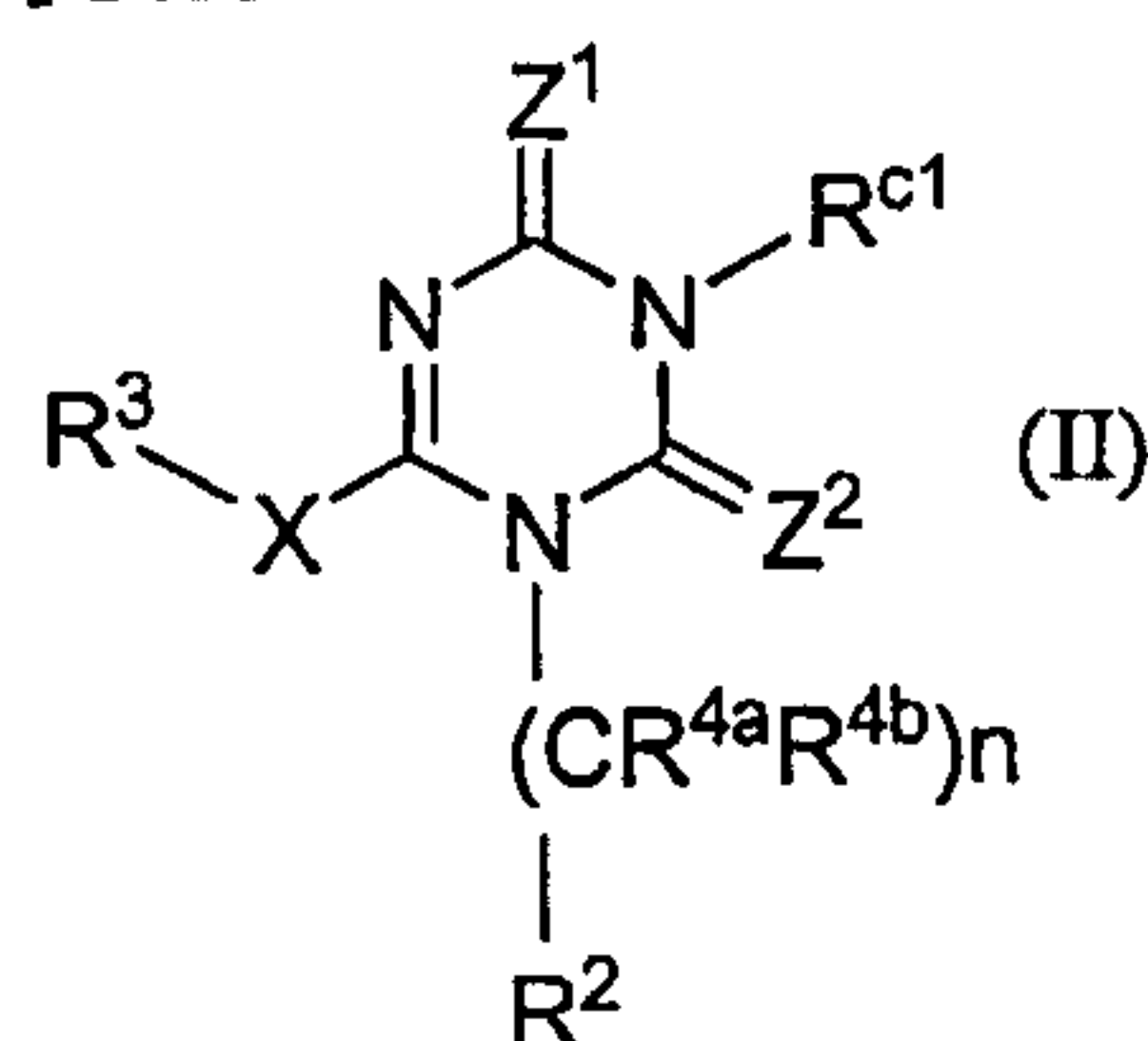
are excluded,

or its pharmaceutically acceptable salt or a solvate thereof.

[0027]

(42) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to the above (41), comprising the compound of the formula (II):

[Chemical Formula 9]



wherein

Z^1 and Z^2 are each independently an oxygen atom, a sulfur atom or $=N-R^x$; R^x , R^{4a} , R^{4b} , n , R^2 , X , and R^3 are as defined in the above (41); and R^{c1} is a hydrogen atom, 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 its pharmaceutically acceptable salt or a solvate thereof.

(43) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to the above (42), comprising the compound wherein Z^1 and Z^2 are both oxygen atoms or both sulfur atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(44) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder, according to the above (42) or (43), comprising the compound wherein Z^1 and Z^2 are both oxygen atoms or its pharmaceutically acceptable salt or a solvate thereof.

(45) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (44), comprising the compound wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof.

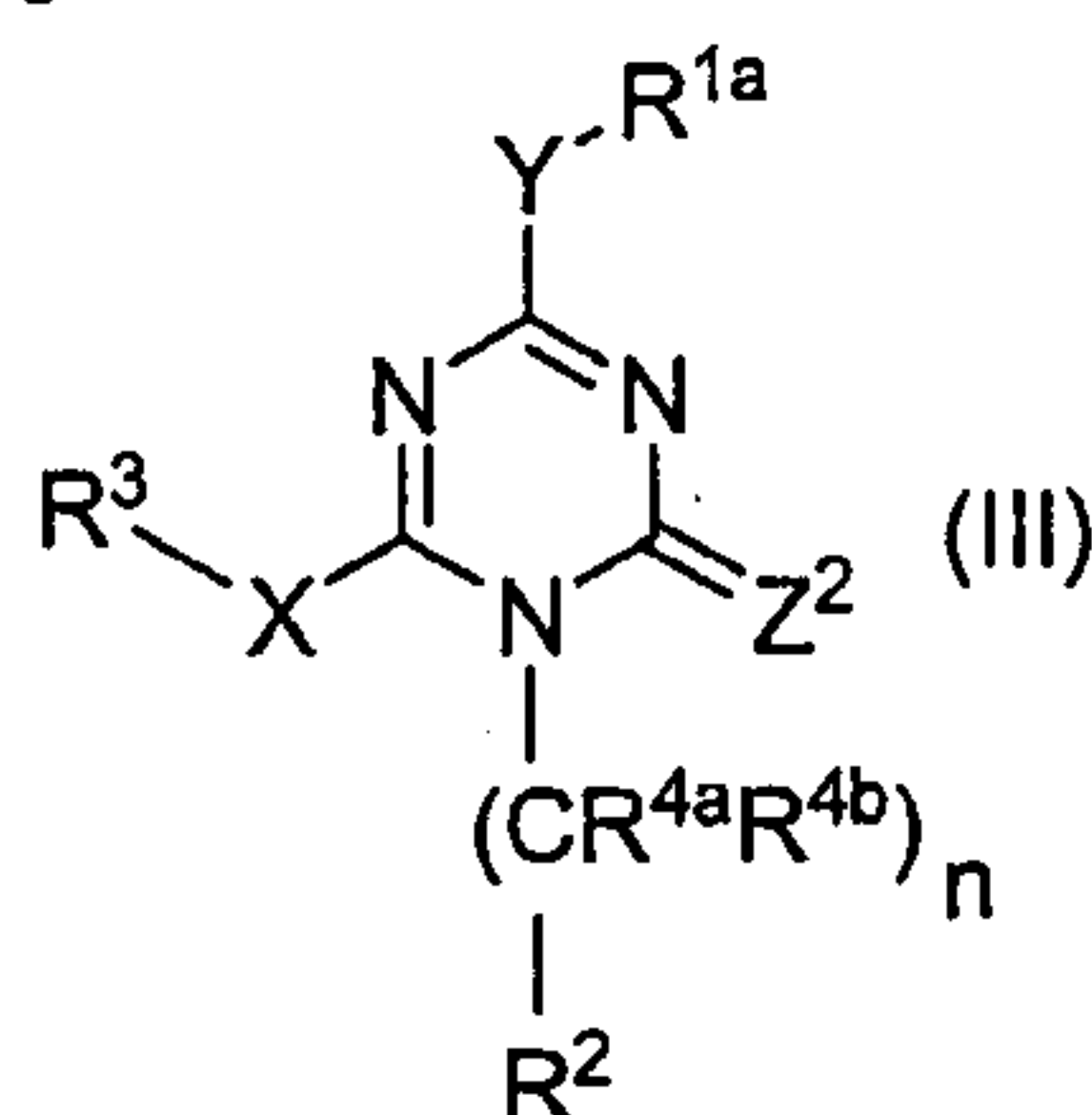
(46) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (45), comprising the compound wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents

selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof.

[0028]

(47) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to the above (41), comprising the compound of the formula (III):

[Chemical Formula 10]



wherein Z^2 is an oxygen atom, a sulfur atom or $=N-R^x$; and R^x , $-Y-$, R^{1a} , R^{4a} , R^{4b} , n , R^2 , $-X-$ and R^3 are as defined in the above (41), or its pharmaceutically acceptable salt or a solvate thereof.

(48) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to the above (47), comprising the compound wherein Z^2 is an oxygen atom or a sulfur atom, or its pharmaceutically acceptable salt or a solvate thereof.

(49) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to the above (47) or (48), comprising the compound wherein $-Y-$ is $-O-$, or its pharmaceutically acceptable salt or a solvate thereof.

(50) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (47) to (49), comprising the compound wherein R^{1a} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocycloxyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof.

[0029]

(51) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (47) to (50), comprising the compound wherein R^{1a} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof.

(52) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (51), comprising the compound wherein n is 1, or its pharmaceutically acceptable salt or a solvate thereof.

(53) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (52), comprising the compound wherein R^{4a} and R^{4b} are both hydrogen atoms, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo, or its pharmaceutically acceptable salt or a solvate thereof.

(54) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (53), comprising the compound wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof.

(55) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (54), comprising the compound wherein R^2 is cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl), aryl optionally substituted with one or more substituents selected from Substituent Group C, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

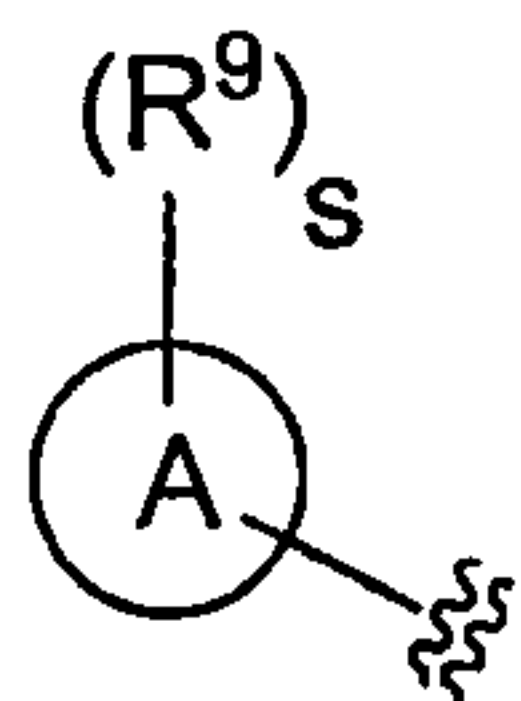
(56) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (55), comprising the compound wherein $-X-$ is $-N(R^5)-$, and R^5 is as defined in the above (41), or its pharmaceutically acceptable salt or a solvate thereof.

(57) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (56), comprising the compound wherein $-X-$ is $-NH-$, or its pharmaceutically acceptable salt or a solvate thereof.

[0030]

(58) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (57), comprising the compound wherein R^3 is a group of the formula:

[Chemical Formula 11]



wherein ring A is an aromatic carbocyclic ring or an aromatic heterocyclic ring;
s is an integer of 0 to 3; and

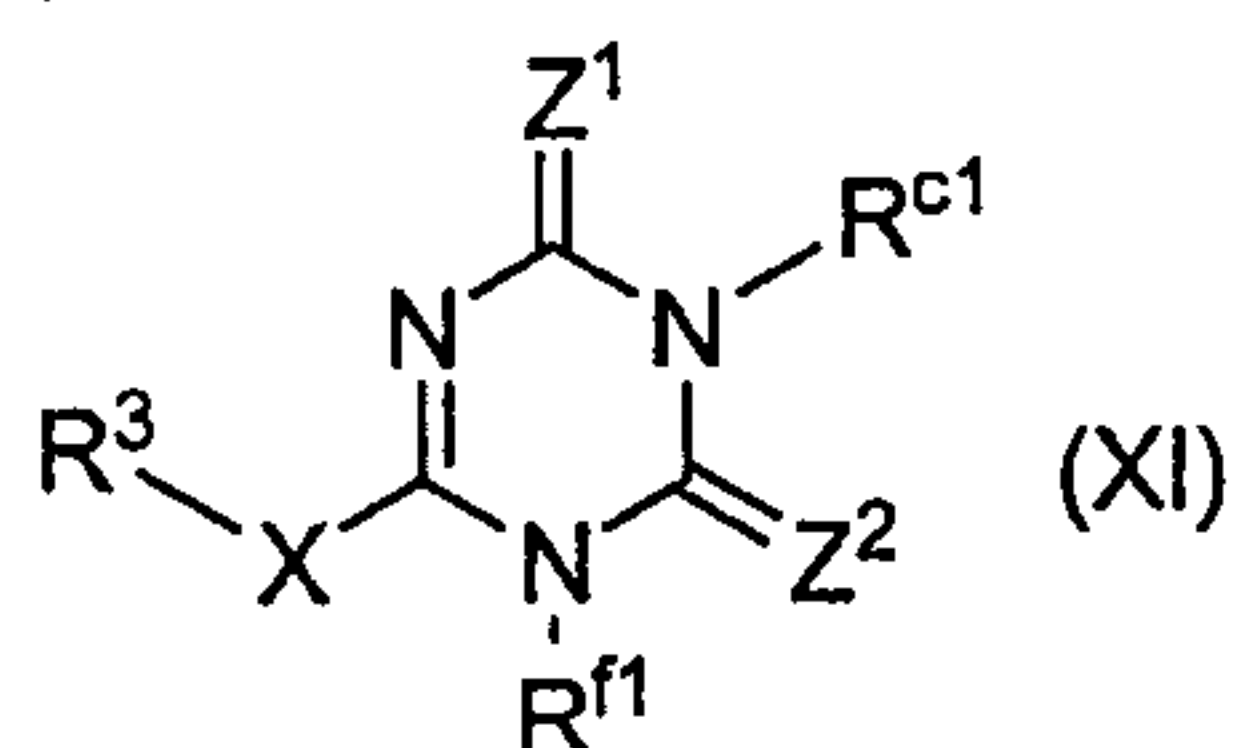
R⁹ is each independently halogen, hydroxy, carboxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, 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 sulfonyl, substituted sulfinyl, 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 heterocyclyloxy, substituted or unsubstituted aryloxy or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof.

(59) The pharmaceutical composition having an analgesic effect or an improving effect of urination disorder according to any one of the above (42) to (58), comprising the compound wherein R³ is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof.

[0031]

(60) A method of producing a compound of the formula (XI):

[Chemical Formula 12]



wherein Z¹ and Z² are each independently an oxygen atom or a sulfur atom,
R^{f1} is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

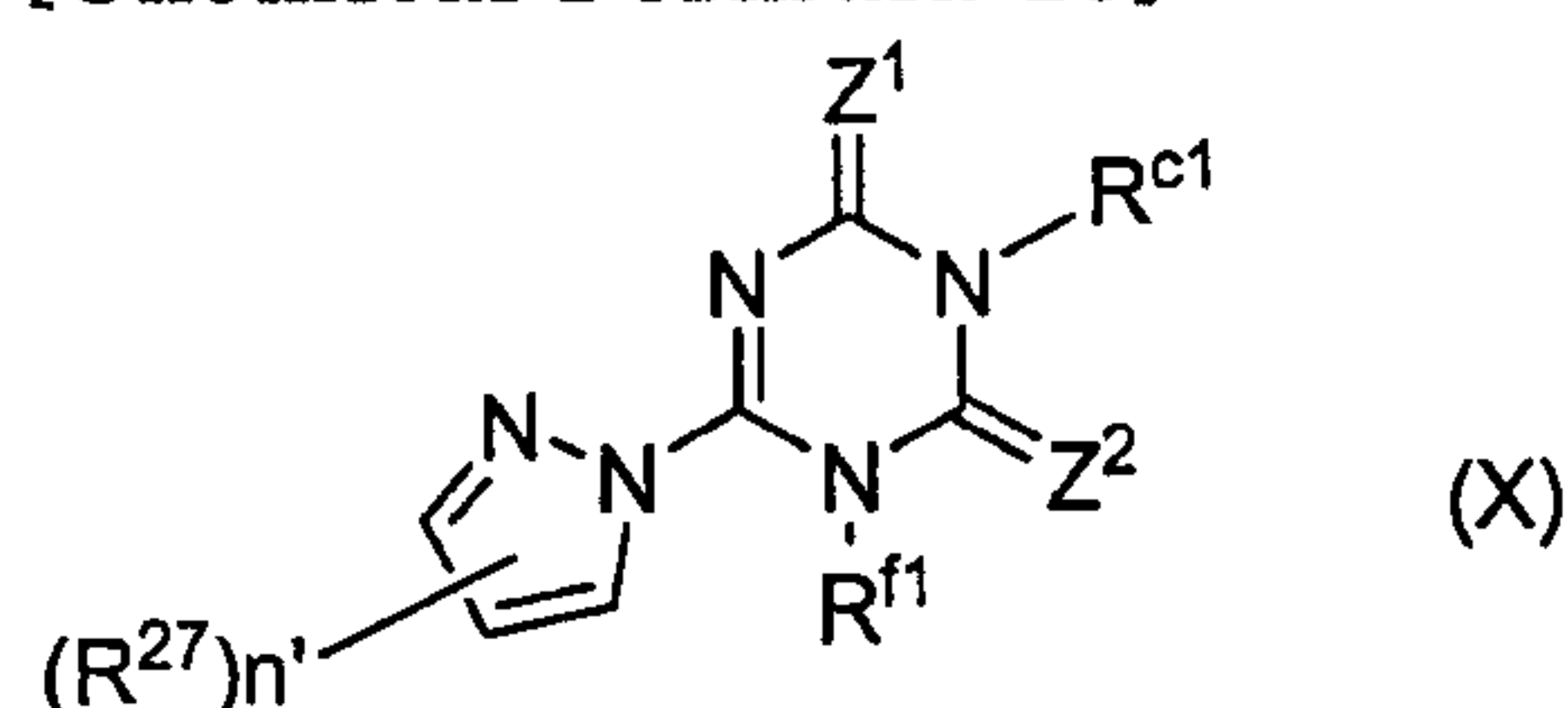
unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; R^{c1} is substituted or unsubstituted alkyl, substituted 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;

R^3 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;

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

R^5 is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl or substituted or unsubstituted acyl, or its pharmaceutically acceptable salt or a solvate thereof, characterized by reacting a compound of the formula (X):

[Chemical Formula 13]



wherein Z^1 , Z^2 , R^{f1} and R^{c1} are as defined above;

R^{27} is substituted or unsubstituted alkyl; and

n' is an integer of 0 to 3 or its salt,

with a compound of the formula: R^3-X'

wherein R^3 is as defined above;

$-X'$ is $-NH(R^5)$; and

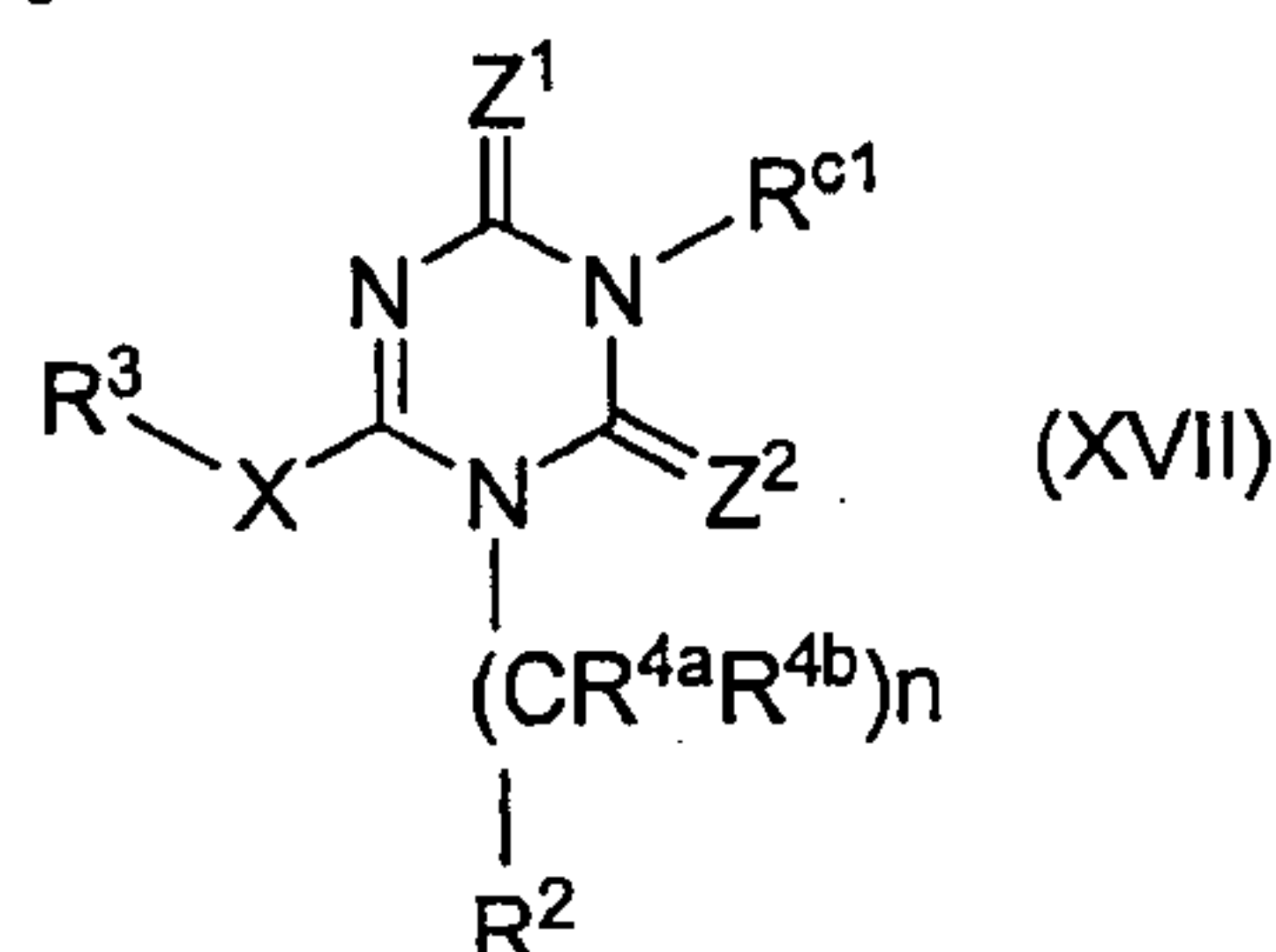
R^5 is as defined above.

In the above (60), the following compound of the formula (XII), its pharmaceutically acceptable salt or a solvate thereof can be used instead of the compound of the formula (X), its pharmaceutically acceptable salt or a solvate thereof.

[0032]

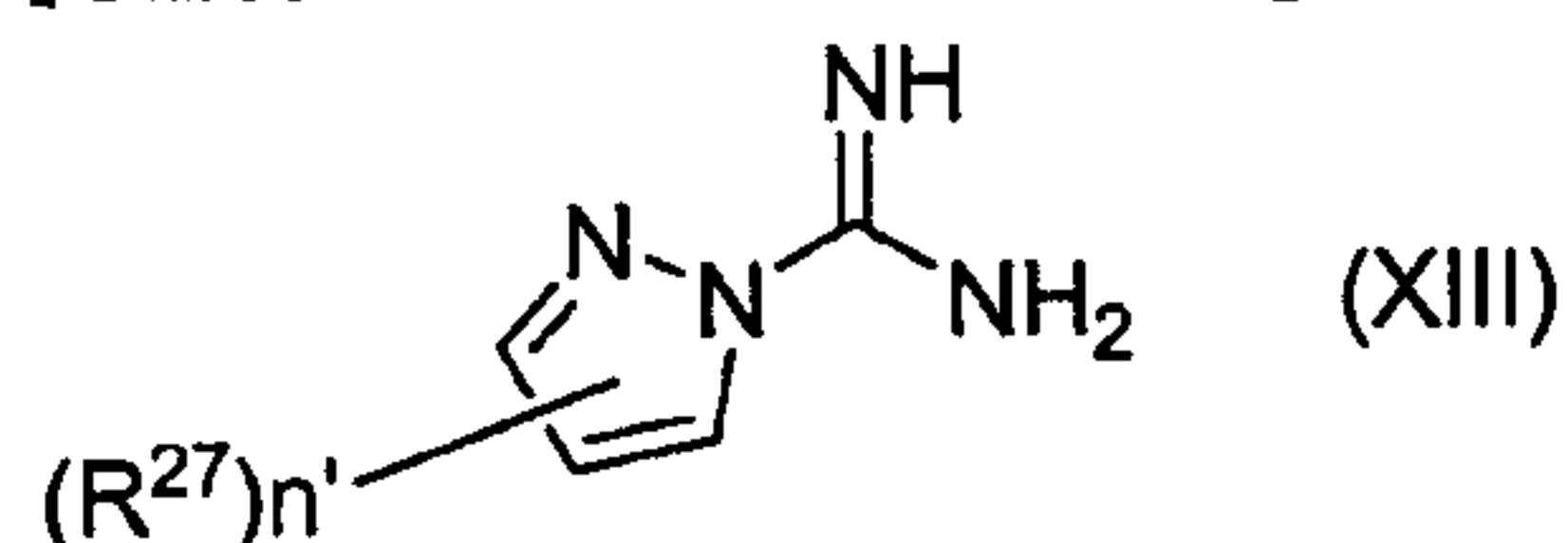
(60') A method of producing a compound of the formula (XVII):

[Chemical Formula 14]



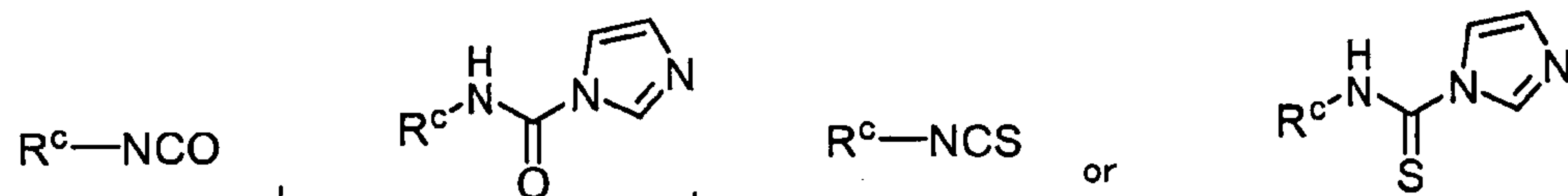
wherein Z^1 , Z^2 , R^{c1} , R^{4a} , R^{4b} , n , R^2 , X and R^3 are as defined in the (62) mentioned below, or its pharmaceutically acceptable salt or a solvate thereof comprising the steps of
i) reacting a compound of the formula (XIII);

[Chemical Formula 15]



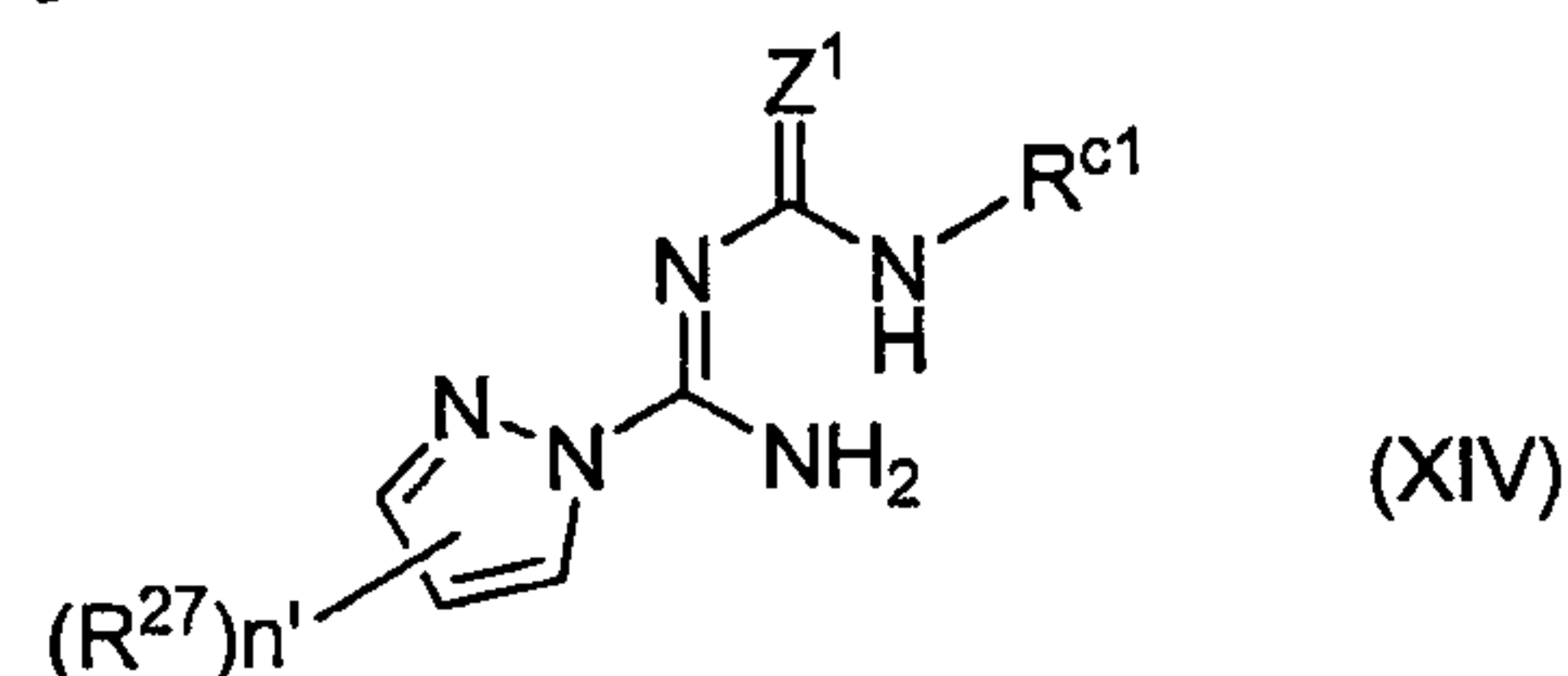
wherein R^{27} and n' are as defined in the above (60) or its salt with a compound of the formula:

[Chemical Formula 16]



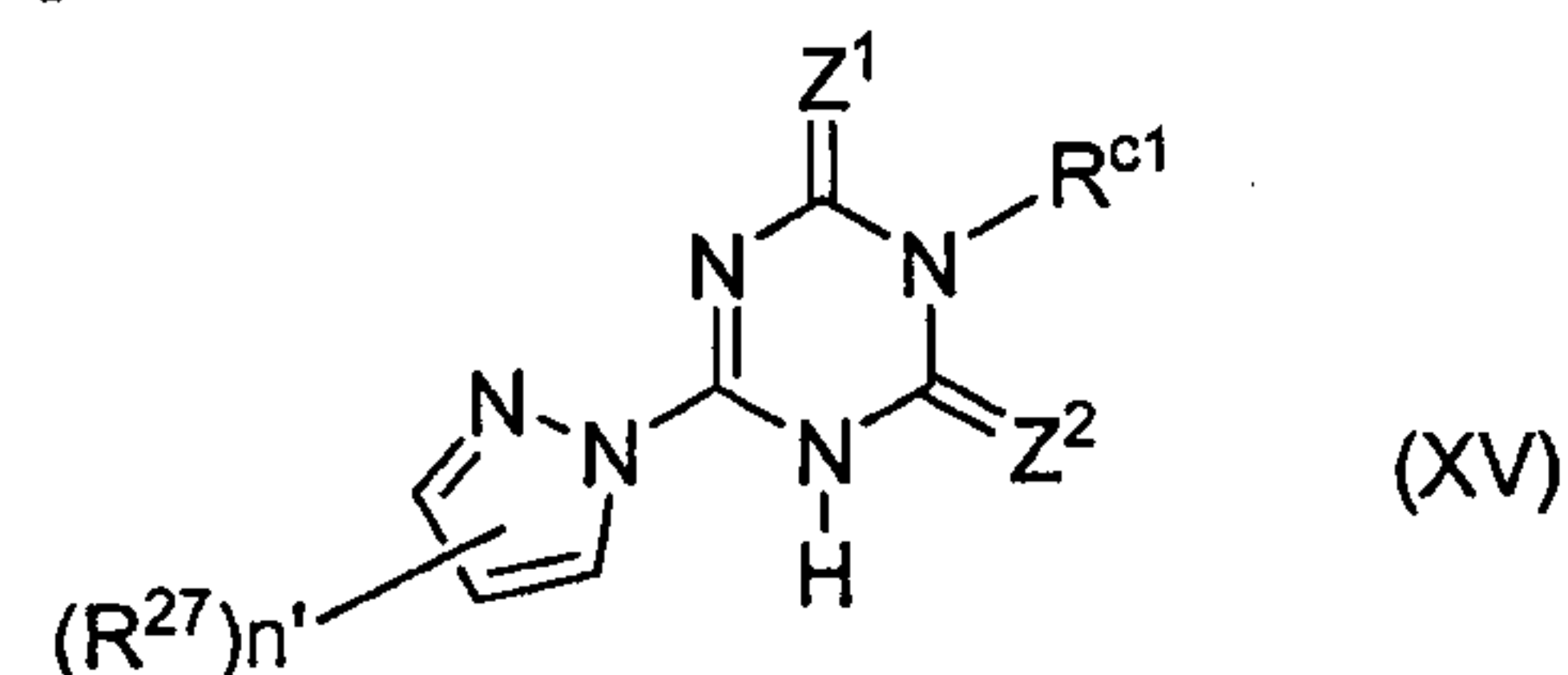
wherein R^c is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl or its salt in the presence of a base to give a compound of the formula (XIV):

[Chemical Formula 17]



wherein Z^1 , R^{c1} , R^{27} and n' are as defined in the above (60) or its salt,
 ii) reacting the compound of the formula (XIV) or its salt with a carbonylating agent or a thiocarbonylating agent in the presence of a base to give a compound of the formula (XV):

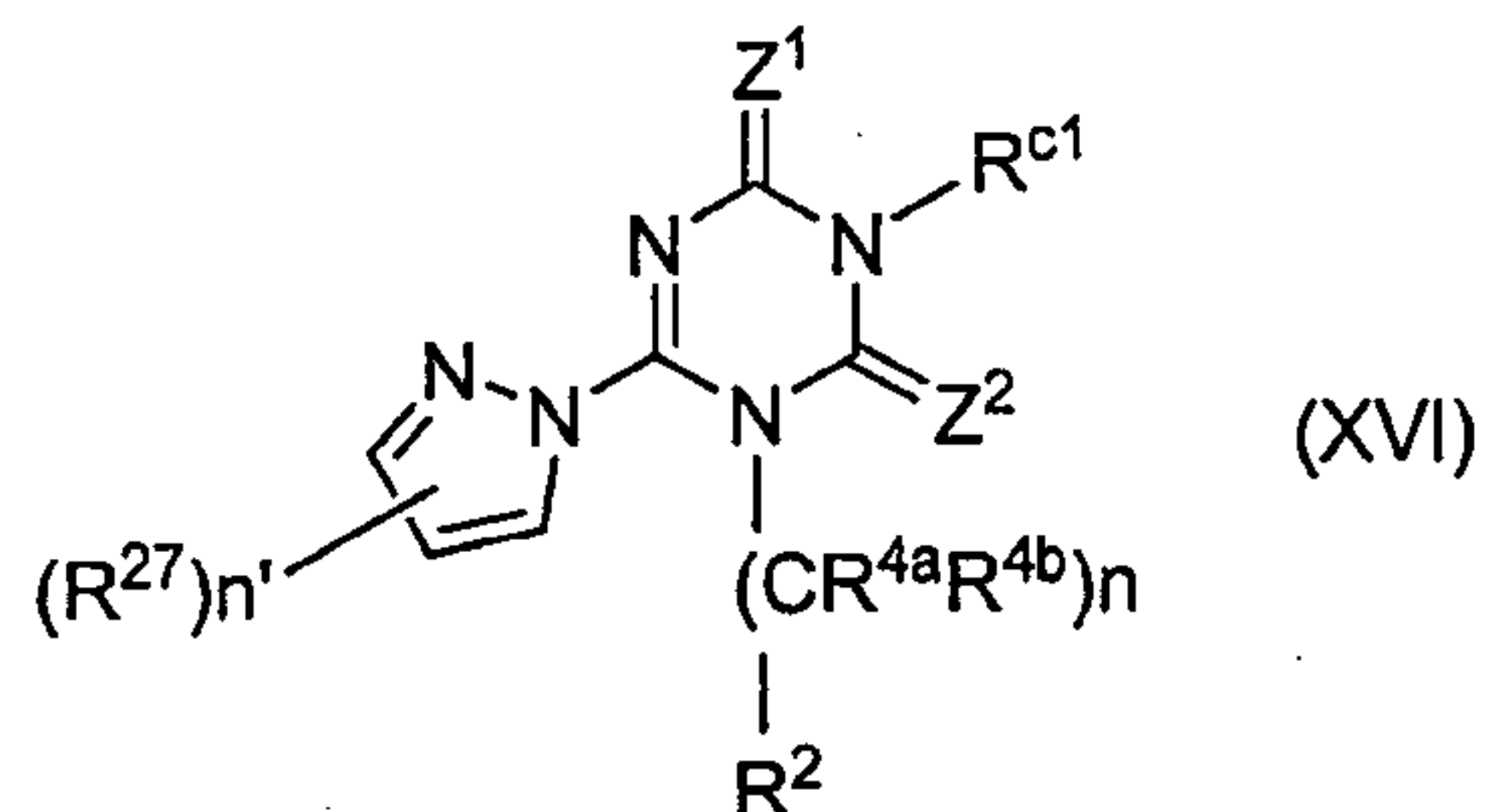
[Chemical Formula 18]



wherein Z^1 , Z^2 , R^{c1} , R^{27} and n' are as defined in the above (60) or its salt,
 iii) reacting the compound of the formula (XV) with a compound of the formula:
 $R^2-(CR^{4a}R^{4b})_n-Y$

wherein R^2 , R^{4a} , R^{4b} and n are as defined in the (62) mentioned below and Y is a leaving group or its salt in the presence of a base to give a compound of the formula (XVI):

[Chemical Formula 19]



wherein Z^1 , Z^2 , R^{c1} , R^{4a} , R^{4b} , n , R^2 , R^{27} and n' are as defined in the (62) mentioned below or its salt,

and

iv) reacting the compound of the formula (XVI) or its salt with a compound of the formula:

R^3-X'

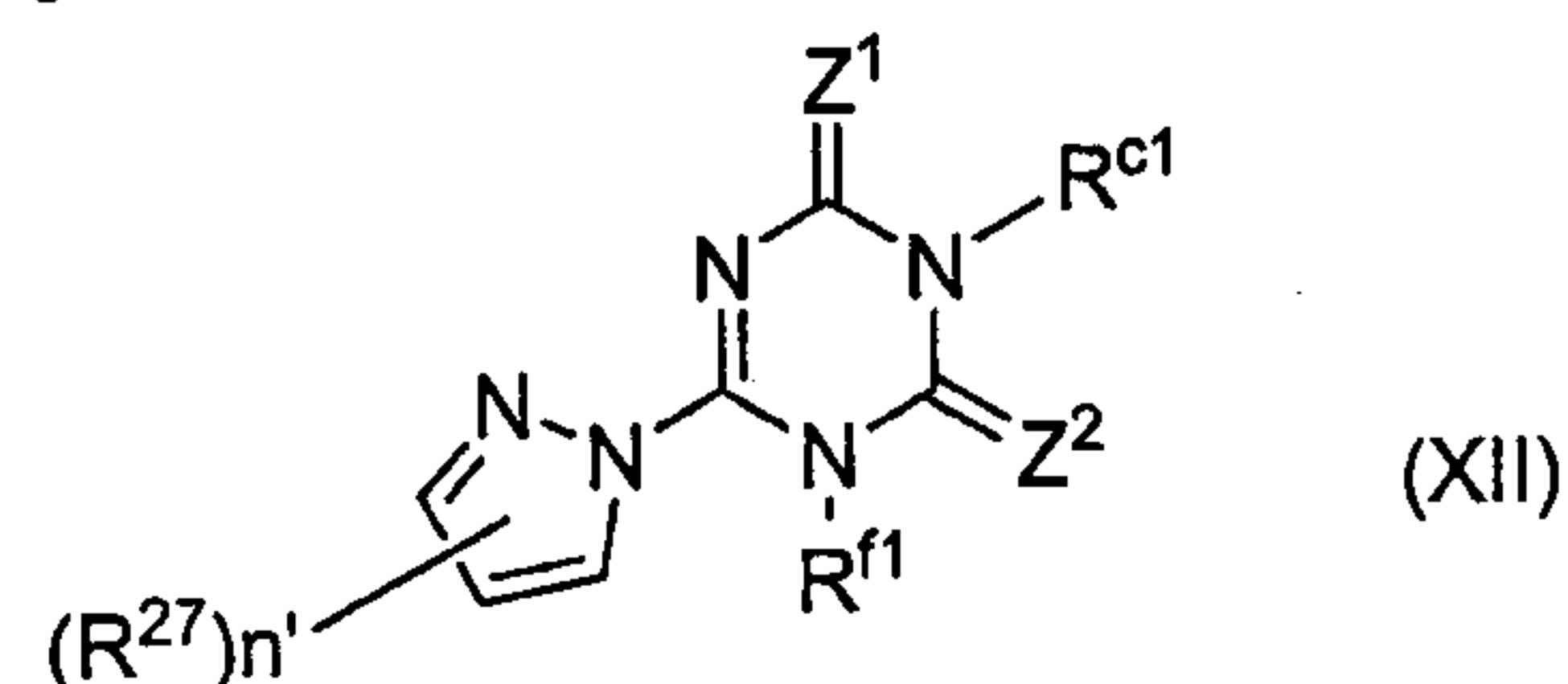
wherein R^3 and $-X'$ are as defined in the above (60) or its salt.

[0034]

In the above (60'), "to give a compound or its salt" includes a case that the compound or its salt are presence in a reaction system and a case that the compound or its salt are isolated.

In the above (60'), a compound of the following formula (XII):

[Chemical Formula 20]



wherein R^{f1} is $-(CR^{4a}R^{4b})_n-R^2$ wherein R^{4a} , R^{4b} , n and R^2 are as defined in the (68) mentioned below; Z^1 , Z^2 , R^{c1} , R^{27} and n' are as defined in the (66) mentioned below, or its pharmaceutically acceptable salt or a solvate thereof can be used instead of the compound of the formula (XVI) or its pharmaceutically acceptable salt or a solvate thereof.

(61) The method according to the above (60) or (60'), wherein Z^1 and Z^2 are oxygen atoms.

(62) The method according to any one of the above (60), (60') and (61), wherein R^{f1} is a group of $-(CR^{4a}R^{4b})_n-R^2$; wherein R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo;

n is an integer of 1 to 4; and

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.

(63) The method according to any one of the above (60), (60'), (61) and (62), wherein R^{c1} is substituted or unsubstituted alkyl.

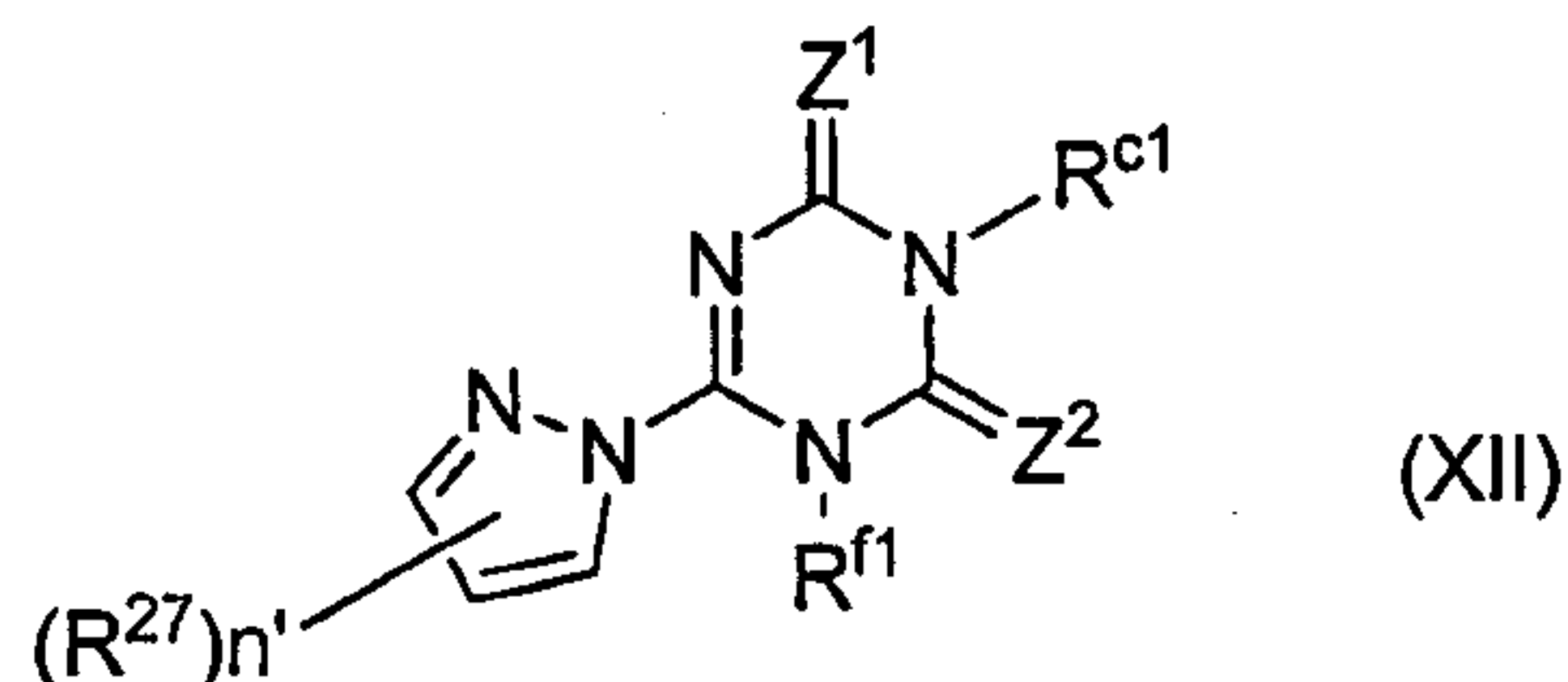
(64) The method according to any one of the above (60), (60'), and (61) to (63), wherein R^5 is a hydrogen atom.

(65) The method according to any one of the above (60), (61'), and (61) to (64), wherein R^3 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0035]

(66) A compound of the formula (XII):

[Chemical Formula 21]



wherein Z^1 and Z^2 are each independently an oxygen atom or a sulfur atom; R^{f1} is a hydrogen atom, 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; R^{c1} is 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; provided that R^{c1} is not unsubstituted alkyl, unsubstituted alkenyl or unsubstituted cycloalkyl when R^{f1} is a hydrogen atom; R^{27} is substituted or unsubstituted alkyl; and n' is an integer of 0 to 3, or its pharmaceutically acceptable salt or a solvate thereof.

(67) The compound according to the above (66), wherein Z^1 and Z^2 are oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(68) The compound according to the above (66) or (67), wherein R^{f1} is a group of $-(CR^{4a}R^{4b})_n-R^2$;

wherein R^{4a} and R^{4b} are each independently a hydrogen atom or substituted or unsubstituted alkyl, or R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo;

n is an integer of 1 to 4; and

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, or its pharmaceutically acceptable salt or a solvate thereof.

(69) The compound according to any one of the above (66) to (68), wherein R^{c1} is substituted or unsubstituted alkyl, or its pharmaceutically acceptable salt or a solvate thereof.

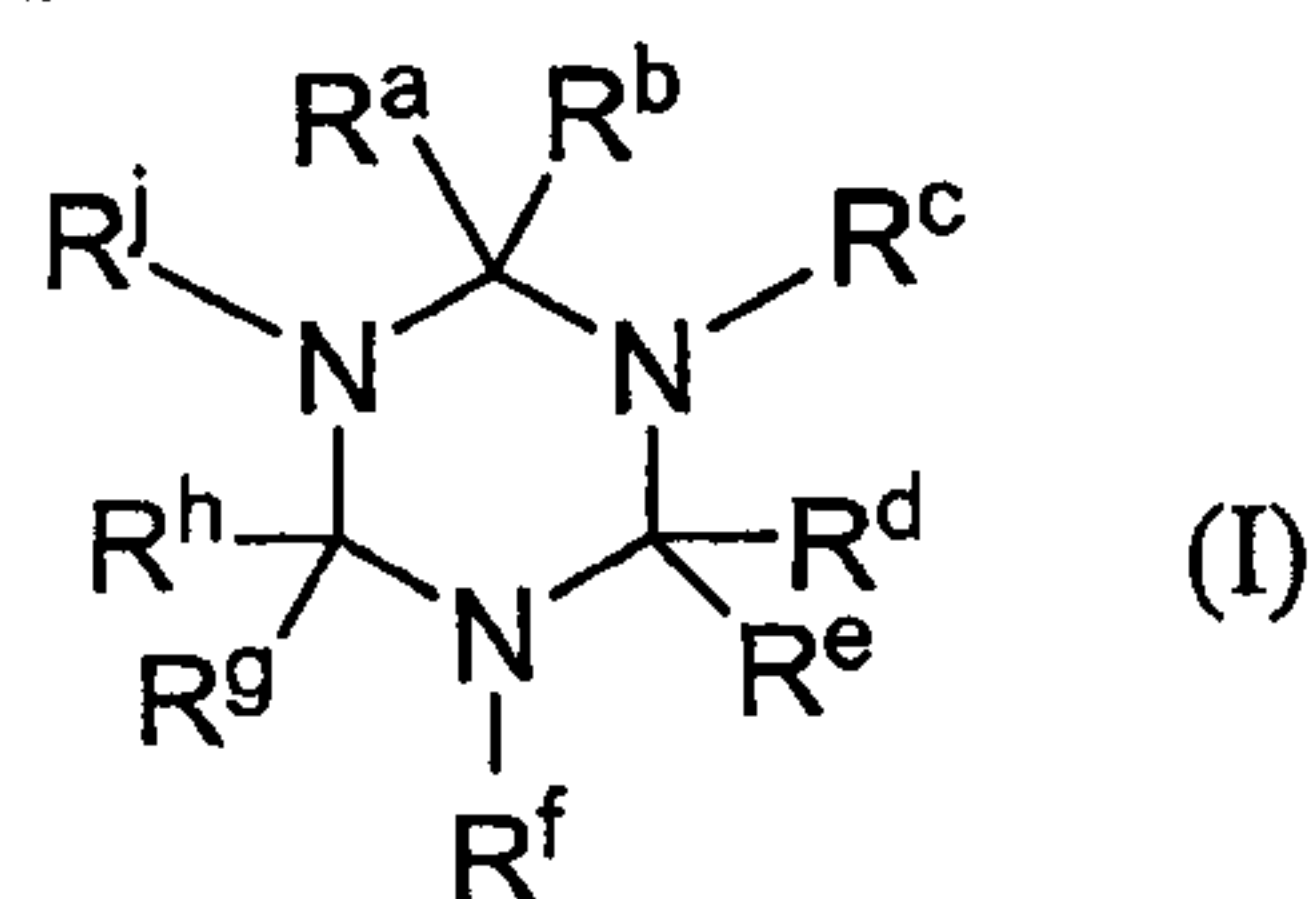
(70) The compound according to any one of the above (66) to (69), wherein R^5 is a hydrogen atom, or its pharmaceutically acceptable salt or a solvate thereof.

[0036]

Furthermore, the present invention relates to the followings:

(1B) A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising a compound of the formula (I):

[Chemical Formula 22]



wherein

(i)

 R^h and R^j are taken together to form a bond; R^a and R^b and/or R^d and R^e are taken together to form oxo, thioxo, or $=N \cdot R^x$; R^x 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 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; $-R^f$ is $-(CR^{4a}R^{4b})_n \cdot R^2$; R^{4a} and R^{4b} are each independently hydrogen, substituted or unsubstituted alkyl, or R^{4a} and R^{4b} are taken together to form oxo or thioxo; n is an integer of 1-4; R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^g is $-X \cdot R^3$; $-X-$ is $-O-$, $-S-$, $-N(R^5)-$, or $-(CR^{5a}R^{5b})-$; R^3 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^5 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl; R^{5a} and R^{5b} are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy;

(ii)

 R^h and R^j are taken together to form a bond; R^a is a group of $-Y \cdot R^{1a}$; 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;

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

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

R^d and R^e are taken together to form oxo or thioxo;

R^f and R^g are as defined in the above (i);

(iii)

R^a and R^b , R^d and R^e , and/or R^g and R^h are taken together to form oxo or thioxo;

R^c is unsubstituted alkyl, unsubstituted alkynyl, alkyl substituted with one or more substituents selected from Substituent Group B (Substituent Group B: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, and nitro), alkenyl substituted with one or more substituents selected from Substituent Group B, or alkynyl substituted with one or more substituents selected from Substituent Group B;

R^f is $-(CR^{4a}R^{4b})-R^6$;

R^j is $-(CR^{4a'}R^{4b'})-R^{6'}$;

R^6 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

$R^{6'}$ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

(iv)

R^j and R^b are taken together to form a bond;

R^a is a group of $-Y-R^{1a}$;

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

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;

R^c 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;

R^d and R^e are taken together to form oxo, thioxo, or $=N-R^x$;

R^x 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;

$-R^f$ is $-(CR^{4a}R^{4b})_n-R^2$;

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

R^{4a} and R^{4b} are taken together to form oxo or thioxo;

n is an integer of 1 to 4;

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^g and R^h are taken together to form $=N-R^3$;

R^3 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, provided that

1) a compound wherein, in (i), $-X-$ is $-NH-$, and R^3 is cyclohexyl substituted with guanidyl, and

2) a compound wherein, in (ii), R^a is substituted phenyl, R^d and R^e are taken together to form thioxo, R^{4a} and R^{4b} are taken together to form oxo, and R^3 is unsubstituted cyclohexyl,

are excluded,

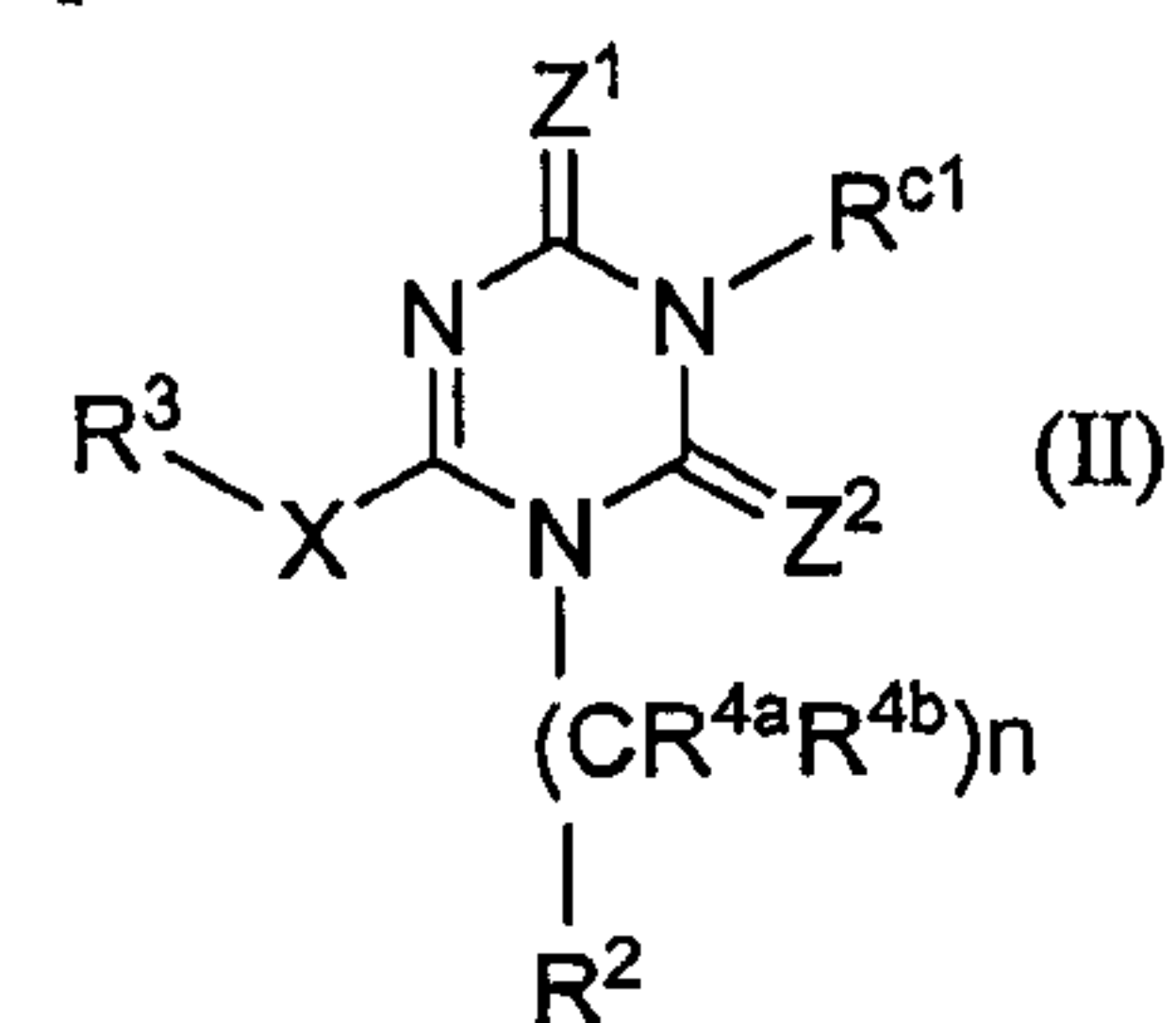
or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0037]

Furthermore, the present invention relates to the mentioned below.

(2) A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the formula (II):

[Chemical Formula 23]



wherein

Z^1 and/or Z^2 is an oxygen atom, a sulfur atom, or $(=)N-R^x$;

R^x , R^{4a} , R^{4b} , n , R^2 , X and R^3 are as defined in the above (1B);

R^{c1} 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 its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(3B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (2B) wherein Z^1 and/or Z^2 is an oxygen atom or a sulfur atom or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(4B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (2B) or (3B) wherein Z^1 and Z^2 are both oxygen atoms, its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

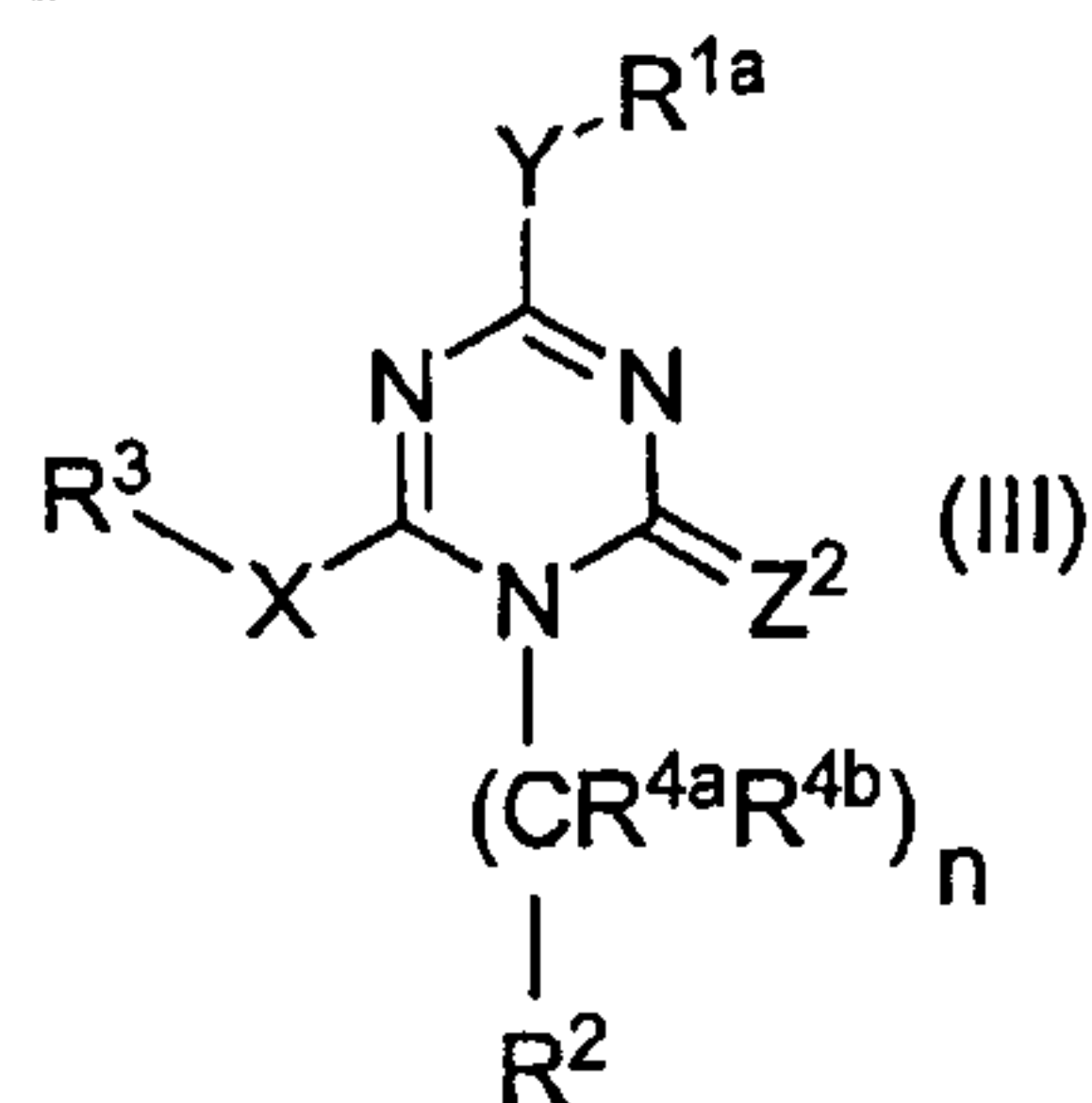
(5B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (4B) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0038]

(6B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (5B) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(7B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder according to the above (1B) comprising the compound of the formula (III):

[Chemical Formula 24]



wherein Z^2 is an oxygen atom, a sulfur atom or $(=)\text{N-R}^x$; R^x , $-\text{Y}-$, R^{1a} , R^{4a} , R^{4b} , n , R^2 , $-\text{X}-$, and R^3 are as defined in the above (1B) or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(8B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (7B) wherein Z^2 is an oxygen atom or a sulfur atom or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(9B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (7B) or (8B) wherein $-\text{Y}-$ is $-\text{O}-$, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(10B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (7B) to (9B) wherein R^{1a} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0039]

(11B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (7B) to (10B) wherein R^{1a} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted

alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(12B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (11B) wherein n is 1, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredients.

(13B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (12B) wherein R^{4a} and R^{4b} are both hydrogen atoms or R^{4a} and R^{4b} are taken together to form oxo, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(14B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (13B) wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

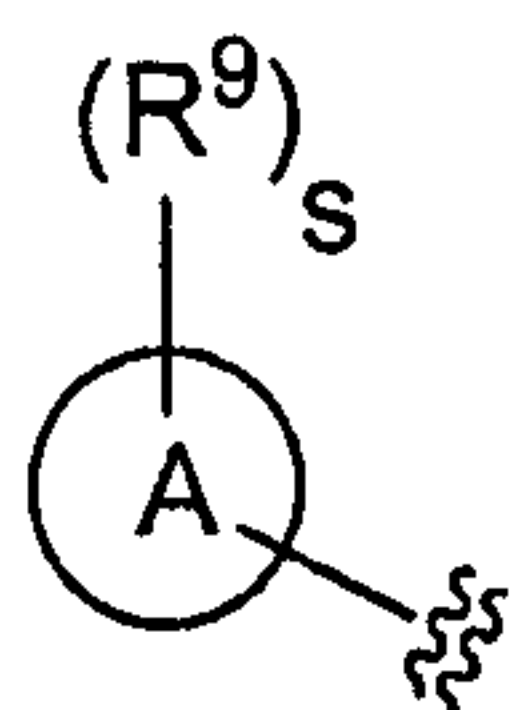
(15B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (14B) wherein R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(16B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (15B) wherein $-X-$ is $-N(R^5)-$ wherein R^5 is as defined in the above (1B), its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.
[0040]

(17B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (16B) wherein $-X-$ is $-NH-$, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(18B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (17B) wherein R^3 is a group of the formula:

[Chemical Formula 25]



wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3;

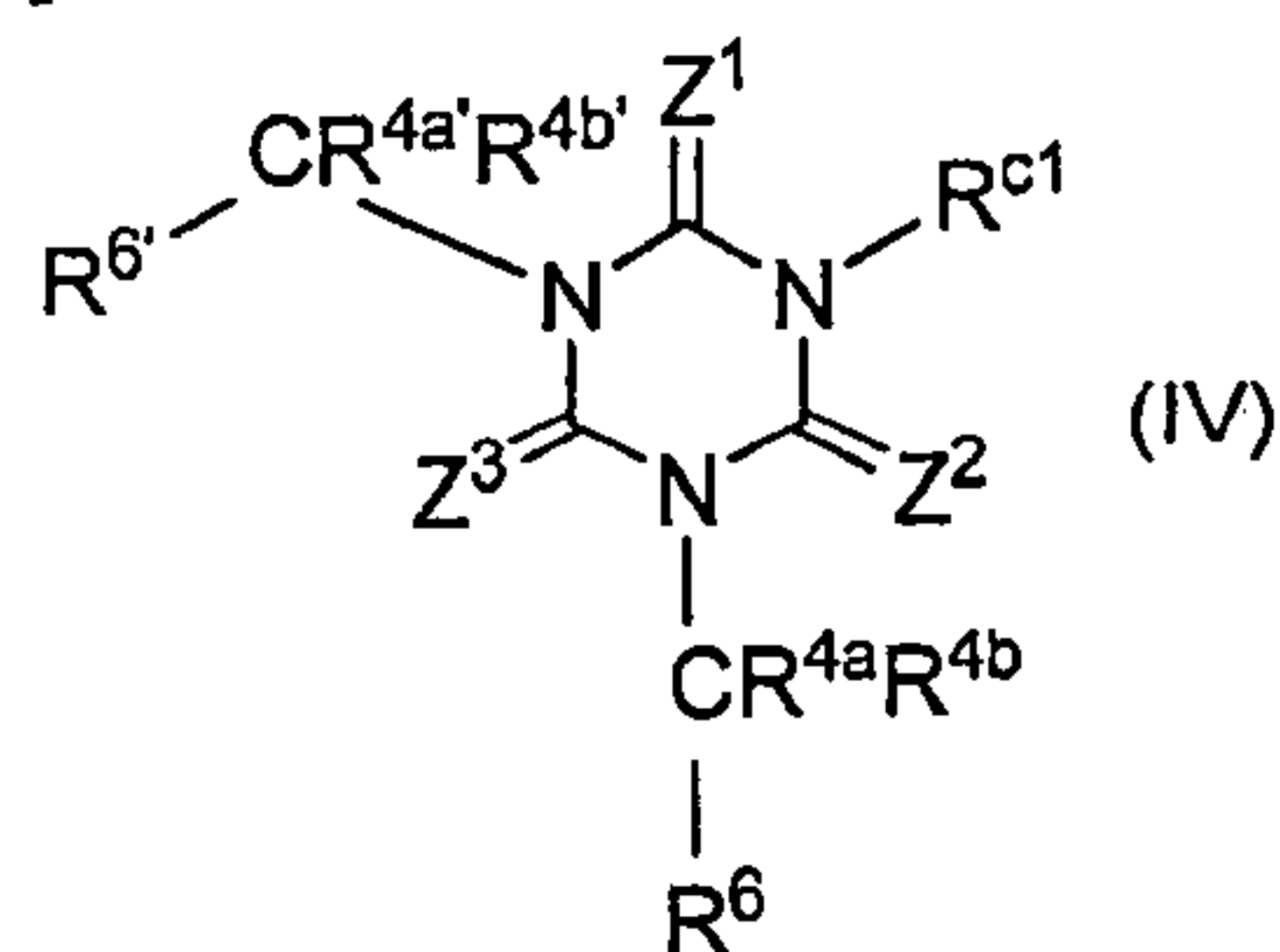
R⁹ are each independently halogen, hydroxy, carboxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted 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 heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(19B) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2B) to (18B) wherein R⁸ is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0041]

(20B) A compound of the formula (IV):

[Chemical Formula 26]



wherein

Z¹, Z², and/or Z³ is an oxygen atom or a sulfur atom;

R^{c1} is unsubstituted alkyl, unsubstituted alkynyl, alkyl substituted with one or more substituents selected from Substituent Group B (Substituent Group B: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, and nitro), alkenyl substituted with one or more substituents selected from Substituent Group B, or alkynyl substituted with one or more substituents selected from Substituent Group B;

R^{4a} is hydrogen or substituted or unsubstituted alkyl;

R^{4b} is hydrogen;

R⁶ is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a'} is hydrogen or substituted or unsubstituted alkyl;

R^{4b'} is hydrogen;

R^{6'} is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or solvate thereof.

(21B) The compound according to the above (20B) wherein Z¹, Z² and Z³ are oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

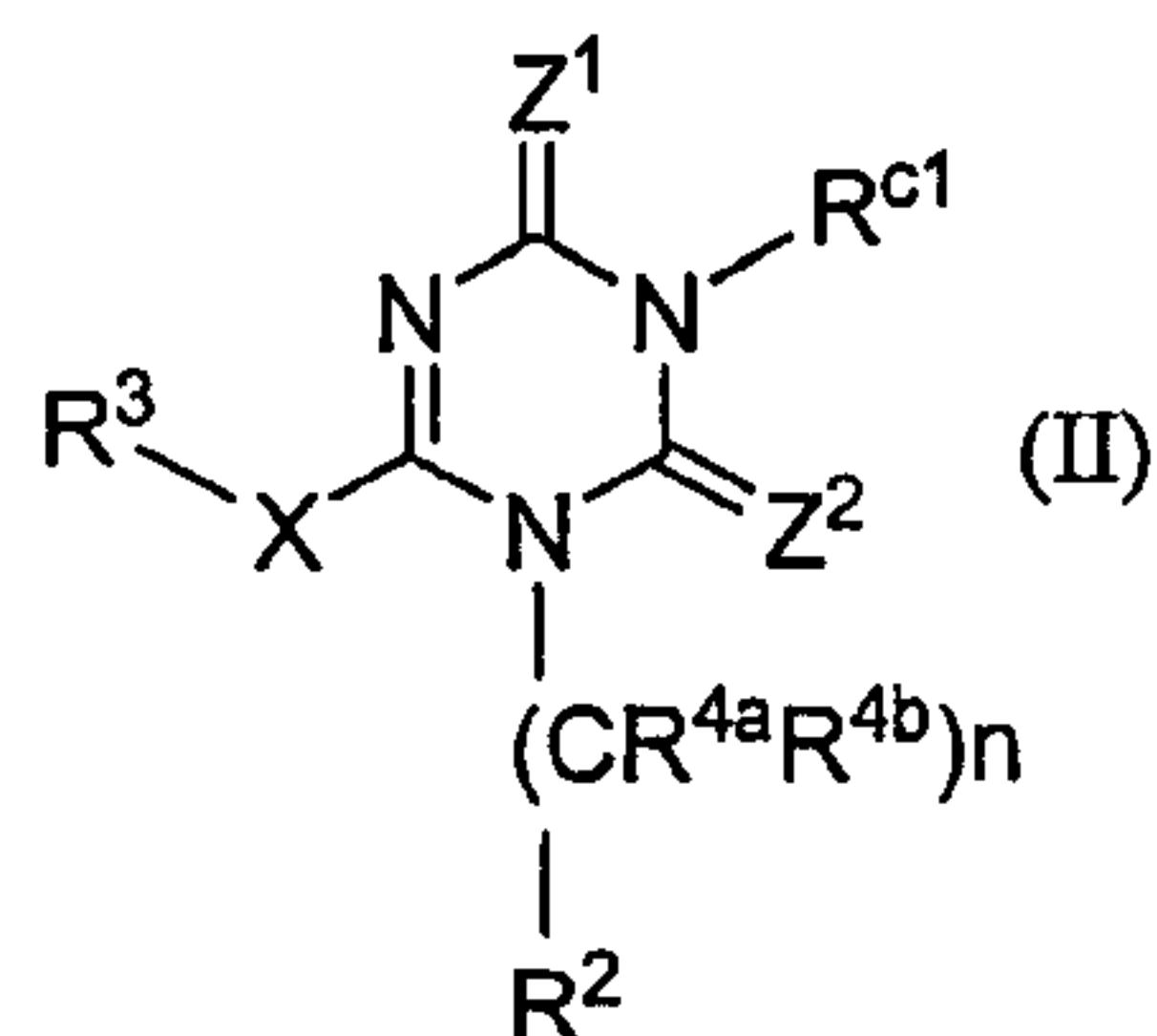
(22B) The compound according to the above (20B) or (21B) wherein R⁶ is cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), aryl optionally substituted with one or more substituents selected from Substituent Group C, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

[0042]

(23B) The compound according to any one of the above (20B) to (22B) wherein R^{6'} is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof.

(24B) A compound of the formula (II):

[Chemical Formula 27]



wherein

Z^1 and/or Z^2 is an oxygen atom, a sulfur atom, or $(=N)-R^x$;

R^x 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^{c1} is hydrogen, alkyl substituted with one or more substituents selected from Substituent Group E (Substituent Group E: sulfo; substituted or unsubstituted sulfamoyl; substituted or unsubstituted imino; substituted or unsubstituted guanidyl; a substituted or unsubstituted non-aromatic heterocyclic group provided that morpholinyl, imidazolidinyl, tetrahydropyranyl and piperidinyl are excluded; substituted or unsubstituted heteroaryl provided that pyridyl is excluded), alkenyl substituted with one or more substituents selected from Substituent Group E, or alkynyl substituted with one or more substituents selected from Substituent Group E; R^{4a} and R^{4b} are each independently hydrogen, substituted or unsubstituted alkyl, or R^{4a} and R^{4b} are taken together to form oxo or thioxo;

n is an integer of 1 to 4;

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;

$-X-$ is $-O-$, $-S-$, $-N(R^5)-$, or $-(CR^{5a}R^{5b})-$;

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

R^{5a} and R^{5b} are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy;

R^3 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, or its pharmaceutically acceptable salt or a solvate thereof.

[0043]

(25B) The compound according to the above (24B) wherein Z^1 and/or Z^2 is an oxygen atom or a sulfur atom, or its pharmaceutically acceptable salt or a solvate thereof.

(26B) The compound according to the above (24B) wherein Z^1 and Z^2 are both oxygen atoms, its pharmaceutically acceptable salt or a solvate thereof.

(27B) The compound according to any one of the above (24B) to (26B) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent

Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof.

(28B) The compound according to any one of the above (24B) to (27B) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof.

(29B) The compound according to any one of the above (24B) to (28B) wherein n is 1, or its pharmaceutically acceptable salt or a solvate thereof.

[0044]

(30B) The compound according to any one of the above (24B) to (29B) wherein R^{4a} and R^{4b} are both hydrogen atoms or R^{4a} and R^{4b} are taken together to form oxo, or its pharmaceutically acceptable salt or a solvate thereof.

(31B) The compound according to any one of the above (24B) to (30B) wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof.

(32B) The compound according to any one of the above (24B) to (31B) wherein R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

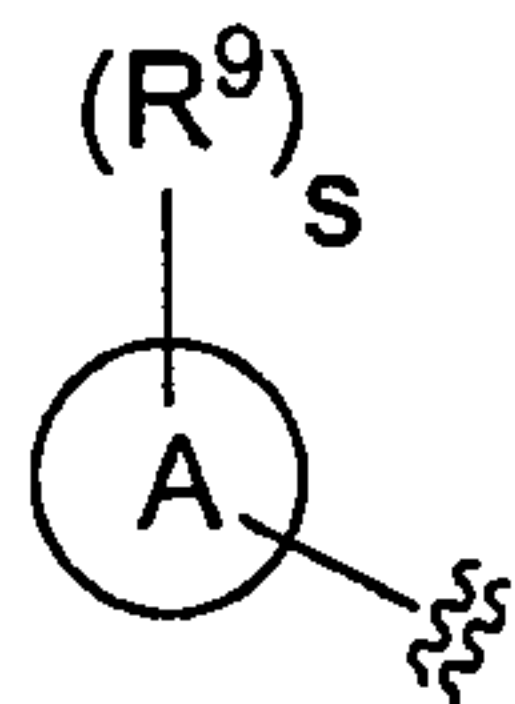
(33B) The compound according to any one of the above (24B) to (33B) wherein $\cdot X \cdot$ is $\cdot N(R^5) \cdot$ (wherein R^5 is as defined in the above (1B)), or its pharmaceutically

acceptable salt or a solvate thereof.

(34B) The compound according to any one of the above (24B) to (33B) wherein X⁻ is -NH⁻, or its pharmaceutically acceptable salt or a solvate thereof.

(35B) The compound according to any one of the above (24B) to (34B) wherein R³ is a group of the formula:

[Chemical Formula 28]



wherein ring A is aryl or heteroaryl;

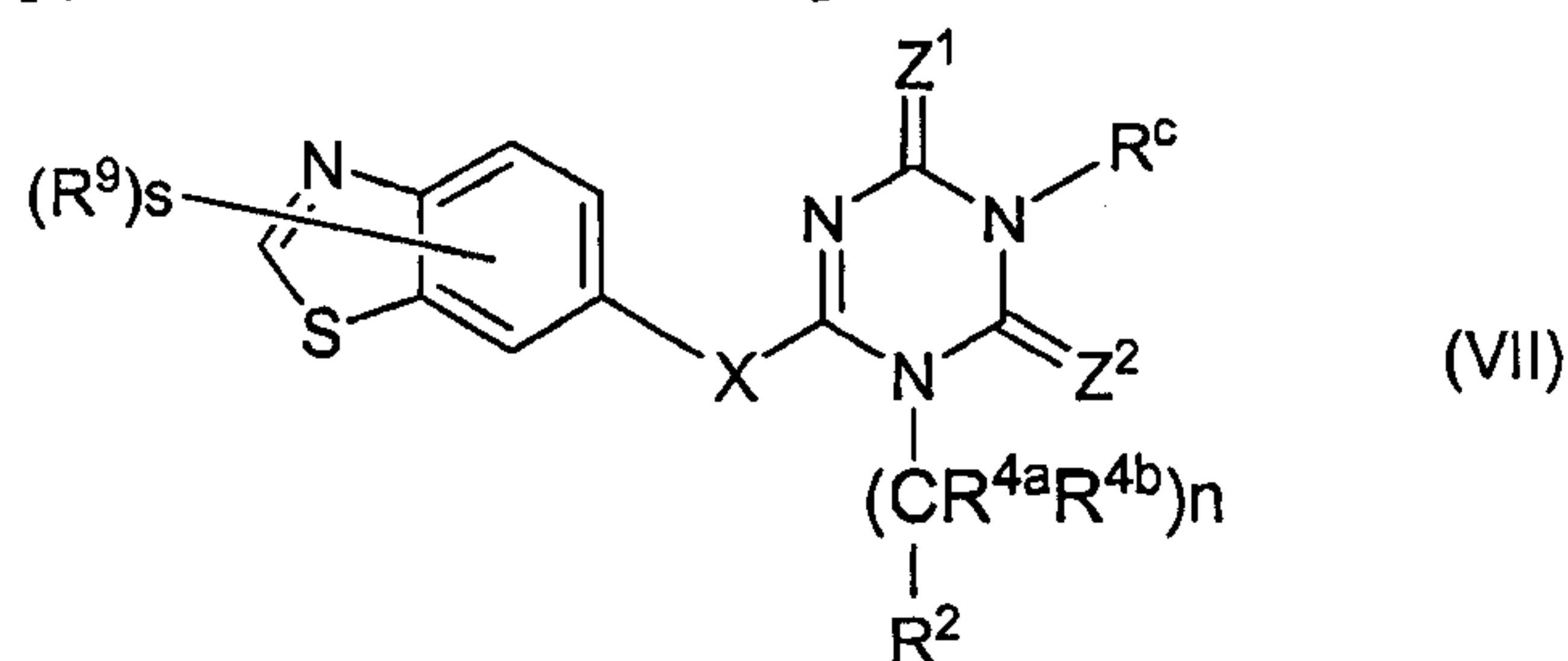
s is an integer of 0 to 3; and

R⁹ are each independently halogen, hydroxy, carboxy, 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 heteroaryloxy, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy), or its pharmaceutically acceptable salt or a solvate thereof.

[0045]

(36B) The compound according to any one of the above (24B) to (35B) wherein R³ is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino) (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; aryloxy; heteroaryloxy; a non-aromatic heterocyclic group; and alkylamino) or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof.

(37B) A compound of the formula (VII):
[Chemical Formula 29]



wherein

Z^1 and/or Z^2 is oxo, thioxo, or $=N-R^x$;

R^x 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 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;

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

n is an integer of 1 to 4;

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;

$-X-$ is $-O-$, $-S-$, $-N(R^5)-$, or $-(CR^{5a}R^{5b})-$;

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

R^{5a} and R^{5b} are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy;

s is an integer of 0 to 3;

R^9 are each independently halogen, hydroxy, carboxy, 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 heterocyclyloxy, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof.

[0046]

(38B) The compound according to the above (37B) wherein Z^1 and Z^2 are both oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(39B) The compound according to the above (37B) or (38B) wherein R^c is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group A, unsubstituted alkynyl, alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof.

(40B) The compound according to any one of the above (37B) to (39B) wherein R^c is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group B" (Substituent Group B": hydroxy, carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group B", unsubstituted alkynyl, alkynyl substituted with one or more substituents selected from Substituent Group B", or its pharmaceutically acceptable salt or a solvate thereof.

(41B) The compound according to any one of the above (37B) to (40B) wherein n is 1 and R^{4a} and R^{4b} are both hydrogen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

[0047]

(42B) The compound according to any one of the above (37B) to (41B) wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof.

(43B) The compound according to any one of the above (37B) to (42B) wherein

R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof given in either of the statements to either of the above (37B)-(42B).

(44B) The compound according to any one of the above (37B) to (43B) wherein -X- is -N(R^5)- wherein R^5 is as defined in the above (37B), or its pharmaceutically acceptable salt or a solvate thereof.

(45B) The compound according to any one of the above (37B) to (44B) wherein X- is -NH-, its pharmaceutically acceptable salt or a solvate thereof.

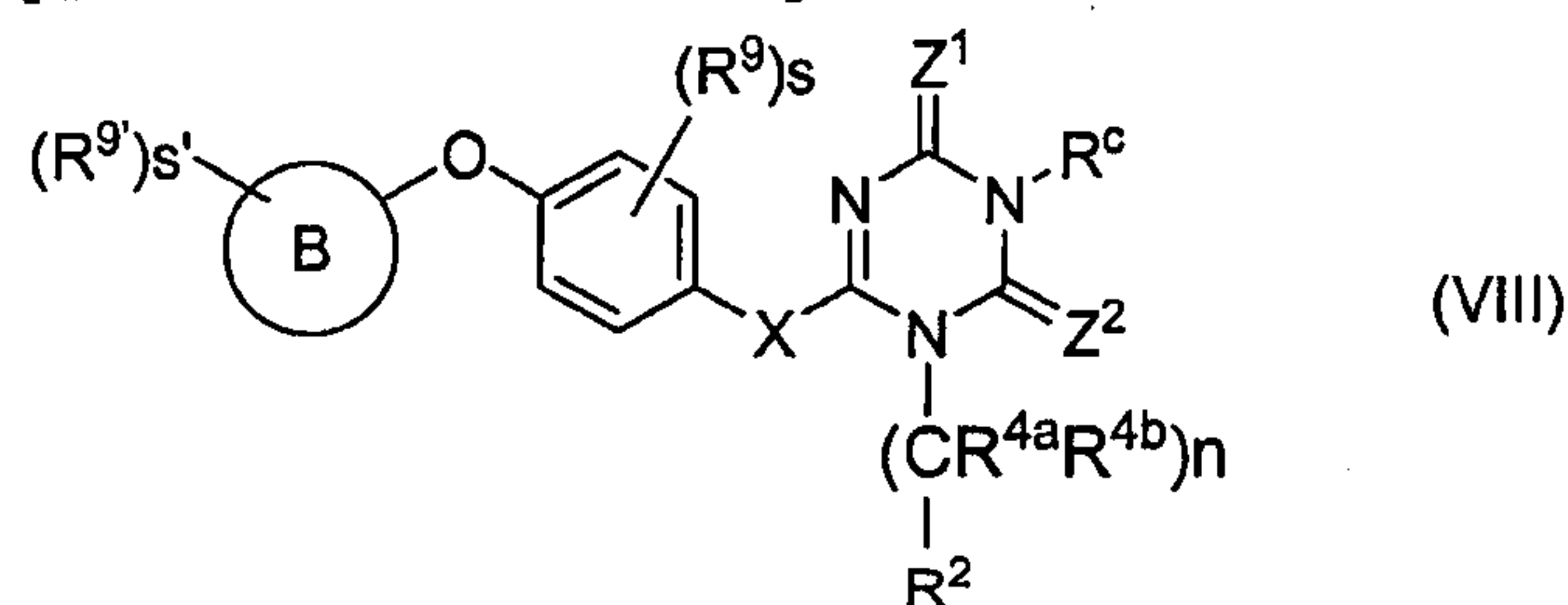
(46B) The compound according to any one of the above (37B) to (45B) wherein s is an integer of 0 to 2, and R^9 are each independently, halogen, hydroxy, carboxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or 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, and substituted or unsubstituted sulfamoyl, or its pharmaceutically acceptable salt or a solvate thereof.

In (46B), a compound wherein s is 0 or 1, or its pharmaceutically acceptable salt or a solvate thereof is preferable.

[0048]

(47B) A compound of the formula (VIII):

[Chemical Formula 30]



wherein

Z^1 and/or Z^2 is oxo, thioxo, or =N- R^* ;

R^* 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 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;

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

n is an integer of 1-4;

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;

$-X-$ is $-O-$, $-S-$, $-N(R^5)-$, or $-(CR^{5a}R^{5b})-$;

ring B is heteroaryl;

s and s' are each independently is an integer of 0 to 3;

R^9 and $R^{9'}$ are each independently halogen, hydroxy, carboxy, 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 heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof.

(48B) The compound according to the above (47B) wherein Z^1 and Z^2 are both oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

[0049]

(49B) The compound according to the above (47B) or (48B) wherein R^c is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group A, unsubstituted alkynyl, alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate

thereof.

(50B) The compound according to any one of the above (47B) to (49B) wherein R^c is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group B" (Substituent Group B": hydroxy, carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group B", unsubstituted alkynyl, alkynyl substituted with one or more substituents selected from Substituent Group B", or its pharmaceutically acceptable salt or a solvate thereof.

(51B) The compound according to any one of the above (47B) to (50B) wherein n is 1 and R^{4a} and R^{4b} are both hydrogen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

(52B) The compound according to any one of the above (47B) to (51B) wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof

(53B) The compound according to any one of the above (47B) to (52B) wherein R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

(54B) The compound according to any one of the above (47B) to (53B) wherein X^- is $-N(R^5)-$ wherein R^5 is as defined in the above (47B), or its pharmaceutically acceptable salt or a solvate thereof.

(55B) The compound according to any one of the above (47B) to (54B) wherein X^- is $-NH-$, or its pharmaceutically acceptable salt or a solvate thereof.

[0050]

(56B) The compound according to any one of the above (47B) to (55B) wherein ring B is thiazole, isothiazole, oxazole, isoxazole, pyrazole, imidazole, triazole, furan, thiophene, thiadiazole, oxadiazole, pyridine, pyrimidine, pyrazine, pyridazine, pyridazine, triazine, or benzoxazole, or its pharmaceutically acceptable salt or a solvate thereof.

(57B) The compound according to any one of the above (47B) to (56B) wherein s and s' are each independently an integer of 0 to 2, and R^9 and $R^{9'}$ are each independently halogen, hydroxy, carboxy, 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, or substituted or unsubstituted sulfamoyl, or its pharmaceutically acceptable salt or a solvate thereof.

In (57B), a compound wherein s is 0, s' is 0 or 1, and $R^{9'}$ is halogen, hydroxy, carboxy, 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, or substituted or unsubstituted sulfamoyl, or its pharmaceutically acceptable salt or solvate thereof is preferable.

(58B) A pharmaceutical composition comprising a compound according to any one of the above (20B) to (57B), or its pharmaceutically acceptable salt or a solvate thereof.

(59B) The pharmaceutical composition according to (58B) wherein the composition has a $P2X_3$ and/or $P2X_{2/3}$ receptor antagonistic effect.

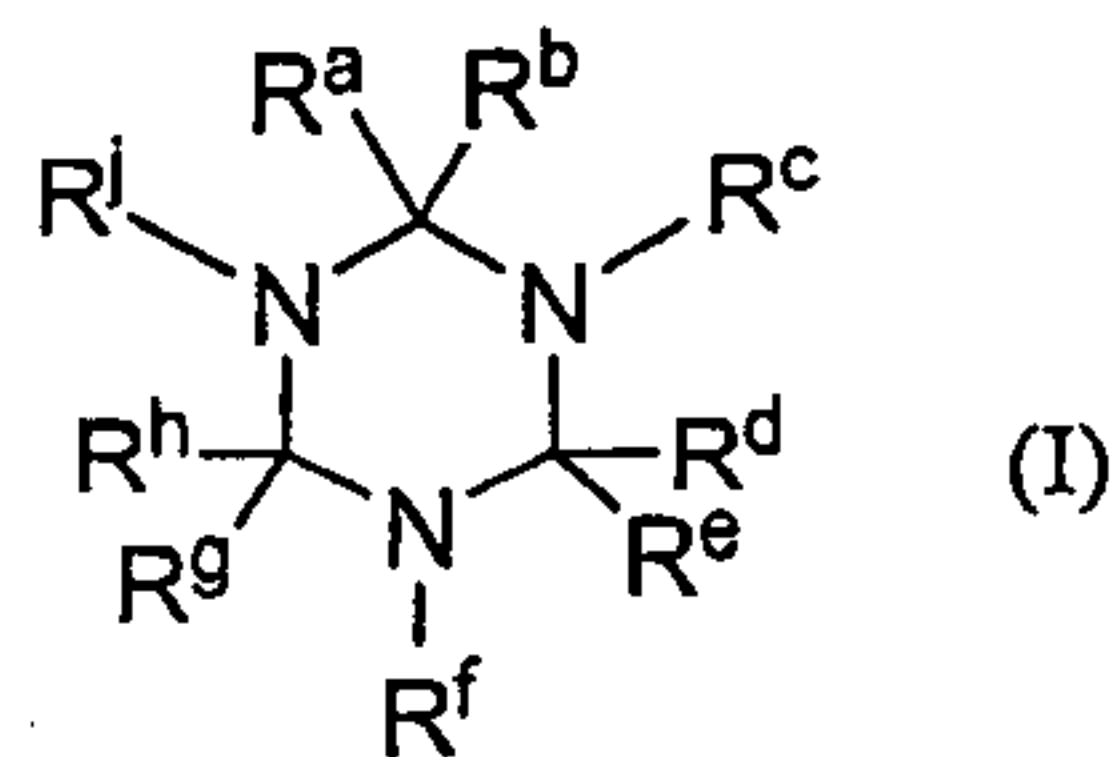
(60B) A compound according to any one of the above (20B) to (57B) for use in a method for treating and/or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor, or its pharmaceutically acceptable salt or a solvate thereof.

(61B) A compound according to any one of the above (20B) to (57B) for use in a method for treating and/or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor, or its pharmaceutically acceptable salt or a solvate thereof.

(62B) A method for treating or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor, comprising administering the compound according to any one of the above (20B) to (57B), or its pharmaceutically acceptable salt or a solvate thereof.

[0051]

(1A) A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the formula (I):
[Chemical Formula 31]



wherein

(i)

R^b and R^j are taken together to form a bond;

R^a and R^b , and/or R^d and R^e are taken together to form oxo, thioxo, or $=N-R^x$;

R^x 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 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;

- R^f is -(CR^{4a}R^{4b})_n-R²;

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

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;

-R^g is -X-R³;

-X- is -O-, -S-, -N(R⁵)-, or -(CR^{5a}R^{5b})-;

R³ 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;

R⁵ is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, or substituted or unsubstituted acyl;

R^{5a} and R^{5b} are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkynyloxy, or substituted or unsubstituted alkenyloxy;

[0052]

(ii)

R^h and Rⁱ are taken together to form a bond;

R^a is a group of -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, or substituted or unsubstituted acyl;

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

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

R^d and R^e are taken together to form oxo or thioxo;

R^f and R^g are as defined in the above (i);

(iii)

R^a and R^b, R^d and R^e, and/or R^g and R^h are taken together to form oxo or thioxo;

R^c is unsubstituted alkyl, unsubstituted alkynyl, alkyl substituted with one or more substituents selected from Substituent Group B (Substituent Group B: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl and nitro), alkenyl substituted with one or more substituents selected from Substituent Group B, or alkynyl substituted with one or more substituents selected from Substituent Group B;

R^f is $-(CR^{4a}R^{4b})-R^6$;

R^j is $-(CR^{4a'}R^{4b'})-R^{6'}$;

R^6 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

$R^{6'}$ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

provided that

1) a compound wherein, in (i), $-X-$ is $-NH-$, and R^3 is cyclohexyl substituted with guanidyl, and

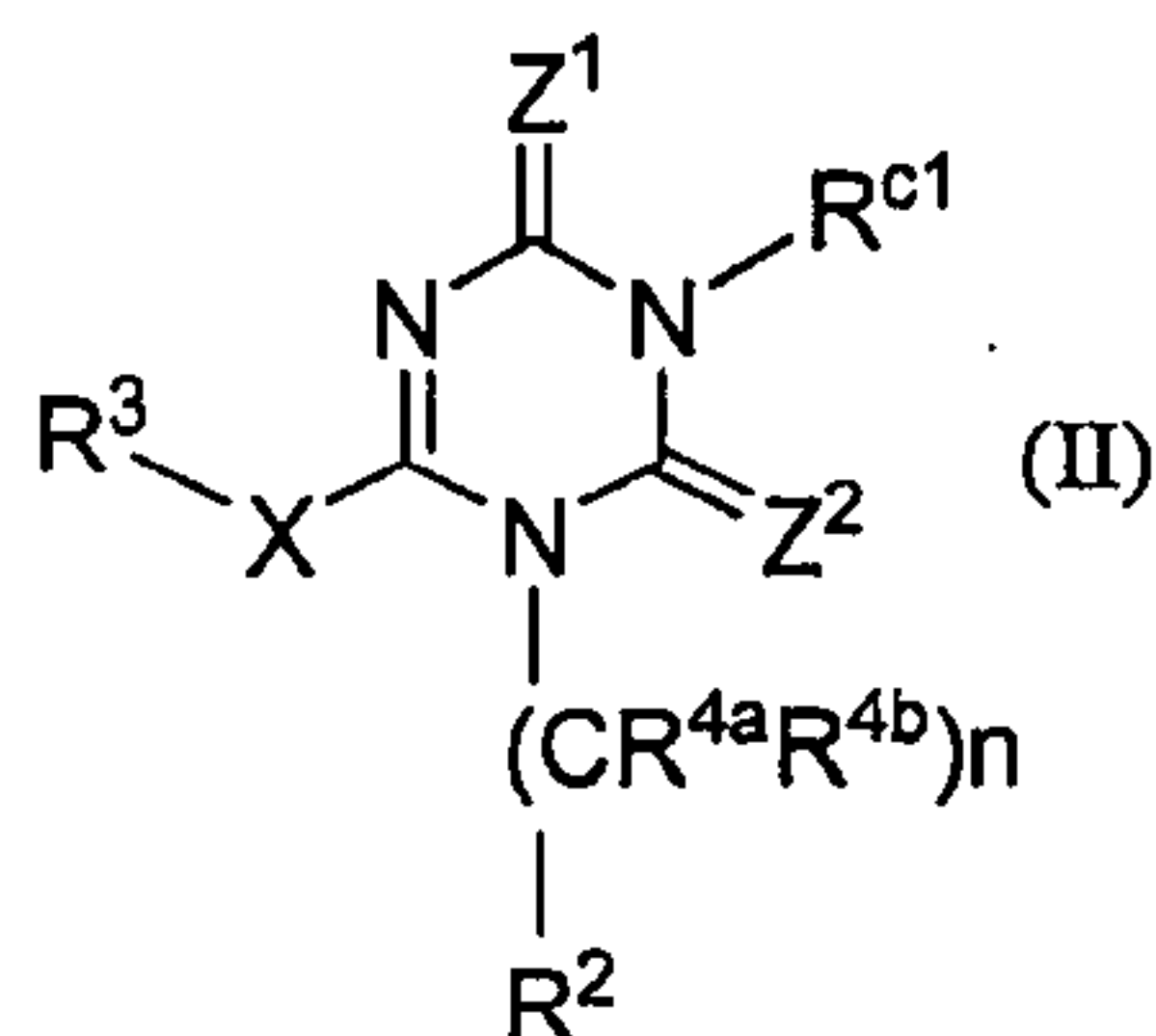
2) a compound wherein, in (ii), R^a is substituted phenyl, R^d and R^e are taken together to form thioxo, R^{4a} and R^{4b} are taken together to form oxo, and R^3 is unsubstituted cyclohexyl,

are excluded,

or its pharmaceutically acceptable salt or solvate thereof as an active ingredient.

[0053]

(2A) A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the formula (II):
[Chemical Formula 32]



wherein

Z^1 and/or Z^2 is oxo, thioxo, or $=N-R^x$;

R^x , R^{4a} , R^{4b} , n , R^2 , X , and R^3 are as defined in the above (1A);

R^{c1} 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 its pharmaceutically

acceptable salt or a solvate thereof as an active ingredient.

(3A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (2A) wherein Z^1 and/or Z^2 is oxo or thioxo, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(4A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (2A) or (3A) wherein Z^1 and Z^2 are both oxo, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

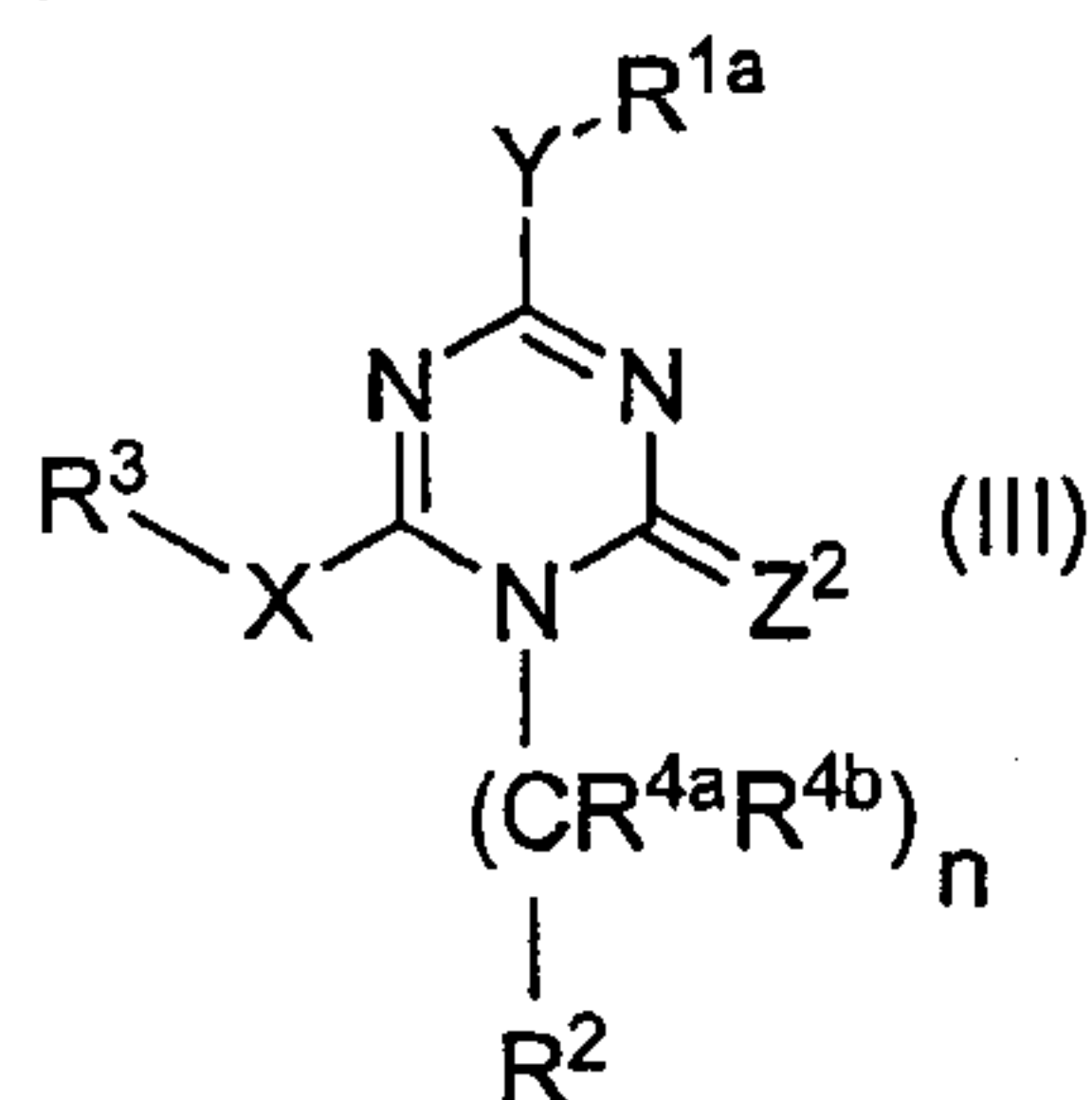
(5A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (4A) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(6A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (5A) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0054]

(7A) A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the formula (III):

[Chemical Formula 33]



wherein Z^2 is oxo, thioxo, or $=\text{N-R}^x$; R^x , $-\text{Y}-$, R^{1a} , R^{4a} , R^{4b} , n , R^2 , $-\text{X}-$, and R^3 are as defined in the above (1A); or its pharmaceutically acceptable salt or solvate thereof as an active ingredient.

(8A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (7A) wherein Z^2 is oxo or thioxo or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(9A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (7A) or (8A) wherein $-\text{Y}-$ is $-\text{O}-$, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(10A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (7A) to (9A) wherein R^{1a} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted heteroaryloxycarbonyl, nitro, oxo, and thioxo), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0055]

(11A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (7A) to (10A) wherein R^{1a} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl,

substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(12A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (16A) wherein n is 1, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(13A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (12A) wherein R^{4a} and R^{4b} are both hydrogen, or R^{4a} and R^{4b} are taken together to form oxo, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(14A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (13A) wherein R^2 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(15A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (2A) to (14A) wherein R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

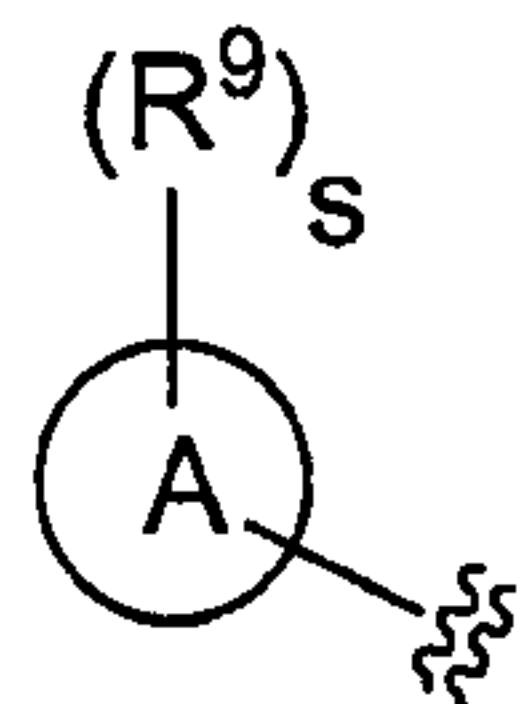
(16A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to the above (2A) to (15A) wherein $-X-$ is $-N(R^5)-$ wherein R^5 is as defined in the above (1A), or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(17A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (16A) wherein $-X-$ is $-NH-$, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0056]

(18A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (17A) wherein R^3 is a group of the formula:

[Chemical Formula 34]



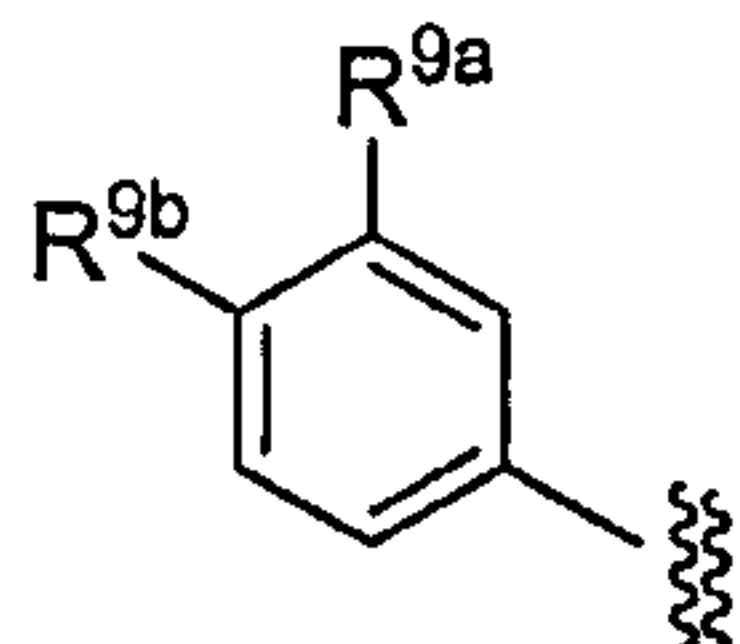
wherein ring A is aryl or heteroaryl;
 s is an integer of 0 to 3;

R⁹ 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 heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0057]

(18A') The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (18A) wherein R³ is a group of the formula:

[Chemical Formula 35]



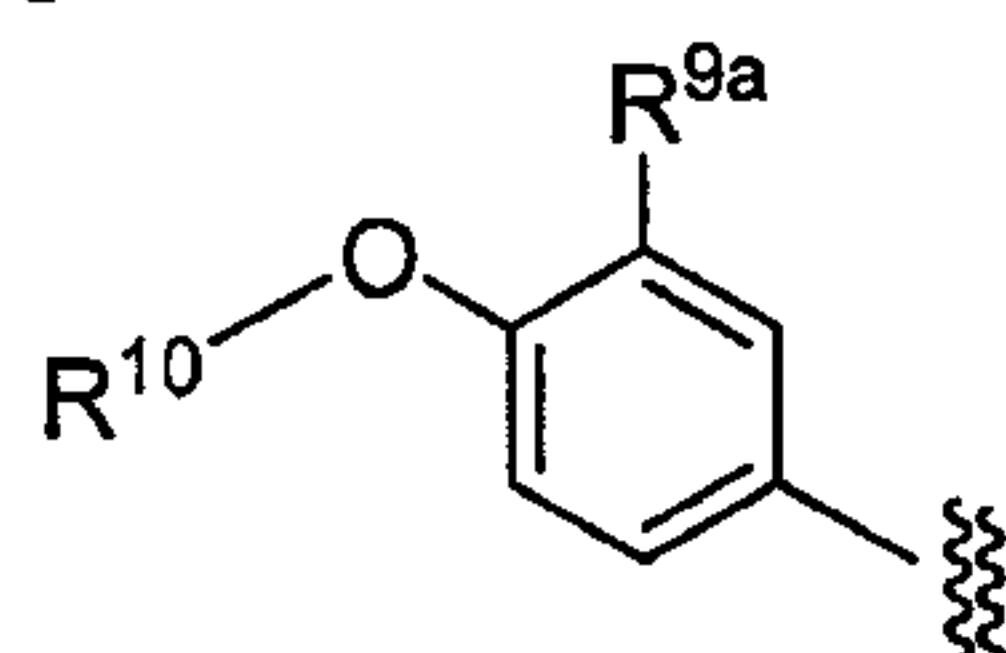
wherein R^{9a} is hydrogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted 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 non-aromatic heteroaryl, substituted or unsubstituted cycloalkyloxy, substituted or unsubstituted cycloalkenyloxy, substituted or unsubstituted non-aromatic heterocyclyloxy, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy;

R^{9b} is 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 heterocycloxy, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(18A") The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (18A) and (18A') wherein R^3 is a group of the formula:

[Chemical Formula 36]



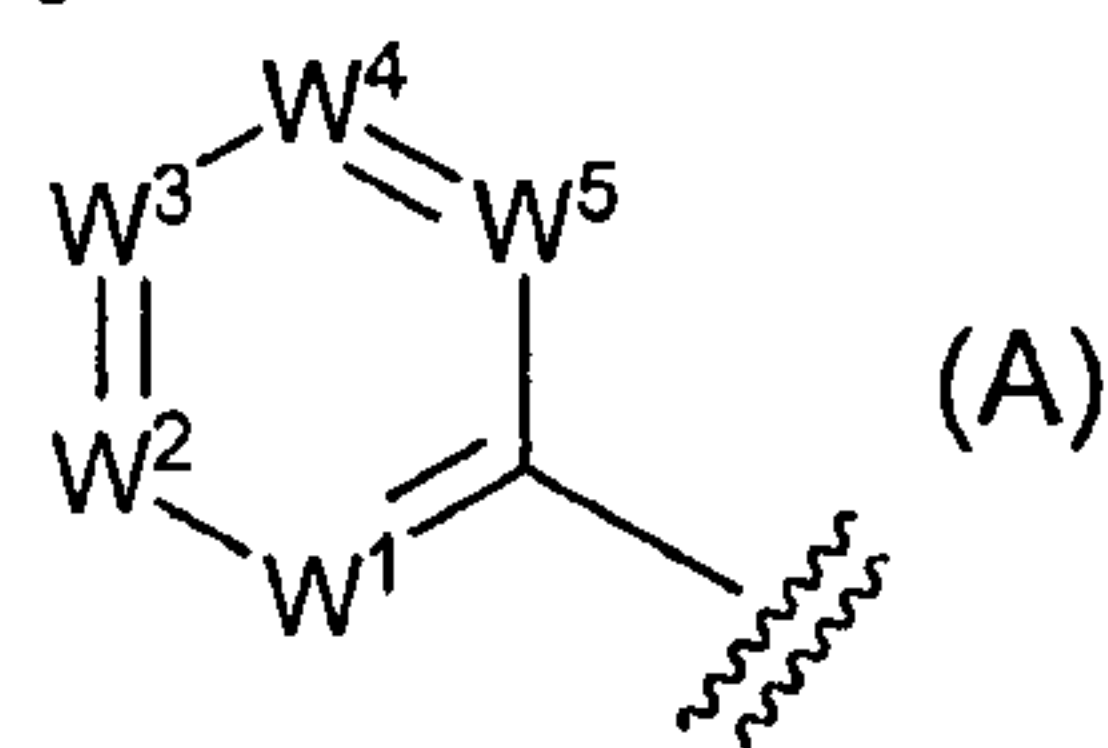
wherein R^{9a} is as defined in the above (18A'); R^{10} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(19A) The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (18A) and (18A') wherein R^3 is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alky; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0058]

(19A') The pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound according to any one of the above (2A) to (18A) wherein R^3 is a group of the formula(A):

[Chemical Formula 37]



wherein $=W^1-W^2=W^3-W^4=W^5-$ is any one selected from the following (a) to (h):

(a): $=C(H)-C(R^{10a})=C(R^{10b})-C(R^{10c})=C(H)-$;

(b): $=N-C(R^{10a})=C(R^{10b})-C(R^{10c})=C(H)-$;

- (c): $=C(H)-N=C(R^{10b})-C(R^{10c})=C(H)-$;
 (d): $=C(H)-C(R^{10a})=N-C(R^{10c})=C(H)-$;
 (e): $=C(H)-C(R^{10a})=C(R^{10b})-N=C(H)-$;
 (f): $=N-C(R^{10a})=C(R^{10b})-C(R^{10c})=N-$;
 (g): $=C(H)-C(R^{10a})=N-C(R^{10c})=C(H)-$; and
 (h): $=C(H)-N=C(R^{10b})-N=C(H)-$;

R^{10a} , R^{10b} , and R^{10c} are each independently hydrogen, 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 heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or heteroaryloxy; or R^{10a} and R^{10b} or R^{10b} and R^{10c} together with the ring atom to which they are attached form a non-aromatic carbocyclic ring, a non-aromatic heterocyclic ring, an aromatic carbocyclic ring or an aromatic heterocyclic ring, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

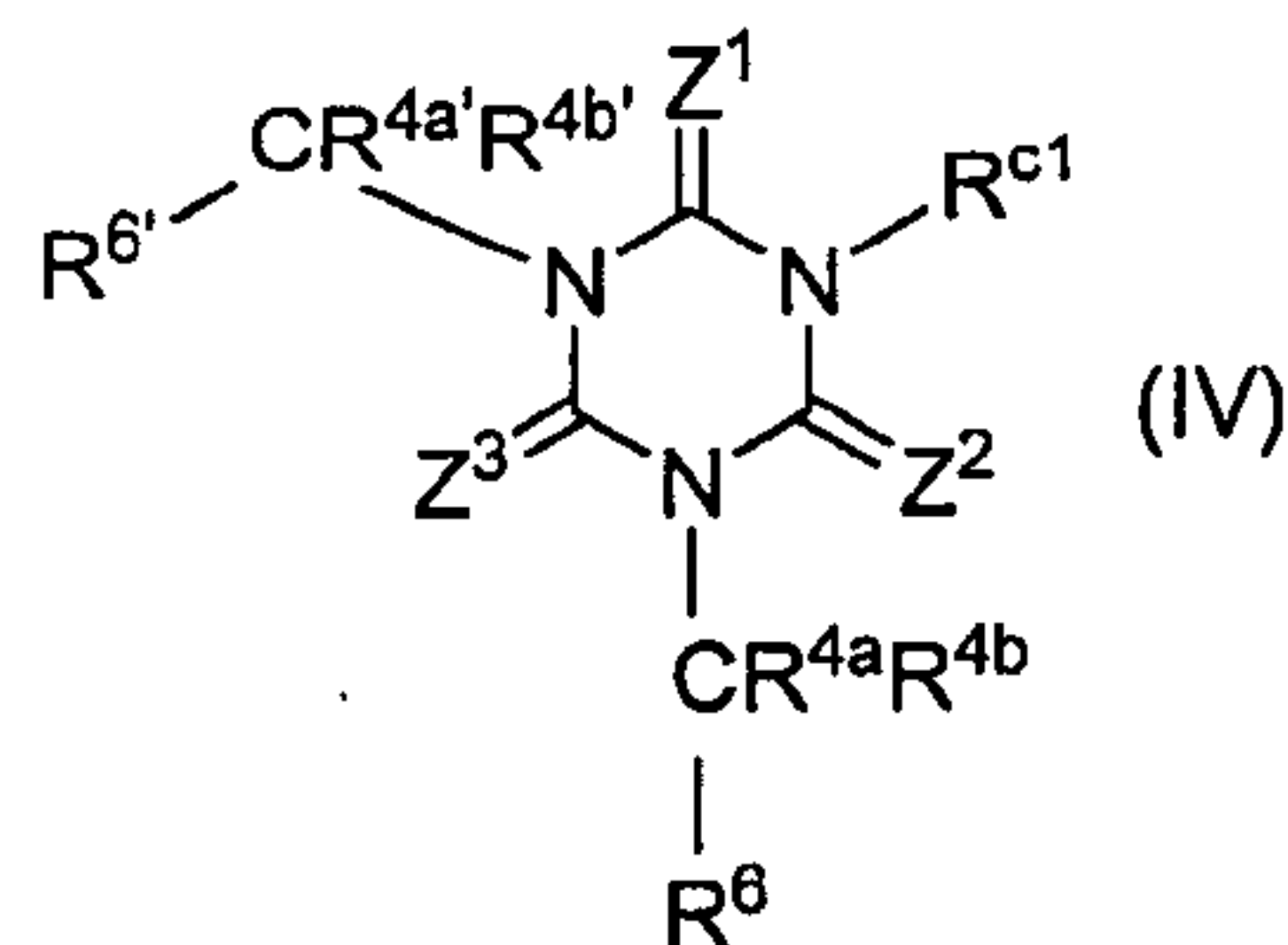
(19A'') A compound described in any one of the above (1A) to (19A), (18A'), (18A'') and (19A') for use in a method for treating, preventing and/or improving pain and/or urination disorder, or its pharmaceutically acceptable salt or a solvate thereof.

(19A''') A method for treating, preventing and/or improving pain and/or urination disorder comprising administering the compound described in any one of the above (1A) to (19A), (18A'), (18A'') and (19A'), or its pharmaceutically acceptable salt or a solvate thereof.

[0059]

(20A) A compound of the formula (IV):

[Chemical Formula 38]



wherein

Z^1 , Z^2 , and/or Z^3 is an oxygen atom or a sulfur atom;

R^{c1} is unsubstituted alkyl, unsubstituted alkynyl, alkyl substituted with one or more substituents selected from Substituent Group B, alkenyl substituted with one or more substituents selected from Substituent Group B, or alkynyl substituted with one or more substituents selected from Substituent Group B;

R^{4a} is hydrogen or substituted or unsubstituted alkyl;

R^{4b} is hydrogen;

R⁶ is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{4a'} is hydrogen or substituted or unsubstituted alkyl;

R^{4b'} is hydrogen;

R^{6'} is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof.

(21A) The compound according to the above (20A) wherein Z¹, Z², and Z³ are oxygen atoms, or its pharmaceutically acceptable salt or a solvate thereof.

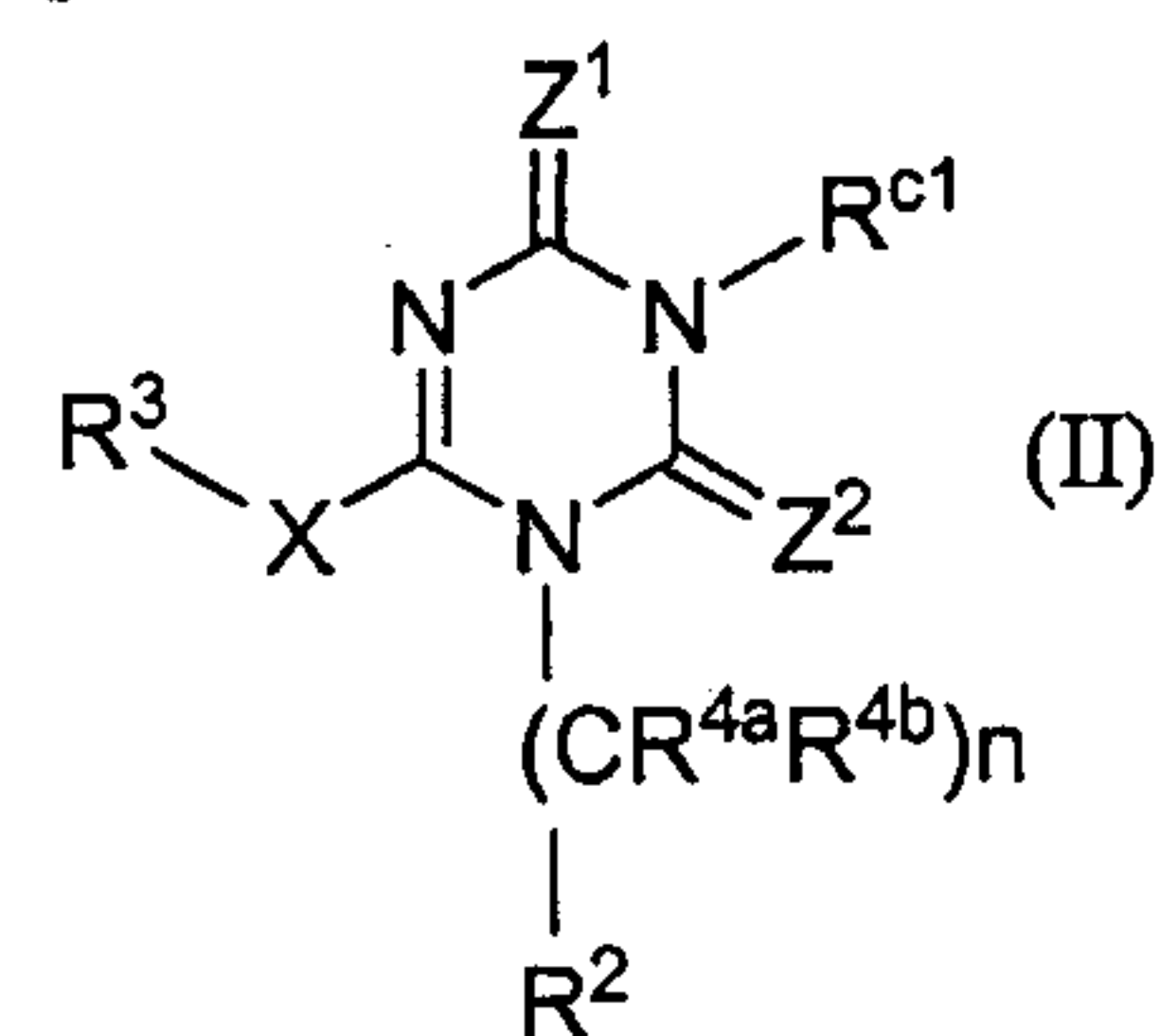
(22A) The compound according to the above (20A) or (22A) wherein R⁶ is cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, aryl optionally substituted with one or more substituents selected from Substituent Group C, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

(23A) The compound according to any one of the above (20A) to (22A) wherein R^{6'} is aryl optionally substituted with one or more substituents selected from Substituent Group D, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof.

[0060]

(24A) A compound of the formula (II):

[Chemical Formula 39]



wherein

Z¹ and/or Z² is oxo, thioxo, or =N-R^x;

R^x, R^{4a}, R^{4b}, n, R², X and R³ are as defined in the above (1A);

R^{c1} is hydrogen, alkyl substituted with one or more substituents selected from Substituent Group E (Substituent Group E: sulfo; substituted or unsubstituted sulfamoyl; substituted or unsubstituted, imino; substituted or unsubstituted guanidyl; a substituted or unsubstituted non-aromatic heterocyclic group provided that morpholinyl, imidazolidinyl, tetrahydropyranyl and piperidinyl are excluded; and substituted or unsubstituted heteroaryl provided that pyridyl are excluded), alkenyl substituted with one or more substituents selected from Substituent Group E, or alkynyl substituted with one or more substituents selected from Substituent Group E, or its pharmaceutically acceptable salt or a solvate thereof.

(25A) The compound according to the above (24A) wherein Z¹ and/or Z² is oxo or thioxo, or its pharmaceutically acceptable salt or a solvate thereof.

(26A) The compound according to the above (24A) or (25A) wherein Z¹ and Z² are both oxo, or its pharmaceutically acceptable salt or a solvate thereof.

(27A) The compound according to any one of the above (24A) to (26A) wherein

R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group B' (Substituent Group B': carboxy, sulfo, a substituted or unsubstituted non-aromatic heterocyclic group, tetrazolyl, substituted or unsubstituted alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group B', or alkynyl substituted with one or more substituents selected from Substituent Group B', or its pharmaceutically acceptable salt or a solvate thereof.

(28A) The compound according to any one of the above (24A) to (27A) wherein n is 1, or its pharmaceutically acceptable salt or a solvate thereof.

(29A) The compound according to any one of the above (24A) to (28A) wherein R^{4a} and R^{4b} are both hydrogen atoms or R^{4a} and R^{4b} are taken together to form oxo, or its pharmaceutically acceptable salt or a solvate thereof.

(30A) The compound according to any one of the above (24A) to (29A) wherein R² is substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof.

[0061]

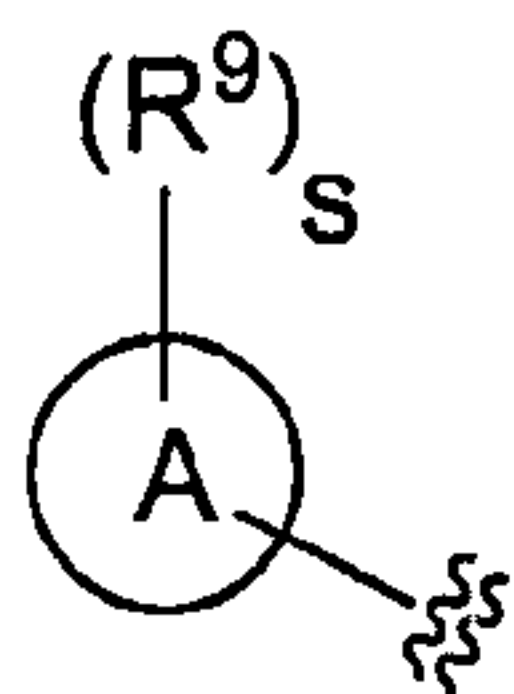
(31A) The compound according to any one of the above (24A) to (30A) wherein R² is aryl substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C, or its pharmaceutically acceptable salt or a solvate thereof.

(32A) The compound according to any one of the above (24A) to (31A) wherein -X- is -N(R⁵)- wherein R⁵ is as defined in the above (1A), or its pharmaceutically acceptable salt or a solvate thereof.

(33A) The compound according to any one of the above (24A) to (32A) wherein X- is -NH-, or its pharmaceutically acceptable salt or a solvate thereof.

(34A) The compound according to any one of the above (24A) to (33A) wherein R³ is a group of the formula:

[Chemical Formula 40]



wherein ring A is aryl or heteroaryl;

s is an integer of 0 to 3;

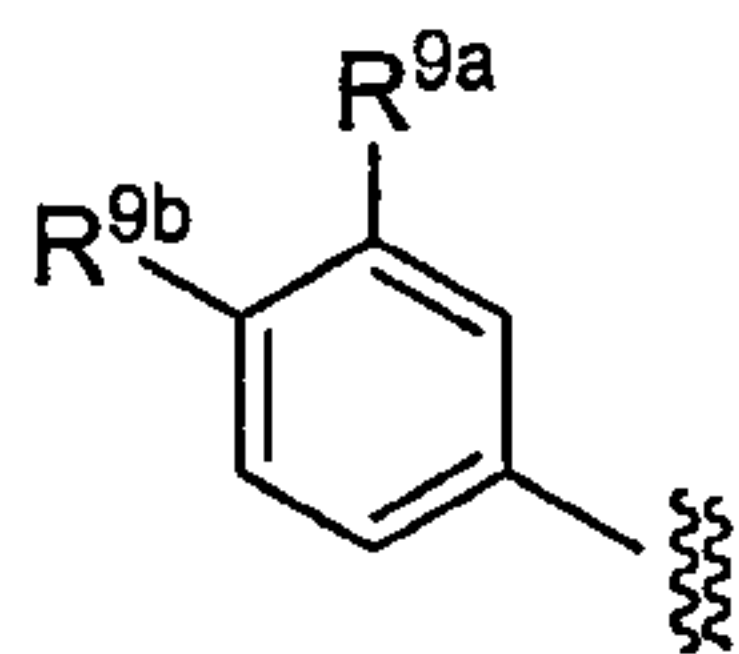
R⁹ are each independently halogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted 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 heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate thereof according to any one of the above (24A) to (33A).

[0062]

(34A') The compound according to any one of the above (24A) to (34A) wherein R³ is a group of the formula:

[Chemical Formula 41]



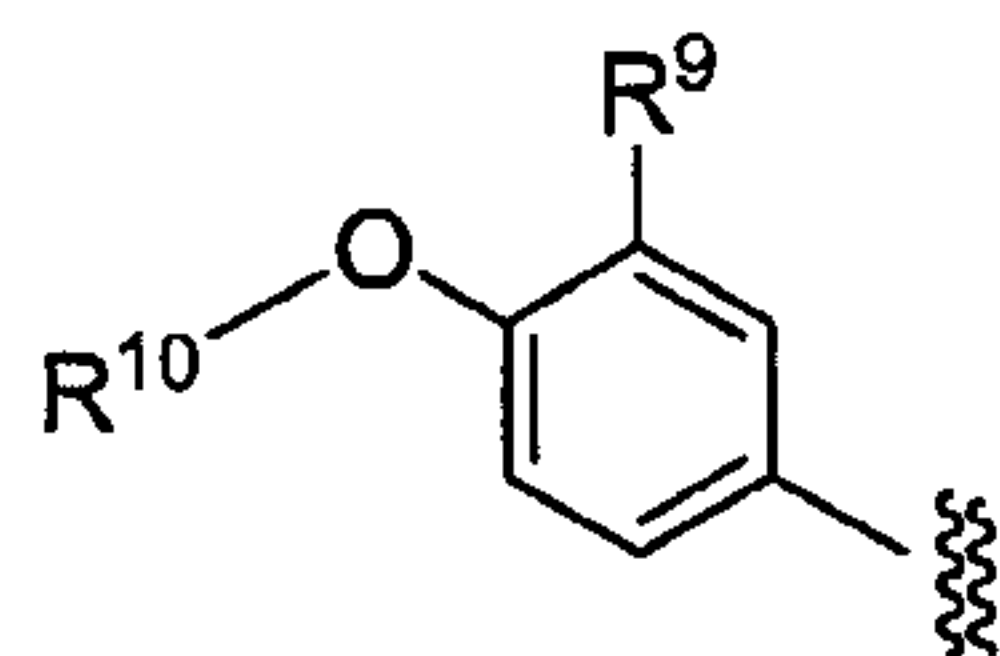
wherein R^{9a} is hydrogen, hydroxy, cyano, nitro, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, substituted or unsubstituted 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 heterocyclyloxy, substituted or unsubstituted aryloxy, or substituted or unsubstituted heteroaryloxy;

R^{9b} is 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 heterocyclyloxy, substituted or unsubstituted aryloxy or substituted or unsubstituted heteroaryloxy, or its pharmaceutically acceptable salt or a solvate

thereof.

(34A'') The compound according to any one of the above (24A) to (34A) and (34A') wherein R³ is a group of the formula:

[Chemical Formula 42]



wherein

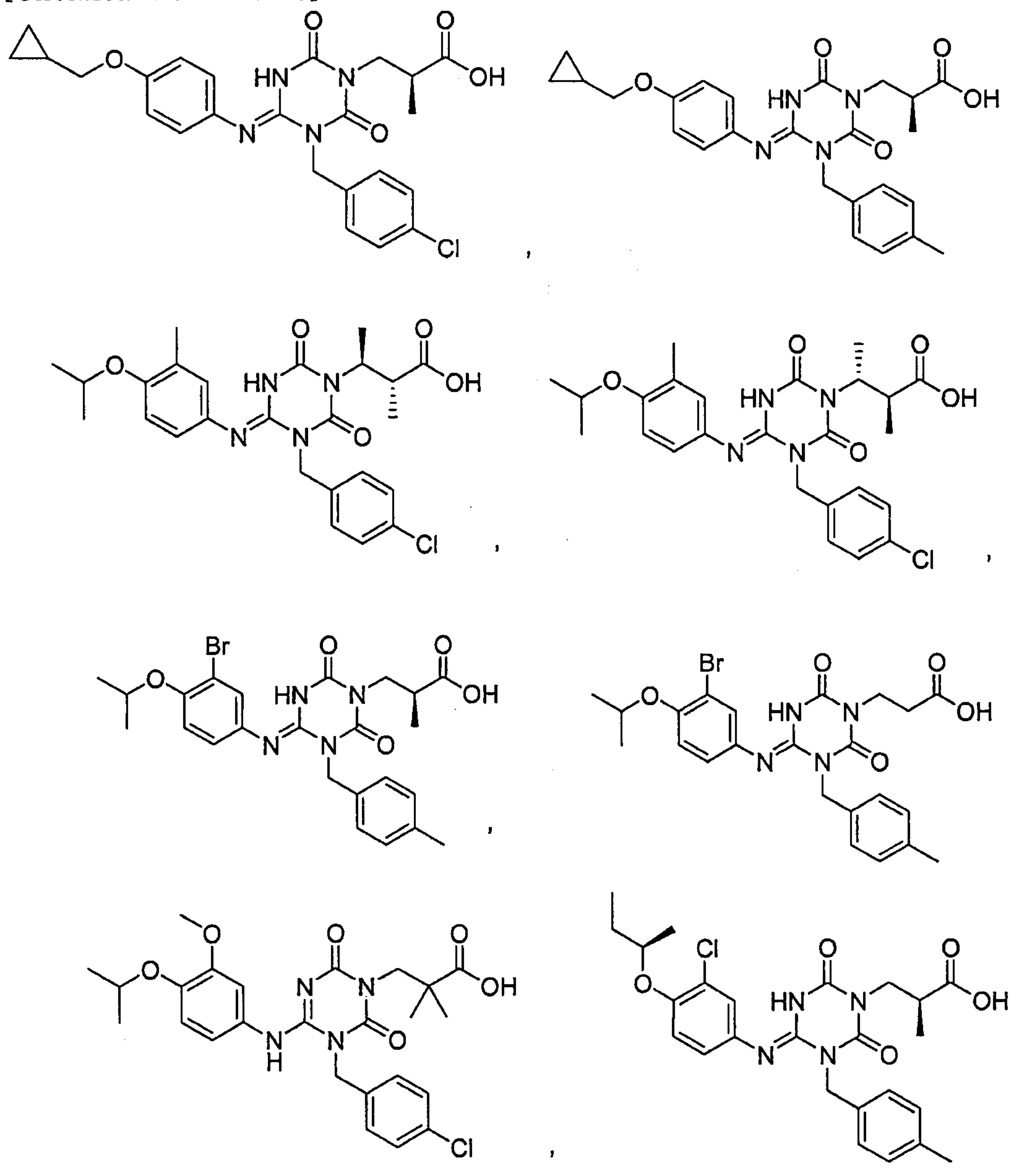
R⁹ is as defined in the above (7A); R¹⁰ is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or its pharmaceutically acceptable salt or a solvate thereof.

[0063]

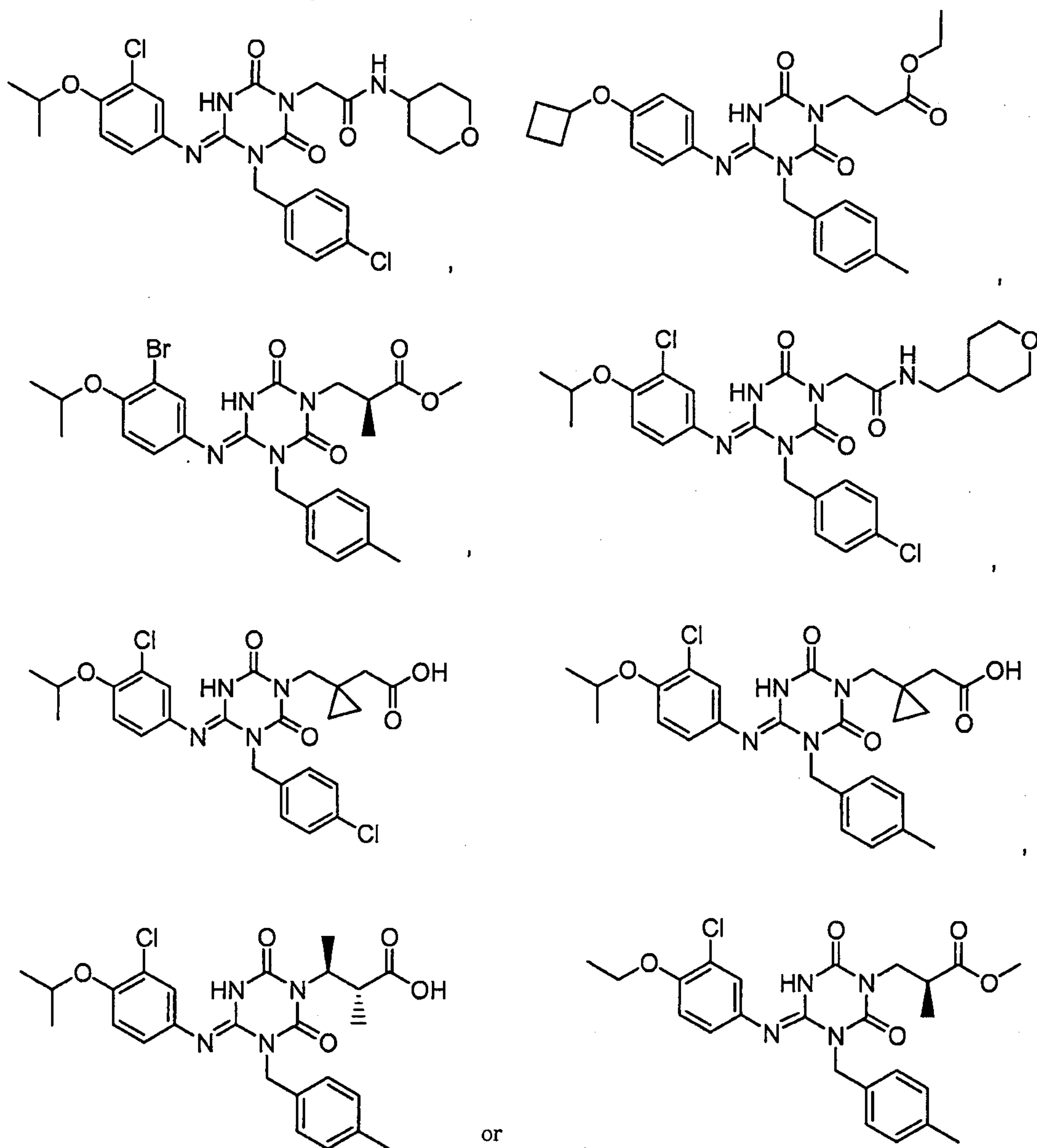
(35A) The compound according to any one of the above (24A) to (34A), (34A') and (34A'') wherein R³ is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D, or its pharmaceutically acceptable salt or a solvate thereof.

(36A) A compound of the following formula:

[Chemical Formula 43]



[Chemical Formula 44]

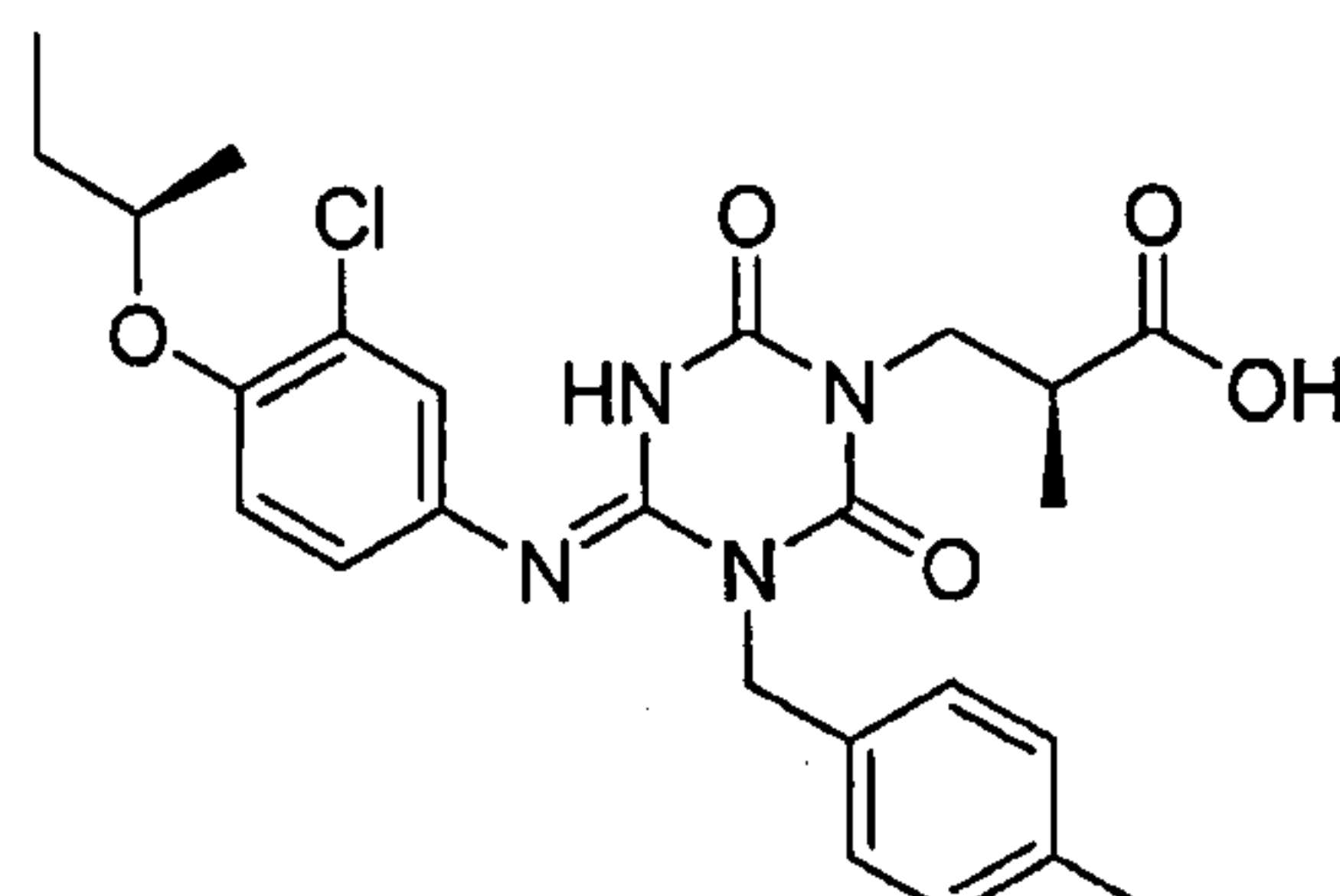
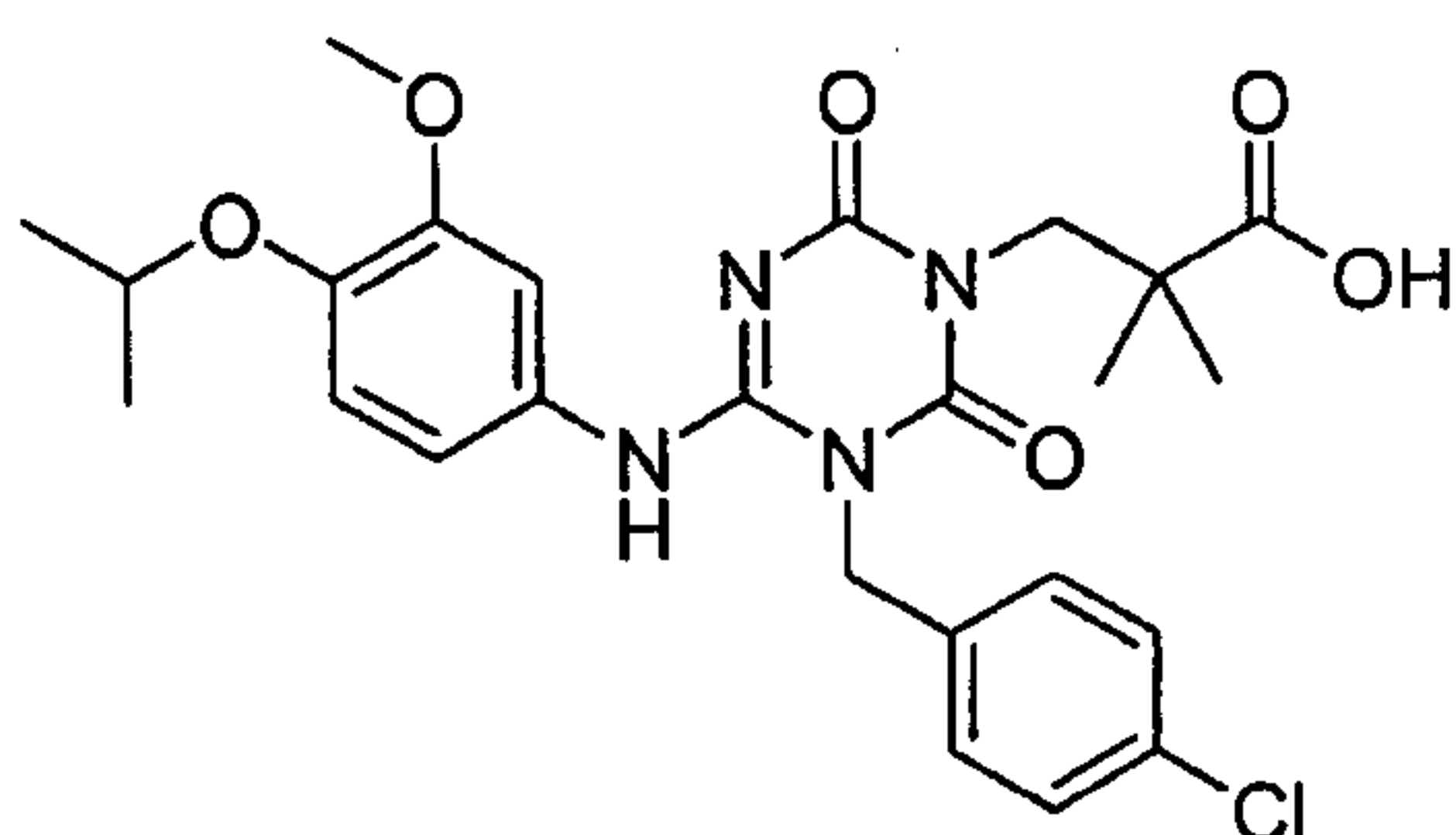
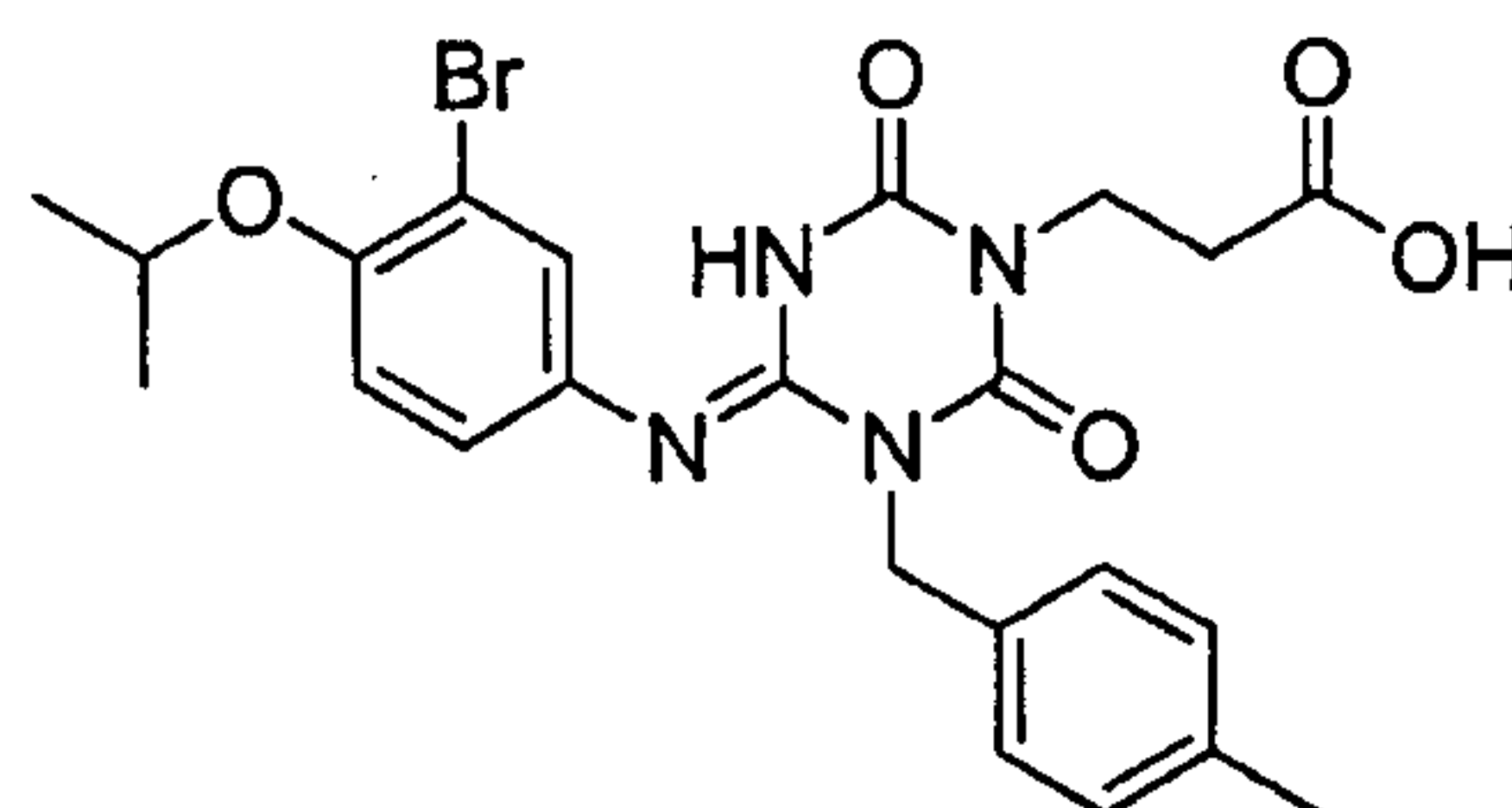
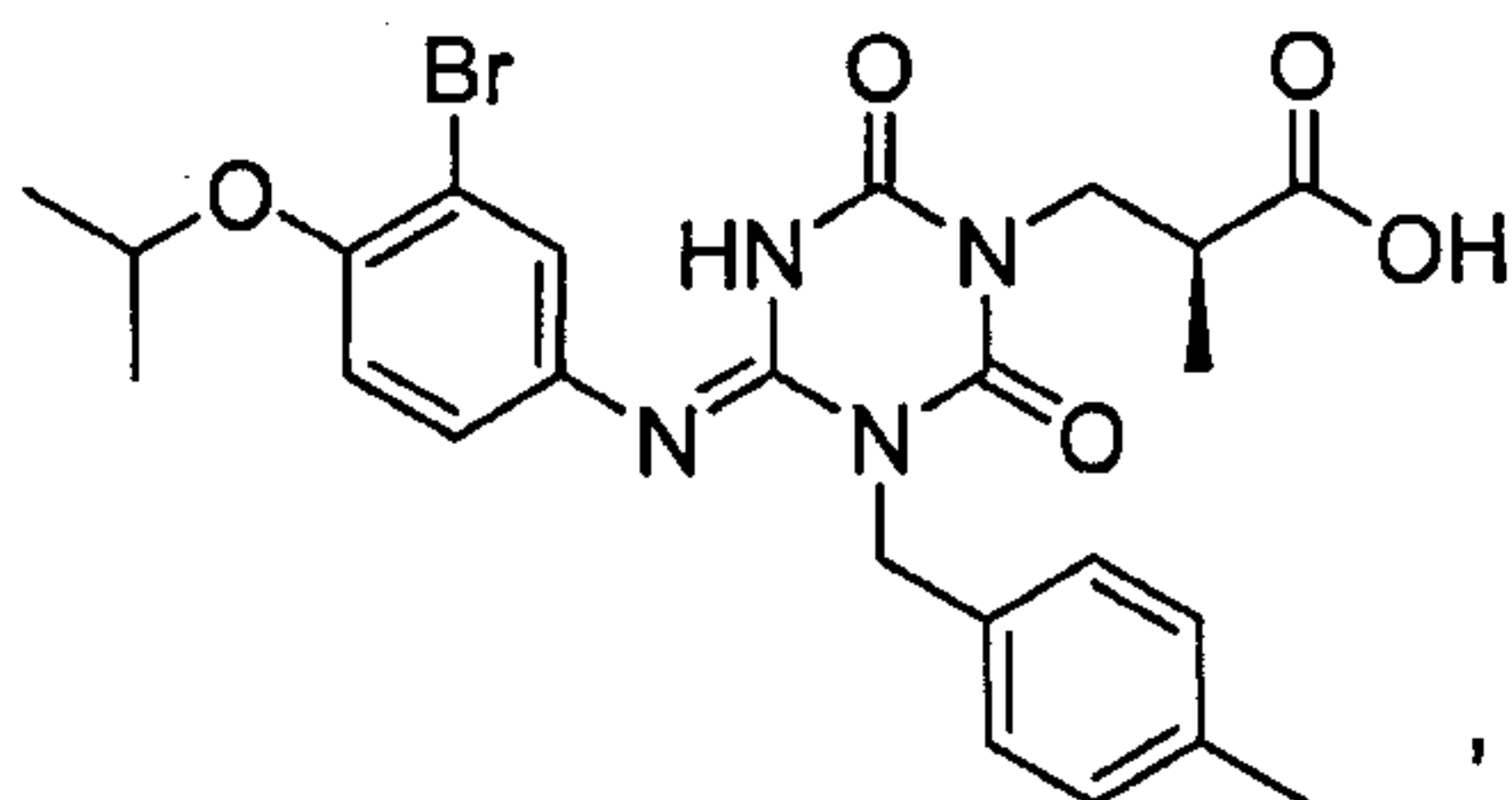
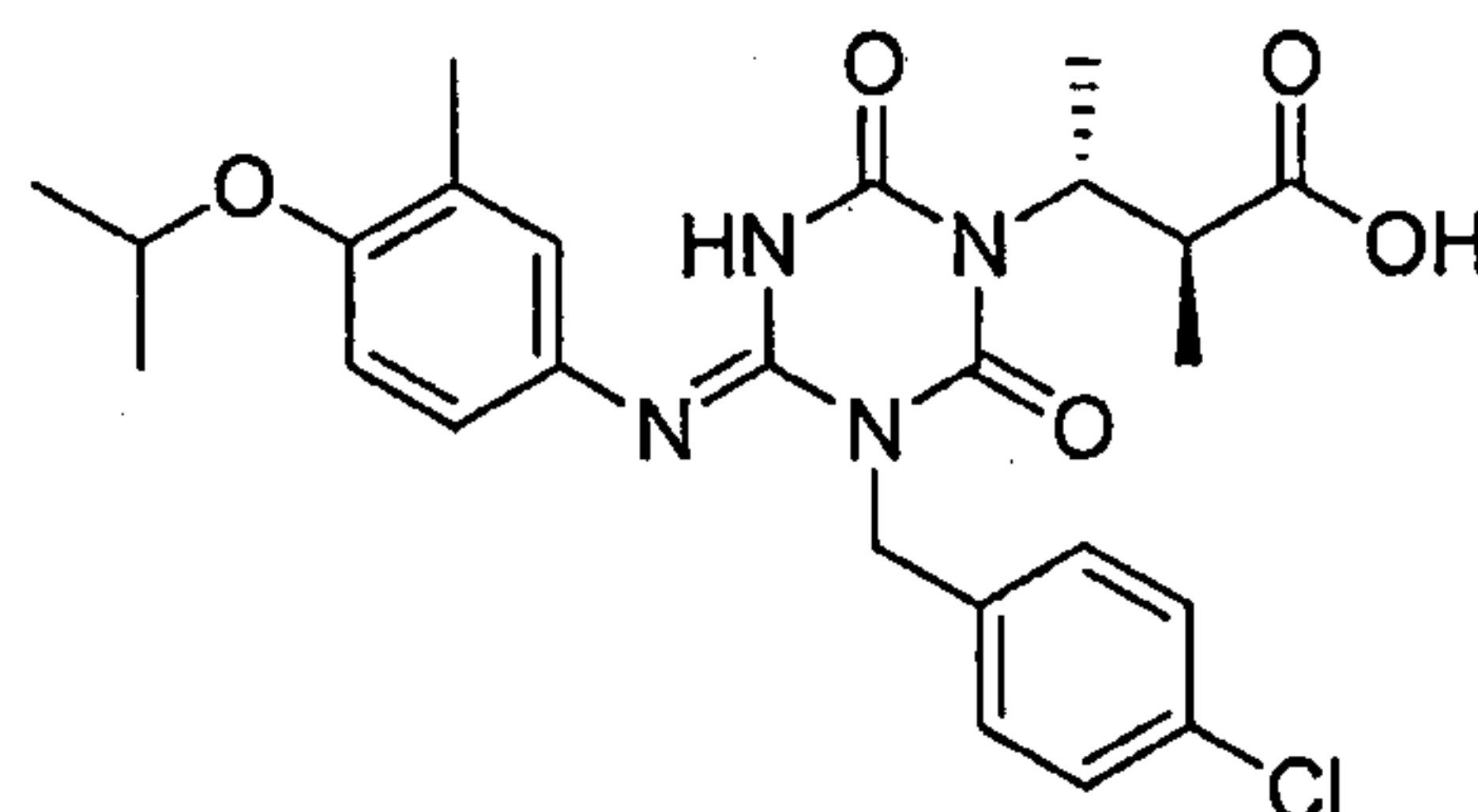
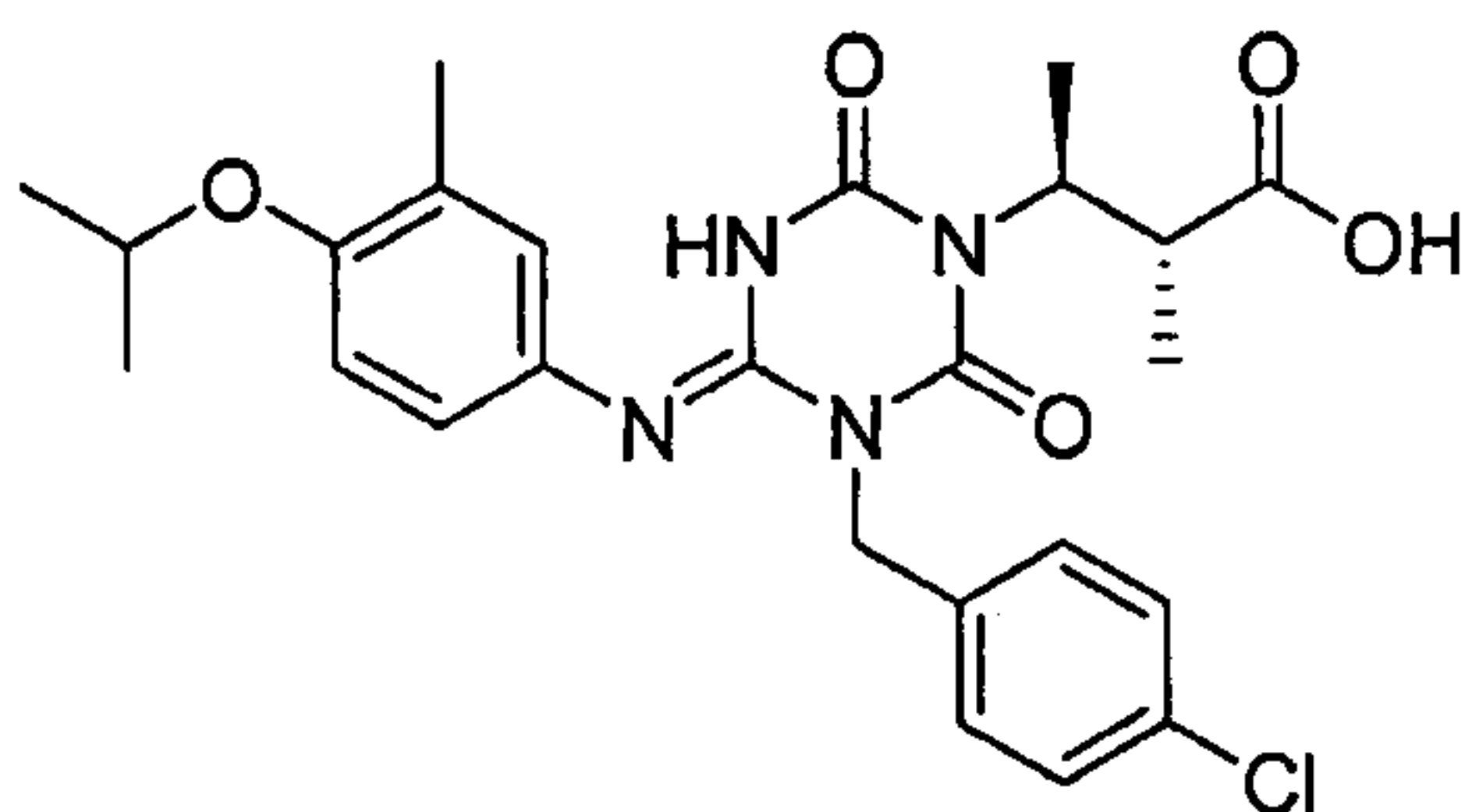
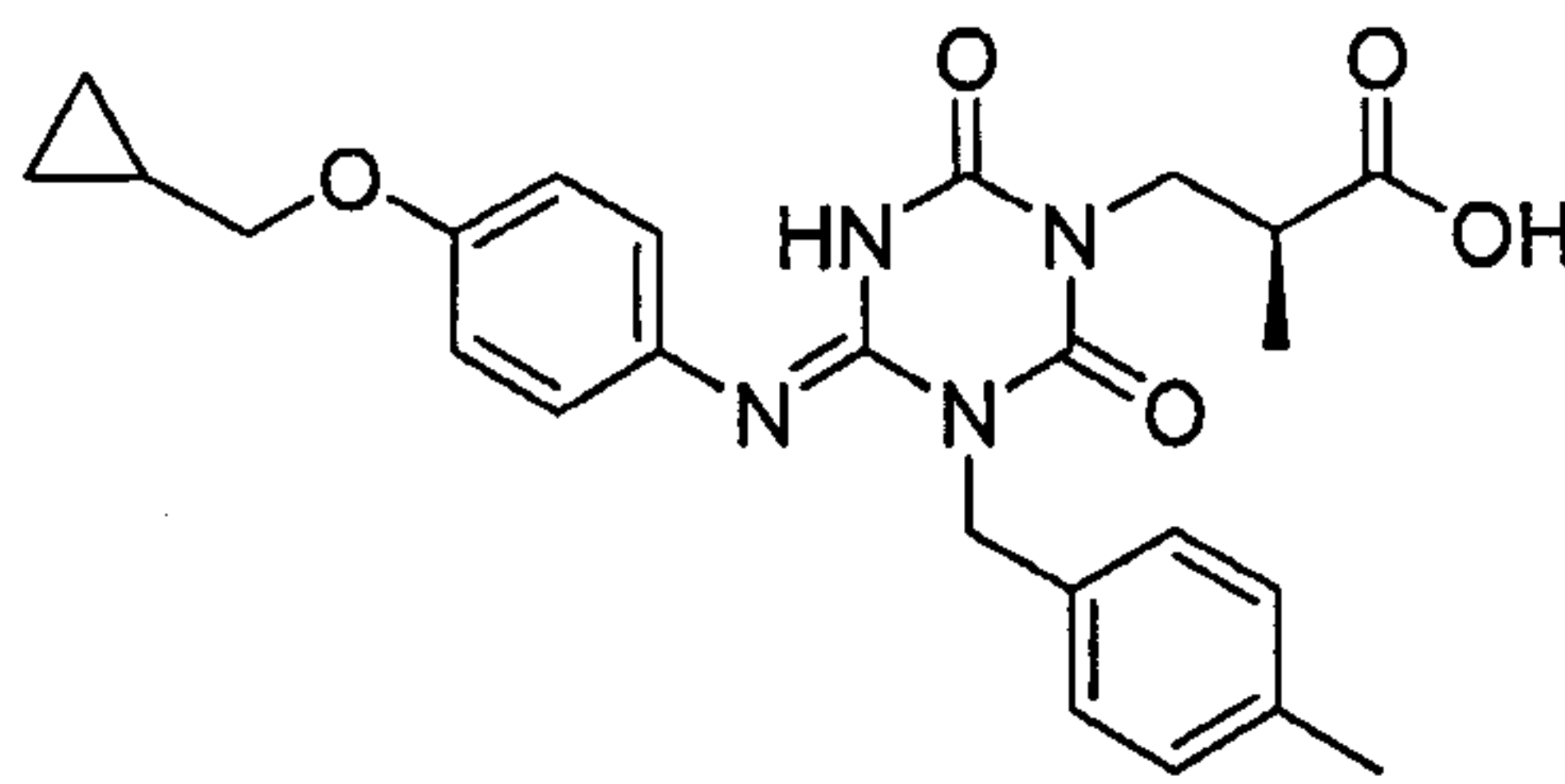
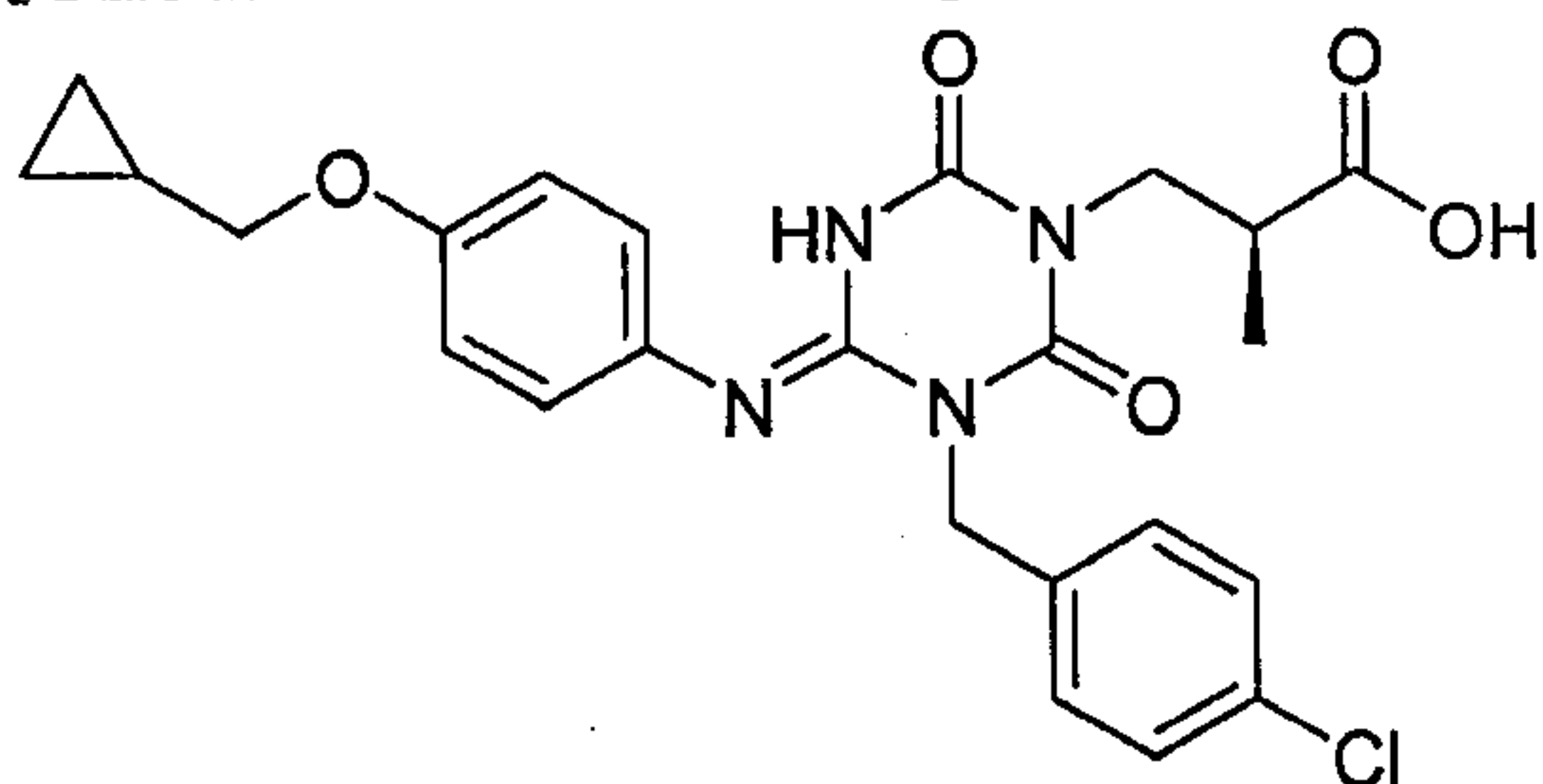


, or its pharmaceutically acceptable salt or a solvate thereof.

[0064]

(36A') A compound of the following formula:

[Chemical Formula 45]

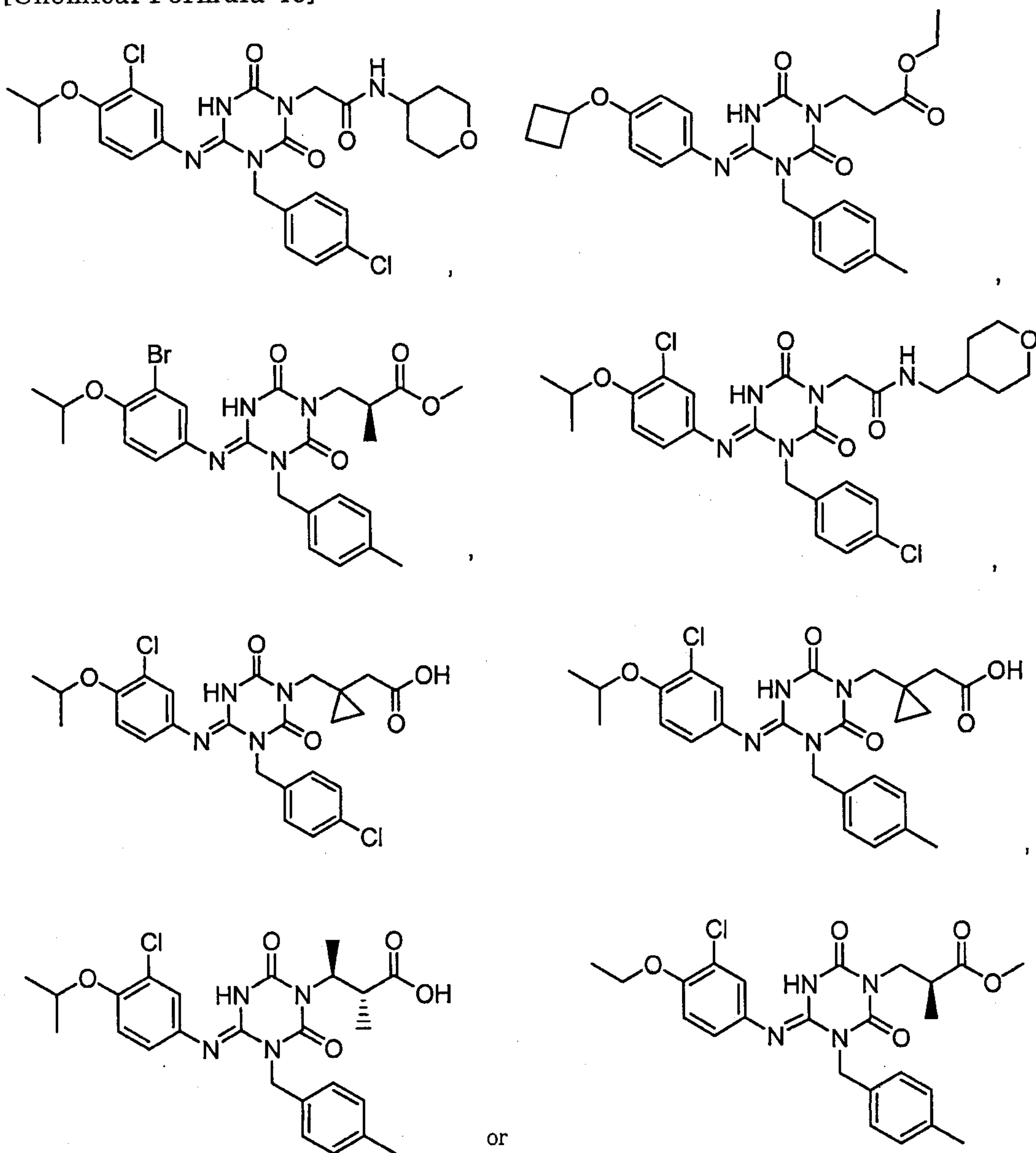


, or its pharmaceutically acceptable salt or a solvate thereof.

[0065]

(36A") A compound of the following formula:

[Chemical Formula 46]

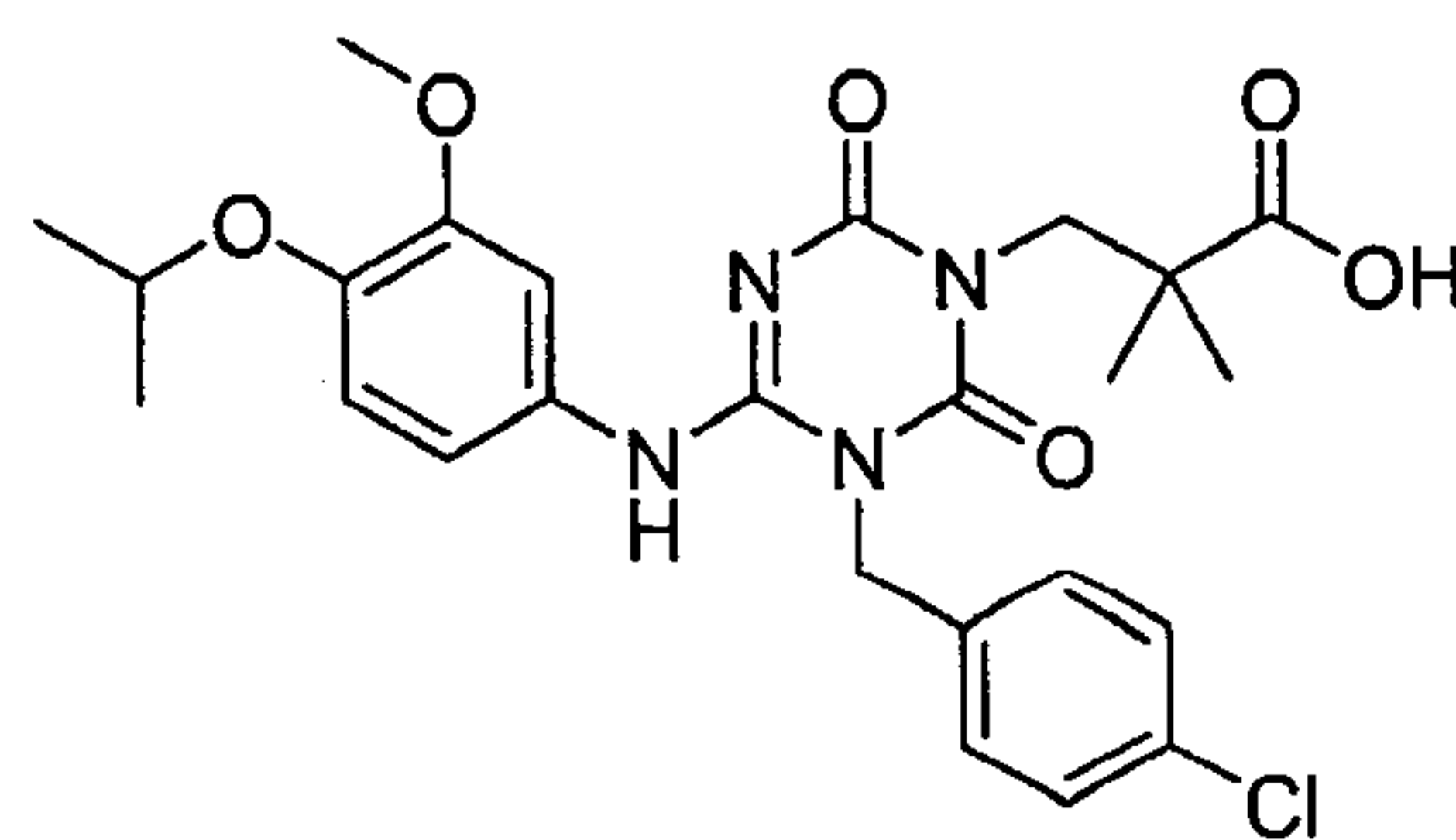
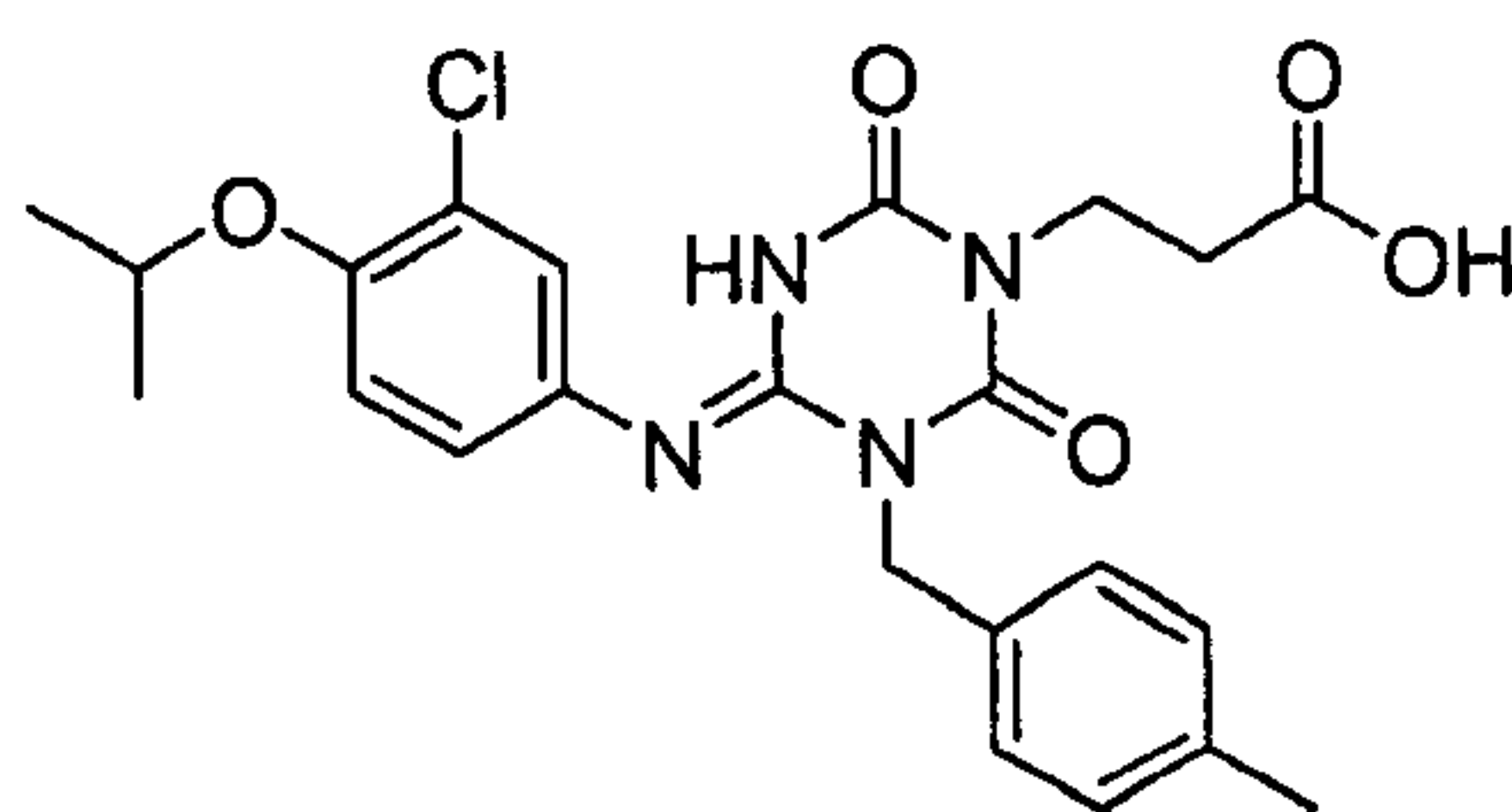
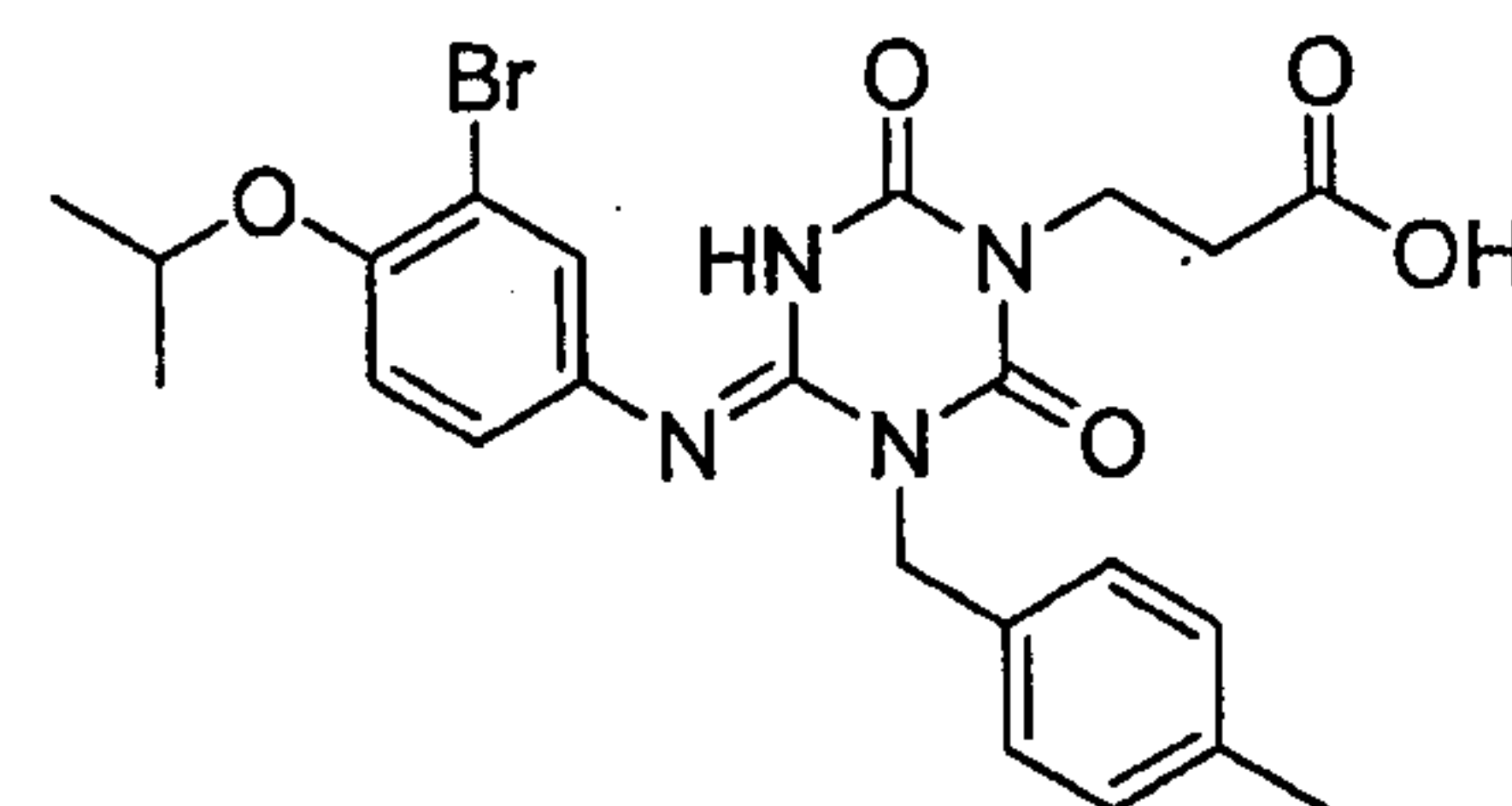
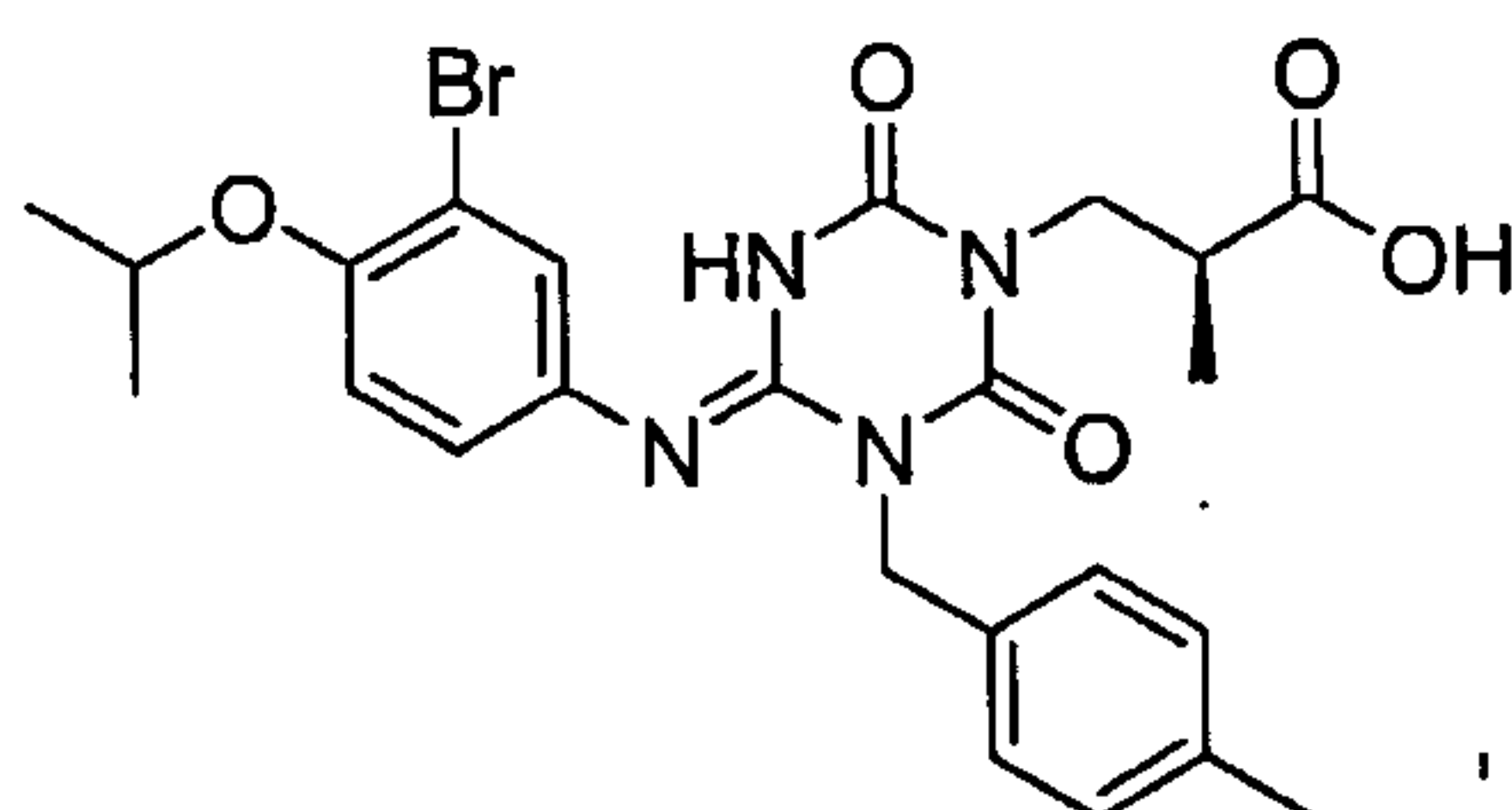
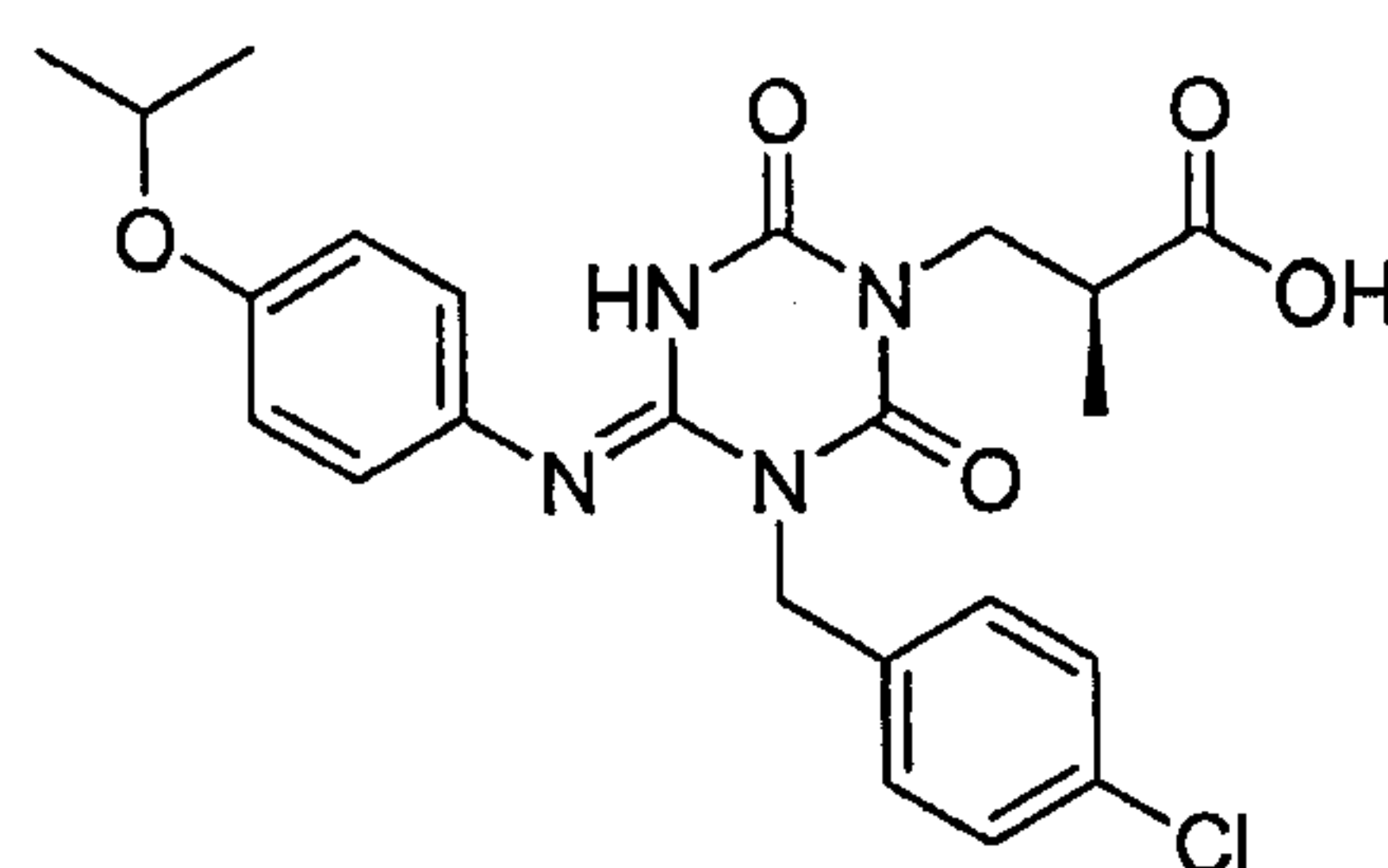
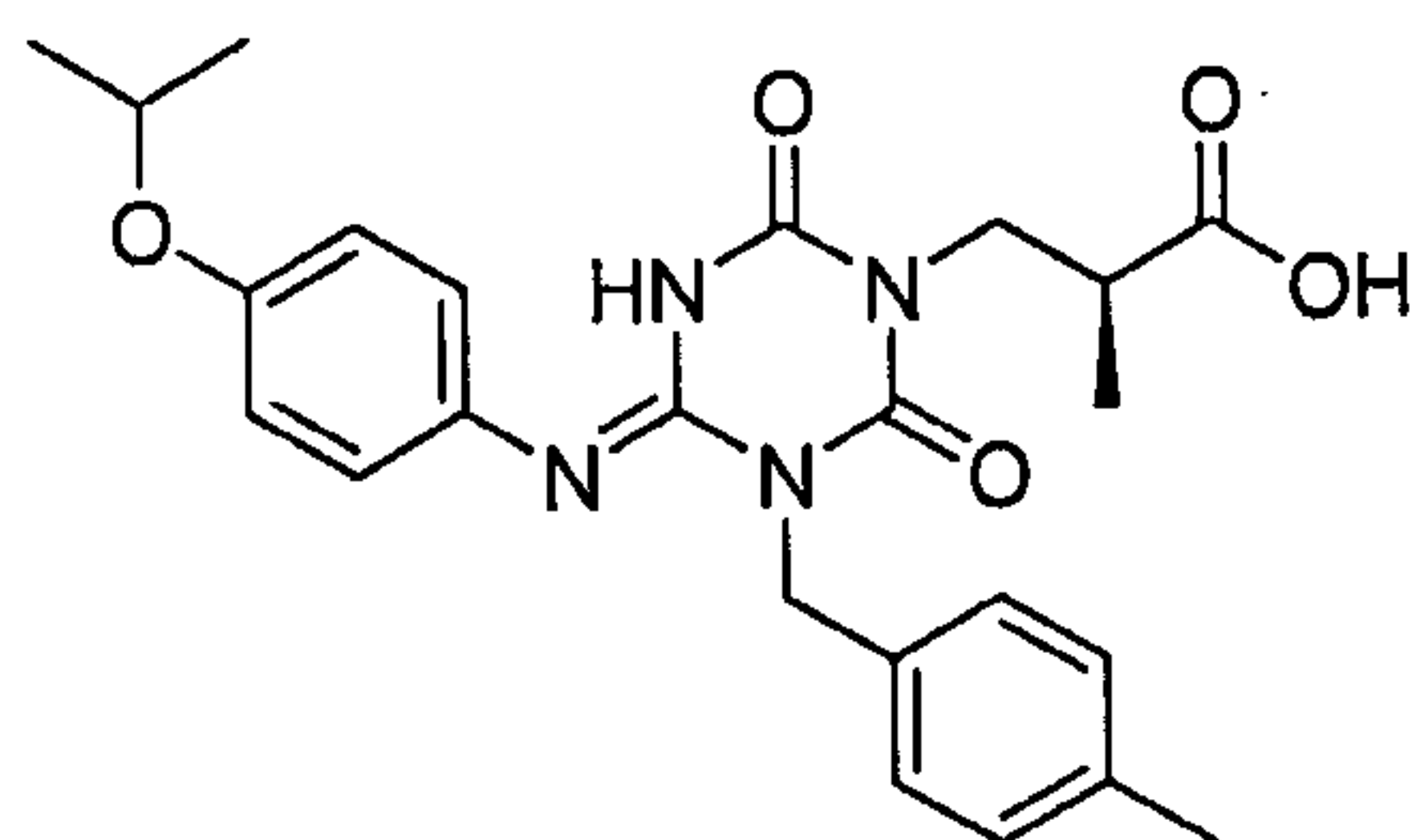
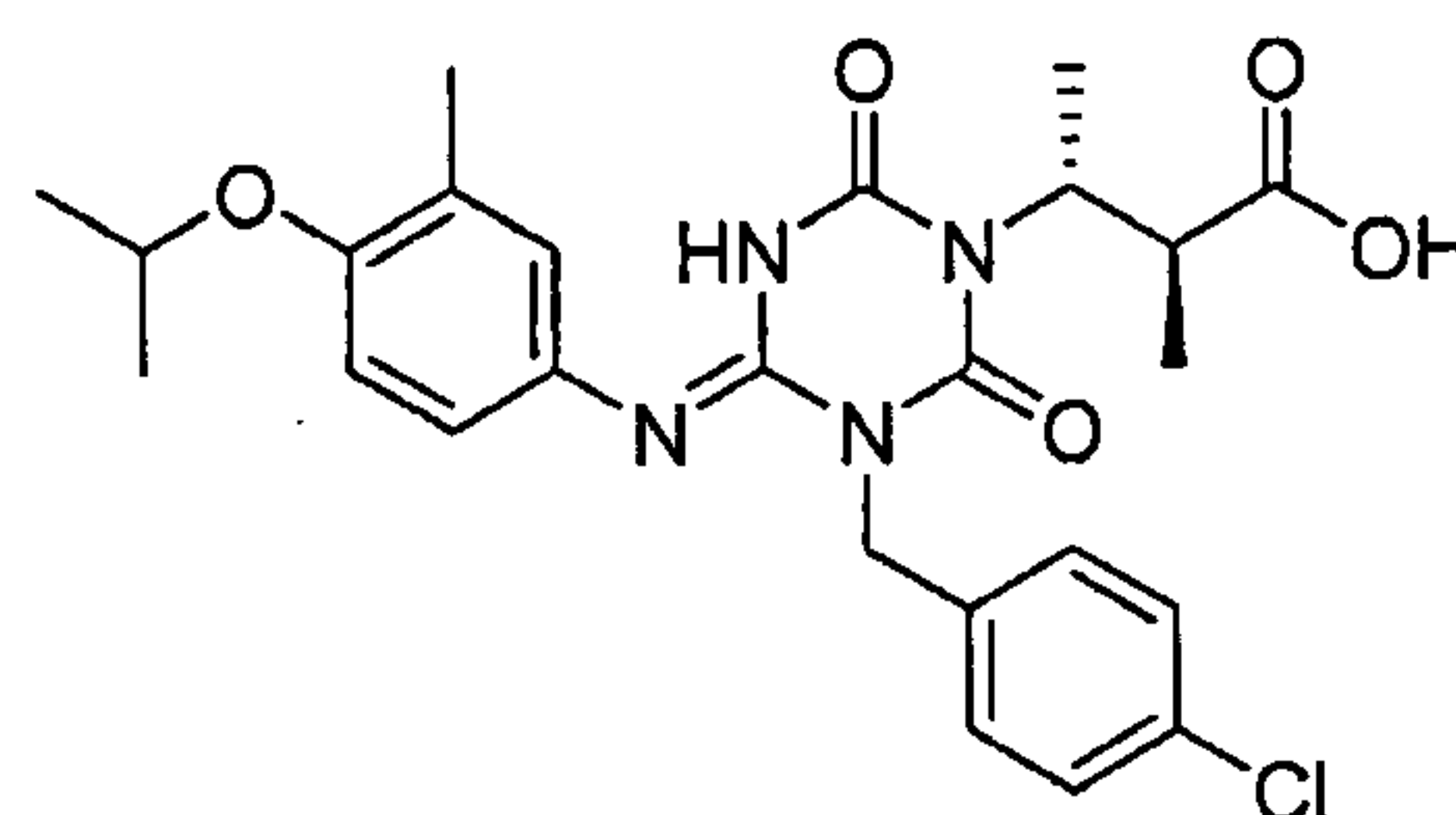
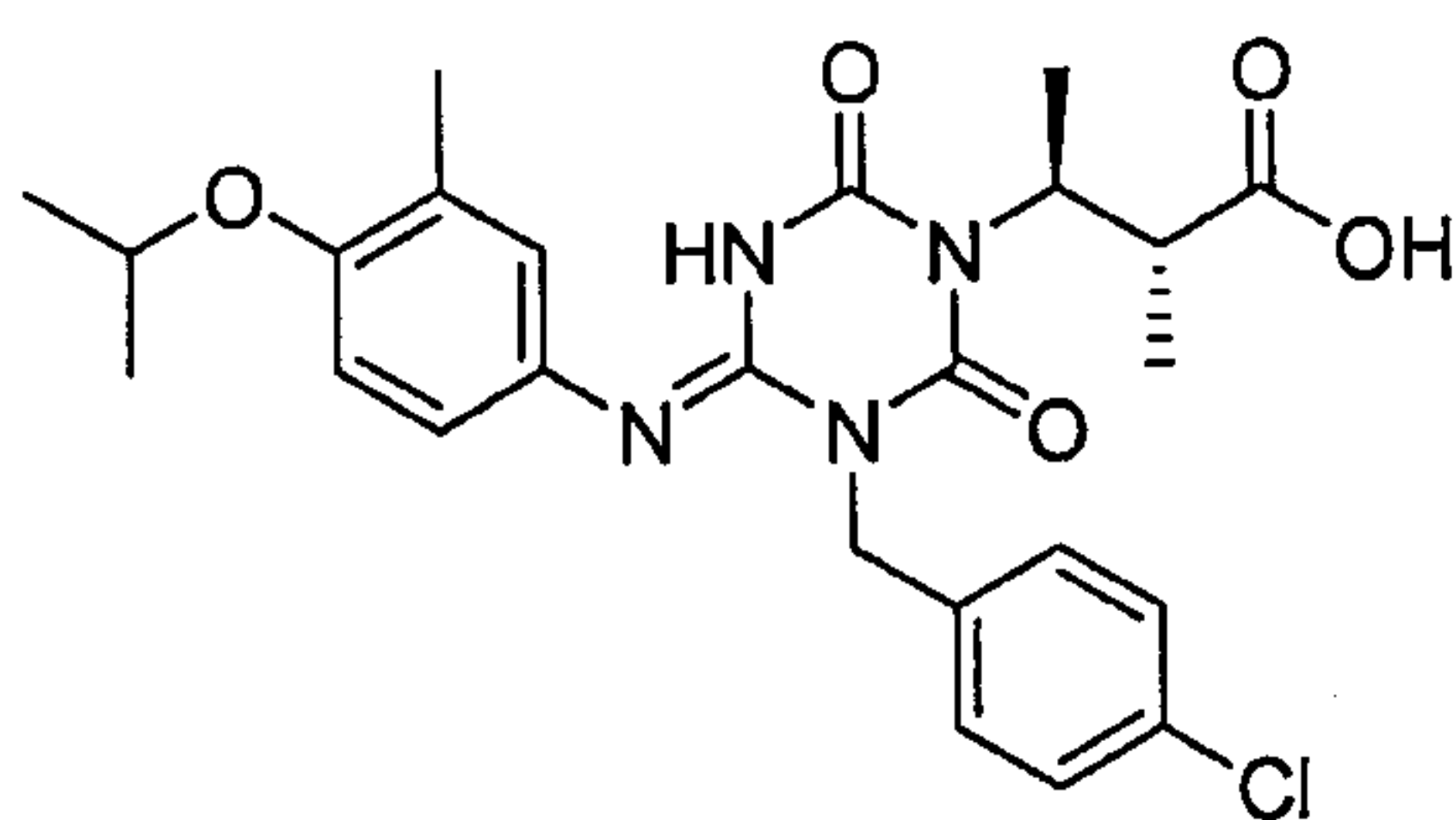
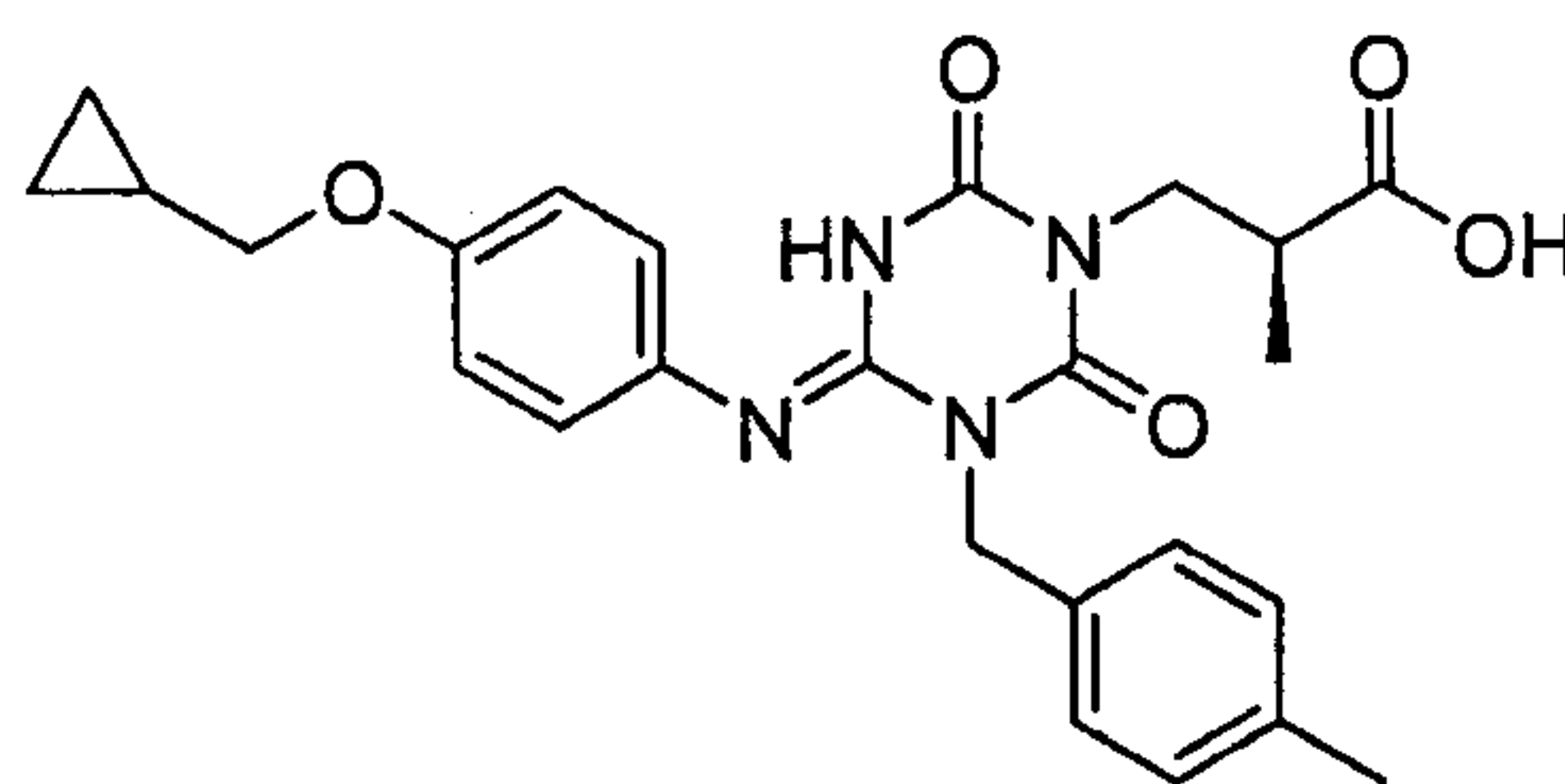
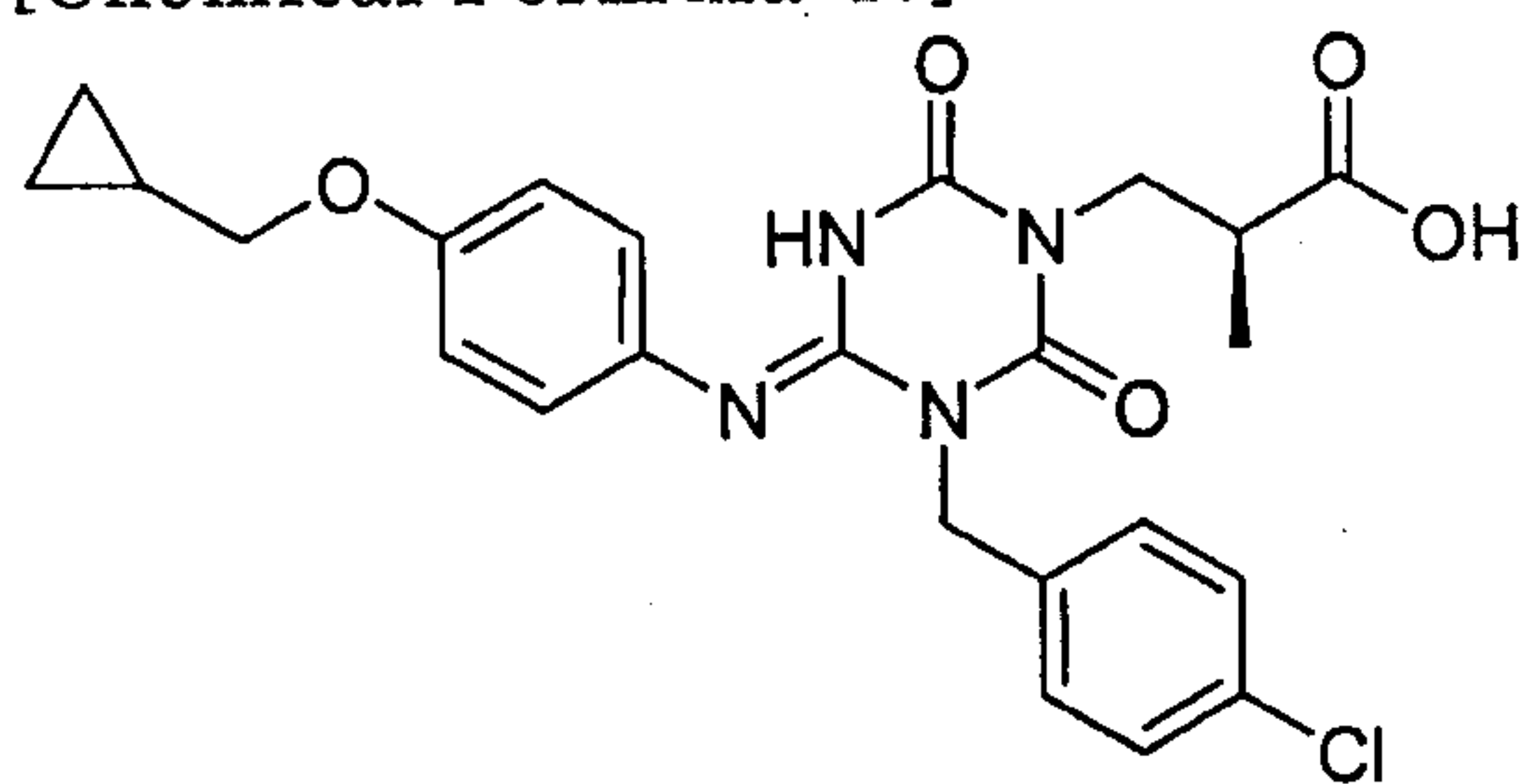


, its pharmaceutically acceptable salt or a solvate thereof.

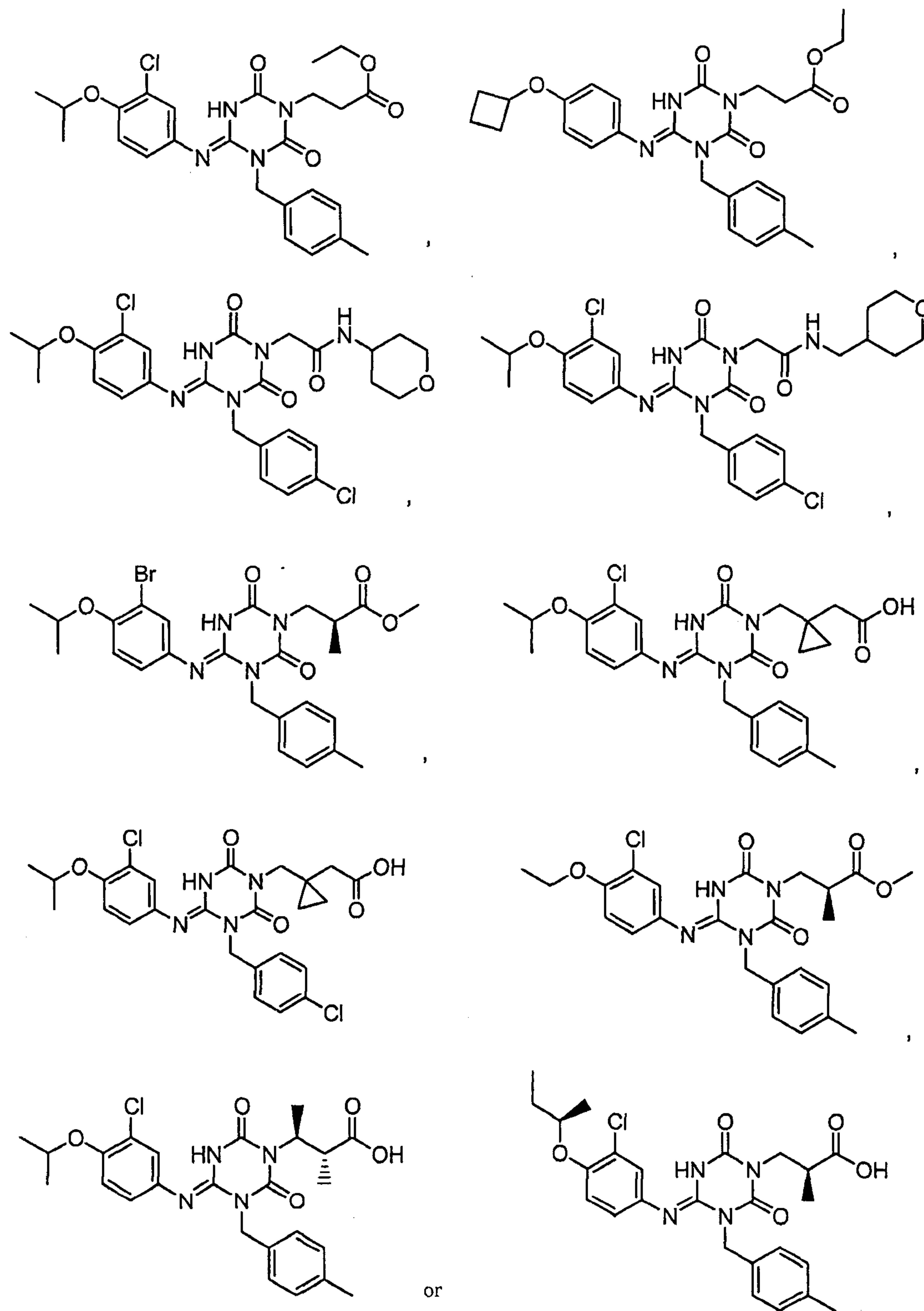
[0066]

(36A''') A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the following formula:

[Chemical Formula 47]



[Chemical Formula 48]



, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.
[0067]

(37A) A pharmaceutical composition comprising the compound according to any one of the above (20A) to (36A), (35A'), (36A'), (35A'') and (36A''), or its pharmaceutically acceptable salt or a solvate thereof.

(37A') A pharmaceutical composition comprising the compound according to any one of the above (20A) to (36A), (35A'), (36A'), (35A'') and (36A'') or its

pharmaceutically acceptable salt or a solvate thereof wherein the composition has a $P2X_3$ and/or $P2X_{2/3}$ receptor antagonistic effect.

(38A) The pharmaceutical composition according to (37A) which has a $P2X_3$ and/or $P2X_{2/3}$ receptor antagonistic effect.

(39A) A compound according to any one of the above (20A) to (36A), (35A'), (36A'), (35A'') and (36A''), 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.

(40A) A method for treating and/or preventing a disease related to $P2X_3$ and/or $P2X_{2/3}$ receptor comprising administering the compound according to (20A) to (36A), (35A'), (36A'), (35A''), (36A'') and (36A'''), or its pharmaceutically acceptable salt or a solvate thereof.

(41A) A compound according to any one of the above (20A) to (36A), (35A'), (36A'), (35A''), (36A'') and (36A'''), or its pharmaceutically acceptable salt or a solvate thereof for use in a method for treating pain and/or urination disorder.

(42A) A method for relieving pain and/or treating urination disorder comprising administering the compound according to (20A) to (36A), (35A'), (36A'), (35A''), (36A'') and (36A''') or its pharmaceutically acceptable salt or a solvate thereof.

[Effect of the Invention]

[0068]

The compound of the invention has an antagonistic effect on $P2X_3$ and/or $P2X_{2/3}$ receptor and is useful in the treatment of diseases or conditions associated with a $P2X_3$ and/or $P2X_{2/3}$ receptor, especially chronic pain, overactive bladder, etc.

[Mode for Carrying Out the Invention]

[0069]

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

[0070]

The term "halogen" means fluoro, chloro, bromo and iodo.

[0071]

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

[0072]

The term "alkyl" includes a straight or branched chain monovalent hydrocarbon group of a carbon number of 1 to 15, as one embodiment a carbon number of 1 to 10, and as another embodiment a carbon number of 1 to 6. Examples include 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, and the like.

[0073]

The alkyl moiety in said "haloalkyl", "hydroxyalkyl", "aminoalkyl", "alkylaminoalkyl", "alkylamino", "alkylimino", "alkylsulfonyl", "alkylsulfamoyl", "alkylcarbamoyl", "arylalkyl", "alkylsilylalkynyl", "alkylsulfonyl", "alkylsulfinyl", "alkylcarbamoyl", "alkylcarbamoylalkyl", "alkylsulfamoyl", "alkylsulfamoylalkyl", "haloalkylcarbamoyl", "hydroxyalkylcarbamoyl", "alkyloxycarbonylalkyl" and "arylalkylamino" is as defined above for "alkyl".

[0074]

The term "alkyloxy" includes an alkyloxy group of which alkyl moiety is as defined above for "alkyl". For example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, etc are exemplified as alkyloxy.

The alkyloxy moiety in said "haloalkyloxy", "arylalkyloxy", "alkyloxycarbonyl", "alkyloxycarbonylalkyl", and "alkyloxyimino" is as defined above for "alkyloxy".

[0075]

For example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, and the like are exemplified as "alkylthio".

[0076]

For example, methyloxycarbonyl, ethyloxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, tert-butyloxycarbonyl, n-pentyloxycarbonyl, and the like are exemplified as "alkyloxycarbonyl".

[0077]

For example, mono- or di- alkylcarbamoyl, such as methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, n-butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, and the like are exemplified as "alkylcarbamoyl".

[0078]

The term "alkenyl" includes linear or branched alkenyl of a carbon number of 2 to 15, as one embodiment a carbon number of 2 to 10, and as another embodiment a carbon number of 2 to 6 having one or more double bonds at any available position. Examples include vinyl, propenyl, isopropenyl, butenyl, isobutenyl, prenyl, butadienyl, pentenyl, isopentenyl, pentadienyl, hexenyl, isohexenyl, hexadienyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl and the like.

[0079]

The alkenyl moiety in said "alkenyloxy", "alkenylthio", "alkenylcarbamoyl", "alkenylsulfamoyl" and "alkenyloxycarbonyl" is as defined above for "alkenyl".

[0080]

The term "alkynyl" includes a linear or branched alkynyl of a carbon number of 2 to 15, as one embodiment a carbon number of 2 to 10, as another embodiment a carbon number 2 to 6. Examples include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl. These have one or more triple bonds at any available position and may further a double bond.

[0081]

The alkynyl moiety in said "alkynyloxy", "alkynylthio" and "alkynyloxycarbonyl" is as defined above for "alkynyl".

[0082]

The term "acyl" includes a group of the formula $R-C(=O)-$, wherein R is, for example, "hydrogen", "alkyl", "alkenyl" or "alkynyl" as defined above and "cycloalkyl", "cycloalkenyl", "non-aromatic heterocyclic group", "aryl" or "heteroaryl" as defined below.

[0083]

The acyl moiety in "acylamino" and "acylimino" is as defined above for "acyl".

[0084]

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.

[0085]

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. As one embodiment, C3 to C8 cycloalkane is exemplified. As another embodiment, C3 to C7 cycloalkane is exemplified. Polycyclic cycloalkyl includes norbornyl, tetrahydronaphthalene-5-yl, tetrahydronaphthalene-6-yl, etc.

Examples of "cycloalkyl" for R^2 are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

Examples of "cycloalkyl" for R^3 are cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

[0086]

The cycloalkyl moiety in said "cycloalkyloxycarbonyl" and "cycloalkyloxy" is as defined above for "cycloalkyl".

[0087]

The term "cycloalkene" includes a non-aromatic monocyclic or polycyclic ring of 3 to 10 carbons containing at least one carbon-carbon double bond. As one embodiment C3 to C8 cycloalkene is exemplified. As another embodiment C3 to C7 cycloalkene is

exemplified. Monocyclic cycloalkene includes, for example, cyclopentene, cyclohexene, etc. Polycyclic cycloalkene includes norbornene, indene, etc.

[0088]

The term "cycloalkenyl" includes a monovalent group derived from "cycloalkene" as defined above. Monocyclic cycloalkenyl includes cyclopentenyl, cyclohexenyl, etc. As one embodiment, C3 to C8 cycloalkane is exemplified. As another embodiment, C3 to C7 cycloalkane is exemplified. Polycyclic cycloalkenyl includes norbornenyl, indene-1-yl, indene-2-yl, indene-3-yl, etc.

[0089]

The cycloalkenyl moiety in said "cycloalkenyloxycarbonyl" and "cycloalkenyloxy" is as defined above for "cycloalkenyl".

[0090]

The term "aromatic carbocyclic ring" includes an aromatic hydrocarbocyclic ring which is monocyclic or fused-cyclic, such as benzene ring, naphthalene ring, anthracene ring, phenanthrene ring, etc.

[0091]

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.

Preferable "aryl" for R³ is phenyl.

[0092]

The aryl moiety in said "aryloxy", "arylthio" and "aryloxycarbonyl" is as defined above for "aryl".

[0093]

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 sulfur 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 sulfur atom in the ring fused to one or more "aromatic carbocyclic ring", "cycloalkane" or "cycloalkene" as defined above.

For example, a monocyclic 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.

[0094]

The term "heterocyclic group" includes a monovalent group derived from "heterocyclic ring" as defined above.

For example, monocyclic non-aromatic heterocyclic groups such as pyrrolinyl,

pyrrolidino, pyrrolidinyl, imidazoliny, imidazolidinyl, pyrazoliny, pyrazolidinyl, piperidino, piperidyl, piperazino, piperazinyl, morpholiny, morpholino, thiomorpholiny, thiomorpholino, tetrahydropyranyl, dihydropyridyl, dihydropyridazinyl, dihydropyrazinyl, dioxanyl, oxathiolanyl, thianyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazoliny, tetrahydroisothiazoliny, 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, oxadiazolyl, etc; and

fused heterocyclic groups such as indolyl, isoindolyl, indazolyl, indoliziny, indoliny, isoindoliny, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, naphthyridiny, quinoxaliny, puriny, pteridinyl, benzopyranyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, benzimidazoliny, benzodioxanyl, tetrahydroquinoline, tetrahydrobenzothienyl, etc. are exemplified.

[0095]

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" or "cycloalkene" as defined above. As a fused ring, indene and the like are exemplified.

[0096]

The term "non-aromatic carbocyclic group" includes a monovalent group derived from "non-aromatic carbocyclic ring" as defined above. For example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cyclopentenyl, cyclohexenyl, norbornyl, tetrahydronaphthalene-5-yl, tetrahydronaphthalene-6-yl, norbornenyl, inden-1-yl, inden-2-yl, inden-3-yl and the like are exemplified.

[0097]

The non-aromatic carbocyclyl moiety in said "non-aromatic carbocyclyloxy" and "non-aromatic carbocyclylalkyloxy" is as defined above for "non-aromatic carbocyclic ring".

[0098]

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 sulfur 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 sulfur 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, benzothiadiazole, benzofuran, isobenzofuran, benzothiophene, benzotriazole, imidazopyridine, triazolopyridine, imidazothiazole, pyrazinopyridazine, benzimidazoline, etc. are exemplified.

[0099]

"Five- or six-membered aromatic heterocyclic ring" includes five- or six-membered rings of "aromatic heterocyclic ring" as defined above. Examples are thiazole, isothiazole, oxazole, isoxazole, thiadiazole, oxadiazole, pyrazole, furan, thiophene, imidazole, triazole, tetrazole, pyridine, pyrimidine, pyrazine, pyridazine, triazine, etc.

[0100]

"Five membered-aromatic heterocyclic ring" includes 6-membered rings of "aromatic heterocyclic ring" as defined above. Examples are thiazole, isothiazole, oxazole, isoxazole, thiadiazole, oxadiazole, pyrazole, furan, thiophen, imidazole, triazole, tetrazole etc.

[0101]

"Six-membered aromatic heterocyclic ring" includes six-membered rings of "aromatic heterocyclic ring" as defined above. Examples are pyridine, pyrimidine, pyrazine, pyridazine, triazine, etc.

[0102]

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 sulfur atom in the ring;

a fused aromatic group consisting of two or more said rings; and

a fused ring consisting of a five- to seven-membered aromatic group having at least one nitrogen atom, oxygen atom, and/or sulfur atom in the ring fused to one or more "aromatic carbocyclic ring" as defined above.

For example, monocyclic heteroaryl 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 heteroaryl such as isoindolyl, indazolyl, indoliziny, isoindolinyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, naphthyridinyl, quinoxalinyl, purinyl, pteridinyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzoxadiazolyl, benzisothiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, imidazopyridyl, triazolopyridyl, imidazothiazolyl, pyrazinopyridazinyl, benzimidazolinyl, etc. are exemplified.

[0103]

One of examples of "heteroaryl" for R² is pyridyl.

Examples of "heteroaryl" for R³ are pyridyl, pyrimidyl, benzofuryl, benzothienyl, indolyl, benzisoxazolyl etc.

One of examples of "heteroaryl" for R³ is pyridyl.

[0104]

The heteroaryl moiety in said "heteroaryloxy" and "heteroaryloxycarbonyl" is as defined above for "heteroaryl".

[0105]

The term "non-aromatic heterocyclic ring" includes non-aromatic rings of "heterocyclic ring" as defined above.

"Non-aromatic heterocyclic ring" includes, a four- to seven-membered non-aromatic ring having at least one nitrogen atom, oxygen atom, and/or sulfur 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 sulfur atom in the ring fused to one or more "cycloalkane" or "cycloalkene" as defined above; and

a fused ring consisting of a five- to seven-membered non-aromatic heterocyclic ring having at least one nitrogen atom, oxygen atom, and/or sulfur atom in the ring fused to one or more "aromatic carbocyclic ring" or "non-aromatic carbocyclic ring" as defined above.

For example, monocyclic non-aromatic heterocyclic ring such as oxetane, thietane, azetidine, pyrroline, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, piperazine, morpholine, thiomorpholine, thiomorpholine, tetrahydropyran, dihydropyridine, dihydropyridazine, dihydropyrazine, dioxane, oxathiolane, thiane, tetrahydrofuran, tetrahydropyran, tetrahydrothiazoline, tetrahydroisothiazoline etc.;

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

[0106]

"Non-aromatic heterocyclic group" includes a monovalent group derived from "non-aromatic heterocyclic ring" as defined above.

Examples are monocyclic non-aromatic heterocyclic group such as pyrrolinyl, pyrrolidine, pyrrolidinyl, imidazolyl, imidazolidinyl, pyrazolyl, pyrazolidinyl, piperidino, piperidyl, piperazine, piperazinyl, morpholyl, morpholino, thiomorpholyl, thiomorpholino, tetrahydropyranyl, dihydropyridyl, dihydropyridazinyl, dihydropyrazinyl, dioxanyl, oxathiolanyl, thianyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiazolyl, tetrahydroisothiazolyl etc. and

a fused heterocyclic group such as benzodioxane, tetrahydroquinoline, benzo[d]oxazole-2(3H) -one, tetrahydrobenzothiophene etc.

[0107]

The non-aromatic heterocyclyl moiety in said "non-aromatic heterocycloxy" and "non-aromatic heterocycloxy carbonyl" is as defined above for "non-aromatic heterocyclic ring".

[0108]

The term "nitrogen-containing non-aromatic heterocyclic group" includes a group derived from a four- to seven-membered non-aromatic ring which contains at least one nitrogen atom in the ring and may contain one or more atoms arbitrarily selected from an oxygen atom and a sulfur atom in the ring and a fused ring consisting of two or more said rings. Examples are pyrrolinyl, pyrrolidino, pyrrolidinyl, piperidino, piperidyl, piperazino, piperazinyl, morpholyl, morpholino, thiomorpholino etc.

[0109]

The non-aromatic heterocyclyl moiety in said "non-aromatic heterocycloxy carbonyl" is as defined above for "non-aromatic heterocyclic ring".

[0110]

Substituents for "substituted alkyl", "substituted alkenyl", "substituted alkynyl", "substituted alkyloxy", "substituted alkenyloxy", "substituted alkynyloxy", "substituted alkylthio", "substituted alkenylthio", "substituted alkynylthio", "substituted alkyloxycarbonyl", "substituted alkenyloxycarbonyl" and "substituted alkynyloxycarbonyl" include but are not limited to one or more same or different substituents selected from the group consisting of:

hydroxy, carboxy, halogen (F, Cl, Br, I), haloalkyloxy (e.g., CF₃O), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), lower alkyloxy (e.g., methoxy, ethoxy,

propoxy, butoxy, etc.) , alkenyloxy (e.g., vinyloxy, allyloxy, etc.) , alkyloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.) , nitro, nitroso, amino, alkylamino (e.g., methylamino, ethylamino, dimethylamino, etc.) , acylamino (e.g., acetylamino, benzoylamino, etc.) , arylalkylamino (e.g., benzylamino, tritylamino) , hydroxyamino, alkylsulfonylamino (e.g., methanesulfonylamino) , alkylsulfinylamino (e.g., methanesulfinylamino), imino, hydroxyimino, alkylimino (e.g., methylimino, ethylimino, dimethylimino, etc.) , alkyloxyimino (e.g., methoxyimino, ethoxyimino, etc.) , acylimino (e.g., acetylimino, 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, piperazinopyrrolidino, 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, alkylthio (e.g., methylthio, etc.) , alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl) , carbamoyl, alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, etc.) , sulfamoyl, alkylsulfamoyl, acyl (e.g., formyl, acetyl, etc.) , formyloxy, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfinio, sulfo, hydrazino, azido, ureido, amidino, guanidino, phthalimido, tri-alkylsilyl (e.g., trimethylsilyl, etc.) , and oxo.

[0111]

As a substituent for "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" for R^c and R^{c1} , the followings are exemplified.

carboxy; hydroxy; oxo; thioxo; halogen; alkyloxy; alkenyloxy; alkynyloxy; alkyloxyalkyloxy; carbamoyl optionally substituted with hydroxy, cyano, alkyl, alkenyl, alkynyl, hydroxyalkyl, hydroxyalkenyl, hydroxyalkynyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, non-aromatic heterocyclalkyl, a non-aromatic heterocyclic group, aryl or heteroaryl; sulfamoyl optionally substituted with hydroxy, cyano, alkyl, alkenyl, alkynyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, non-aromatic heterocyclalkyl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkenyl, heteroaryl, aryl, or heteroaryl; amino optionally substituted with hydroxy, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl; imino optionally substituted with hydroxy, alkyloxy, alkenyloxy, or alkynyloxy; guanidyl optionally substituted with cyanoalkyl; cycloalkyl optionally substituted with carboxy, alkyl, hydroxyalkyl, carboxyalkyl, arylalkyl, heteroarylalkyl, alkyloxyarylmethyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, cycloalkyloxyalkyl, cycloalkenyloxyalkyl, non-aromatic heterocycloxyalkyl, aryloxyalkyl, heteroaryloxyalkyl, oxo or thioxo; a non-aromatic heterocyclic group optionally substituted with carboxy, alkyl, hydroxyalkyl, carboxyalkyl, alkyloxycarbonyl, arylalkyl, alkyloxyarylmethyl, non-aromatic heterocycloxyalkyl, or oxo; aryl optionally substituted with halogen or alkyloxycarbonyl; heteroaryl optionally substituted with carboxy, alkyloxy, alkyloxycarbonyl, non-aromatic heterocycloxyalkyloxy; alkyloxycarbonyl; alkenyloxycarbonyl; alkynyloxycarbonyl; cycloalkyloxycarbonyl; cycloalkenyloxycarbonyl; non-aromatic heterocycloxyloxycarbonyl; aryloxycarbonyl; or heteroaryloxycarbonyl etc.

[0112]

As a substituent for "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" for R^c and R^{c1} , the followings are exemplified.

halogen; hydroxy; carboxy; alkyloxy; alkyloxyalkyloxy; sulfo;
 cycloalkyl optionally substituted with carboxy, alkyl, hydroxyalkyl, carboxyalkyl,
 alkyloxycarbonyl, arylalkyl, alkyloxyarylmethyl, non-aromatic heterocycloxyalkyl, or
 oxo;
 a non-aromatic heterocyclic group optionally substituted with carboxy, alkyl,
 hydroxyalkyl, carboxyalkyl, alkyloxycarbonyl, arylalkyl, alkyloxyarylmethyl,
 non-aromatic heterocycloxyalkyl, or oxo;
 aryl optionally substituted with halogen or alkyloxycarbonyl;
 heteroaryl optionally substituted with carboxy, alkyloxy, alkyloxycarbonyl, or
 non-aromatic heterocycloxyalkyloxy;
 alkyloxycarbonyl; alkenyloxycarbonyl; alkynyloxycarbonyl; cycloalkyloxycarbonyl;
 cycloalkenyloxycarbonyl; non-aromatic heterocycloxyloxycarbonyl; aryloxycarbonyl;
 heteroaryloxycarbonyl;
 carbamoyl optionally substituted with hydroxy, cyano, alkyl, hydroxyalkyl, haloalkyl,
 non-aromatic heterocyclylalkyl or a non-aromatic heterocyclic group;
 sulfamoyl optionally substituted with hydroxy, cyano, alkyl, hydroxyalkyl, haloalkyl,
 non-aromatic heterocyclylalkyl or a non-aromatic heterocyclic group;
 amino optionally substituted with hydroxy, alkyloxycarbonyl, alkenyloxycarbonyl, or
 alkynyloxycarbonyl;
 imino optionally substituted with hydroxy, alkyloxy, alkenyloxy, or alkynyloxy;
 guanidyl optionally substituted with cyanoalkyl; oxo; thioxo etc.

[0113]

As a substituent for "substituted alkyl", "substituted alkenyl", and "substituted
 alkynyl" for R^c and R^{C1} , the followings are exemplified.

halogen; hydroxy; carboxy; alkyloxy; alkyloxyalkyloxy; sulfo; cycloalkyl;
 a non-aromatic heterocyclic group optionally substituted with carboxy, alkyl,
 hydroxyalkyl, carboxyalkyl, alkyloxycarbonyl, arylalkyl, alkyloxyarylmethyl,
 non-aromatic heterocycloxyalkyl, or oxo;
 aryl optionally substituted with halogen, or alkyloxycarbonyl;
 heteroaryl optionally substituted with carboxy, alkyloxy, alkyloxycarbonyl, or
 non-aromatic heterocycloxyalkyloxy;
 alkyloxycarbonyl; alkenyloxycarbonyl; alkynyloxycarbonyl; cycloalkyloxycarbonyl;
 cycloalkenyloxycarbonyl; non-aromatic heterocycloxyloxycarbonyl; aryloxycarbonyl;
 heteroaryloxycarbonyl;
 carbamoyl optionally substituted with hydroxy, cyano, alkyl, hydroxyalkyl, haloalkyl,
 non-aromatic heterocyclylalkyl or a non-aromatic heterocyclic group;
 sulfamoyl;
 amino optionally substituted with hydroxy, or alkyloxycarbonyl;
 imino optionally substituted with hydroxy, or alkyloxy;
 guanidyl optionally substituted with cyanoalkyl;
 oxo; thioxo etc.

[0114]

As a substituent for "substituted alkyl", "substituted alkenyl", and "substituted
 alkynyl" for R^c and R^{C1} , the followings are exemplified:

fluoro, hydroxy, carboxy, methyloxy, methyloxymethyloxy, sulfo, methyloxycarbonyl,
 ethyloxycarbonyl, t-butyloxycarbonyl, tetrahydropyranylmethyloxycarbonyl,
 methylcarbamoyl, hydroxycarbamoyl, dihydroxyisopropylcarbamoyl, aminocarbamoyl,
 cyanocarbamoyl, trifluoromethylcarbamoyl, hydroxyethylcarbamoyl,
 tetrahydropyranylcarbamoyl, tetrahydropyranylethylcarbamoyl, sulfamoyl,

hydroxyamino, methyloxycarbonylamino, t-butyloxycarbonylamino, hydroxyimino, methoxyimino, guanidyl, cyanomethylguanidyl, cyclopropyl, carboxypyrrolidinyl, oxetanyl, oxodihydrooxadiazolyl, dimethyldioxaranyl, oxopyrrolidinyl, methyloxopyrrolidinyl, hydroxyethyloxopyrrolidinyl, carboxymethyloxopyrrolidinyl, oxodihydropyrrolidinyl, methyloxycarbonylmethyloxopyrrolidinyl, morpholinyl, piperazinyl, t-butyloxycarbonylpiperazinyl, oxo(phenylmethyl) (methyl) piperazinyl, oxo(methyloxyphenylmethyl) (methyl) piperazinyl, tetrahydropyranyloxyethyloxopiperazinyl, phenyl, chlorophenyl, ethyloxycarbonylphenyl, triazolyl, tetrazolyl, carboxyisoxazolyl, methyloxycarbonylisoxazolyl, ethyloxycarbonylisoxazolyl, oxazolyl, carboxyfuranyl, methyloxycarbonylfuranyl, methyloxypyridyl, carboxypyridyl, methyloxycarbonylpyridyl, hydroxyethyloxypyridyl, ethyloxycarbonylthiazolyl, tetrahydropyranyloxyethyloxypyridinyl, oxo etc.

[0115]

Substituents for "substituted acyl" are selected from the substituents as defined above for "substituted alkyl", the above "alkyl", the above "alkenyl" and the above "alkynyl". If R in acyl ($R-C(=O)-$) is "cycloalkyl", "cycloalkenyl", "non-aromatic heterocyclic group", "aryl", or "heteroaryl", then each ring may be substituted with alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl, etc.), haloalkyl (e.g., CF_3 , CH_2CF_3 , CH_2CCl_3 , etc.), alkenyl, alkynyl (e.g., ethynyl), alkyloxy (e.g., methoxy, ethoxy, isopropoxy), halogen (e.g., fluoro, chloro etc.) or the like.

[0116]

Substituents for "substituted carbamoyl", "substituted thiocarbamoyl" and "substituted sulfamoyl" are one or more same or different groups selected from, but are not limited to, the group consisting of:

hydroxy, carboxy, halogen (F, Cl, Br, I), alkyl (e.g., methyl, ethyl), alkenyl (e.g., vinyl), alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), alkyloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), amino, 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 and acyl (e.g., formyl, acetyl, etc.).

[0117]

Substituents for "substituted sulfonyl" or "substituted sulfinyl" are selected from the above "substituted or unsubstituted alkyl", the above "substituted or unsubstituted alkenyl", the above "substituted or unsubstituted alkynyl", the after-mentioned "substituted or unsubstituted cycloalkyl", the after-mentioned "substituted or unsubstituted cycloalkenyl", the after-mentioned "a substituted or unsubstituted non-aromatic heterocyclic group", the after-mentioned "substituted or unsubstituted aryl", and the after-mentioned "substituted or unsubstituted heteroaryl". If R in $R-S(=O)_2-$ or $R-S(=O)-$ is "cycloalkyl", "cycloalkenyl", "non-aromatic heterocyclic group", "aryl", "heteroaryl" or the like, then each ring may be substituted with alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl, etc.), haloalkyl (e.g., CF_3 , CH_2CF_3 , CH_2CCl_3 , etc.), alkenyl, alkynyl (e.g., ethynyl), alkyloxy (e.g., methoxy, ethoxy, isopropoxy), halogen (e.g., fluoro, chloro etc.) or the like.

[0118]

Substituents for "substituted amino", "substituted imino" and "substituted guanidyl" are one or more same or different groups selected from, but are not limited to, the group consisting of:

alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl etc.), haloalkyl (e.g., CF_3 , CH_2CF_3 ,

CH₂CCl₃, etc.), hydroxyalkyl (e.g., hydroxyethyl, -C(CH₃)₂CH₂OH, etc.), alkenyl (e.g., vinyl), alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), alkyloxy (e.g., methoxy, ethoxy, propoxy, butoxy, etc.), haloalkyloxy (e.g., CF₃O), alkenyloxy (e.g., vinyloxy, allyloxy, etc.), alkyloxycarbonyl (methoxycarbonyl, tert-butyloxycarbonyl, etc.), alkyloxycarbonylalkyl, amino, alkylamino (e.g., methylamino, ethylamino, dimethylamino, etc.), acylamino (e.g., acetylamino, benzoylamino, etc.), arylalkylamino (e.g., benzylamino, tritylamino), hydroxyamino, imino, hydroxyimino, alkylimino (e.g., methylimino, ethylimino, dimethylimino, etc.), alkyloxyimino (e.g., methoxyimino, ethoxyimino, etc.), acylimino (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, piperazino, piperazinyl, morpholinyl, morpholino etc.), heteroaryl (e.g., pyridyl, thienyl, thiazolyl, furyl etc.), heteroarylalkyl (e.g., pyridylmethyl, thienylmethyl, thiazolylmethyl, furylmethyl etc.), non-aromatic heterocyclyloxy (piperazinooxy, piperidinooxy etc.), heteroaryloxy (pyridyloxy etc.), hydroxy, halogen, (F, Cl, Br, I), cyano, acyl (e.g., formyl, acetyl, etc.), alkylsulfonyl (e.g., methanesulfonyl etc.), alkylsulfinyl (e.g., methansulfinyl), carbamoyl, alkylcarbamoyl (e.g., methylcarbamoyl etc.), alkylcarbamoylalkyl (e.g., methylcarbamoylmethyl etc.), carbamoylalkyl (e.g., carbamoylmethyl etc.), carboxyalkyl (e.g., carboxymethyl etc.), sulfamoyl, alkylsulfamoyl (e.g., methylsulfamoyl etc.), alkylsulfamoylalkyl (e.g., methylsulfamoylmethyl etc.), and sulfamoylalkyl (e.g., sulfamoylmethyl etc.) .

[0119]

Substituents for "substituted cycloalkyl", "substituted cycloalkenyl", "substituted aryl", "substituted phenyl", "substituted heterocyclic group", "substituted heteroaryl", "a substituted non-aromatic carbocyclic group", "a substituted non-aromatic heterocyclic group", "a substituted nitrogen-containing non-aromatic heterocyclic group", "substituted cycloalkyloxycarbonyl", "substituted cycloalkyenyloxycarbonyl", "substituted non-aromatic heterocyclyloxycarbonyl", "substituted aryloxycarbonyl", "substituted heteroaryloxycarbonyl", "a substituted cyclopropane ring", "a substituted cyclopropene ring", "a substituted oxetane ring", "a substituted thietane ring" and "a substituted azetizine ring" are one or more same or different groups selected from, but are not limited to, the group consisting of:

alkyl (e.g., methyl, ethyl, isopropyl, tert-butyl etc.), haloalkyl (e.g., CF₃, CH₂CF₃, CH₂CCl₃, etc.), haloalkyloxy (e.g., CF₃O, CHCF₂O etc.), alkenyl (e.g., vinyl), alkynyl (e.g., ethynyl), cycloalkyl (e.g., cyclopropyl), cycloalkenyl (e.g., cyclopropenyl), alkyloxy (e.g., methoxy, ethoxy, propoxy, butoxy, etc.), alkenyloxy (e.g., vinyloxy, allyloxy, etc.), alkyloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), nitro, nitroso, amino, alkylamino (e.g., methylamino, ethylamino, dimethylamino, etc.), acylamino (e.g., acetylamino, benzoylamino, etc.), arylalkylamino (e.g., benzylamino, tritylamino), hydroxyamino, amino substituted with one or two same or different substituent selected from the after-mentioned substituent Group Y, imino, hydroxy imino, alkylimino (e.g., methylimino, ethylimino, dimethylimino etc.), alkyloxyimino (e.g., methoxyimino, ethoxyimino etc.), acylimino (e.g., acetylimino, benzoylimino etc.), azido, aryl (e.g., phenyl etc.), arylalkyl (e.g., benzyl etc.), unsubstituted non-aromatic carbocyclyloxy (e.g., cyclopropyloxy etc.), non-aromatic carbocyclyloxy substituted with one or more same or different substituents selected from the after-mentioned Substituent Group Z, unsubstituted non-aromatic carbocyclylalkyloxy (e.g., cyclopropylmethyloxy etc.), non-aromatic carbocyclylalkyloxy substituted with one or more same or different substituents selected from the after-mentioned Substituent Group Z, unsubstituted

aryloxy (e.g., phenoxy etc.), aryloxy substituted with one or more same or different substituents selected from the after-mentioned Substituent Group Z, unsubstituted arylalkyloxy (e.g., benzyloxy etc.), arylalkyloxy substituted with one or more same or different substituents selected from the after-mentioned Substituent Group Z, a non-aromatic heterocyclic group (e.g., pyrrolinyl, pyrrolidino, piperidino, piperidyl, piperazino, piperazinyl, morpholinyl, morpholino etc.), heteroaryl (e.g., pyridyl, thienyl, thiazolyl, furyl etc.), heteroarylalkyl (e.g., pyridylmethyl, thienylmethyl, thiazolylmethyl, furylmethyl etc.), unsubstituted non-aromatic heterocyclyloxy (e.g., piperazinooxy, piperizinooxy etc.), non-aromatic heterocyclyloxy substituted with one or more same or different substituents selected from the after-mentioned Substituent Group Z, unsubstituted heteroaryloxy (e.g., pyridyloxy etc.), heteroaryloxy substituted with one or more same or different substituents selected from the after-mentioned Substituent Group Z, cyano, isocyano, isocyanato, thiocyanato, isothiocyanato, mercapto, alkylthio (e.g., methylthio etc.), alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl), substituted or unsubstituted carbamoyl (e.g., carbamoyl, N-methyl-N-methoxycarbamoyl etc.), substituted or unsubstituted alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, dimethylcarbamoyl, hydroxyethylcarbamoyl, trifluoromethylcarbamoyl, trifluoroethylcarbamoyl etc.), sulfamoyl, alkylsulfamoyl, hydroxy, carboxy, halogen (F, Cl, Br, I), acyl (e.g., formyl, acetyl etc.), formyloxy, thioformyl, thiocarboxy, dithiocarboxy, thiocarbamoyl, sulfinio, sulfo, hydrazino, azido, ureido, amidino, guanidino, phthalimido and oxo.

A substituent Group Y includes hydroxy alkyl (e.g., hydroxyethyl, $-C(CH_3)_2CH_2OH$ etc.), alkyloxycarbonyl (methoxycarbonyl, tert-butyloxycarbonyl etc.), alkyloxycarbonylalkyl, alkylsulfonyl (e.g., methanesulfonyl etc.), alkylsulfinyl (e.g., methanesulfinyl etc.), carbamoyl, alkylcarbamoyl (e.g., methylcarbamoyl etc.), alkylcarbamoylalkyl (e.g., methylcarbamoylmethyl etc.), carbamoylalkyl (e.g., carbamoylmethyl etc.), carboxyalkyl (e.g., carboxymethyl etc.), sulfamoyl, alkylsulfamoyl (e.g., methylsulfamoyl etc.), alkylsulfamoylalkyl (e.g., methylsulfamoylmethyl etc.) and sulfamoylalkyl (e.g., sulfamoylmethyl etc.).

A substituent Group Z includes halogen, hydroxy, carboxy, cyano, nitro, alkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylthio, alkenylthio, alkynylthio, acyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, carbamoyl, alkylcarbamoyl, haloalkylcarbamoyl, hydroxyalkylcarbamoyl, cyanocarbamoyl, amino, acylamino, amino substituted with one or two same or different substituent selected from the above substituent Group Y, sulfamoyl, methylsulfonyl, methylsulfinyl, cycloalkyl, cycloalkenyl, a non-aromatic heterocyclic group, aryl, heteroaryl, cycloalkyloxy, cycloalkenyloxy, non-aromatic heterocyclyloxy, aryloxy and heteroaryloxy.

[0120]

As substituents for "substituted aryl" and "substituted heteroaryl" for R^2 , halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, a non-aromatic heterocyclic group, alkylsilylalkynyl and the like are exemplified.

[0121]

As substituents for "substituted aryl" and "substituted heteroaryl" for R^2 , halogen, alkyl, alkenyl, alkynyl, alkyloxy, cycloalkyl, alkylsilylalkynyl and the like are exemplified.

[0122]

As substituents for "substituted aryl" and "substituted heteroaryl" for R^2 , fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, propenyl, vinyl, ethynyl, methyl oxy, cyclopropyl, trimethylsilylethynyl and the like are exemplified.

[0123]

As substituents for "substituted aryl" and "substituted heteroaryl" for R³,
 halogen; hydroxy;
 alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino,
 alkenyloxyimino, alkynyloxyimino, dialkylamino, alkyloxy, alkenyloxy, alkynyloxy,
 cycloalkyl, cycloalkenyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl;
 alkenyl optionally substituted with cycloalkyl, cycloalkenyl or a non-aromatic heterocyclic
 group;
 alkynyl optionally substituted with cycloalkyl, cycloalkenyl or a non-aromatic heterocyclic
 group;
 unsubstituted alkyloxy;
 alkyloxy substituted with a non-aromatic heterocyclic group optionally substituted with
 halogen, alkyloxy, alkenyloxy, alkynyloxy, aryl, alkyl, alkenyl or alkynyl;
 alkylthio; alkenylthio; alkynylthio; cycloalkyl; cycloalkenyl; a non-aromatic heterocyclic
 group; alkylamino; alkenyl amino; alkynylamino and the like are exemplified.

[0124]

As substituents for "substituted aryl" and "substituted heteroaryl" for R³ are
 halogen; hydroxy;
 alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino,
 alkyloxy, cycloalkyl, or heteroarylalkyl;
 alkenyl optionally substituted with cycloalkyl;
 alkynyl optionally substituted with cycloalkyl;
 alkyloxy optionally substituted with a non-aromatic heterocyclic group optionally
 substituted with halogen, alkyloxy, aryl, or alkyl;
 alkylthio; cycloalkyl; cycloalkenyl; a non-aromatic heterocyclic group; alkylamino and the
 like are exemplified.

[0125]

As substituents for "substituted aryl" and "substituted heteroaryl" for R³, chloro,
 bromo, fluoro, hydroxy, methyl, trifluoromethyl, methyloxymethyl, cyanomethyl,
 difluoroethyl, methyloxyiminomethyl, isopropyl, propyl, trifluoroisopropyl,
 dimethylaminomethyl, butyl, isobutyl, isopropyloxymethyl, pentyl, cyclopropylethyl,
 cyclopentylmethyl, pyridylmethyl, methylisopropenyl, vinyl, cyclopropylvinyl, methyl
 propenyl, cyclopentylidenemethyl, cyclopropylethynyl, hydroxyethyl, methyloxy,
 difluoromethyloxy, trifluoromethyloxy, ethyloxy, propyloxy, methyloxy ethyloxy,
 oxetanyloxy, cyclobutyloxy, cyclopentyloxy, s-butyloxy, isobutyloxy, cyclopropylmethyloxy,
 tetrahydropyranyloxy, 2-methylbutyloxy, dimethylbutyloxy, pentanyloxy,
 pentane-3-yloxy, dimethylpyridyloxy, methyl pyridyloxy, pyridyloxy, phenyloxy,
 methylthio, ethylthio, cyclopentyl, cyclopentenyl, cyclohexyl, piperazinyl, piperidinyl,
 azepanyl and the like are exemplified.

[0126]

Examples of "heteroaryloxy" as substituents for "substituted aryl" and
 "substituted heteroaryl" for R³ include pyrrolyloxy, pyrazinyloxy, pyrazolyloxy, indolyloxy,
 tetrazolyloxy, furyloxy, thienyloxy, pyridyloxy, imidazolyloxy, triazolyloxy, tetrazolyloxy,
 triazinyloxy, pyridazinyloxy, pyrimidinyloxy, pyrazinyloxy, isooxazolyloxy, thiazolyloxy,
 isothiazolyloxy, thiadiazolyloxy, oxazolyloxy, oxadiazolyloxy and the like.

[0127]

As substituents for "substituted aryl" and "substituted heteroaryl" for R³,
 unsubstituted heteroaryloxyl, heteroaryloxyl substituted with one or more same or
 different substituents selected from the above Substituent Group Z and the like are

exemplified. Further, halogen, hydroxy, carboxy, cyano, nitro, alkyl, haloalkyl, haloalkyloxy, alkyloxy, amino and the like are exemplified. The above heteroaryloxy includes the following groups which are unsubstituted or substituted with one or more same or different substituents selected from the above Substituent Group Z:

pyrrolyloxy, pyrazinyloxy, pyrazolyloxy, indolyloxy, tetrazolyloxy, furyloxy, thienyloxy, pyridyloxy, imidazolyloxy, triazolyloxy, tetrazolyloxy, triazinyloxy, pyridazinyloxy, pyrimidinyloxy, pyrazinyloxy, isooxazolyloxy, thiazolyloxy, isothiazolyloxy, thiadiazolyloxy, oxazolyloxy, and oxadiazolyloxy and the like.

[0128]

As substituents for "substituted heteroaryl" for R^3 , halogen; alkyl; alkenyl; alkynyl; alkyloxy; alkenyloxy; alkynyloxy; cycloalkyloxy, cycloalkenyloxy; aryloxy; heteroaryloxy and the like are exemplified.

[0129]

As substituents for "substituted heteroaryl" for R^3 , halogen; alkyl; alkyloxy; cycloalkyloxy and the like are exemplified.

[0130]

As substituents for "substituted non-aromatic heterocyclic group" for R^3 , arylalkyl, heteroarylalkyl, aryl, heteroaryl and the like are exemplified.

[0131]

As substituents for "substituted non-aromatic heterocyclic group" for R^3 , arylalkyl, aryl and the like are exemplified.

[0132]

As substituents for "substituted non-aromatic heterocyclic group" for R^3 , phenylmethyl, phenyl and the like are exemplified.

[0133]

As substituents for "substituted amino" for $R^{9'}$, carbamoyl, alkylcarbamoyl (e.g., methylcarbamoyl etc.), alkylcarbamoylalkyl (e.g., methylcarbamoylmethyl etc.), carbamoylalkyl (e.g., carbamoylmethyl etc.), carboxyalkyl (e.g., carboxymethyl etc.) and the like are exemplified.

[0134]

Examples of "substituted or unsubstituted alkyl" for R^{30} and R^{31} are methyl, monofluoromethyl, difluoromethyl, trifluoromethyl, ethyl and the like.

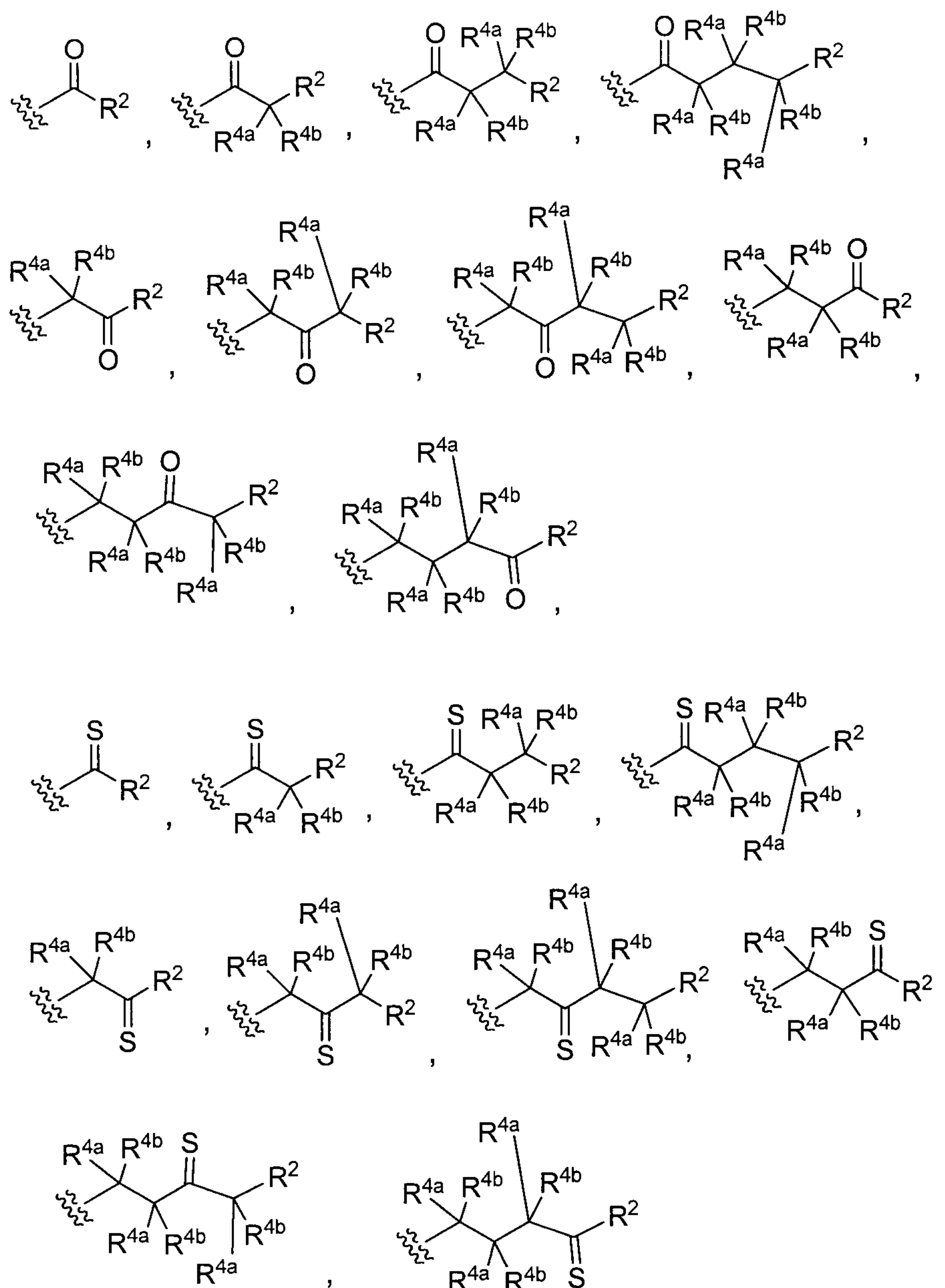
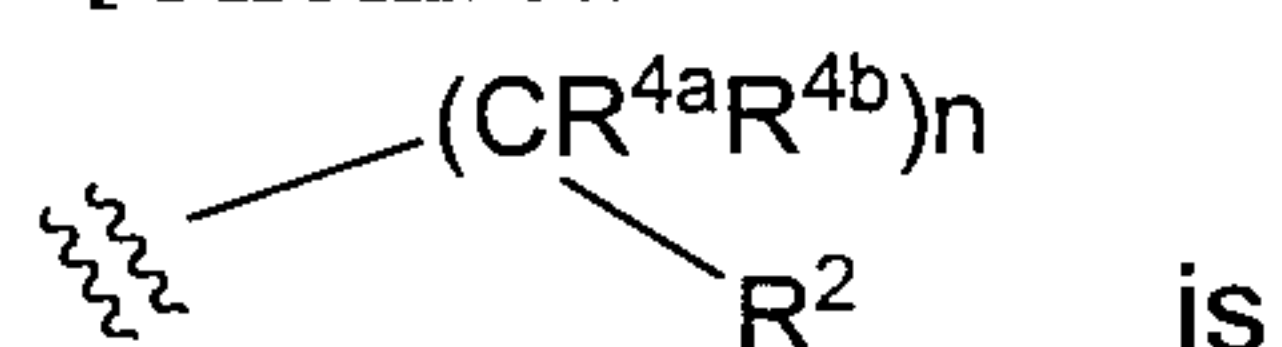
[0135]

Examples of $R^{9'}$ are halogen, hydroxy, carboxy, cyano, nitro, alkyl, hydroxyalkyl, aminoalkyl, alkylaminoalkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, alkylthio, alkenylthio, alkynylthio, acyl, alkyloxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, carbamoyl, alkylcarbamoyl, haloalkylcarbamoyl, hydroxyalkylcarbamoyl, cyanocarbamoyl, amino, acylamino, amino substituted with one or two same or different substituents selected from the above Substituent Group Y, sulfamoyl, methylsulfonyl, methylsulfinyl and the like.

[0136]

In general formula (VIII), general formula (IX), general formula (VII), general formula (IV), general formula (I), general formula (II) or general formula (III), " R^{4a} and R^{4b} attached to the same carbon atom are taken together to form oxo or thioxo" includes the followings:

[Chemical Formula 49]

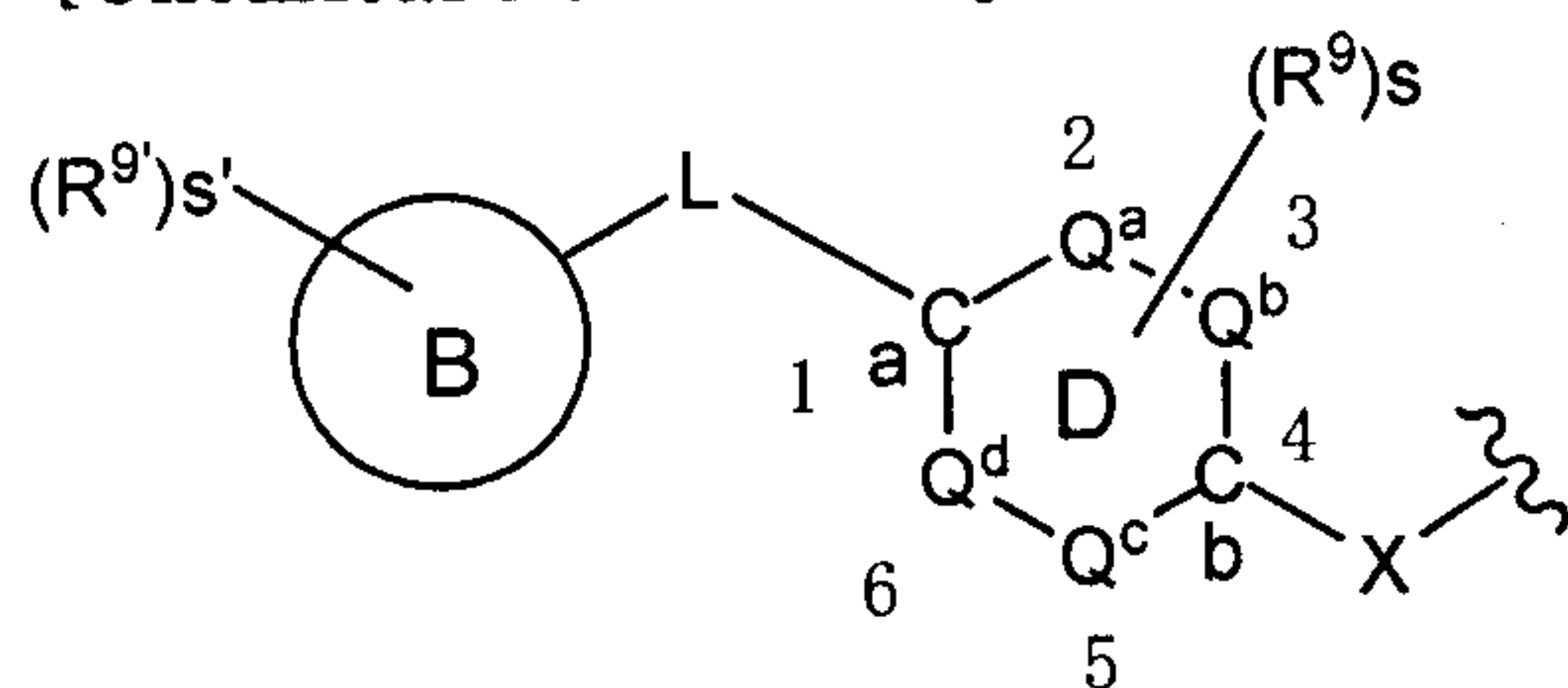


wherein n , R^{4a} , R^{4b} and R^2 are as defined in the above (1) and the like.

[0137]

In general formula (VIII), the positions of carbon atom a, Q^a atom, Q^b atom, carbon atom b, Q^c atom and Q^d atom which constitute a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring as ring D is defined as 1-position, 2-position, 3-position, 4-position, 5-position and 6-position, respectively. Each of the position numbers of these atoms is different from position number based on IUPAC nomenclature. That is, "carbon atom a is positioned on ring D in a 1,4 relationship with respect to carbon atom b" includes the followings:

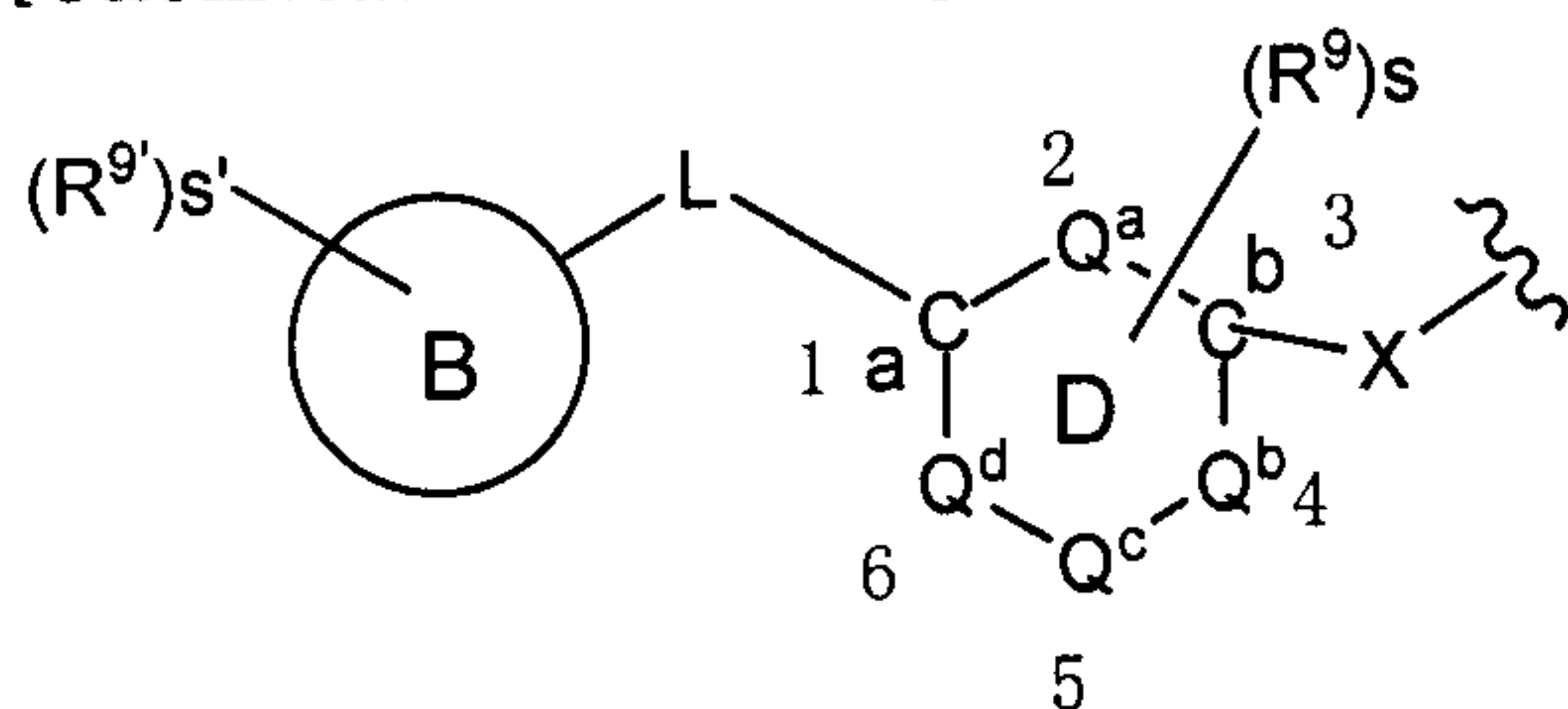
[Chemical Formula 50]



wherein Q^a atom, Q^b atom, Q^c atom and Q^d atom are each independently a carbon atom or a nitrogen atom, $-X-$, $-L-$, ring D, ring B, s, s', R^9 and $R^{9'}$ are as defined in the above (1).
[0138]

In general formula (VIII), the positions of carbon atom a, Q^a atom, Q^b atom, carbon atom b, Q^c atom and Q^d atom which constitute a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring as ring D is defined as 1-position, 2-position, 3-position, 4-position, 5-position and 6-position, respectively. Each of the position numbers of these atoms is different from position number based on IUPAC nomenclature. That is, "carbon atom a is positioned on ring D in a 1,3 relationship with respect to carbon atom b" includes the followings:

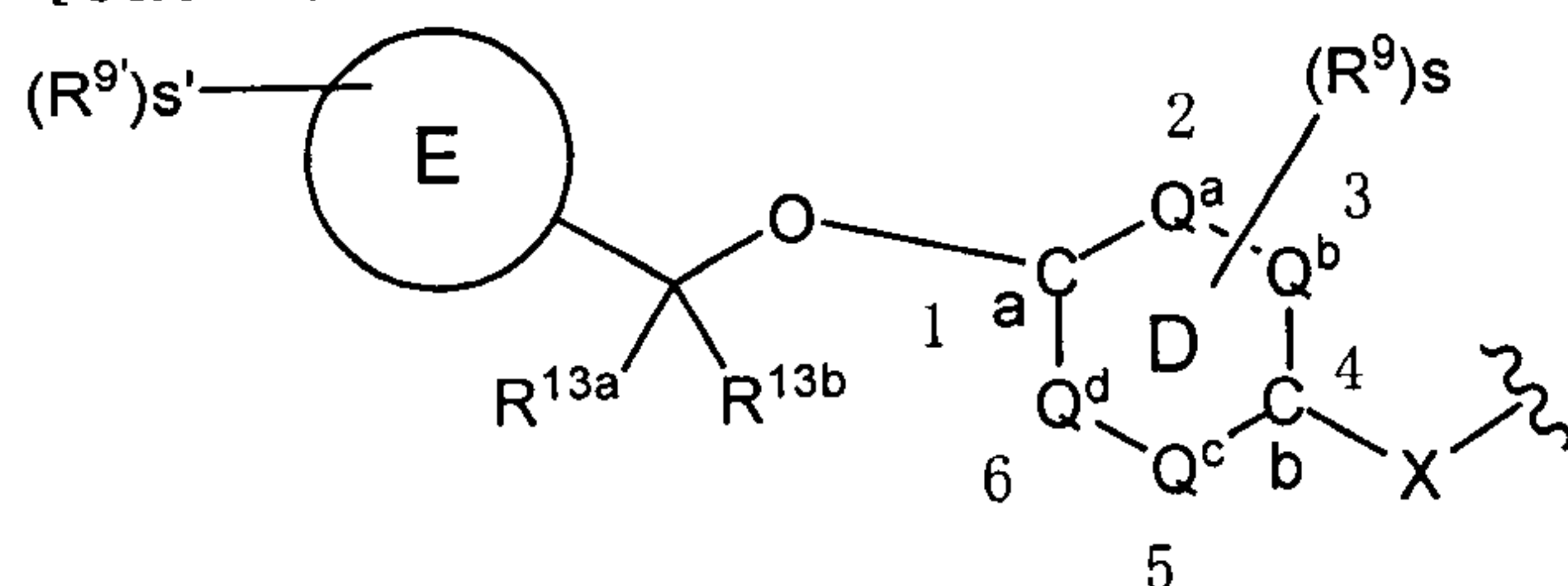
[Chemical Formula 51]



wherein Q^a atom, Q^b atom, Q^c atom and Q^d atom are each independently a carbon atom or a nitrogen atom, $-X-$, $-L-$, ring D, ring B, s, s', R^9 and $R^{9'}$ are as defined in the above (1).
[0139]

In general formula (IX), the positions of carbon atom a, Q^a atom, Q^b atom, carbon atom b, Q^c atom and Q^d atom which constitute a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring as ring D is defined as 1-position, 2-position, 3-position, 4-position, 5-position and 6-position, respectively. Each of the position numbers of these atoms is different from position number based on IUPAC nomenclature. That is, "carbon atom a is positioned on ring D in a 1,4 relationship with respect to carbon atom b" includes the followings:

[Chemical Formula 52]



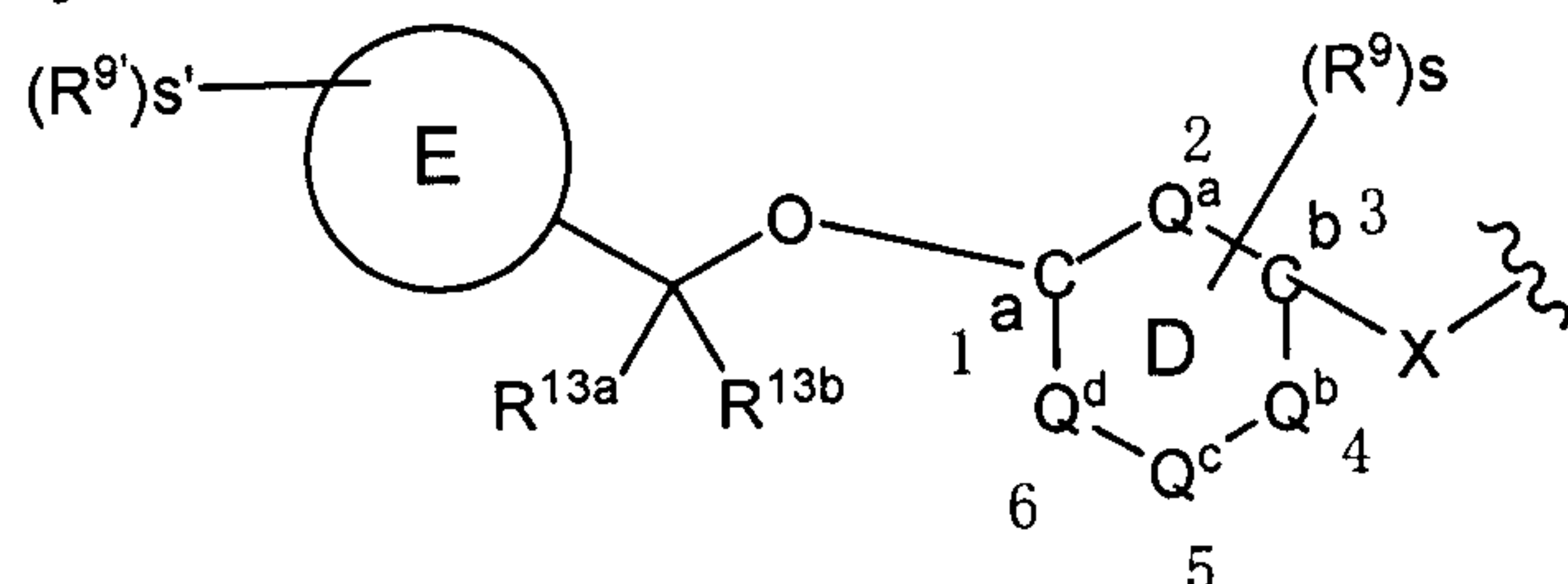
wherein Q^a atom, Q^b atom, Q^c atom and Q^d atom are each independently a carbon atom or a nitrogen atom, $-X-$, $-L-$, ring D, R^{13a} , R^{13b} , ring E, s, s', R^9 and $R^{9'}$ are as defined in the above (8).

[0140]

In general formula (IX), each of the position of carbon atom a, Q^a atom, Q^b atom,

carbon atom b, Q^c atom and Q^d atom which constitute a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring as ring D is defined as 1-position, 2-position, 3-position, 4-position, 5-position and 6-position, respectively. Each of the position numbers of these atoms is different from position number based on IUPAC nomenclature. That is, "carbon atom a is positioned on ring D in a 1,3 relationship with respect to carbon atom b" includes the followings:

[Chemical Formula 53]

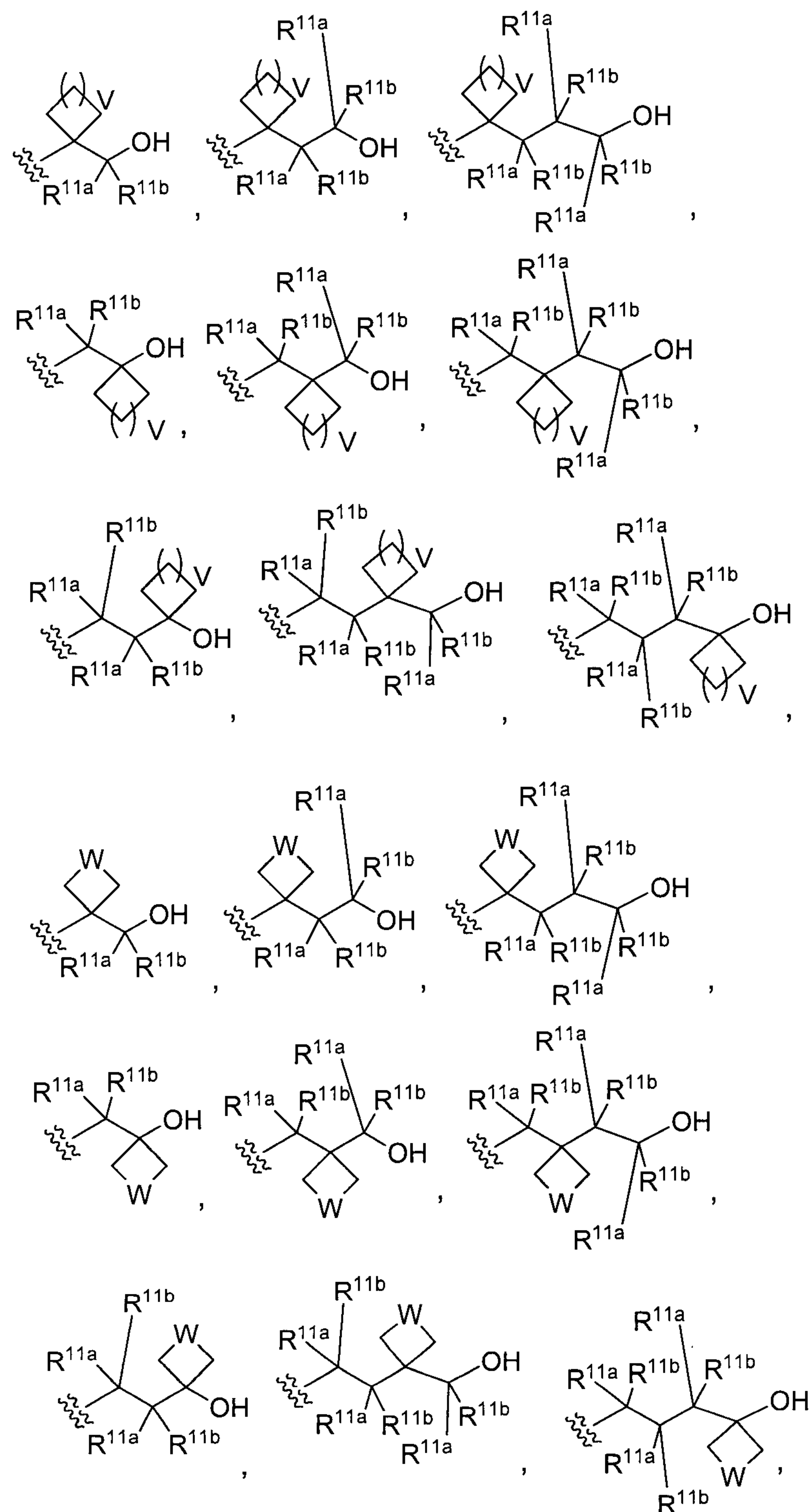
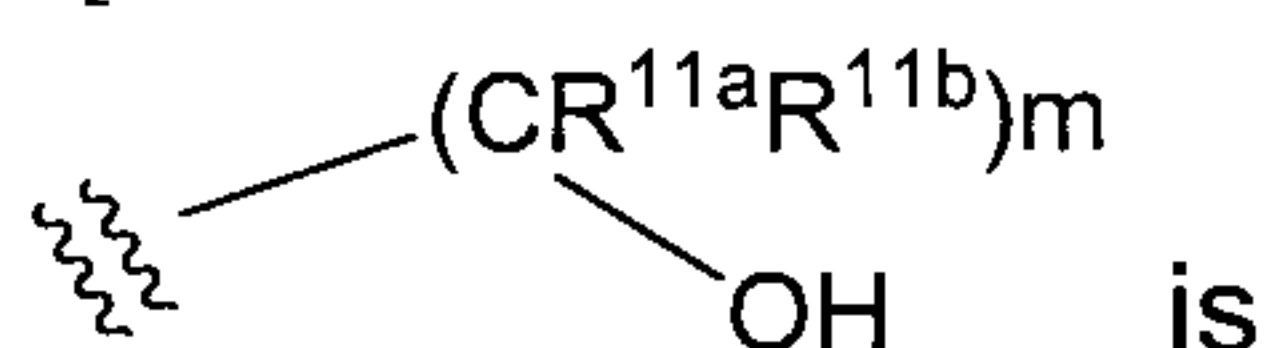


wherein Q^a atom, Q^b atom, Q^c atom and Q^d atom are each independently a carbon atom or a nitrogen atom, -X-, -L-, ring D, R^{13a}, R^{13b}, ring E, s, s', R⁹ and R^{9'} are as defined in the above (8).

[0141]

In general formula (VIII), general formula (IX), and general formula (VII), "R^{11a} and R^{11b} together with the carbon atom to which they are attached form a substituted or unsubstituted cycloalkane ring, a substituted or unsubstituted cycloalkene ring, or a substituted or unsubstituted non-aromatic heterocyclic ring" includes the followings:

[Chemical Formula 54]



wherein m , R^{11a} and R^{11b} are as defined in the above (21);

v is an integer of 0 to 3 (e.g., 0 or 1, and e.g., 0);

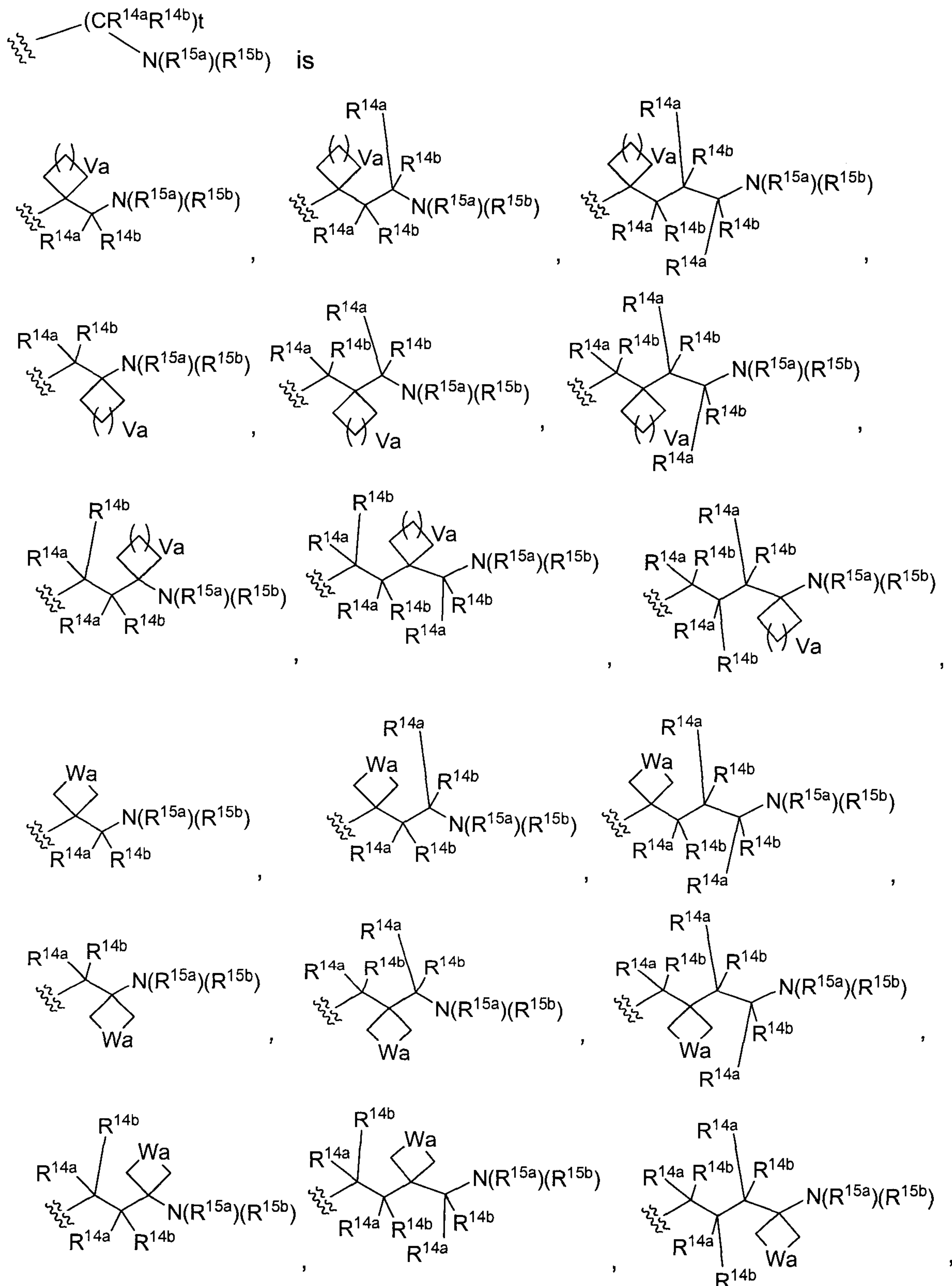
$-W-$ is $-O-$, $-S-$ or $-N(R^{17})-$ (e.g., $-O-$);

R^{17} is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl and the like.

[0142]

In general formula (VIII), general formula (IX), and general formula (VII), "R^{14a} and R^{14b} together with the carbon atom to which they are attached form a substituted or unsubstituted cycloalkane ring, a substituted or unsubstituted cycloalkene ring, or a substituted or unsubstituted non-aromatic heterocyclic ring" includes the followings:

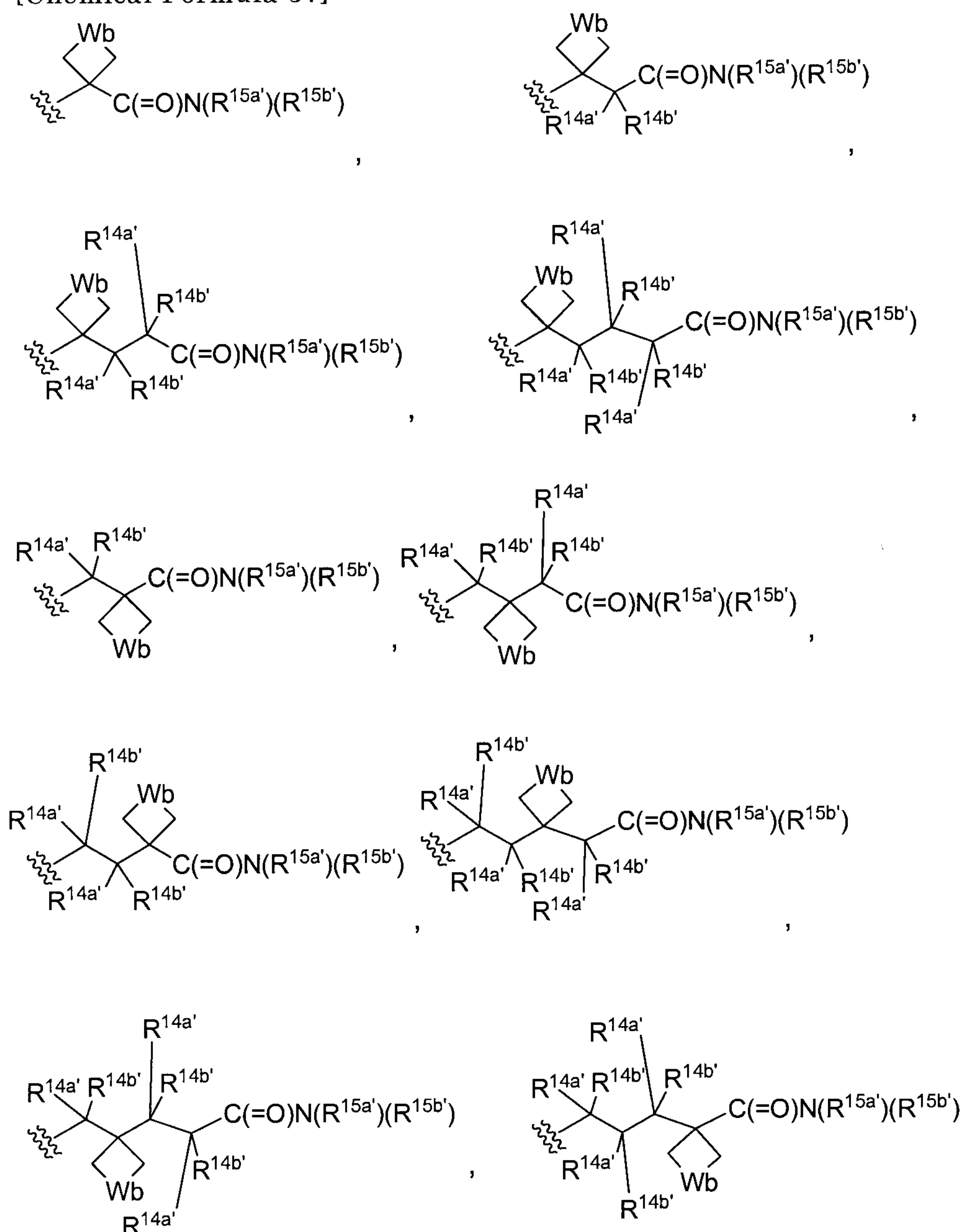
[Chemical Formula 55]



wherein t , R^{14a} and R^{14b} are as defined in the above (24);

va is an integer of 0 to 3 (e.g., 0 or 1, and e.g., 0) ;

[Chemical Formula 57]



wherein t , R^{14a} and R^{14b} are as defined in the above (24);

va is an integer of 0 to 3 (e.g., 0 or 1, and e.g., 0);

$-Wa-$ is $-O-$, $-S-$ or $-N(R^{17a})-$ (e.g., $-O-$);

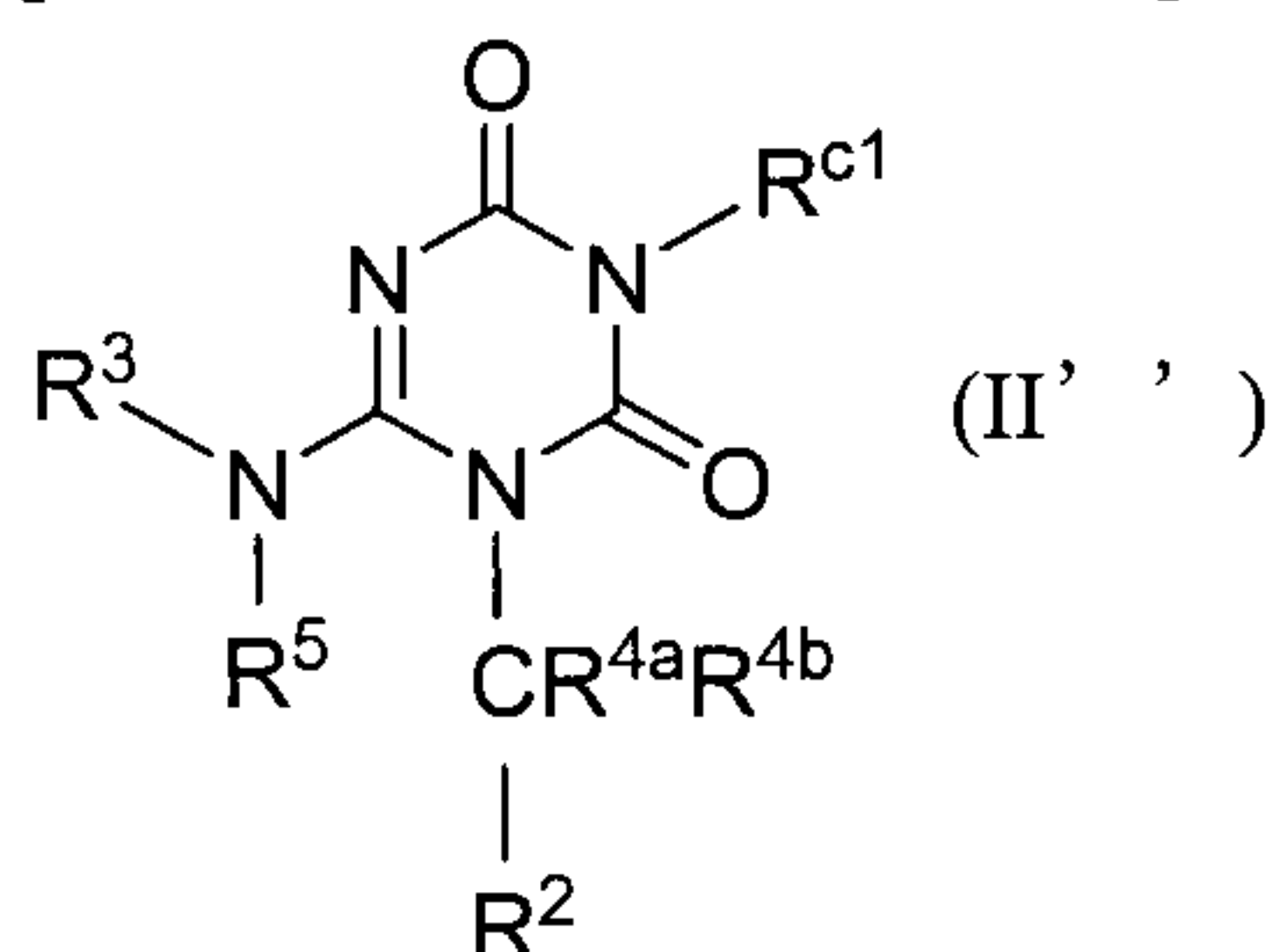
R^{17a} is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted acyl and the like.

[0145]

One embodiment of the compound of the present invention or the composition of the present invention is mentioned below.

The following (II''-A) to (II''-C) are embodiments of a pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the formula (II''):

[Chemical Formula 58]



or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(II''-A)

A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group A, or alkynyl substituted with one or more substituents selected from Substituent Group A;

R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C;

R^3 is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), heteroaryl optionally substituted with one or more substituents selected from Substituent Group D;

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

R^5 is hydrogen,

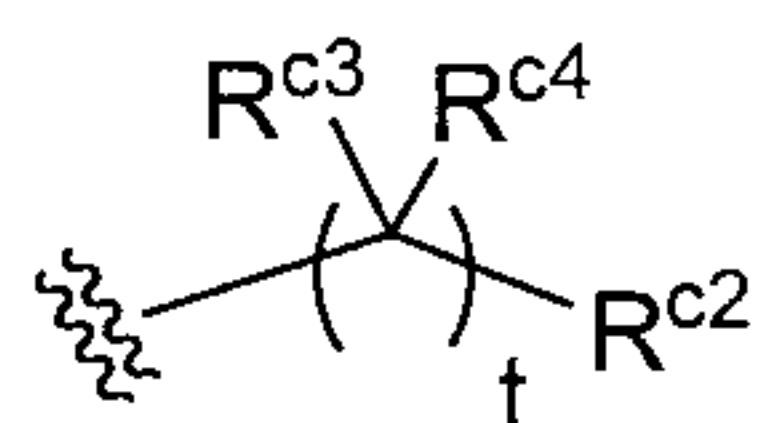
or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0146]

(II''-B)

A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound wherein R^{c1} is a group of the formula:

[Chemical Formula 59]



wherein t is an integer of 1 to 4;

R^{c2} is halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxylcarbonyl, substituted or unsubstituted heteroaryloxylcarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl, substituted or unsubstituted alkylthio, substituted or unsubstituted alkenylthio, substituted or unsubstituted alkynylthio, substituted or unsubstituted acyl, substituted or unsubstituted cycloalkyloxycarbonyl, substituted or unsubstituted cycloalkenyloxycarbonyl, substituted or unsubstituted non-aromatic heterocyclyloxycarbonyl, substituted or unsubstituted aryloxylcarbonyl, substituted or unsubstituted heteroaryloxylcarbonyl, or nitro;

R^{c3} and R^{c4} are each independently hydrogen, hydroxy, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl,

or

(i) R^{c3} and R^{c4} are taken together to form oxo or thioxo, or,

(ii) R^{c3} and R^{c4} attached to the same carbon atom, are taken together to form $-(CR^{c5}R^{c6})_x$; R^{c5} and R^{c6} are each independently hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl;

R^2 is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group C;

x is an integer of 1 to 4;

R^3 is aryl optionally substituted with one or more substituents selected from Substituent Group D, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D;

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

R^5 is hydrogen,

its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0147]

(II''-C)

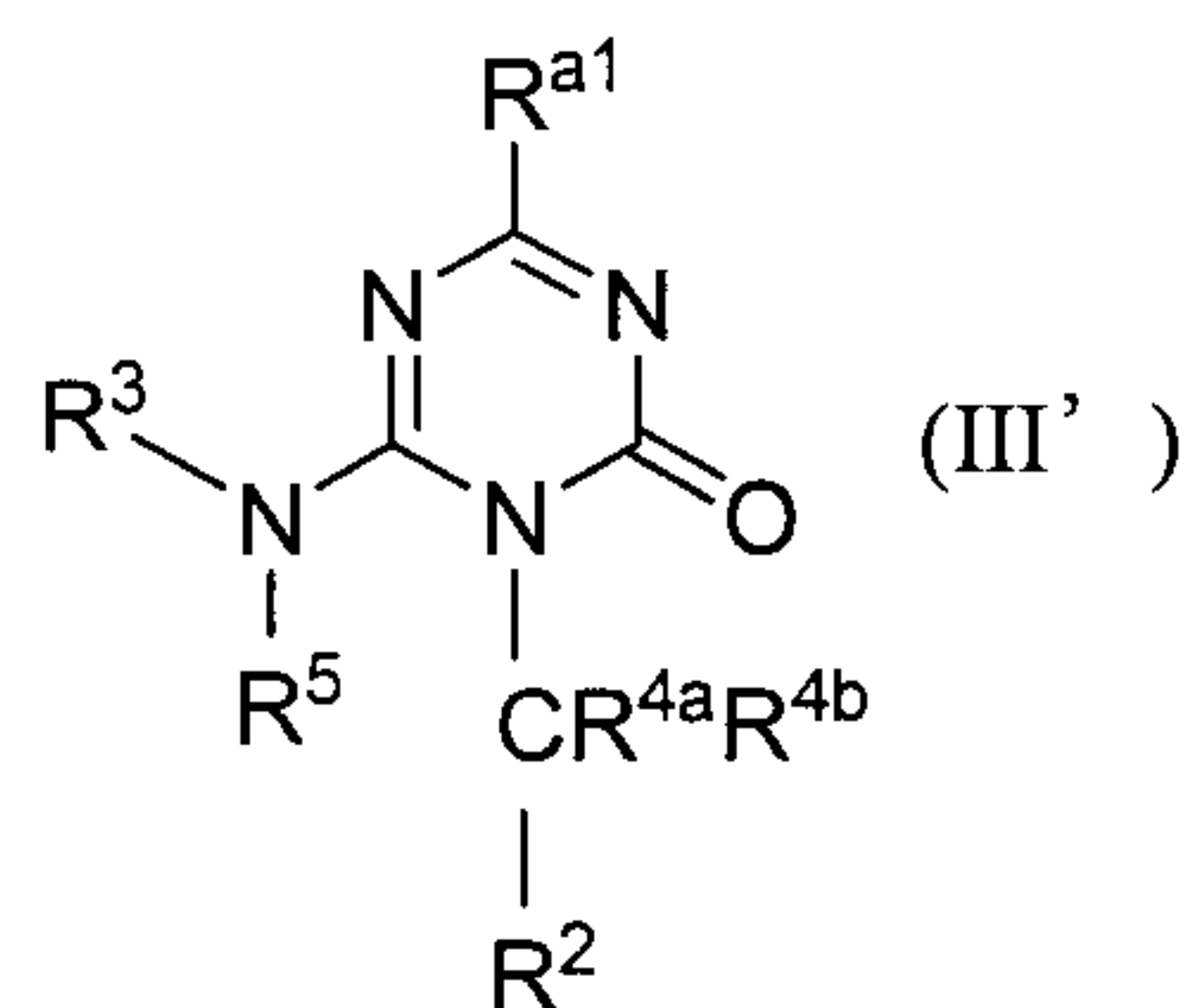
A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the above (II''-A) wherein R^{c1} is alkyl substituted with one or more substituents selected from Substituent Group E (Substituent Group E: sulfo; substituted or unsubstituted sulfamoyl; substituted or unsubstituted imino; substituted or unsubstituted guanidyl; a substituted or unsubstituted non-aromatic heterocyclic group (provided that the heterocyclic group is morpholino, imidazolidine,

tetrahydropyranyl and piperizino) and substituted or unsubstituted heteroaryl (provided that the heteroaryl is pyridino)), alkenyl optionally substituted with one or more substituents selected from Substituent Group E, or alkynyl substituted with one or more substituents selected from Substituent Group E, or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient. [0148]

One embodiment of the compound of the present invention or the composition of the present invention is mentioned below.

The following (III''-A) to (III''-C) are embodiments of a pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound of the formula (III''):

[Chemical Formula 60]



or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient . [0149]

(III'-A)

A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound wherein R^{a1} is alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxy carbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), alkenyl substituted with one or more substituents selected from Substituent Group A, alkynyl substituted with one or more substituents selected from Substituent Group A, alkyloxy substituted with one or more substituents selected from Substituent Group A, alkenyloxy substituted with one or more substituents selected from Substituent Group A, alkynyloxy substituted with one or more substituents selected from Substituent Group A, alkylthio substituted with one or more substituents selected from Substituent Group A, alkenylthio substituted with one or more substituents selected from Substituent Group A, alkynylthio substituted with one or more substituents selected from Substituent Group A, alkylamino substituted with one or more substituents selected from Substituent Group A, alkenylamino substituted with one or more substituents selected from Substituent Group A or alkynylamino substituted with one or more substituents selected from Substituent Group A,

R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl) or heteroaryl

optionally substituted with one or more substituents selected from Substituent Group C; R^3 is aryl optionally substituted with one or more substituents selected from Substituent Group D (Substituent Group D: halogen; hydroxy; alkyl optionally substituted with halogen, hydroxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, or heteroaryl; alkenyl optionally substituted with cycloalkyl; alkynyl optionally substituted with cycloalkyl; alkyloxy optionally substituted with halogen, alkyloxy, cycloalkyl, aryl or a non-aromatic heterocyclic group optionally substituted with alkyl; alkylthio; cycloalkyl; cycloalkenyl; cycloalkyloxy; aryloxy; heteroaryloxy optionally substituted with alkyl; a non-aromatic heterocyclic group; and alkylamino), or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D;

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

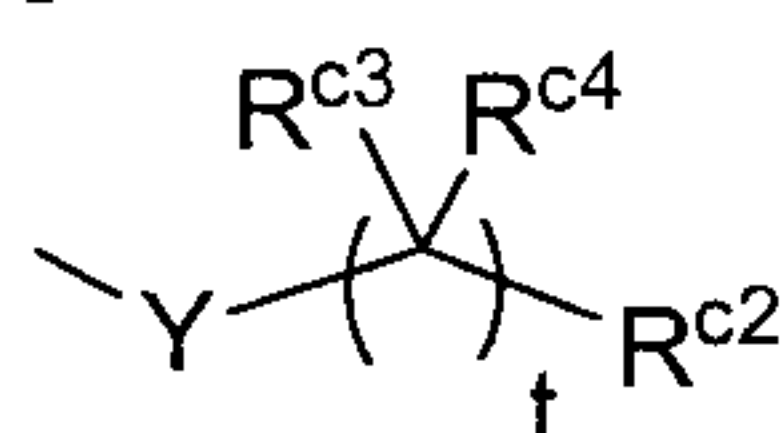
R^5 is hydrogen,

or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

(III'-B)

A pharmaceutical composition having an analgesic effect and/or an improving effect of urination disorder comprising the compound wherein R^{a1} is

[Chemical Formula 61]



wherein -Y- is -O-, -S- or -NR^Y-;

R^Y is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted acyl; and other symbols are as defined in the above II'-B;

R^{c5} and R^{c6} are each independently, hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl;

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

x is an integer of 1 to 4;

R^3 is aryl optionally substituted with one or more substituents selected from Substituent Group D, or heteroaryl optionally substituted with one or more substituents selected from Substituent Group D;

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

R^5 is hydrogen,

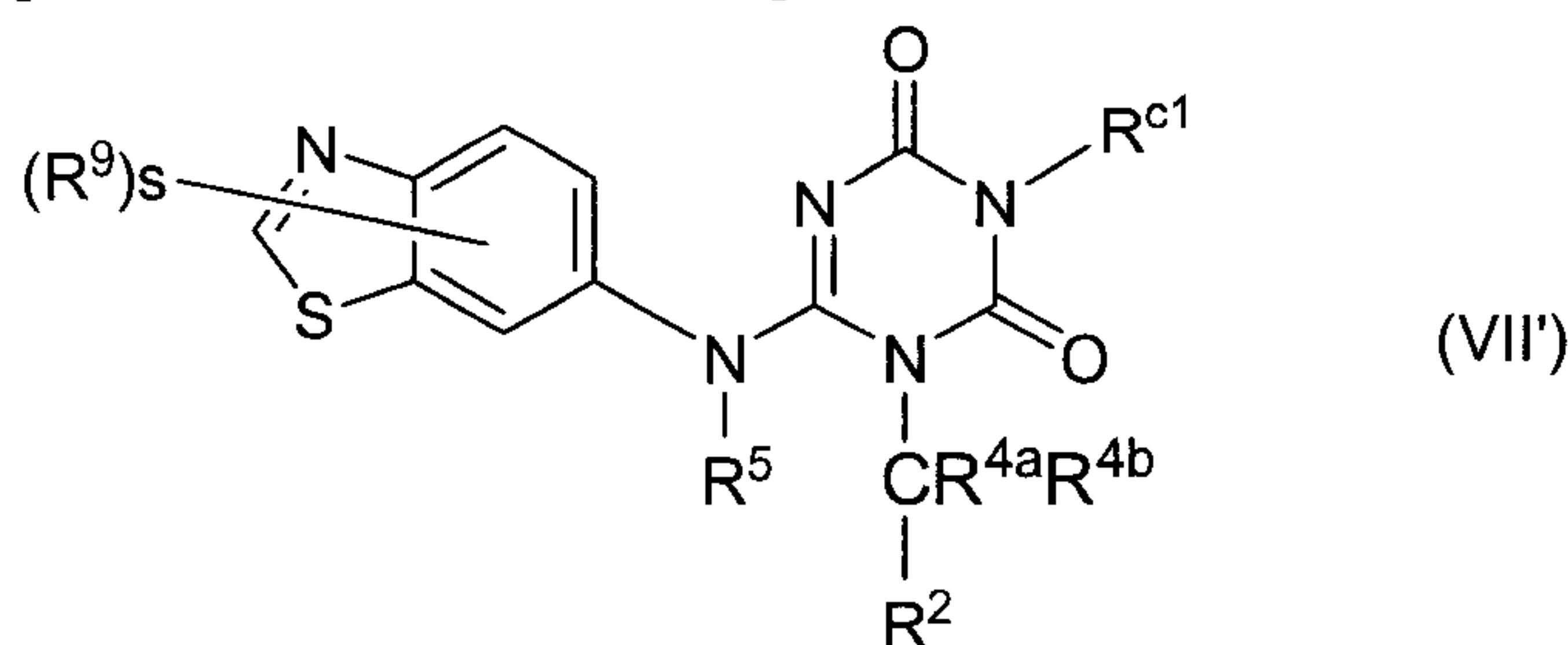
or its pharmaceutically acceptable salt or a solvate thereof as an active ingredient.

[0150]

One embodiment of the compound of the present invention is mentioned below.

A compound of the formula (VII'):

[Chemical Formula 62]



wherein

R^{c1} is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy,

substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), unsubstituted alkenyl, alkenyl substituted with one or more substituents selected from Substituent Group A, unsubstituted alkynyl or alkynyl substituted with one or more substituents selected from Substituent Group A;

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

R^2 is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyl oxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C;

R^5 is hydrogen;

R^9 is halogen, hydroxy, carboxy, cyano, alkyloxy, unsubstituted alkyl, alkyl optionally substituted with one or more substituents selected from Substituent Group F (Substituent Group F: halogen, hydroxy, carboxy, cyano, alkyloxyimino, dialkylamino, alkyloxy, cycloalkyl, and heteroaryl), unsubstituted alkenyl, alkenyl optionally substituted with one or more substituents selected from Substituent Group F, unsubstituted alkynyl, or alkynyl optionally substituted with one or more substituents selected from Substituent Group F;

and s is an integer of 0 to 2,

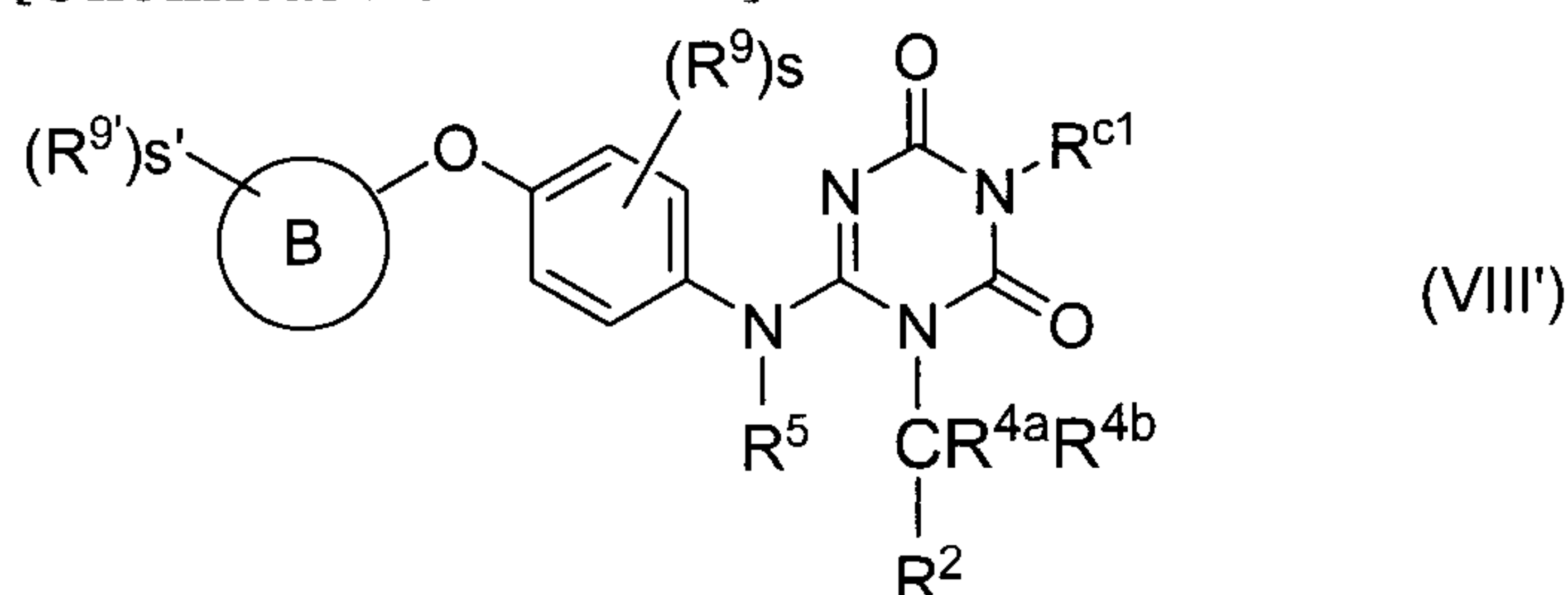
its pharmaceutically acceptable salt or a solvate thereof.

[0151]

One embodiment of the compound of the present invention is mentioned below.

A compound of the formula (VIII'):

[Chemical Formula 63]



wherein

R^{c1} is unsubstituted alkyl, alkyl substituted with one or more substituents selected from Substituent Group A (Substituent Group A: halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, and substituted or unsubstituted guanidyl), unsubstituted alkenyl, alkenyl substituted with one or more

substituents selected from Substituent Group A, unsubstituted alkynyl or alkynyl substituted with one or more substituents selected from Substituent Group A;

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

R² is aryl optionally substituted with one or more substituents selected from Substituent Group C (Substituent Group C: halogen, alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, and alkylsilylalkynyl), heteroaryl optionally substituted with one or more substituents selected from Substituent Group C, or cycloalkyl optionally substituted with one or more substituents selected from Substituent Group C;

R⁵ is hydrogen;

R⁹ is halogen, hydroxy, carboxy, 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, or substituted or unsubstituted heteroaryl; s is an integer of 0 to 2;

ring B is thiazole, isothiazole, oxazole, isoxazole, pyrazole, imidazole, triazole, furan, thiophen, oxadiazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, triazine or benzoxazole;

R^{9'} is halogen, hydroxy, carboxy, 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 alkynyloxy carbonyl, 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, or substituted or unsubstituted heteroaryl; s' is an integer of 0 to 2;

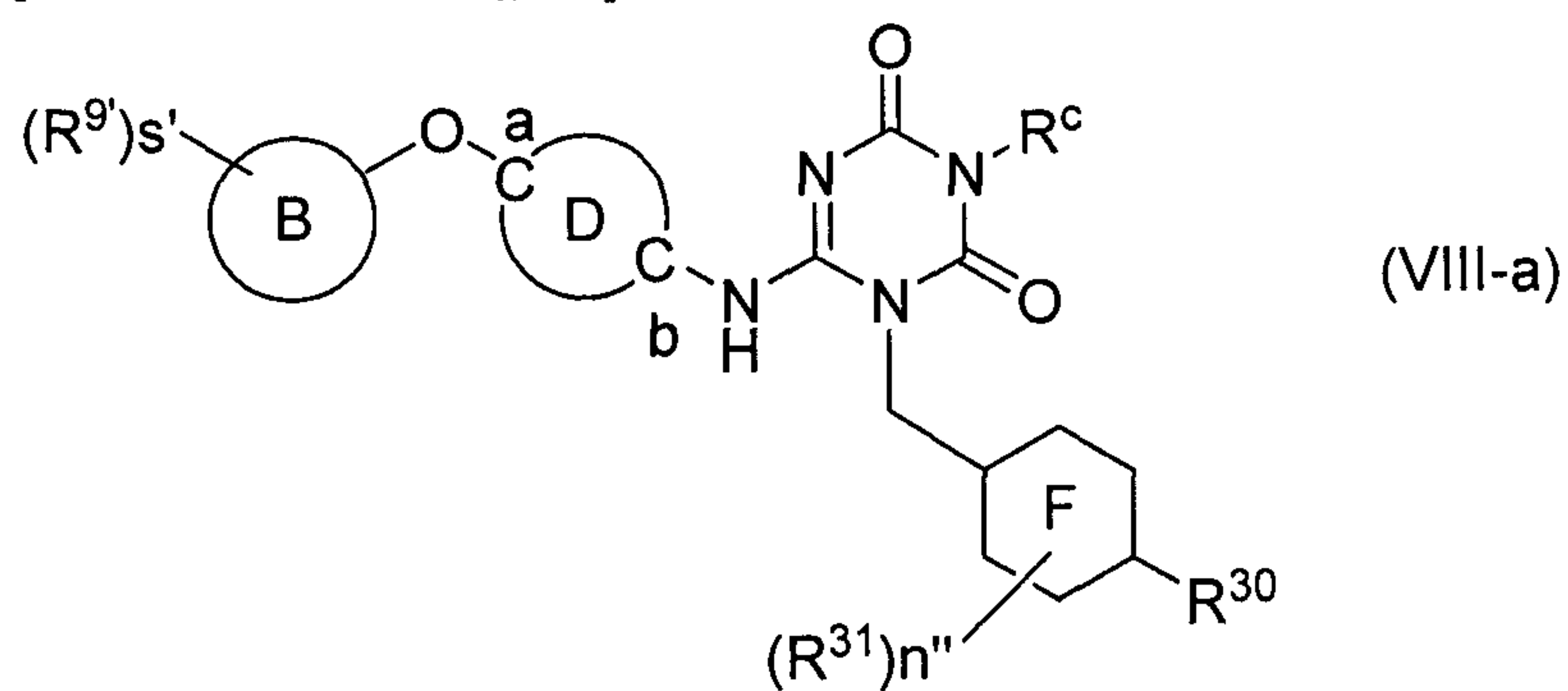
or its pharmaceutically acceptable salt or a solvate thereof.

[0152]

The following embodiments are examples of the compound (VIII) of the present invention.

A compound of the formula (VIII-a):

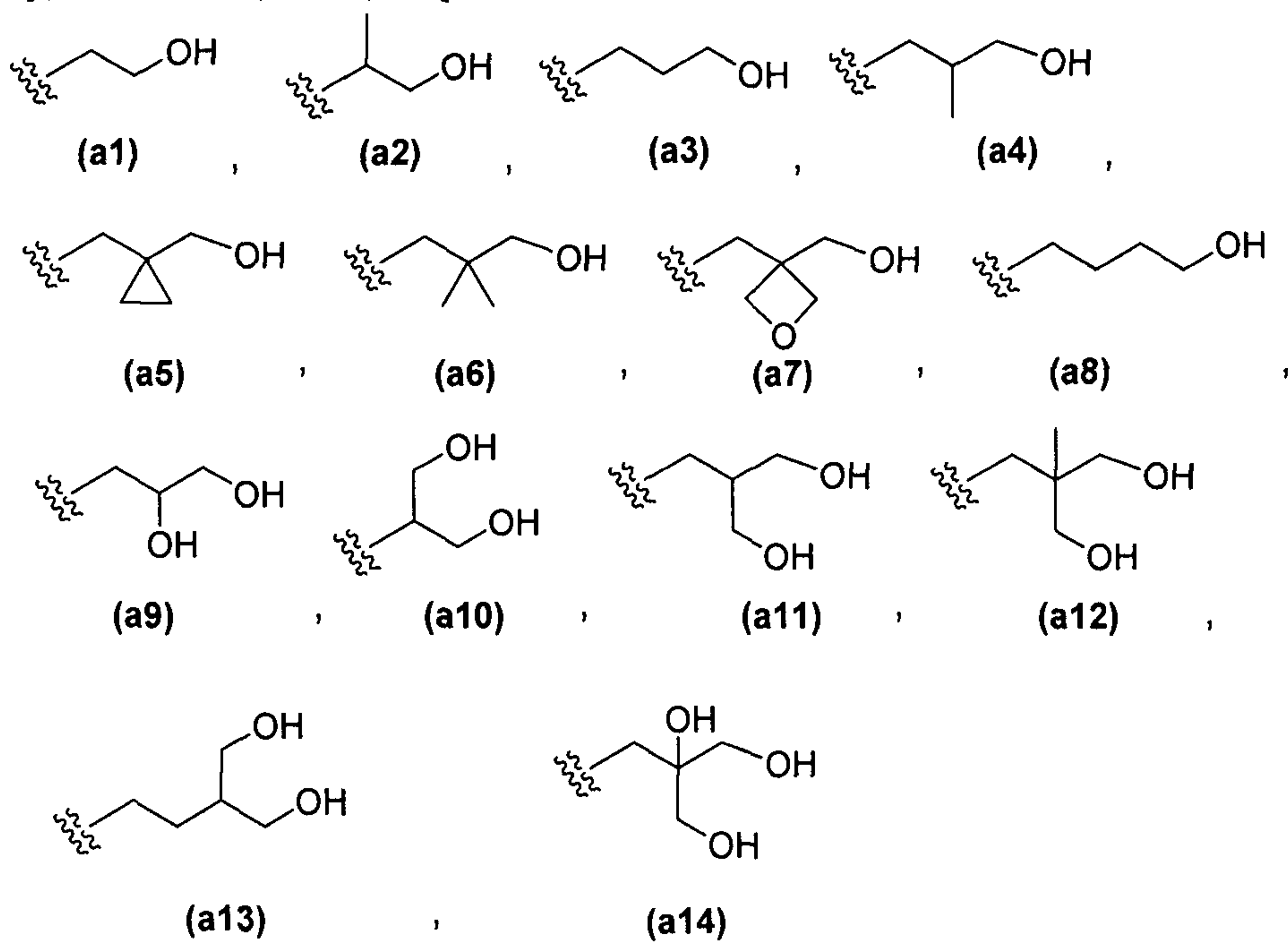
[Chemical Formula 64]



wherein

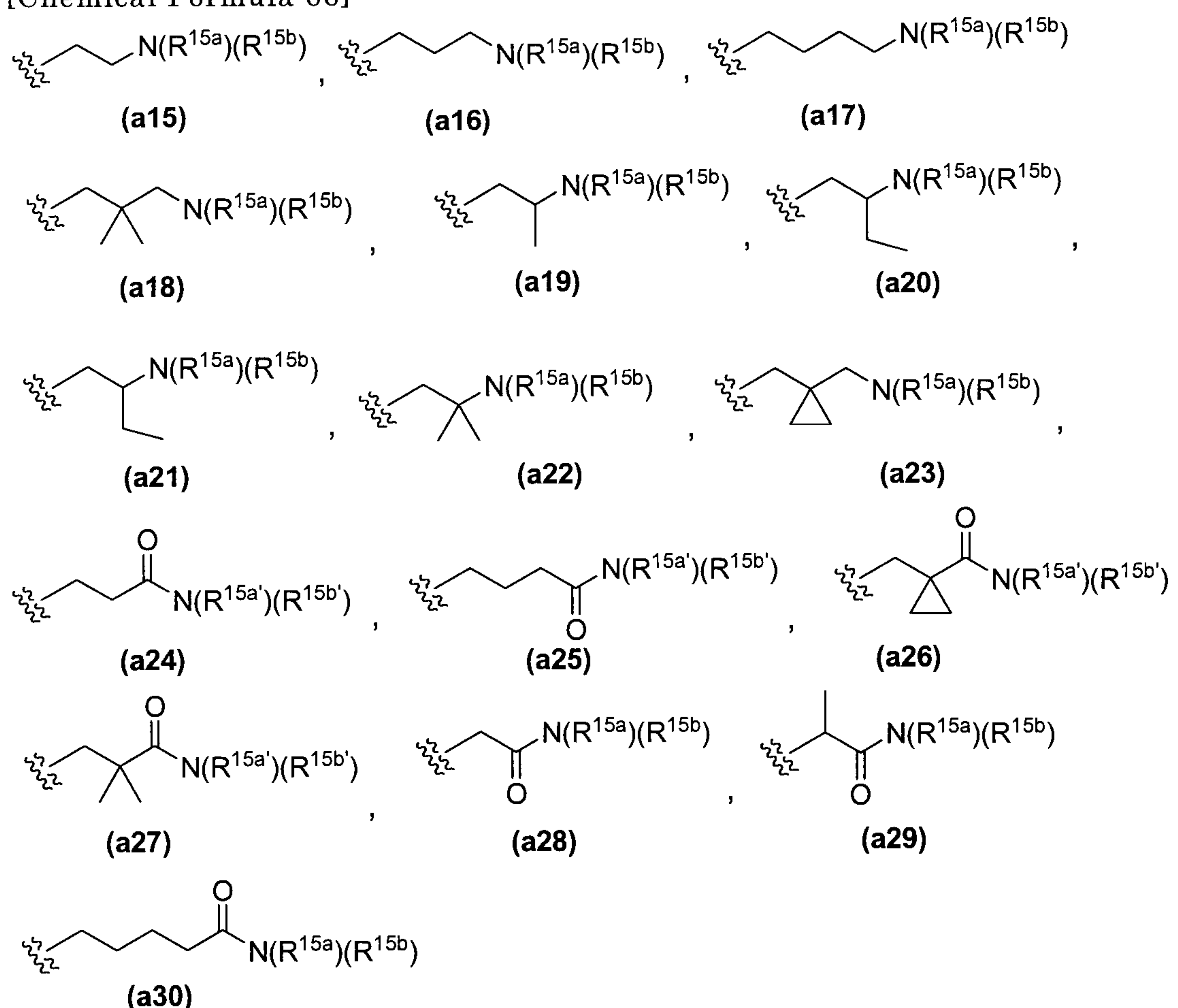
 R^c is selected from the following (a1) to (a32):

[Chemical Formula 65]



[0153]

[Chemical Formula 66]



wherein R^{15a} , R^{15b} , $R^{15a'}$ and $R^{15b'}$ are each independently selected from the following (b1) and (b2):

(b1) a hydrogen atom, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted acyl, substituted sulfonyl or substituted sulfinyl, and

(b2) a hydrogen atom, methyl, ethyl, acetyl or trifluoroacetyl,

(a31) ethyl; and

(a32) methyl;

ring F is selected from the following (c1) to (c3)

(c1) a benzene ring;

(c2) a pyridine ring; and

(c3) a cyclohexane ring;

R^{30} is selected from the following (d1) and (d2):

(d1) halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; and

(d2) fluoro, chloro, methyl, monofluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R^{31} is halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

[0154]

n" is 0 or 1;

ring D is selected from the following (e1) and (e2):

(e1) a benzene ring; and

(e2) a pyridine ring;

relationship of carbon atom a and carbon atom b on the ring D are selected from the following (f1) and (f2):

(f1) 1,4 relationship; and

(f2) 1,3 relationship;

ring B is selected from the following (g1) to (g12):

(g1) a thiazole ring;

(g2) an isothiazole ring;

(g3) an oxazole ring;

(g4) an isoxazole ring;

(g5) a thiadiazole ring;

(g6) an oxadiazole ring;

(g7) a pyridine ring;

(g8) a pyrimidine ring;

(g9) a pyrazine ring;

(g10) a pyridazine ring;

(g11) a triazine ring; and

(g12) a pyrazole ring;

s' is selected from the following (h1) and (h2):

(h1) 0; and

(h2) 1;

when s' is 1, then R^{9'} is selected from the following (i1) to (i14):

(i1) hydroxy;

(i2) carboxy;

(i3) cyano;

(i4) alkyl substituted with hydroxy, carboxy, cyano, carbamoyl, amino, sulfamoyl, methanesulfonyl or methanesulfinyl;

(i5) substituted or unsubstituted carbamoyl;

(i6) alkylcarbamoyl or alkenylcarbamoyl;

(i7) substituted or unsubstituted amino;

(i8) amino substituted with carbamoyl, alkylcarbamoyl, alkylcarbamoylalkyl, carbamoylalkyl or carboxyalkyl;

(i9) substituted or unsubstituted sulfamoyl;

(i10) alkylsulfamoyl or alkenylsulfamoyl;

(i11) substituted sulfonyl;

(i12) substituted sulfinyl;

(i13) unsubstituted alkyl, or alkyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; and

(i14) unsubstituted alkyl.

[0155]

The compound of the formula (VIII-a) of the present invention includes the

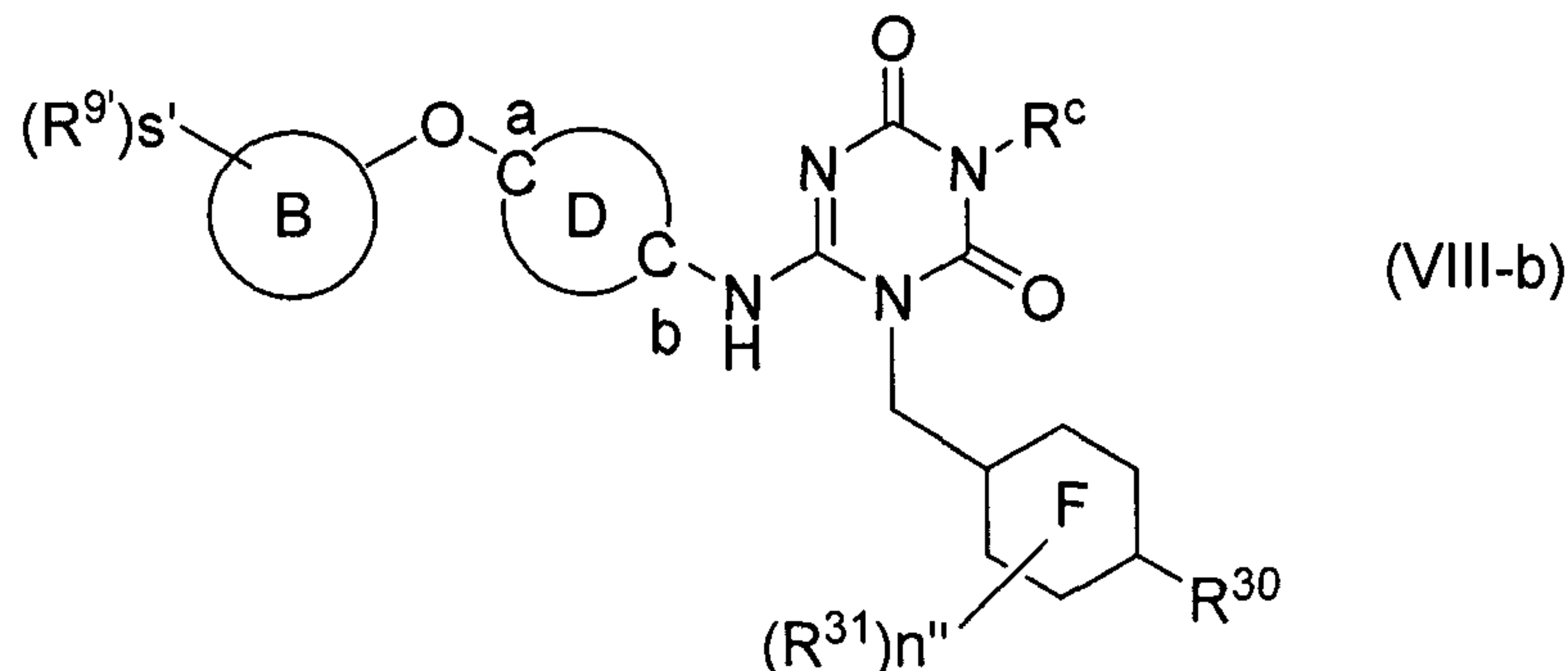
compounds comprising the combination of some or all of options of the above (a1) to (a32), (b1) and (b2), (c1) to (c3), (d1) and (d2), (e1) and (e2), (f1) and (f2), (g1) to (g12), (h1) and (h2), and (i1) to (i14).

[0156]

The following embodiments are examples of the compound (VIII) of the present invention.

A compound of the formula (VIII-b):

[Chemical Formula 67]



wherein

R^c is a group selected from the following (ba1) to (ba16):

(ba1) a group of the formula: $\text{-(CR}^{11}\text{aR}^{11}\text{b)}_m\text{-OH}$

wherein R^{11a} and R^{11b} are each independently, a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, or R^{11a} and R^{11b} together with the carbon atom to which they are attached form a substituted or unsubstituted cyclopropane ring, a substituted or unsubstituted cyclopropene ring, a substituted or unsubstituted oxetane ring, a substituted or unsubstituted thietane ring, or a substituted or unsubstituted azetidine ring; m is an integer of 2 to 4;

(ba2) a group of the formula: $-(CR^{11a}R^{11b})_m-OH]$

wherein R^{11a} is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl;

R^{11b} is a group of the formula: $-(CR^{12a}R^{12b})_u-OH$

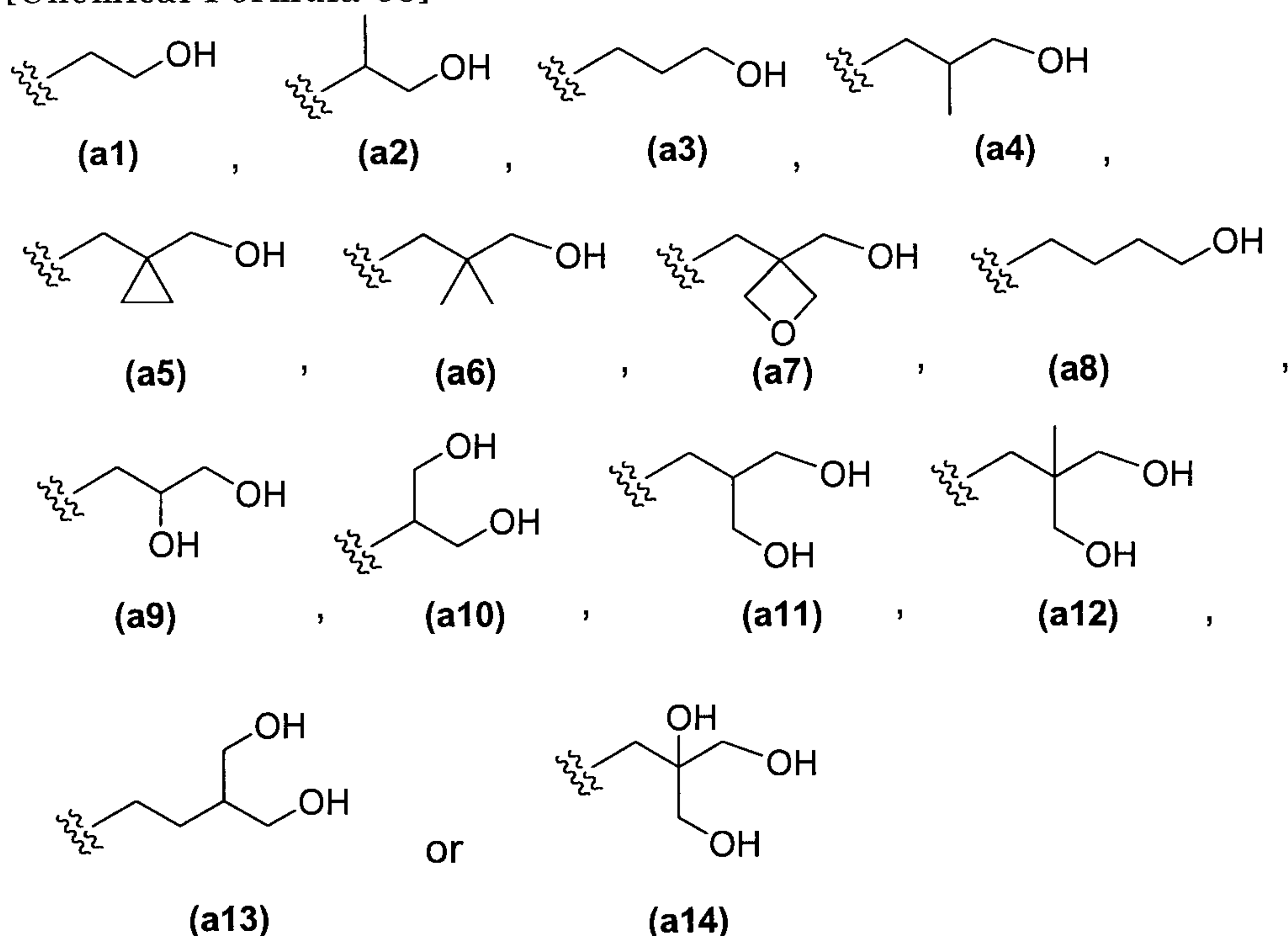
wherein R^{12a} and R^{12b} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl; u is an integer of 0 to 2;

m is an integer of 2 to 4;

[0157]

(ba3) a group of the formula:

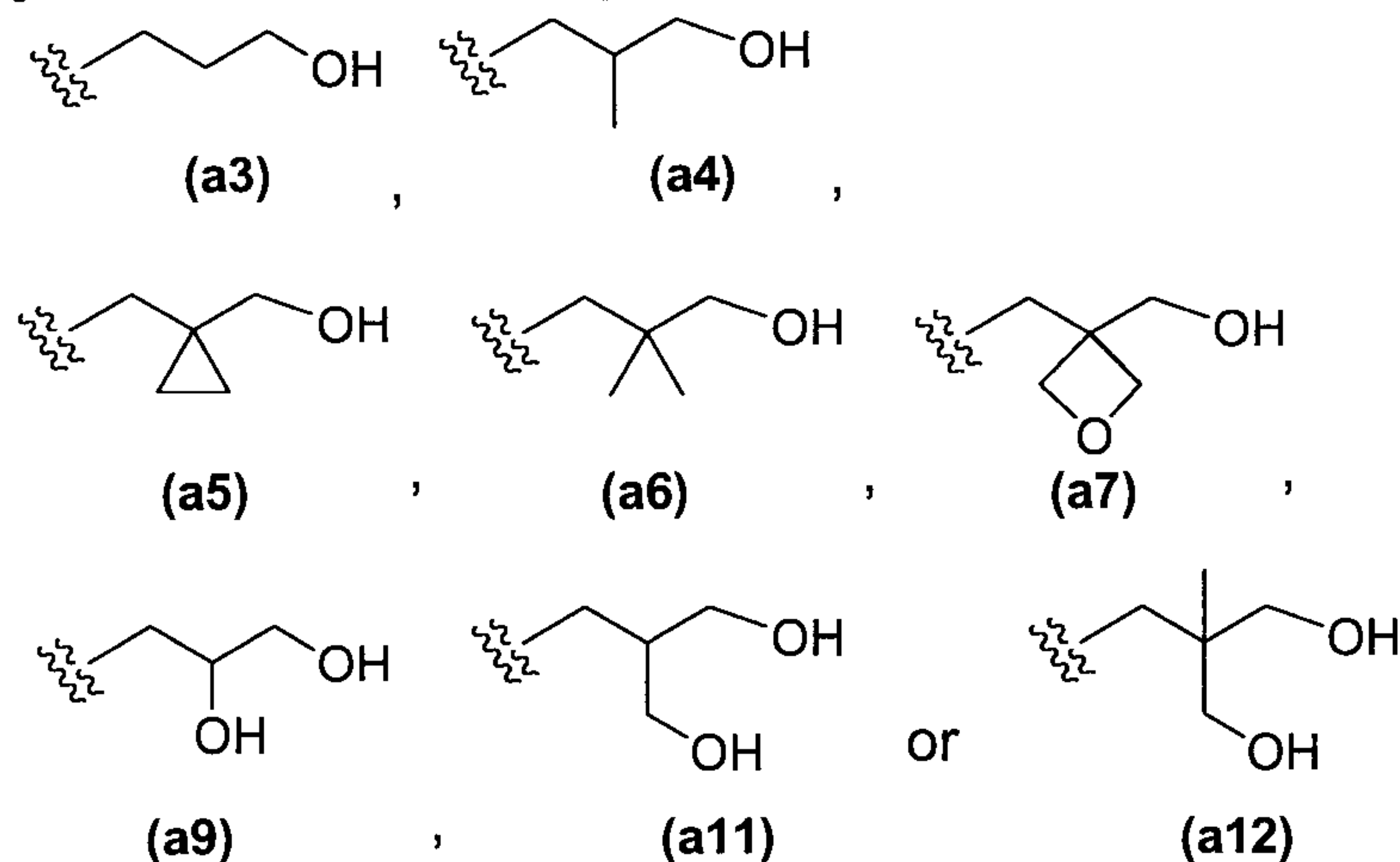
[Chemical Formula 68]



[0158]

(ba4) a group of the formula:

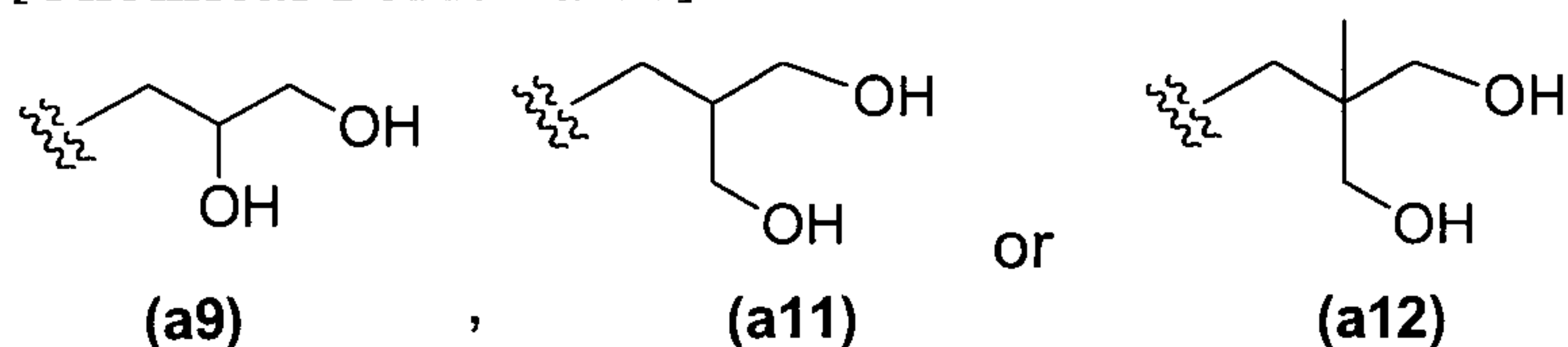
[Chemical Formula 69]



[0159]

(ba5) a group of the formula:

[Chemical Formula 70]

(ba6) a group of the formula: $-(\text{CR}^{14a}\text{R}^{14b})_t\text{-N}(\text{R}^{15a})(\text{R}^{15b})$

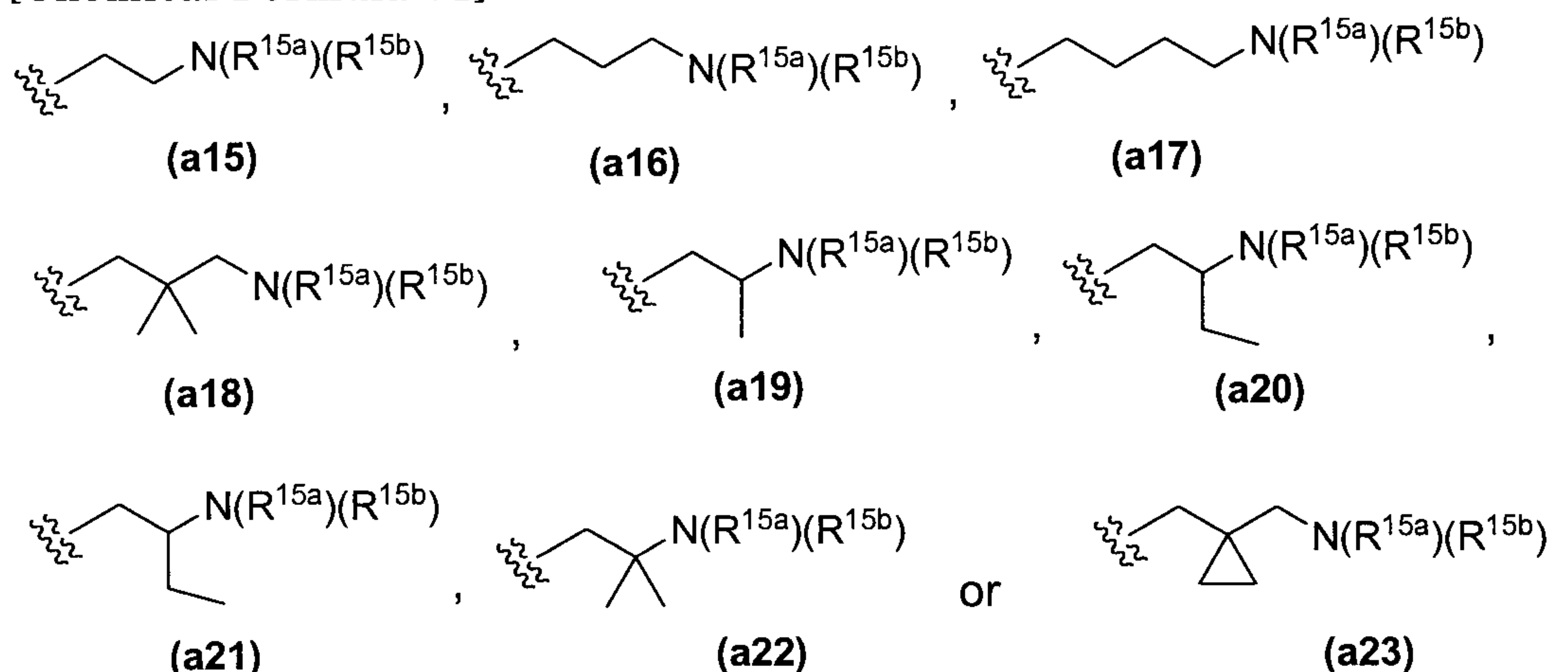
wherein R^{14a} and R^{14b} are each independently hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, or R^{14a} and R^{14b} together with the carbon atom to which they are attached form a substituted or unsubstituted cyclopropane ring, a substituted or unsubstituted cyclopropene ring, a substituted or unsubstituted oxetane ring, a substituted or unsubstituted thietane ring, or

a substituted or unsubstituted azetizine ring; t is an integer of 2 to 4; R^{15a} and R^{15b} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted acyl, substituted sulfonyl or substituted sulfinyl;

[0160]

(ba7) a group of the formula:

[Chemical Formula 71]

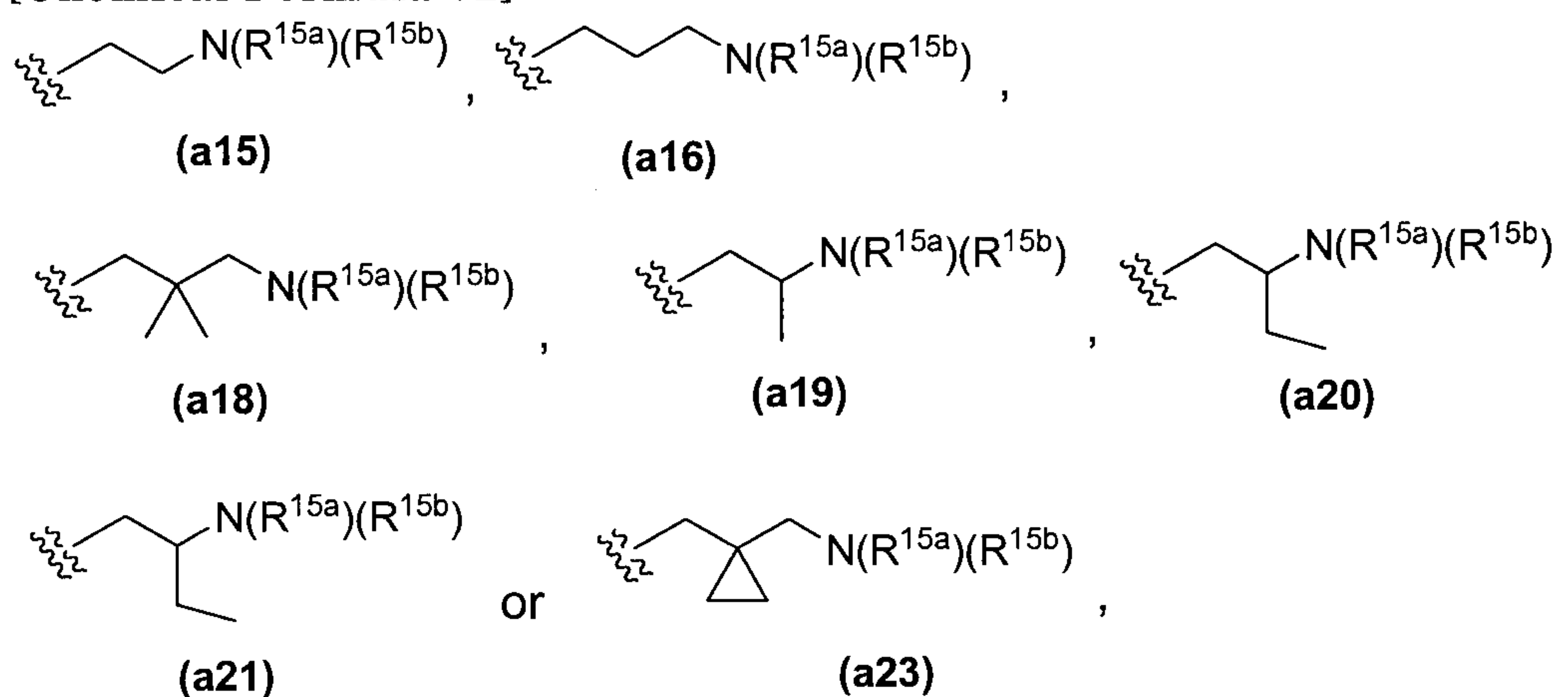


wherein R^{15a} and R^{15b} are as defined in the above (ba6);

[0161]

(ba8) a group of the formula:

[Chemical Formula 72]



wherein R^{15a} and R^{15b} are as defined in the above (ba6);

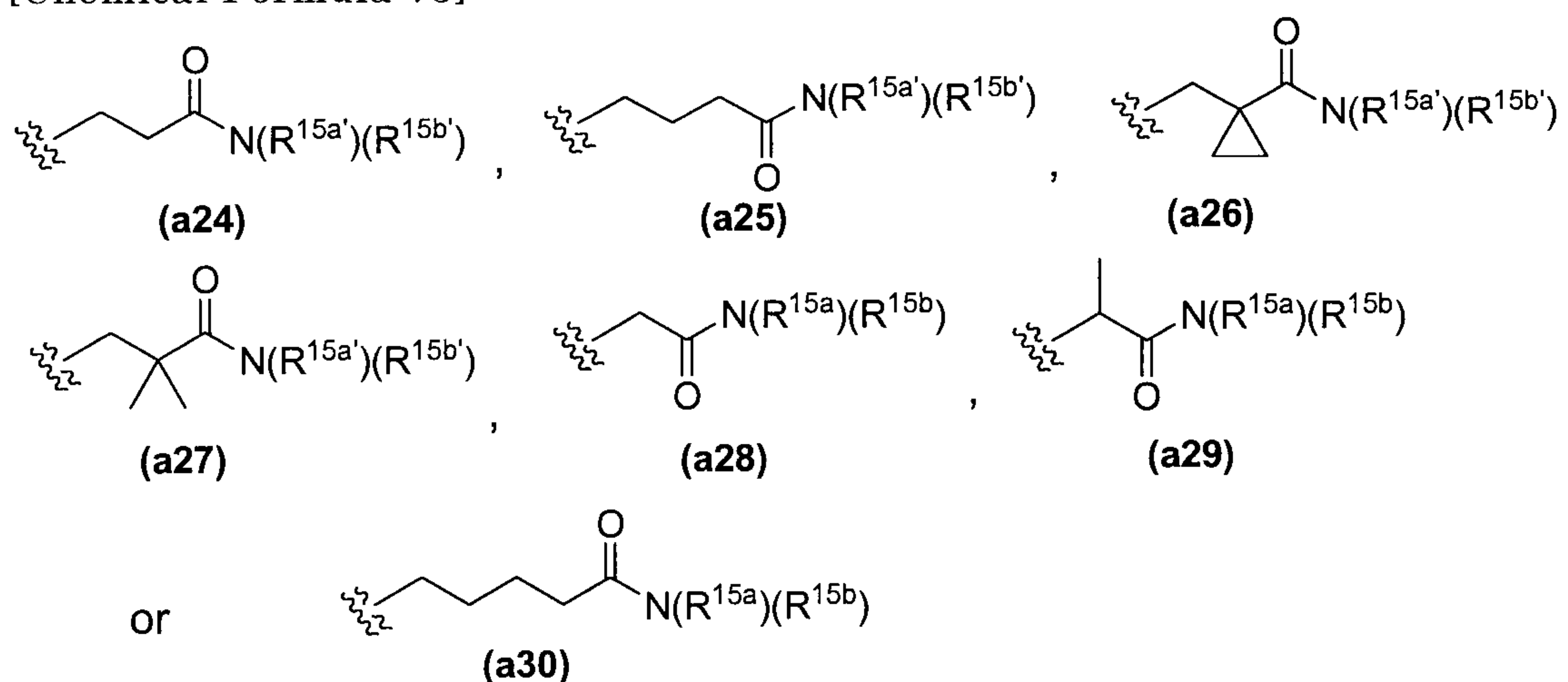
(ba9) a group of the formula: $-(\text{CR}^{14a'}\text{R}^{14b'})_t-\text{C}(=\text{O})\text{N}(\text{R}^{15a'})\text{R}^{15b'}$

wherein R^{14a'} and R^{14b'} are each independently a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, or R^{14a'} and R^{14b'} together with the carbon atom to which they are attached form a substituted or unsubstituted cyclopropane ring, a substituted or unsubstituted cyclopropene ring, a substituted or unsubstituted oxetane ring, a substituted or unsubstituted thietane ring, or a substituted or unsubstituted azetizine ring; t' is an integer of 1 to 4; R^{15a'} and R^{15b'} are each independently a hydrogen atom, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted acyl, substituted sulfonyl or substituted sulfinyl;

[0162]

(ba10) a group of the formula:

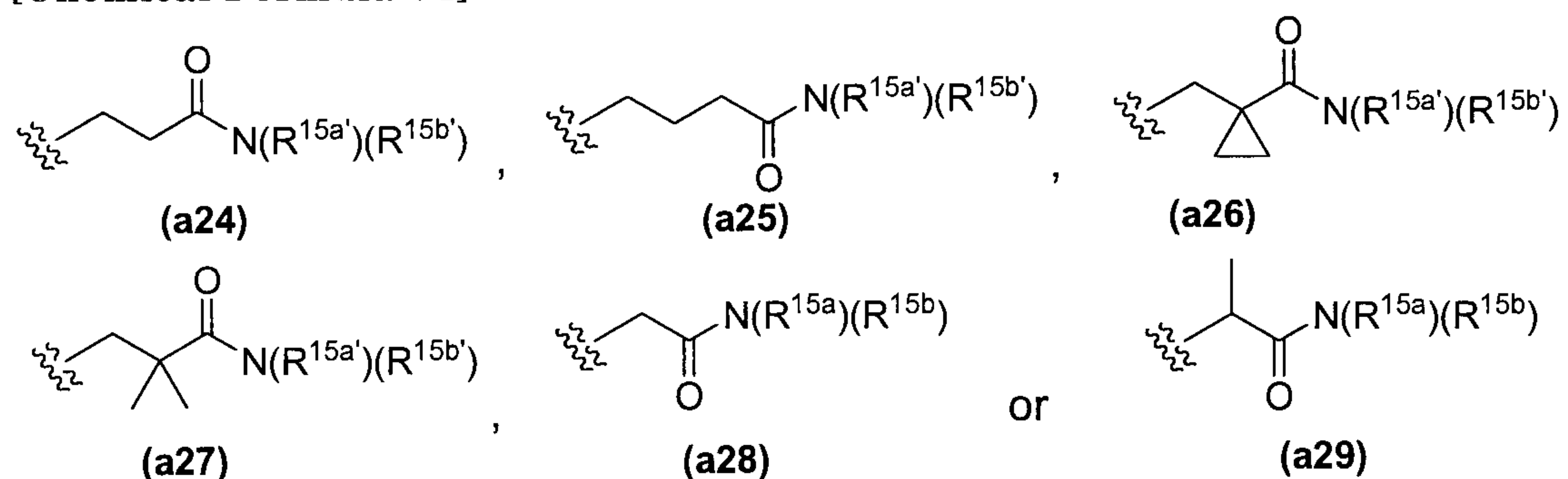
[Chemical Formula 73]

wherein $R^{15a'}$ and $R^{15b'}$ are as defined in the above (ba9);

[0163]

(ba11) a group of the formula:

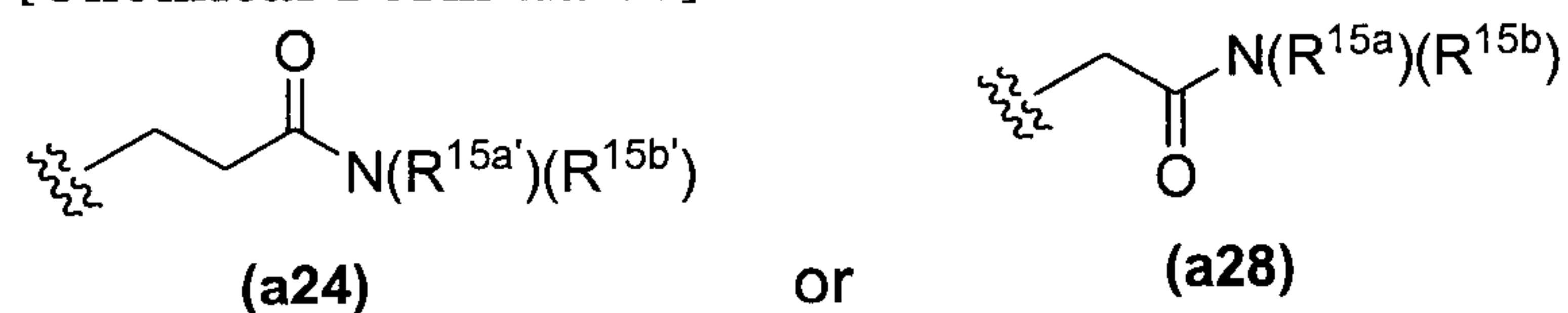
[Chemical Formula 74]

wherein $R^{15a'}$ and $R^{15b'}$ are as defined in the above (ba9);

[0164]

(ba12) a group of the formula:

[Chemical Formula 75]

wherein $R^{15a'}$ and $R^{15b'}$ are as defined in the above (ba9);

(ba13) unsubstituted alkyl; or alkyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy;

(ba14) unsubstituted alkyl;

(ba15) methyl; ethyl; methyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or ethyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; and

(ba16) methyl or ethyl;

ring F is a group selected from the following (bc1) and (bc2):

(bc1) a benzene ring, a pyridine ring or a cyclohexane ring; and

(bc2) a benzene ring;

R^{30} is a group selected from the following (bd1) and (bd2):

(bd1) halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; and

(bd2) fluoro, chloro, methyl, monofluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R^{31} is halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

n'' is 0 or 1;

[0165]

ring D a group selected from the following (be1) to (be4):

(be1) a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring;

(be2) a benzene ring or a pyridine ring;

(be3) a benzene ring; and

(be4) a pyridine ring;

relationship of carbon atom a and carbon atom b on ring D is selected from the following (bf1) to (bf3):

(bf1) 1, 4 relationship or 1, 3 relationship;

(bf2) 1, 4 relationship; and

(bf3) 1, 3 relationship;

ring B is a group selected from the following (bg1) to (bg9):

(bg1) an aromatic heterocyclic ring;

(bg2) a five- or six-membered aromatic heterocyclic ring;

(bg3) a thiazole ring, an isothiazole ring, an oxazole ring, an isoxazole ring, a thiadiazole ring, an oxadiazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, a triazine ring, or a pyrazole ring;

(bg4) a thiazole ring, an isoxazole ring, a thiadiazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring;

(bg5) a six-membered aromatic heterocyclic ring;

(bg6) a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring or a triazine ring;

(bg7) a five-membered aromatic heterocyclic ring;

(bg8) a thiazole ring, an isothiazole ring, an oxazole ring, an isoxazole ring, a thiadiazole ring, an oxadiazole ring or a pyrazole ring; and

(bg9) a thiazole ring, an isoxazole ring or a thiadiazole ring;

s' is a group selected from the following (bh1) to (bh3):

(bh1) 0 or 1;

(bh2) 0; and

(bh3) 1;

when s' is 1, then $R^{9'}$ is a group selected from the following (bi1) to (bi7):

(bi1) hydroxy; carboxy; cyano; alkyl substituted with hydroxy, carboxy, cyano, carbamoyl, amino, sulfamoyl, methanesulfonyl or methanesulfinyl; substituted or unsubstituted carbamoyl; substituted or unsubstituted amino; substituted or unsubstituted sulfamoyl; substituted sulfonyl; or substituted sulfinyl;

(bi2) hydroxy; carboxy; cyano; alkyl substituted with hydroxy, carboxy, cyano, carbamoyl,

amino, sulfamoyl, methanesulfonyl or methansulfinyl; carbamoyl; alkylcarbamoyl; amino substituted with alkyl, haloalkyl, hydroxy alkyl, alkyloxy, haloalkyloxy, carbamoyl, alkylcarbamoyl, alkylcarbamoylalkyl, carbamoylalkyl or carboxyalkyl; sulfamoyl; alkylsulfamoyl; alkylsulfonyl; or alkylsulfinyl;

(bi3) carboxy; carbamoyl; alkylcarbamoyl; sulfamoyl; alkylsulfamoyl or alkylsulfonyl;

(bi4) alkyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or unsubstituted alkyl;

(bi5) unsubstituted alkyl;

(bi6) methyl; ethyl; methyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or ethyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; and

(bi7) methyl or ethyl,

or its pharmaceutically acceptable salt or a solvate thereof.

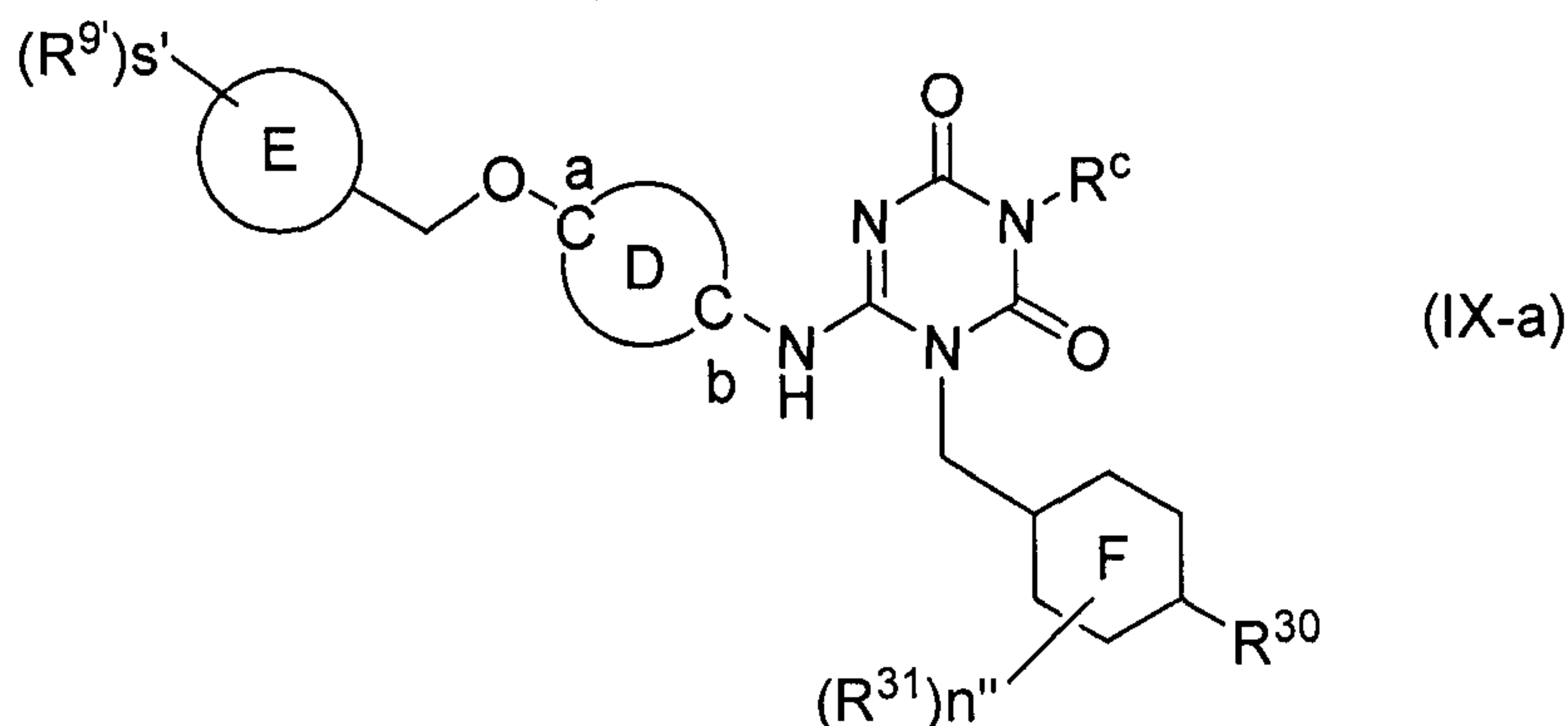
The compound of the formula (VIII-b) of the present invention includes the compounds comprising the combination of some or all of options of the above (ba1) to (ba16), (bc1) and (bc2), (bd1) and (bd2), (be1) to (be4), (bf1) to (bf3), (bg1) to (bg9), (bh1) to (bh3) and (bi1) to (bi7).

[0166]

The following embodiments are examples of the compound (IX) of the present invention.

A compound of the formula (IX-a) :

[Chemical Formula 76]



wherein

R^c is a group selected from the following (ca1) to (ca5):

(ca1) a group of the formula: $-(CR^{11a}R^{11b})_m \cdot OH$

wherein R^{11a} and R^{11b} are each independently, a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl, or R^{11a} and R^{11b} together with the carbon atom to which they are attached form a substituted or unsubstituted cyclopropane ring, a substituted or unsubstituted cyclopropene ring, a substituted or unsubstituted oxetane ring, a substituted or unsubstituted thietane ring, or a substituted or unsubstituted azetizine ring; m is an integer or 2 to 4;

(ca2) R^c is a group of the formula: $-(CR^{11a}R^{11b})_m \cdot OH$

wherein R^{11a} is a hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted alkynyl;

R^{11b} is a group of the formula: $-(CR^{12a}R^{12b})_u \cdot OH$;

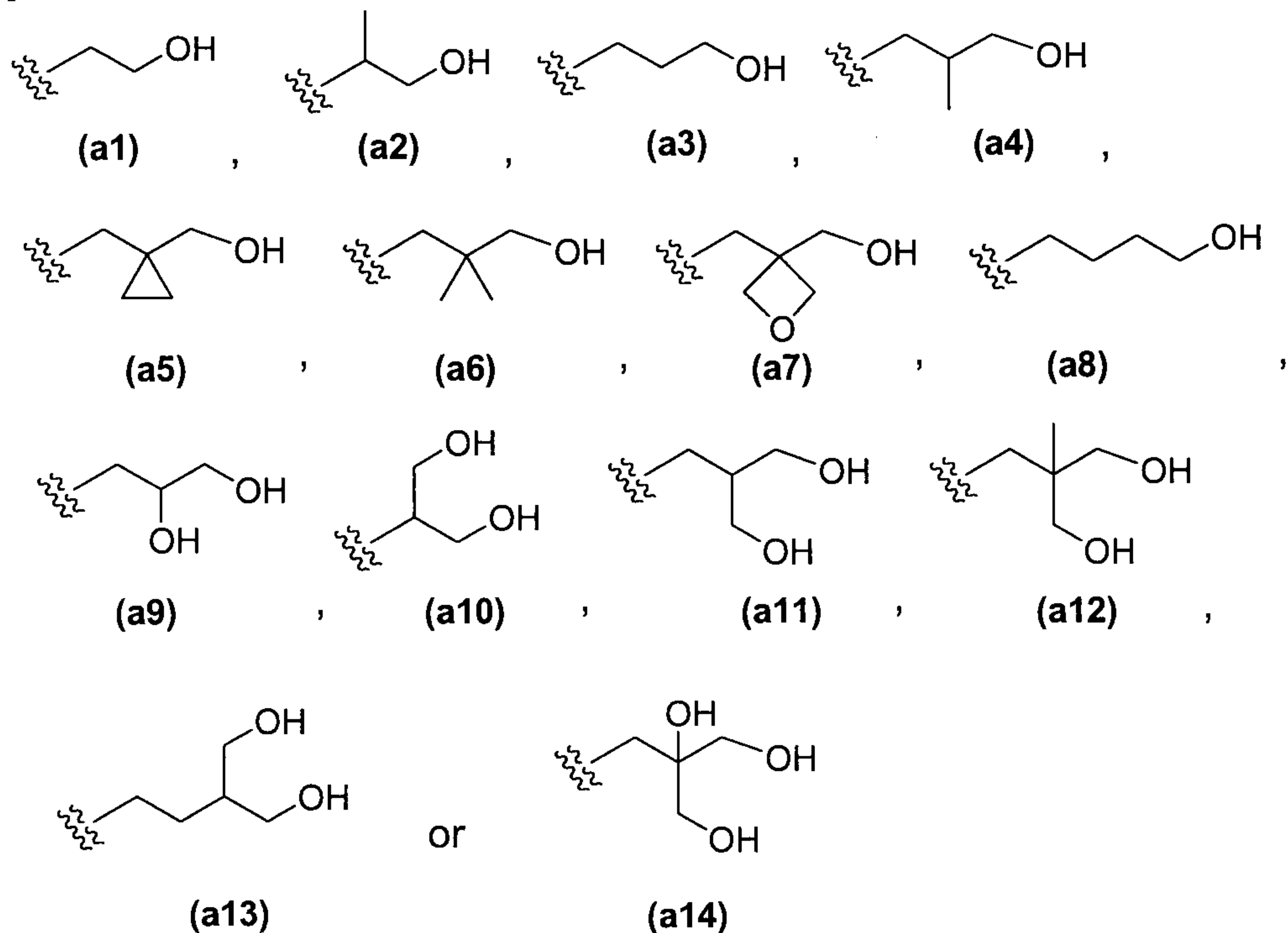
wherein R^{12a} and R^{12b} are each independently, hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, or substituted or unsubstituted

alkynyl; u is an integer of 0 to 2; m is an integer of 2 to 4;

[0167]

(ca3) a group of the formula:

[Chemical Formula 77]

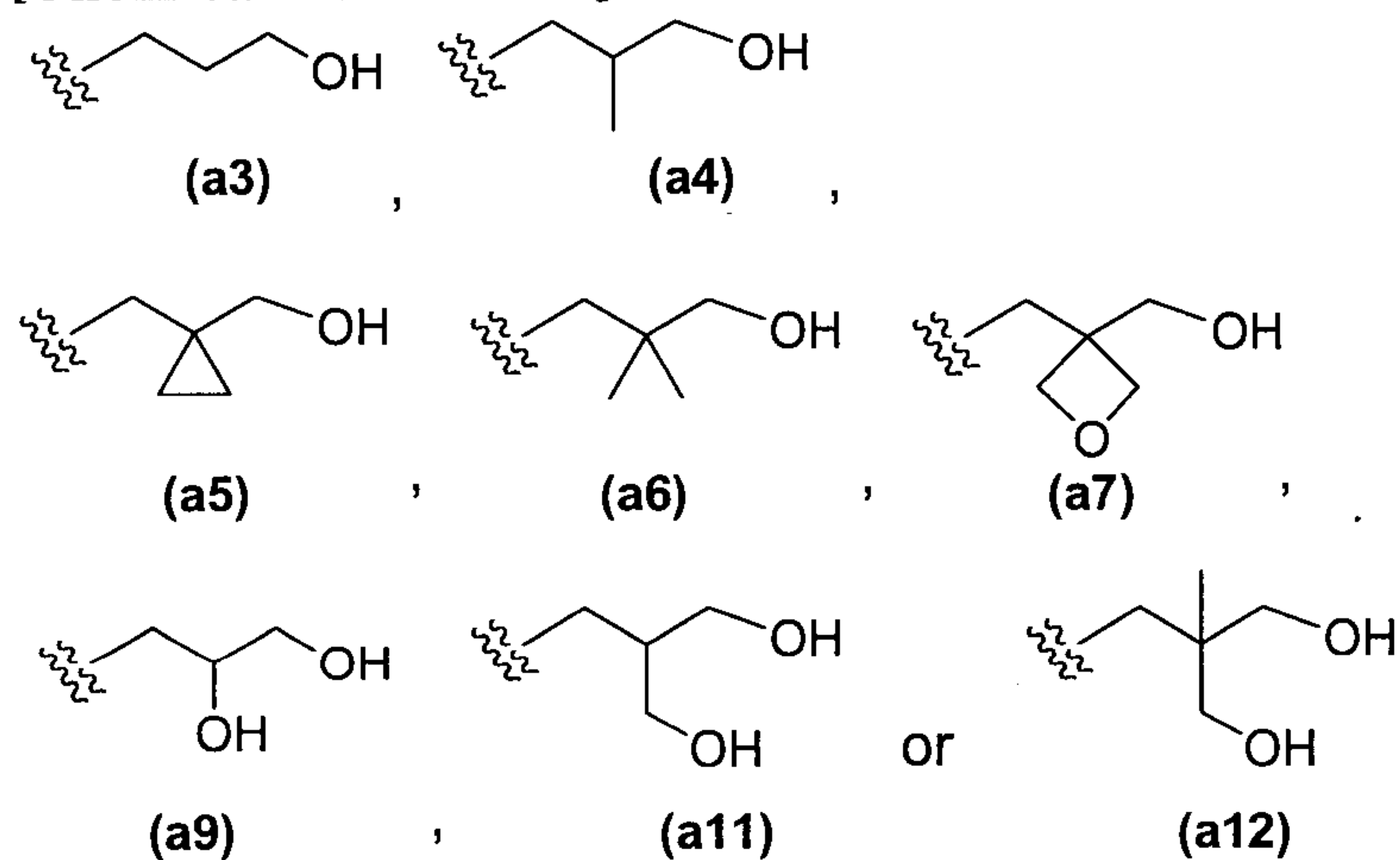


;

[0168]

(ca4) a group of the formula:

[Chemical Formula 78]

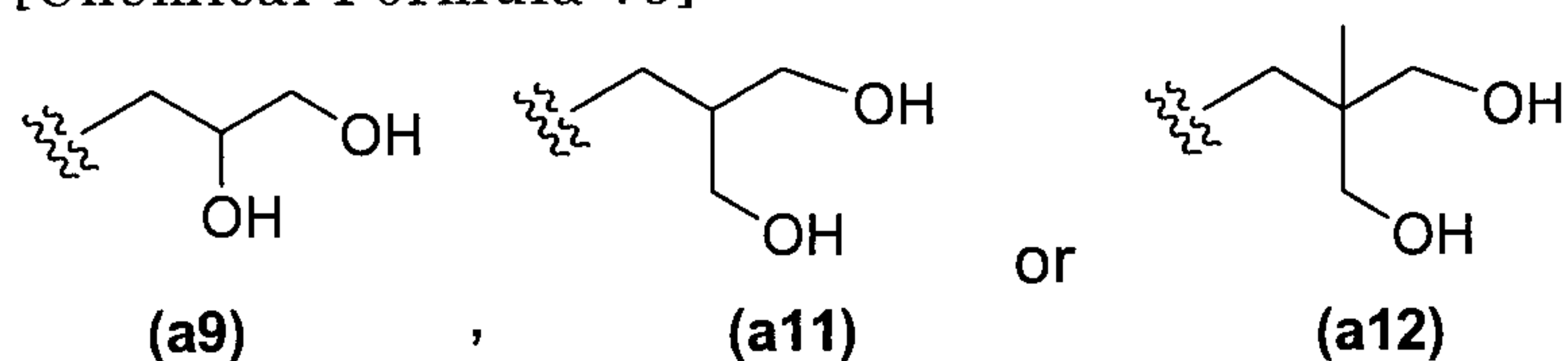


; and

[0169]

(ca5) a group of the formula:

[Chemical Formula 79]



;

ring F is a group selected from the following (cc1) and (cc2):

(cc1) a benzene ring, a pyridine ring or a cyclohexane ring; and

(cc2) a benzene ring;

R³⁰ is a group selected from the following (cd1) and (cd2):

(cd1) halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl; and

(cd2) fluoro, chloro, methyl, monofluoromethyl, difluoromethyl, trifluoromethyl or ethyl;

R³¹ is halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl;

[0170]

n'' is 0 or 1;

ring D is a group selected from the following (ce1) to (ce4):

(ce1) a benzene ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring;

(ce2) a benzene ring or a pyridine ring;

(ce3) a benzene ring; and

(ce4) a pyridine ring;

relationship of carbon atom a and carbon atom b on ring D is selected from the following (cf1) to (cf3):

(cf1) 1,4 relationship, or 1,3 relationship;

(cf2) 1,4 relationship; and

(cf3) 1,3 relationship;

ring E is a group selected from the following (cg1) to (cg3):

(cg1) a cycloalkane ring or a cycloalkene ring;

(cg2) a cycloalkane ring; and

(cg3) a cyclopropane ring;

s' is

(ch1) 0 or 1;

(ch2) 0; and

(ch3) 1;

when s' is 1, then R^{9'} is a group selected from the following (ci1) to (ci4):

(ci1) alkyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or unsubstituted alkyl;

(ci2) unsubstituted alkyl;

(ci3) methyl; ethyl; methyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or ethyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; and

(ci4) methyl or ethyl,

or its pharmaceutically acceptable salt or a solvate thereof.

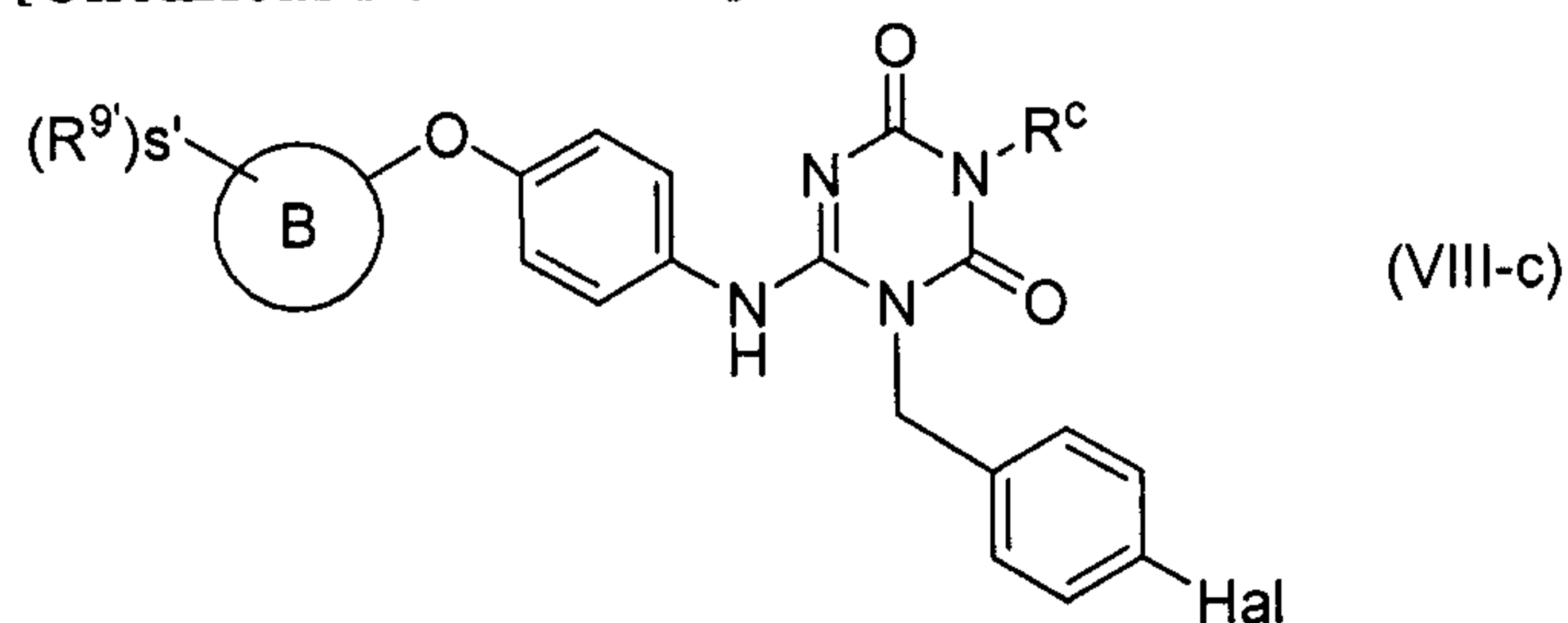
The compound of the formula (VIII-b) of the present invention includes the compounds comprising the combination of some or all of options of the above (ca1) to (ca5), (cc1) and (cc2), (cd1) and (cd2), (ce1) to (ce4), (cf1) to (cf3), (cg1) to (cg3), (ch1) to (ch3) and (ci1) to (ci4).

[0171]

The following embodiments are examples of the compound (VIII) of the present invention.

A compound of the formula (VIII-c):

[Chemical Formula 80]



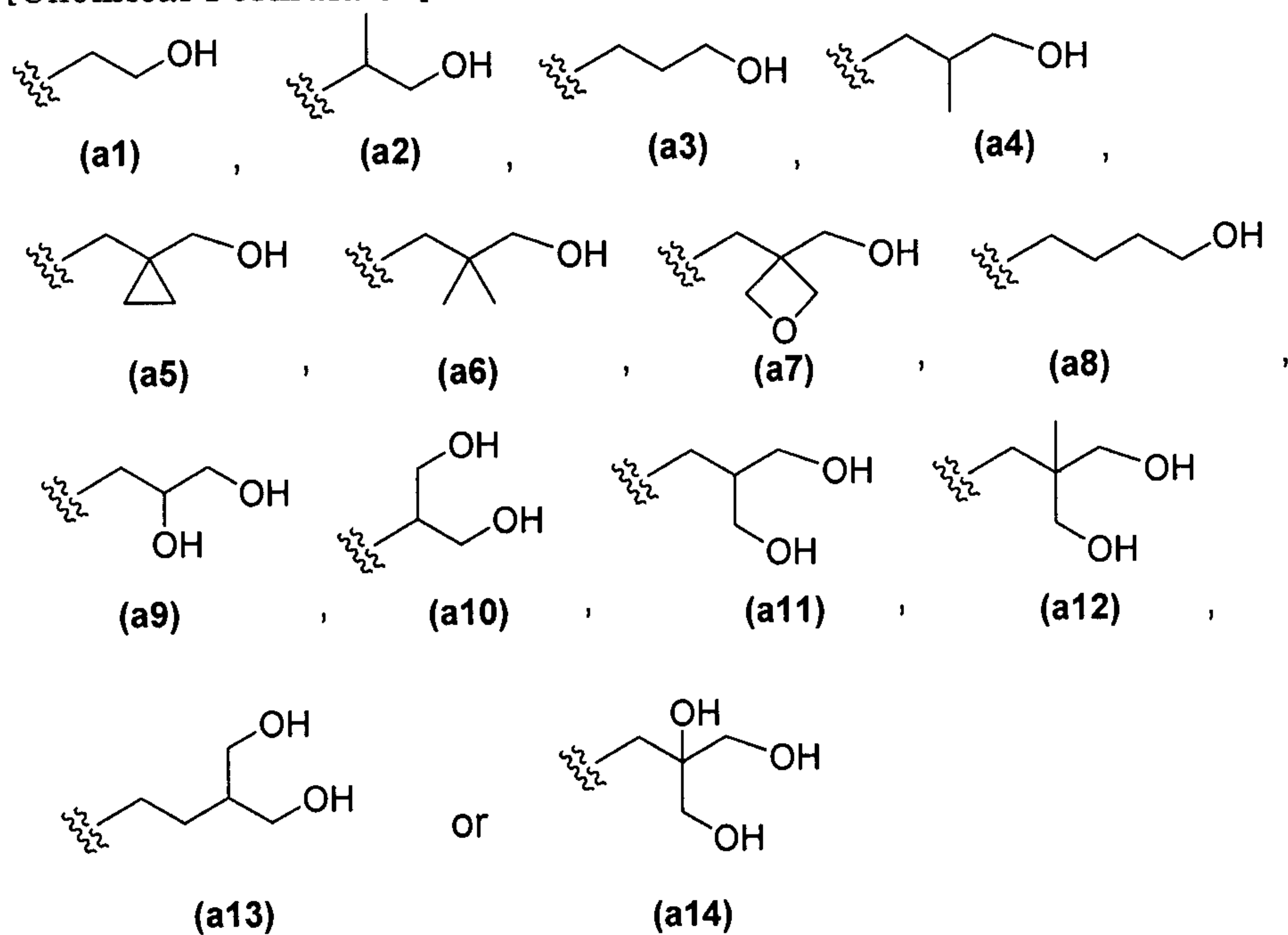
wherein

Hal is halogen;

R^c is

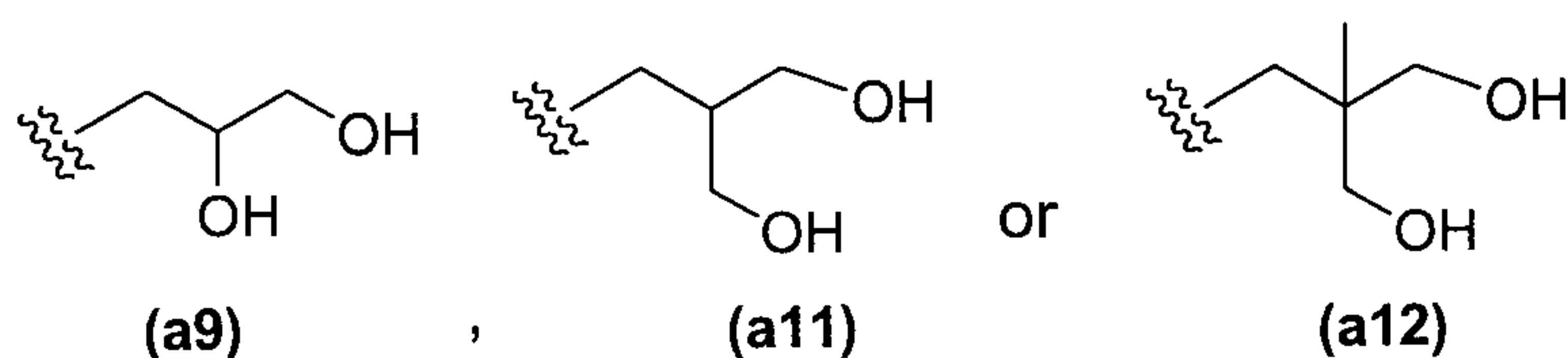
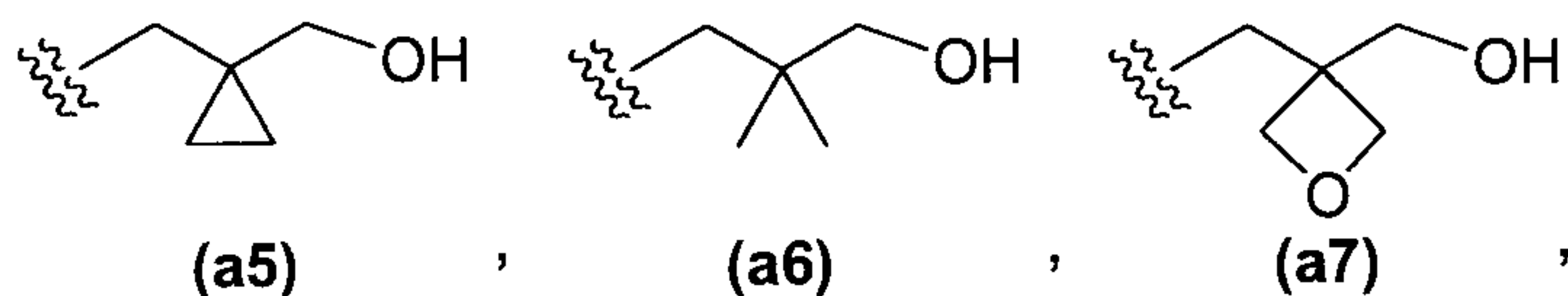
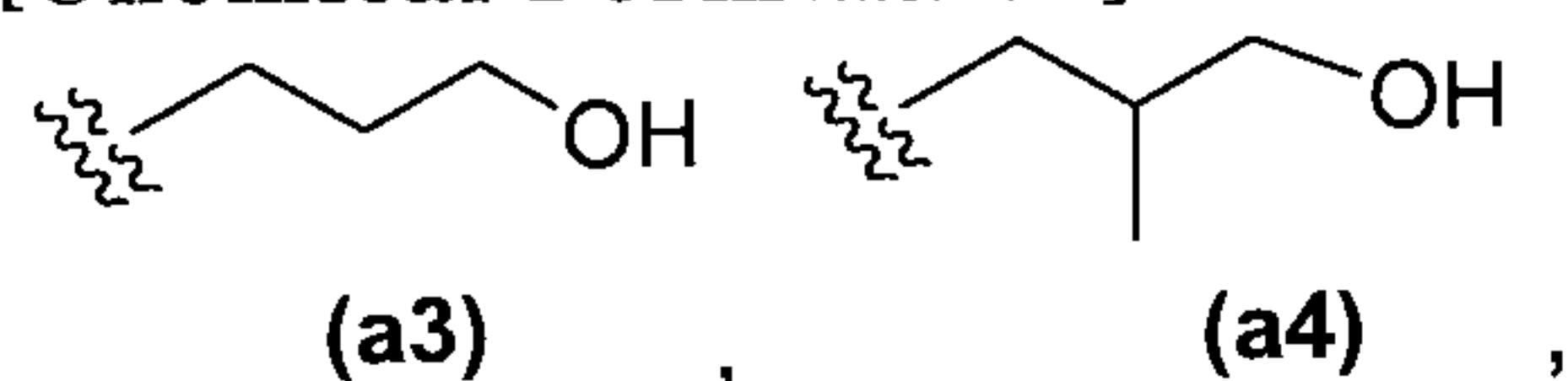
(da1) a group of the formula:

[Chemical Formula 81]



(da2) a group of the formula:

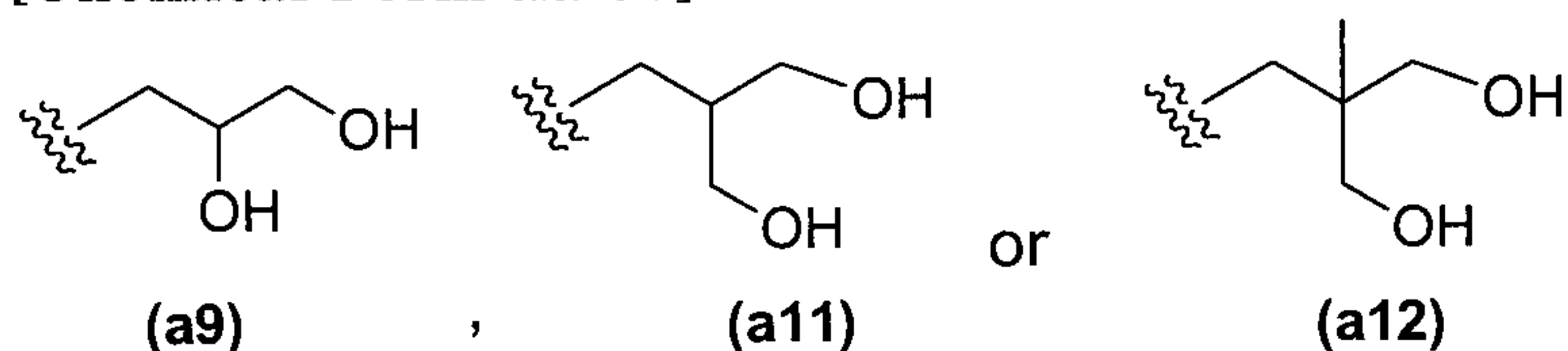
[Chemical Formula 82]



; or

(da3) a group of the formula :

[Chemical Formula 83]



;

[0172]

ring B is:

(dg1) an aromatic heterocyclic ring;

(dg2) a five- or six-membered aromatic heterocyclic ring;

(dg3) a thiazole ring, an isothiazole ring, an oxazole ring, an isoxazole ring, a thiadiazole ring, an oxadiazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring, a triazine ring, or a pyrazole ring;

(dg4) a thiazole ring, an isoxazole ring, a thiadiazole ring, a pyridine ring, a pyrimidine ring, a pyrazine ring or a pyridazine ring;

(dg5) a six-membered aromatic heterocyclic ring;

(dg6) a pyridine ring, a pyrimidine ring, a pyrazine ring, a pyridazine ring or a triazine ring;

(dg7) a five-membered aromatic heterocyclic ring;

(dg8) a thiazole ring, an isothiazole ring, an oxazole ring, an isoxazole ring, a thiadiazole ring, an oxadiazole ring, or a pyrazole ring; or

(dg9) a thiazole ring, an isoxazole ring or a thiadiazole ring;

a group of the formula (R⁹)s' is:

(dj1) s' is 0;

(dj2) s' is 1, and R⁹ is hydroxy; carboxy; cyano; alkyl substituted with hydroxy, carboxy, cyano, carbamoyl, amino, sulfamoyl, methanesulfonyl or methansulfinyl; substituted or unsubstituted carbamoyl; substituted or unsubstituted amino; substituted or unsubstituted sulfamoyl; substituted sulfonyl; or substituted sulfinyl;(dj3) s' is 1, and R⁹ is hydroxy; carboxy; cyano; alkyl substituted with hydroxy, carboxy, cyano, carbamoyl, amino, sulfamoyl, methanesulfonyl or methansulfinyl; carbamoyl; alkylcarbamoyl; amino substituted with alkyl, haloalkyl, hydroxyalkyl, alkyloxy, haloalkyloxy, carbamoyl, alkylcarbamoyl, alkylcarbamoylalkyl, carbamoylalkyl or

carboxyalkyl; sulfamoyl; alkylsulfamoyl; alkylsulfonyl; or alkylsulfinyl;

(dj4) s' is 1, and R⁹ is carboxy; carbamoyl; alkylcarbamoyl; sulfamoyl; alkylsulfamoyl or alkylsulfonyl;

(dj5) s' is 1, and R⁹ is alkyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or unsubstituted alkyl;

(bj6) s' is 1, and R⁹ is unsubstituted alkyl;

(dj7) s' is 1, and R⁹ is methyl; ethyl; methyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or ethyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; and

(dj8) s' is 1, and R⁹ is methyl or ethyl,

or its pharmaceutically acceptable salt or a solvate thereof.

[0173]

The compound of the formula (VIII-c) of the present invention includes the compounds comprising the combination of some or all of options of the above. Specifically, the following combinations are included,

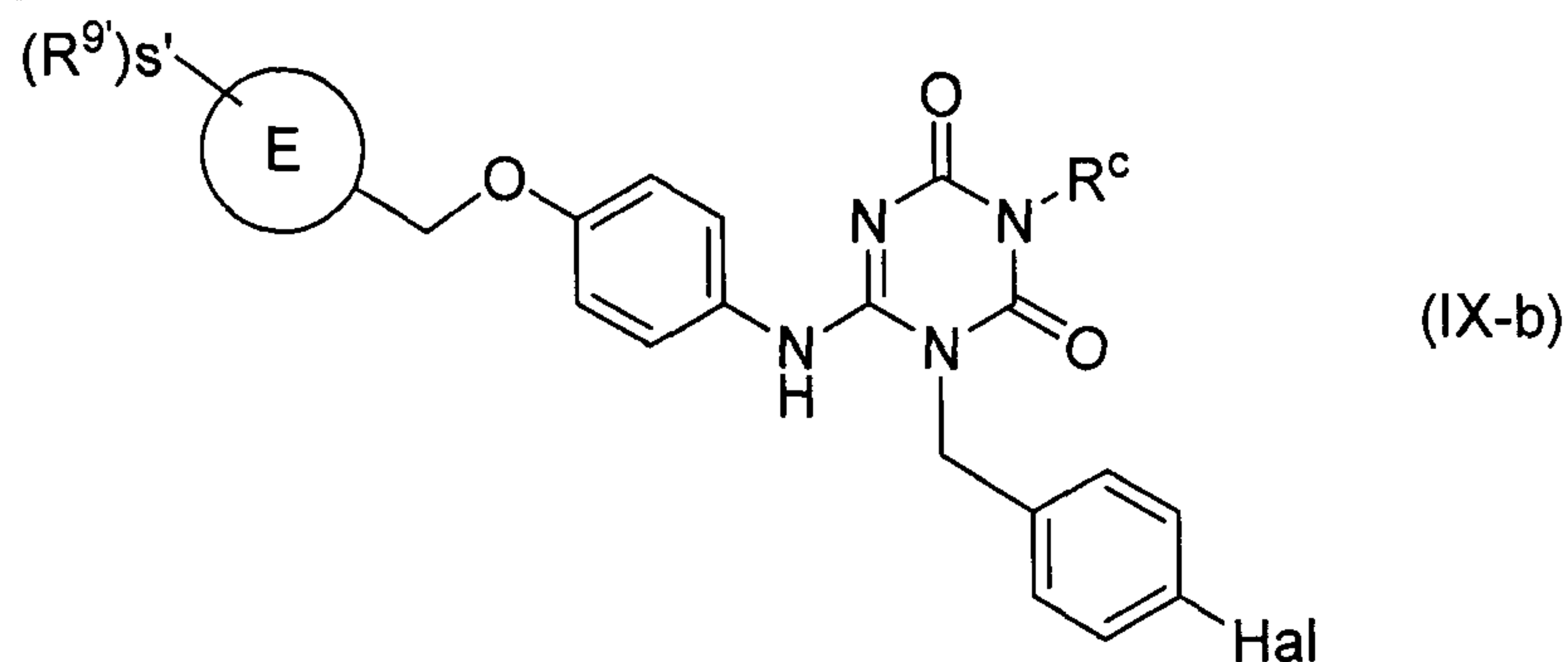
(da1, dg3, di3), (da1, dg3, di4), (da1, dg3, di5), (da1, dg3, di6), (da1, dg3, di7), (da1, dg3, di8), (da1, dg4, di1), (da1, dg4, di2), (da1, dg4, di3), (da1, dg4, di4), (da1, dg4, di5), (da1, dg4, di6), (da1, dg4, di7), (da1, dg4, di8), (da1, dg5, di1), (da1, dg5, di2), (da1, dg5, di3), (da1, dg5, di4), (da1, dg5, di5), (da1, dg5, di6), (da1, dg5, di7), (da1, dg5, di8), (da1, dg6, di1), (da1, dg6, di2), (da1, dg6, di3), (da1, dg6, di4), (da1, dg6, di5), (da1, dg6, di6), (da1, dg6, di7), (da1, dg6, di8), (da1, dg7, di1), (da1, dg7, di2), (da1, dg7, di3), (da1, dg7, di4), (da1, dg7, di5), (da1, dg7, di6), (da1, dg7, di7), (da1, dg7, di8), (da1, dg8, di1), (da1, dg8, di2), (da1, dg8, di3), (da1, dg8, di4), (da1, dg8, di5), (da1, dg8, di6), (da1, dg8, di7), (da1, dg8, di8), (da1, dg9, di1), (da1, dg9, di2), (da1, dg9, di3), (da1, dg9, di4), (da1, dg9, di5), (da1, dg9, di6), (da1, dg9, di7), (da1, dg9, di8), (da2, dg1, di1), (da2, dg1, di2), (da2, dg1, di3), (da2, dg1, di4), (da2, dg1, di5), (da2, dg1, di6), (da2, dg1, di7), (da2, dg1, di8), (da2, dg2, di1), (da2, dg2, di2), (da2, dg2, di3), (da2, dg2, di4), (da2, dg2, di5), (da2, dg2, di6), (da2, dg2, di7), (da2, dg2, di8), (da2, dg3, di1), (da2, dg3, di2), (da2, dg3, di3), (da2, dg3, di4), (da2, dg3, di5), (da2, dg3, di6), (da2, dg3, di7), (da2, dg3, di8), (da2, dg4, di1), (da2, dg4, di2), (da2, dg4, di3), (da2, dg4, di4), (da2, dg4, di5), (da2, dg4, di6), (da2, dg4, di7), (da2, dg4, di8), (da2, dg5, di1), (da2, dg5, di2), (da2, dg5, di3), (da2, dg5, di4), (da2, dg5, di5), (da2, dg5, di6), (da2, dg5, di7), (da2, dg5, di8), (da2, dg6, di1), (da2, dg6, di2), (da2, dg6, di3), (da2, dg6, di4), (da2, dg6, di5), (da2, dg6, di6), (da2, dg6, di7), (da2, dg6, di8), (da2, dg7, di1), (da2, dg7, di2), (da2, dg7, di3), (da2, dg7, di4), (da2, dg7, di5), (da2, dg7, di6), (da2, dg7, di7), (da2, dg7, di8), (da2, dg8, di1), (da2, dg8, di2), (da2, dg8, di3), (da2, dg8, di4), (da2, dg8, di5), (da2, dg8, di6), (da2, dg8, di7), (da2, dg8, di8), (da2, dg9, di1), (da2, dg9, di2), (da2, dg9, di3), (da2, dg9, di4), (da2, dg9, di5), (da2, dg9, di6), (da2, dg9, di7), (da2, dg9, di8), (da3, dg1, di1), (da3, dg1, di2), (da3, dg1, di3), (da3, dg1, di4), (da3, dg1, di5), (da3, dg1, di6), (da3, dg1, di7), (da3, dg1, di8), (da3, dg2, di1), (da3, dg2, di2), (da3, dg2, di3), (da3, dg2, di4), (da3, dg2, di5), (da3, dg2, di6), (da3, dg2, di7), (da3, dg2, di8), (da3, dg3, di1), (da3, dg3, di2), (da3, dg3, di3), (da3, dg3, di4), (da3, dg3, di5), (da3, dg3, di6), (da3, dg3, di7), (da3, dg3, di8), (da3, dg4, di1), (da3, dg4, di2), (da3, dg4, di3), (da3, dg4, di4), (da3, dg4, di5), (da3, dg4, di6), (da3, dg4, di7), (da3, dg4, di8), (da3, dg5, di1), (da3, dg5, di2), (da3, dg5, di3), (da3, dg5, di4), (da3, dg5, di5), (da3, dg5, di6), (da3, dg5, di7), (da3, dg5, di8), (da3, dg6, di1), (da3, dg6, di2), (da3, dg6, di3), (da3, dg6, di4), (da3, dg6, di5), (da3, dg6, di6), (da3, dg6, di7), (da3, dg6, di8), (da3, dg7, di1), (da3, dg7, di2), (da3, dg7, di3), (da3, dg7, di4), (da3, dg7, di5), (da3, dg7, di6), (da3, dg7, di7), (da3, dg7, di8), (da3, dg8, di1), (da3, dg8, di2), (da3, dg8, di3), (da3, dg8, di4), (da3, dg8, di5), (da3, dg8, di6), (da3, dg8, di7), (da3, dg8, di8), (da3, dg9, di1), (da3, dg9, di2), (da3, dg9,

di3), (da3, dg9, di4), (da3, dg9, di5), (da3, dg9, di6), (da3, dg9, di7), (da3, dg9, di8)
[0174]

The following embodiments are examples of the compound (IX) of the present invention.

A compound of the formula (IX-b):

[Chemical Formula 84]



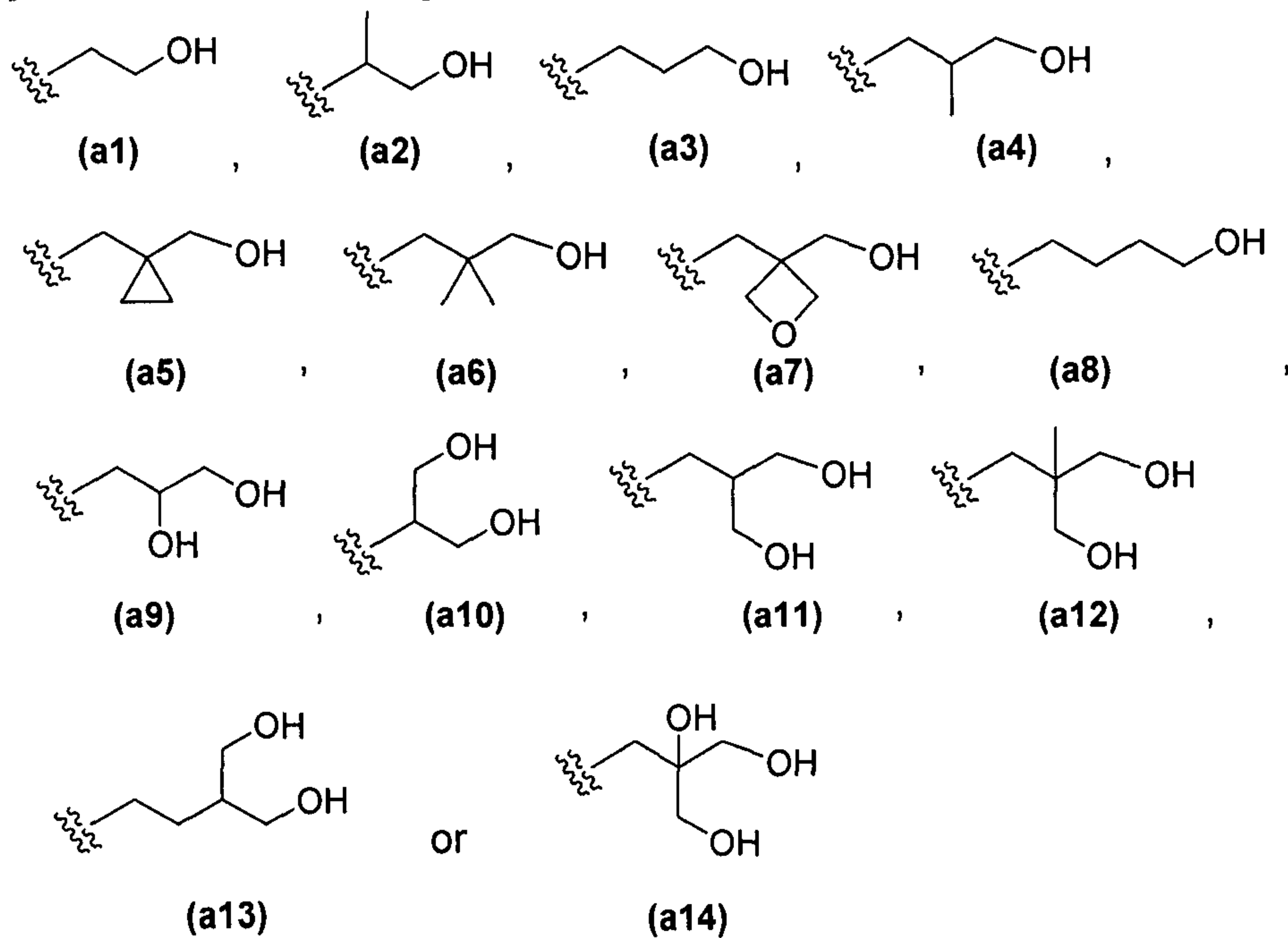
wherein

Hal is halogen;

R^c is

(ea1) a group of the formula:

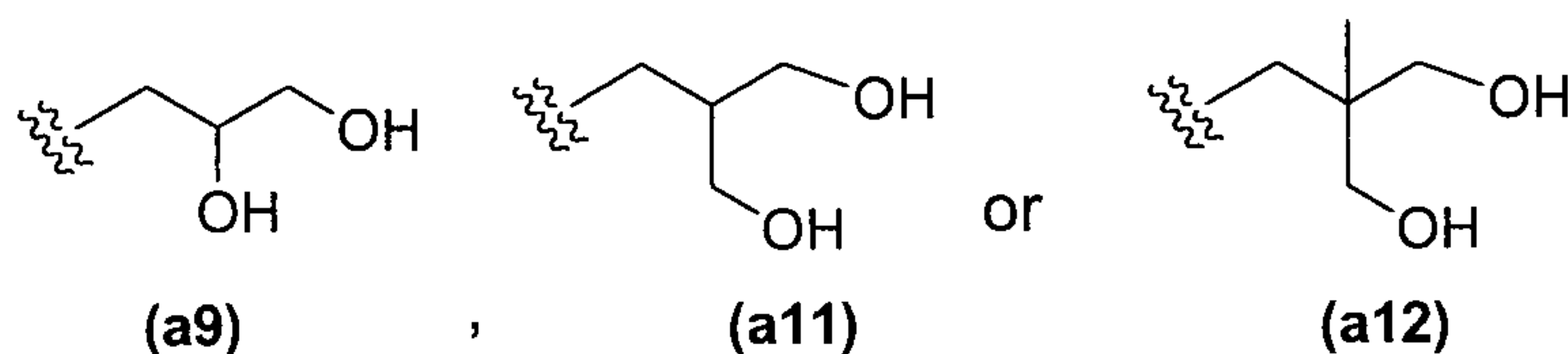
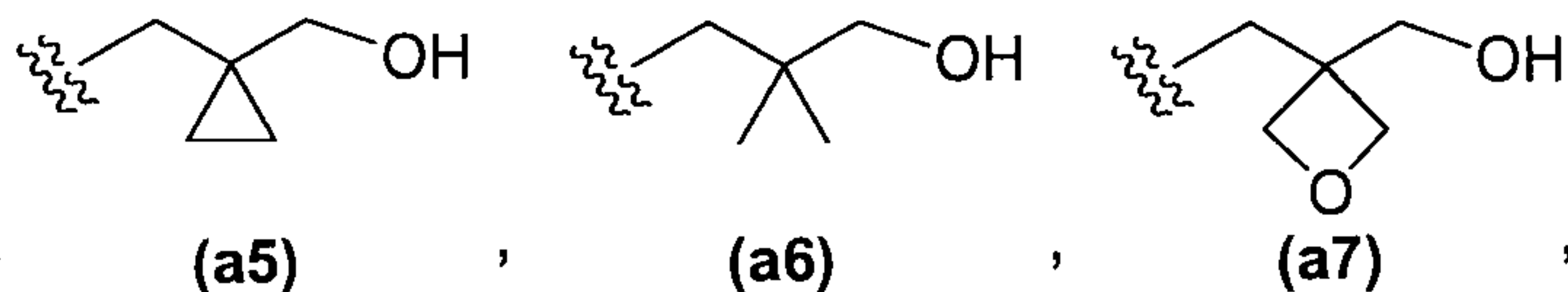
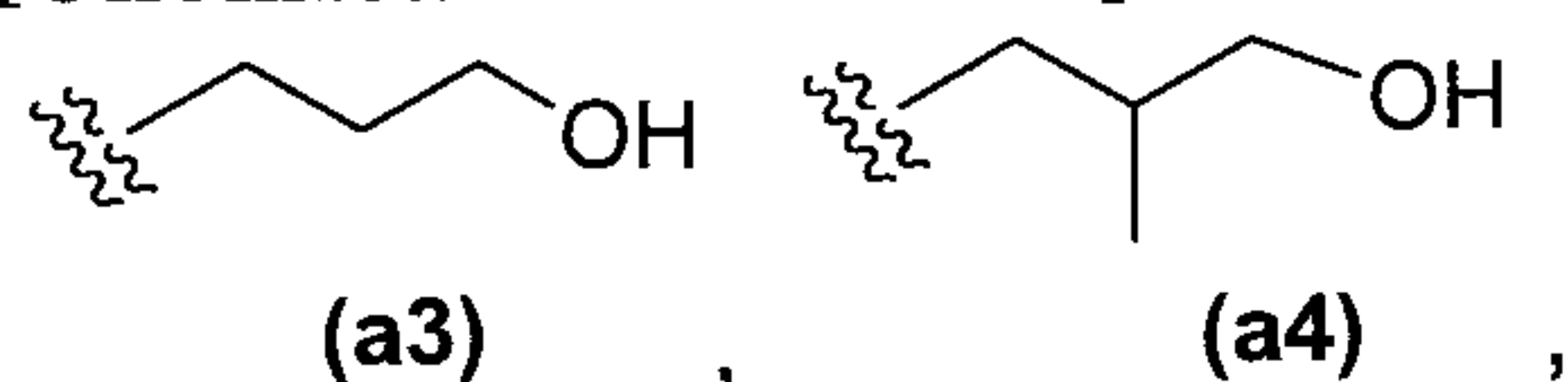
[Chemical Formula 85]



;

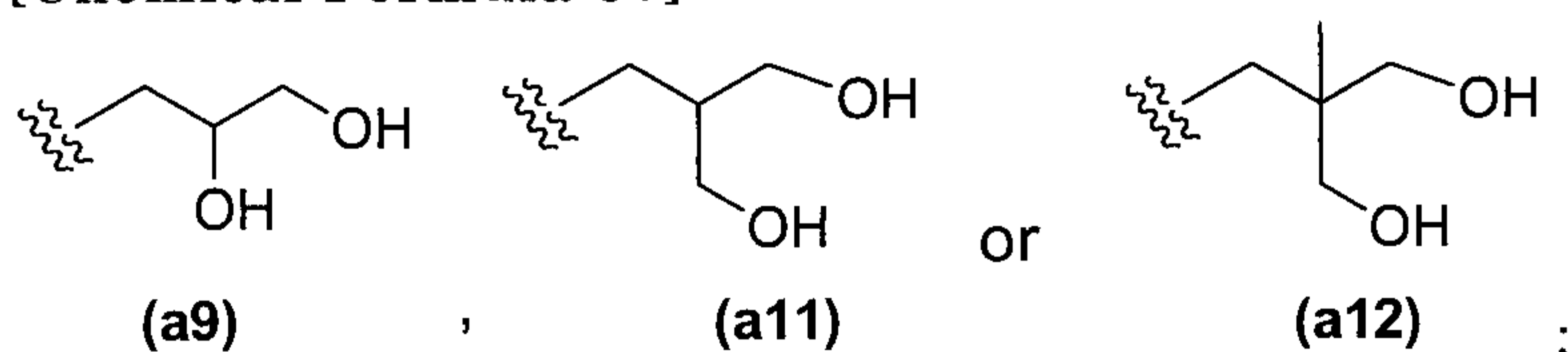
(ea2) a group of the formula:

[Chemical Formula 86]



(ea3) a group of the formula:

[Chemical Formula 87]



[0175]

ring E is

(eg1) a cycloalkane ring or a cycloalkene ring;

(eg2) a cycloalkane ring;

(eg3) a cyclopropane ring;

a group of the formula: $(R^{9'})_{s'}$ is(ej1) s' is 0;(ej2) s' is 1, and $R^{9'}$ is alkyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or unsubstituted alkyl;(ej3) s' is 1, and $R^{9'}$ is unsubstituted alkyl;(ej4) s' is 1, and $R^{9'}$ is methyl; ethyl; methyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or ethyl substituted with halogen, haloalkyloxy, cycloalkyl, cycloalkenyl, alkyloxy or alkenyloxy; or(ej5) s' is 1, and $R^{9'}$ is methyl or ethyl,

or its pharmaceutically acceptable salt or a solvate thereof .

[0176]

The compound of the formula (IX-b) of the present invention includes the compounds comprising the combination of some or all of options of the above. Specifically, the following combinations are included.

(ea1, eg1, ei1), (ea1, eg1, ei2), (ea1, eg1, ei3), (ea1, eg1, ei4), (ea1, eg1, ei5), (ea1, eg2, ei1), (ea1, eg2, ei2), (ea1, eg2, ei3), (ea1, eg2, ei4), (ea1, eg2, ei5), (ea1, eg3, ei1), (ea1, eg3, ei2), (ea1, eg3, ei3), (ea1, eg3, ei4), (ea1, eg3, ei5), (ea2, eg1, ei1), (ea2, eg1, ei2), (ea2, eg1, ei3), (ea2, eg1, ei4), (ea2, eg1, ei5), (ea2, eg2, ei1), (ea2, eg2, ei2), (ea2, eg2, ei3), (ea2, eg2, ei4), (ea2, eg2, ei5), (ea2, eg3, ei1), (ea2, eg3, ei2), (ea2, eg3, ei3), (ea2, eg3, ei4), (ea2, eg3, ei5), (ea3, eg1, ei1), (ea3, eg1, ei2), (ea3, eg1, ei3), (ea3, eg1, ei4), (ea3, eg1, ei5), (ea3, eg2, ei1), (ea3, eg2, ei2), (ea3, eg2, ei3), (ea3, eg2, ei4), (ea3, eg2, ei5), (ea3, eg3, ei1), (ea3, eg3, ei2), (ea3, eg3, ei3), (ea3, eg3, ei4), (ea3, eg3, ei5)

[0177]

The following is a general method for synthesizing the compounds of this

invention. The starting materials and reagents used for synthesizing these compounds are commercially available or can be manufactured in accordance with a widely known method in this field using commercially available compounds.

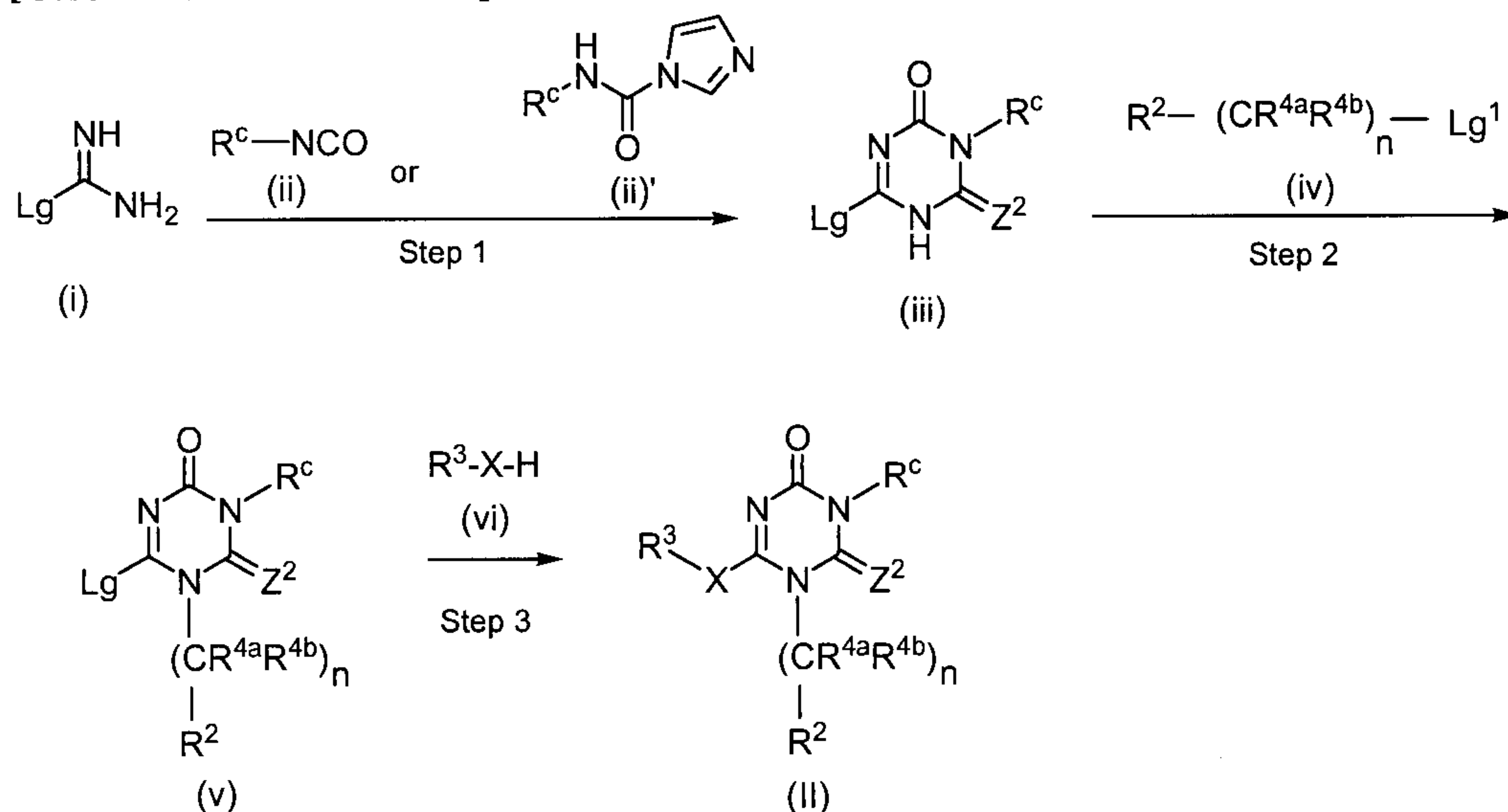
[0178]

For example, the compounds of the general formula (I), general formula (II), general formula (III), general formula (IV), general formula (VII), general formula (VIII) and general formula (IX) described in this invention can be manufactured by the following synthesis route:

[0179]

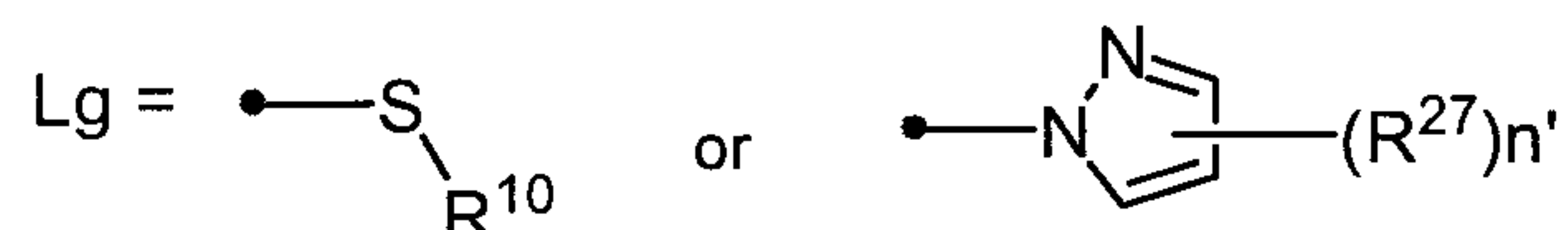
[Method A]

[Chemical Formula 88]



wherein, Lg is a leaving group of the formula:

[Chemical Formula 89]



R^{10} is alkyl, R^{27} is alkyl, n' is an integer from 0 to 3, Lg^1 is a leaving group and other symbols are as defined above.

(Step 1)

The compound (i) or its hydrochloride or bromate is reacted with isocyanate (ii) or 1-carbamoyl imidazole (ii)' in a solvent, such as N,N-dimethylformamide, N,N-dimethylacetamide, N,N'-dimethyl imidazolidinone and dimethylsulfoxide, in the presence of a base, such as DBU, triethylamine and pyridine (preferably DBU) at a temperature between -20 and 50°C , preferably at a temperature between -10°C and below zero. After that, the compound (iii) can be manufactured by reacting the reactive mixture with a carbonylating or thiocarbonylating agent, such as 1,1'-carbonyldiimidazole, 1,1'-thiocarbonyldiimidazole, phosgene, thiophosgene and triphosgene, etc., and a base, such as DBU, triethylamine or pyridine (preferably DBU) at a temperature between -20 and 50°C , preferably at a temperature between -10°C and below zero.

(Step 2)

The compound (v) can be manufactured by reacting the compound (iii) with the compound (iv) in a solvent, such as acetonitrile, acetone, DMF and DMSO, in the presence of a base, such as potassium carbonate and sodium carbonate, at a temperature between

50 °C to reflux, preferably at reflux.

The examples of leaving group include halogen and $-\text{OSO}_2(\text{C}_t\text{F}_{2t+1})$ wherein t is an integer from 1 to 4. As halogen, chloro, iodo and bromo are preferred. As $-\text{OSO}_2(\text{C}_t\text{F}_{2t+1})$ group, $-\text{OTf}$ group (trifluoromethanesulfonate) is preferred. This leaving group can also be used in the aforementioned (60').

The base and/or carbonylating agent or thiocarbonylating agent in (Step 1) and (Step 2) can also be used in the aforementioned (60').

The "carbonylating agent" and "thiocarbonylating agent" include a reagent that is used in a reaction where $-\text{C}(=\text{O})$ or $-\text{C}(=\text{S})-$ is inserted.

(Step 3)

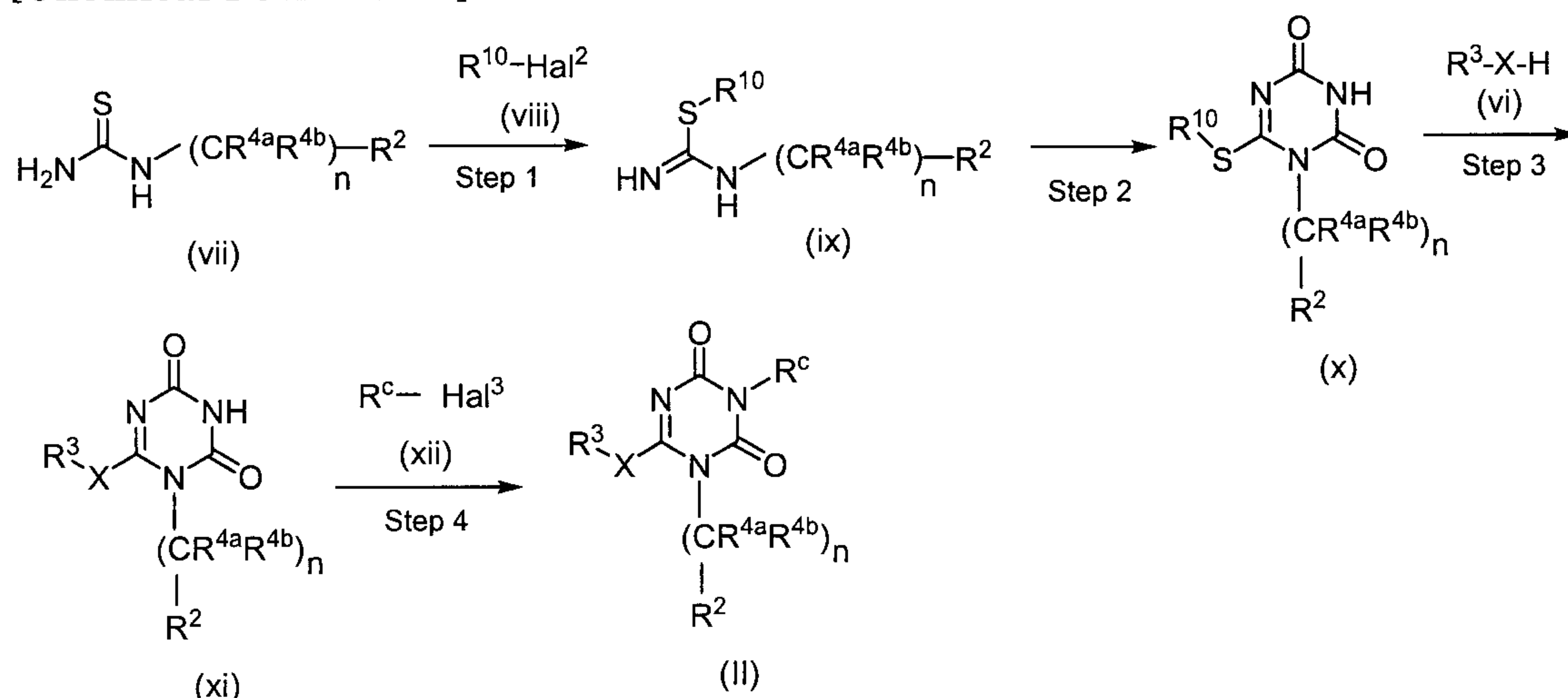
The compound indicated by the general formula (II) can be manufactured by reacting the compound (v) with the compound (vii) in a solvent, such as NMP, DMF and DMSO, or under solvent-free conditions under microwave irradiation at a temperature between 150°C and 250°C, preferably at a temperature between 200°C and 230°C, or in a solvent, such as *t*-butanol, in the presence of an acid, such as acetic acid, at a temperature between 60°C and 150°C, preferably at a temperature between 80°C and 120°C.

Using optically active isocyanate (ii) enables to synthesize optically active compound (II).

[0180]

[Method B]

[Chemical Formula 90]



wherein Hal^2 and Hal^3 are halogen and other symbols are as defined above.

(Step 1)

The compound (ix) can be manufactured by reacting the compound (vii) with alkylating agent (viii), such as methyl iodide and ethyl iodide, in a solvent, such as methanol and ethanol, at a temperature between -40 and 30°C , preferably below zero.

(Step 2)

The compound (x) can be manufactured by reacting the compound (ix) with isocyanate, such as *N*-(chlorocarbonyl) isocyanate, in a solvent, such as dichloromethane, chloroform, 1,2-dichloroethane, in the presence of a base, such as triethylamine and *N,N*-diisopropylethylamine, at a temperature between -20 and 30°C , preferably below zero.

(Step 3)

The compound (xi) can be manufactured by reacting the compound (x) with the compound (vi) in a solvent, such as *t*-butanol, isopropanol, ethanol and acetonitrile, in the presence of an acid, such as acetic acid, formic acid and methanesulfonic acid, at reflux.

(Step 4)

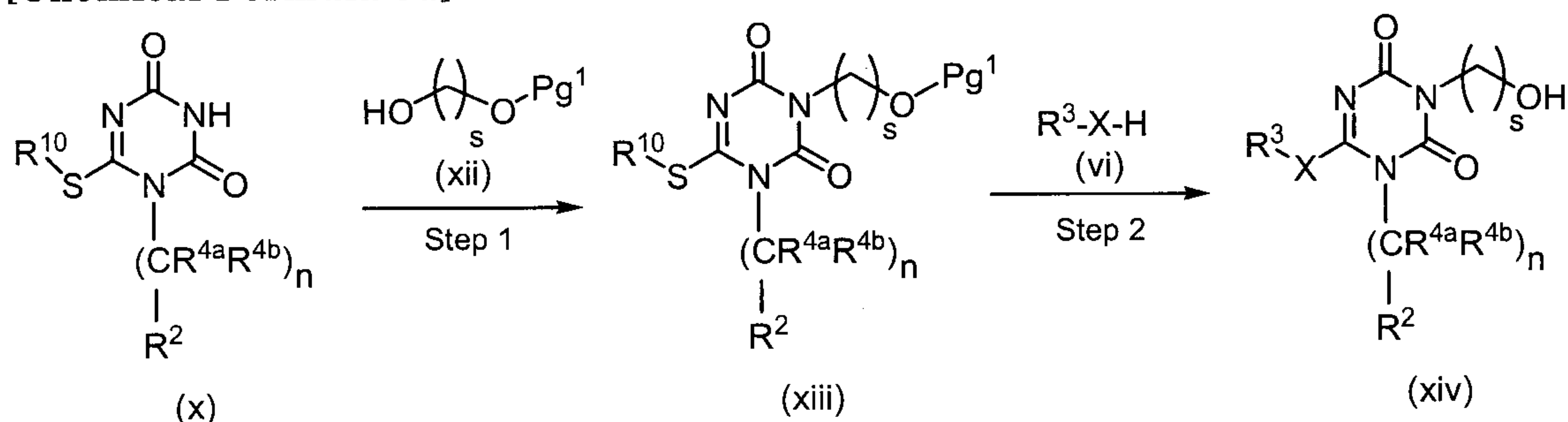
The compound indicated by the general formula (II) can be manufactured by reacting the compound (xi) with the compound (xii) in a solvent, such as DMF and NMP, in the presence of a base, such as potassium t-butoxide and sodium hydride, at a temperature between 40 and 100°C, preferably at a temperature between 50 and 70°C.

Using optically-active compound (xii) enables to synthesize optically-active compound (II).

[0181]

[Method C]

[Chemical Formula 91]



wherein Pg¹ is an appropriate hydroxy protecting group, s is an integer from 1 to 4 and other symbols are as defined above.

(Step 1)

The compound (xiii) can be manufactured by reacting a mixture of the compound (x) obtained by the method B, the alcohol (xii) whose one hydroxyl group is protected, such as 2-(tetrahydro-2H-pyran-2-yloxy) ethanol and a solvent, such as THF and dioxane, etc, with triphenylphosphine, and diethyl azodicarboxylate, etc.

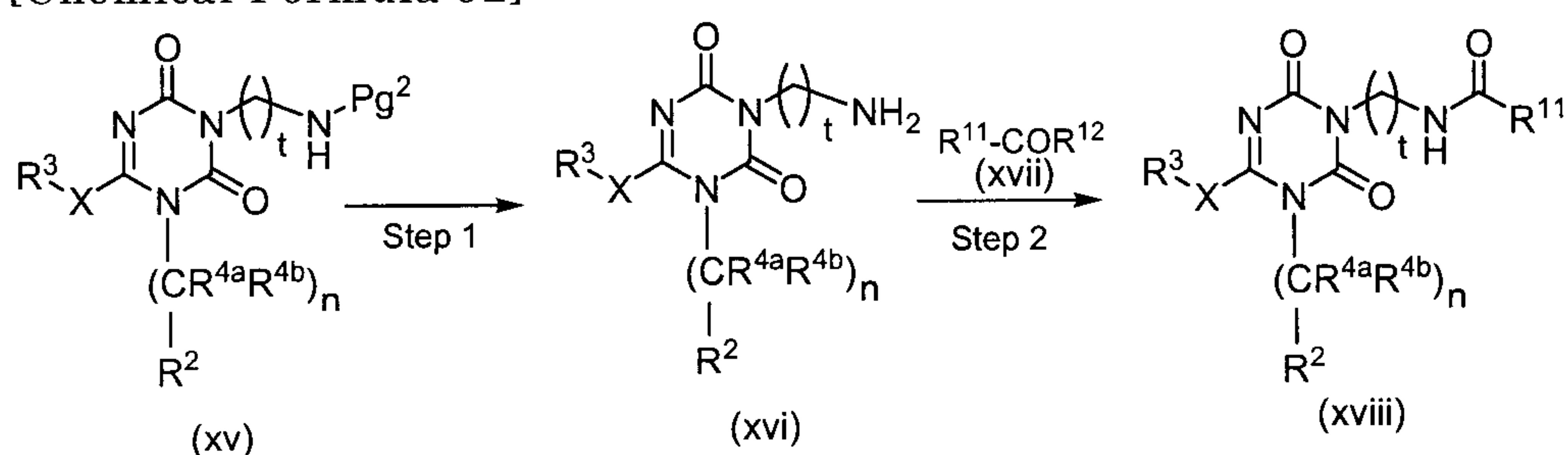
(Step 2)

The compound (xiv) can be manufactured by reacting the compound (xiii) with the compound (vi) in the presence of an acid, such as formic acid and acetic acid, etc., at reflux.

[0182]

[Method D]

[Chemical Formula 92]



wherein Pg² is an appropriate amino protecting group, R¹¹ is substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted 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, R¹² is hydroxy or halogen, t is an integer from 1 to 4 and other symbols are as defined above.)

(Step 1)

The compound (xvi) can be manufactured by reacting the compound (xv) obtained by the

method A or B with acid, such as hydrochloric acid-dioxane solution, hydrochloric acid-methanol, hydrochloric acid-ethyl acetate solution and trifluoroacetic acid, etc.
(Step 2)

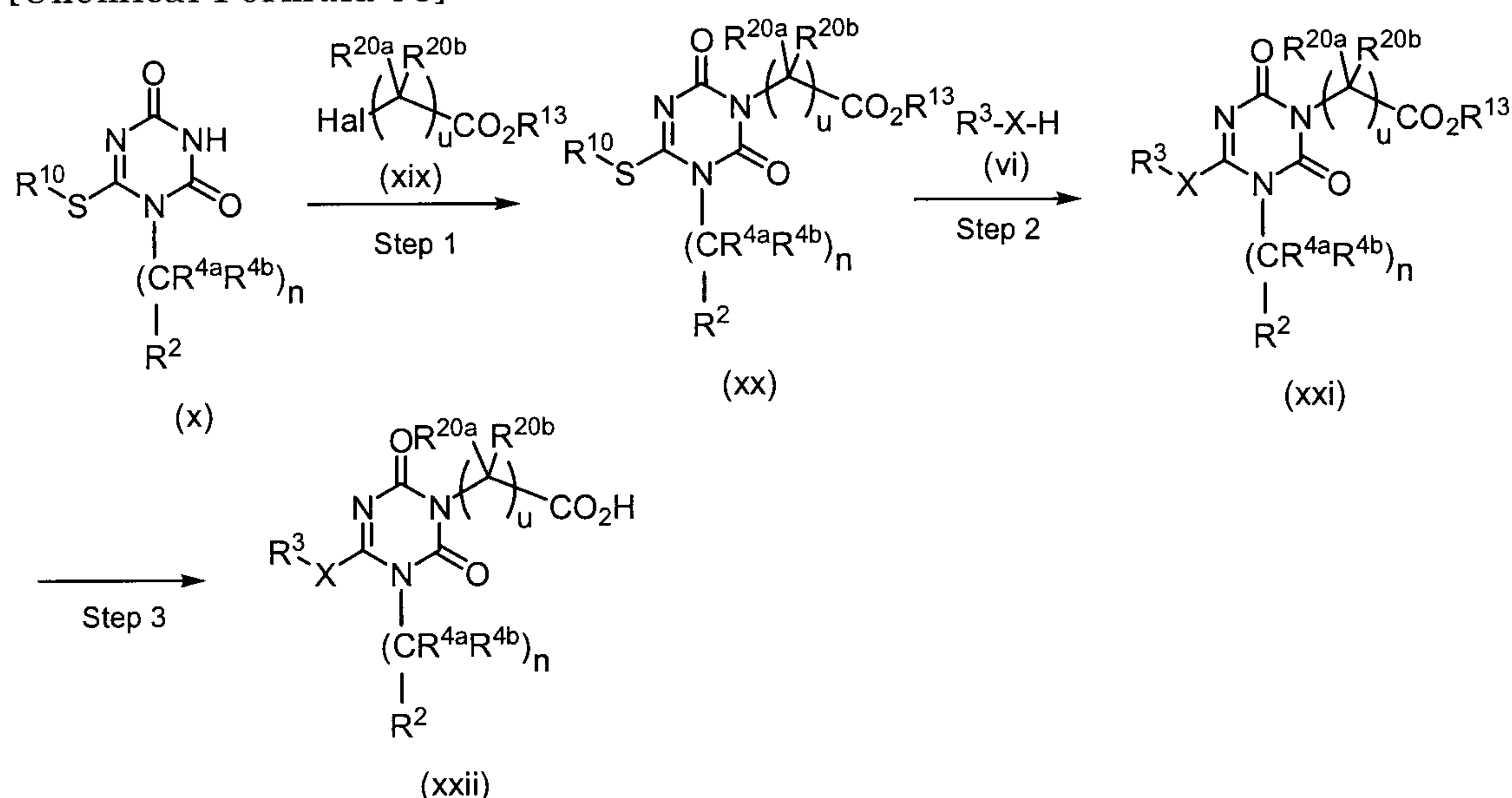
The compound (xviii) can be manufactured by reacting the compound (xvi) with the acid halide (xvii) (R^{12} is halogen) in a solvent, such as THF and dioxane, etc., in the presence of a base, such as triethylamine and diisopropylethylamine, etc. If necessary, dimethylaminopyridine, etc., can be added.

Alternatively, the compound (xviii) can be manufactured by reacting the compound (xvi) with the carboxylic acid (xvii, R^{12} is hydroxy) in a solvent, such as THF and DMF, in the presence of a condensing agent, such as 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, and a base, such as triethylamine and diisopropylethylamine, etc.

[0183]

[Method E]

[Chemical Formula 93]



wherein R^{13} is substituted or unsubstituted alkyl, R^{20a} and R^{20b} are hydrogen, halogen, cyano, hydroxy, carboxy, sulfo, substituted or unsubstituted alkyloxy, substituted or unsubstituted alkenyloxy, substituted or unsubstituted alkynyloxy, 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 alkyloxycarbonyl, substituted or unsubstituted alkenyloxycarbonyl, substituted or unsubstituted alkynyloxycarbonyl, substituted or unsubstituted carbamoyl, substituted or unsubstituted sulfamoyl, substituted or unsubstituted amino, substituted or unsubstituted imino, substituted or unsubstituted guanidyl or R^{20a} and R^{20b} are taken together to form oxo or thioxo, u is an integer from 1 to 4, and other symbols are as defined above.
(Step 1)

The compound (xx) can be manufactured by reacting the compound (x) obtained by the method B with the compound (xix) in a solvent, such as DMF, NMP and THF, in the presence of a base, such as DBU, potassium *t*-butoxide and sodium hydride, at a temperature between 0 and 80°C, preferably at a temperature between 30 and 50°C.
(Step 2)

The compound (xxi) can be manufactured by reacting the compound (xx) with the

compound (vi) in a solvent, such as t-butanol, isopropanol, ethanol and acetonitrile, in the presence of an acid such as formic acid, acetic acid and methanesulfonic acid, etc., at reflux.

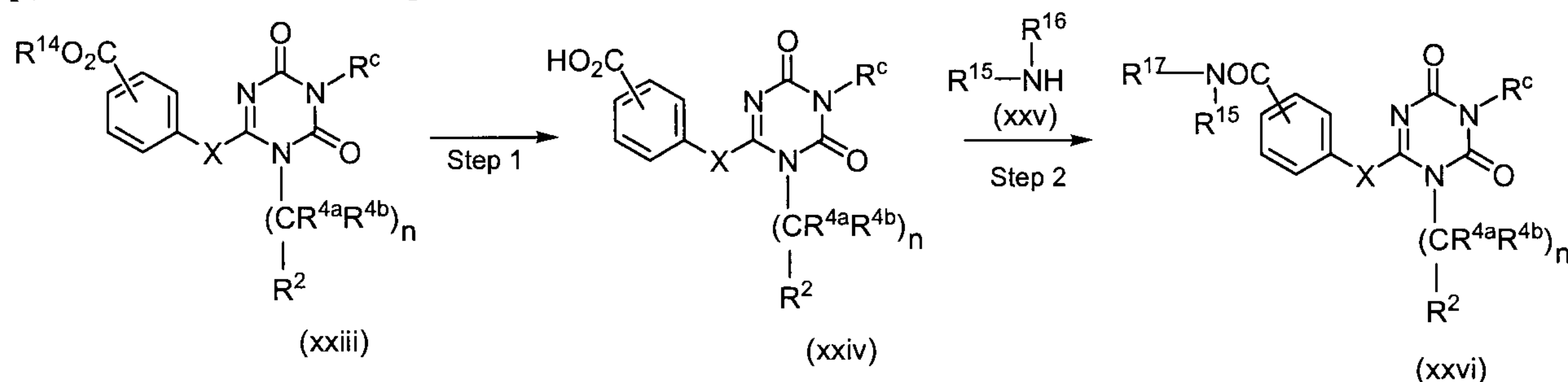
(Step 3)

The compound (xxii) can be manufactured by reacting the compound (xxi) with a solution, such as lithium hydroxide aqueous solution, sodium hydroxide aqueous solution and potassium hydroxide aqueous solution, in a solvent, such as methanol and ethanol, or in a mixture of such solvent and a solvent, such as THF and dioxane, etc.

[0184]

[Method F]

[Chemical Formula 94]



wherein R^{14} is substituted or unsubstituted alkyl, R^{15} and R^{16} are each independently substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted 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, u is an integer from 1 to 4 and other symbols are as defined above.

(Step 1)

The compound (xxiv) can be manufactured by reacting the compound (xxiii) obtained by the method A or B with a solution, such as lithium hydroxide aqueous solution, sodium hydroxide aqueous solution and potassium hydroxide aqueous solution, in a solvent, such as methanol and ethanol, or in a mixture of such solvent and a solvent, such as dioxane and THF, etc.

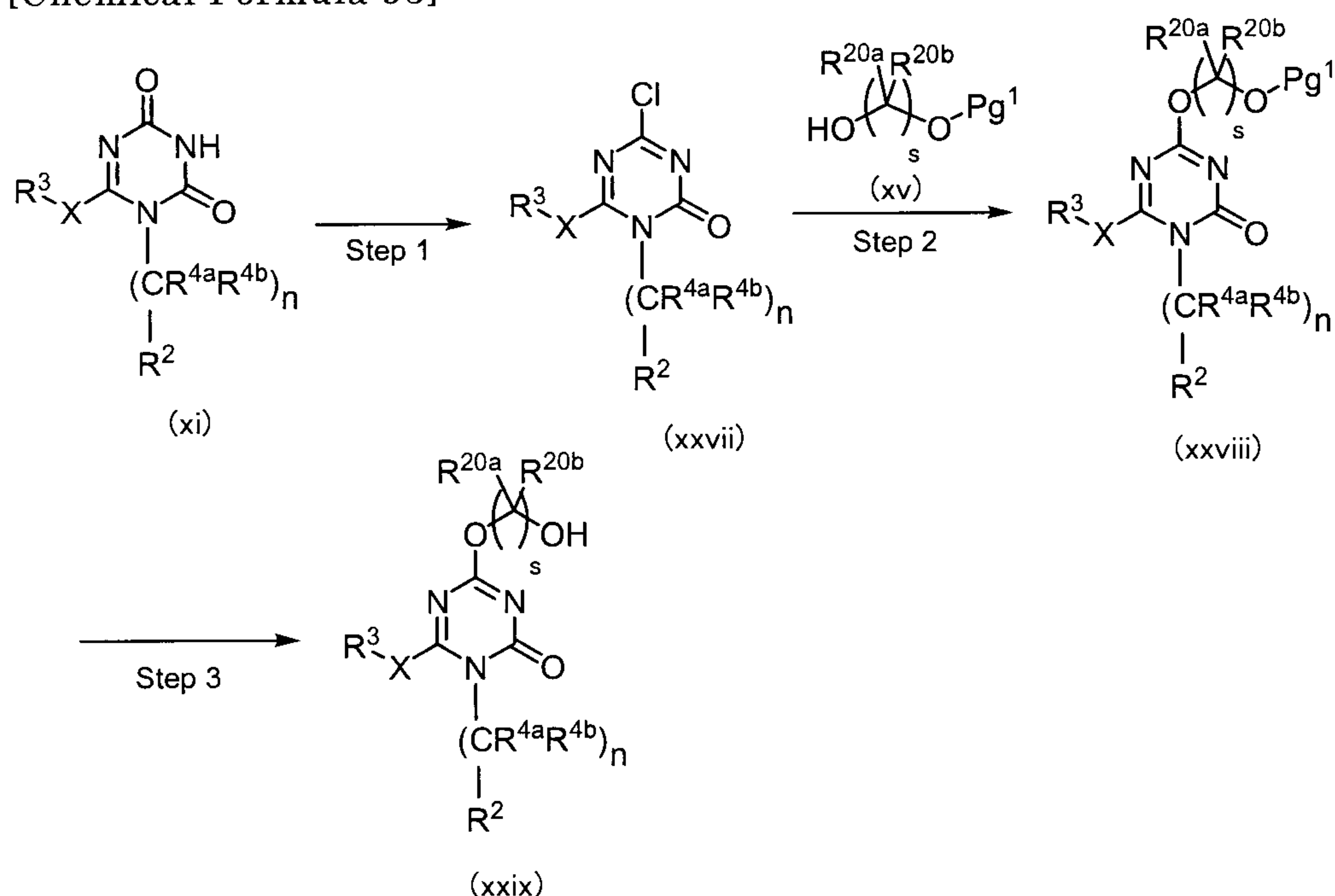
(Step 2)

The compound (xxvi) can be manufactured by reacting the compound (xxiv) with the compound (xxv) in a solvent, such as THF, DMF and NMP, in the presence of a condensing agent, such as 1-hydroxybenzotriazole, HOAt, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, HATU and PyBOP, and a base, such as triethylamine and diisopropylethylamine, etc.

[0185]

[Method G]

[Chemical Formula 95]



wherein Pg^1 is an appropriate hydroxy protecting group and other symbols are as defined above.

(Step 1)

The compound (xxvii) can be manufactured by reacting the compound (xi) obtained by the method B with a halogenating agent, such as phosphorous oxychloride and phosphorous oxybromide, under solvent-free conditions or in a solvent, such as toluene and tetrahydrofuran, at a temperature between 0 and 100°C, preferably at a temperature between 40 and 60°C.

(Step 2)

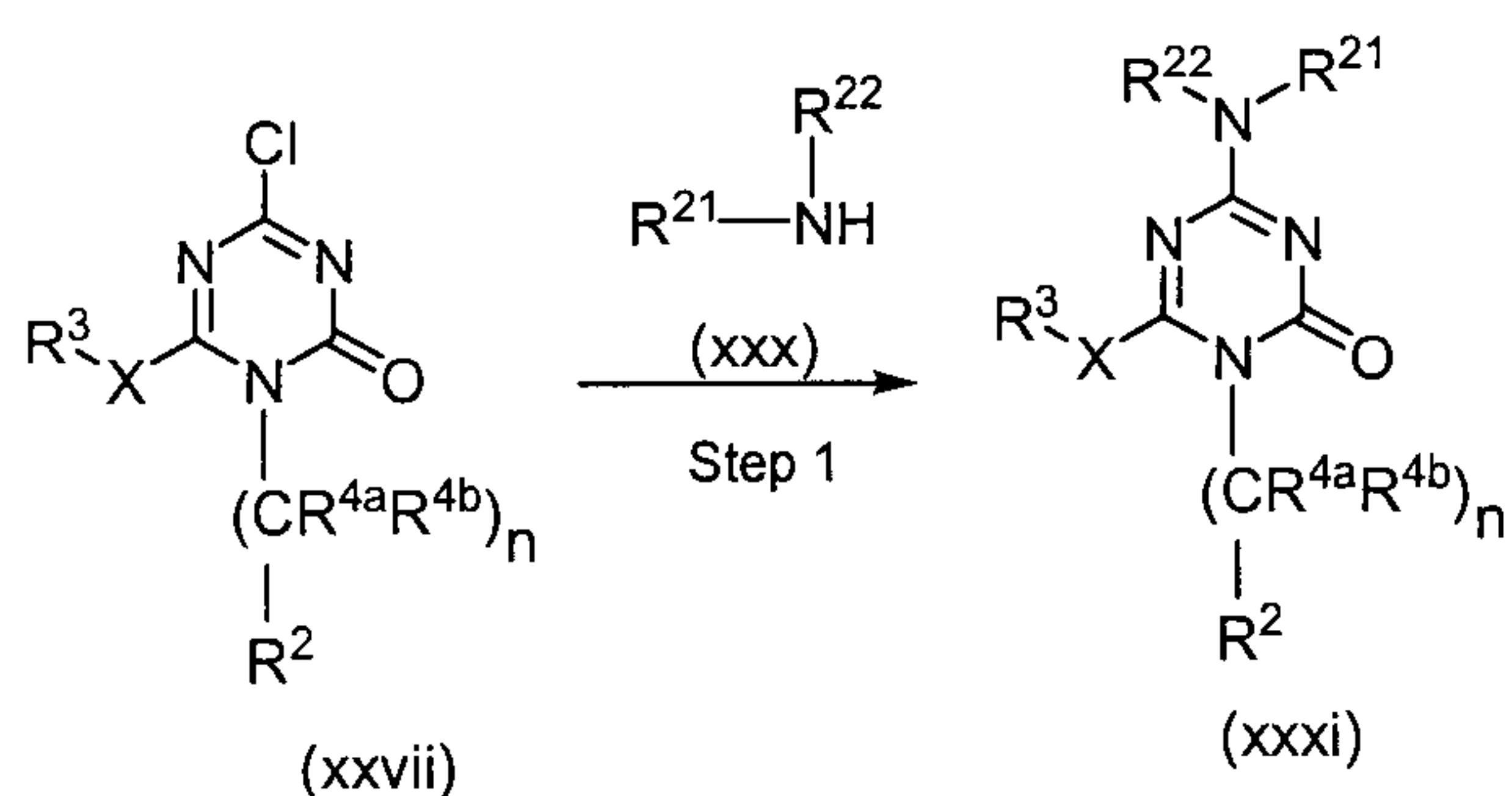
The compound (xxviii) can be manufactured by reacting a mixture of the alcohol (xv) whose one hydroxyl group is protected, such as 2-(tetrahydro-2H-pyran-2-yloxy) ethanol, and a solvent, such as THF, dioxane and DMF, with the compound (xv) after adding a base, such as sodium hydride and potassium t-butoxide.

(Step 3)

The compound (xxix) can be manufactured by reacting the compound (xxviii) with an acid, such as hydrochloric acid, p-toluenesulfonic acid or its hydrate and pyridine p-toluenesulfonate, in a solvent, such as methanol, etc.

[0186]

[Method H]



[Chemical Formula 96]

wherein R^{21} is substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted alkenyl,

substituted or unsubstituted 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^{22} is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted acyl, and other symbols are as defined above.

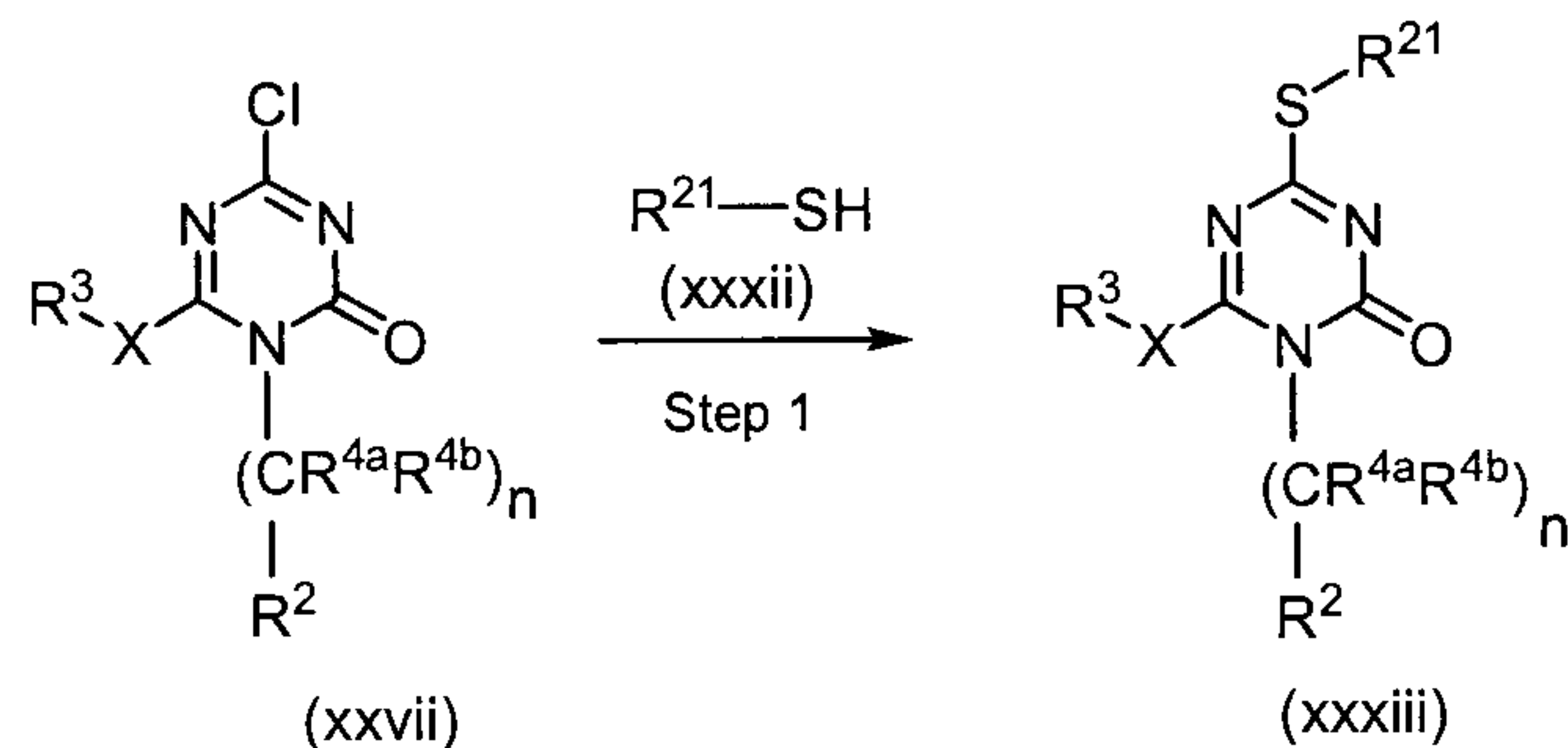
(Step 1)

The compound (xxxi) can be manufactured by reacting the compound (xxvii) obtained by the method G with the compound (xxx) in a solvent, such as THF and dioxane, etc.

[0187]

[Method I]

[Chemical Formula 97]



wherein the symbols in the formula are as defined above.

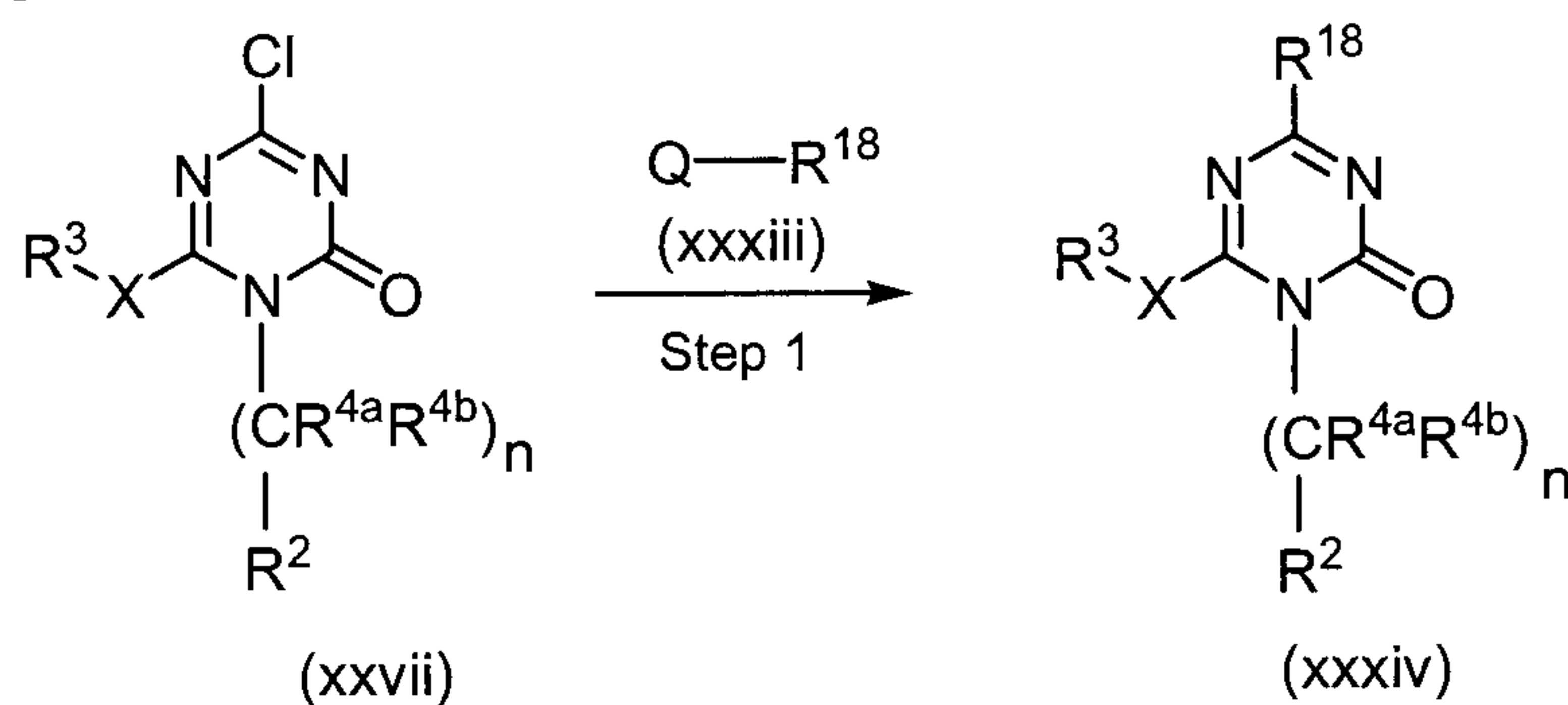
(Step 1)

The compound (xxxiii) can be manufactured by reacting the compound (xxvii) obtained by the method G with the compound (xxxii) in a solvent, such as THF and dioxane, after adding a base, such as sodium hydride, etc.

[0188]

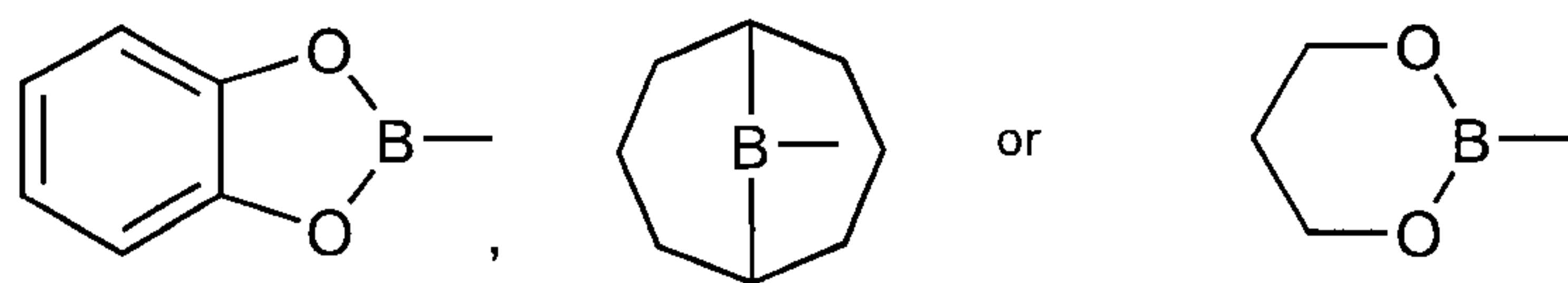
[Method J]

[Chemical Formula 98]



wherein R^{18} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl, Q is dihydroxyboran, dialkoxyboran or dialkylboran,

[Chemical Formula 99]



and other symbols are as defined above.

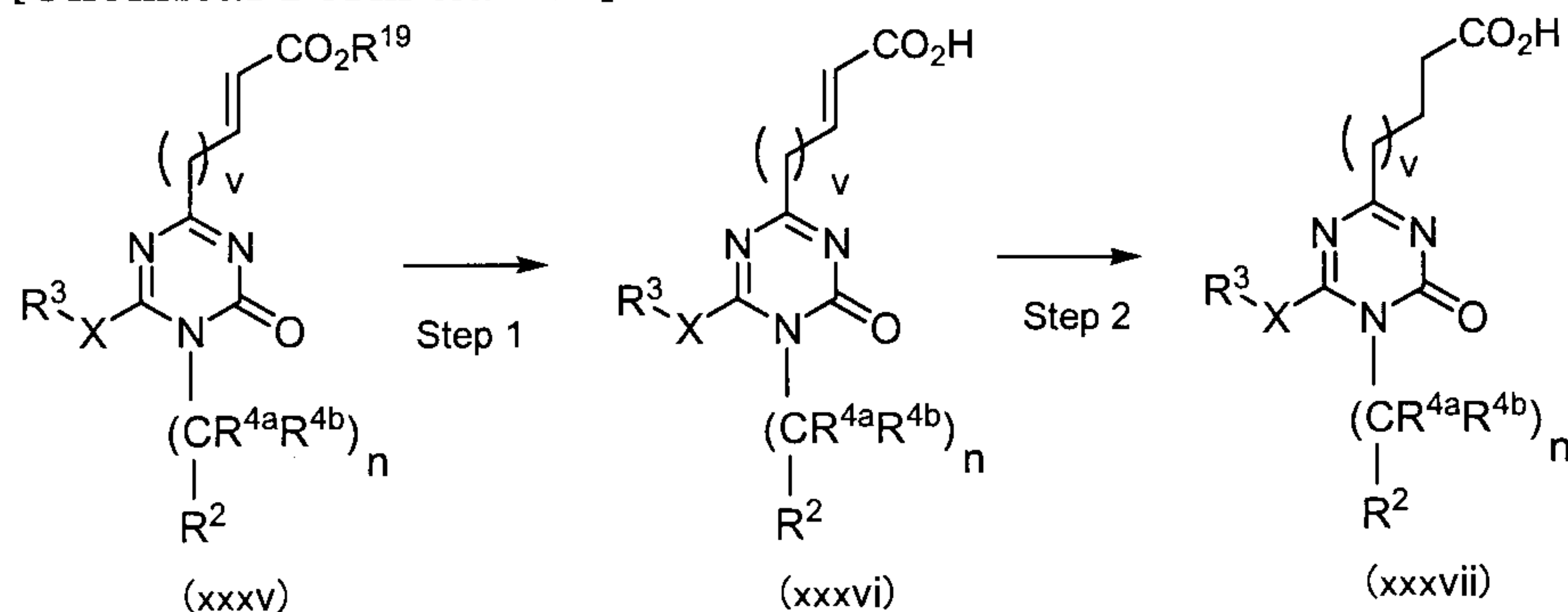
The compound (xxxiv) can be manufactured by reacting the compound (xxvii) obtained by the method G with the compound (xxxiii) in a solvent, such as THF and dioxane, in the presence of a palladium catalyst, and a solution, such as potassium carbonate, cesium carbonate and sodium carbonate aqueous solution, etc., at a temperature between 50°C

and reflux, preferably at reflux, or under microwave irradiation at a temperature of 120 and 200°C, preferably at a temperature between 130 and 150°C.

[0189]

[Method K]

[Chemical Formula 100]



wherein R¹⁹ is substituted or unsubstituted alkyl, v is an integer from 0 to 4 and other symbols are as defined above.

The compound (xxxvi) can be manufactured by hydrolyzing the compound (xxxv) using a mixture of an ethers solvent, such as dioxane, THF and DME, etc., an alcohols solvent, such as ethanol and methanol, or a solvent, such as DMF, DMA, DMSO and NMP, and water, as well as using a base, such as sodium hydroxide and lithium hydroxide. Although the preferable reaction temperature is room temperature, it can be increased if the reaction proceeds slowly.

[0190]

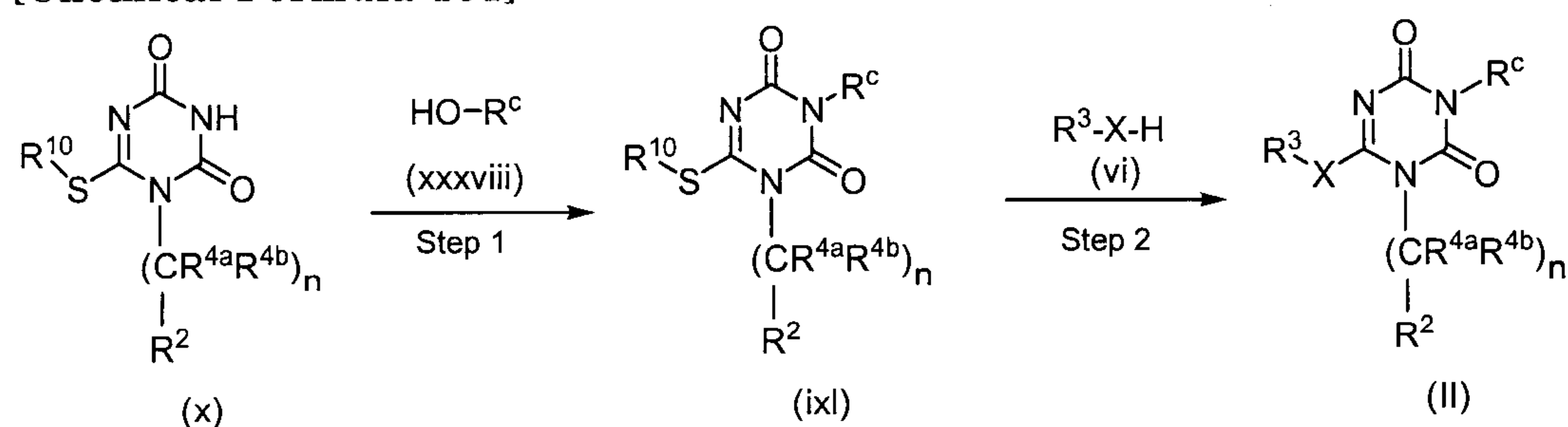
(Step 2)

The compound (xxxvii) can be obtained by dissolving the compound (xxxvi) in an alcohols solvent, such as methanol and ethanol, and performing catalytic reduction using a hydrogenation reactor (such as H-Cube [10%Pt-C, H₂ = 1 atm]) or a metallic catalyst, such as palladium-carbon, platinum oxide and chlorotris (triphenylphosphine) rodiumu (I), etc.

[0191]

[Method L]

[Chemical Formula 101]



wherein the symbols in the formula are as defined above.

(Step 1)

The compound (ix1) can be manufactured by reacting a mixture of the compound (x) obtained by the method B, the alcohol (xxxviii) and a solvent, such as THF and dioxane, with triphenylphosphine, etc., and diethyl azodicarboxylate, etc.

(Step 2)

The compound (II) can be manufactured by reacting the compound (ix1) with the compound (vi) in the presence of an acid, such as formic acid and acetic acid, at reflux.

Using the optically-active alcohol (xxxviii) enables to synthesize the optically-active compound (II).

The alcohol used as an intermediate (xxxviii) is commercially available or can be manufactured according to a method specified in the following documents:

Tetrahedron (1993), 49(11), 2325-44.

Chemical Communications (2008), (47), 6408-6410.

Tetrahedron (1990), 46(24), 8207-28.

Synlett (1994), (3), 199-200.

Bulletin of the Chemical Society of Japan (1994), 67(8), 2244-7

Canadian Journal of Chemistry (1996), 74, 1731-1737

Chemistry--A European Journal (2010), 16(2), 577-587

Bioorganic & Medicinal Chemistry Letters (2009), 19(21), 6196-6199.

Chemische Berichte (1985), 118(10), 3966-79.

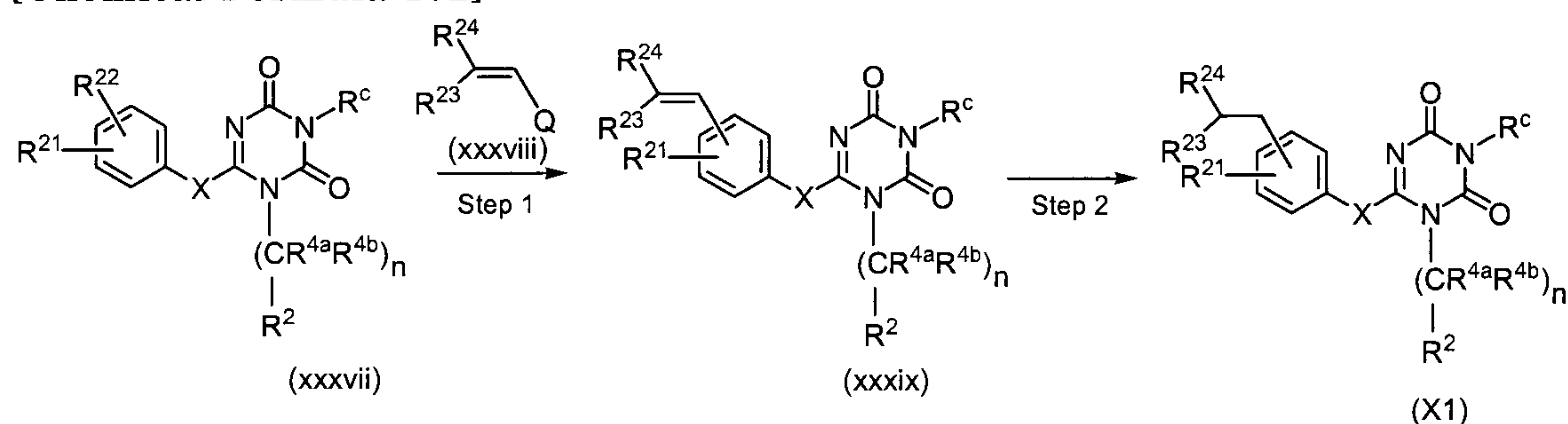
Tetrahedron: Asymmetry (1992), 3(4), 515-16.

Organic Letters (1999), 1(6), 957-959.

Chimia (1986), 40(5), 172-3.

[Method M]

[Chemical Formula 102]



wherein R²¹ is hydrogen, substituted or unsubstituted alkyl or substituted or unsubstituted alkoxy, etc., R²² is bromo or iodo, R²³ and R²⁴ are each independently substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkyl, a substituted or unsubstituted non-aromatic heterocyclic group, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl, and other symbols are as defined above.

(Step 1)

The compound (xxxix) can be manufactured by reacting the compound (xxxvii) obtained by the method from A to F or L with the compound (xxxviii) in a solvent, such as THF and dioxane, in the presence of a palladium catalyst and a solution, such as potassium carbonate, cesium carbonate and sodium carbonate aqueous solution, etc., at a temperature between 50°C and reflux, preferably at reflux, or under microwave irradiation at a temperature between 120 and 200°C, preferably at a temperature between 130 and 150°C.

[0192]

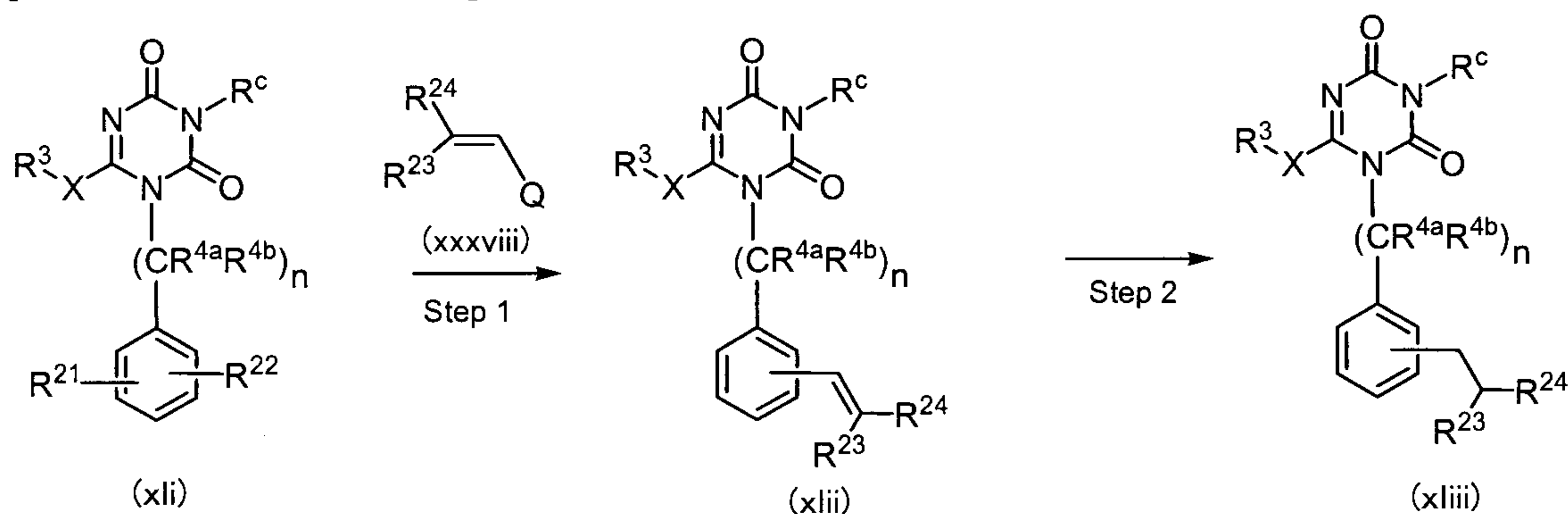
(Step 2)

The compound (x1) can be obtained by dissolving the compound (xxxix) in an alcohol solvent, such as methanol and ethanol, and performing catalytic reduction using a hydrogenation reactor (such as H-Cube (10%Pt-C, H₂=1 atm)) or a metallic catalyst, such as palladium-carbon, platinum oxide, chlorotris (triphenylphosphine) rhodium (I), etc.

[0193]

[Method N]

[Chemical Formula 103]



wherein the symbols in the formula are as defined above.

(Step 1)

The compound (xlii) can be manufactured by reacting the compound (xli) obtained by the method from A to F or L with the compound (xxxviii) in a solvent, such as THF and dioxane, in the presence of a palladium catalyst and a solution, such as potassium carbonate, cesium carbonate and sodium carbonate aqueous solution, etc., at a temperature between 50°C and reflux, preferably at reflux, or under microwave irradiation at a temperature between 120 and 200°C, preferably at a temperature between 130 and 150°C.

[0194]

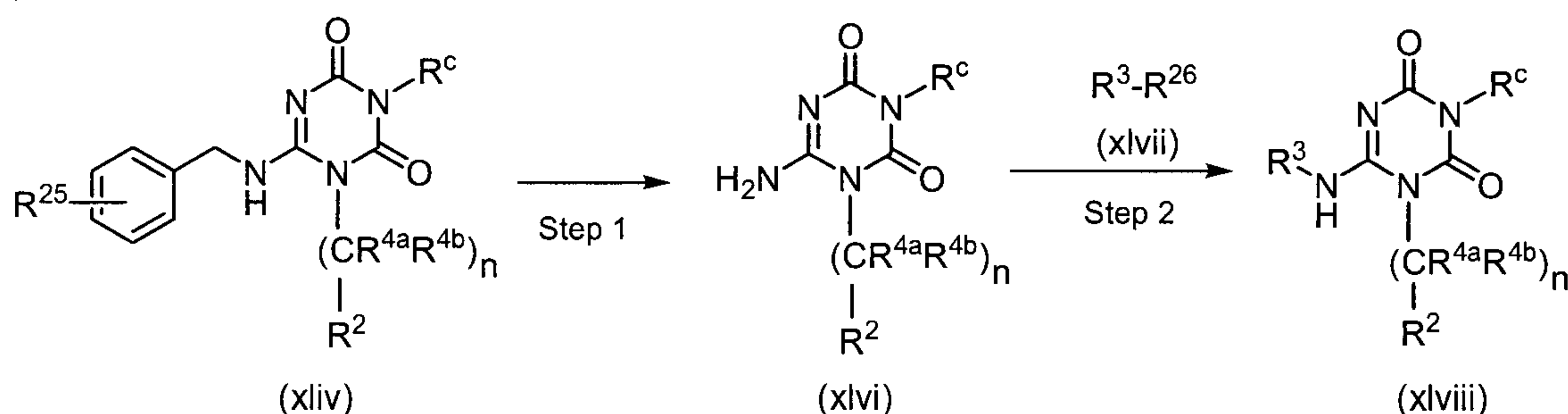
(Step 2)

The compound (xliii) can be obtained by dissolving the compound (xlii) in an alcohols solvent, such as methanol and ethanol, and performing catalytic reduction using a hydrogenation reactor (such as H-Cube (10%Pt-C, H₂=1 atm)) or a metallic catalyst, such as palladium-carbon, platinum oxide and chlorotris (triphenylphosphine) rhodium (I), etc.

[0195]

[Method O]

[Chemical Formula 104]



wherein R²⁵ is substituted or unsubstituted alkyl or substituted or unsubstituted alkoxy, R²⁶ is bromo or iodo, and other symbols are as defined above.

(Step 1)

The compound (xlvii) can be obtained from the compound (xliv) in the presence of Lewis acid or trifluoroacetic acid, etc., under solvent-free conditions or in an appropriate solvent at a temperature between 0°C and reflux.

[0196]

(Step 2)

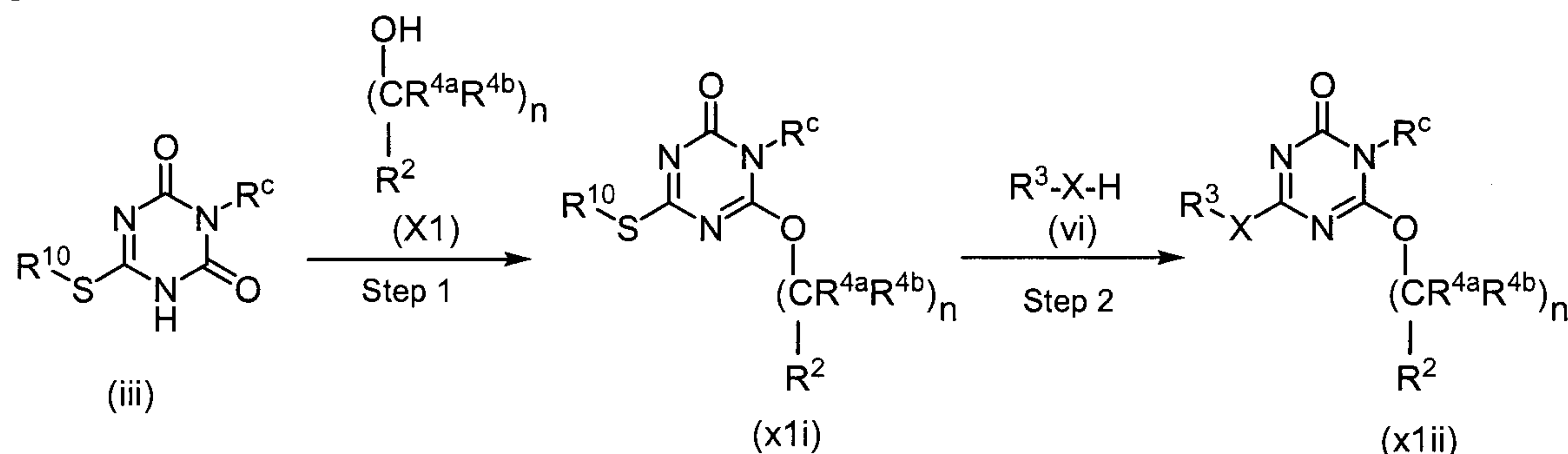
The compound (xlviii) can be manufactured by reacting the compound (xlvii) with the compound (xlviii) in a solvent, such as THF and dioxane, in the presence of a palladium catalyst and a solution, such as potassium carbonate, cesium carbonate and sodium carbonate aqueous solution, etc., at a temperature between 50°C and reflux, preferably at

reflux, or under microwave irradiation at a temperature of 120 and 200°C, preferably at a temperature between 130 and 150°C.

[0197]

[Method P]

[Chemical Formula 105]



wherein the symbols in the formula are as defined above.

(Step 1)

The compound (x1i) can be manufactured by reacting a mixture of the compound (iii) obtained by the method A, the alcohol (x1) and a solvent, such as THF and dioxane, with triphenylphosphine, etc., and diethyl azodicarboxylate, etc.

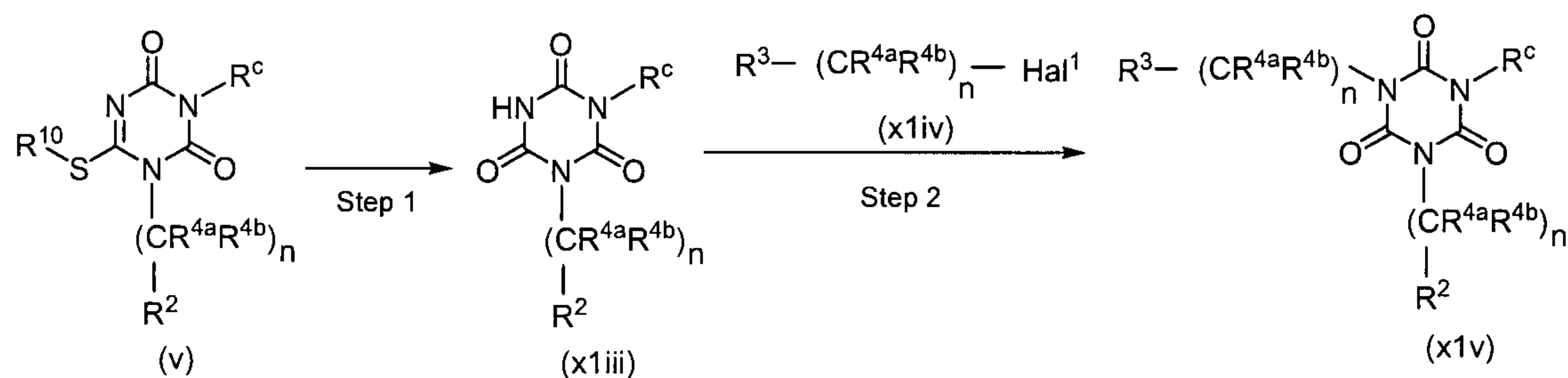
(Step 2)

The compound (x1ii) can be manufactured by reacting the compound (x1i) with the compound (vi) in the presence of formic acid and acetic acid, etc., at reflux.

[0198]

[Method Q]

[Chemical Formula 106]



wherein the symbols in the formula are as defined above.

(Step 1)

The compound (x1iii) can be manufactured by reacting the compound (v) obtained by the method A in a solvent, such as water, acetic acid and methanol, in the presence of an oxidation agent, such as hydrogen peroxide water and MCPBA, at a temperature between -20 and 100°C, preferably at room temperature.

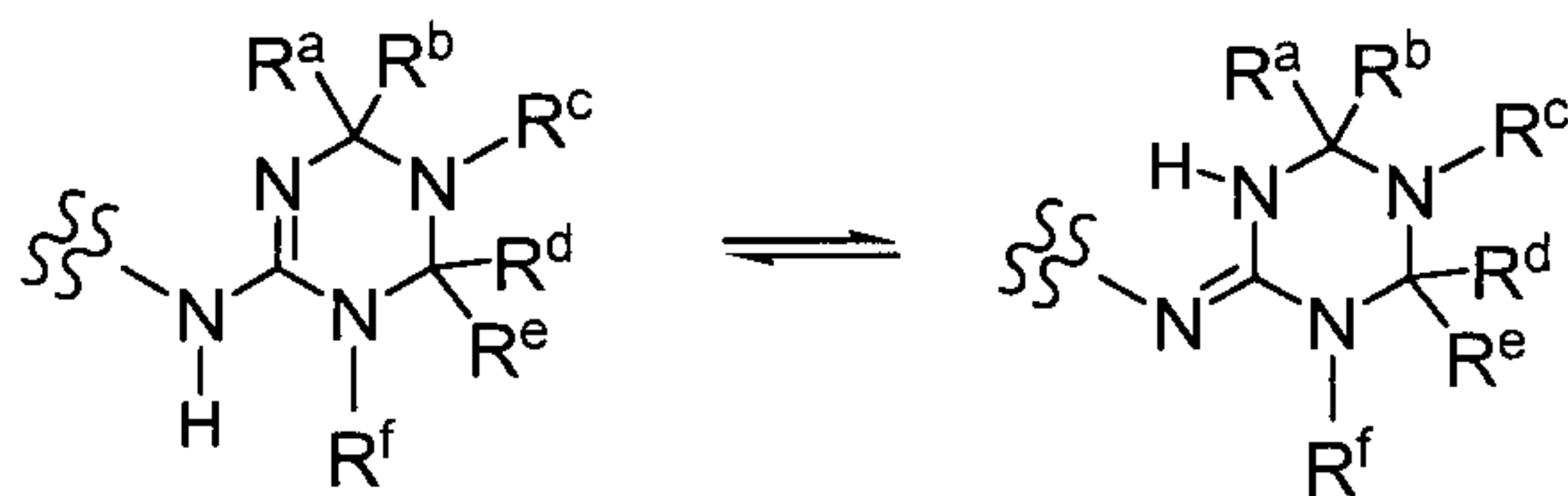
(Step 2)

The compound (x1v) can be manufactured by reacting the compound (x1iii) with the compound (x1iv) in a solvent, such as acetonitrile, acetone, DMF and DMSO, in the presence of a base, such as potassium carbonate and sodium carbonate, at a temperature between 50 °C and reflux, preferably at reflux.

[0199]

The compounds of this invention (I) are not limited to a specific isomer but include all possible isomers and racemates. For example, they include a tautomer as shown below. The compounds indicated by the formula (VIII), formula (IX) and formula (VII), etc., also include similar tautomers.

[Chemical Formula 107]



[0200]

In addition, one or more hydrogen atoms, carbon atoms or other atoms of the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like can be replaced by an isotope of the hydrogen atom, carbon atom or other atoms. Compounds of the formula (I), formula (VIII), formula (IX), formula (VII) and the like include all radiolabeled forms of compounds of the formula (I), formula (VIII), formula (IX), formula (VII) and the like. The “radiolabeled,” “radiolabeled form” and the like of the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like are encompassed by the present invention and useful as a research and/or diagnostic tool in metabolism pharmacokinetic studies and in binding assays. It is also useful for a medicament.

[0201]

Examples of isotopes that can be incorporated into the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, iodine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , ^{123}I and ^{36}Cl , respectively. Radiolabeled compounds of the present 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), formula (VIII), formula (IX), formula (VII) and the like with tritium gas in the presence of a suitable catalyst such as Pd/C, in the presence or absence of a base. Other suitable methods for preparing tritiated compounds can be found in *Isotopes in the Physical and Biomedical Sciences, Vol. 1, Labeled Compounds (Part A)* Chapter 6, (1987). ^{14}C -labeled compounds can be prepared by employing starting materials having a ^{14}C carbon.

[0202]

The compounds of the above formula (I), formula (VIII), formula (IX), formula (VII) and the like or its salt can be converted into hydrate or solvate thereof by known methods. Examples of suitable solvates are solvate with acetone, 2-butanol, 2-propanol, ethanol, ethyl acetate, tetrahydrofuran, diethyl ether or the like. For example, it includes a non-toxic and water-soluble hydrate or solvate such as a solvate with ethanol.

As pharmaceutically acceptable salt of the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like, examples include salts with alkaline metals (e.g. lithium, sodium and potassium), alkaline earth metals (e.g. calcium and barium), magnesium, transition metal (e.g. zinc and iron), ammonia, organic bases (e.g. trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, diethanolamine, ethylenediamine, pyridine, picoline, quinoline), and amino acids, and salts with inorganic acids (e.g. hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, hydrobromic acid, phosphoric acid and hydroiodic acid) and organic acids (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, citric acid, lactic acid, tartaric acid, oxalic acid, maleic acid, fumaric acid, mandelic acid, glutaric acid, malic acid, benzoic acid, phthalic acid, ascorbic acid, benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid and ethanesulfonic acid). Especially

preferable are salts with hydrochloric acid, sulfuric acid, phosphoric acid, tartaric acid, or methanesulfonic acid. These salts may be formed by usual methods.

The compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like or its pharmaceutically acceptable salt may form solvate such as hydrate, and/or crystalline polymorphism, and the present invention also includes such various kinds of solvate and crystalline polymorphism. The "solvate" includes a compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like which coordinate arbitrary number of solvent molecules such as water molecules. The compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like or its pharmaceutically acceptable salt can adhere water or form hydrate by absorbing water molecules after leaving in the atmosphere. Moreover, the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like or its pharmaceutically acceptable salt can form the crystalline polymorphism by recrystallization.

The compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like of the present invention or its pharmaceutically acceptable salt may form prodrug, and the present invention also includes such various kinds of prodrug. Prodrug is a derivative of the compound of the present invention having a group which can be chemically or metabolically decomposed and the one which becomes a pharmaceutically active compound of the present invention by solvolysis or physiological conditions in vivo. Prodrug includes a compound which converts into the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like by enzymatical oxidation, reduction, hydrolysis or the like under physiological conditions in a living body, and a compound which converts into the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like by hydrolyzing by stomach acid or the like. The method of selecting suitable prodrug derivatives and the method of manufacturing them are disclosed in Design of Prodrugs, Elsevier, and Amsterdam 1985. Prodrug itself may possess the activity.

When the compound of the formula (I), formula (VIII), formula (IX), formula (VII) and the like or its pharmaceutically acceptable salt has a hydroxy group, examples of the prodrug includes acyloxy derivatives and sulfonyloxy derivatives which can be manufactured by reacting a compound having a hydroxy group with a suitable acid halide, suitable acid anhydride, suitable sulfonyl chloride, suitable sulfonylanhydride and mixed anhydride. For example, CH_3COO^- , $\text{C}_2\text{H}_5\text{COO}^-$, t-BuCOO^- , $\text{C}_{15}\text{H}_{31}\text{COO}^-$, PhCOO^- , $(\text{m-NaOOCPh})\text{COO}^-$, $\text{NaOOCCH}_2\text{CH}_2\text{COO}^-$, $\text{CH}_3\text{CH}(\text{NH}_2)\text{COO}^-$, $\text{CH}_2\text{N}(\text{CH}_3)_2\text{COO}^-$, CH_3SO_3^- , $\text{CH}_3\text{CH}_2\text{SO}_3^-$, CF_3SO_3^- , $\text{CH}_2\text{FSO}_3^-$, $\text{CF}_3\text{CH}_2\text{SO}_3^-$, $\text{p-CH}_3\text{-O-PhSO}_3^-$, PhSO_3^- , and $\text{p-CH}_3\text{PhSO}_3^-$ are exemplified.

[0203]

The compound of the general formula (I), formula (VIII), formula (IX), formula (VII) and the like has an antagonistic effect 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, 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, complex regional pain 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, ABC syndrome, 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, pain of bladder such as overactive bladder, bladder inflammation etc., incontinence, pollakiuria, urinary urgency, cystatrophia, prostatic hypertrophy, prostatitis, prostate pain, detrusor hyperreflexia, urination disorder, nervous pollakiuria, chronic prostatitis, chronic cystitis, etc.

[0204]

"A pharmaceutical composition having an improving effect of urination disorder" includes "a pharmaceutical composition for treating overactive bladder", "a pharmaceutical composition for treating interstitial bladder cystitis" and the like.

[0205]

The compound of the present invention or the pharmaceutical composition of the present 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 encompassed by the present invention or the pharmaceutical composition encompassed by the present invention is advantageous because of its high P2X₃ receptor inhibitor activity in the presence of RSA, high metabolic stability, high oral absorption, good bioavailability, low clearance, long half-life, prolonged duration of action, low activity of hepatic enzyme inhibition, high unbound fraction in serum and/or high safety etc.

[0206]

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

[0207]

For use of the compound of the present 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.

[0208]

For the pharmaceutical composition of the present 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.

[0209]

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

[0210]

Means for administration of the present pharmaceutical composition may be selected depending on dosage form, patient's 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.

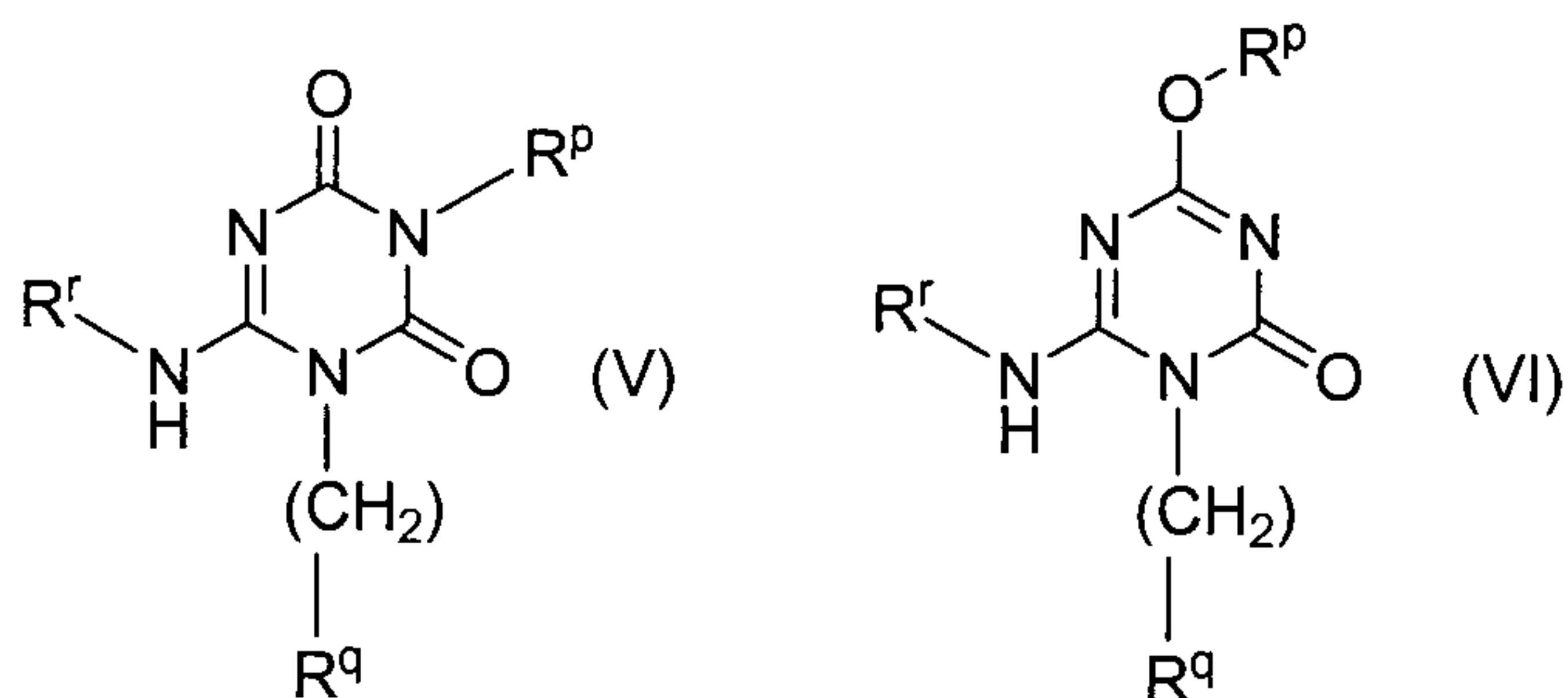
[0211]

Dose of the present compound in the present pharmaceutical composition can be determined depending on the choice of route for administration, patient's 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 vary 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 present invention may be administered once a day or in several times at a divided dosage in a day.

[0212]

In some embodiments of the present compounds, there is provided compounds of the following general formula (V) and the general formula (VI) having the following groups are provided:

[Chemical Formula 108]



wherein R^p, R^q, and R^r are selected from the following Tables 1 to 3.

[Table 1]

	R _p
R _{p1}	HO(CH ₂) ₂
R _{p2}	HO(CH ₂) ₃
R _{p3}	(HOCH ₂) ₂ CHCH ₂
R _{p4}	(HOCH ₂) ₂ C(Me)CH ₂
R _{p5}	HOCH ₂ CH(OH)CH ₂
R _{p6}	HOCO(CH ₂) ₂
R _{p7}	HOCOC(Me) ₂ CH ₂
R _{p8}	HOCOC(–CH ₂ CH ₂ –)CH ₂
R _{p9}	HOCOCH(Me)CH ₂
R _{p10}	HOCOCH(Me)CH(Me)
R _{p11}	HOCOC(CH ₂) ₃

[Table 2]

	R _q
R _{q1}	4-Me-Ph
R _{q2}	4-Et-Ph
R _{q3}	4-Cl-Ph
R _{q4}	4-Br-Ph
R _{q5}	cyclohexyl

[Table 3]

	Rr		Rr
Rr1	2-Me-benzothiazol-6-yl	Rr20	2-Piperidino-5-pyridyl
Rr2	2-Me-benzothiazol-5-yl	Rr21	5-c-PrCH ₂ O-2-pyridyl
Rr3	2-Me-benzimidazol-6-yl	Rr22	5-c-BuO-2-pyridyl
Rr4	2-Me-benthoiphen-5-yl	Rr23	5-PhO-2-pyridyl
Rr5	3-Me-benzisoxazol-6-yl	Rr24	5-Piperidino-2-pyridyl
Rr6	3-Me-2H-1,4-benzoxazin-7-yl	Rr25	2-c-BuO-3-Cl-5-pyridyl
Rr7	7-Me-1,8-naphthyridin-3-yl	Rr26	2-c-BuO-3-Me-5-pyridyl
Rr8	7-Me-quinolin-3-yl	Rr27	2-c-PentylO-3-Cl-5-pyridyl
Rr9	2-Me-quinazolin-6-yl	Rr28	2-c-PentylO-3-Me-5-pyridyl
Rr10	4-c-PrO-Ph	Rr29	2-PhO-3-Cl-5-pyridyl
Rr11	3-Me-4-c-PrO-Ph	Rr30	3-Me-4-i-PrCONH-Ph
Rr12	3-Cl-4-c-PrO-Ph	Rr31	3-Cl-4-i-PrCONH-Ph
Rr13	4-c-PrCH ₂ -Ph	Rr32	3-Me-4-i-PrNHCO-Ph
Rr14	3-Me-4-c-PrCH ₂ -Ph	Rr33	3-Cl-4-i-PrNHCO-Ph
Rr15	3-Cl-4-c-PrCH ₂ -Ph	Rr34	3-Me-4-i-PrSO ₂ NH-Ph
Rr16	4-c-BuCH ₂ -Ph	Rr35	3-Cl-4-i-PrSO ₂ NH-Ph
Rr17	3-MeO-4-c-BuCH ₂ -Ph	Rr36	3-Me-4-i-PrNHSO ₂ -Ph
Rr18	2-c-PrCH ₂ O-5-pyridyl	Rr37	3-Cl-4-i-PrNHSO ₂ -Ph
Rr19	2-PhO-5-pyridyl		

In the above tables, Me is methyl, Et is ethyl, i-Pr is isopropyl, c-Pr is cyclopropyl, c-Bu is cyclobutyl, and Ph is phenyl.

[0213]

The combination of Rp, Rq and Rr, i.e., (Rp, Rq, Rr), is any one of the following combinations:

(Rp, Rq, Rr) =
 (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, Rq1, Rr23), (Rp1, Rq1, Rr24),
 (Rp1, Rq1, Rr25), (Rp1, Rq1, Rr26), (Rp1, Rq1, Rr27), (Rp1, Rq1, Rr28), (Rp1, Rq1, Rr29), (Rp1, Rq1, Rr30),
 (Rp1, Rq1, Rr31), (Rp1, Rq1, Rr32), (Rp1, Rq1, Rr33), (Rp1, Rq1, Rr34), (Rp1, Rq1, Rr35), (Rp1, Rq1, Rr36),
 (Rp1, Rq1, Rr37), (Rp1, Rq2, Rr1), (Rp1, Rq2, Rr2), (Rp1, Rq2, Rr

Rq4,Rr22),(Rp2,Rq4,Rr23),(Rp2,Rq4,Rr24),(Rp2,Rq4,Rr25),(Rp2,Rq4,Rr26),(Rp2,Rq4,Rr27),
(Rp2,Rq4,Rr28),(Rp2,Rq4,Rr29),(Rp2,Rq4,Rr30),(Rp2,Rq4,Rr31),(Rp2,Rq4,Rr32),(Rp2,Rq4,Rr33),
(Rp2,Rq4,Rr34),(Rp2,Rq4,Rr35),(Rp2,Rq4,Rr36),(Rp2,Rq4,Rr37),(Rp2,Rq5,Rr1),(Rp2,Rq5,Rr2),
(Rp2,Rq5,Rr3),(Rp2,Rq5,Rr4),(Rp2,Rq5,Rr5),(Rp2,Rq5,Rr6),(Rp2,Rq5,Rr7),(Rp2,Rq5,Rr8),
(Rp2,Rq5,Rr9),(Rp2,Rq5,Rr10),(Rp2,Rq5,Rr11),(Rp2,Rq5,Rr12),(Rp2,Rq5,Rr13),(Rp2,Rq5,Rr14),
(Rp2,Rq5,Rr15),(Rp2,Rq5,Rr16),(Rp2,Rq5,Rr17),(Rp2,Rq5,Rr18),(Rp2,Rq5,Rr19),(Rp2,Rq5,Rr20),
(Rp2,Rq5,Rr21),(Rp2,Rq5,Rr22),(Rp2,Rq5,Rr23),(Rp2,Rq5,Rr24),(Rp2,Rq5,Rr25),(Rp2,Rq5,Rr26),
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(Rp2,Rq5,Rr33),(Rp2,Rq5,Rr34),(Rp2,Rq5,Rr35),(Rp2,Rq5,Rr36),(Rp2,Rq5,Rr37),(Rp3,Rq1,Rr1),
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(Rp4,Rq4,Rr25),(Rp4,Rq4,Rr26),(Rp4,Rq4,Rr27),(Rp4,Rq4,Rr28),(Rp4,Rq4,Rr29),(Rp4,Rq4,Rr30),
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(Rp4,Rq4,Rr37),(Rp4,Rq5,Rr1),(Rp4,Rq5,Rr2),(Rp4,Rq5,Rr3),(Rp4,Rq5,Rr4),(Rp4,Rq5,Rr5),
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,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,Rq2,Rr23),(Rp4,Rq2,Rr24),(Rp4,Rq2,Rr25),(Rp4,Rq2,Rr26),(Rp4,Rq2,Rr27),(Rp4,Rq2,Rr28),(Rp4,Rq2,Rr29),(Rp4,Rq2,Rr30),(Rp4,Rq2,Rr31),(Rp4,Rq2,Rr32),(Rp4,Rq2,Rr33),(Rp4,Rq2,Rr34),(Rp4,Rq2,Rr35),(Rp4,Rq2,Rr36),(Rp4,Rq2,Rr37),(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,Rq3,Rr23),(Rp4,Rq3,Rr24),(Rp4,Rq3,Rr25),(Rp4,Rq3,Rr26),(Rp4,Rq3,Rr27),(Rp4,Rq3,Rr28),(Rp4,Rq3,Rr29),(Rp4,Rq3,Rr30),(Rp4,Rq3,Rr31),(Rp4,Rq3,Rr32),(Rp4,Rq3,Rr33),(Rp4,Rq3,Rr34),(Rp4,Rq3,Rr35),(Rp4,Rq3,Rr36),(Rp4,Rq3,Rr37),(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,Rq4,Rr23),(Rp4,Rq4,Rr24),(Rp4,Rq4,Rr25),(Rp4,Rq4,Rr26),(Rp4,Rq4,Rr27),(Rp4,Rq4,Rr28),(Rp4,Rq4,Rr29),(Rp4,Rq4,Rr30),(Rp4,Rq4,Rr31),(Rp4,Rq4,Rr32),(Rp4,Rq4,Rr33),(Rp4,Rq4,Rr34),(Rp4,Rq4,Rr35),(Rp4,Rq4,Rr36),(Rp4,Rq4,Rr37),(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,Rq5,Rr23),(Rp4,Rq5,Rr24),(Rp4,Rq5,Rr25),(Rp4,Rq5,Rr26),(Rp4,Rq5,Rr27),(Rp4,Rq5,Rr28),(Rp4,Rq5,Rr29),(Rp4,Rq5,Rr30),(Rp4,Rq5,Rr31),(Rp4,Rq5,Rr32),(Rp4,Rq5,Rr33),(Rp4,Rq5,Rr34),(Rp4,Rq5,Rr35),(Rp4,Rq5,Rr36),(Rp4,Rq5,Rr37),(Rp5,Rq1,Rr1),(Rp5,Rq1,Rr2),(Rp5,Rq1,Rr3),(Rp5,Rq1,Rr4),(Rp5,Rq1,Rr5),(Rp5,Rq1,Rr6),(Rp5,Rq1,Rr7),(Rp5,Rq1,Rr8),(Rp5,Rq1,Rr9),(Rp5,Rq1,Rr10),(Rp5,Rq1,Rr11),(Rp5,Rq1,Rr12),(Rp5,Rq1,Rr13),(Rp5,Rq1,Rr14),(Rp5,Rq1,Rr15),(Rp5,Rq1,Rr16),(Rp5,Rq1,Rr17),(Rp5,Rq1,Rr18),(Rp5,Rq1,Rr19),(Rp5,Rq1,Rr20),(Rp5,Rq1,Rr21),(Rp5,Rq1,Rr22),(Rp5,Rq1,Rr23),(Rp5,Rq1,Rr24),(Rp5,Rq1,Rr25),(Rp5,Rq1,Rr26),(Rp5,Rq1,Rr27),(Rp5,Rq1,Rr28),(Rp5,Rq1,Rr29),(Rp5,Rq1,Rr30),(Rp5,Rq1,Rr31),(Rp5,Rq1,Rr32),(Rp5,Rq1,Rr33),(Rp5,Rq1,Rr34),(Rp5,Rq1,Rr35),(Rp5,Rq1,Rr36),(Rp5,Rq1,Rr37),(Rp5,Rq2,Rr1),(Rp5,Rq2,Rr2),(Rp5,Rq2,Rr3),(Rp5,Rq2,Rr4),(Rp5,Rq2,Rr5),(Rp5,Rq2,Rr6),(Rp5,Rq2,Rr7),(Rp5,Rq2,Rr8),(Rp5,Rq2,Rr9),(Rp5,Rq2,Rr10),(Rp5,Rq2,Rr11),(Rp5,Rq2,Rr12),(Rp5,Rq2,Rr13),(Rp5,Rq2,Rr14),(Rp5,Rq2,Rr15),(Rp5,Rq2,Rr16),(Rp5,Rq2,Rr17),(Rp5,Rq2,Rr18),(Rp5,Rq2,Rr19),(Rp5,Rq2,Rr20),(Rp5,Rq2,Rr21),(Rp5,Rq2,Rr22),(Rp5,Rq2,Rr23),(Rp5,Rq2,Rr24),(Rp5,Rq2,Rr25),(Rp5,Rq2,Rr26),(Rp5,Rq2,Rr27),(Rp5,Rq2,Rr28),(Rp5,Rq2,Rr29),(Rp5,Rq2,Rr30),(Rp5,Rq2,Rr31),(Rp5,Rq2,Rr32),(Rp5,Rq2,Rr33),(Rp5,Rq2,Rr34),(Rp5,Rq2,Rr35),(Rp5,Rq2,Rr36),(Rp5,Rq2,Rr37),(Rp5,Rq3,Rr1),(Rp5,Rq3,Rr2),(Rp5,Rq3,Rr3),(Rp5,Rq3,Rr4),(Rp5,Rq3,Rr5),(Rp5,Rq3,Rr6),(Rp5,Rq3,Rr7),(Rp5,Rq3,Rr8),(Rp5,Rq3,Rr9),(Rp5,Rq3,Rr10),(Rp5,Rq3,Rr11),(Rp5,Rq3,Rr12),(Rp5,Rq3,Rr13),(Rp5,Rq3,Rr14),(Rp5,Rq3,Rr15),(Rp5,Rq3,Rr16),(Rp5,Rq3,Rr17),(Rp5,Rq3,Rr18),(Rp5,Rq3,Rr19),(Rp5,Rq3,Rr20),(Rp5,Rq3,Rr21),(Rp5,Rq3,Rr22),(Rp5,Rq3,Rr23),(Rp5,Rq3,Rr24),(Rp5,Rq3,Rr25),(Rp5,Rq3,Rr26),(Rp5,Rq3,Rr27),(Rp5,Rq3,Rr28),(Rp5,Rq3,Rr29),(Rp5,Rq3,Rr30),(Rp5,Rq3,Rr31),(Rp5,Rq3,Rr32),(Rp5,Rq3,Rr33),(Rp5,Rq3,Rr34),(Rp5,Rq3,Rr35),(Rp5,Rq3,Rr36),(Rp5,Rq3,Rr37),(Rp5,Rq4,Rr1),(Rp5,Rq4,Rr2),(Rp5,Rq4,Rr3),(Rp5,Rq4,Rr4),(Rp5,Rq4,Rr5),(Rp5,Rq4,Rr6),(Rp5,Rq4,Rr7),(Rp5,Rq4,Rr8),(Rp5,Rq4,Rr9),(Rp5,Rq4,Rr10),(Rp5,Rq4,Rr11),(Rp5,Rq4,Rr12),(Rp5,Rq4,Rr13),(Rp5,Rq4,Rr14),(Rp5,Rq4,Rr15),(Rp5,Rq4,Rr16),(Rp5,Rq4,Rr17),(Rp5,Rq4,Rr18),(Rp5,Rq4,Rr19),(Rp5,Rq4,Rr20),(Rp5,Rq4,Rr21),(R

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Rp11,Rq3,Rr36),(Rp11,Rq3,Rr37),(Rp11,Rq4,Rr1),(Rp11,Rq4,Rr2),(Rp11,Rq4,Rr3),(Rp11,Rq4,Rr4),(Rp11,Rq4,Rr5),(Rp11,Rq4,Rr6),(Rp11,Rq4,Rr7),(Rp11,Rq4,Rr8),(Rp11,Rq4,Rr9),(Rp11,Rq4,Rr10),(Rp11,Rq4,Rr11),(Rp11,Rq4,Rr12),(Rp11,Rq4,Rr13),(Rp11,Rq4,Rr14),(Rp11,Rq4,Rr15),(Rp11,Rq4,Rr16),(Rp11,Rq4,Rr17),(Rp11,Rq4,Rr18),(Rp11,Rq4,Rr19),(Rp11,Rq4,Rr20),(Rp11,Rq4,Rr21),(Rp11,Rq4,Rr22),(Rp11,Rq4,Rr23),(Rp11,Rq4,Rr24),(Rp11,Rq4,Rr25),(Rp11,Rq4,Rr26),(Rp11,Rq4,Rr27),(Rp11,Rq4,Rr28),(Rp11,Rq4,Rr29),(Rp11,Rq4,Rr30),(Rp11,Rq4,Rr31),(Rp11,Rq4,Rr32),(Rp11,Rq4,Rr33),(Rp11,Rq4,Rr34),(Rp11,Rq4,Rr35),(Rp11,Rq4,Rr36),(Rp11,Rq4,Rr37),(Rp11,Rq5,Rr1),(Rp11,Rq5,Rr2),(Rp11,Rq5,Rr3),(Rp11,Rq5,Rr4),(Rp11,Rq5,Rr5),(Rp11,Rq5,Rr6),(Rp11,Rq5,Rr7),(Rp11,Rq5,Rr8),(Rp11,Rq5,Rr9),(Rp11,Rq5,Rr10),(Rp11,Rq5,Rr11),(Rp11,Rq5,Rr12),(Rp11,Rq5,Rr13),(Rp11,Rq5,Rr14),(Rp11,Rq5,Rr15),(Rp11,Rq5,Rr16),(Rp11,Rq5,Rr17),(Rp11,Rq5,Rr18),(Rp11,Rq5,Rr19),(Rp11,Rq5,Rr20),(Rp11,Rq5,Rr21),(Rp11,Rq5,Rr22),(Rp11,Rq5,Rr23),(Rp11,Rq5,Rr24),(Rp11,Rq5,Rr25),(Rp11,Rq5,Rr26),(Rp11,Rq5,Rr27),(Rp11,Rq5,Rr28),(Rp11,Rq5,Rr29),(Rp11,Rq5,Rr30),(Rp11,Rq5,Rr31),(Rp11,Rq5,Rr32),(Rp11,Rq5,Rr33),(Rp11,Rq5,Rr34),(Rp11,Rq5,Rr35),(Rp11,Rq5,Rr36),(Rp11,Rq5,Rr37).

[0214]

Following examples illustrate the present invention in more detail, but the present invention is not limited by 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]undeca-7-ene

NMP: N-methyl-2-pyrrolidone

HOAt: 1-hydroxy-7-azabenzotriazole

HATU: 2-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate

PyBOP: benzotriazole-1-yl-oxytrispyrrolidinophosphonium hexafluorophosphate

rt: room temperature

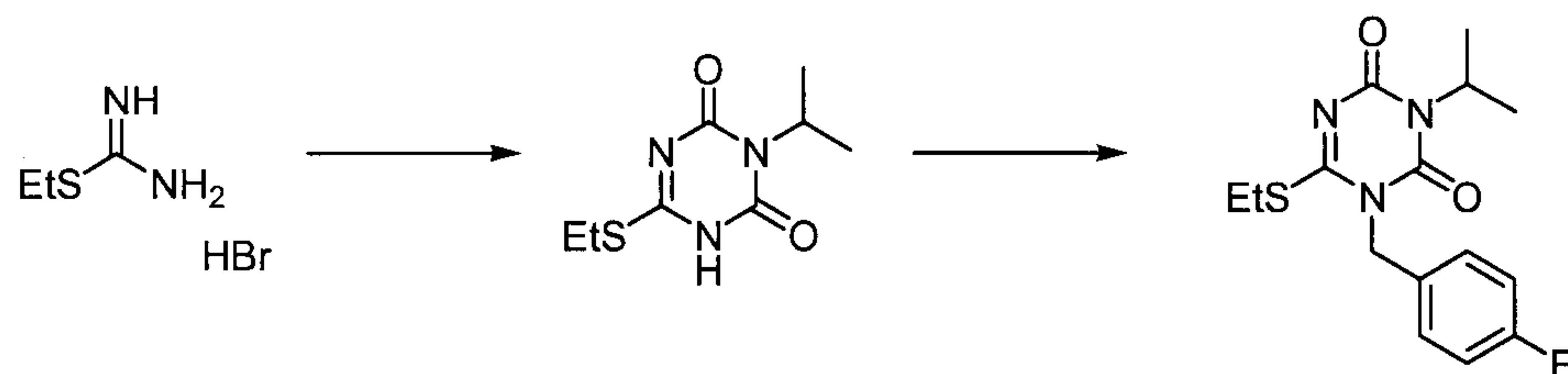
M: mol/L

[Example 1]

[0215]

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

[Chemical Formula 109]



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

reaction mixture were added 1,1'-carbonyldiimidazole (15.57 g, 96 mmol) and DBU (18.0 mL, 120 mmol) under ice-cooling, and the resulting mixture was stirred for additional 2 hours. To the reaction mixture was added 2mol/L hydrochloric acid (240 mL) under ice-cooling over 50 minutes, and the precipitated solid was filtered off. The resulting solid was dissolved in ethyl acetate, and the mixture was dried over anhydrous magnesium sulfate and concentrated in vacuo to give 6-(ethylthio)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (12.29 g, Yield: 71%) as pale 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)-dion (4.09 g, 19 mmol), potassium carbonate (7.88 g, 57 mmol) and acetonitrile (80 mL), 4-fluorbenzyl bromide (3.55 mL, 28.5 mmol) was added, and the resulting mixture was heated under reflux for 1.5 hours. To the mixture was added iced water (200 mL), and the mixture was extracted with ethyl acetate (100 mL). The extract was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by ethyl acetate and hexane to give 6-(ethylthio)-1-(4-fluorbenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (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).

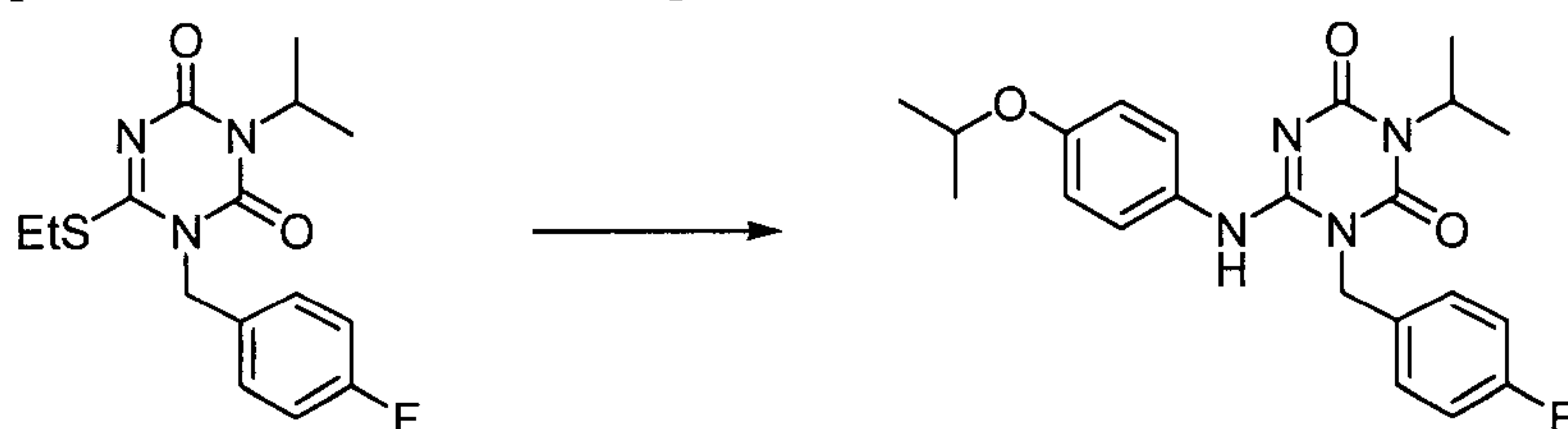
[Example 2]

[0216]

Preparation of

1-(4-fluorbenzyl)-6-(4-isopropoxyphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (I-0133)

[Chemical Formula 110]



A mixture of 6-(ethylthio)-1-(4-fluorbenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (0.323 g, 1 mmol), 4-isopropoxyaniline (0.907 g, 6 mmol) and 1-methyl-2-pyrrolidone (1 mL) was stirred at 230°C for 30 minutes under microwave irradiation. To the mixture was added water (100 mL), and the resulting mixture was extracted with ethyl acetate (100 mL). The extract was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by ethyl acetate and hexane to give

1-(4-fluorbenzyl)-6-(4-isopropoxyphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (0.21 g, Yield: 51%) as colorless solid.

Melting point: 176-177°C

¹H-NMR (δ 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).

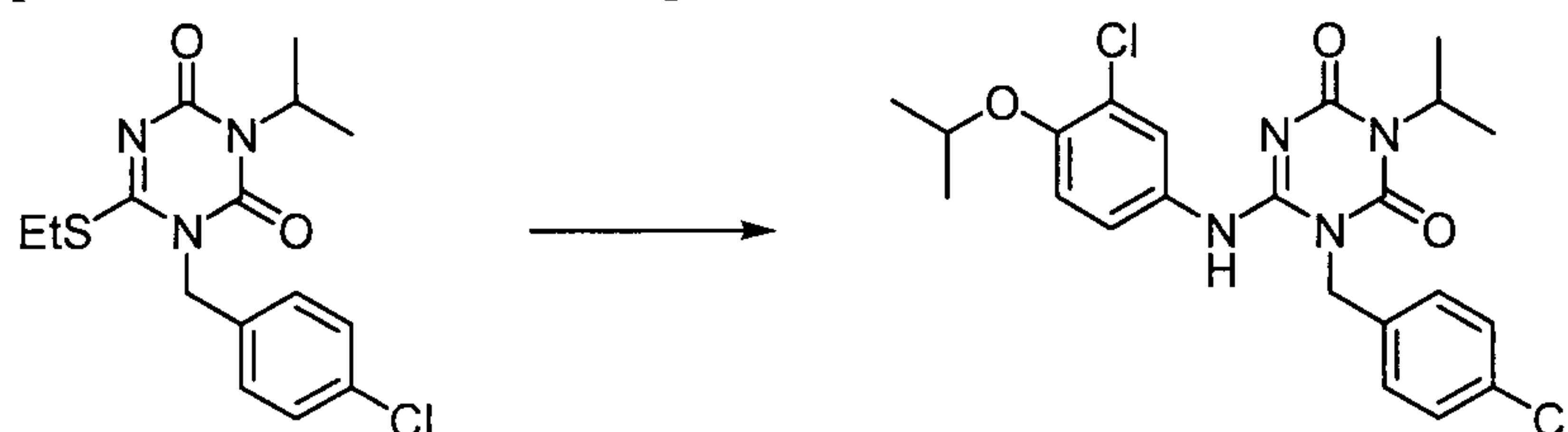
[Example 3]

[0217]

Preparation of

6-(3-chloro-4-isopropoxyphenylamino)-1-(4-chlorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (I-0228)

[Chemical Formula 111]



A mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (0.60 g, 1.78 mmol), 3-chloro-4-isopropoxyaniline (0.99 g, 5.3 mmol) and acetic acid (10 mL) was stirred at 90°C for 6 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL), and extracted with ethyl acetate (100 mL). The extract was washed by saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by diethyl ether and hexane to give 6-(3-chloro-4-isopropoxyphenylamino)-1-(4-chlorobenzyl)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (0.605 g, Yield: 73%) as colorless solid.

Melting point: 167°C

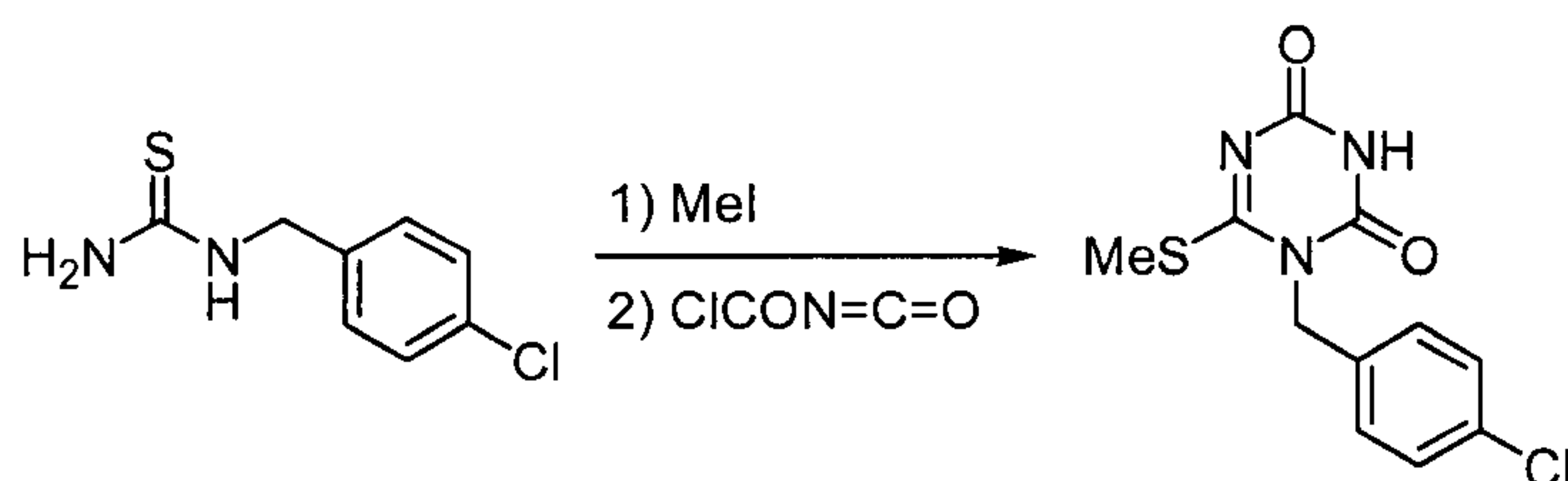
¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (6H, d, J=6.0 Hz), 1.34 (6H, d, J=6.9 Hz), 4.62 (1H, m), 4.83 (1H, sept, J=6.9 Hz), 5.18 (2H, brs), 7.12-7.15 (2H, m), 7.34-7.37 (3H, m), 7.43 (2H, d, J=8.7 Hz), 9.23 (1H, brs).

[Example 4]

[0218]

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

[Chemical Formula 112]



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. The 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 gradually under ice-cooling. The resulting mixture was stirred at room temperature for 1 hour. The precipitated solid was filtered

off and the resulting solid was washed by small amount on dichloromethane. The mixture was dried under reduced pressure to give 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dion (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).

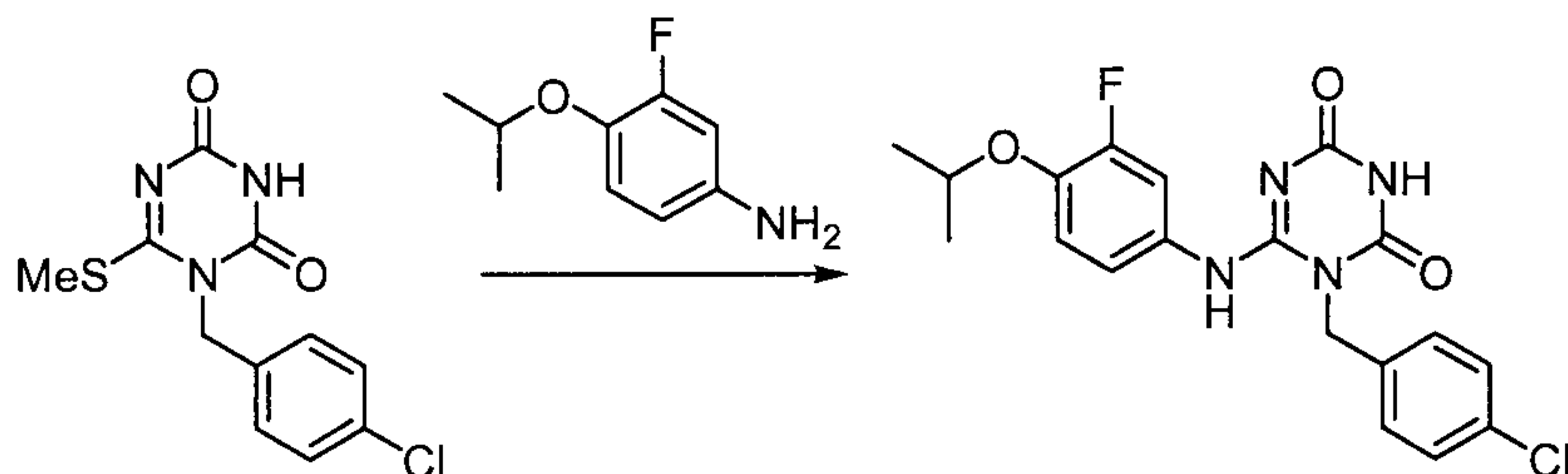
[Example 5]

[0219]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion (I-0269)

[Chemical Formula 113]



A mixture of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dion (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 under reflux for 8 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (300 mL), and the resulting mixture was extracted with ethyl acetate (100 mL). The extract was washed by saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue is precipitated by diisopropyl ether to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion (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).

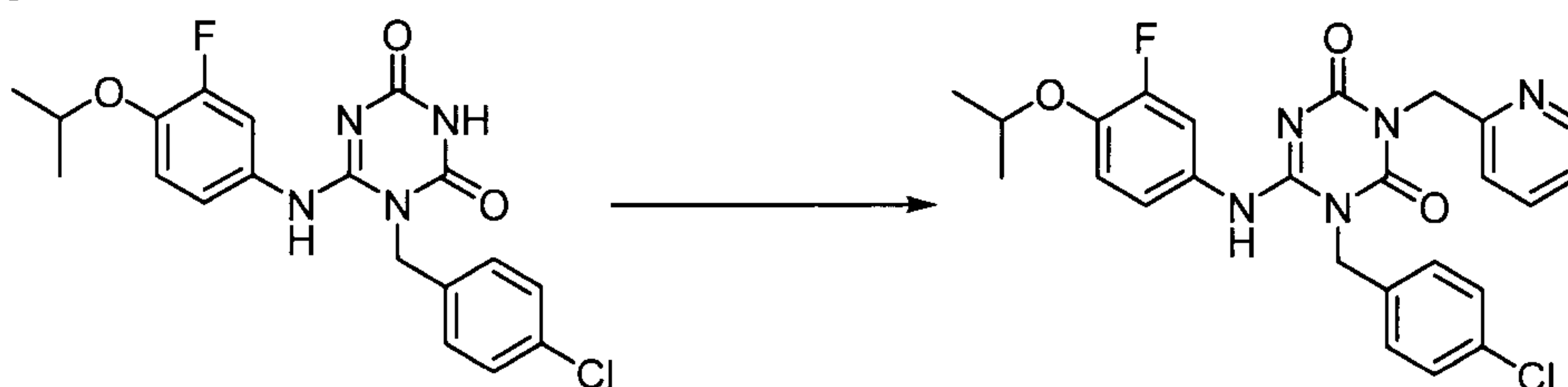
[Example 6]

[0220]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-pyridylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (I-300)

[Chemical Formula 114]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion (0.15 g, 0.37 mmol) and DMF (3 mL) was added potassium tert-butoxide (0.09 mg, 0.82 mmol) at room temperature and stirred 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. To the reaction mixture was added water (20 mL), and the mixture was extracted with ethyl acetate (20 mL×2). The extract was washed by brine (20 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-pyridylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (0.069 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).

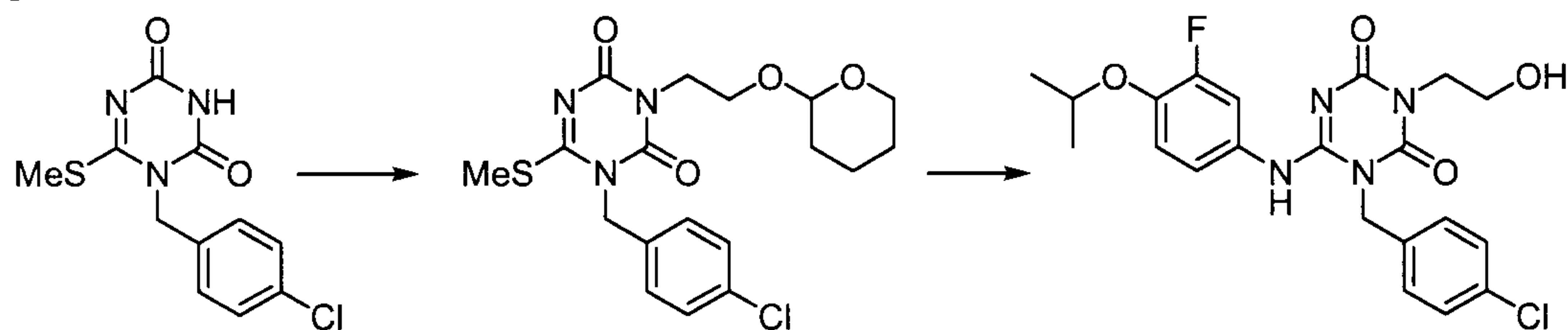
[Example 7]

[0221]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxyethyl)-1,3,5-triazine-2,4(1H,3H)-dion (I-0273)

[Chemical Formula 115]



To a mixture of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dion (0.28 g, 1 mmol), 2-(tetrahydro-2H-pyran-2-yloxy)ethanol (0.15 g, 1.000 mmol), triphenylphosphine (0.53 g, 2 mmol) and THF (5 mL) was gradually added diisopropyl azodicarboxylate (0.23 ml, 1.2 mmol) under ice-cooling, and then the mixture was stirred at room temperature for 3 hours. To the reaction mixture was added water (20 mL), and the resulting mixture was extracted with ethyl acetate (20 mL×2). The extract was washed by brine (20 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by 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)-dion (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-yloxy)ethyl]-1,3,5-triazine-2,4(1H,3H)-dion (0.32 g, 0.78 mmol), 3-fluoro-4-isopropoxyaniline (0.40 g, 2.4 mmol) and acetic acid (3 mL) was stirred at 100°C for 3 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL), and extracted with chloroform (100 mL×2). The extract was dried over anhydrous sodium sulphate and concentrated in

vacuo. The resulting residue was purified by silica gel column chromatography (methanol/chloroform), and The obtained residue was precipitated by 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)-dion (0.12 g, Yield: 33%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (6H, d, J=5.9 Hz), 1.96 (1H, t, J=5.9 Hz), 3.83 (2H, m), 4.05 (2H, m), 4.47 (1H, sept, J=5.9 Hz), 5.17 (2H, s), 6.48 (1H, m), 6.58 (1H, m), 6.97 (1H, m), 7.30 (2H, d, J=8.5), 7.47 (2H, d, J=8.5), 7.56 (1H, brs).

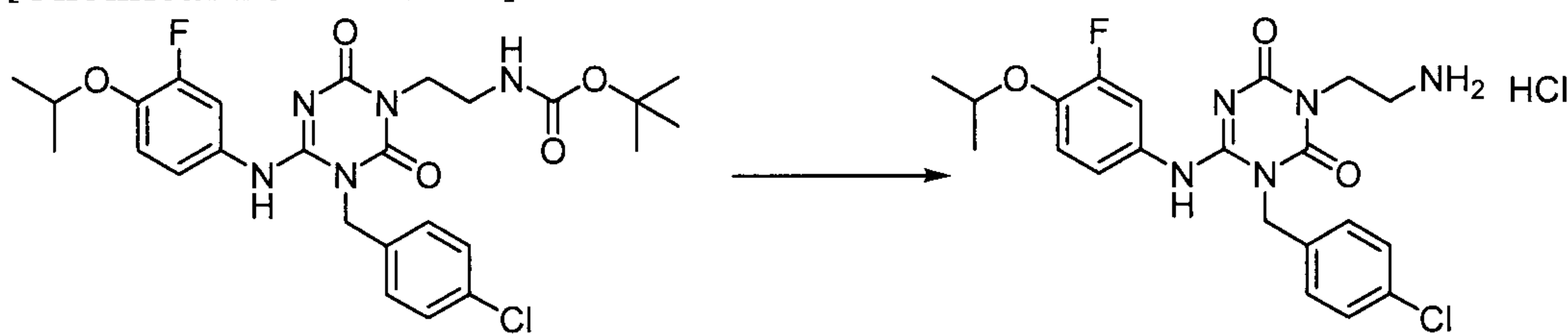
[Example 8]

[0222]

Preparation of

3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion hydrochloride (I-0290)

[Chemical Formula 116]



To

3-(2-t-butoxycarbonylaminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion (0.44 g, 0.8 mmol) was added 4mol/L hydrogen chloride in dioxane (5 mL) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The resulting precipitated solid was filtered off. The resulting solid was washed by diethyl ether and 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)-dion hydrochloride (0.31 g, Yield: 81%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 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).

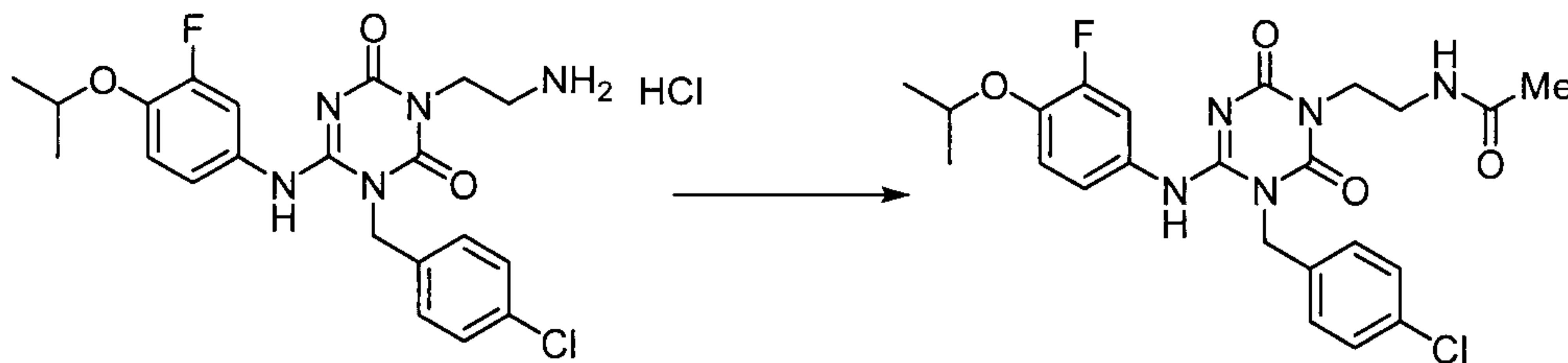
[Example 9]

[0223]

Preparation of

3-(2-acetylaminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion (I-0292)

[Chemical Formula 117]



To a mixture of

3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion hydrochloride (0.104 g, 0.22 mmol), triethylamine (0.074 mL, 0.54 mmol),

dimethylaminopyridine (0.026 g, 0.22 mmol) and THF (2 mL) was added dropwise acetyl chloride (0.023 mL, 0.32 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added water (20 mL), and the mixture was extracted with ethyl acetate (10 mL×2). The extract was washed by brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by 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)-dion (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), 4.00 (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).

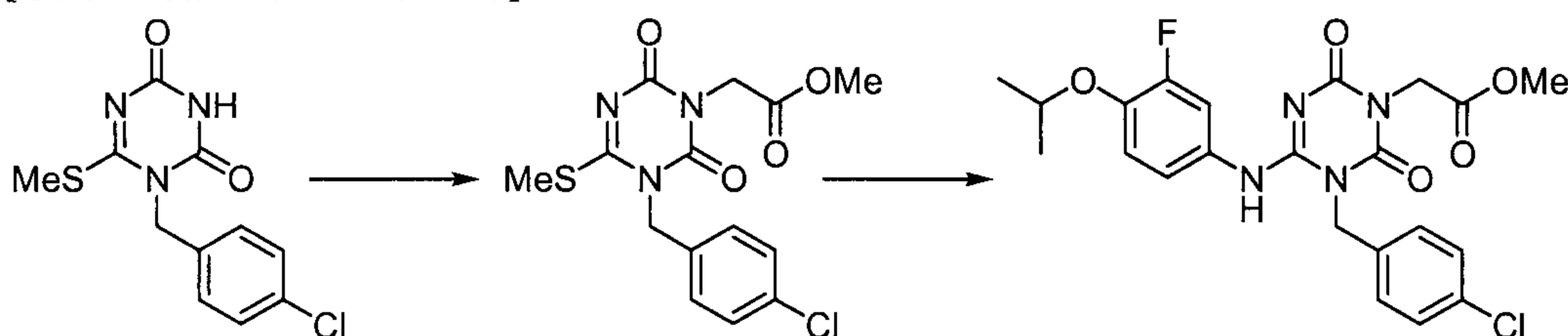
[Example 10]

[0224]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methoxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (I-0338)

[Chemical Formula 118]



To a mixture of 1-(4-chlorobenzyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dion (0.28 g, 1 mmol) and THF (3 mL) was added DBU (0.166 mL, 1.1 mmol), and the mixture was stirred at room temperature for 5 minutes. Further, methyl bromoacetate (0.104 mL, 1.1 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature for 3 hours. To the reaction mixture was added water (20 mL). The precipitated solid was filtered off, dried, and purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-3-(methoxycarbonylmethyl)-6-(methylthio)-1,3,5-triazine-2,4(1H,3H)-dion (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)-dion (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. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 mL), and the resulting mixture was extracted with ethyl acetate (10 mL). The extract was washed by brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane), and The obtained residue was precipitated by diisopropyl ether to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methoxycarbonylmethyl)-1,3,5

-triazine-2,4(1H,3H)-dion (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).

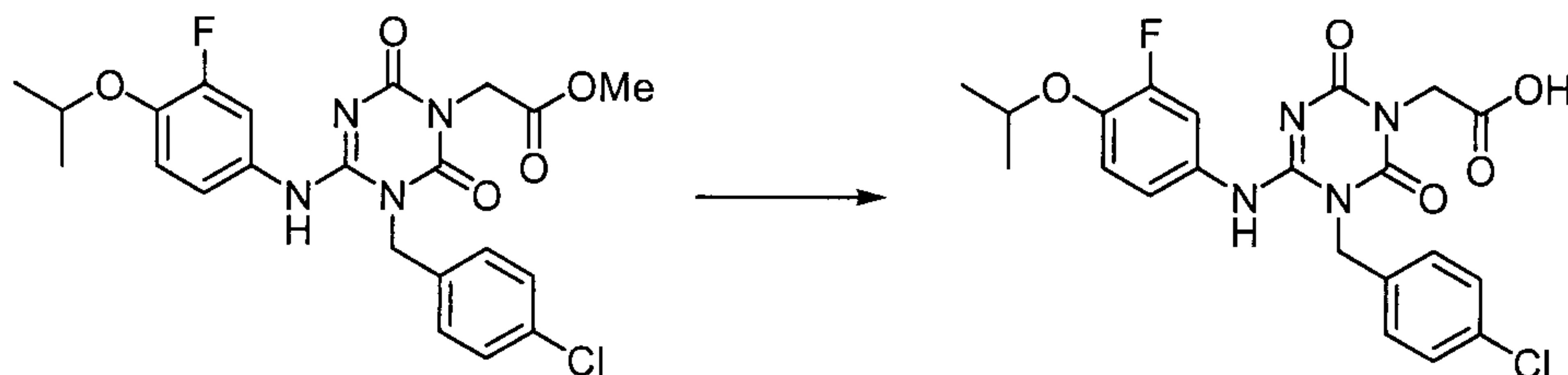
[Example 11]

[0225]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(hydroxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (I-0284)

[Chemical Formula 119]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methoxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (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 mixture was stirred at room temperature for 1hour. The pH of the mixture was adjusted with 2mol/L hydrochloric acid to a pH of less than 2. To the mixture was added brine (20 mL), and the resulting mixture was extracted by chloroform (10 mL×3). The extract was dried over anhydrous sodium sulphate and concentrated in vacuo. The obtained residue was precipitated by diethyl ether and hexane to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(hydroxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (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).

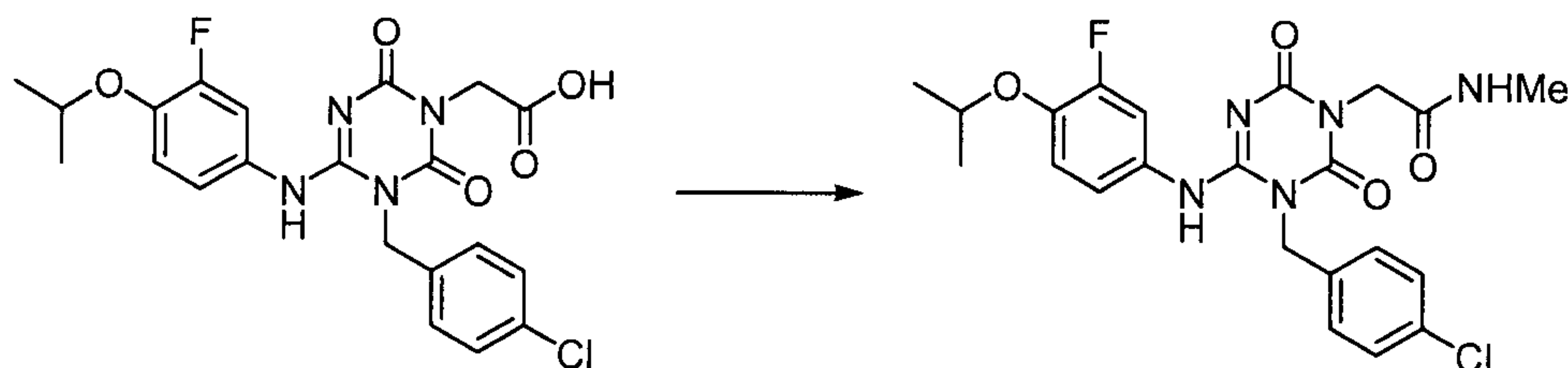
[Example 12]

[0226]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methylcarbamoylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (I-0294)

[Chemical Formula 120]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(hydroxycarbonylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (0.083 g, 0.19 mmol) and DMF (2 mL) were added methylamine hydrochloride (0.015 g, 0.21 mmol), 1-hydroxybenzotriazole hydrate (0.03 g, 0.2 mmol),

4-dimethylaminopyridine (0.002 g, 0.02 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.038 g, 0.2 mmol) and triethylamine (0.03 mL, 0.21 mmol), and the resulting mixture was stirred at 60°C for 4 hours. The reaction mixture was poured into water (20 mL), and extracted with ethyl acetate (20 mL). The extract was washed by brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by diisopropyl ether to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(methylcarbamoylmethyl)-1,3,5-triazine-2,4(1H,3H)-dion (0.076 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).

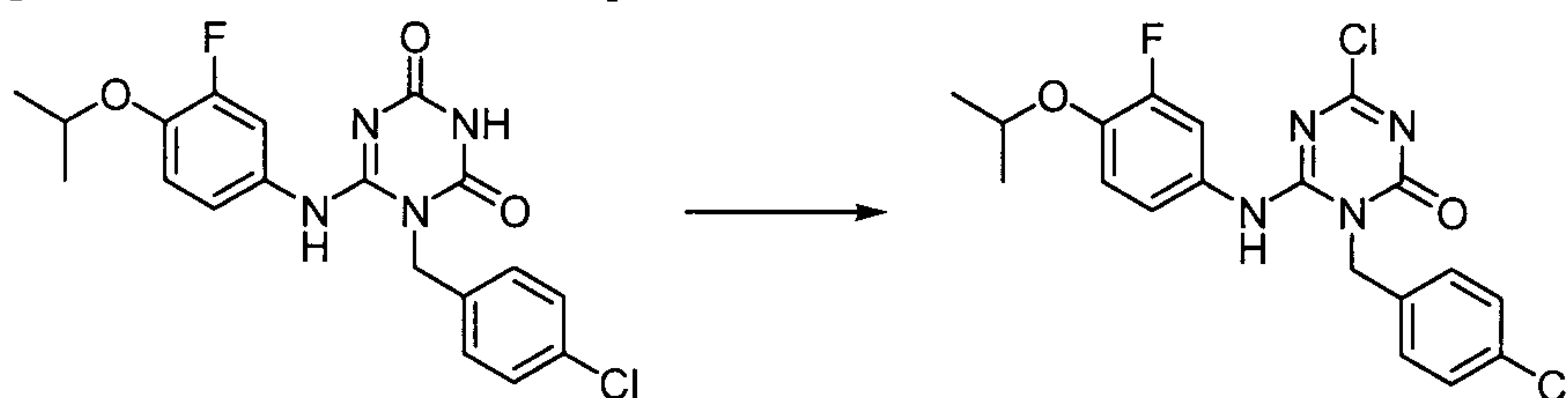
[Example 13]

[0227]

Preparation of

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

[Chemical Formula 121]



Phosphorus oxychloride (2.24 mL, 24 mmol) was added to 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2,4(1H,3H)-dion (0.486 g, 1.2 mmol), and the mixture was stirred at 50°C for 2 hours. The resulting mixture was concentrated in vacuo. The resulting residue was dissolved in ethyl acetate (30 mL), and the mixture was washed by saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL). The extract was dried over anhydrous sodium sulphate and concentrated in vacuo to give 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.57 g) as crude product.

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).

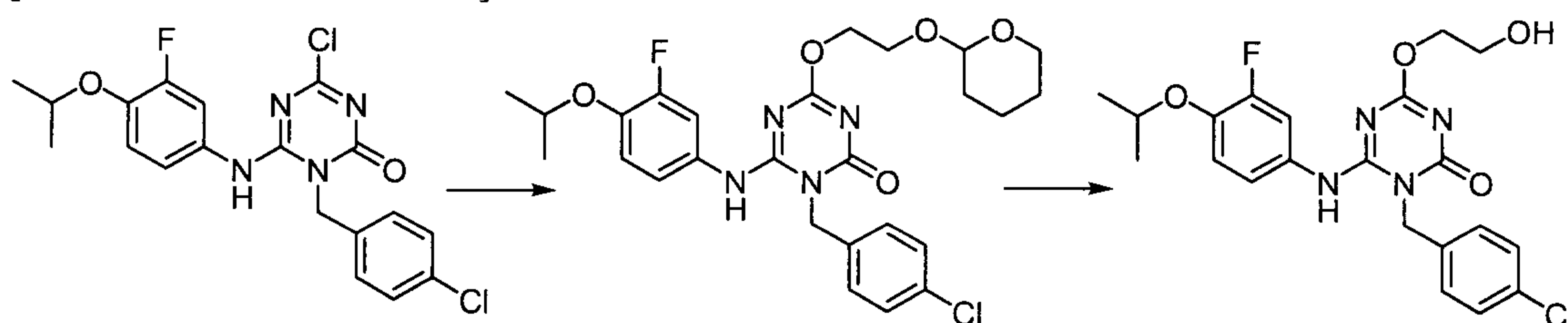
[Example 14]

[0228]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-4-(2-hydroxyethoxy)-1,3,5-triazine-2(1H)-one (I-0434)

[Chemical Formula 122]



To a mixture of 2-(tetrahydro-2H-pyran-2-yloxy)ethanol (0.17 mL, corresponding to 1.25 mmol) and THF (5.6 mL) was added 60% sodium hydride (0.05 g, 1.25 mmol), and the mixture was stirred at room temperature for 10 minutes. To the mixture was added a solution of crude

4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.224 g, corresponding to 0.5 mmol) in THF (2 mL) under ice-cooling, and the resulting mixture was stirred at room temperature for 5 hours. To the reaction mixture was added half-saturated aqueous ammonium chloride (50 mL), and the mixture was extracted with ethyl acetate (50 mL). The extract was washed by brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by 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 as 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 (0.08 g, 0.4 mmol), and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into half-saturated aqueous sodium bicarbonate (10 mL), and the mixture was extracted with ethyl acetate (20 mL). The extract was washed by brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (methanol/chloroform). The obtained residue was precipitated by 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).

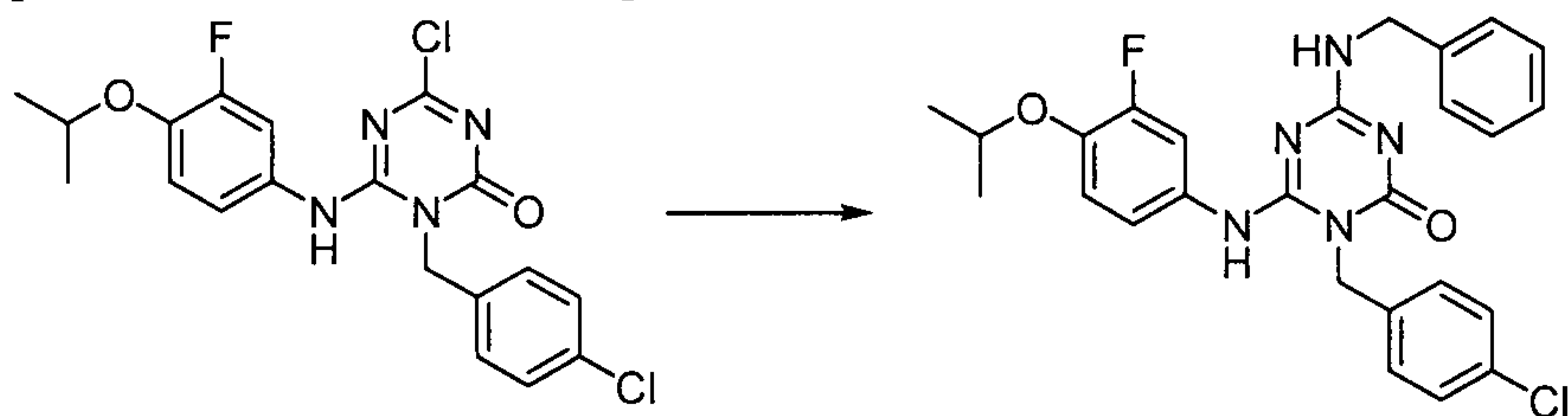
[Example 15]

[0229]

Preparation of

4-benzylamino-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (I-0435)

[Chemical Formula 123]



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, corresponding to 0.4 mmol) and THF (4.7 mL) was added benzylamine (0.108 mL, 1 mmol), and the mixture was stirred at room temperature for 6 hours. To the reaction mixture were added water (10 mL) and ethyl acetate (10 mL), and the precipitated solid was filtered off. The resulting solid was washed by 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).

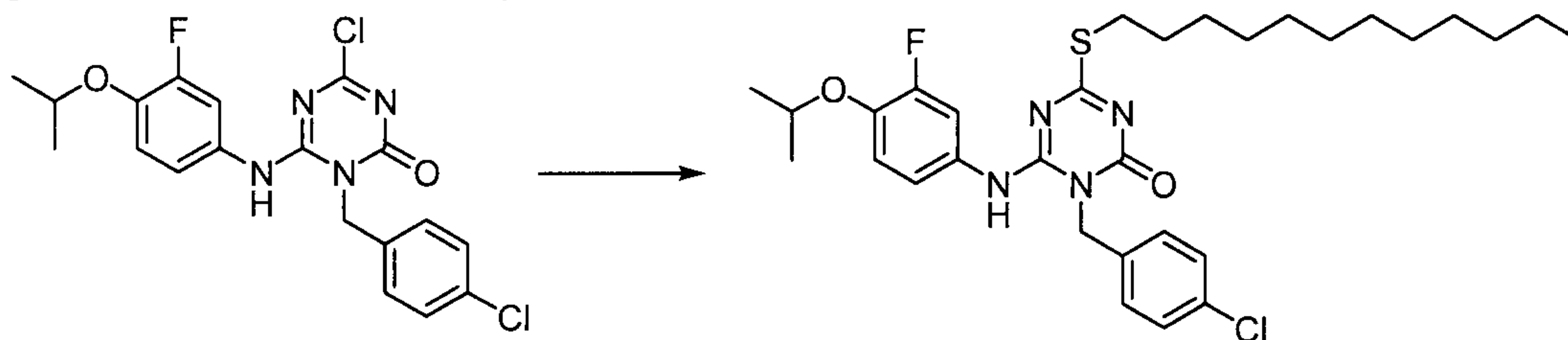
[Example 16]

[0230]

Preparation of

1-(4-chlorobenzyl)-4-(dodecylthio)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (I-0436)

[Chemical Formula 124]



To a mixture of 1-dodecanthiol (0.24 mL, 1.0 mmol) and THF (4.8 mL) was added 60% sodium hydride (0.045 g, 1.0 mmol), and the mixture was stirred at room temperature for 10 minutes. To the resulting mixture was added a solution of crude 4-chloro-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.19 g, corresponding to 0.4 mmol) in THF (2 mL) under ice-cooling, and the mixture was stirred at 50°C for 5 hours. To the reaction mixture was added half-saturated aqueous ammonium chloride (50 mL), and the mixture was extracted with ethyl acetate (50 mL). The extract was washed by brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by hexane to give

1-(4-chlorobenzyl)-4-(dodecylthio)-6-(3-fluoro-4-isopropoxyphenylamino)-1,3,5-triazine-2(1H)-one (0.092 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).

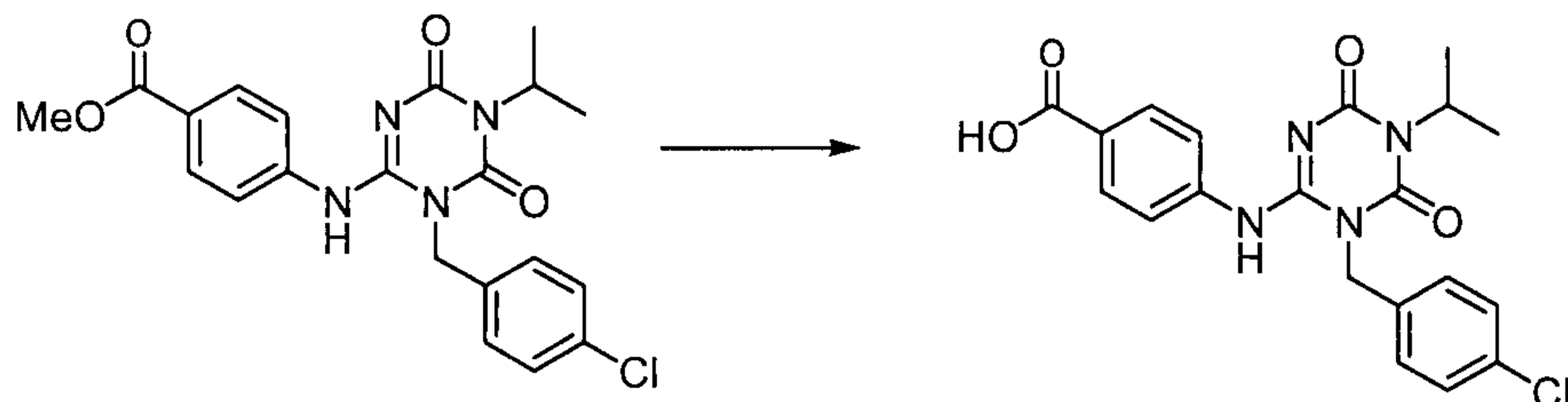
[Example 17]

[0231]

Preparation of

1-(4-chlorobenzyl)-6-(4-hydroxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (I-0252)

[Chemical Formula 125]



To a mixture of

1-(4-chlorobenzyl)-6-(4-methoxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (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 mixture was stirred at room temperature for 8 hours. The reaction mixture was poured into water (50 mL), adjusted with 2mol/L hydrochloric acid to a pH of less than 3, and extracted with ethyl acetate (50 mL×2). The extract was washed by brine (50 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting solid was washed by diethyl ether to give 1-(4-chlorobenzyl)-6-(4-hydroxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (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).

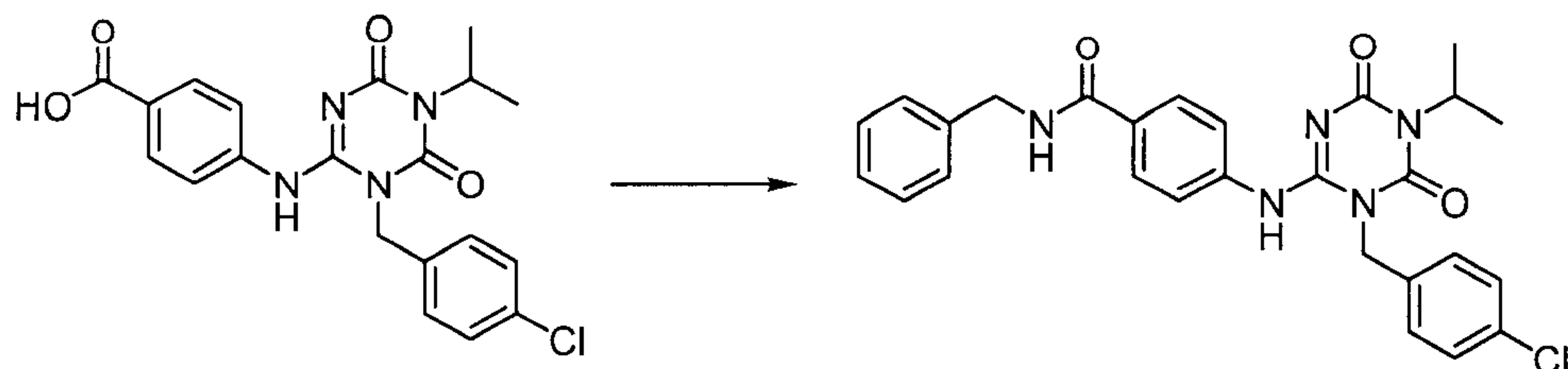
[Example 18]

[0232]

Preparation of

1-(4-chlorobenzyl)-6-[4-(N-benzylcarbonyl)phenylamino]-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (I-0259)

[Chemical Formula 126]



To a mixture of

1-(4-chlorobenzyl)-6-(4-hydroxycarbonylphenylamino)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dion (0.08 g, 0.19 mmol) and THF (2 mL) were added benzylamine (0.023 mL, 0.21 mmol), 1-hydroxybenzotriazole (0.03 g, 0.21 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.041 g, 0.2 mmol) and triethylamine (0.03 mL, 0.21 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into water (30

mL), and the mixture was extracted with ethyl acetate (30 mL). The extract was washed by brine (30 mL), dried over anhydrous sodium sulphate, concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by diethyl ether to give 1-(4-chlorobenzyl)-6-[4-(N-benzylcarbamoyl)phenylamino]-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.07 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).

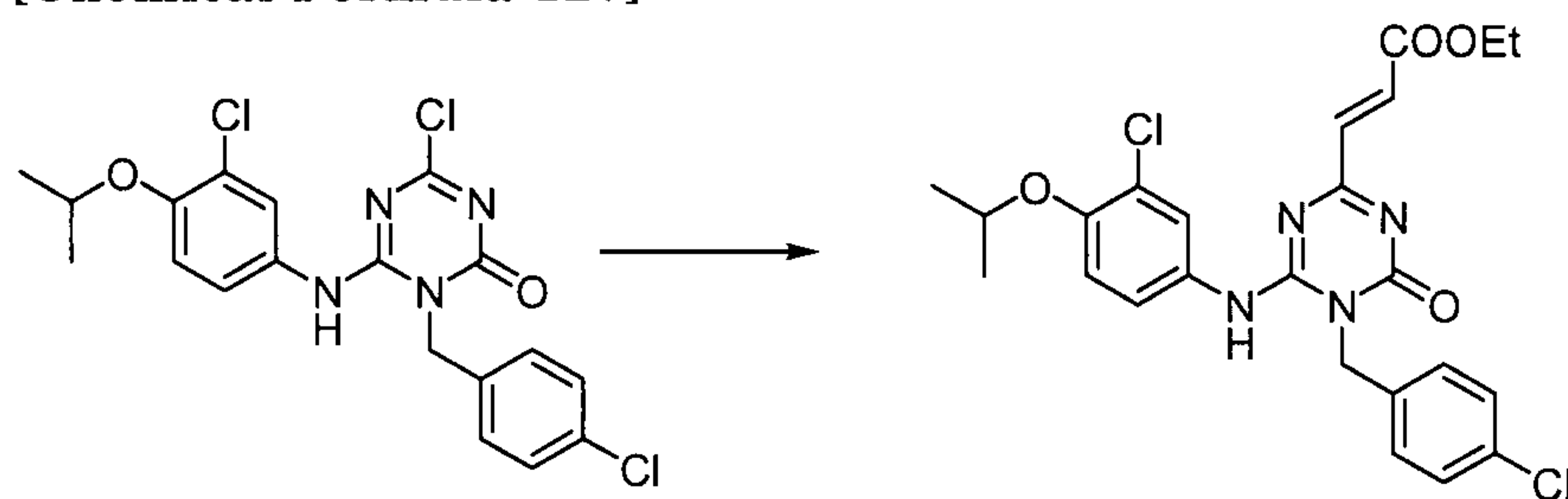
[Example 19]

[0233]

Preparation of

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-4-hydroxycarbonylethyl-1,3,5-triazine-2(1H)-one (I-0579)

[Chemical Formula 127]

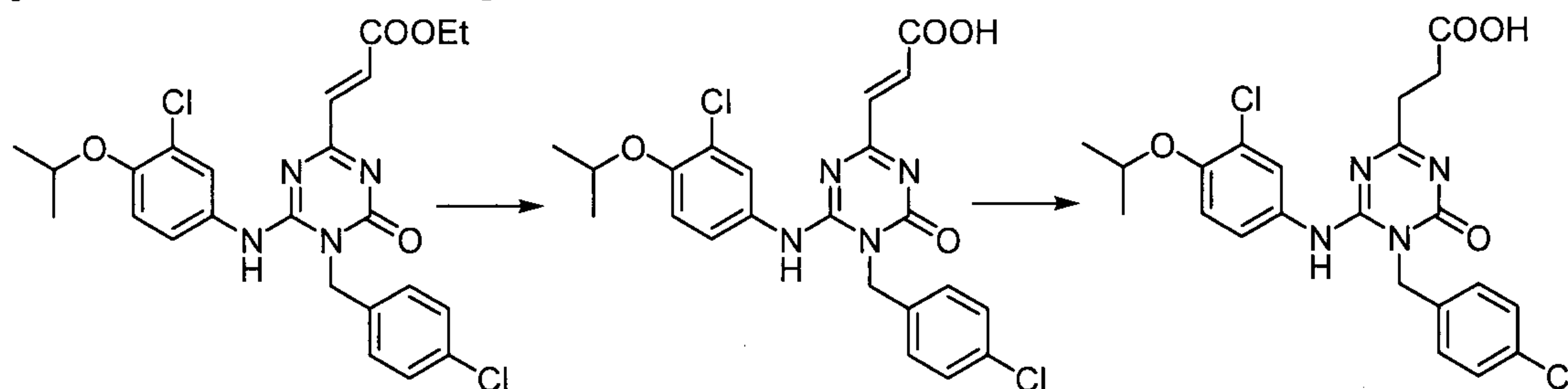


To a mixture of

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-tert-butylphosphino)ferrocene]dichloropalladium (II) (22.23 mg, 0.034 mmol) and THF (3 mL) were added (E)-ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)acrylate (0.063 g, 0.49 mmol) and 2 mol/L potassium carbonate (0.682 mL, 1.364 mmol) under nitrogen atmosphere, and the resulting mixture was heated at reflux for 7 hours. To the mixture was added 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 by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 50-80%) to give 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-ethoxycarbonylethyl-1,3,5-triazine-2(1H)-one (0.05 g, Yield: 30%) as pale orange oil.

¹H-NMR (δ ppm TMS/DMSO-d₆): 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 128]



To a mixture of

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-ethoxycarbonylethenyl-1,3,5-triazine-2(1H)-one (0.05 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 by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-4-hydroxycarbonylethenyl-1,3,5-triazine-2(1H)-one (27 mg, Yield: 57%) as pale orange oil.

The obtained intermediate was dissolved in methanol (3 mL) and conducted by catalytic reduction by using H-Cube (10% Pt-C, H₂ = 1atm). Then, the mixture was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 50-80%) to give

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylamino)-4-hydroxycarbonylethyl-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).

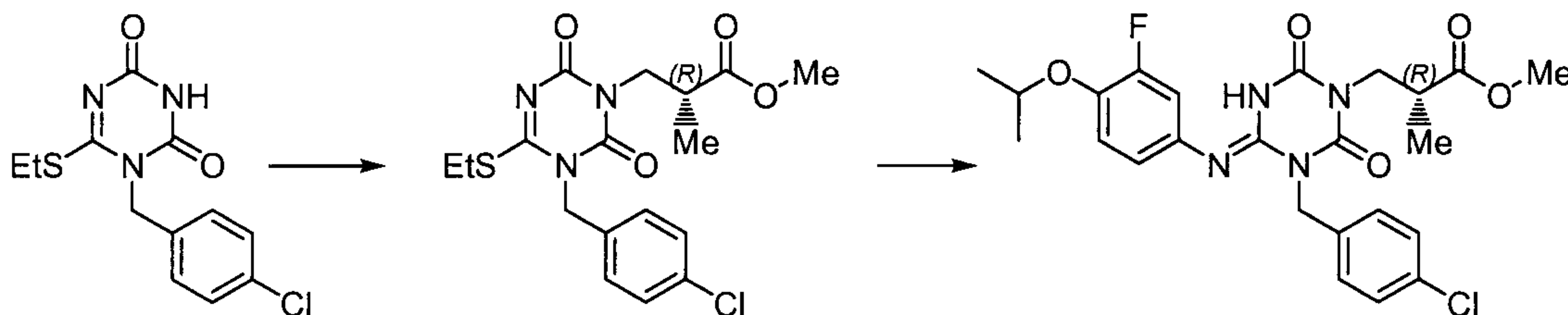
[Example 20]

[0234]

Preparation of

(R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4-dion (I-0461)

[Chemical Formula 129]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (1.00 g, 3.4 mmol), di-2-methoxyethylazodicarboxylate (1.02 g, 4.4 mmol), triphenylphosphine (1.15 g, 4.4 mmol) and dioxane (8 mL) was gradually added (R)-(-)-3-methyl 2-hydroxyisobutyrate (0.52 g, 4.4 mmol), and the mixture was stirred at room temperature for 1hour. To the reaction mixture was added water (40 mL), and the resulting mixture was extracted with ethyl acetate (20 mL×2). The extract was washed by brine (20 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by 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)-dion (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)-dion (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) was heated at reflux over night. The reaction mixture was poured into saturated aqueous sodium bicarbonate (40 mL), and the mixture was extracted

with ethyl acetate (40 mL×2). The extract was washed by 2mol/L aqueous hydrochloric acid (20 mL×2), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by diethyl ether to give (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (0.29 g, Yield: 71%) as pale purple powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.19 (3H, d, J=5.7 Hz), 1.37 (6H, d, J=5.7 Hz), 2.90 (1H, m), 3.60 (3H, s), 3.91 (1H, m), 4.10 (1H, m), 4.47 (1H, sept, J=5.7 Hz), 5.16 (2H, m), 6.49-6.62 (2H, m), 6.96 (1H, m), 7.29-7.47 (5H, m).

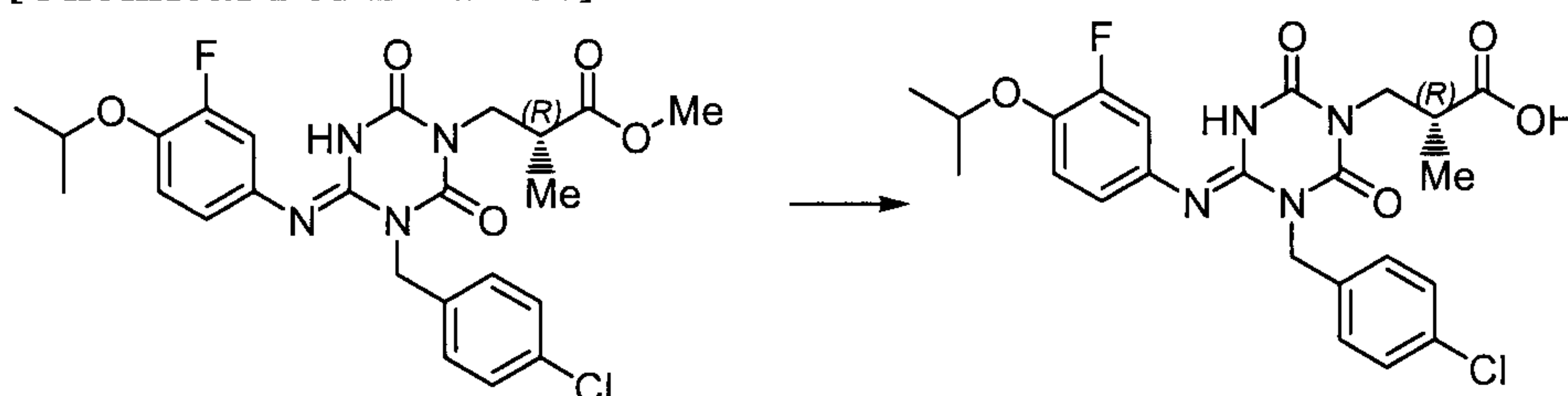
[Example 21]

[0235]

Preparation of

(R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (I-0464)

[Chemical Formula 130]



To a mixture of

(R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (0.26 g, 0.5 mmol) and dioxane (4 mL) was added 1mol/L lithium hydroxide (1.6 mL), and the mixture was stirred at 50°C for 6 hours. To the mixture was added water (50 mL), adjusted with 2mol/L hydrochloric acid to a pH of about 3, and the precipitated solid was filtered off. The solid was dried at 40°C to give (R)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazine-2,4(1H,3H)-dion (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).

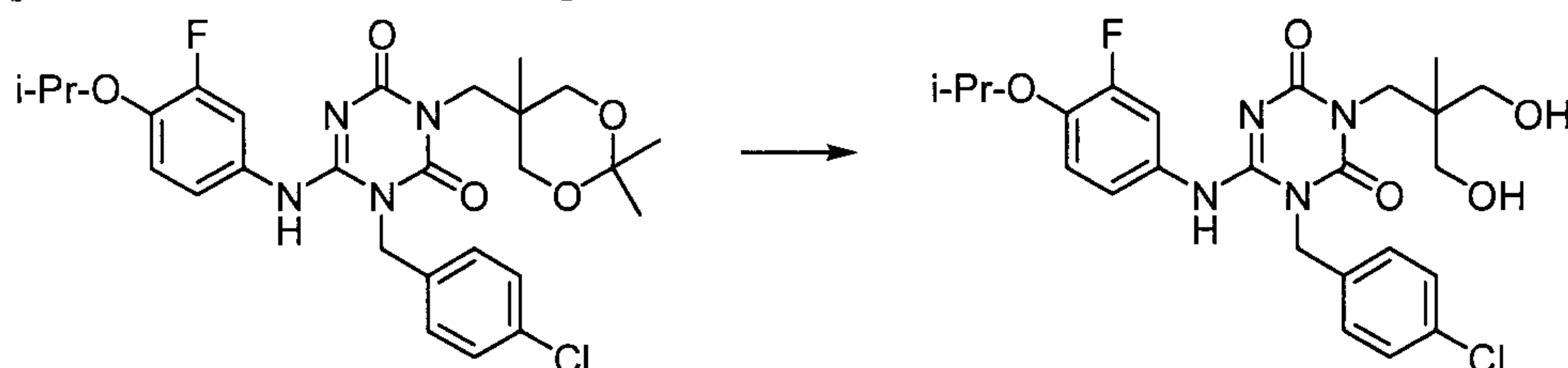
[Example 22]

[0236]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-[2,2-di(hydroxymethyl)propyl]-1,3,5-triazine-2,4(1H,3H)-dion (I-0274)

[Chemical Formula 131]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylamino)-3-(2,2,5-trimethyl-1,3-dioxane5-yl)methyl-1,3,5-triazine-2,4(1H,3H)-dion (7.9 g, 14.44 mmol) and methanol (160 mL) was added p-toluenesulfonic acid monohydrate (5.49 g, 28.9 mmol) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into saturated aqueous sodium bicarbonate (200 mL), and extracted with ethyl acetate (300 mL×2). The extract was washed by brine (300 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by water and the filtered off. The residue was dried 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)-dion (5.12 g, Yield: 70%) as a 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).

Elementary analysis

Calculated value C₂₄H₂₈ClFN₄O₅·1/3H₂O,

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

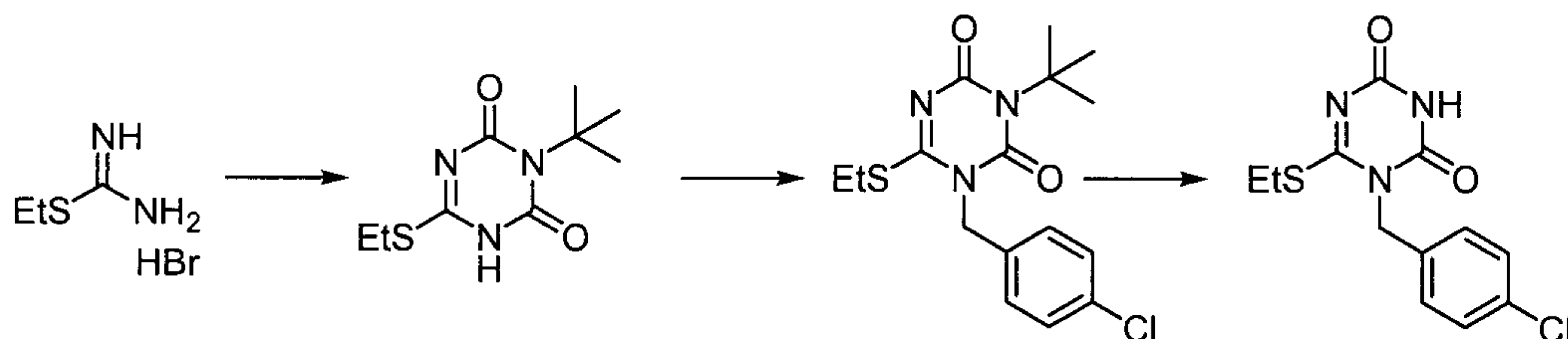
Karl Fischer water determination: 1.02%

[Example 23]

[0237]

Preparation of 1-(4-chlorobenzyl)-6-(Ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion

[Chemical Formula 132]



To a mixture of S-ethylisothiourea hydrobromide (1.85 g, 10 mmol) and DMF (9.3 mL) were added t-butyliisocyanide (1.2 mL, 10.5 mmol) and DBU (1.9 mL, 12.8 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 6 hours. To the reaction mixture were added 1,1'-carbonyldiimidazole (1.95 g, 12 mmol) and DBU (1.9 mL, 12.8 mmol) under ice-cooling, and the resulting mixture was stirred for additional 2 hours. To the mixture was added 2mol/L hydrochloric acid (80 mL) under ice-cooling over about 50 minutes, and the precipitated solid was filtered off. The resulting solid was dissolved in ethyl acetate, and the mixture was dried over anhydrous magnesium sulfate and concentrated in vacuo to give 6-(ethylthio)-3-t-butyl-1,3,5-triazine-2,4(1H,3H)-dion (1.15g, Yield: 50%) as pale brown solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (3H, t, J=7.3 Hz), 1.55 (9H, s), 3.03 (2H, q, J=7.3), 12.30 (1H, brs)

To a mixture of 6-(ethylthio)-3-t-butyl-1,3,5-triazine-2,4(1H,3H)-dion (22.93 g, 100 mmol), 4-chlorobenzylbromide (22.60 g, 110 mmol) and acetonitrile (200 mL) was added potassium carbonate (17.97 g, 130 mmol), and the mixture was heated at reflux for 3 hours. The

reaction mixture was filtered to remove the insoluble. The filtrate was concentrated in vacuo to give 39.9g of crude

3-*t*-butyl-1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1*H*,3*H*)-dion as pale brown oil. To the obtained crude product was added trifluoroacetic acid (100 mL) under ice-cooling, and the mixture was stirred at room temperature for 17 hours. The reaction mixture was concentrated in vacuo to give crude residue. The residue was precipitated to give 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1*H*,3*H*)-dion (29.03 g, Yield: 97%) as pale brown solid.

¹H-NMR (δ ppm TMS/d₆-DMSO): 1.25 (3H, t, J=7.3 Hz), 3.08 (2H, q, J=7.3 Hz), 5.02 (2H, s), 7.30-7.33 (2H, m), 7.39-7.42 (2H, m), 11.61 (1H, s).

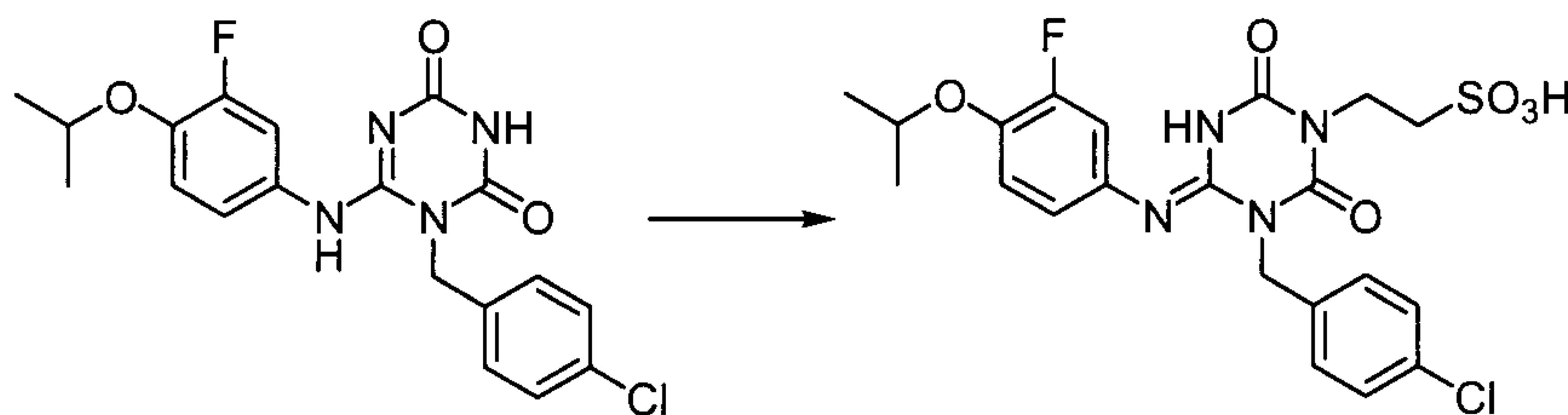
[Example 24]

[0238]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-sulfoethyl)-1,3,5-triazinane-2,4-dion (I-0654)

[Chemical Formula 133]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-1,3,5-triazine-2,4(1*H*,3*H*)-dion (100 mg, 0.247 mmol) and DMF (2 mL) was added cesium carbonate (105 mg, 0.321 mmol), and the mixture was stirred at room temperature for 5 minutes. Further, 2-bromoethanesulfonic acid sodium (62.5 mg, 0.296 mmol) was added to the mixture, and the resulting mixture was stirred at 120°C for 1 hour. To the reaction mixture was added 1mol/L aqueous hydrochloric acid to be acidic. The resulting mixture was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-sulfoethyl)-1,3,5-triazinane-2,4-dion (22 mg, Yield: 17%) as pale brown solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=6.1 Hz), 2.62-2.67 (2H, m), 3.93-3.99 (2H, m), 4.54 (1H, sept, J=6.1 Hz), 5.17 (2H, s), 6.90 (1H, m), 7.07-7.12 (2H, m), 7.35-7.42 (4H, m).

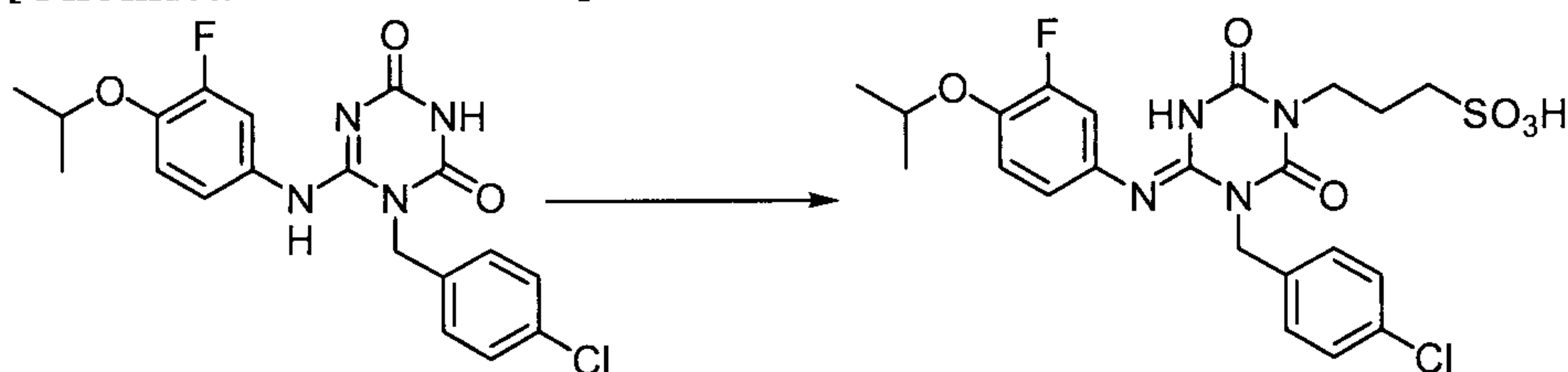
[Example 25]

[0239]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(3-sulfopropyl)-1,3,5-triazinane-2,4-dion (I-0645)

[Chemical Formula 134]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-1,3,5-triazine-(1H,3H)-2,4-dione (200 mg, 0.494 mmol) and DMF (4 mL) was added potassium tert-butoxide (83 mg, 0.741 mmol), and the mixture was stirred at room temperature for 10 minutes. Further, 1,3-propanesultone (91 mg, 0.741 mmol) was added and the resulting mixture was stirred at 90°C for 2 hours. To the reaction mixture was added 4mol/L hydrogen chloride in dioxane (20 mL) to be acidic. The mixture was concentrated in vacuo and the resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%). The resulting residue was precipitated by ethyl acetate to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(3-sulfopropyl)-1,3,5-triazinane-2,4-dione (96 mg, Yield: 37%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=6.1 Hz), 1.81 (2H, m), 2.35-2.40 (2H, m), 3.70-3.74 (2H, m), 4.54 (1H, sept, J=6.1 Hz), 5.19 (2H, s), 6.90 (1H, m), 7.07-7.13 (2H, m), 7.34-7.42 (4H, m).

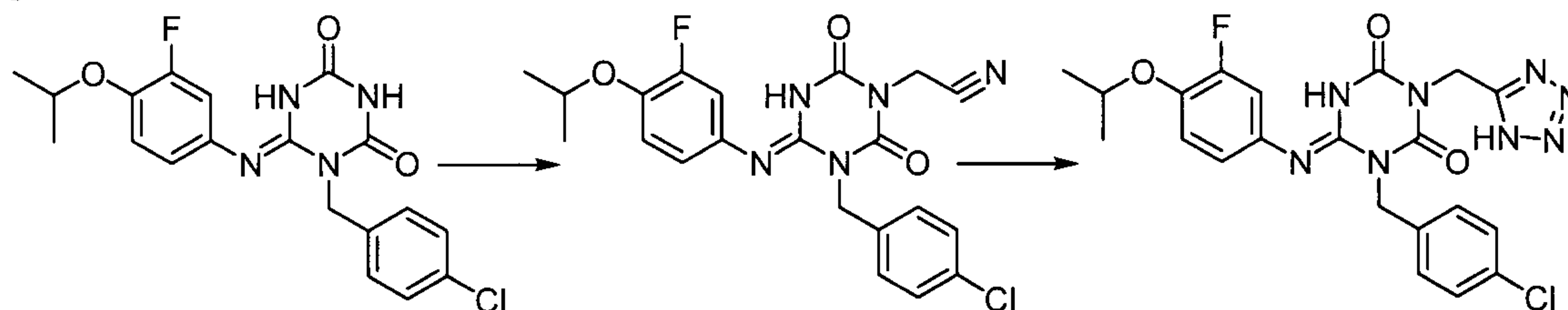
[Example 26]

[0240]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(5-tetrazolylmethyl)-1,3,5-triazinane-2,4-dione (I-1297)

[Chemical Formula 135]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4(1H,3H)-dione (1.214 g, 3 mmol), 2-bromoacetonitrile (0.4 g, 3.3 mmol) and DMF (6 mL) was added potassium carbonate (0.54 g, 3.9 mmol), and the mixture was stirred at 60°C for 1 hour. To the reaction mixture was added water (150 mL), and the mixture was extracted with ethyl acetate (150 mL). The extract was washed by brine (150 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The obtained residue was precipitated by ethyl acetate and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-cyanomethyl-1,3,5-triazinane-2,4-dione (0.78 g, Yield: 59%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (6H, d, J=6.1 Hz), 4.47 (1H, sept, J=6.1 Hz), 4.69 (2H, s), 5.18 (2H, s), 6.49 (1H, m), 6.59 (1H, m), 6.99 (1H, m), 7.32 (2H, d, J=6.6 Hz), 7.49 (2H, d,

$J=6.6$ Hz), 7.74 (1H, s).

To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-cyanomethyl-1,3,5-triazinane-2,4-dion (0.10g, 0.23 mmol), ammonium chloride (84 mg, 1.58 mmol) and DMF (2 mL) was added sodium azide (73.2 mg, 1.13 mmol), and the mixture was stirred at 95°C for 2 hours. To the reaction mixture was added water (150 mL), and the mixture was extracted with ethyl acetate (150 mL). The extract was washed by brine (150 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by HPLC and the obtained residue was precipitated by ethyl ether to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(5-tetrazolylmethyl)-1,3,5-triazinane-2,4-dion (60 mg, Yield: 55%) as colorless powder.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, $J=5.9$ Hz), 4.59 (1H, m), 5.15-5.27 (4H, m), 6.60 (1H, brs), 7.00-7.45 (7H, m), 9.44 (1H, mbrs).

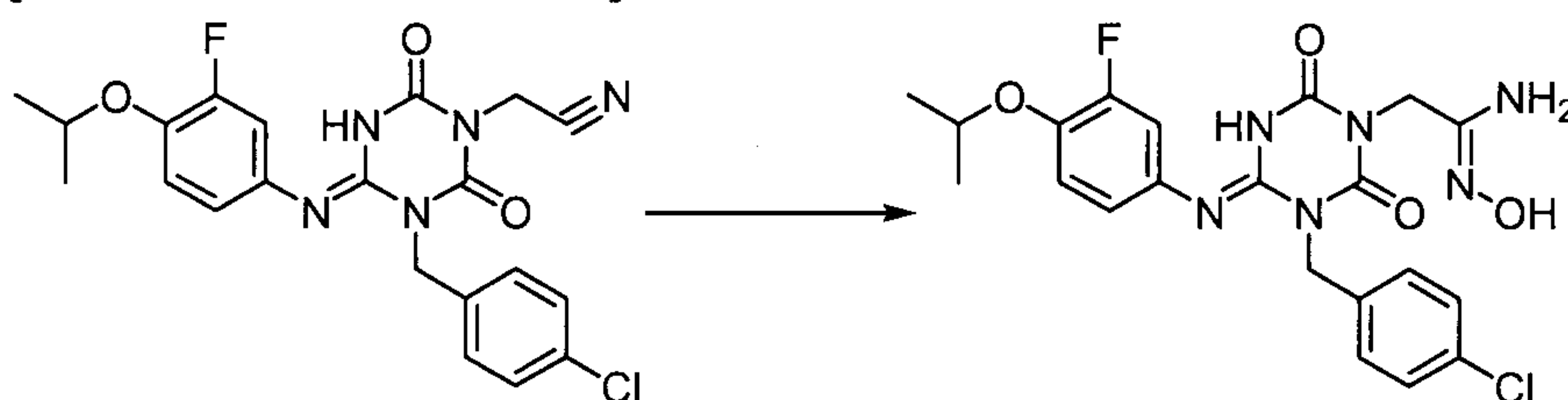
[Example 27]

[0241]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-amino-2-hydroxyiminoethyl)-1,3,5-triazinane-2,4-dion (I-0599)

[Chemical Formula 136]



To a mixture of sodium methoxide (34.1 mg, 0.63 mmol) and methanol (2 mL) was added hydroxylamine hydrochloride (43.8 mg, 0.631 mmol) under ice-cooling. After the mixture was neutralized,

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-cyanomethyl-1,3,5-triazinane-2,4-dion (0.14 g, 0.315 mmol) was added and the resulting mixture was heated at reflux for 2 hours. To the mixture was added water (150 mL), and the mixture was extracted with ethyl acetate (150 mL). The extract was washed by brine (150 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was precipitated by ethyl ether to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-amino-2-hydroxyiminoethyl)-1,3,5-triazinane-2,4-dion (91 mg, Yield: 61%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, $J=5.9$ Hz), 4.34 (2H, brs), 4.58 (1H, m), 5.25 (2H, brs), 5.43 (2H, brs), 7.00-7.45 (7H, m), 8.99 (1H, brs), 9.28 (1H, brs).

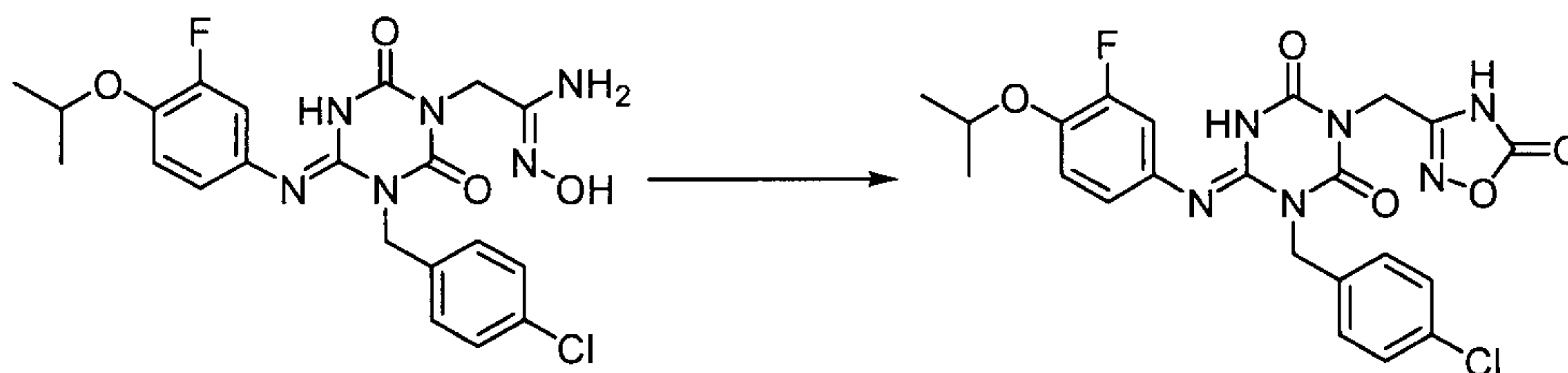
[Example 28]

[0242]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethyl)-1,3,5-triazinane-2,4-dion (I-0601)

[Chemical Formula 137]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-amino-2-hydroxyiminoethyl)-1,3,5-triazinane-2,4-dione (80 mg, 0.17 mmol) and pyridine (2 mL) was added ethyl chlorocarbonate (20 mg, 0.19 mmol), and the mixture was stirred at room temperature overnight. Further, the reaction mixture was heated at reflux for 7 hours. The resulting reaction mixture was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-ylmethyl)-1,3,5-triazinane-2,4-dione (20 mg, Yield: 24%) as colorless amorphous.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.9 Hz), 4.60 (1H, sept, J=5.9 Hz), 4.86 (2H, s), 5.27 (2H, s), 7.00-7.50 (7H, m), 9.44 (1H, brs), 12.48 (1H, brs).

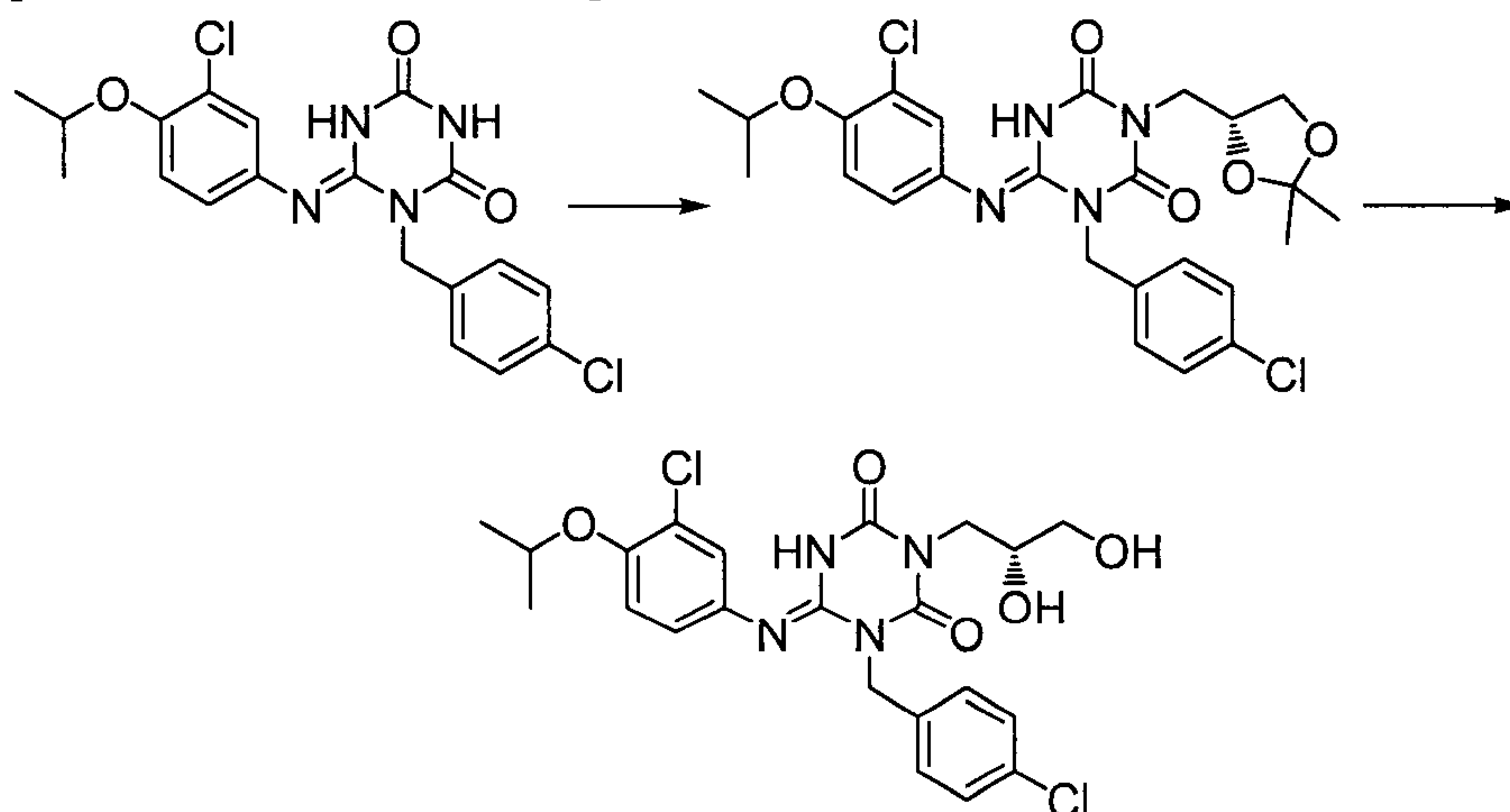
[Example 29]

[0243]

Preparation of

(R)-1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(2,3-dihydroxypropyl)-1,3,5-triazinane-2,4-dione (I-0638)

[Chemical Formula 138]



A mixture of

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dione (300 mg, 0.712 mmol), (S)-4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane (222 mg, 1.14 mmol), potassium tert-butoxide (176 mg, 1.57 mmol) and DMF (6 mL) was stirred at 60°C for 16 hours. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(R)-1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-[(2,2-dimethyl-1,3-dioxolane-4-yl)methyl]-1,3,5-triazinane-2,4-dione (116 mg, Yield: 30%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.23-1.32 (12H, m), 3.73-3.76 (2H, m), 3.94-3.98 (2H, m), 4.24-4.26 (1H, m), 4.64 (1H, brs), 5.25 (2H, s), 7.16-7.25 (2H, m), 7.38-7.47 (5H, m), 9.30 (1H, s).

To a solution of

(R)-1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-[(2,2-dimethyl-1,3-dioxolane-4-yl)methyl]-1,3,5-triazinane-2,4-dione (110 mg, 0.205 mmol) in methanol (4 mL) was added p-toluenesulfonic acid monohydrate (59 mg, 0.31 mmol), and the mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated, and the residue was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by dichloromethane and hexane to give (R)-1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(2,3-dihydroxypropyl)-1,3,5-triazinane-2,4-dione (88 mg, Yield: 86%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (6H, d, J=5.6 Hz), 3.68-3.84 (4H, m), 4.54 (1H, brs), 4.73 (1H, brs), 5.25 (2H, s), 7.16-7.25 (2H, m), 7.38-7.46 (5H, m), 9.23 (1H, s).

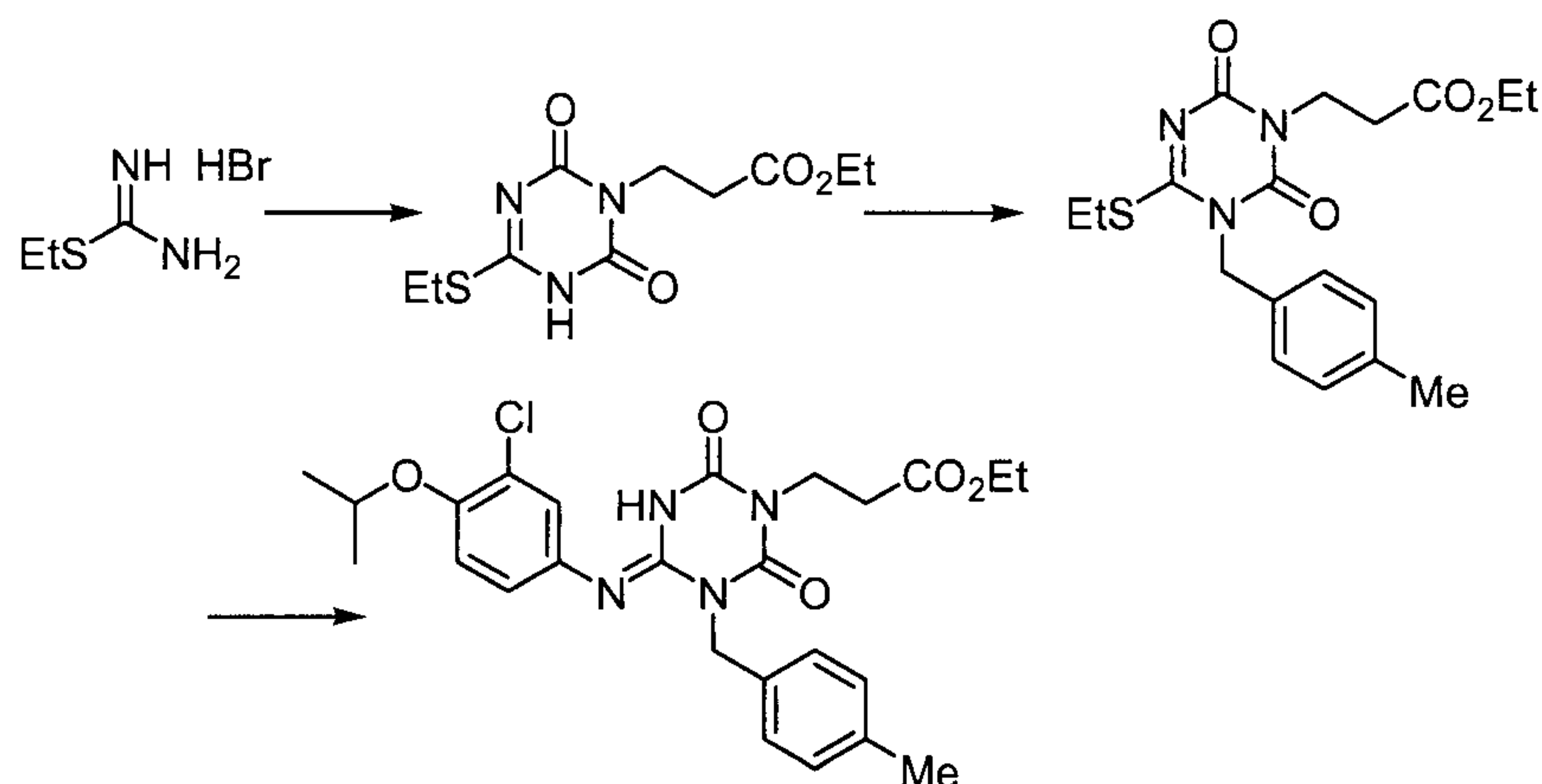
[Example 30]

[0244]

Preparation of

6-(3-chloro-4-isopropoxyphenylimino)-3-(2-ethoxycarbonyl-ethyl)-1-(4-methylbenzyl)-1,3,5-triazinane-2,4-dione (I-0866)

[Chemical Formula 139]



To a mixture of S-ethylisothiourea hydrobromide (6.00 g, 32.4 mmol) and DMF (30 mL) were added ethyl 6-isocyanatocaproate (4.48 mL, 34.0 mmol) and DBU (5.13 mL, 34.0 mmol) under ice-cooling, and the mixture was stirred under ice-cooling for 5 hours. To the reaction mixture were added 1,1'-carbonyldiimidazole (6.31 g, 38.9 mmol) and DBU (7.33 mL, 49.0 mmol) under ice-cooling, and the mixture was stirred at room temperature for 1 hour. To the reaction mixture was added 2mol/L hydrochloric acid (96 mL) under ice-cooling over 15 minutes, and the mixture was extracted with ethyl acetate. The extract was washed by water and brine, dried over anhydrous sodium sulphate. The extract was concentrated in vacuo to give 6-(ethylthio)-3-(2-ethoxycarbonyl-ethyl)-1,3,5-triazine-2,4(1H,3H)-dione (7.86 g, Yield: 89%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.22 (3H, t, J = 7.1 Hz), 1.33 (3H, t, J = 7.3 Hz), 2.67 (2H, t,

$J = 7.2$ Hz), 3.16 (2H, q, $J = 7.3$ Hz), 4.07-4.17 (4H, m).

To the mixture of 6-(ethylthio)-3-(2-ethoxycarbonylethyl)-1,3,5-triazine-2,4(1H,3H)-dion (4.00 g, 14.6 mmol), 4-methylbenzylbromide (3.25 g, 17.6 mmol) and acetonitrile (80 mL) was added potassium carbonate (3.03 g, 22.0 mmol), and the mixture was heated at reflux for 2 hours. The reaction mixture was filtered off to remove insoluble, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

6-(ethylthio)-3-(2-ethoxycarbonylethyl)-1-(4-methylbenzyl)-1,3,5-triazine-2,4(1H,3H)-dion (5.10 g, Yield: 92%) as pale yellow solid.

$^1\text{H-NMR}$ (δ ppm TMS/ CDCl_3): 1.25 (3H, t, $J = 7.1$ Hz), 1.37 (3H, t, $J = 7.4$ Hz), 2.35 (3H, s), 2.71 (2H, t, $J = 7.3$ Hz), 3.21 (2H, q, $J = 7.4$ Hz), 4.12 (2H, q, $J = 7.1$ Hz), 4.24 (2H, t, $J = 7.3$ Hz), 5.09 (2H, s), 7.16 (4H, d, $J = 8.2$ Hz), 7.23 (4H, d, $J = 8.2$ Hz).

A mixture of

6-(ethylthio)-3-(2-ethoxycarbonylethyl)-1-(4-methylbenzyl)-1,3,5-triazine-2,4(1H,3H)-dion (398 mg, 1.05 mmol), 3-chloro-4-isopropoxyaniline (294 mg, 1.58 mmol), acetic acid (0.905 mL) and t-butanol (4 mL) was heated at reflux for 5 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate, and the mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

6-(3-chloro-4-isopropoxyphenylimino)-3-(2-ethoxycarbonylethyl)-1-(4-methylbenzyl)-1,3,5-triazinane-2,4-dion (393 mg, Yield: 74%) as pale pink solid.

$^1\text{H-NMR}$ (δ ppm TMS/ DMSO-d_6): 1.13-1.20 (3H, m), 1.28 (6H, d, $J = 6.1$ Hz), 2.28 (3H, s), 2.55 (2H, t, $J = 6.9$ Hz), 3.33-3.39 (2H, m), 3.98-4.06 (2H, m), 4.60-4.62 (1H, m), 5.21 (2H, s), 7.12-7.23 (6H, m), 7.41-7.46 (1H, m), 9.26 (1H, brs).

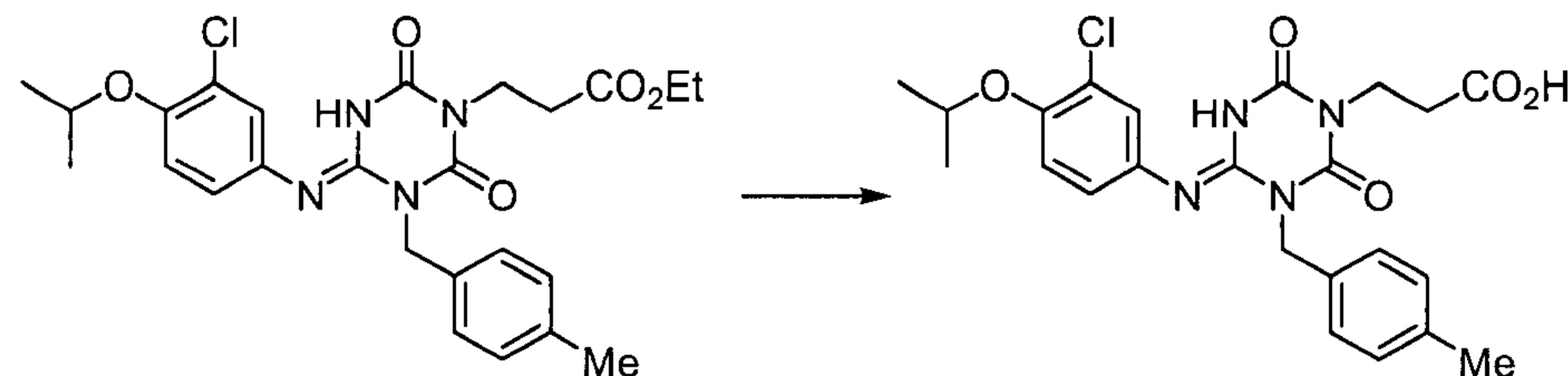
[Example 31]

[0245]

Preparation of

6-(3-chloro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylethyl)-1-(4-methylbenzyl)-1,3,5-triazinane-2,4-dion (I-0896)

[Chemical Formula 140]



To a mixture of

6-(3-chloro-4-isopropoxyphenylimino)-3-(2-ethoxycarbonylethyl)-1-(4-methylbenzyl)-1,3,5-triazinane-2,4-dion (371 mg, 0.741 mmol), methanol (2 mL) and THF (2 mL) was added 1mol/L lithium hydroxide (2.4 mL, and the mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated. To the reaction mixture was added 2mol/L hydrochloric acid (1.3 mL). The precipitated crystalline was filtered off, and the residue was precipitated by ethyl acetate/hexane to give

6-(3-chloro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylethyl)-1-(4-methylbenzyl)-1,3,

5-triazinane-2,4-dion (247 mg, Yield: 71%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (6H, d, J = 5.8 Hz), 2.28 (3H, s), 2.49-2.52 (2H, m), 3.93-3.95 (2H, m), 4.59-4.62 (1H, m), 5.19 (2H, s), 7.12-7.23 (7H, m).

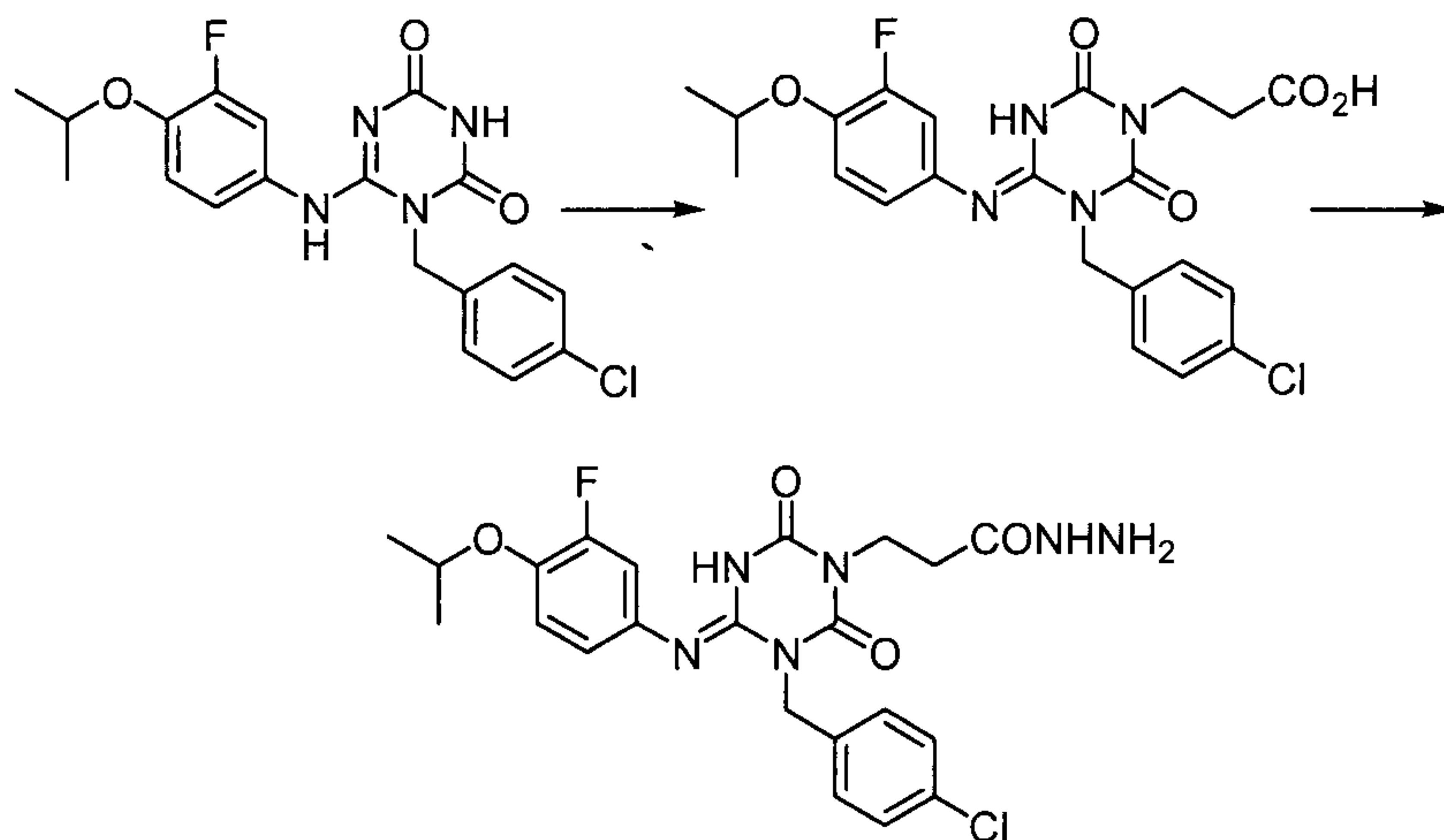
[Example 32]

[0246]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydrazinecarbonylethyl)-1,3,5-triazinane-2,4-dion (I-0644)

[Chemical Formula 141]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-1,3,5-triazine-2,4(1H,3H)-dion (2 g, 4.94 mmol) and DMF (30 mL) was added potassium tert-butoxide (1.331 g, 11.86 mmol) at room temperature and the resulting mixture was stirred for 5 minutes. Further, to the reaction mixture was added methylacrylate (1.074 mL, 11.86 mmol), and the resulting mixture was stirred at 60°C for 1.5 hours. To the reaction mixture were added potassium tert-butoxide (0.554 g, 4.94 mmol) and methylacrylate (0.448 mL, 4.94 mmol), and the resulting mixture was stirred at 60°C for 2 hours. Water (0.5 mL) was added to the mixture and the resulting mixture was stirred at 80°C for 2 hours. The reaction mixture was concentrated in vacuo and 2mol/L aqueous hydrochloric acid (80 mL) was added to the resulting residue. The mixture was extracted with ethyl acetate (50 mL×3). The extract was washed by brine (100 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (methanol/chloroform). The resulting residue was precipitated by ethyl acetate and hexane to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylethyl)-1,3,5-triazinane-2,4-dion (1.64 g, Yield: 70%) as colorless solid.

¹H-NMR (δ ppm TMS / CDCl₃): 1.37 (6H, d, J=6.1 Hz), 2.71 (2H, t, J=7.2 Hz), 4.16 (2H, t, J=7.2 Hz), 4.47 (1H, sept, J=6.1 Hz), 5.17 (2H, s), 6.50 (1H, br. d, J=8.8 Hz), 6.60 (1H, br. d, 11.1 Hz), 6.97 (1H, t, J=8.8 Hz), 7.31 (2H, d, J=8.2 Hz), 7.48 (2H, d, J=8.2 Hz), 7.57 (1H, br. s).

To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylethyl)-1,3,5-

triazinane-2,4-dion (300 mg, 0.629 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (287 mg, 0.755 mmol), triethylamine (0.13 mL, 0.94 mmol) and DMF (6 mL) was added hydrazine monohydrate (0.015 g, 0.21 mmol), and the mixture was stirred at room temperature overnight. The mixture was added to water (200 mL), and the resulting mixture was extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%). The resulting residue was precipitated by ethyl acetate and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydrazinecarbonylethyl)-1,3,5-triazinane-2,4-dion (184 mg, Yield: 60%) as colorless solid.

¹H-NMR (δ ppm TMS / CDCl₃): 1.31 (6H, m), 2.55 (4H, m), 4.08 (2H, m), 4.42 (1H, m), 5.16 (1H, m), 6.48 (2H, m), 6.90 (2H, m), 7.28 (2H, m), 7.40 (1H, m).

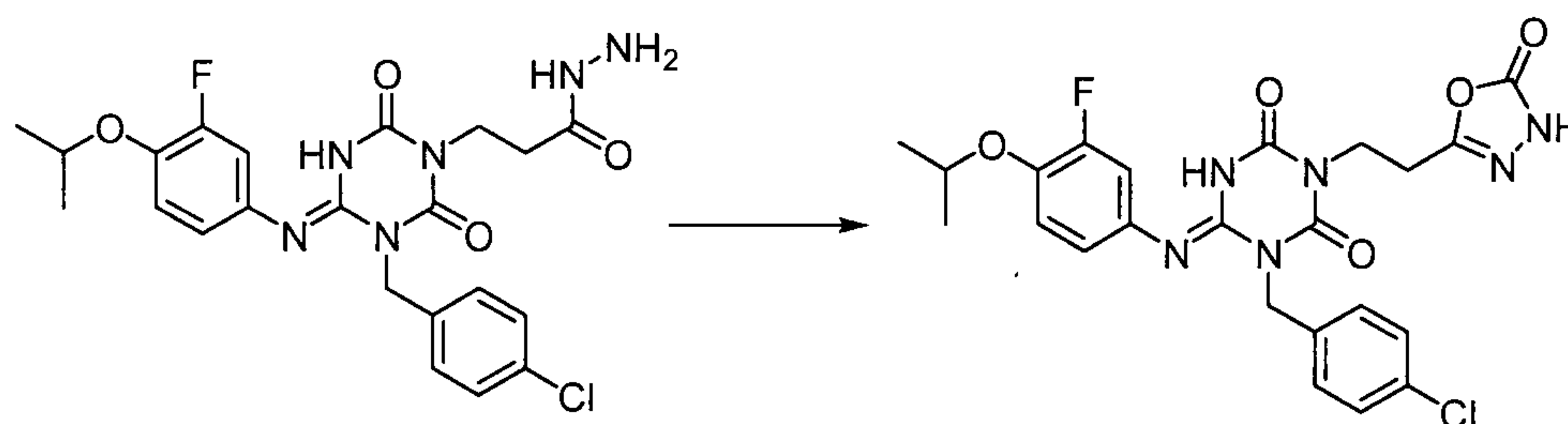
[Example 33]

[0247]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl-1,3,5-triazinane-2,4-dion (I-0646)

[Chemical Formula 142]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydrazinecarbonylethyl)-1,3,5-triazinane-2,4-dion (134.6 mg, 0.274 mmol) and DMF (2 mL) was added

1,1'-carbonyldiimidazole (53.3 mg, 0.329 mmol), and the mixture was stirred at room temperature overnight. The mixture was added to water (200 mL), and extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was precipitated by hexane to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl-1,3,5-triazinane-2,4-dion (113 mg, Yield: 80%) as colorless powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (6H, d, J=6.1 Hz), 2.89 (2H, m), 4.16 (2H, m), 4.48 (1H, sept, J=6.0 Hz), 5.16 (2H, s), 6.49-6.62 (2H, m), 6.98 (1H, t, J=9.0 Hz), 7.31-7.48 (4H, m), 8.00-8.40 (1H, m).

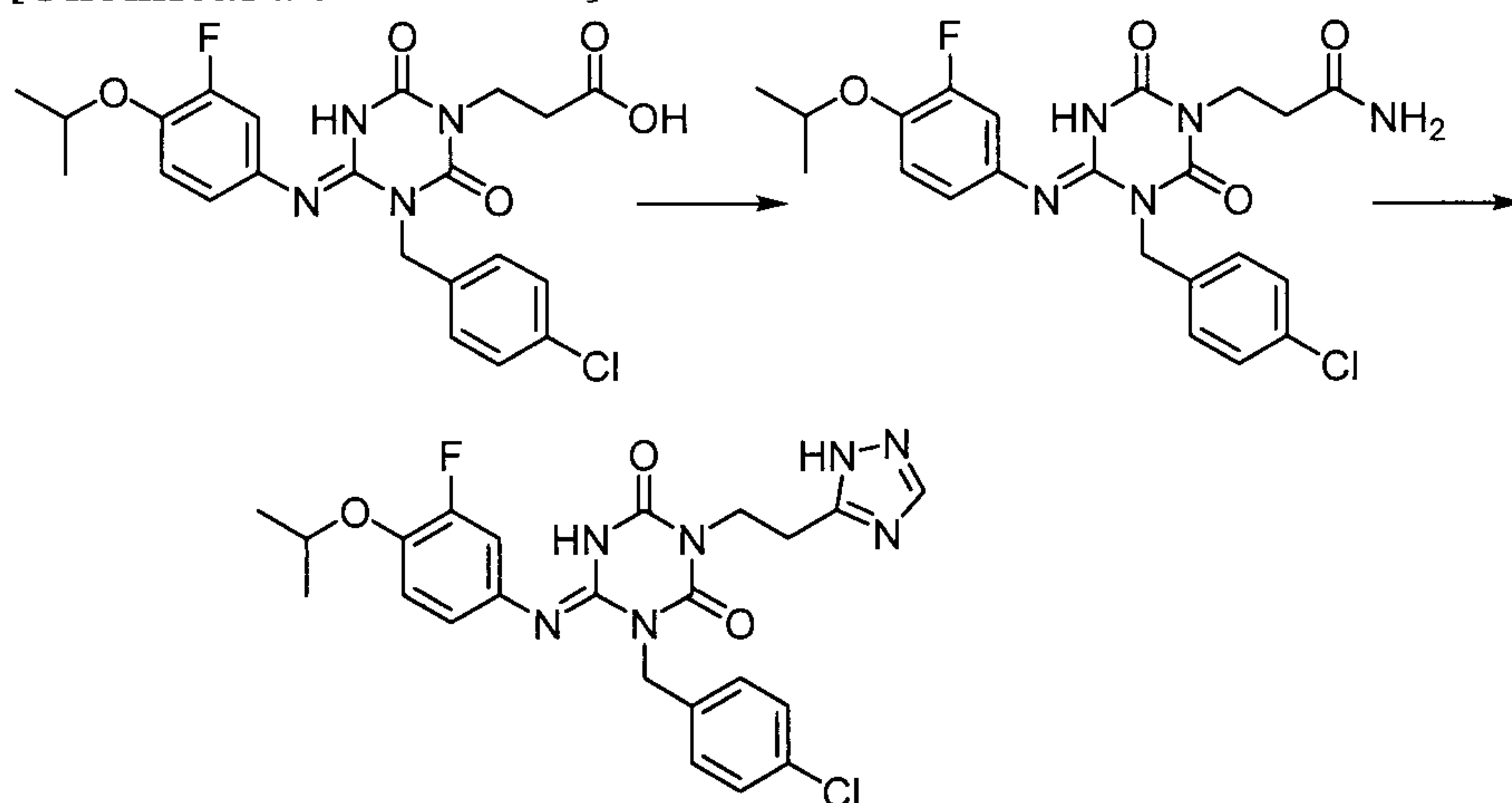
[Example 34]

[0248]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-[2-(1,2,4-triazol-5-yl)ethyl]-1,3,5-triazinane-2,4-dion (I-0672)

[Chemical Formula 143]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-ethyl)-1,3,5-triazinane-2,4-dione (2.86 g, 6 mmol) and DMF (20 mL) were added ammonium chloride (0.385 g, 7.20 mmol), 1-hydroxybenzotriazole hydrate (1.011 g, 6.60 mmol), 4-dimethylaminopyridine (0.073 g, 0.600 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.265 g, 6.60 mmol) and triethylamine (0.998 mL, 7.20 mmol), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water (200 mL), and the mixture was extracted with ethyl acetate (200 mL). The extract was washed by saturated aqueous sodium bicarbonate (200 mL) and brine (200 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-carbamoyl-ethyl)-1,3,5-triazinane-2,4-dione (2.29 g, Yield: 84%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (6H, d, J=6.1 Hz), 2.34 (2H, t, J=7.6 Hz), 3.90 (2H, t, J=7.6 Hz), 4.55 (1H, m), 5.22 (2H, brs), 6.50 (1H, brs), 6.84 (brs), 7.00-7.40 (7H, m), 9.25 (1H, brs)

A mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-carbamoyl-ethyl)-1,3,5-triazinane-2,4-dione (150 mg, 0.315 mmol) and N,N-dimethylformamide dimethyl acetal (2 mL) was stirred at 80°C for 1.5 hours. The reaction mixture was concentrated in vacuo. To the residue were added acetic acid (1 mL) and hydrazine monohydrate (0.046 mL, 0.944 mmol), and the mixture was stirred at 90°C for 0.5 hour. The reaction mixture was poured into water (200 mL), and the resulting mixture was extracted with chloroform (200 mL×2). The extract was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-[2-(1,2,4-triazol-5-yl)ethyl]-1,3,5-triazinane-2,4-dione (75.3 mg, Yield: 48%) as colorless powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (6H, d, J=6.3 Hz), 3.20 (2H, t, J=6.4 Hz), 4.24 (2H, t, J=6.4 Hz), 4.47 (1H, sept, J=5.9 Hz), 5.14 (2H, s), 6.48-6.52 (1H, m), 6.59 (1H, dd, J=11.7, 2.6 Hz), 6.97 (1H, t, 8.5 Hz), 7.30 (2H, d, J=8.2 Hz), 7.46 (2H, d, J=8.2 Hz), 7.78-7.89 (1H, m), 11.2 (1H, brs).

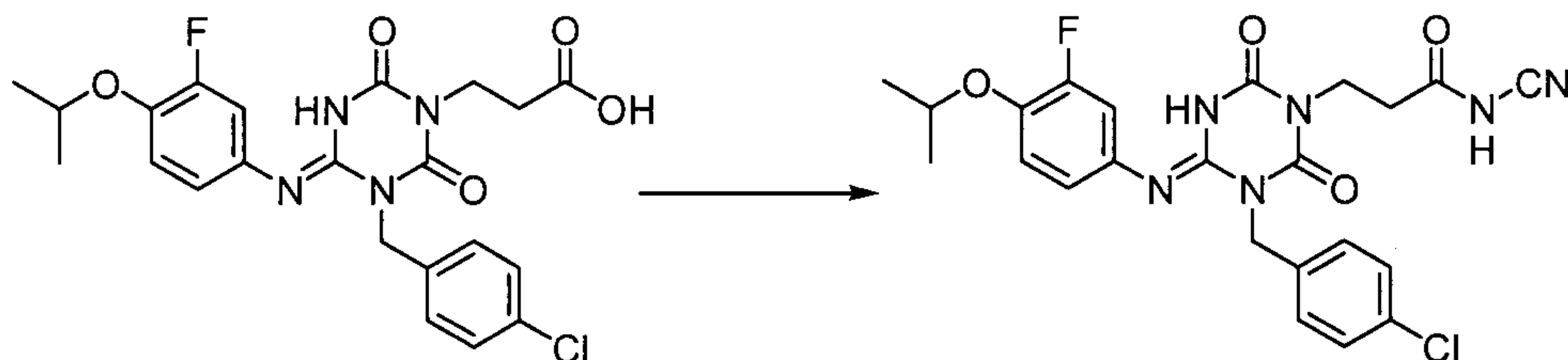
[Example 35]

[0249]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-[2-(cyanocarbamoyl)ethyl]-1,3,5-triazinane-2,4-dion (I-0758)

[Chemical Formula 144]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl)ethyl-1,3,5-triazinane-2,4-dion (300 mg, 0.629 mmol), triethylamine (0.105 mL, 0.755 mmol) and DMF (3 mL), methyl chlorocarbonate (0.063 mL, 0.755 mmol) was added under ice-cooling, and the resulting mixture was stirred at 0°C for 2 hours. To the mixture were added cyanamide monosodium salt (121 mg, 1.89 mmol) and 4-dimethylaminopyridine (23 mg, 0.19 mmol), and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water (200 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-[2-(cyanocarbamoyl)ethyl]-1,3,5-triazinane-2,4-dion (20 mg, Yield: 6%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=5.8 Hz), 2.50 (2H, m), 3.93-3.97 (2H, m), 4.42-4.64 (1H, m), 5.06, 5.23 (2H, s), 6.43-6.60 (1H, m), 7.01-7.10 (2H, m), 7.28-7.43 (4H, m), 9.26 (1H, s).

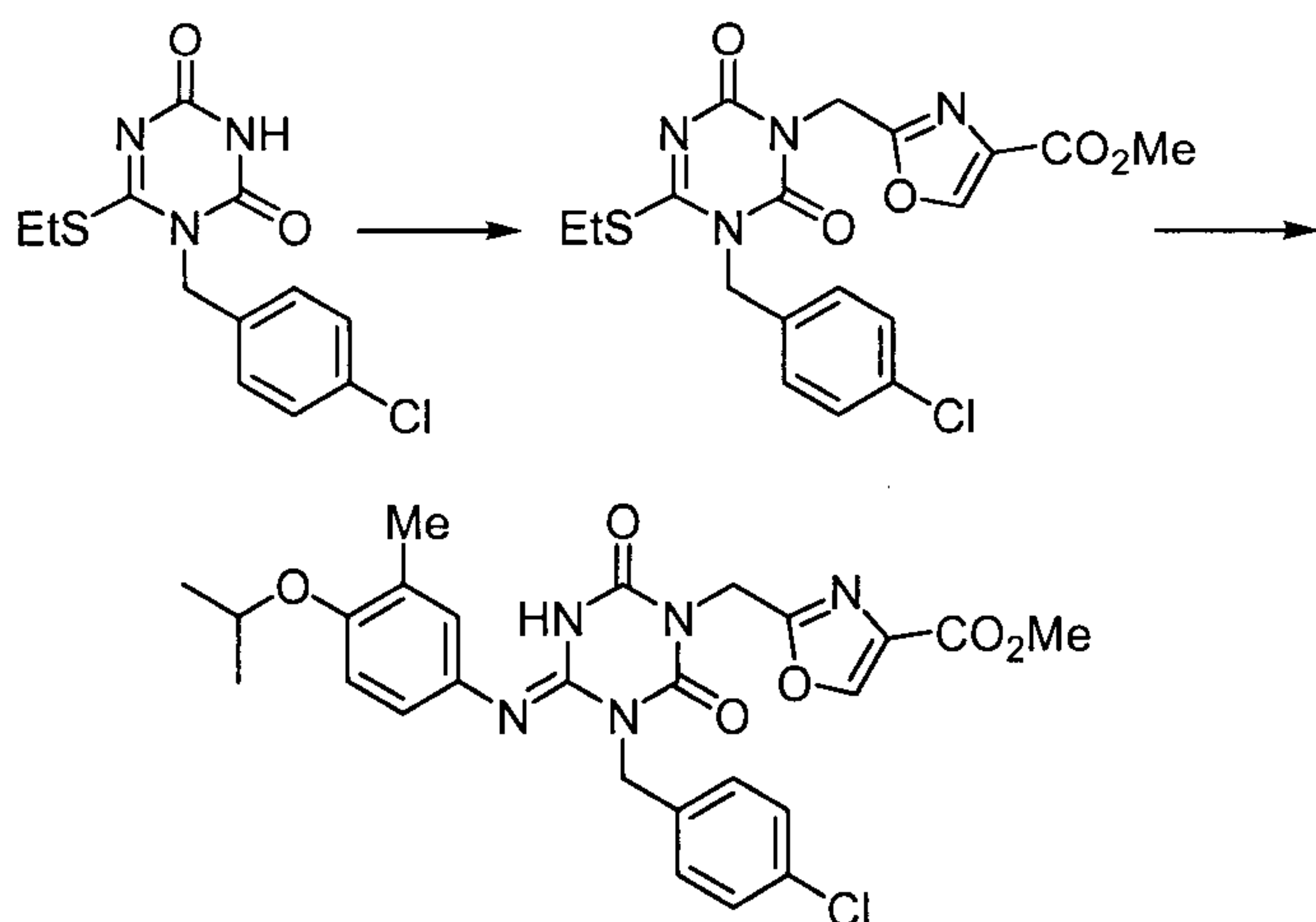
[Example 36]

[0250]

Preparation of

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(4-methoxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion (I-0780)

[Chemical Formula 145]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (300 mg,

1.01 mmol) and DMF (3 mL) were added potassium carbonate (167 mg, 1.21 mmol) and methyl 2-(chloromethyl)-1,3-oxazole-4-carboxylate (212 mg, 1.21 mmol), and the resulting mixture was stirred at 70°C for 2 hours. The reaction mixture was poured into water (200 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to give

1-(4-chlorobenzyl)-6-(ethylthio)-3-(4-methoxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion (520 mg) as crude product as yellow amorphous.

To the obtained crude

1-(4-chlorobenzyl)-6-(ethylthio)-3-(4-methoxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion were added 3-methyl-4-isopropoxyaniline (248 mg, 1.5 mmol), t-butyl alcohol (8 mL) and acetic acid (0.86 mL), and the resulting mixture was heated under reflux for 5 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL), and extracted with ethyl acetate (100 mL). The extract was washed by saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(4-methoxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion (535 mg, Yield: 99%) as colorless amorphous.

¹H-NMR (δ ppm TMS/CDCl₃): 1.31, 1.35 (6H, d, J=6.1 Hz), 2.15, 2.20 (3H, s), 3.91 (3H, s), 4.47 (1H, sept, J=6.1 Hz), 5.17, 5.19, 5.23, 5.32 (4H, m), 6.57-6.63 (2H, m), 6.82-6.88 (1H, m), 7.28-7.34 (2H, m), 7.45-7.53 (2H, m), 8.17 (1H, s).

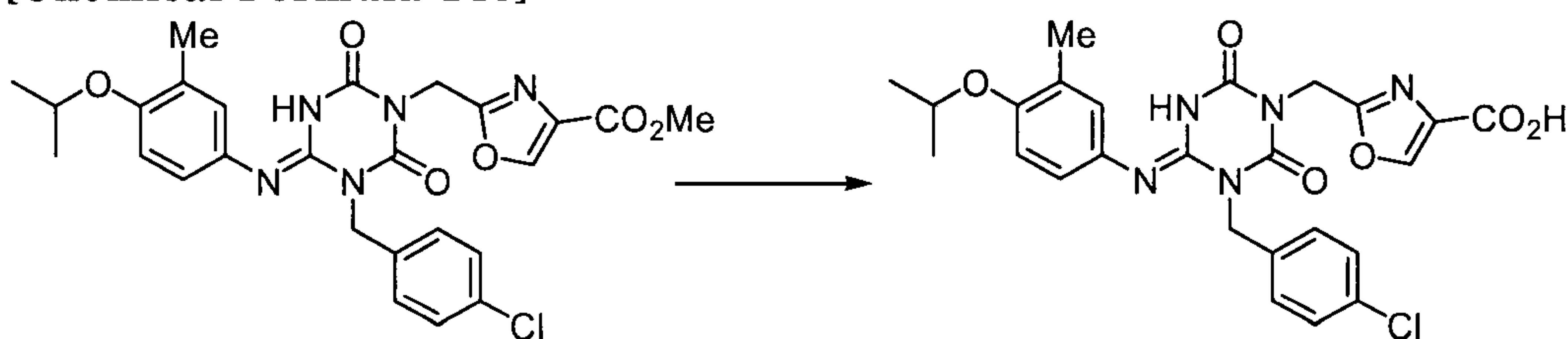
[Example 37]

[0251]

Preparation of

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(4-hydroxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion (I-0800)

[Chemical Formula 146]



To a mixture of

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(4-methoxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion (520 mg, 0.963 mmol), methanol (5 mL), and water (2.5 mL) was added 4mol/L lithium hydroxide (0.722 mL), and the resulting mixture was stirred at room temperature for 2 hours. To the mixture were added water (100 mL) and 2mol/L hydrochloric acid (10 mL), and the resulting mixture was extracted with ethyl acetate (300 mL). The extract was washed by brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(4-hydroxycarbonyl-2-oxazolyl)-1,3,5-triazinane-2,4-dion (370 mg, Yield: 73%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.35 (6H, d, J=5.9 Hz), 2.19 (3H, s), 4.47 (1H, sept, J=5.9 Hz), 5.20 (2H, s), 5.20 (2H, s), 6.64-6.81 (3H, m), 7.31-7.59 (4H, m), 8.26 (1H, s).

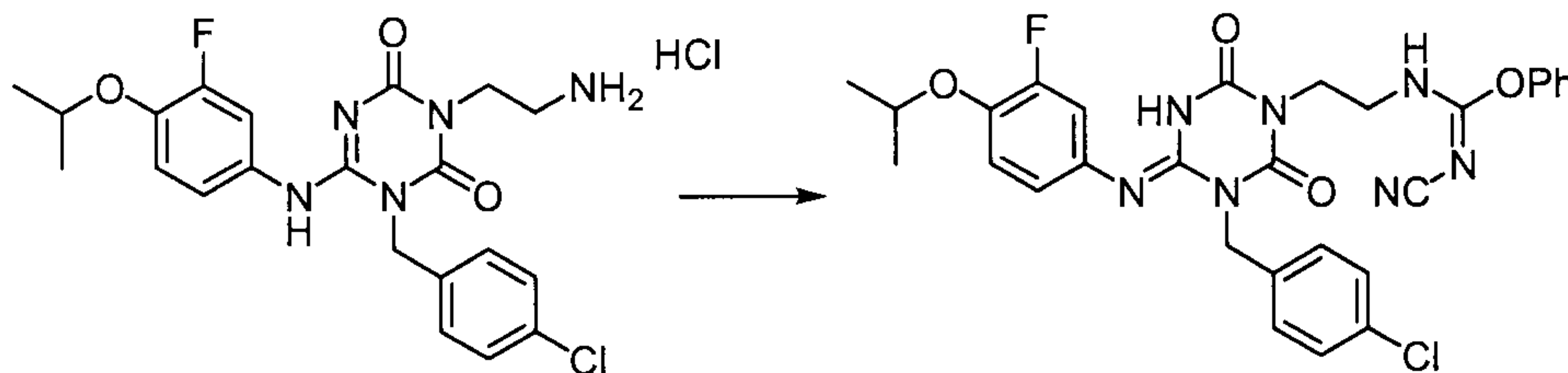
[Example 38]

[0252]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-cyanoimino-4-phenoxy-3-isobutyl)-1,3,5-triazinane-2,4-dion (I-0652)

[Chemical Formula 147]



To a mixture of

3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dion hydrochloride (200 mg, 0.413 mmol) and ethyl ether (8 mL) were added triethylamine (0.126 mL, 0.908 mmol) and diphenyl-N-cyanocarbonimidate (216 mg, 0.908 mmol), and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-cyanoimino-4-phenoxy-3-azabutyl)-1,3,5-triazinane-2,4-dion (170 mg, Yield: 70%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.40 (6H, d, J=6.0 Hz), 3.70 (2H, m), 4.07 (2H, m), 4.49 (1H, sept, J=6.0 Hz), 5.17 (2H, s), 6.47-6.61 (1H, m), 6.94 (1H, t, J=8.7 Hz), 7.16-7.20 (4H, m), 7.30-7.46 (4H, m), 7.79 (1H, m), 8.25 (1H, s).

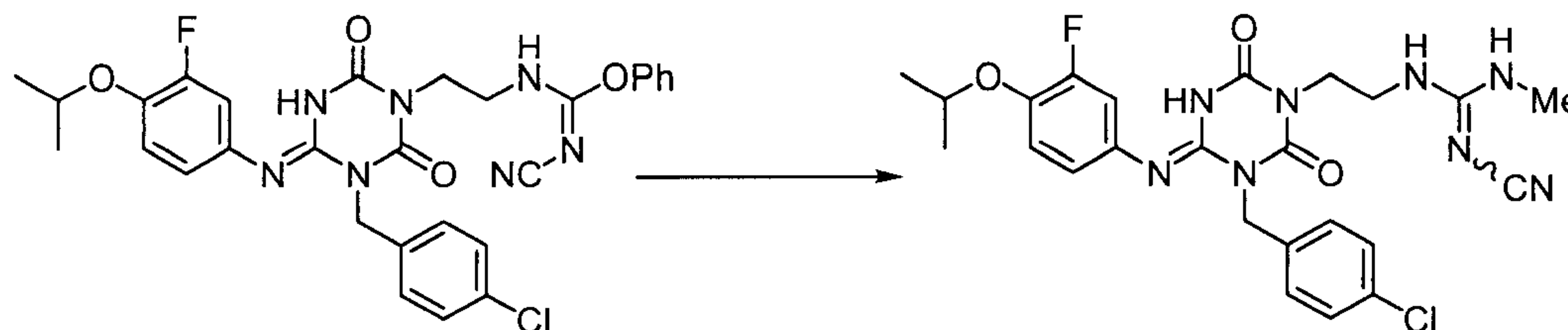
[Example 39]

[0253]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-cyanoimino-4-methylamino-3-azabutyl)-1,3,5-triazinane-2,4-dion (I-0653)

[Chemical Formula 148]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-cyanoimino-4-phenoxy-3-azabutyl)-1,3,5-triazinane-2,4-dion (155 mg, 0.262 mmol), 2-propanol (2 mL) and ethyl acetate (1 mL) was added 2mol/L methylamine in THF (1.964 mL, 3.93 mmol), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The resulting residue was precipitated by ethyl acetate and hexane to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-cyanoimino-4-methylamino-3-azabutyl)-1,3,5-triazinane-2,4-dion (135 mg, Yield: 98%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (6H, d, J=5.9 Hz), 2.71-2.84 (3H, m), 3.47-3.56 (2H, m), 4.01-4.16 (2H, m), 4.48 (1H, sept, J=5.9 Hz), 5.18-5.27 (2H, m), 5.40-5.46 (1H, m), 6.57-6.68 (1H, m), 6.80-7.02 (2H, m), 7.32 (2H, d, J=8.4 Hz), 7.49 (2H, d, J=8.4 Hz), 7.73 (1H, br. s).

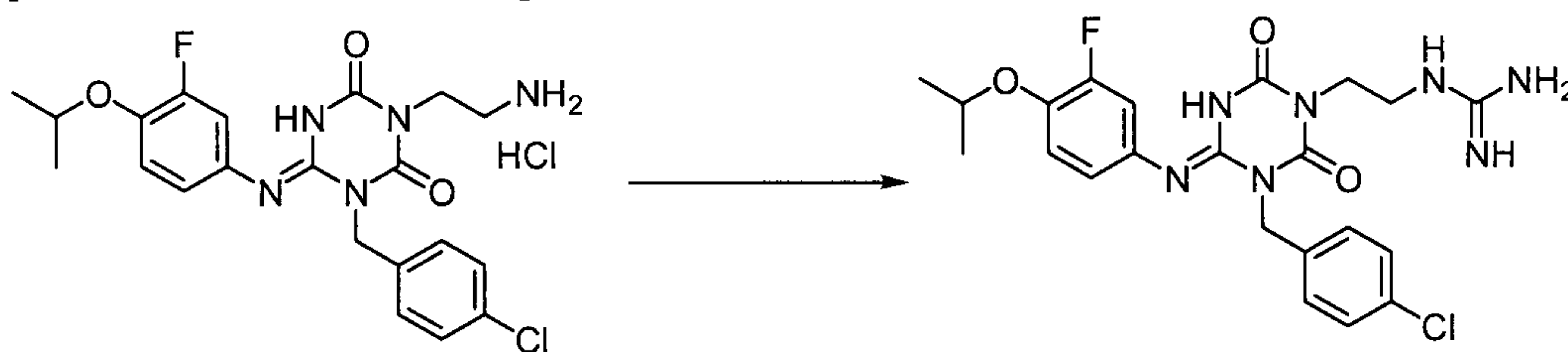
[Example 40]

[0254]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-imino-4-amino-3-azabutyl)-1,3,5-triazinane-2,4-dion (I-0659)

[Chemical Formula 149]



To a mixture of

3-(2-aminoethyl)-1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dion hydrochloride (150 mg, 0.31 mmol) and DMF (3 mL) were added diisopropylethylamine (0.270 mL, 1.548 mmol) and 1H-pyrazole-1-carboxyimidate hydrochloride (136 mg, 0.929 mmol), and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water (200 mL) and extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%).

The resulting residue was precipitated by ethyl acetate to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(4-imino-4-amino-3-azabutyl)-1,3,5-triazinane-2,4-dion (96 mg, Yield: 63%) as flesh color solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.22 (6H, d, J=6.1 Hz), 3.19 (2H, m), 3.70 (2H, t, J=6.25 Hz), 4.35 (1H, sept, J=5.9 Hz), 5.09 (2H, s), 6.65-6.68 (1H, m), 6.84 (1H, t, J=9.0 Hz), 7.07 (1H, dd, J=14.3, 2.4 Hz), 7.17 (2H, brs), 7.30-7.38 (4H, m), 7.59 (1H, m).

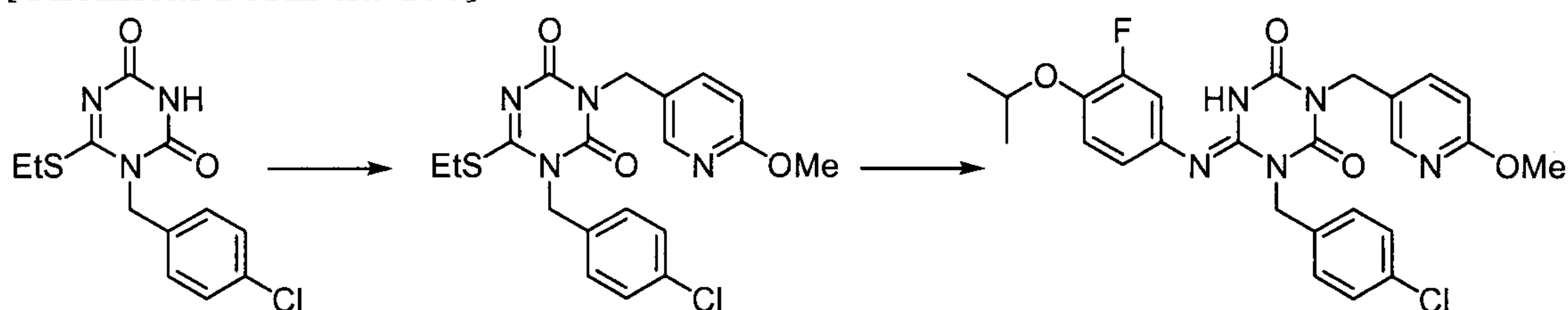
[Example 41]

[0255]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(6-methoxy-3-pyridyl)methyl-1,3,5-triazinane-2,4-dion (I-0641)

[Chemical Formula 150]



To a mixture of 1-(4-chlorobenzyl)-6-(Ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (0.5 g, 1.68

mmol), (6-methoxy-3-pyridyl)methanol (0.3 g, 2.18 mmol), triphenylphosphine (0.57 g, 2.18 mmol) and dioxane (10 mL) was gradually added di-2-methoxyethylazodicarboxylate (0.57 g, 2.18 mmol), and the mixture was stirred at room temperature overnight. To the reaction mixture was added water (200 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1-(4-chlorobenzyl)-6-(ethylthio)-3-(6-methoxy-3-pyridyl)methyl-1,3,5-triazinane-2,4-dion (0.64 g, Yield: 91%) as colorless amorphous.

¹H-NMR (δ ppm TMS/CDCl₃): 1.40 (3H, t, J=7.2 Hz), 3.25 (2H, q, J=7.4 Hz), 3.96 (3H, s), 5.06 (2H, s), 5.11 (2H, s), 6.73 (1H, d, J=8.66 Hz), 7.29-7.38 (4H, m), 7.82 (1H, dd, J=8.4, 2.4 Hz), 8.39 (1H, m).

The mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-(6-methoxy-3-pyridyl)methyl-1,3,5-triazine-2,4-dion (0.32 g, 0.76 mmol), 3-fluoro-4-isopropoxyaniline (0.19 g, 1.15 mmol), t-butanol (6.4 mL) and acetic acid (0.66 mL) was heated at reflux for 24 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL), and extracted with ethyl acetate (100 mL). The extract was washed by saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over anhydrous magnesium sulfate. The extract was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The resulting residue was precipitated by hexane to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(6-methoxy-3-pyridyl)methyl-1,3,5-triazinane-2,4-dion (0.33 g, Yield: 82%) as colorless powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (6H, d, J=6.1 Hz), 3.93 (3H, s), 4.74 (1H, sept, J=6.1 Hz), 4.93 (2H, s), 5.16 (2H, s), 6.47 (1H, m), 6.58 (1H, m), 6.70 (1H, d, J=8.8 Hz), 6.96 (1H, t, J=8.8 Hz), 7.29-7.49 (4H, m), 7.71 (1H, m), 8.30 (1H, m).

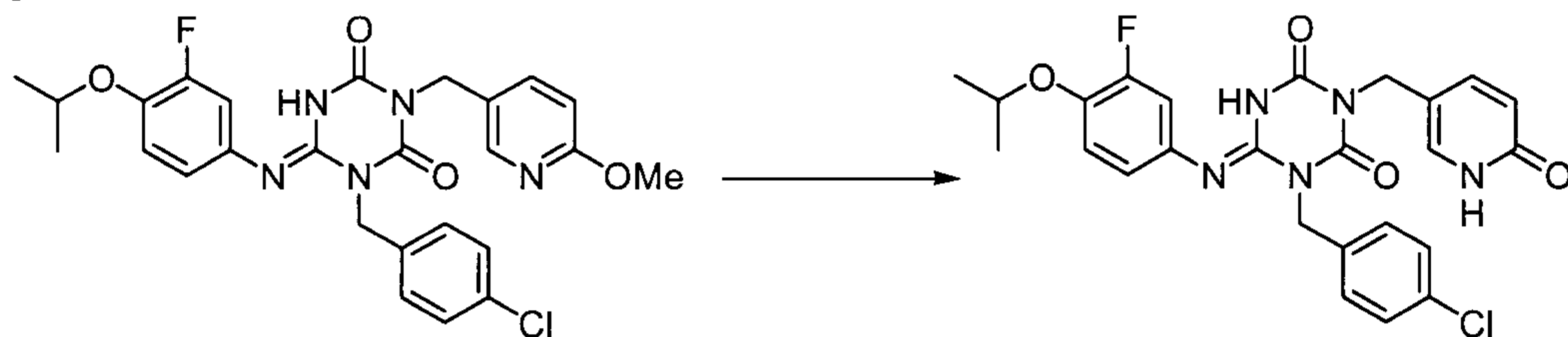
[Example 42]

[0256]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(6-oxo-1,6-dihydro-3-pyridyl)methyl-1,3,5-triazinane-2,4-dion (I-0649)

[Chemical Formula 151]



A mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(6-methoxy-3-pyridyl)methyl-1,3,5-triazinane-2,4-dion (245 mg, 0.466 mmol), sodium iodide (209 mg, 1.397 mmol), acetonitrile (5 mL) and chlorotrimethylsilane (0.179 mL, 1.397 mmol) was heated at reflux for 1 hour. The reaction mixture was poured into water (200 mL) and extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous

magnesium sulfate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(6-oxo-1,6-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4-dione (237 mg, Yield: 99%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=6.0 Hz), 4.62 (3H, m), 5.22 (2H, m), 6.26 (1H, d, J=9.3 Hz), 7.05-7.15 (2H, m), 7.31-7.42 (5H, m), 9.31 (1H, m), 11.5 (1H, m).

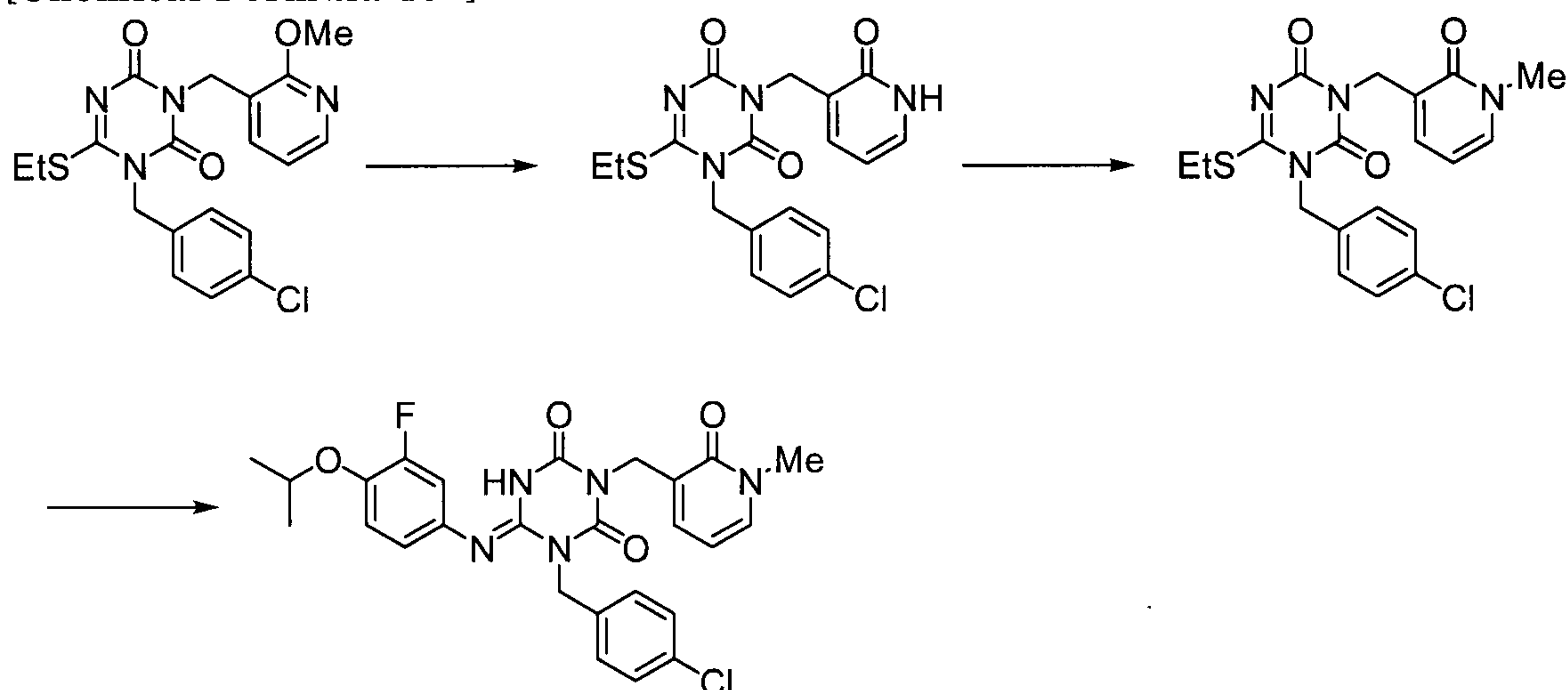
[Example 43]

[0257]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(1-methyl-2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4-dione (I-0689)

[Chemical Formula 152]



A mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methyl-2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (340 mg, 0.812 mmol), sodium iodide (365 mg, 2.44 mmol), chlorotrimethylsilane (0.311 mL, 2.44 mmol) and acetonitrile (14 mL) was stirred at 100°C for 1 hour. To the reaction mixture was added 10% aqueous sodium hydrogensulfate, and the resulting mixture was extracted with ethyl acetate and THF. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give 1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (260 mg, Yield: 79%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (3H, t, J=7.6 Hz), 3.13 (2H, q, J=7.6 Hz), 4.70 (2H, s), 5.09 (2H, s), 6.14 (1H, t, J=6.8 Hz), 7.20 (1H, d, J=6.0 Hz), 7.31 (1H, d, J=6.0 Hz), 7.37-7.43 (4H, m), 11.71 (1H, s).

A mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (150 mg, 0.370 mmol), 60% sodium hydride (21 mg, 0.52 mmol), trifluoromethanesulfonic acid methyl ester (0.049 mL, 0.45 mmol) and DMF (3 mL) was stirred at room temperature for 3 hours. To the mixture was added 10% aqueous citric acid and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The

resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-6-(ethylthio)-3-(1-methyl-2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4(1H,3H)-dion (130 mg, Yield: 84%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (3H, t, J=7.6 Hz), 3.13 (2H, q, J=7.6 Hz), 3.46 (3H, s), 4.72 (2H, s), 5.09 (2H, s), 6.17 (1H, t, J=6.8 Hz), 7.20 (1H, d, J=6.0 Hz), 7.37-7.43 (4H, m), 7.63 (1H, d, J=6.0 Hz).

A mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-(1-methyl-2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4(1H,3H)-dion (125 mg, 0.298 mmol), 3-fluoro-4-isopropoxyaniline (76 mg, 0.45 mmol), acetic acid (0.256 mL) and t-butanol (2.4 mL) was heated at reflux for 9 hours. The reaction mixture was concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(1-methyl-2-oxo-1,2-dihydro-3-pyridyl)methyl-1,3,5-triazine-2,4-dion (50 mg, Yield: 32%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.6 Hz), 3.45 (3H, s), 4.57 (1H, brs), 4.68 (2H, s), 5.24 (2H, brs), 5.09 (2H, s), 6.17 (1H, t, J=6.8 Hz), 7.11-7.14 (3H, m), 7.42 (4H, brs), 7.62 (1H, d, J=6.0 Hz).

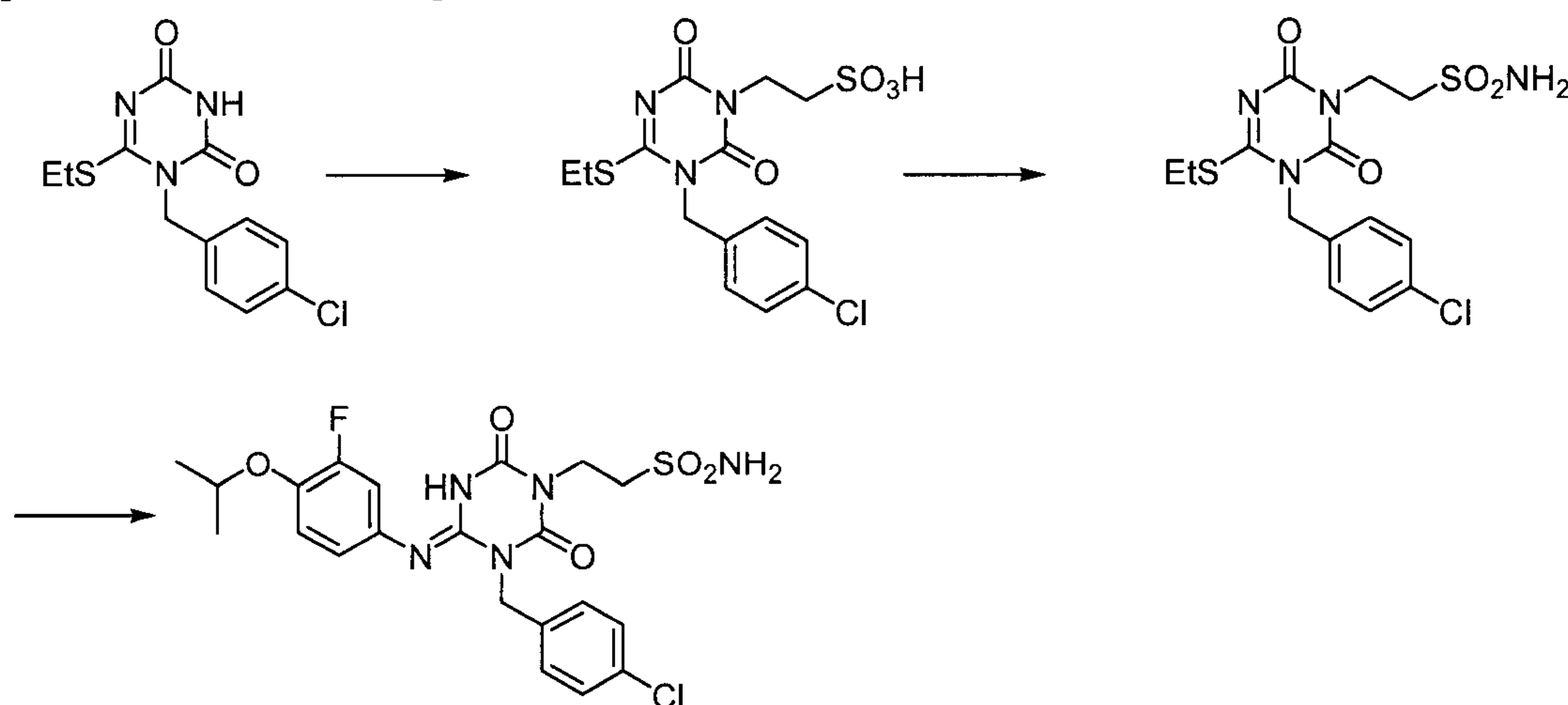
[Example 44]

[0258]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-sulfamoyl-ethyl)-1,3,5-triazine-2,4-dion (I-0693)

[Chemical Formula 153]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (500 mg, 1.679 mmol) and N-methyl-2-pyrrolidone (2.5 mL) were added cesium carbonate (1094 mg, 3.36 mmol) and 2-bromoethanesulfonic acid sodium (709 mg, 3.36 mmol), and the resulting mixture was stirred at 140°C under microwave irradiation for 1 hour. To the reaction mixture was added 2mol/L aqueous hydrochloric acid (2.5 mL) and purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give 1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-sulfoethyl)-1,3,5-triazine-2,4(1H,3H)-dion (120 mg, Yield: 18%) as pale yellow amorphous.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04, 1.24 (3H, t, J=7.0 Hz), 2.63-2.72 (2H, m), 3.09, 3.42 (2H, q, J=7.0 Hz), 3.91-4.03 (2H, m), 4.83 (2H, s), 7.35-7.38 (4H, m), 11.7 (1H, s).

To 1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-sulfoethyl)-1,3,5-triazine-2,4(1H,3H)-dion (120 mg, 0.296 mmol) was added phosphorus oxychloride (2.5 mL), and the mixture was heated at reflux for 2 hours. The reaction mixture was concentrated in vacuo and the resulting residue was dissolved in dioxane (5 mL). The dioxane solution of the residue was gradually added to 0.5mol/L ammonia in dioxane (5.9 mL) under ice-cooling, and the resulting mixture was stirred at room temperature overnight. The precipitated insoluble were filtered off and the filtrate was concentrated in vacuo. The resulting residue was purified by HPLC to give

1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-sulfamoylethyl)-1,3,5-triazine-2,4(1H,3H)-dion (7.4 mg, Yield: 6%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.37 (3H, t, J=7.5 Hz), 3.22 (2H, q, J=7.5 Hz), 3.48-3.51 (2H, m), 4.43-4.49 (2H, m), 5.12 (1H, s), 5.20 (2H, s), 7.25-7.35 (4H, m).

A mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-sulfamoylethyl)-1,3,5-triazine-2,4(1H,3H)-dion (6.9 mg, 0.017 mmol), 3-fluoro-4-isopropoxyaniline (4.33 mg, 0.026 mmol), t-butanol (1 mL) and acetic acid (0.015 mL) was heated at reflux for 24 hours. The reaction was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-sulfamoylethyl)-1,3,5-triazine-2,4-dion (5 mg, Yield: 57%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.25 (6H, d, J=5.8 Hz), 3.19-3.26 (2H, m), 4.06-4.12 (2H, m), 4.50 (1H, sept, J=5.8 Hz), 5.17 (2H, s), 6.83-7.38 (9H, m).

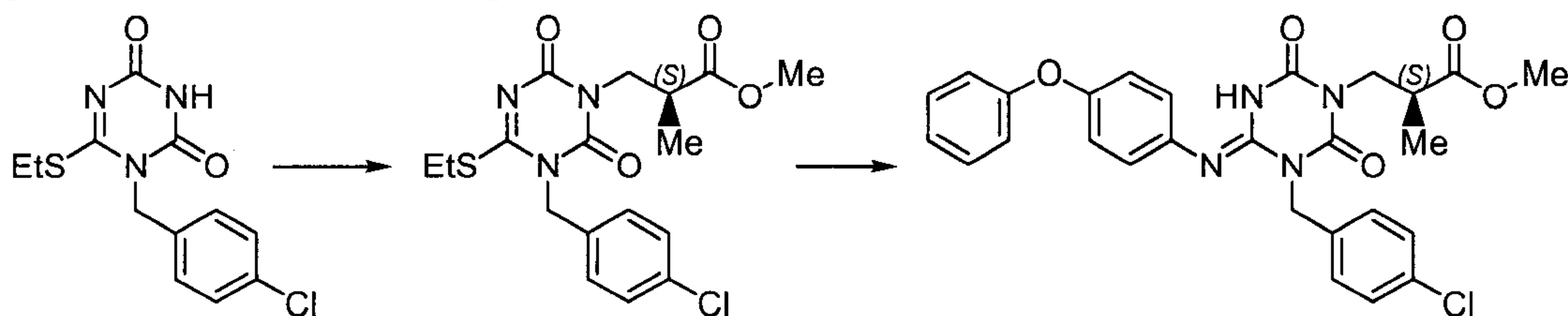
[Example 45]

[0259]

Preparation of

(S)-1-(4-chlorobenzyl)-3-(2-methoxycarbonylpropyl)-6-(4-phenoxy-phenylimino)-1,3,5-triazine-2,4-dion (I-0989)

[Chemical Formula 154]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (5.96 g, 20 mmol), triphenylphosphine (6.29 g, 24 mmol), (S)-3-methyl 2-hydroxyisobutyrate (2.84 g, 24 mmol) and dioxane (40 mL) was added di-2-methoxyethylazodicarboxylate (5.62 g, 24 mmol) over 10 minutes, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into water (250 mL) and the resulting mixture was extracted with ethyl acetate (250 mL). The extract was washed by brine (250 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The

resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4-dione (6.0 g, Yield: 75%) as colorless solid.

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

(S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonylpropyl)-1,3,5-triazine-2,4-dione (0.279 g, 0.7 mmol), 4-phenoxyaniline (0.194 g, 1.05 mmol), acetic acid (0.6 mL) and t-butanol (6 mL) was heated at reflux for 5 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (150 mL), and the resulting mixture was extracted with ethyl acetate (150 mL). The extract was washed by brine (150 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-1-(4-chlorobenzyl)-3-(2-methoxycarbonylpropyl)-6-(4-phenoxyphenylimino)-1,3,5-triazine-2,4-dione (0.34 g, Yield: 93%) as pale brown amorphous.

¹H-NMR (δ ppm TMS/CDCl₃): 1.19 (3H, d, J=7.1 Hz), 2.90 (1H, m), 3.61 (3H, s), 3.90 (1H, m), 4.12 (1H, m), 5.15 (1H, d, J=14.3 Hz), 5.23 (1H, d, J=14.3 Hz), 6.80 (2H, d, J=8.5 Hz), 7.01-7.40 (10H, m), 7.50 (2H, d, J=8.5 Hz).

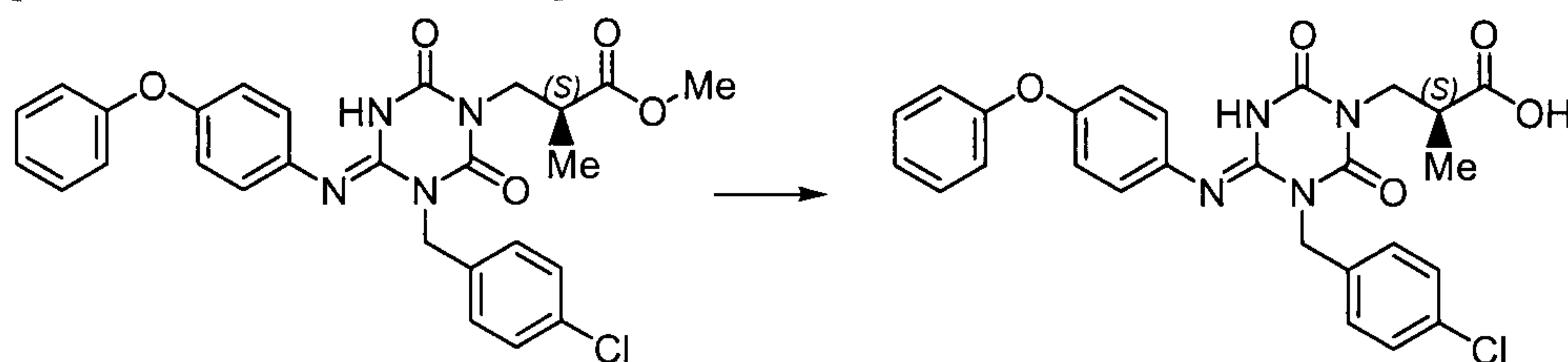
[Example 46]

[0260]

Preparation of

(S)-1-(4-chlorobenzyl)-3-(2-hydroxycarbonylpropyl)-6-(4-phenoxyphenylimino)-1,3,5-triazine-2,4-dione (I-0991)

[Chemical Formula 155]



To a mixture of

(S)-1-(4-chlorobenzyl)-3-(2-methoxycarbonylpropyl)-6-(4-phenoxyphenylimino)-1,3,5-triazine-2,4-dione (0.313 g, 0.6 mmol), methanol (1 mL) and THF (1 mL) was added 4mol/L lithium hydroxide (0.75 mL), and the resulting mixture was stirred at 60°C for 1 hour. To the reaction mixture were added water (100 mL) and 2mol/L hydrochloric acid (2 mL) and the resulting mixture was extracted with ethyl acetate (100 mL). The extract was washed by brine (100 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-chlorobenzyl)-3-(2-hydroxycarbonylpropyl)-6-(4-phenoxyphenylimino)-1,3,5-triazine-2,4-dione (0.29 g, Yield: 95%) as pale brown powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.20 (3H, d, J=6.6 Hz), 2.95 (1H, m), 3.90 (1H, m), 4.10 (1H, m), 5.19 (2H, s), 6.79 (2H, d, J=8.5 Hz), 6.98-7.36 (9H, m), 7.47 (2H, d, J=8.0 Hz), 7.80 (1H, s).

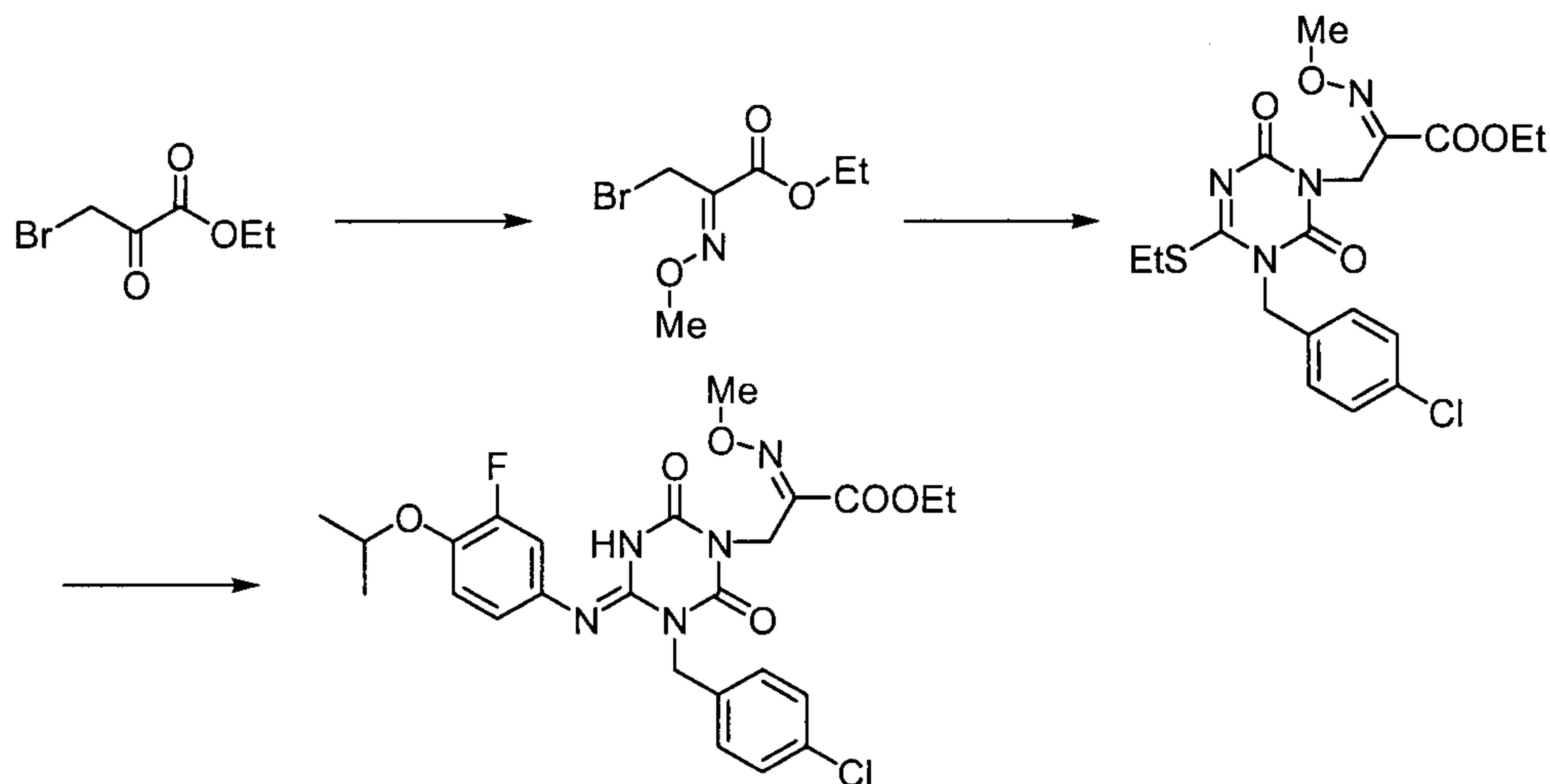
[Example 47]

[0261]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-ethoxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazine-2,4-dione (I-0735)

[Chemical Formula 156]



To a mixture of ethyl 3-bromo-2-oxopropionate (5.85 g, 30 mmol) and ethanol (30 mL) was added O-methoxyamine hydrochloride (5.01 g, 60.0 mmol), and the resulting mixture was stirred at room temperature for 3 hours. To the reaction mixture was added water (200 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo to give crude ethyl 3-bromo-2-methoxyiminopropionate 6.02g as colorless oil.

To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dione (1.49 g, 5 mmol), ethyl 3-bromo-2-methoxyiminopropionate (1.34 g, 6.00 mmol), and DMF (10 mL) was added potassium carbonate (0.898 g, 6.50 mmol), and the resulting mixture was stirred at 60°C for 2 hours. To the reaction mixture was added water (200 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-ethoxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazine-2,4(1H,3H)-dione (2.10 g, Yield: 95%) as colorless oil.

¹H-NMR (δ ppm TMS/CDCl₃): 1.28-1.38 (6H, m), 3.21 (2H, q, J=7.4 Hz), 4.03 (3H, s), 4.28 (2H, q, J=7.1 Hz), 4.97 (2H, s), 5.11 (2H, s), 7.26-7.34 (4H, m).

A mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-ethoxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazine-2,4(1H,3H)-dione (0.35 g, 0.8 mmol), 3-fluoro-4-isopropoxyaniline (0.20 g, 1.2 mmol), acetic acid (0.72 g, 12 mmol) and t-butanol (7 mL) was heated at reflux overnight. The reaction mixture was poured into saturated aqueous sodium bicarbonate (100 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane)

to give

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-ethoxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazinane-2,4-dion (0.31 g, Yield: 70%) as colorless amorphous.

¹H-NMR (δ ppm TMS/CDCl₃): 1.30 (3H, t, J=7.3 Hz), 1.37 (6H, d, J=6.1 Hz), 4.04 (3H, s), 4.27 (2H, q, J=7.3 Hz), 4.48 (1H, sept, J=6.1 Hz), 4.89 (2H, s), 5.17 (2H, s), 6.48-6.52 (1H, m), 6.60 (1H, dd, J=11.7, 2.6 Hz), 6.97 (1H, t, J=8.5 Hz), 7.28-7.47 (5H, m).

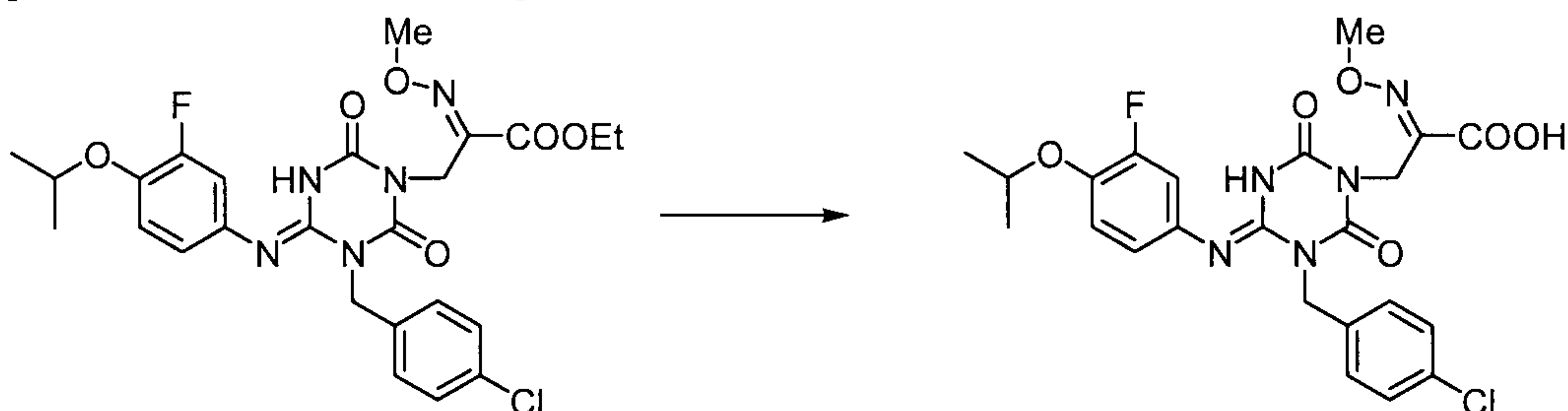
[Example 48]

[0262]

Preparation of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazinane-2,4-dion (I-0737)

[Chemical Formula 157]



To a mixture of

1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-ethoxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazinane-2,4-dion (0.29 g, 0.53 mmol), methanol (3 mL) and water (1.5 mL) was added 4mol/L lithium hydroxide (0.4 mL), and the resulting mixture was stirred at room temperature overnight. To the reaction mixture was added water (100 mL). The pH of the mixture was adjusted with 2mol/L hydrochloric acid to a pH of about 3, and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give 1-(4-chlorobenzyl)-6-(3-fluoro-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-methoxyiminoethyl)-1,3,5-triazinane-2,4-dion (0.27 g, Yield: 99%) as colorless powder.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.28 (6H, d, J=6.0 Hz), 3.81 (3H, s), 4.53 (1H, sept, J=6.0 Hz), 4.68 (2H, s), 5.21 (2H, s), 7.05 (3H, m), 7.41 (4H, m).

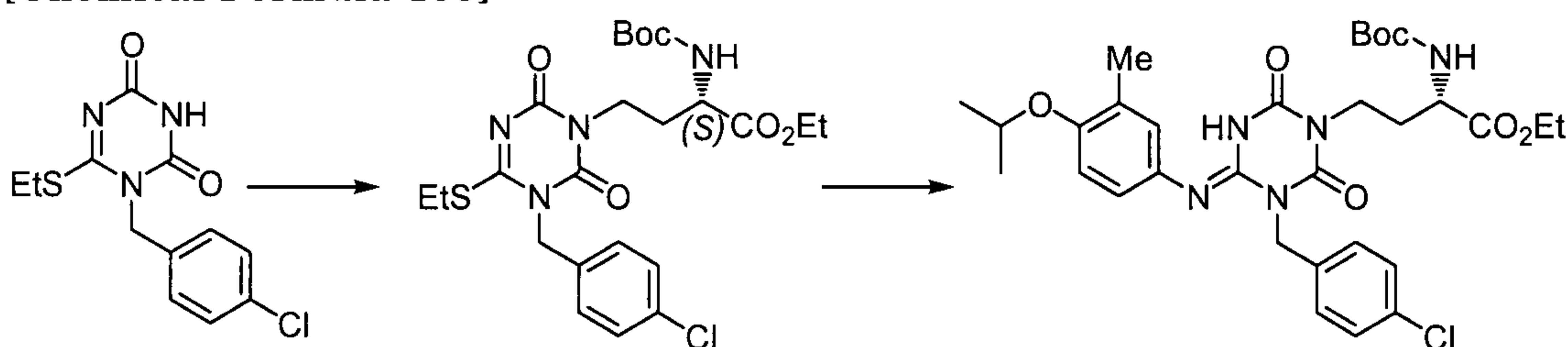
[Example 49]

[0263]

Preparation of

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-ethoxycarbonyl-propyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dion (I-0717)

[Chemical Formula 158]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (1.2 g, 4.03 mmol), (S)-4-hydroxy-2-t-butoxycarbonylamino-ethyl butyrate (1.034 g, 4.18 mmol), triphenylphosphine (1.268 g, 4.84 mmol) and dioxane (12 mL) was gradually added di-2-methoxyethylazodicarboxylate (1.133 g, 4.84 mmol), and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water (200 mL), and the resulting mixture was extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-ethoxycarbonylpropyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (2.15 g, Yield: 100%) as colorless amorphous.

¹H-NMR (δ ppm TMS/CDCl₃): 1.23 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.4 Hz), 1.42 (9H, s), 2.10-2.16 (2H, m), 3.17 (2H, q, J=7.4 Hz), 3.97-4.02 (2H, m), 4.05-4.14 (2H, m), 4.34 (1H, m), 5.06 (2H, m), 5.49 (1H, m), 7.28-7.35 (4H, m).

A mixture of

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-ethoxycarbonylpropyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (500 mg, 0.949 mmol), 3-methyl-4-isopropoxyaniline (235 mg, 1.423 mmol), acetic acid (0.814 mL) and t-butanol (10 mL) was heated at reflux overnight. The reaction mixture was added to saturated aqueous sodium bicarbonate (100 mL), and the resulting mixture was extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The resulting residue was precipitated by methanol to give

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-ethoxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dion (550 mg, Yield: 92%) as pale purple powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.24-1.32 (3H, m), 1.35 (6H, d, J=6.1 Hz), 1.45 (9H, s), 2.05-2.14 (2H, m), 2.19 (3H, s), 3.94 (2H, t, J=7.2 Hz), 4.09-4.18 (2H, m), 4.33-4.40 (1H, m), 4.46 (1H, sept, J=6.1 Hz), 5.17 (2H, s), 5.31 (1H, m), 6.54-6.60 (2H, m), 6.82 (1H, d, J=8.4 Hz), 7.29-7.53 (5H, m).

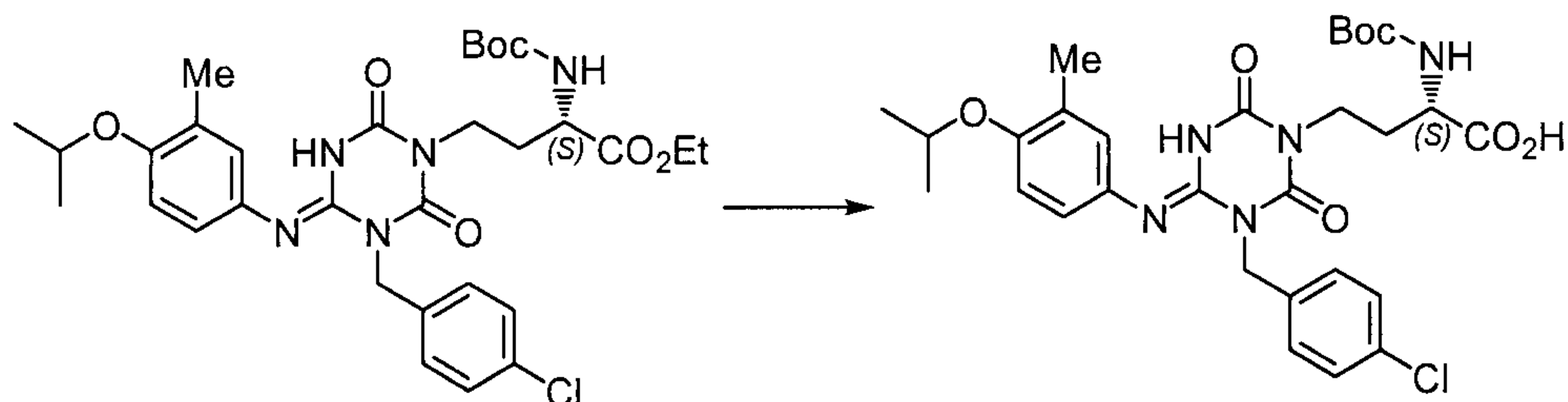
[Example 50]

[0264]

Preparation of

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-hydroxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dion (I-0732)

[Chemical Formula 159]



To a mixture of

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-ethoxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dione (530 mg, 0.841 mmol), methanol (5 mL) and water (2.5 mL) was added 4mol/L lithium hydroxide (0.63 mL), and the resulting mixture was stirred at room temperature for 2 hours. To the reaction mixture were added water (100 mL) and saturated aqueous ammonium chloride (10 mL), and the resulting mixture was extracted with ethyl acetate (300 mL). The extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to give (S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-hydroxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dione (474 mg, Yield: 94%) as pale purple amorphous.

¹H-NMR (δ ppm TMS/CDCl₃): 1.33 (6H, d, J=5.8 Hz), 1.44 (9H, s), 2.17 (5H, m), 3.97 (2H, m), 4.32 (1H, m), 4.45 (1H, sept, J=5.8 Hz), 5.17 (2H, s), 5.40 (1H, m), 6.60-6.81 (3H, m), 7.33-7.46 (4H, m).

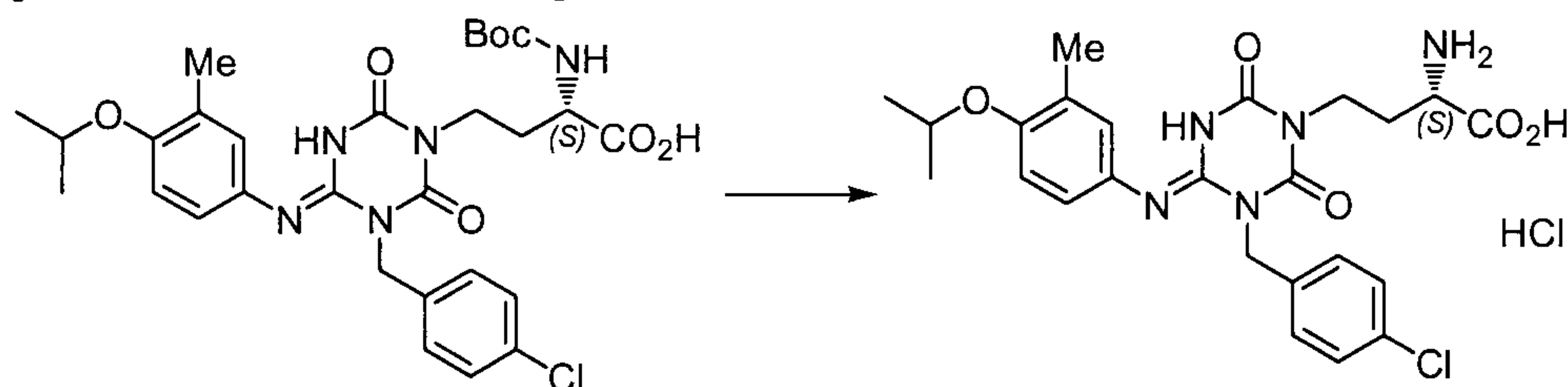
[Example 51]

[0265]

Preparation of

(S)-1-(4-chlorobenzyl)-3-(3-amino-3-hydroxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dione hydrochloride (I-0736)

[Chemical Formula 160]



To a mixture of

(S)-1-(4-chlorobenzyl)-3-(3-t-butoxycarbonylamino-3-hydroxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dione (460 mg, 0.764 mmol) and dioxane (2.3 mL) was added 4mol/L hydrogen chloride in dioxane (3.82 mL) under ice-cooling, and the resulting mixture was stirred at room temperature for 2 hours. To the reaction mixture were added ethyl acetate (2 mL) and hexane (10 mL). The precipitated solid was filtered off and obtained solid was washed by hexane. The obtained solid was dried under reduced pressure to give (S)-1-(4-chlorobenzyl)-3-(3-amino-3-hydroxycarbonylpropyl)-6-(3-methyl-4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dione hydrochloride (403 mg, Yield: 98%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=6.1 Hz), 1.94-2.14 (2H, m), 2.10 (3H, s), 3.86-3.96 (3H, m), 4.54 (1H, sept, J=6.1 Hz), 5.25 (2H, s), 6.90-7.03 (3H, m), 7.36 (2H, d, J=8.7 Hz), 7.43 (2H, d, J=8.7 Hz), 8.30 (3H, brs), 9.28 (1H, brs).

[Example 52]

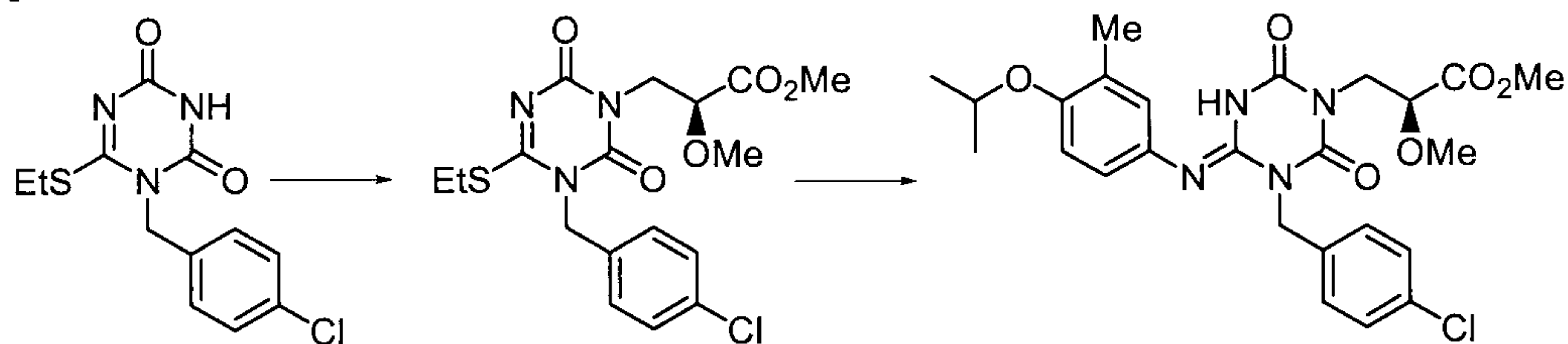
[0266]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-meth

oxy-ethyl)-1,3,5-triazine-2,4-dion (I-0806)

[Chemical Formula 161]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dion (550 mg, 1.85 mmol), di-2-methoxyethylazodicarboxylate (606 mg, 2.59 mmol), triphenylphosphine (969 mg, 3.69 mmol) and dioxane (11 mL) was gradually added (S)-3-hydroxy-2-methoxy-methyl propionate (297 mg, 2.22 mmol), and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water, the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonyl-2-methoxy-ethyl)-1,3,5-triazine-2,4(1H,3H)-dion (559 mg, Yield: 73%) as colorless oil.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (3H, t, J=7.6 Hz), 3.12 (2H, q, J=7.6 Hz), 3.27 (3H, s), 3.61 (3H, s), 3.99-4.10 (3H, m), 5.08 (2H, s), 7.32 (2H, d, J=8.0 Hz), 7.44 (2H, d, J=8.0 Hz).

A mixture of

(S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonyl-2-methoxy-ethyl)-1,3,5-triazine-2,4(1H,3H)-dion (300 mg, 0.725 mmol), 3-methyl-4-isopropoxyaniline (180 mg, 1.09 mmol), acetic acid (0.622 mL) and t-butanol (6 mL) was heated at reflux for 8 hours. The reaction mixture was added to saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-methoxyethyl)-1,3,5-triazine-2,4-dion (365 mg, Yield: 97%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.6 Hz), 2.11 (3H, s), 3.26 (3H, s), 3.57 (3H, s), 3.98-4.05 (3H, m), 4.56 (1H, sept, J=5.9 Hz), 5.26 (2H, s), 6.94 (1H, d, J=8.0 Hz), 7.04-7.07 (2H, m), 7.33 (2H, d, J=8.0 Hz), 7.46 (2H, d, J=8.0 Hz), 9.25 (1H, s).

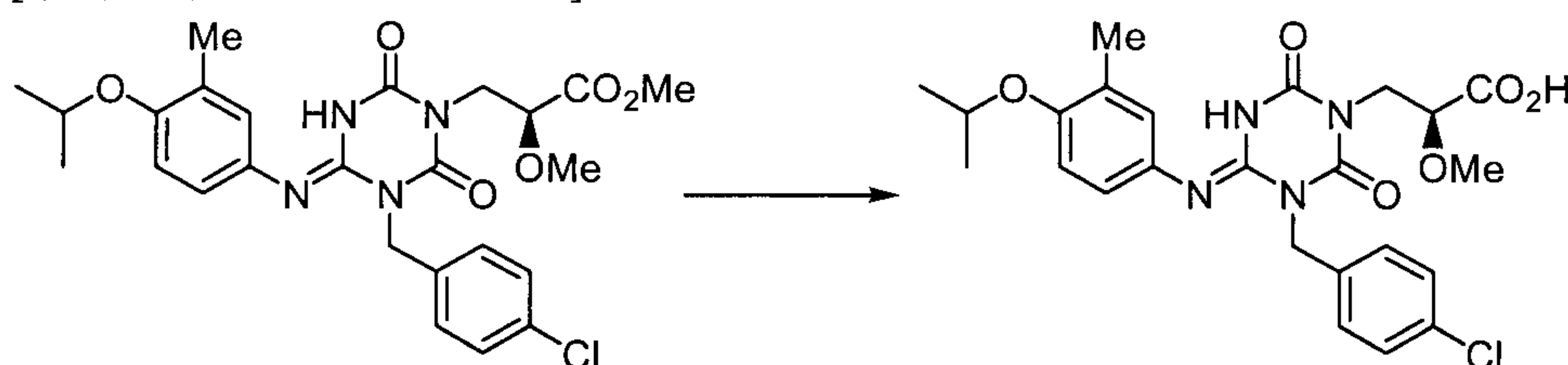
[Example 53]

[0267]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-methoxyethyl)-1,3,5-triazine-2,4-dion (I-0807)

[Chemical Formula 162]



To a mixture of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-methoxyethyl)-1,3,5-triazinane-2,4-dione (340 mg, 0.658 mmol), methanol (2 mL) and THF (2 mL) was added 1mol/L lithium hydroxide (2 mL), and the resulting mixture was stirred at 60°C for 30 minutes. To the reaction mixture was added 10% aqueous citric acid, extracted with ethyl acetate. The extract was washed, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by dichloromethane and hexane to give (S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-methoxyethyl)-1,3,5-triazinane-2,4-dione (243 mg, Yield: 74%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=5.6 Hz), 2.11 (3H, s), 3.25 (3H, s), 3.94-4.05 (3H, m), 4.55 (1H, sept, J=5.9 Hz), 5.27 (2H, s), 6.93 (1H, d, J=8.0 Hz), 7.04-7.07 (2H, m), 7.33 (2H, d, J=8.0 Hz), 7.45 (2H, d, J=8.0 Hz), 9.20 (1H, s), 12.89 (1H, brs).

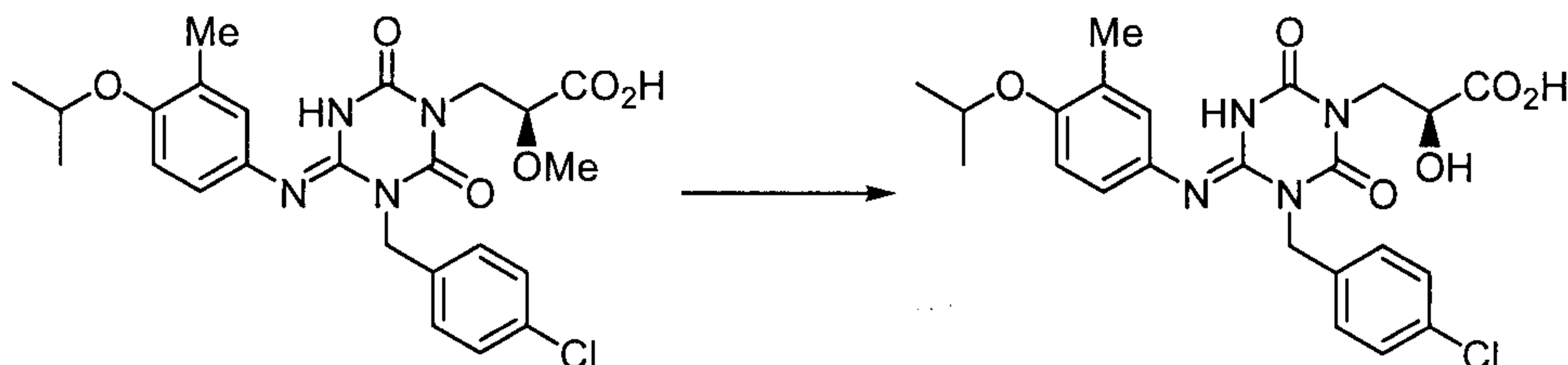
[Example 54]

[0268]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-hydroxyethyl)-1,3,5-triazinane-2,4-dione (I-0852)

[Chemical Formula 163]



To a solution of sodium iodide (119 mg, 0.795 mmol) in acetonitrile (3.2 mL) were added chlorotrimethylsilane (0.102 mL, 0.795 mmol) and (S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-methoxyethyl)-1,3,5-triazinane-2,4-dione (80 mg, 0.16 mmol), and the resulting mixture was heated at reflux for 4 hours. The reaction mixture was added to 10% aqueous sodium hydrogensulfate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give (S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-hydroxyethyl)-1,3,5-triazinane-2,4-dione (23 mg, Yield: 30%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (6H, d, J=5.6 Hz), 2.11 (3H, s), 3.93-3.95 (2H, m), 4.24-4.28 (1H, m), 4.55 (1H, sept, J=5.9 Hz), 5.27 (2H, s), 6.93 (1H, d, J=8.0 Hz), 7.04-7.07 (2H, m), 7.34 (2H, d, J=8.0 Hz), 7.45 (2H, d, J=8.0 Hz), 9.15 (1H, s), 12.57 (1H, brs).

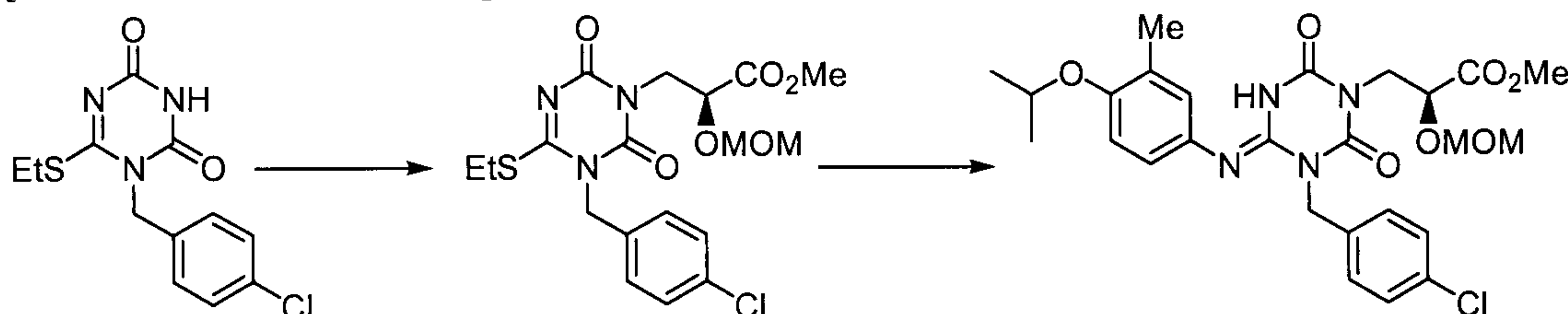
[Example 55]

[0269]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-[2-methoxycarbonyl-2-(methoxymethoxy)ethyl]-1,3,5-triazine-2,4-dione (I-0993)

[Chemical Formula 164]



To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dione (440 mg, 1.48 mmol), di-2-methoxyethylazodicarboxylate (485 mg, 2.07 mmol), triphenylphosphine (775 mg, 2.96 mmol) and dioxane (9 mL) was gradually added

(S)-3-hydroxy-2-methoxy-methoxypropanoic acid methyl (291 mg, 1.77 mmol), and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-[2-methoxycarbonyl-2-(methoxymethoxy)ethyl]-1,3,5-triazine-2,4(1H,3H)-dione (650 mg, Yield: 99%) as colorless oil.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.26 (3H, t, J=7.6 Hz), 3.07-3.15 (5H, m), 3.63 (3H, s), 4.01-4.21 (2H, m), 4.38-4.44 (1H, m), 4.58 (2H, s), 5.09 (2H, s), 7.33 (2H, d, J=8.0 Hz), 7.44 (2H, d, J=8.0 Hz).

A mixture of

(S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-[2-methoxycarbonyl-2-(methoxymethoxy)ethyl]-1,3,5-triazine-2,4(1H,3H)-dione (650 mg, 1.46 mmol), 3-methyl-4-isopropoxyaniline (363 mg, 2.20 mmol), acetic acid (1.26 mL) and t-butanol (6.5 mL) was heated at reflux for 6 hours.

The reaction mixture was added to saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-[2-methoxycarbonyl-2-(methoxymethoxy)ethyl]-1,3,5-triazine-2,4-dione (590 mg, Yield: 74%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.6 Hz), 2.11 (3H, s), 3.17 (3H, s), 3.59 (3H, s), 3.97-4.12 (2H, m), 4.34-4.40 (1H, m), 4.56 (3H, s), 5.26 (2H, s), 6.95 (1H, d, J=8.0 Hz), 7.04 (2H, brs), 7.35 (2H, d, J=8.0 Hz), 7.46 (2H, d, J=8.0 Hz), 9.25 (1H, s).

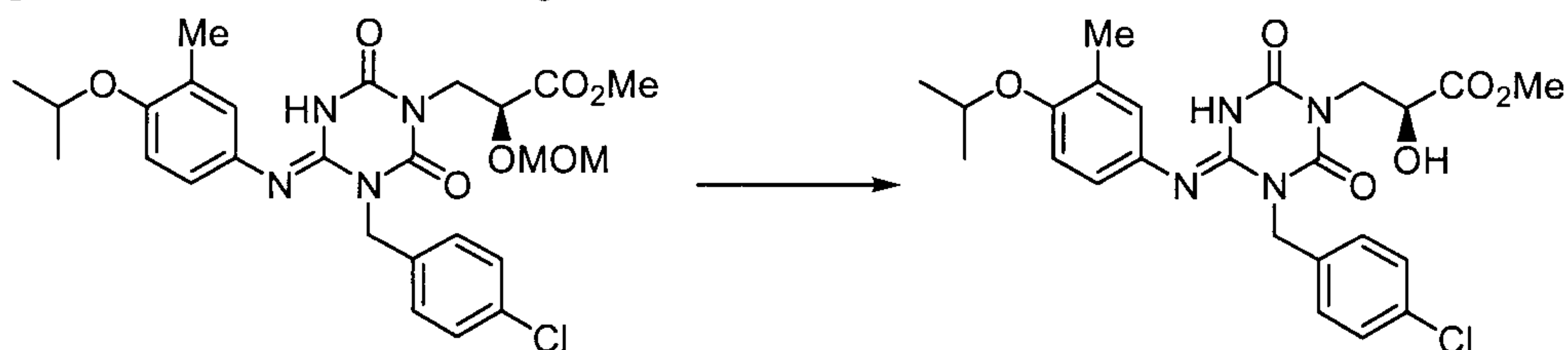
[Example 56]

[0270]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-hydroxyethyl)-1,3,5-triazine-2,4-dione (I-0994)

[Chemical Formula 165]



A mixture of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-[2-methoxycarbonyl-2-(methoxymethoxy)ethyl]-1,3,5-triazinane-2,4-dione (585 mg, 1.07 mmol) and 4mol/L hydrogen chloride in dioxane (6 mL), and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was added to saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo to give (S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-hydroxyethyl)-1,3,5-triazinane-2,4-dione (537 mg, Yield: 100%) as pale purple solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.6 Hz), 2.11 (3H, s), 3.53 (3H, s), 3.94-3.96 (2H, m), 4.27-4.30 (1H, m), 4.54-4.57 (1H, m), 5.26 (2H, s), 5.72-5.79 (1H, m), 6.94 (1H, d, J=8.0 Hz), 7.04-7.07 (2H, m), 7.35 (2H, d, J=8.0 Hz), 7.46 (2H, d, J=8.0 Hz), 9.20 (1H, s).

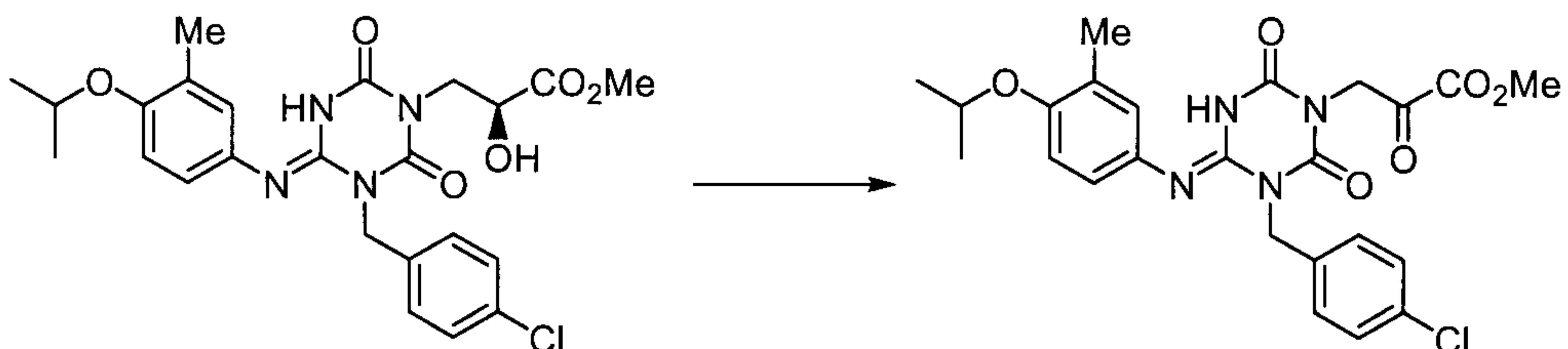
[Example 57]

[0271]

Preparation of

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-oxoethyl)-1,3,5-triazinane-2,4-dione (I-0996)

[Chemical Formula 166]



To a solution of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-hydroxyethyl)-1,3,5-triazinane-2,4-dione (150 mg, 0.298 mmol) in dichloromethane (6 mL) was added 0.3mol/L Dess-Martin reagent in dichloromethane (1.19 mL, 0.358 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture were added 10% aqueous sodium hydrogensulfate and saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 50-80%), to give

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-oxoethyl)-1,3,5-triazinane-2,4-dione (17 mg, Yield: 11%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.6 Hz), 2.12 (3H, s), 3.81 (3H, s), 4.54-4.57 (1H, m), 5.03 (2H, s), 5.28 (2H, s), 6.94 (1H, d, J=8.0 Hz), 7.05 (2H, brs), 7.35 (2H,

d, J=8.0 Hz), 7.47 (2H, d, J=8.0 Hz), 9.37 (1H, s).

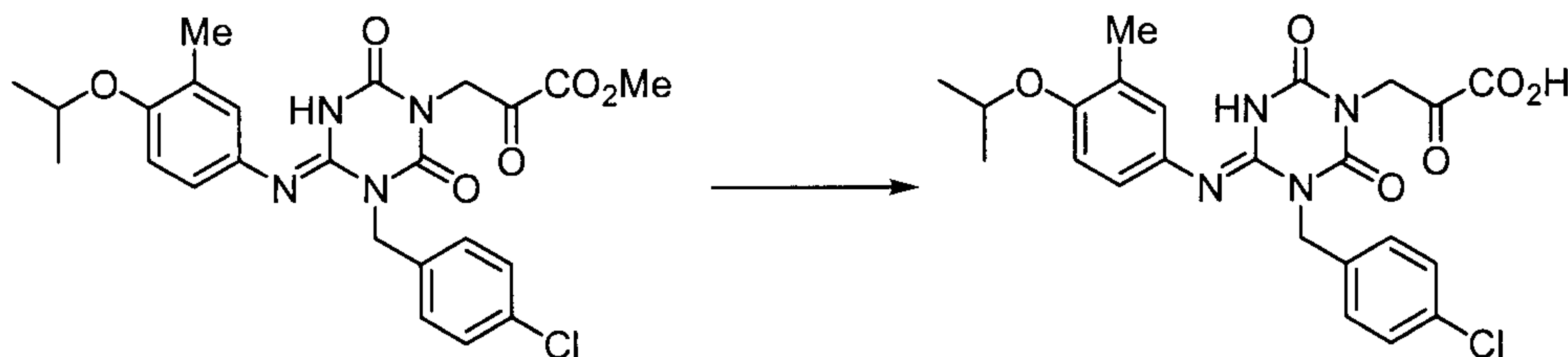
[Example 58]

[0272]

Preparation of

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-oxoethyl)-1,3,5-triazinane-2,4-dione (I-1009)

[Chemical Formula 167]



To a mixture of

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonyl-2-oxoethyl)-1,3,5-triazinane-2,4-dione (15 mg, 0.030 mmol), methanol (0.3 mL) and THF (0.3 mL) was added 1mol/L lithium hydroxide (0.09 mL), and the resulting mixture was stirred at 50°C for 3 hours. To the reaction mixture was added 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by dichloromethane and hexane to give

1-(4-chlorobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonyl-2-oxoethyl)-1,3,5-triazinane-2,4-dione (5 mg, Yield: 34%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.27 (6H, d, J=5.6 Hz), 2.11 (3H, s), 4.53-4.57 (1H, m), 4.98 (2H, s), 5.28 (2H, s), 6.94 (1H, d, J=8.0 Hz), 7.05 (2H, brs), 7.35 (2H, d, J=8.0 Hz), 7.47 (2H, d, J=8.0 Hz), 9.35 (1H, s).

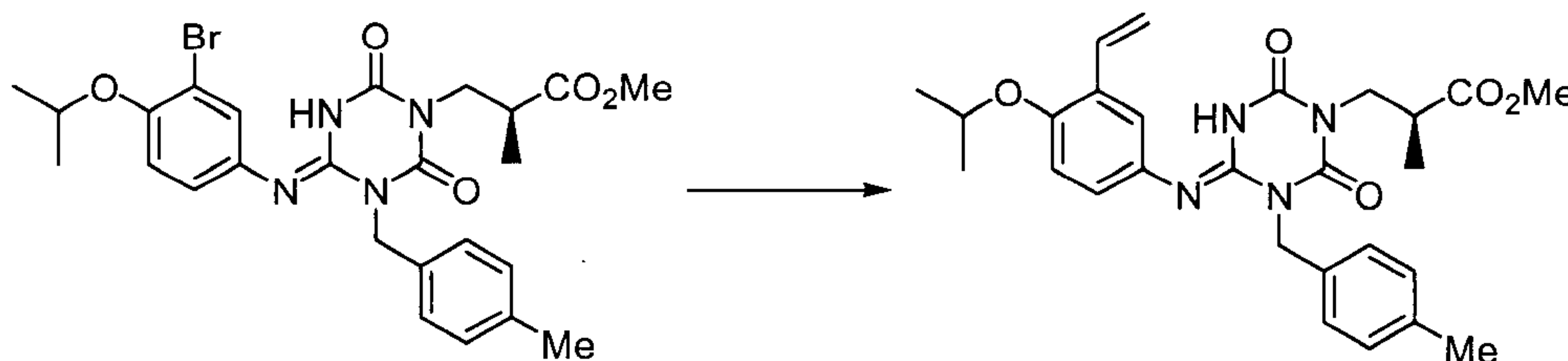
[Example 59]

[0273]

Preparation of

(S)-1-(4-methylbenzyl)-6-(3-vinyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (I-0907)

[Chemical Formula 168]



A mixture of

(S)-1-(4-methylbenzyl)-6-(3-bromo-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (350 mg, 0.642 mmol), vinyl boronic acid pinacol ester (0.163 mL, 0.963 mmol), dichloro[1,1'-bis(di-tert-butylphosphino)ferrocene]palladium(II) (42 mg, 0.064 mmol), THF (7 mL), and 2mol/L aqueous potassium carbonate (1.28 mL) was heated at reflux for 40 minutes. To the reaction mixture was added water and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was

purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-1-(4-methylbenzyl)-6-(3-vinyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (302 mg, Yield: 96%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04-1.07 (3H, m), 1.27 (6H, d, J=5.6 Hz), 2.28 (3H, s), 2.80-2.83 (1H, m), 3.49 (3H, s), 3.78-3.97 (2H, m), 4.58-4.61 (1H, m), 5.24-5.28 (3H, m), 5.70 (1H, d, J=16.0 Hz), 6.90-7.04 (2H, m), 7.20 (5H, s), 7.39 (1H, s), 9.24 (1H, s).

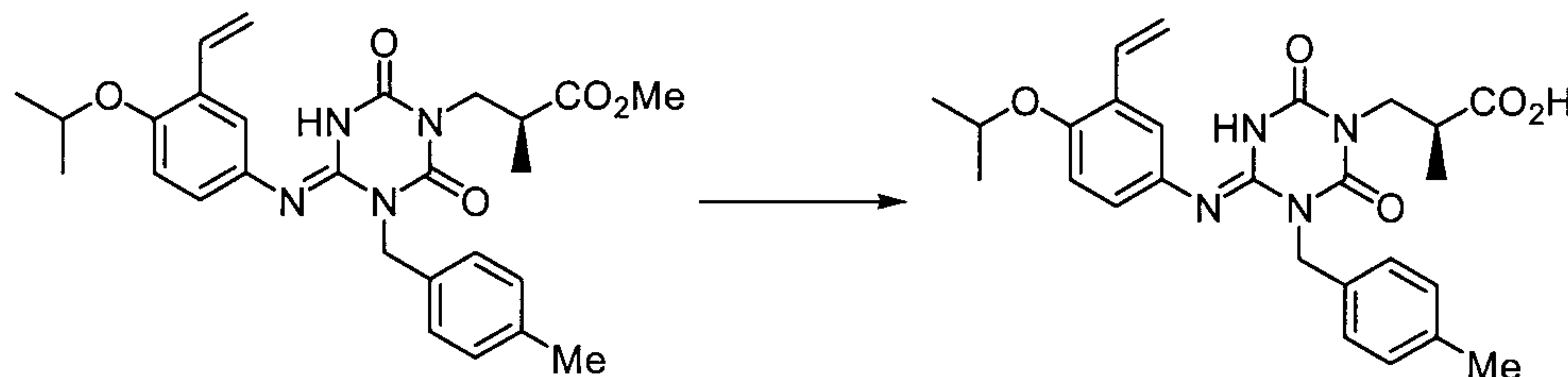
[Example 60]

[0274]

Preparation of

(S)-1-(4-methylbenzyl)-6-(3-vinyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (I-0910)

[Chemical Formula 169]



To a mixture of

(S)-1-(4-methylbenzyl)-6-(3-vinyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (85 mg, 0.17 mmol), methanol (0.6 mL) and THF (0.6 mL) was added 1mol/L lithium hydroxide (0.52 mL), and the resulting mixture was stirred at room temperature for 3 days. To the reaction mixture was added 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-methylbenzyl)-6-(3-vinyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (59 mg, Yield: 71%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04-1.07 (3H, m), 1.27 (6H, d, J=5.6 Hz), 2.28 (3H, s), 2.80-2.83 (1H, m), 3.78-3.97 (2H, m), 4.58-4.61 (1H, m), 5.24-5.28 (3H, m), 5.70 (1H, d, J=16.0 Hz), 6.90-7.04 (2H, m), 7.20-7.38 (5H, m), 7.47 (1H, s), 9.24 (1H, brs).

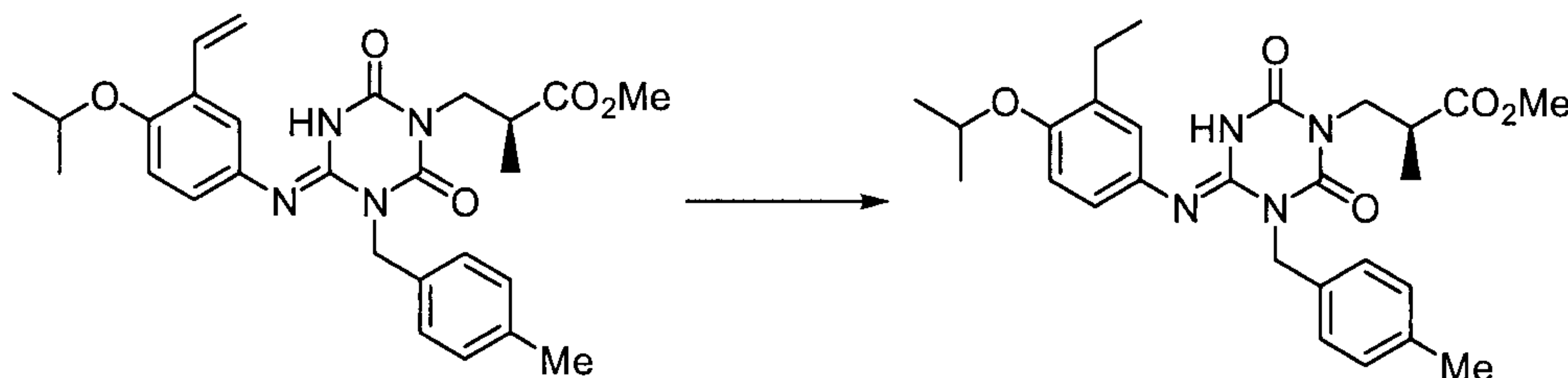
[Example 61]

[0275]

Preparation of

(S)-1-(4-methylbenzyl)-6-(3-ethyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (I-0908)

[Chemical Formula 170]



A solution of

(S)-1-(4-methylbenzyl)-6-(3-vinyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-

1,3,5-triazinane-2,4-dion (200 mg, 0.406 mmol) in methanol (20 mL) was hydrogenated under 5% Pt/C. The reaction mixture was concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-methylbenzyl)-6-(3-ethyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (188 mg, Yield: 94%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.03-1.12 (6H, m), 1.27 (6H, d, J=5.6 Hz), 2.28 (3H, s), 2.50-2.53 (2H, m), 2.80-2.83 (1H, m), 3.56 (3H, s), 3.78-3.96 (2H, m), 4.56-4.58 (1H, m), 5.20 (2H, m), 6.93-7.11 (3H, m), 7.20 (4H, s), 9.16 (1H, s).

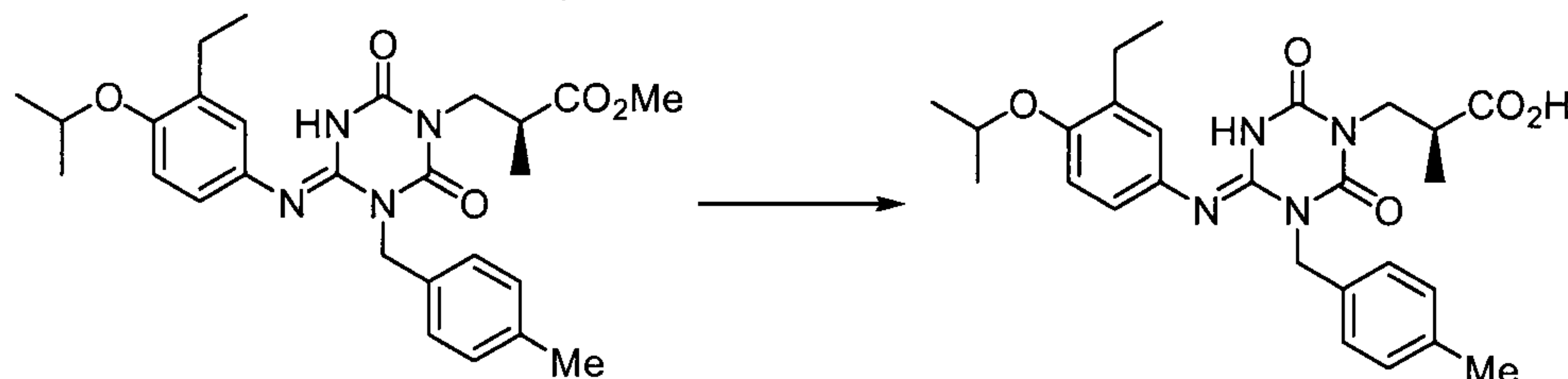
[Example 62]

[0276]

Preparation of

(S)-1-(4-methylbenzyl)-6-(3-ethyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (I-0911)

[Chemical Formula 171]



To a mixture of

(S)-1-(4-methylbenzyl)-6-(3-ethyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (160 mg, 0.324 mmol), methanol (1 mL) and THF(1 mL) was added 1mol/L lithium hydroxide (1 mL), and the resulting mixture was stirred at 60°C for 1 hour. To the reaction mixture was added 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-methylbenzyl)-6-(3-ethyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (122 mg, Yield: 79%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.01 (3H, d, J=6.8 Hz), 1.10 (3H, t, J=7.6 Hz), 1.27 (6H, d, J=5.6 Hz), 2.28 (3H, s), 2.50-2.53 (2H, m), 2.80-2.83 (1H, m), 3.78-3.96 (2H, m), 4.56-4.58 (1H, m), 5.24 (2H, m), 6.81-7.19 (3H, m), 7.28 (4H, s), 9.11 (1H, s), 12.30 (1H, brs).

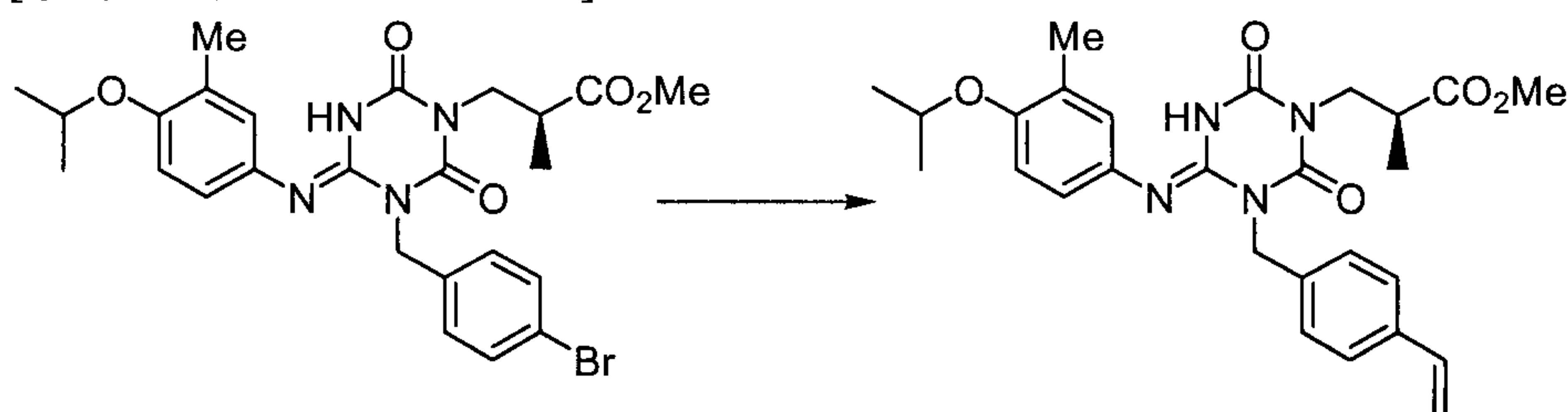
[Example 63]

[0277]

Preparation of

(S)-1-(4-vinylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dion (I-0892)

[Chemical Formula 172]



To a mixture of

(S)-1-(4-bromobenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (300 mg, 0.550 mmol), vinyl boronic acid pinacol ester (0.140 mL, 0.825 mmol), dichloro[1,1'-bis(di-tert-butylphosphino)ferrocene]palladium(II) (36 mg, 0.055 mmol), THF (6 mL) and 2mol/L aqueous potassium carbonate (1.10 mL) was heated at reflux for 1 hour. To the reaction mixture was added water and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-1-(4-vinylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (256 mg, Yield: 95%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04 (3H, d, J=6.8 Hz), 1.27 (6H, d, J=5.6 Hz), 2.11 (3H, s), 2.80-2.83 (1H, m), 3.49 (3H, s), 3.79-3.96 (2H, m), 4.53-4.56 (1H, m), 5.24-5.27 (3H, m), 5.83 (1H, d, J=16.0 Hz), 6.69-6.76 (1H, m), 6.93 (1H, d, J=8.0 Hz), 7.05-7.07 (2H, m), 7.28 (2H, d, J=8.0 Hz), 7.49 (2H, d, J=8.0 Hz), 9.19 (1H, s).

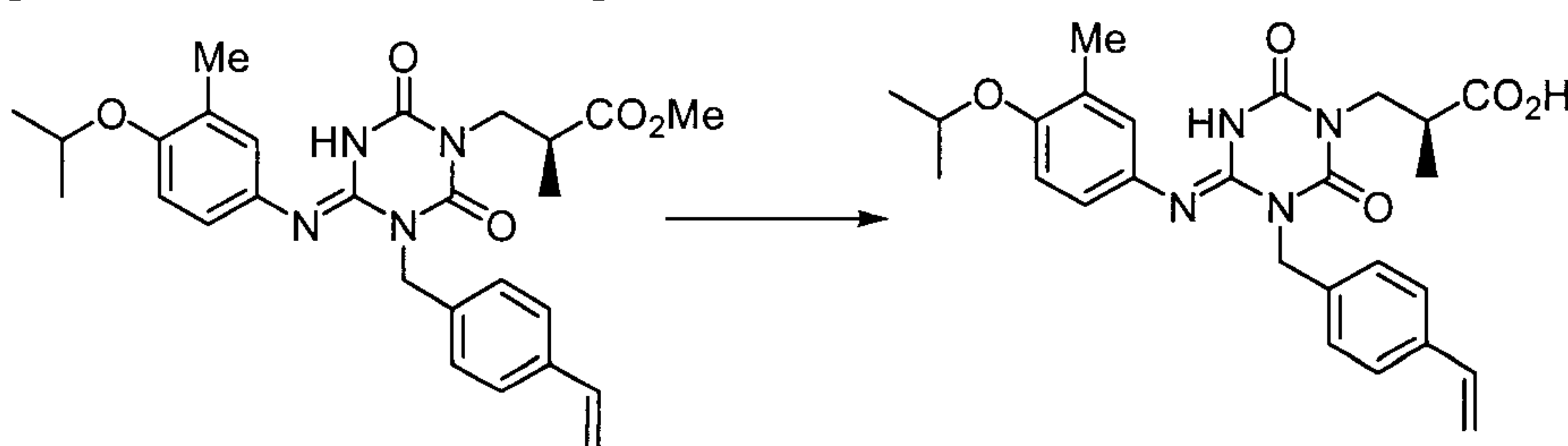
[Example 64]

[0278]

Preparation of

(S)-1-(4-vinylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (I-0897)

[Chemical Formula 173]



A mixture of

(S)-1-(4-vinylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (50 mg, 0.10 mmol), methanol (0.4 mL) and THF (0.4 mL) was added 1mol/L lithium hydroxide (0.3 mL), and the resulting mixture was stirred at room temperature 6 hours. To the reaction mixture was added 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-vinylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (36 mg, Yield: 74%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.01 (3H, d, J=6.8 Hz), 1.26 (6H, d, J=5.6 Hz), 2.10 (3H, s), 2.76-2.80 (1H, m), 3.78-3.97 (2H, m), 4.50-4.55 (1H, m), 5.24-5.27 (3H, m), 5.83 (1H, d, J=16.0 Hz), 6.69-6.76 (1H, m), 6.93 (1H, d, J=8.0 Hz), 7.04-7.07 (2H, m), 7.28 (2H, d, J=8.0 Hz), 7.49 (2H, d, J=8.0 Hz), 9.14 (1H, s), 12.29 (1H, brs).

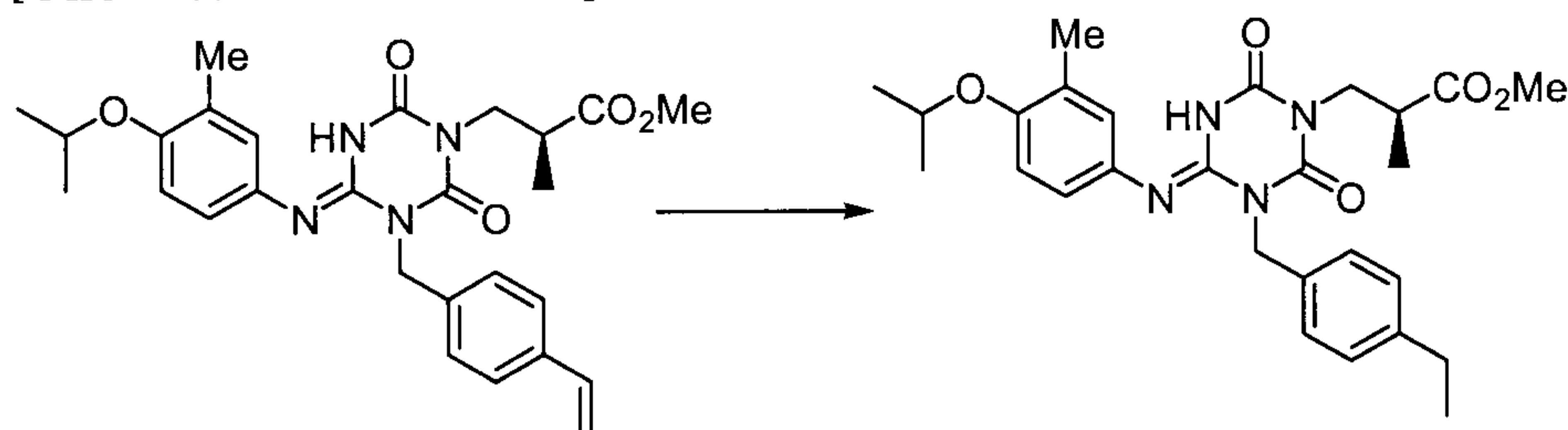
[Example 65]

[0279]

Preparation of

(S)-1-(4-ethylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (I-0894)

[Chemical Formula 174]



A solution of

(S)-1-(4-vinylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (190 mg, 0.386 mmol) in methanol (19 mL) was hydrogenated under 5% Pt/C. The reaction mixture was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-1-(4-ethylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (99 mg, Yield: 52%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04 (3H, d, J=6.8 Hz), 1.15 (3H, t, J=7.6 Hz), 1.27 (6H, d, J=5.6 Hz), 2.11 (3H, s), 2.58 (2H, q, J=7.6 Hz), 2.79-2.84 (1H, m), 3.47 (3H, s), 3.78-3.96 (2H, m), 4.53-4.57 (1H, m), 5.23 (2H, s), 6.93 (1H, d, J=8.0 Hz), 7.05-7.08 (2H, m), 7.22 (4H, s), 9.18 (1H, s).

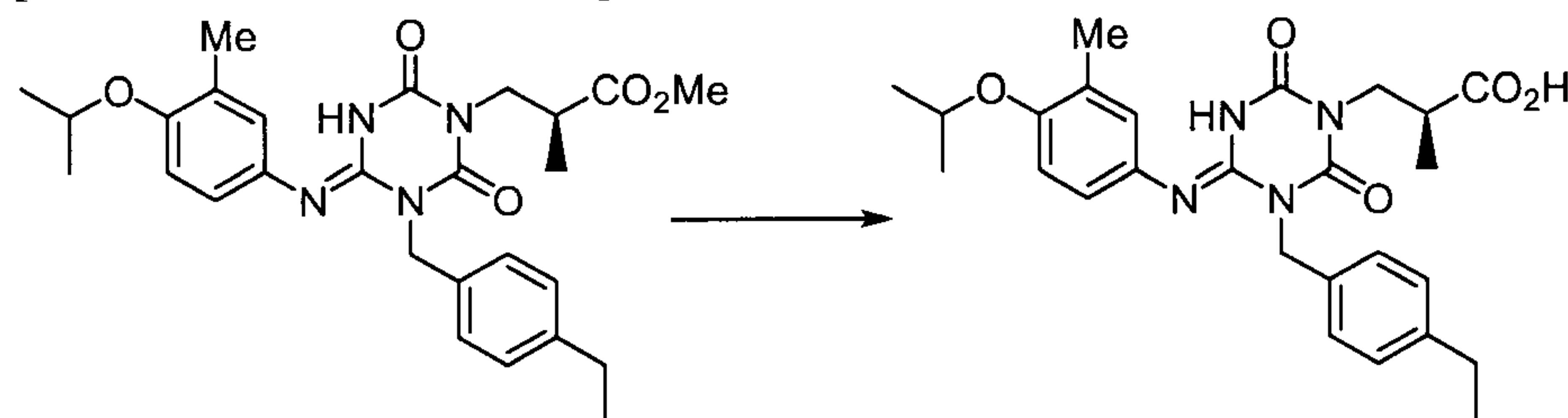
[Example 66]

[0280]

Preparation of

(S)-1-(4-ethylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (I-0898)

[Chemical Formula 175]



To a mixture of

(S)-1-(4-ethylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (94 mg, 0.19 mmol), methanol (1 mL) and THF (1 mL) was added 1mol/L lithium hydroxide (0.57 mL), and the resulting mixture was stirred at 60°C for 3 hours. To the reaction mixture was added 10% aqueous citric acid, and the resulting

mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give

(S)-1-(4-ethylbenzyl)-6-(3-methyl-4-isopropoxyphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (78 mg, Yield: 85%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.01 (3H, d, J=6.8 Hz), 1.16 (3H, t, J=7.6 Hz), 1.26 (6H, d, J=5.6 Hz), 2.10 (3H, s), 2.58 (2H, q, J=7.6 Hz), 2.79-2.84 (1H, m), 3.74-3.97 (2H, m), 4.53-4.57 (1H, m), 5.24 (2H, s), 6.92 (1H, d, J=8.0 Hz), 7.05-7.08 (2H, m), 7.22 (4H, s), 9.12 (1H, s), 12.31 (1H, brs).

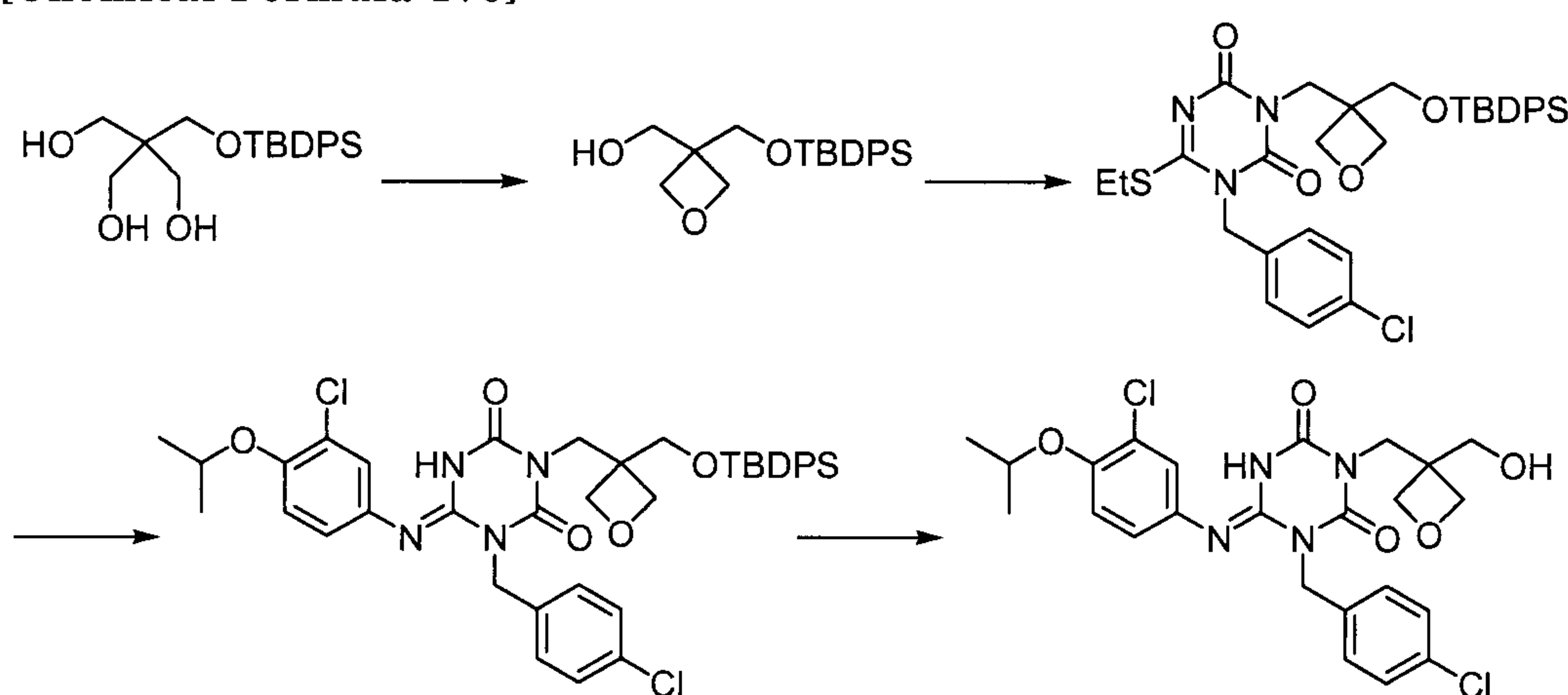
[Example 67]

[0281]

Preparation of

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(1-hydroxymethyl-3-oxacyclobutyl)methyl-1,3,5-triazinane-2,4-dione (I-1010)

[Chemical Formula 176]



To a solution of 2-(t-butyl-diphenylsilyloxymethyl)-2-hydroxymethyl-propane-1,3-diol (441 mg, 1.18 mmol) in THF (9 mL) were added 1.67 mol/L n-butyllithium/n-hexane solution (1.55 mL, 2.59 mmol) and p-toluenesulfonyl chloride (247 mg, 1.30 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 20 hours. To the reaction mixture was added water, and the resulting mixture was extracted with diethyl ether. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(t-butyl-diphenylsilyloxymethyl)-1-hydroxymethyl-3-oxacyclobutane (148 mg, Yield: 35%) as colorless oil.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.01 (9H, s), 3.67 (2H, d, J = 4.8 Hz), 3.80 (2H, s), 4.33-4.36 (4H, m), 4.90-4.93 (1H, m), 7.42-7.47 (6H, m), 7.63 (4H, d, J = 6.8 Hz).

To a mixture of 1-(4-chlorobenzyl)-6-(ethylthio)-1,3,5-triazine-2,4(1H,3H)-dione (150 mg, 0.504 mmol), 1-(t-butyl-diphenylsilyloxymethyl)-1-hydroxymethyl-3-oxacyclobutane (198 mg, 0.554 mmol), triphenylphosphine (198 mg, 0.756 mmol) and dioxane (2 mL) was added di-2-methoxyethylazodicarboxylate (165 mg, 0.705 mmol), and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added water, extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous

sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-6-(ethylthio)-3-[1-(t-butyl-diphenylsilyloxymethyl)-3-oxacyclobutyl]methyl-1,3,5-triazine-2,4(1H,3H)-dion (273 mg, Yield: 85%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 0.99 (9.0H, s), 1.26 (3.0H, t, J = 7.2 Hz), 3.11 (2.0H, q, J = 7.2 Hz), 3.86 (2.0H, s), 4.11 (2.0H, s), 4.20 (2.0H, d, J = 6.1 Hz), 4.47 (2.0H, d, J = 6.1 Hz), 5.06 (2.0H, s), 7.32-7.37 (4.0H, m), 7.41-7.47 (6.0H, m), 7.61 (4.0H, d, J = 7.3 Hz).

A mixture of

1-(4-chlorobenzyl)-6-(ethylthio)-3-[1-(t-butyl-diphenylsilyloxymethyl)-3-oxacyclobutyl]methyl-1,3,5-triazine-2,4(1H,3H)-dion (273 mg, 0.429 mmol), 3-chloro-4-isopropoxyaniline (119 mg, 0.644 mmol), acetic acid (0.368 mL) and t-butanol (3 mL) was heated at reflux for 7 hours. The reaction mixture was added to saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-[1-(t-butyl-diphenylsilyloxymethyl)-3-oxacyclobutyl]methyl-1,3,5-triazinane-2,4-dion (248 mg, Yield: 76%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.00 (9H, s), 1.29 (6H, d, J = 5.8 Hz), 3.83 (2H, s), 4.05 (2H, s), 4.19 (2H, d, J = 6.1 Hz), 4.44 (2H, d, J = 6.1 Hz), 4.57-4.66 (1H, m), 5.22 (2H, s), 7.10-7.50 (13H, m), 7.61 (4H, d, J = 7.1 Hz), 9.35 (1H, brs).

To a solution of 1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-[1-(t-butyl-diphenylsilyloxymethyl)-3-oxacyclobutyl]methyl-1,3,5-triazinane-2,4-dion (240 mg, 0.316 mmol) in THF (3 mL) was added a solution of 1mol/L tetra-n-butylammonium fluoride in THF (0.88 mL, 0.88 mmol), and the resulting mixture was stirred at 45°C for 3 hours. The reaction mixture was added to aqueous ammonium chloride, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(1-hydroxymethyl-3-oxacyclobutyl)methyl-1,3,5-triazinane-2,4-dion (120 mg, Yield: 73%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.29 (6H, d, J = 5.8 Hz), 3.61 (2H, d, J = 4.5 Hz), 3.95 (2H, s), 4.18 (2H, d, J = 6.1 Hz), 4.40 (2H, d, J = 6.1 Hz), 4.60-4.62 (1H, m), 4.93-4.95 (1H, m), 5.22 (2H, s), 7.12-7.44 (7H, m).

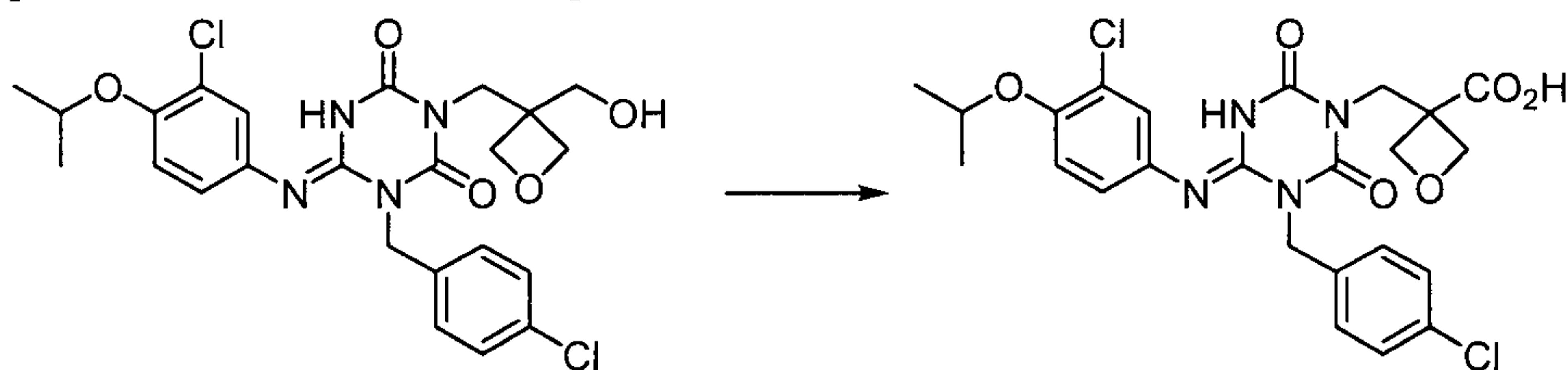
[Example 68]

[0282]

Preparation of

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(1-hydroxycarbonyl-3-oxacyclobutyl)methyl-1,3,5-triazinane-2,4-dion (I-1011)

[Chemical Formula 177]



To a solution of

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(1-hydroxymethyl-3-oxacyclobutyl)methyl-1,3,5-triazinane-2,4-dione (50 mg, 0.096 mmol) in acetone (0.8 mL) was added 2.67 mol/L Jones reagent (0.079 mL, 0.21 mmol), and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture were added isopropanol and water, and the resulting mixture was extracted with ethyl acetate. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give

1-(4-chlorobenzyl)-6-(3-chloro-4-isopropoxyphenylimino)-3-(1-hydroxycarbonyl-3-oxacyclobutyl)methyl-1,3,5-triazinane-2,4-dione (8 mg, Yield: 16%) as colorless solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.36 (6H, d, J = 6.0 Hz), 4.43 (2H, s), 4.44-4.52 (1H, m), 4.67 (2H, d, J = 6.7 Hz), 4.76 (2H, d, J = 6.7 Hz), 5.16 (2H, s), 6.65-6.67 (1H, m), 6.86-6.90 (2H, m), 7.31 (2H, d, J = 8.4 Hz), 7.41 (2H, d, J = 8.4 Hz).

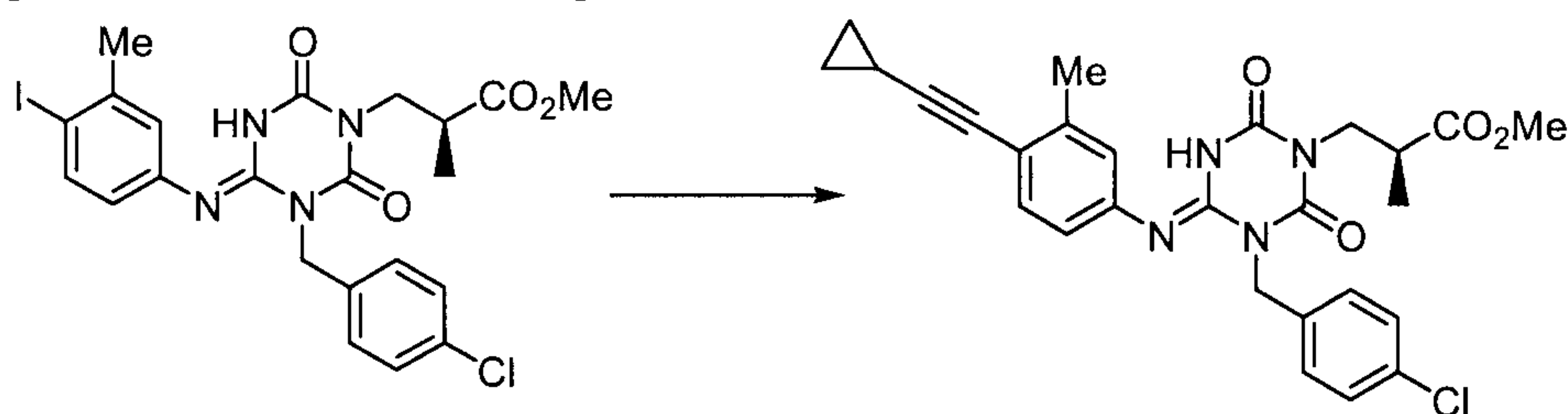
[Example 69]

[0283]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-cyclopropylethynylphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (I-1041)

[Chemical Formula 178]



A mixture of

(S)-1-(4-chlorobenzyl)-6-(4-iodo-3-methylphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (268 mg, 0.471 mmol), ethynylcyclopropane (0.080 mL, 0.94 mmol), bis(triphenylphosphine)palladium (II) dichloride (8.3 mg, 0.012 mmol), cuprous iodide (I) (4.5 mg, 0.024 mmol), triethylamine (0.131 mL, 0.942 mmol) and DMF (3 mL) was stirred at 60°C for 2 hours. To the reaction mixture was added 5% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-cyclopropylethynylphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (200 mg, Yield: 84%) as brown solid.

¹H-NMR (δ ppm TMS/CDCl₃): 0.75-0.95 (4H, m), 1.18 (3H, d, J=6.9 Hz), 1.49 (1H, m), 2.37 (3H, s), 2.89 (1H, m), 3.60 (3H, s), 3.87 (1H, dd, J=6.0, 13.8 Hz), 4.09 (1H, m), 5.10-5.24 (2H, m), 6.57 (1H, m), 6.63 (1H, m), 7.26-7.36 (4H, m), 7.48 (2H, d, J=8.4 Hz).

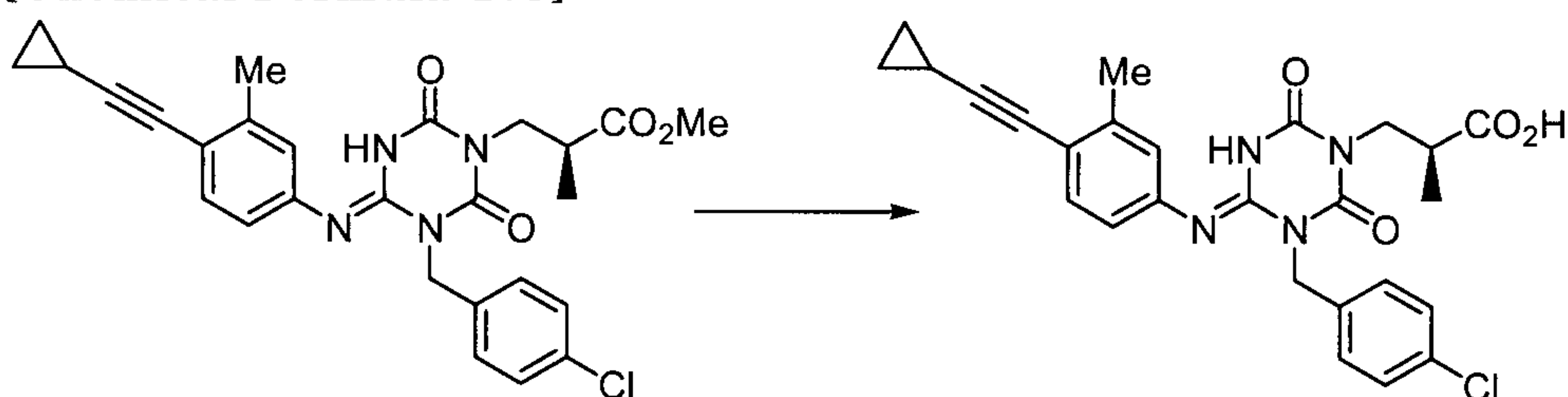
[Example 70]

[0284]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-cyclopropylethynylphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (I-1042)

[Chemical Formula 179]



To a mixture of

(S)-1-(4-chlorobenzyl)-6-(3-methyl-4-cyclopropylethynylphenylimino)-3-(2-methoxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (180 mg, 0.355 mmol), methanol (1 mL) and THF (1 mL) was added 1mol/L sodium hydroxide (1.1 mL), and the resulting mixture was stirred at room temperature for 2.5 hours. To the reaction mixture was added 2mol/L hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-chlorobenzyl)-6-(3-methyl-4-cyclopropylethynylphenylimino)-3-(2-hydroxycarbonylpropyl)-1,3,5-triazinane-2,4-dione (78 mg, Yield: 85%) as pale brown solid.

¹H-NMR (δ ppm TMS/CDCl₃): 0.75-0.95 (4H, m), 1.19 (3H, d, J=6.9 Hz), 1.48 (1H, m), 2.35 (3H, s), 2.92 (1H, m), 3.87 (1H, dd, J=6.3, 13.5 Hz), 4.10 (1H, dd, J=7.2, 13.2 Hz), 5.16 (2H, s), 6.55 (1H, m), 6.61 (1H, s), 7.24-7.34 (3H, m), 7.44 (2H, d, J=8.4 Hz), 7.66 (1H, s).

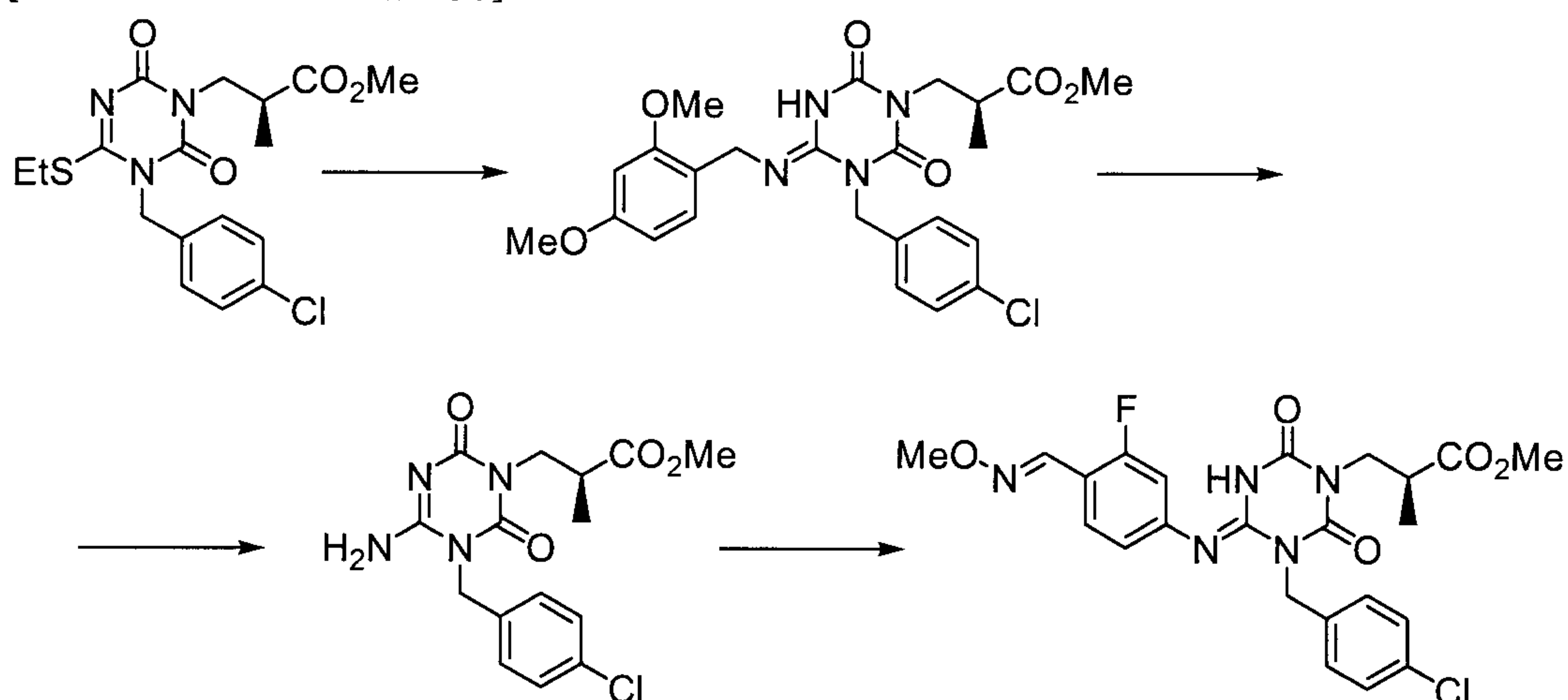
[Example 71]

[0285]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyiminomethylphenylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dione (I-0881)

[Chemical Formula 180]



A mixture of (S)-1-(4-chlorobenzyl)-6-(ethylthio)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (1.00 g, 2.51 mmol), 2,4-dimethoxybenzylamine (630 mg, 3.77 mmol), acetic acid (2.16 mL) and t-butanol (20 mL) was heated at reflux for 15 hours. The reaction mixture was added to saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate. The extract was washed by 2mol/L hydrochloric acid and brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-1-(4-chlorobenzyl)-6-(2,4-dimethoxybenzylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (1.19 g, Yield: 94%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04 (3H, d, J=6.8 Hz), 2.82 (1H, q, J=6.8 Hz), 3.48 (3H, s), 3.72 (6H, s), 3.77-3.82 (1H, m), 3.90-3.95 (1H, m), 4.37 (2H, s), 5.15 (2H, s), 6.35 (1H, d, J=8.4 Hz), 6.51 (1H, s), 6.73 (1H, d, J=8.4 Hz), 7.27 (2H, d, J=7.6 Hz), 7.44 (2H, d, J=7.6 Hz), 7.94 (1H, brs).

A solution of (S)-1-(4-chlorobenzyl)-6-(2,4-dimethoxybenzylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (1.15 g, 2.29 mmol) in trifluoroacetic acid (11 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo, and the residue was extracted with chloroform. The extract was washed by saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-6-amino-1-(4-chlorobenzyl)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (0.80 g, Yield: 99%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04 (3H, d, J=6.8 Hz), 2.81 (1H, q, J=6.8 Hz), 3.49 (3H, s), 3.74-3.81 (1H, m), 3.89-3.94 (1H, m), 5.03 (2H, s), 7.27 (2H, d, J=7.6 Hz), 7.43 (2H, d, J=7.6 Hz), 7.86 (2H, brs).

A mixture of (S)-6-amino-1-(4-chlorobenzyl)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4(1H,3H)-dione (80 mg, 0.35 mmol), 3-fluoro-4-methoxyiminomethylaniline (146 mg, 0.414 mmol), acetic acid palladium (7.7 mg, 0.034 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene (30 mg, 0.052 mmol),

cesium carbonate (157 mg, 0.483 mmol) and dioxane (2.4 mL) was heated at reflux for 24 hours. To the reaction mixture was added water, and the resulting mixture was extracted with ethyl acetate and THF. The extract was washed by brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-1-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyiminomethylphenylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dion (53 mg, Yield: 31%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.07 (3H, d, J=6.8 Hz), 2.81 (1H, q, J=6.8 Hz), 3.50 (3H, s), 3.83 (1H, brs), 3.90 (4H, brs), 5.09 (2H, s), 6.65-6.69 (1H, m), 7.41 (5H, brs), 7.63 (1H, brs), 8.25 (1H, s), 10.97 (1H, brs).

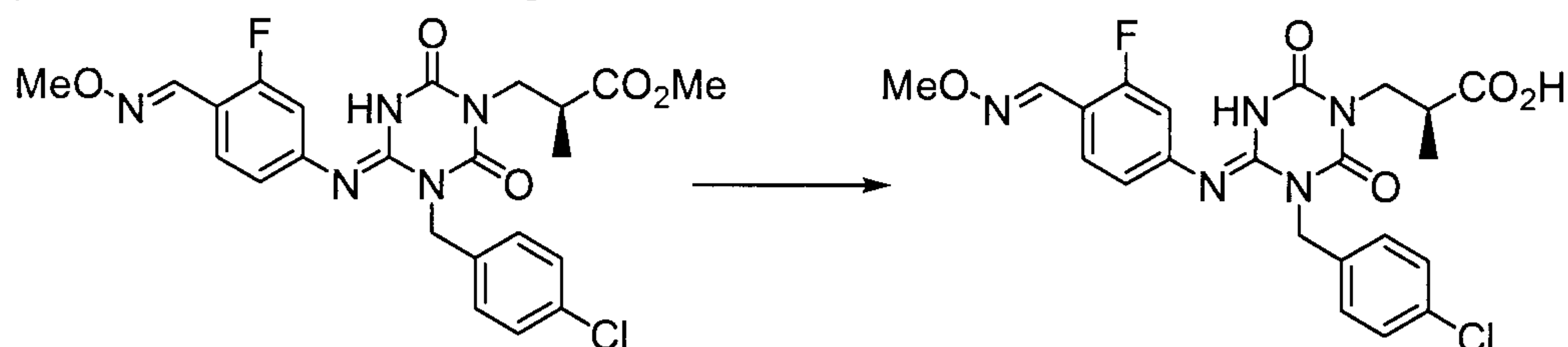
[Example 72]

[0286]

Preparation of

(S)-1-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyiminomethylphenylimino)-3-(2-hydroxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dion (I-0893)

[Chemical Formula 181]



To a mixture of

(S)-1-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyiminomethylphenylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dion (50 mg, 0.099 mmol), methanol (1 mL) and THF (1 mL) was added 1mol/L lithium hydroxide (0.3 mL), and the resulting mixture was stirred at 60°C for 2 hours. To the reaction mixture was added 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give (S)-1-(4-chlorobenzyl)-6-(3-fluoro-4-methoxyiminomethylphenylimino)-3-(2-hydroxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dion (44 mg, Yield: 91%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.04 (3H, d, J=6.8 Hz), 2.76 (1H, q, J=6.8 Hz), 3.81 (1H, brs), 3.90 (4H, brs), 5.12 (2H, s), 6.67 (1H, brs), 7.40 (5H, s), 7.65 (1H, brs), 8.24 (1H, s), 10.92 (1H, brs), 12.36 (1H, brs).

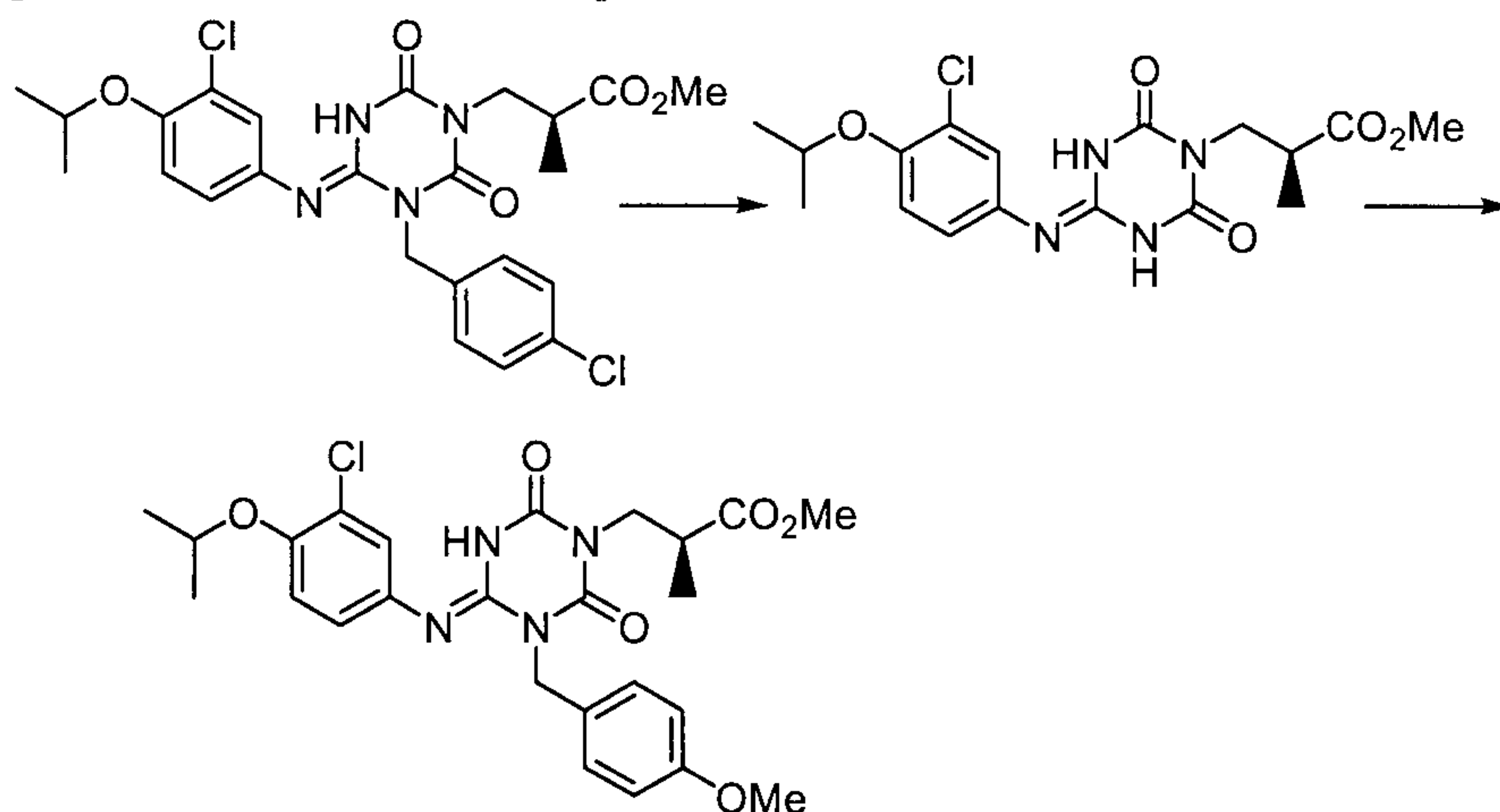
[Example 73]

[0287]

Preparation of

(S)-6-(3-chloro-4-isopropoxyphenylimino)-1-(4-methoxybenzyl)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dion (I-1143)

[Chemical Formula 182]



A mixture of

(S)-6-(3-chloro-4-isopropoxyphenylimino)-1-(4-chlorobenzyl)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (800 mg, 1.53 mmol) in methanol (75 mL) and DMF (5 mL) was hydrogenated under 10% Pd/C. The reaction mixture was concentrated in vacuo. The resulting residue was purified by high speed liquid chromatography (0.3% HCO₂H H₂O/MeCN 40-70%) to give

(S)-6-(3-chloro-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (498 mg, Yield: 82%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.05 (3H, d, J=6.8 Hz), 1.29 (6H, d, J=5.6 Hz), 2.81 (1H, q, J=6.8 Hz), 3.56 (3H, s), 3.77-3.82 (1H, m), 3.87-3.92 (1H, m), 4.62 (1H, sept, J=5.6 Hz), 7.16 (1H, d, J=8.4 Hz), 7.34 (1H, d, J=8.4 Hz), 7.69 (1H, s), 8.14 (1H, s).

To a mixture of

(S)-6-(3-chloro-4-isopropoxyphenylimino)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (480 mg, 1.21 mmol), 4-methoxybenzyl chloride (341 mg, 2.18 mmol) and DMF (10 mL) was added potassium carbonate (301 mg, 2.18 mmol), and the resulting mixture was stirred at room temperature 12 hours. To the reaction mixture was added water, extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (S)-6-(3-chloro-4-isopropoxyphenylimino)-1-(4-methoxybenzyl)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (190 mg, Yield: 30%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.05 (3H, d, J=6.8 Hz), 1.29 (6H, d, J=5.6 Hz), 2.81 (1H, q, J=6.8 Hz), 3.49 (3H, s), 3.73 (3H, s), 3.77-3.82 (1H, m), 3.87-3.92 (1H, m), 4.64 (1H, sept, J=5.6 Hz), 5.20 (2H, s), 6.94 (2H, d, J=7.2 Hz), 7.16-7.28 (4H, m), 7.47 (1H, s), 9.28 (1H, s).

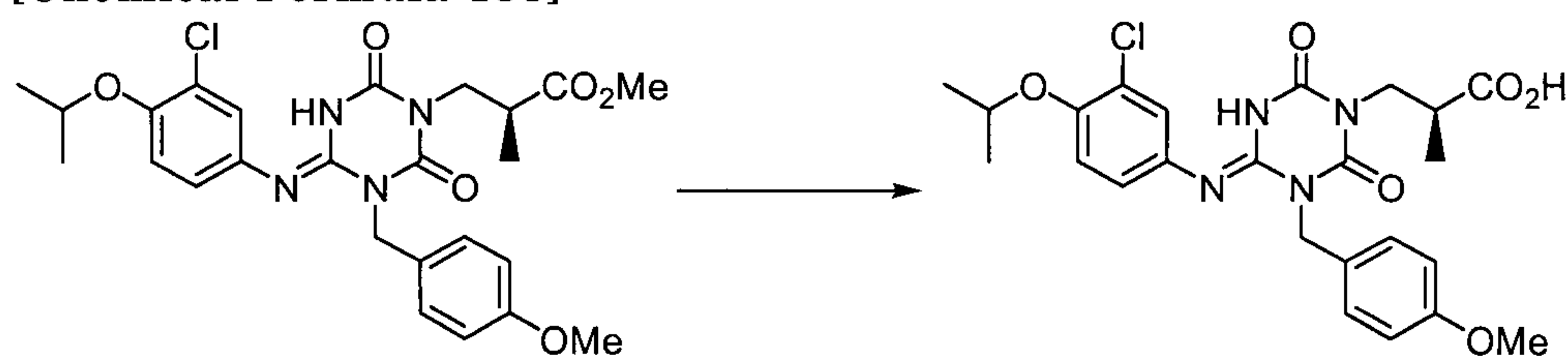
[Example 74]

[0288]

Preparation of

(S)-6-(3-chloro-4-isopropoxyphenylimino)-1-(4-methoxybenzyl)-3-(2-hydroxycarbonylpropyl)methyl-1,3,5-triazine-2,4-dione (I-1159)

[Chemical Formula 183]



To a mixture of

(S)-6-(3-chloro-4-isopropoxyphenylimino)-1-(4-methoxybenzyl)-3-(2-methoxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dione (180 mg, 0.348 mmol), methanol (2 mL) and THF (2 mL) was added 1mol/L lithium hydroxide (1 mL), and the resulting mixture was stirred at 50°C for 5 hours. To the reaction mixture was added 10% aqueous citric acid, and the resulting mixture was extracted with ethyl acetate. The extract was washed by water, dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by ethyl acetate and hexane to give

(S)-6-(3-chloro-4-isopropoxyphenylimino)-1-(4-methoxybenzyl)-3-(2-hydroxycarbonylpropyl)methyl-1,3,5-triazinane-2,4-dione (160 mg, Yield: 91%) as colorless solid.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.02 (3H, d, J=6.8 Hz), 1.29 (6H, d, J=5.6 Hz), 2.76 (1H, q, J=6.8 Hz), 3.73 (3H, s), 3.77-3.82 (1H, m), 3.87-3.92 (1H, m), 4.63 (1H, sept, J=5.6 Hz), 5.21 (2H, s), 6.93 (2H, d, J=7.2 Hz), 7.15-7.28 (4H, m), 7.47 (1H, s), 9.23 (1H, s), 12.33 (1H, brs).

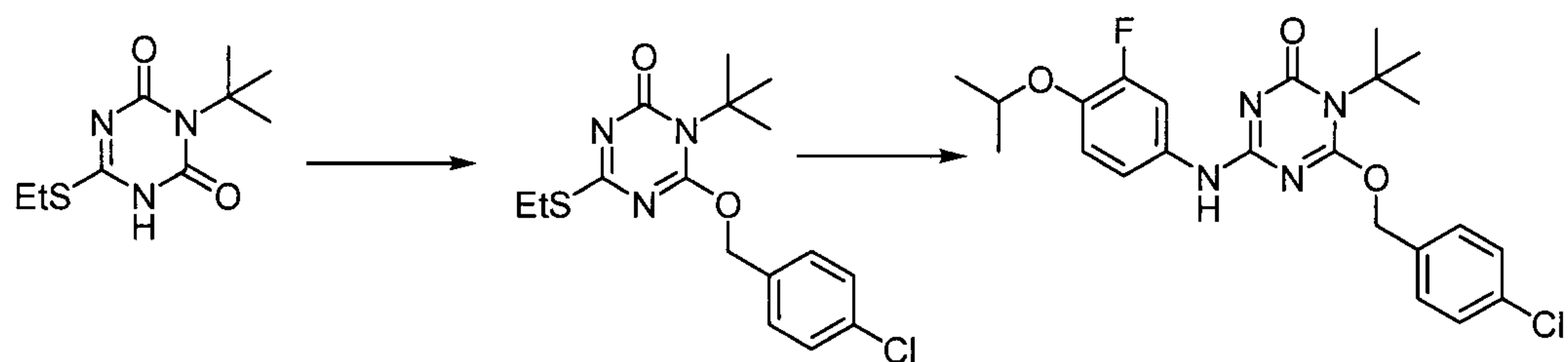
[Example 75]

[0289]

Preparation of

6-(4-chlorobenzoyloxy)-4-(3-fluoro-4-isopropoxyphenylimino)-1-t-butyl-1,3,5-triazine-2(1H)-one (I-1296)

[Chemical Formula 184]



To a mixture of 6-(ethylthio)-3-t-butyl-1,3,5-triazine-2,4(1H,3H)-dione (1.0 g, 4.4 mmol), 4-chlorobenzyl alcohol (1.02 g, 4.4 mmol), triphenylphosphine (1.49 g, 5.7 mmol) and THF (10 mL) was gradually added di-2-methoxyethylazodicarboxylate (1.33 g, 5.7 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was water (200 mL), and the resulting mixture was extracted with ethyl acetate (200 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give crude 6-(4-chlorobenzoyloxy)-4-ethylthio-1-t-butyl-1,3,5-triazine-2(1H)-one. To the obtained crude product were added 3-fluoro-4-isopropoxyaniline (0.18 g, 1.09 mmol) and acetic acid (10 mL), and the resulting mixture was stirred at room temperature for 2.5 hours. To the reaction mixture was added saturated aqueous sodium bicarbonate (200 mL), and the resulting mixture was extracted with ethyl acetate (300 mL). The extract was washed by brine (200 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The

resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The resulting residue was precipitated by ethyl acetate and hexane to give 6-(4-chlorobenzoyloxy)-4-(3-fluoro-4-isopropoxyphenylimino)-1-t-butyl-1,3,5-triazine-2(1H)-one (0.12 g, Yield: 6%) as a white powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.35(6H, d, J=6.1 Hz), 1.66 (9H, s), 4.48 (1H, sept, J=6.1 Hz), 5.37 (2H, s), 6.93 (1H, m), 7.26-7.43 (7H, m).

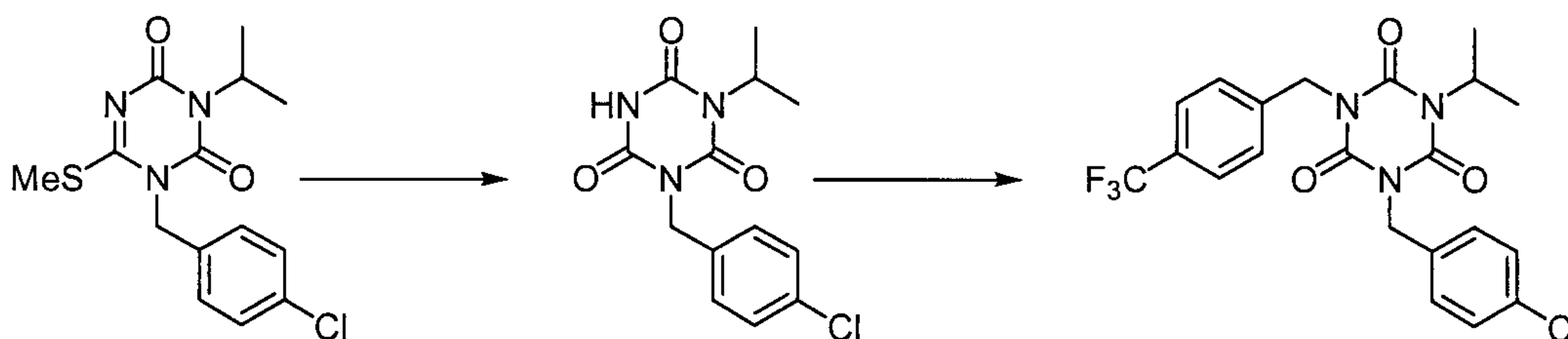
[Example 76]

[0290]

Preparation of

1-(4-chlorobenzyl)-3-isopropyl-5-(4-trifluoromethylbenzyl)-1,3,5-triazine-2,4,6-trione (I-1289)

[Chemical Formula 185]



To a mixture of

1-(4-chlorobenzyl)-6-(methylthio)-3-isopropyl-1,3,5-triazine-2,4(1H,3H)-dione (0.2 g, 0.6 mmol) and acetic acid (10 mL) was added 30% hydrogen peroxide solution (0.7 g, 6 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture was added brine (30 mL), and the resulting mixture was extracted with dichloromethane (30 mL×2). The extract was washed by brine (30 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was precipitated by hexane to give 1-(4-chlorobenzyl)-3-isopropyl-1,3,5-triazine-2,4,6-trione (0.2 g) as a white powder.

¹H-NMR (δ ppm TMS/DMSO-d₆): 1.35 (6H, d, J = 6.9 Hz), 4.81 (1H, q, J = 6.9 Hz), 4.84 (2H, s), 7.36 (4H, d, J = 8.7 Hz), 11.66 (1H, s).

To a mixture of 1-(4-chlorobenzyl)-3-isopropyl-1,3,5-triazine-2,4,6-trione (80 mg, 0.27 mmol), 4-trifluorobenzyl alcohol (52.4 mg, 0.3 mmol), triphenylphosphine (92 mg, 0.35 mmol) and THF (2 mL) was gradually added di-2-methoxyethylazodicarboxylate (82 mg, 0.35 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The resulting residue was precipitated by hexane to give 1-(4-chlorobenzyl)-3-isopropyl-5-(4-trifluoromethylbenzyl)-1,3,5-triazine-2,4,6-trione (65 mg, Yield: 53%) as a white powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.45 (6H, d, J = 6.9 Hz), 4.96 (1H, m), 4.98 (2H, s), 5.05 (2H, s), 7.26-7.32 (2H, m), 7.36-7.44 (2H, m), 7.52-7.62 (4H, m).

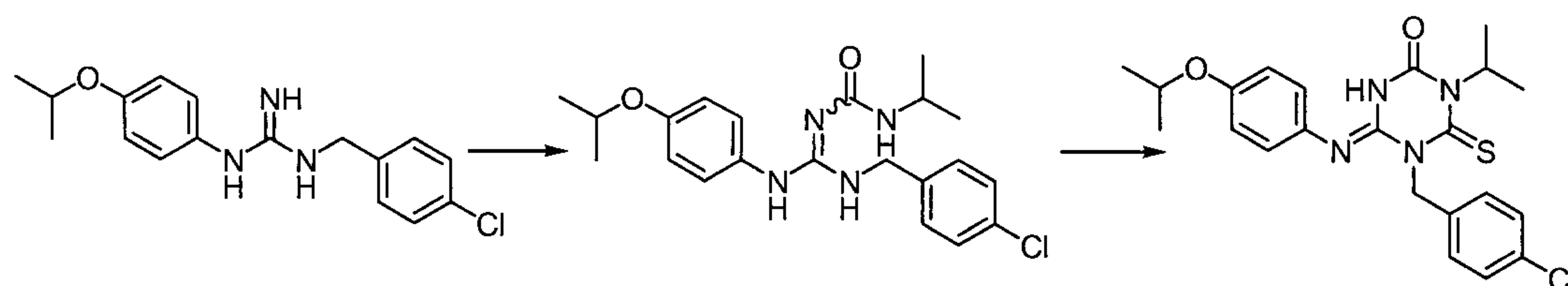
[Example 77]

[0291]

Preparation of

1-(4-chlorobenzyl)-3-isopropyl-6-(4-isopropoxyphenylimino)-2-thioxo-1,3,5-triazinane-4-one (I-2253)

[Chemical Formula 186]



To a suspension of 1-(4-chlorobenzyl)-3-(4-isopropoxyphenyl)guanidine (500 mg, 1.57 mmol) in toluene (5.0 mL) was added 2-isocyanatepropane (0.187 mL, 1.89 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 17 hours. The resulting pale yellow solution was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give 1-((4-chlorobenzylamino)(4-isopropoxyphenylamino)methylene)-3-isopropylurea (629 mg, Yield: 99%) as colorless gum.

The isopropylurea derivative (201 mg, 0.500 mmol) was dissolved in THF (2.2 mL). To the mixture was added thiophosgene (0.042 mL, 0.550 mmol), and the resulting mixture was heated at reflux for 16 hours. Further, potassium carbonate (152 mg, 1.10 mmol) was added to the mixture, and the resulting mixture was heated at reflux for 2.5 hours. To the resulting solution was added ethyl acetate (50 mL), and the resulting mixture was washed by water (20 mL×2) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by reversed-phase HPLC (0.1% formic acid in acetonitrile/water) and silica gel column chromatography (ethyl acetate/hexane) to give 1-(4-chlorobenzyl)-3-isopropyl-6-(4-isopropoxyphenylimino)-2-thioxo-1,3,5-triazinane-4-one (0.32 mg, Yield: 0.1%) as colorless oil.

¹H-NMR (δ ppm TMS/CDCl₃): 1.34 & 1.37 (d x 2, 6H), 1.53 (d, 6H), 4.52-4.64 (m, 1H), 5.17 (s, 2H), 5.86-5.97 (m, 1H), 6.85 & 7.39 (s x 2, 1H), 6.98 (d, 2H), 7.08 (d, 2H), 7.28 (d, 2H), 7.45 (d, 2H).

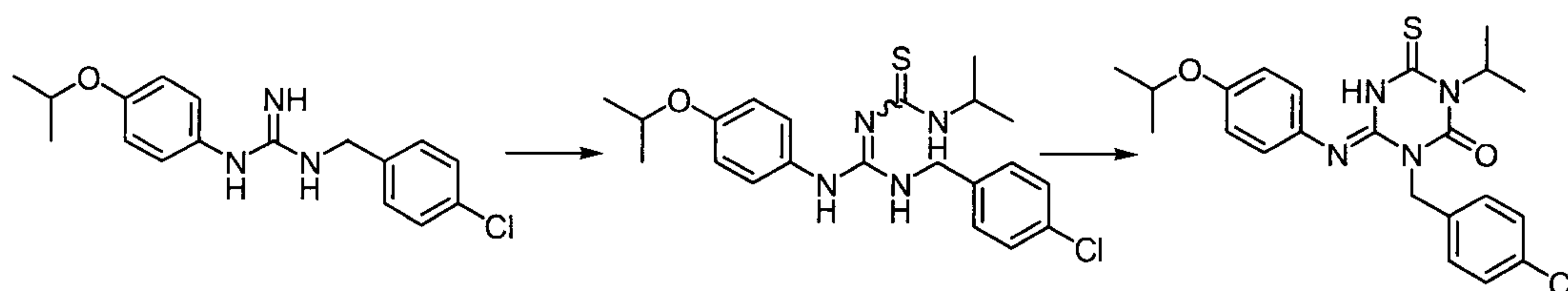
[Example 78]

[0292]

Preparation of

1-(4-chlorobenzyl)-3-isopropyl-6-(4-isopropoxyphenylimino)-4-thioxo-1,3,5-triazinane-2-one (I-2254)

[Chemical Formula 187]



To a suspension of 1-(4-chlorobenzyl)-3-(4-isopropoxyphenyl)guanidine (654 mg, 2.06 mmol) in toluene (6.5 mL) was added isopropyl isocyanate (0.307 mL, 2.88 mmol) under ice-cooling, and the resulting mixture was stirred at room temperature for 18 hours, 60°C for 2 hours, and 70°C for 2.5 hours. The resulting mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (ethyl acetate/hexane)

to give

1-((4-chlorobenzylamino)(4-isopropoxyphenylamino)methylene)-3-isopropylthiourea (619 mg, Yield:72%) as white solid.

The thiourea derivative (200 mg, 0.477mmol) was dissolved in THF (2.0 mL), and carbonyldiimidazole (77 mg, 0.477 mmol) was added to the solution under ice-cooling. The resulting mixture was heated at reflux for 22 hours under nitrogen atmosphere. Further, carbonyldiimidazole (77mg, 0.477 mmol) and triethylamine (0.066 mL, 0.477 mmol) were added to the mixture, and the resulting mixture was heated at reflux for 3.5 hours. To the mixture was added ethyl acetate (50 mL), and the resulting mixture was washed by water (20 mL×2) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane), and the resulting residue was precipitated by ethyl acetate/hexane to give aimed 1-(4-chlorobenzyl)-3-isopropyl-6-(4-isopropoxyphenylimino)-4-thioxo-1,3,5-triazinane-2-one (8.3 mg, Yield: 3.9%) as a white powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.35 (d, 6H), 1.49 (d, 6H), 4.45-4.55 (m, 1H), 5.14 (s, 2H), 5.65-5.80 (m, 1H), 6.74 (d, 2H), 6.89 (d, 2H), 7.30 (d, 2H), 7.48 (d, 2H), 8.48 (br, s, 1H).

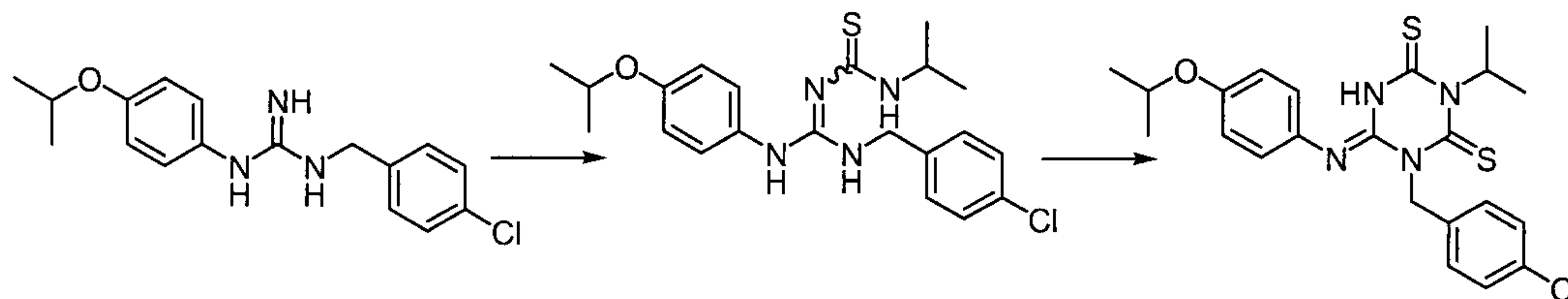
[Example 79]

[0293]

Preparation of

1-(4-chlorobenzyl)-3-isopropyl-6-(4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dithione (I-2256)

[Chemical Formula 188]



In the similar manner as described the above,

1-((4-chlorobenzylamino)(4-isopropoxyphenylamino)methylene)-3-isopropylthiourea was synthesized. The thiourea derivative (199 mg, 0.475 mmol) was dissolved in THF (2.0 mL). To the colorless solution was added thiophosgene (0.040 mL, 0.522 mmol) under ice-cooling, and the resulting mixture was stirred for 2 hours in an ice-bath. To the resulting yellow solution was added ethyl acetate (50 mL), and washed by saturated aqueous sodium bicarbonate (20 mL×2), 5% aqueous citric acid (20 mL×2), and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The resulting residue was crystallized by ethyl acetate/hexane to give 1-(4-chlorobenzyl)-3-isopropyl-6-(4-isopropoxyphenylimino)-1,3,5-triazinane-2,4-dithione (14.8 mg; Yield6.8%) as yellow crystalline.

¹H-NMR (δ ppm TMS/CDCl₃): 1.16 (d, 6H), 1.32 (d, 6H), 4.00 & 4.61 (br, s x 2, 1H), 4.44-4.54 (m, 1H), 6.08 (s, 2H), 6.82 (d, 2H), 6.99 (d, 2H), 7.26 (d, 2H), 7.46 (d, 2H).

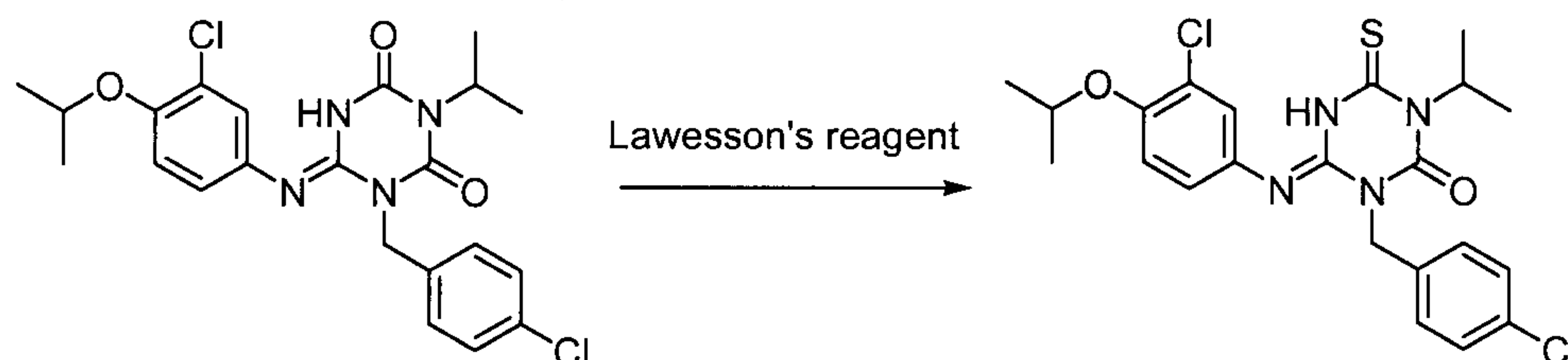
[Example 80]

[0294]

Preparation of

1-(4-chlorobenzyl)-3-isopropyl-6-(3-chloro-4-isopropoxyphenylimino)-4-thioxo-1,3,5-triazine-2-one (I-2257)

[Chemical Formula 189]



To a suspension of

6-(3-chloro-4-isopropoxyphenylamino)-1-(4-chlorobenzyl)-3-1,3,5-triazine-2,4-dione (95.4 mg, 0.206 mmol) in toluene (2.0 mL) was added Lawesson's reagent (666 mg, 1.65 mmol). The resulting mixture was heated at reflux for 10 hours. To the resulting yellow suspension was added ethyl acetate, and the insoluble are filtered off by using Celite. The filtrate (about 100 mL) was washed by saturated aqueous sodium bicarbonate (30 mL×2) and brine (15 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane). The residue was crystallized by hot hexane to give 1-(4-chlorobenzyl)-3-isopropyl-6-(3-chloro-4-isopropoxyphenylimino)-4-thioxo-1,3,5-triazine-2-one (73.7 mg, Yield:75%) as white solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.39 (d, 6H), 1.50 (d, 6H), 4.43-4.57 (m, 1H), 5.12 (s, 2H), 5.65-5.81 (m, 1H), 6.66 (dd, 1H), 6.89 (d, 1H), 6.95 (d, 1H), 7.31 (d, 1H), 7.47 (d, 1H), 8.41 (br, s, 1H).

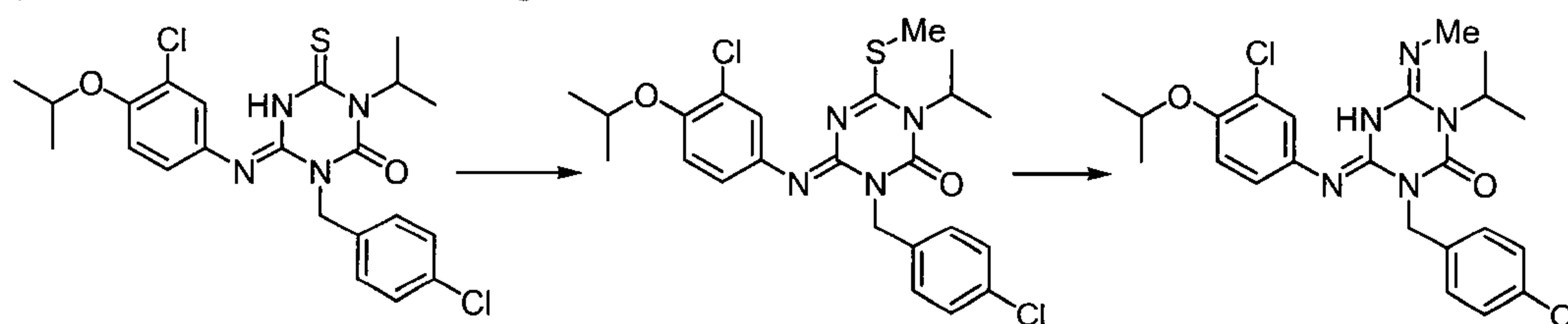
[Example 81]

[0295]

Preparation of

1-(4-chlorobenzyl)-3-isopropyl-6-(3-chloro-4-isopropoxyphenylimino)-4-methylimino-1,3,5-triazine-2-one (I-2259)

[Chemical Formula 190]



To a solution of 4-thiocarbonyl derivative (37.5 mg, 0.078 mmol) in acetone (0.8 mL) was added methyl iodide (0.0073 mL, 0.117 mmol), and resulting mixture was heated at reflux for 15 hours. Methyl iodide and solvate were removed under reduced pressure, and methanol (0.36 mL) and 40% methylaminemethanol solution (0.04 mL, 0.391 mmol) were added to the residue. The resulting mixture was heated at reflux for 8.5 hours, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give aimed 1-(4-chlorobenzyl)-3-isopropyl-6-(3-chloro-4-isopropoxyphenylimino)-4-methylimino-1,3,5-triazine-2-one (23.6 mg, Yield: 63%) as pale yellow oil.

¹H-NMR (δ ppm TMS/CDCl₃): 1.35 (d, 6H), 1.47 (d, 6H), 2.90 (d, 3H), 4.45 (sept. 1H), 4.70

(br, s, 1H), 4.82 (sept. 1H), 5.20 (s, 2H), 6.88 (d, 1H), 7.00 (dd, 1H), 7.26 (d, 2H), 7.40 (d, 1H), 7.50 (d, 2H).

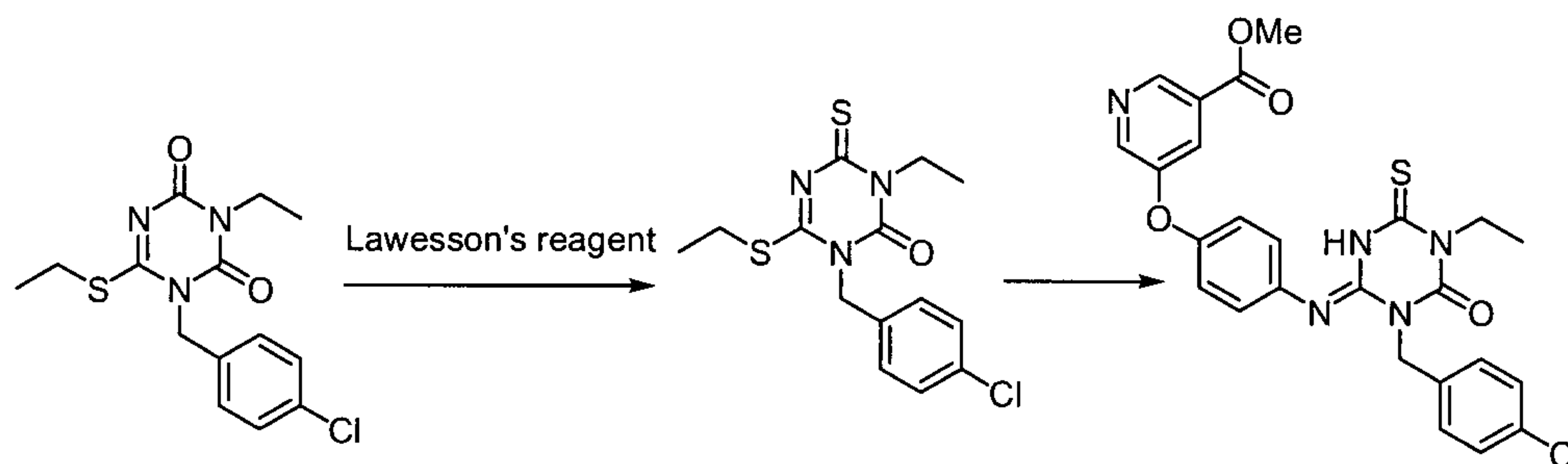
[Example 82]

[0296]

Preparation of

1-(4-chlorobenzyl)-3-ethyl-6-[4-(5-methoxycarbonyl-3-pyridyloxy)phenylimino]-4-thioxo-1,3,5-triazine-2-one (I-2262)

[Chemical Formula 191]



To a solution of 1-(4-chlorobenzyl)-3-ethyl-6-(ethylthio)-1,3,5-triazine-2,4-(1H, 3H)-dione (1.02g, 3.13 mmol) in toluene (10 mL) was added Lawesson's reagent (2.53 g, 6.26 mmol), and the resulting mixture was stirred at reflux for 3 hours. To the resulting yellow suspension was added ethyl acetate (200 mL), and the resulting mixture was washed by water (100 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-3-ethyl-6-(ethylthio)-4-thioxo-3,4-dihydro-1,3,5-triazine-2 (1H)-one (939 mg, Yield: 88%) as yellow solid.

4-Thioxo derivative (257 mg, 0.752 mmol) and 5-(4-aminophenoxy)nicotinic acid methyl ester (257 mg, 1.05 mmol) were suspended in t-butanol (2.5 mL), and the suspension was heated at reflux for 5 hours. To the resulting reaction mixture was added ethyl acetate (60 mL), and the mixture was washed by saturated aqueous sodium bicarbonate (25 mL×2) and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give

1-(4-chlorobenzyl)-3-ethyl-6-[4-(5-methoxycarbonyl-3-pyridyloxy)phenylimino]-4-thioxo-1,3,5-triazine-2-one (258 mg, Yield: 66%) as white solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.30 (t, 3H), 3.94 (s, 3H), 4.35 (q, 2H), 5.19 (s, 2H), 6.87 (dt, 2H), 7.07 (dt, 2H), 7.32 (dt, 2H), 7.51 (dt, 2H), 7.85 (dd, 1H), 8.40 (br, s, 1H), 8.60 (d, 1H), 8.96 (d, 1H).

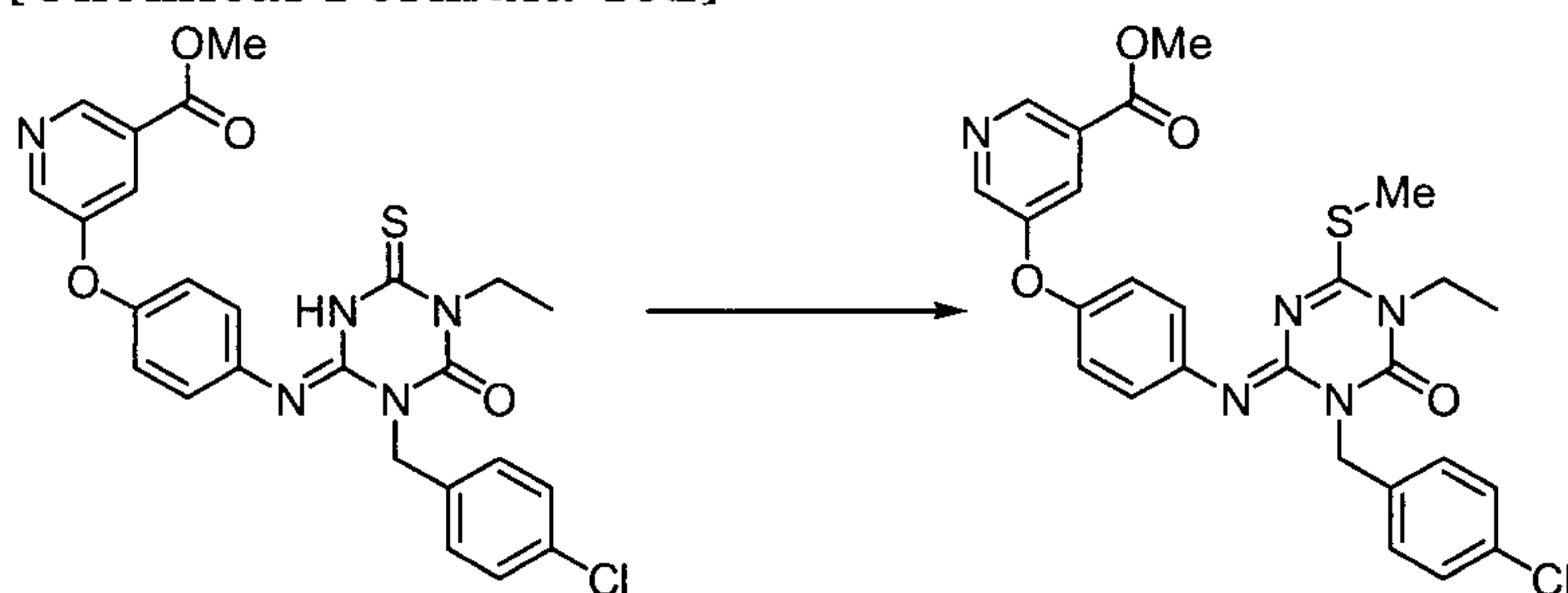
[Example 83]

[0297]

Preparation of

1-(4-chlorobenzyl)-3-ethyl-4-methylthio-6-[4-(5-methoxycarbonyl-3-pyridyloxy)phenylimino]-1,3,5-triazine-2-(1H)-one (I-2264)

[Chemical Formula 192]



Thiocarbonyl derivative (50 mg, 0.095 mmol) was suspended in acetone (1.0 mL), and methyl iodide (0.009 mL, 0.143 mmol) was added to the suspension. The mixture was stirred at room temperature for 15 hours and at 40°C for 15 hours. To the reaction mixture was added ethyl acetate (30 mL). The organic layer was washed by saturated aqueous sodium bicarbonate (10 mL×2) and brine (10 mL), dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane), 1-(4-chlorobenzyl)-3-ethyl-4-methylthio-6-[4-(5-methoxycarbonyl-3-pyridyloxy)phenylimino]o-1,3,5-triazine-2-(1H)-one (40.5 mg, Yield:79%) as white solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.30 (t, 3H), 2.32 (s, 3H), 3.92 (s, 3H), 3.93 (q, 2H), 5.22 (s, 2H), 6.97 (d, 2H), 7.08 (d, 2H), 7.29 (d, 2H), 7.54 (d, 2H), 7.73-7.79 (m, 1H), 8.54 (d, 1H), 8.89 (s, 1H).

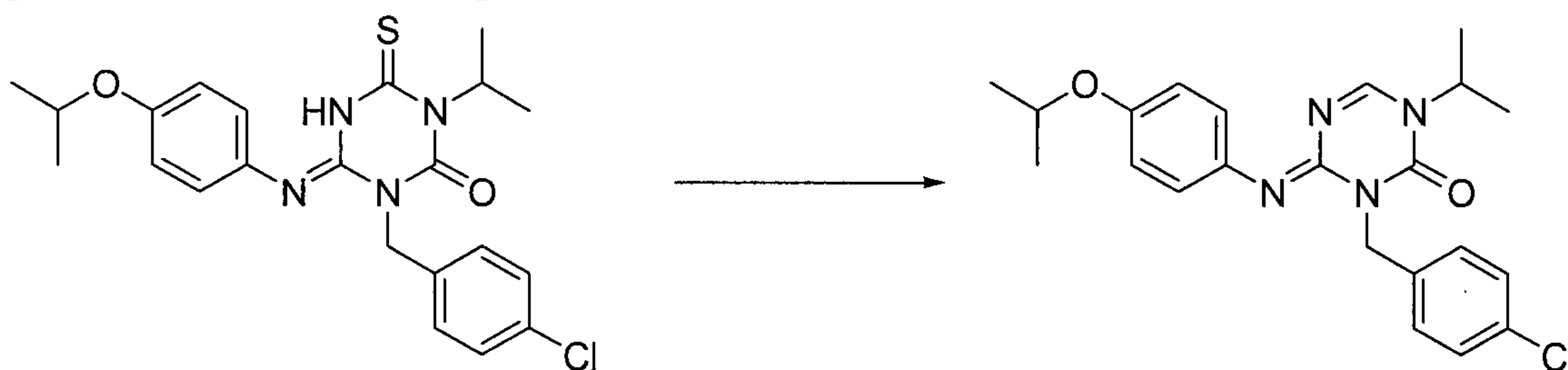
[Example 84]

[0298]

Preparation of

(E)-3-(4-chlorobenzyl)-4-(4-isopropoxyphenylimino)-1-isopropyl-3,4-dihydro-1,3,5-triazine-2(1H)-one (I-2276)

[Chemical Formula 193]



(Reference: Tetrahedron Lett. 2004, 45, 7197-7199.)

To a solution of thiocarbonyl derivative (49.3 mg, 0.111 mmol) in methanol (1.0 mL) was added hydrogen peroxide urea (52.1 mg, 0.554 mmol), and the resulting mixture was stirred at room temperature for 5.5 hours. To the reaction mixture was added ethyl acetate (30 mL), and the mixture was washed by 5% aqueous citric acid (15 mL×2), saturated aqueous sodium bicarbonate (15 mL×2) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane) to give (E)-3-(4-chlorobenzyl)-4-(4-isopropoxyphenylimino)-1-isopropyl-3,4-dihydro-1,3,5-triazine-2(1H)-one (31.6 mg, Yield: 69%) as brown solid.

¹H-NMR (δ ppm TMS/CDCl₃): 1.32 (d, 6H, J = 6.1 Hz), 1.37 (d, 6H, J = 6.6 Hz), 4.44-4.50 (m, 1H), 4.66-4.72 (m, 1H), 5.21 (s, 2H), 6.84 (d, 2H, J = 11.7 Hz), 6.91 (d, 2H, J = 6.6 Hz),

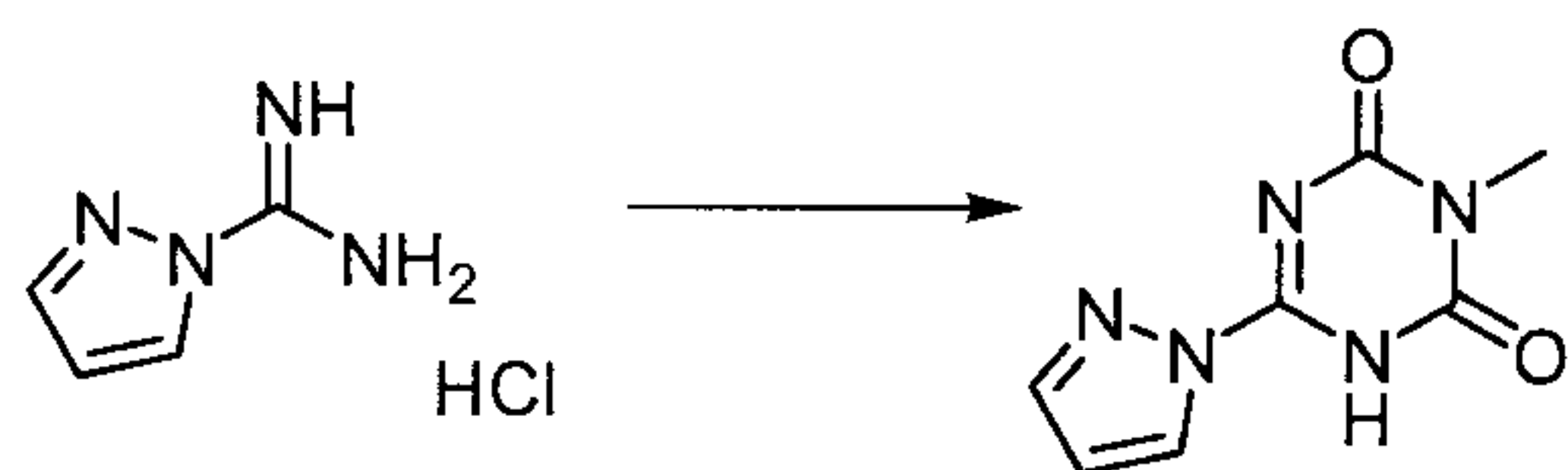
7.28 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 8.1 Hz), 7.61 (s, 1H).

[Example 85]

[0299]

Preparation of 2-methyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion

[Chemical Formula 194]



To a mixture of methylamine hydrochloride (276 g, 4.09 mol) and DMA (2 L) was added DBU (679 mL, 4.50 mol) at 10°C over 4 minutes. Then, 1,1'-carbonyldiimidazole (730 g, 4.50 mol) was added to the mixture at 20°C, and the resulting mixture was stirred at 0°C for 2 hours. To the reaction mixture was added 1-amidinopyrazole-hydrochloride (500 g, 3.41 mol) at -5°C over 3 minutes. Then, DBU (540 mL, 3.58 mol) was added to the mixture at 10°C over 25 minutes, and the resulting mixture was stirred at 45°C for 7.5 hours. Further, to the reaction mixture was added 1,1'-carbonyldiimidazole (830 g, 5.11 mol), and DBU (771 mL, 5.11 mol) was added to the mixture at 6°C over 2 hours. The resulting mixture was stirred at 0°C for 40 minutes. To the reaction mixture was added 2.8 mol/L hydrochloric acid (10 L) at 20°C over 1 hour. The precipitated solid was filtered off to give 2-methyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion (421 g, Yield: 64%) as pale brown powder.

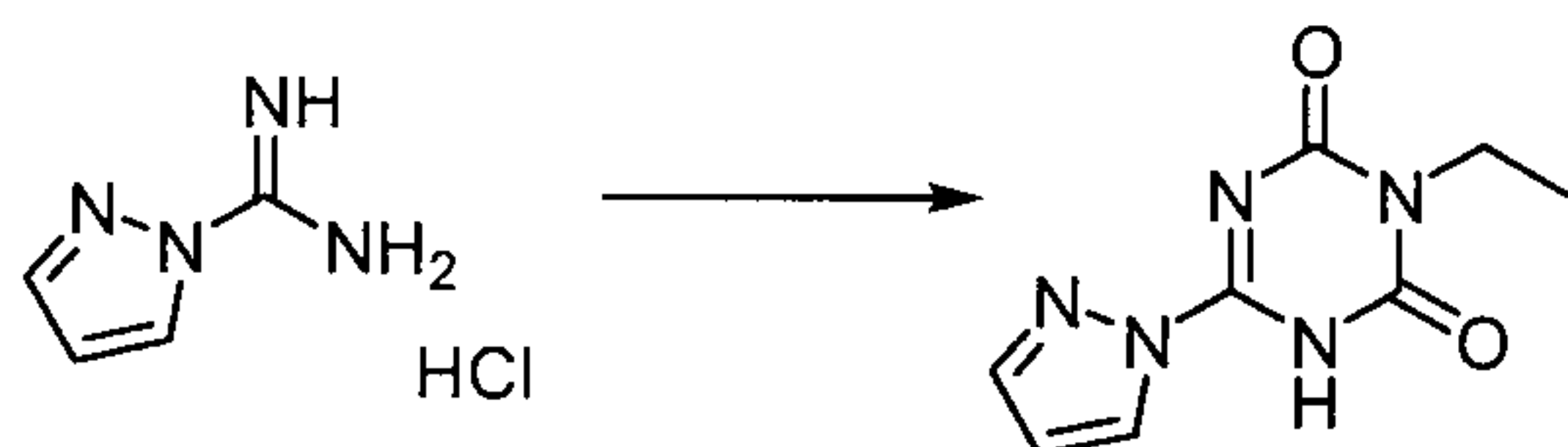
¹H-NMR (δ ppm TMS/DMSO-d₆): 3.16 (3H, s), 6.71 (1H, dd, J= 3.0, 1.5 Hz), 8.04 (1H, d, J= 1.0 Hz), 8.57 (1H, d, = 3.0 Hz).

[Example 86]

[0300]

Preparation of 2-ethyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion

[Chemical Formula 195]



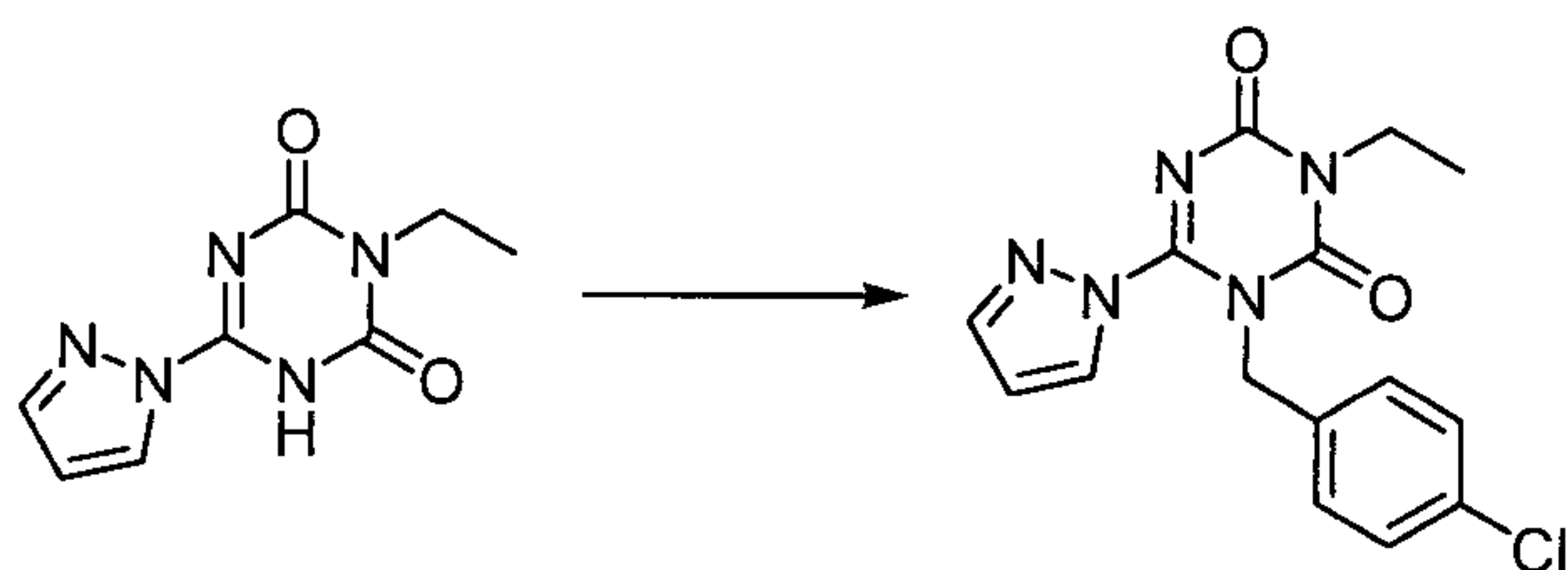
To the mixture of 1-amidinopyrazole-hydrochloride (58.6 g, 400 mmol), ethyl isocyanate (33.2 mL, 420 mmol) and DMA (240 mL) was added DBU (63.3 mL, 420 mmol) dropwise at -10°C over 15 minutes, and the resulting mixture was stirred under ice-cooling for 30 minutes. To the reaction mixture was added 1,1'-carbonyldiimidazole (30 g, 600 mmol) under ice-cooling, and DBU (93 mL, 620 mmol) was added -5°C over 30 minutes to the mixture. The resulting mixture was stirred under ice-cooling for 1 hour. Further, the mixture was stirred at room temperature for 1 hour. To the mixture was added 2mol/L hydrochloric acid (1.16 L) at 20°C over 1 hour. The precipitated solid was filtered off to give 2-ethyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion (73.0 g, Yield: 88%) as pale brown powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.30 (6H, t, J=7.0 Hz), 4.02 (2H, q, J=7.0 Hz), 6.59 (1H, m), 7.34 (1H, m), 8.48 (1H, m), 9.79 (1H, brs).

[Example 87]

[0301]

Preparation of 1-(4-chlorobenzyl)-2-ethyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion (II-3)



To a mixture of 2-ethyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion (89 g, 480 mmol), 4-chlorobenzylbromide (108 g, 528 mmol) and DMA (400 mL) was added diisopropylethylamine (92 mL, 528 mmol) dropwise at room temperature over 10 minutes, and the mixture was stirred at 60°C for 2 hours. To the reaction mixture was added water (800 mL) dropwise under ice-cooling for 40 minutes, and hexane (200 mL) was added to the mixture. The precipitated solid was filtered off to give 1-(4-chlorobenzyl)-2-ethyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion (II-3, 156 g, Yield: 97.6%) as pale brown powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.30 (3H, t, J=7.1 Hz), 4.04 (2H, q, J=7.1 Hz), 5.86 (2H, s), 6.48 (1H, m), 7.02 (2H, d, J=8.6 Hz), 7.20-7.25 (2H, m), 7.84 (1H, m), 8.33 (1H, m).

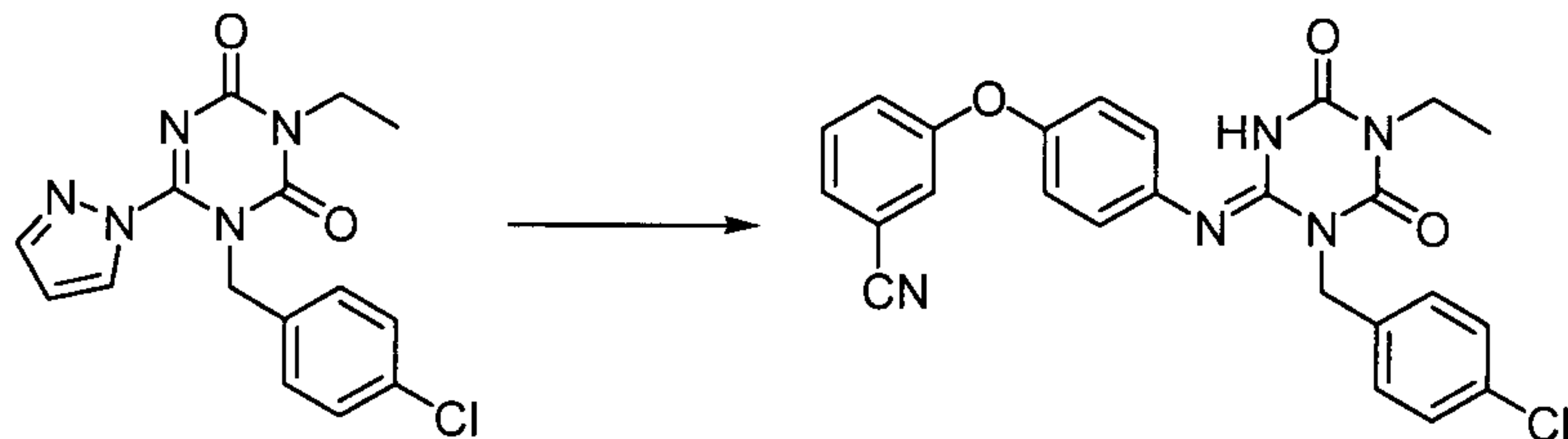
[Example 88]

[0302]

Preparation of

1-(4-chlorobenzyl)-6-[4-(3-cyanophenoxy)phenylimino]-3-ethyl-1,3,5-triazinane-2,4-dion (I-2305)

[Chemical Formula 196]



A mixture of 1-(4-chlorobenzyl)-2-ethyl-6-(1-pyrazolyl)-1,3,5-triazine-2,4(1H,3H)-dion (0.30 g, 0.9 mmol), 4-(3-cyanophenoxy)aniline (0.209 g, 1 mmol) and t-butanol (6 mL) was stirred at 90°C for 15 hours. To the reaction mixture was added 50% ethyl acetate/hexane (6 mL), and the precipitated solid was filtered off to give 1-(4-chlorobenzyl)-6-[4-(3-cyanophenoxy)phenylimino]-3-ethyl-1,3,5-triazinane-2,4-dion (I-2305, 0.385 g, Yield: 89.8%) as pale brown powder.

¹H-NMR (δ ppm TMS/CDCl₃): 1.24 (3H, t, J=7.2 Hz), 3.91 (2H, q, J=7.2 Hz), 5.20 (2H, s), 6.84 (2H, d, J=8.7 Hz), 7.04 (2H, d, J=8.4 Hz), 7.2-7.46 (6H, m), 7.51 (2H, d, J=8.4 Hz).

[0303]

The following compound of the invention and intermediate thereof were synthesized in a manner similar to those described in the above general procedures for the synthesis of the compound of the invention 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 compound of the present invention were measured under any one of the following 2 conditions (Method 1 and 2), and a retention time and $[M+H]^+$ are shown.

(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 100% solvent [B] for 3 minutes was performed, and 100% 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 100% solvent [B] for 3 minutes was performed, and 100% 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 100% solvent [B] for 3 minutes was performed, and 100% solvent [B] was maintained for 1 minute.

(Method 4)

Column: Develo sil RPAq, (50x4.6mm)

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 100% solvent [B] for 4.5 minutes was performed, and 100% solvent [B] was maintained for 10 minutes.

(Method 5)

Column: ACQUITY UPLC (registered trademark) BEH C18 (1.7 μ m, i.d.2.1x3.0mm)

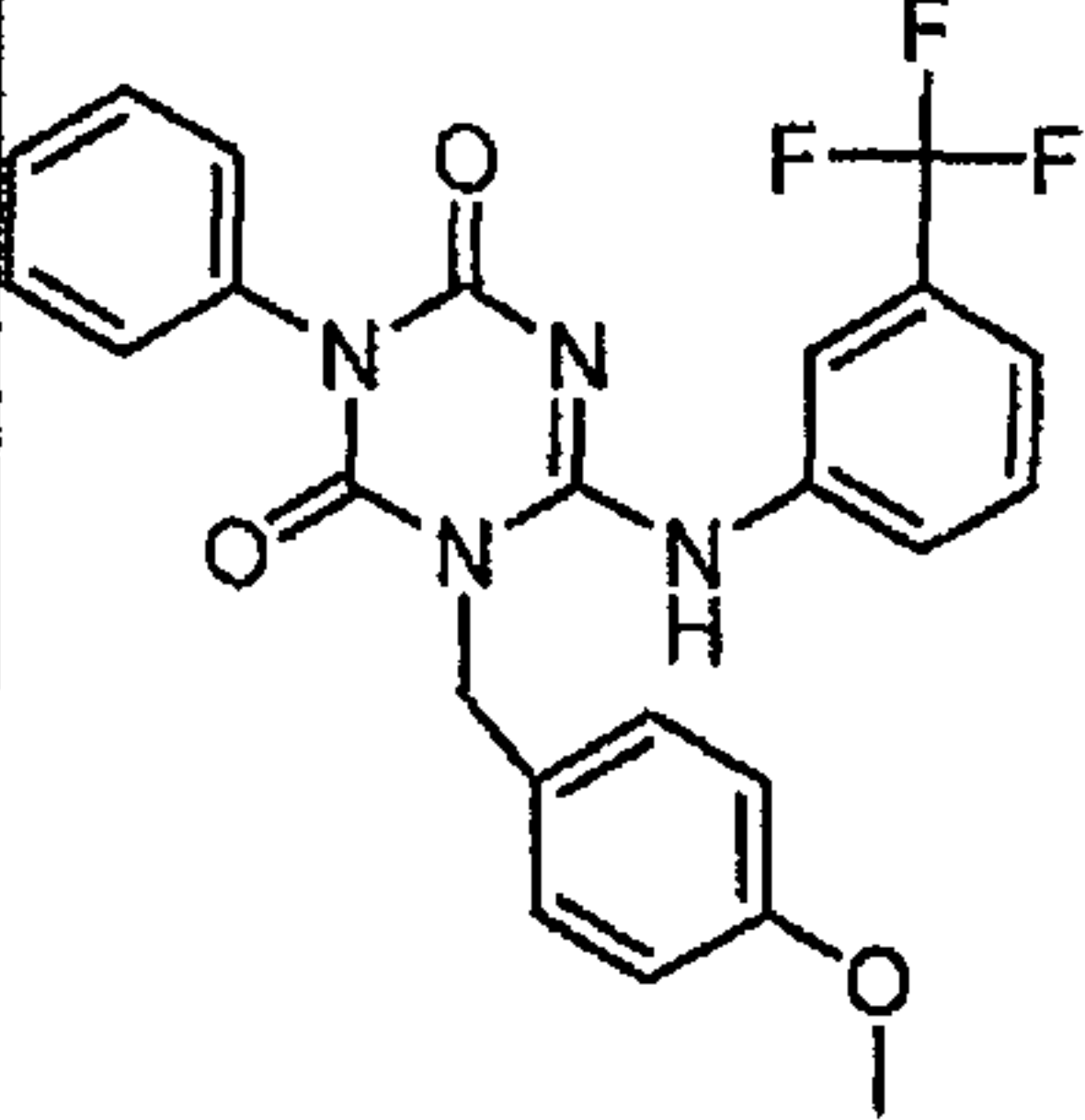
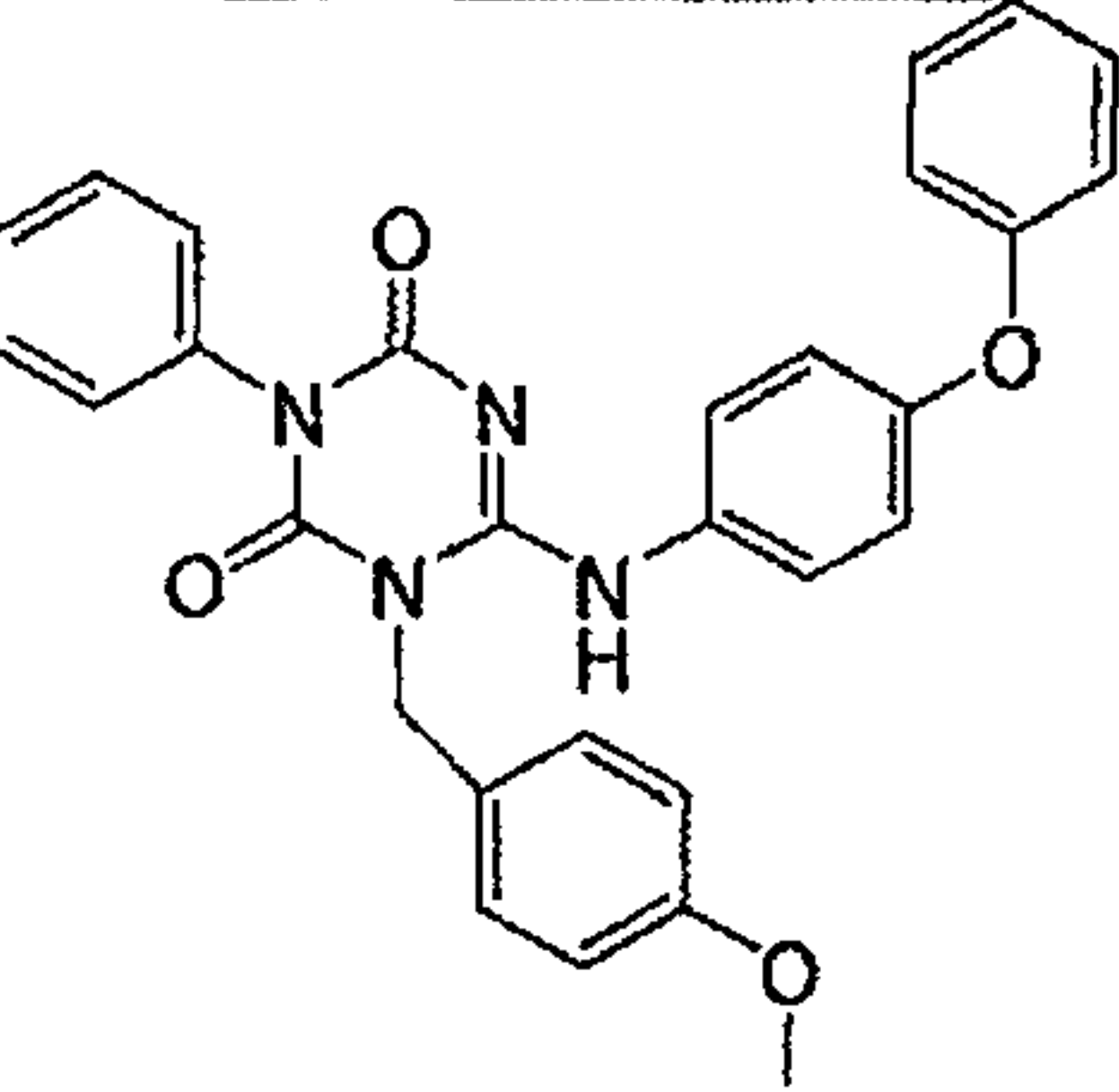
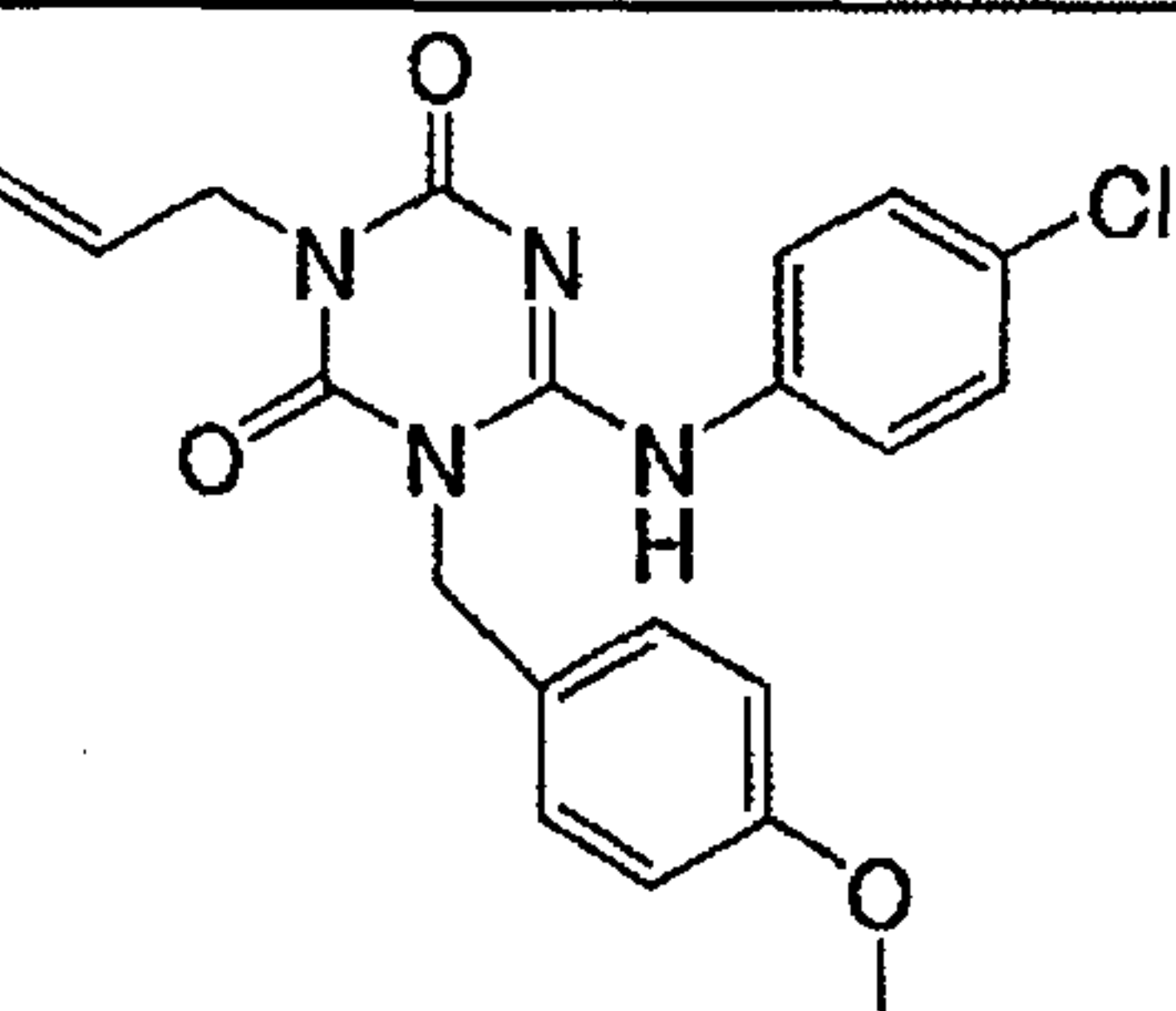
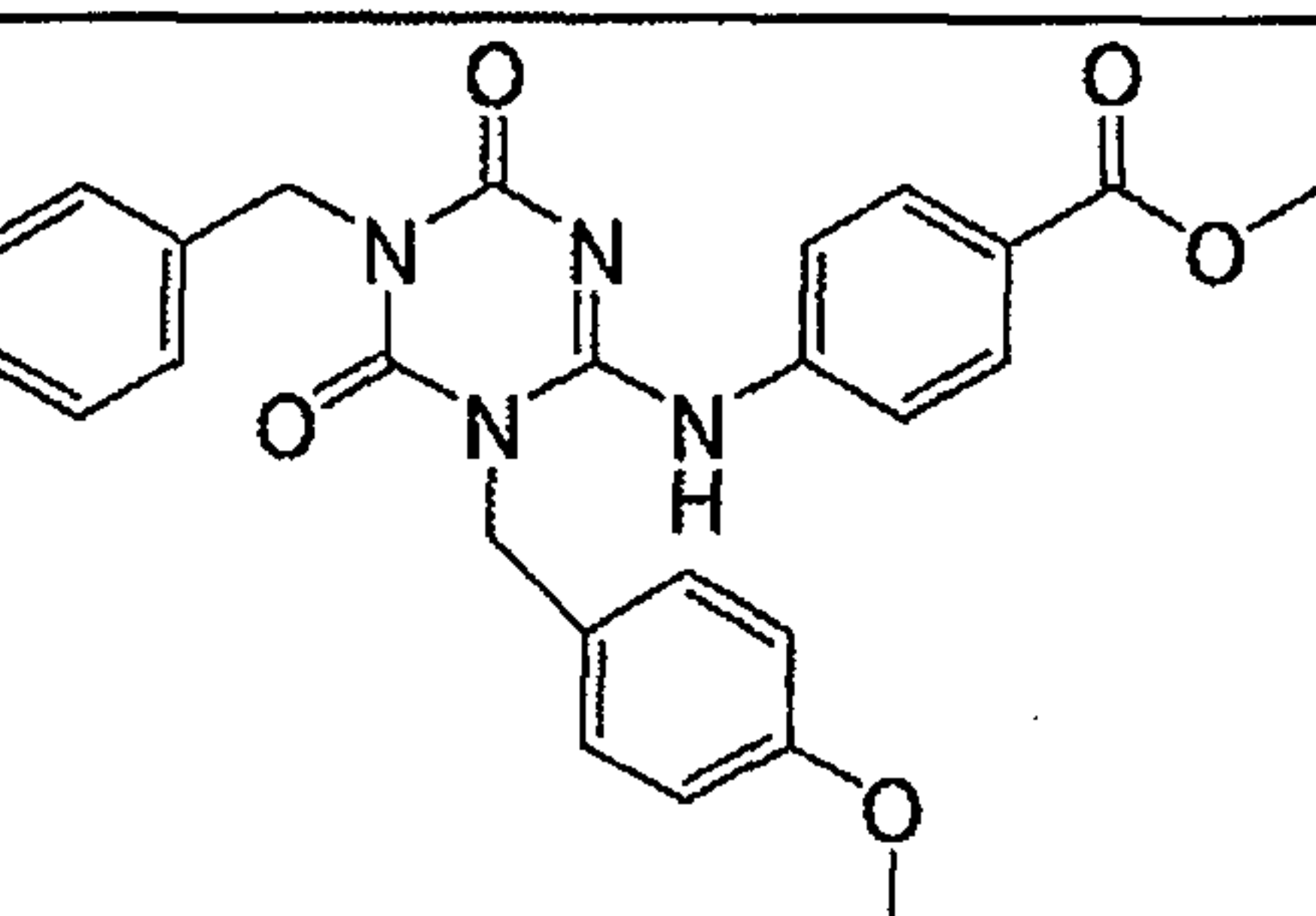
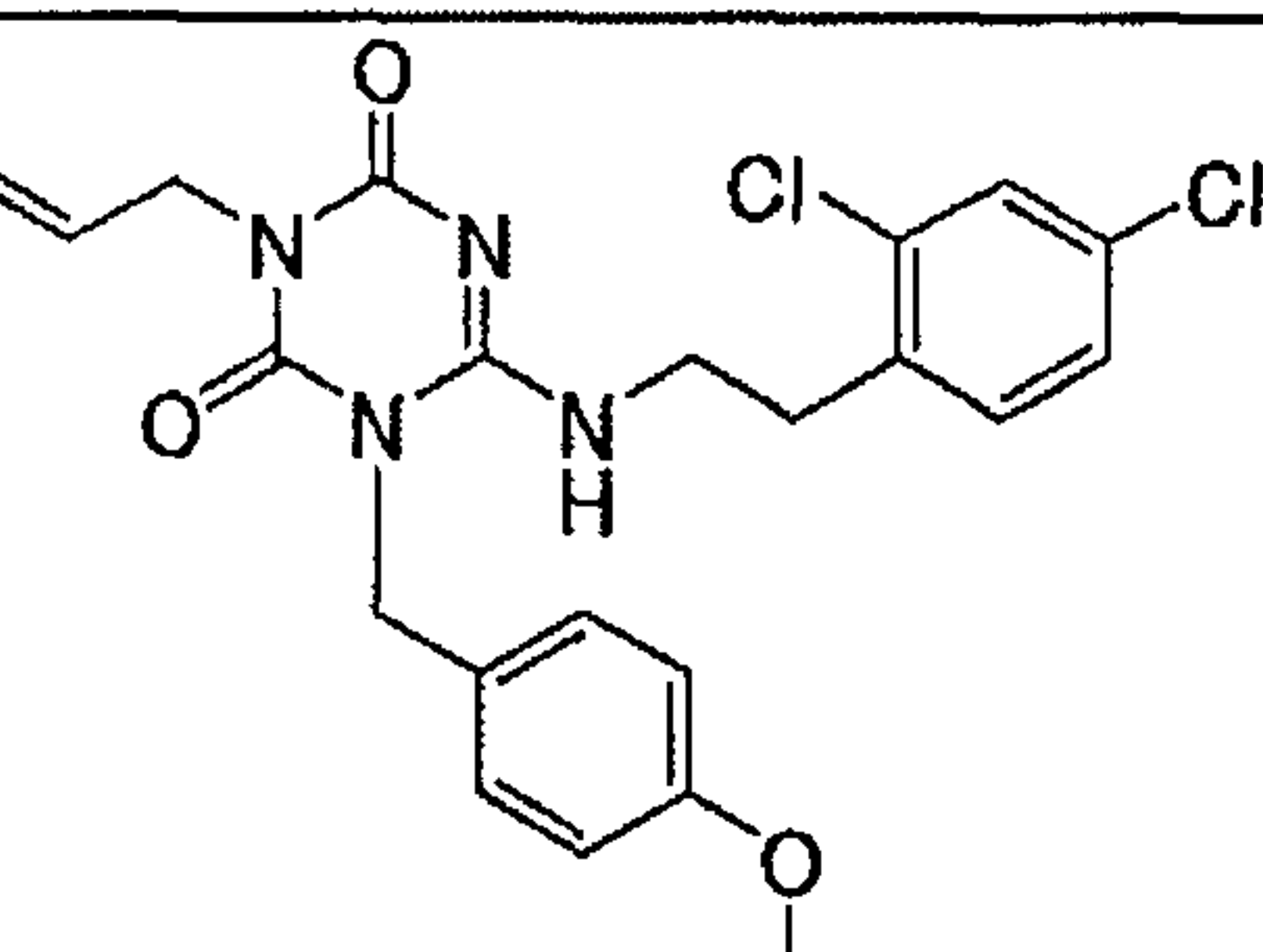
Flow rate: 0.8 mL/min

UV detection wavelength: 254nm

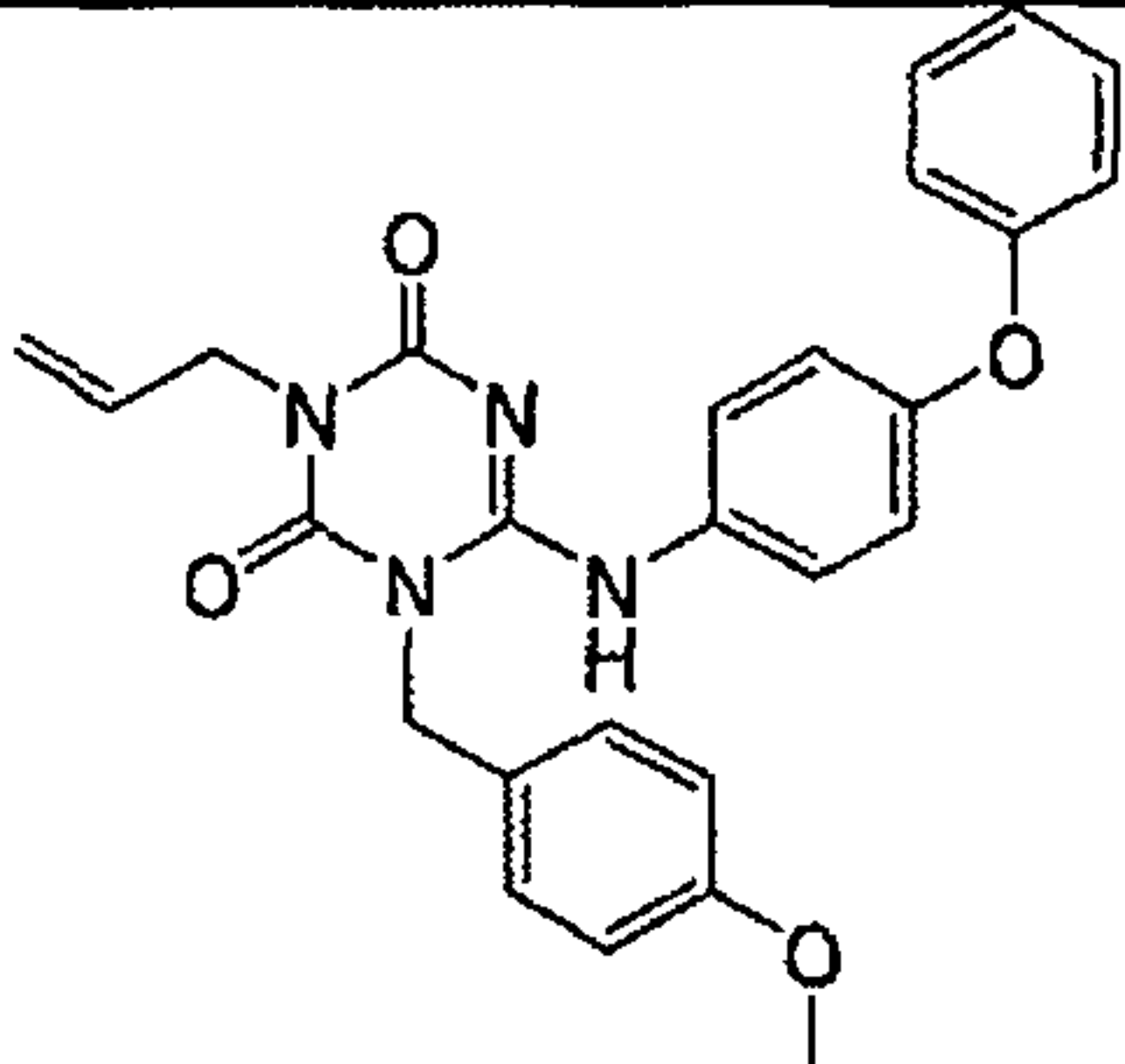
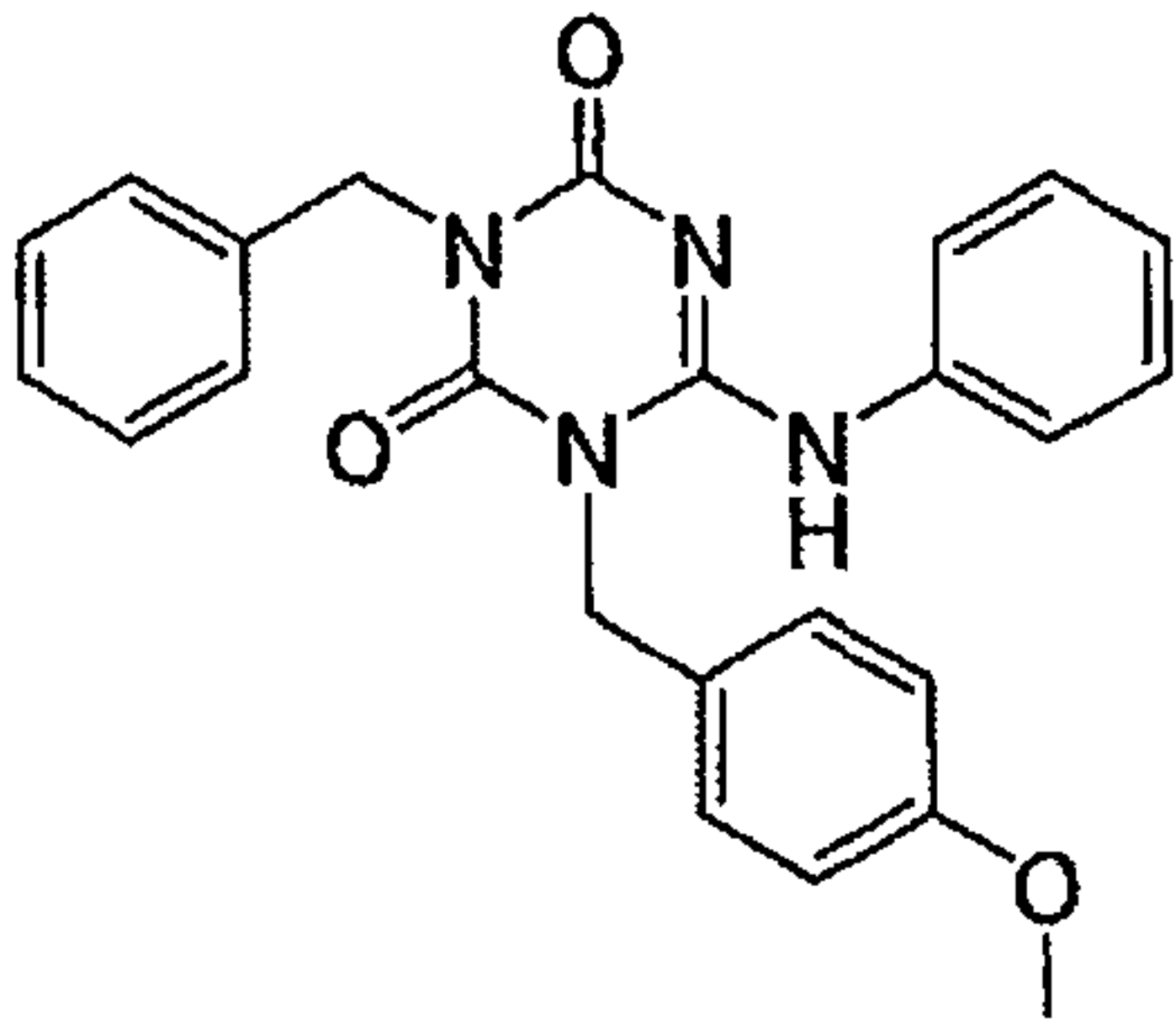
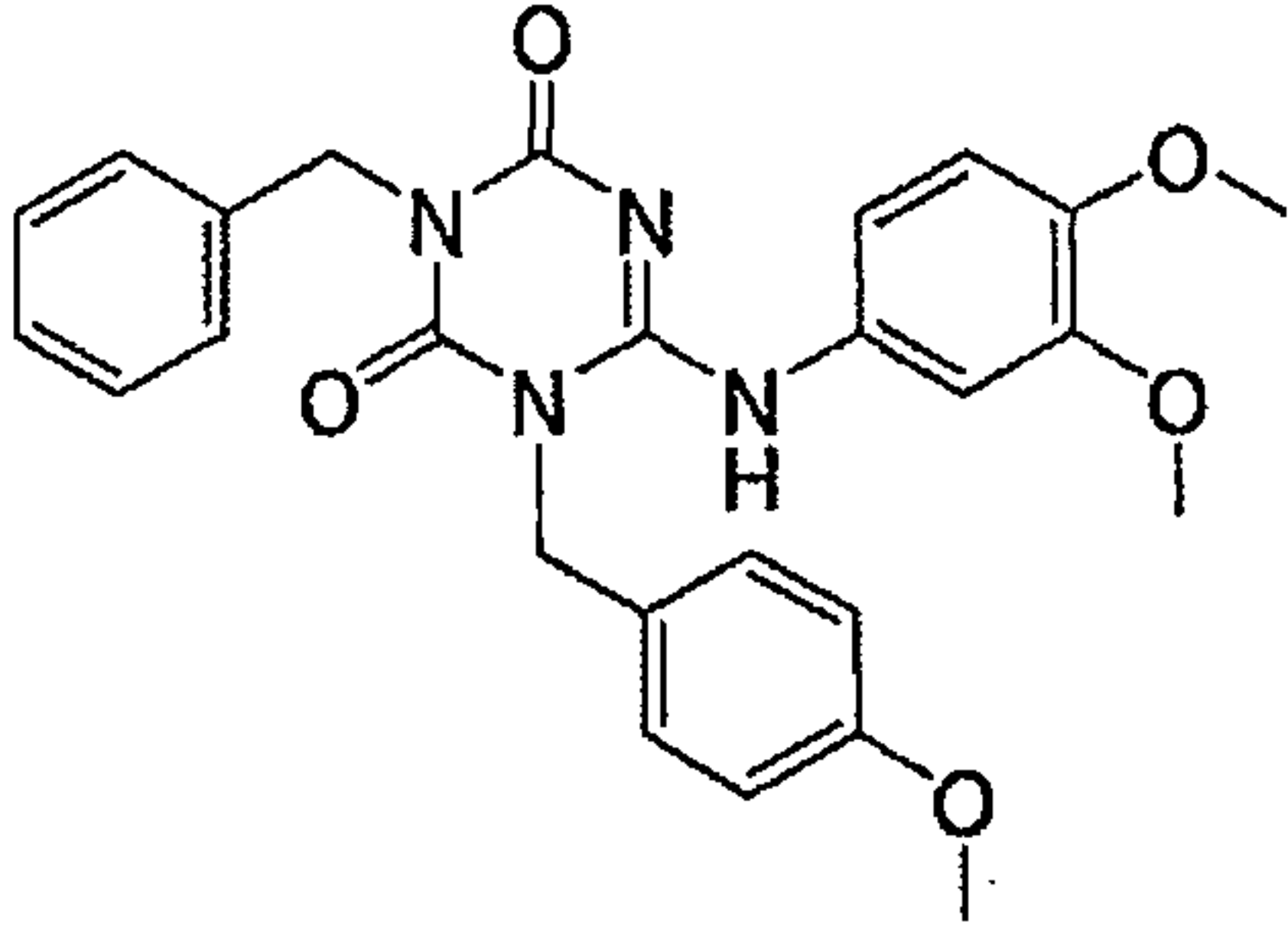
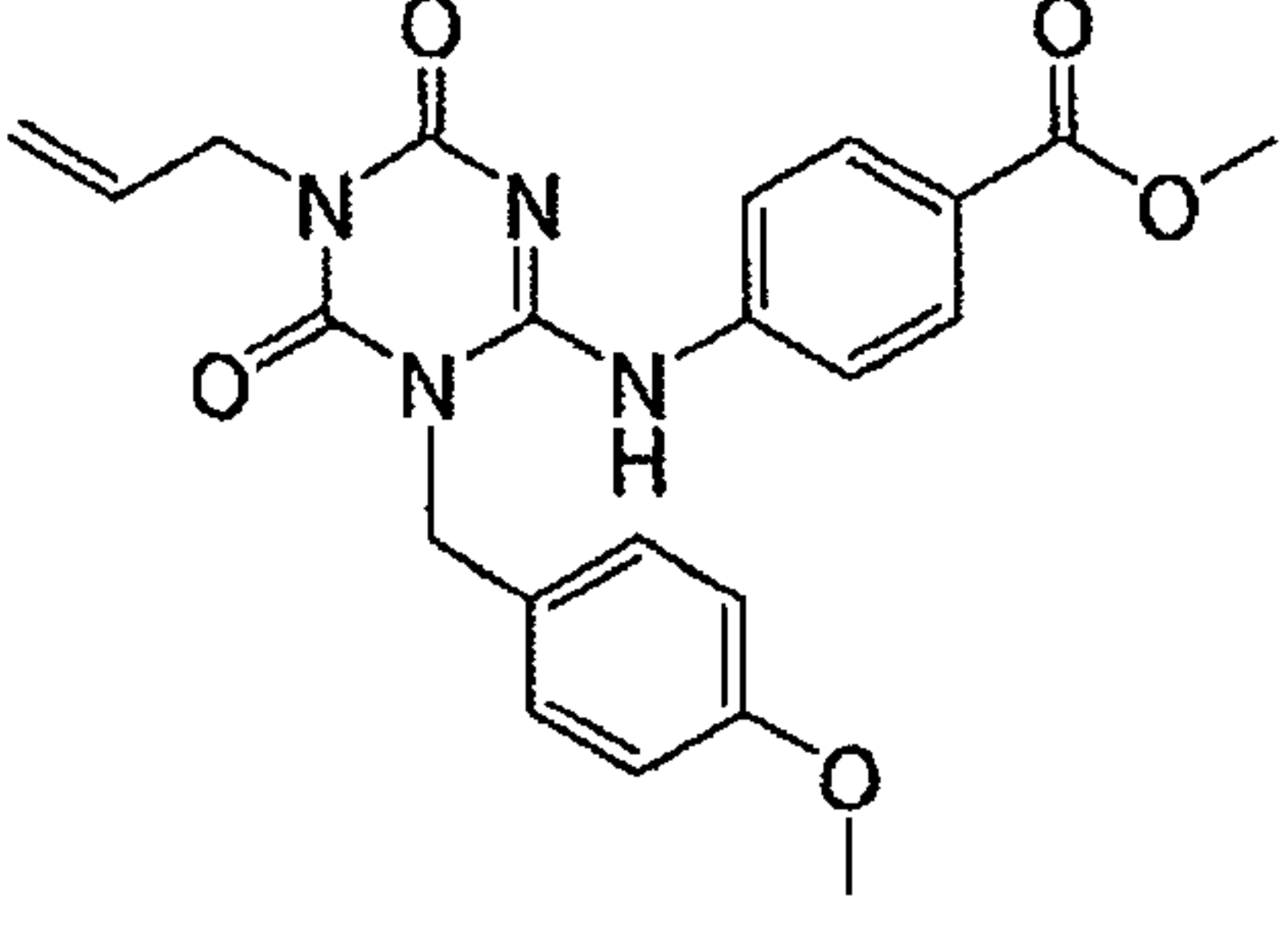
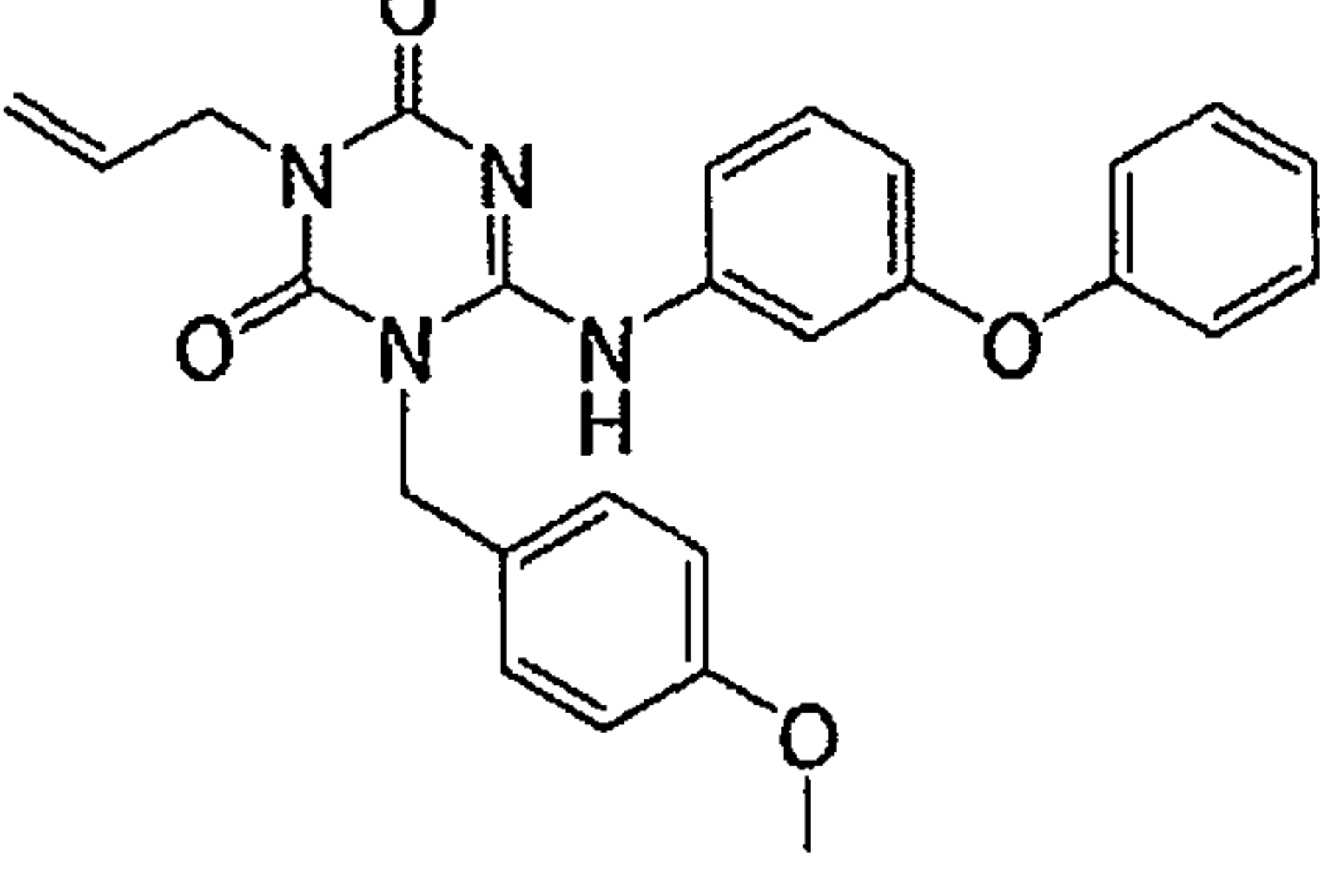
Mobile phase: [A] is 0.1% formic acid-containing aqueous solution, and [B] is 0.1% formic acid-containing acetonitrile solution

Gradient: Linear gradient of 10% to 100% solvent [B] for 3.5 minutes was performed, and 100% solvent [B] was maintained for 0.5 minute.

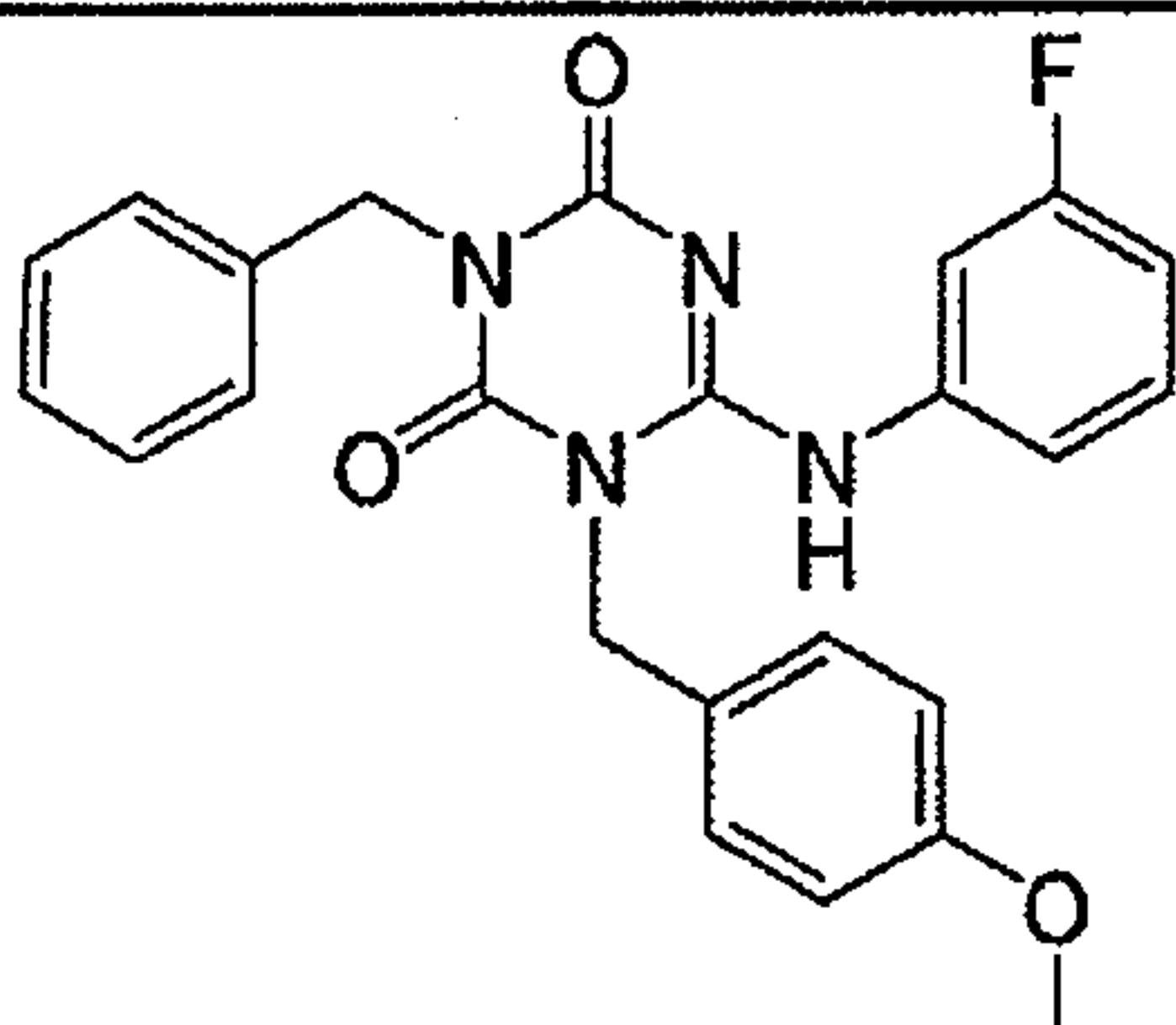
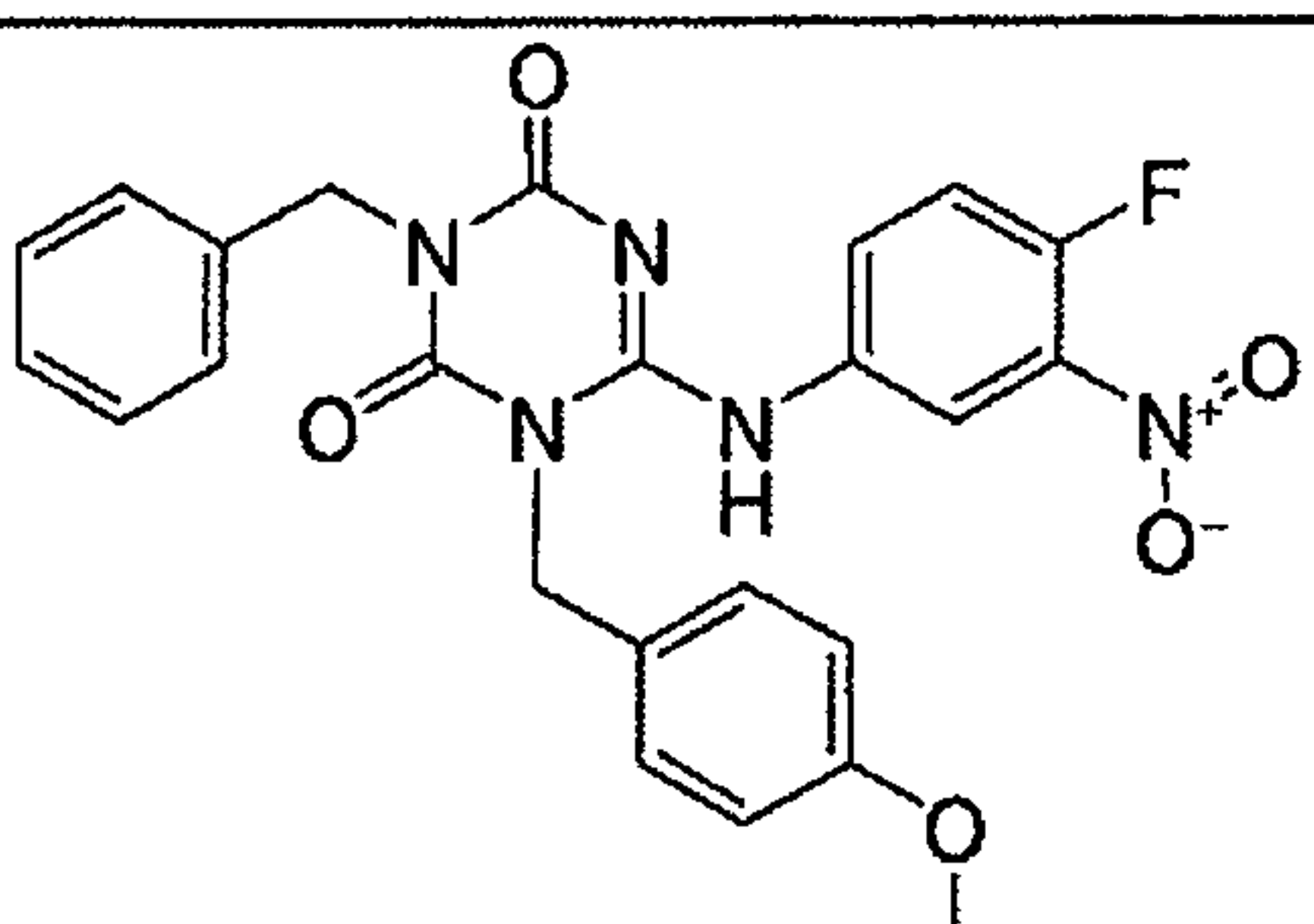
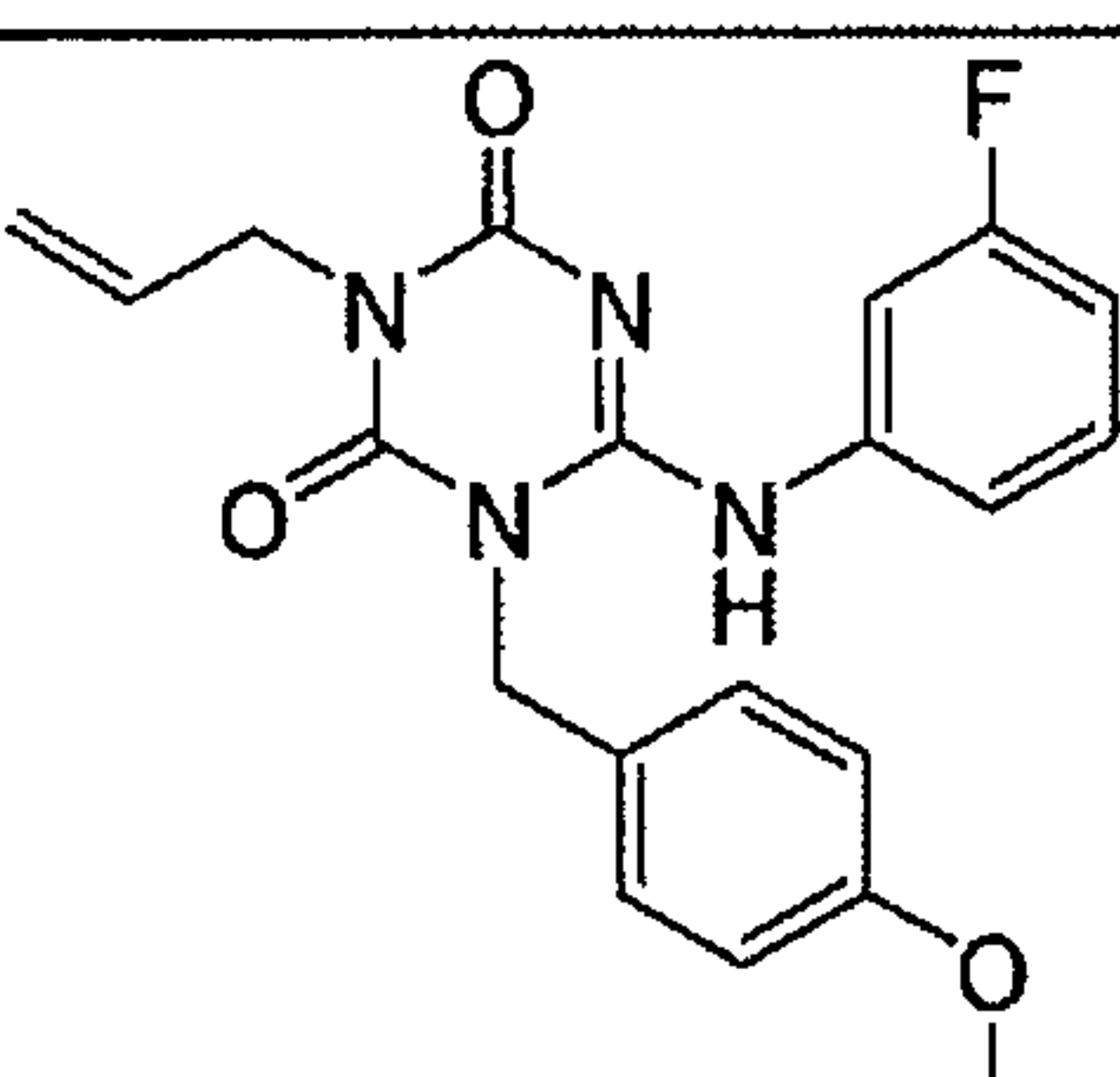
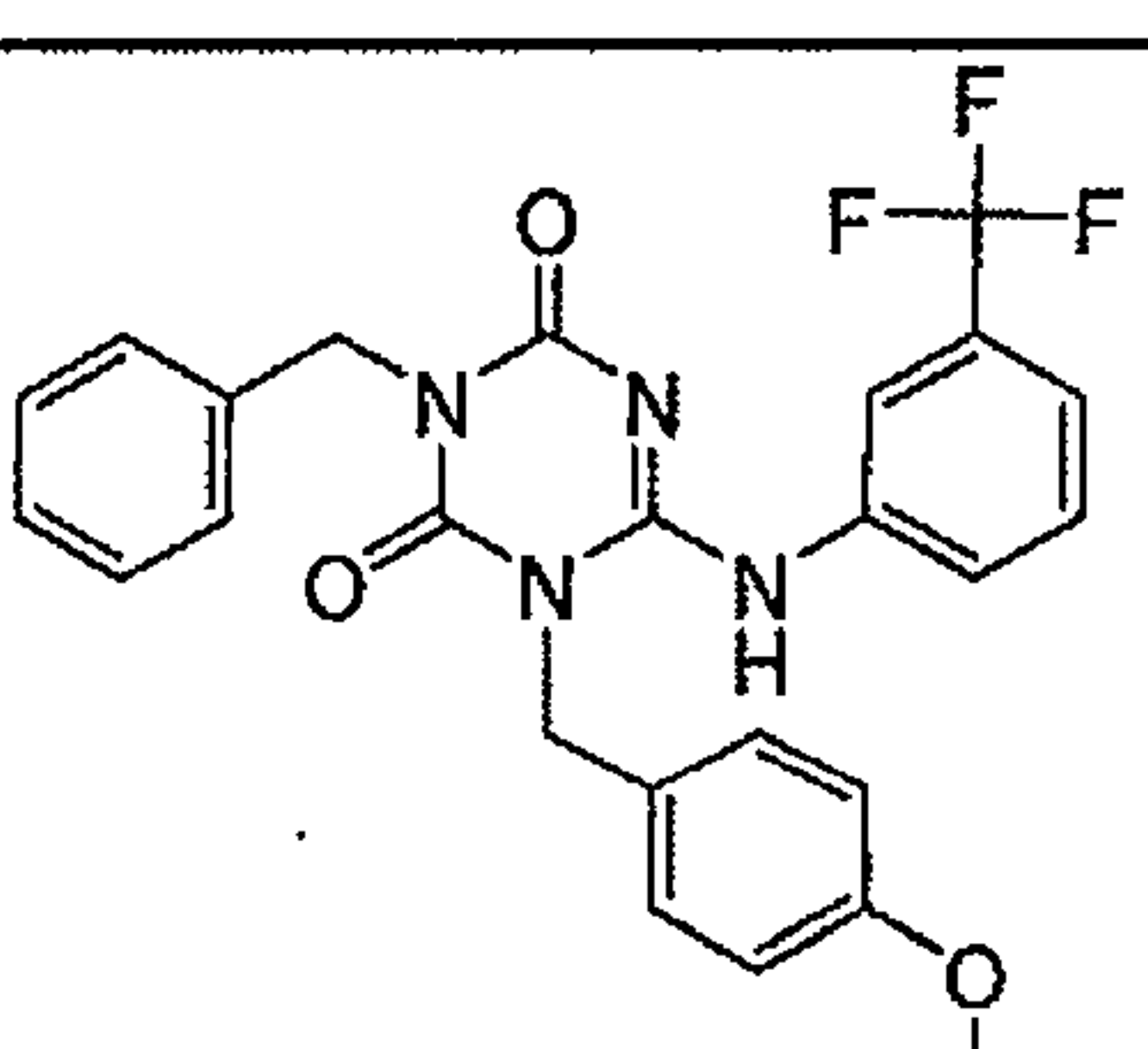
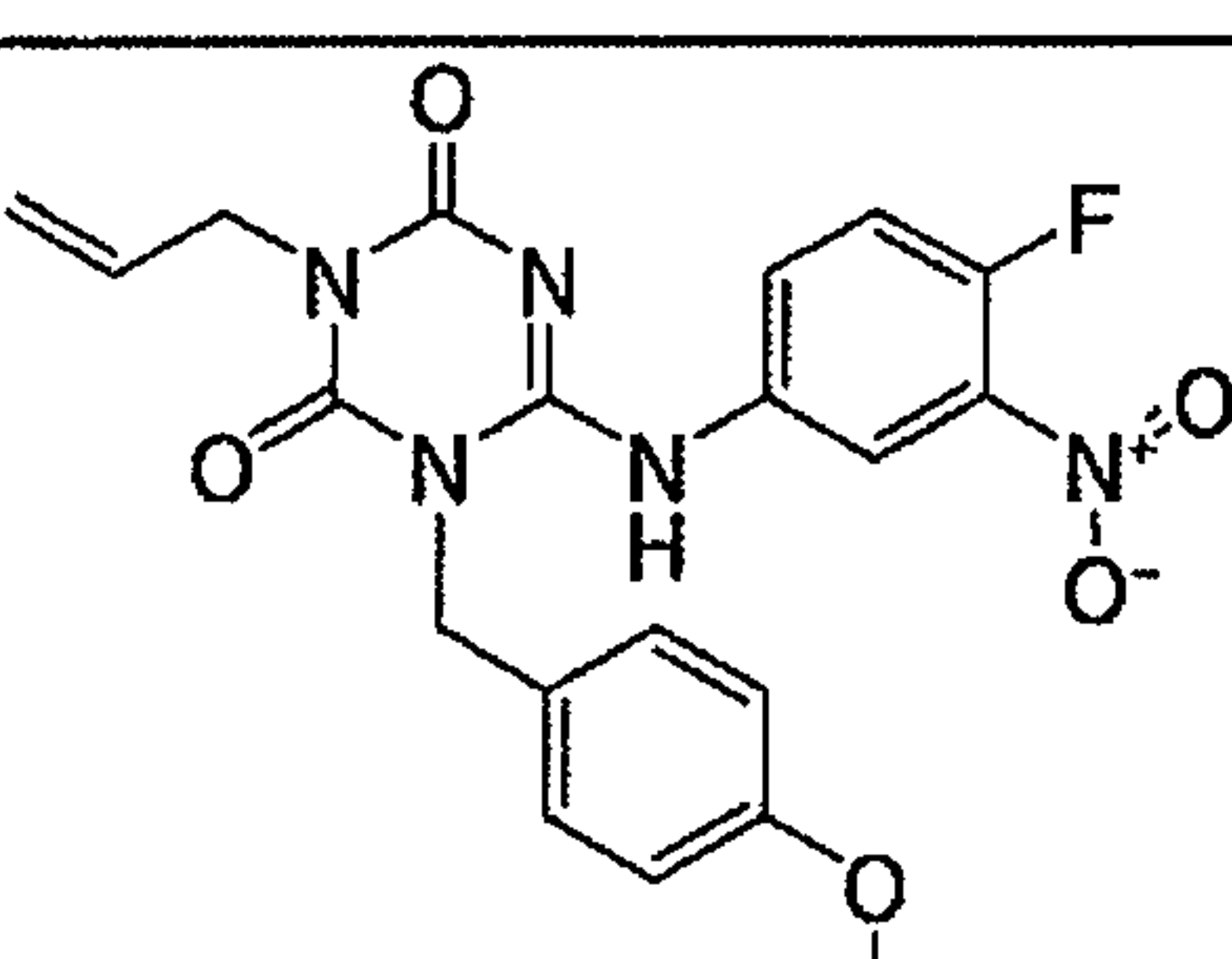
[Table 4]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0001	2.46	469	3
	I-0002	2.49	493	3
	I-0003	2.31	399	3
	I-0004	2.47	473	3
	I-0005	2.37	461	3

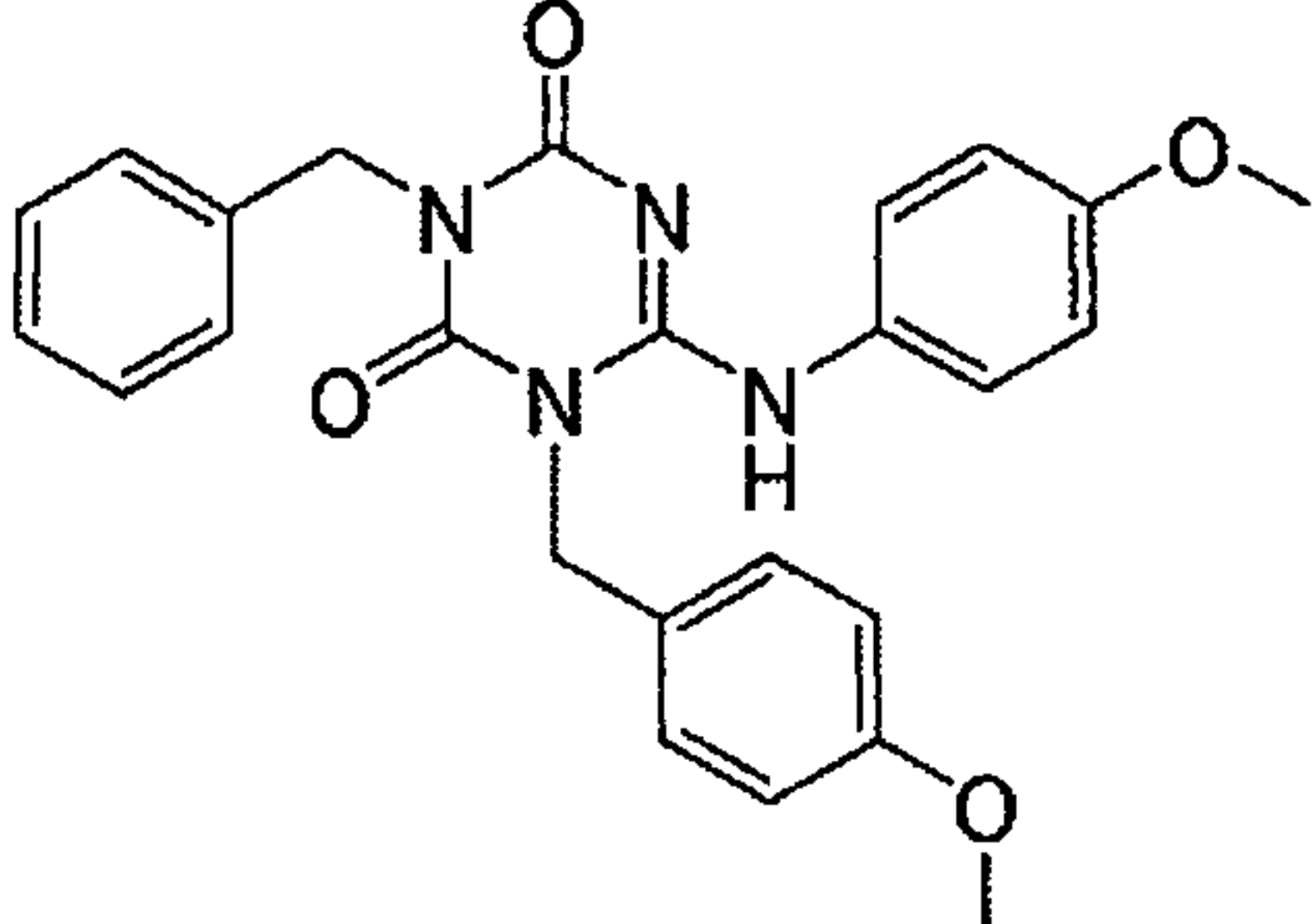
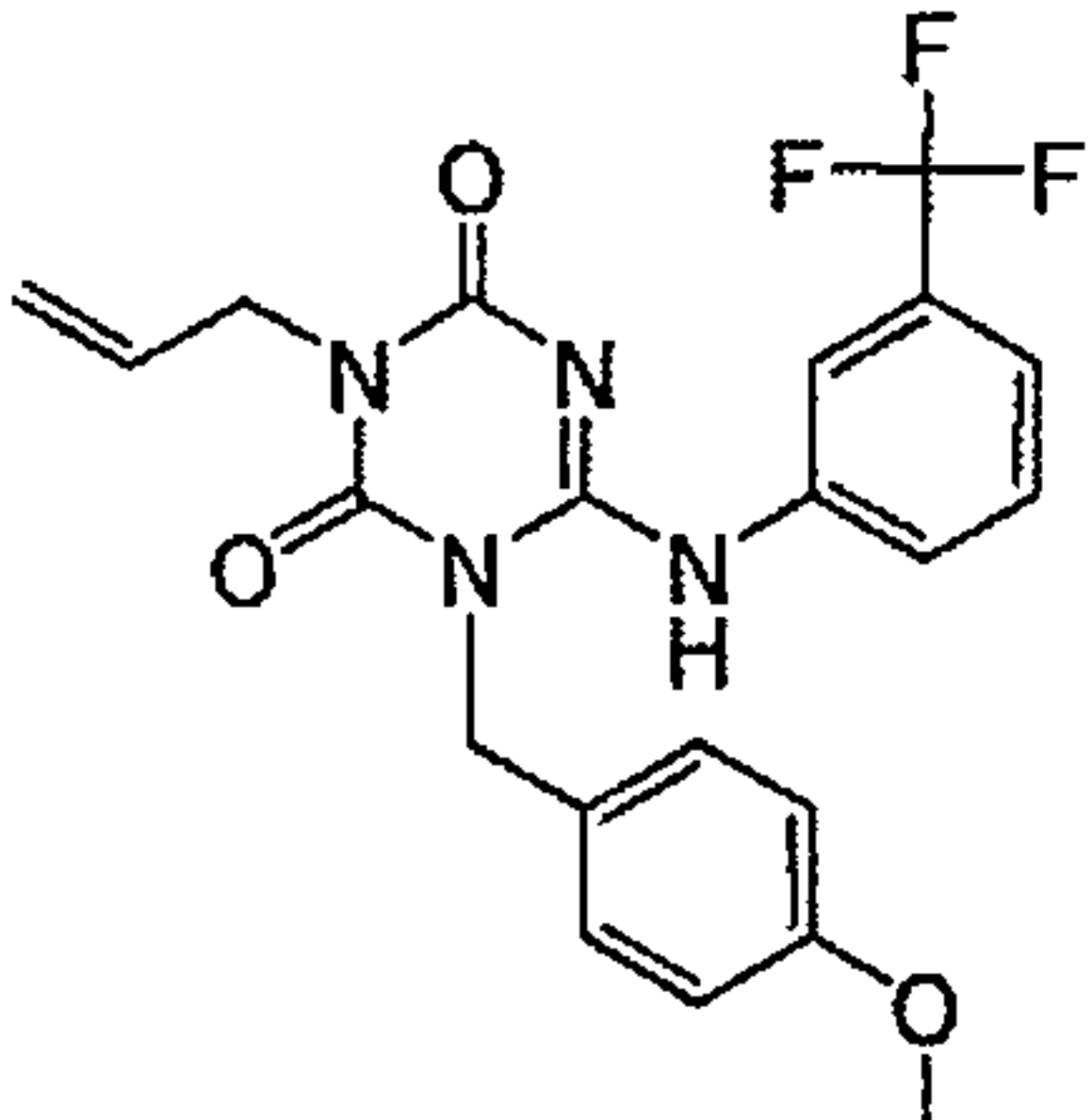
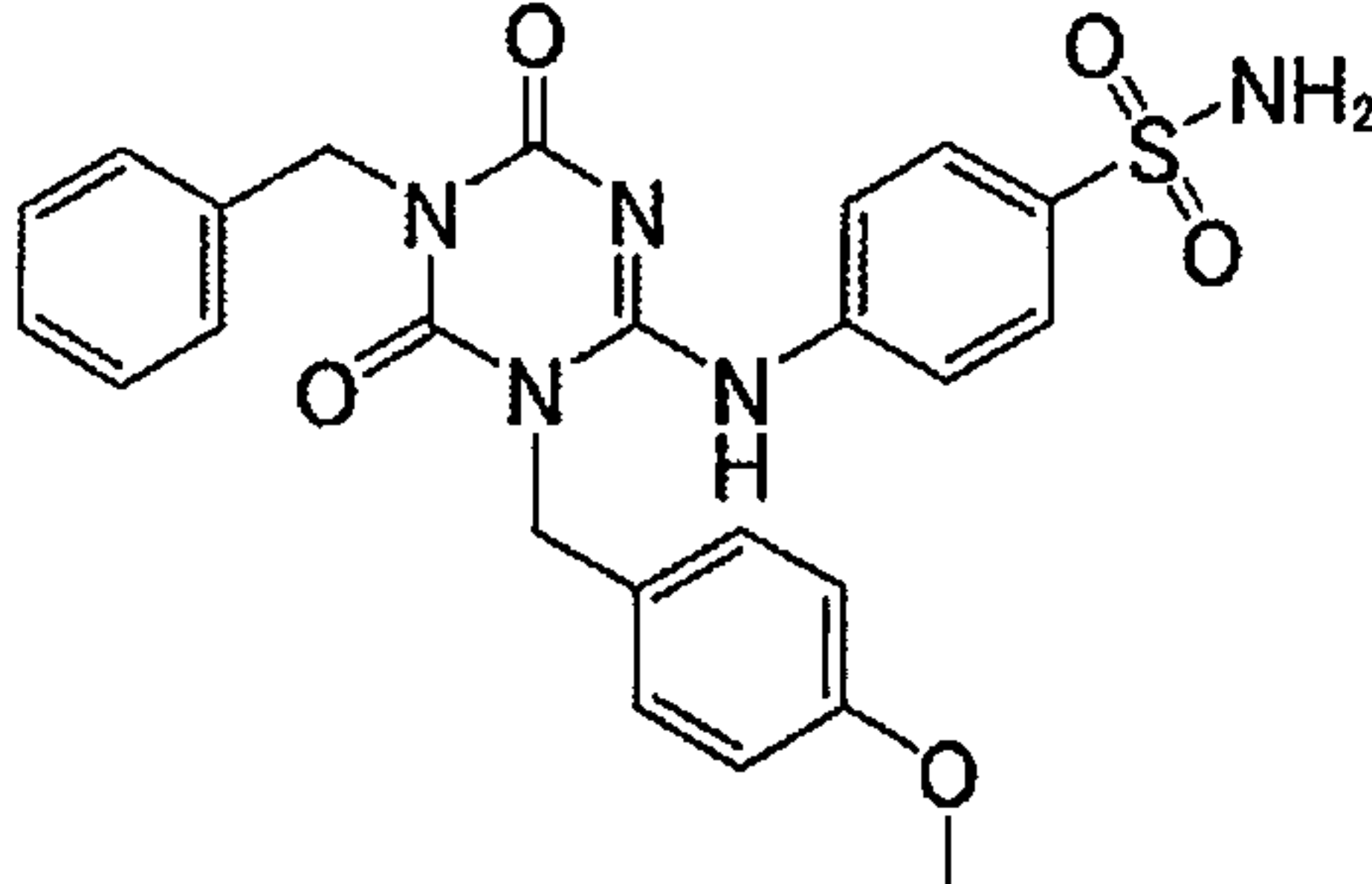
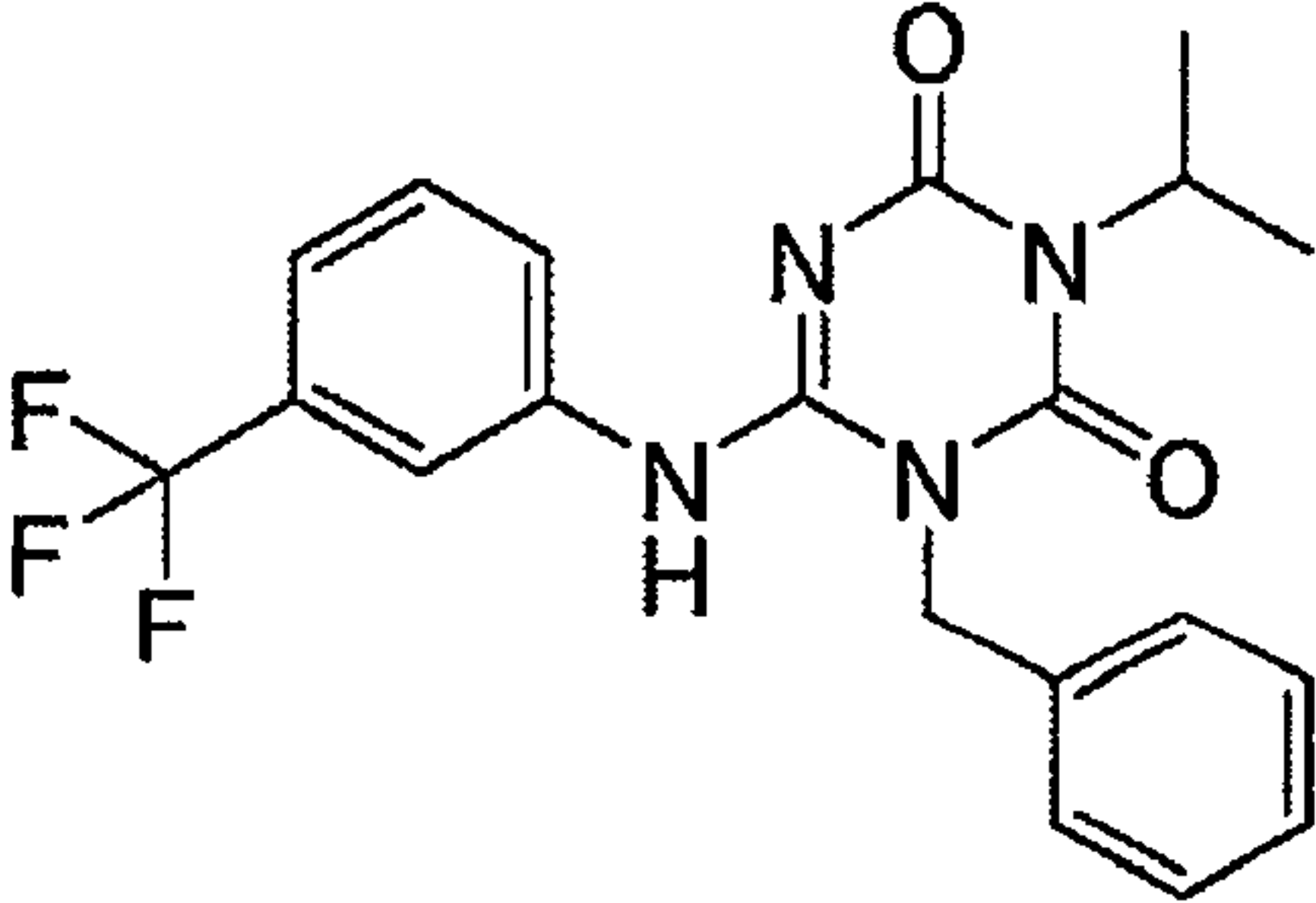
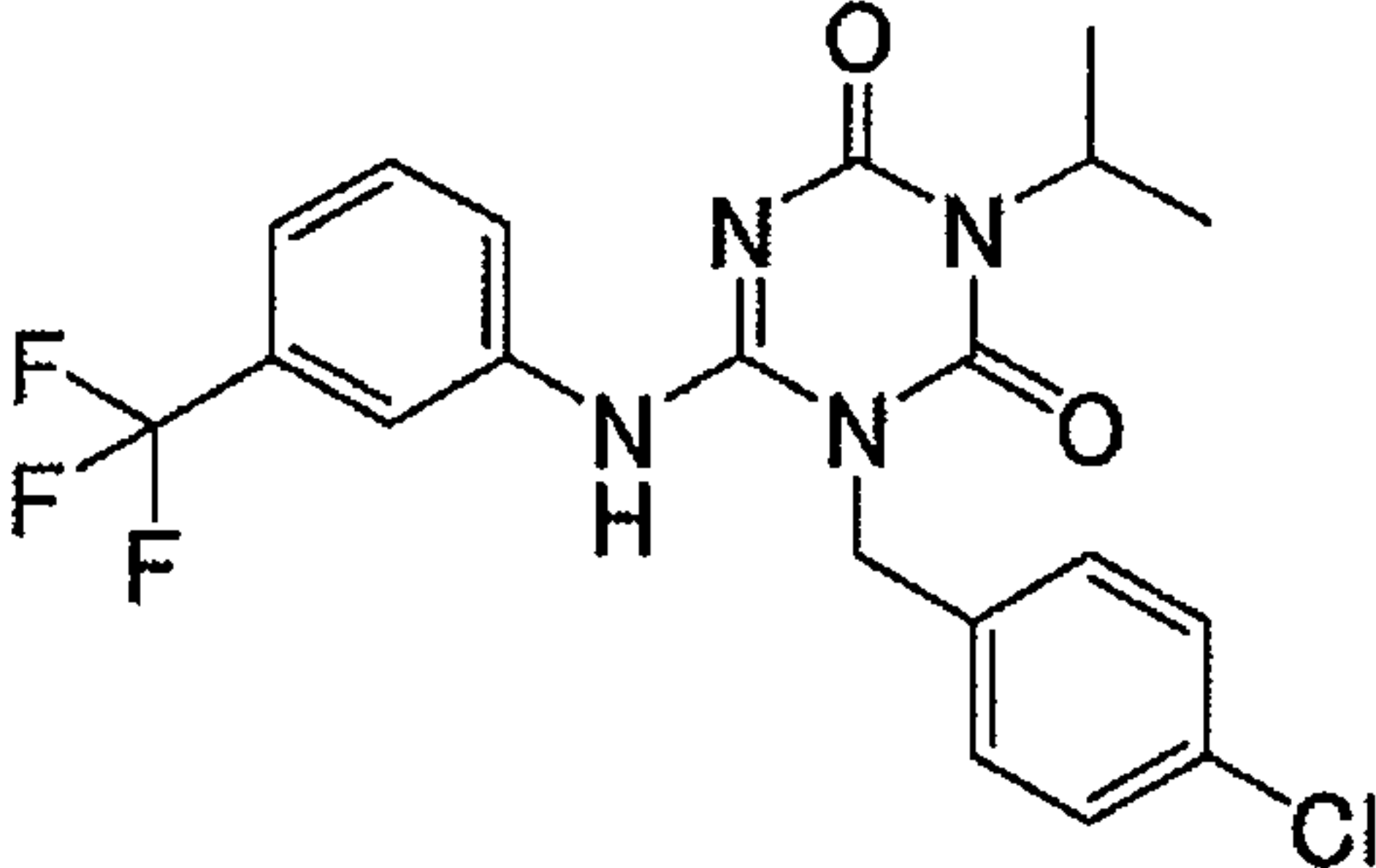
[Table 5]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0006	2.48	457	3
	I-0007	2.34	415	3
	I-0008	2.22	475	3
	I-0009	2.23	423	3
	I-0010	2.48	457	3

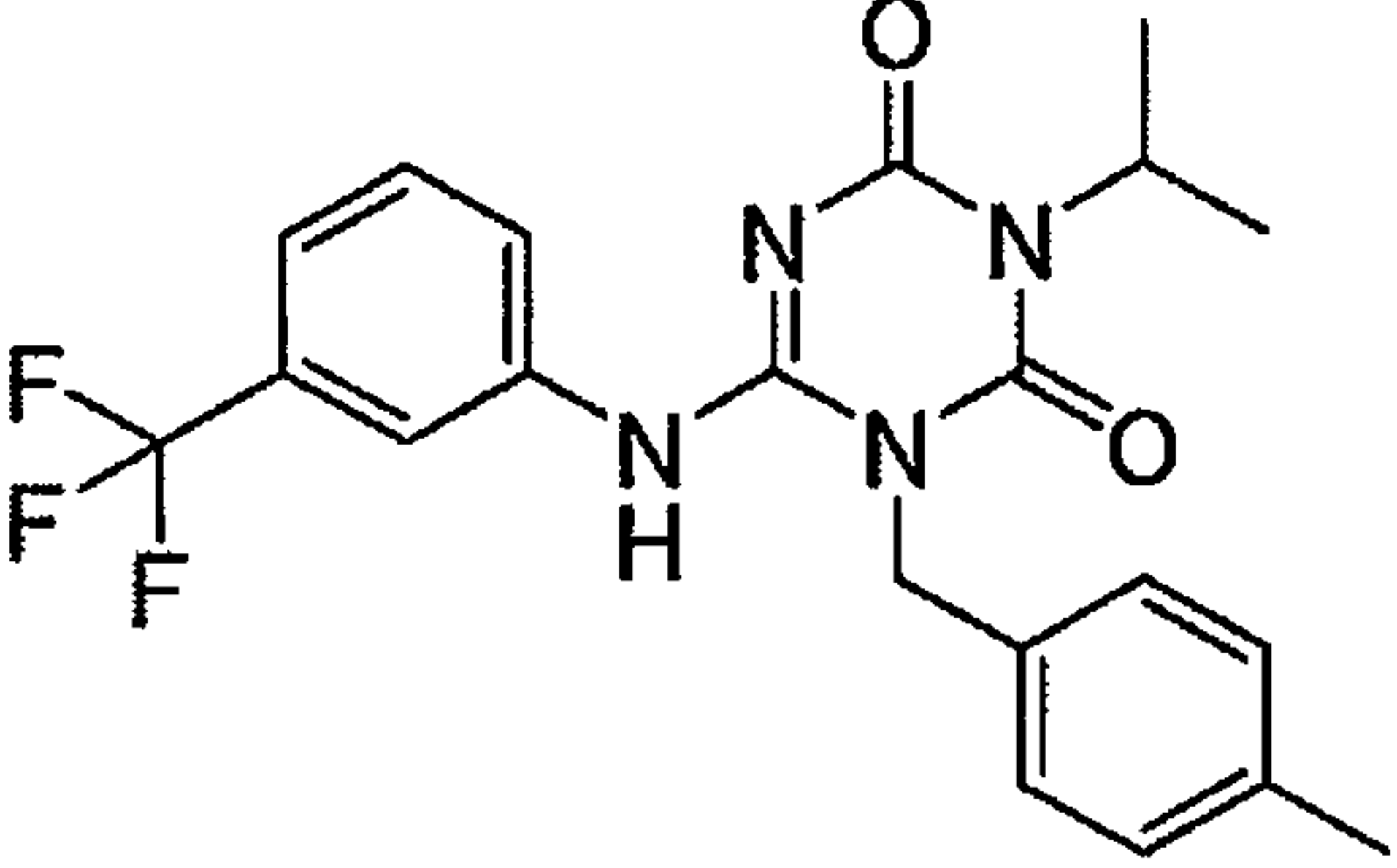
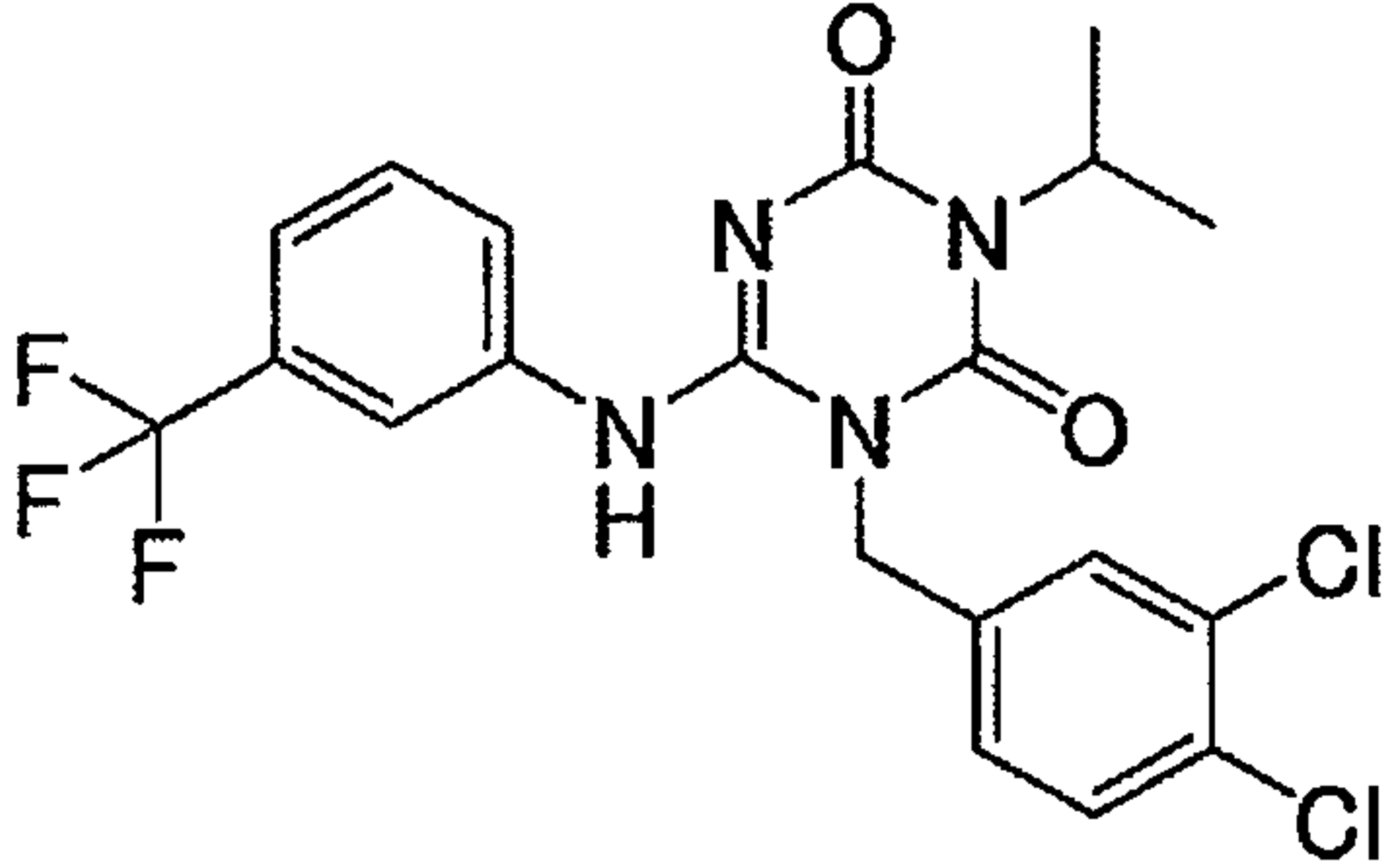
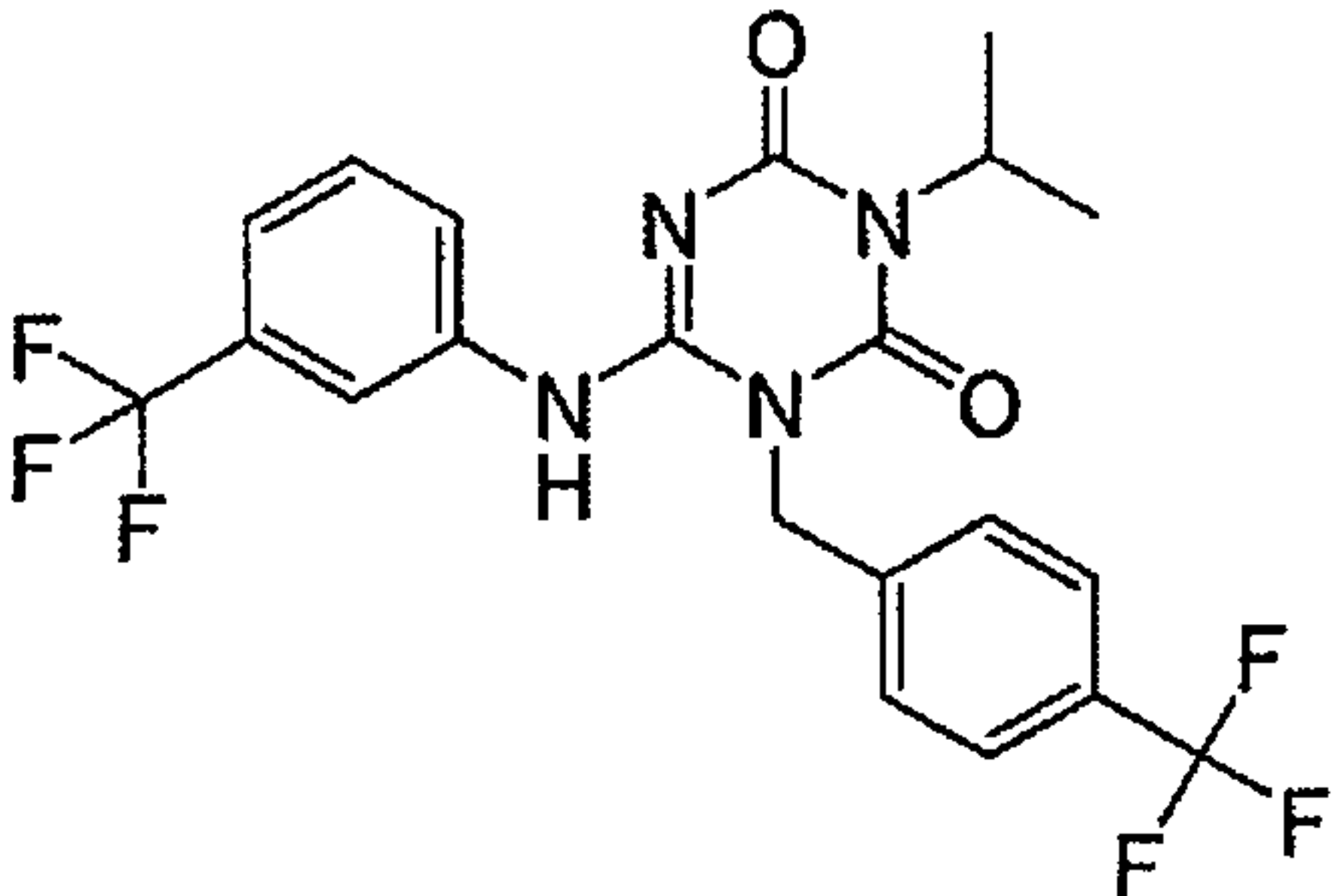
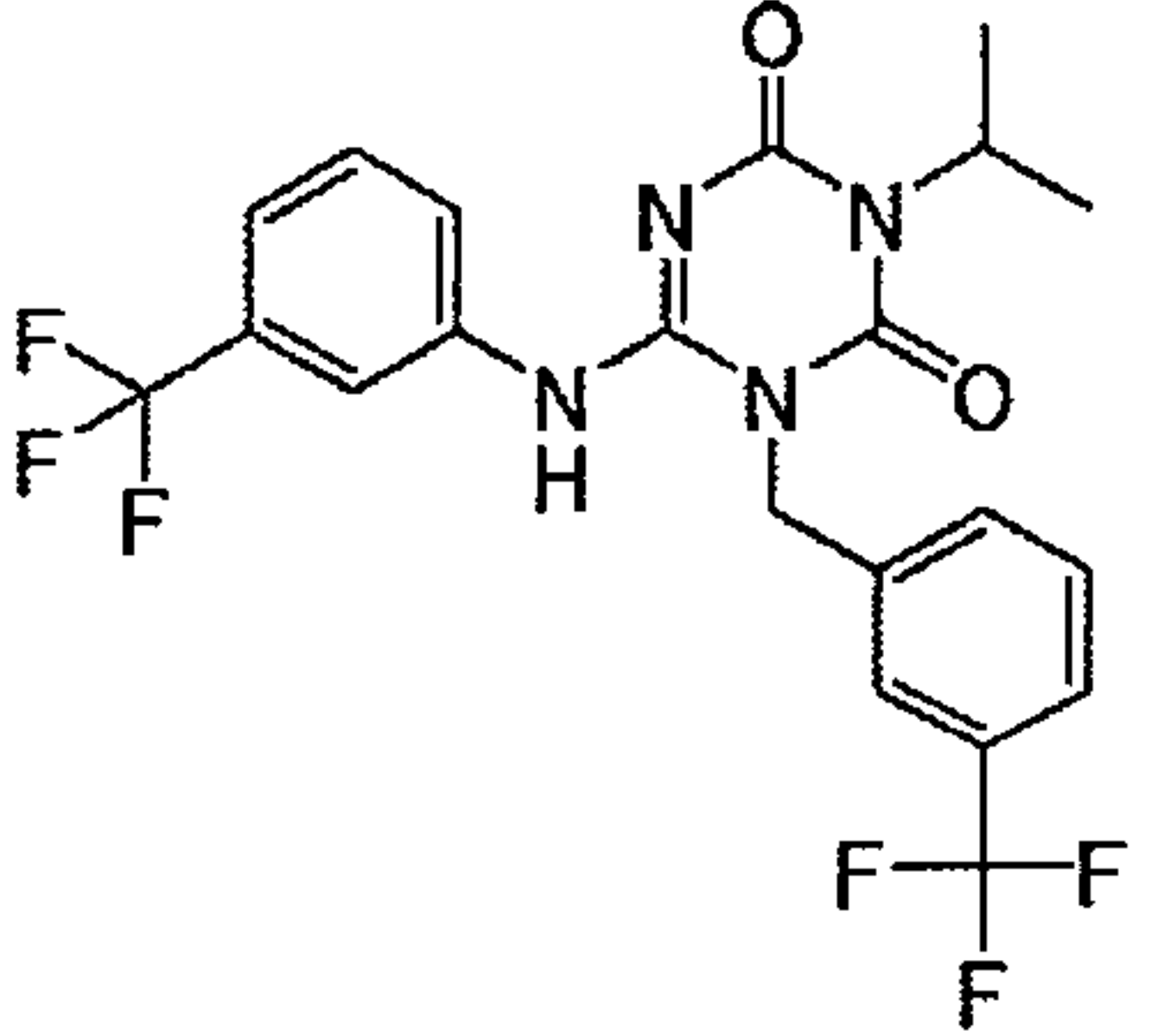
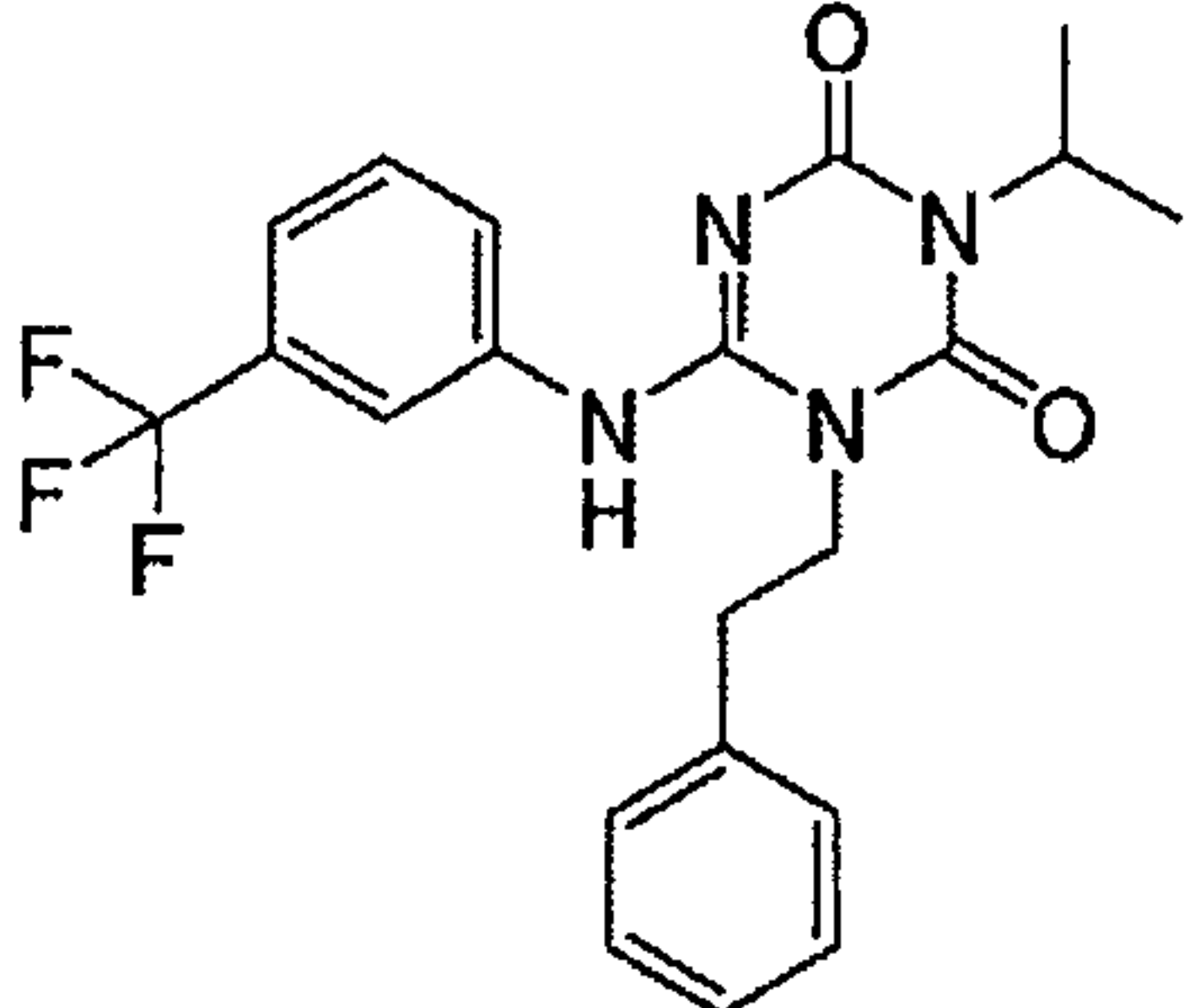
[Table 6]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0011	2.47	433	3
	I-0012	2.51	478	3
	I-0013	2.23	383	3
	I-0014	2.65	483	3
	I-0015	2.29	428	3

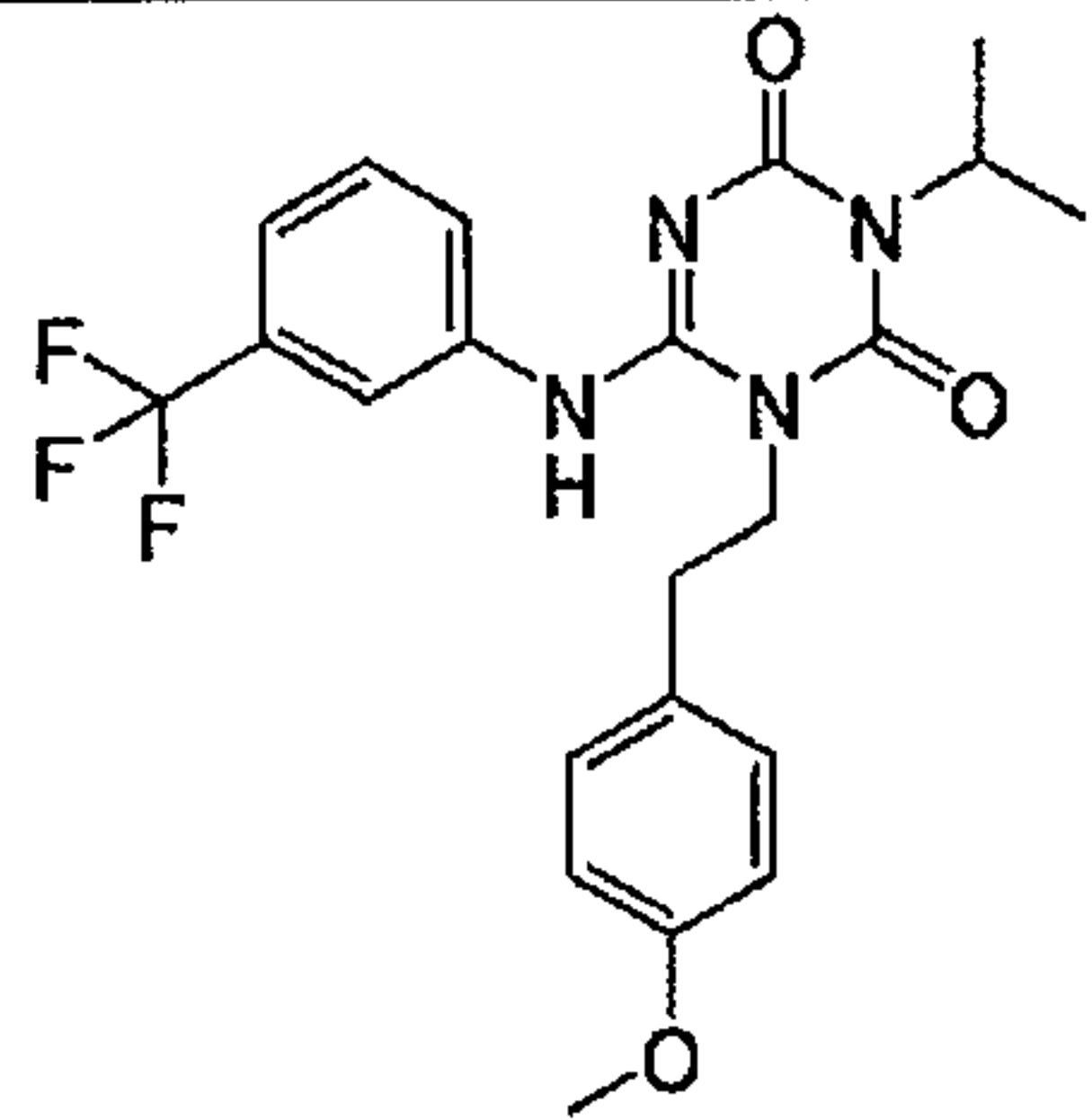
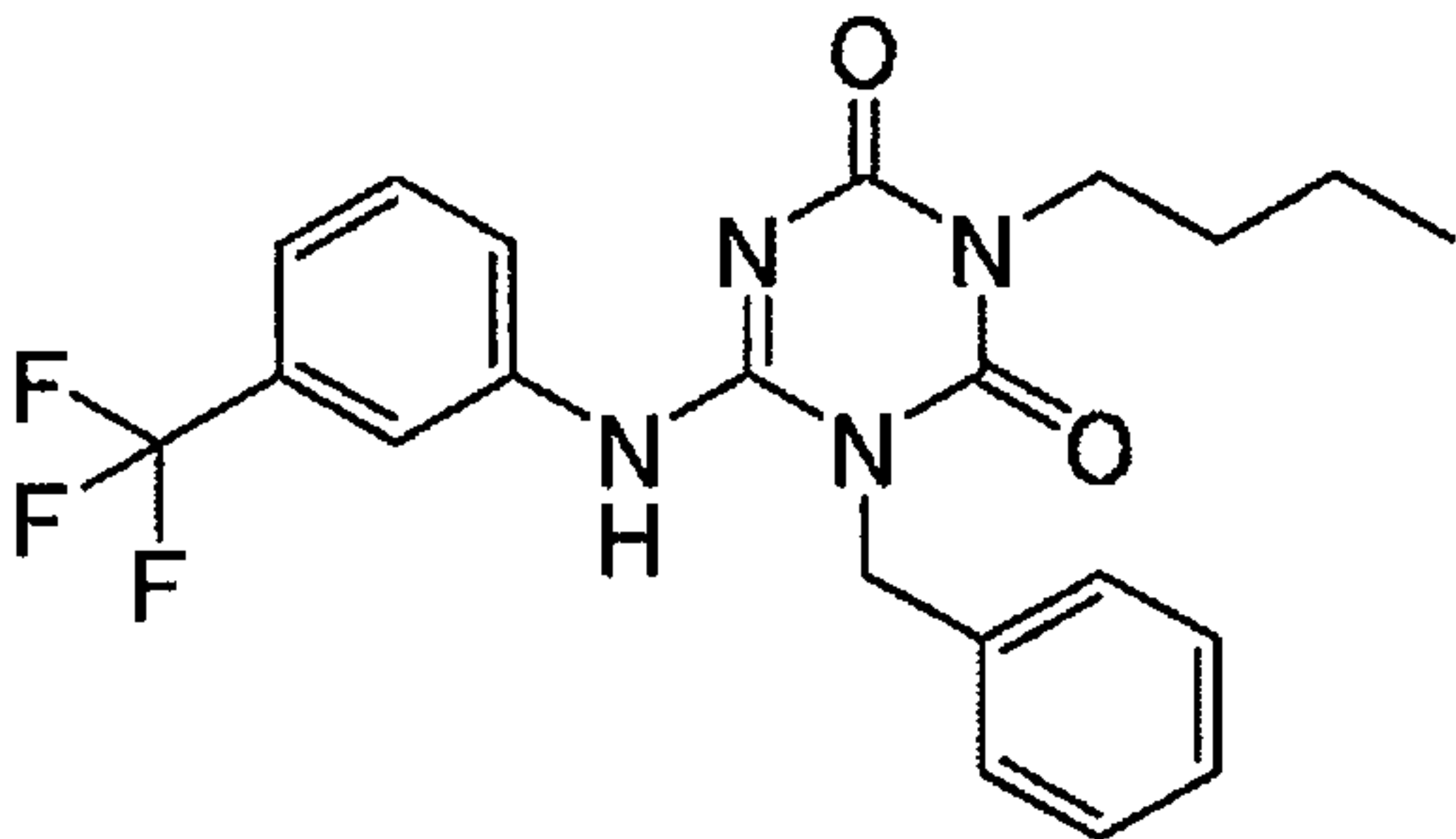
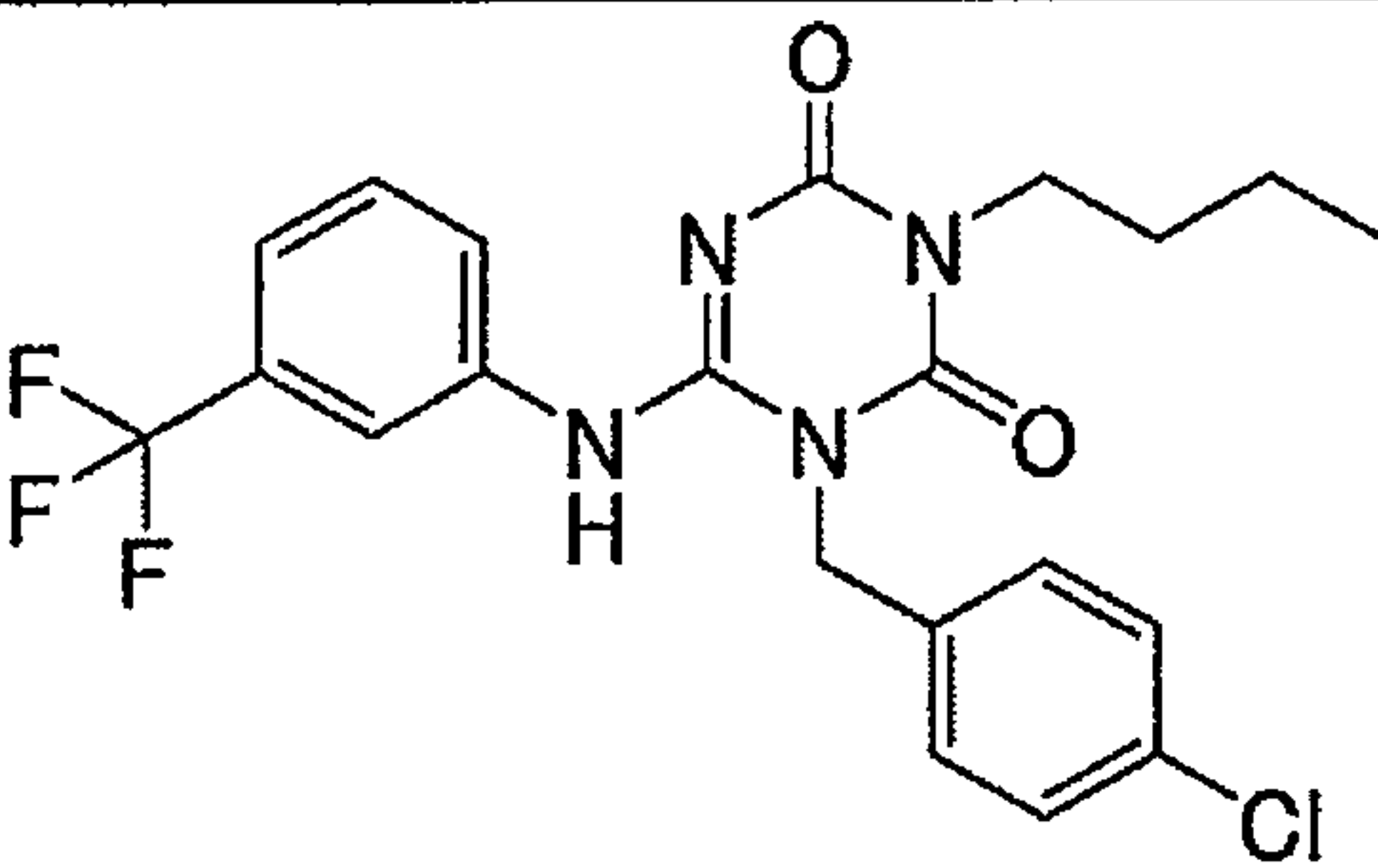
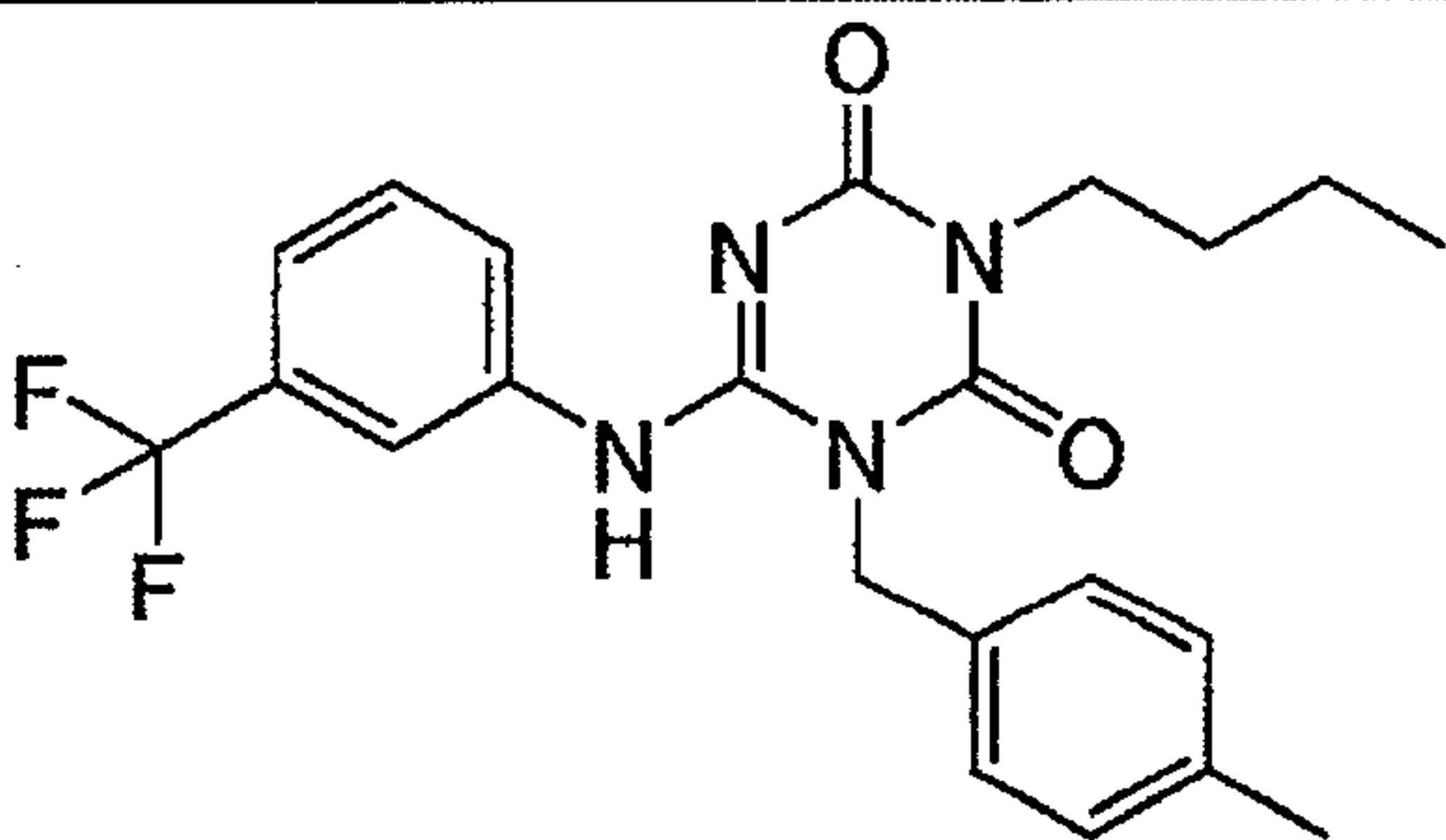
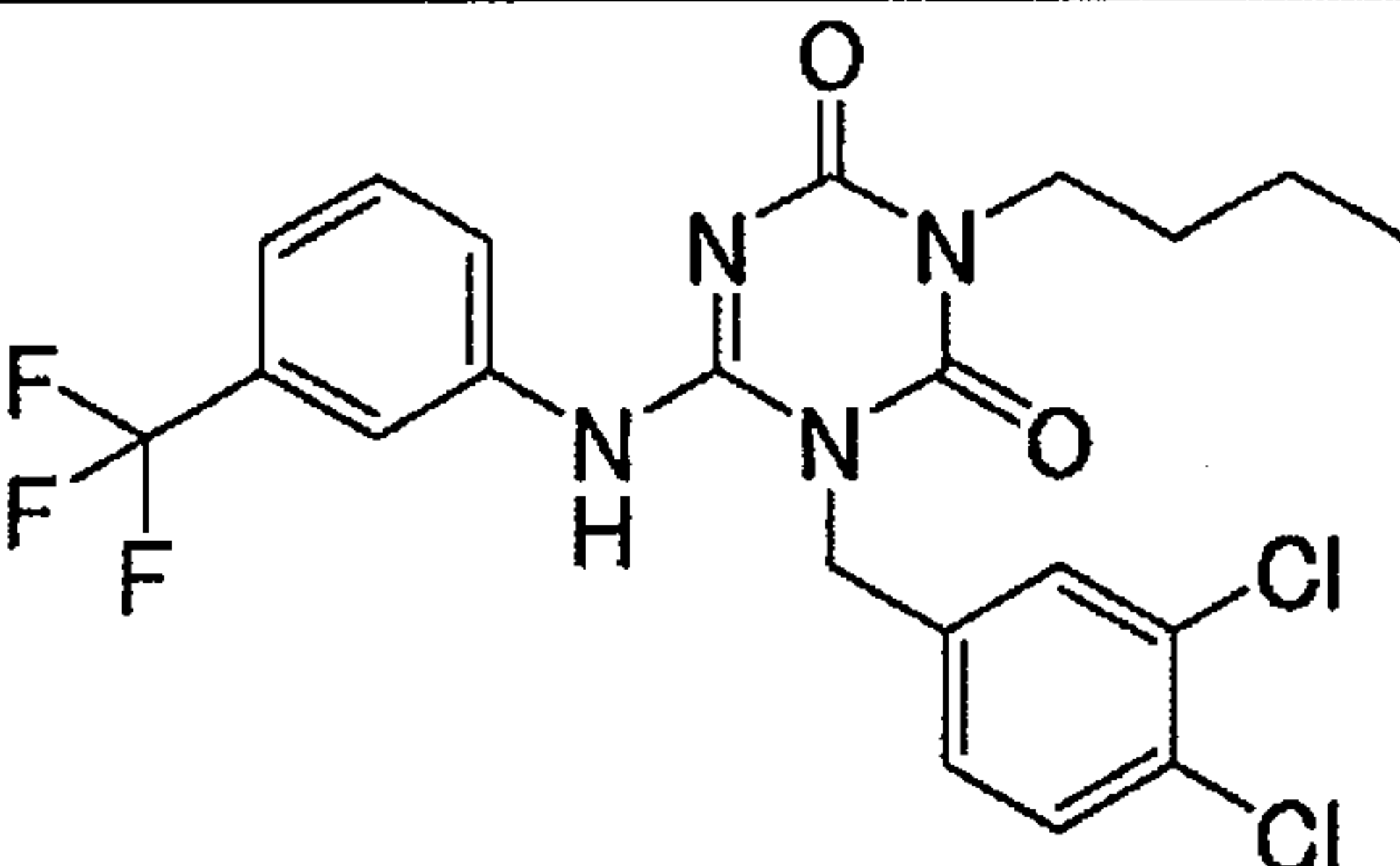
[Table 7]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0016	2.29	445	3
	I-0017	2.45	433	3
	I-0018	2.09	494	3
	I-0019	2.16	405	4
	I-0020	3.88	439	4

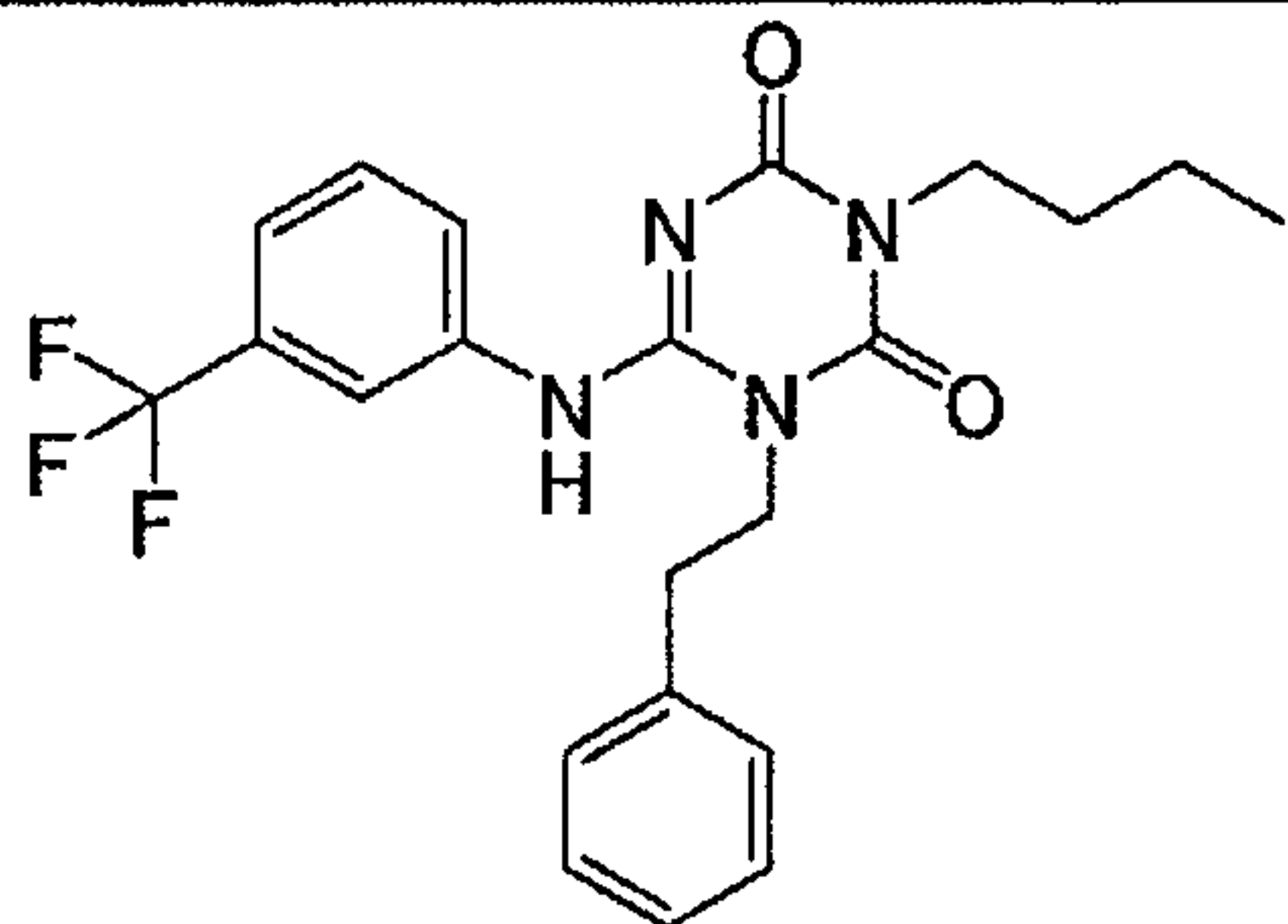
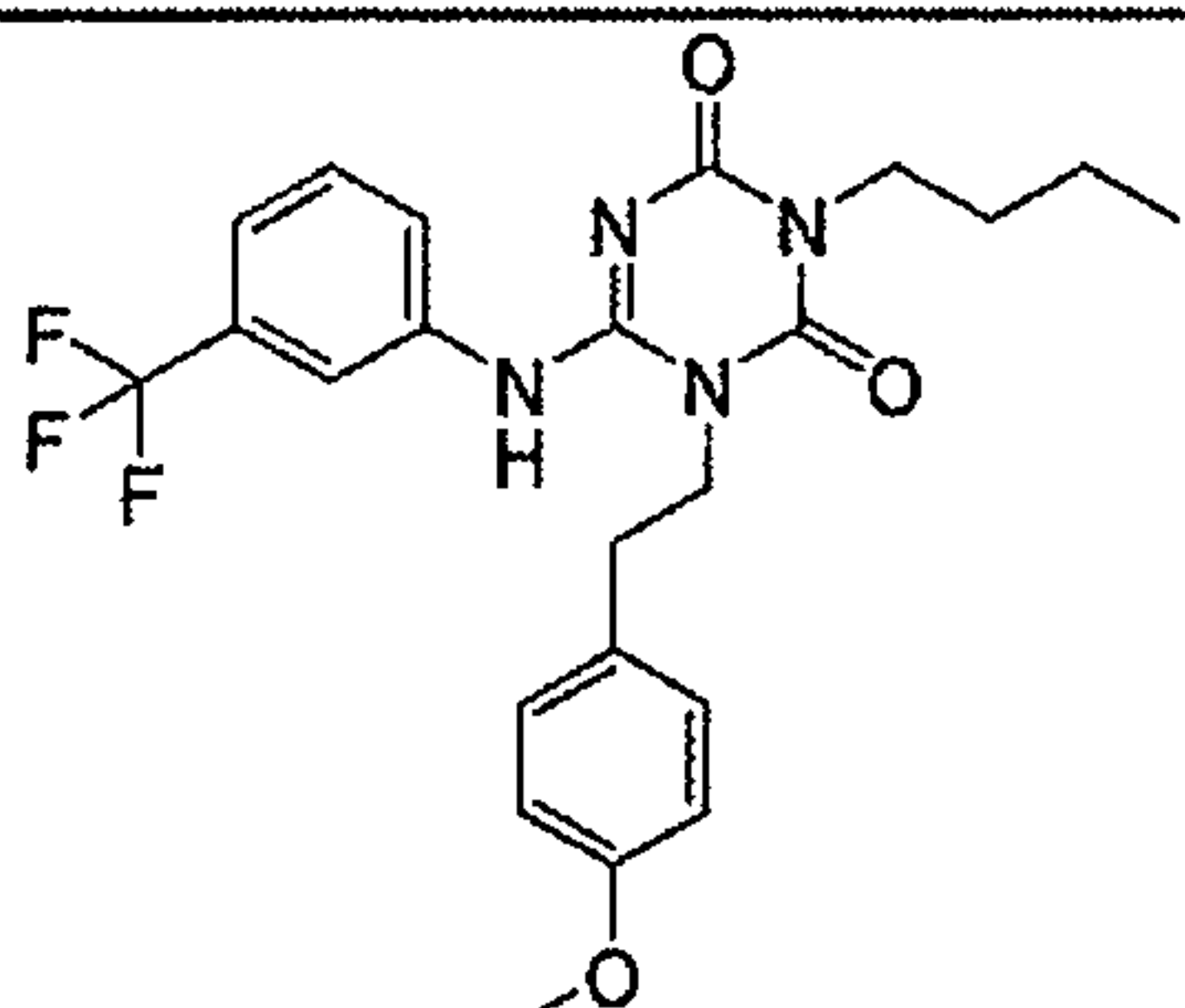
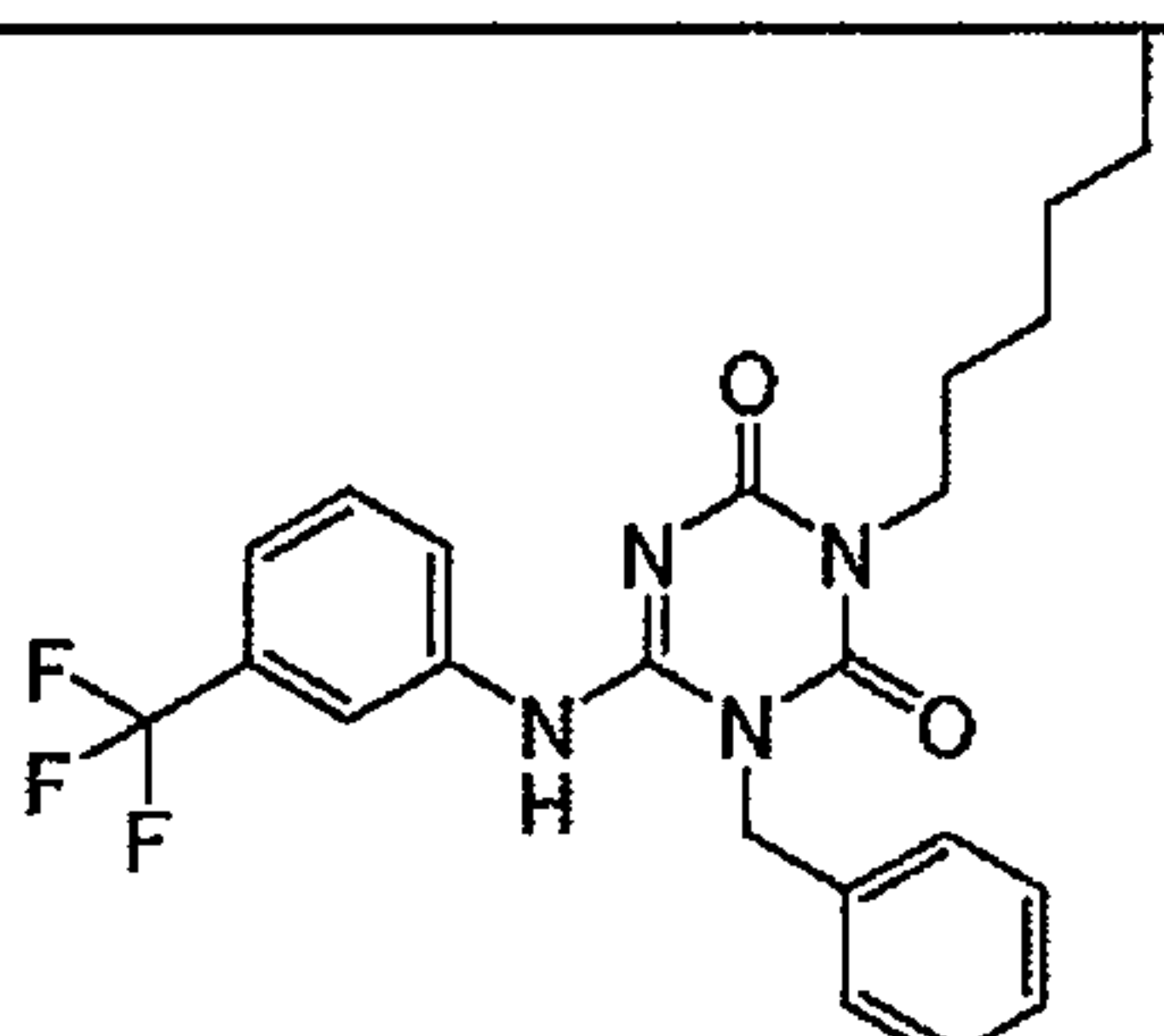
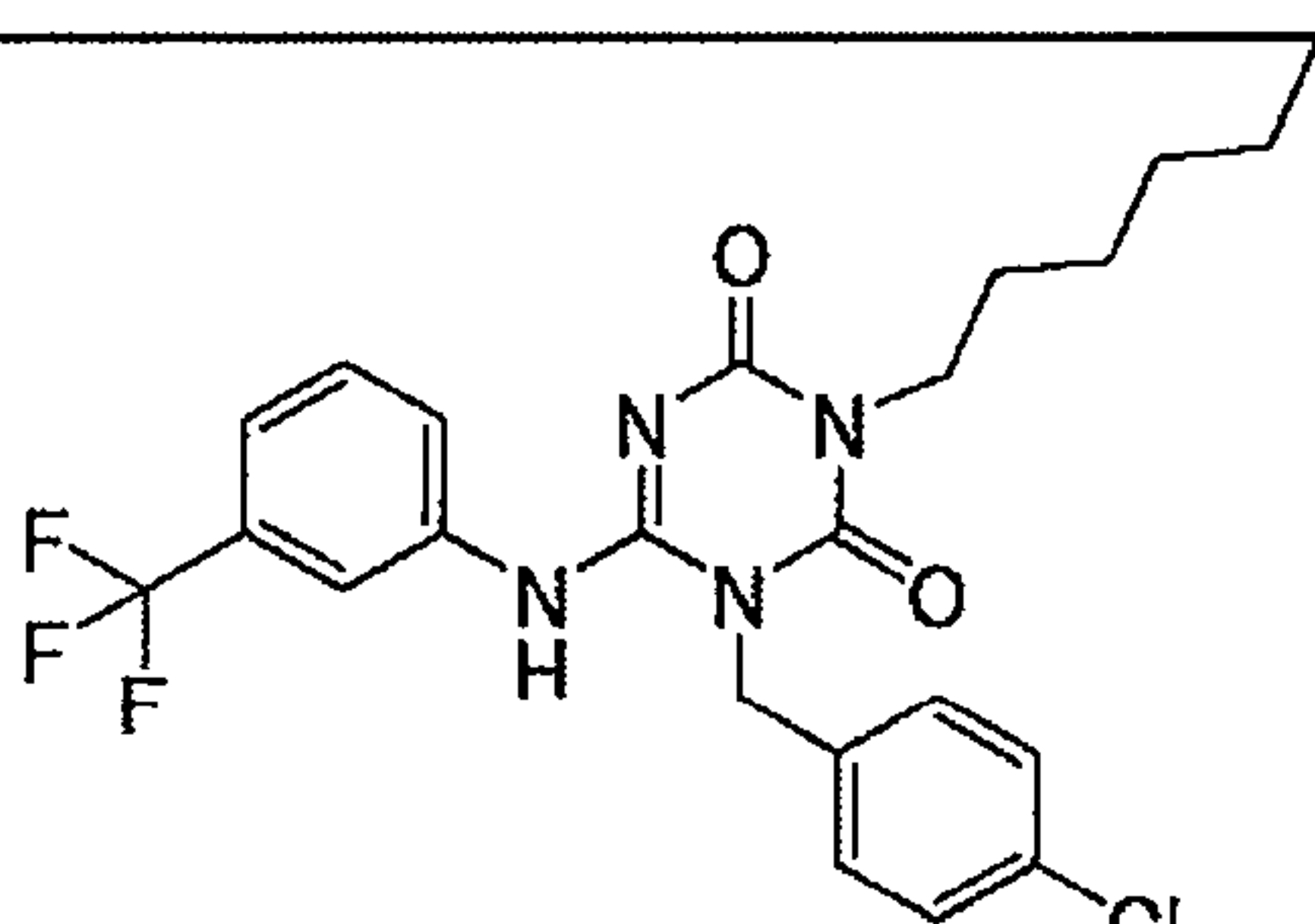
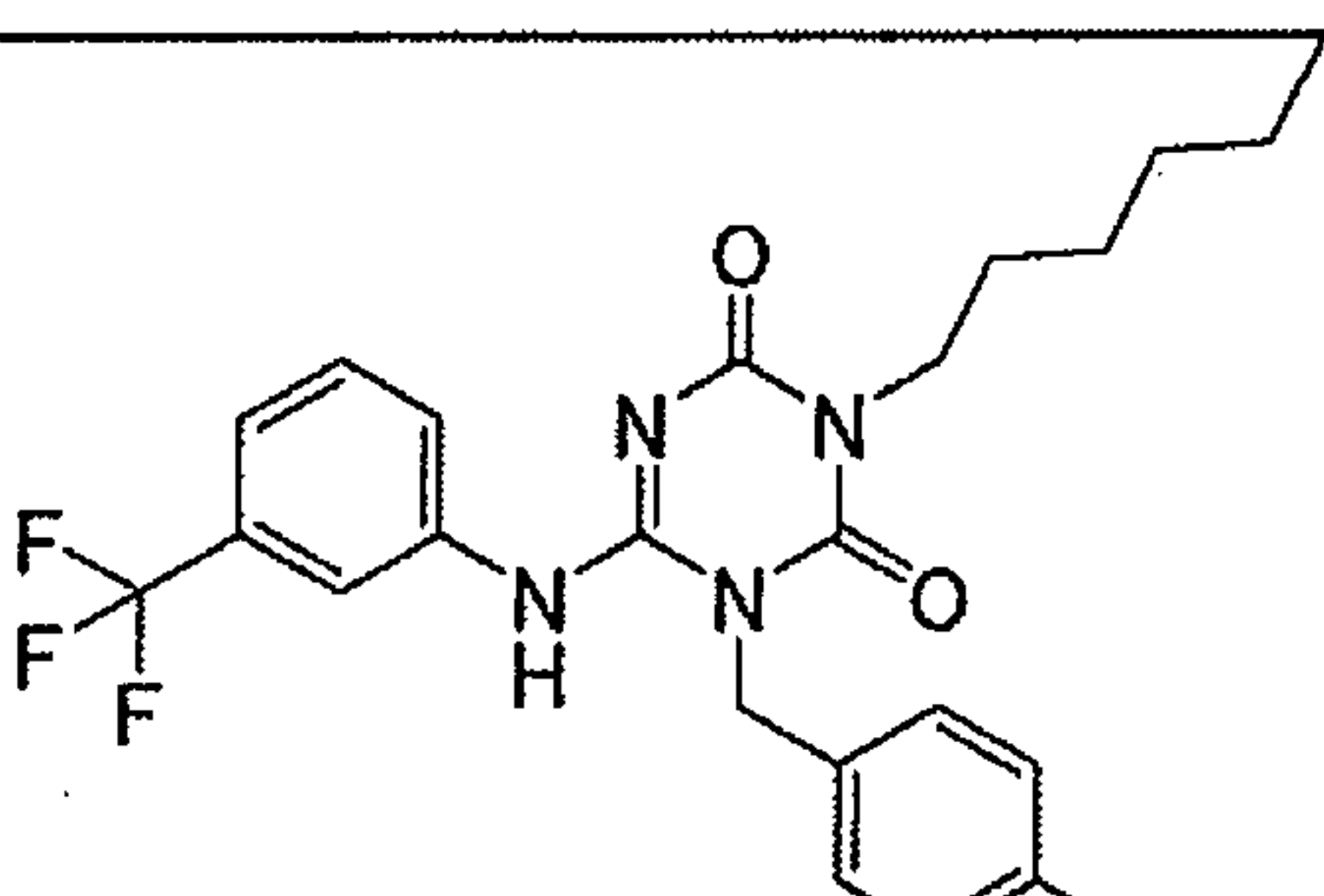
[Table 8]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0021	3.63	419	4
	I-0022	4.43	474	4
	I-0023	3.91	473	4
	I-0024	3.93	473	4
	I-0025	3.33	419	4

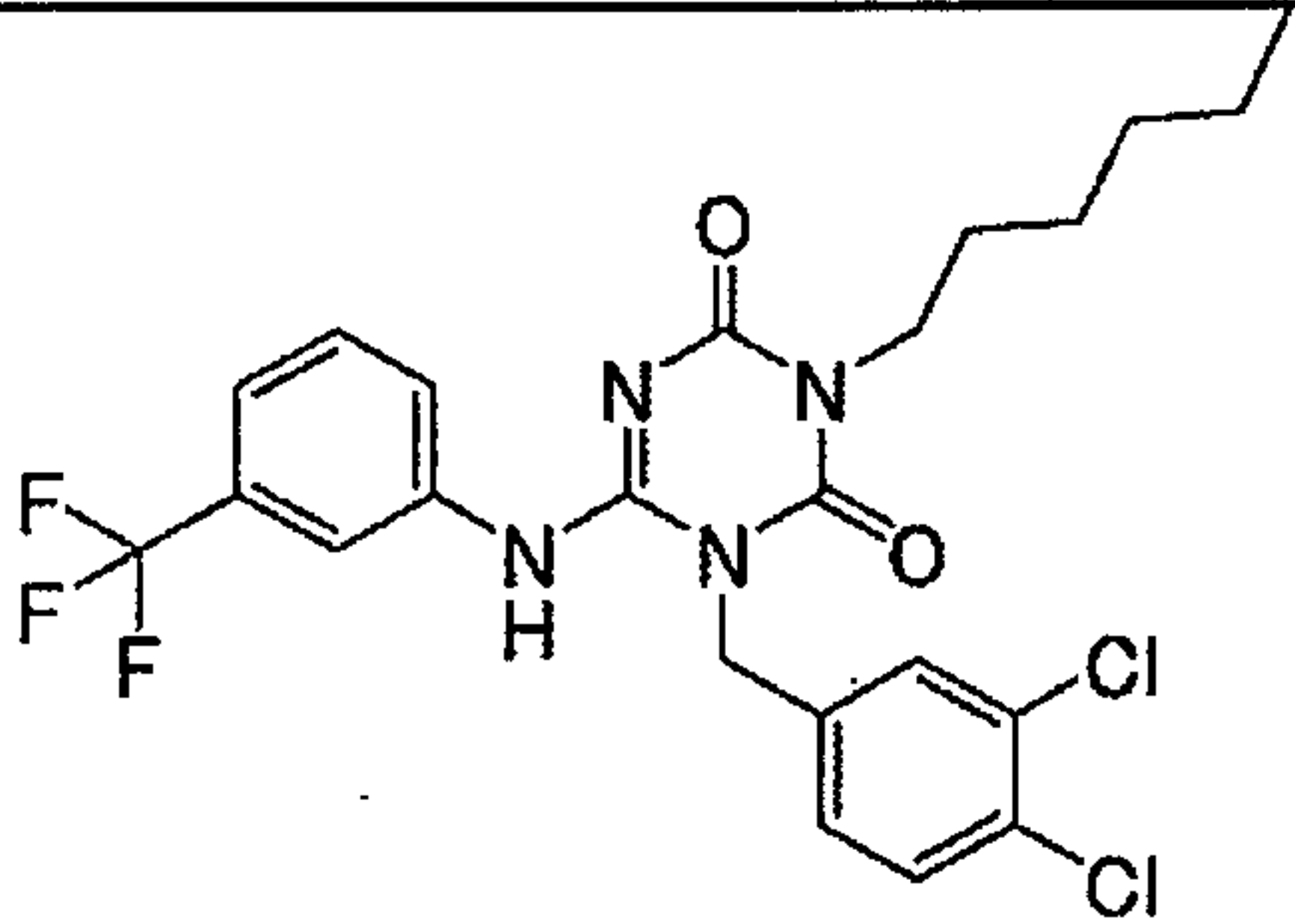
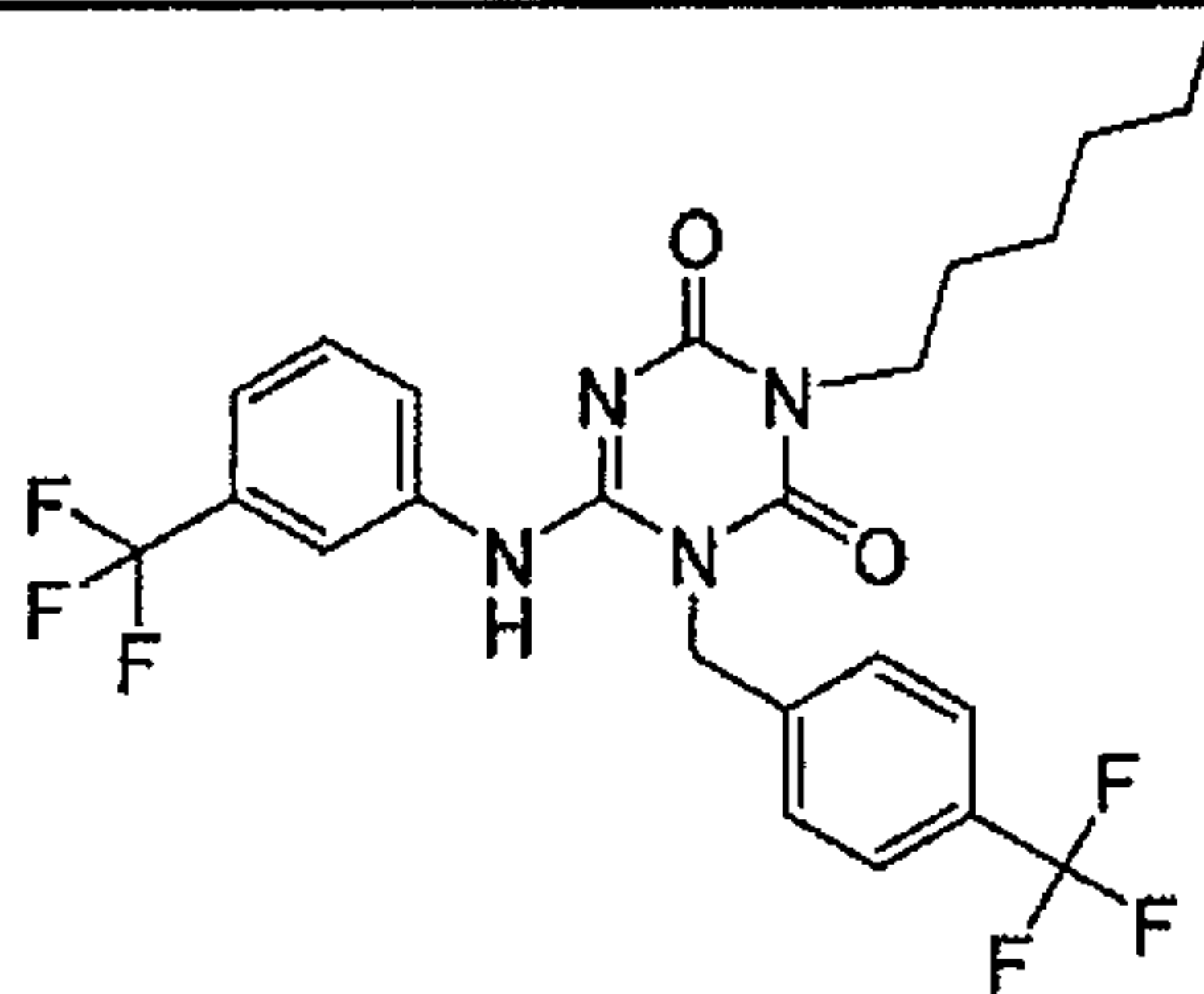
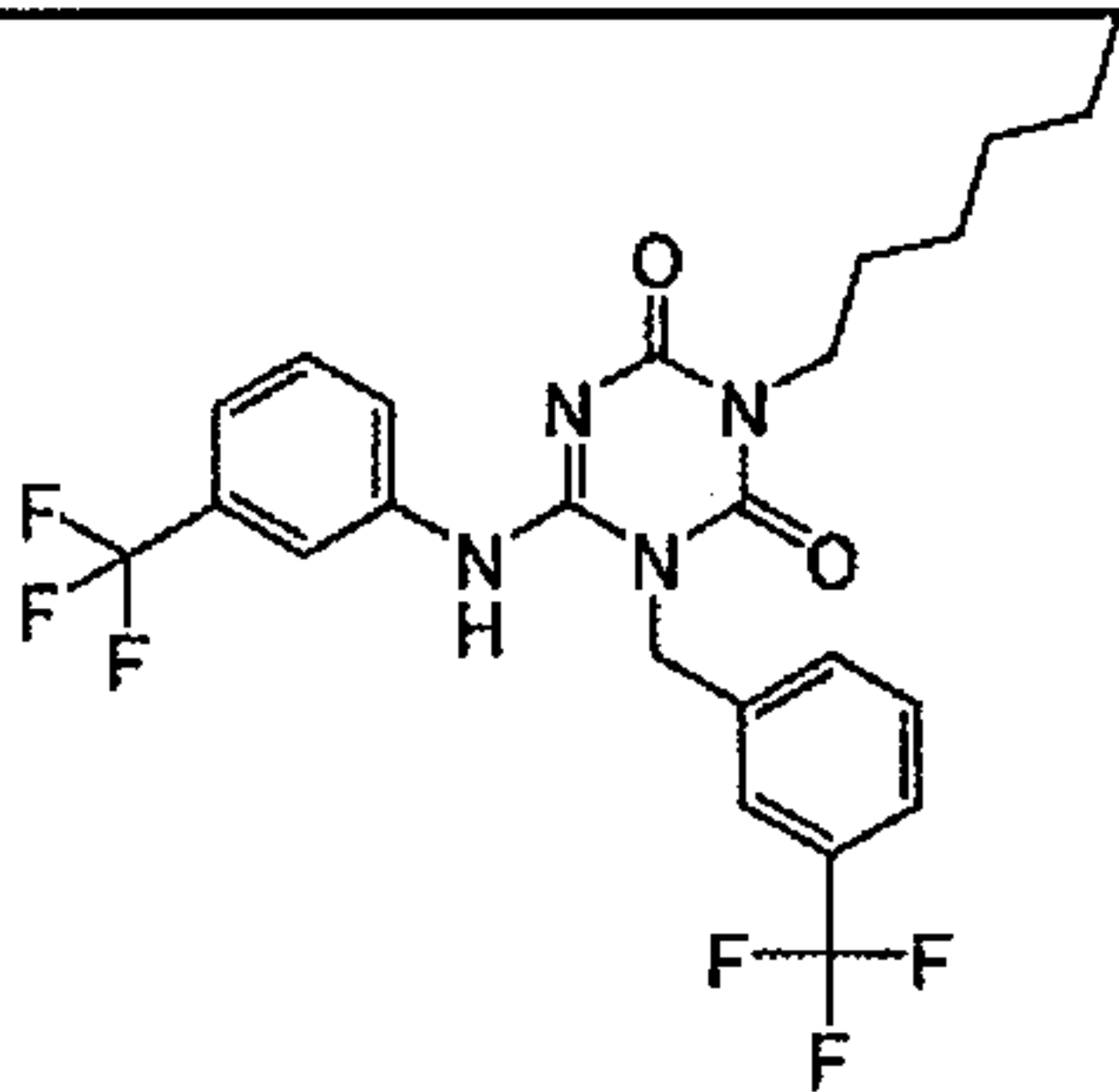
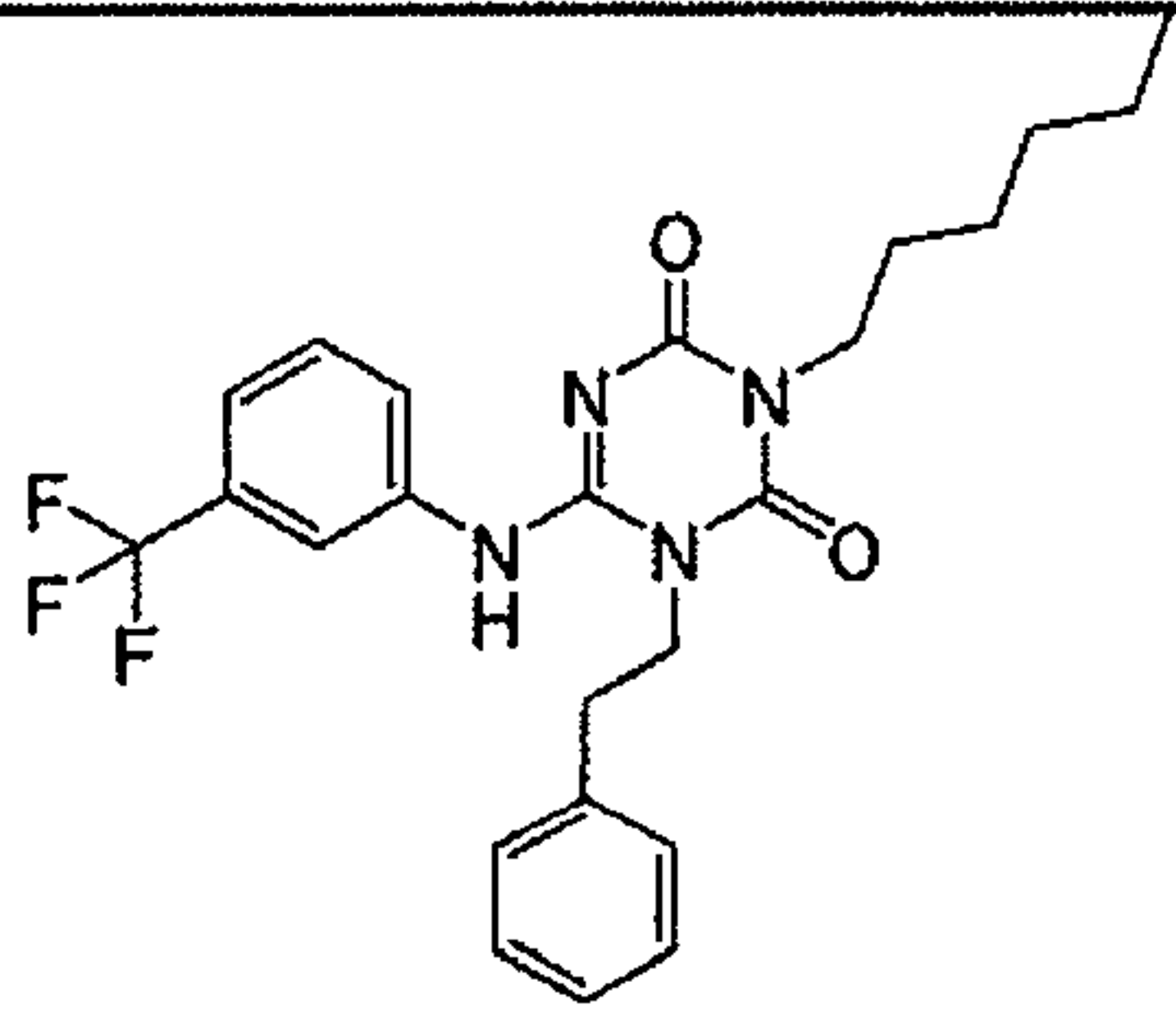
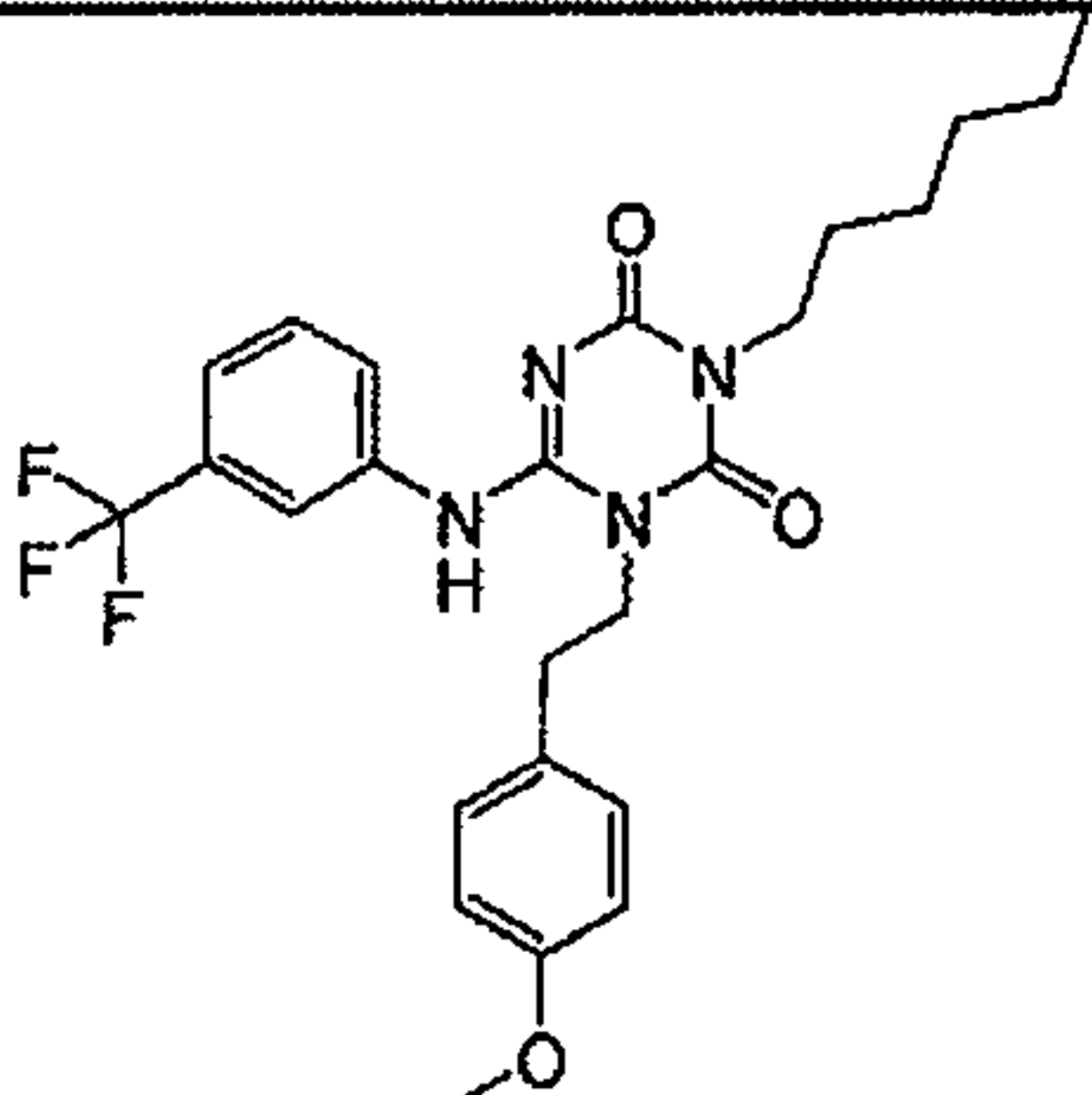
[Table 9]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0026	3.16	449	4
	I-0027	2.46	419	4
	I-0028	3.27	453	4
	I-0029	2.95	433	4
	I-0030	3.94	488	4

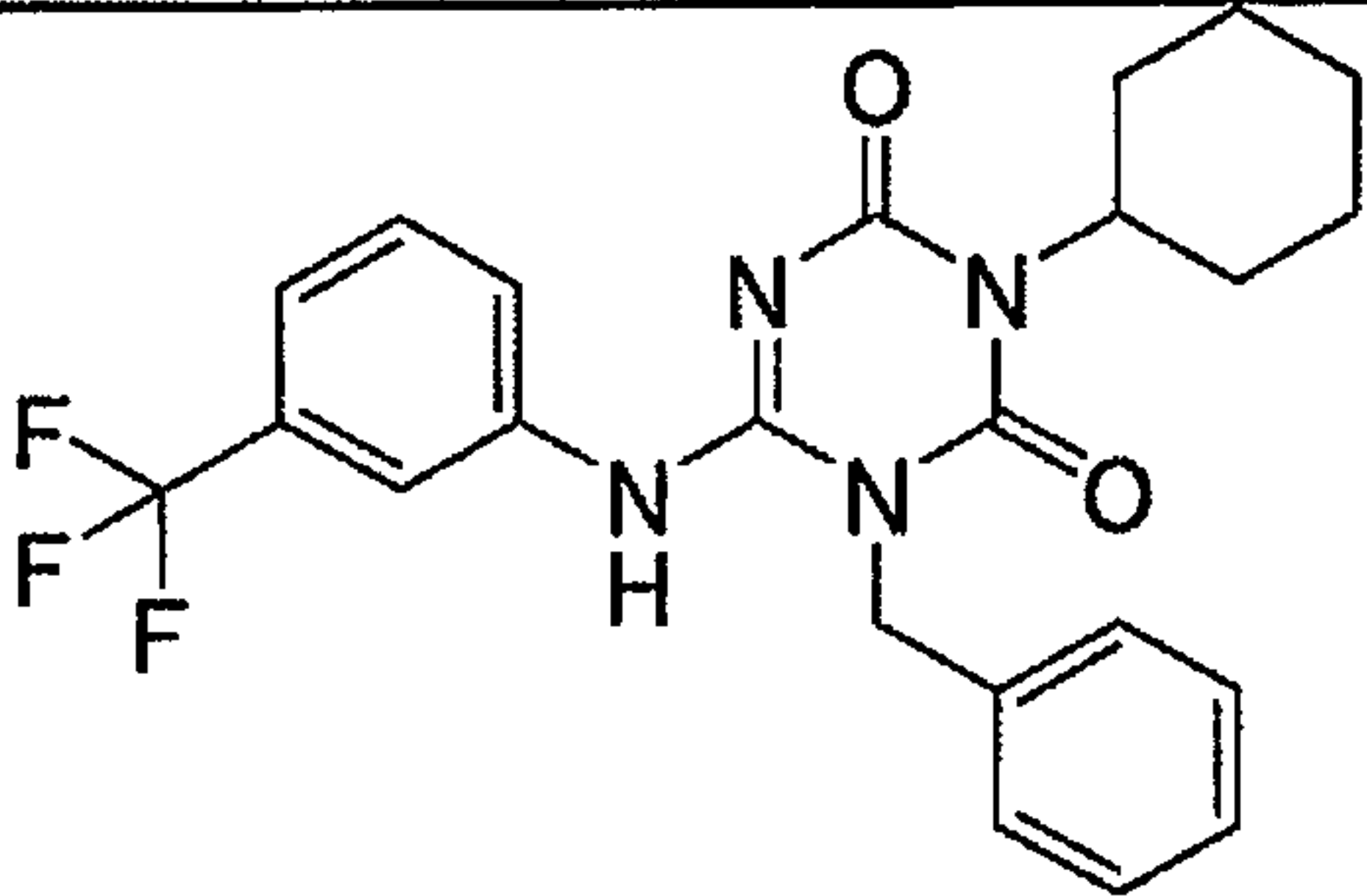
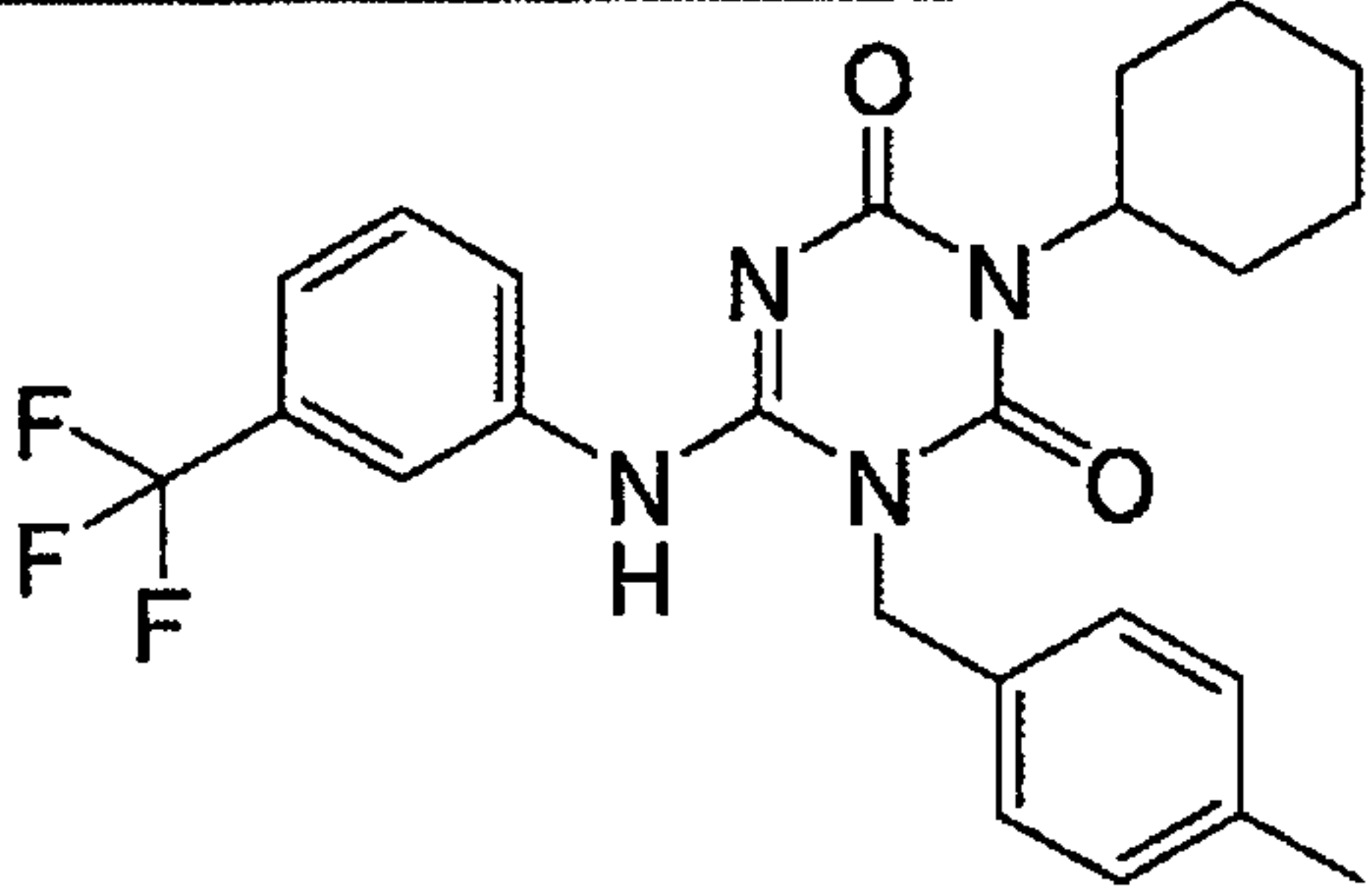
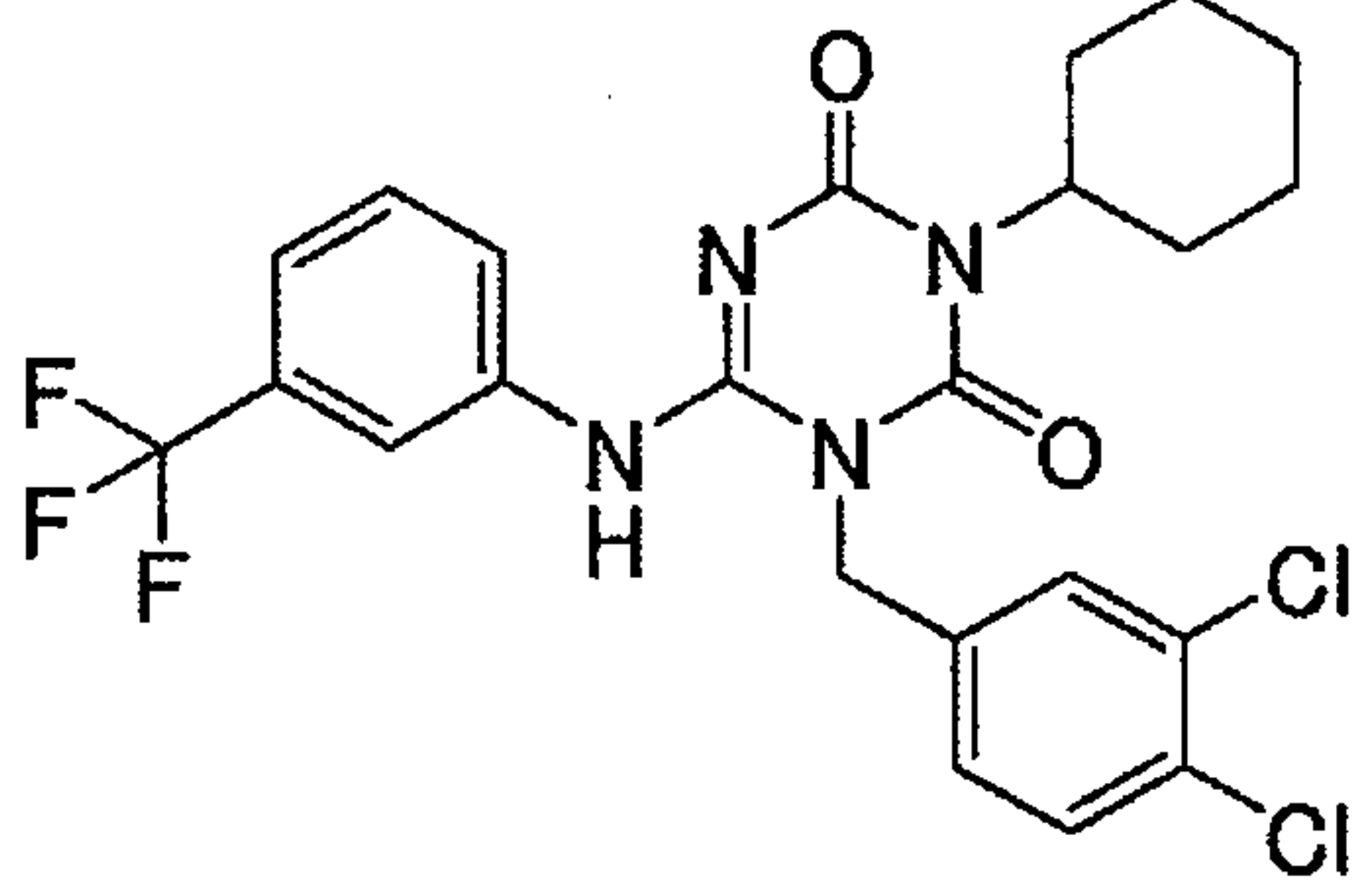
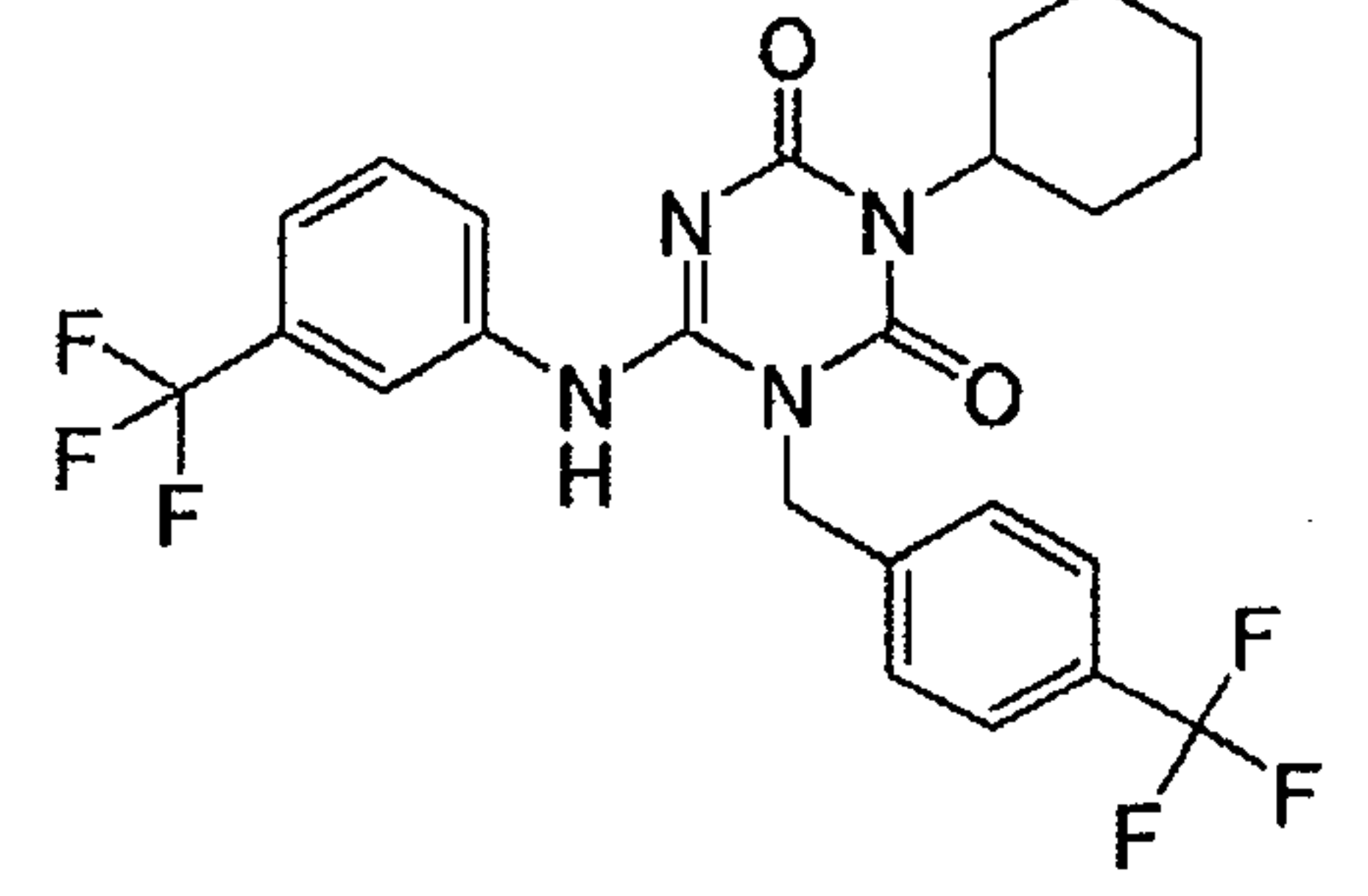
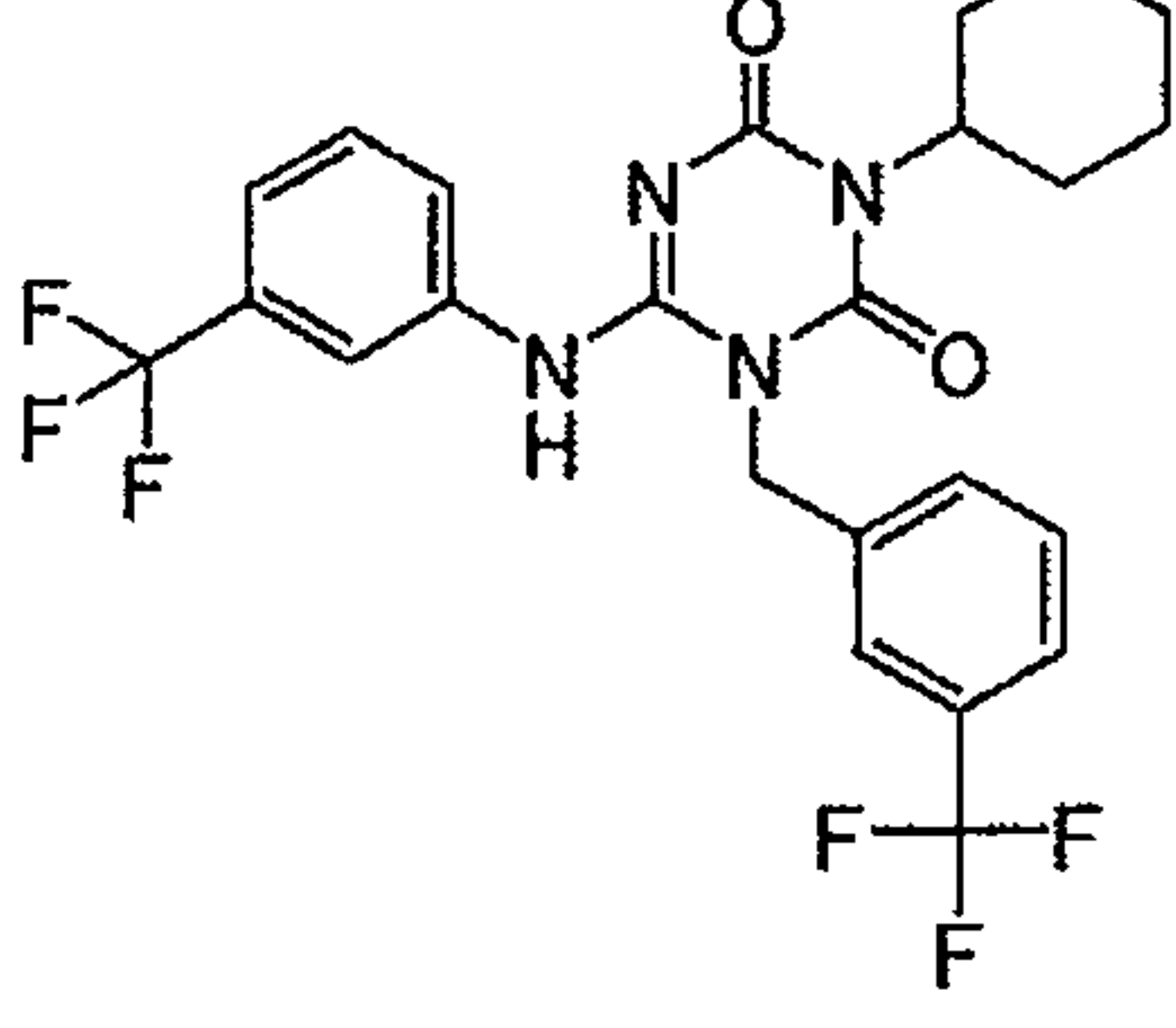
[Table 10]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0031	2.61	433	4
	I-0032	2.39	463	4
	I-0033	4.31	447	4
	I-0034	4.86	481	4
	I-0035	4.68	461	4

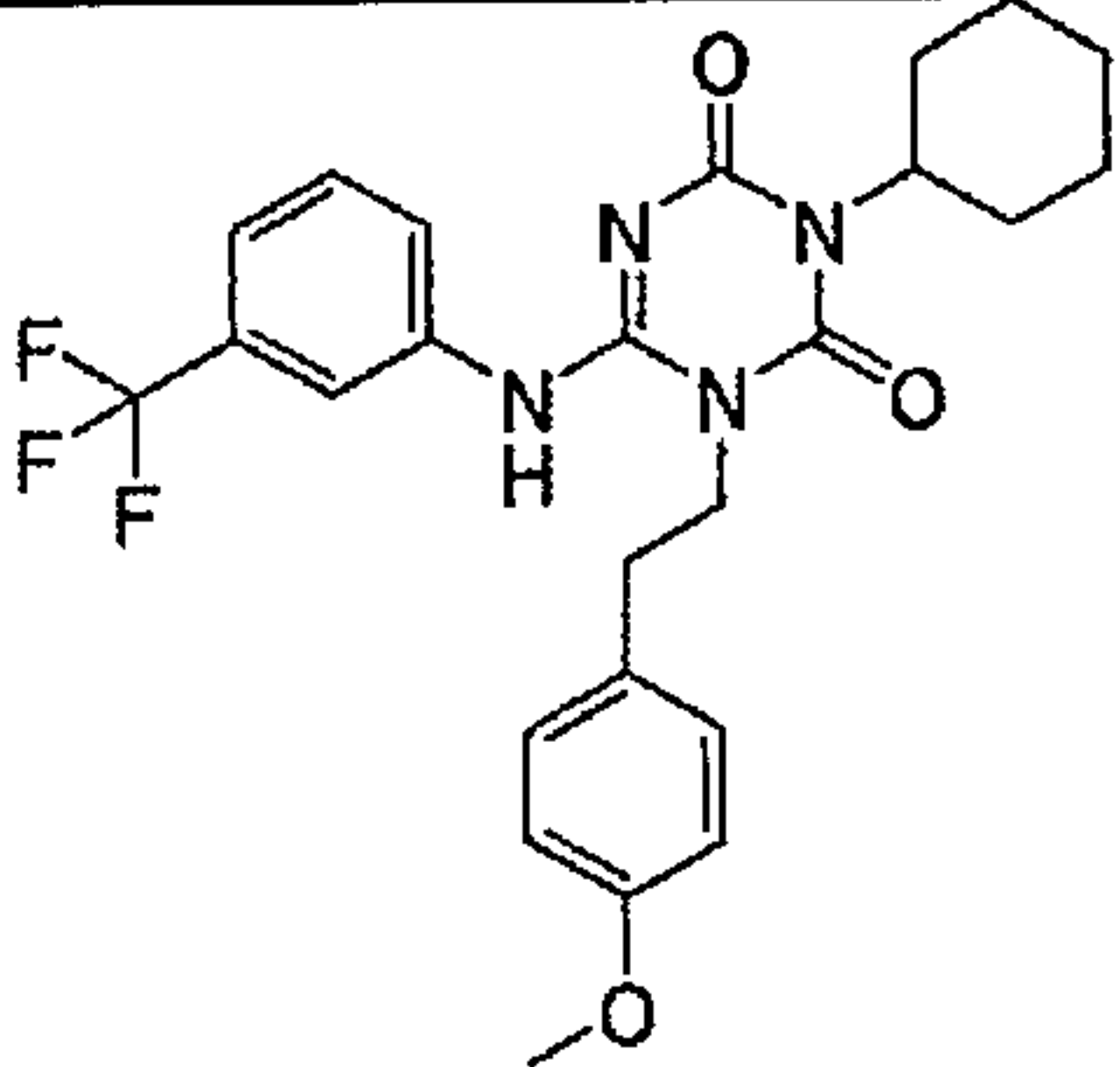
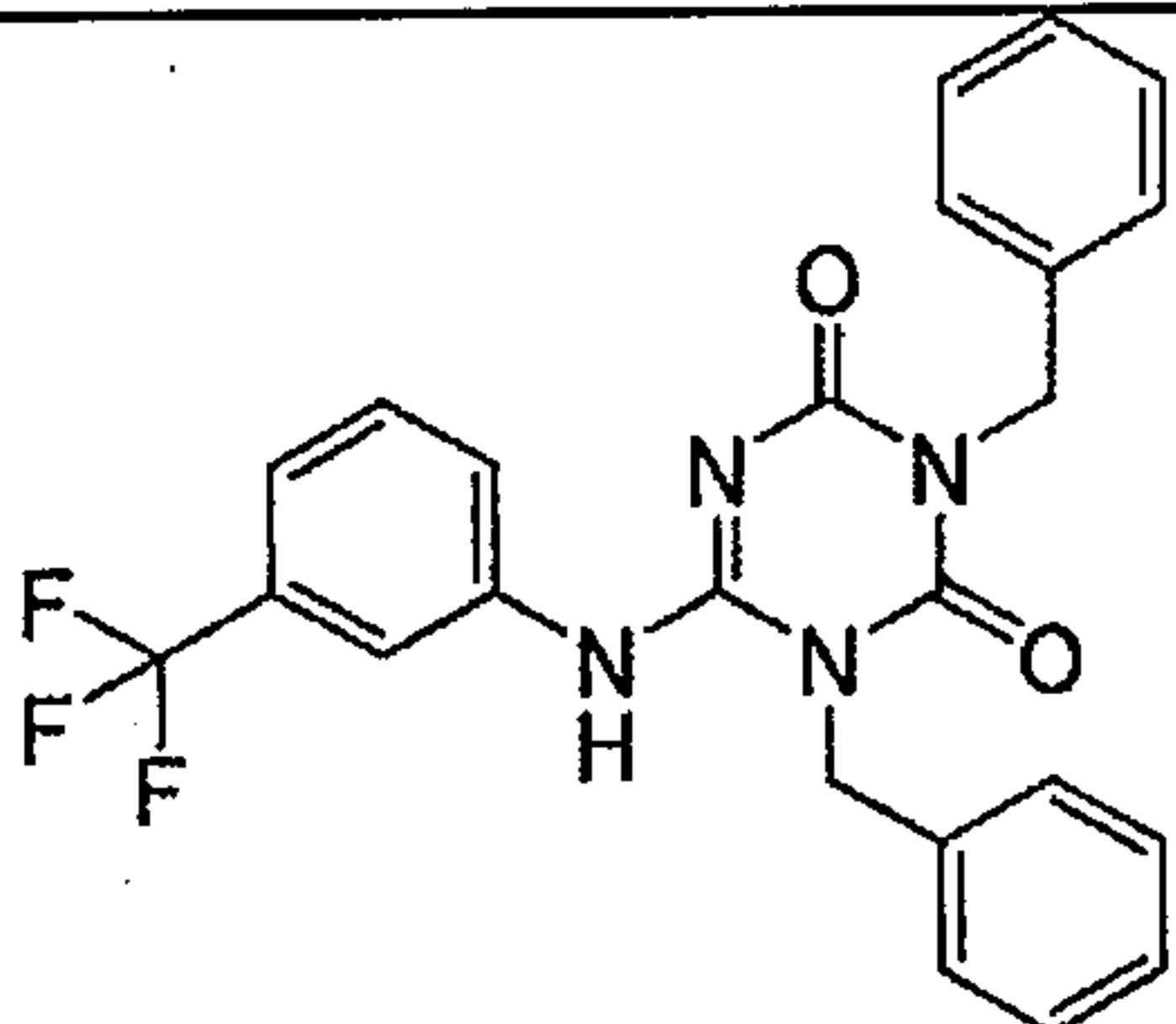
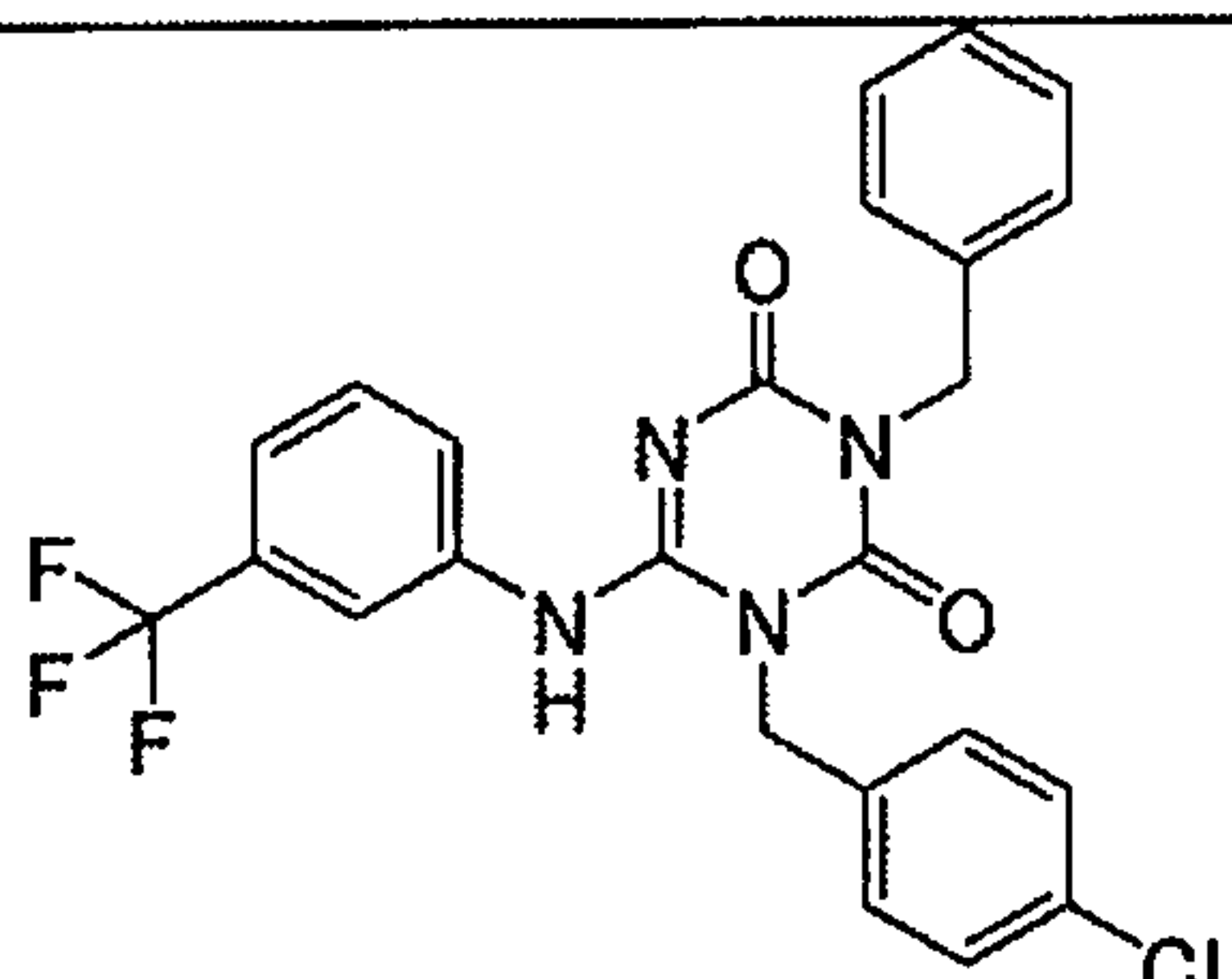
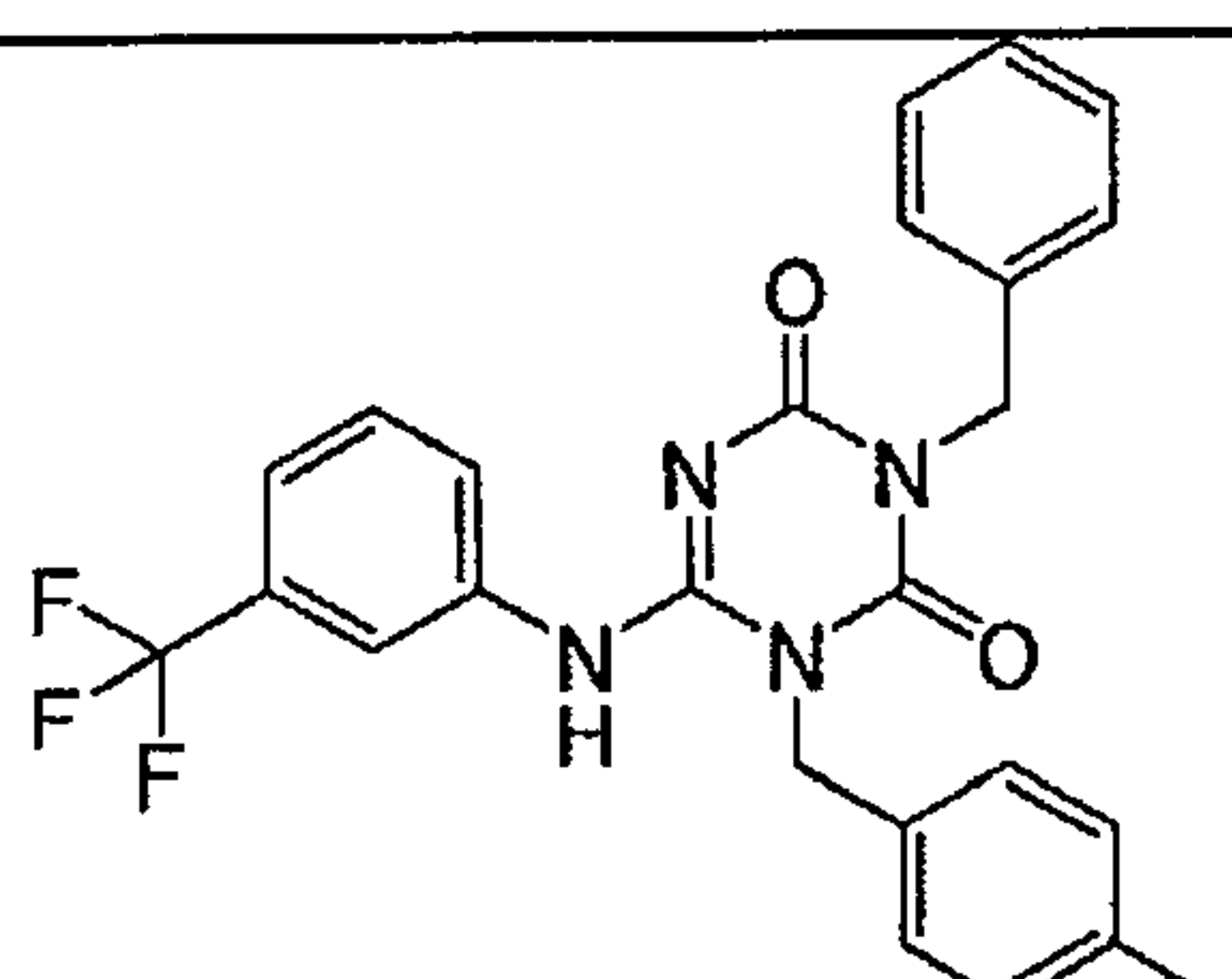
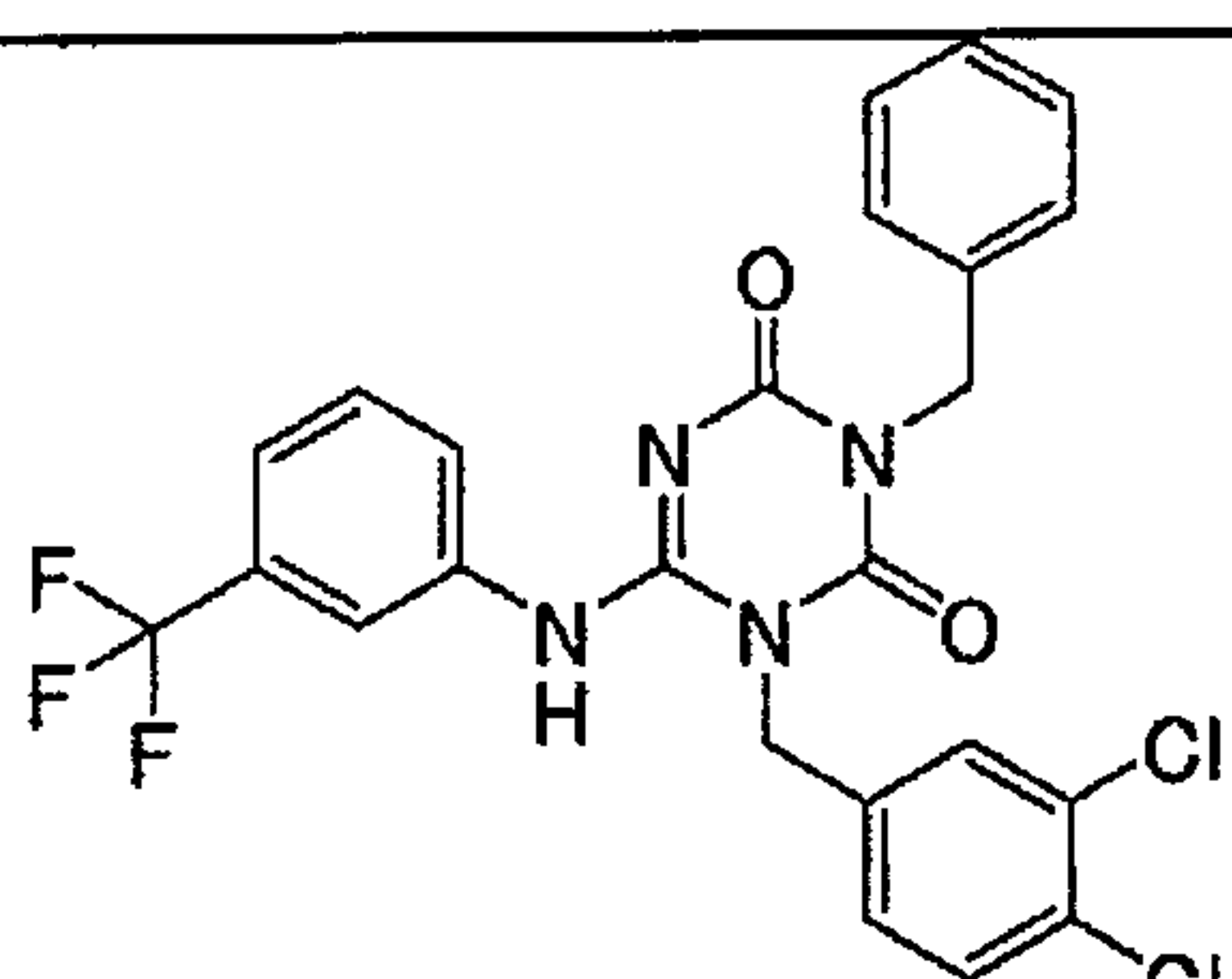
[Table 11]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0036	3.73	516	4
	I-0037	4.80	515	4
	I-0038	4.83	515	4
	I-0039	3.67	461	4
	I-0040	3.47	491	4

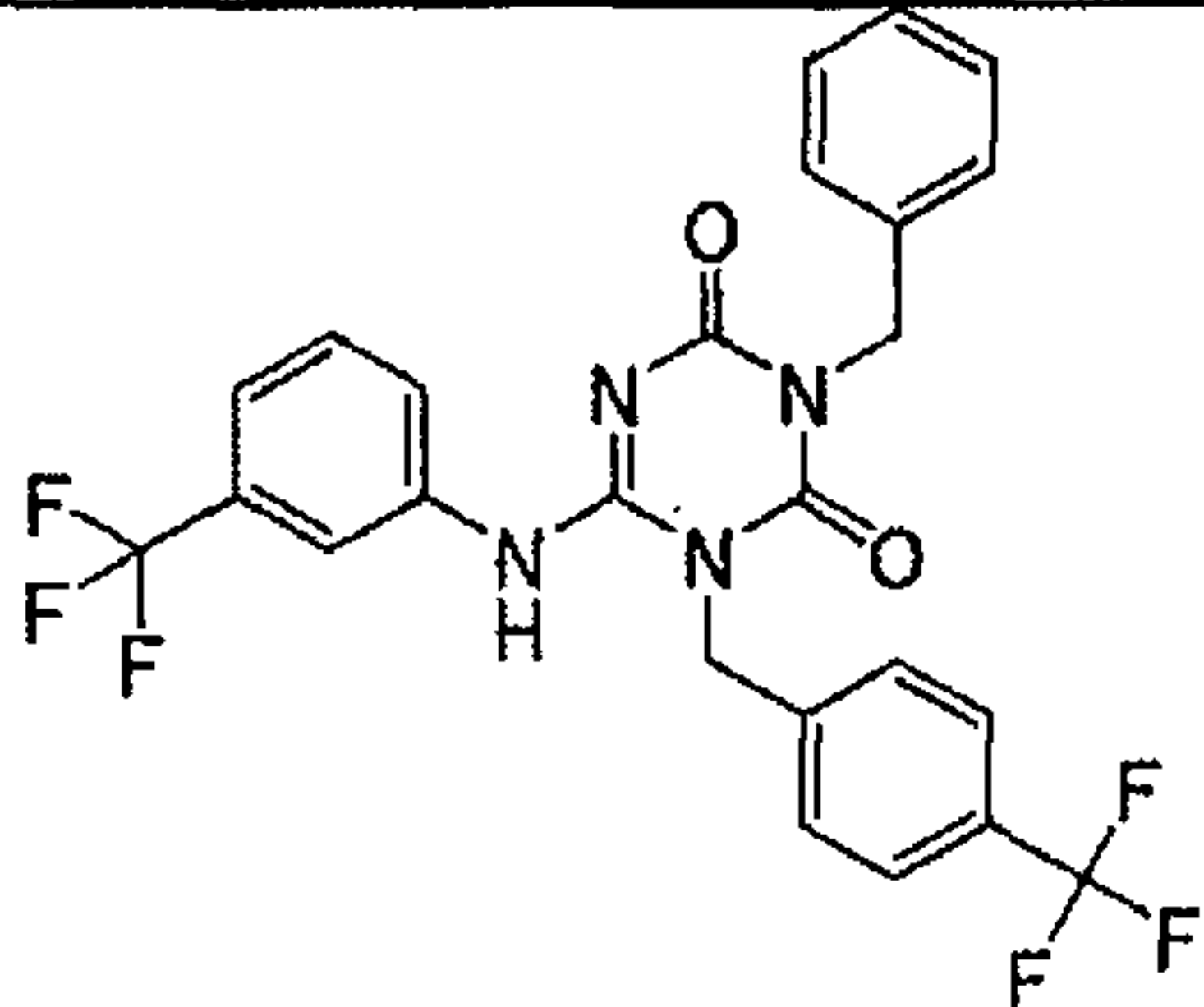
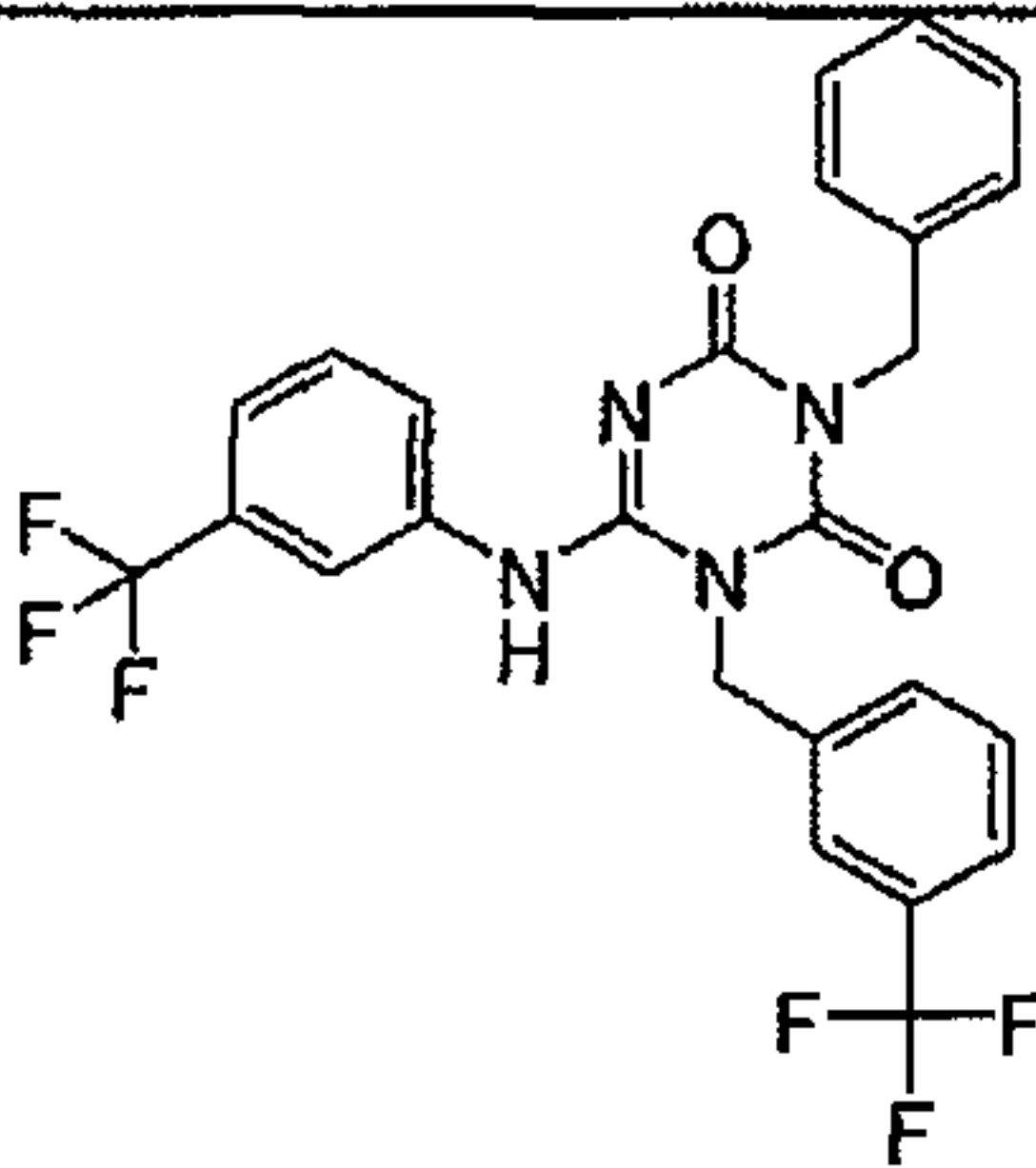
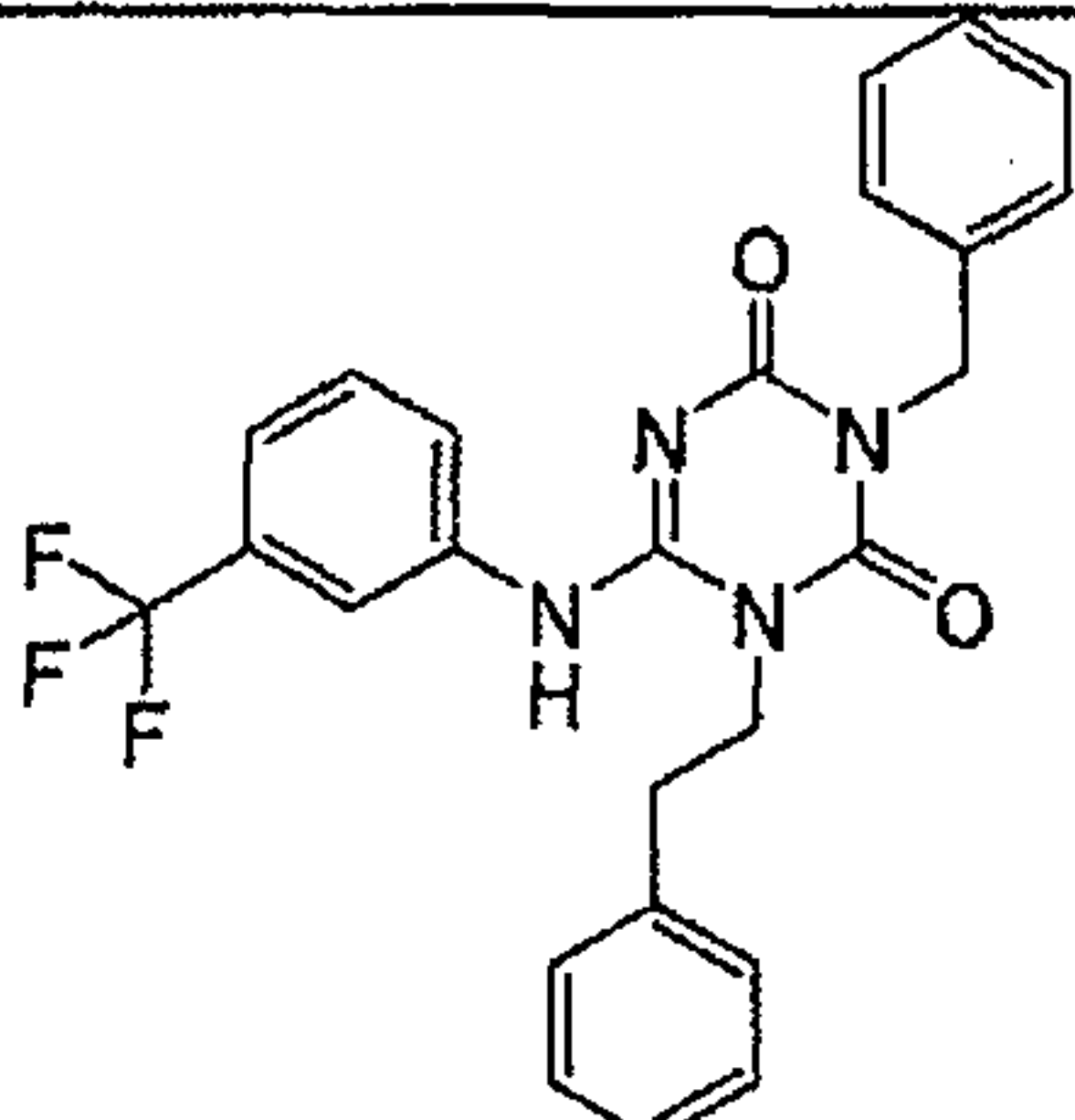
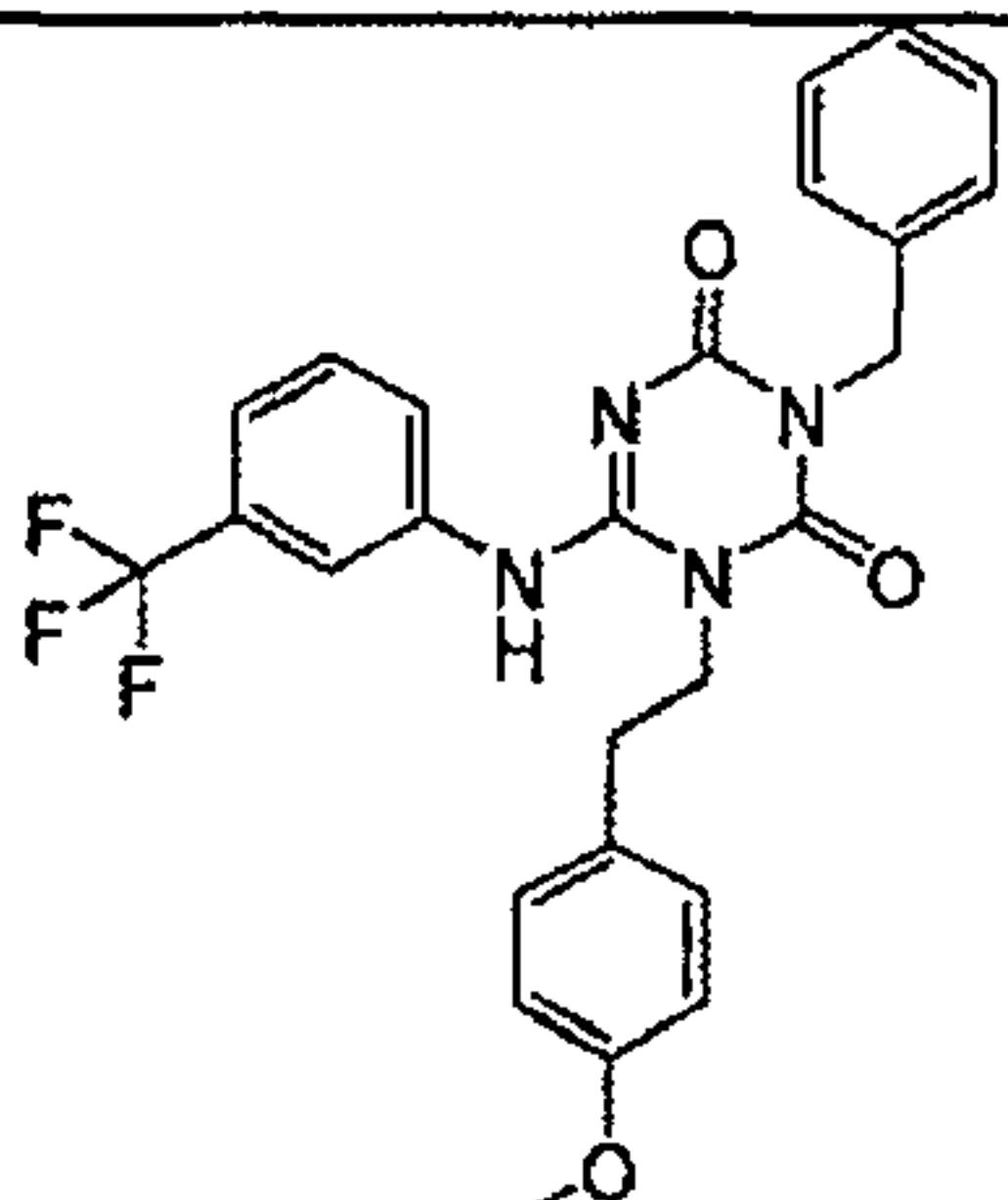
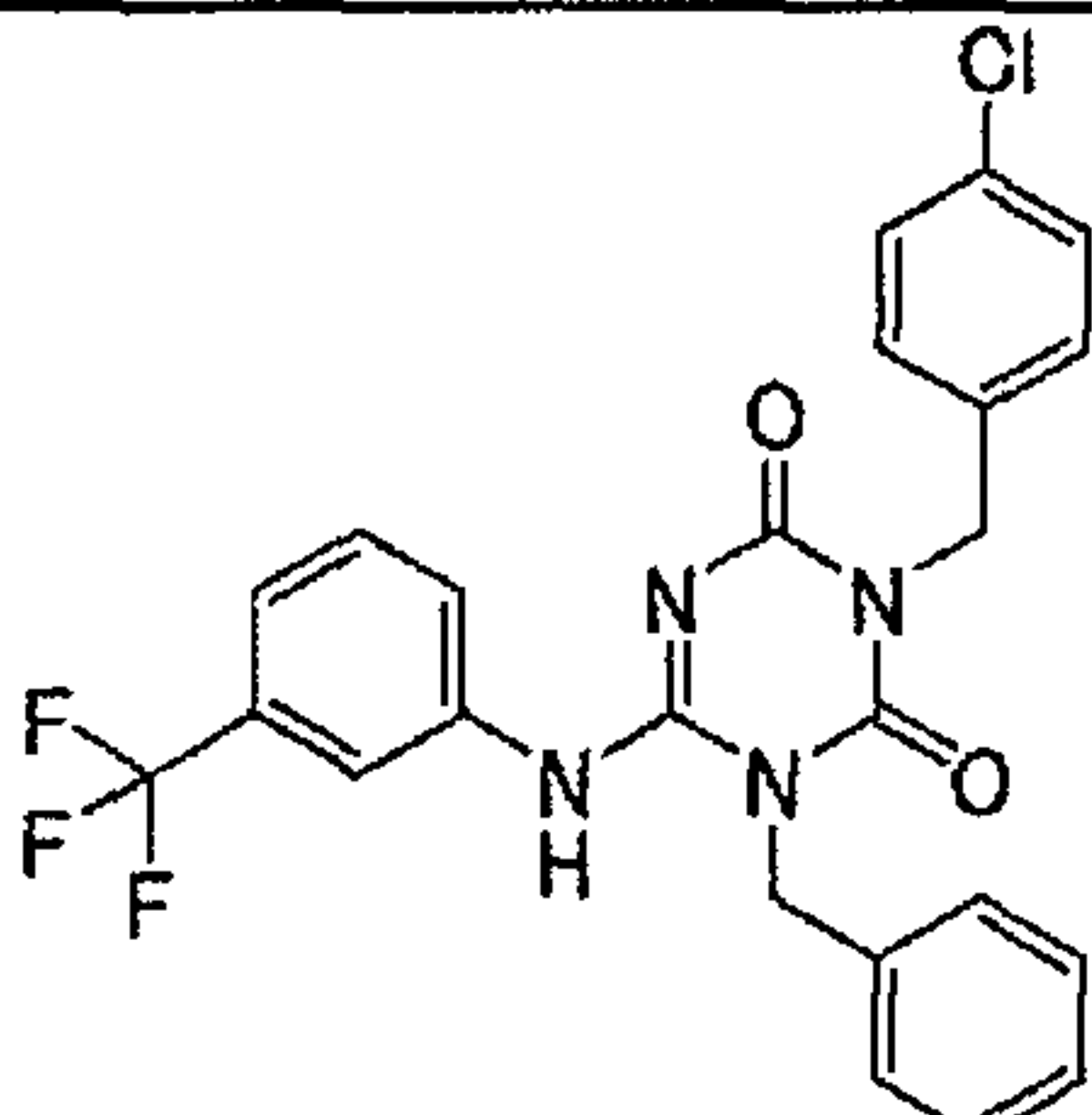
[Table 12]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0041	4.09	445	4
	I-0042	4.45	459	4
	I-0043	3.51	514	4
	I-0044	4.62	513	4
	I-0045	4.65	513	4

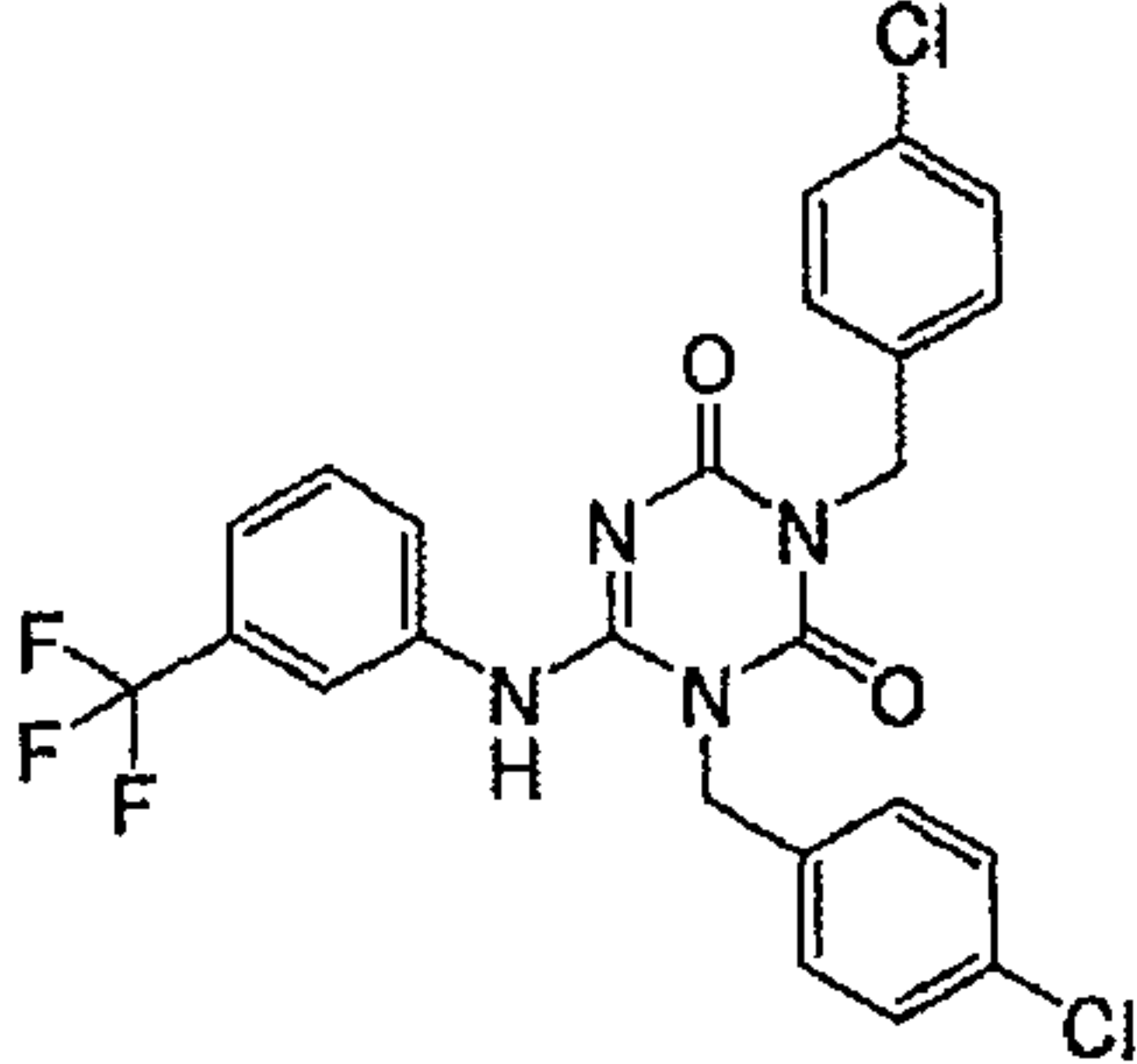
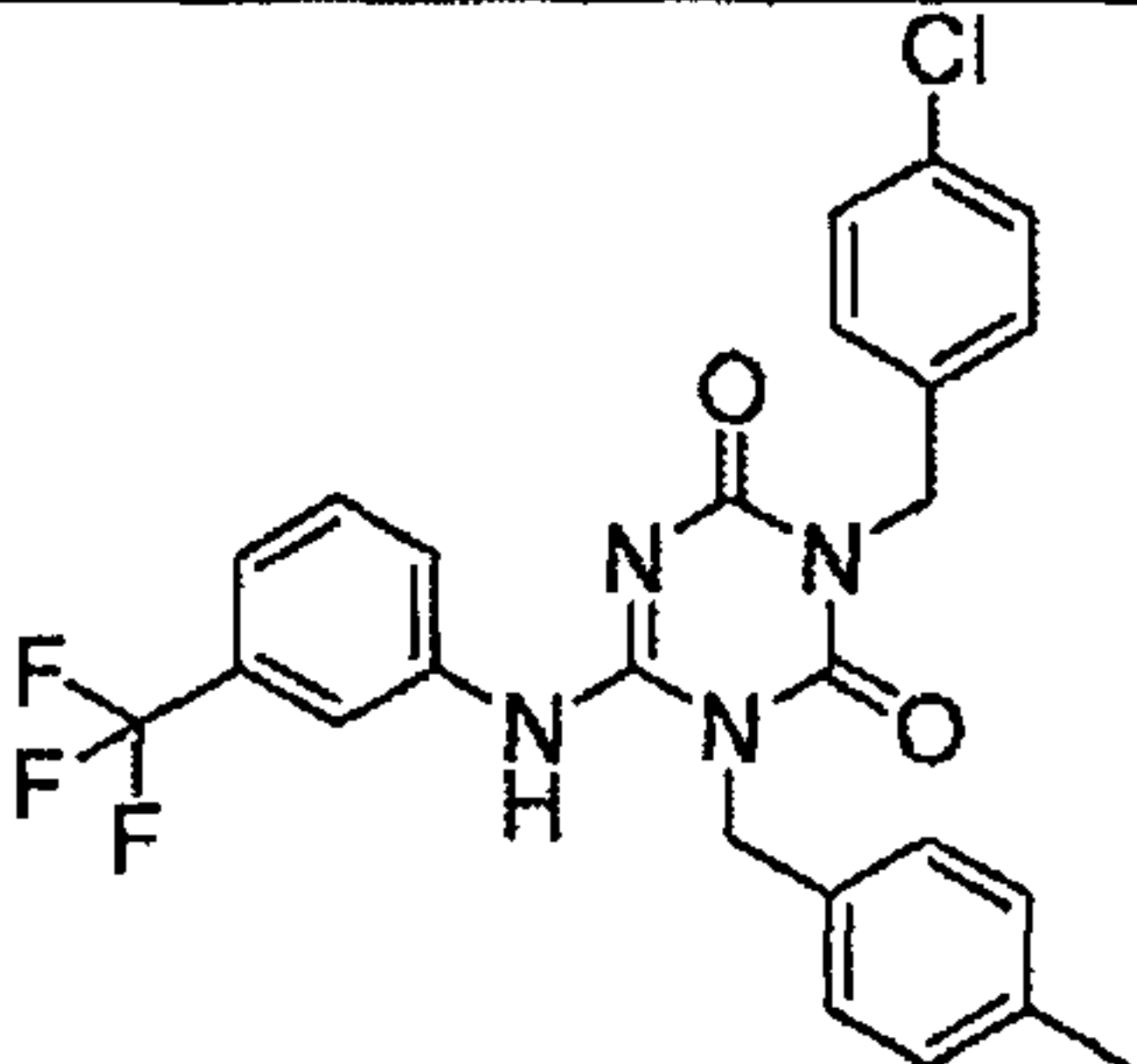
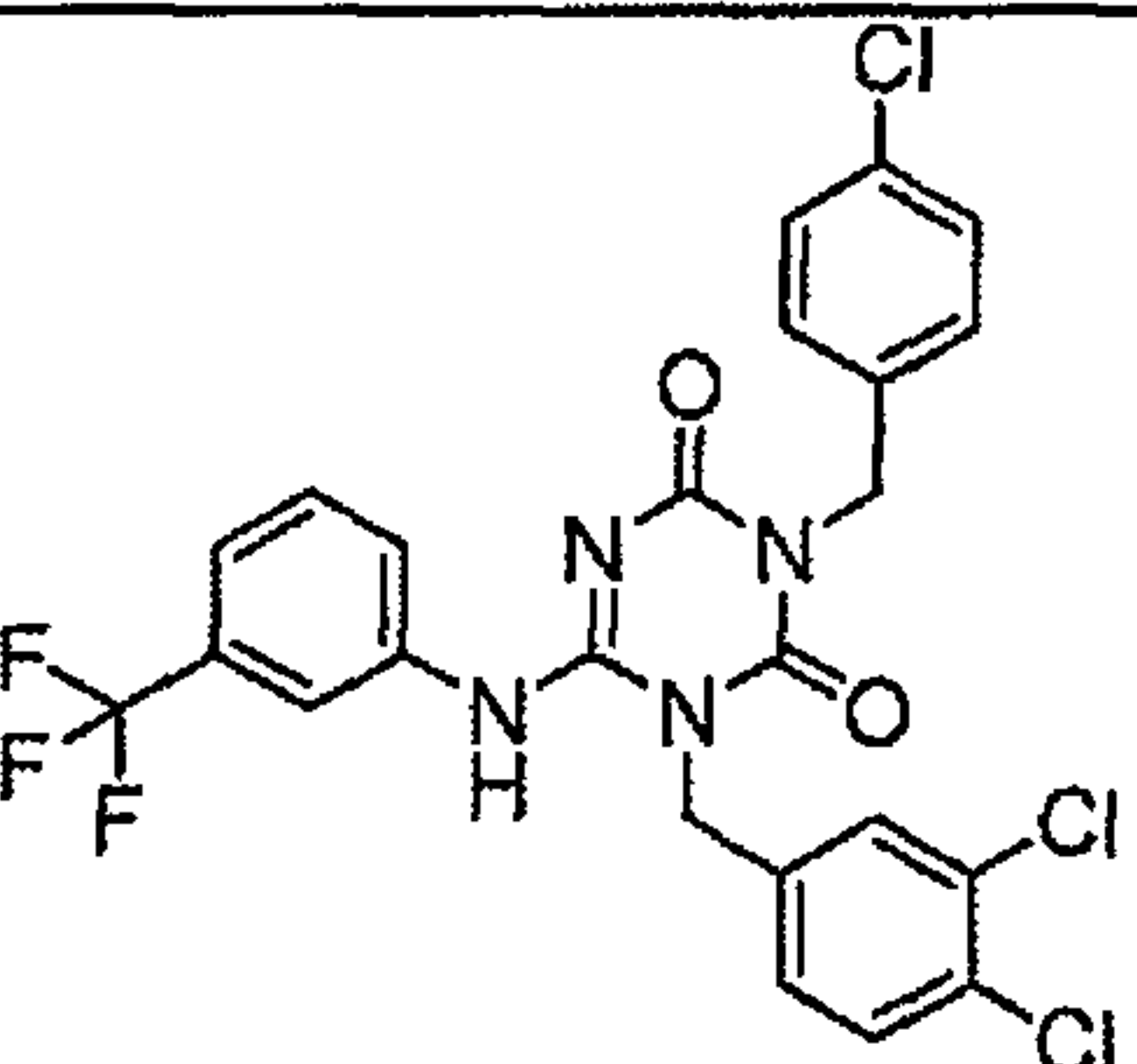
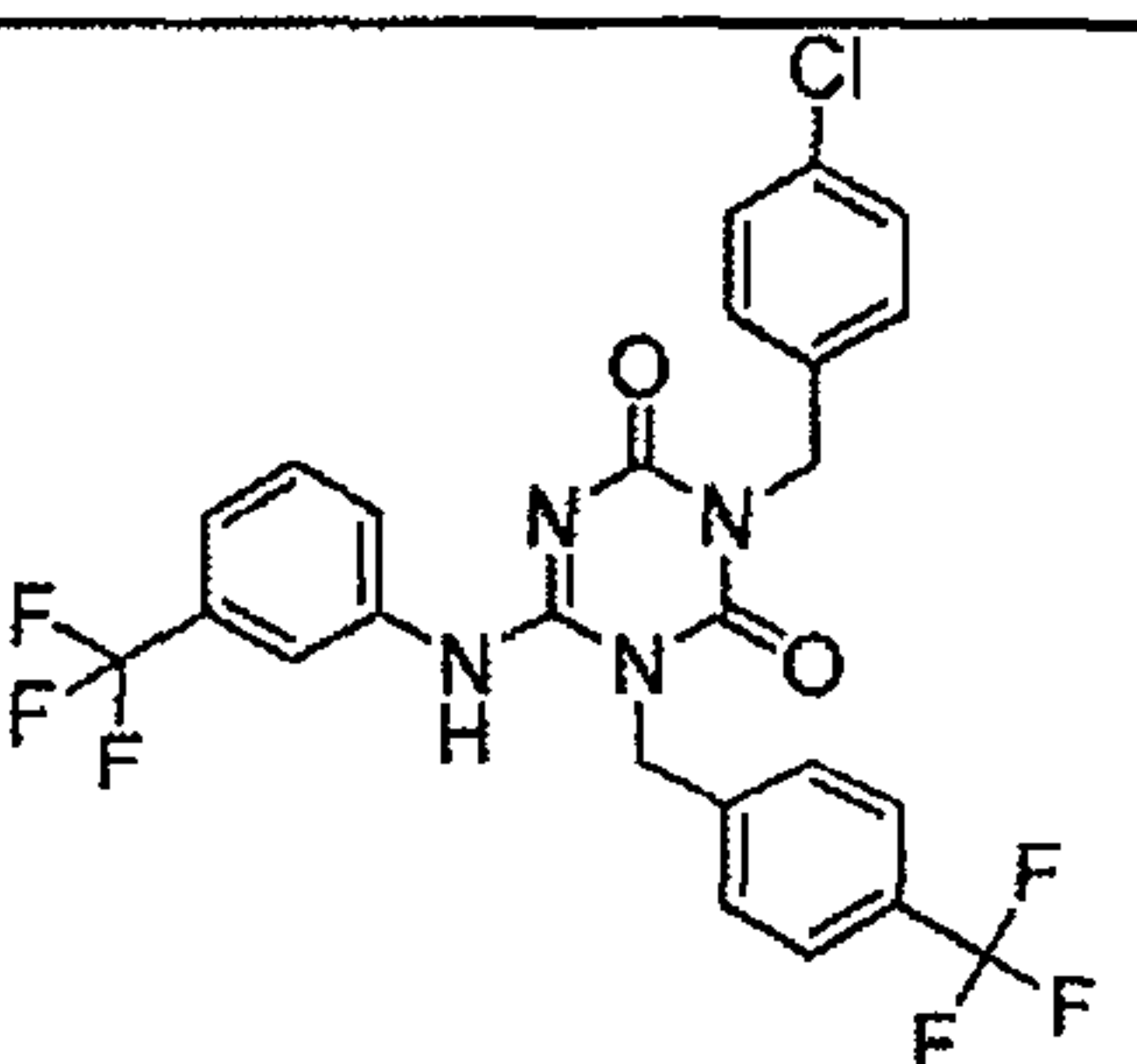
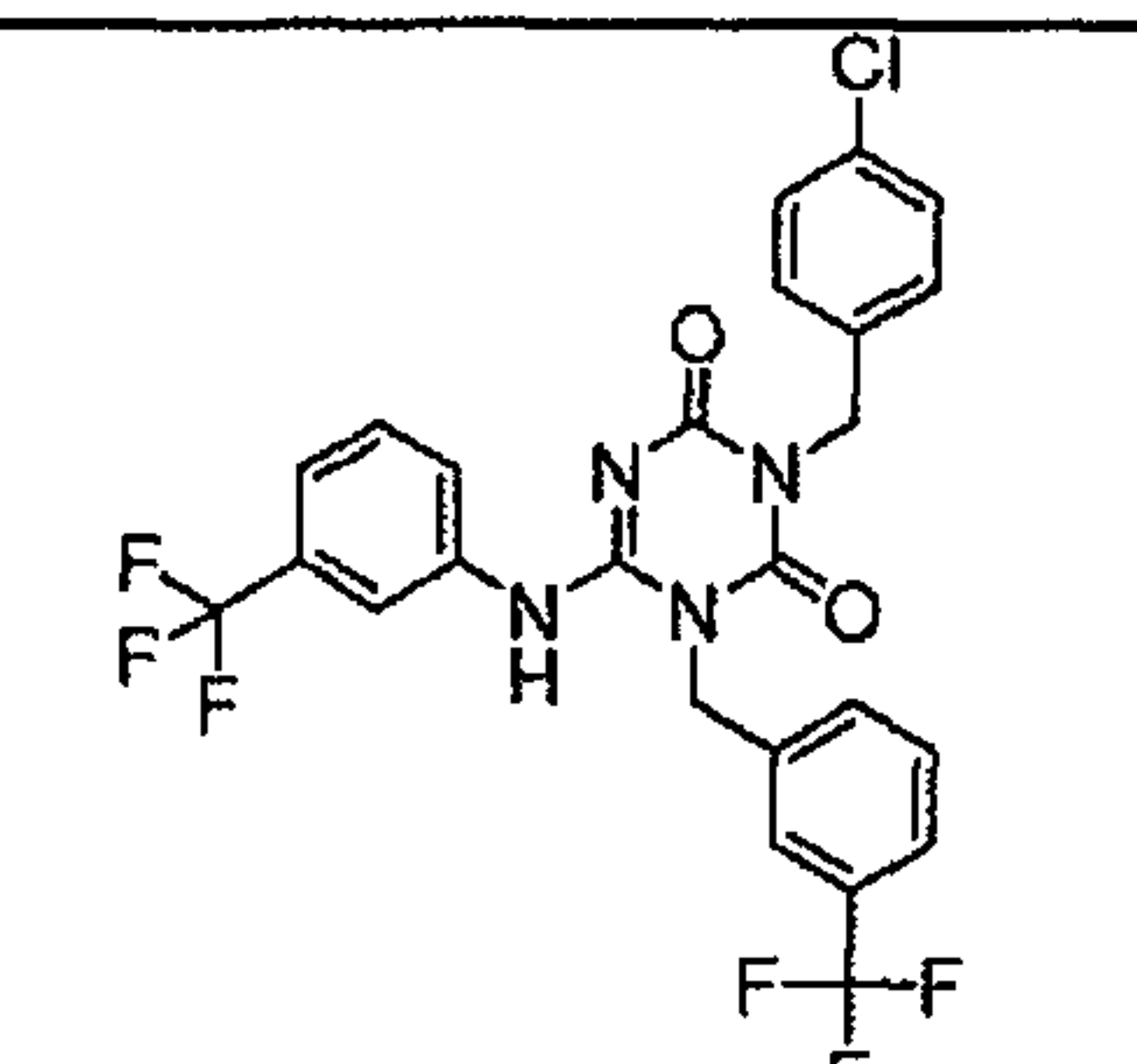
[Table 13]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0046	3.17	489	4
	I-0047	3.46	453	4
	I-0048	4.09	487	4
	I-0049	3.83	467	4
	I-0050	4.56	522	4

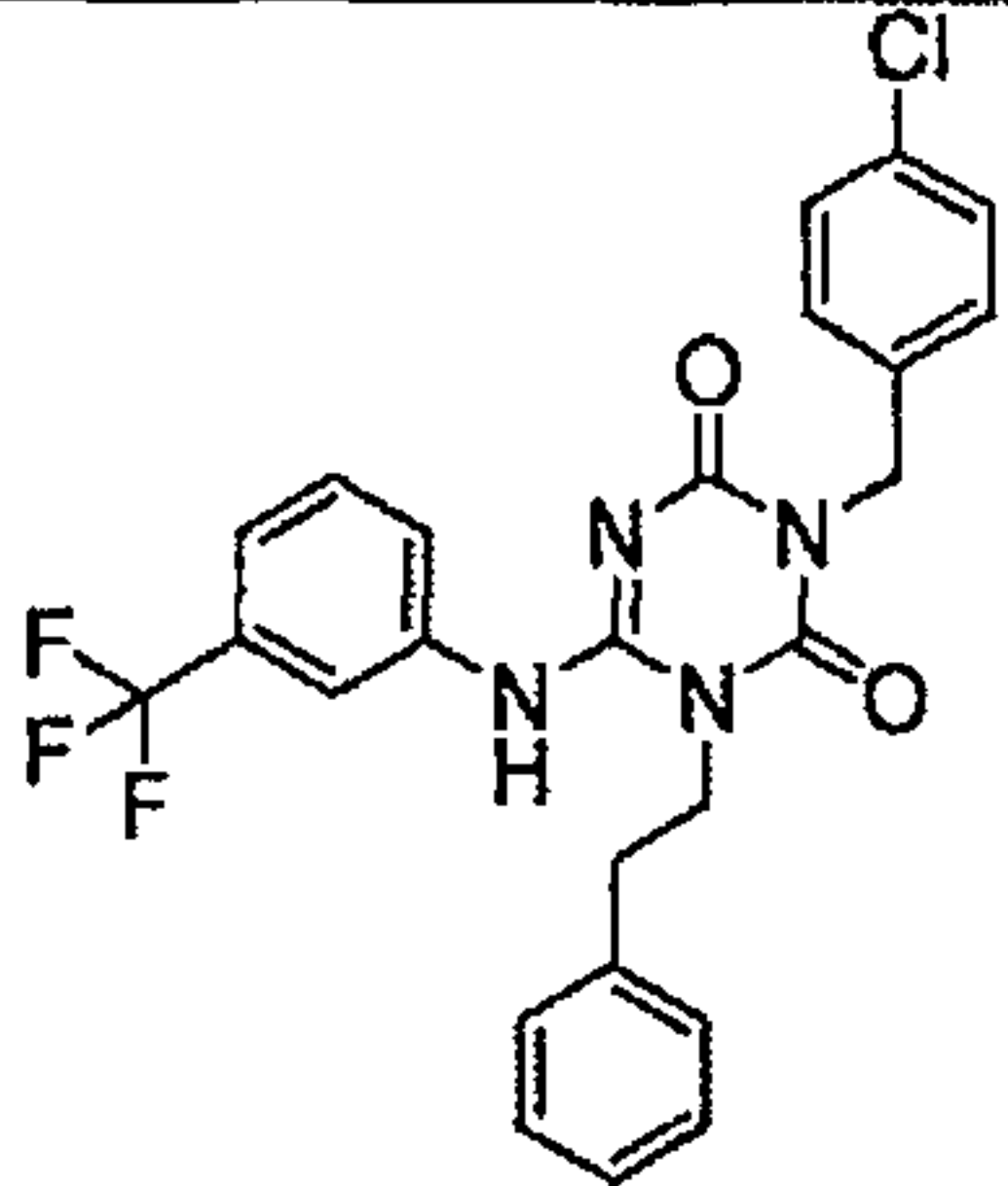
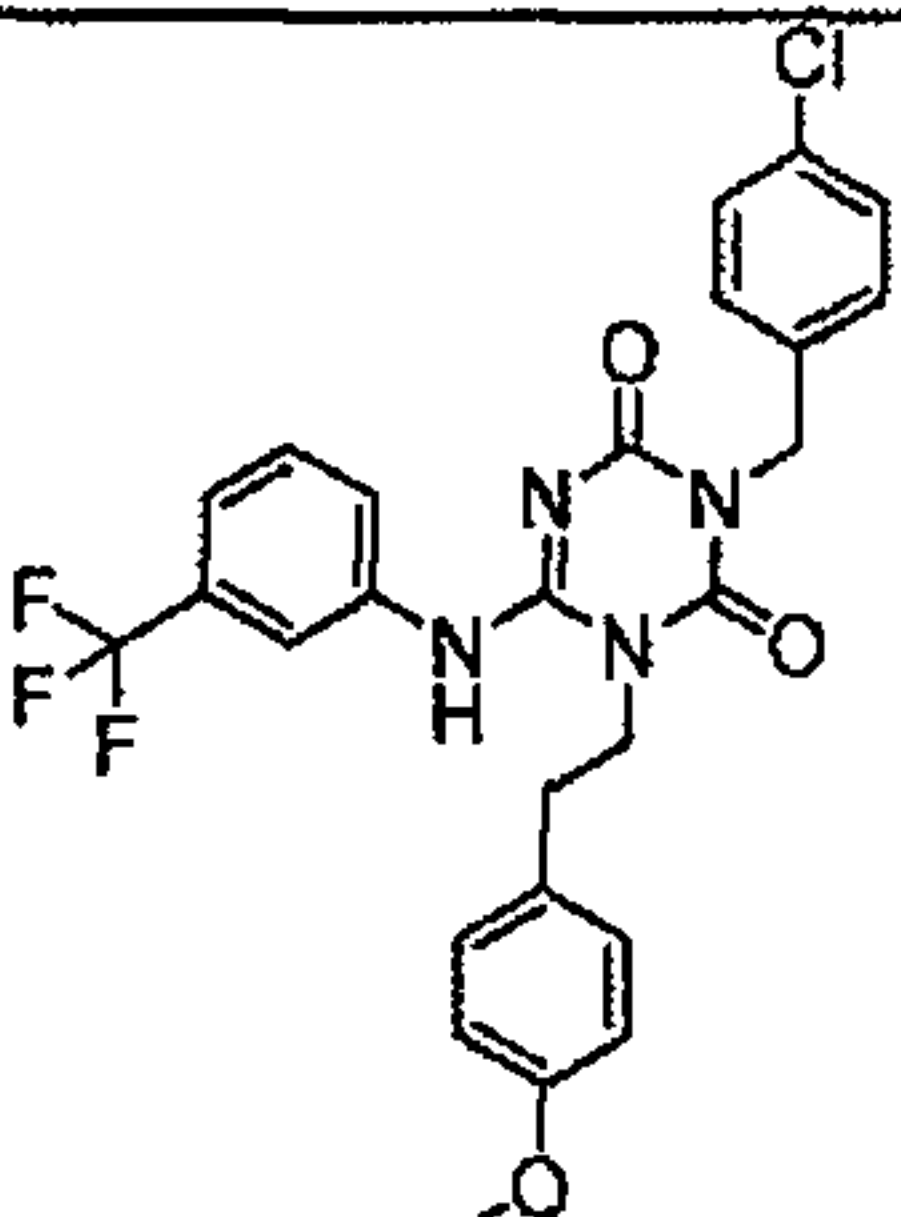
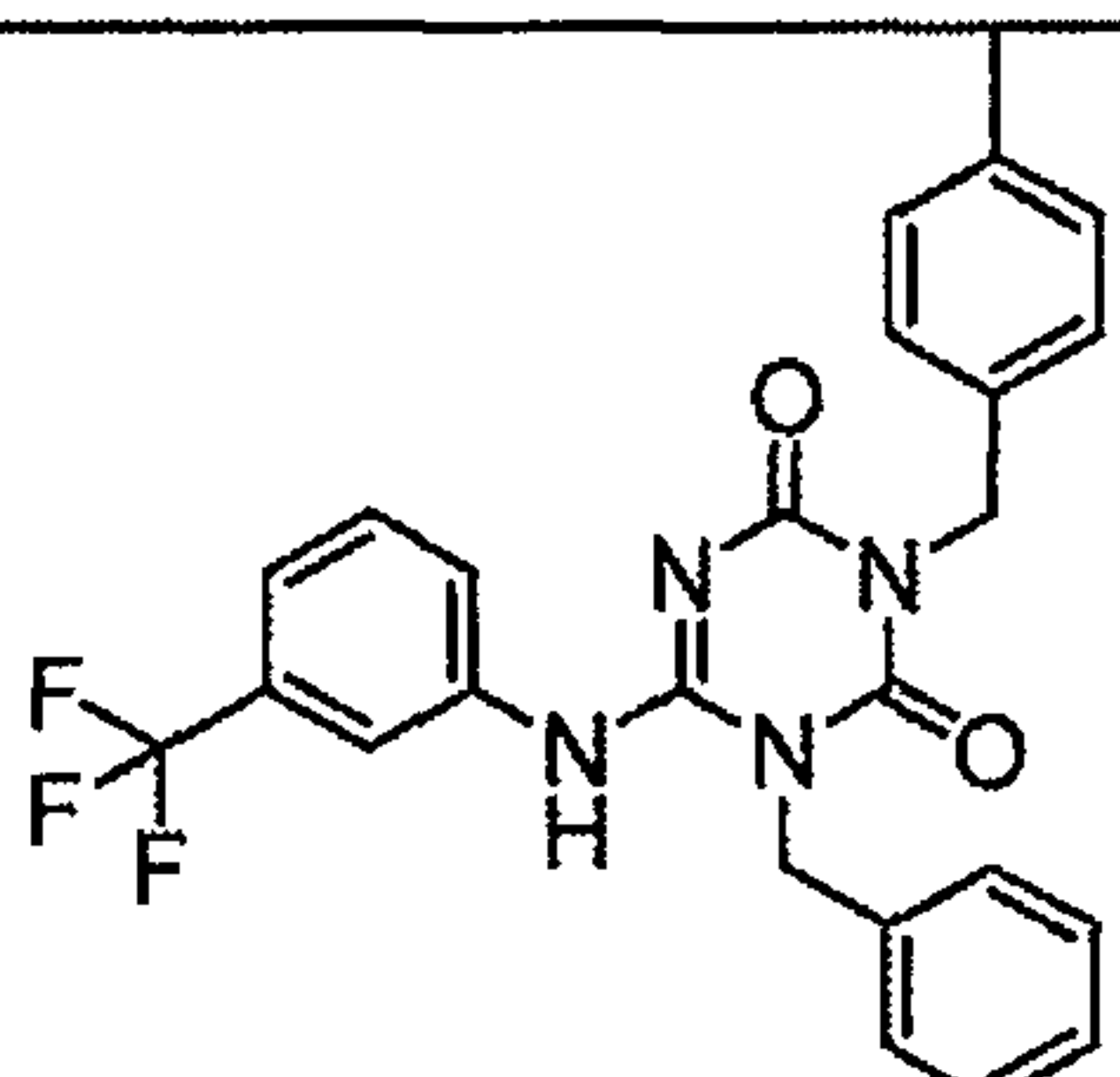
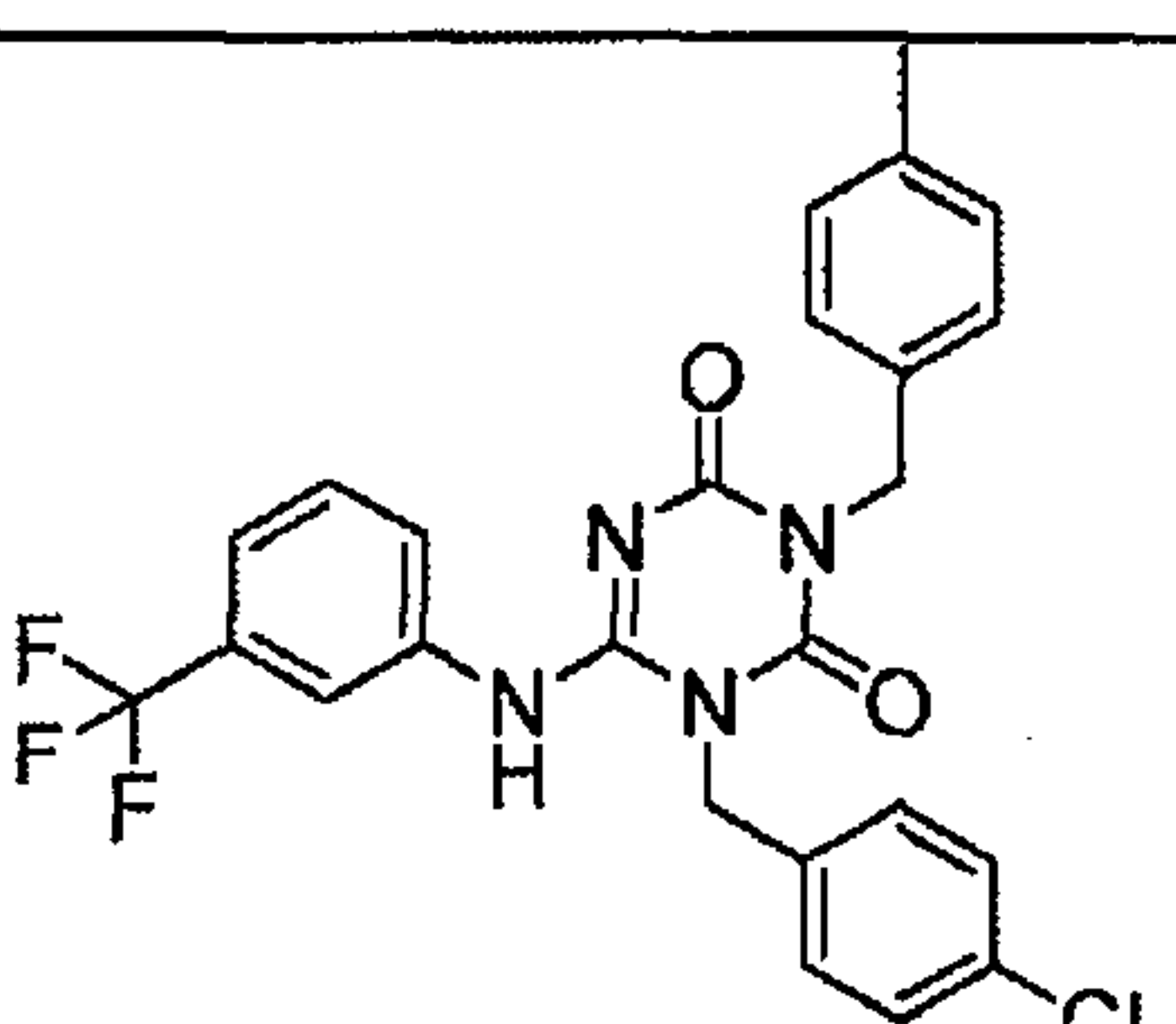
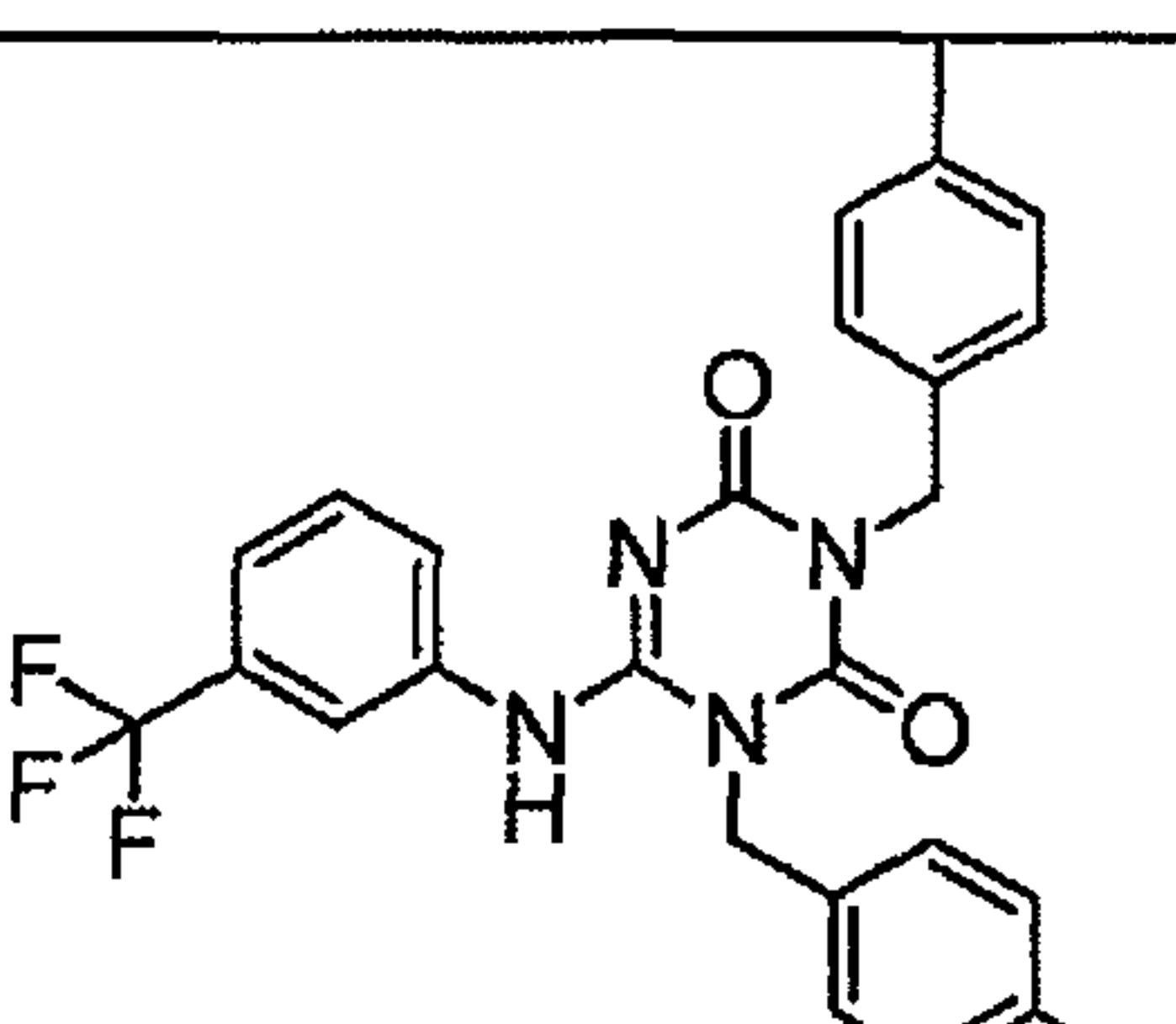
[Table 14]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0051	4.09	521	4
	I-0052	4.12	521	4
	I-0053	3.57	467	4
	I-0054	3.42	497	4
	I-0055	3.90	487	4

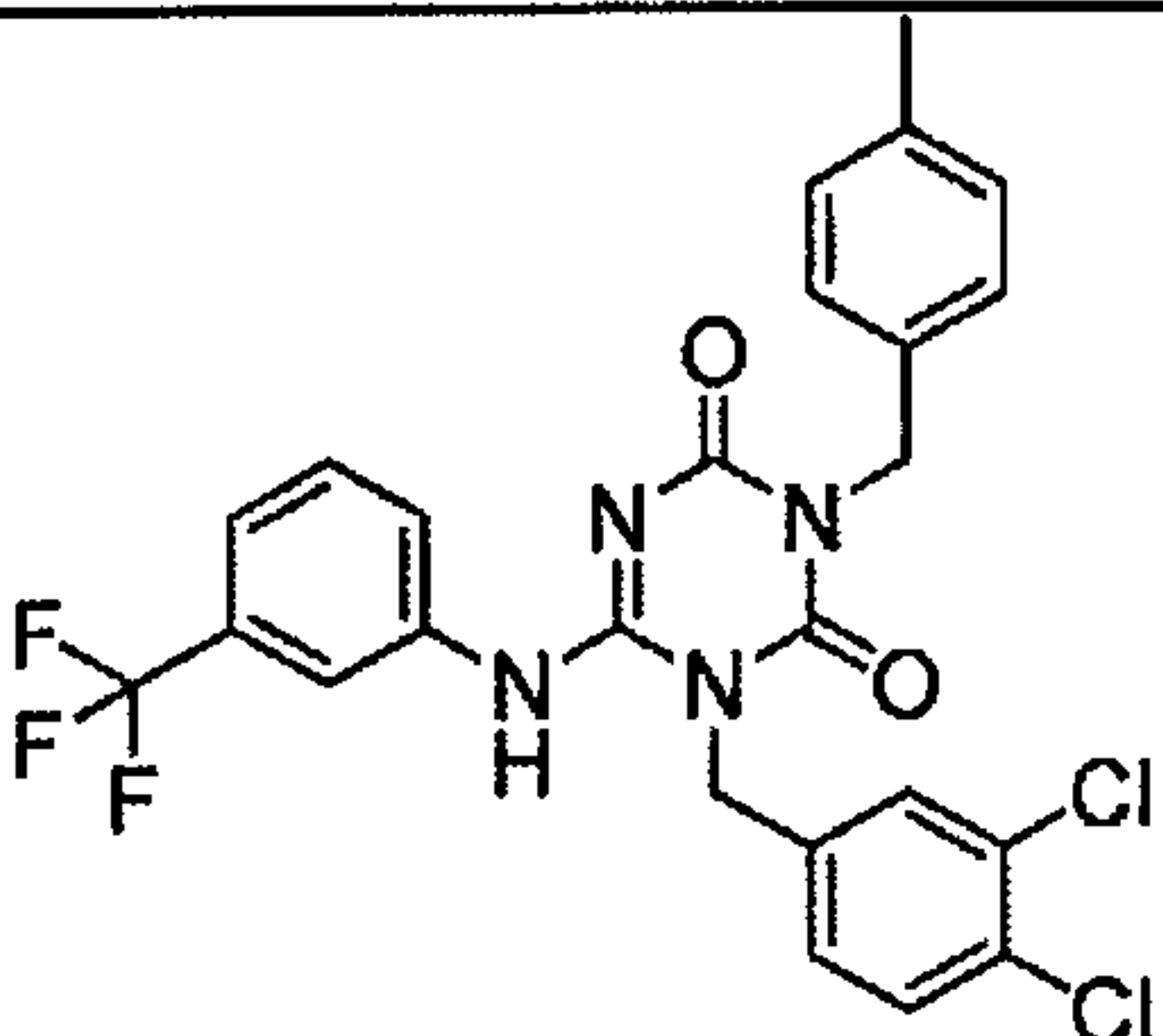
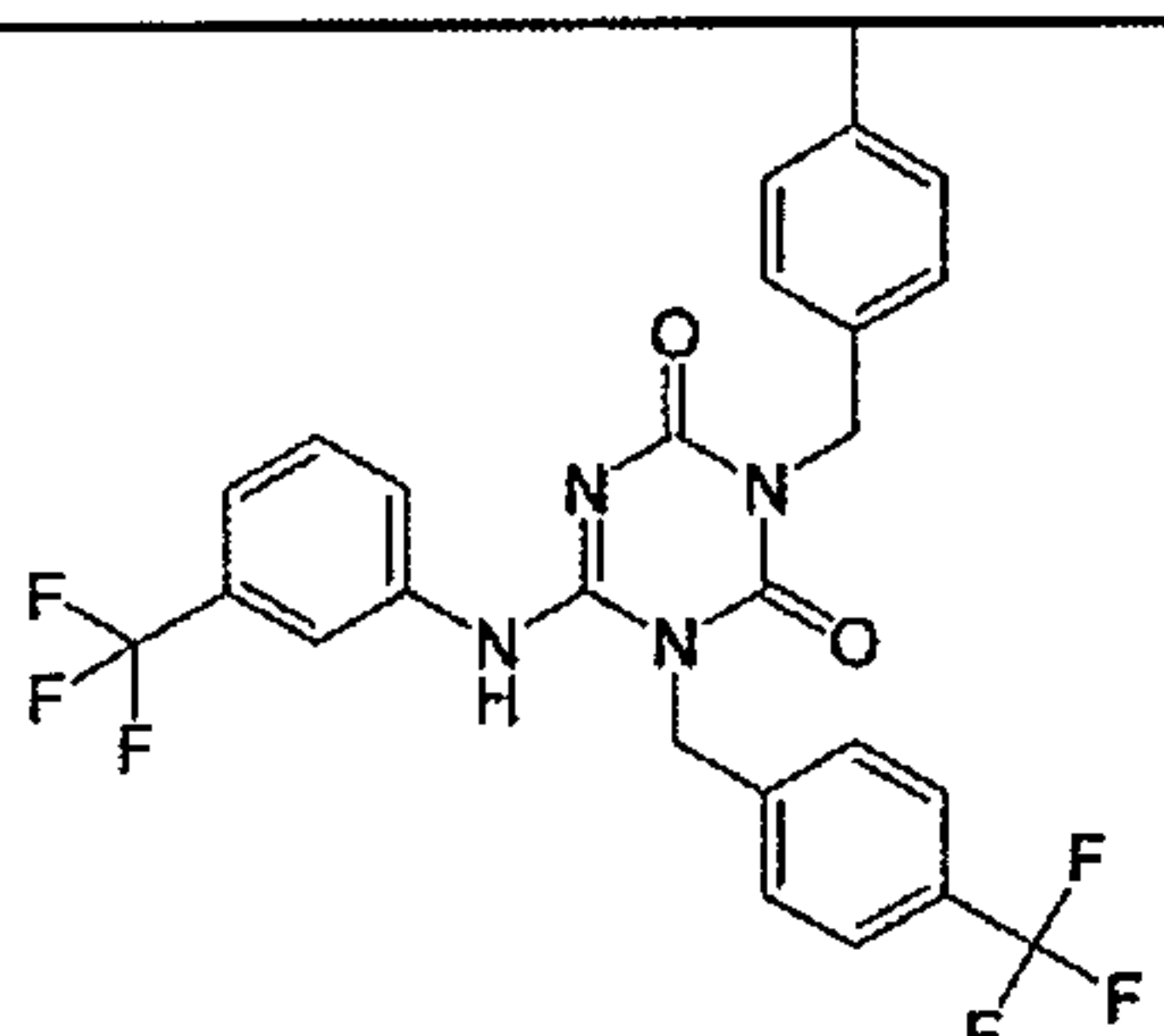
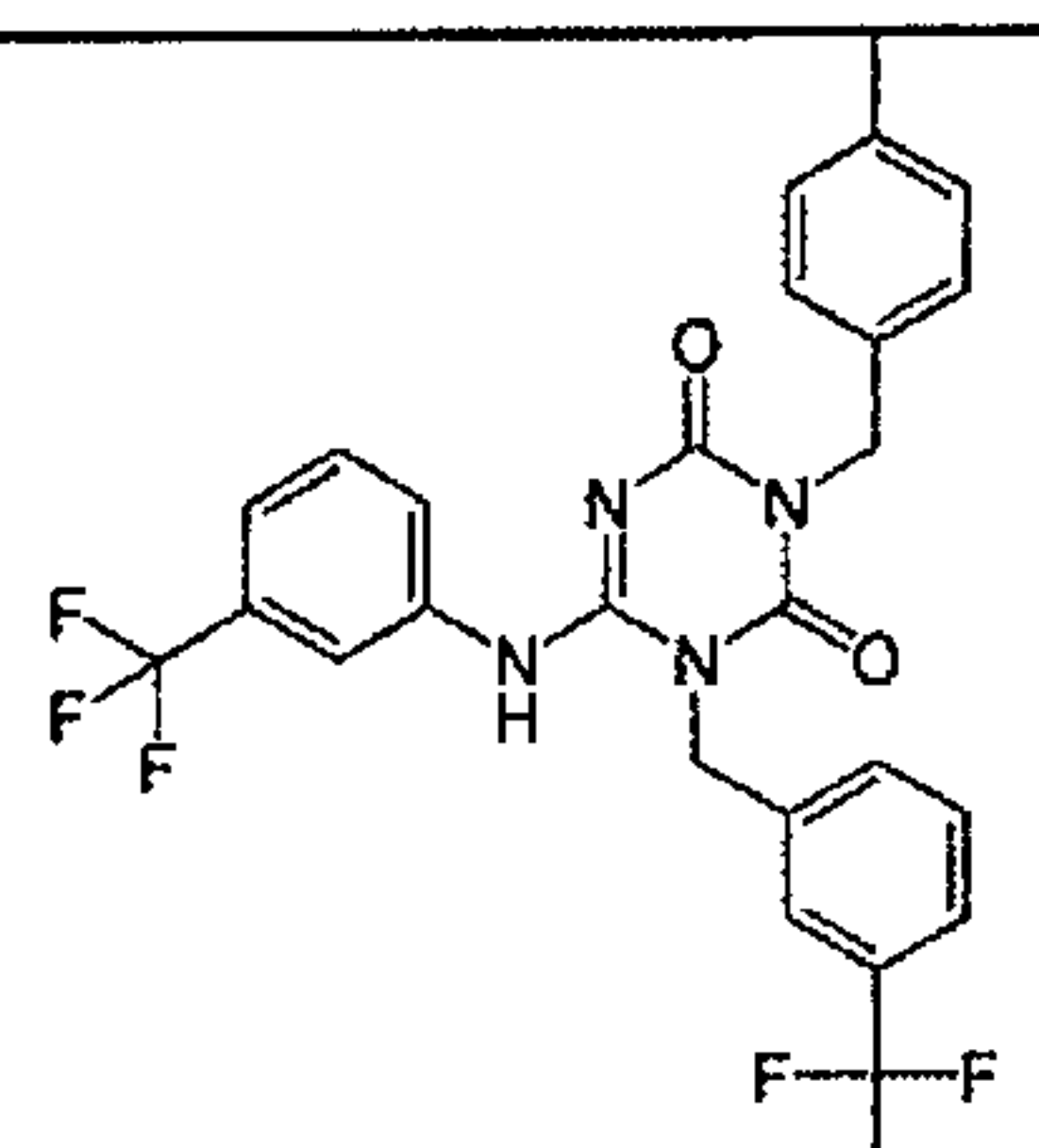
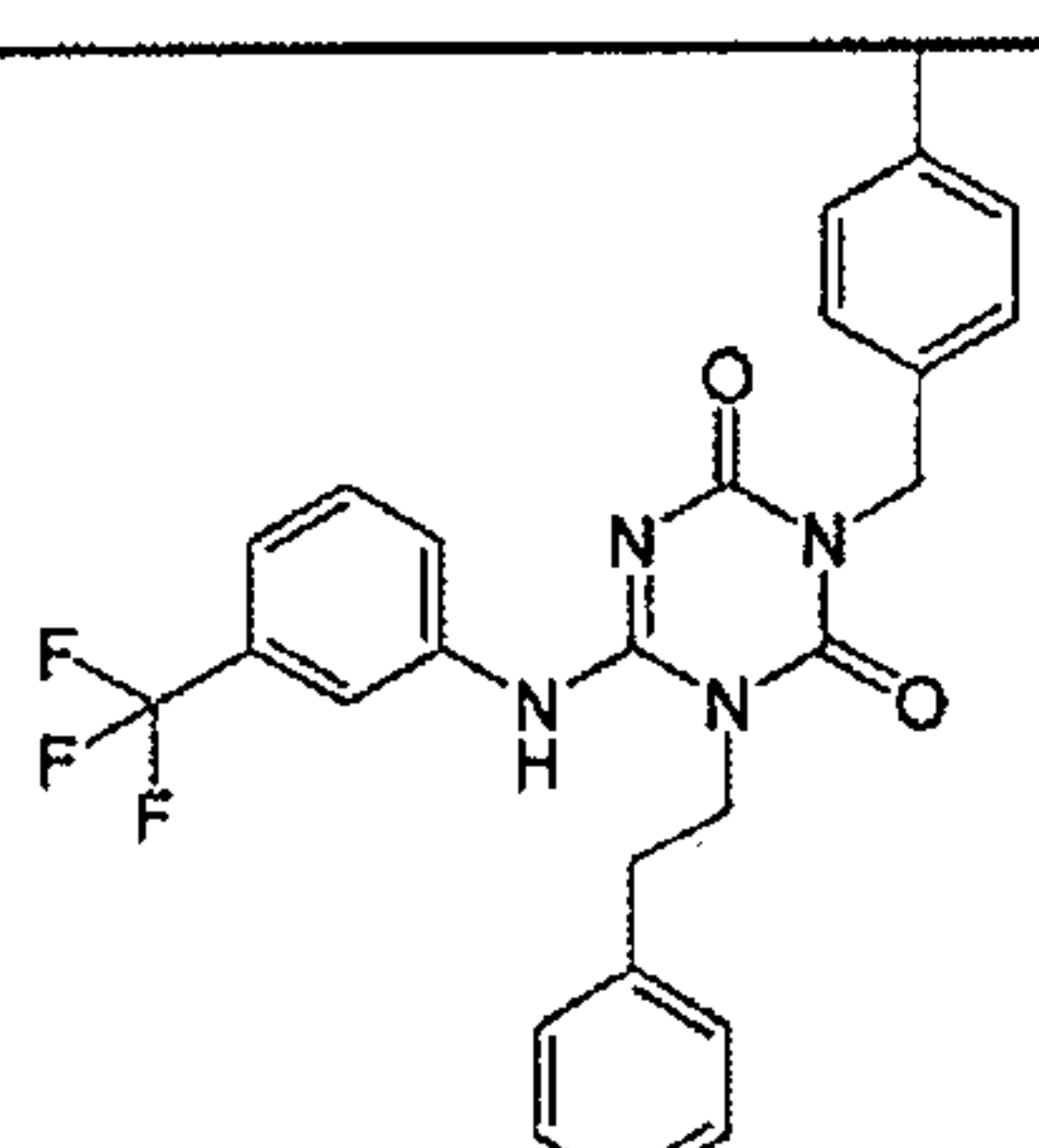
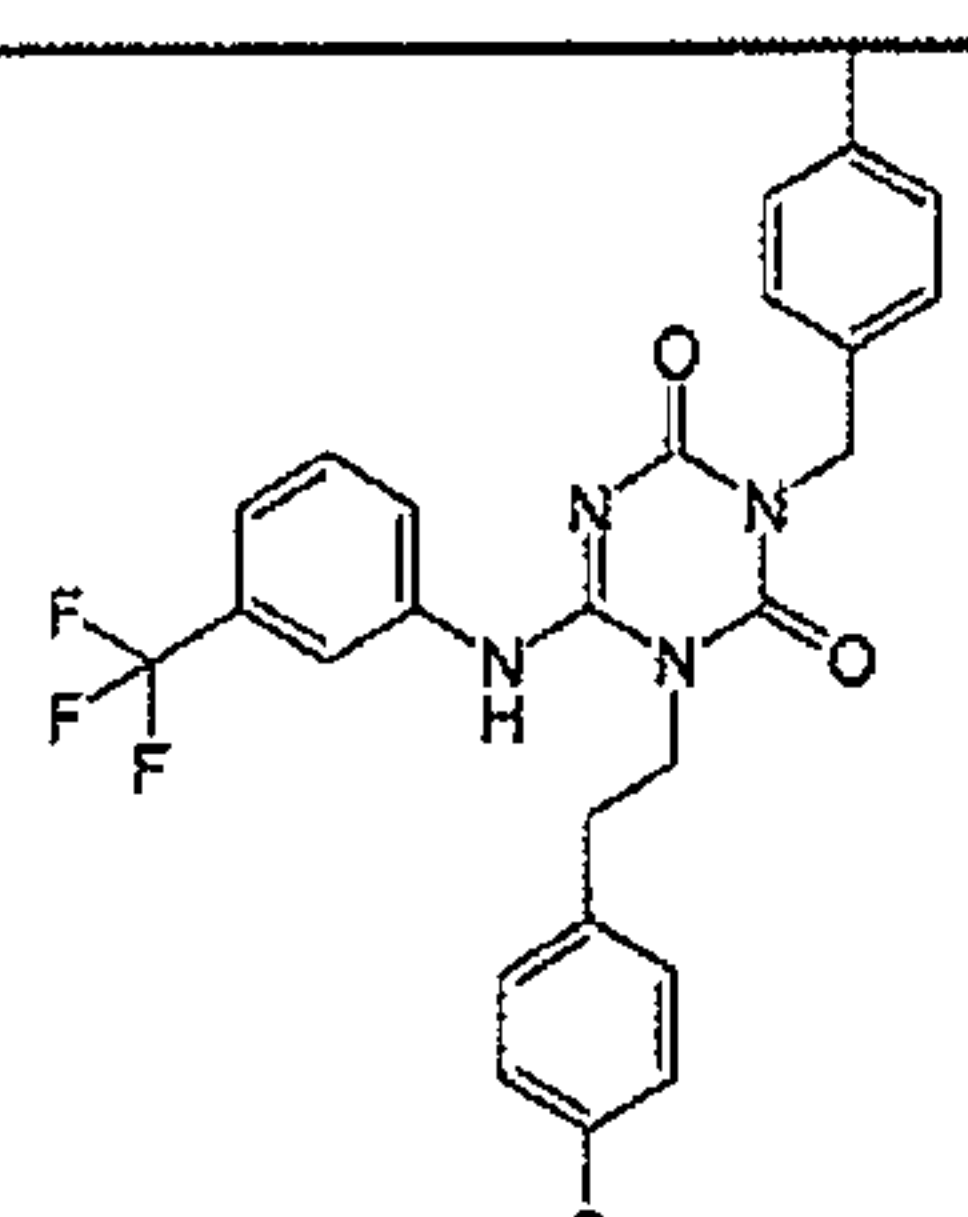
[Table 15]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0056	4.49	522	4
	I-0057	4.26	501	4
	I-0058	4.94	556	4
	I-0059	4.45	555	4
	I-0060	4.50	555	4

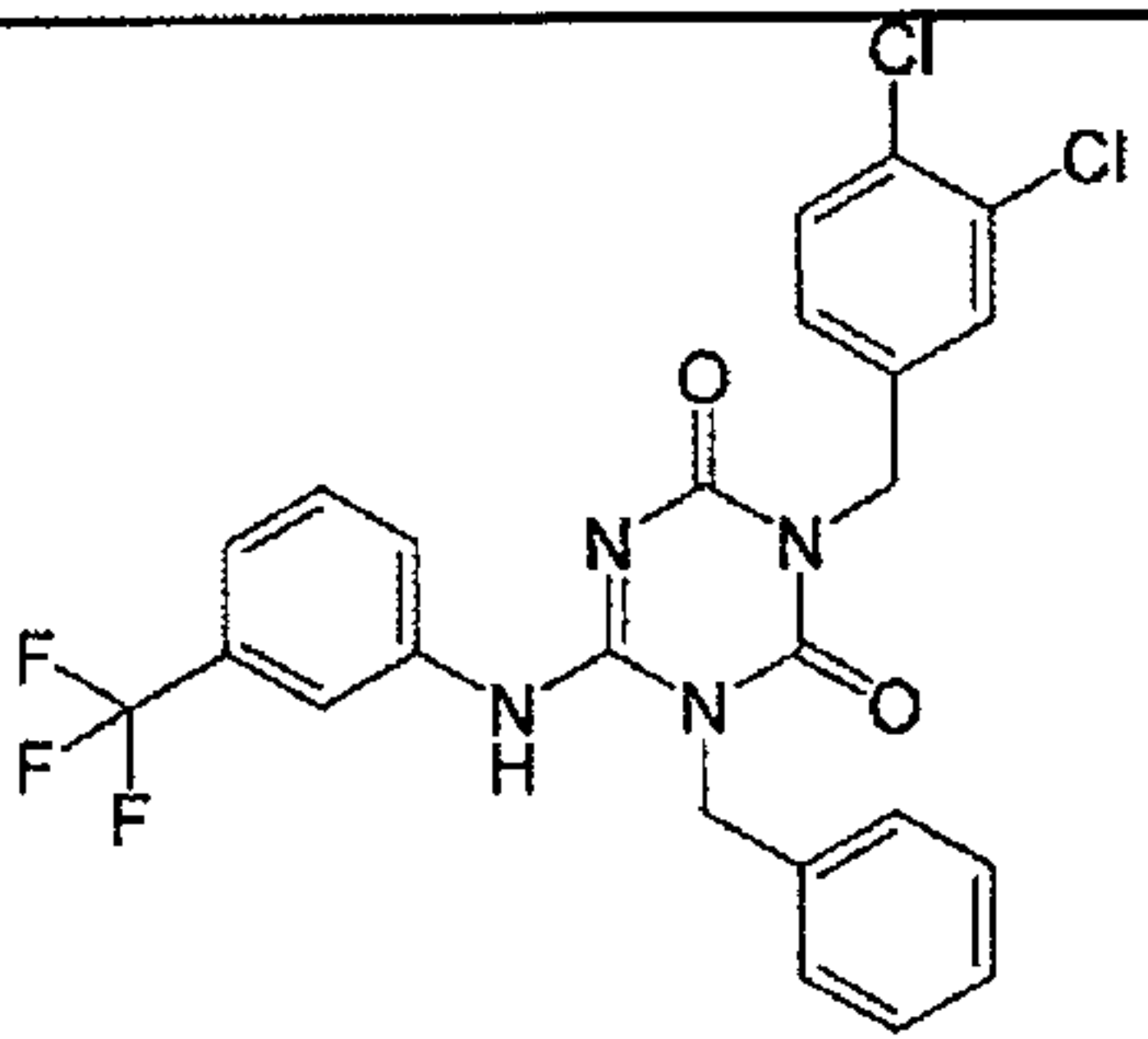
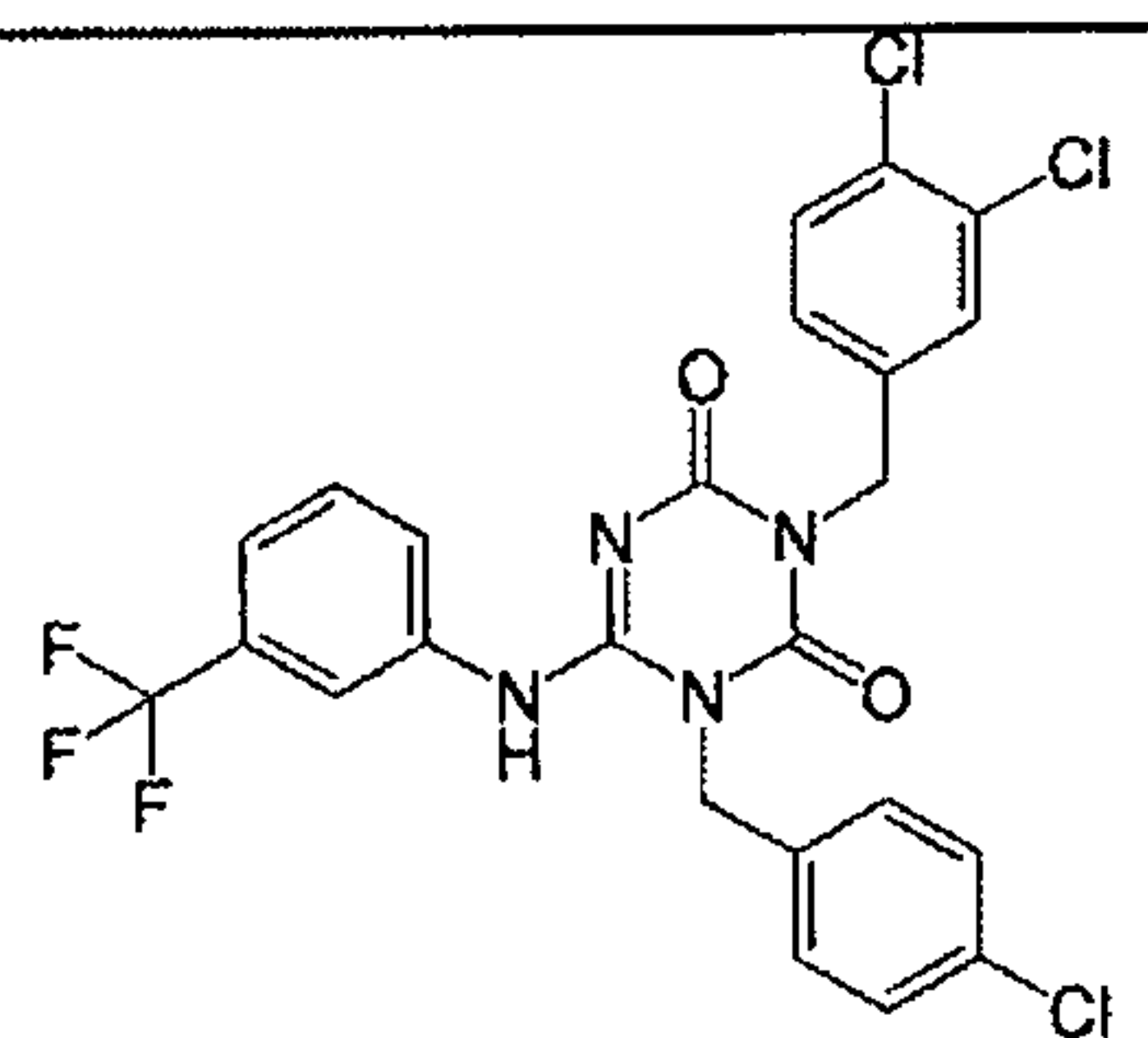
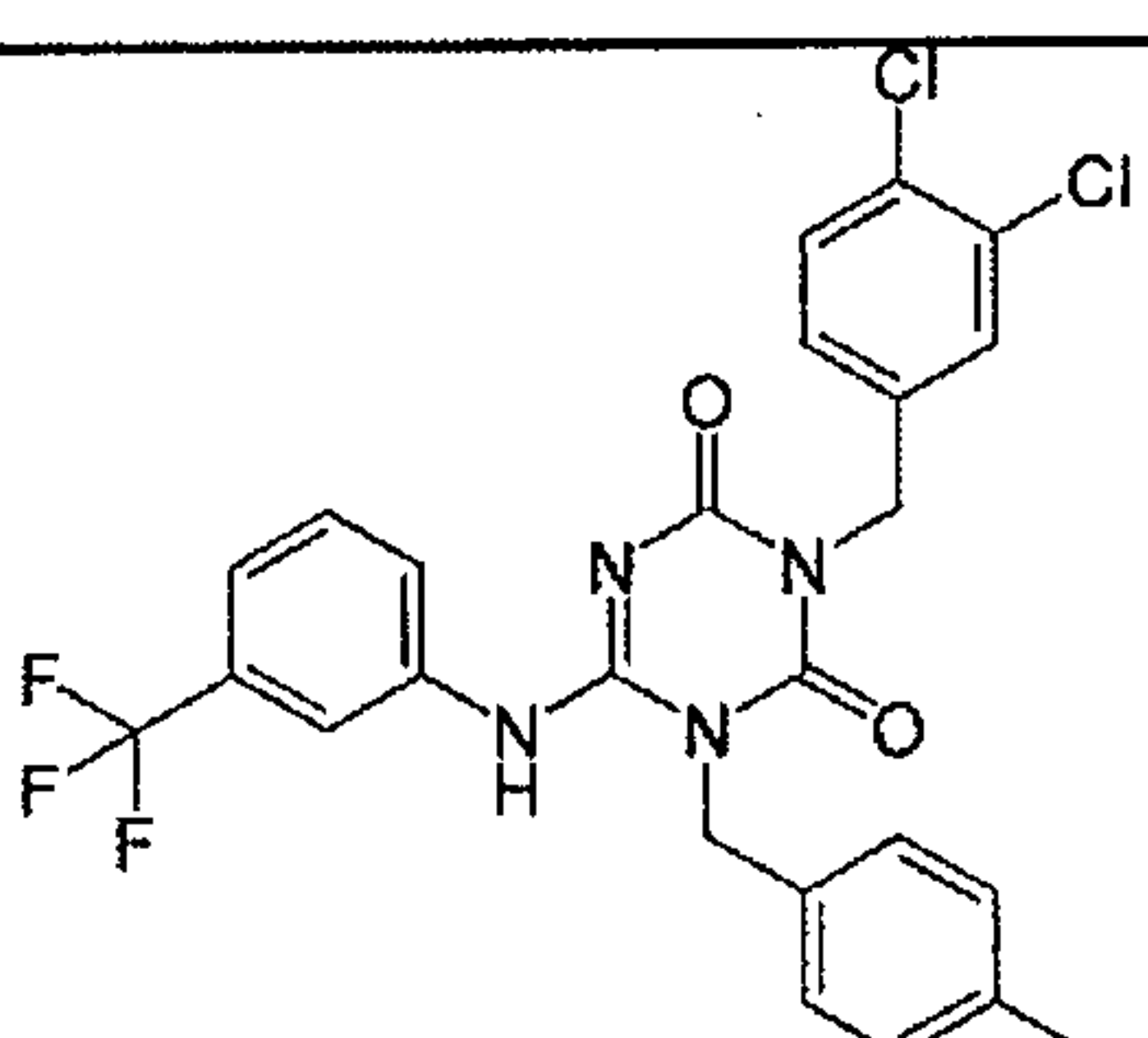
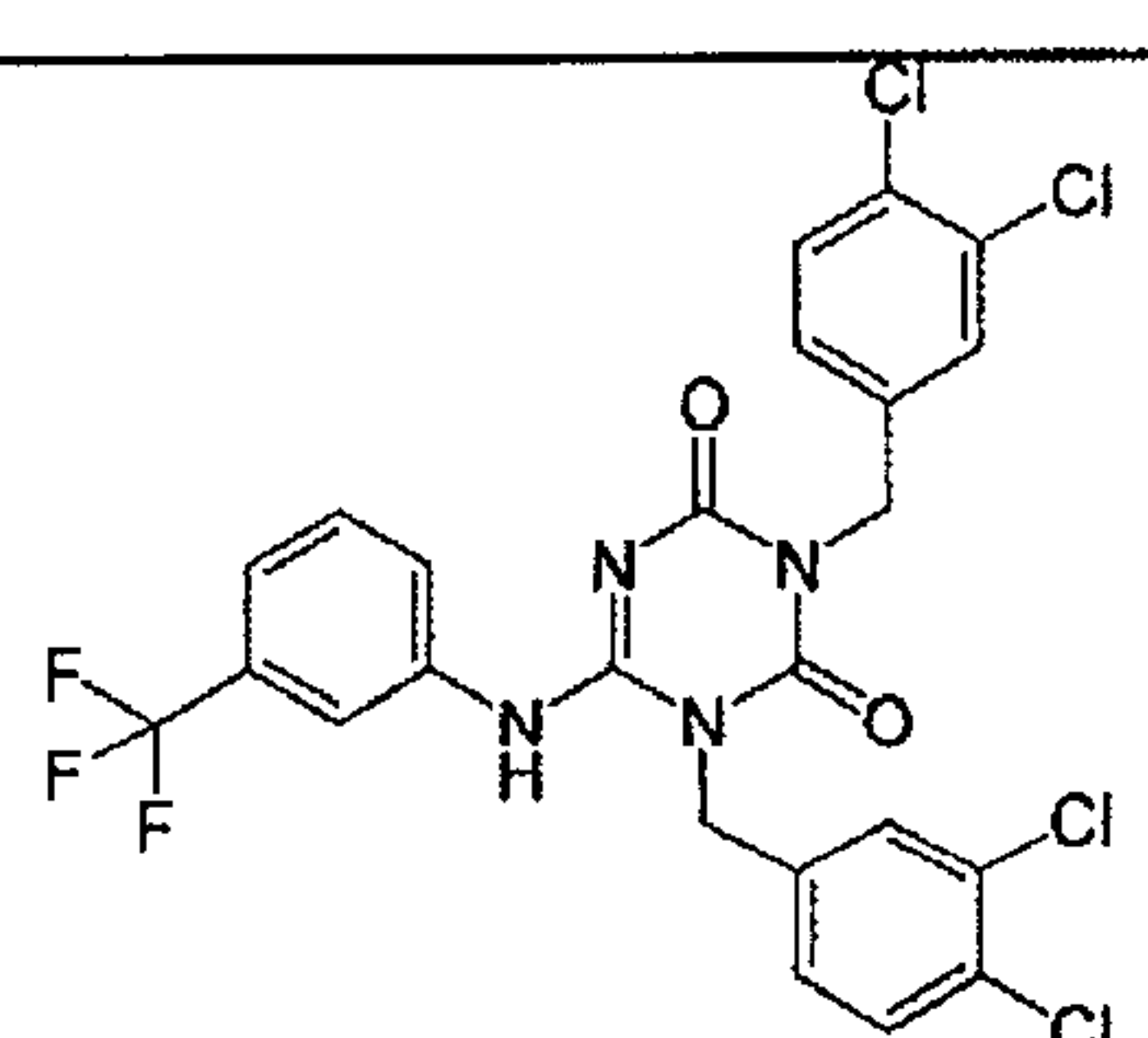
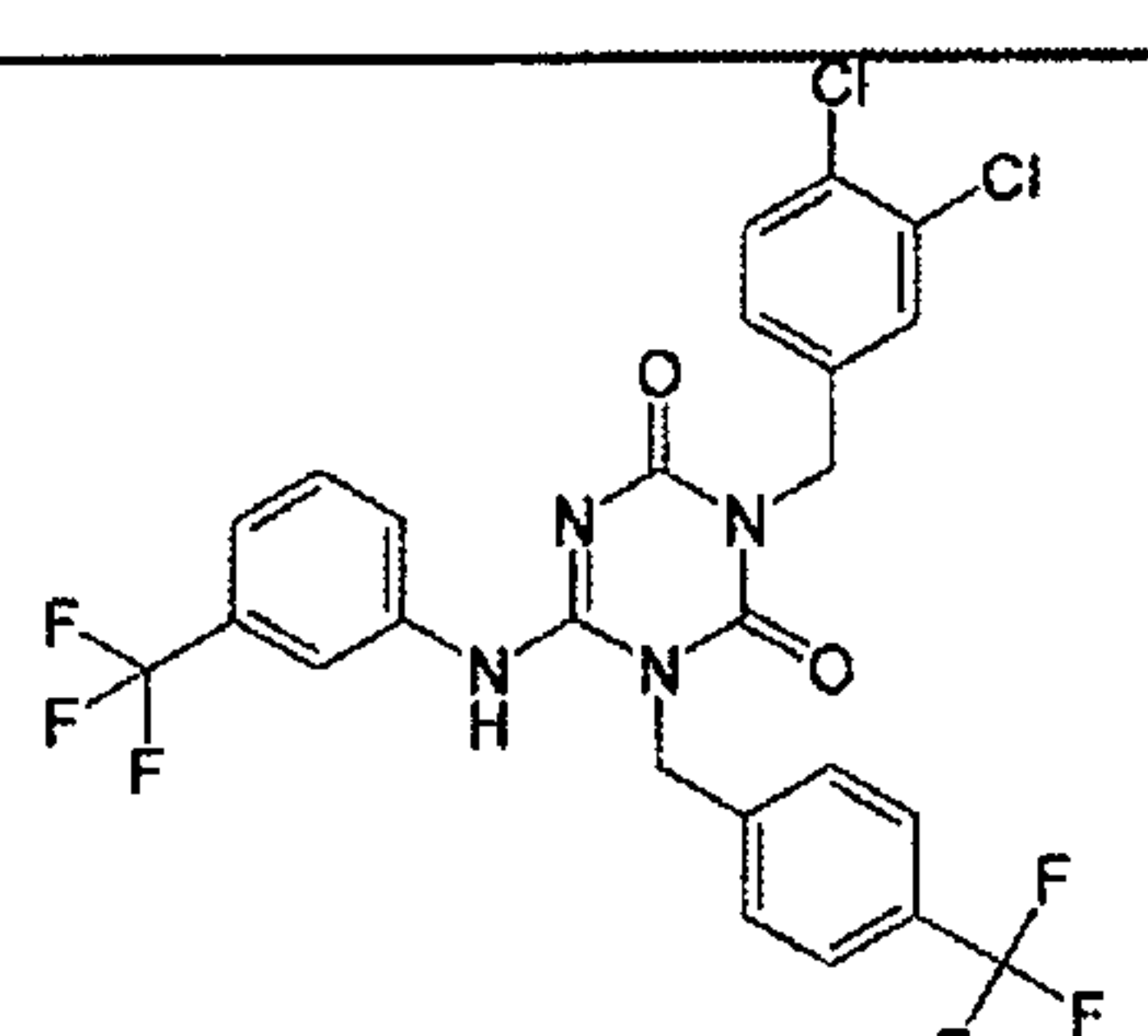
[Table 16]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0061	3.99	501	4
	I-0062	3.86	531	4
	I-0063	2.81	467	4
	I-0064	2.40	501	4
	I-0065	3.32	481	4

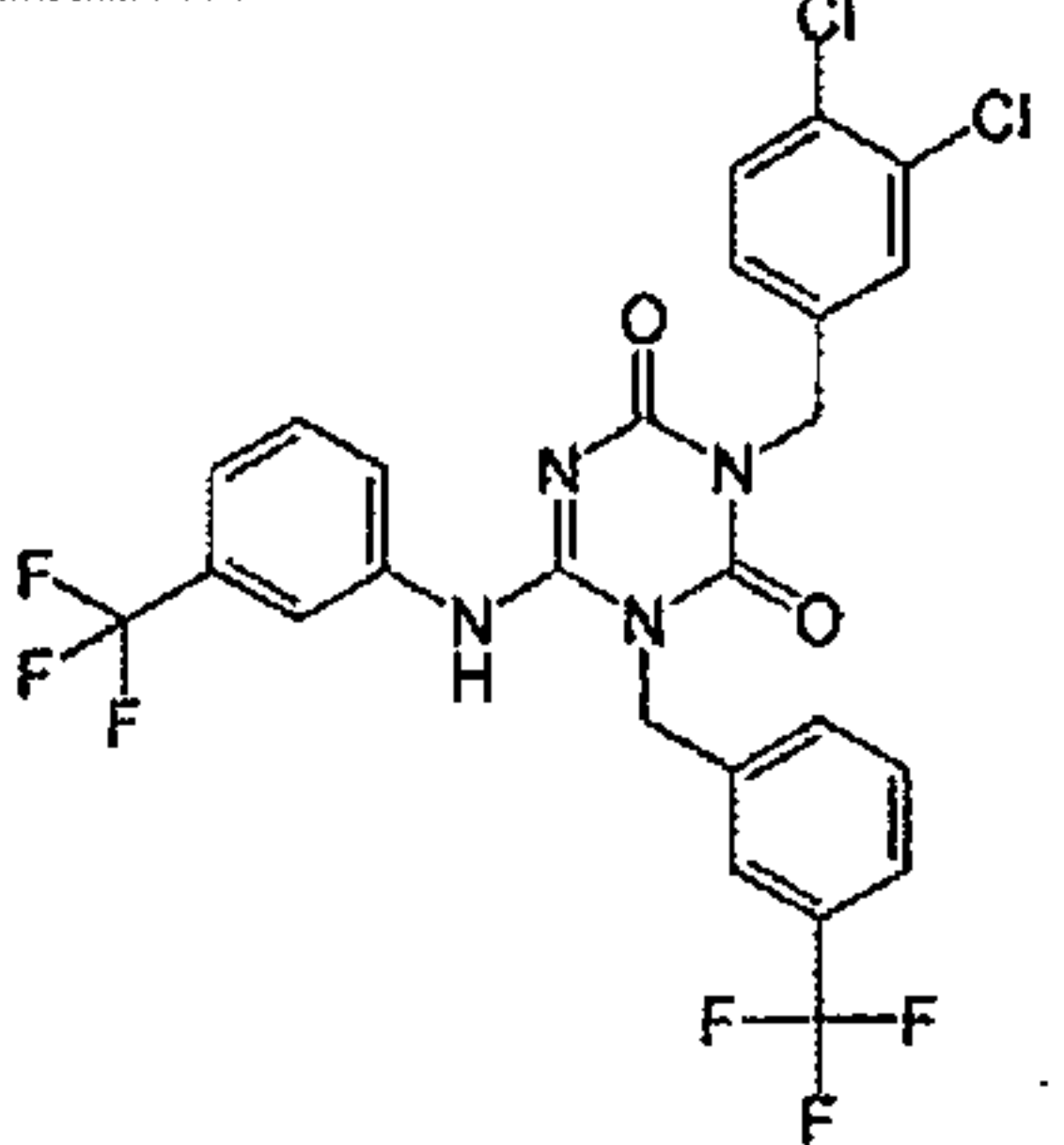
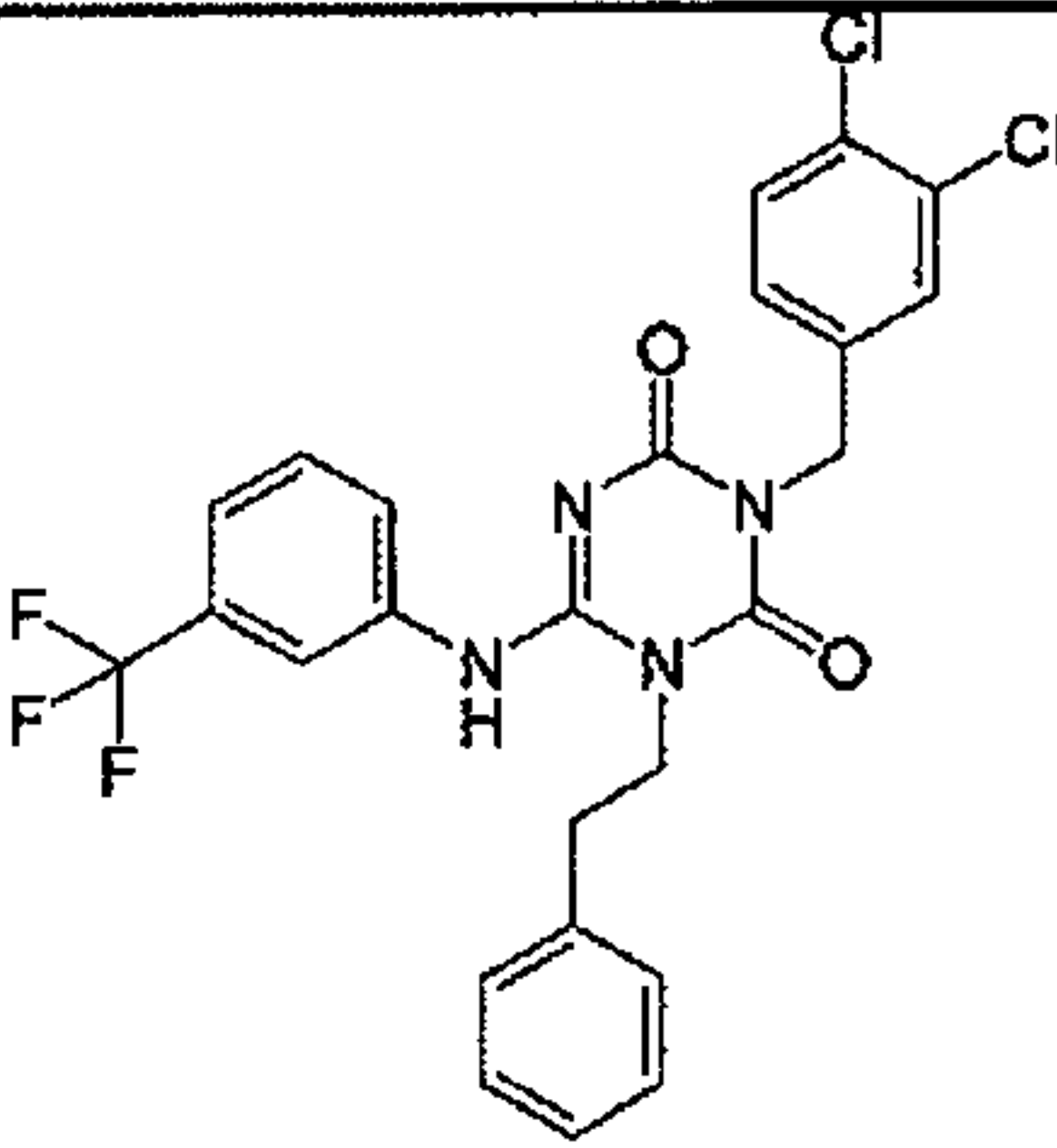
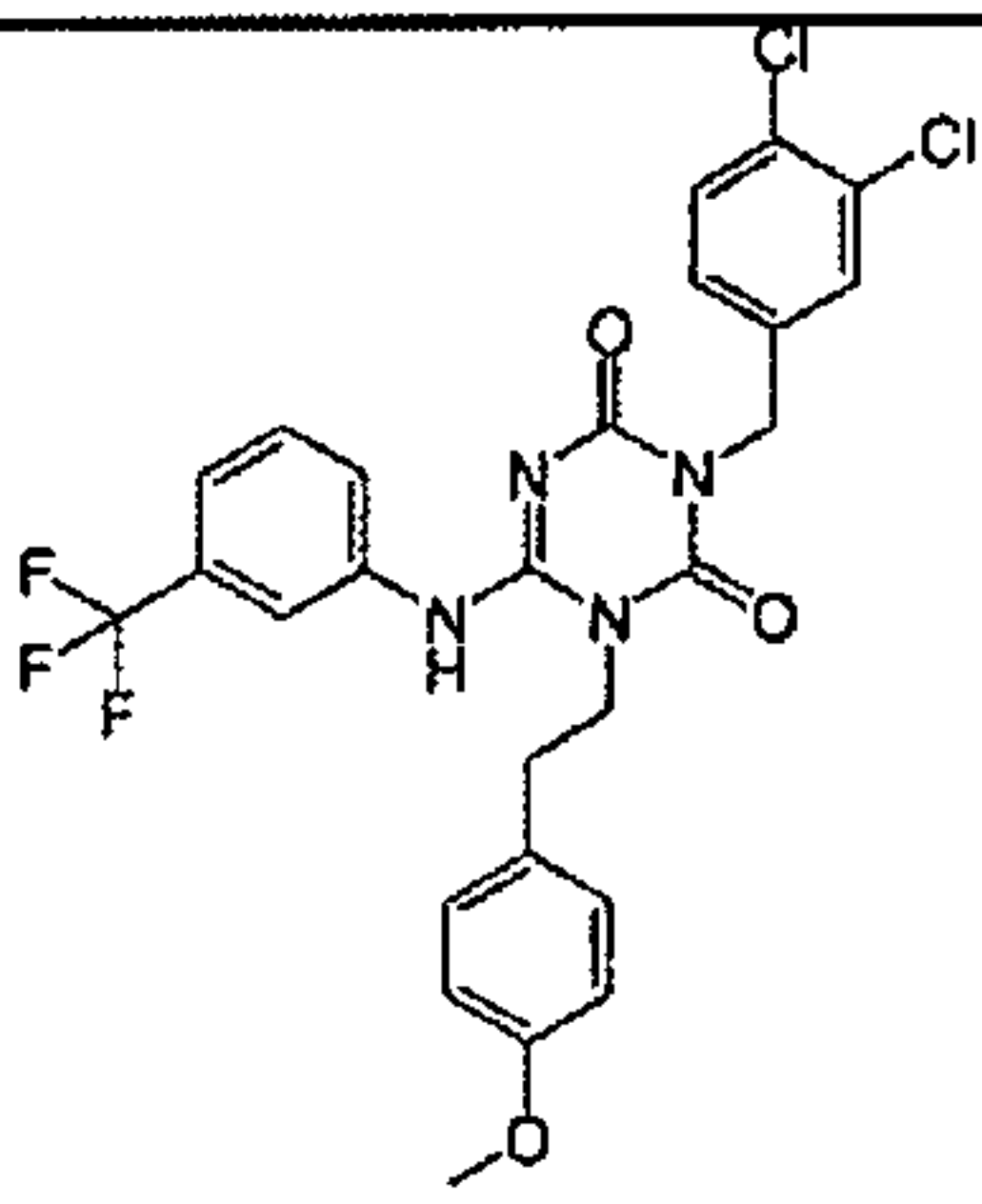
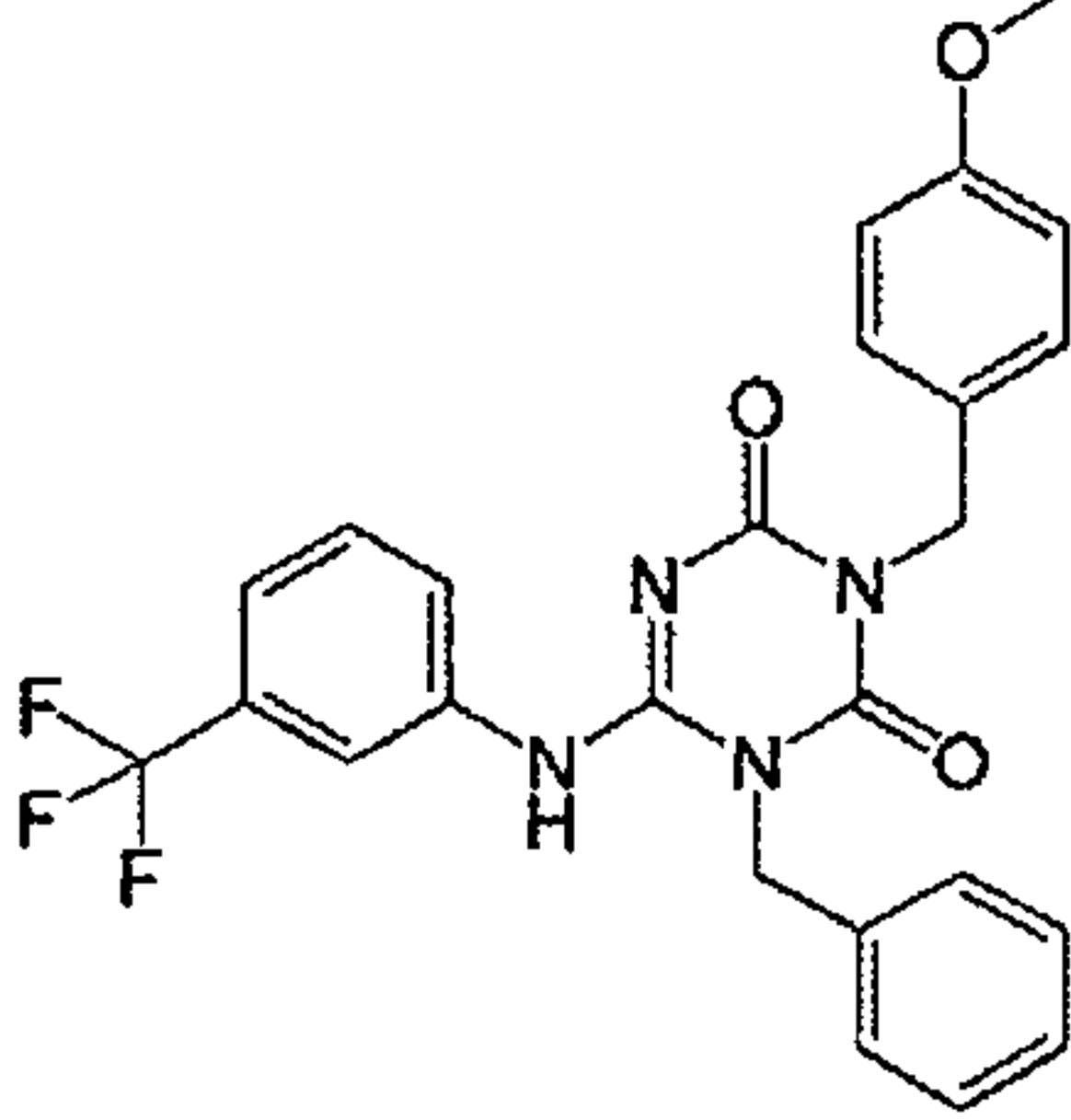
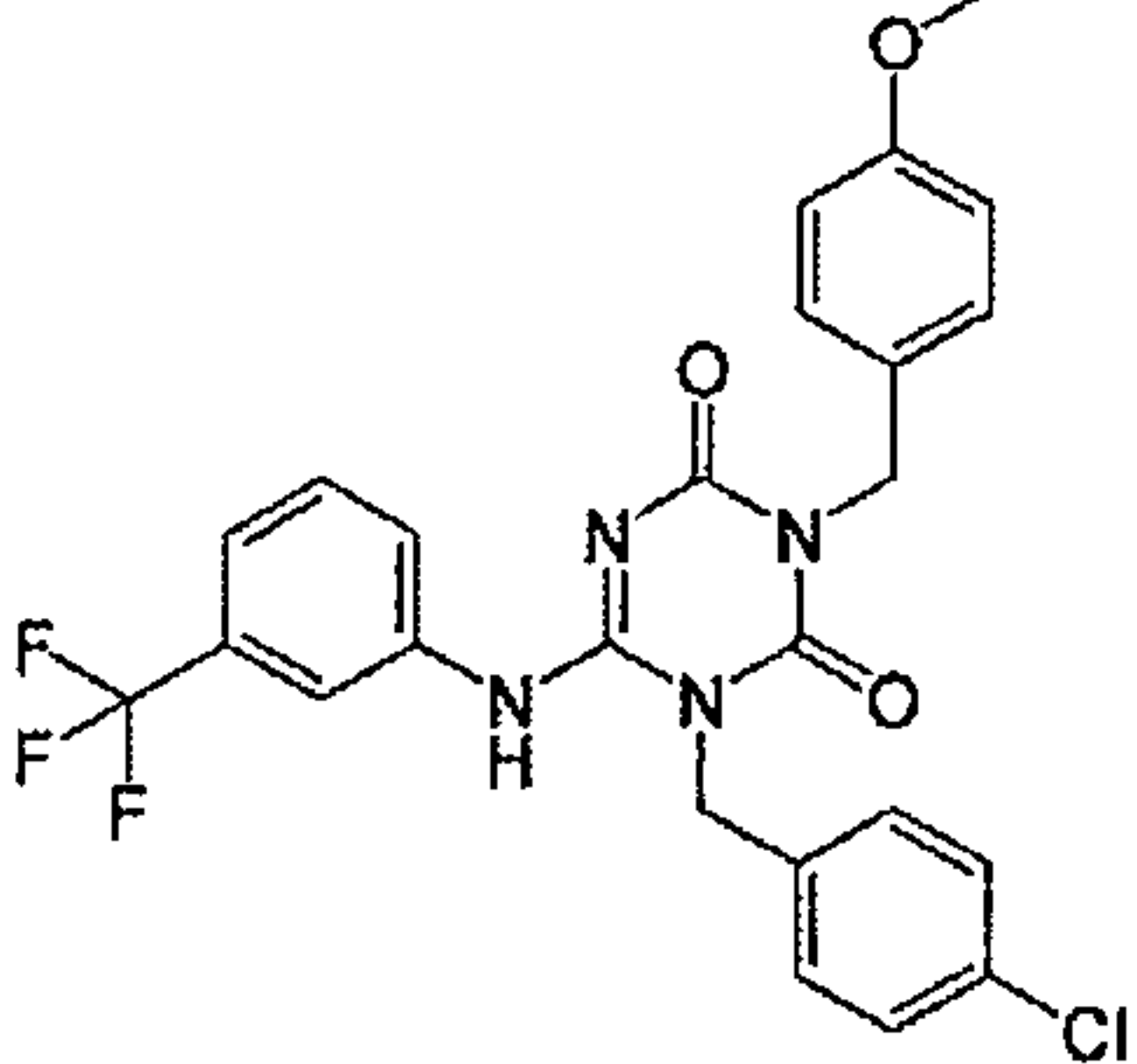
[Table 17]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0066	4.30	534	4
	I-0067	3.60	535	4
	I-0068	3.60	535	4
	I-0069	3.91	481	4
	I-0070	2.76	511	4

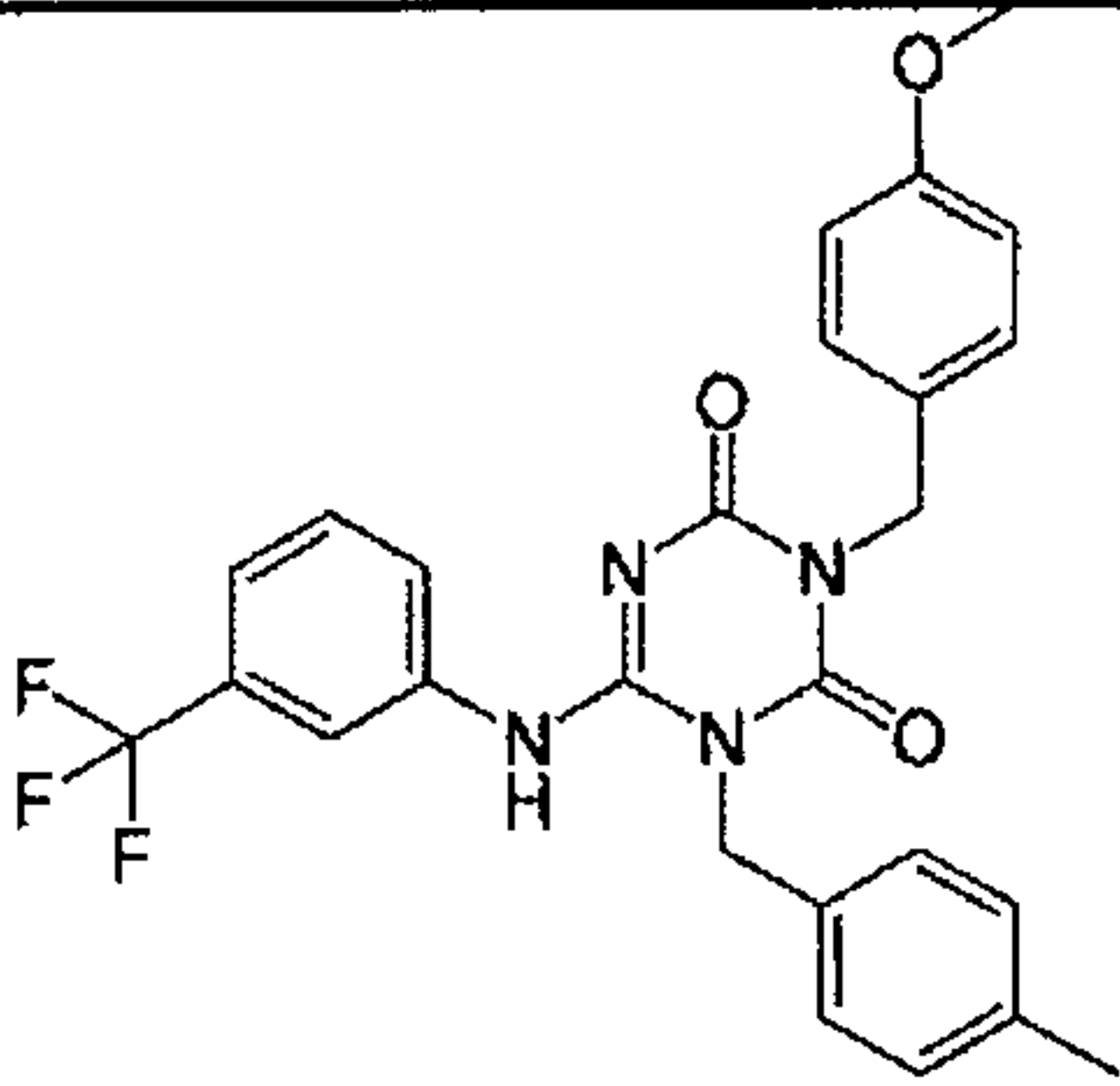
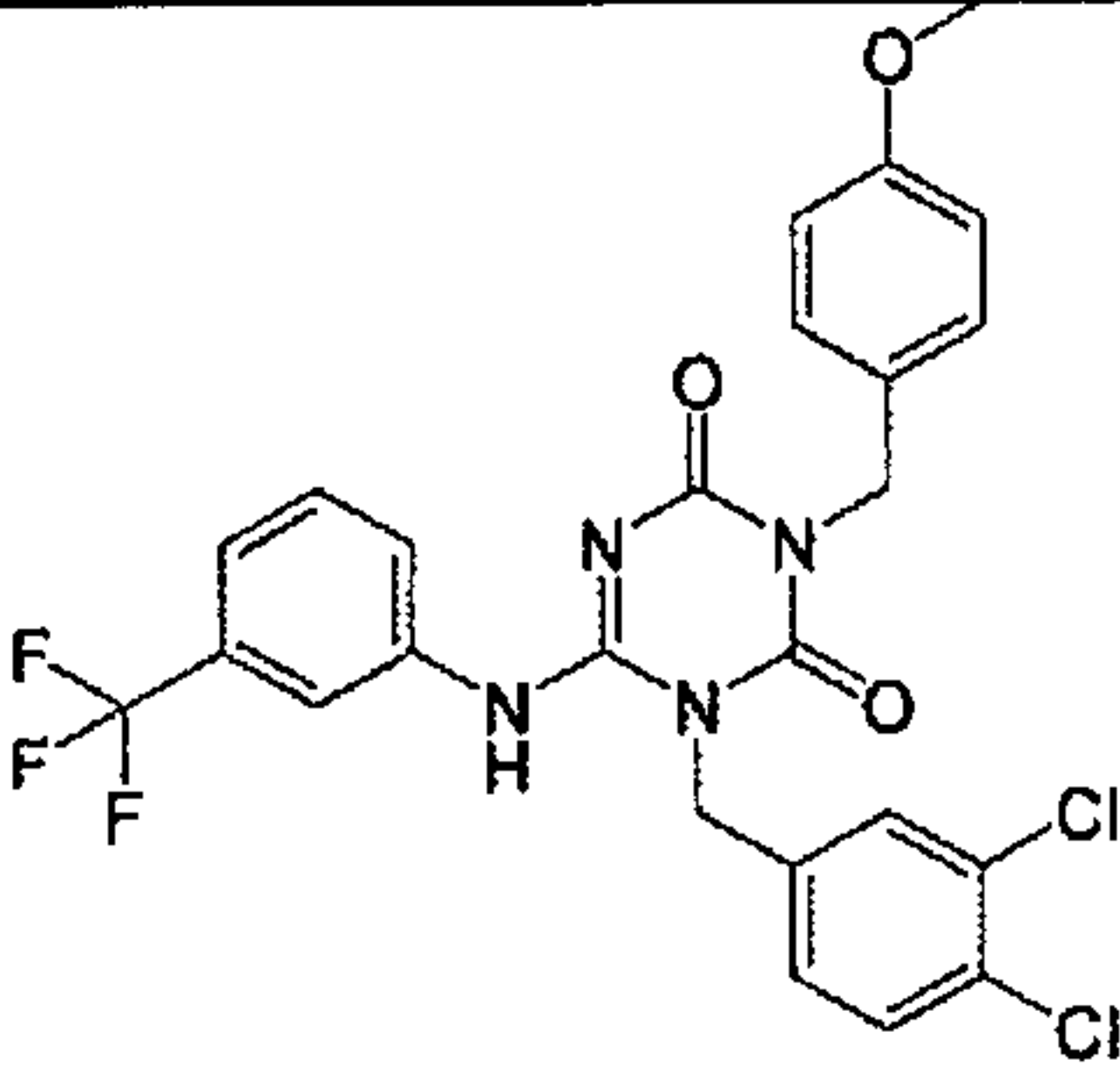
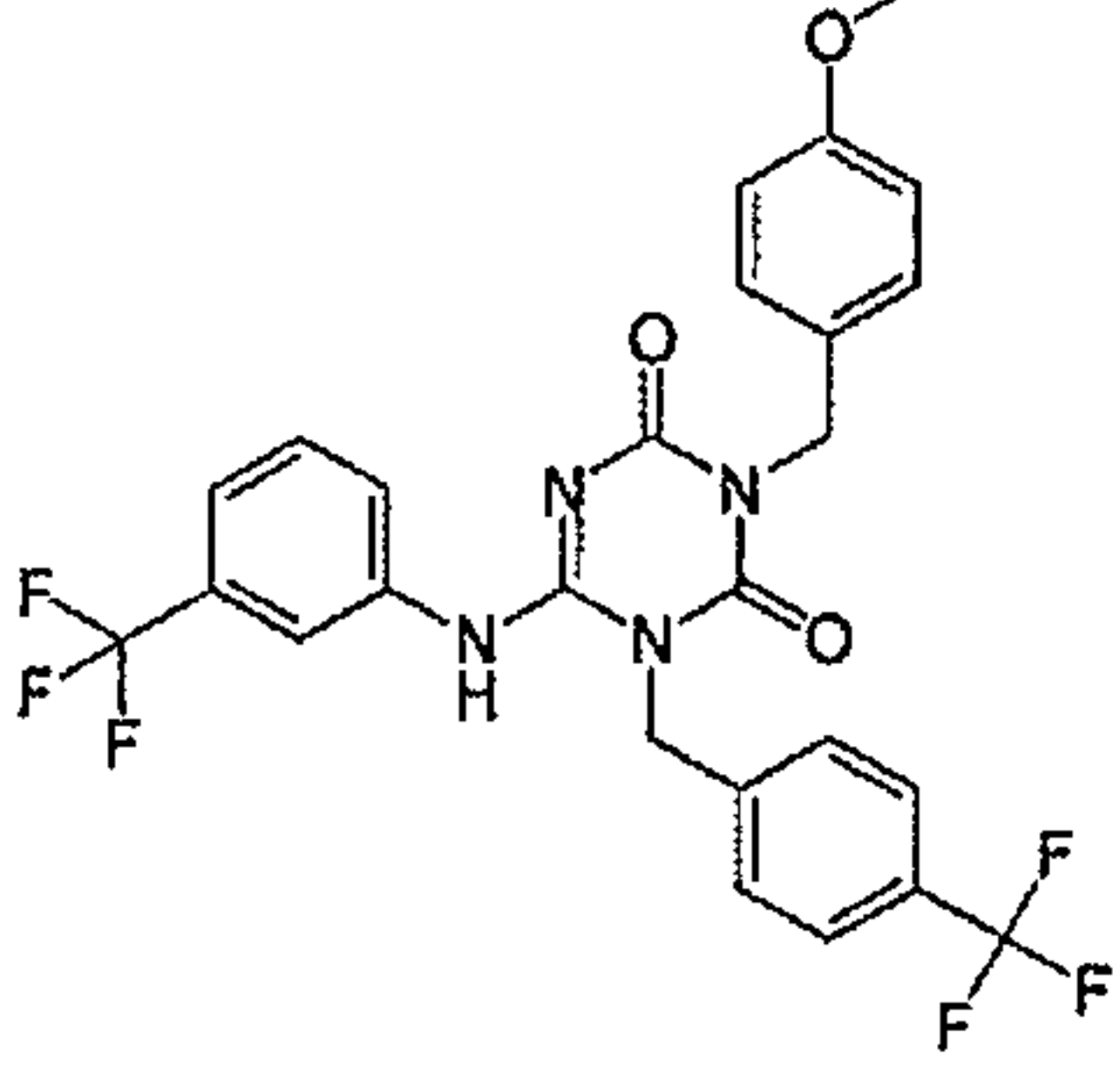
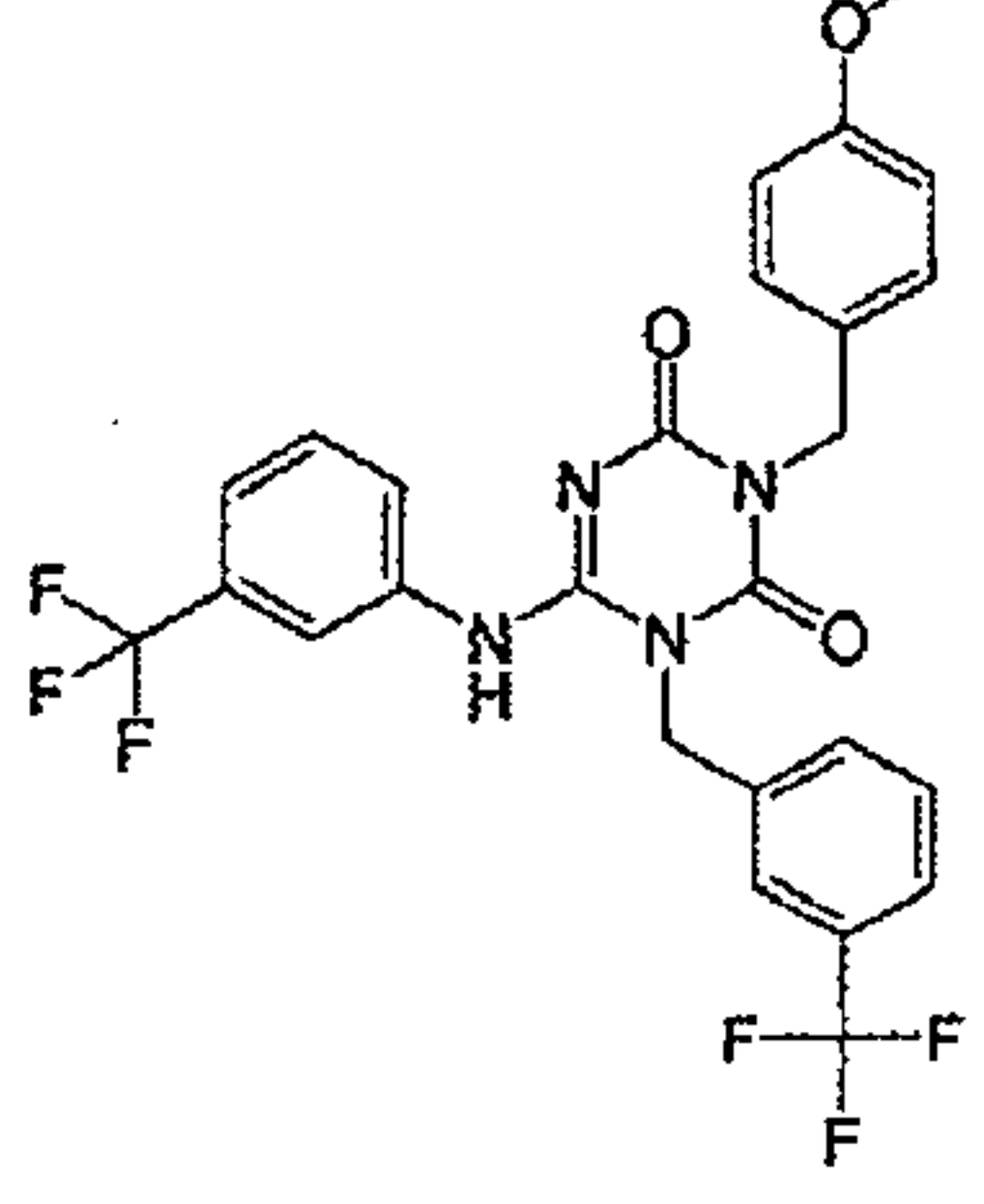
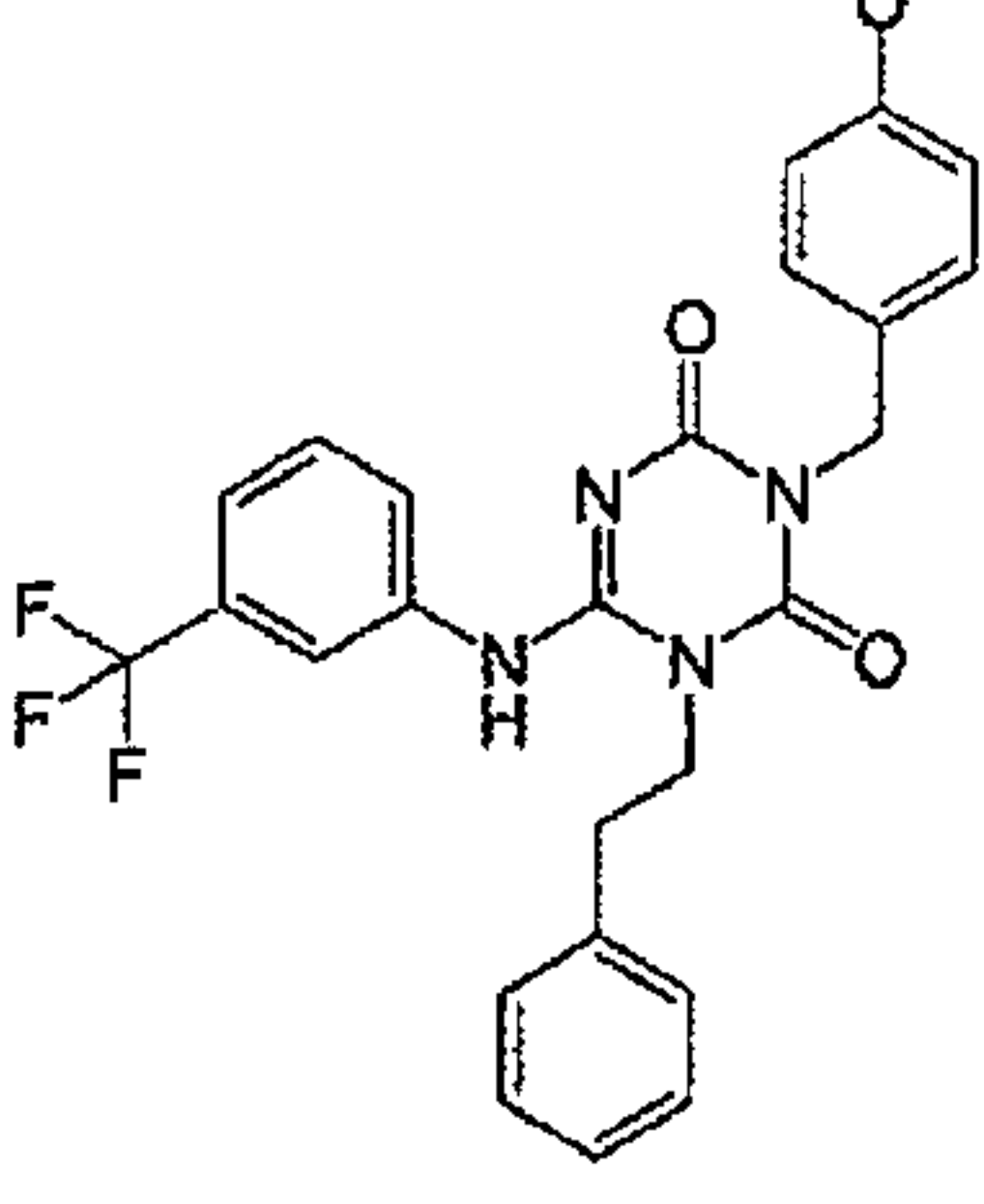
[Table 18]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0071	3.43	522	4
	I-0072	4.12	556	4
	I-0073	3.86	536	4
	I-0074	4.68	591	4
	I-0075	4.07	590	4

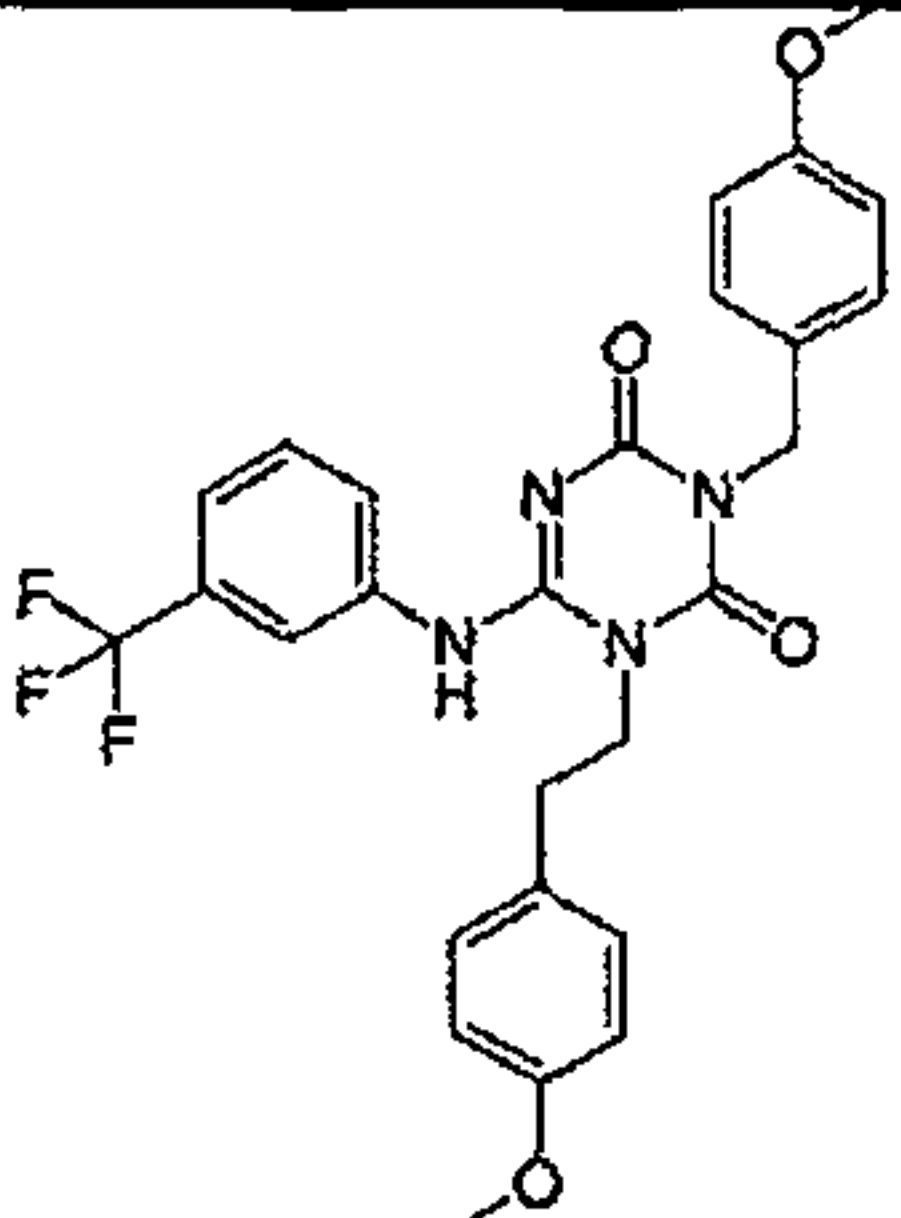
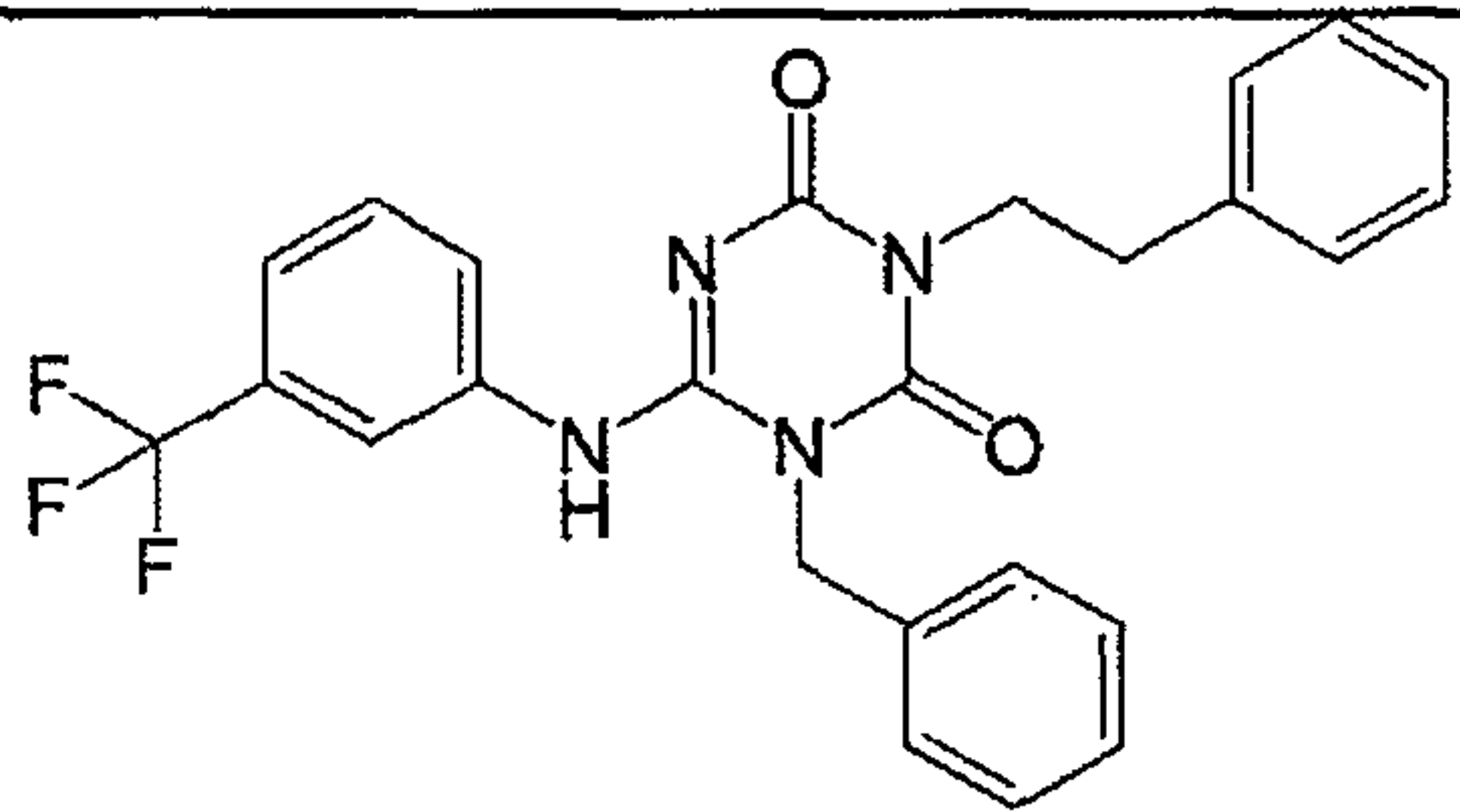
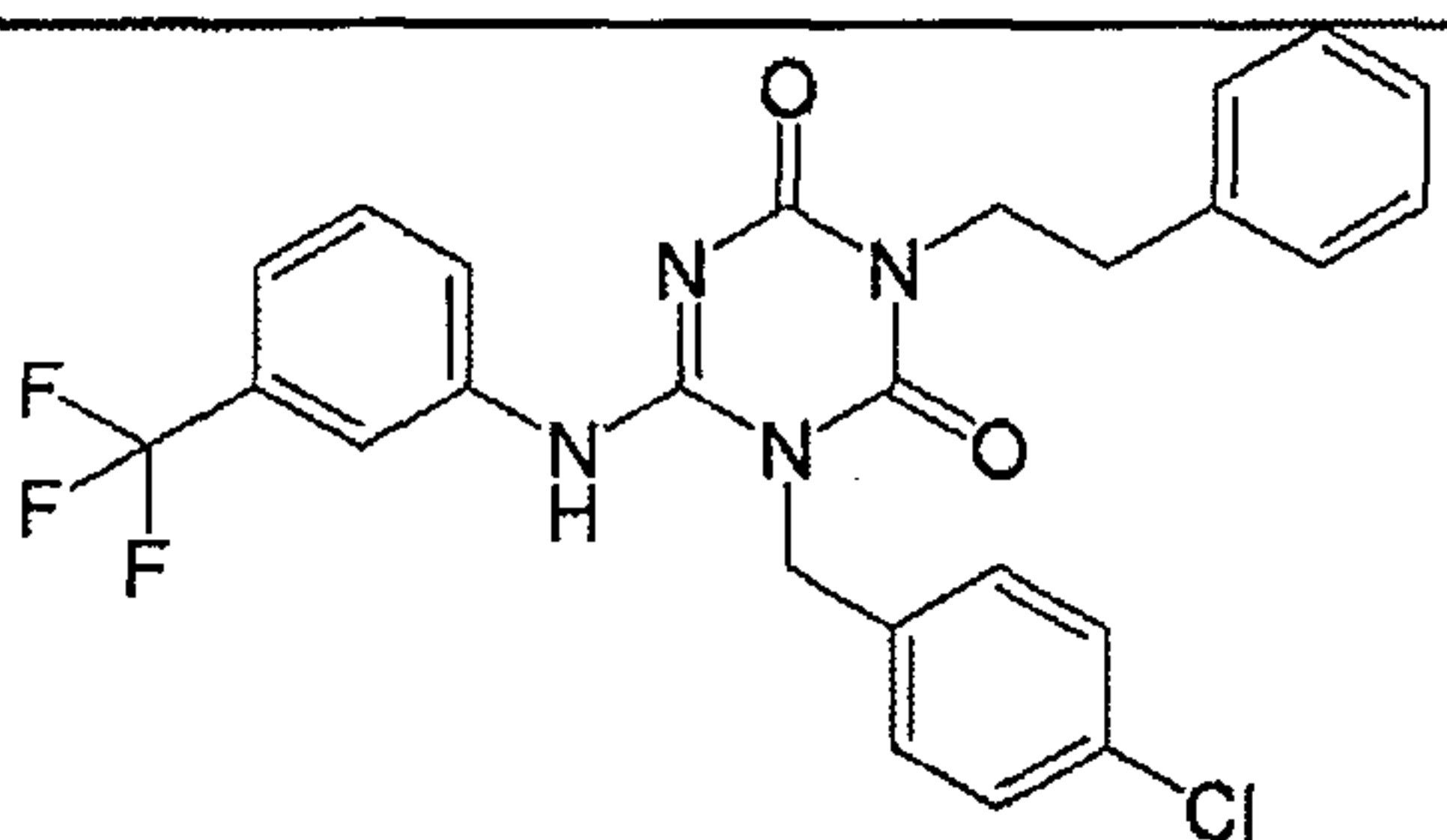
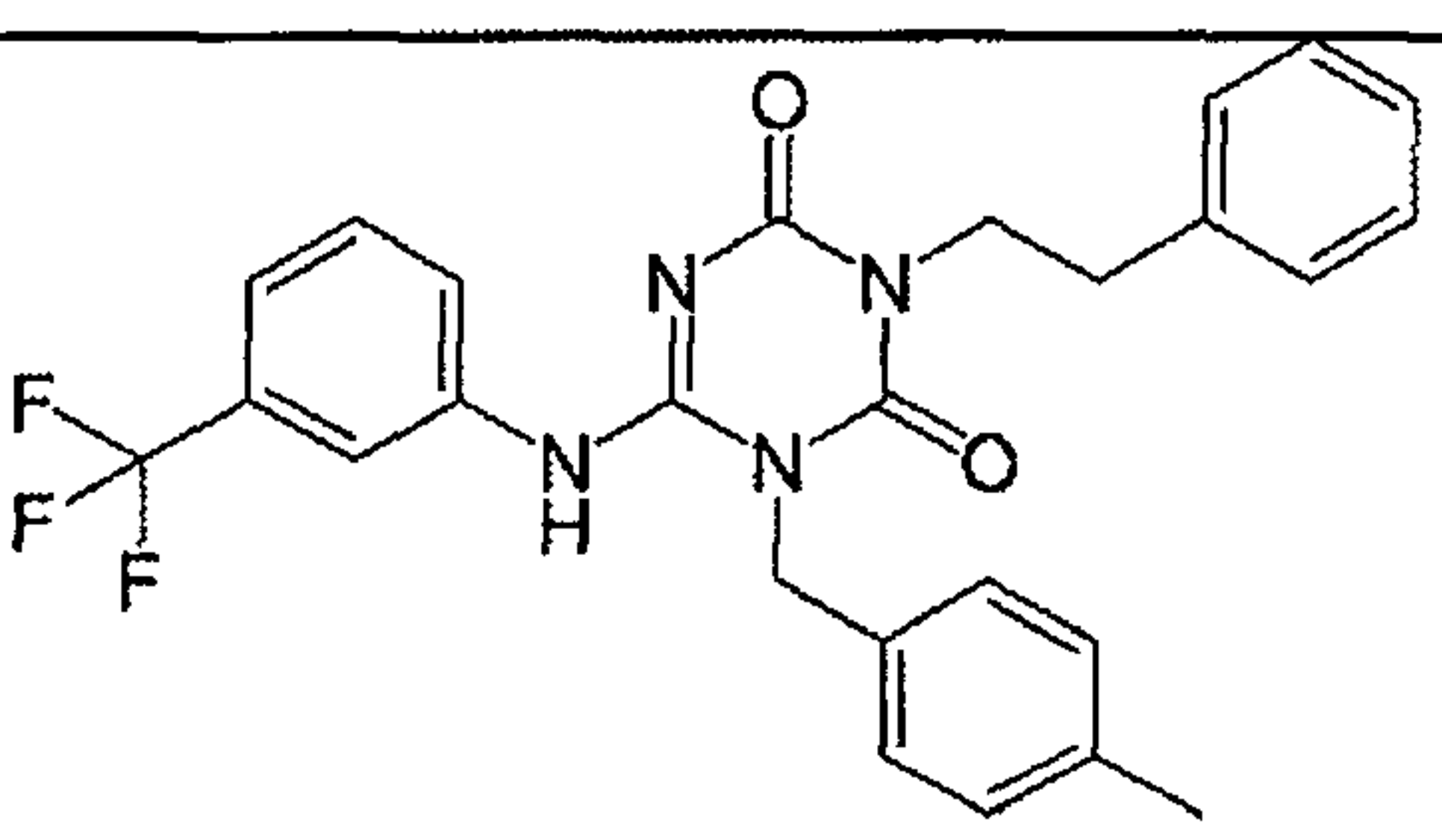
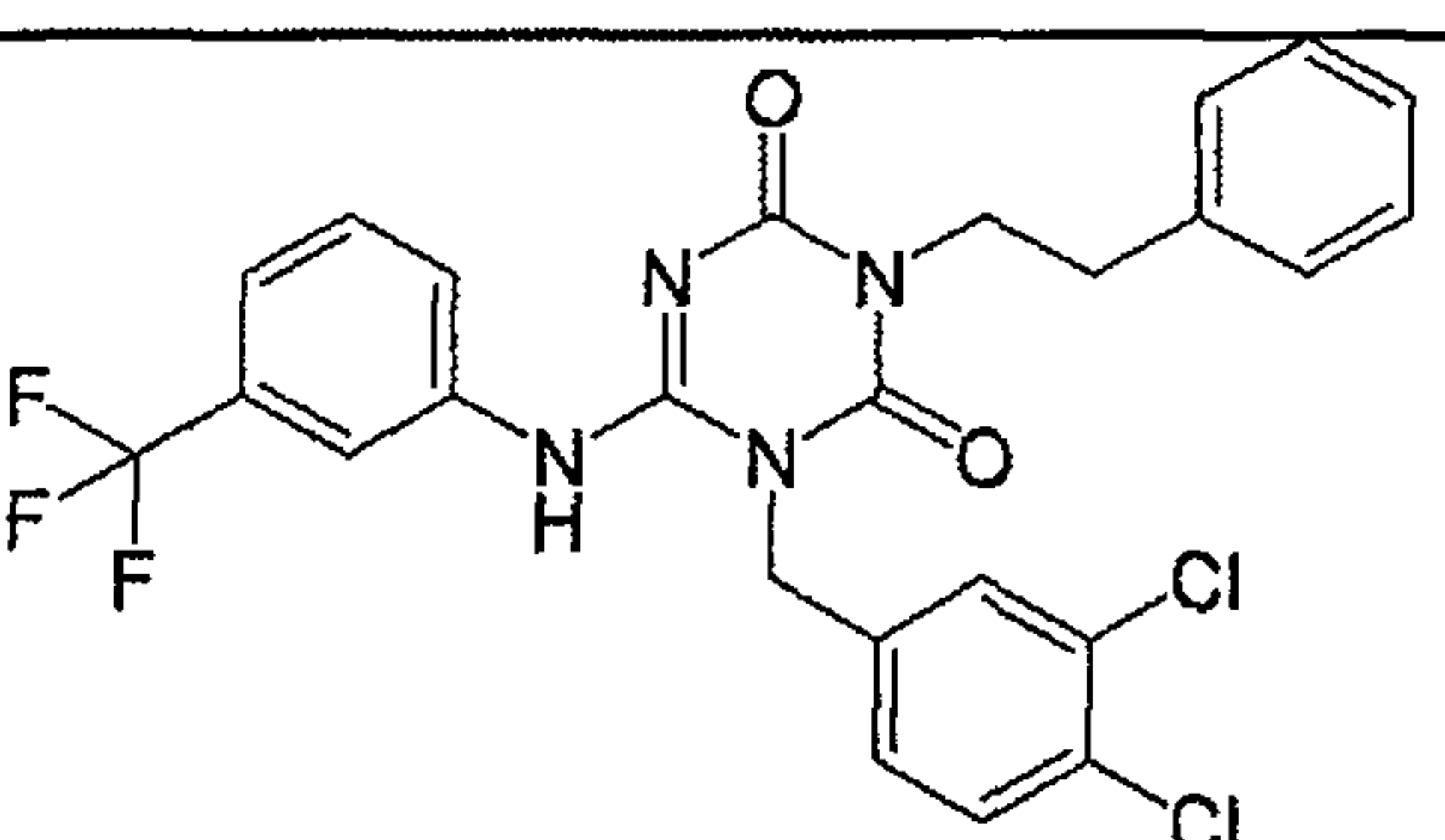
[Table 19]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0076	4.11	590	4
	I-0077	3.55	536	4
	I-0078	3.49	566	4
	I-0079	2.38	483	4
	I-0080	3.21	517	4

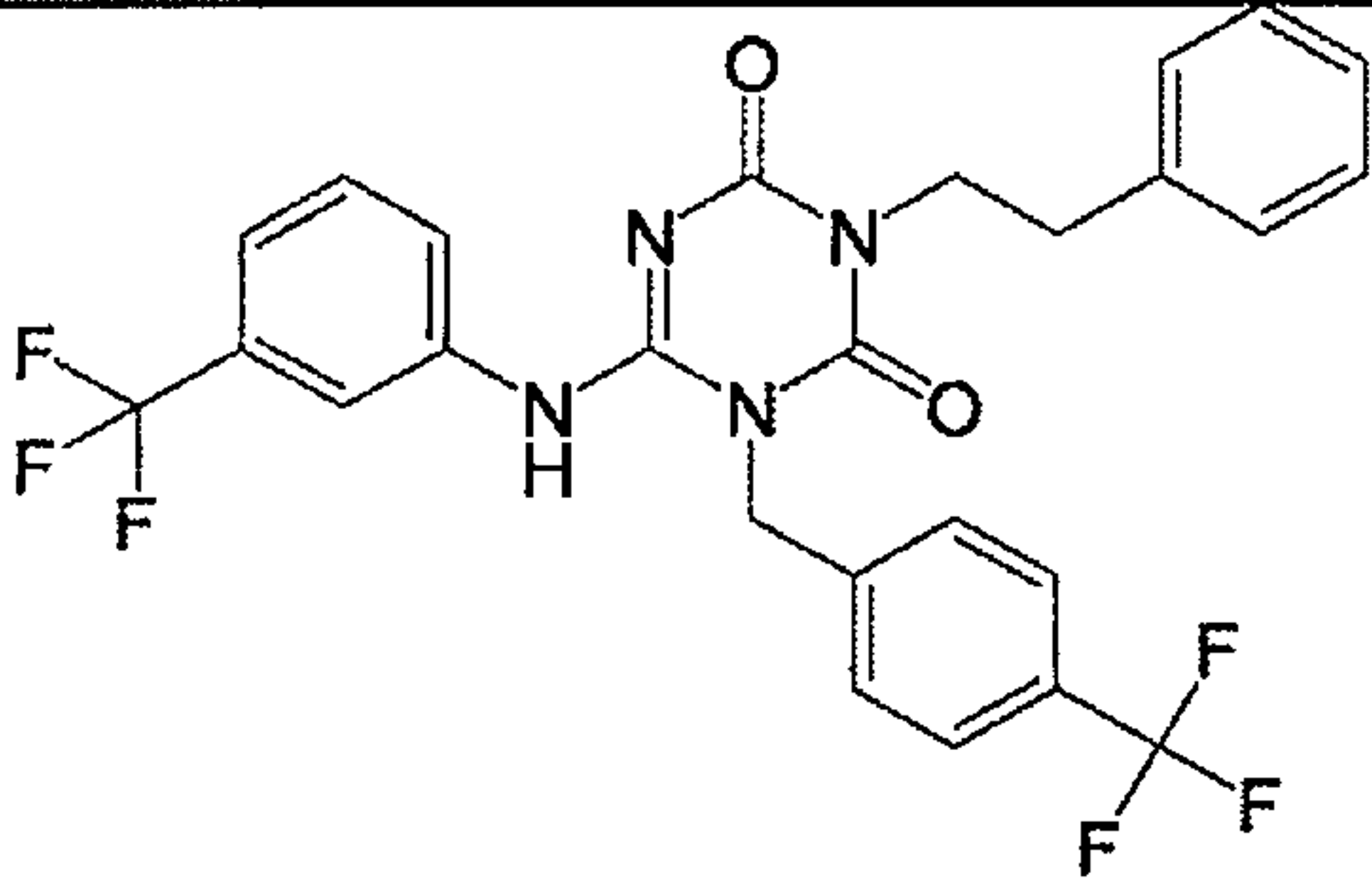
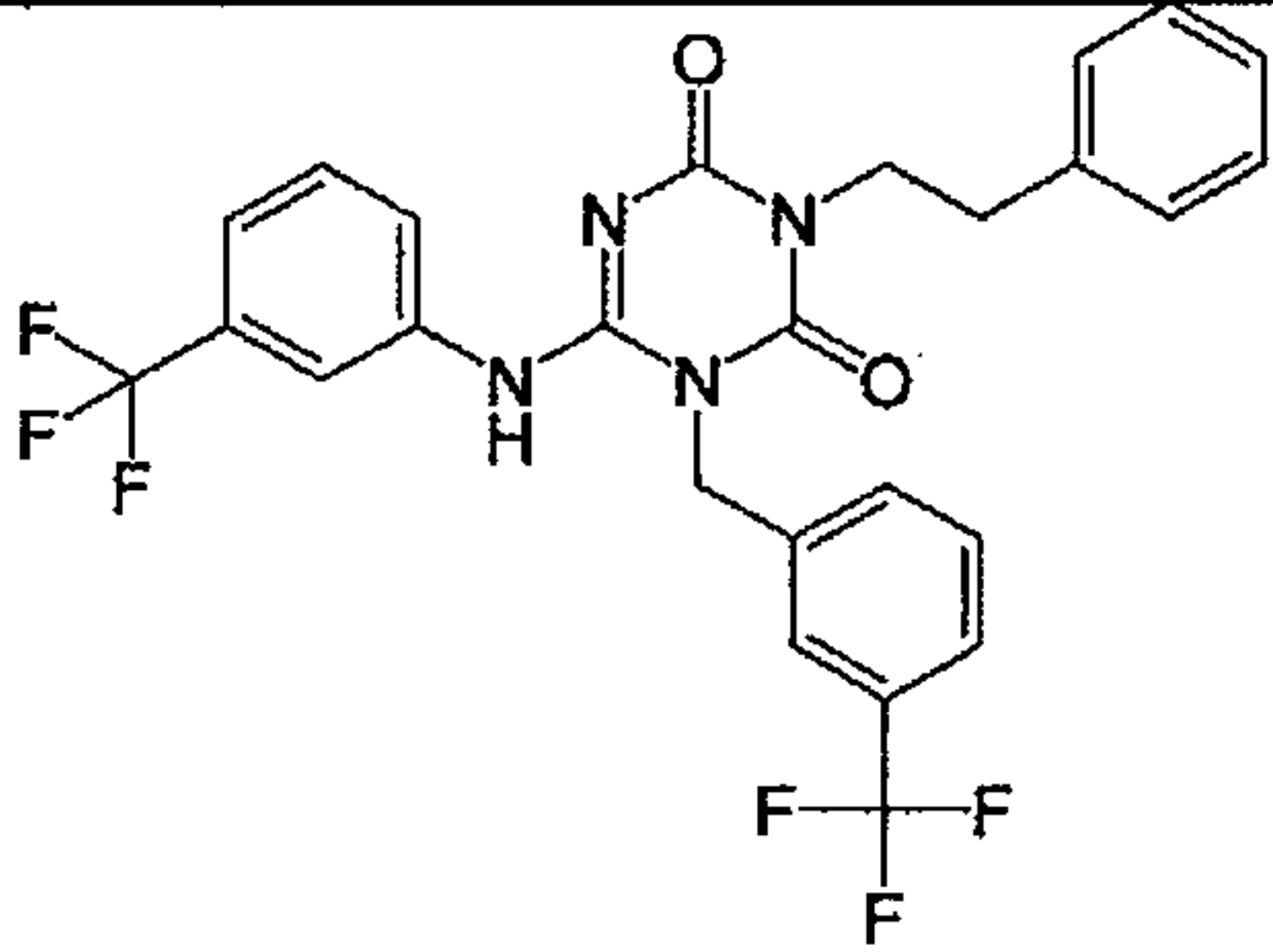
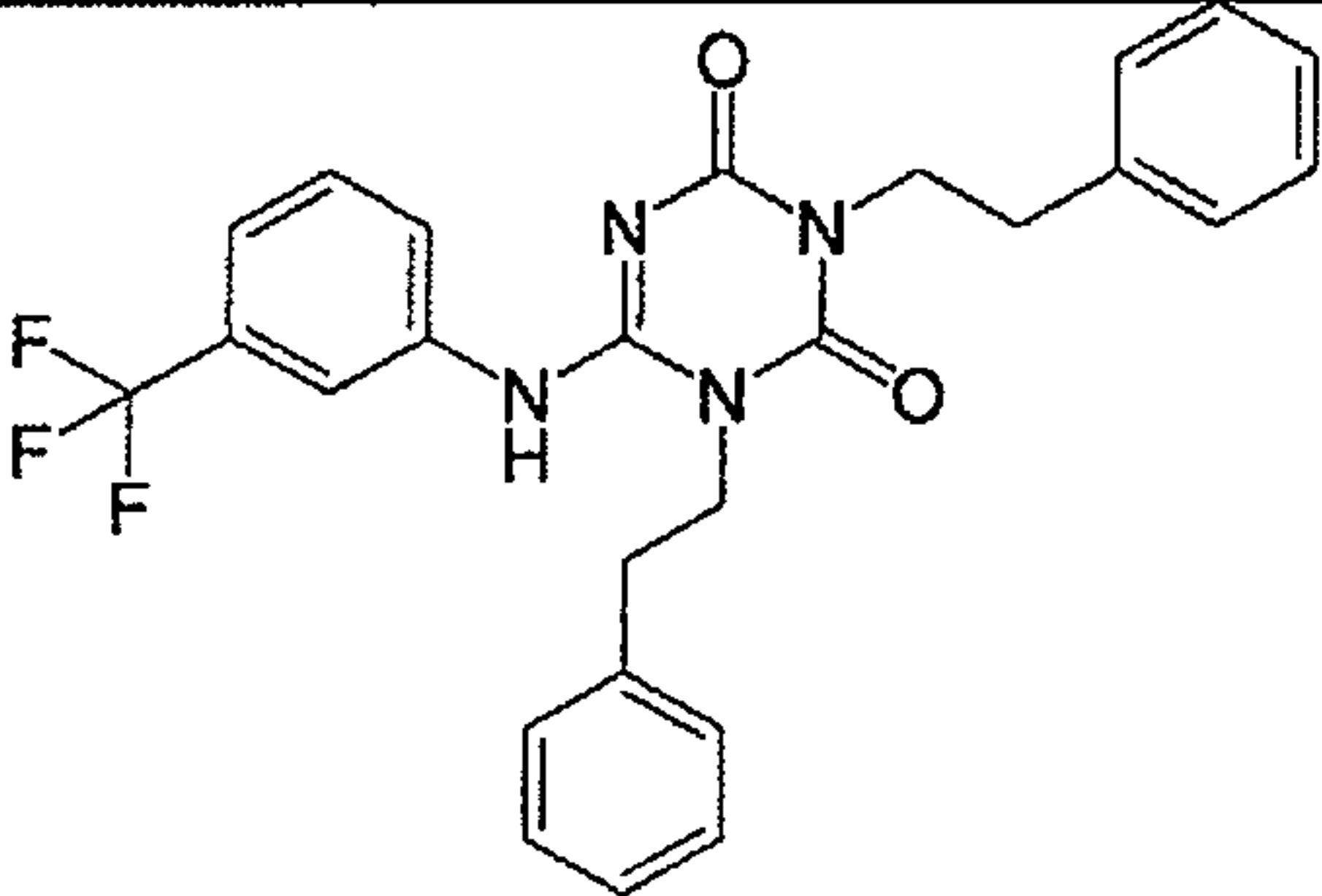
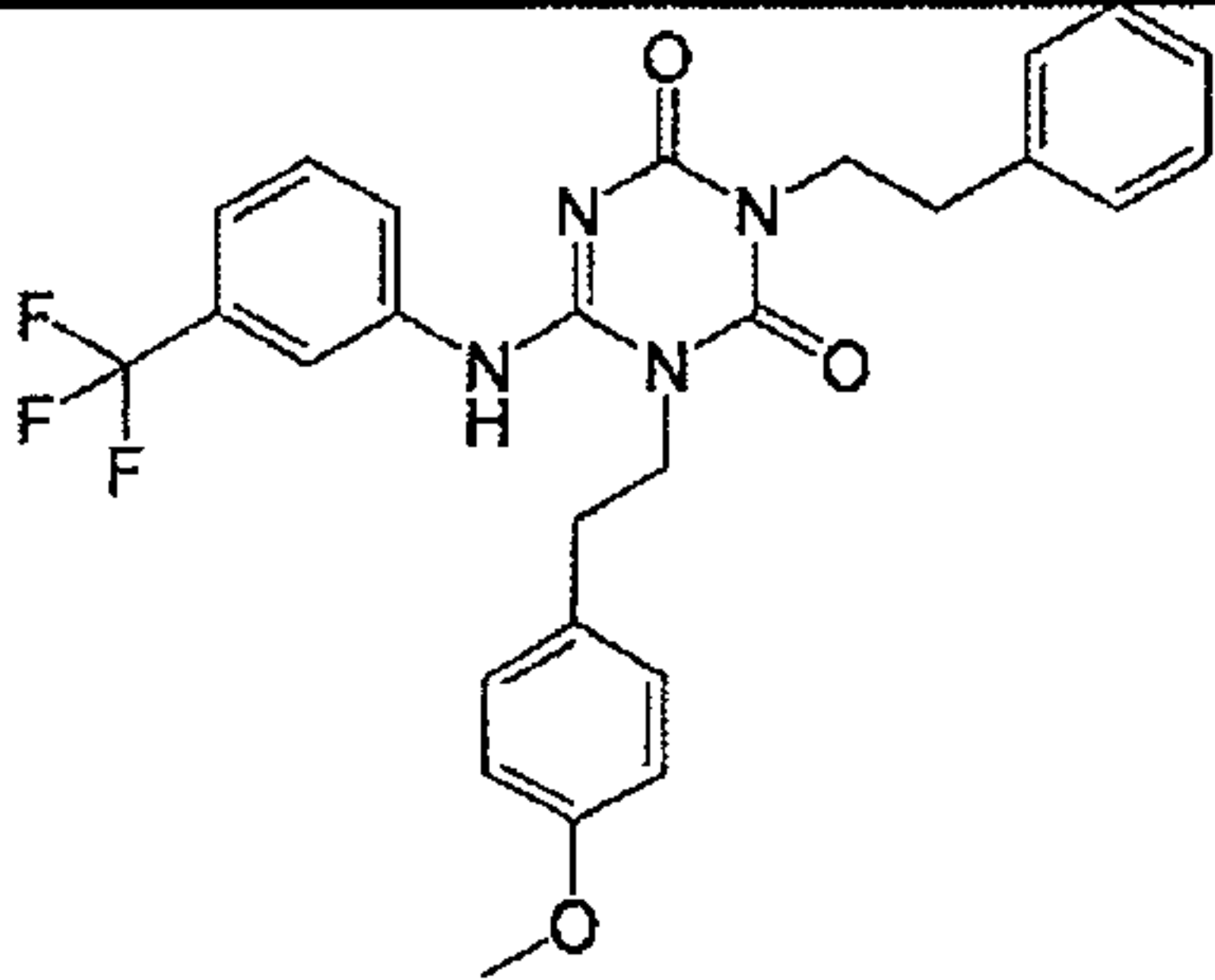
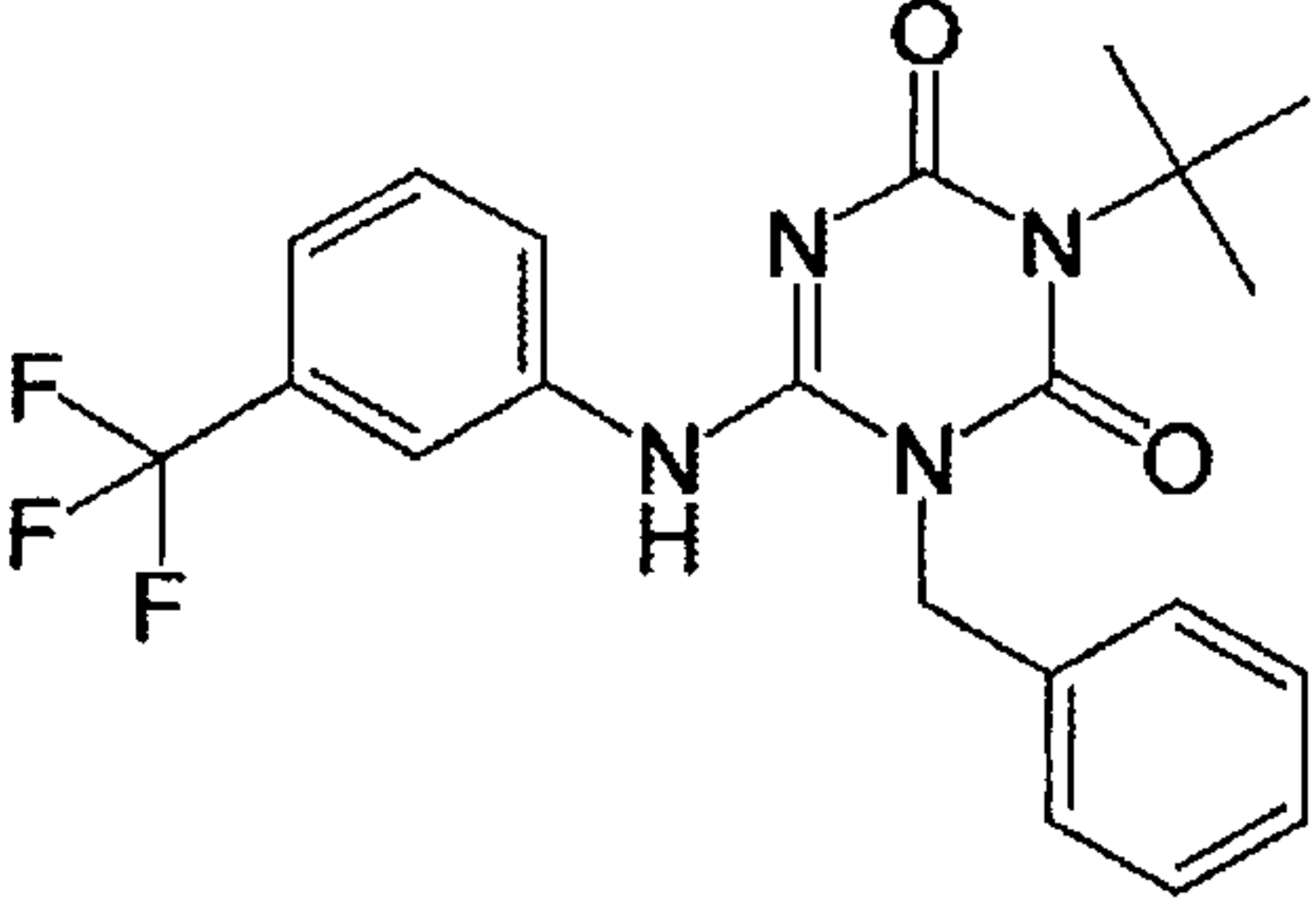
[Table 20]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0081	2.85	497	4
	I-0082	3.85	552	4
	I-0083	3.22	551	4
	I-0084	3.23	551	4
	I-0085	2.48	497	4

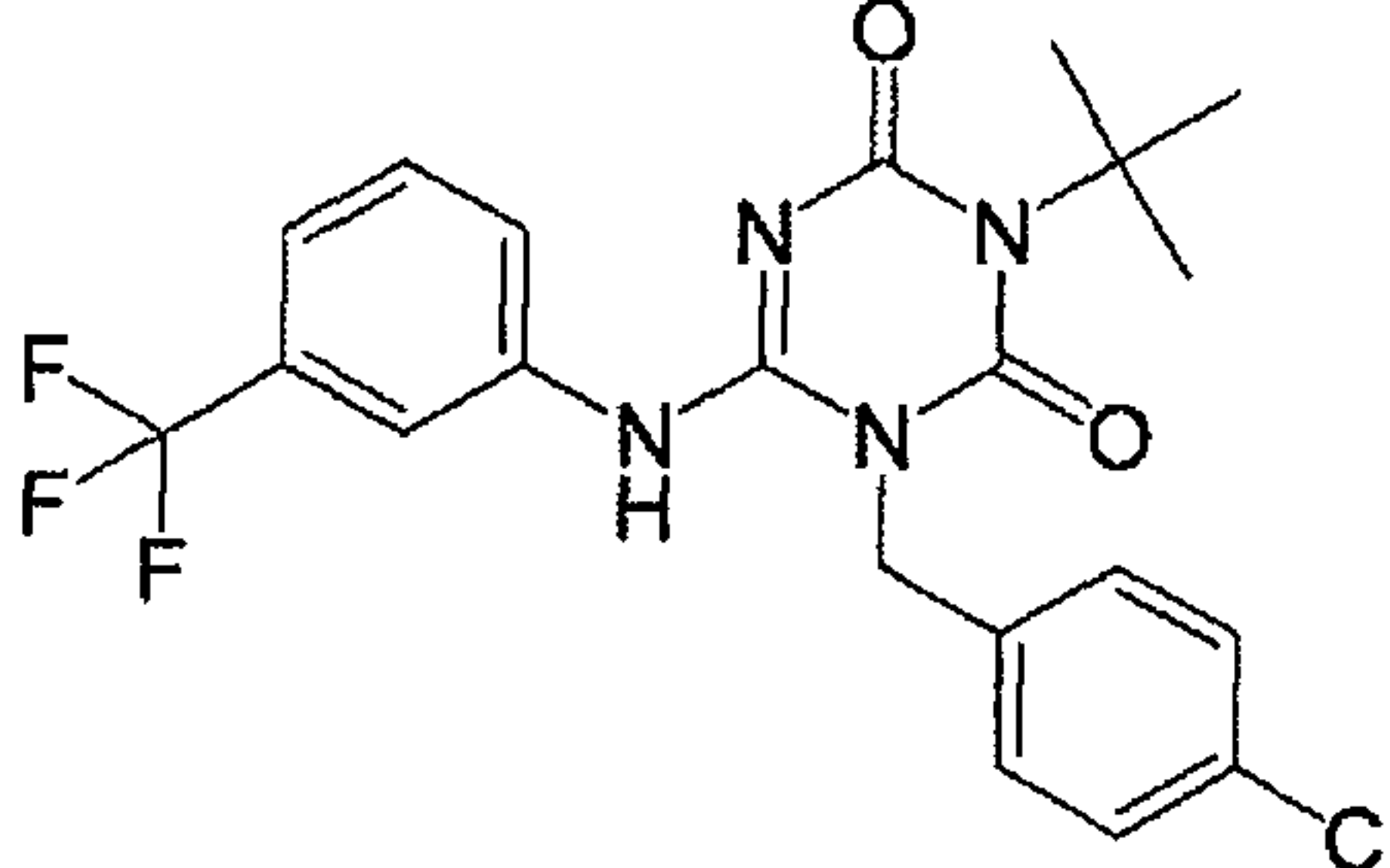
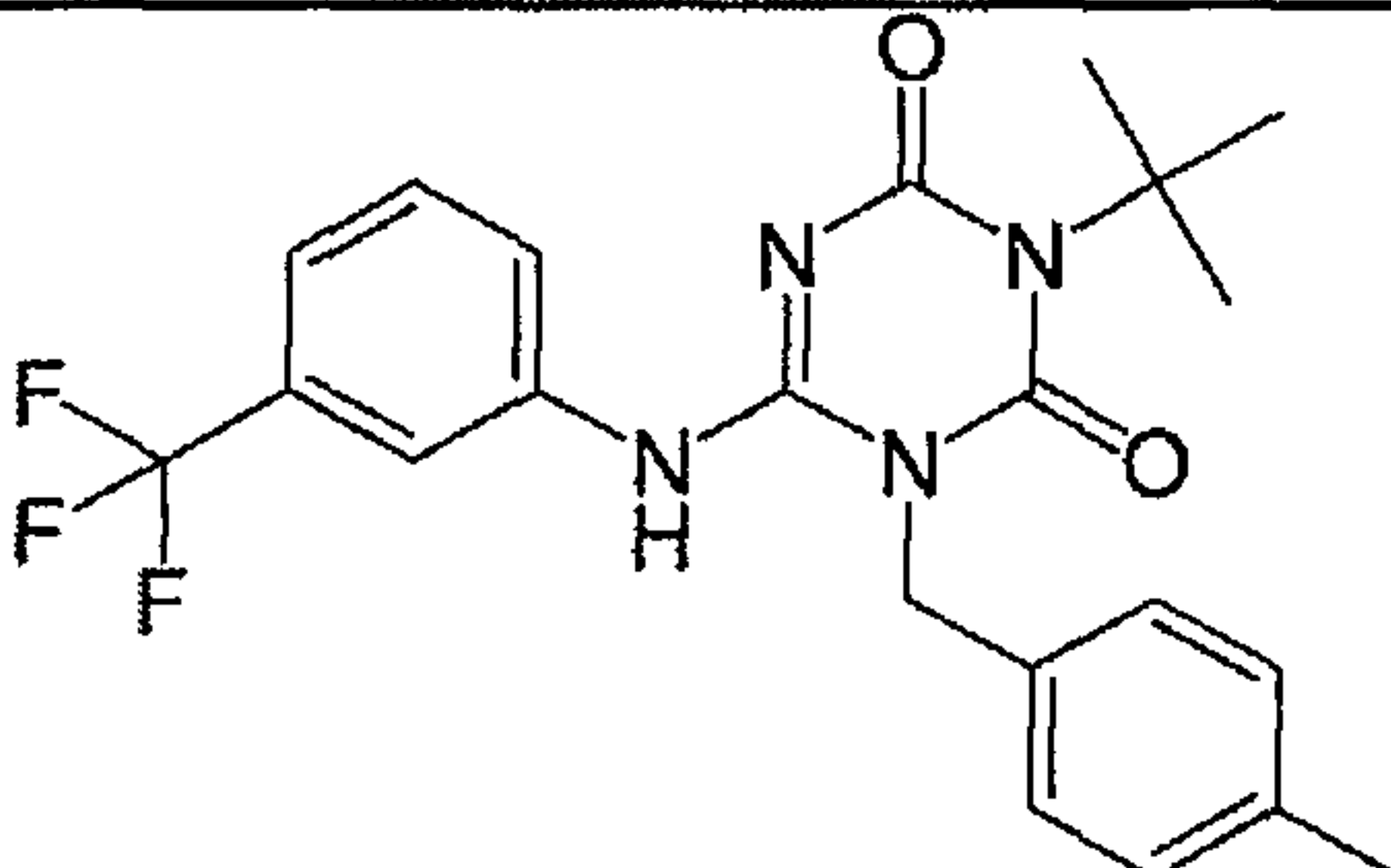
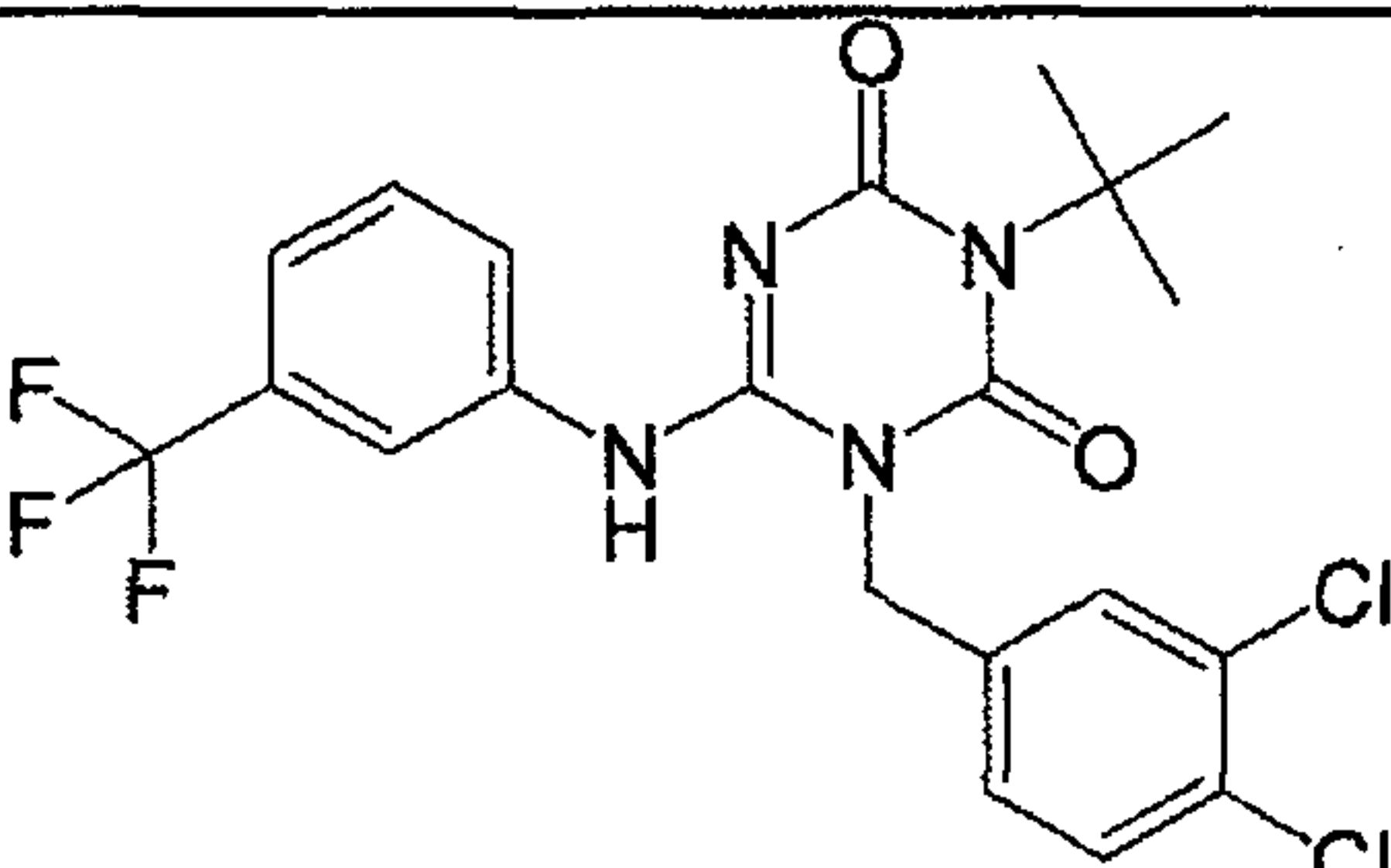
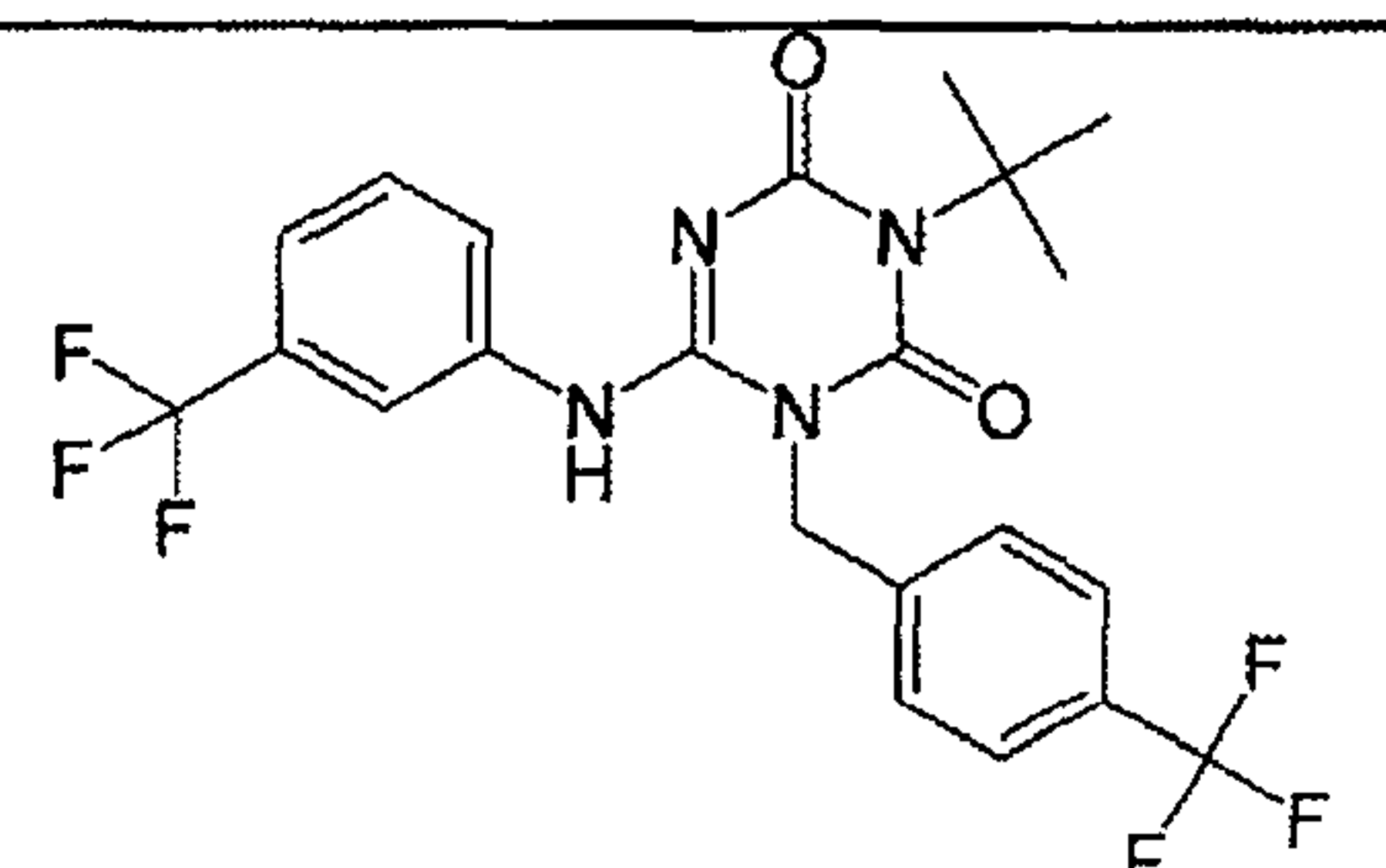
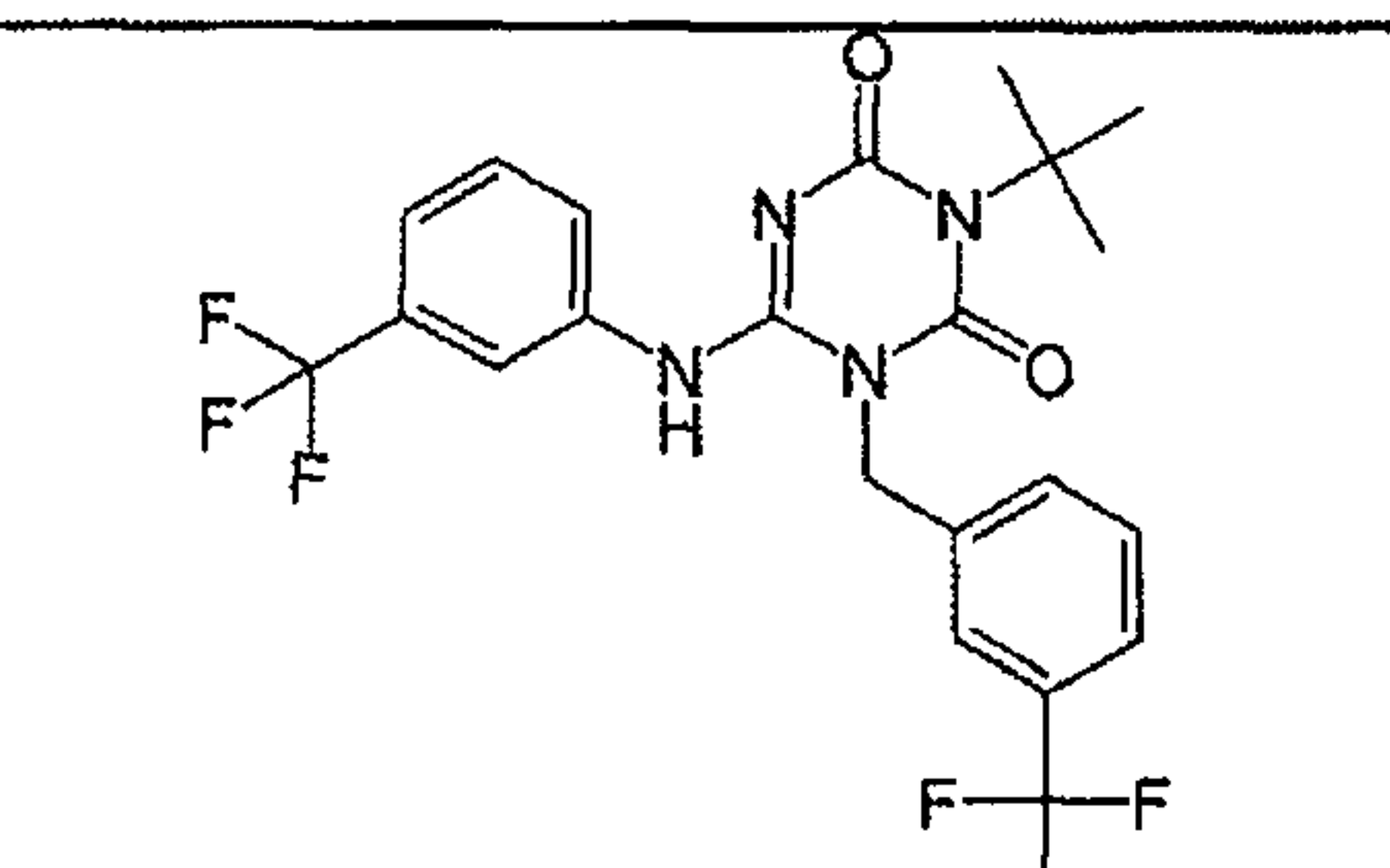
[Table 21]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0086	2.29	527	4
	I-0087	2.75	467	4
	I-0088	3.54	501	4
	I-0089	3.19	481	4
	I-0090	4.15	536	4

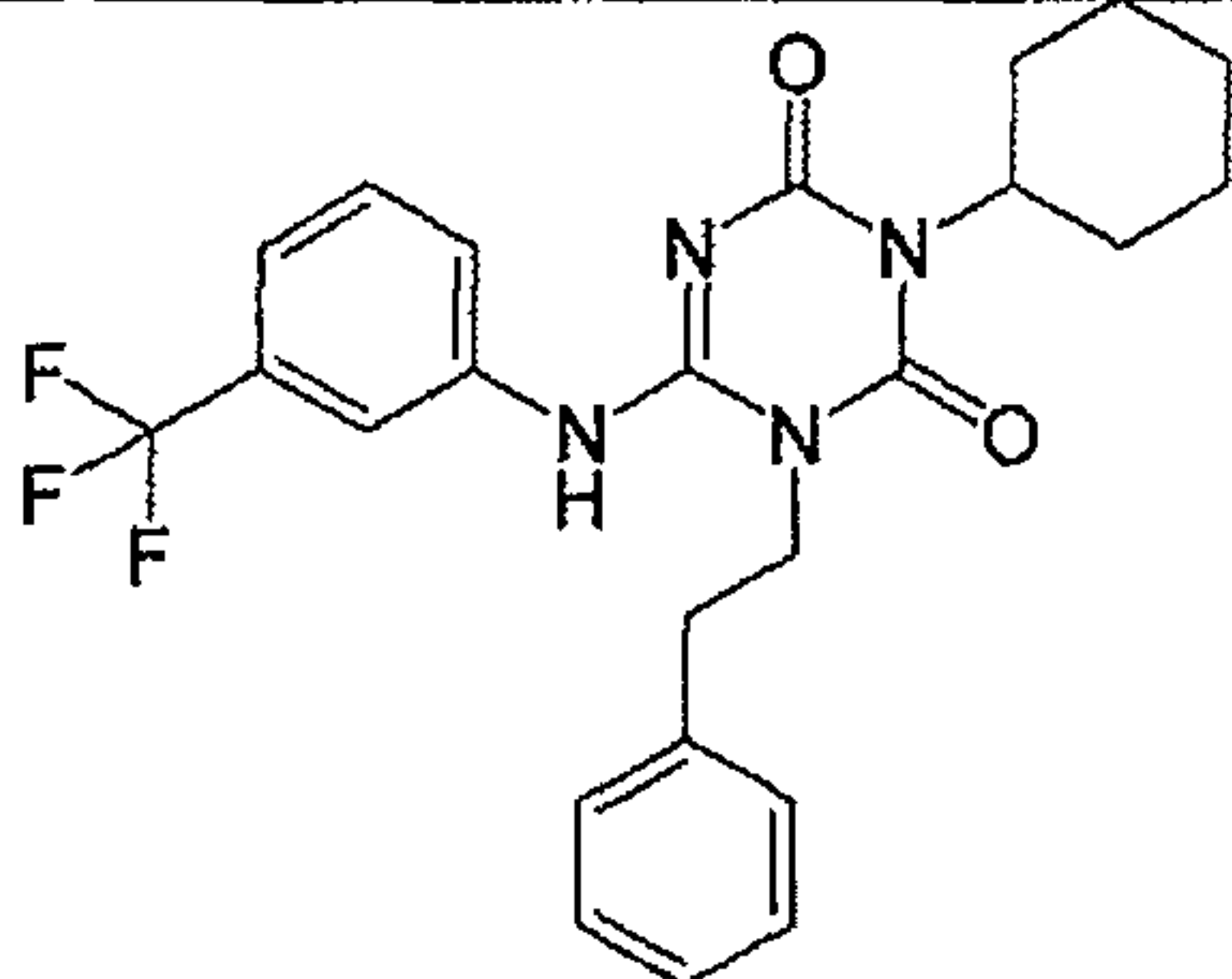
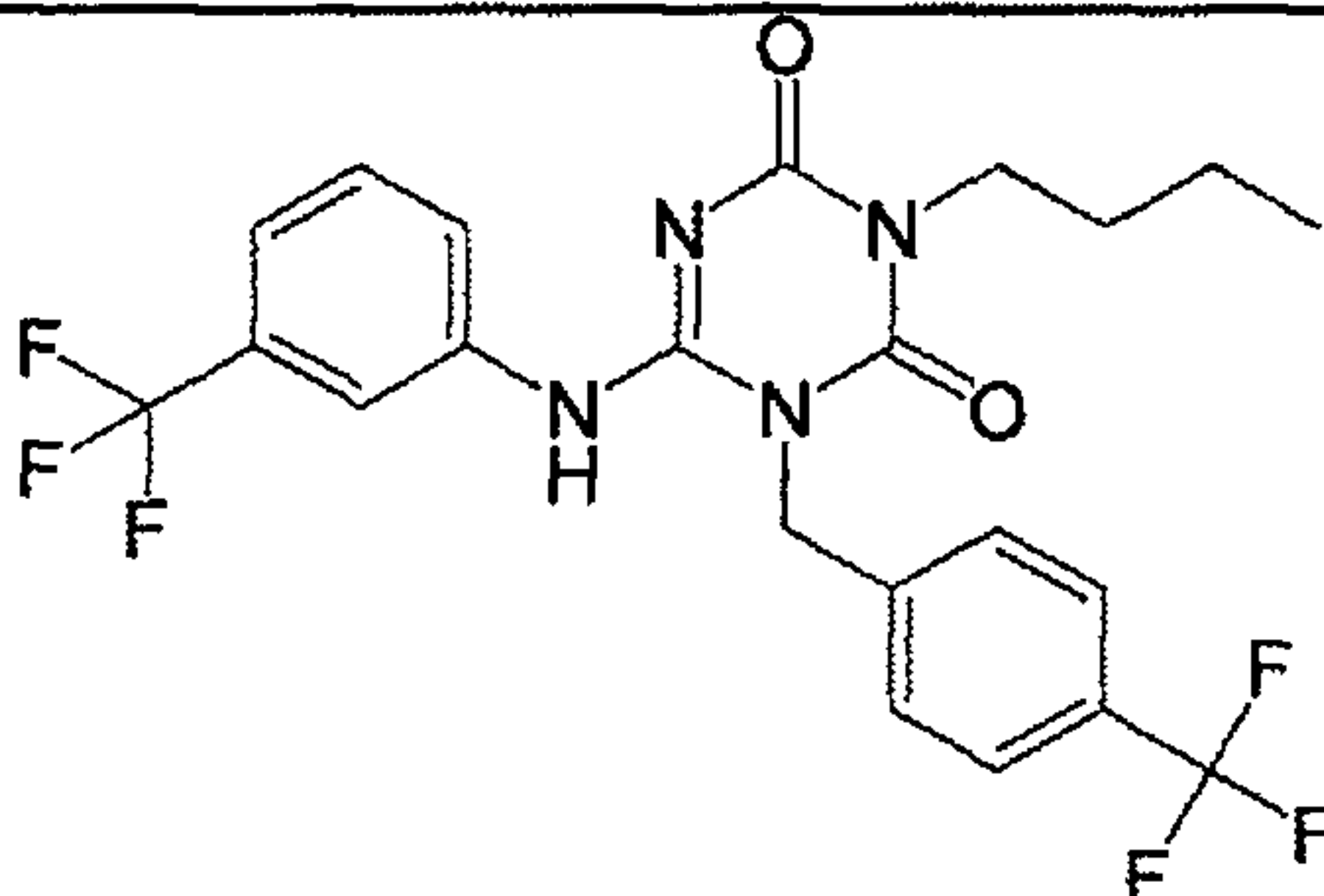
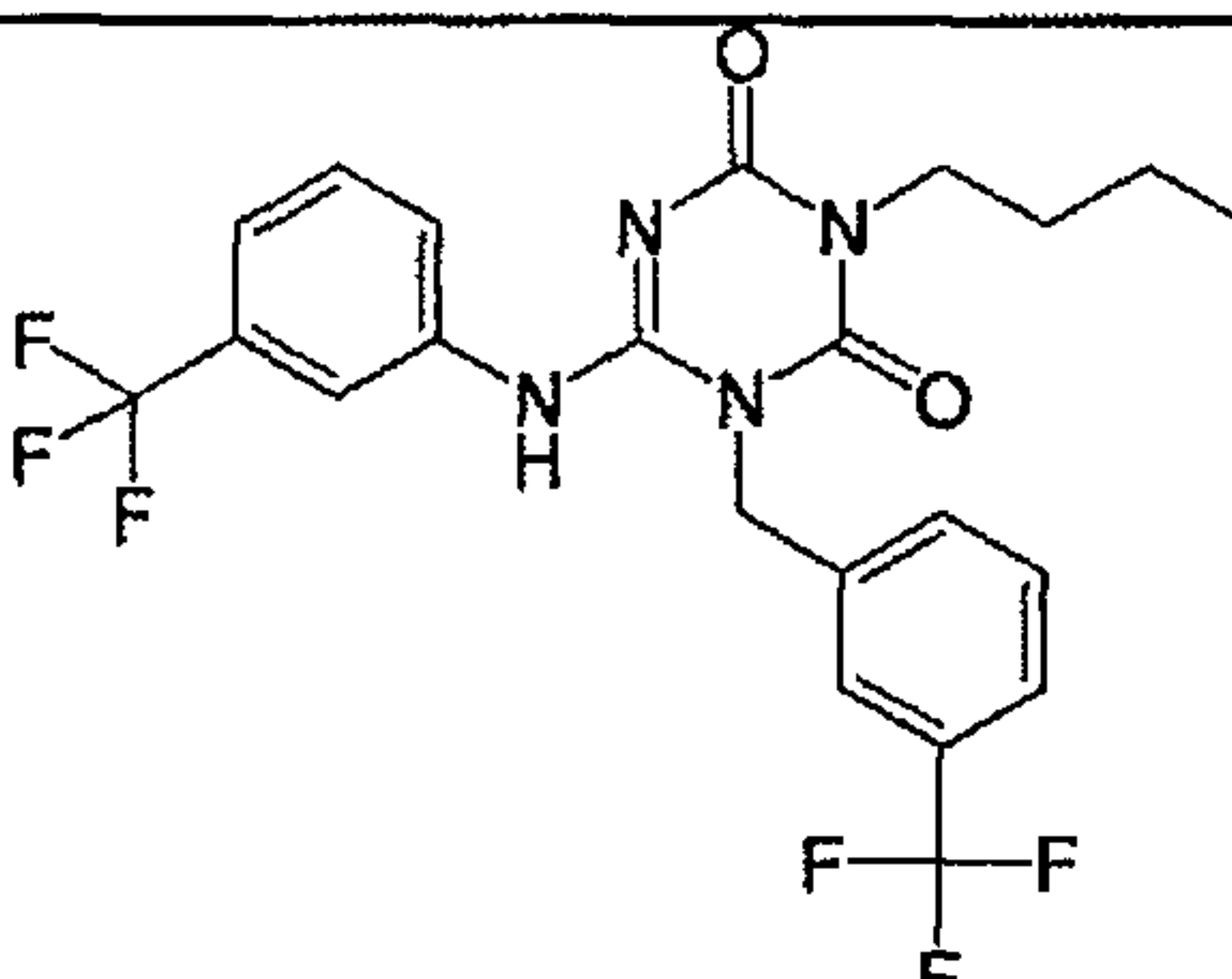
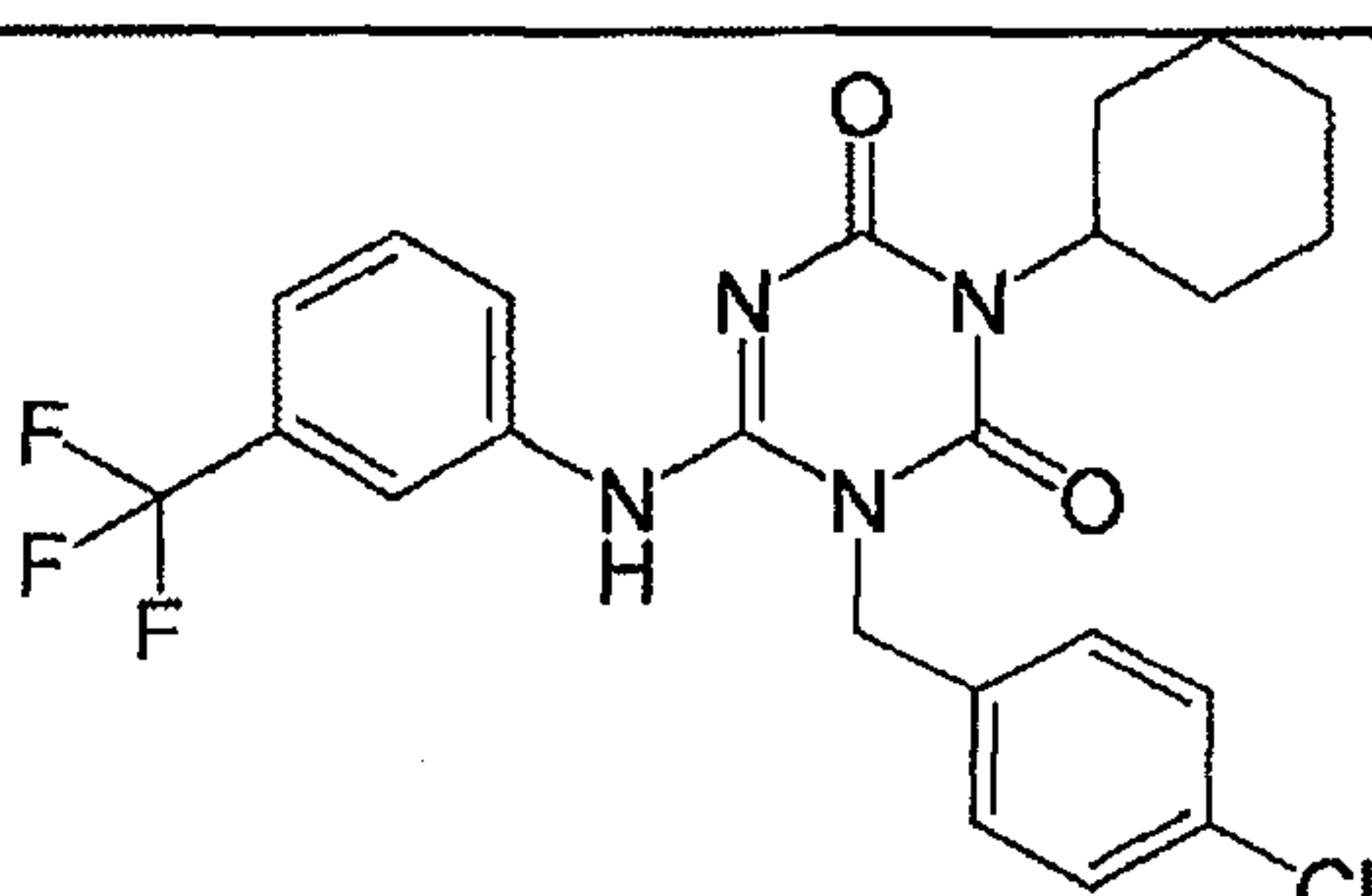
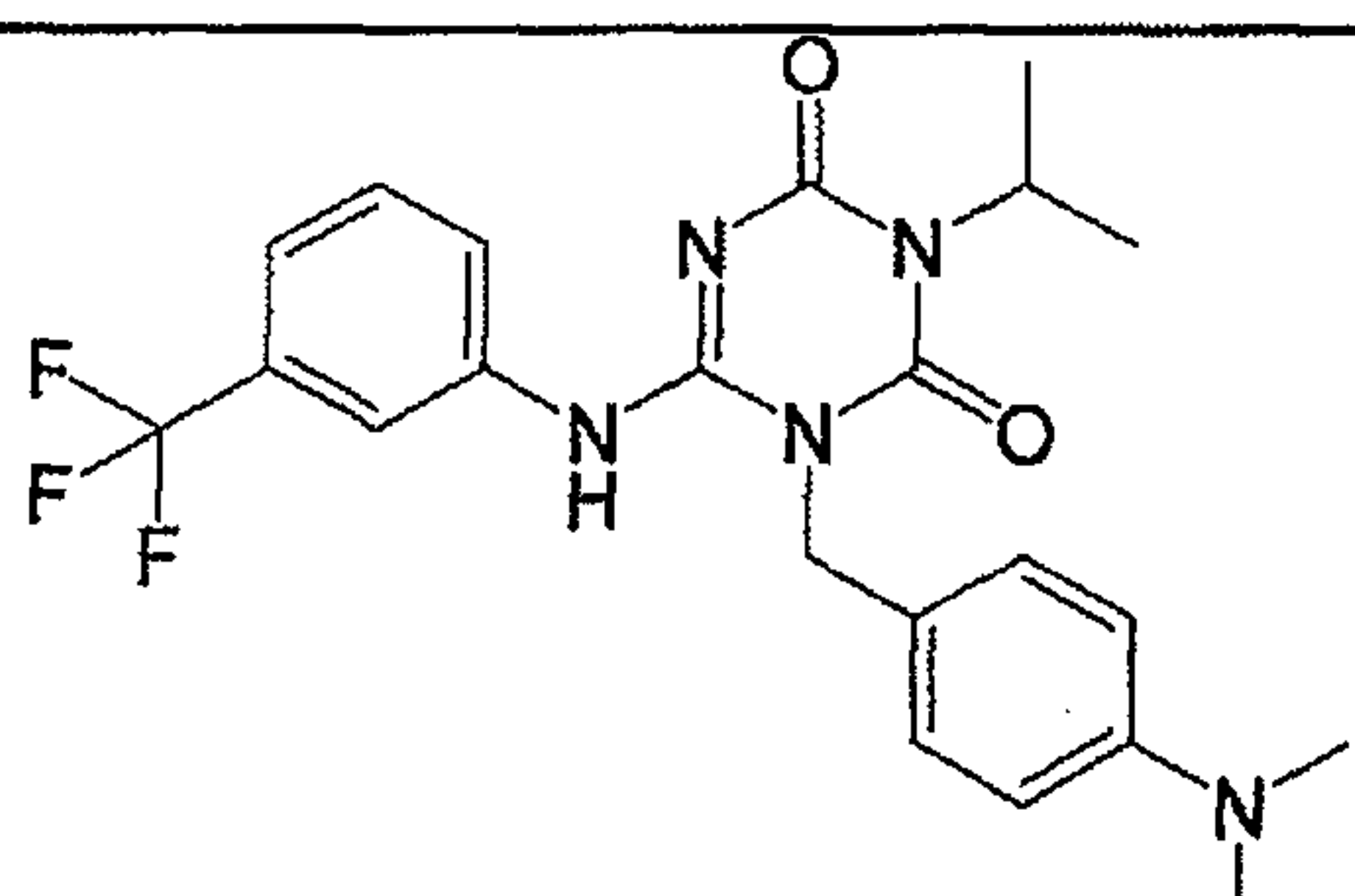
[Table 22]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0091	3.49	535	4
	I-0092	3.57	535	4
	I-0093	3.03	481	4
	I-0094	2.79	511	4
	I-0095	3.58	419	4

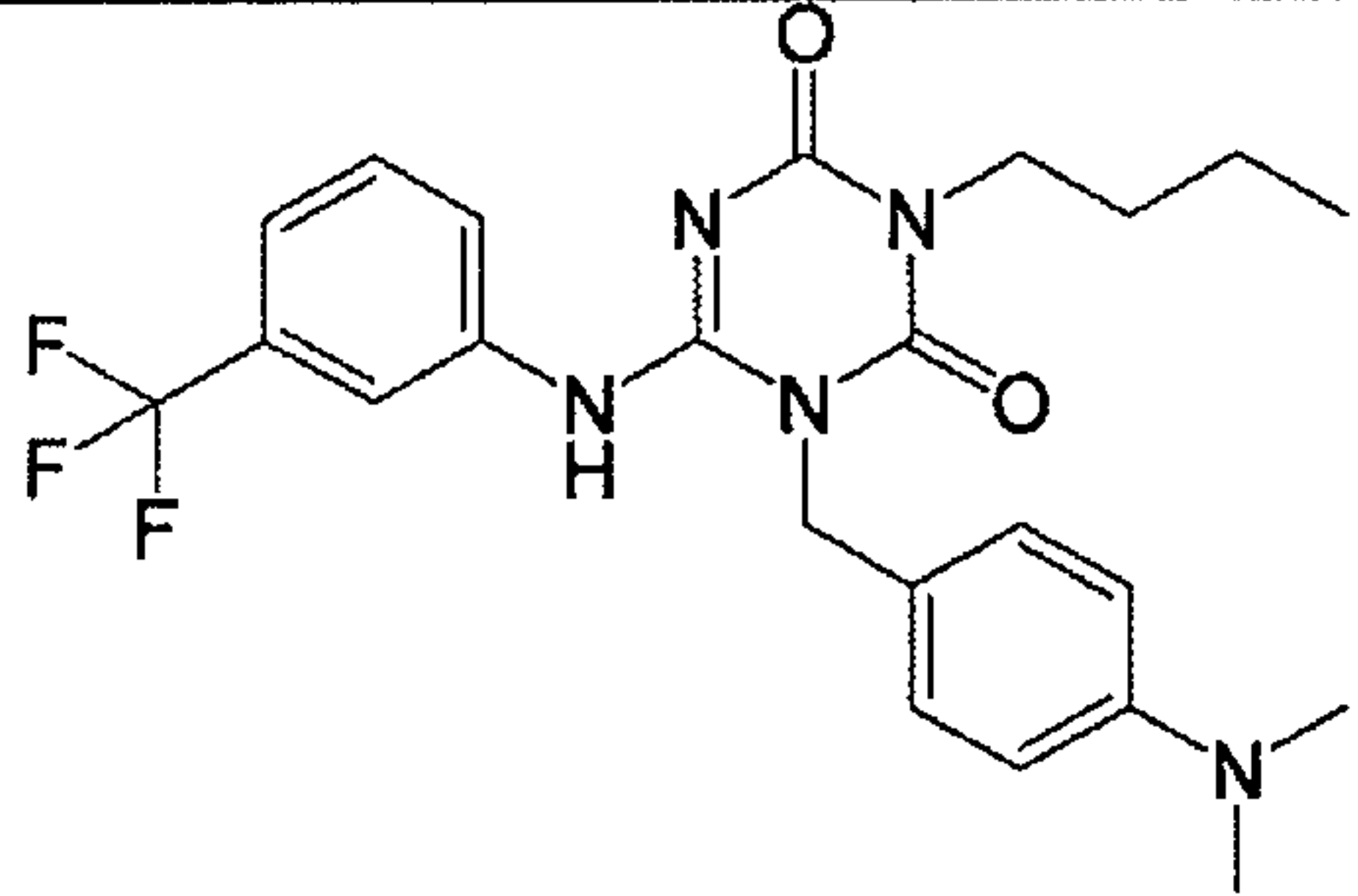
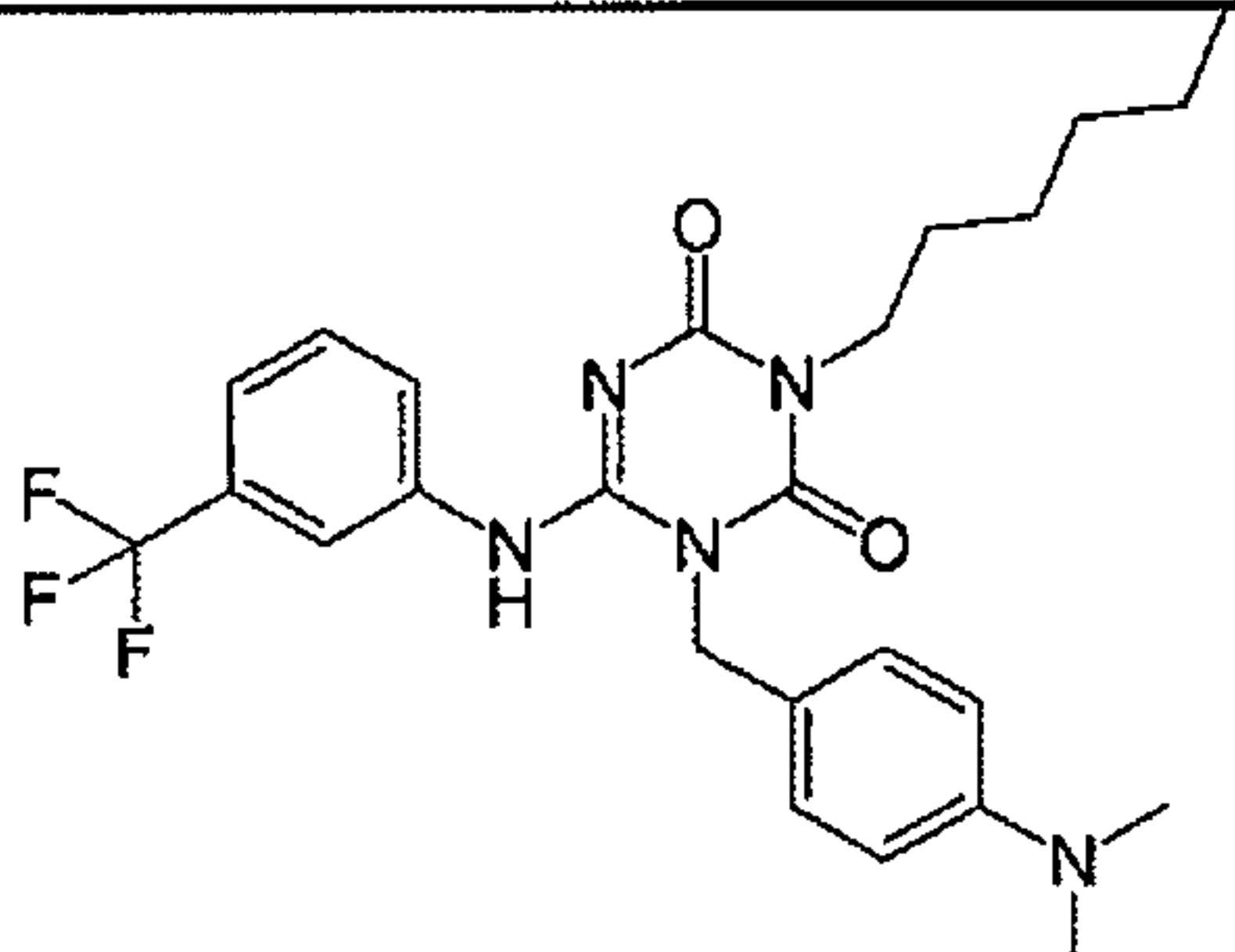
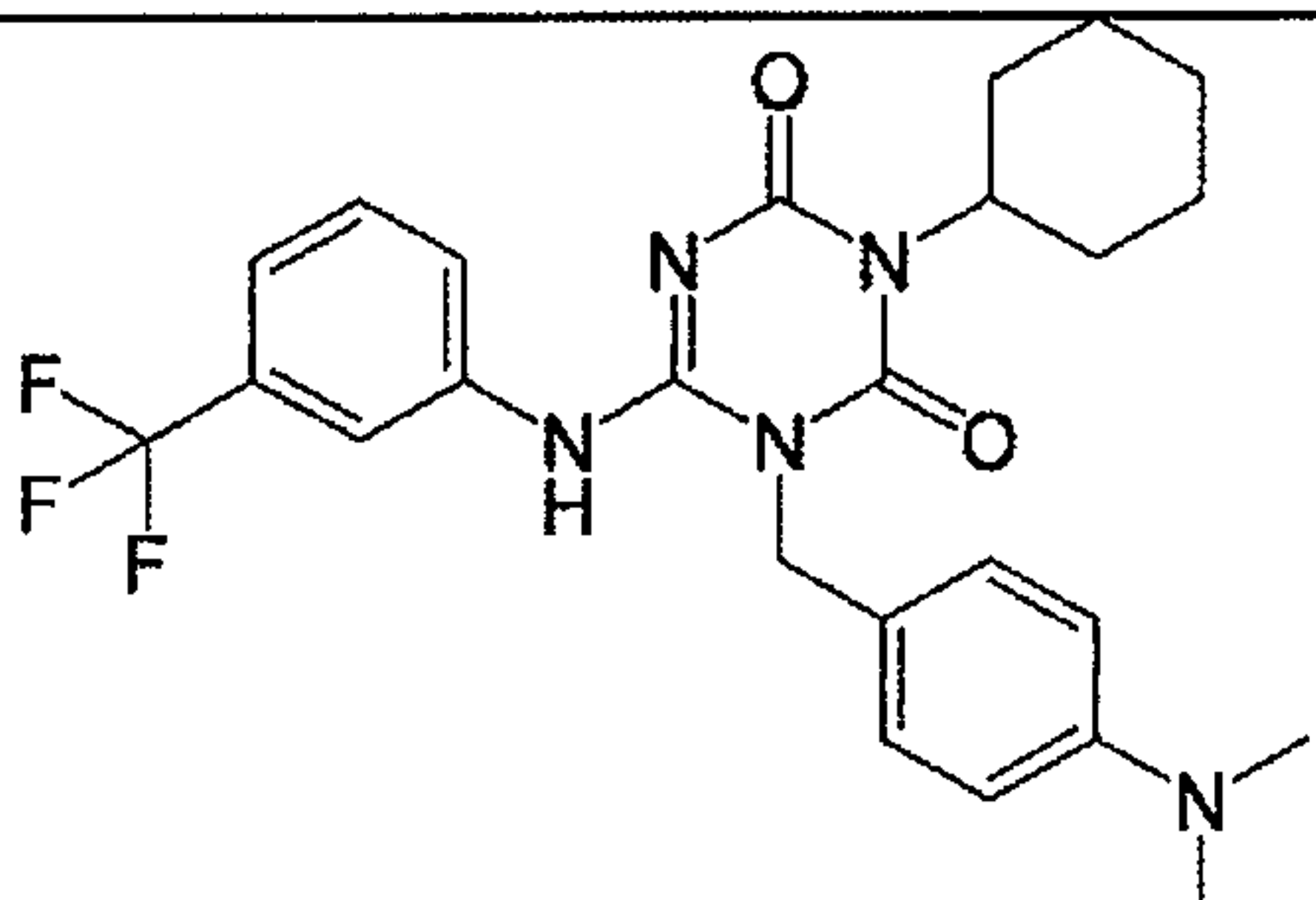
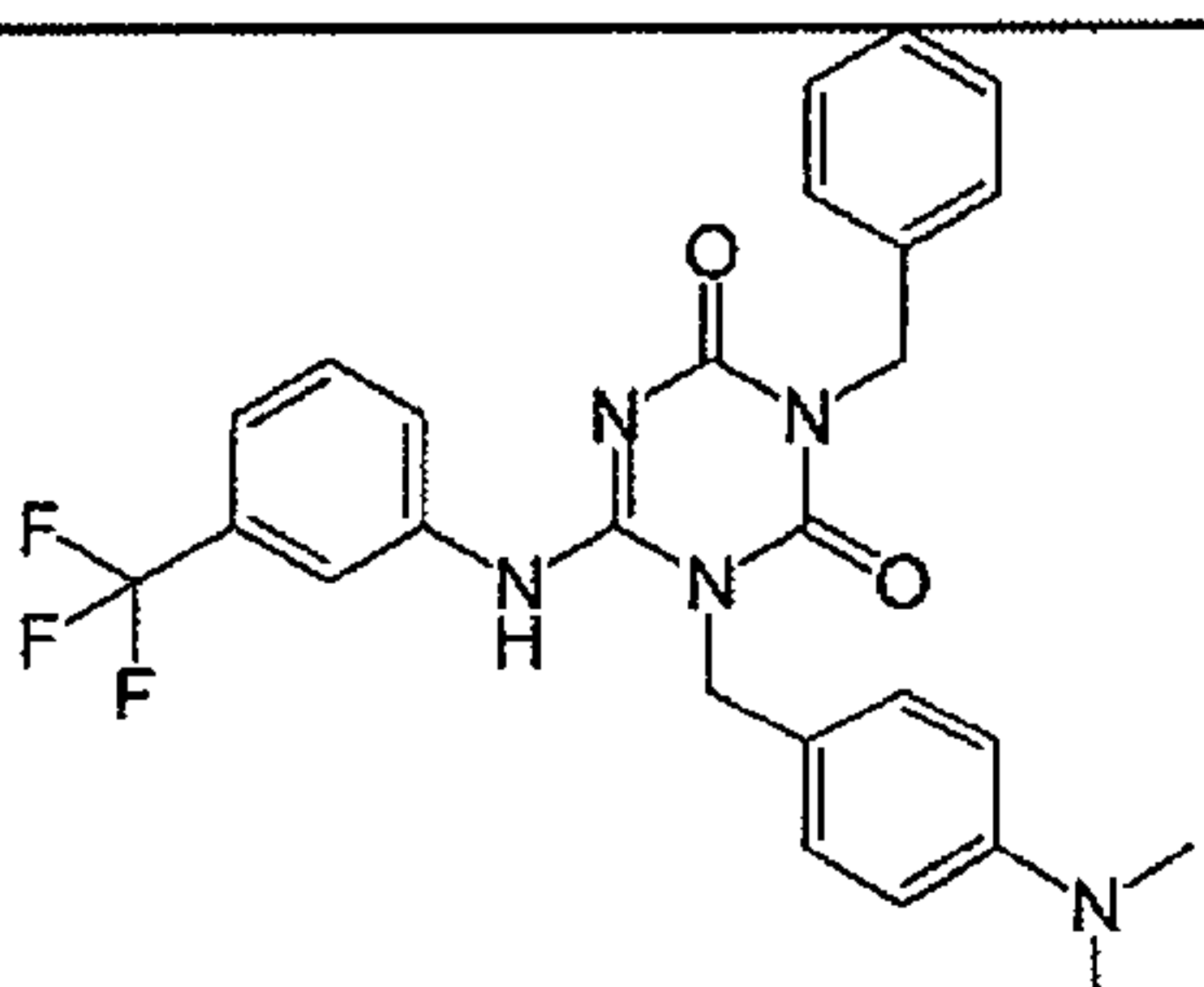
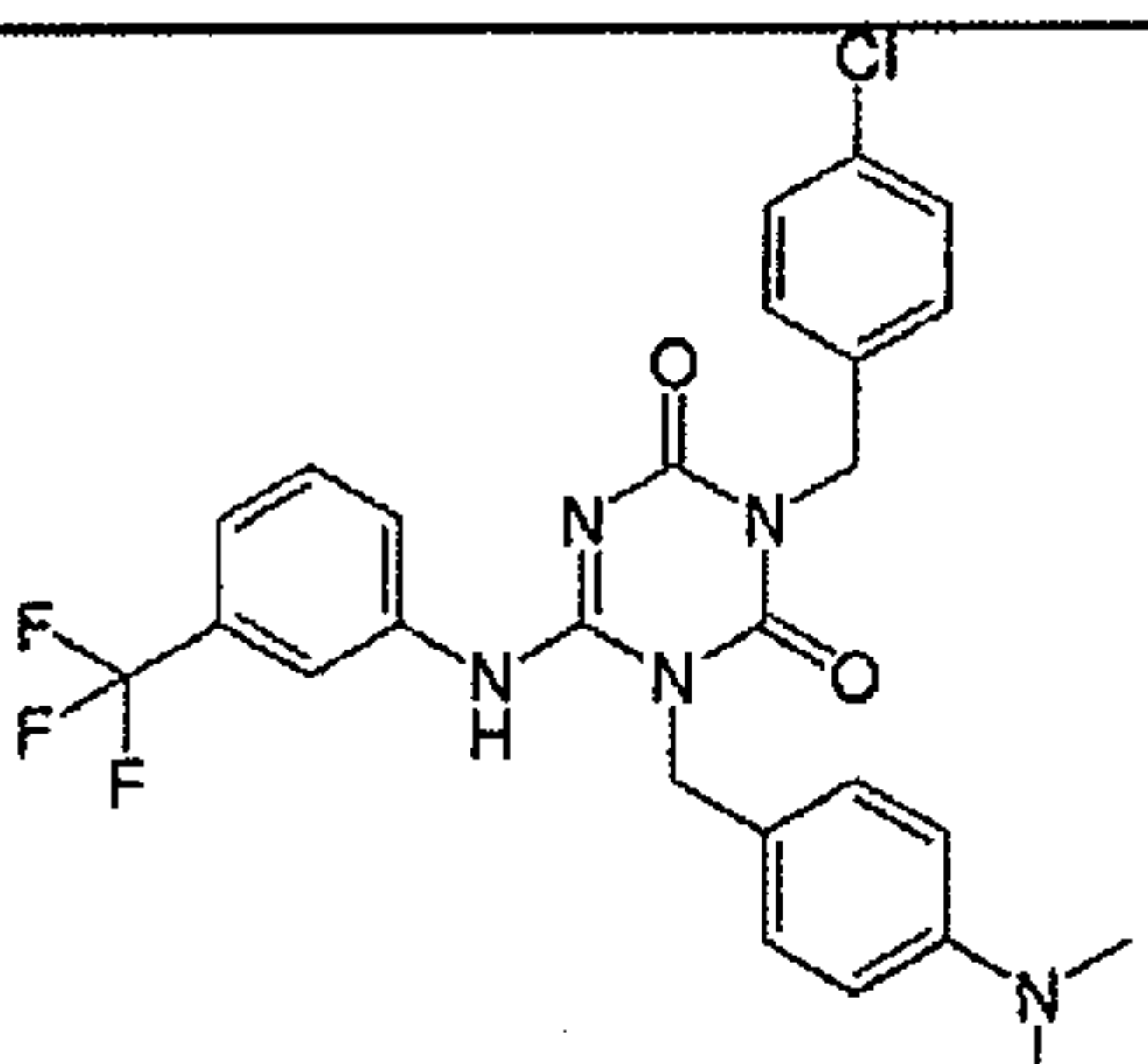
[Table 23]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0096	4.22	453	4
	I-0097	4.21	433	4
	I-0098	4.03	488	4
	I-0099	3.38	487	4
	I-0100	4.24	487	4

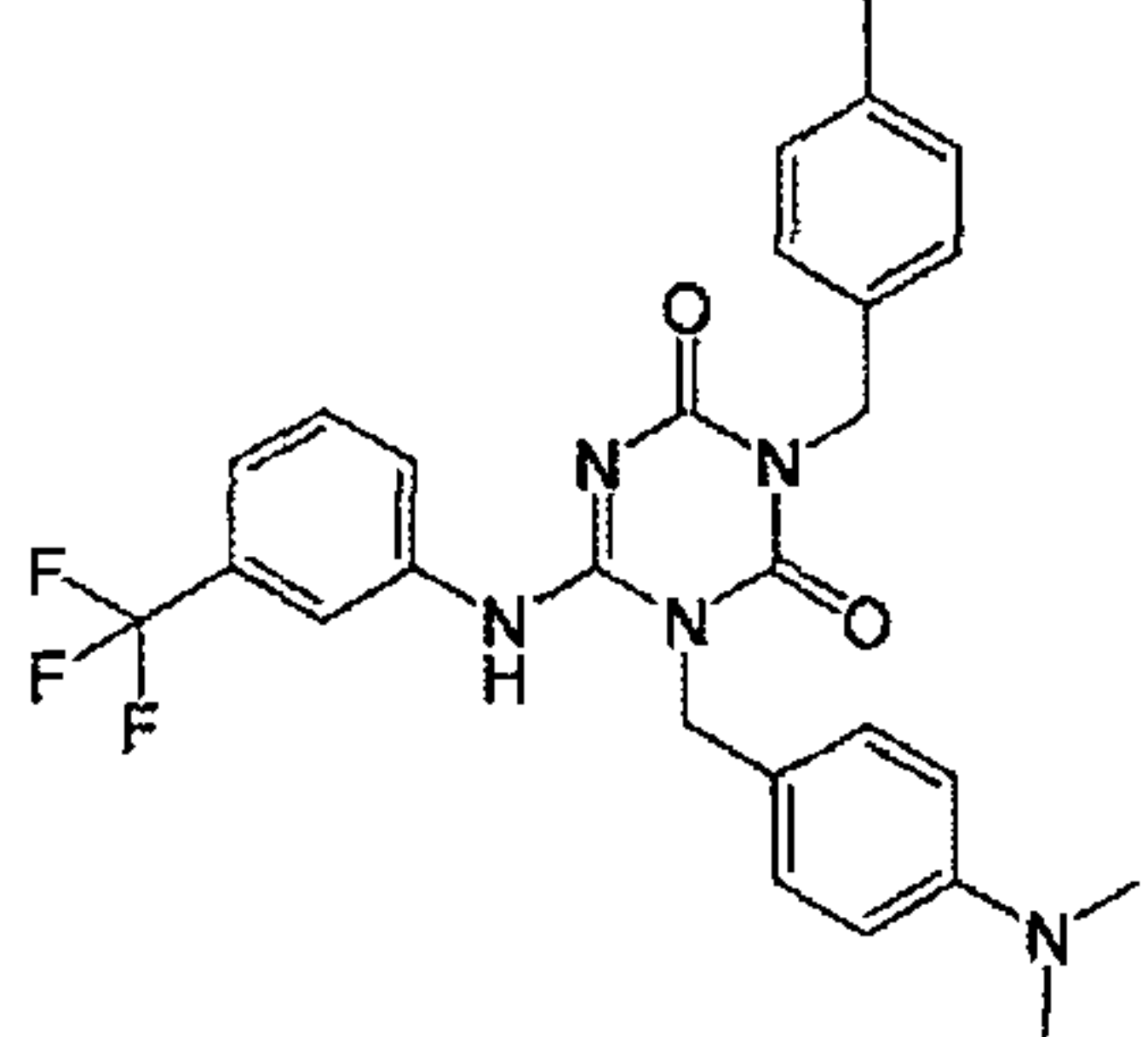
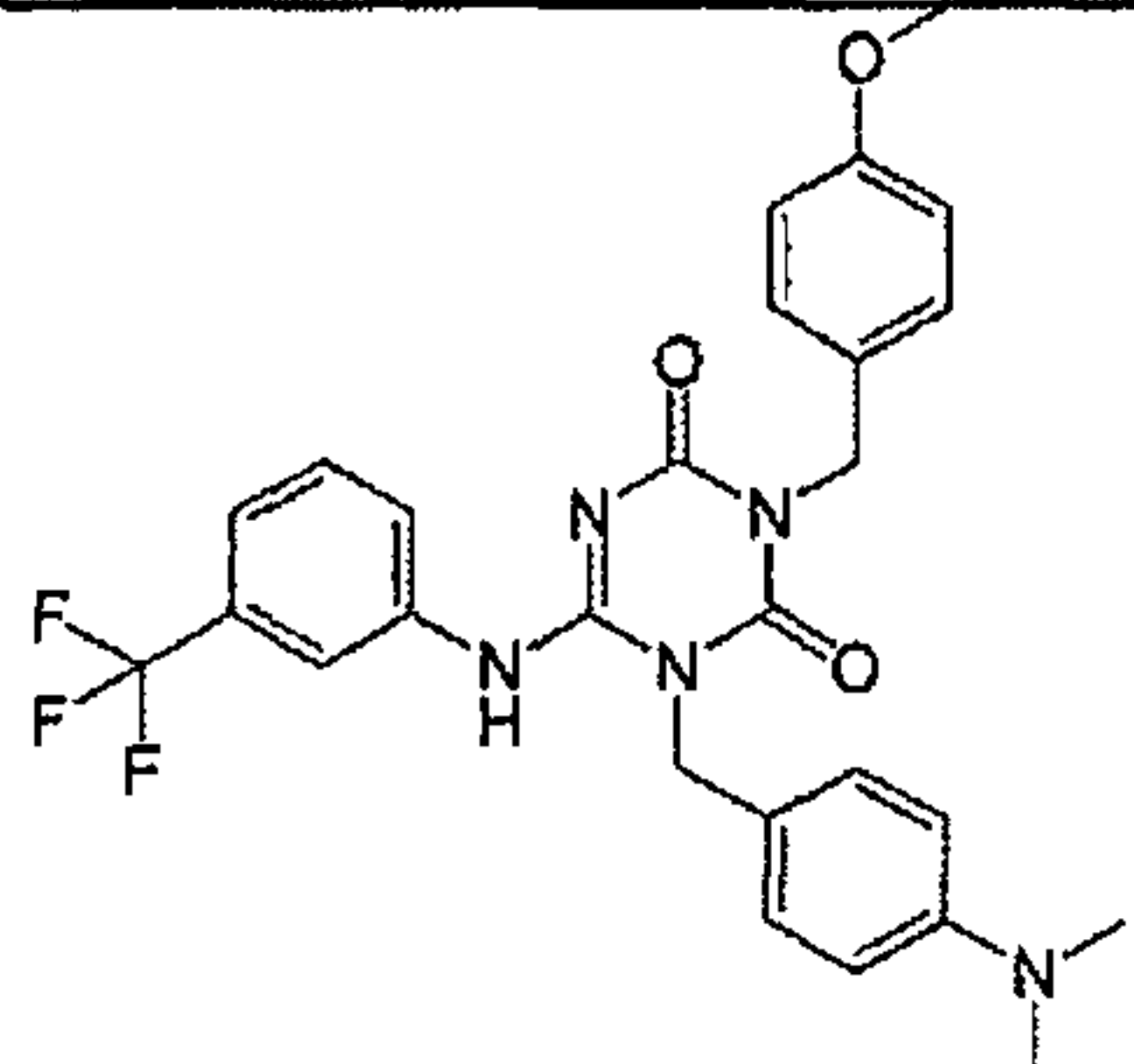
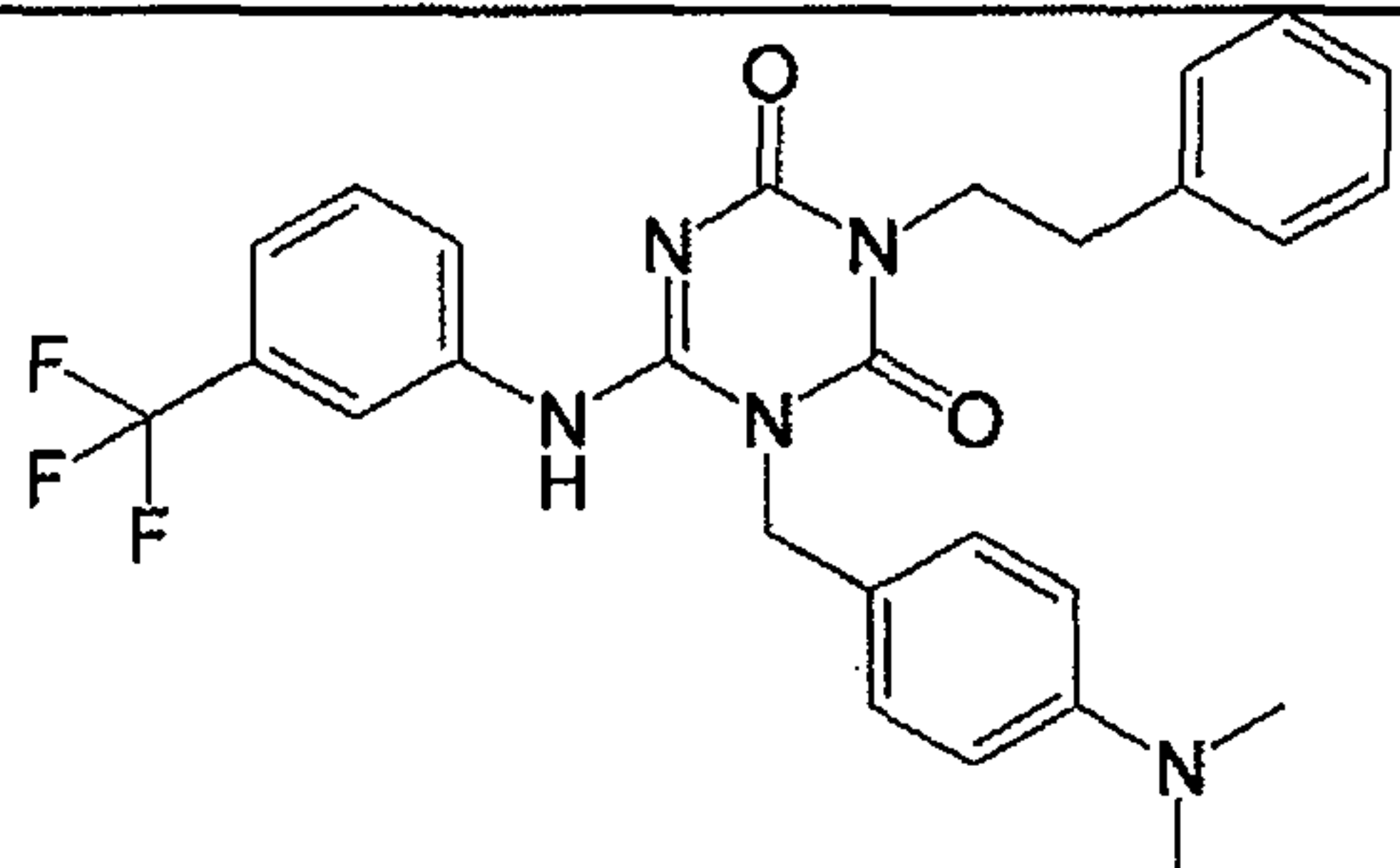
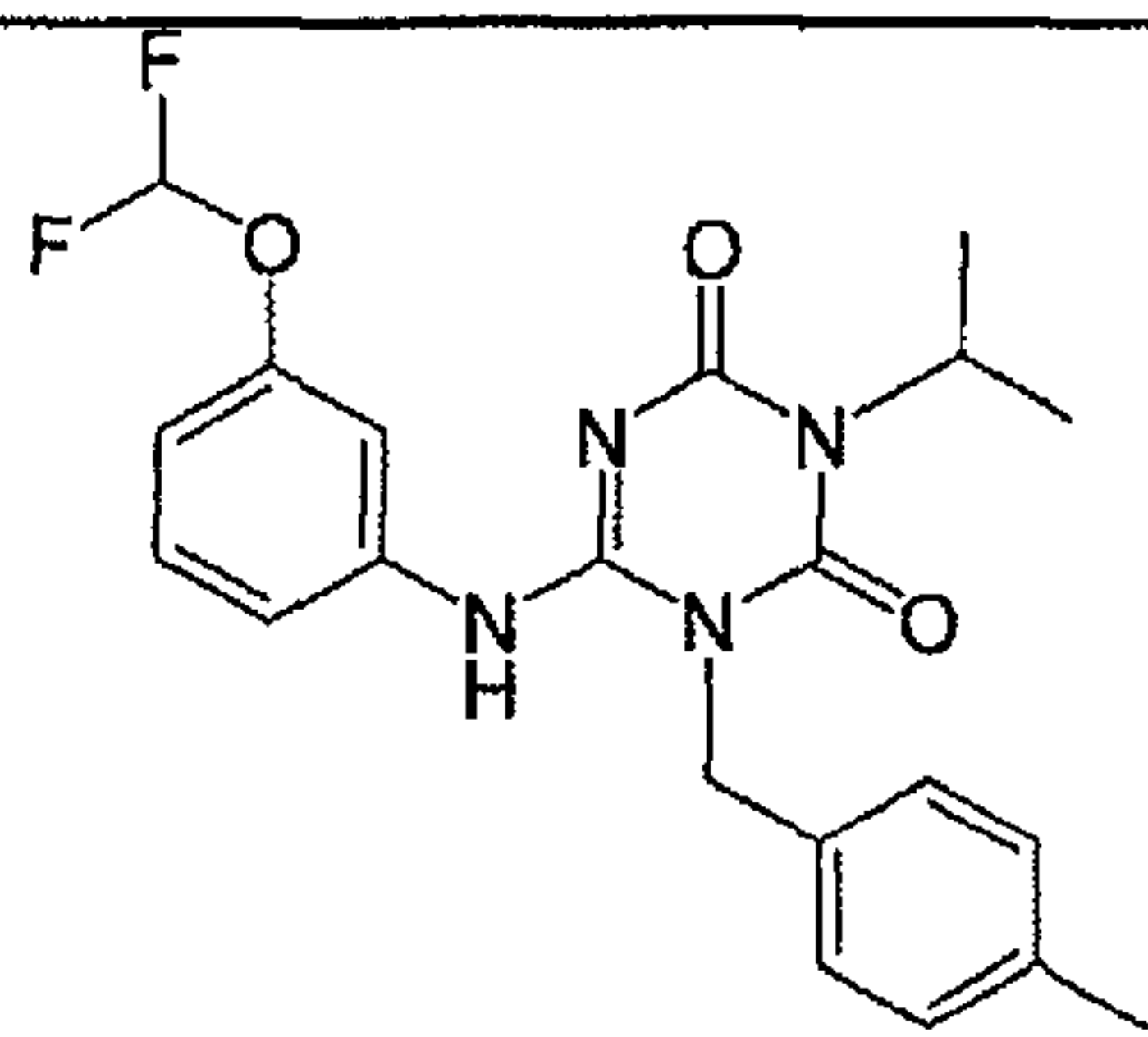
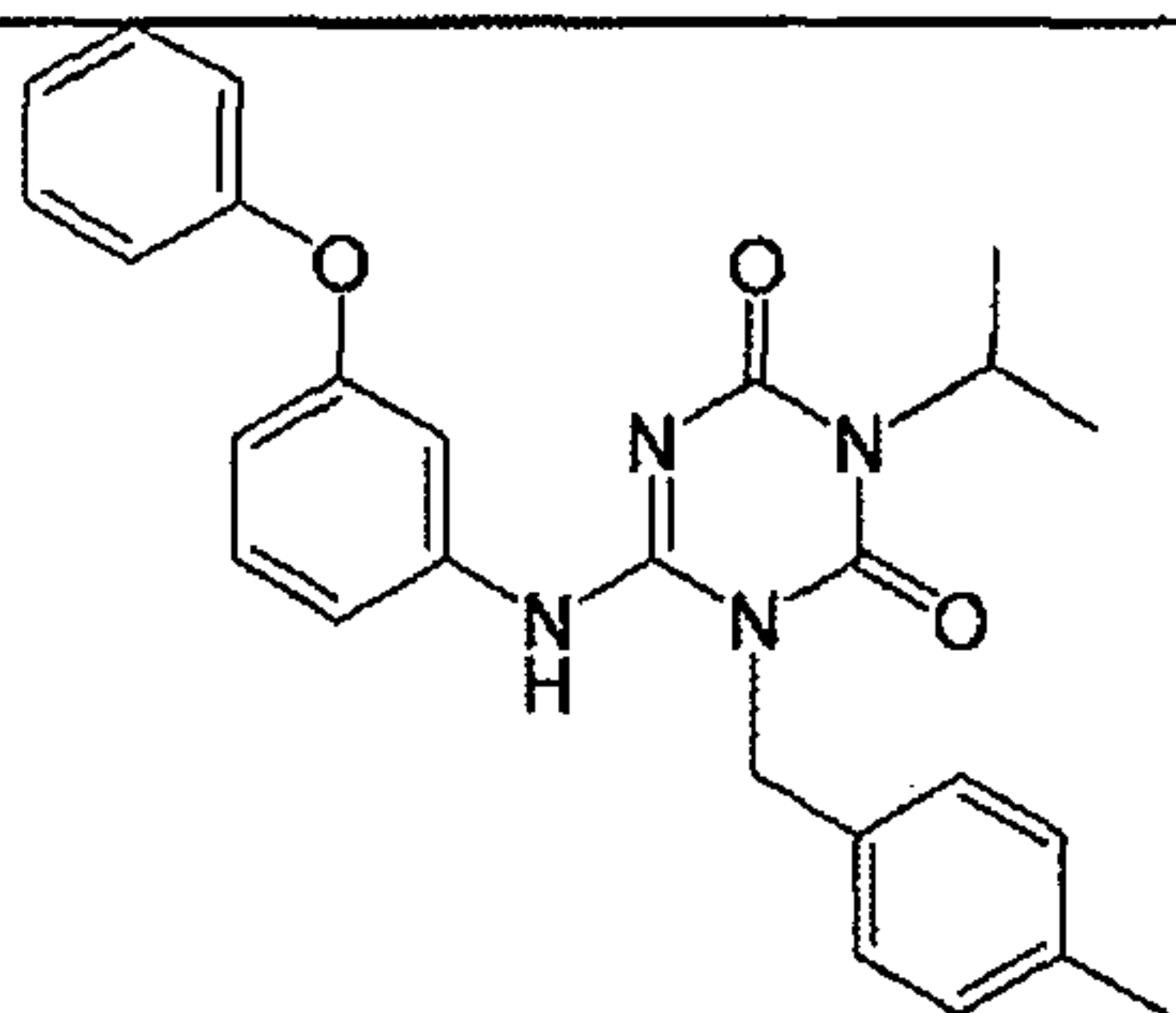
[Table 24]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0101	3.38	459	4
	I-0102	4.16	487	4
	I-0103	4.18	487	4
	I-0104	4.69	479	4
	I-0105	3.38	448	4

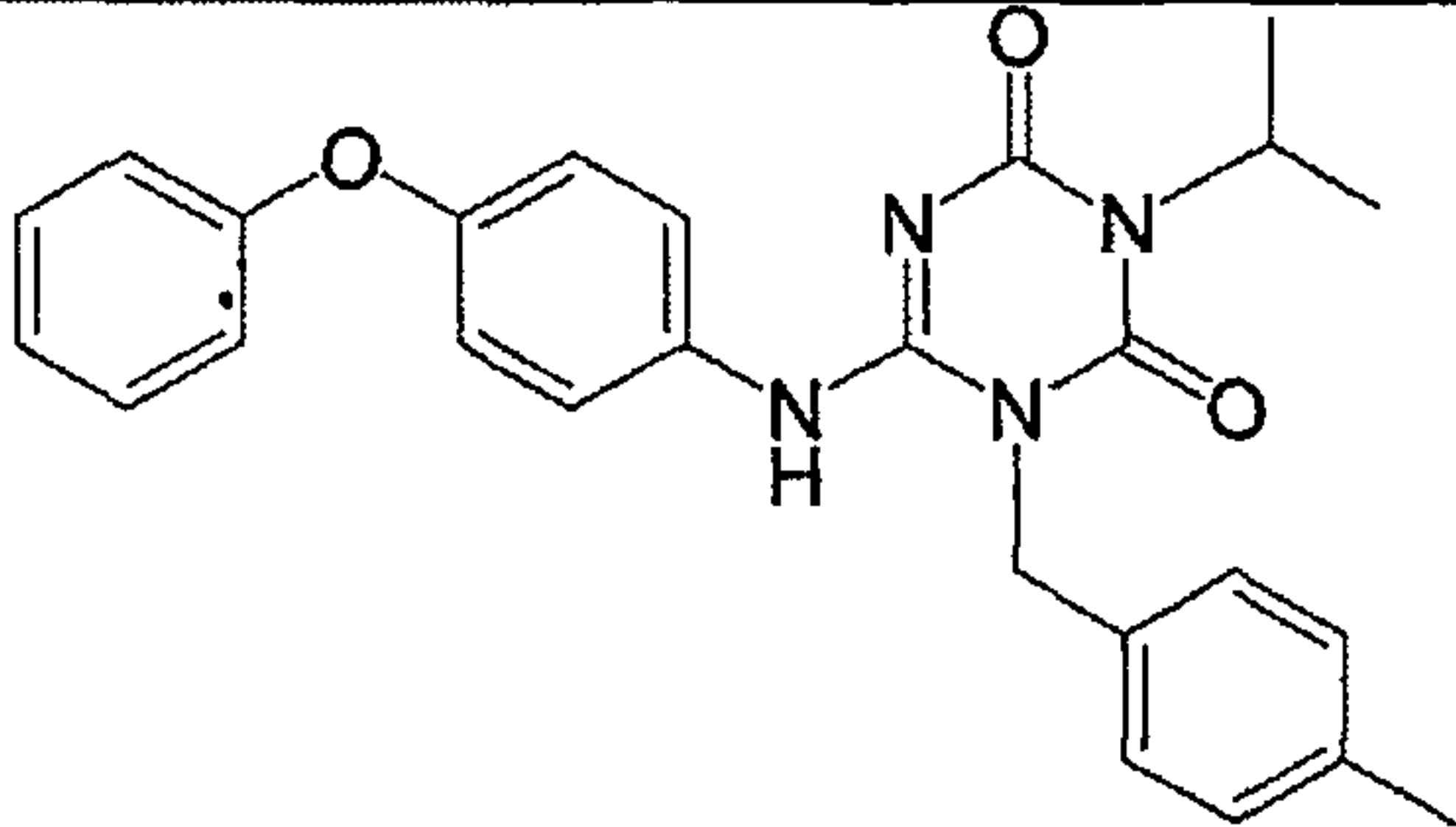
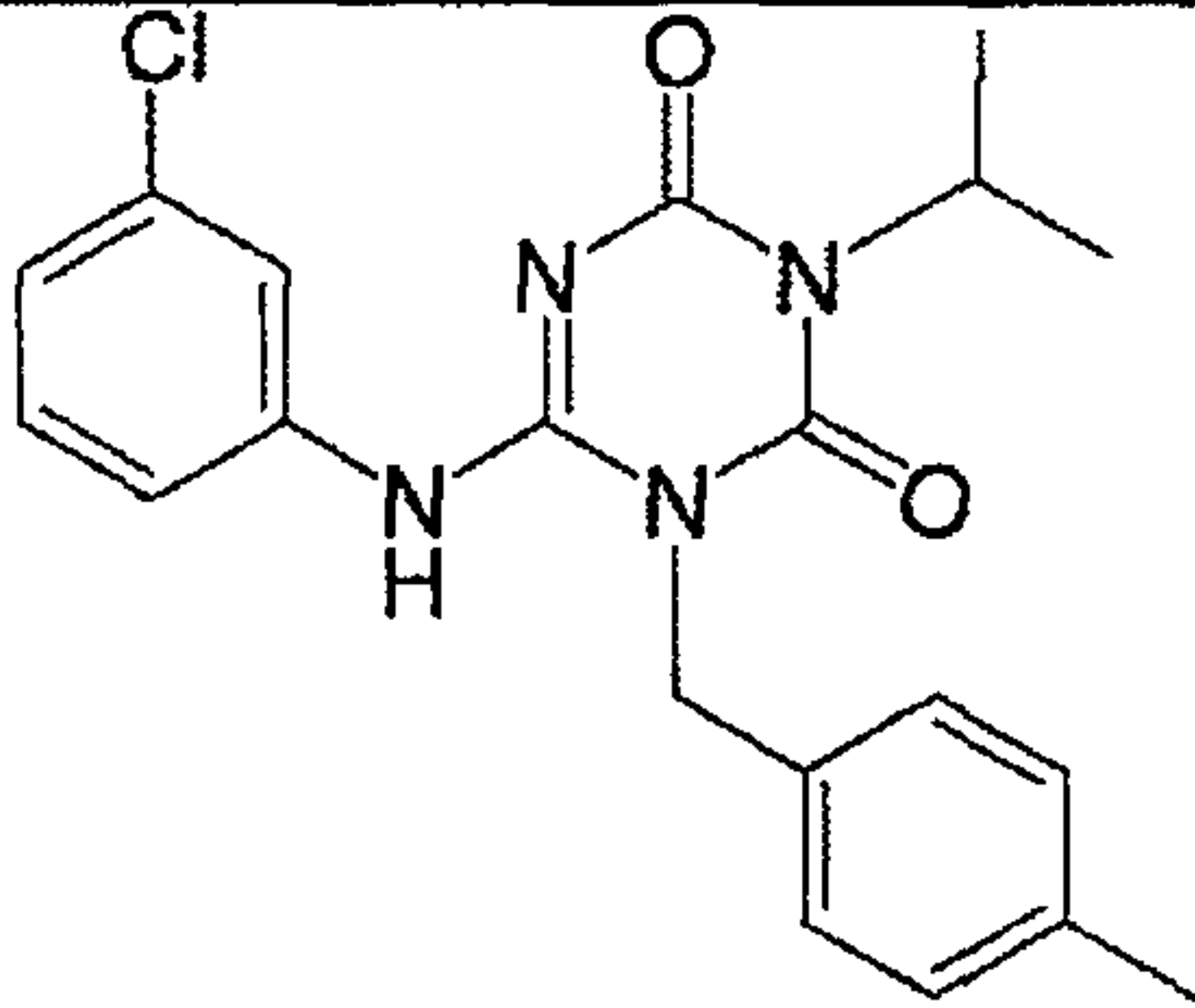
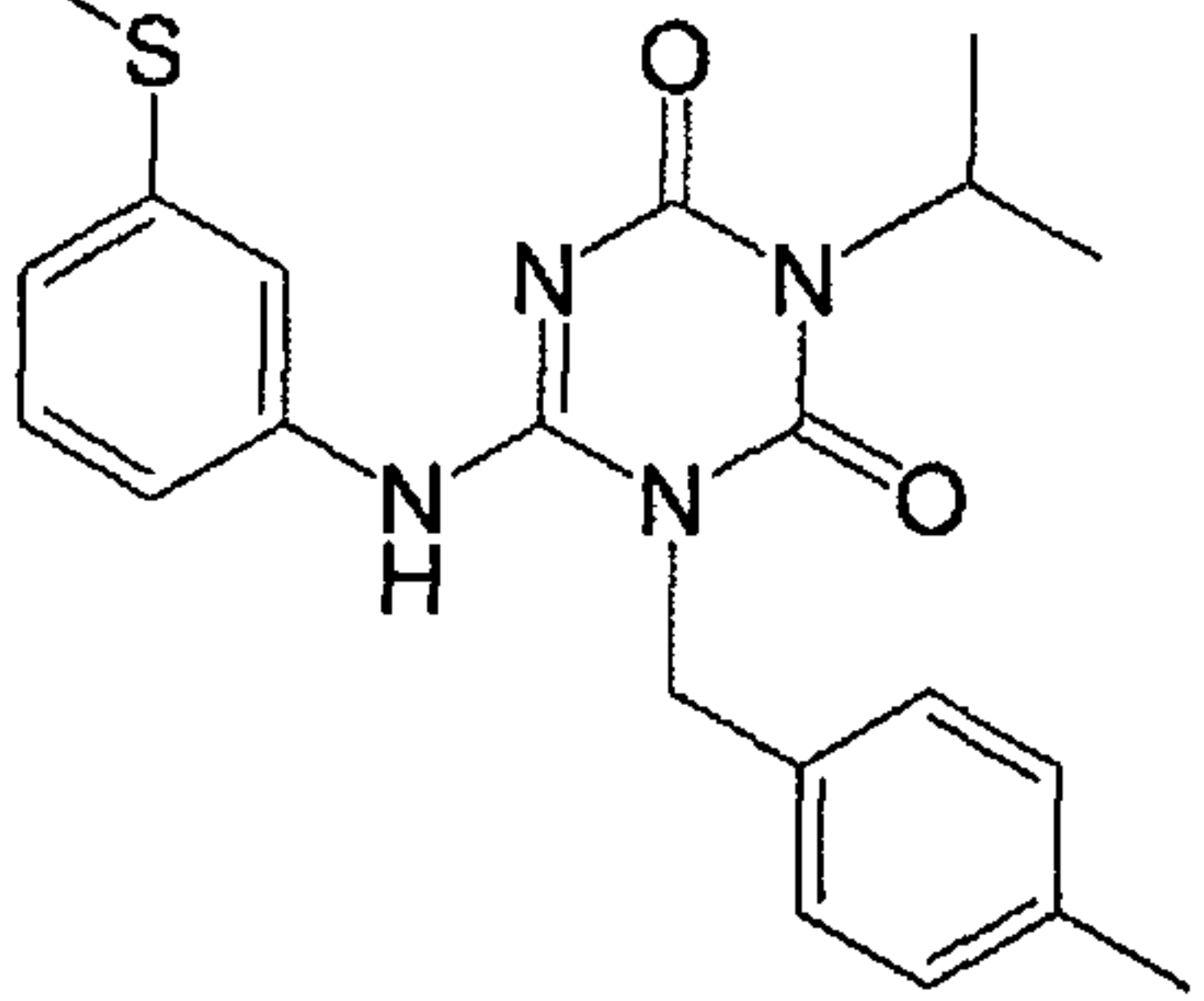
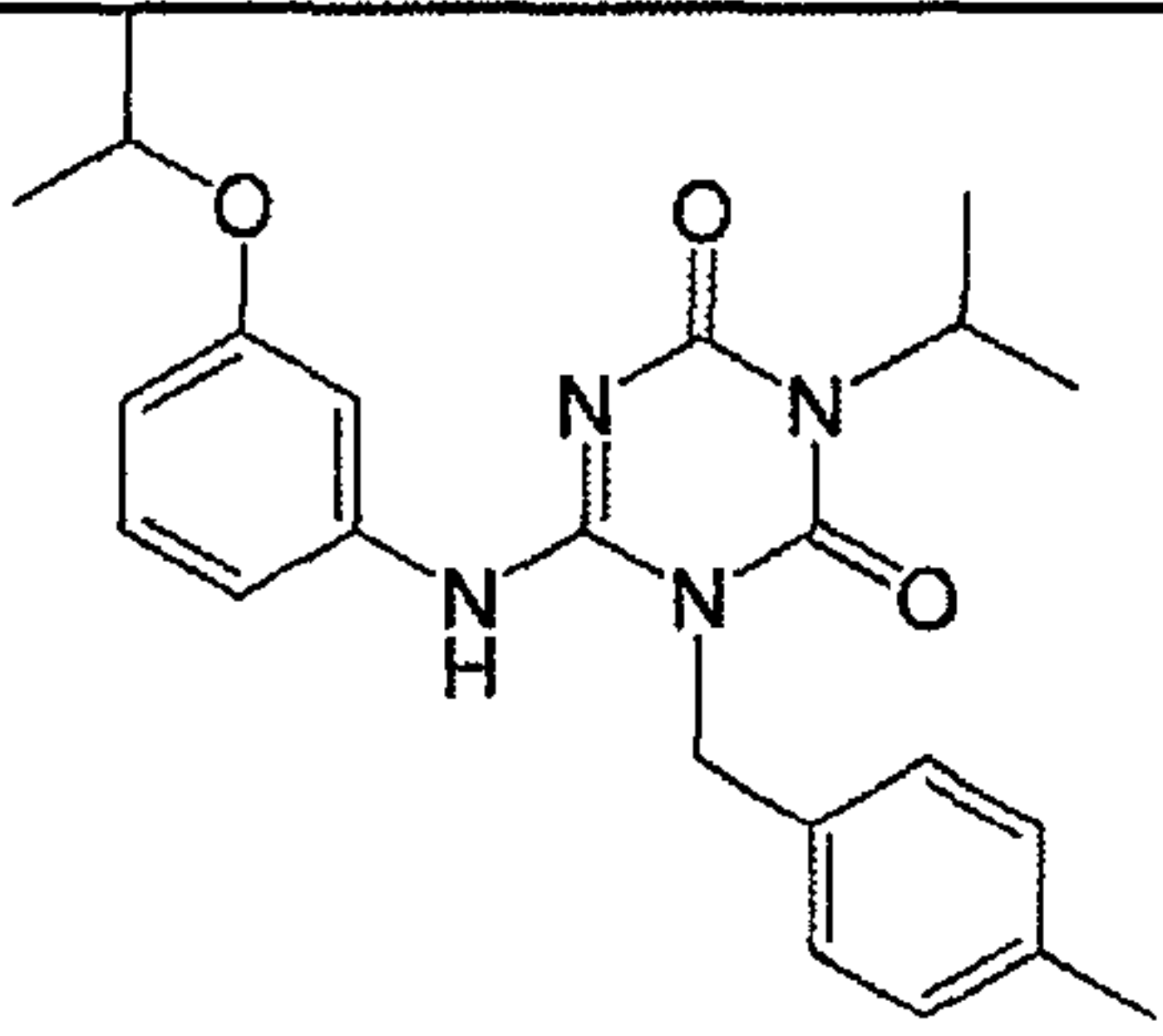
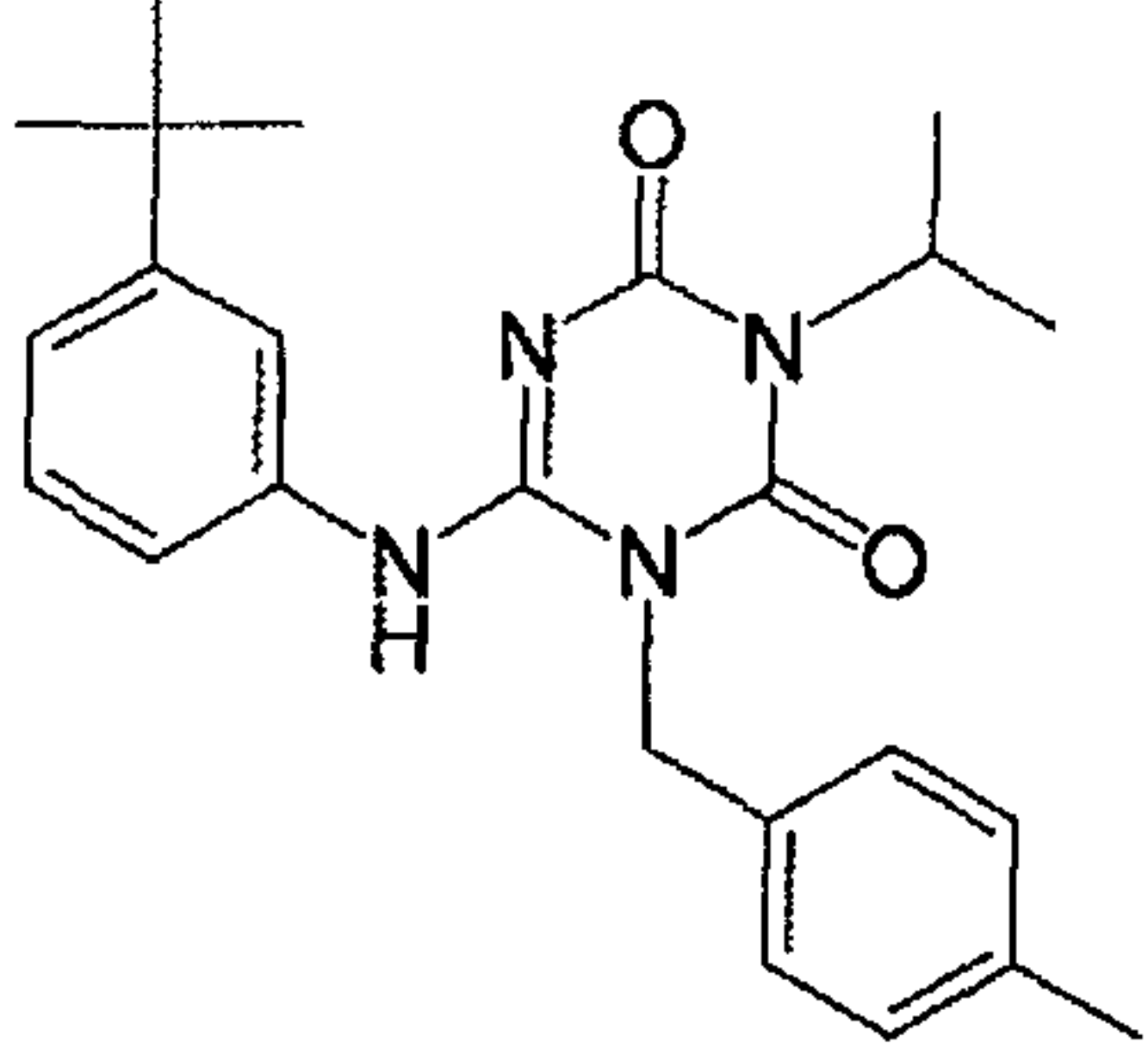
[Table 25]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0106	3.59	462	4
	I-0107	4.05	490	4
	I-0108	3.85	488	4
	I-0109	3.66	496	4
	I-0110	3.97	530	4

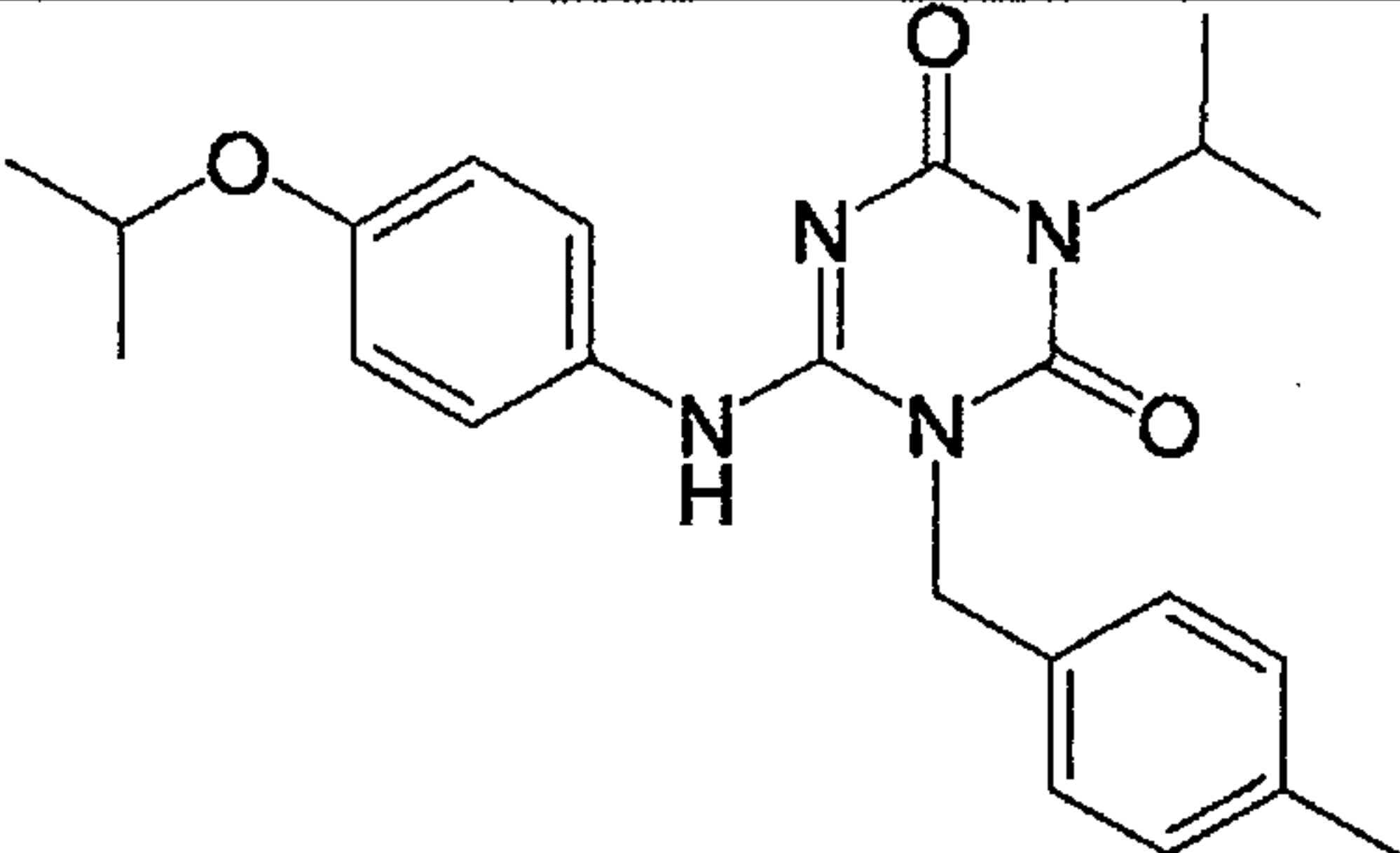
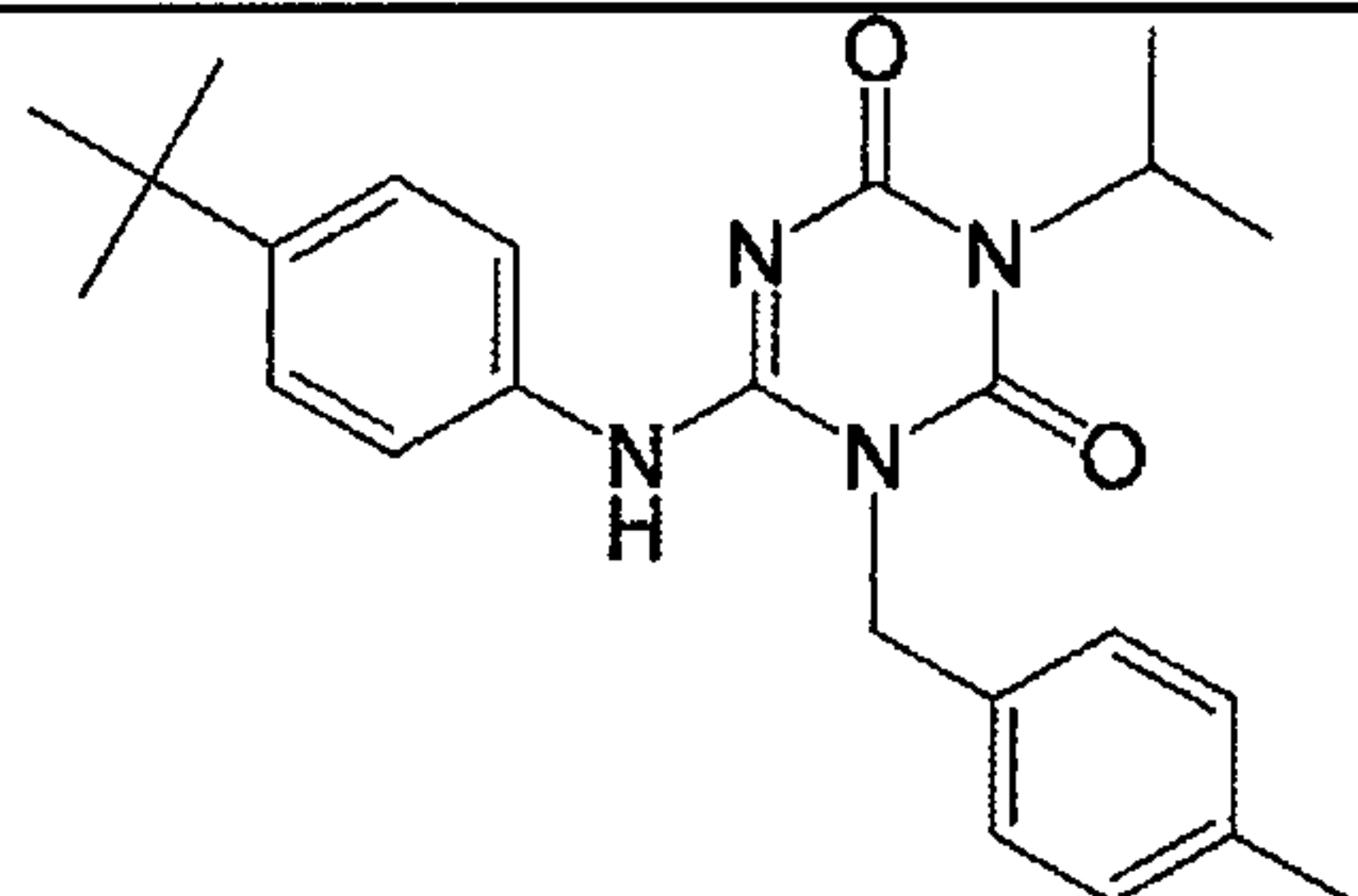
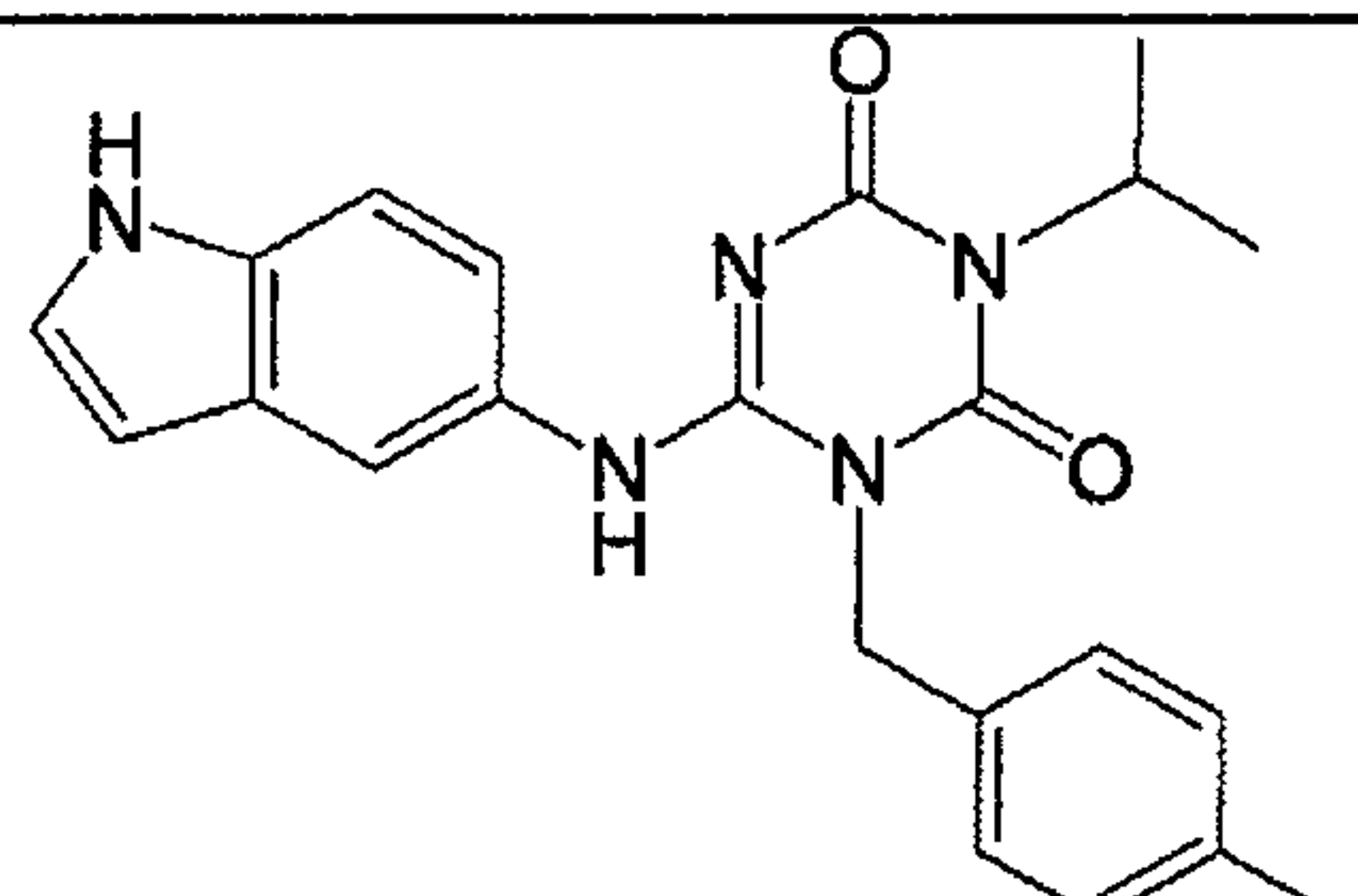
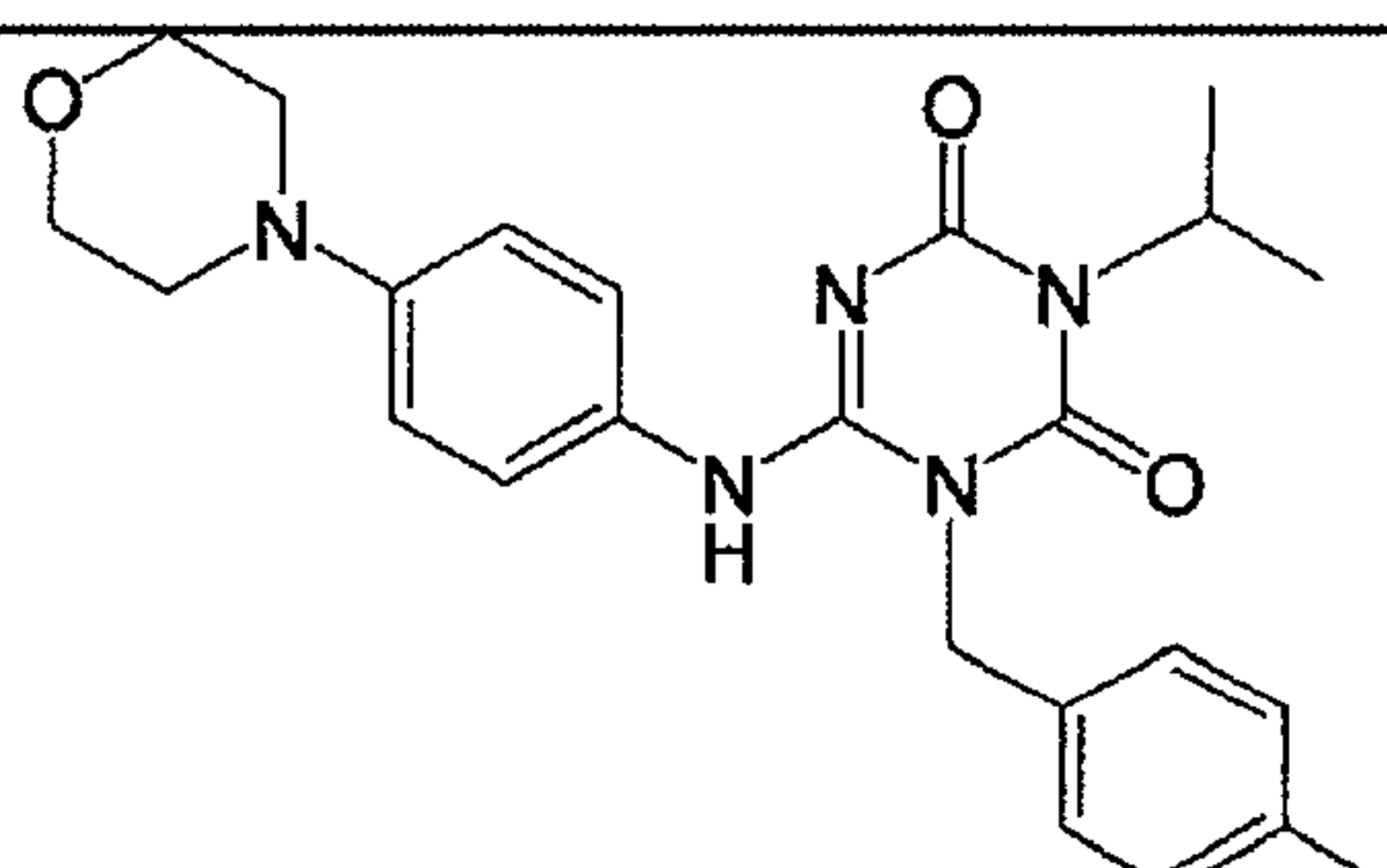
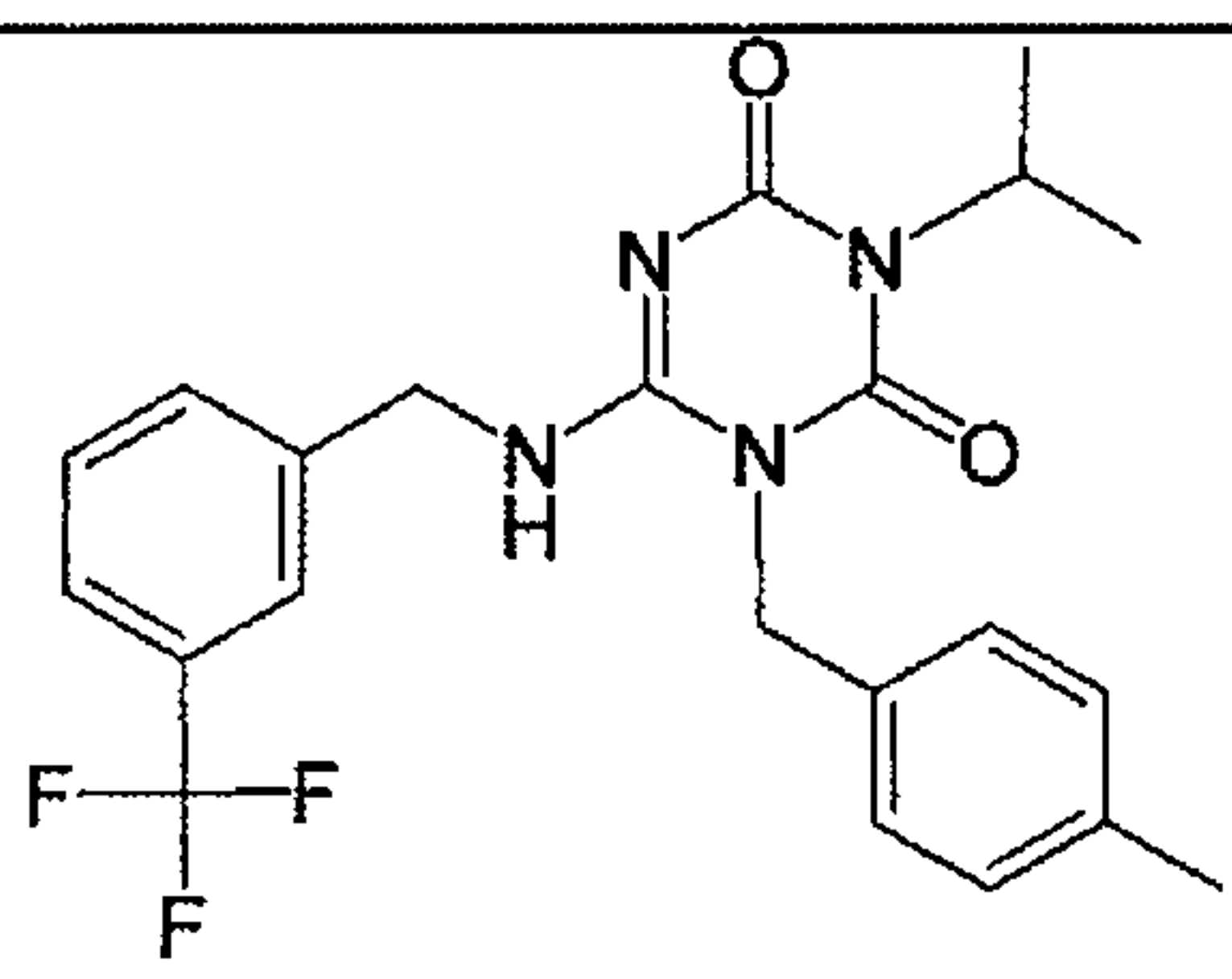
[Table 26]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0111	3.84	510	4
	I-0112	3.67	526	4
	I-0113	3.77	510	4
	I-0114	2.44	417	1
	I-0115	2.67	443	1

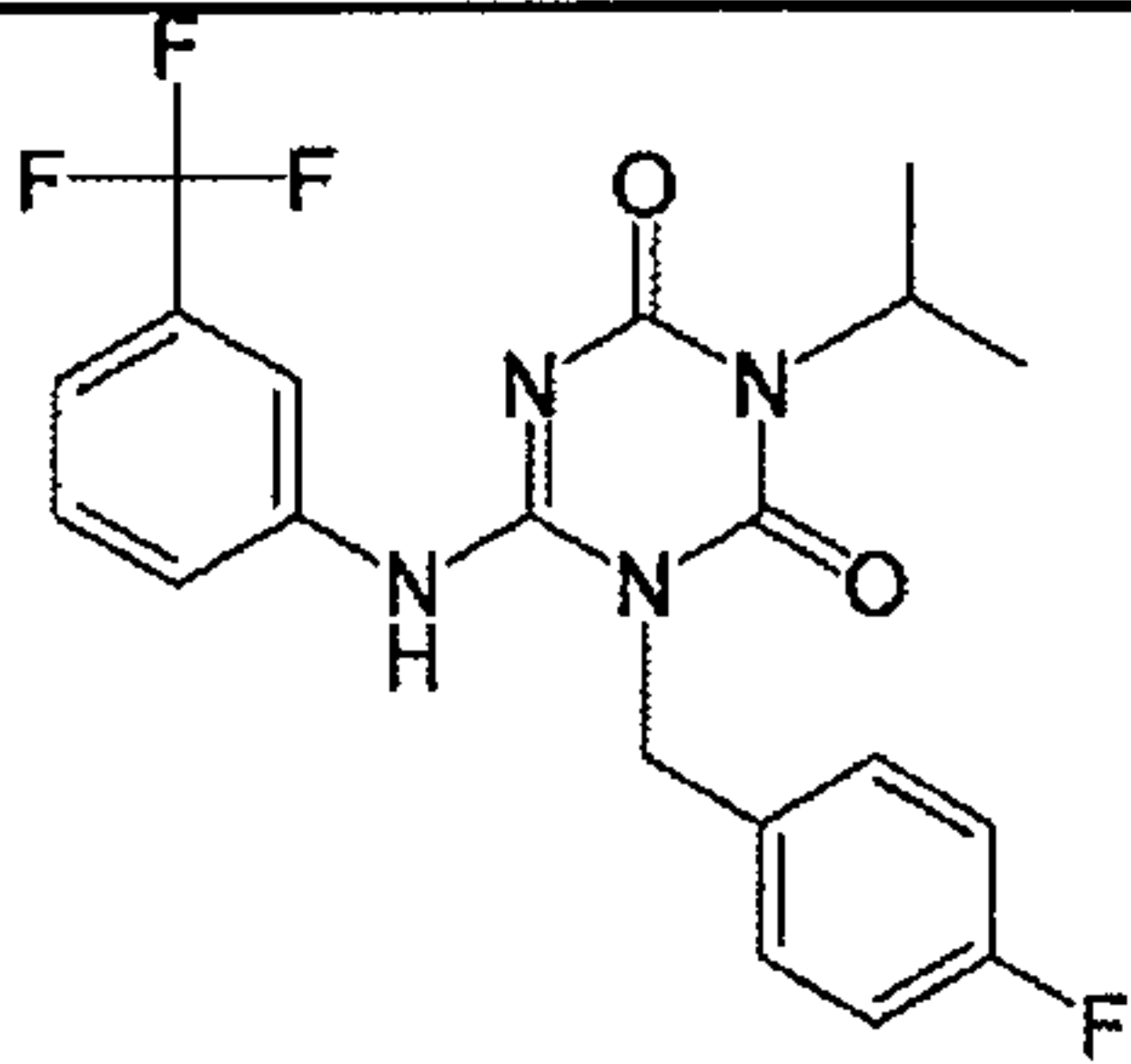
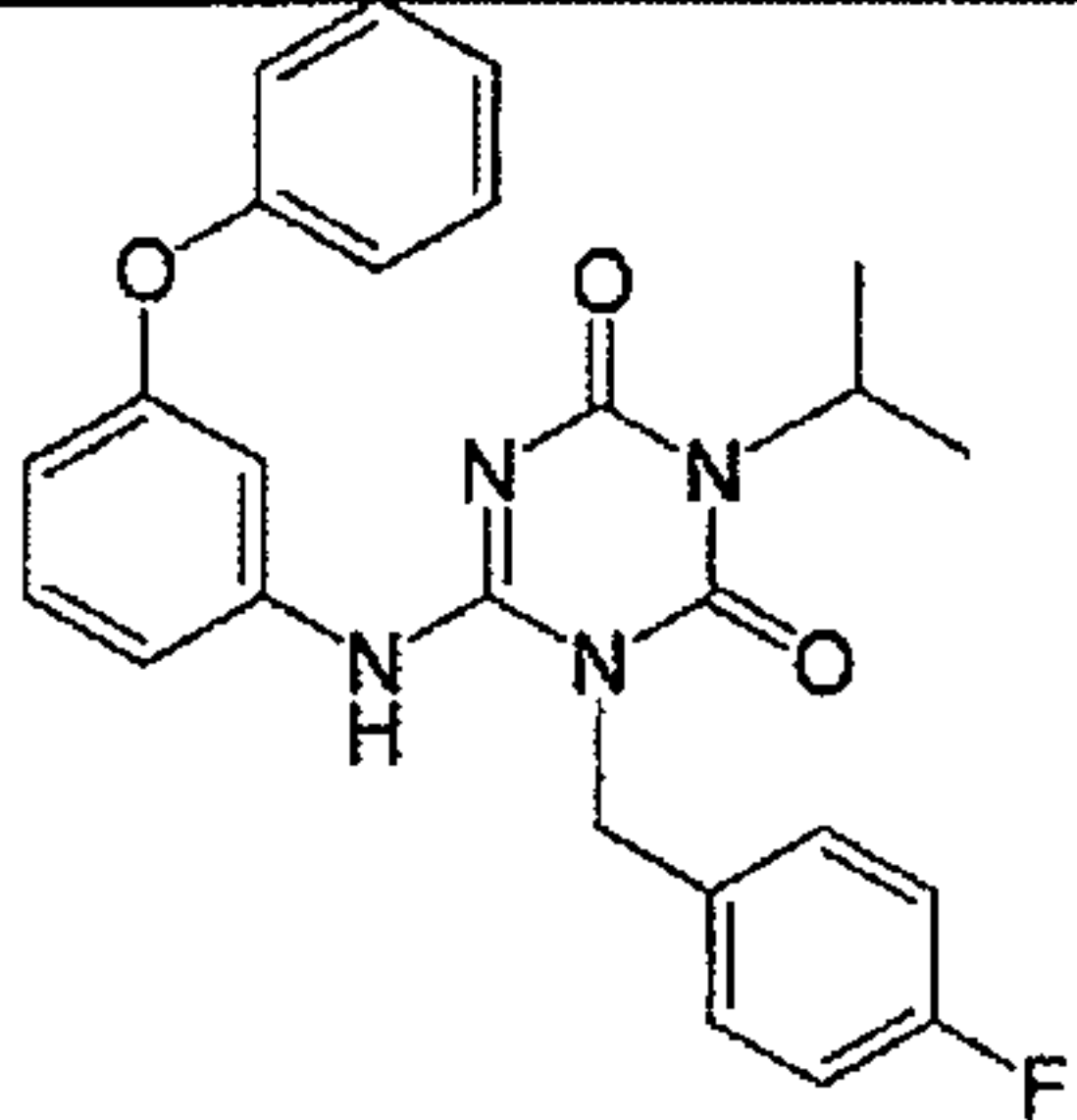
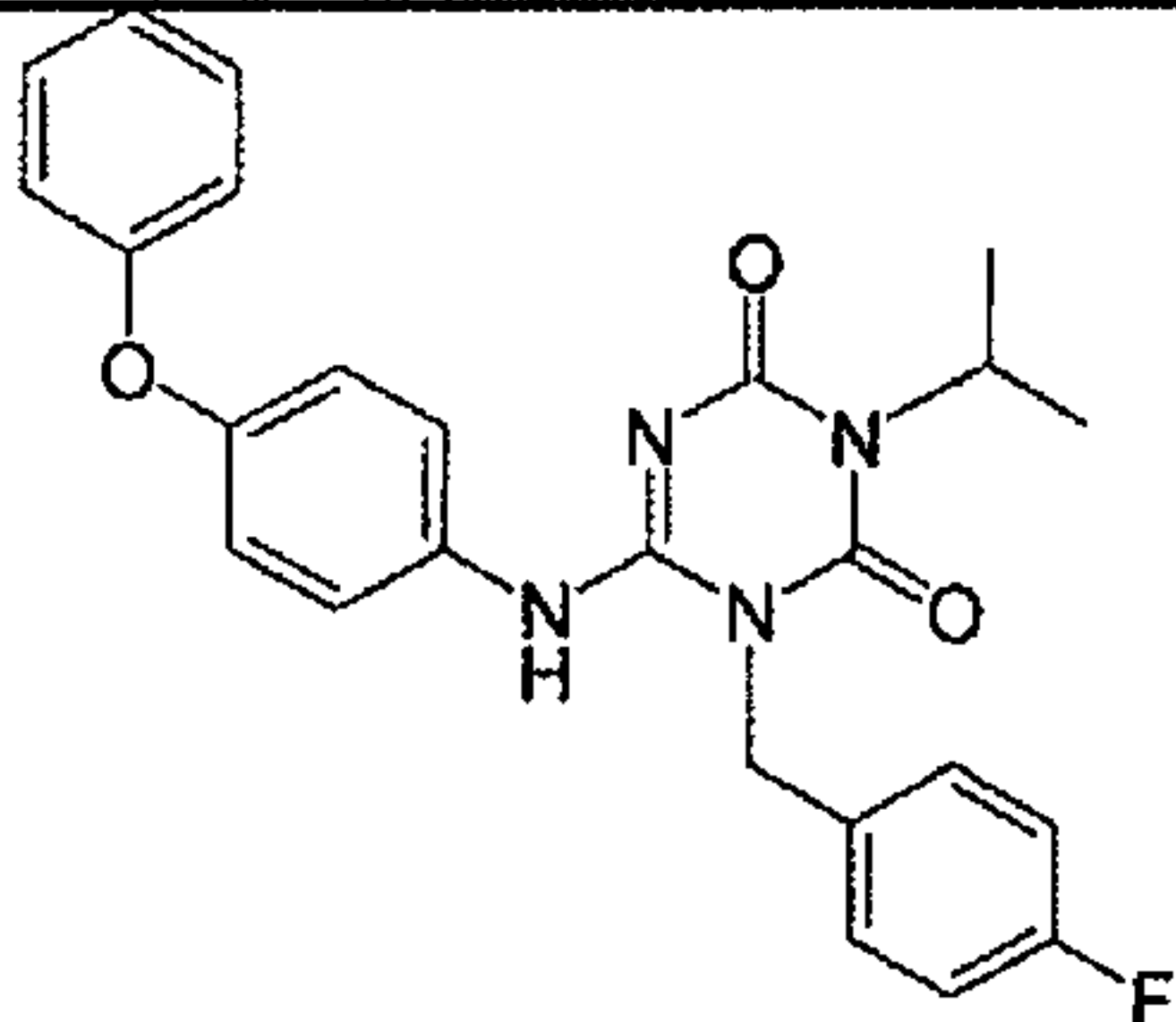
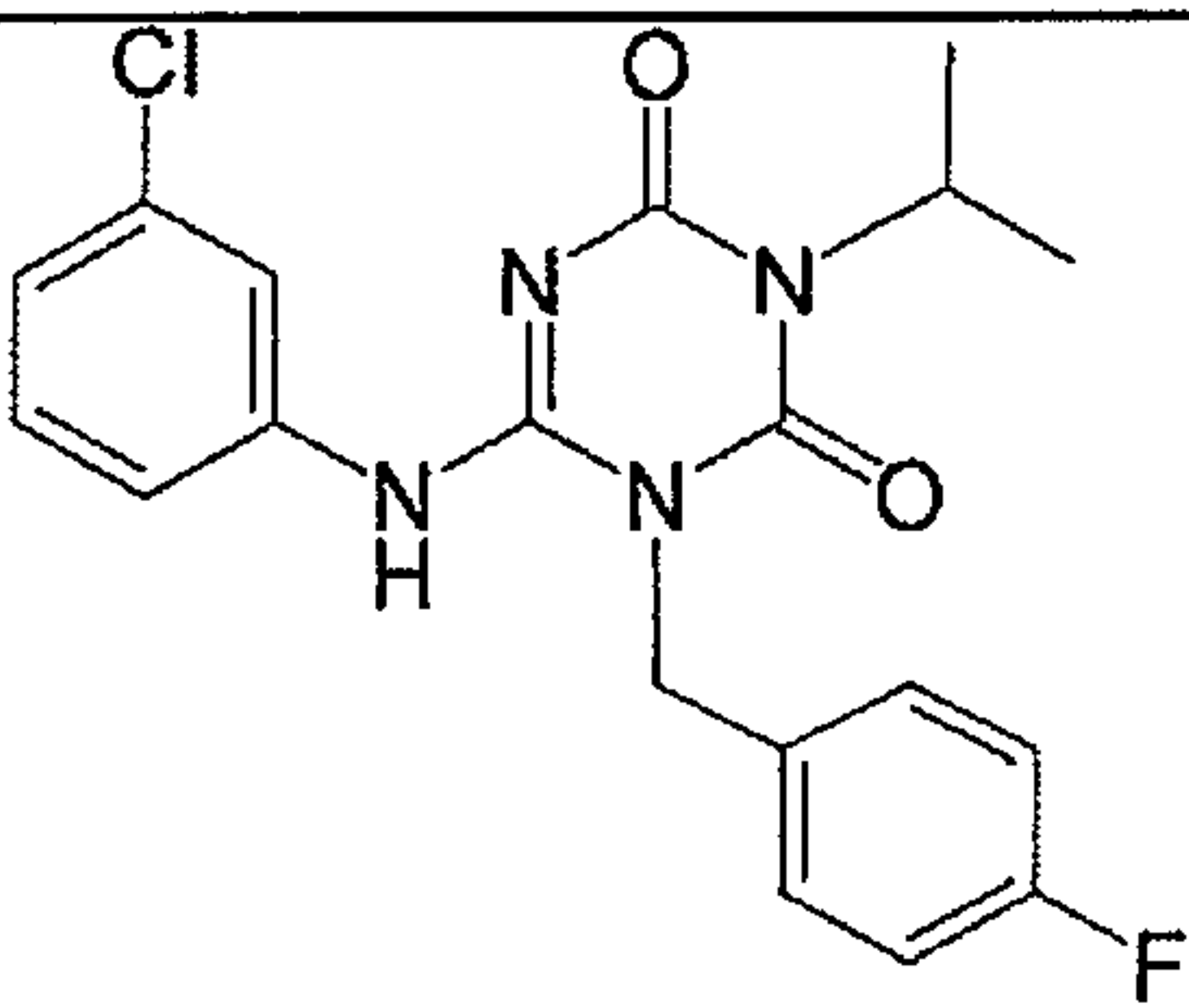
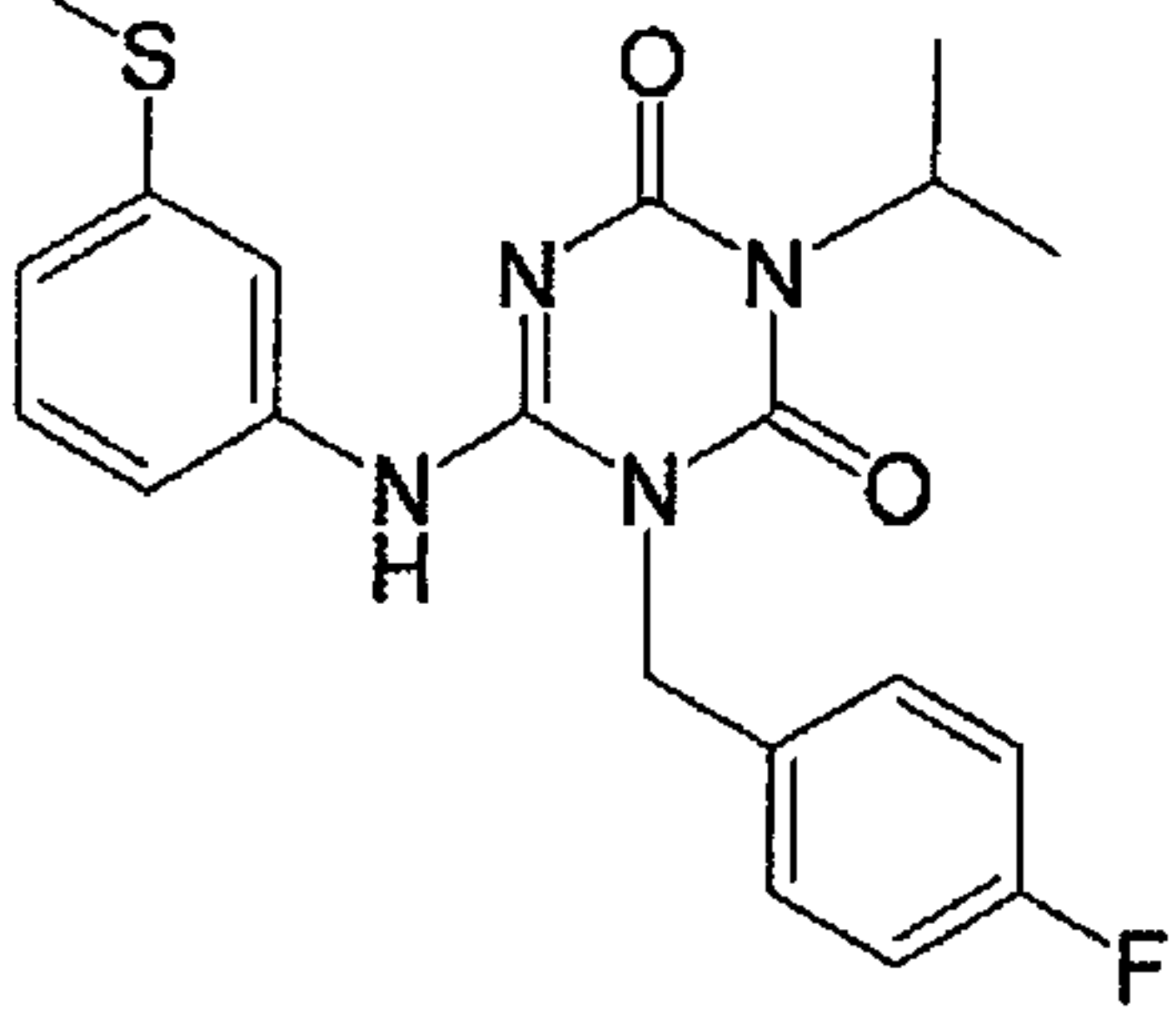
[Table 27]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0116	2.59	443	1
	I-0117	2.52	385	1
	I-0118	2.44	397	1
	I-0119	2.52	409	1
	I-0120	2.70	407	1

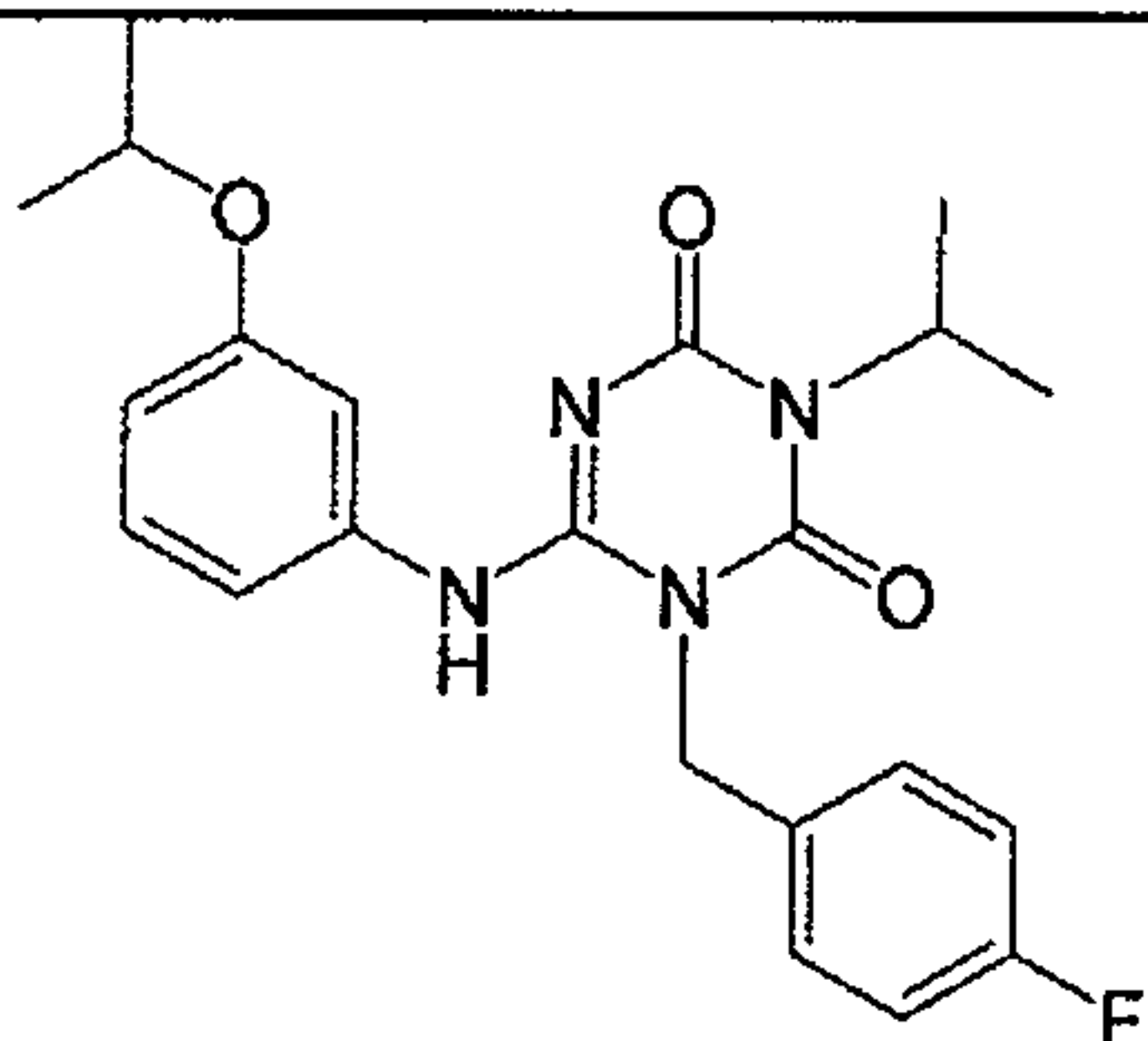
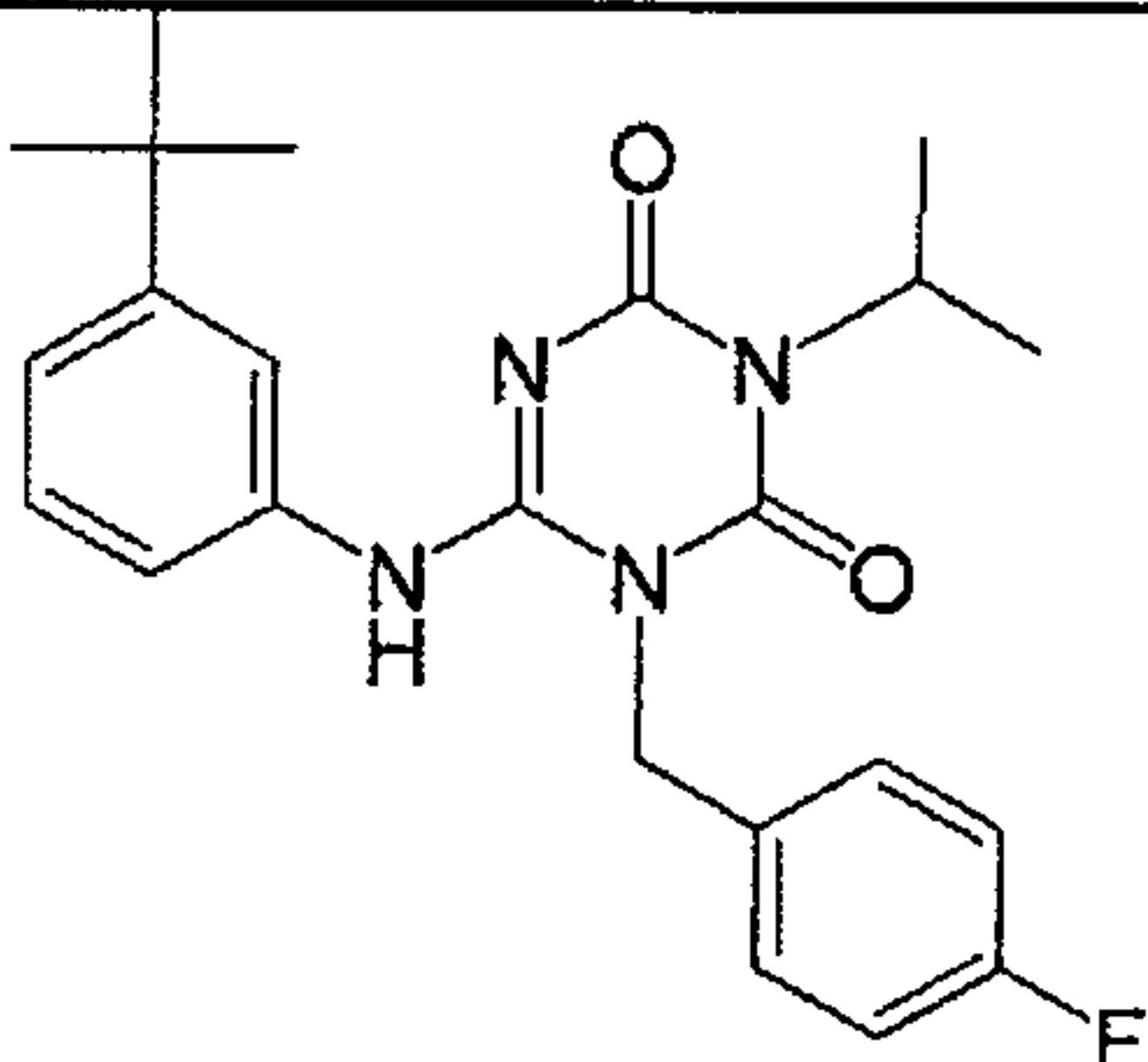
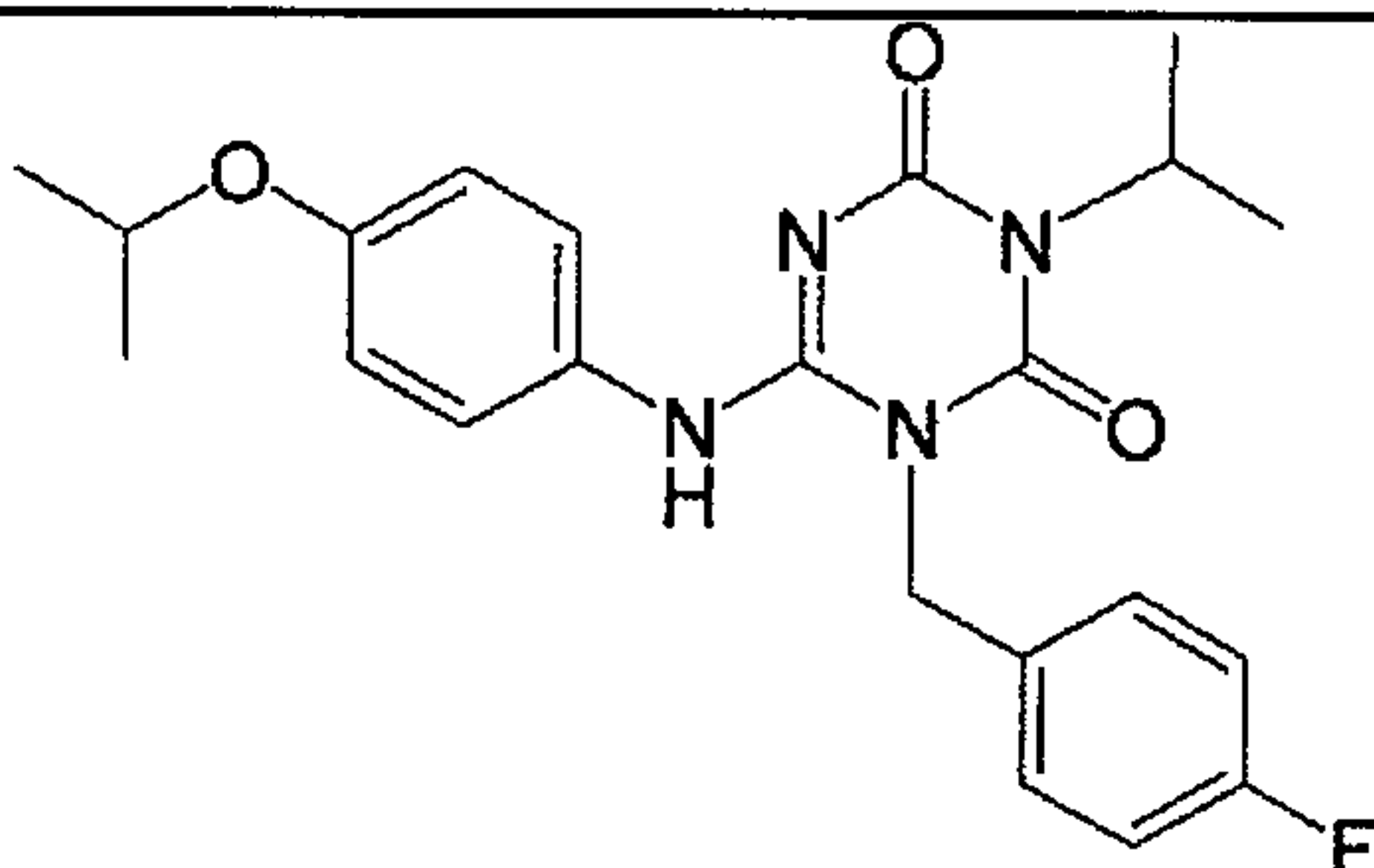
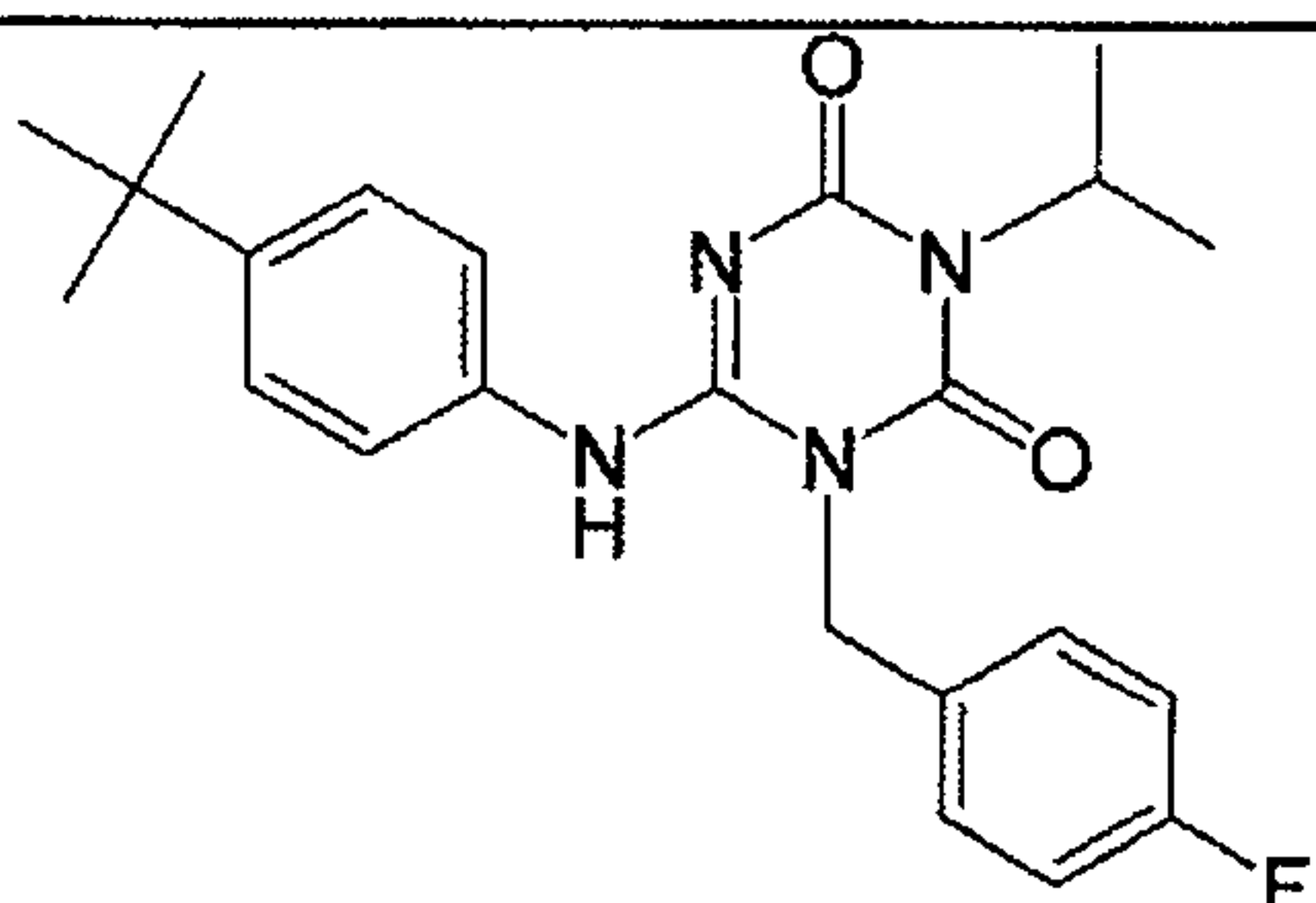
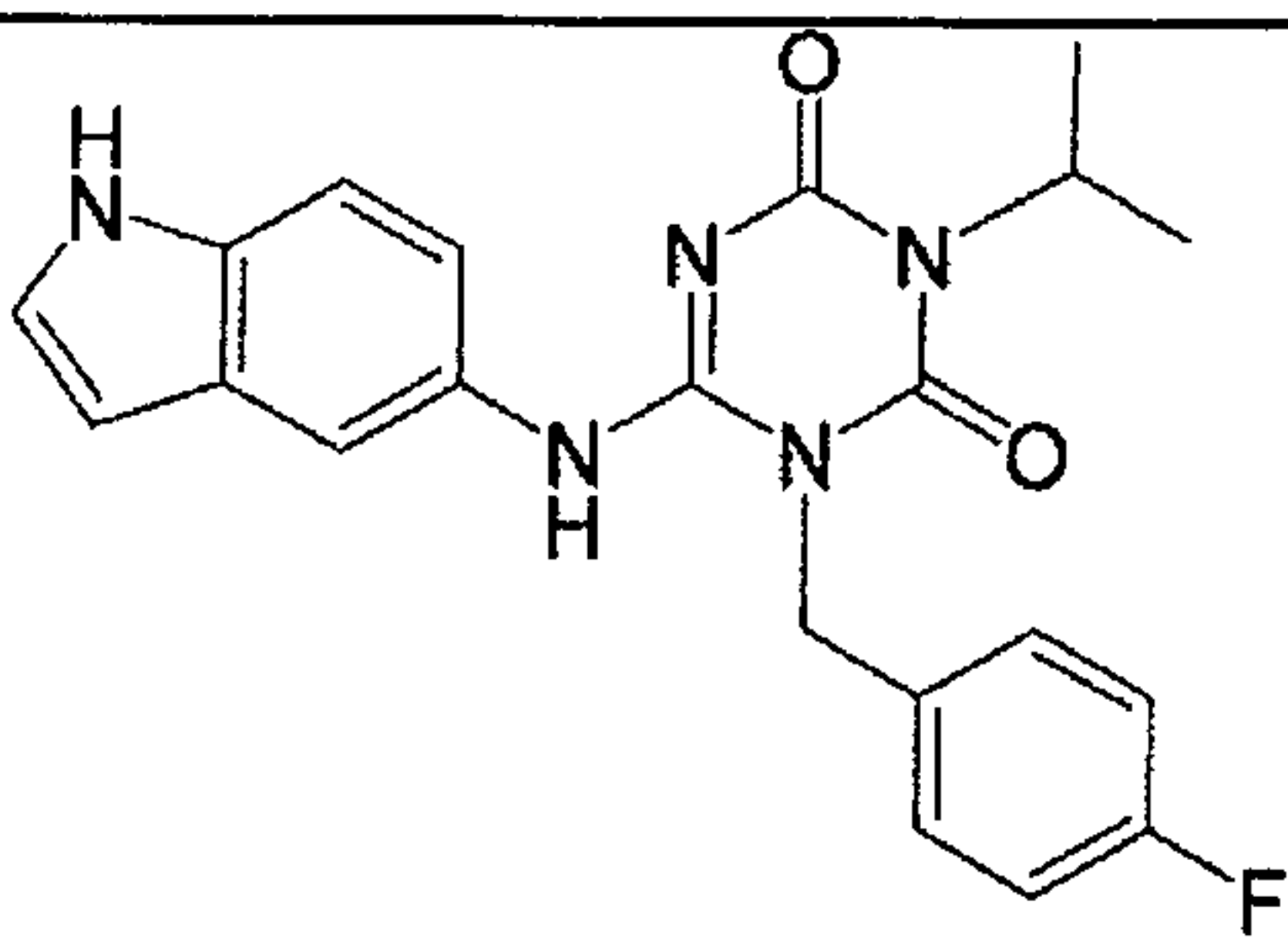
[Table 28]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0121	2.40	409	1
	I-0122	2.68	407	1
	I-0123	2.05	390	1
	I-0124	2.04	436	1
	I-0125	2.31	433	1

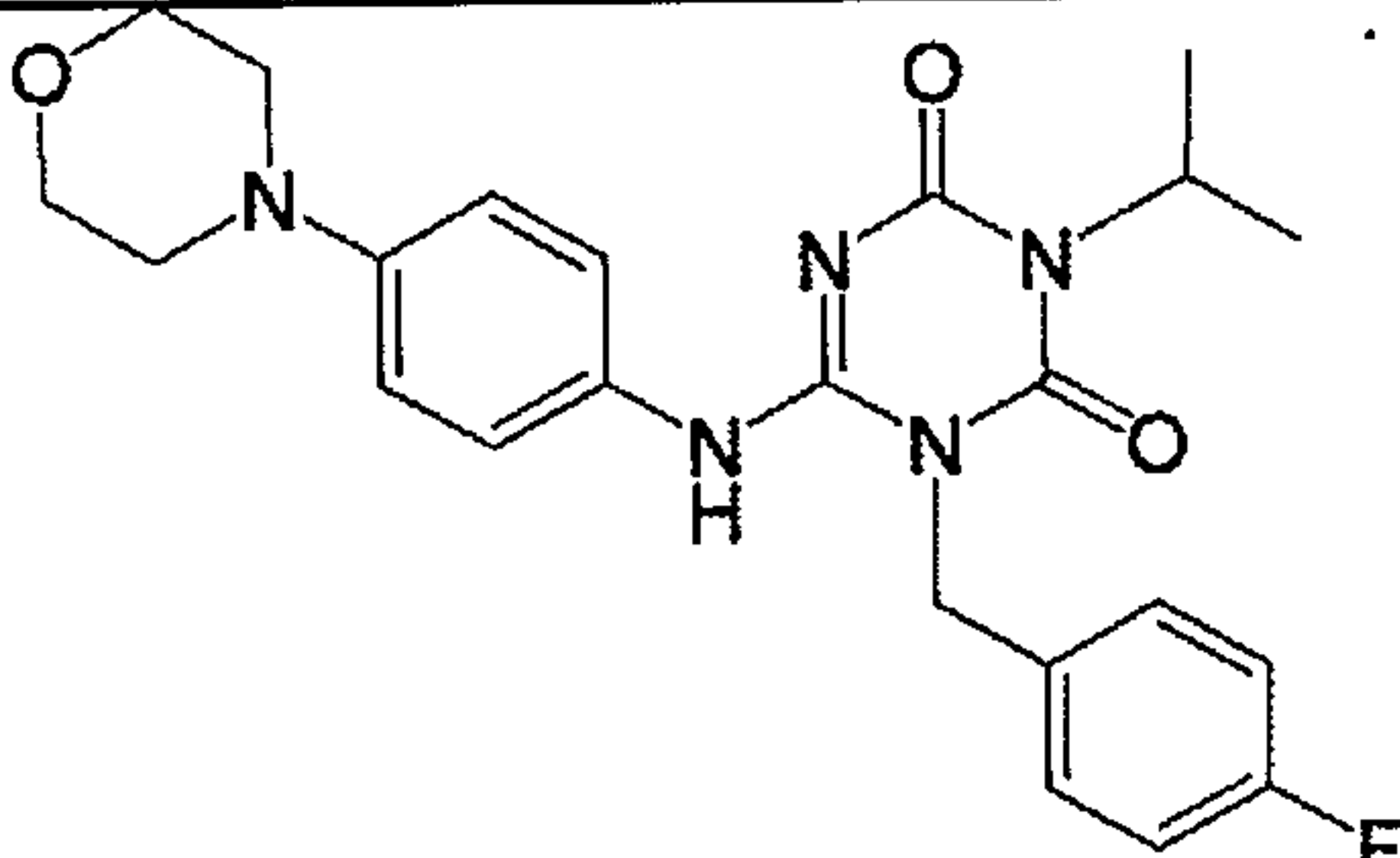
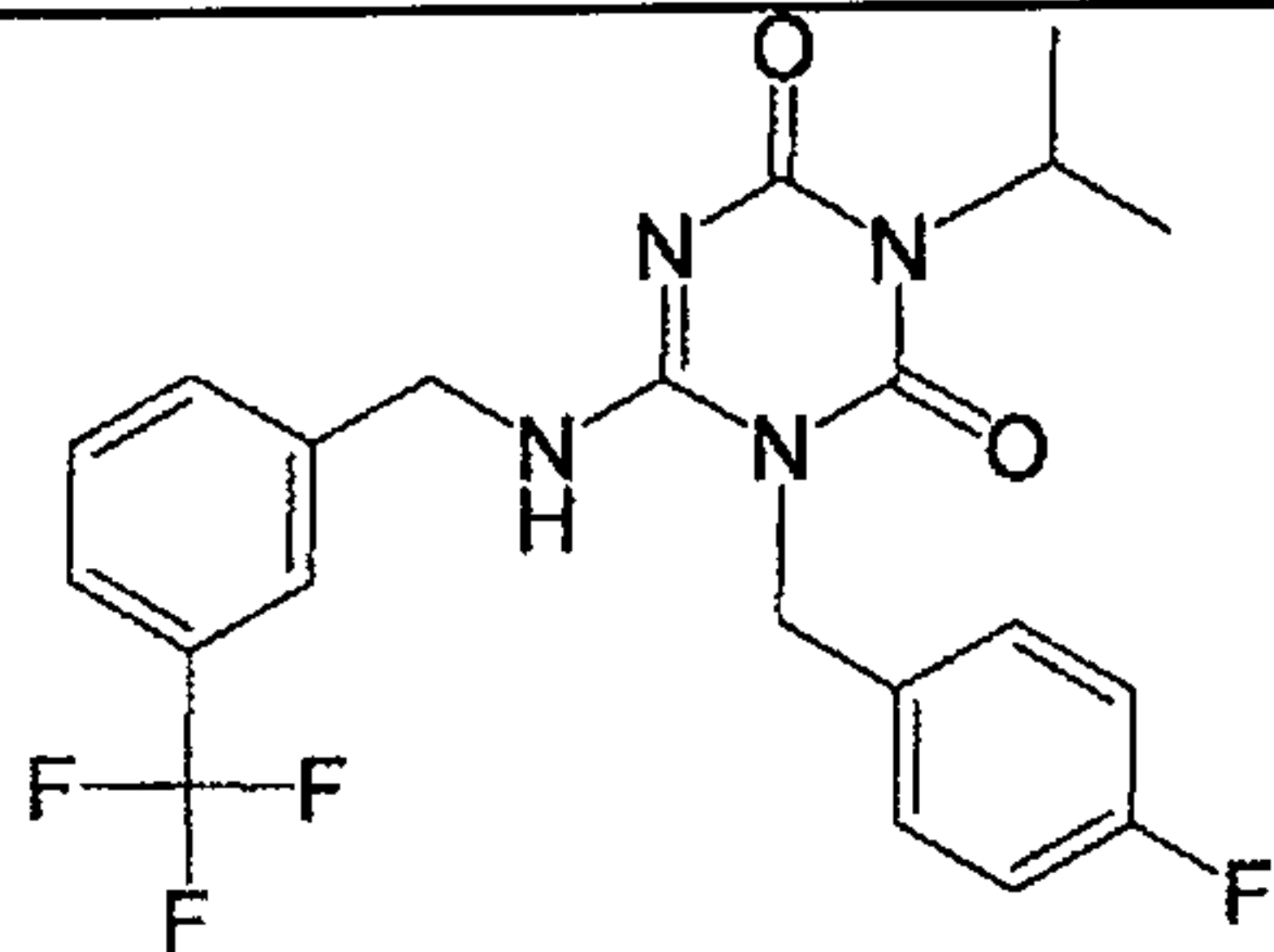
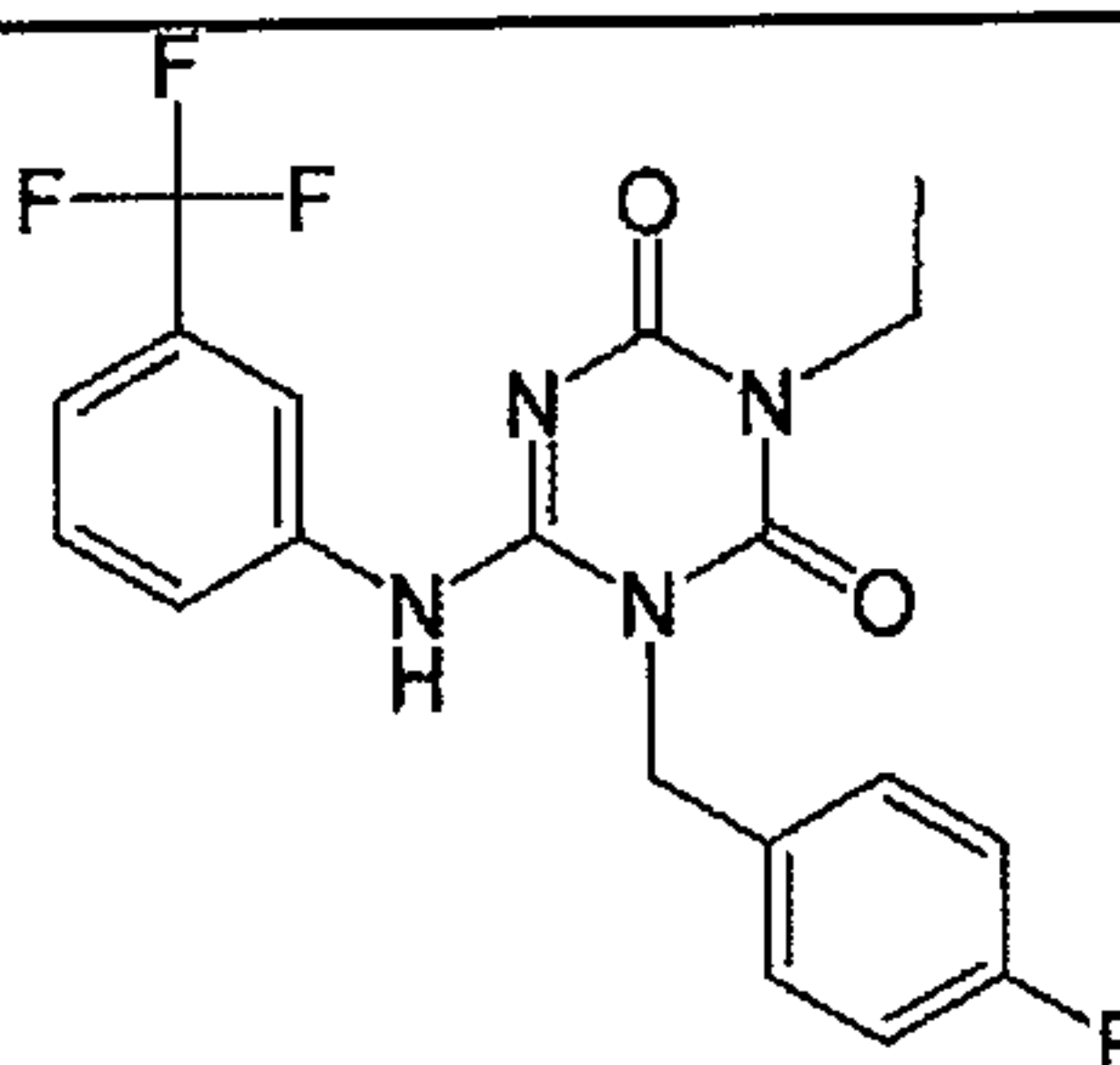
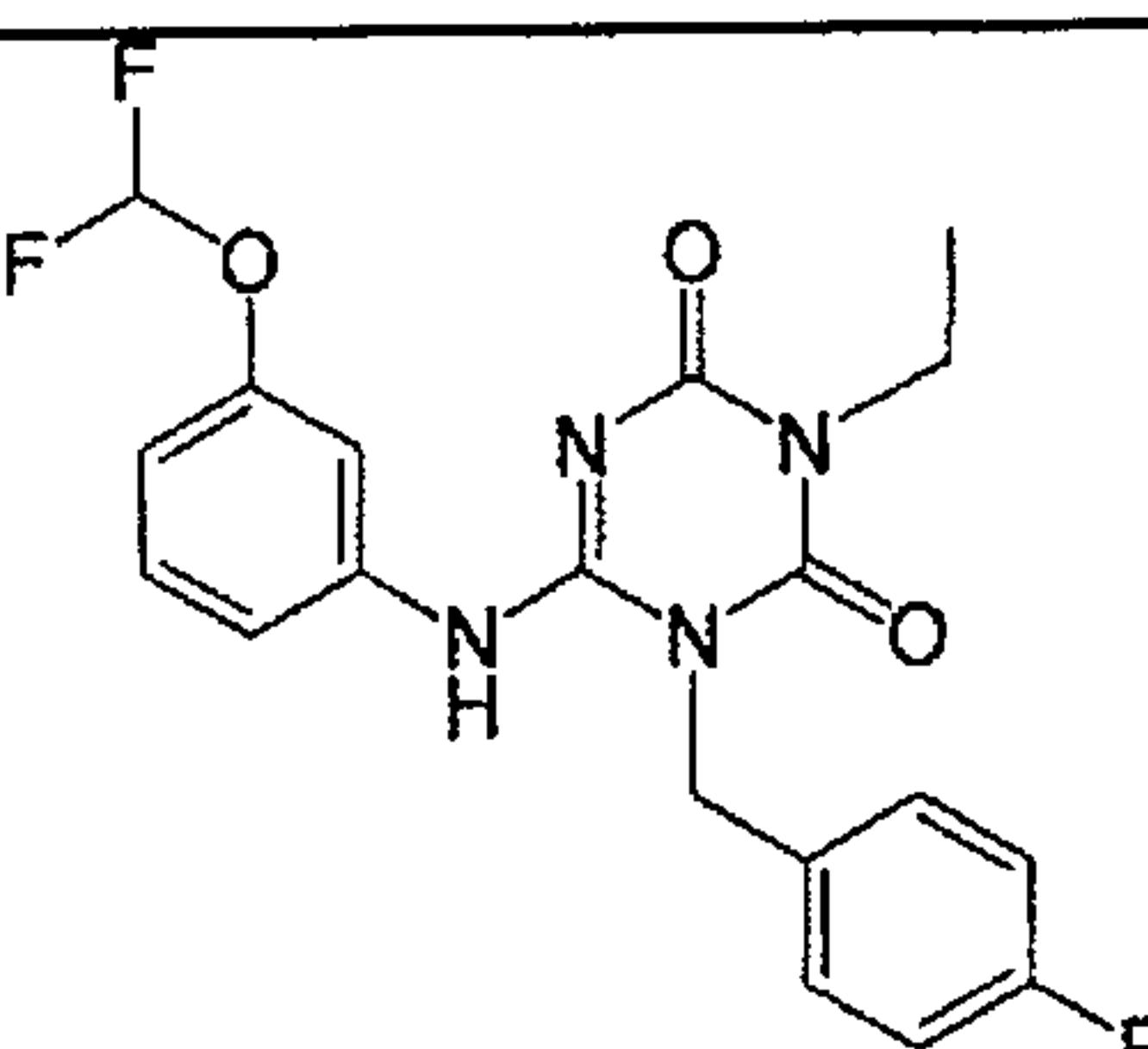
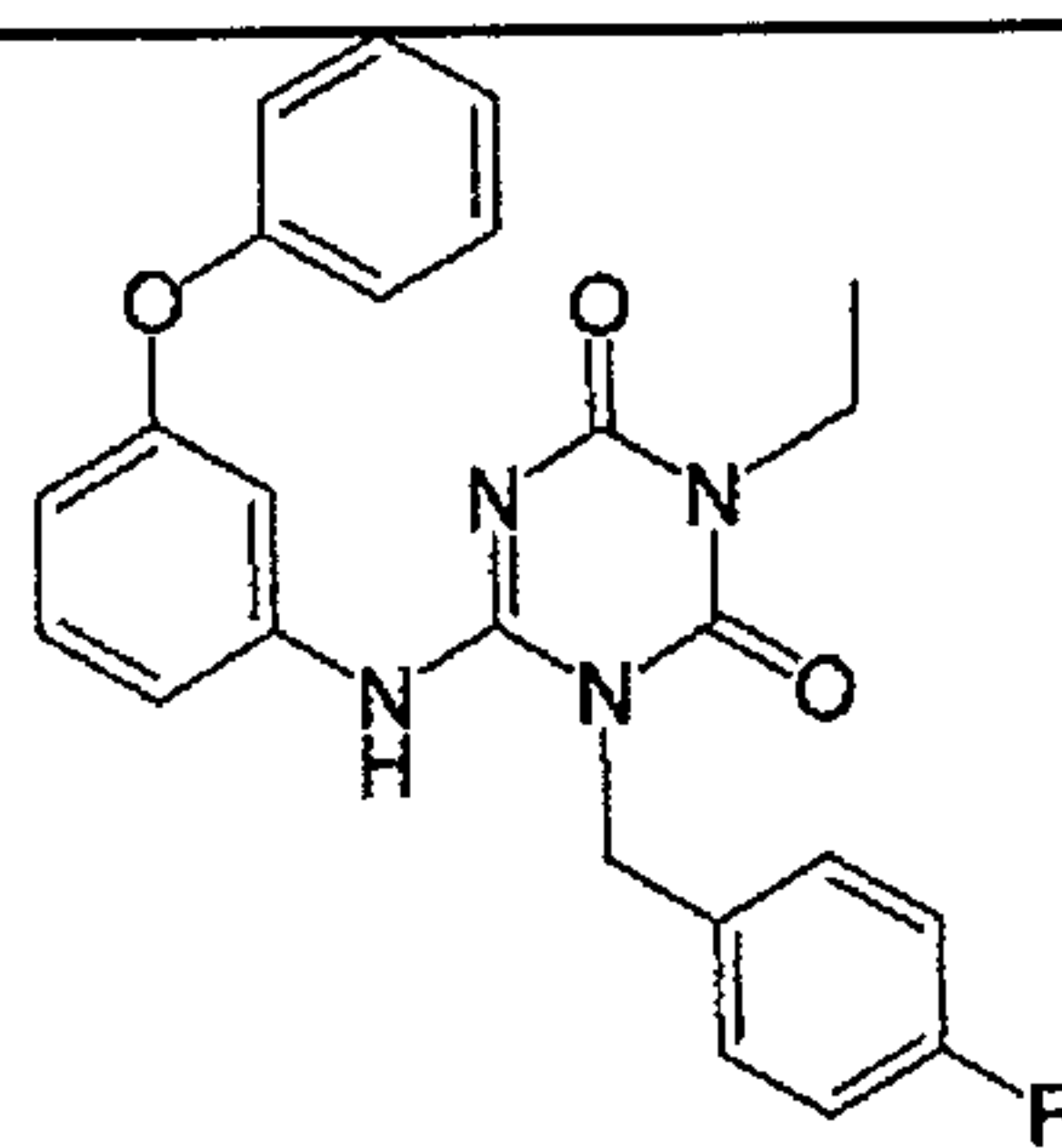
[Table 29]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0126	2.51	423	1
	I-0127	2.60	447	1
	I-0128	2.52	447	1
	I-0129	2.44	389	1
	I-0130	2.36	401	1

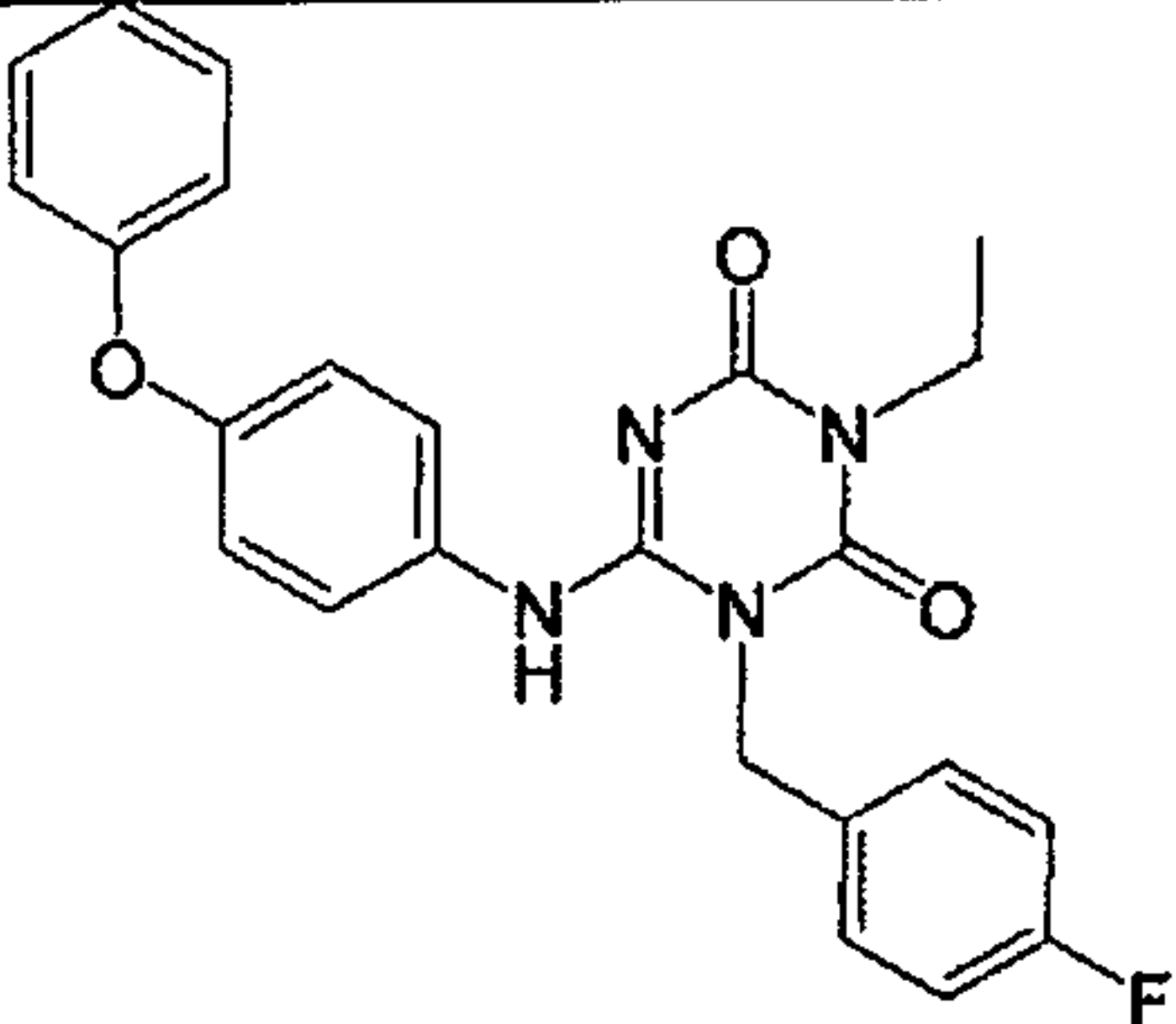
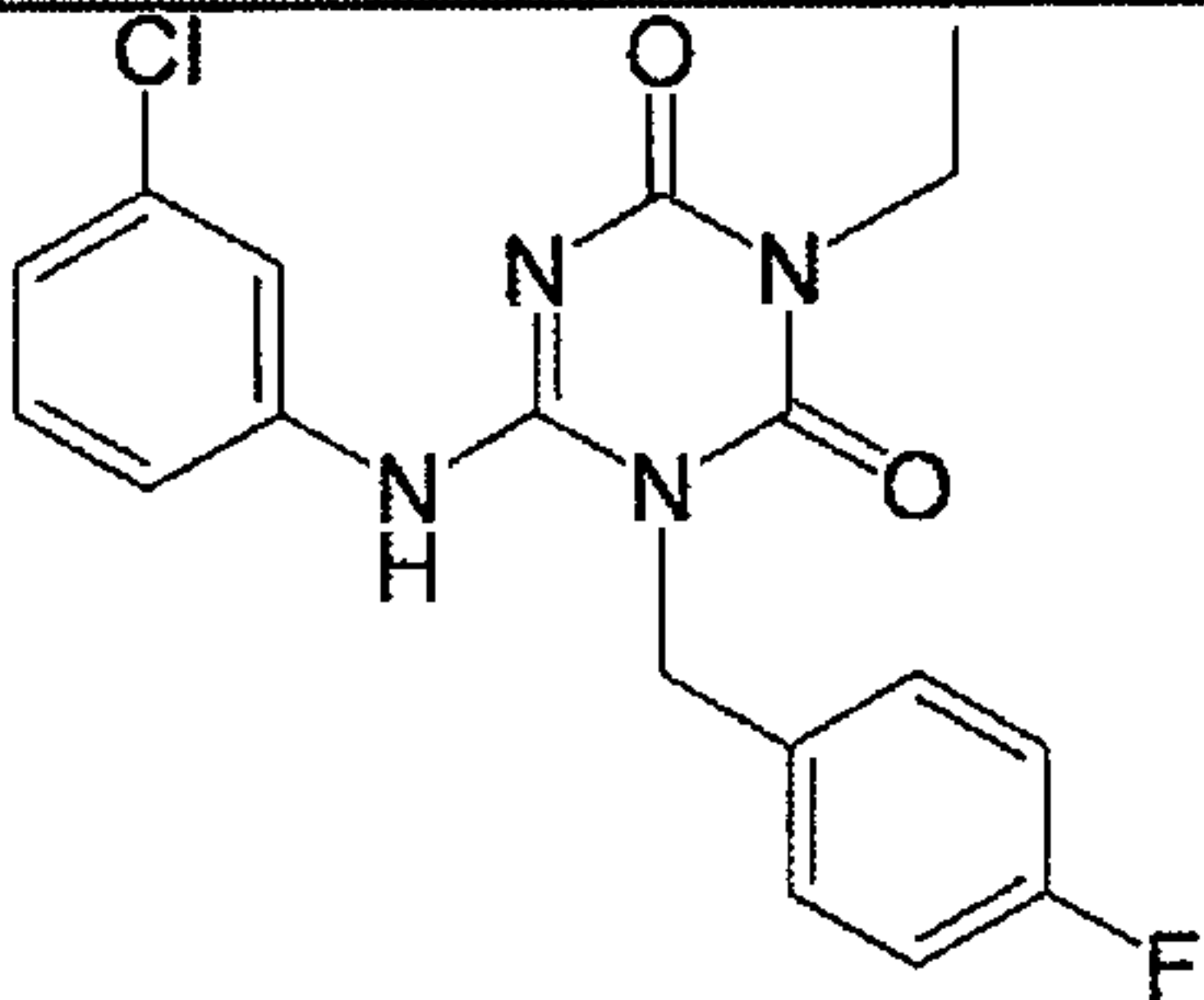
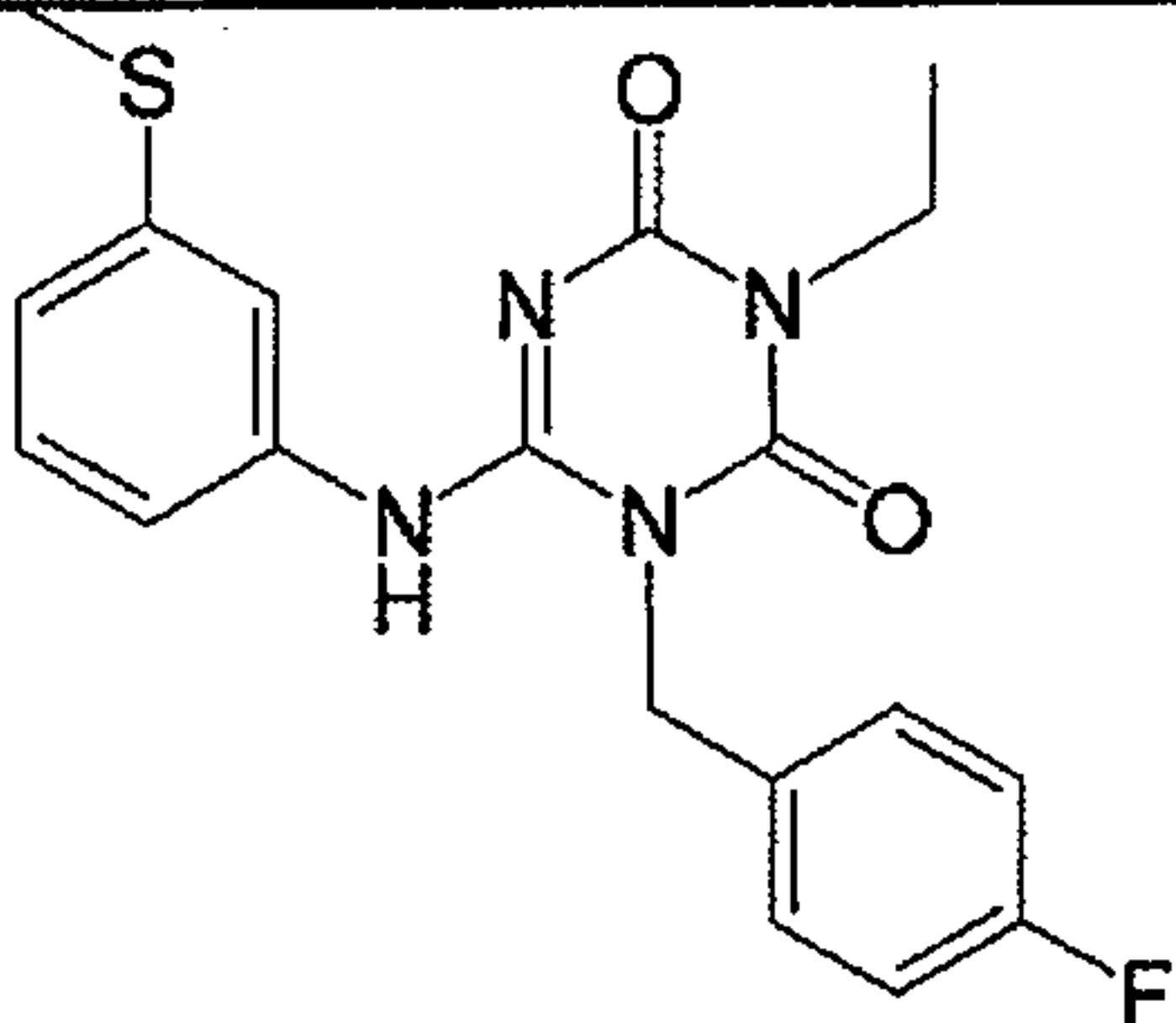
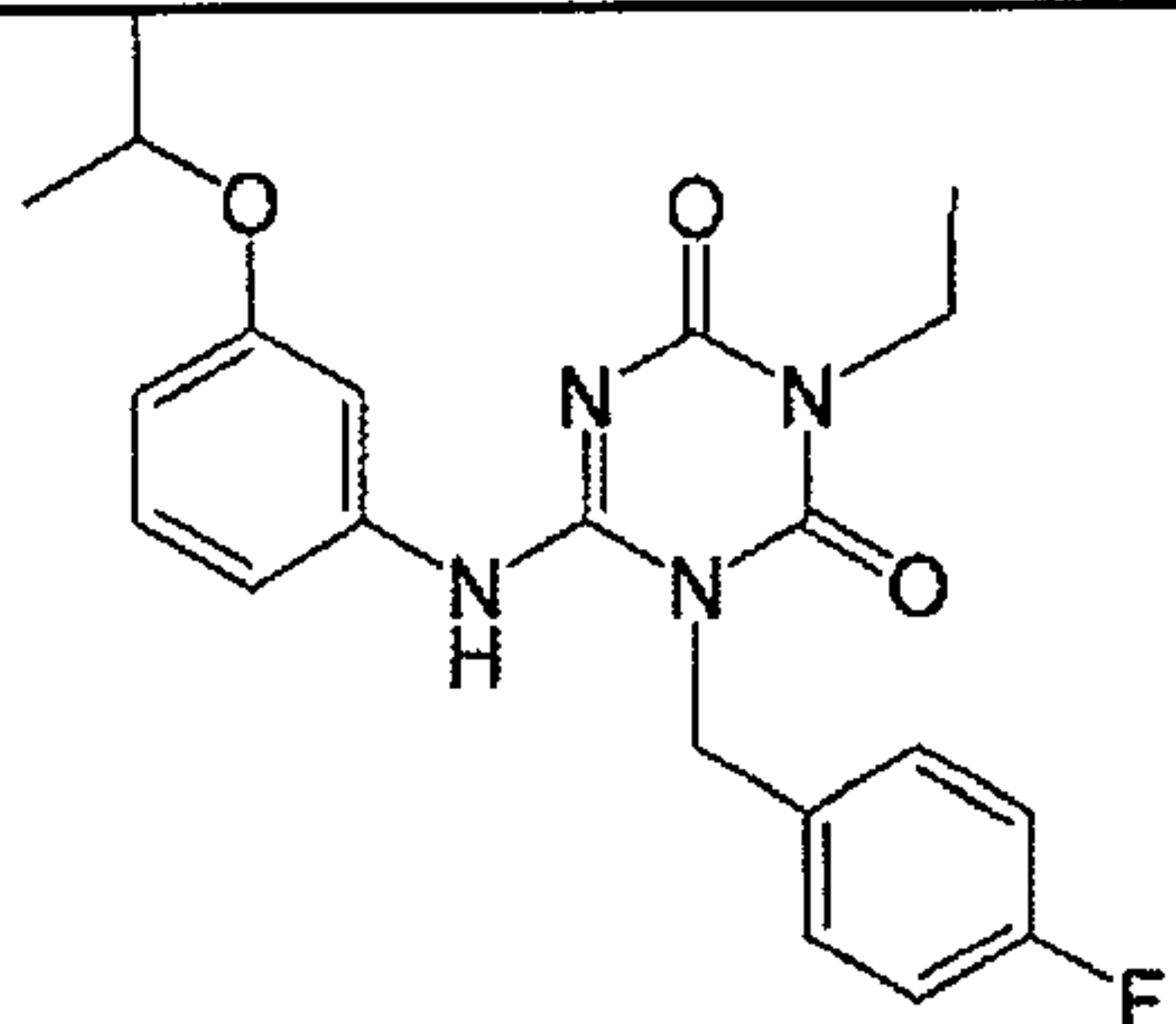
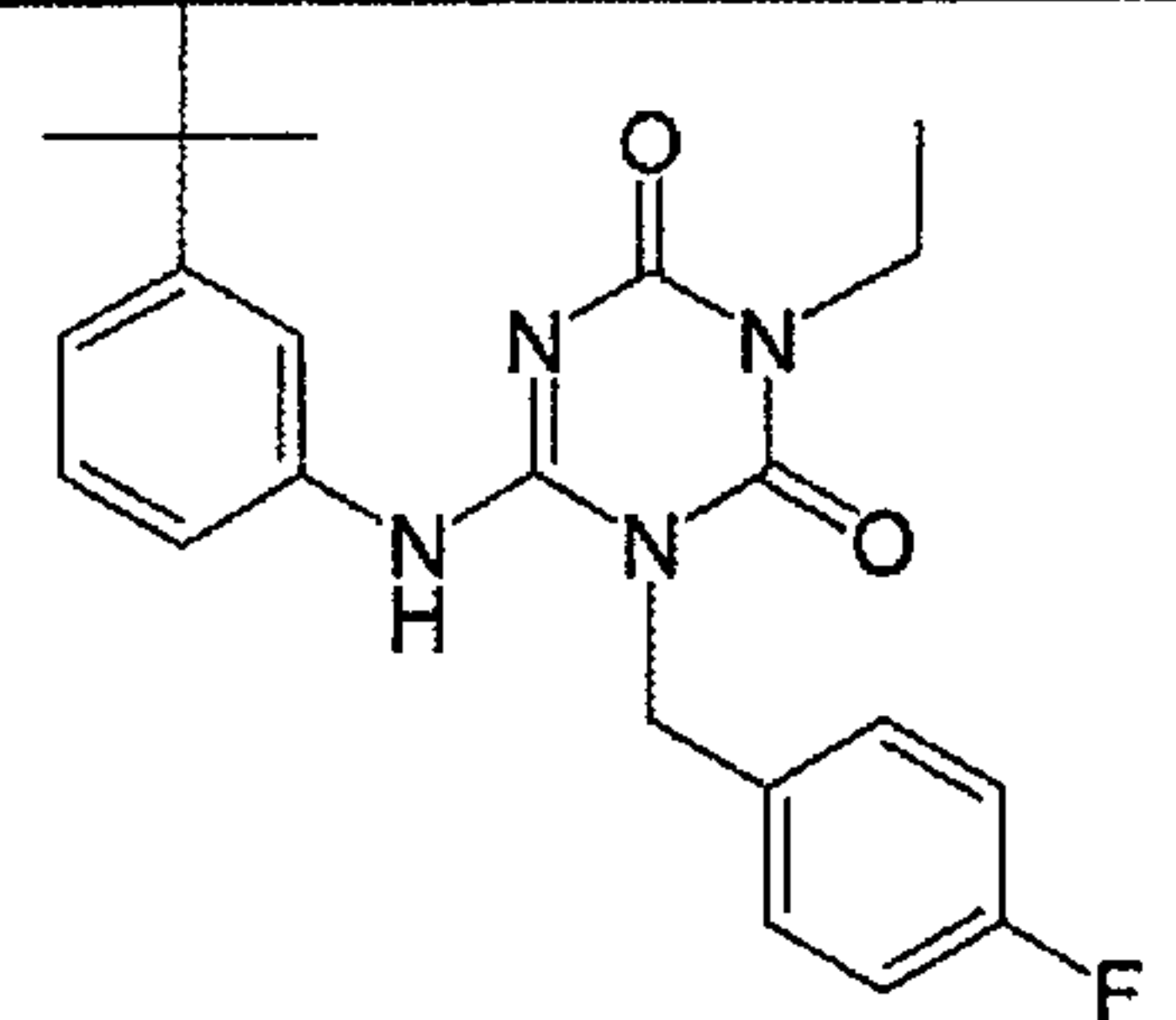
[Table 30]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0131	2.44	413	1
	I-0132	2.60	411	1
	I-0133	2.31	413	1
	I-0134	2.58	411	1
	I-0135	1.96	394	1

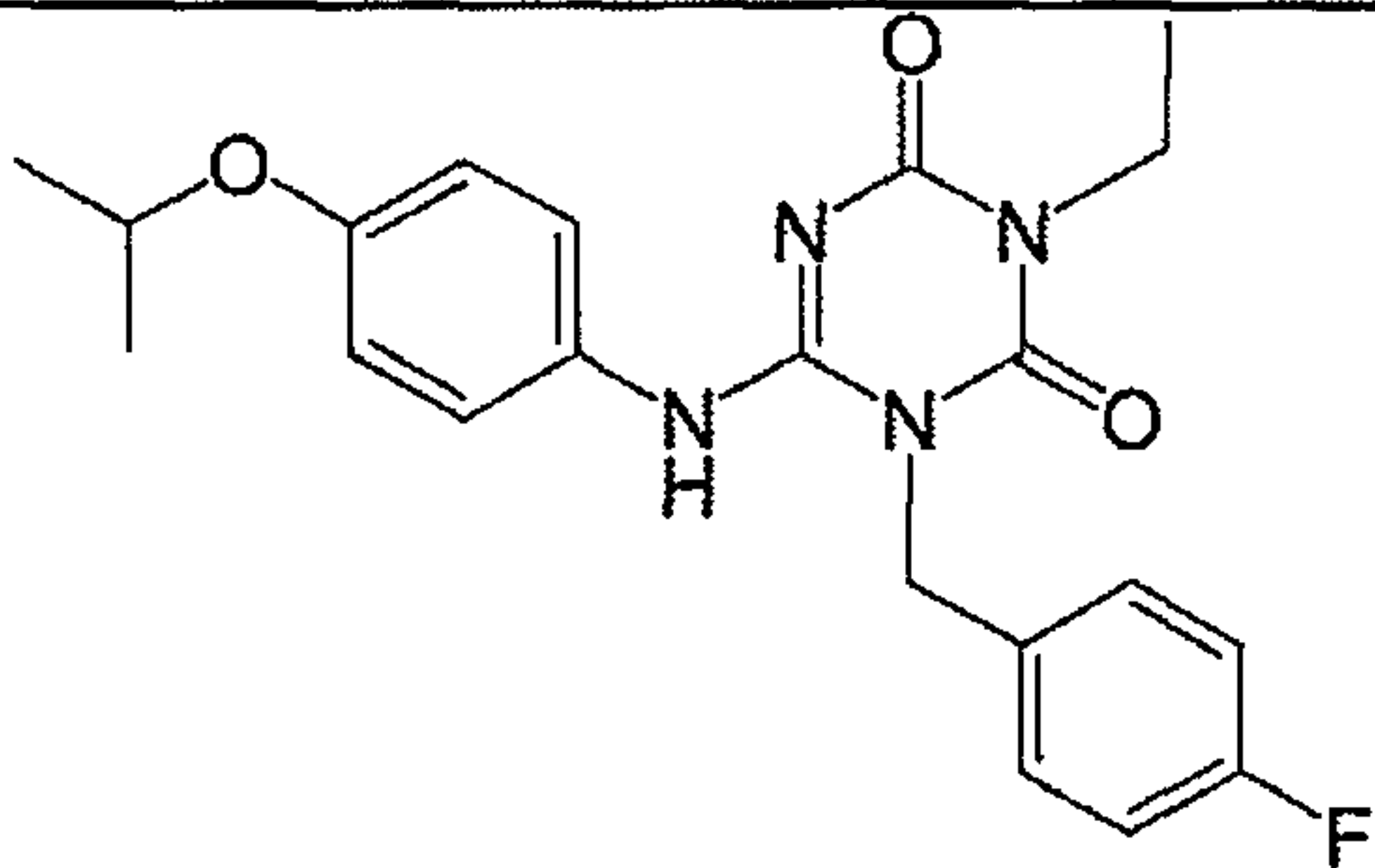
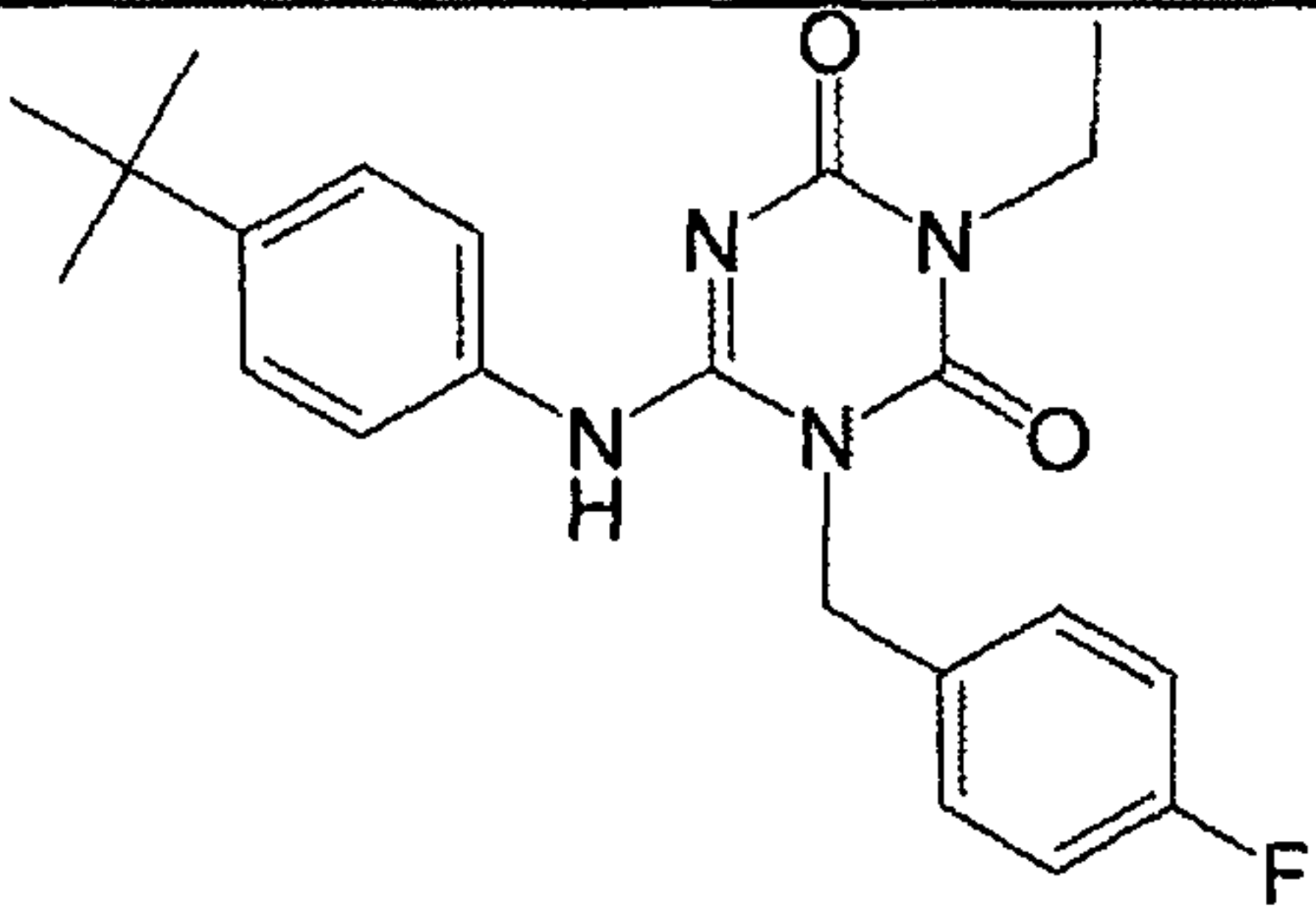
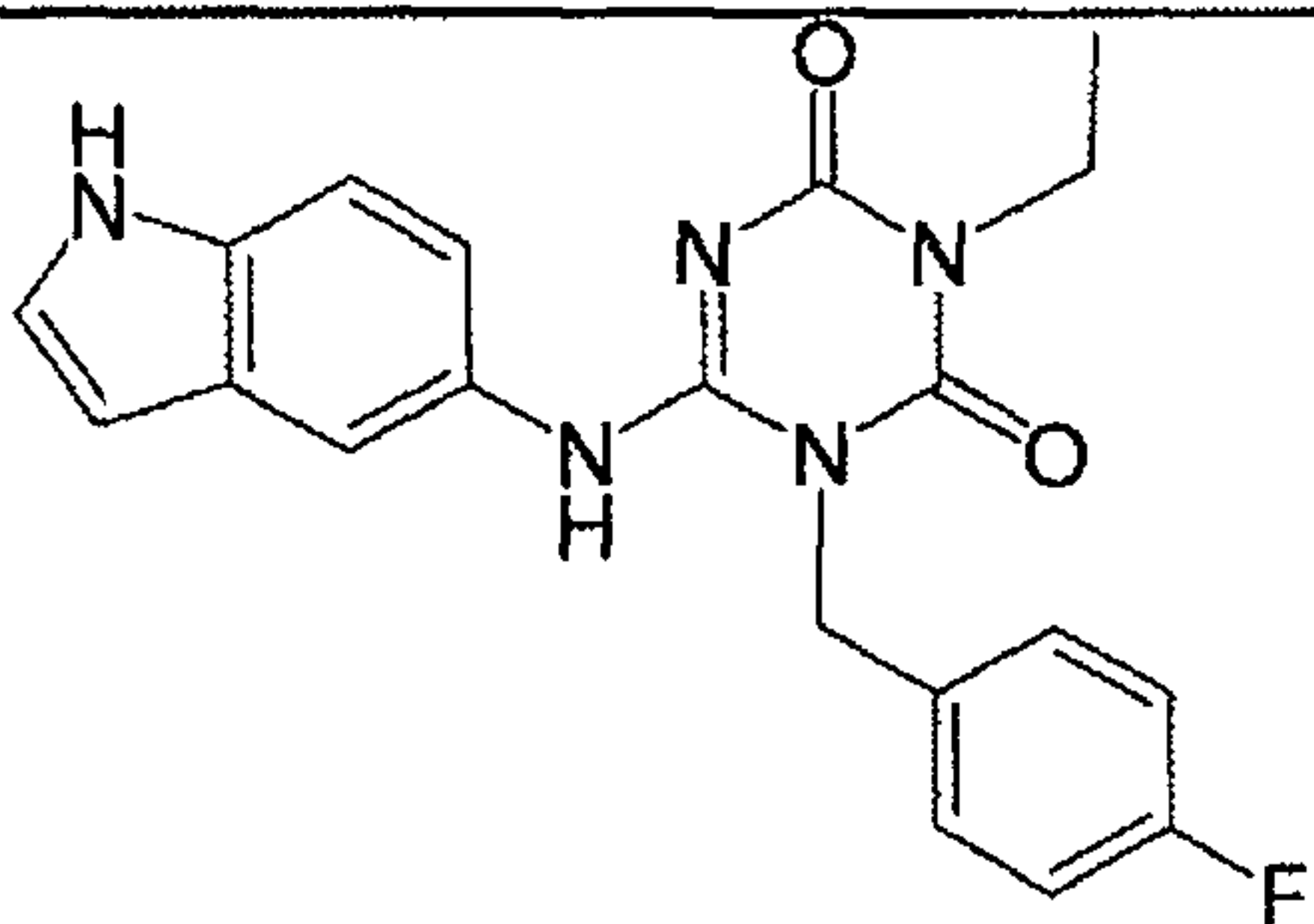
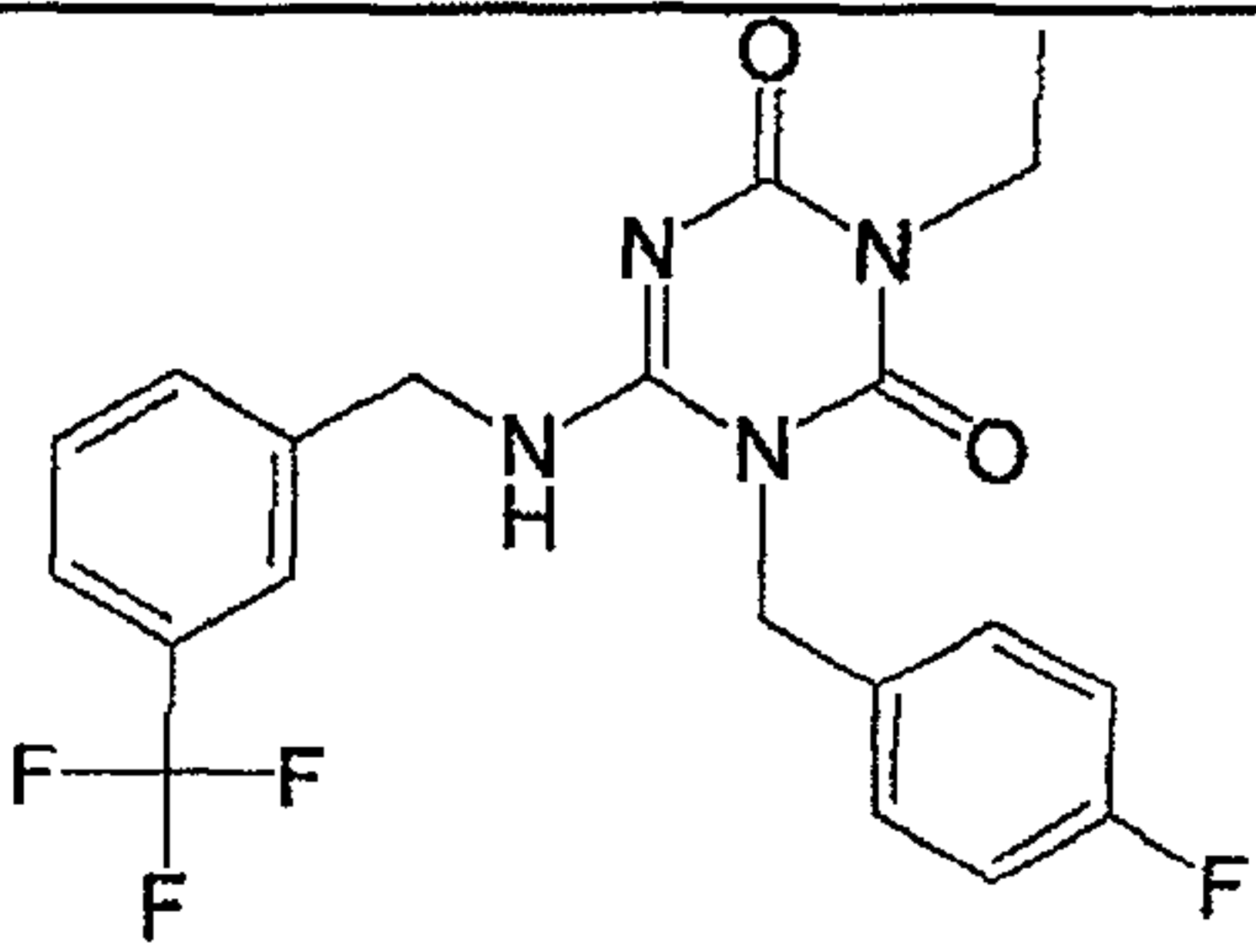
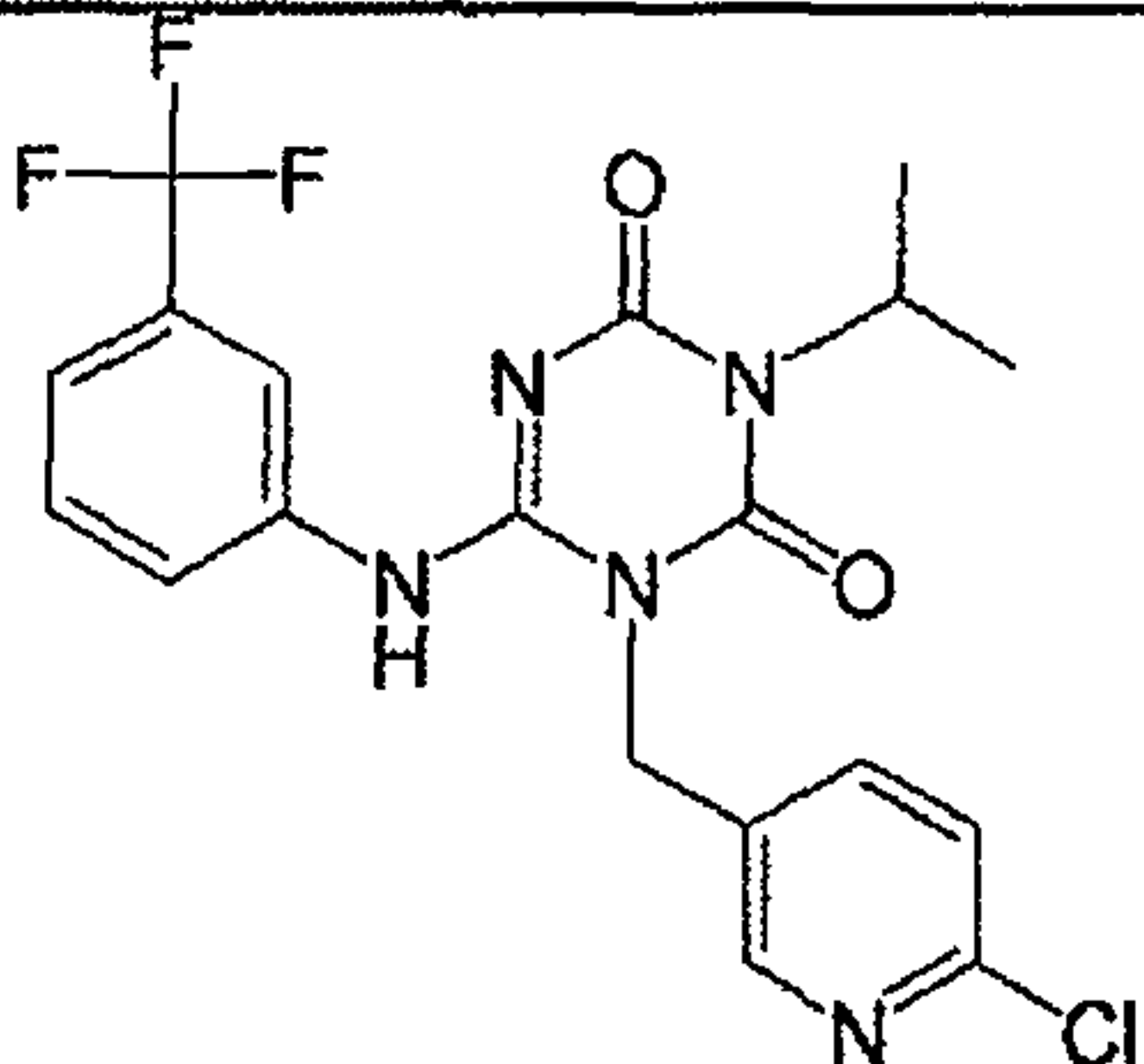
[Table 31]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0136	1.93	440	1
	I-0137	2.18	437	1
	I-0138	2.35	409	1
	I-0139	2.18	407	1
	I-0140	2.44	433	1

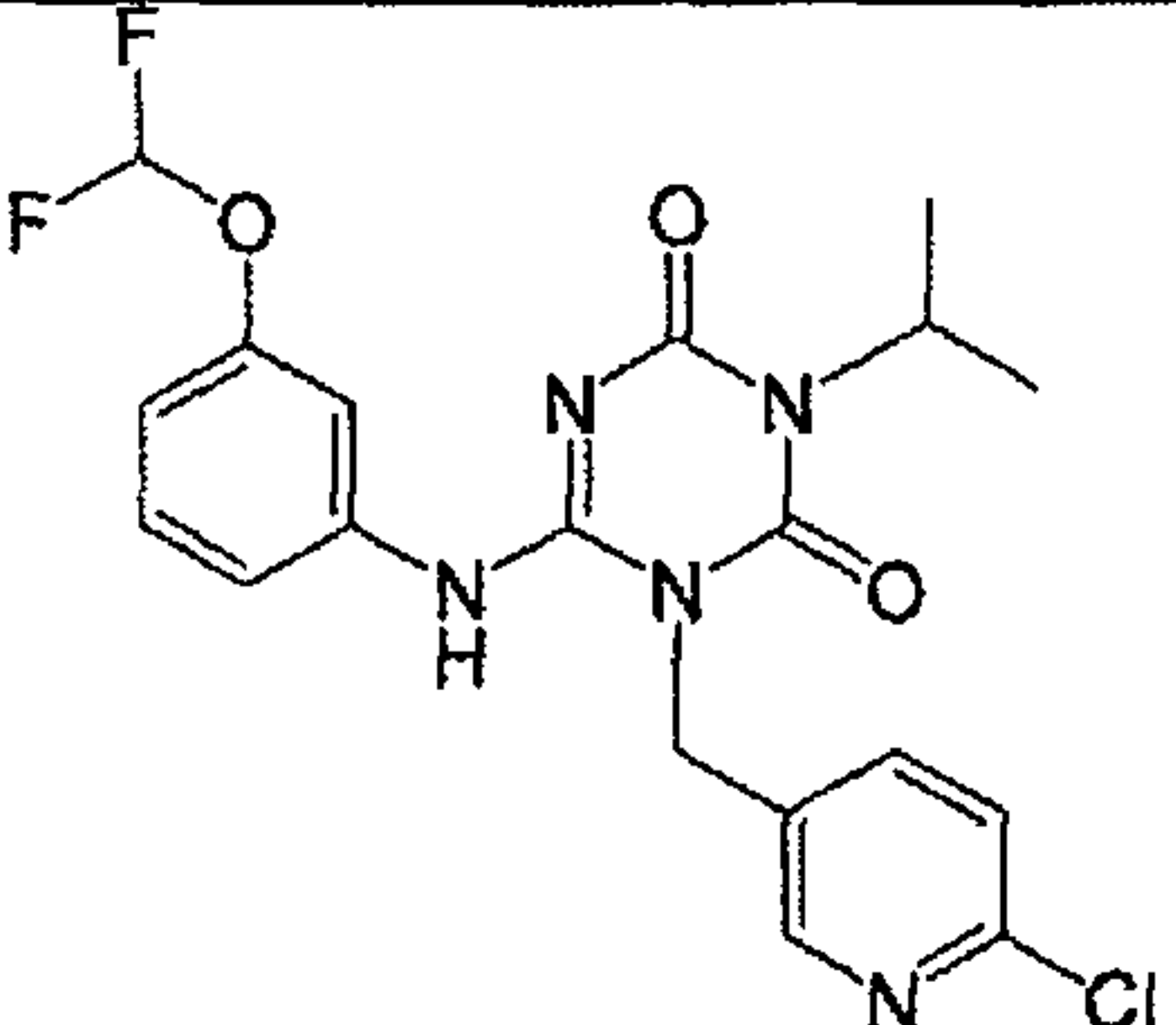
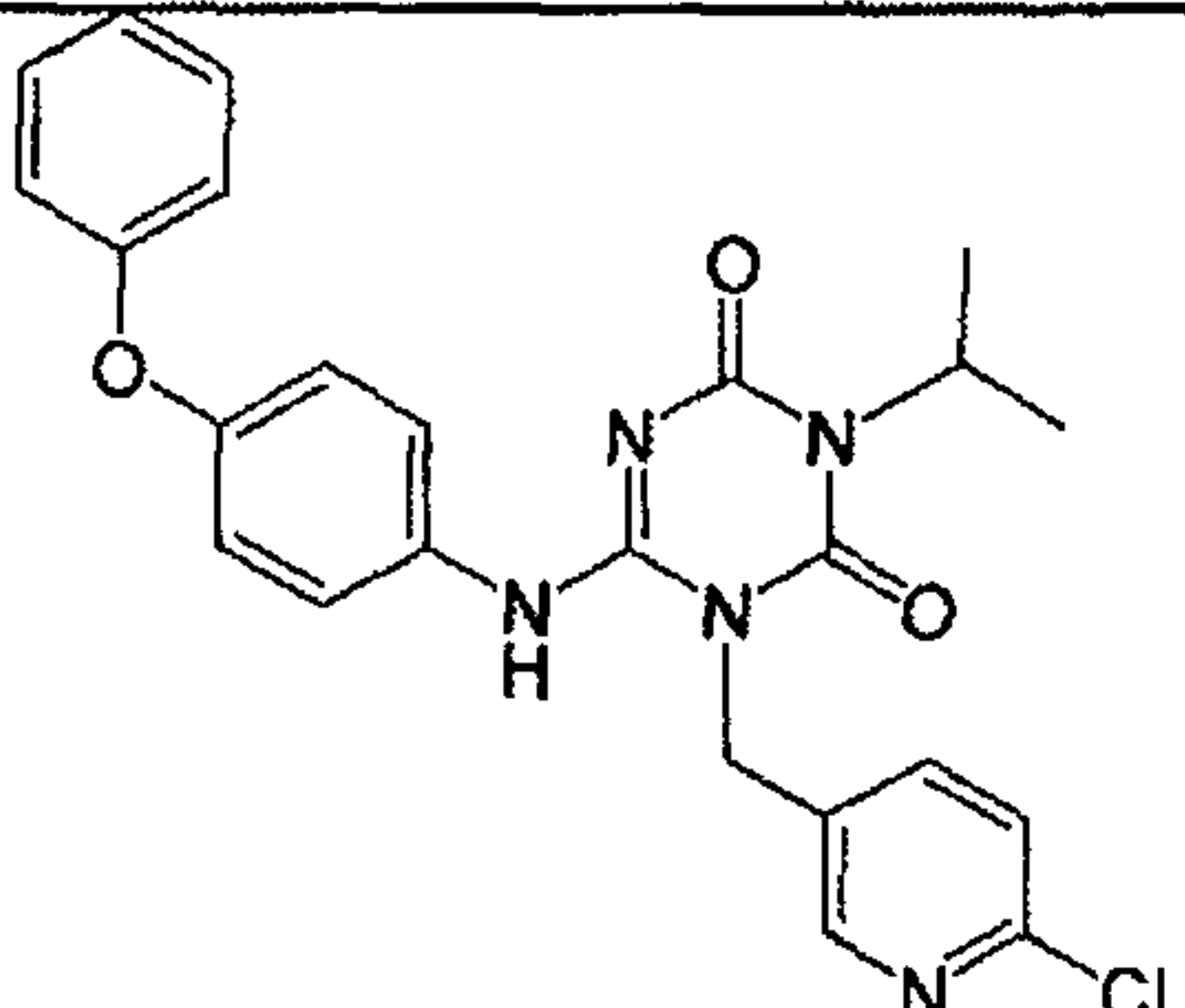
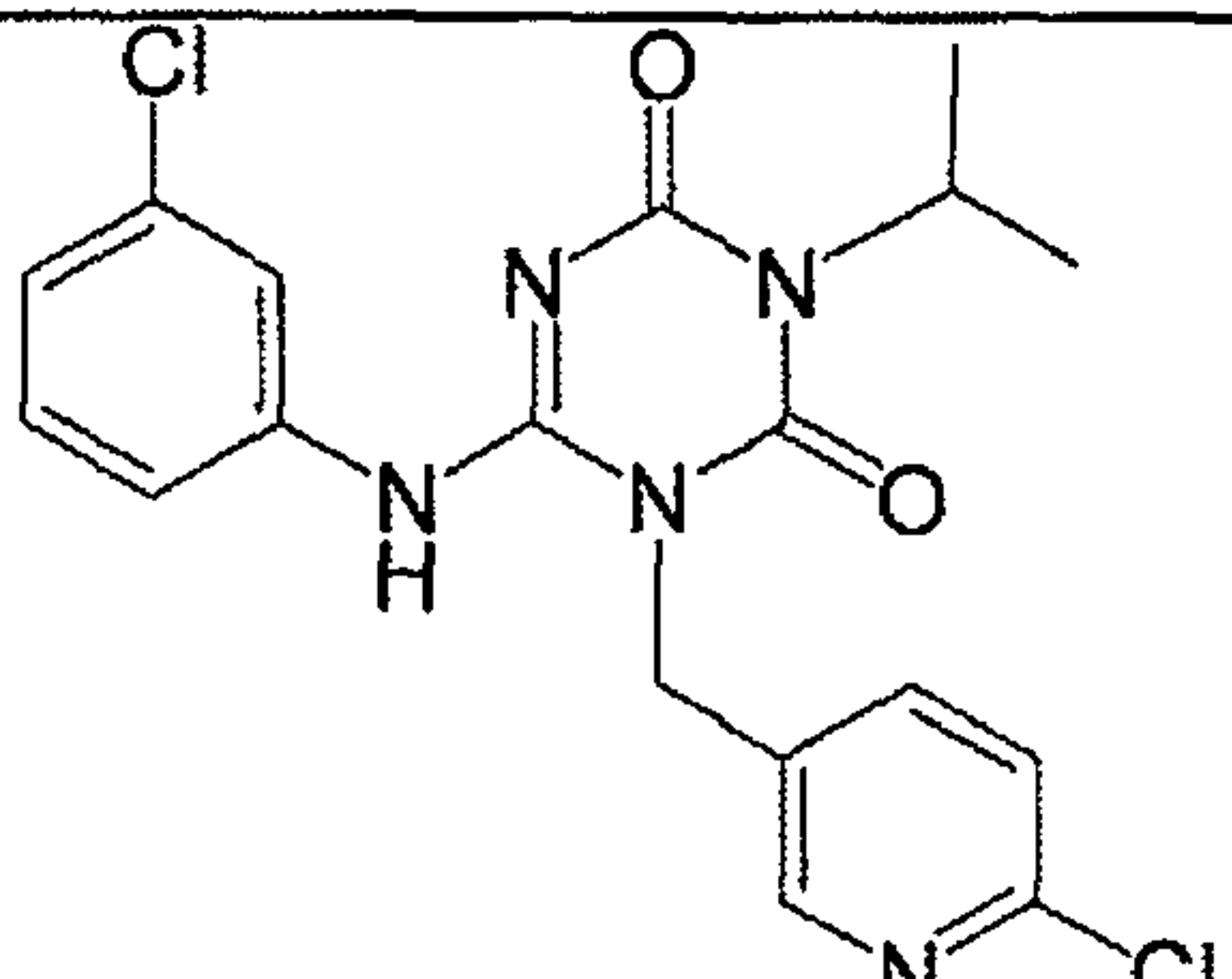
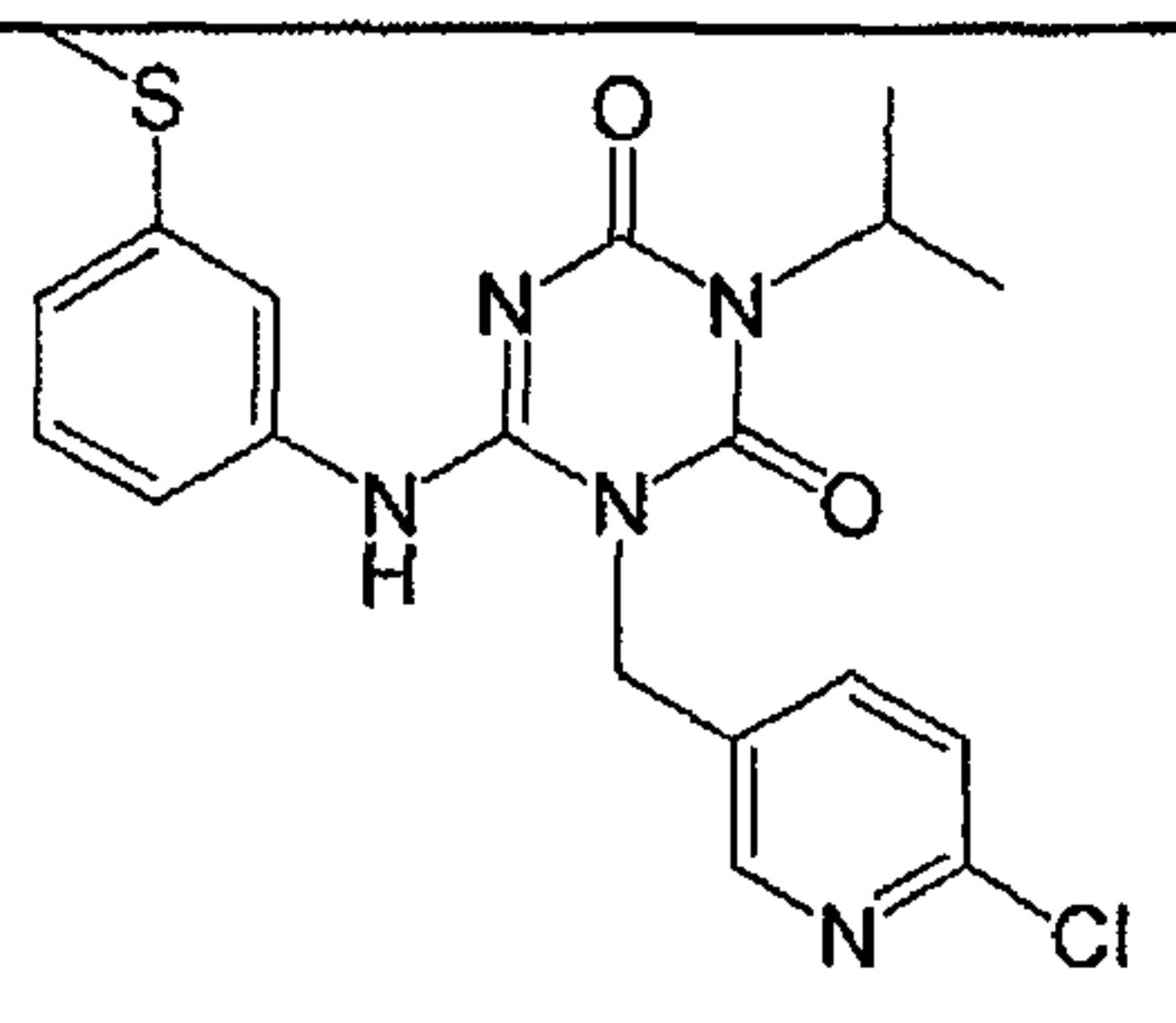
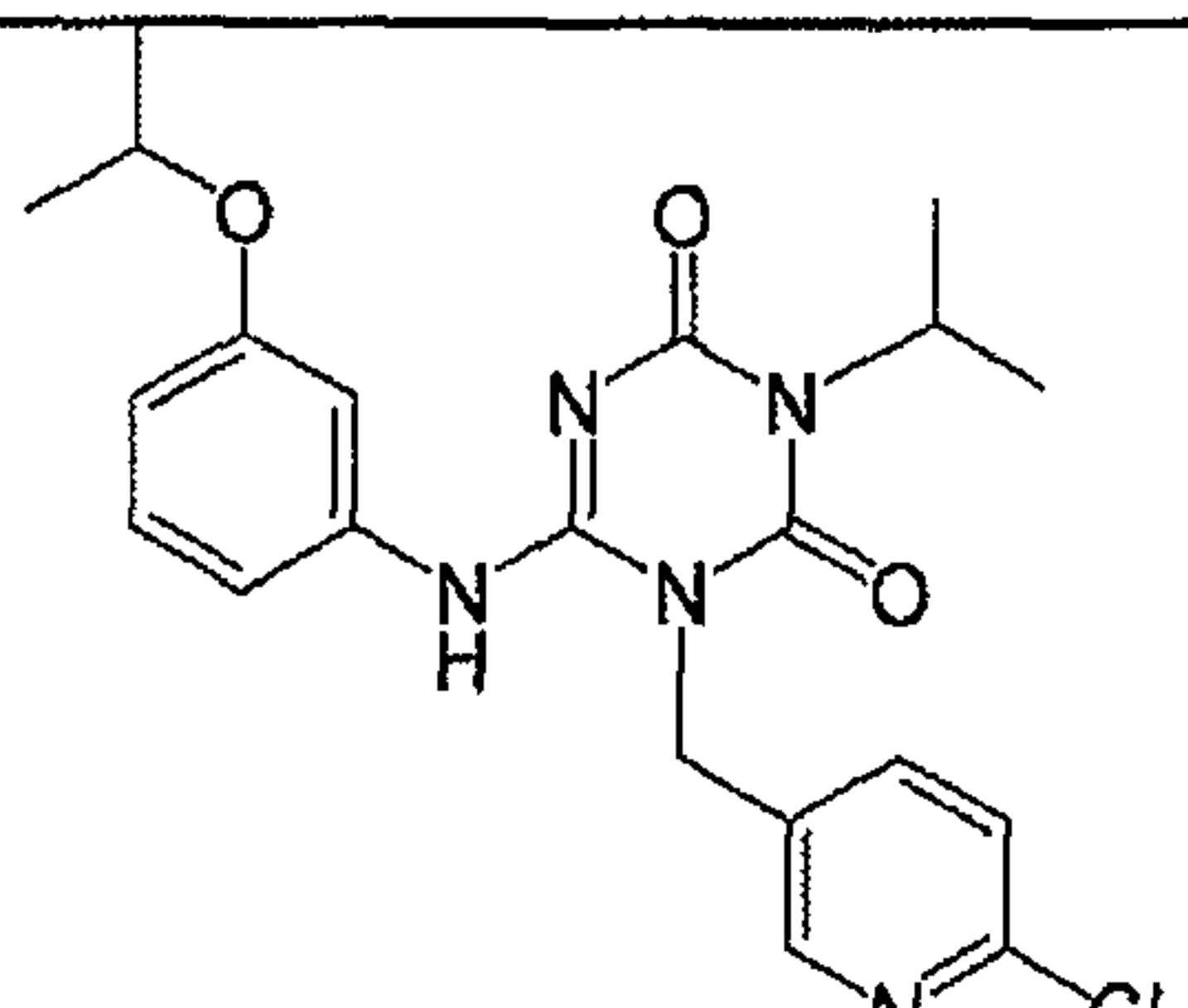
[Table 32]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0141	2.37	433	1
	I-0142	2.26	374	1
	I-0143	2.17	387	1
	I-0144	2.27	399	1
	I-0145	2.45	397	1

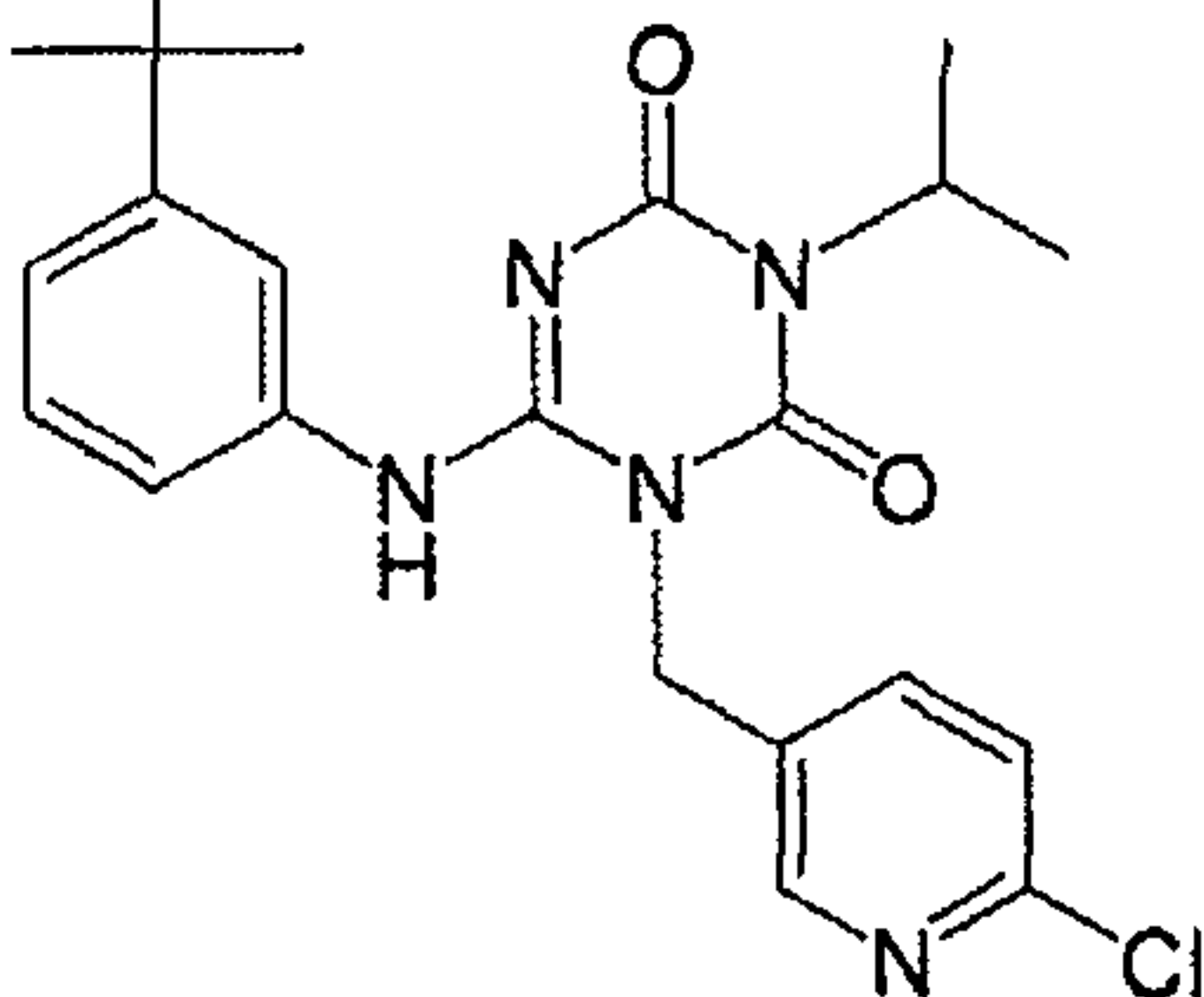
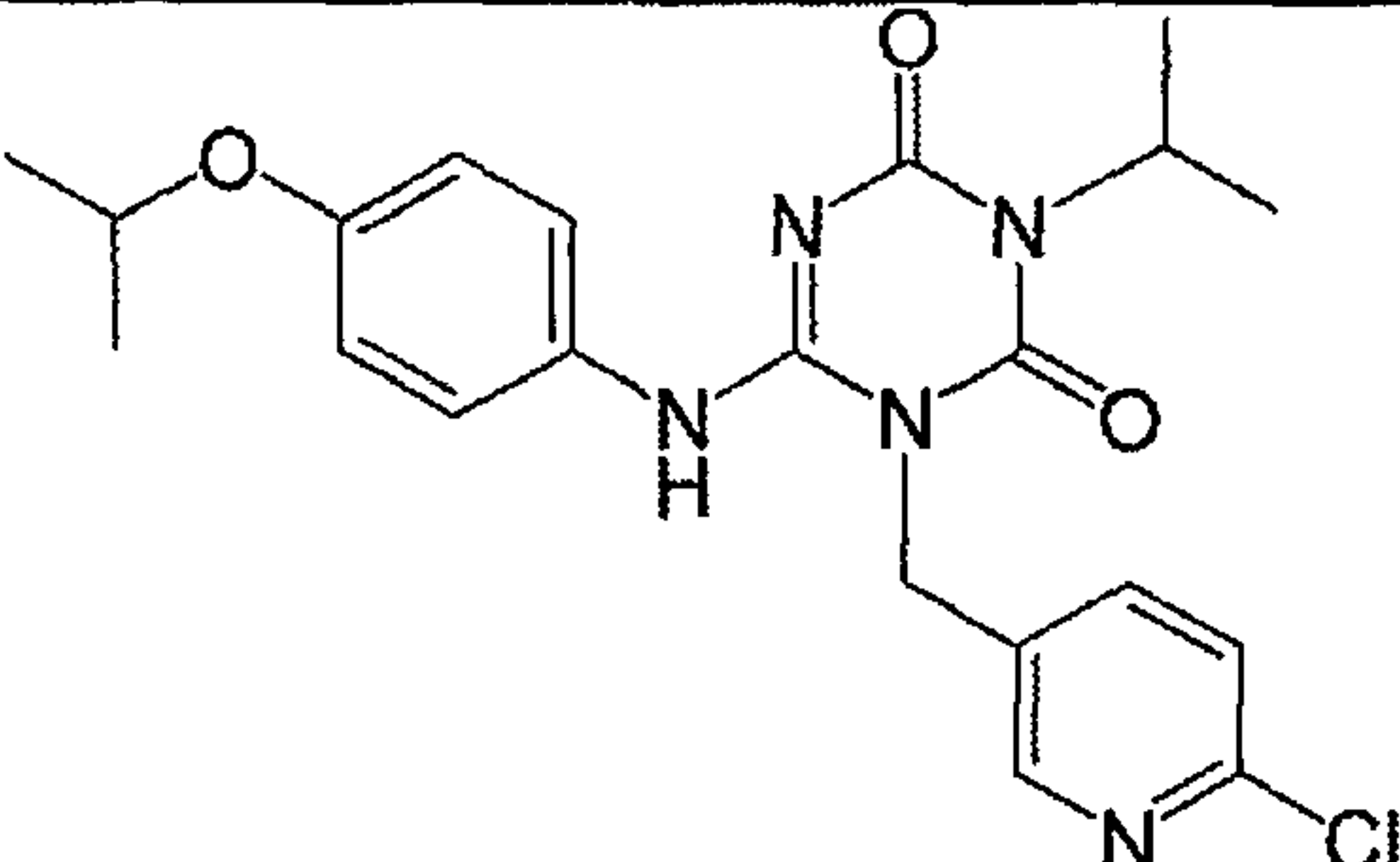
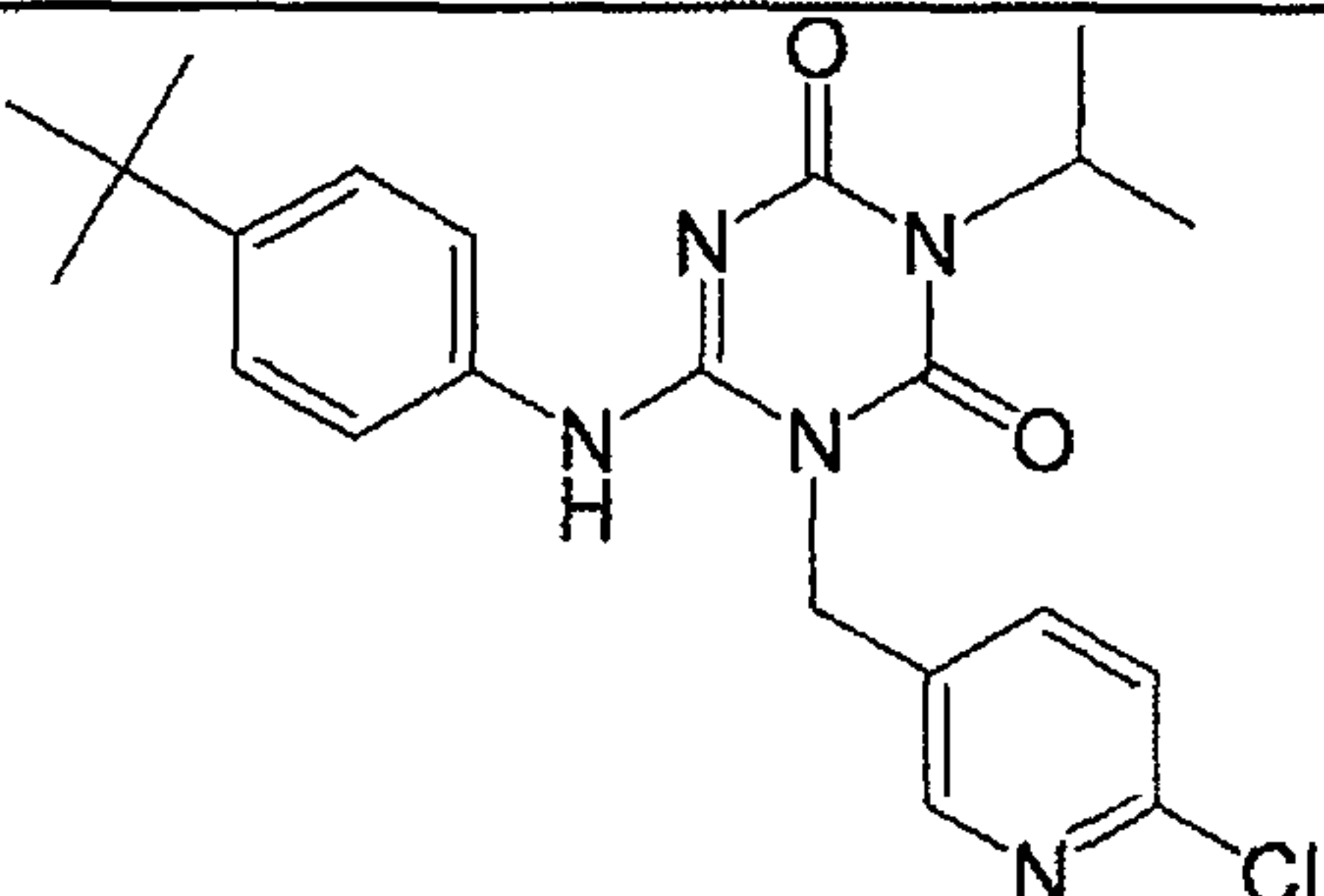
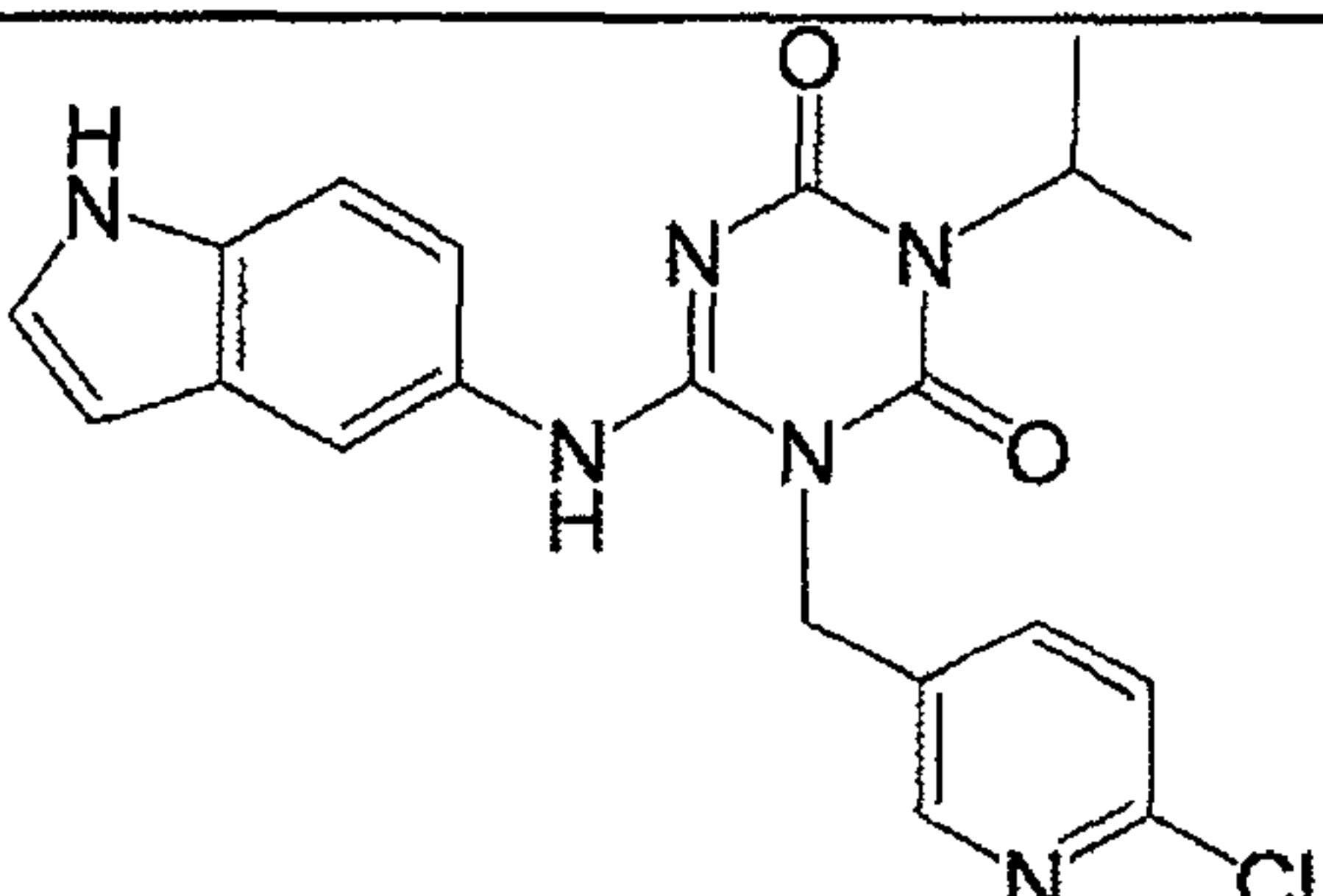
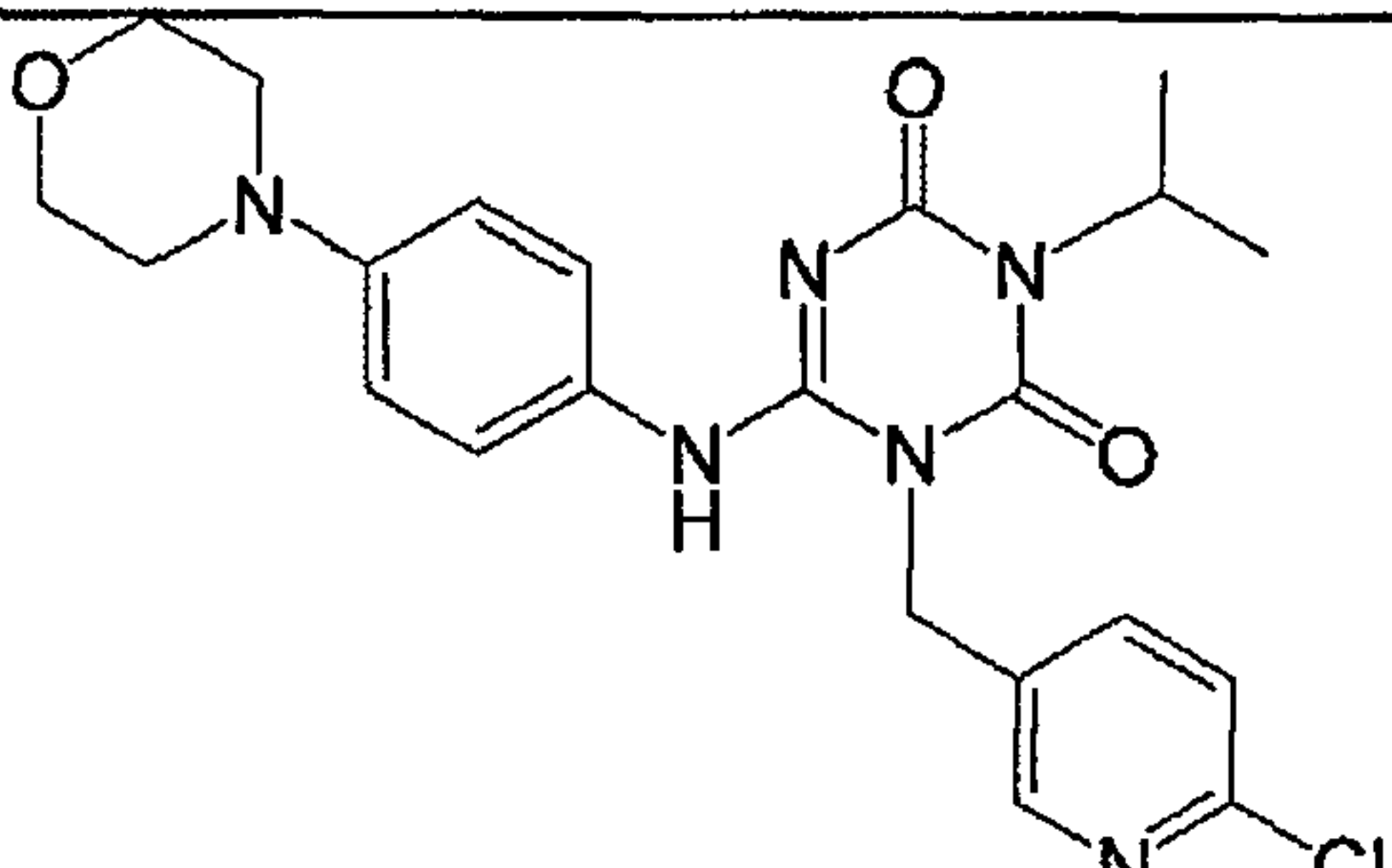
[Table 33]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0146	2.13	399	1
	I-0147	2.42	397	1
	I-0148	1.78	380	1
	I-0149	2.04	423	1
	I-0150	2.40	440	1

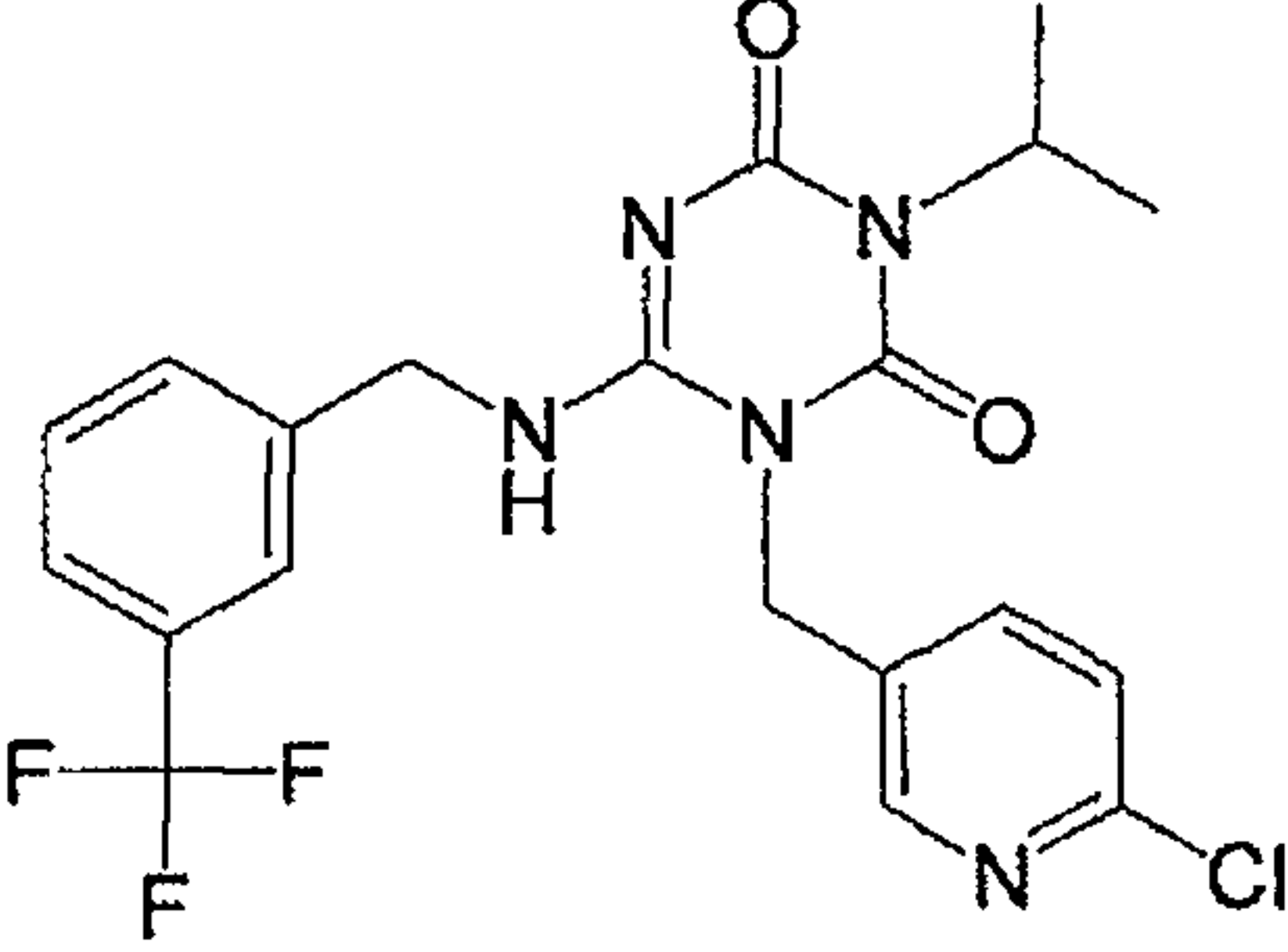
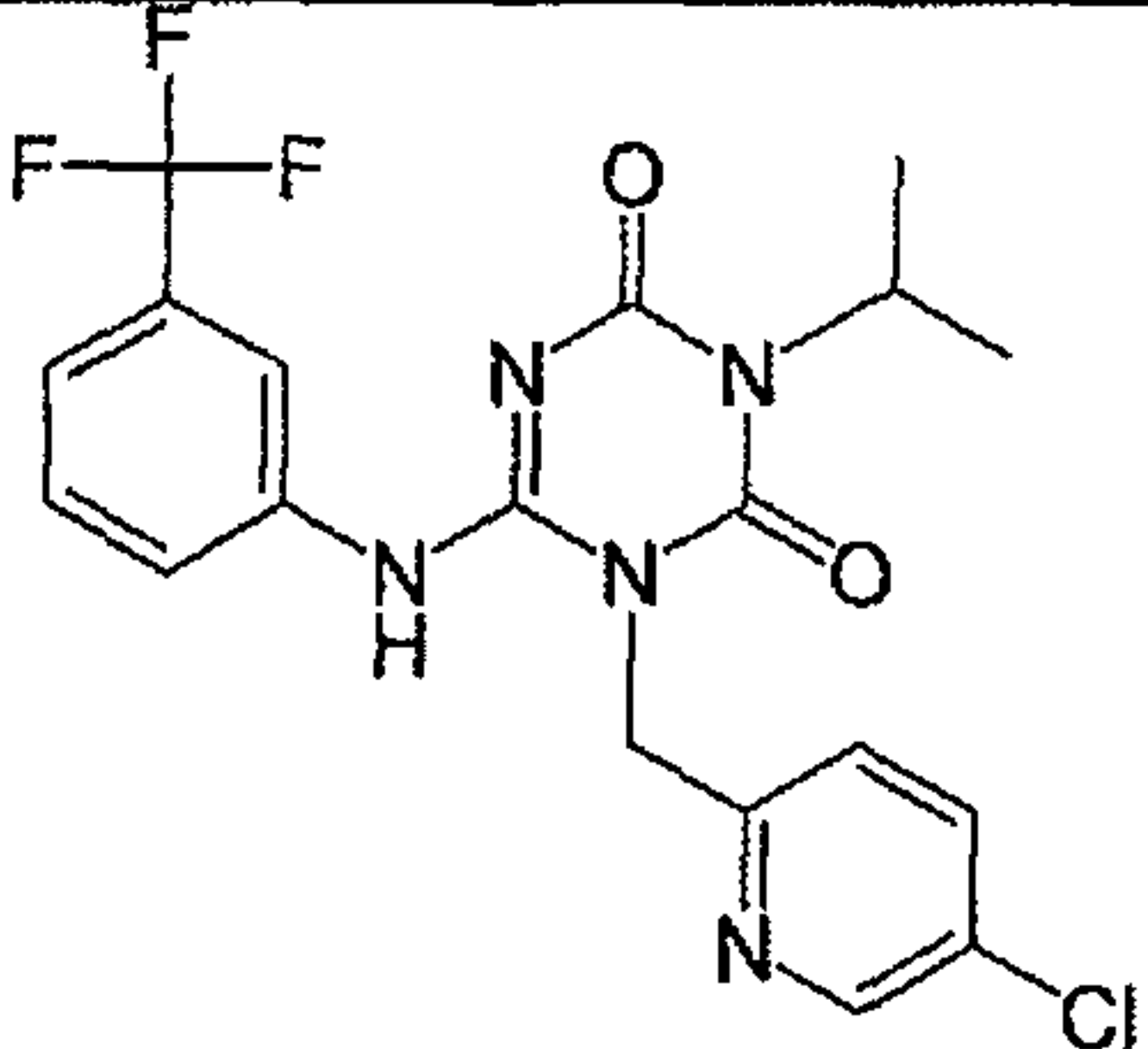
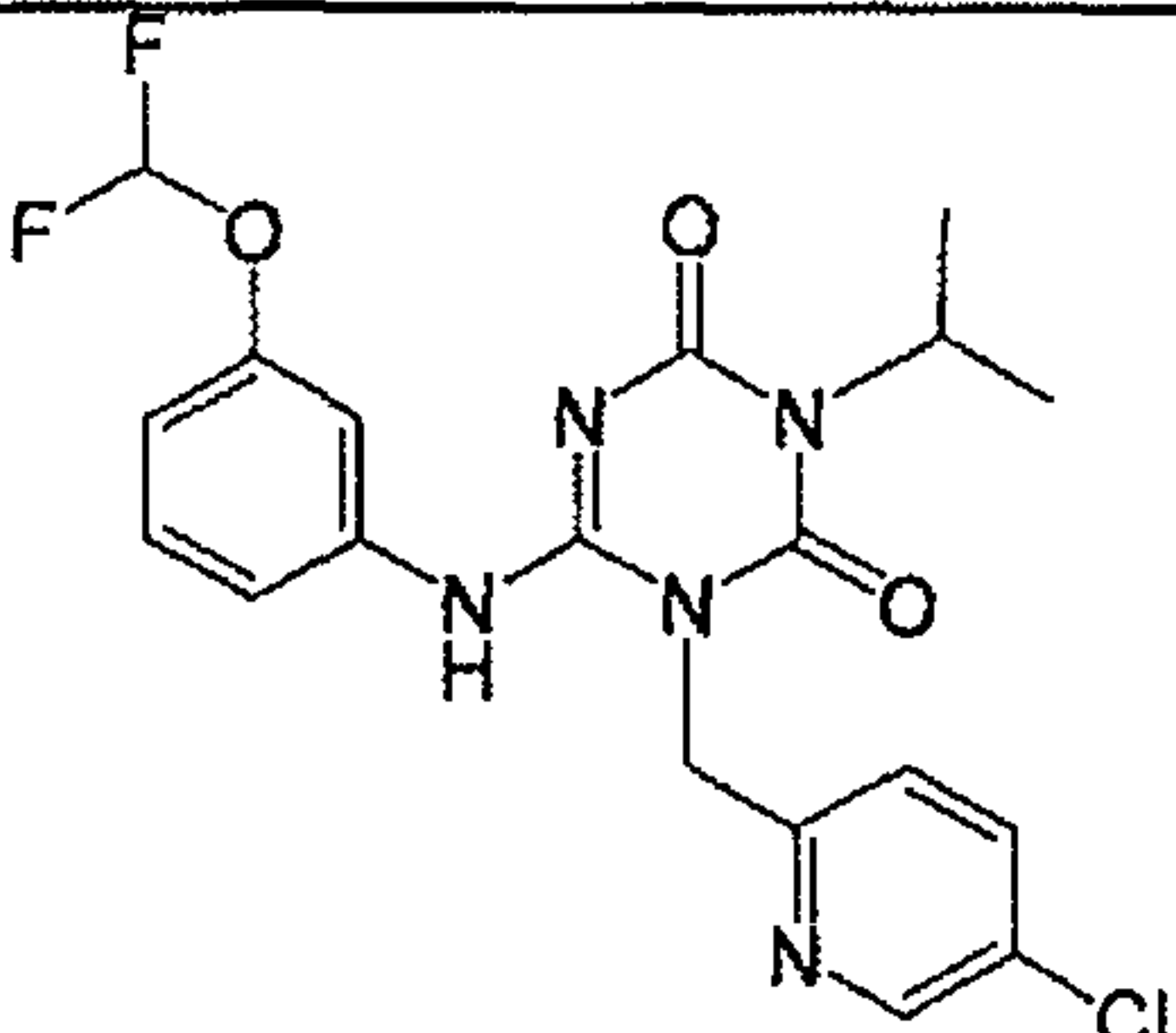
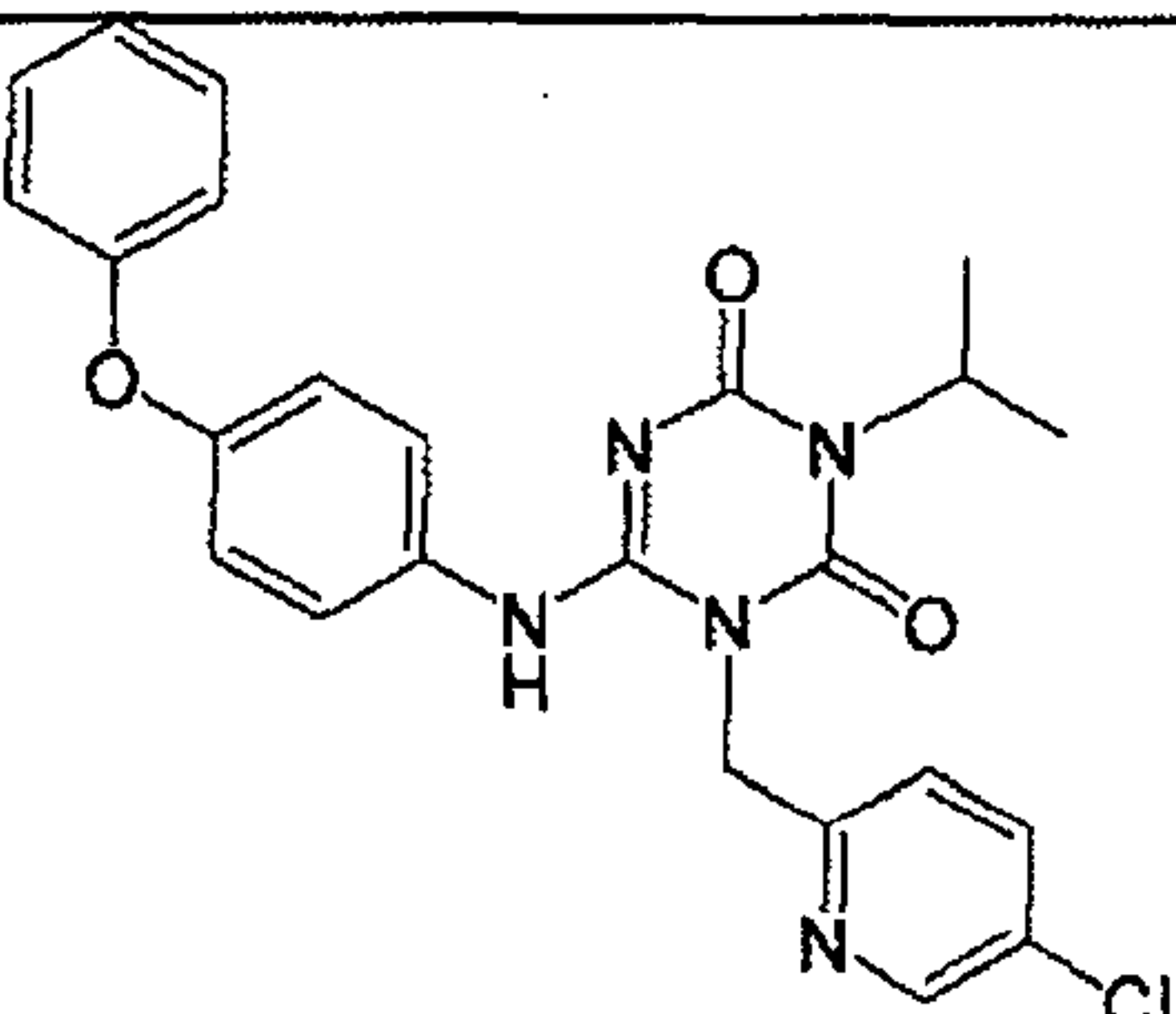
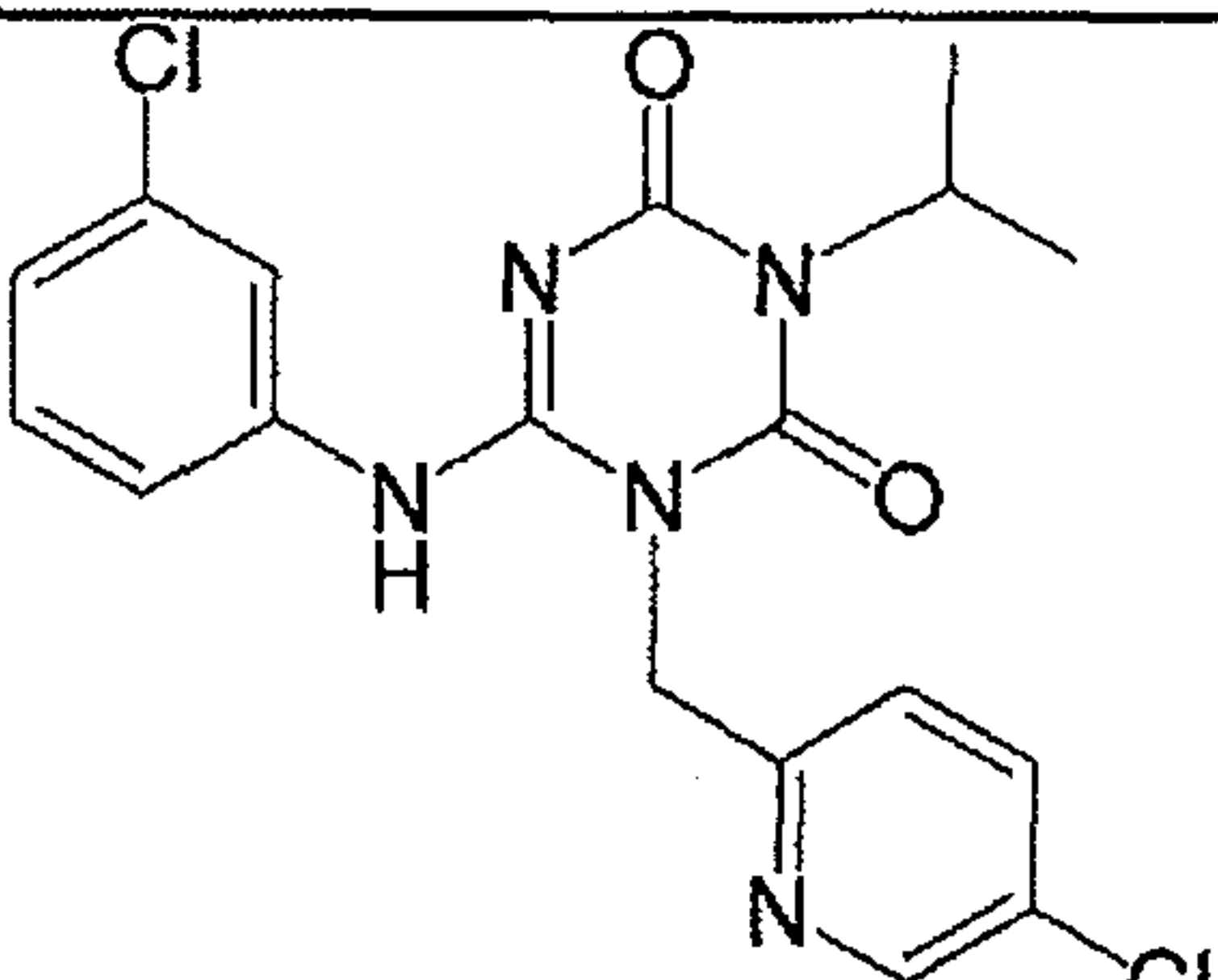
[Table 34]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0151	2.24	438	1
	I-0152	2.44	464	1
	I-0153	2.30	407	1
	I-0154	2.25	418	1
	I-0155	2.34	430	1

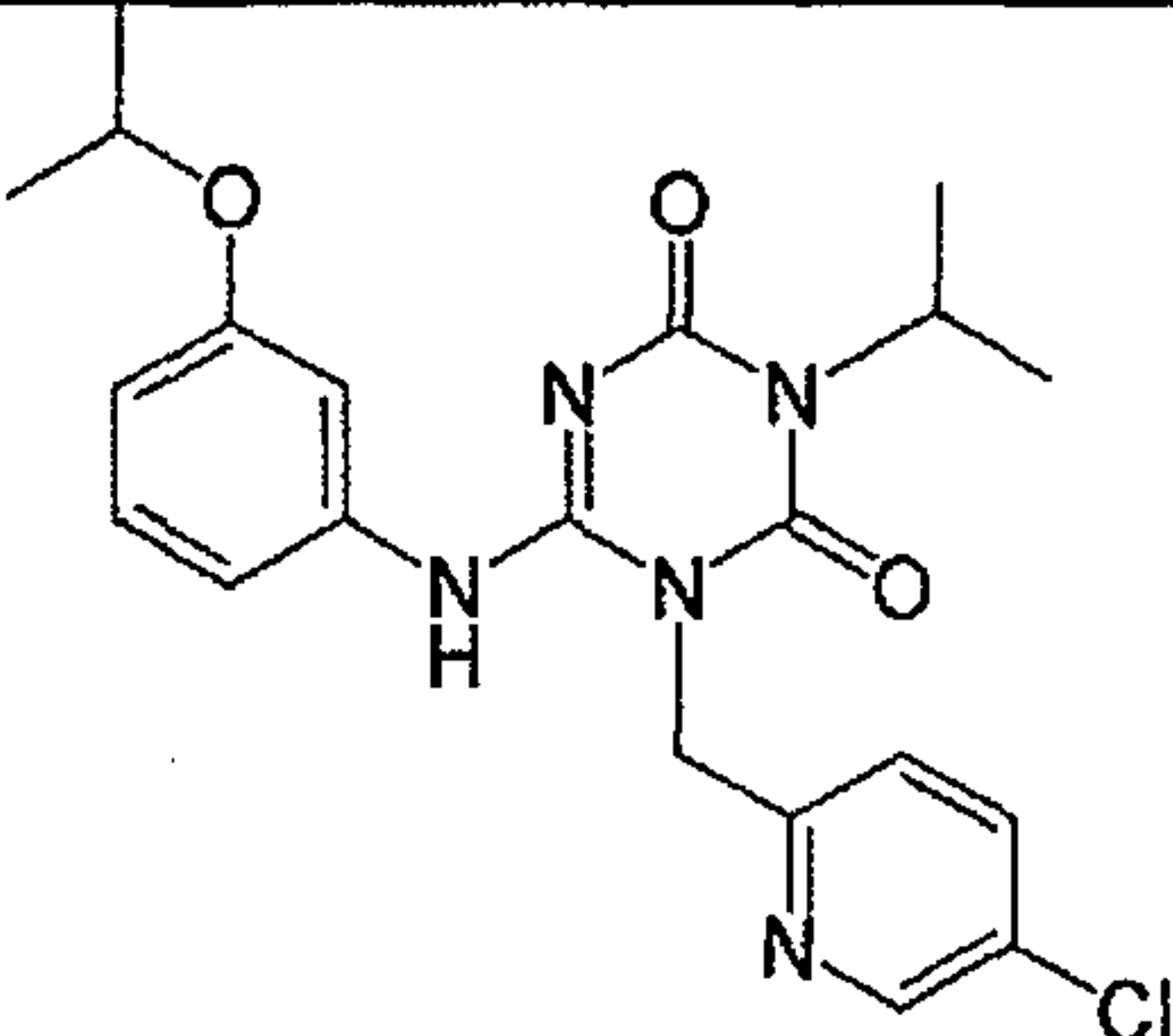
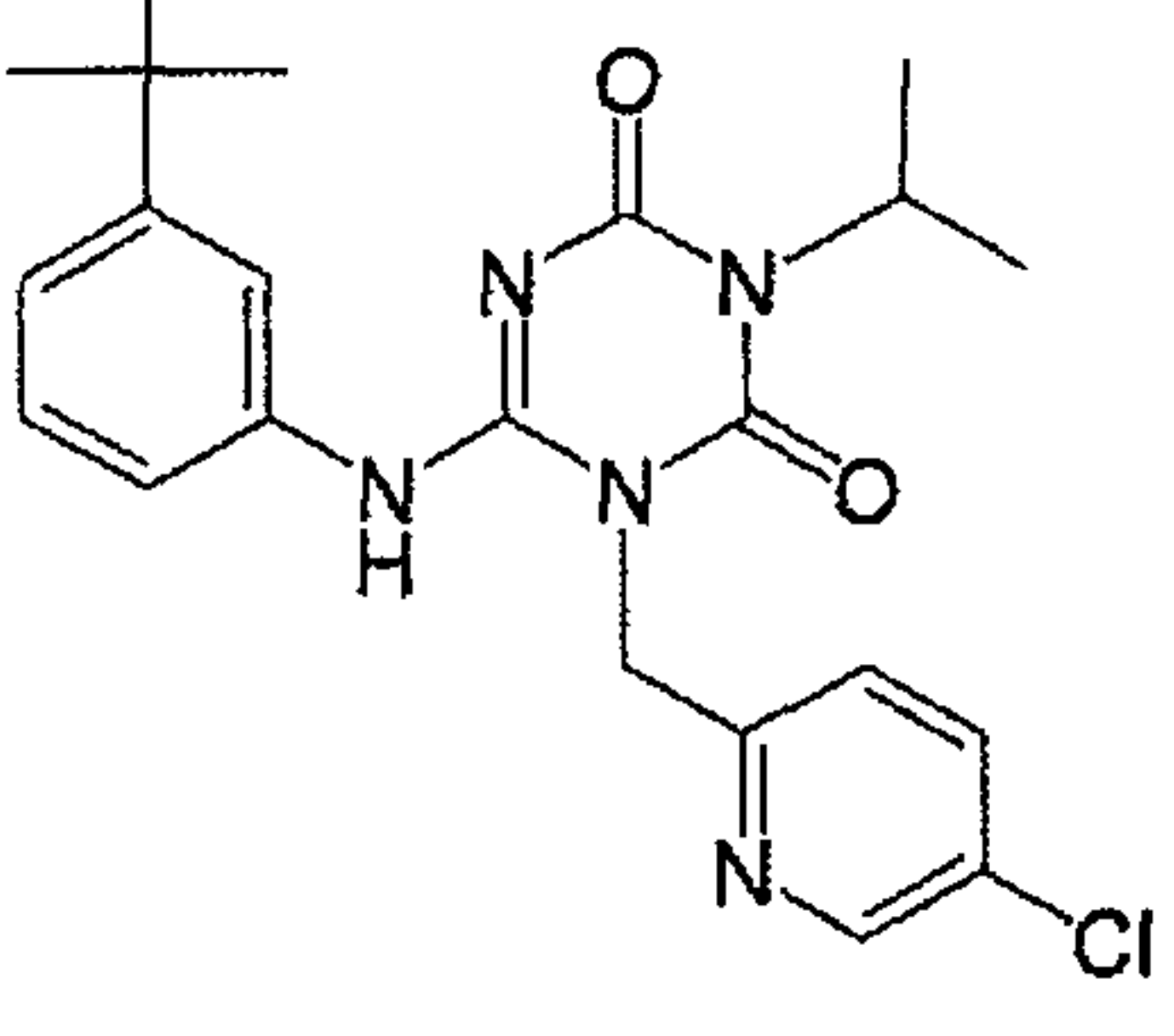
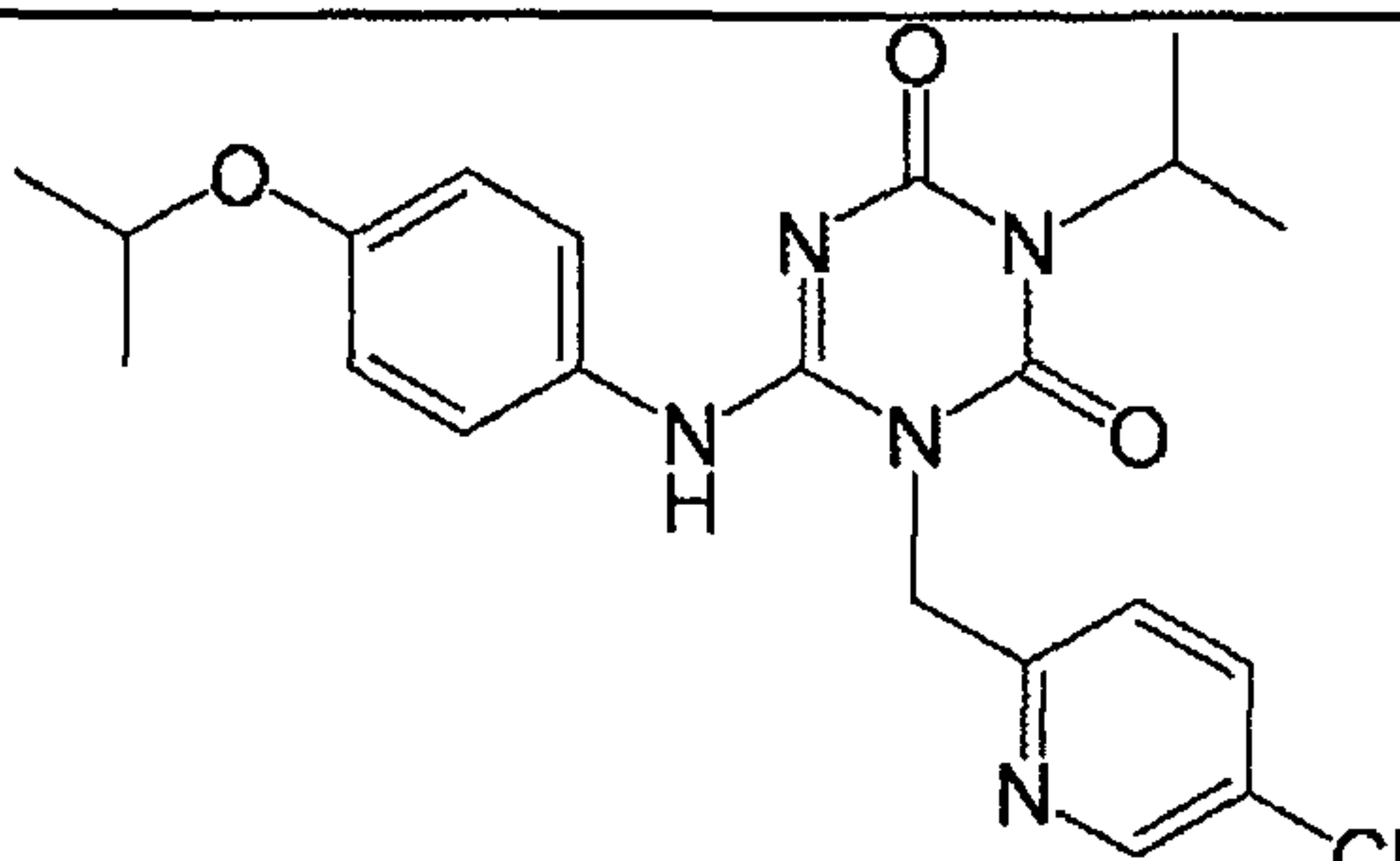
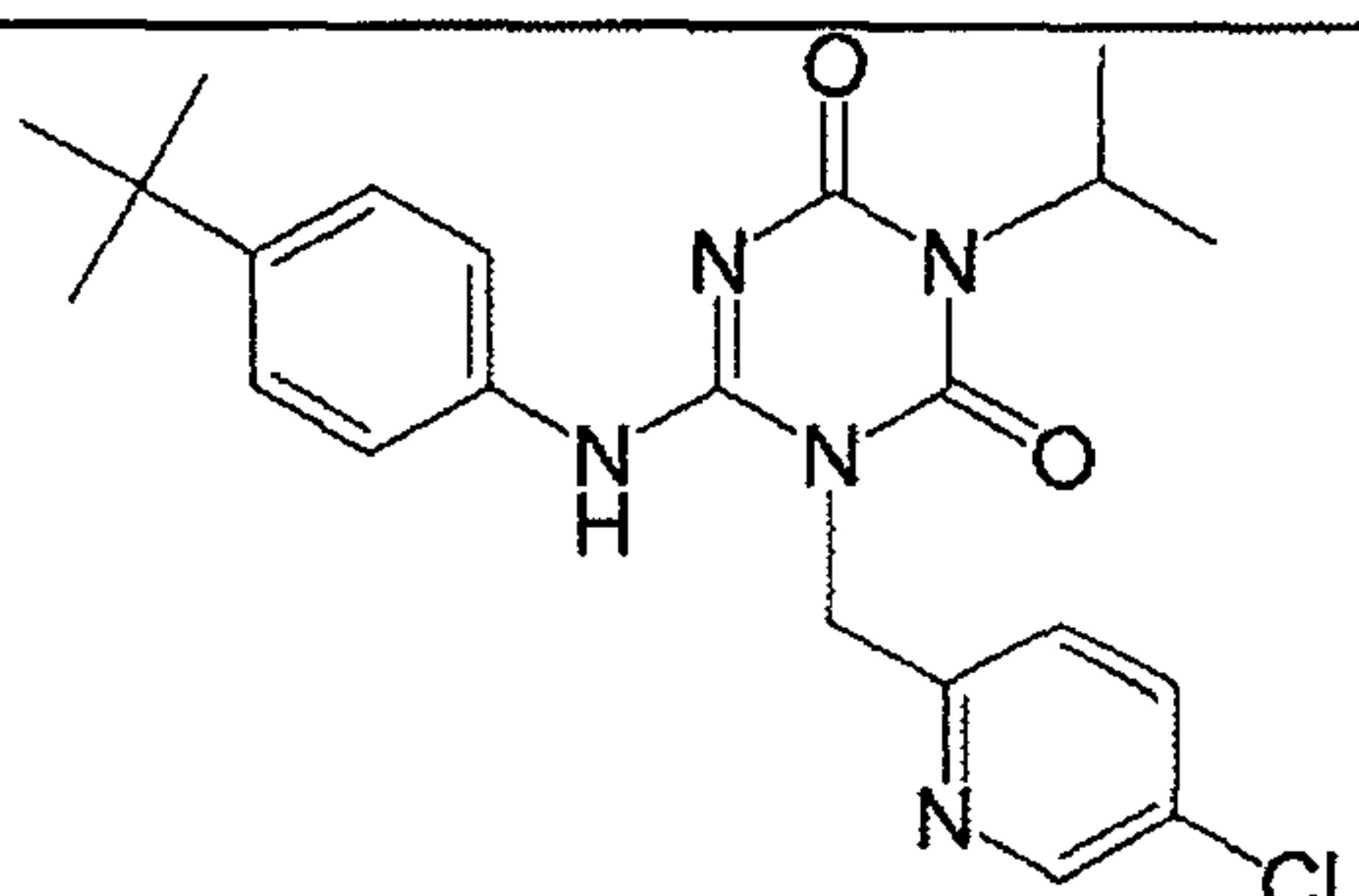
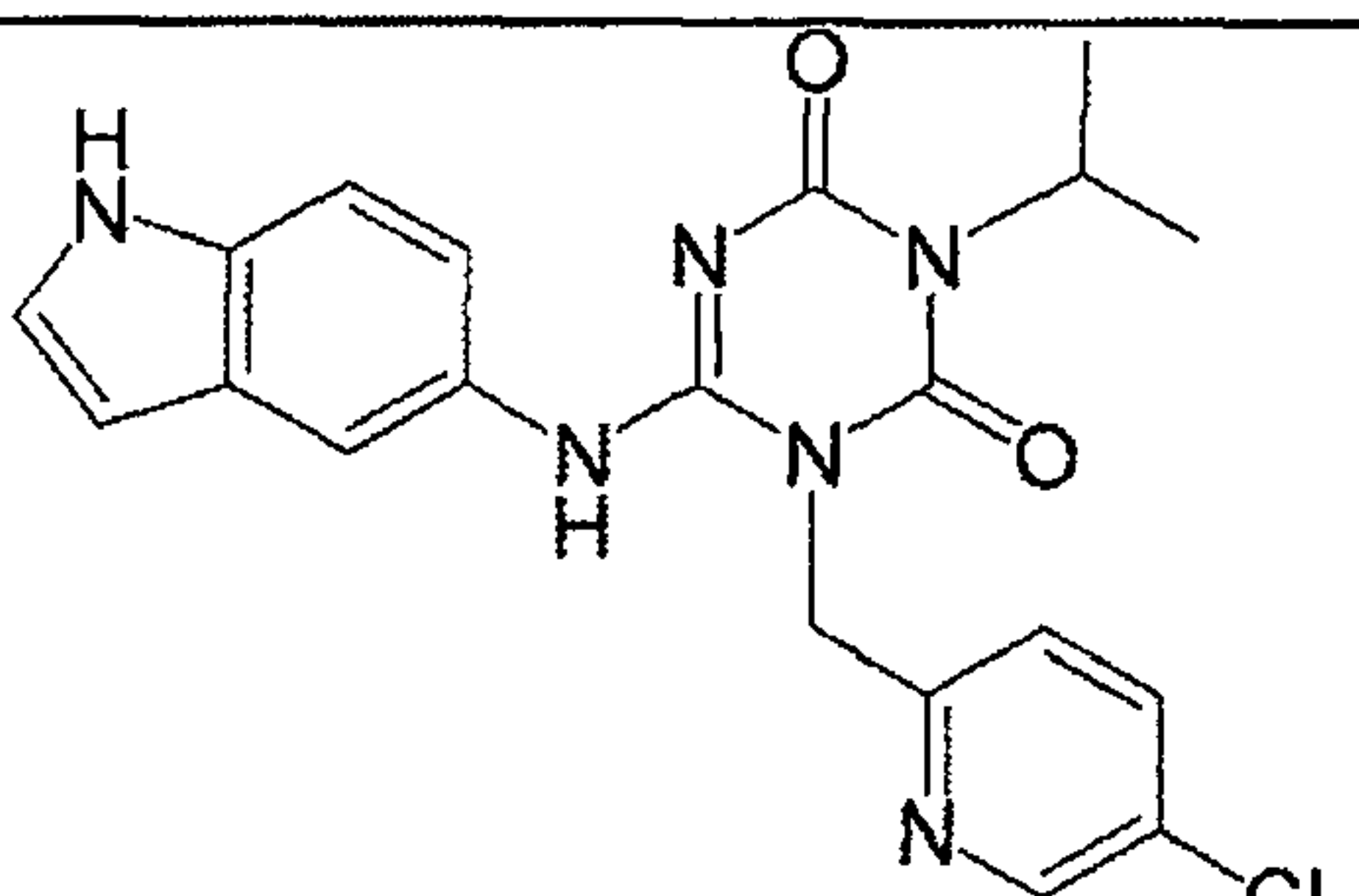
[Table 35]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0156	2.53	428	1
	I-0157	2.21	430	1
	I-0158	2.51	428	1
	I-0159	1.83	411	1
	I-0160	1.77	457	1

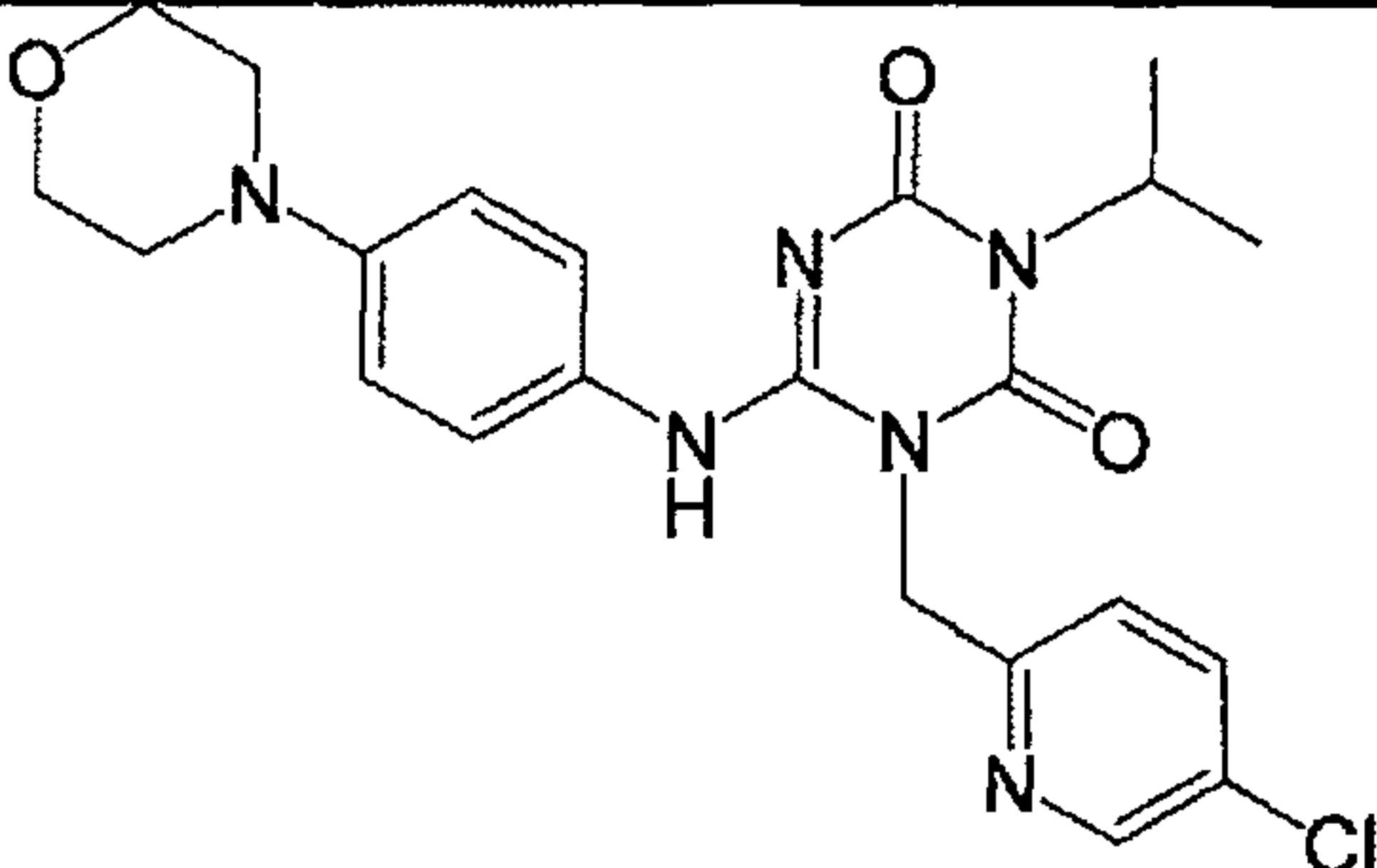
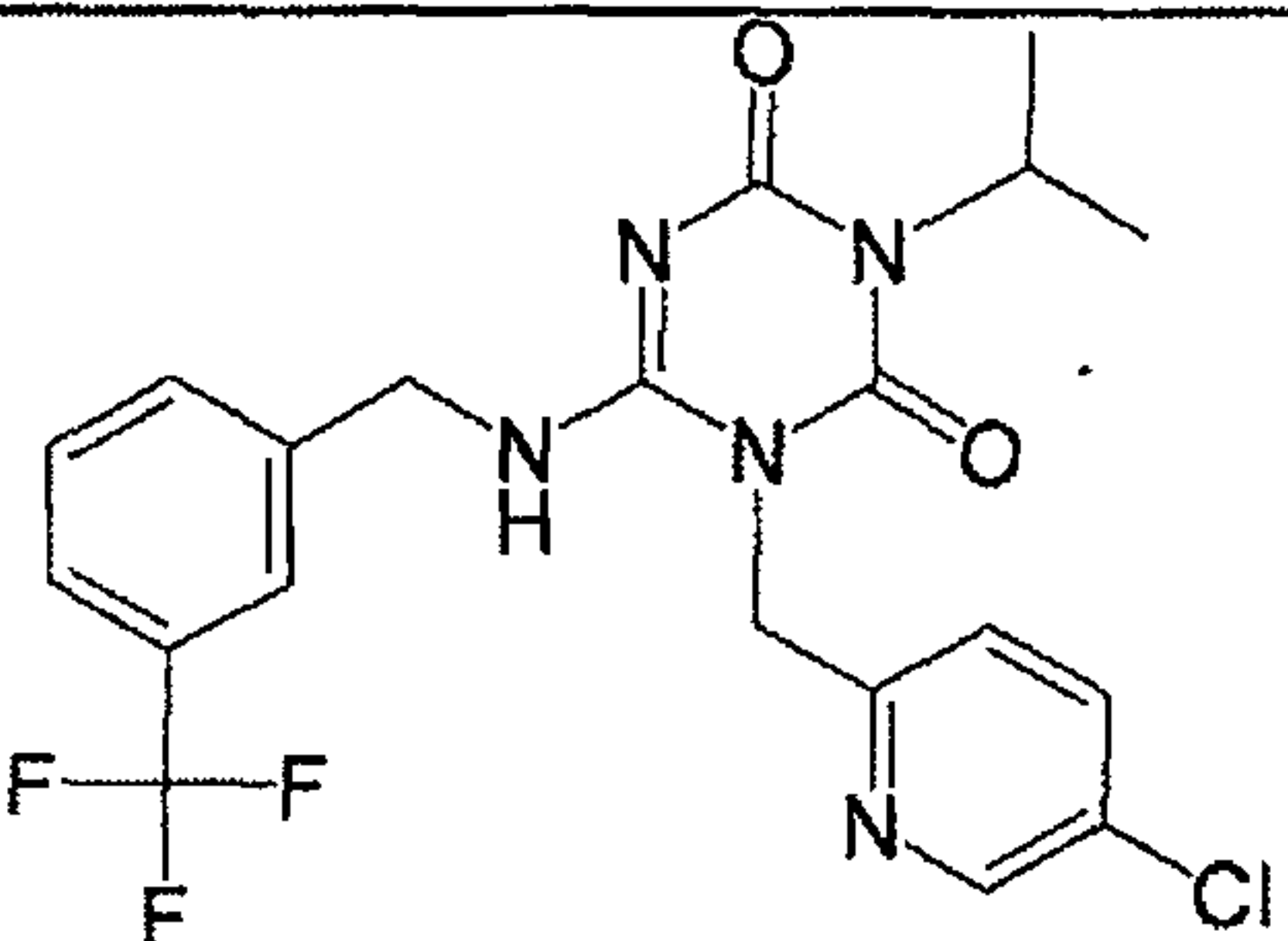
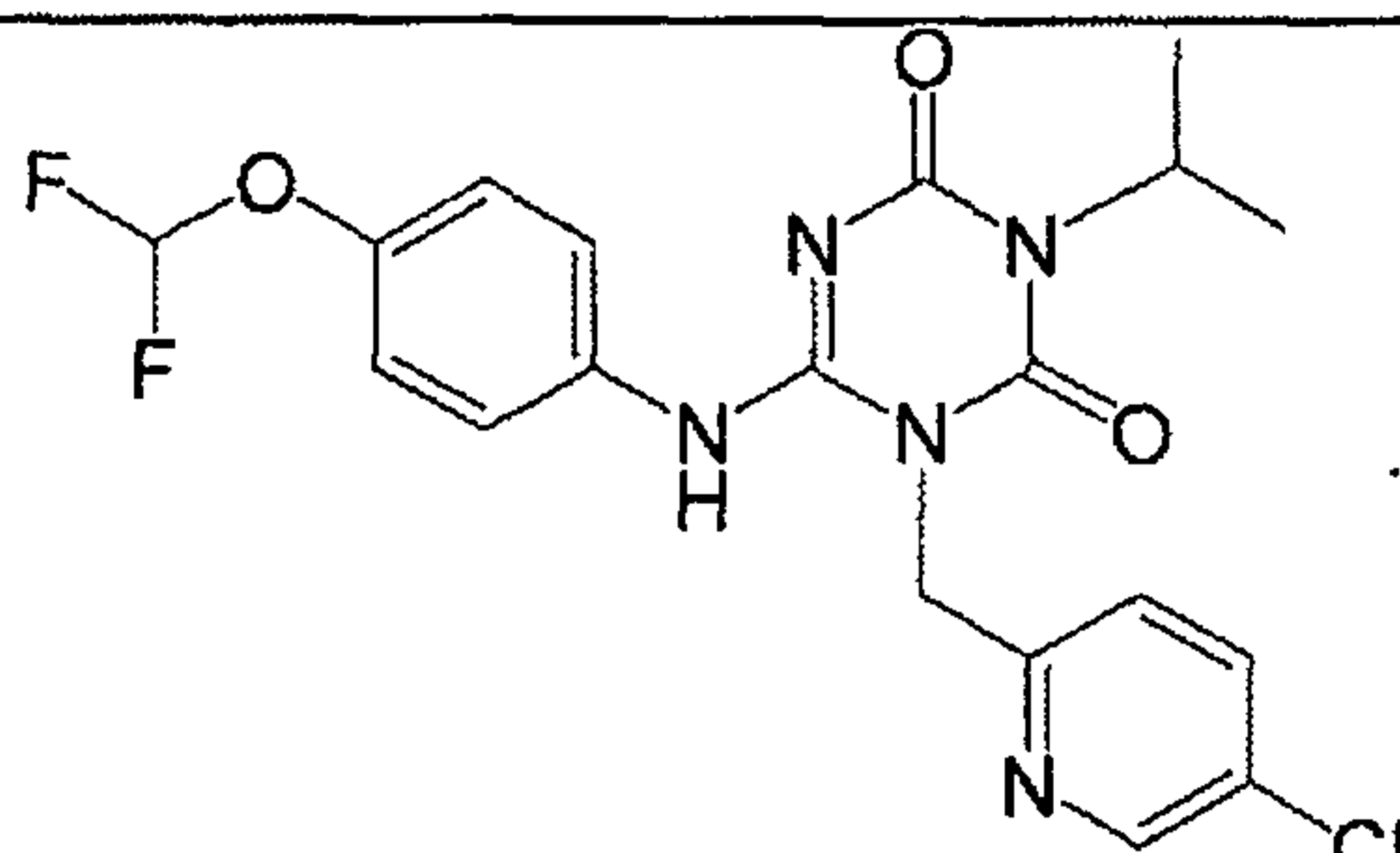
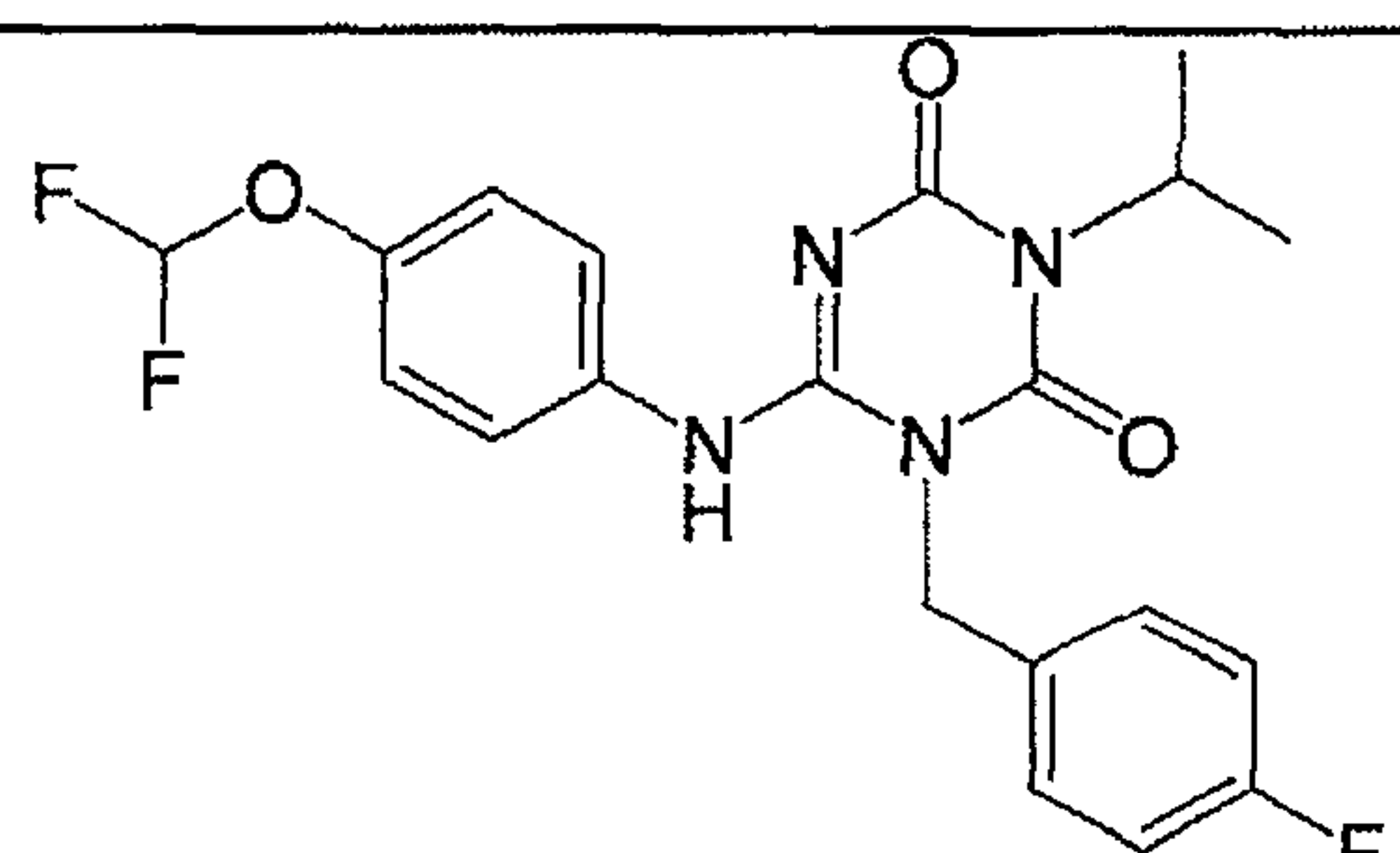
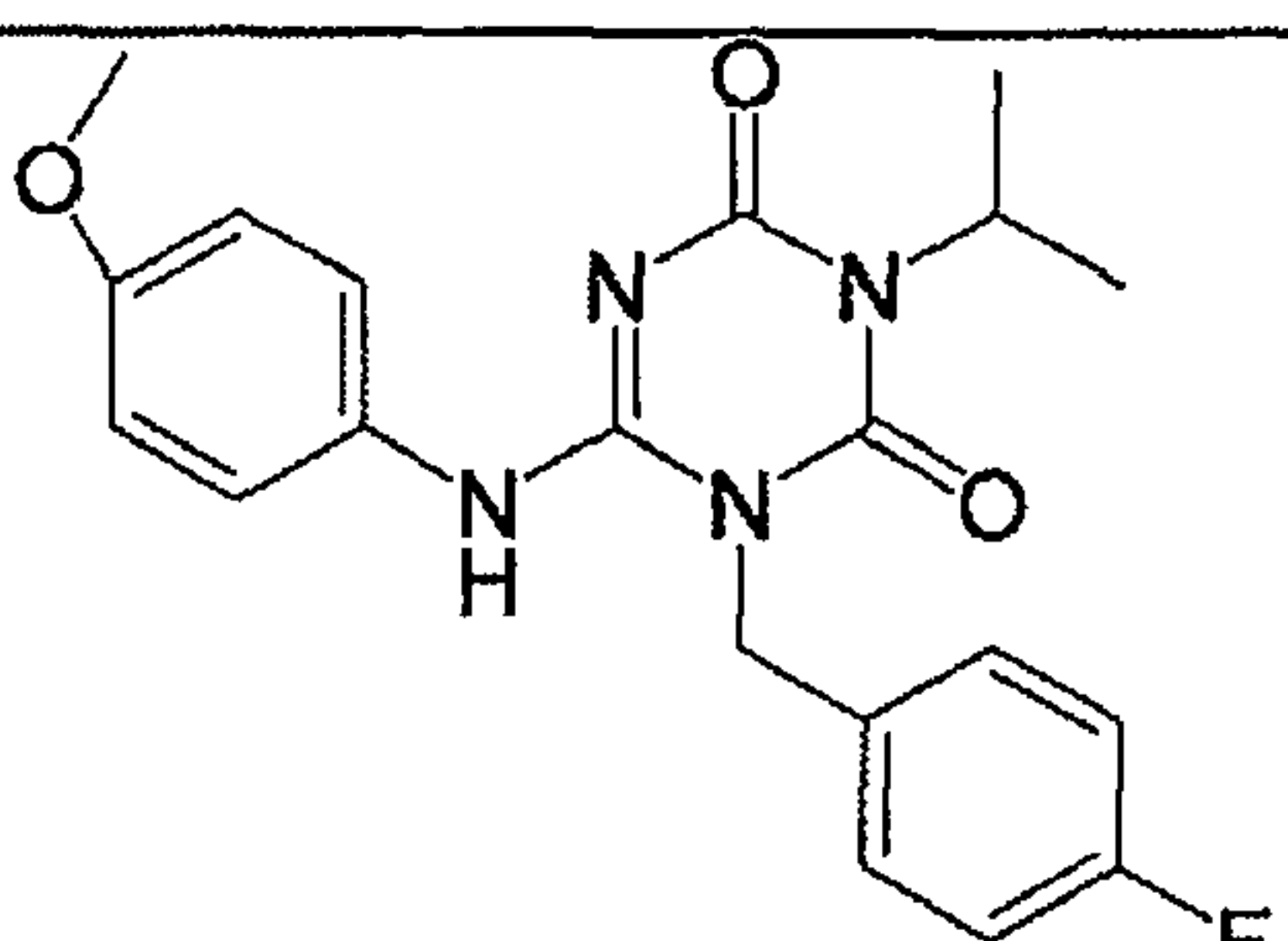
[Table 36]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0161	2.04	454	1
	I-0162	2.40	440	1
	I-0163	2.24	438	1
	I-0164	2.48	464	1
	I-0165	2.31	407	1

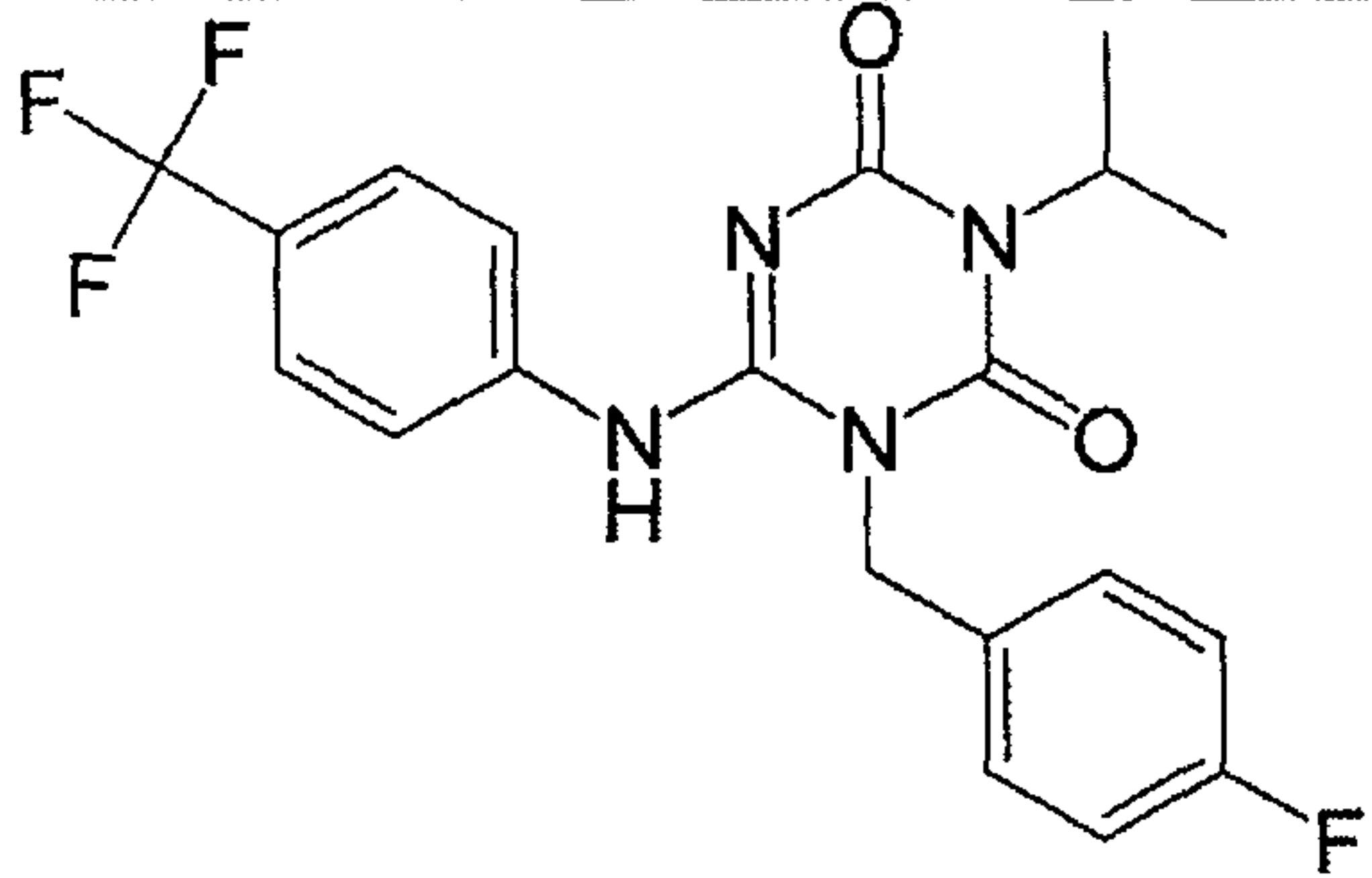
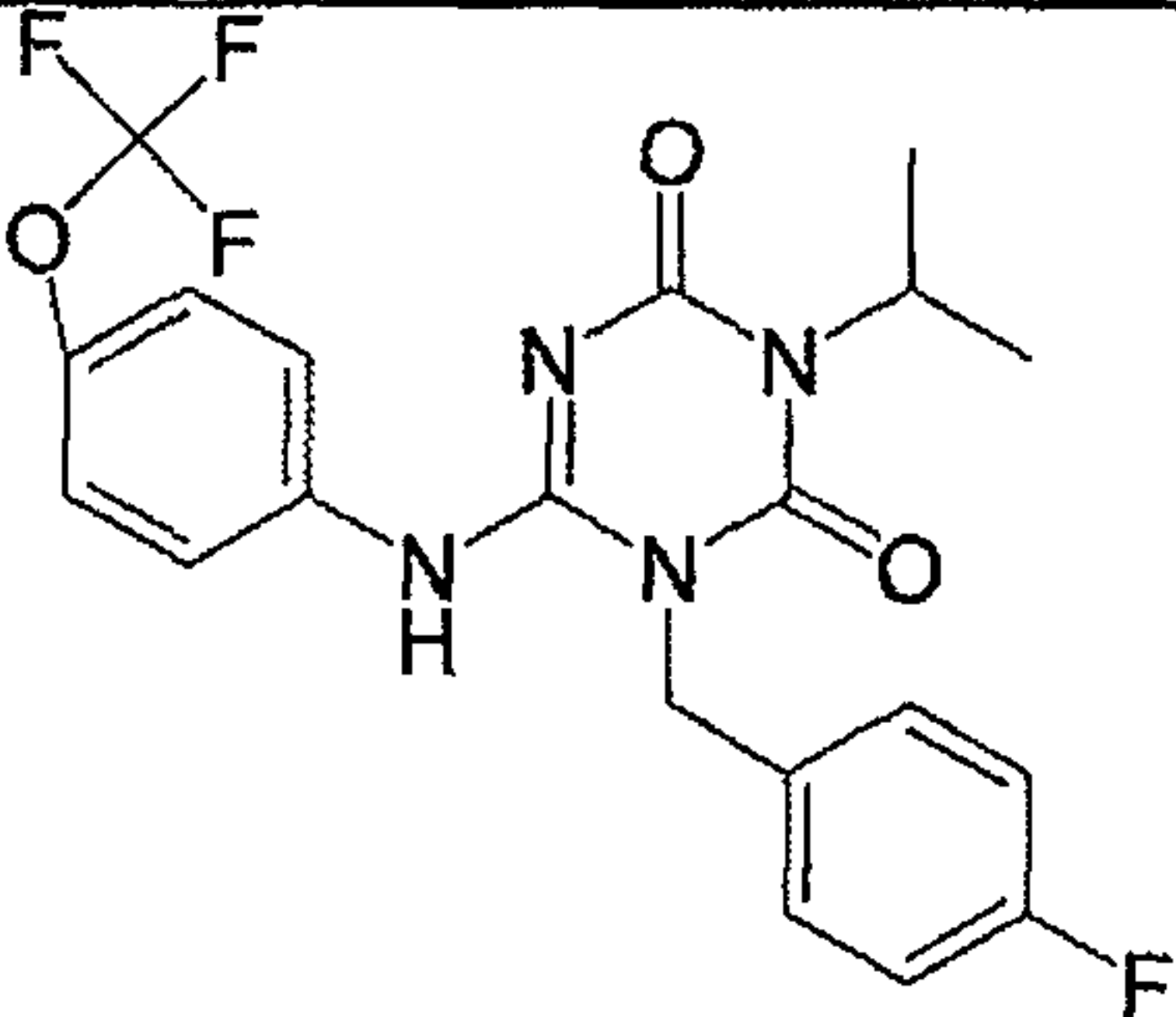
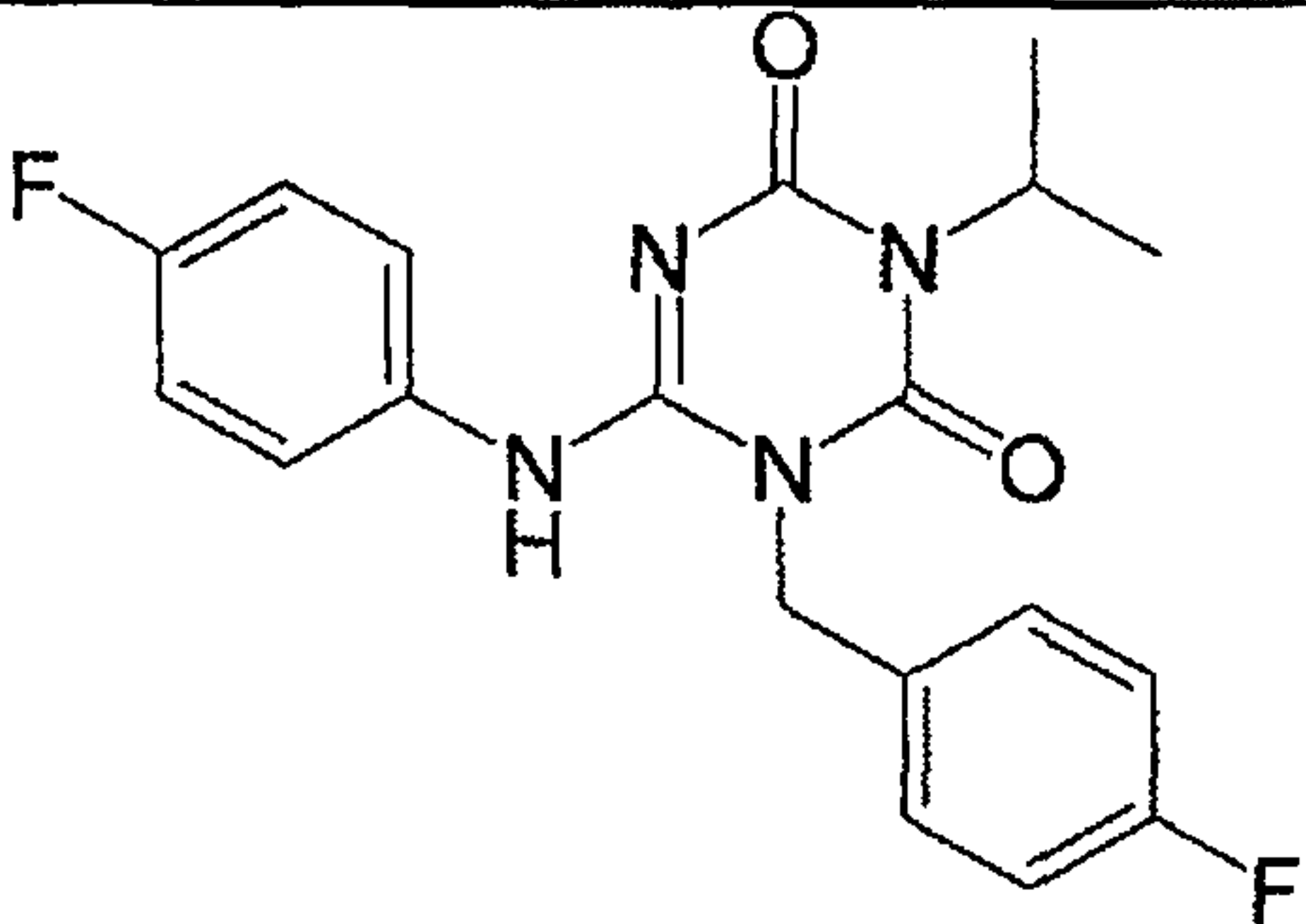
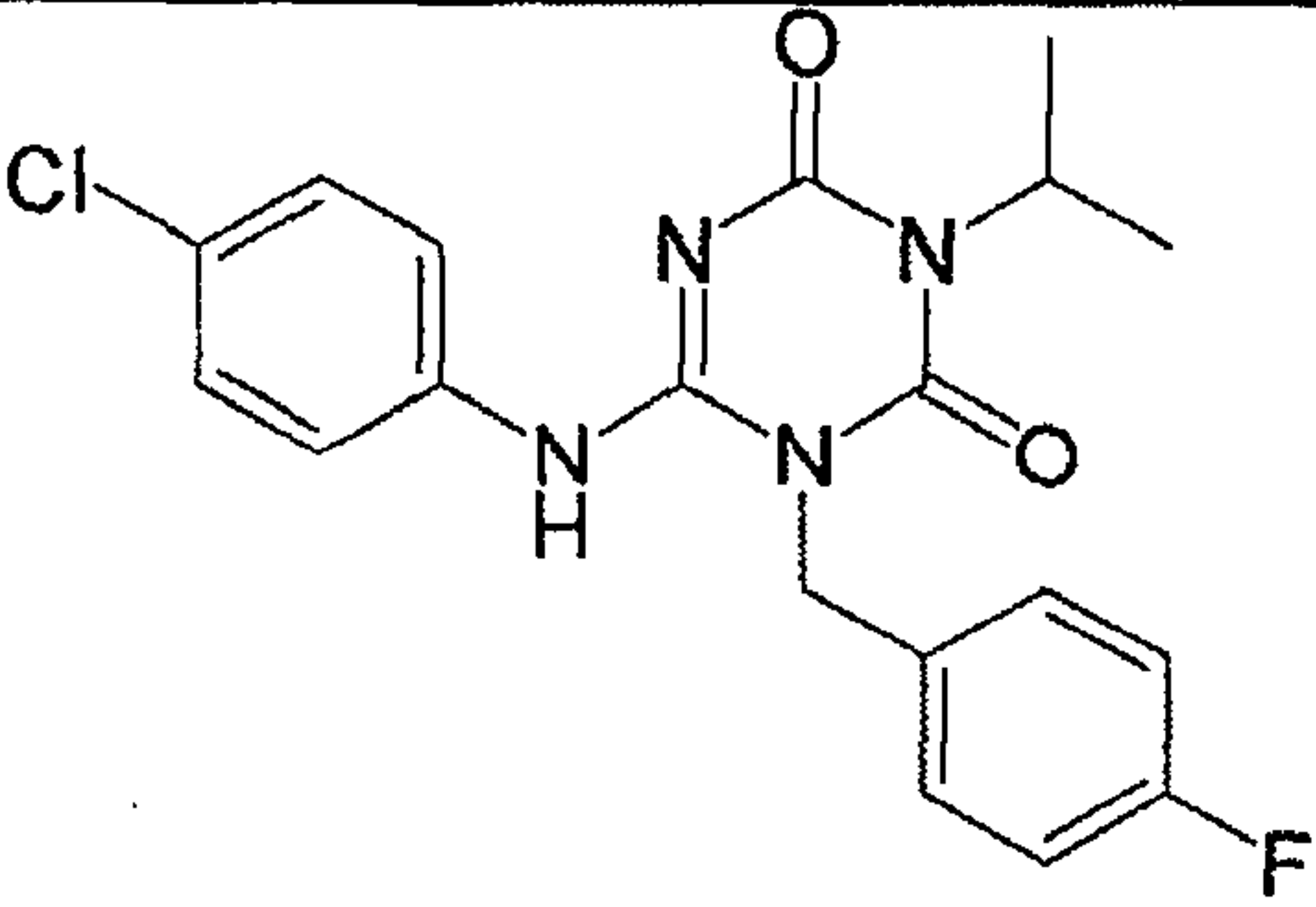
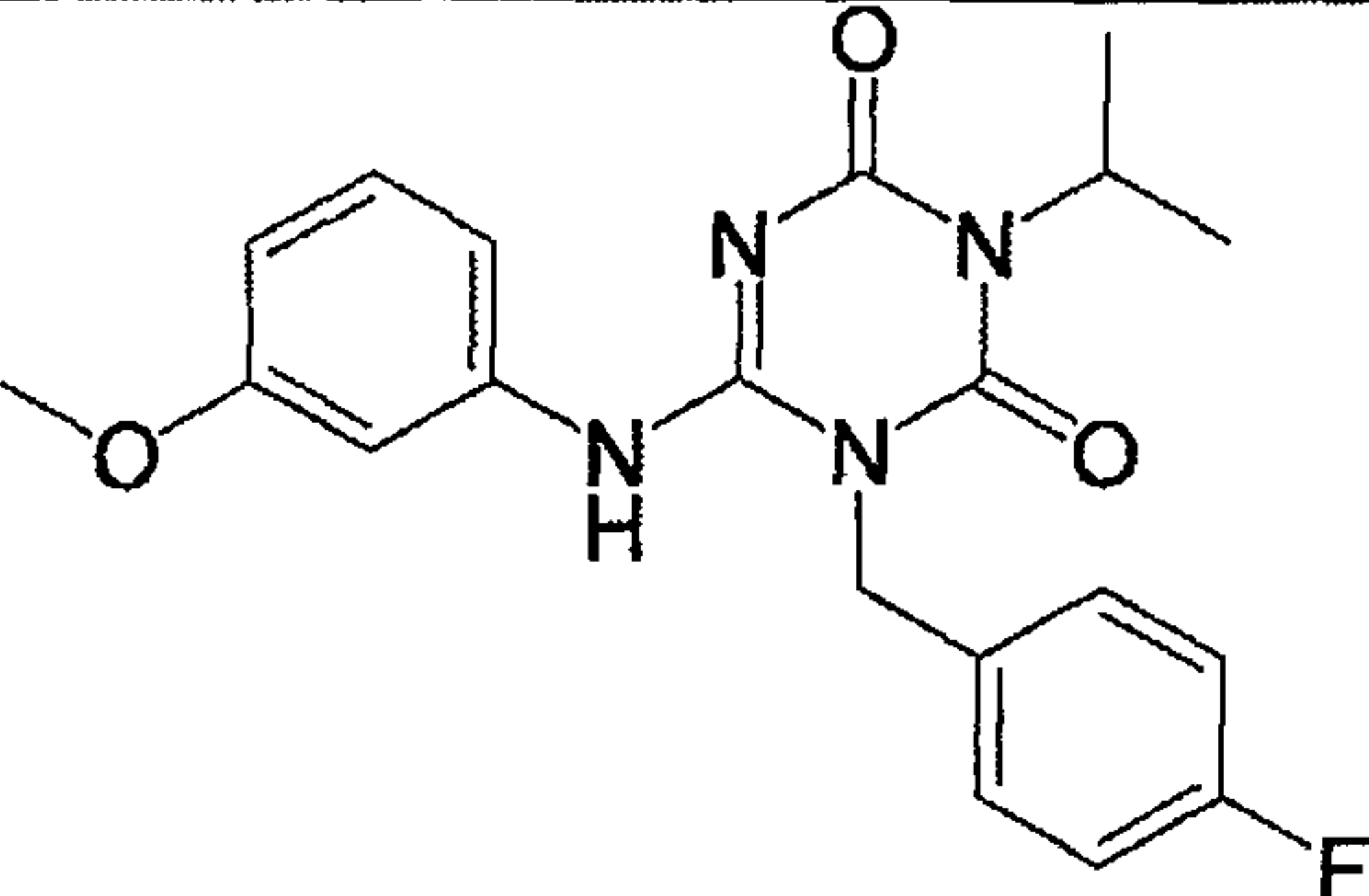
[Table 37]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0166	2.38	430	1
	I-0167	2.58	428	1
	I-0168	2.31	430	1
	I-0169	2.60	430	1
	I-0170	1.94	411	1

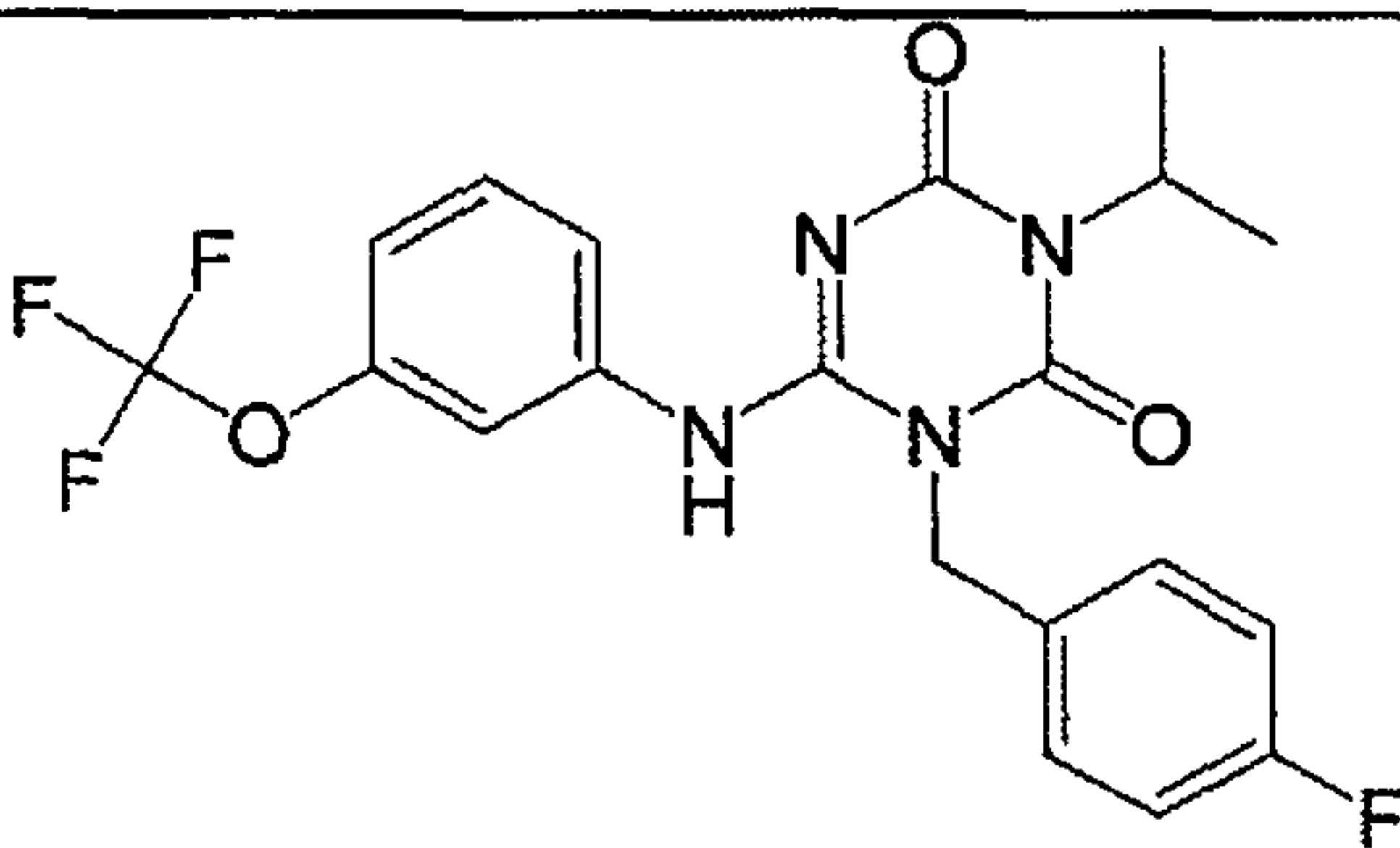
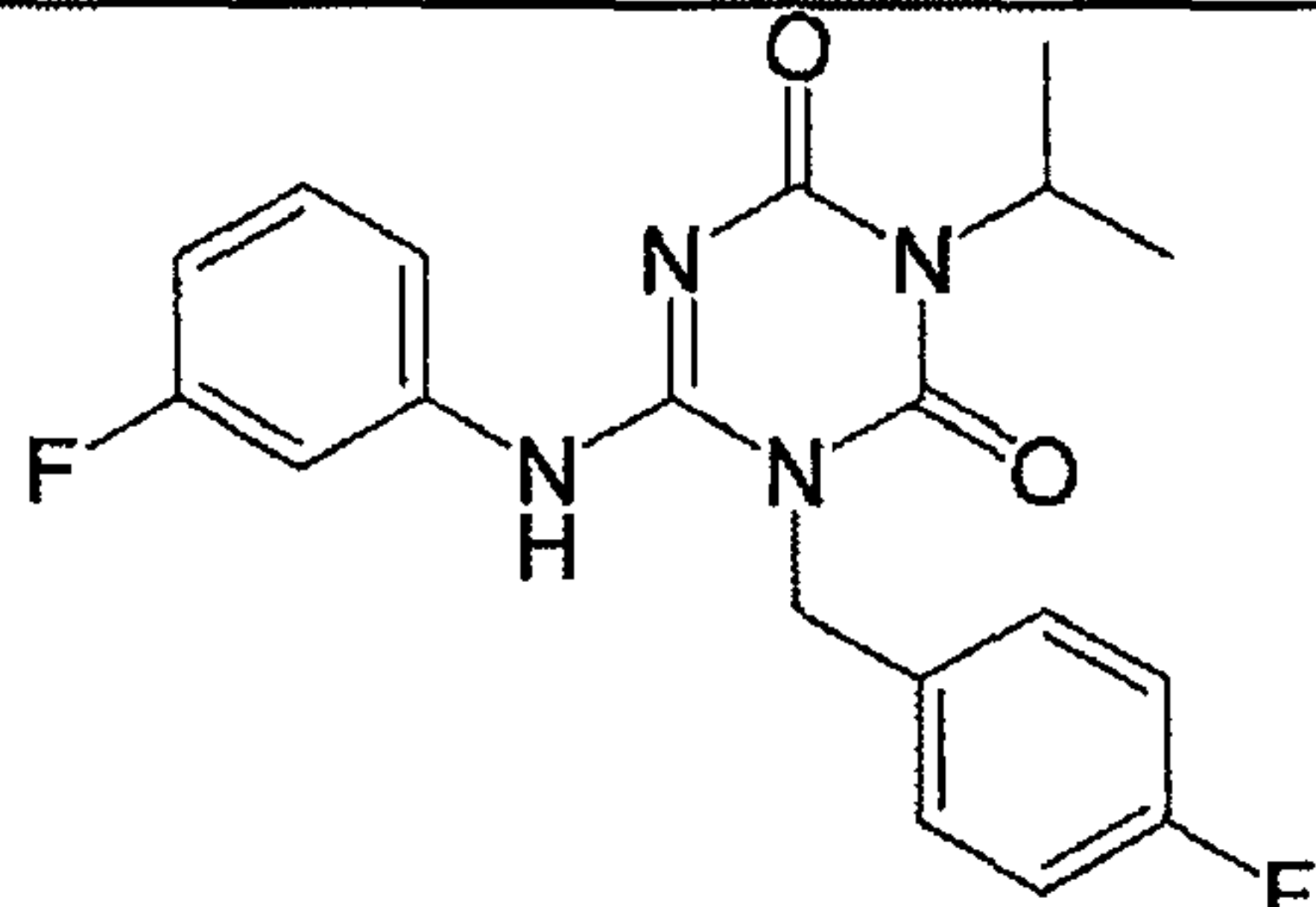
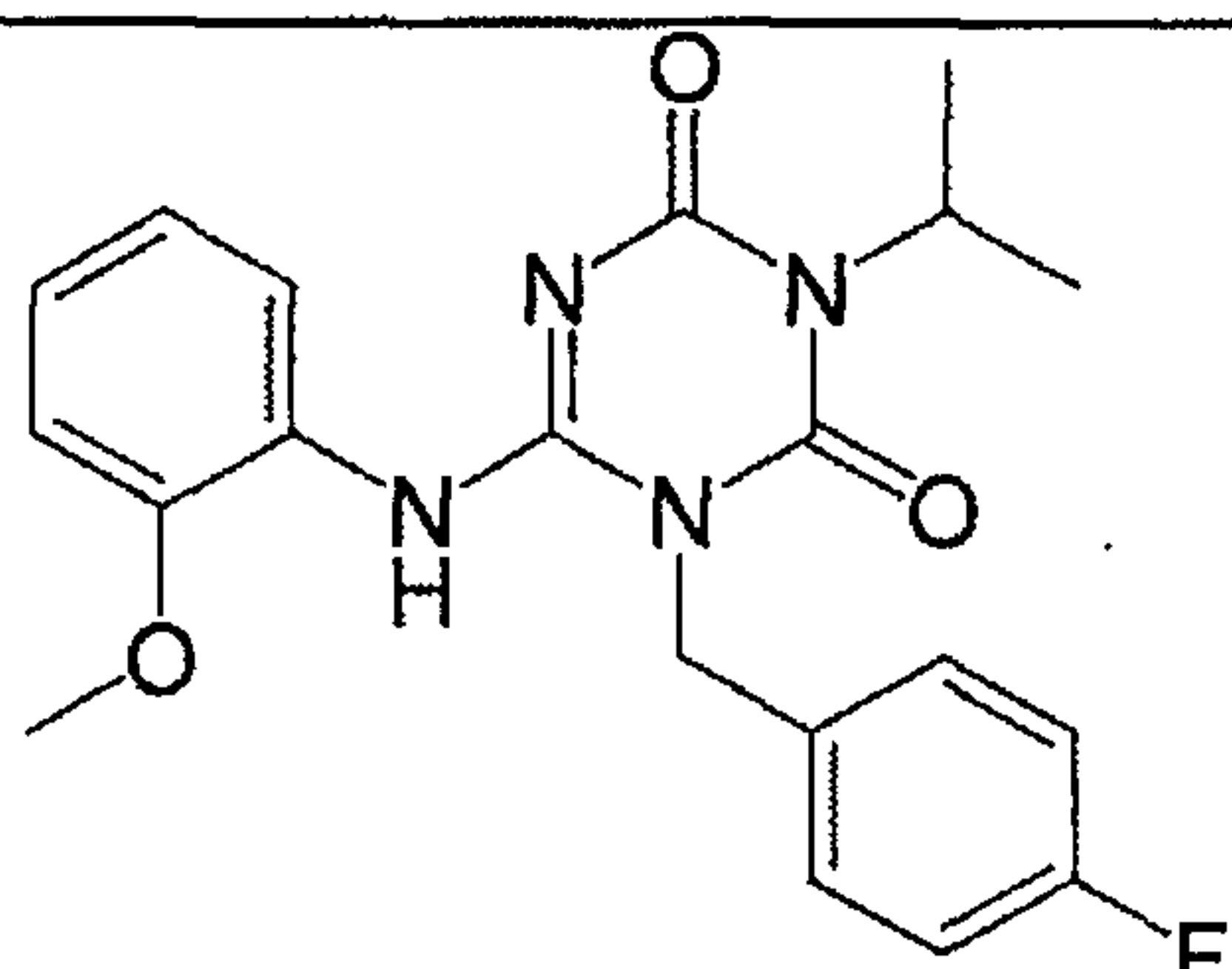
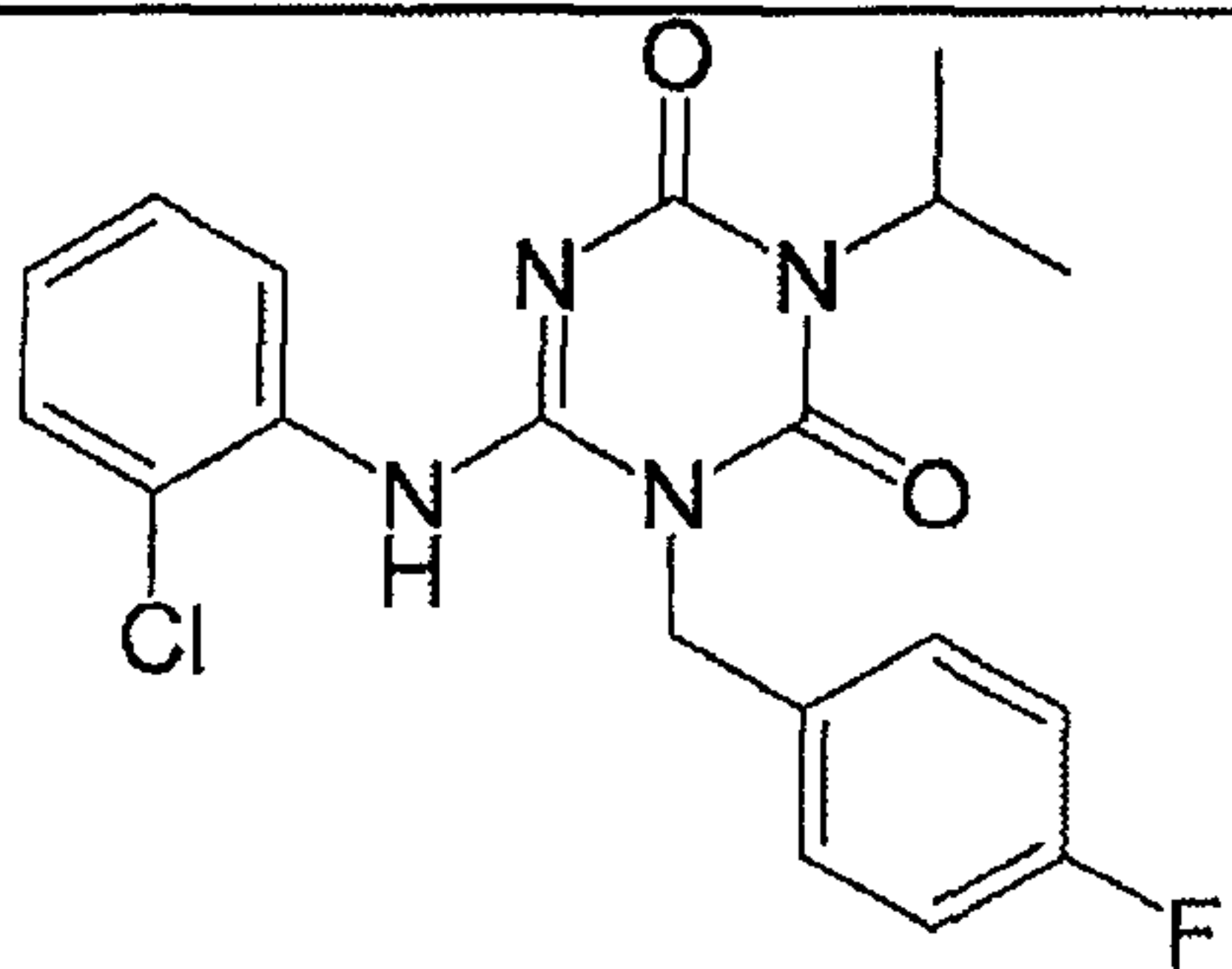
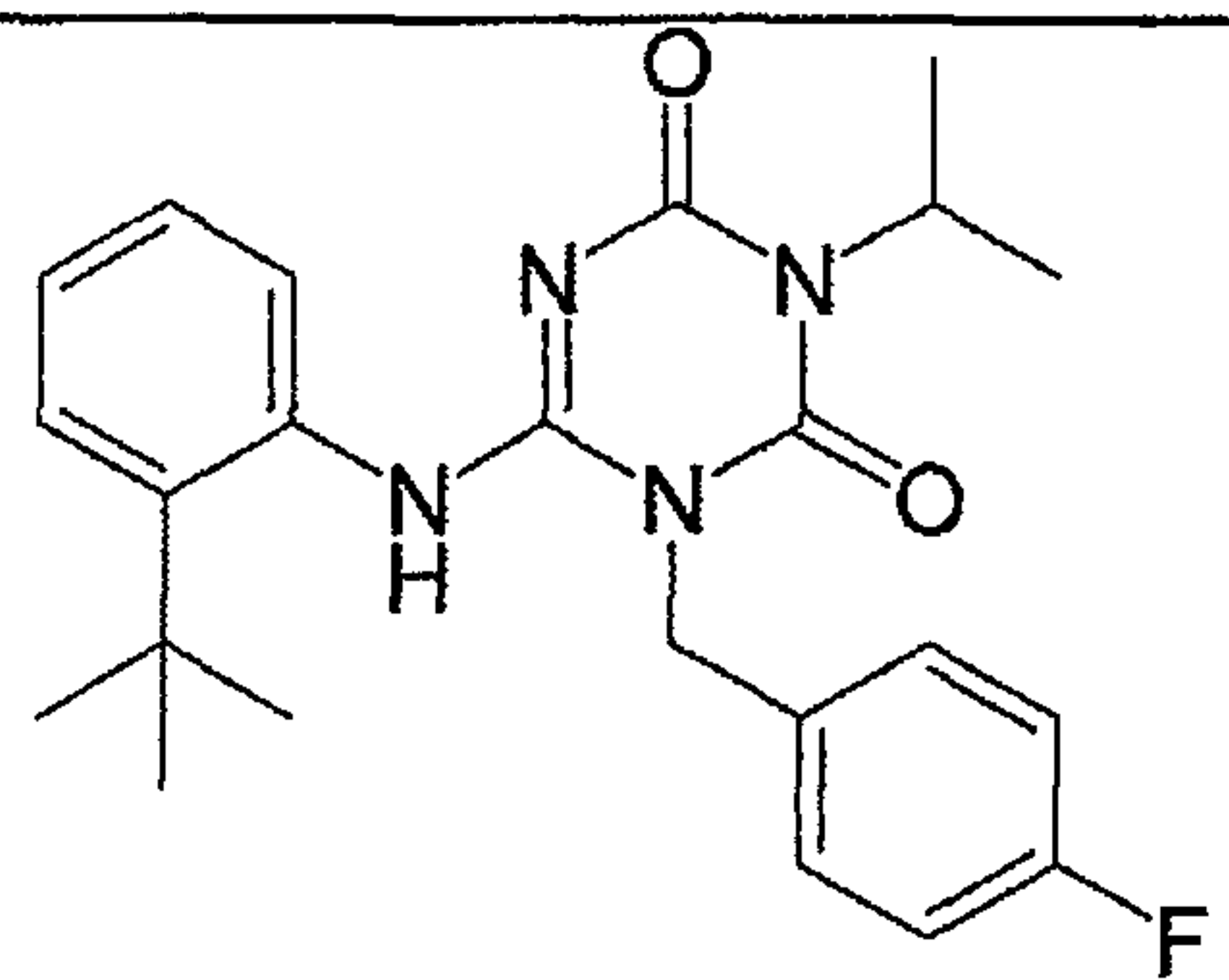
[Table 38]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0171	1.92	457	1
	I-0172	2.20	454	1
	I-0173	2.30	438	3
	I-0174	2.38	421	3
	I-0175	2.20	385	3

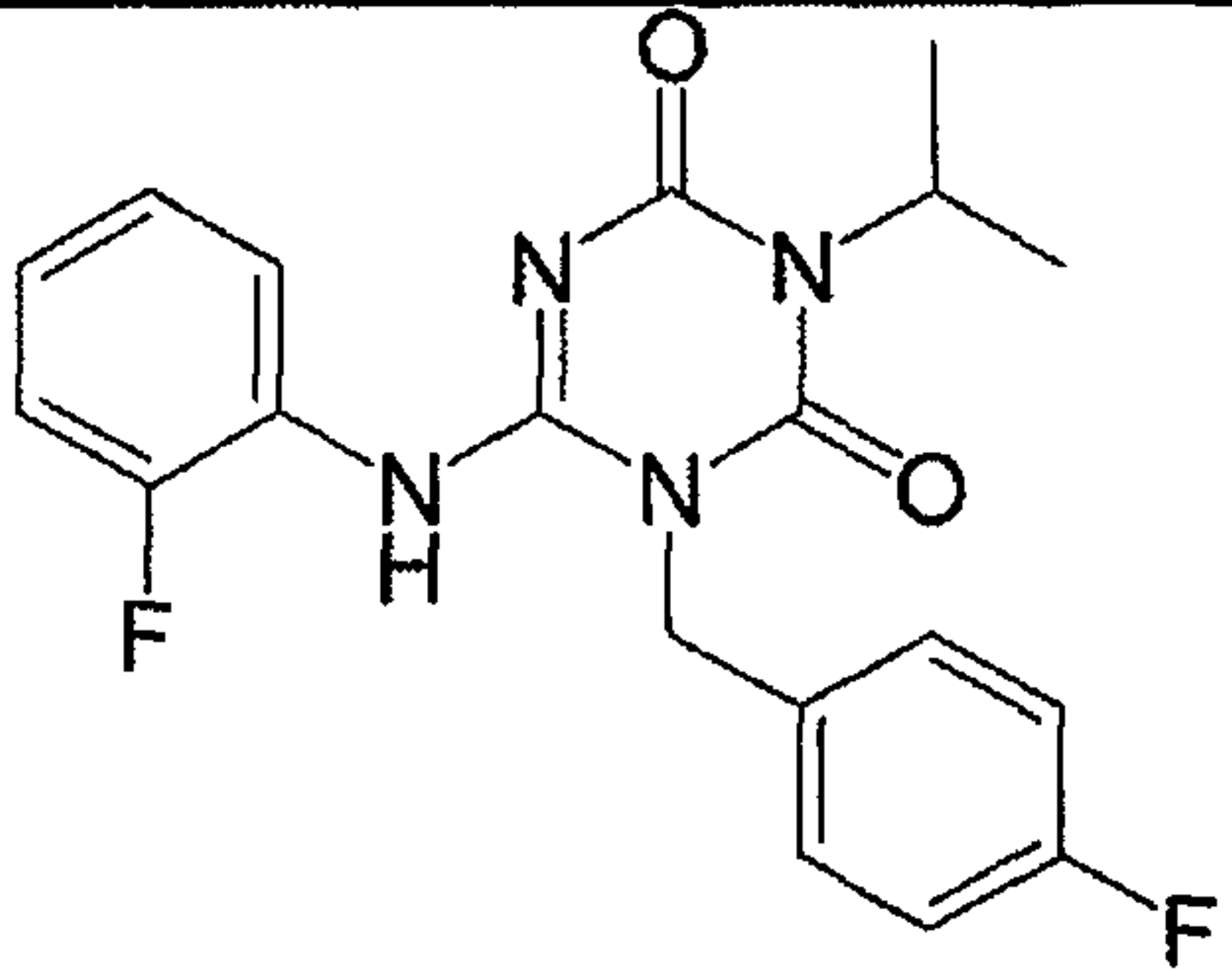
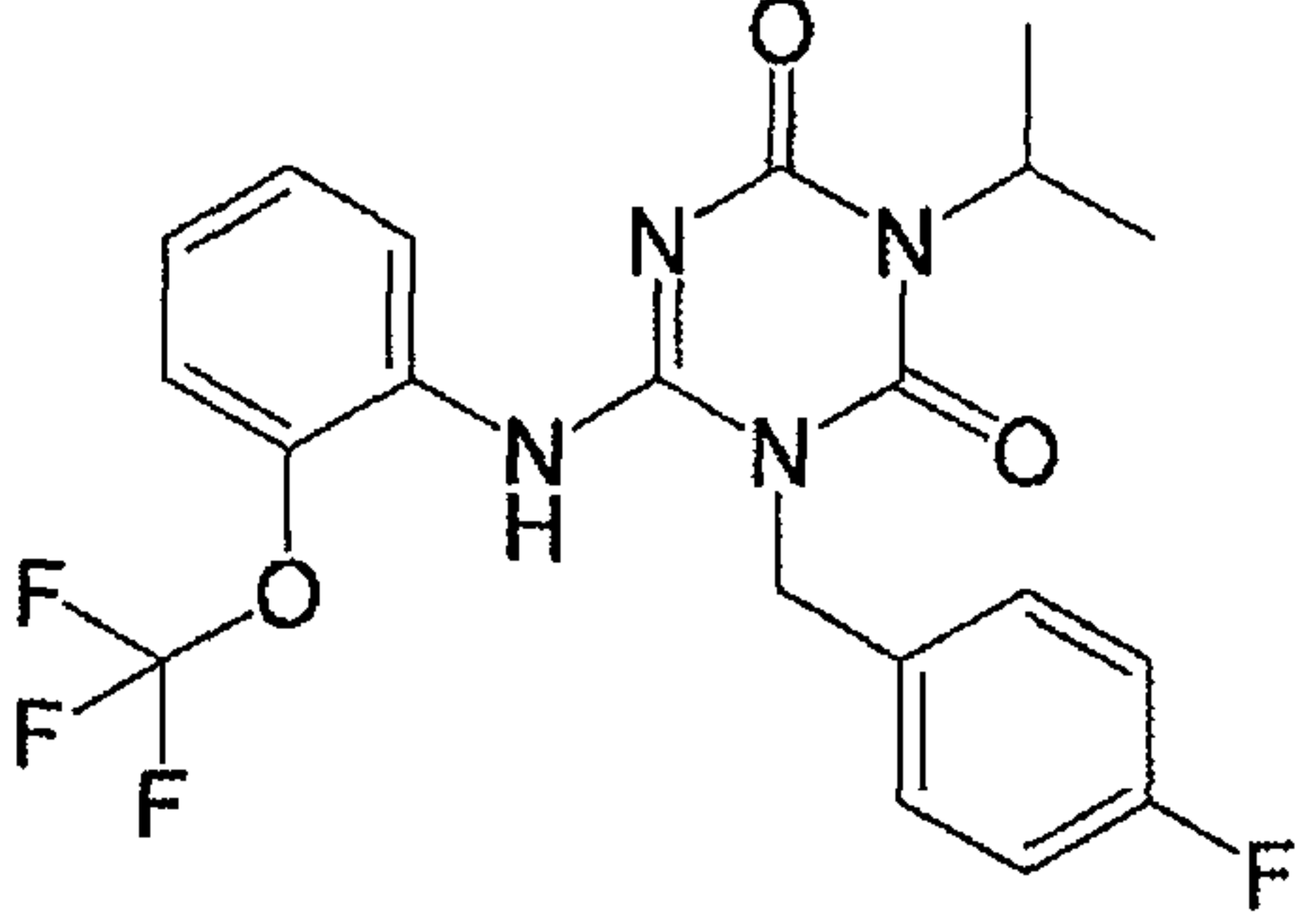
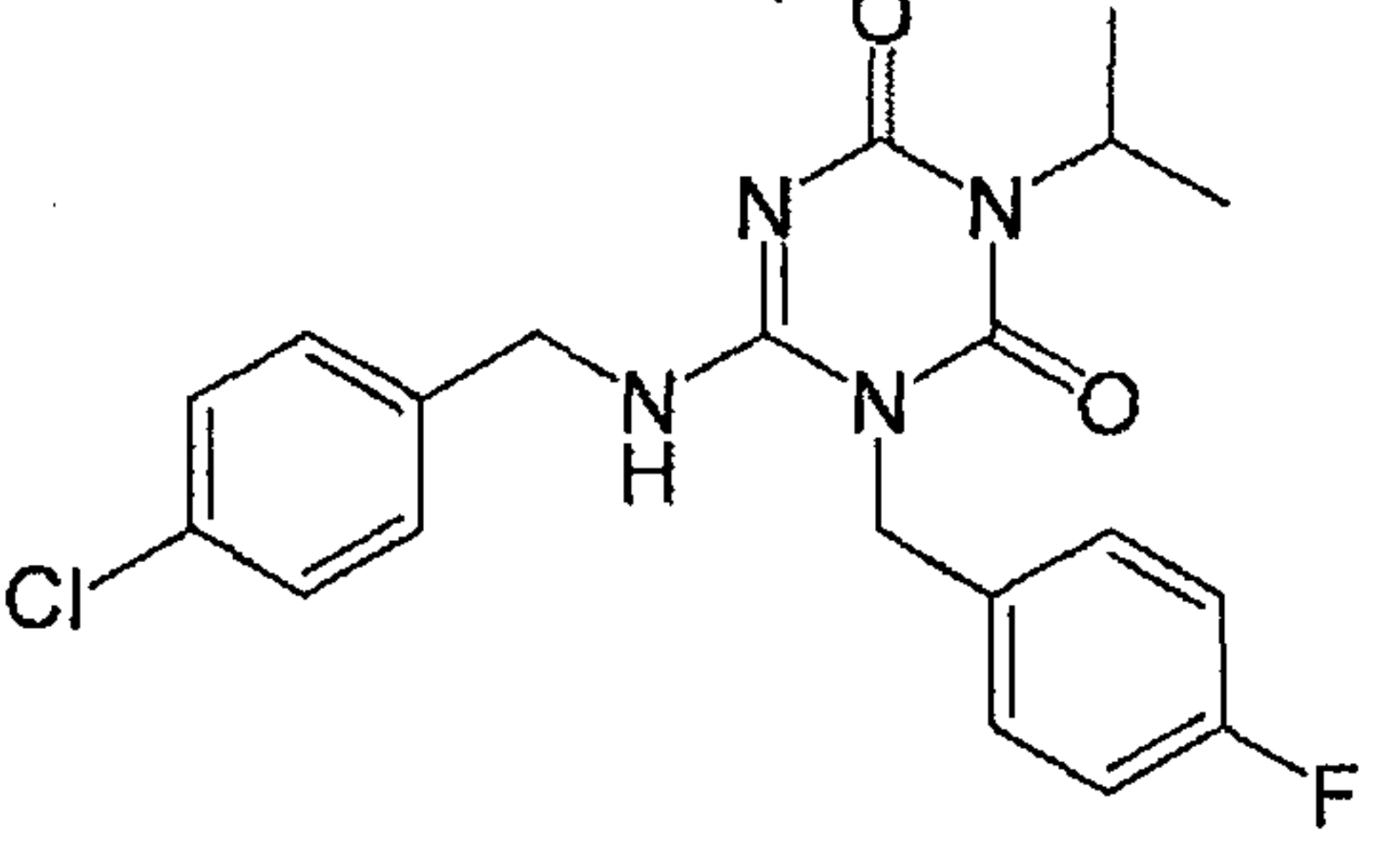
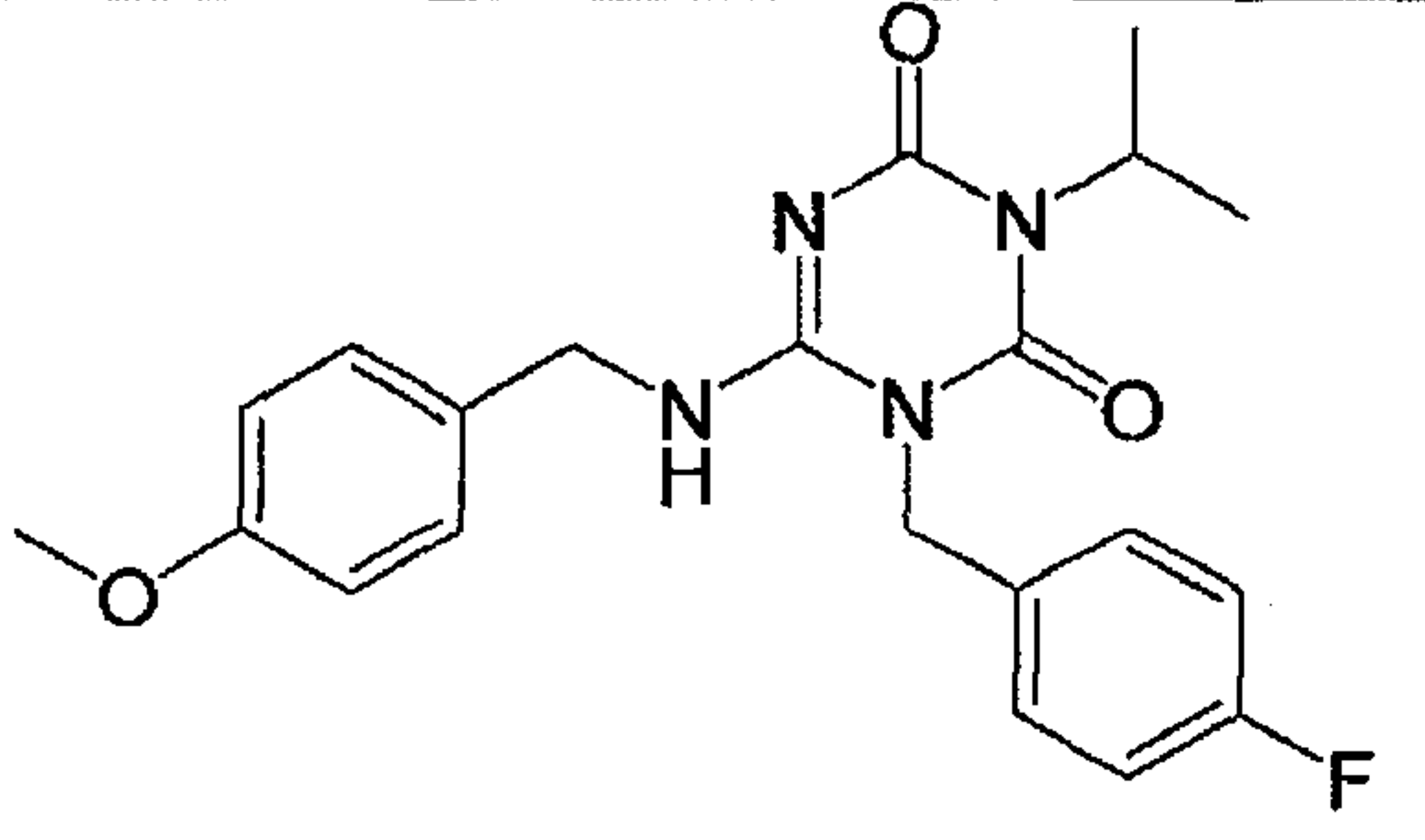
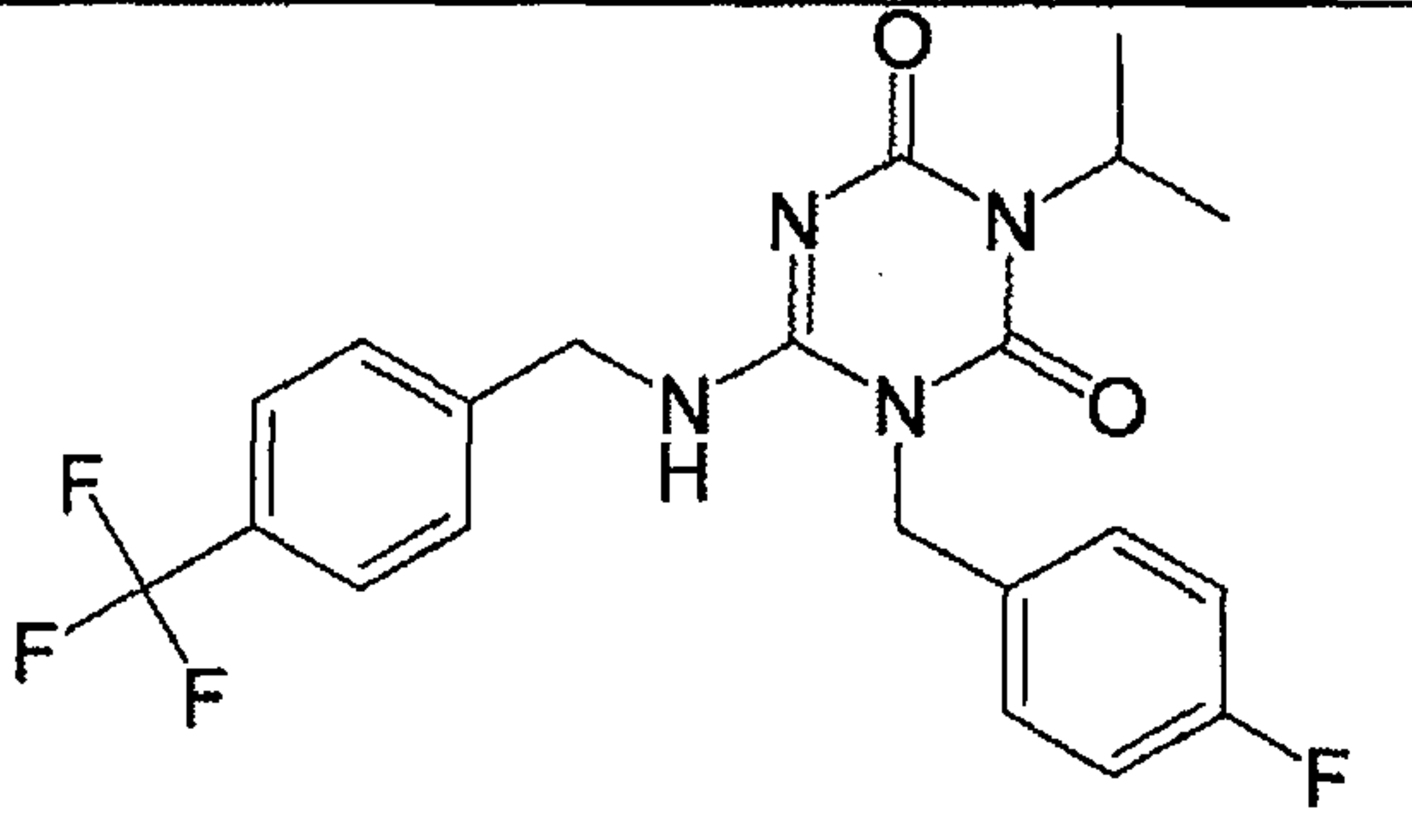
[Table 39]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0176	2.70	423	3
	I-0177	2.70	439	3
	I-0178	2.30	373	3
	I-0179	2.50	389	3
	I-0180	2.40	385	3

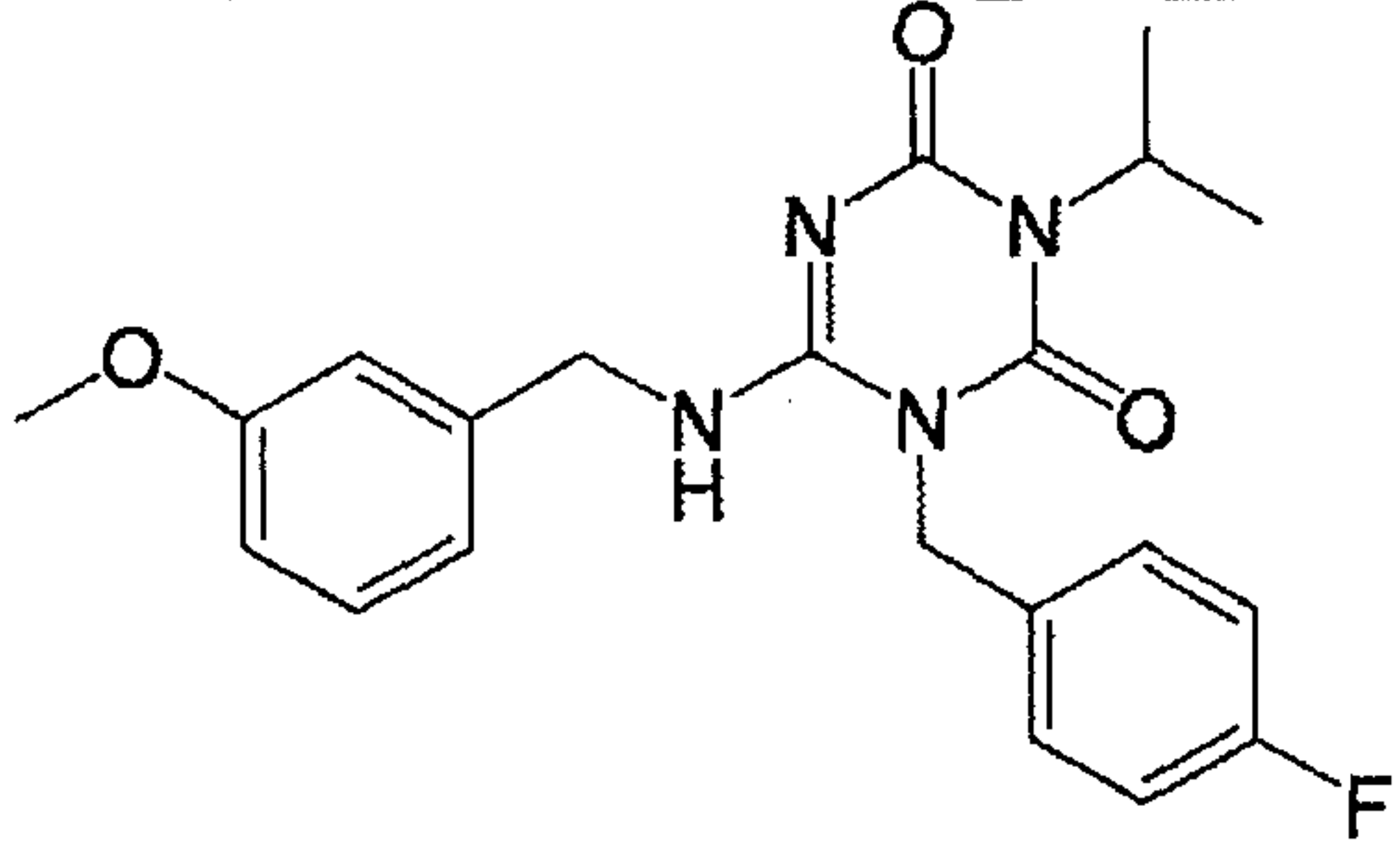
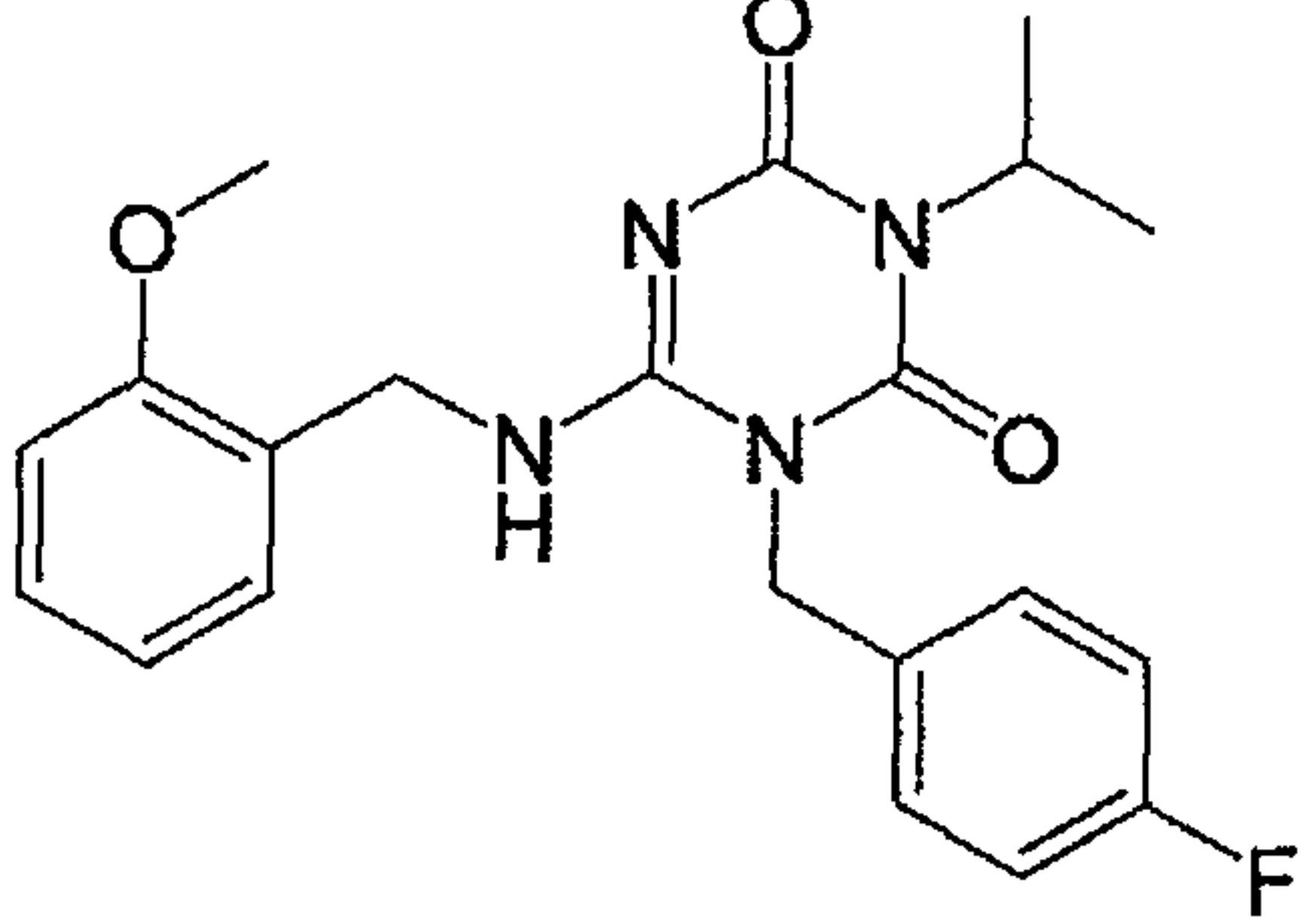
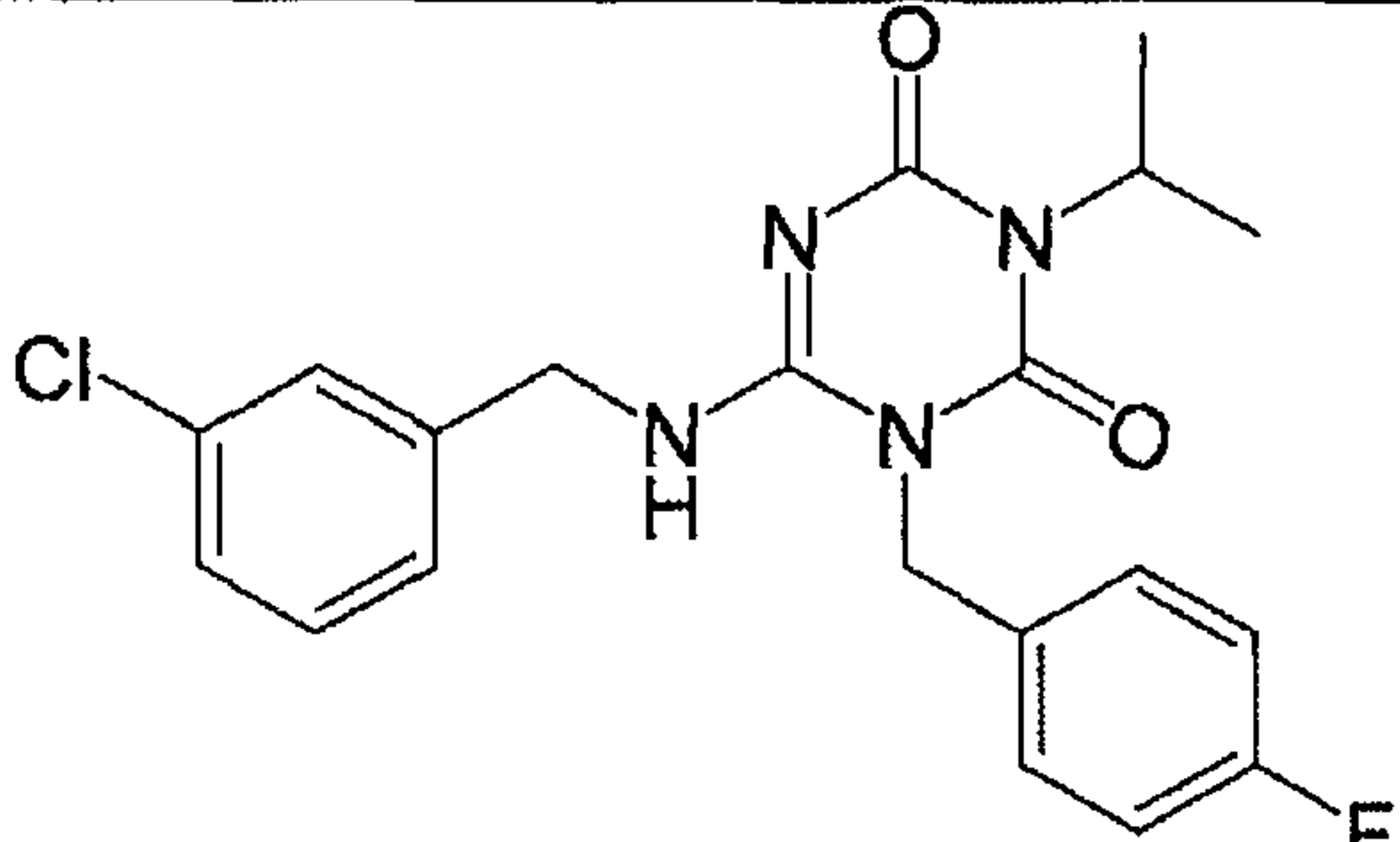
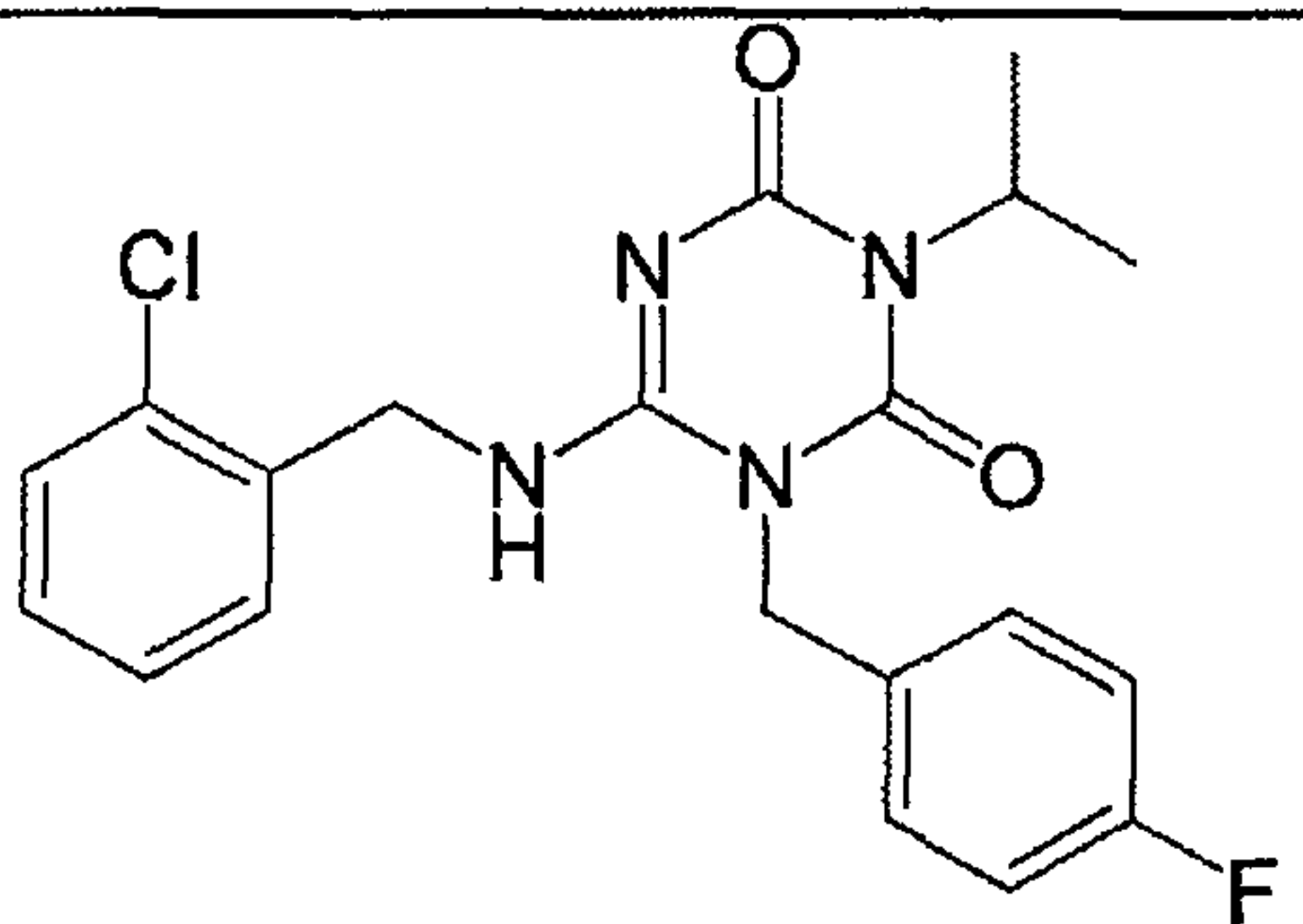
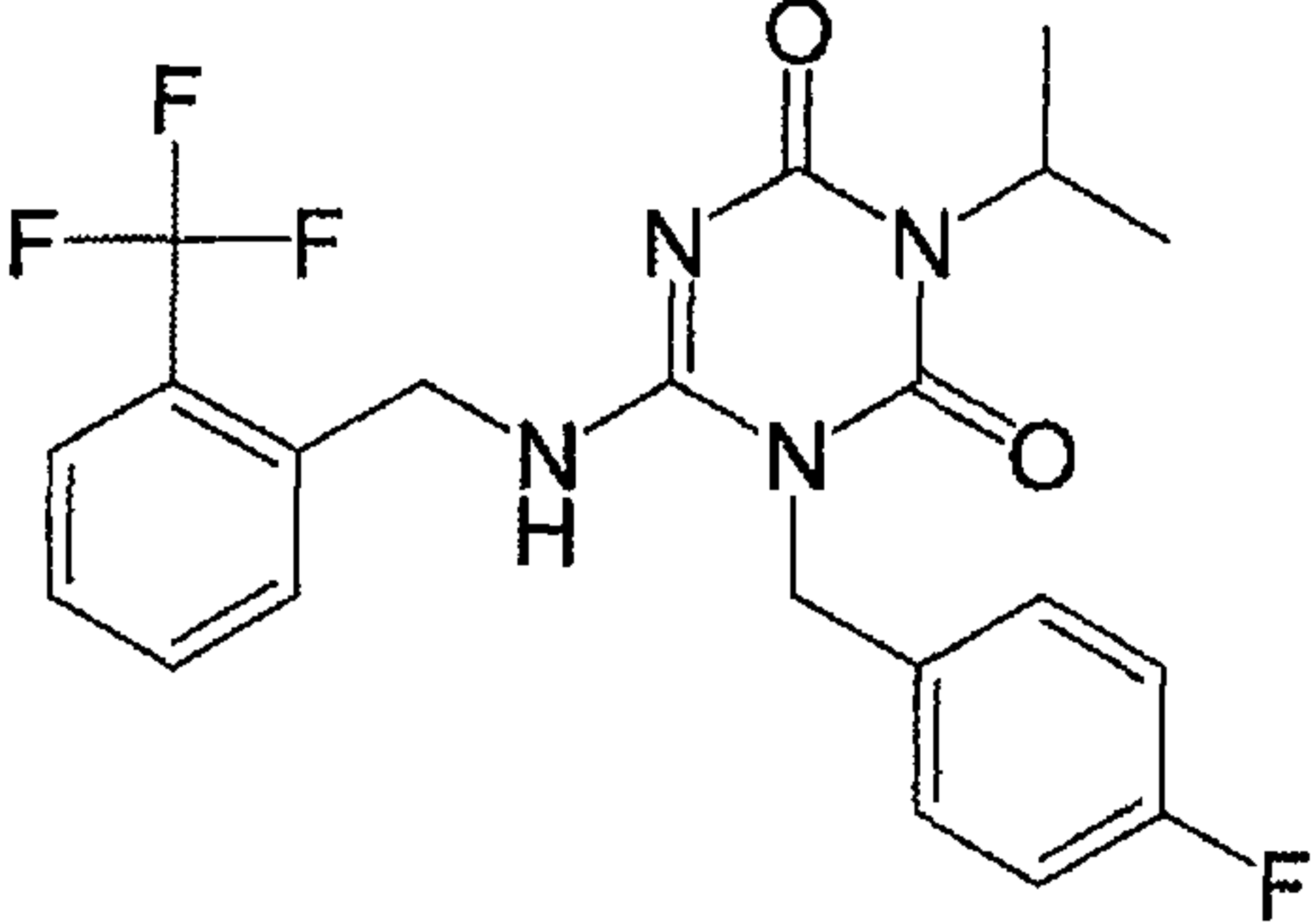
[Table 40]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0181	2.70	439	3
	I-0182	2.40	373	3
	I-0183	2.30	385	3
	I-0184	2.60	389	3
	I-0185	2.90	411	3

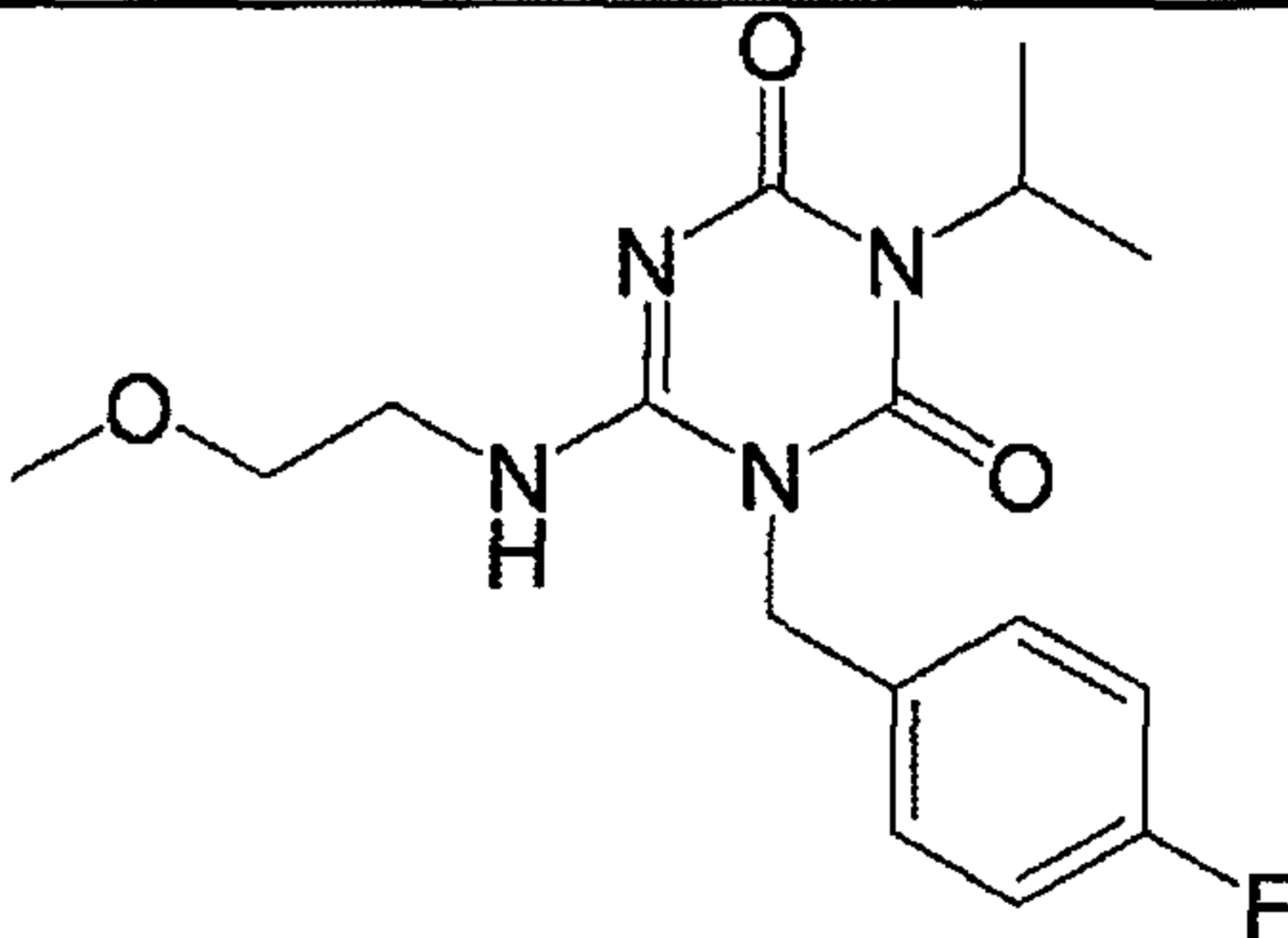
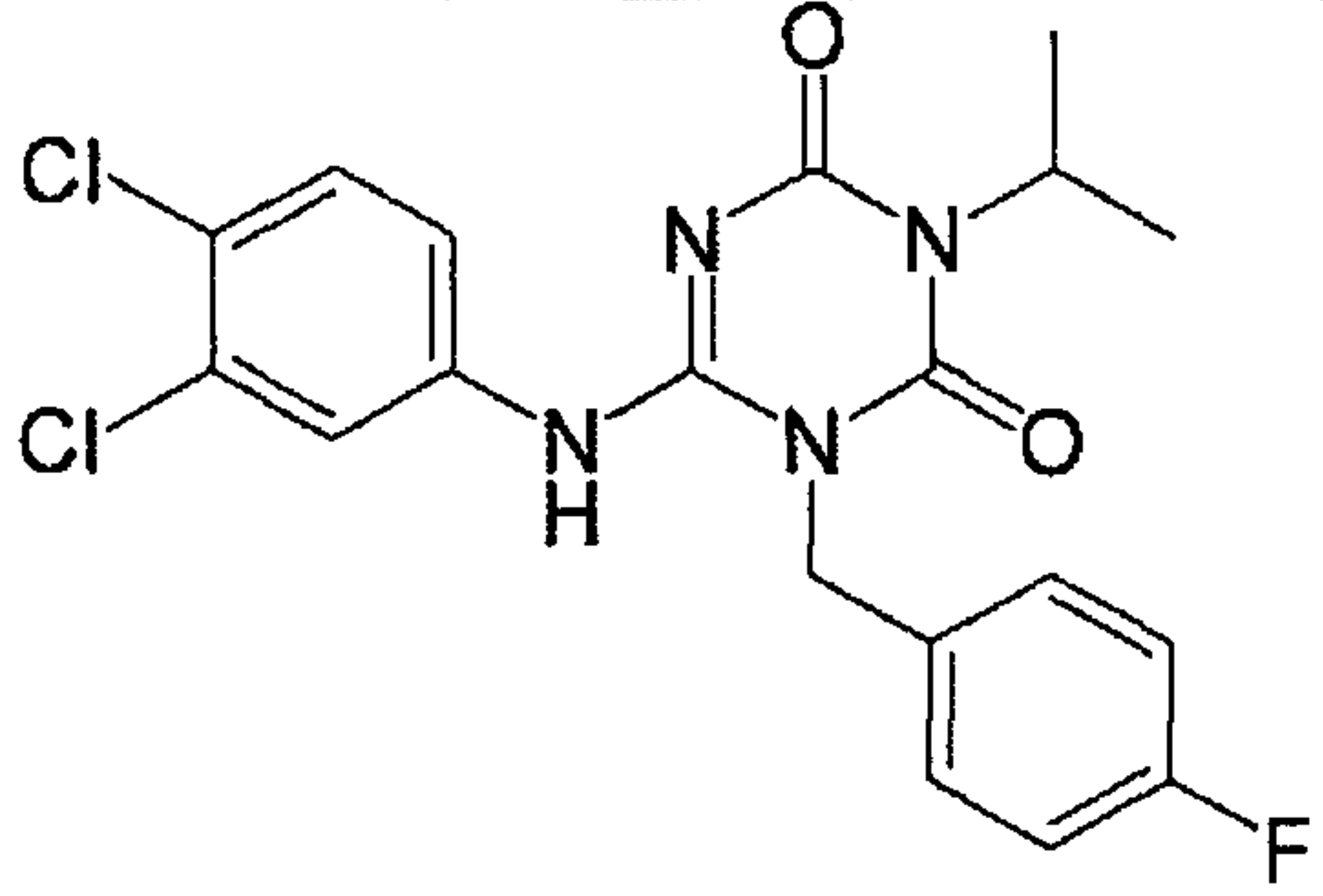
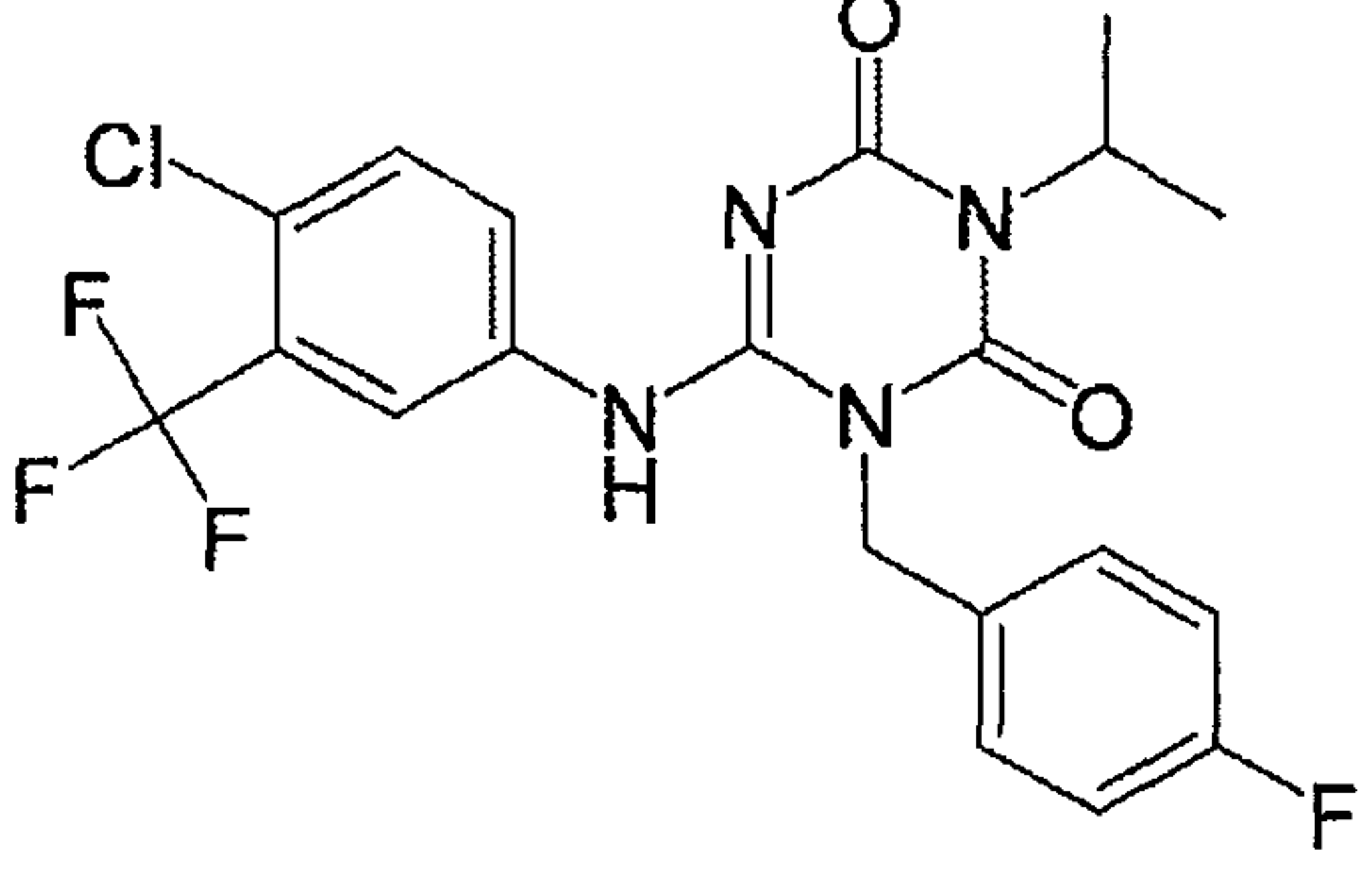
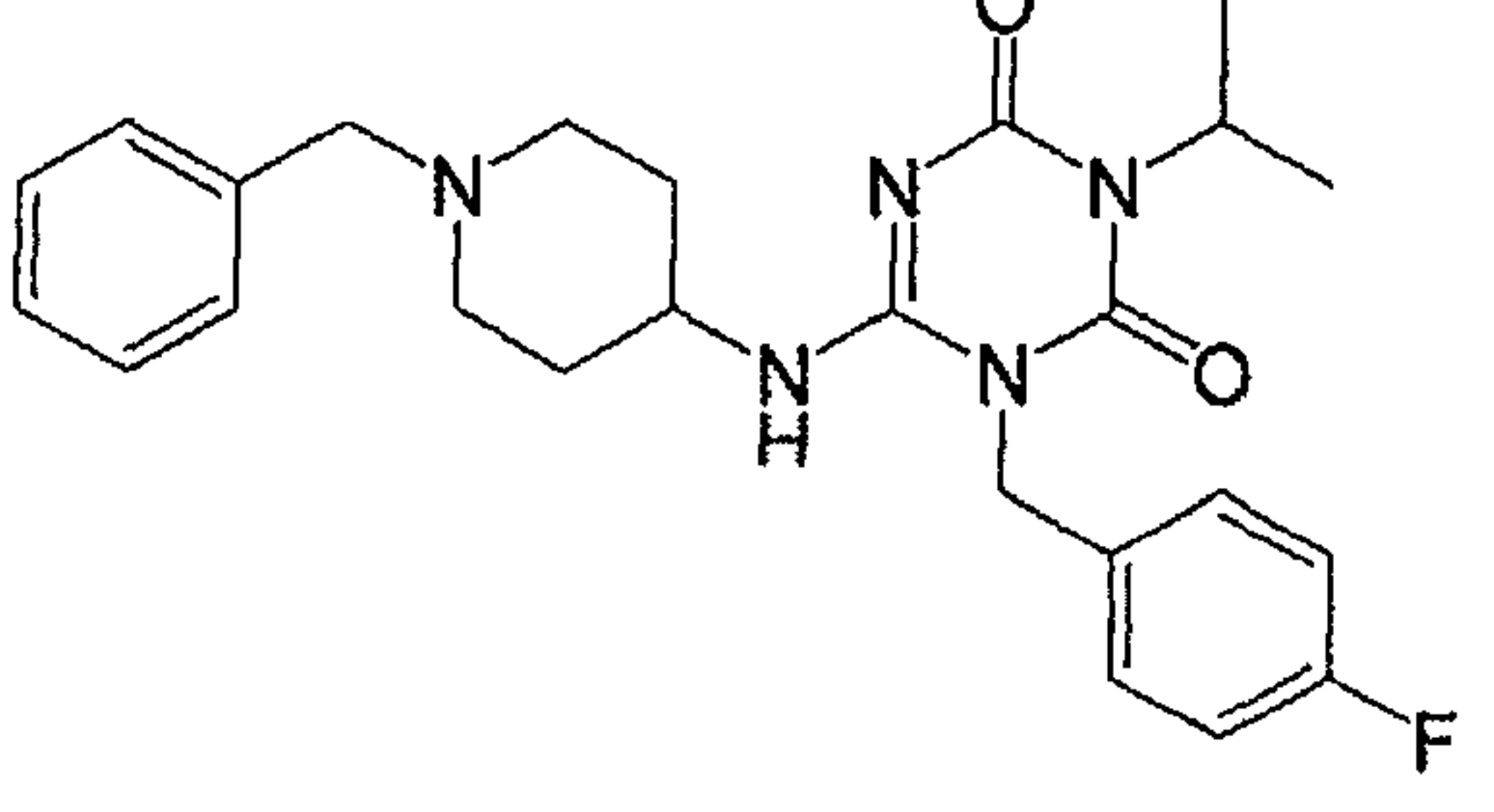
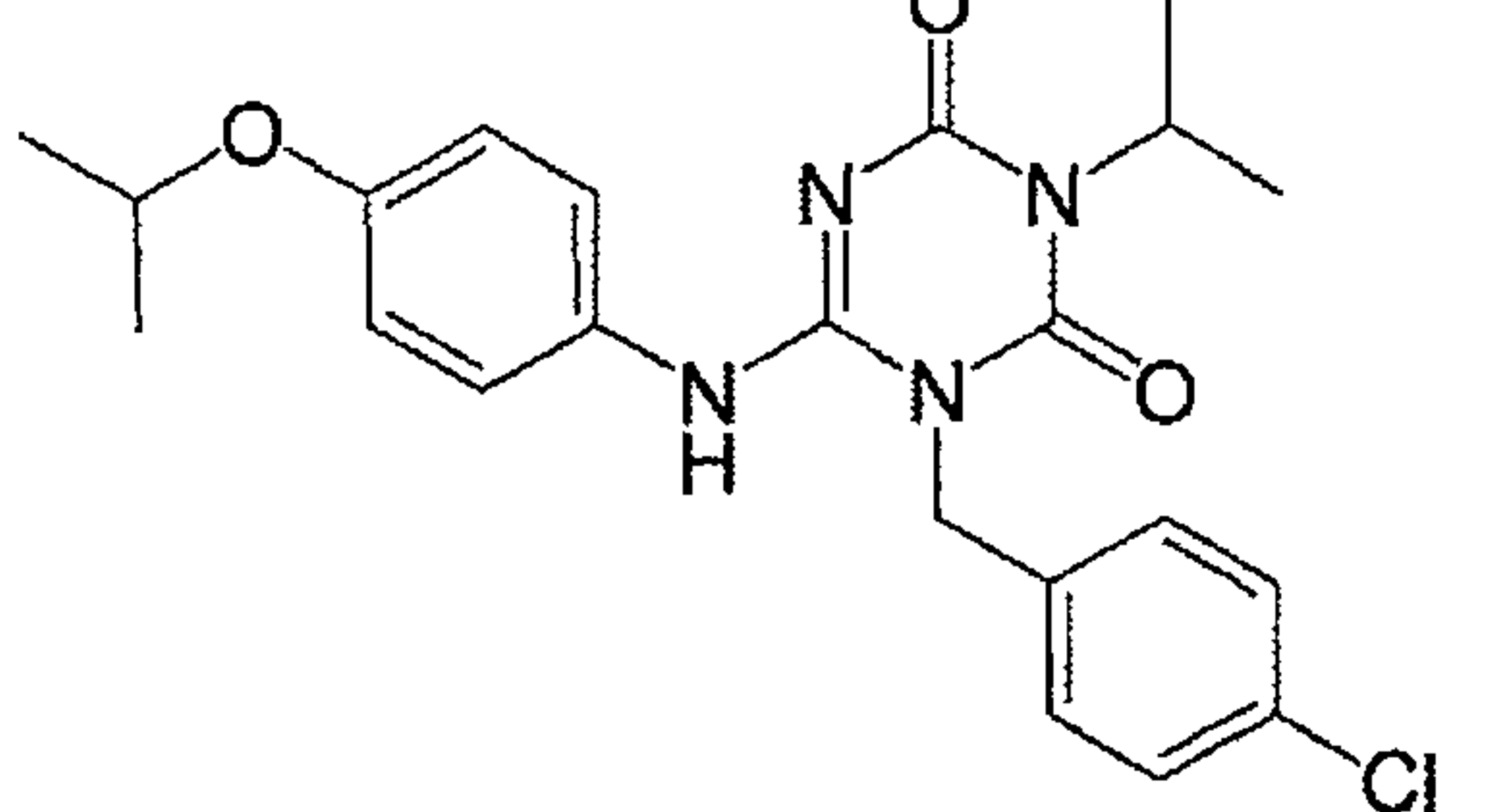
[Table 4i]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0186	2.40	373	3
	I-0187	2.70	439	3
	I-0188	1.20	403	3
	I-0189	1.20	399	3
	I-0190	2.10	437	3

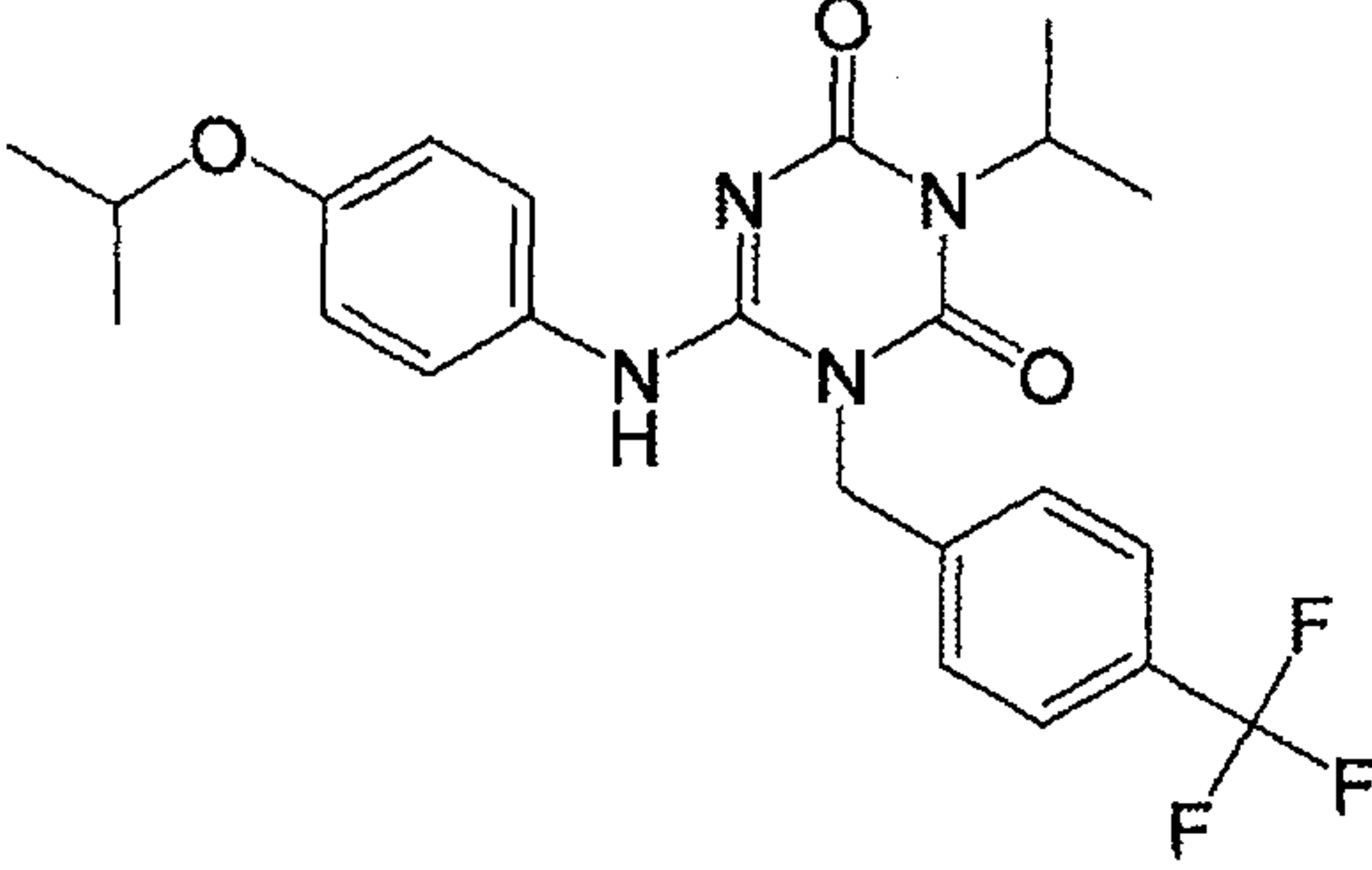
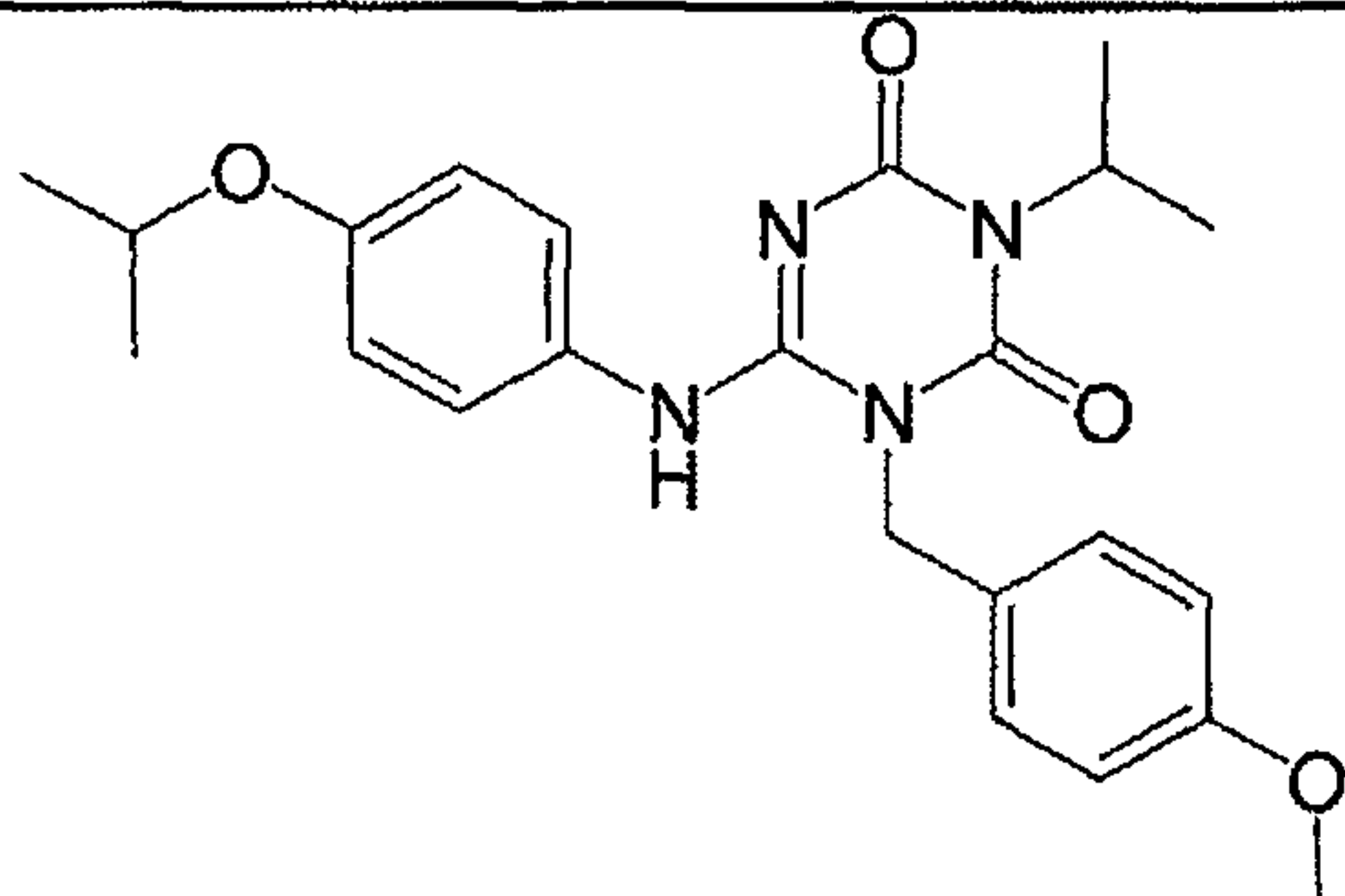
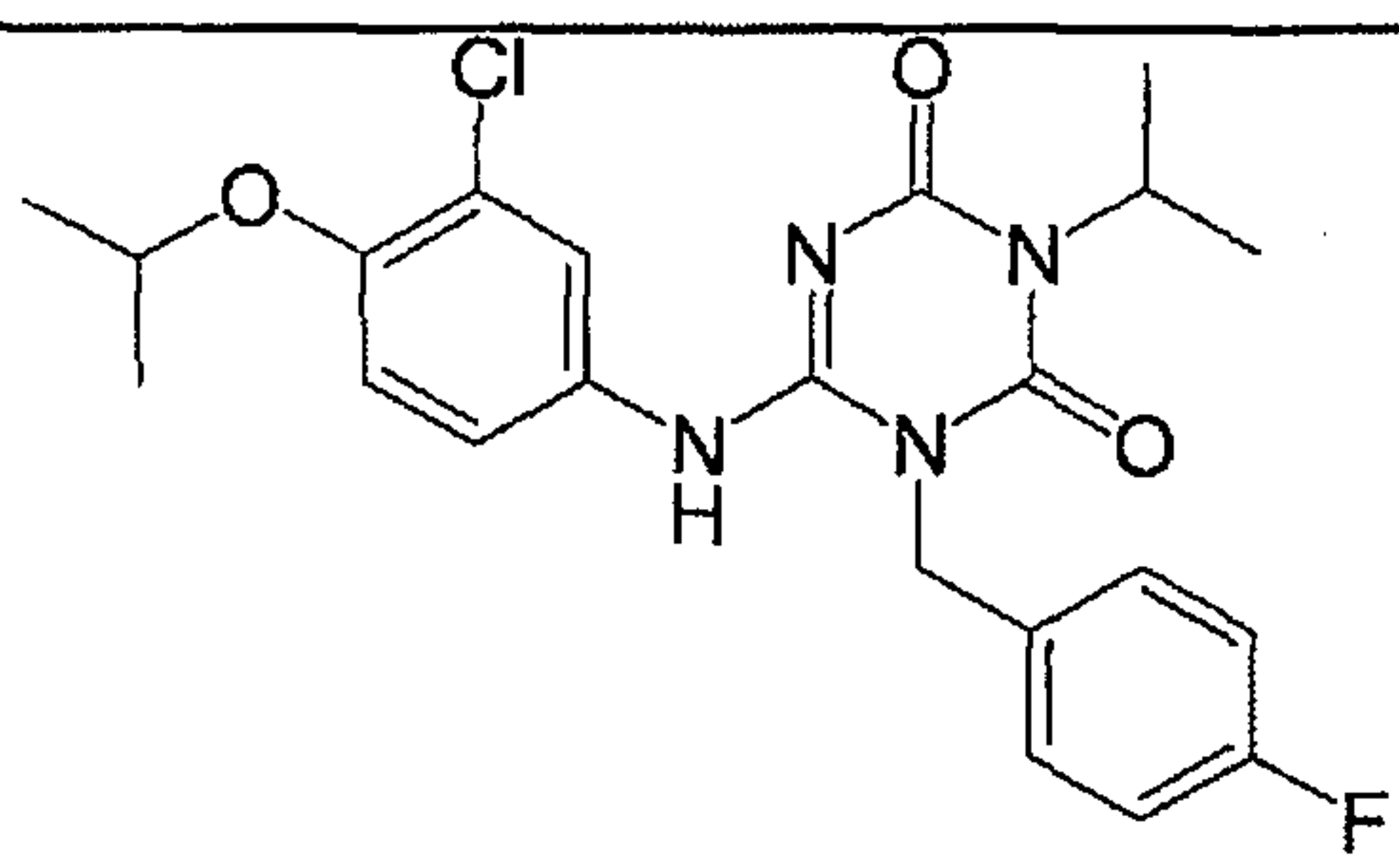
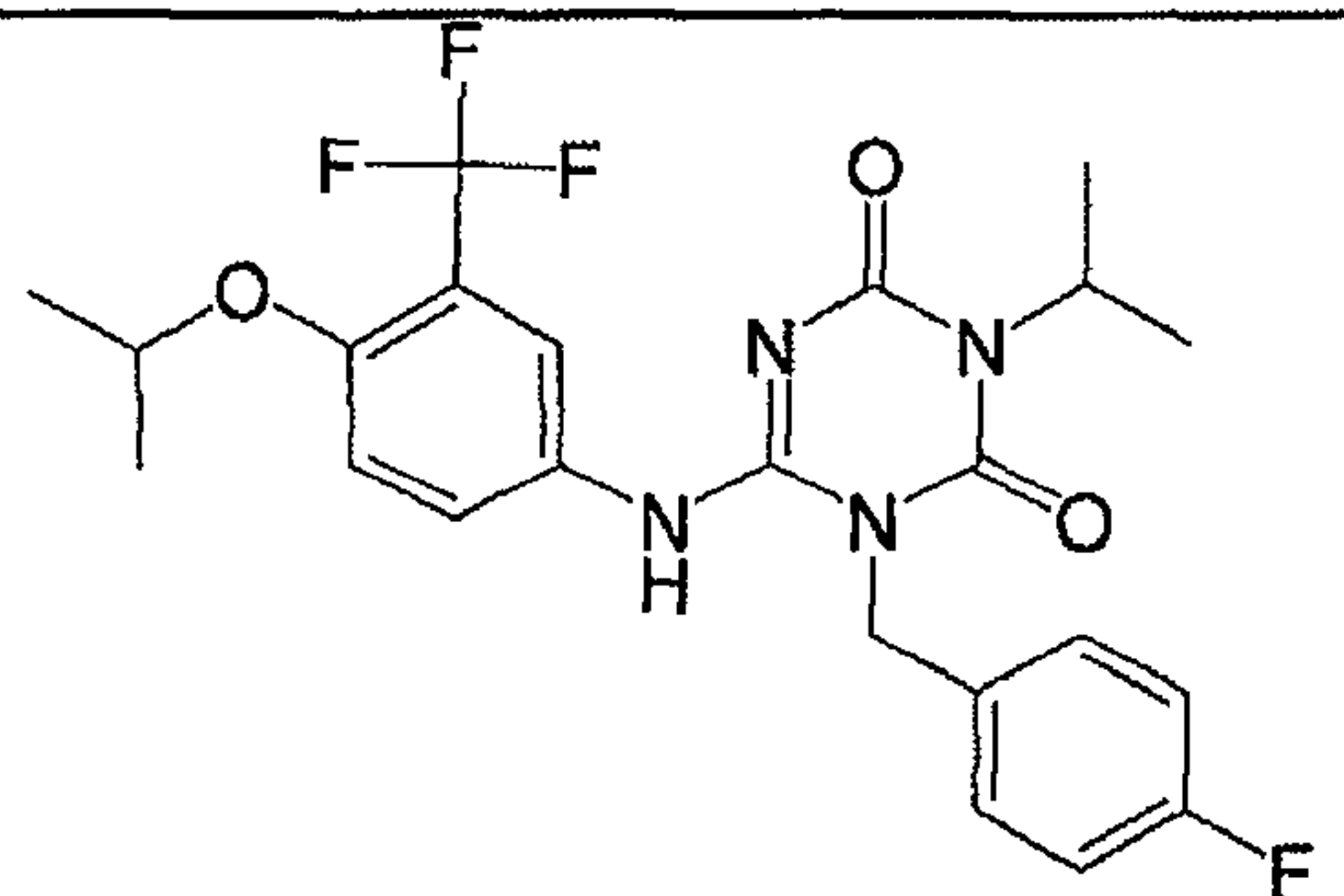
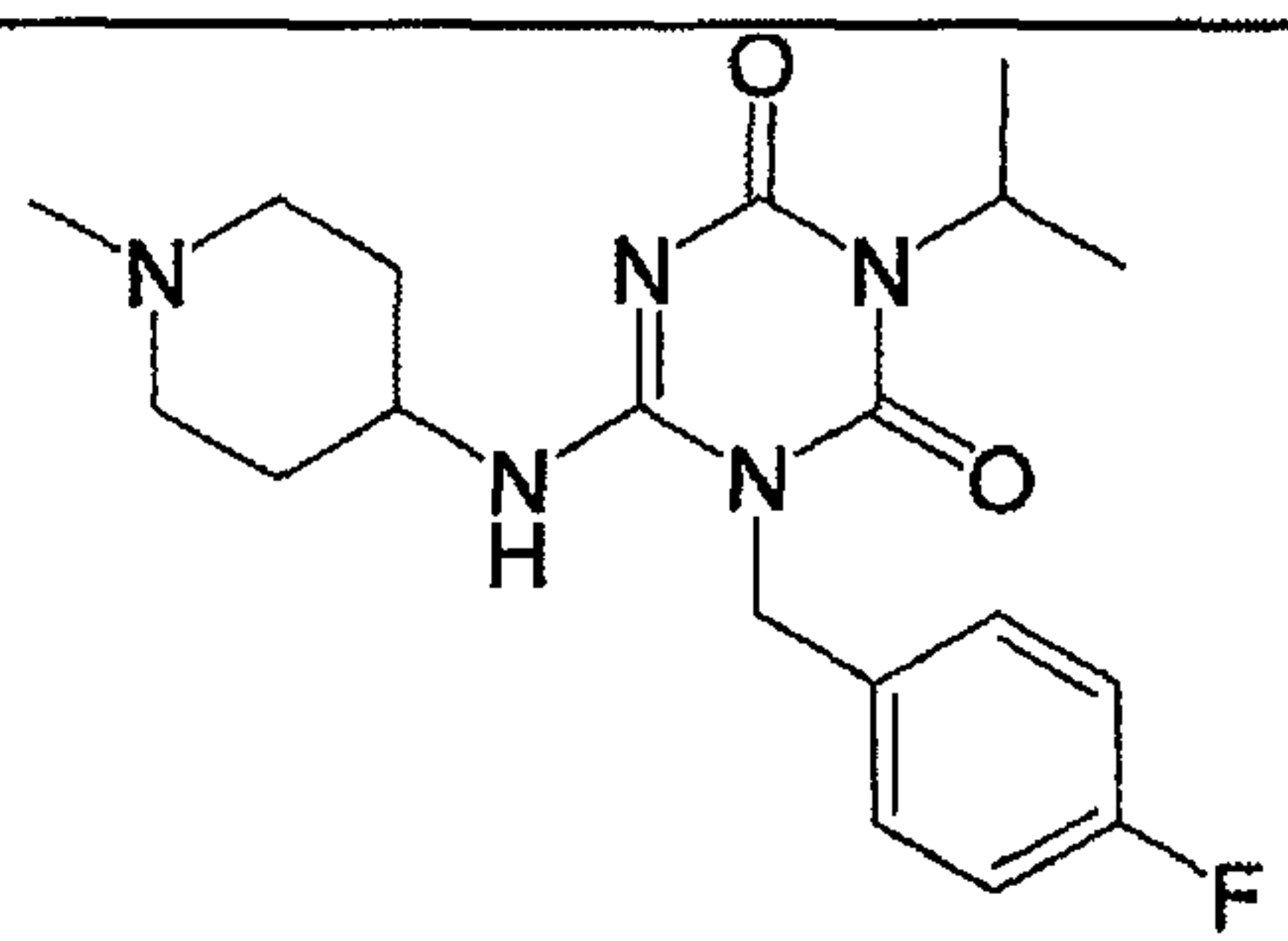
[Table 42]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0191	1.90	399	3
	I-0192	1.90	399	3
	I-0193	2.20	403	3
	I-0194	2.20	403	3
	I-0195	2.30	437	3

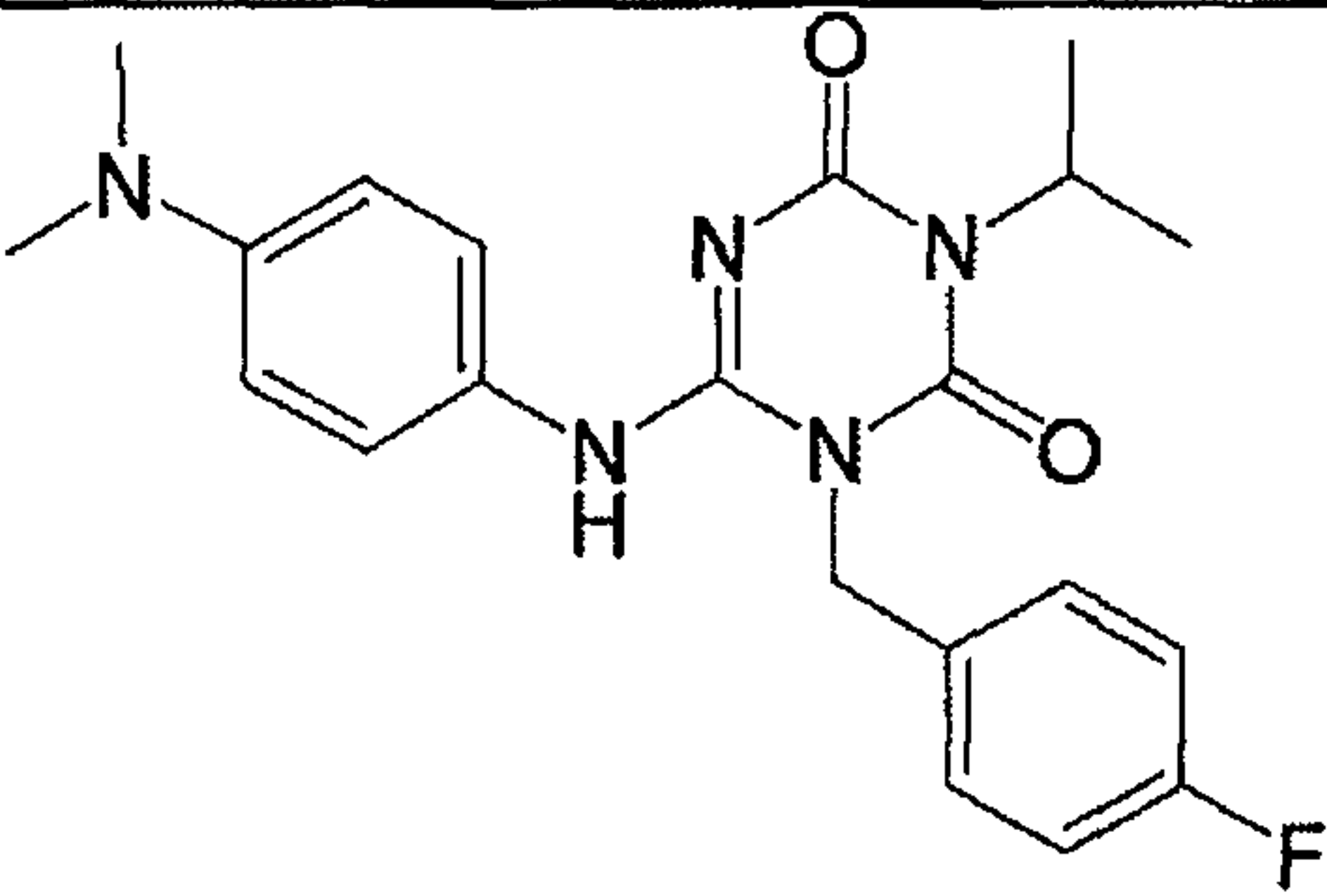
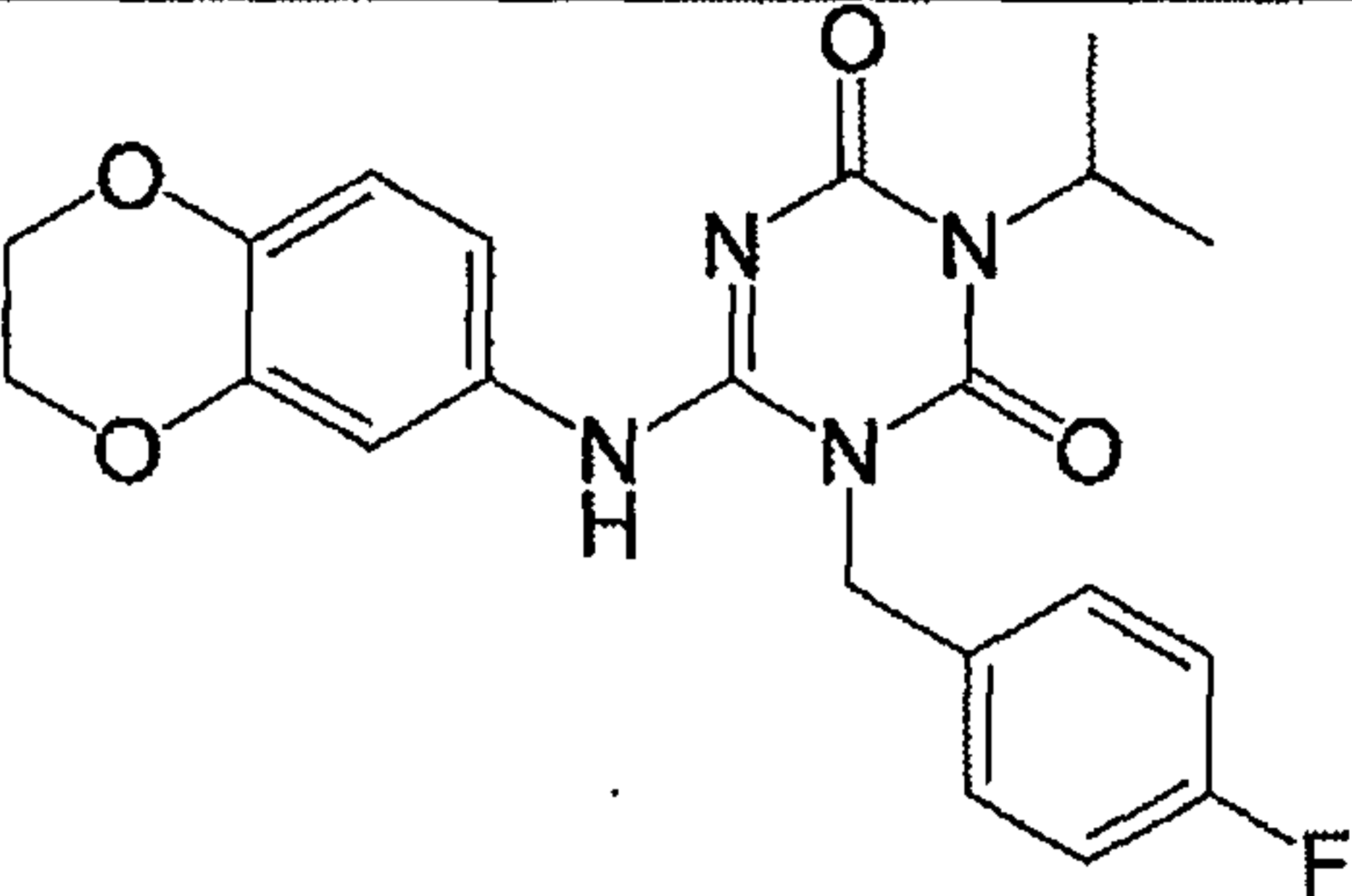
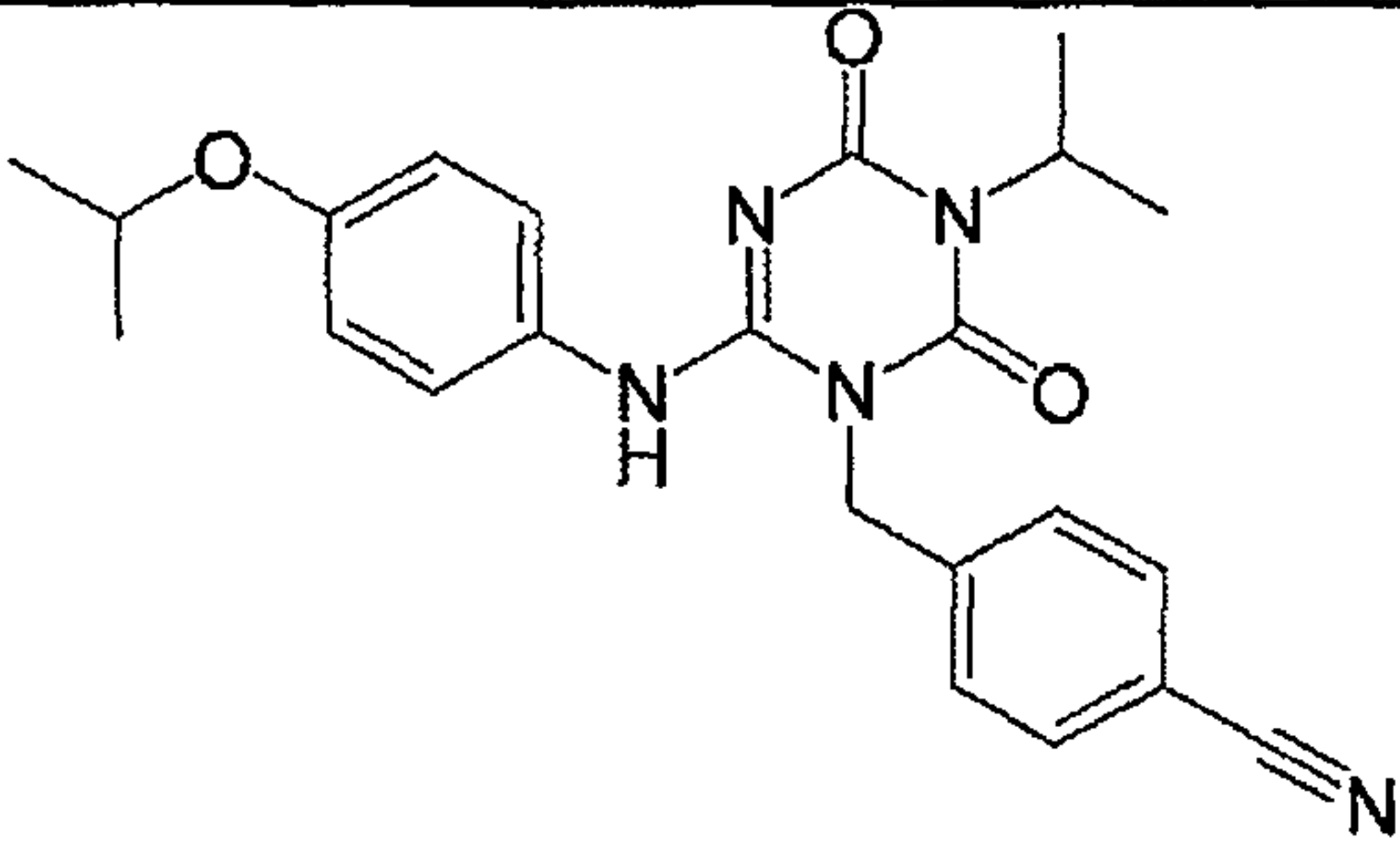
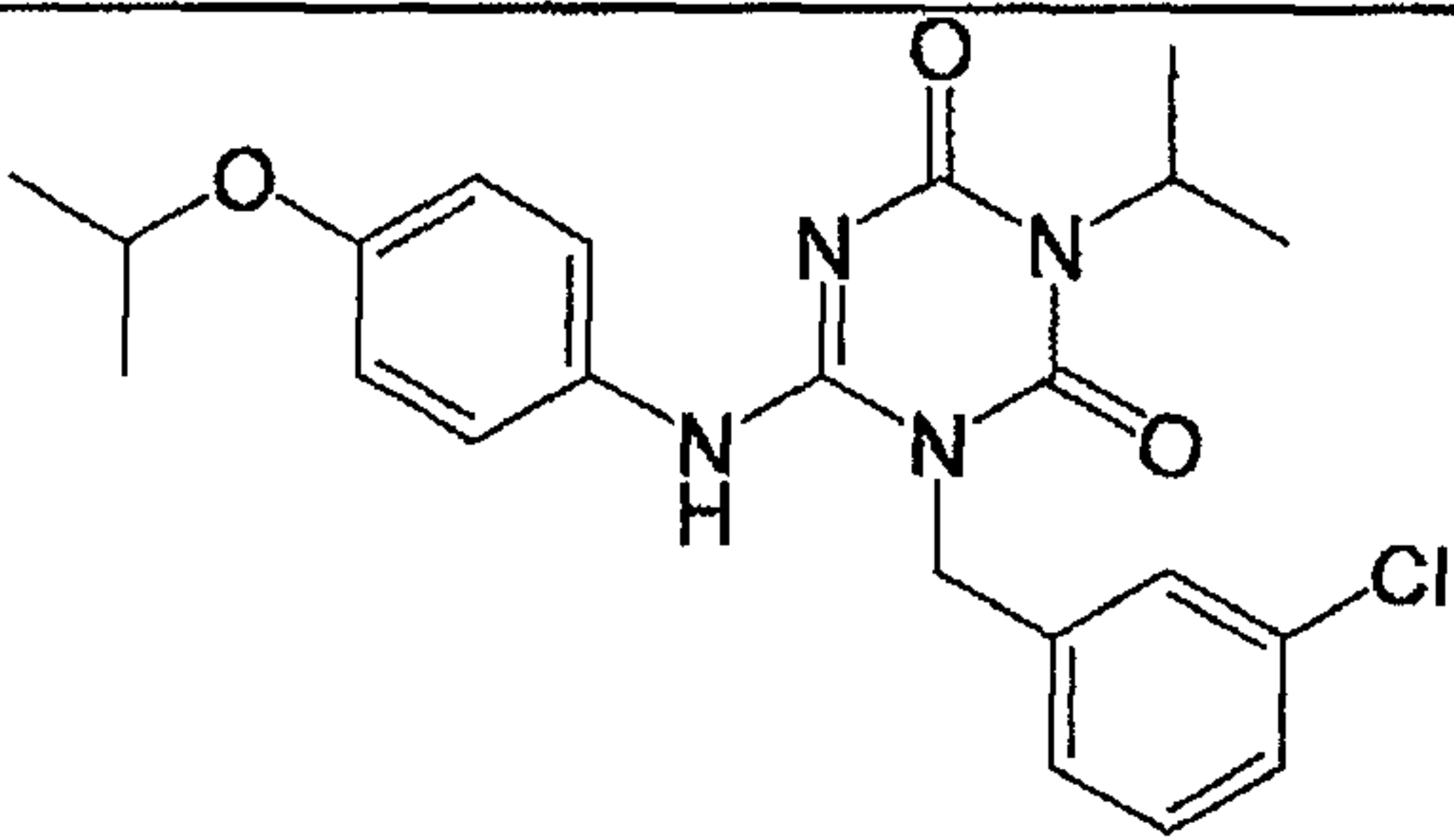
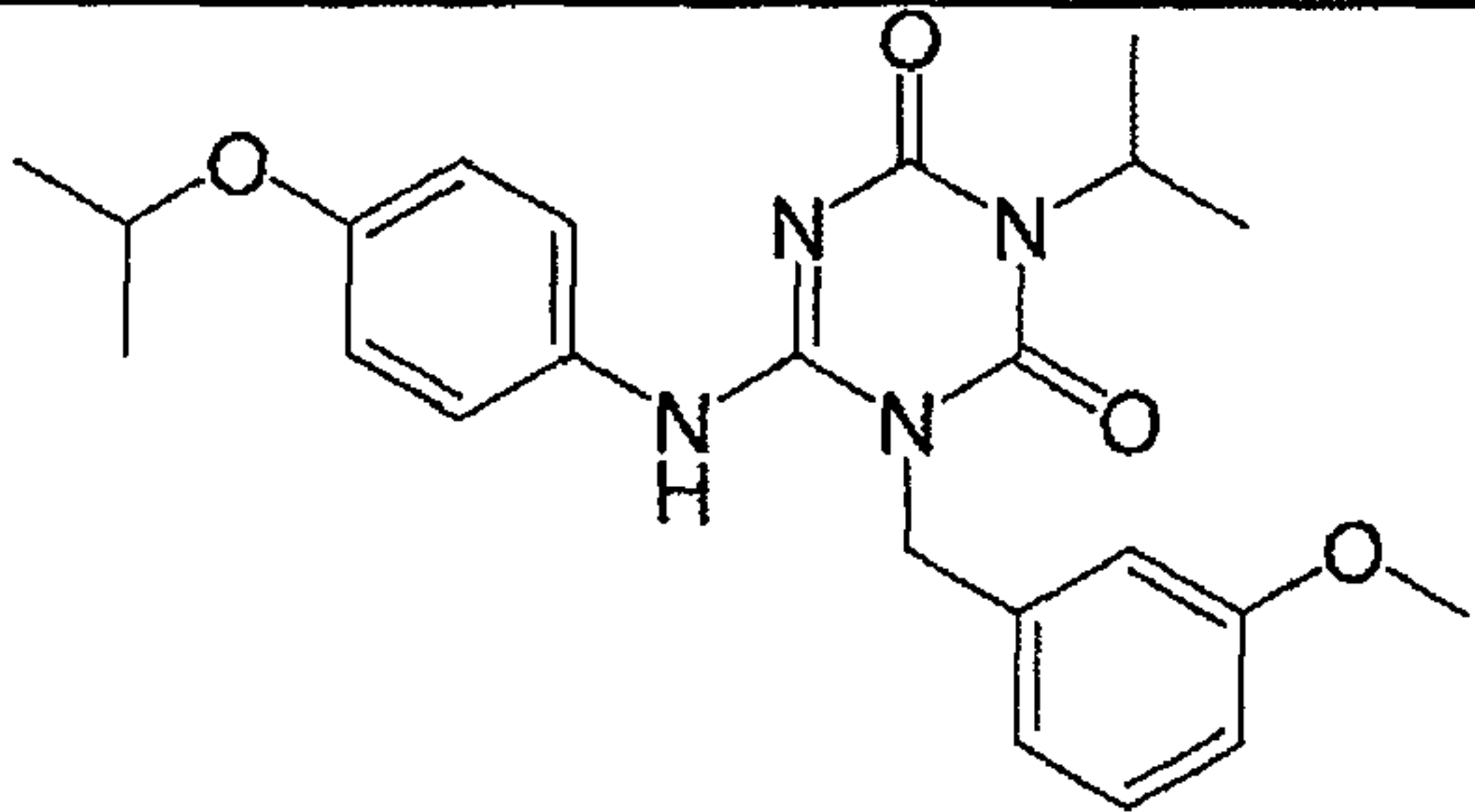
[Table 43]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0196	1.70	337	3
	I-0197	2.80	424	3
	I-0198	2.80	457	3
	I-0199	1.40	452	3
	I-0200	2.60	429	3

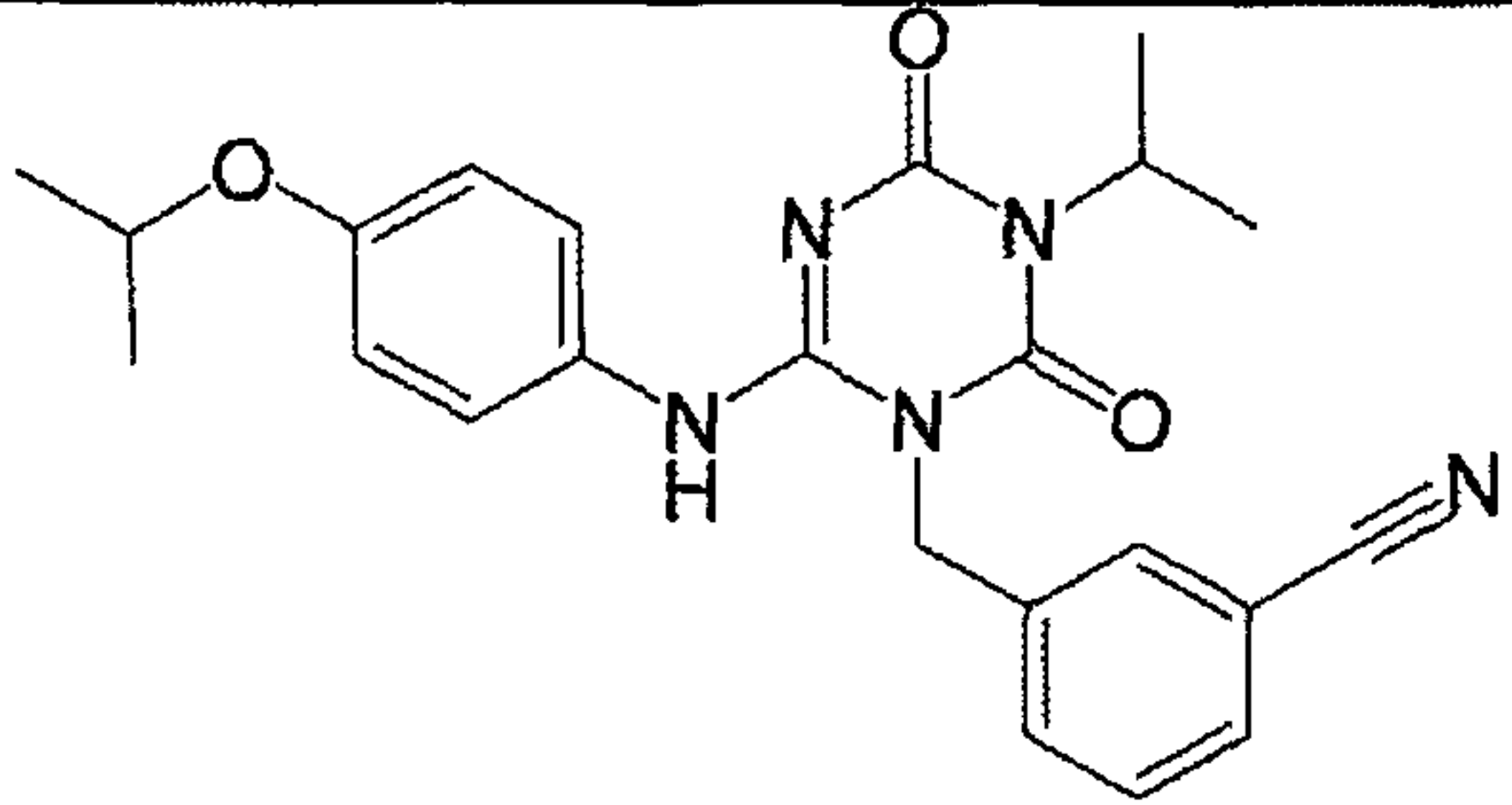
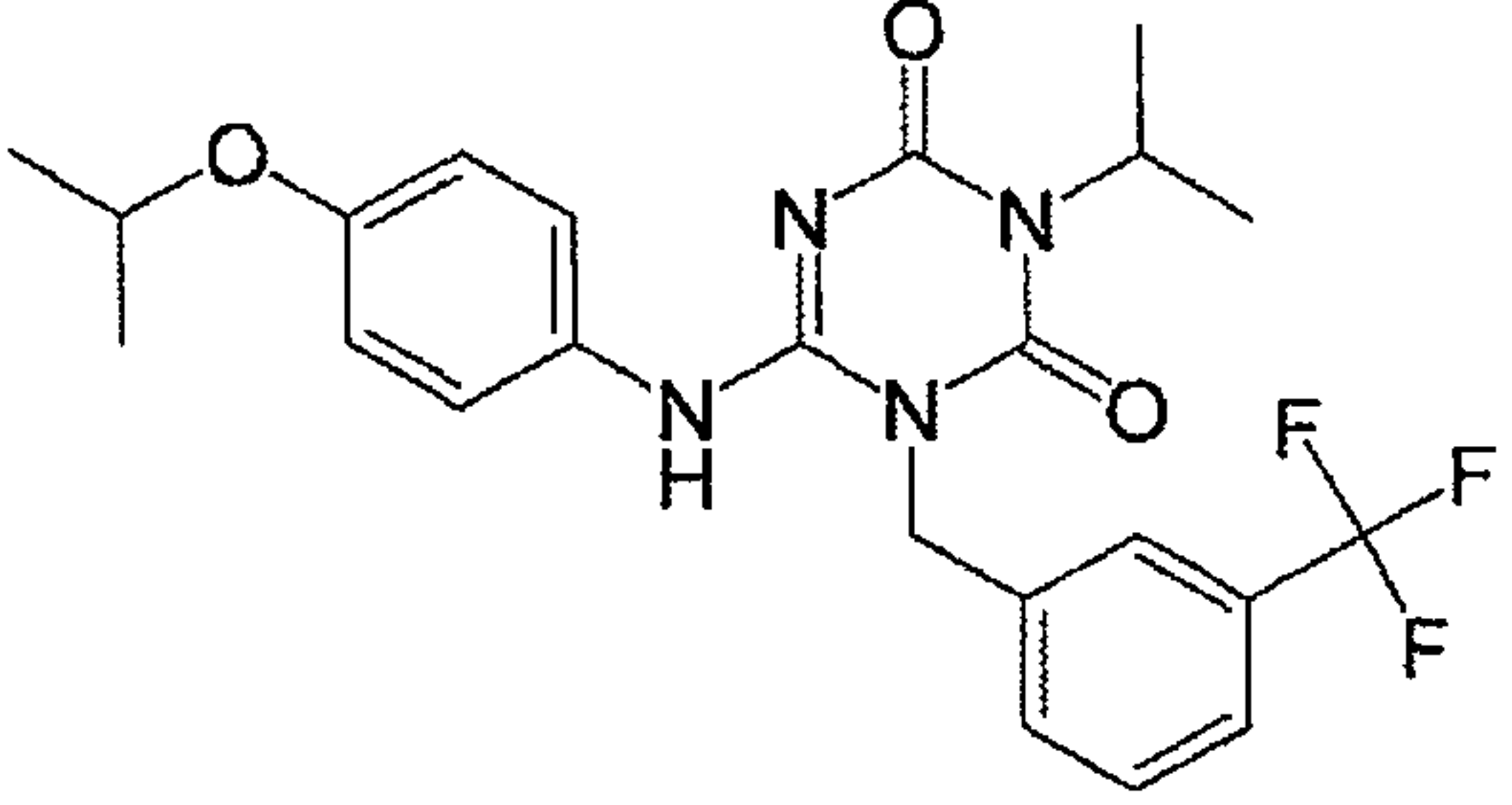
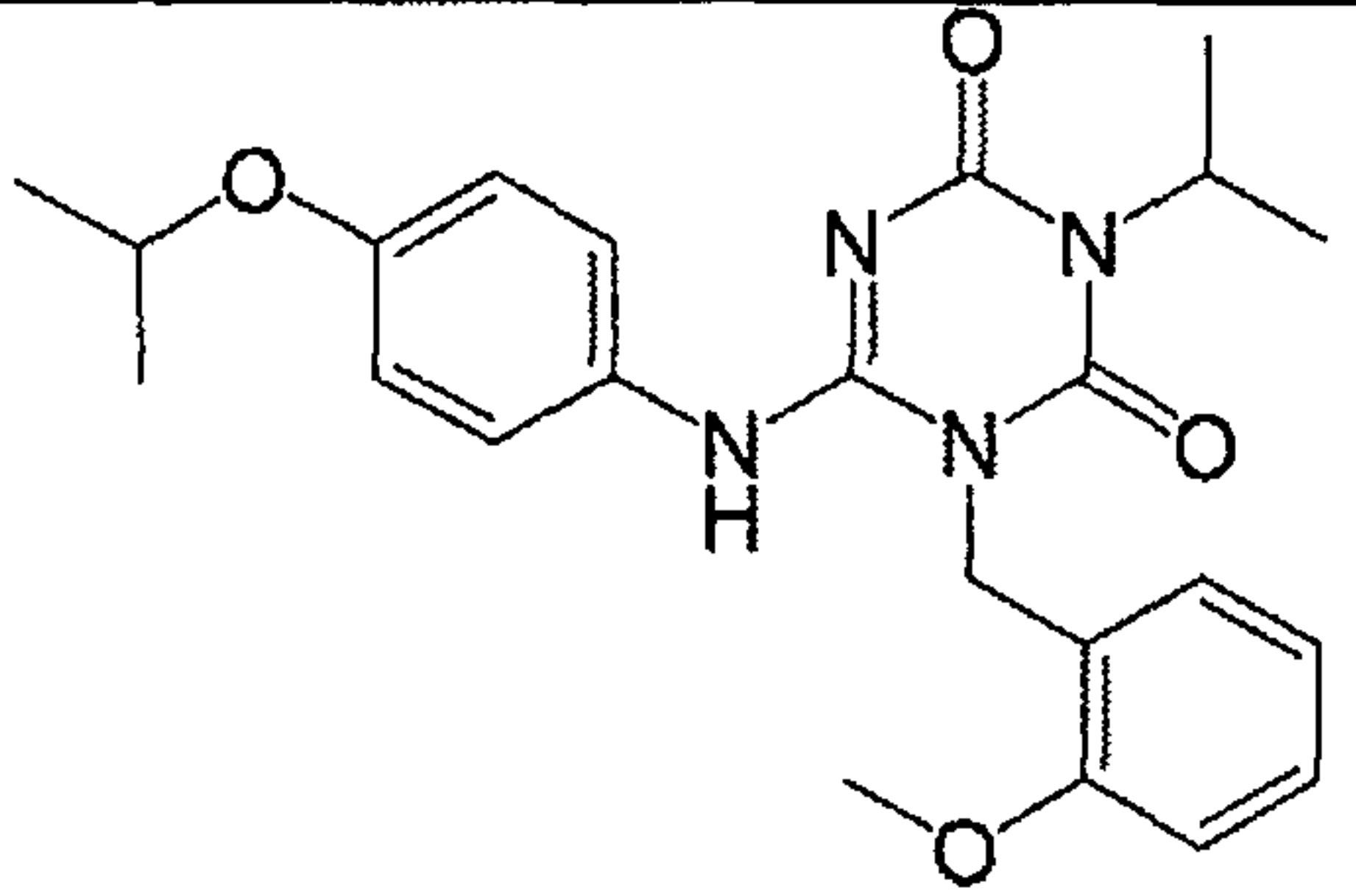
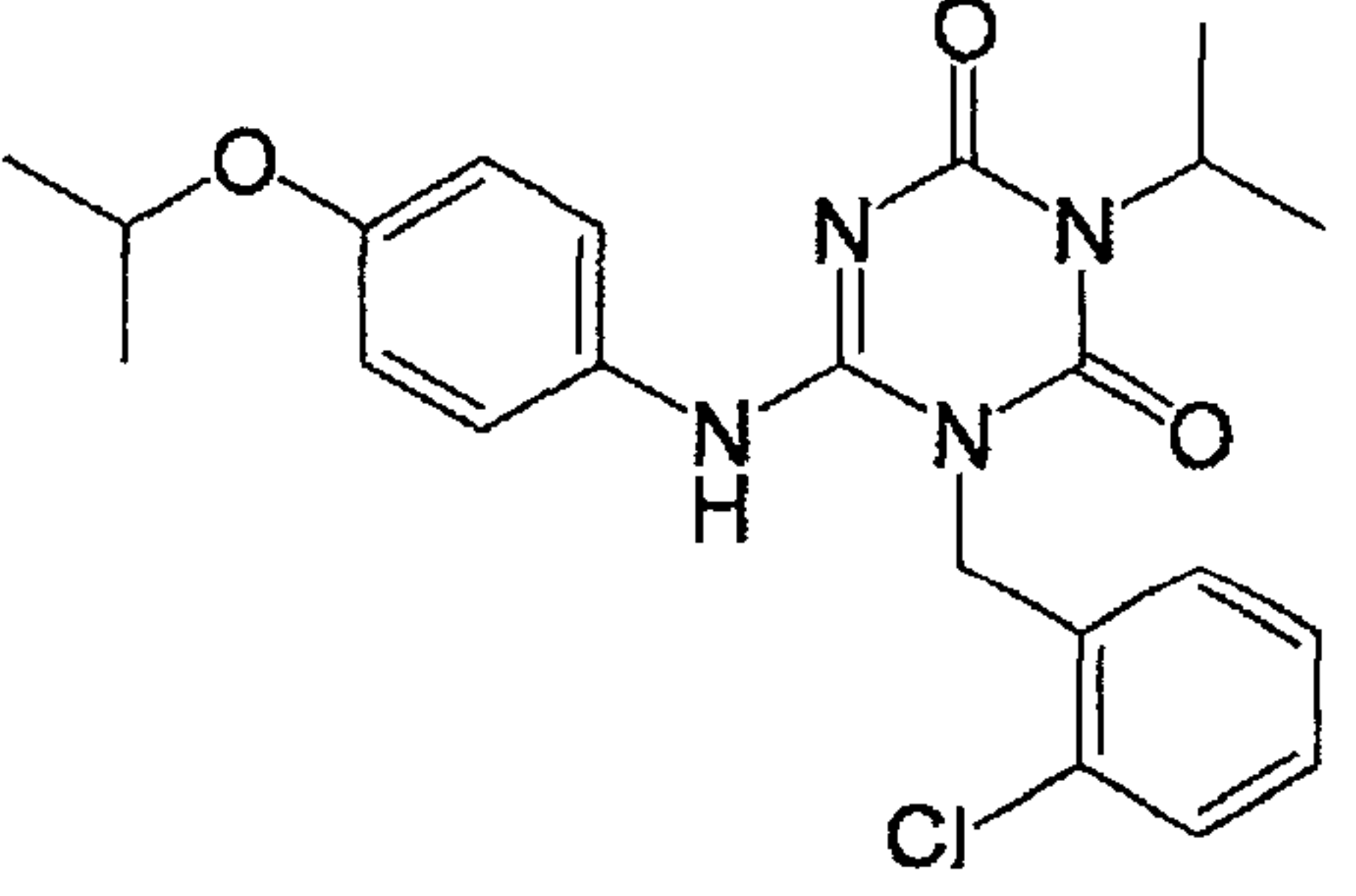
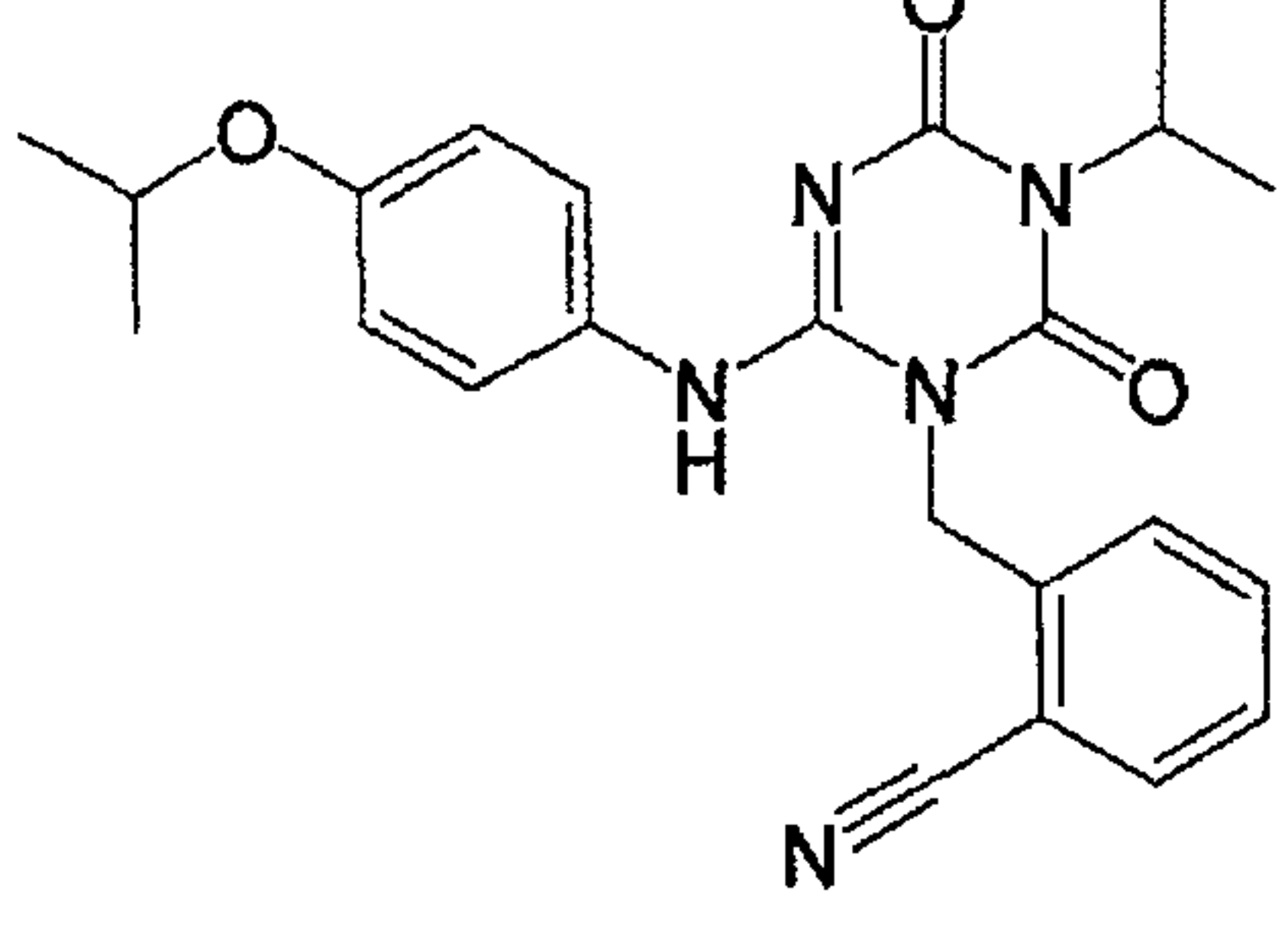
[Table 44]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0201	2.70	463	3
	I-0202	2.40	425	3
	I-0203	2.70	447	3
	I-0204	2.80	481	3
	I-0205	1.20	376	3

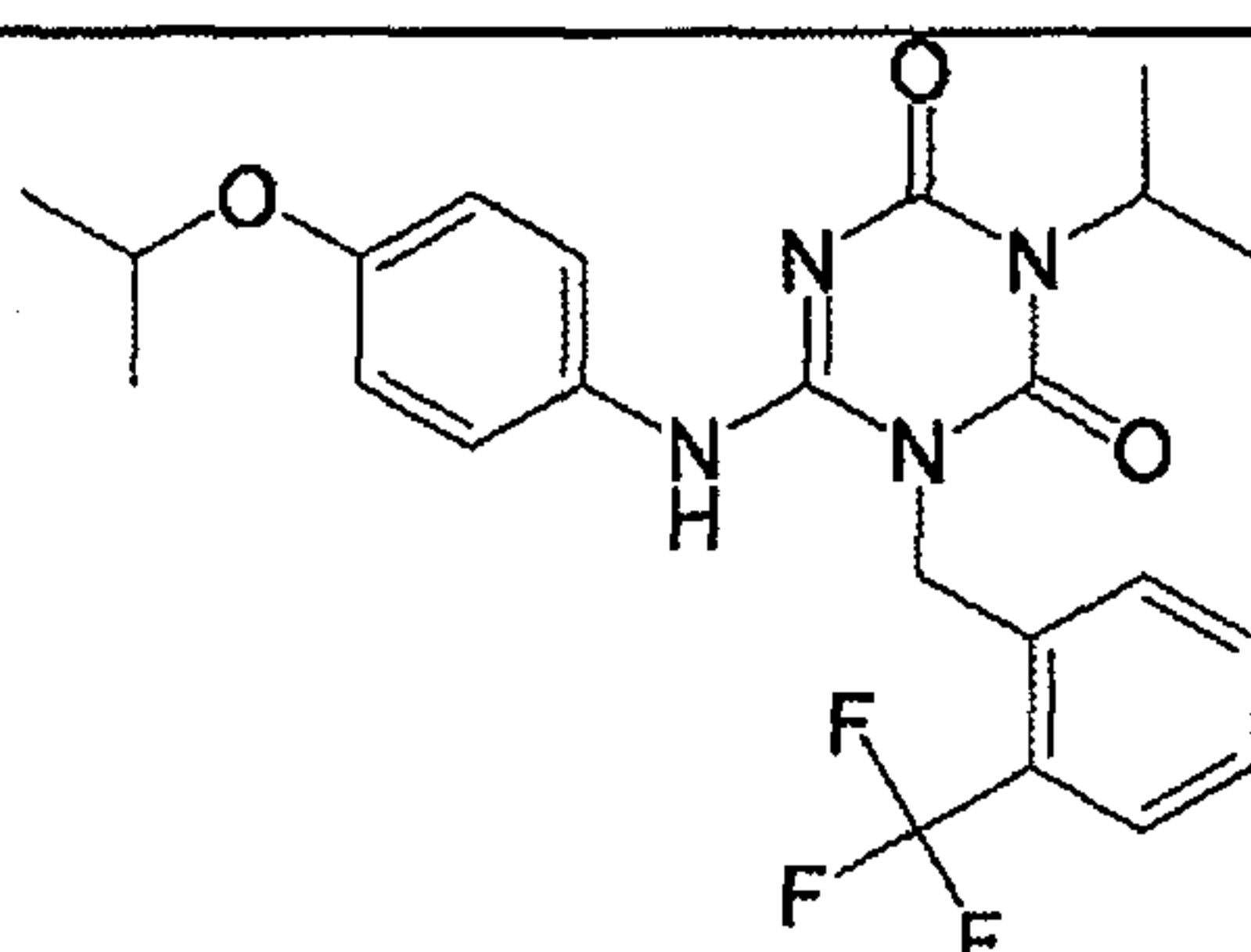
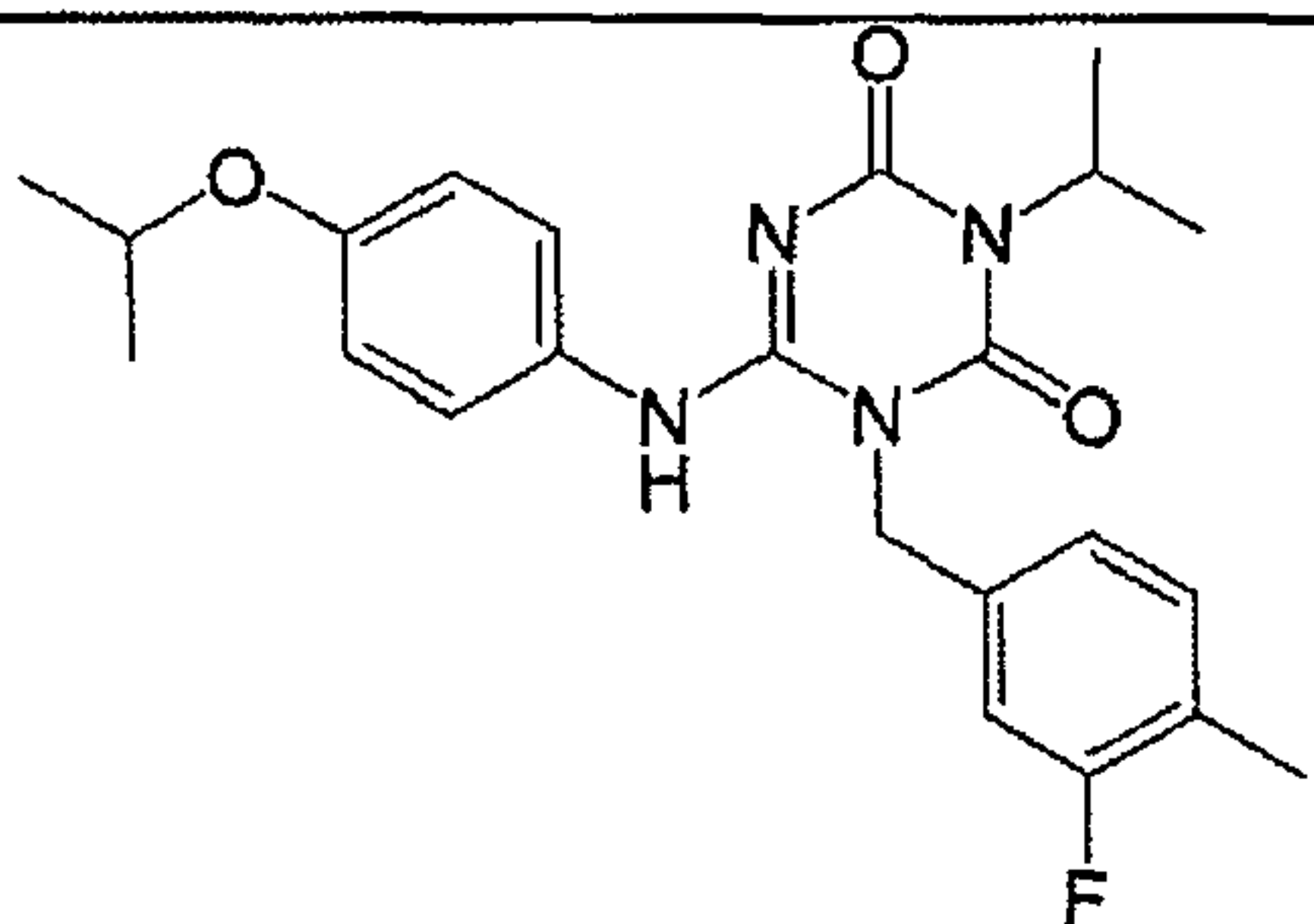
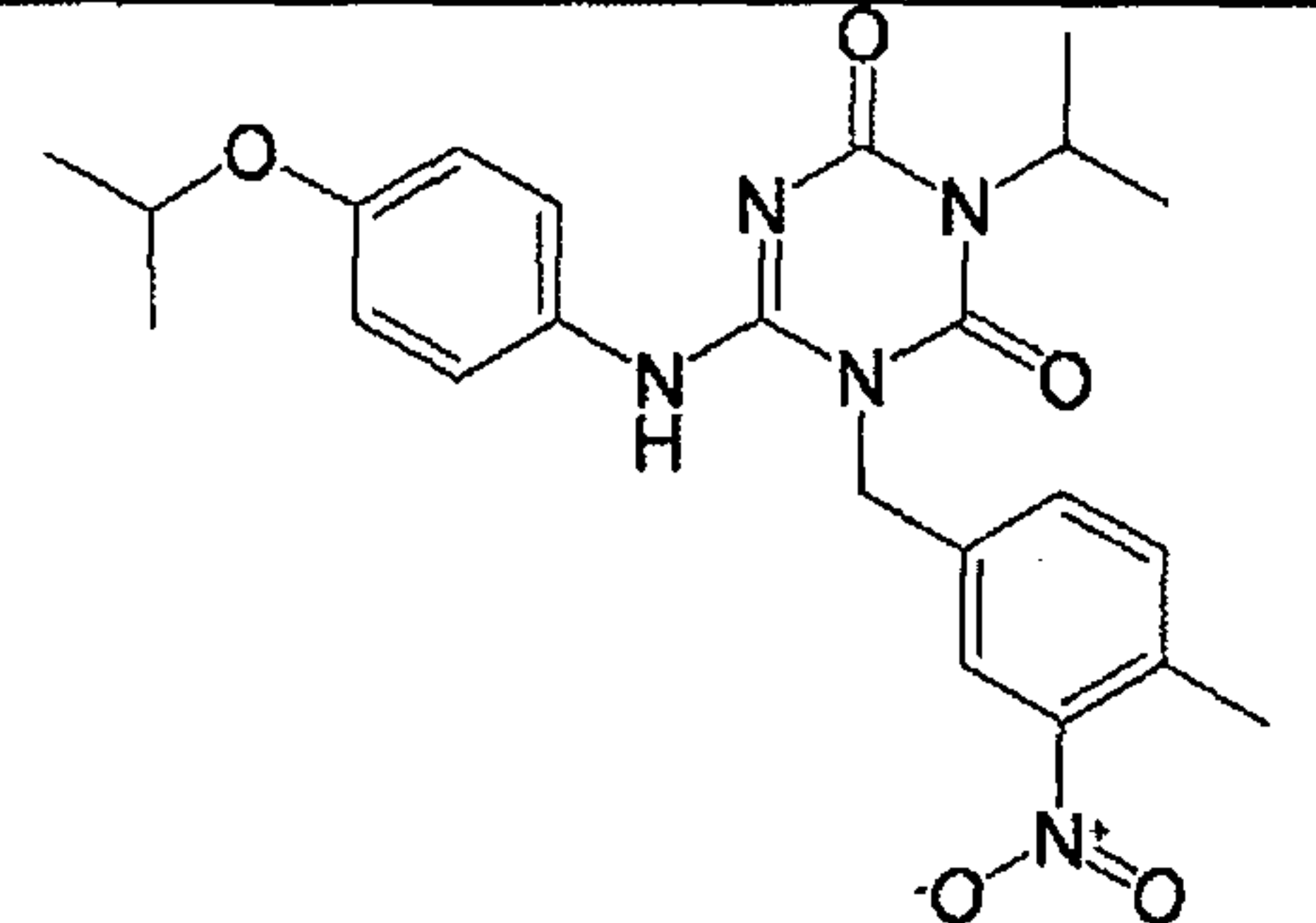
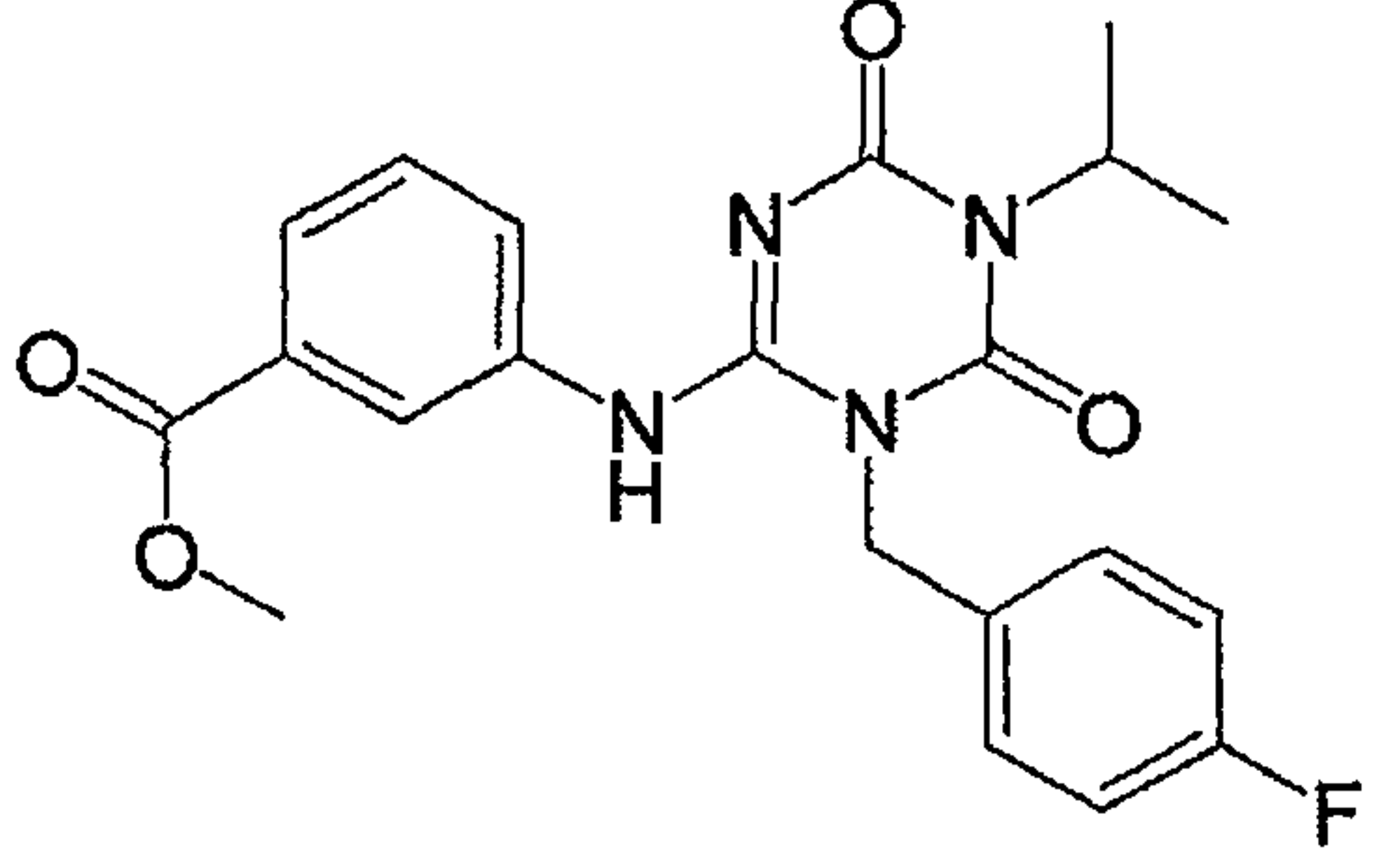
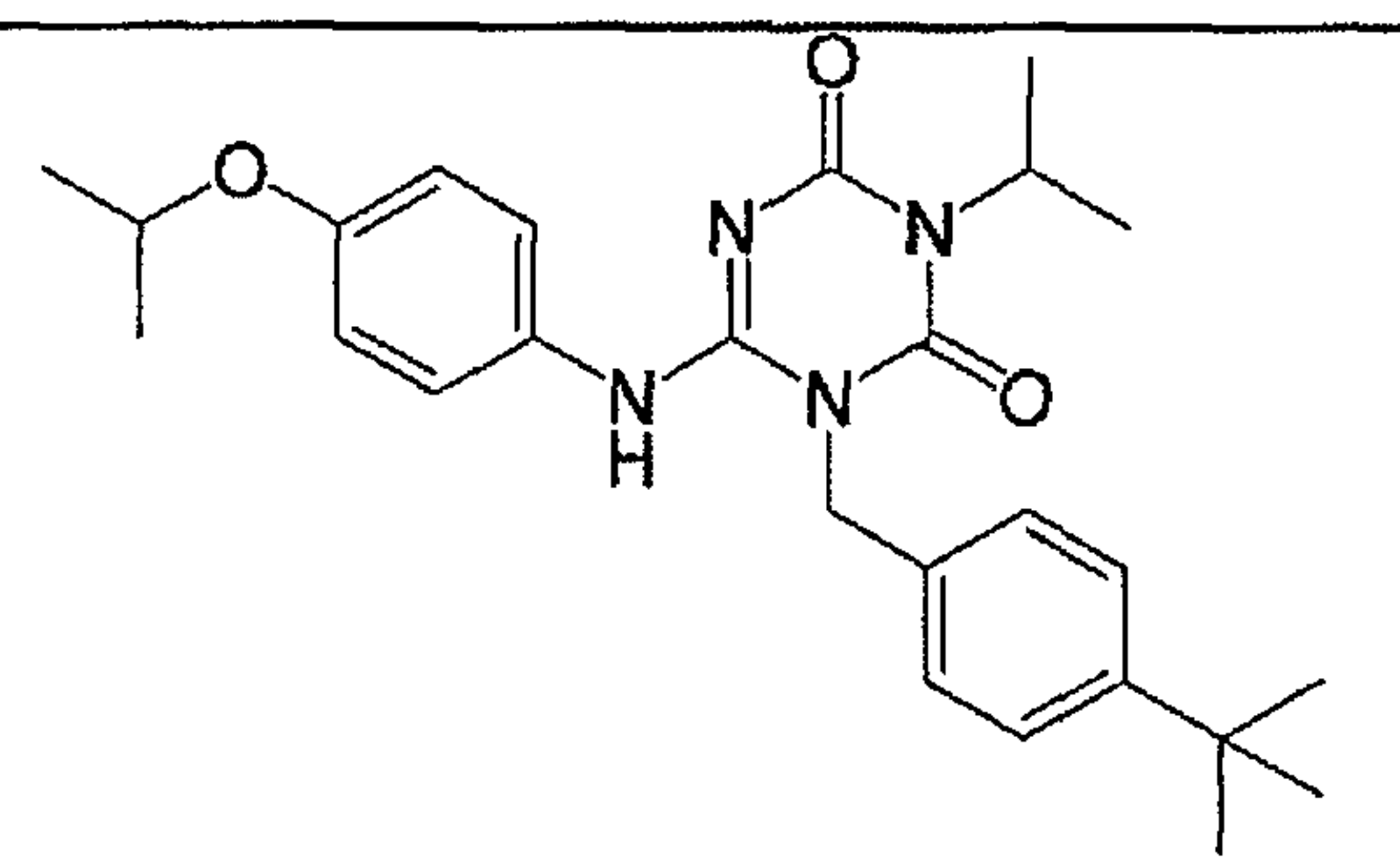
[Table 45]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0206	1.80	398	3
	I-0207	2.20	413	3
	I-0208	2.30	420	3
	I-0209	2.60	429	3
	I-0210	2.40	425	3

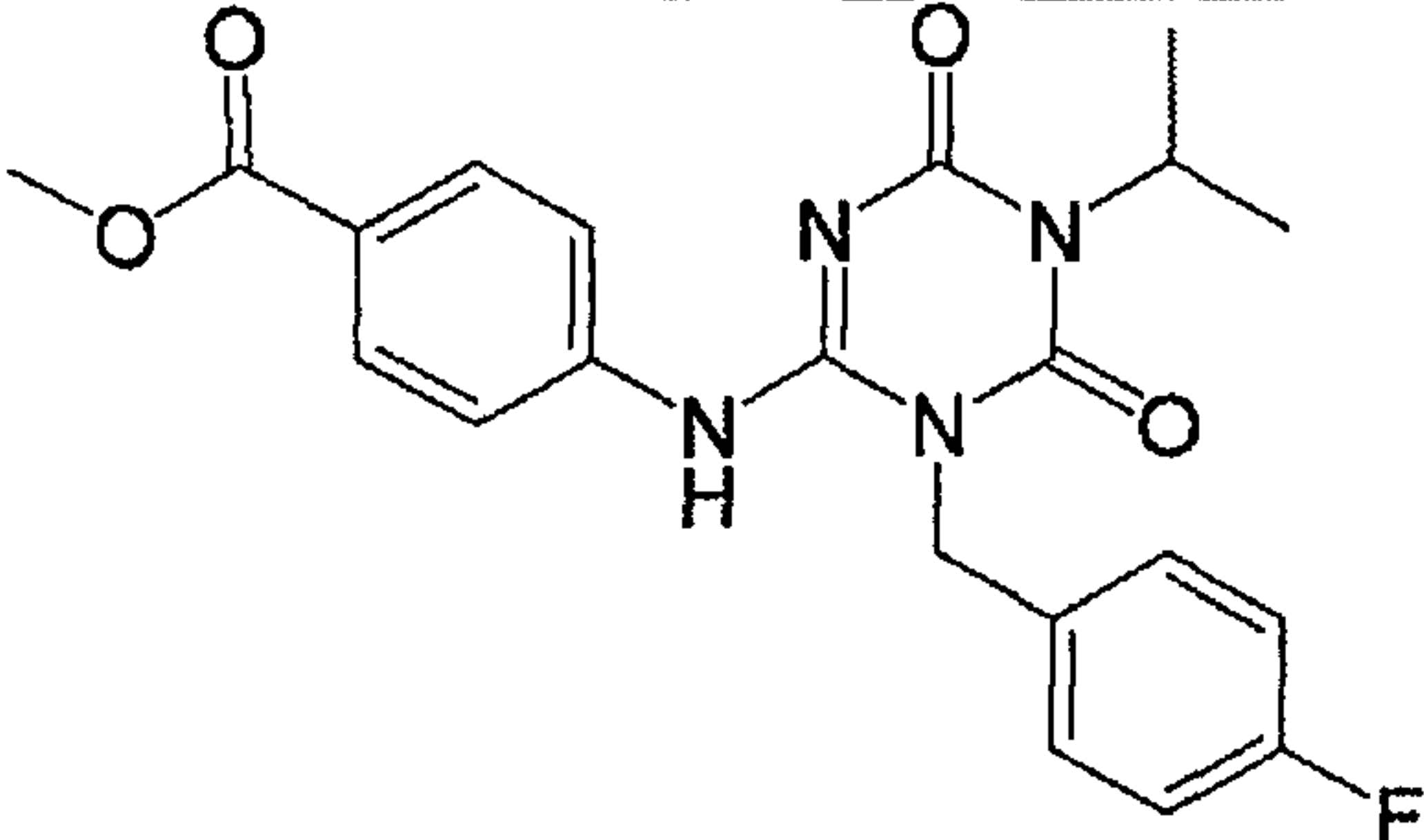
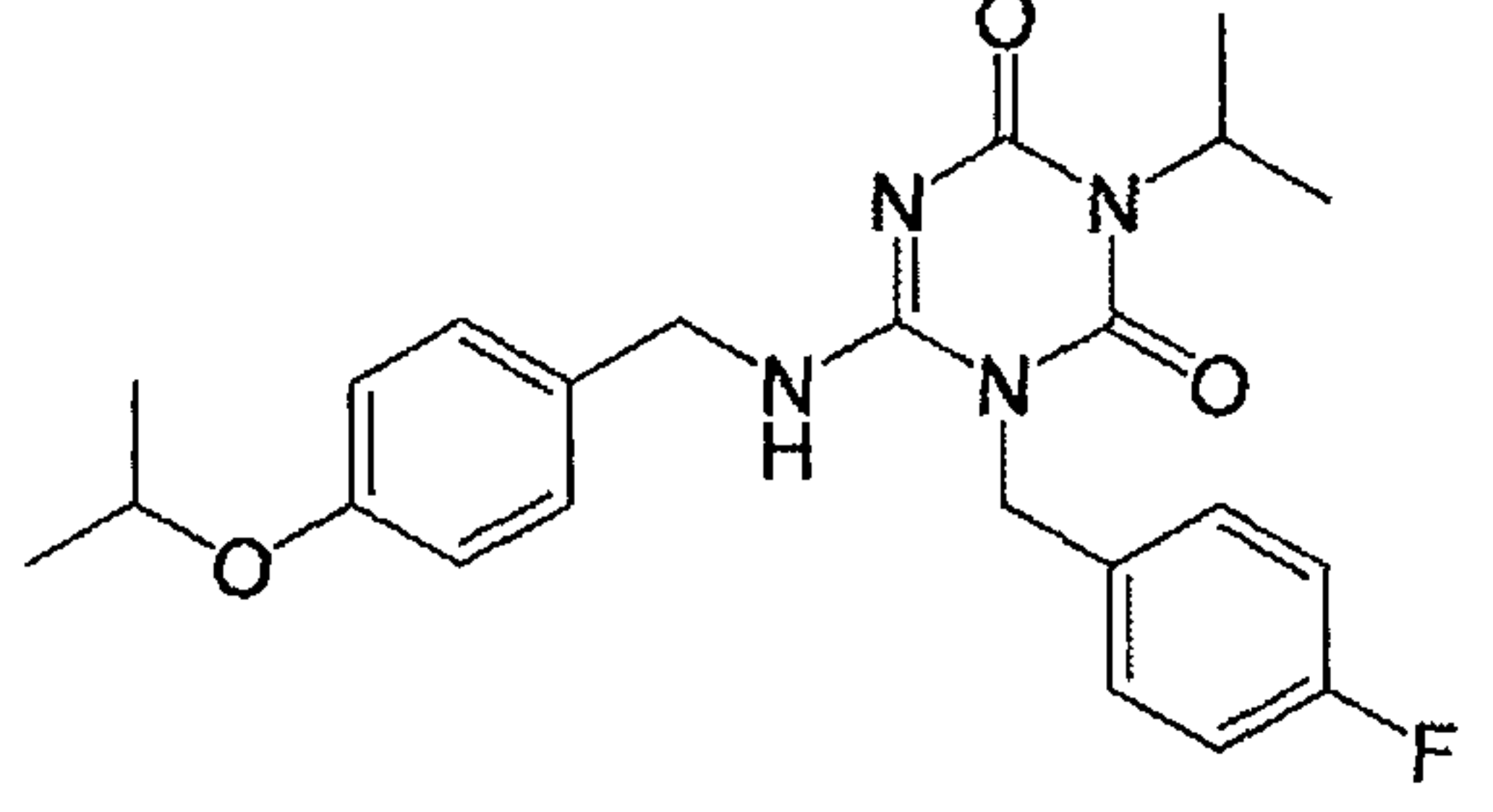
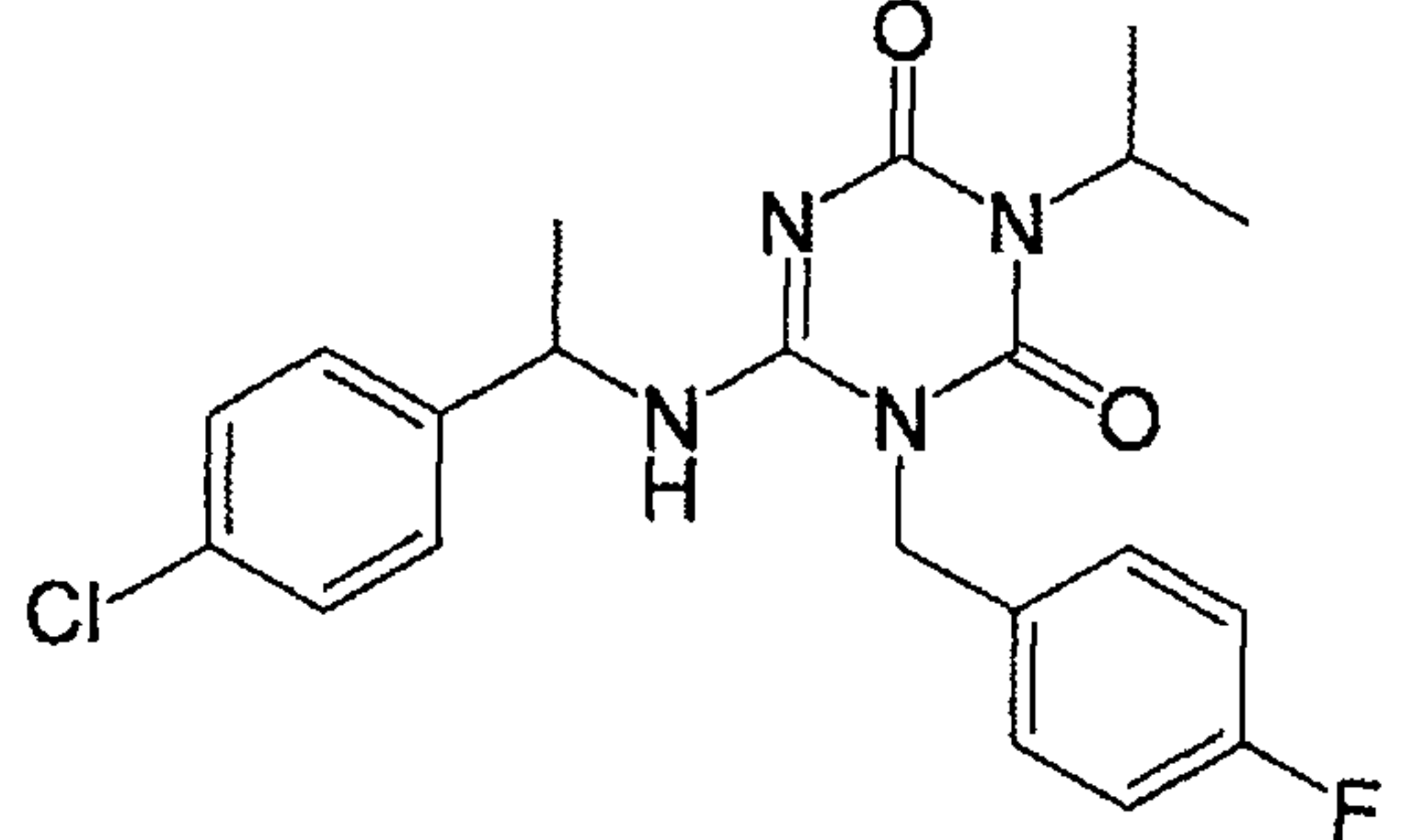
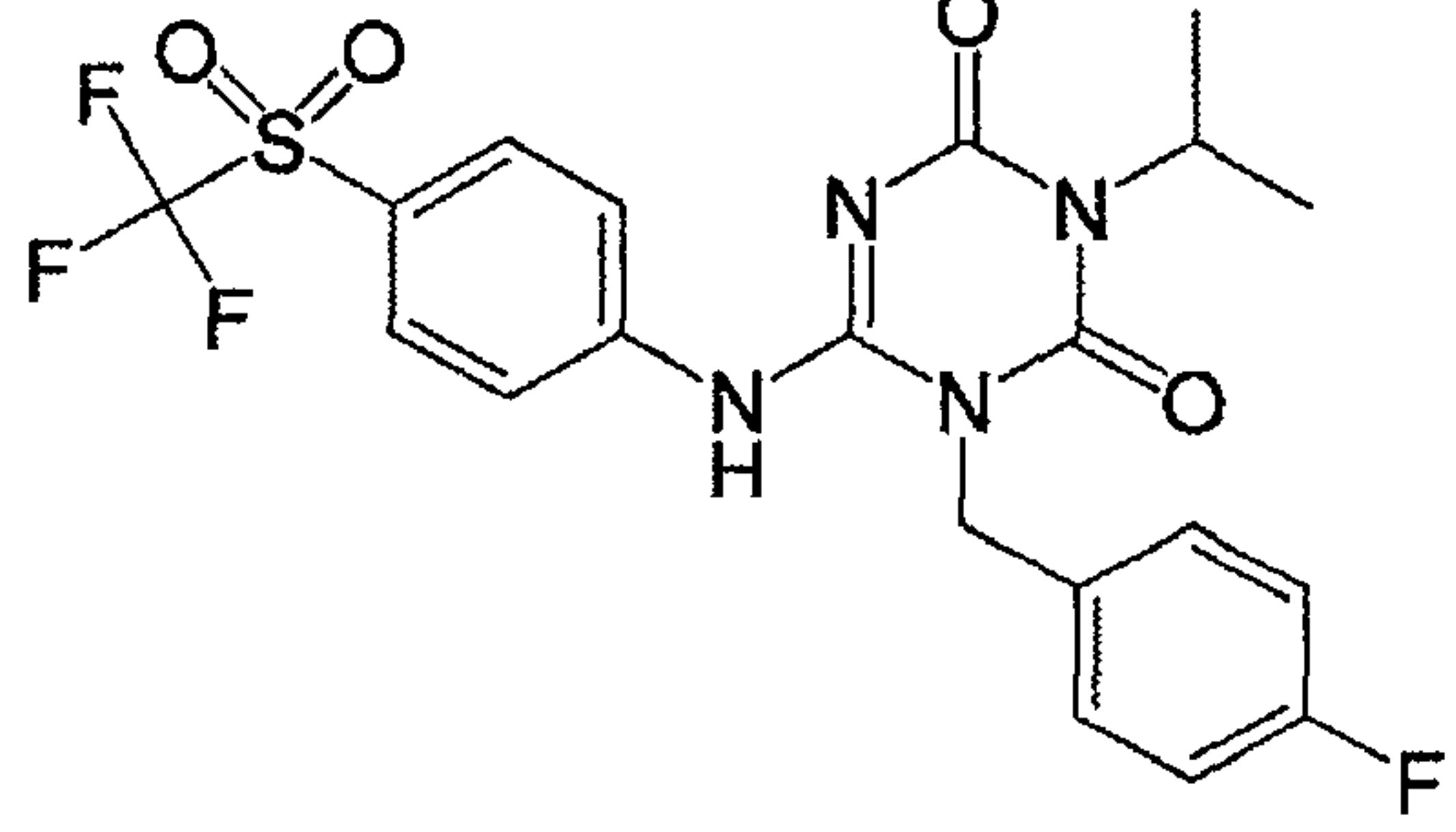
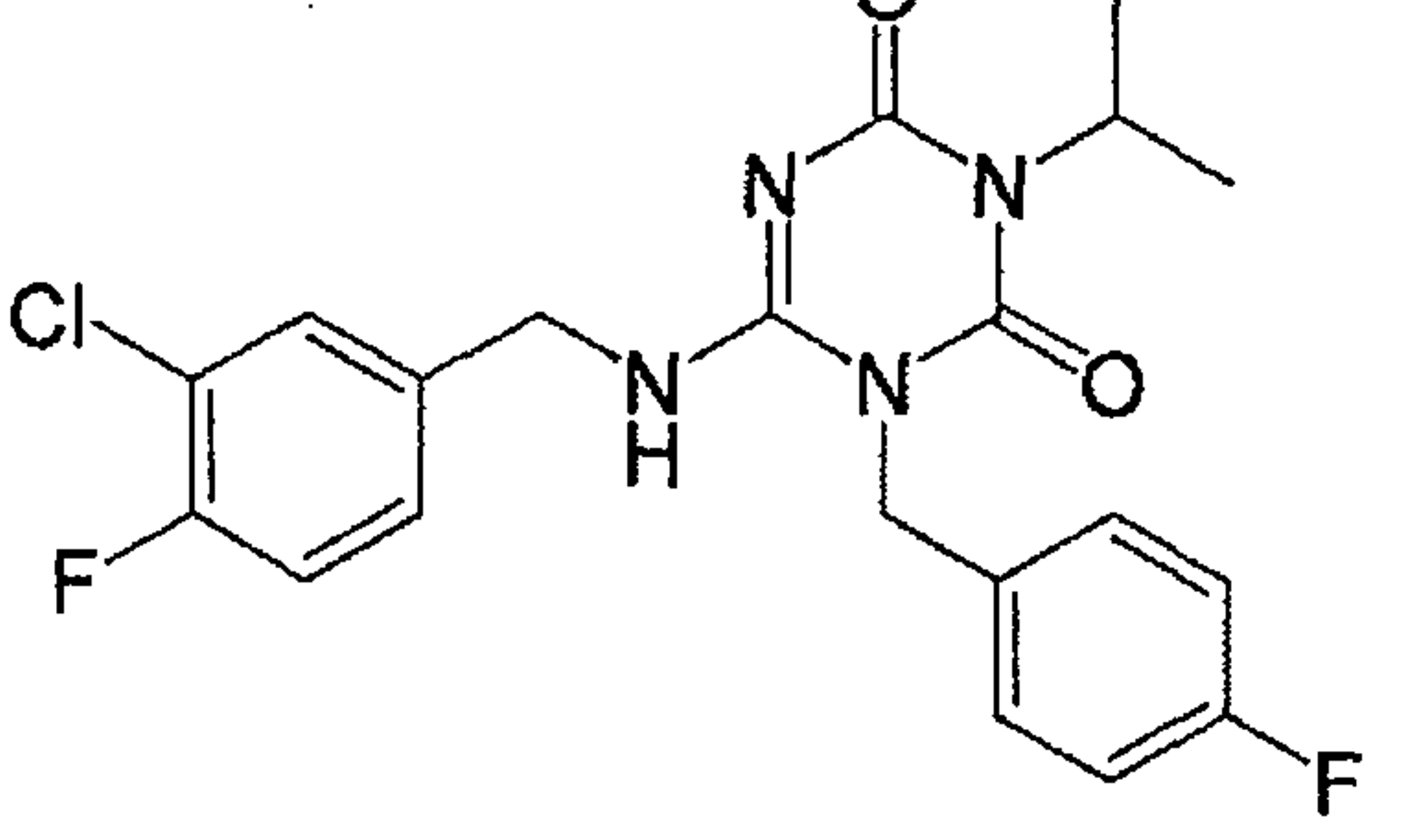
[Table 46]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0211	2.40	420	3
	I-0212	2.70	463	3
	I-0213	2.40	425	3
	I-0214	2.60	429	3
	I-0215	2.40	420	3

[Table 47]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0216	2.70	463	3
	I-0217	2.60	427	3
	I-0218	2.50	454	3
	I-0219	2.40	413	3
	I-0220	2.90	451	3

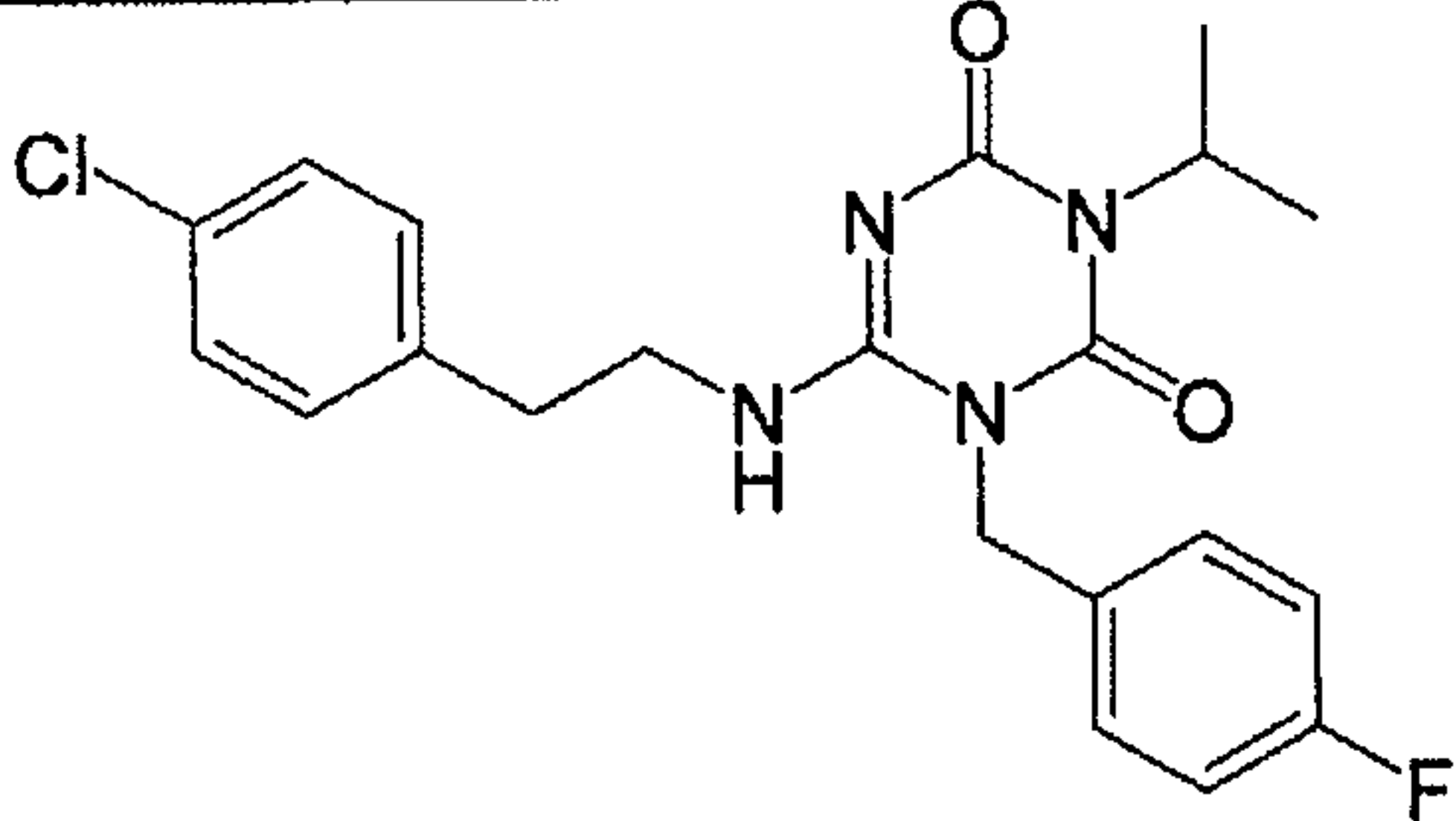
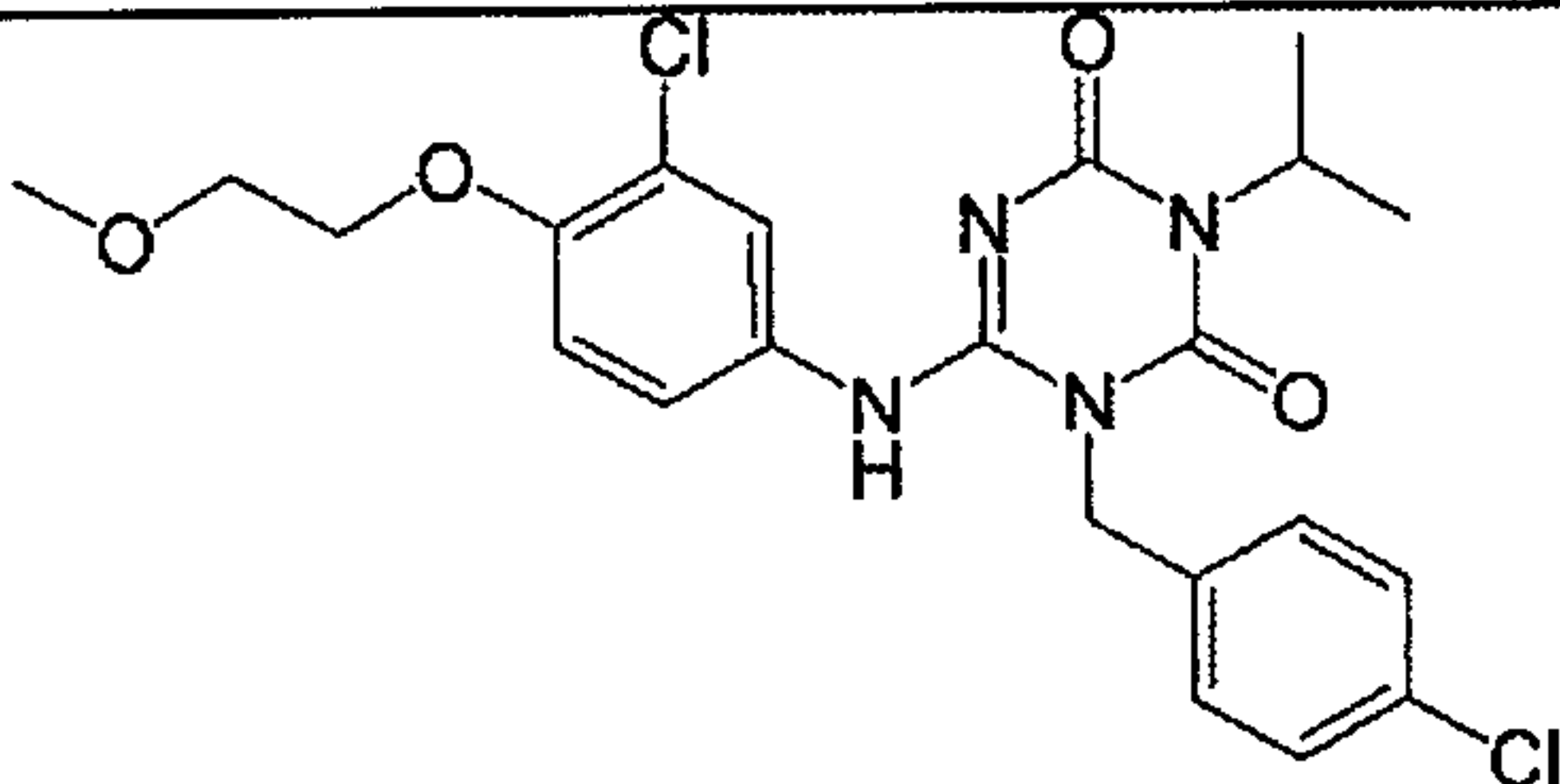
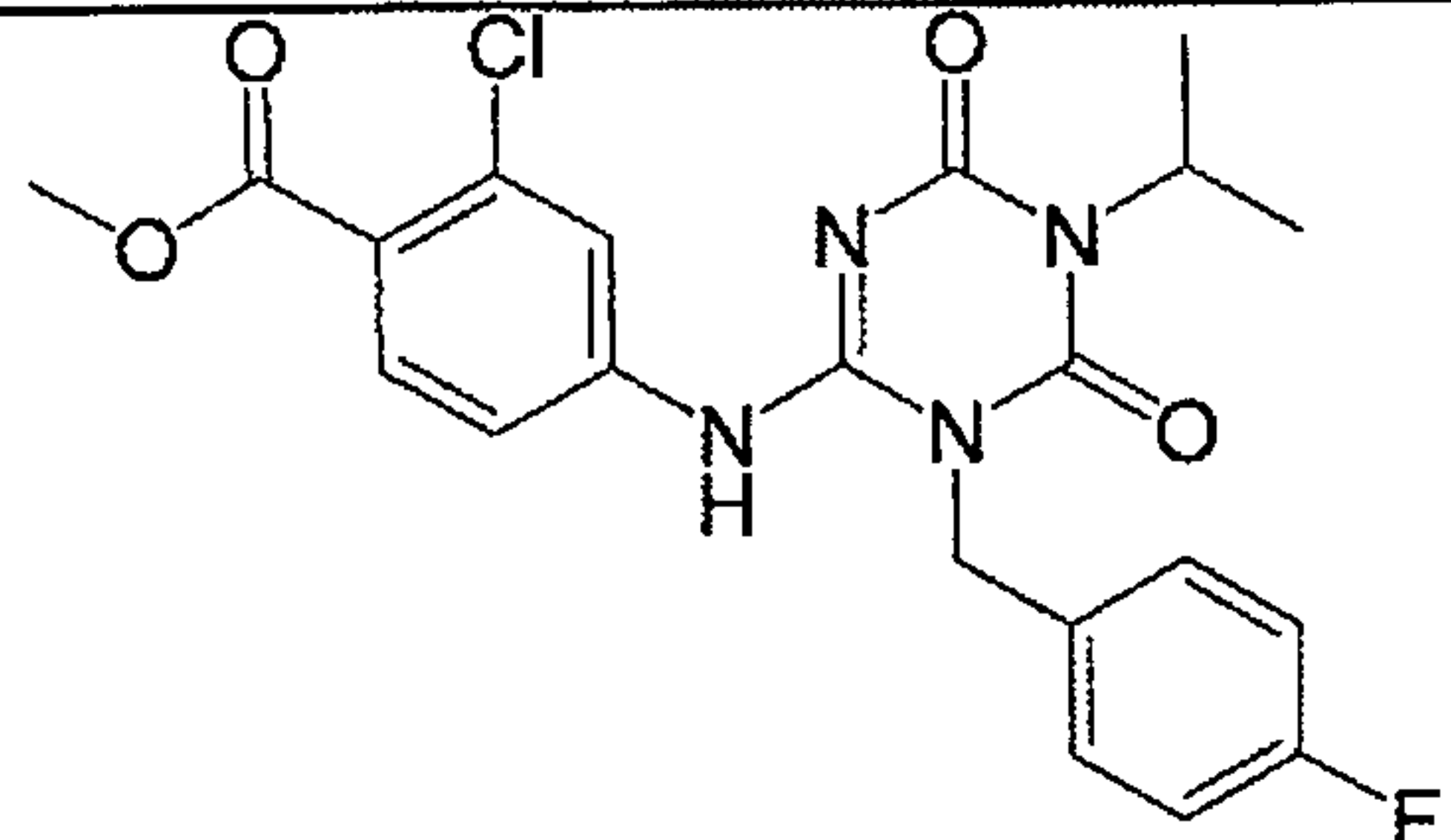
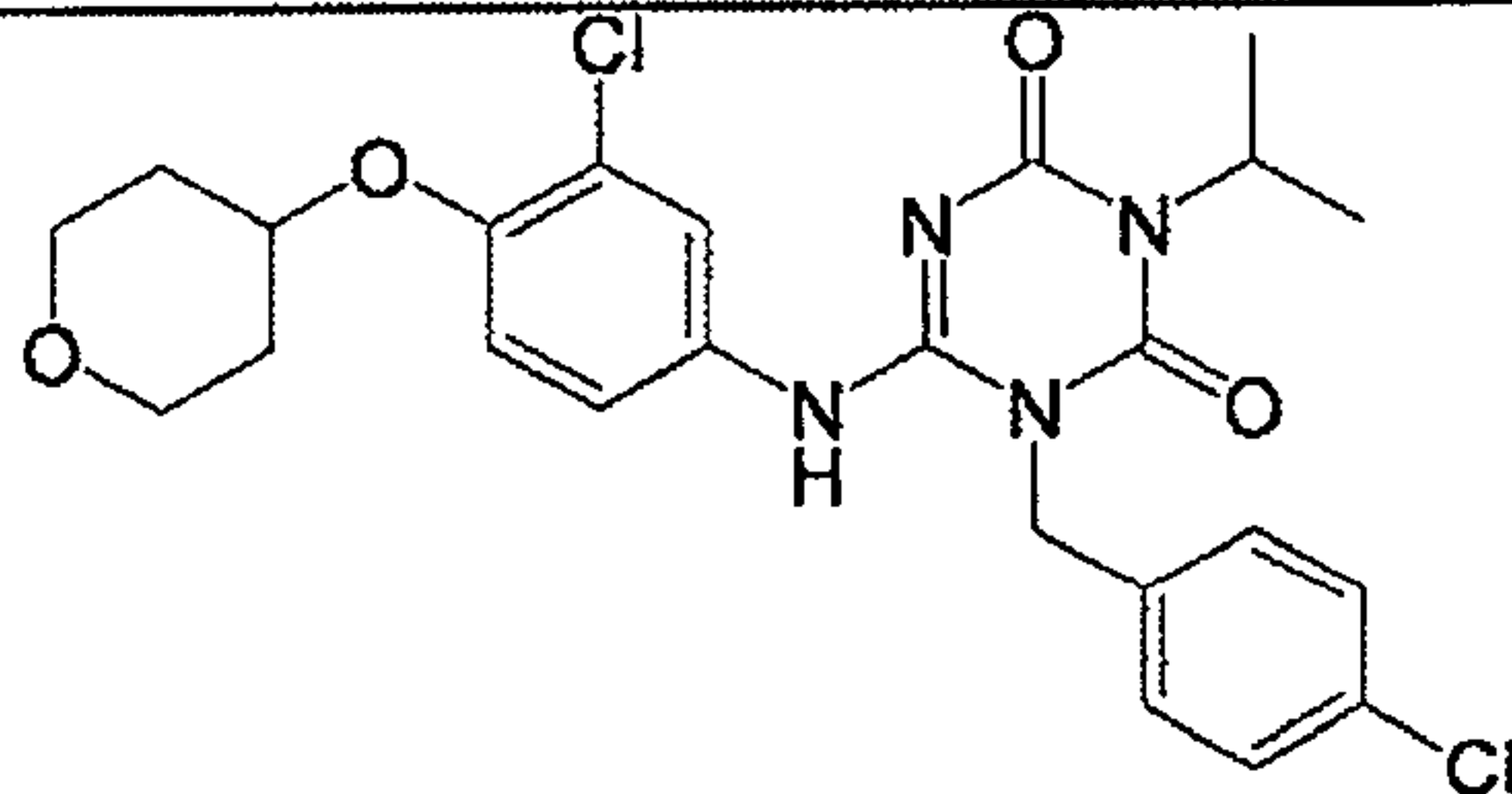
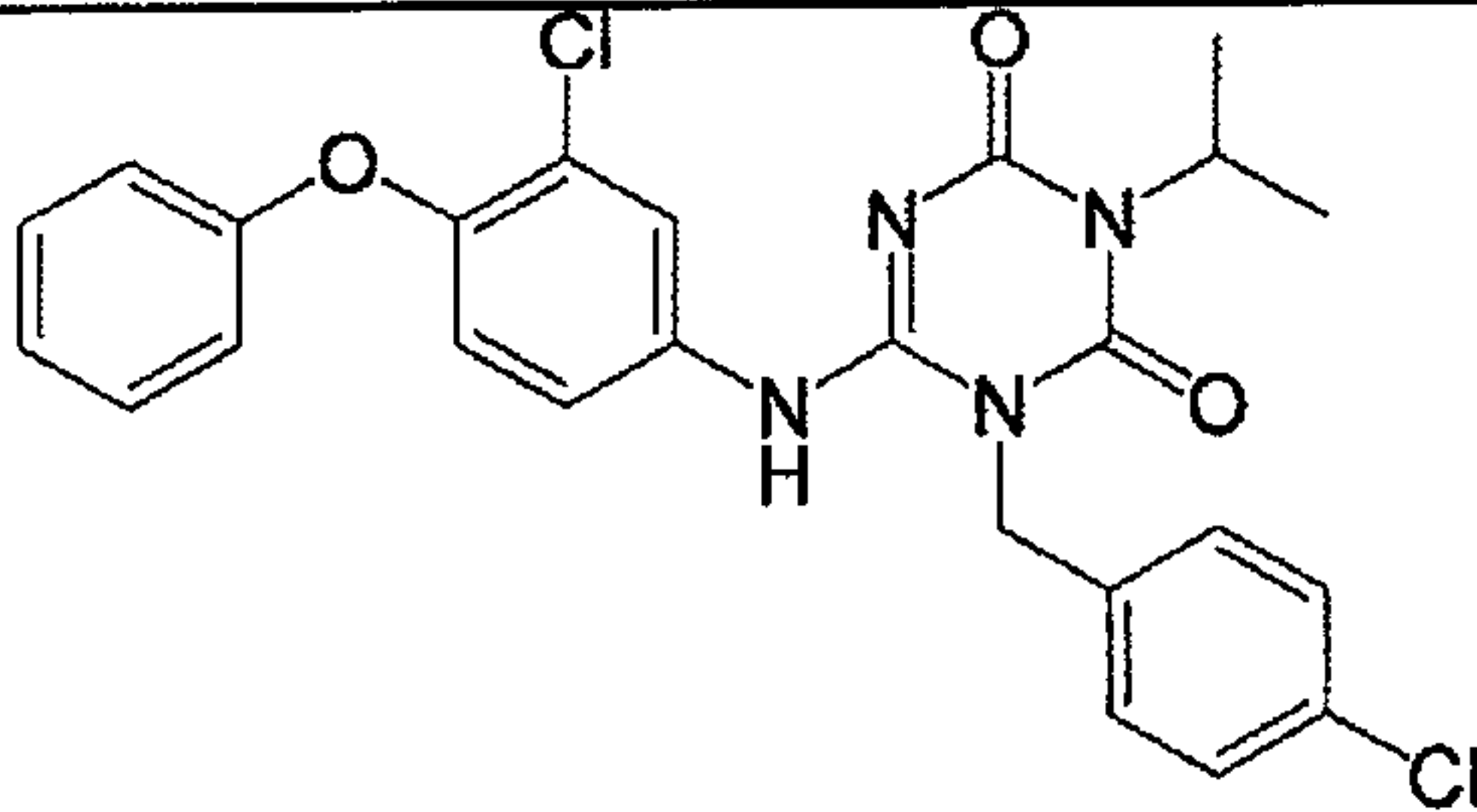
[Table 48]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0221	2.40	413	3
	I-0222	2.40	427	3
	I-0223	2.40	417	3
	I-0224	2.70	487	3
	I-0225	2.30	421	3

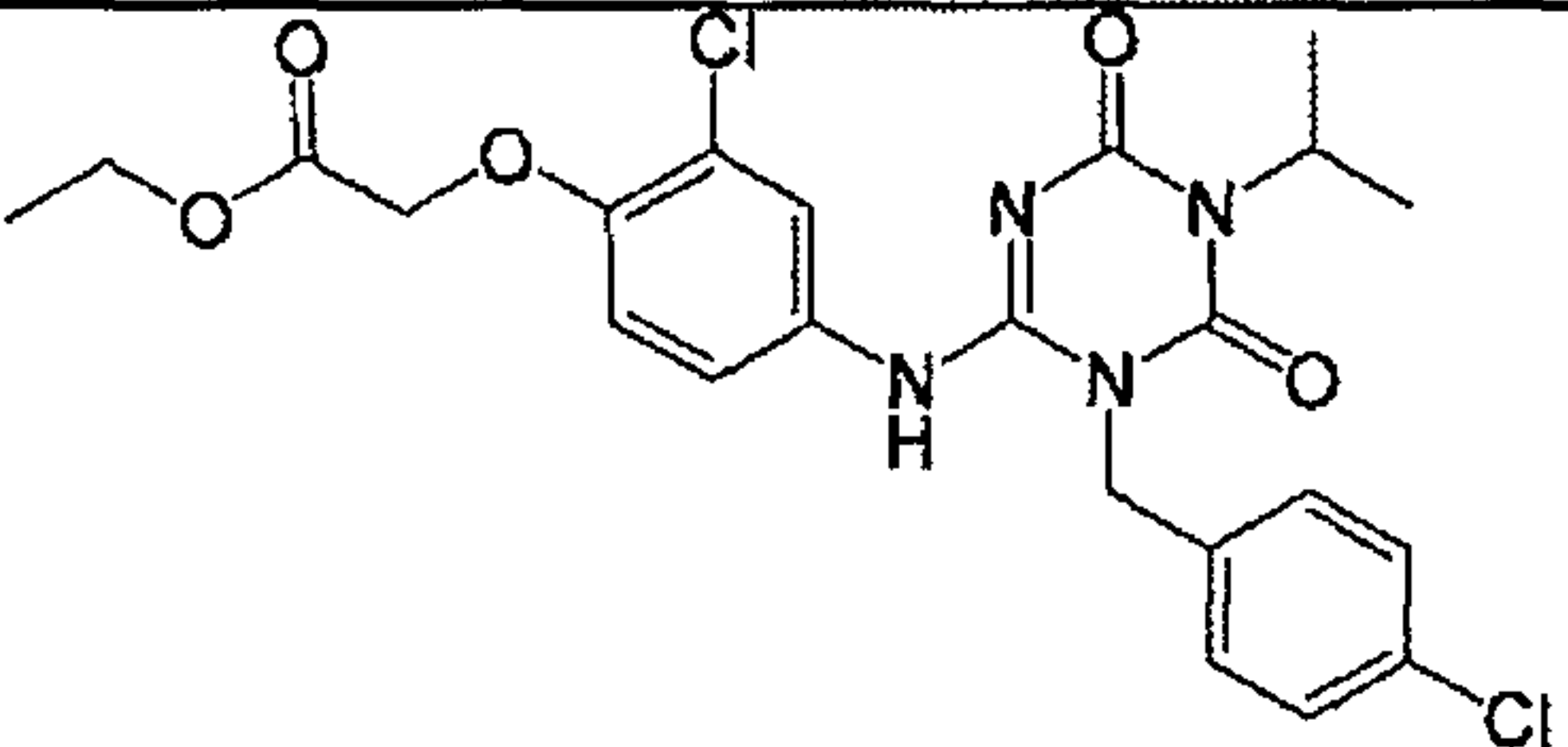
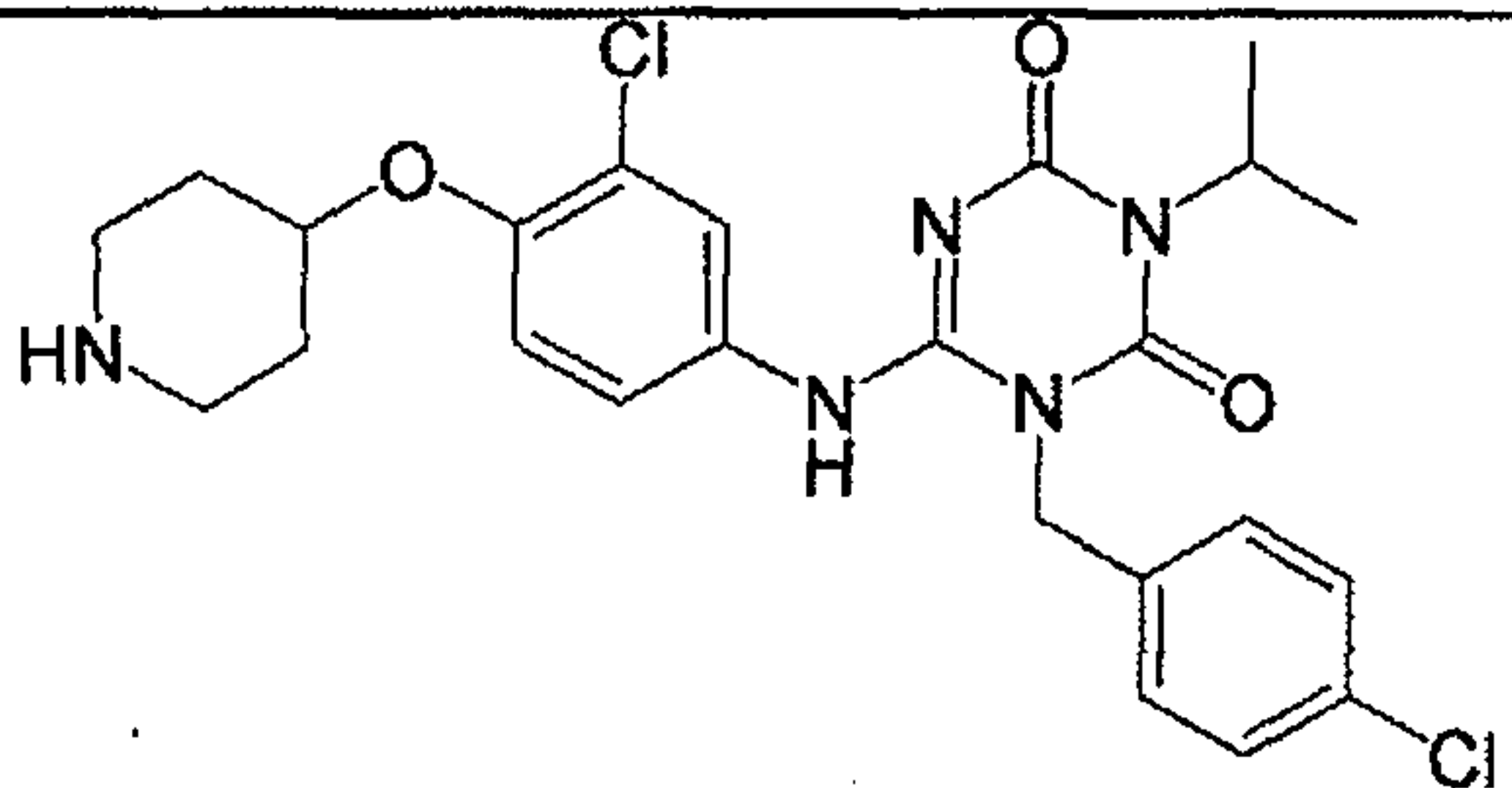
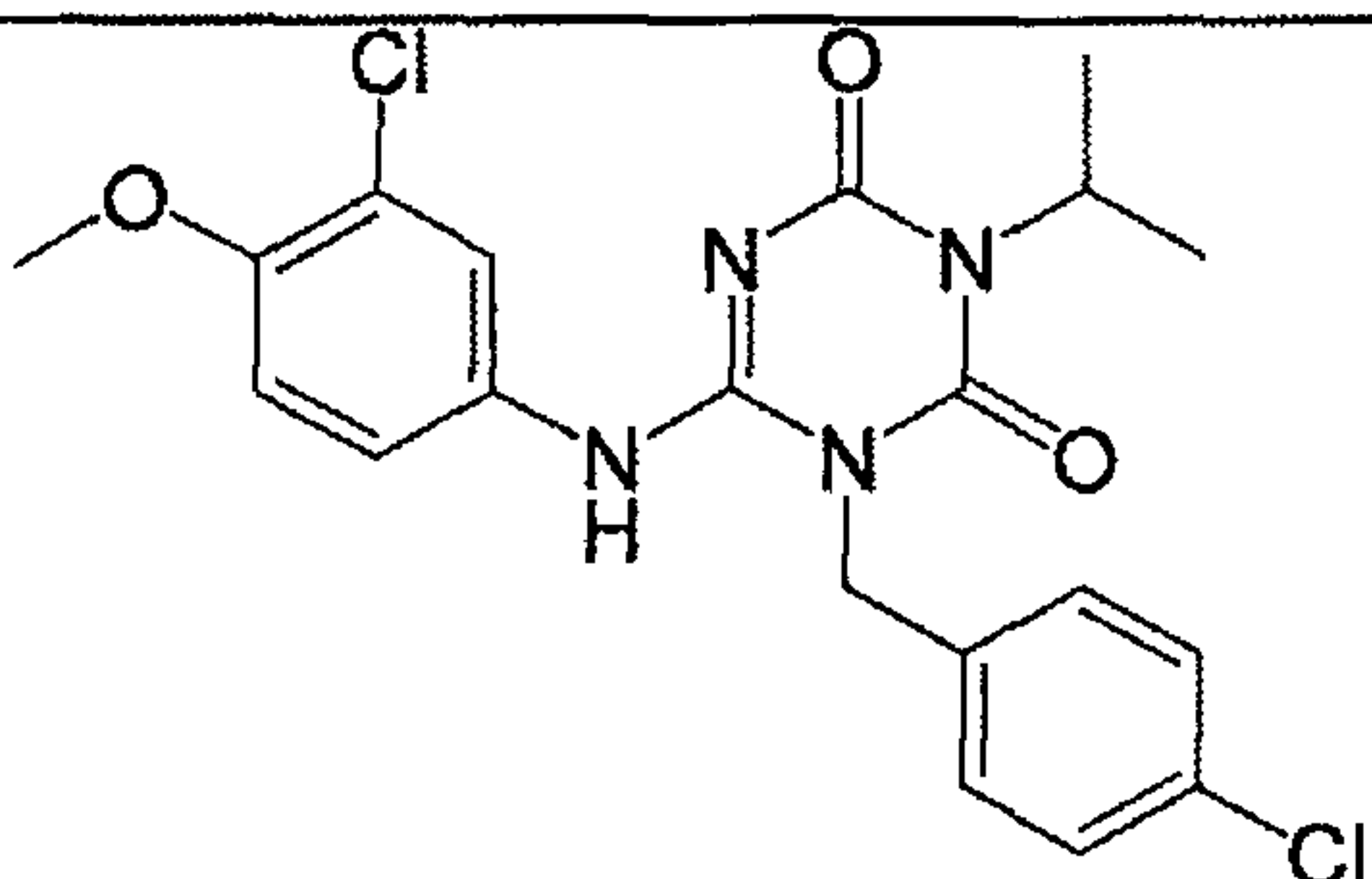
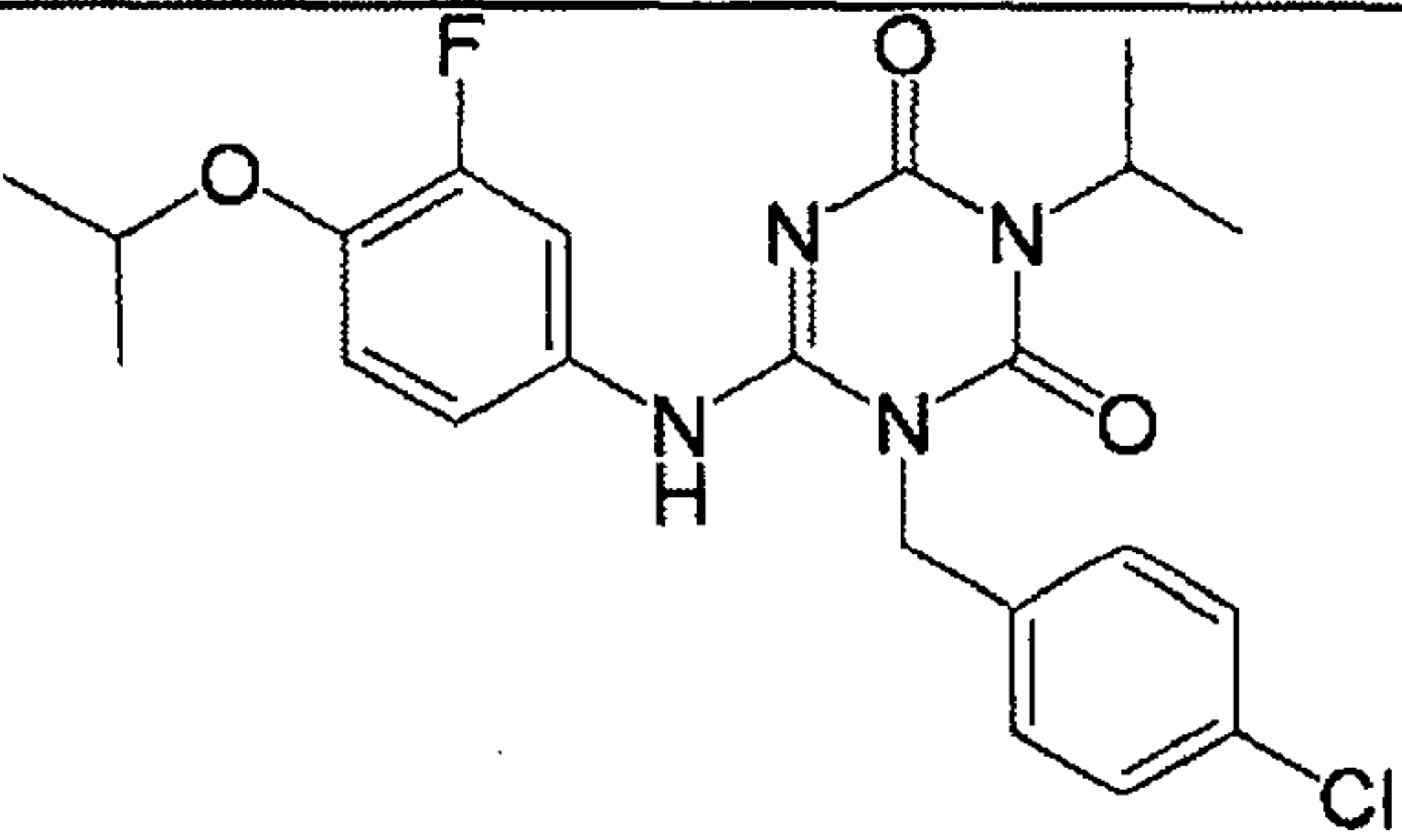
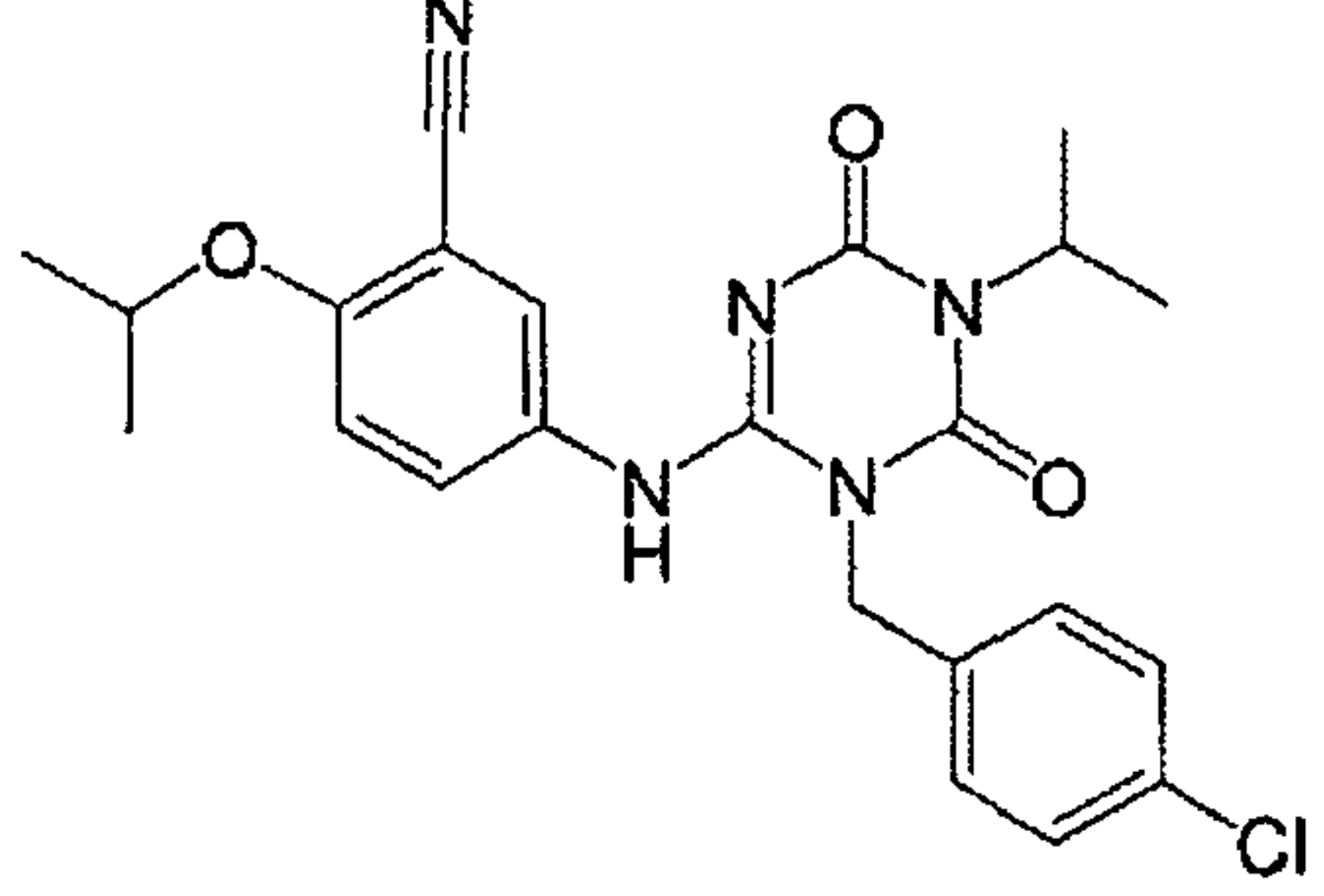
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Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0231	2.40	417	3
	I-0232	2.40	447	3
	I-0233	2.40	417	3
	I-0234	2.60	465	3
	I-0235	2.60	464	3

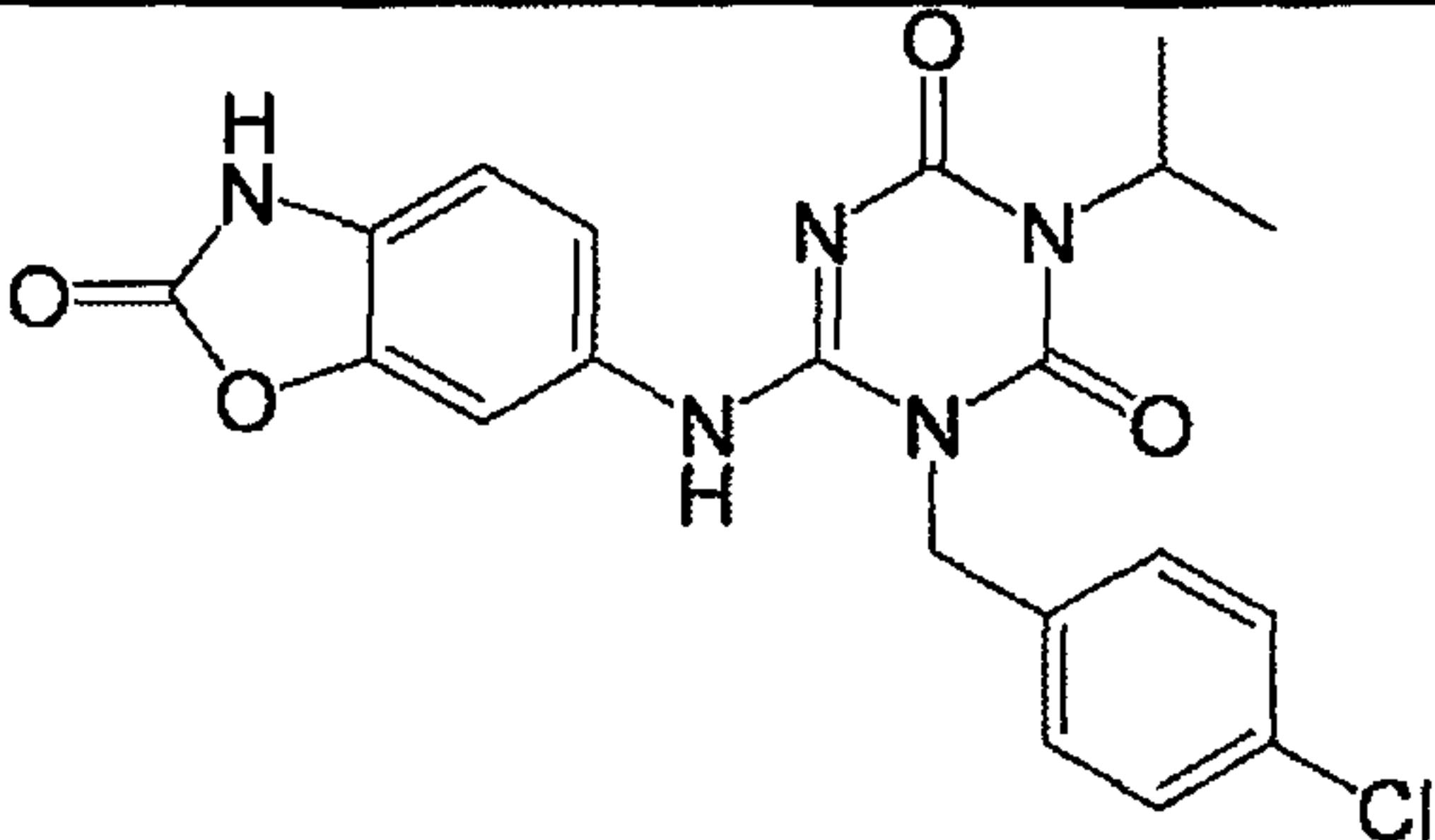
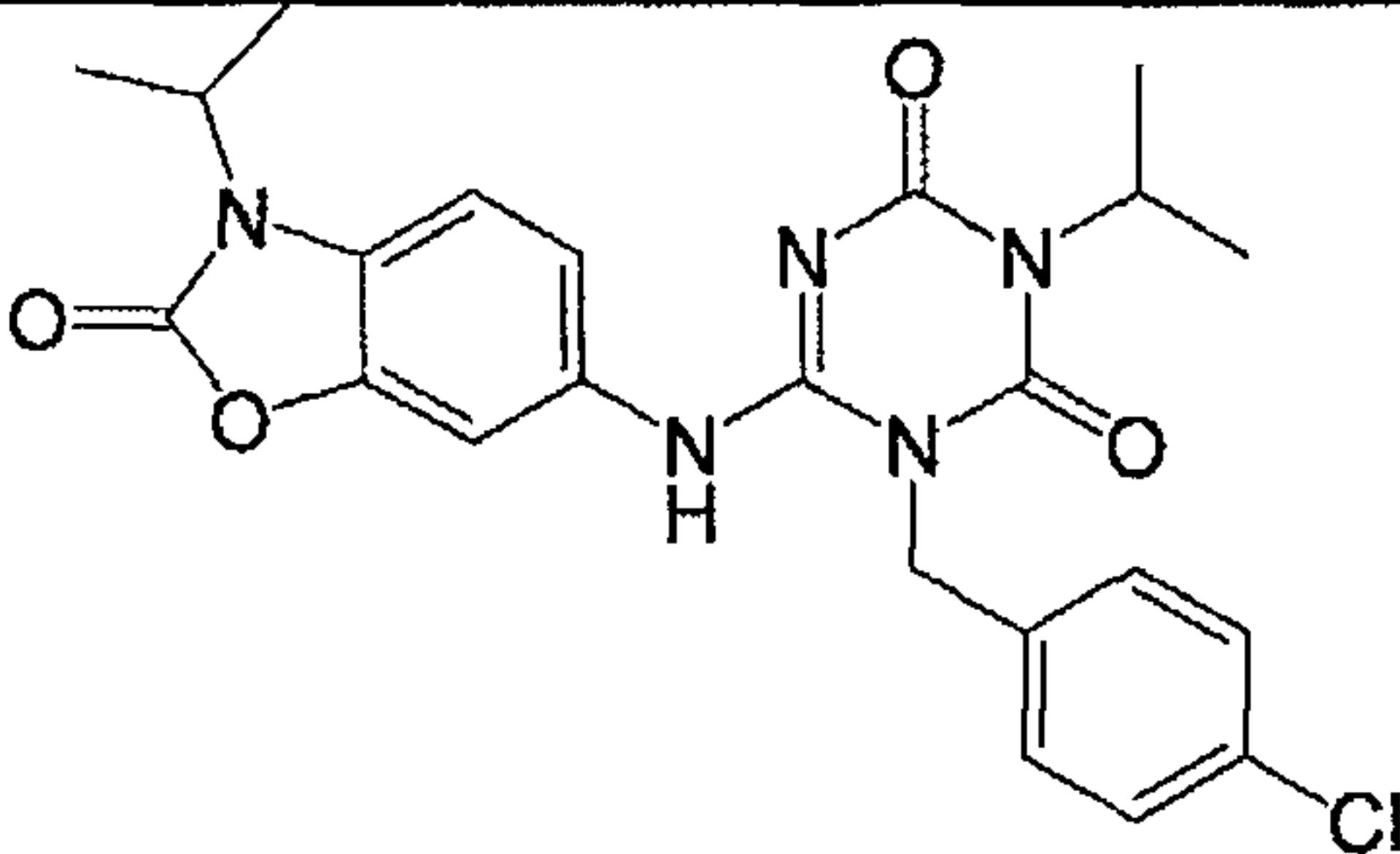
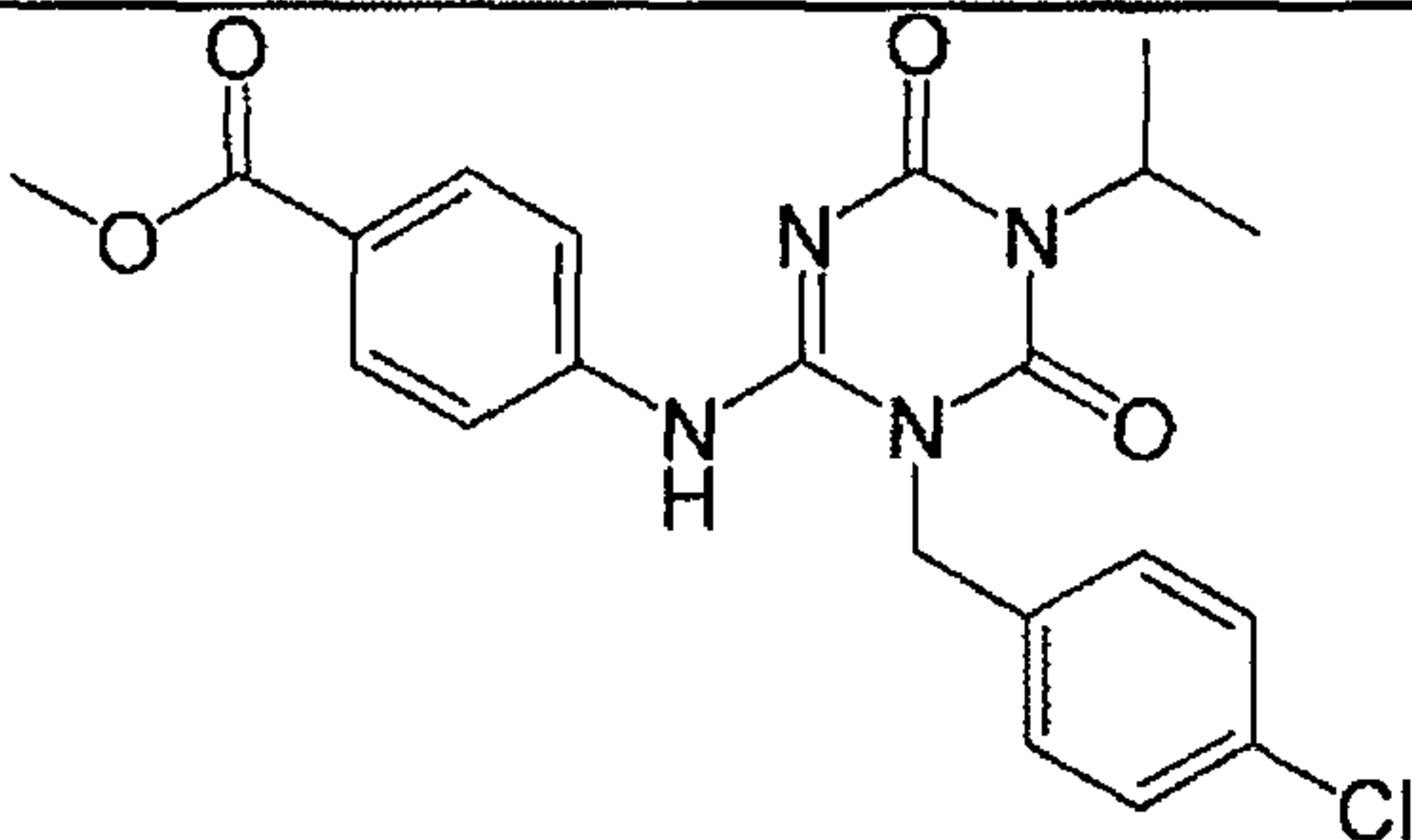
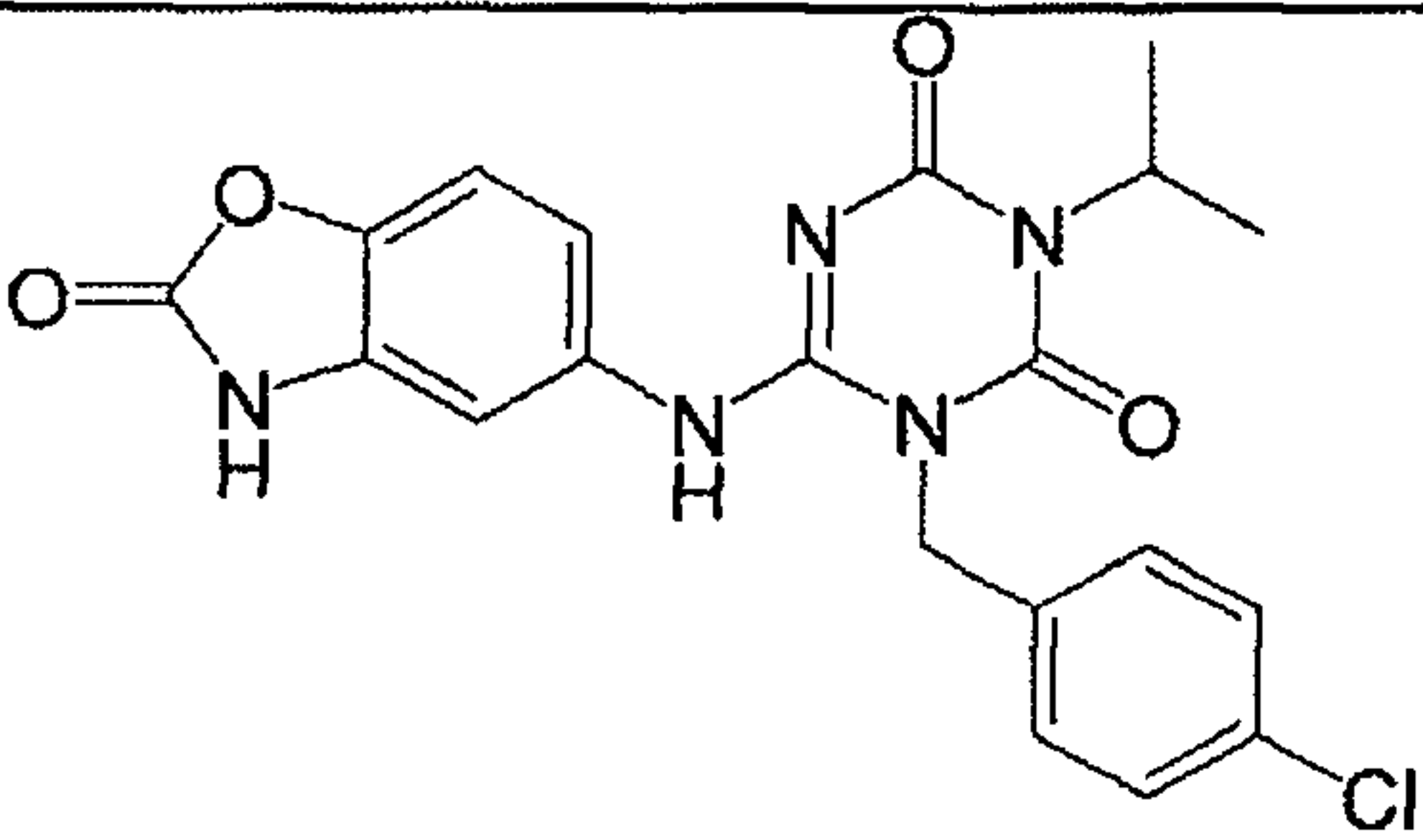
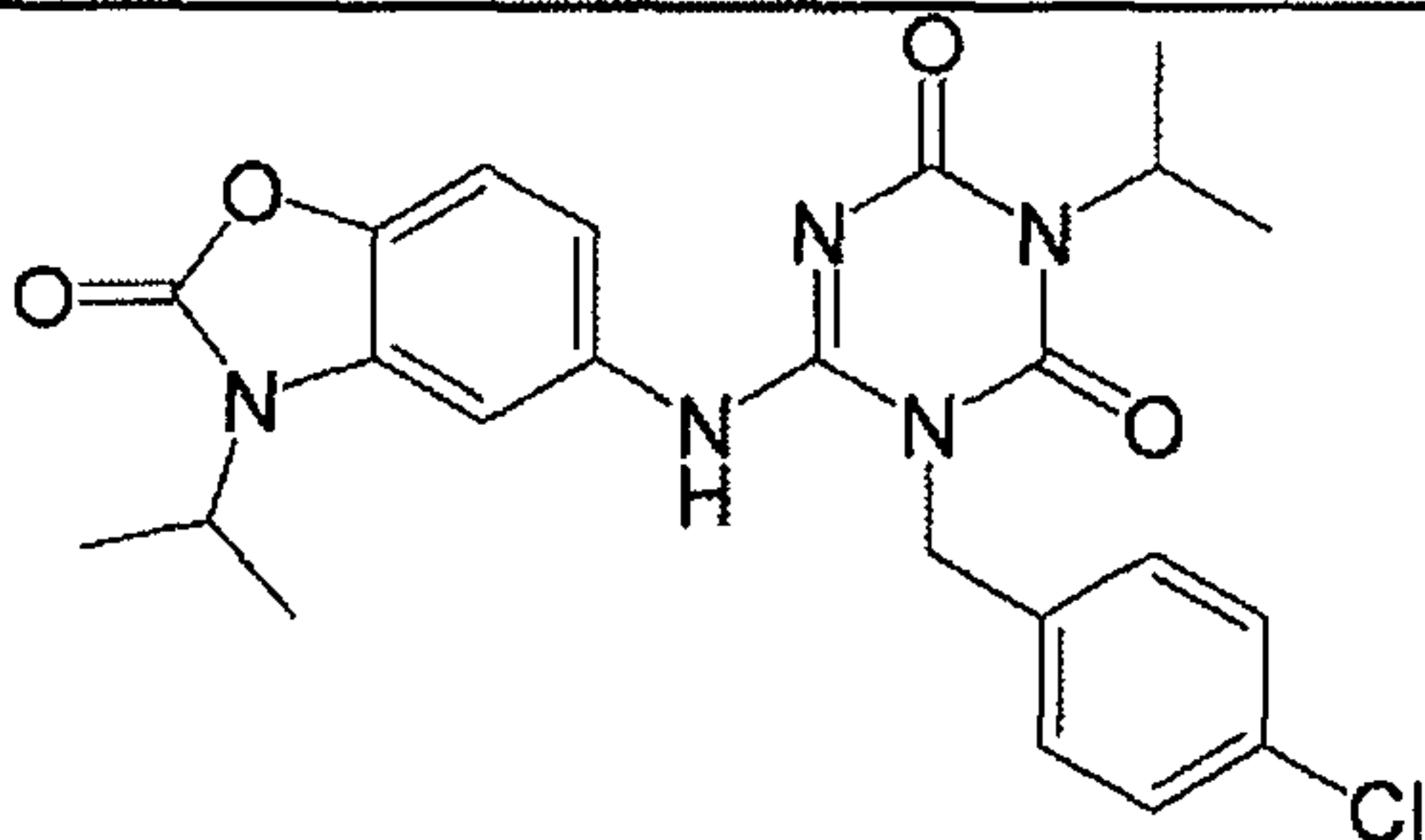
[Table 51]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0236	2.40	417	3
	I-0237	2.60	479	3
	I-0238	2.70	447	3
	I-0239	2.70	505	3
	I-0240	3.10	497	3

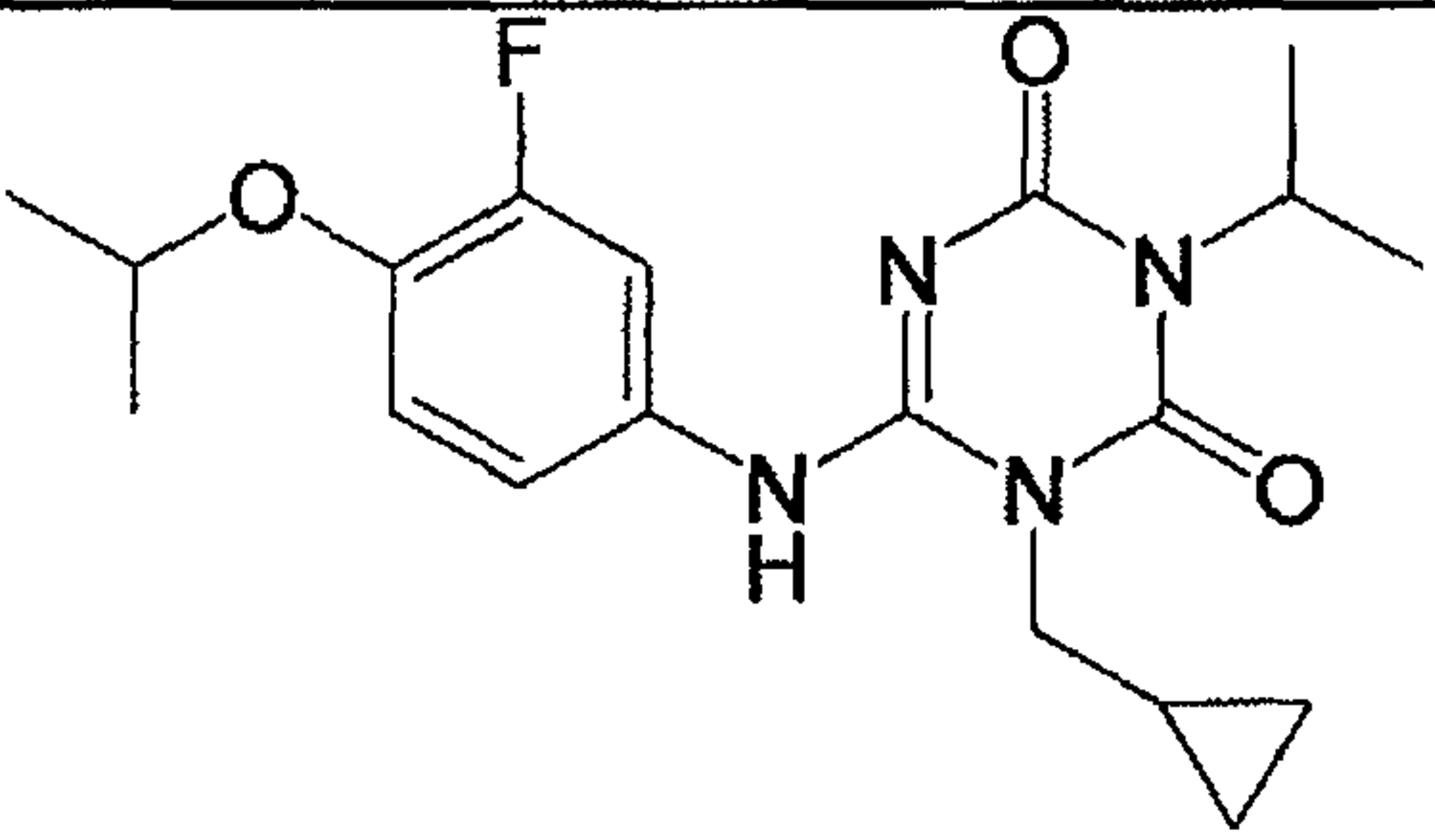
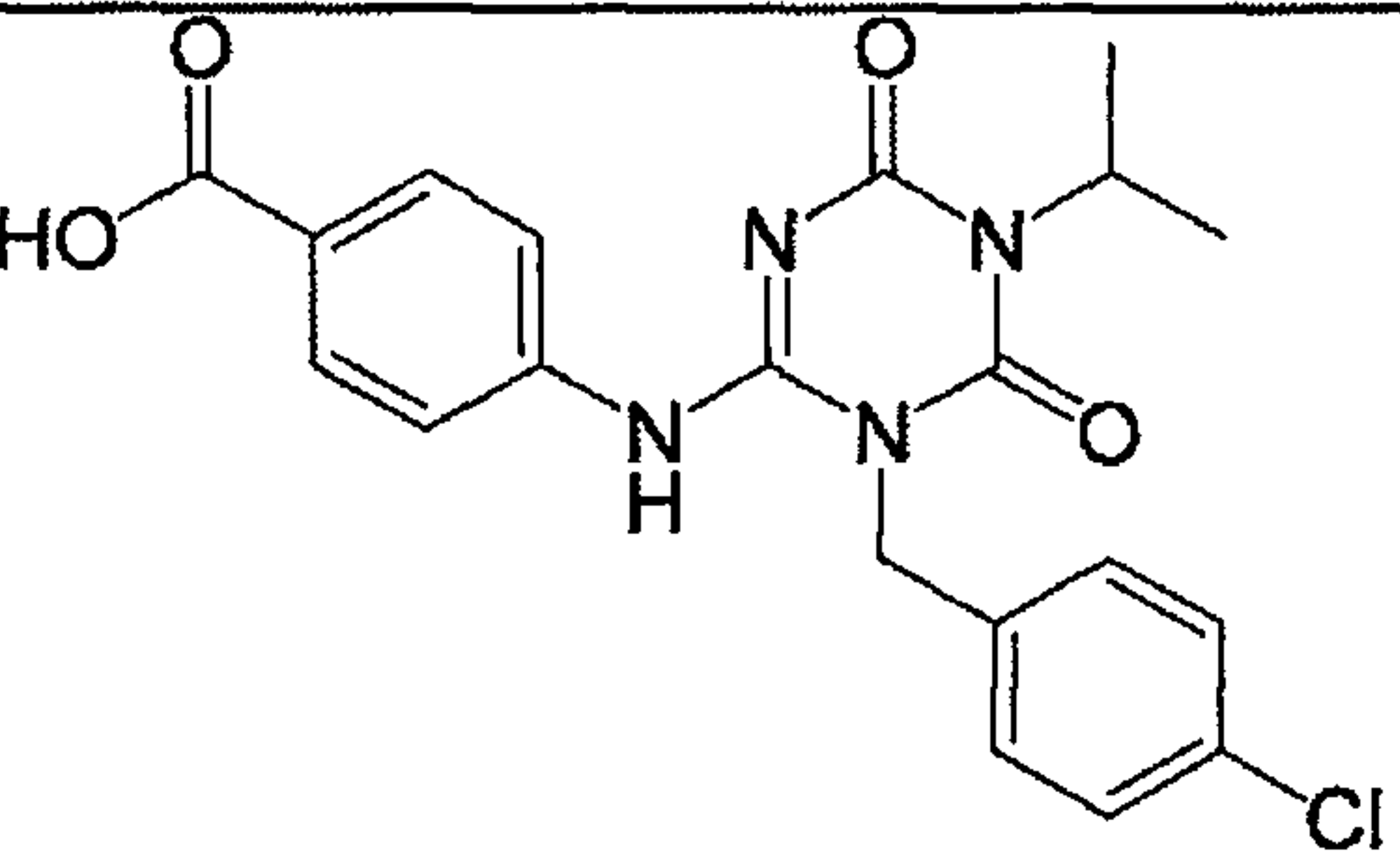
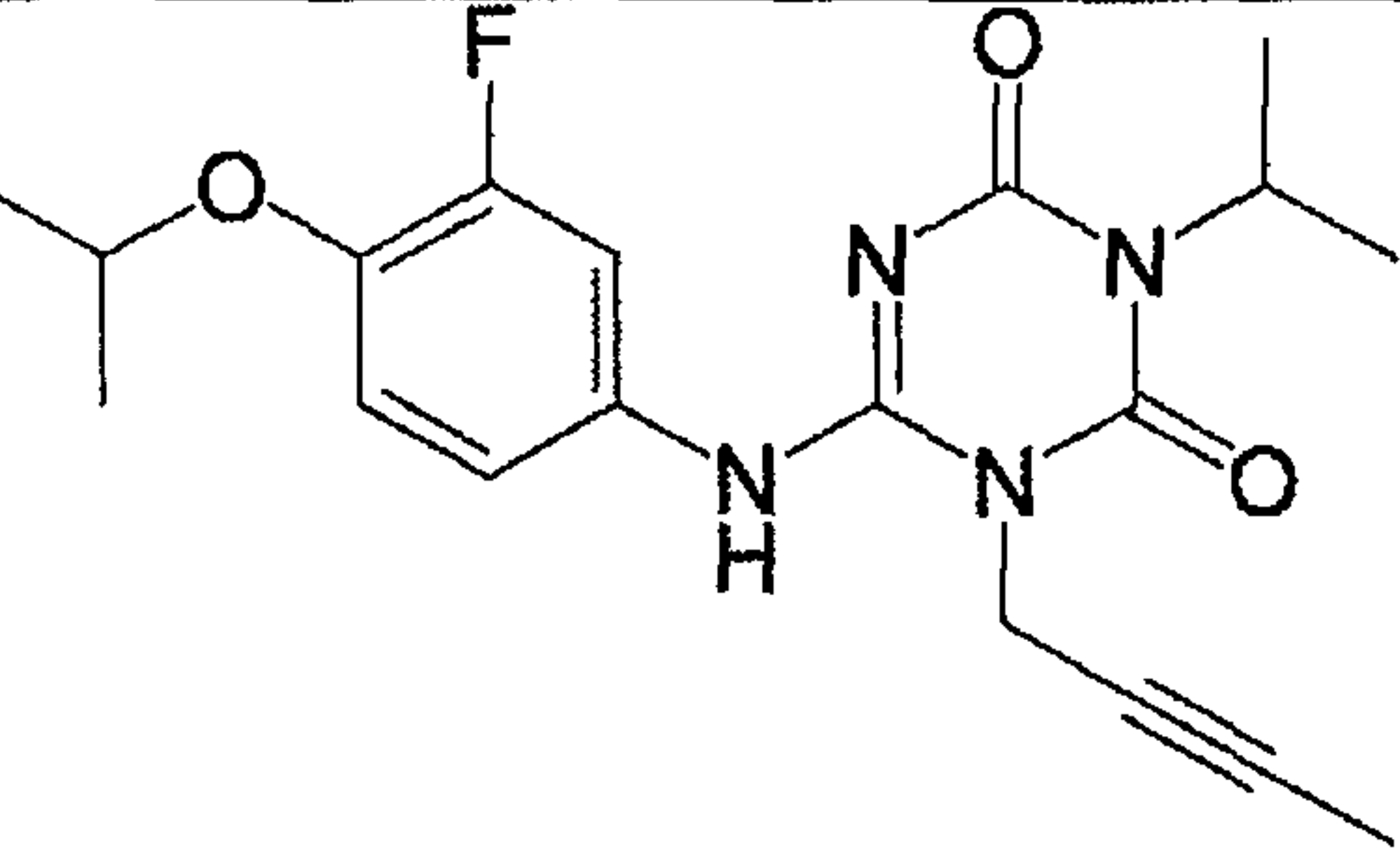
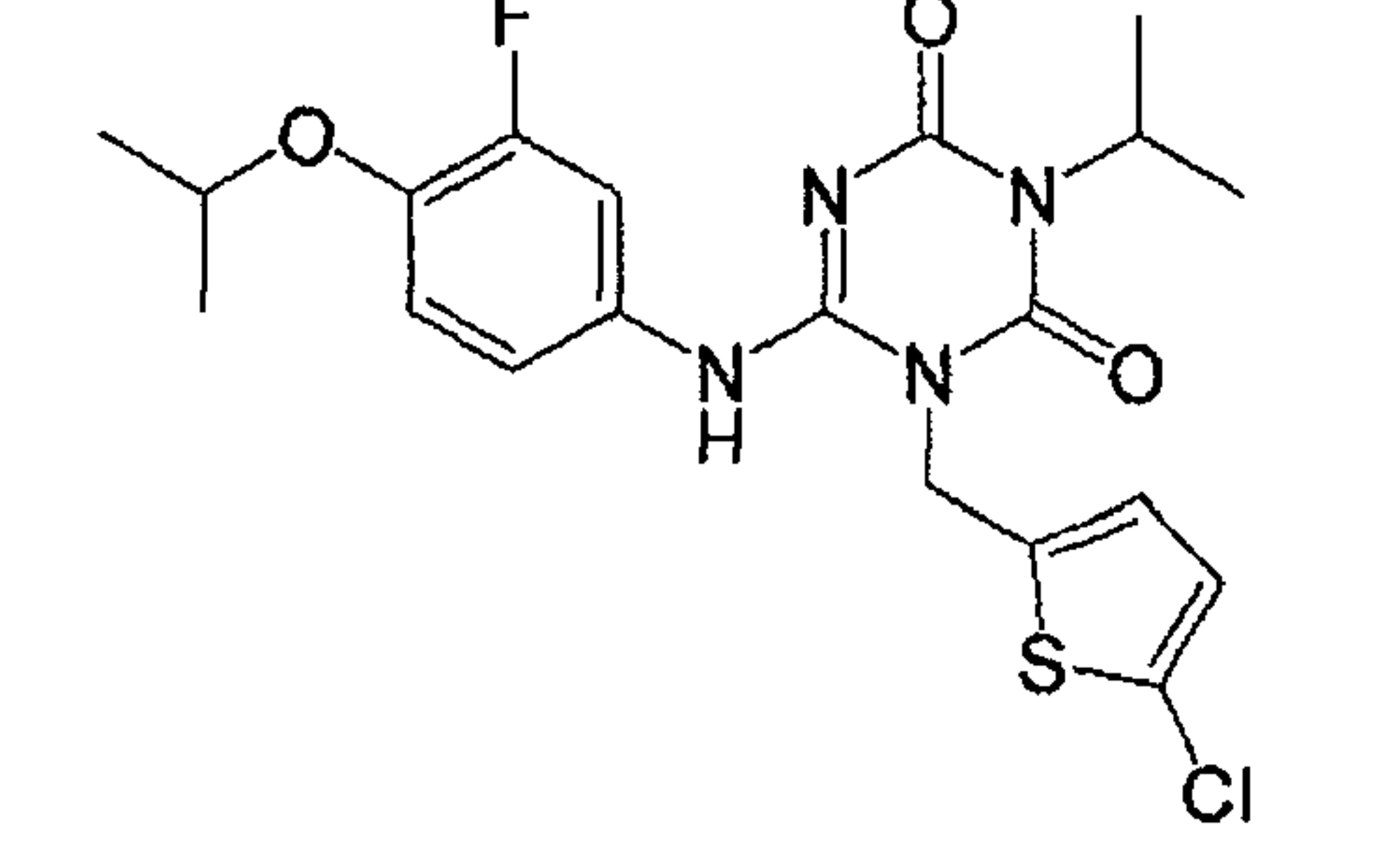
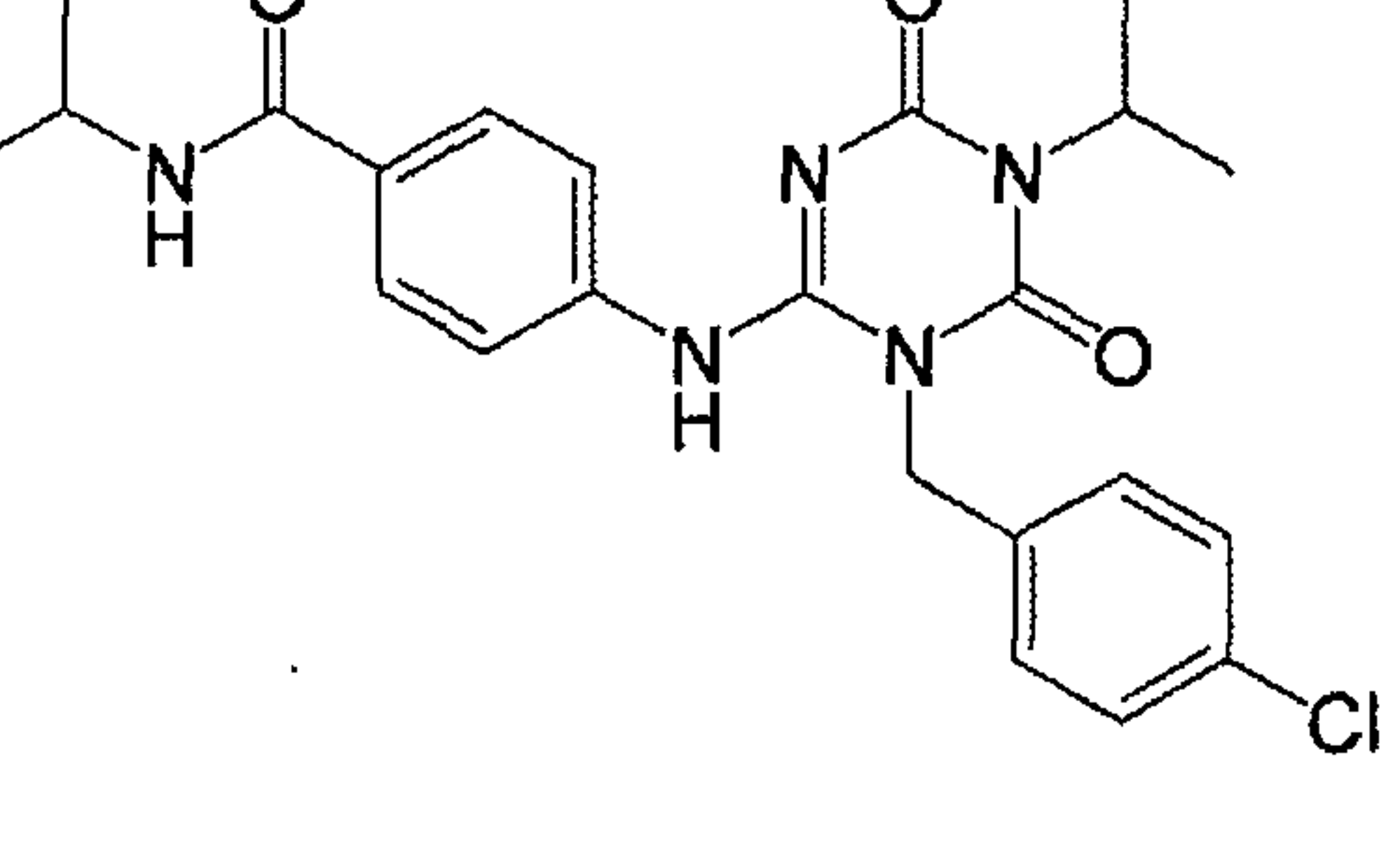
[Table 52]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0241	2.70	507	3
	I-0242	1.60	505	3
	I-0243	2.60	435	3
	I-0244	2.80	447	3
	I-0245	2.70	454	3

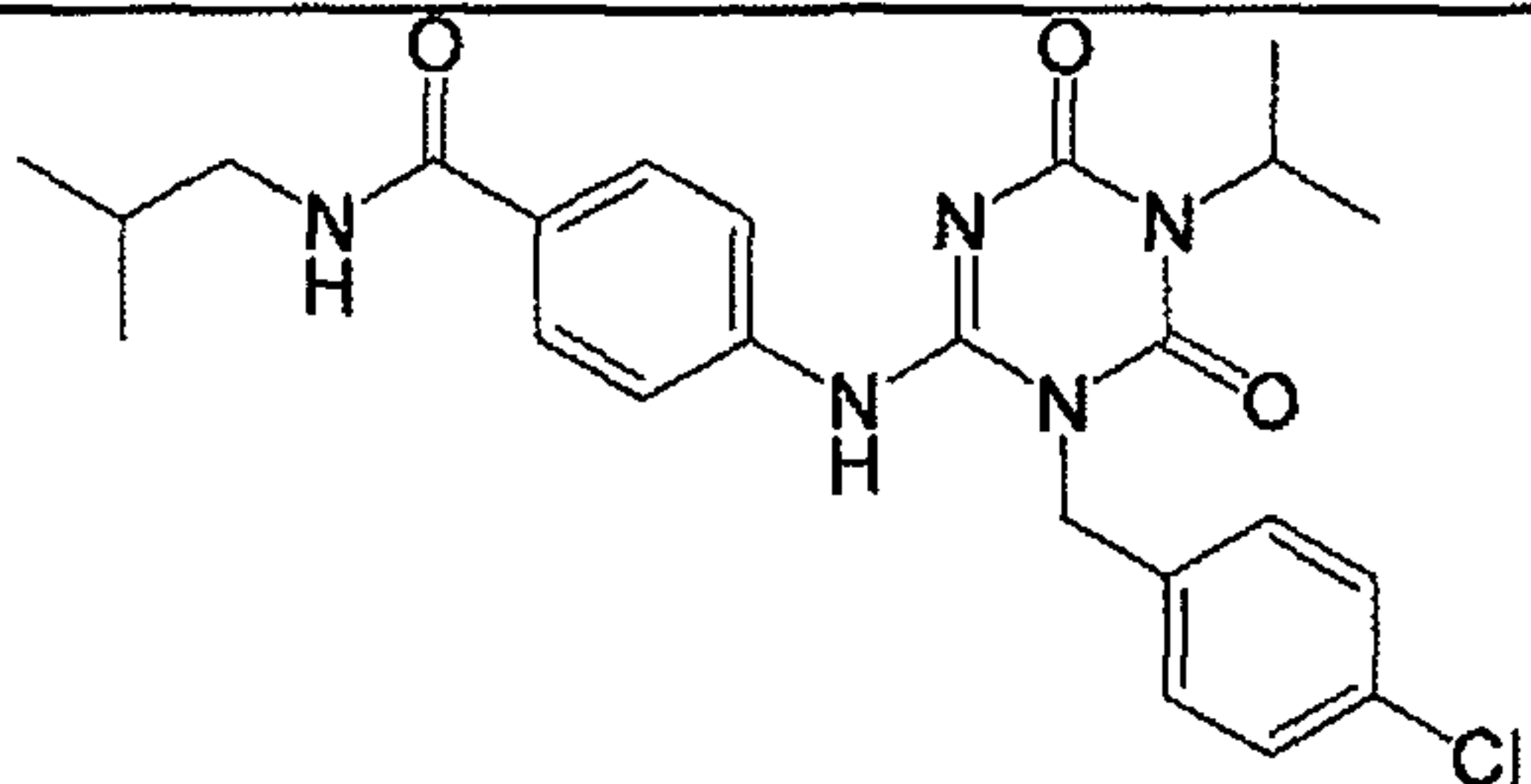
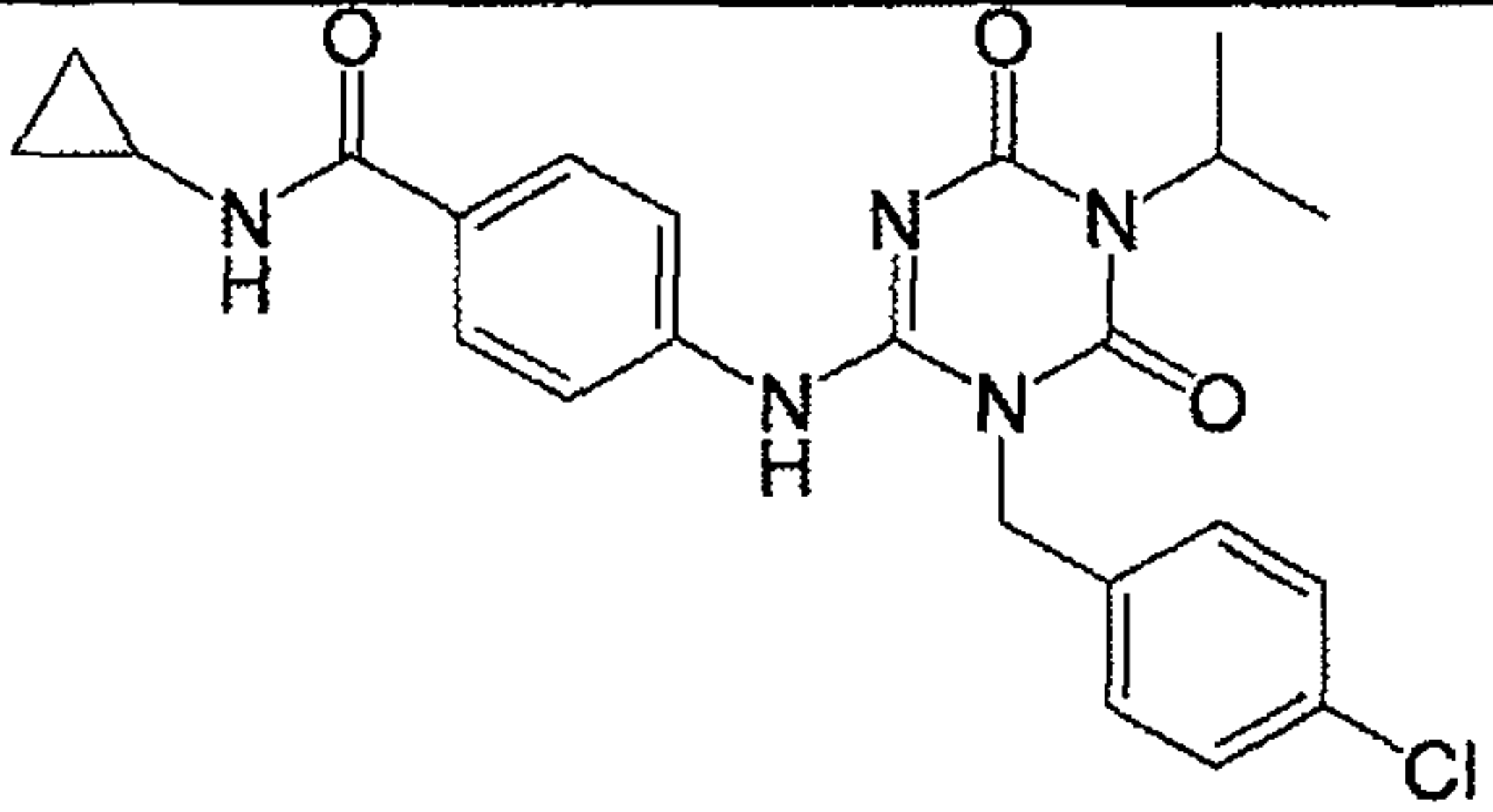
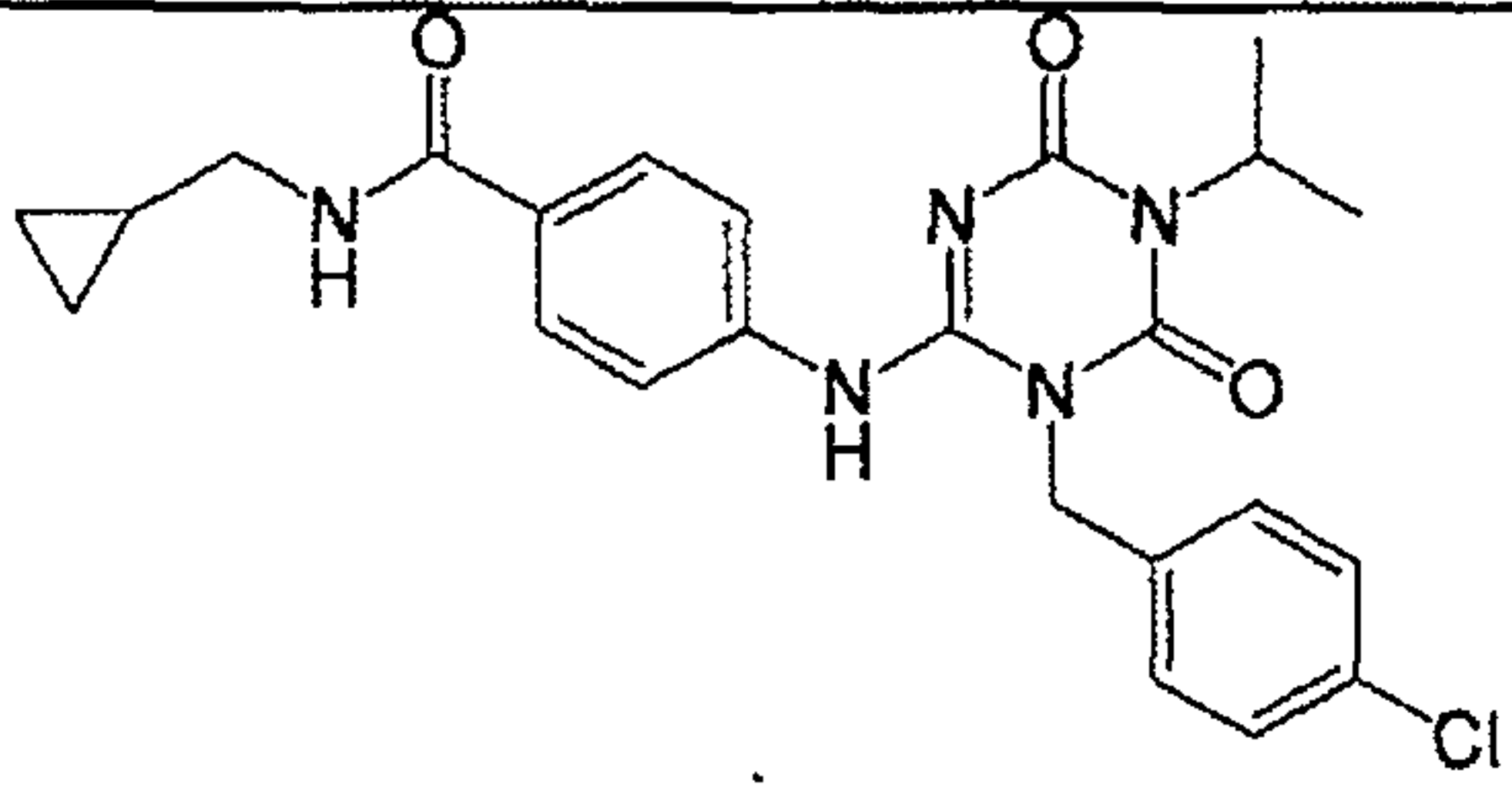
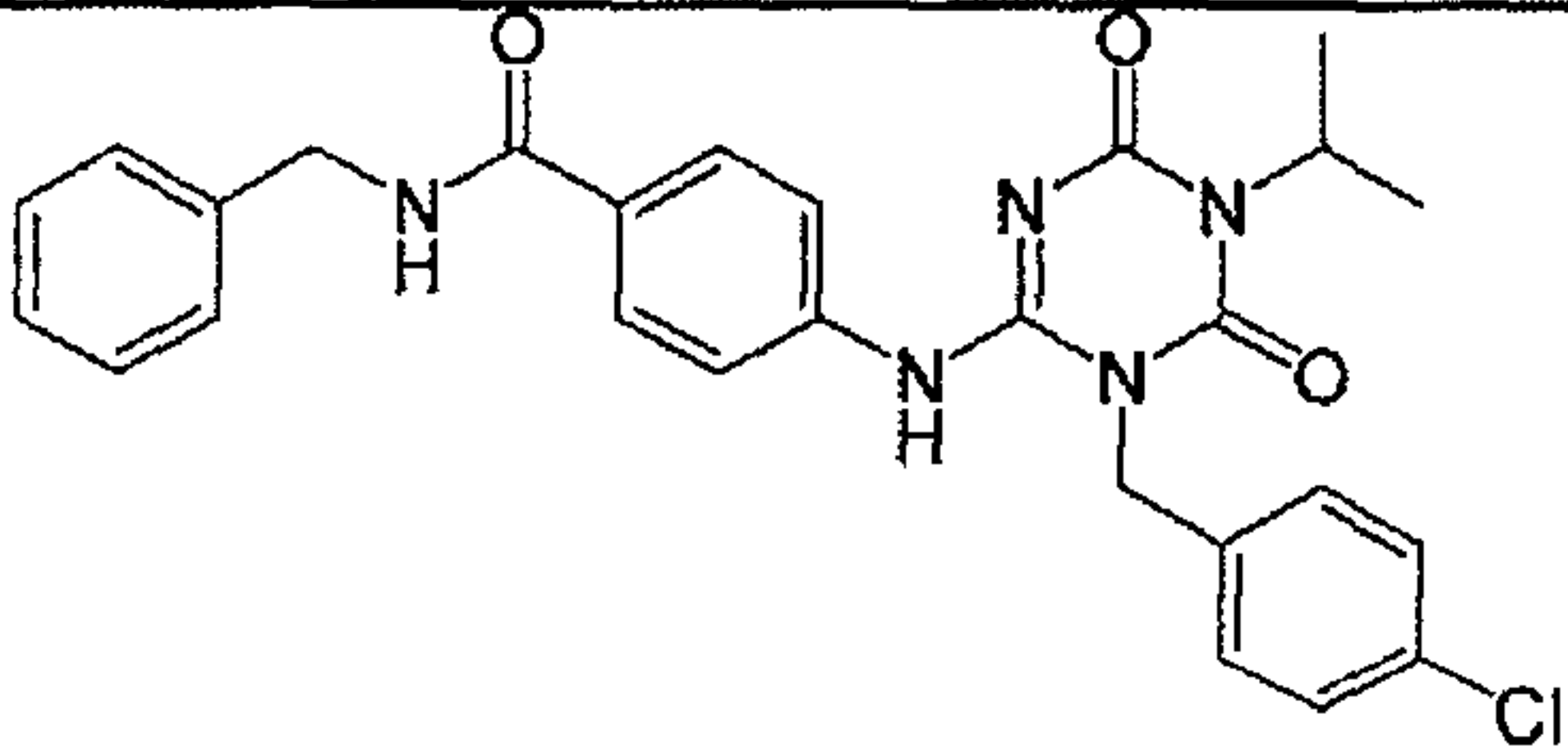
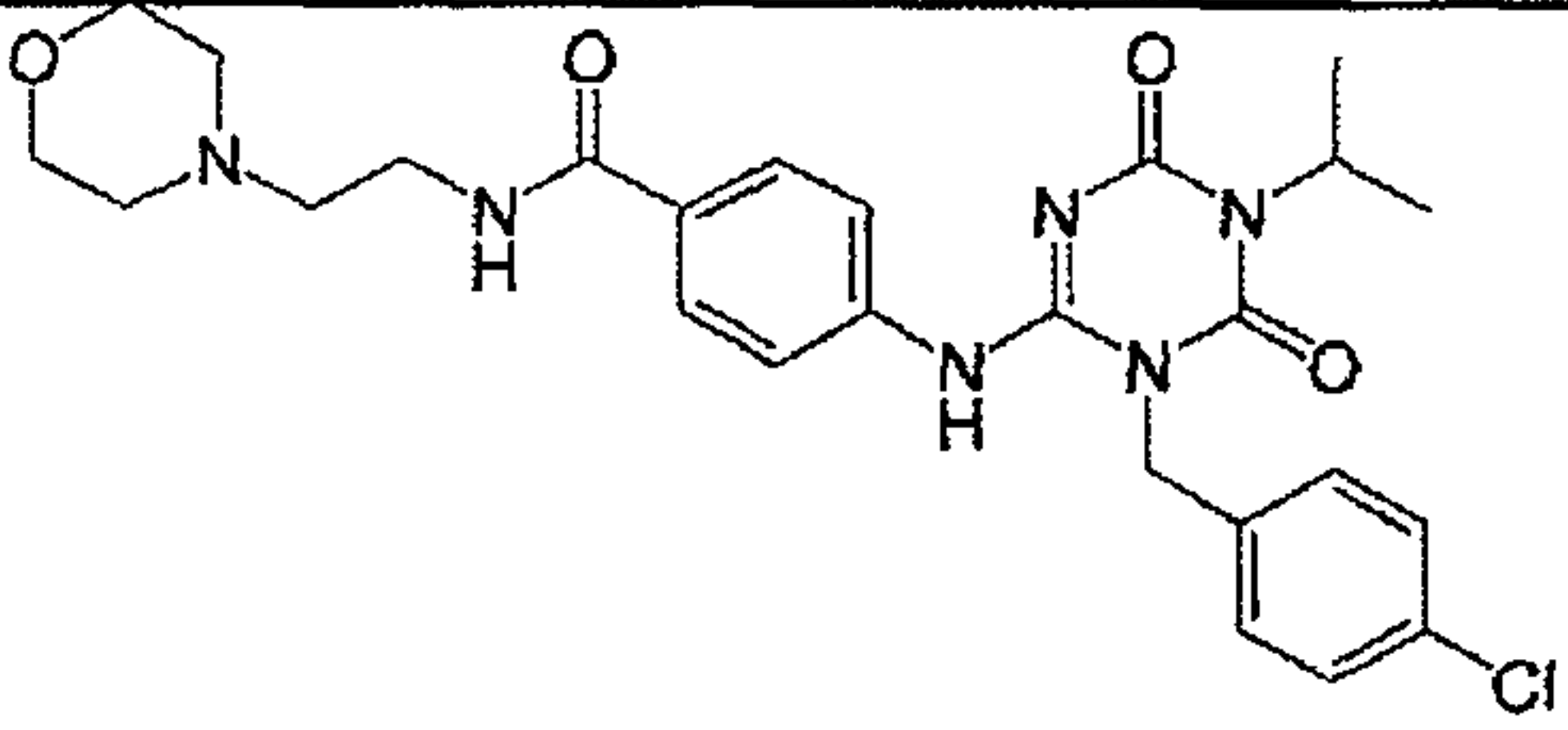
[Table 53]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0246	2.20	428	3
	I-0247	2.50	470	3
	I-0248	2.60	429	3
	I-0249	2.20	428	3
	I-0250	2.60	470	3

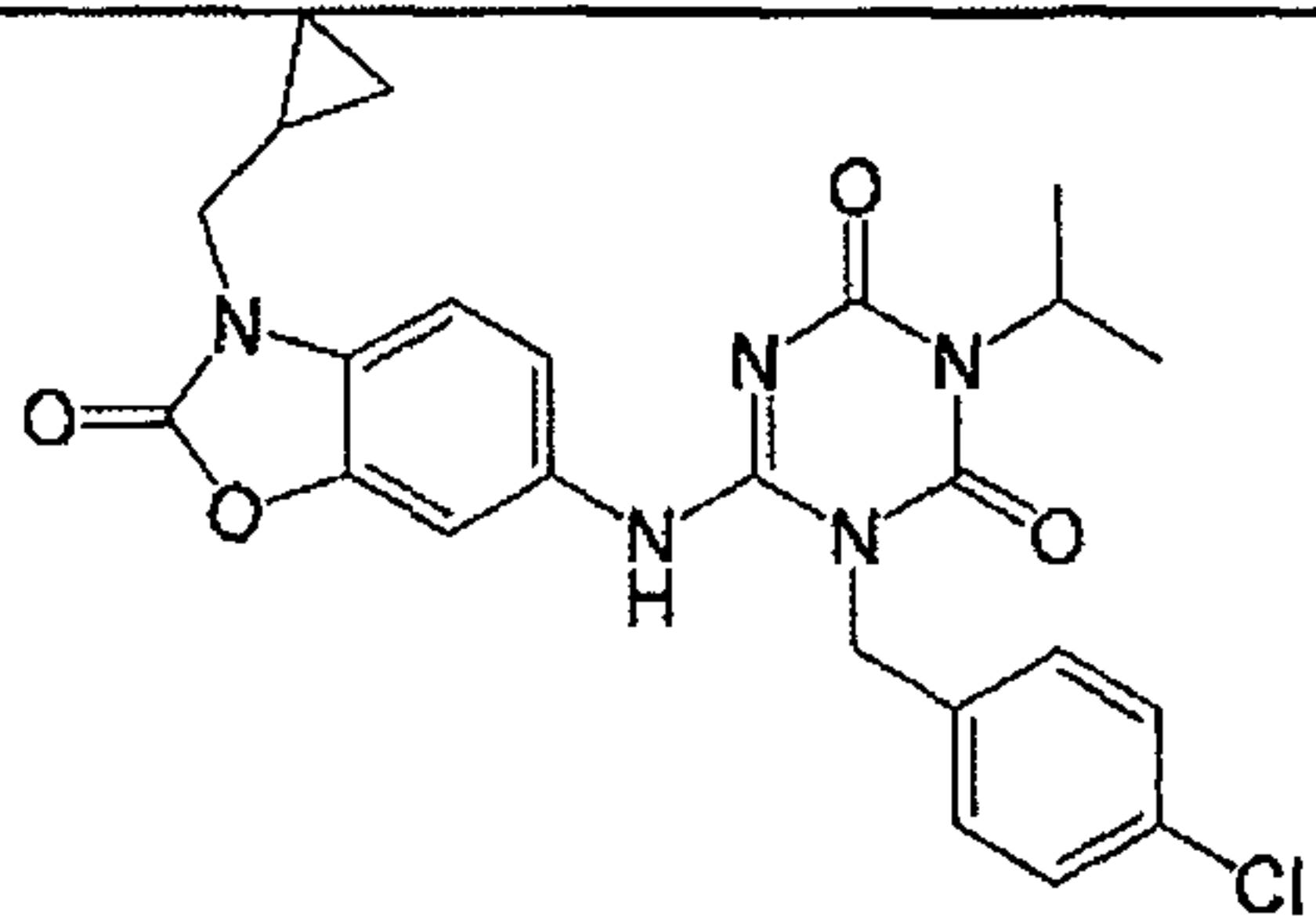
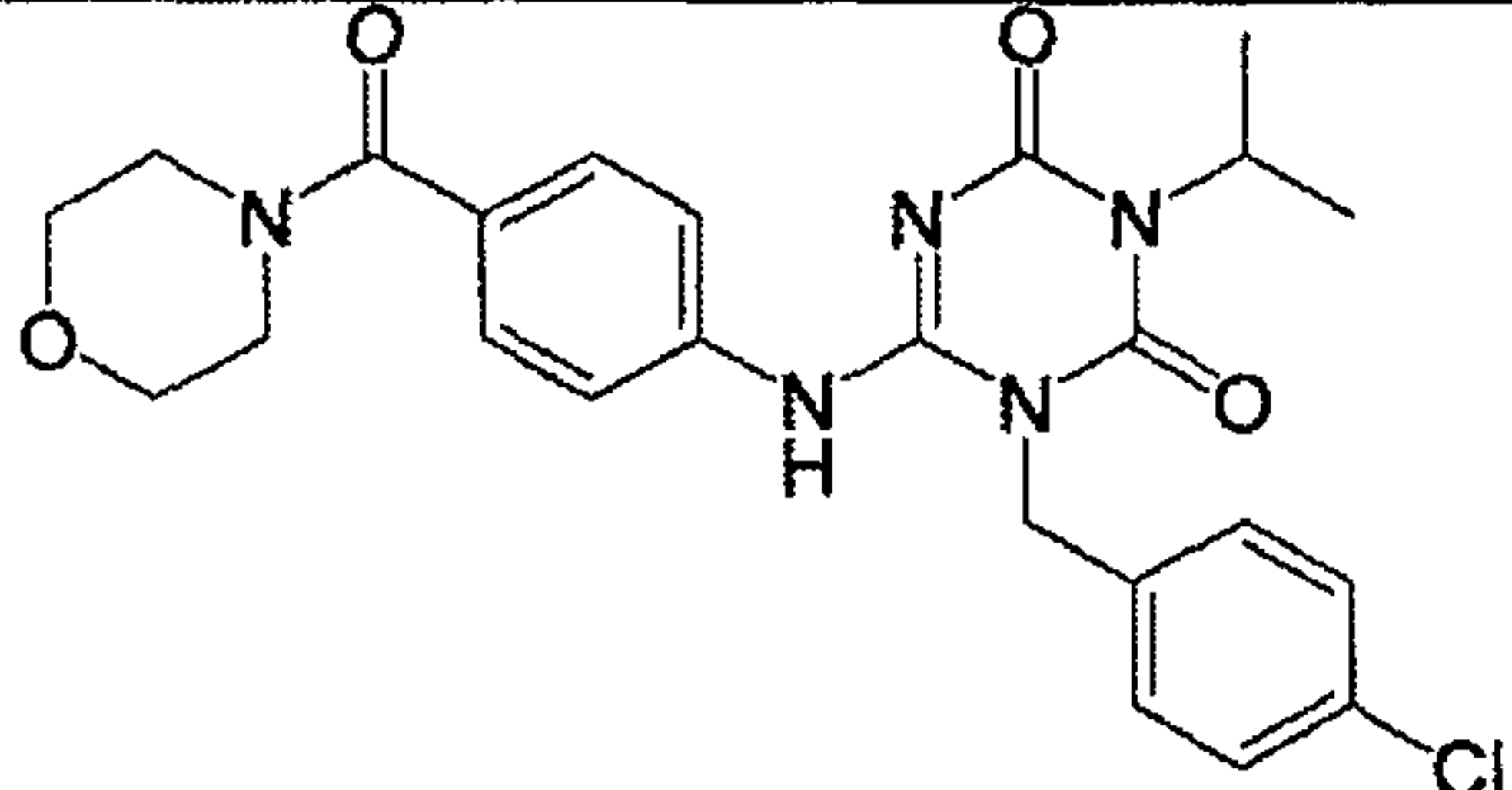
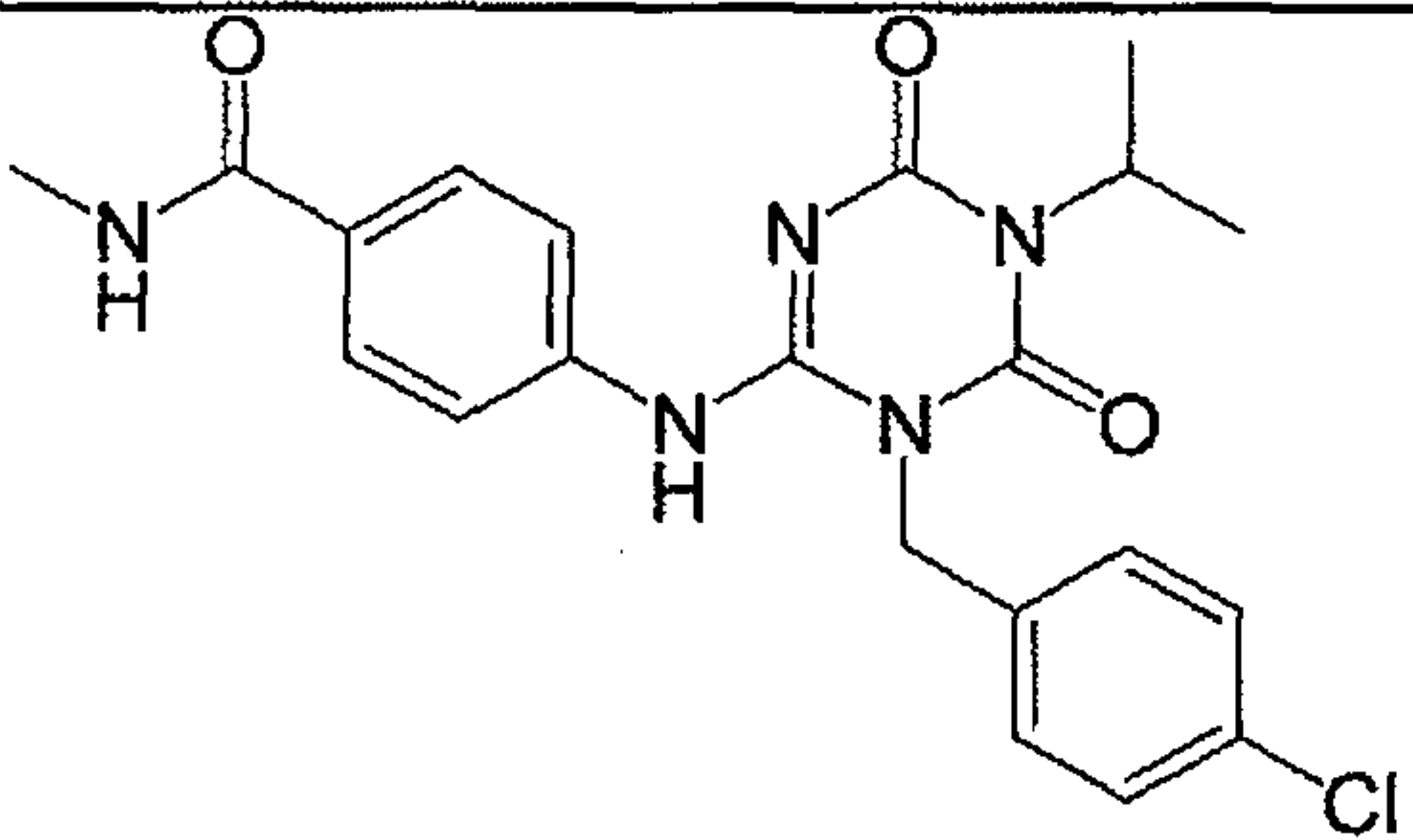
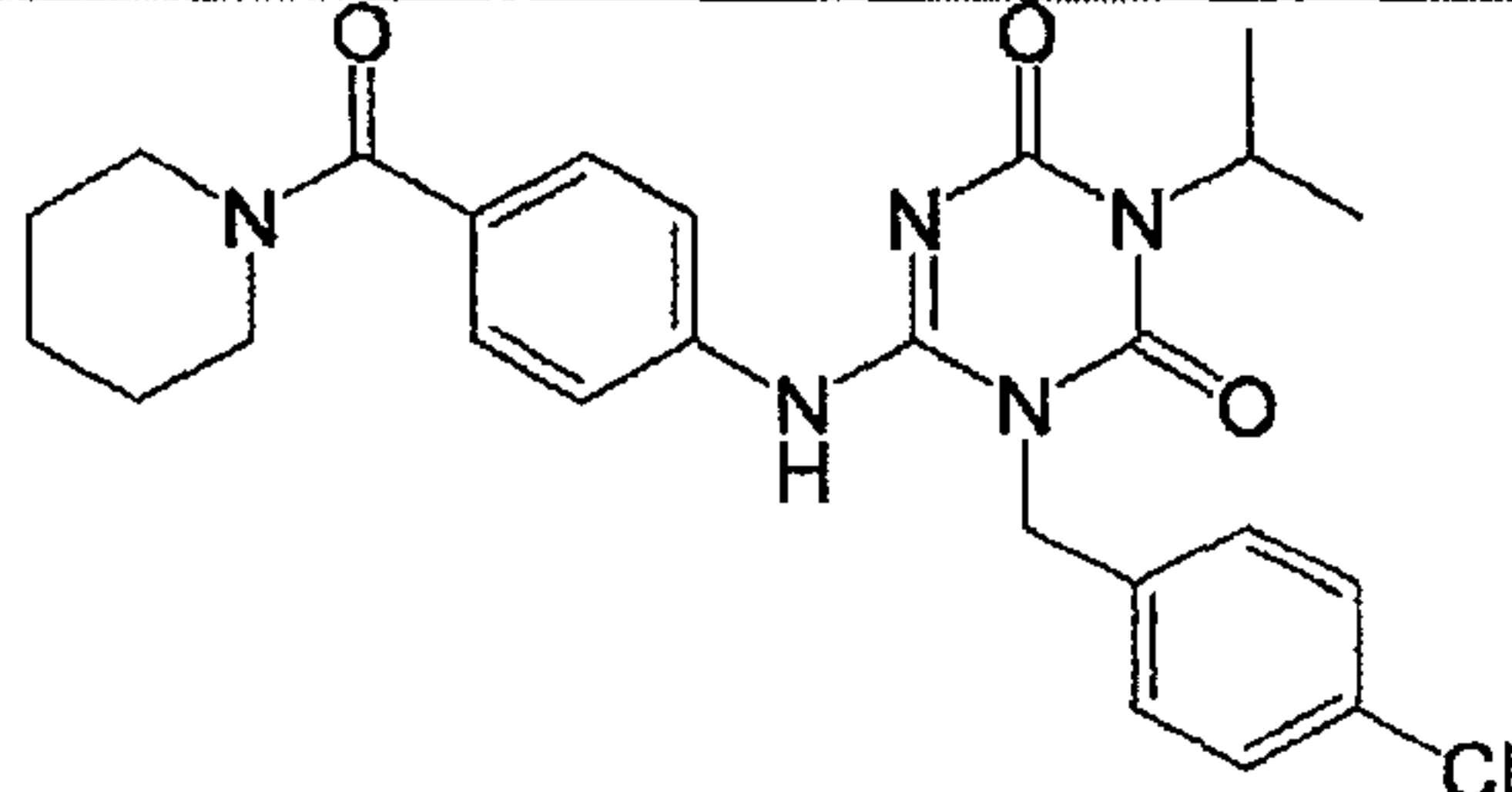
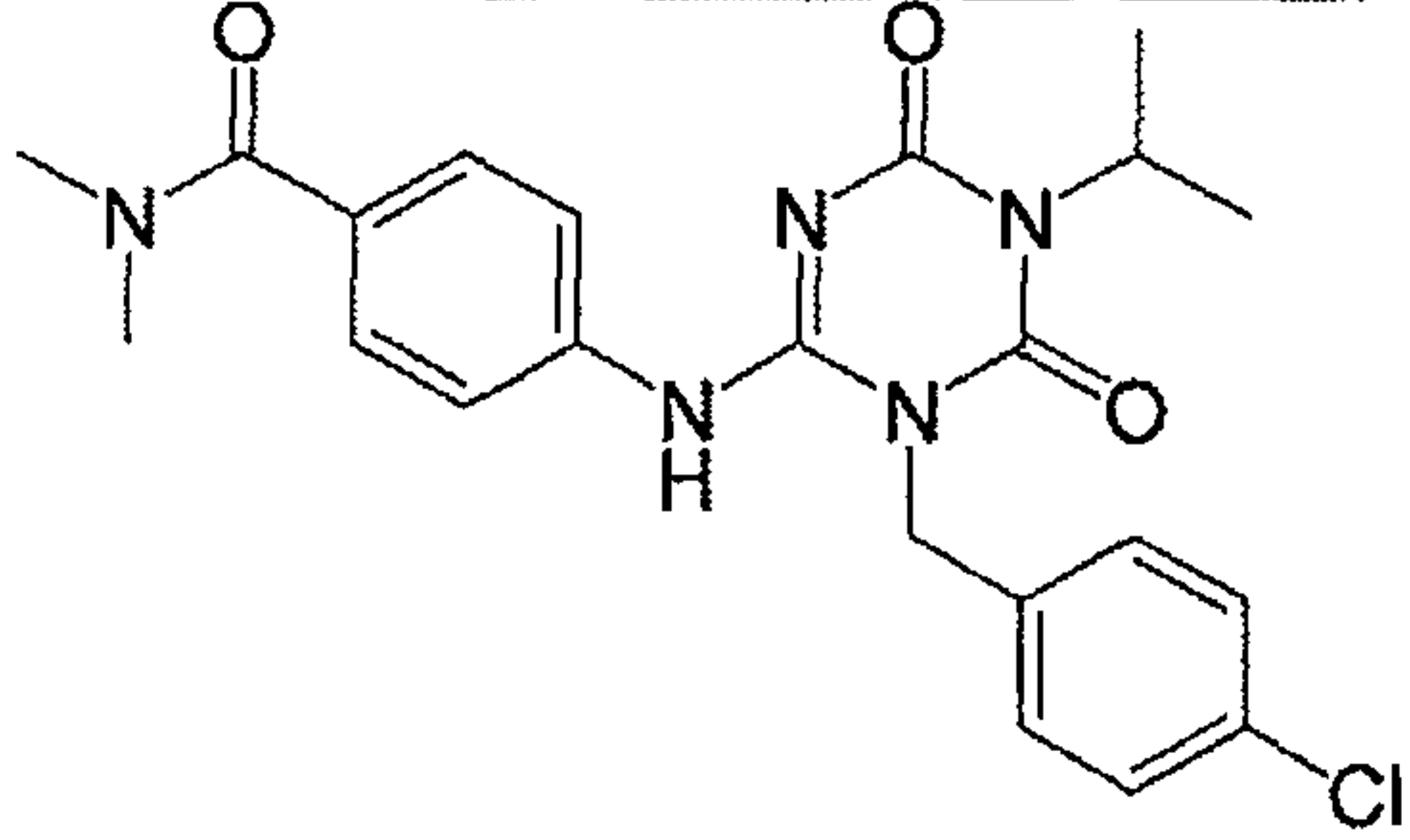
[Table 54]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0251	2.40	377	3
	I-0252	2.30	415	3
	I-0253	2.30	375	3
	I-0254	2.90	453	3
	I-0255	2.40	456	3

[Table 55]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0256	2.50	470	3
	I-0257	2.20	454	3
	I-0258	2.40	468	3
	I-0259	2.50	504	3
	I-0260	1.50	528	3

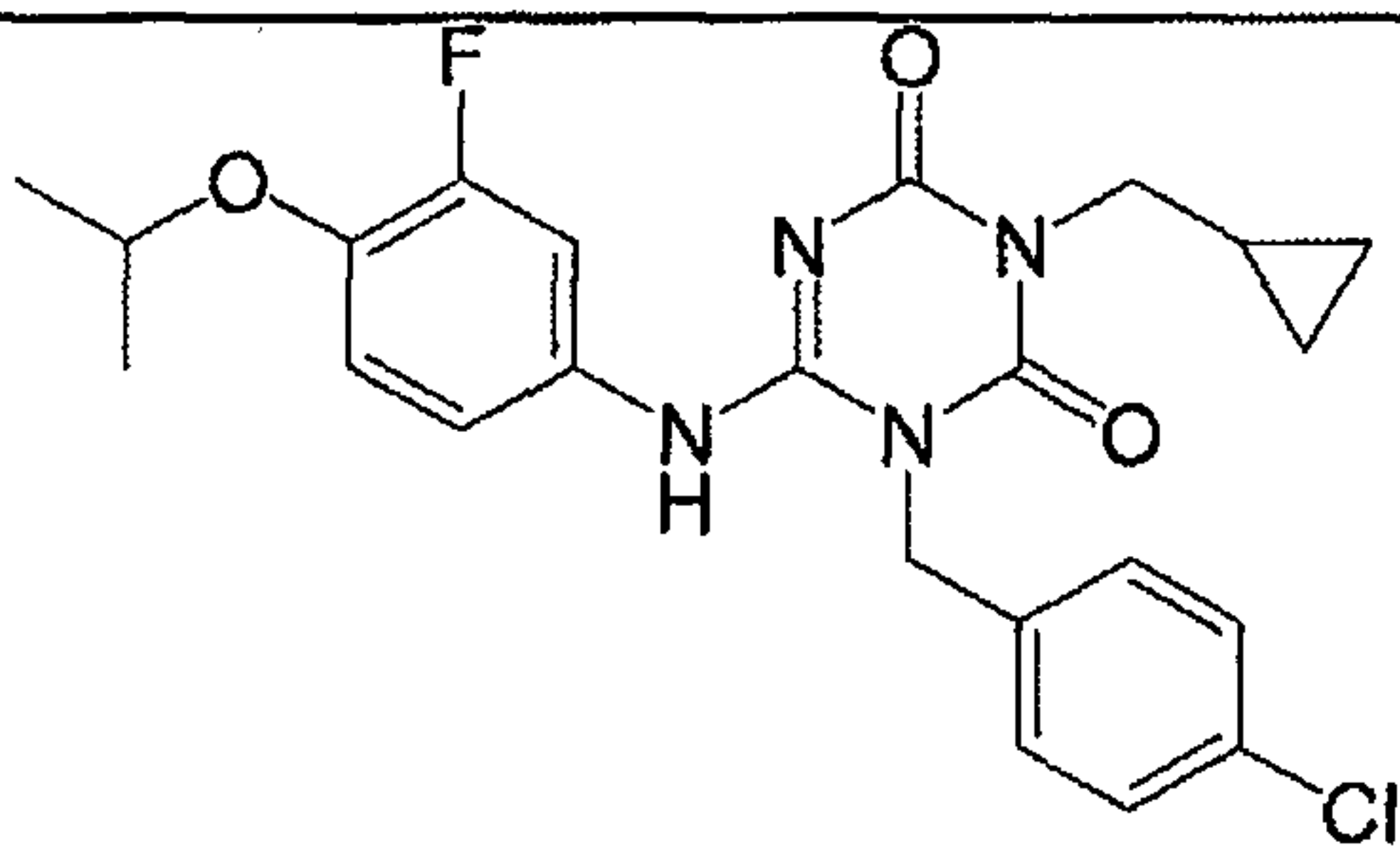
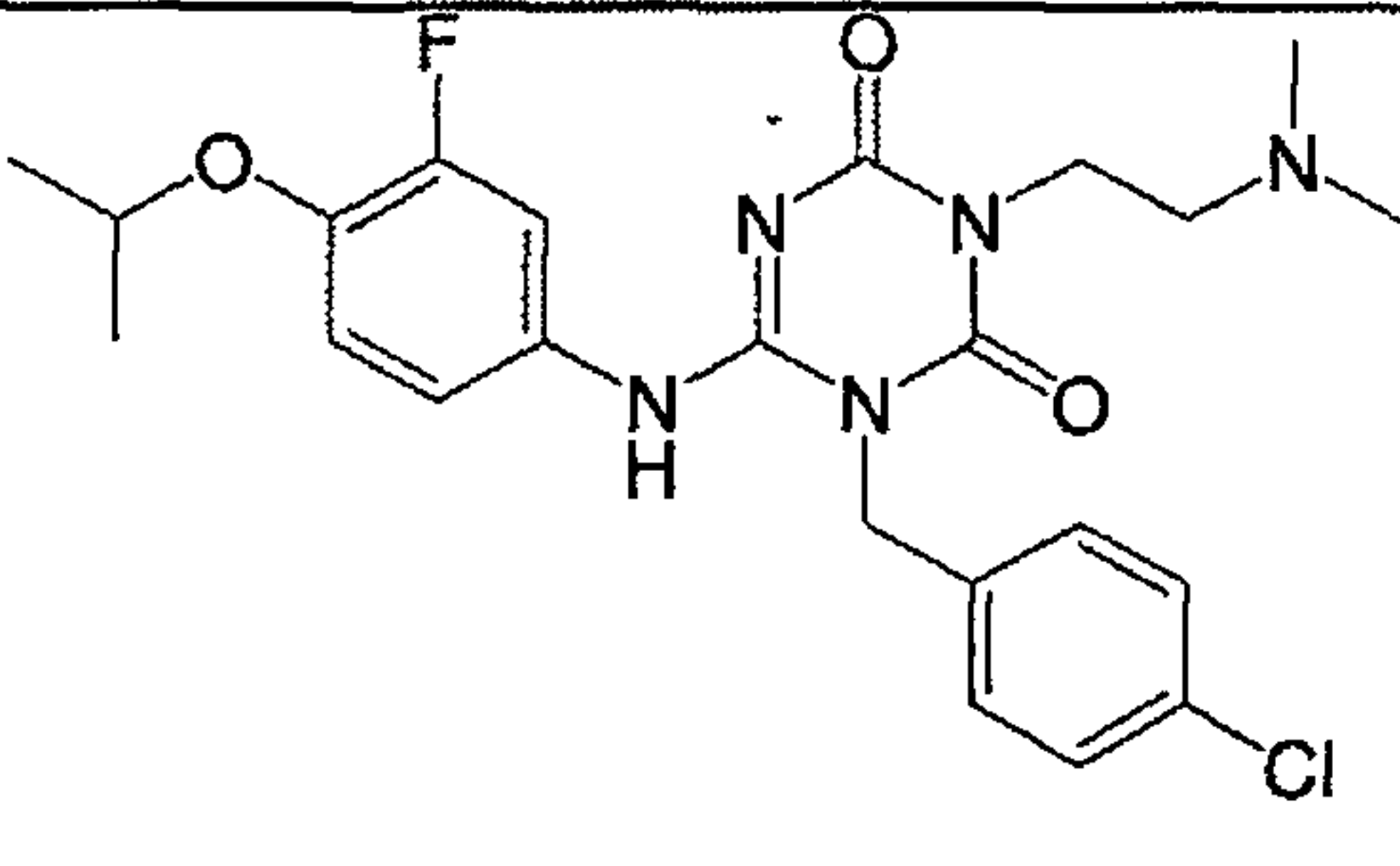
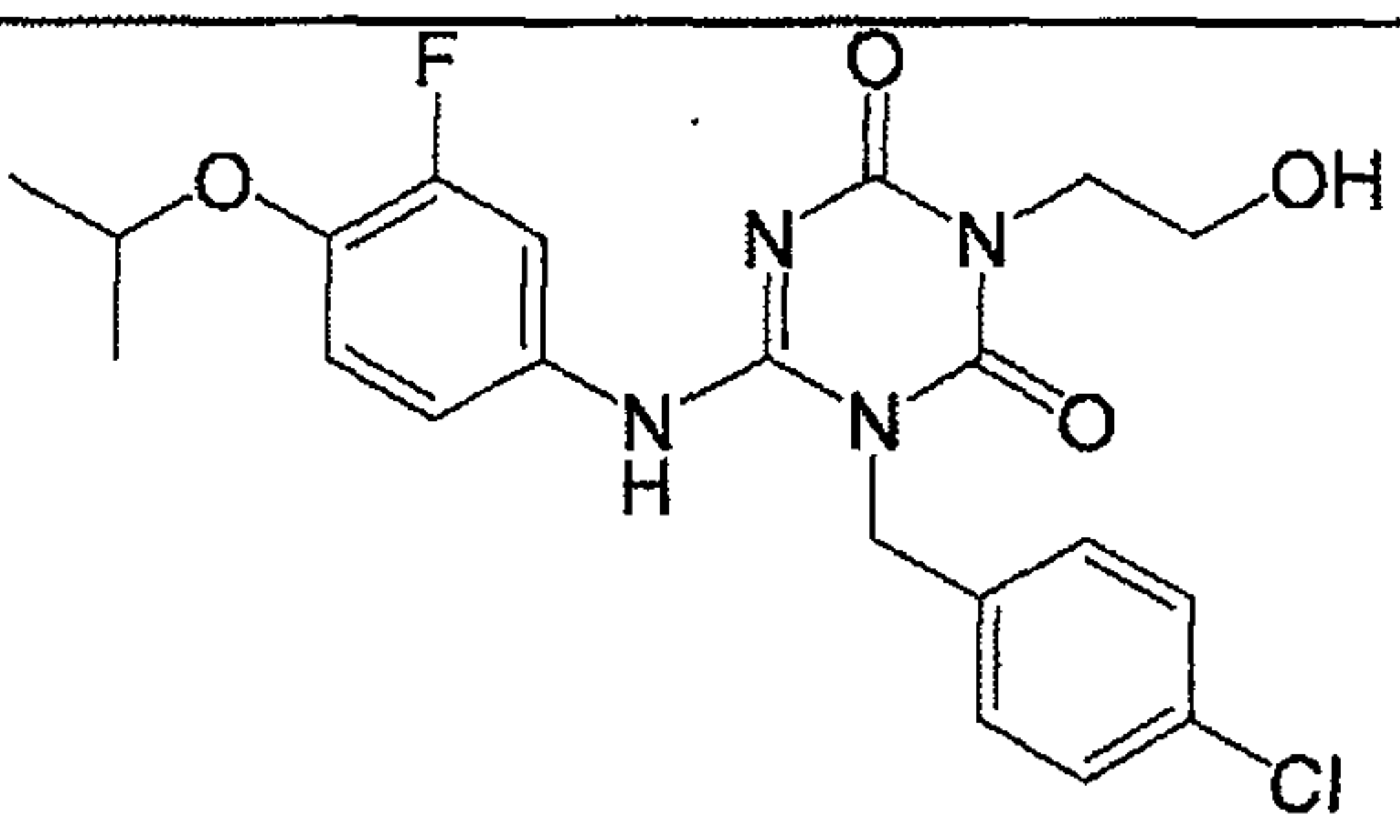
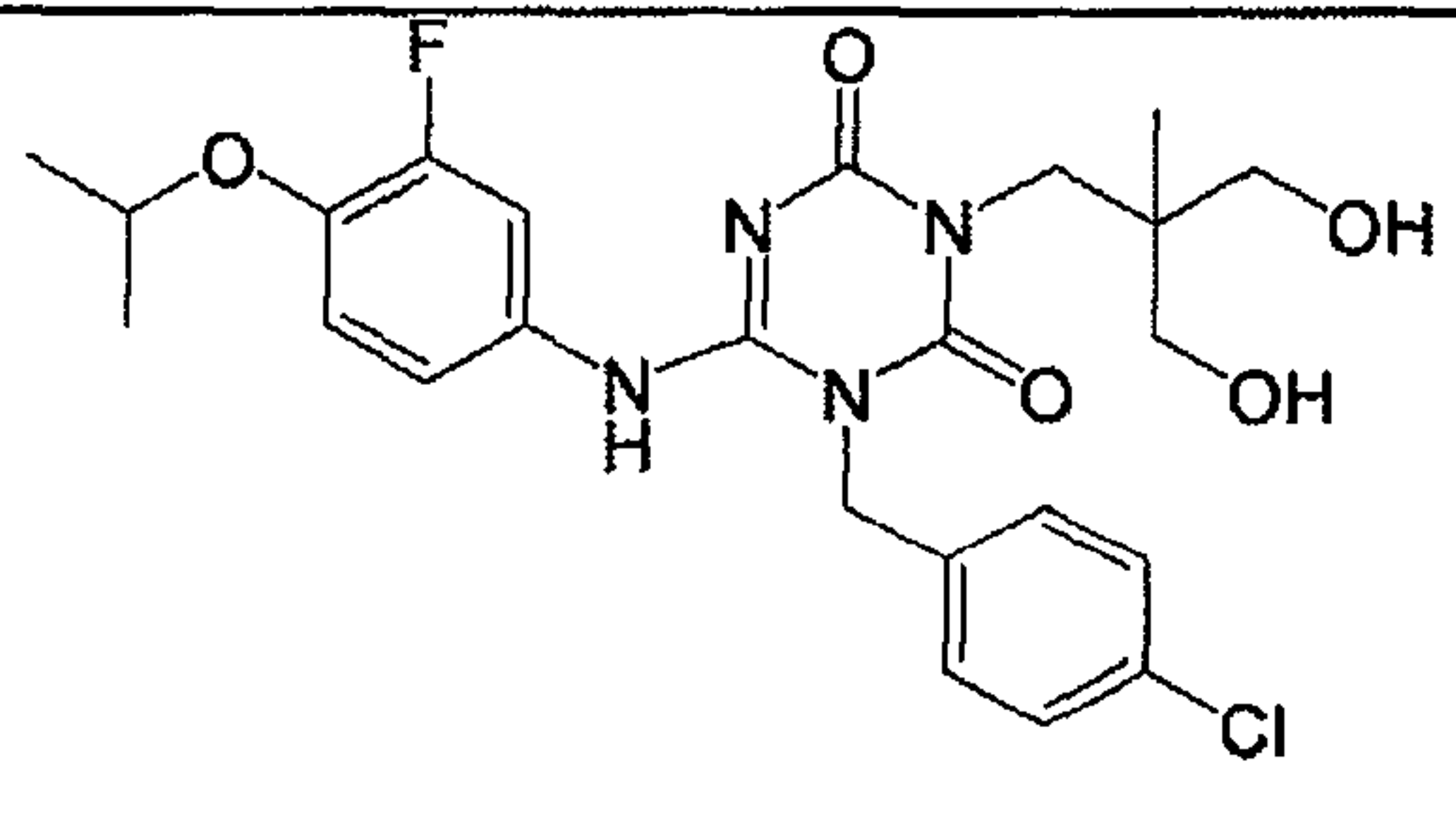
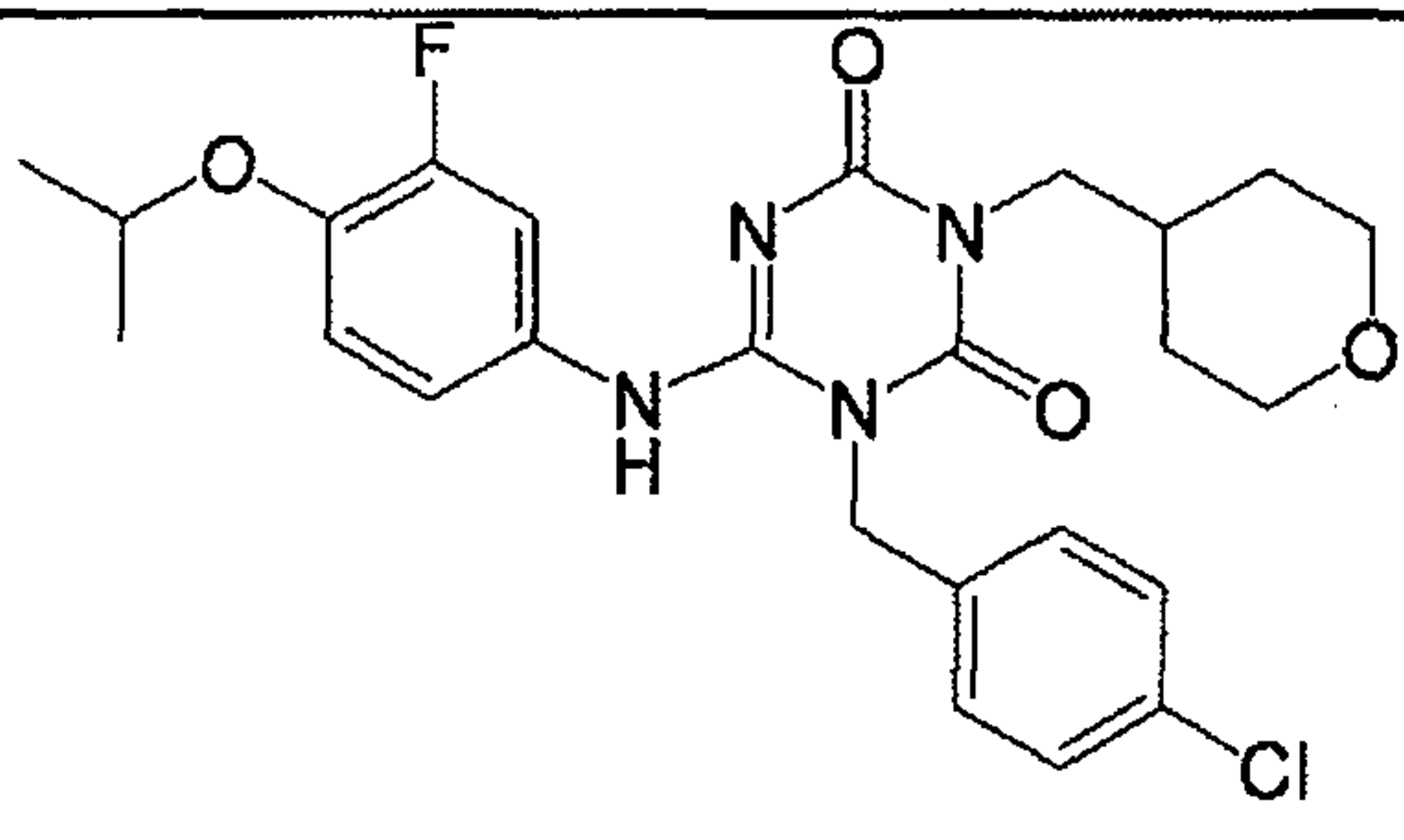
[Table 56]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0261	2.60	482	3
	I-0262	2.20	484	3
	I-0263	2.10	428	3
	I-0264	2.50	482	3
	I-0265	2.30	442	3

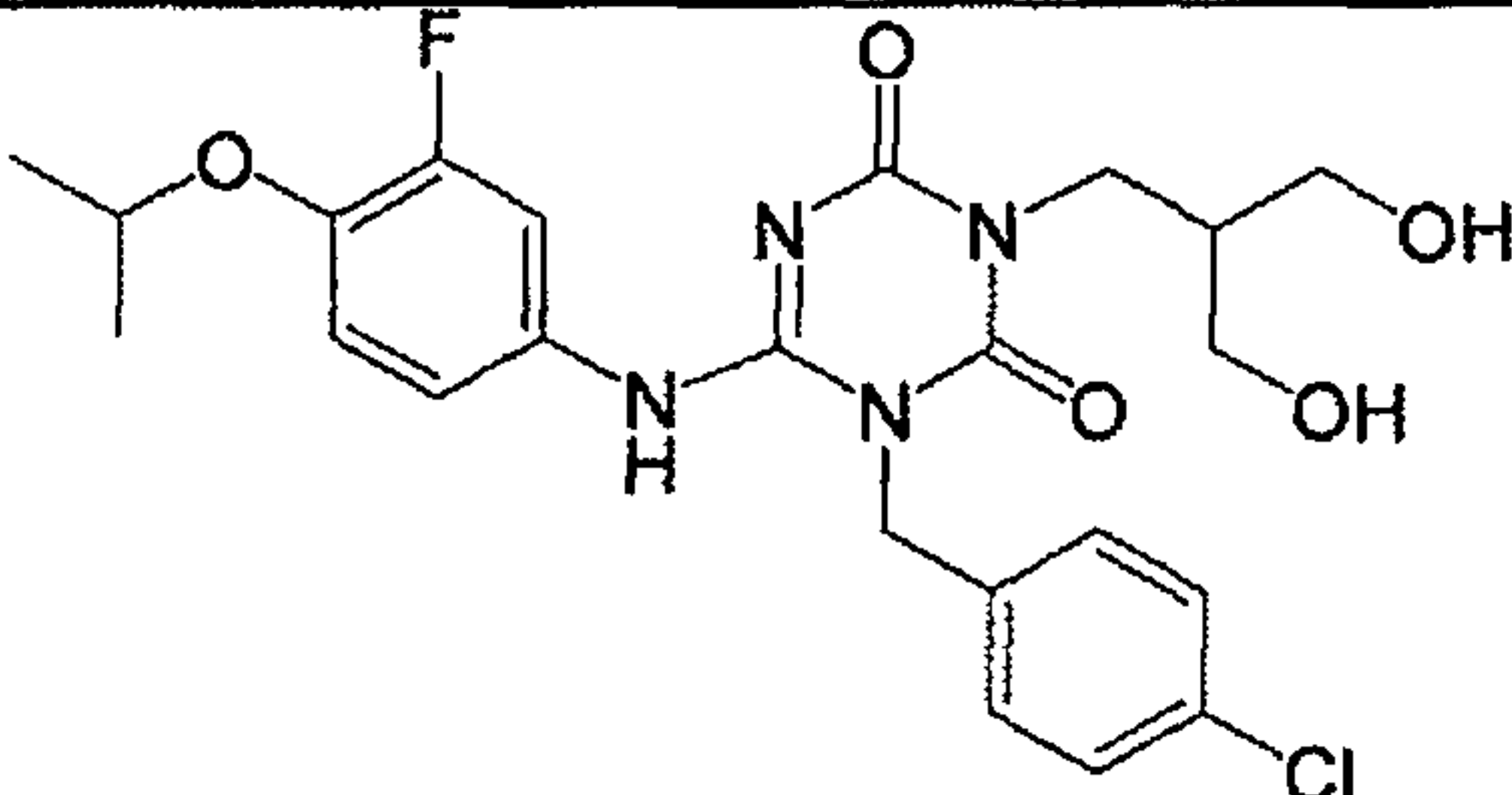
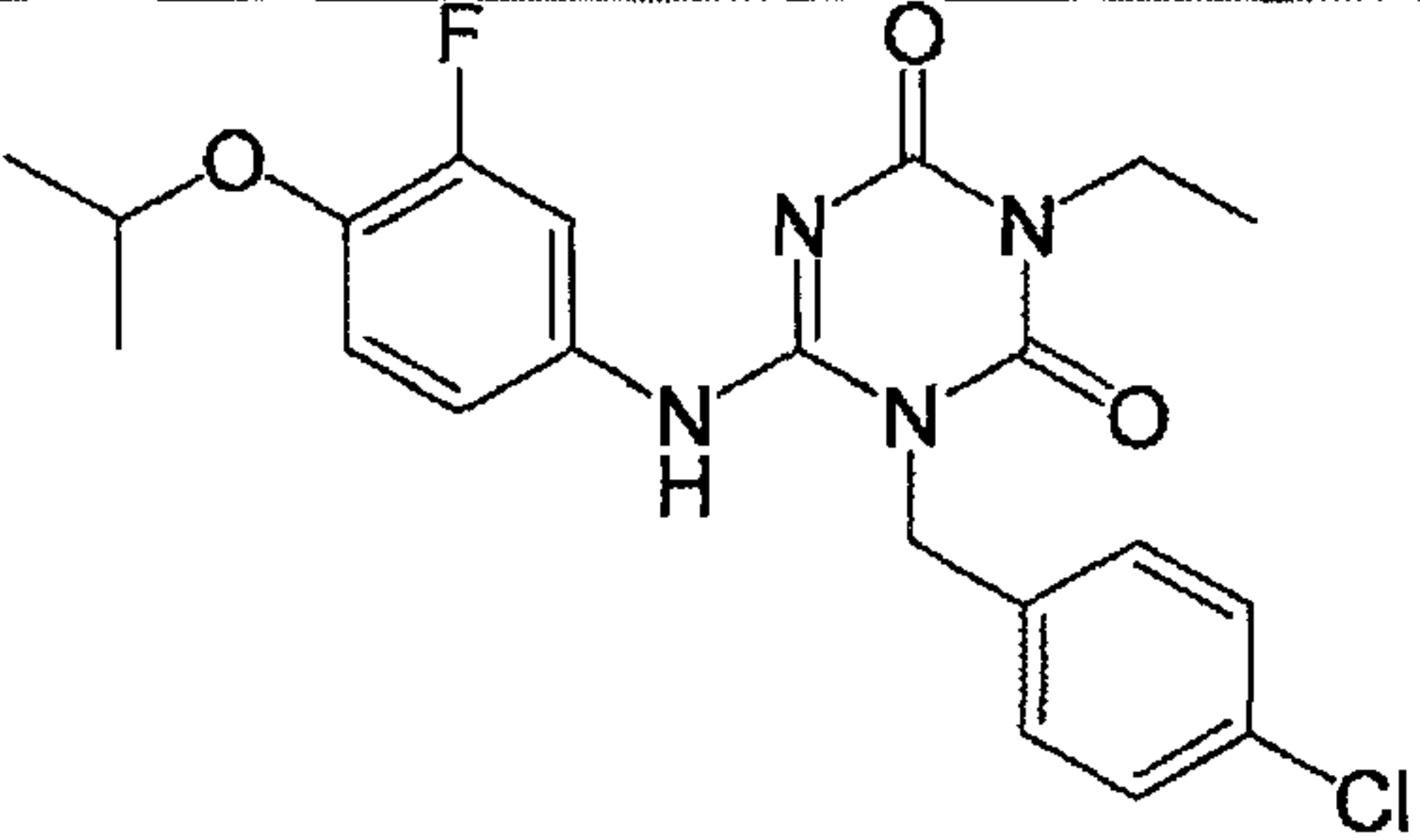
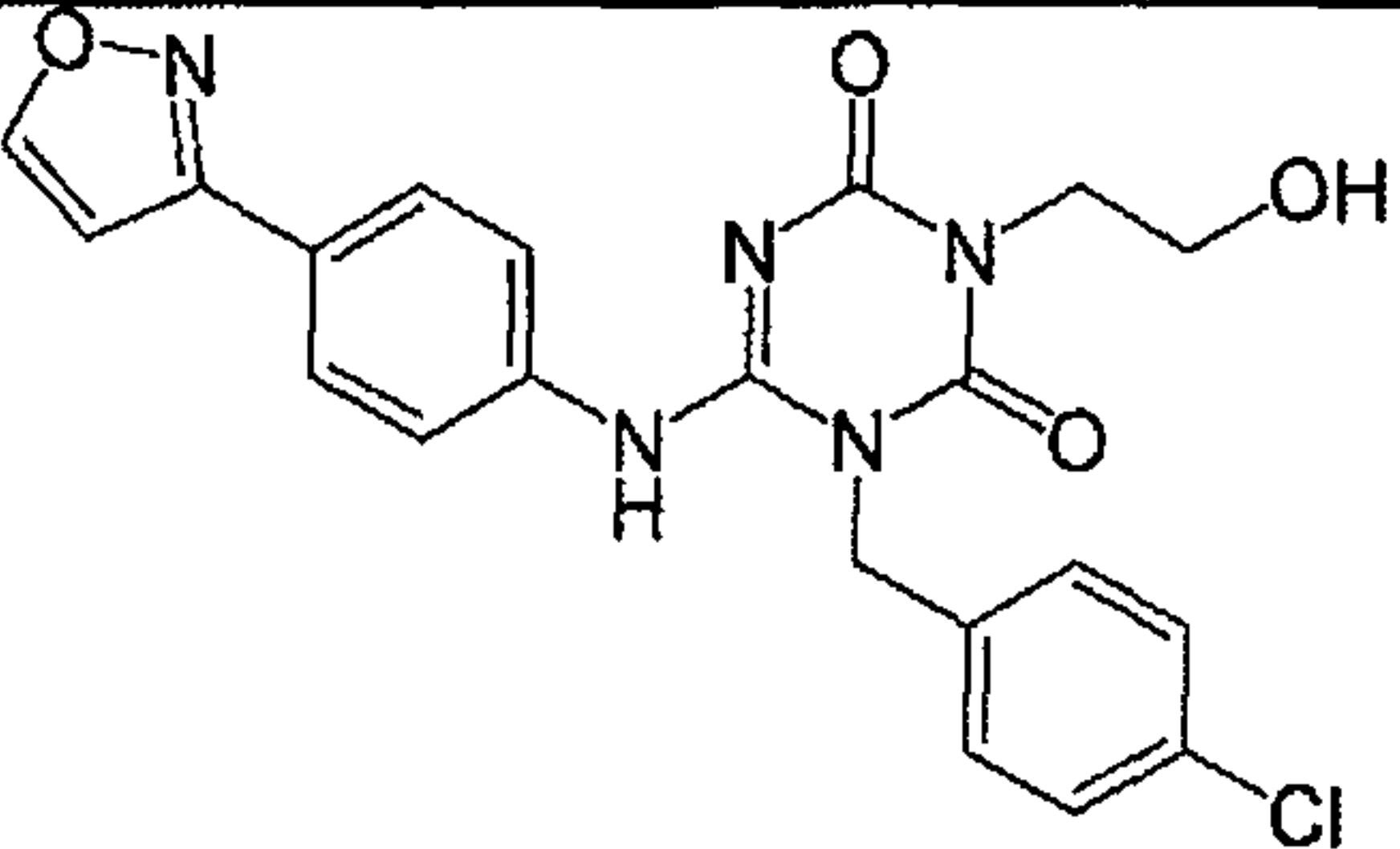
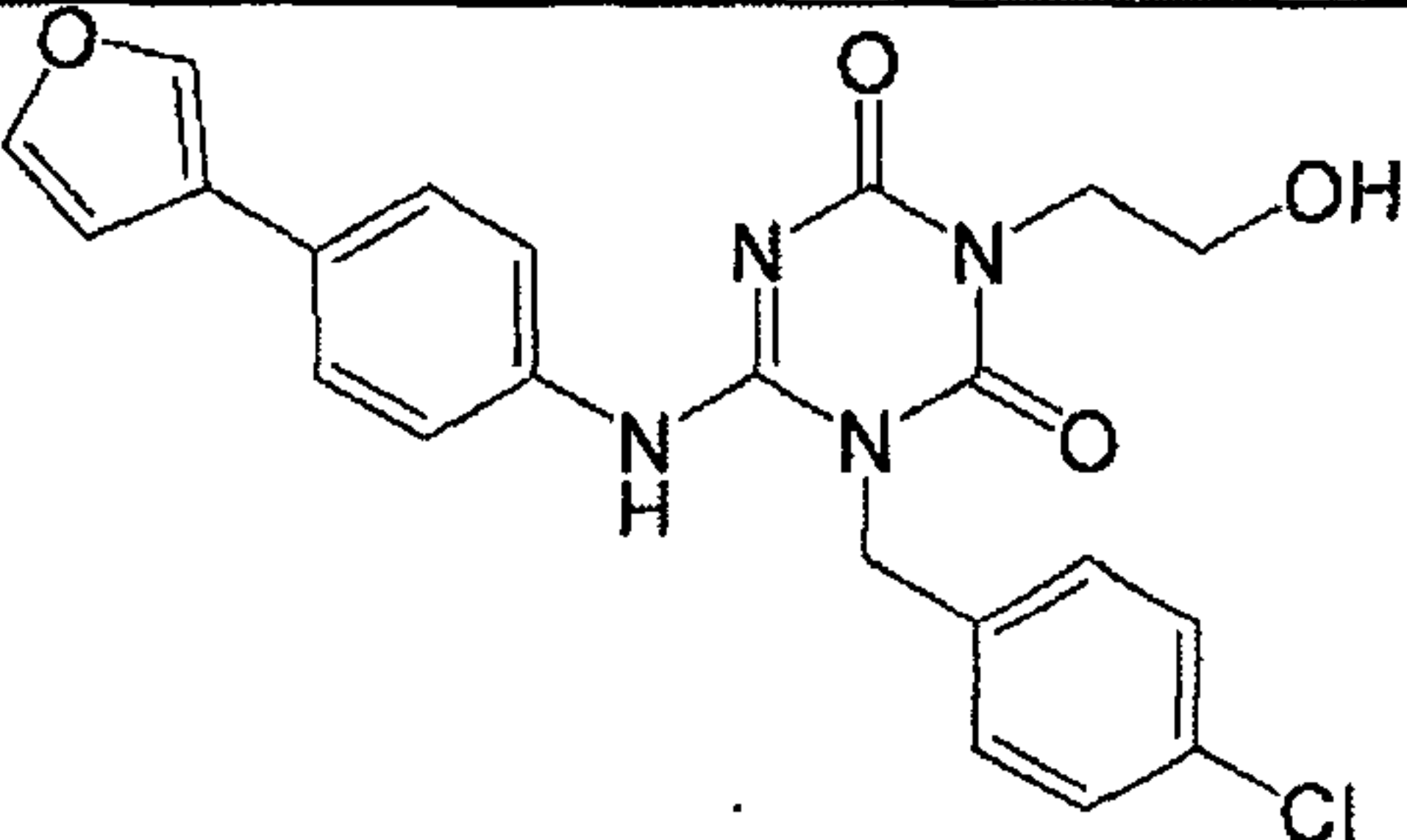
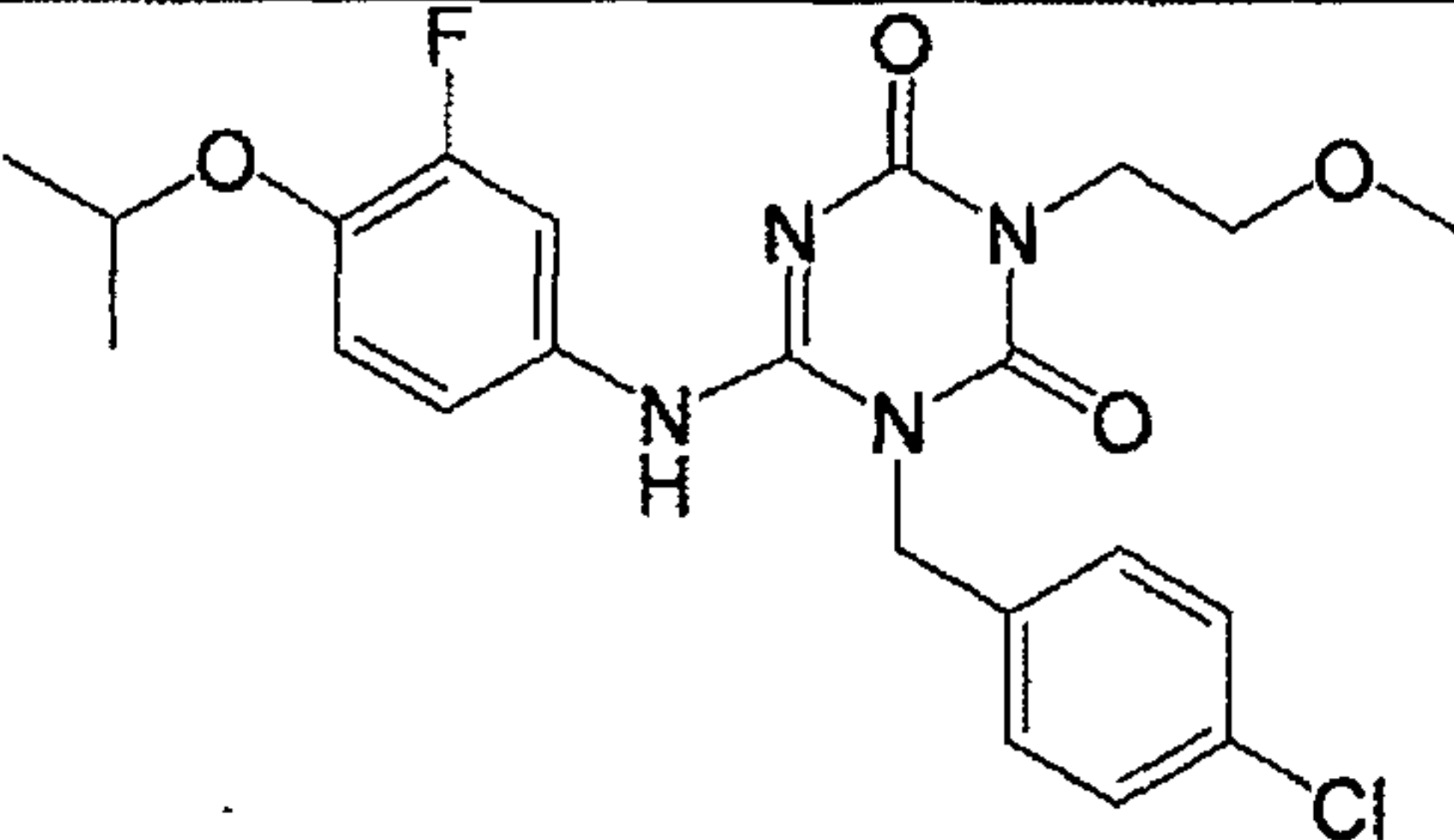
[Table 57]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0266	2.60	490	3
	I-0267	2.00	458	3
	I-0268	2.60	484	3
	I-0269	2.03	405	1
	I-0270	2.42	477	1

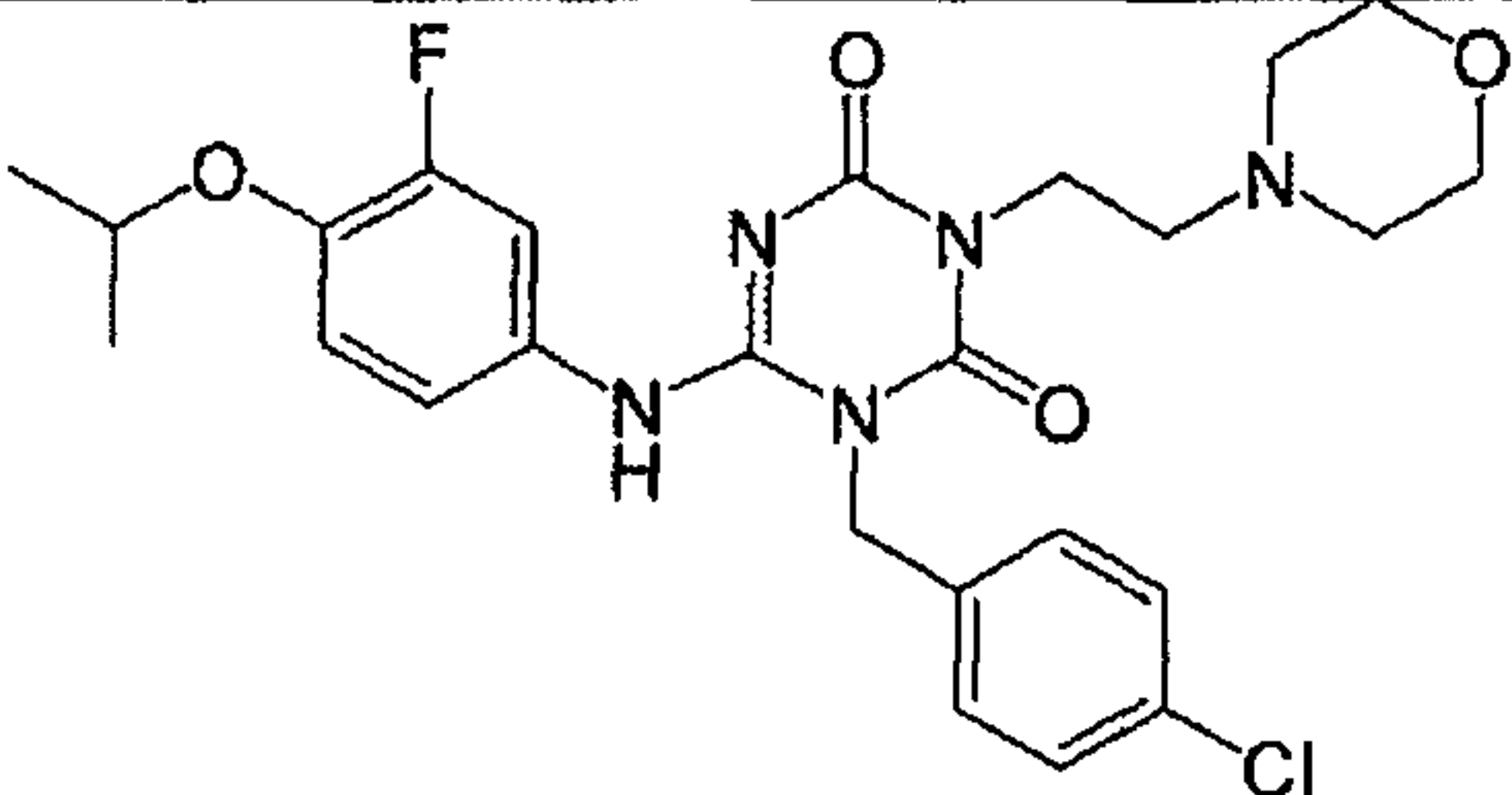
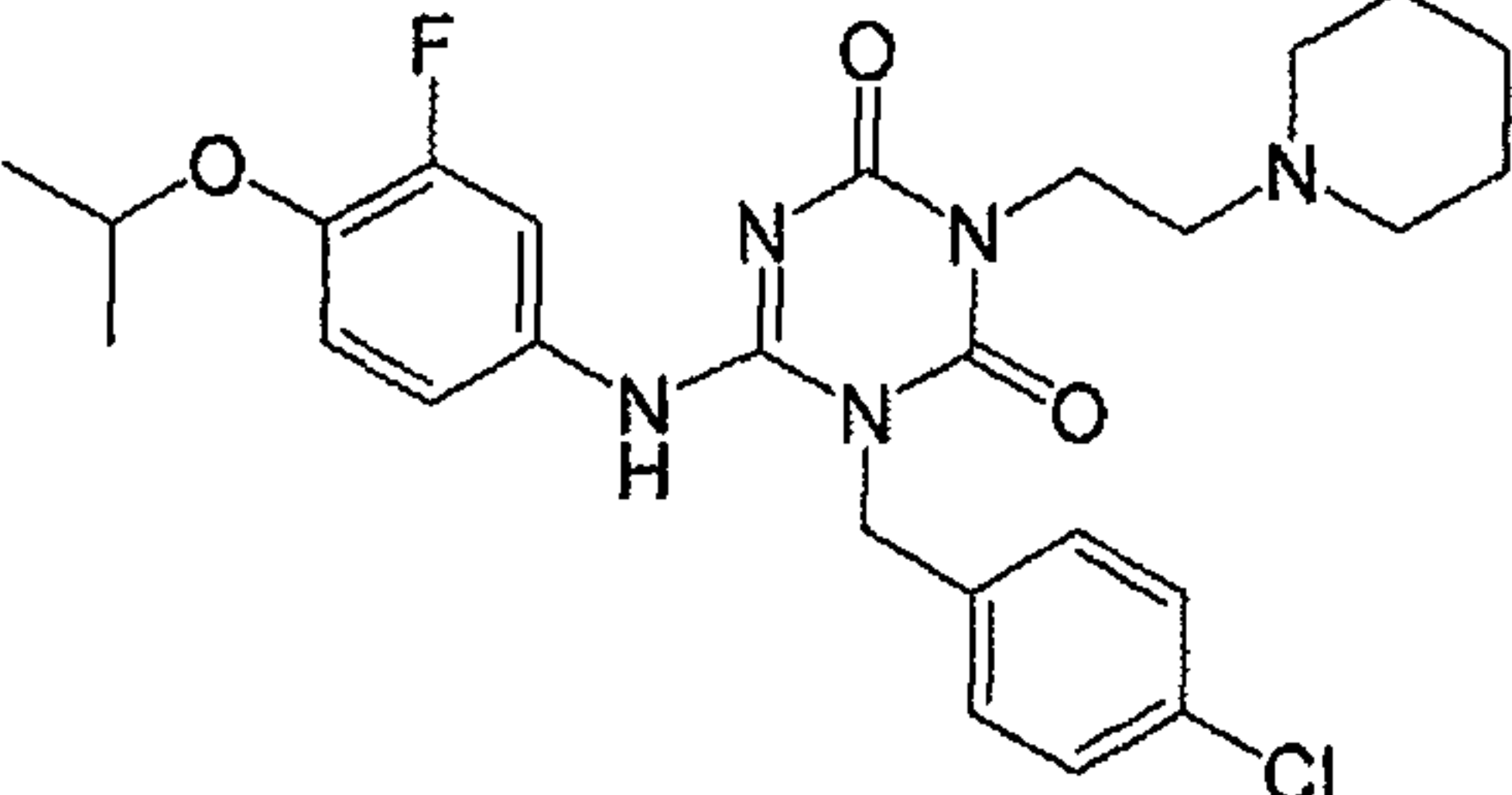
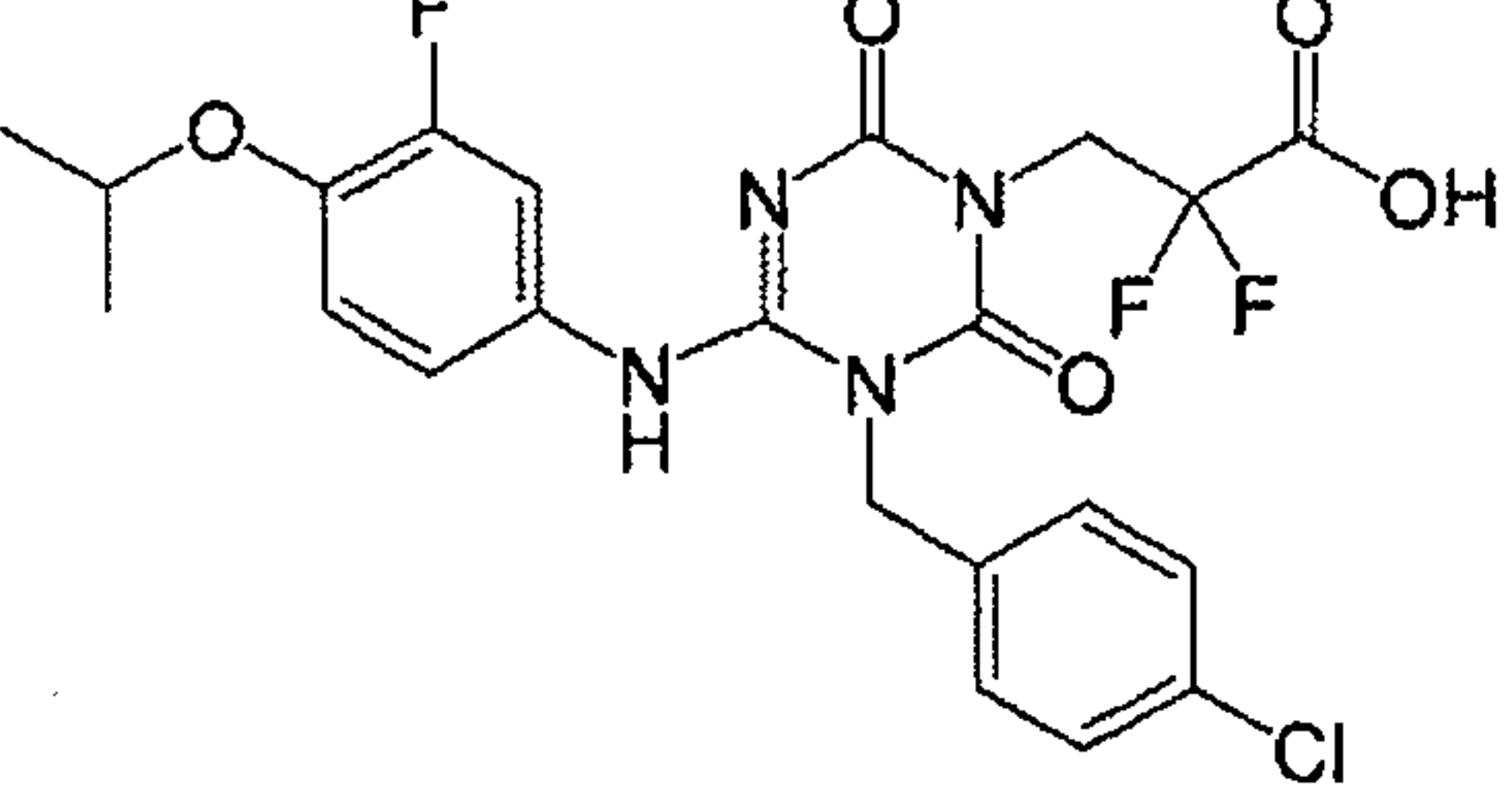
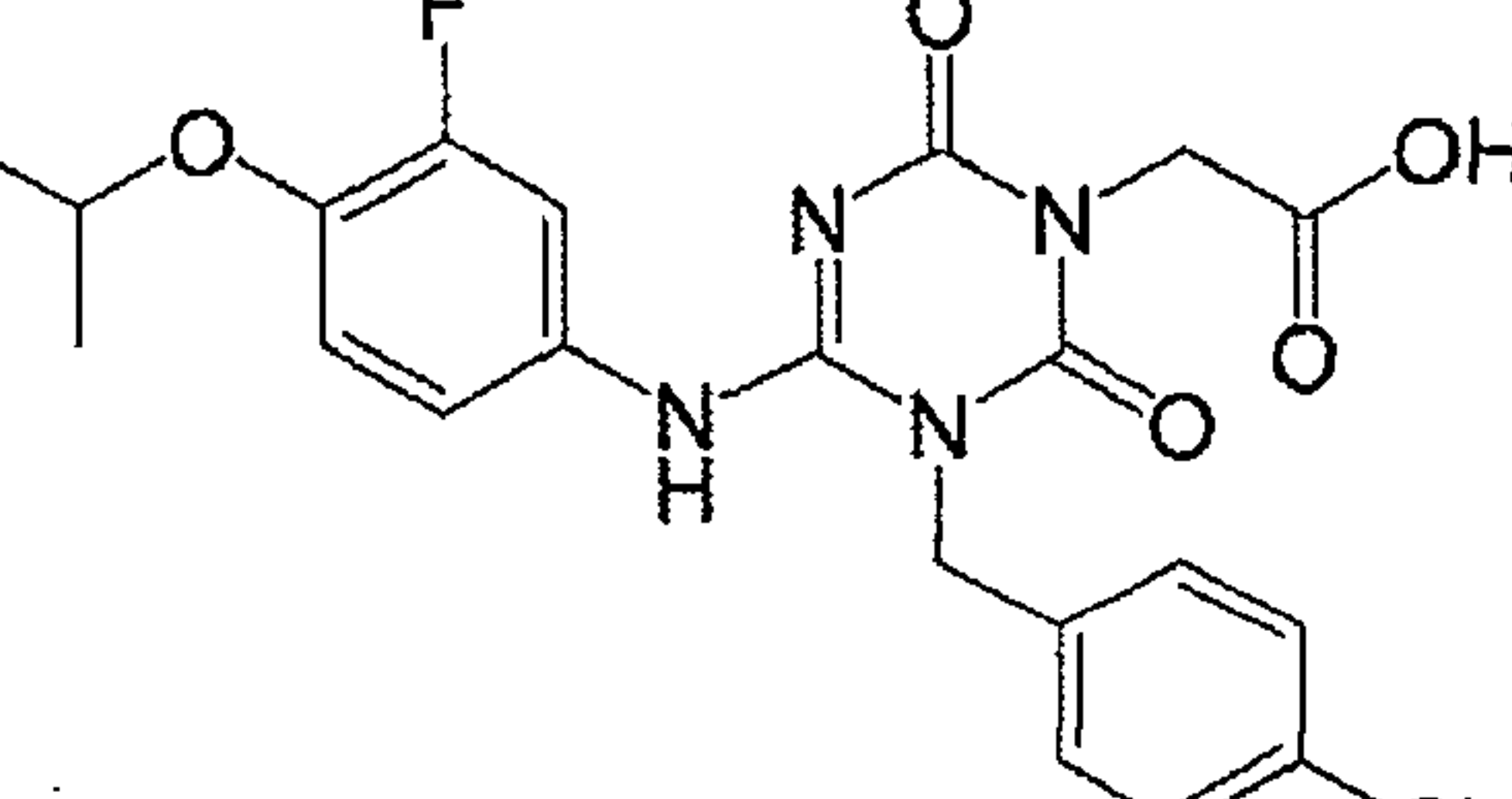
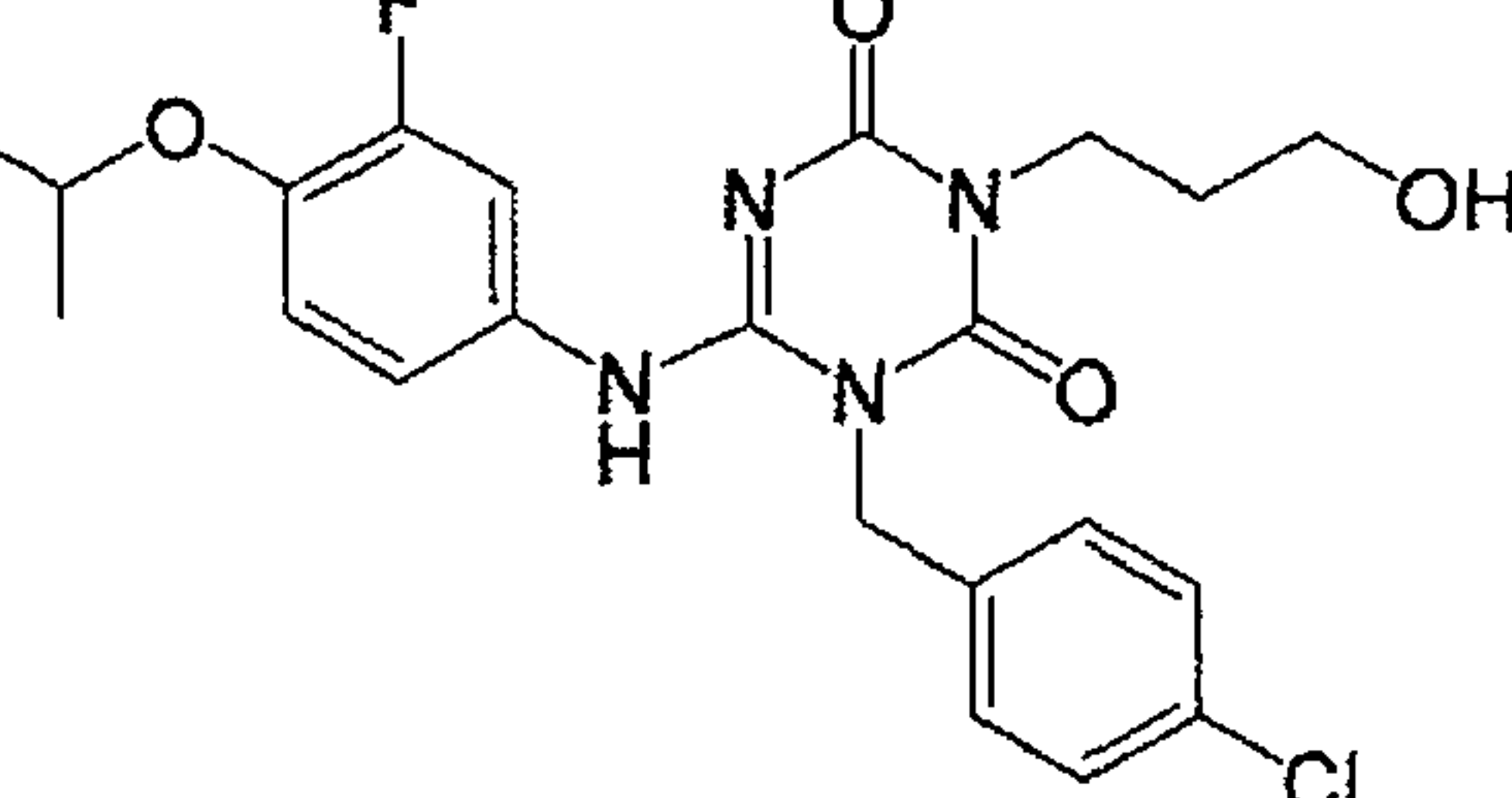
[Table 58]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0271	2.49	459	1
	I-0272	1.44	476	1
	I-0273	1.96	449	1
	I-0274	1.98	507	1
	I-0275	2.27	503	1

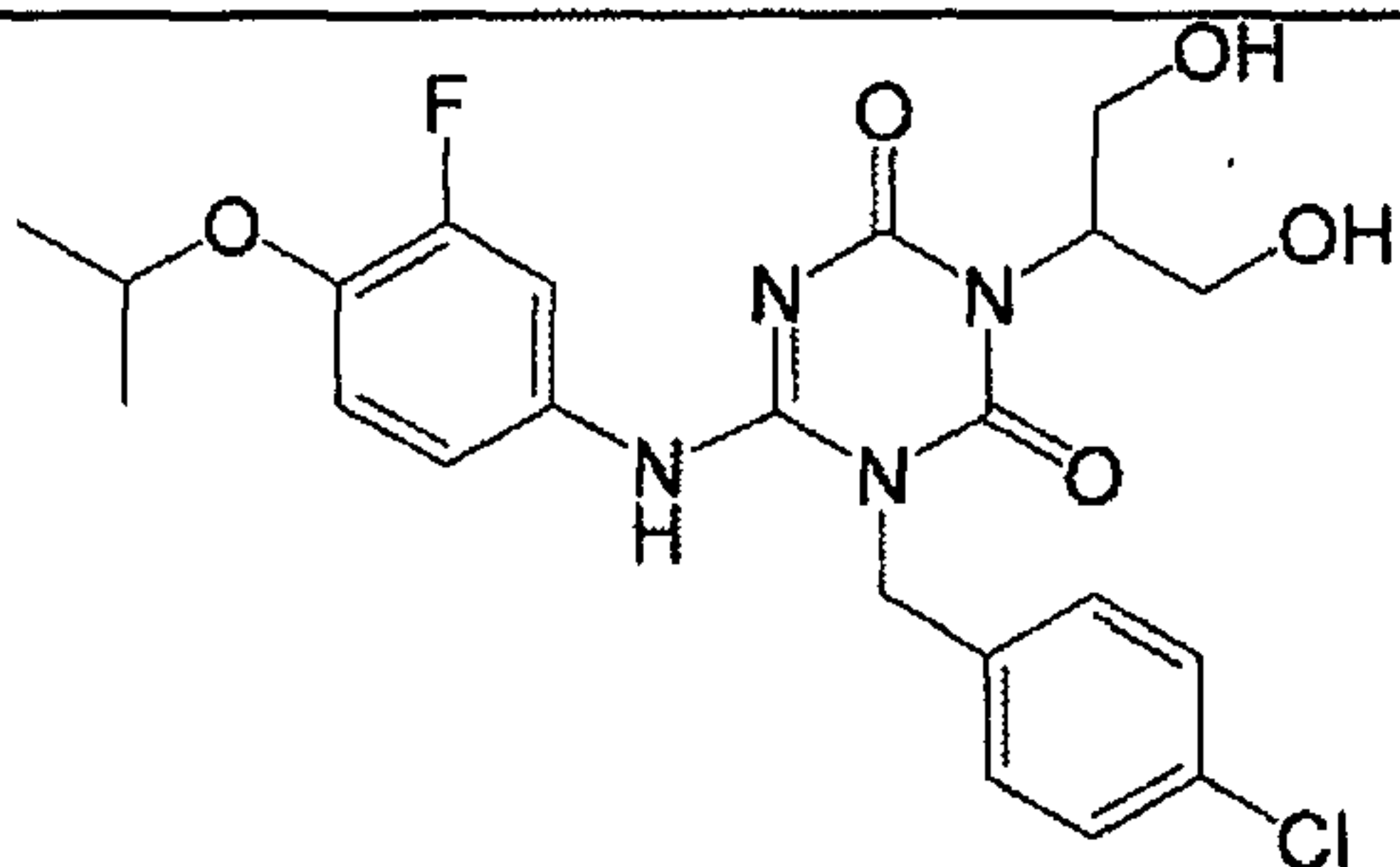
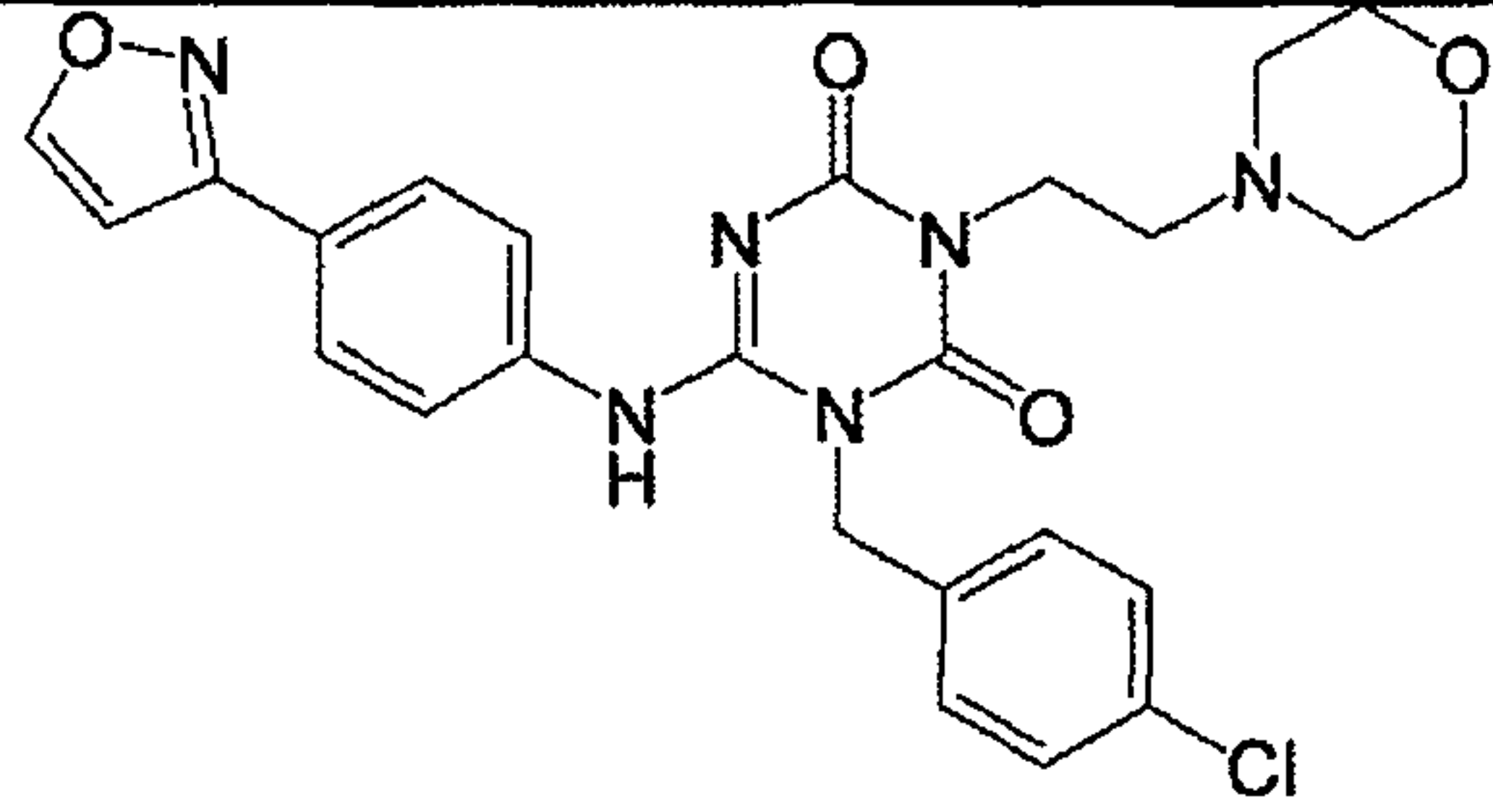
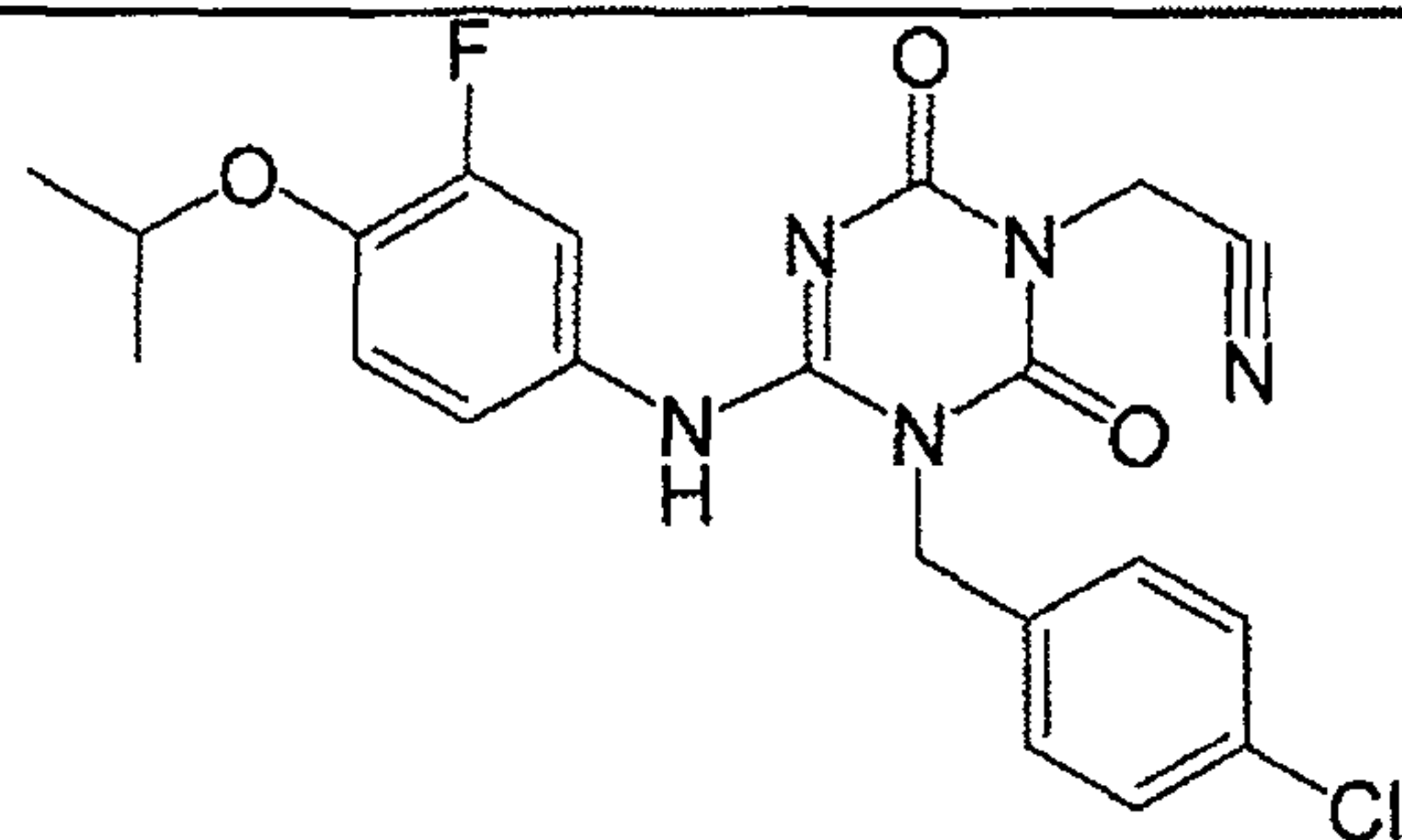
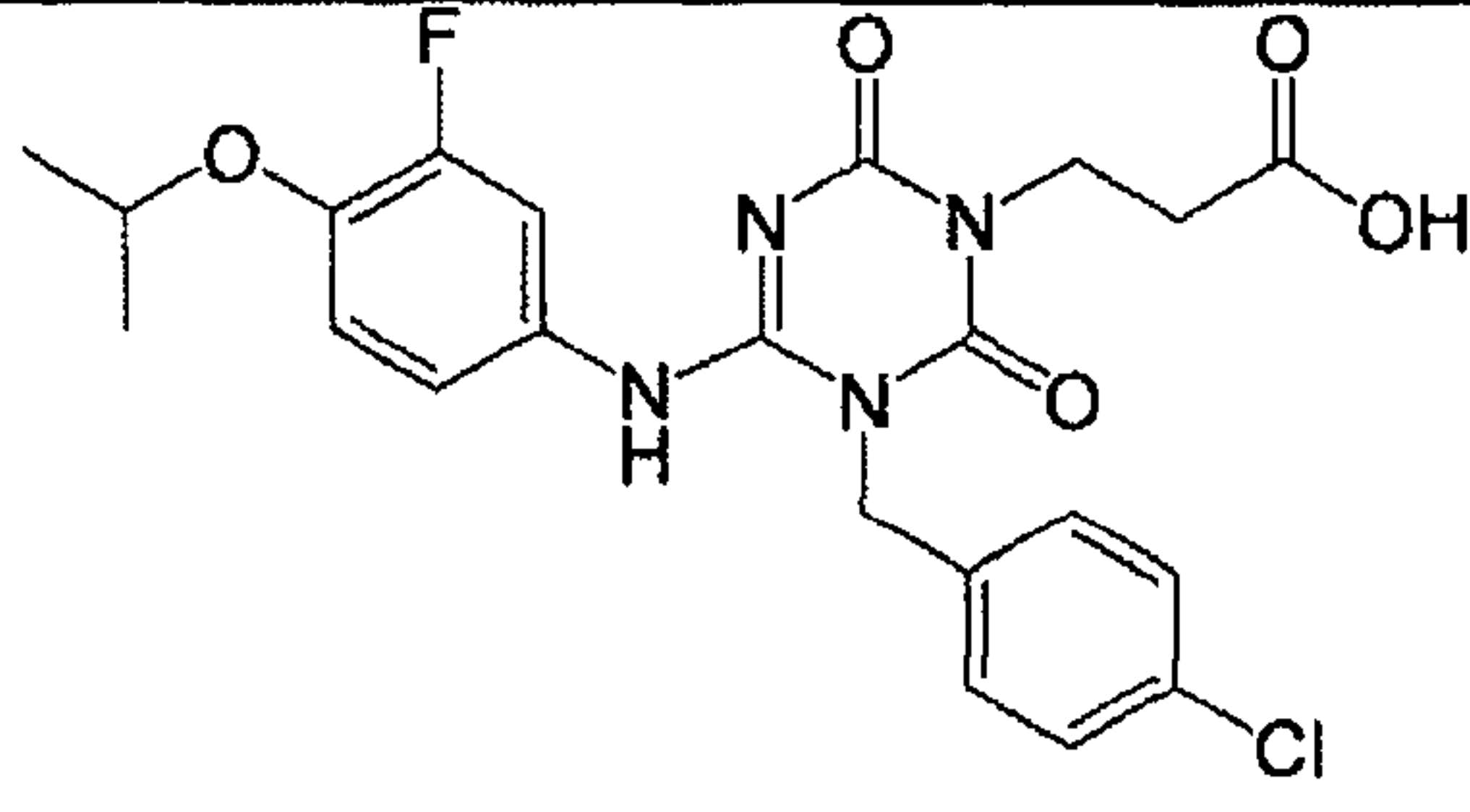
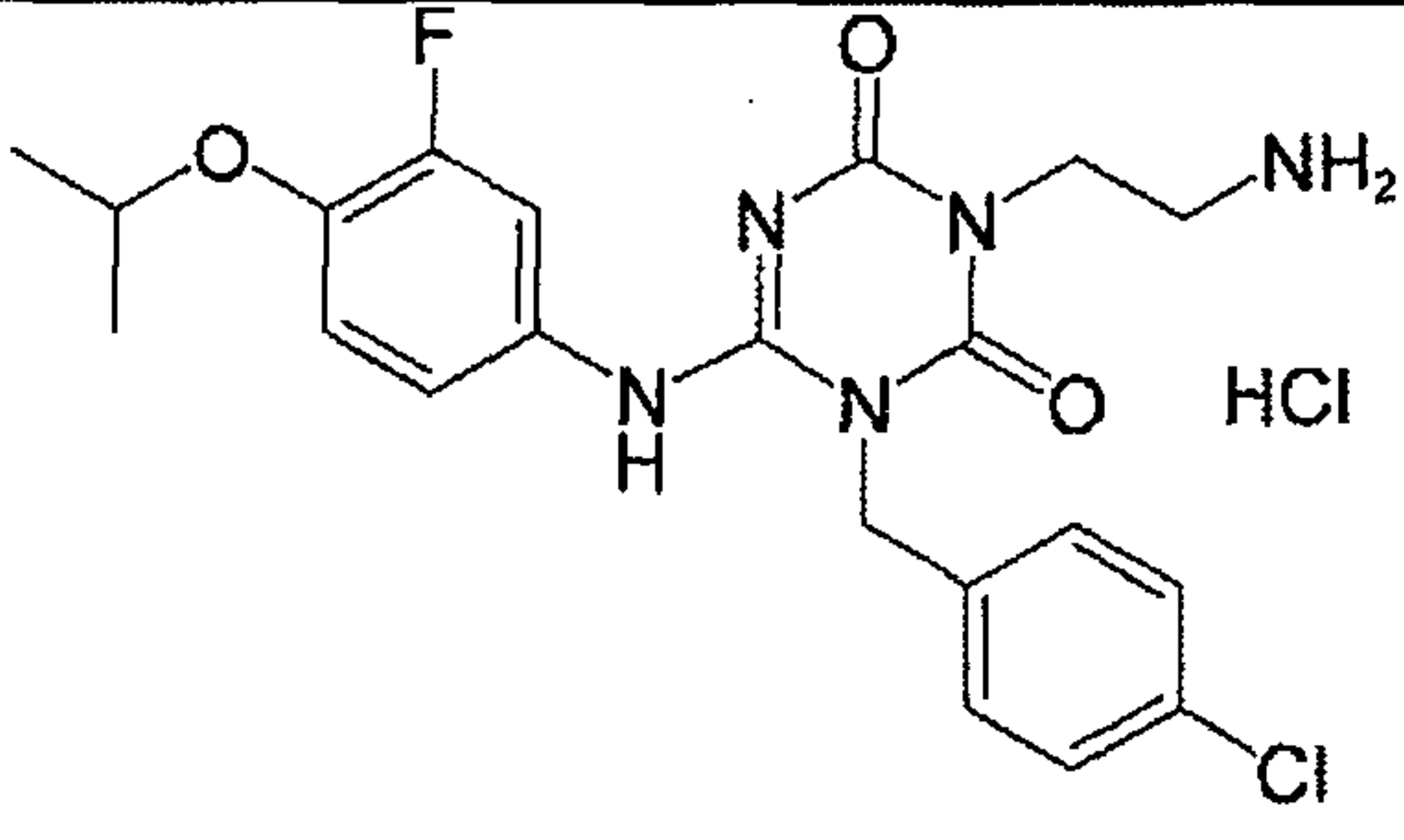
[Table 59]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0276	1.85	493	1
	I-0277	2.34	433	1
	I-0278	1.70	440	1
	I-0279	1.90	439	1
	I-0280	2.21	463	1

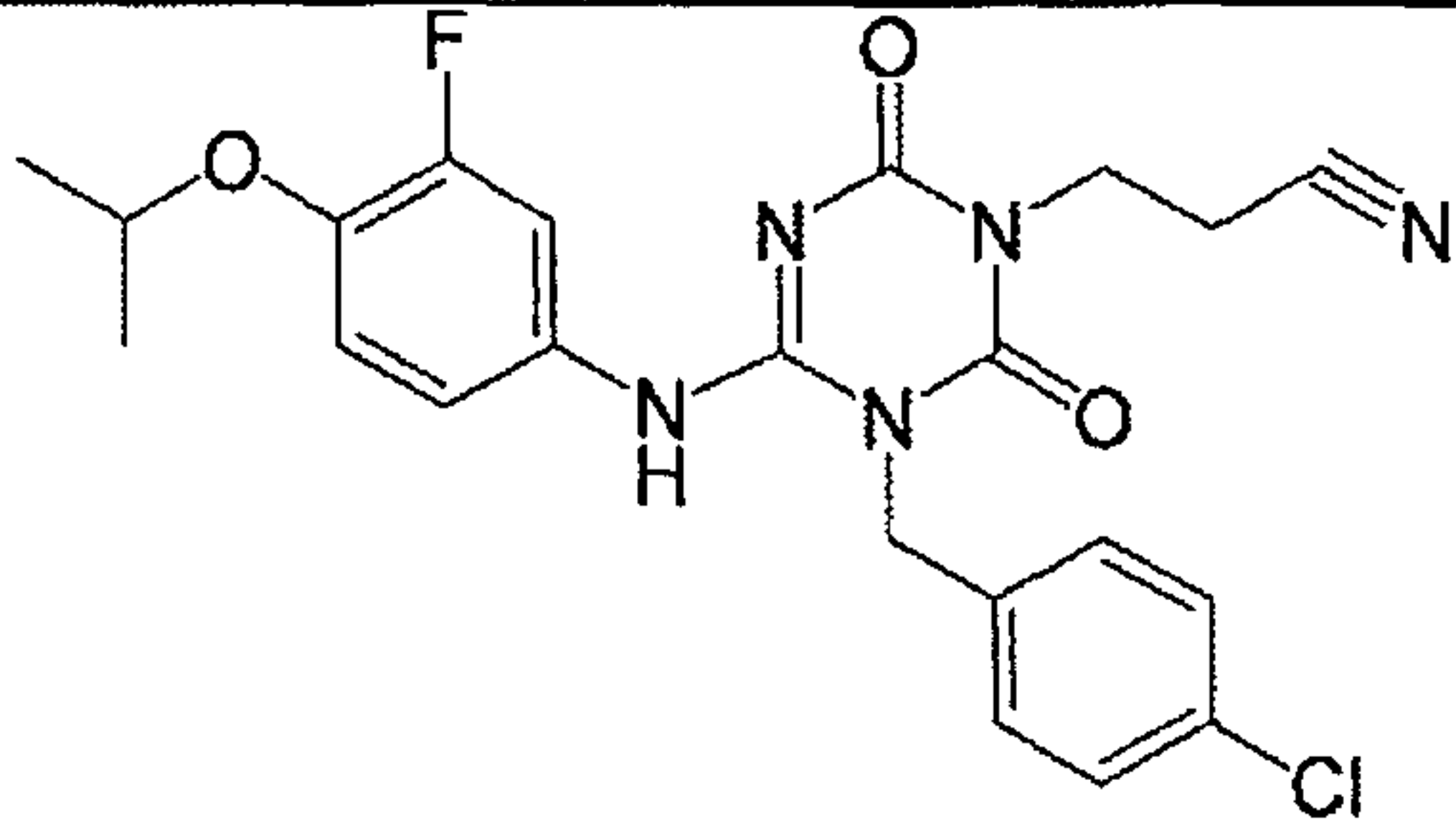
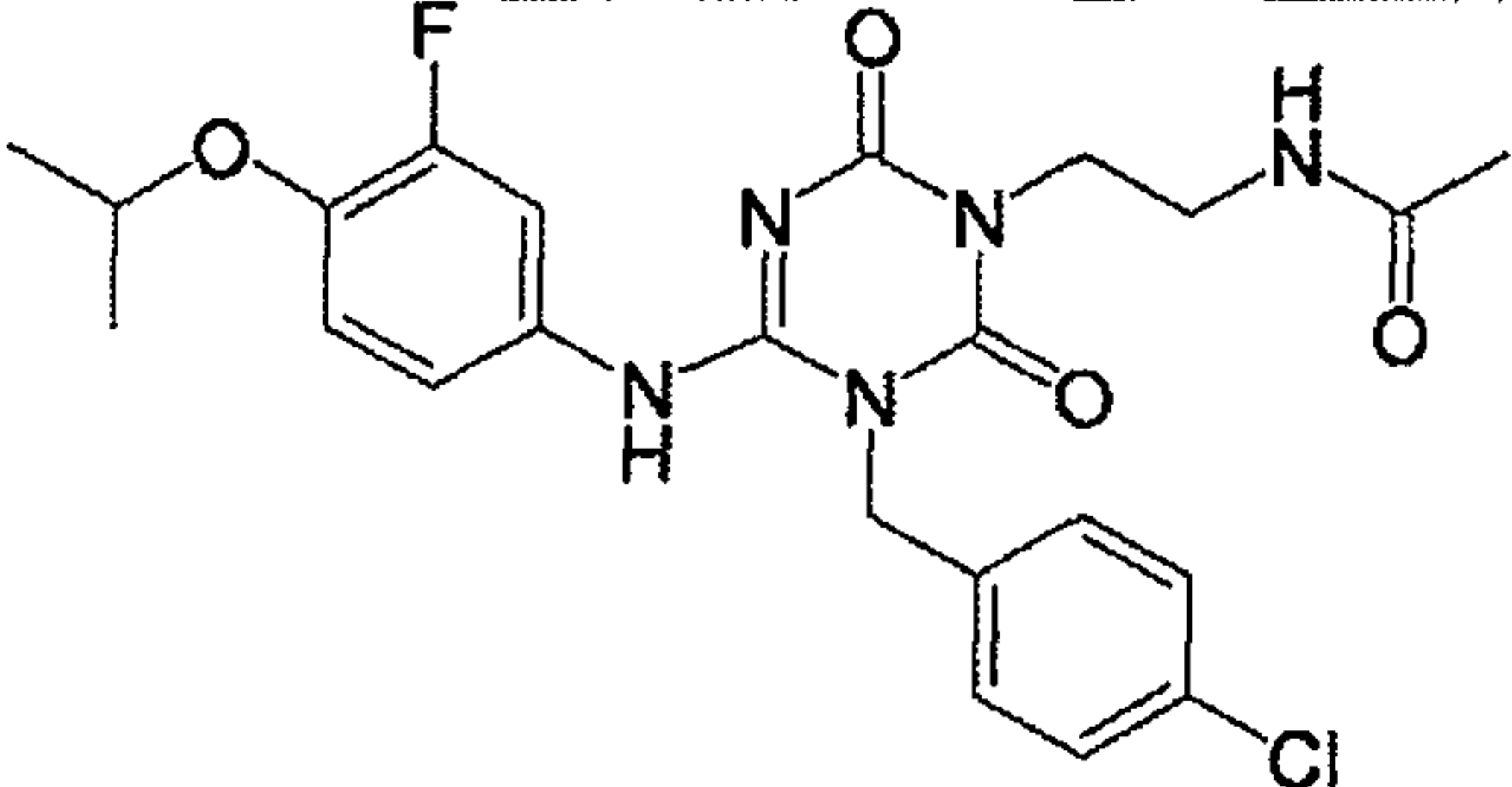
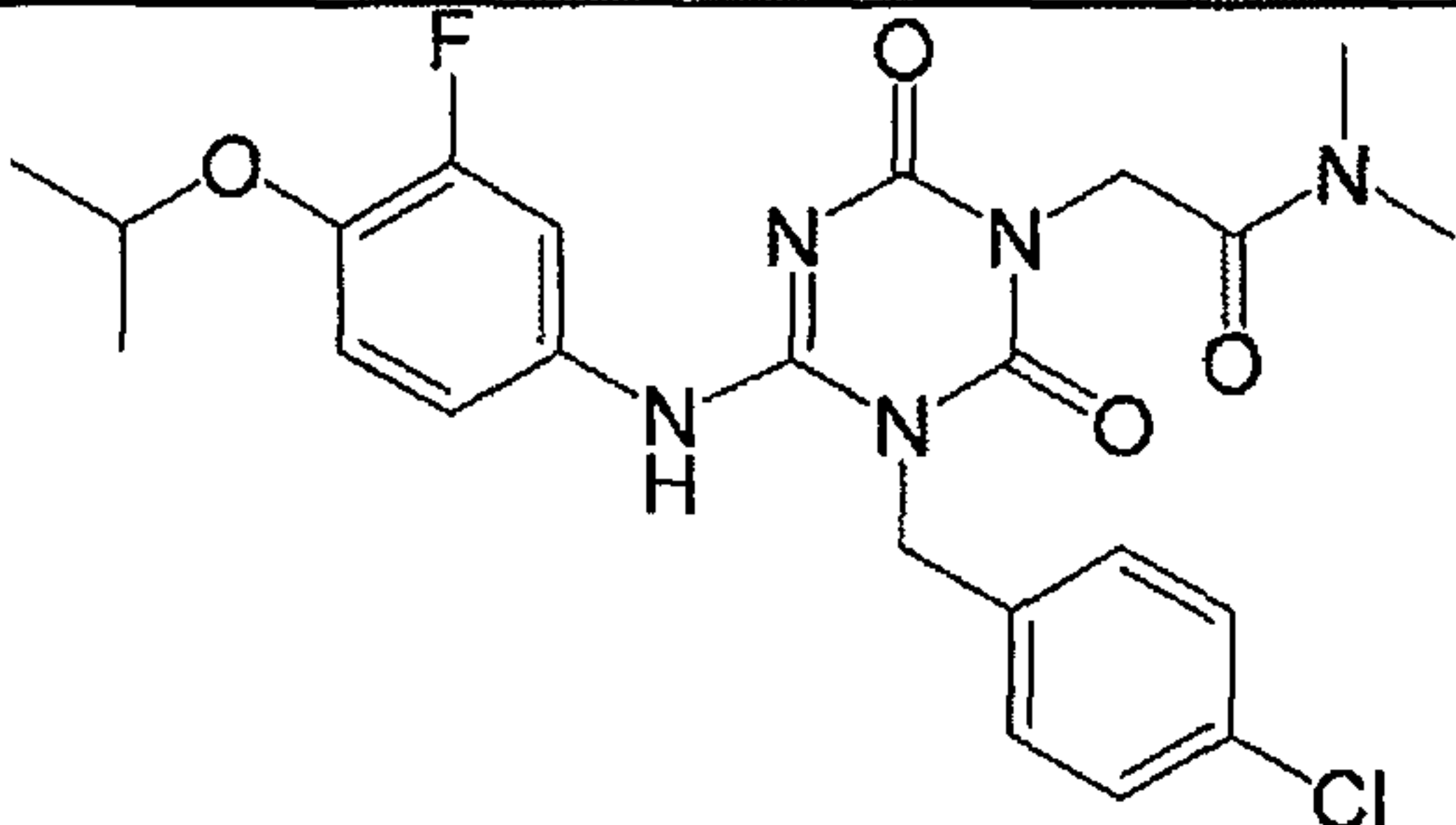
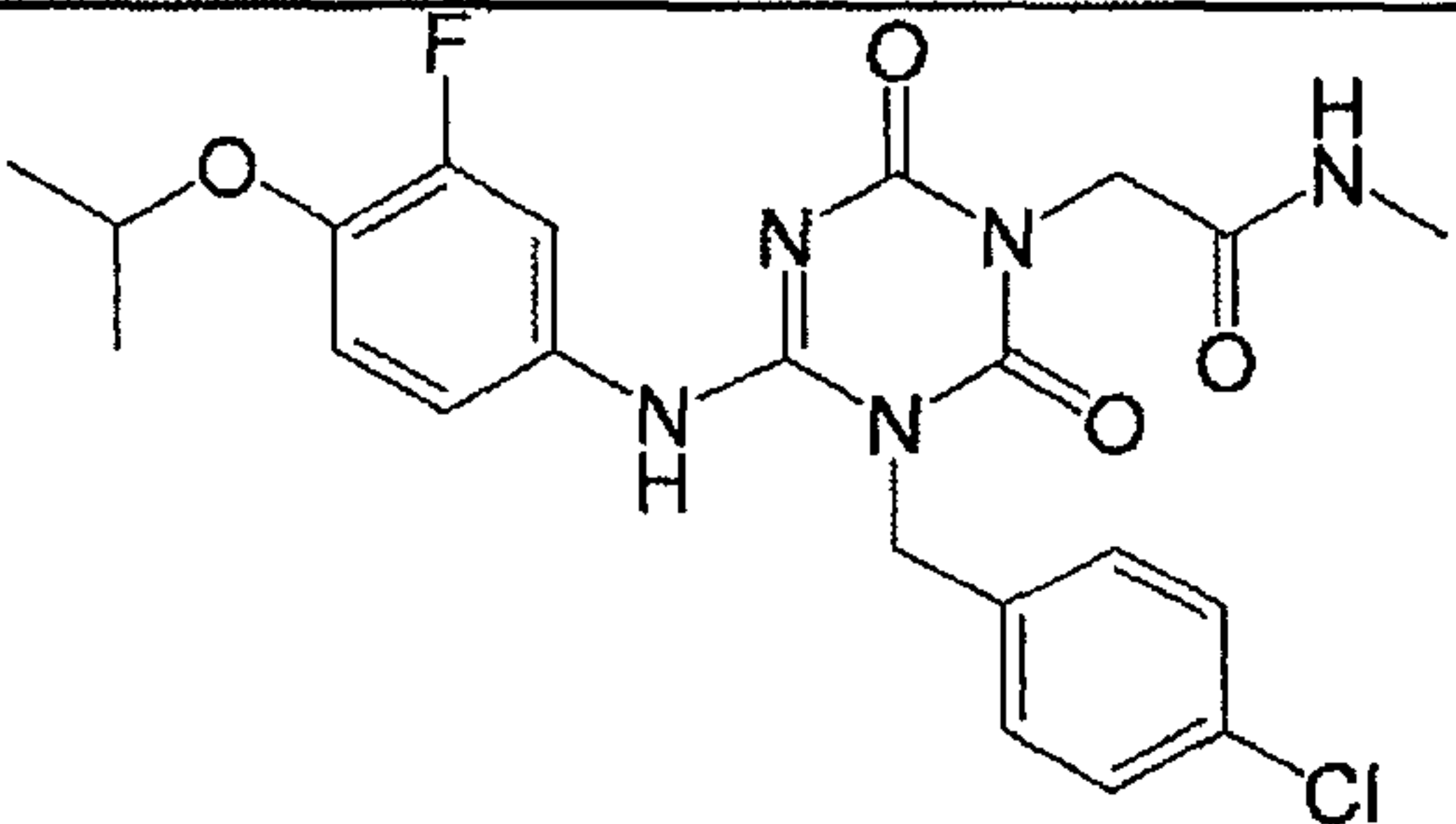
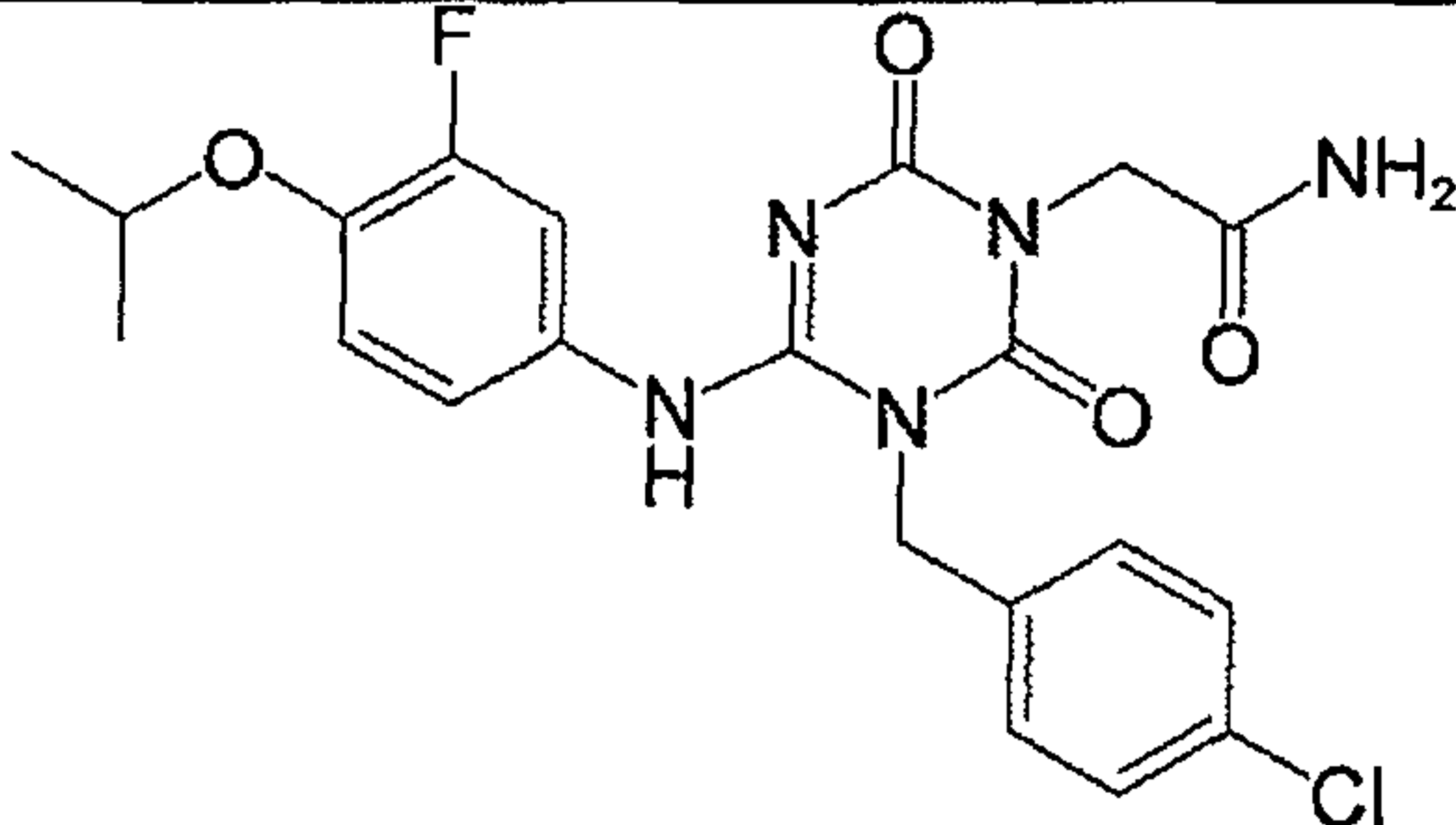
[Table 60]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0281	1.47	518	1
	I-0282	1.50	516	1
	I-0283	1.82	513	1
	I-0284	1.96	463	1
	I-0285	2.00	463	1

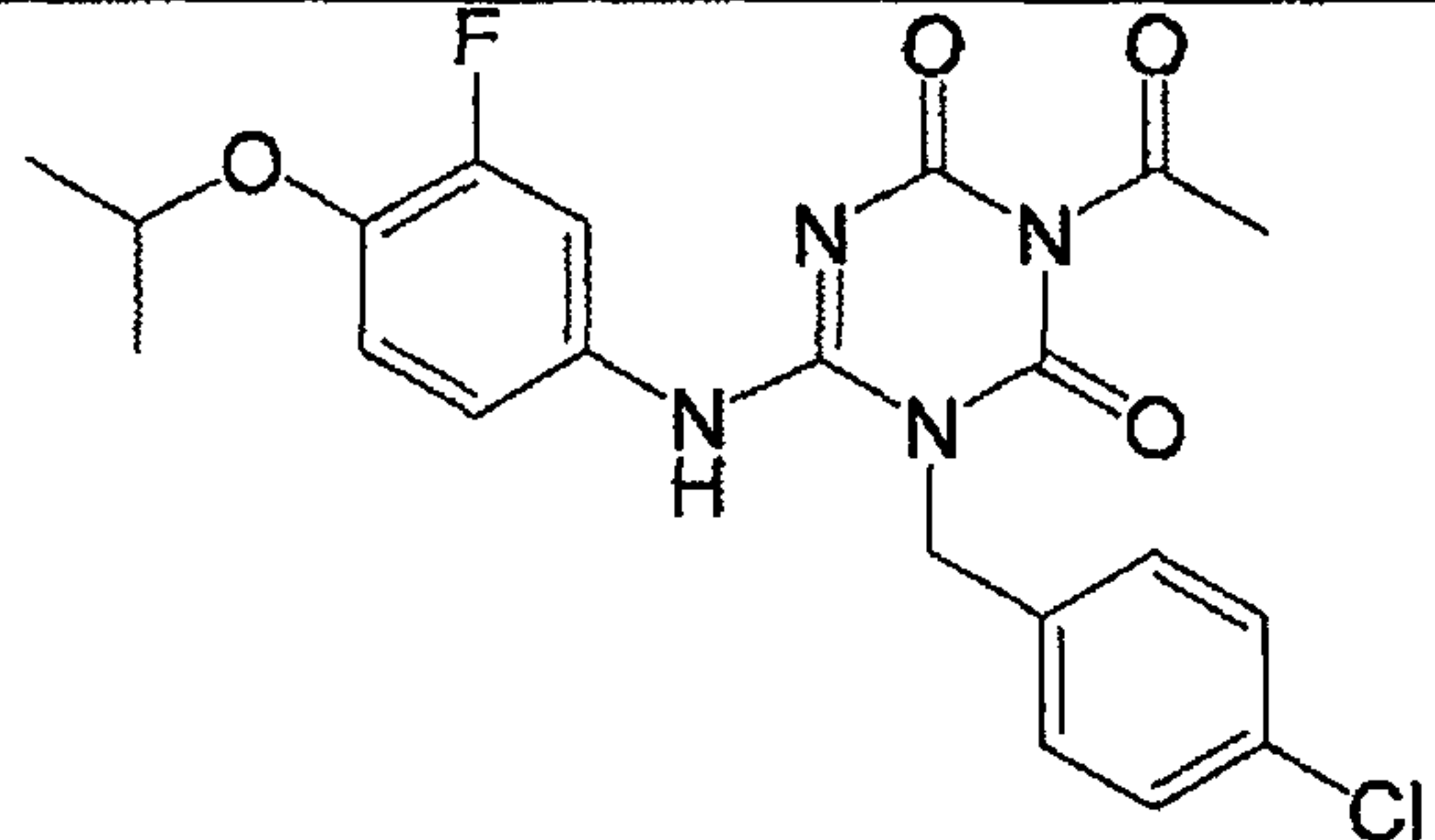
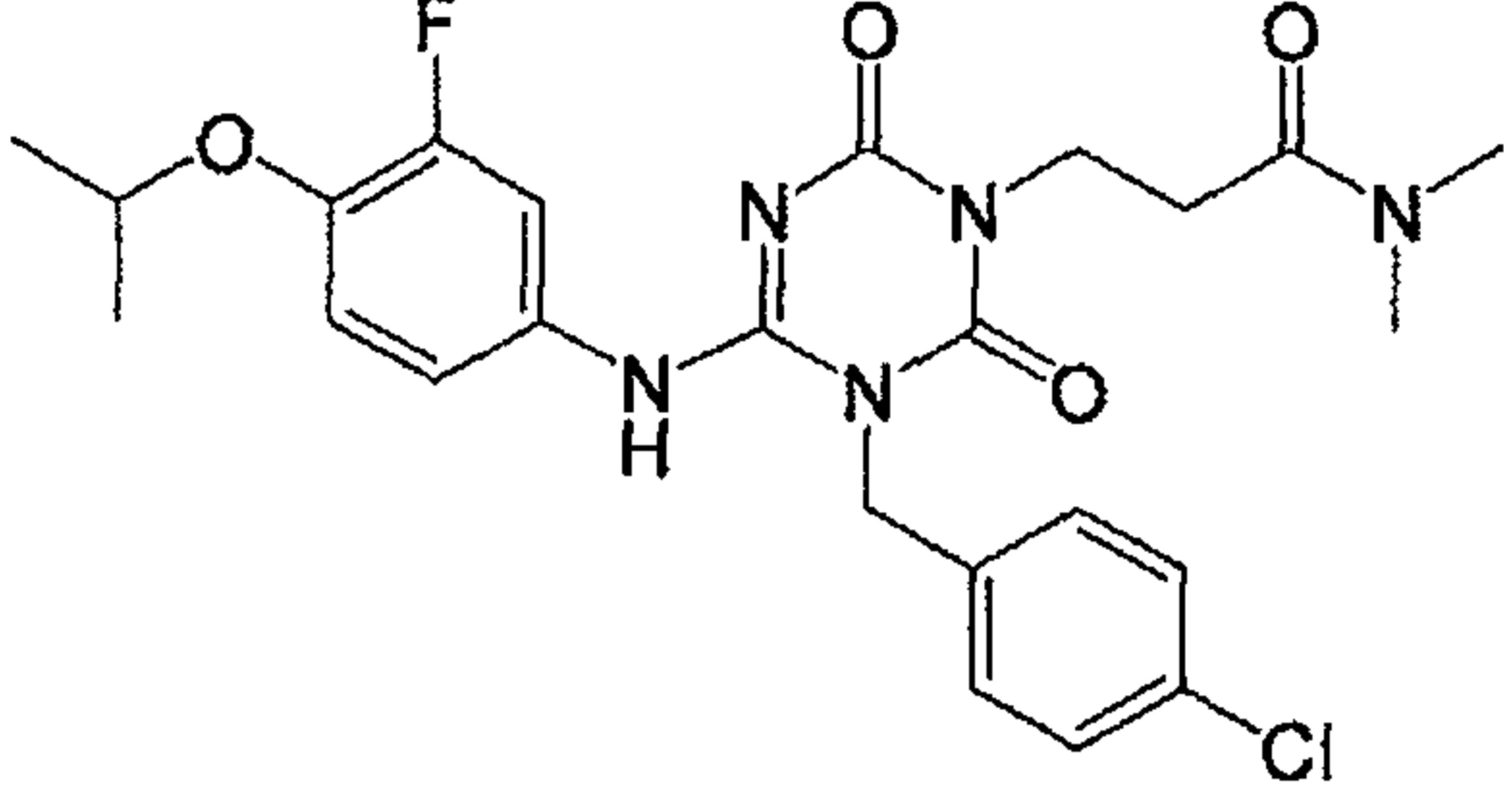
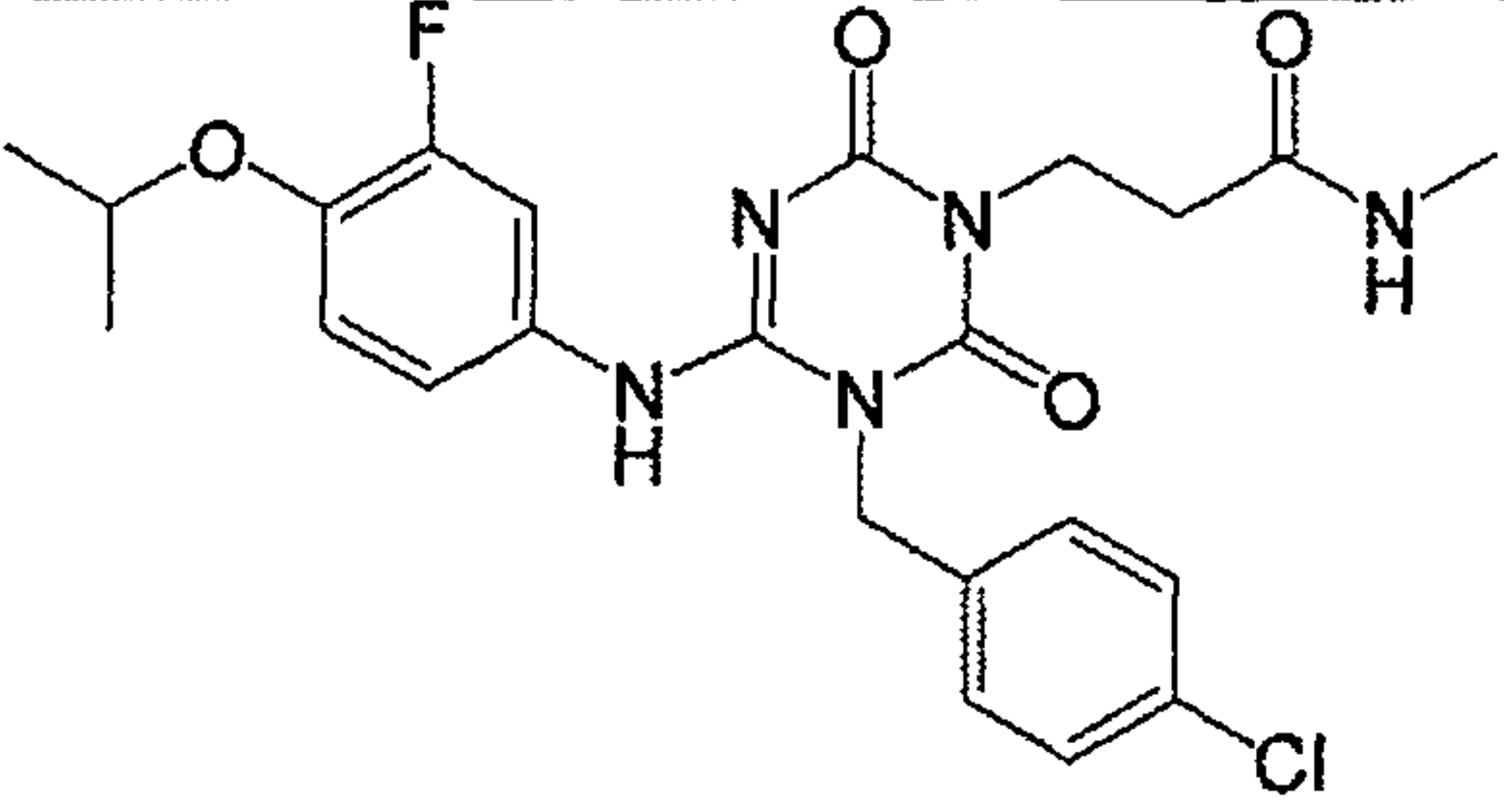
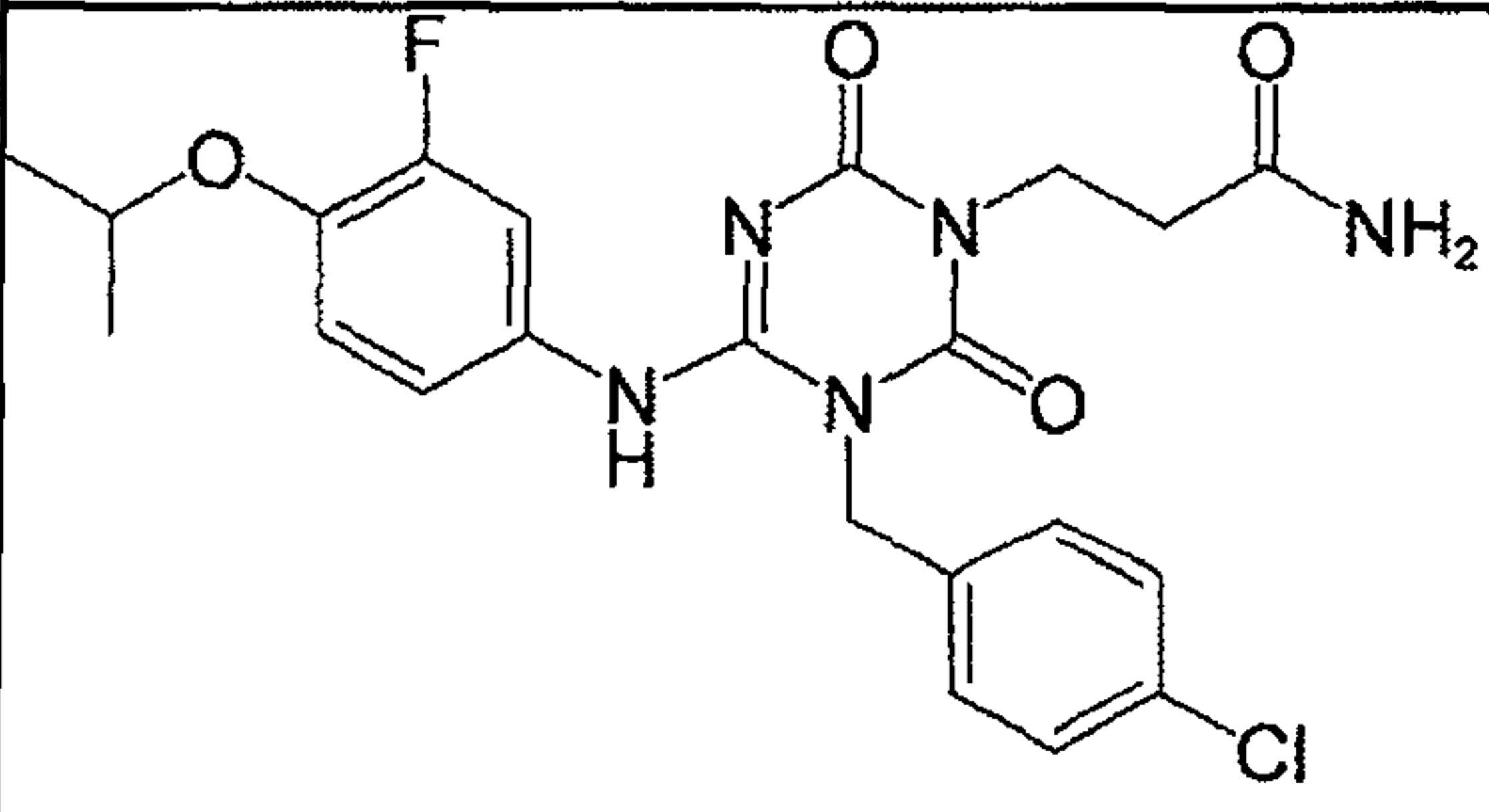
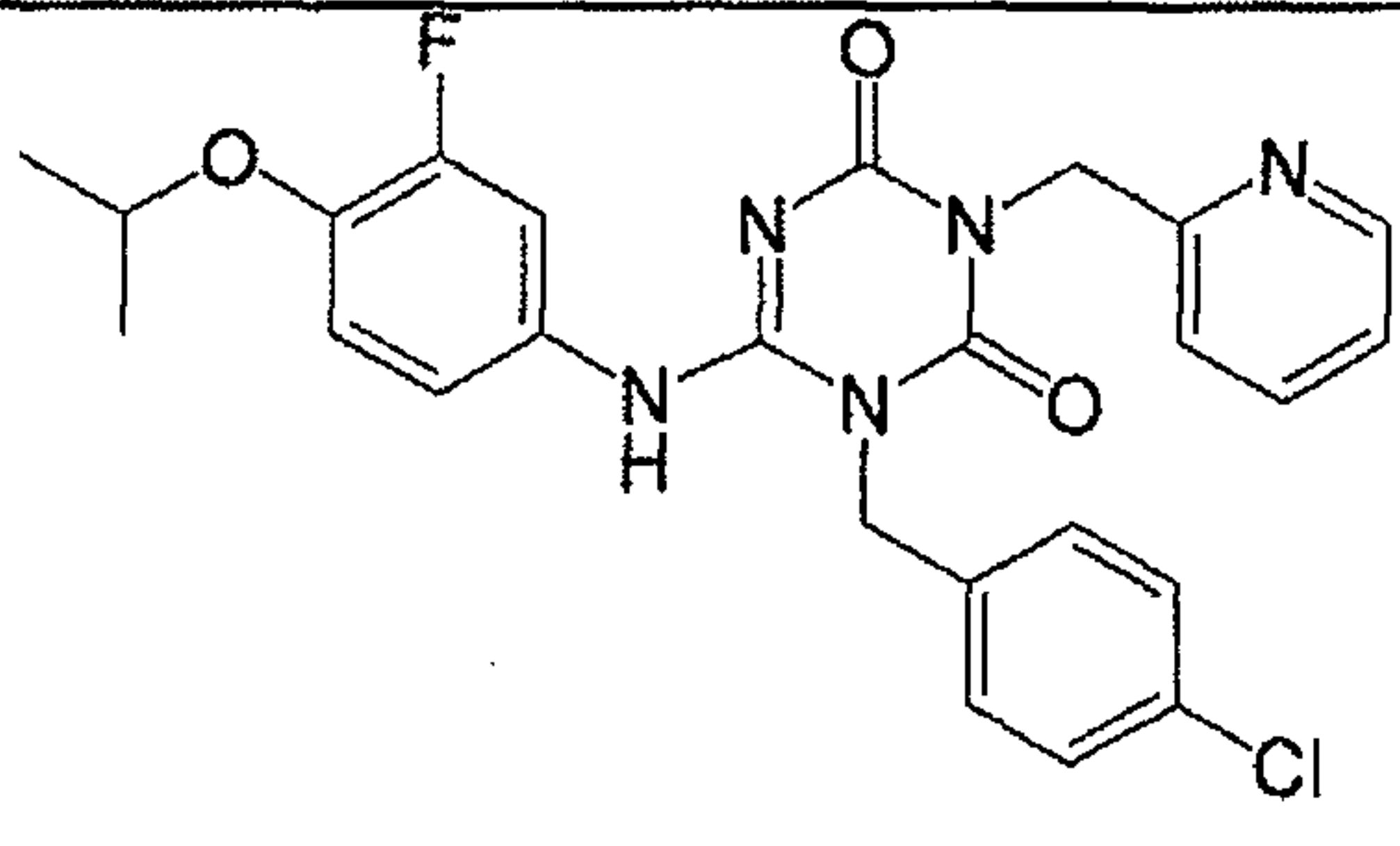
[Table 61]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0286	1.80	479	1
	I-0287	1.30	509	1
	I-0288	2.15	444	1
	I-0289	2.00	477	1
	I-0290	1.40	448	1

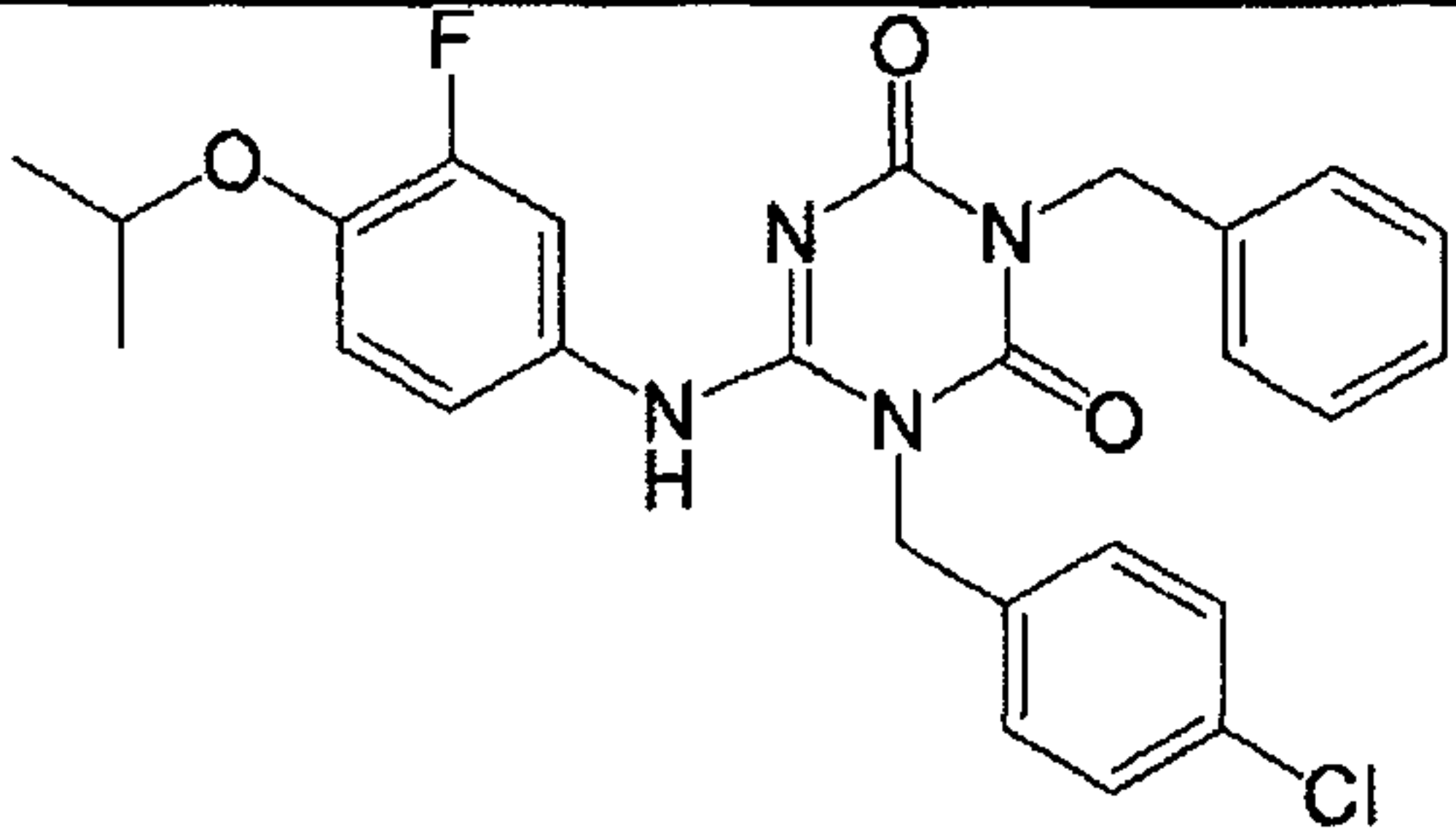
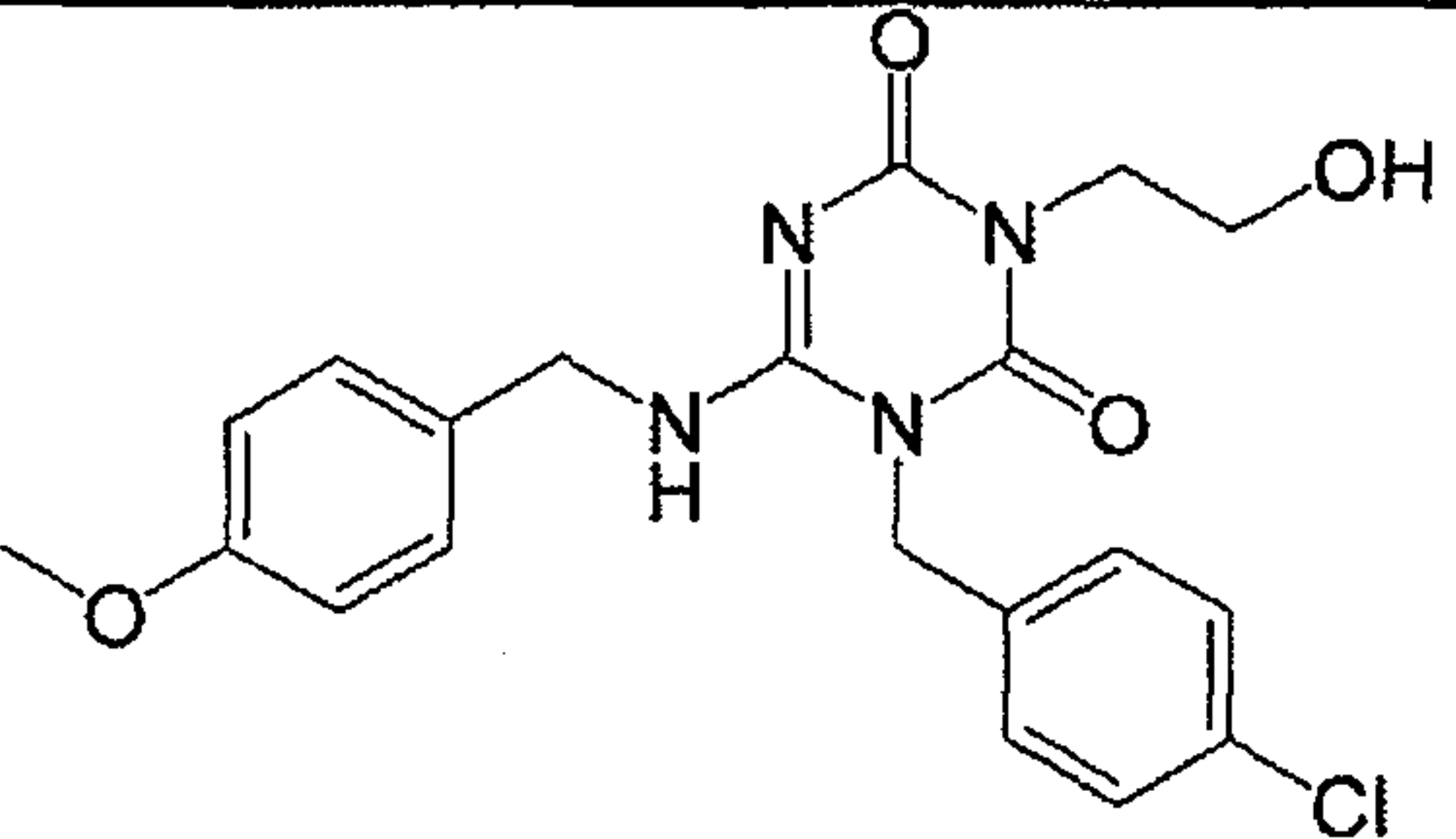
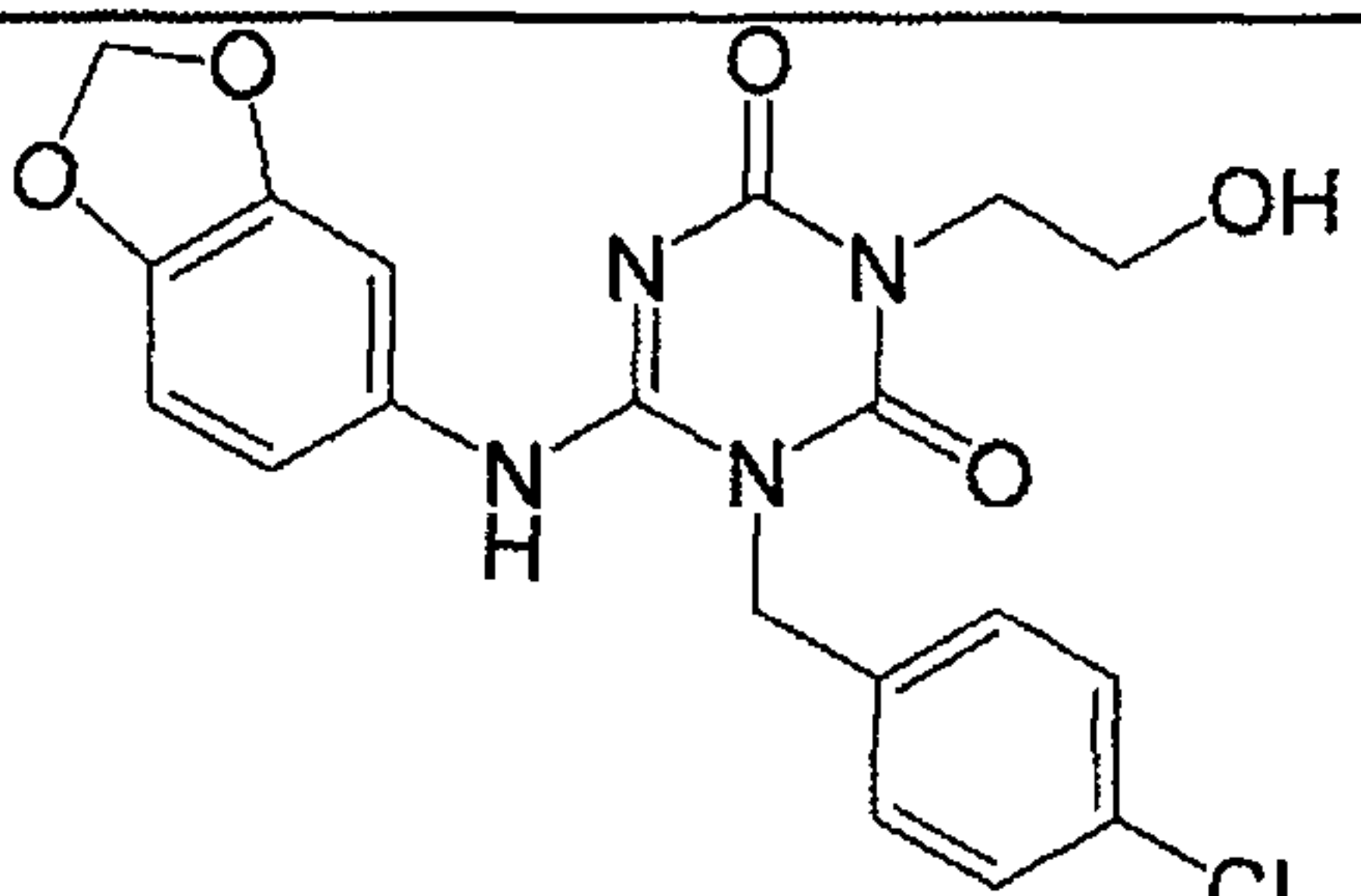
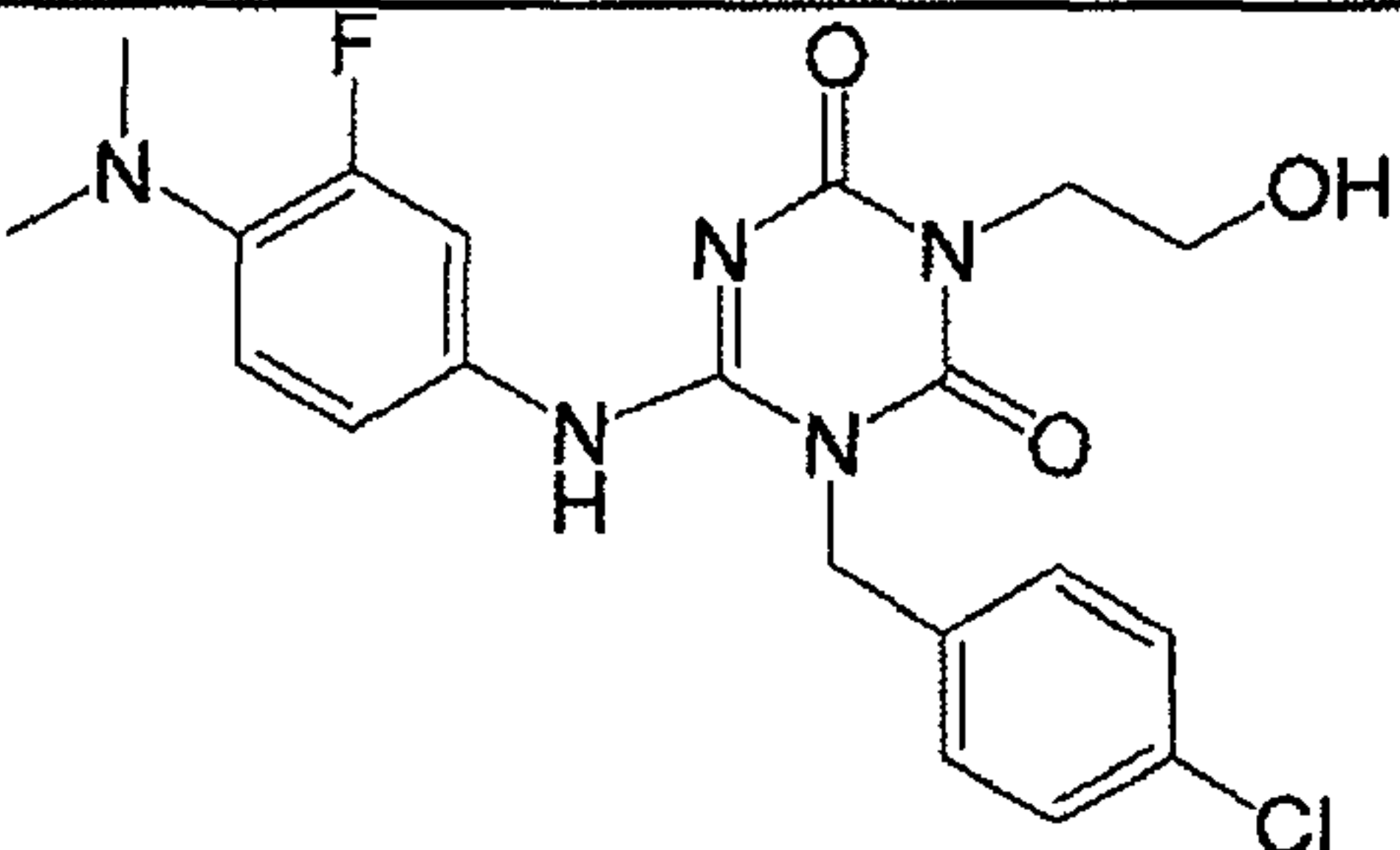
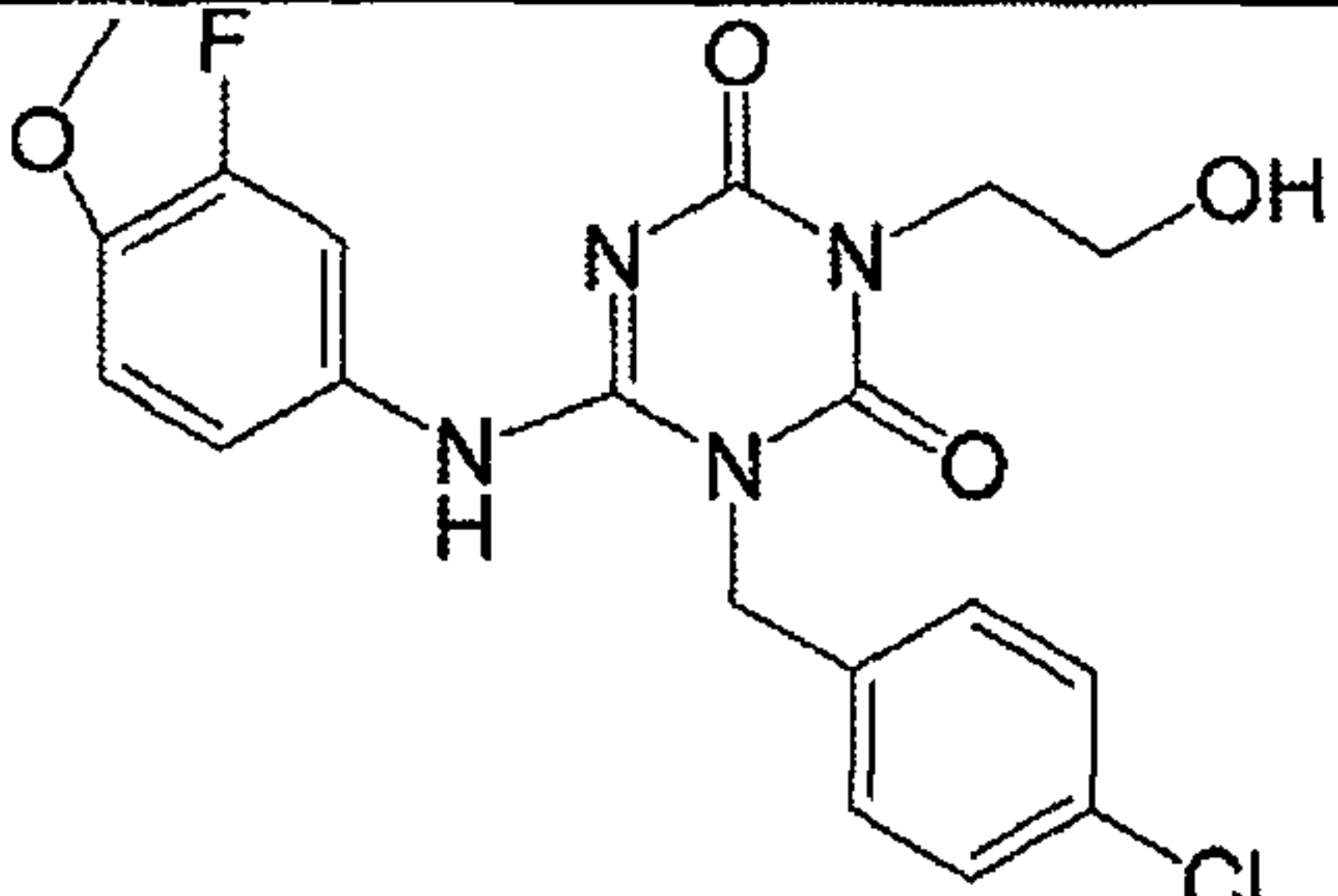
[Table 62]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0291	2.15	458	1
	I-0292	1.90	489	1
	I-0293	2.00	490	1
	I-0294	1.91	476	1
	I-0295	1.85	462	1

[Table 63]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0296	2.18	447	1
	I-0297	2.04	504	1
	I-0298	1.90	490	1
	I-0299	1.86	476	1
	I-0300	2.06	496	1

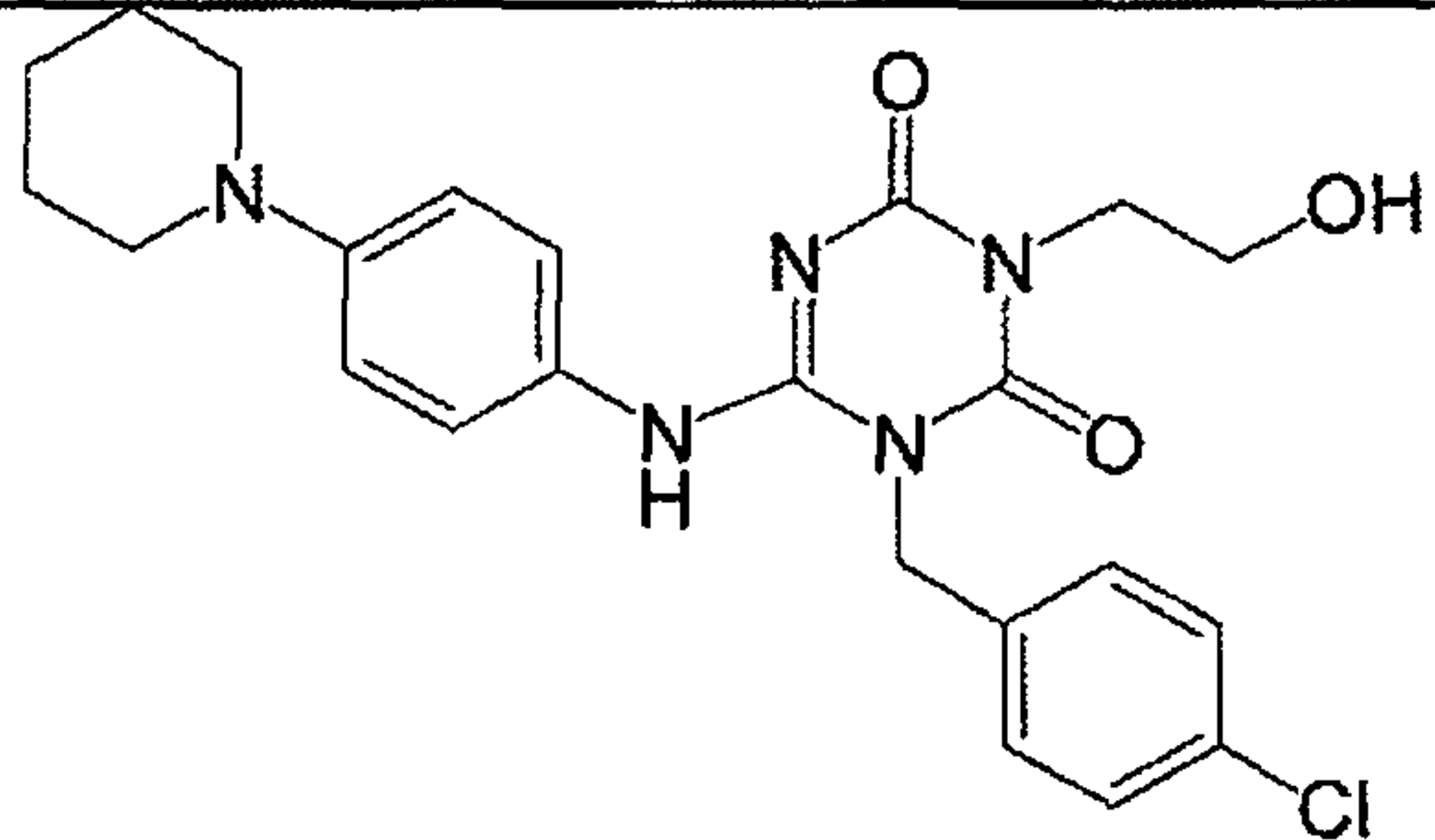
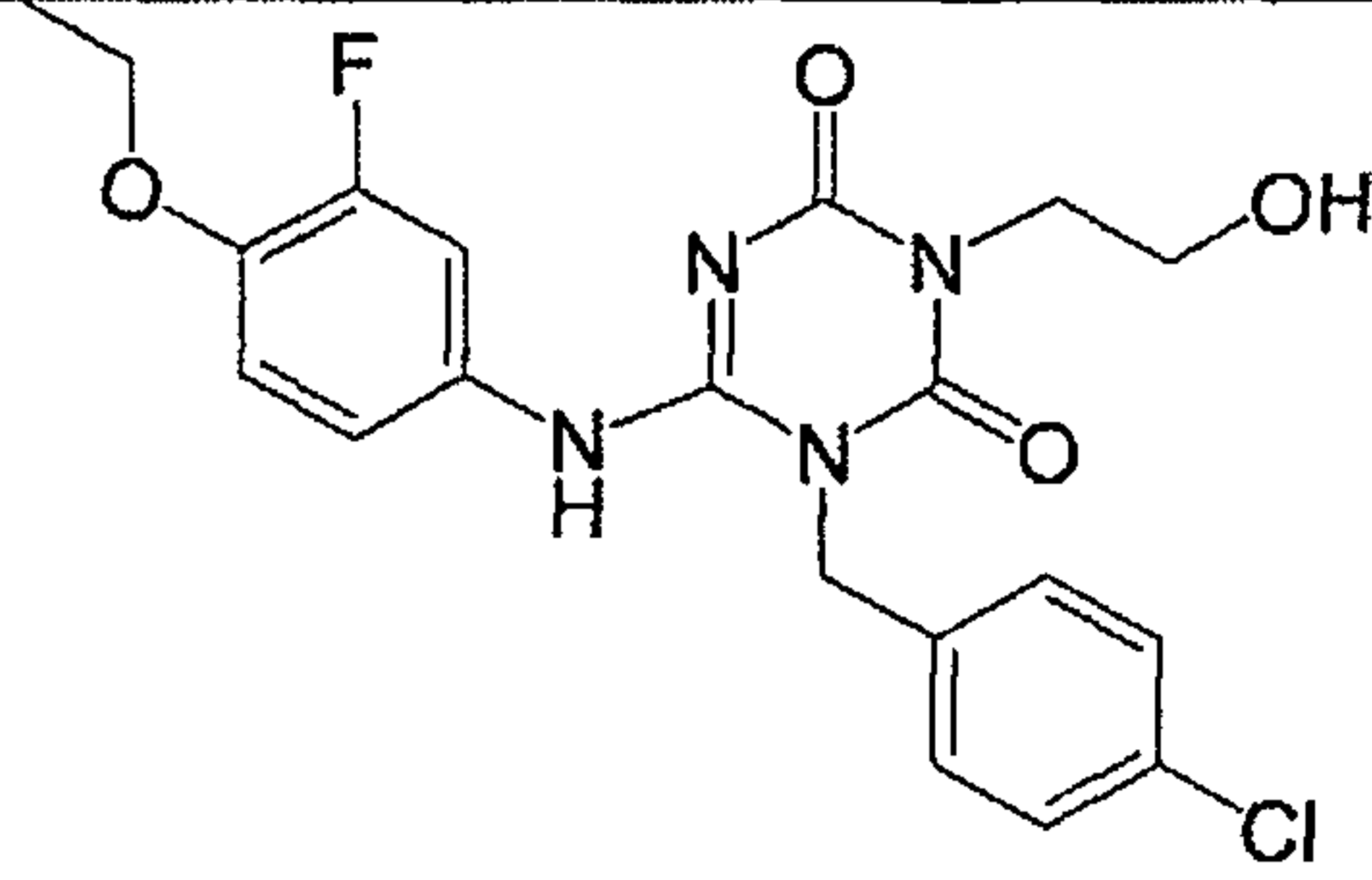
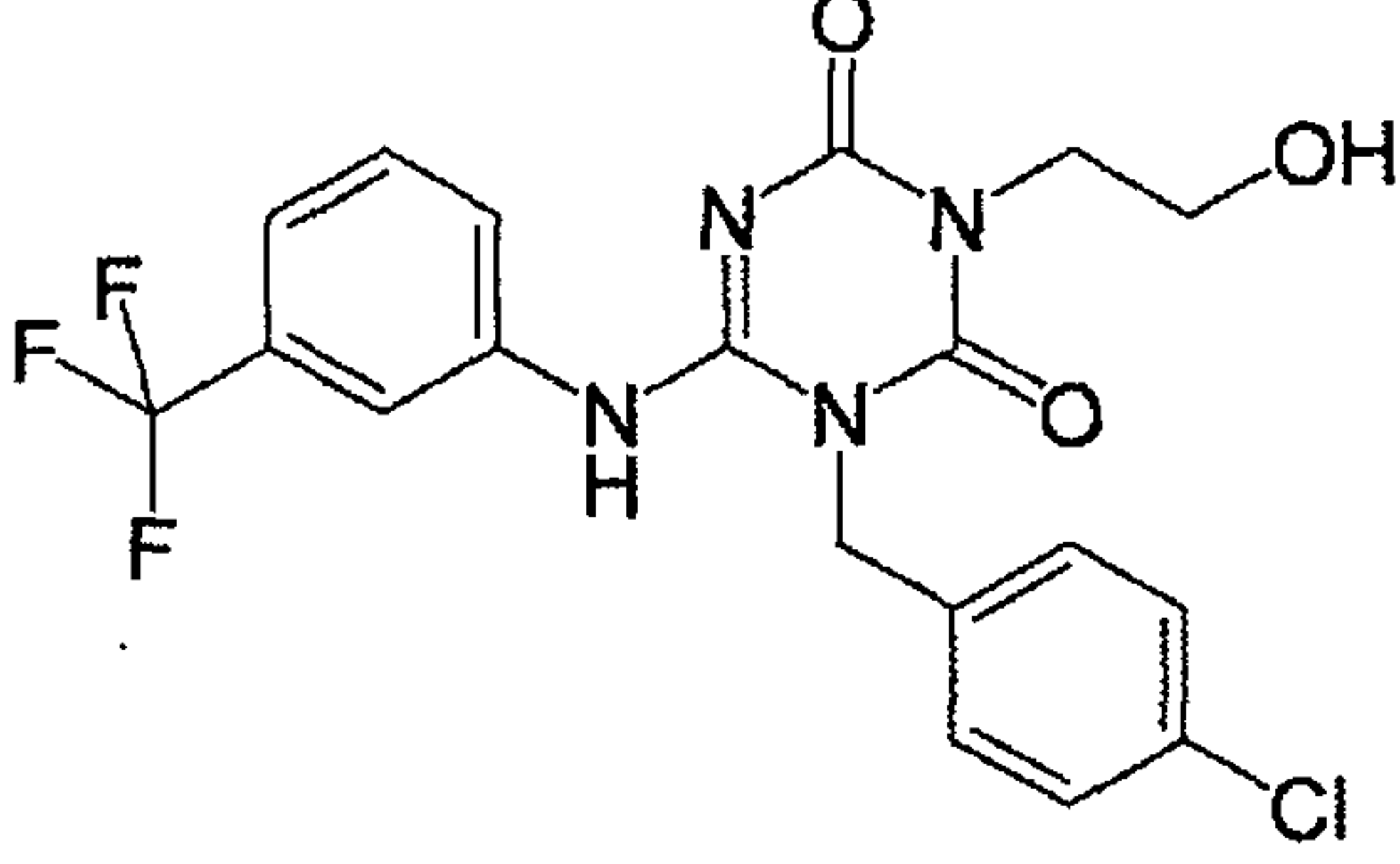
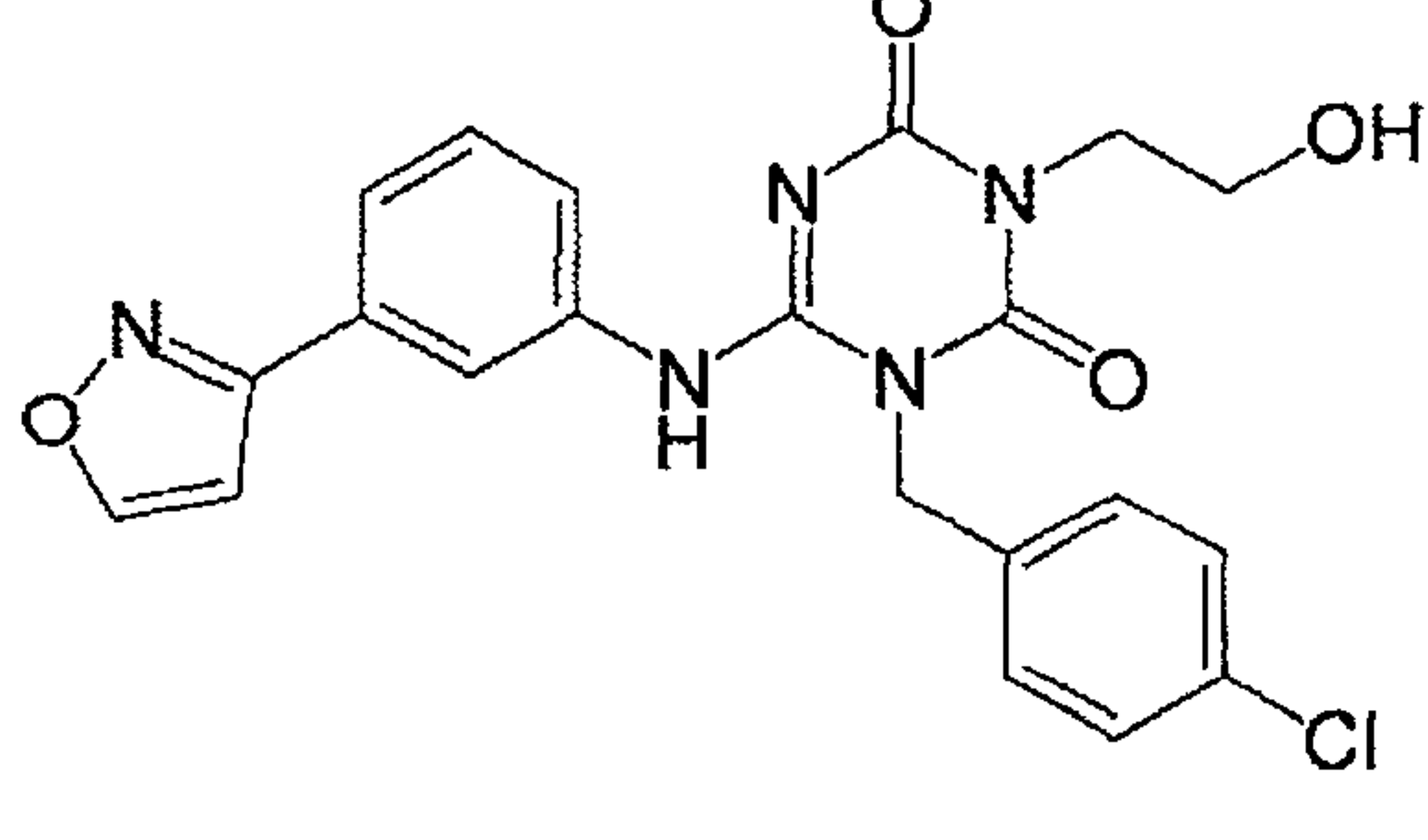
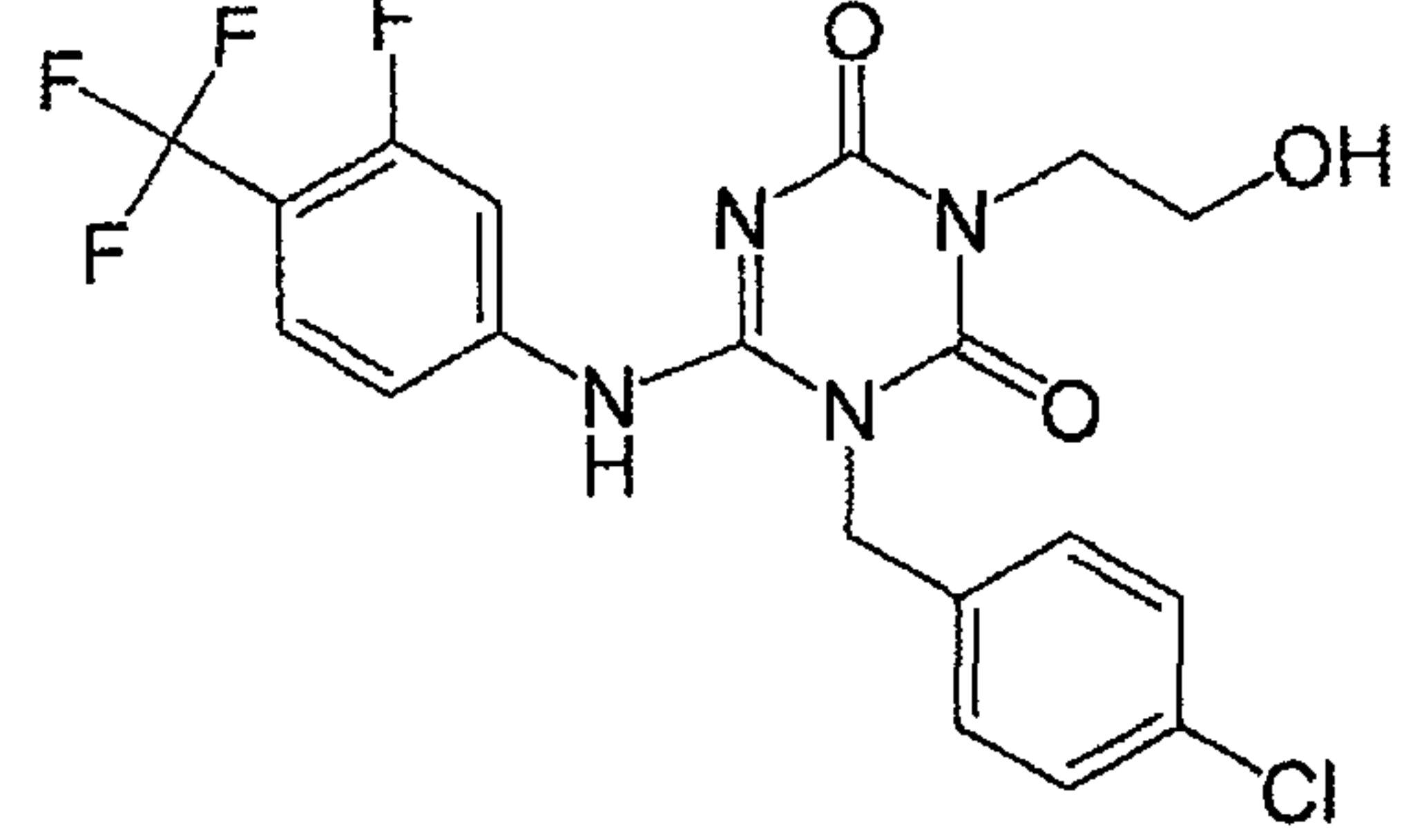
[Table 64]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0301	2.53	495	1
	I-0302	1.50	417	1
	I-0303	1.60	417	1
	I-0304	1.50	434	1
	I-0305	1.69	421	1

[Table 65]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0306	1.11	444	1
	I-0307	1.72	417	1
	I-0308	1.80	391	1
	I-0309	2.09	457	1
	I-0310	2.21	455	1

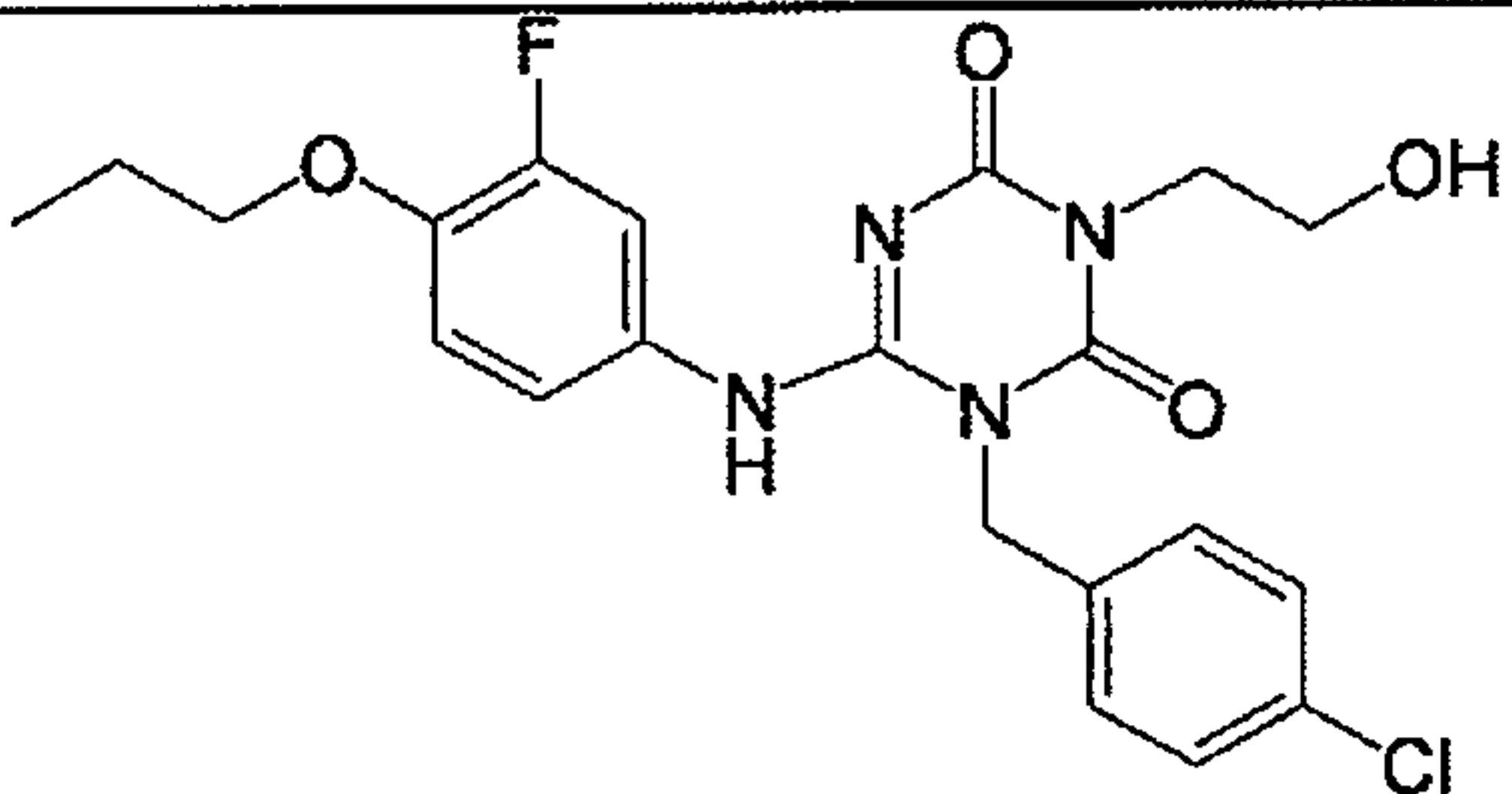
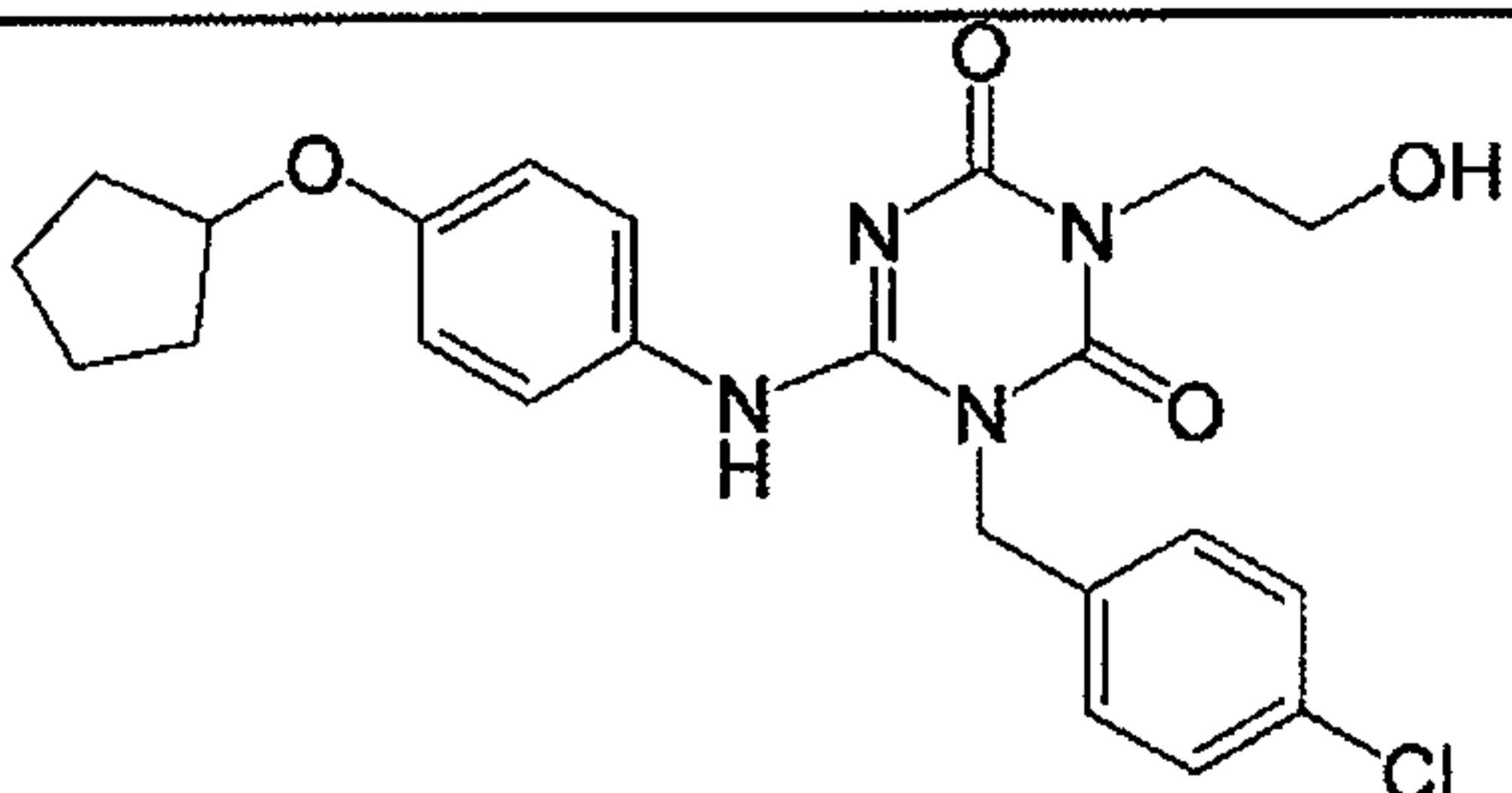
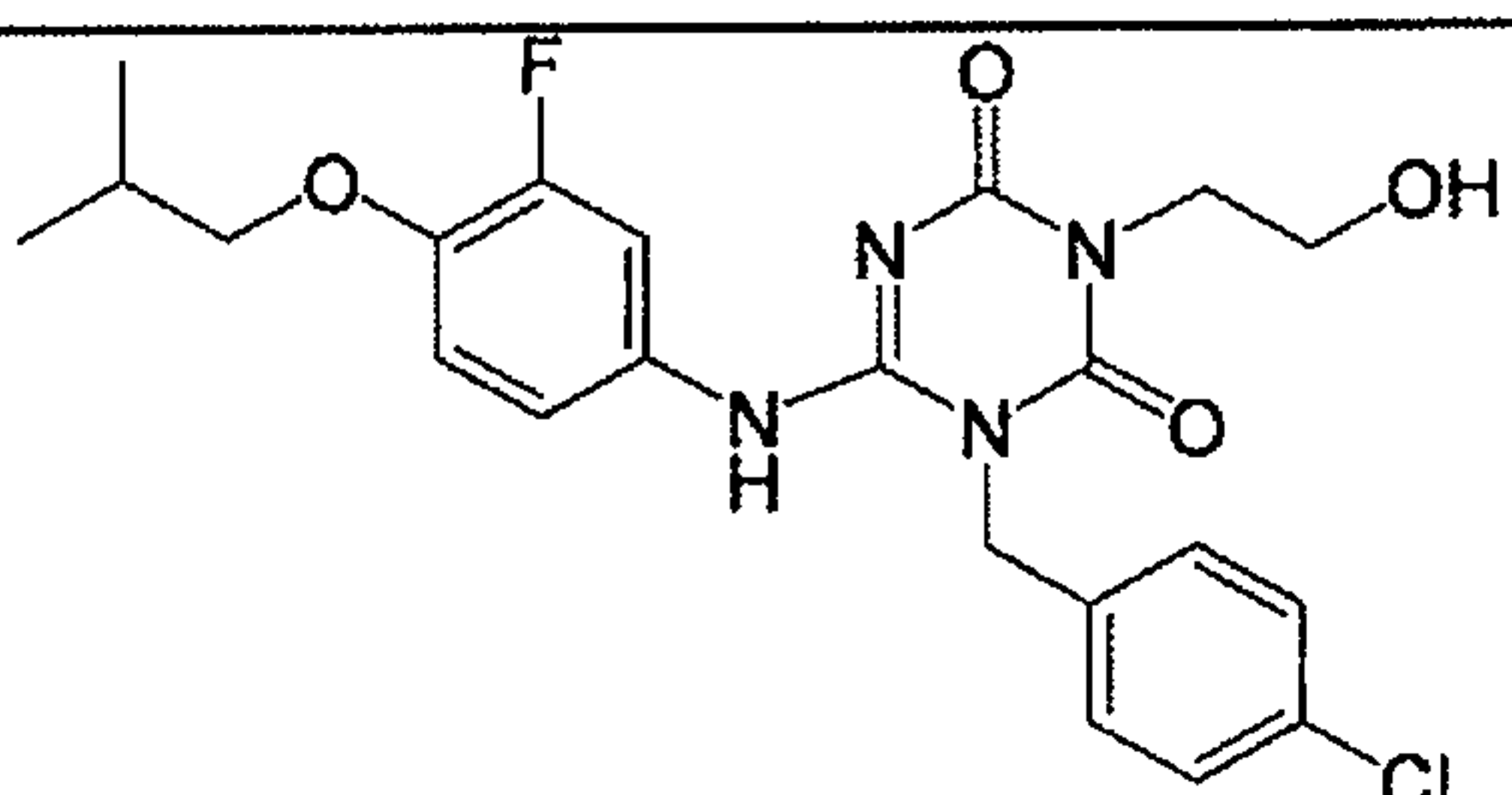
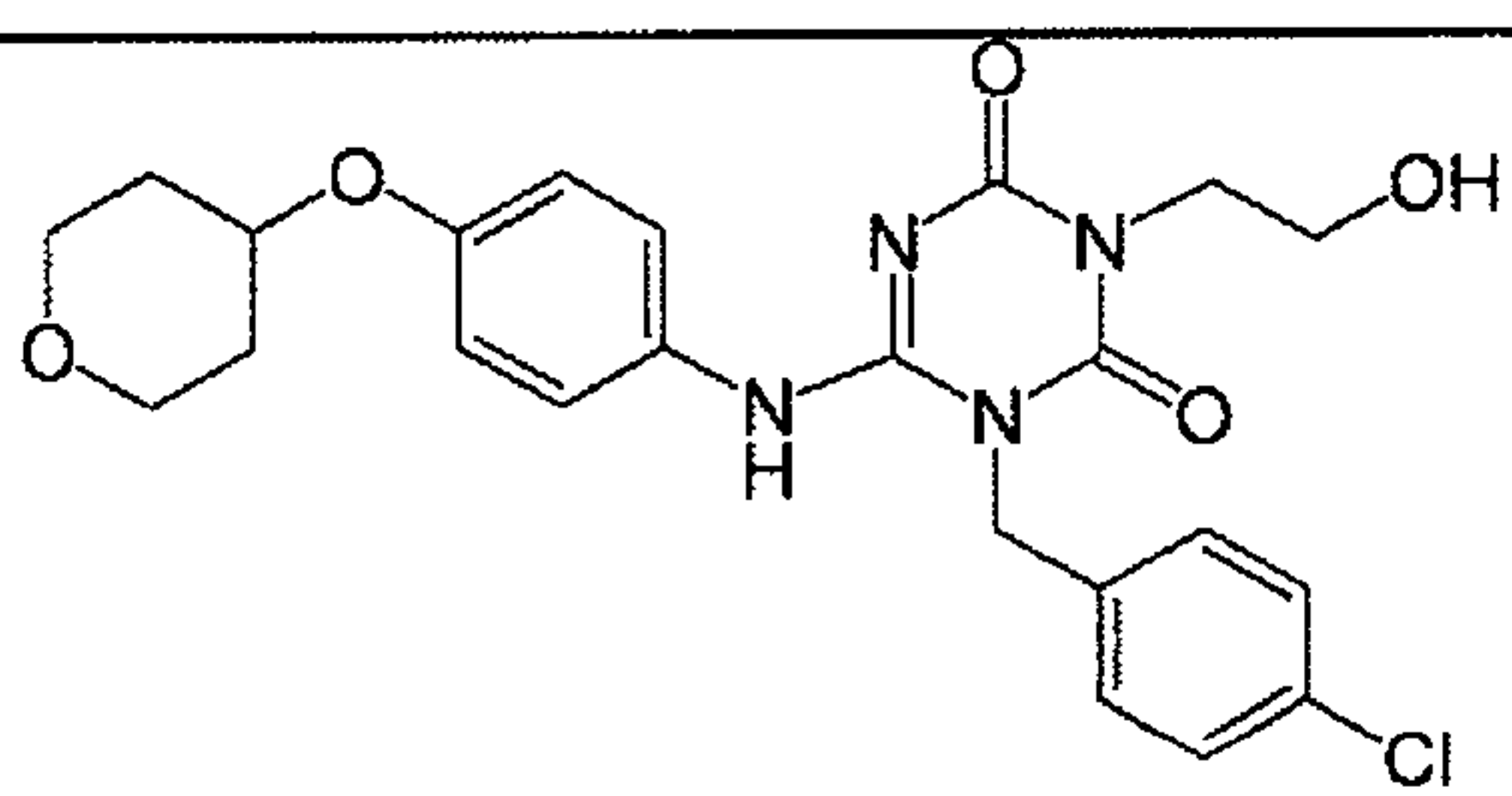
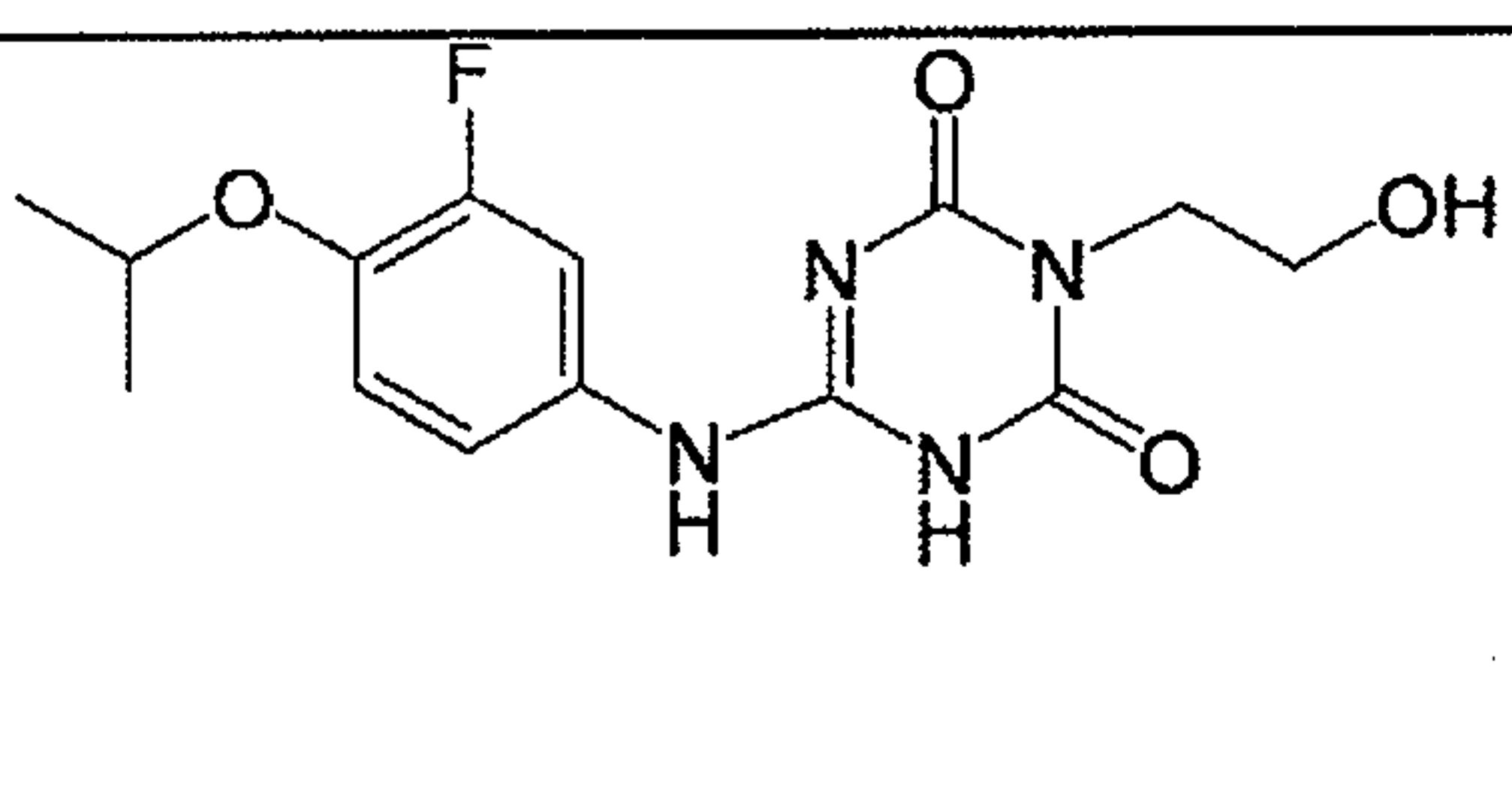
[Table 66]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0311	1.14	456	1
	I-0312	1.83	435	1
	I-0313	2.00	441	2
	I-0314	1.70	440	2
	I-0315	2.09	459	2

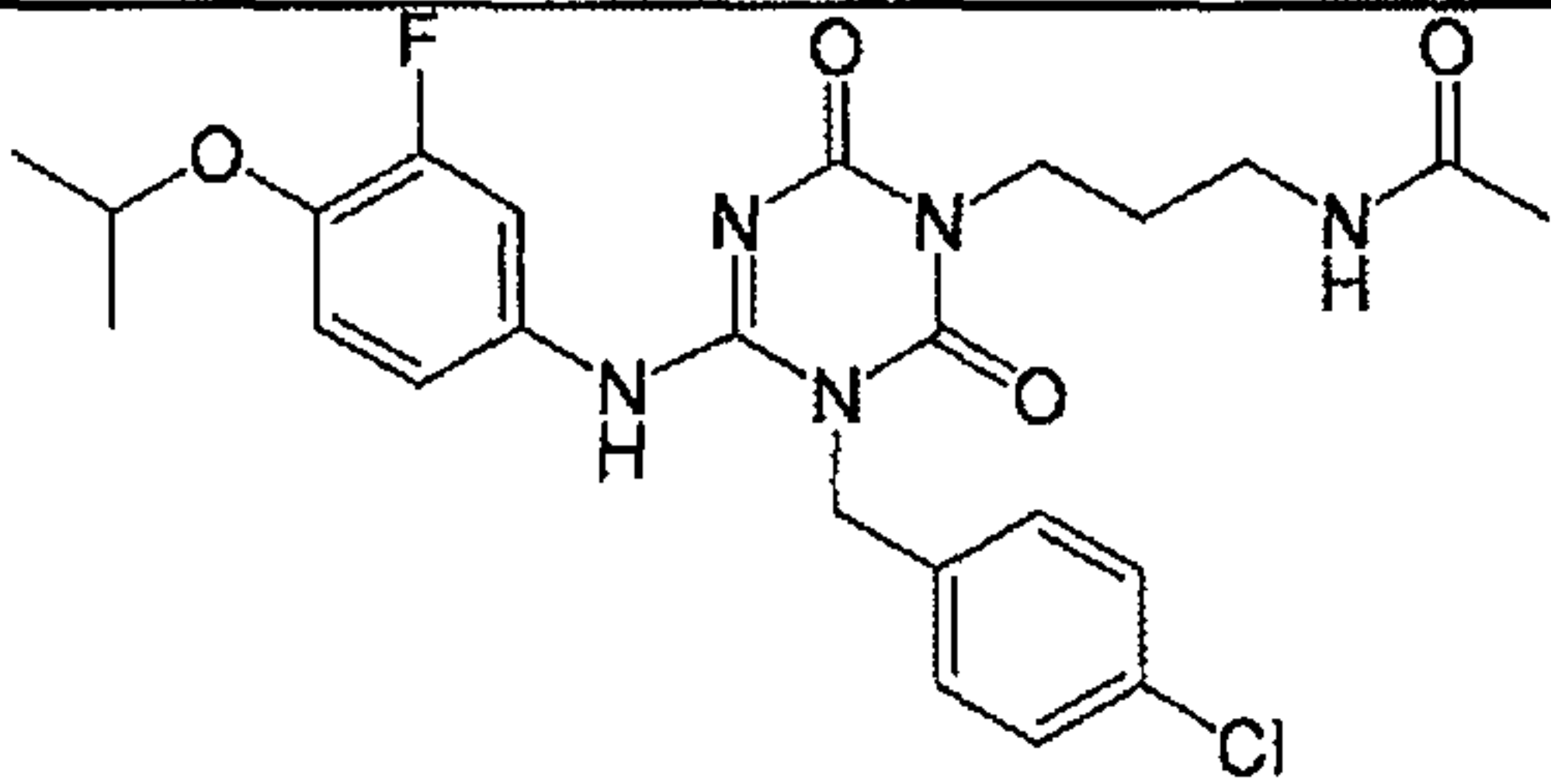
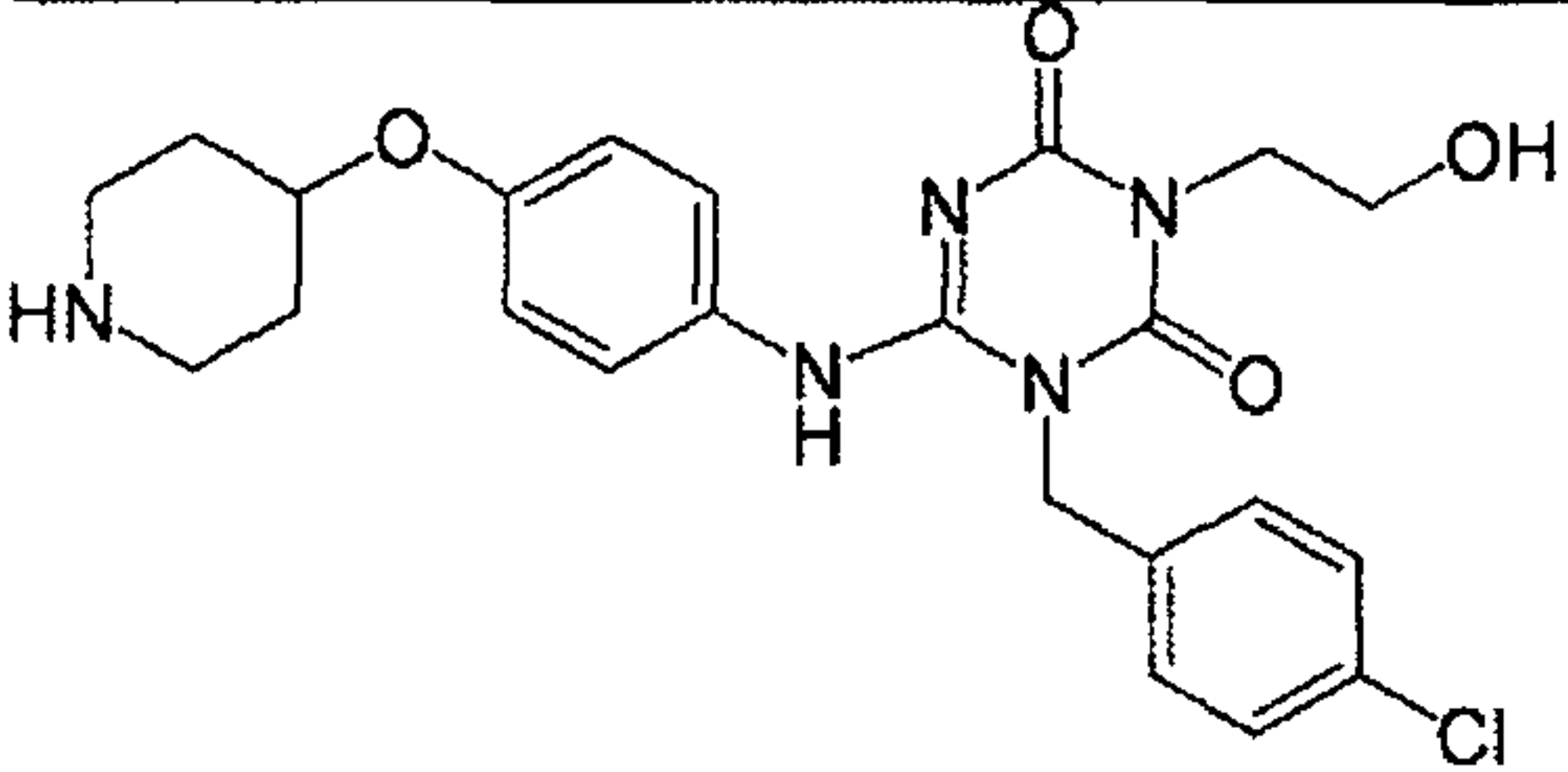
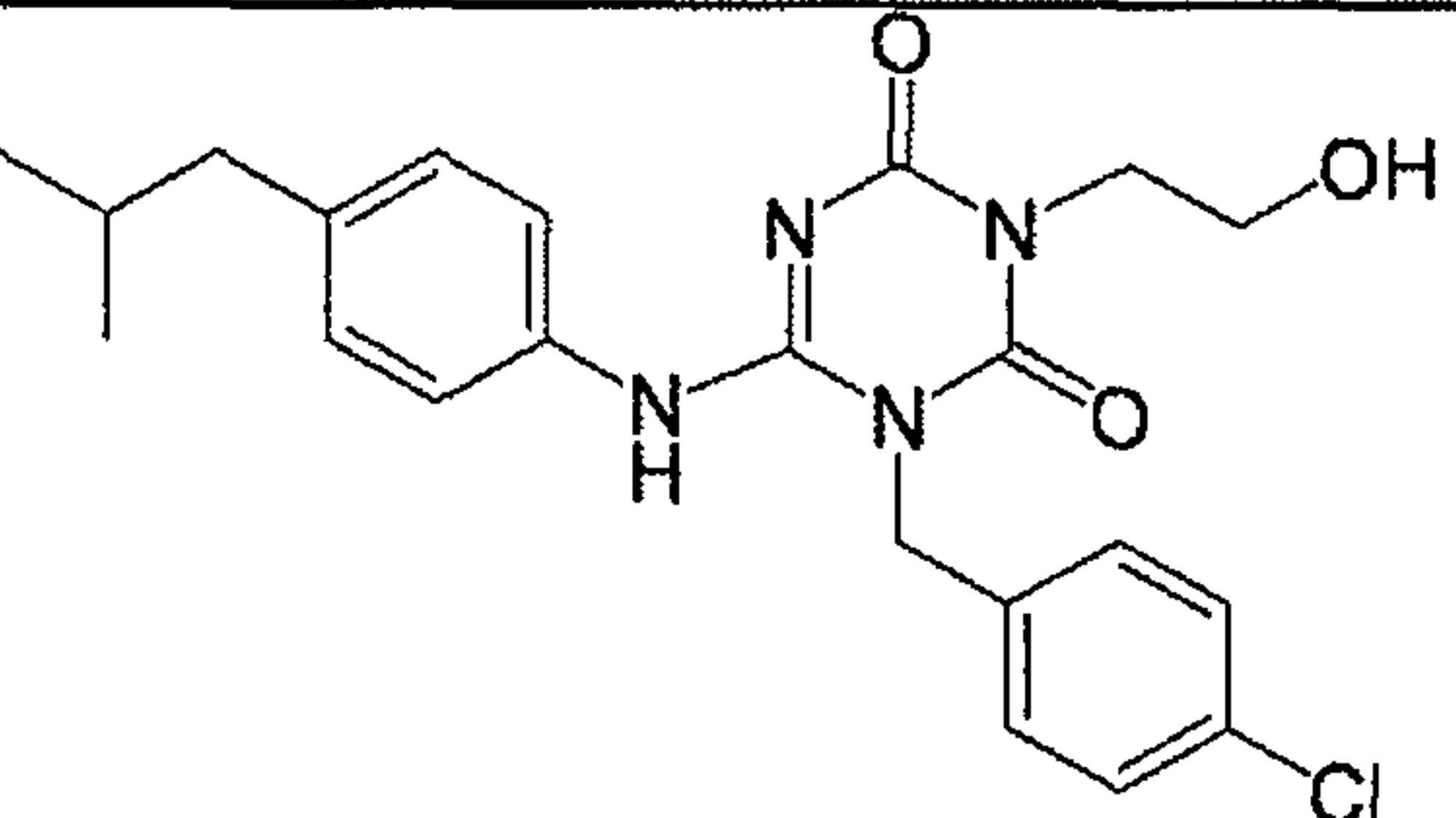
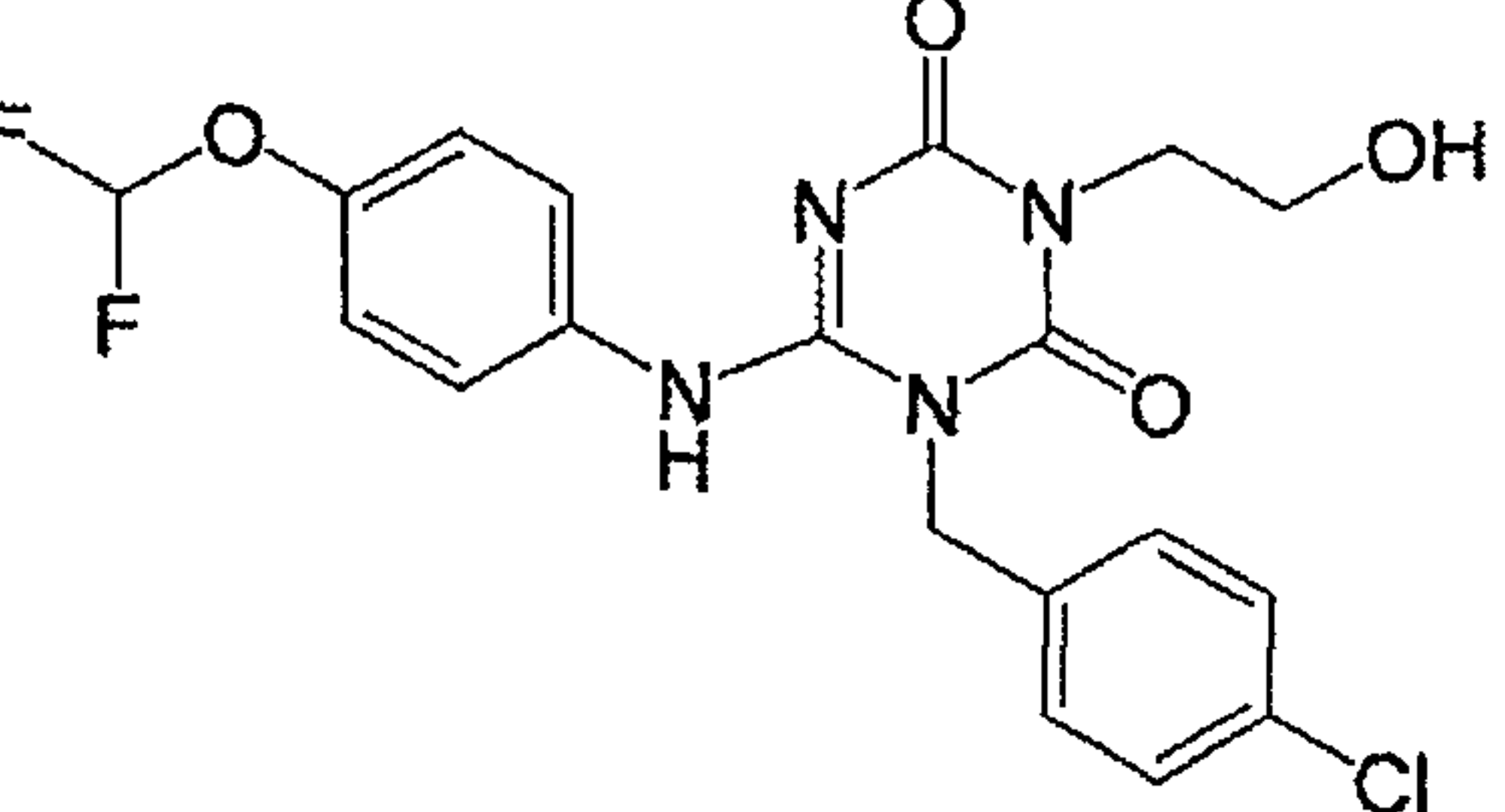
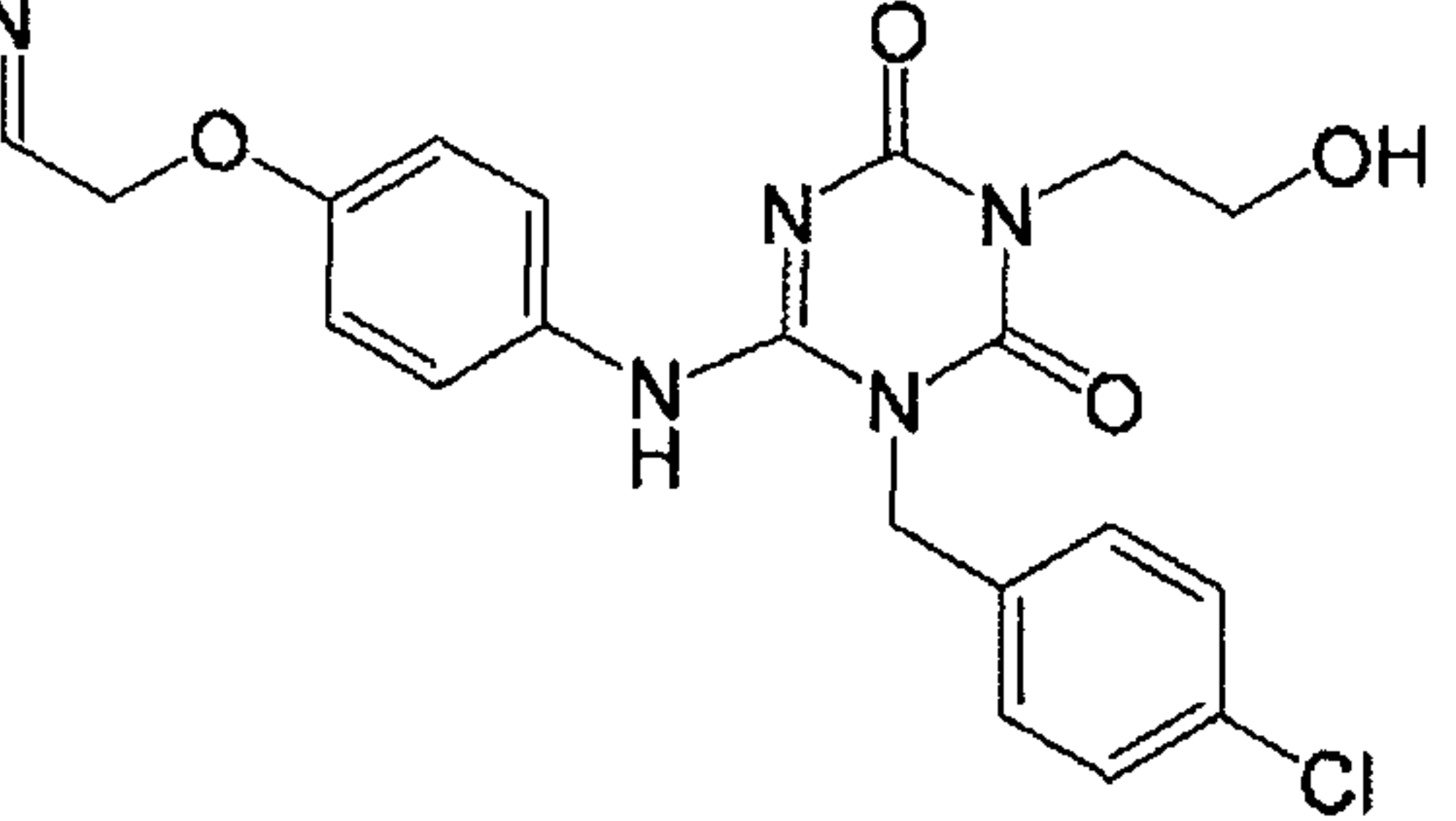
[Table 67]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0316	1.84	409	2
	I-0317	1.40	462	2
	I-0318	2.01	415	2
	I-0319	1.68	379	2
	I-0320	1.83	431	2

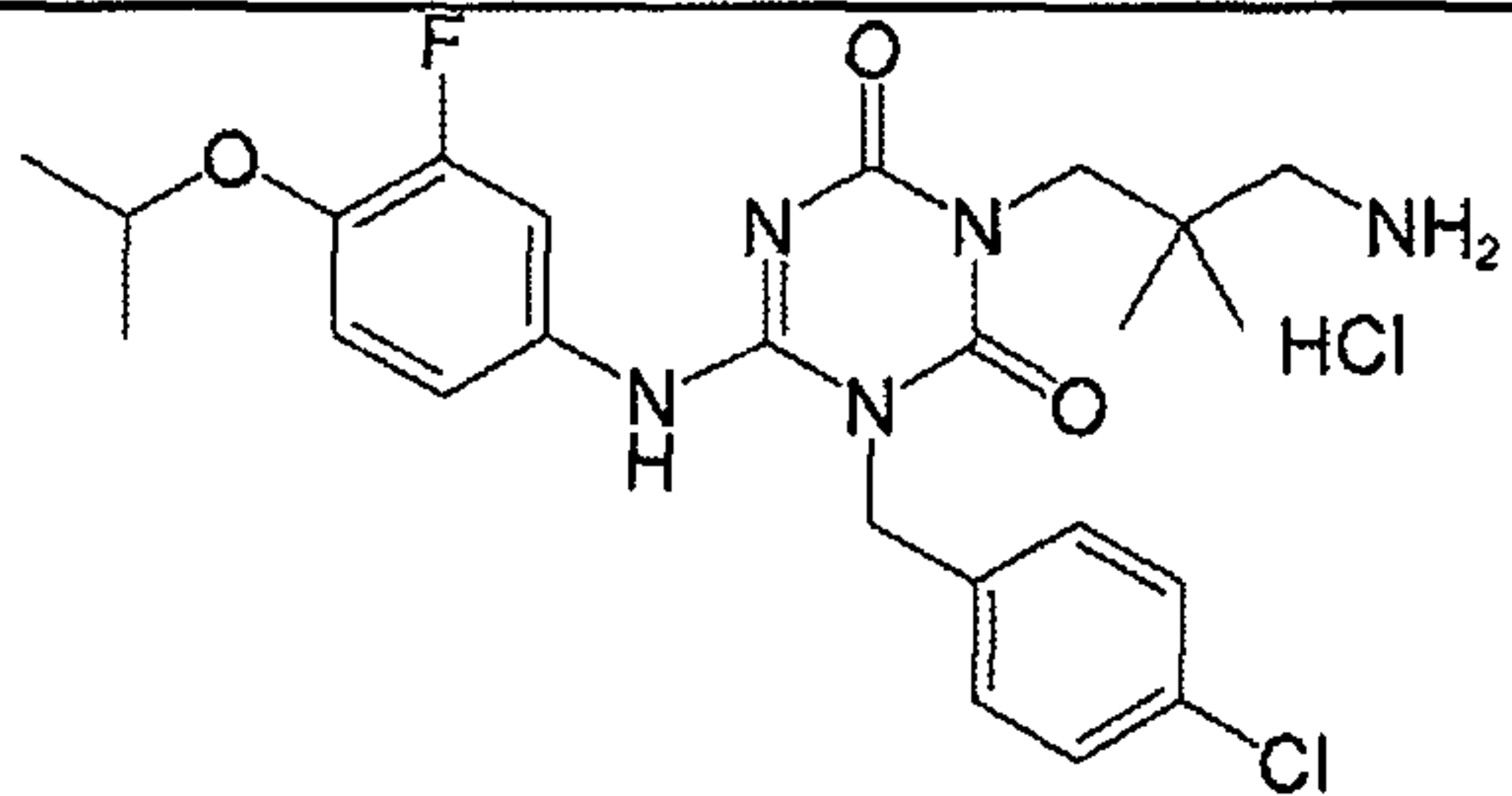
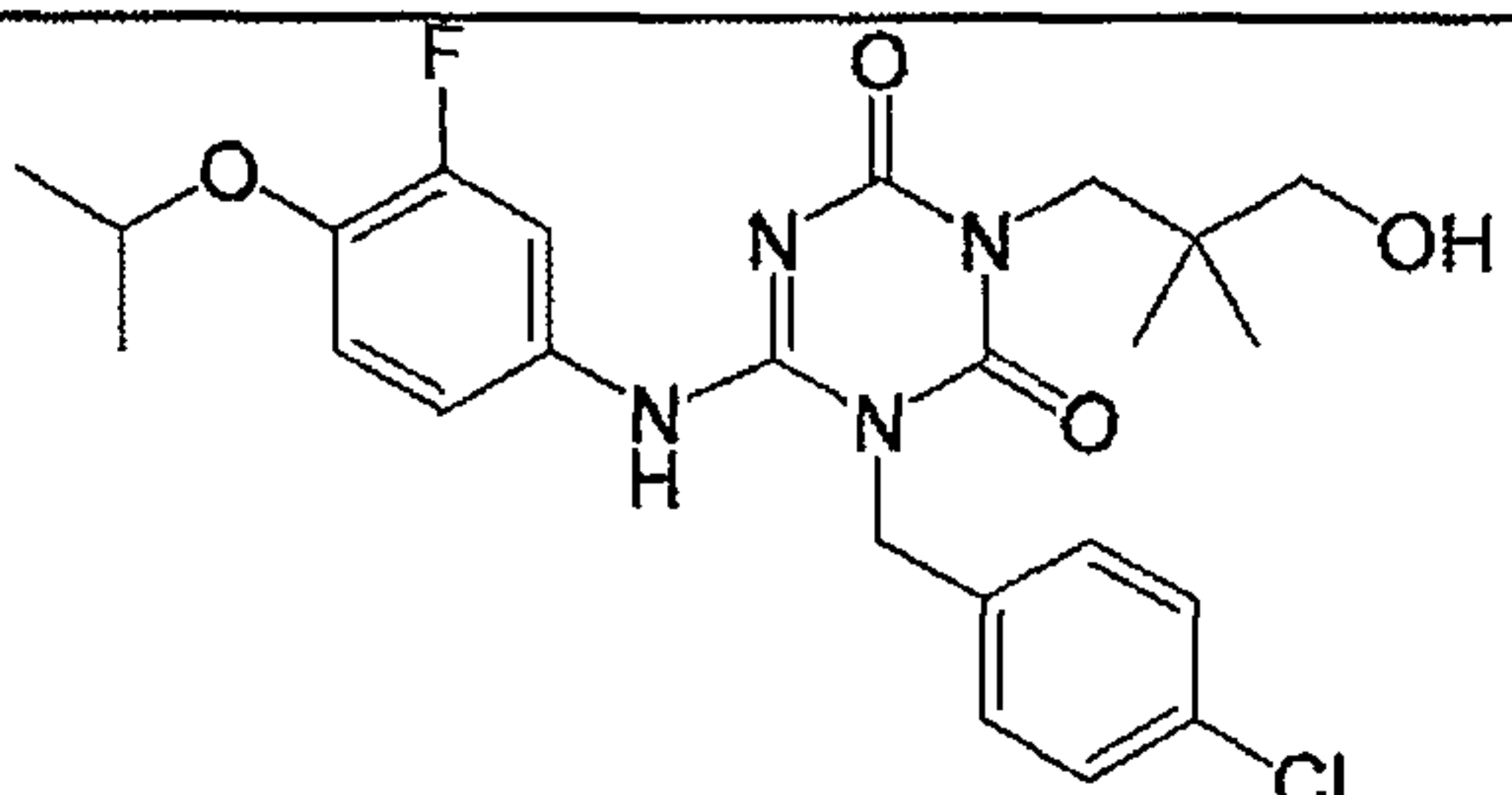
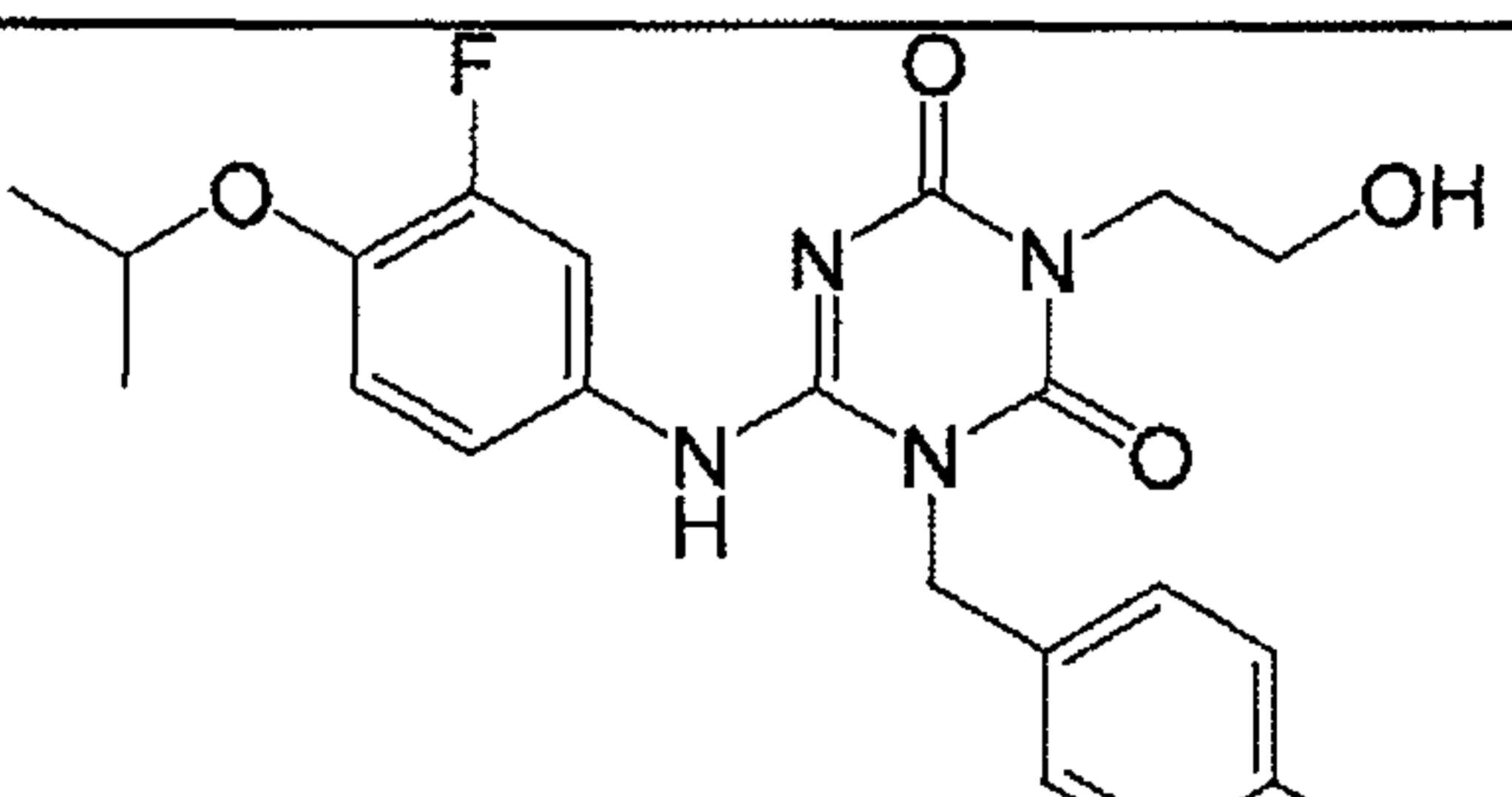
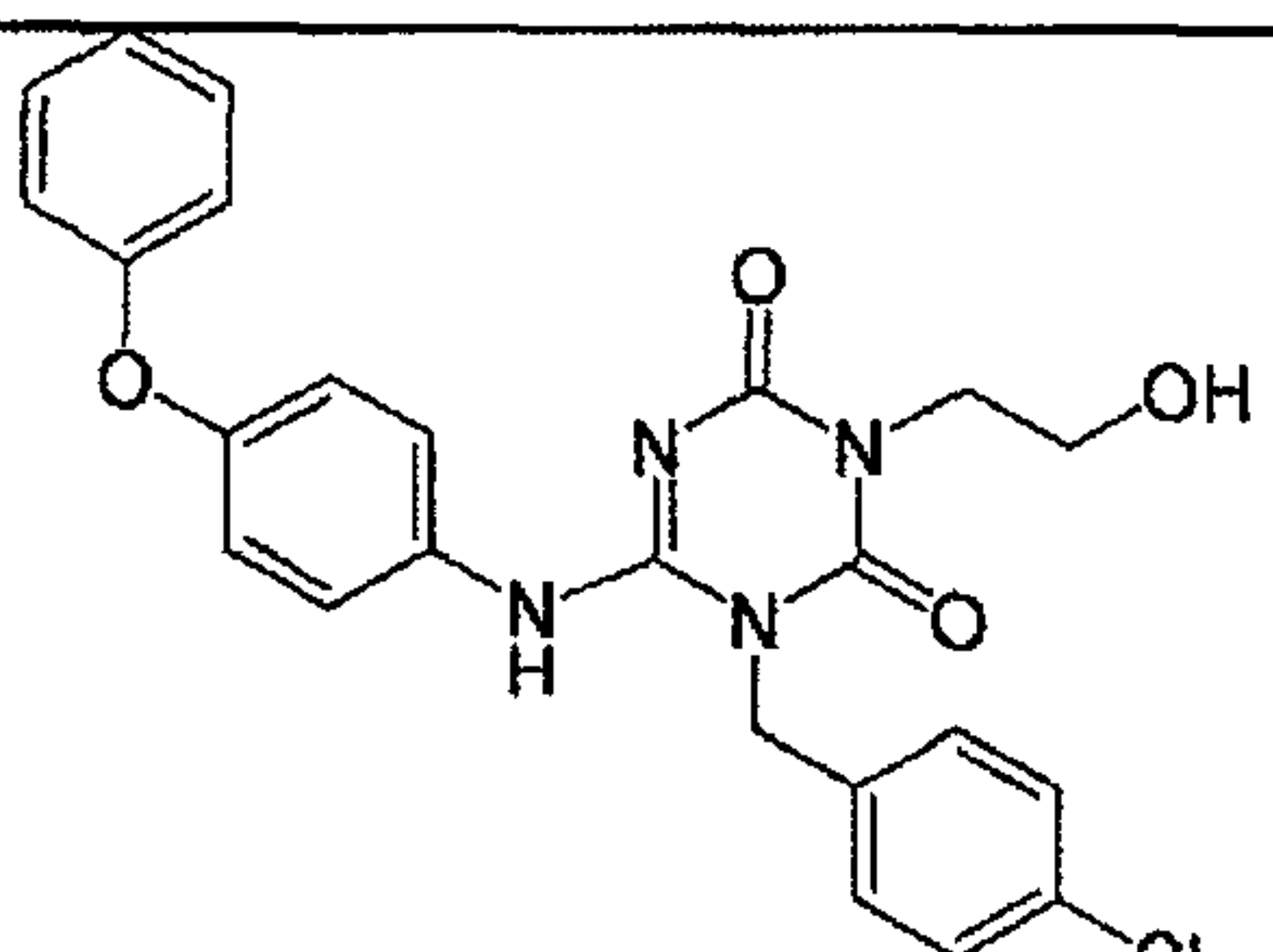
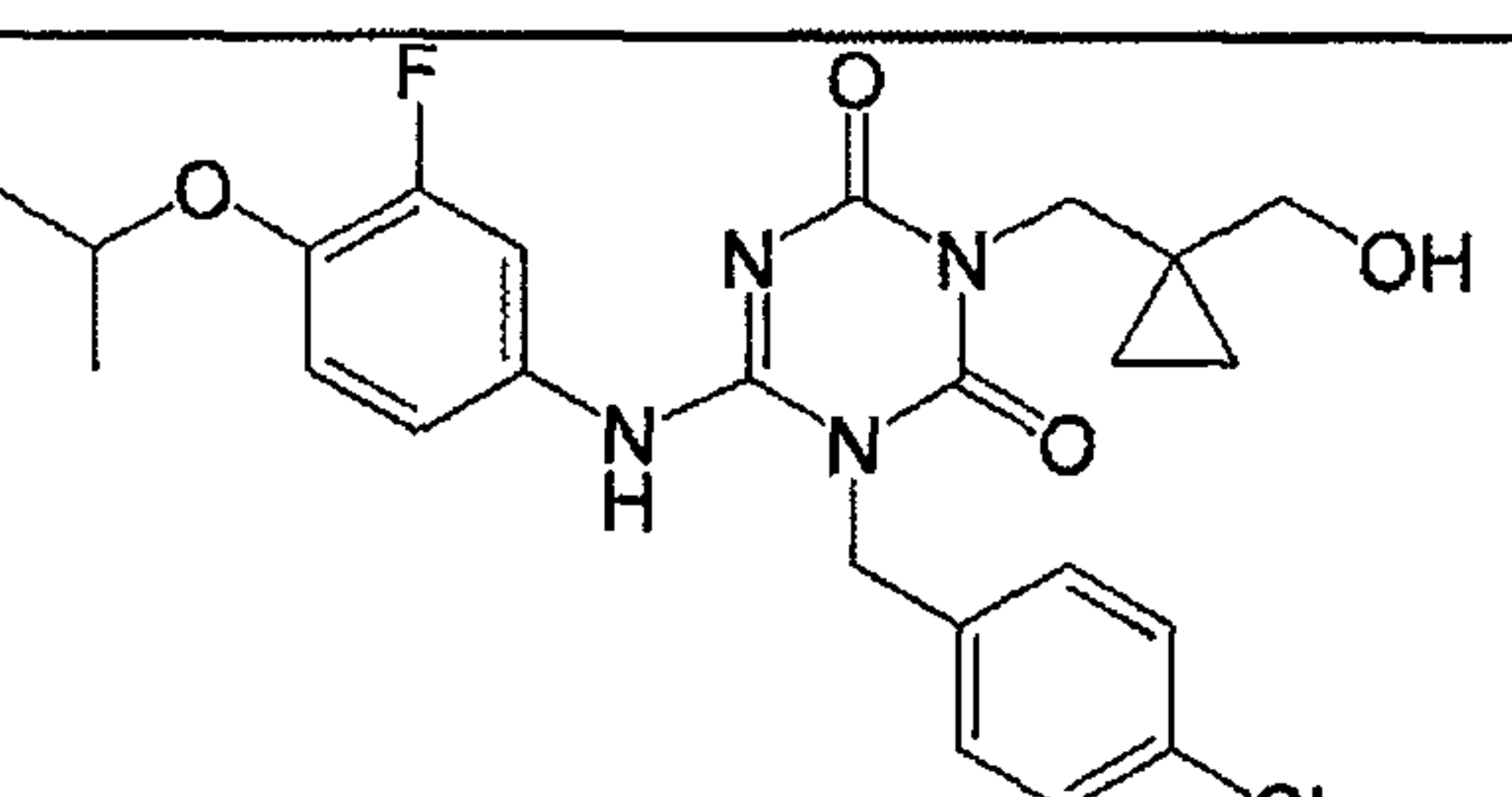
[Table 68]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0321	1.99	449	2
	I-0322	2.03	457	2
	I-0323	2.16	463	2
	I-0324	1.61	473	2
	I-0325	1.10	325	2

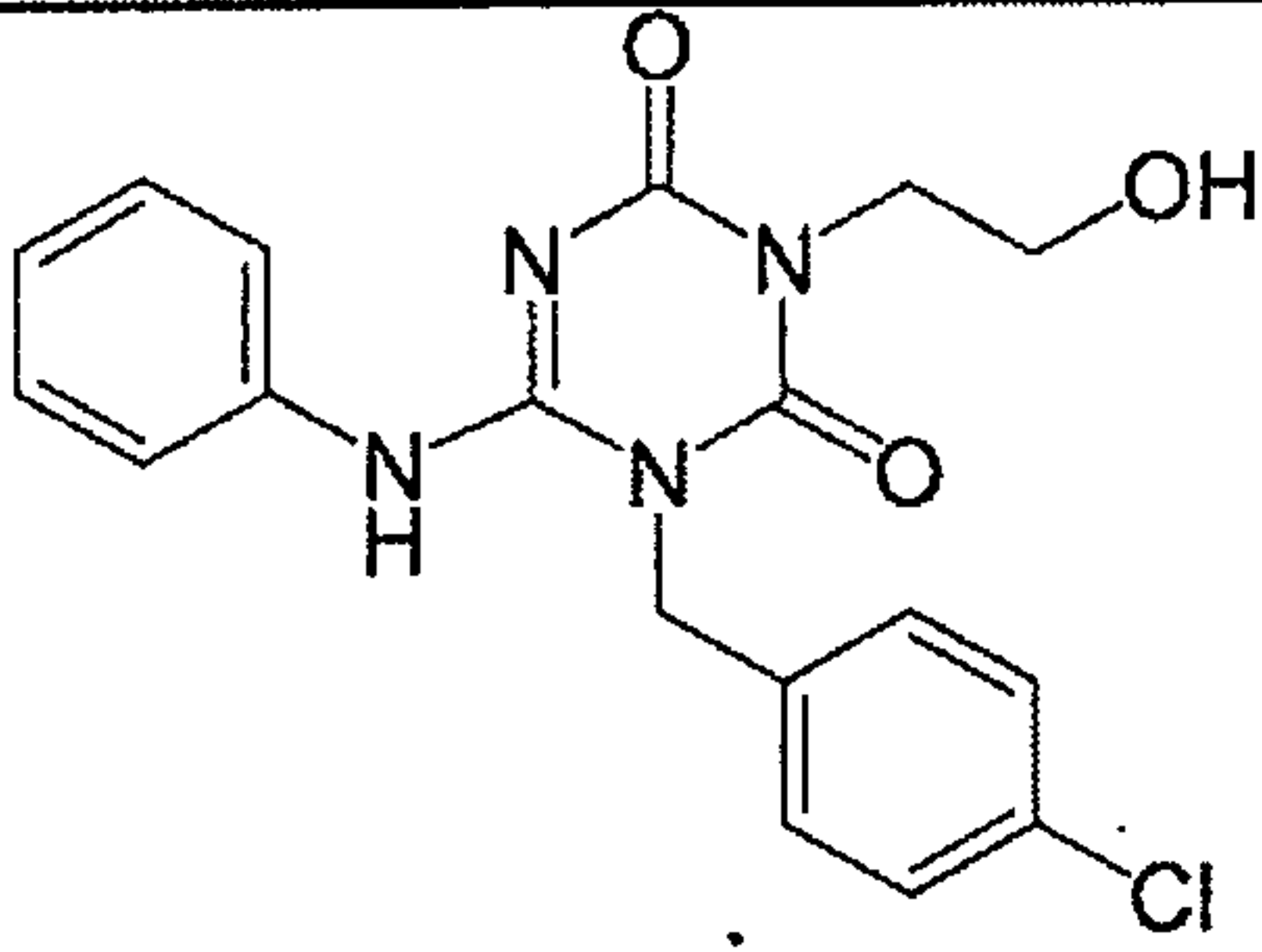
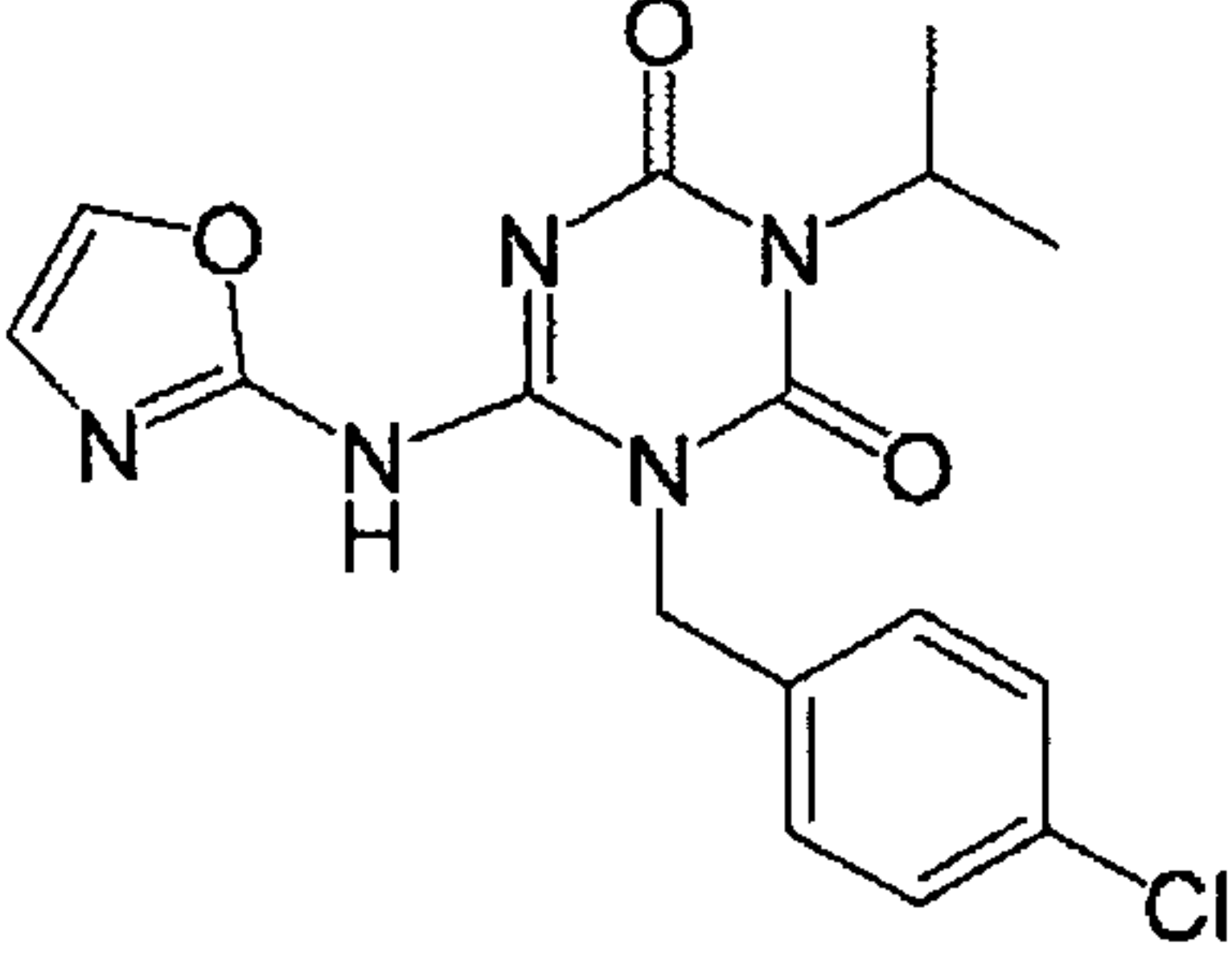
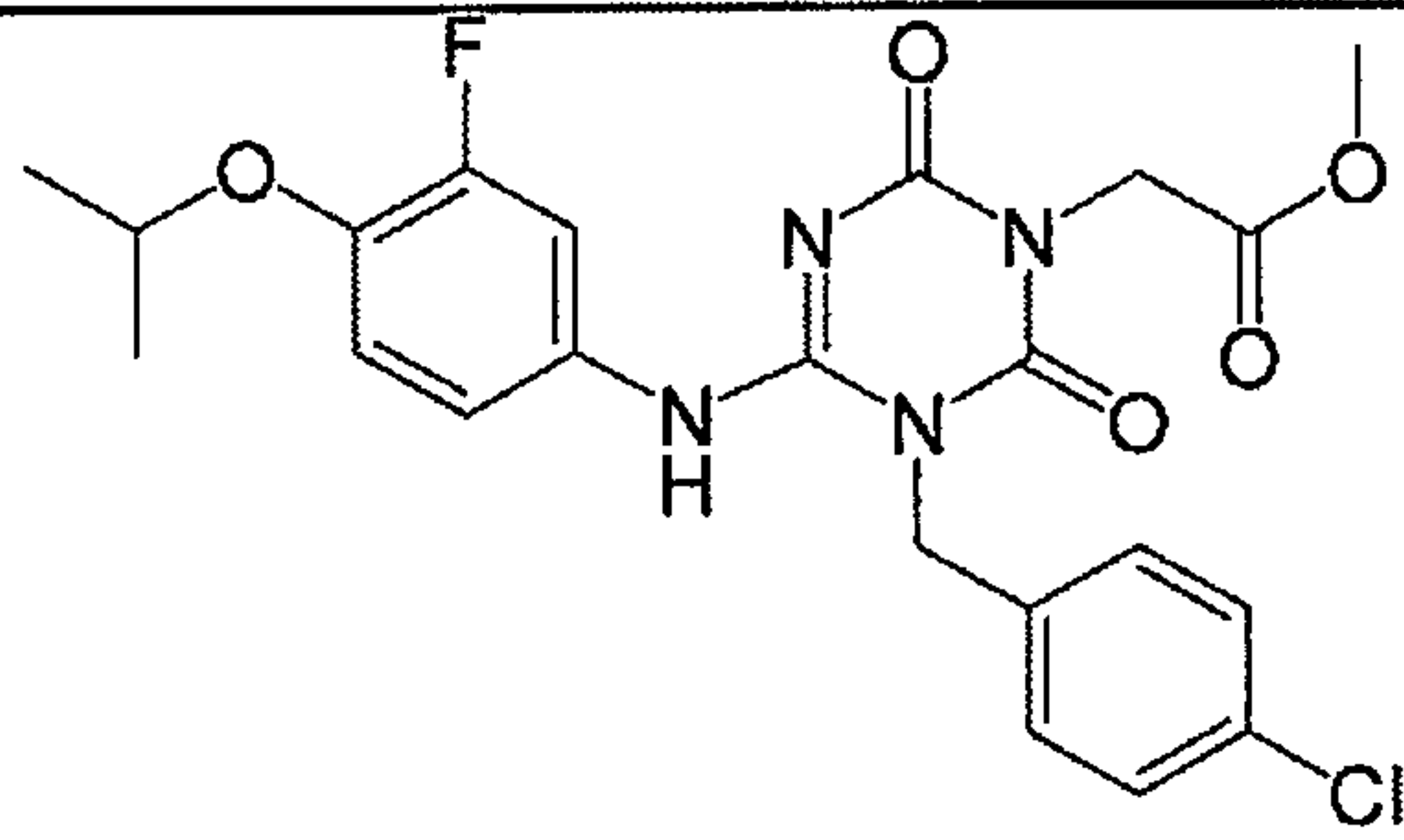
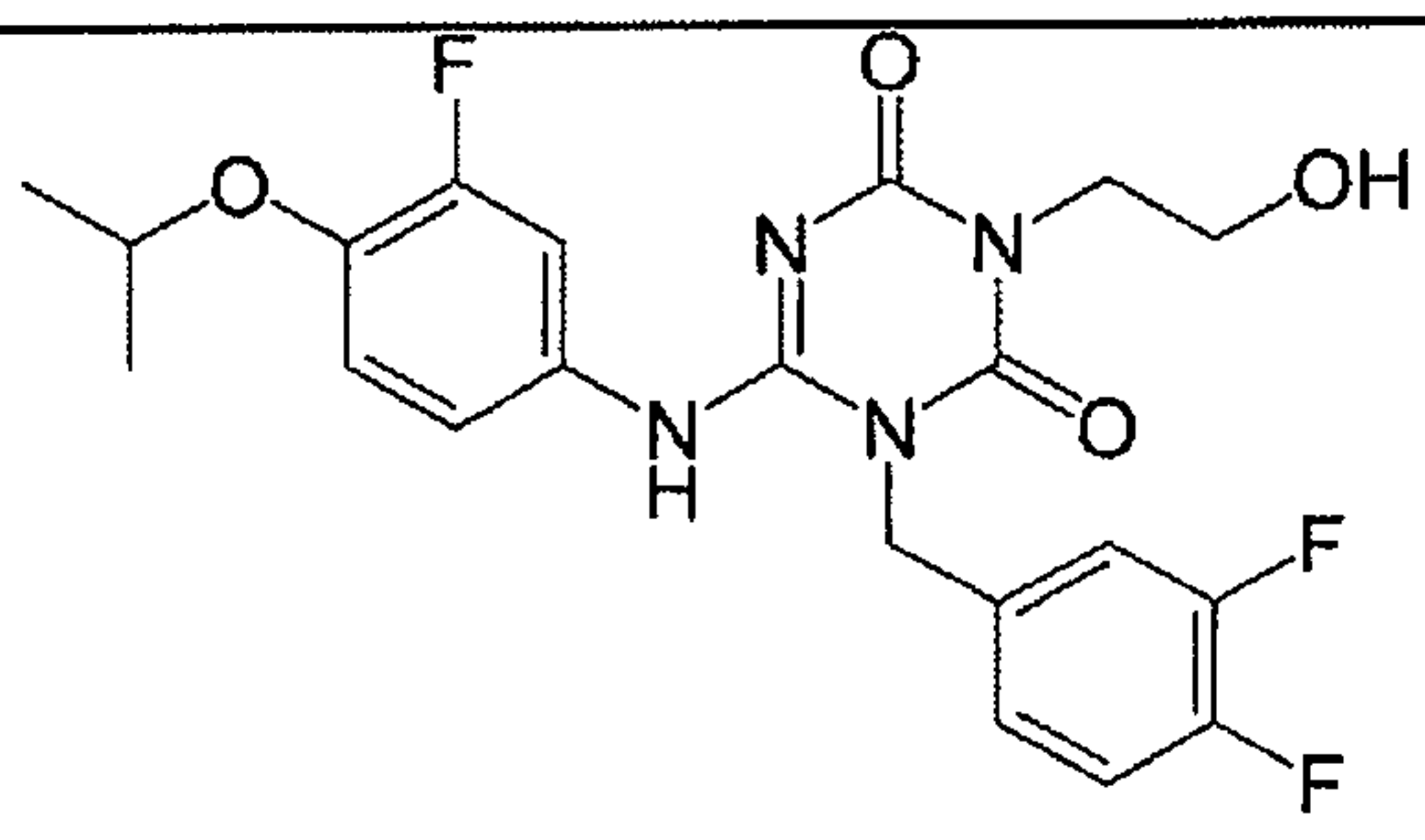
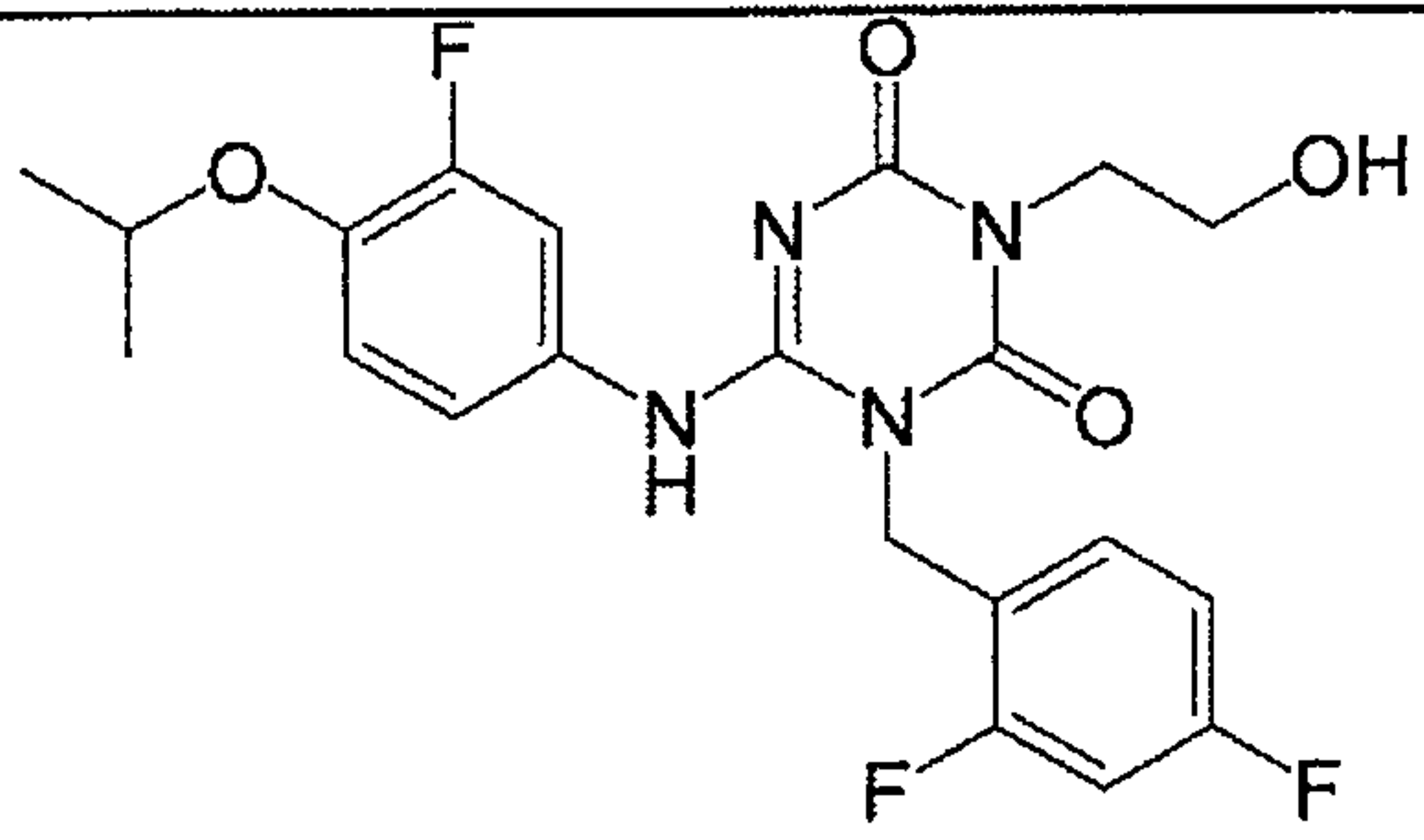
[Table 69]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0326	1.93	504	2
	I-0327	1.03	472	2
	I-0328	2.15	429	2
	I-0329	1.80	439	2
	I-0330	1.56	428	2

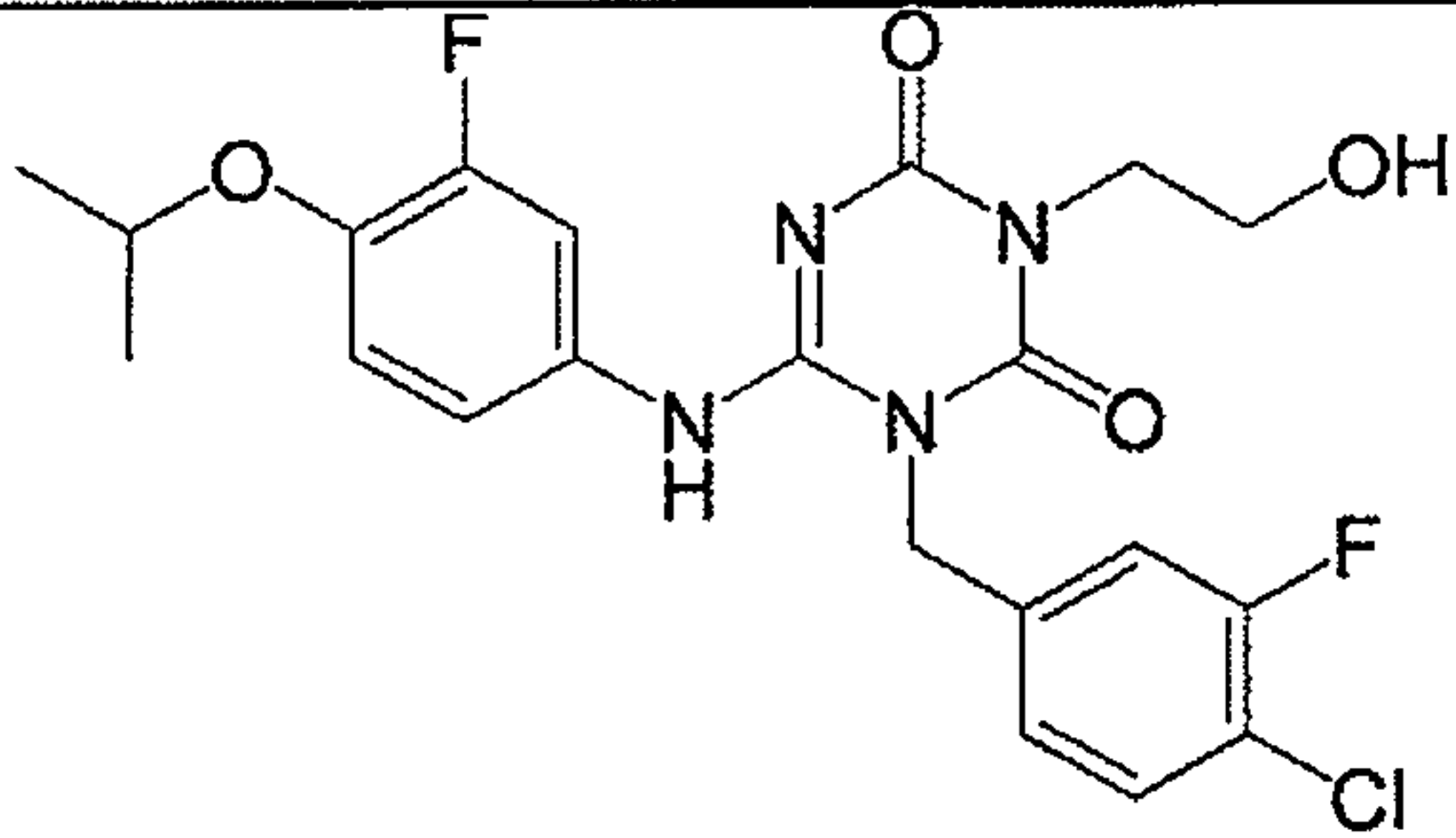
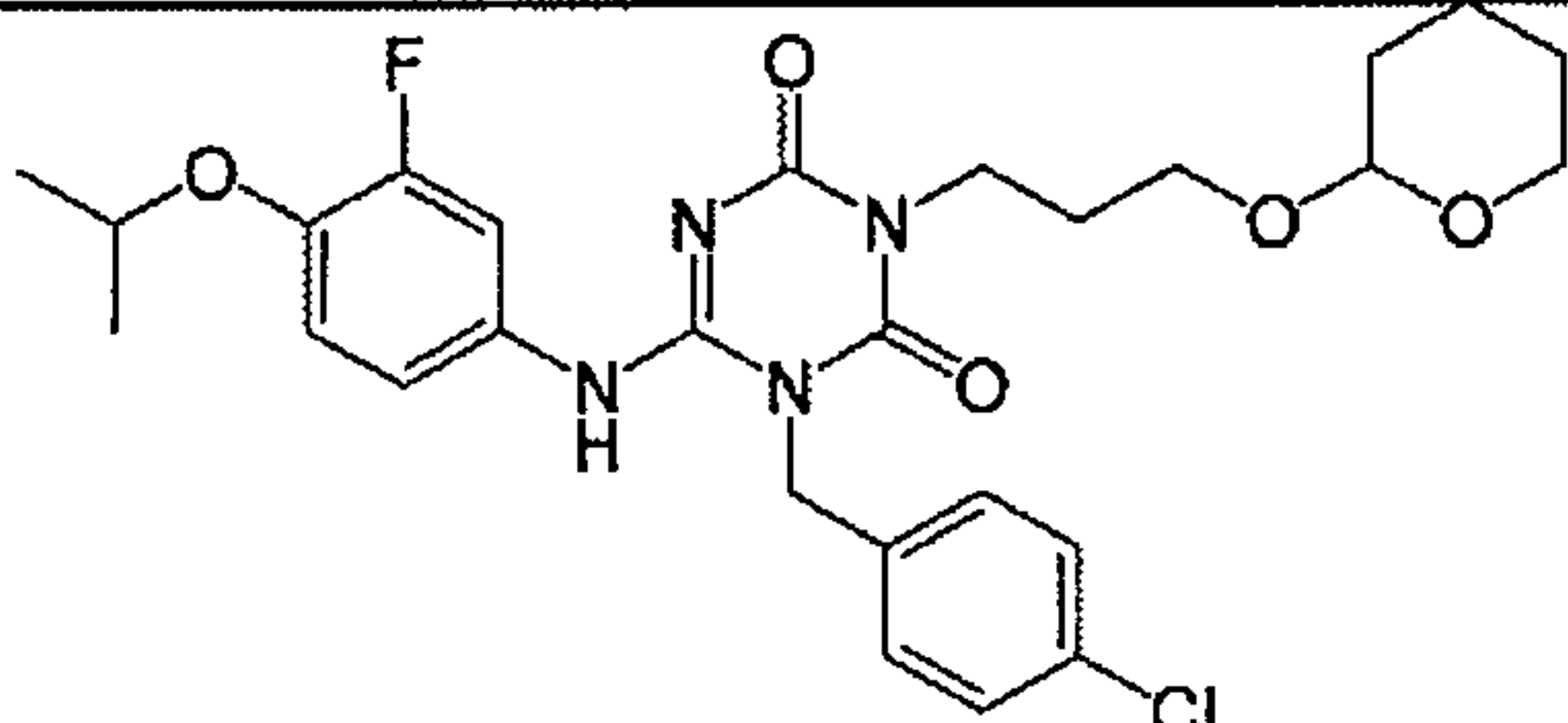
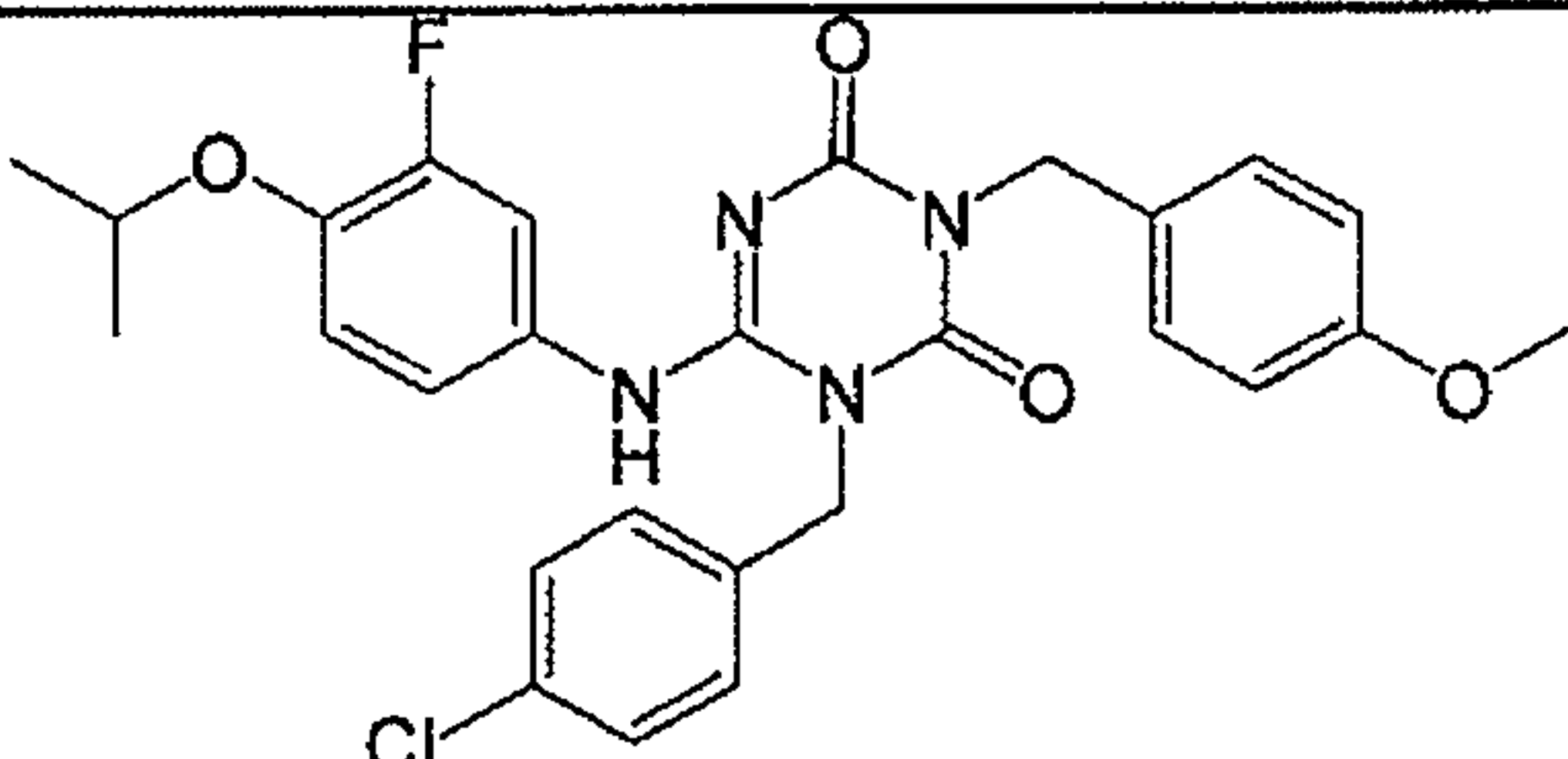
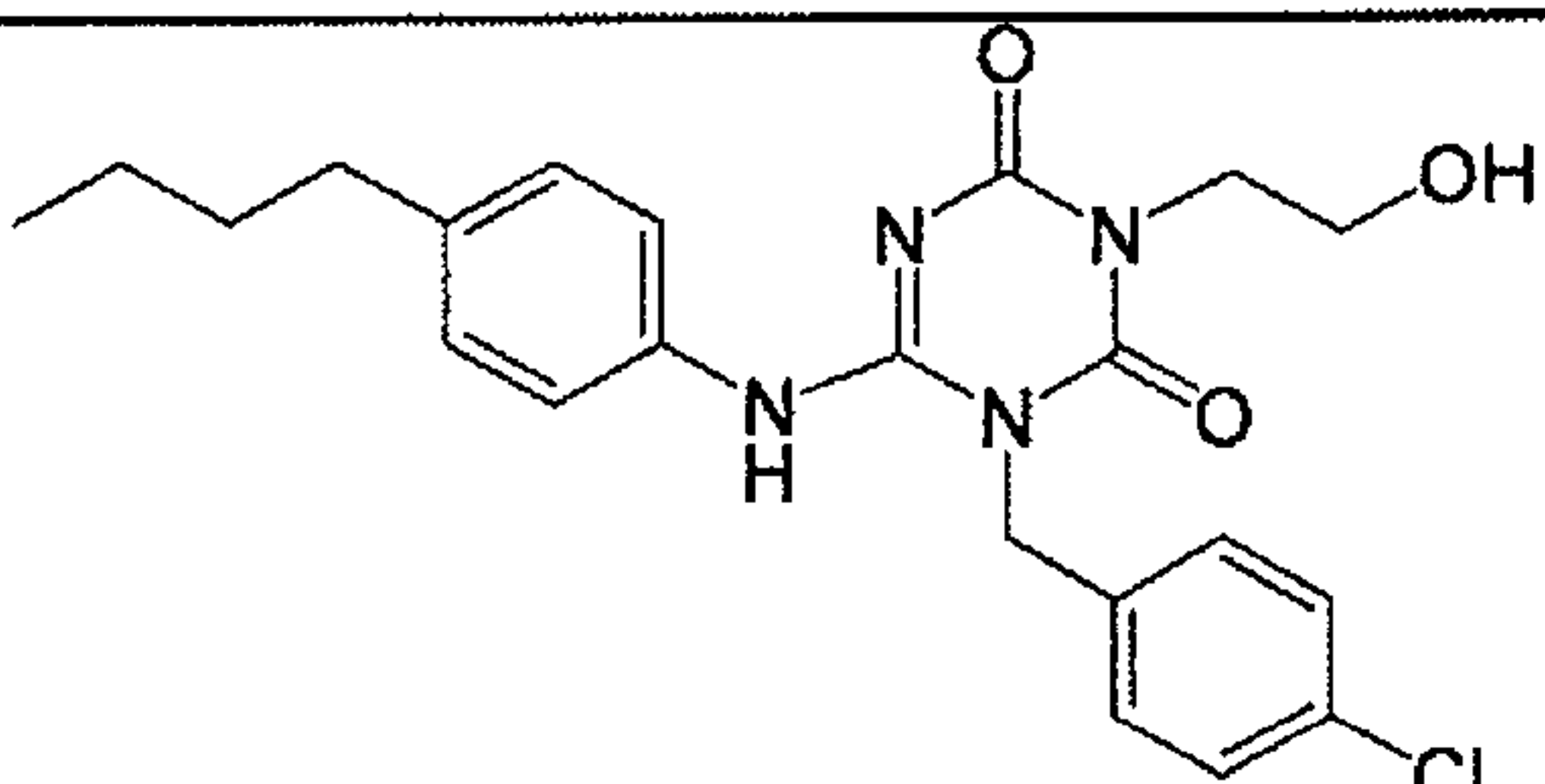
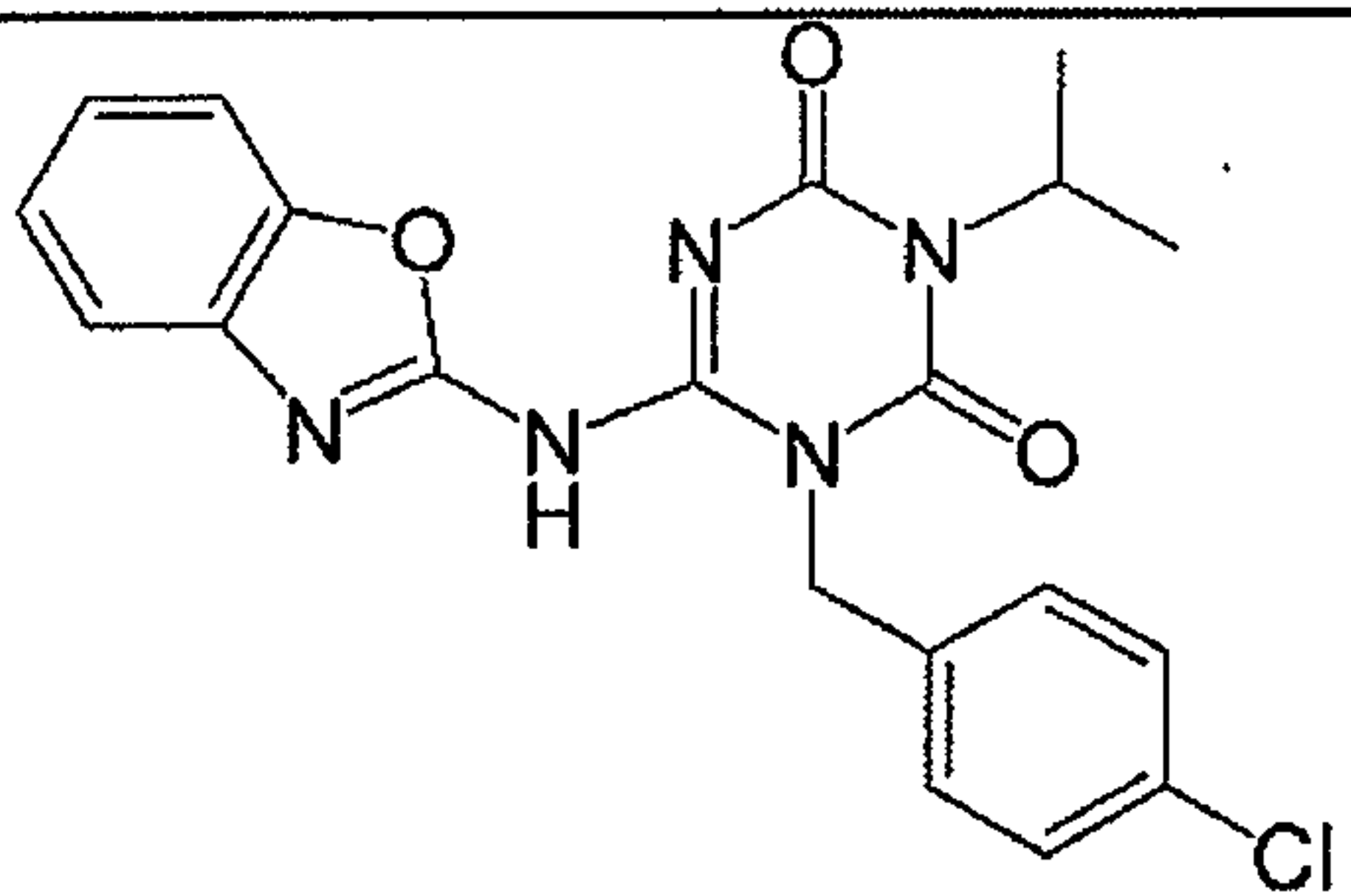
[Table 70]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0331	1.49	490	2
	I-0332	2.26	491	2
	I-0333	1.80	433	2
	I-0334	2.35	465	3
	I-0335	2.19	489	2

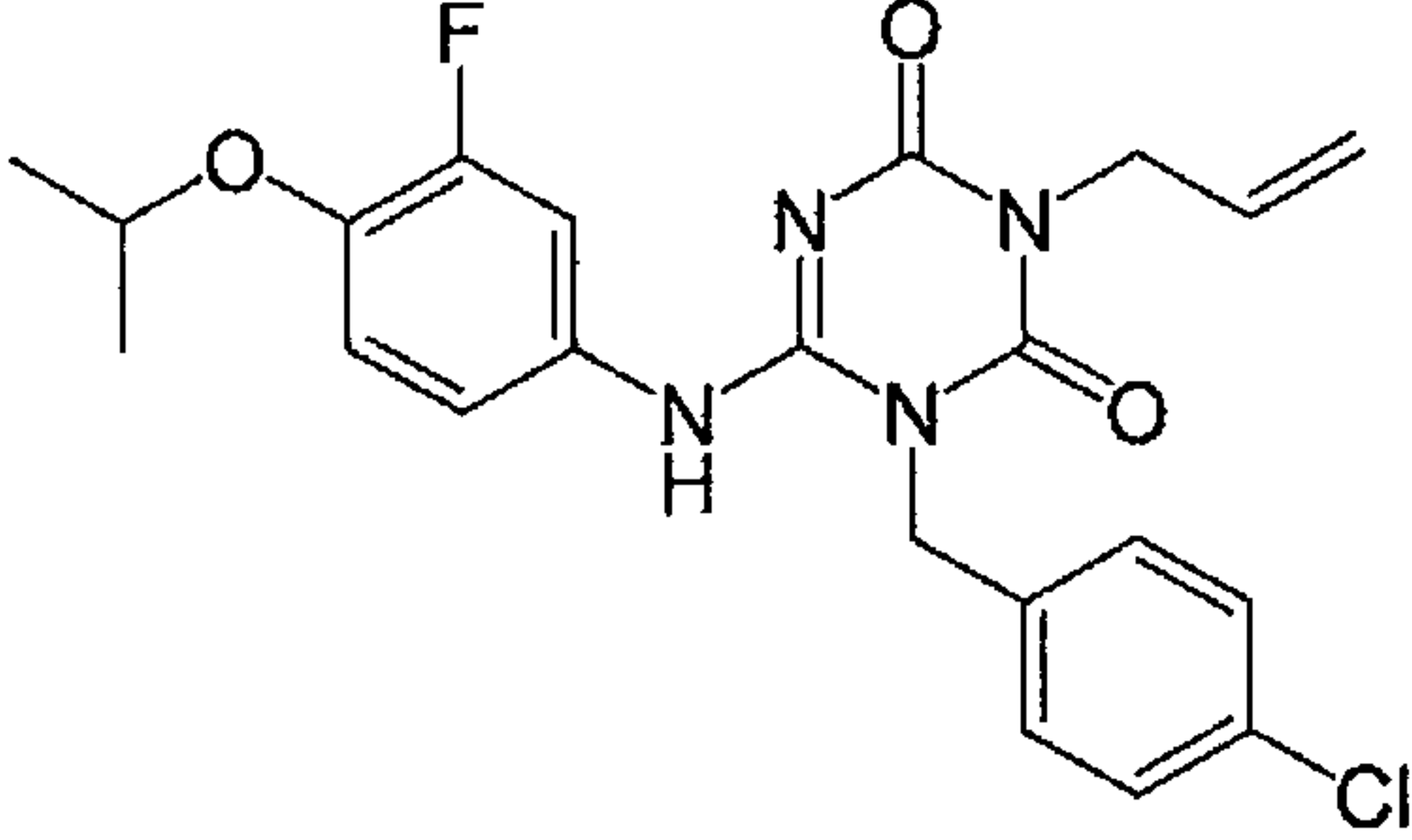
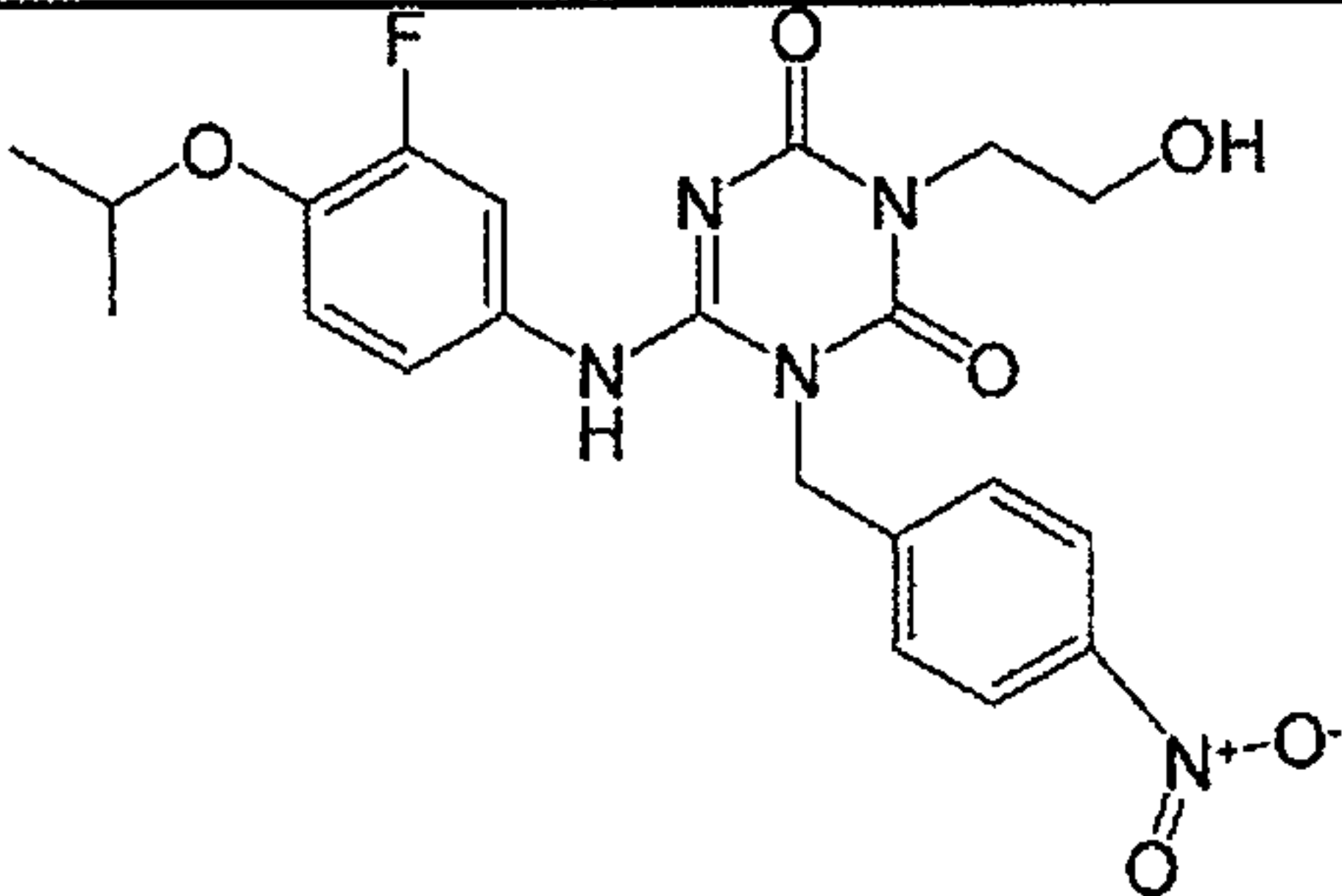
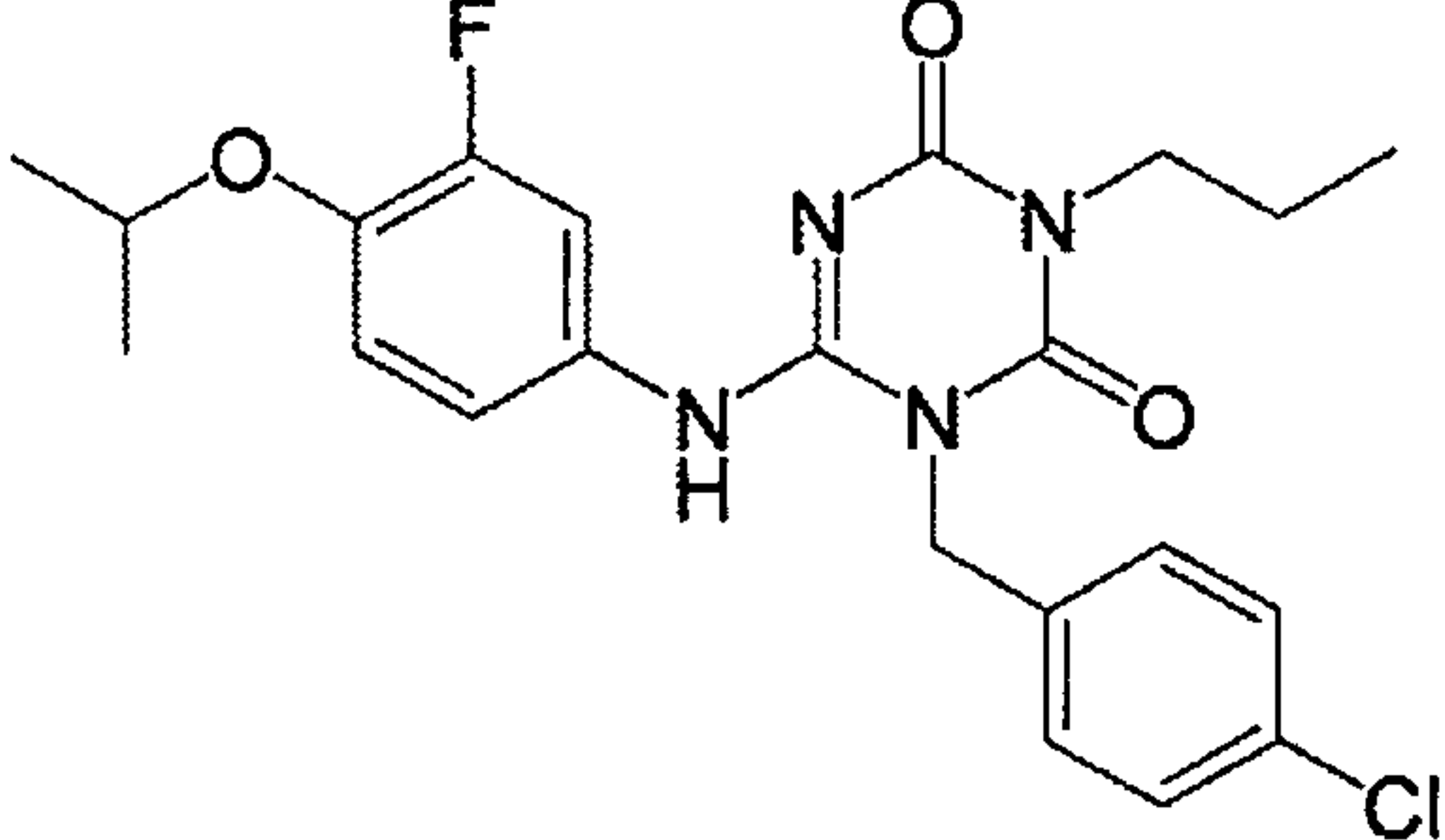
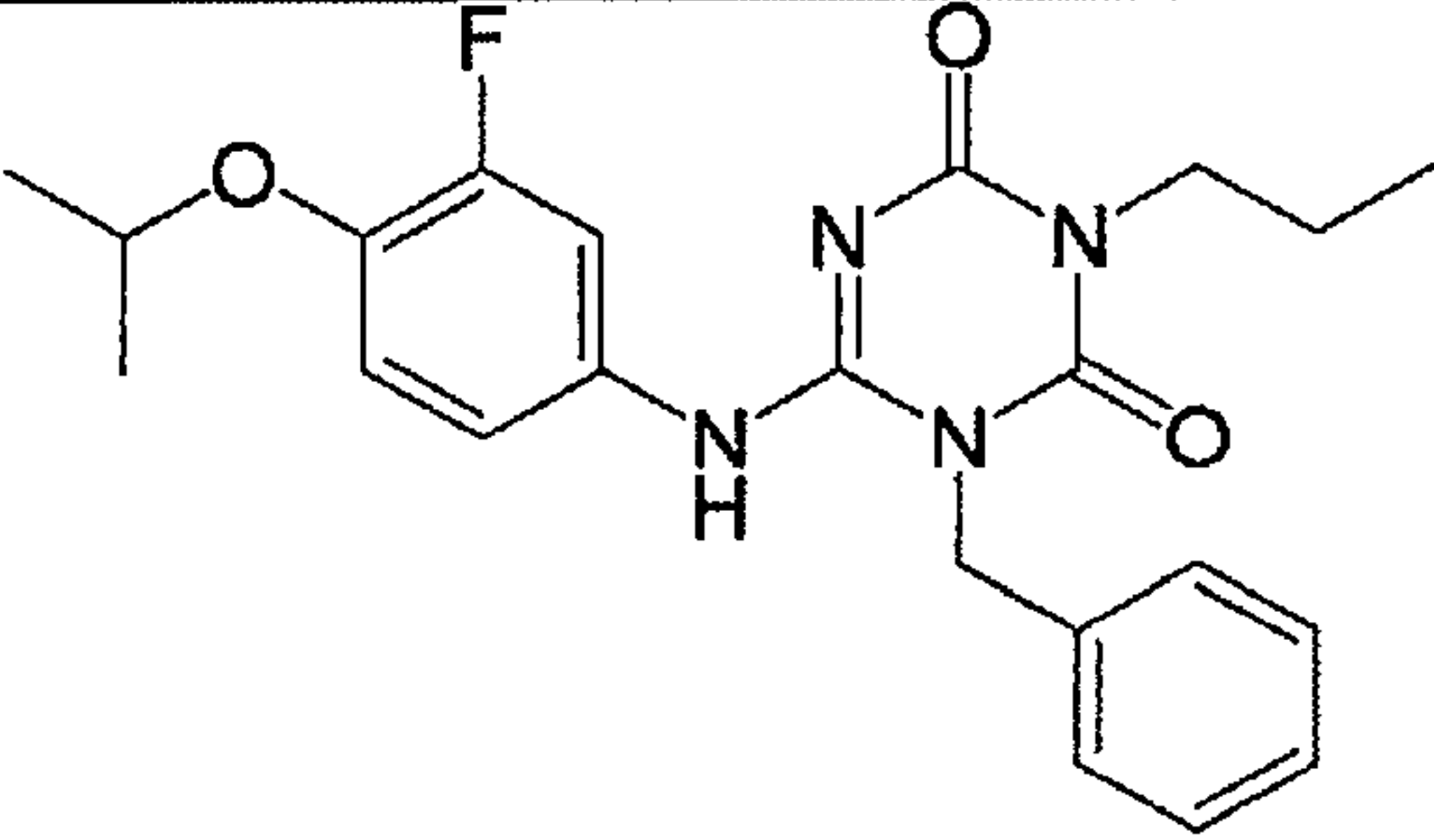
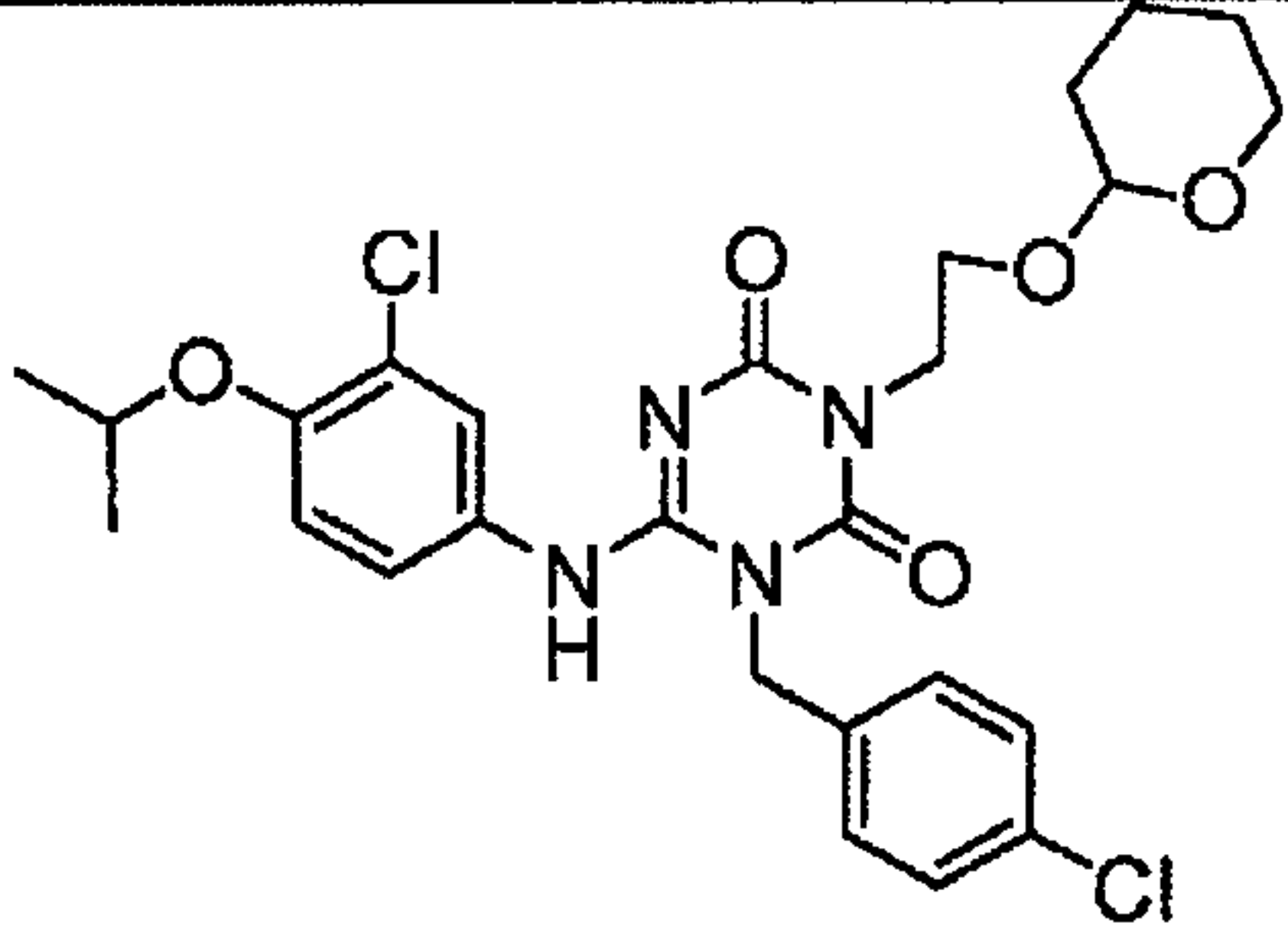
[Table 71]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0336	1.61	373	2
	I-0337	2.39	362	2
	I-0338	2.45	477	3
	I-0339	1.88	451	2
	I-0340	1.84	451	2

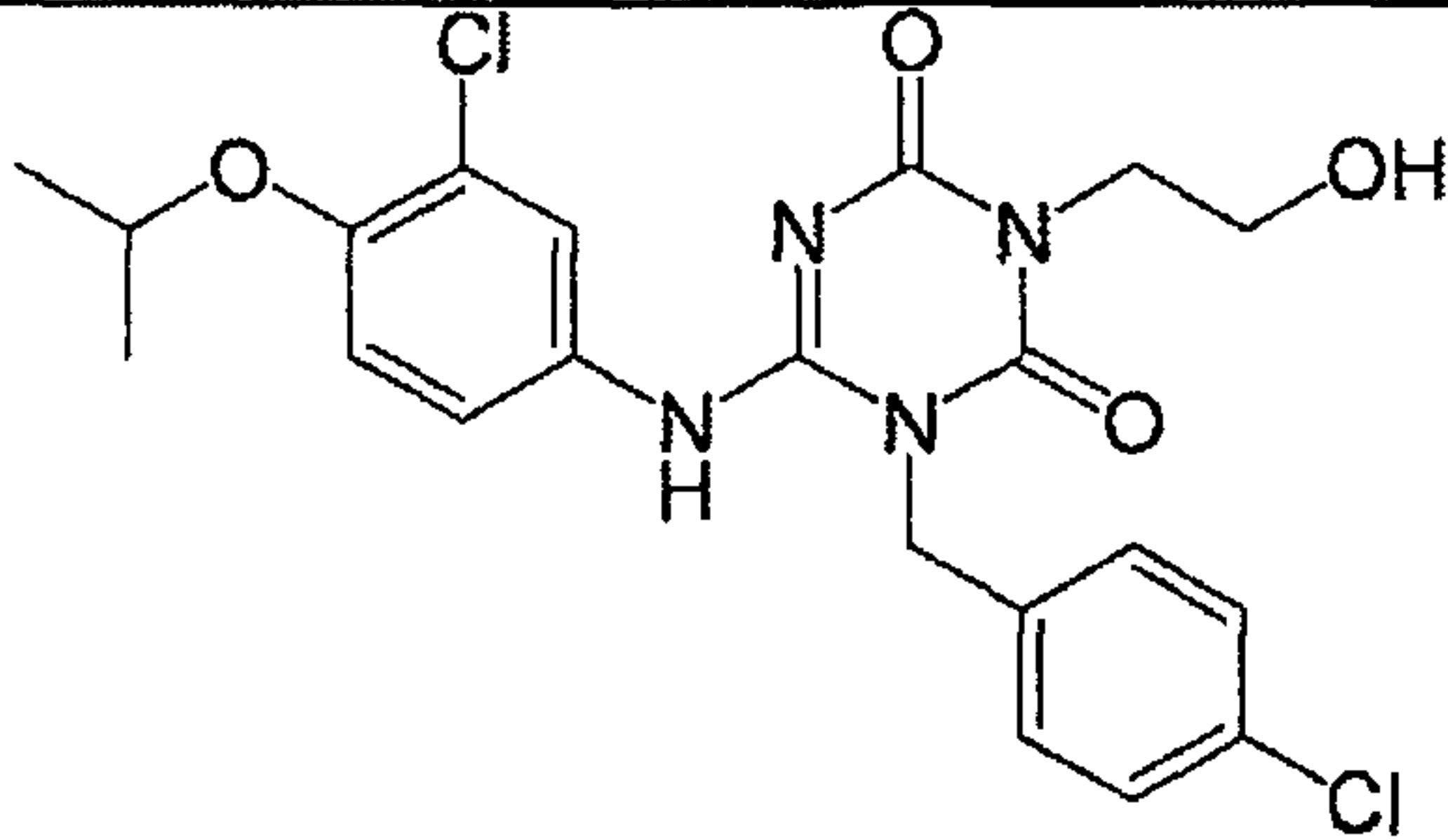
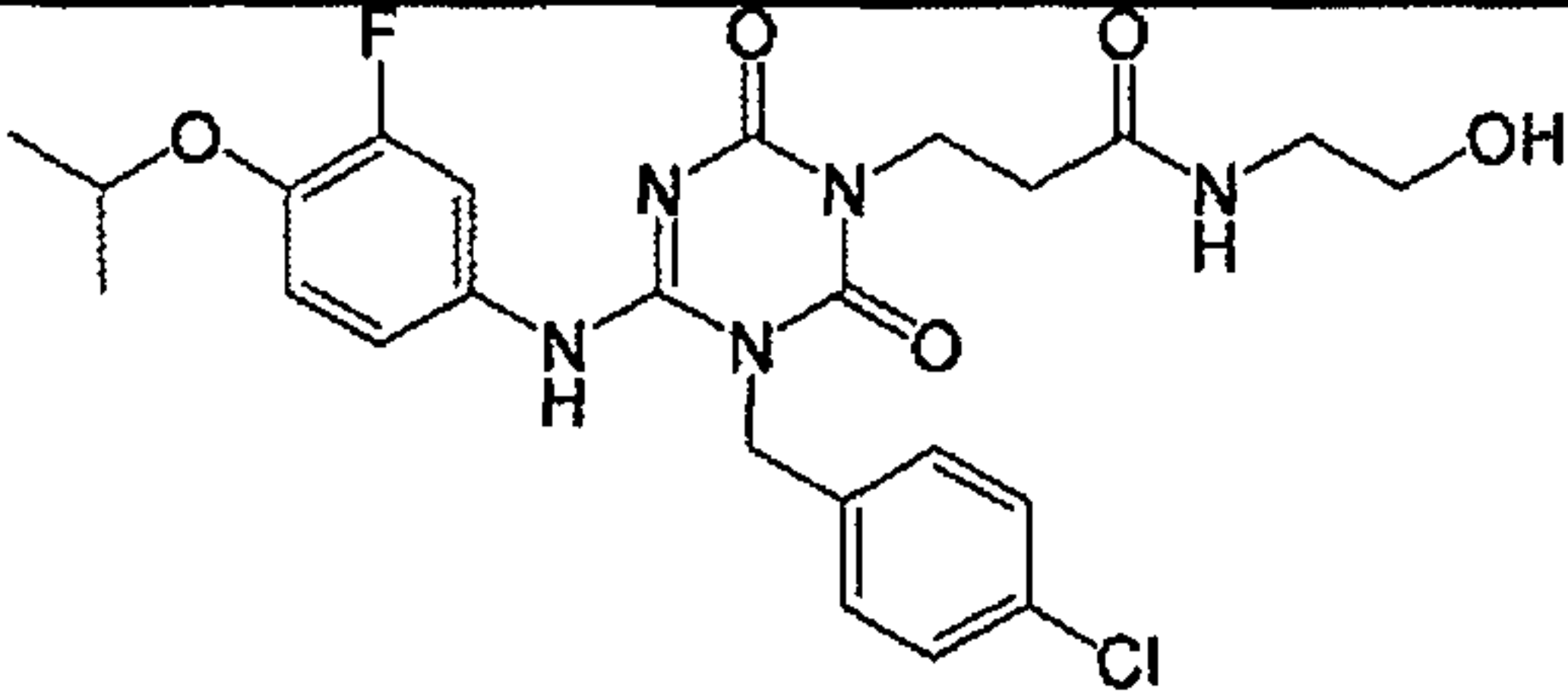
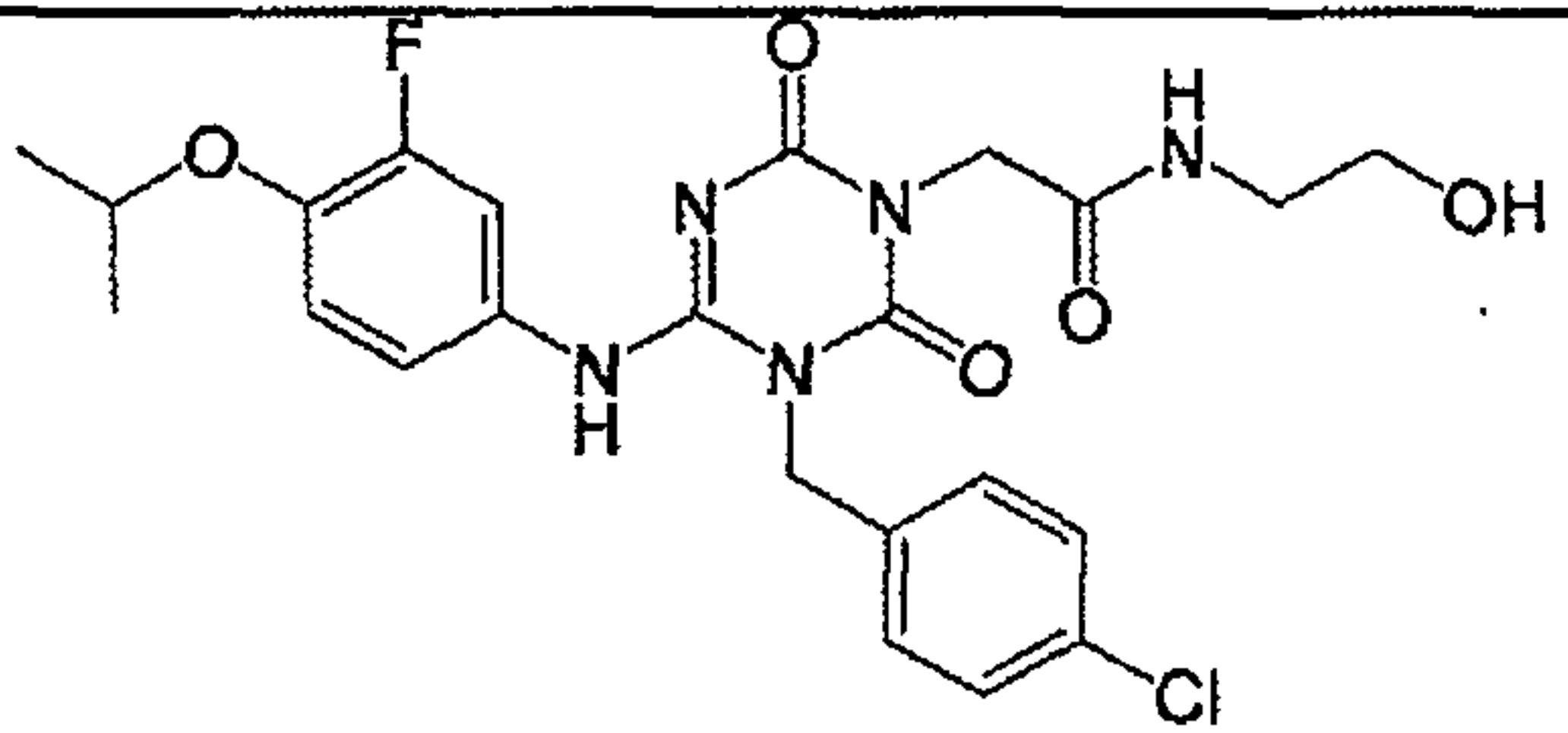
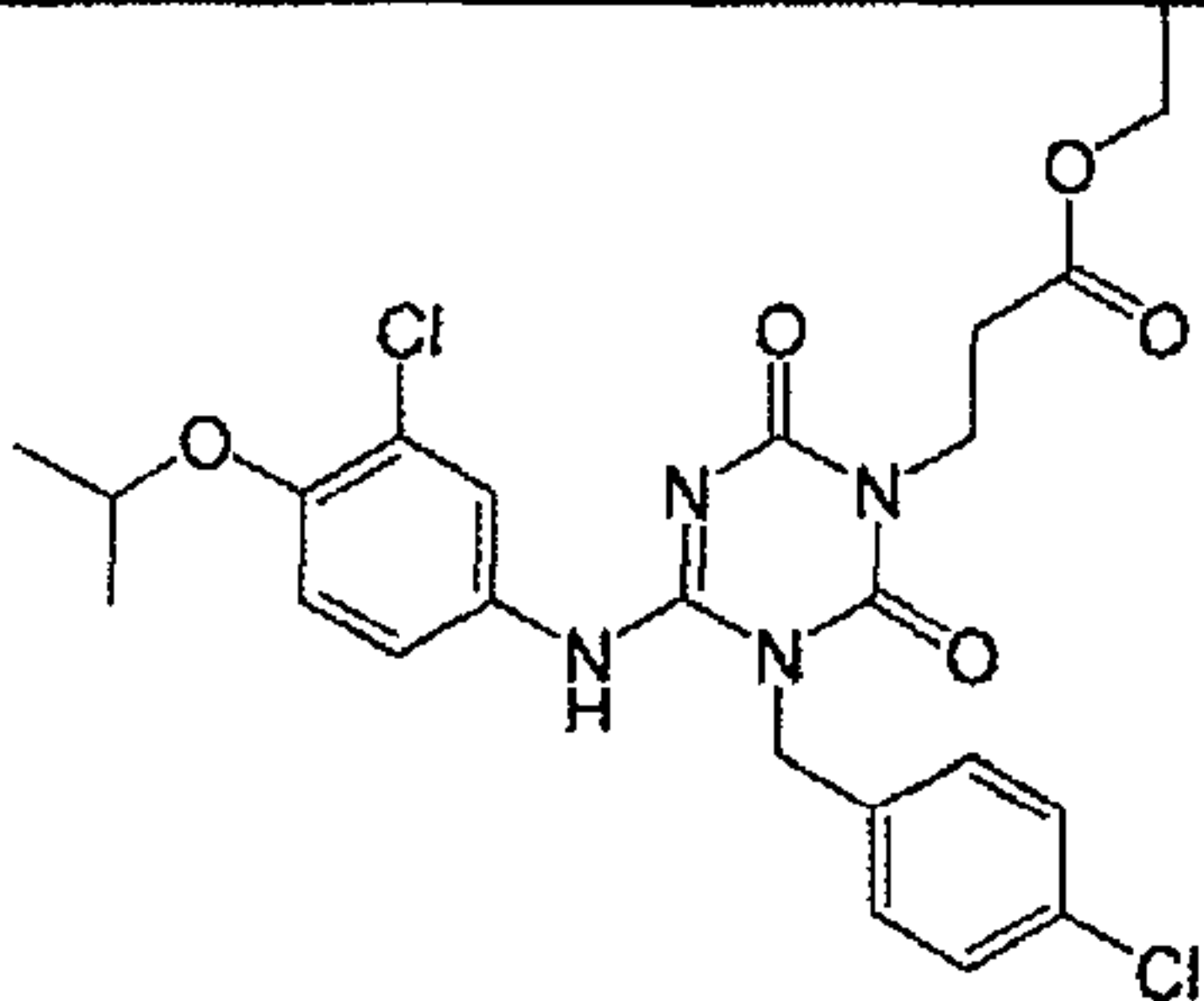
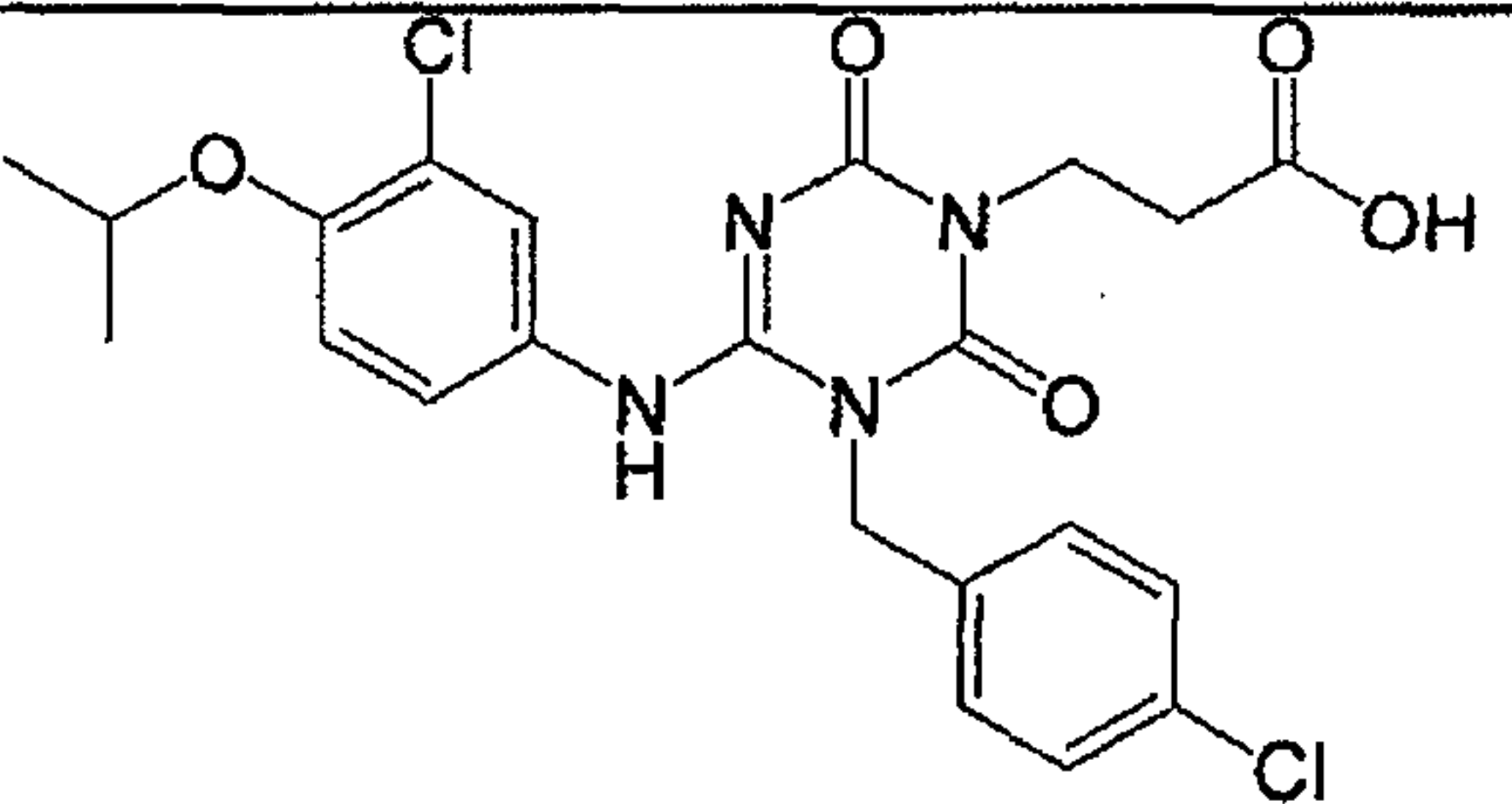
[Table 72]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0341	2.01	467	2
	I-0342	2.81	548	3
	I-0343	2.50	525	2
	I-0344	2.48	429	3
	I-0345	2.74	412	2

[Table 73]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0346	2.34	445	2
	I-0347	1.78	460	2
	I-0348	2.45	447	2
	I-0349	2.20	413	2
	I-0350	2.55	549	2

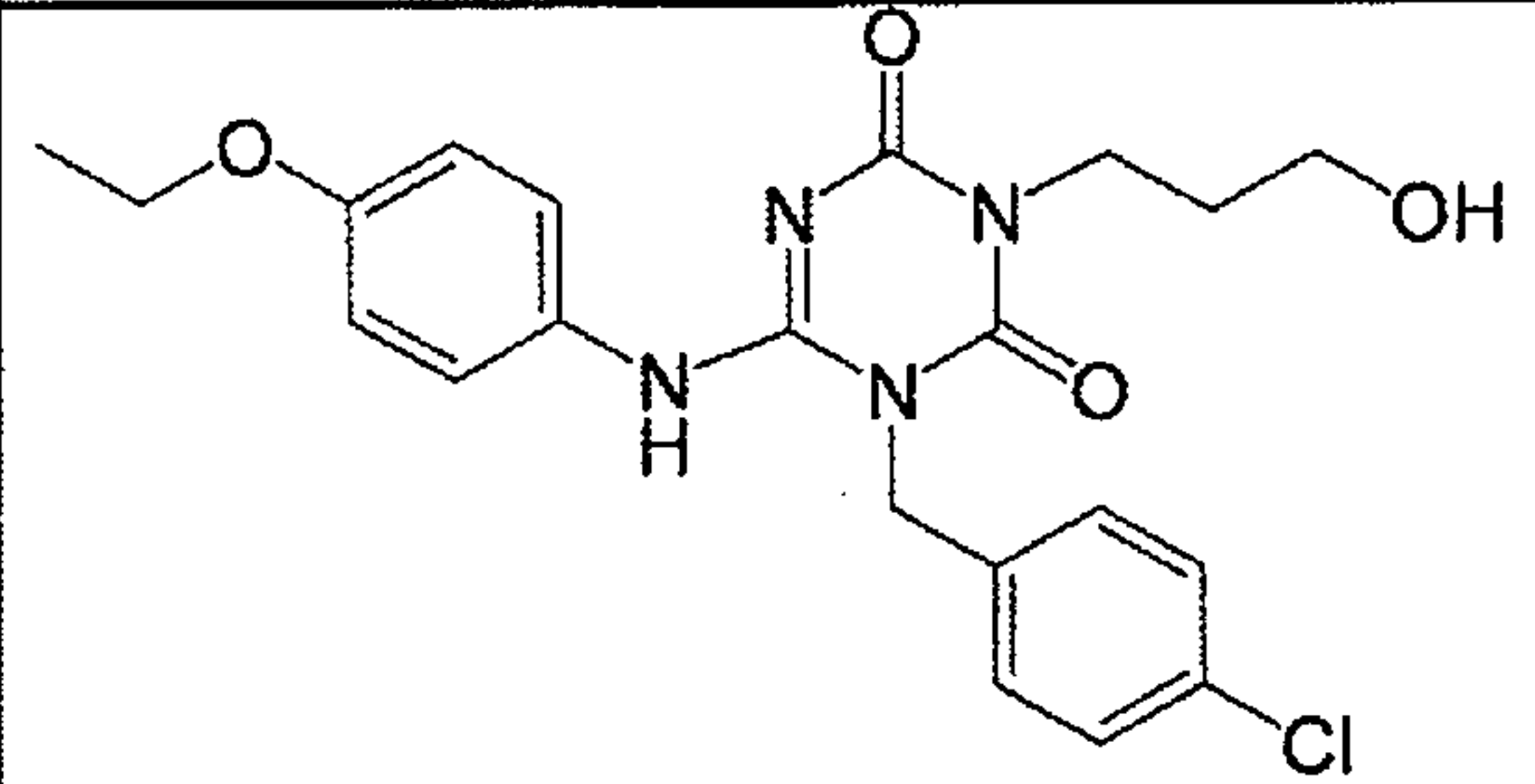
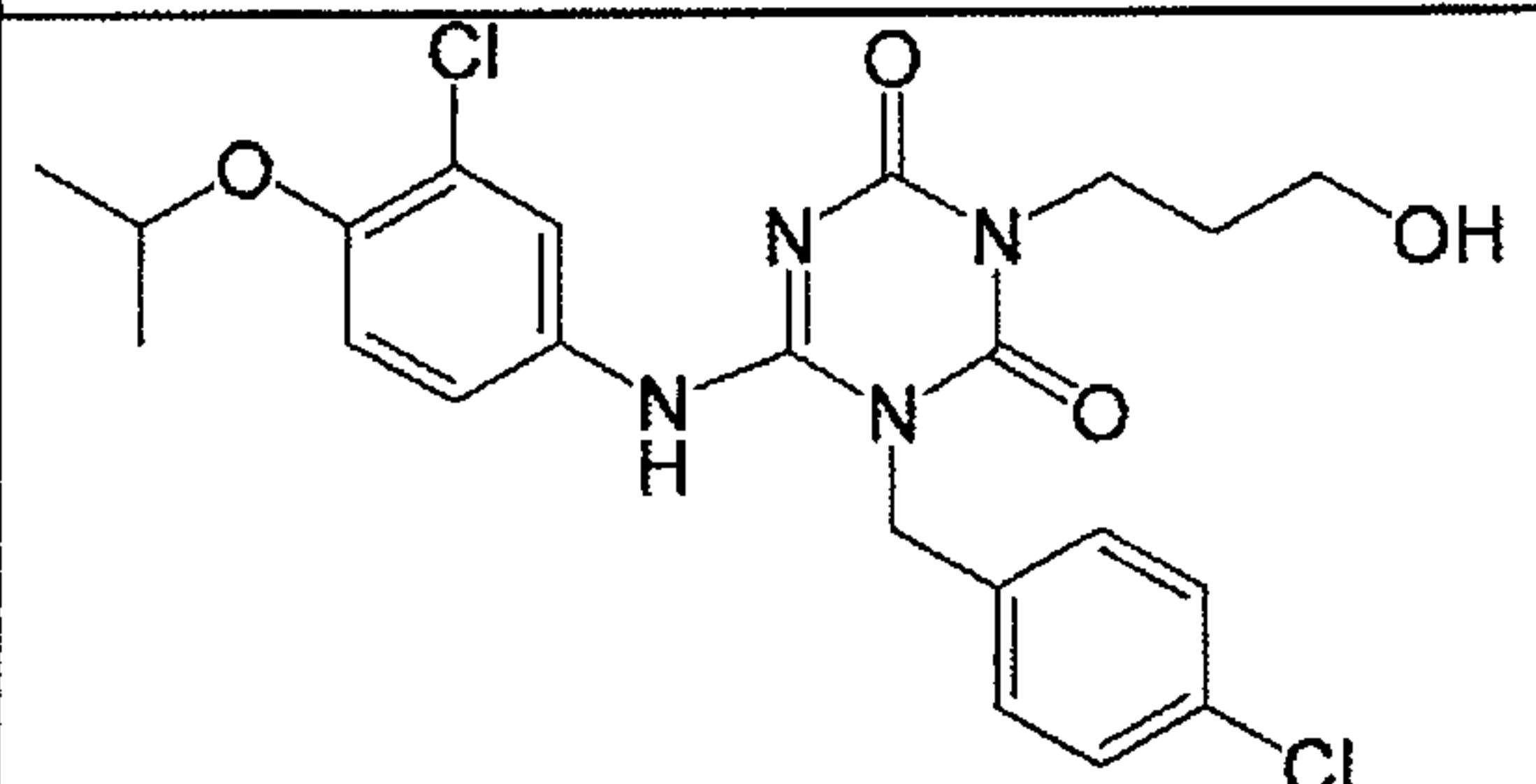
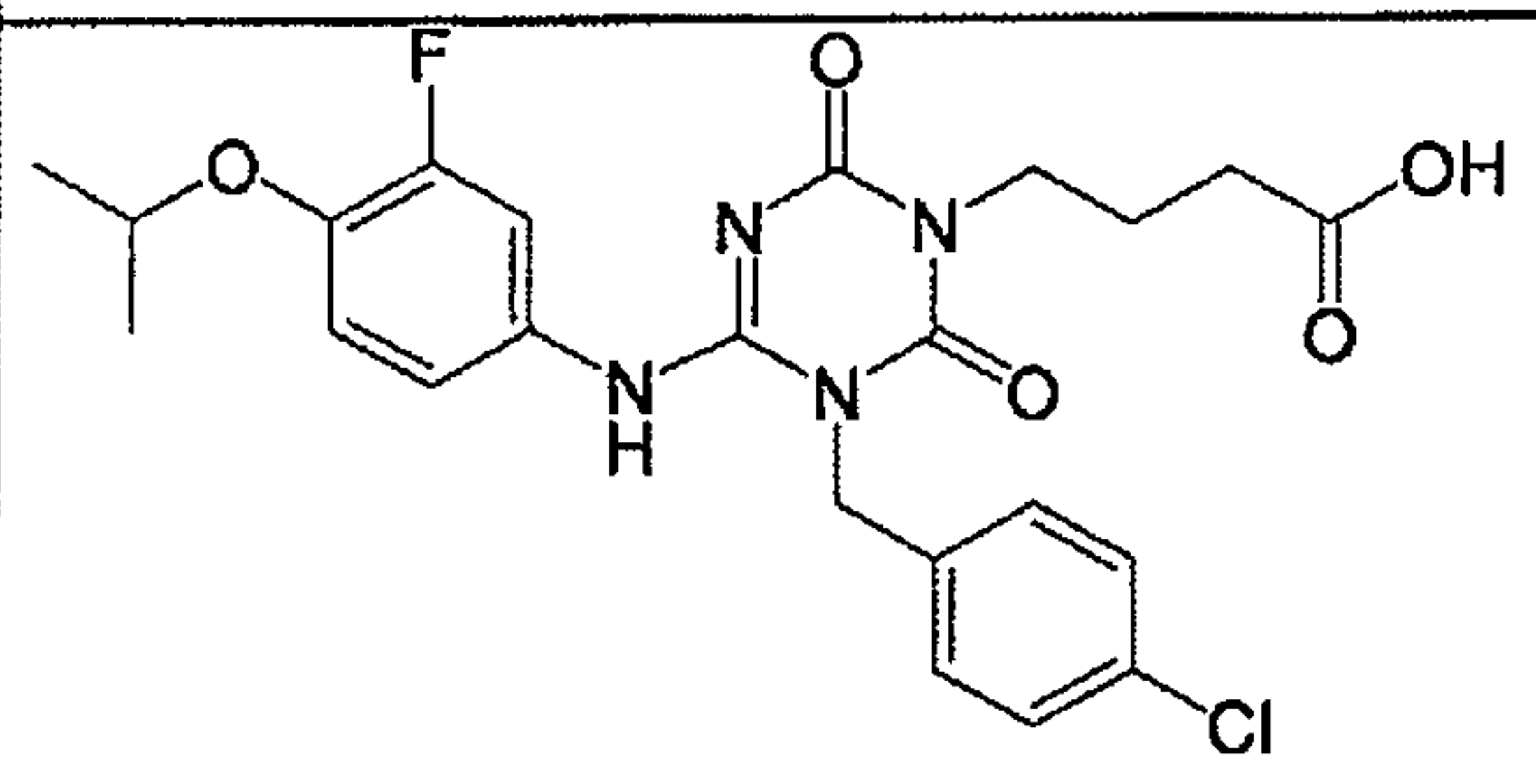
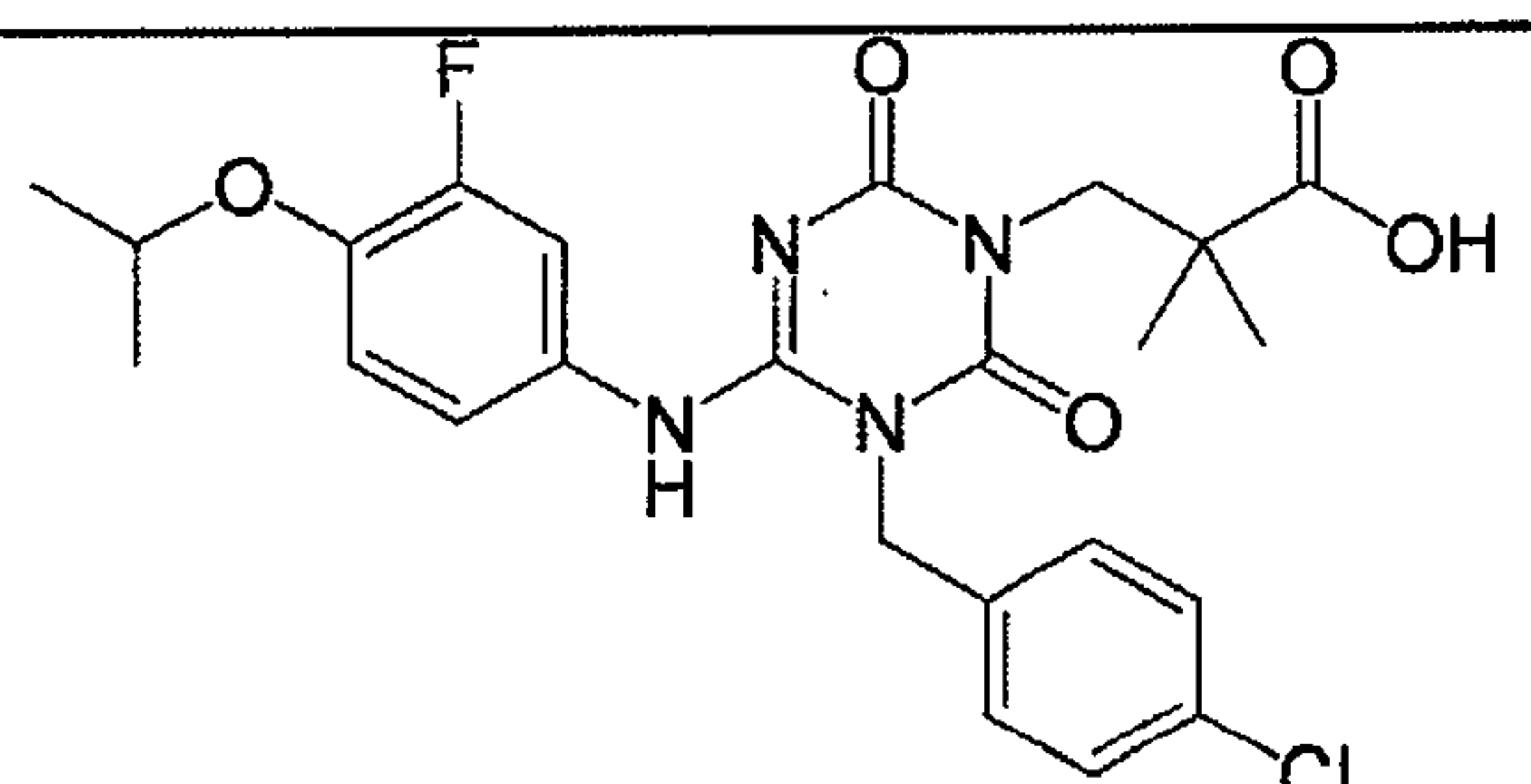
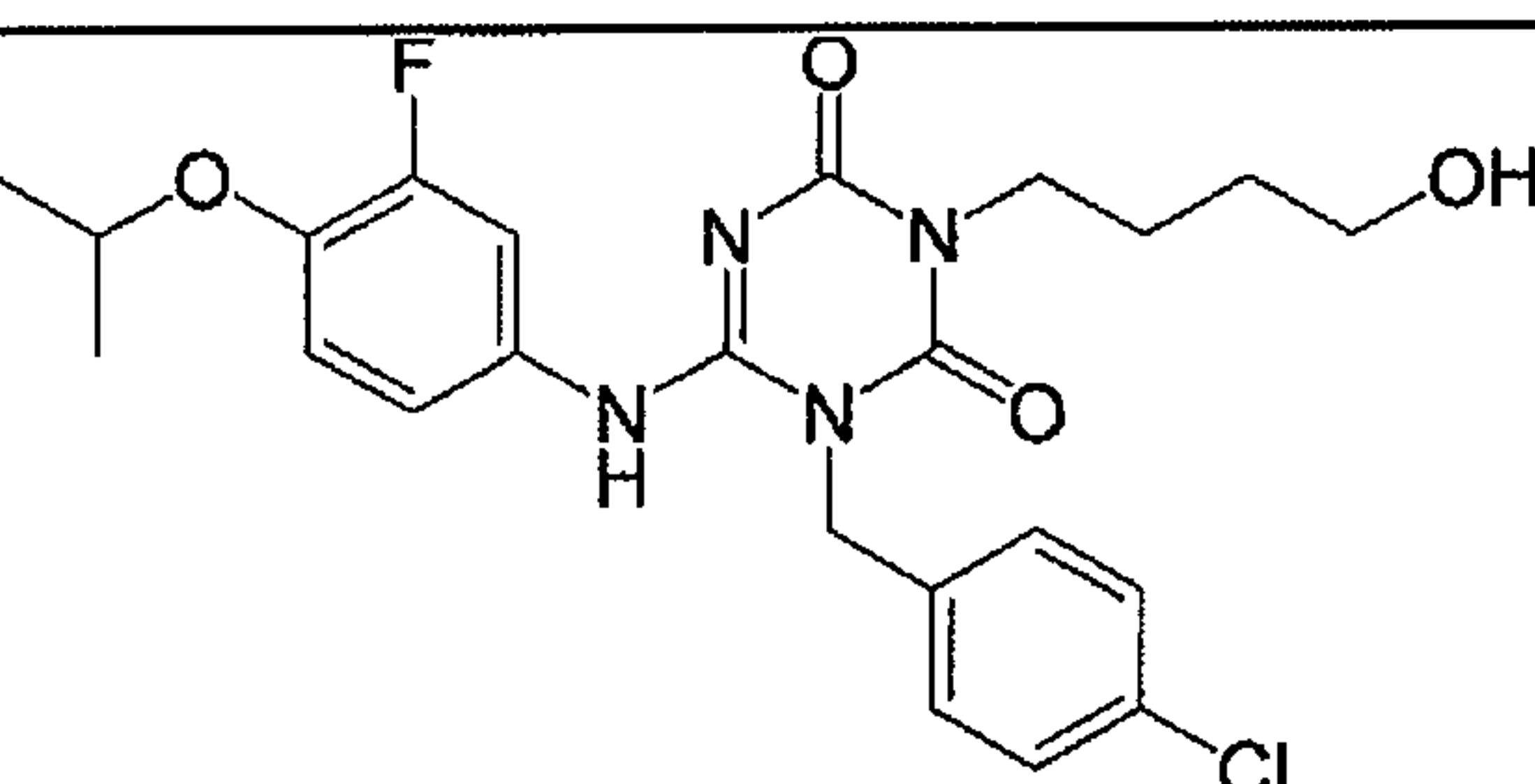
[Table 74]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0351	2.06	465	2
	I-0352	1.78	520	2
	I-0353	1.77	506	2
	I-0354	2.47	521	2
	I-0355	2.10	493	2

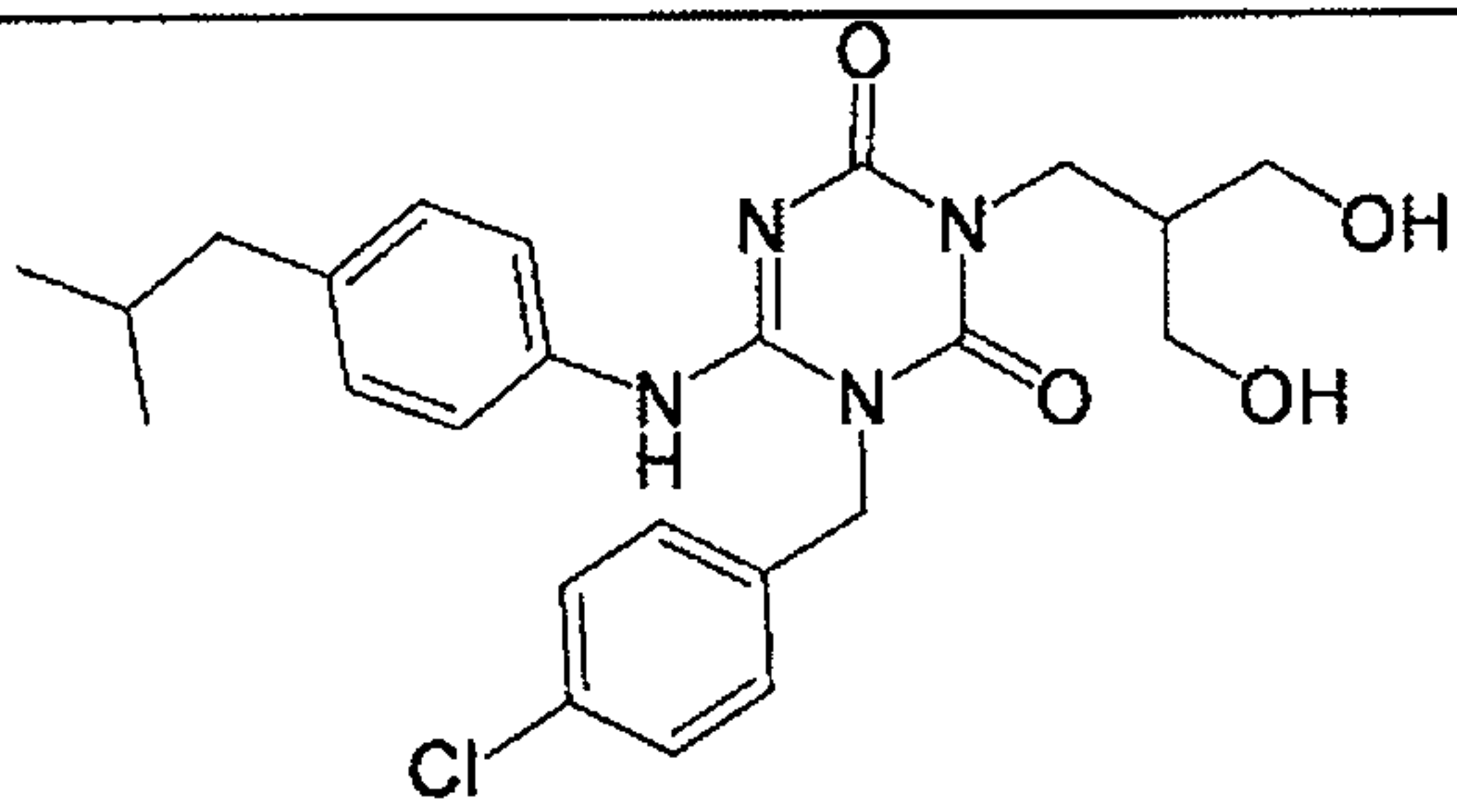
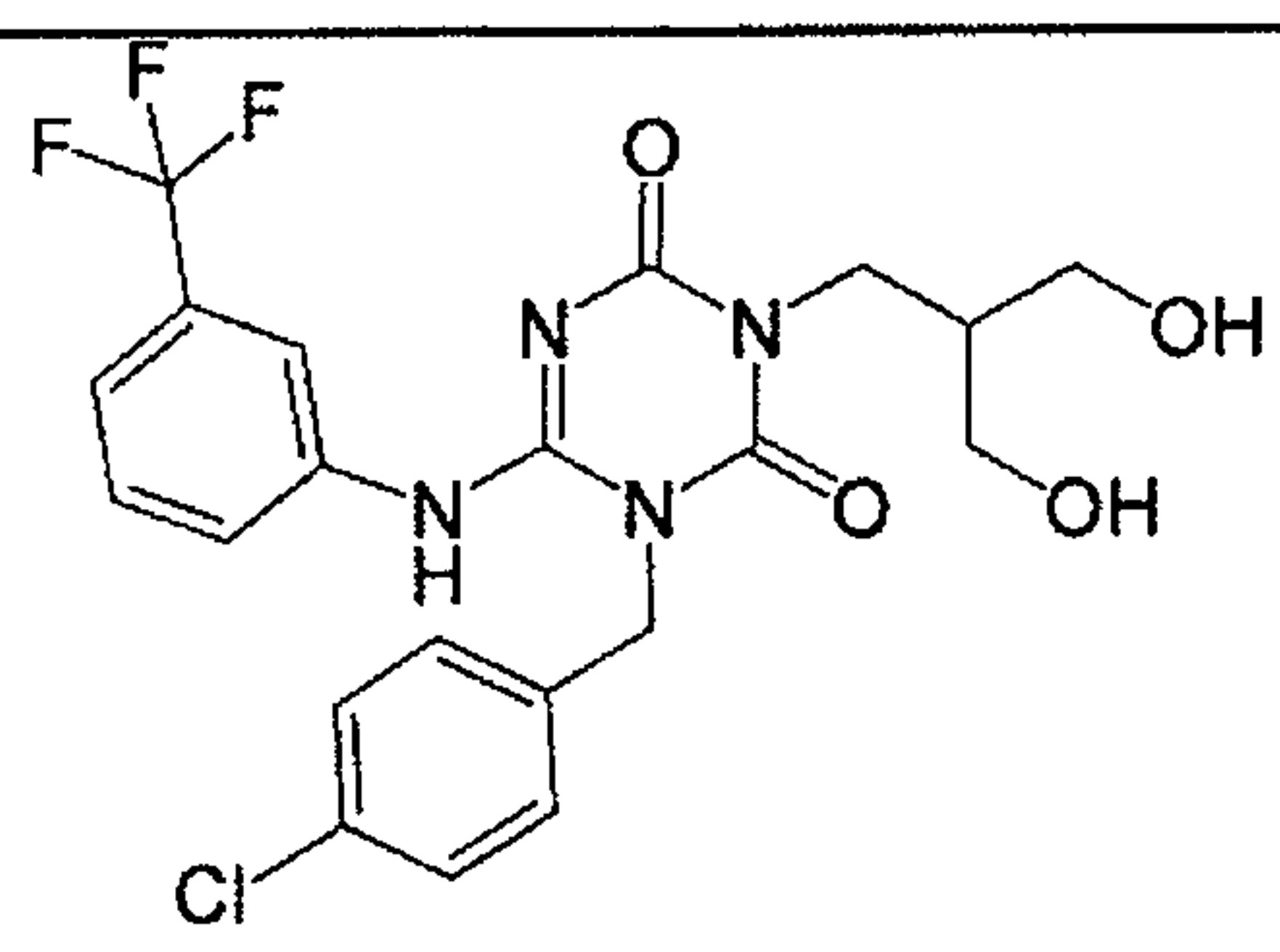
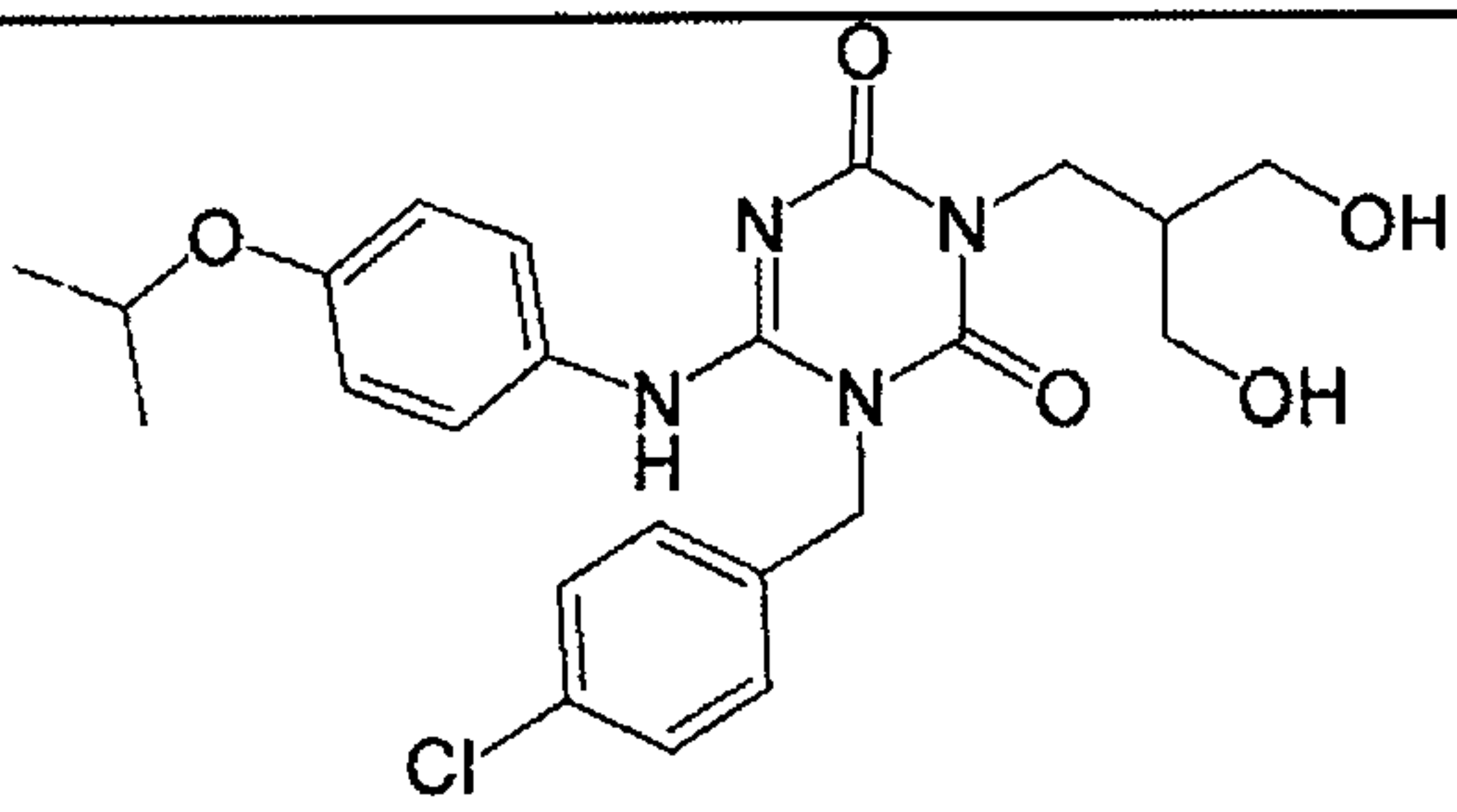
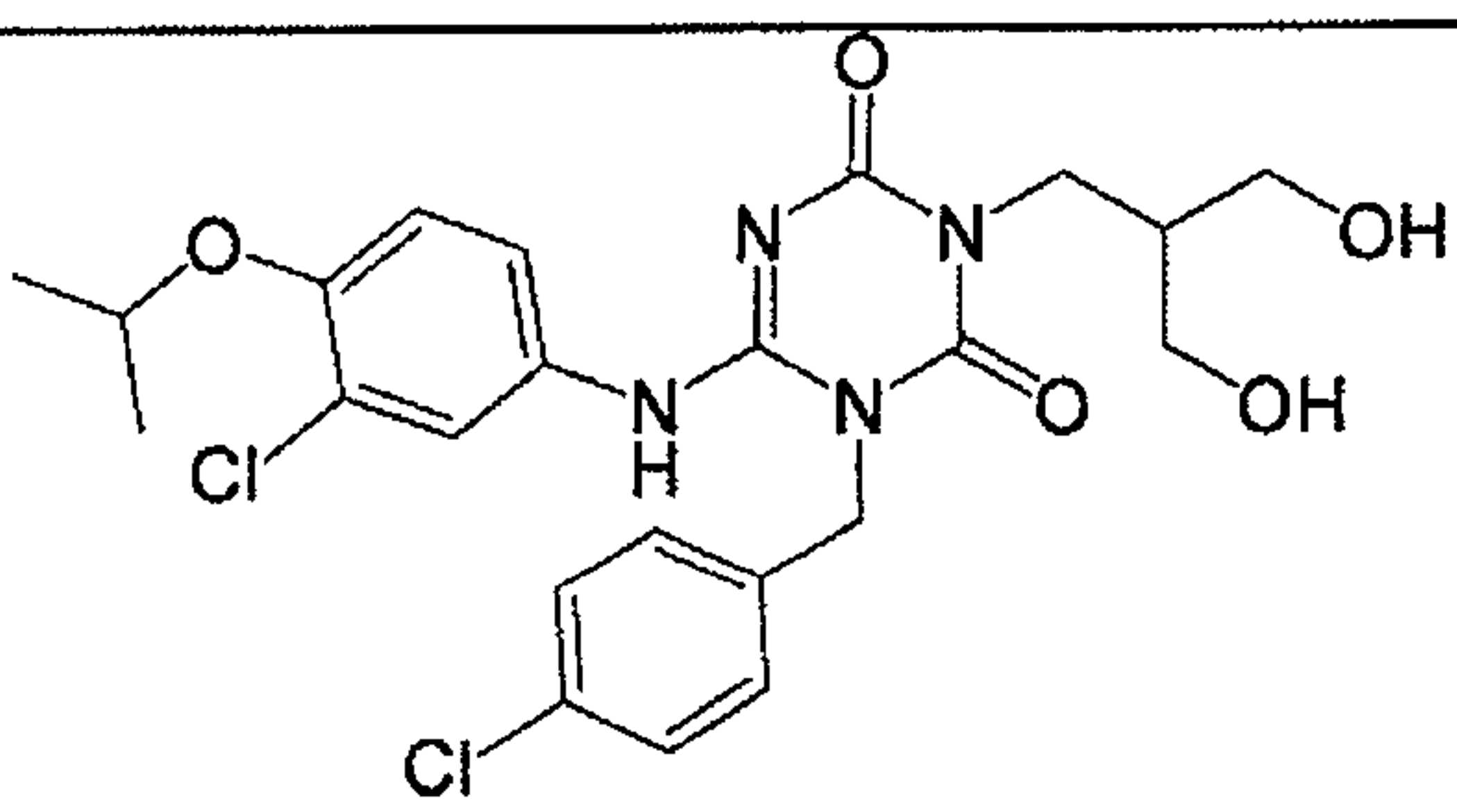
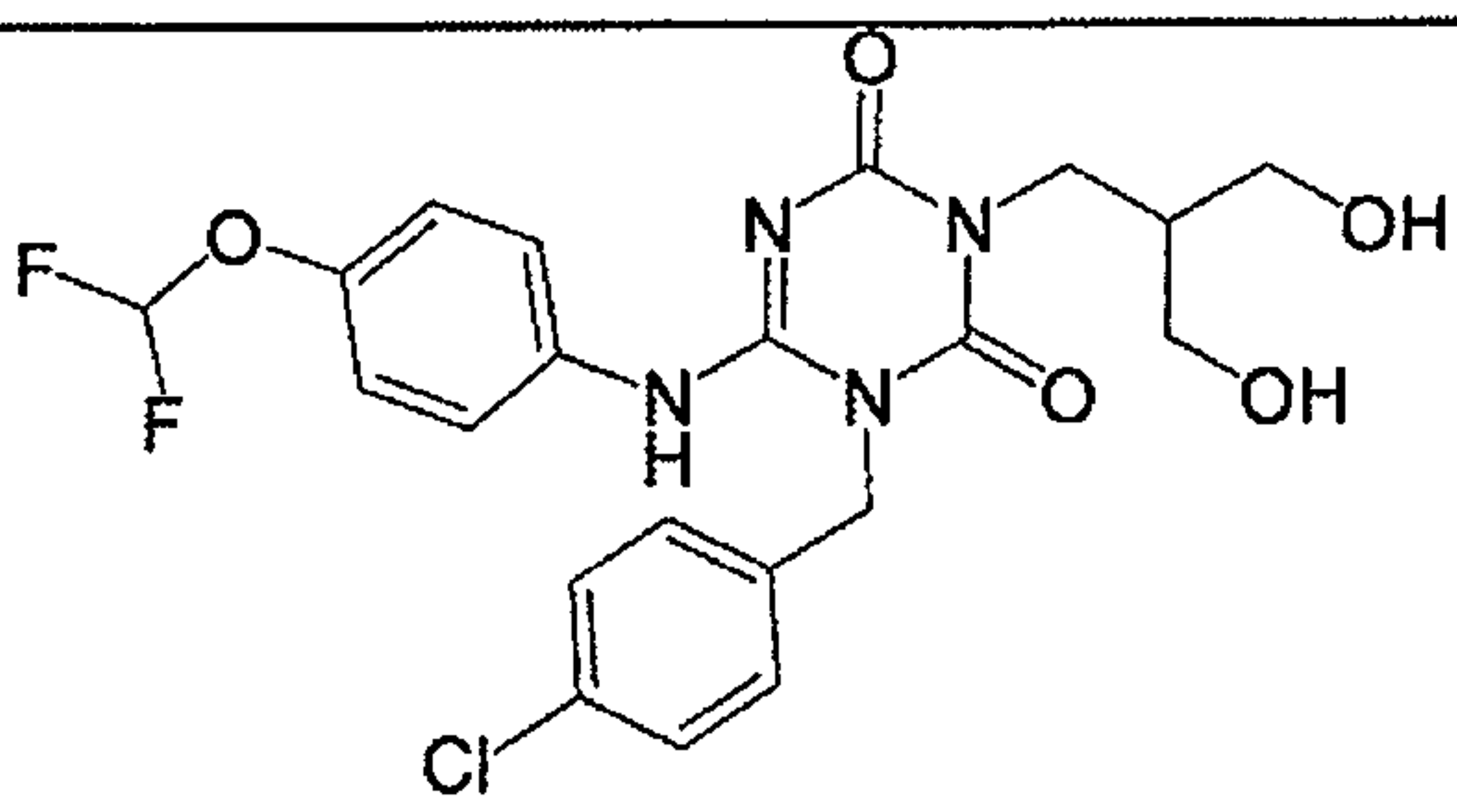
[Table 75]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0356	2.33	505	2
	I-0357	2.07	455	2
	I-0358	2.23	442	2
	I-0359	1.85	445	2
	I-0360	1.84	453	2

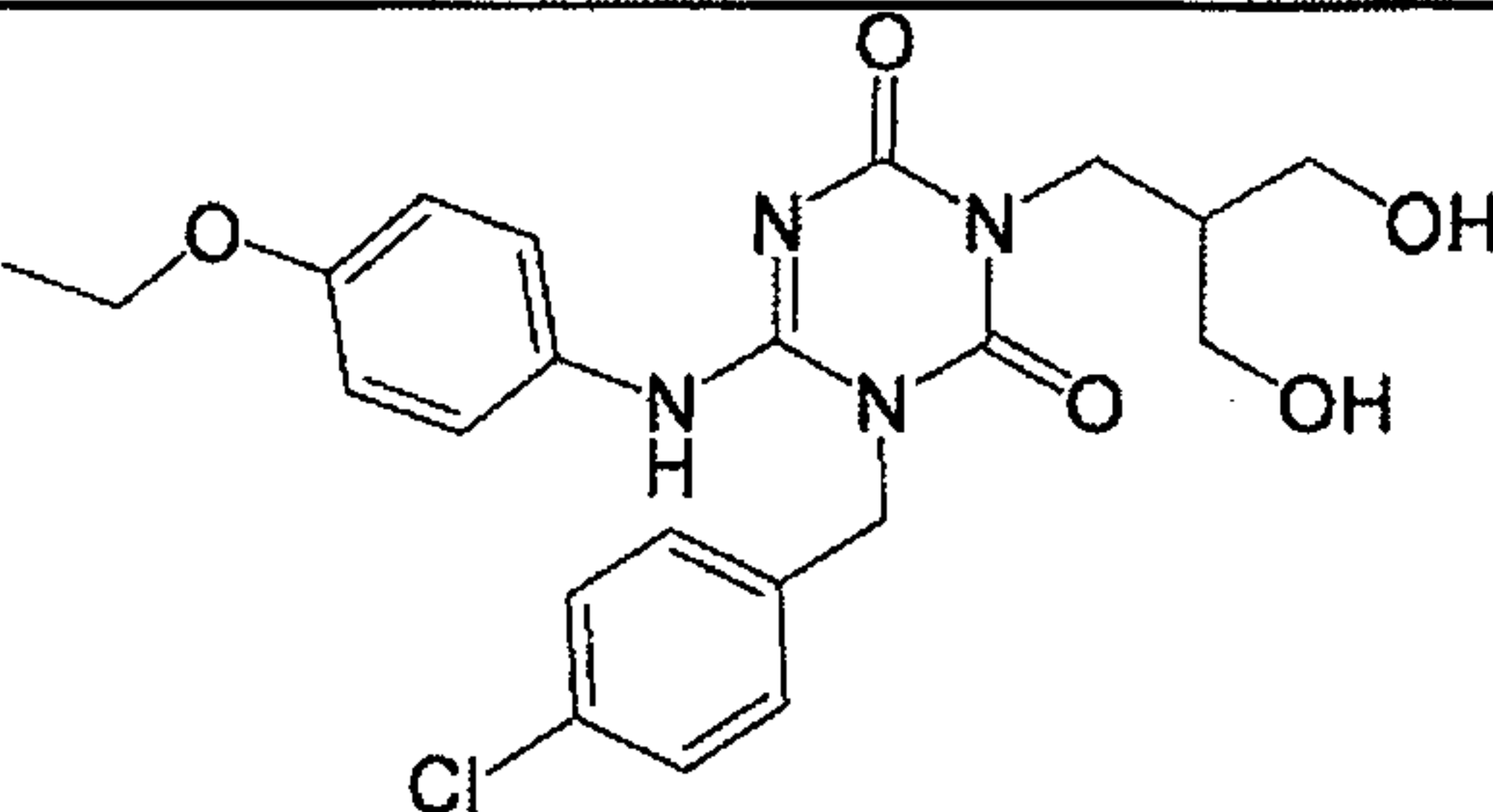
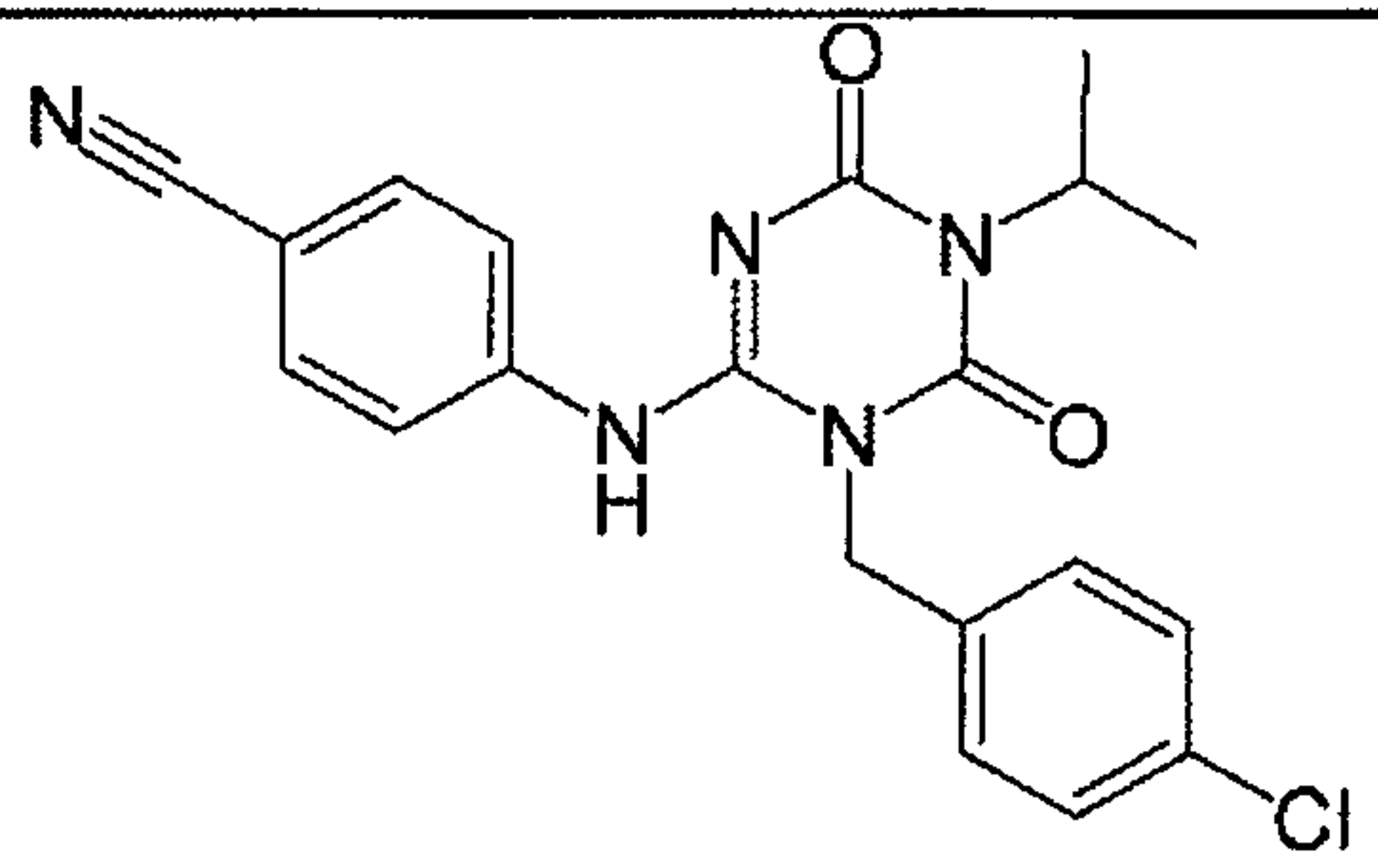
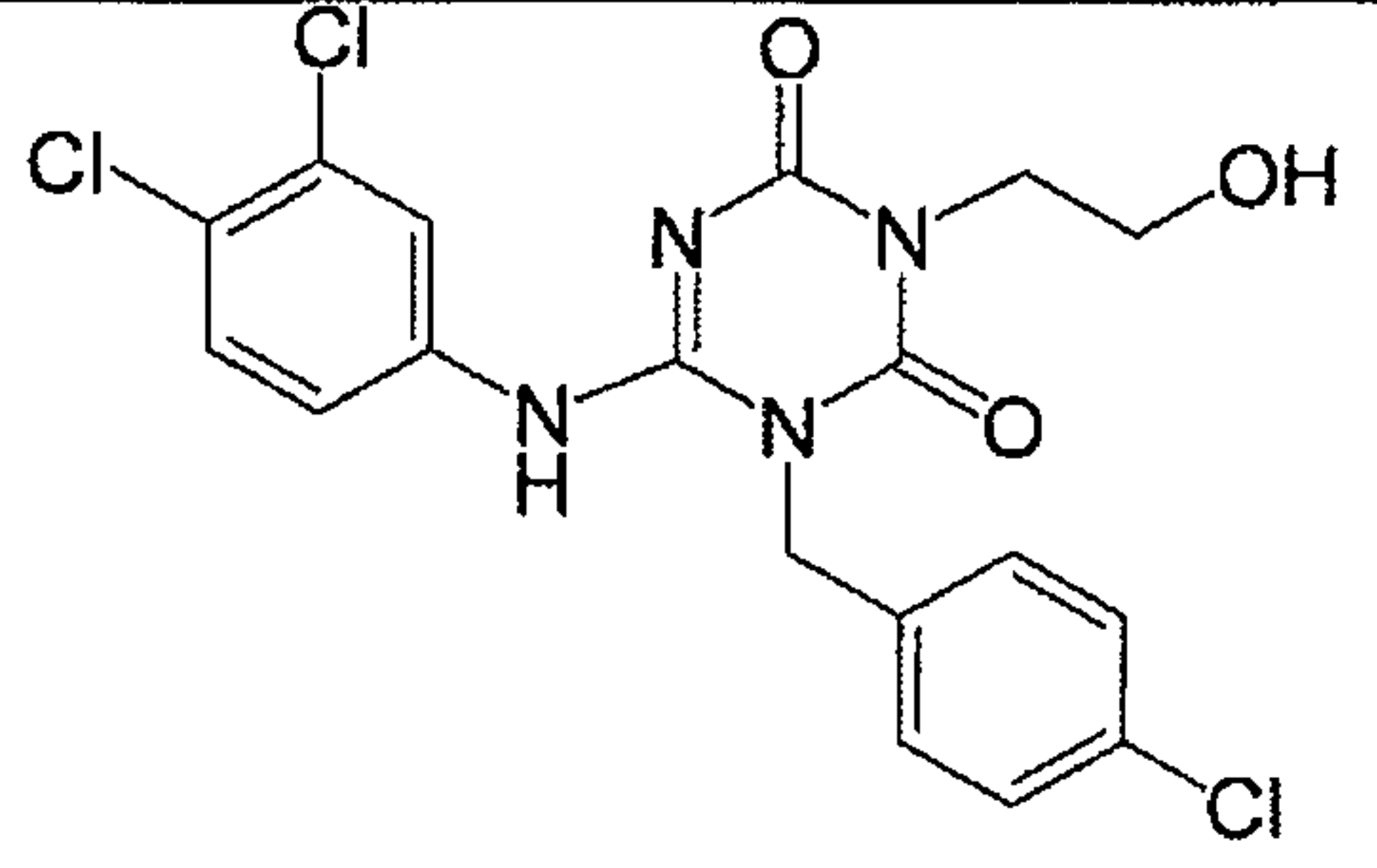
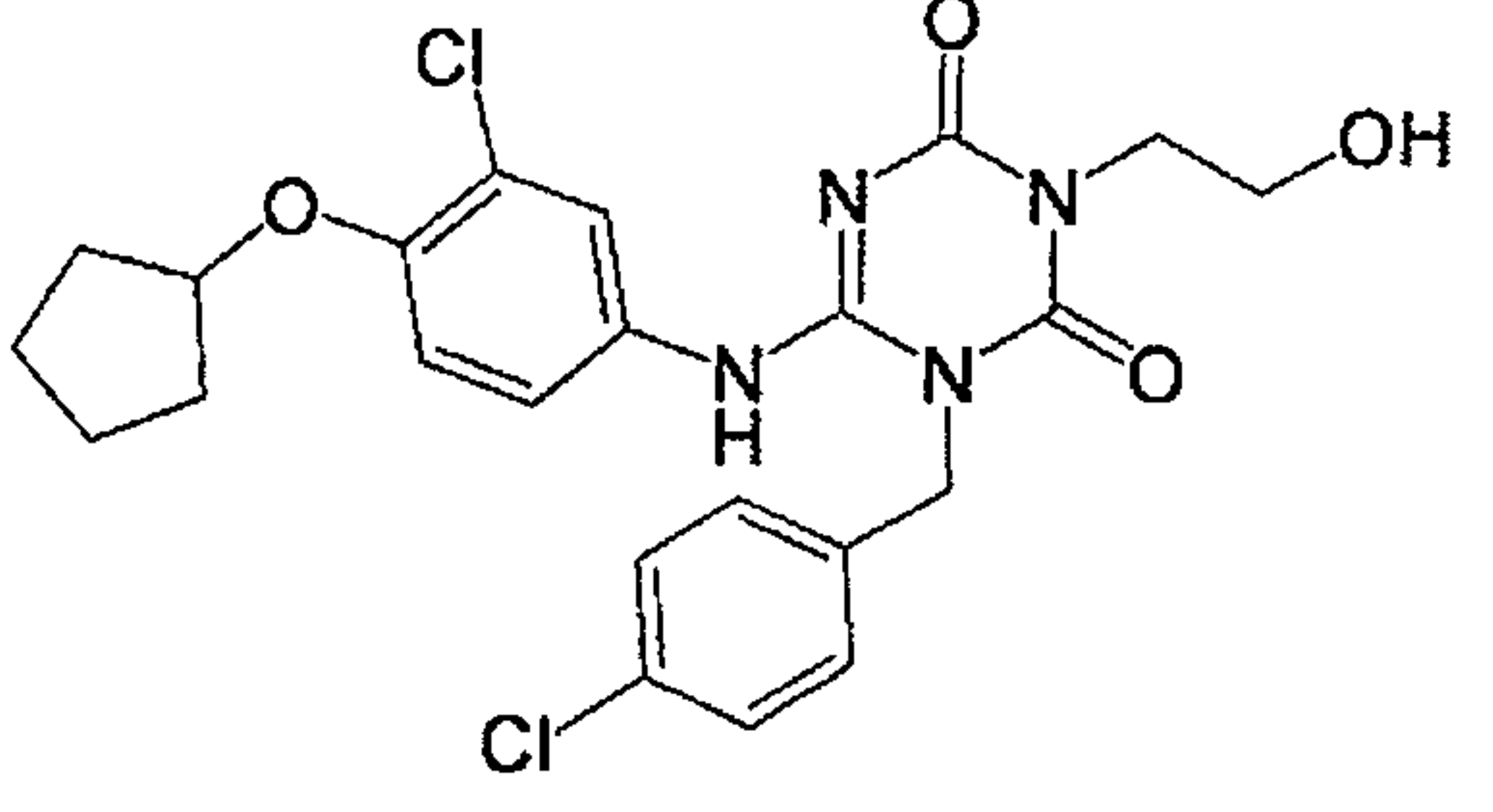
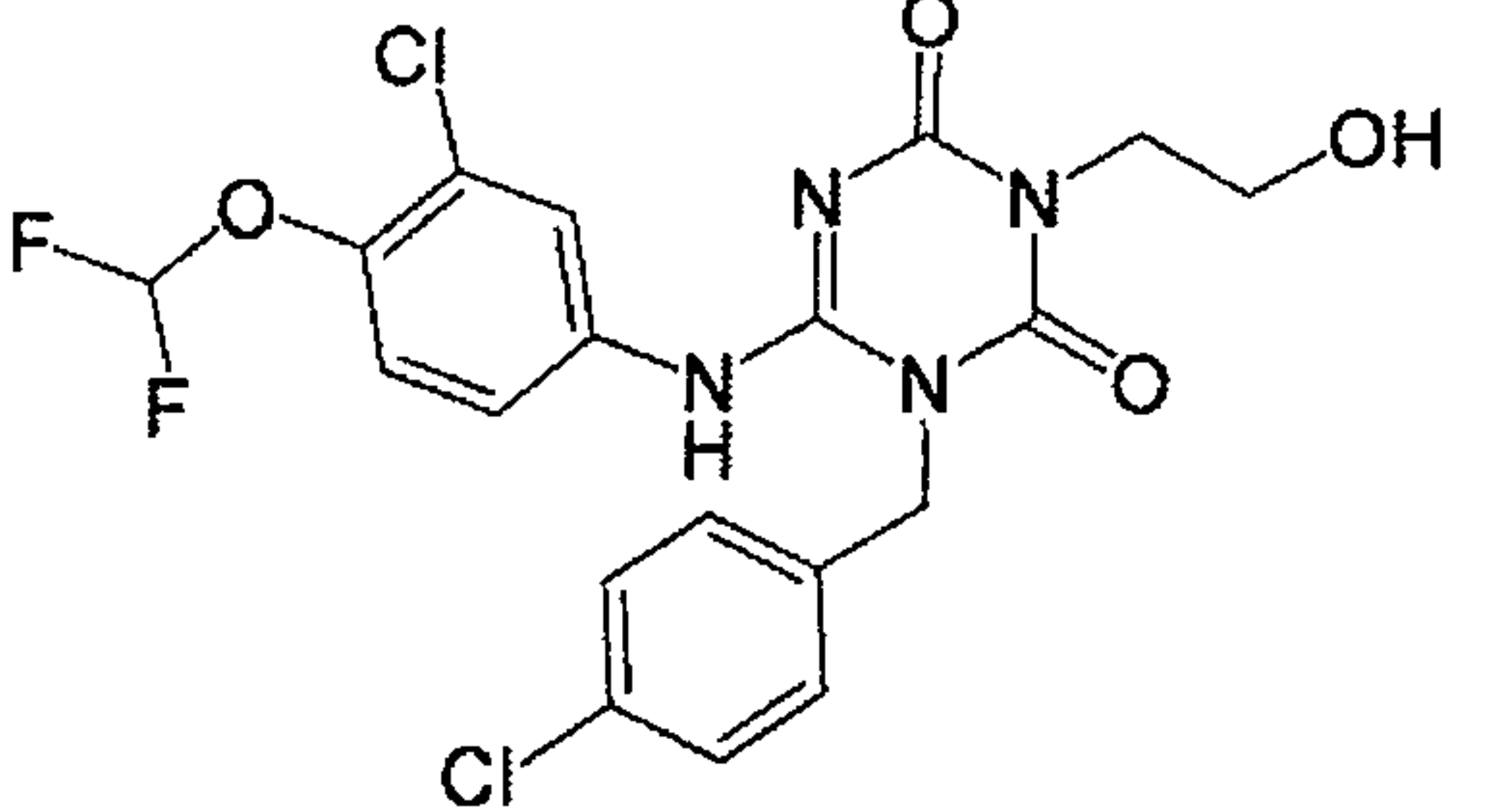
[Table 76]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0361	1.77	431	2
	I-0362	2.12	479	2
	I-0363	2.05	491	2
	I-0364	2.12	505	2
	I-0365	2.03	477	2

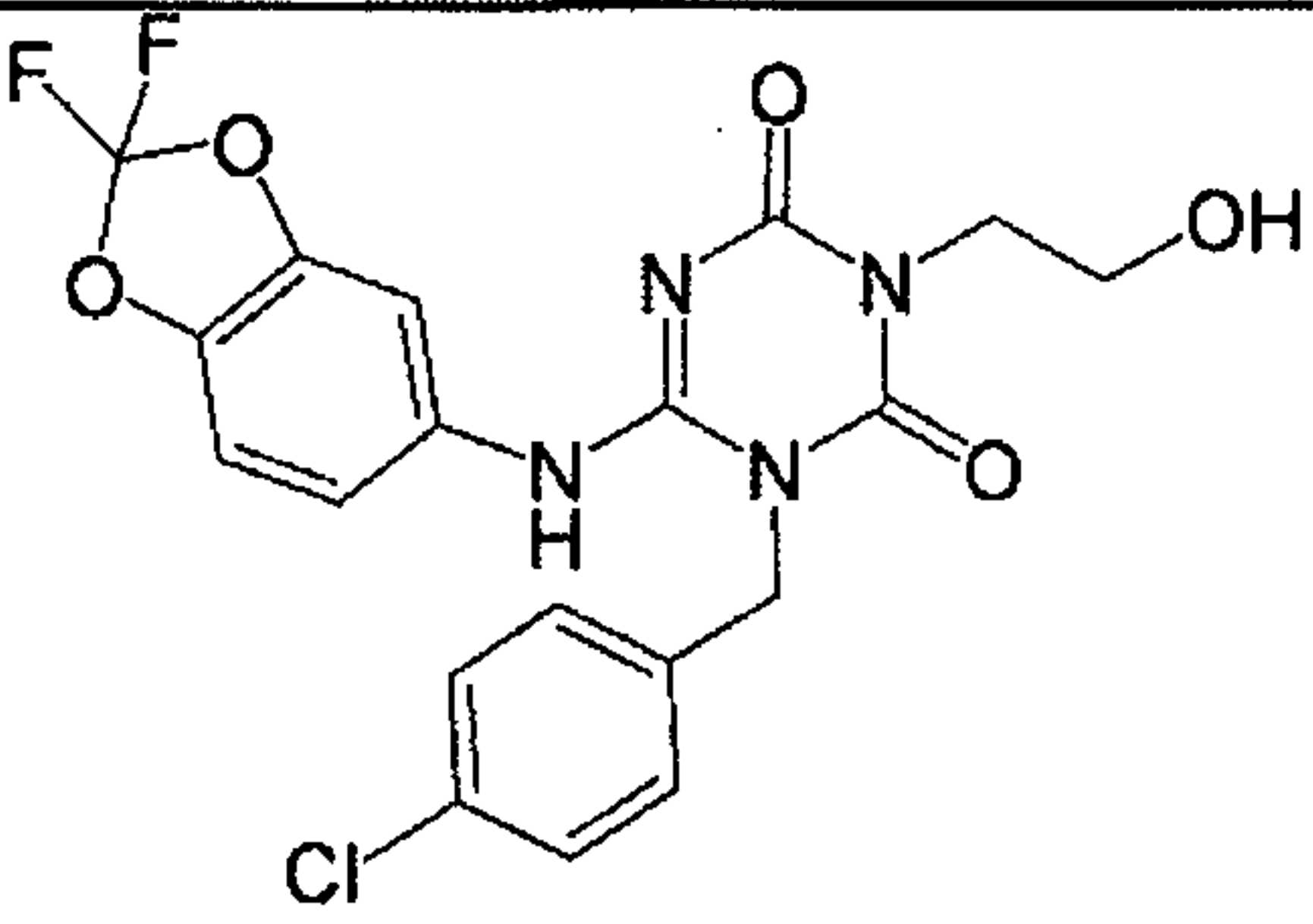
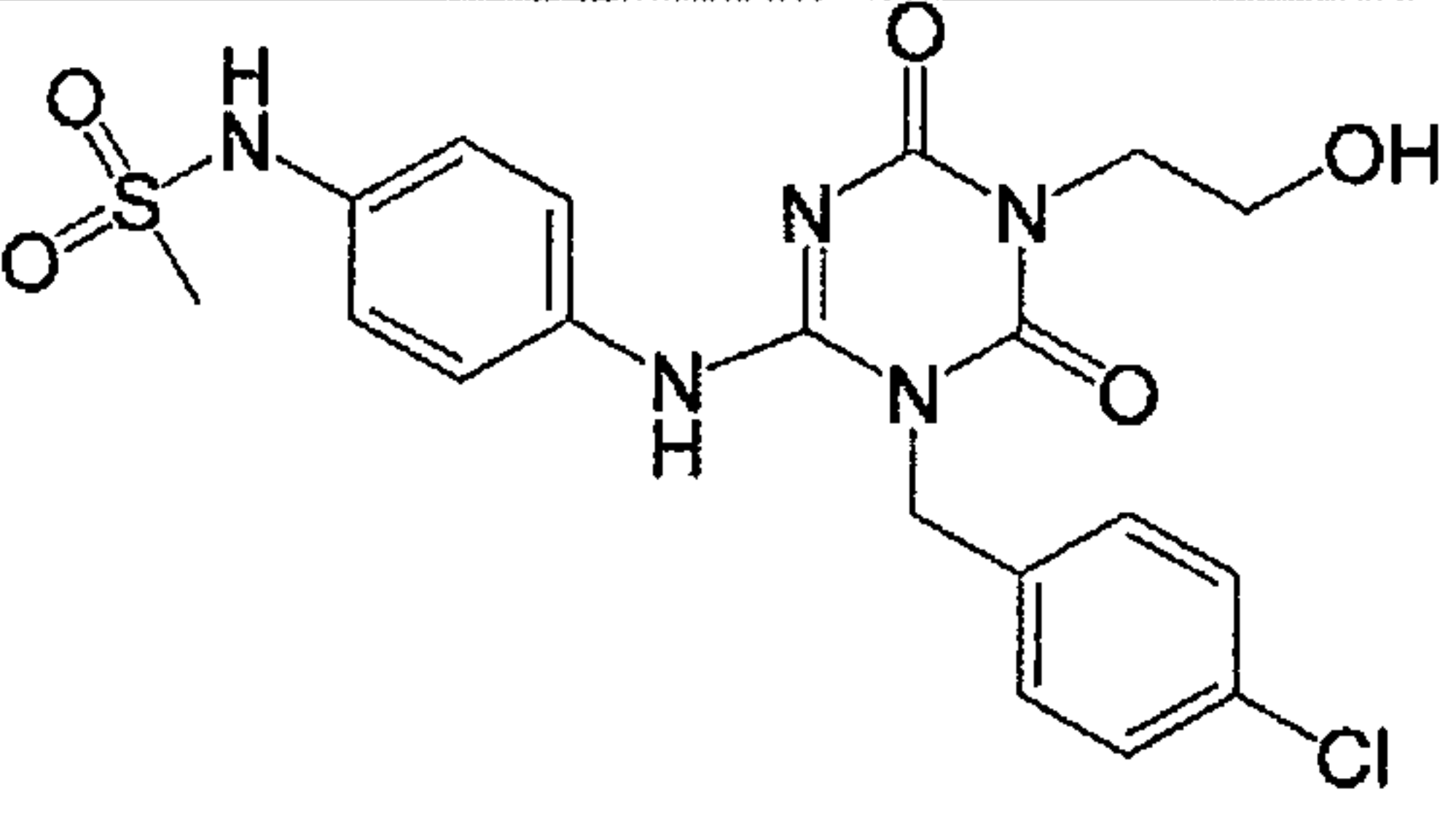
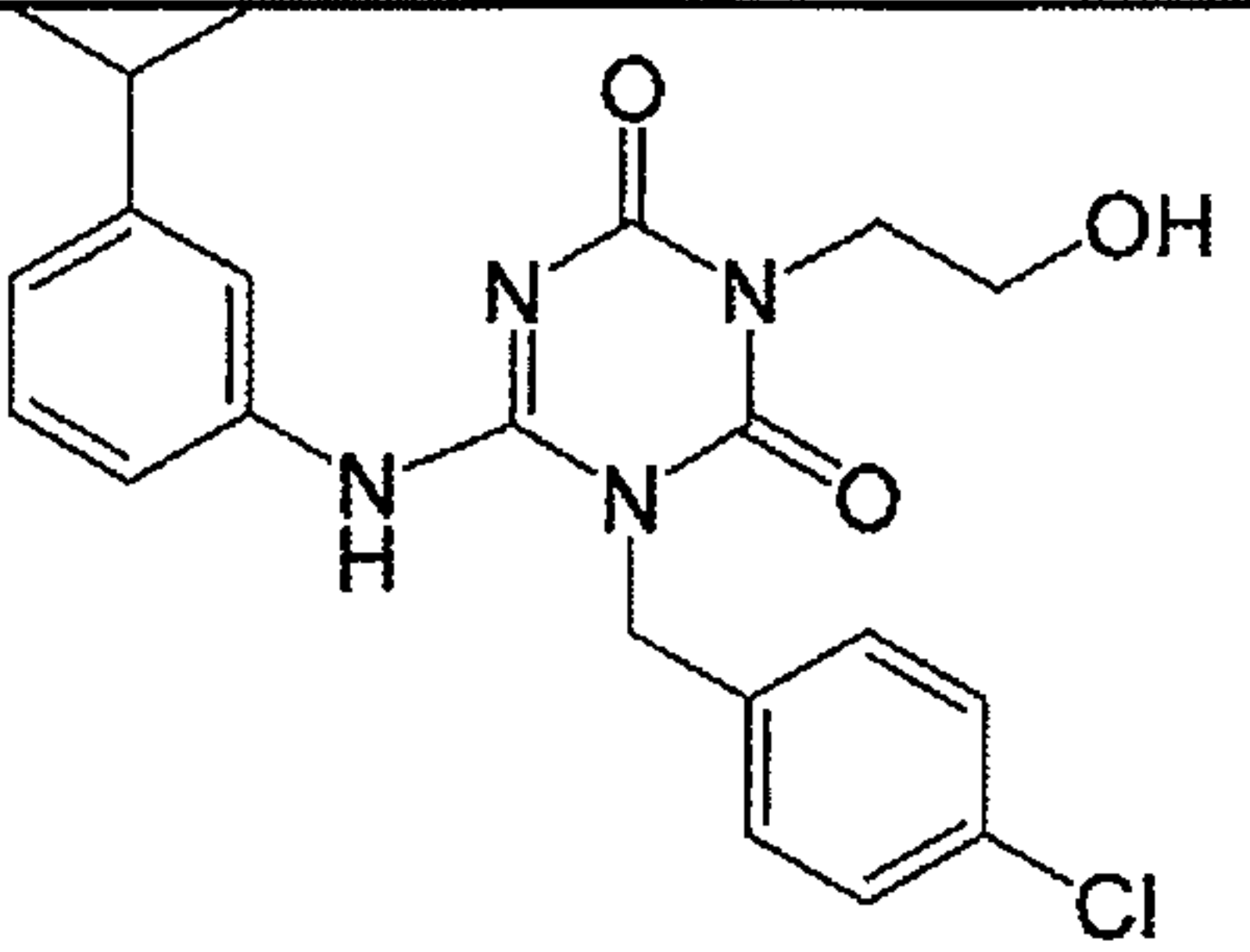
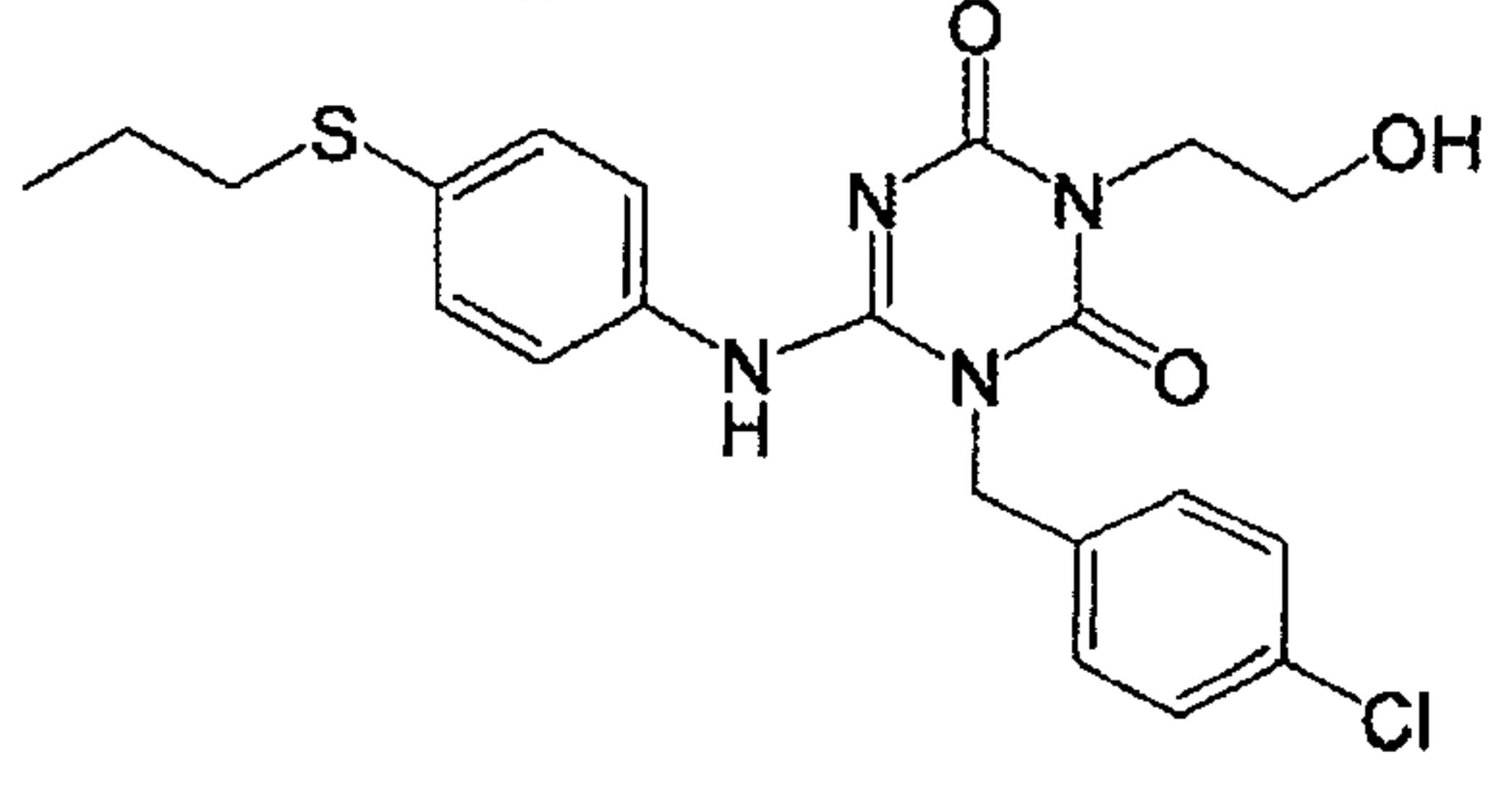
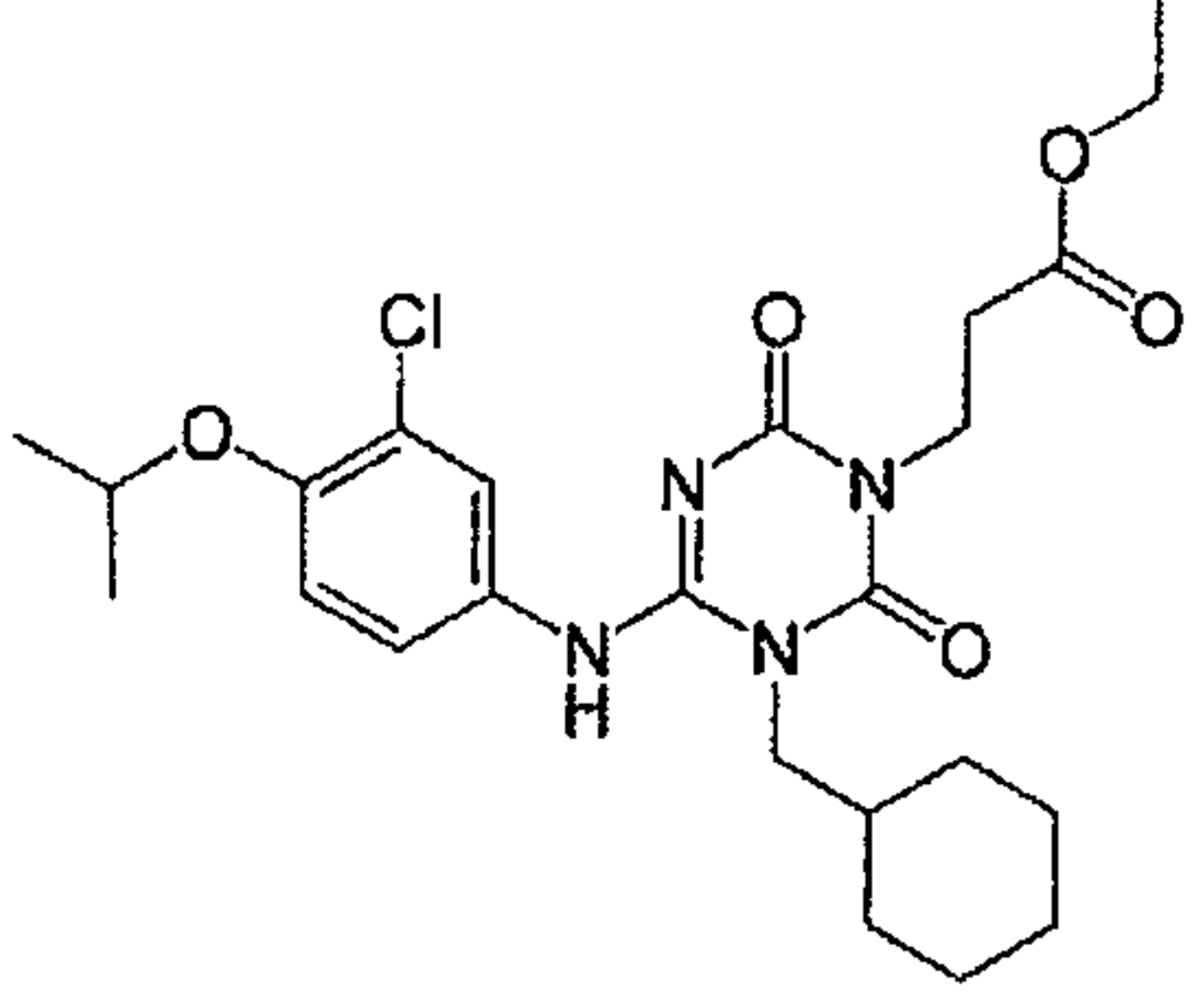
[Table 77]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0366	2.33	473	3
	I-0367	2.17	485	3
	I-0368	2.00	475	3
	I-0369	2.24	510	3
	I-0370	1.98	483	3

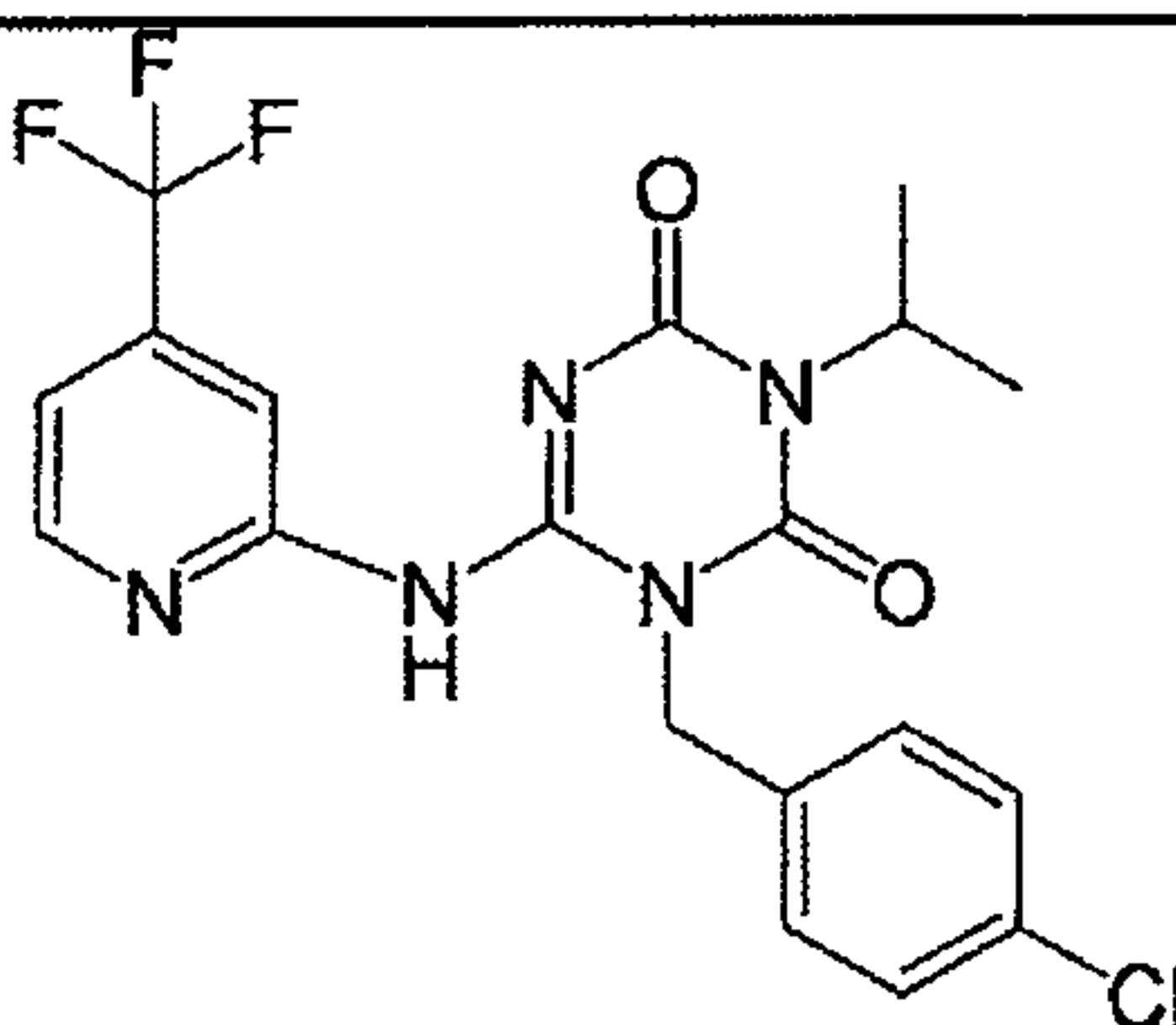
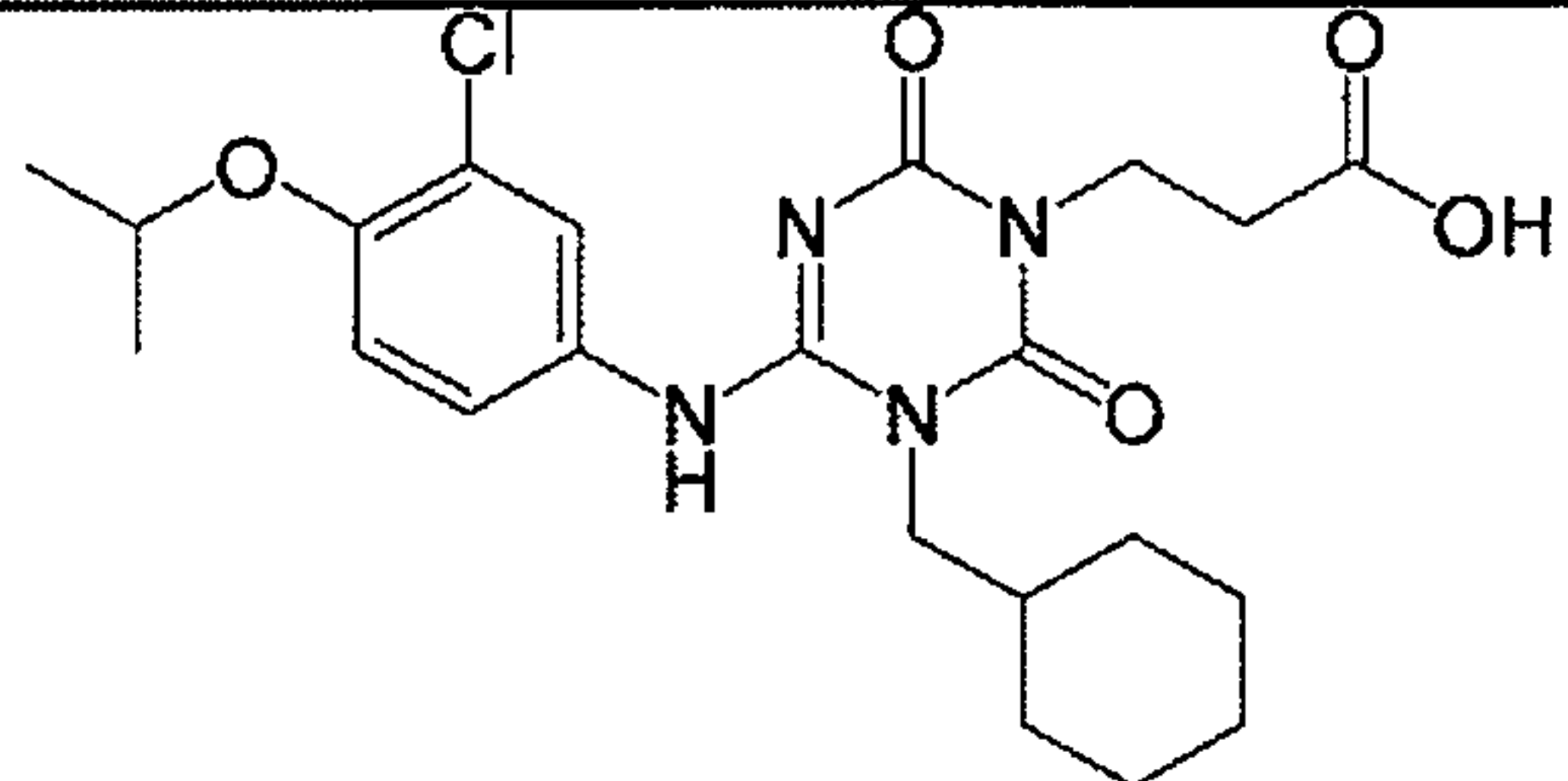
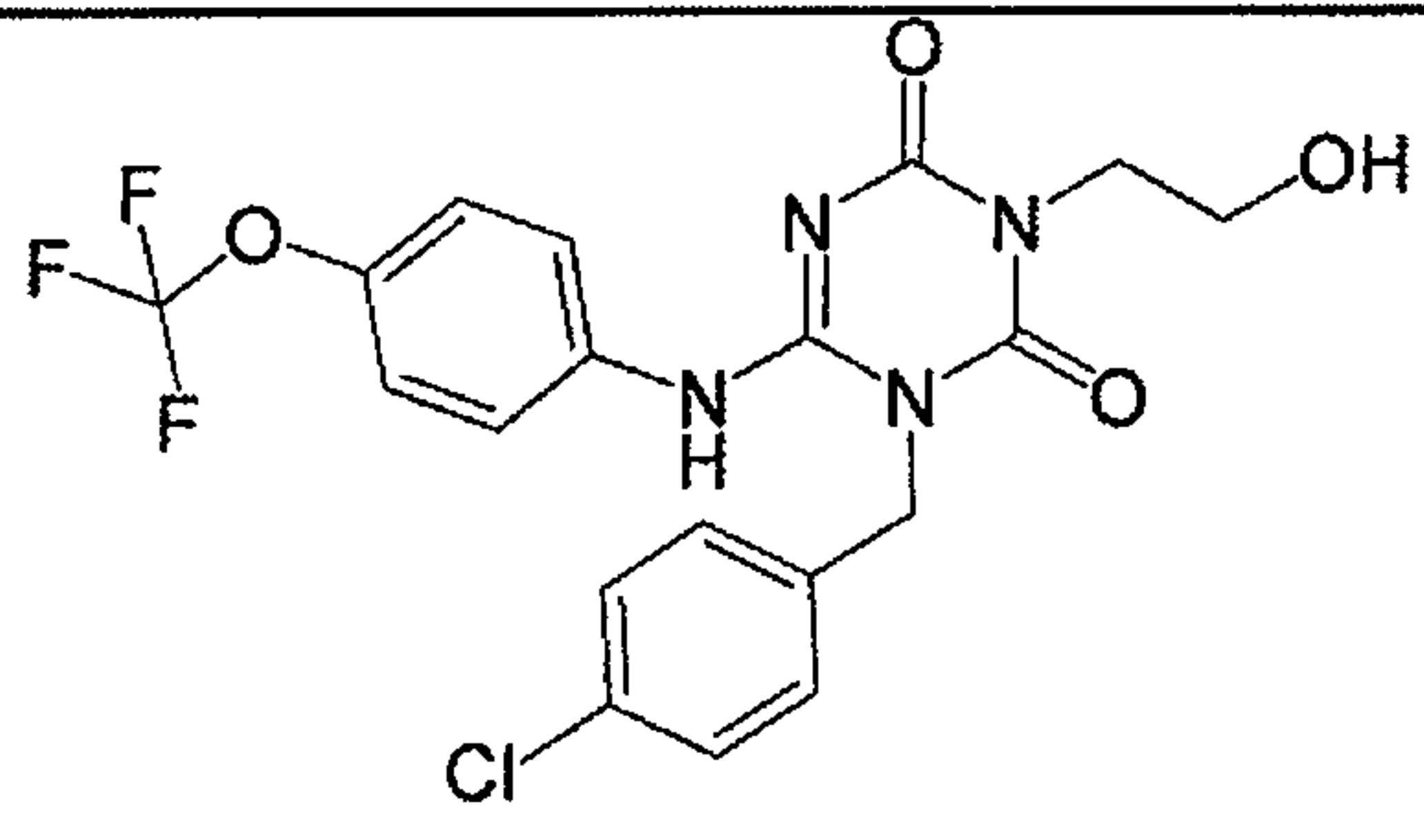
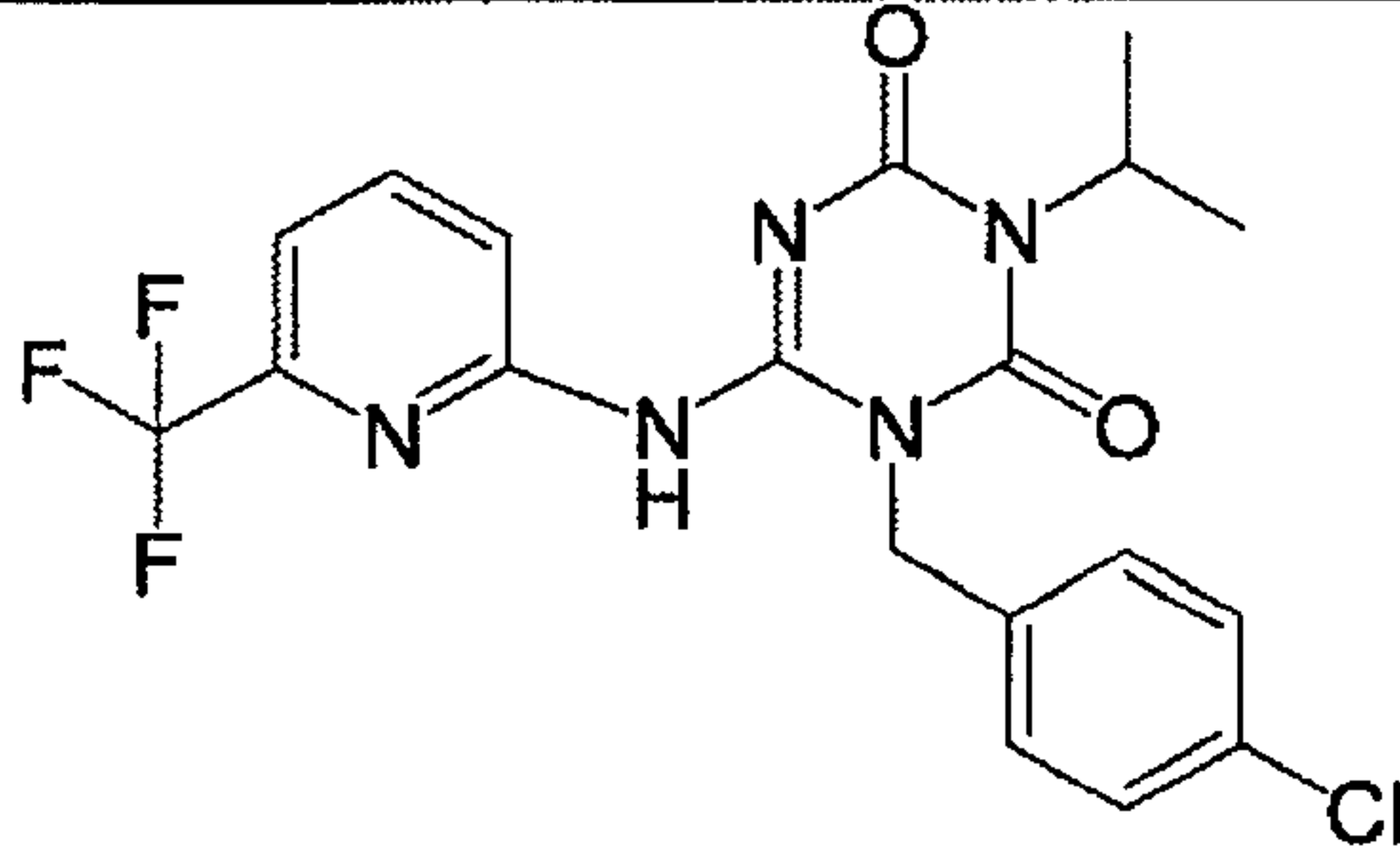
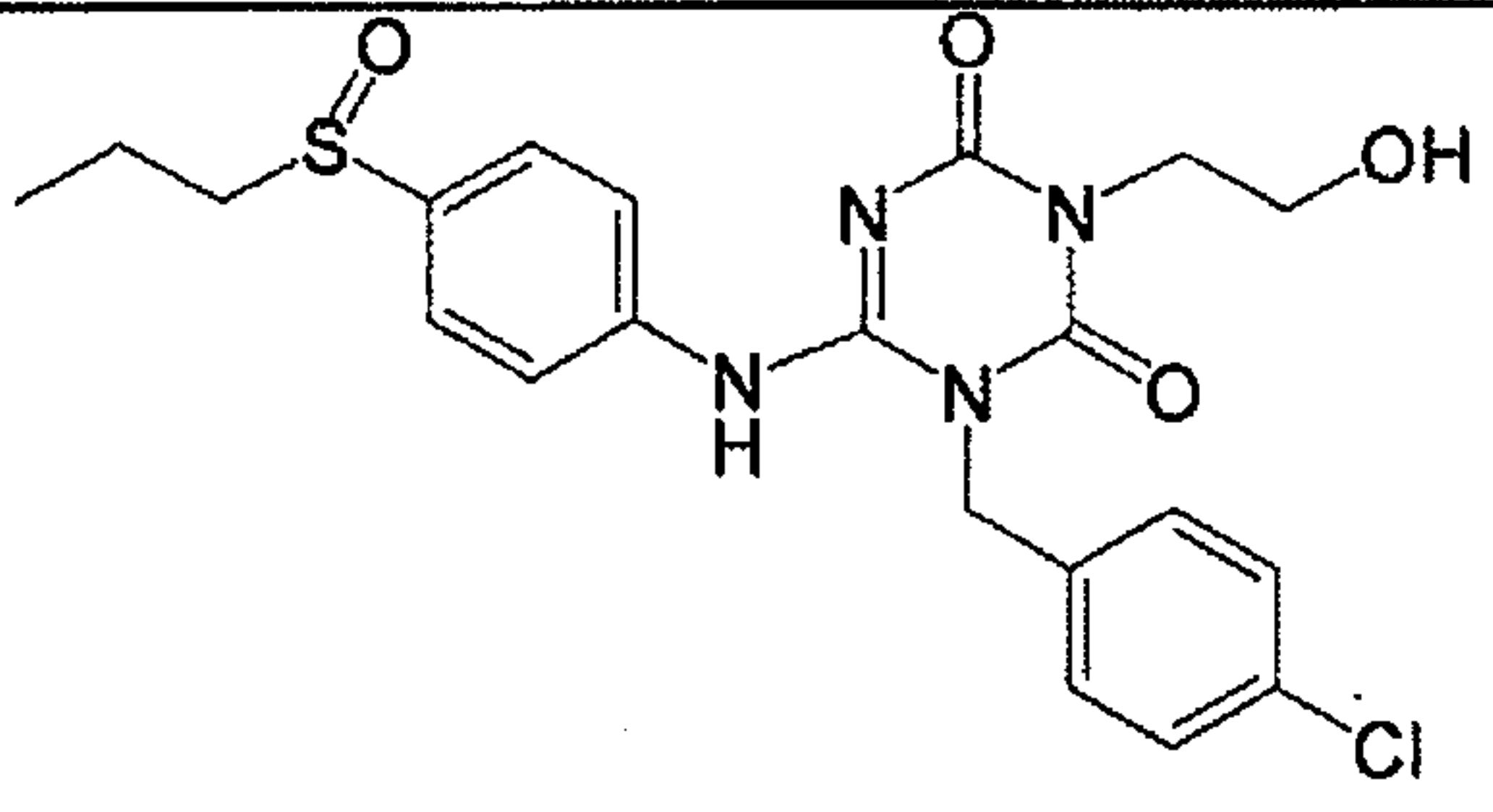
[Table 78]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0371	1.88	461	3
	I-0372	2.27	396	2
	I-0373	2.17	443	2
	I-0374	2.28	491	2
	I-0375	2.32	473	3

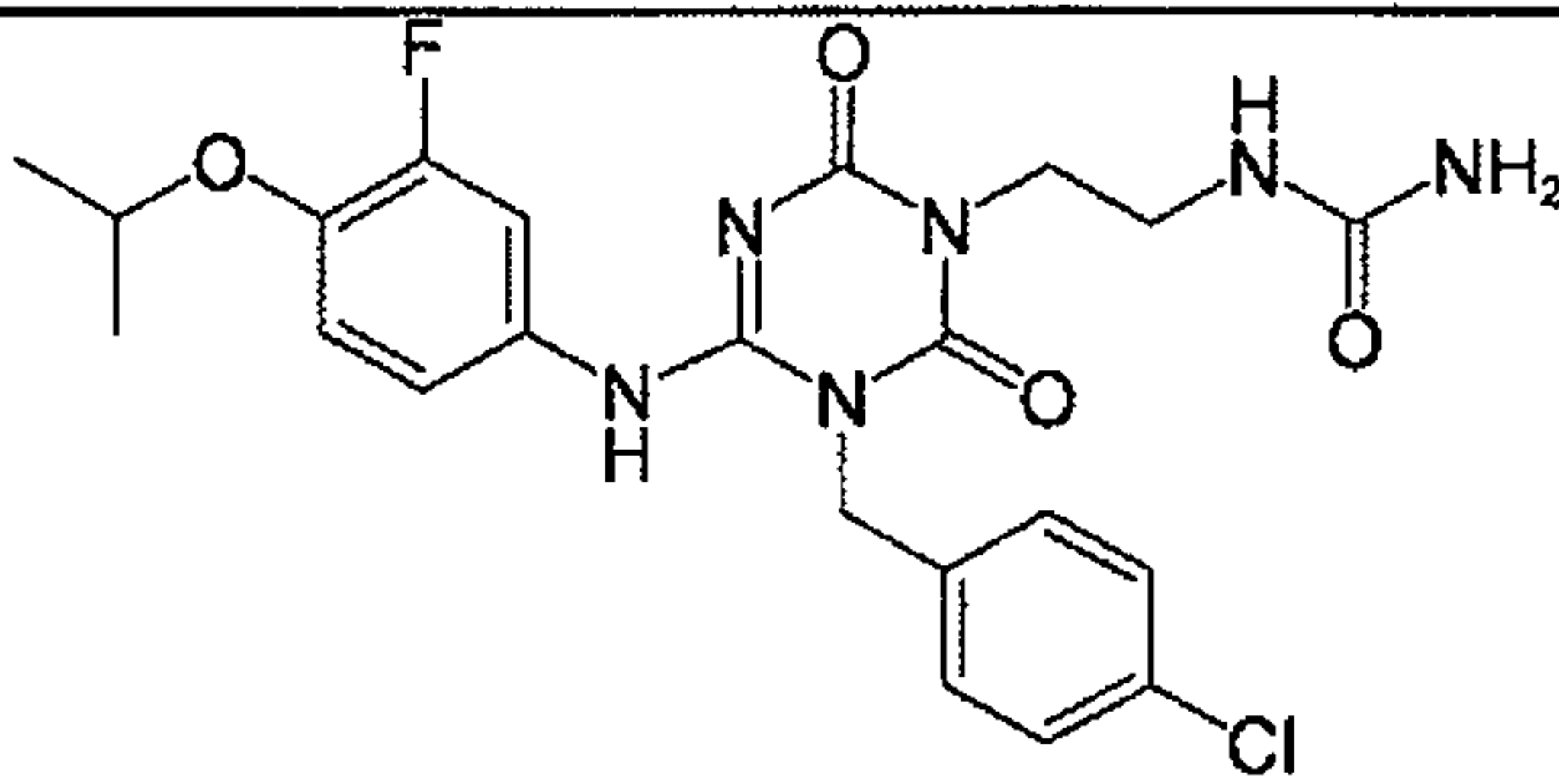
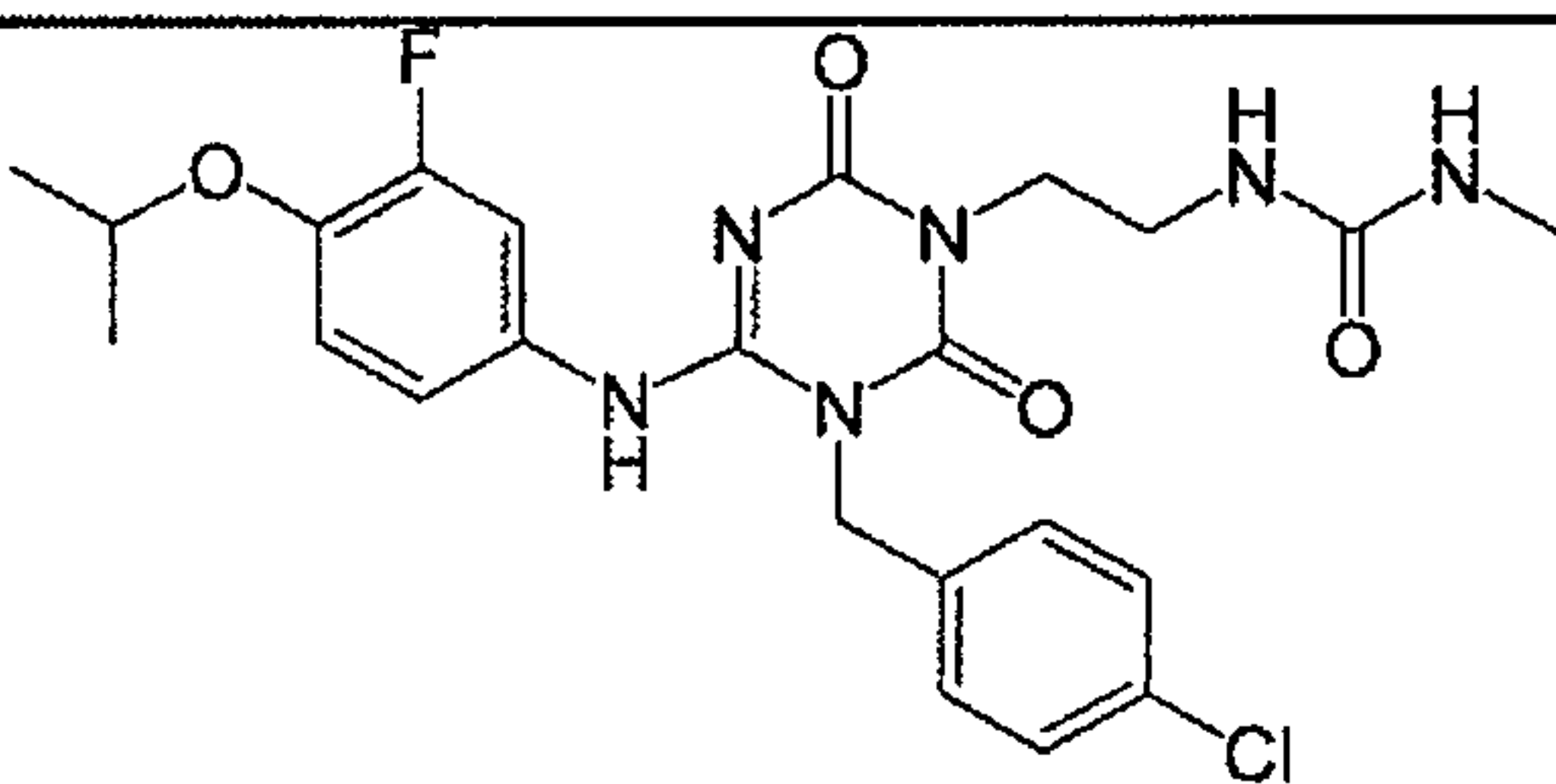
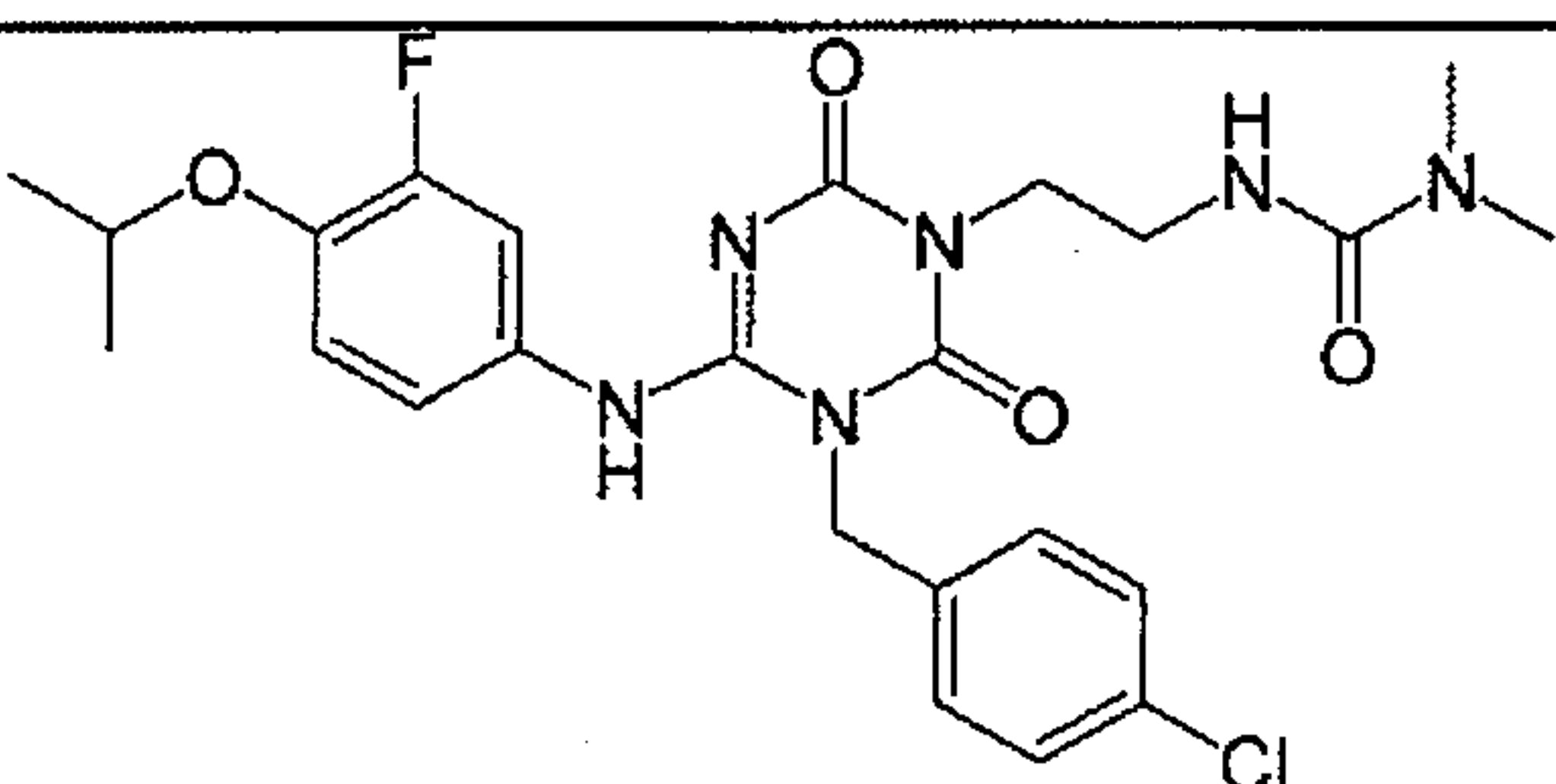
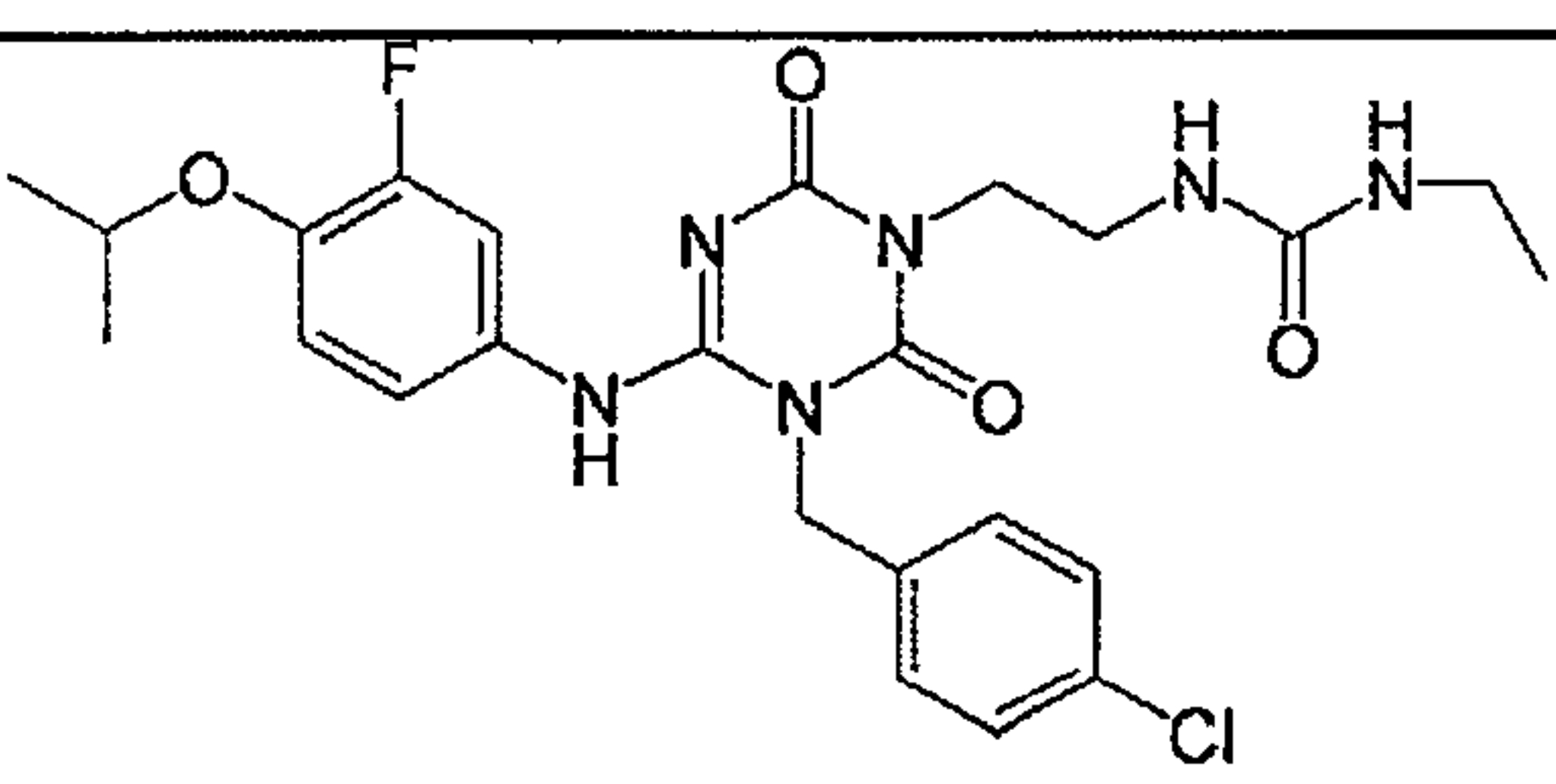
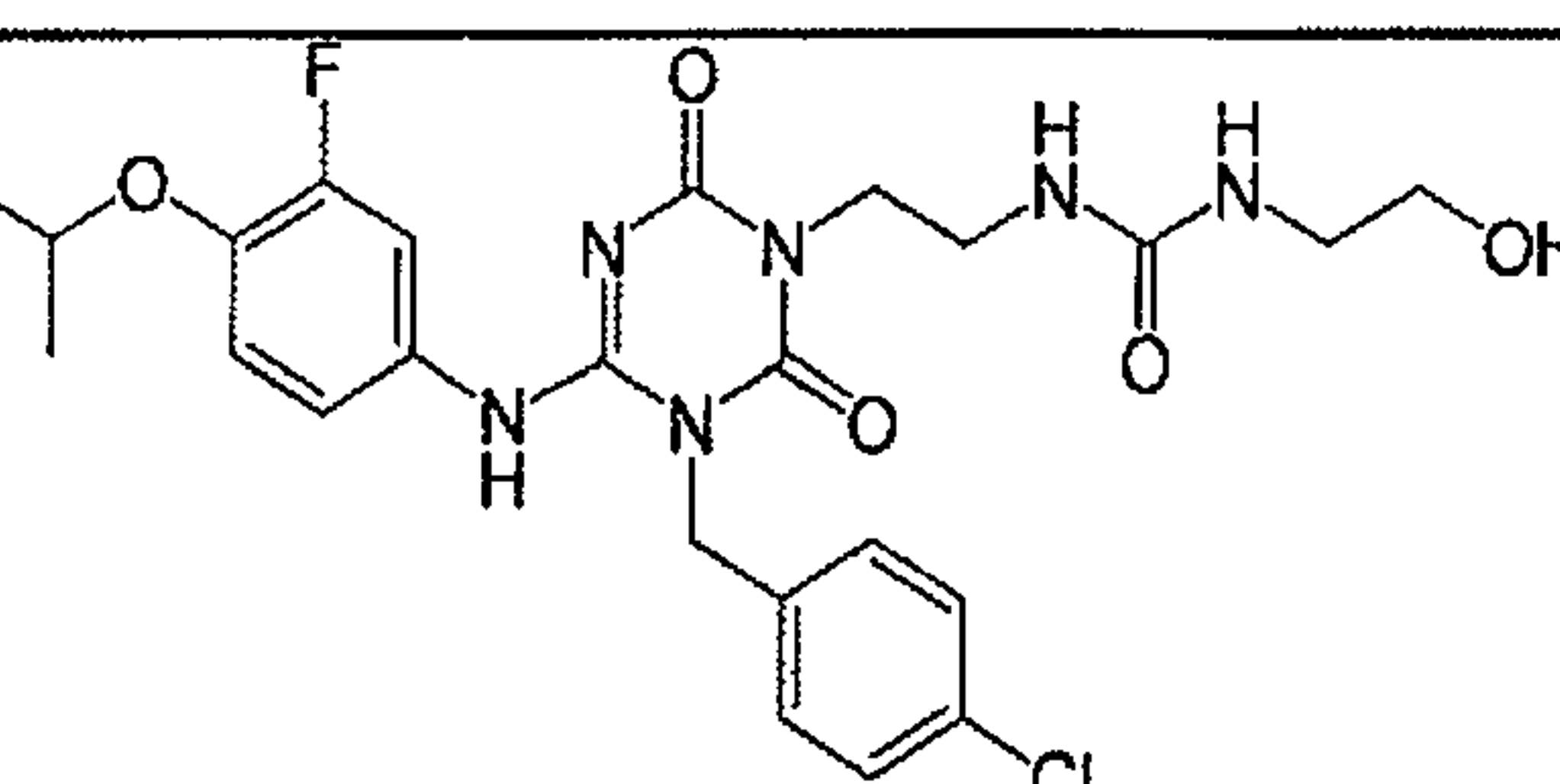
[Table 79]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0376	2.30	453	3
	I-0377	1.41	446	2
	I-0378	2.02	415	2
	I-0379	2.11	447	2
	I-0380	2.49	493	2

[Table 80]

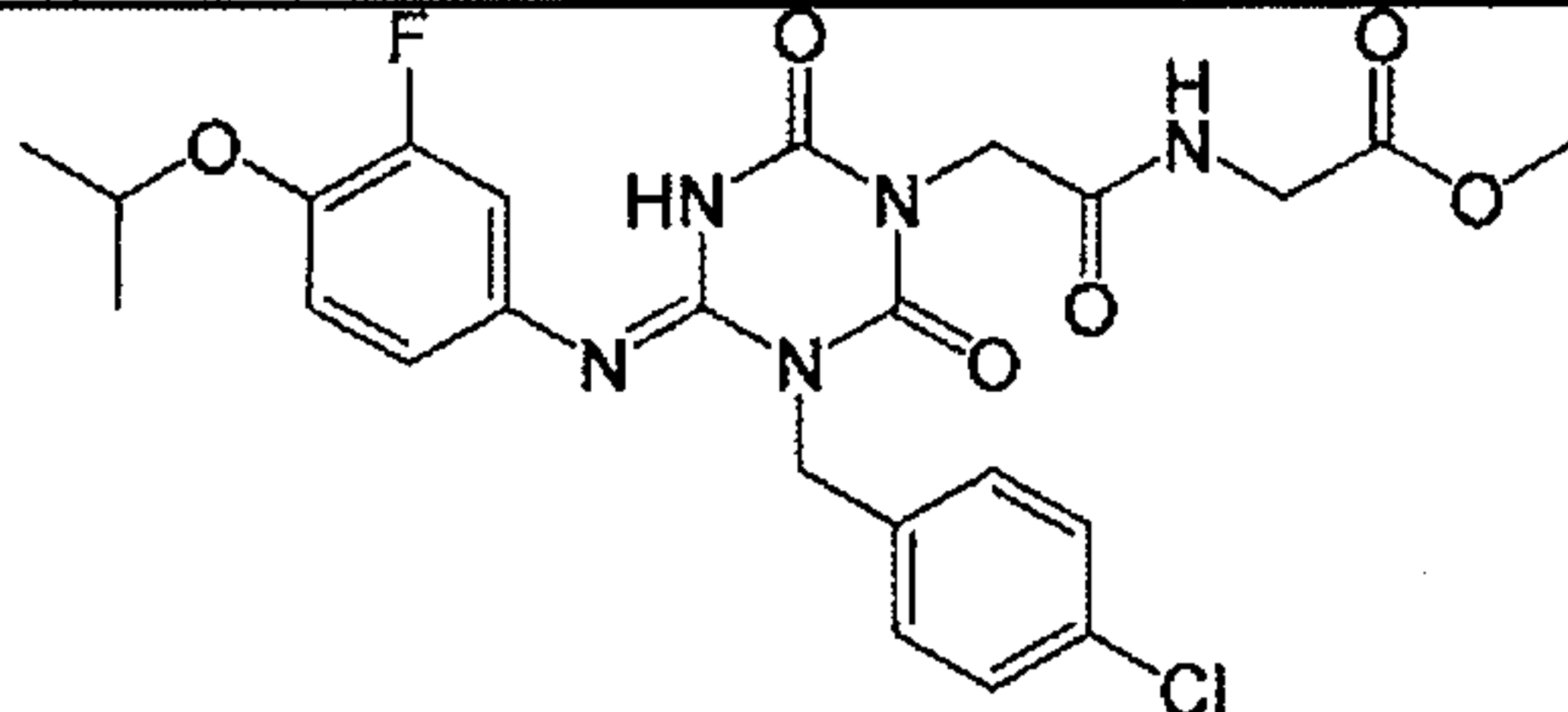
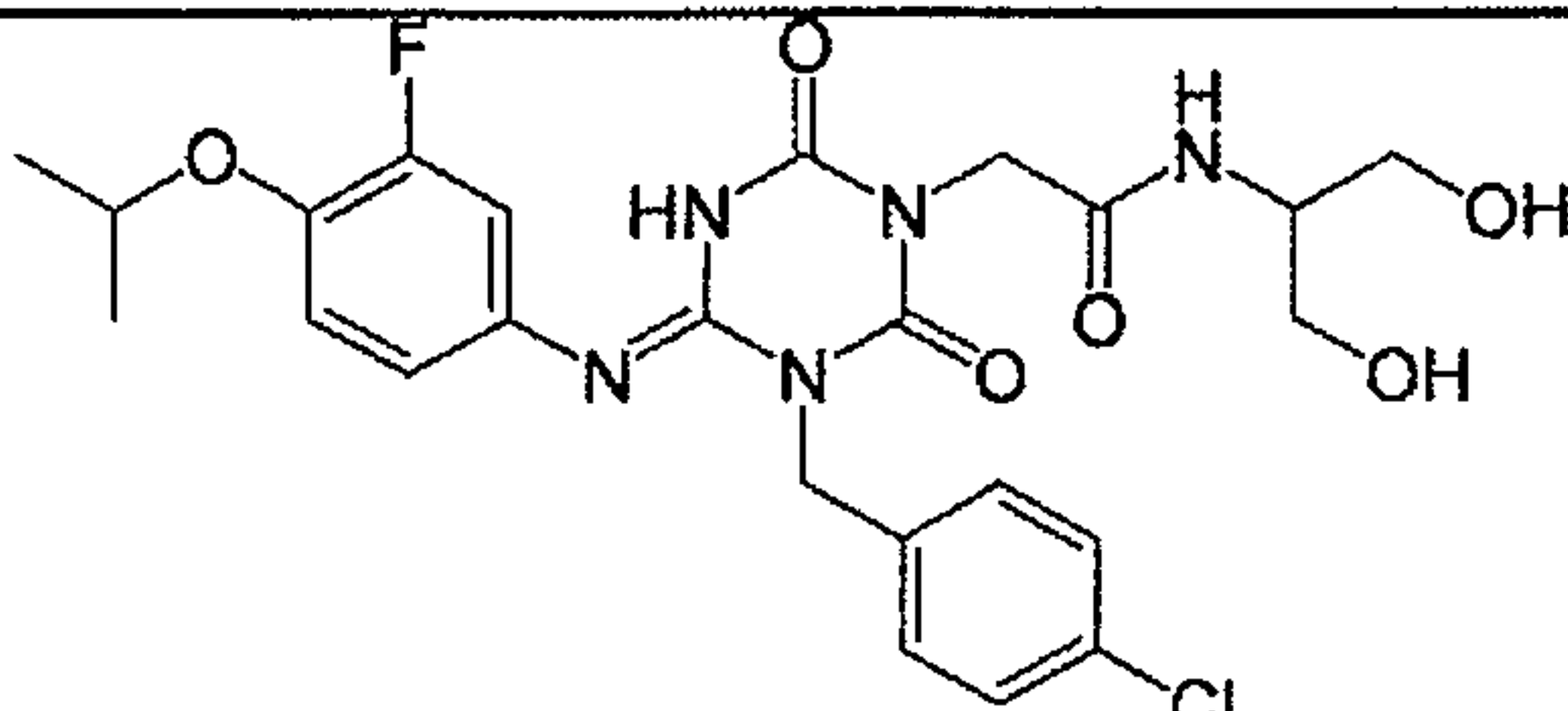
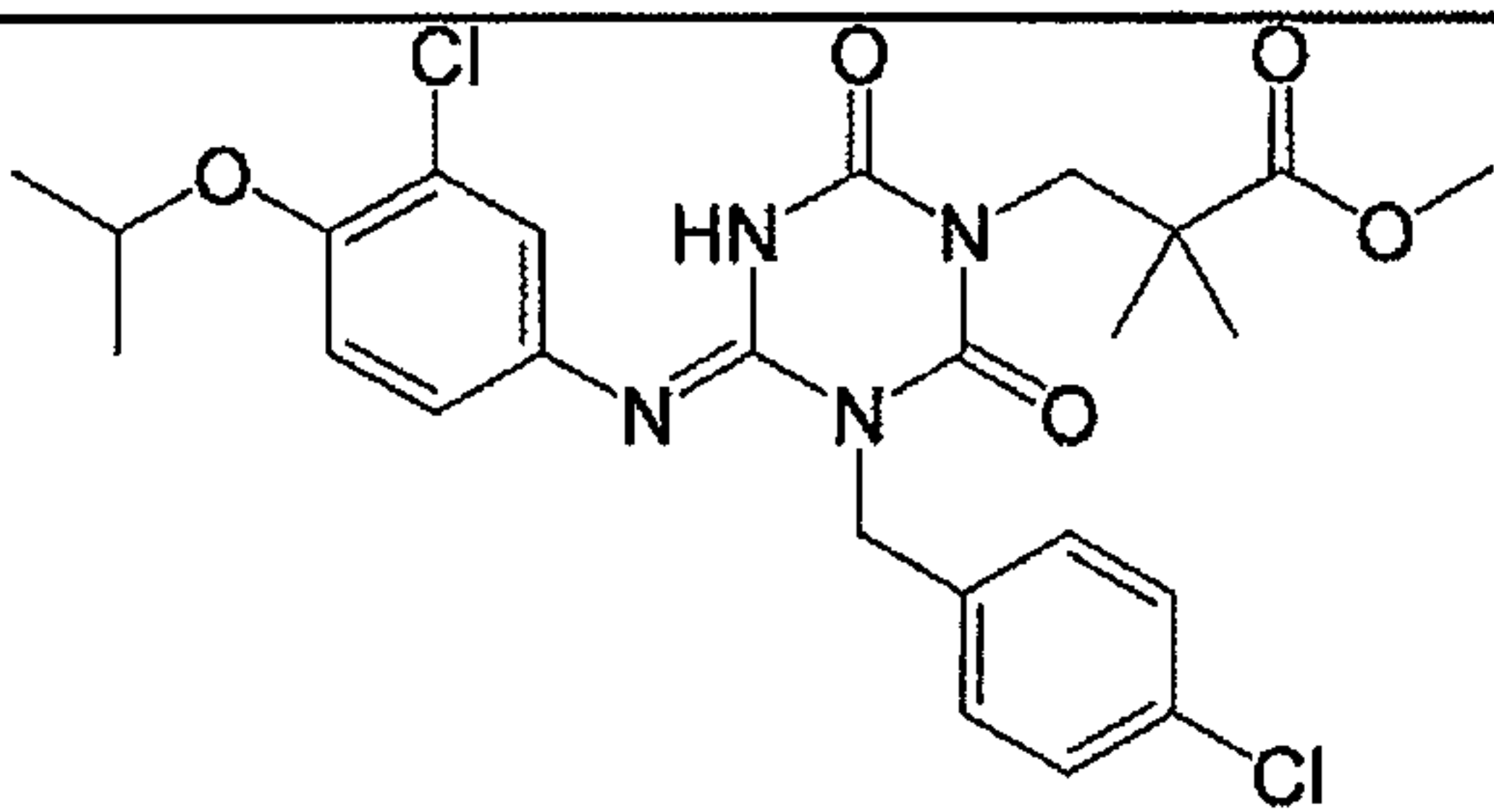
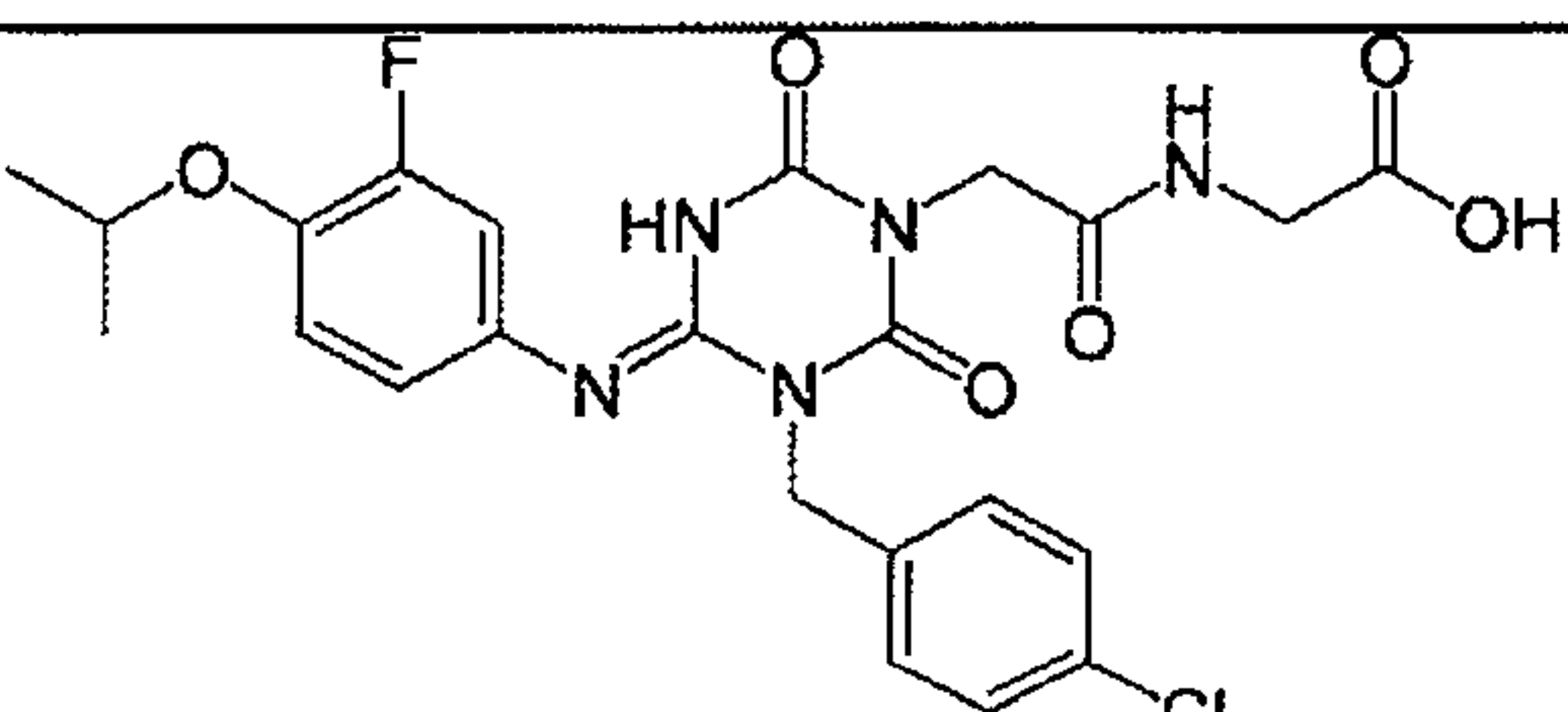
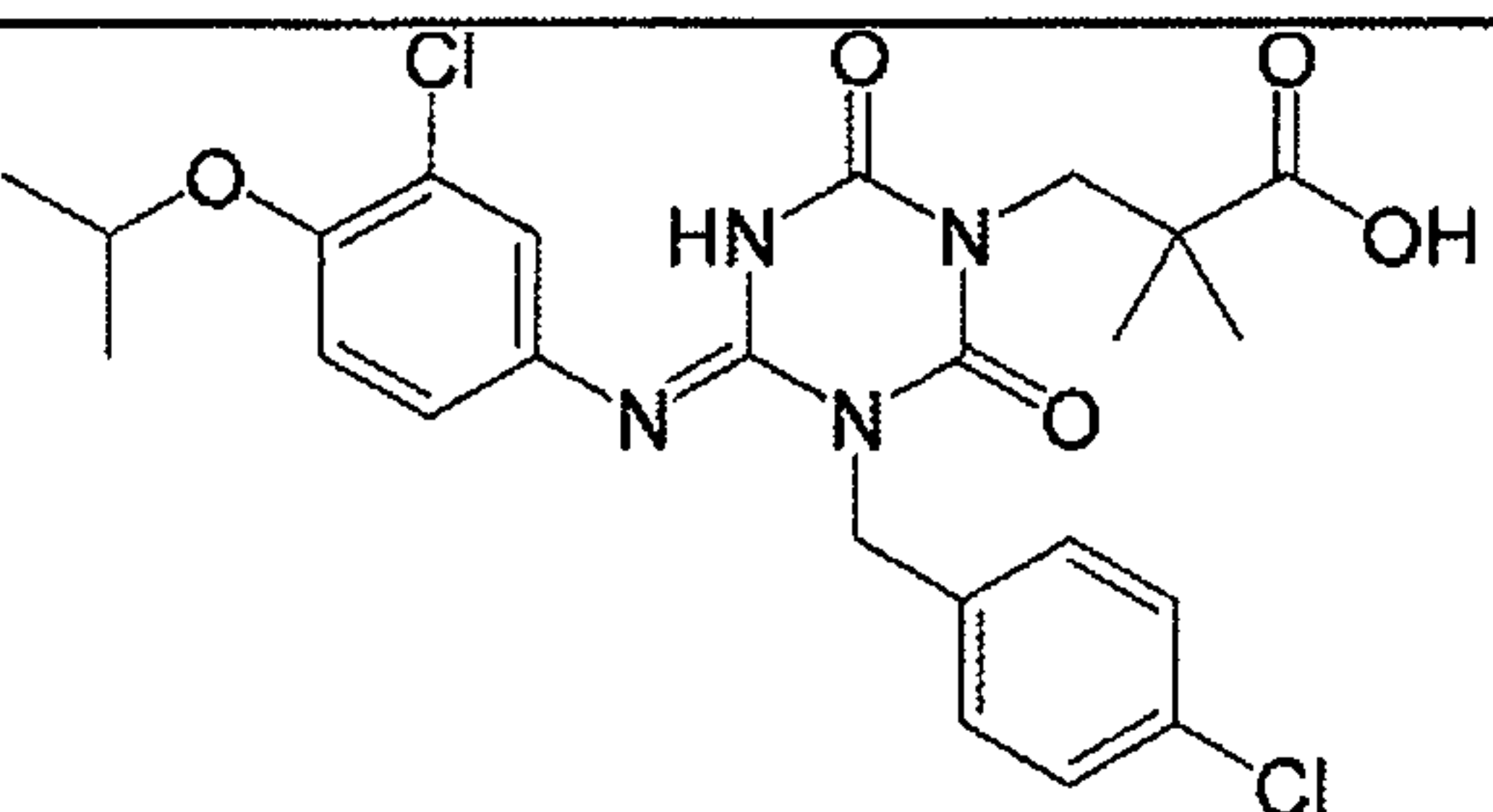
Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0381	3.04	440	3
	I-0382	2.09	465	2
	I-0383	2.32	457	3
	I-0384	2.77	440	2
	I-0385	1.56	463	2

[Table 81]

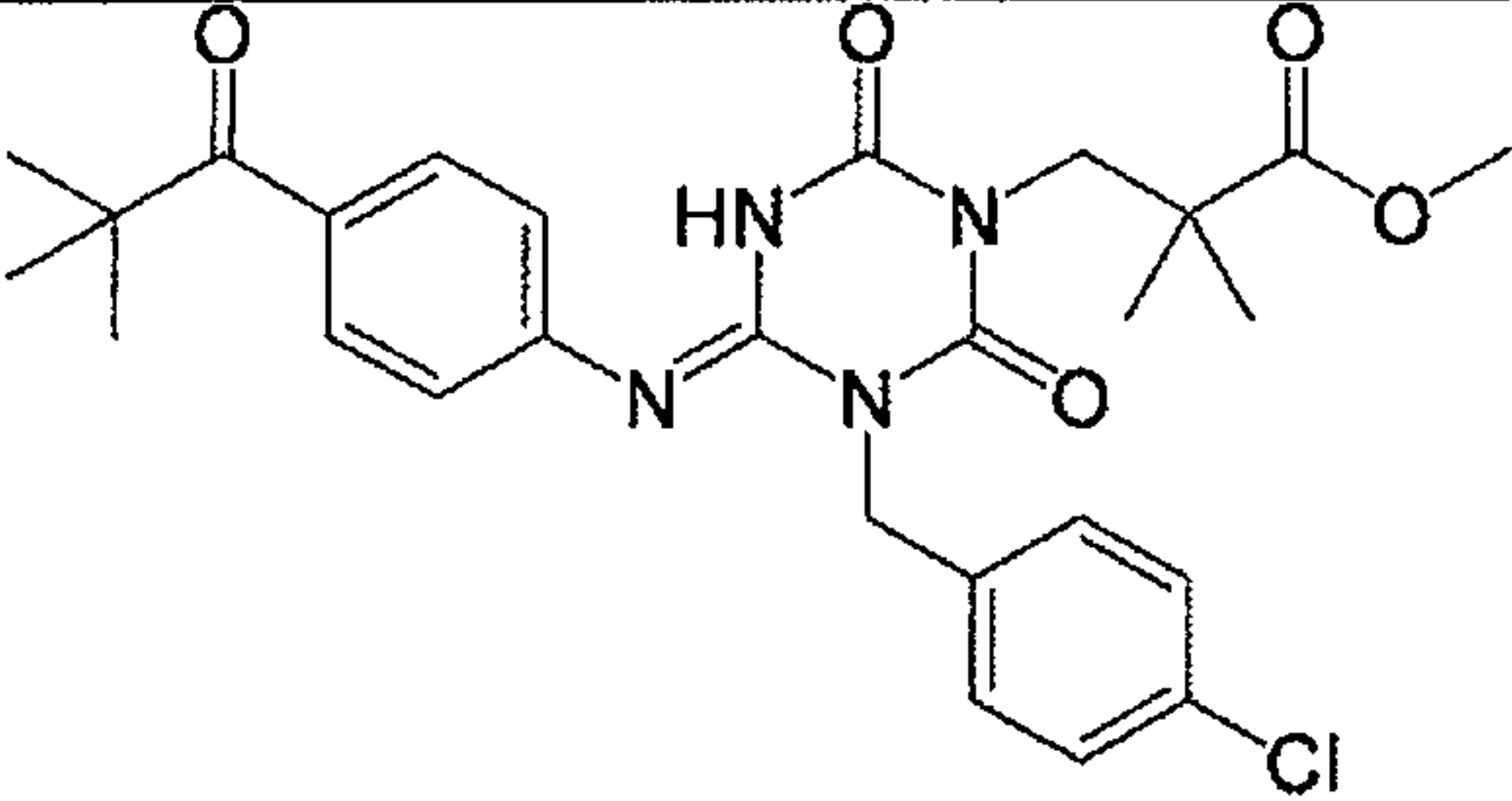
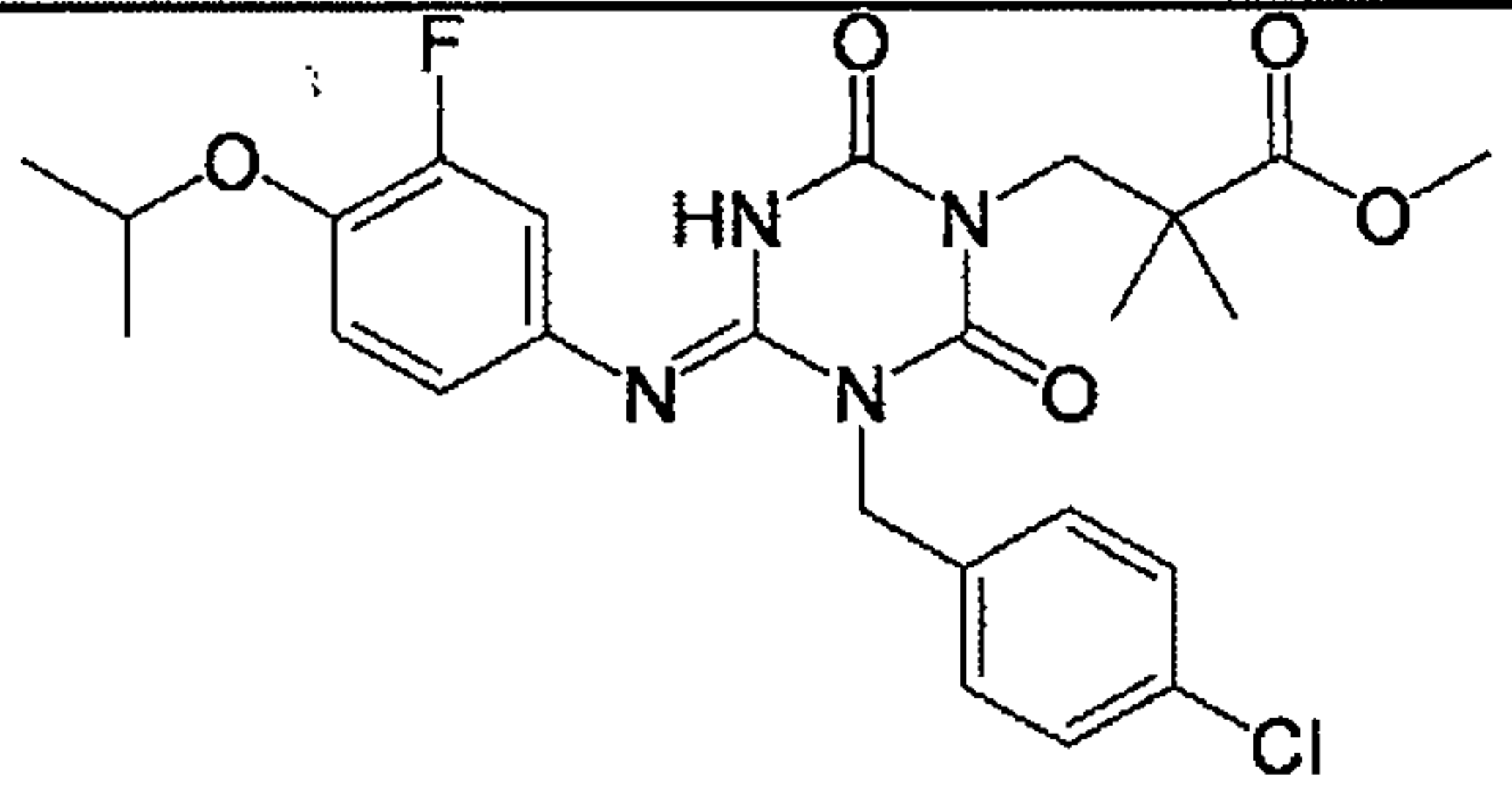
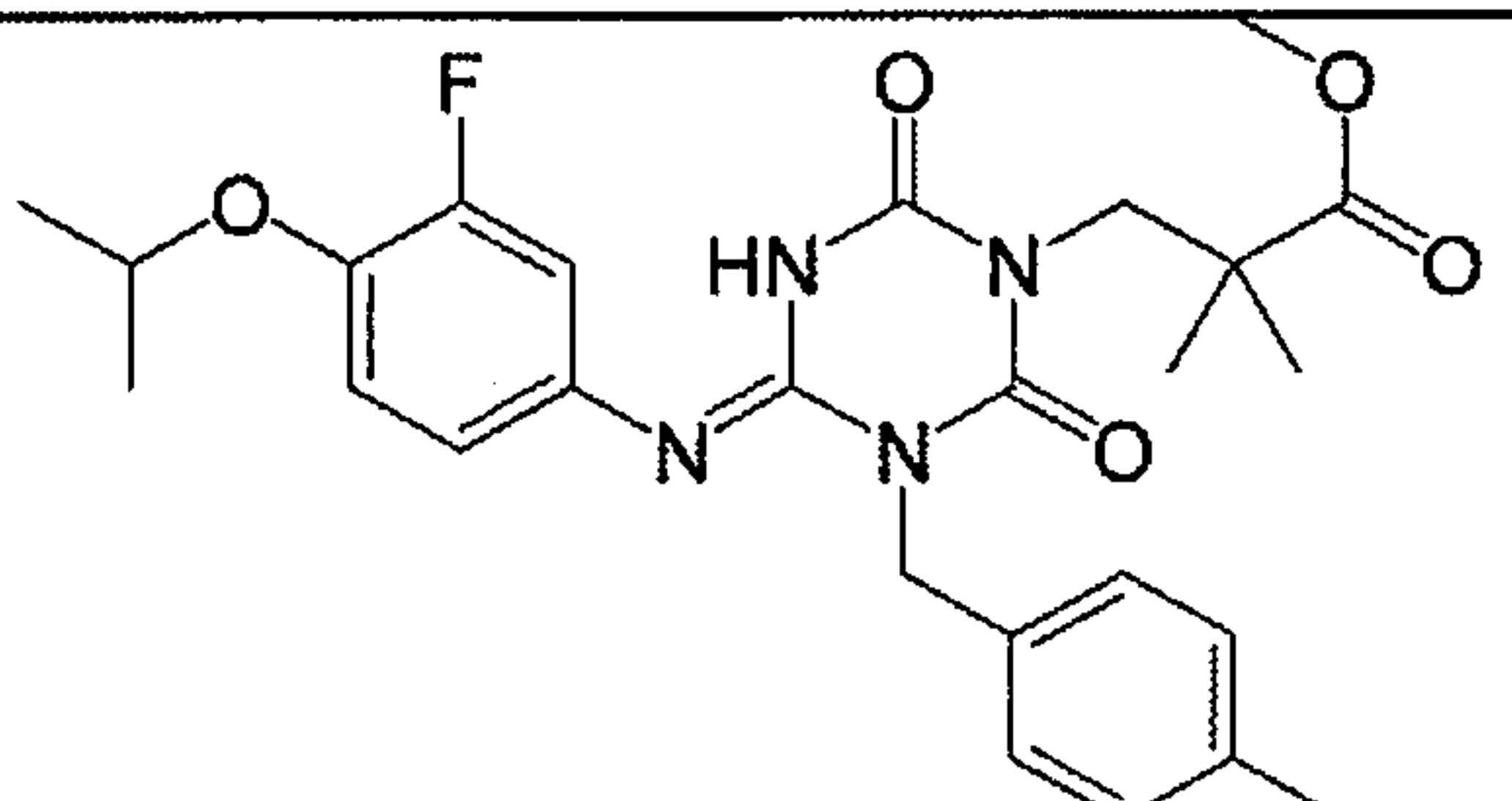
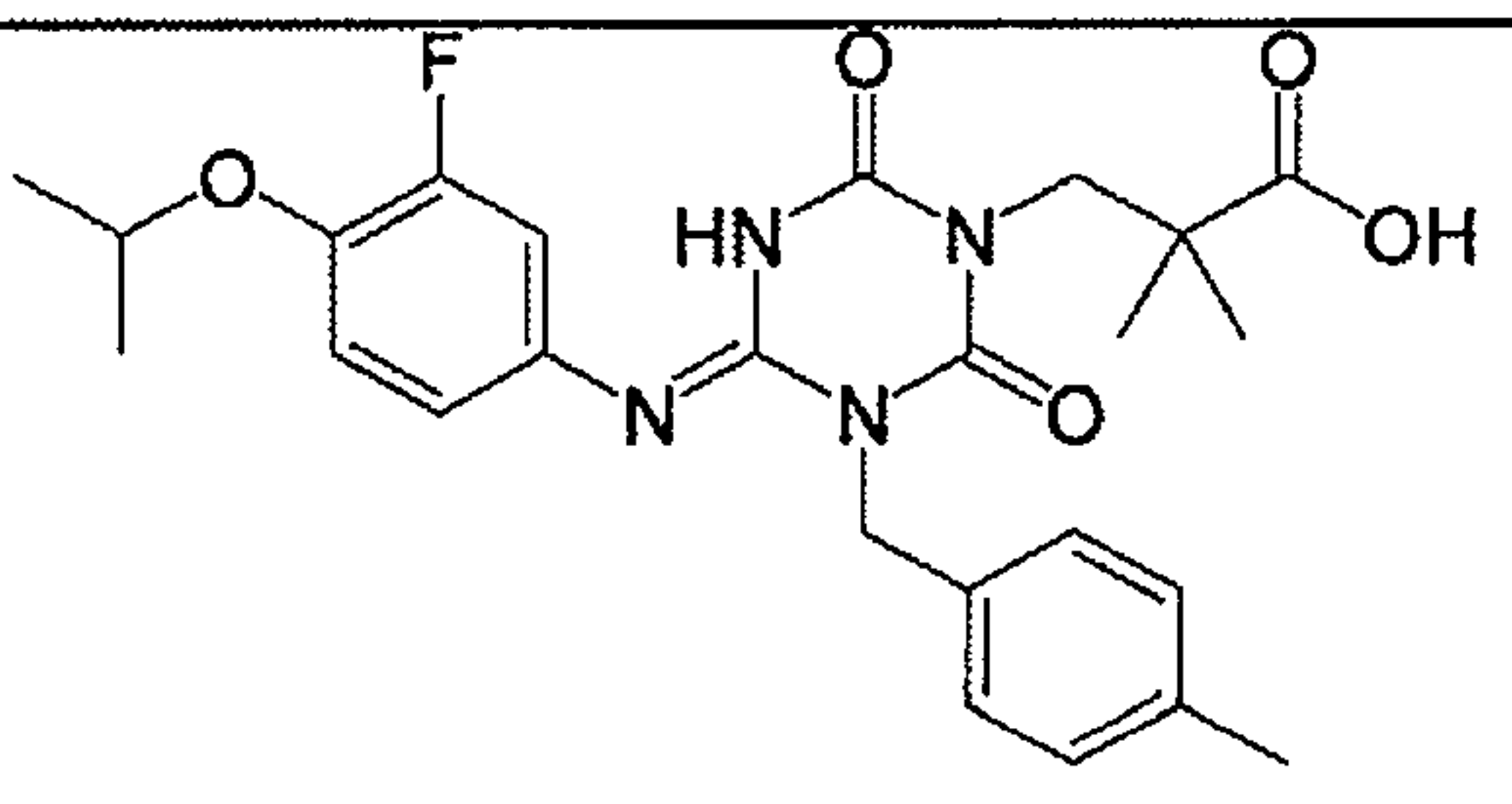
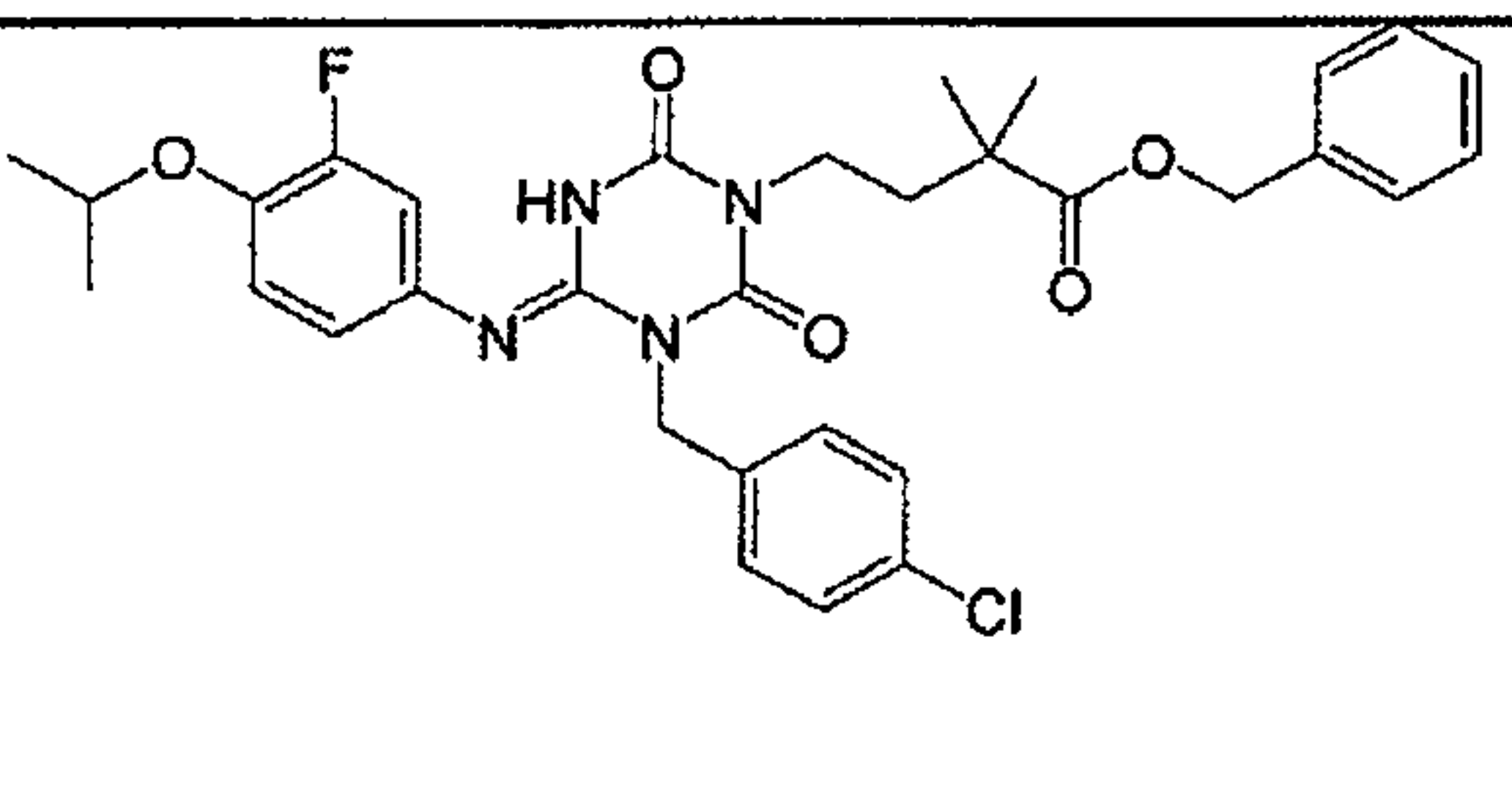
Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0386	1.81	491	2
	I-0387	1.86	505	2
	I-0388	1.98	519	2
	I-0389	1.94	519	2
	I-0390	1.77	535	2

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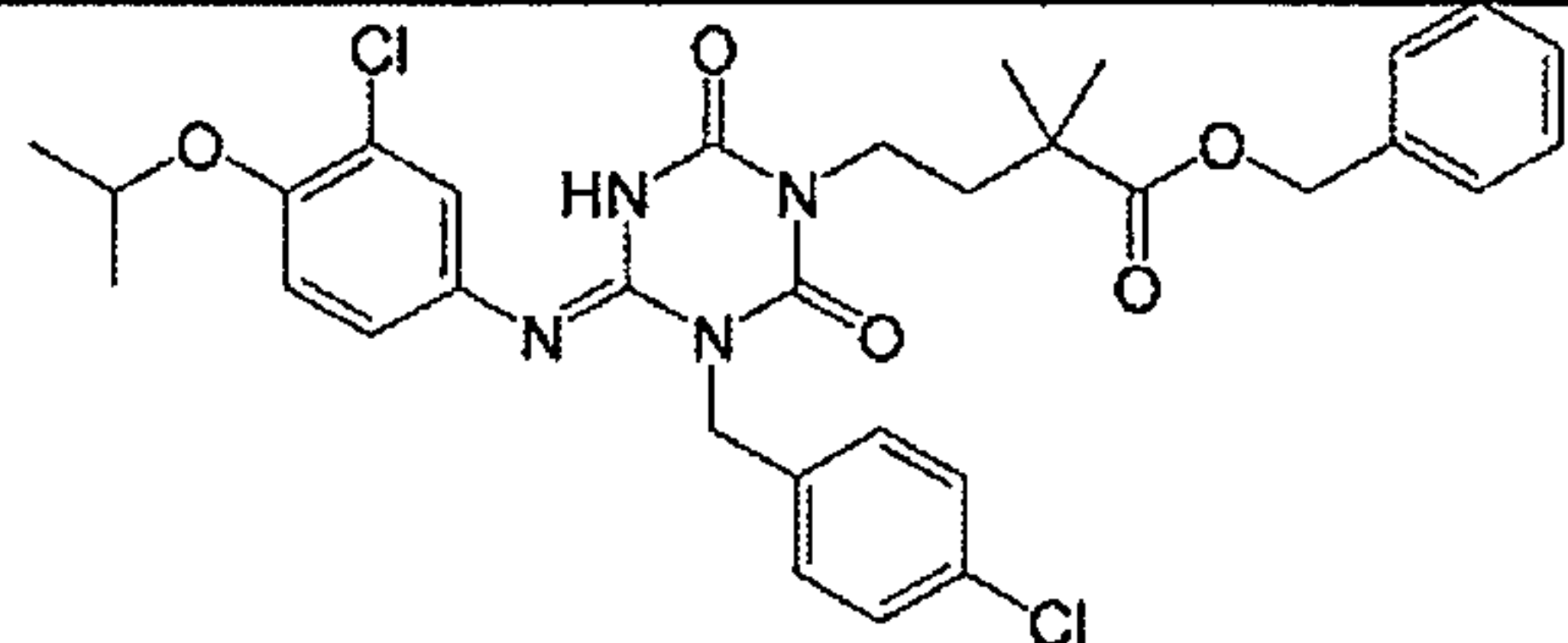
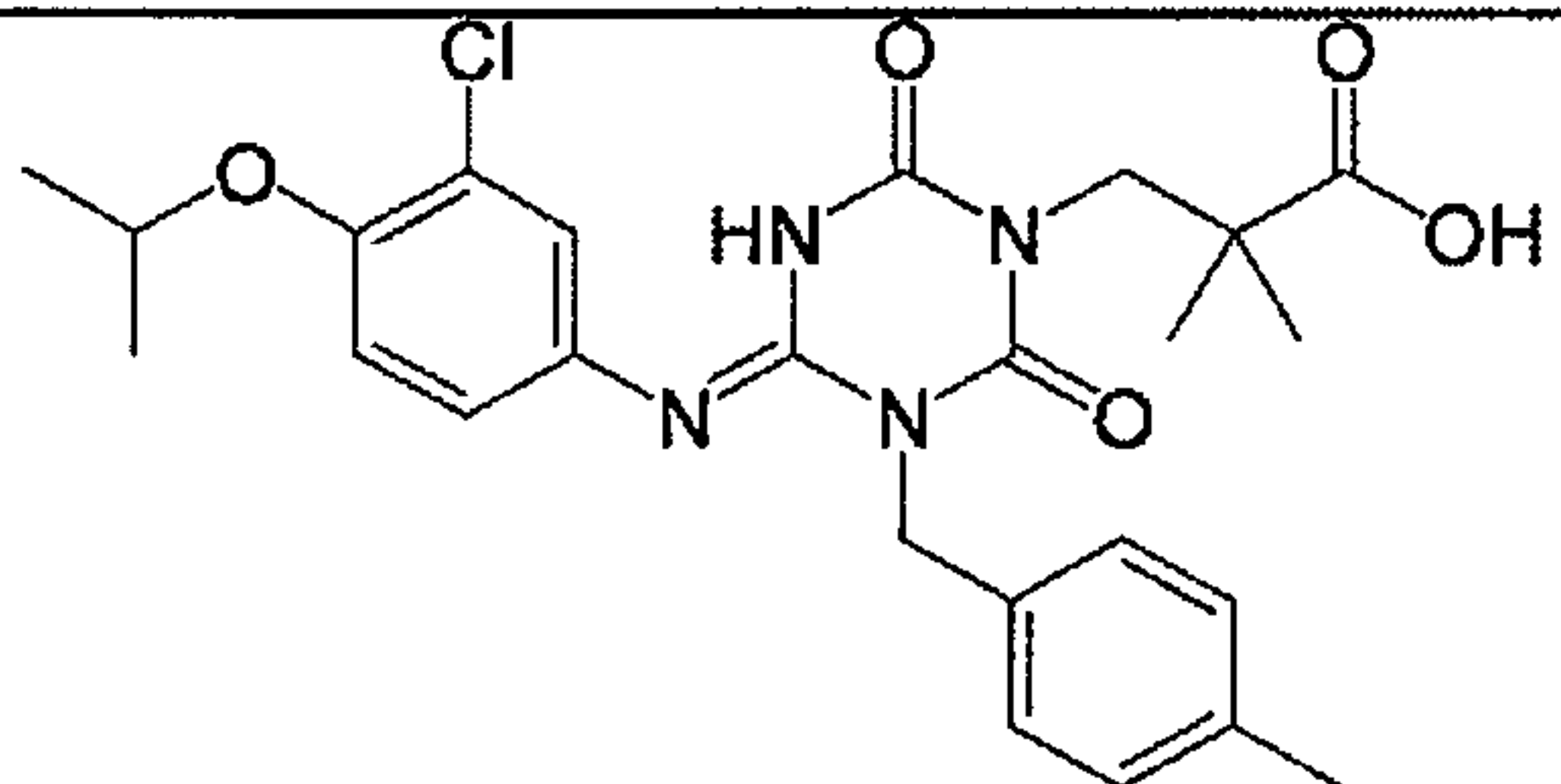
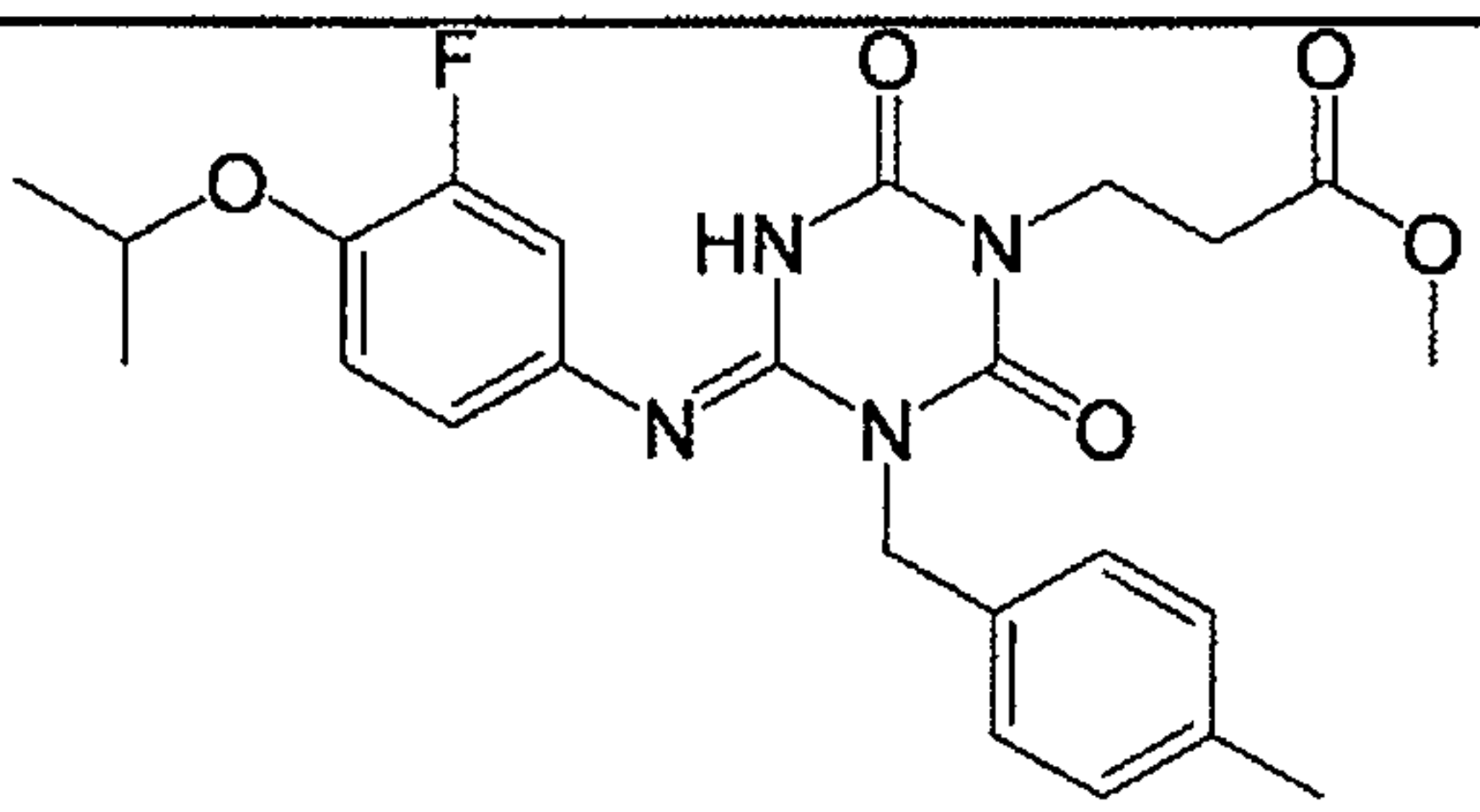
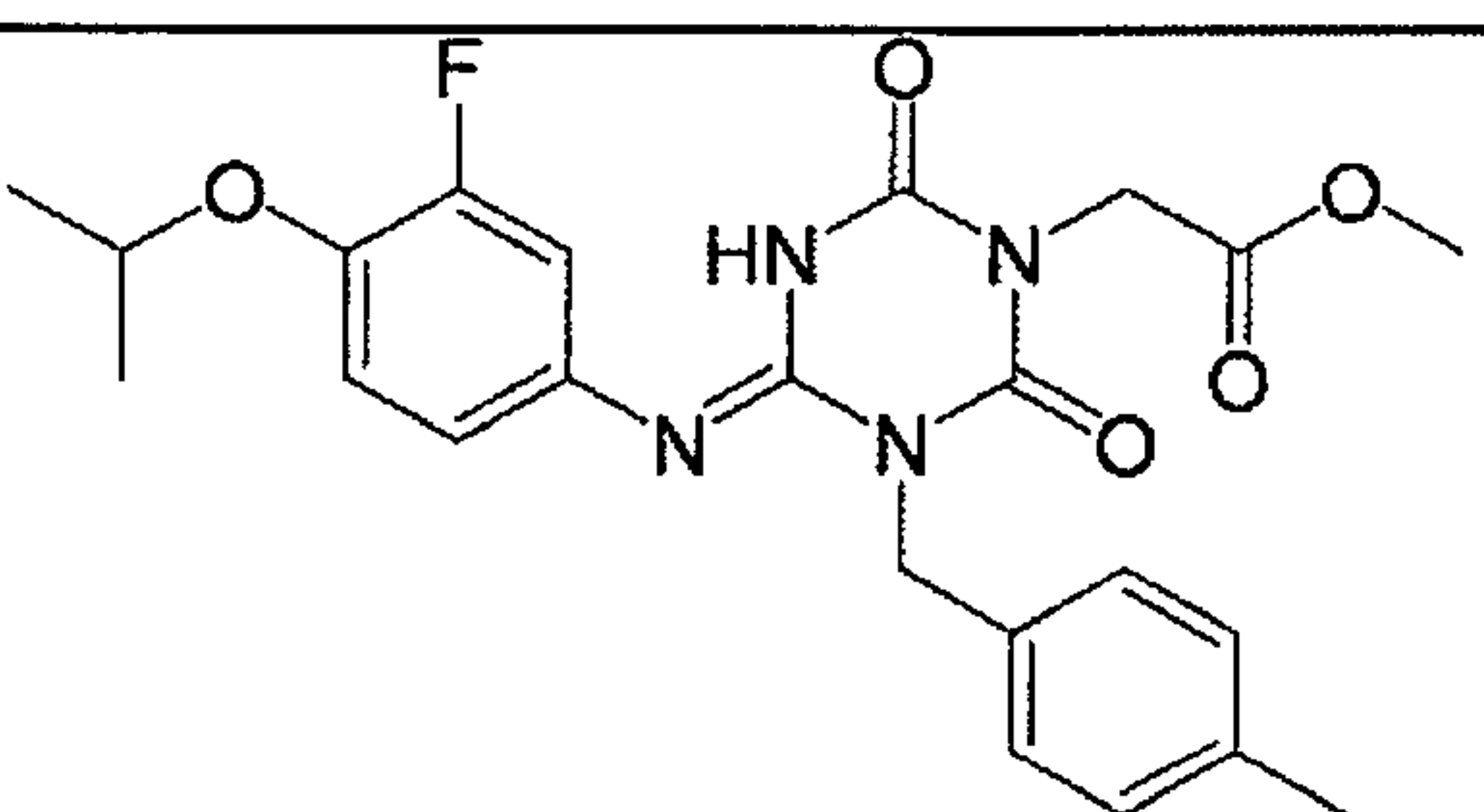
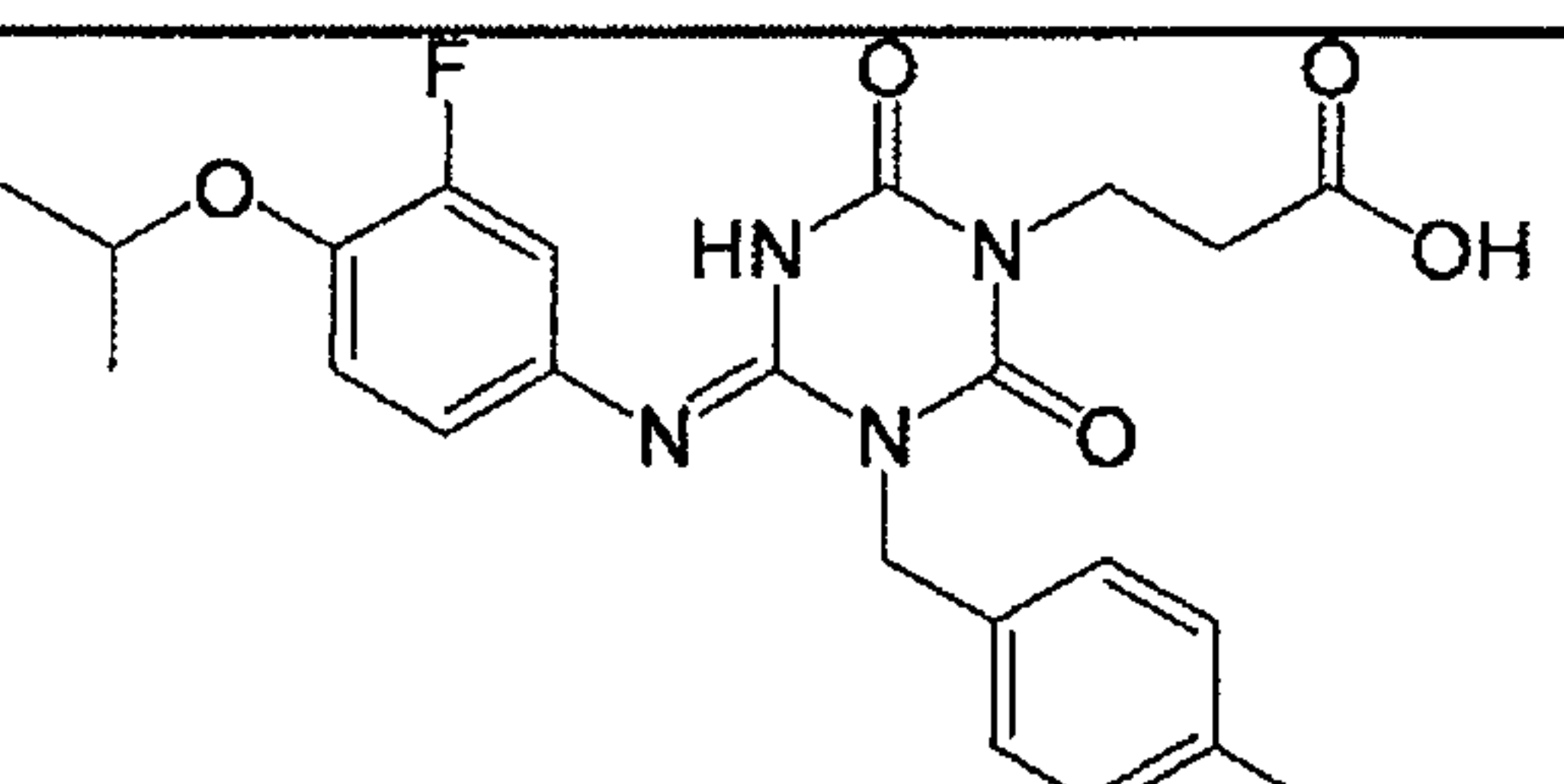
[Table 83]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0396	1.94	534	2
	I-0397	1.69	536	2
	I-0398	2.51	535	2
	I-0399	1.81	520	2
	I-0400	2.24	521	2

[Table 84]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0401	2.49	527	2
	I-0402	2.40	519	2
	I-0403	2.32	499	2
	I-0404	2.04	485	2
	I-0405	2.74	609	2

[Table 85]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0406	2.84	625	2
	I-0407	2.16	501	2
	I-0408	2.13	471	2
	I-0409	2.09	457	2
	I-0410	1.92	457	2

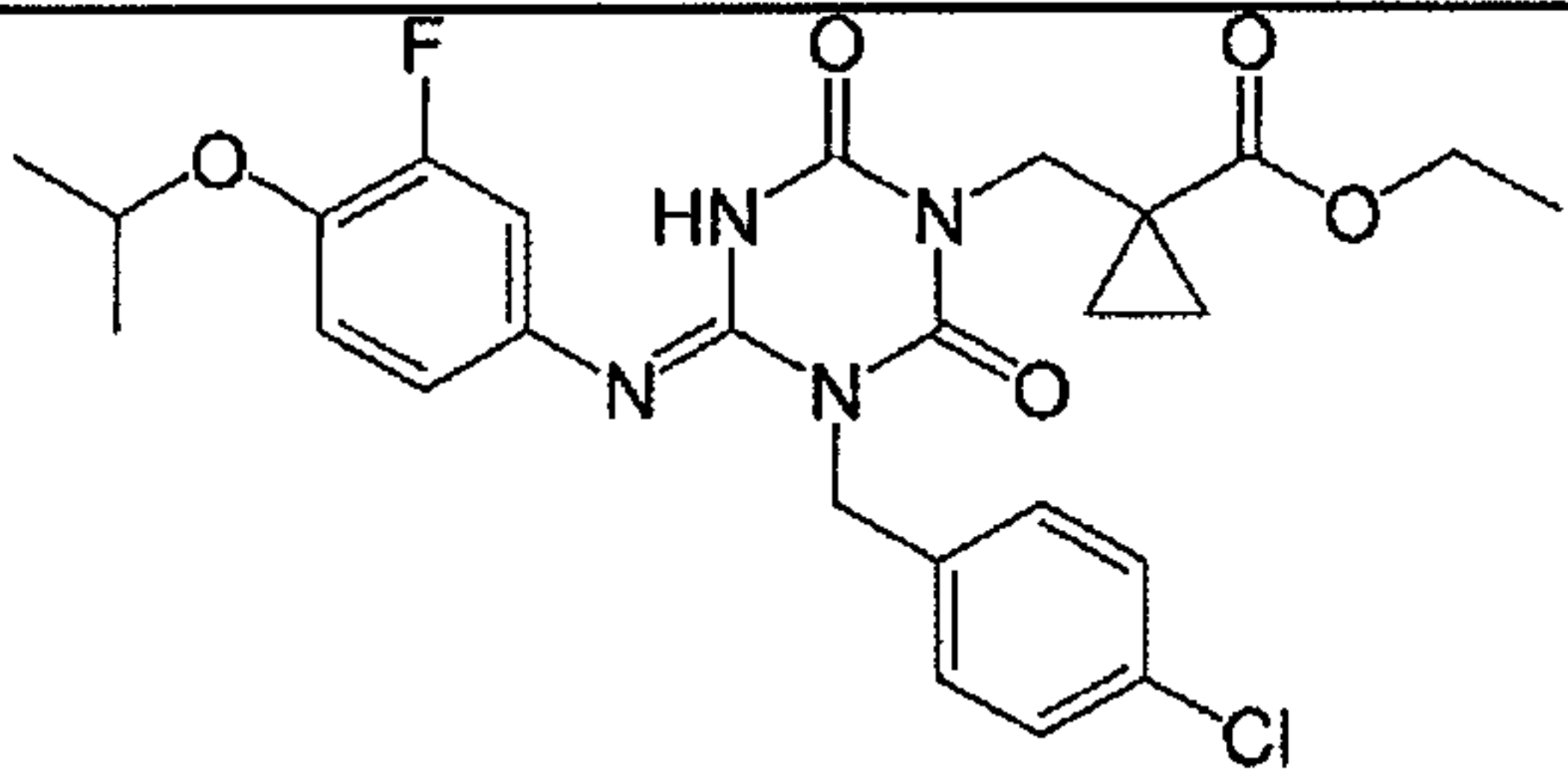
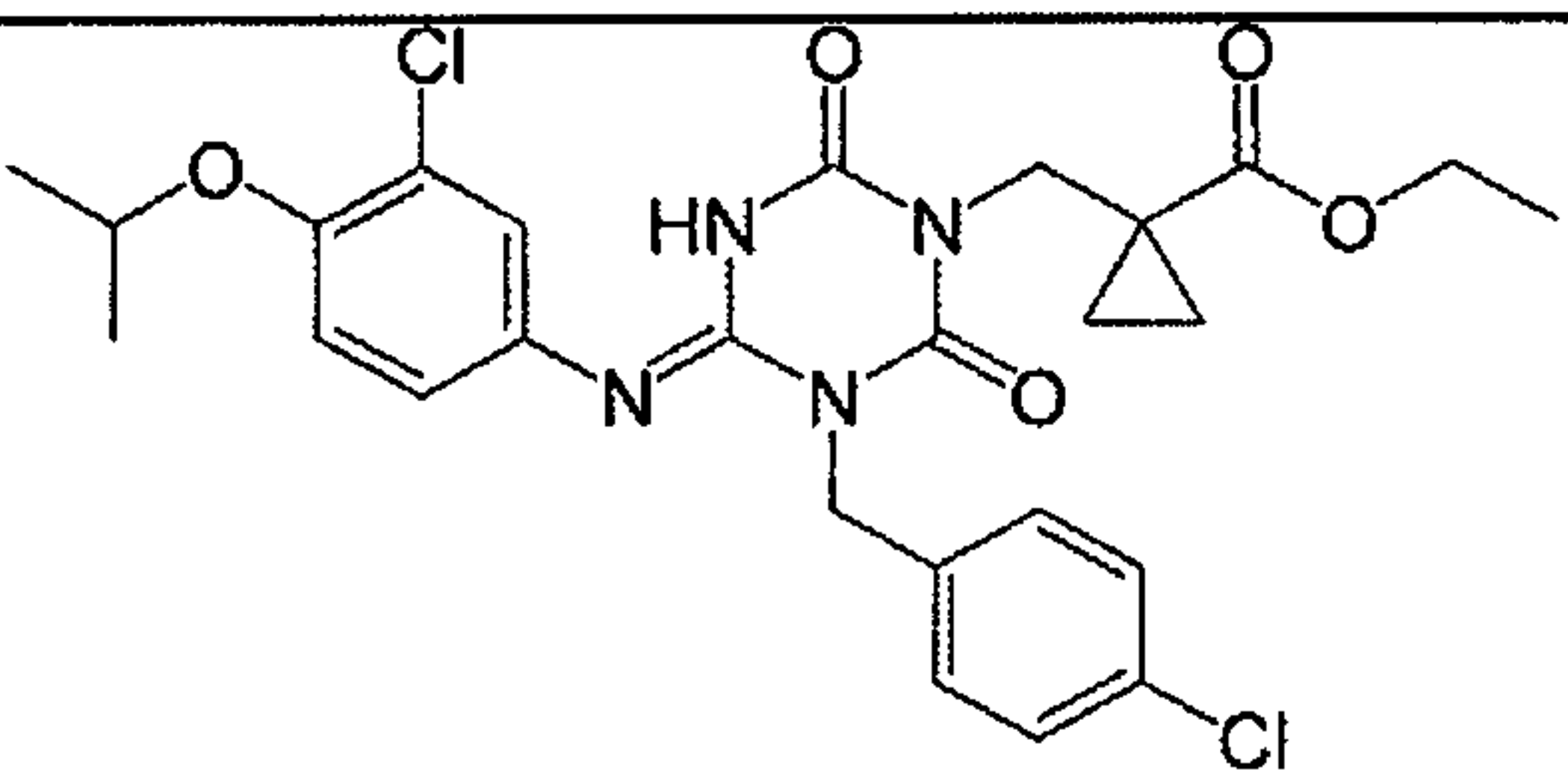
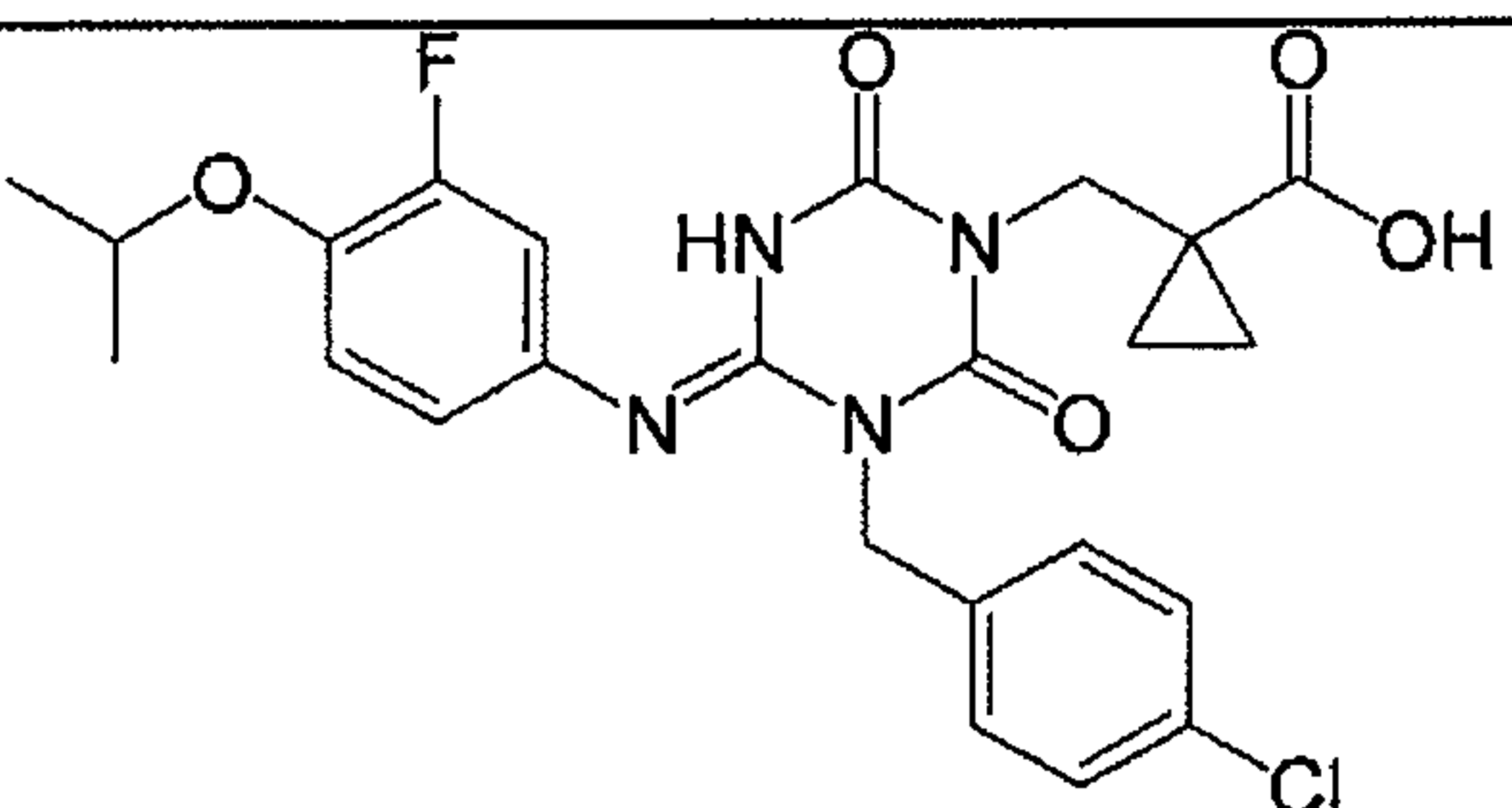
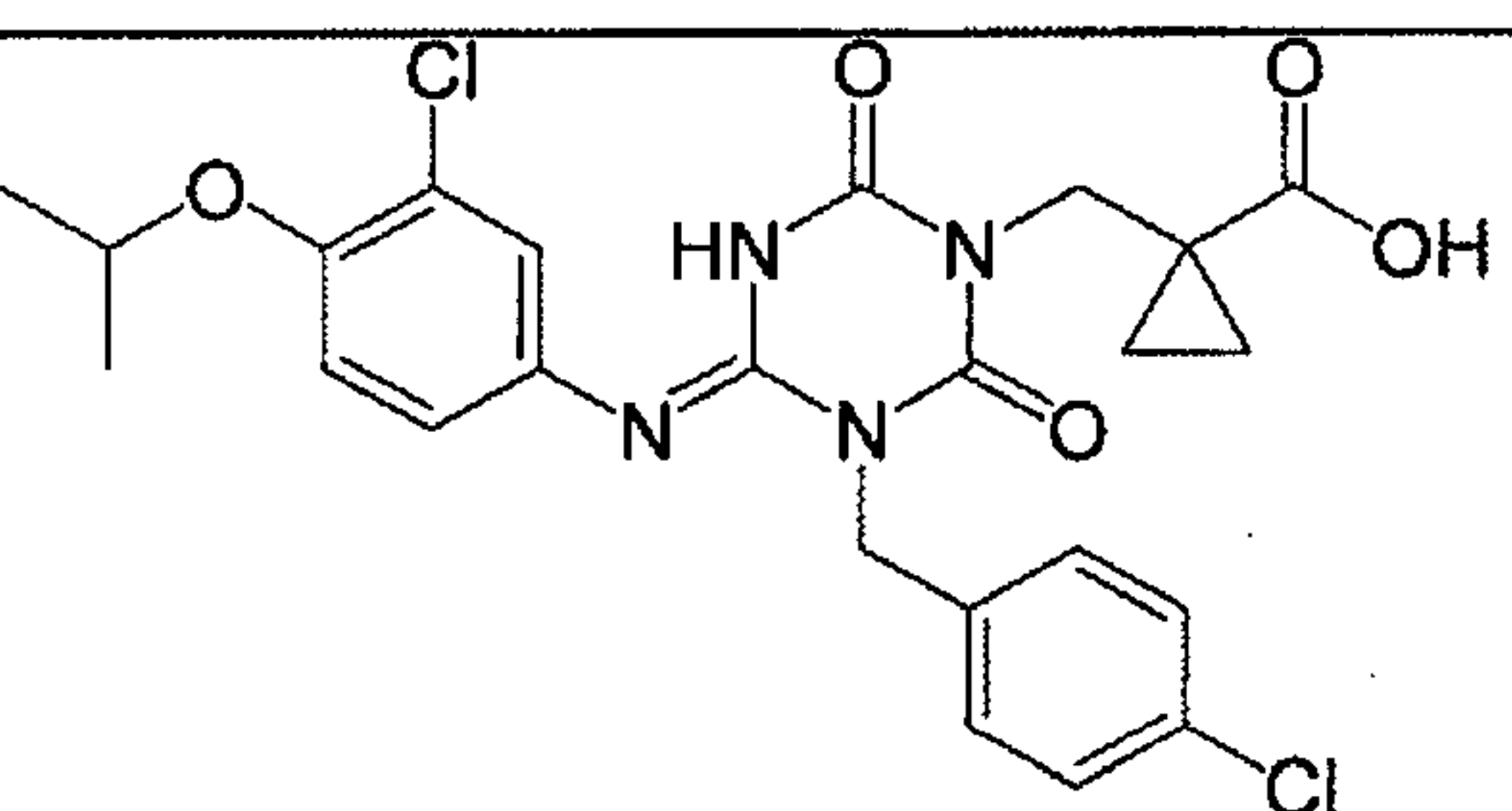
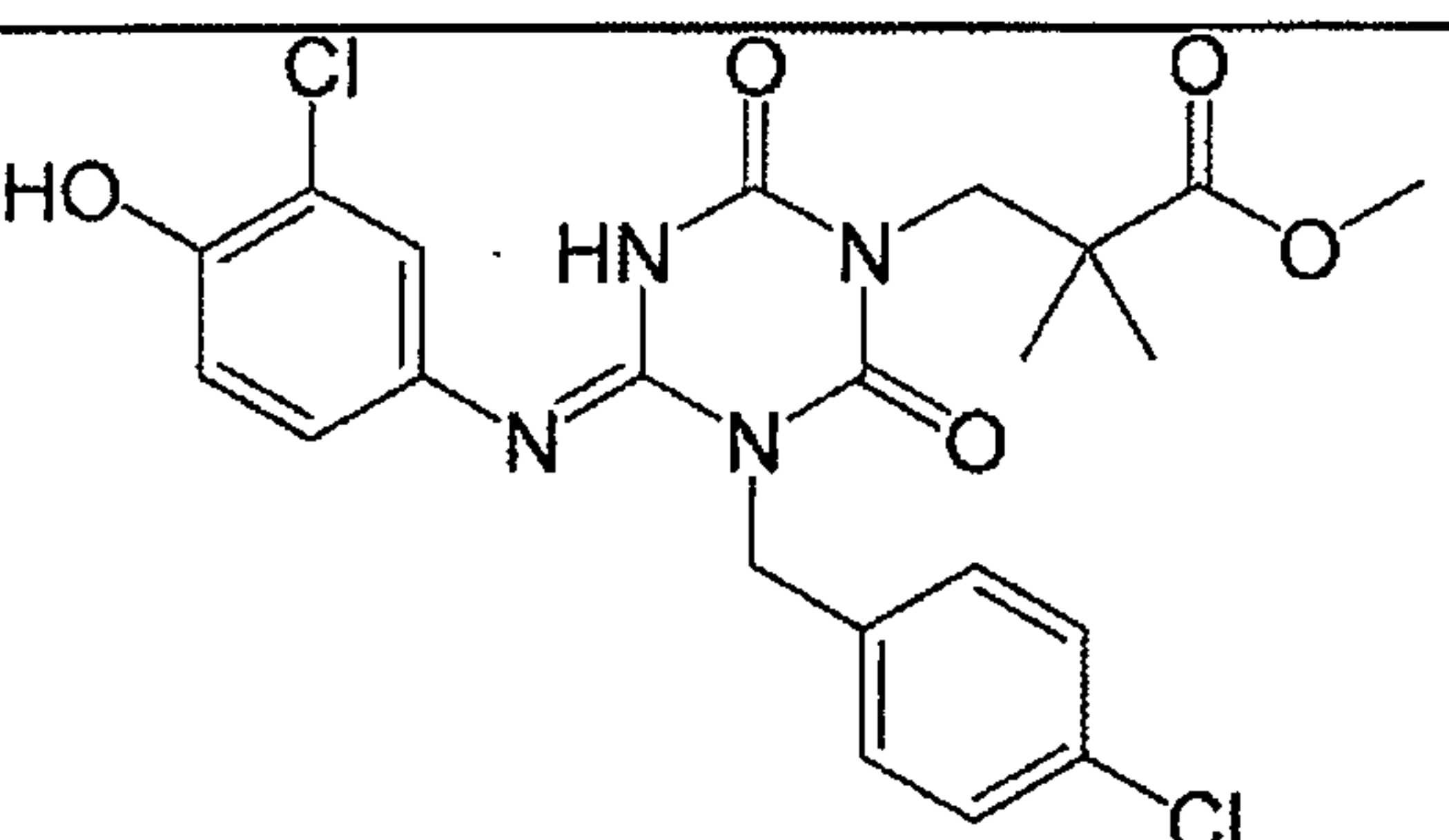
[Table 86]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0411	1.87	443	2
	I-0412	2.10	503	2
	I-0413	1.63	516	2
	I-0414	1.84	528	2
	I-0415	1.74	500	2

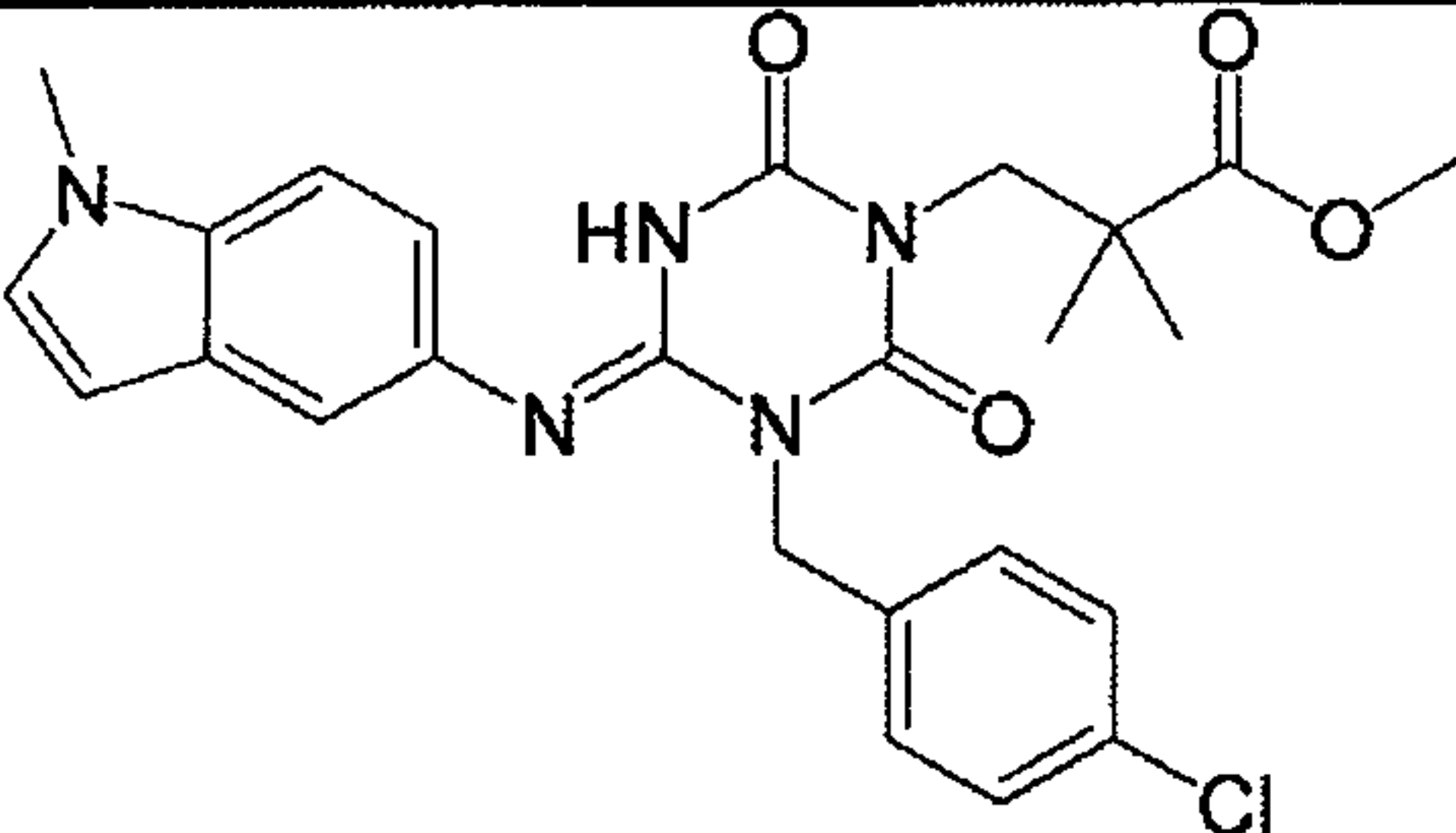
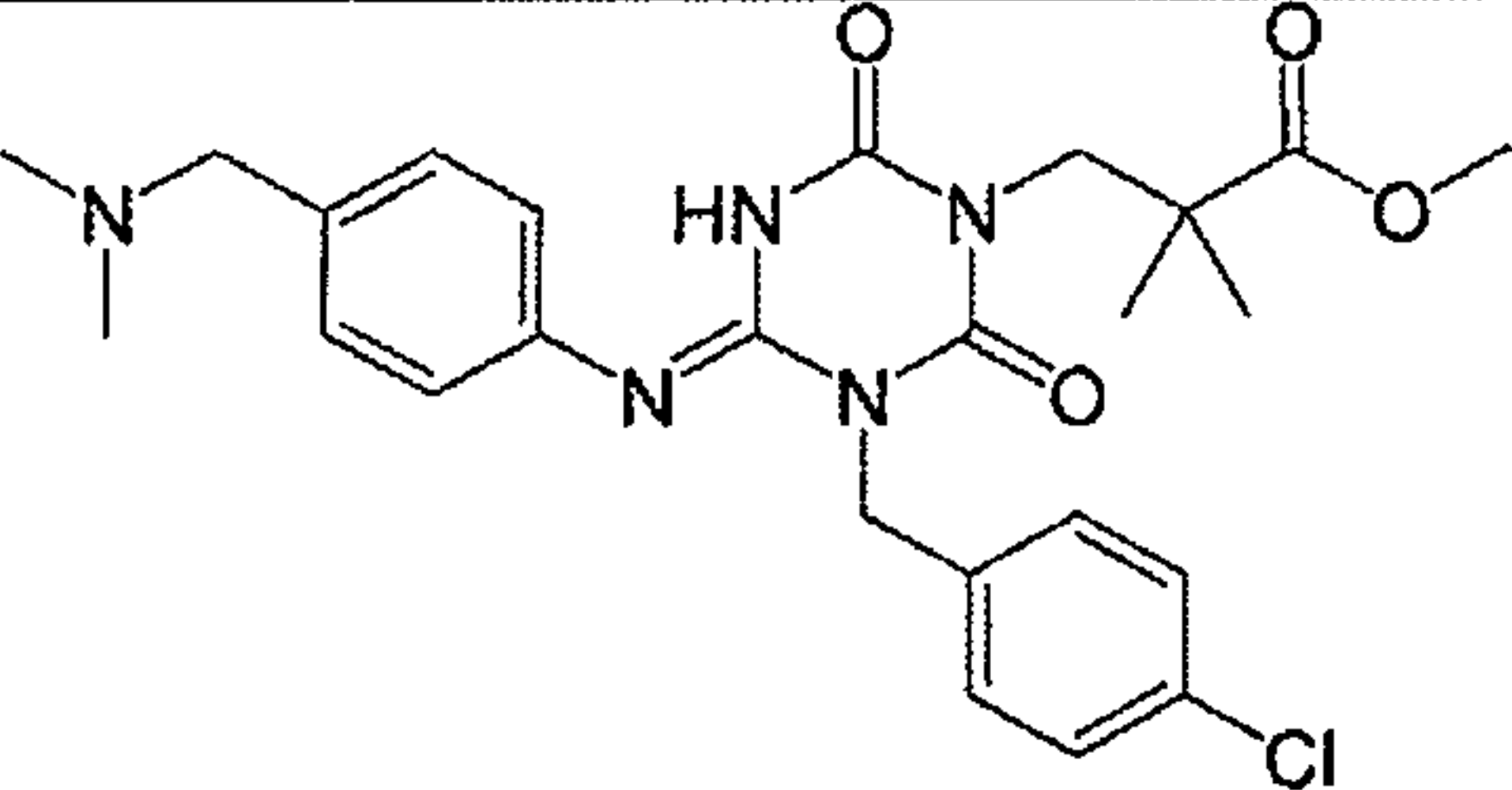
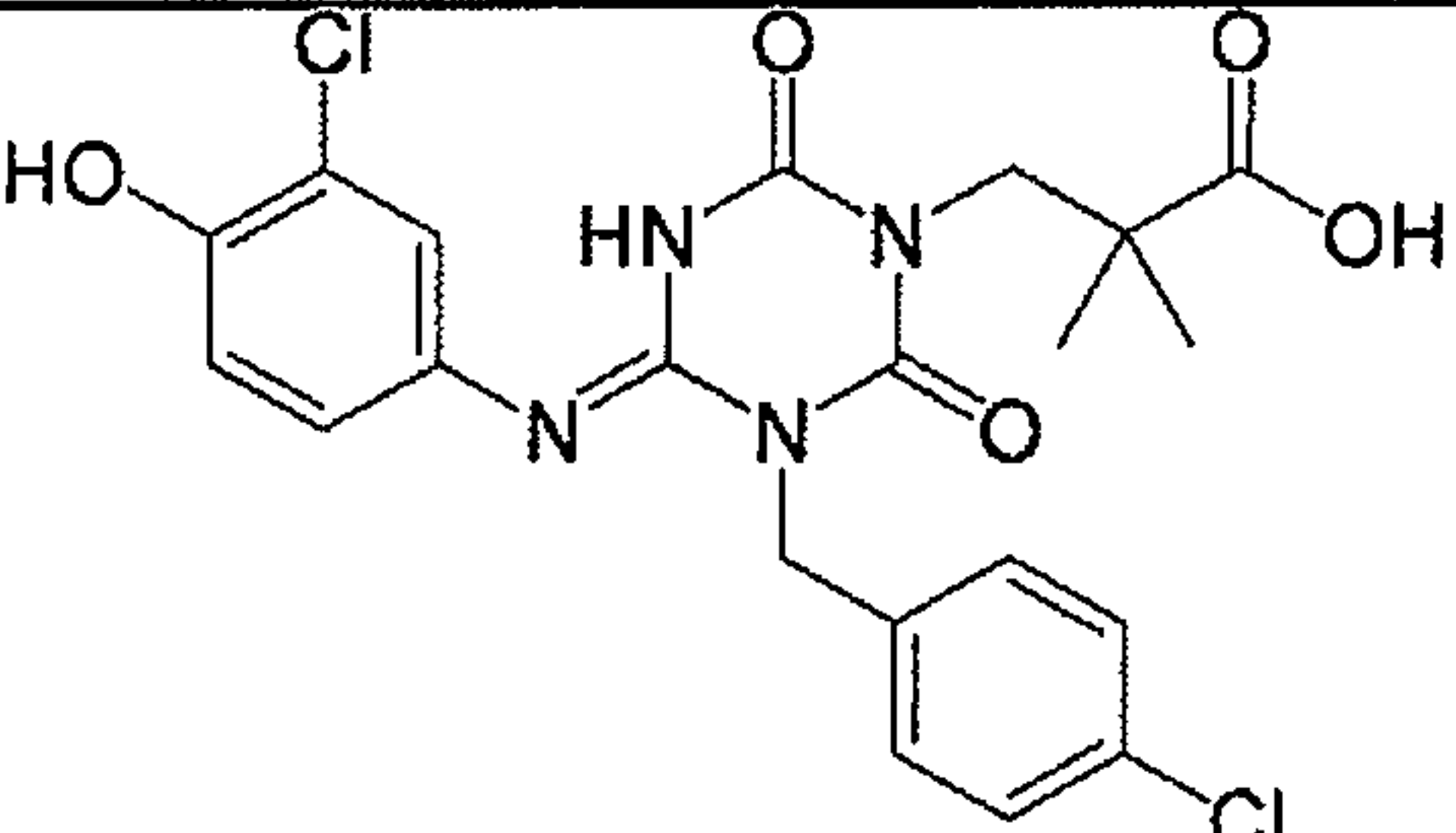
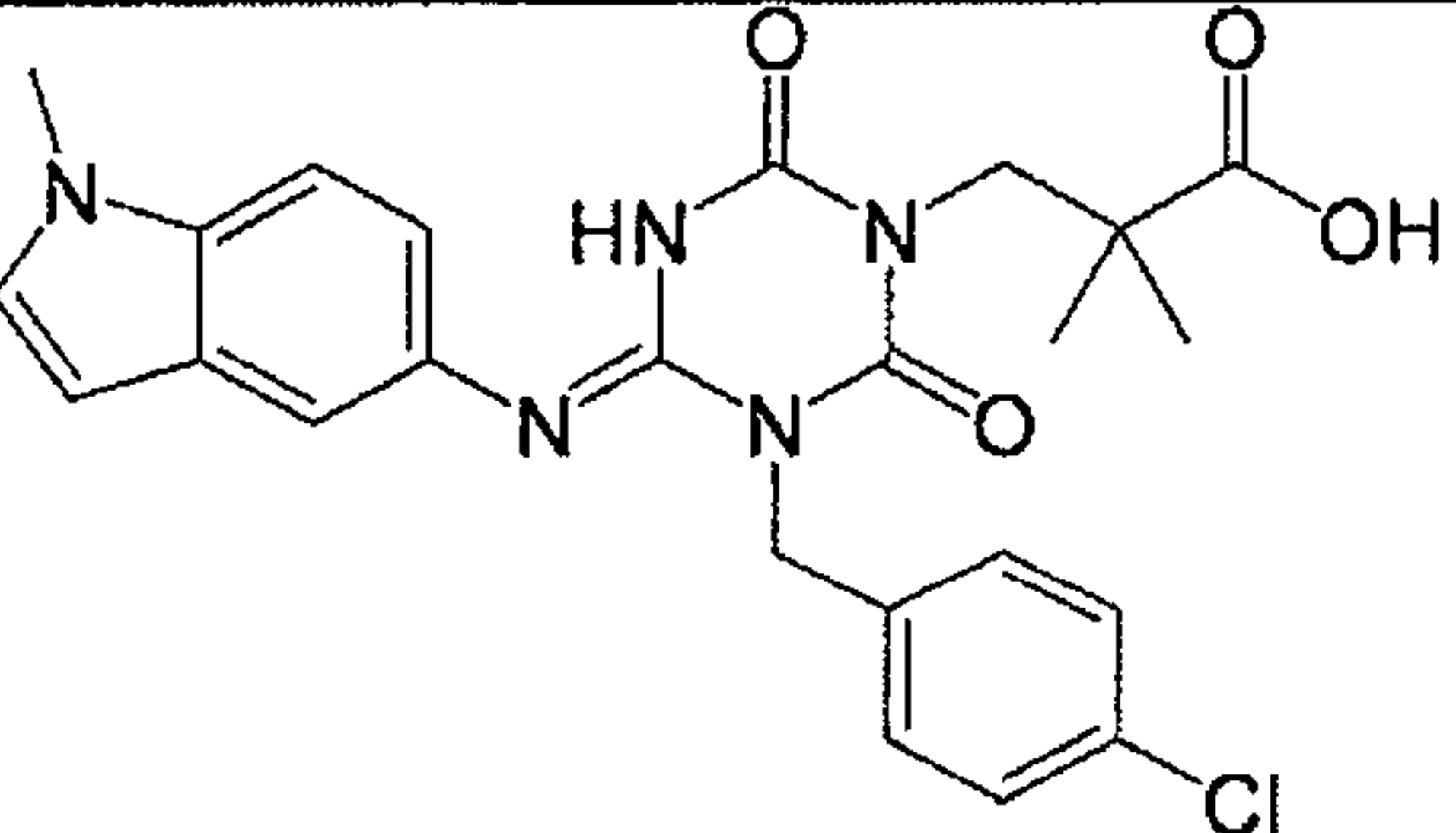
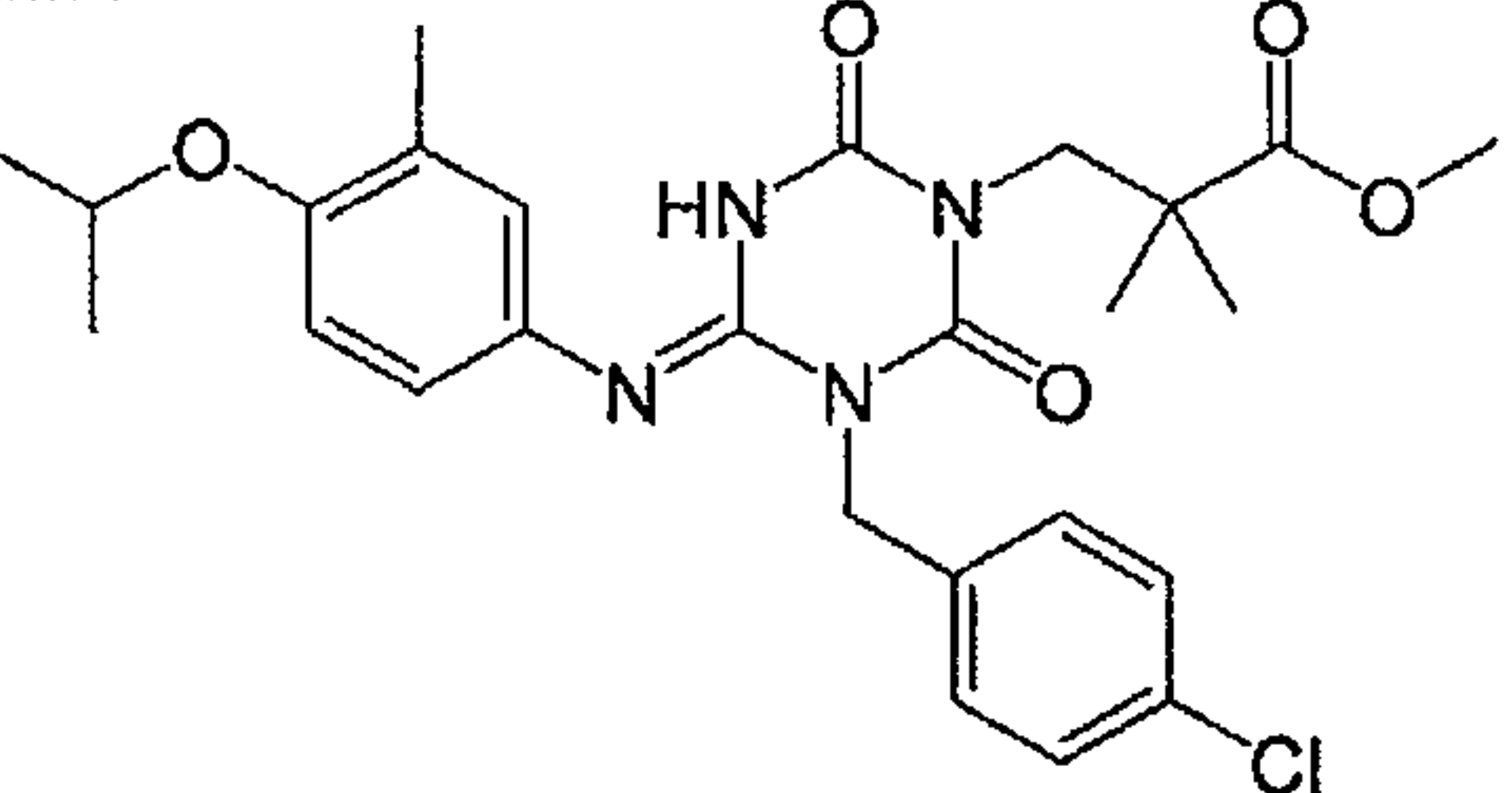
[Table 87]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0416	1.78	514	2
	I-0417	1.79	514	2
	I-0418	1.78	526	2
	I-0419	2.21	519	2
	I-0420	2.32	535	2

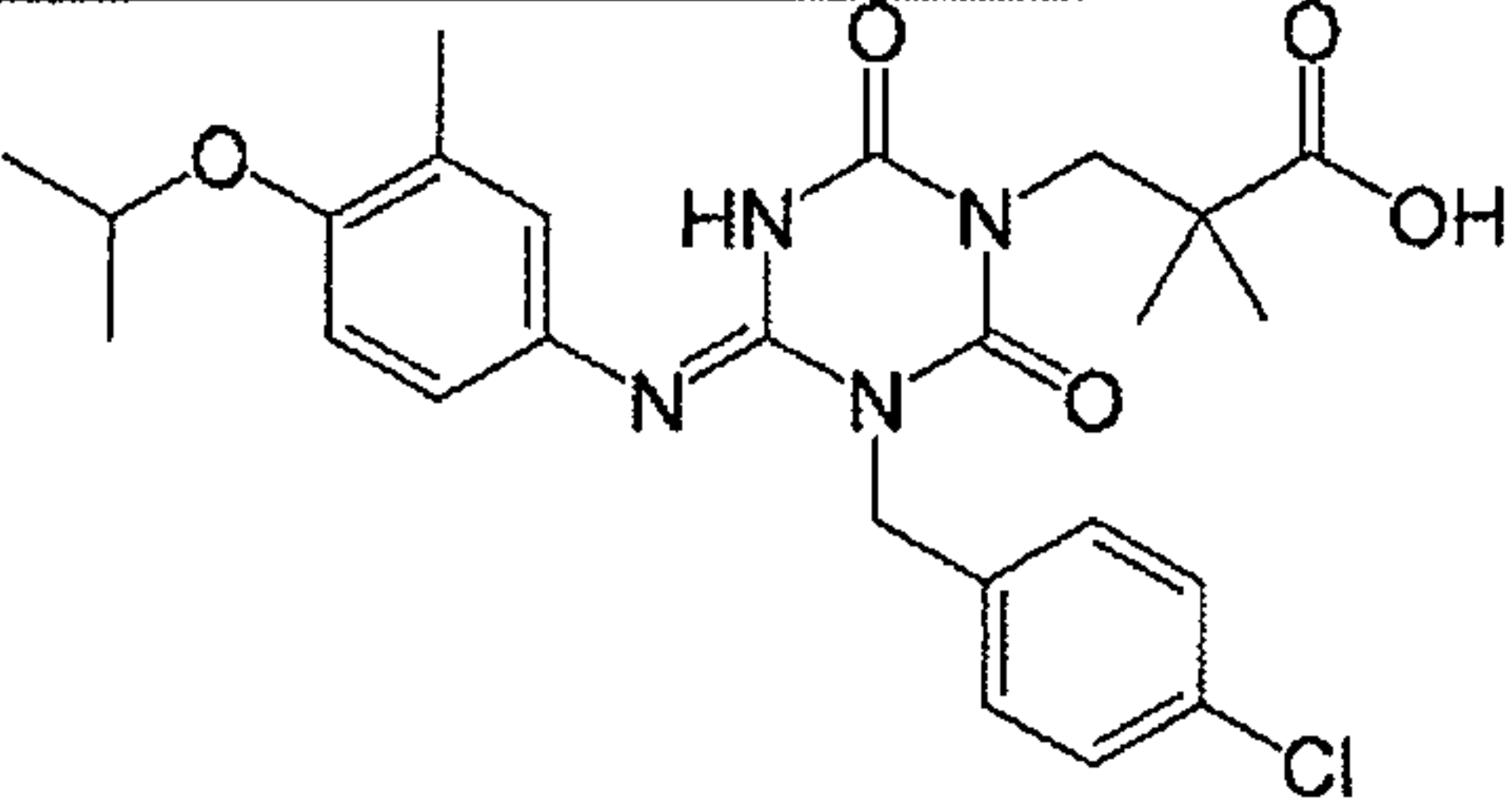
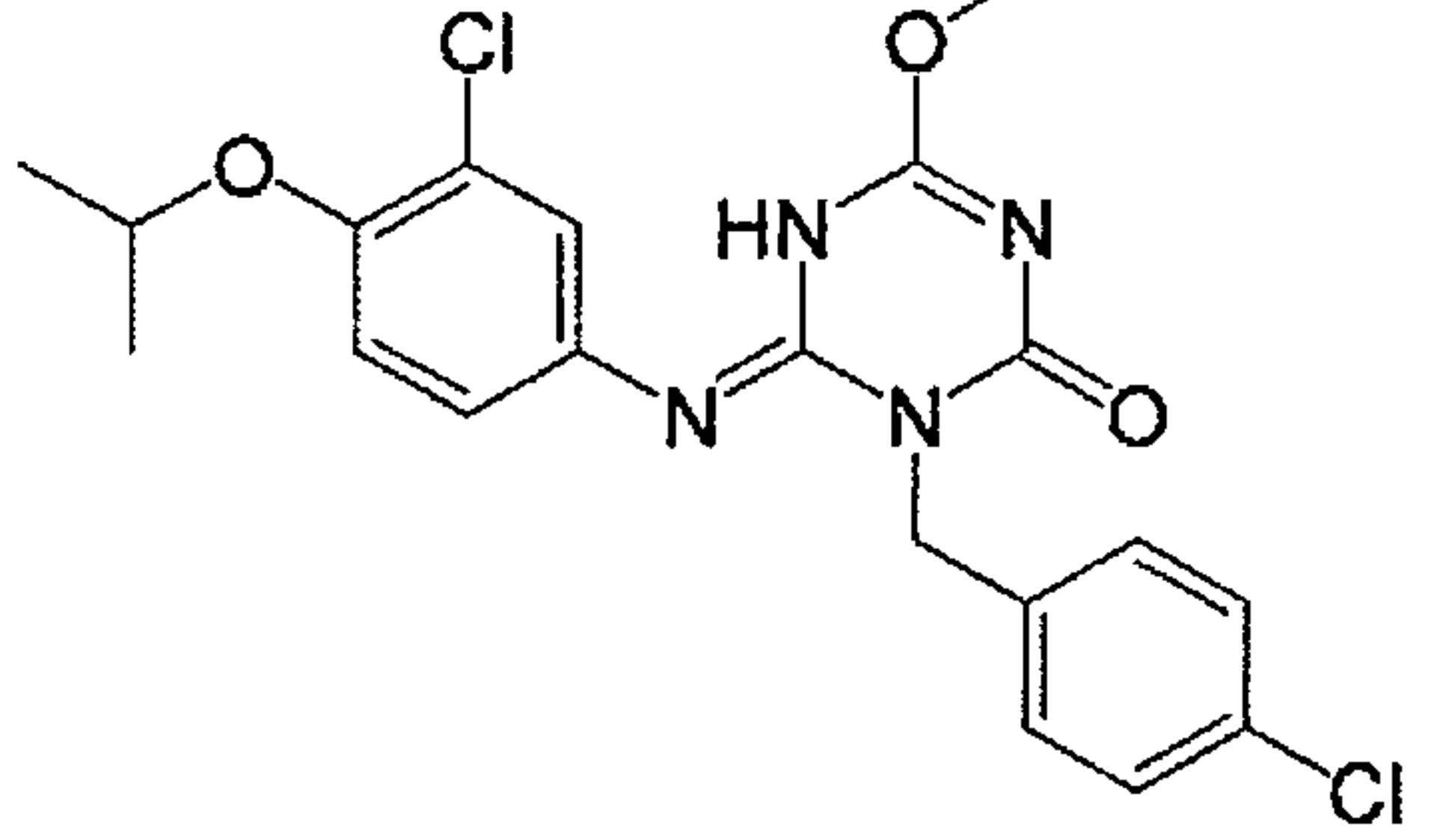
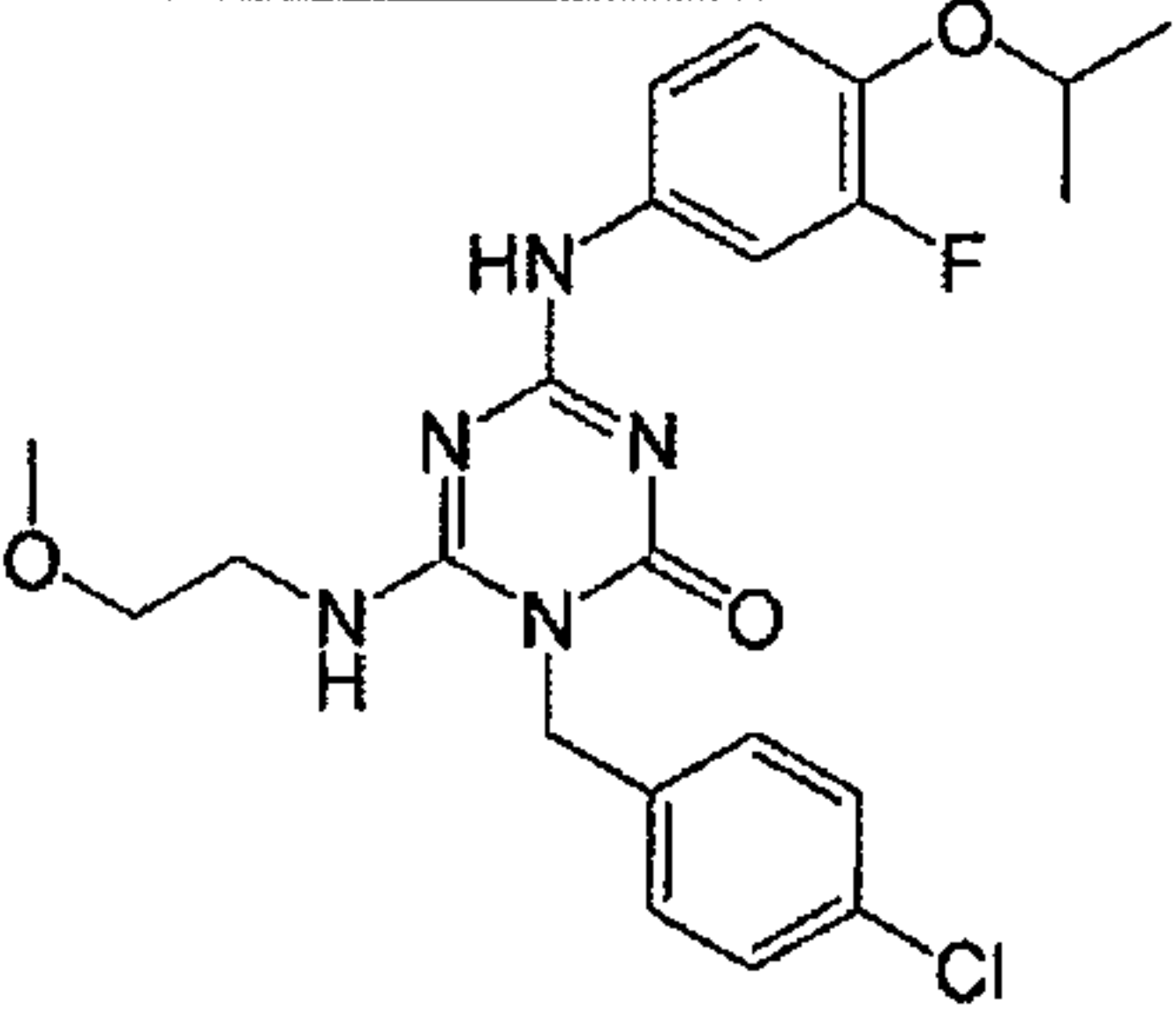
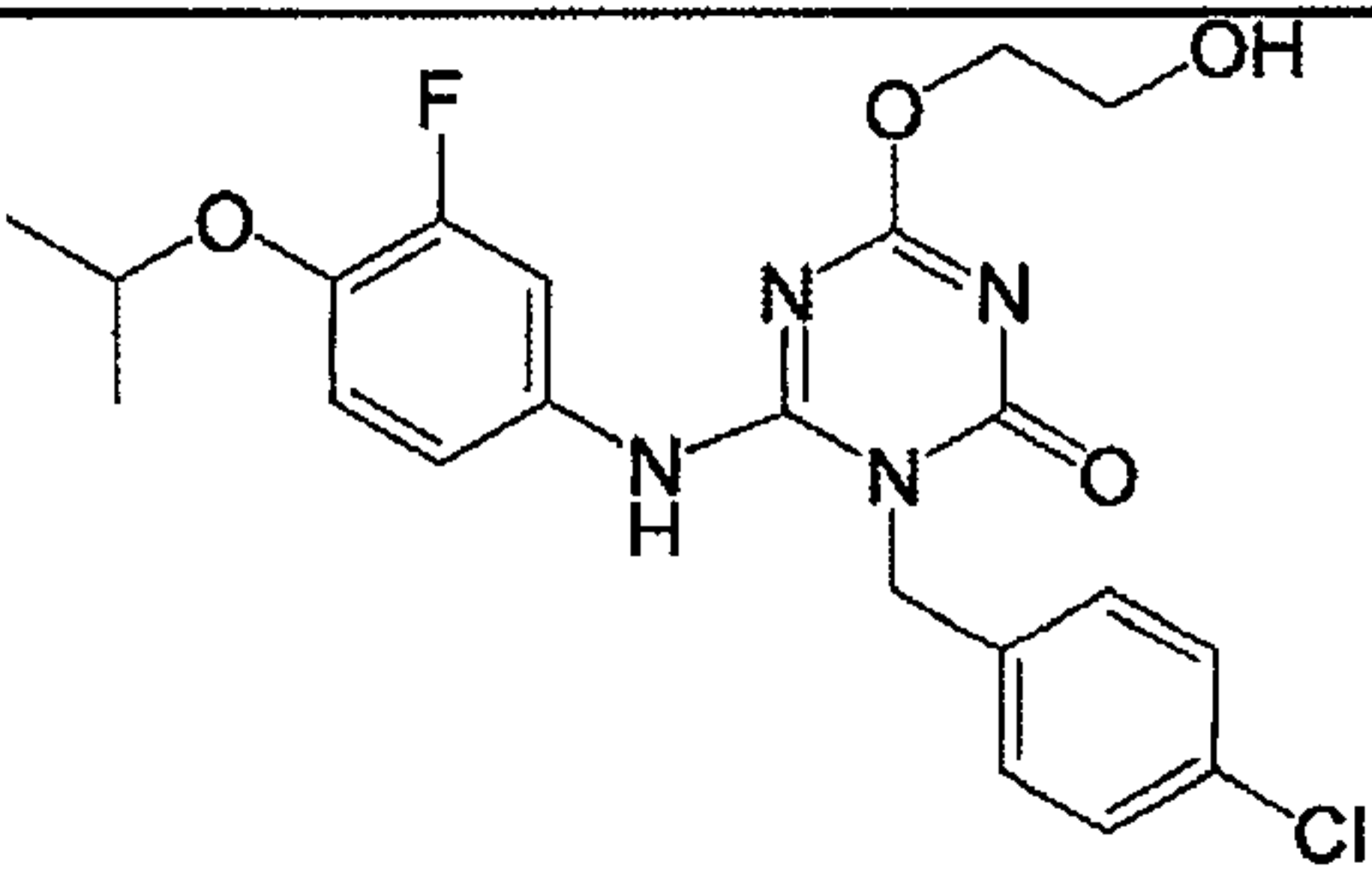
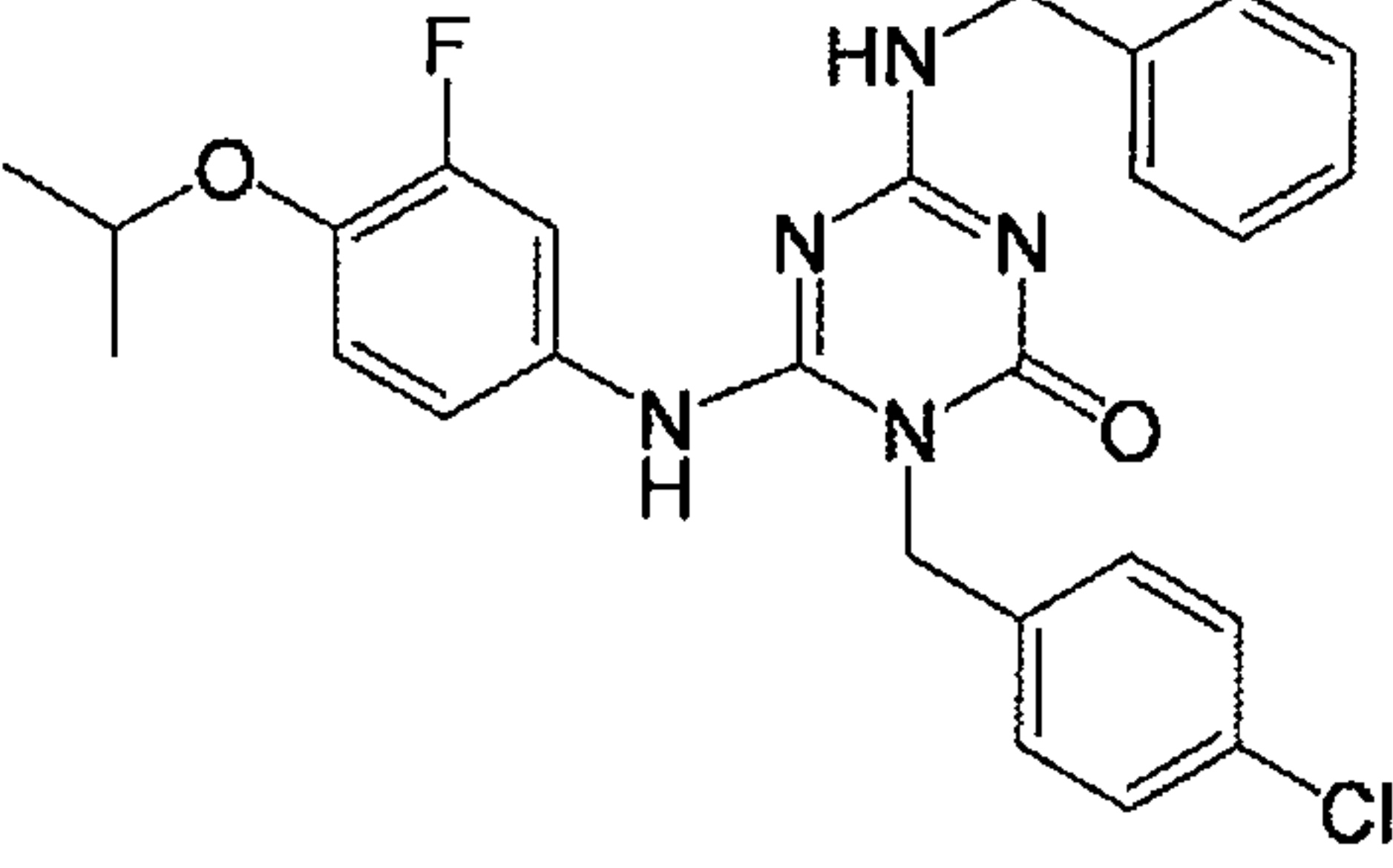
[Table 88]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0421	2.45	531	2
	I-0422	2.53	547	2
	I-0423	2.09	503	2
	I-0424	2.20	519	2
	I-0425	1.99	493	2

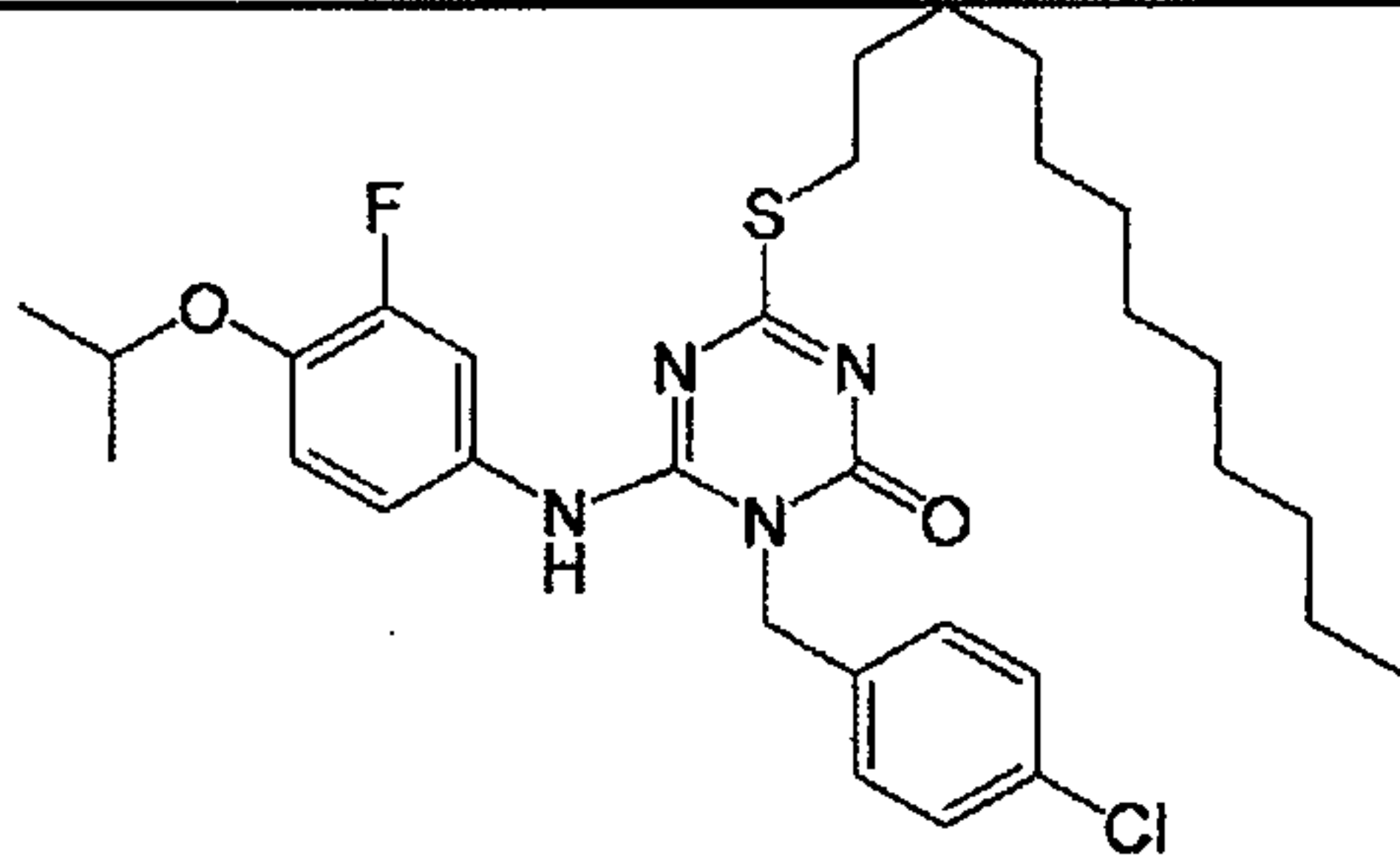
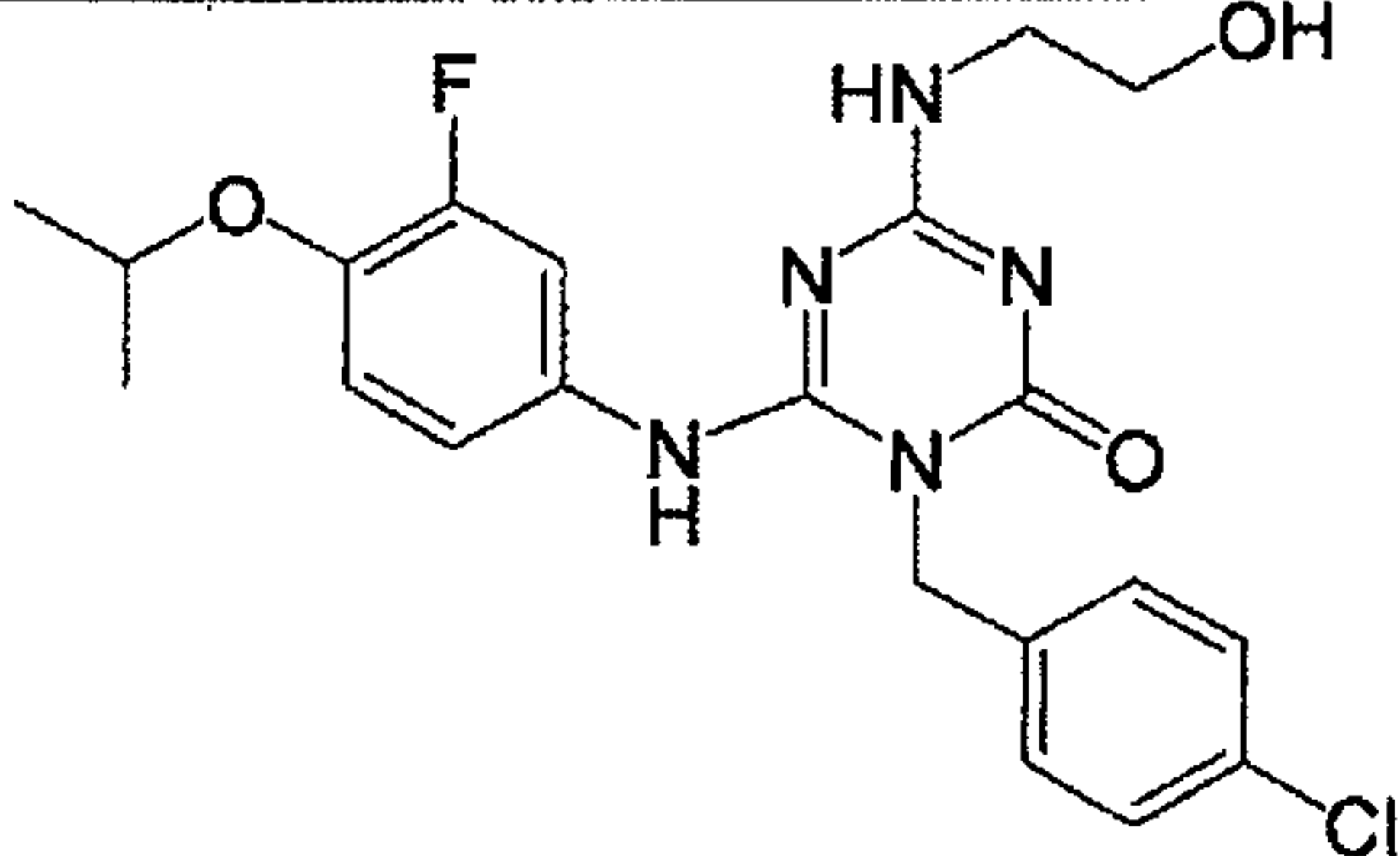
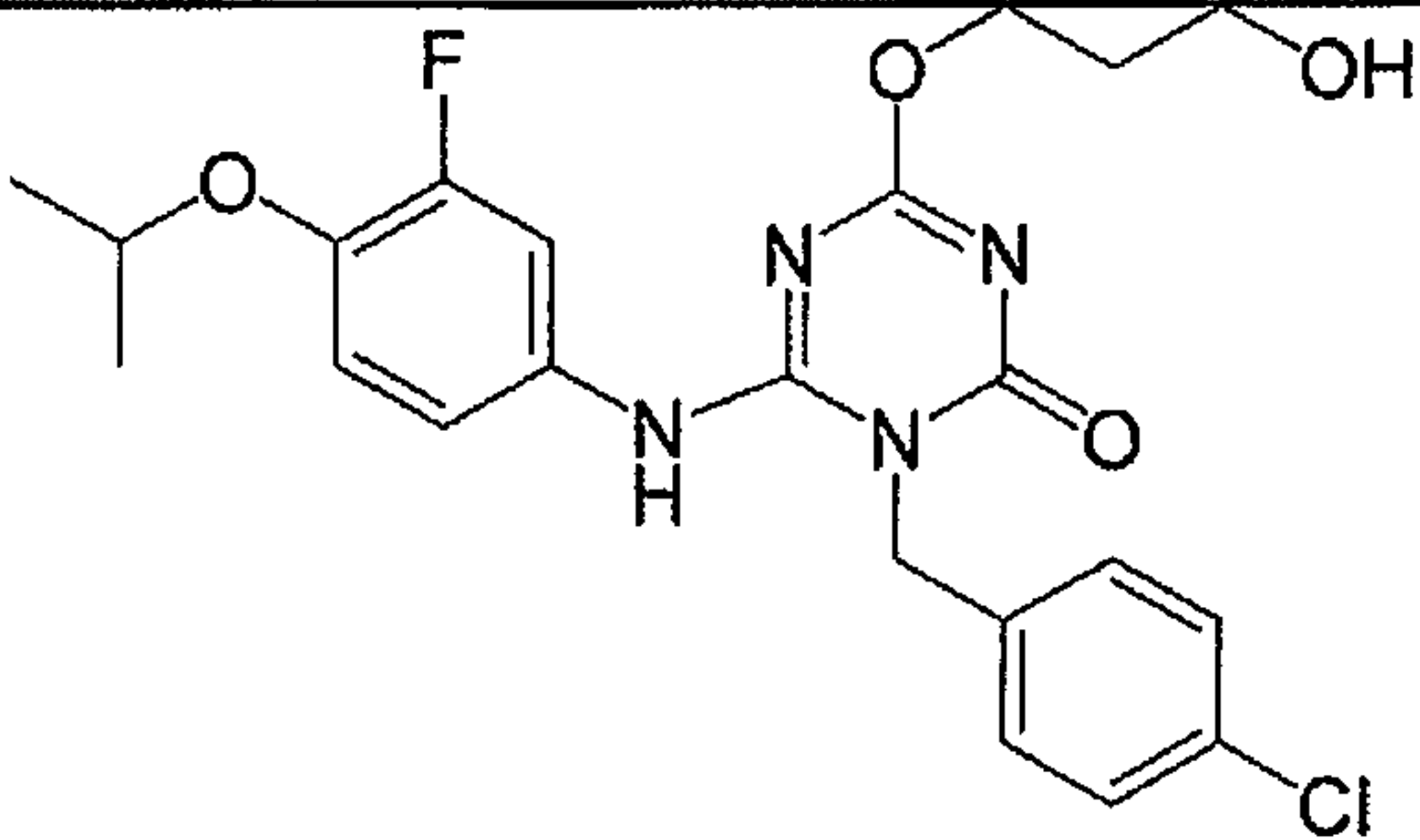
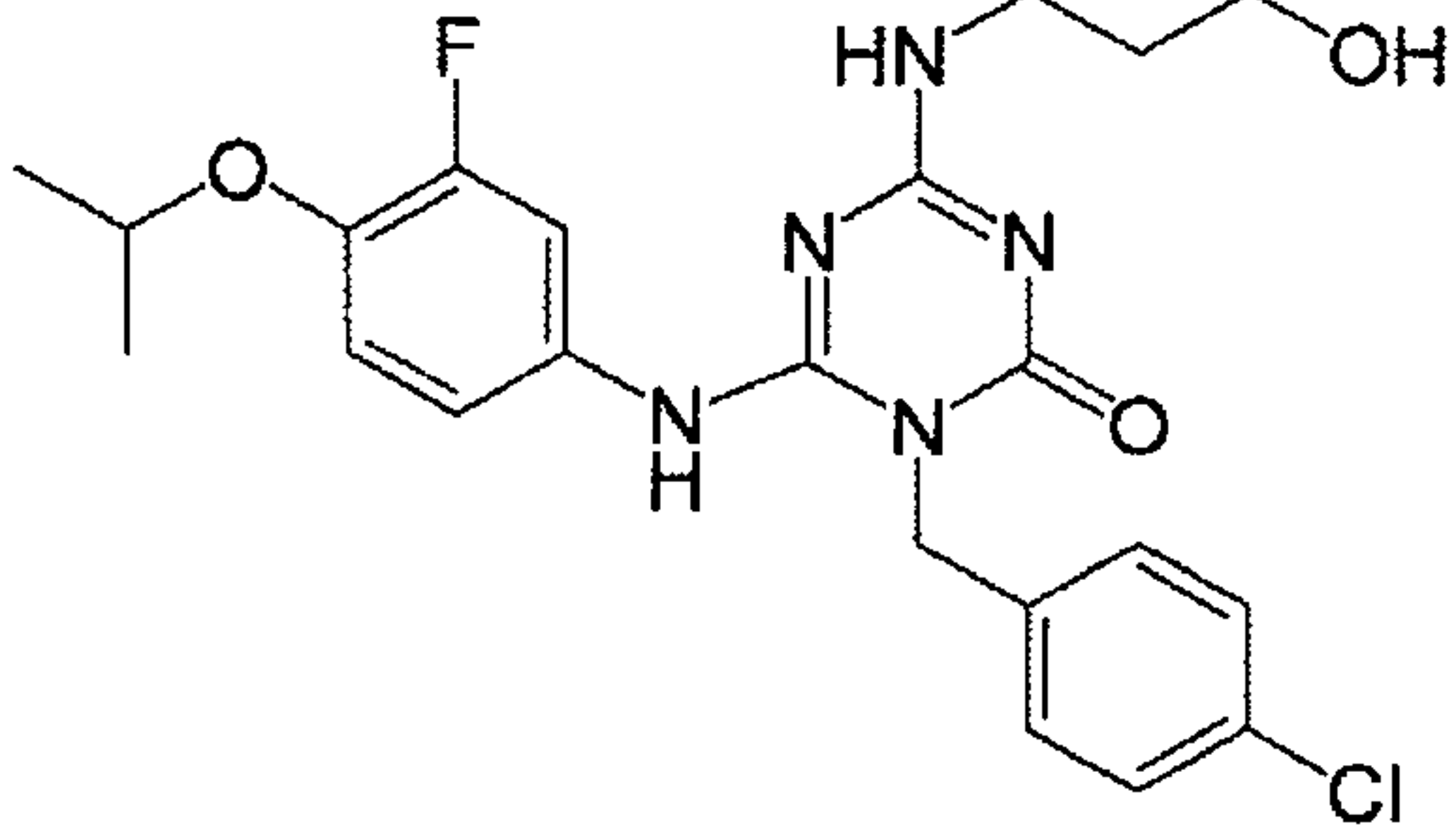
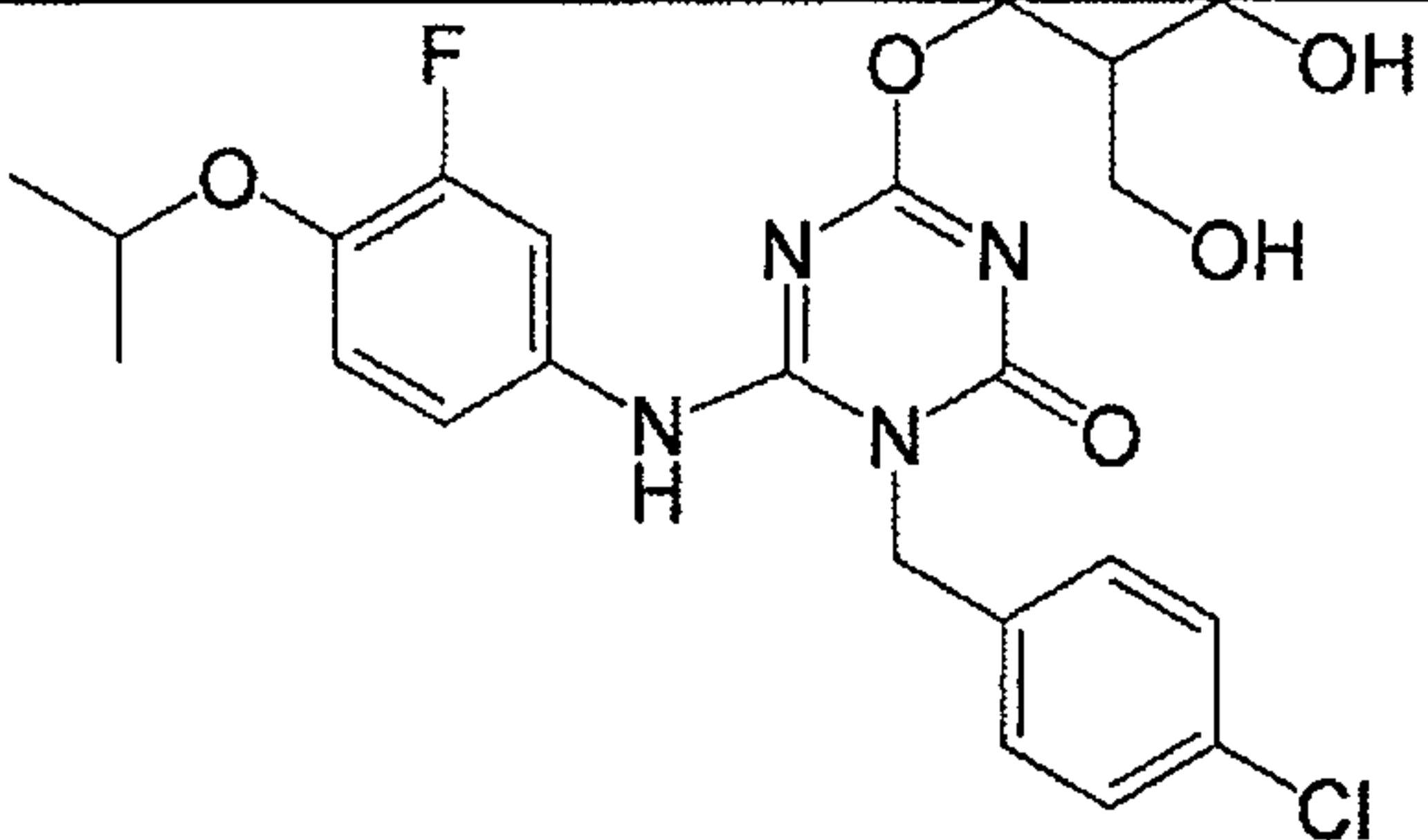
[Table 89]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0426	2.12	496	2
	I-0427	1.25	500	2
	I-0428	1.72	479	2
	I-0429	1.85	482	2
	I-0430	2.44	515	2

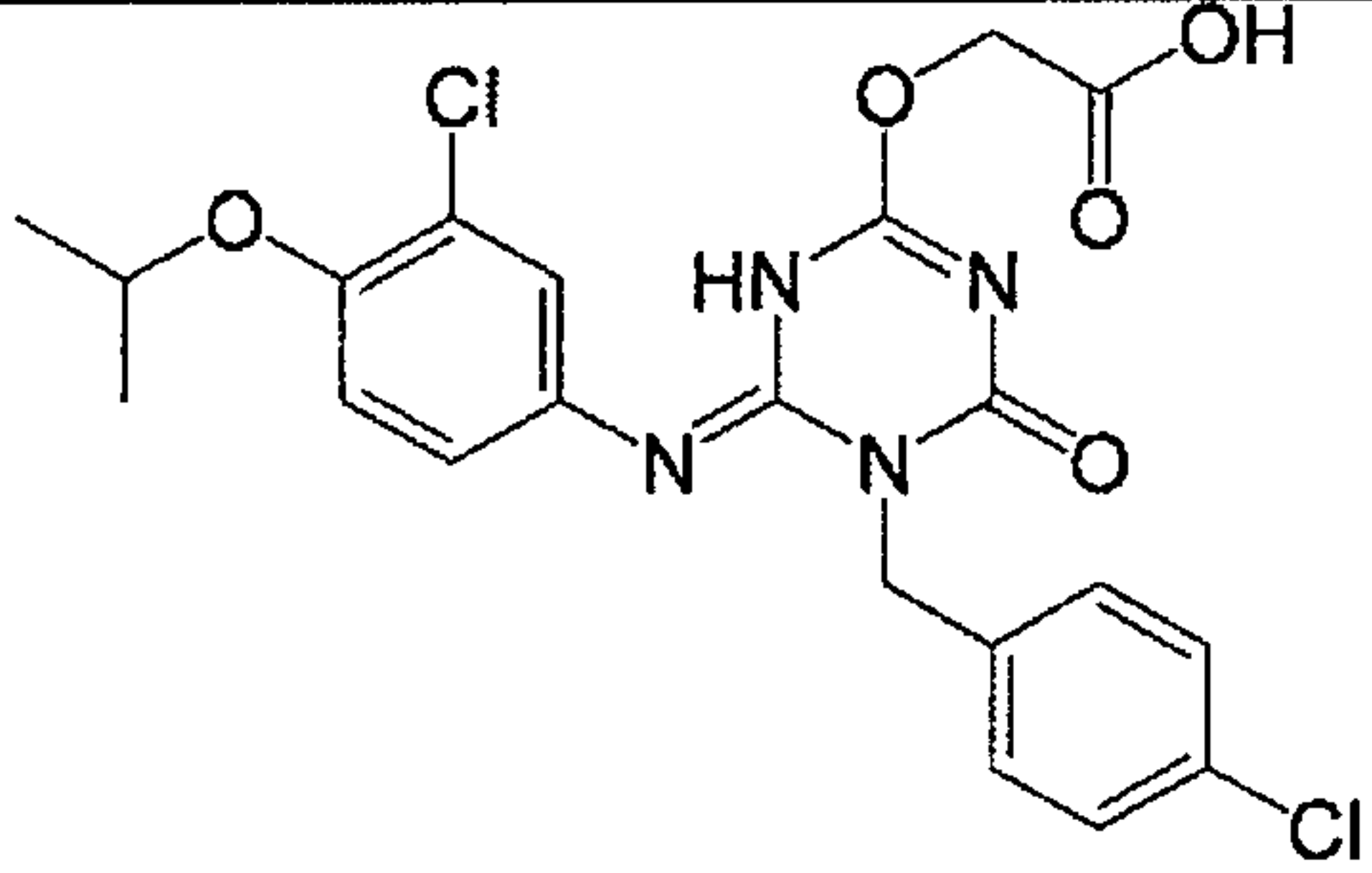
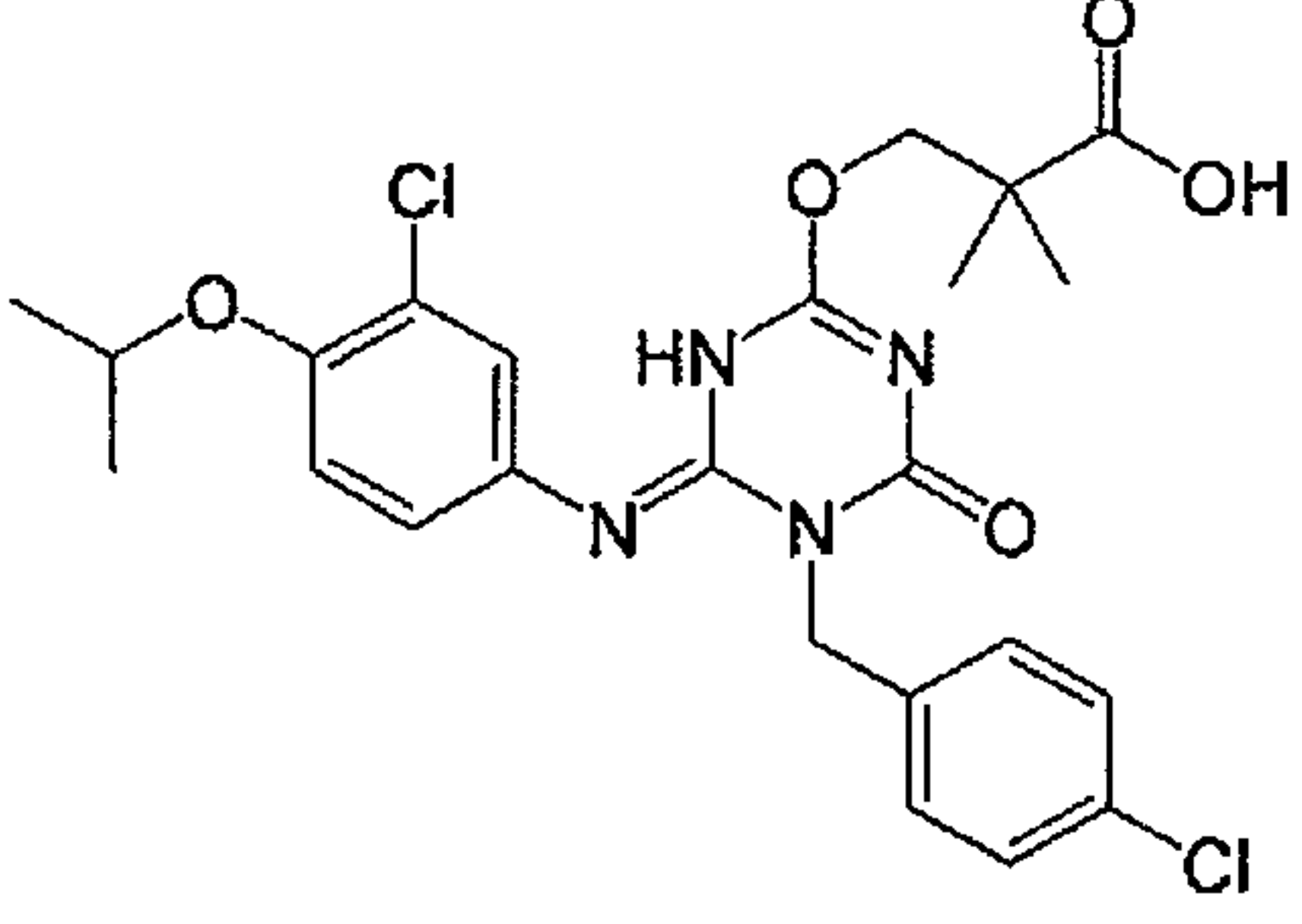
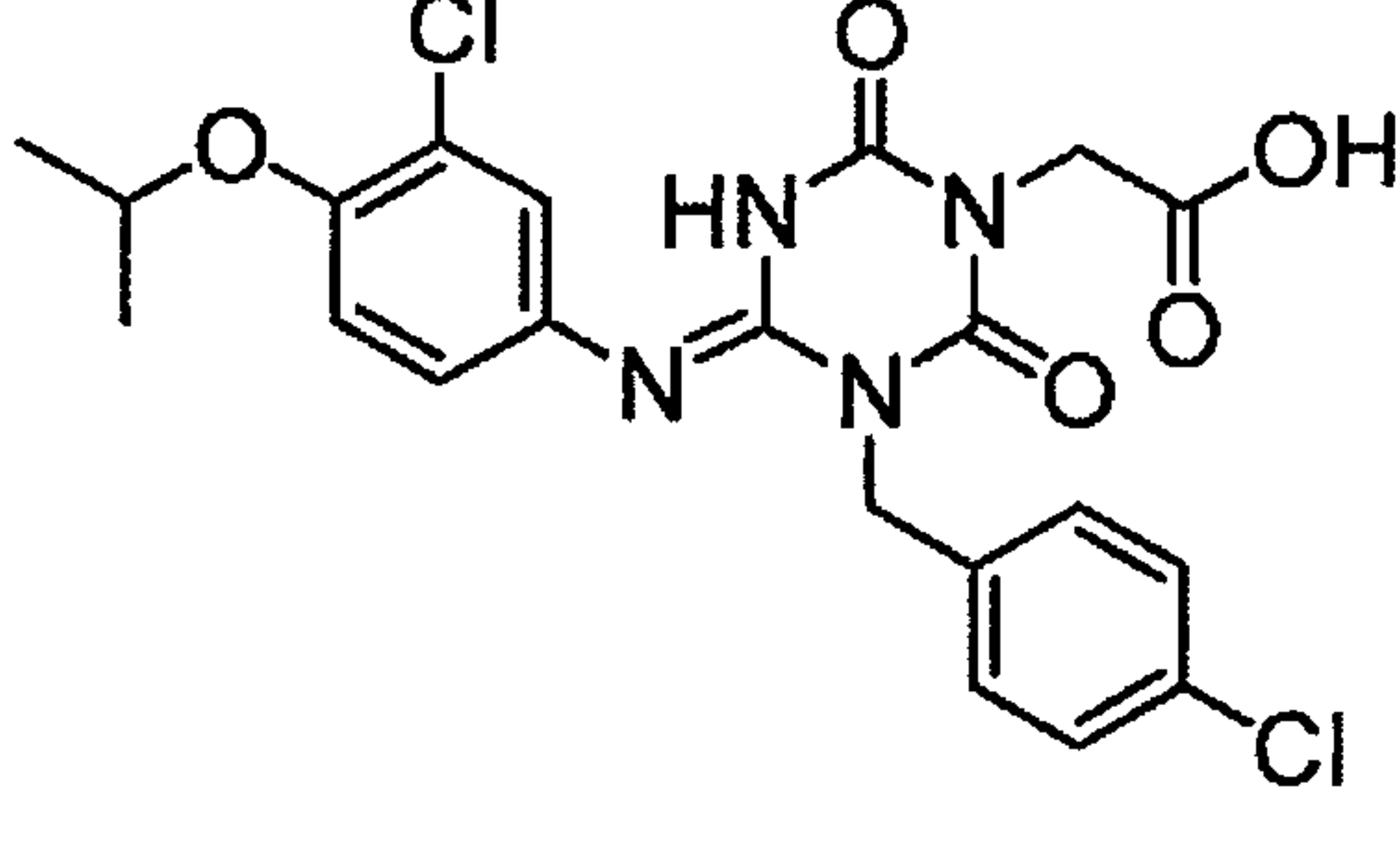
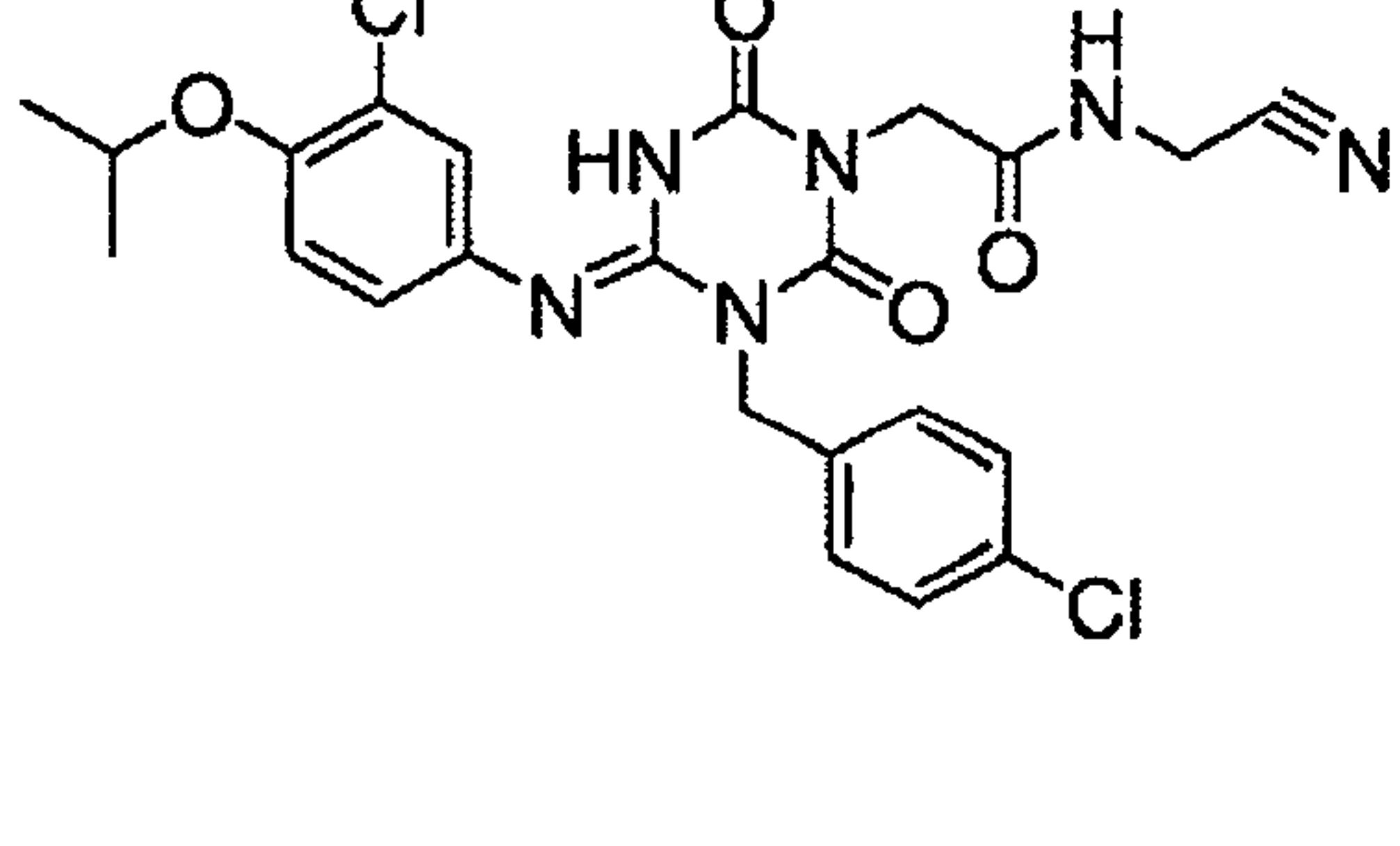
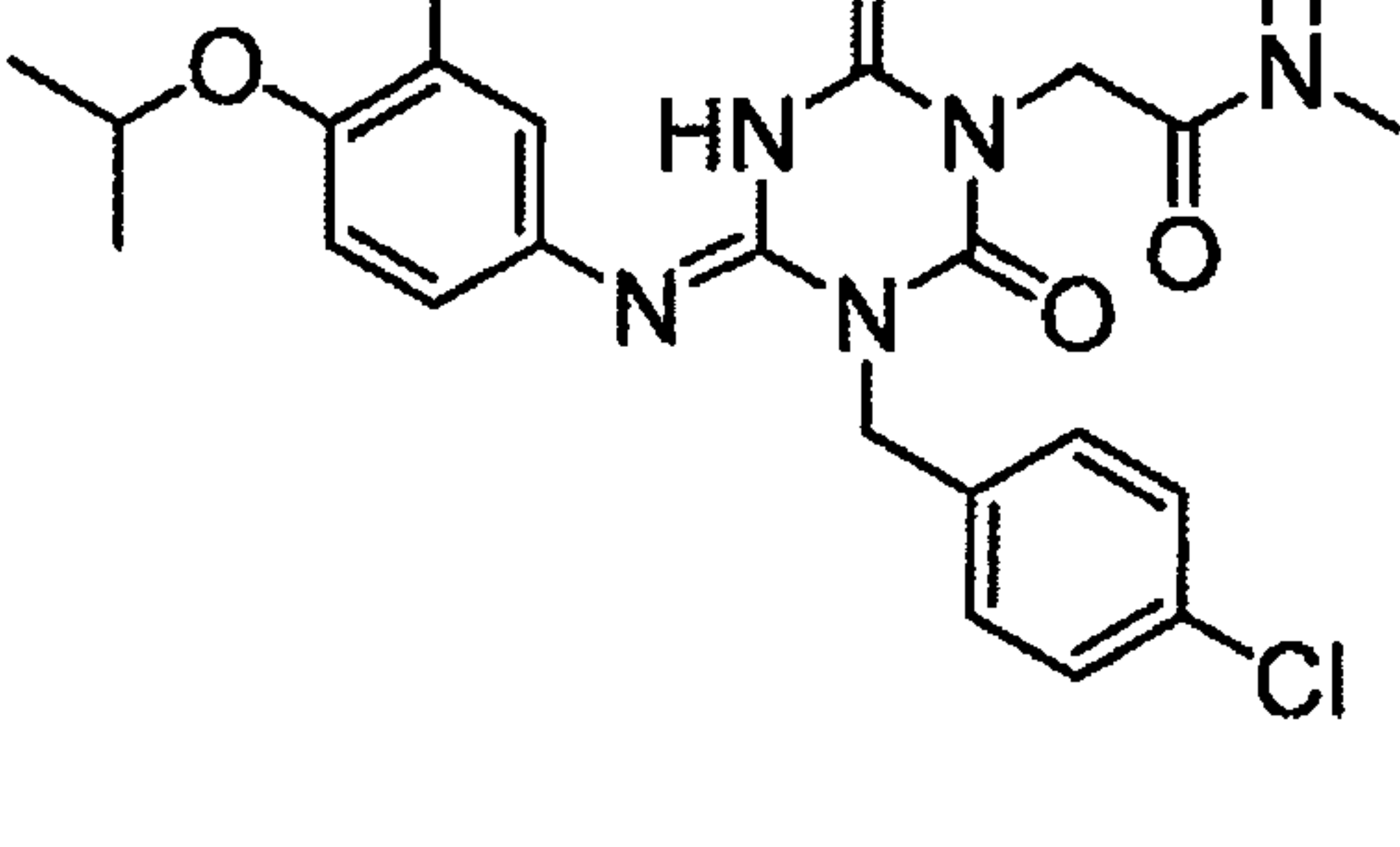
[Table 90]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0431	2.15	501	2
	I-0432	2.10	435	1
	I-0433	1.79	462	1
	I-0434	1.80	449	1
	I-0435	1.90	494	1

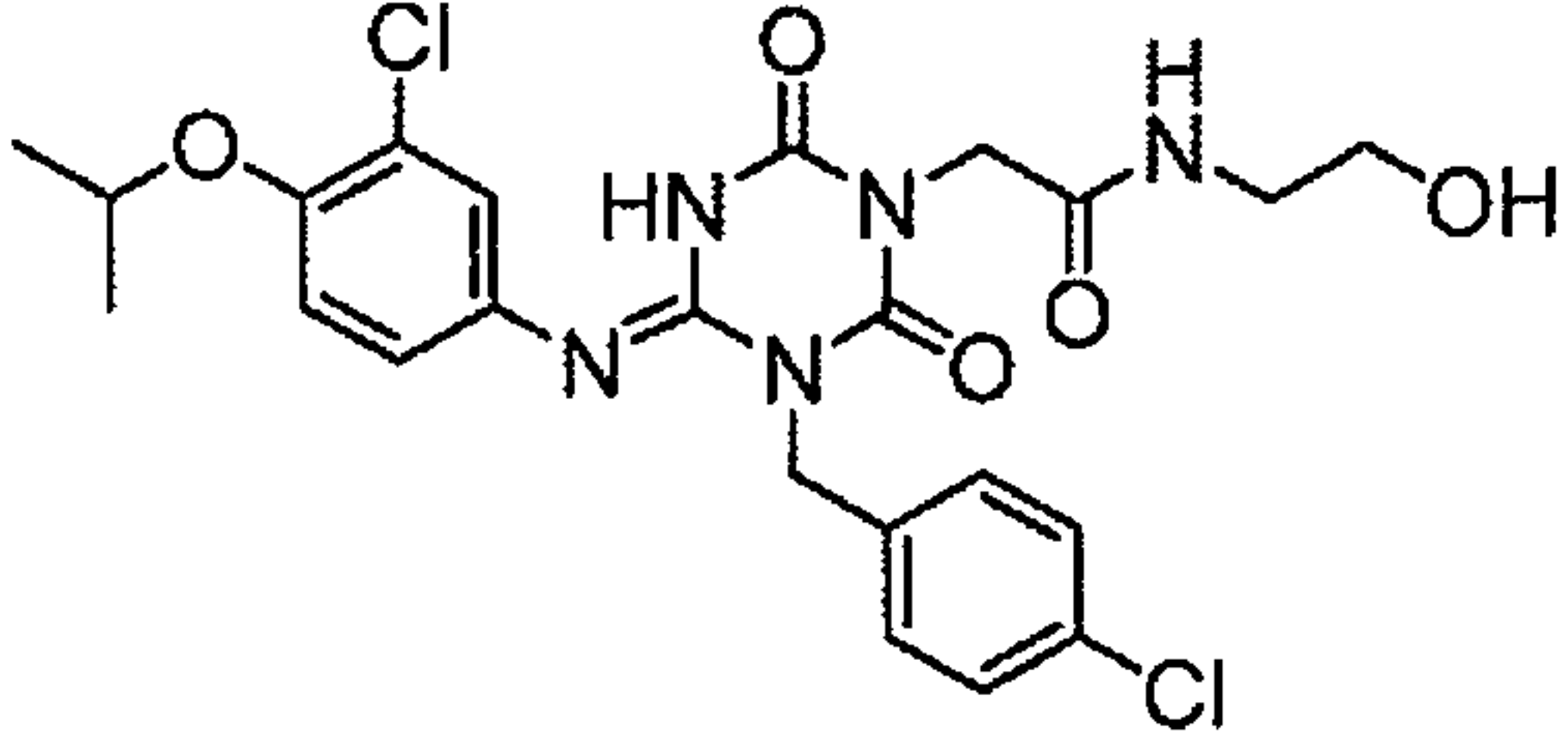
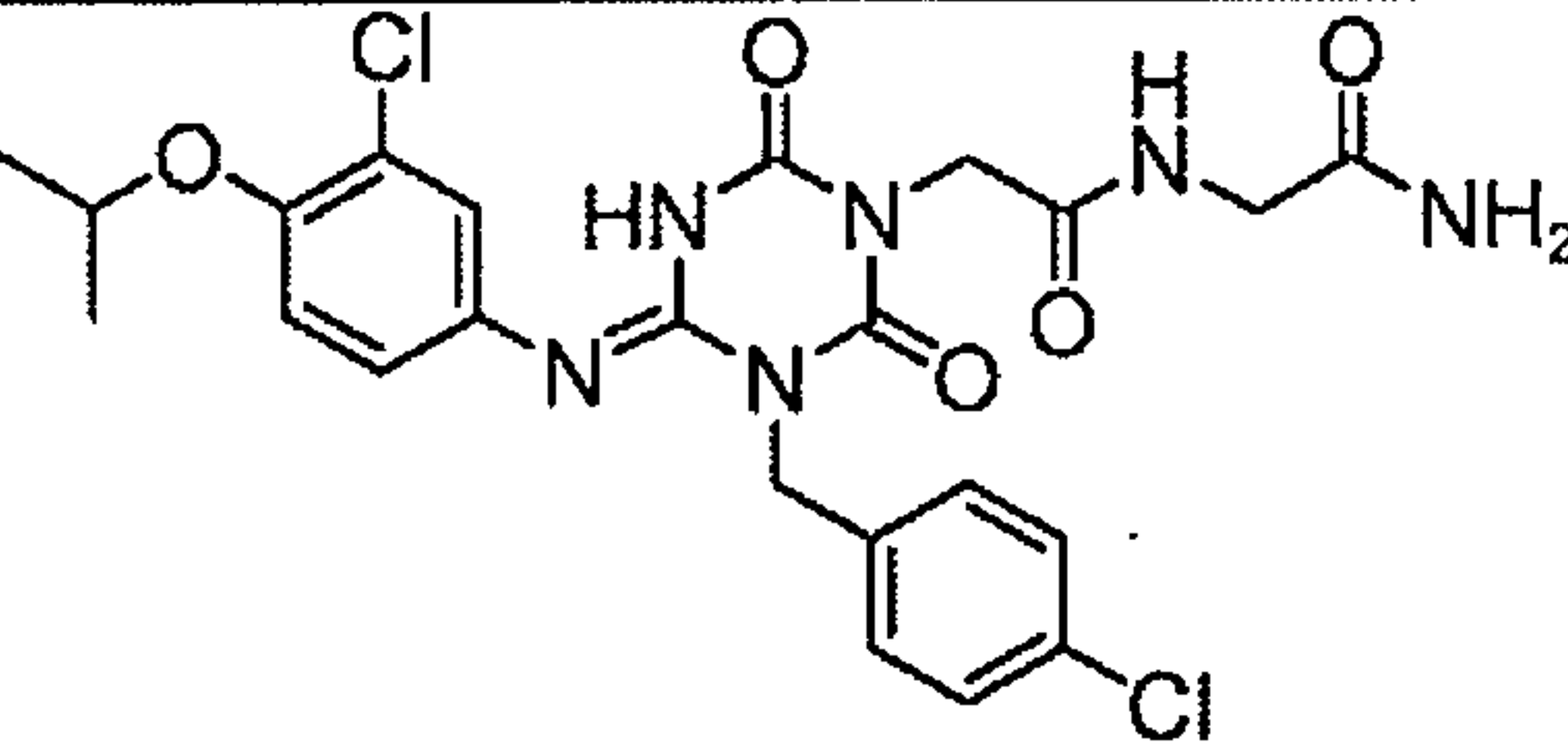
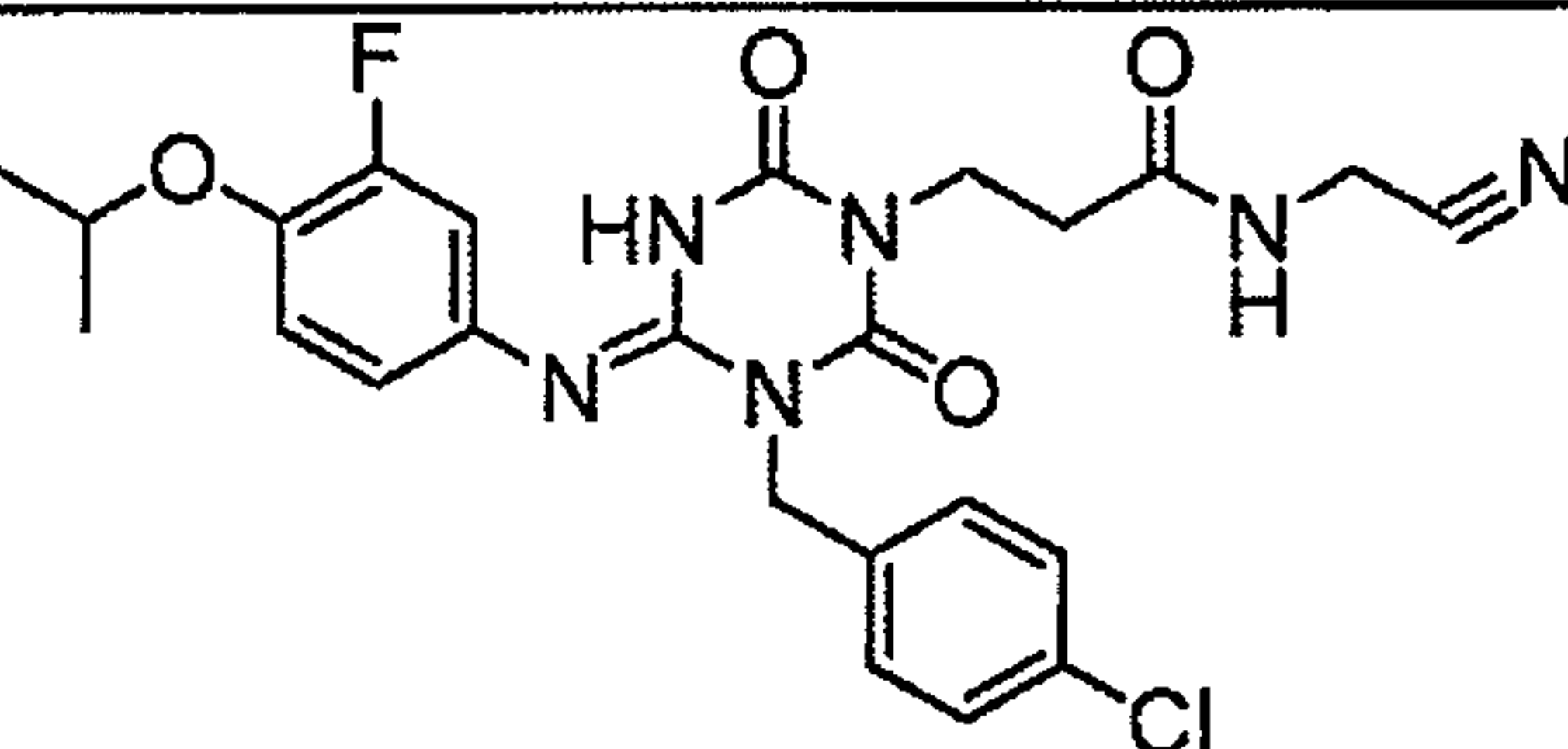
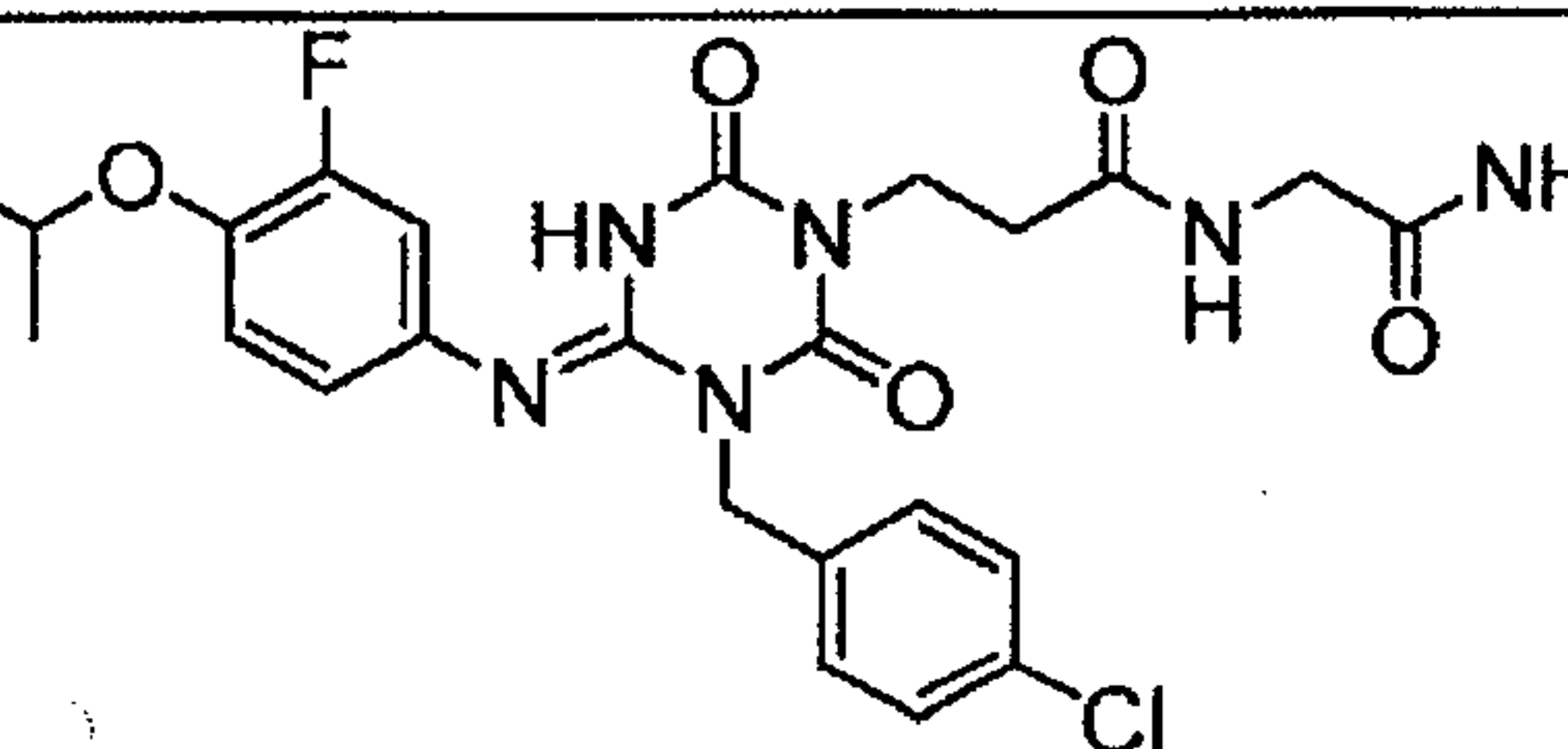
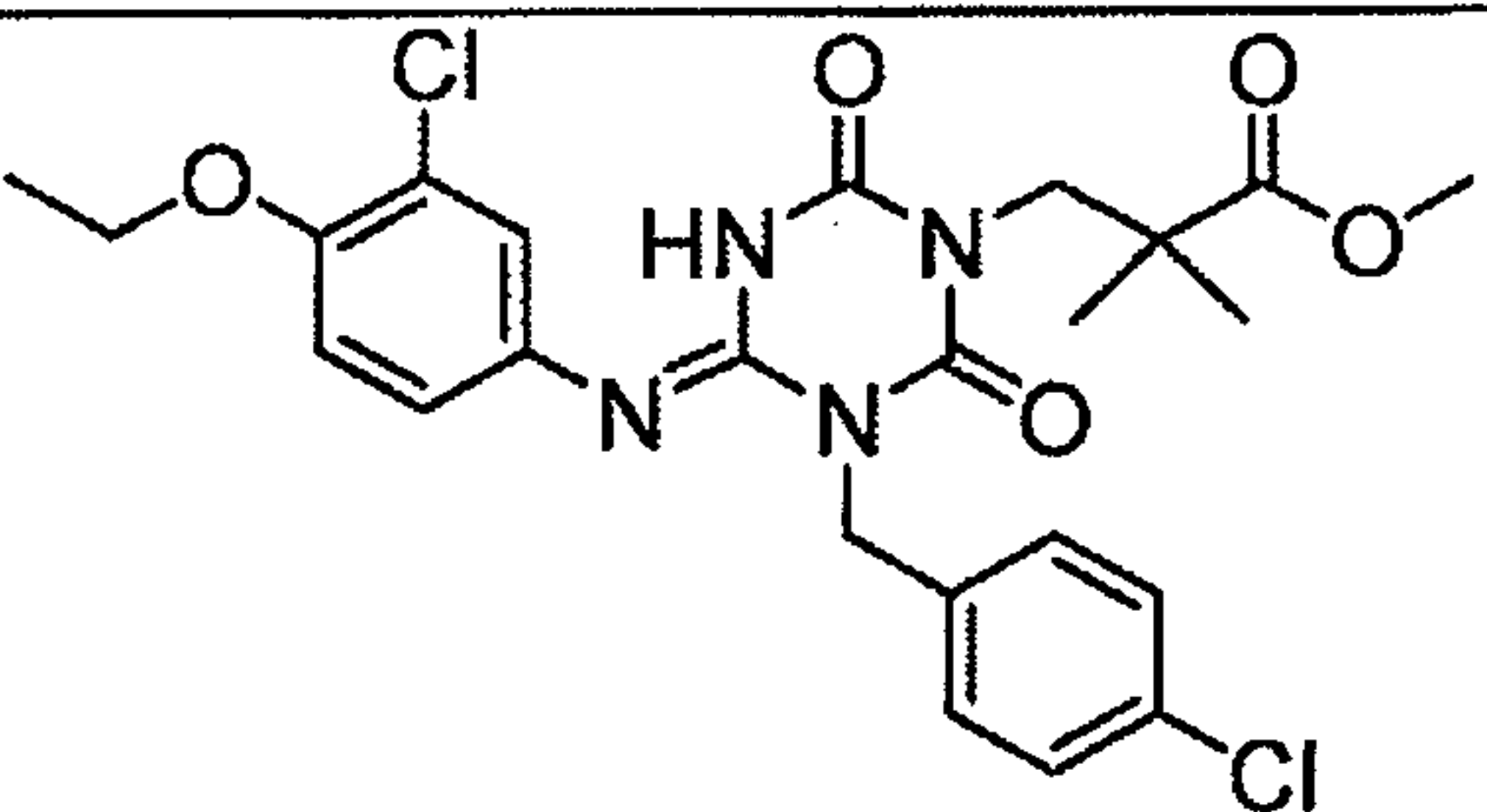
[Table 91]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0436	3.40	590	1
	I-0437	1.50	448	2
	I-0438	1.80	464	2
	I-0439	1.50	462	2
	I-0440	1.70	493	2

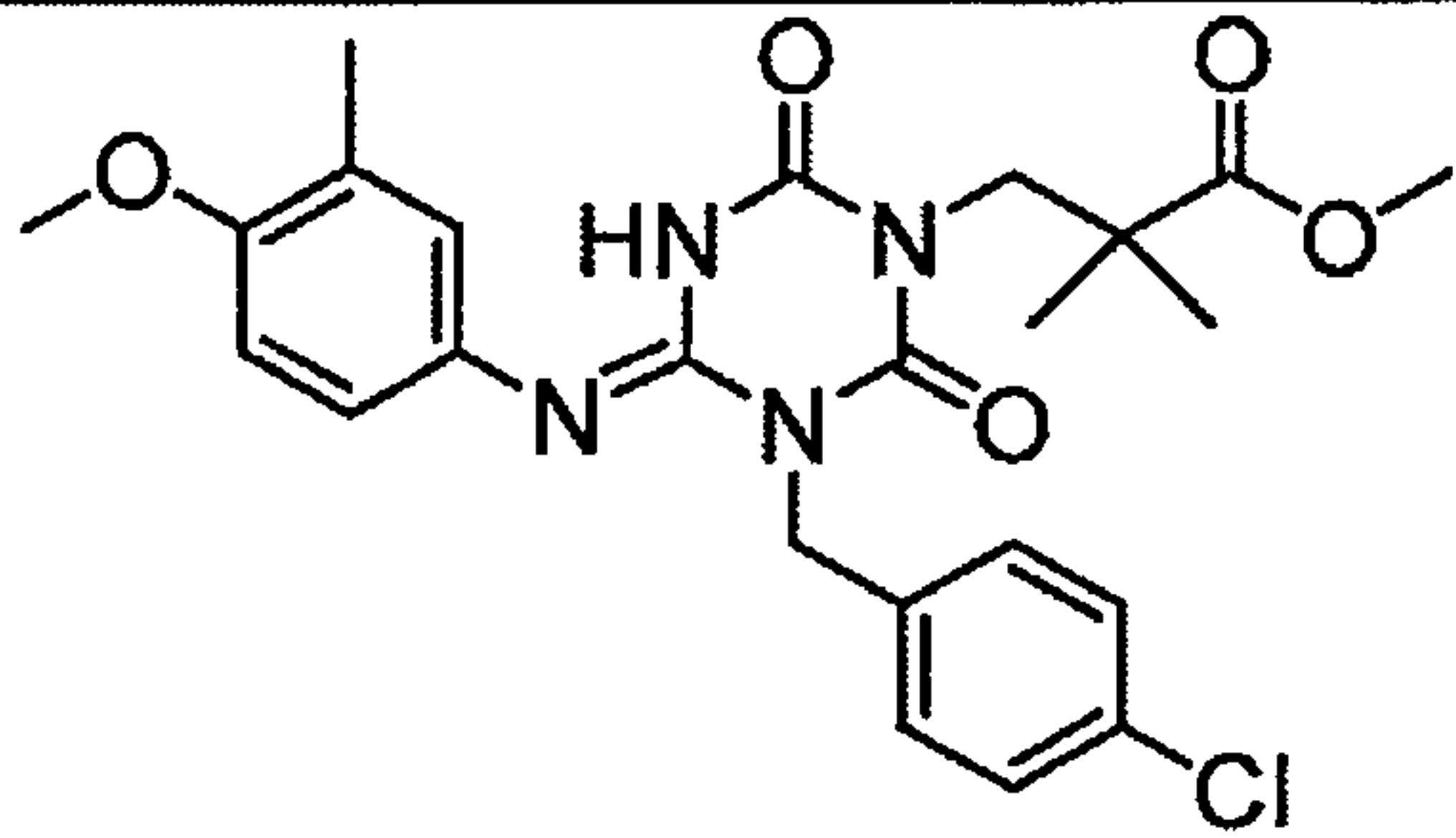
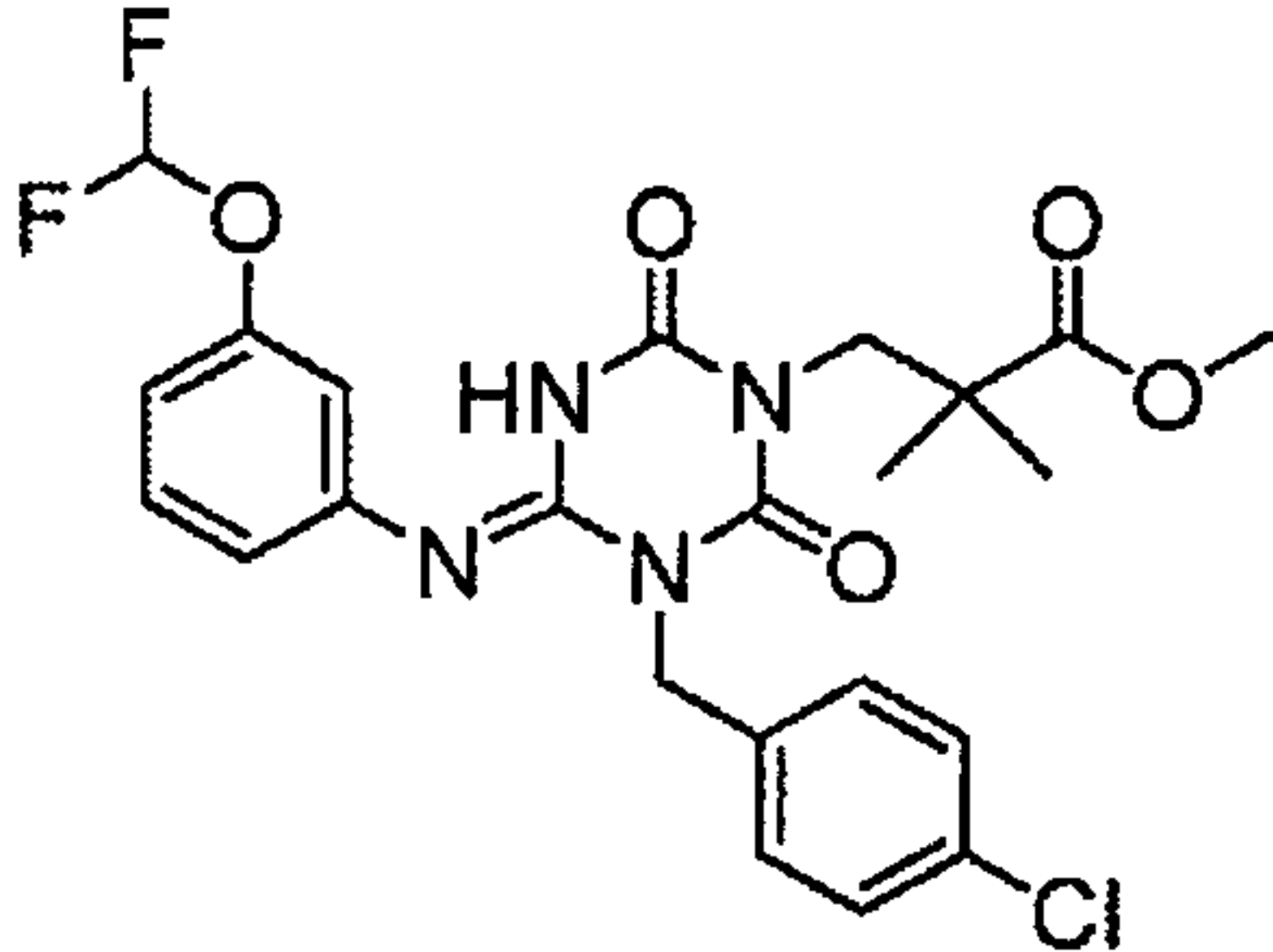
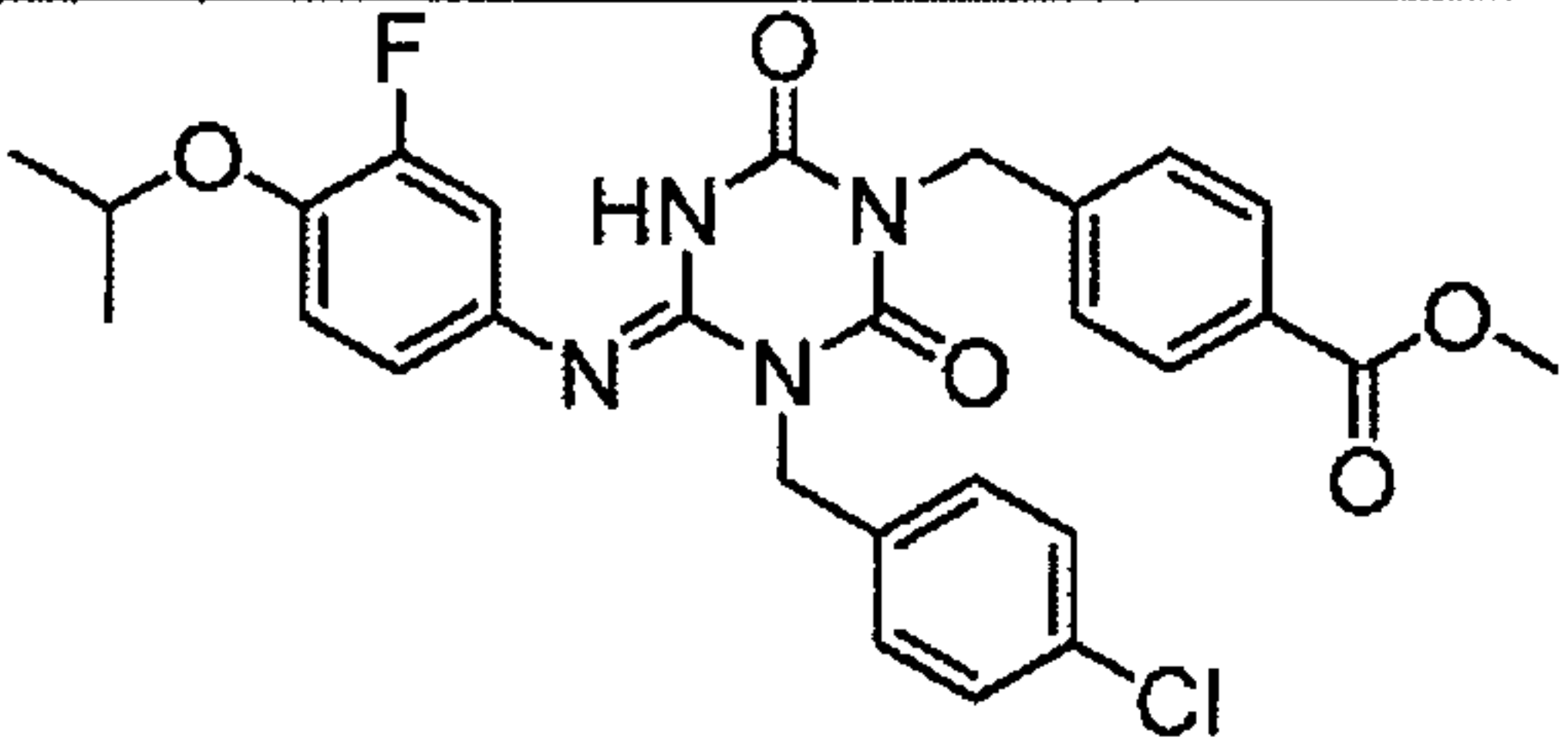
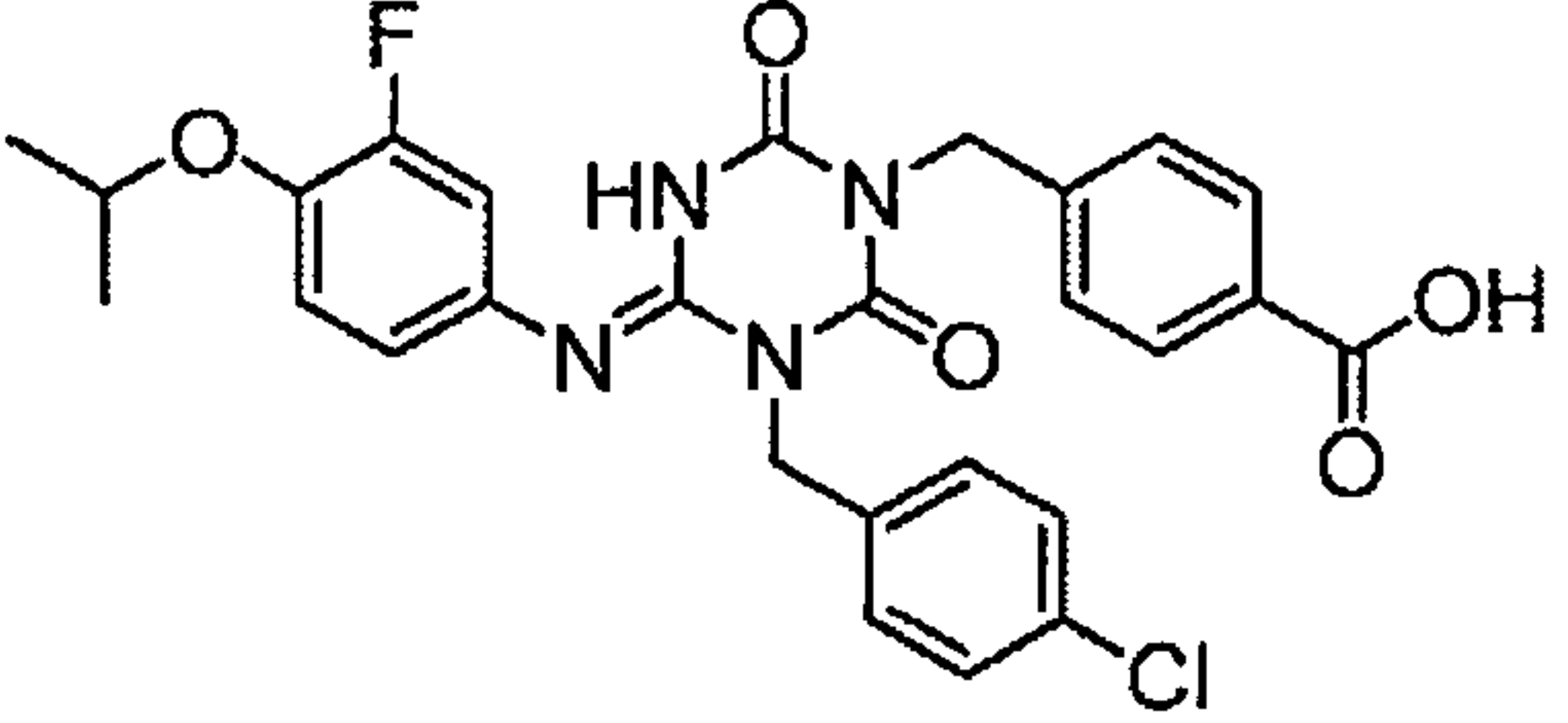
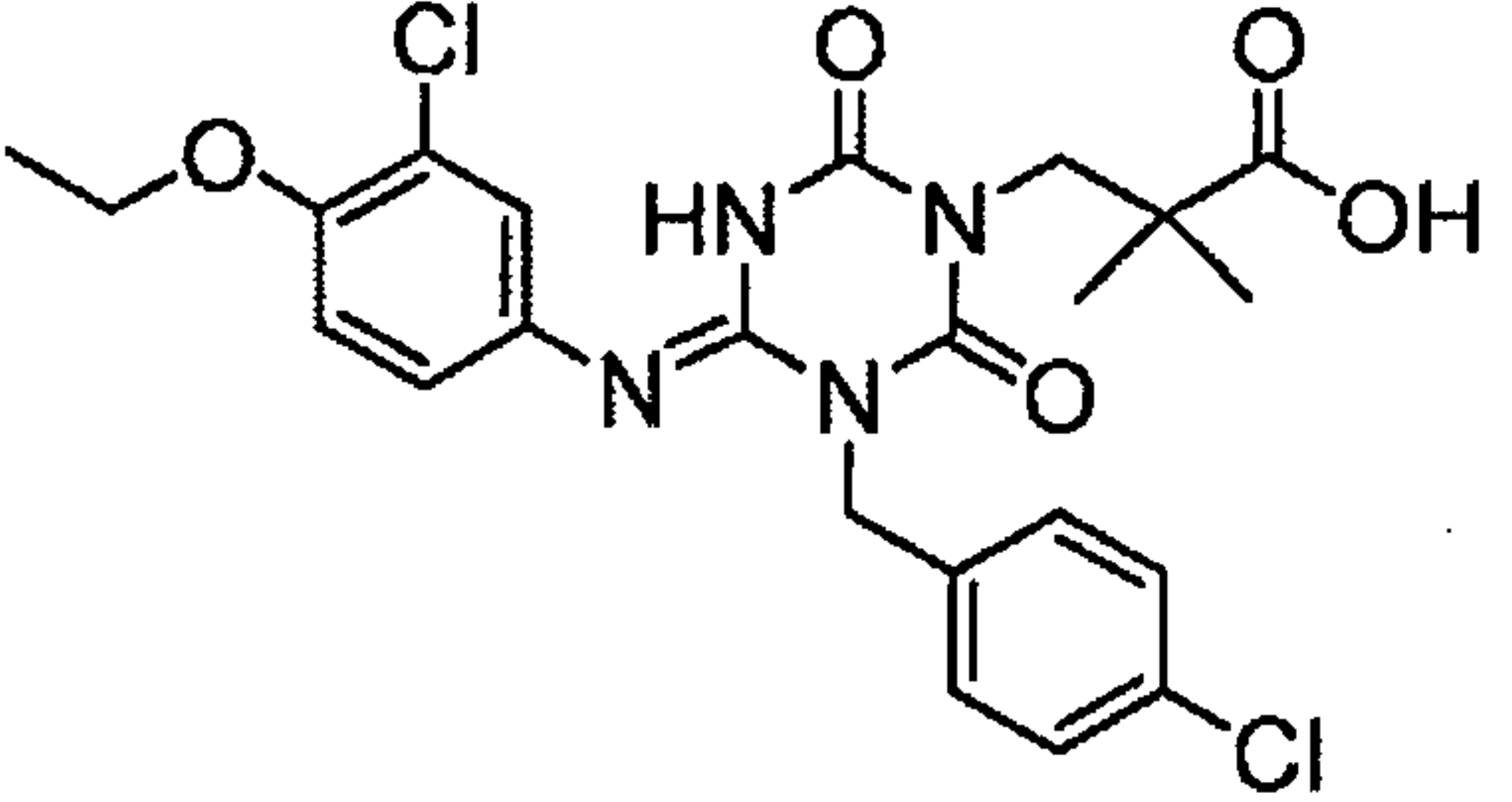
[Table 92]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0441	1.88	479	1
	I-0442	2.09	521	1
	I-0443	2.06	479	2
	I-0444	2.21	517	3
	I-0445	2.16	492	3

[Table 93]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0446	2.03	522	3
	I-0447	1.98	535	3
	I-0448	2.11	515	3
	I-0449	1.87	533	3
	I-0450	2.43	521	2

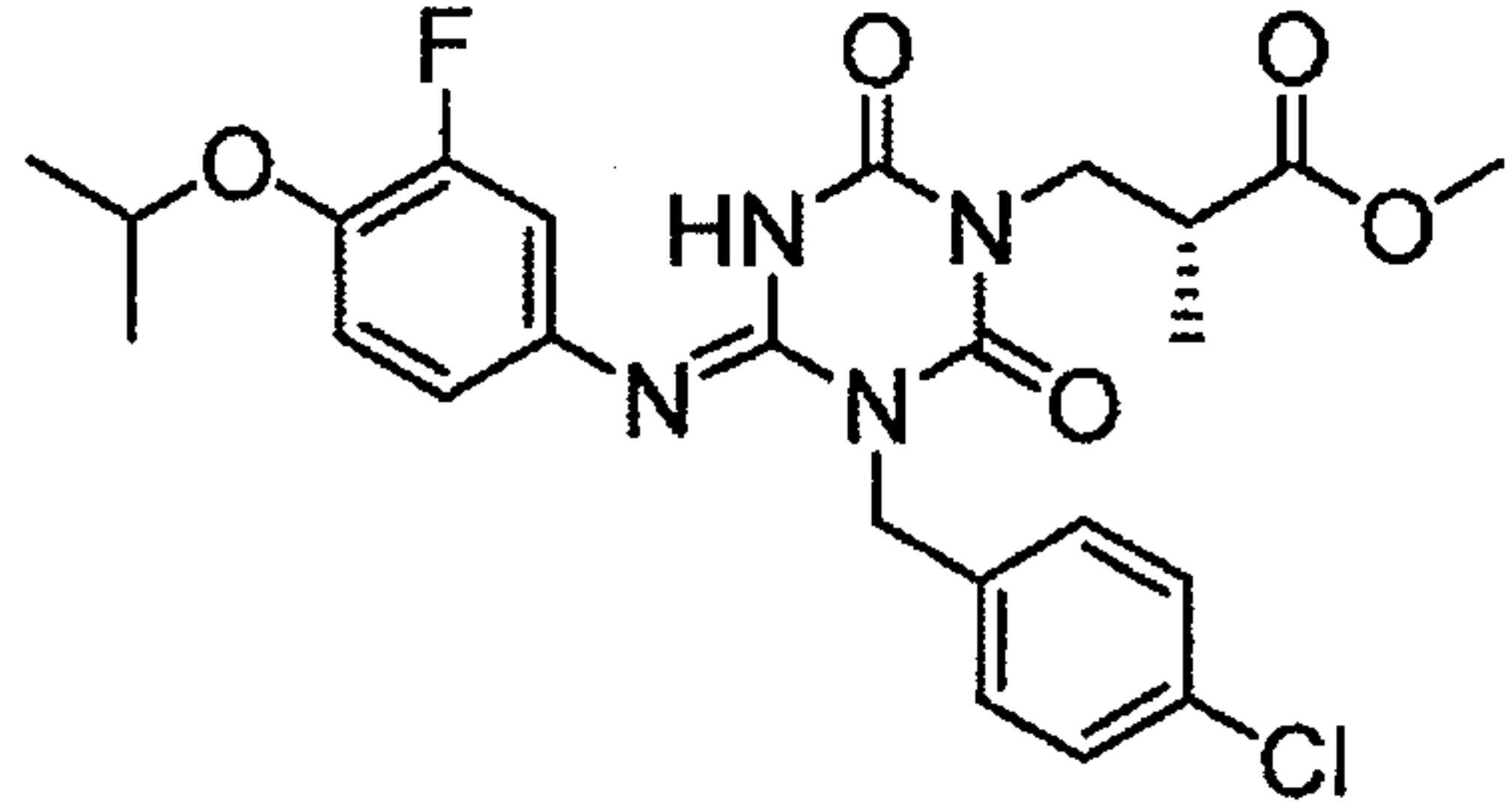
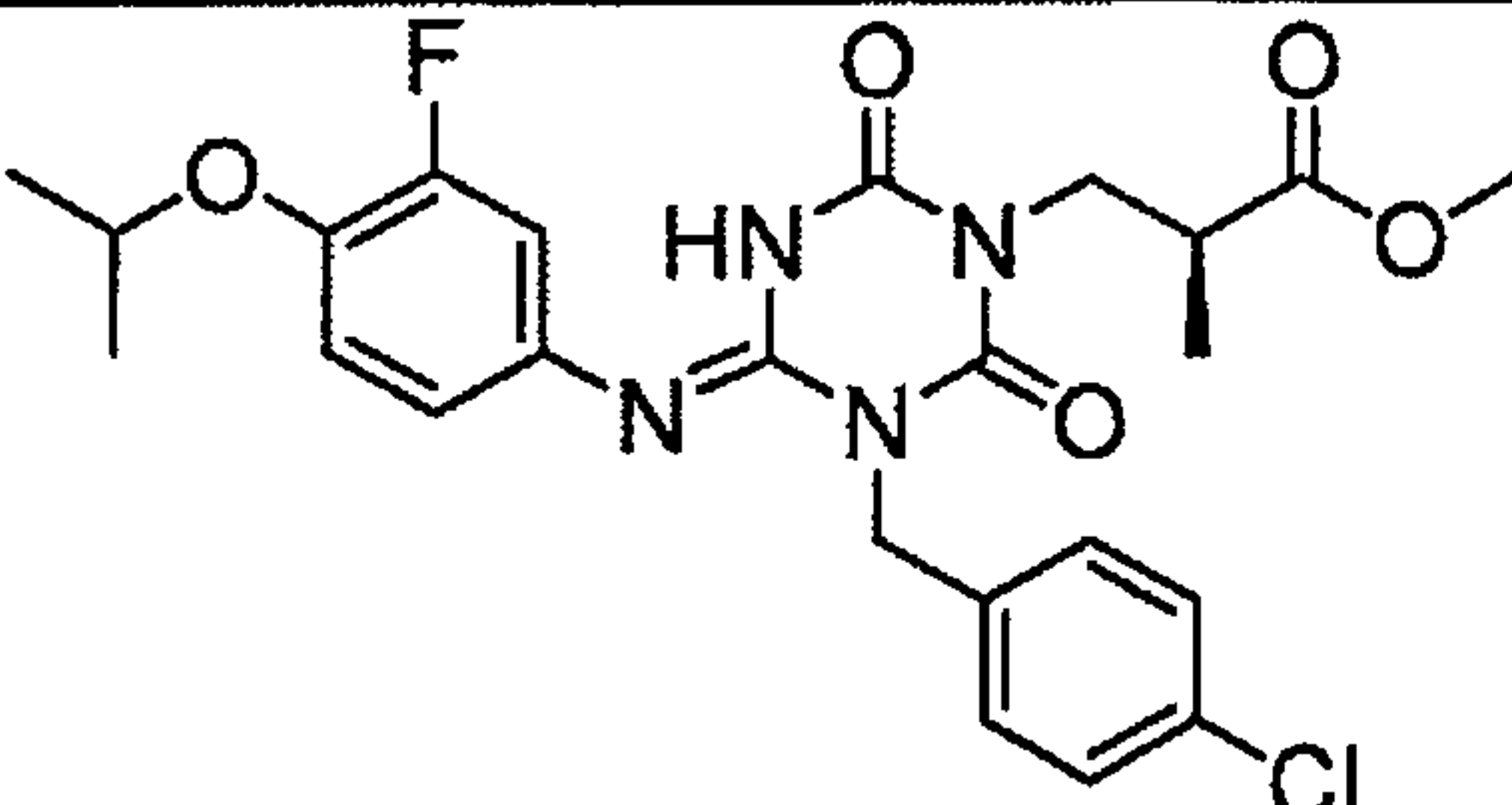
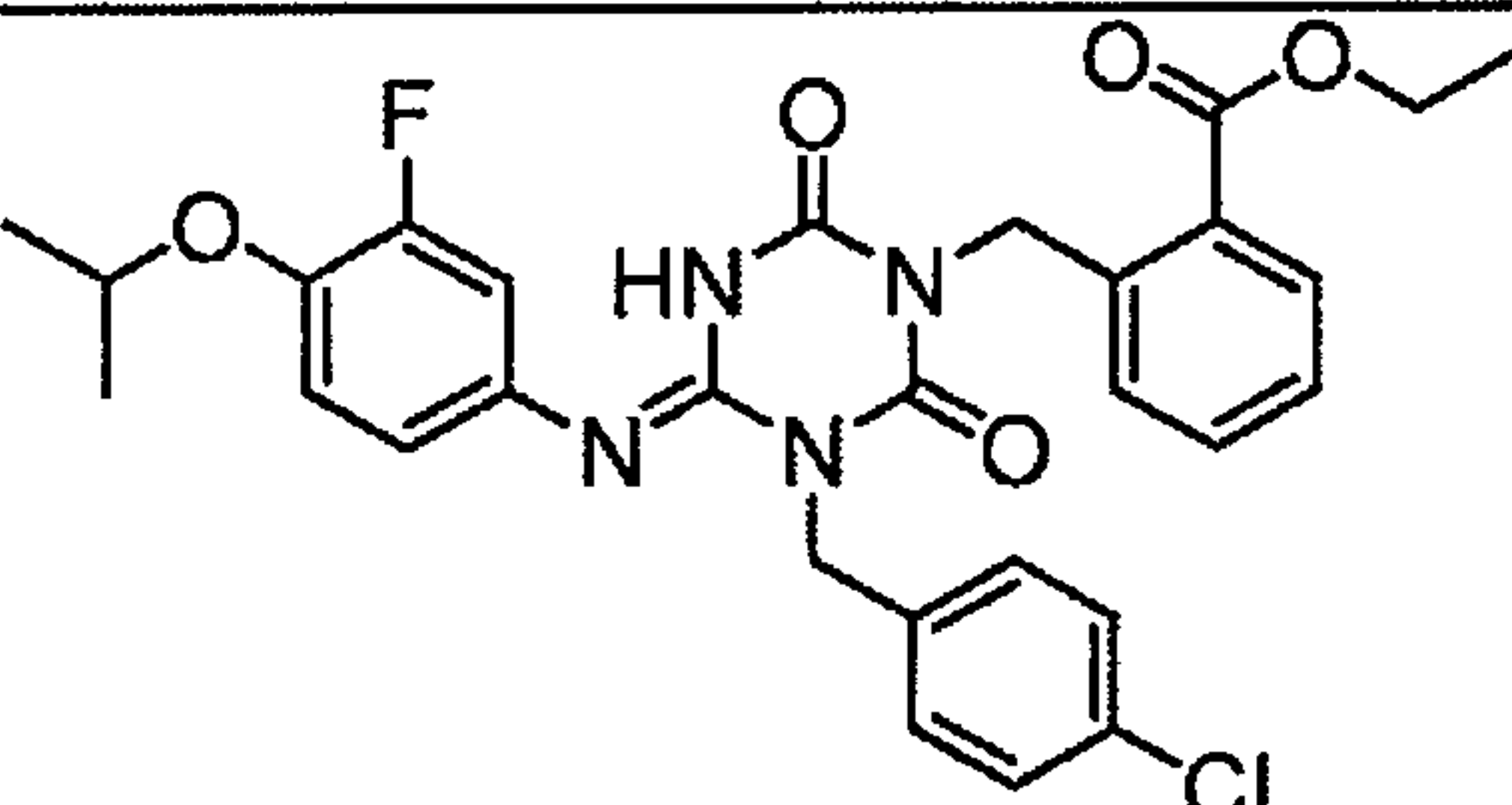
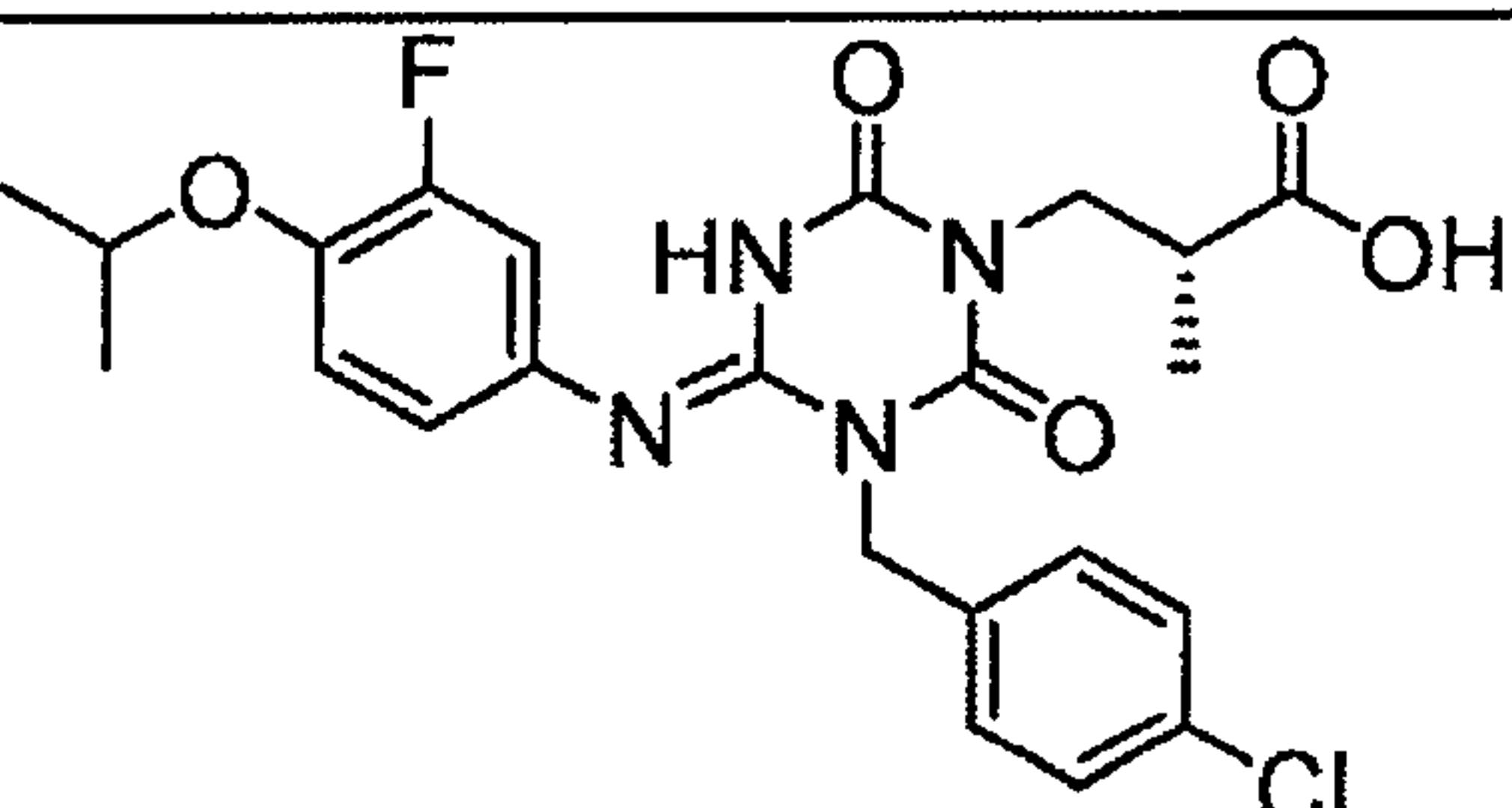
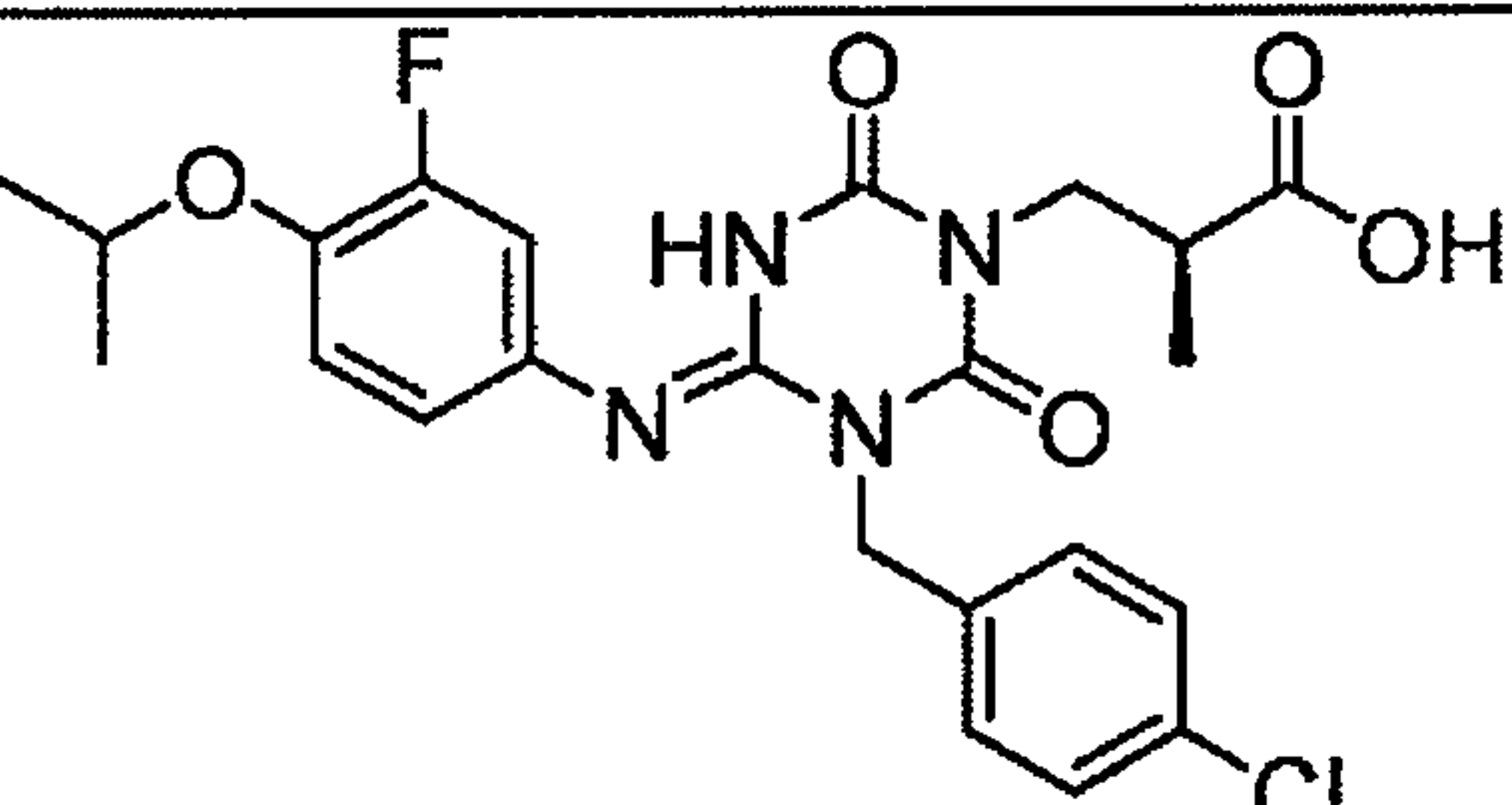
[Table 94]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0451	2.23	487	2
	I-0452	2.50	509	3
	I-0453	2.61	553	3
	I-0454	2.33	539	3
	I-0455	2.31	507	2

[Table 95]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0456	2.10	473	2
	I-0457	2.22	495	2
	I-0458	2.67	511	2
	I-0459	2.63	553	3
	I-0460	2.36	539	3

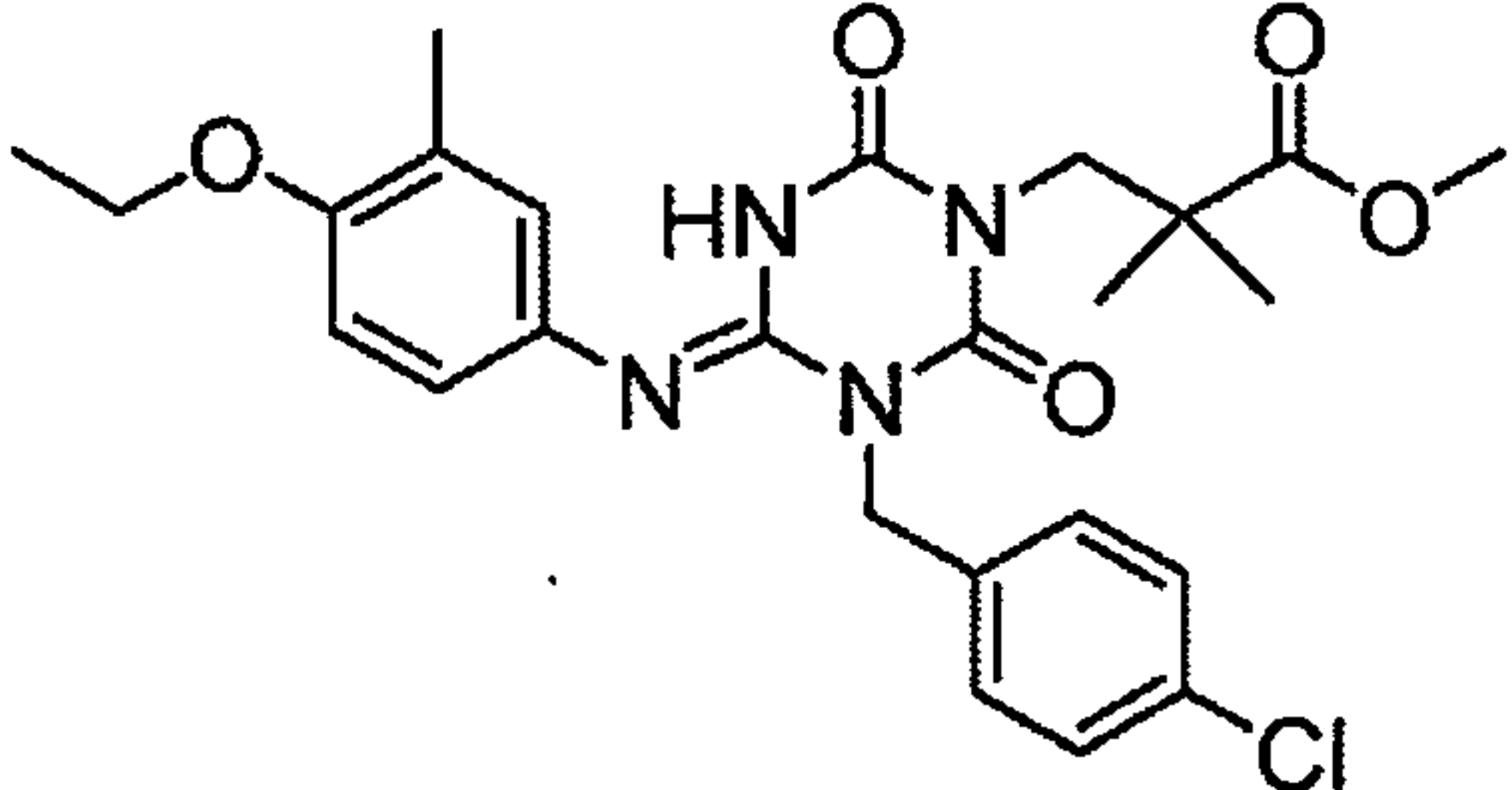
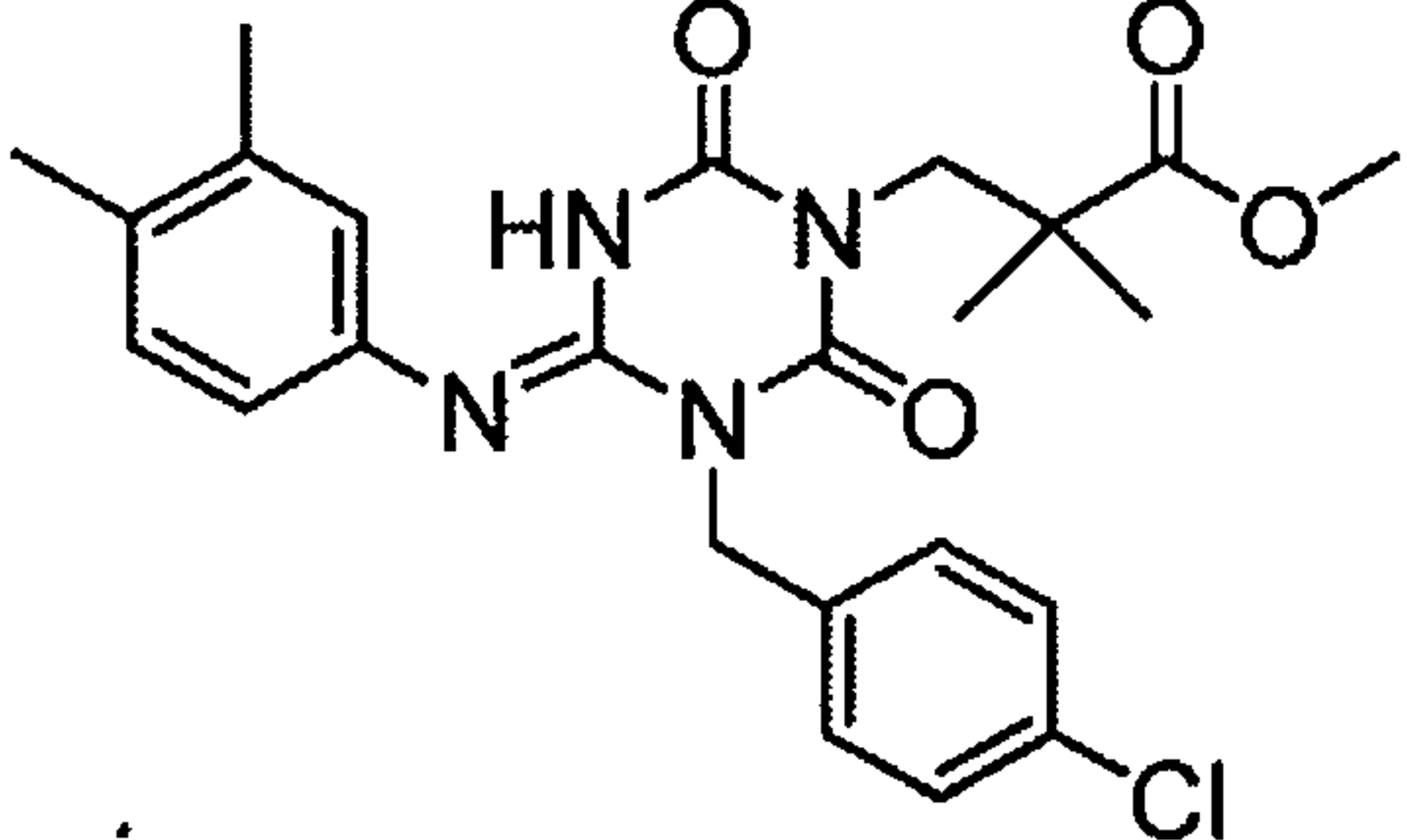
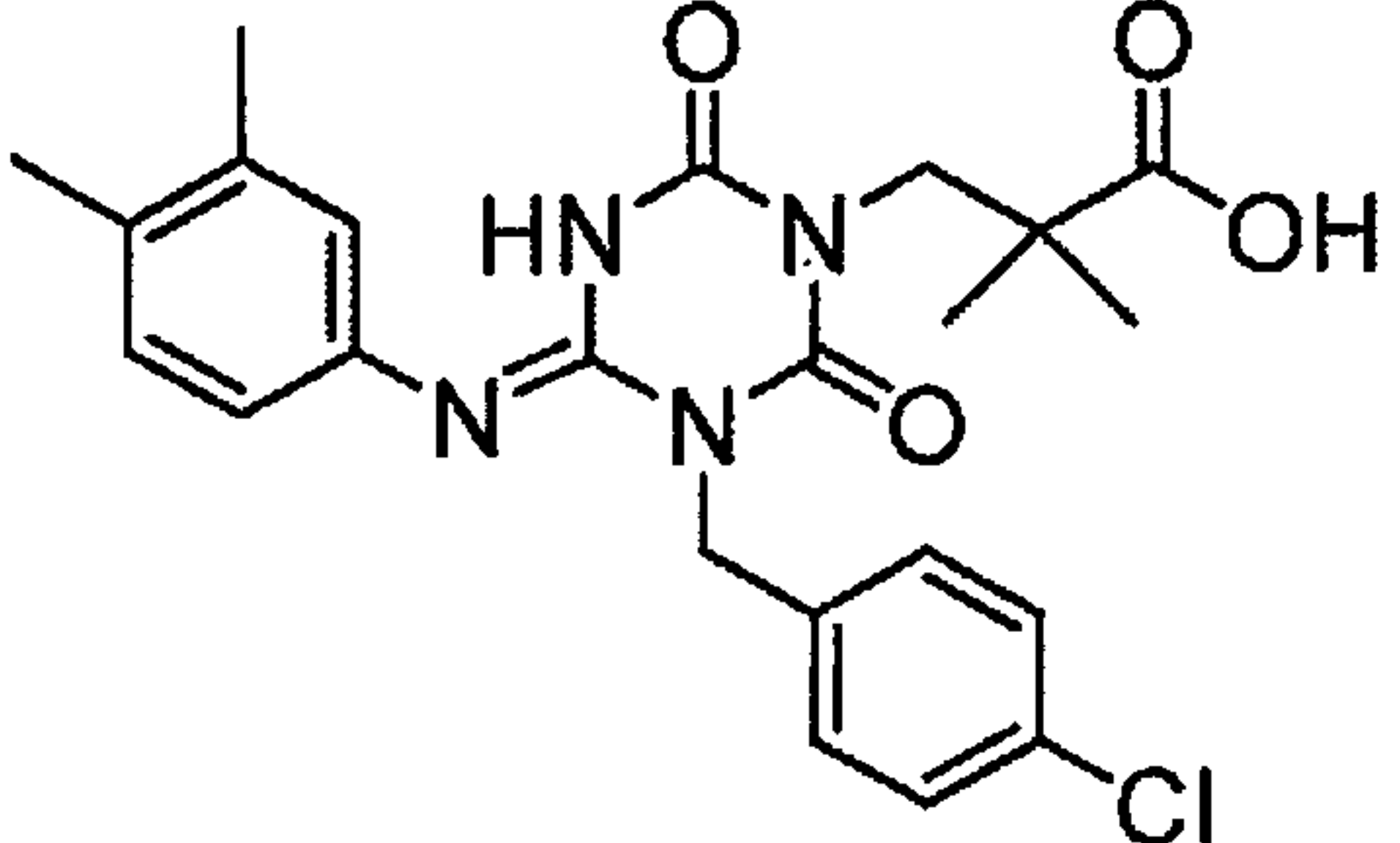
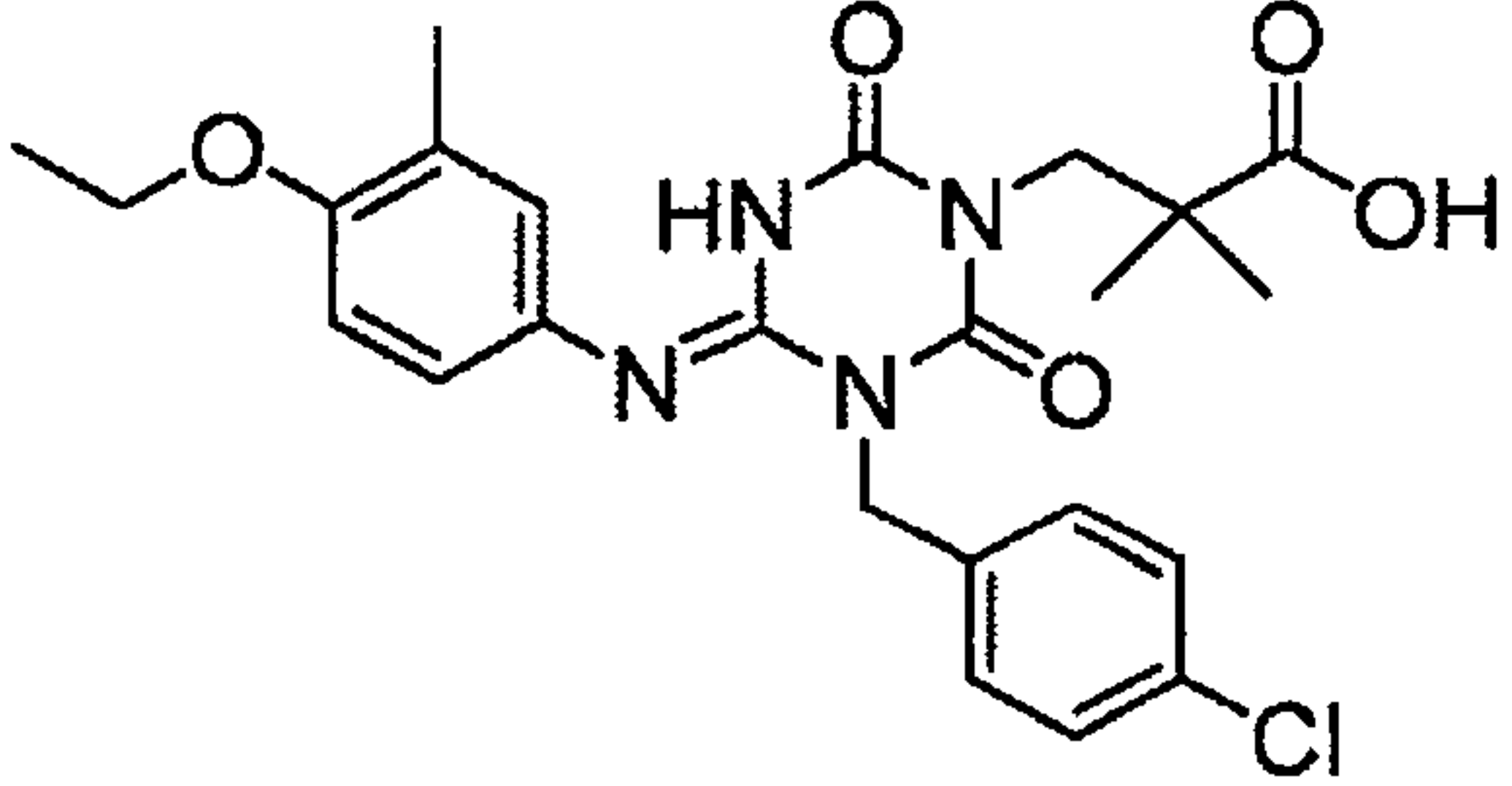
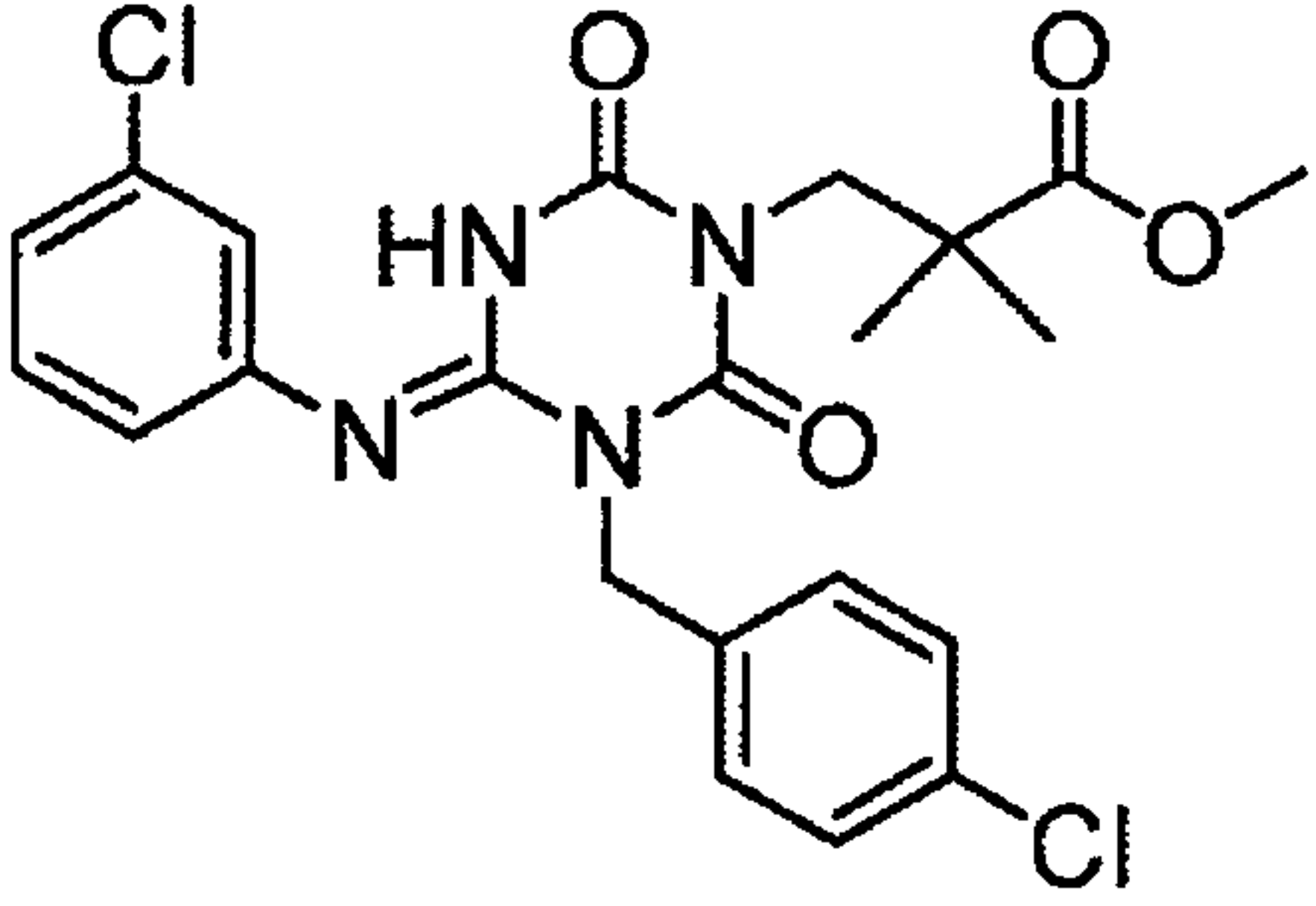
[Table 96]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0461	2.29	505	2
	I-0462	2.30	505	2
	I-0463	2.74	567	3
	I-0464	2.22	491	3
	I-0465	2.22	491	3

[Table 97]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0466	2.41	521	2
	I-0467	2.41	521	2
	I-0468	2.38	539	3
	I-0469	2.34	507	3
	I-0470	2.33	507	3

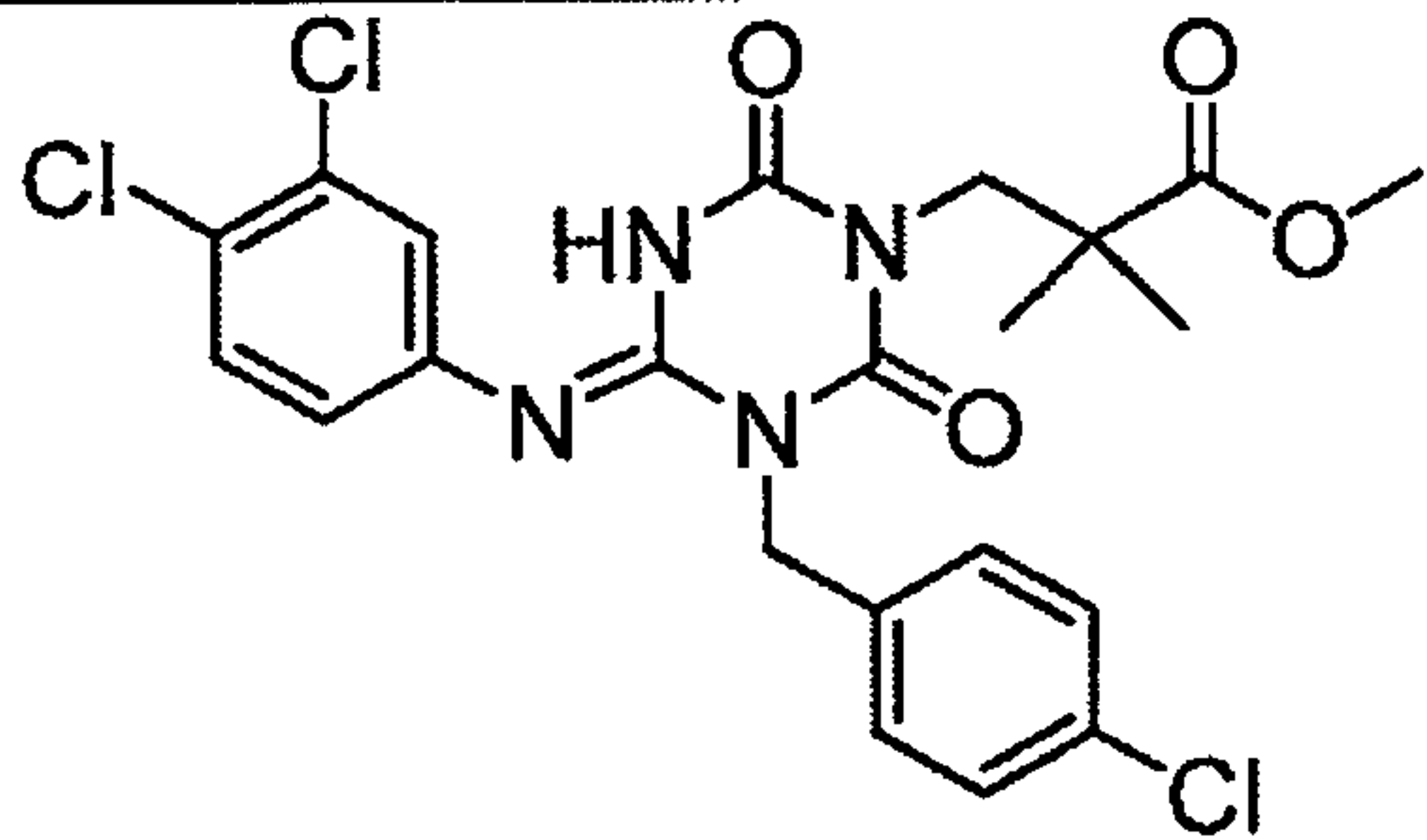
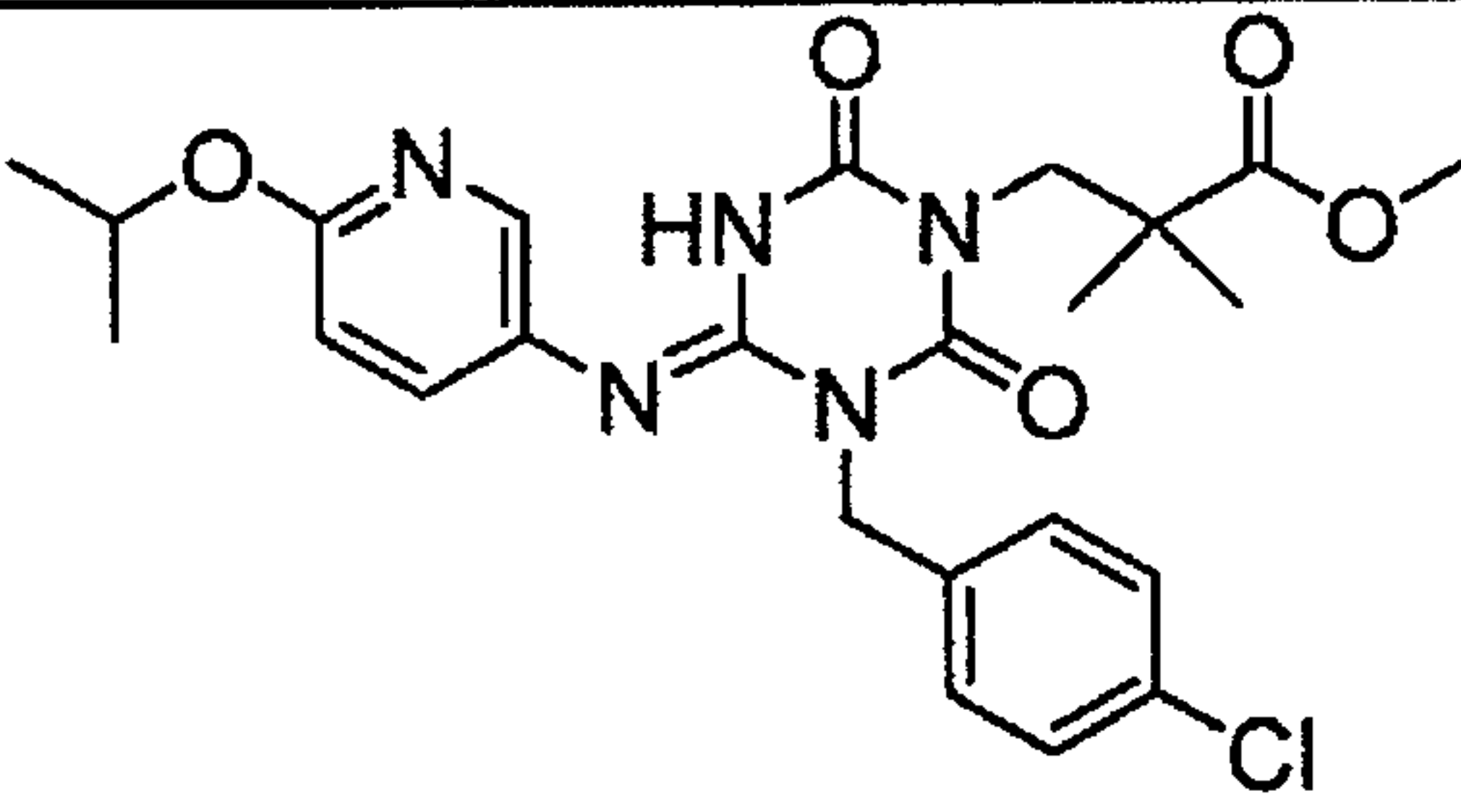
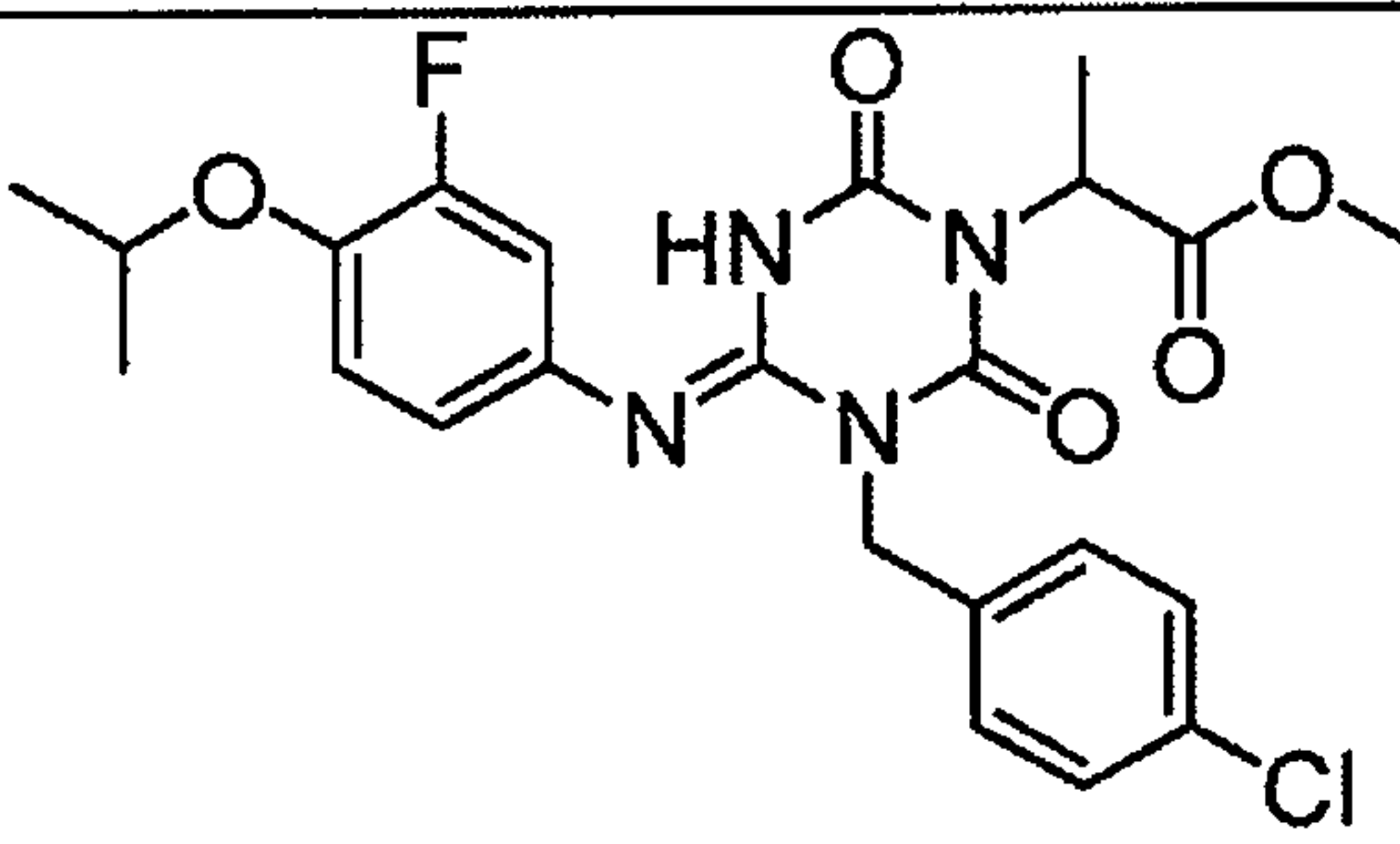
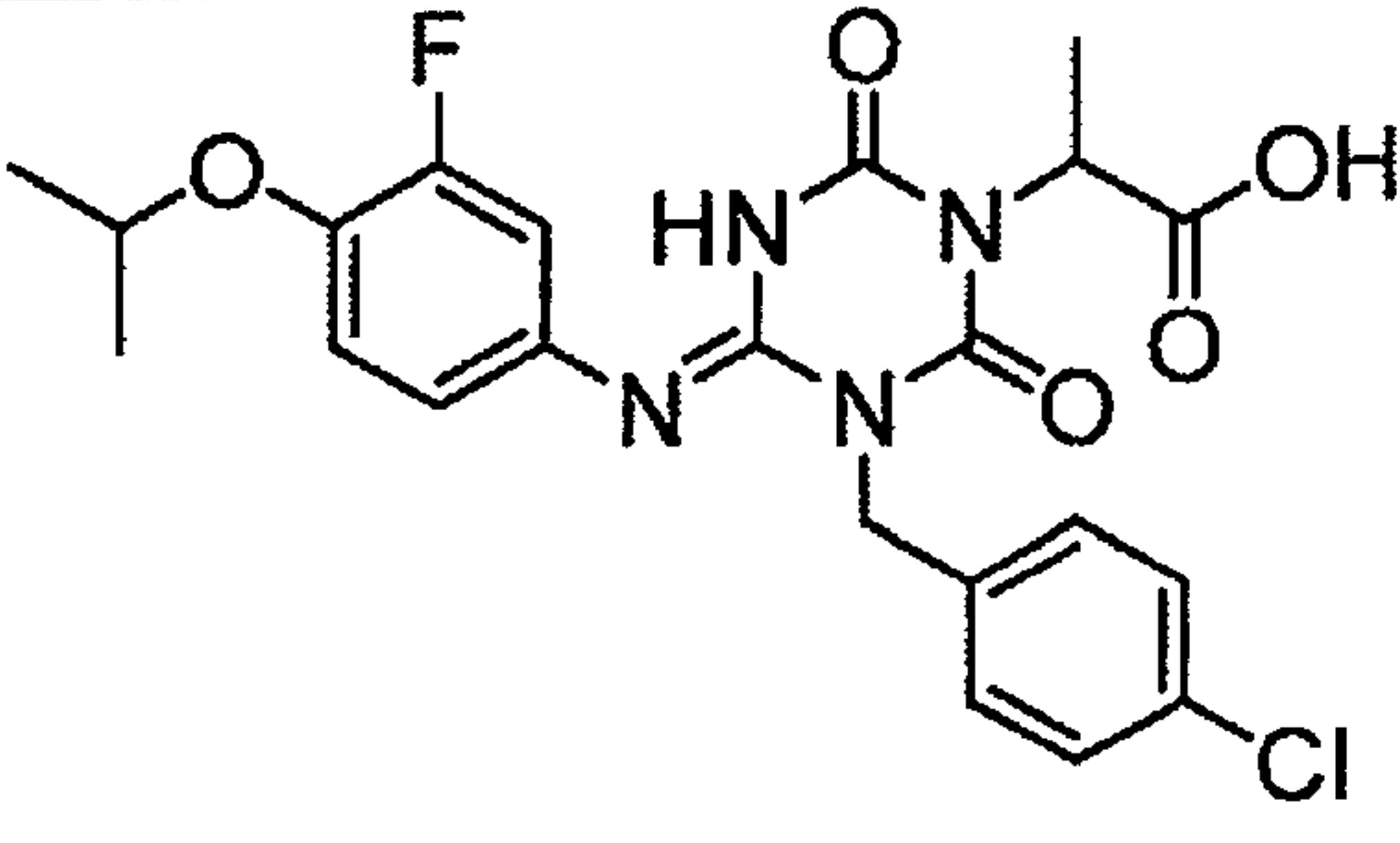
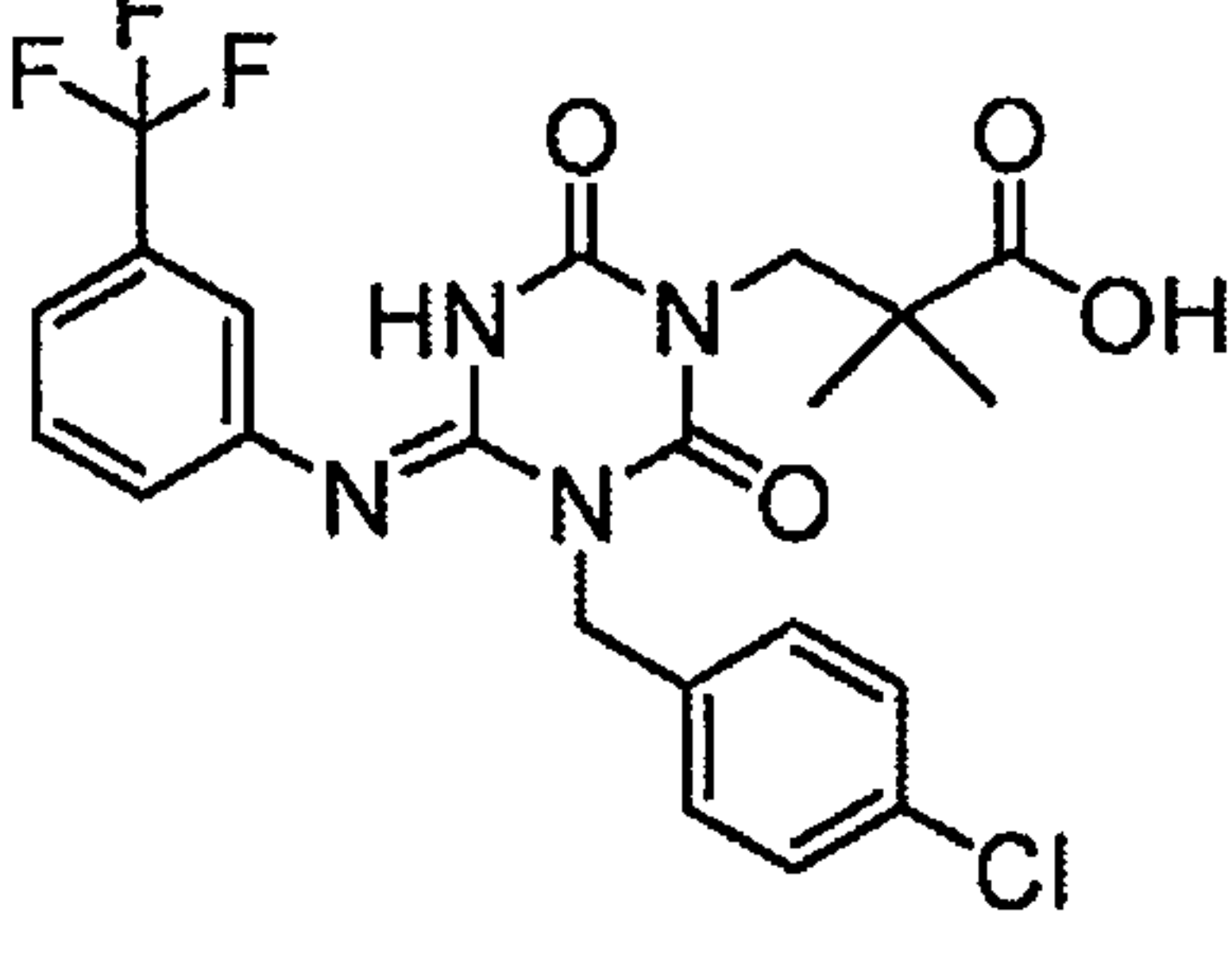
[Table 98]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0471	2.33	501	2
	I-0472	2.31	471	2
	I-0473	2.02	457	2
	I-0474	2.06	487	2
	I-0475	2.41	477	2

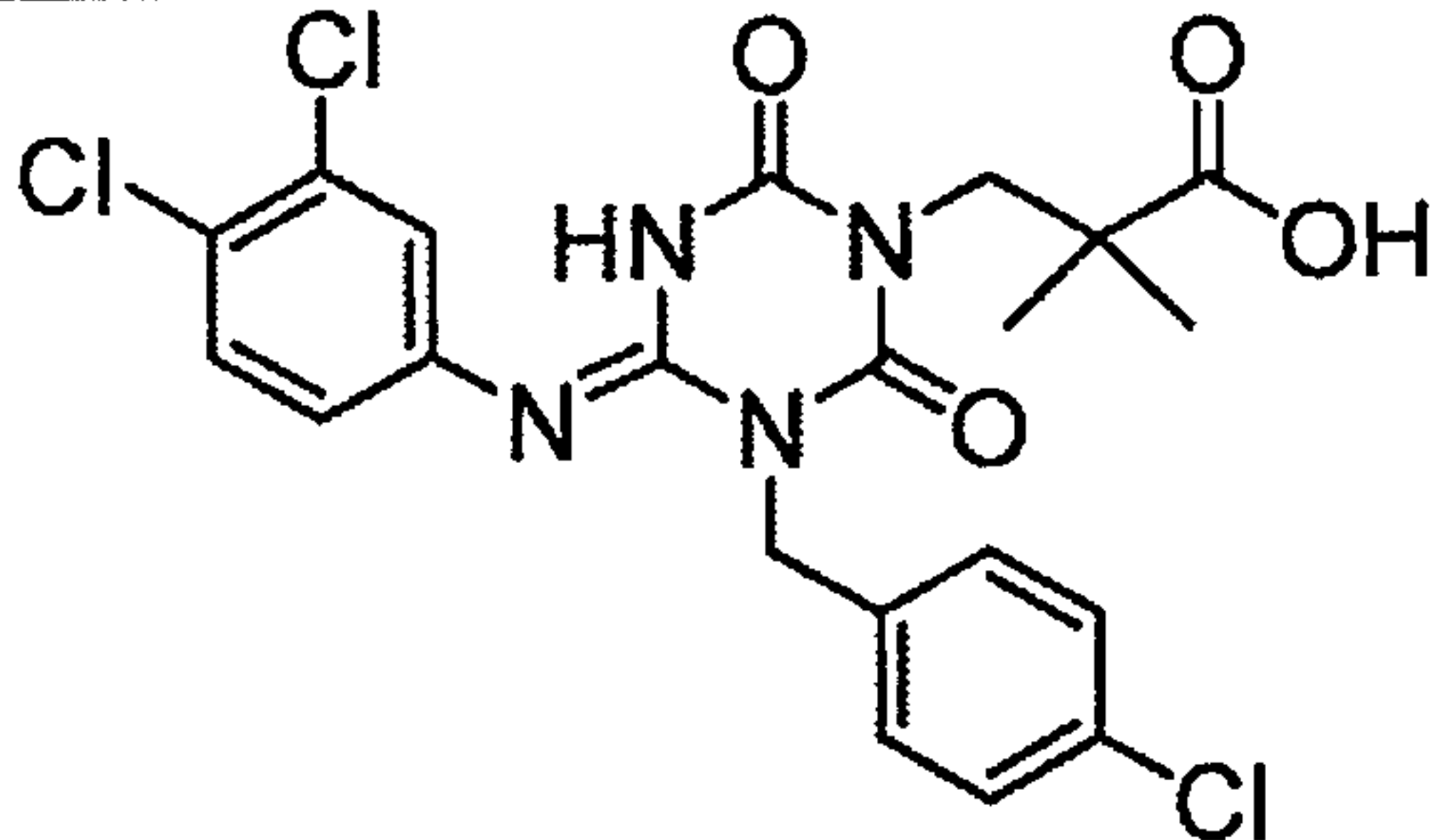
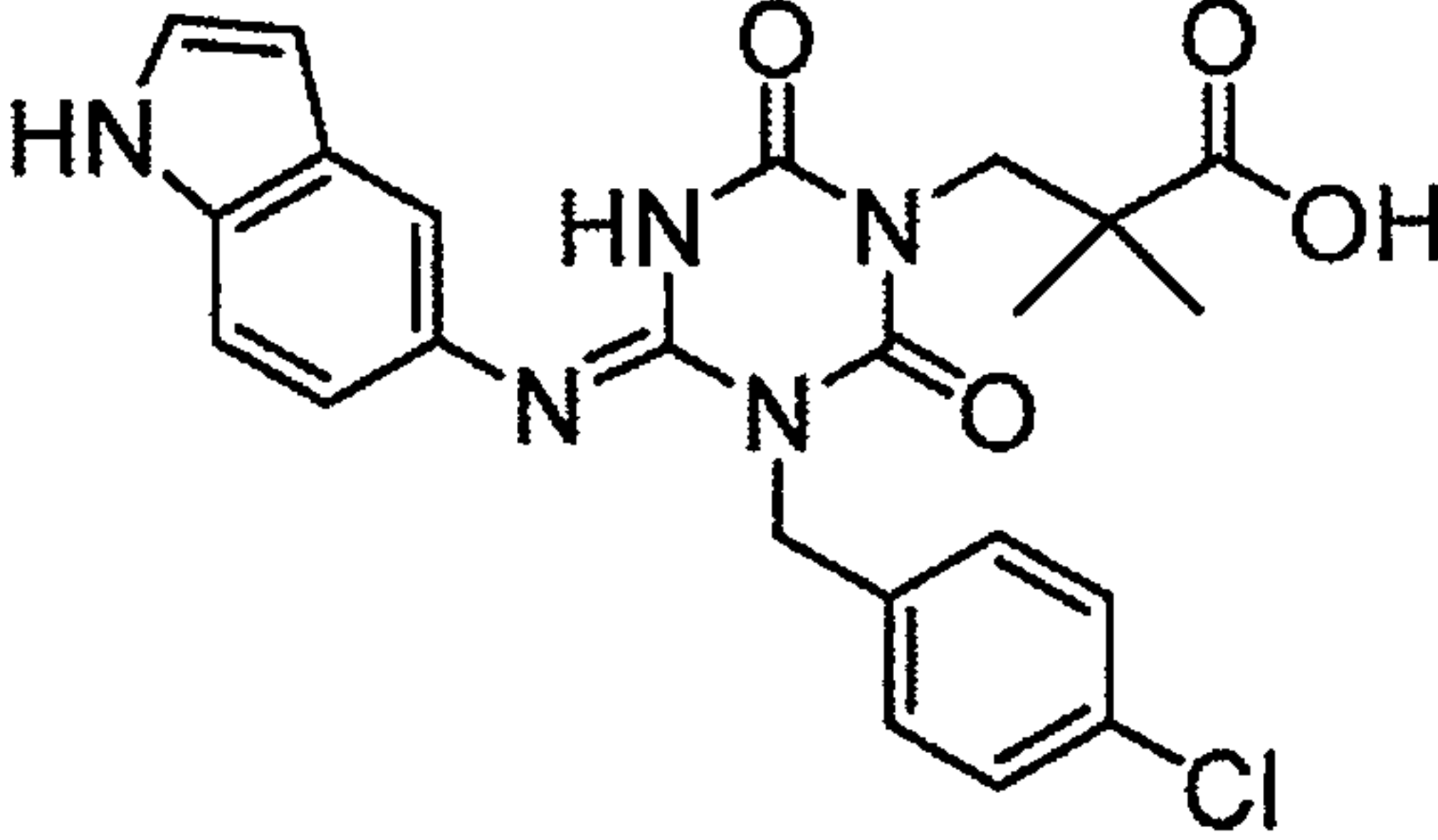
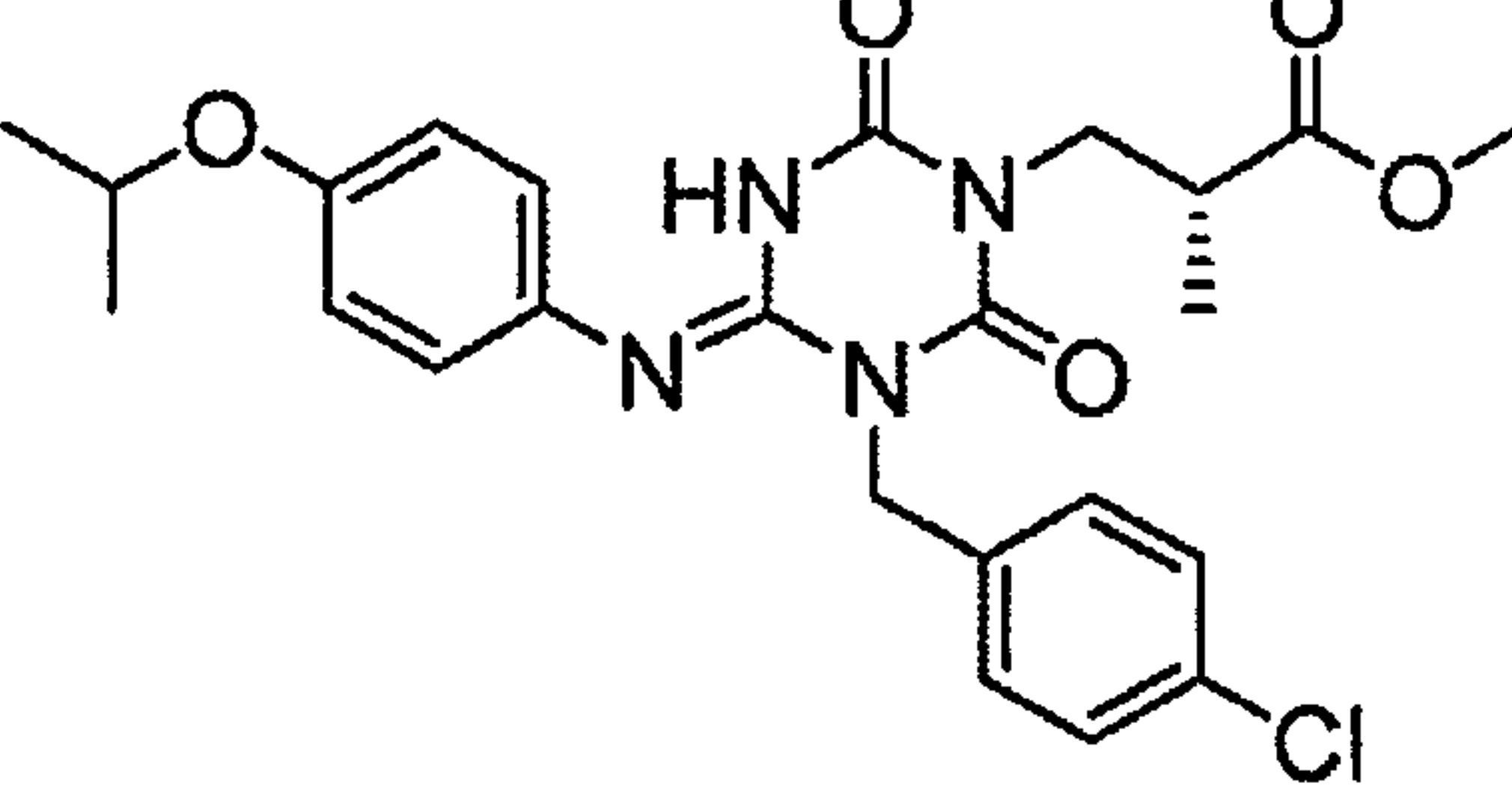
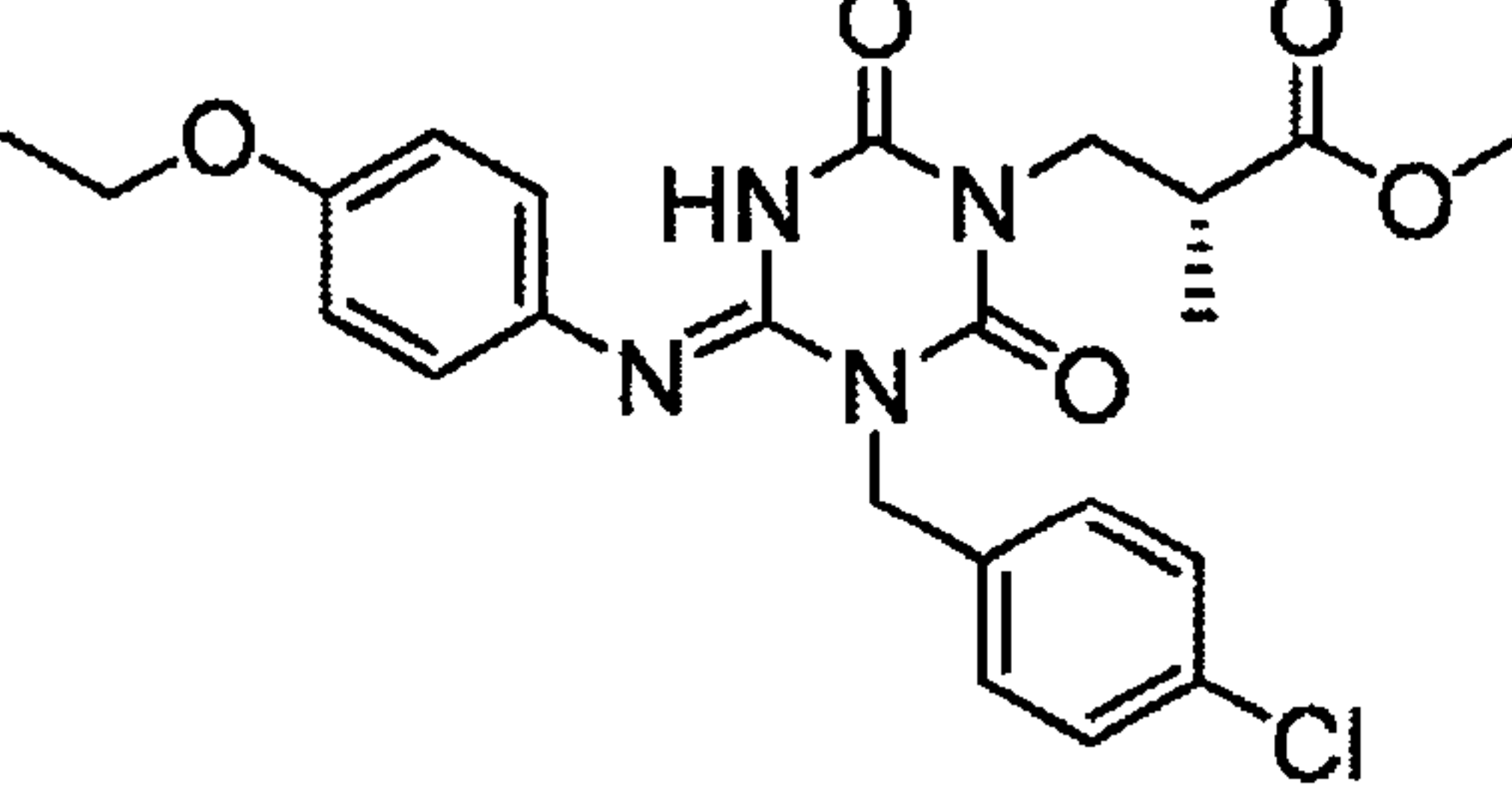
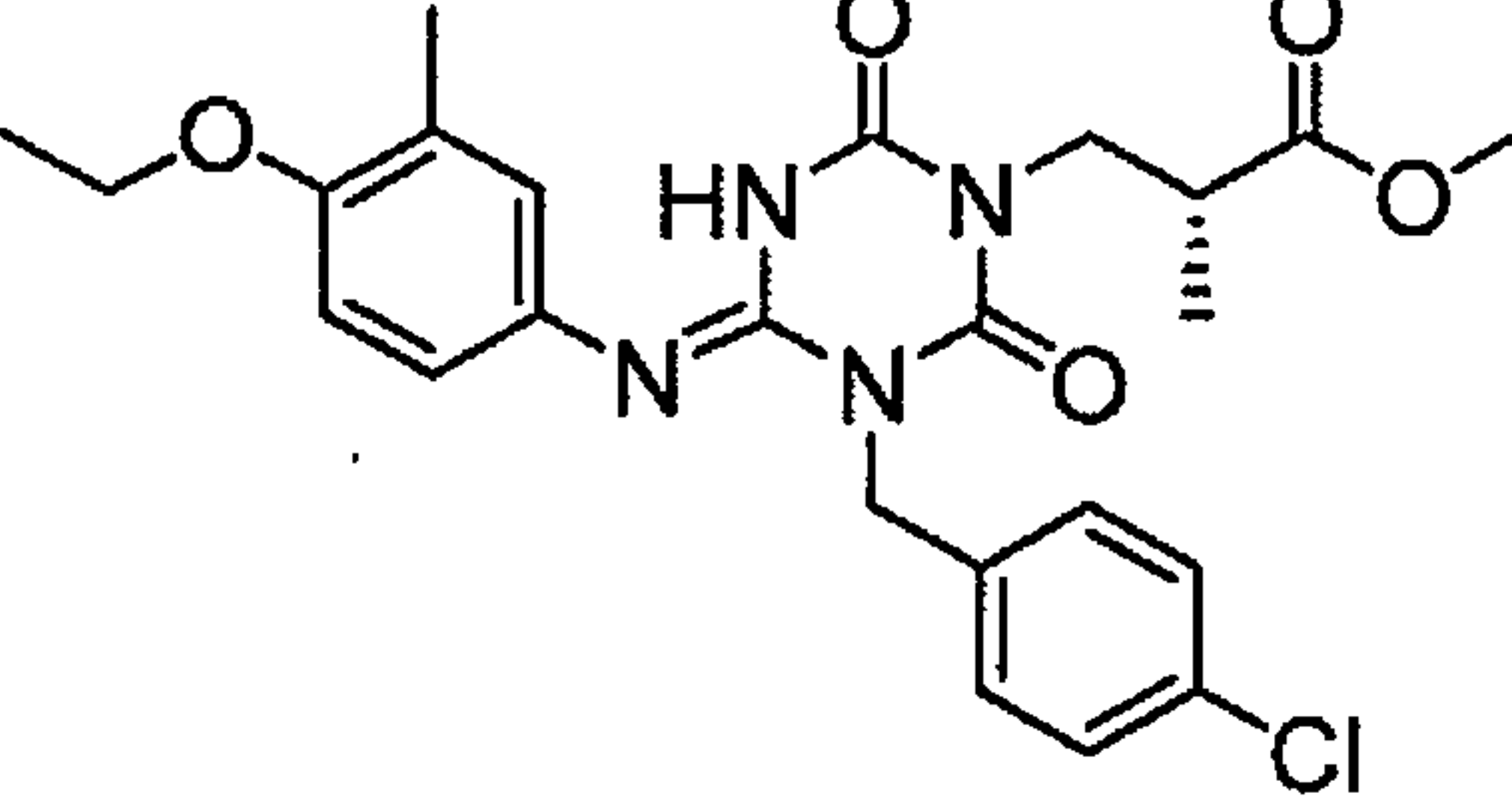
[Table 99]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0476	2.50	527	2
	I-0477	2.29	463	3
	I-0478	2.41	513	3
	I-0479	2.15	482	3
	I-0480	2.63	511	3

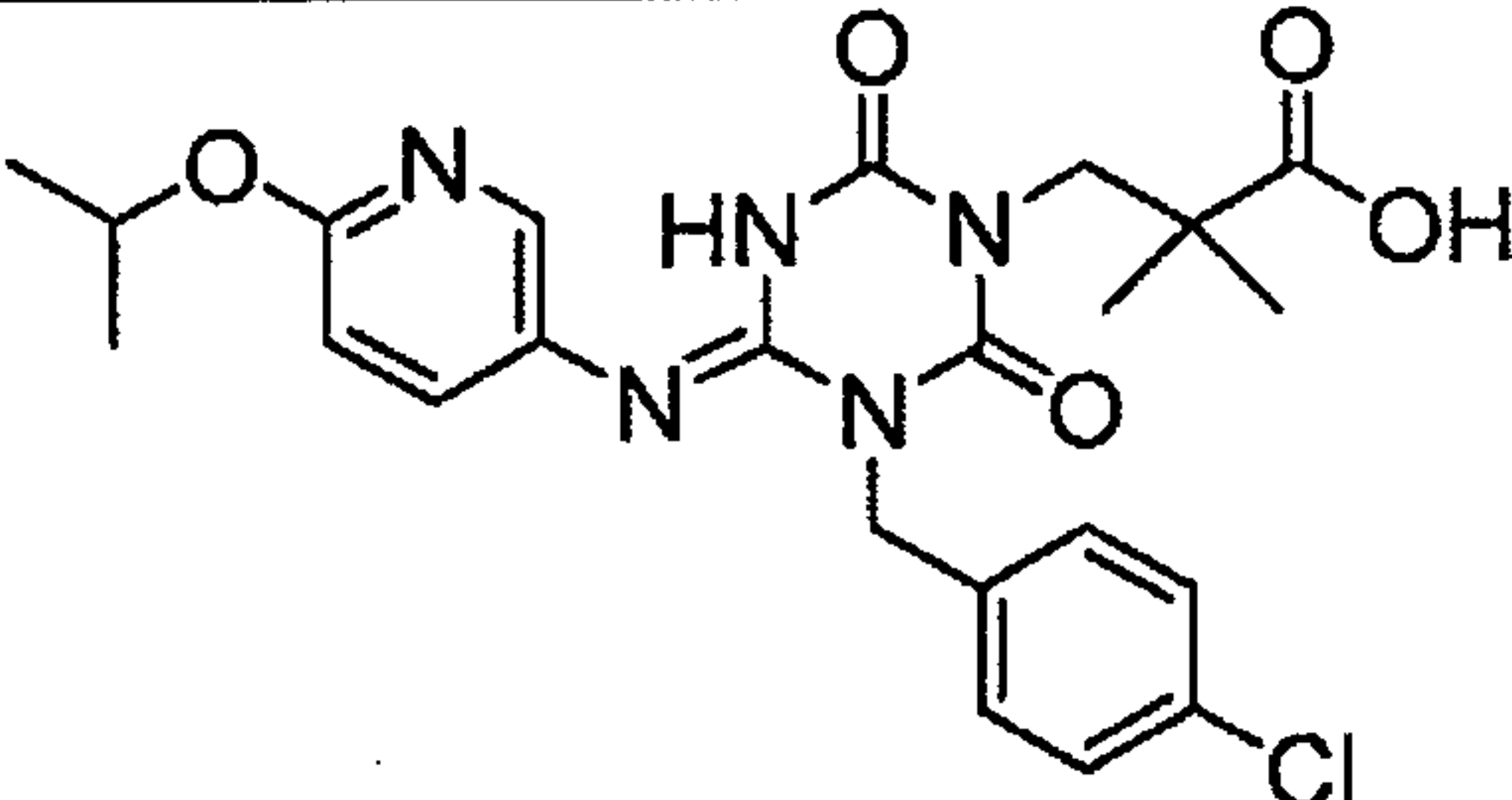
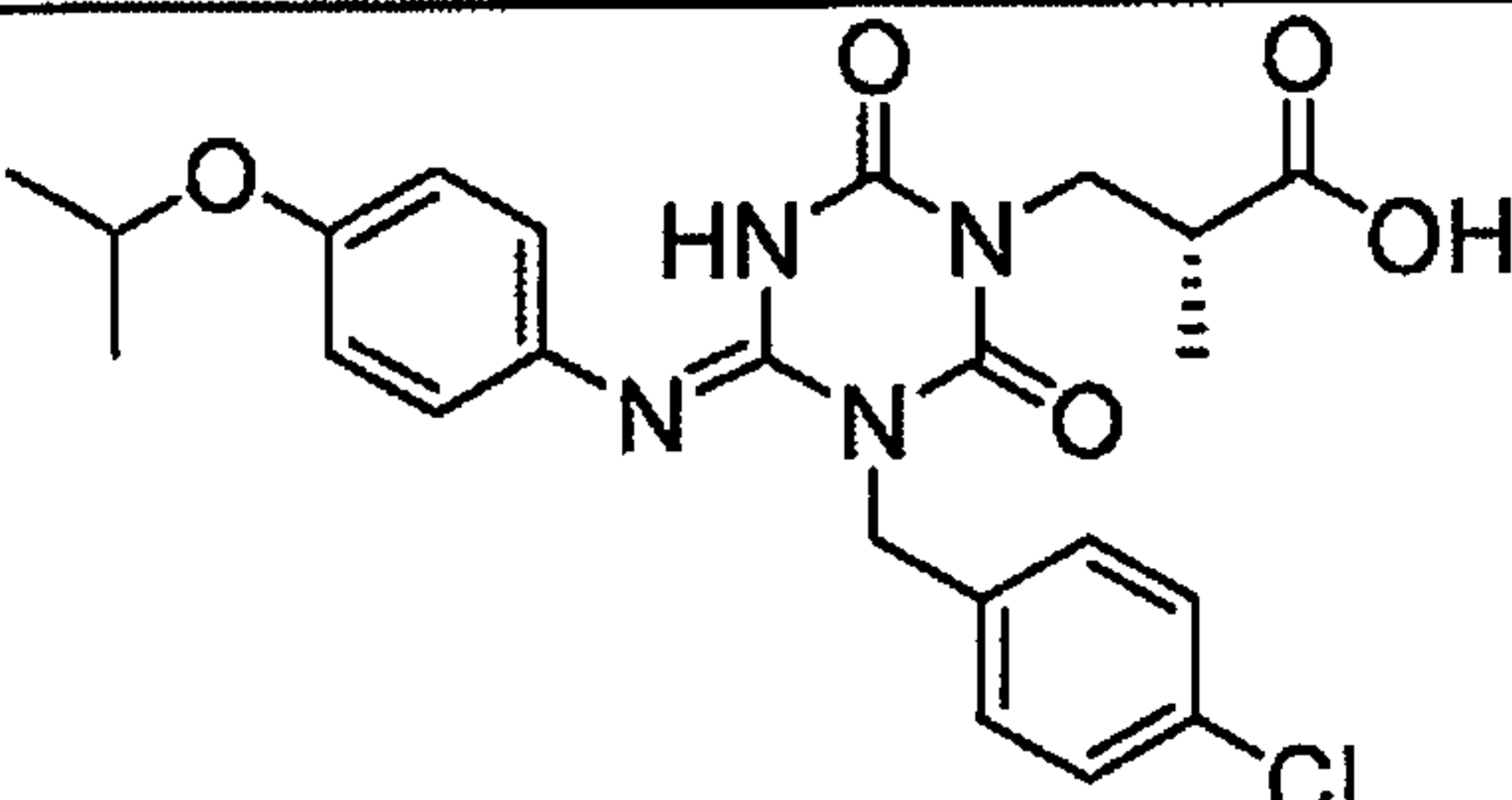
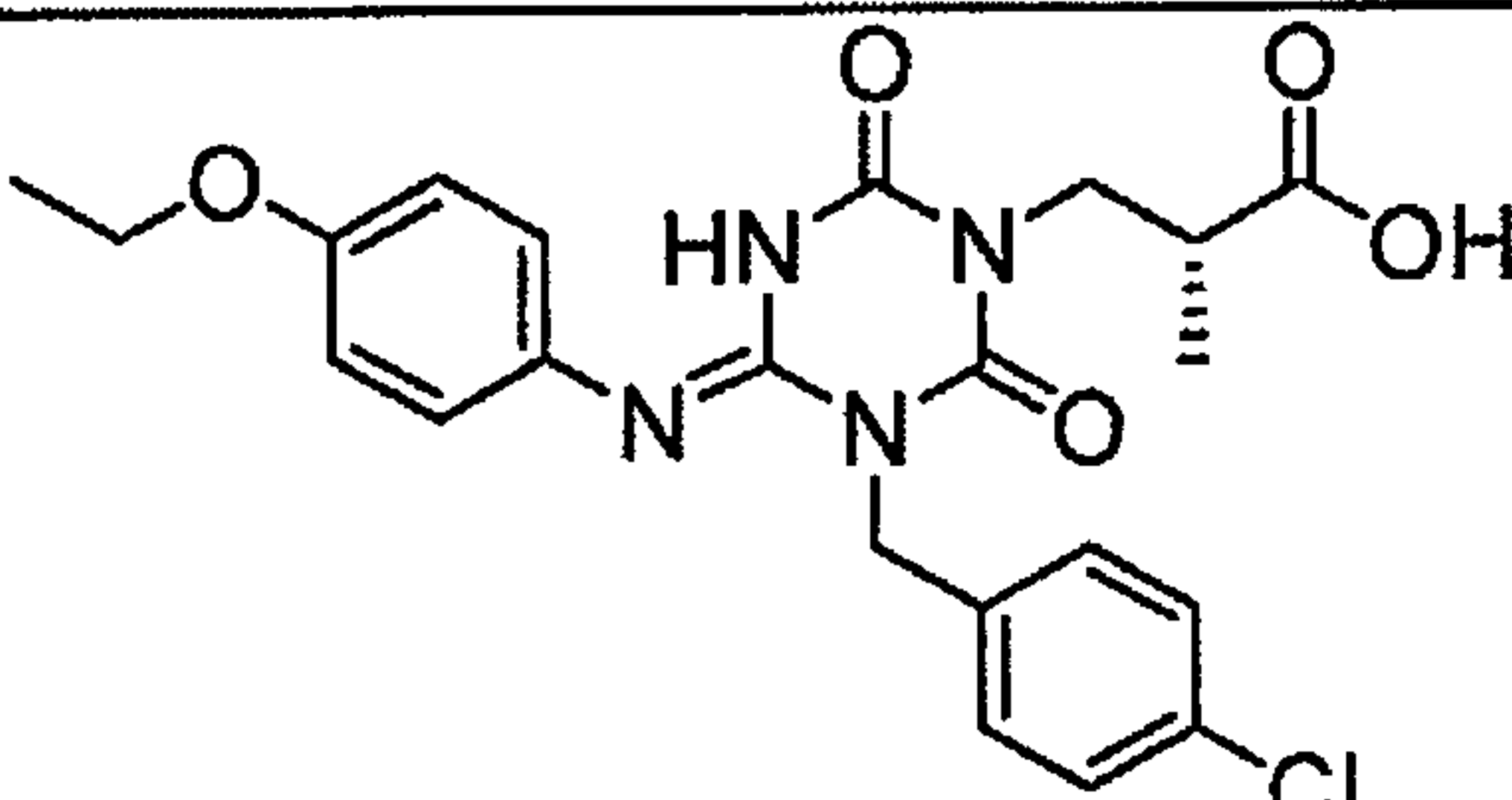
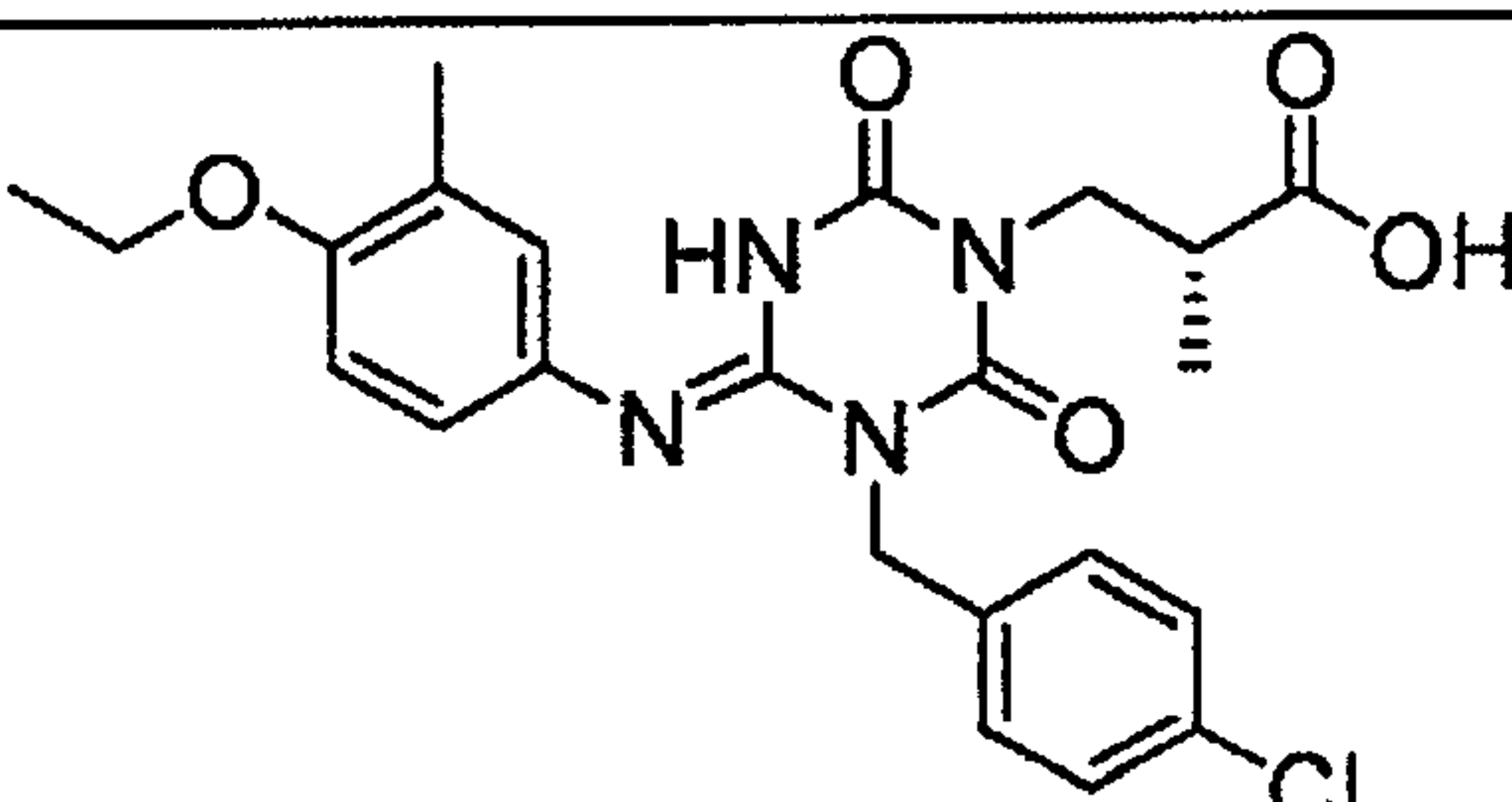
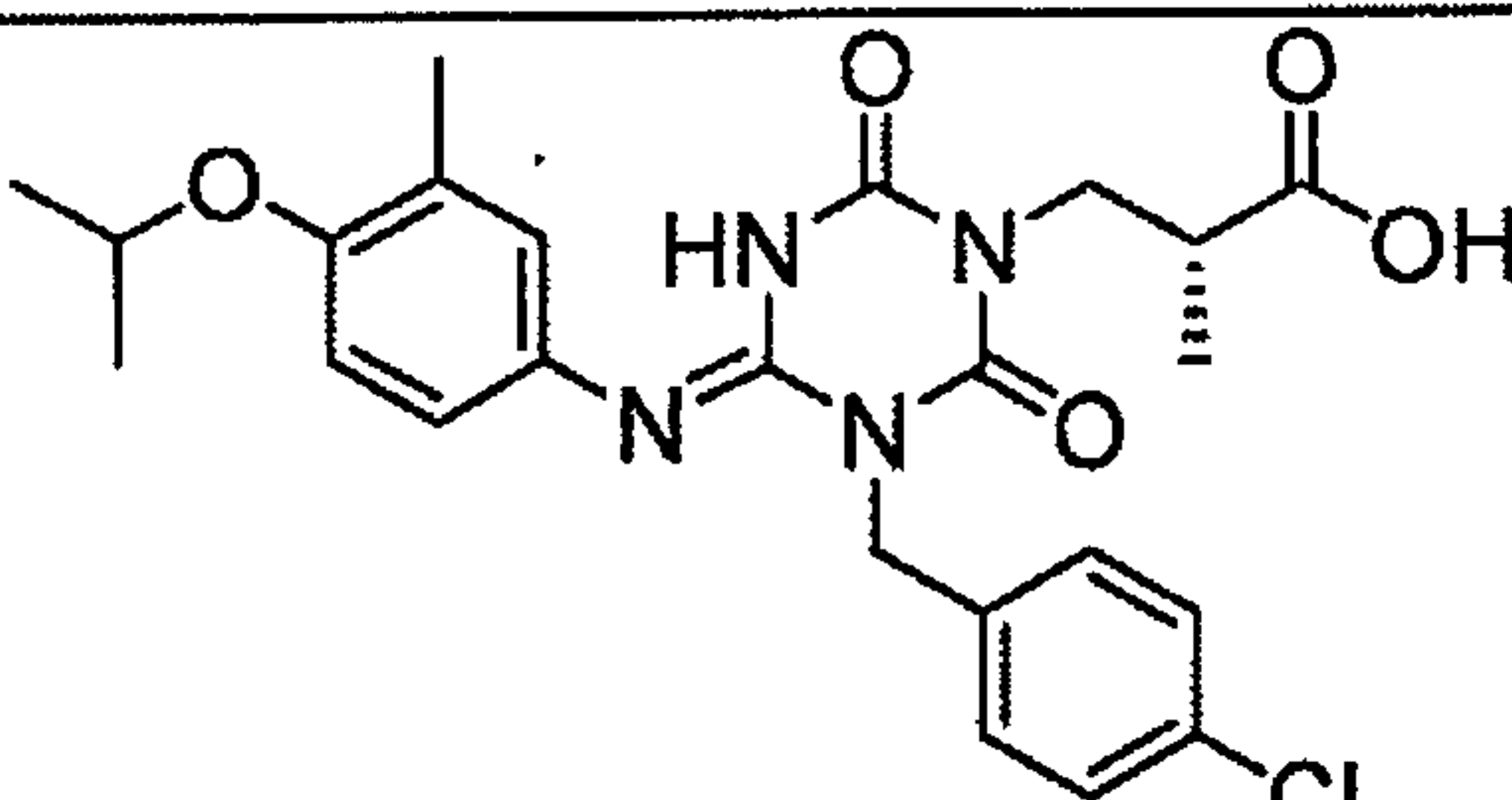
[Table 100]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0481	2.75	512	3
	I-0482	1.78	502	2
	I-0483	2.42	491	3
	I-0484	2.18	477	3
	I-0485	2.20	497	2

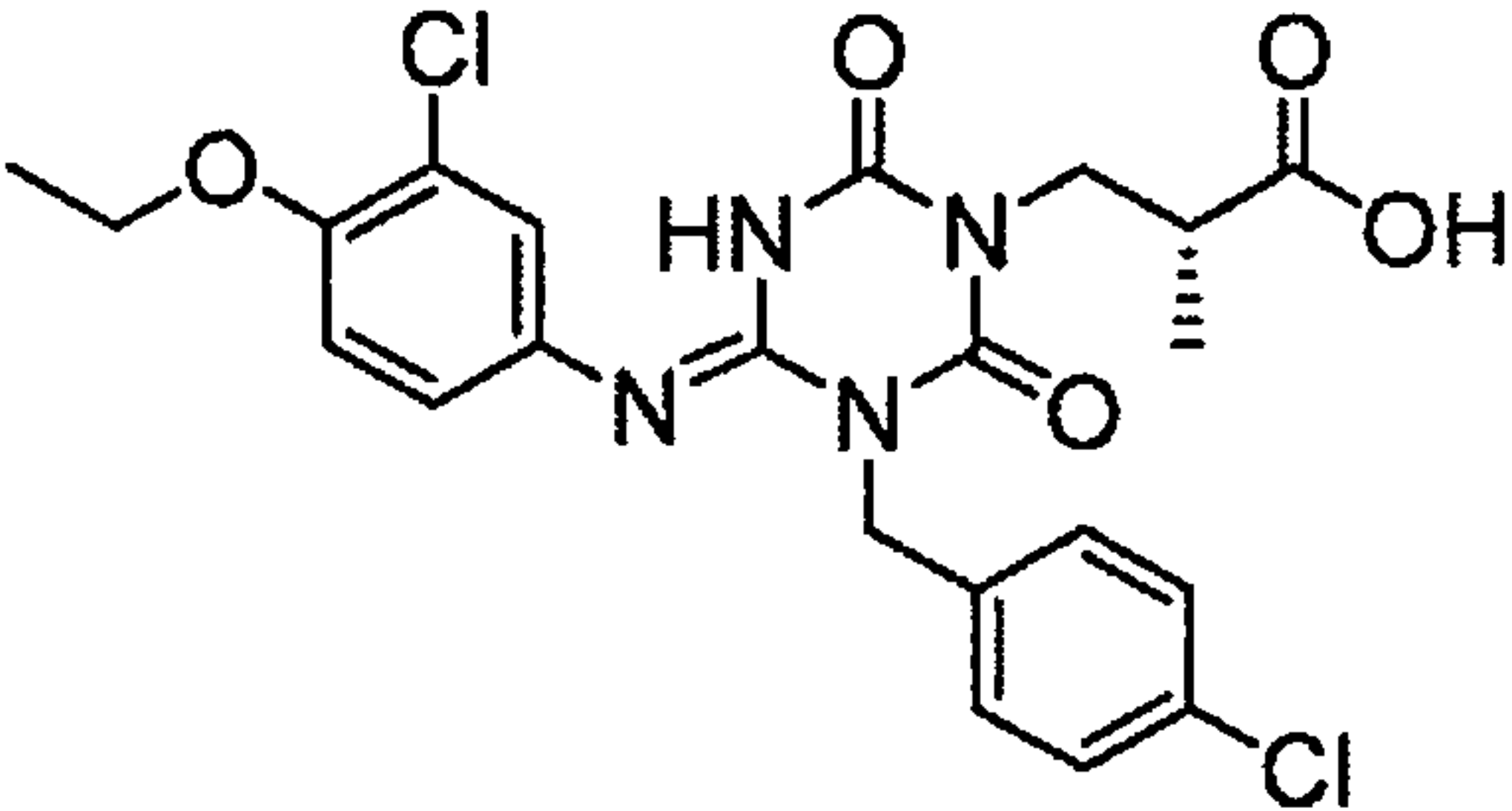
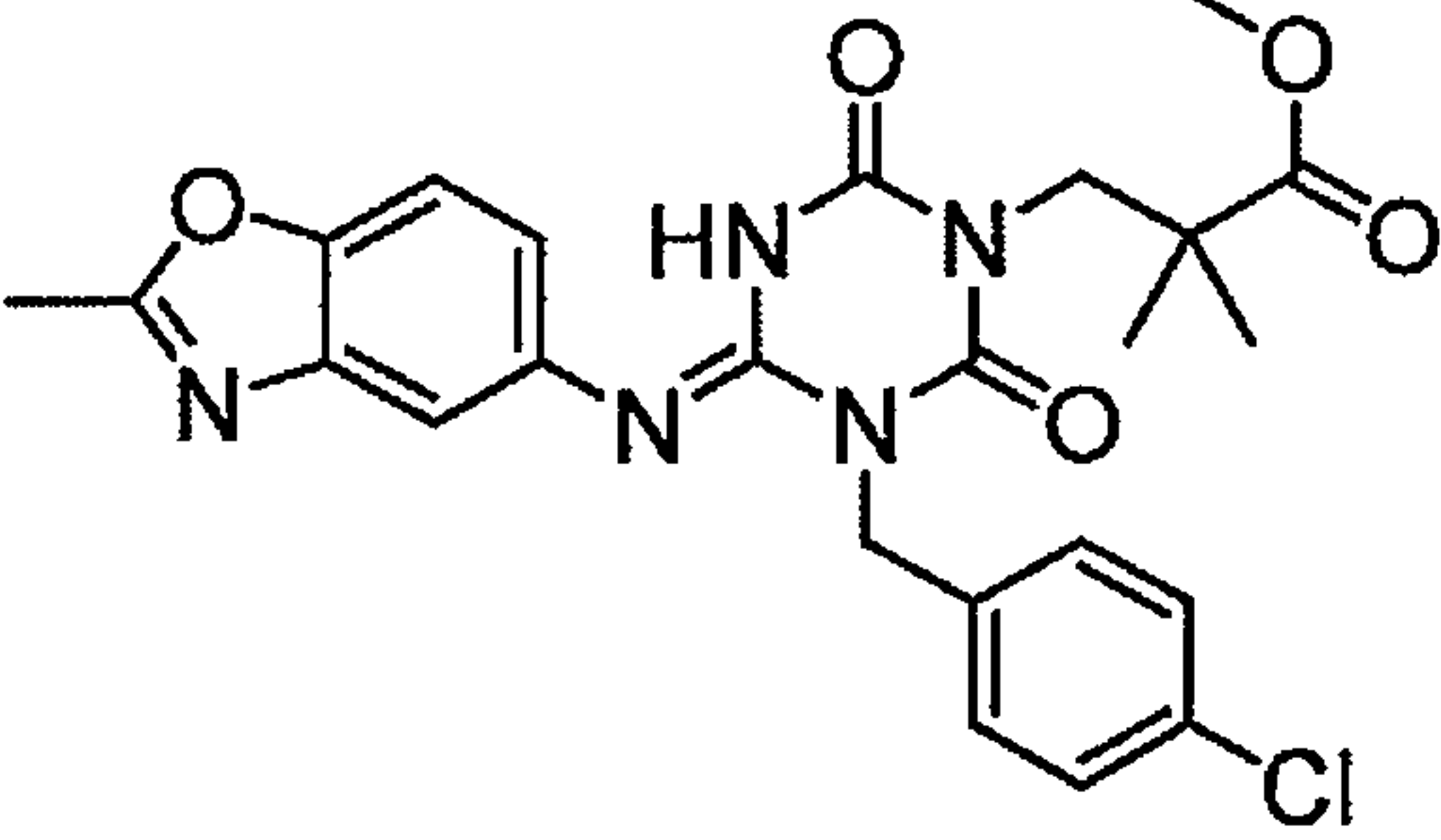
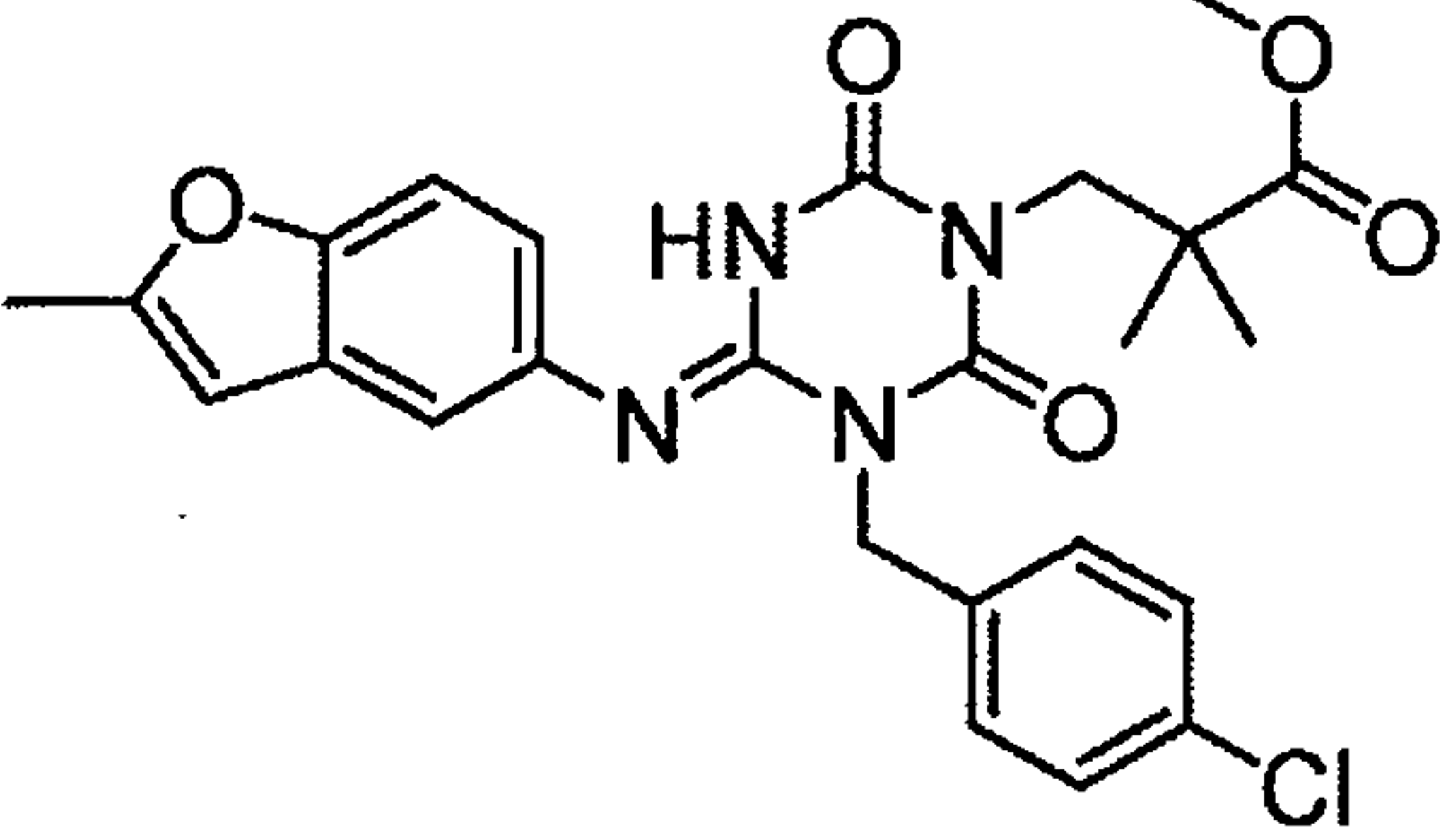
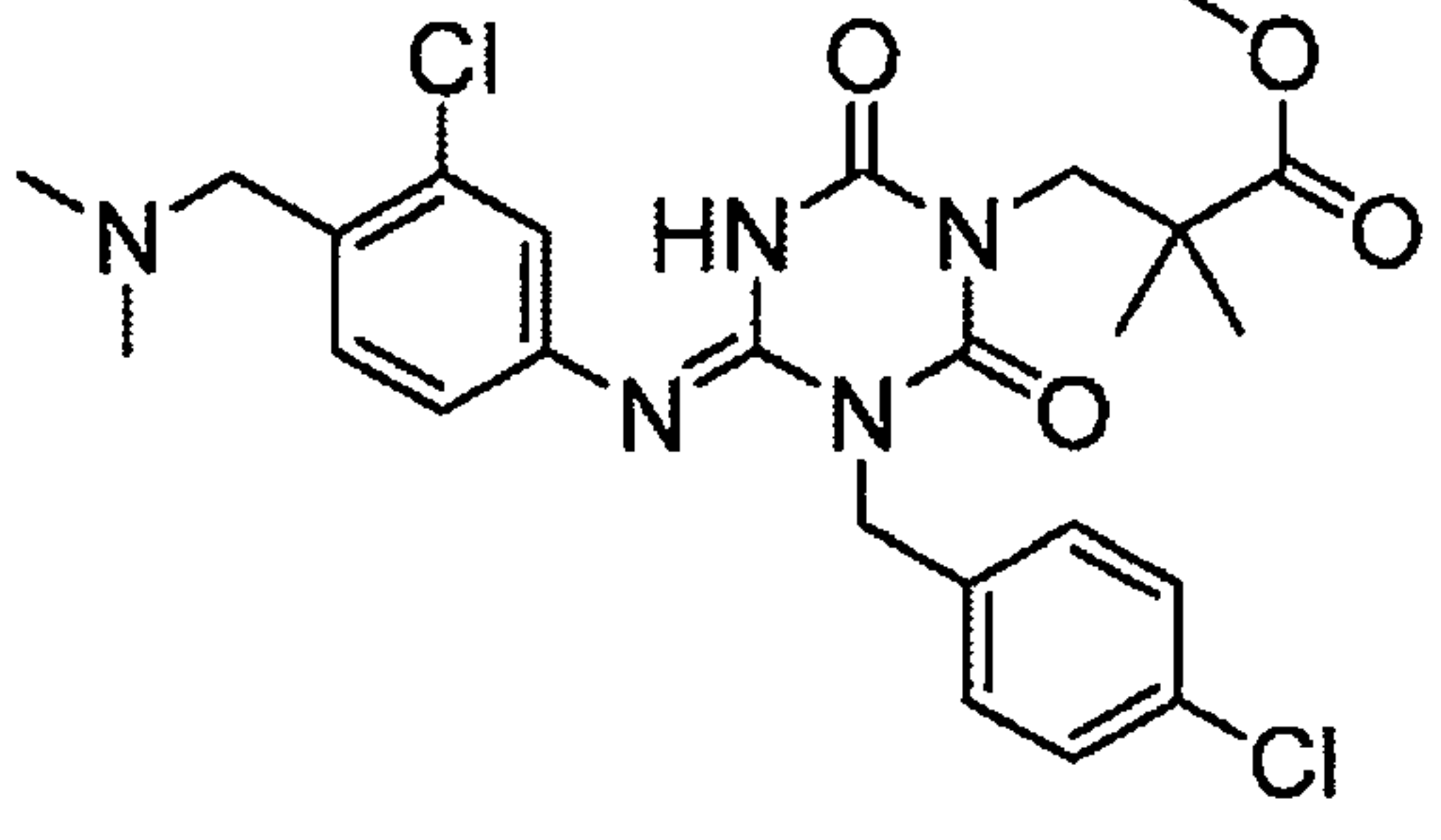
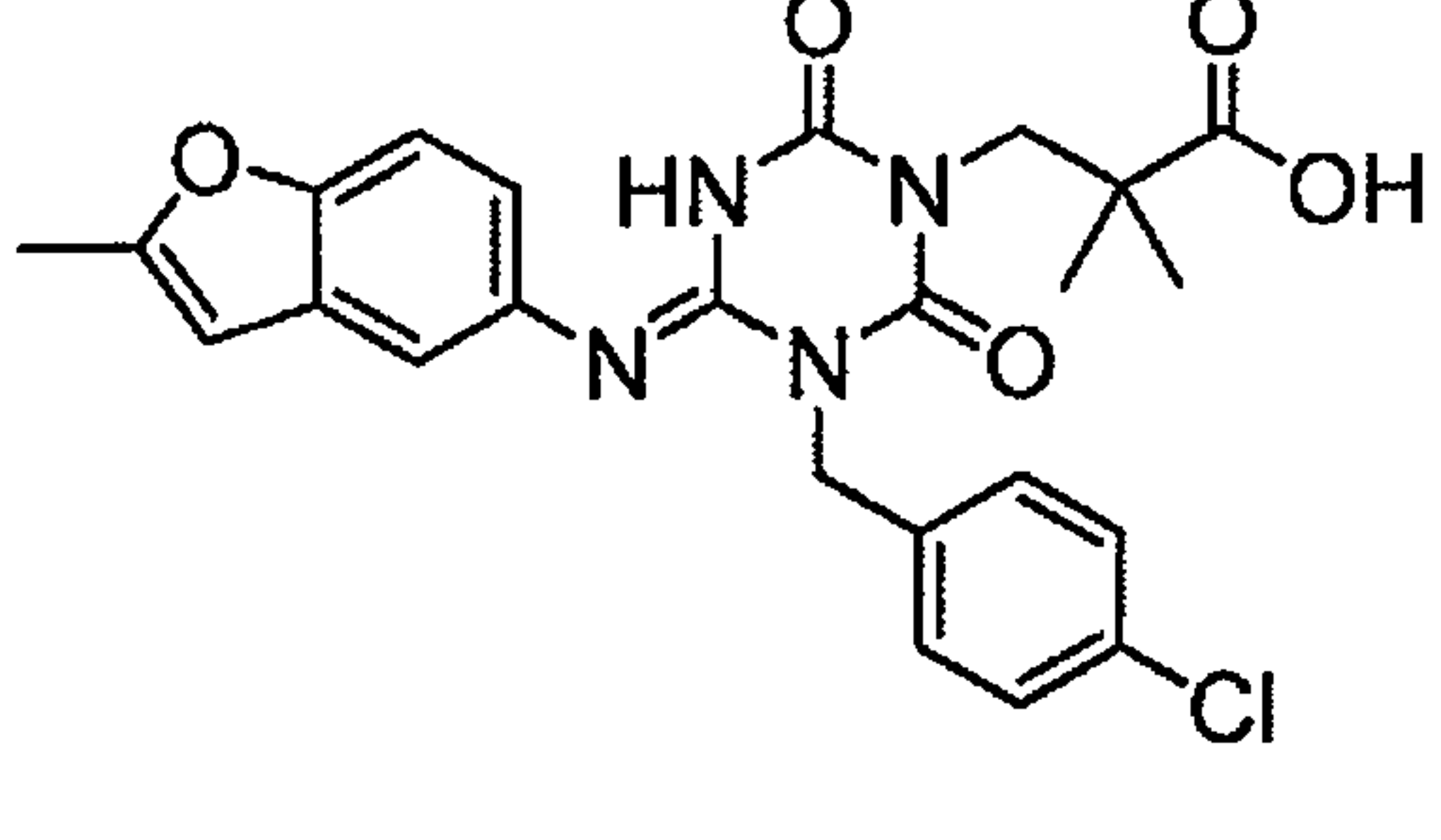
[Table 101]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0486	2.31	499	2
	I-0487	1.71	468	2
	I-0488	2.17	487	2
	I-0489	2.06	473	2
	I-0490	2.22	487	2

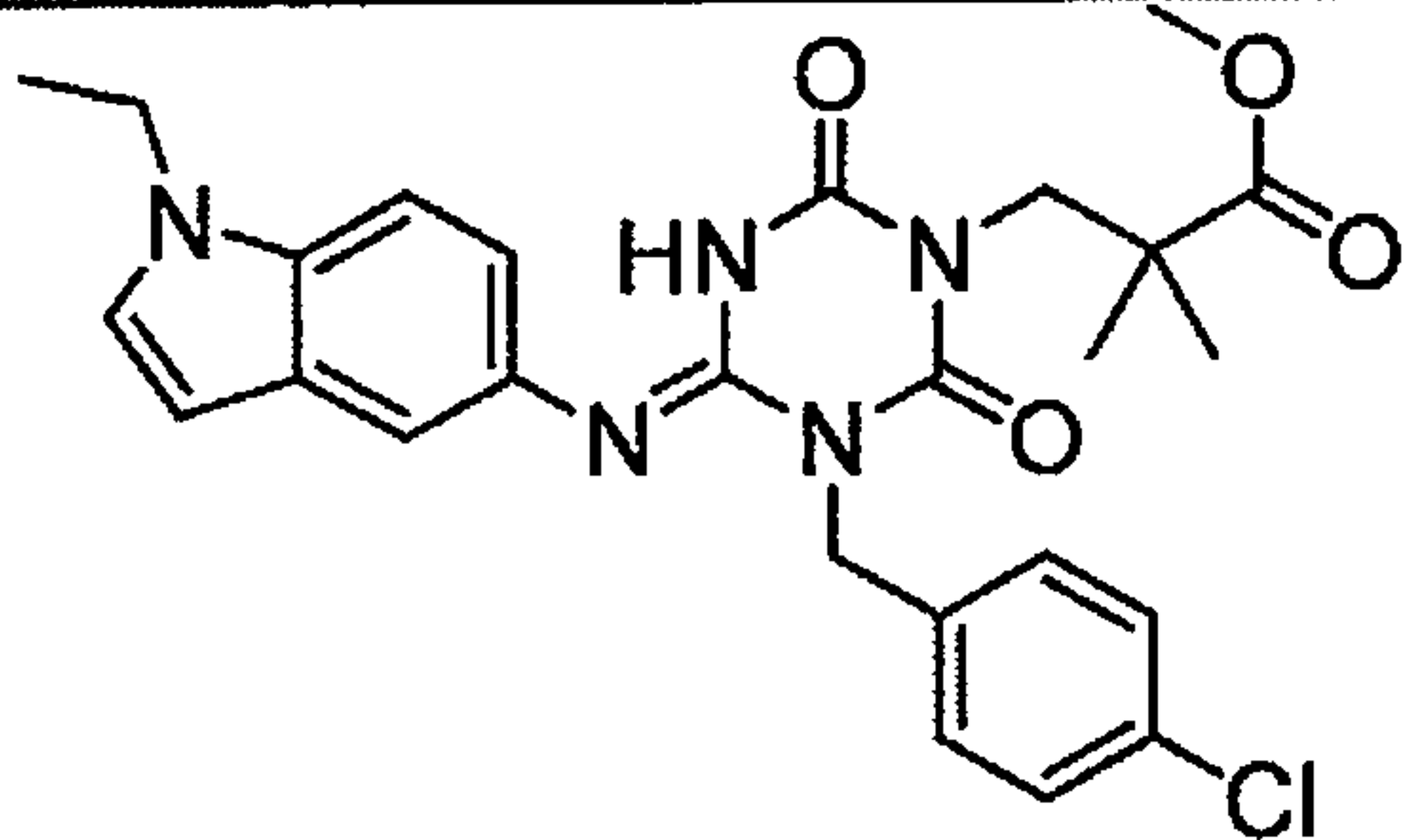
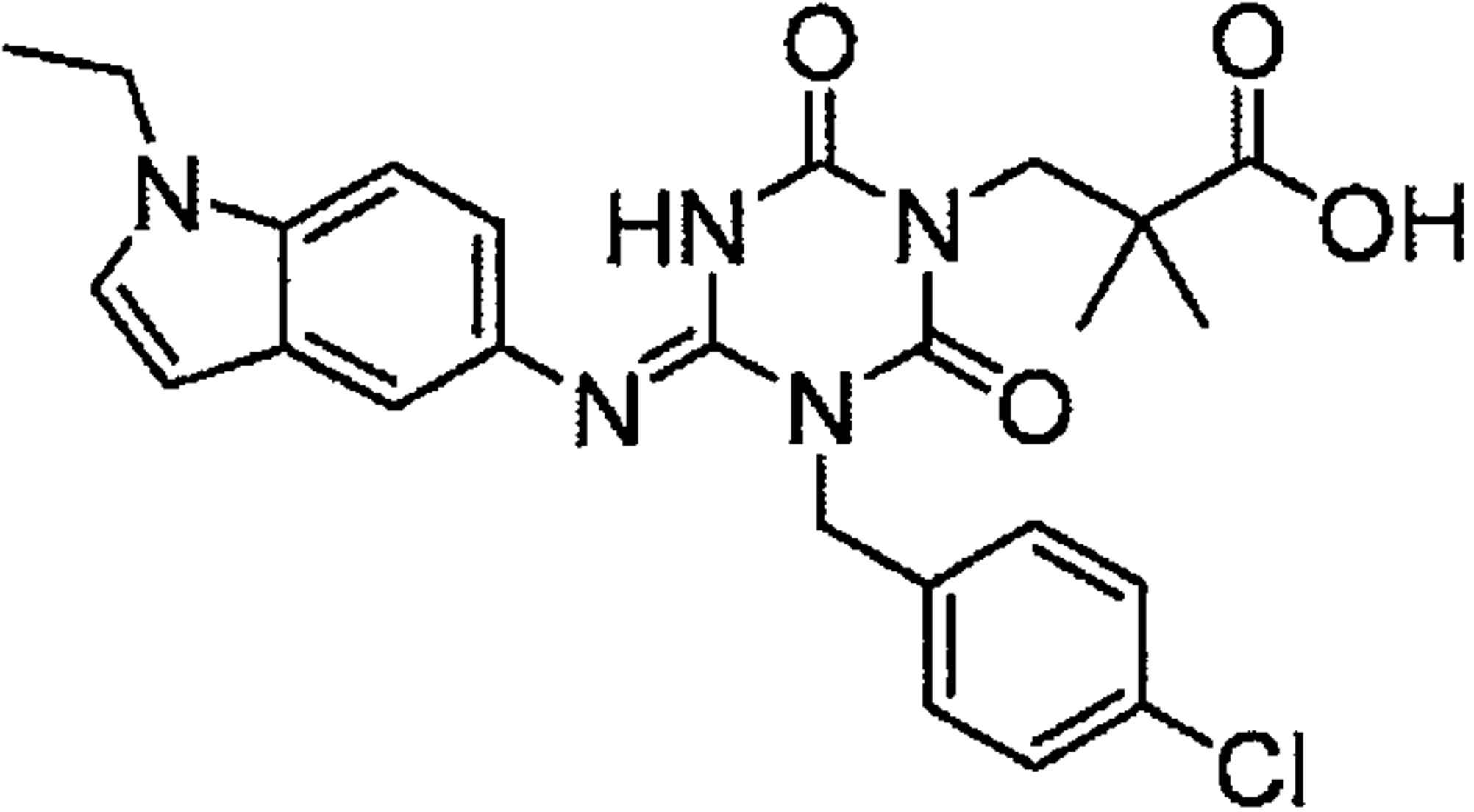
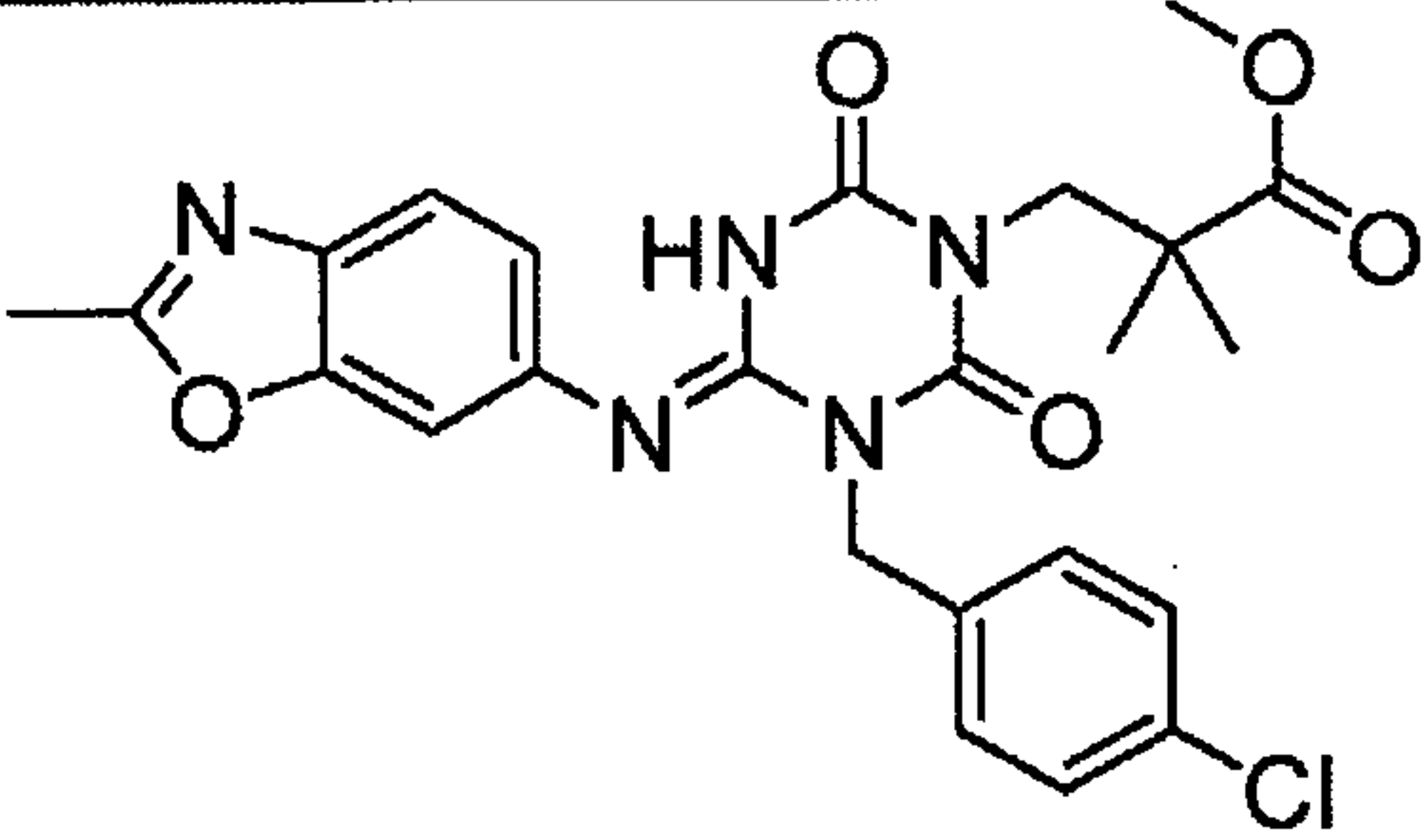
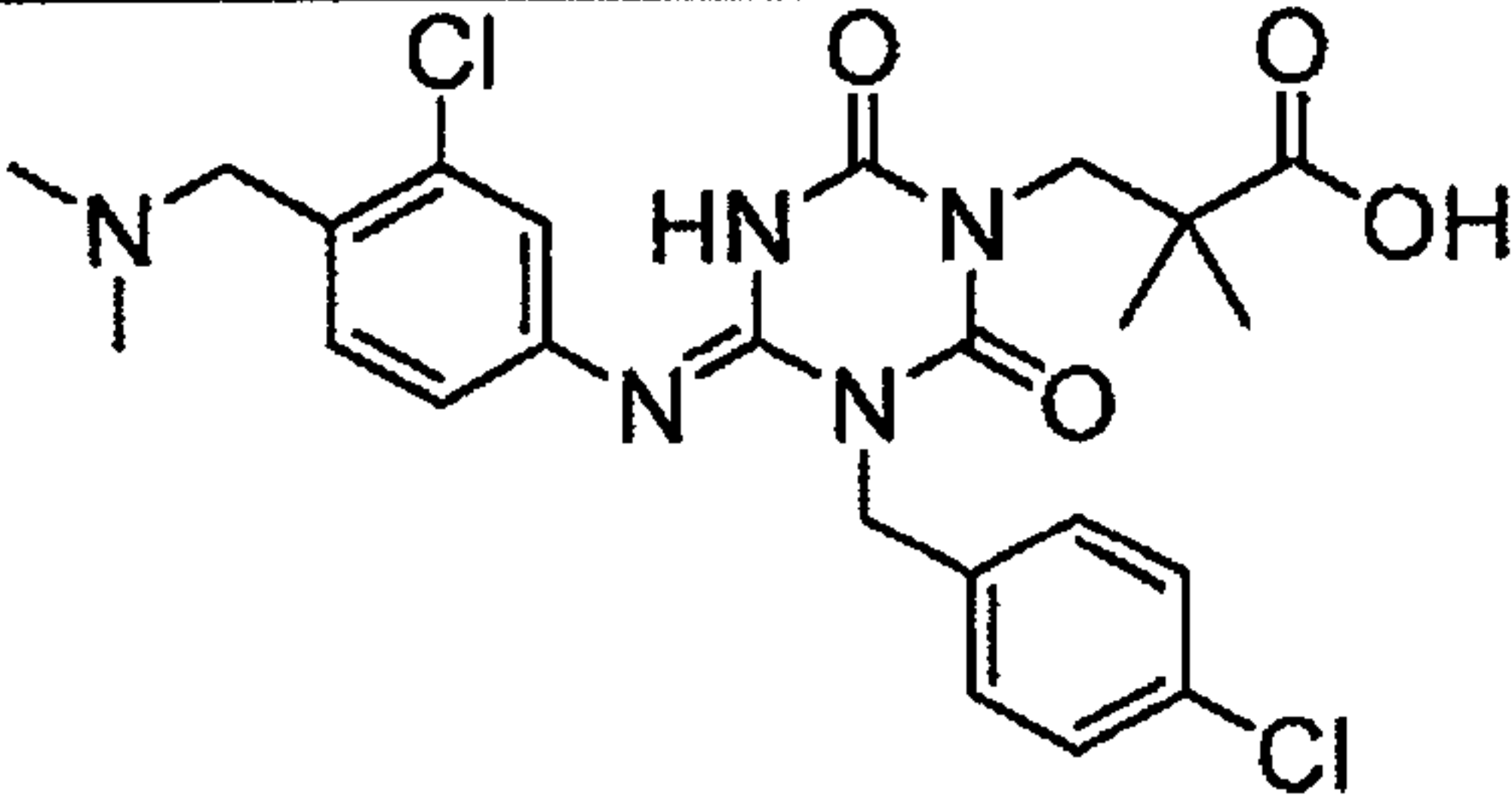
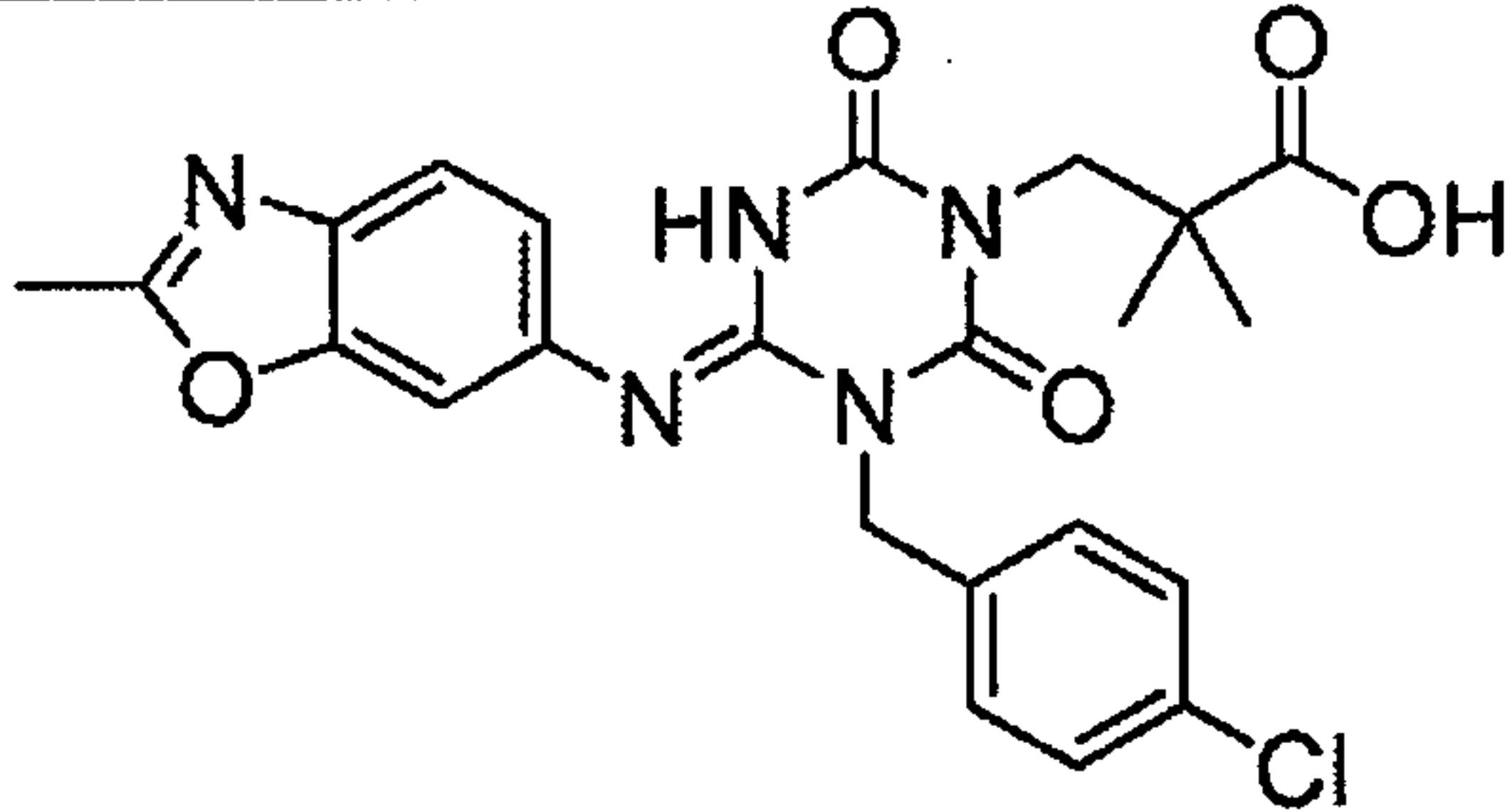
[Table 102]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0491	1.53	488	2
	I-0492	1.93	473	2
	I-0493	1.82	459	2
	I-0494	1.98	473	2
	I-0495	2.08	487	2

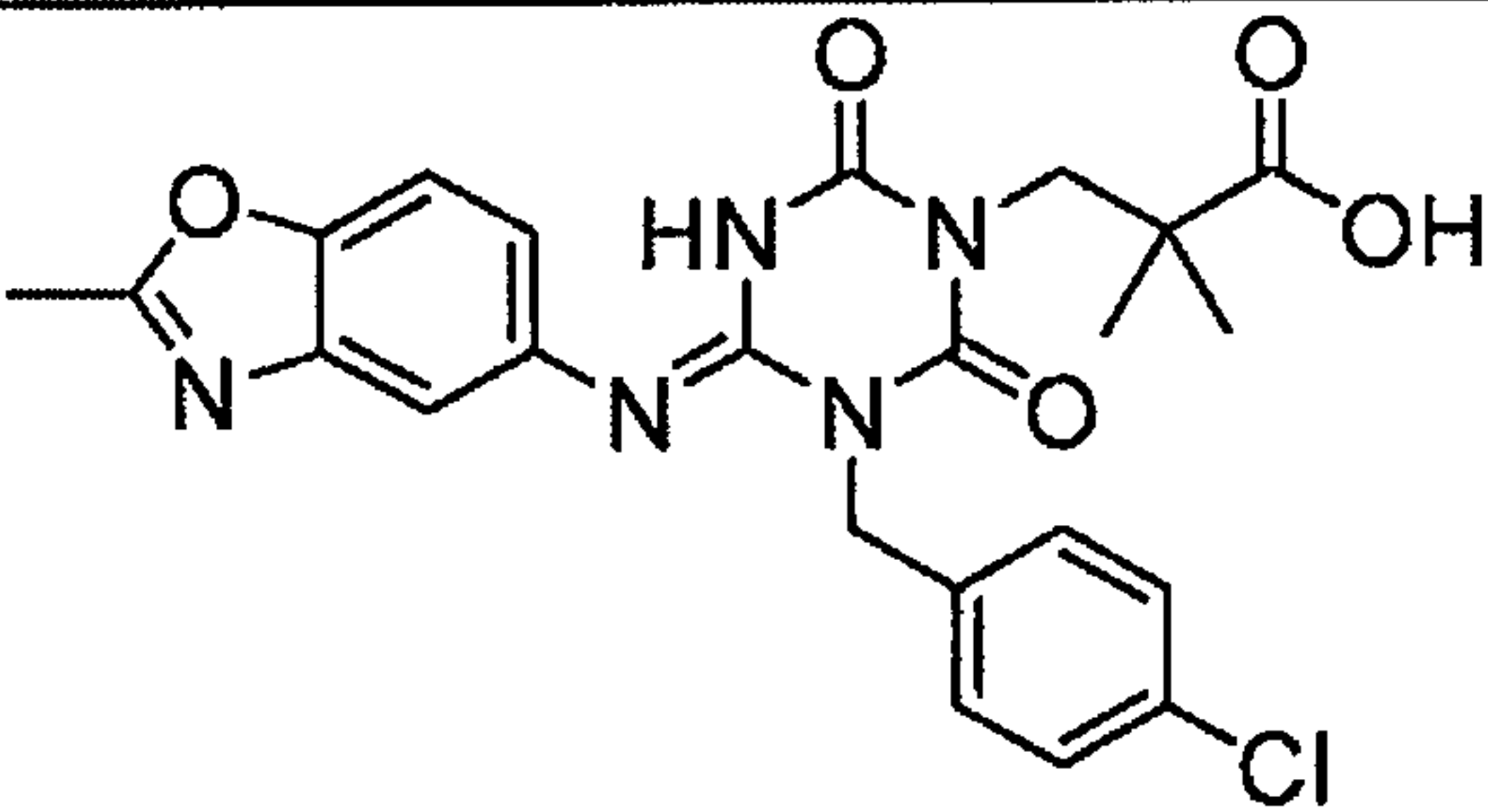
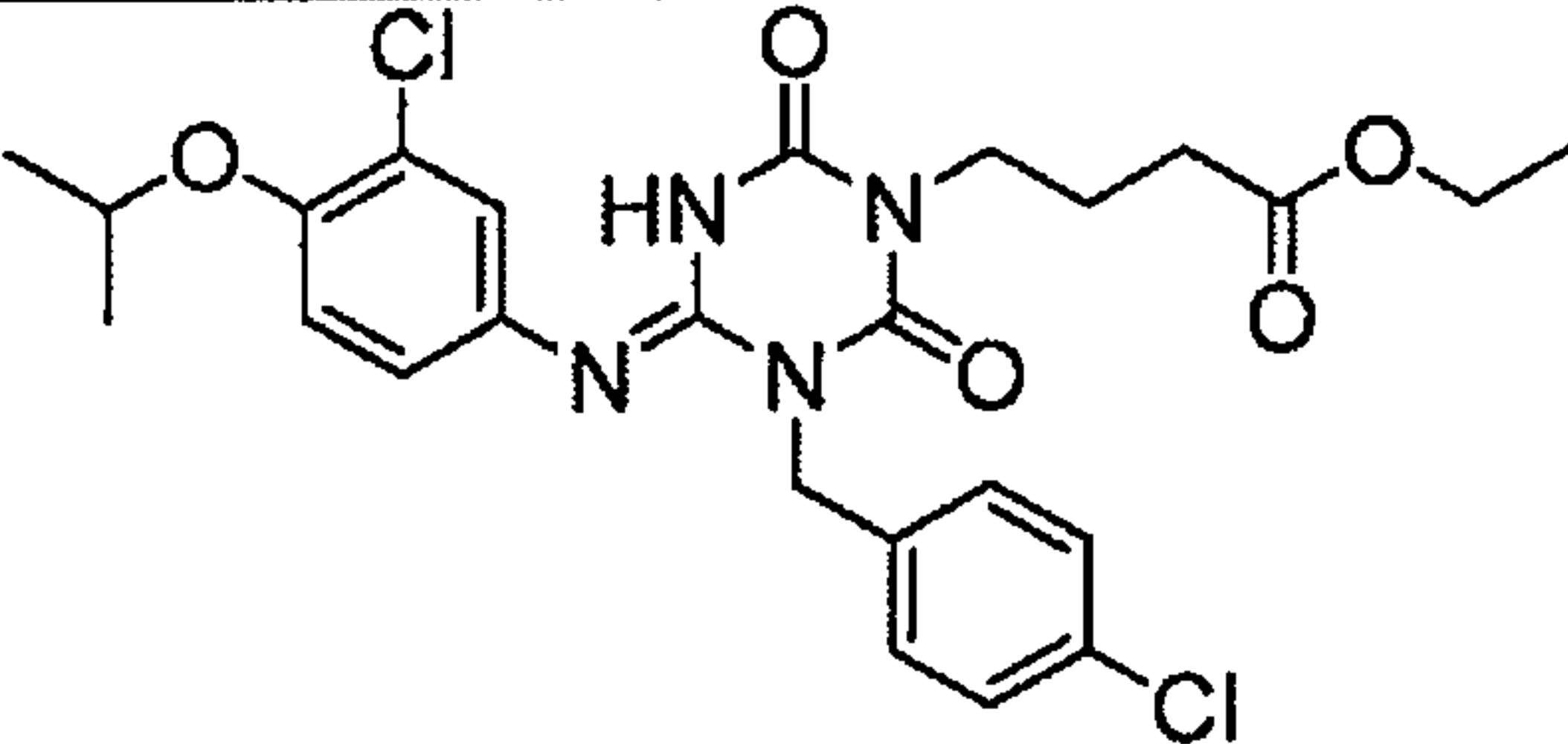
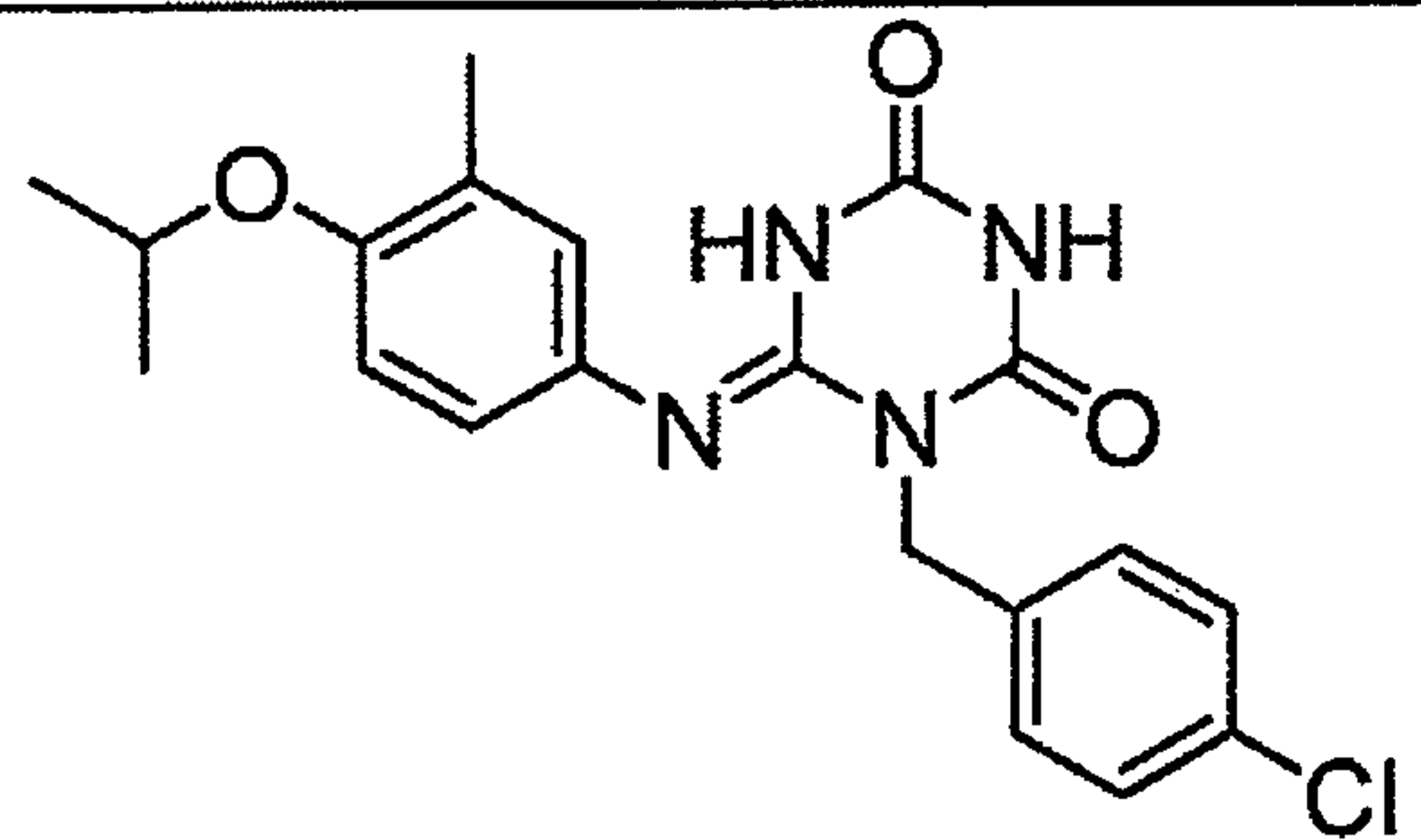
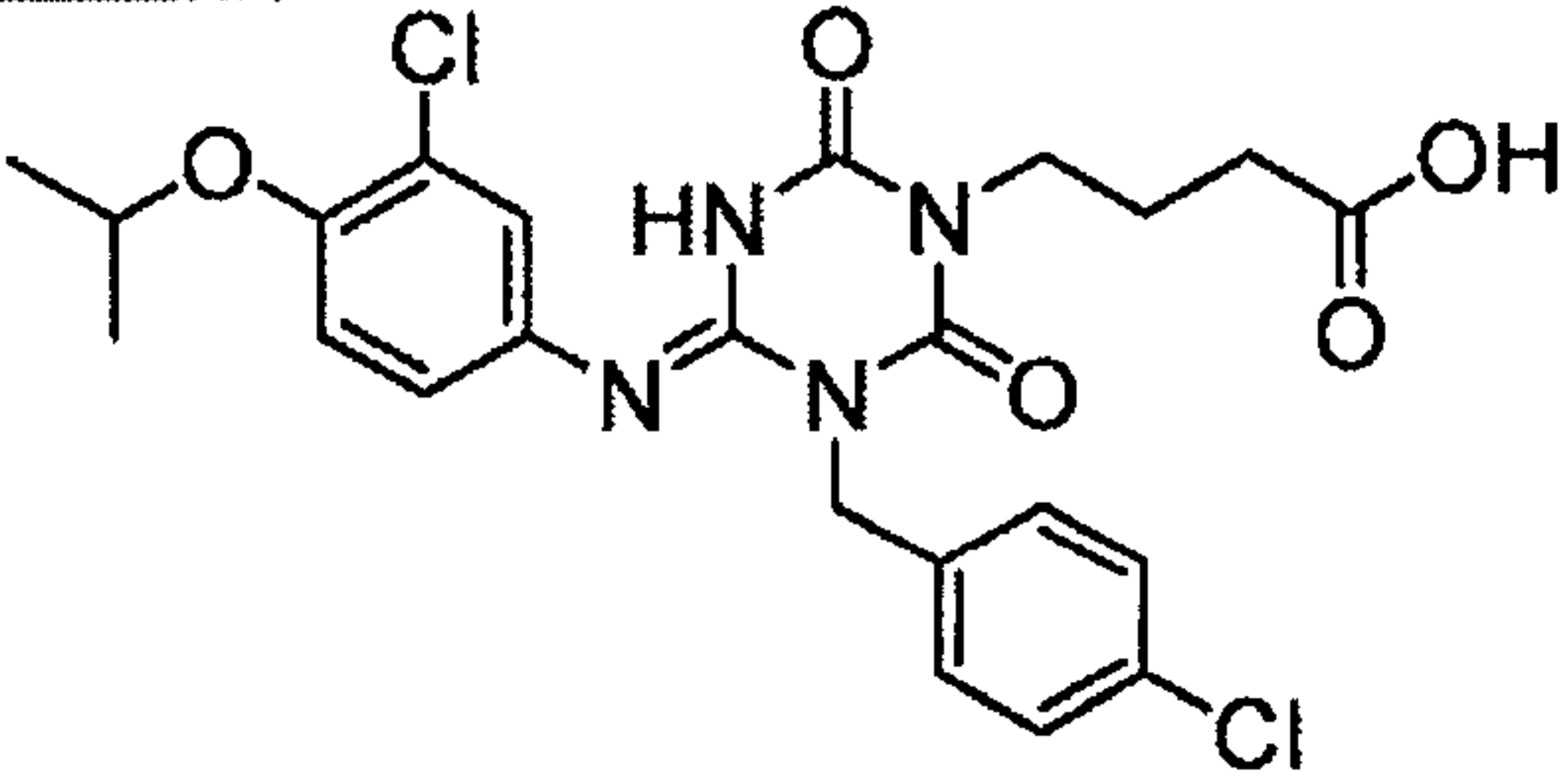
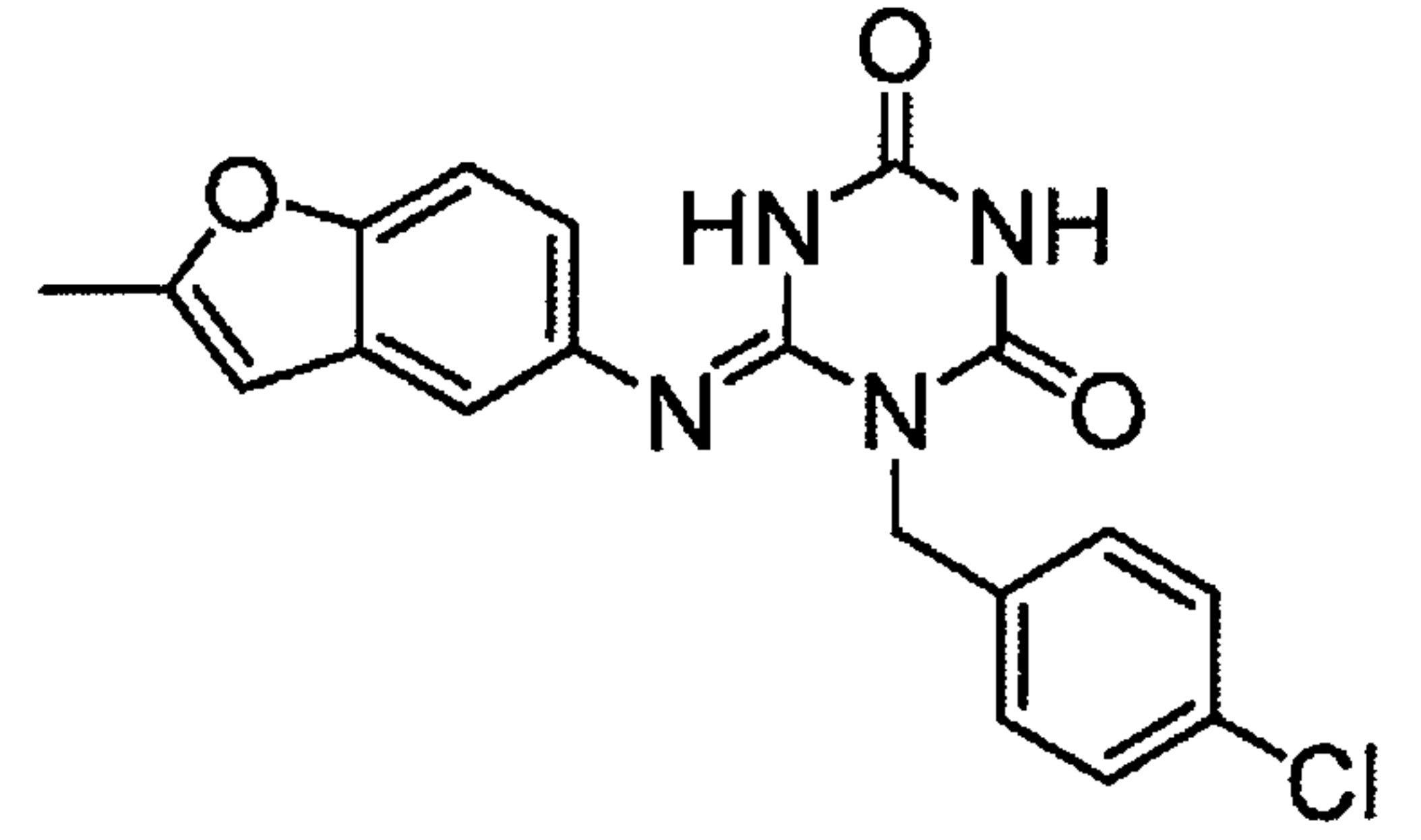
[Table 103]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0496	2.03	493	2
	I-0497	1.98	498	2
	I-0498	2.28	497	2
	I-0499	1.62	534	2
	I-0500	2.00	483	2

[Table 104]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0501	2.23	510	2
	I-0502	1.96	496	2
	I-0503	2.04	498	2
	I-0504	1.43	520	2
	I-0505	1.75	484	2

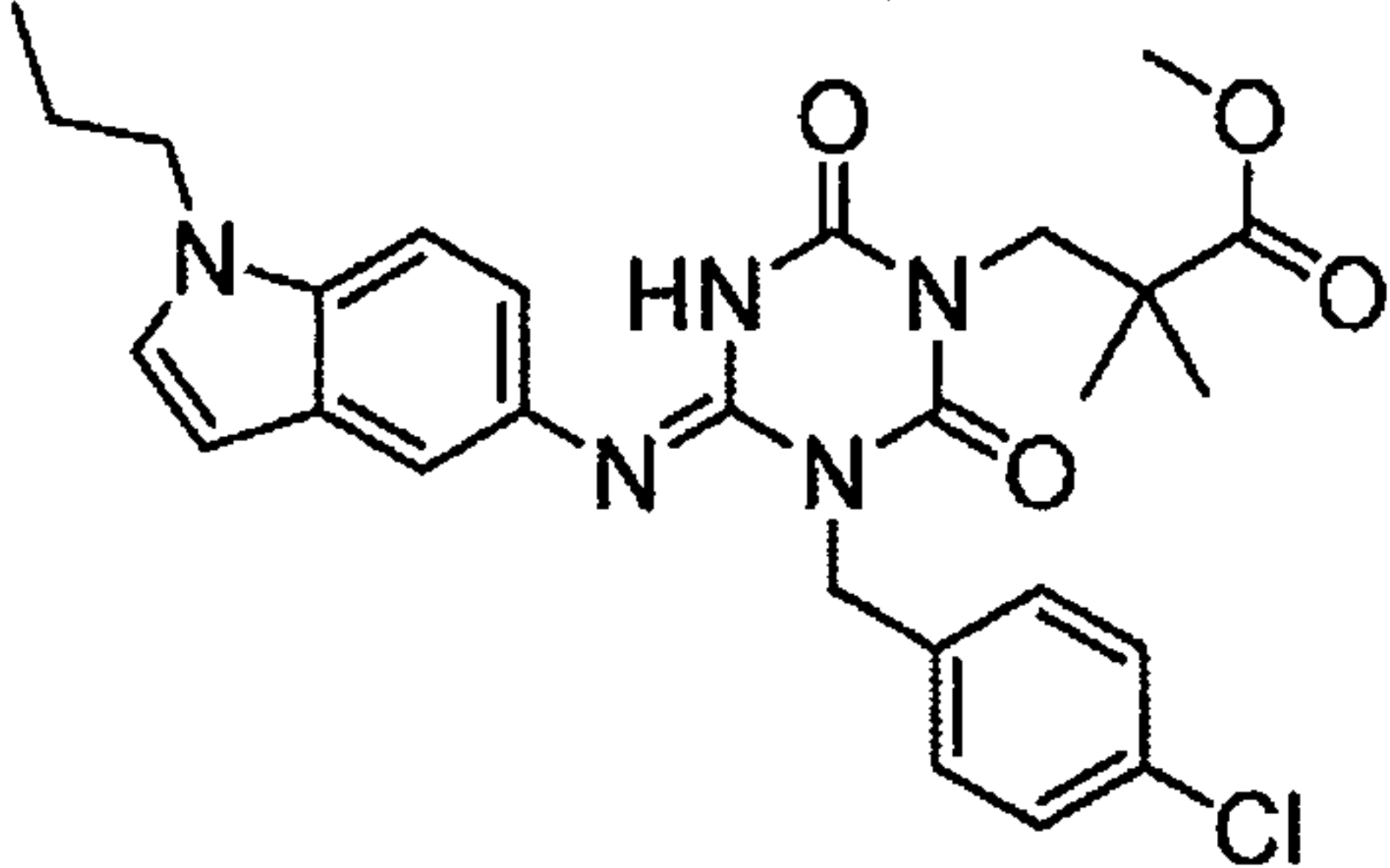
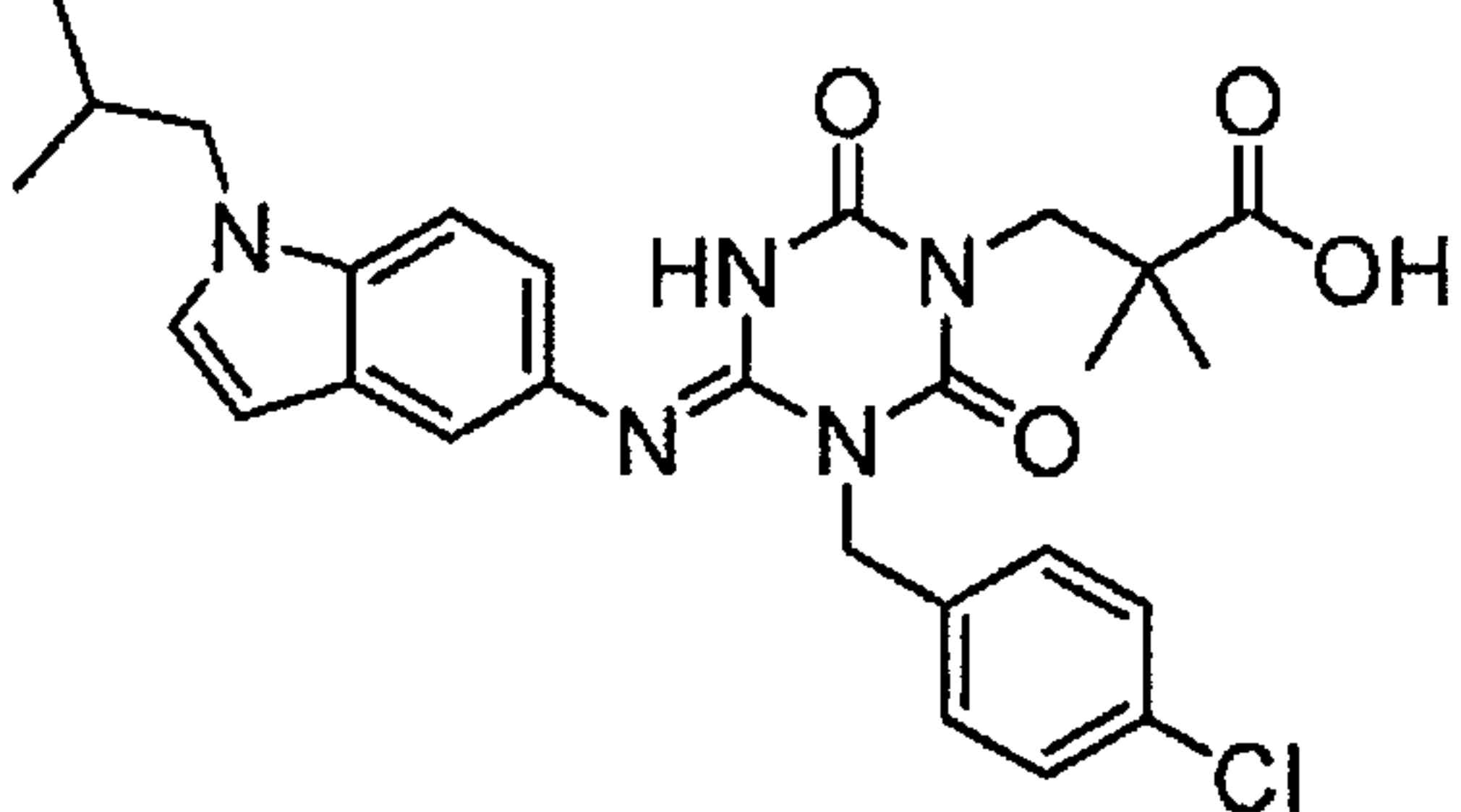
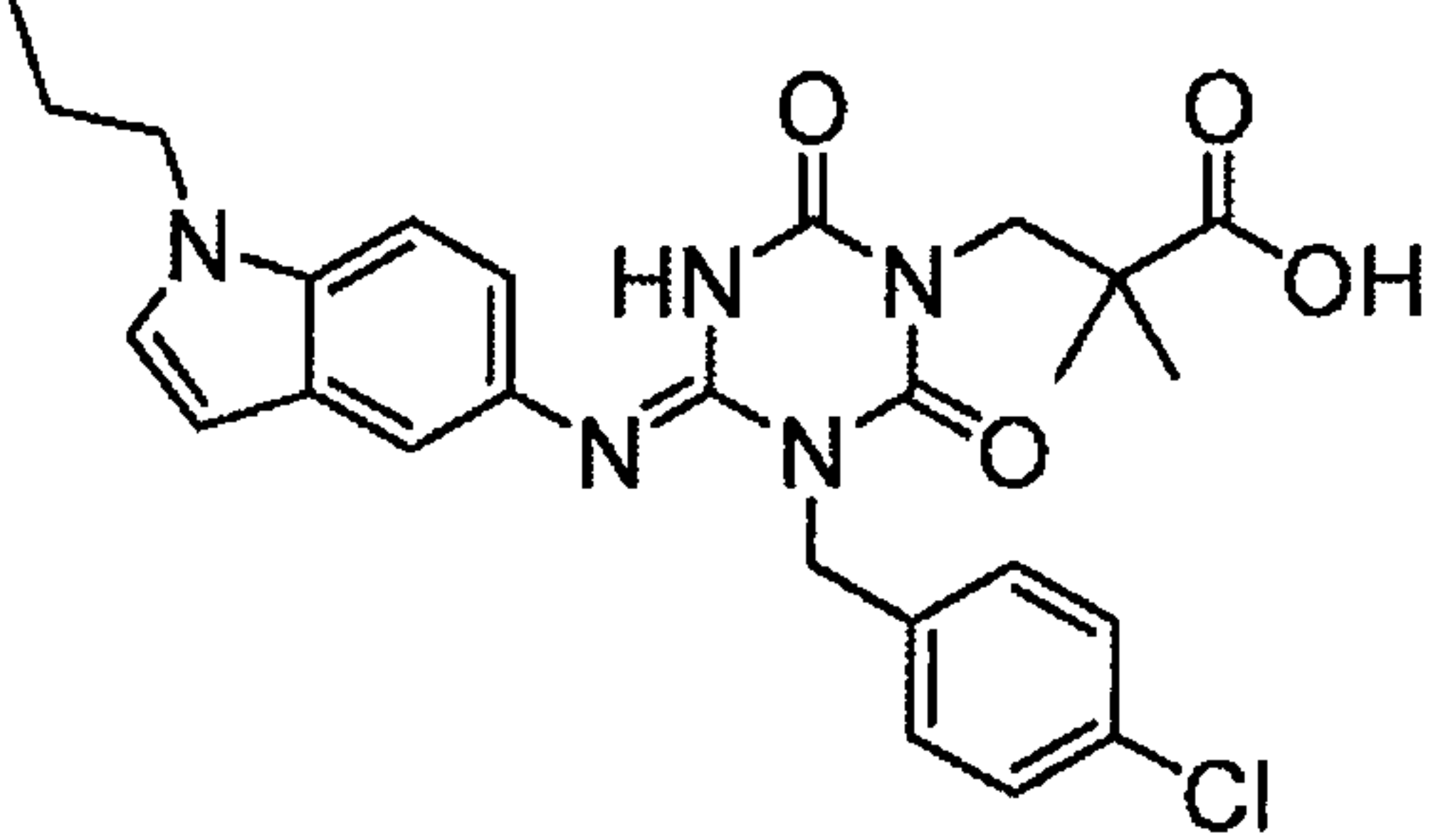
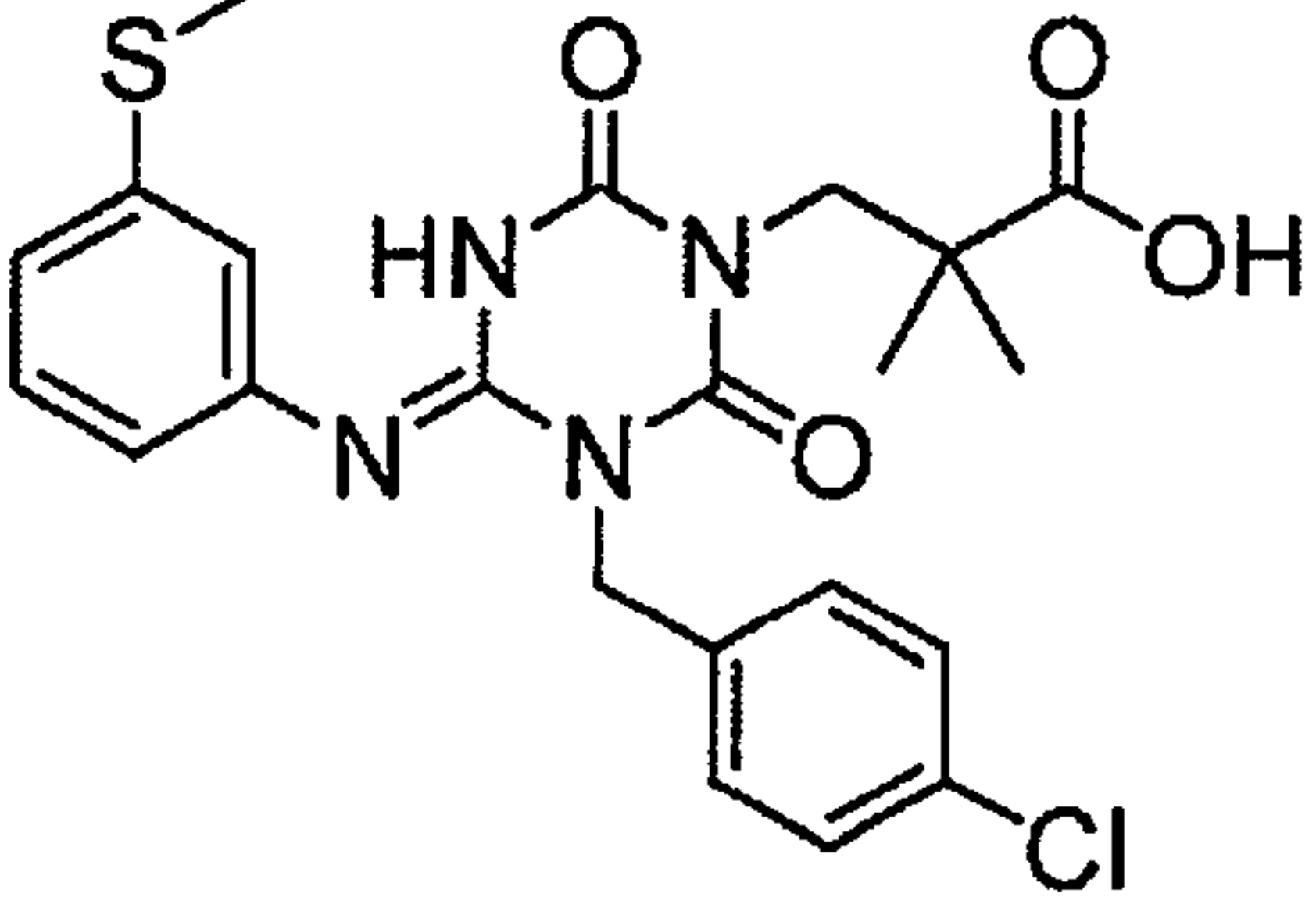
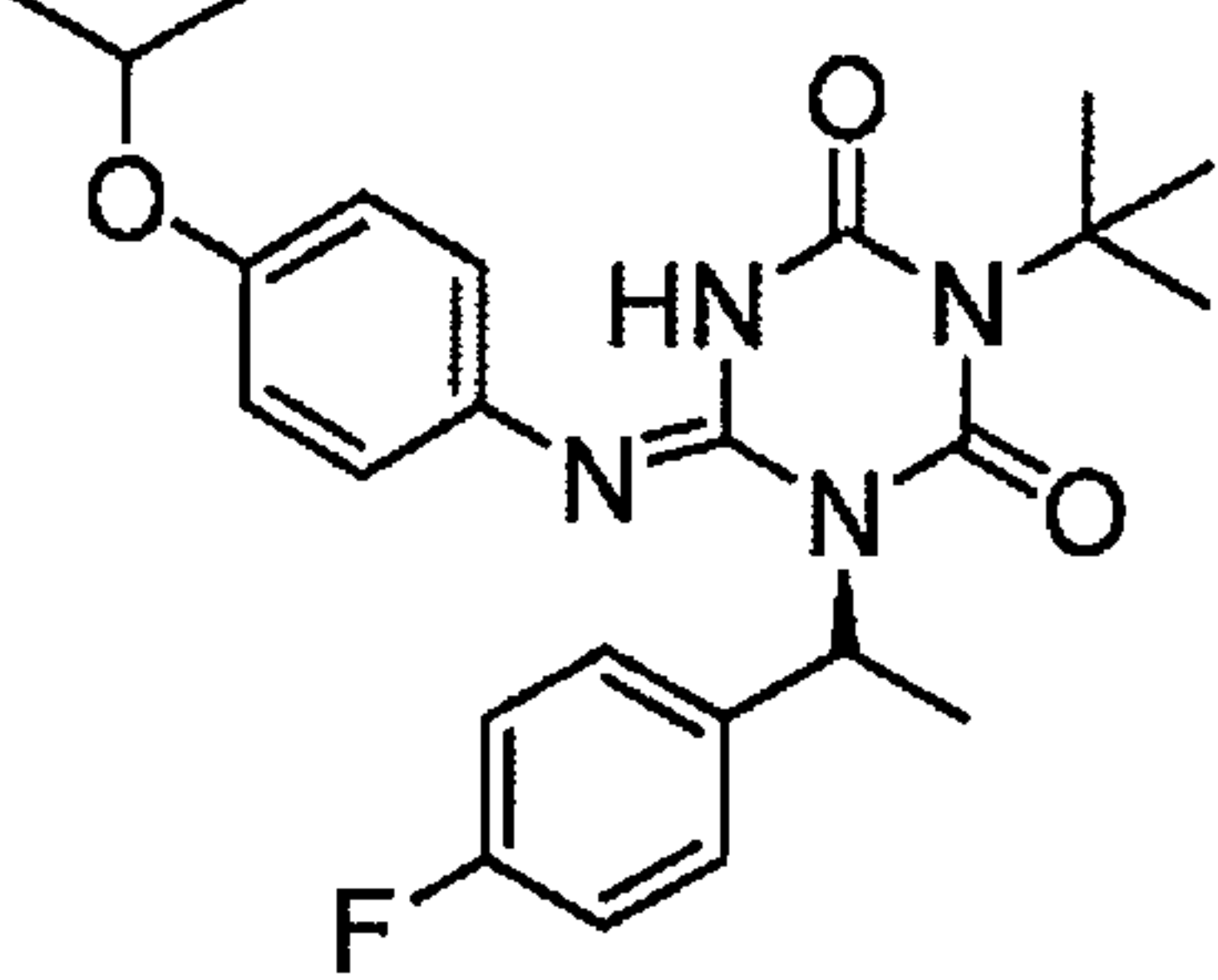
[Table 105]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0506	1.74	484	2
	I-0507	2.50	535	2
	I-0508	2.03	401	2
	I-0509	2.13	507	2
	I-0510	1.85	383	2

[Table 106]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0511	2.41	515	2
	I-0512	2.06	487	2
	I-0513	2.25	497	2
	I-0514	1.89	469	2
	I-0515	2.44	538	2

[Table 107]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0516	2.34	524	2
	I-0517	2.17	524	2
	I-0518	2.07	510	2
	I-0519	2.23	475	3
	I-0520	2.67	441	3

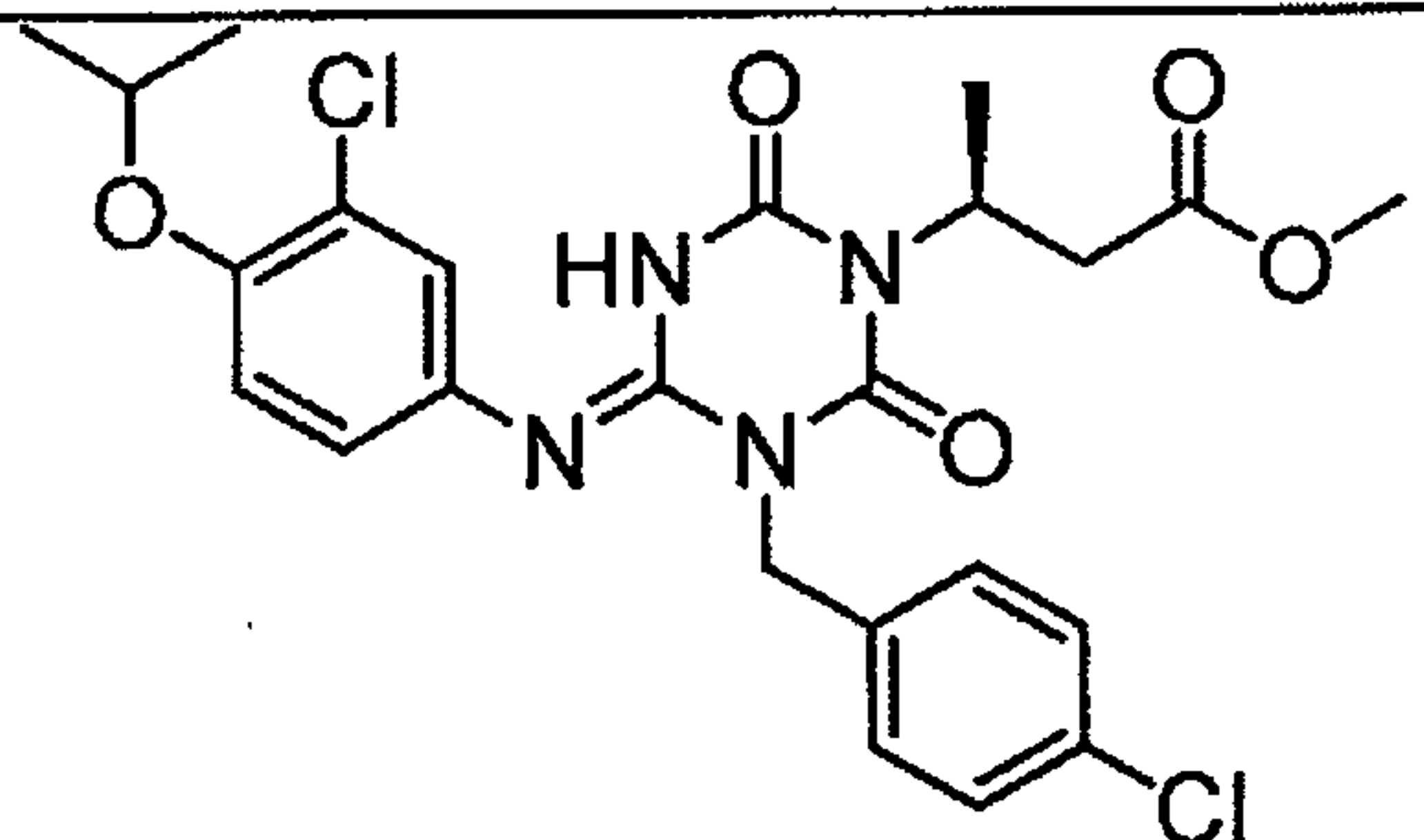
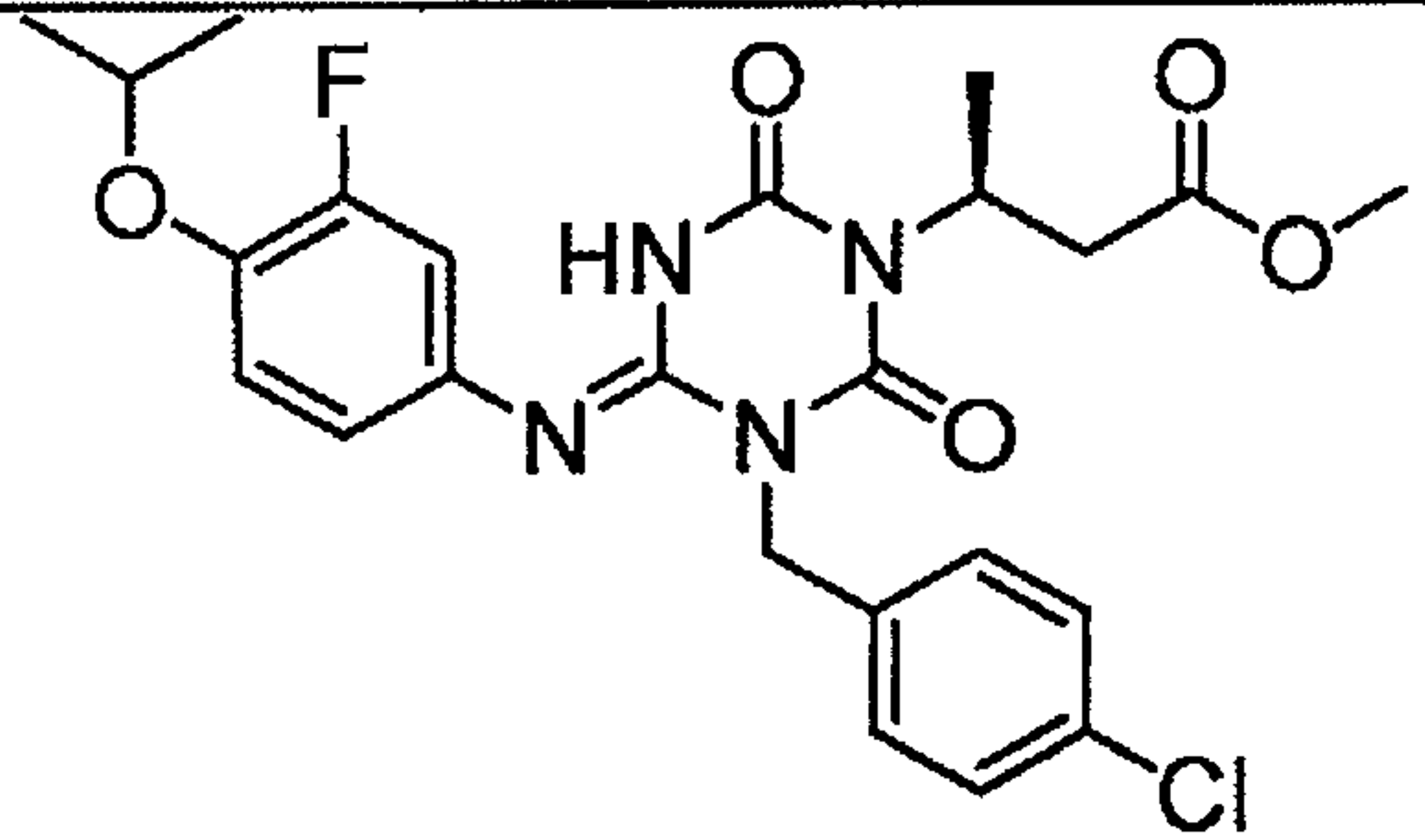
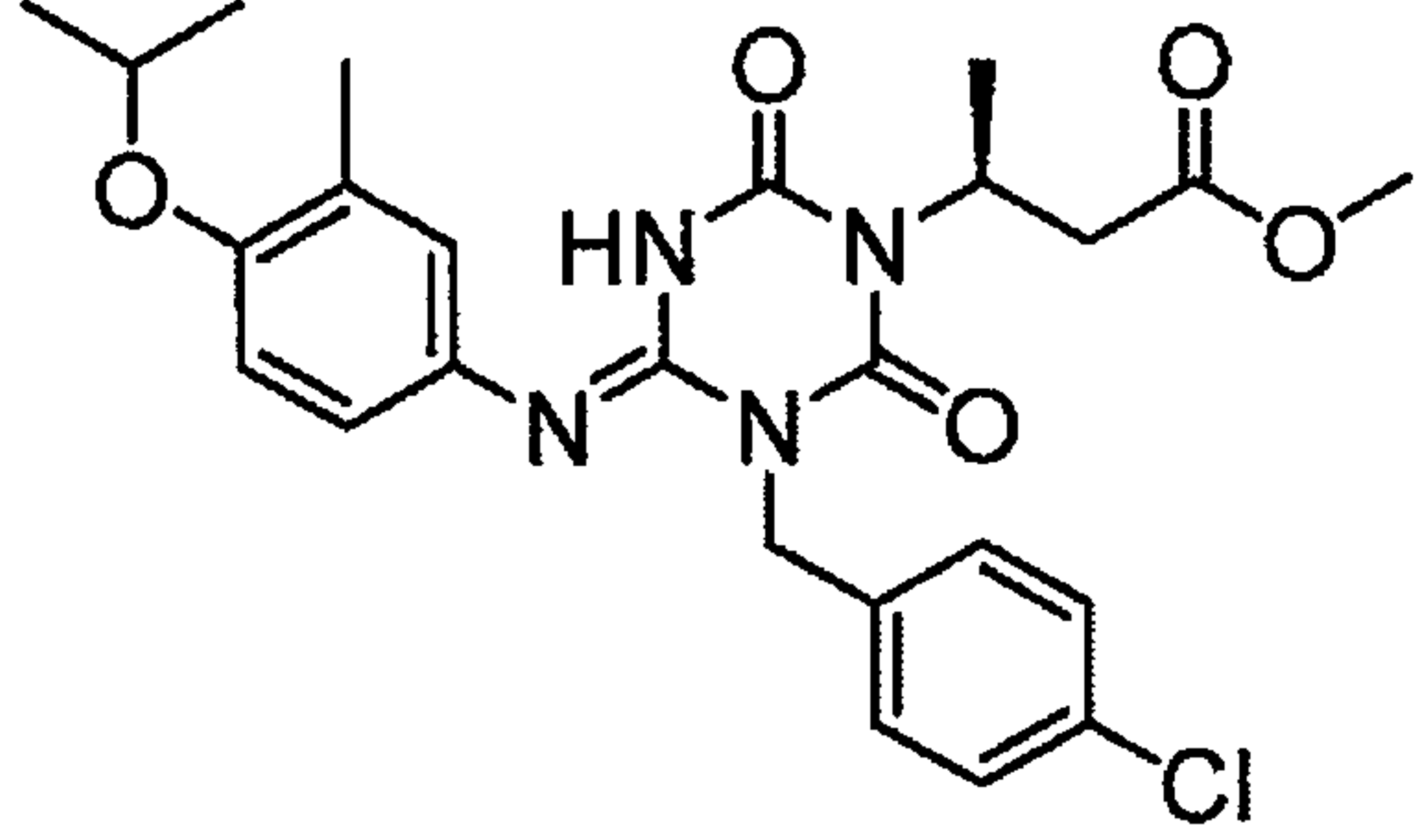
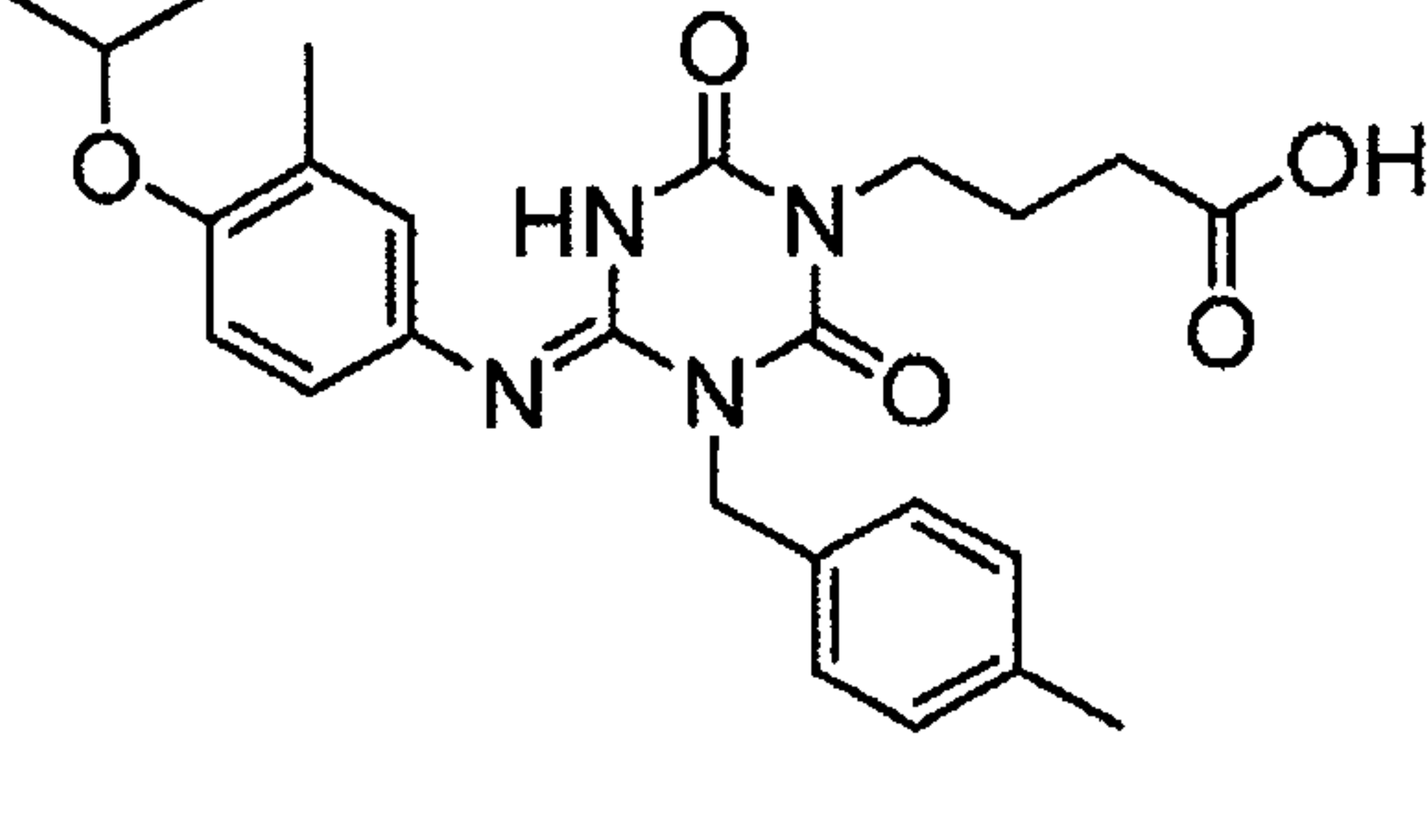
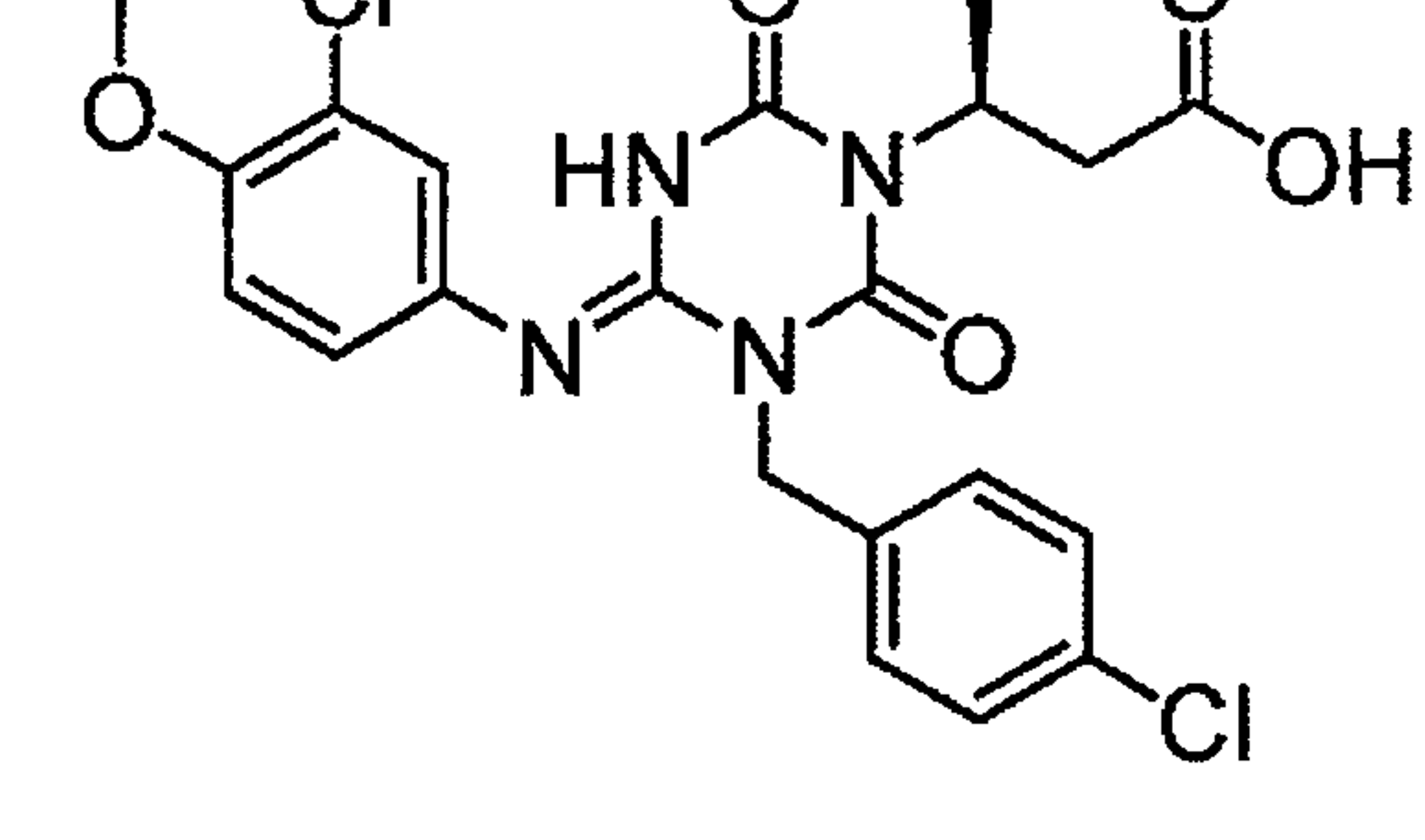
[Table 108]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0521	2.75	533	3
	I-0522	2.75	533	3
	I-0523	2.50	519	3
	I-0524	2.40	485	3
	I-0525	2.62	516	3

[Table 109]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0526	2.18	471	3
	I-0527	2.28	487	3
	I-0528	2.25	487	3
	I-0529	2.00	449	3
	I-0530	2.55	495	3

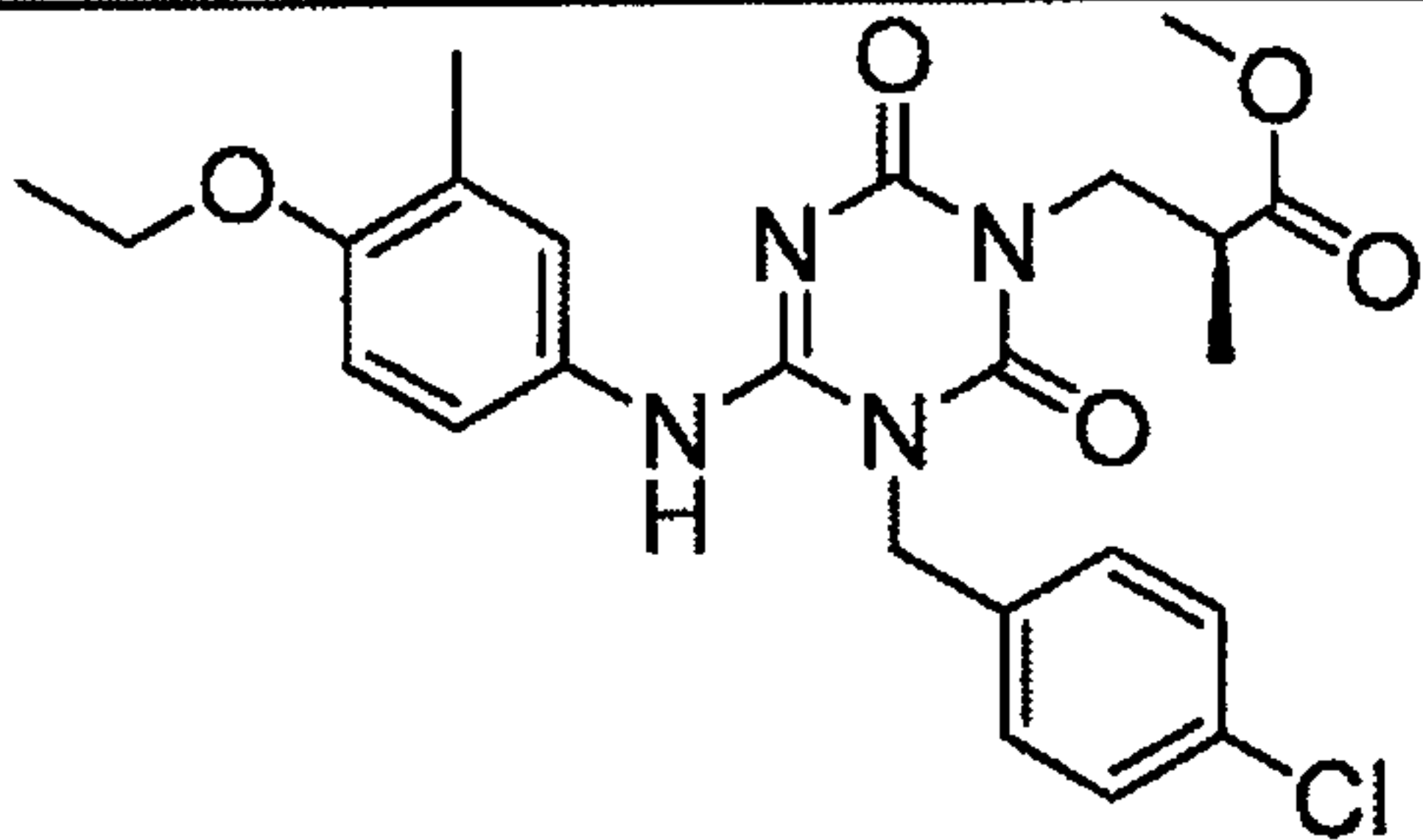
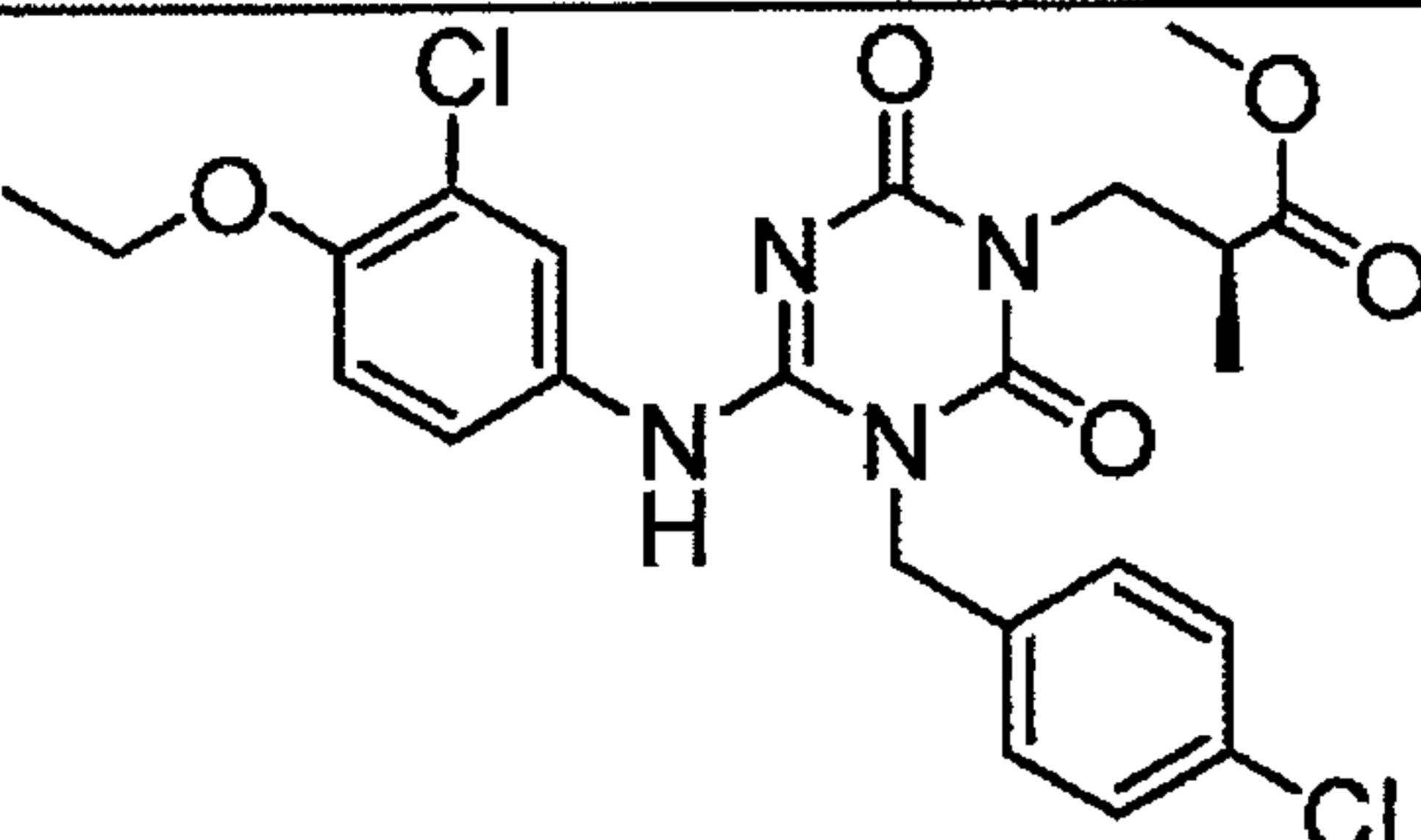
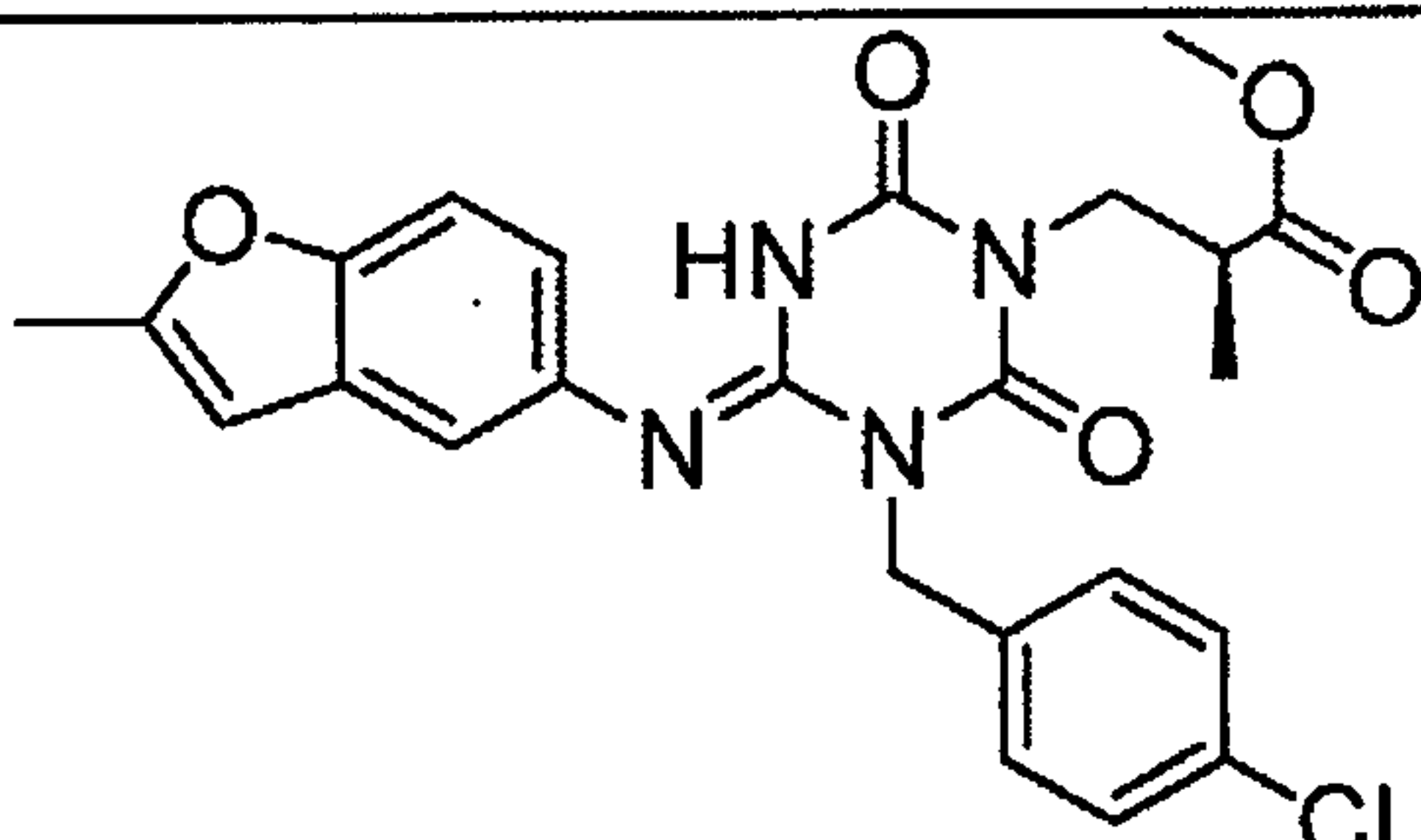
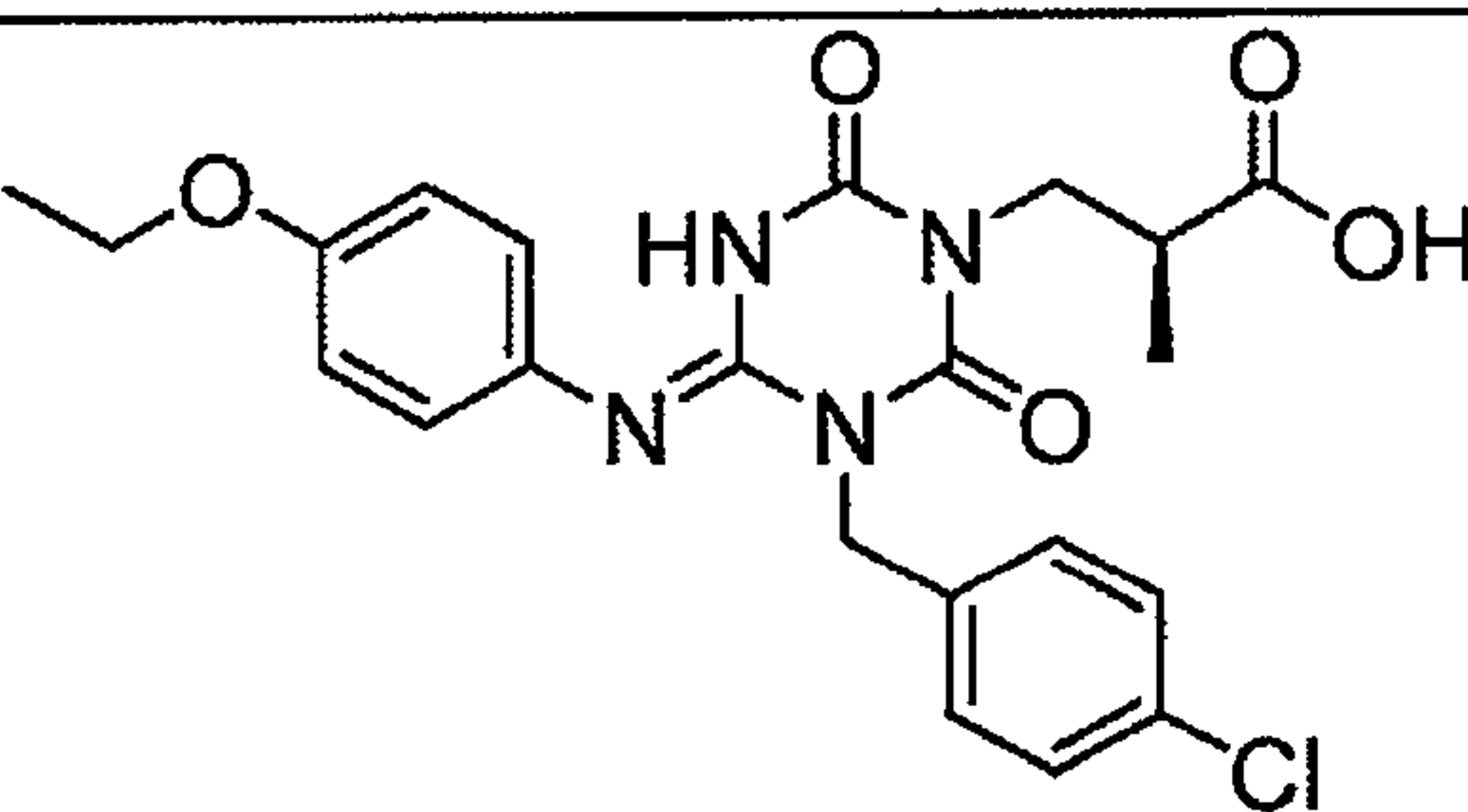
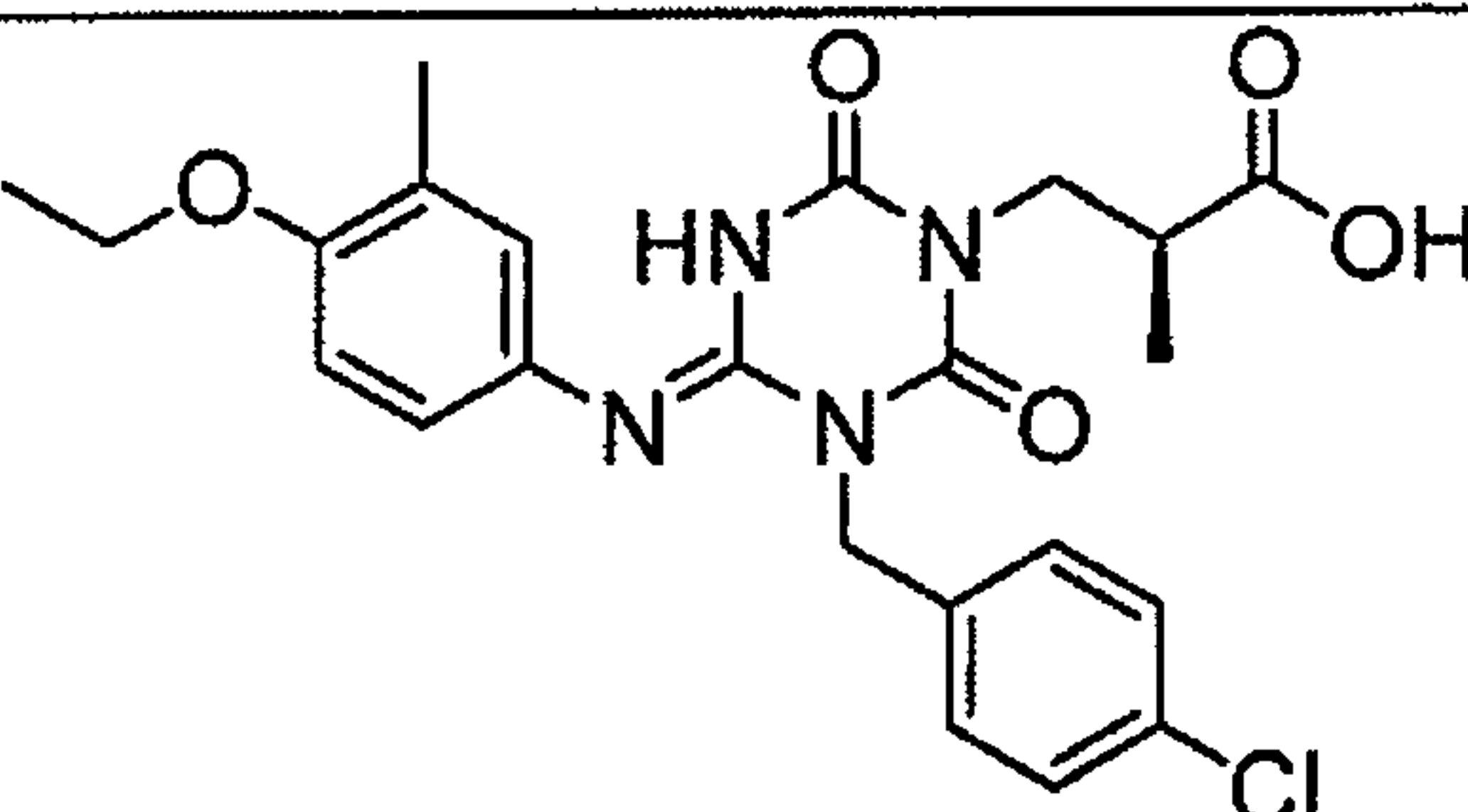
[Table 110]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0531	2.64	521	3
	I-0532	2.53	505	3
	I-0533	2.57	501	3
	I-0534	2.20	467	3
	I-0535	2.38	507	3

[Table 111]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0536	2.26	491	3
	I-0537	2.30	487	3
	I-0538	2.18	487	2
	I-0539	2.07	473	2
	I-0540	2.33	501	2

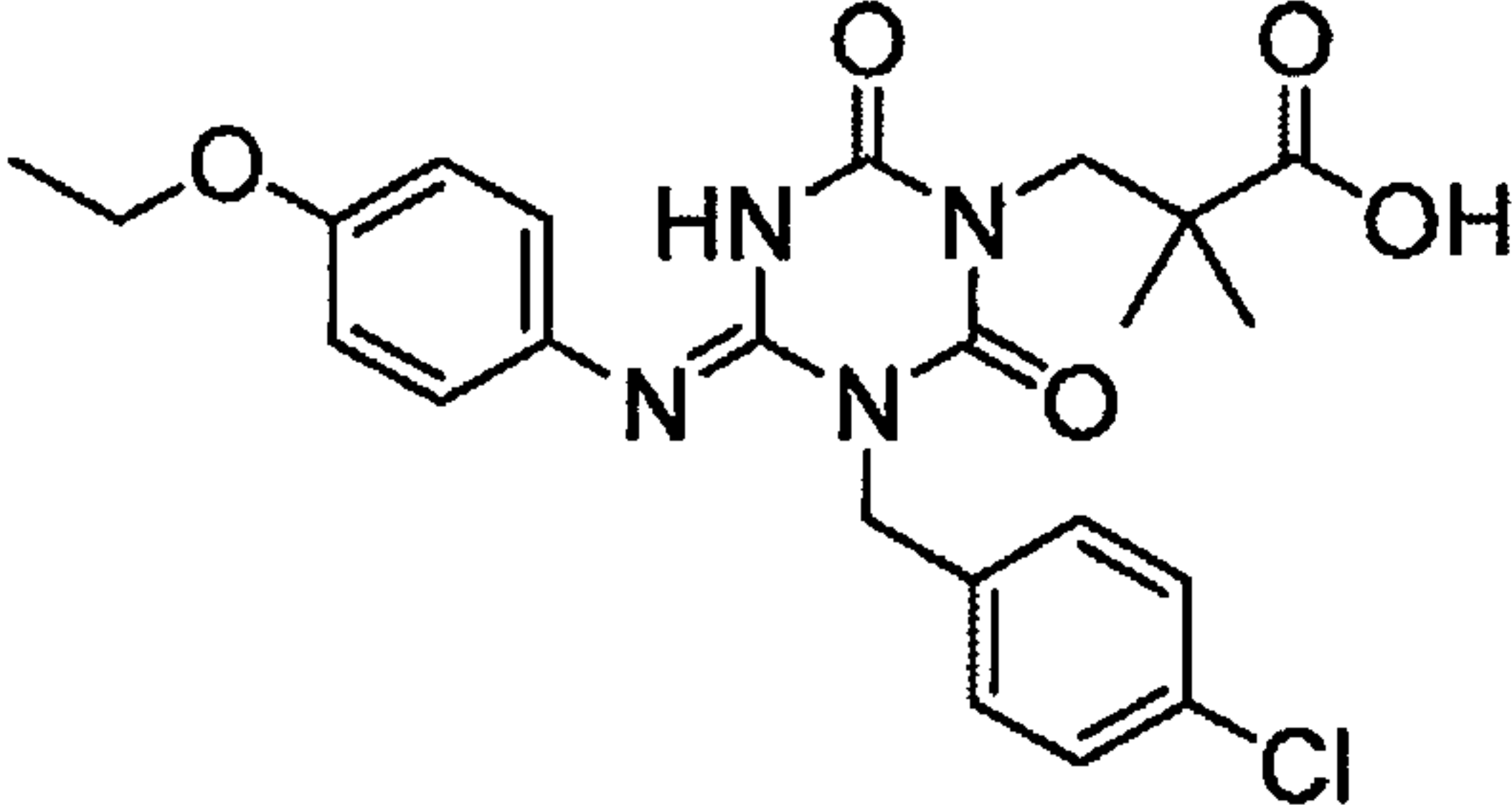
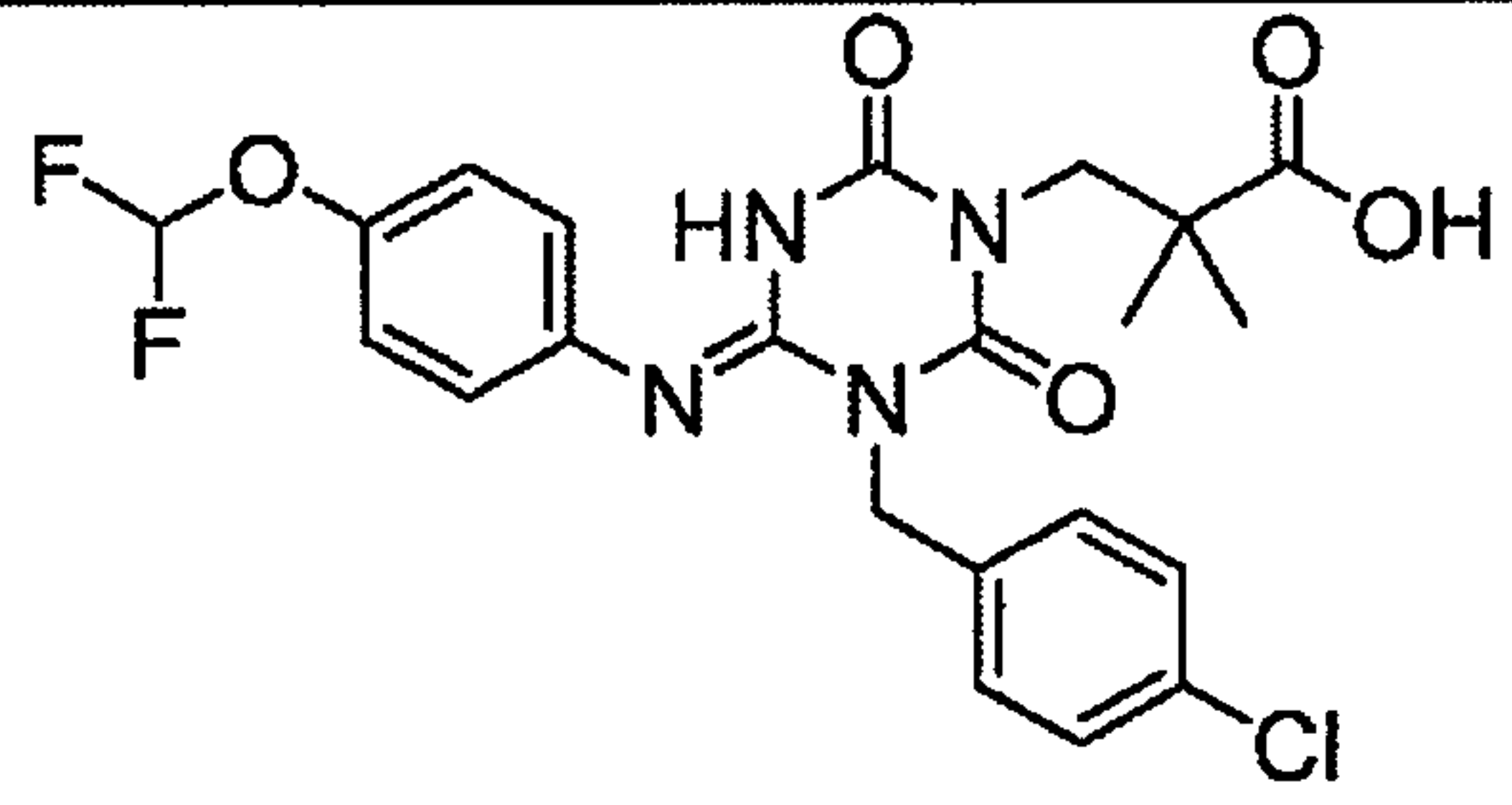
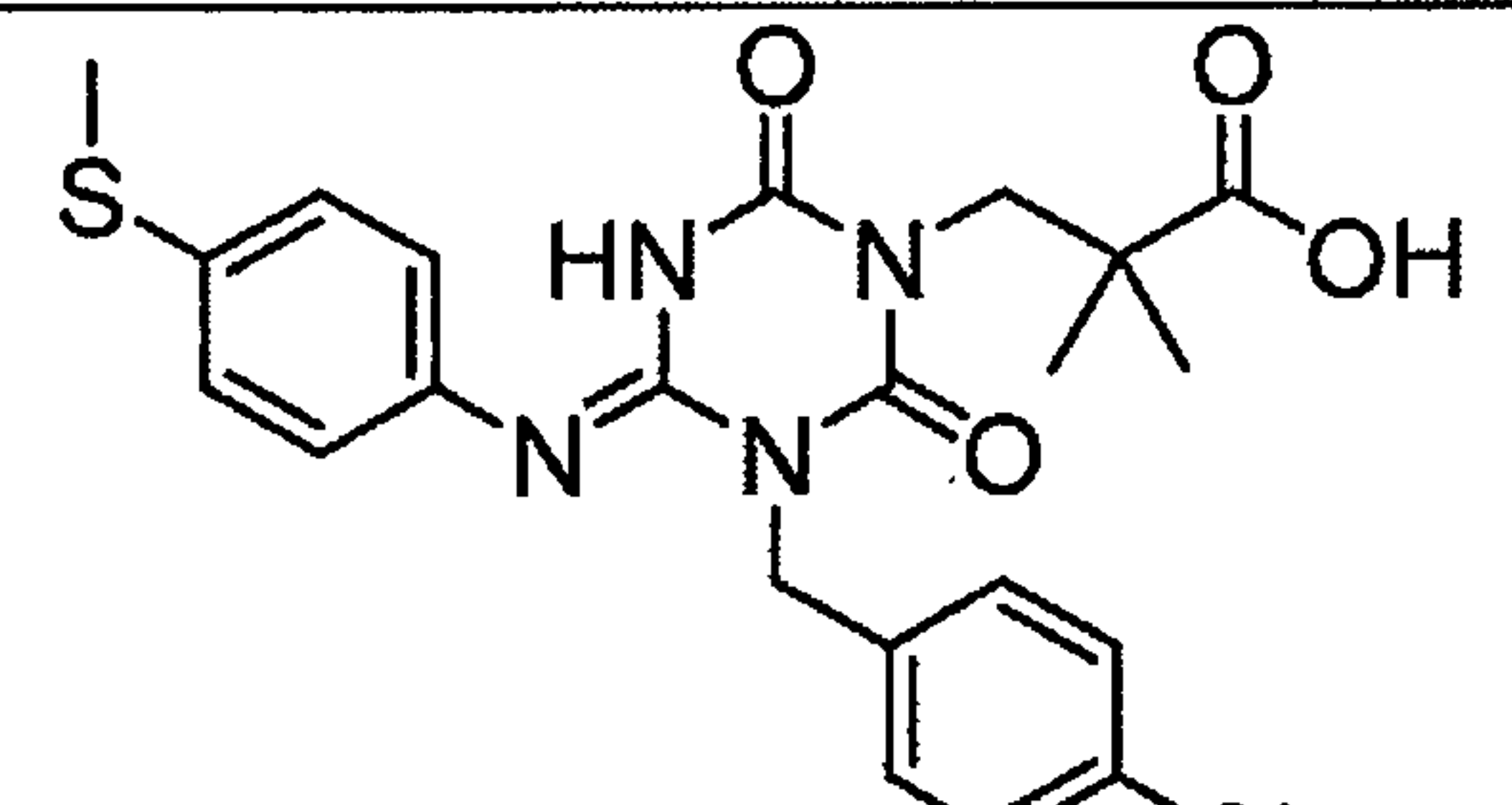
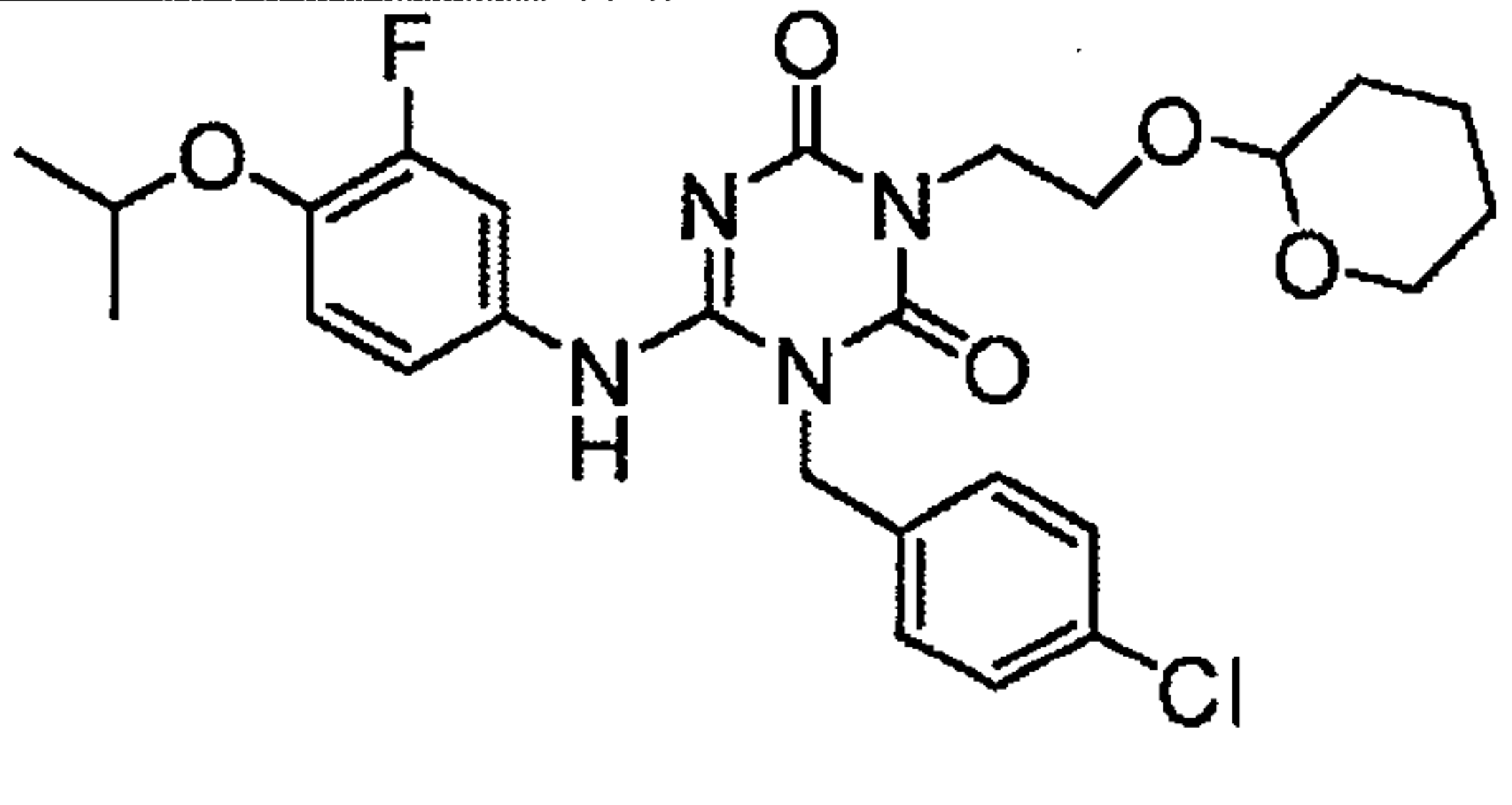
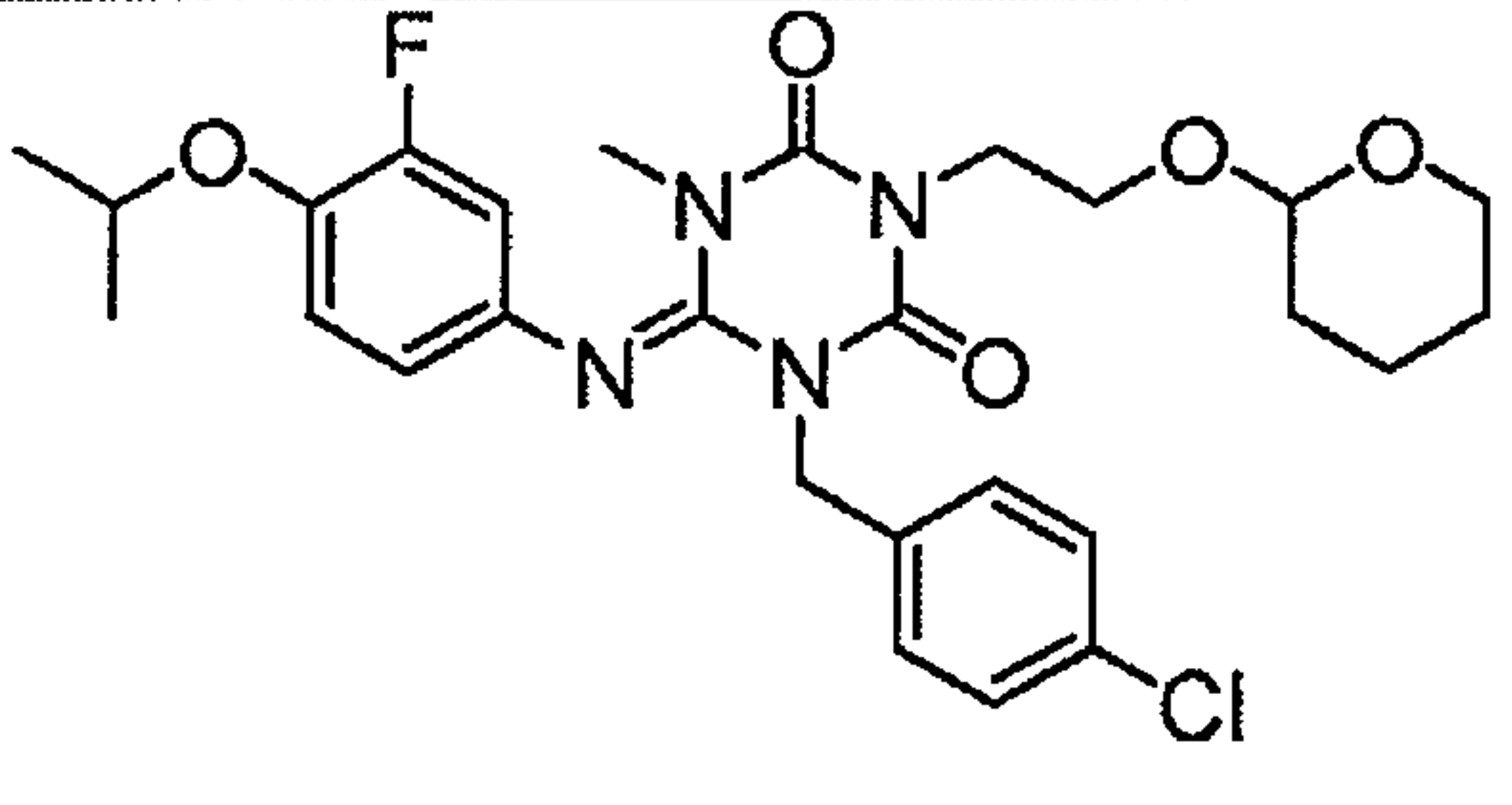
[Table 112]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0541	2.23	487	2
	I-0542	2.29	507	2
	I-0543	2.16	483	2
	I-0544	1.82	459	2
	I-0545	1.98	473	2

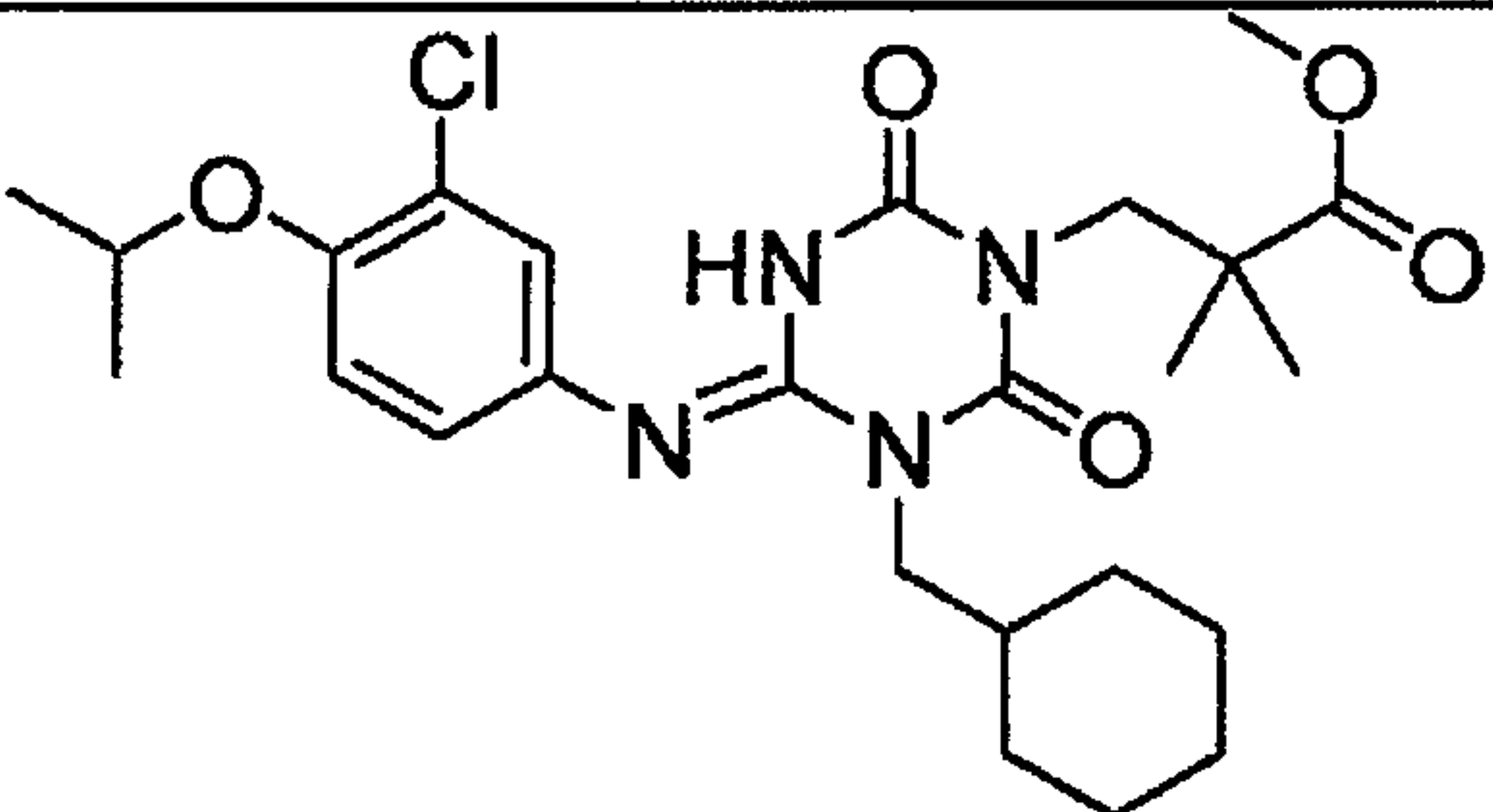
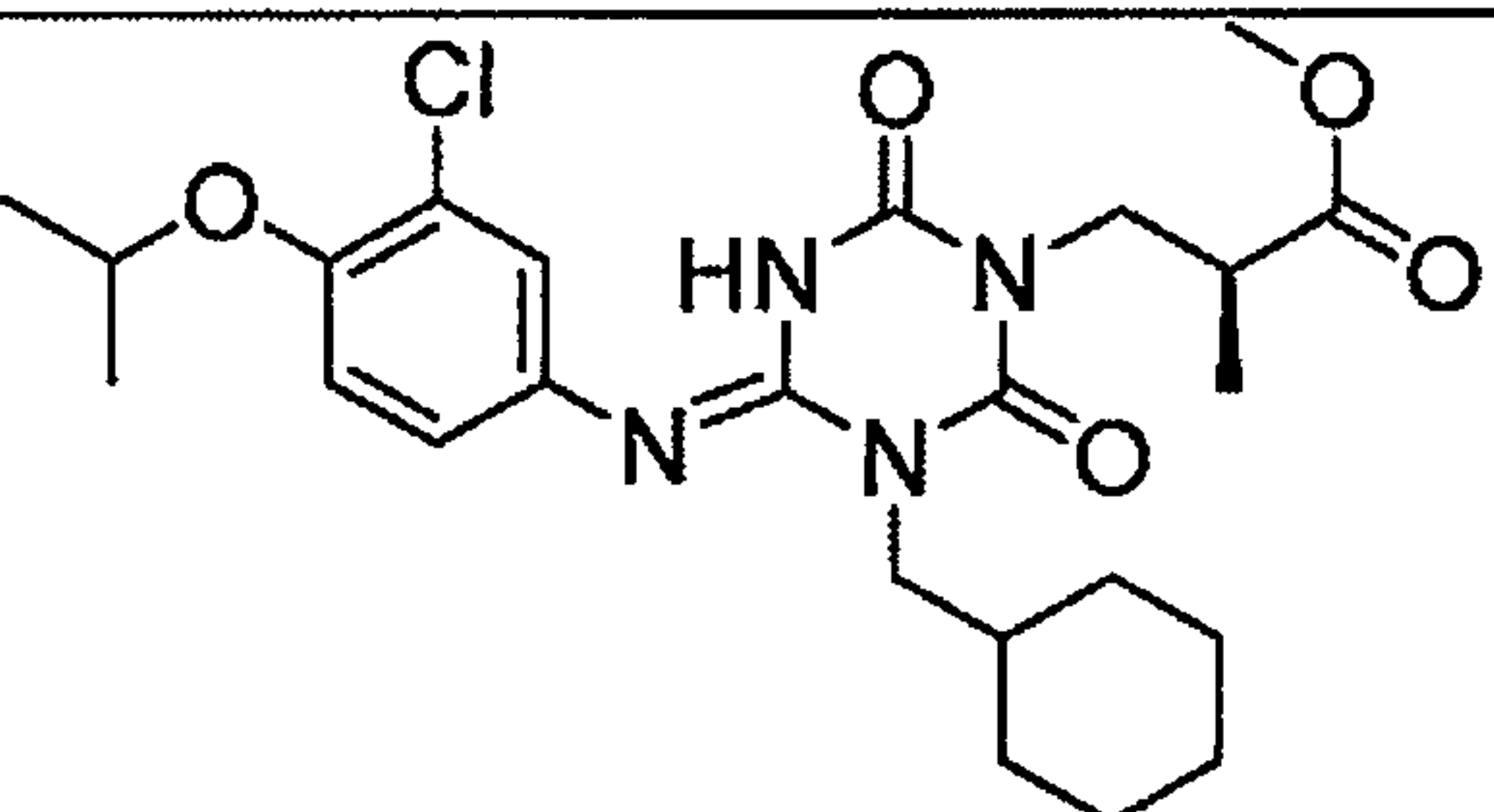
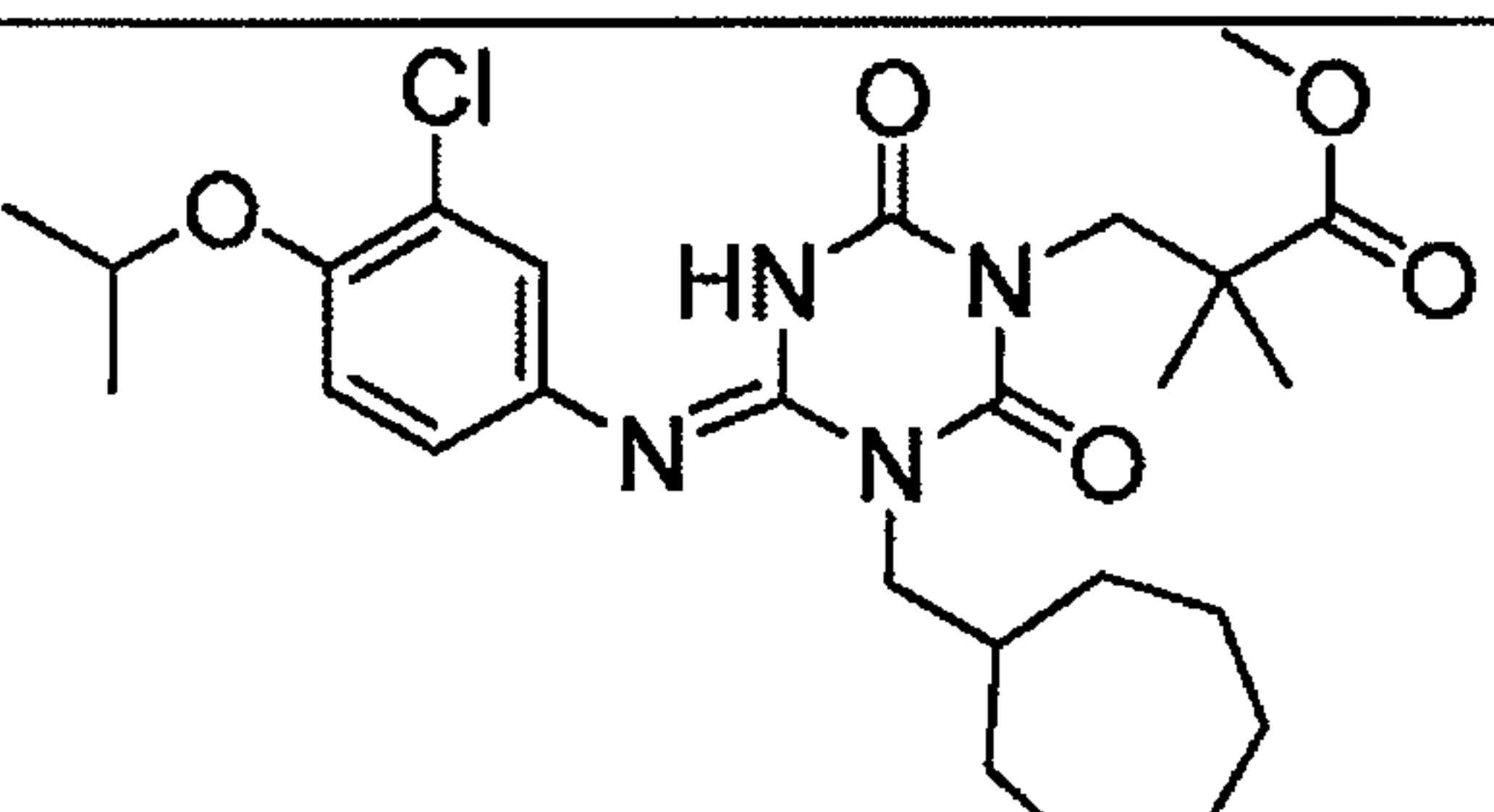
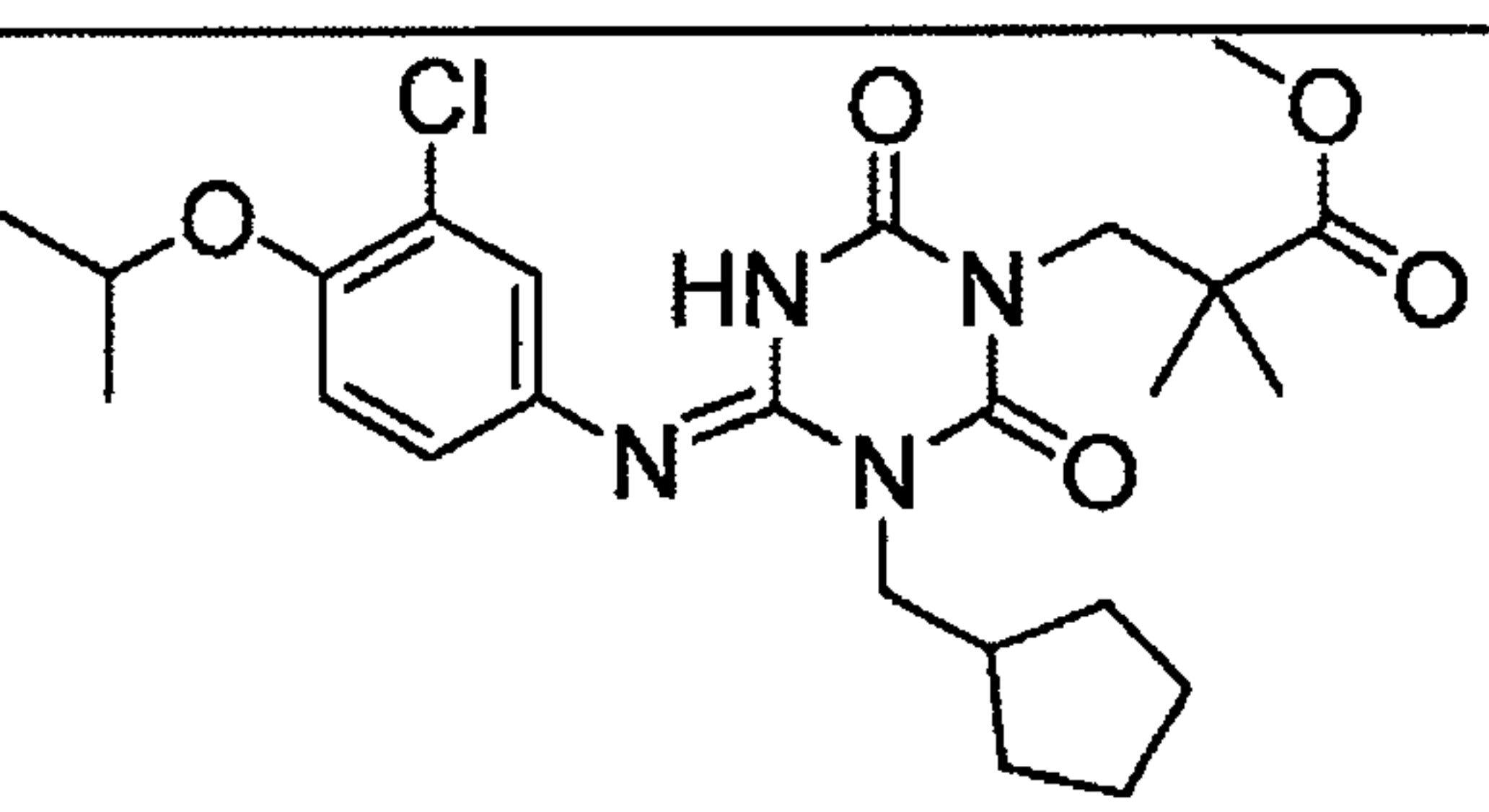
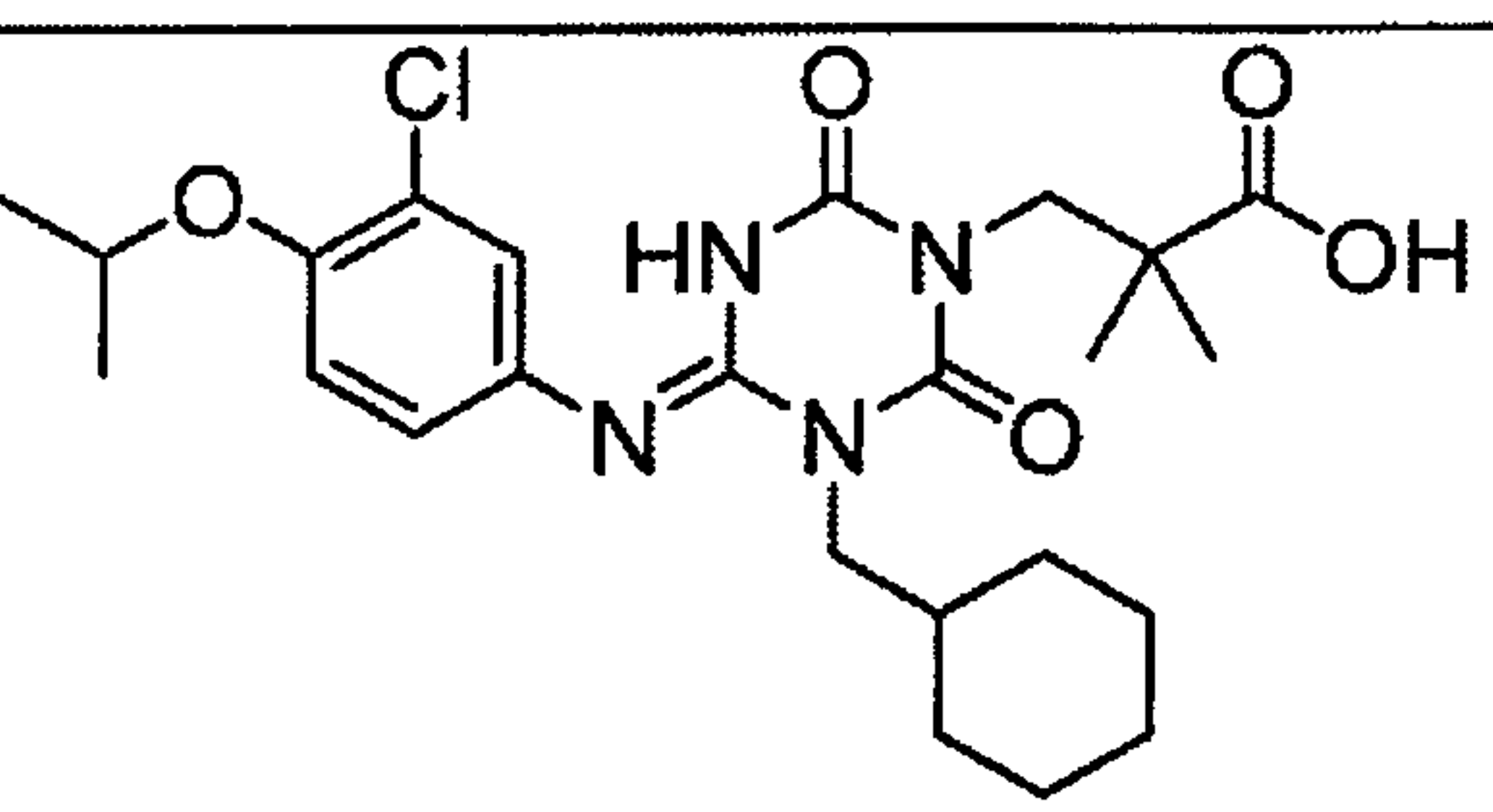
[Table 113]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0546	1.91	473	2
	I-0547	2.09	487	2
	I-0548	2.03	493	2
	I-0549	1.91	469	2
	I-0550	1.99	487	2

[Table 114]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0551	1.90	473	2
	I-0552	1.97	495	2
	I-0553	1.99	475	2
	I-0554	2.41	533	2
	I-0555	2.76	547	2

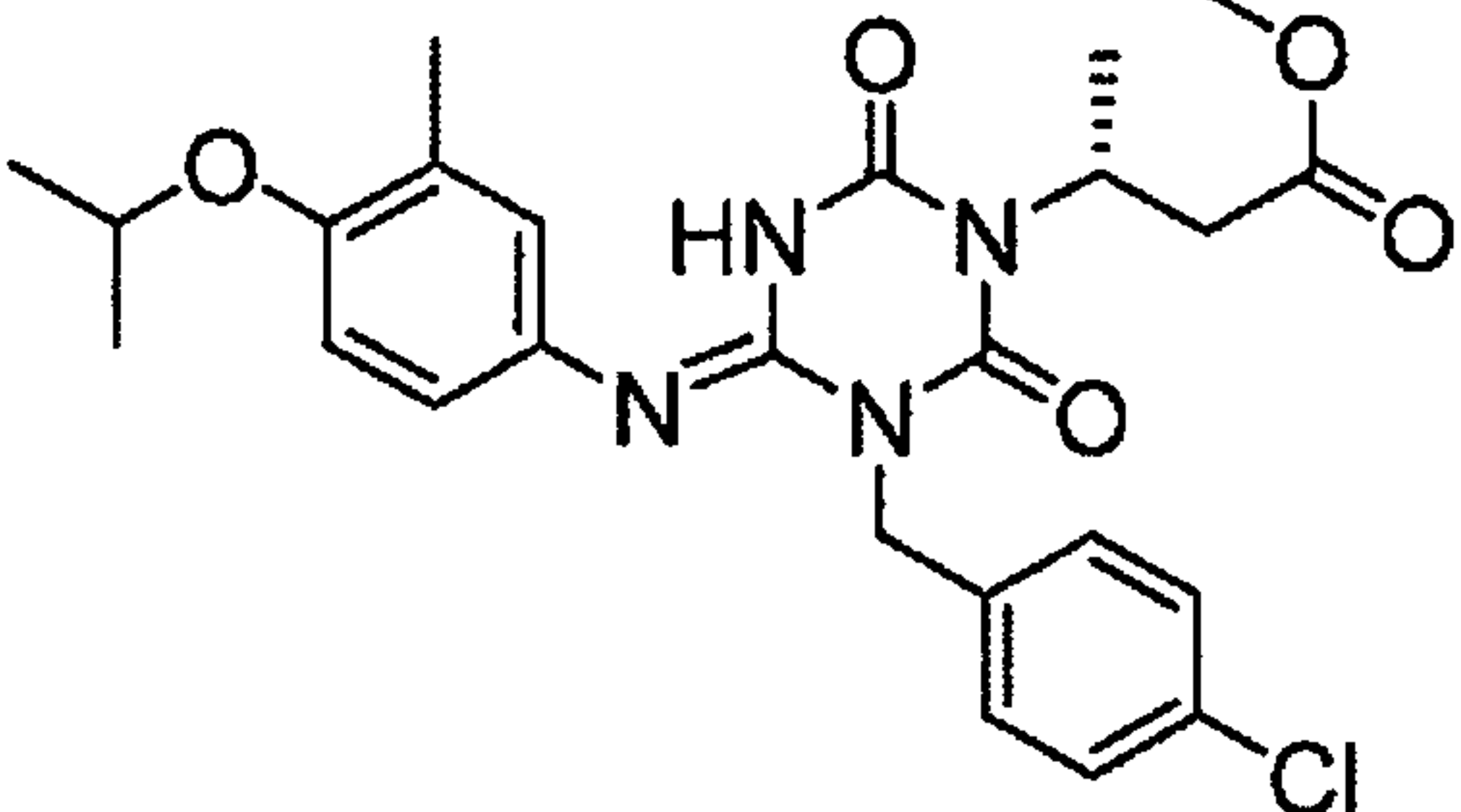
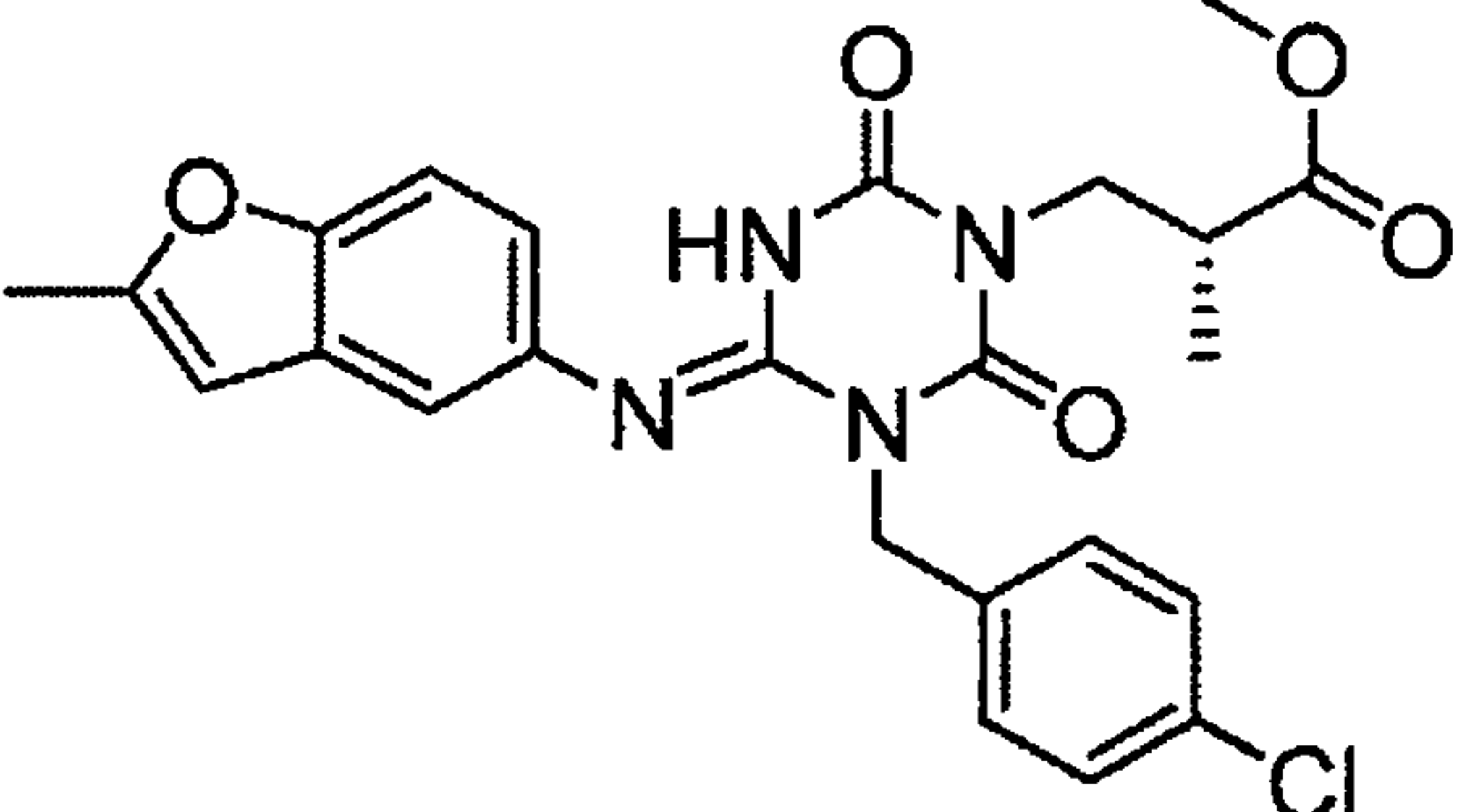
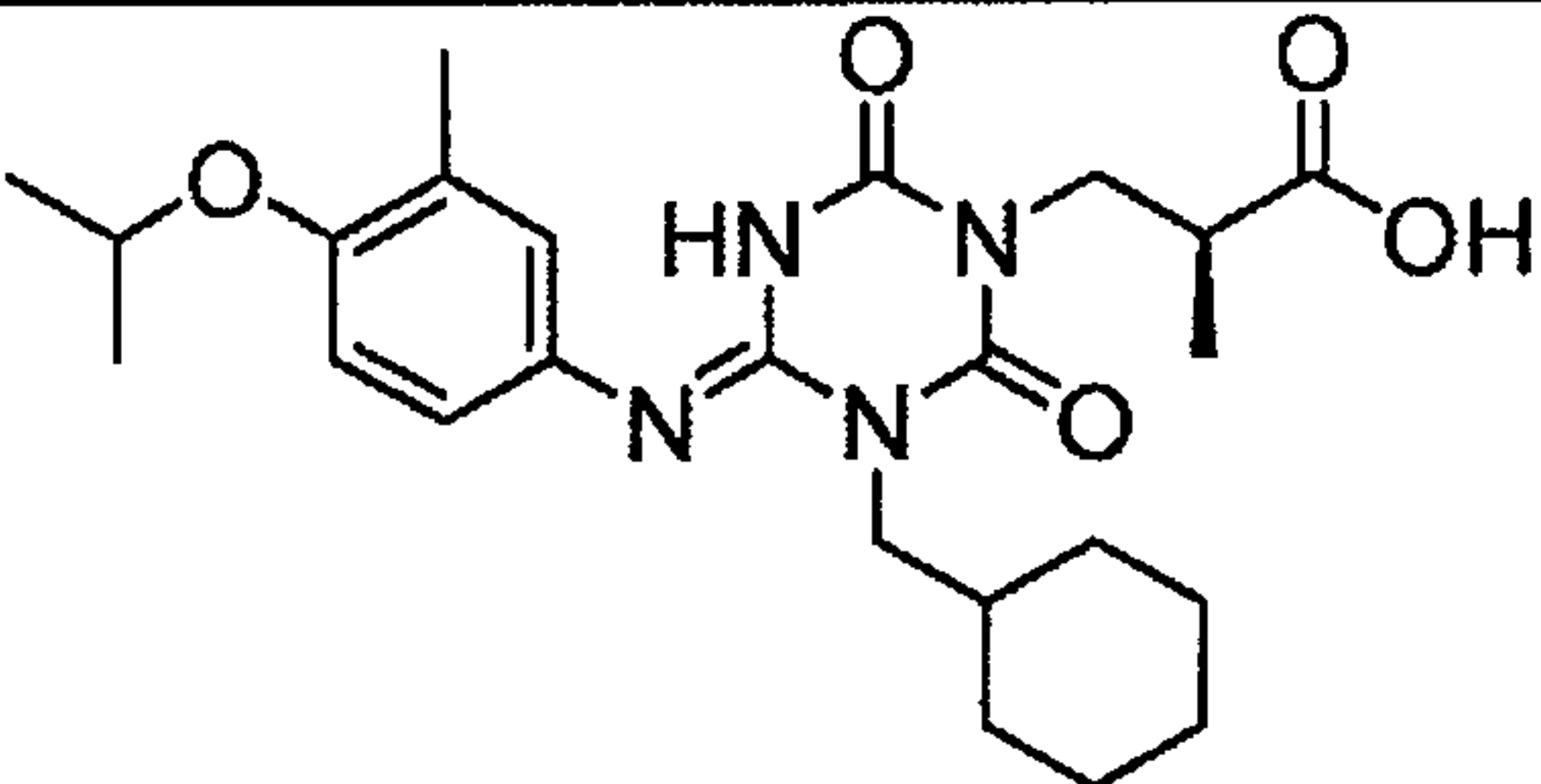
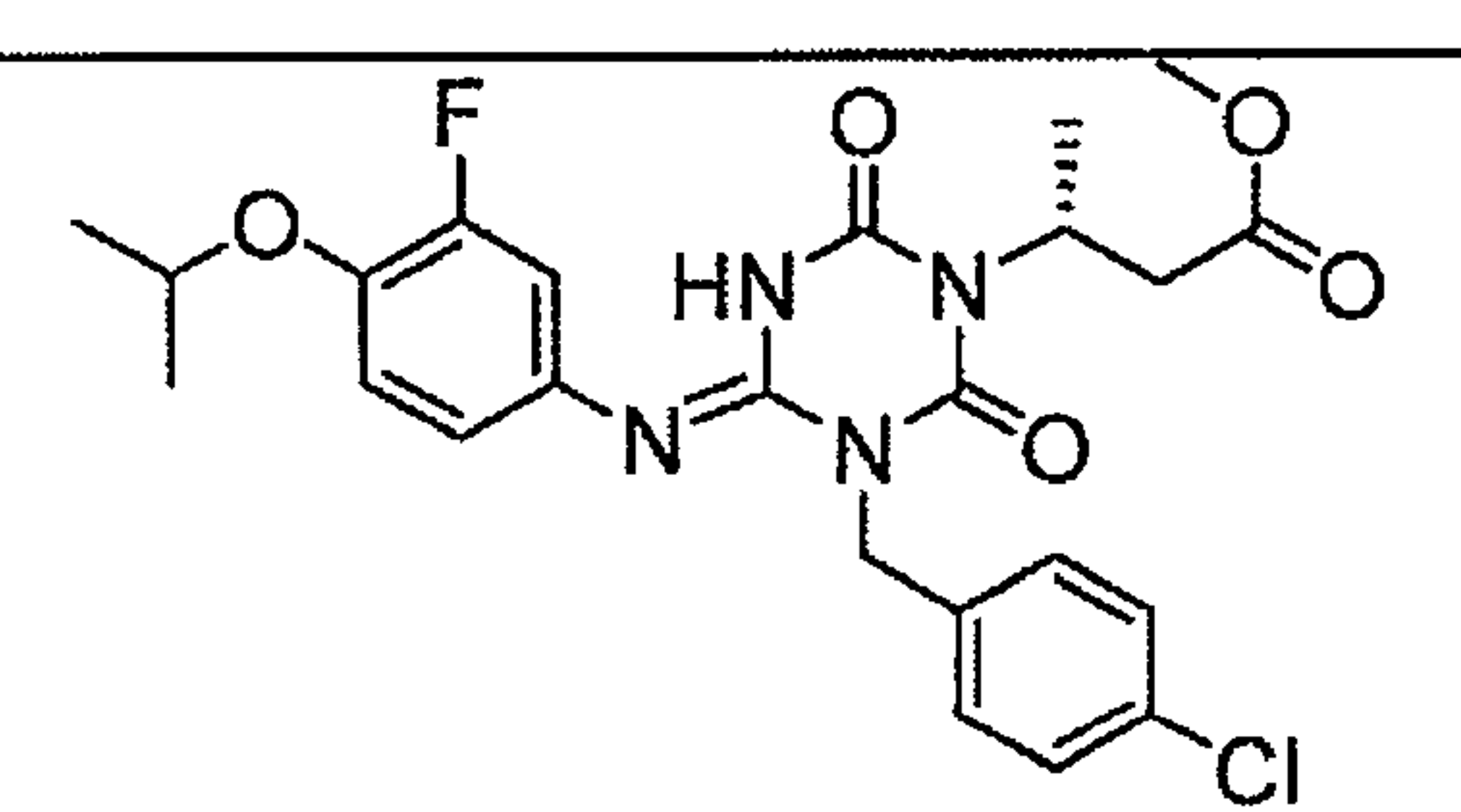
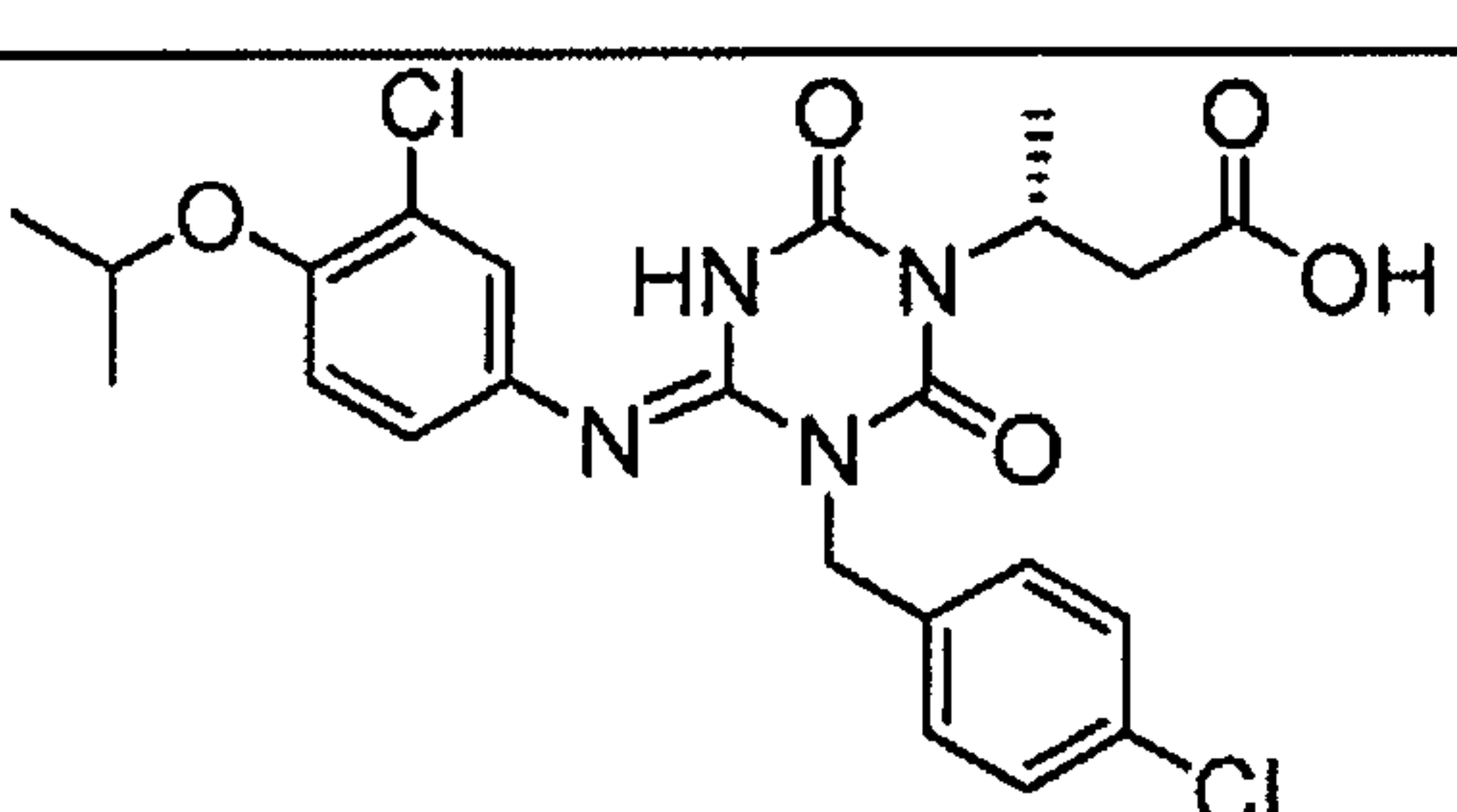
[Table 115]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0556	2.53	507	2
	I-0557	2.42	493	2
	I-0558	2.65	521	2
	I-0559	2.43	493	2
	I-0560	2.23	493	2

[Table 116]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0561	2.16	479	2
	I-0562	2.35	507	2
	I-0563	2.12	479	2
	I-0564	2.37	473	2
	I-0565	2.44	521	2

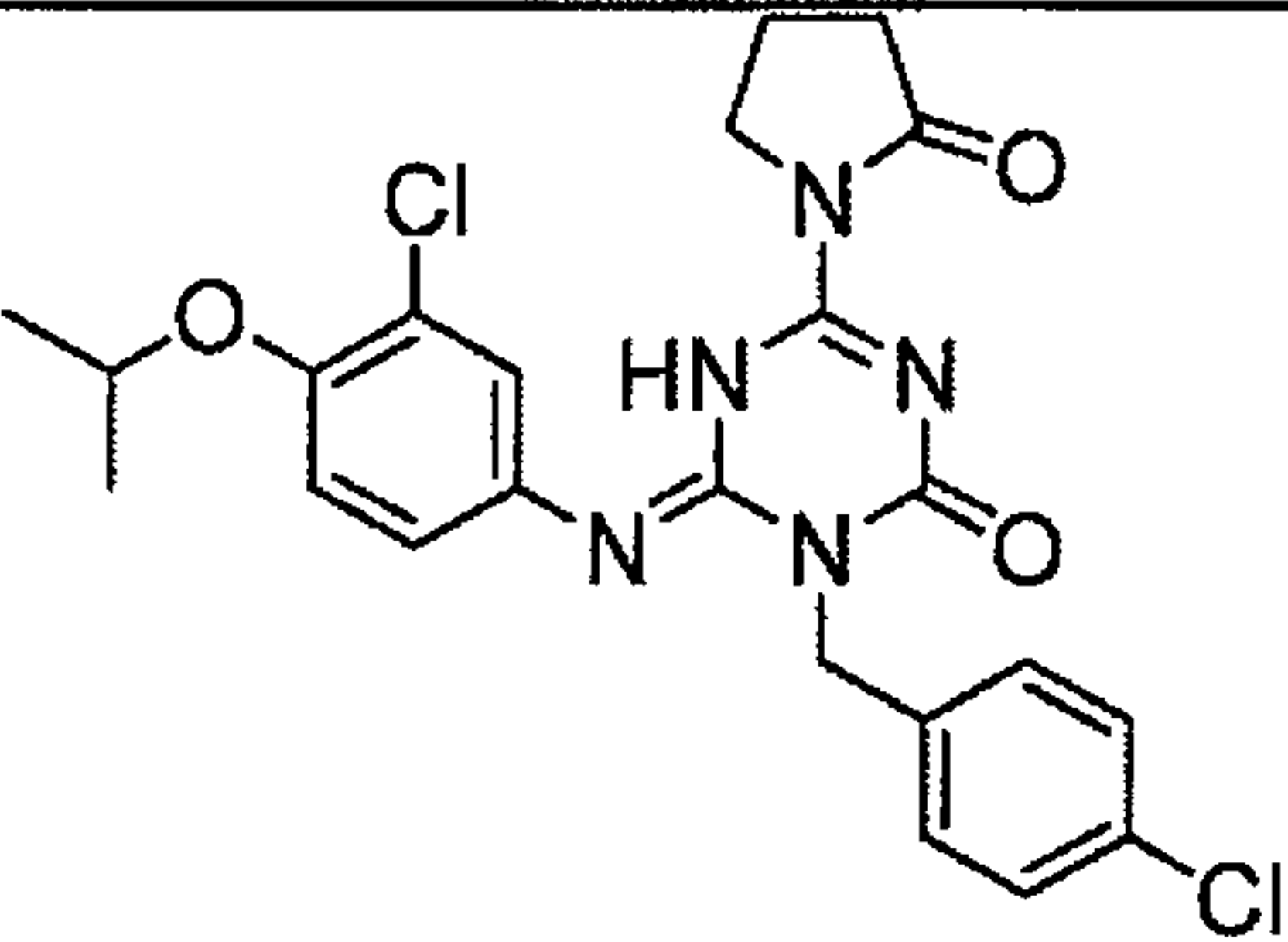
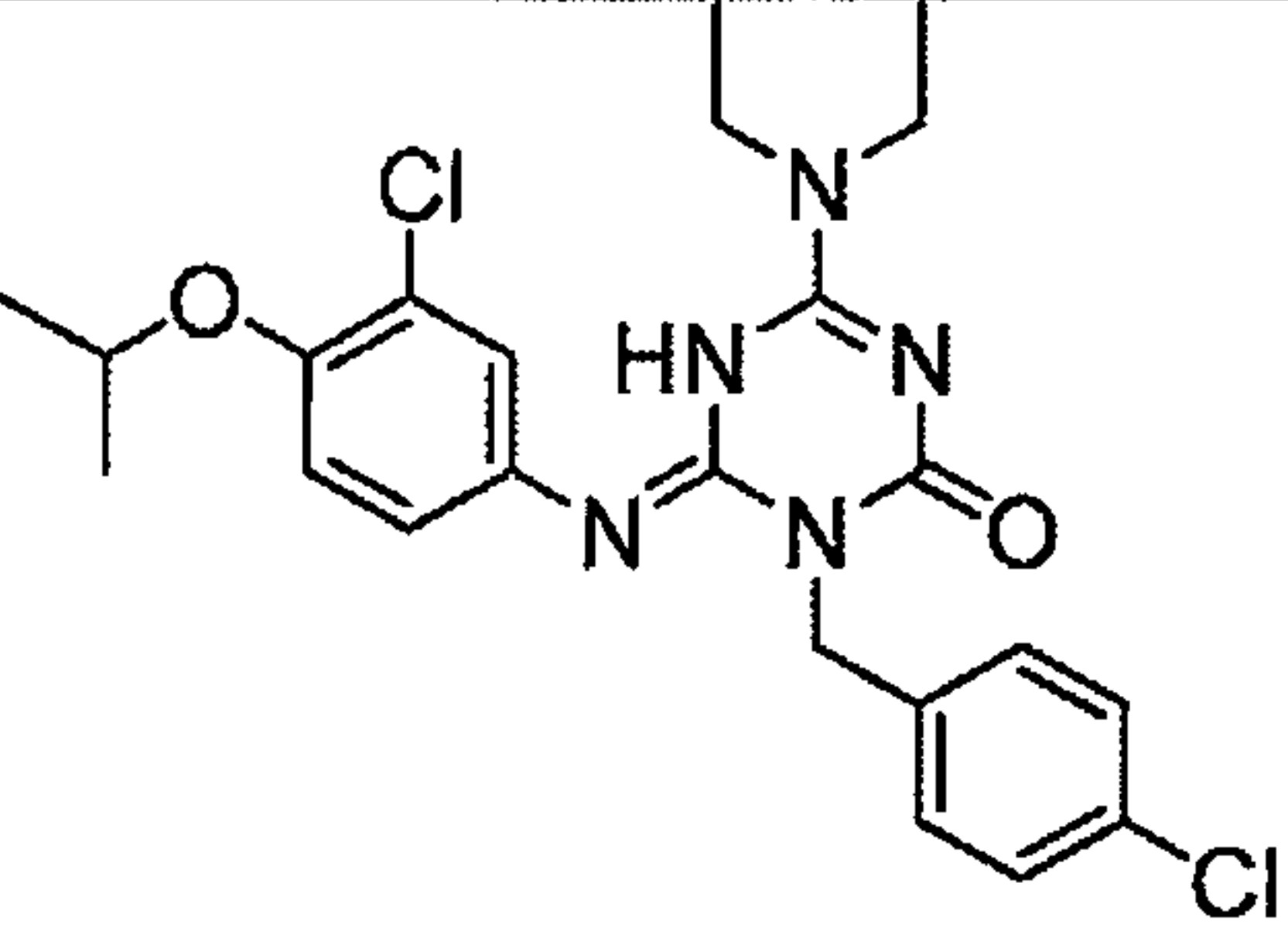
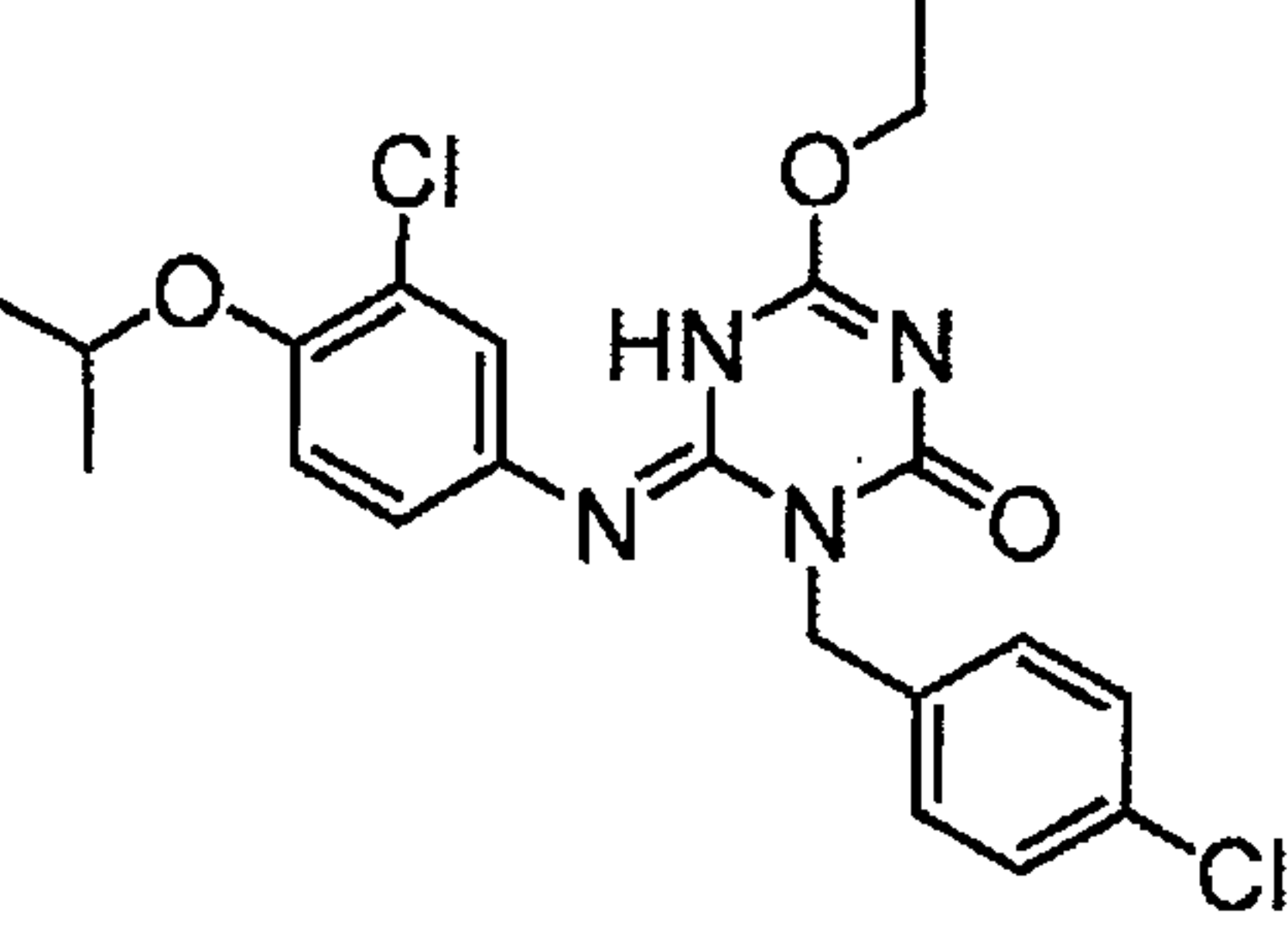
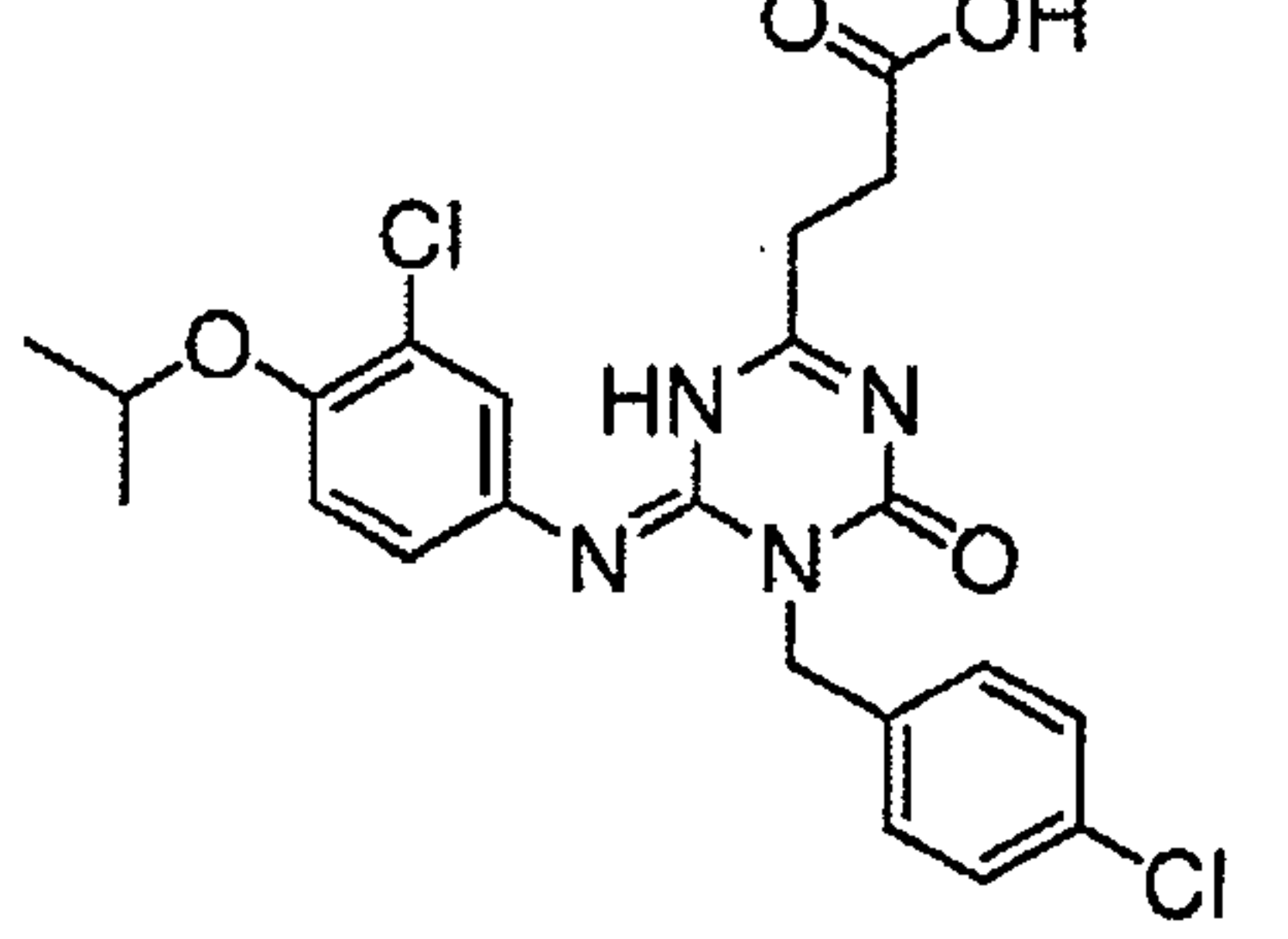
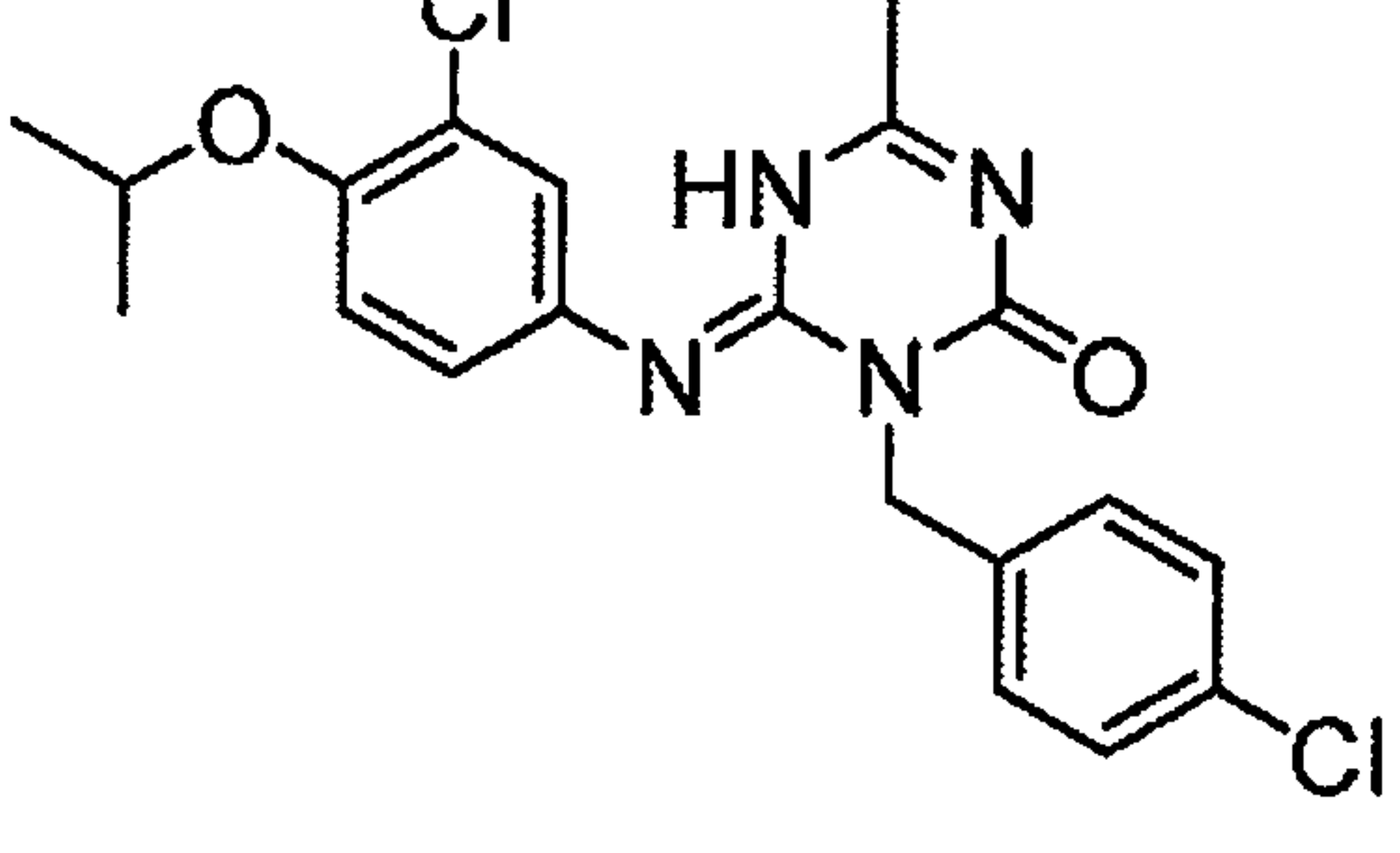
[Table 117]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0566	2.37	501	2
	I-0567	2.16	483	2
	I-0568	2.09	459	2
	I-0569	2.34	505	2
	I-0570	2.18	507	2

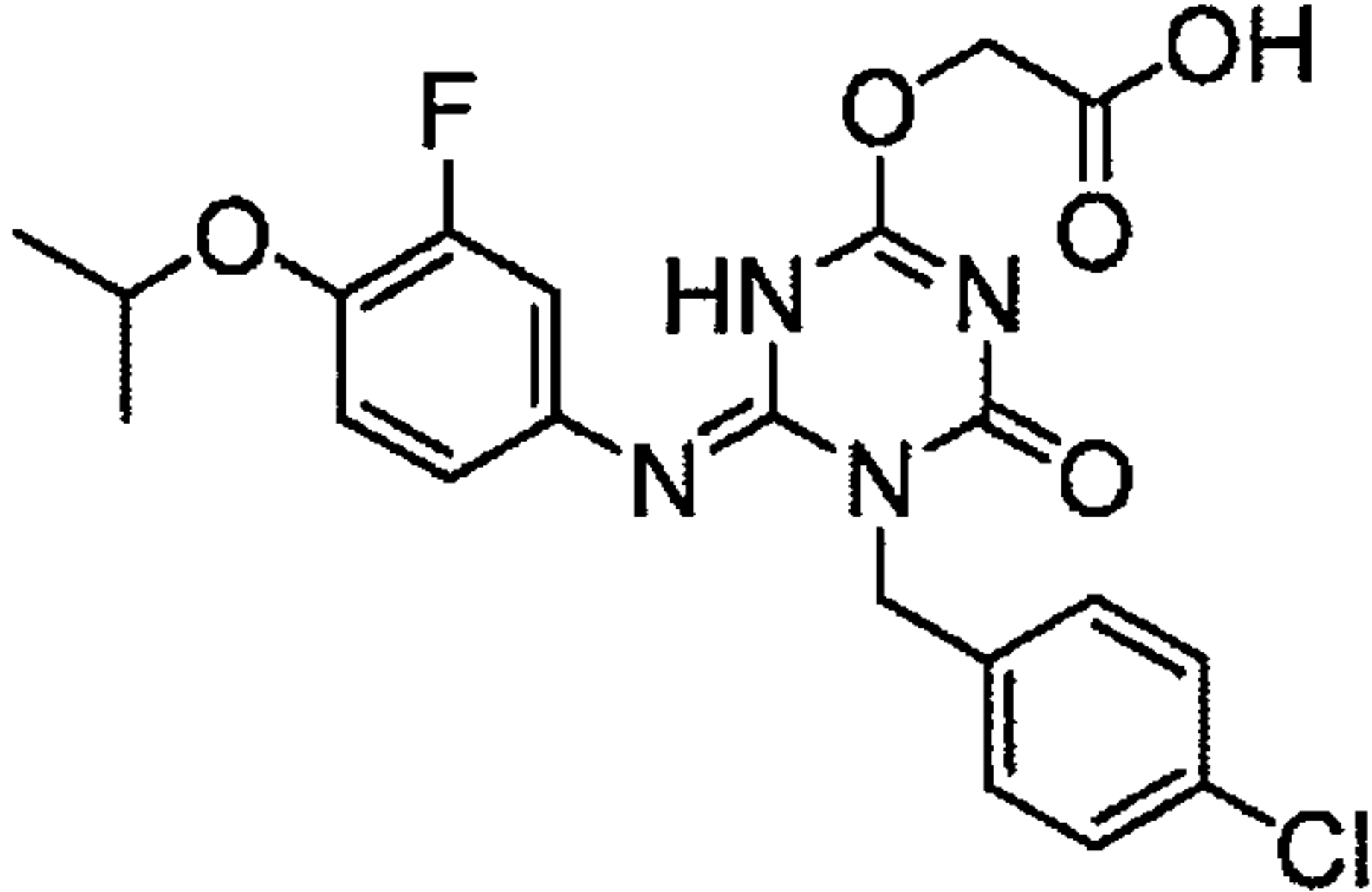
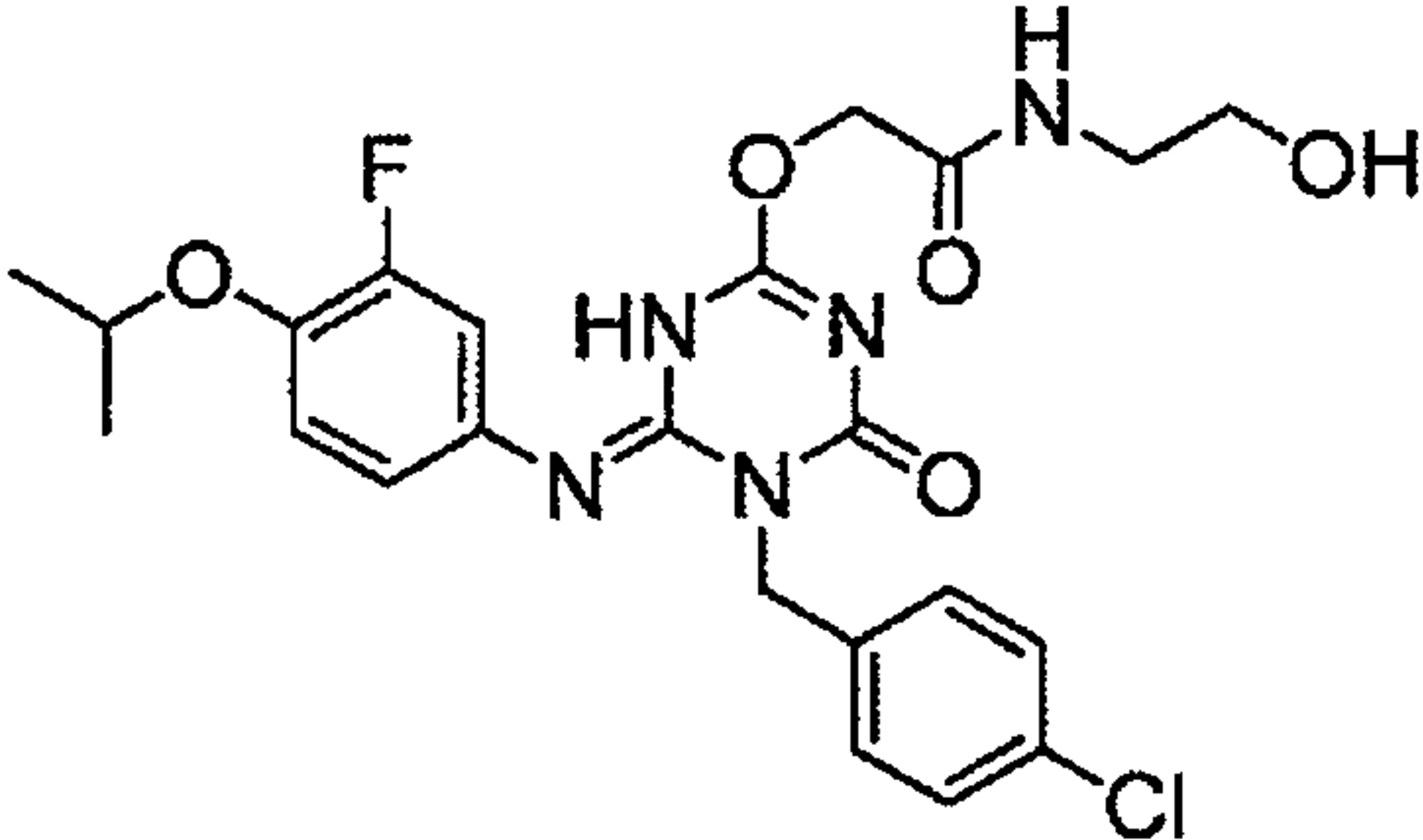
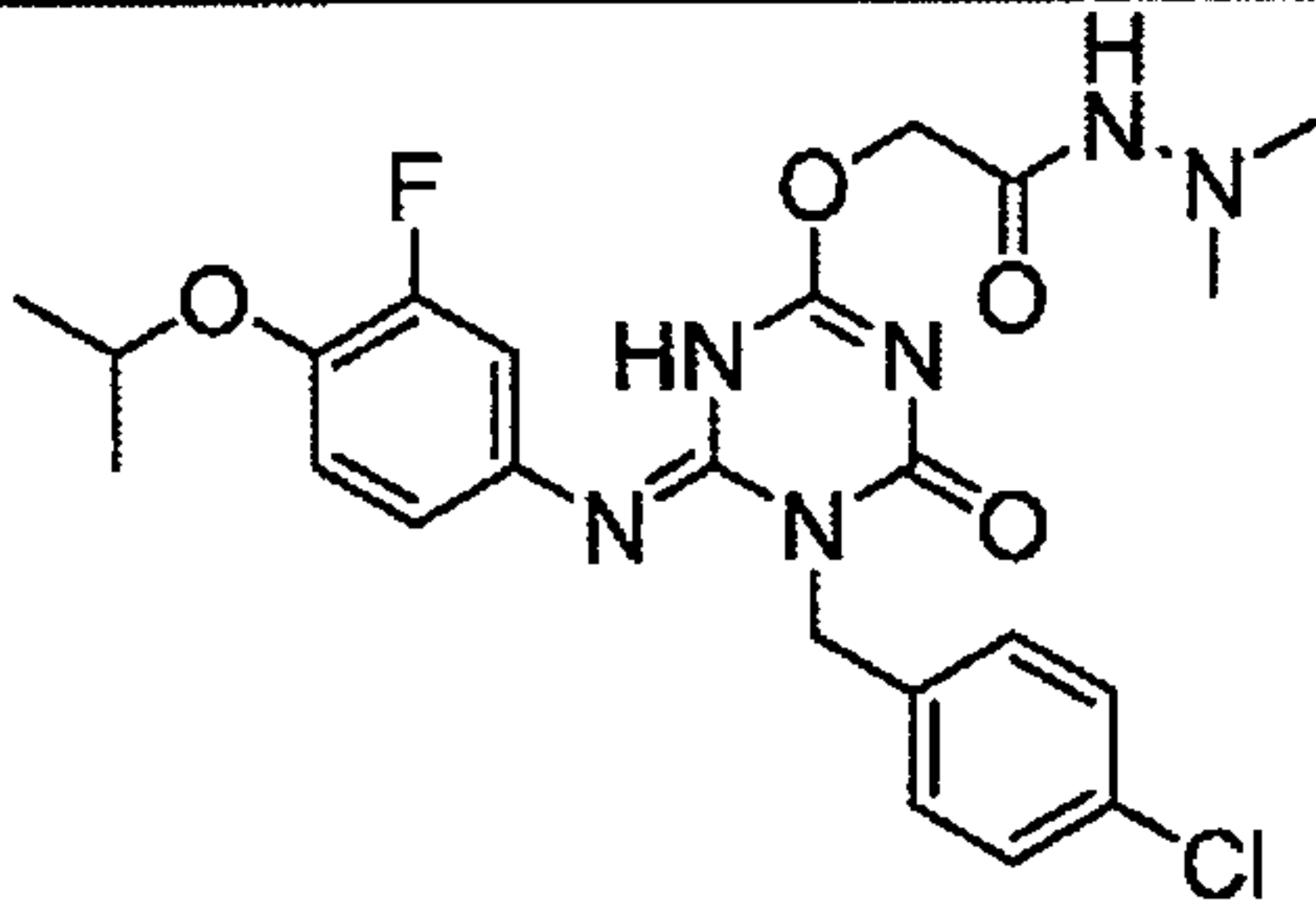
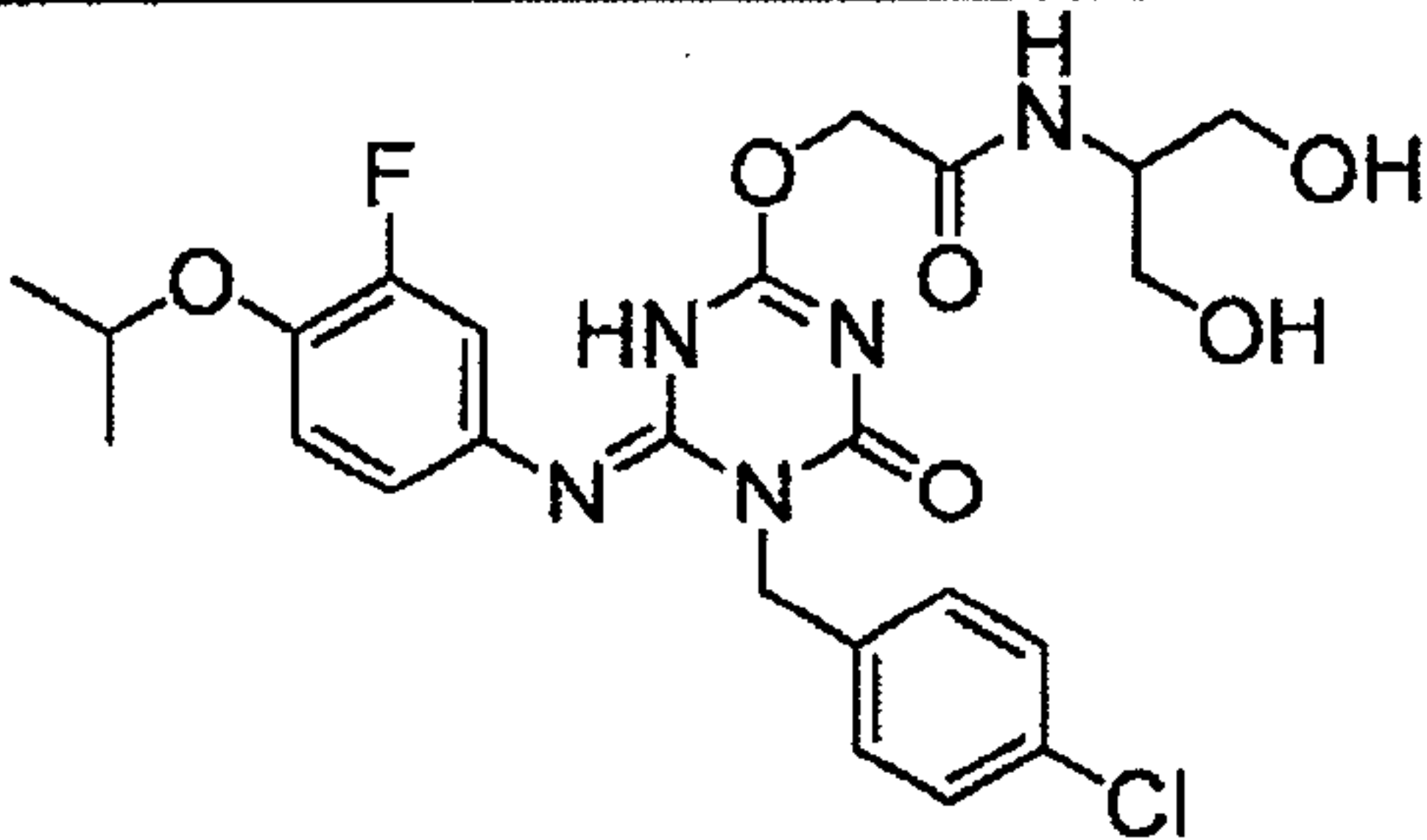
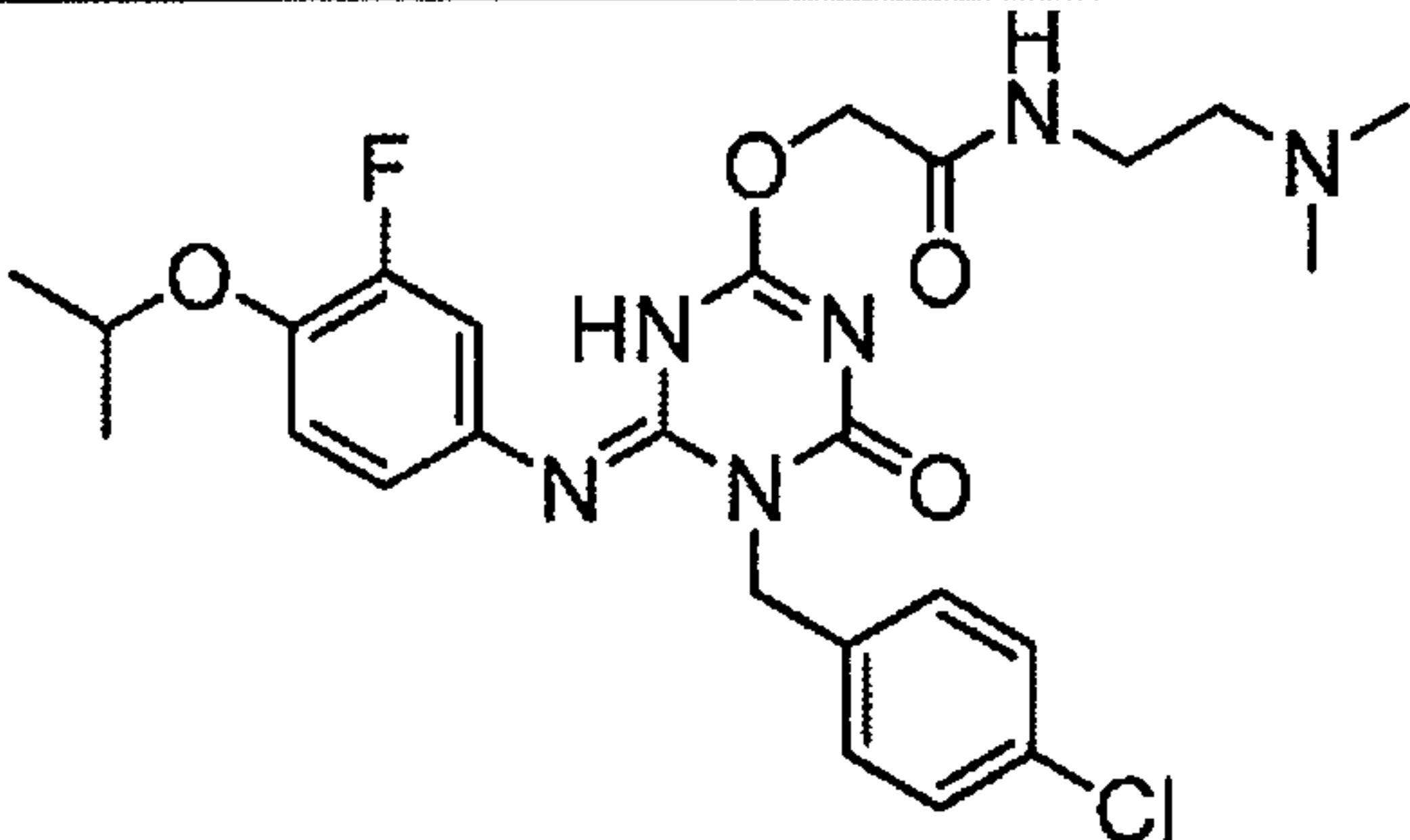
[Table 118]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0571	2.28	491	3
	I-0572	2.32	487	3
	I-0573	2.11	469	3
	I-0574	2.41	477	3
	I-0575	1.74	478	2

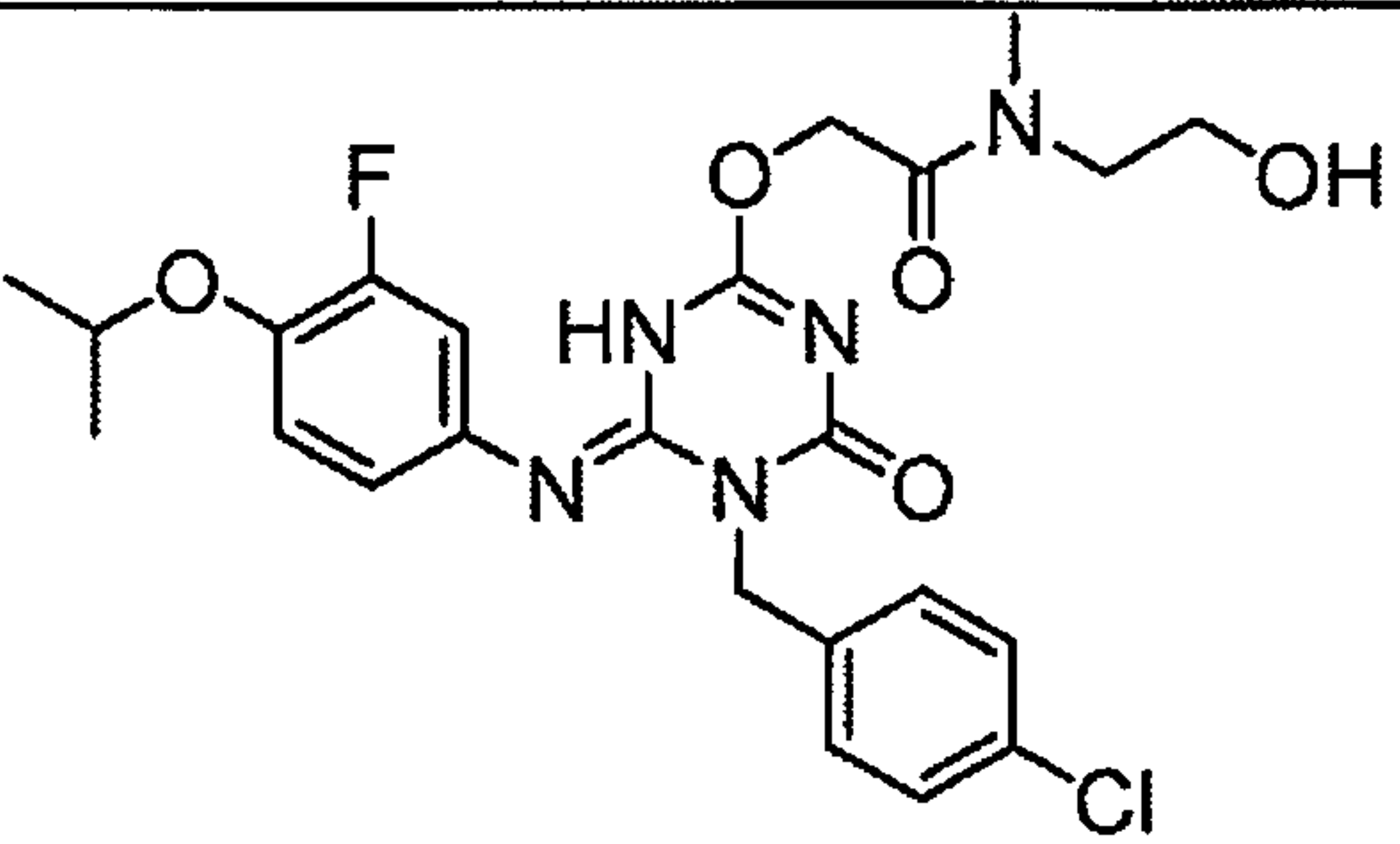
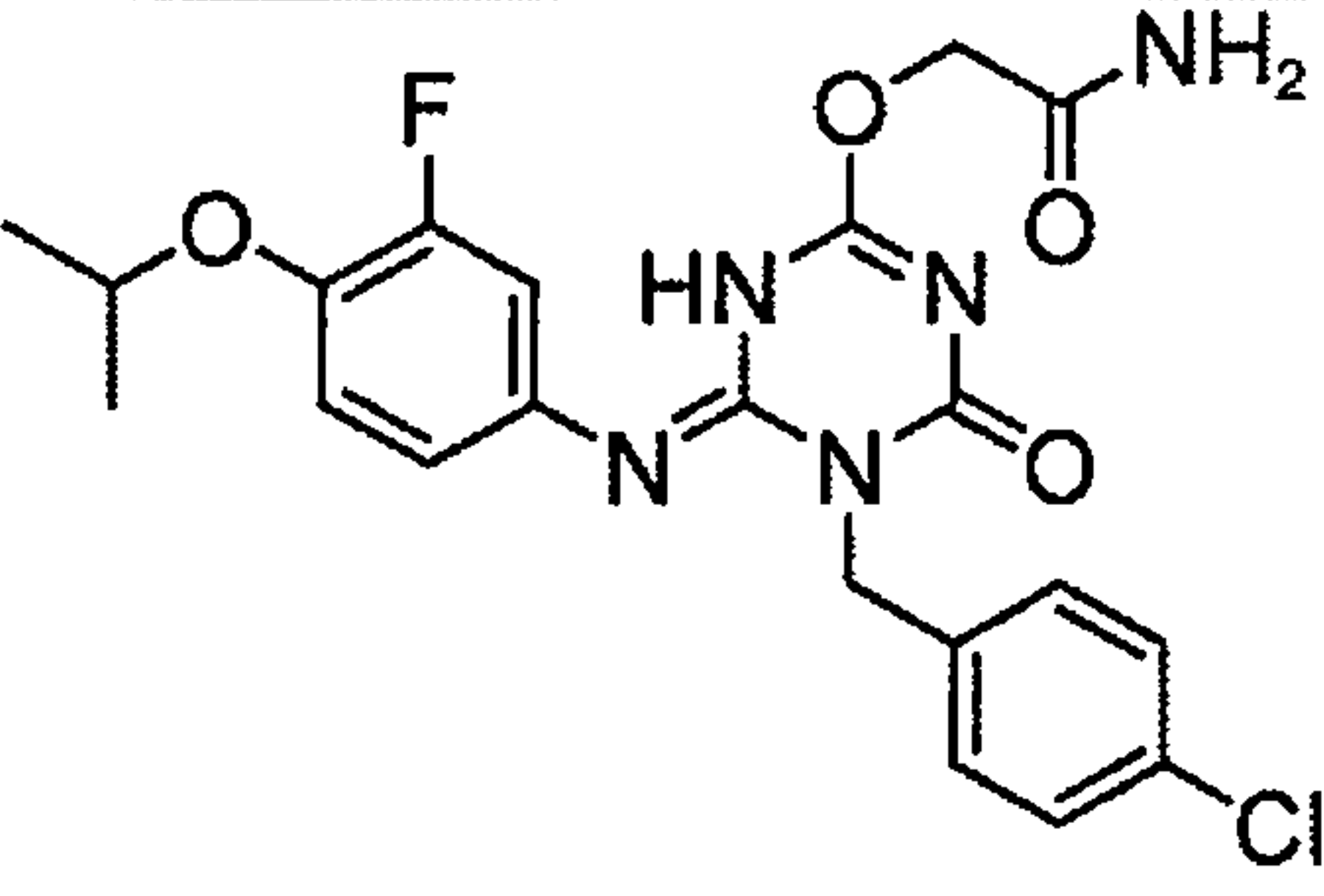
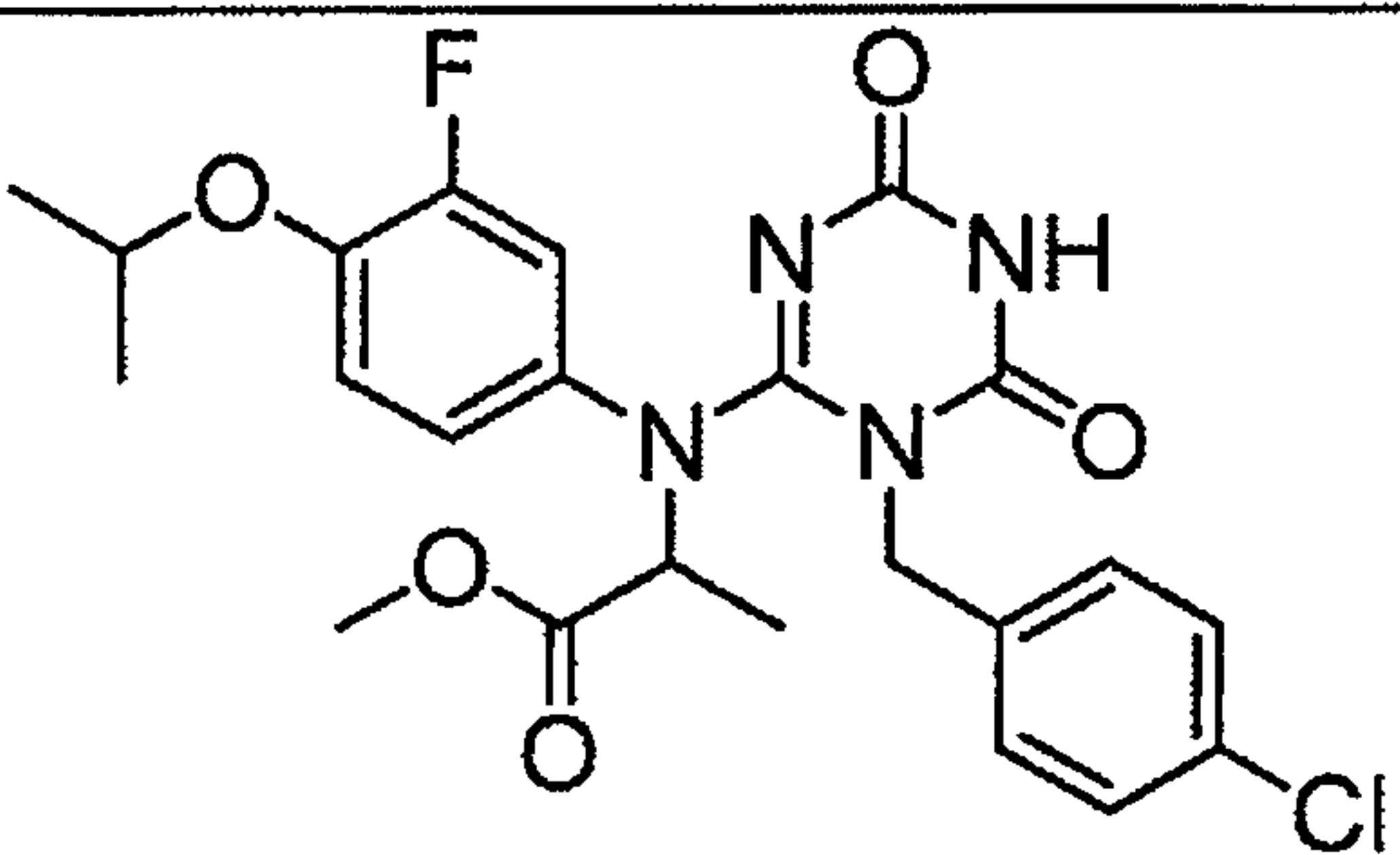
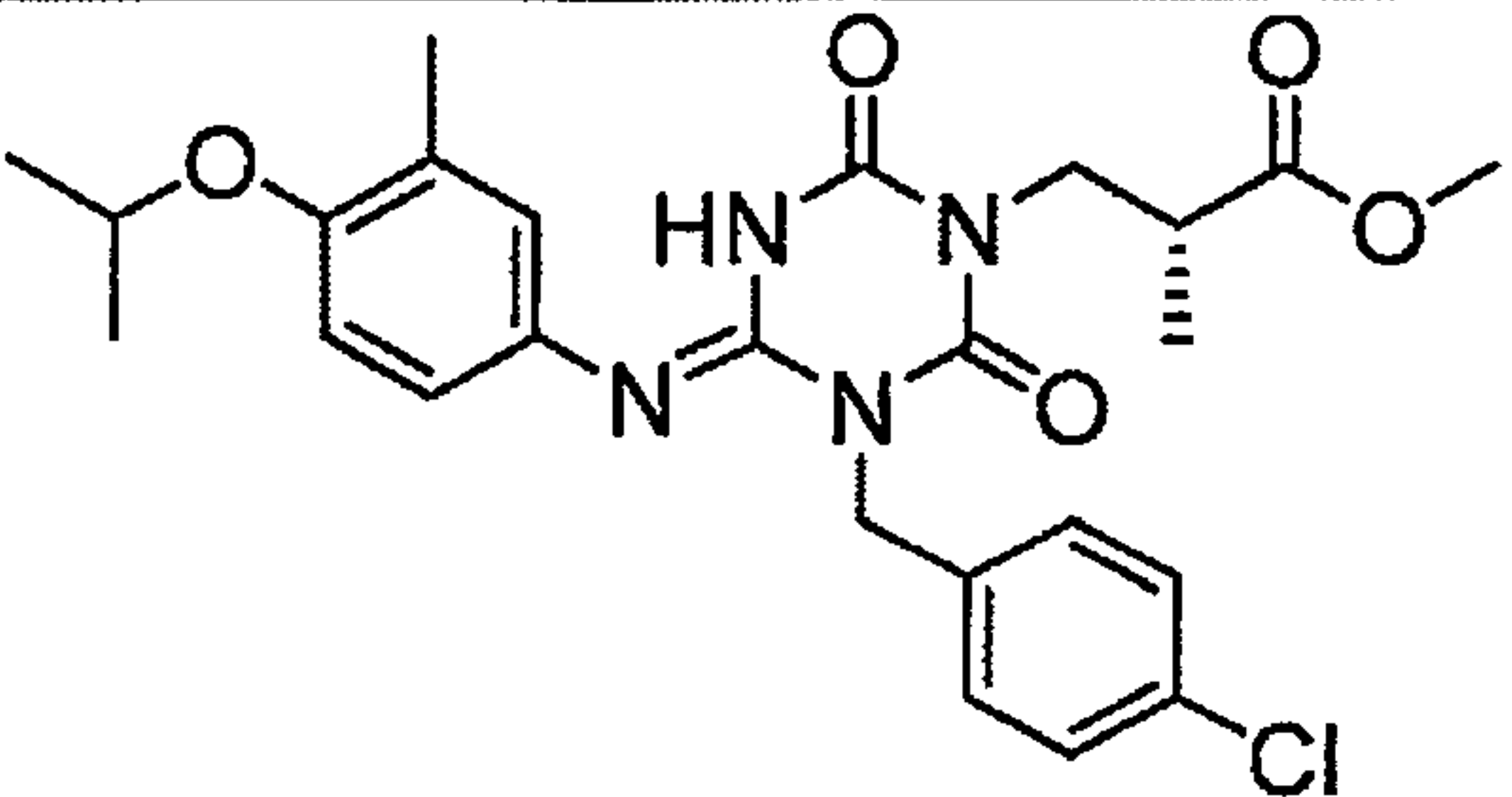
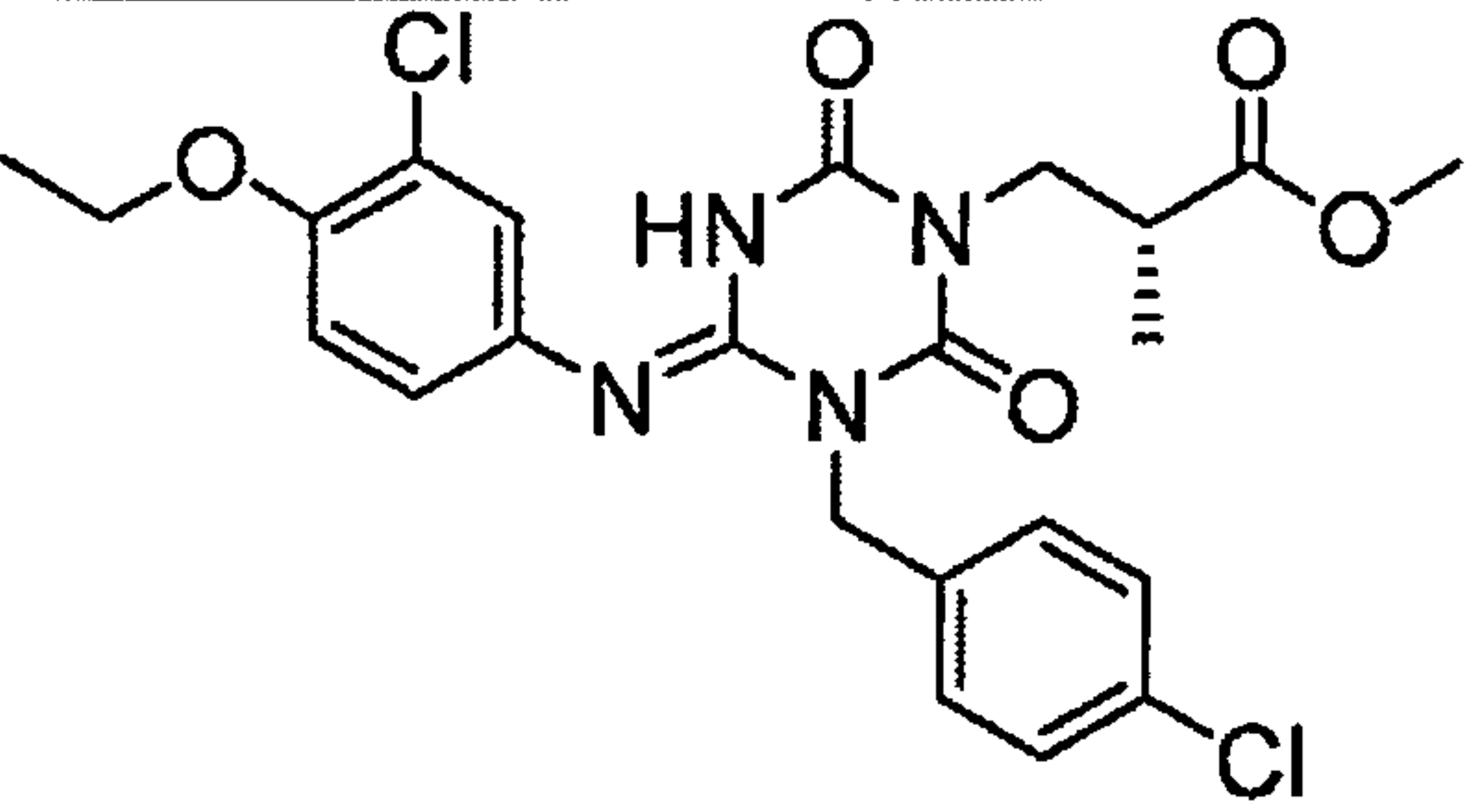
[Table 119]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0576	2.44	488	2
	I-0577	2.04	476	2
	I-0578	2.21	449	2
	I-0579	2.07	477	2
	I-0580	2.28	419	2

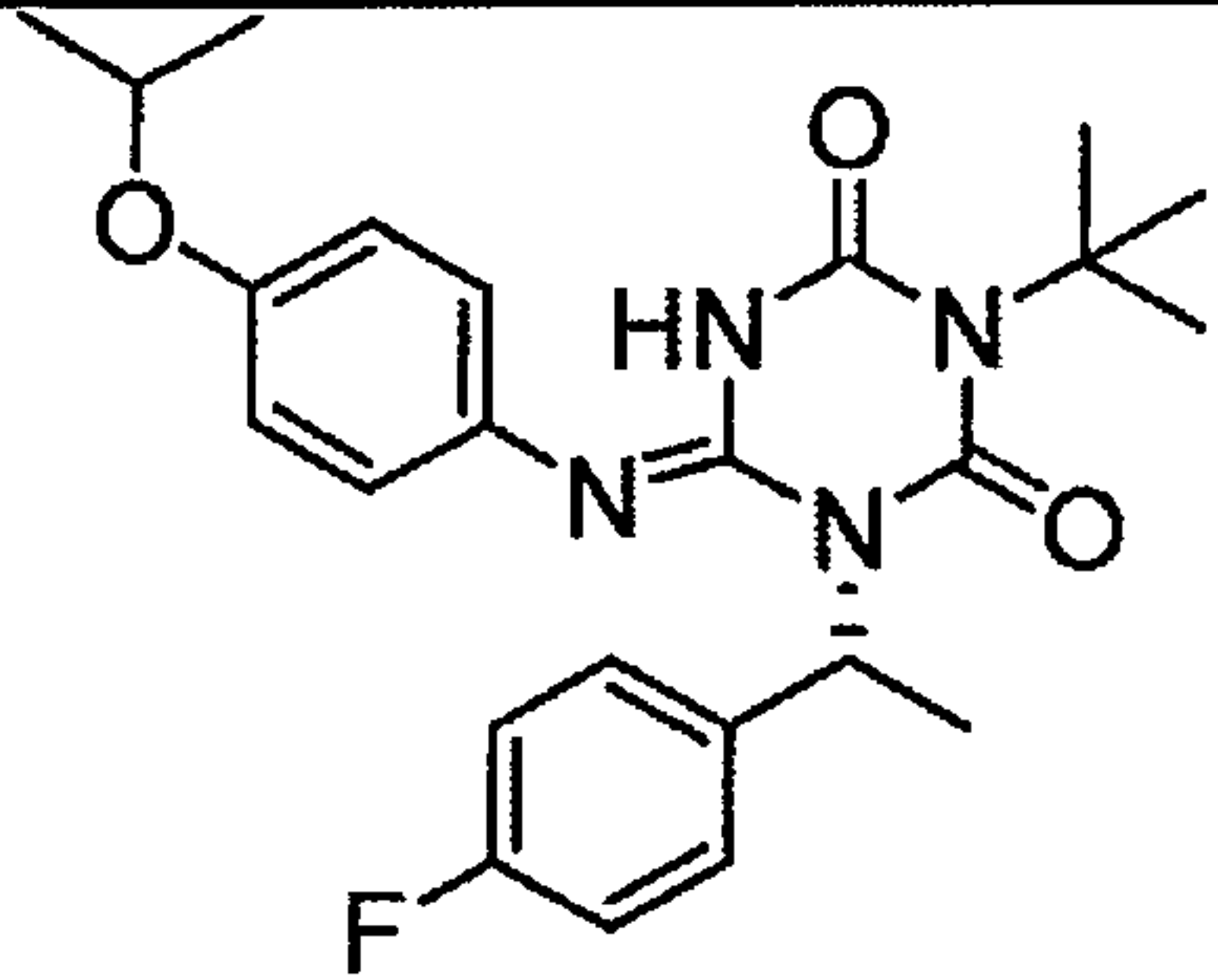
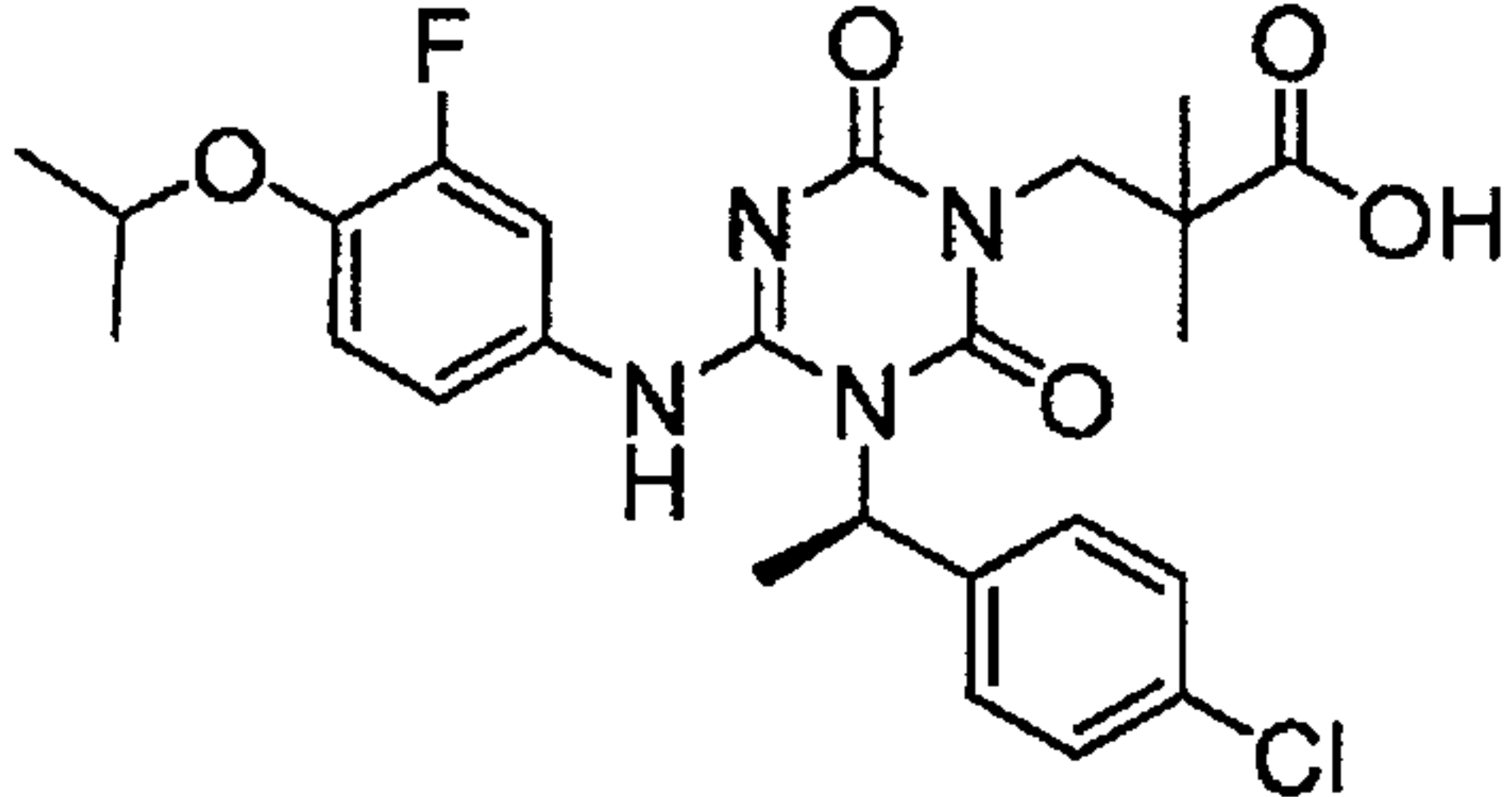
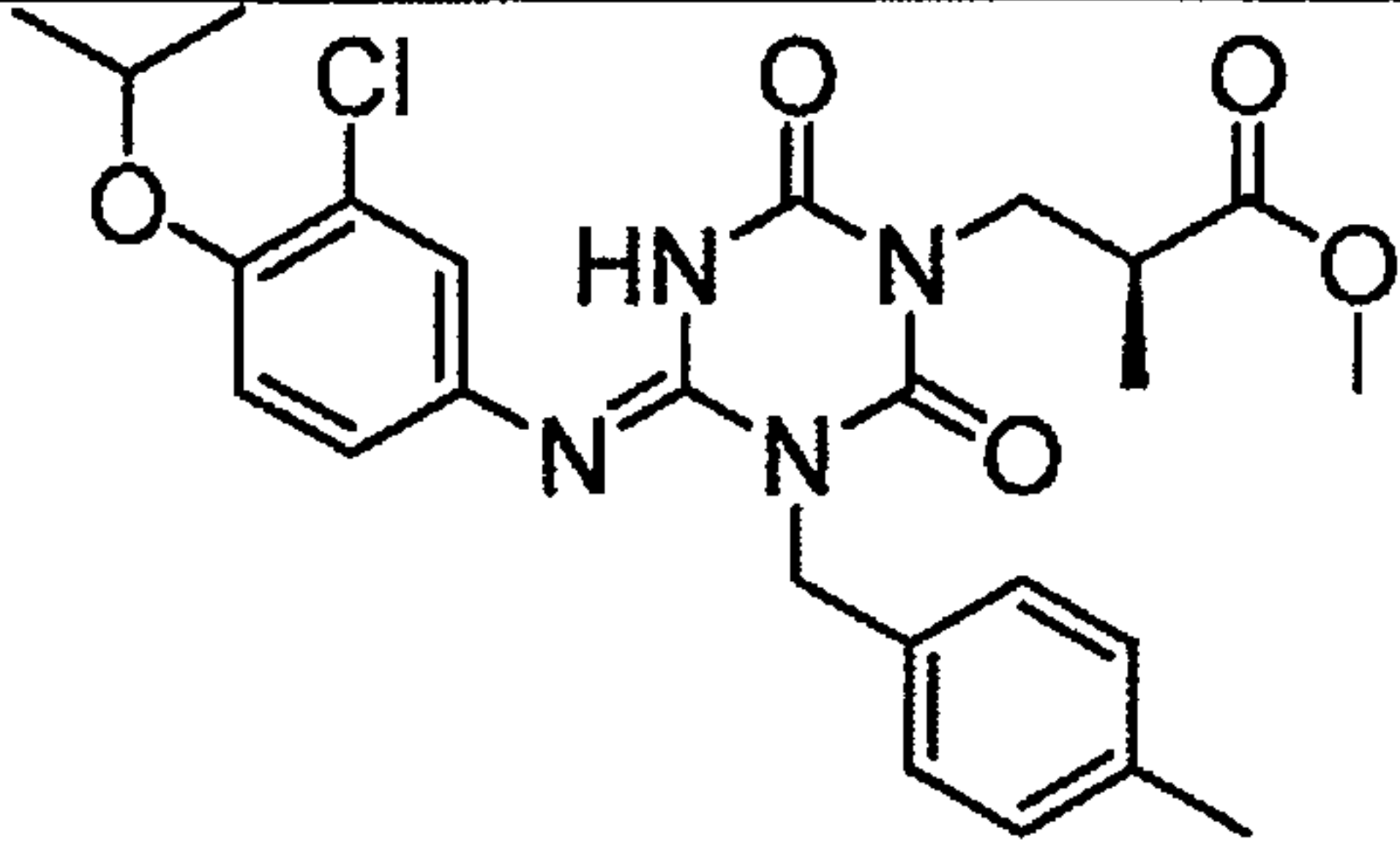
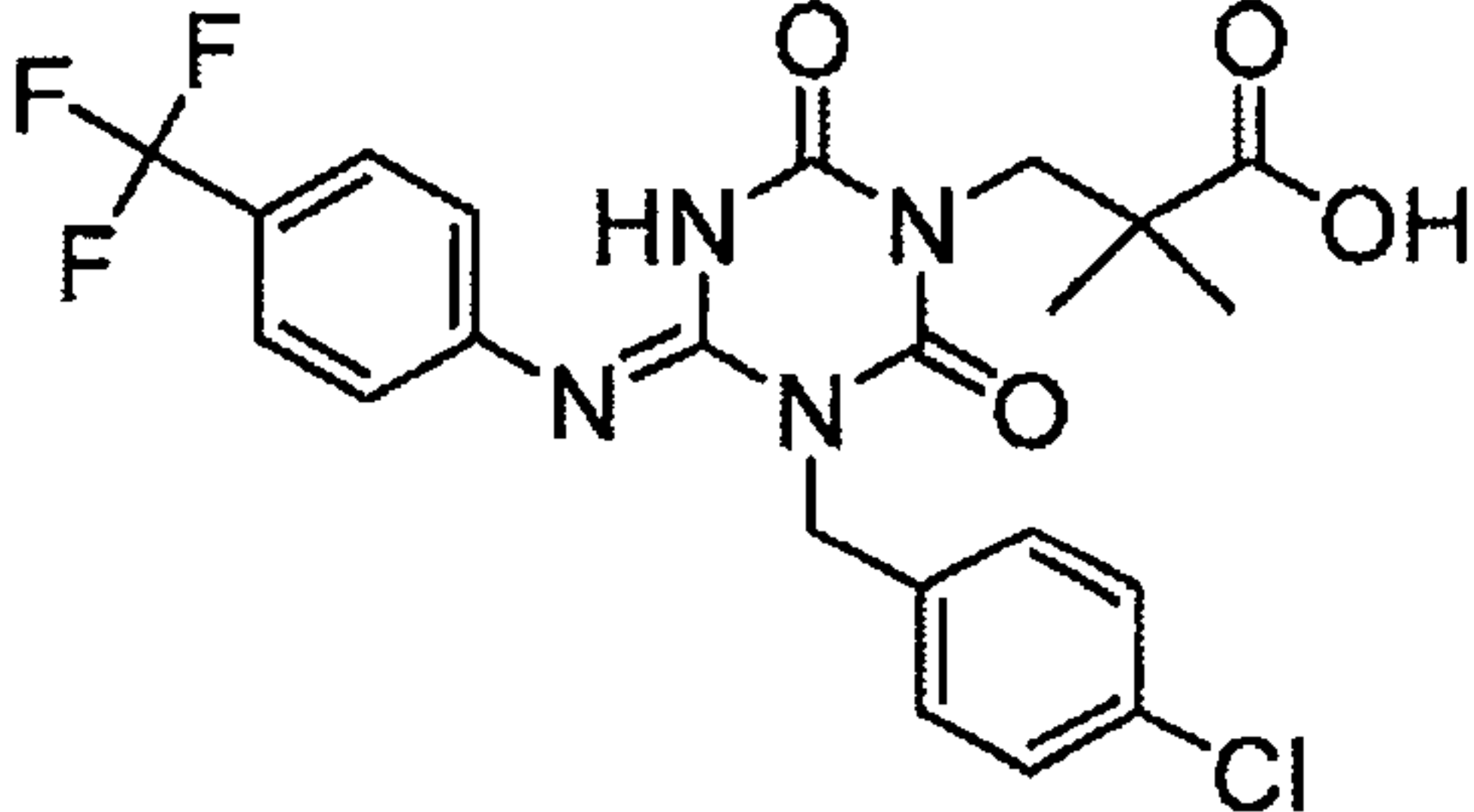
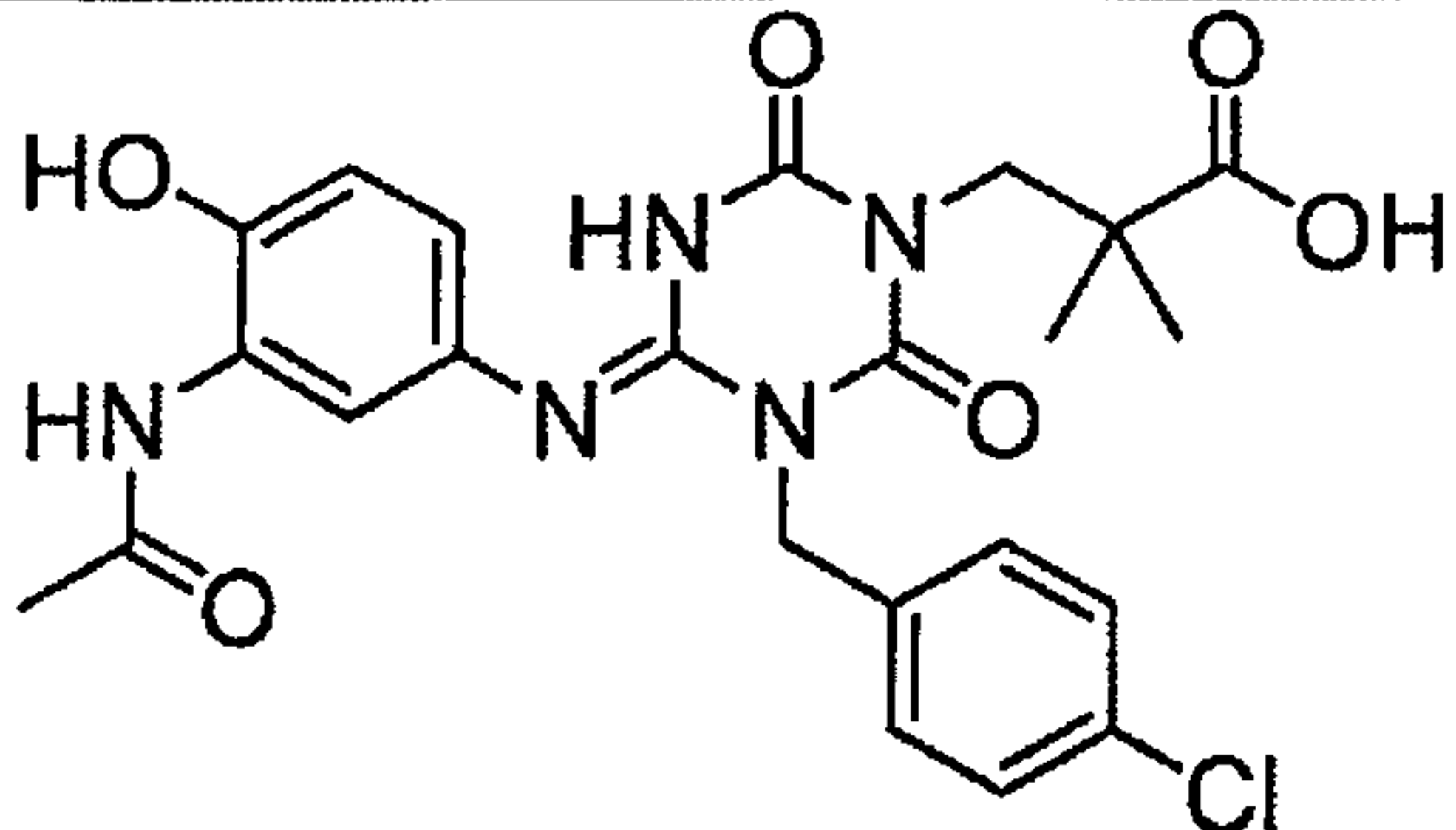
[Table 120]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0581	1.78	463	2
	I-0582	1.62	506	2
	I-0583	1.72	505	2
	I-0584	1.56	536	2
	I-0585	1.40	533	2

[Table 121]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0586	1.65	520	2
	I-0587	1.66	462	2
	I-0588	2.24	491	3
	I-0589	2.53	501	3
	I-0590	2.50	507	3

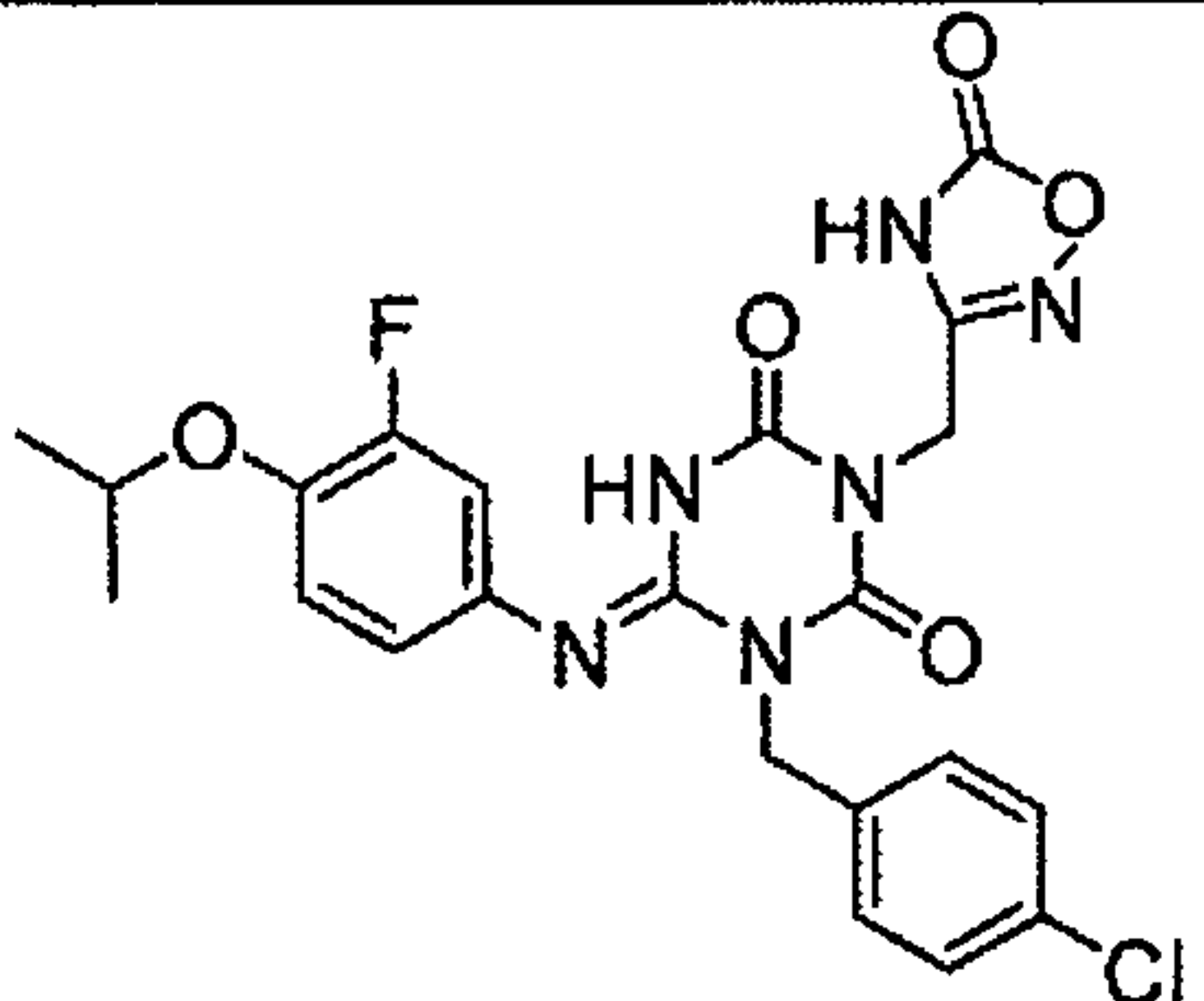
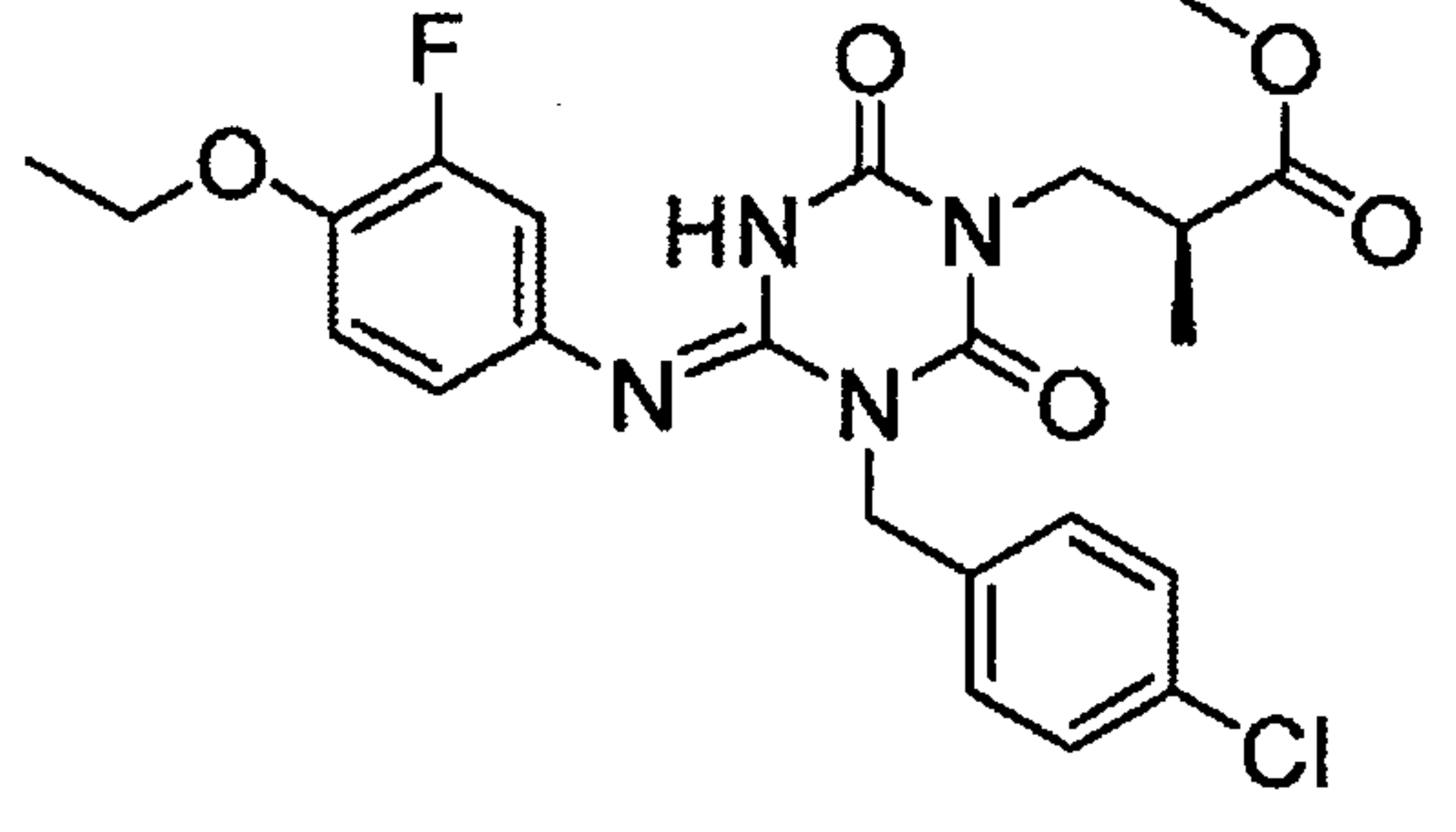
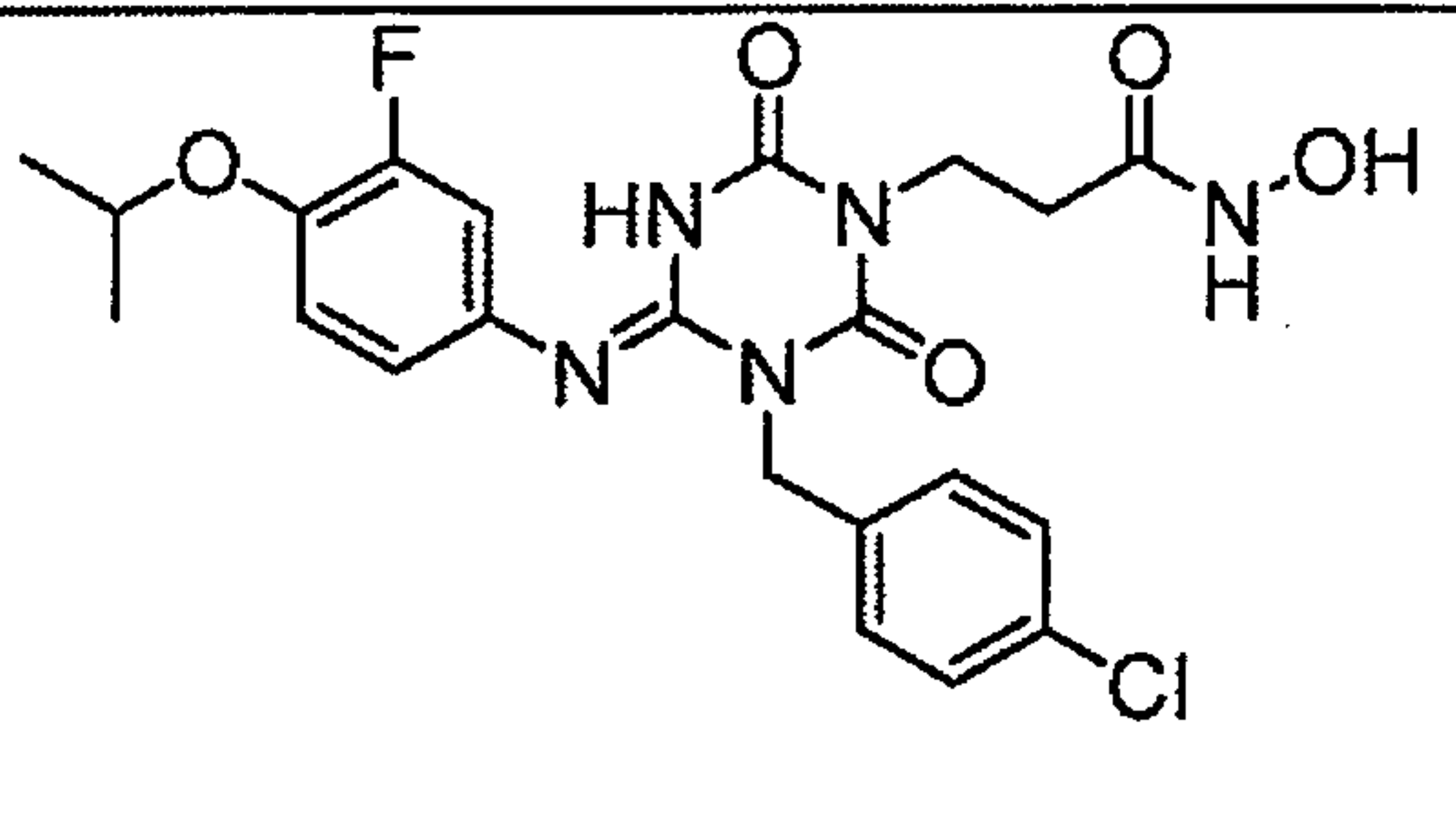
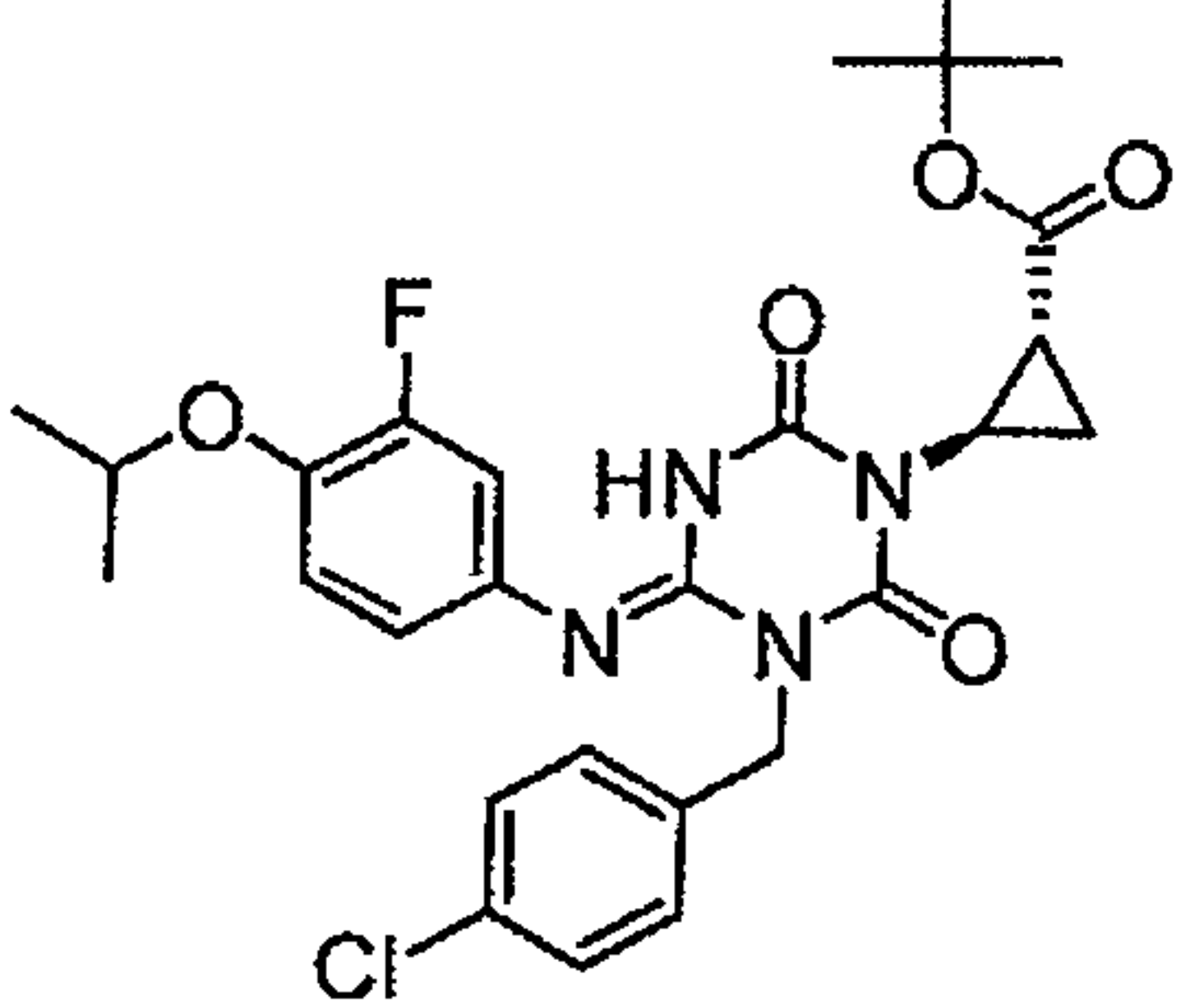
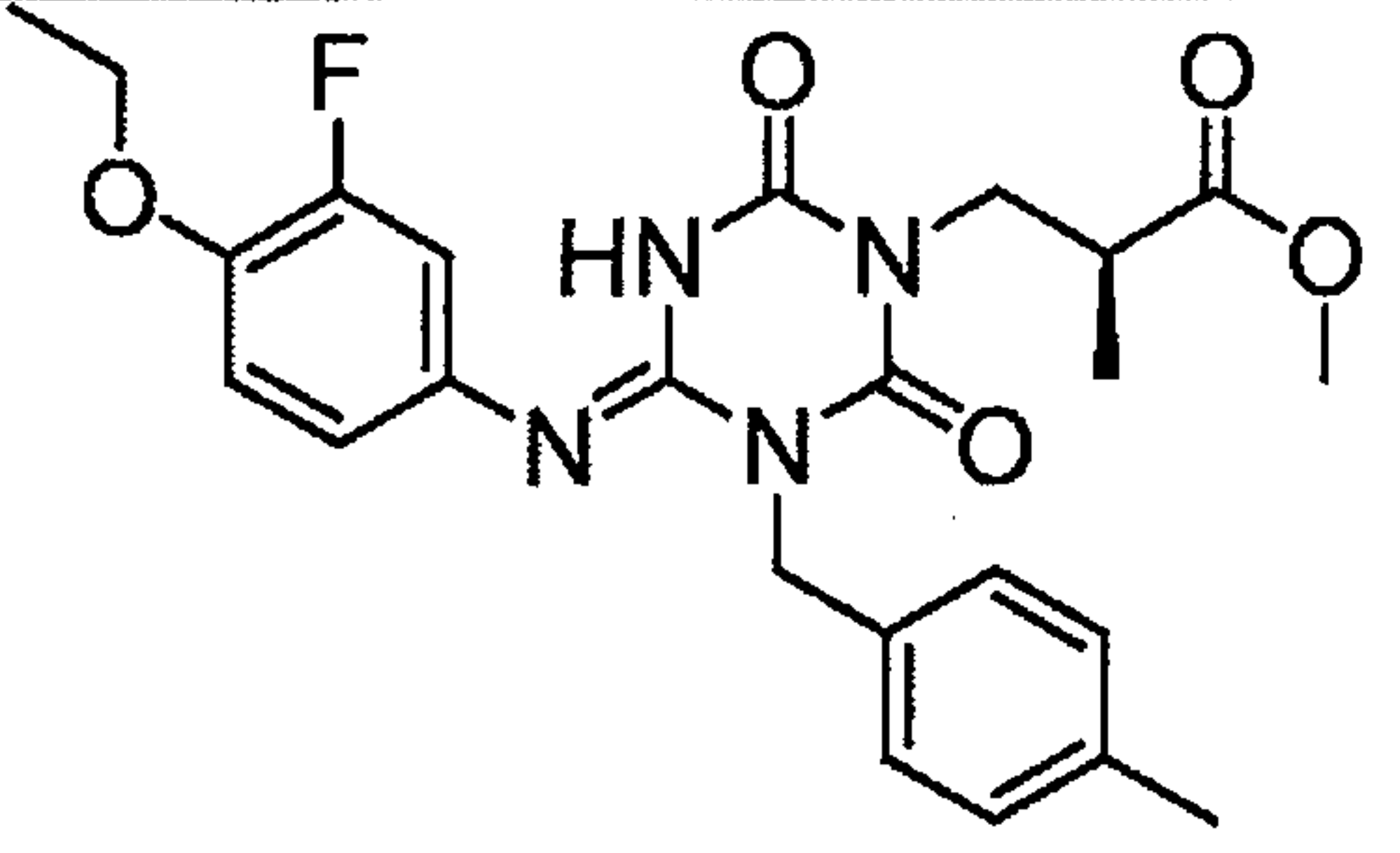
[Table 122]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0591	2.67	441	3
	I-0592	2.50	519	3
	I-0593	2.56	501	3
	I-0594	2.40	497	2
	I-0595	1.49	502	3

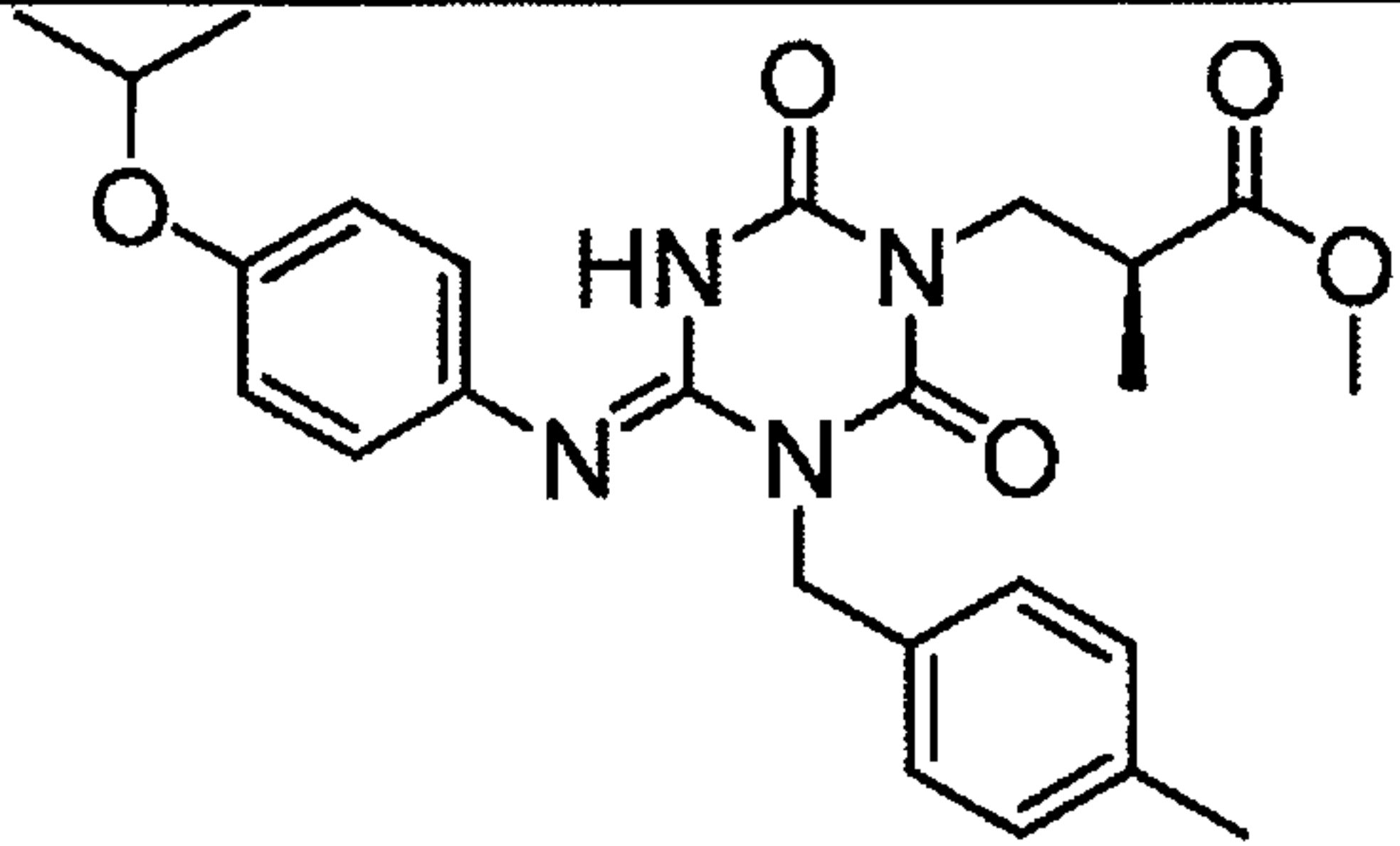
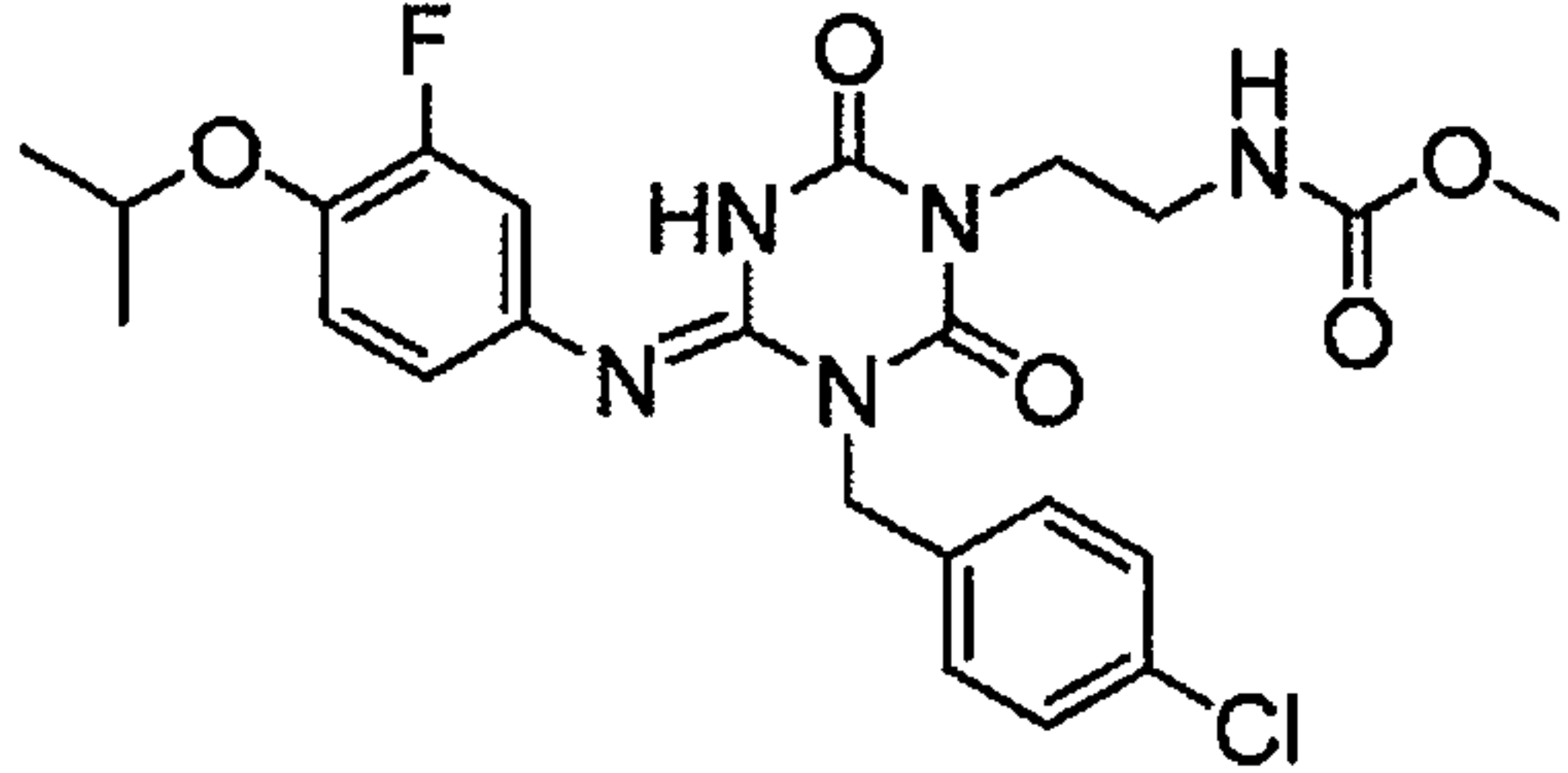
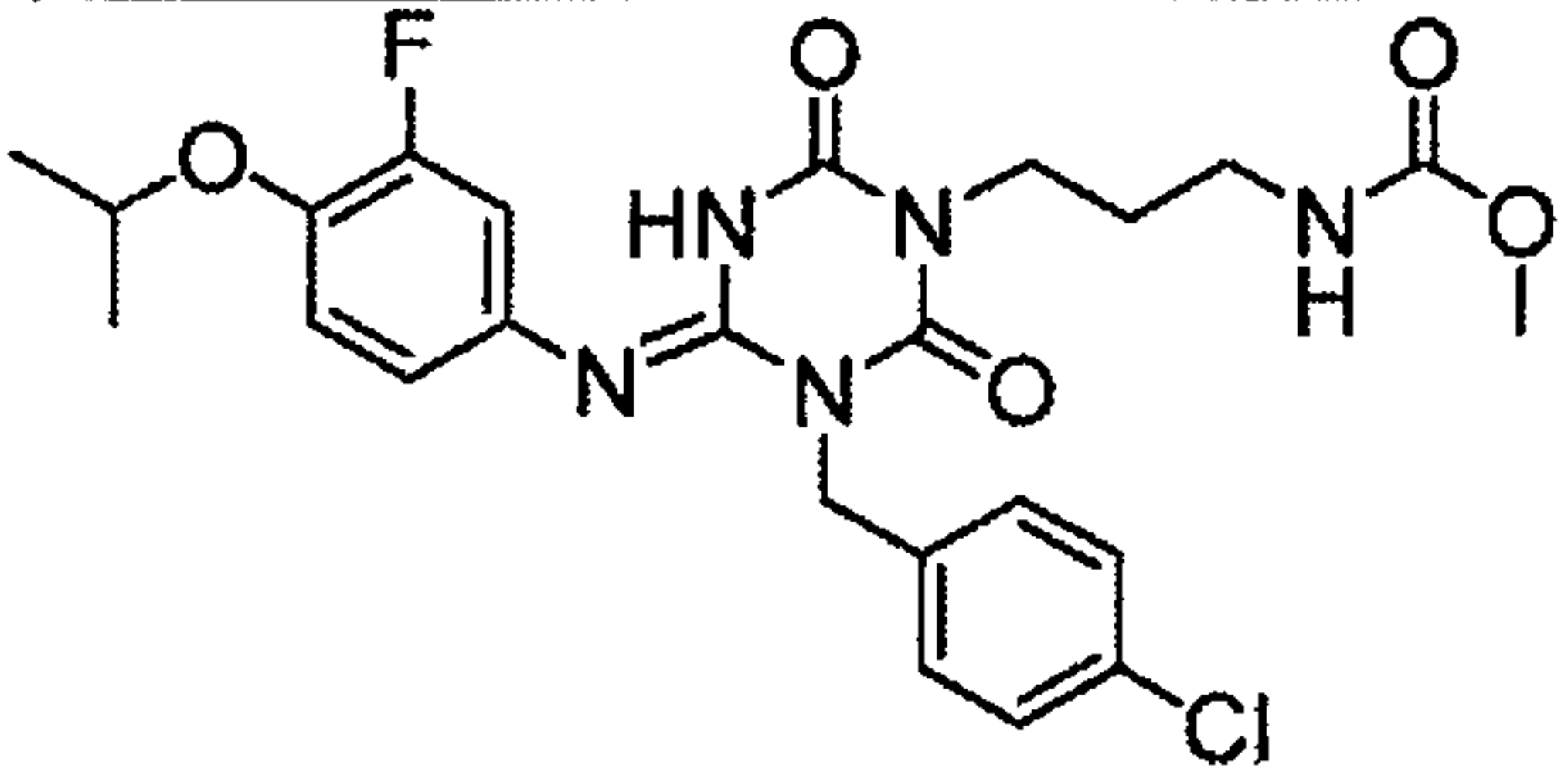
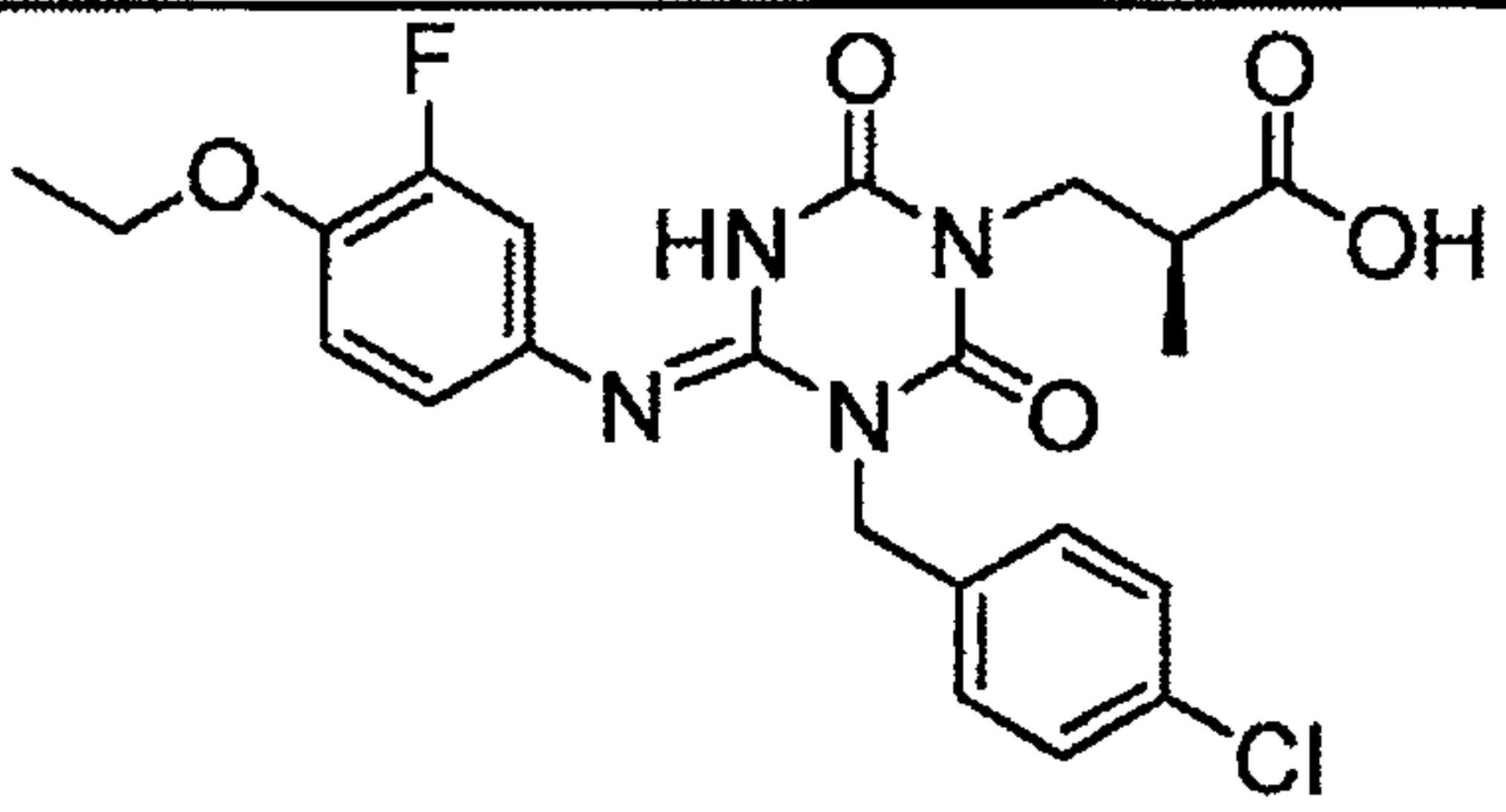
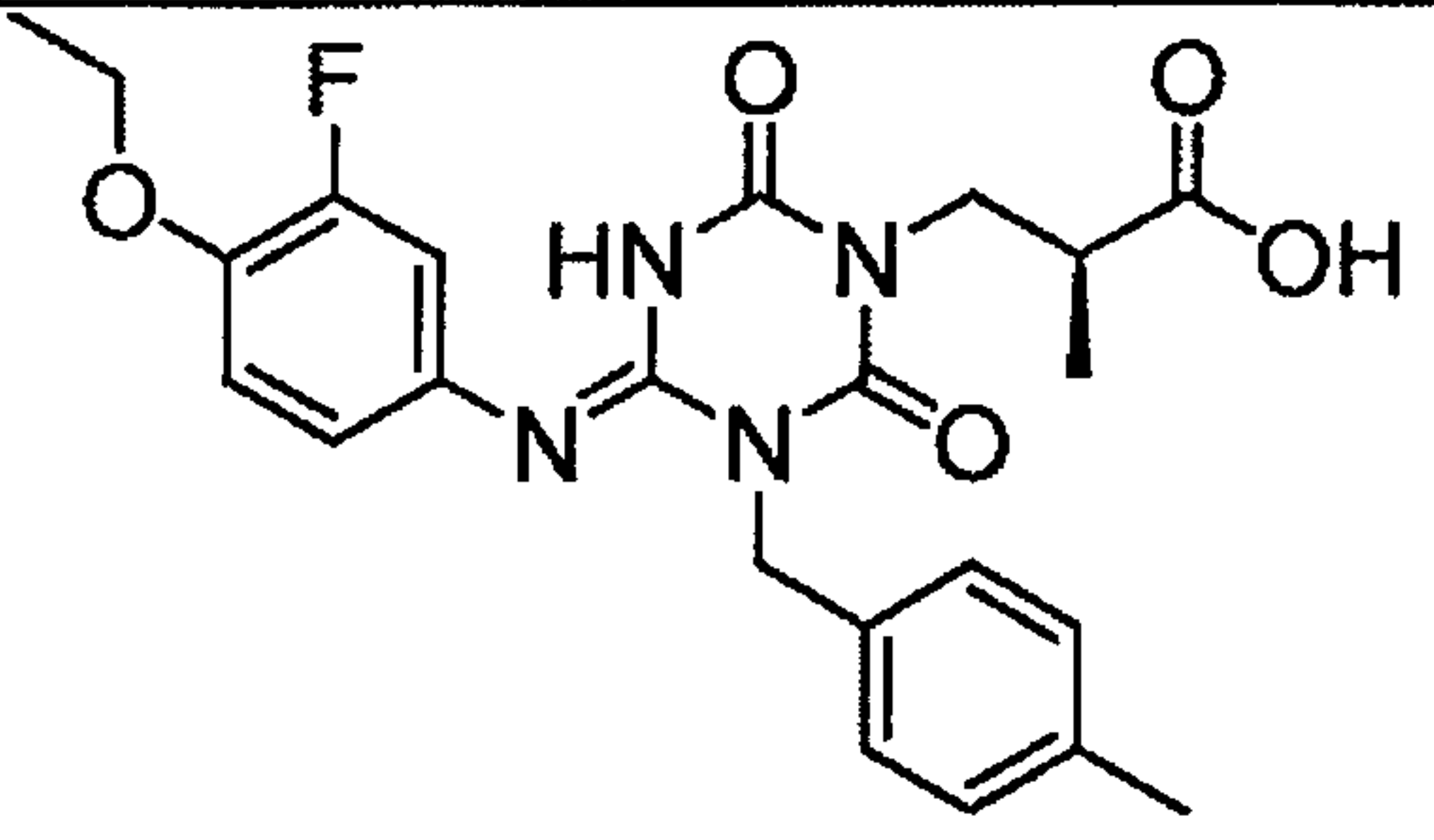
[Table 123]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0596	2.08	501	3
	I-0597	2.19	510	2
	I-0598	1.93	496	2
	I-0599	1.69	477	3
	I-0600	1.67	507	3

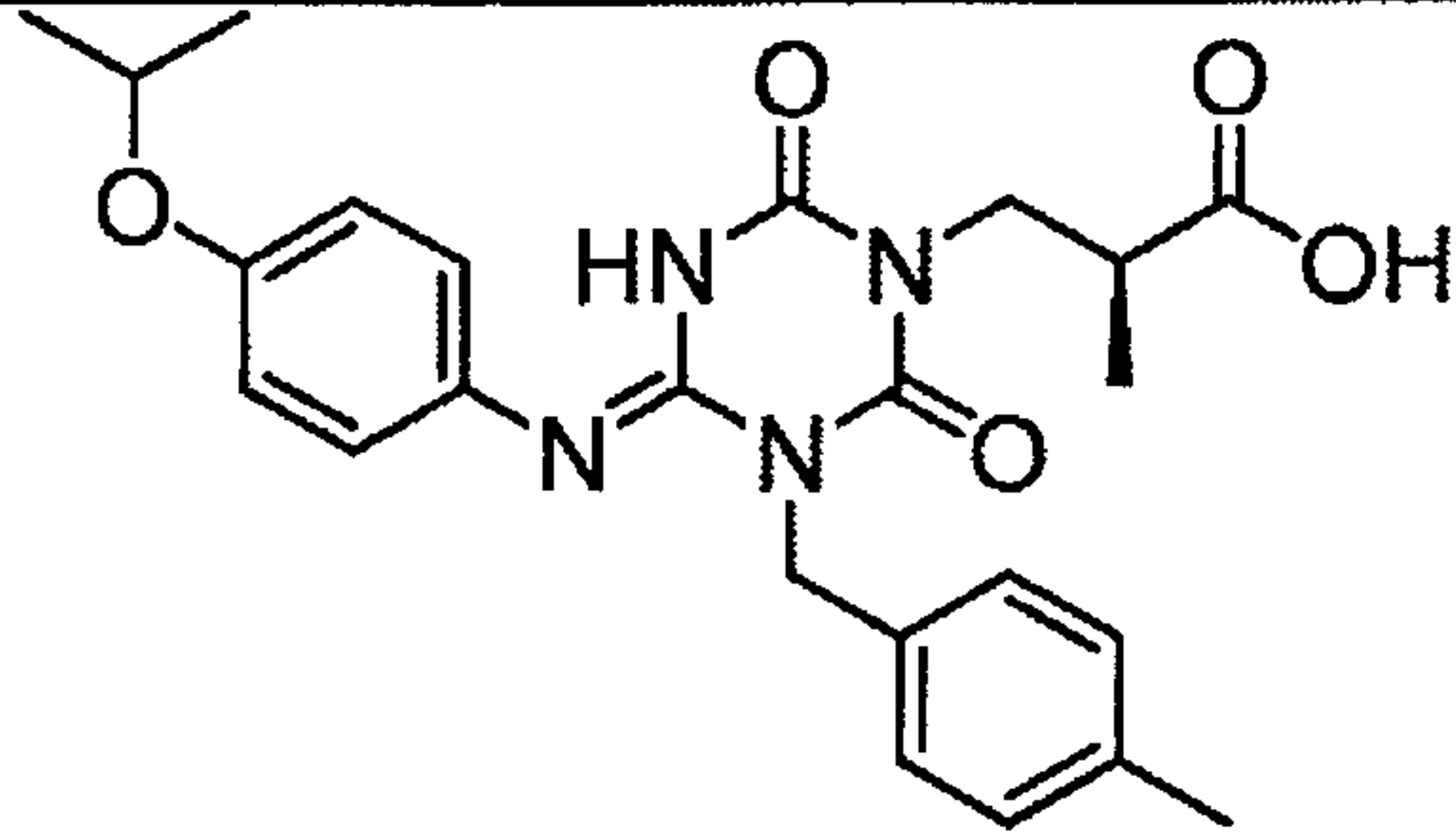
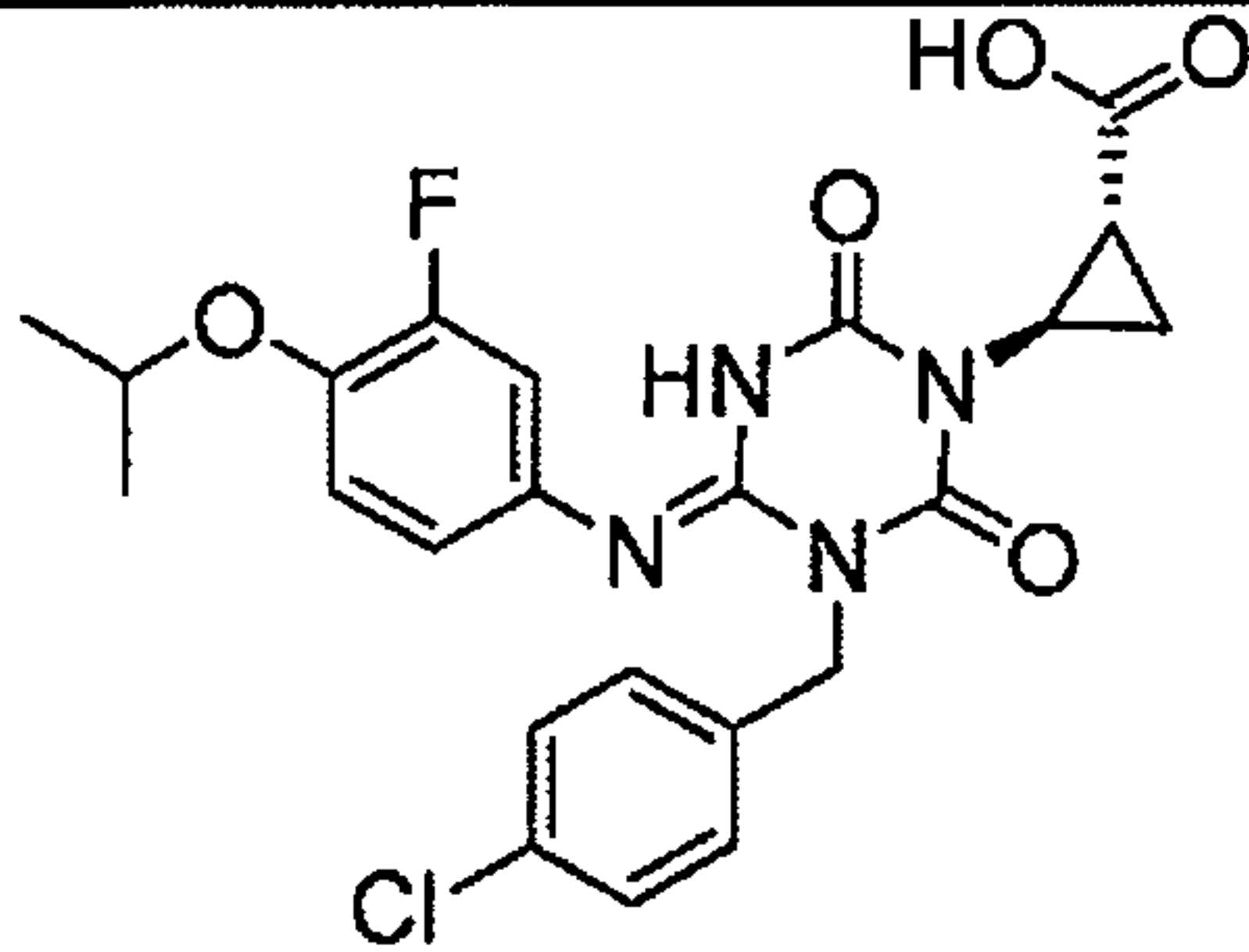
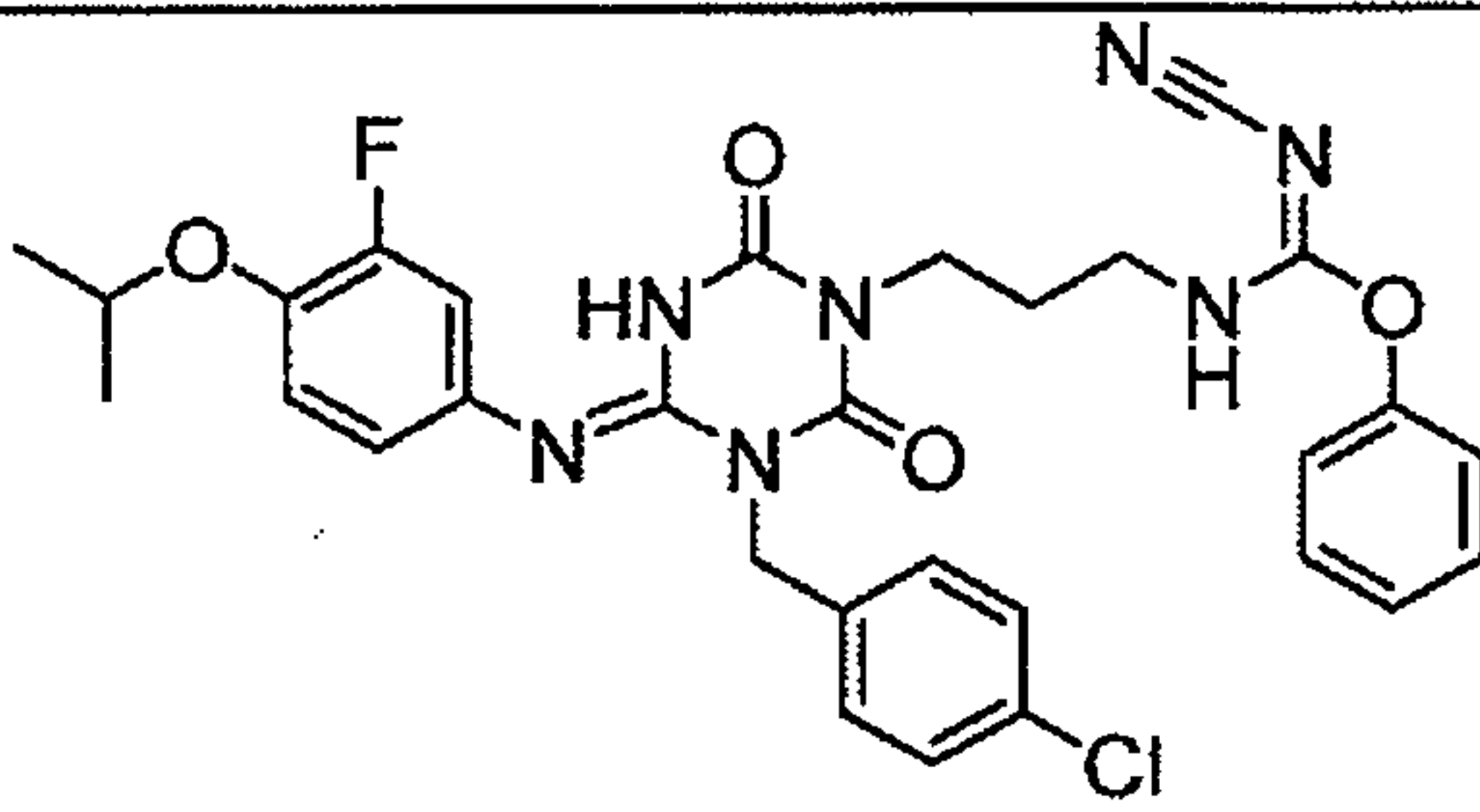
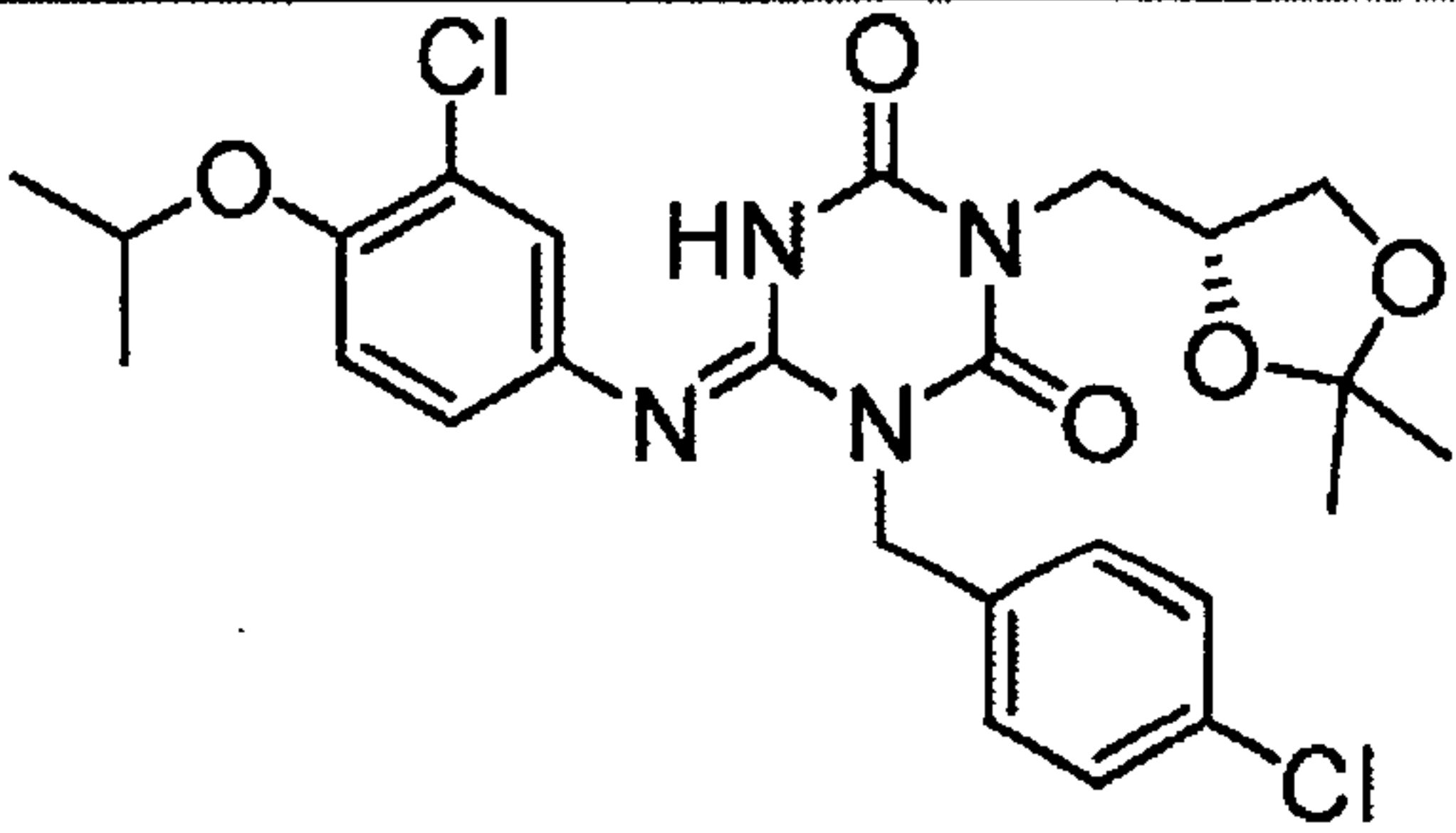
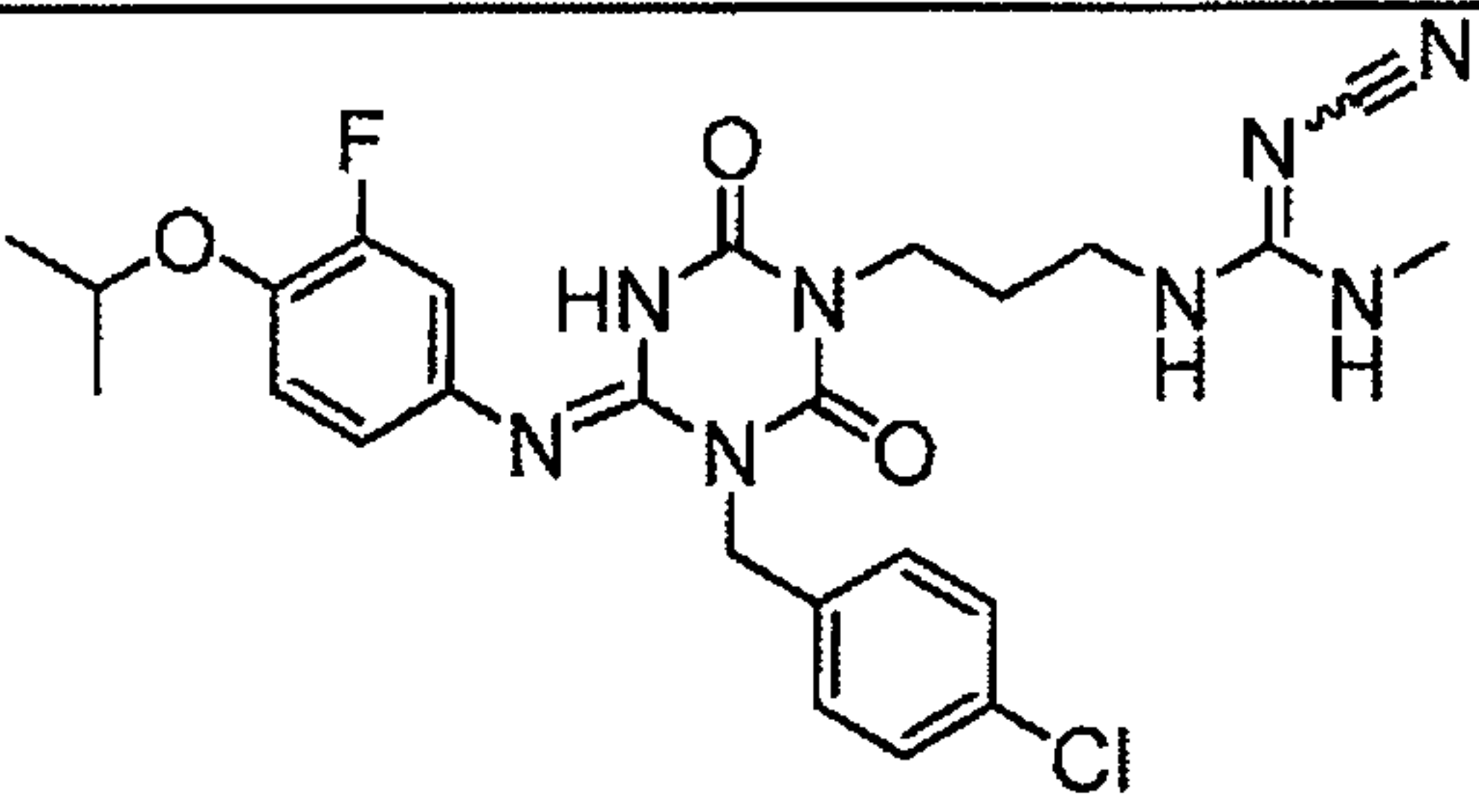
[Table 124]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0601	2.14	503	3
	I-0602	2.17	491	2
	I-0603	1.74	492	2
	I-0604	2.73	545	3
	I-0605	2.32	471	3

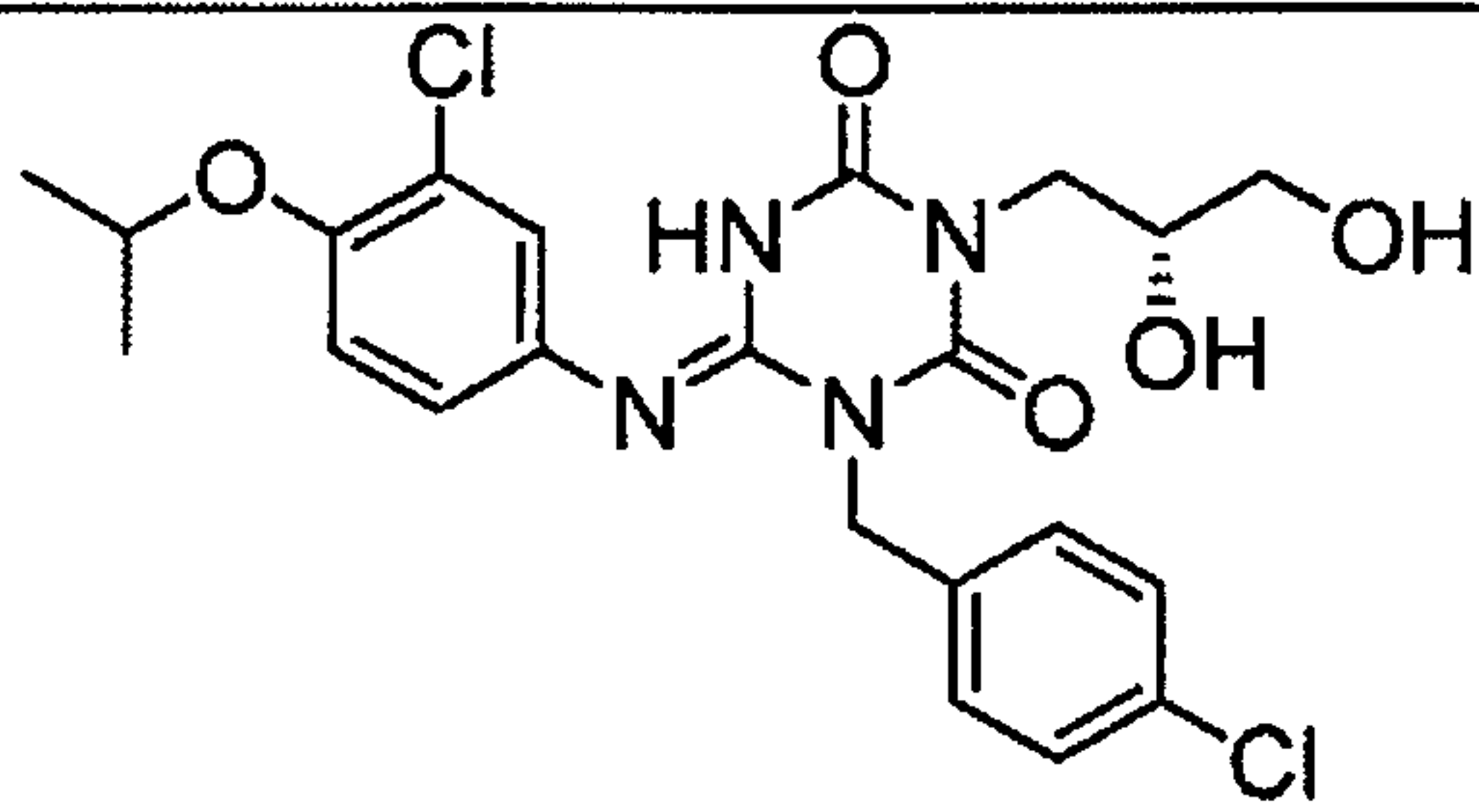
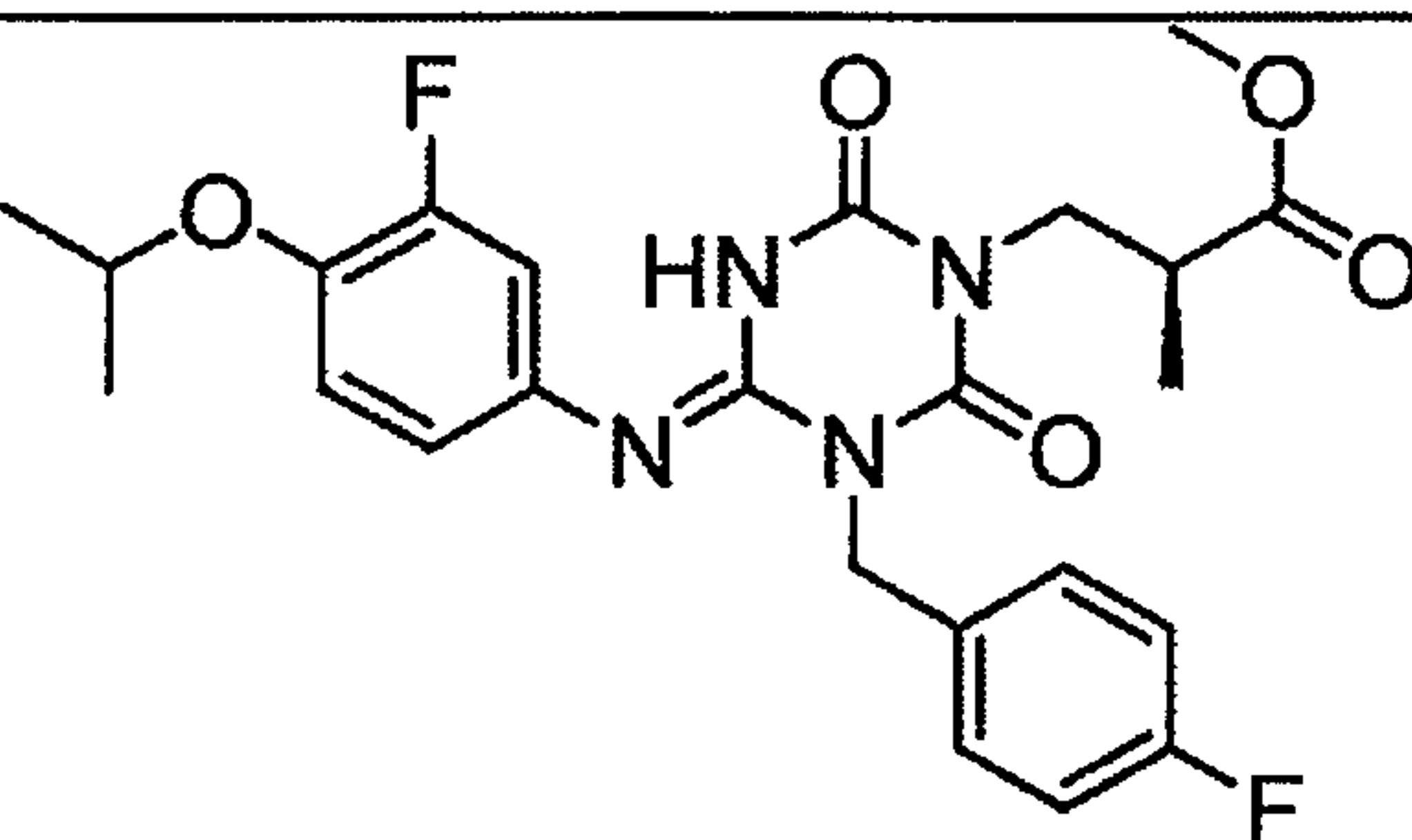
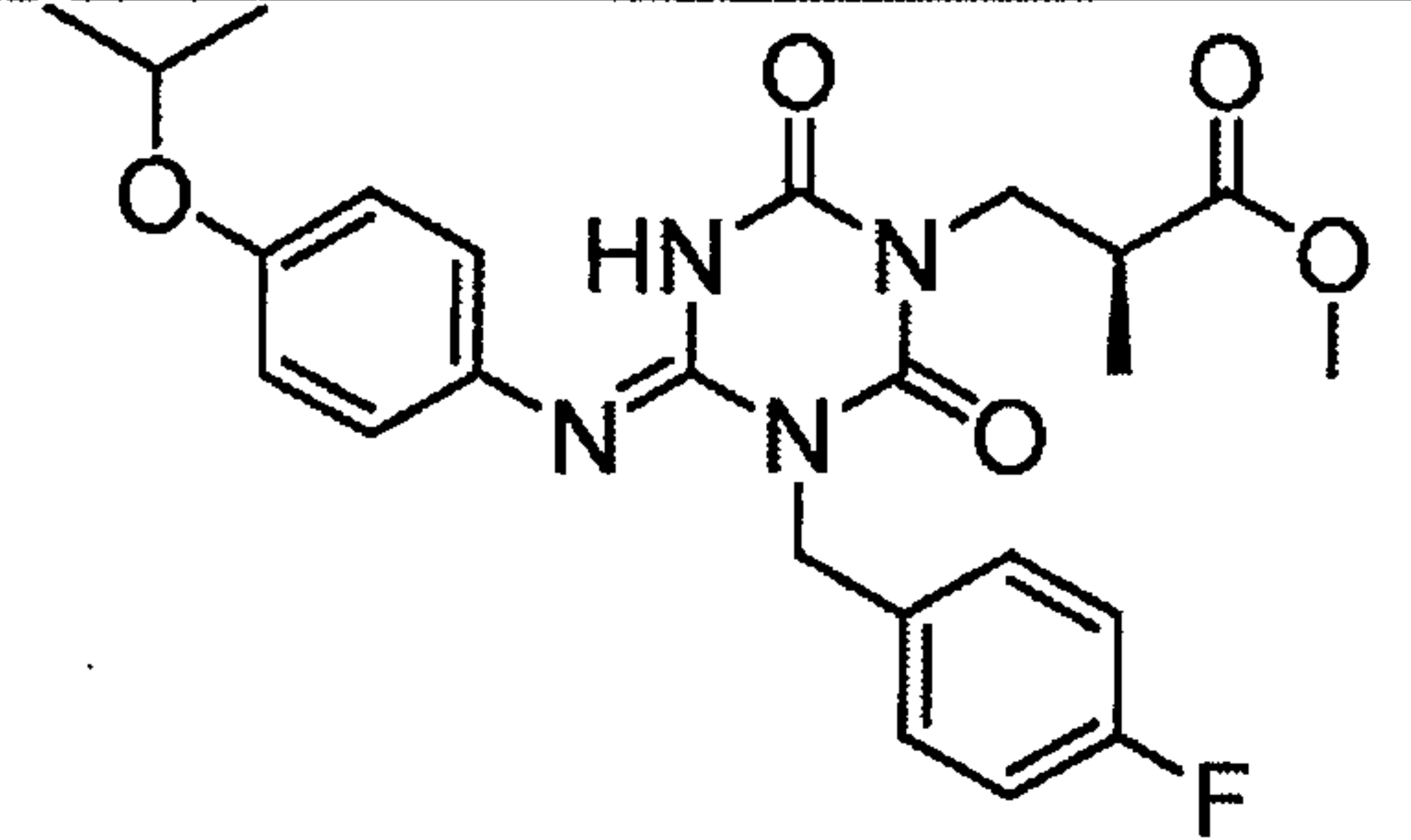
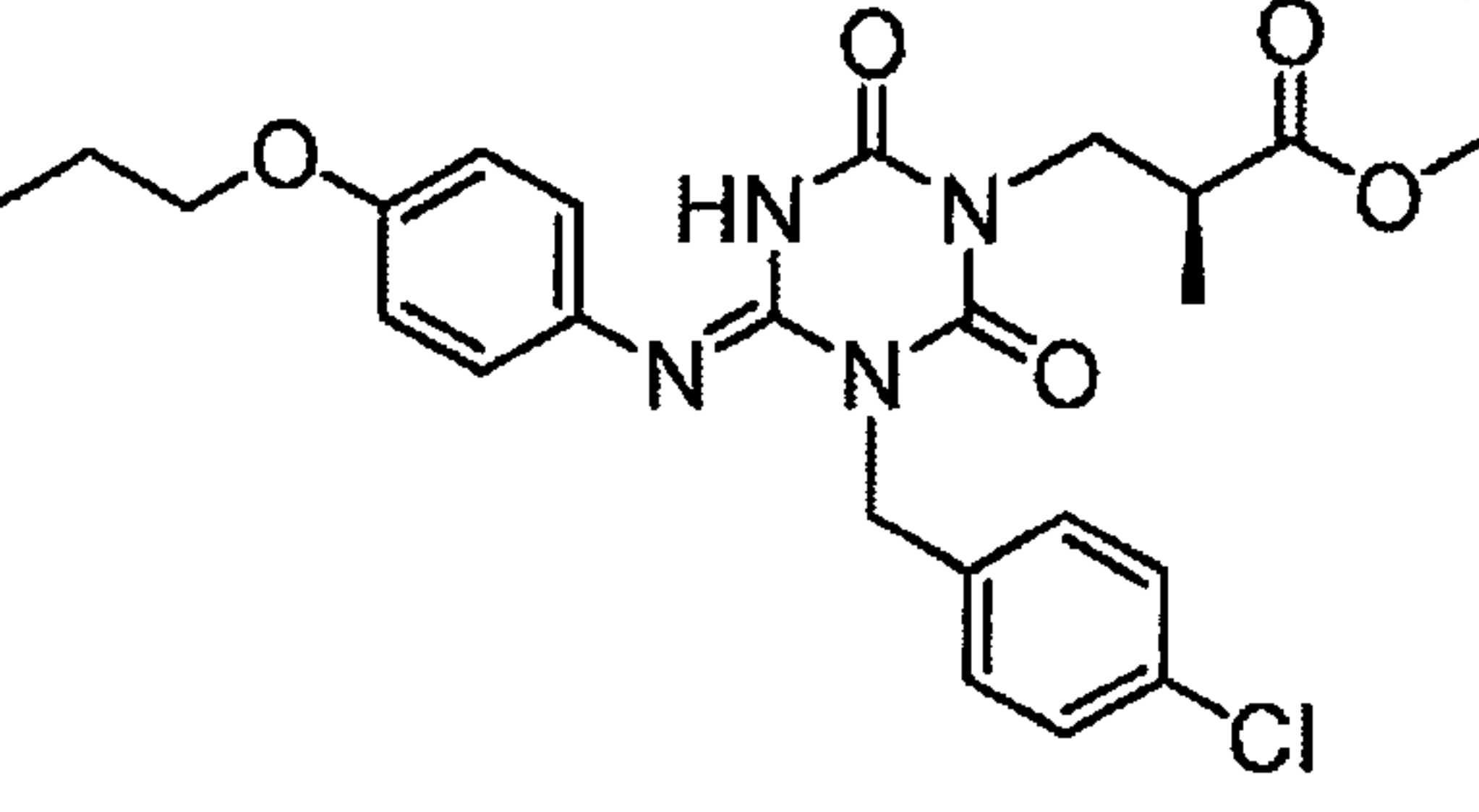
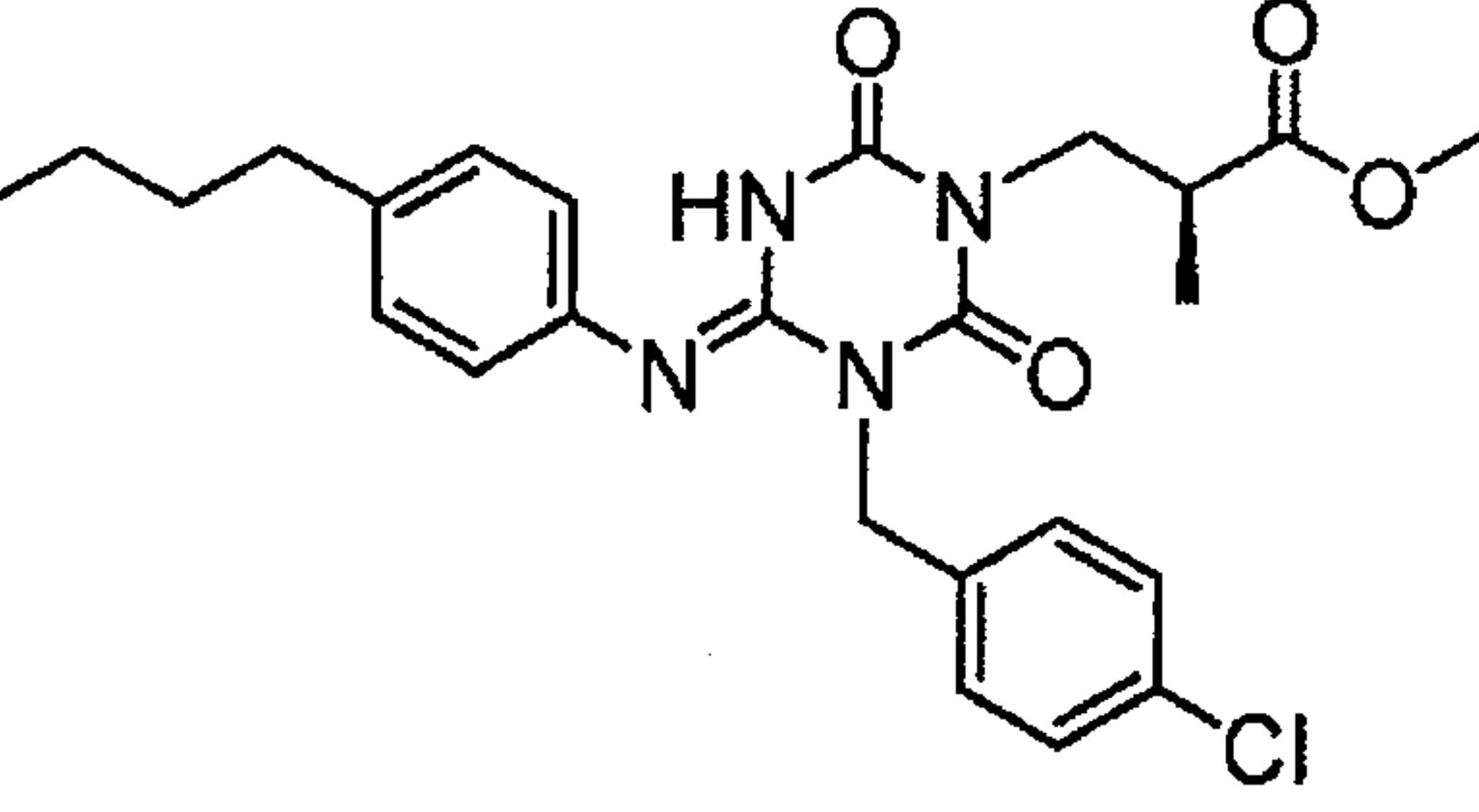
[Table 125]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0606	2.33	467	3
	I-0607	2.05	506	2
	I-0608	2.11	520	2
	I-0609	1.92	477	2
	I-0610	1.84	457	2

[Table 126]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0611	1.86	454	2
	I-0612	1.96	489	2
	I-0613	2.30	606	2
	I-0614	2.43	535	2
	I-0615	1.96	543	2

[Table 127]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0616	1.91	495	2
	I-0617	2.14	489	2
	I-0618	2.26	471	3
	I-0619	2.43	487	3
	I-0620	2.71	485	3

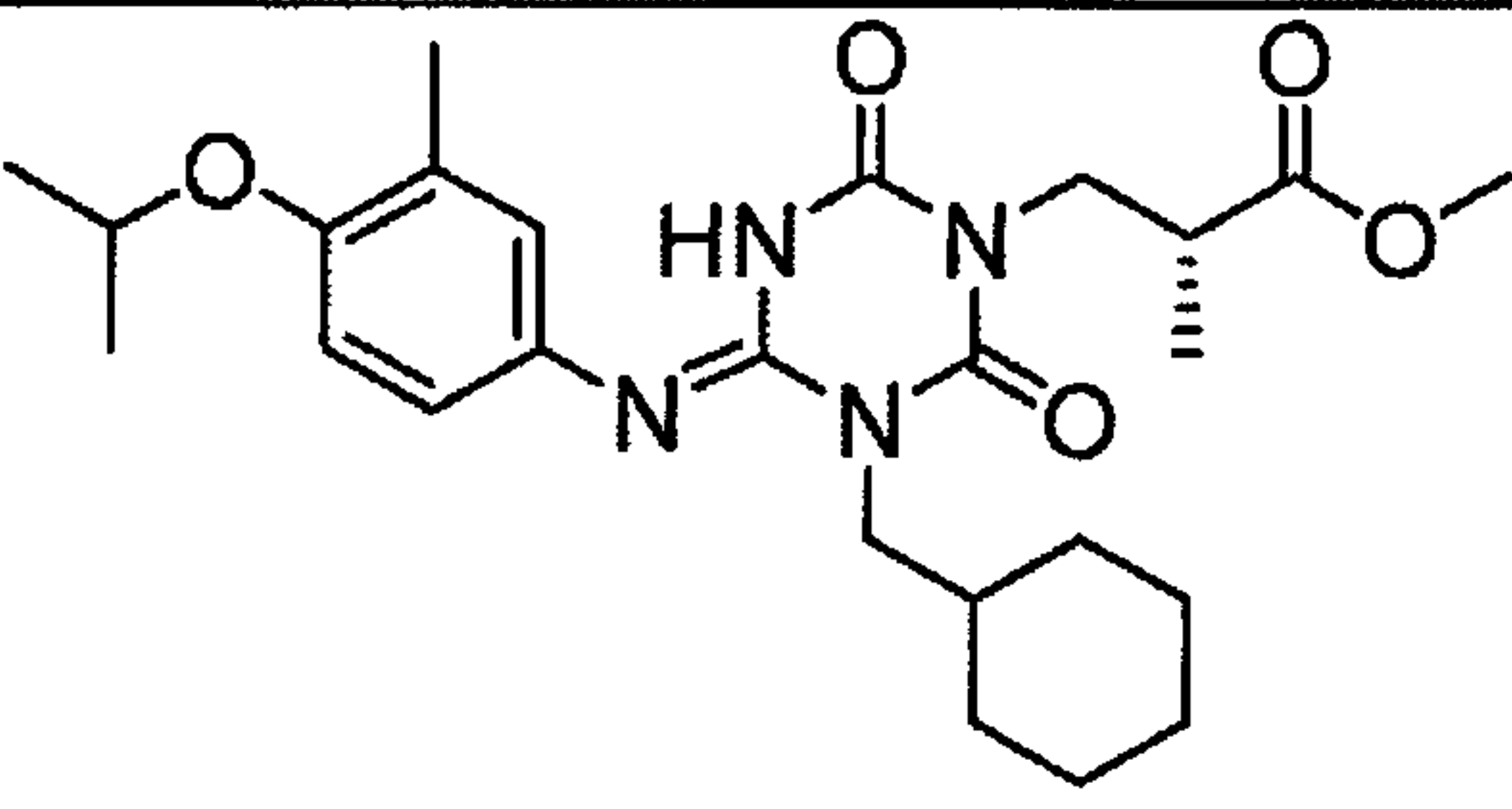
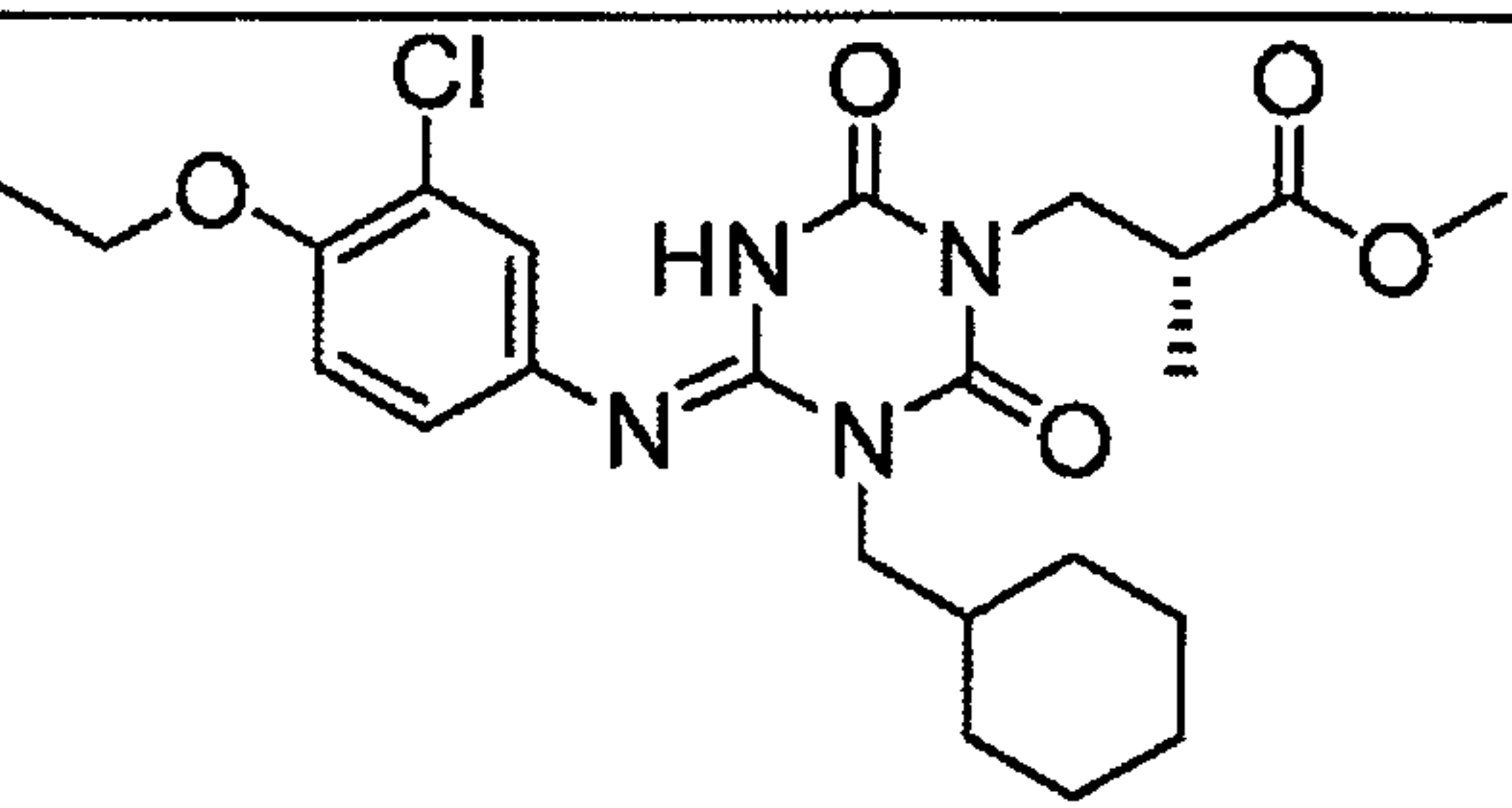
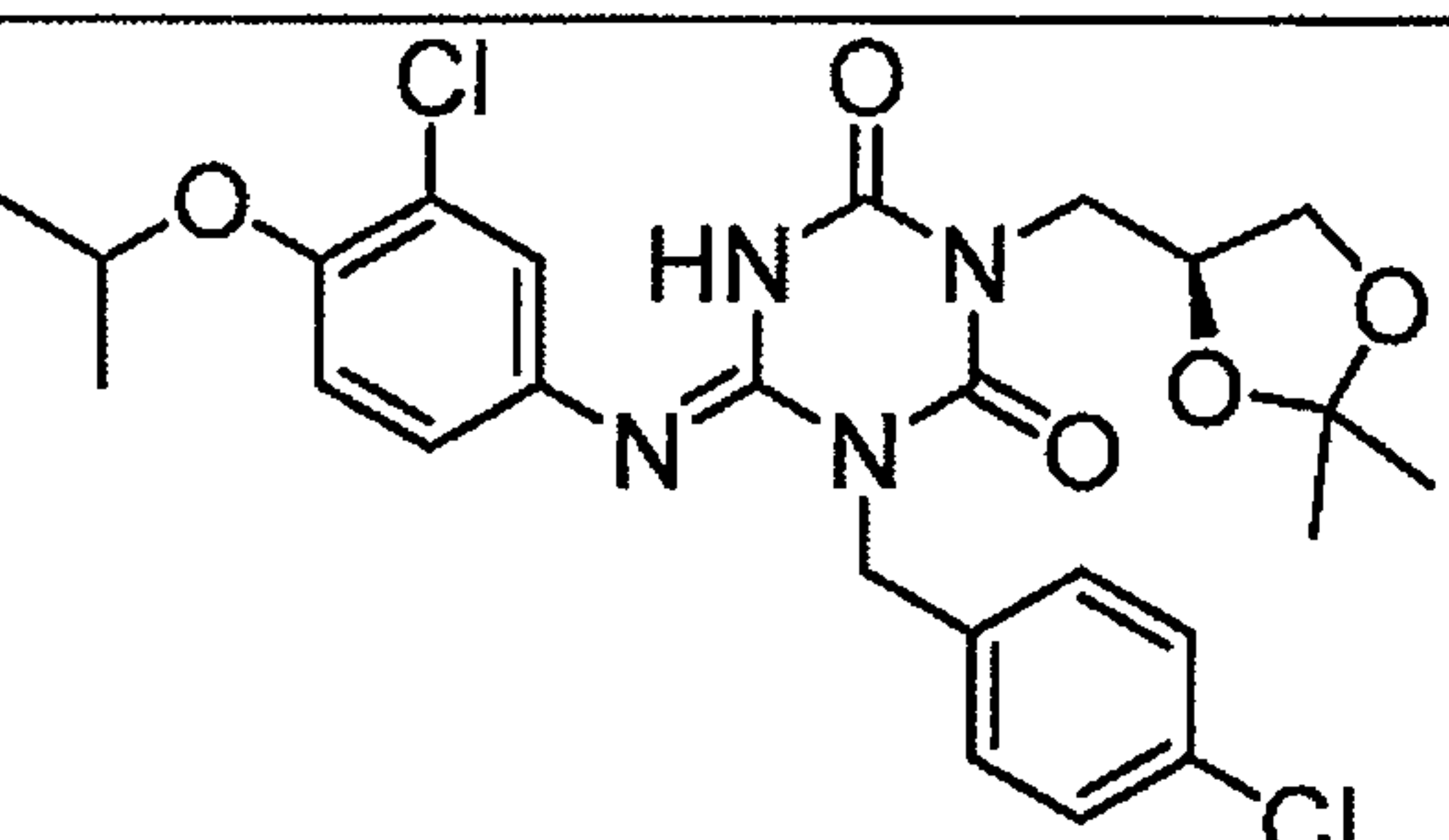
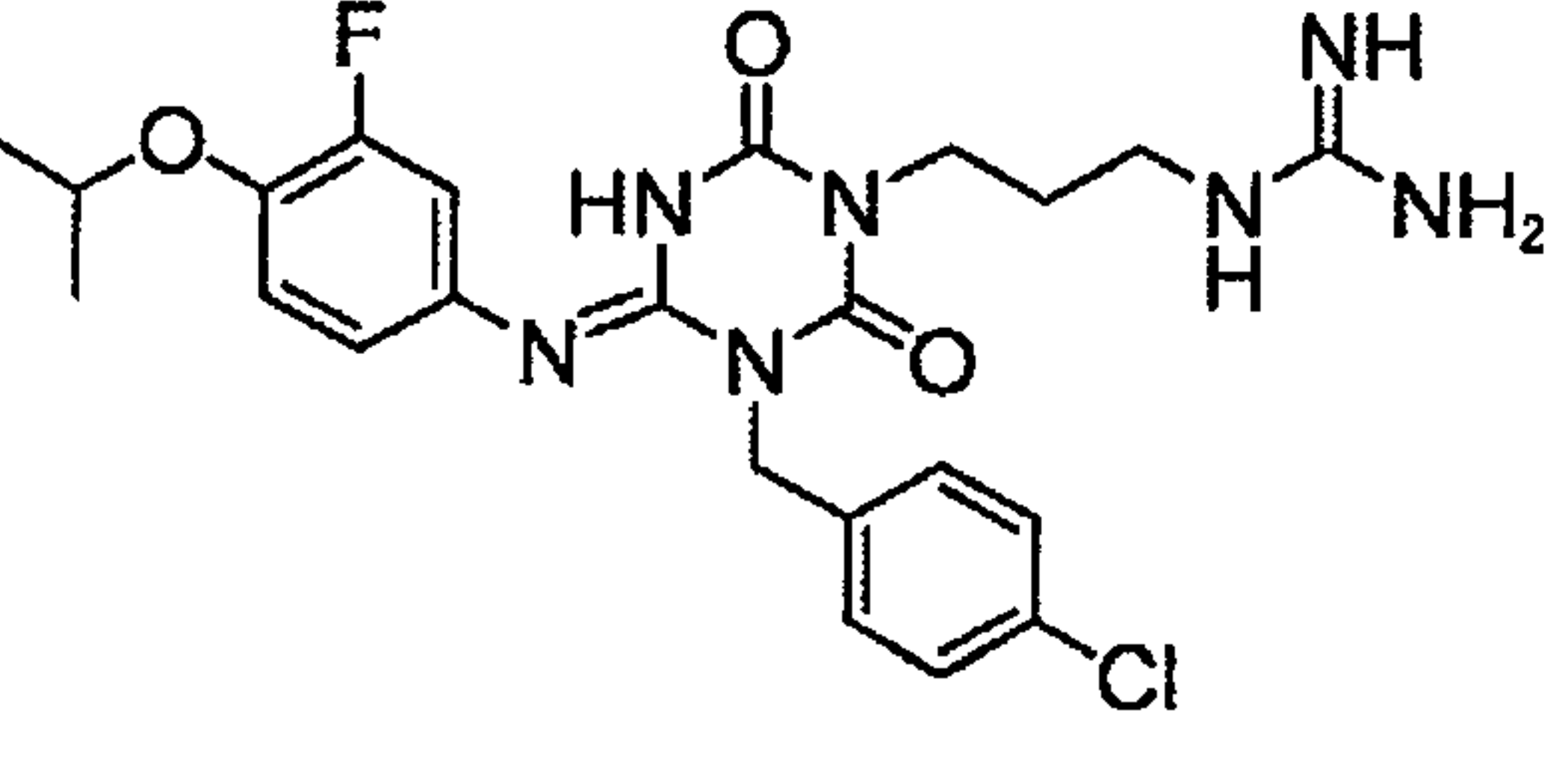
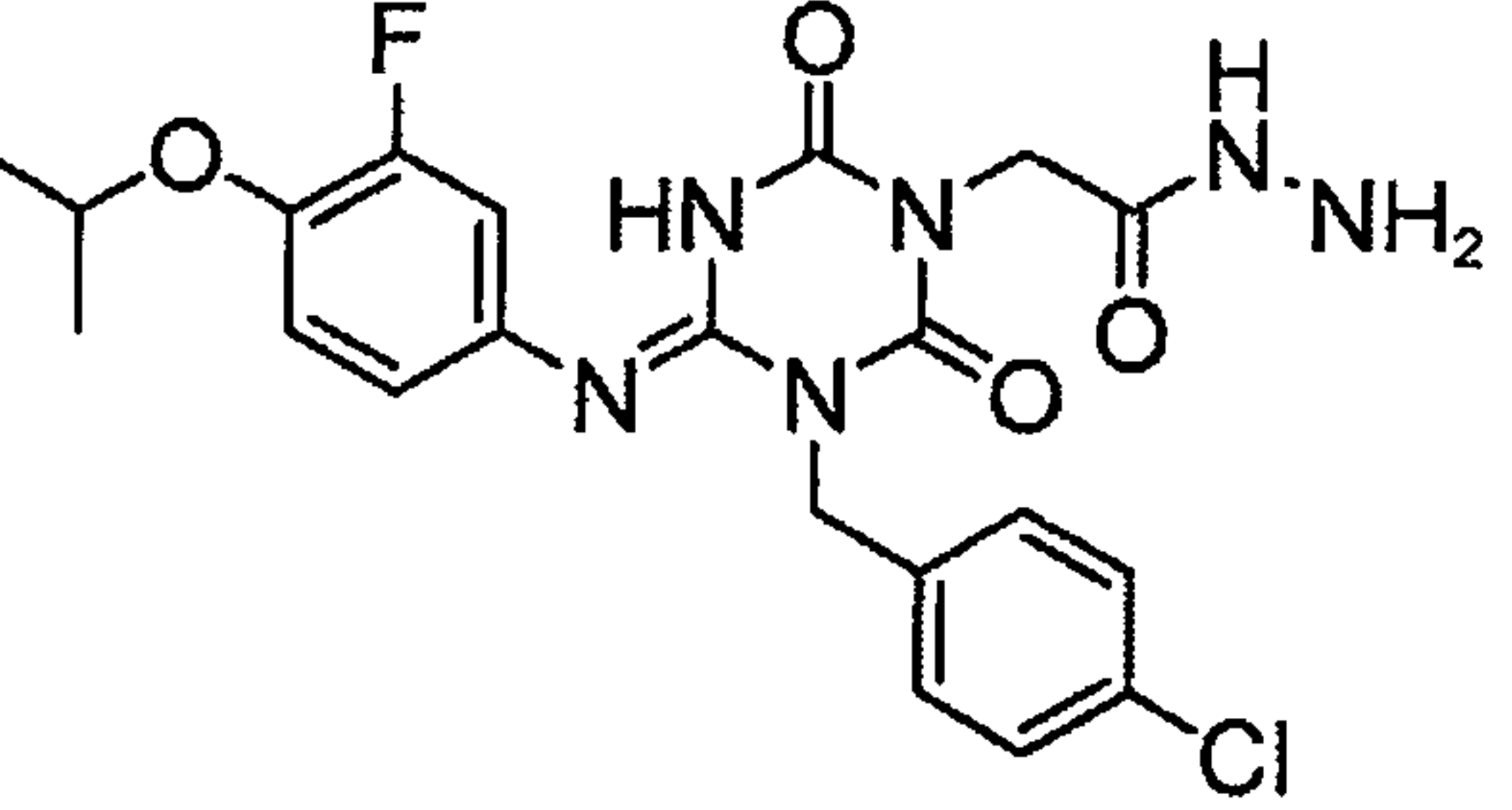
[Table 128]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0621	2.57	471	3
	I-0622	2.56	497	3
	I-0623	2.16	473	3
	I-0624	2.54	471	3
	I-0625	2.40	485	3

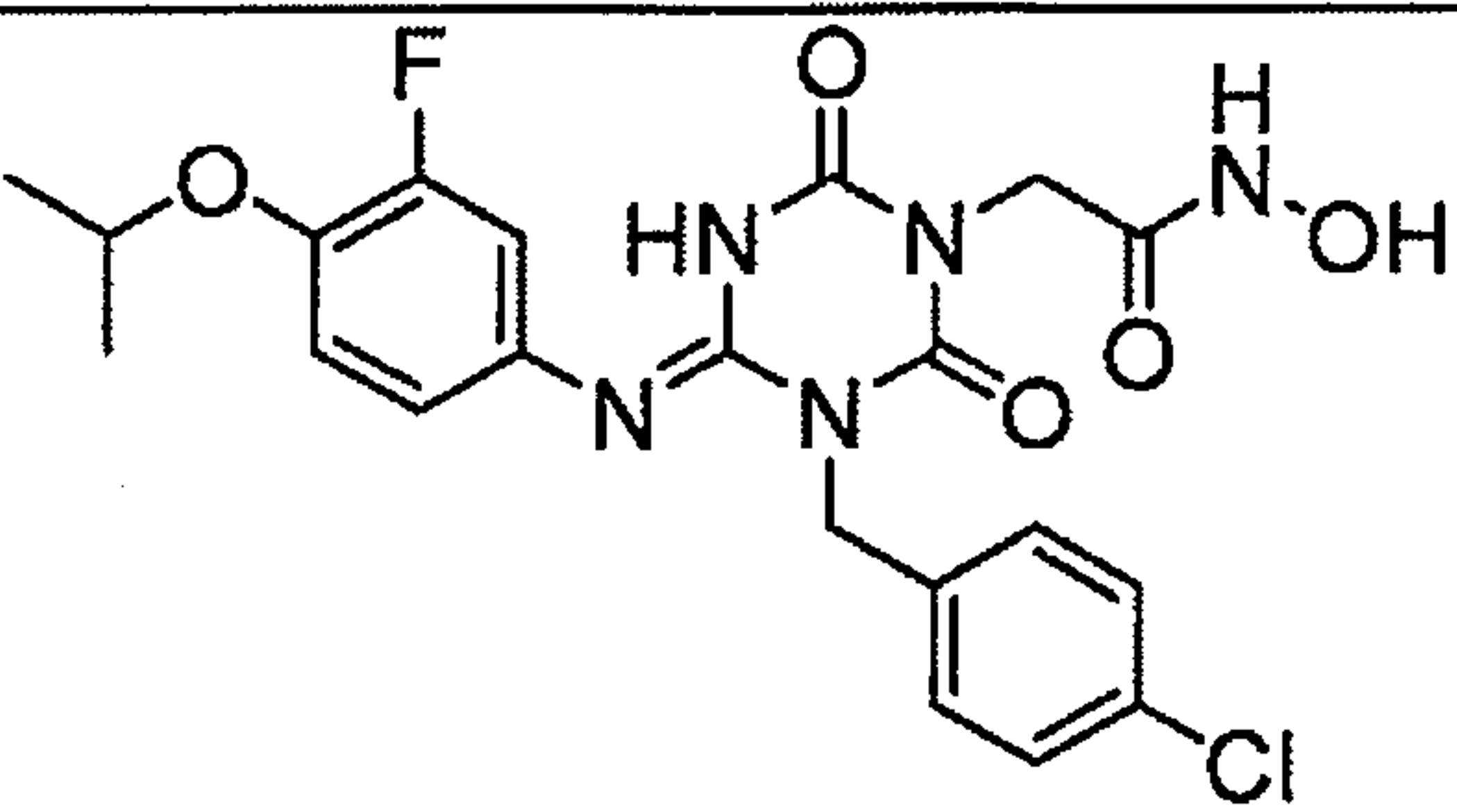
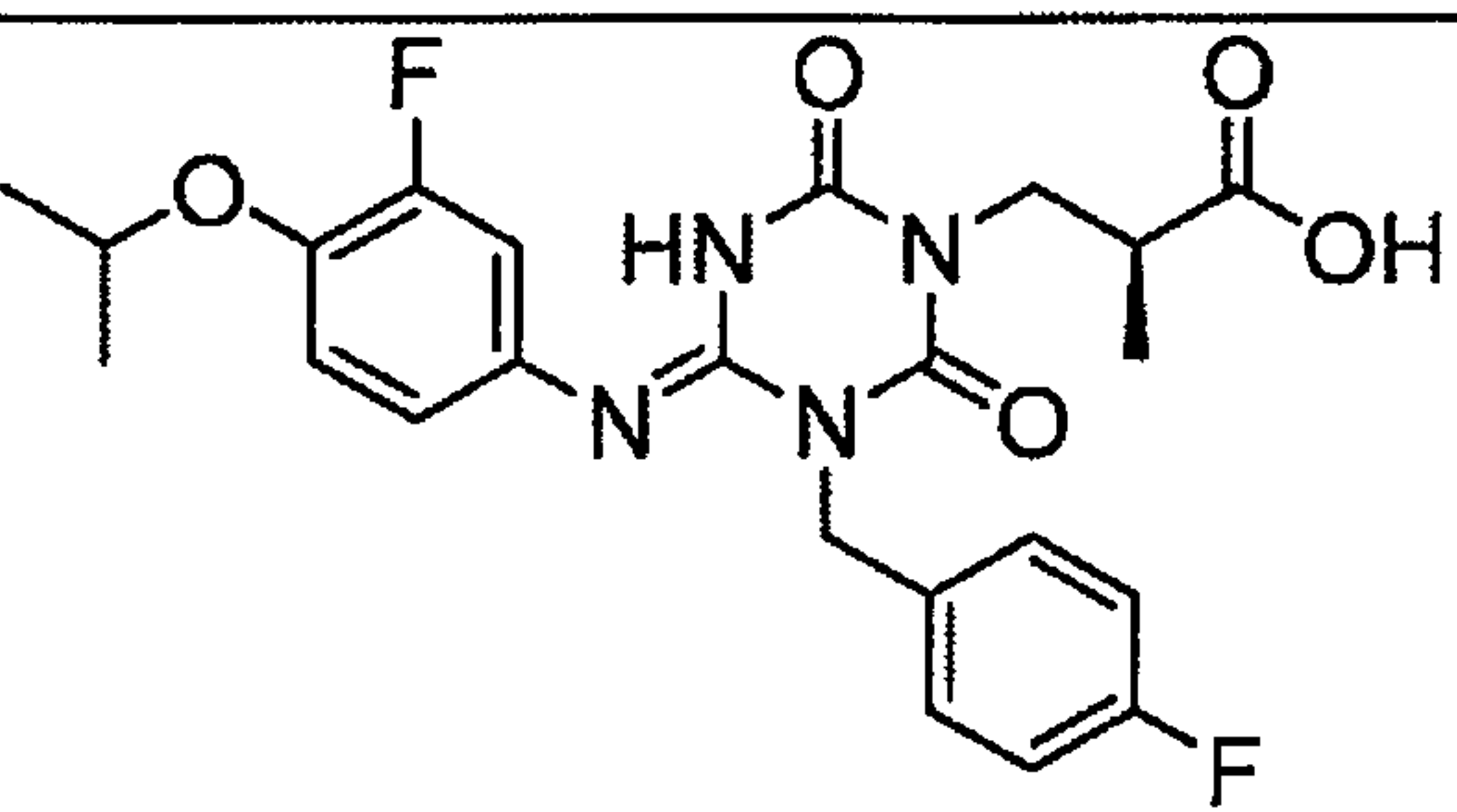
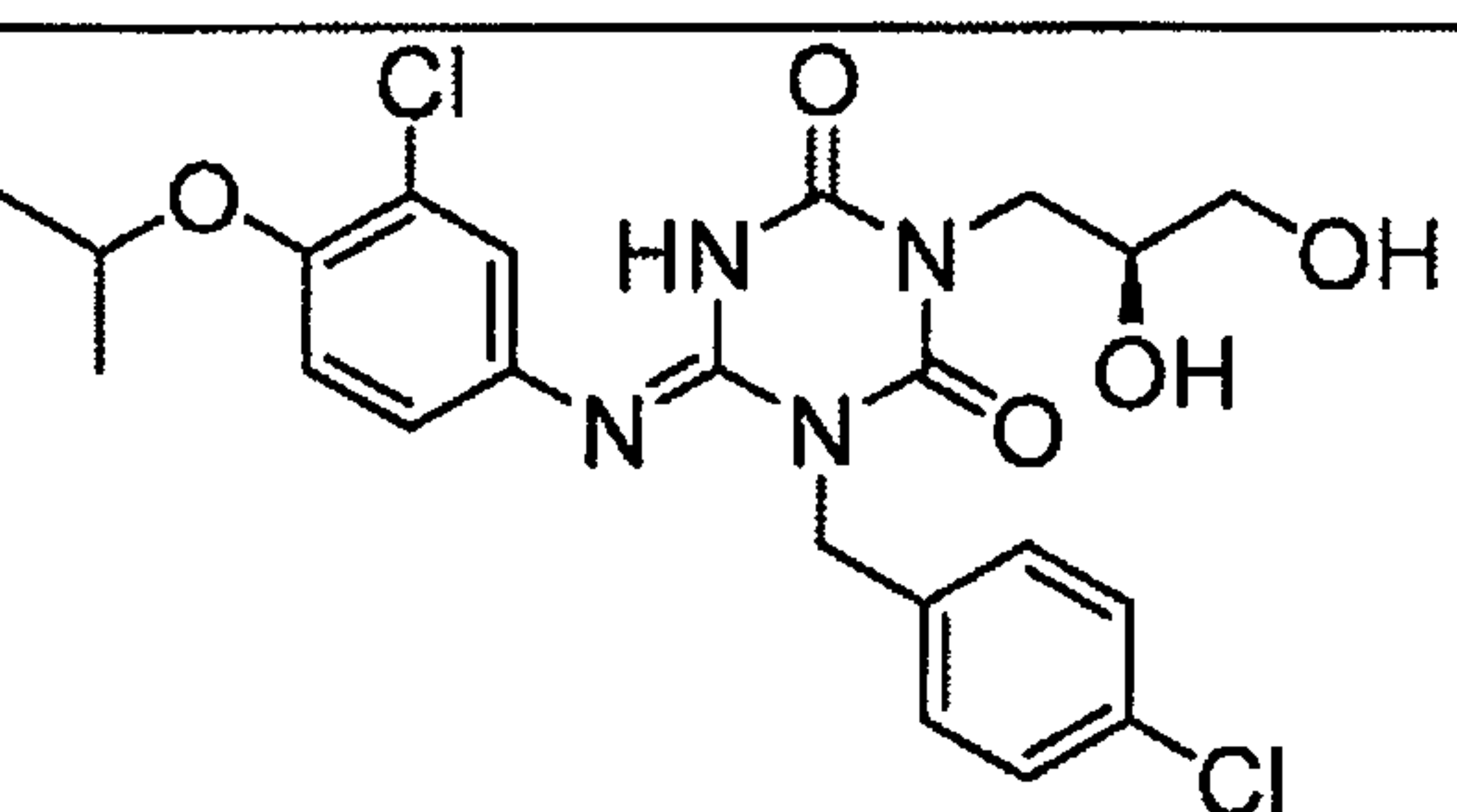
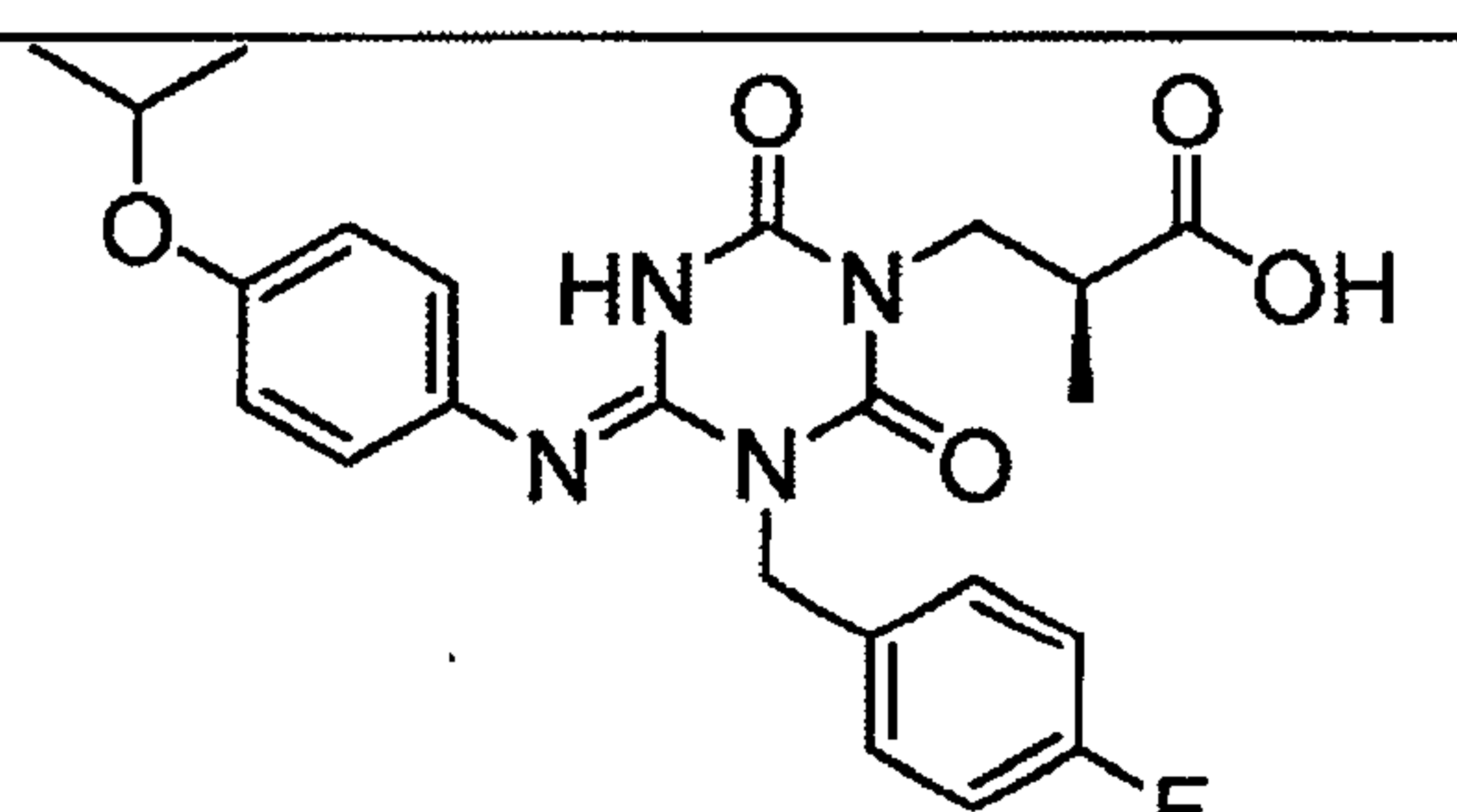
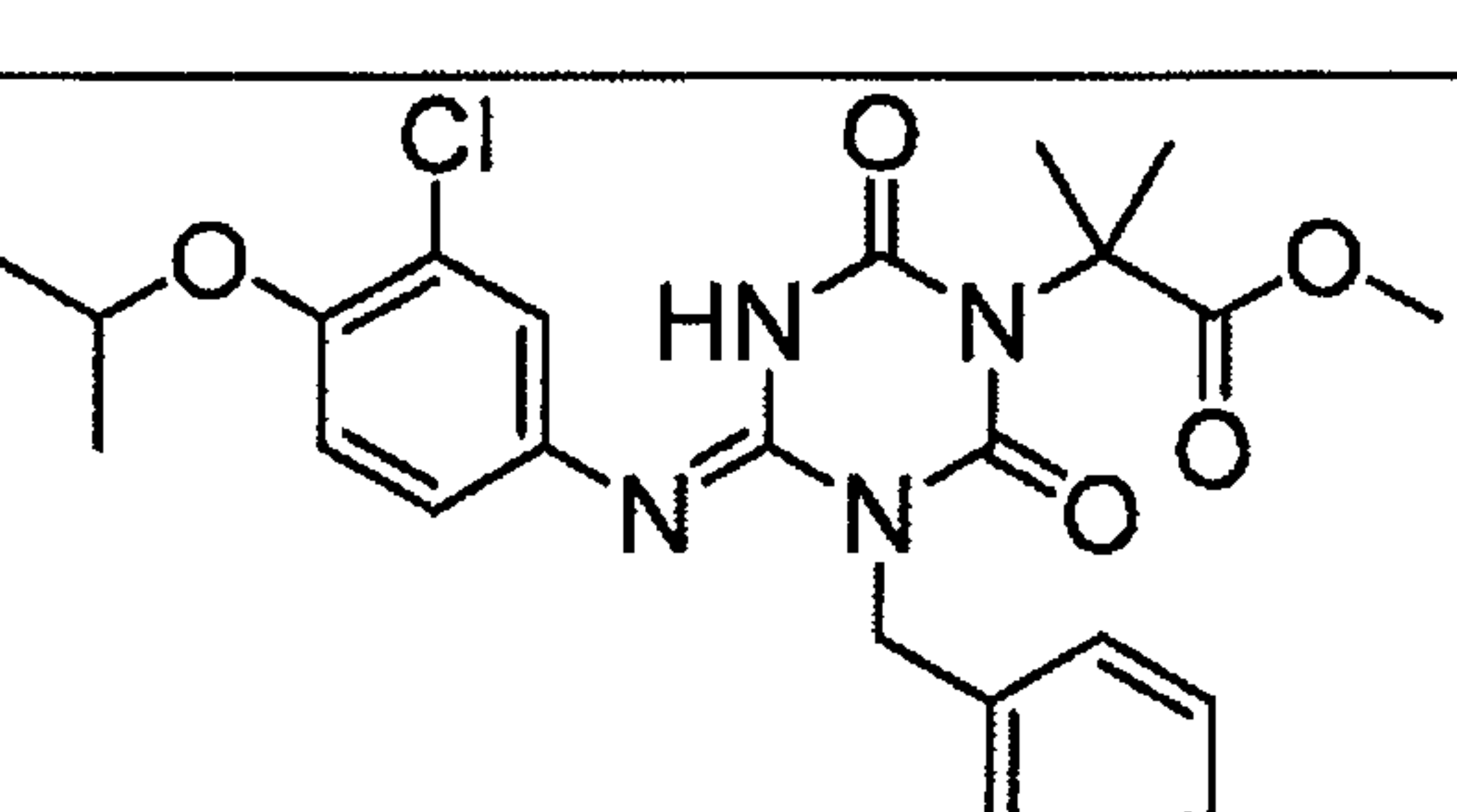
[Table 129]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0626	2.46	505	3
	I-0627	2.31	457	3
	I-0628	2.29	483	3
	I-0629	2.14	471	3
	I-0630	2.21	491	3

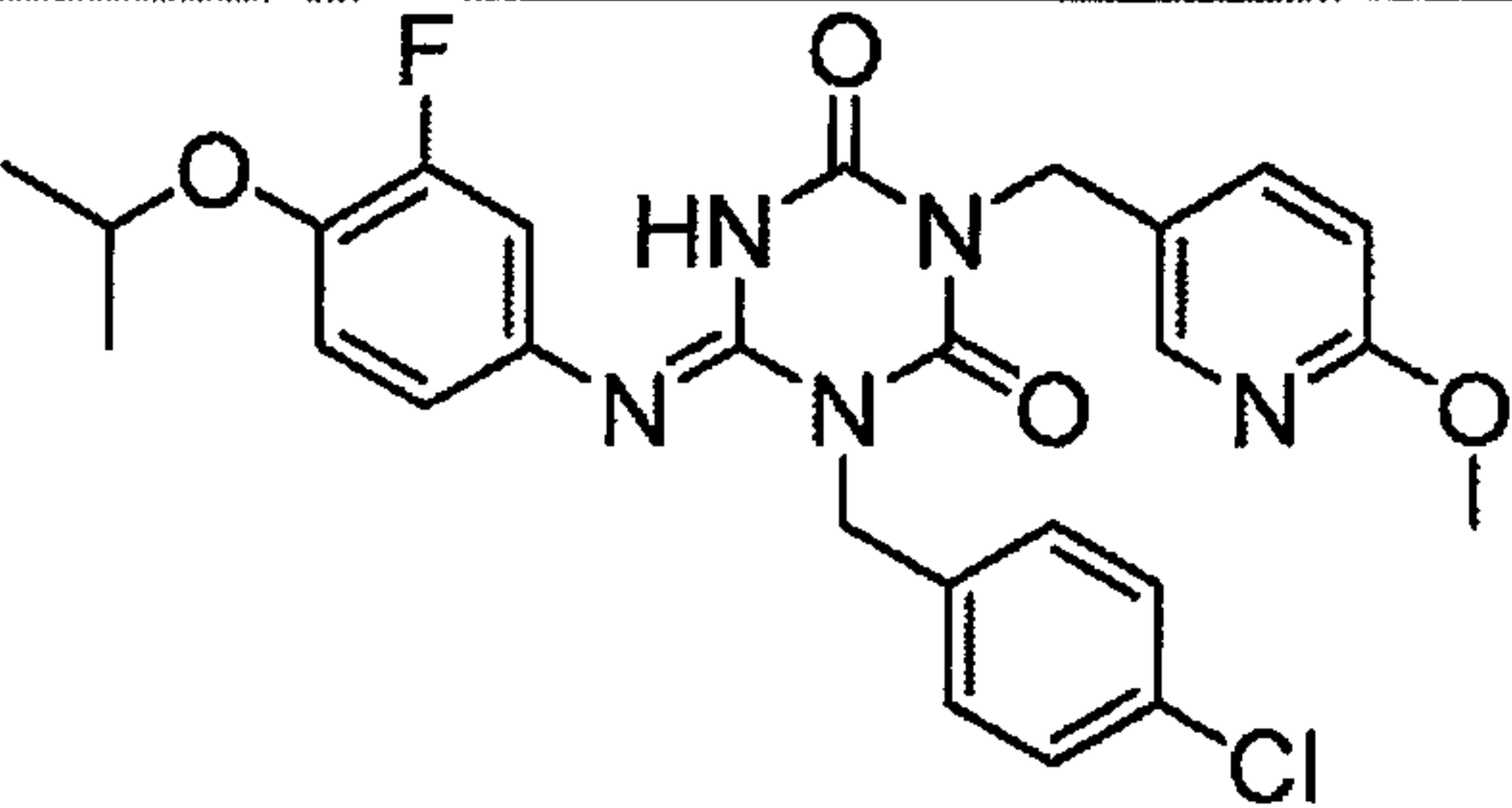
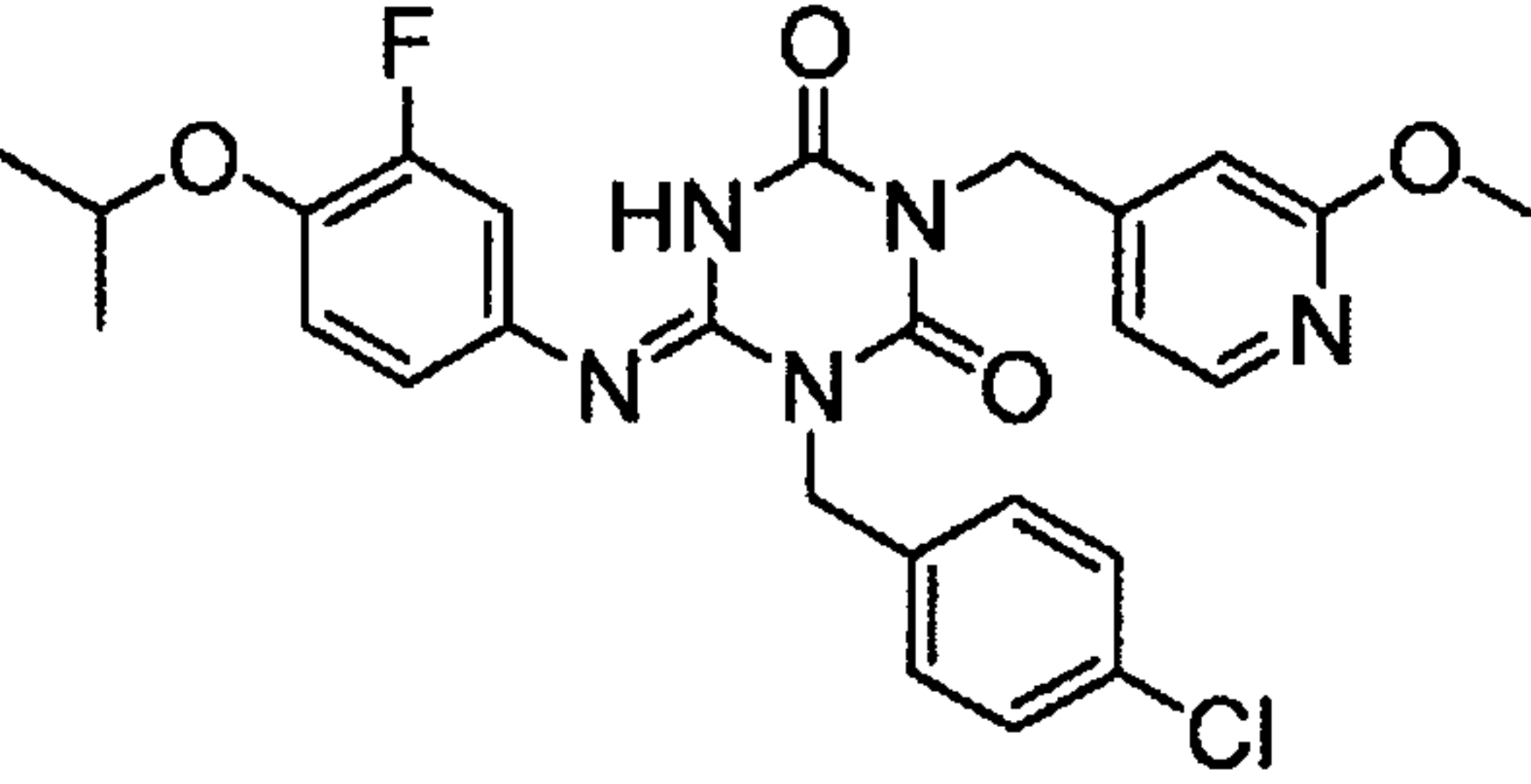
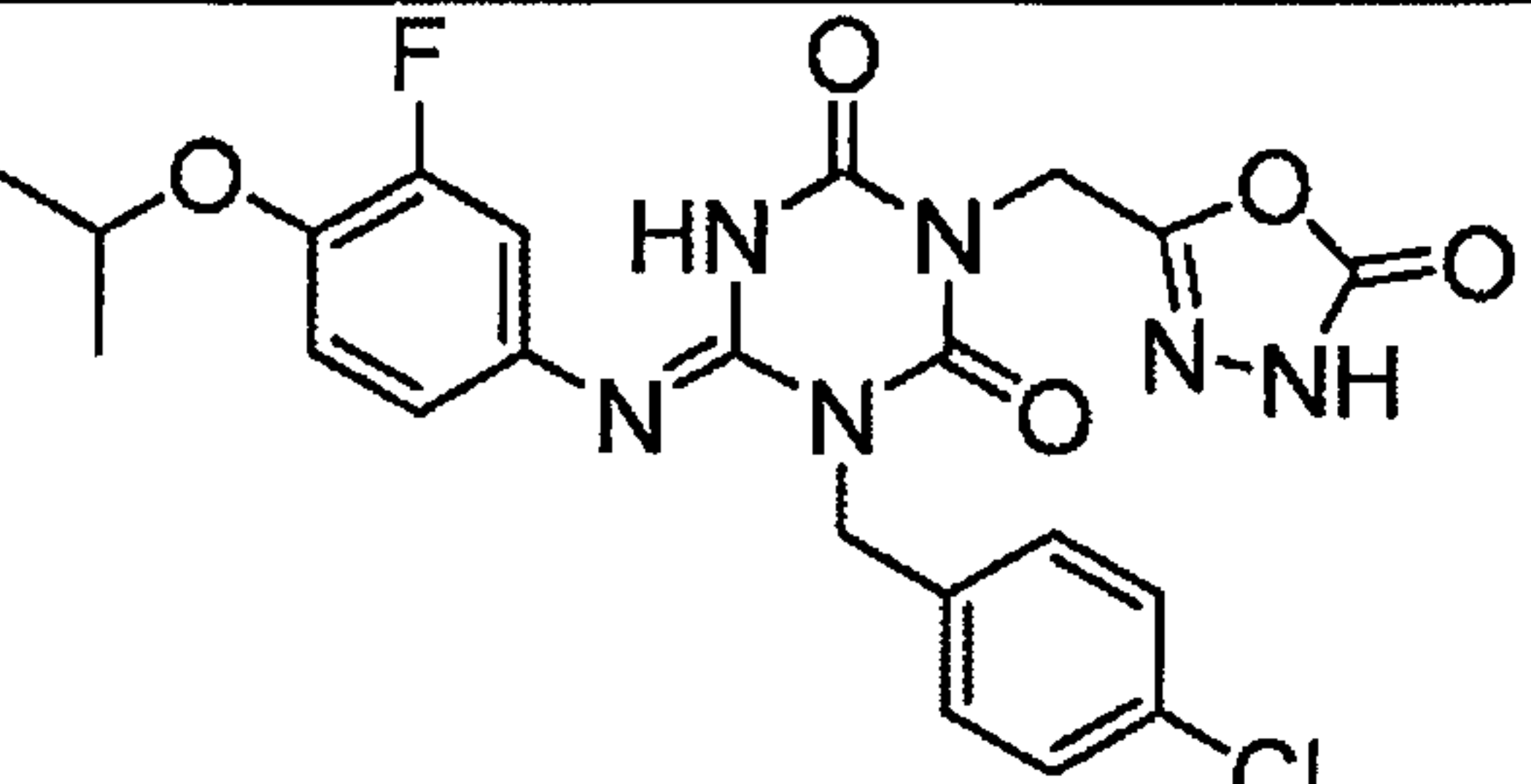
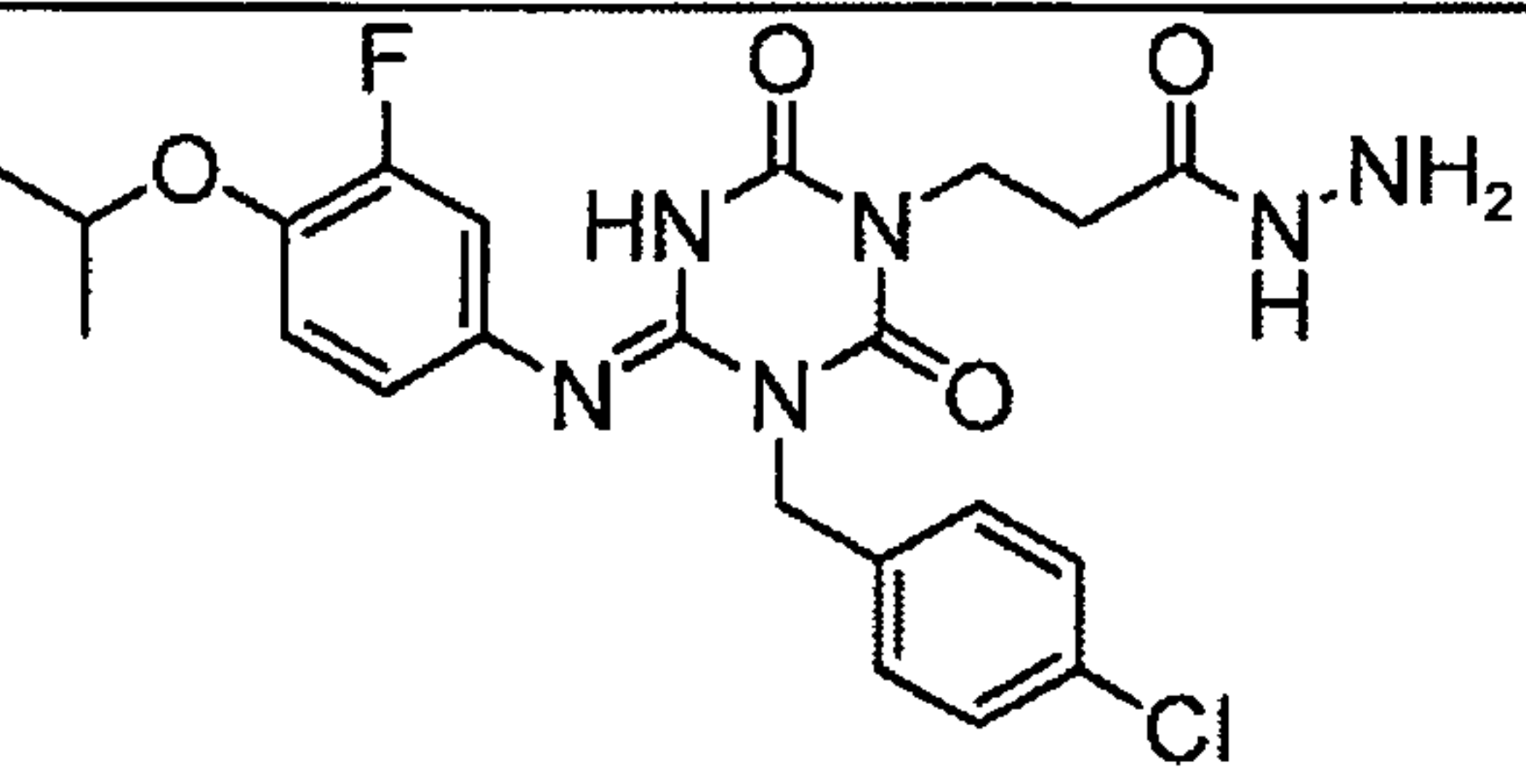
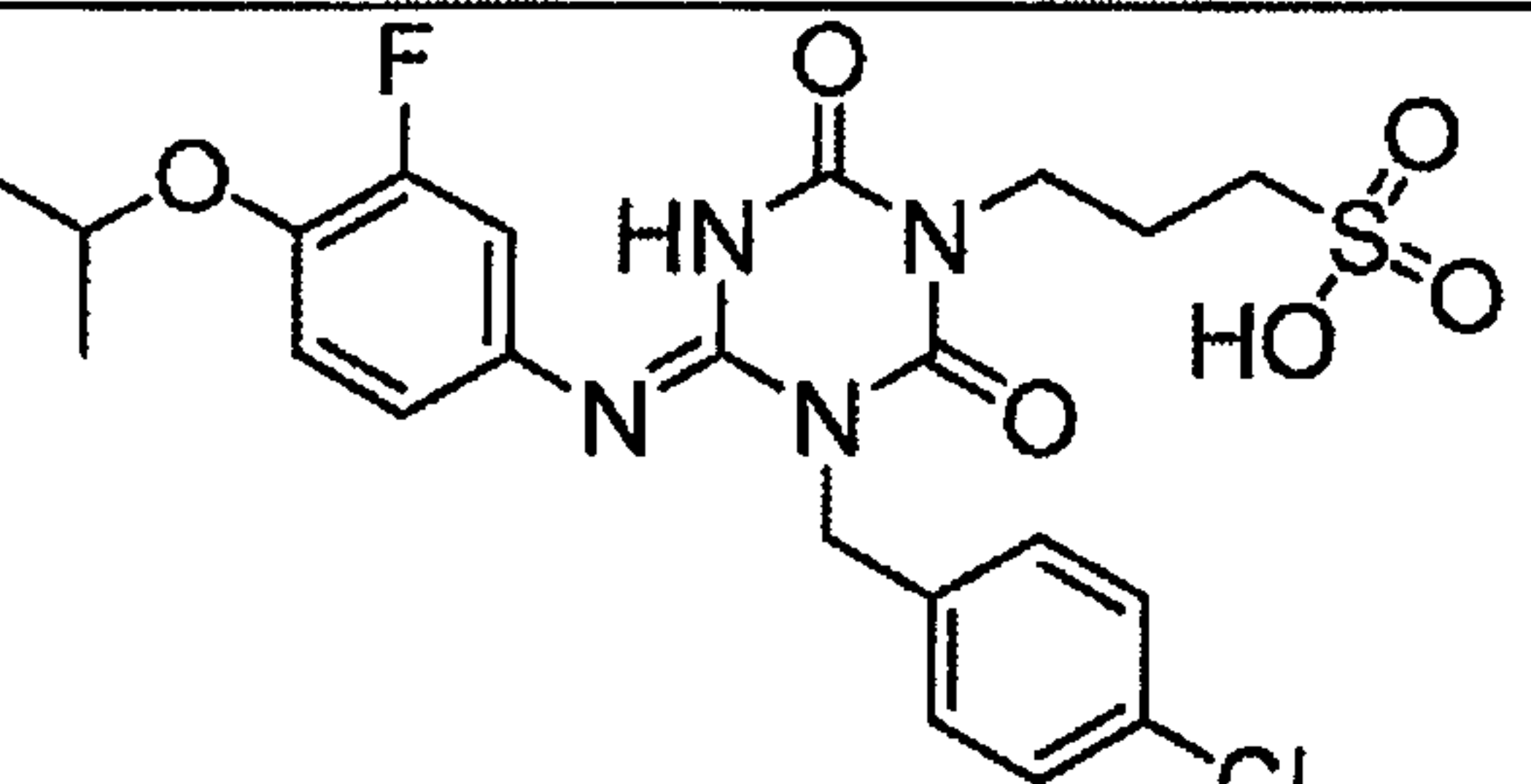
[Table 130]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0631	2.36	473	2
	I-0632	2.29	479	2
	I-0633	2.43	535	2
	I-0634	1.60	504	2
	I-0635	1.70	477	2

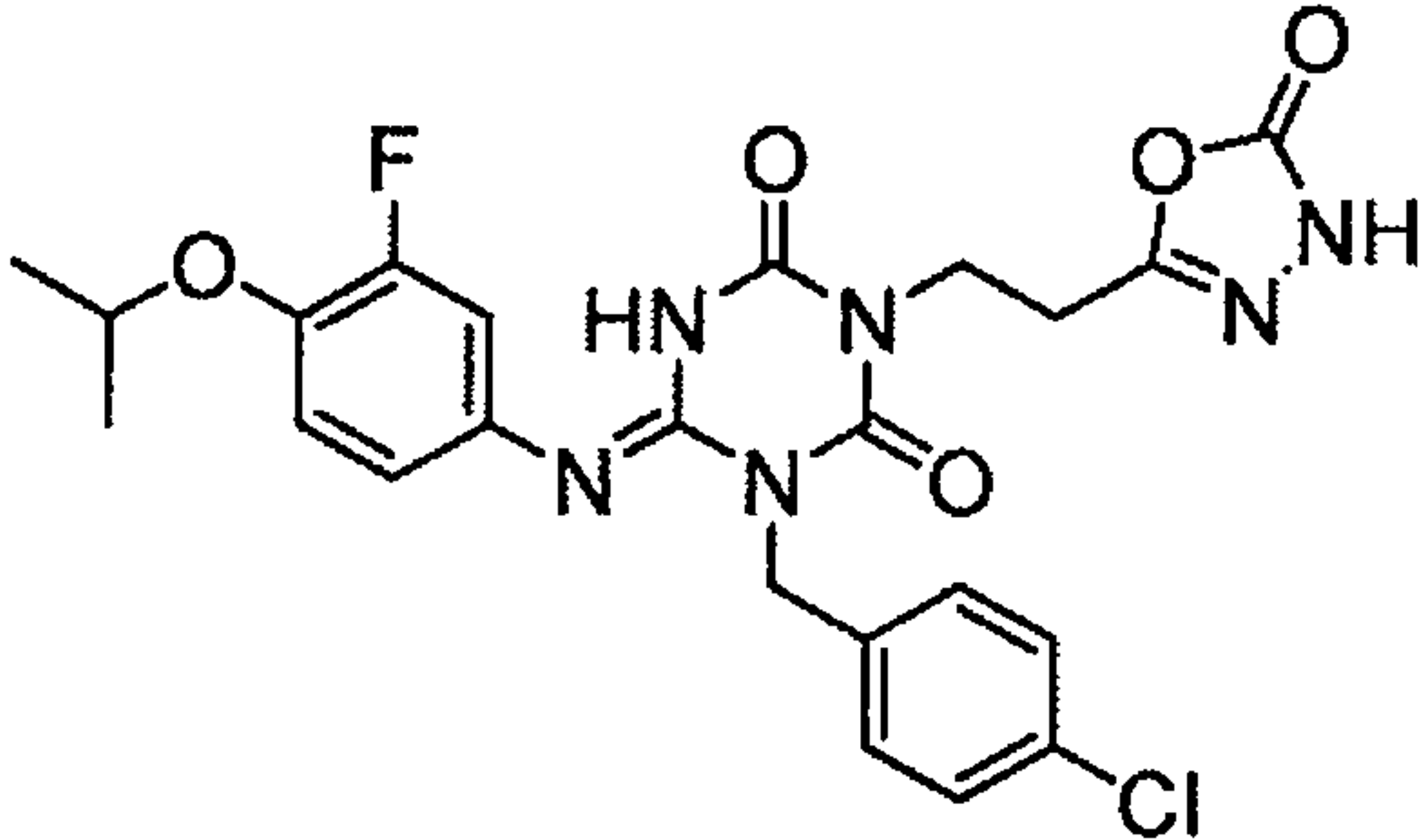
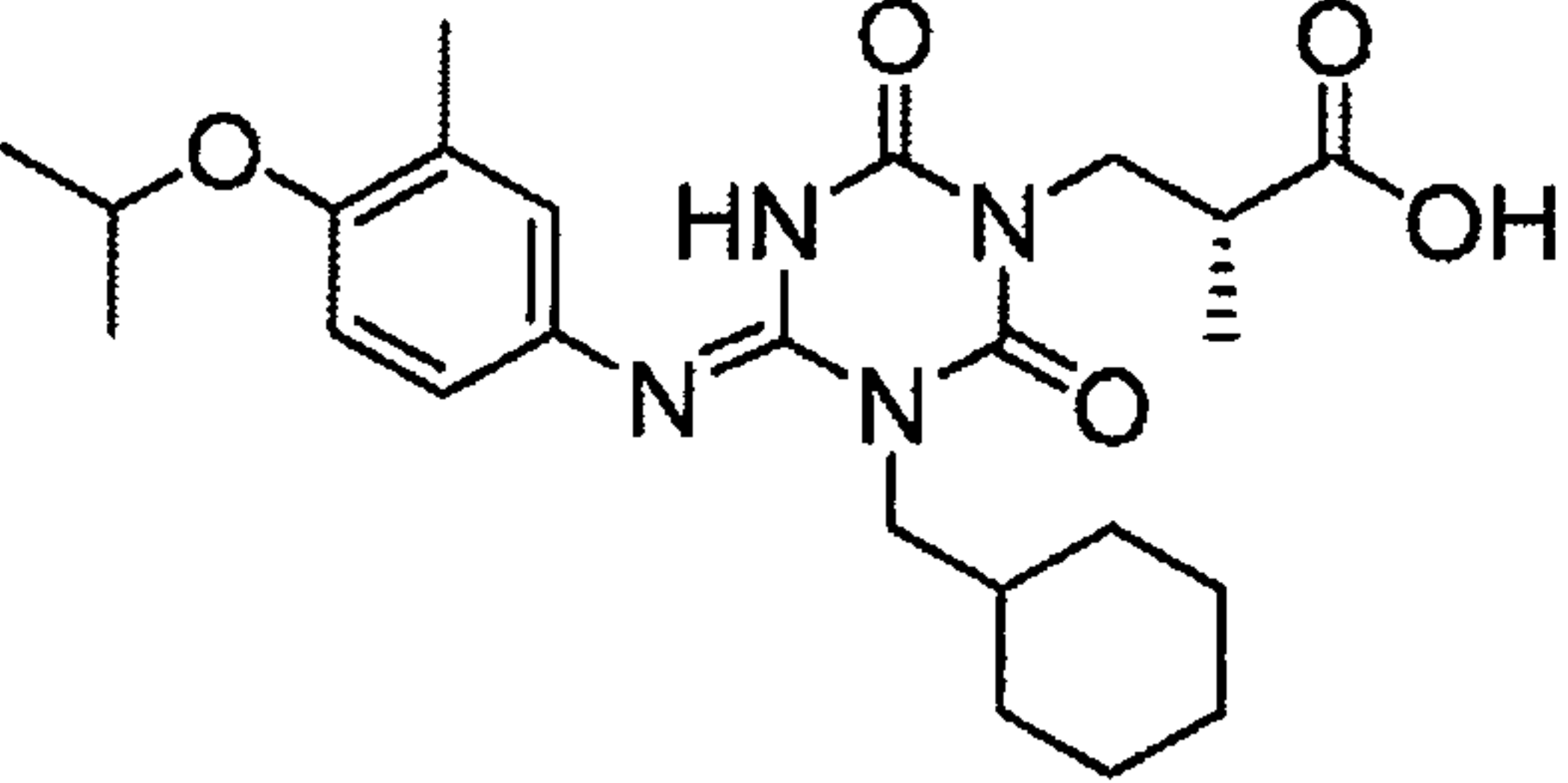
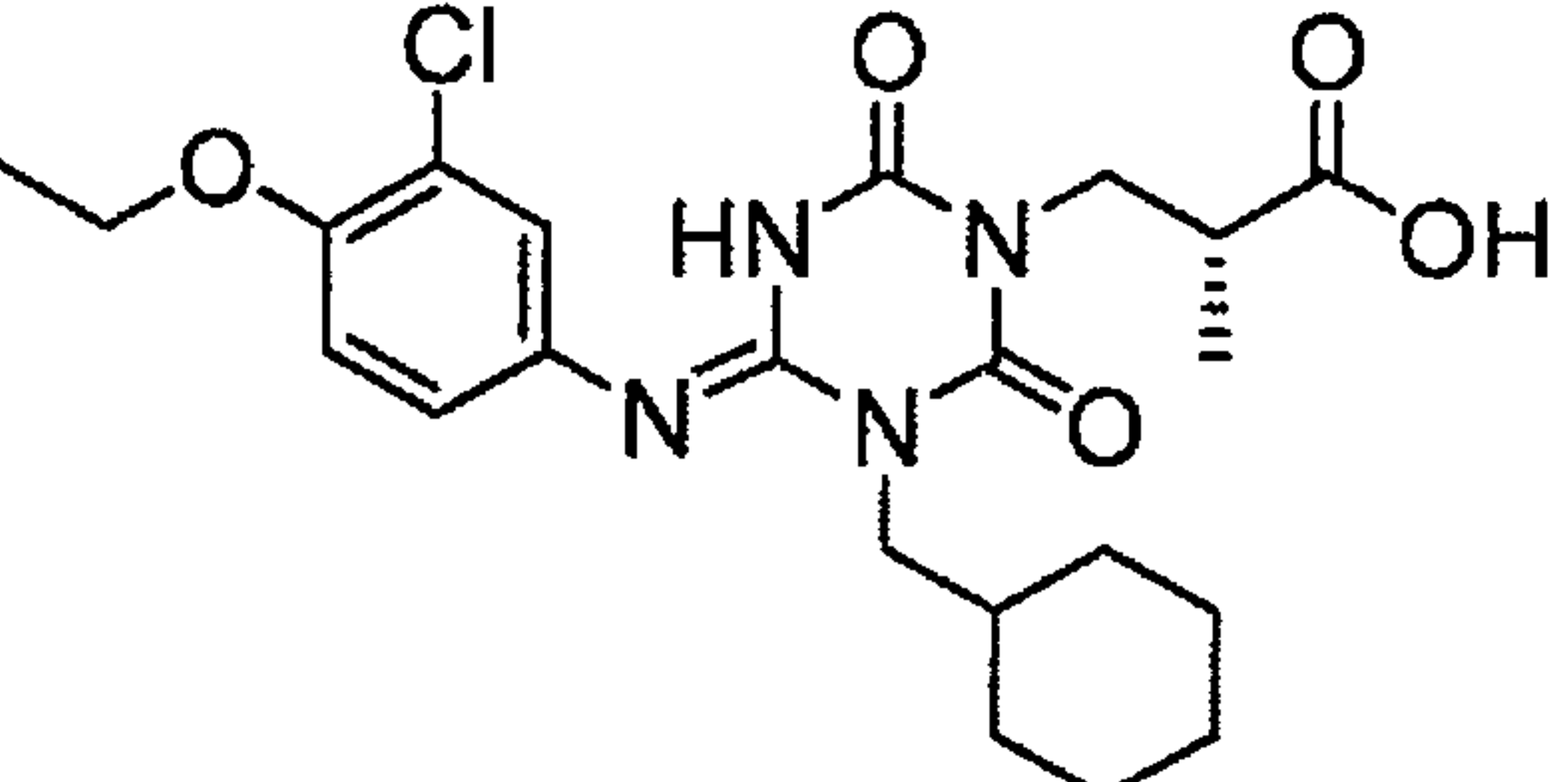
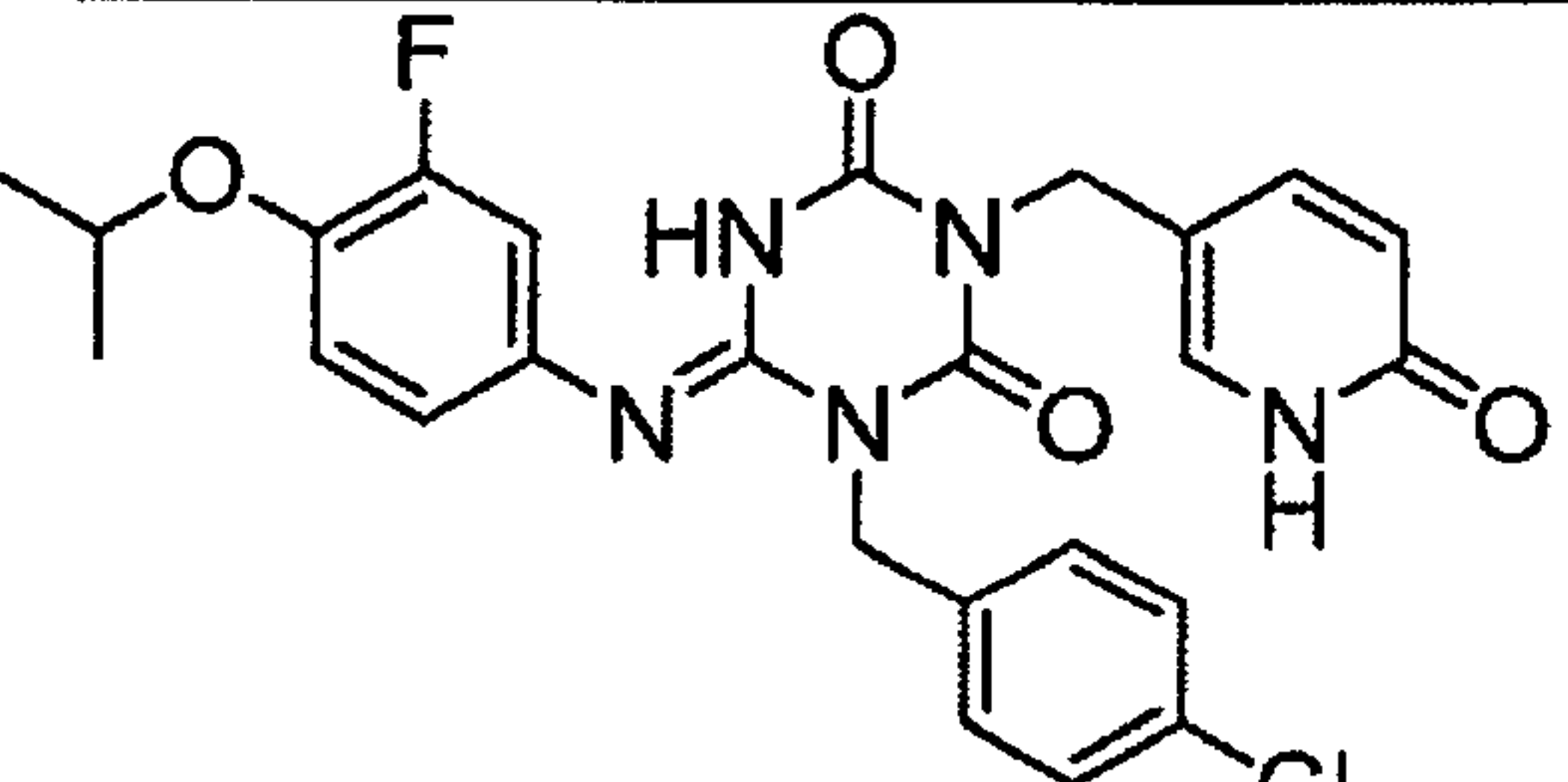
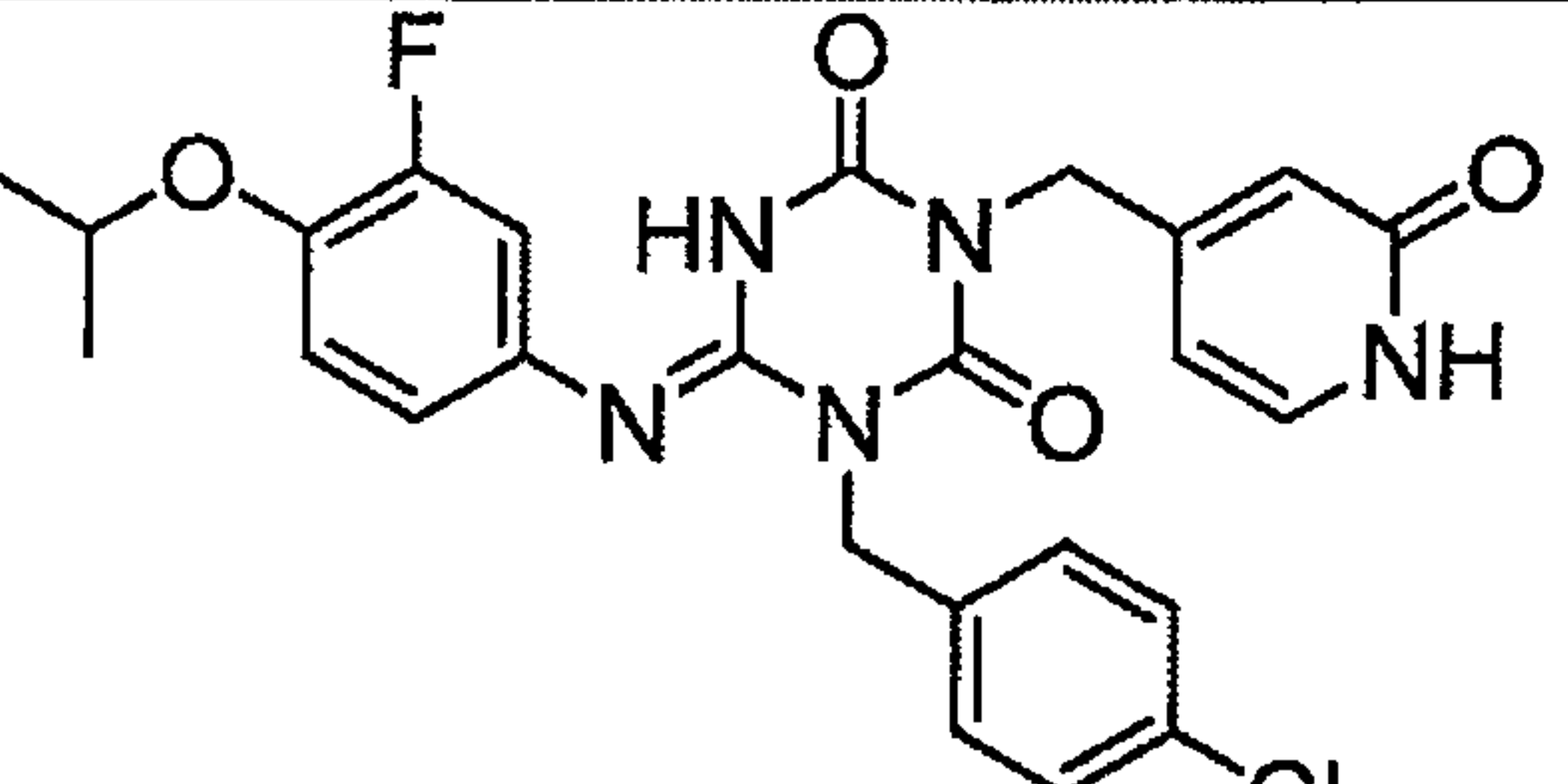
[Table 131]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0636	1.75	478	2
	I-0637	1.90	475	2
	I-0638	1.91	495	2
	I-0639	2.00	457	3
	I-0640	2.43	521	2

[Table 132]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0641	2.34	526	2
	I-0642	2.29	526	2
	I-0643	1.94	503	2
	I-0644	1.69	491	2
	I-0645	1.72	527	2

[Table 133]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0646	1.97	517	2
	I-0647	2.09	459	2
	I-0648	2.01	465	2
	I-0649	1.85	512	2
	I-0650	1.83	512	2

[Table 134]

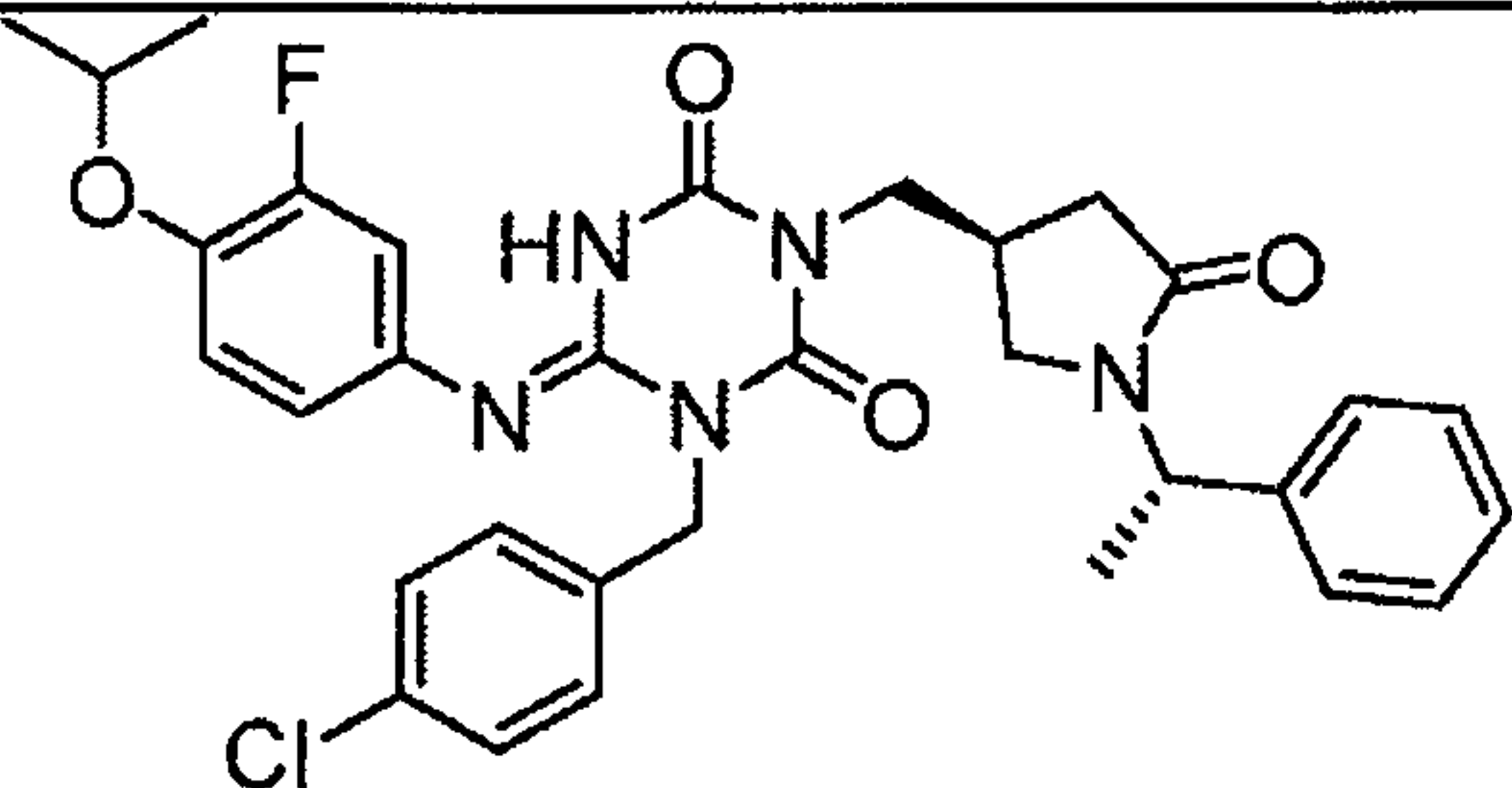
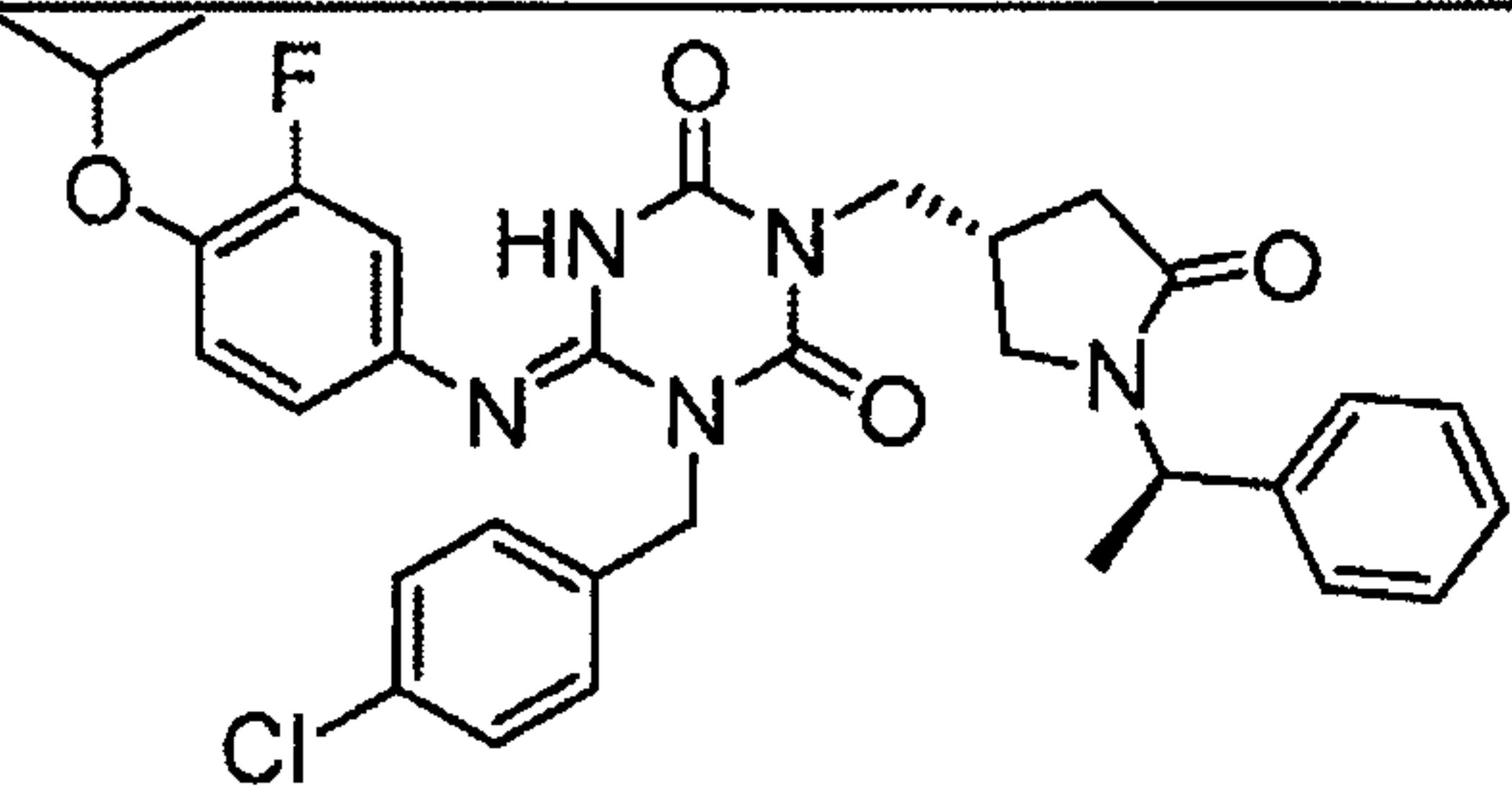
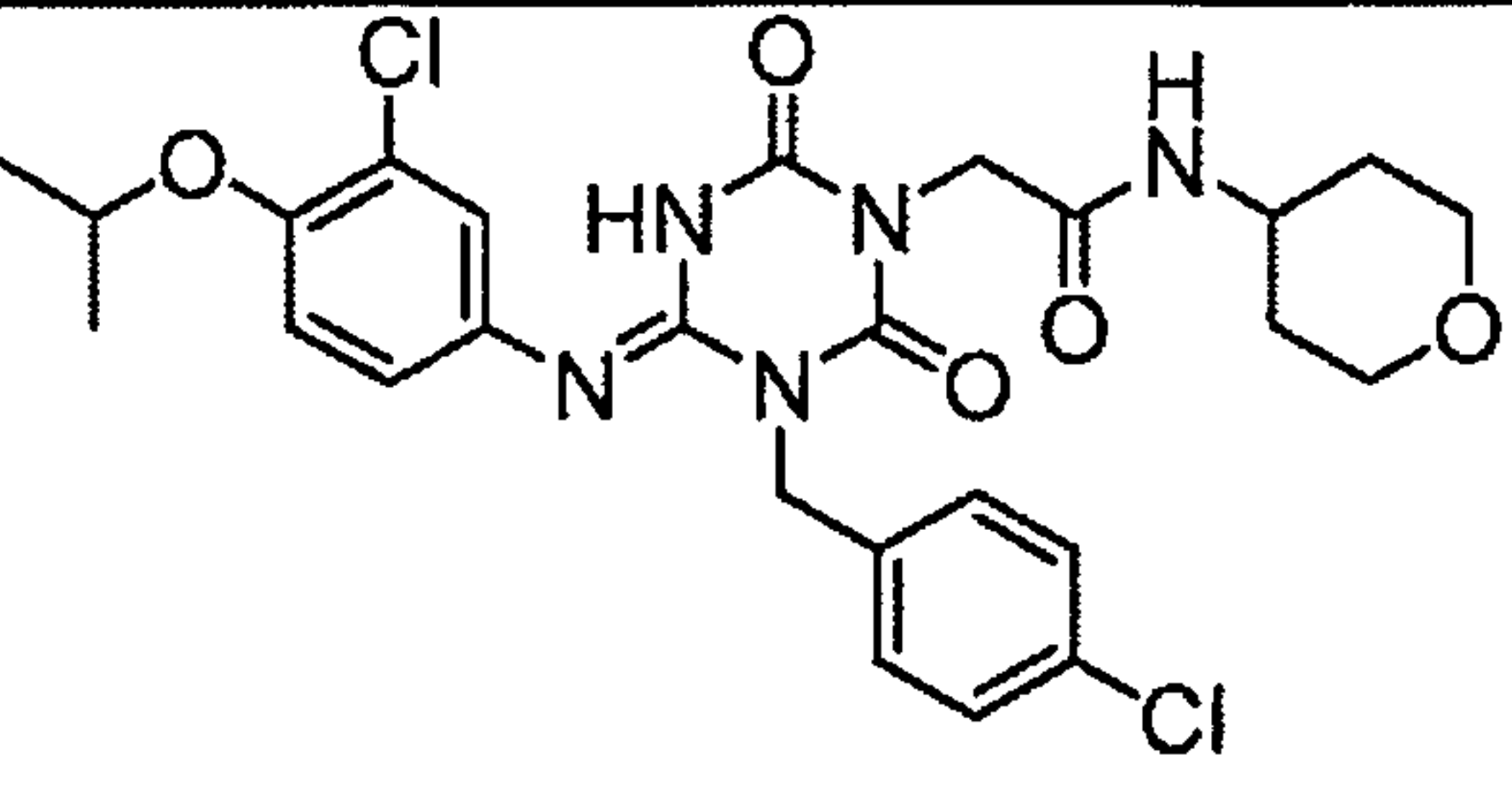
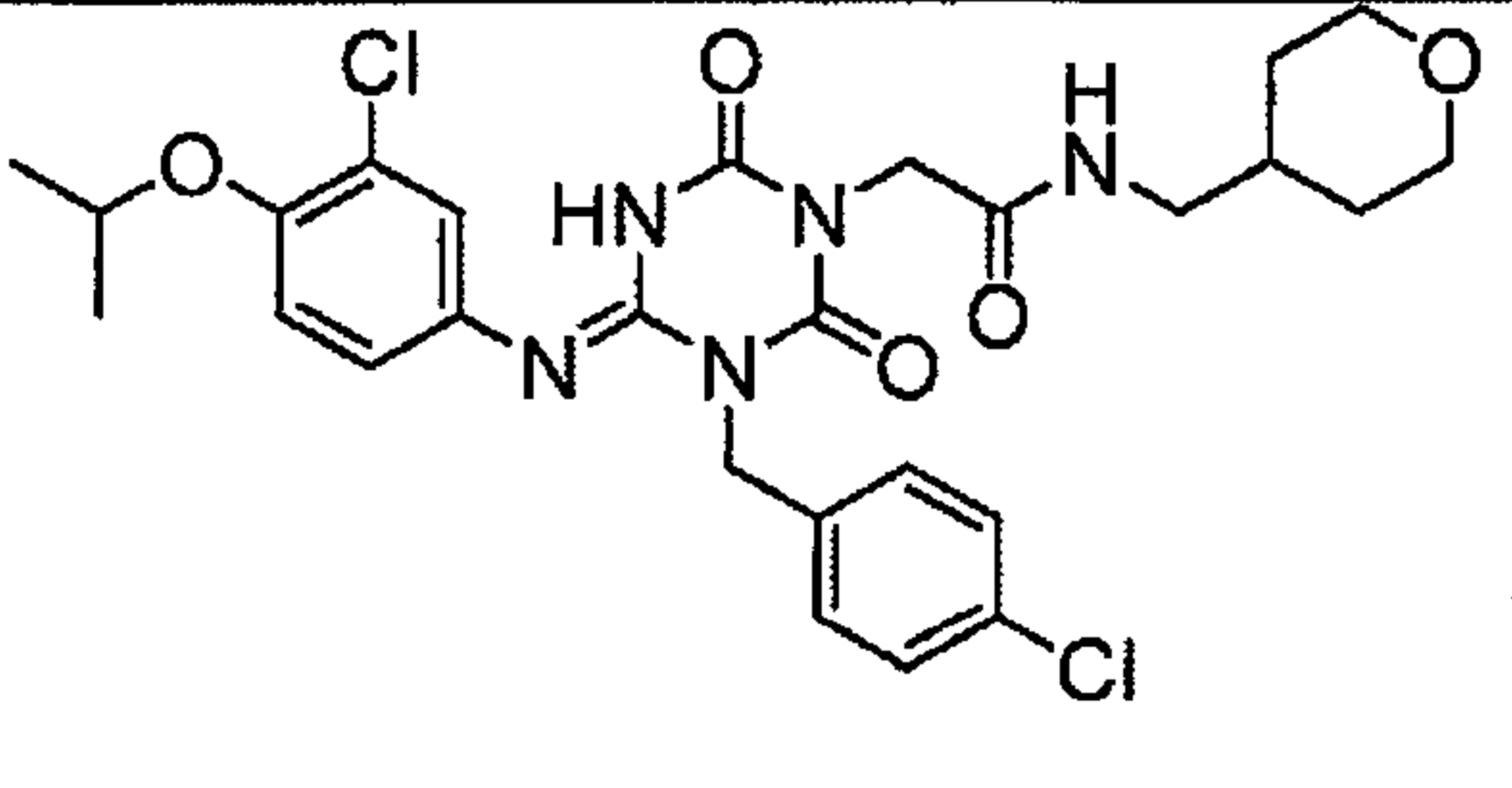
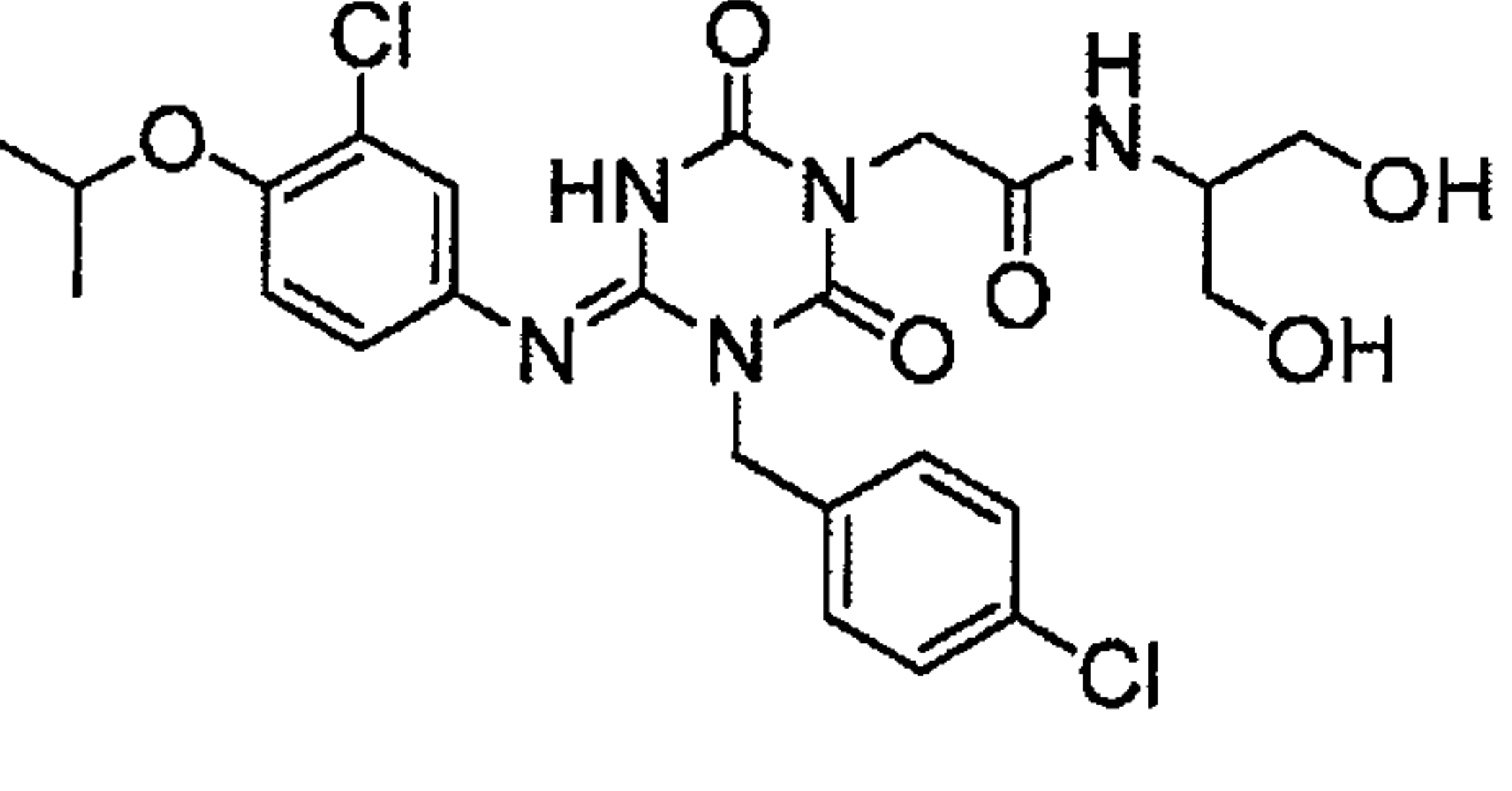
Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0651	2.14	507	2
	I-0652	2.24	592	2
	I-0653	1.90	529	2
	I-0654	1.64	513	2
	I-0655	2.47	513	3

[0319]

[Table 135]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0656	2.44	501	3
	I-0657	1.93	473	3
	I-0658	2.21	499	3
	I-0659	1.49	490	2
	I-0660	2.28	493	2

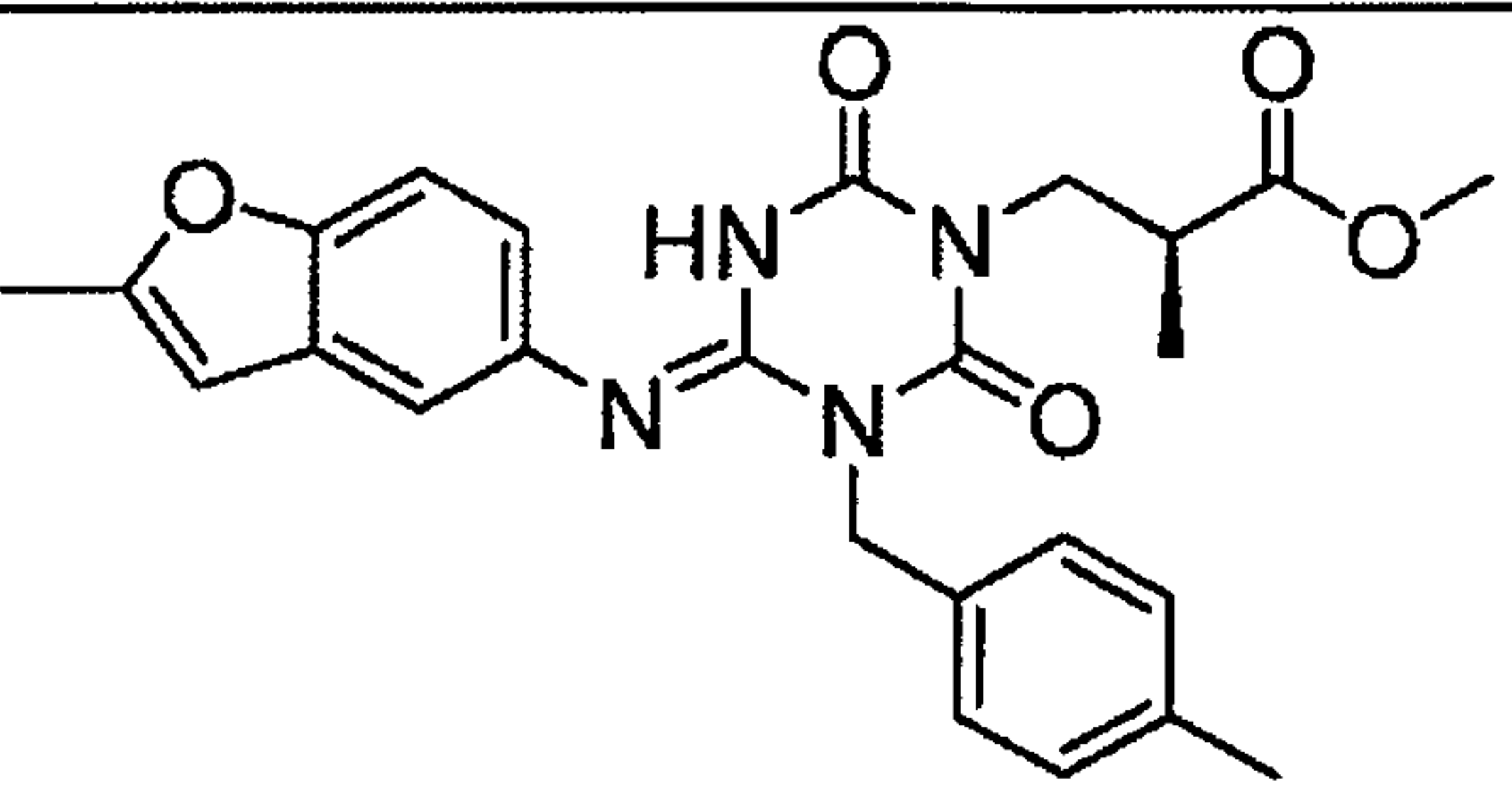
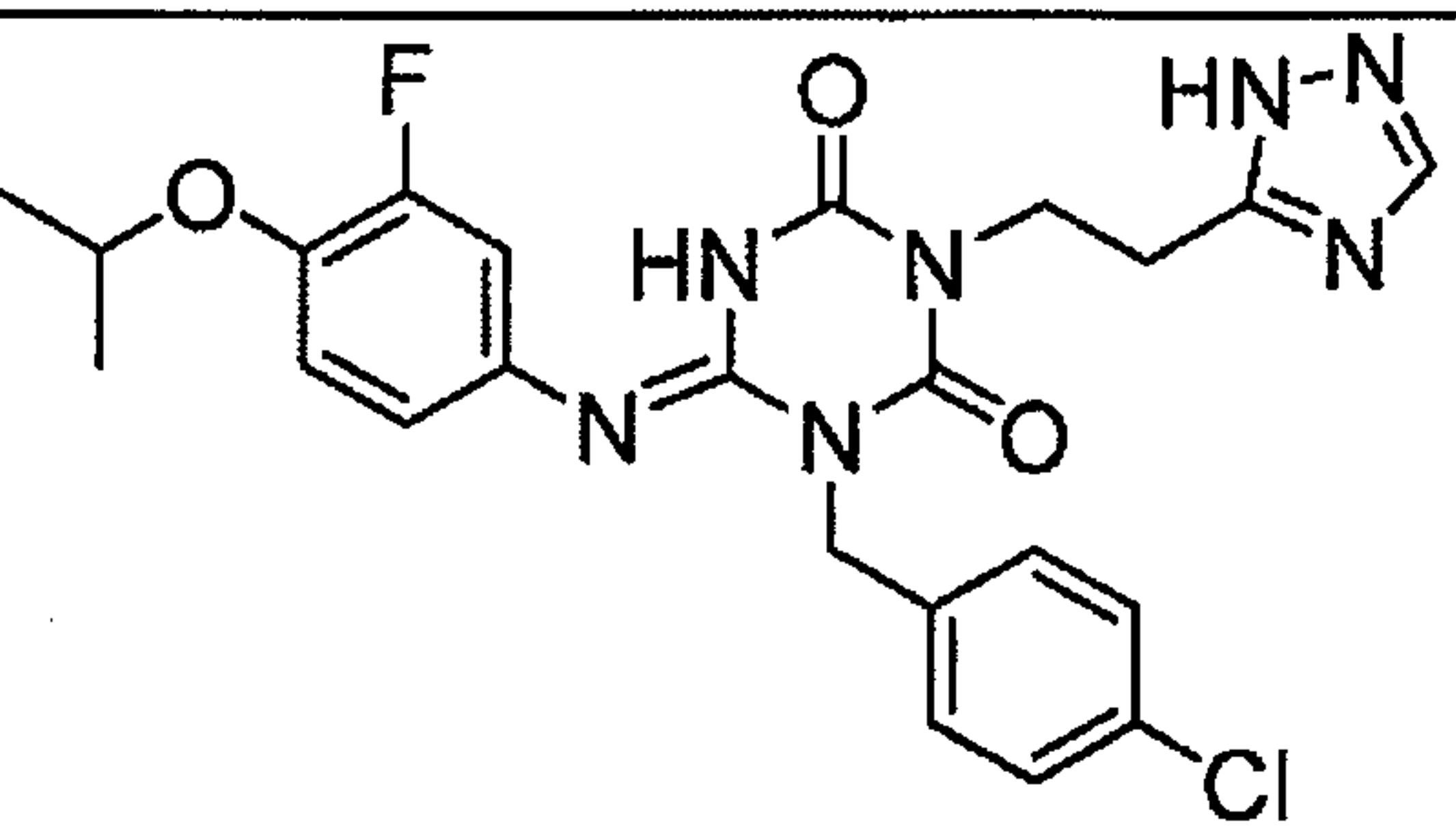
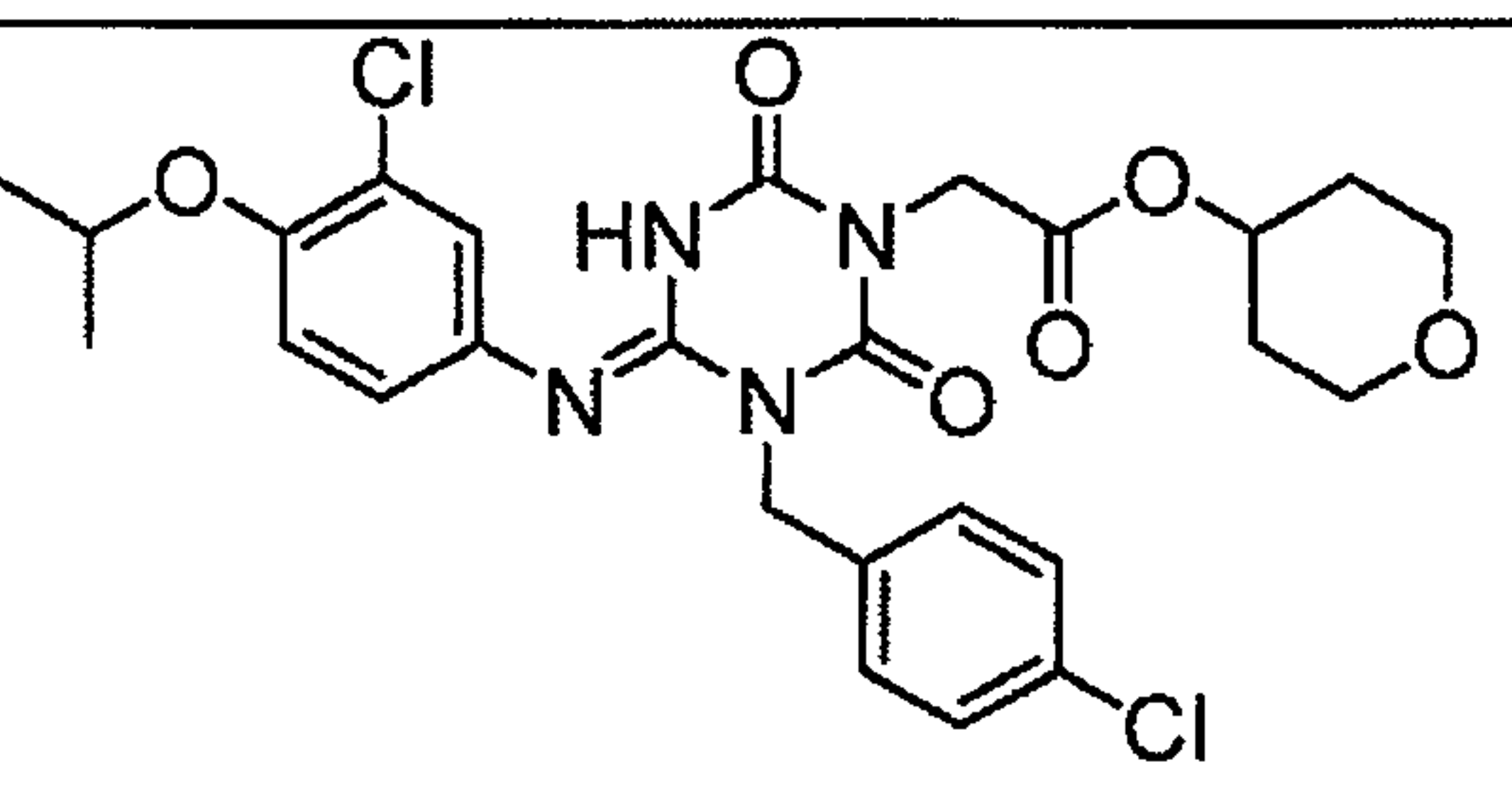
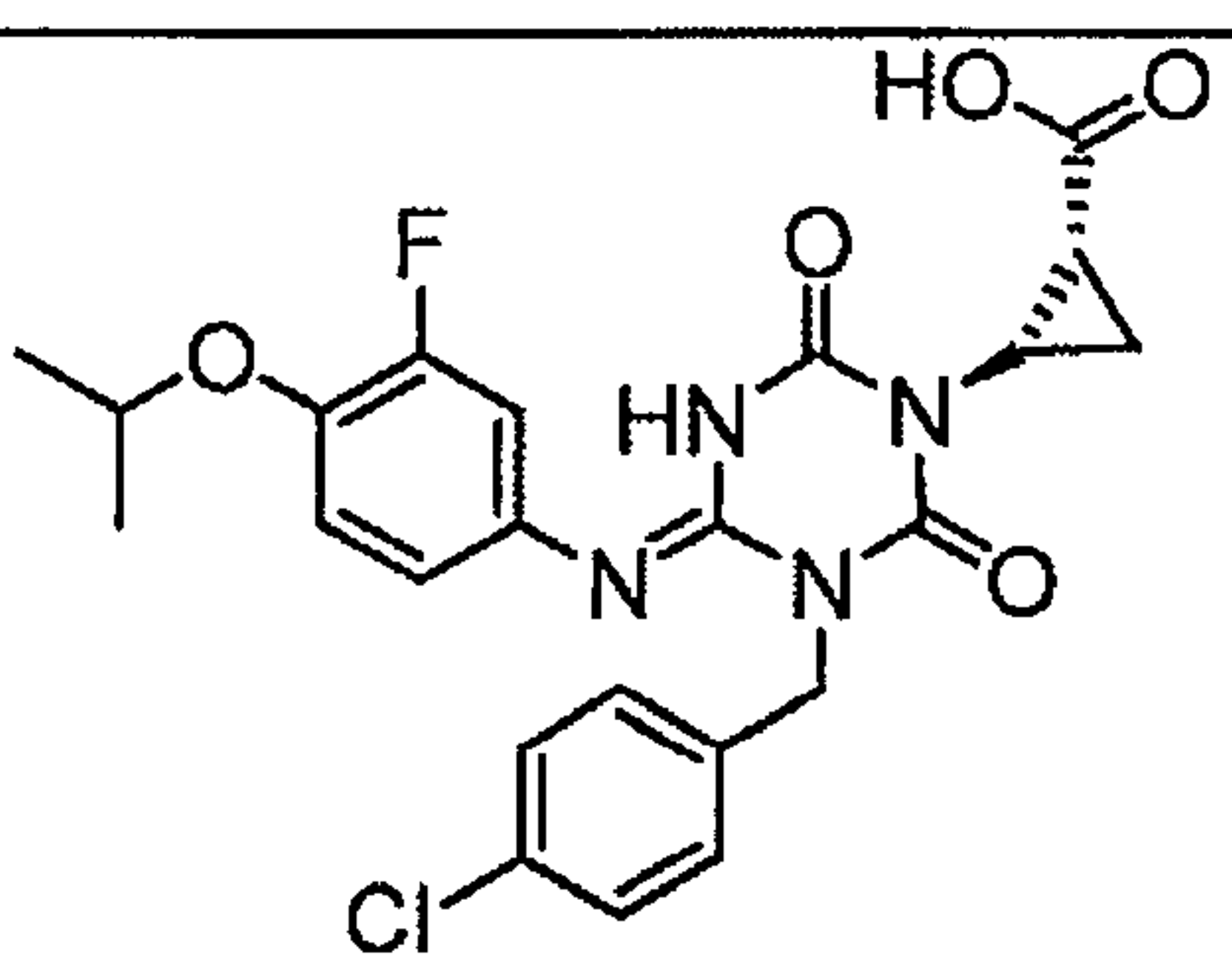
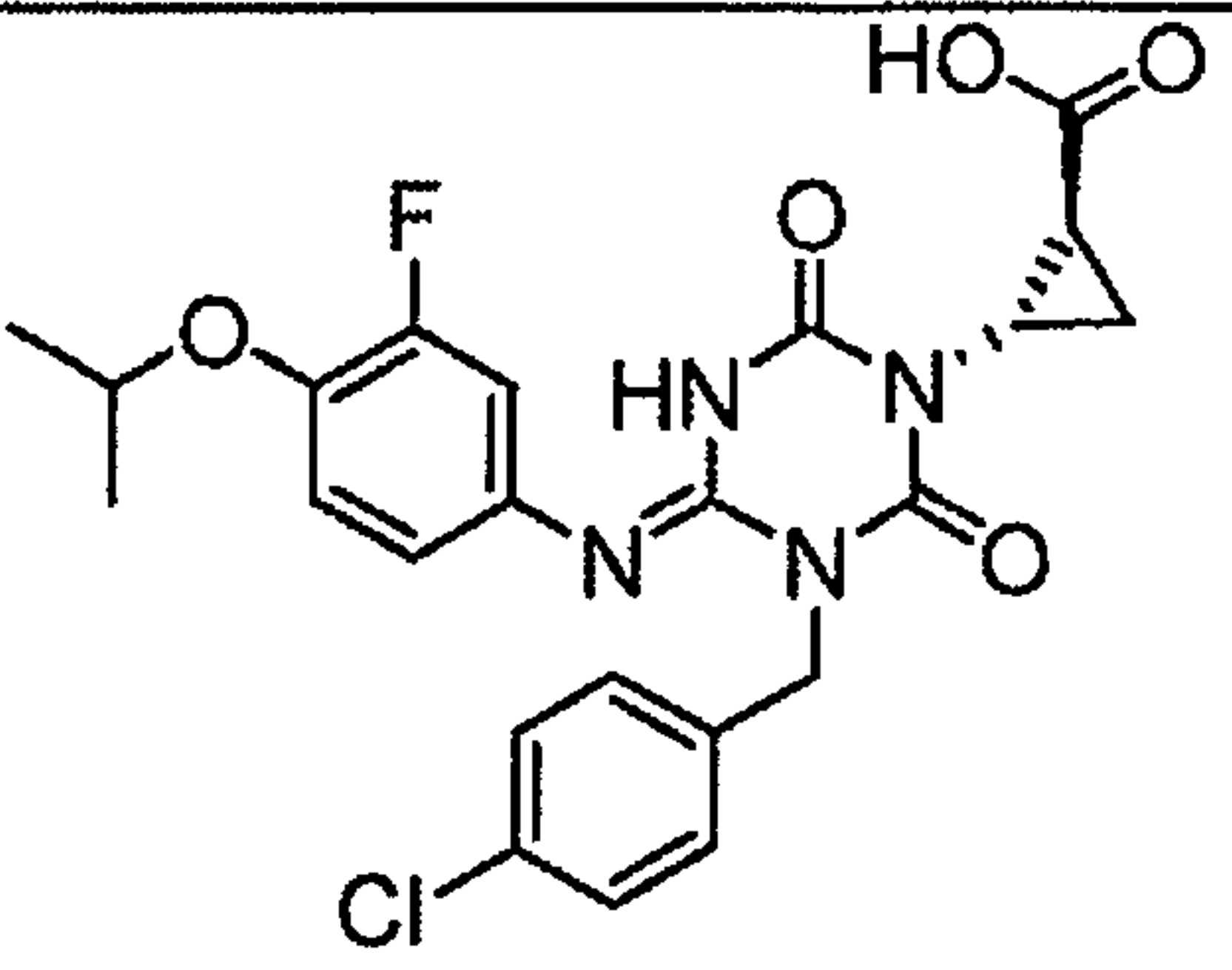
[Table 136]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0661	2.35	606	2
	I-0662	2.35	606	2
	I-0663	2.04	562	2
	I-0664	2.06	576	2
	I-0665	1.79	552	2

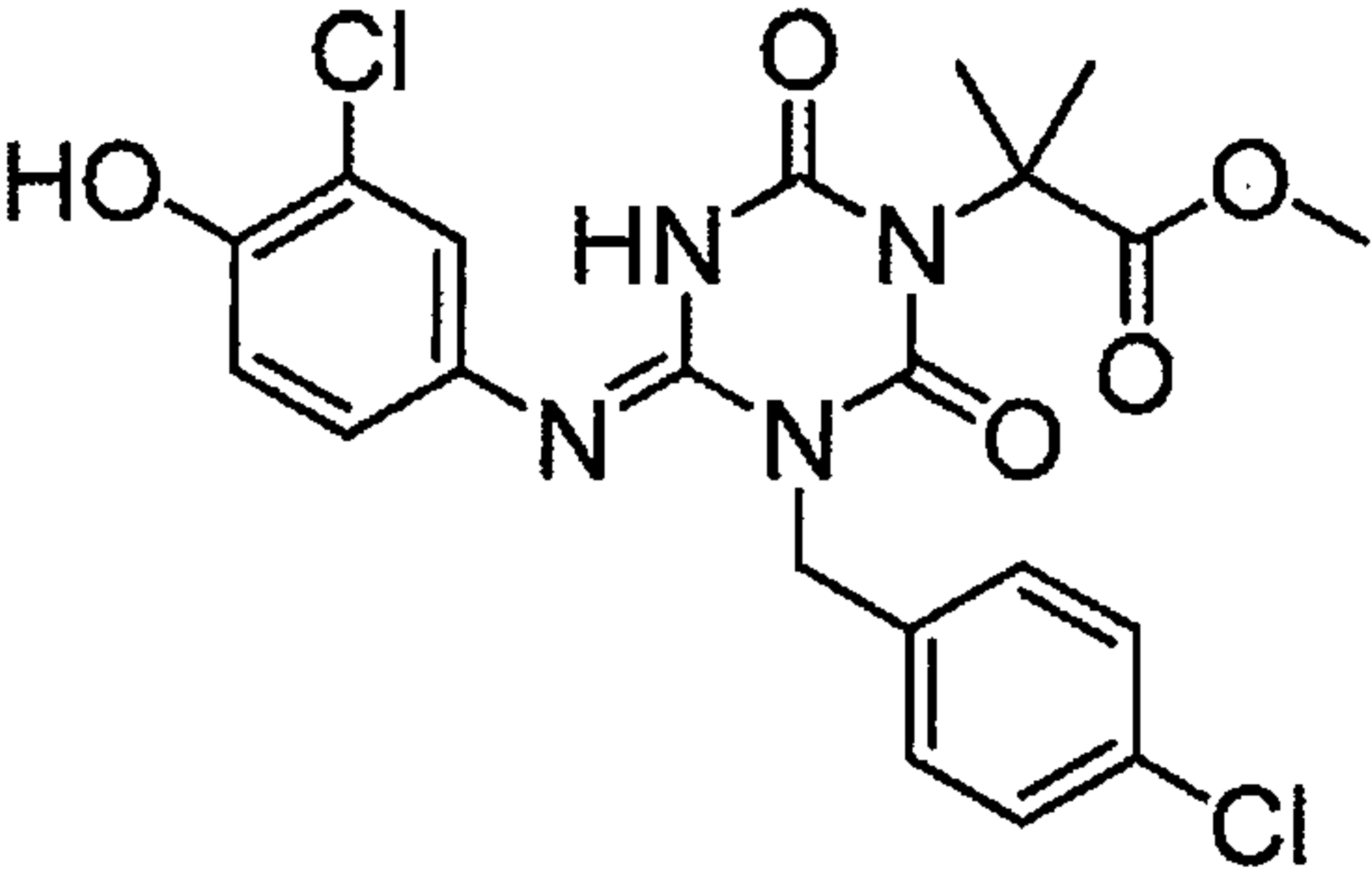
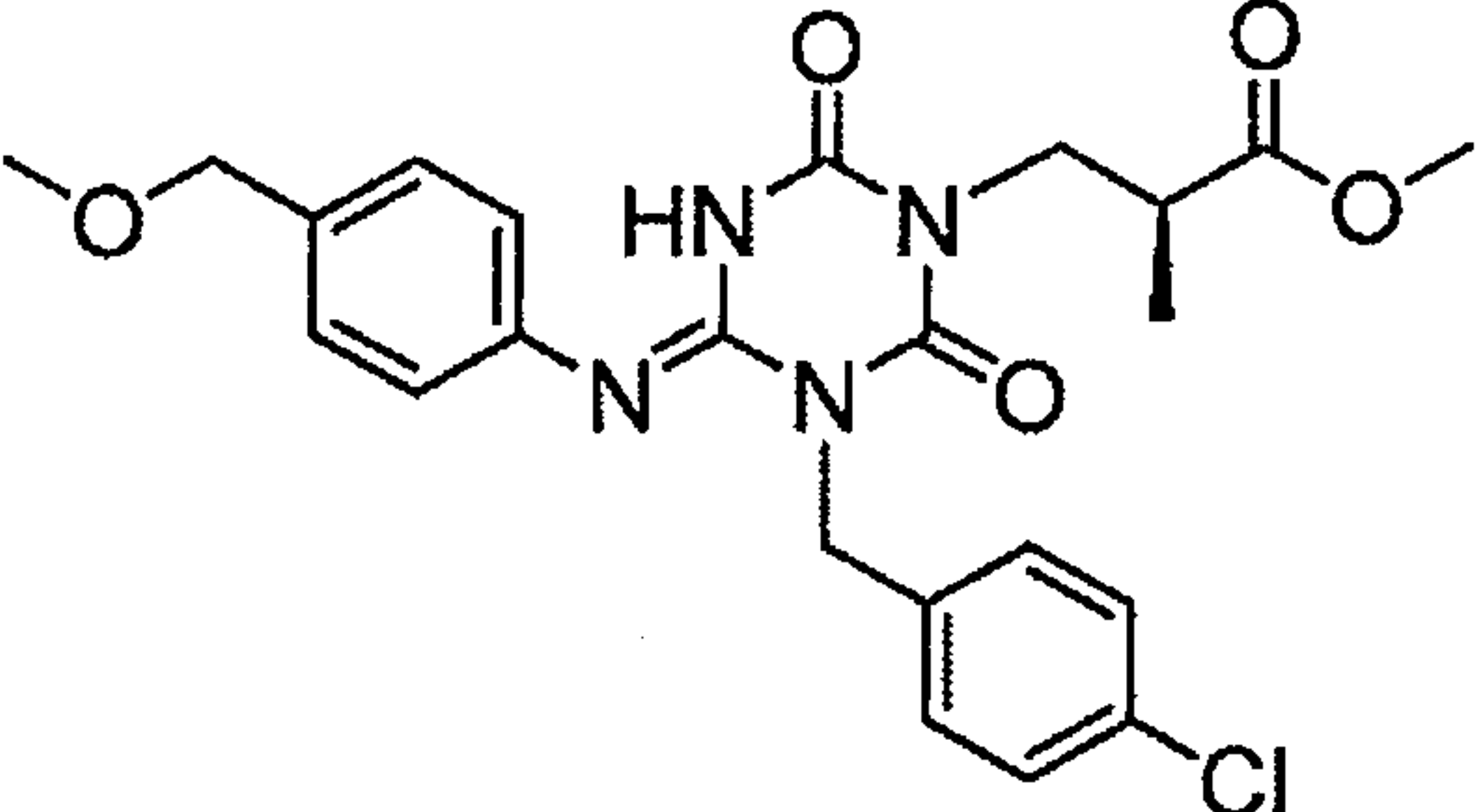
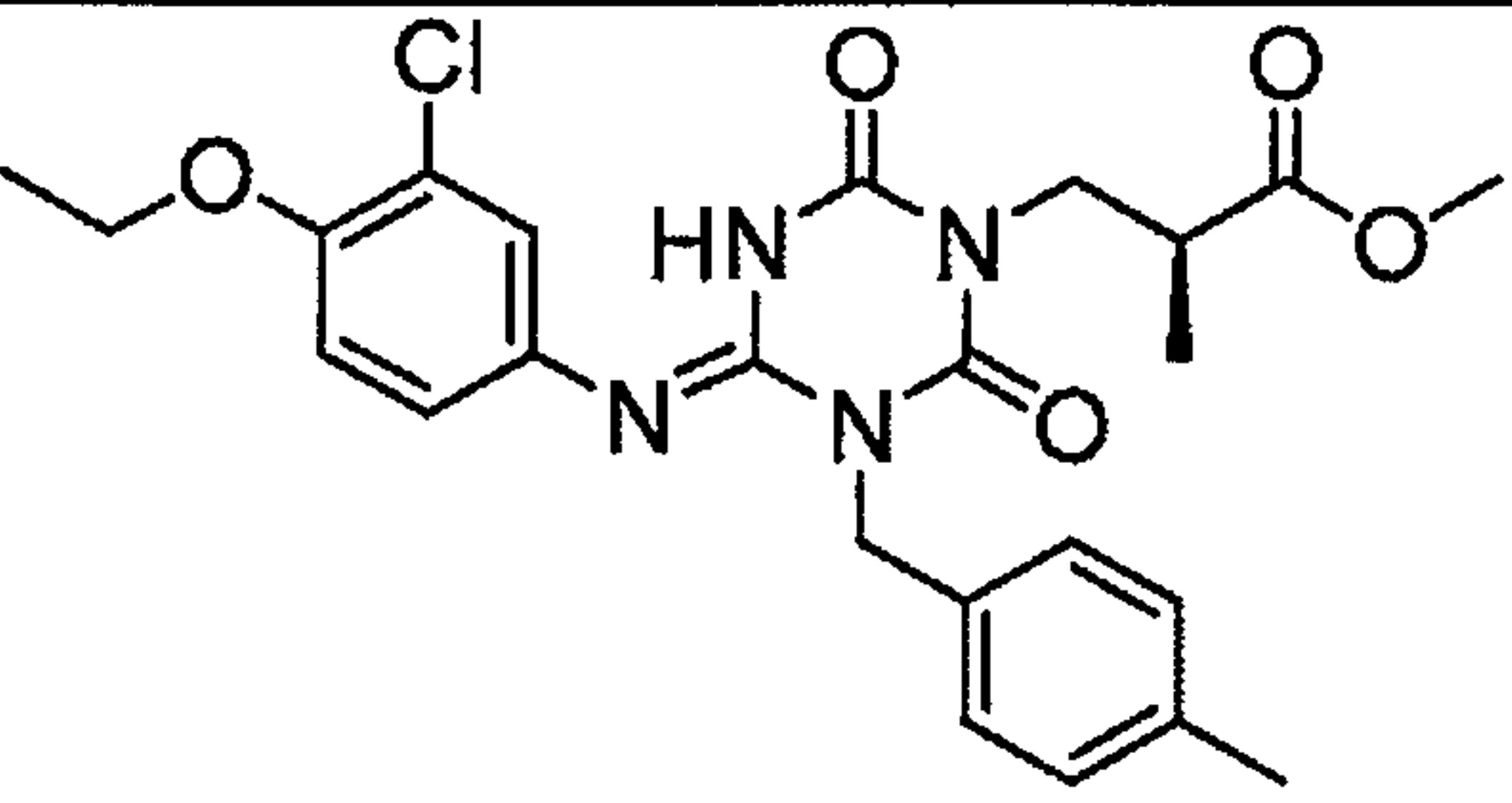
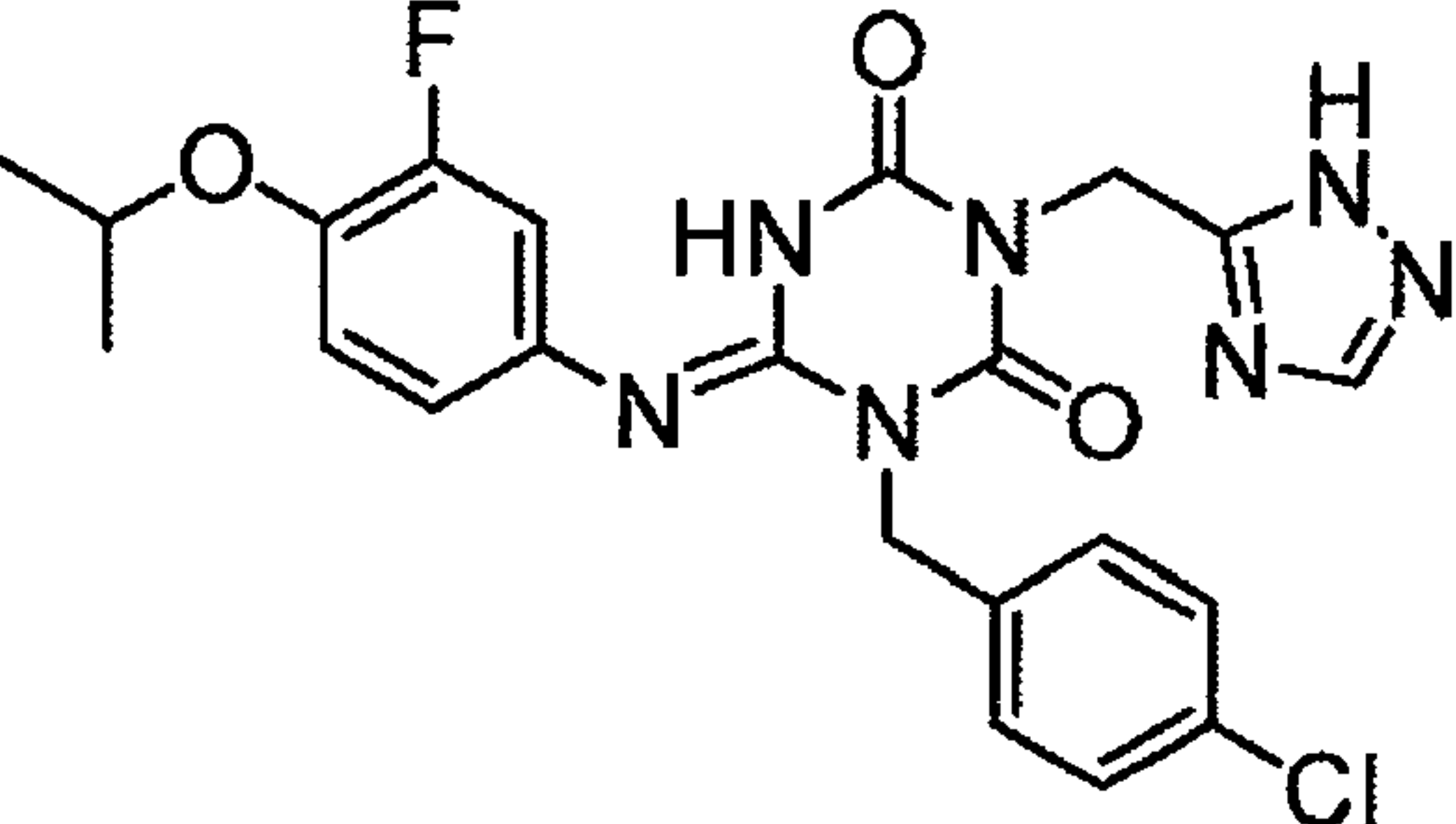
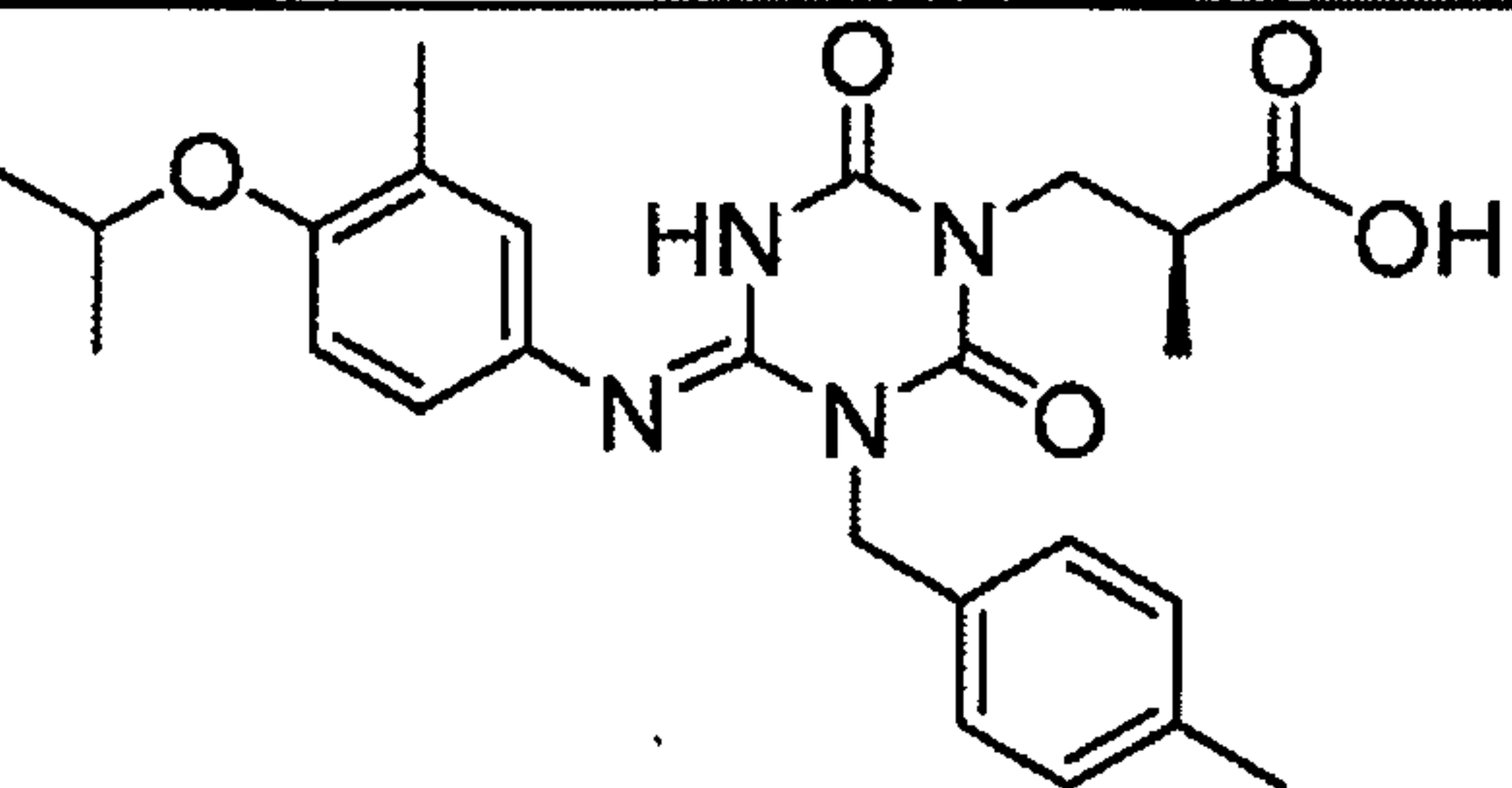
[Table 137]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0666	2.13	590	2
	I-0667	2.34	577	2
	I-0668	1.67	459	3
	I-0669	1.98	487	2
	I-0670	2.28	481	2

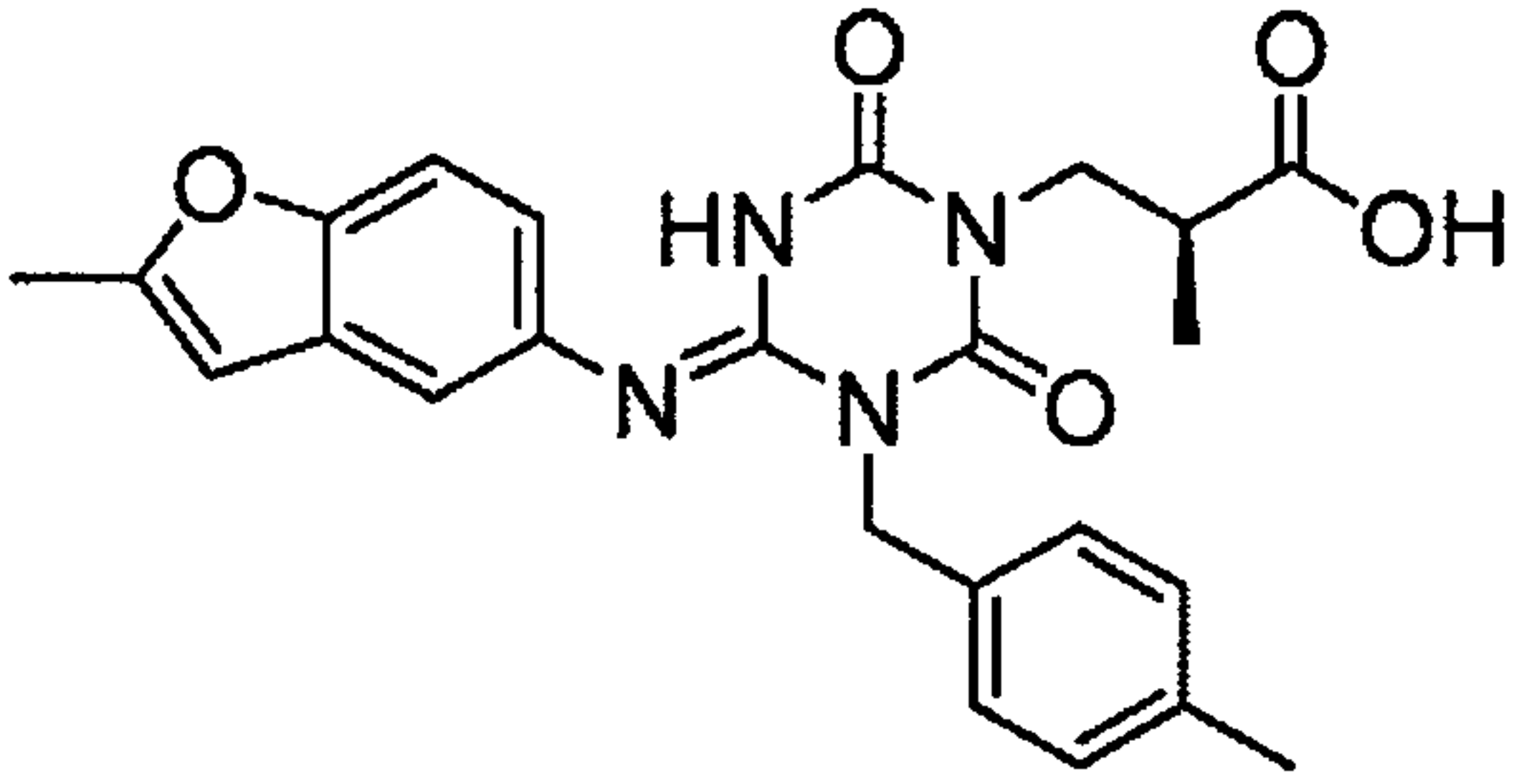
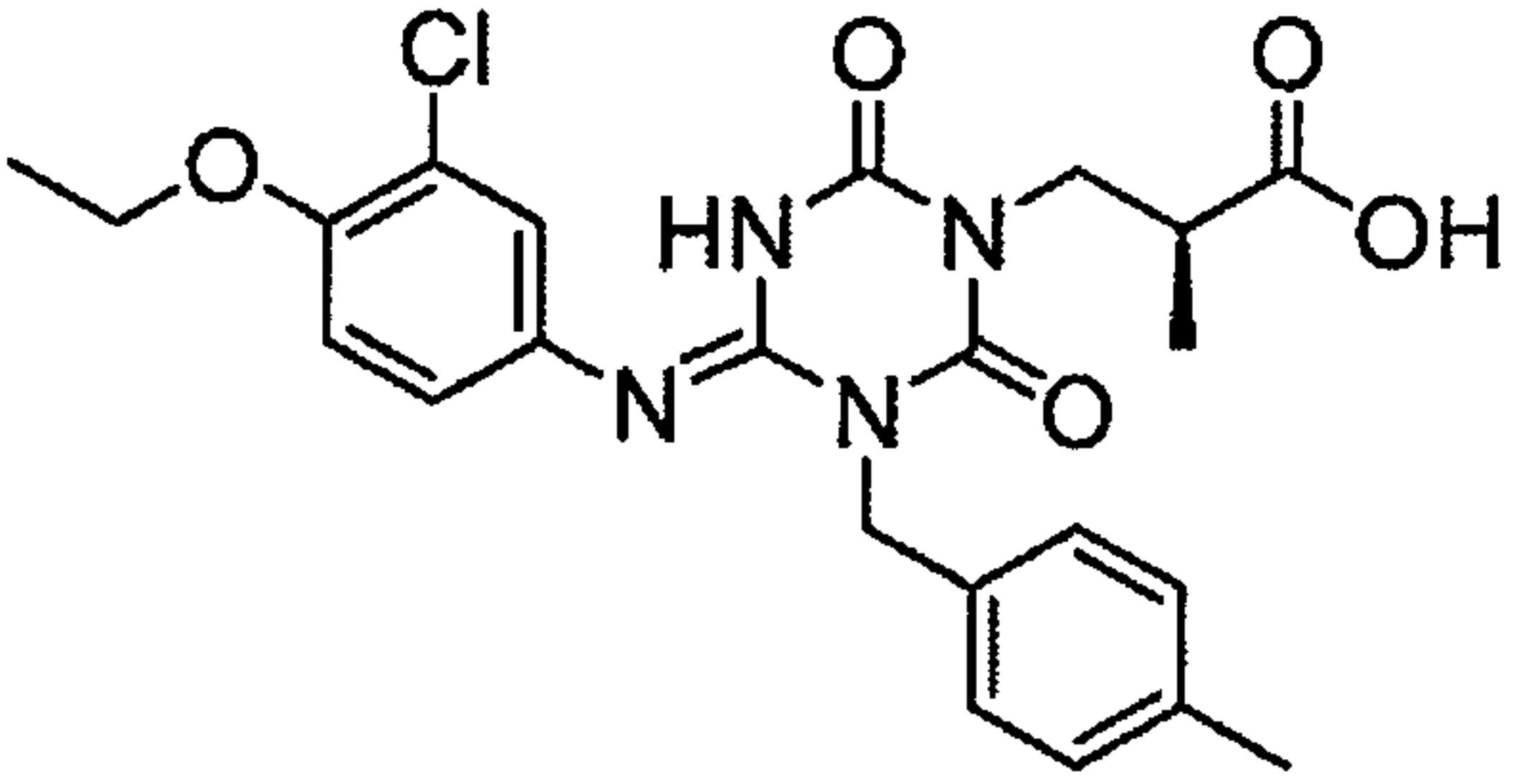
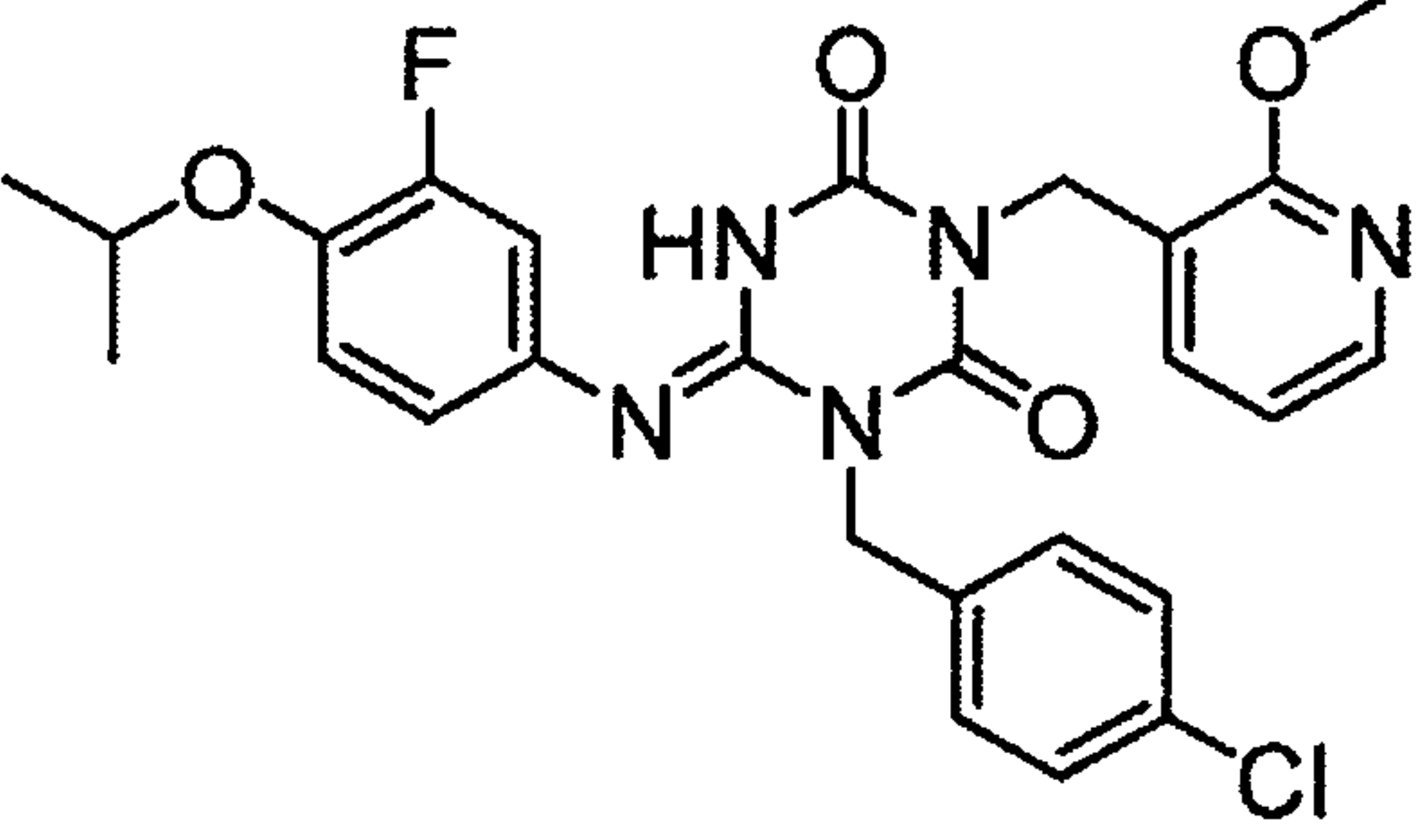
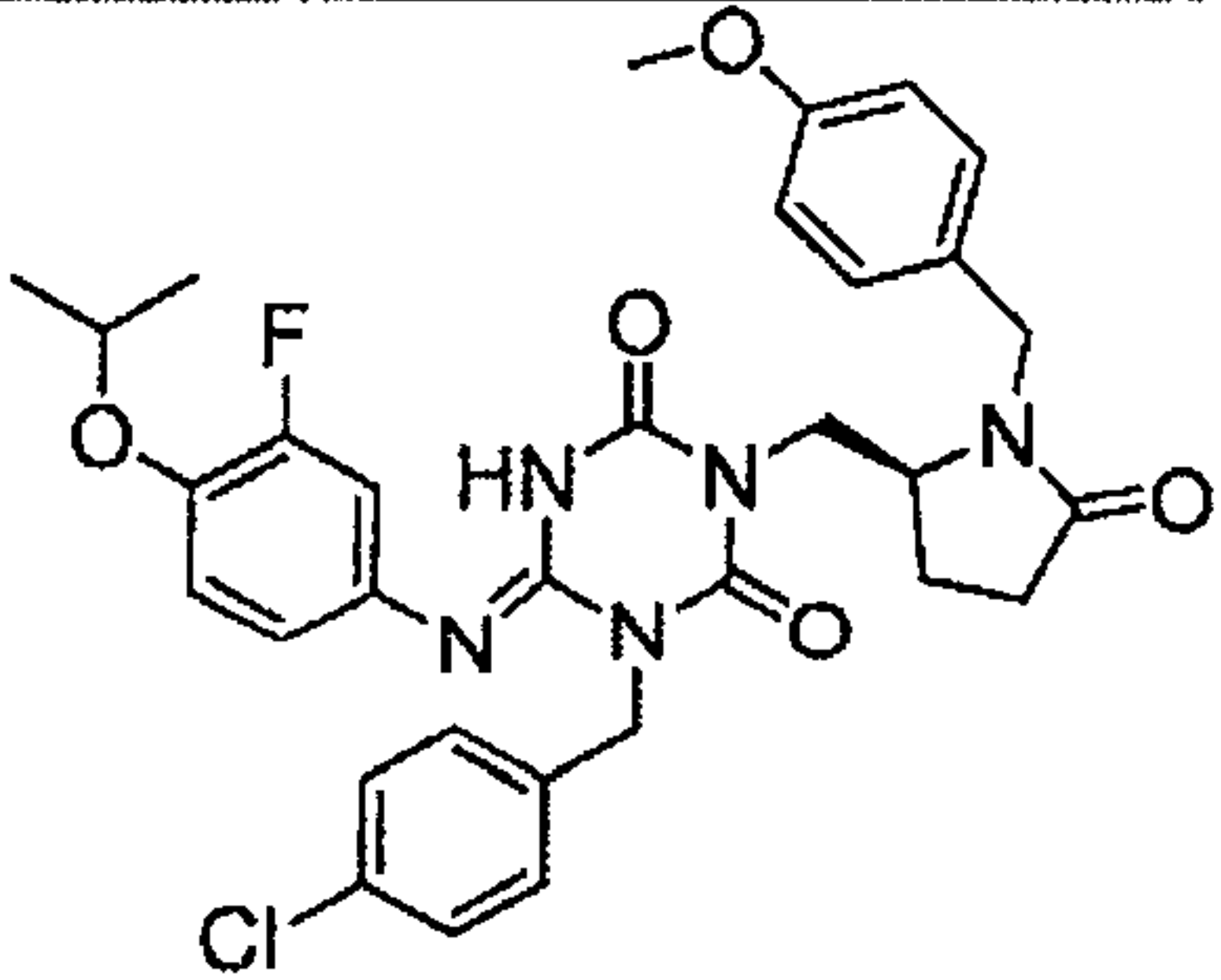
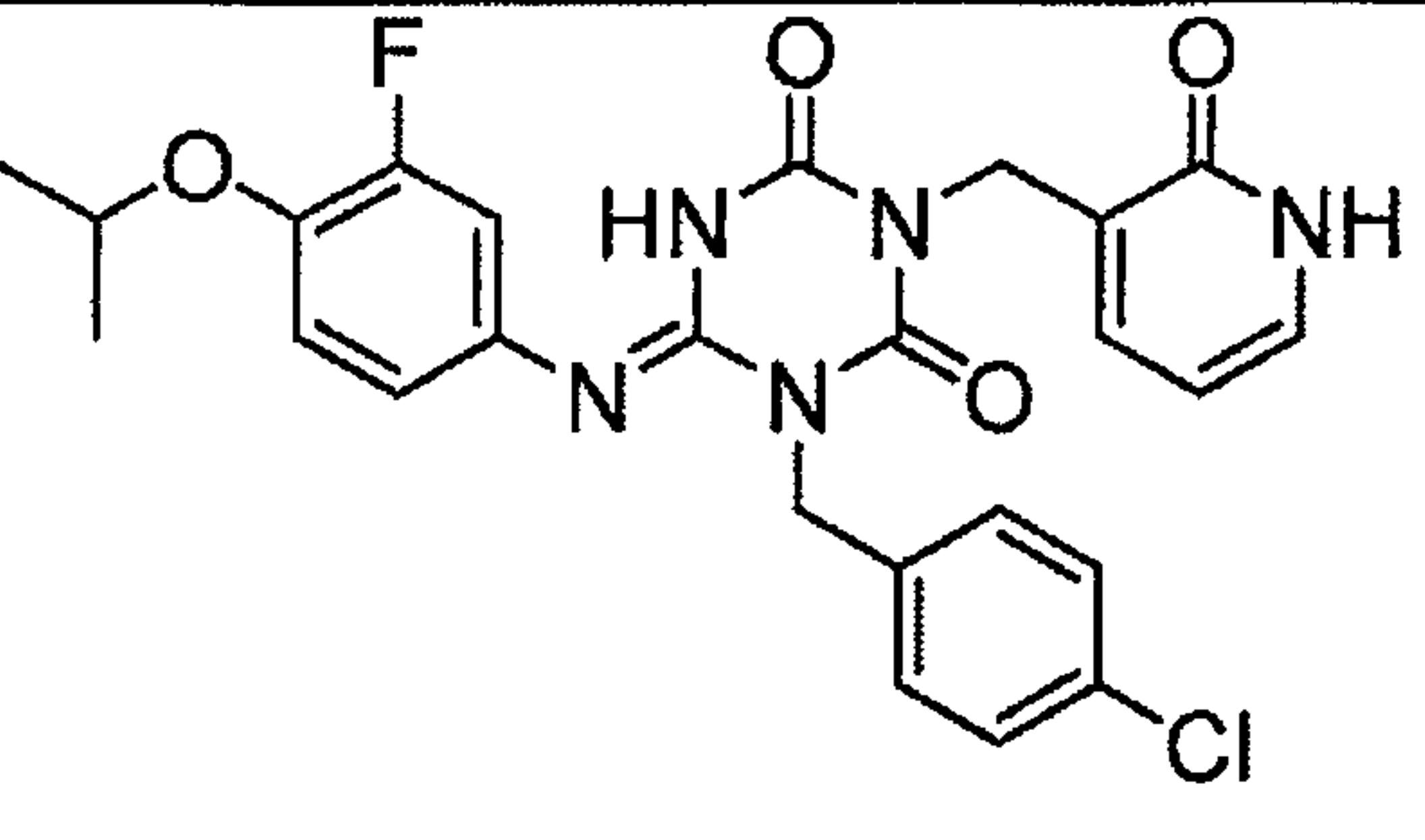
[Table 138]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0671	2.09	463	2
	I-0672	1.81	500	2
	I-0673	2.29	563	2
	I-0674	1.96	489	2
	I-0675	1.96	489	2

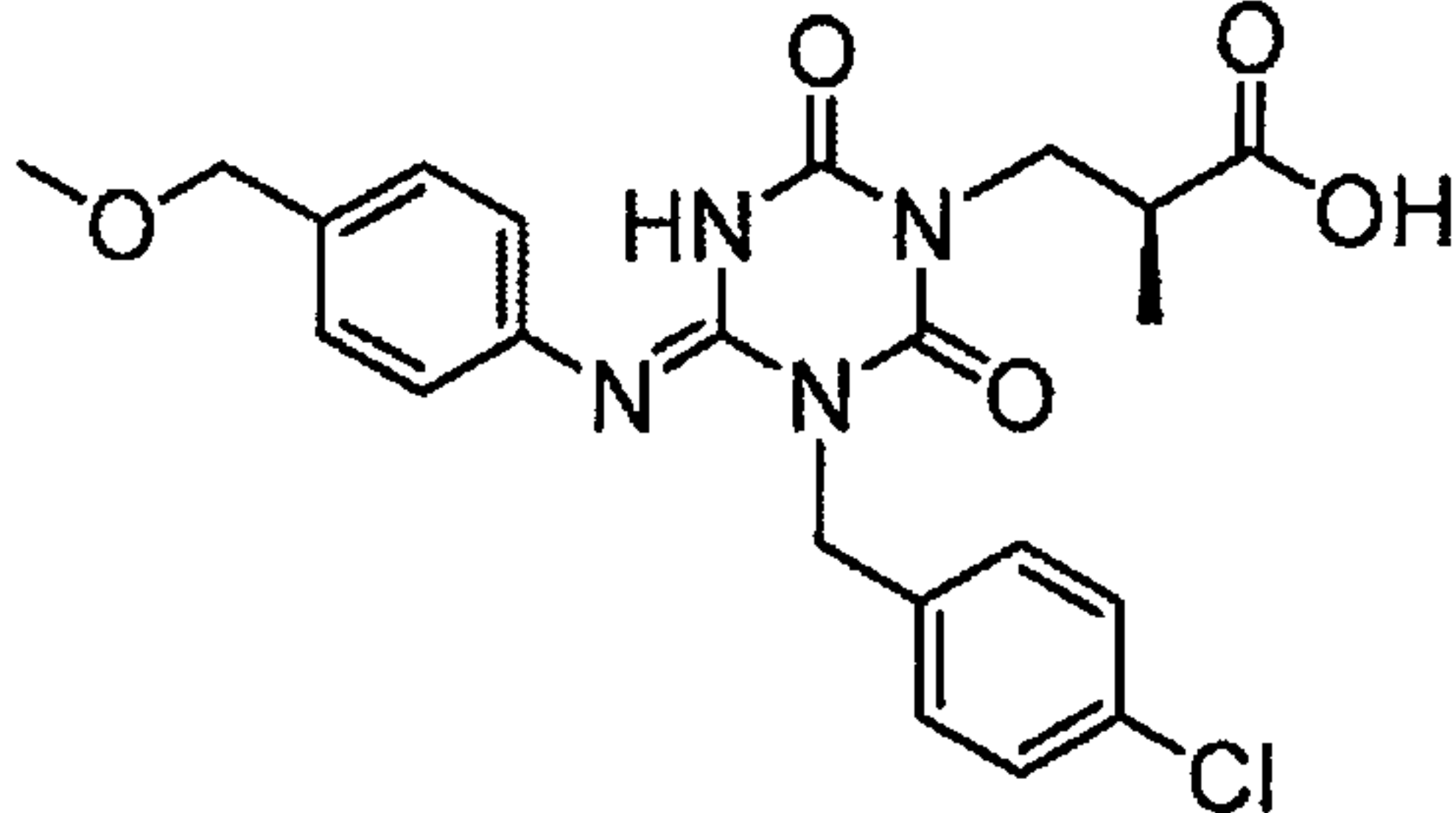
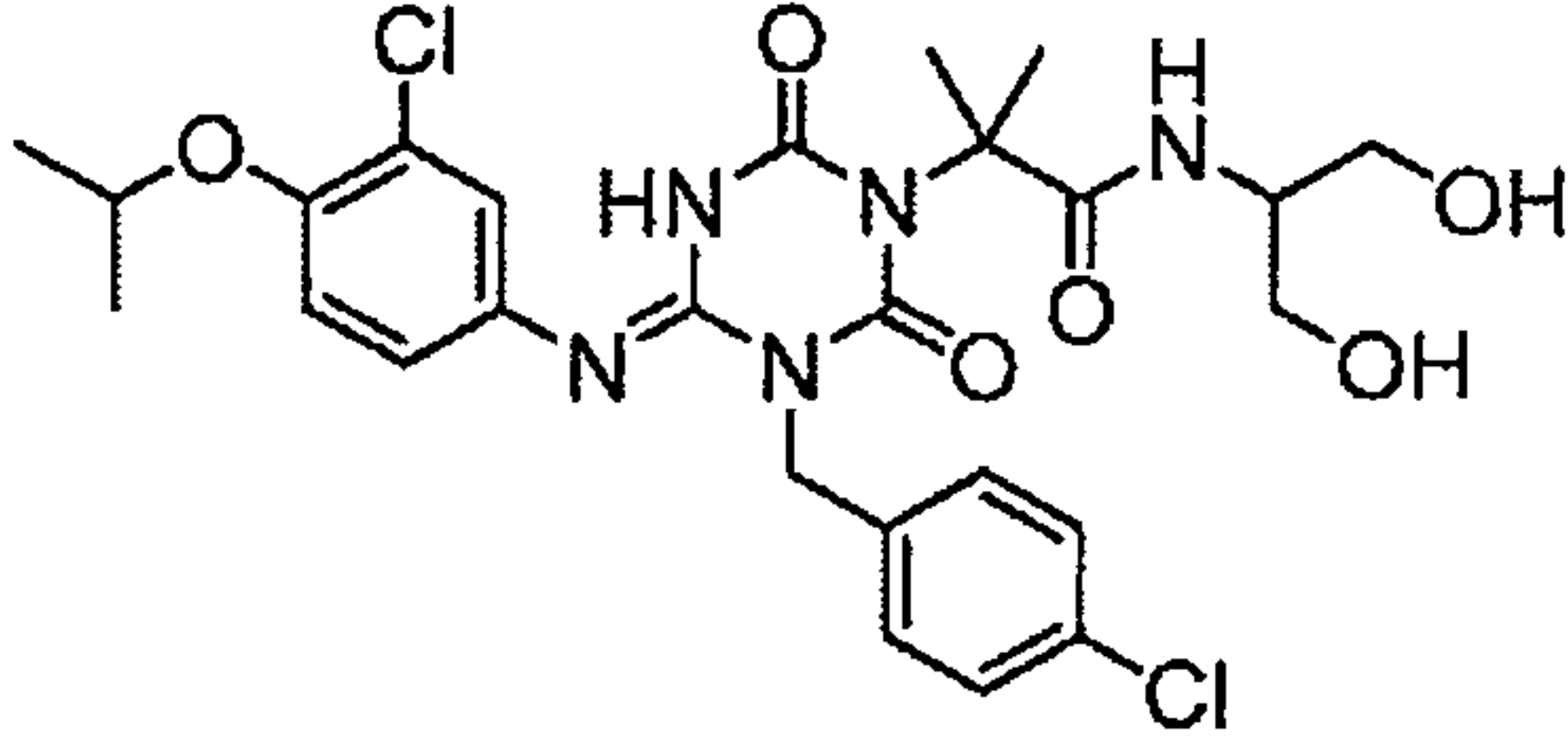
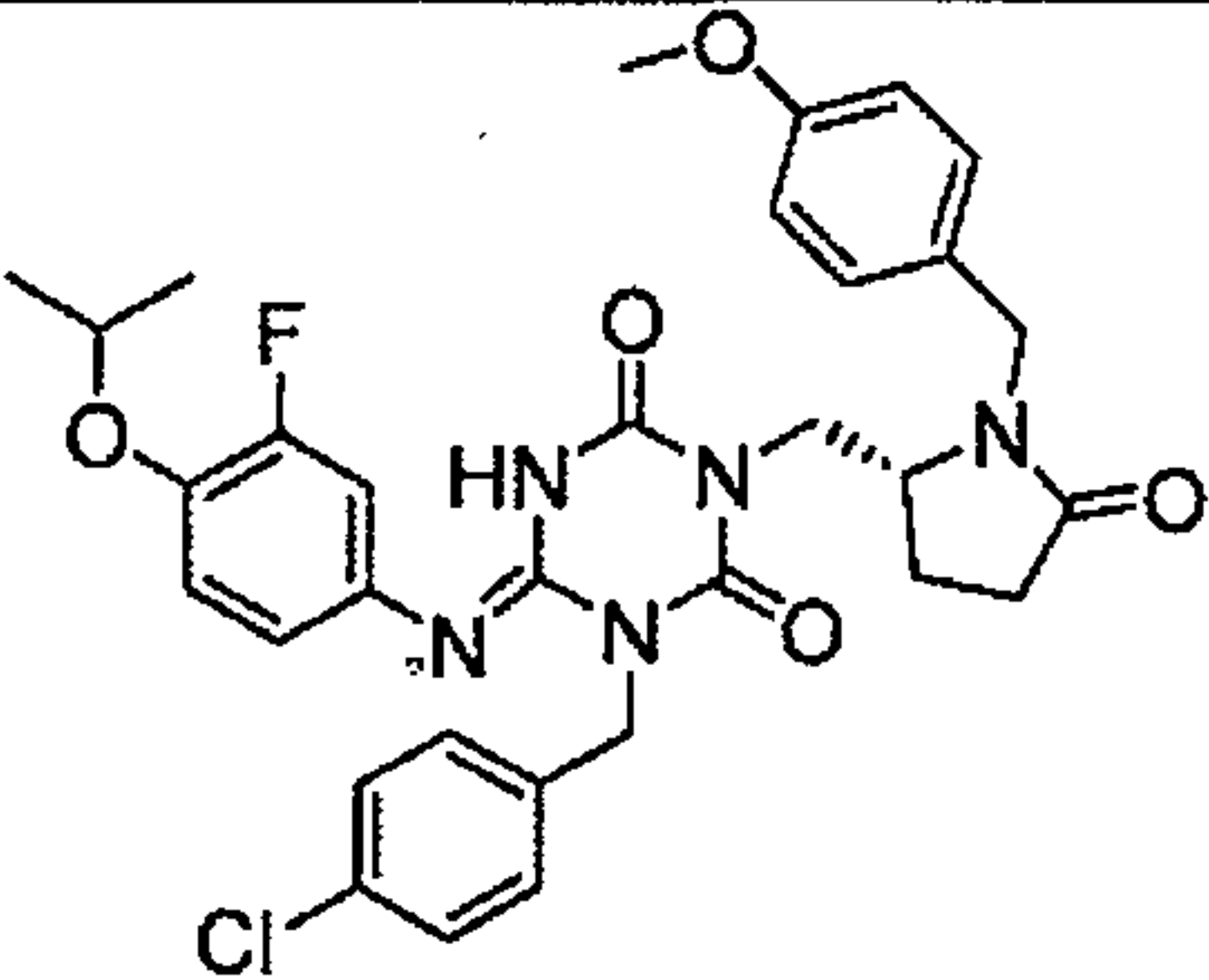
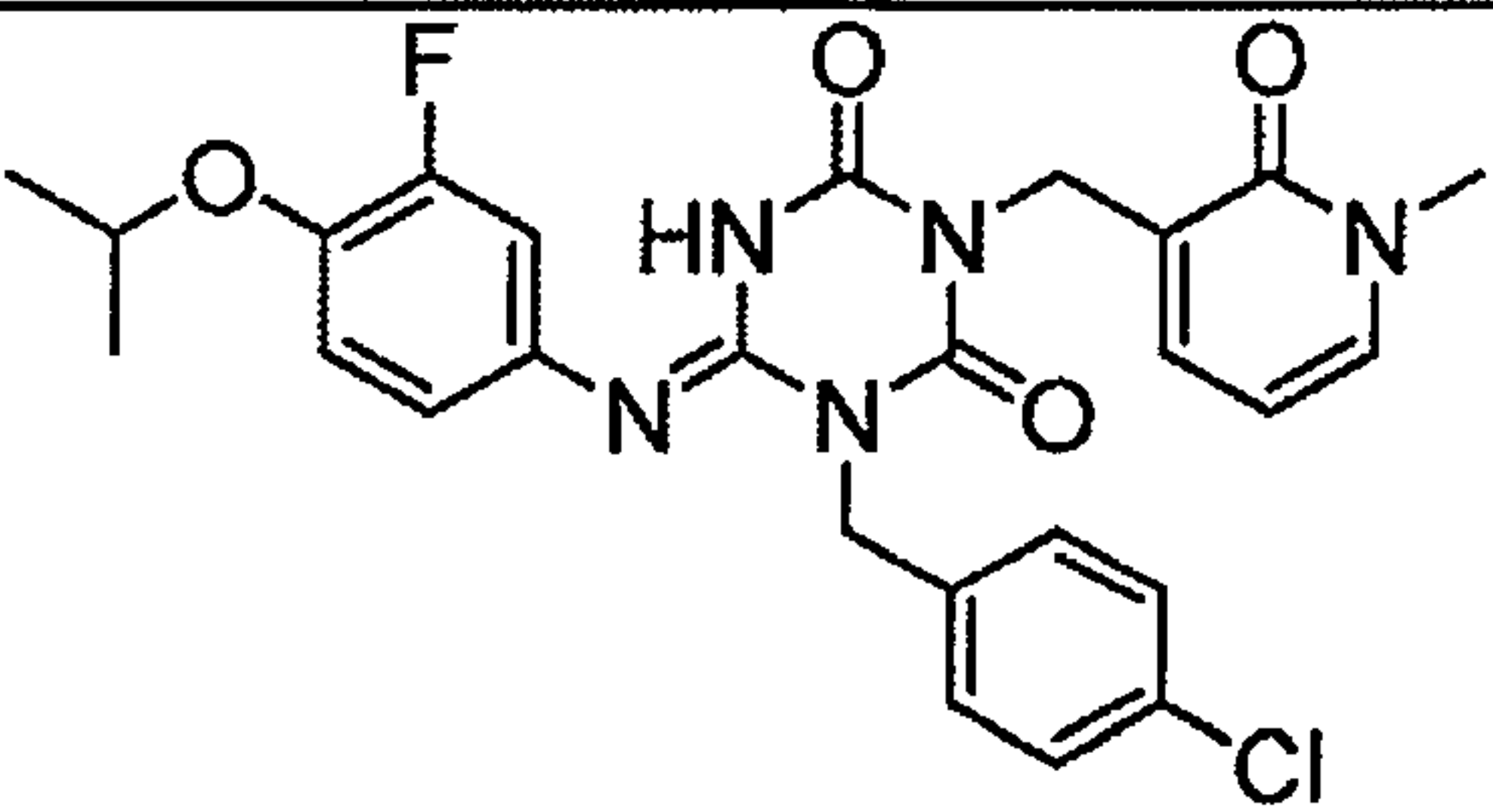
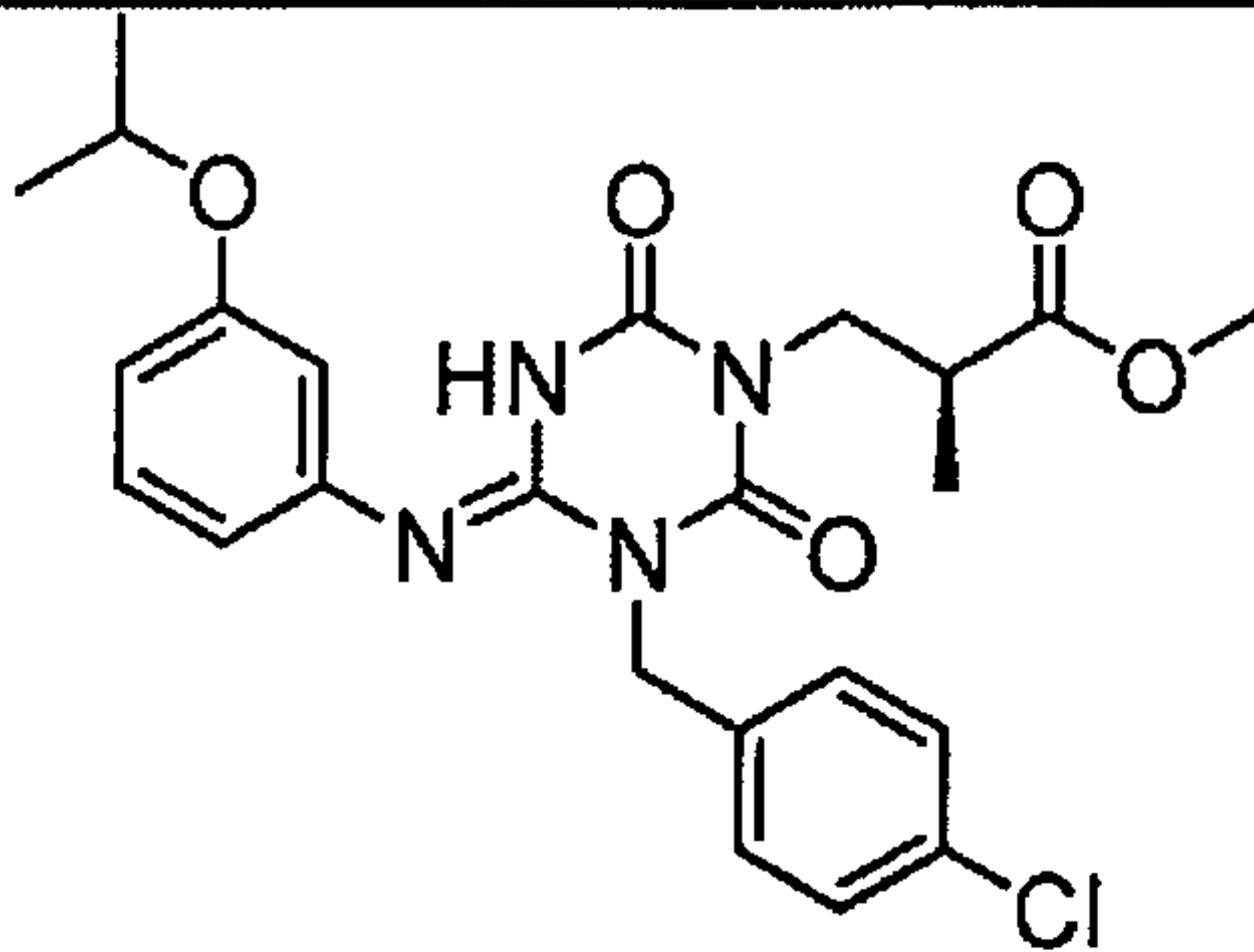
[Table 139]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0676	1.94	479	2
	I-0677	2.19	472	3
	I-0678	2.23	487	2
	I-0679	1.81	486	2
	I-0680	2.04	467	2

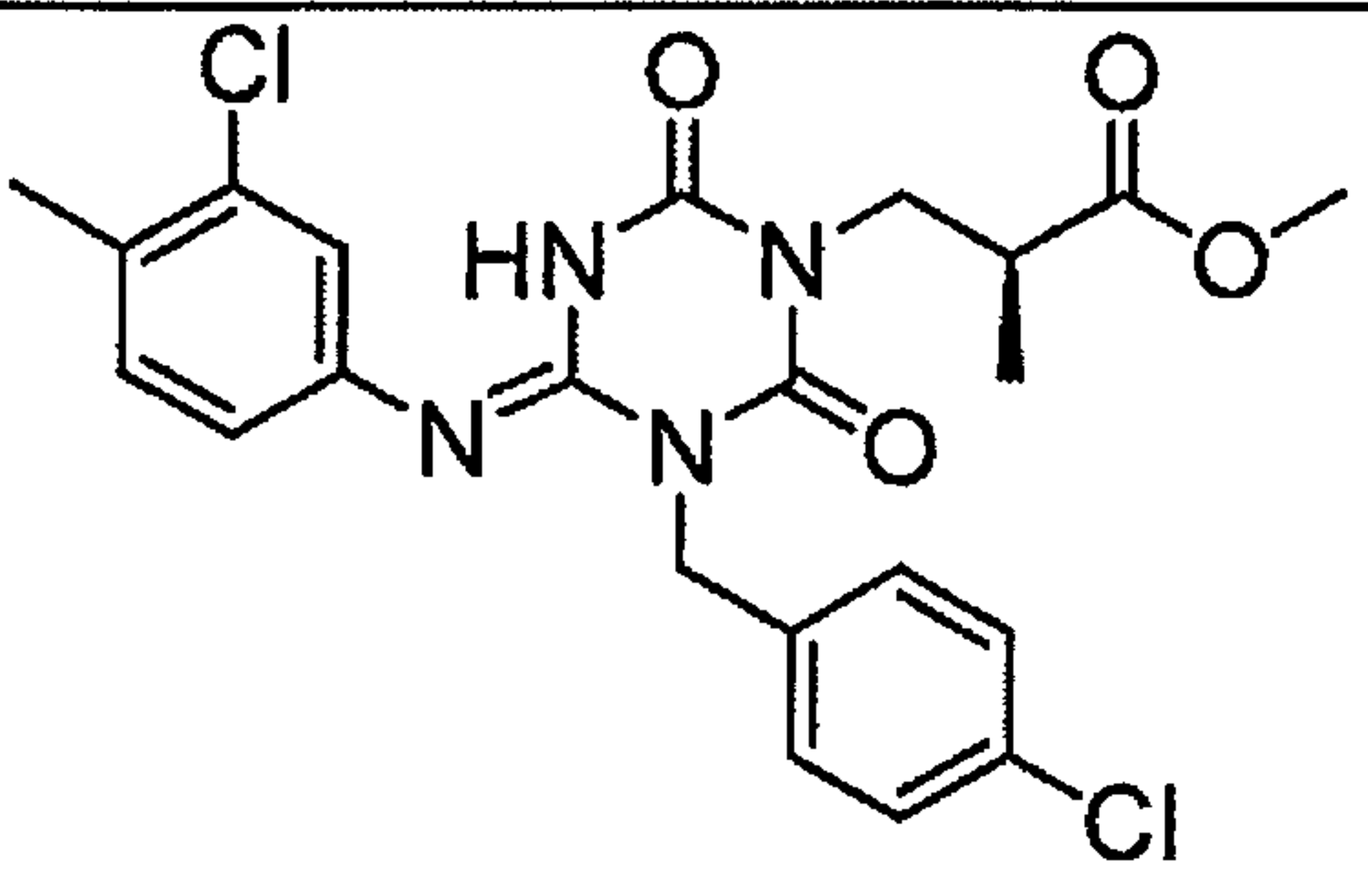
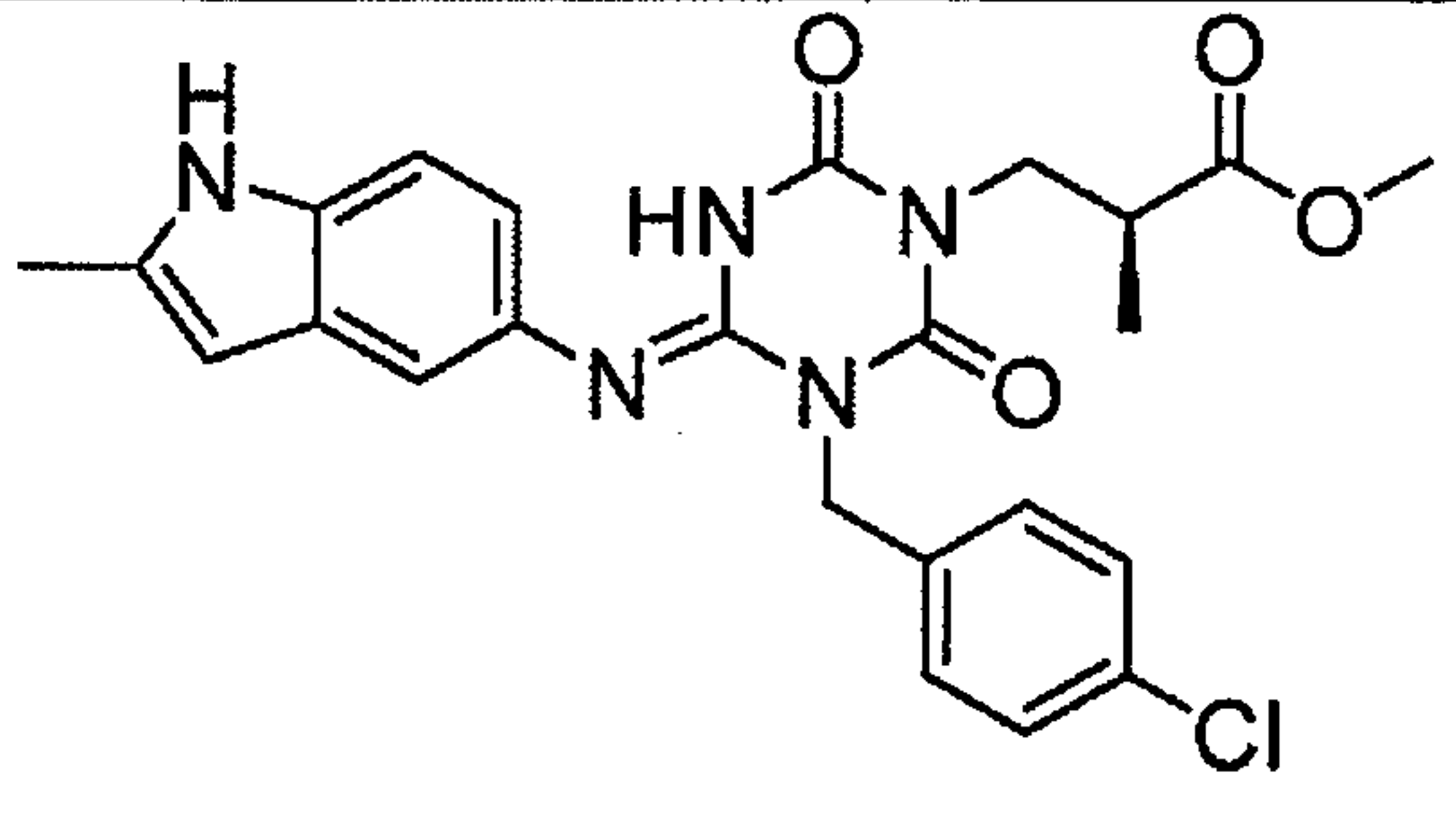
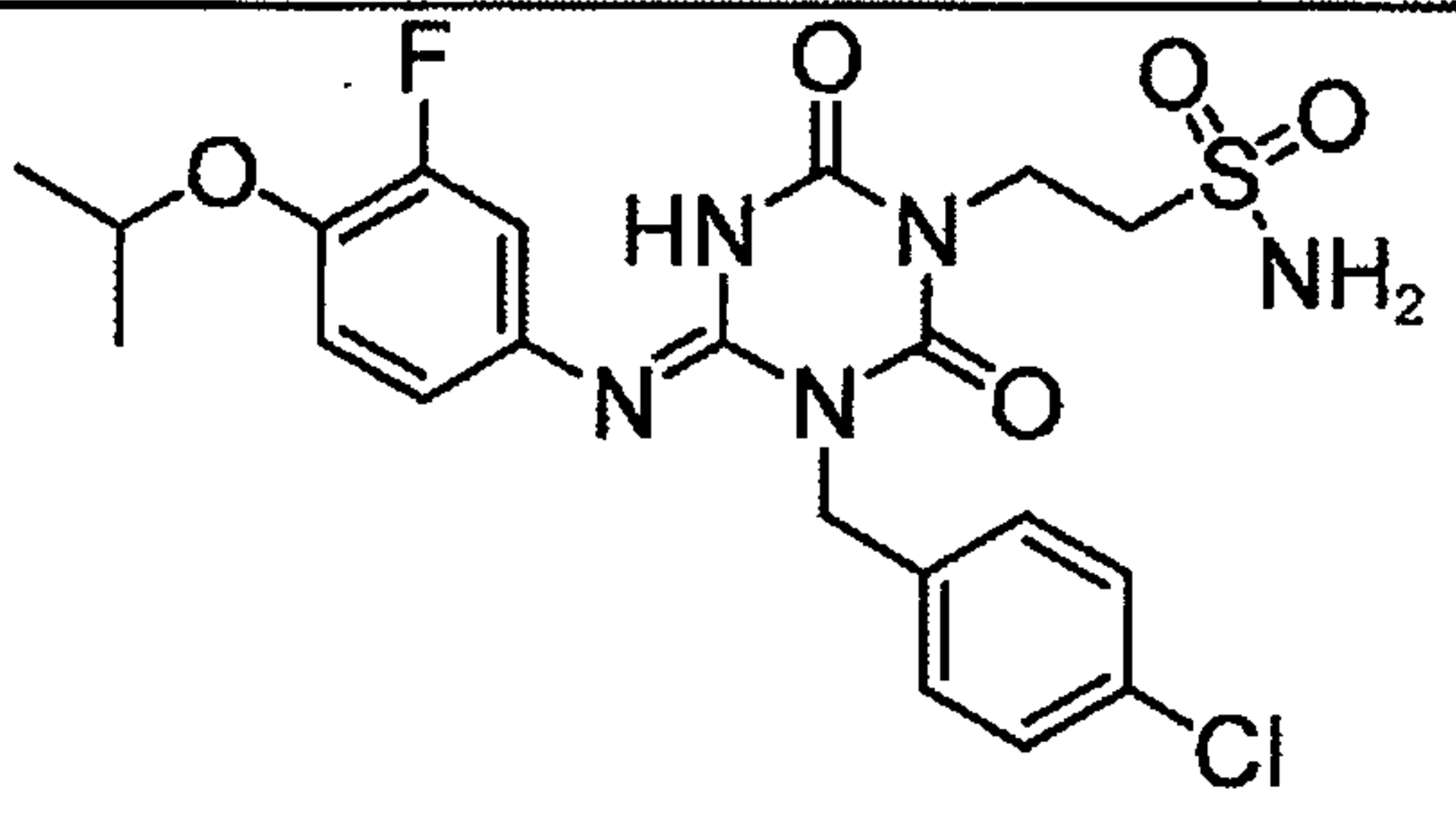
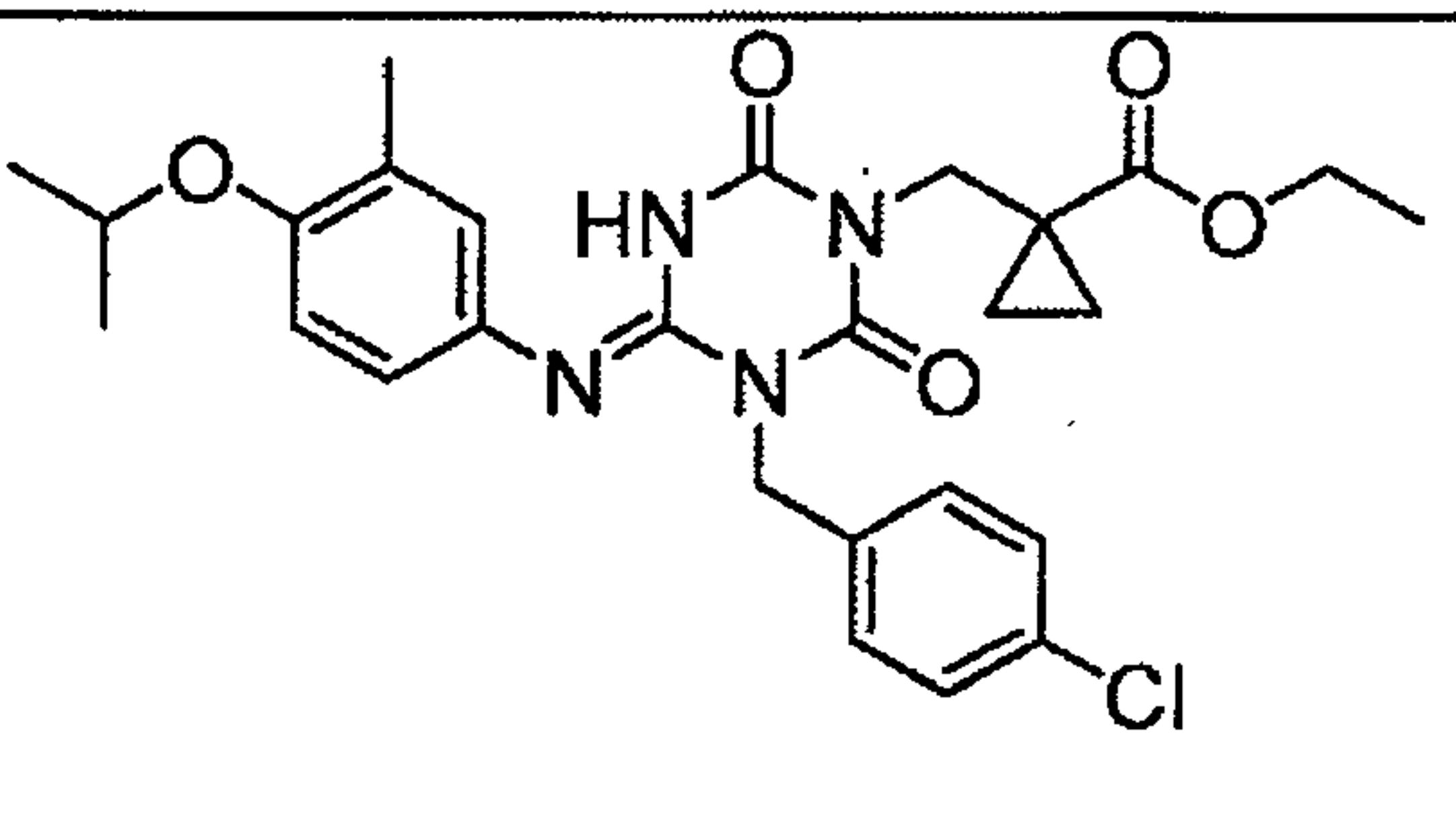
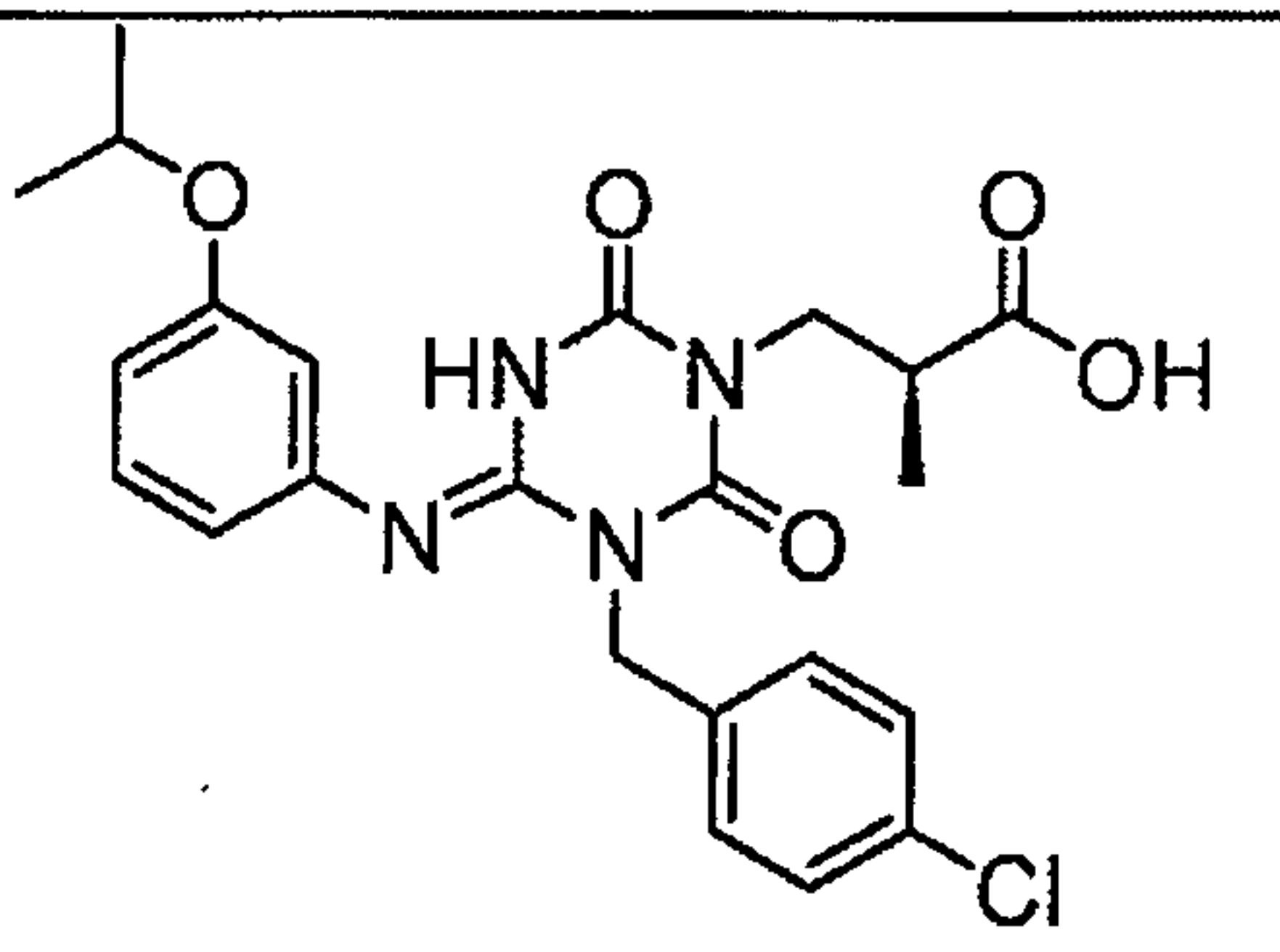
[Table 140]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0681	1.87	449	2
	I-0682	1.99	473	2
	I-0683	2.35	526	2
	I-0684	2.51	622	3
	I-0685	1.90	512	2

[Table 141]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0686	1.91	459	3
	I-0687	1.86	580	2
	I-0688	2.51	622	3
	I-0689	1.97	526	2
	I-0690	2.31	487	2

[Table 142]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0691	2.39	477	2
	I-0692	1.96	482	2
	I-0693	1.92	512	2
	I-0694	2.48	527	2
	I-0695	2.05	473	2

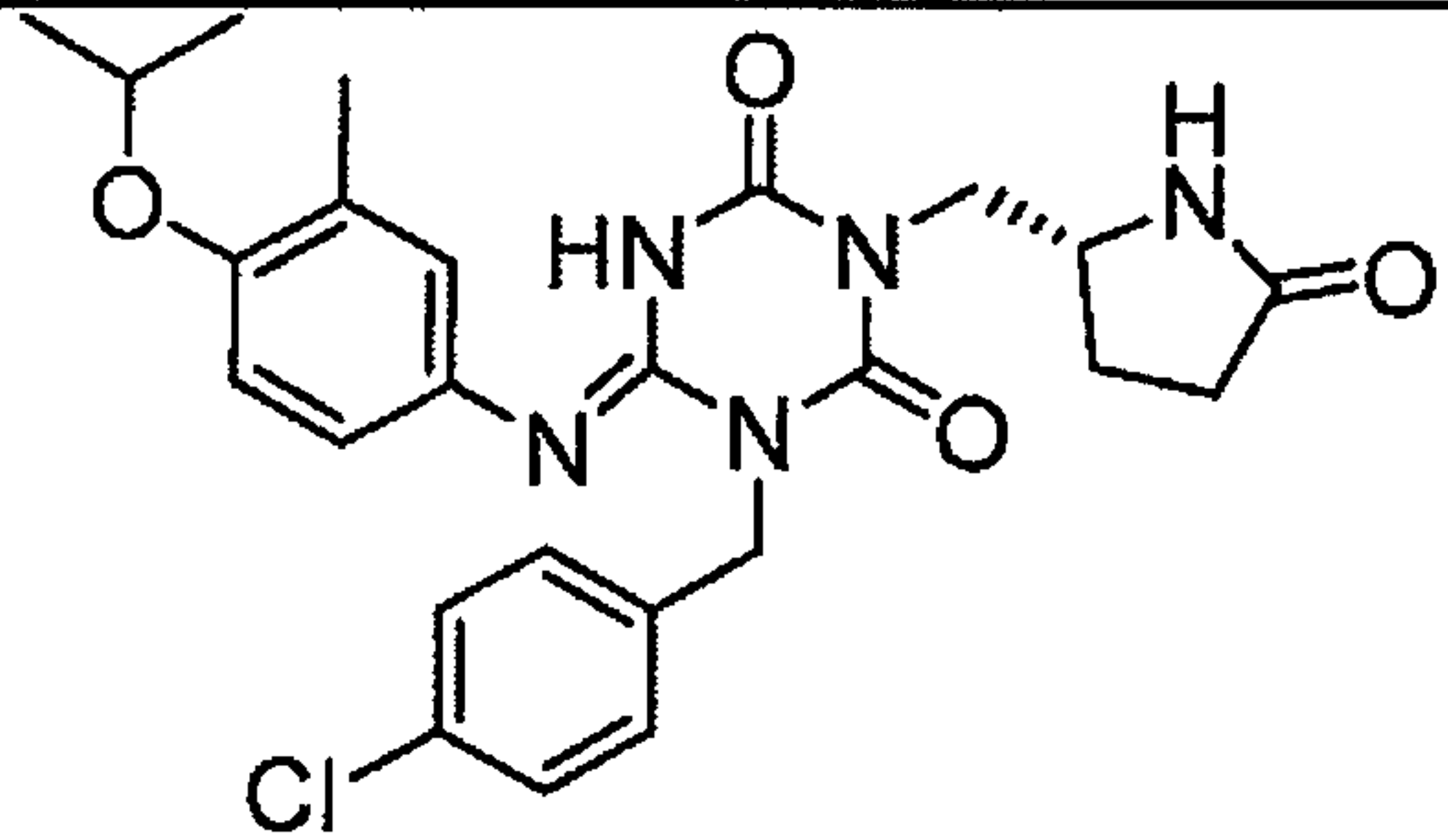
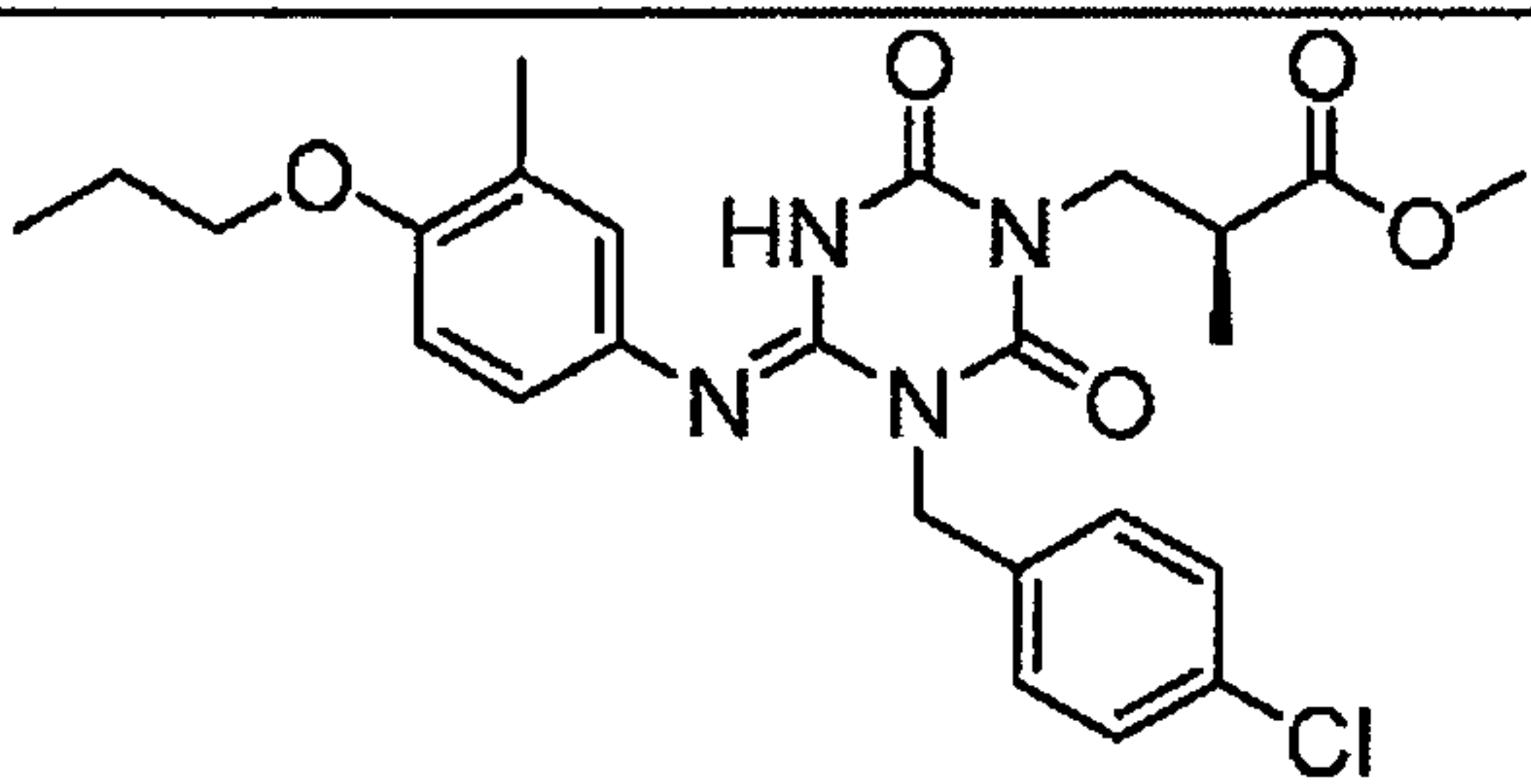
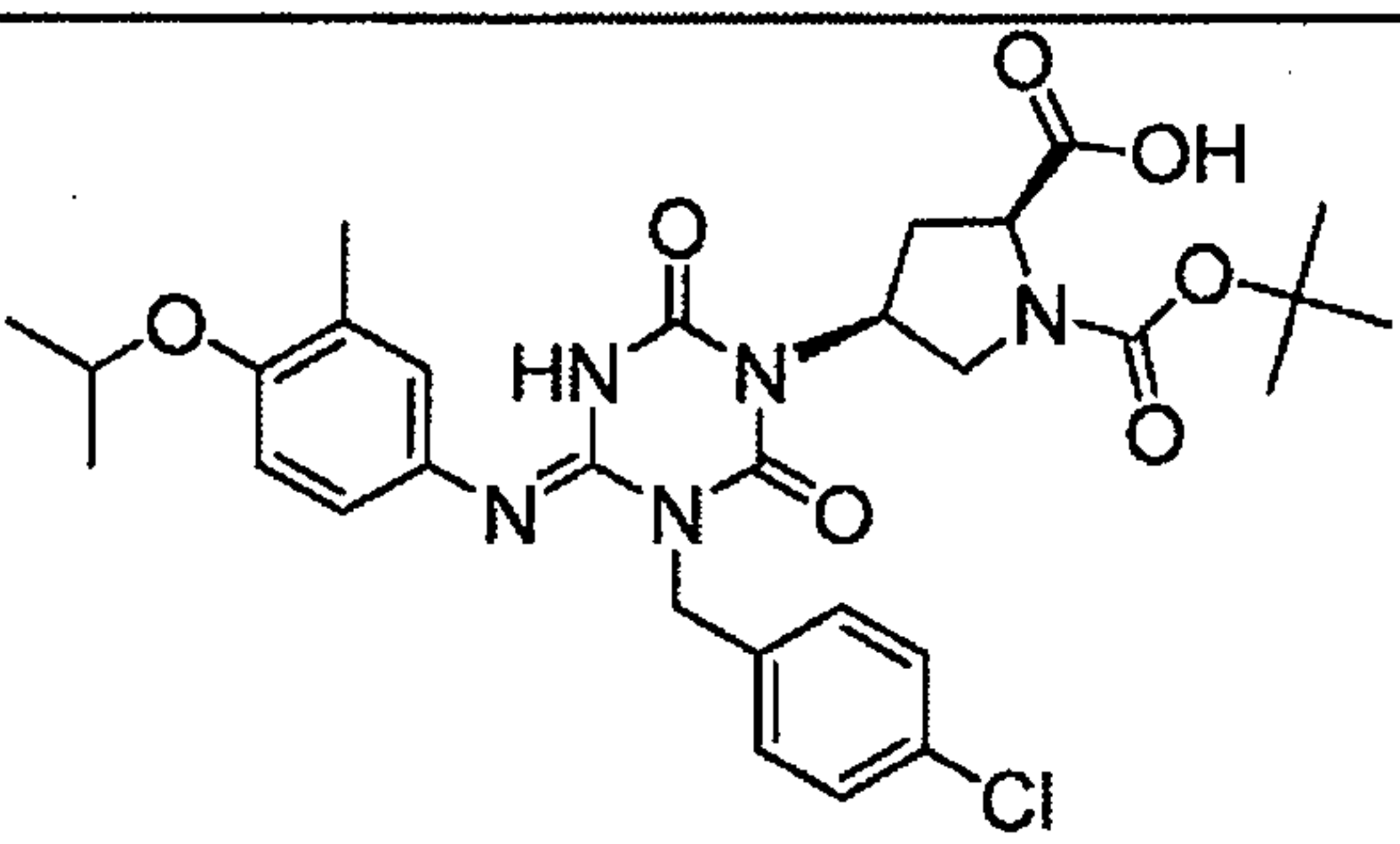
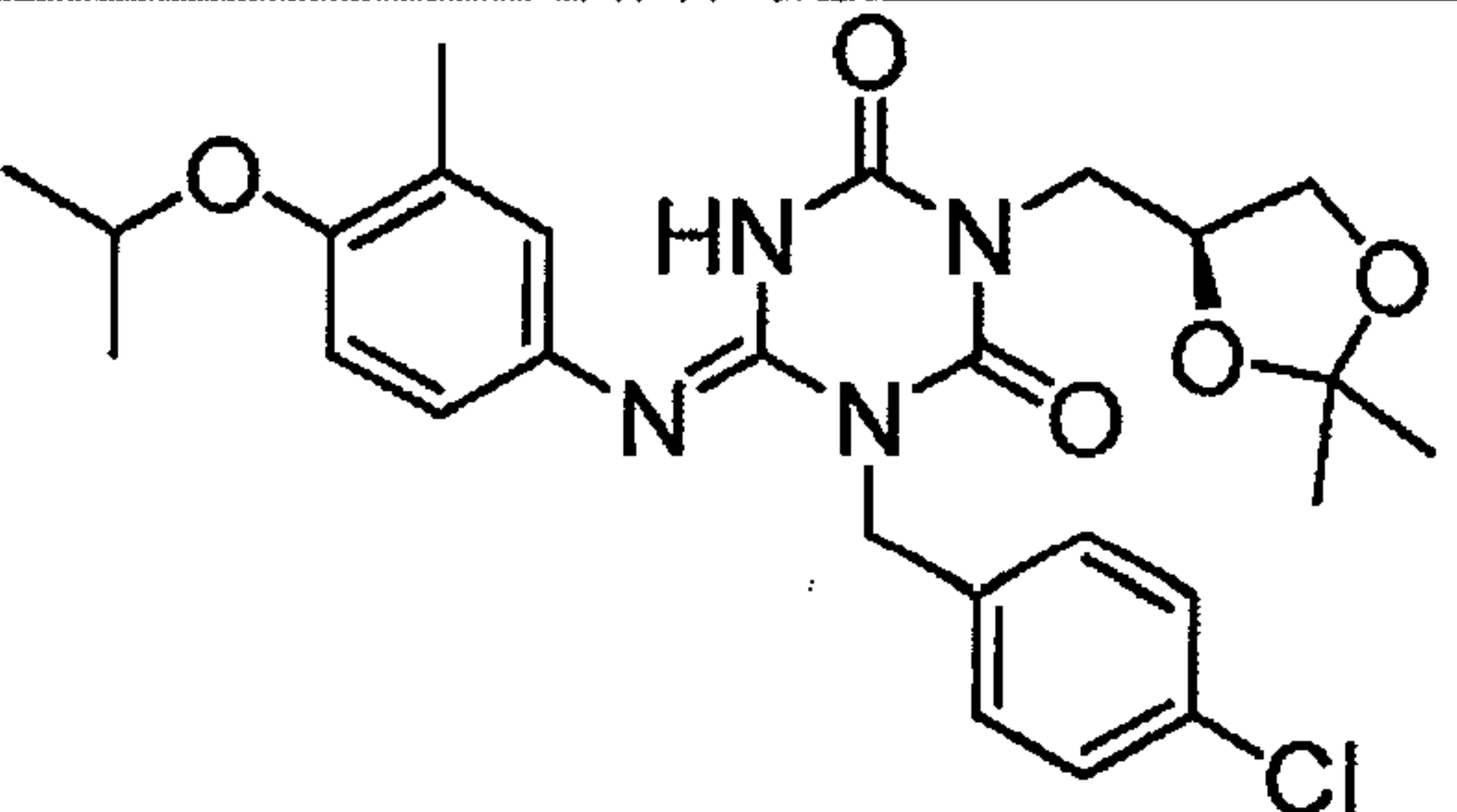
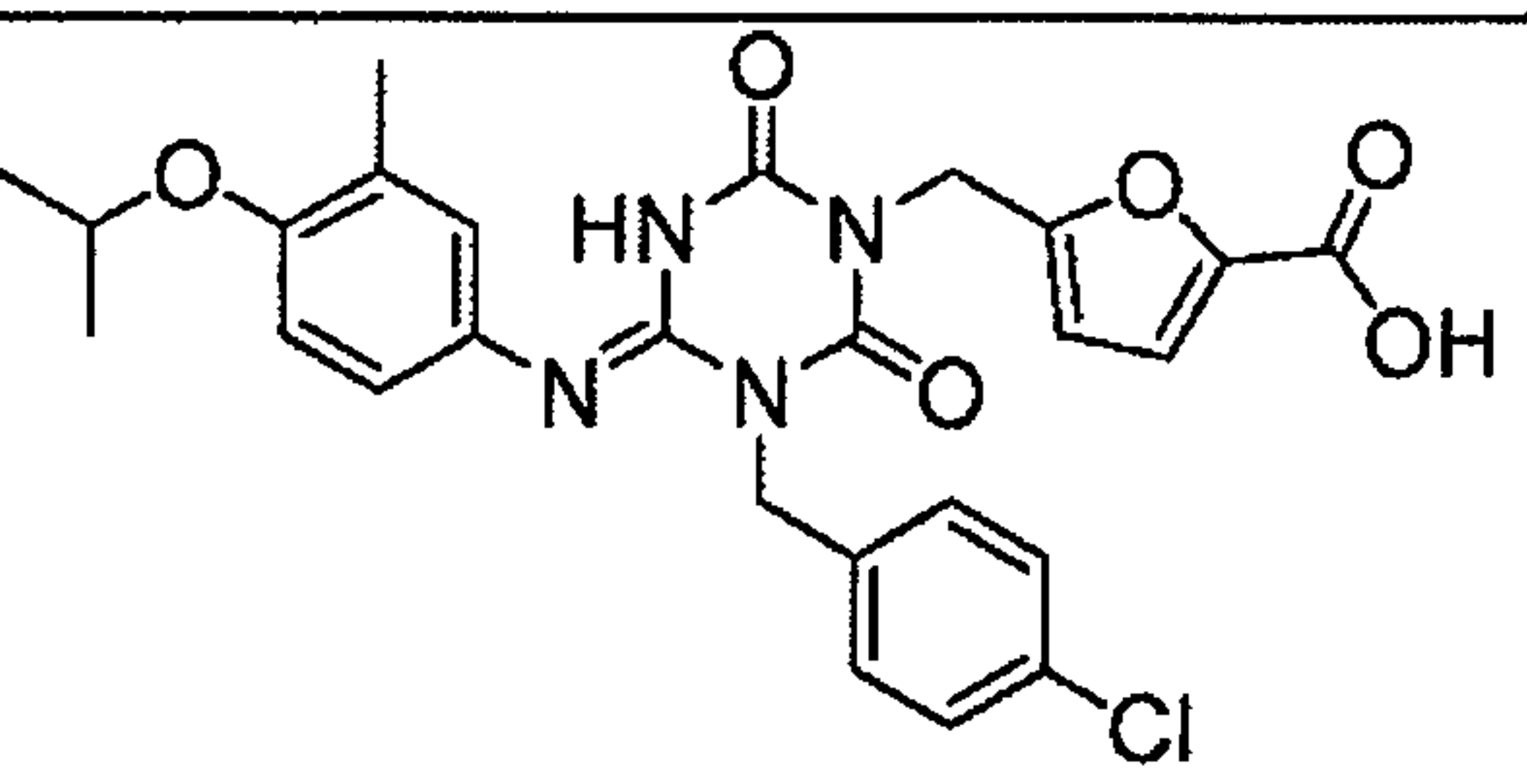
[Table 143]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0696	2.12	463	2
	I-0697	1.73	468	2
	I-0698	2.12	499	2
	I-0699	2.51	628	2
	I-0700	2.34	539	2

[Table 144]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0701	2.94	557	3
	I-0702	2.16	493	2
	I-0703	2.10	512	2
	I-0704	1.94	542	2
	I-0705	1.94	550	2

[Table 145]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0706	2.16	499	3
	I-0707	2.59	501	3
	I-0708	2.28	614	2
	I-0709	2.37	515	2
	I-0710	2.09	525	2

[Table 146]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0711	2.34	487	3
	I-0712	2.28	636	2
	I-0713	1.93	552	2
	I-0714	2.56	636	2
	I-0715	2.16	552	2

[Table 147]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0716	1.58	514	2
	I-0717	2.56	630	2
	I-0718	2.64	555	2
	I-0719	1.68	489	2
	I-0720	2.24	487	2

[Table 149]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0726	2.24	568	2
	I-0727	2.53	501	3
	I-0728	2.53	501	3
	I-0729	2.57	545	3
	I-0730	2.69	516	3

[Table 150]

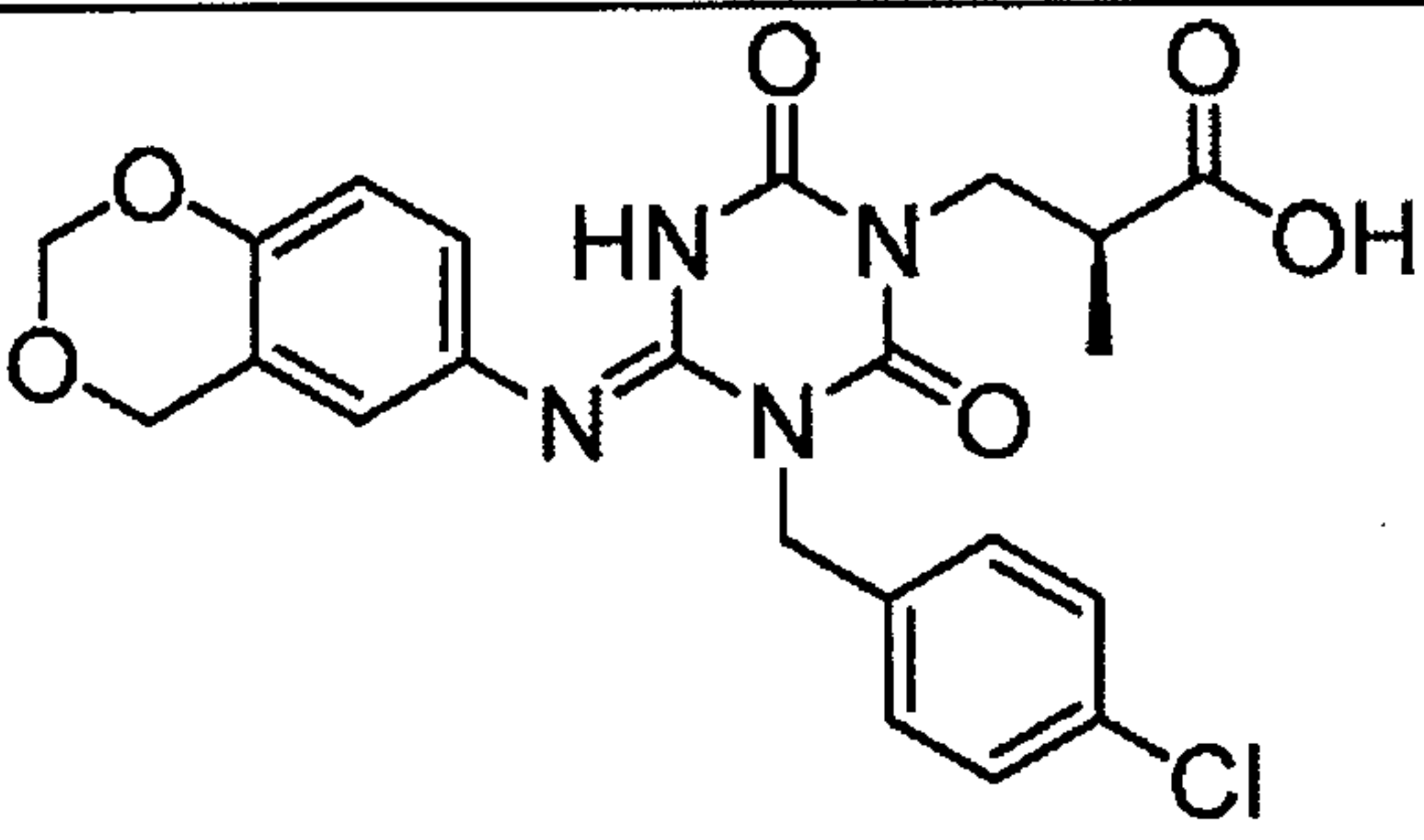
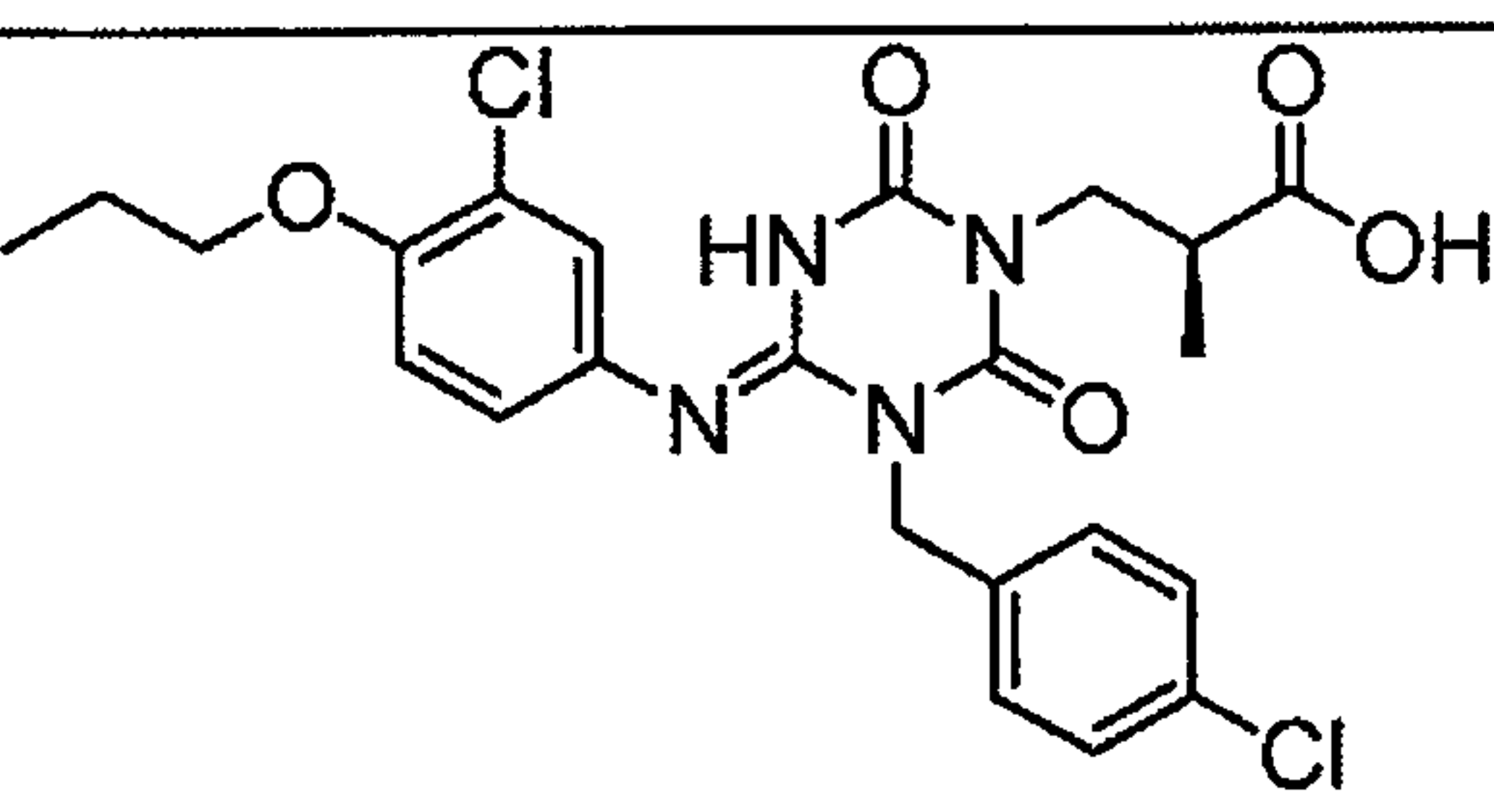
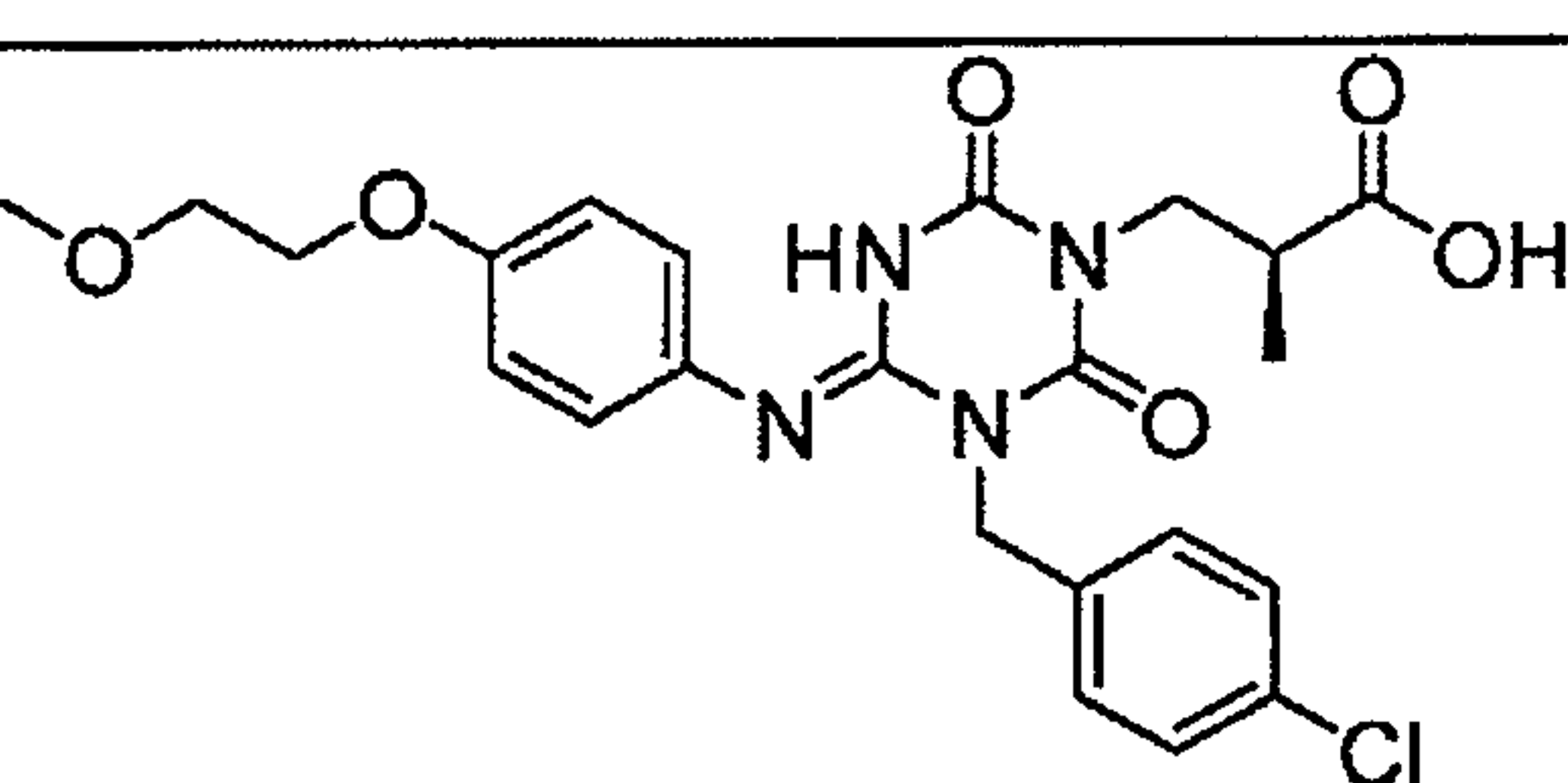
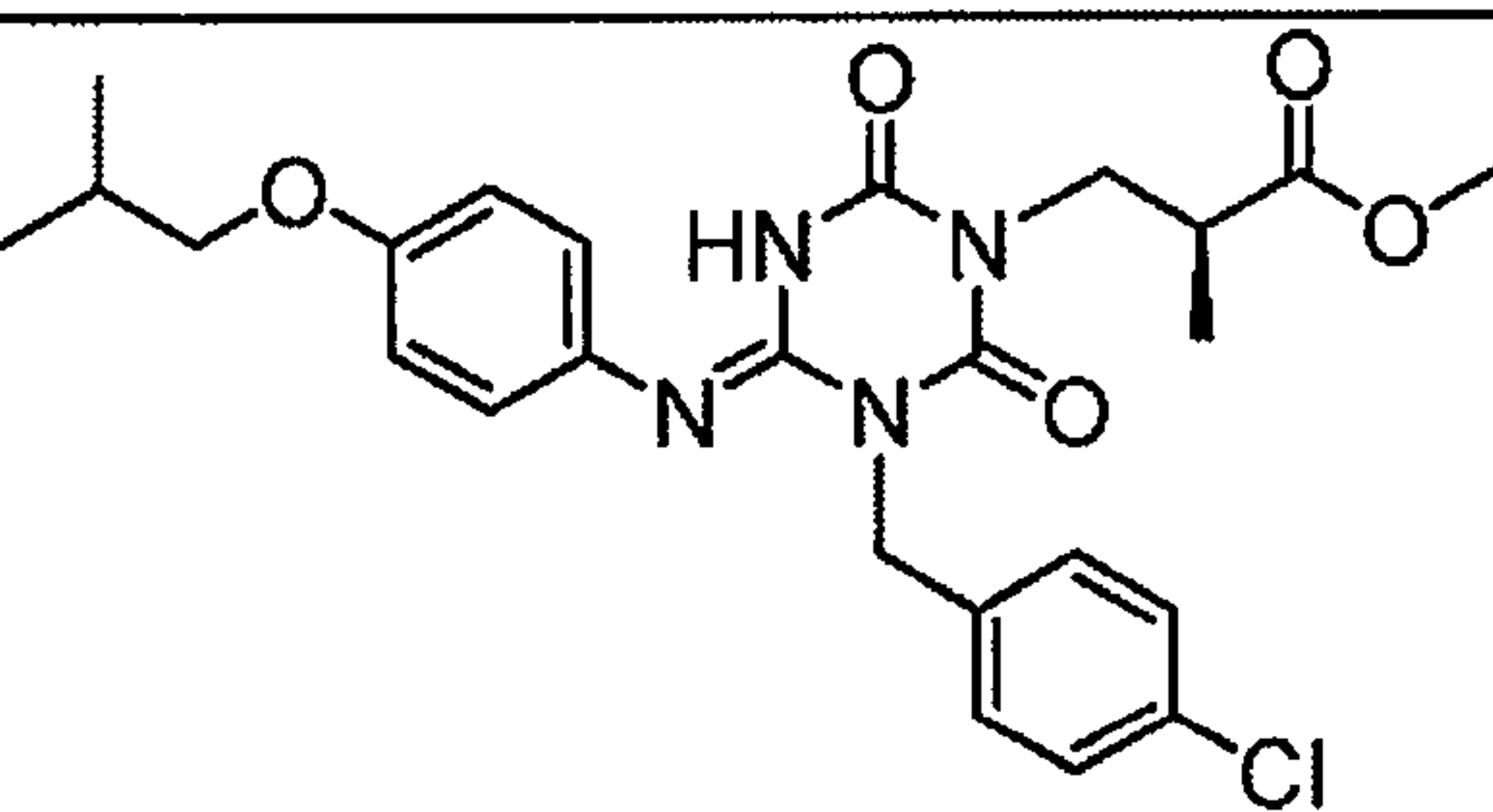
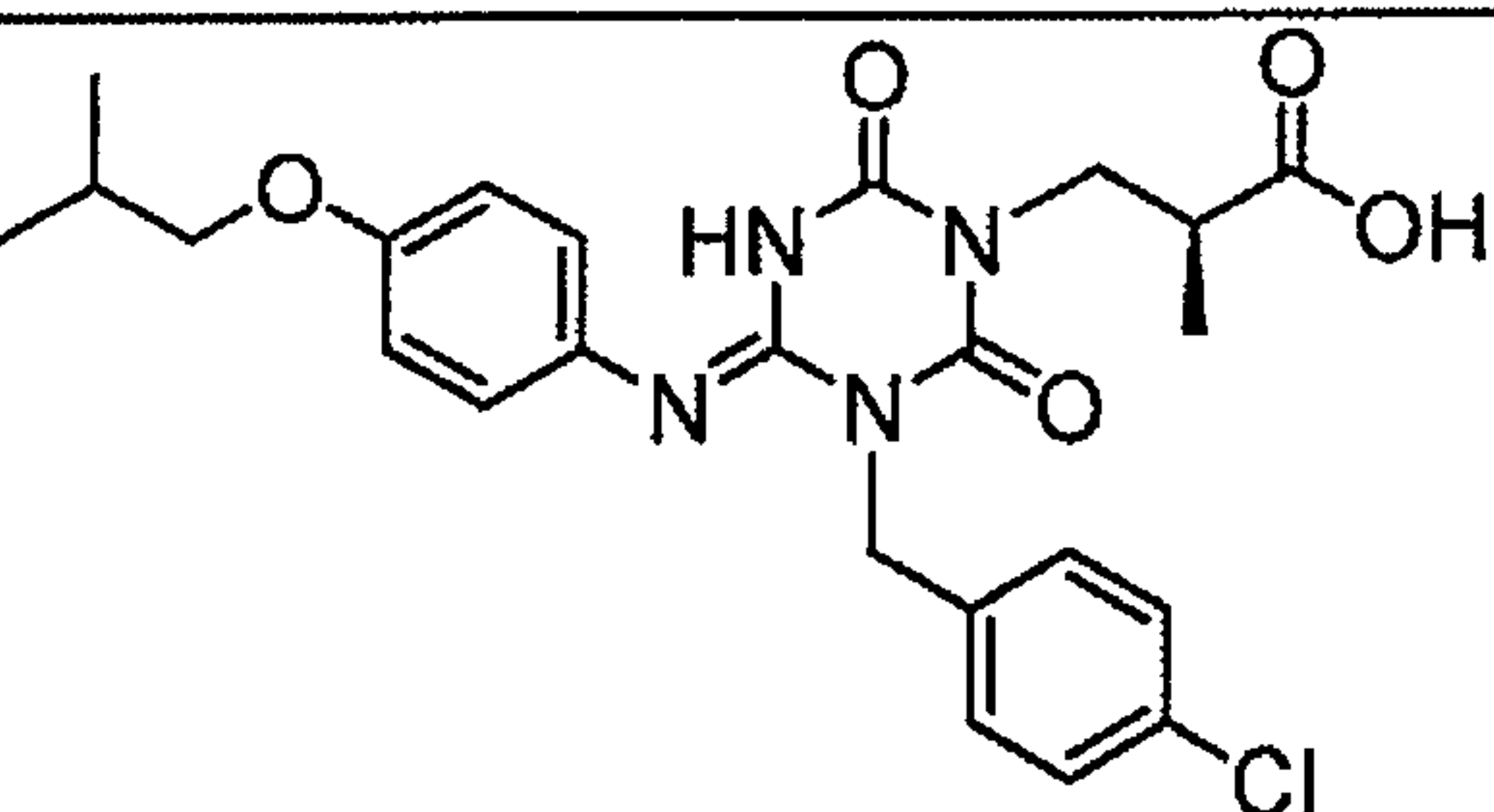
Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0731	2.68	516	3
	I-0732	2.26	602	2
	I-0733	1.45	475	2
	I-0734	1.95	473	2
	I-0735	2.30	548	2

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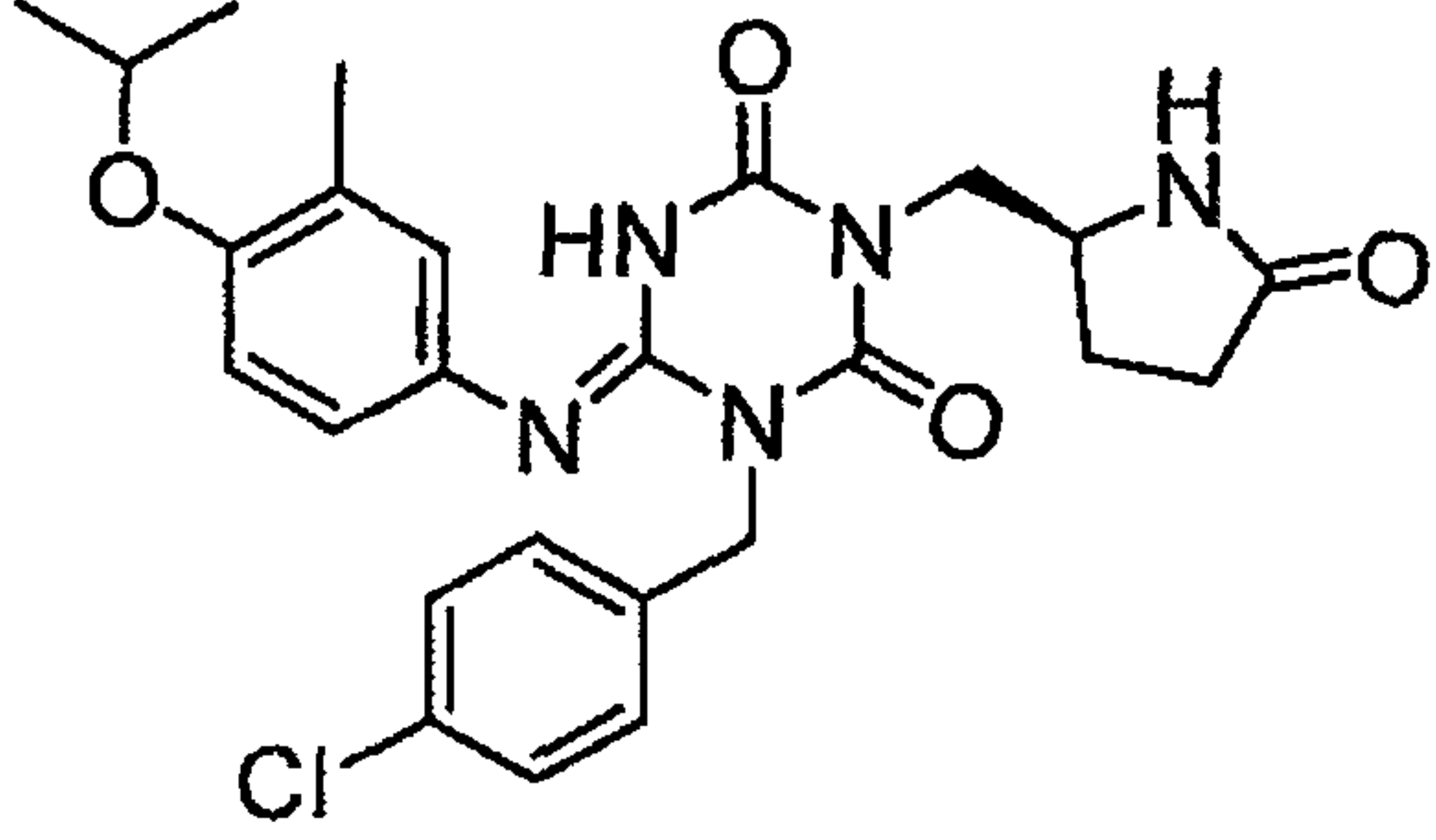
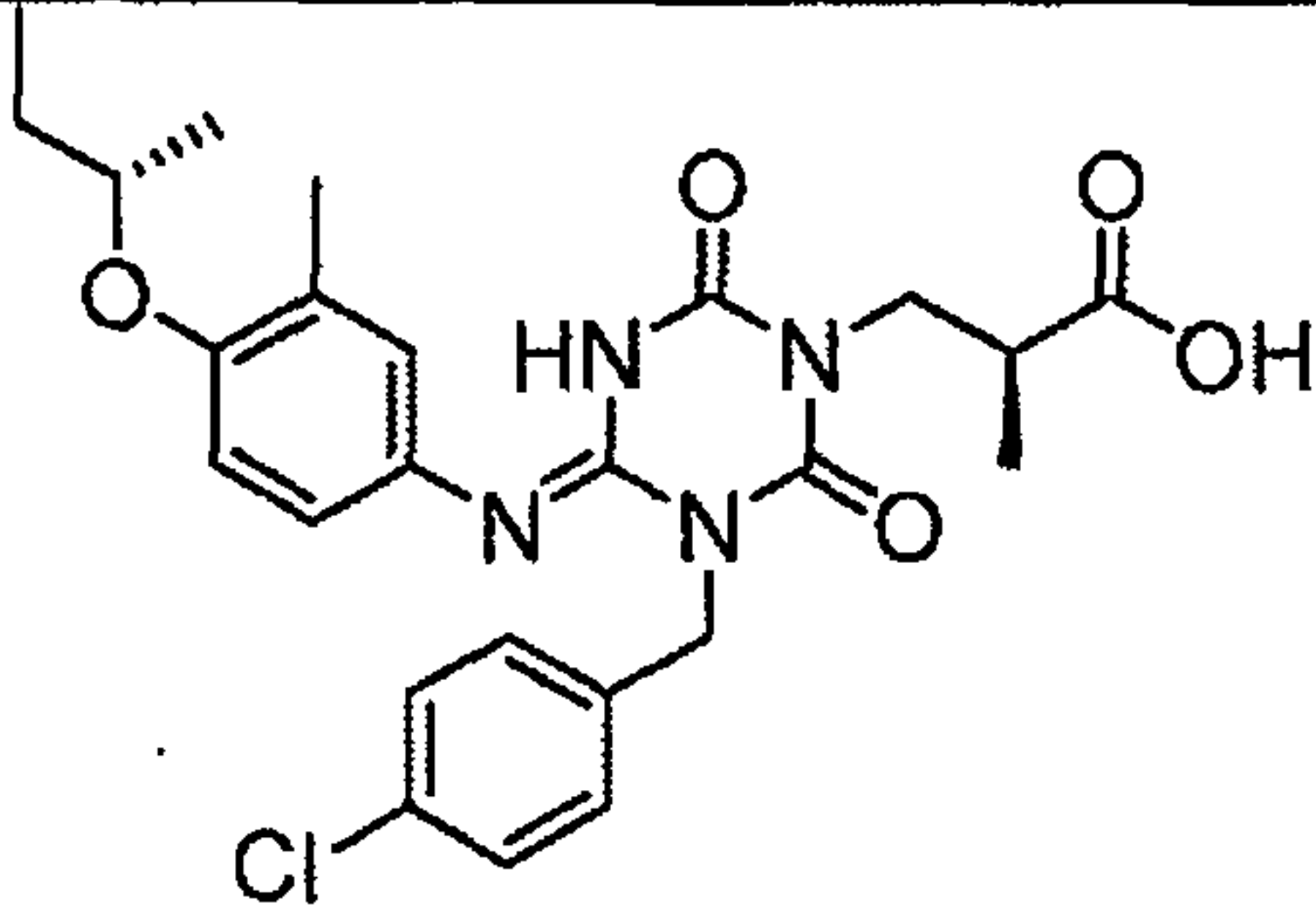
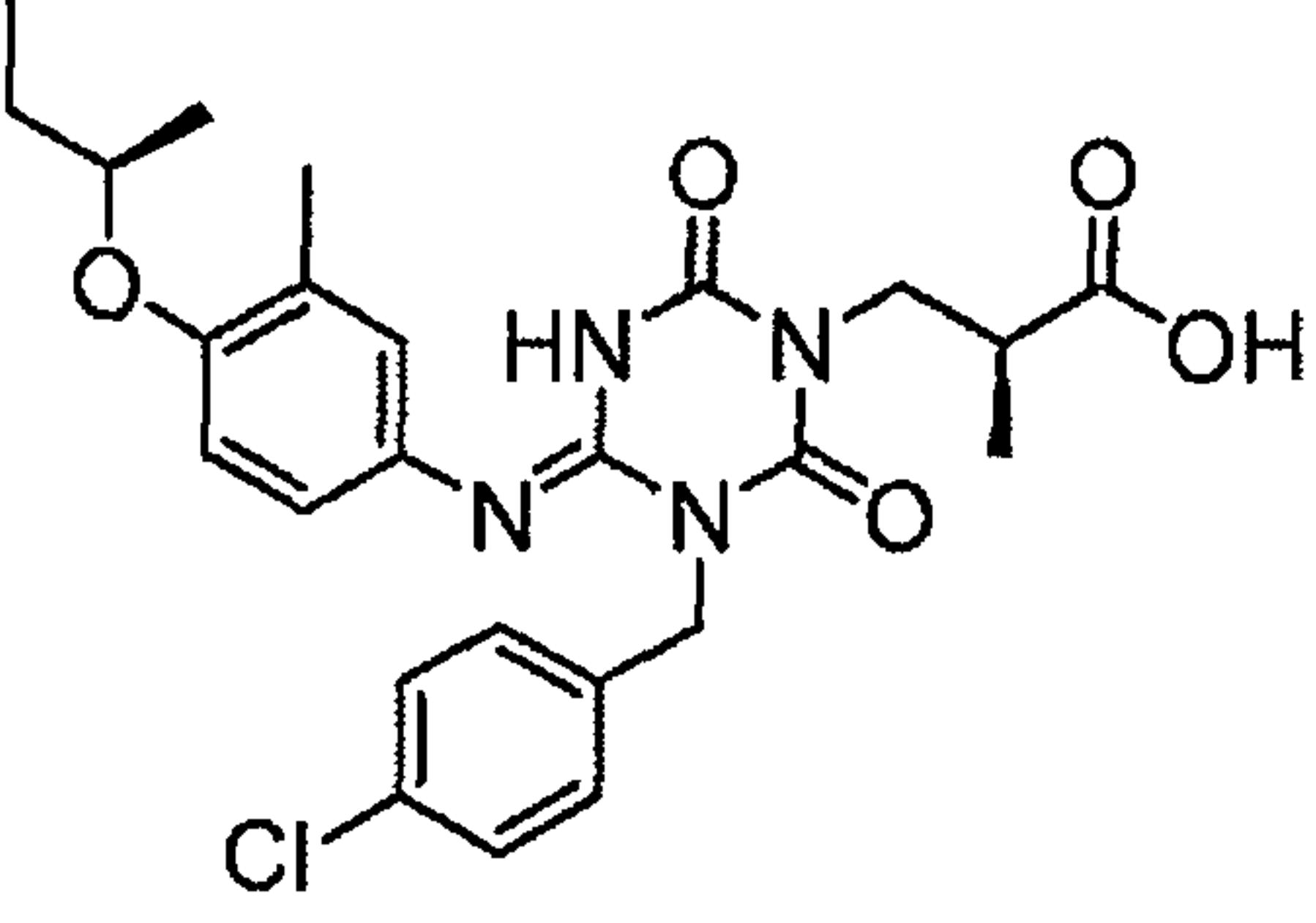
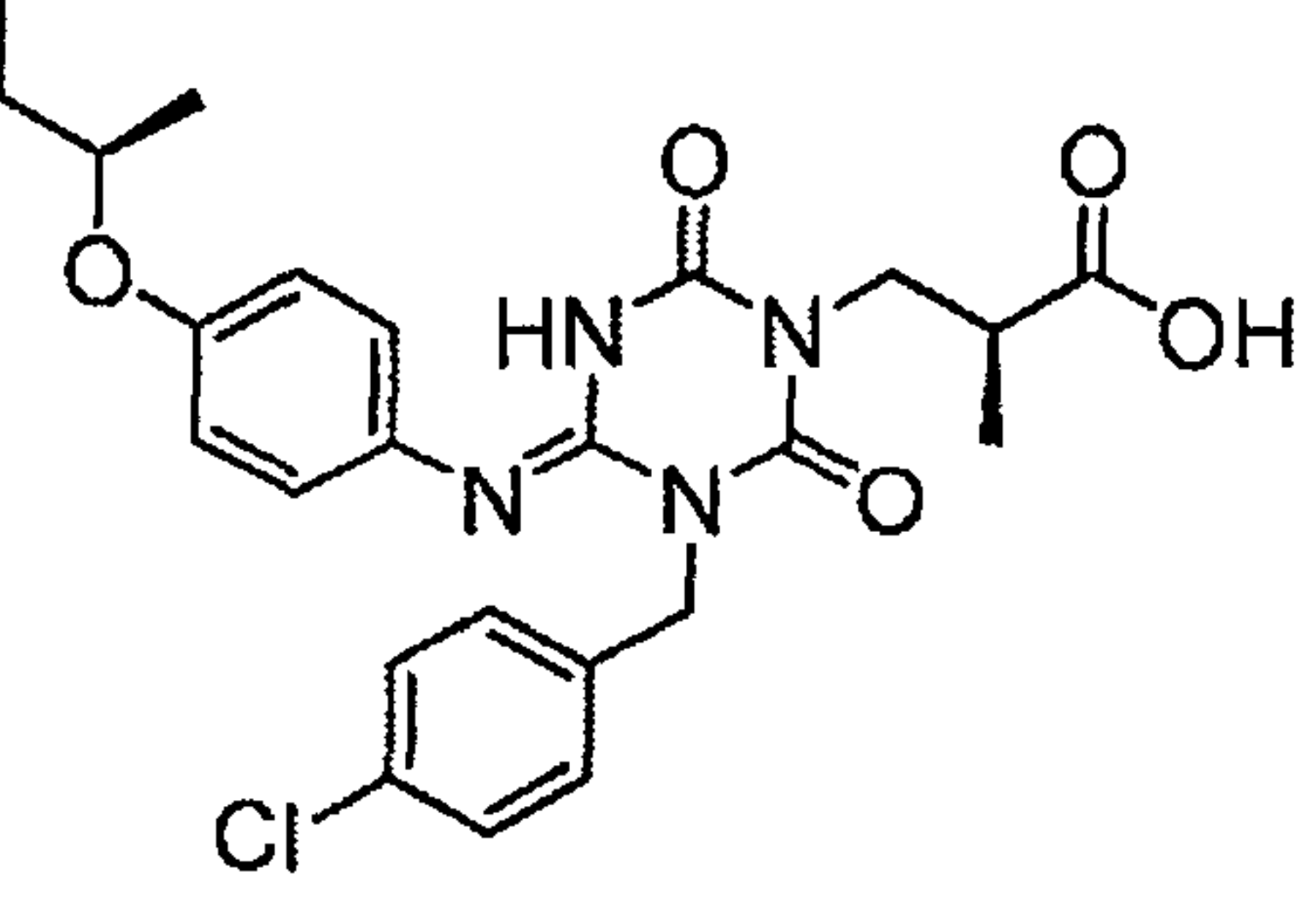
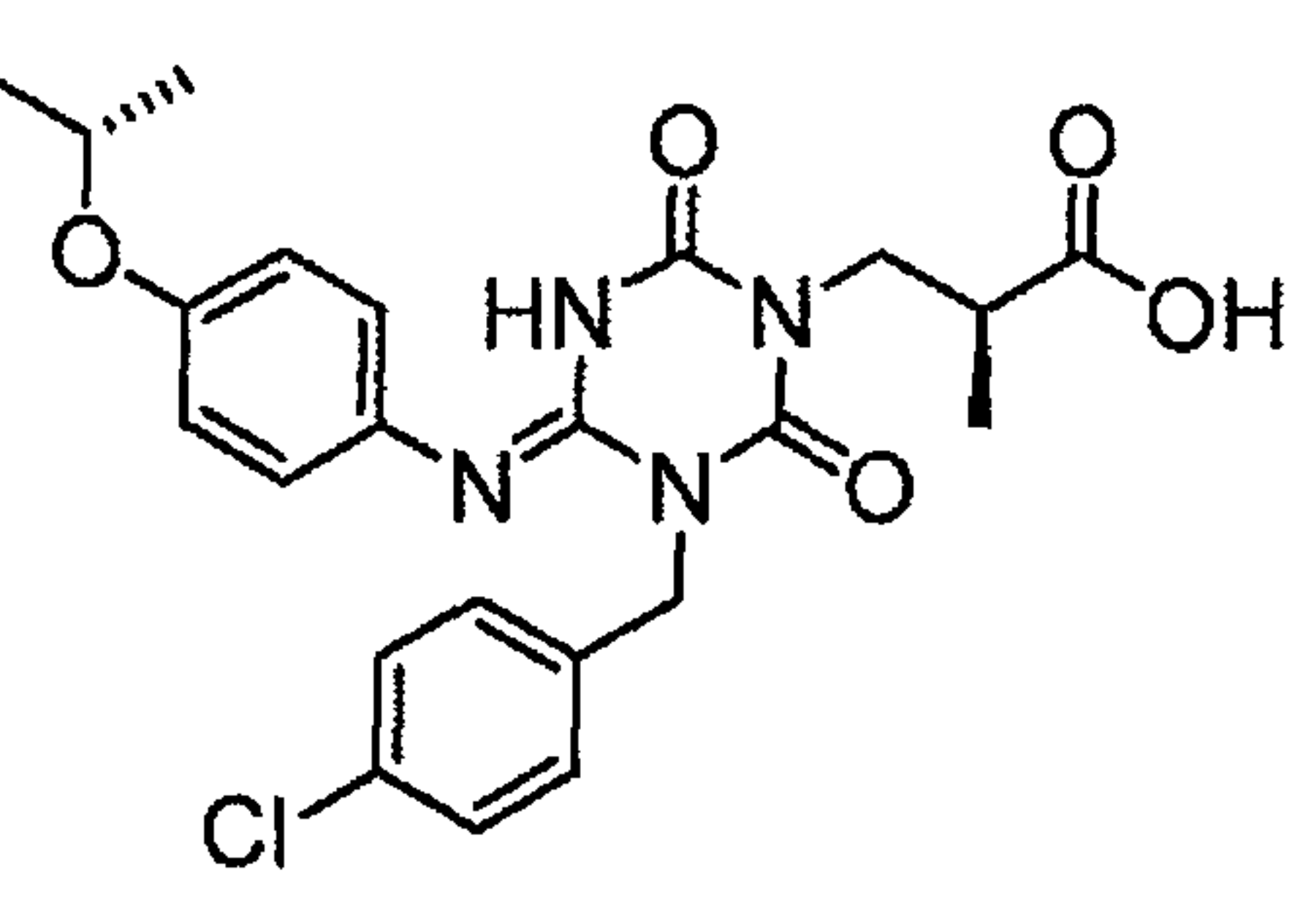
[Table 152]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0741	1.95	509	2
	I-0742	1.56	547	2
	I-0743	2.66	521	3
	I-0744	2.13	487	3
	I-0745	2.13	503	3

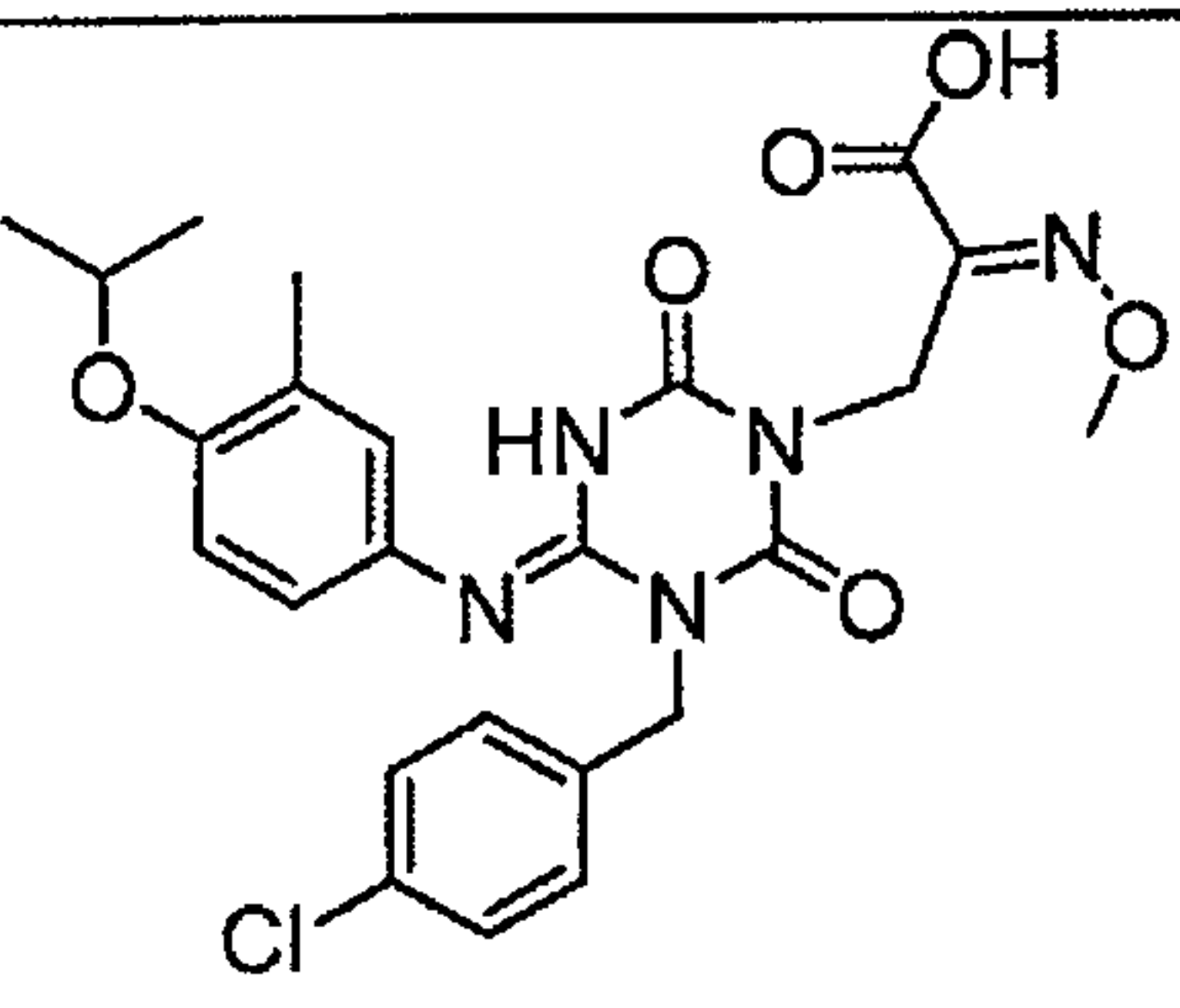
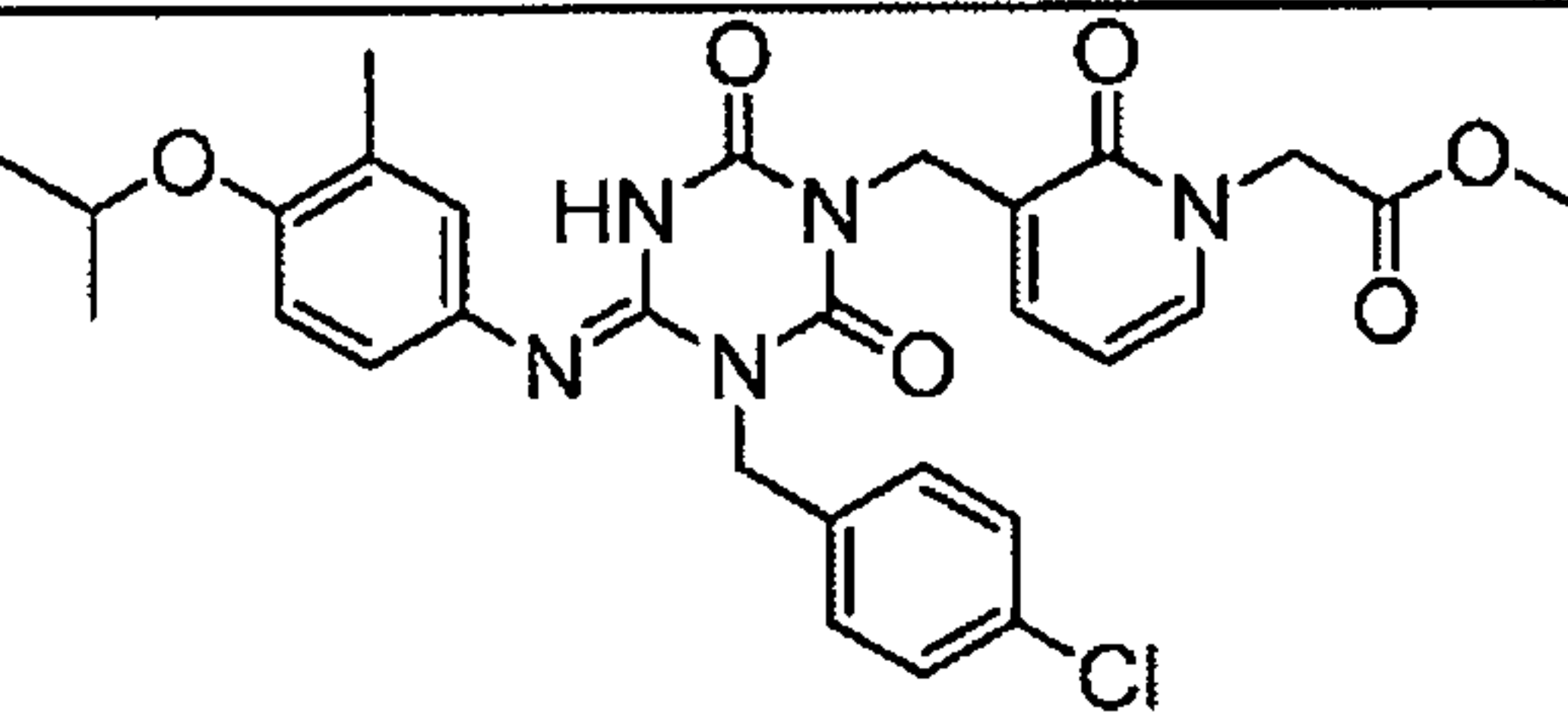
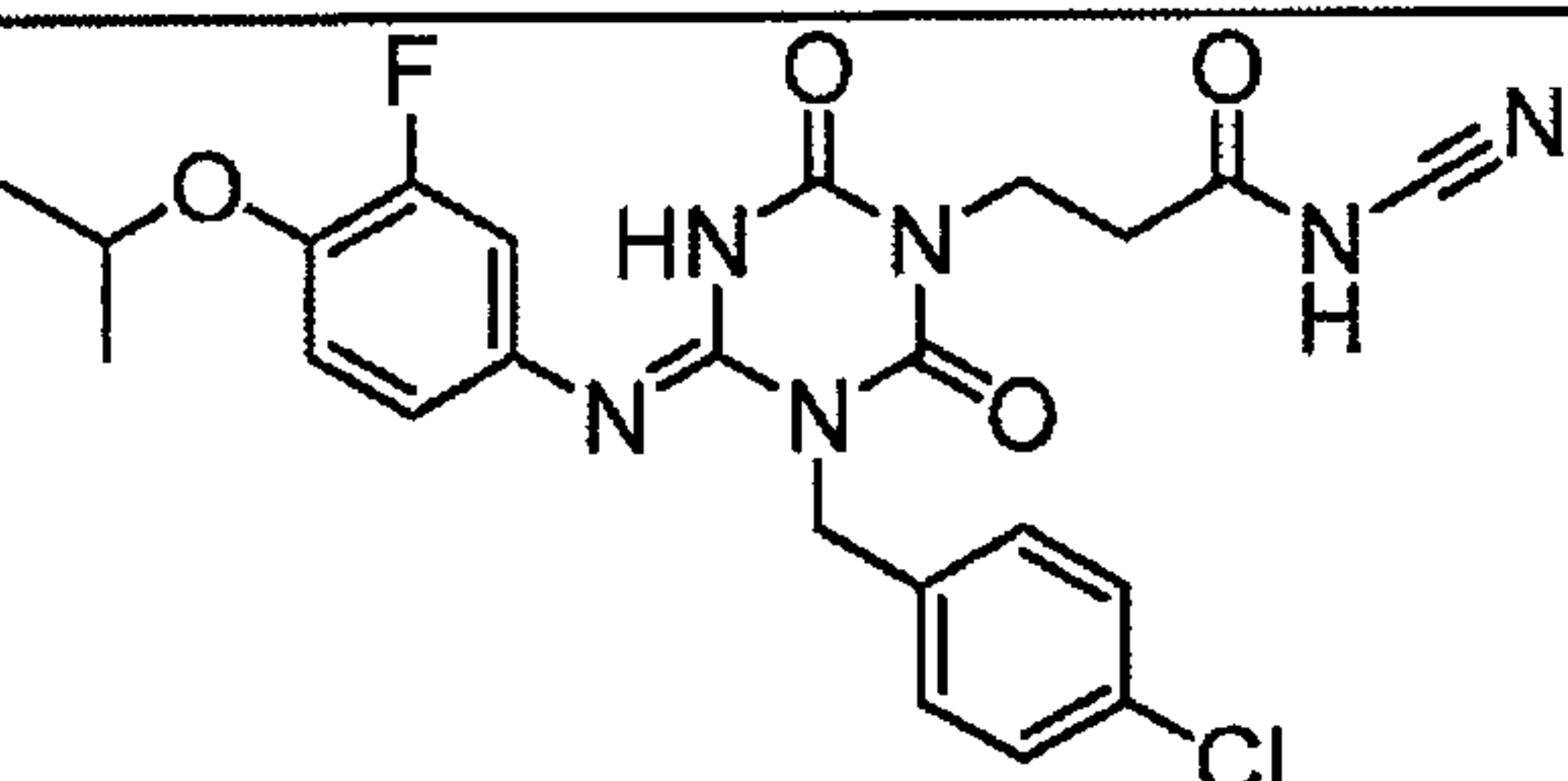
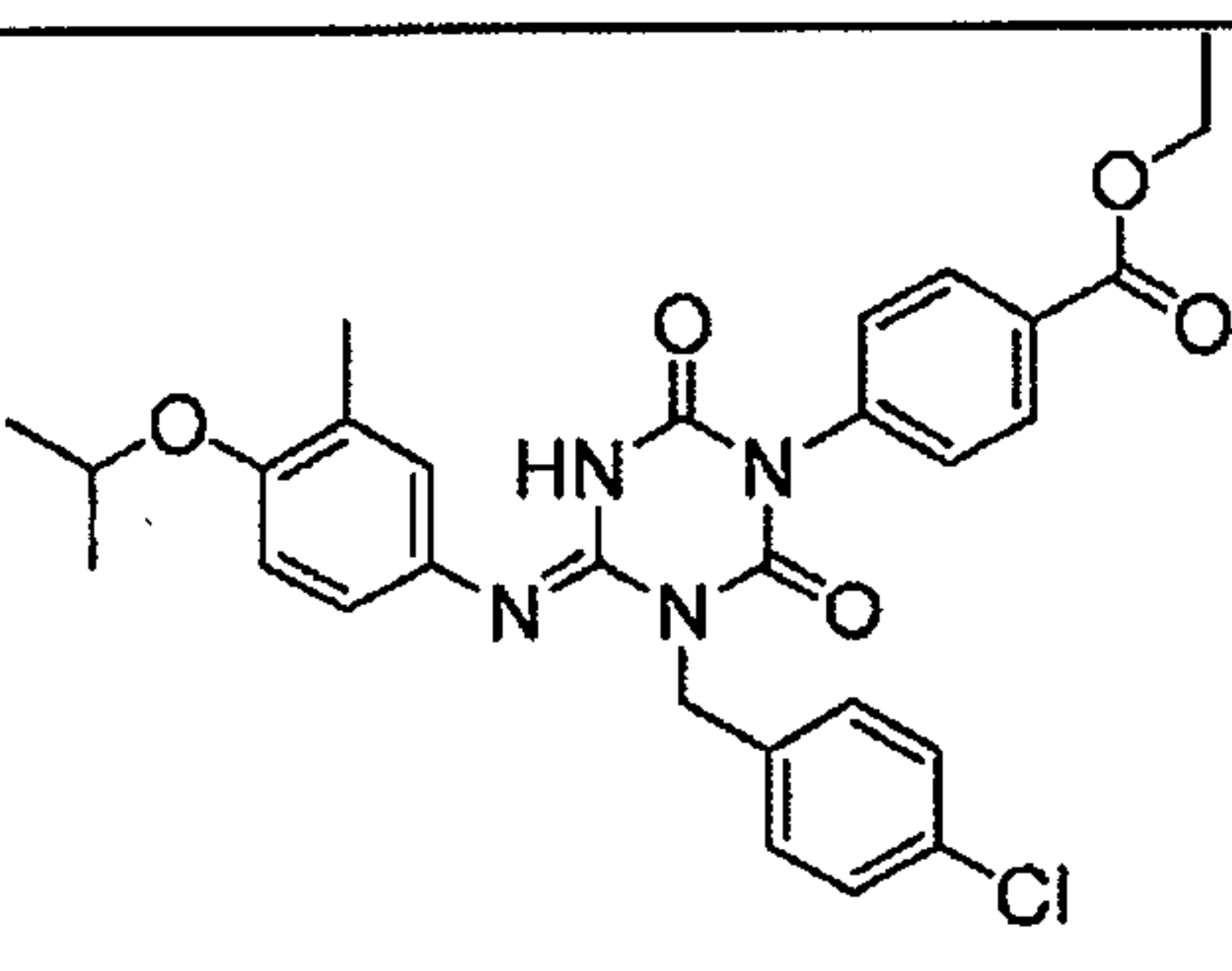
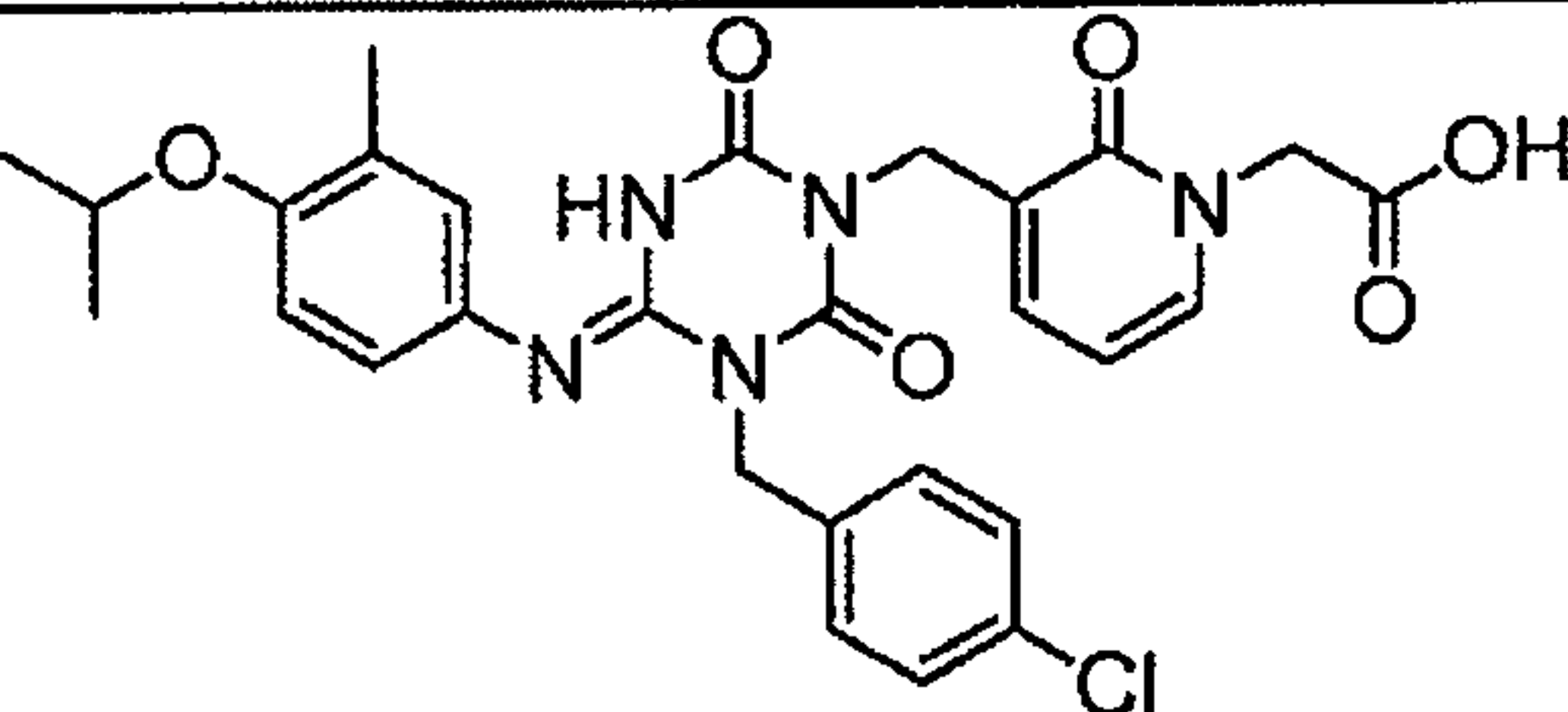
[Table 153]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0746	1.86	473	3
	I-0747	2.40	507	3
	I-0748	1.86	489	3
	I-0749	2.57	501	3
	I-0750	2.32	487	3

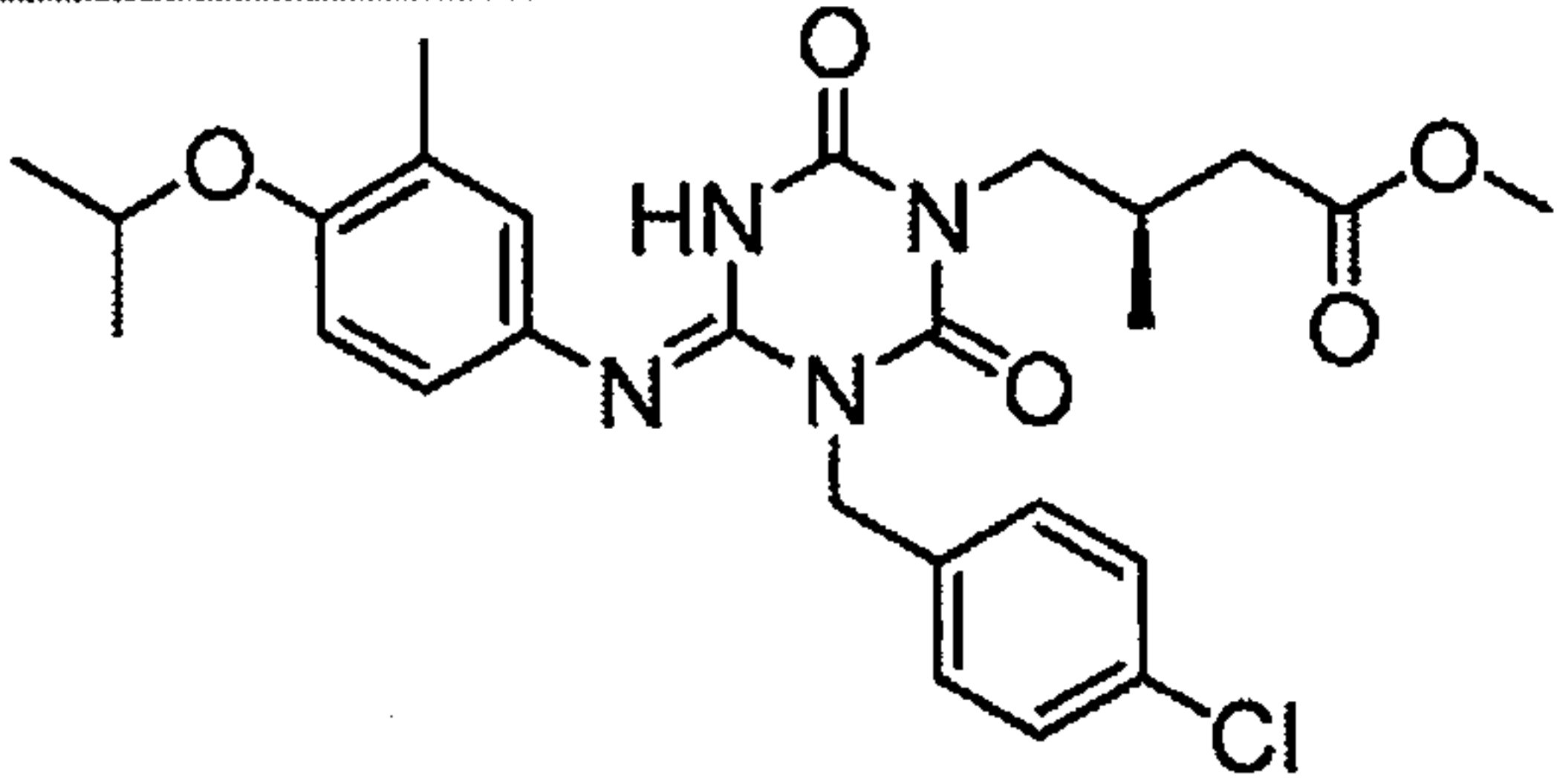
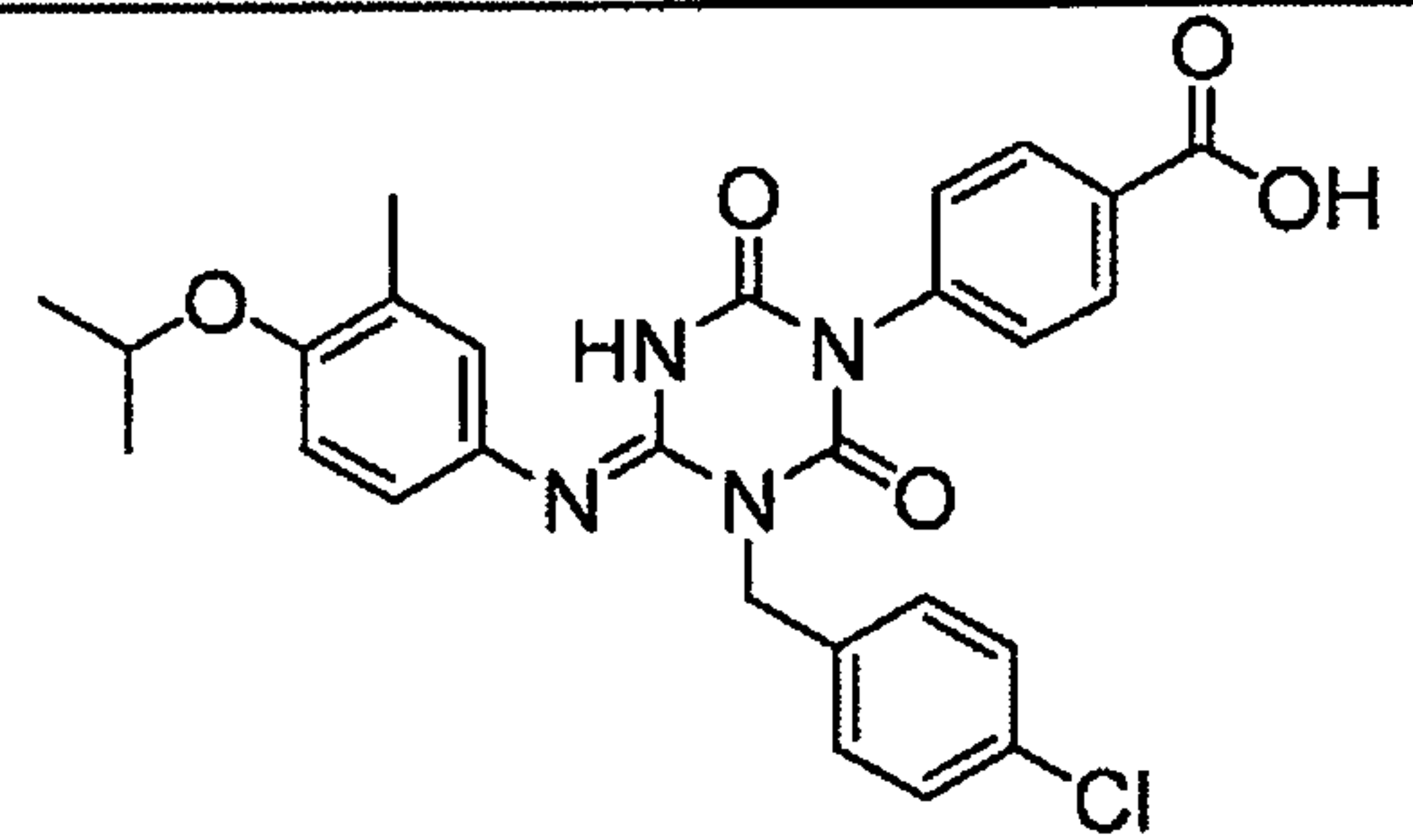
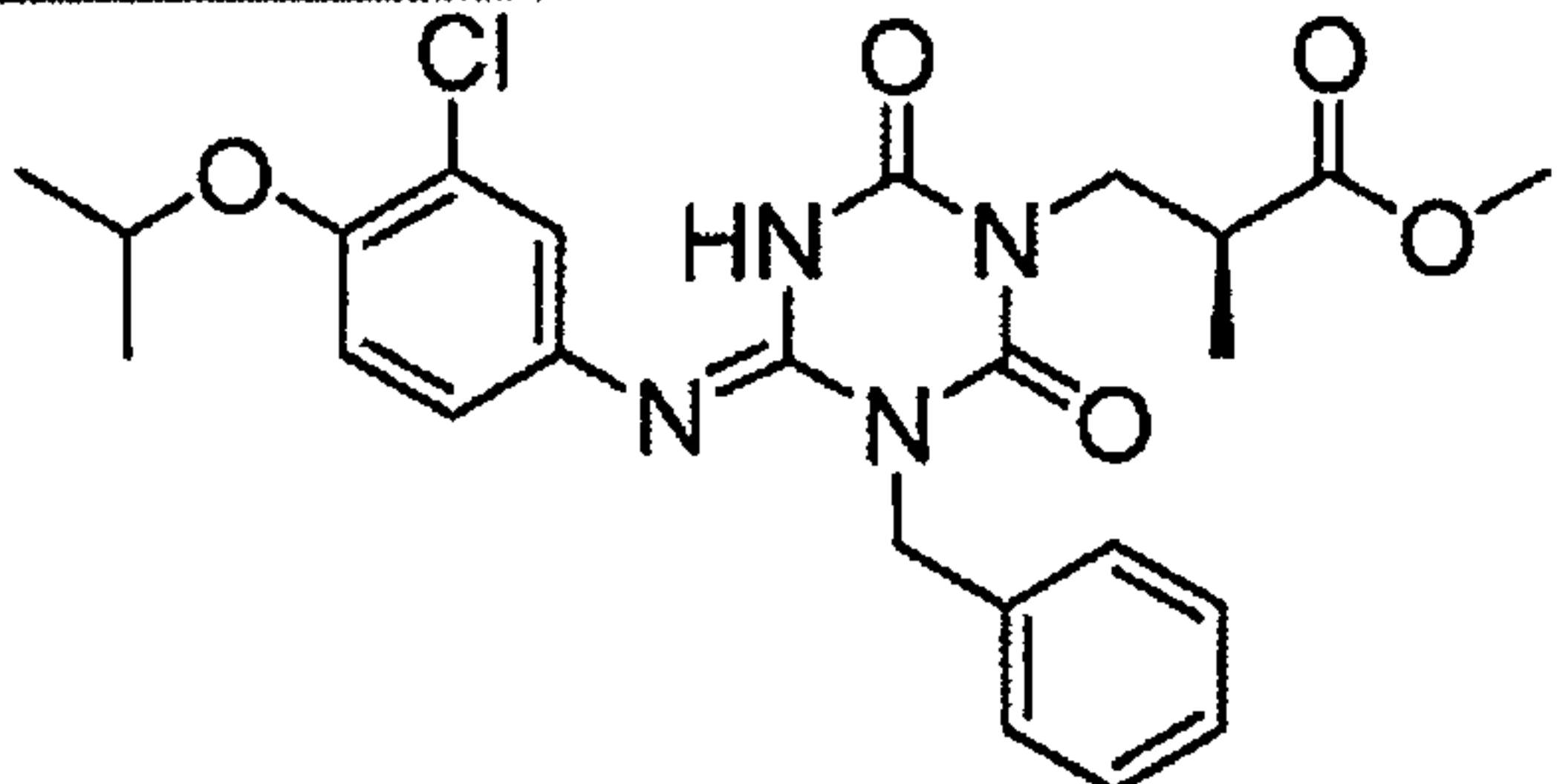
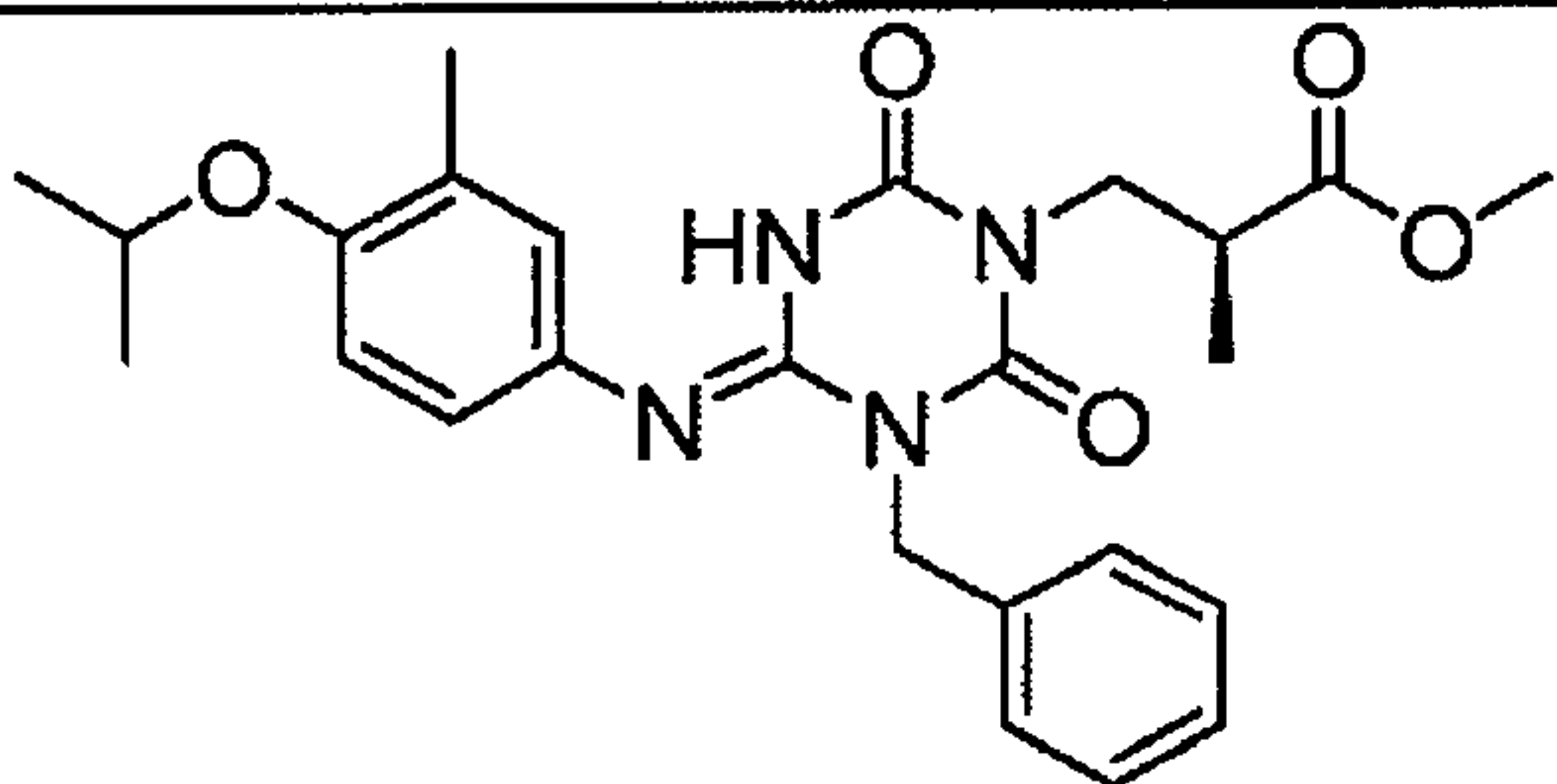
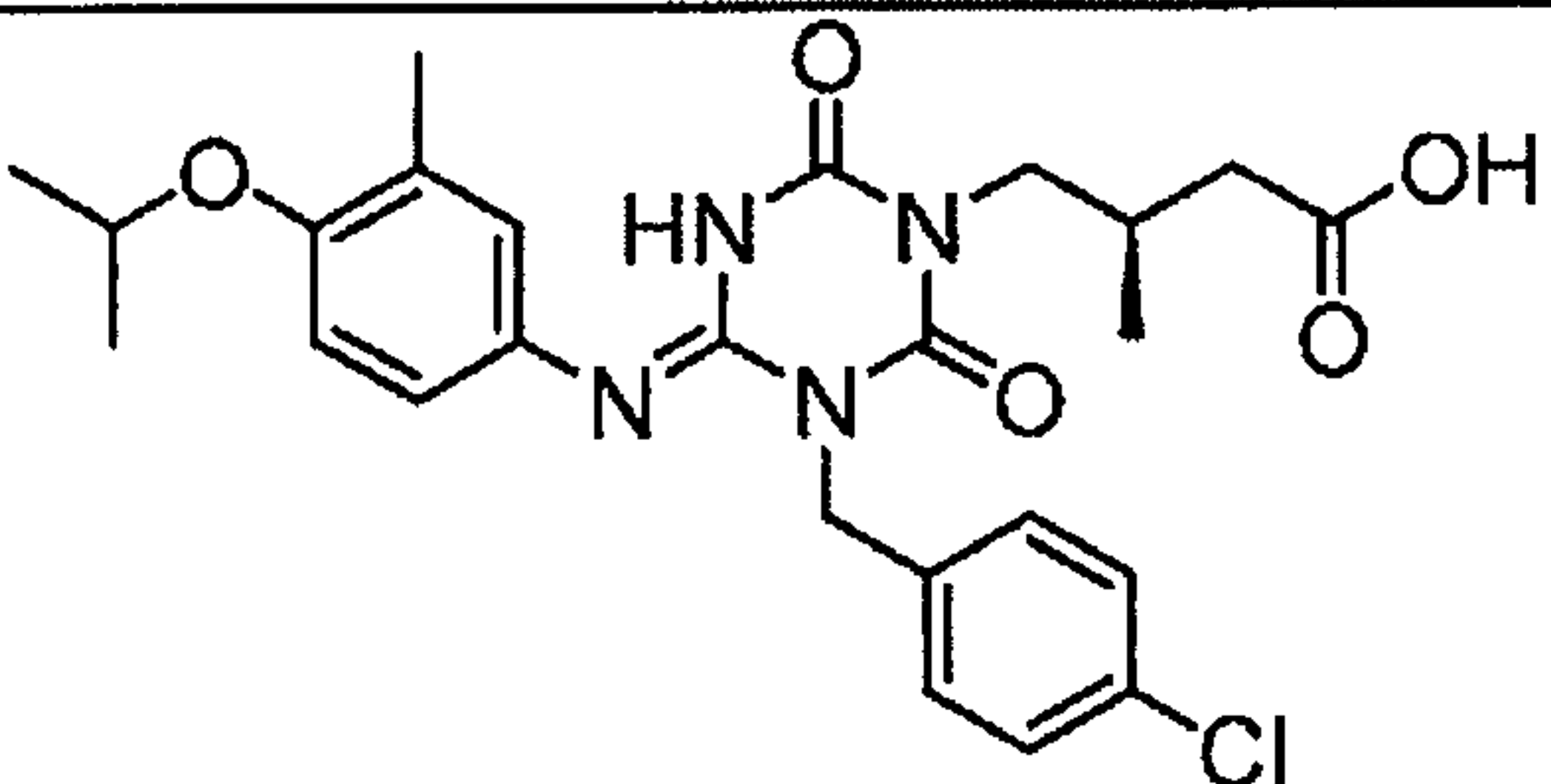
[Table 154]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0751	2.17	499	3
	I-0752	2.43	502	3
	I-0753	2.43	502	3
	I-0754	2.07	487	2
	I-0755	2.07	487	2

[Table 155]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0756	2.03	516	2
	I-0757	2.09	580	2
	I-0758	2.00	501	2
	I-0759	2.45	549	2
	I-0760	1.96	566	2

[Table 156]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0761	2.40	515	2
	I-0762	2.12	521	2
	I-0763	2.23	487	2
	I-0764	2.13	467	2
	I-0765	2.13	501	2

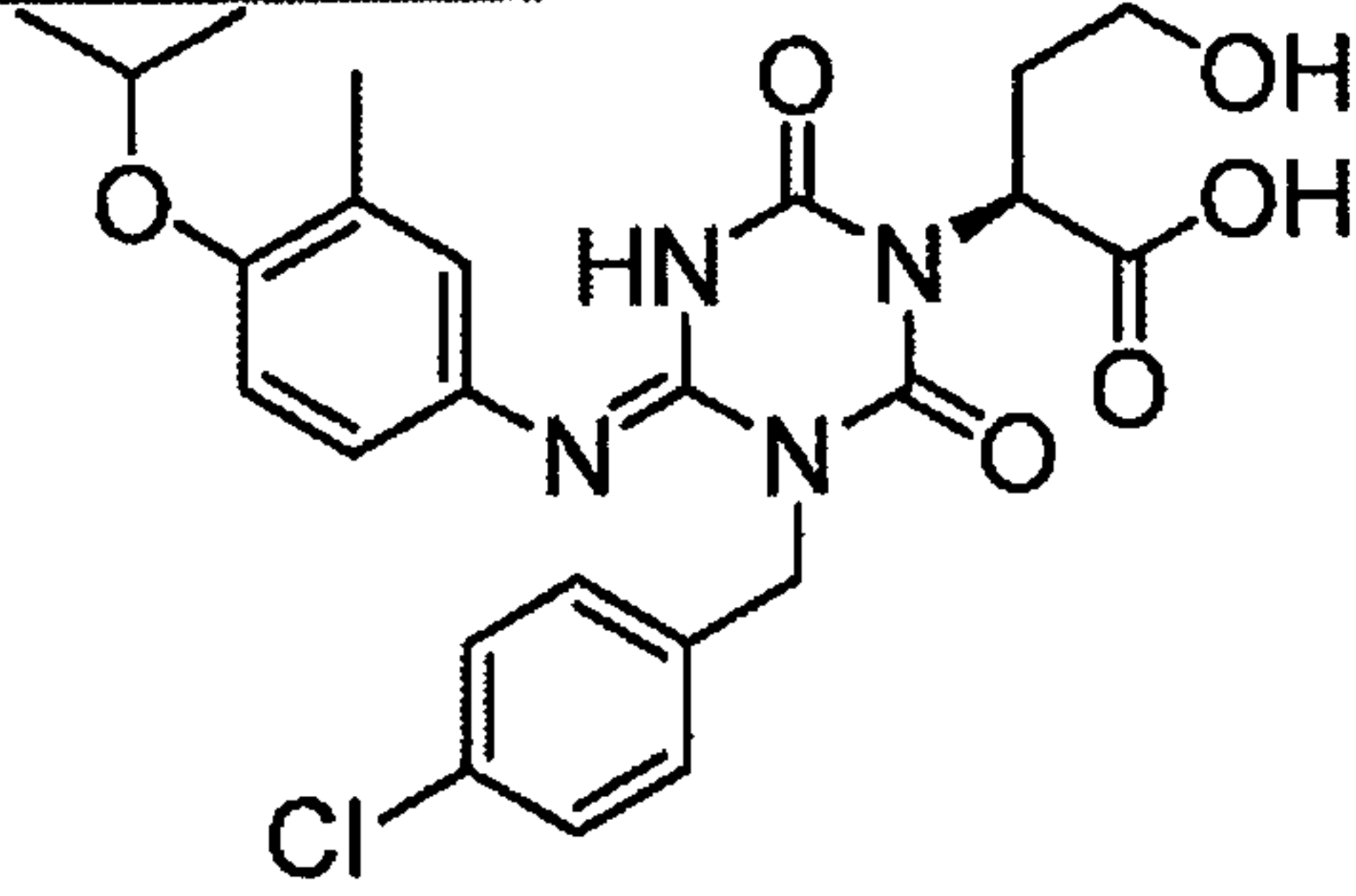
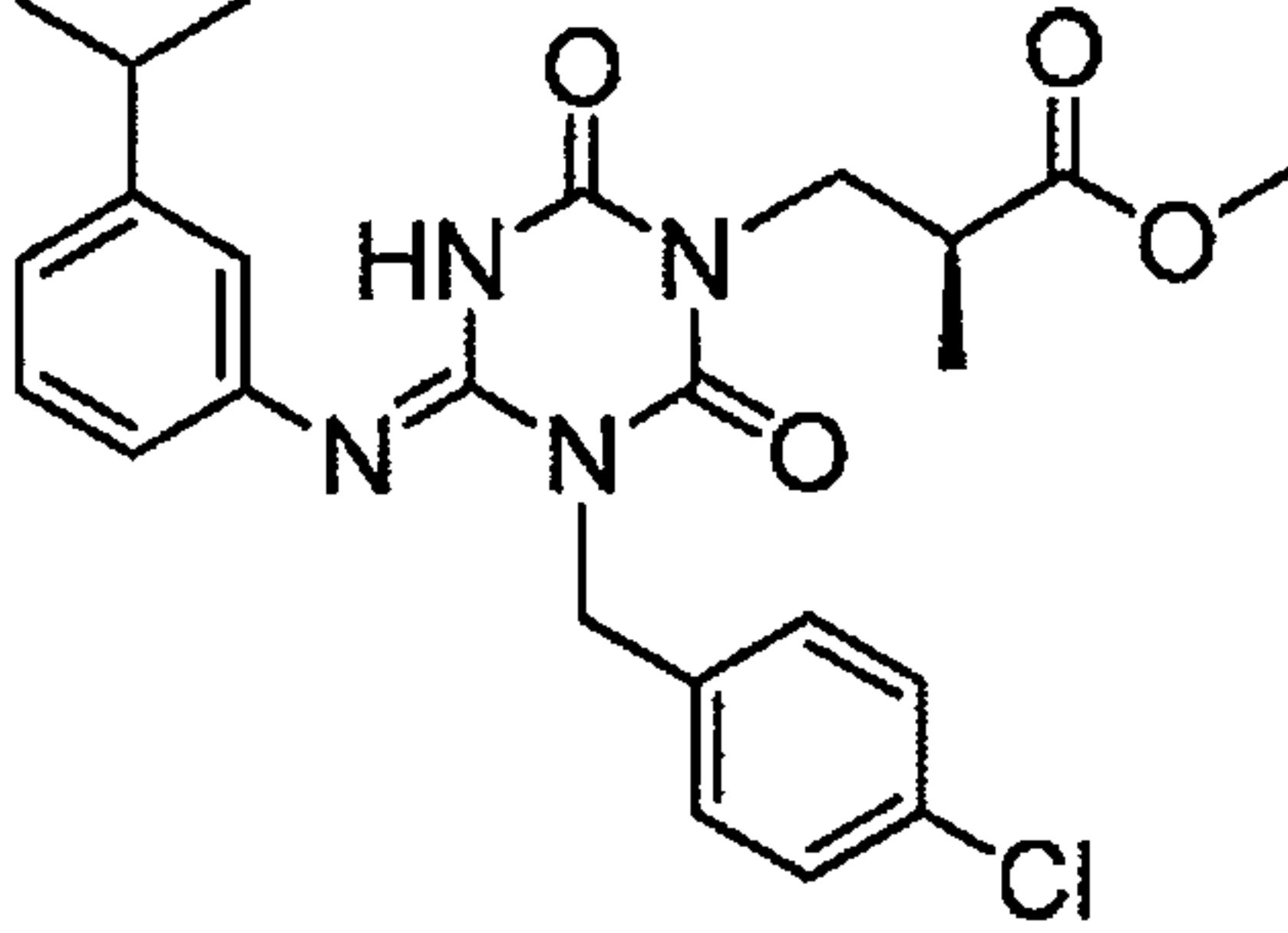
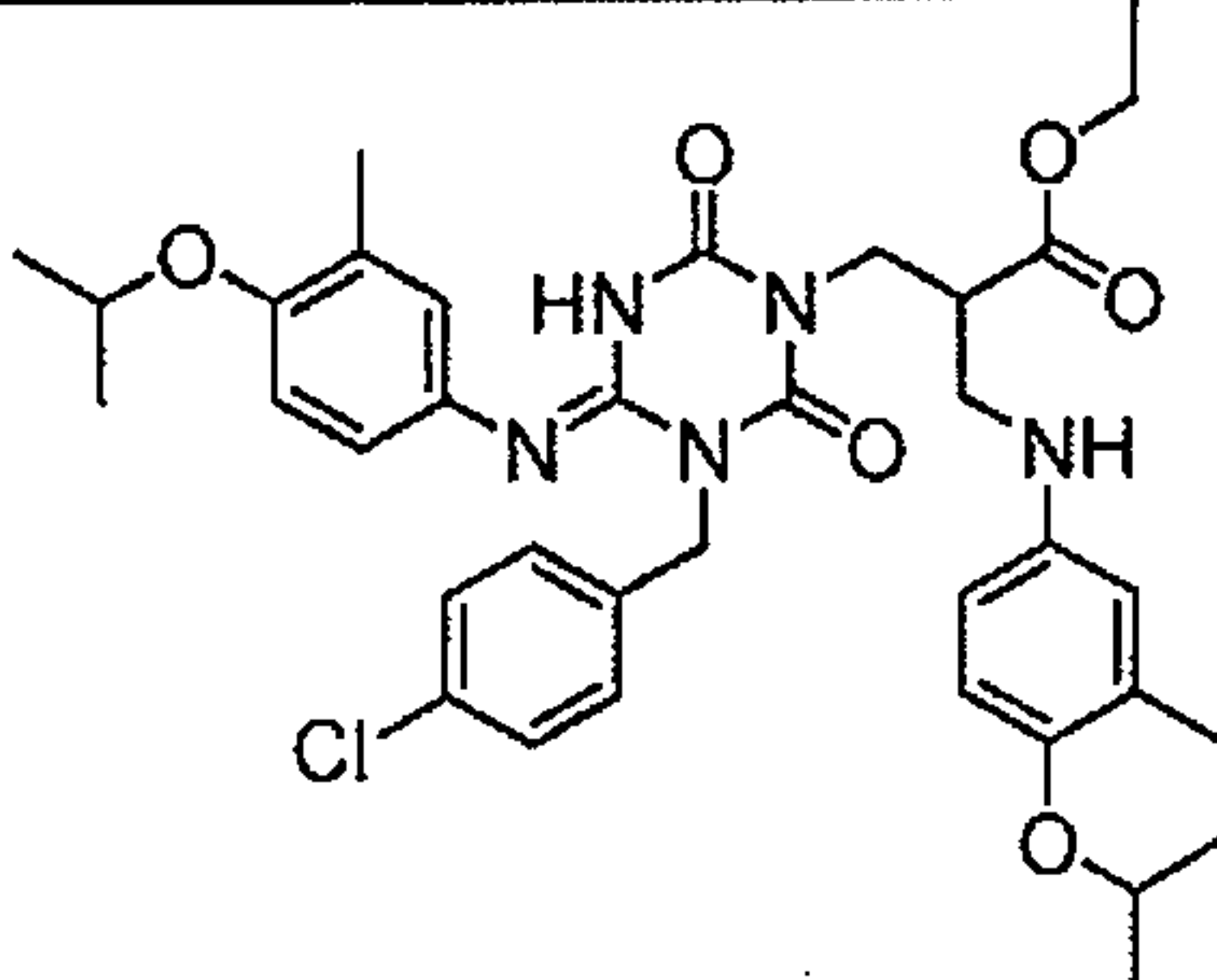
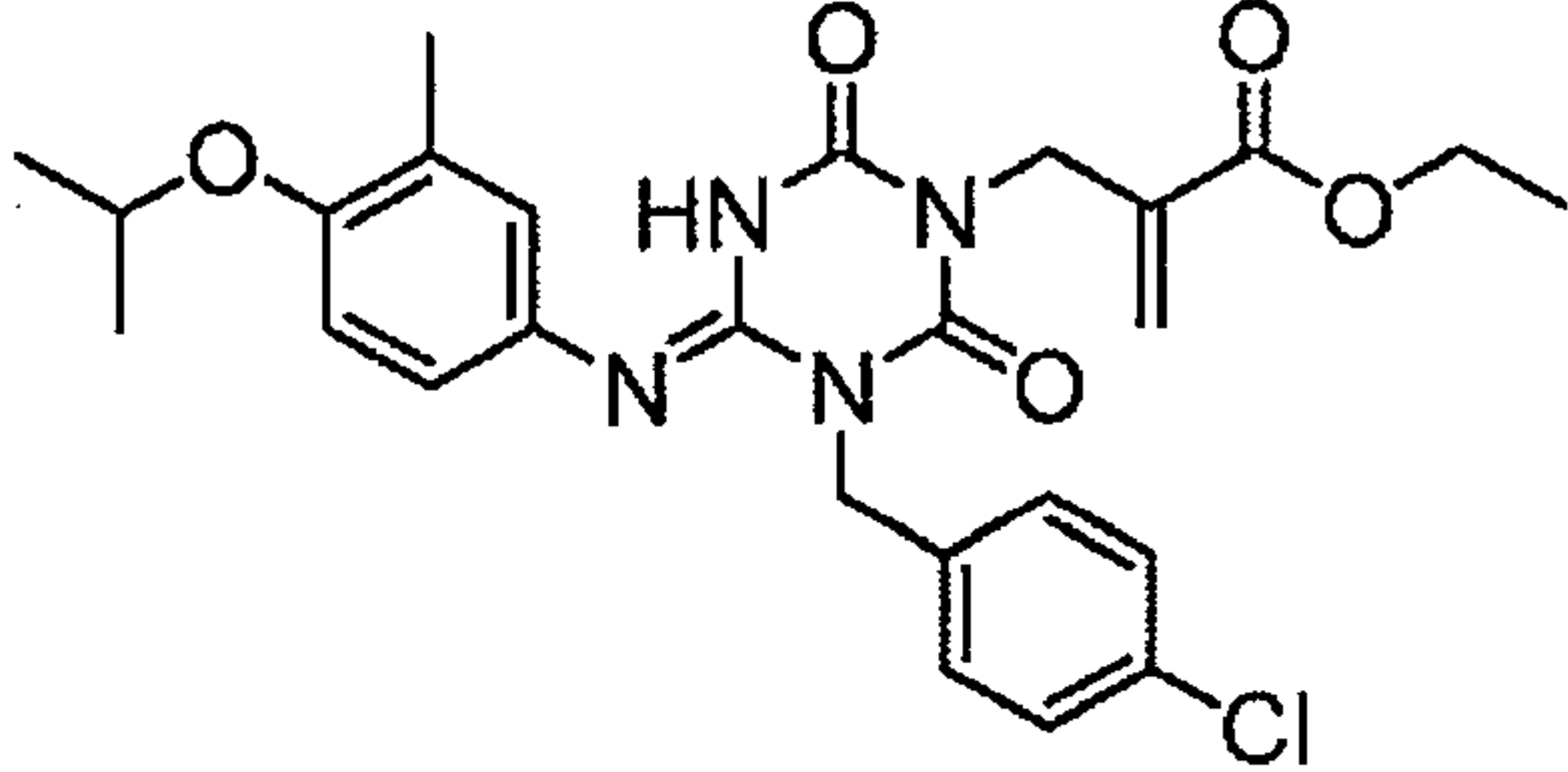
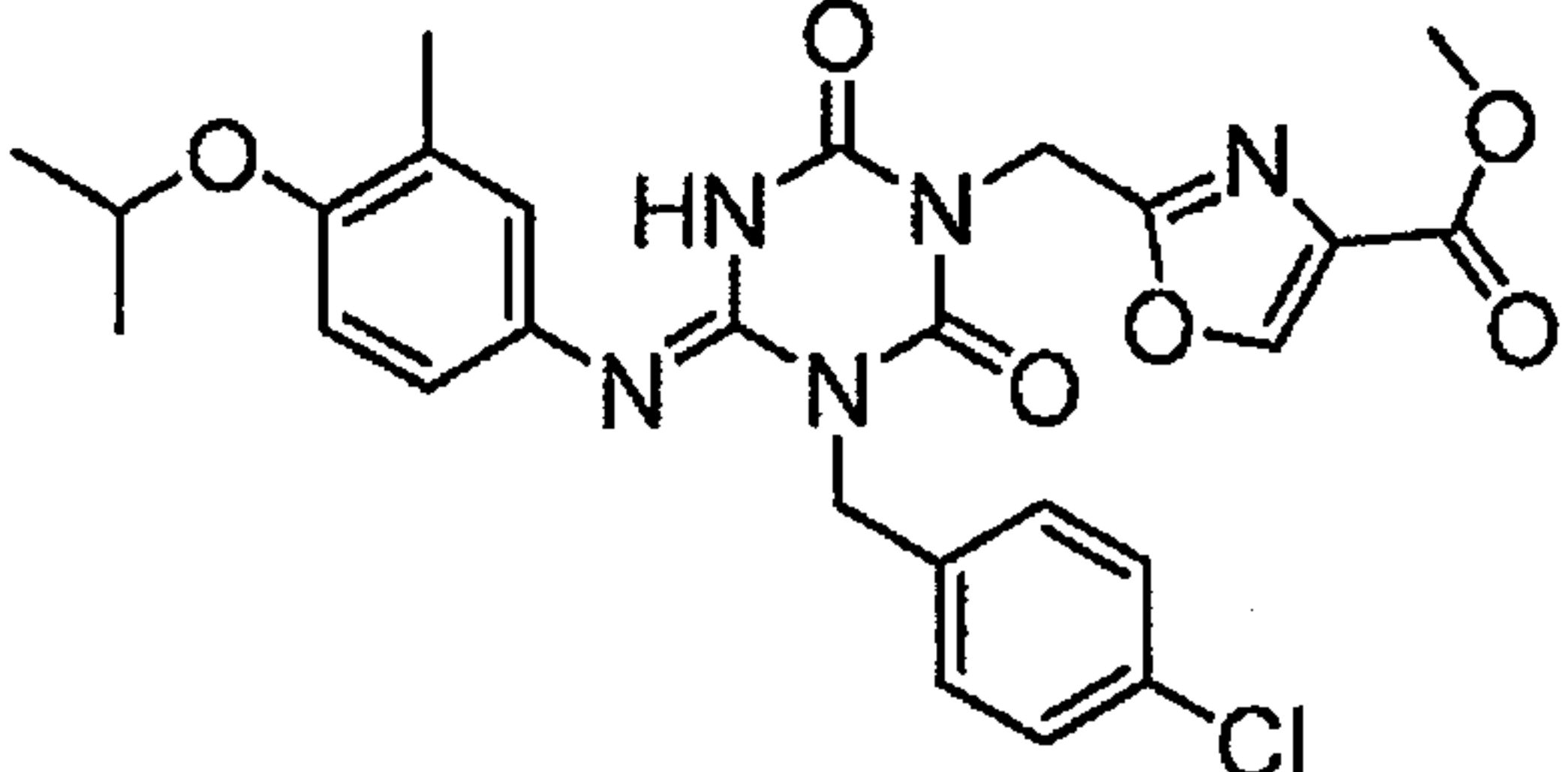
[Table 157]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0766	2.39	502	3
	I-0767	2.38	537	3
	I-0768	2.49	457	3
	I-0769	2.48	469	3
	I-0770	2.13	471	3

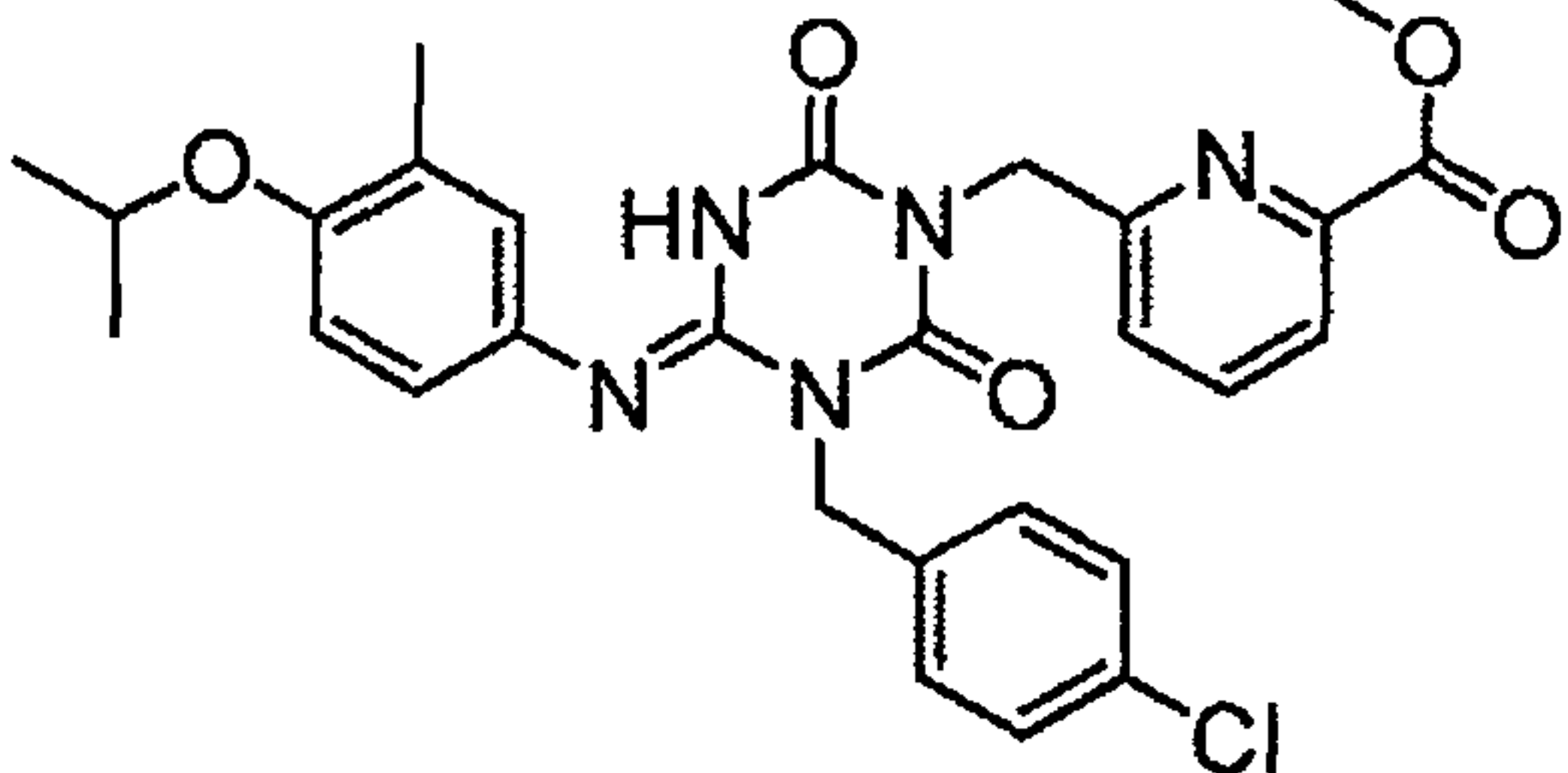
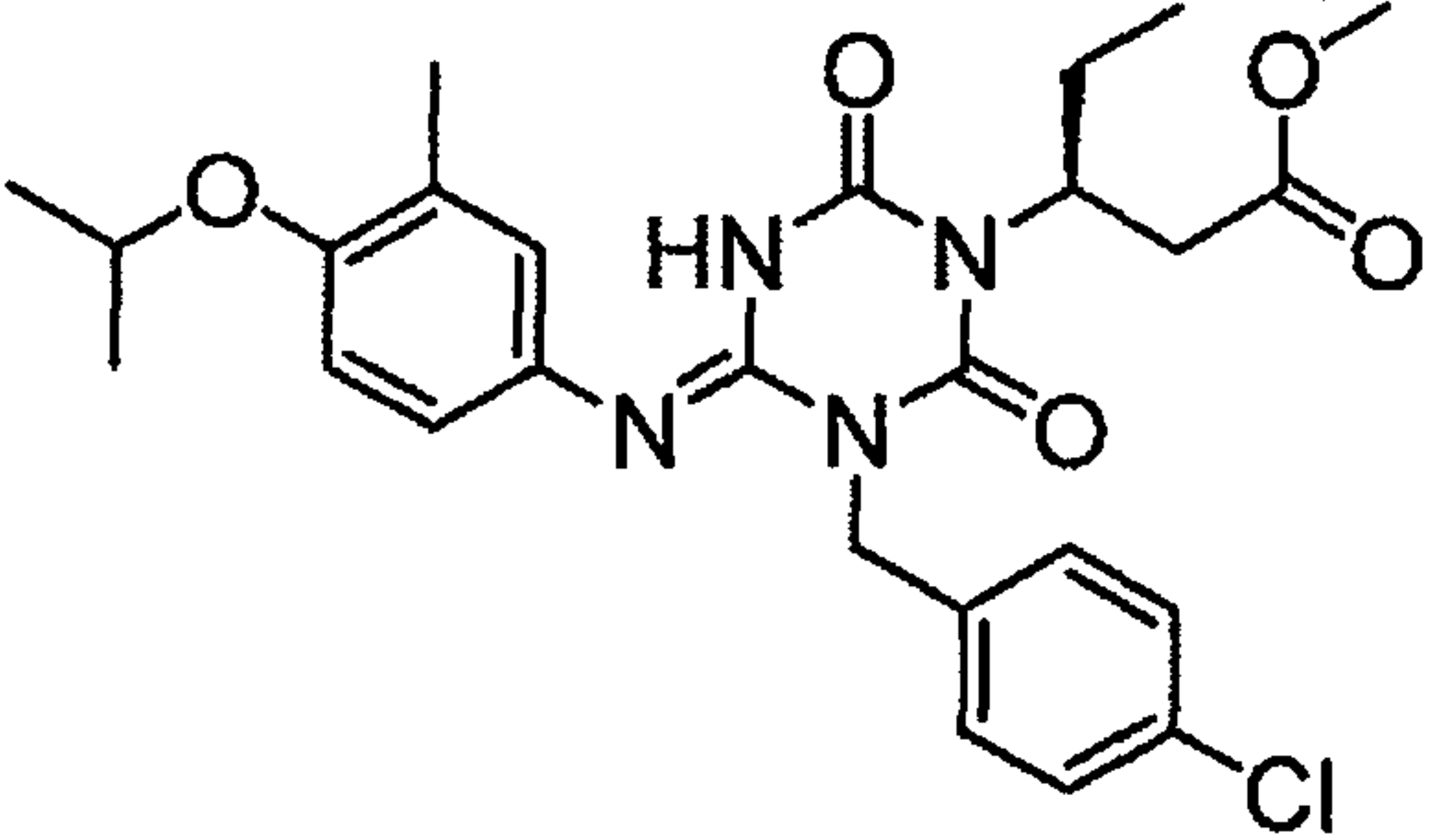
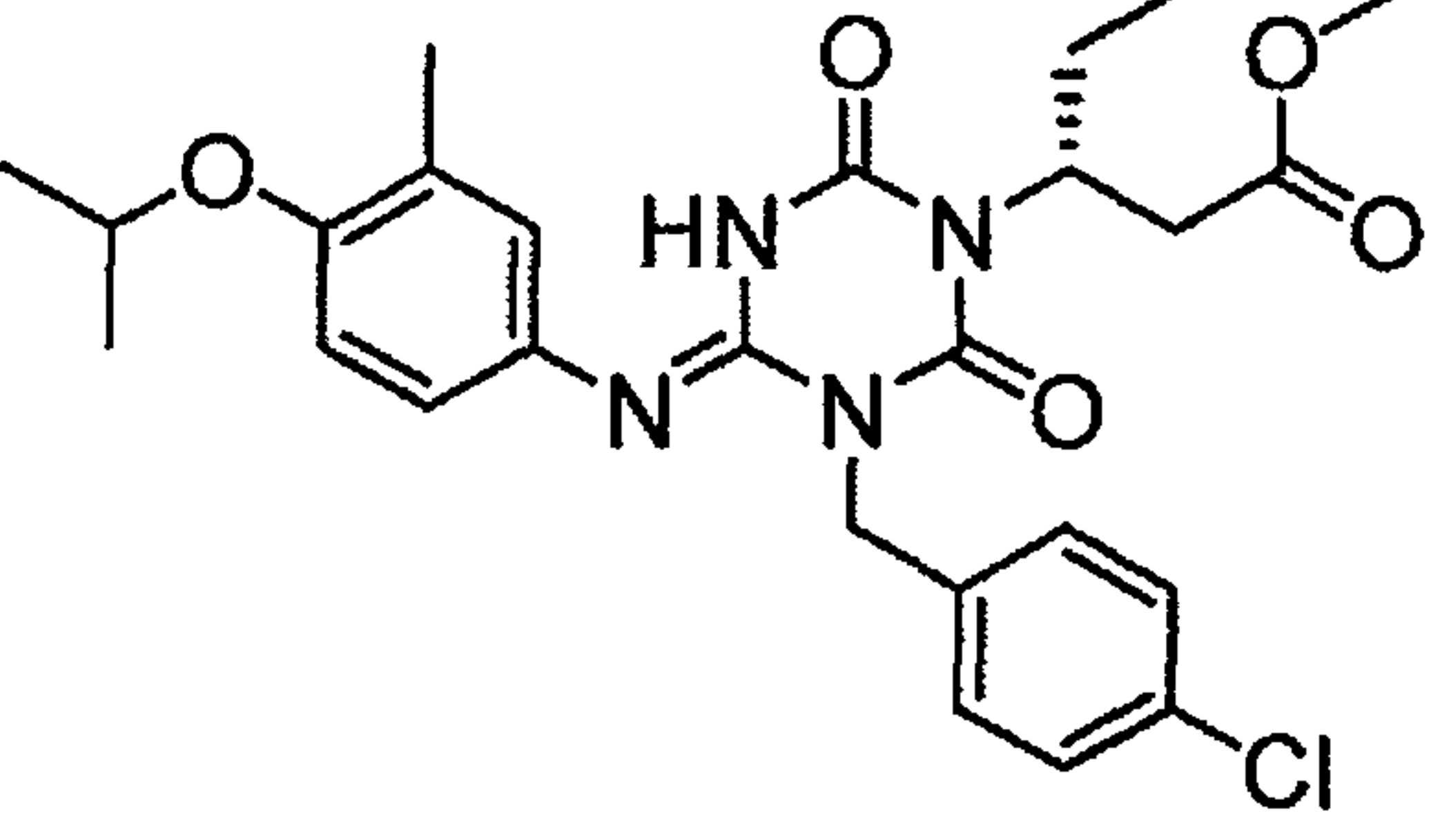
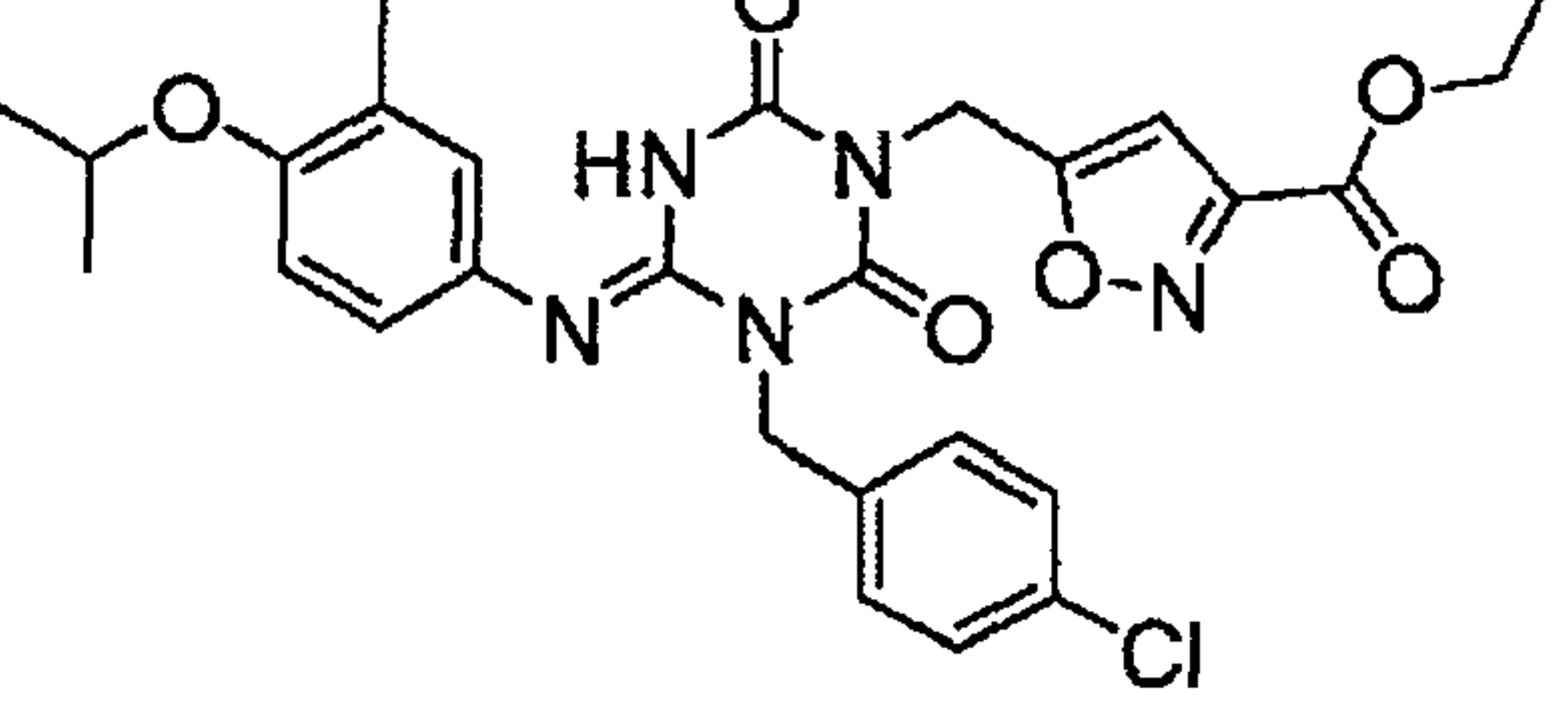
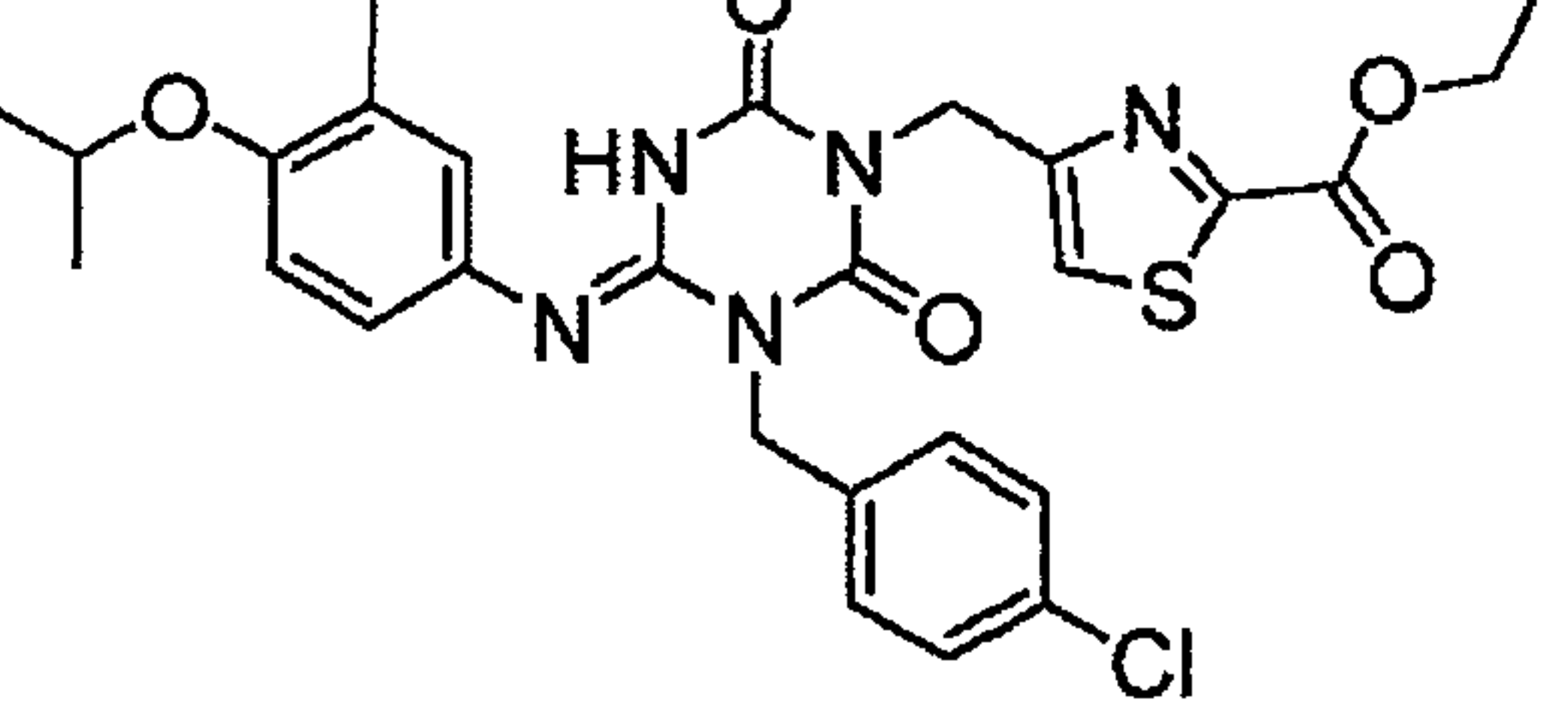
[Table 158]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0771	2.20	443	3
	I-0772	2.20	455	3
	I-0773	1.86	457	3
	I-0774	2.02	513	2
	I-0775	2.14	485	2

[Table 159]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0776	1.84	503	2
	I-0777	2.56	471	3
	I-0778	2.75	678	2
	I-0779	2.42	513	2
	I-0780	2.18	540	2

[Table 160]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0781	2.24	550	2
	I-0782	2.45	515	2
	I-0783	2.45	515	2
	I-0784	2.38	554	2
	I-0785	2.37	570	2

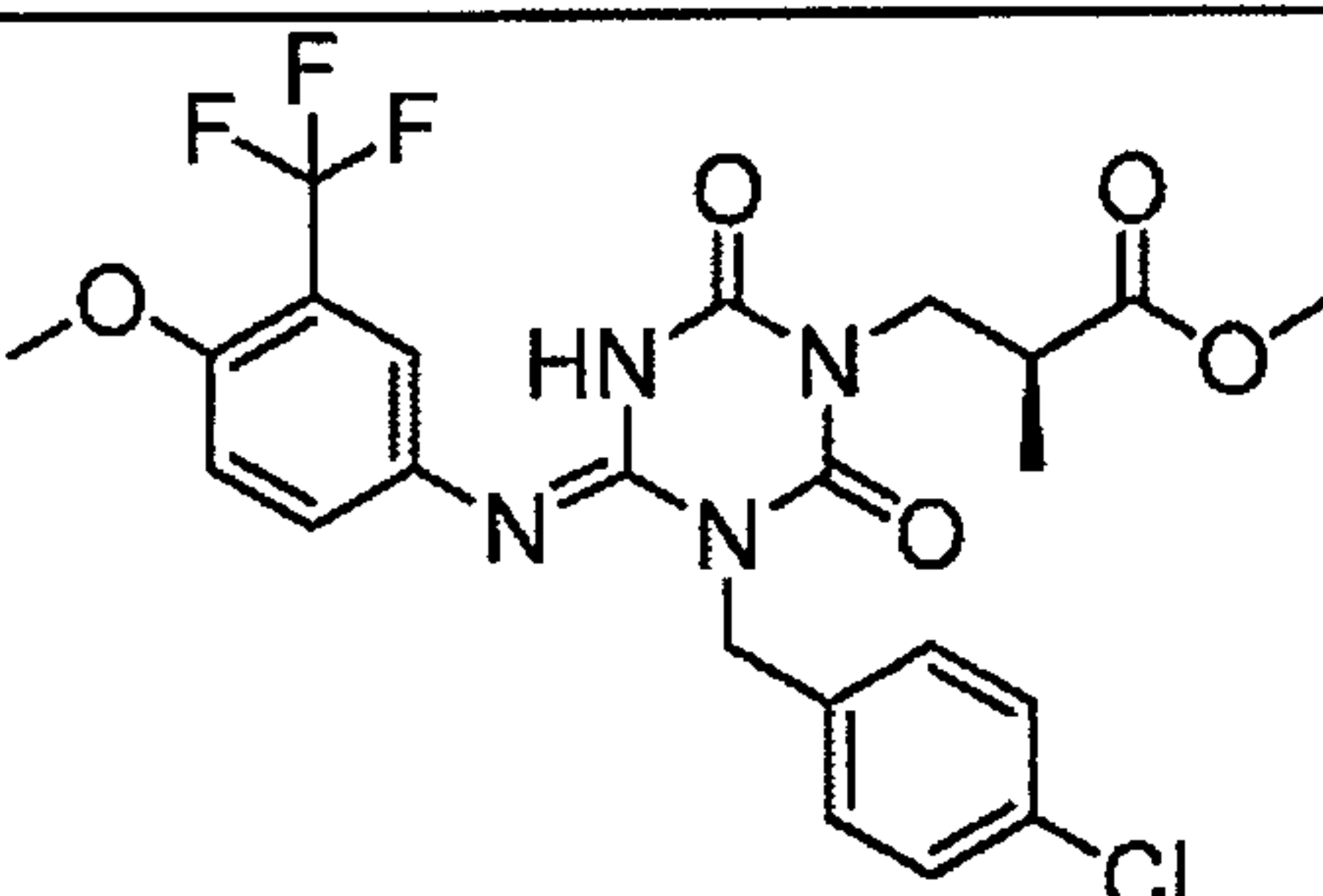
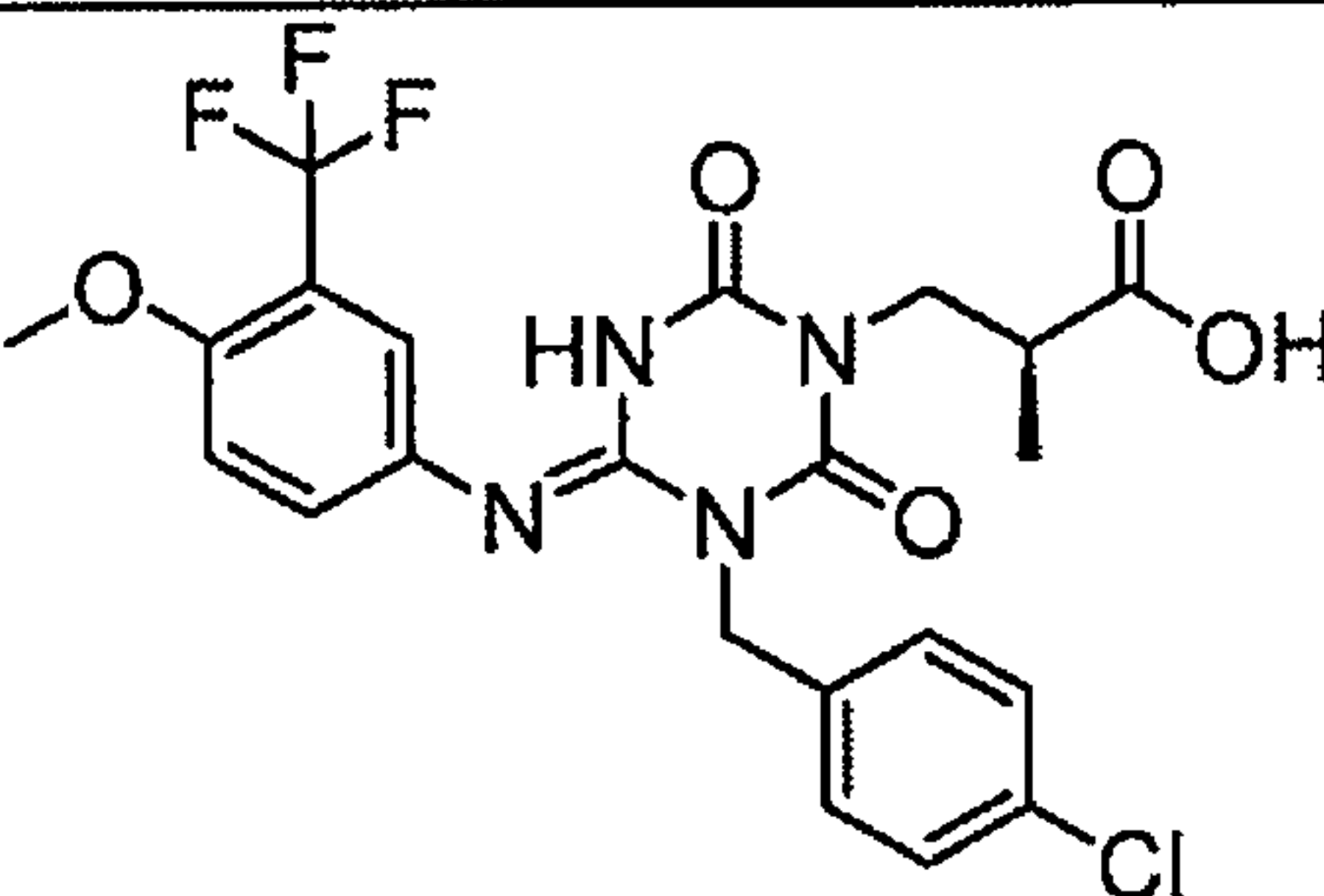
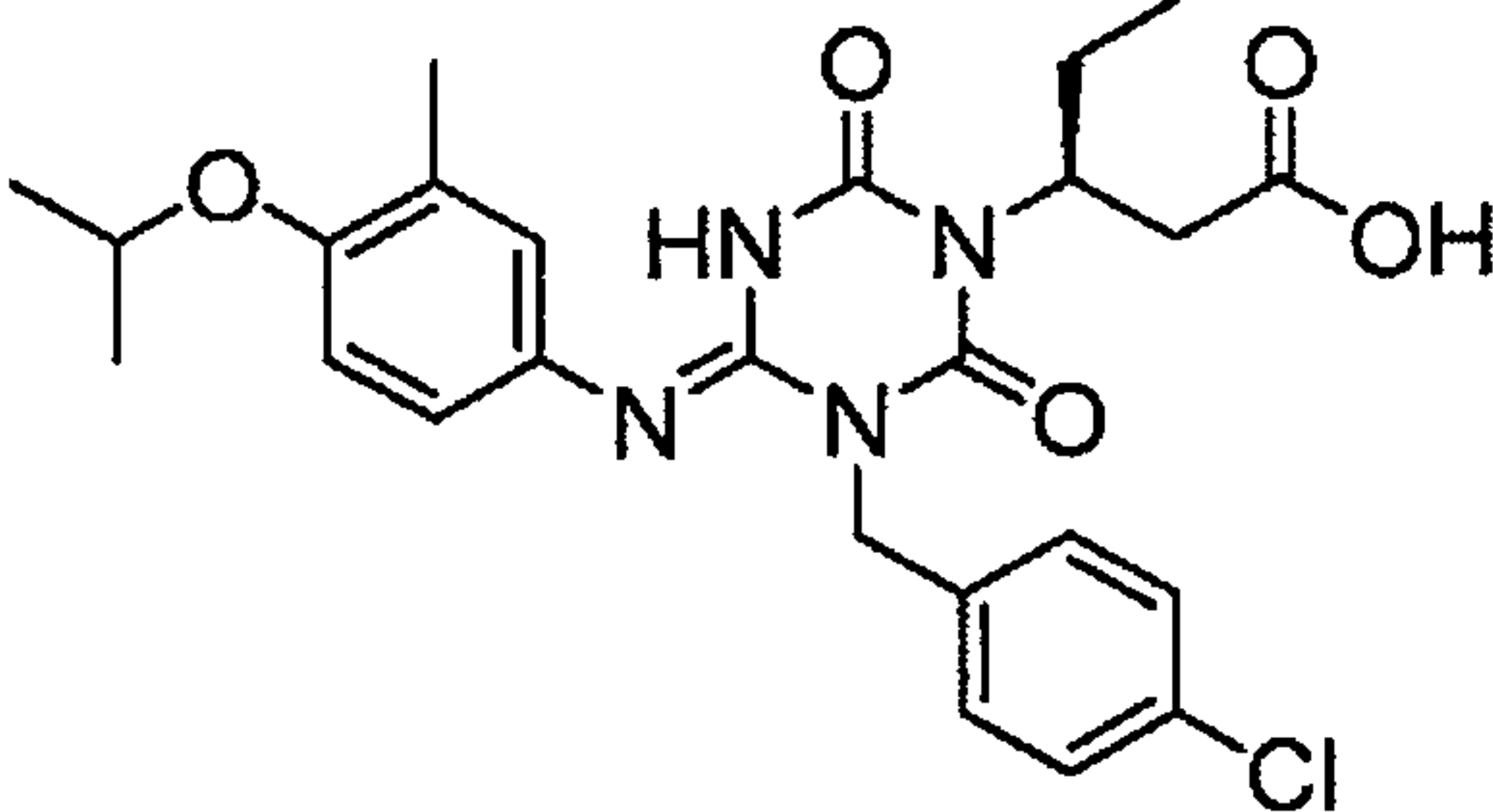
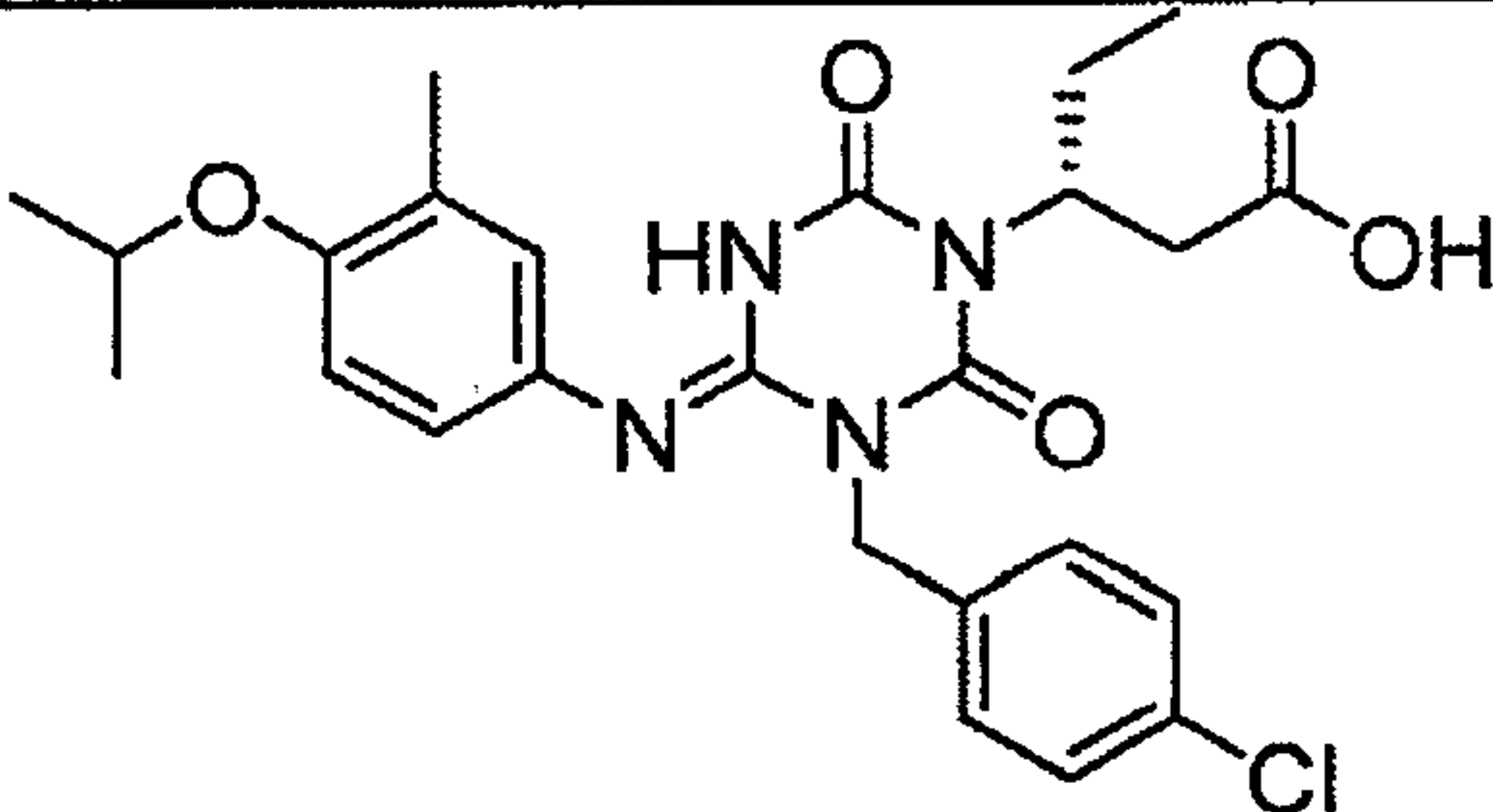
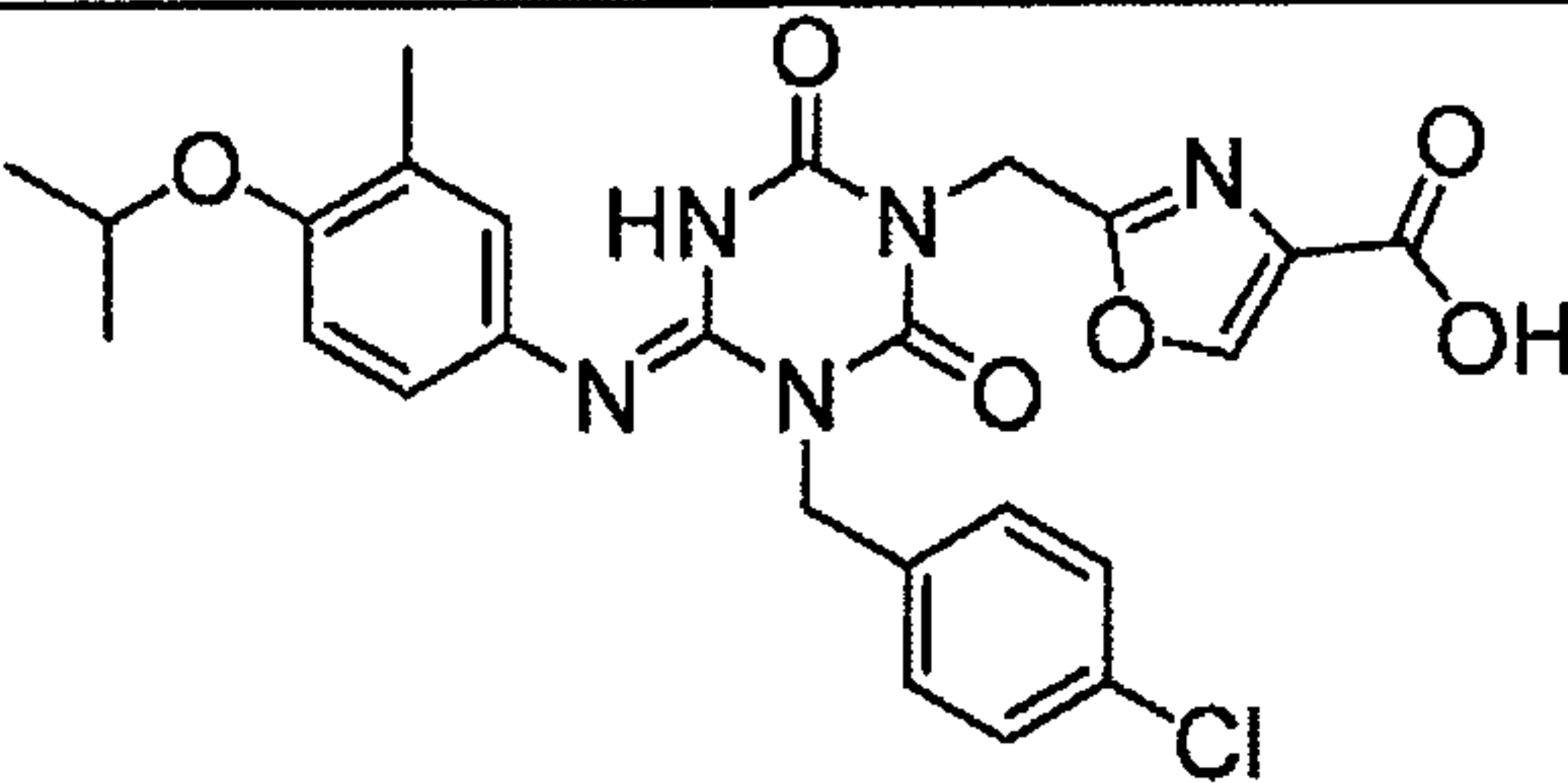
[Table 161]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0786	1.99	500	2
	I-0787	2.05	556	2
	I-0788	1.86	530	2
	I-0789	2.11	523	3
	I-0790	1.53	494	3

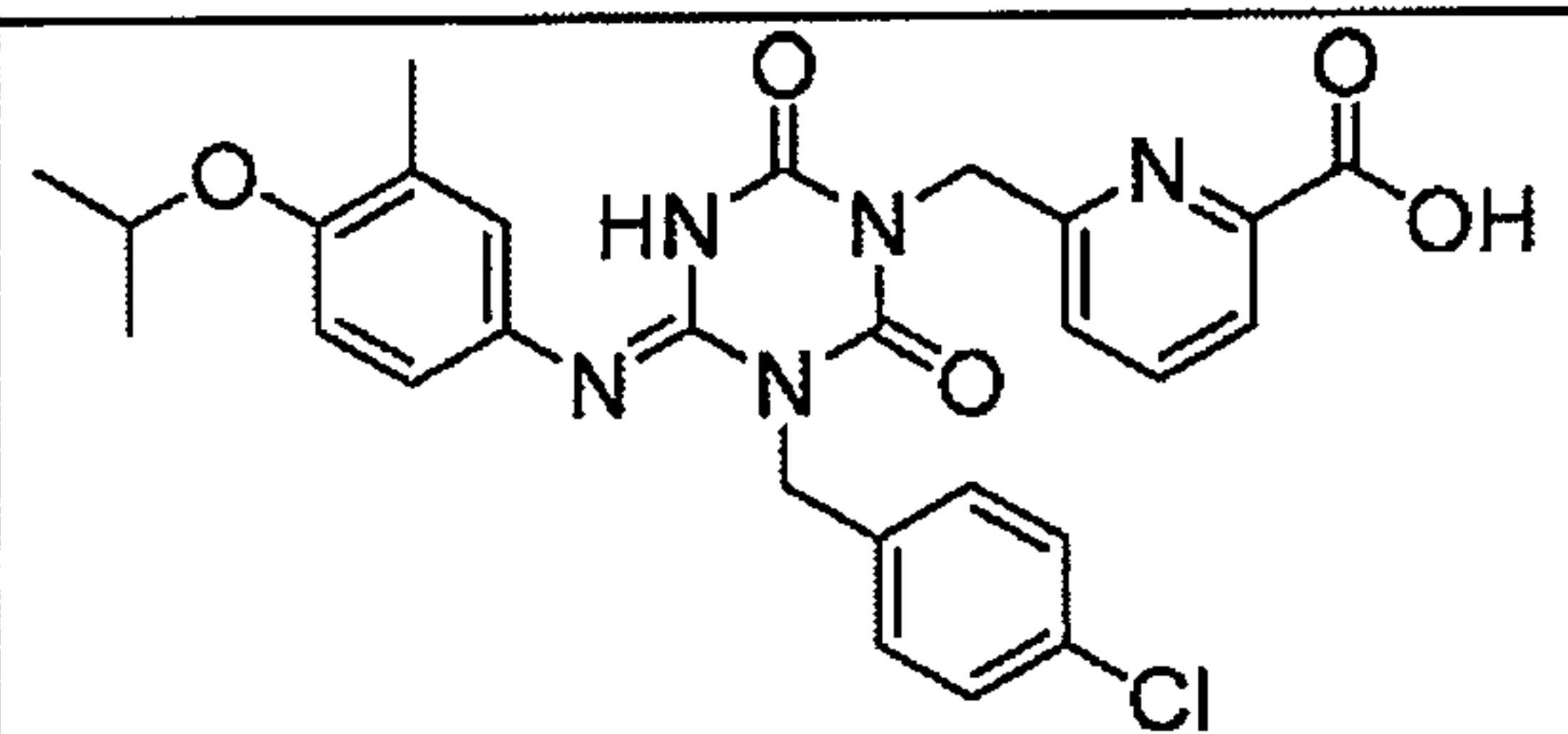
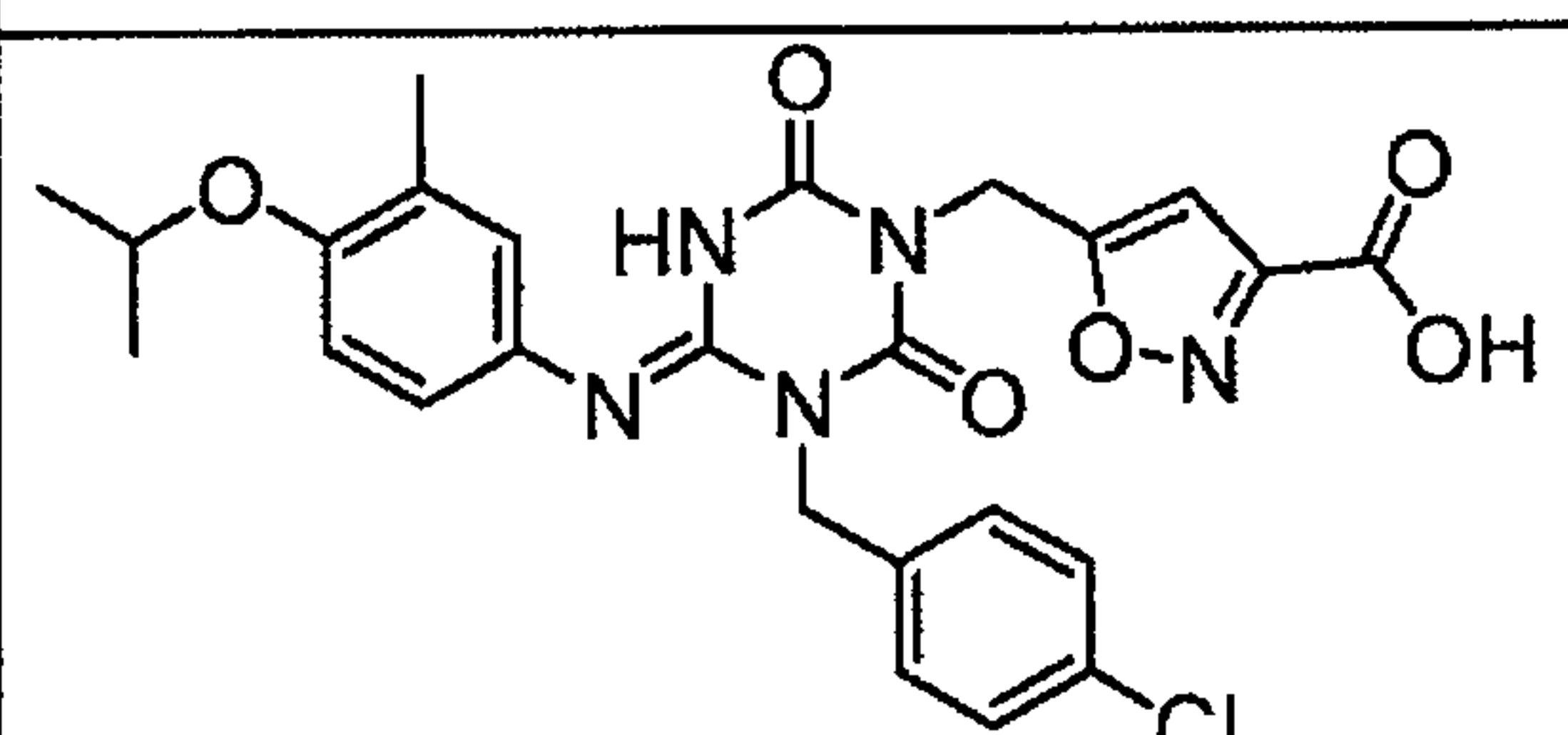
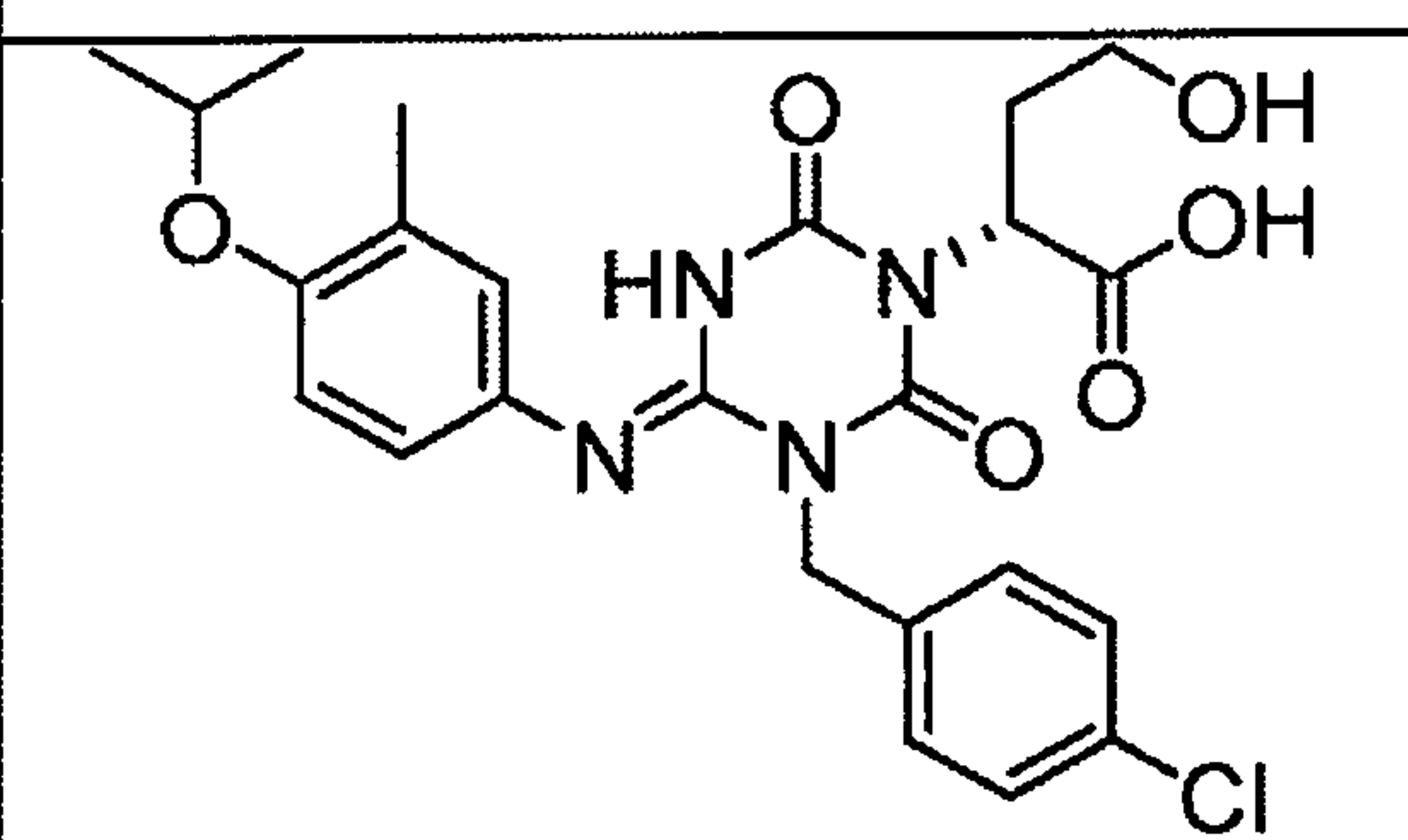
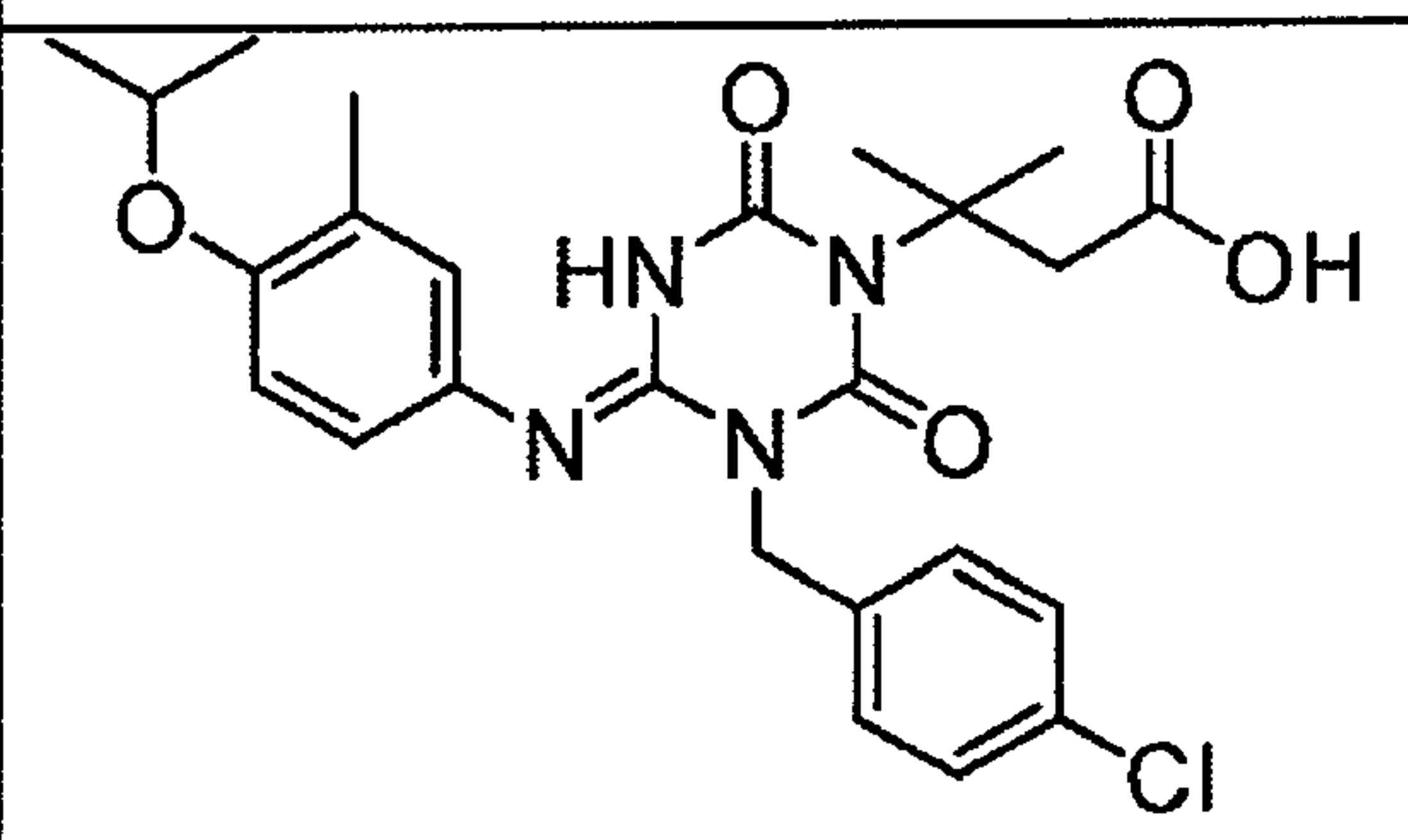
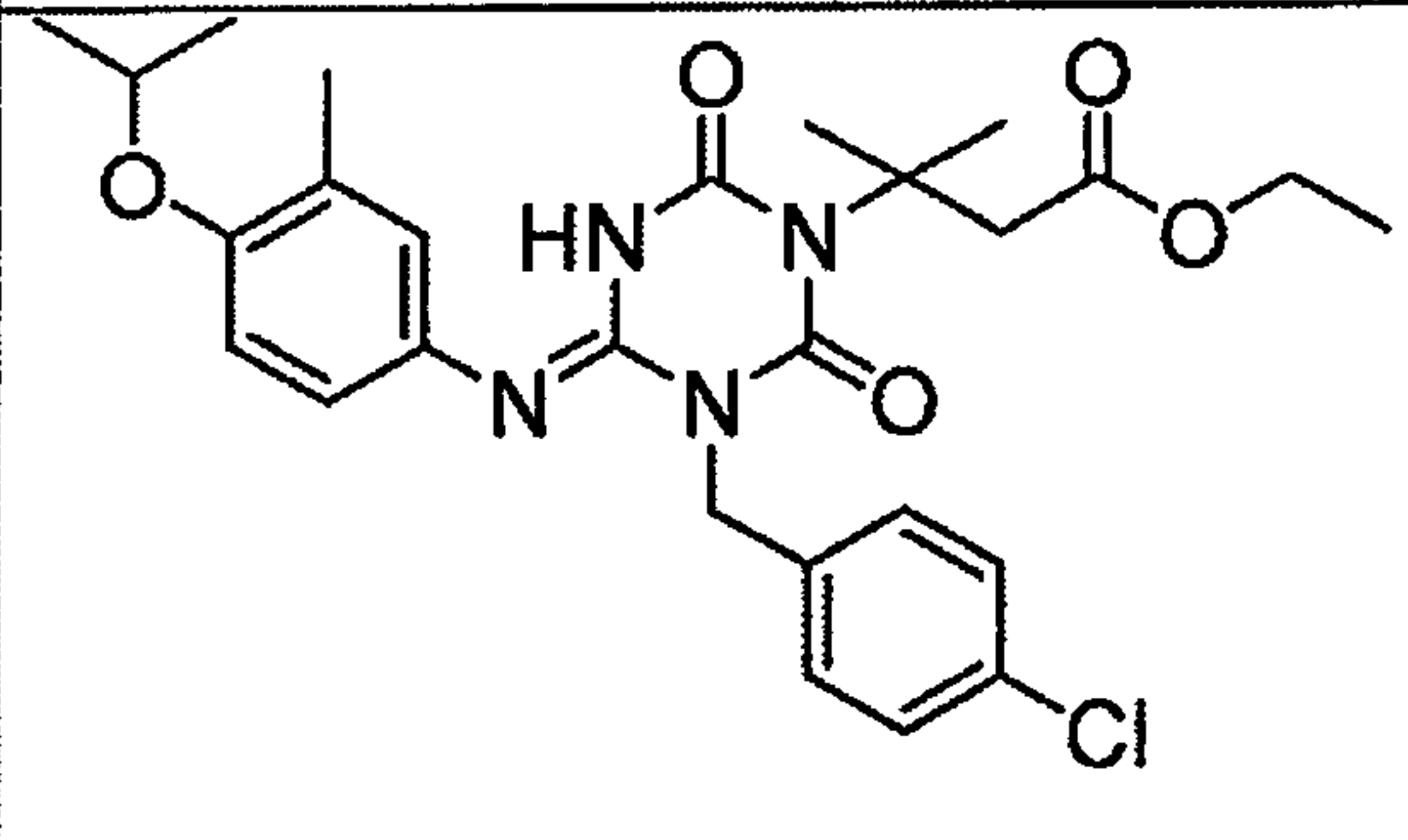
[Table 162]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0791	2.57	483	3
	I-0792	2.31	457	3
	I-0793	2.30	469	3
	I-0794	1.97	473	2
	I-0795	1.92	453	2

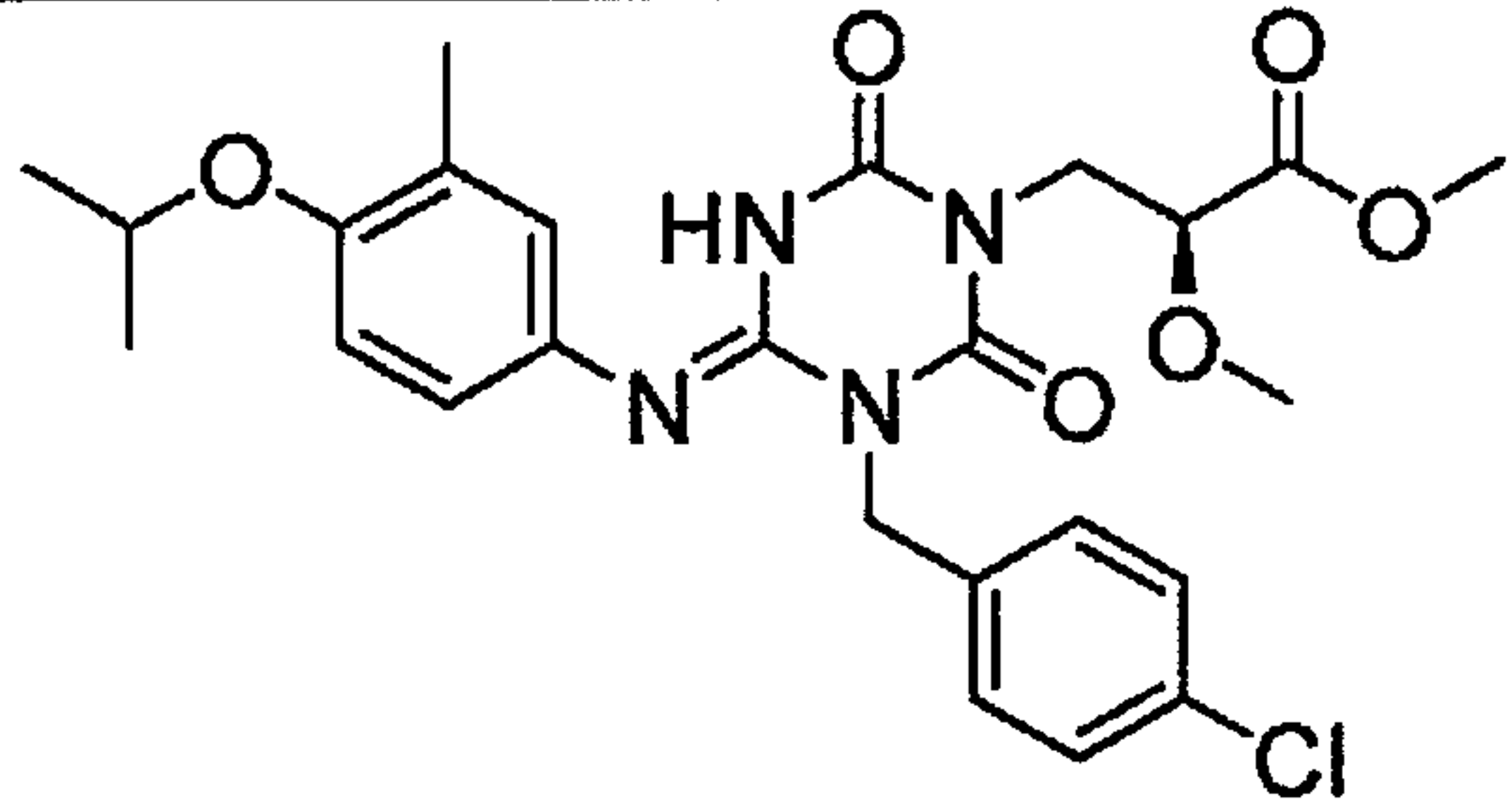
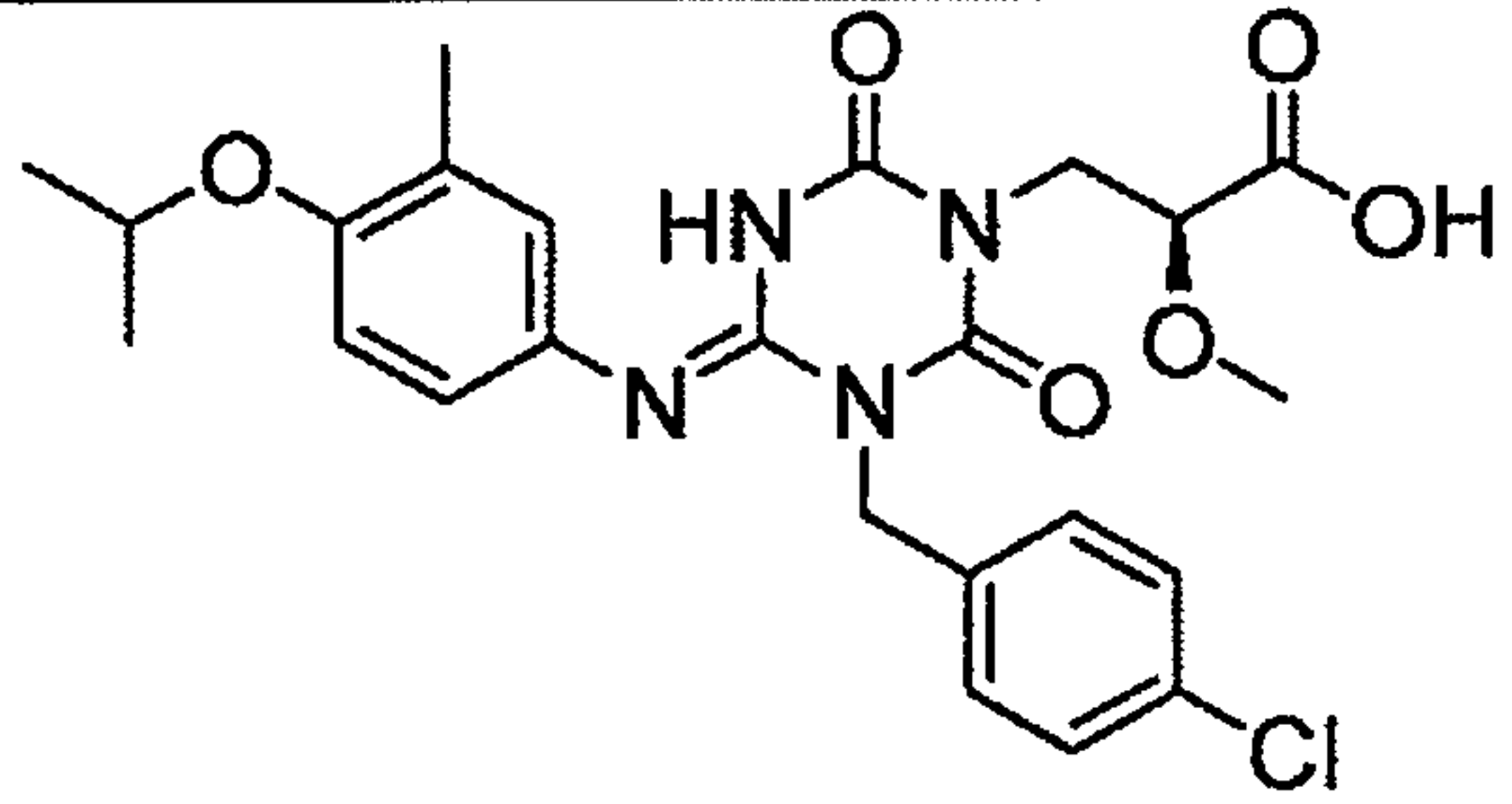
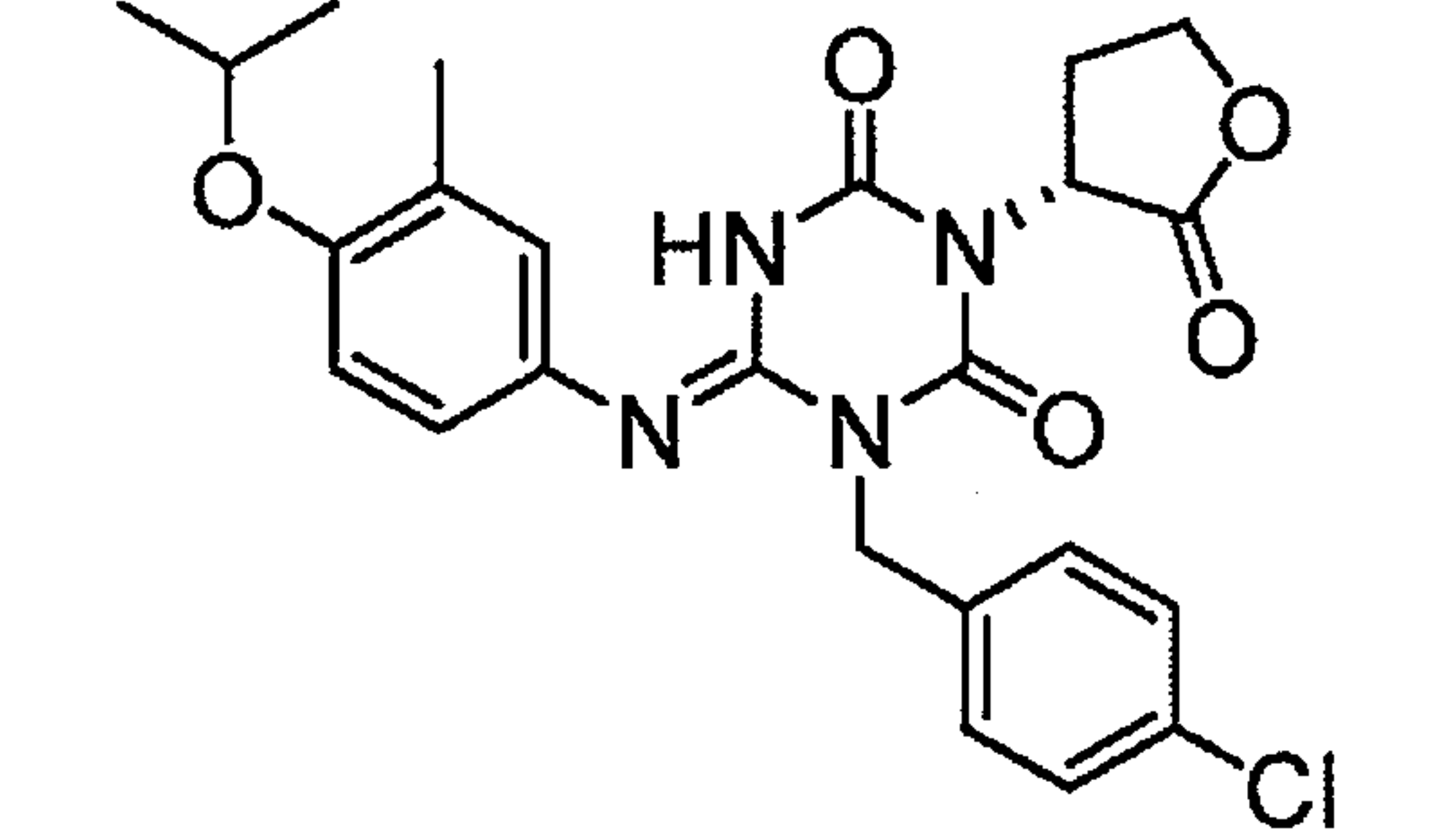
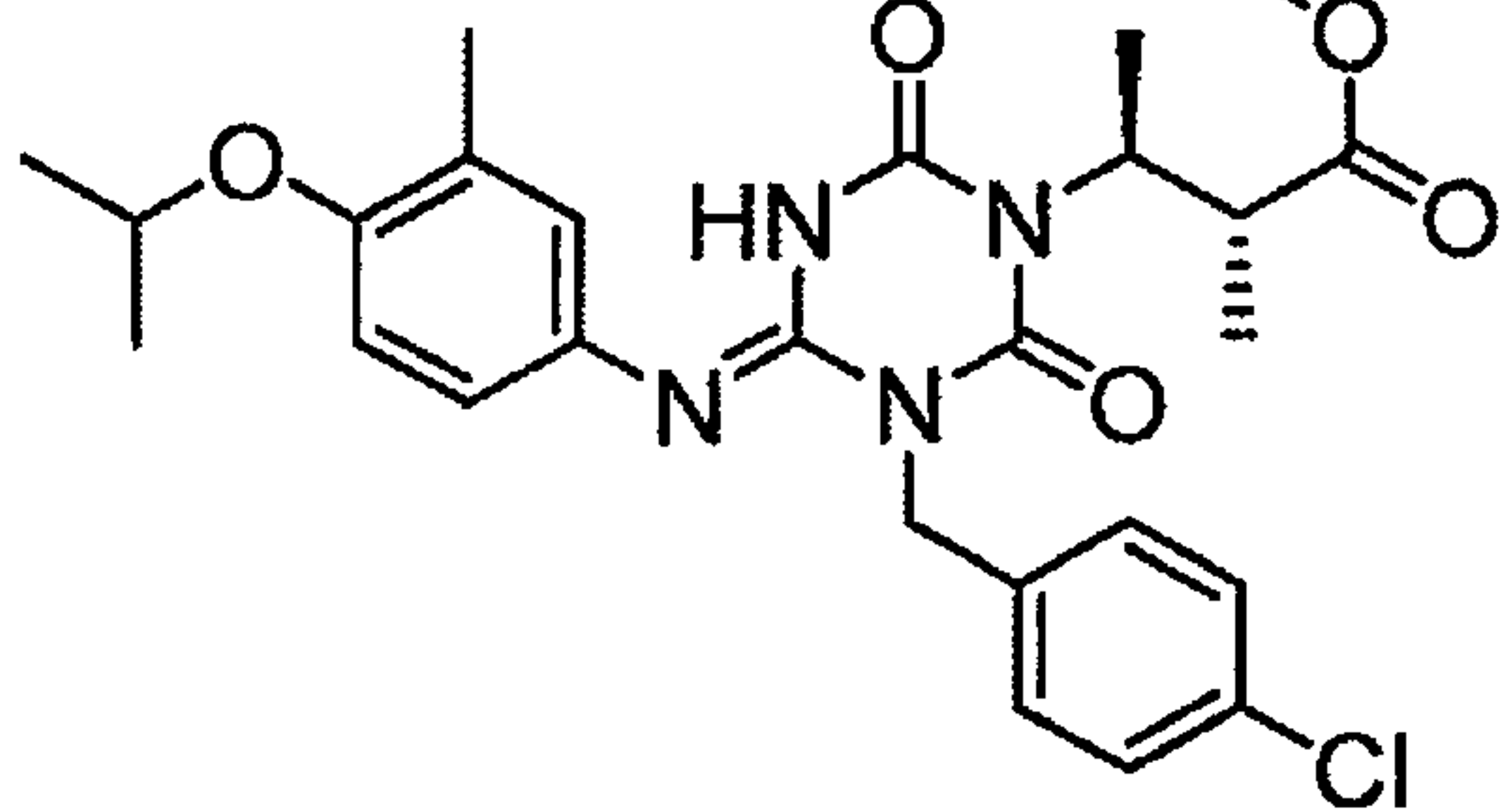
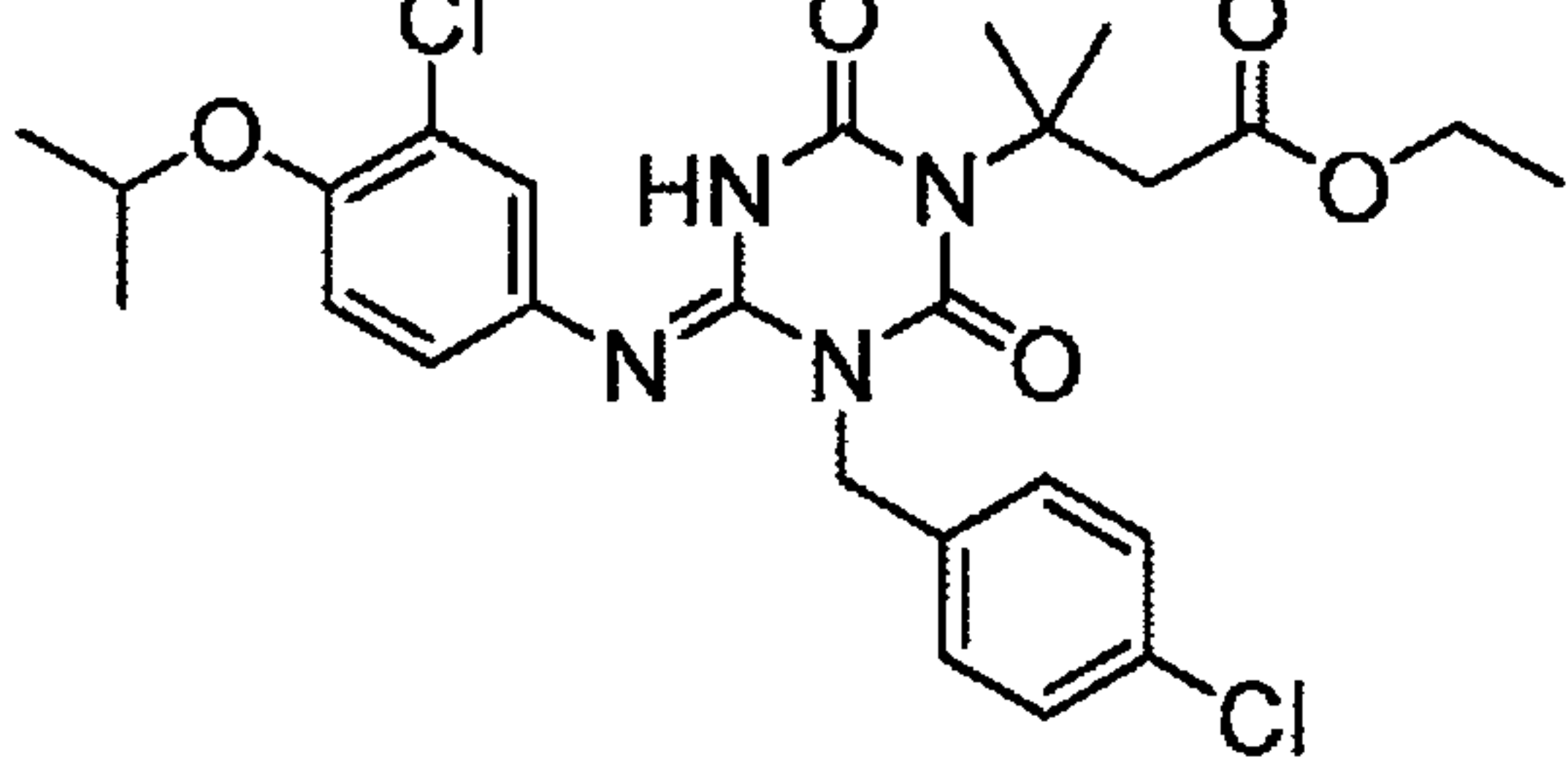
[Table 163]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0796	2.28	527	2
	I-0797	2.04	513	2
	I-0798	2.19	501	2
	I-0799	2.19	501	2
	I-0800	1.98	526	2

[Table 164]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0801	2.04	536	2
	I-0802	2.03	526	2
	I-0803	2.04	503	3
	I-0804	2.17	501	2
	I-0805	2.54	529	2

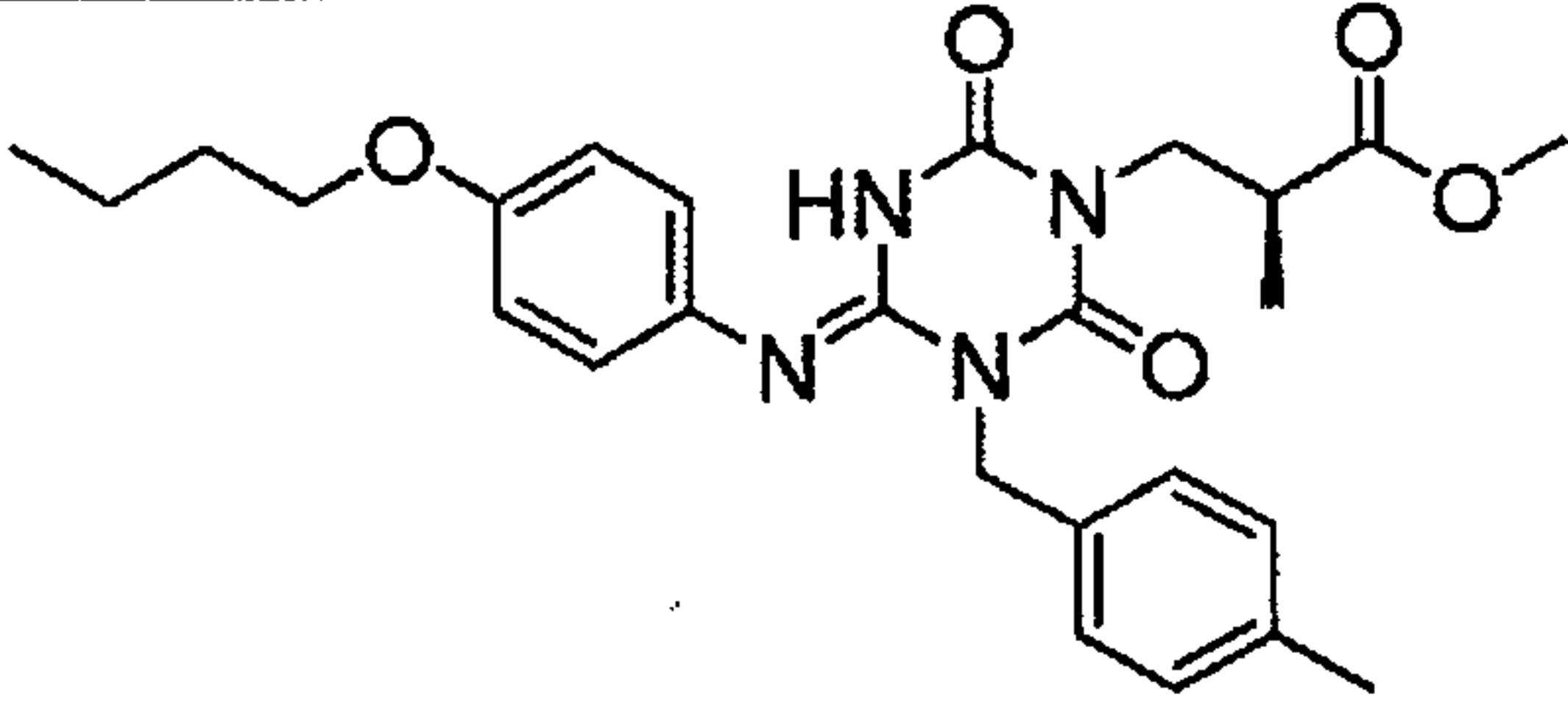
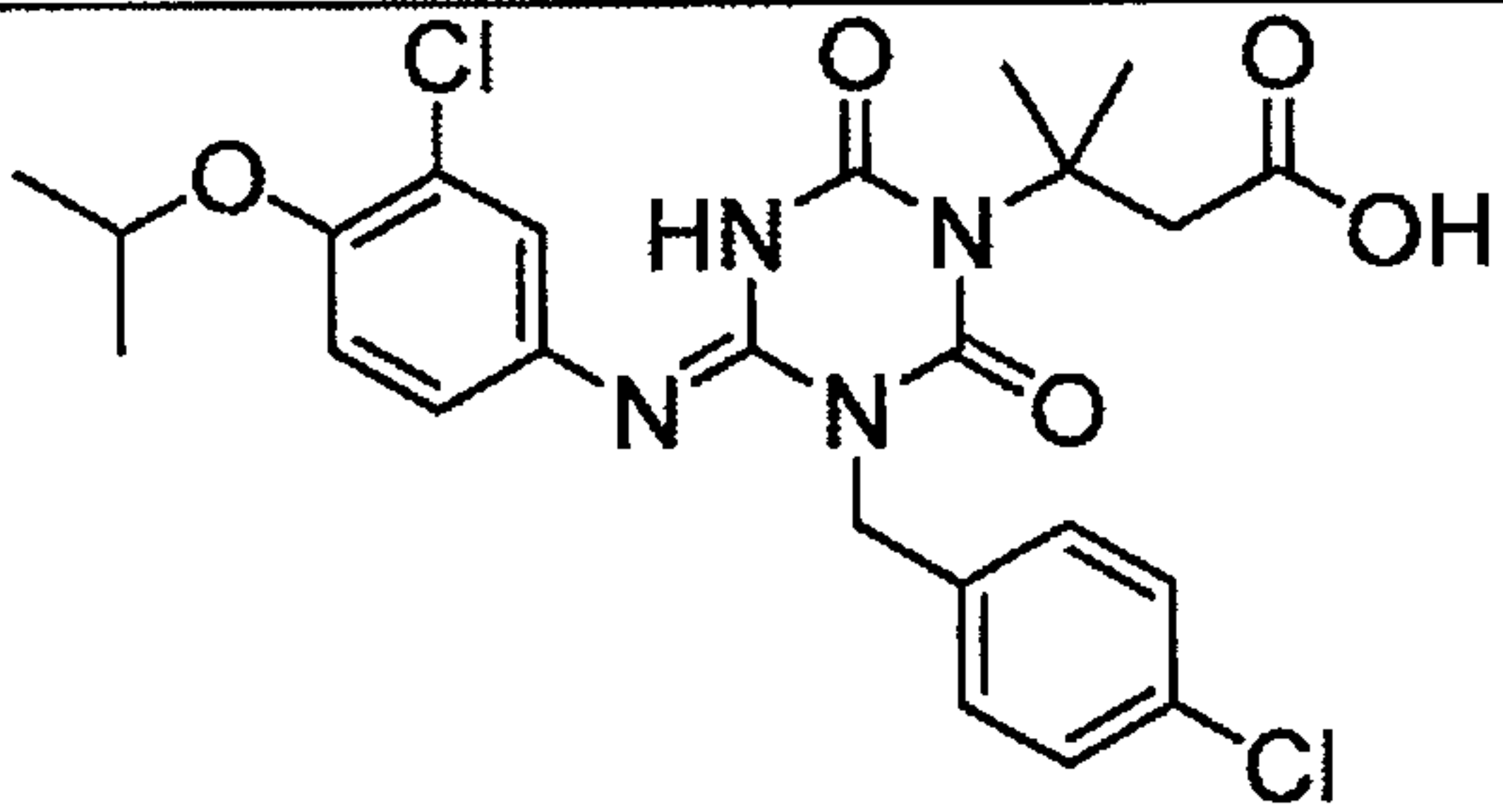
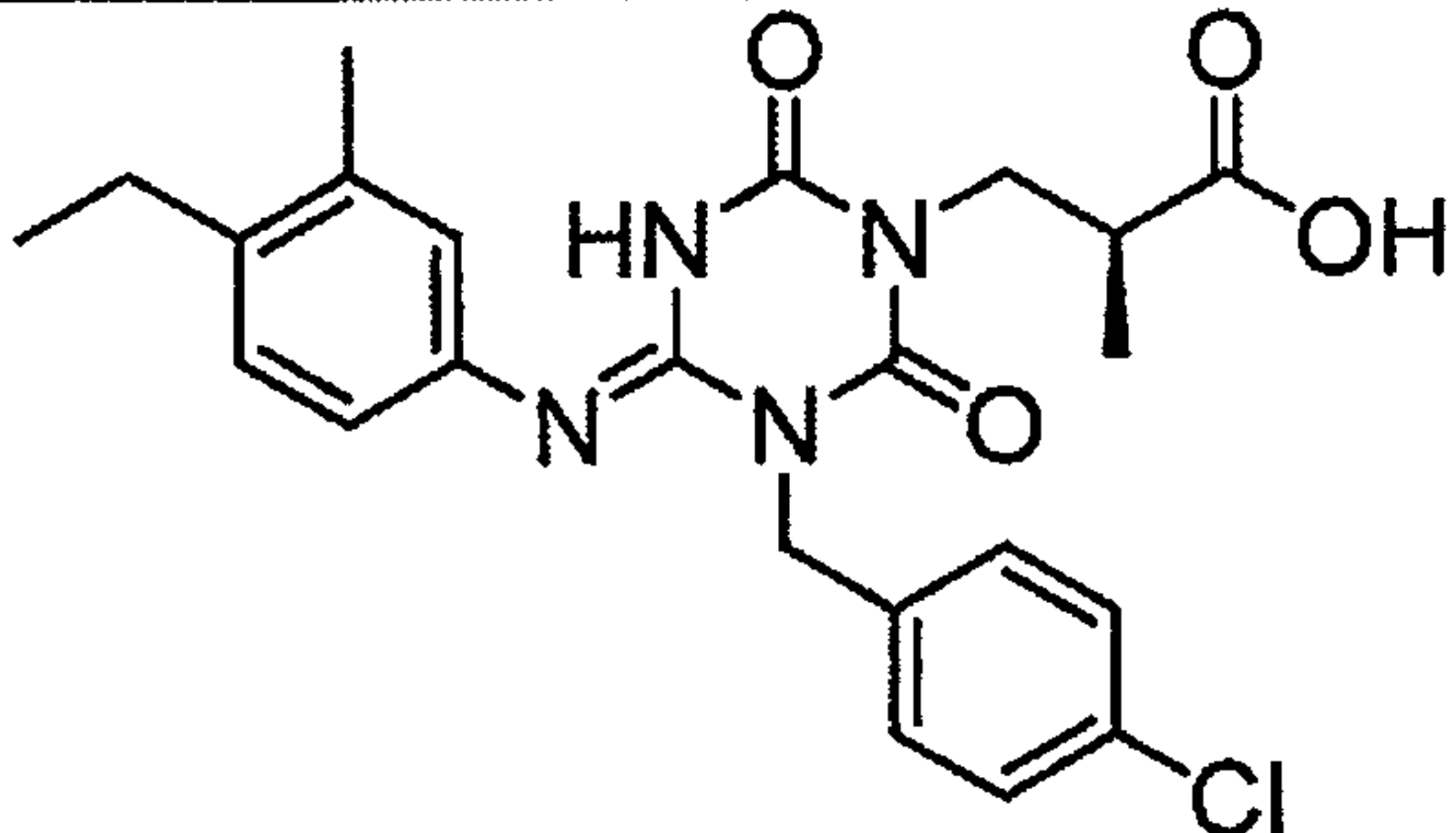
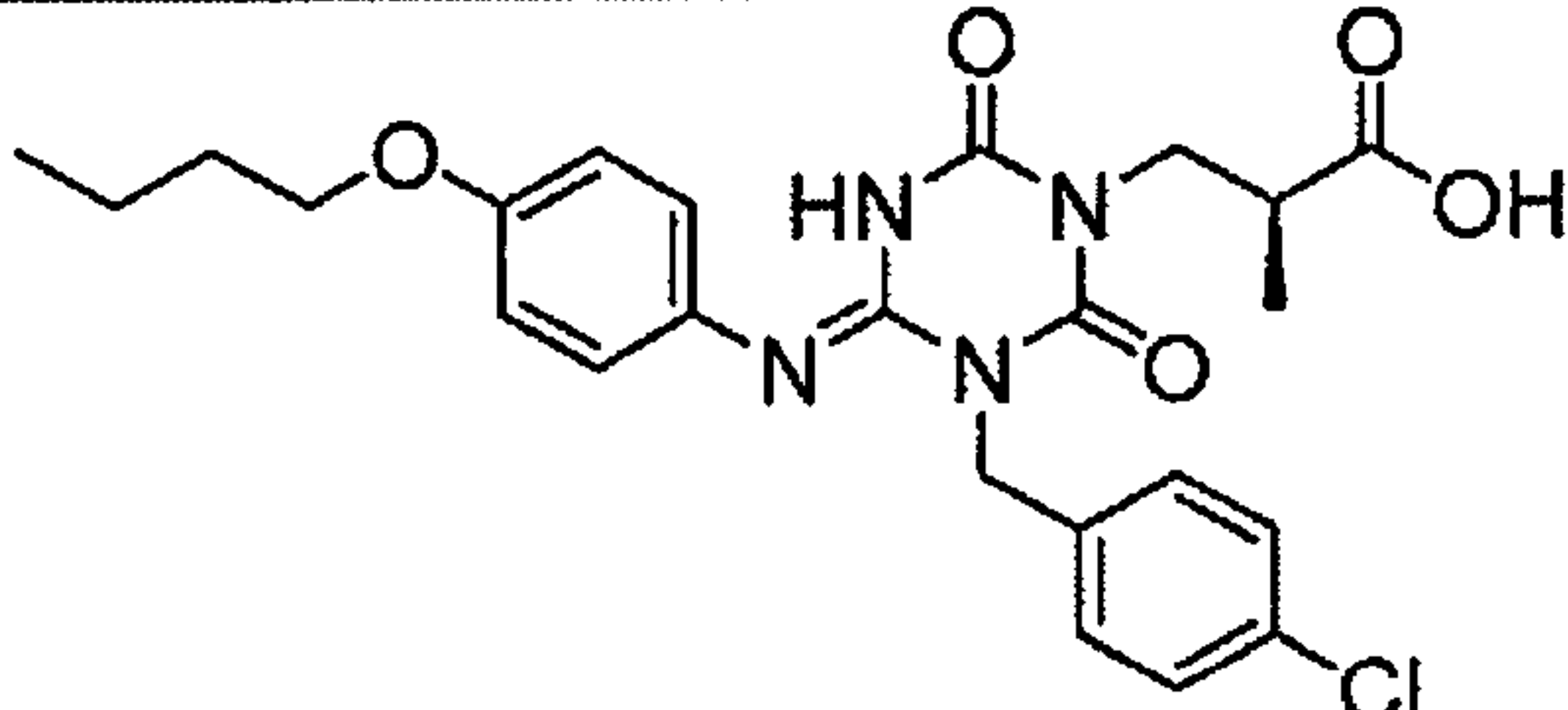
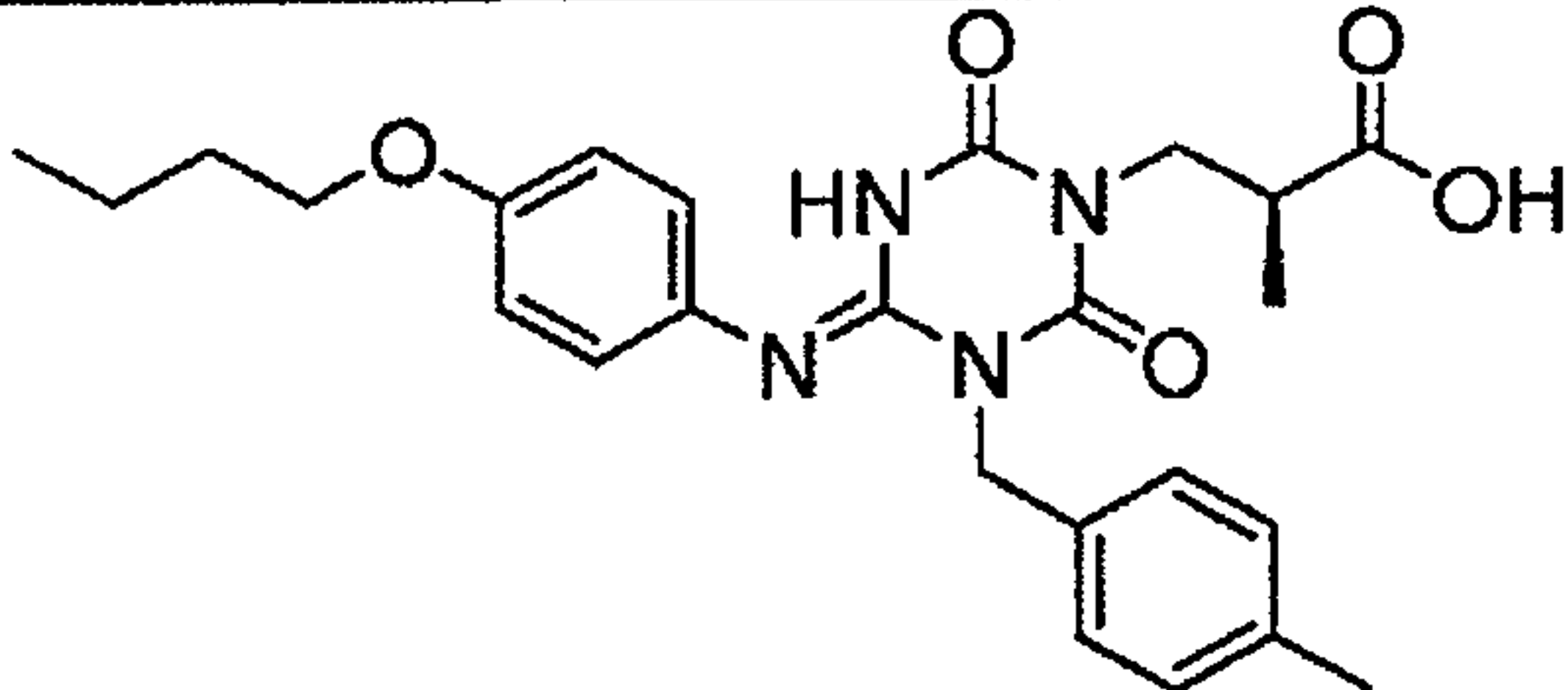
[Table 165]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0806	2.22	517	2
	I-0807	2.00	503	2
	I-0808	2.33	485	3
	I-0809	2.47	515	2
	I-0810	2.85	549	3

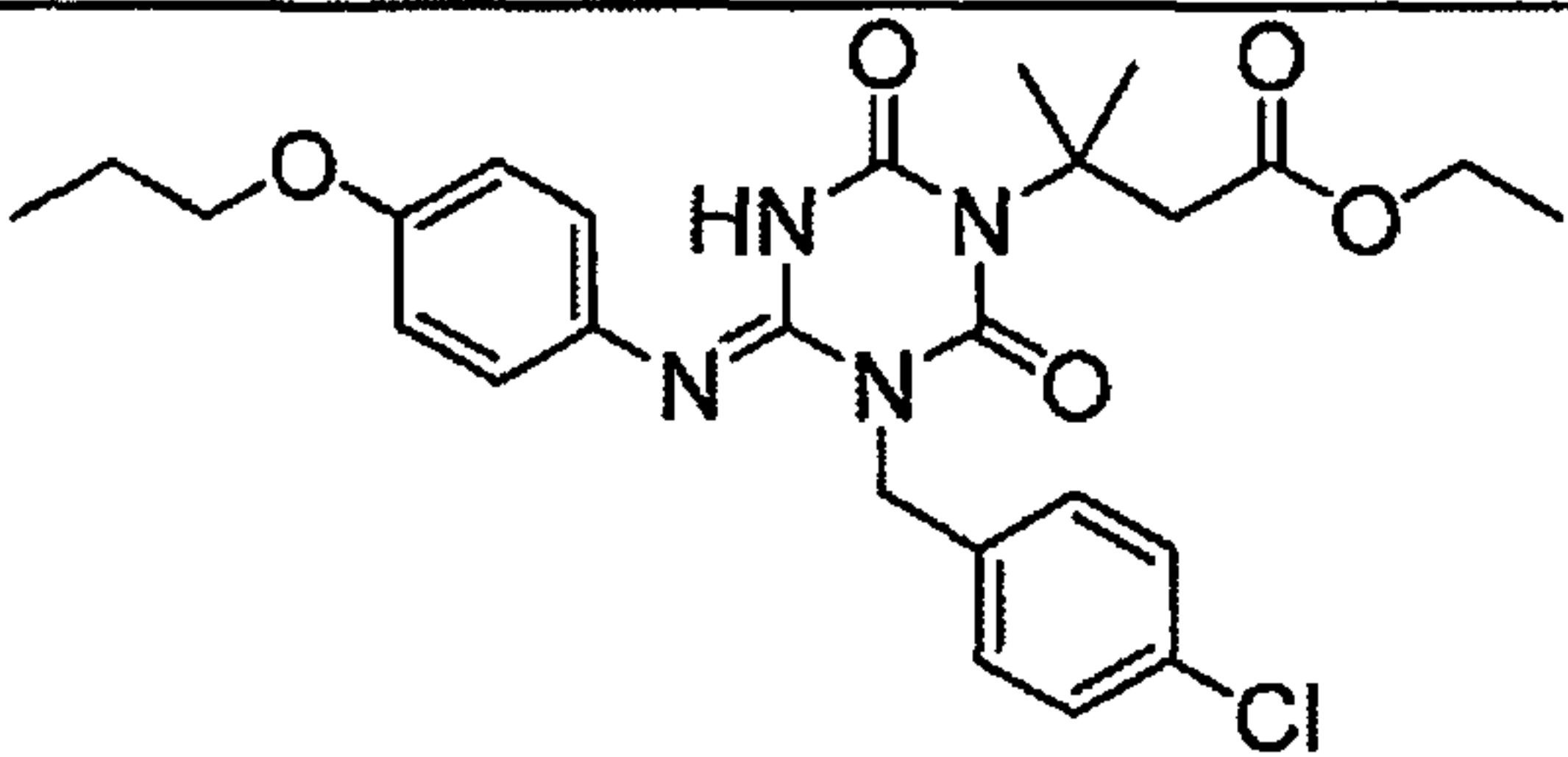
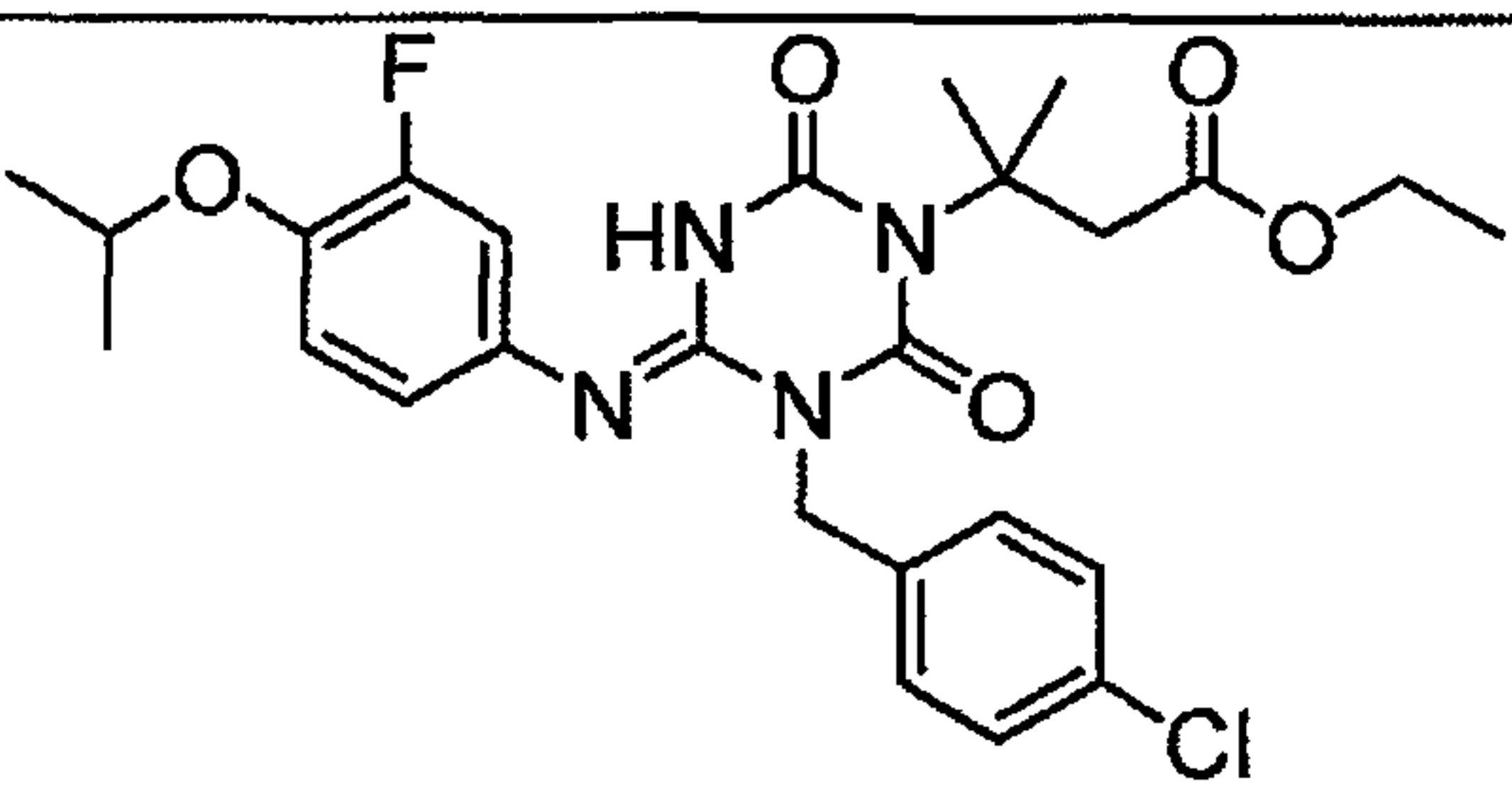
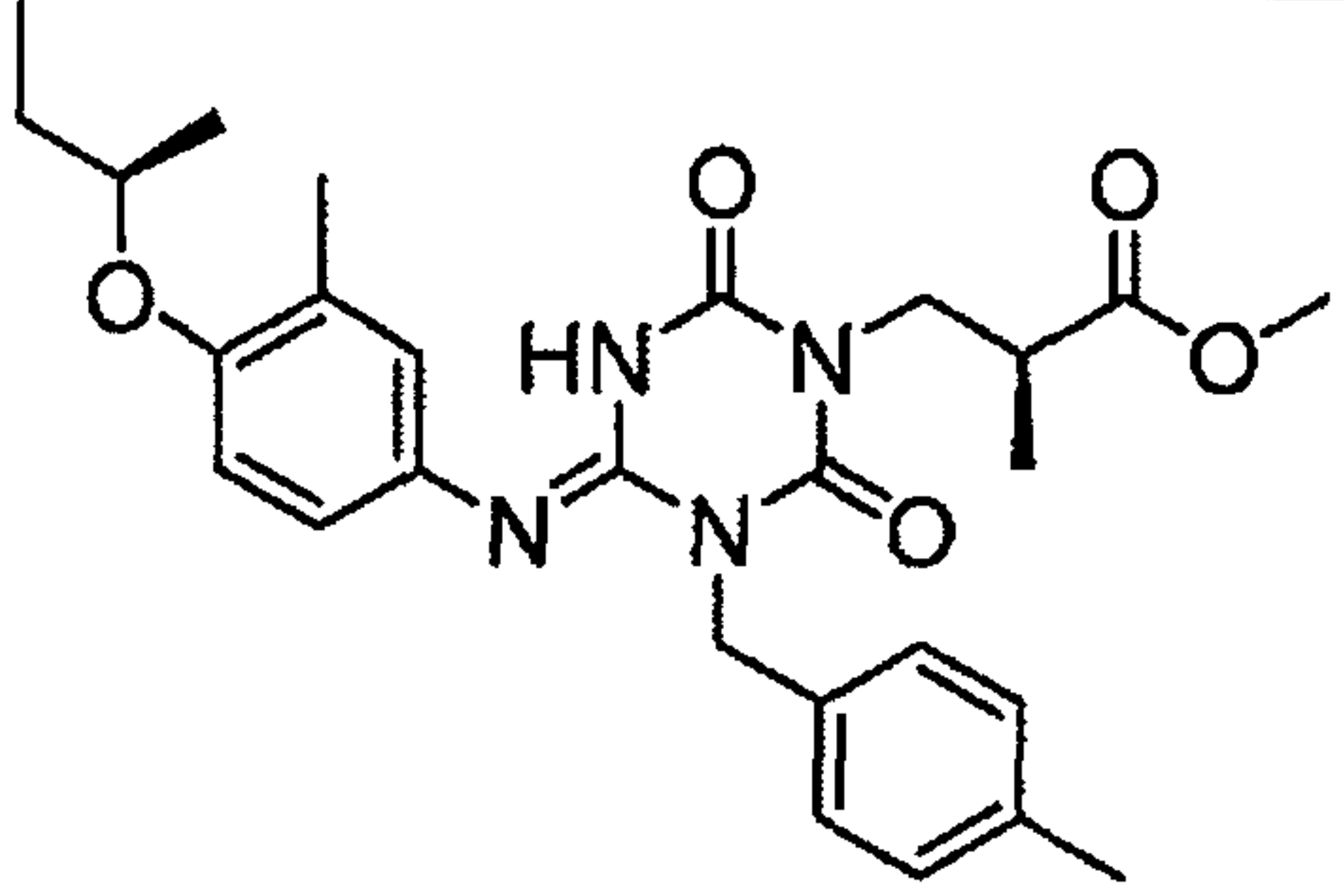
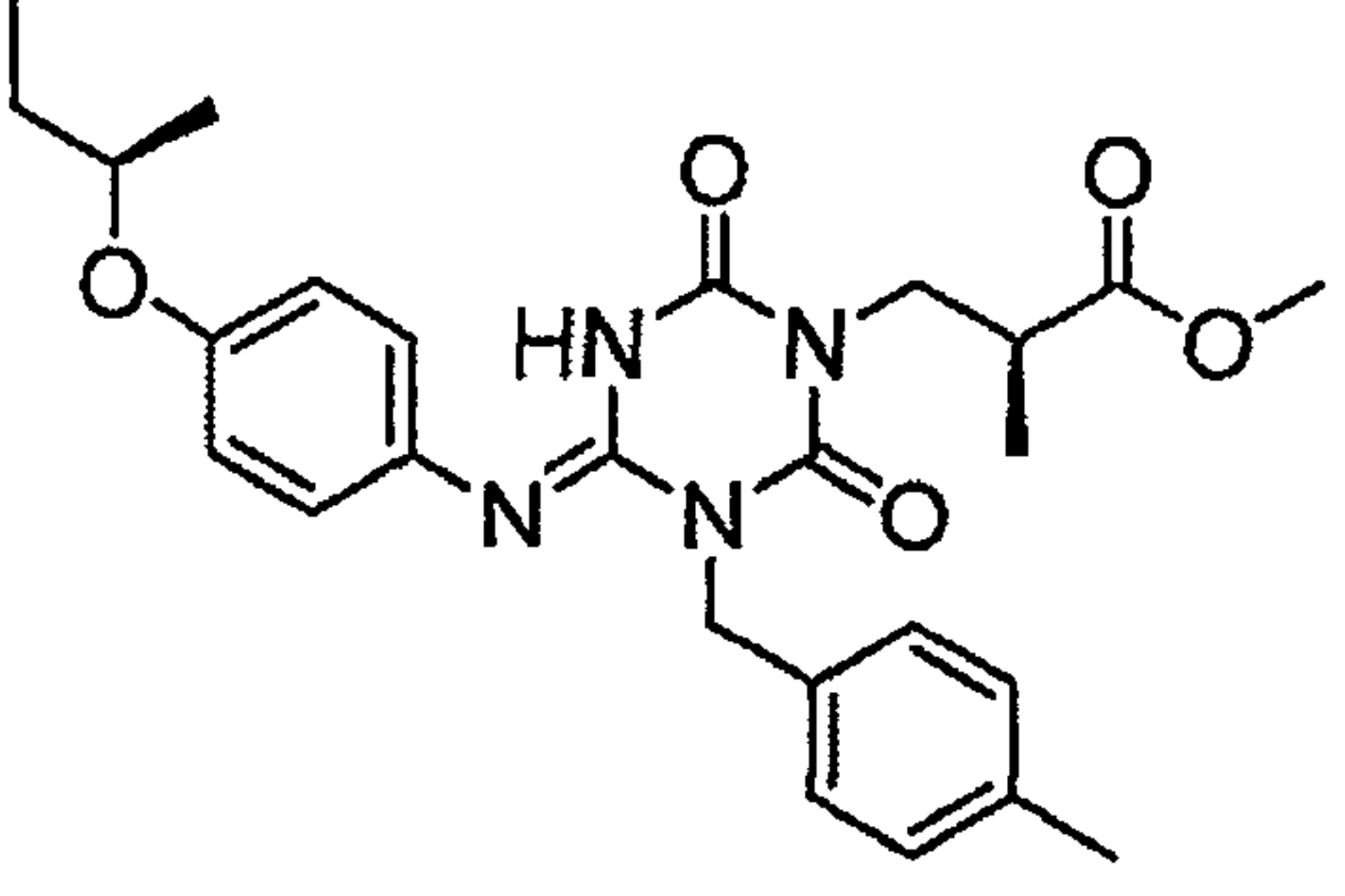
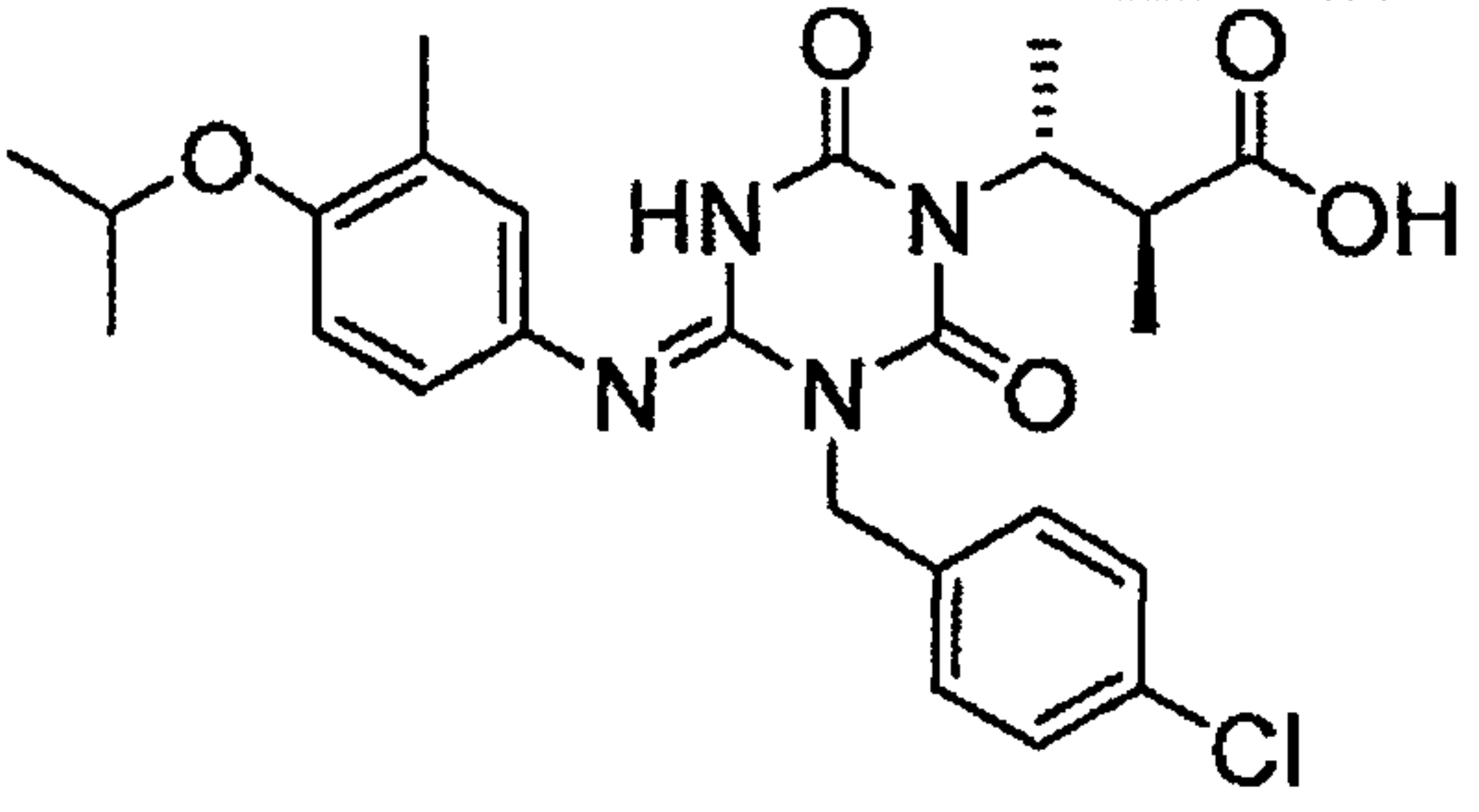
[Table 166]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0811	2.69	515	3
	I-0812	2.53	481	3
	I-0813	2.38	467	3
	I-0814	2.58	501	3
	I-0815	2.55	471	3

[Table 167]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0816	2.52	481	3
	I-0817	2.45	521	3
	I-0818	2.27	457	3
	I-0819	2.32	487	3
	I-0820	2.27	467	3

[Table 168]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0821	2.69	515	3
	I-0822	2.75	533	3
	I-0823	2.61	495	3
	I-0824	2.47	481	3
	I-0825	2.20	501	2

[Table 169]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0826	2.19	501	2
	I-0827	2.07	467	2
	I-0828	1.92	453	2
	I-0829	2.29	487	3
	I-0830	2.35	505	3

[Table 170]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0831	2.51	515	2
	I-0832	2.45	495	2
	I-0833	2.17	499	2
	I-0834	2.12	479	2
	I-0835	2.28	501	2

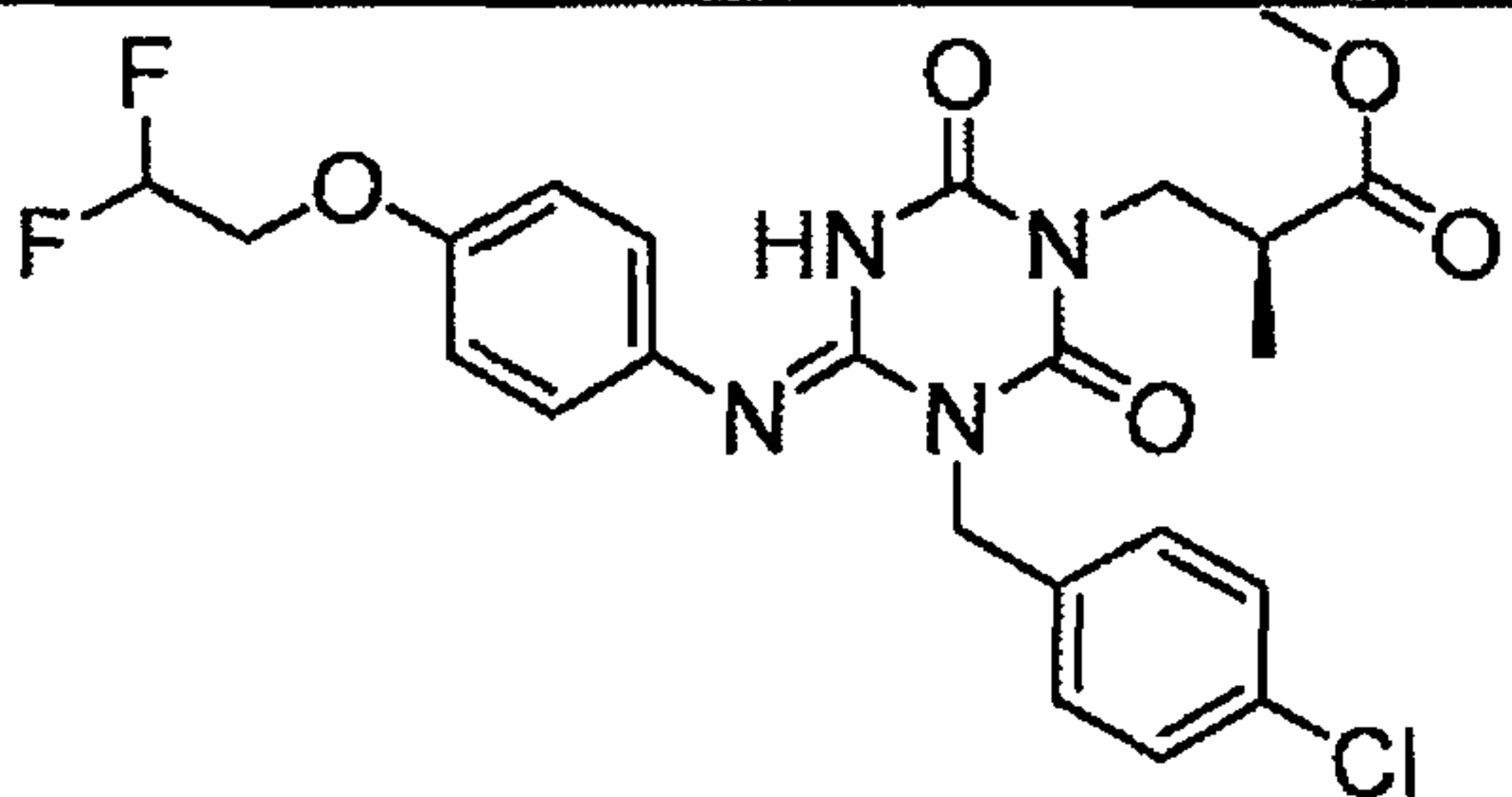
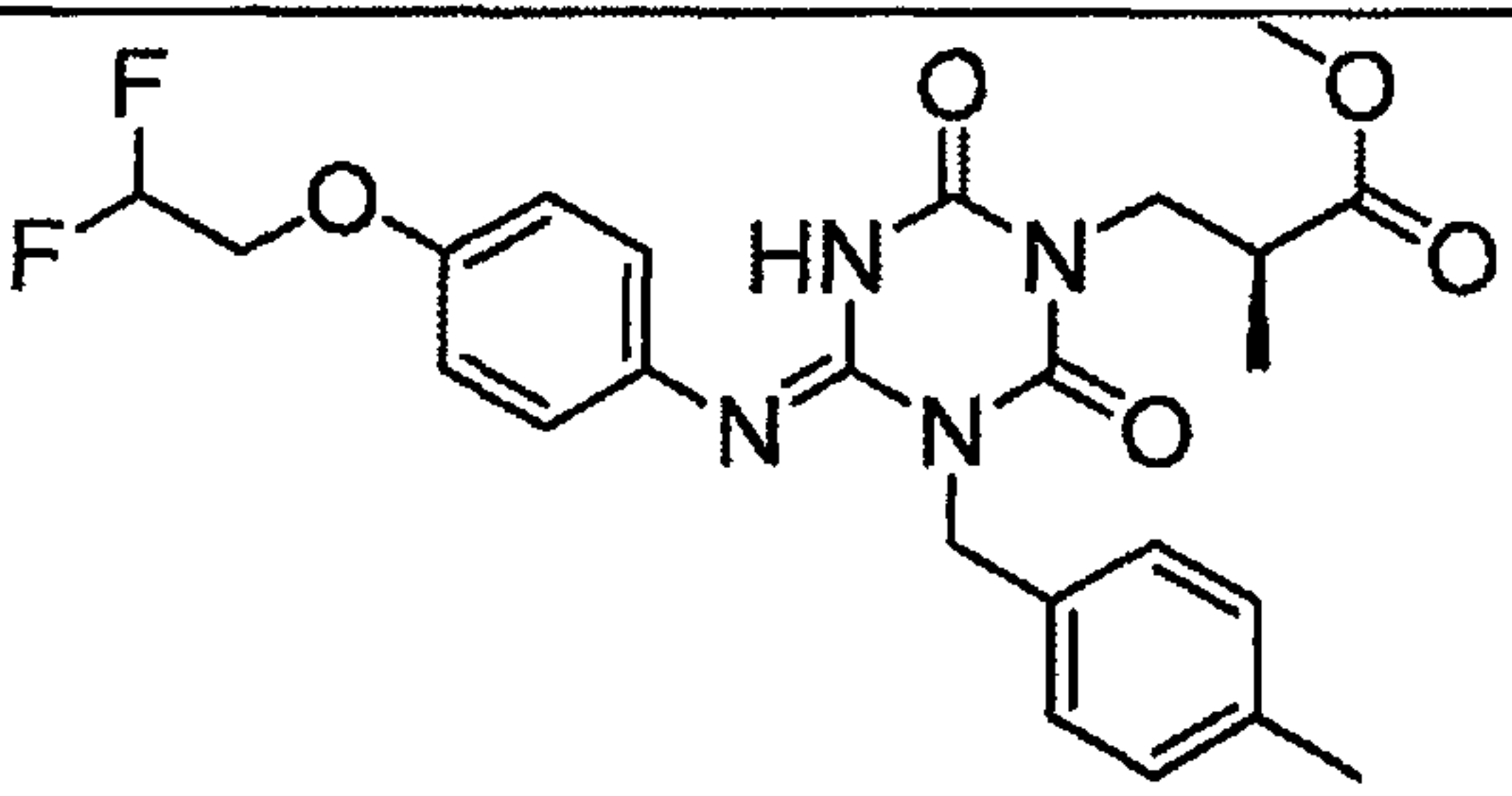
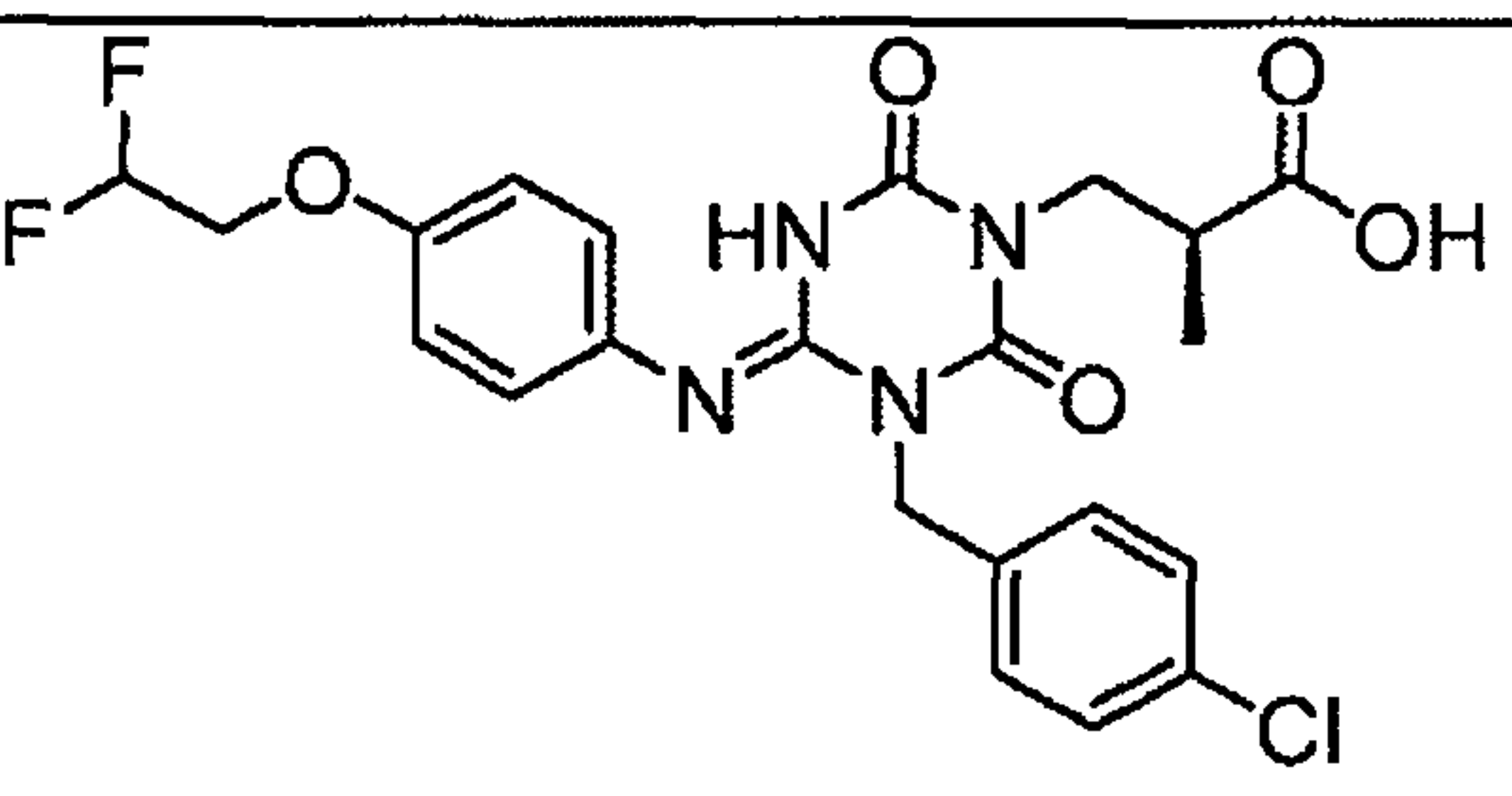
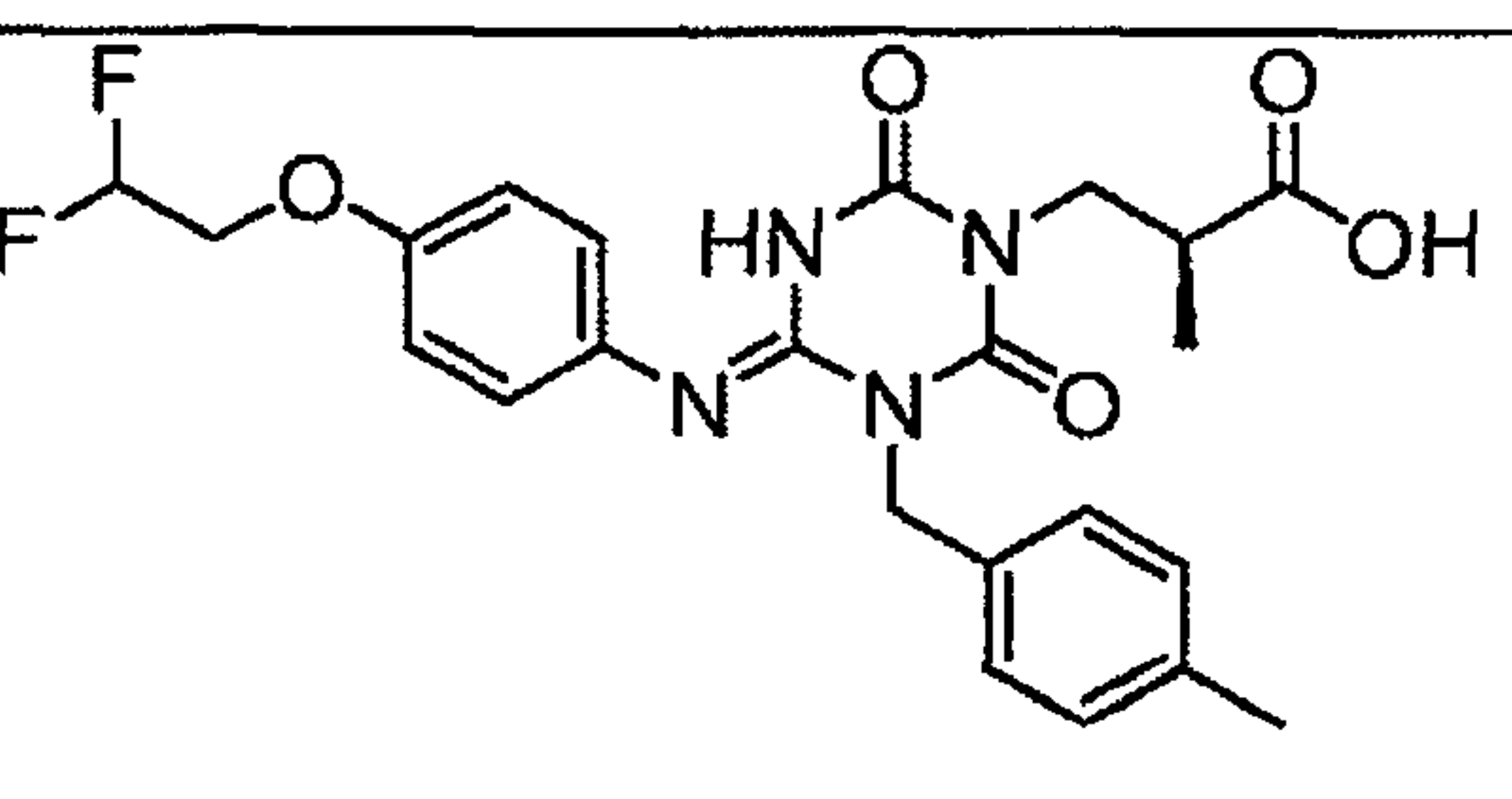
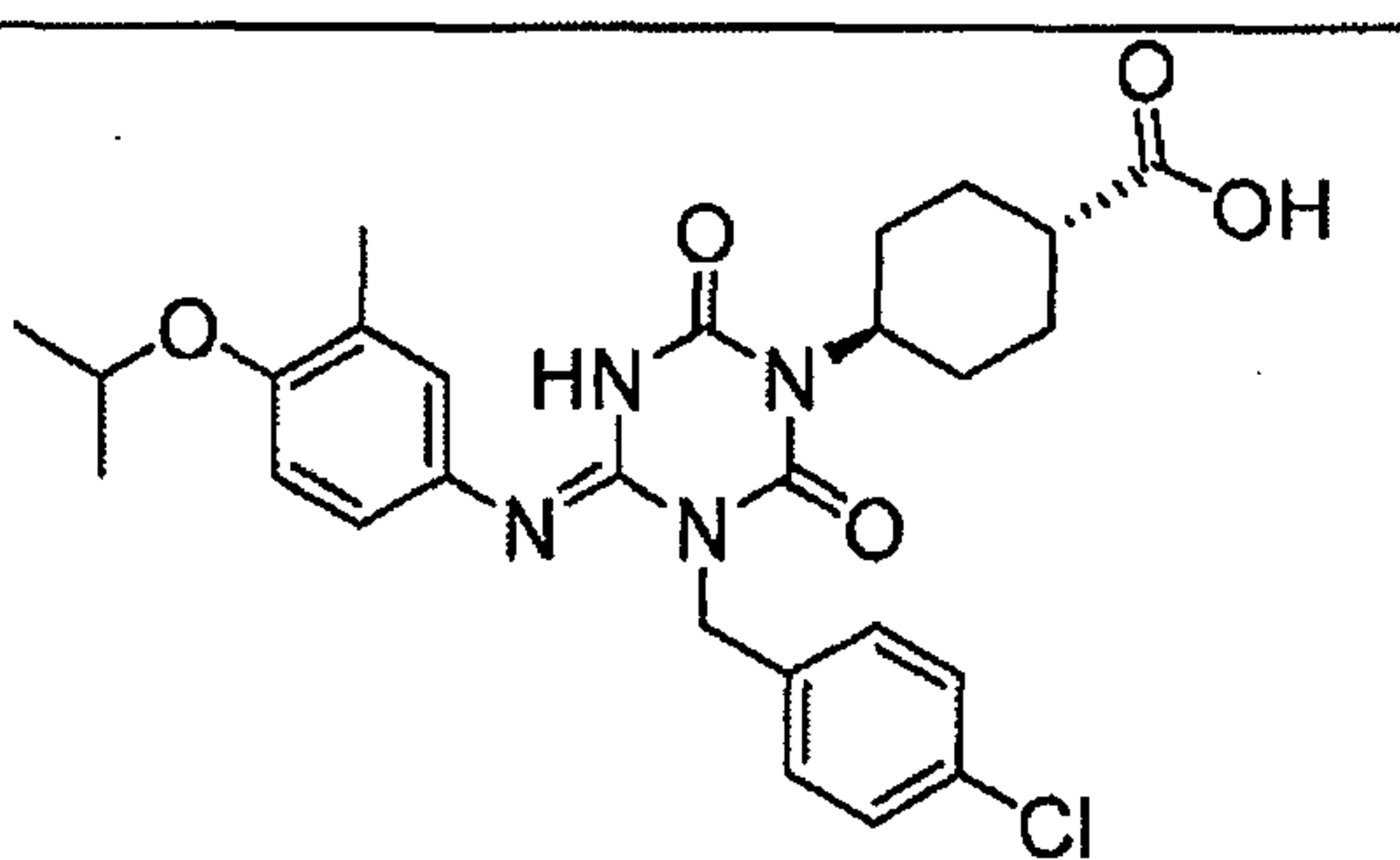
[Table 171]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0836	2.22	481	2
	I-0837	1.94	485	2
	I-0838	1.89	465	2
	I-0839	2.56	501	3
	I-0840	2.33	487	3

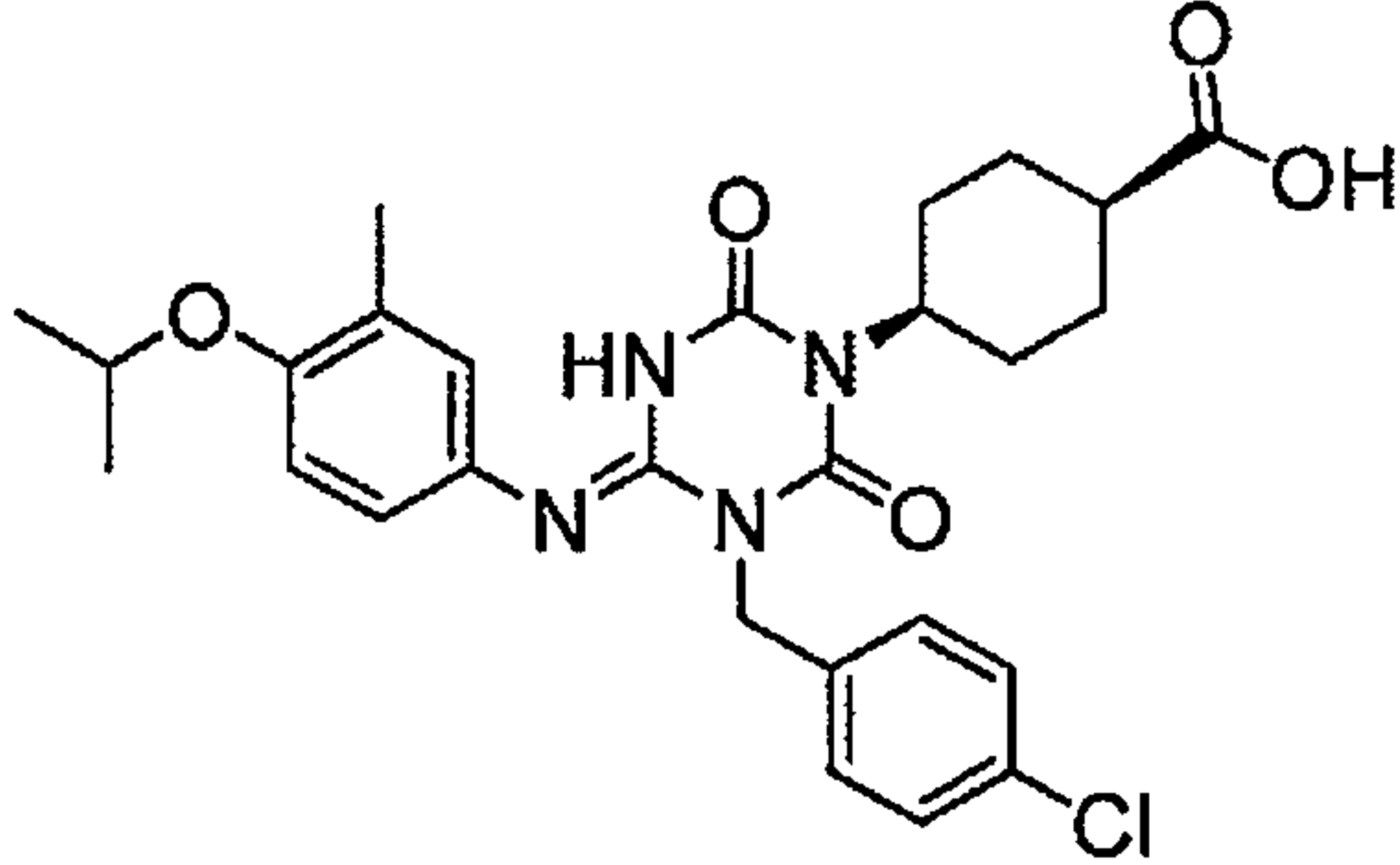
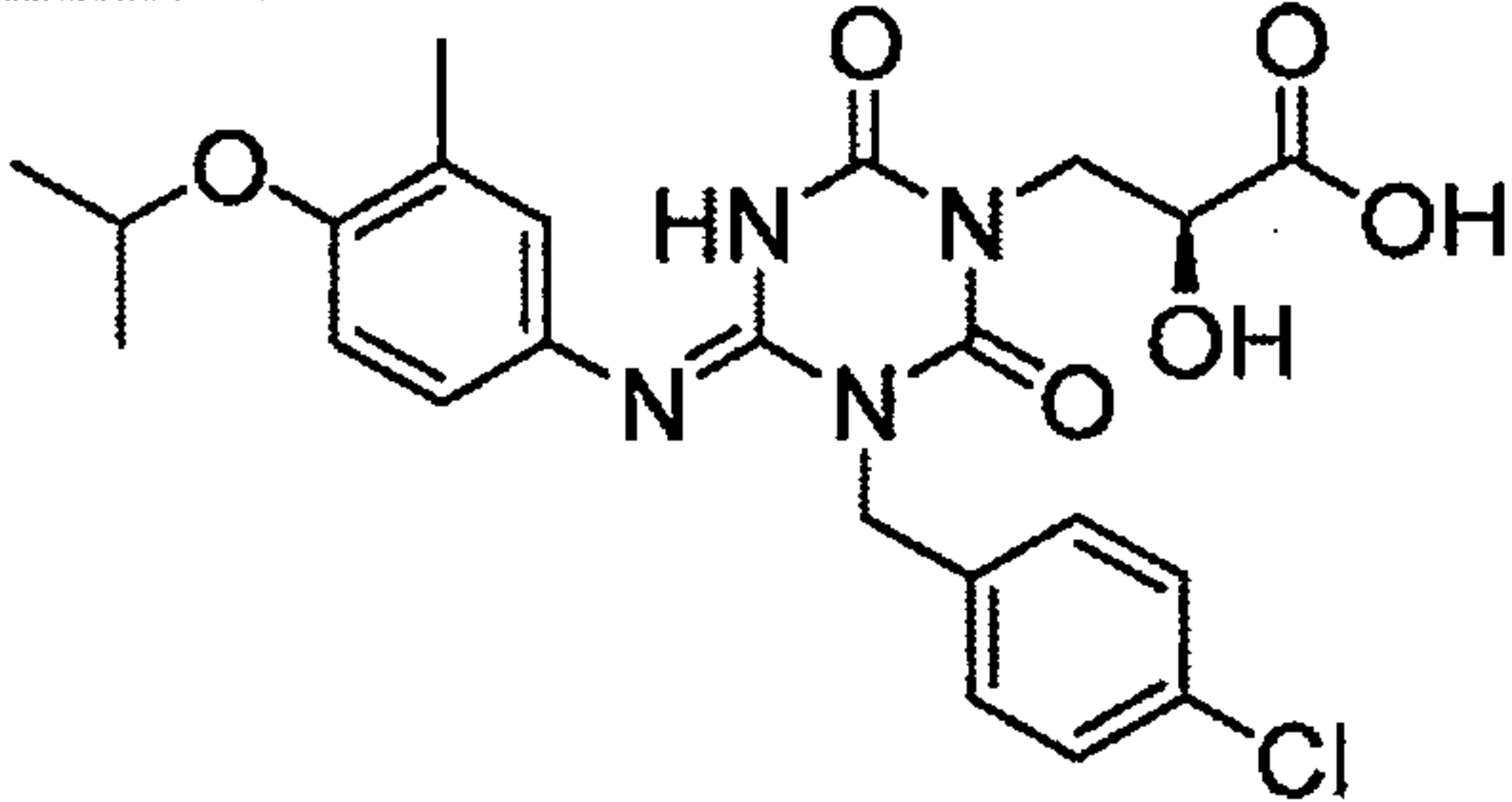
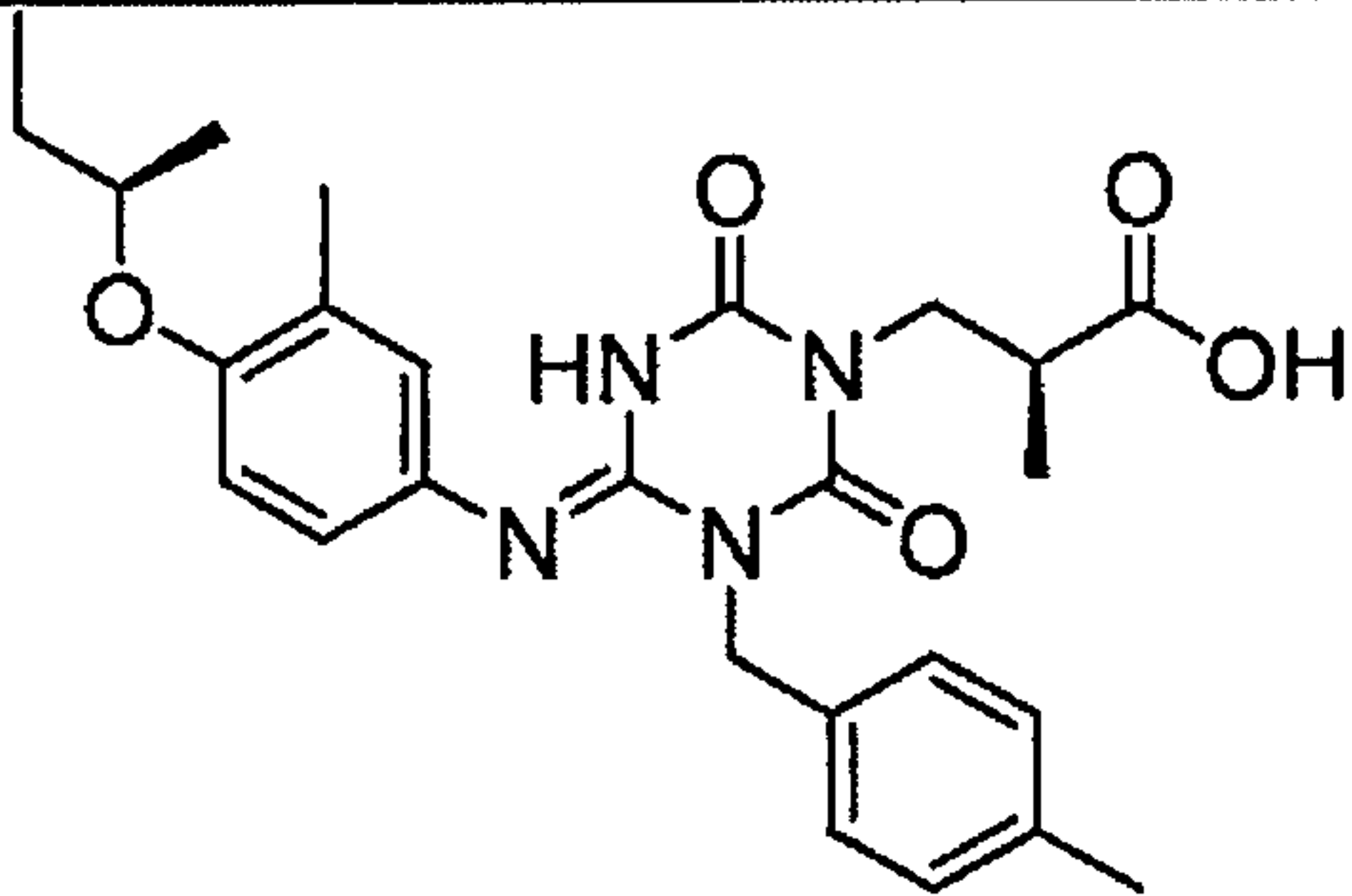
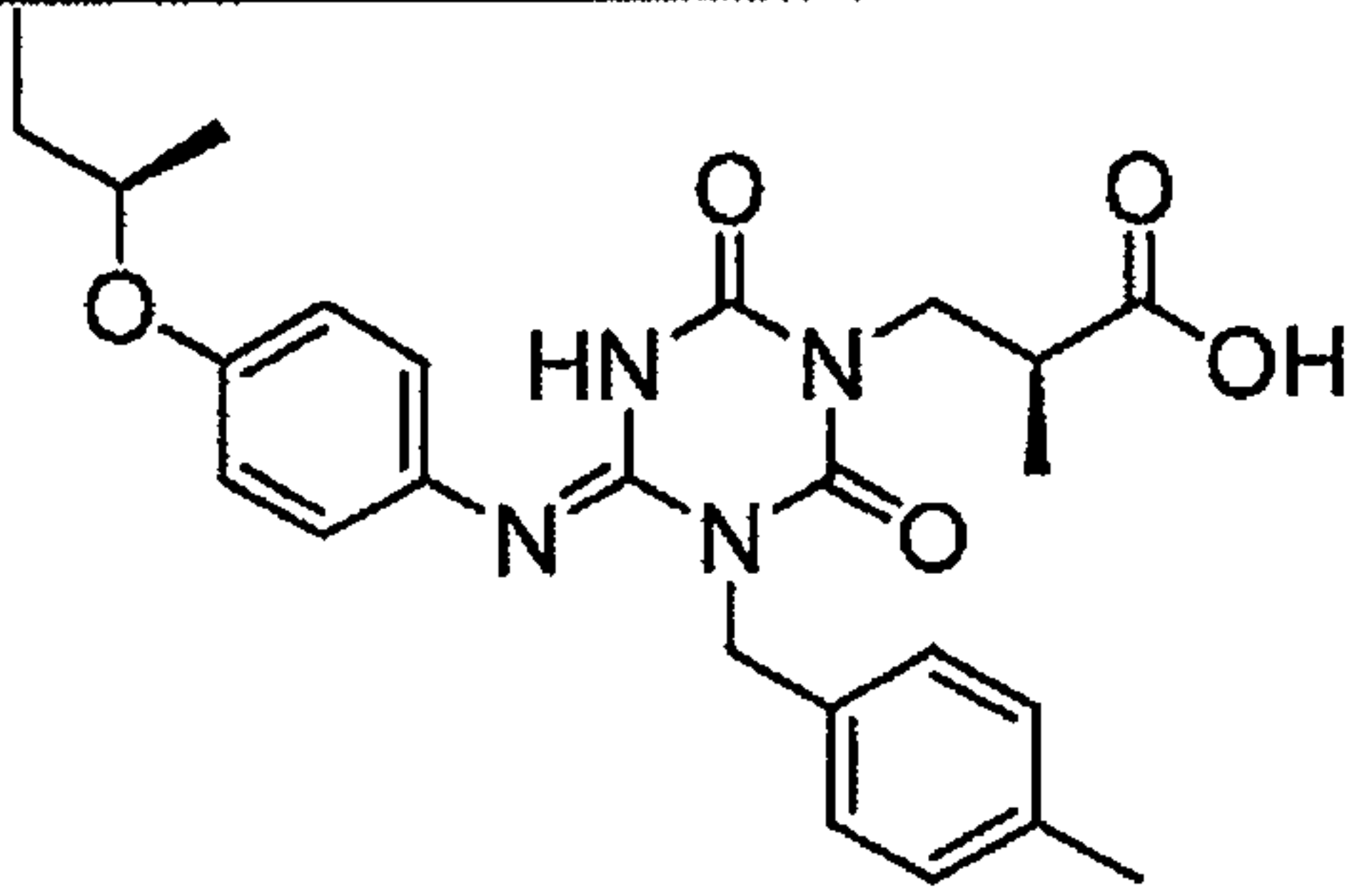
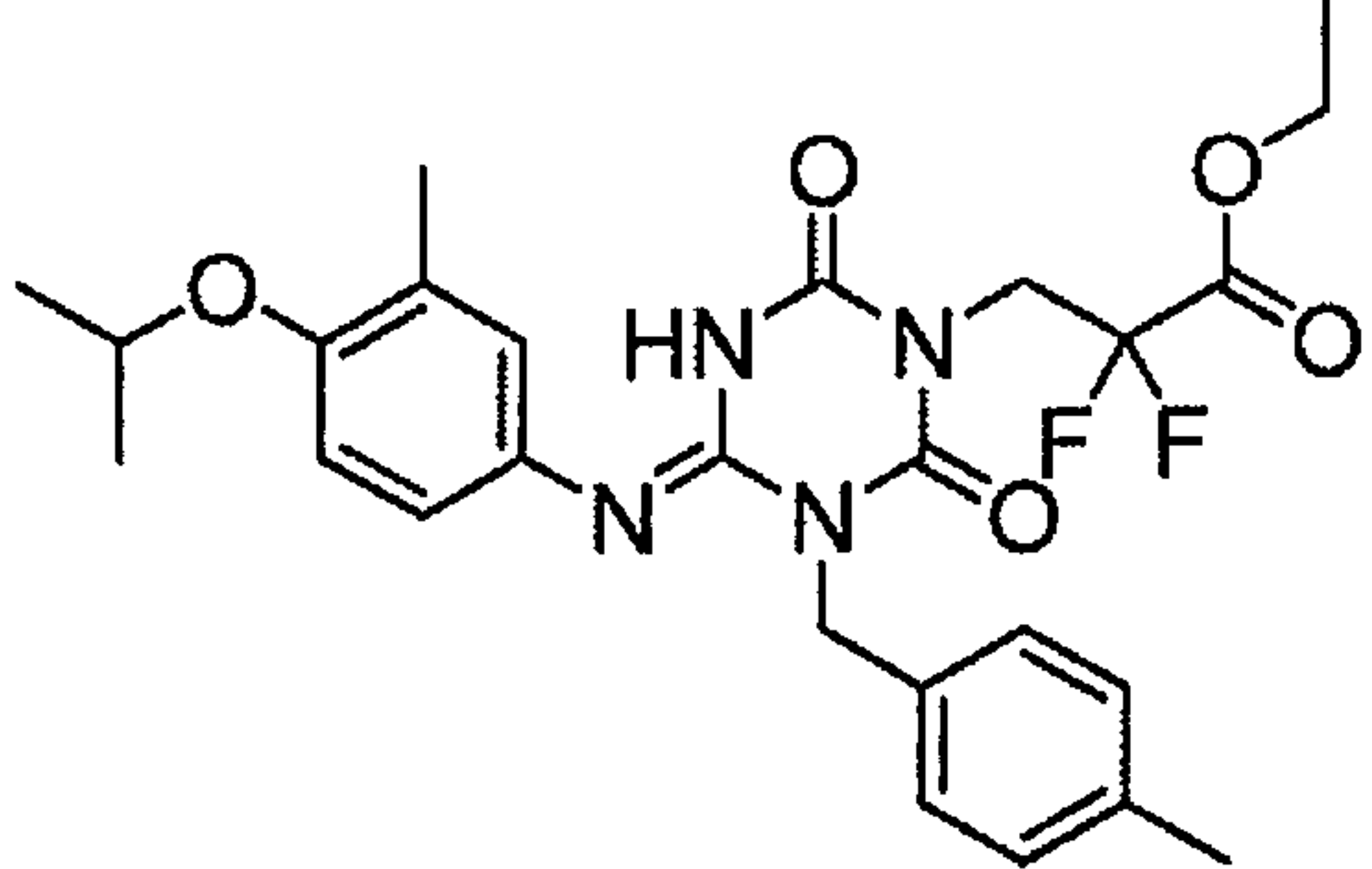
[Table 172]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0841	2.44	511	2
	I-0842	1.96	485	3
	I-0843	2.20	497	3
	I-0844	1.70	471	3
	I-0845	2.39	519	3

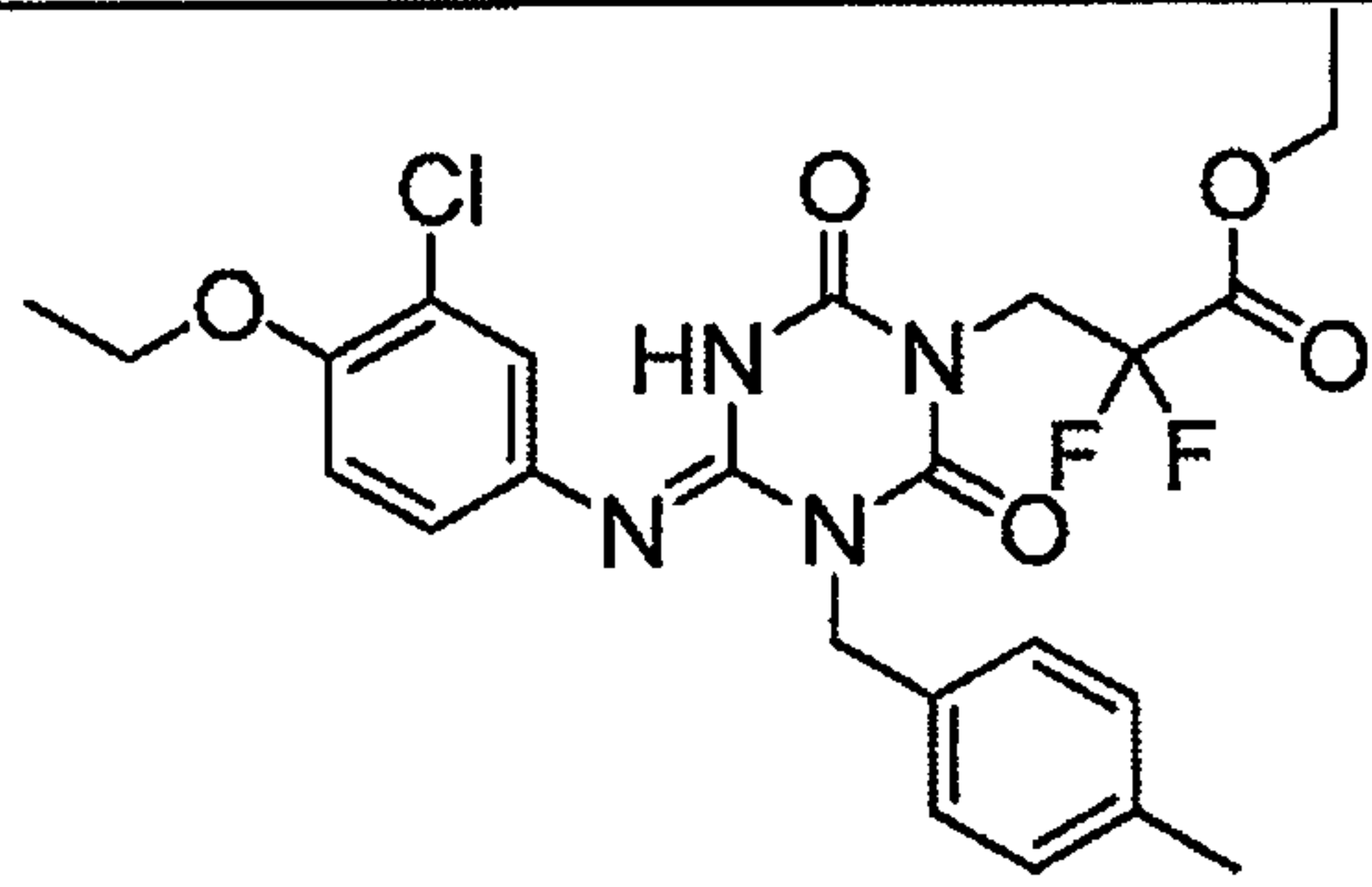
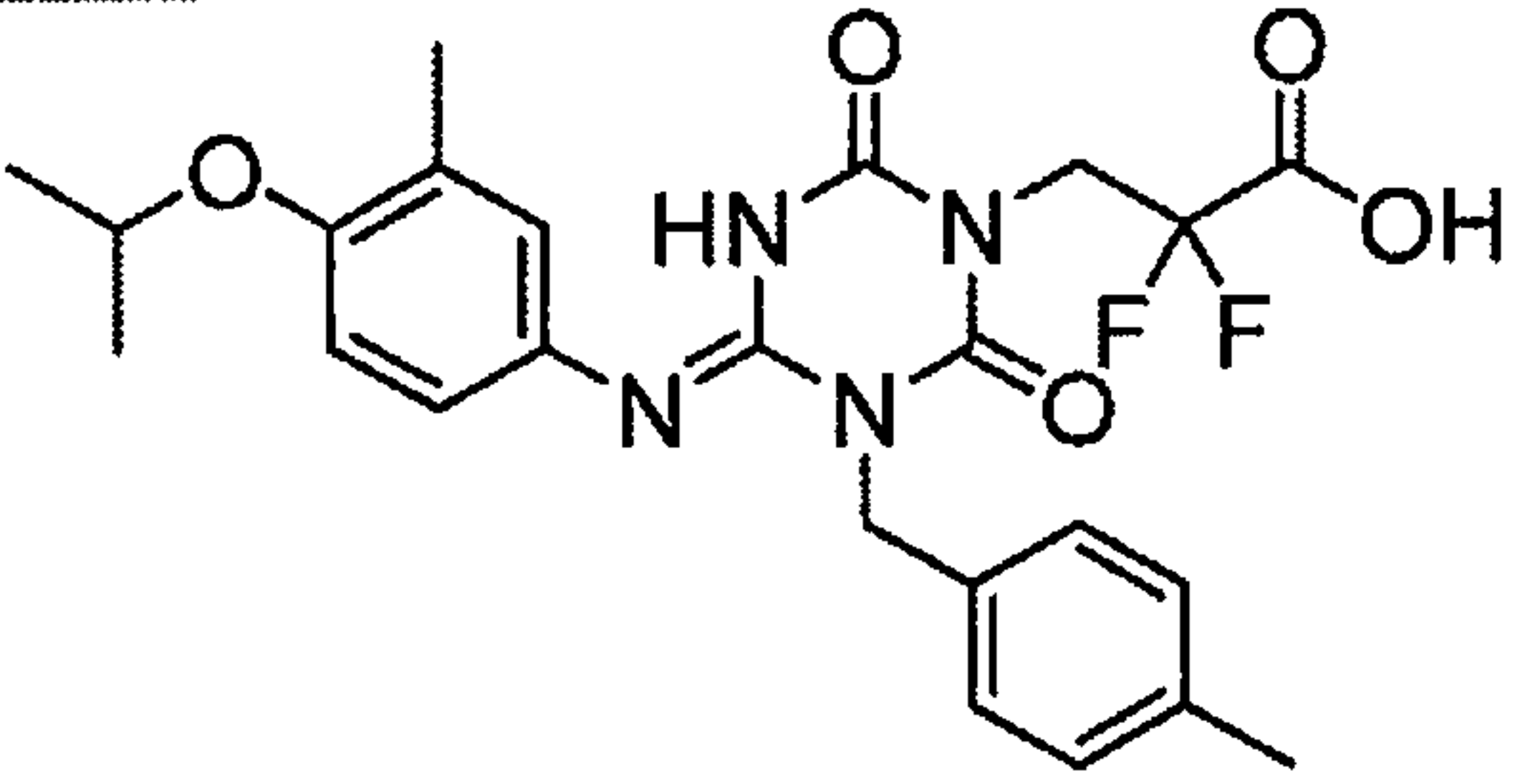
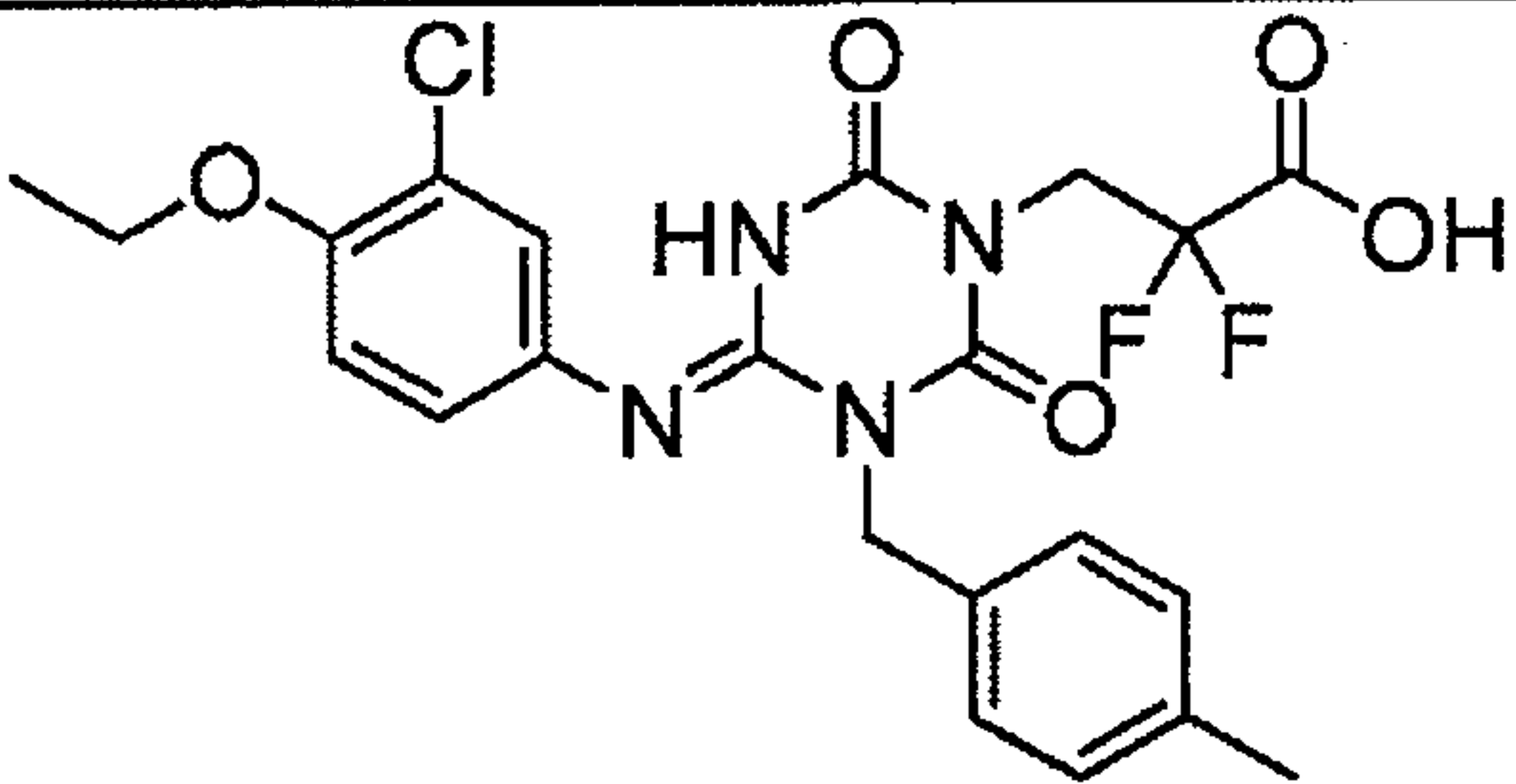
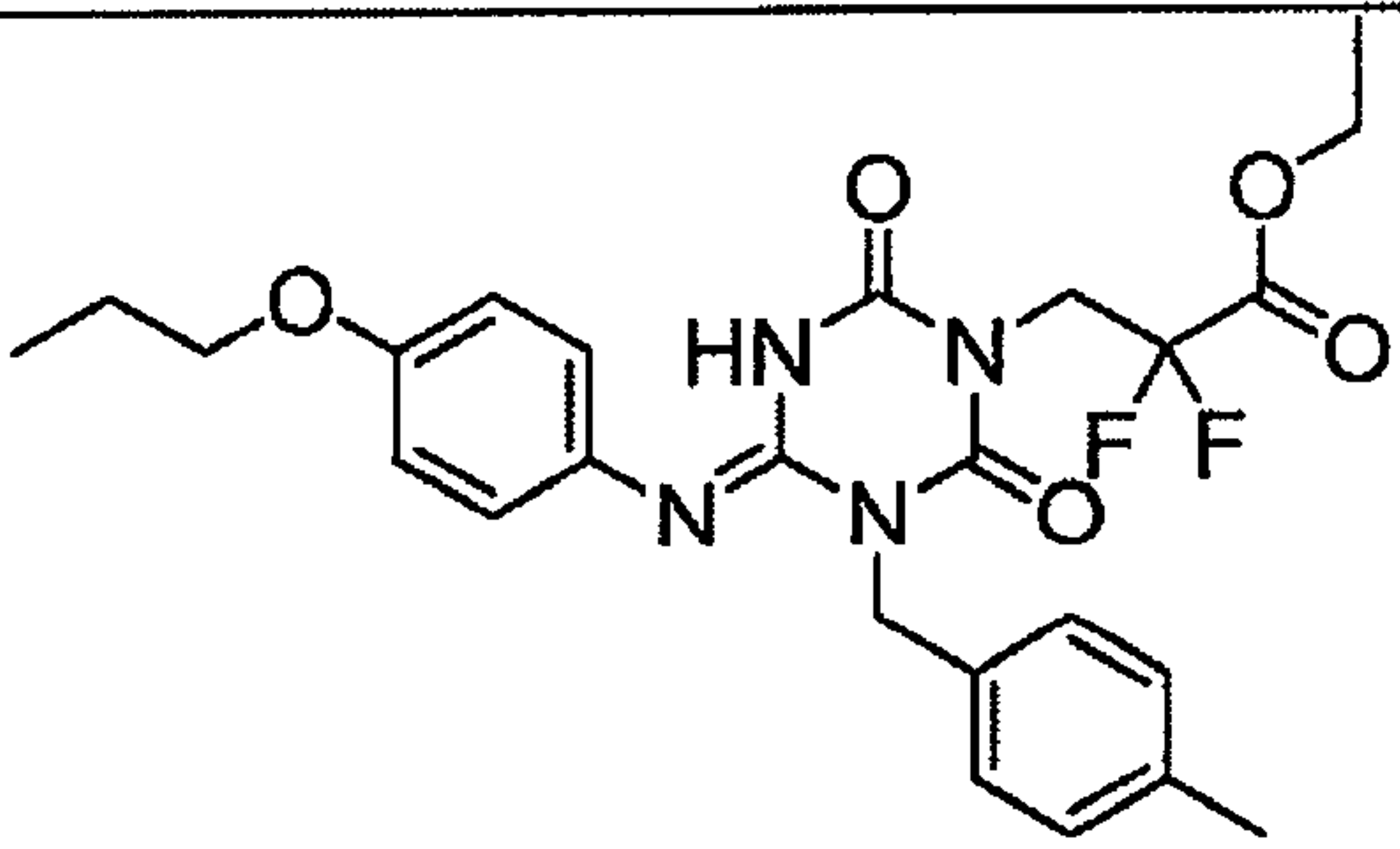
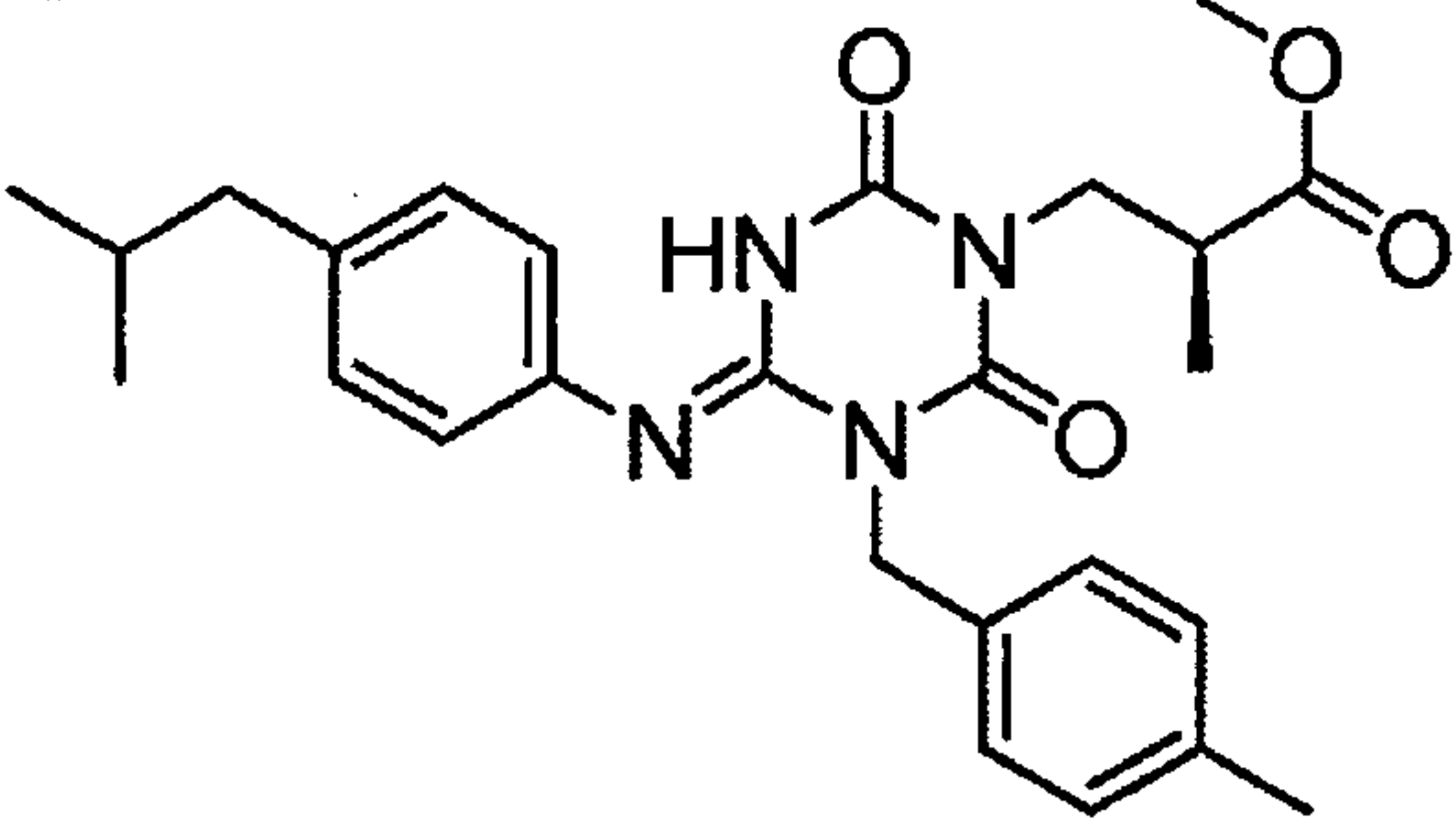
[Table 173]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0846	2.28	509	3
	I-0847	2.20	489	3
	I-0848	1.83	495	2
	I-0849	1.77	475	2
	I-0850	2.24	527	2

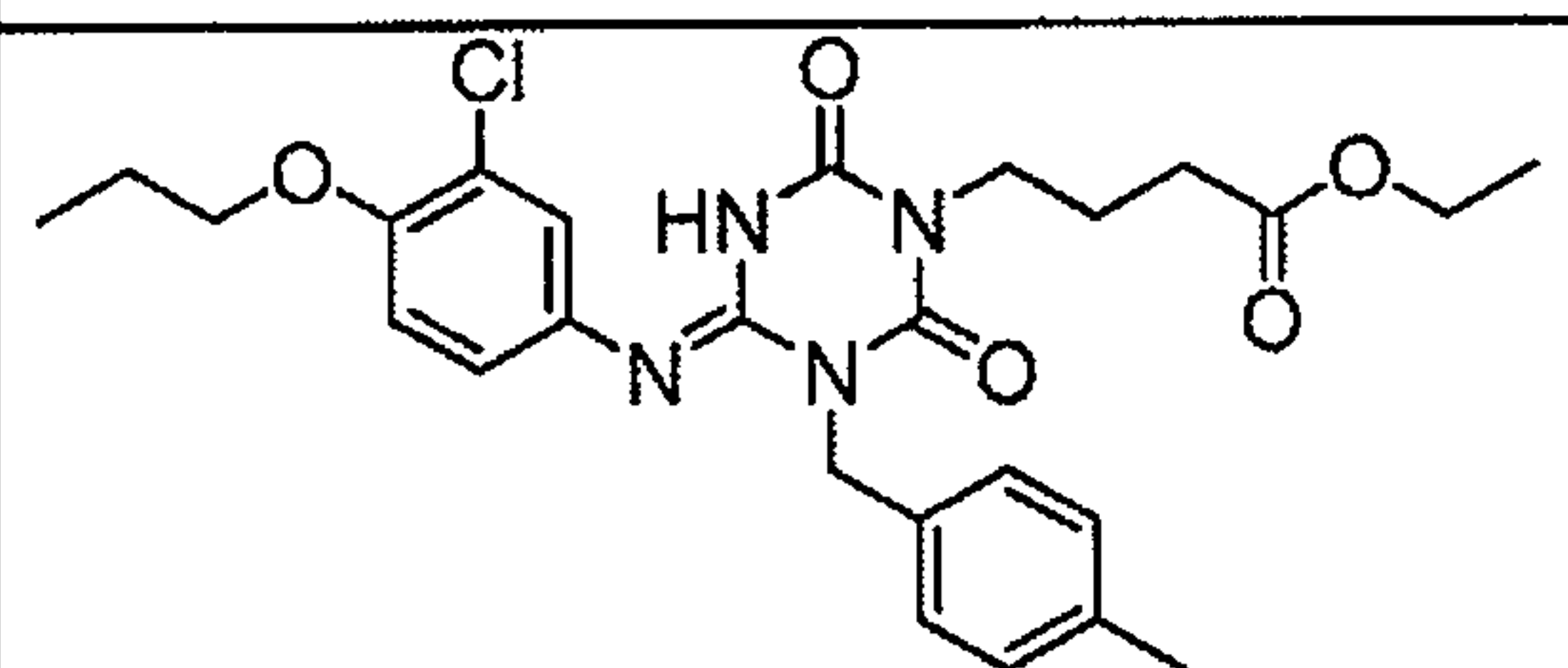
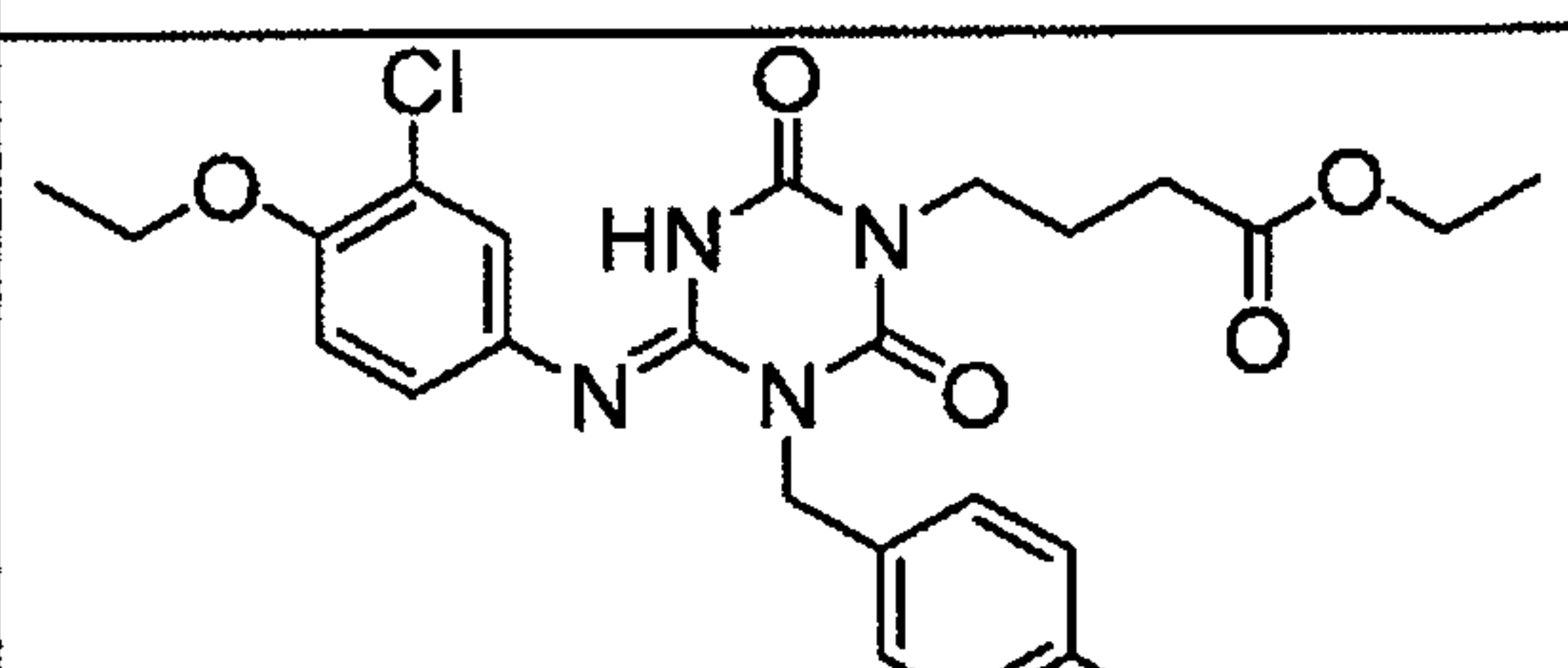
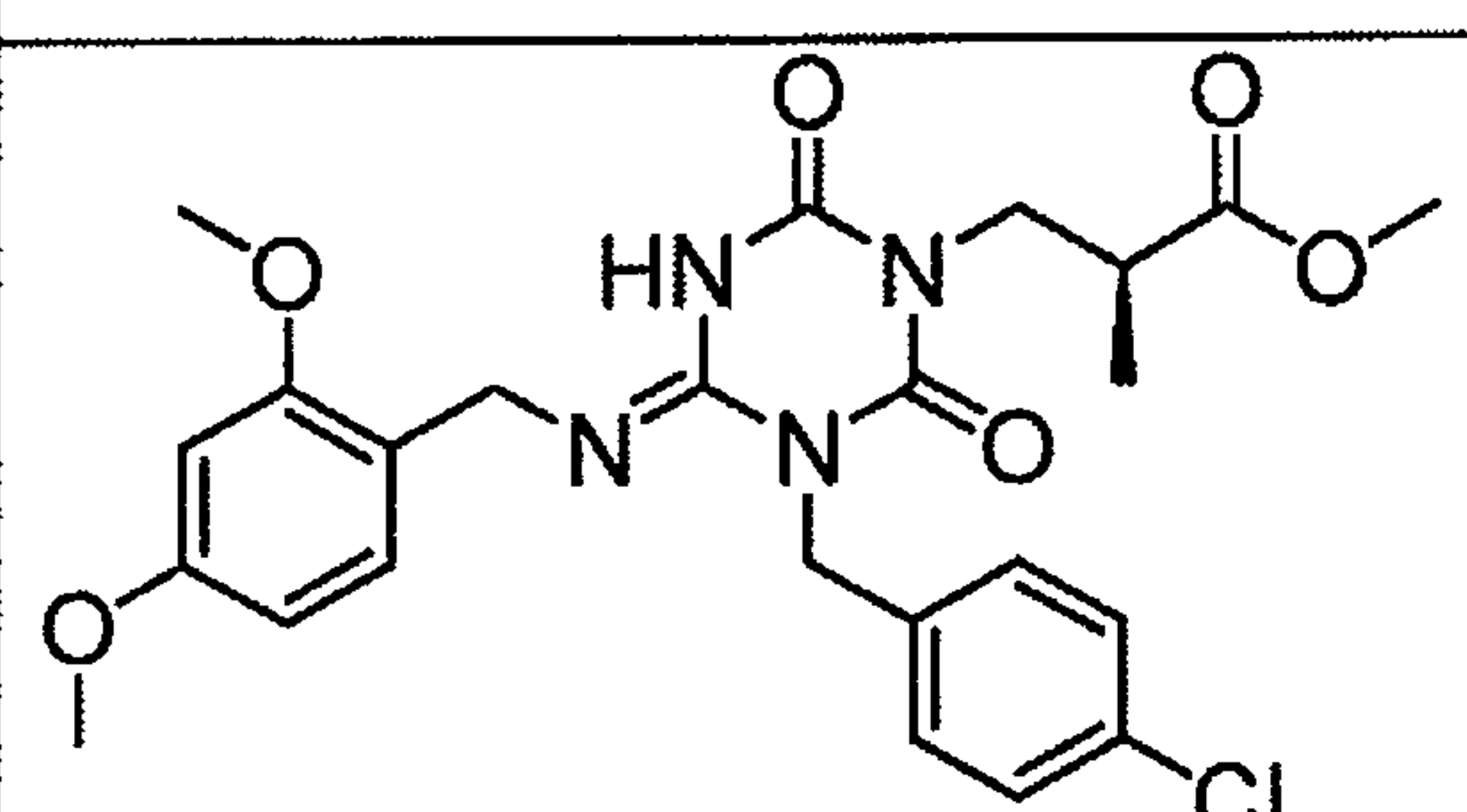
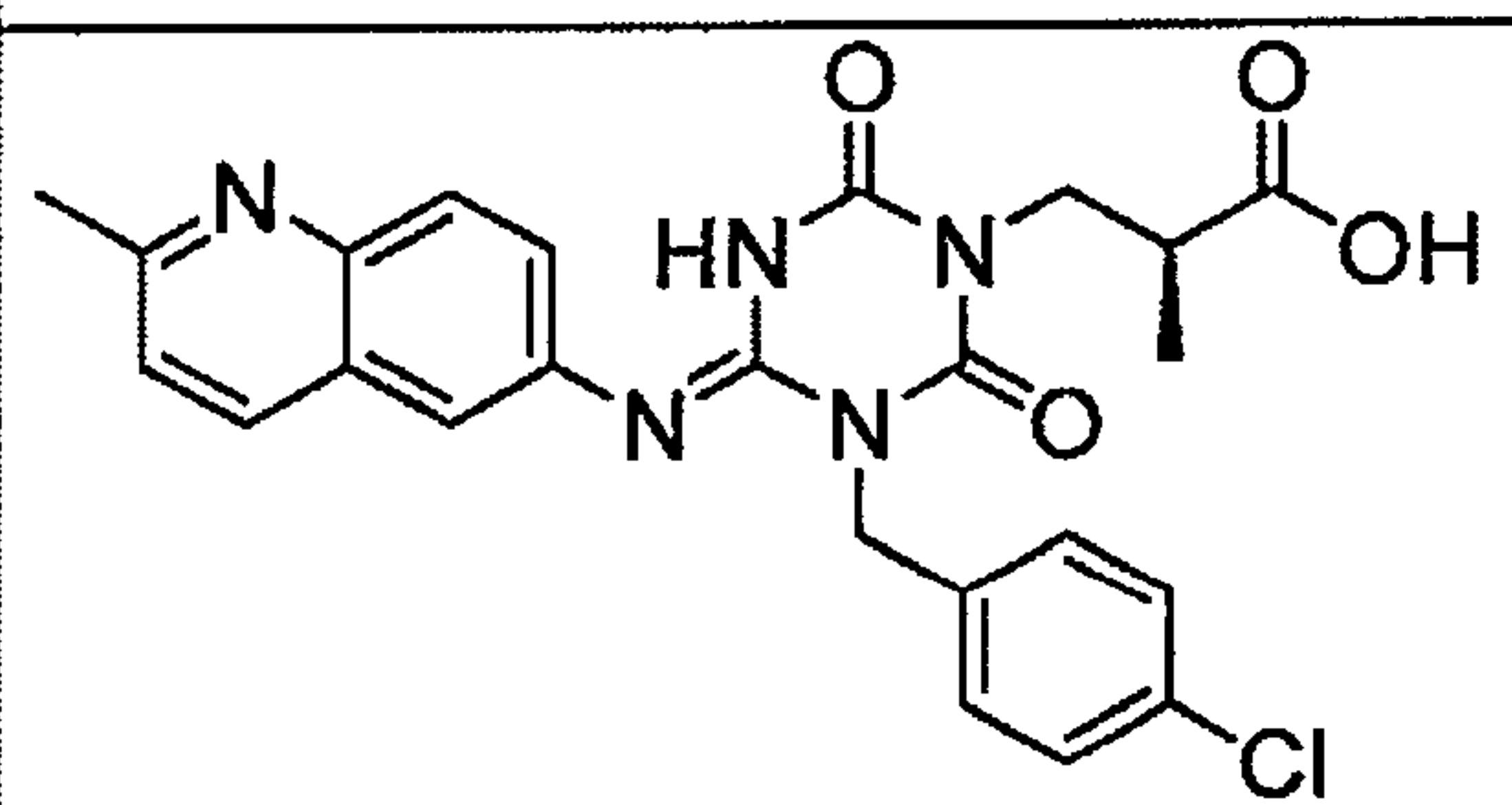
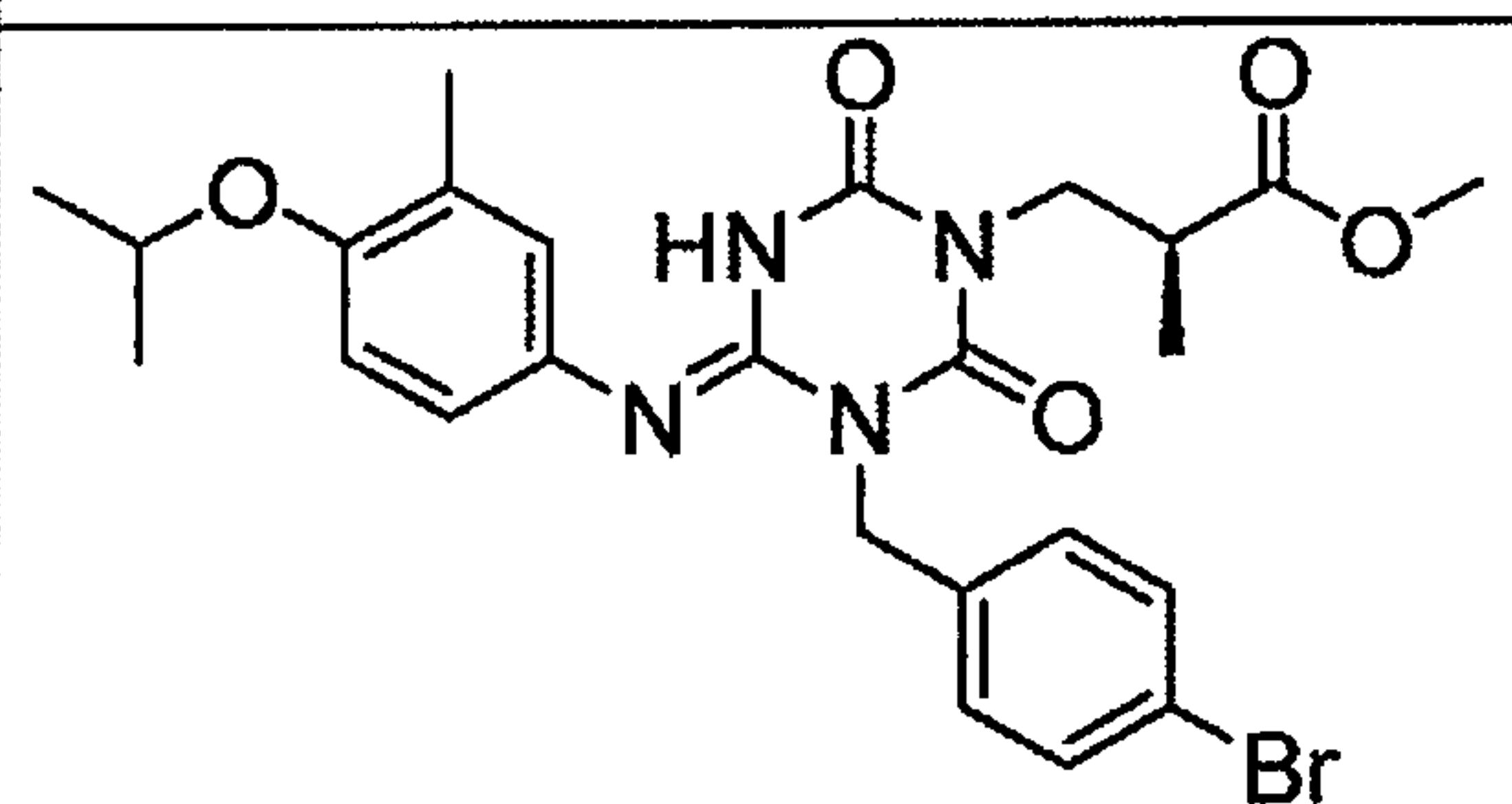
[Table 174]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0851	2.25	527	2
	I-0852	1.87	489	2
	I-0853	2.37	481	3
	I-0854	2.21	467	3
	I-0855	2.39	517	2

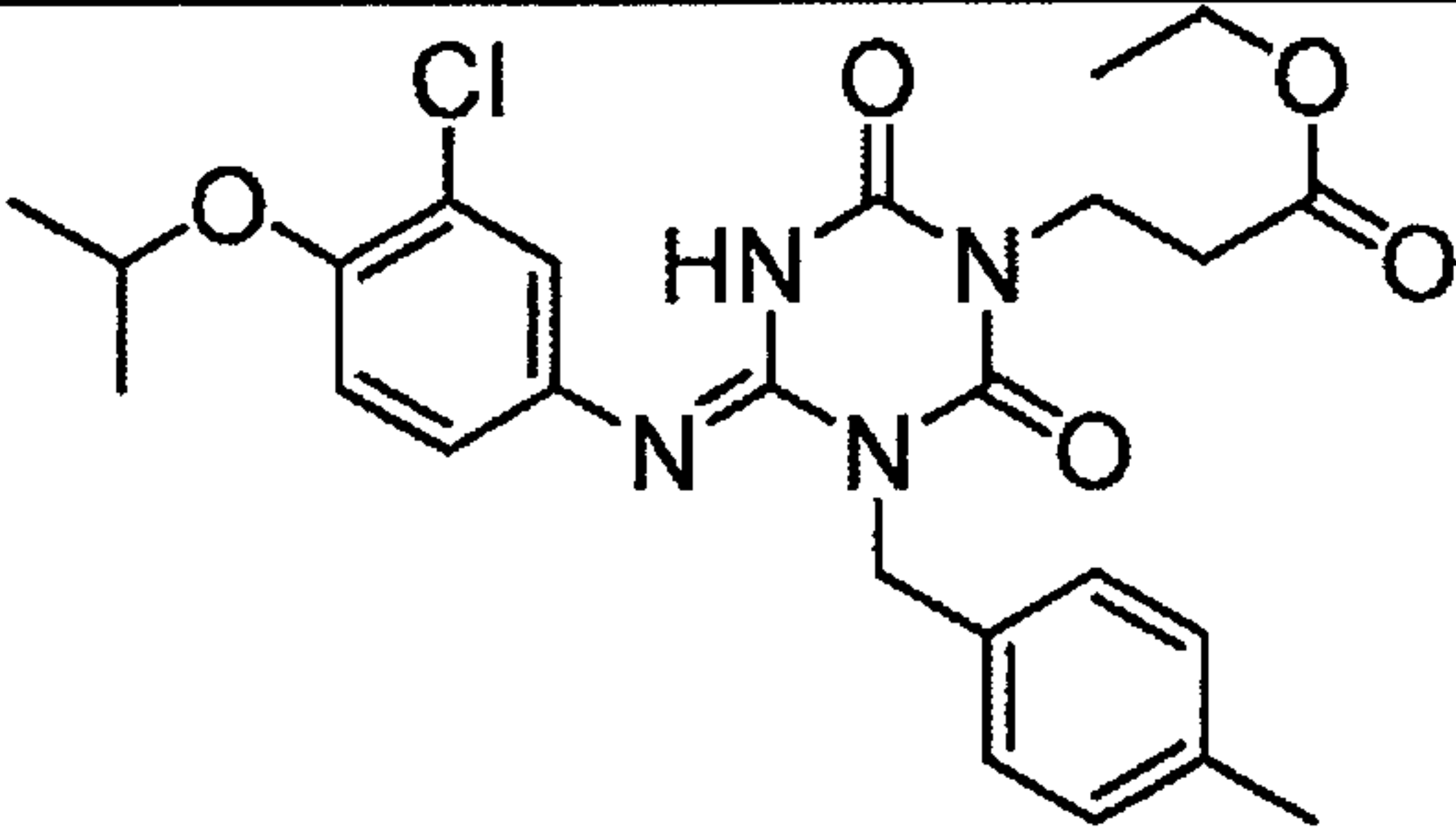
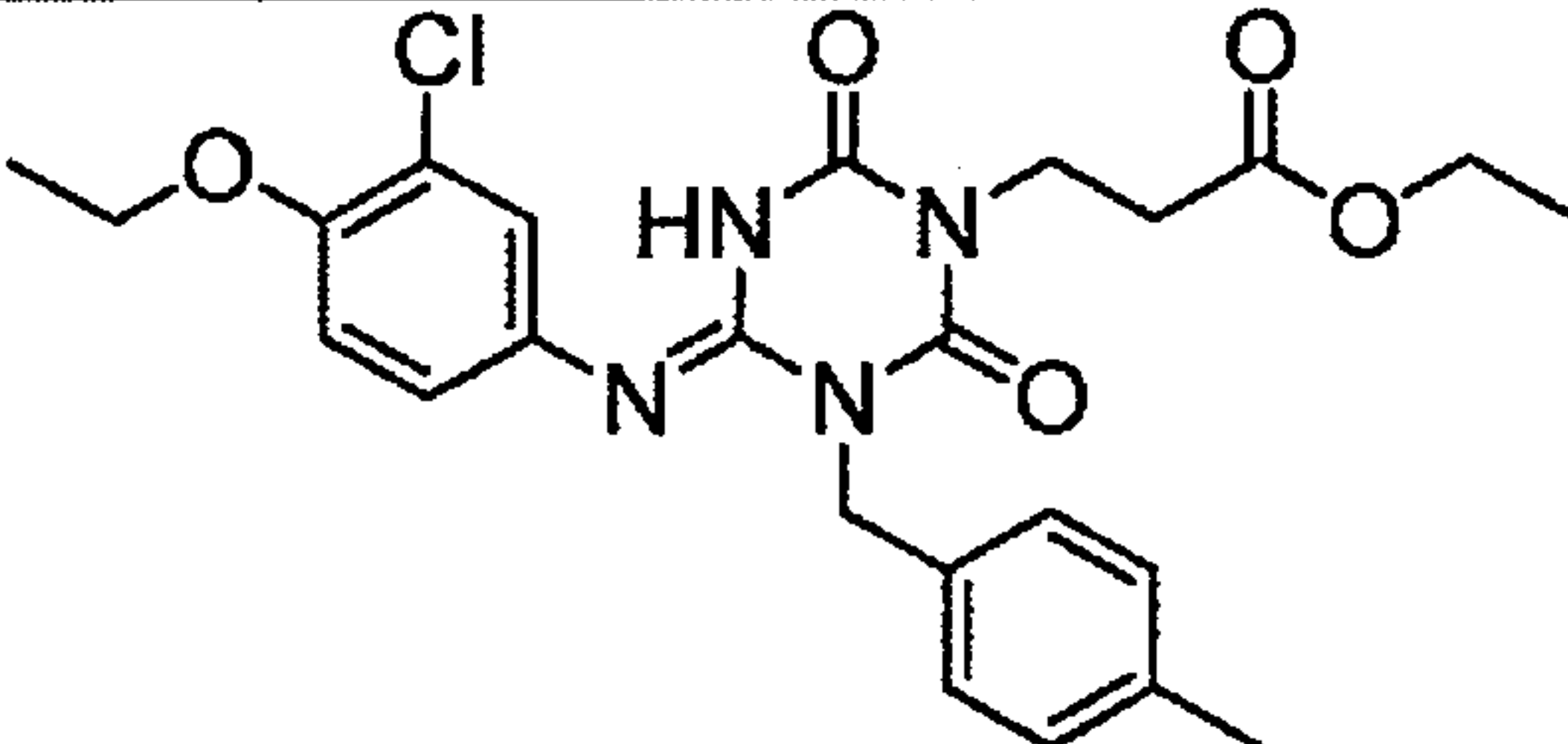
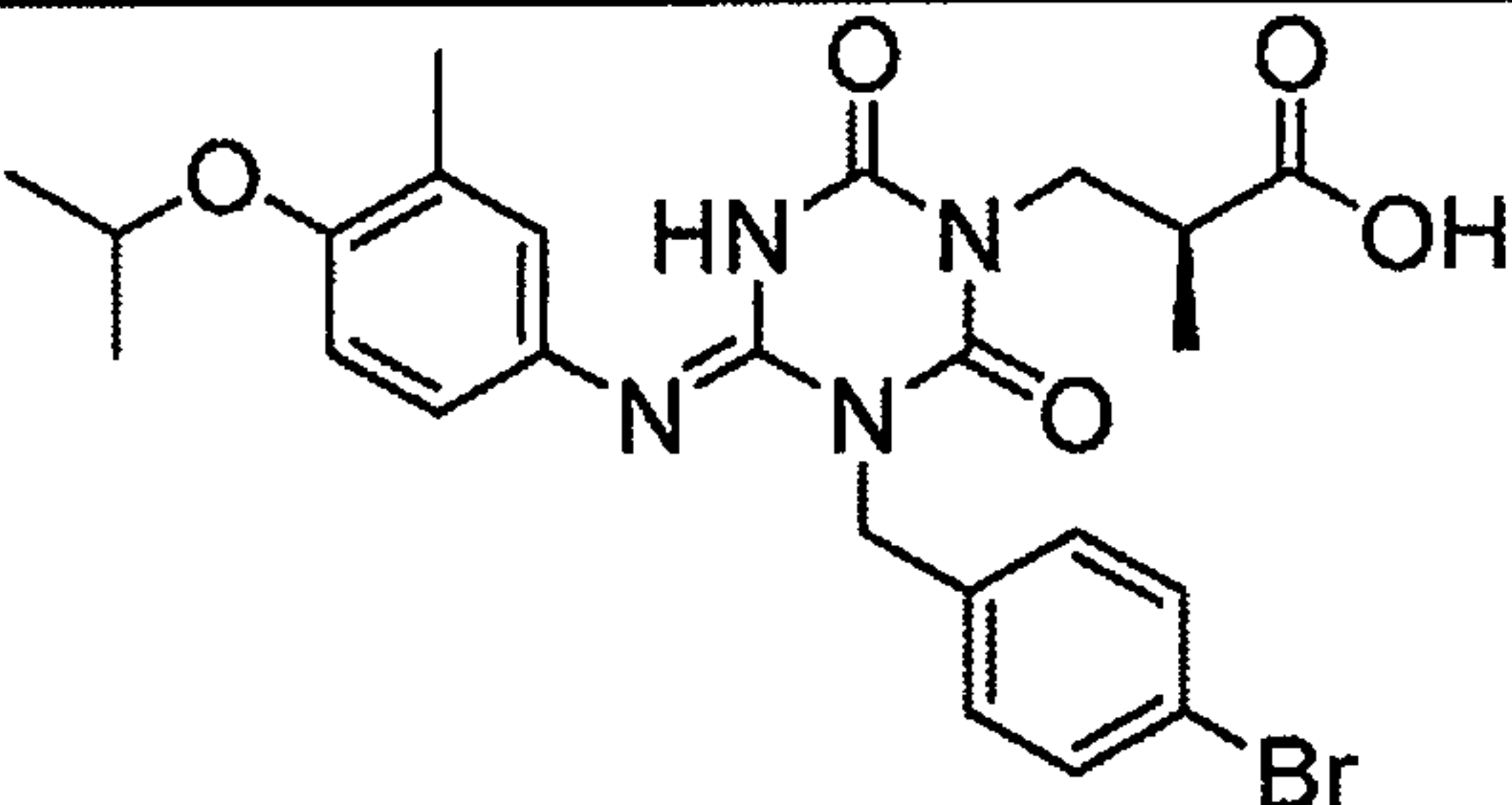
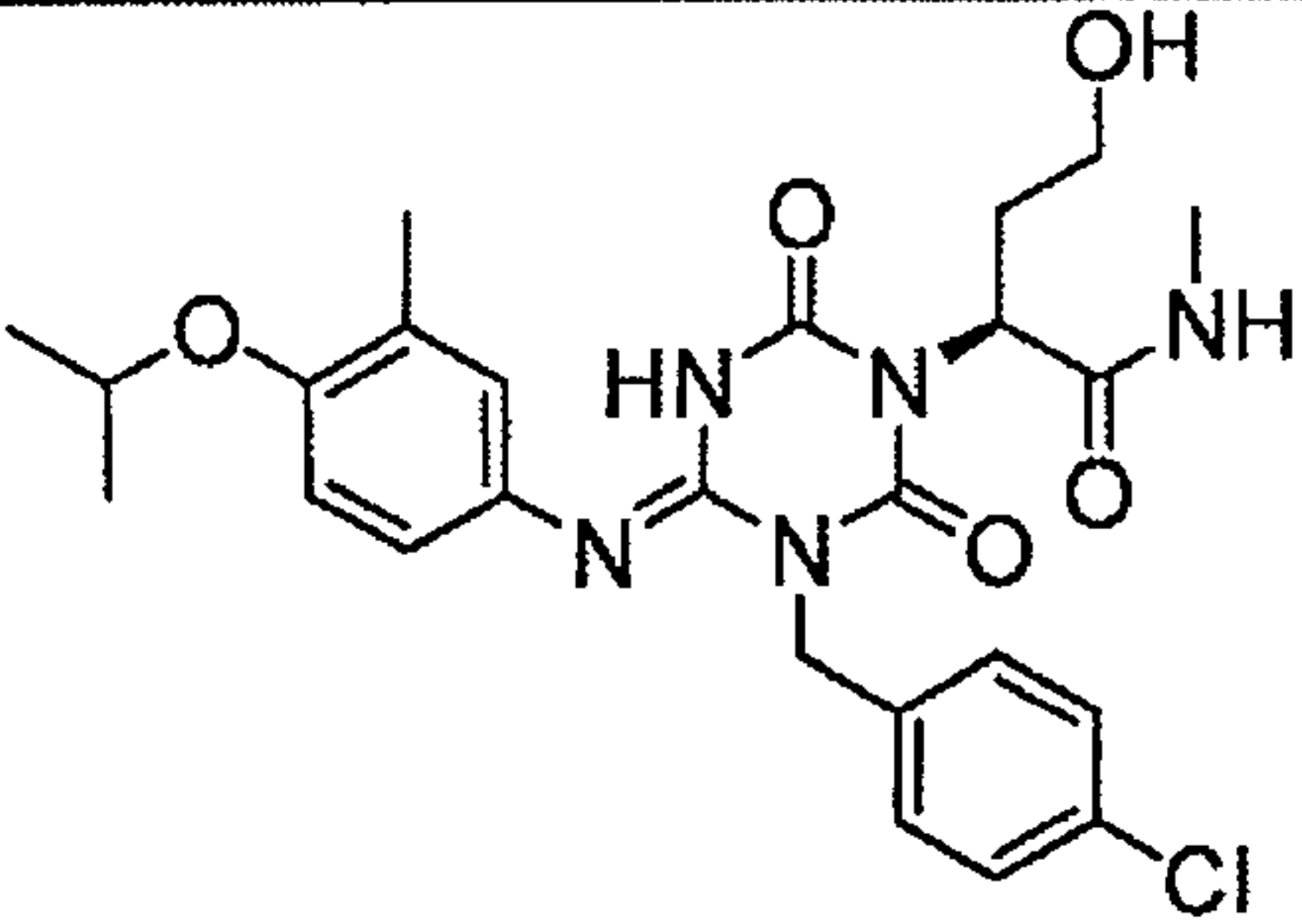
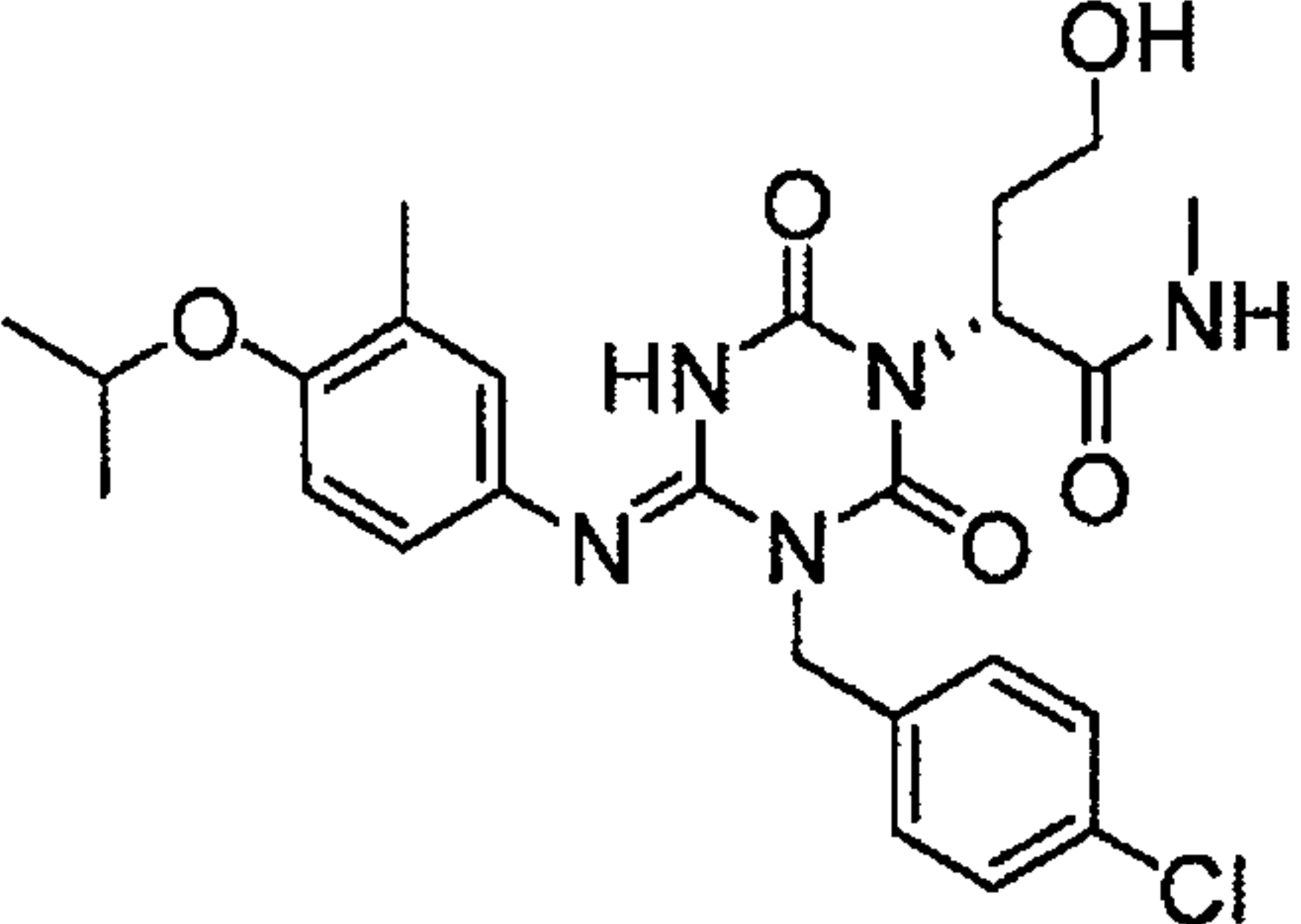
[Table 175]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0856	2.32	523	2
	I-0857	1.84	489	2
	I-0858	1.70	495	2
	I-0859	2.30	503	2
	I-0860	2.42	465	2

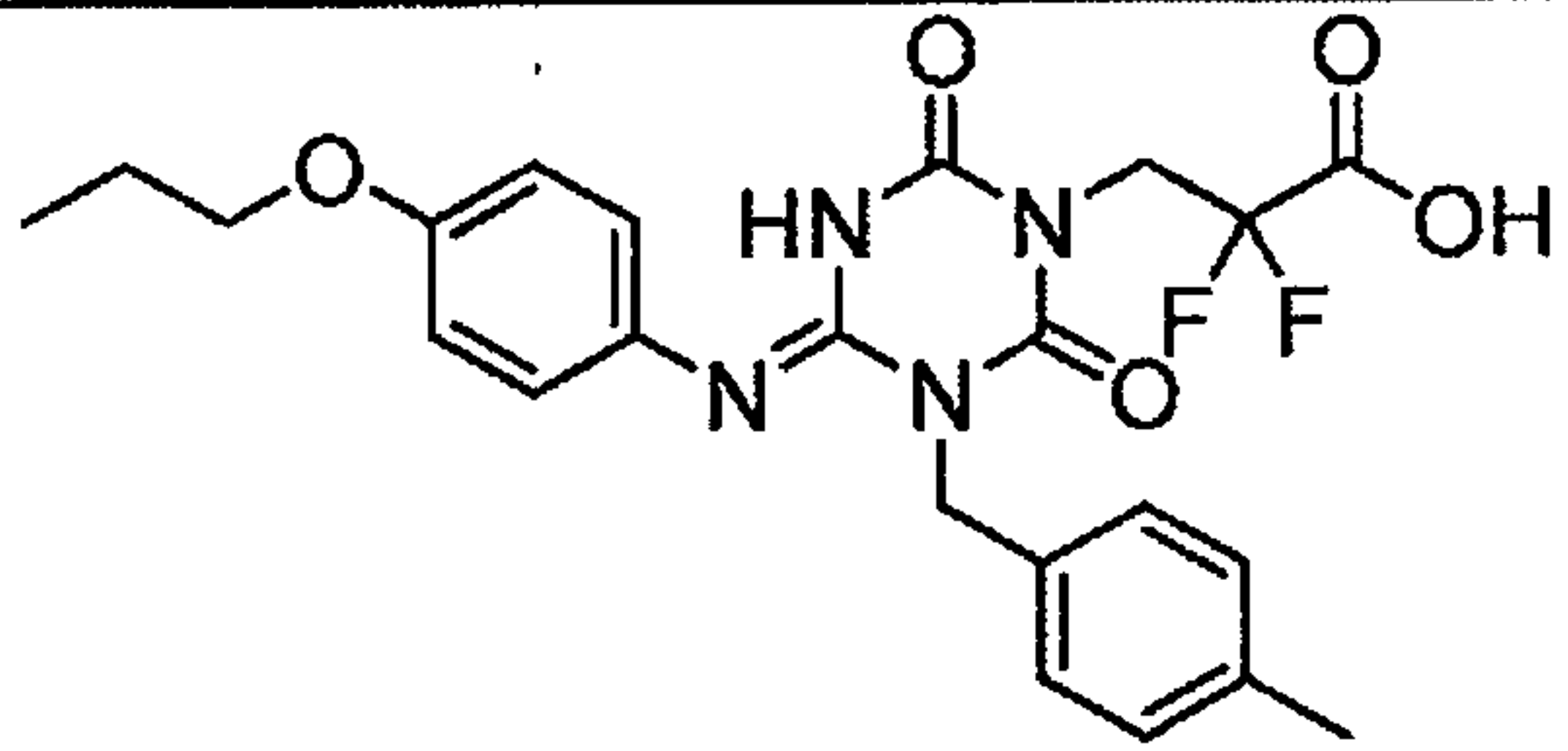
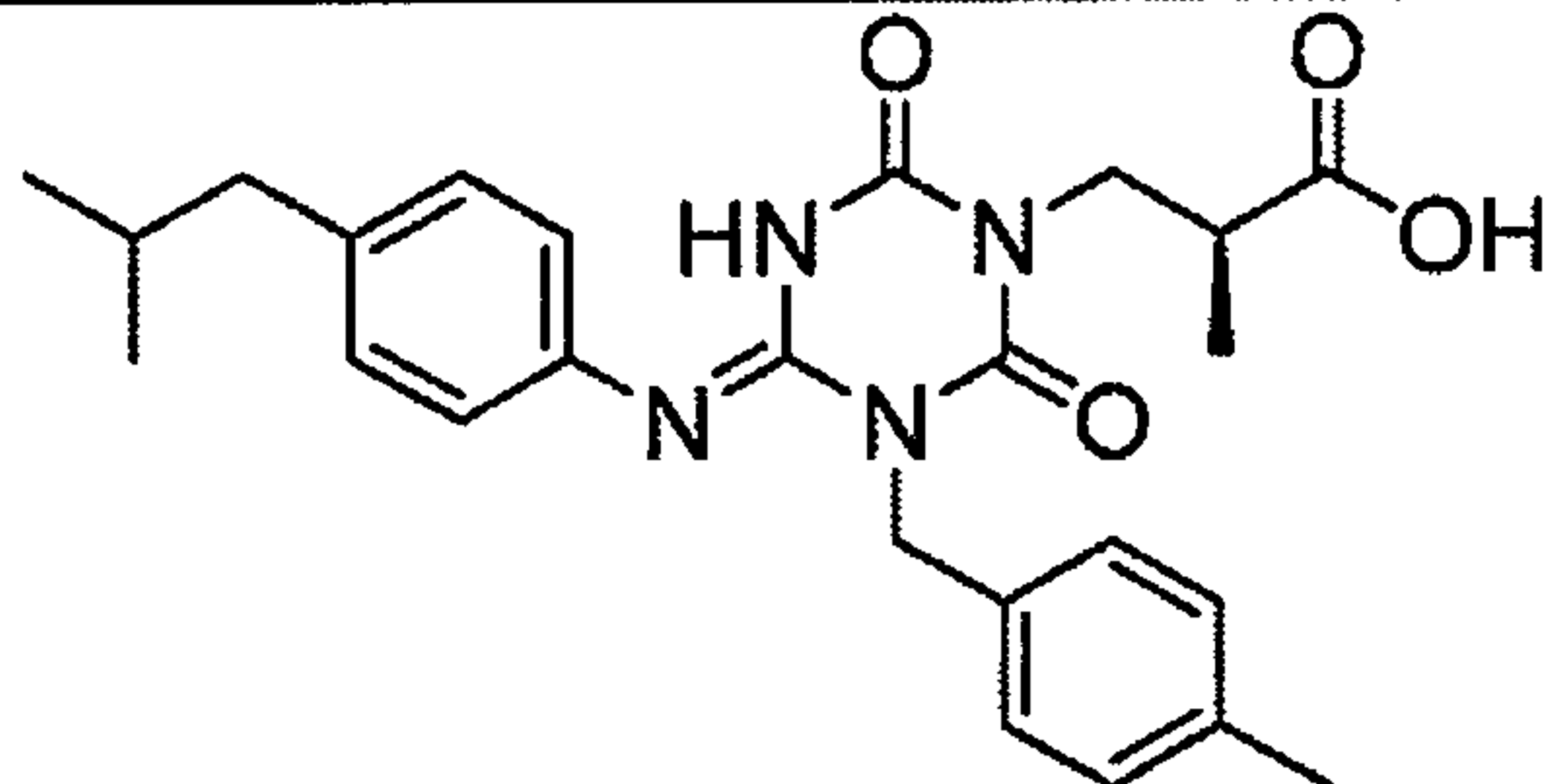
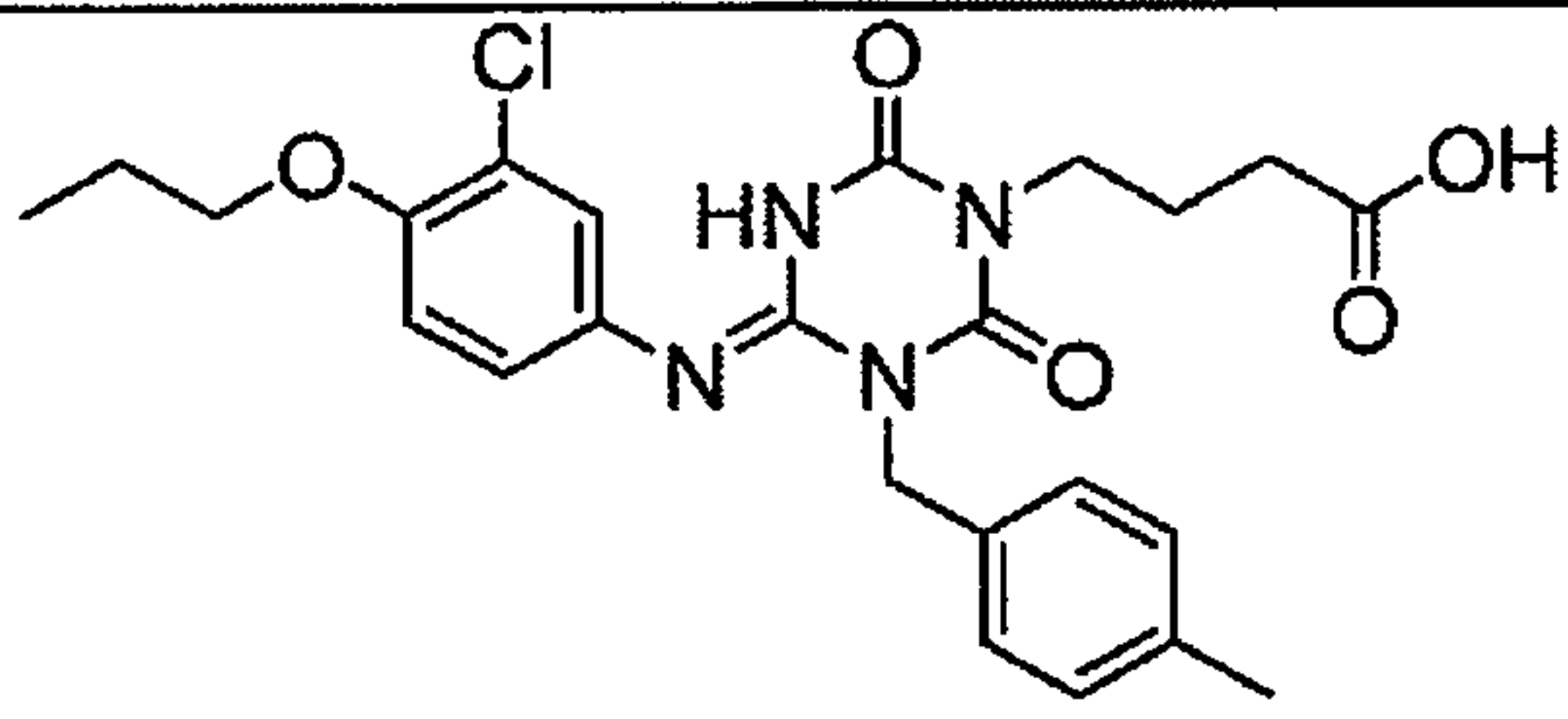
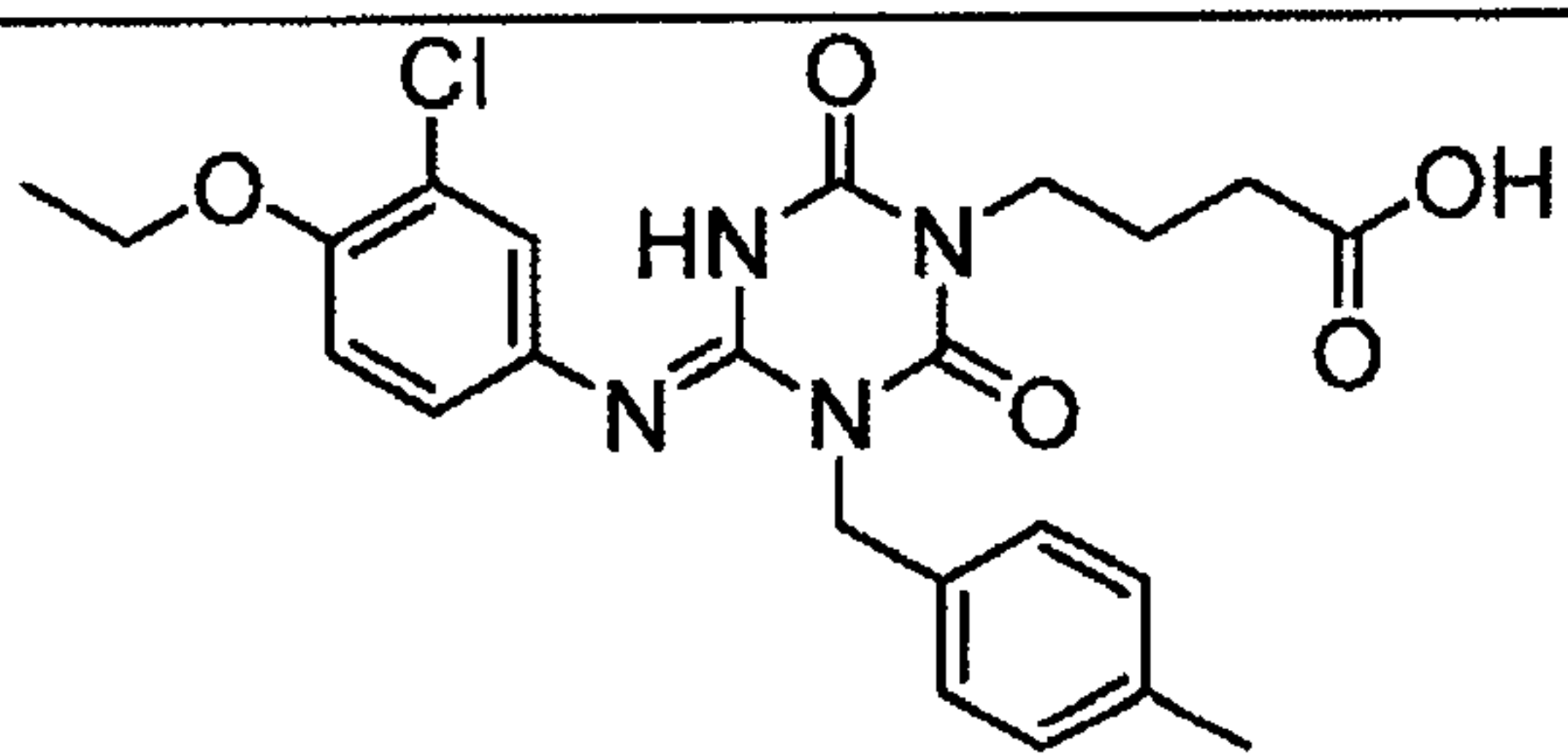
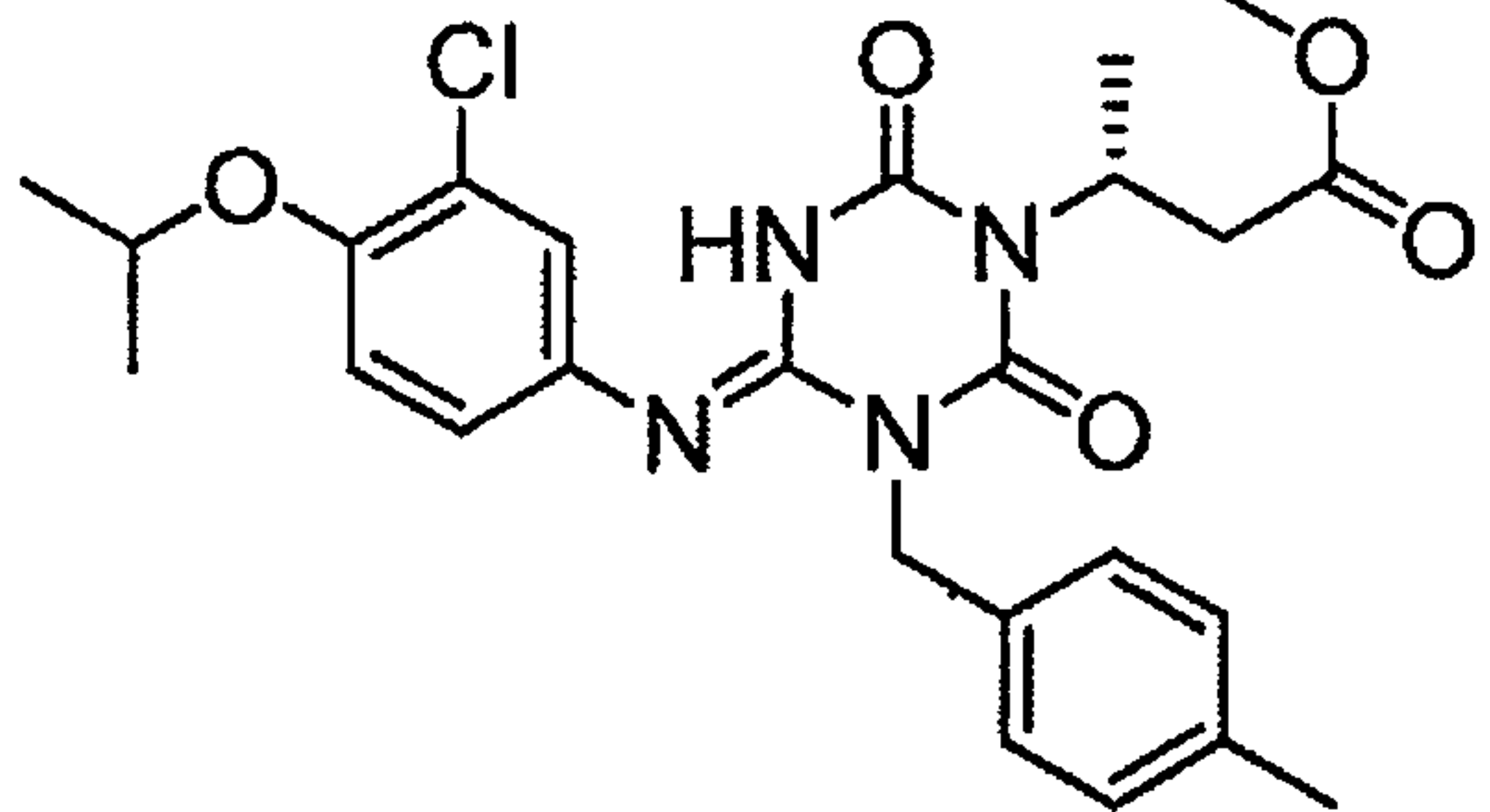
[Table 176]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0861	2.44	515	2
	I-0862	2.29	501	2
	I-0863	1.95	503	2
	I-0864	1.35	480	3
	I-0865	2.37	545	2

[Table 177]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0866	2.35	501	2
	I-0867	2.22	487	2
	I-0868	2.11	531	2
	I-0869	1.83	516	2
	I-0870	1.83	516	2

[Table 178]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0871	1.73	475	2
	I-0872	2.17	451	2
	I-0873	2.09	487	2
	I-0874	2.14	473	3
	I-0875	2.36	501	2

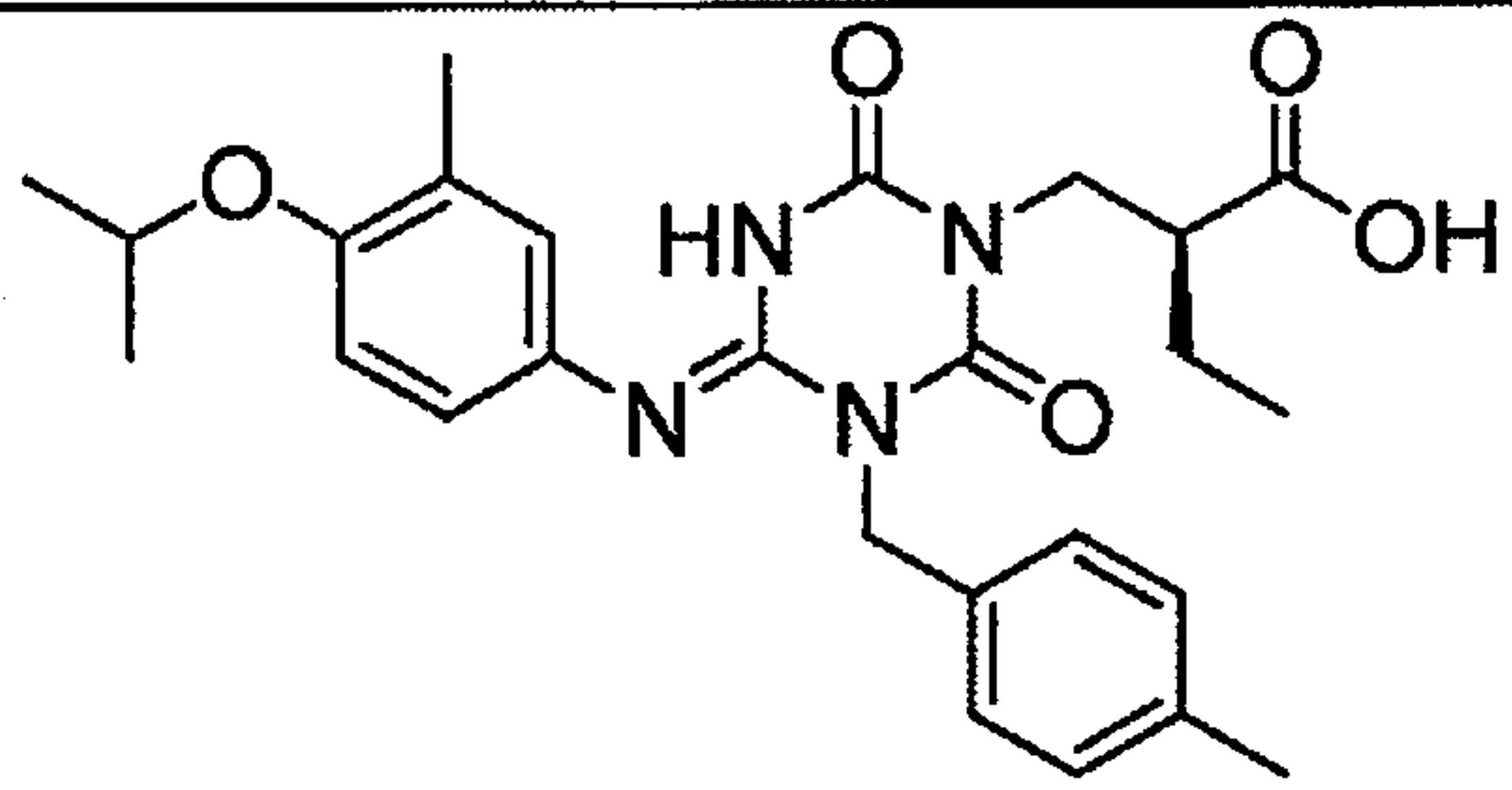
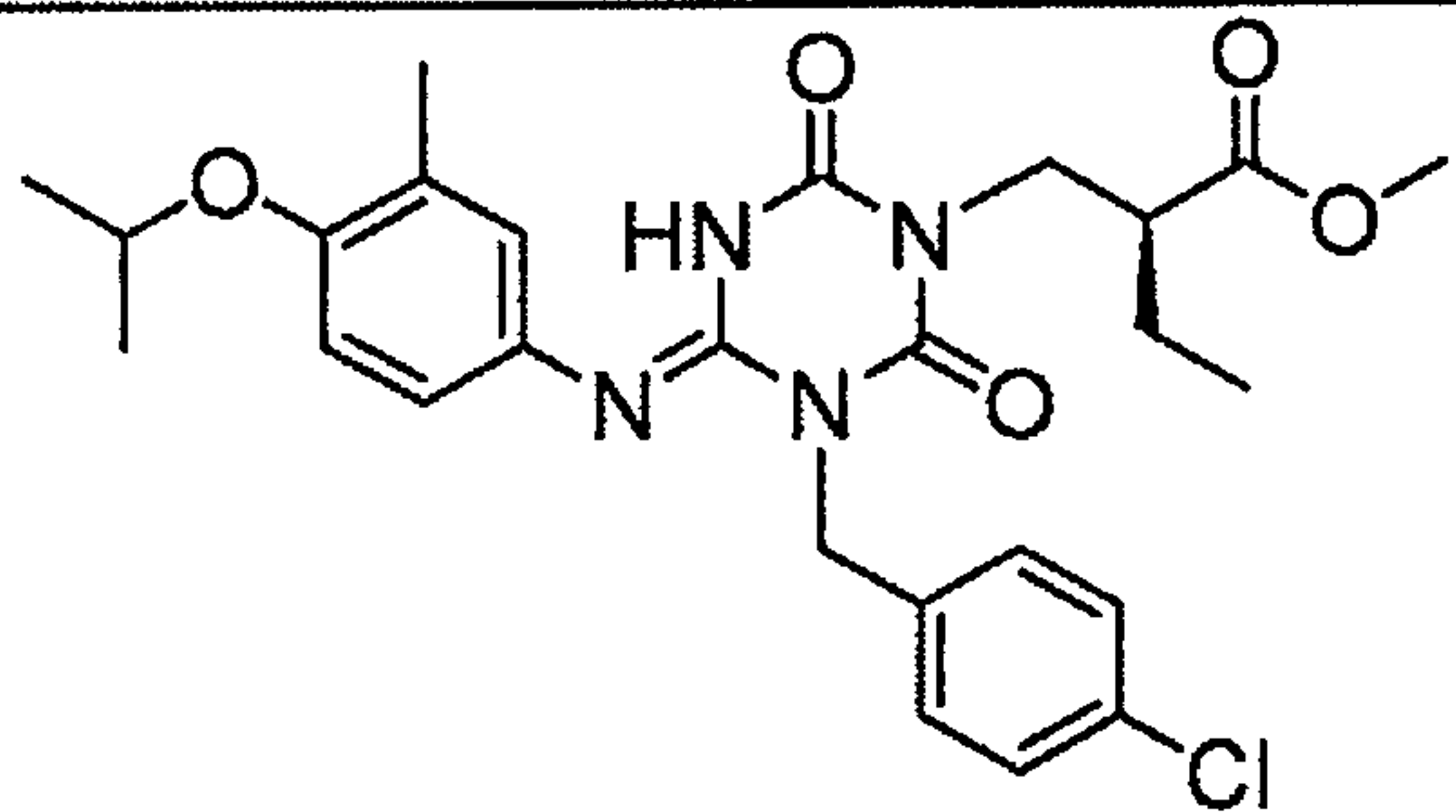
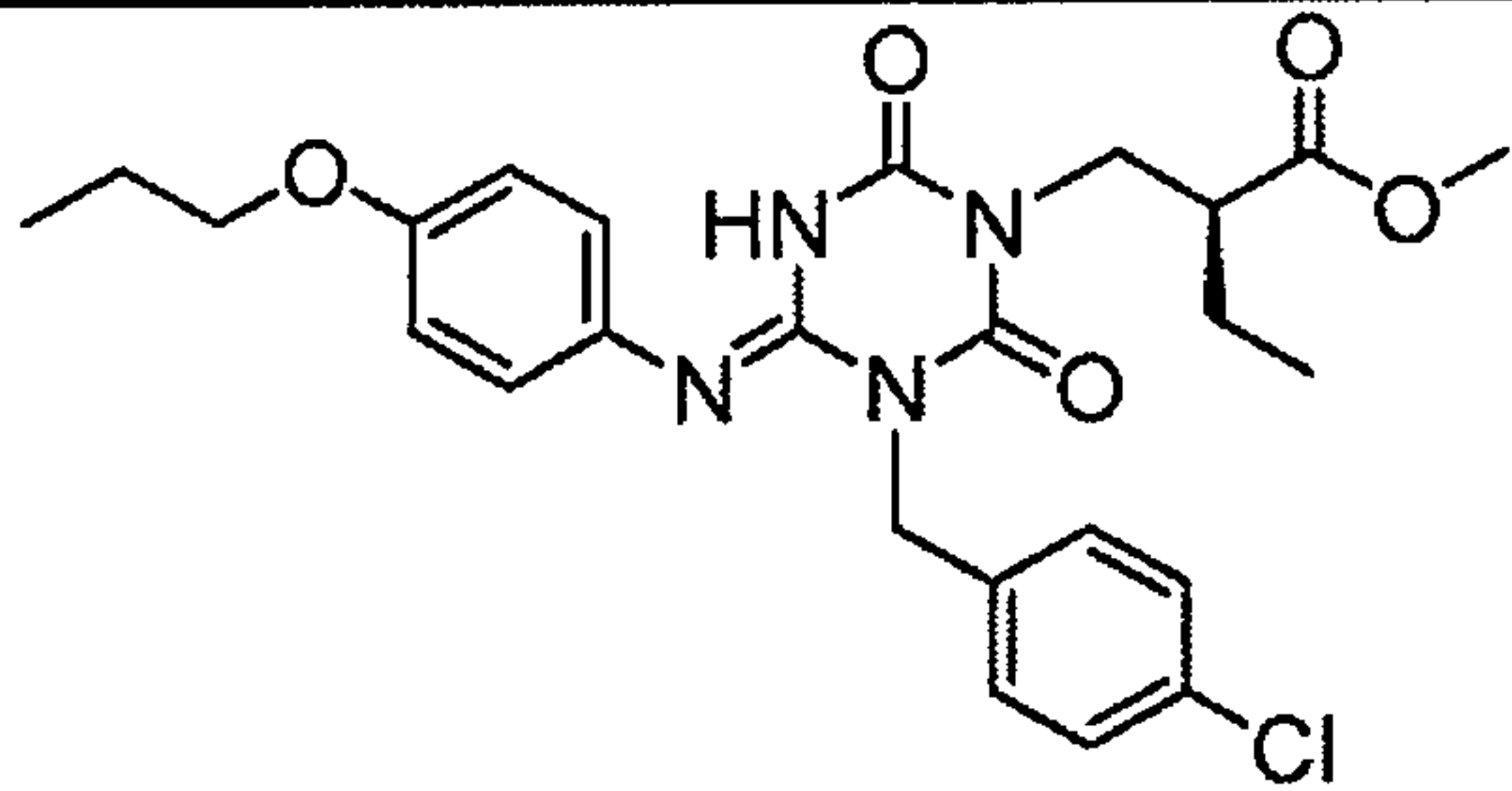
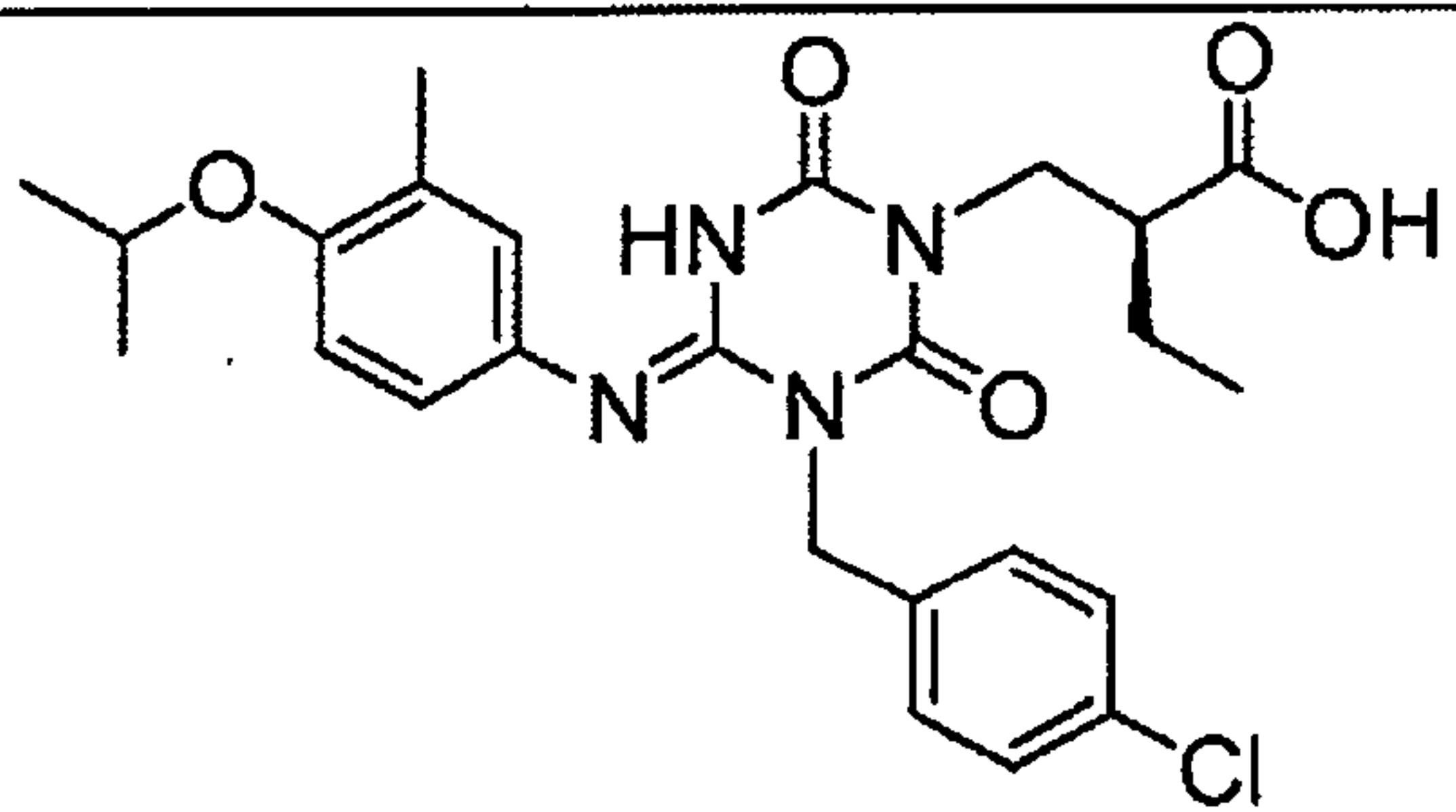
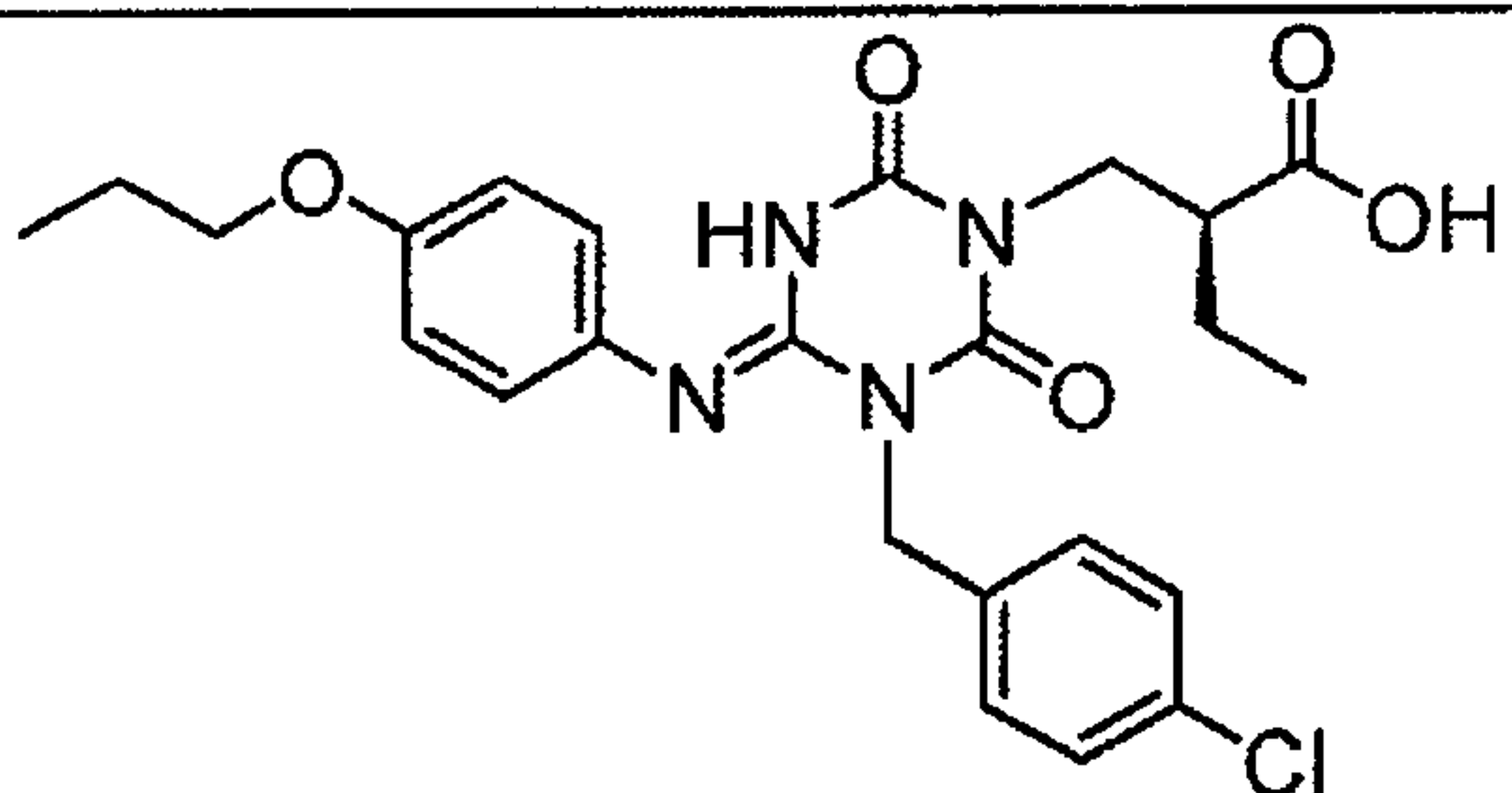
[Table 179]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0876	2.24	487	2
	I-0877	2.39	501	2
	I-0878	2.32	487	3
	I-0879	2.20	473	3
	I-0880	2.15	487	2

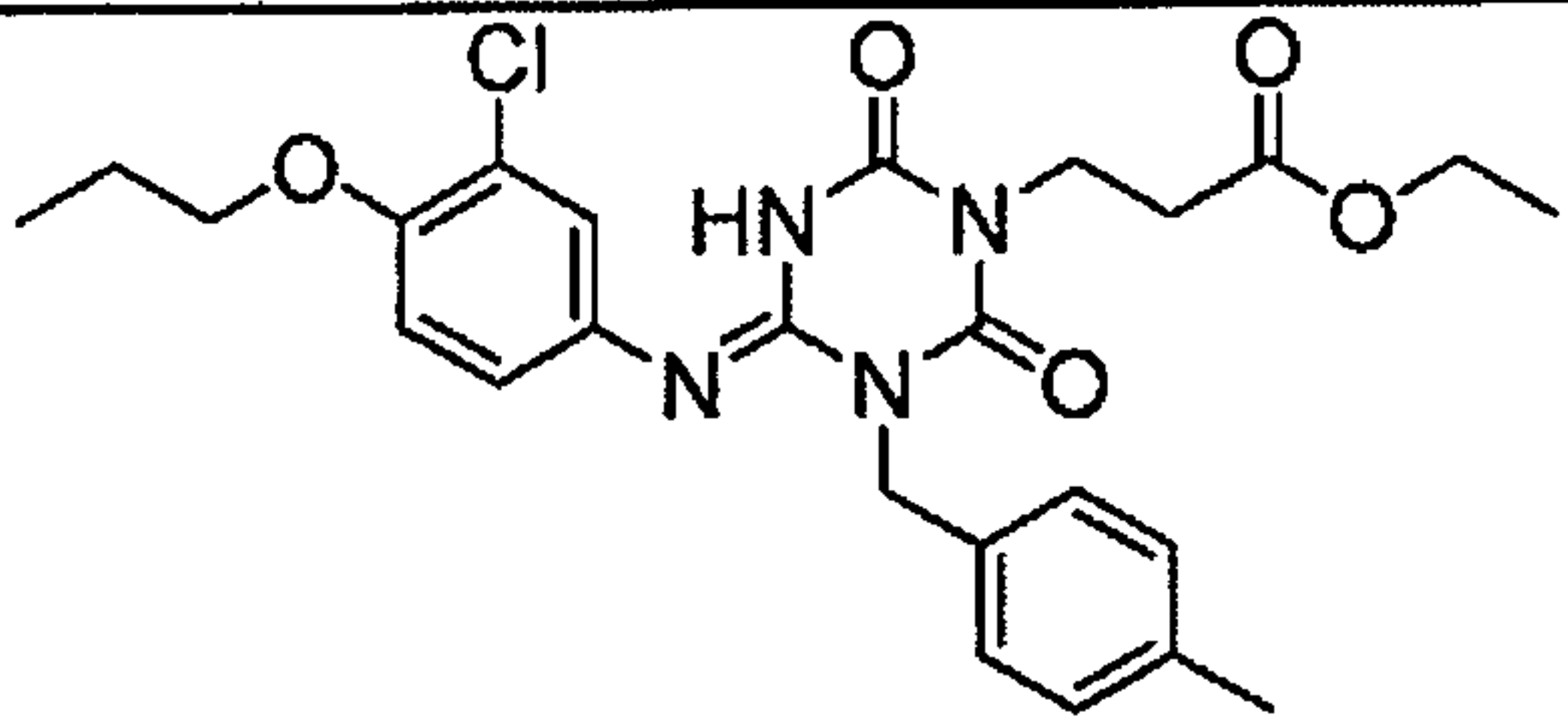
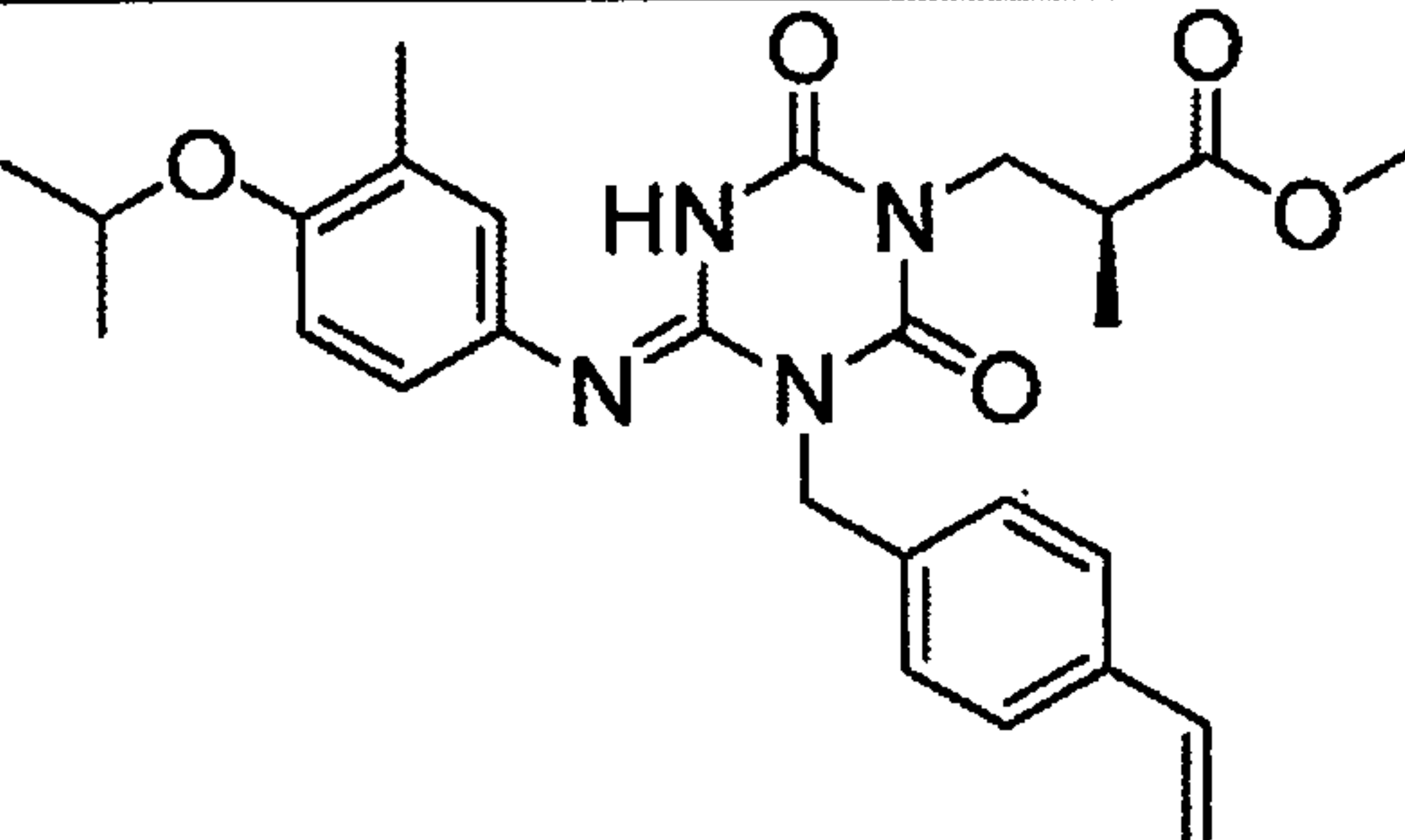
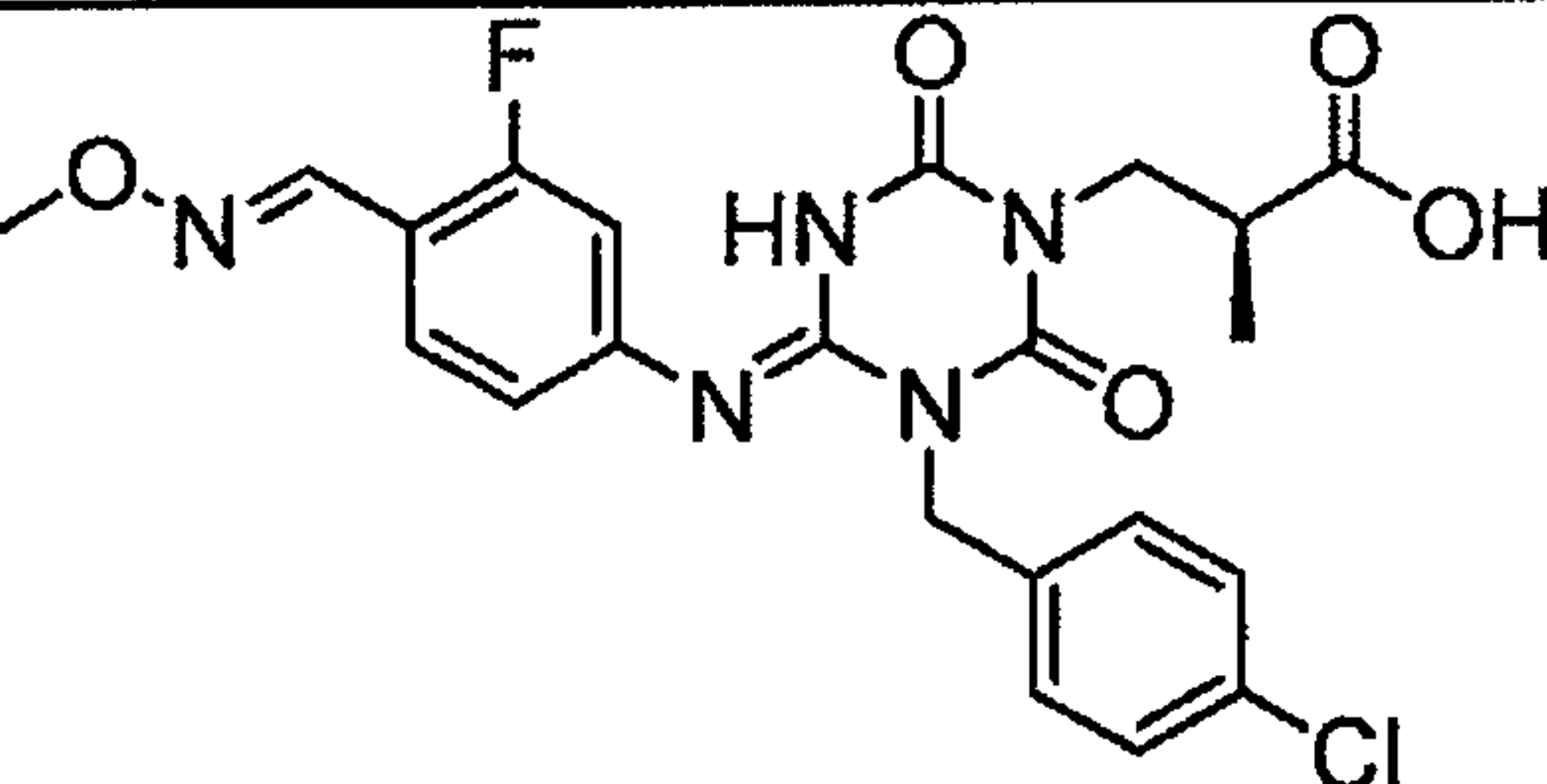
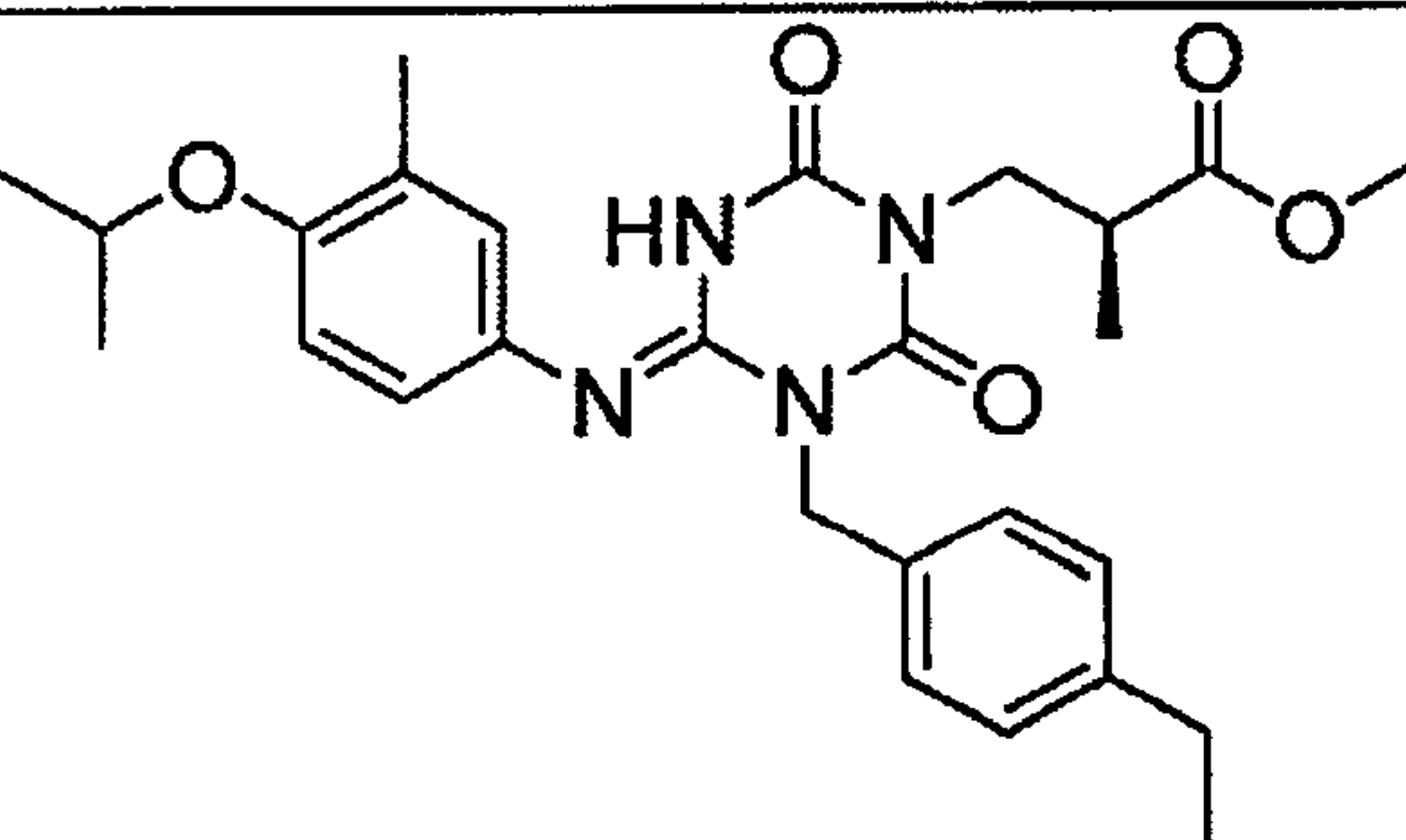
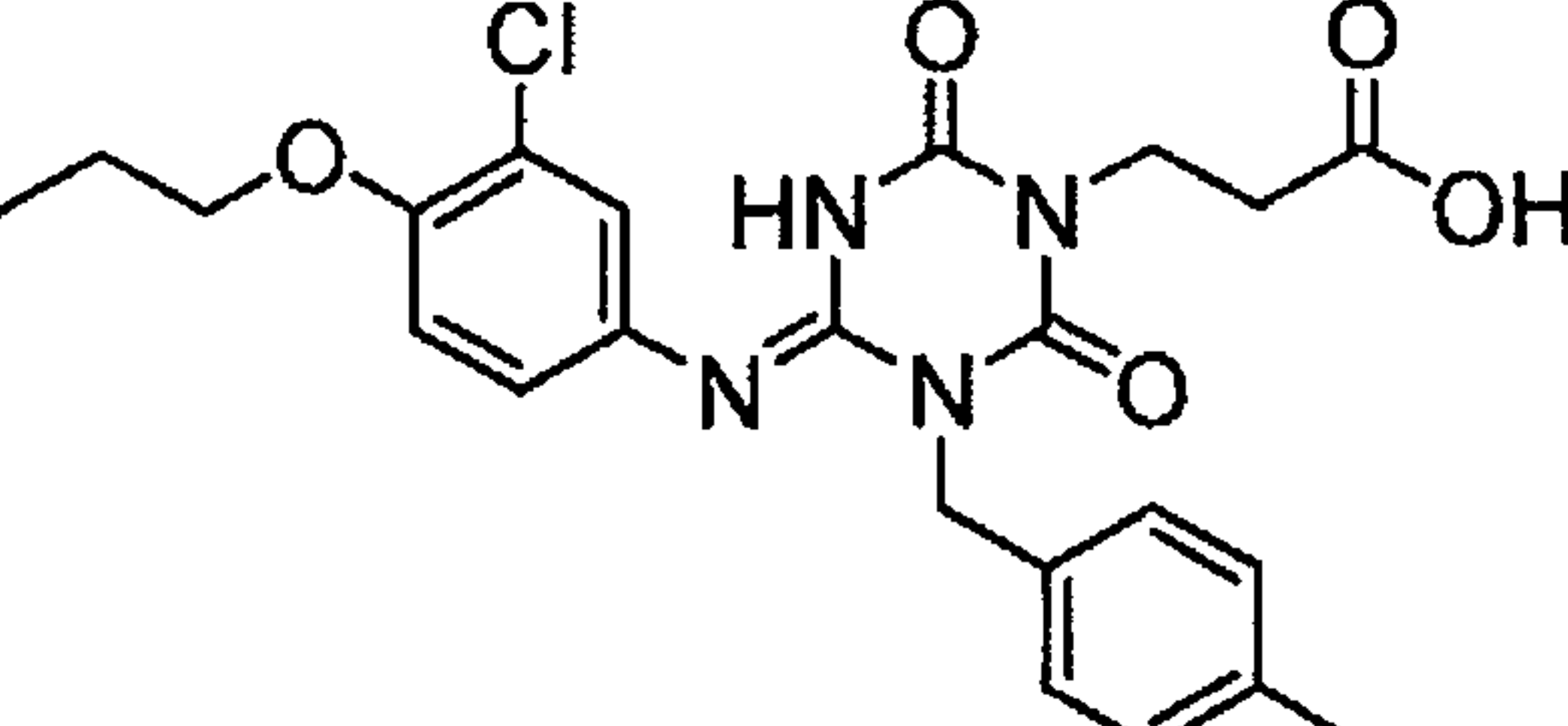
[Table 180]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0881	2.37	504	2
	I-0882	1.89	459	2
	I-0883	2.27	481	2
	I-0884	2.37	495	2
	I-0885	1.99	467	2

[Table 181]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0886	2.10	481	2
	I-0887	2.64	515	3
	I-0888	2.53	501	3
	I-0889	2.36	501	3
	I-0890	2.25	487	3

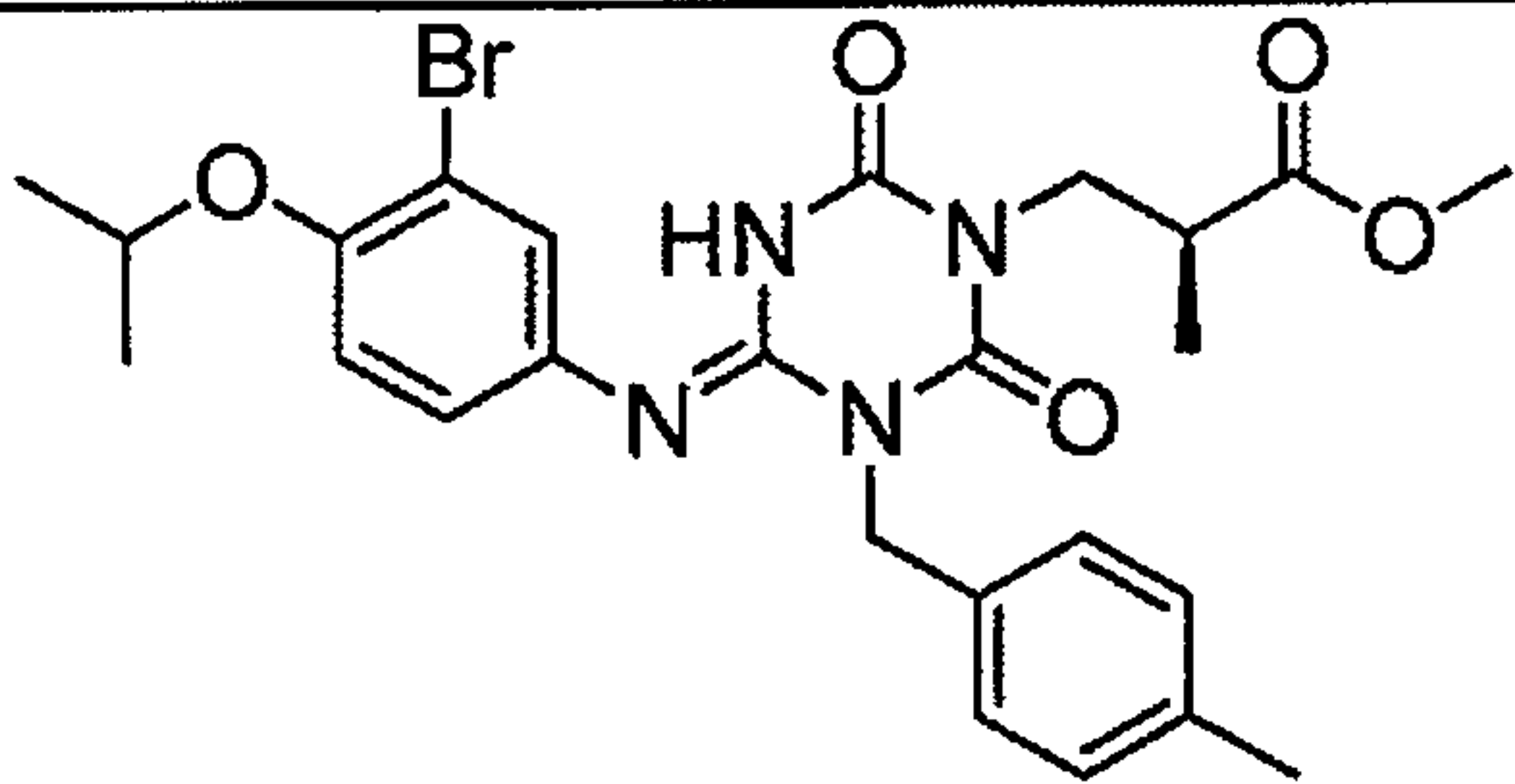
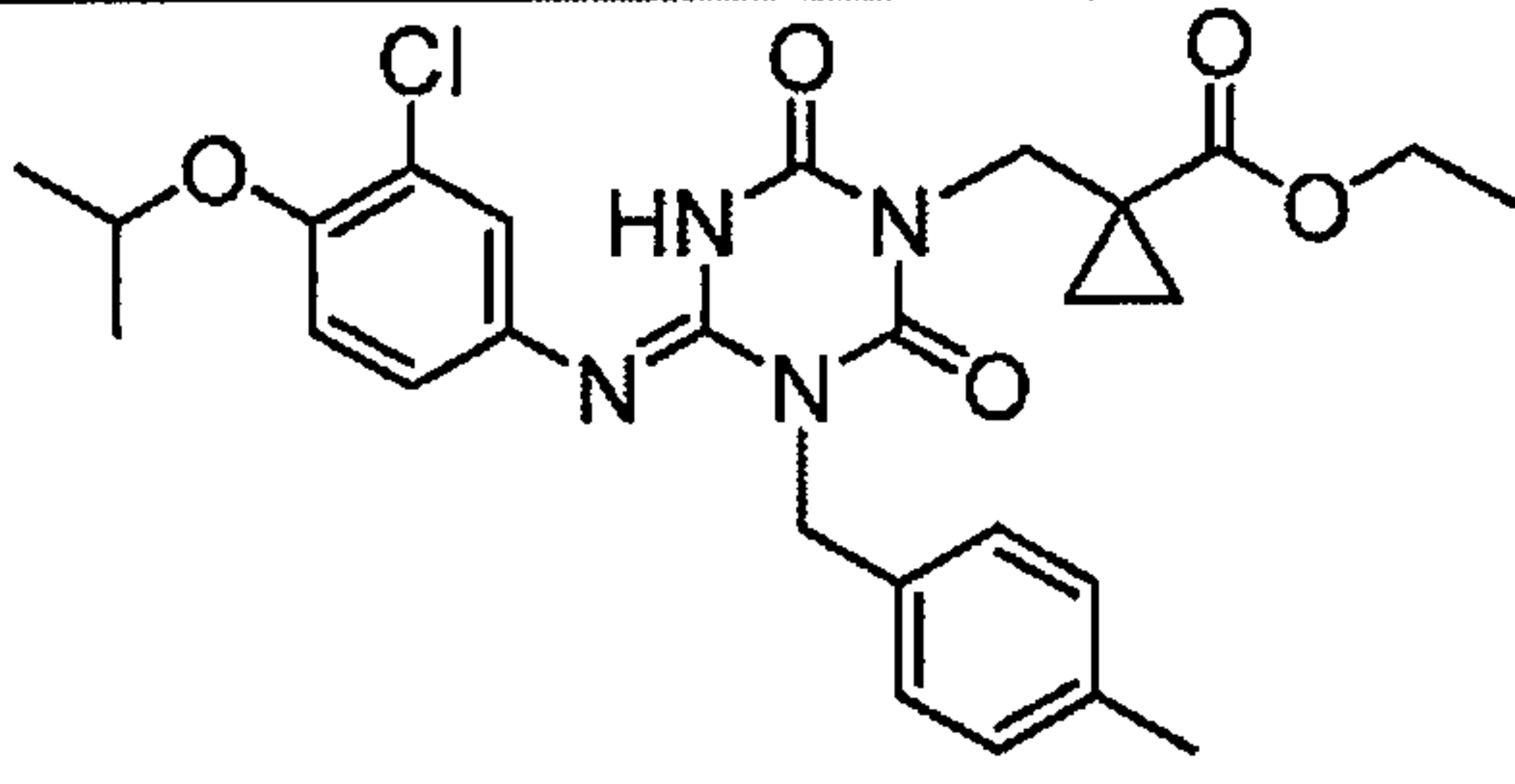
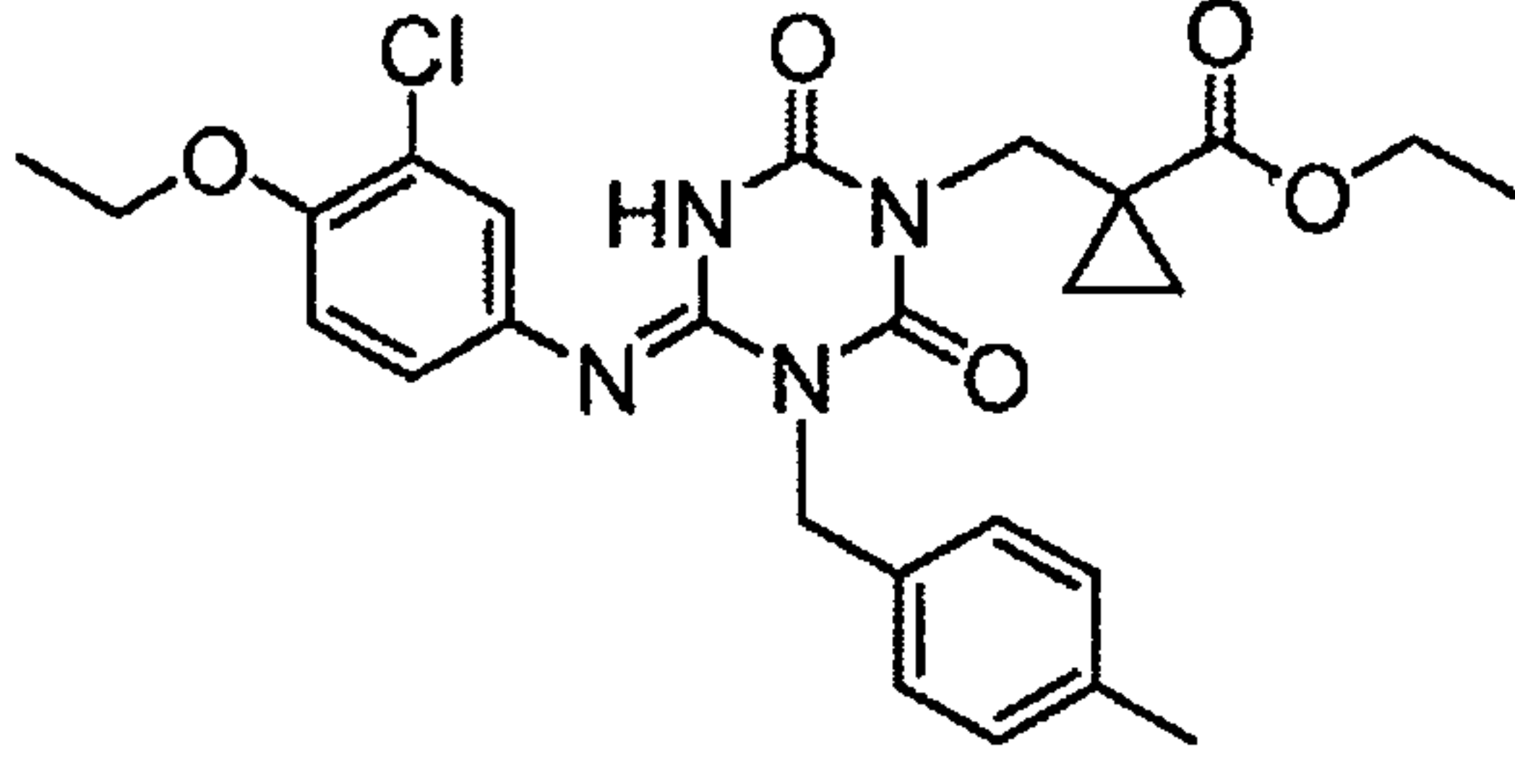
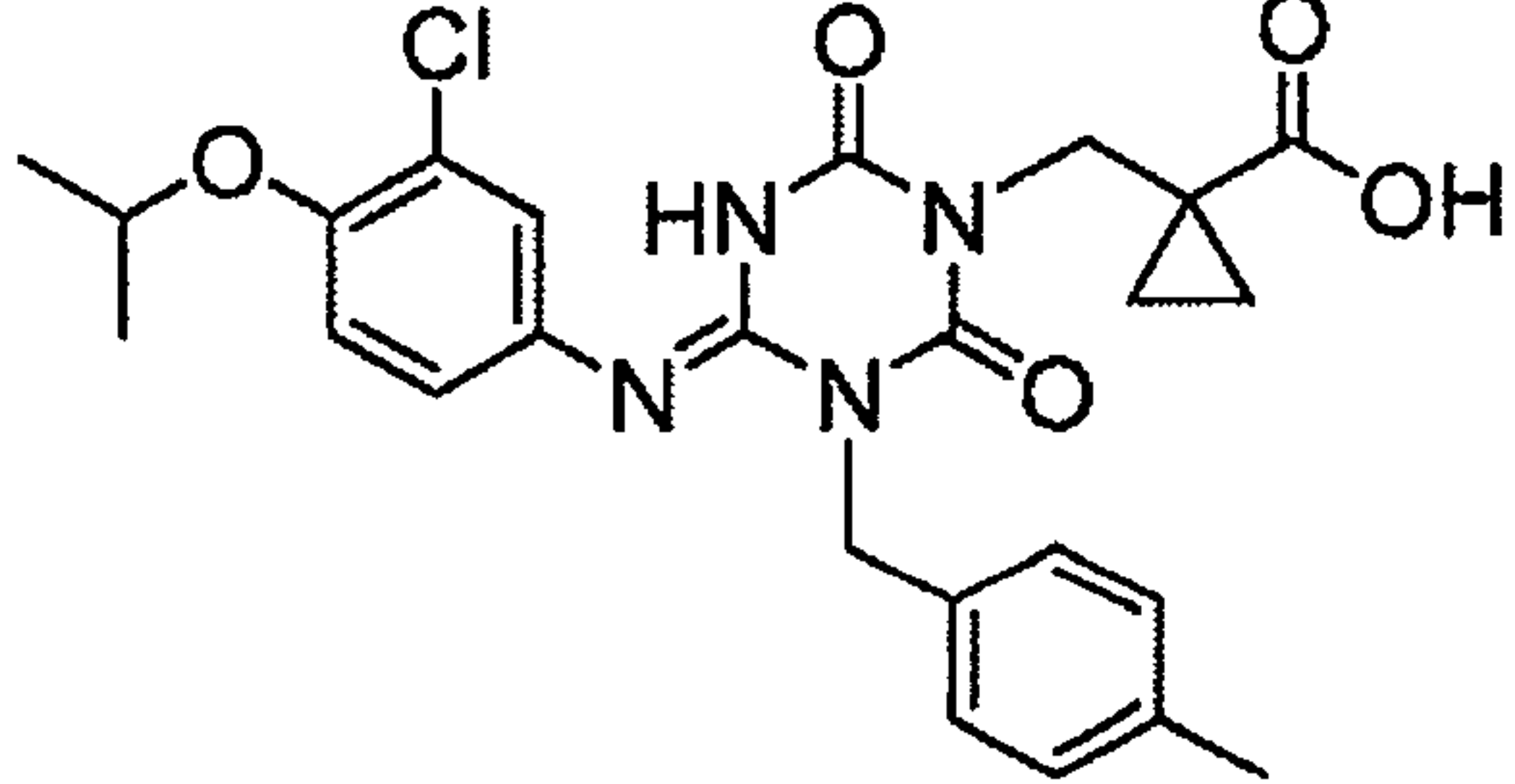
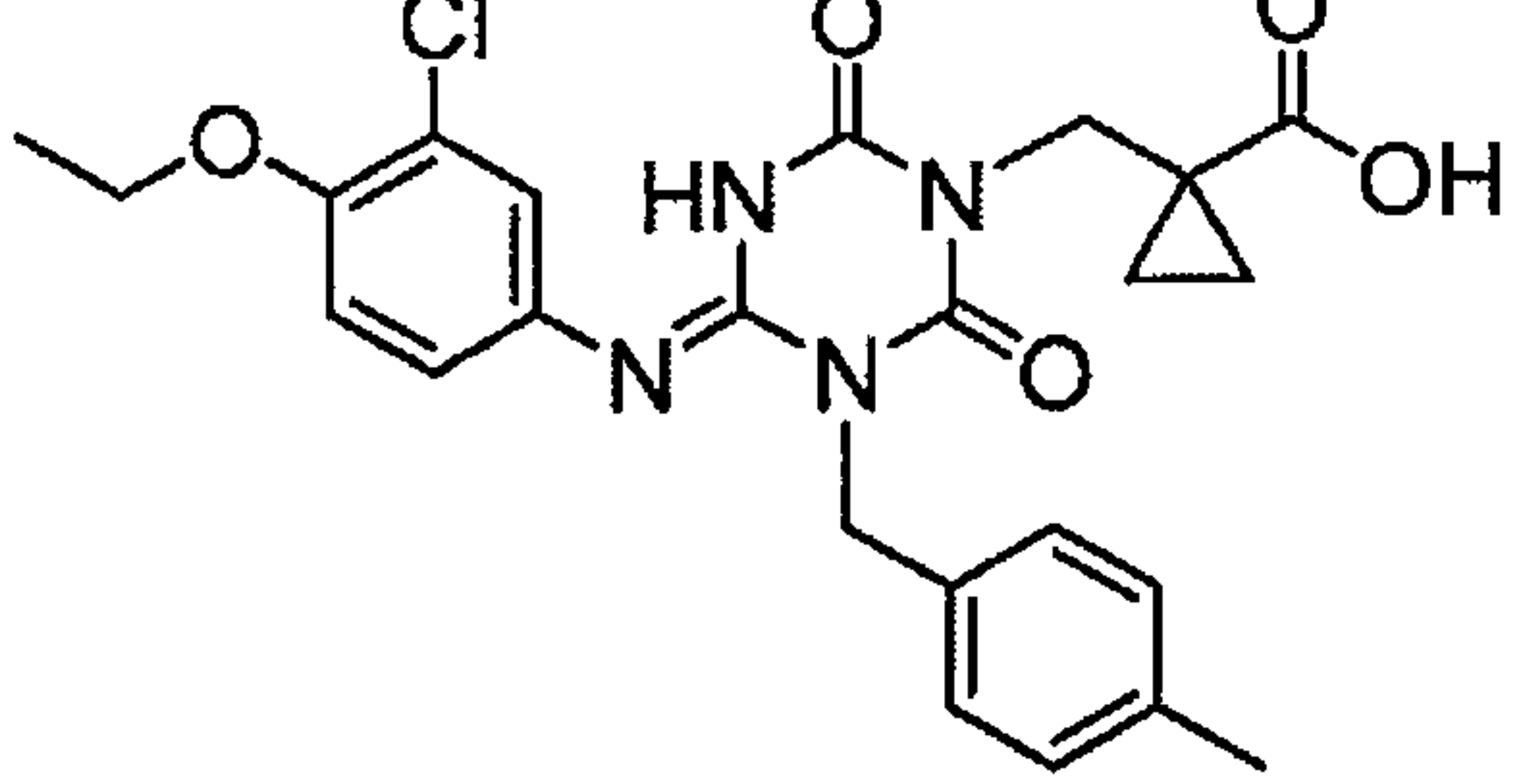
[Table 182]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0891	2.61	501	3
	I-0892	2.31	493	2
	I-0893	2.11	490	2
	I-0894	2.39	495	2
	I-0895	2.27	473	3

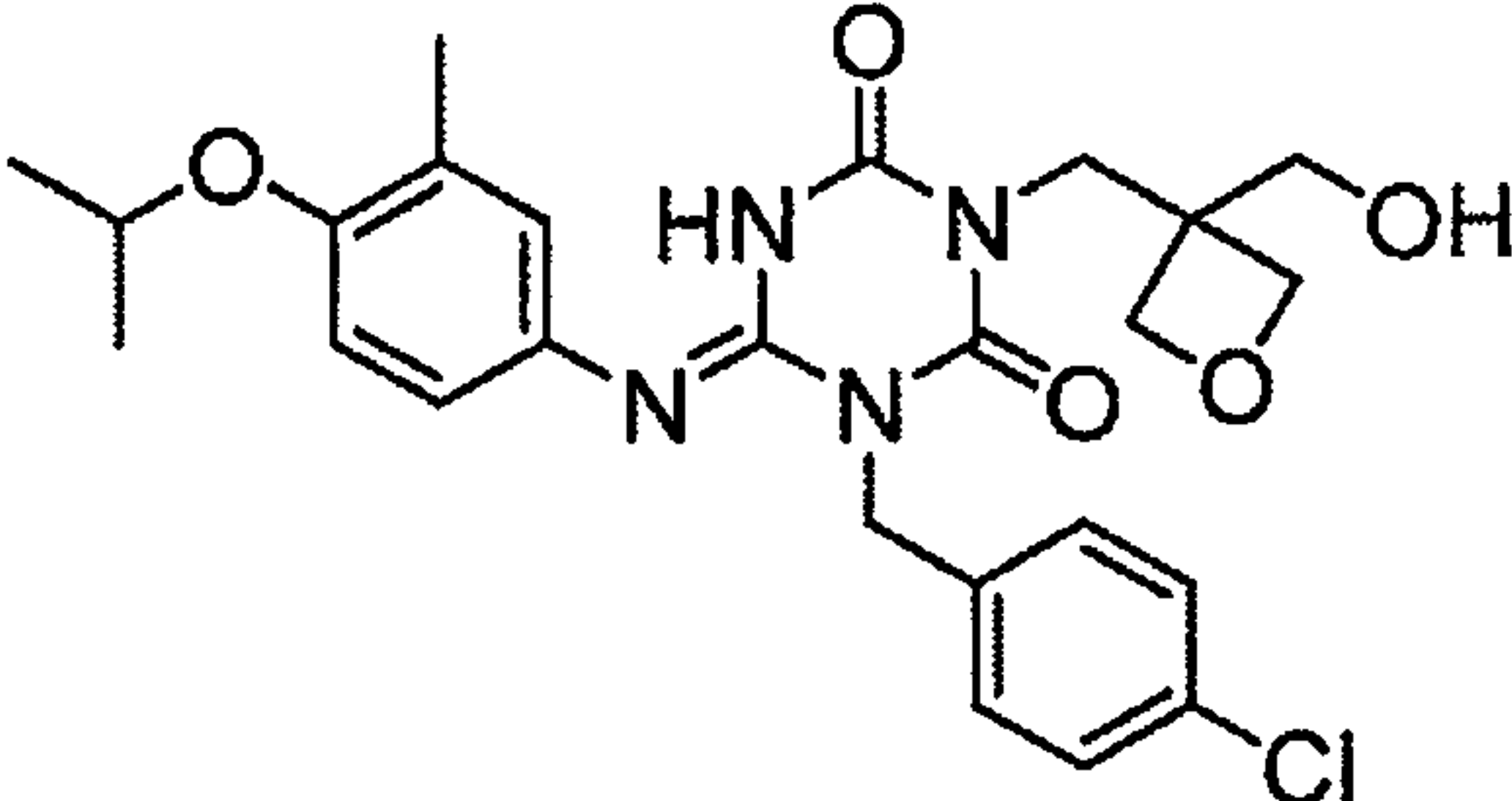
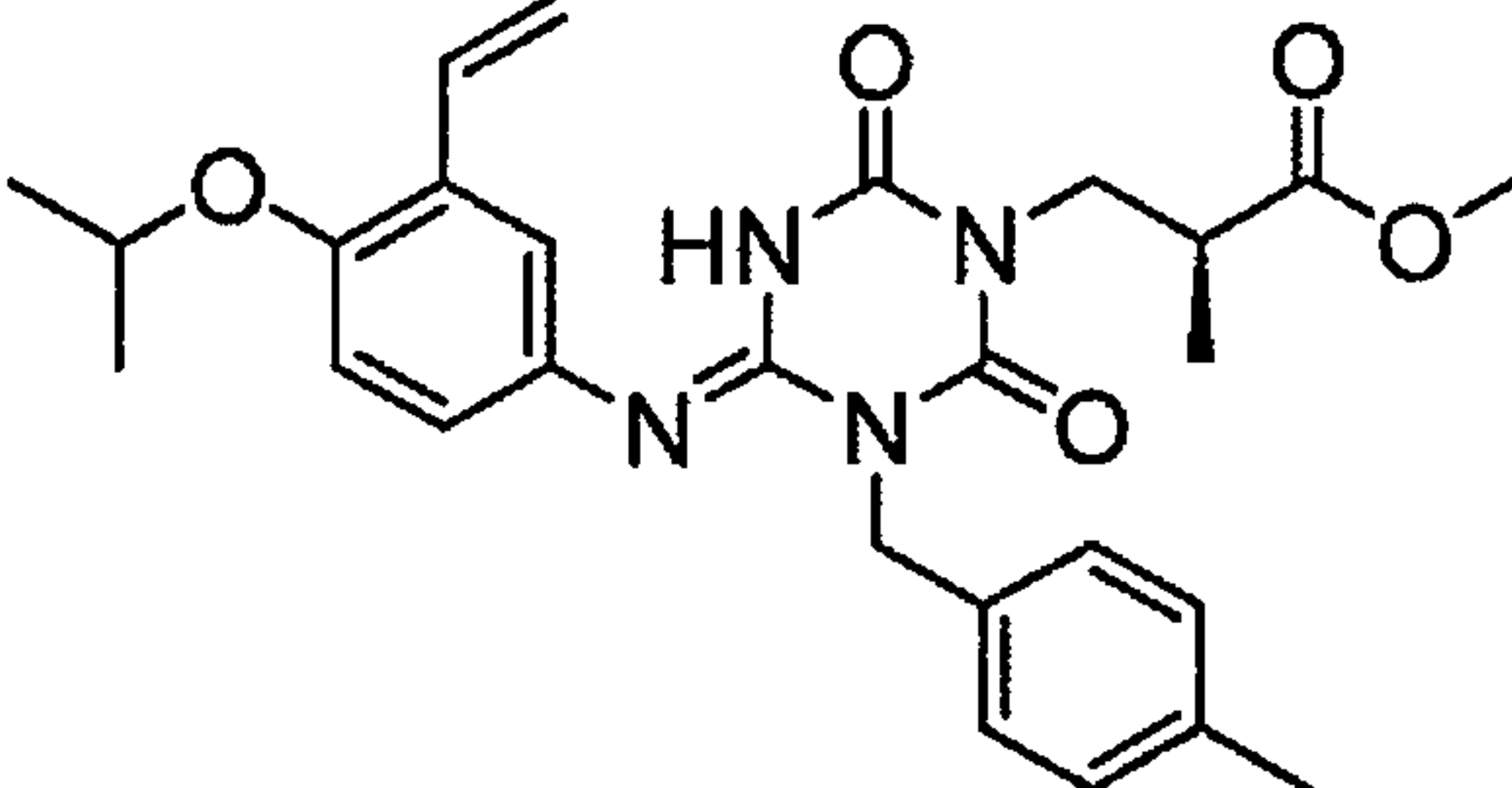
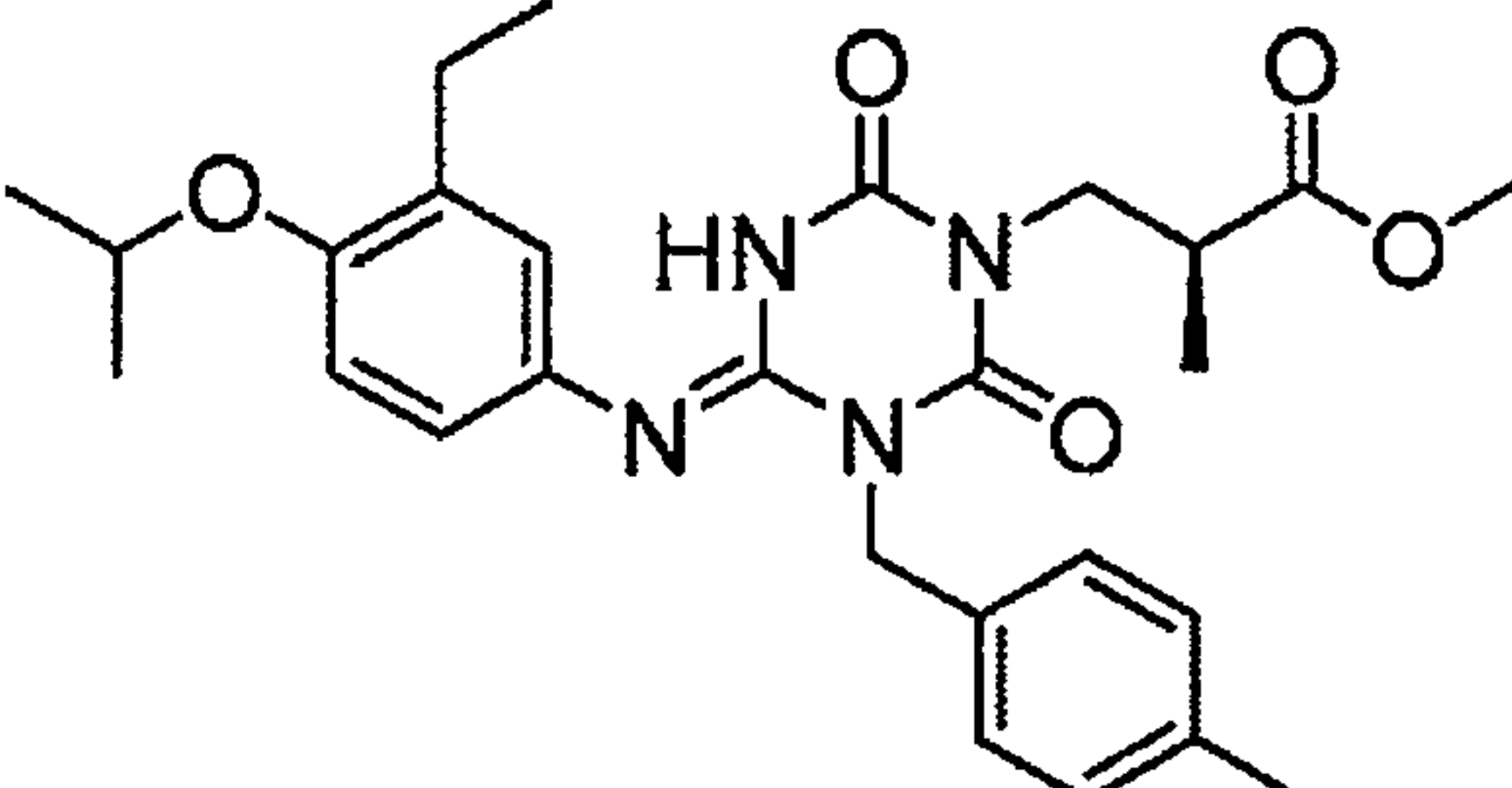
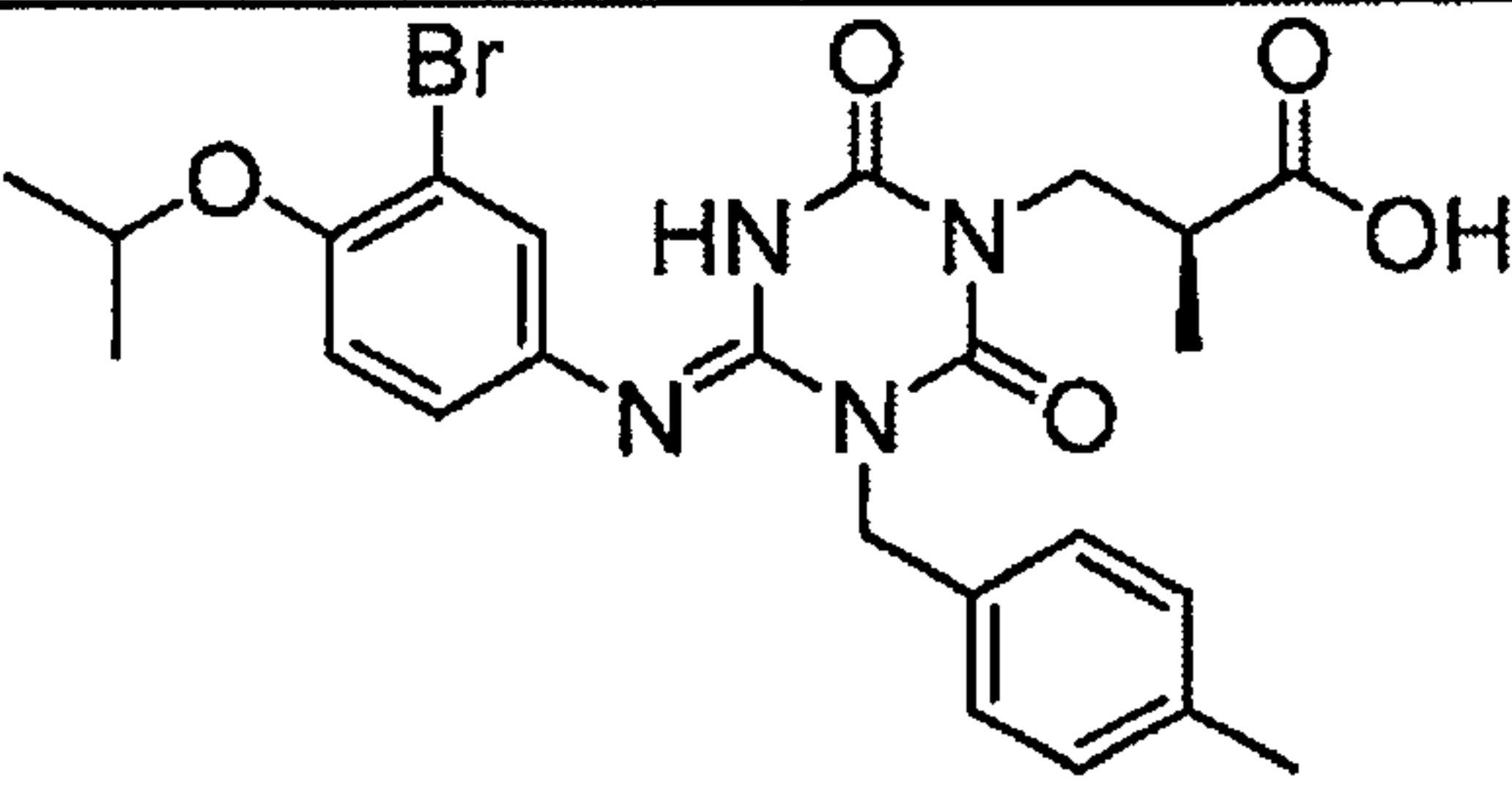
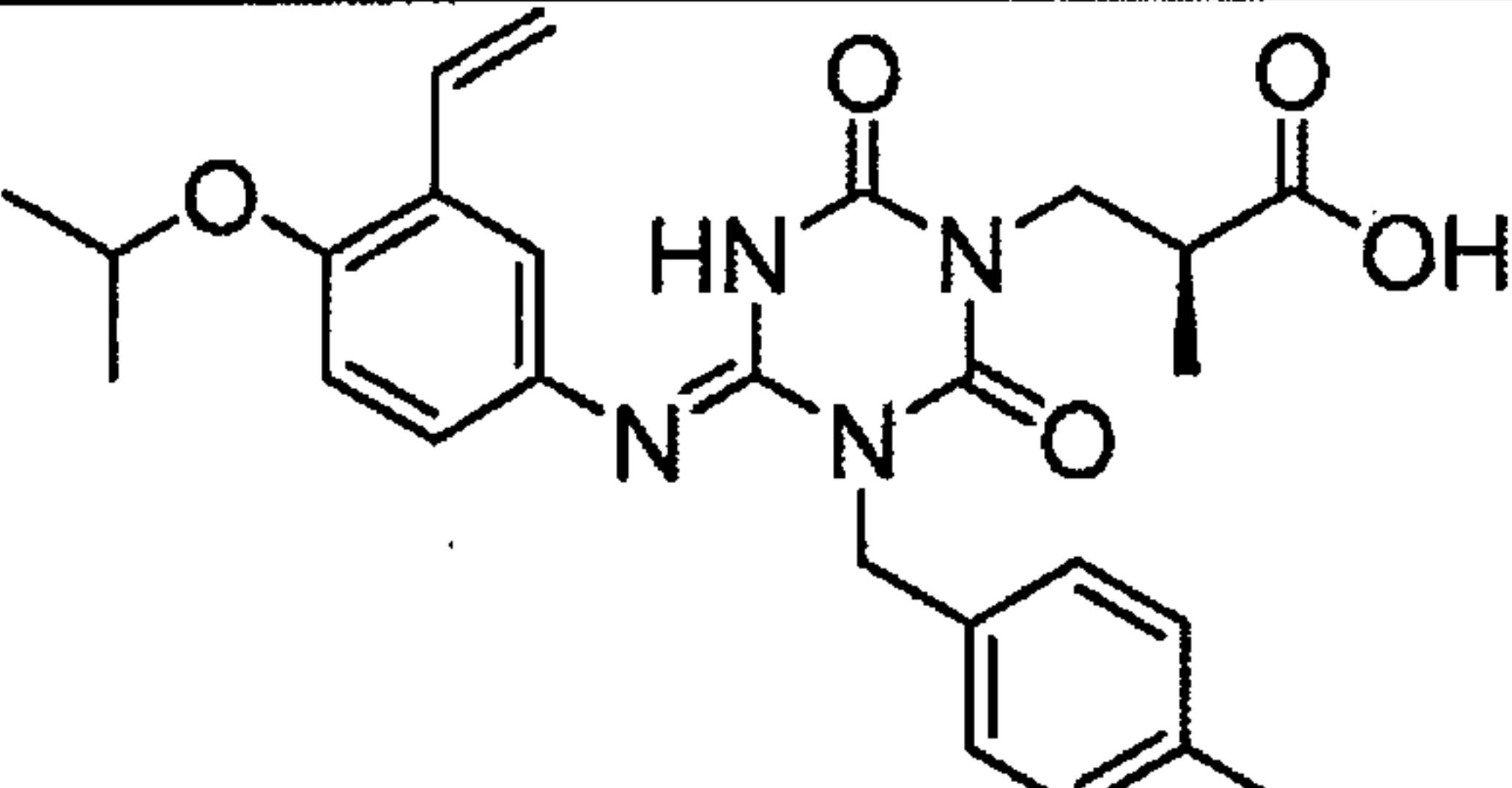
[Table 183]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0896	2.02	473	2
	I-0897	2.07	479	2
	I-0898	2.14	481	2
	I-0899	2.36	501	2
	I-0900	2.33	513	2

[Table 184]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0901	2.37	545	2
	I-0902	2.48	527	2
	I-0903	2.38	513	2
	I-0904	2.34	499	3
	I-0905	2.22	485	3

[Table 185]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0906	1.99	501	2
	I-0907	2.33	493	2
	I-0908	2.39	495	2
	I-0909	2.11	531	2
	I-0910	2.09	479	2

[Table 186]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0911	2.15	481	2
	I-0912	2.52	493	3
	I-0913	2.49	505	3
	I-0914	2.16	265	3
	I-0915	2.13	477	3

[Table 187]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0916	2.43	521	2
	I-0917	2.54	535	2
	I-0918	2.44	533	2
	I-0919	2.37	513	2
	I-0920	2.09	487	2

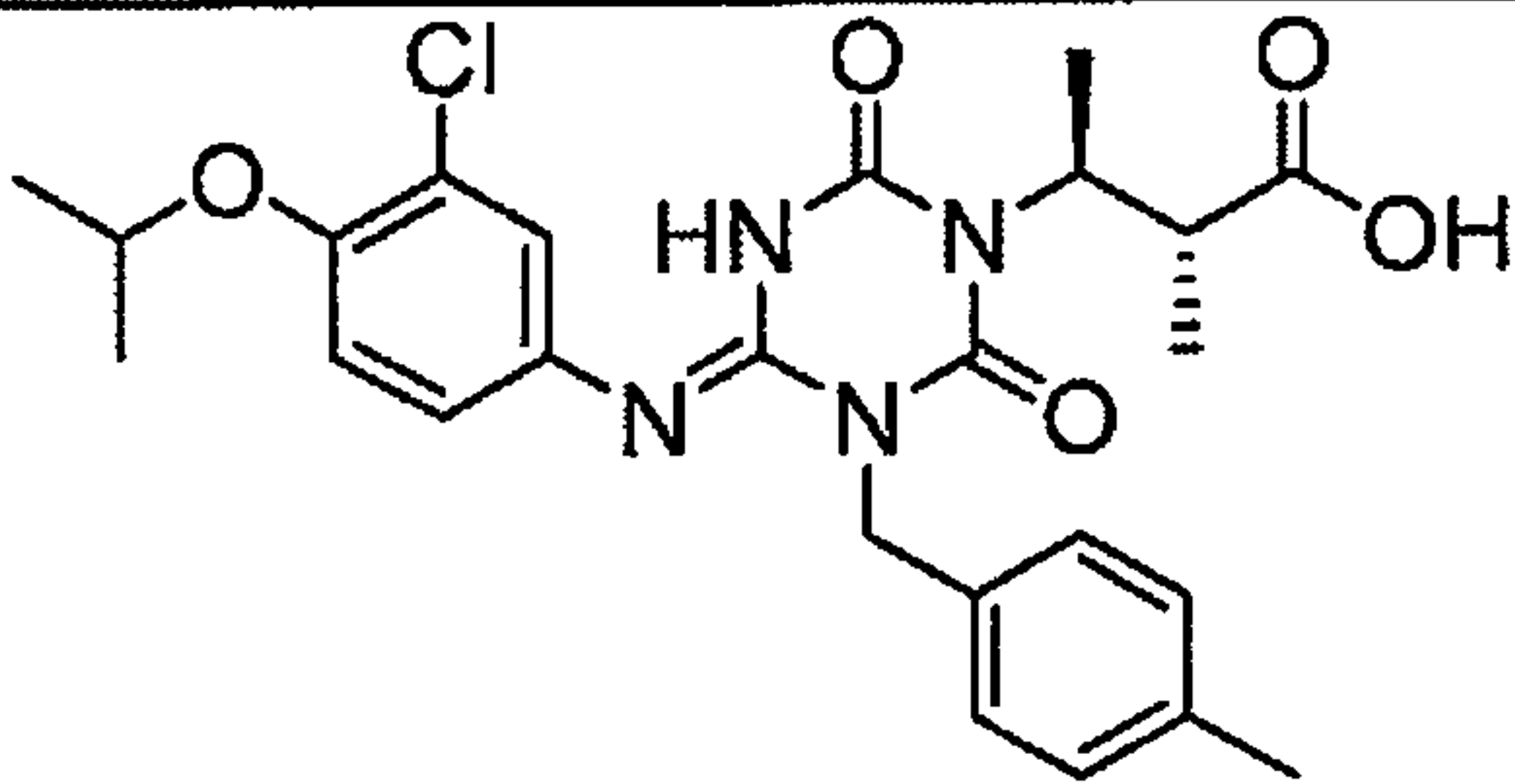
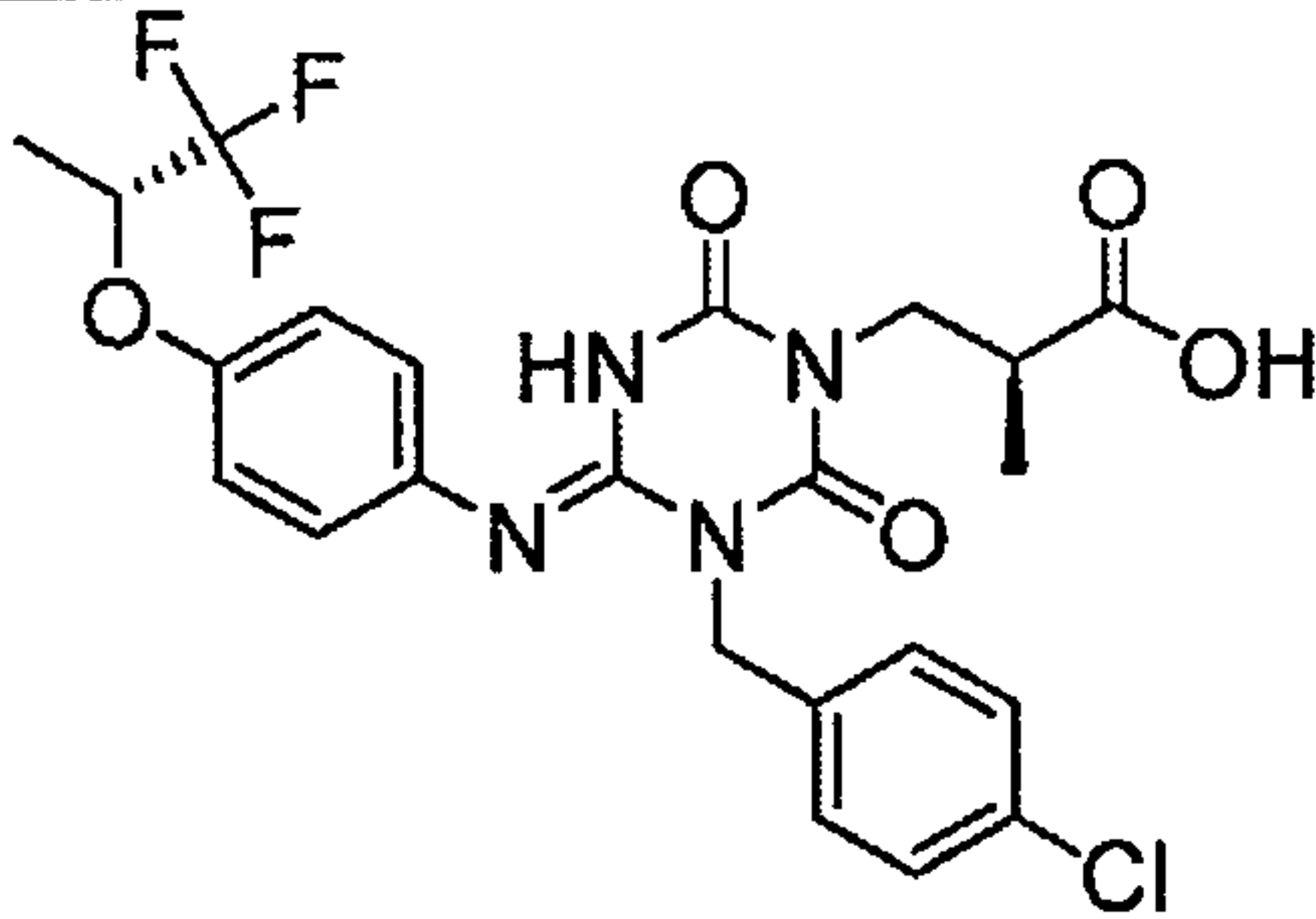
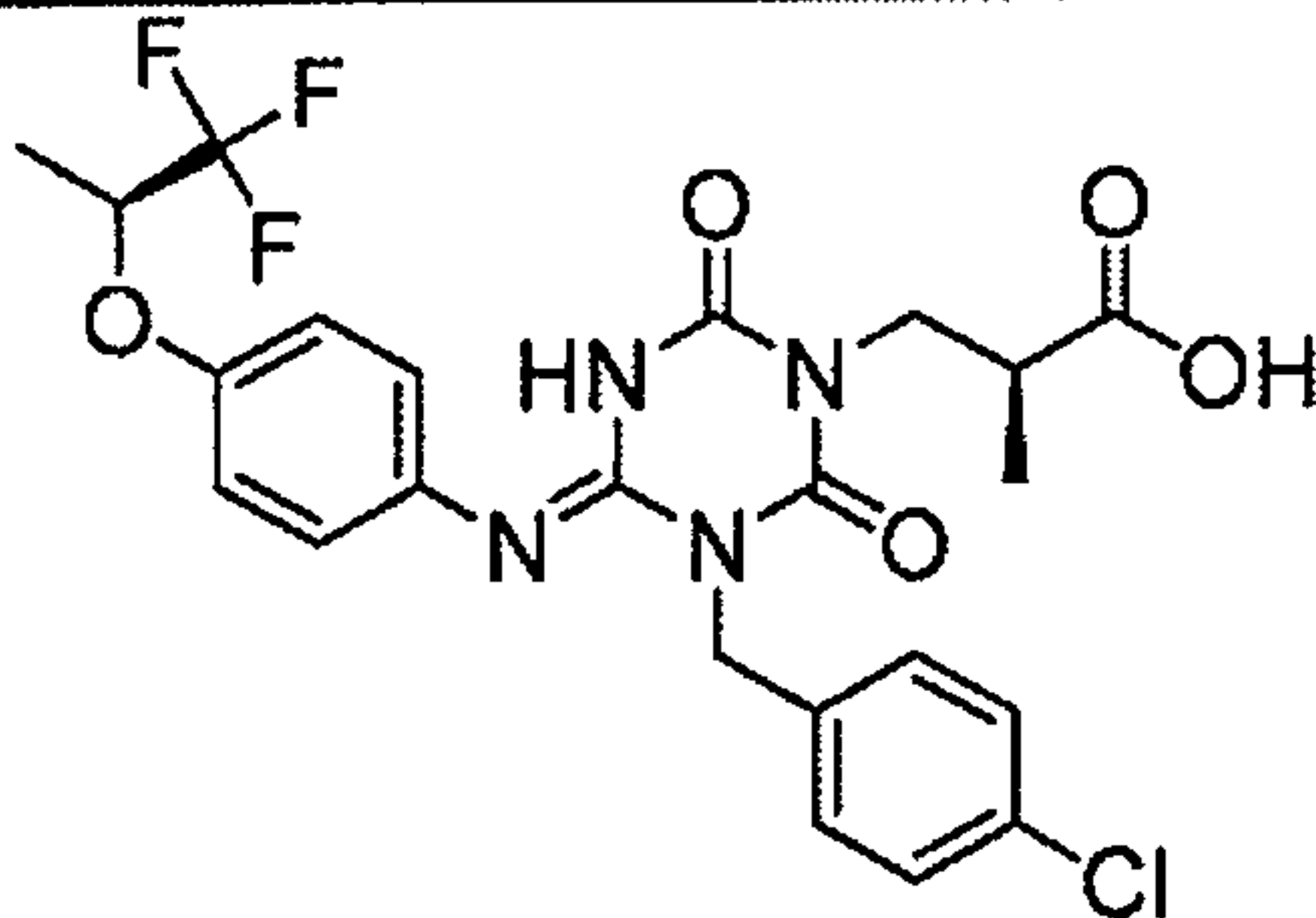
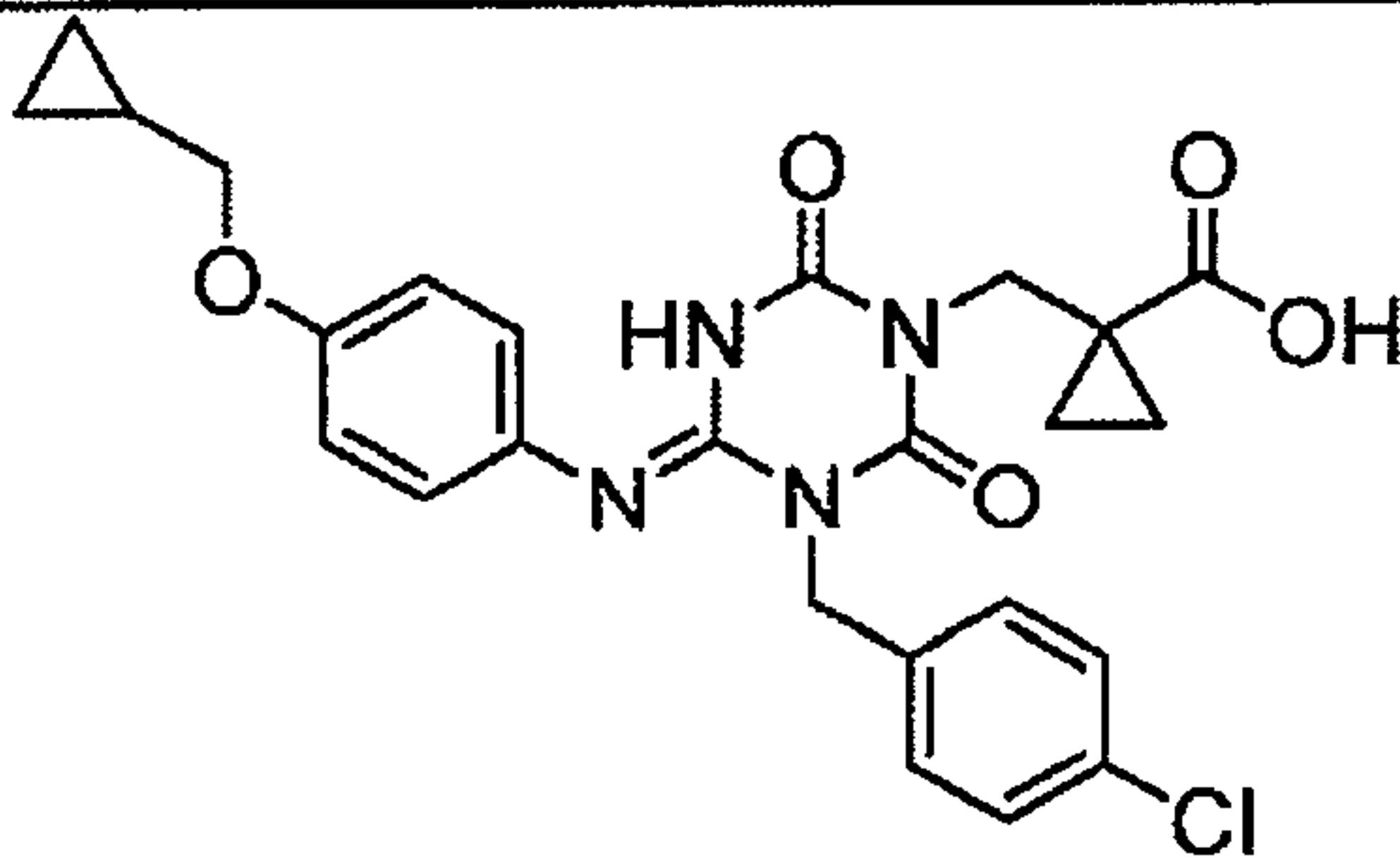
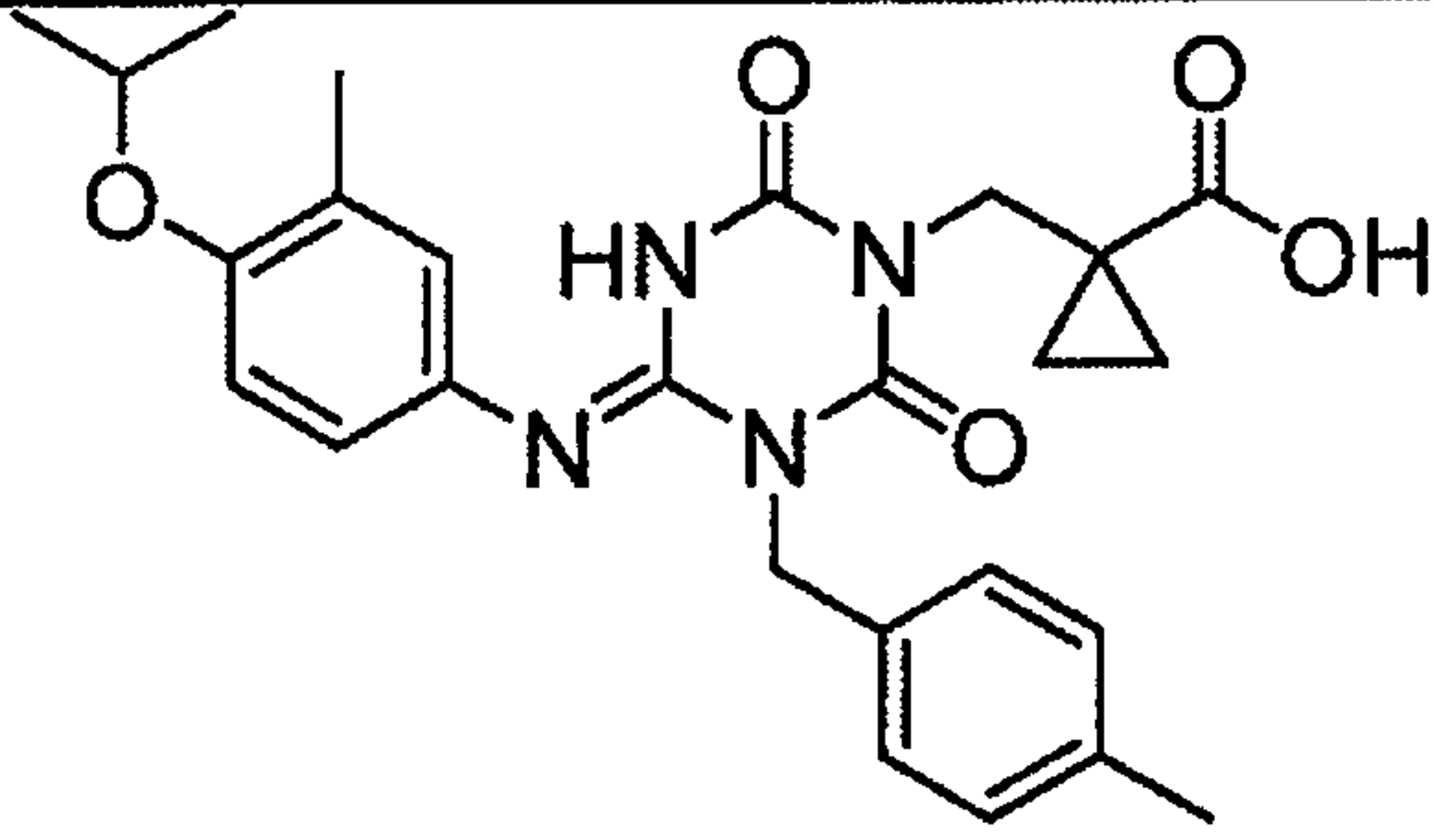
[Table 188]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0921	2.06	499	2
	I-0922	2.15	507	2
	I-0923	2.26	521	2
	I-0924	2.07	505	2
	I-0925	2.01	485	2

[Table 189]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0926	2.29	481	2
	I-0927	2.40	495	2
	I-0928	2.46	515	2
	I-0929	2.24	467	3
	I-0930	2.34	481	3

[Table 190]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0931	2.41	501	3
	I-0932	2.05	527	2
	I-0933	2.05	527	2
	I-0934	1.97	497	2
	I-0935	2.08	479	2

[Table 191]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0936	2.23	467	3
	I-0937	2.42	481	3
	I-0938	2.66	495	3
	I-0939	2.51	481	3
	I-0940	2.56	525	3

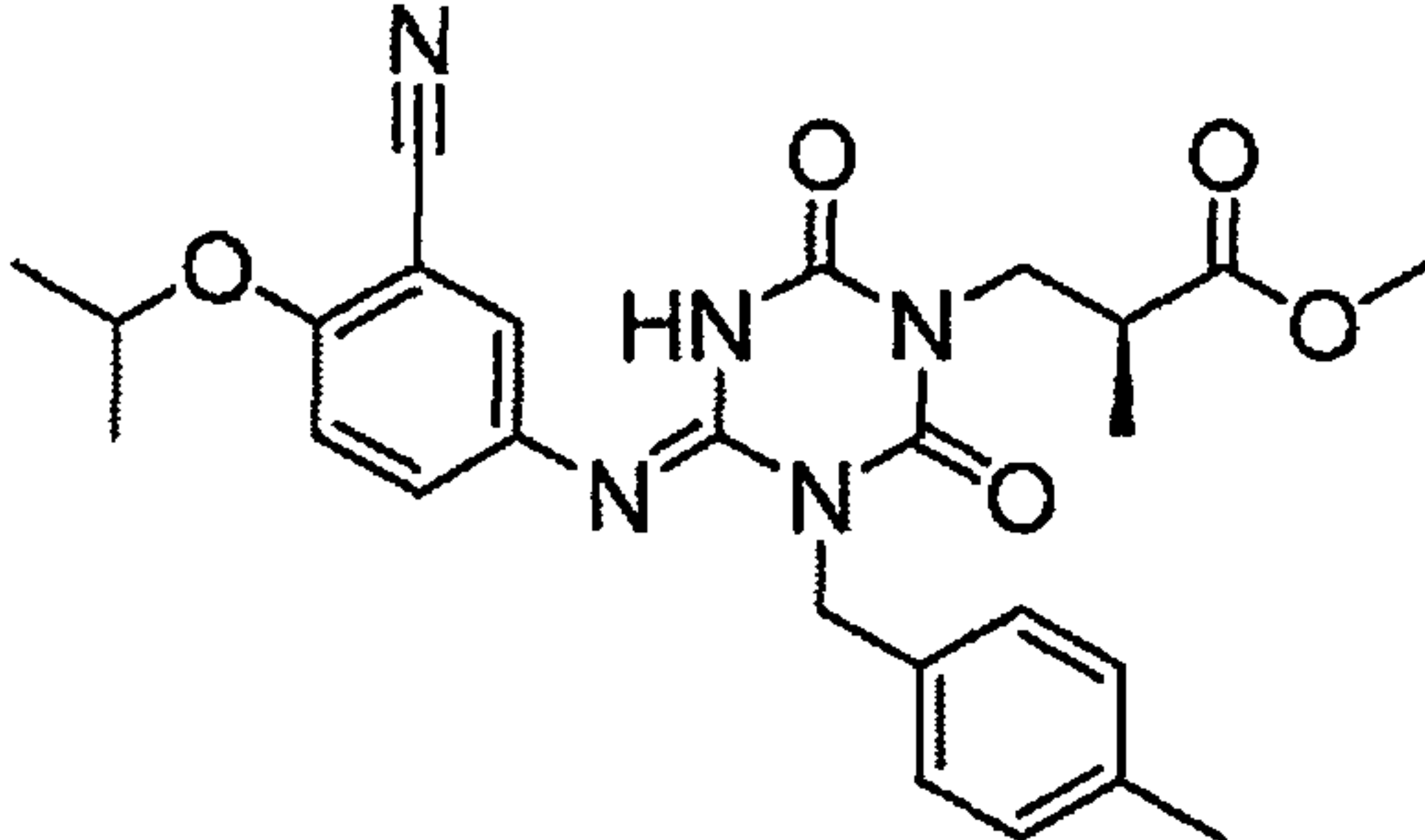
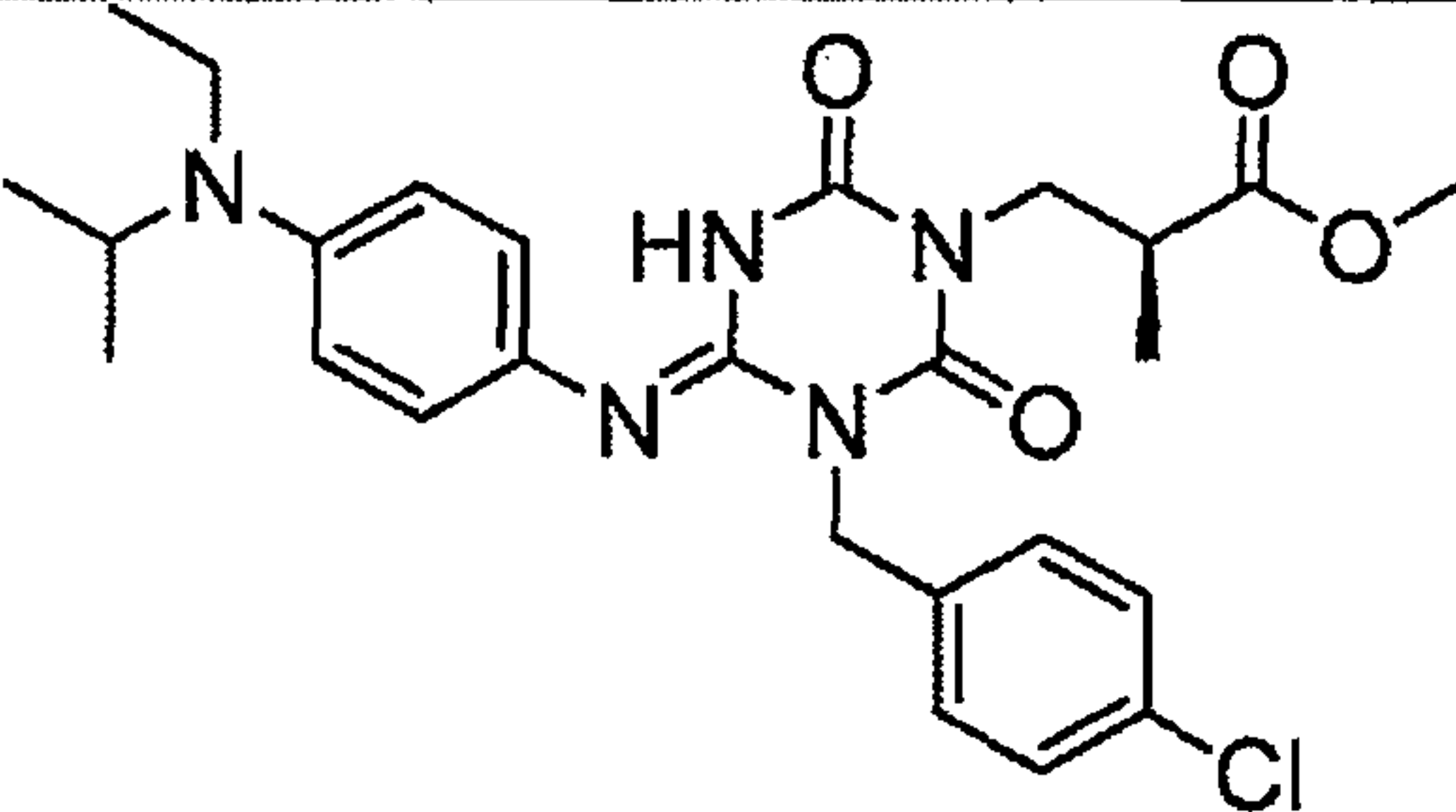
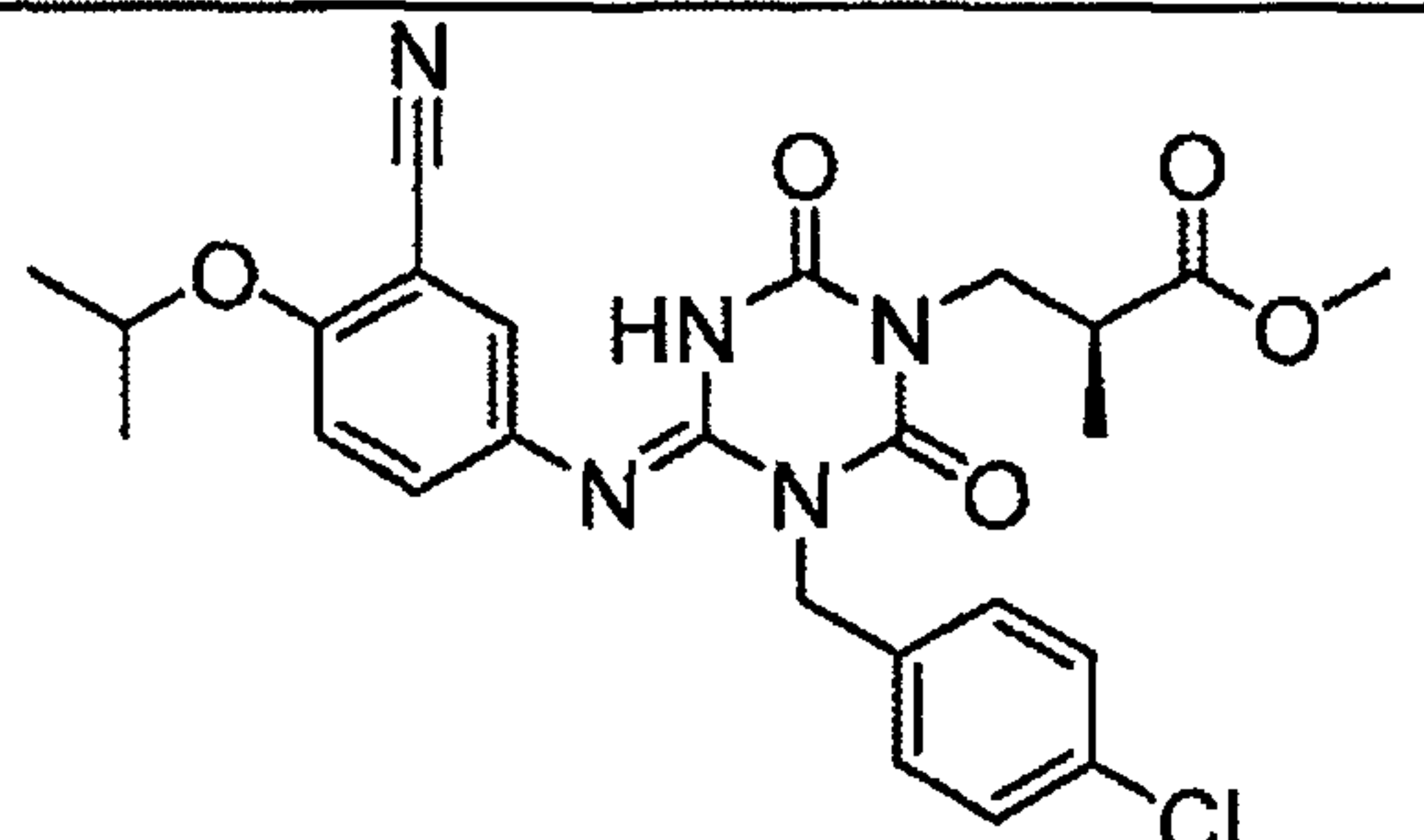
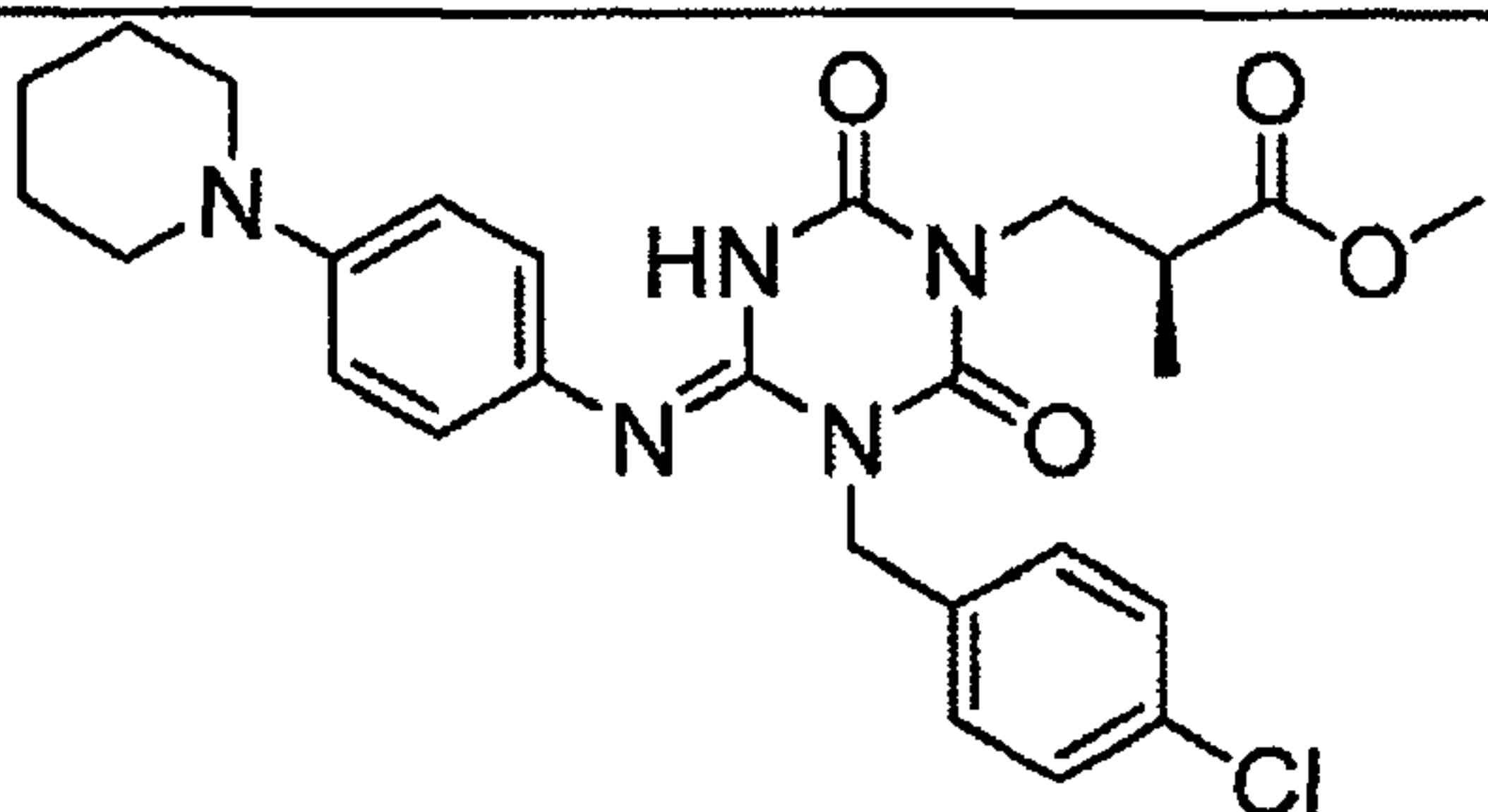
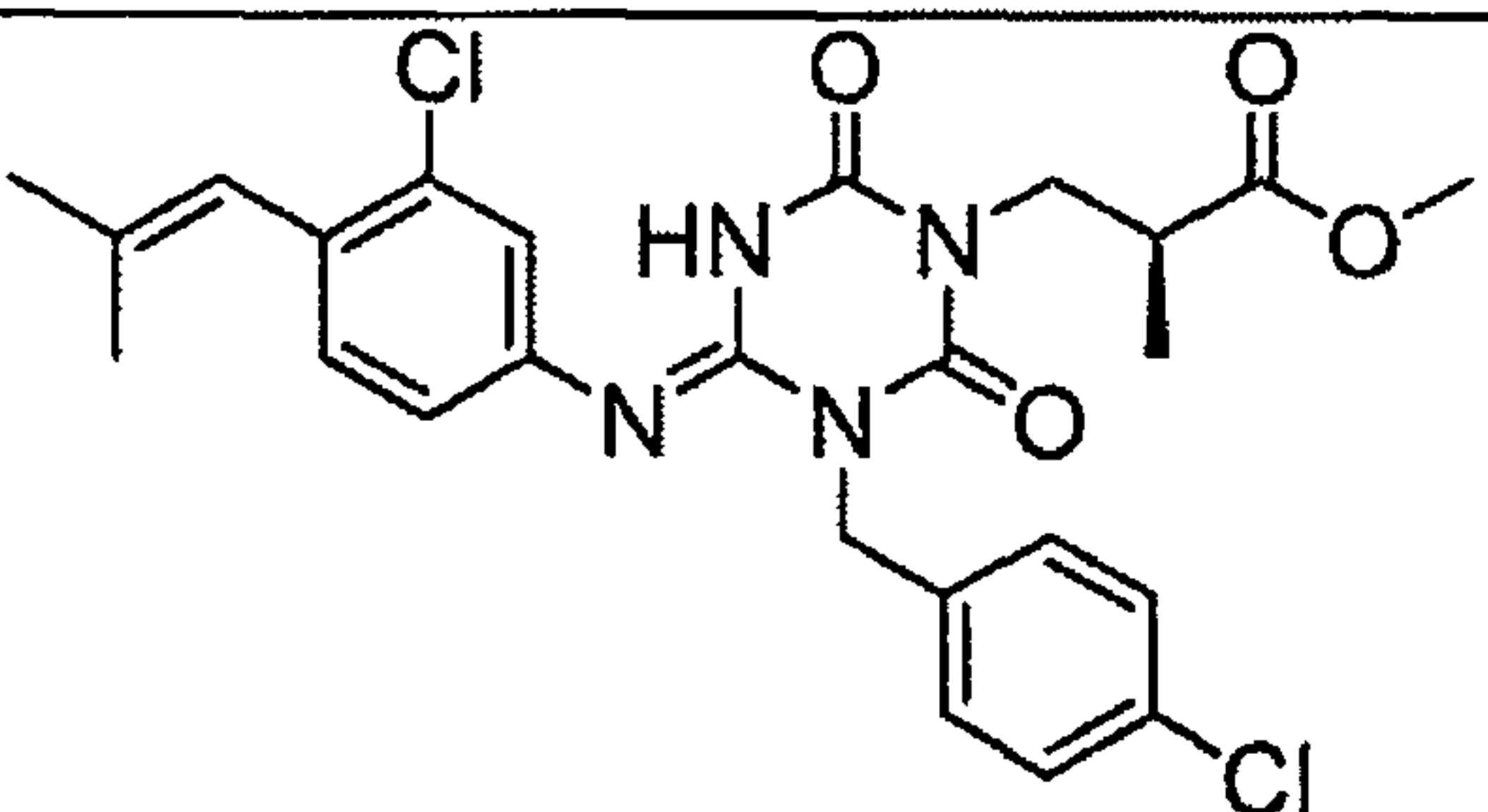
[Table 192]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0941	2.64	507	3
	I-0942	2.30	541	2
	I-0943	2.29	541	2
	I-0944	2.75	563	2
	I-0945	2.19	491	2

[Table 193]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0946	1.97	477	2
	I-0947	2.78	499	3
	I-0948	2.74	497	3
	I-0949	2.54	485	3
	I-0950	2.50	483	3

[Table 194]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0951	2.13	492	2
	I-0952	1.49	514	2
	I-0953	2.21	512	2
	I-0954	1.52	512	2
	I-0955	2.86	517	3

[Table 195]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0956	2.63	522	3
	I-0957	2.57	513	3
	I-0958	2.55	513	3
	I-0959	2.62	503	3
	I-0960	1.98	498	2

[Table 196]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0961	1.90	478	2
	I-0962	1.34	498	2
	I-0963	1.34	500	2
	I-0964	2.36	508	3
	I-0965	2.27	493	2

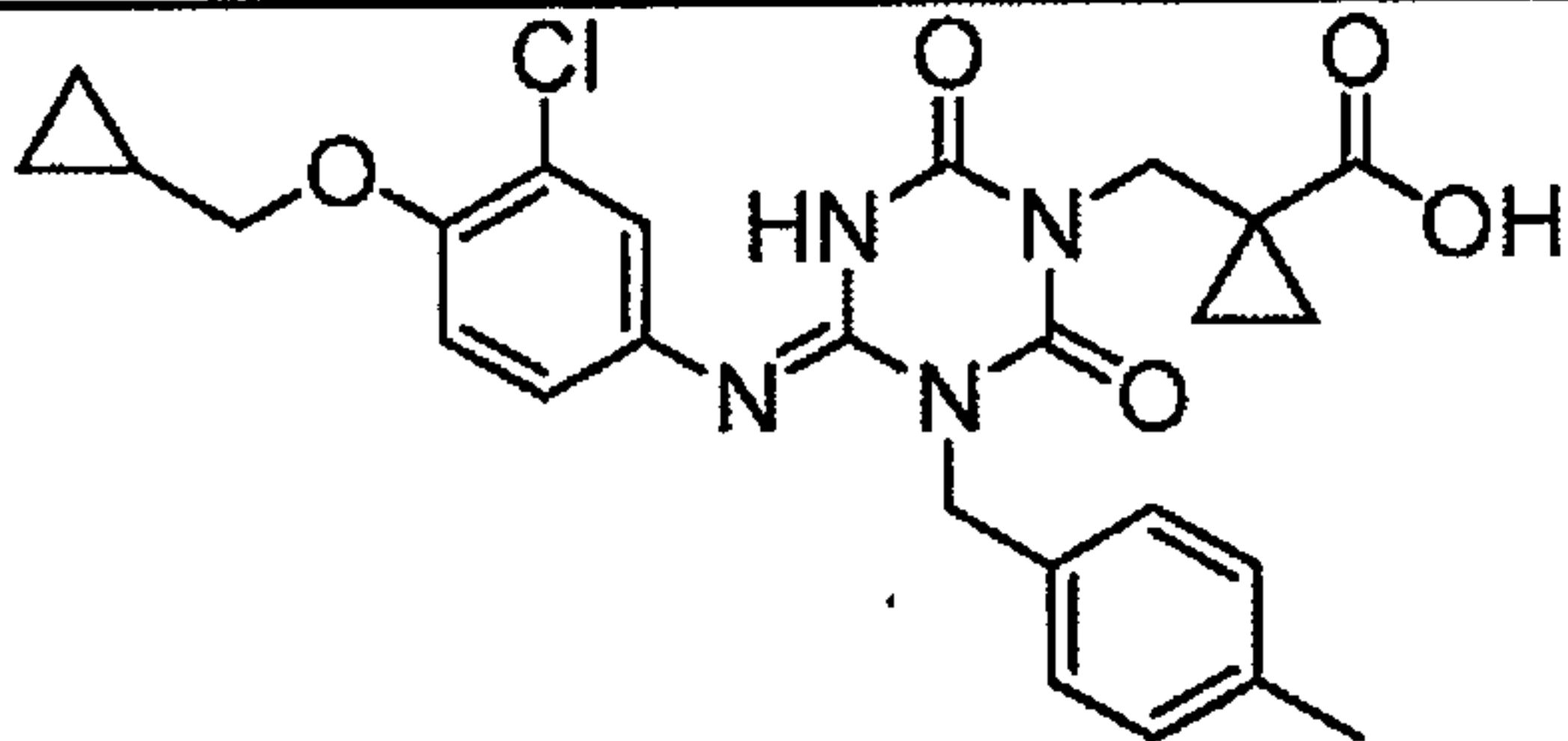
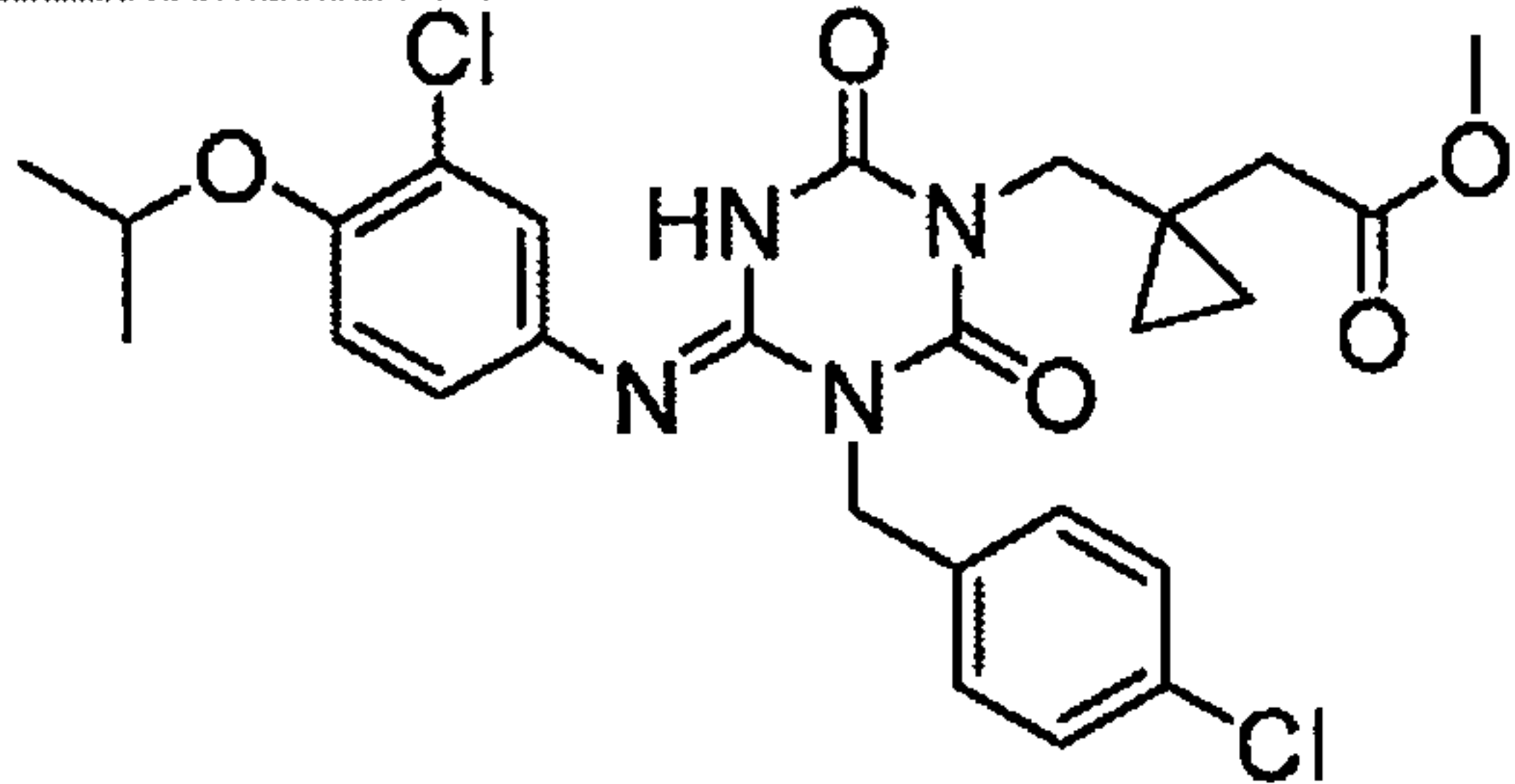
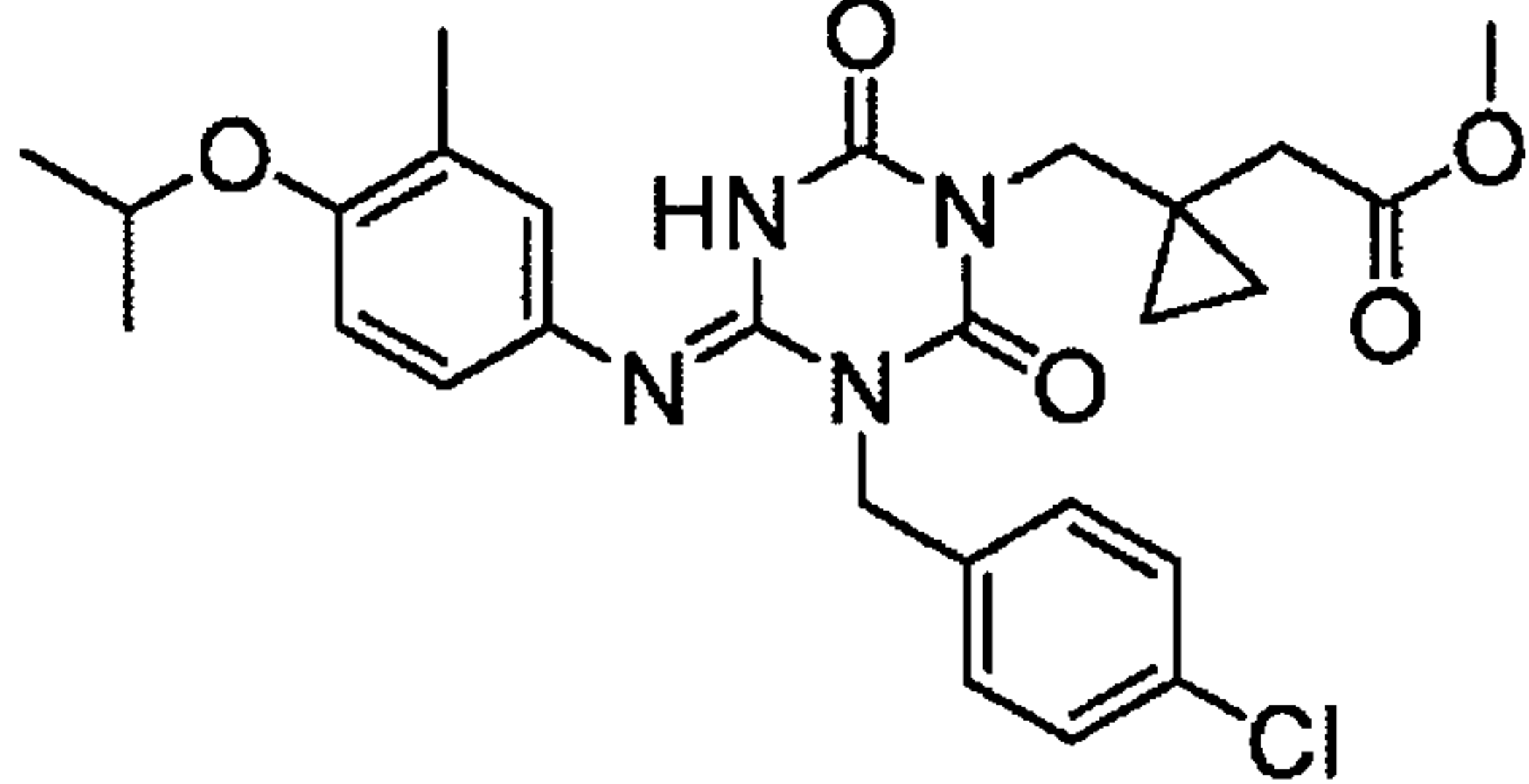
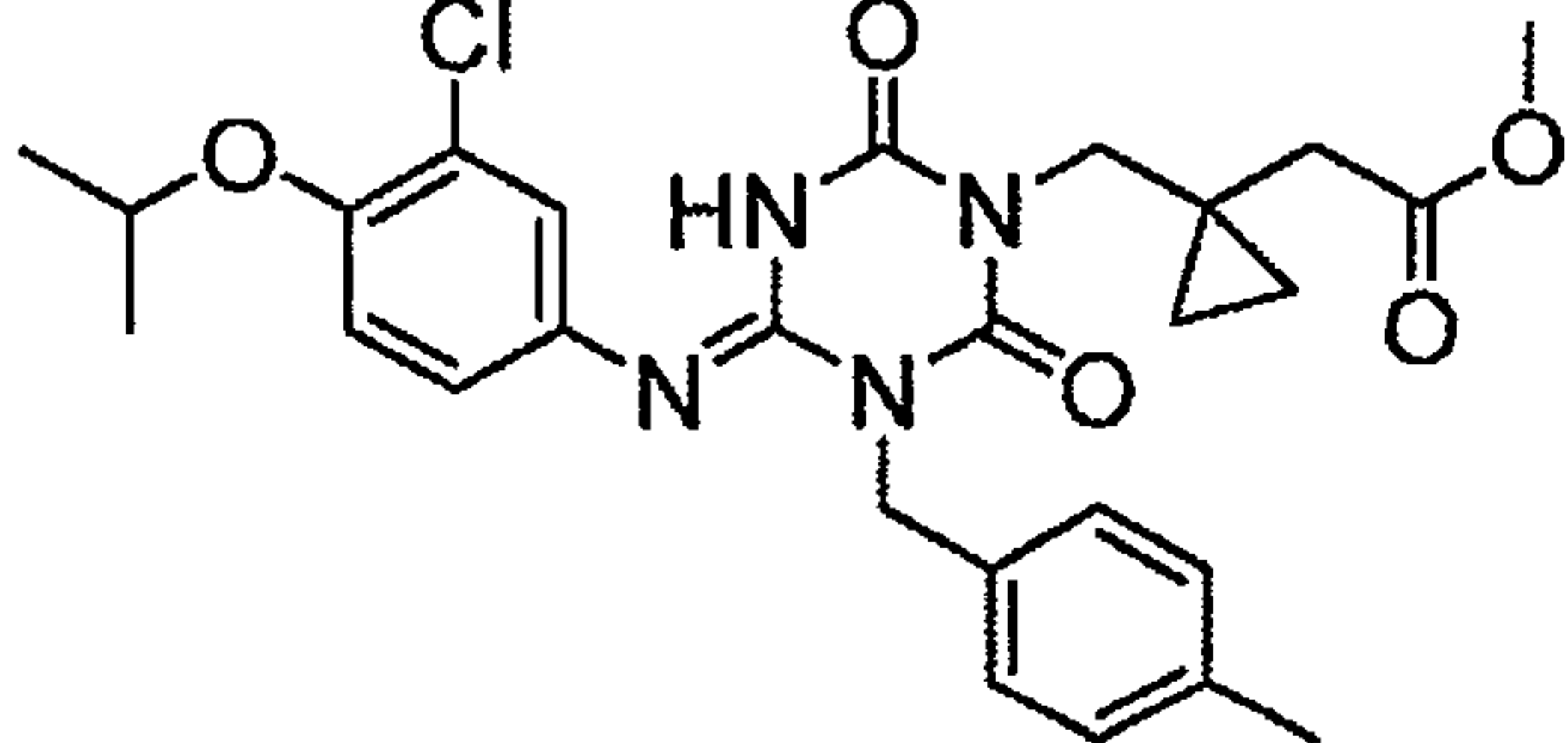
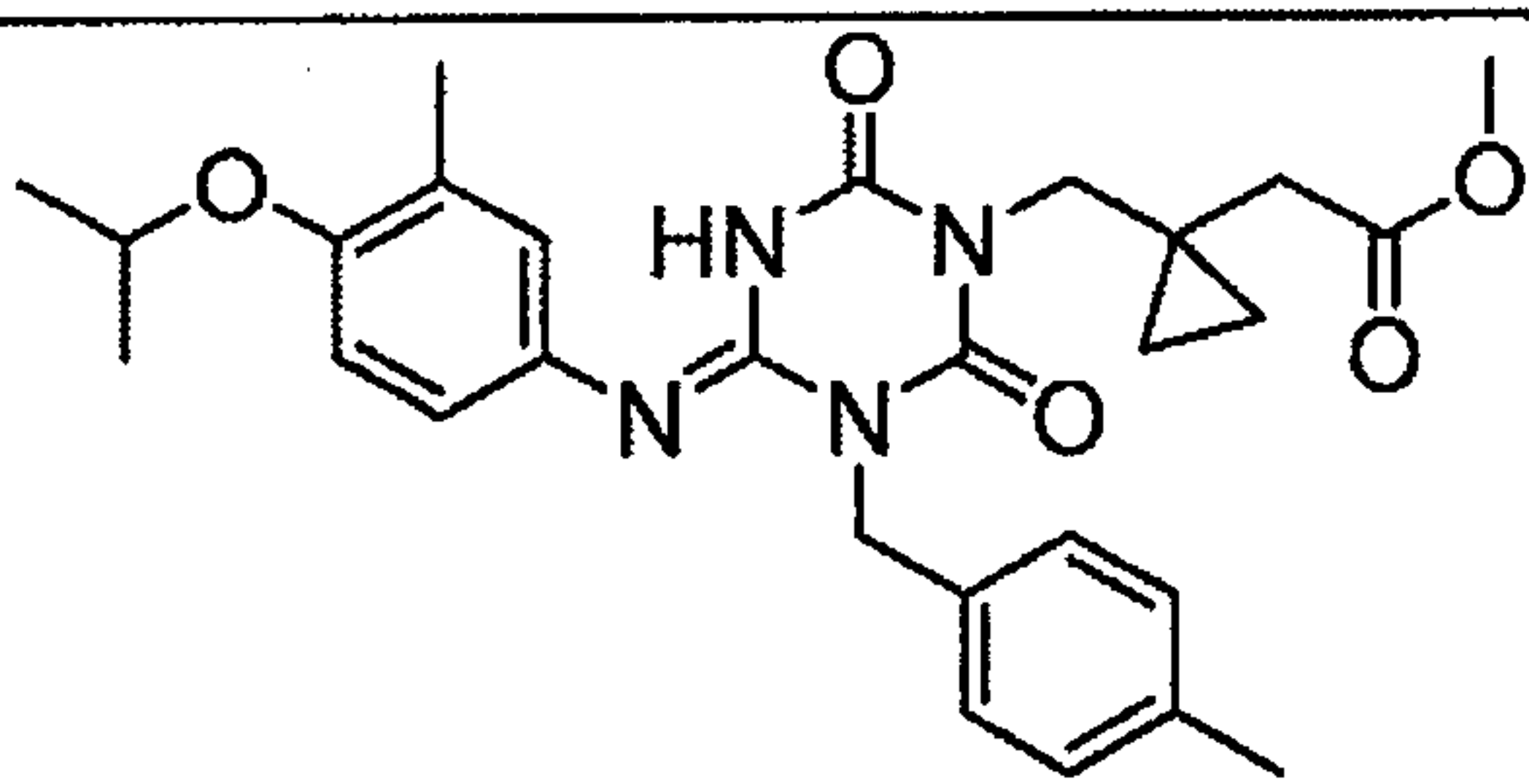
[Table 197]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0966	2.35	501	2
	I-0967	2.35	499	2
	I-0968	2.23	485	3
	I-0969	2.45	527	2
	I-0970	2.47	539	2

[Table 198]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0971	2.30	499	3
	I-0972	2.19	479	3
	I-0973	2.27	487	3
	I-0974	2.28	485	3
	I-0975	2.40	513	3

[Table 199]

Structure	Compound No.	Retention Time (min)	[M+H]	Method
	I-0976	2.34	511	3
	I-0977	2.52	547	2
	I-0978	2.43	527	2
	I-0979	2.43	527	2
	I-0980	2.37	507	2

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 386

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 386

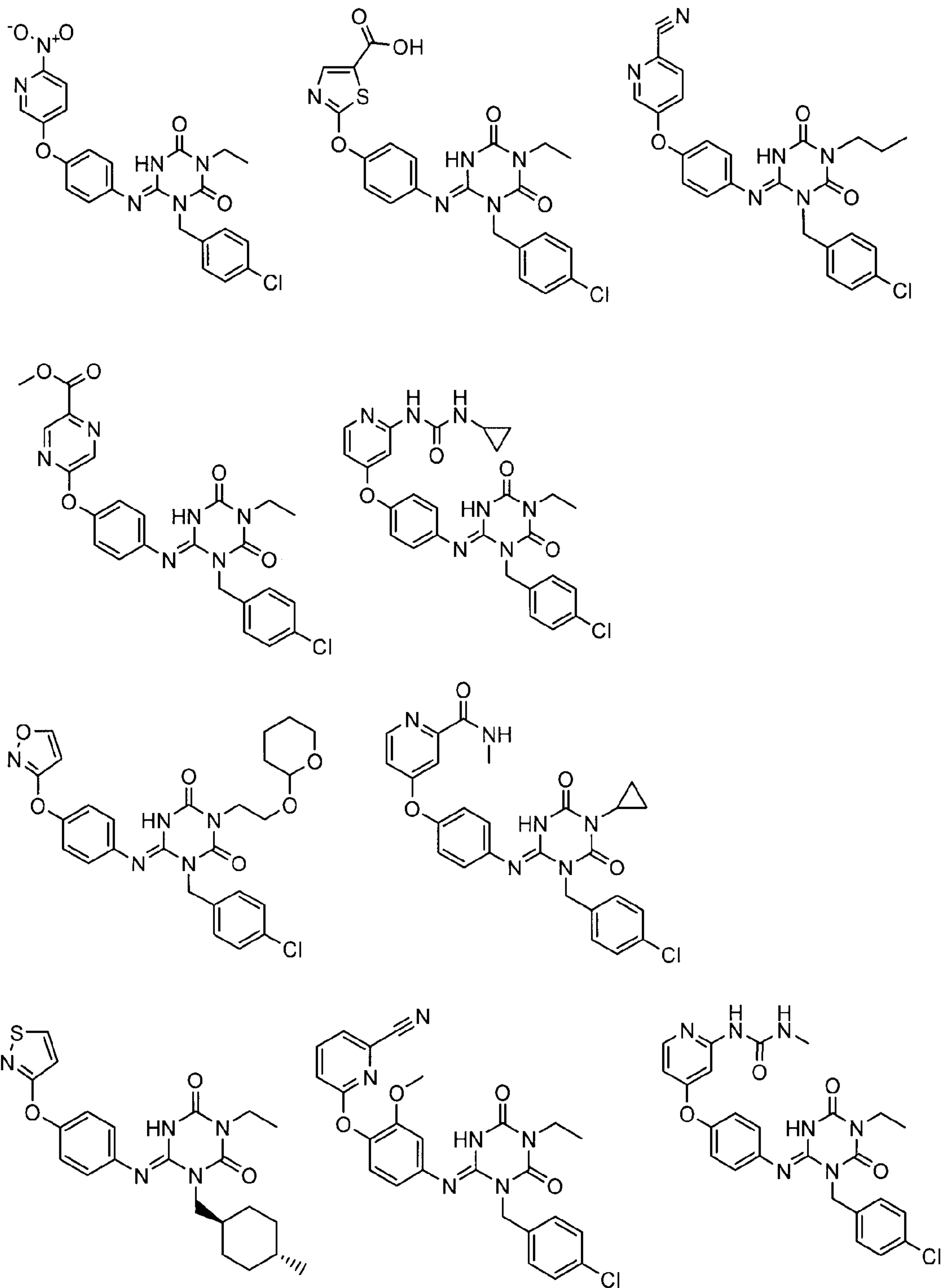
NOTE: For additional volumes, please contact the Canadian Patent Office

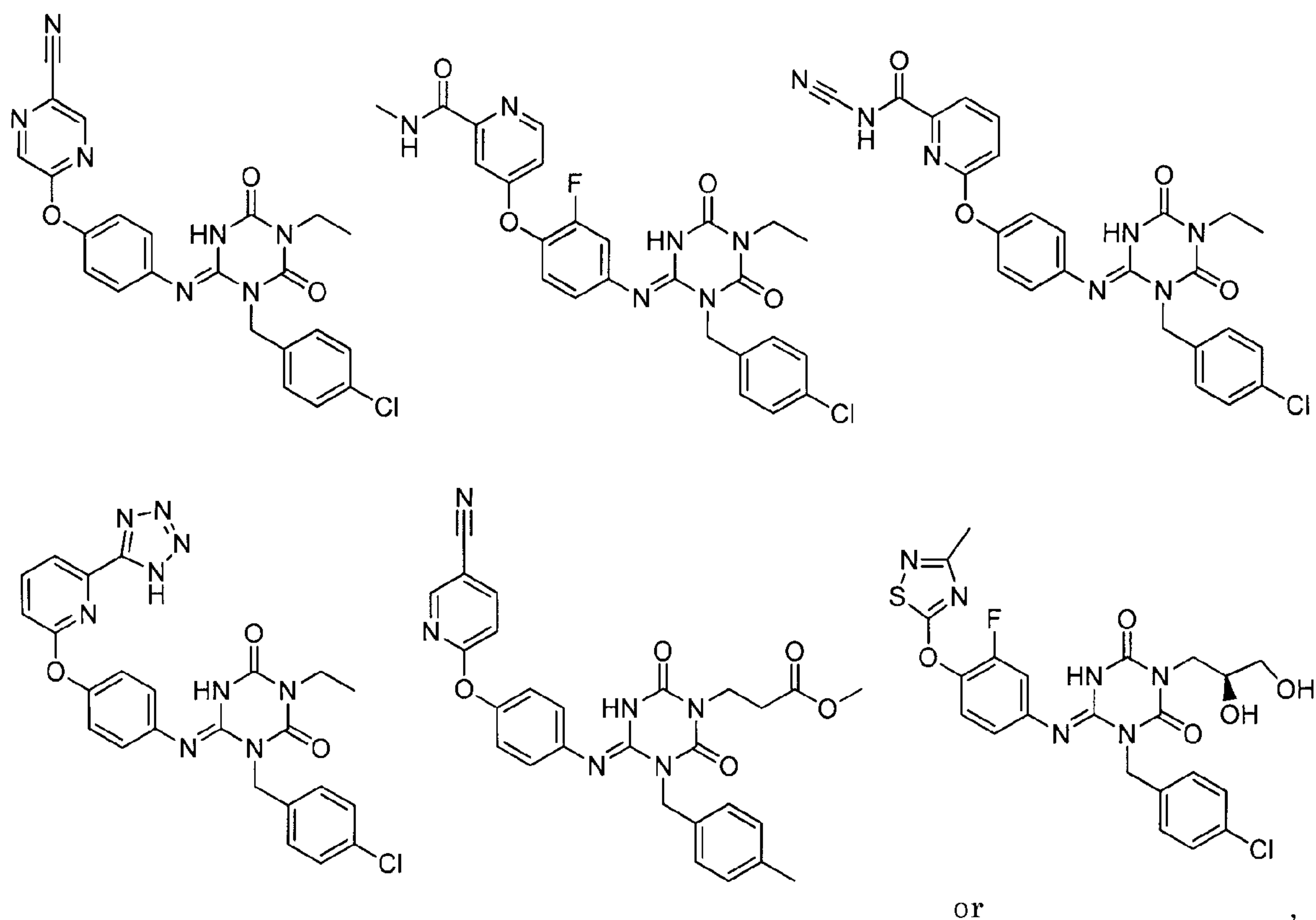
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CLAIMS

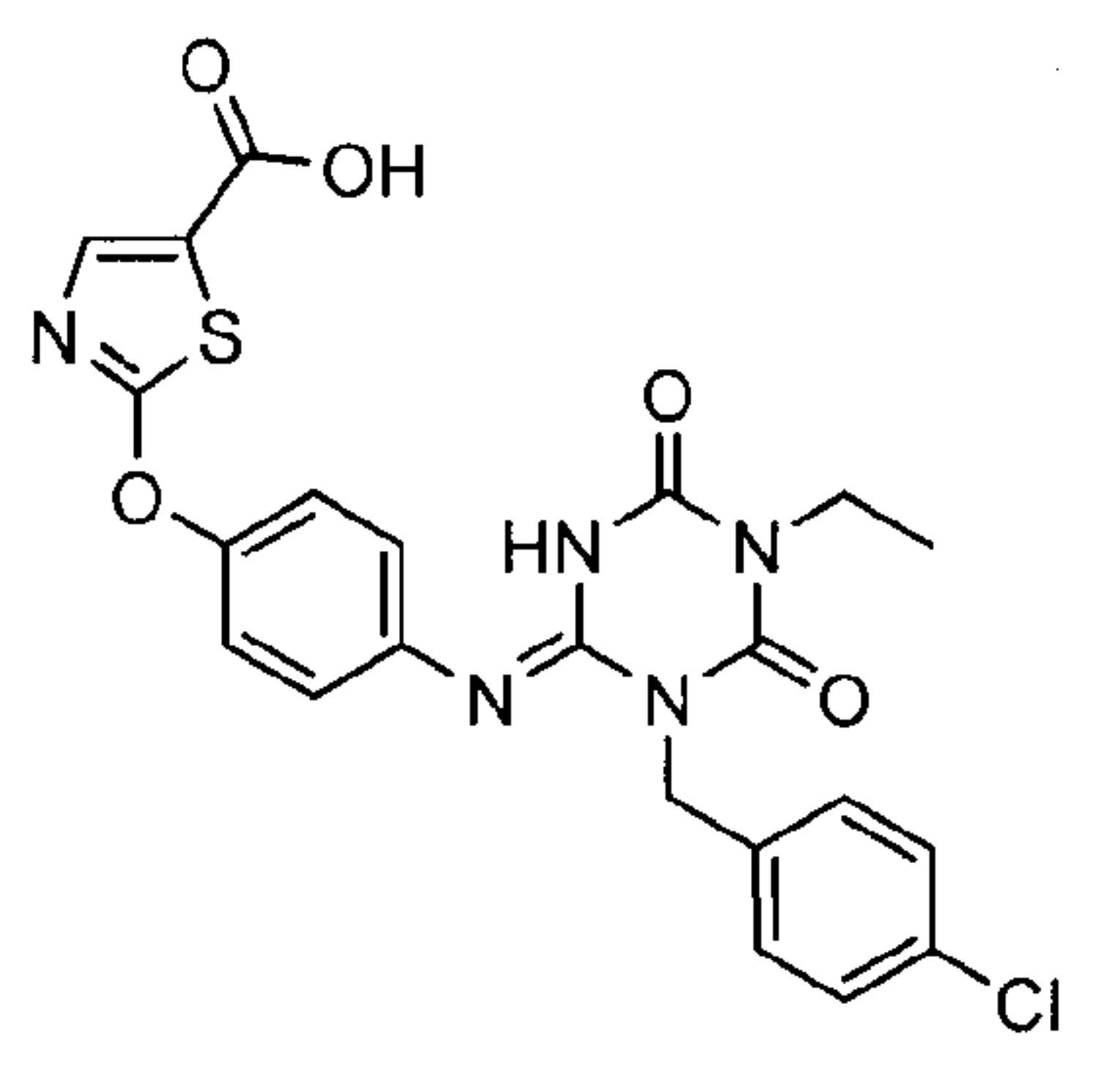
1. A compound of the formula:





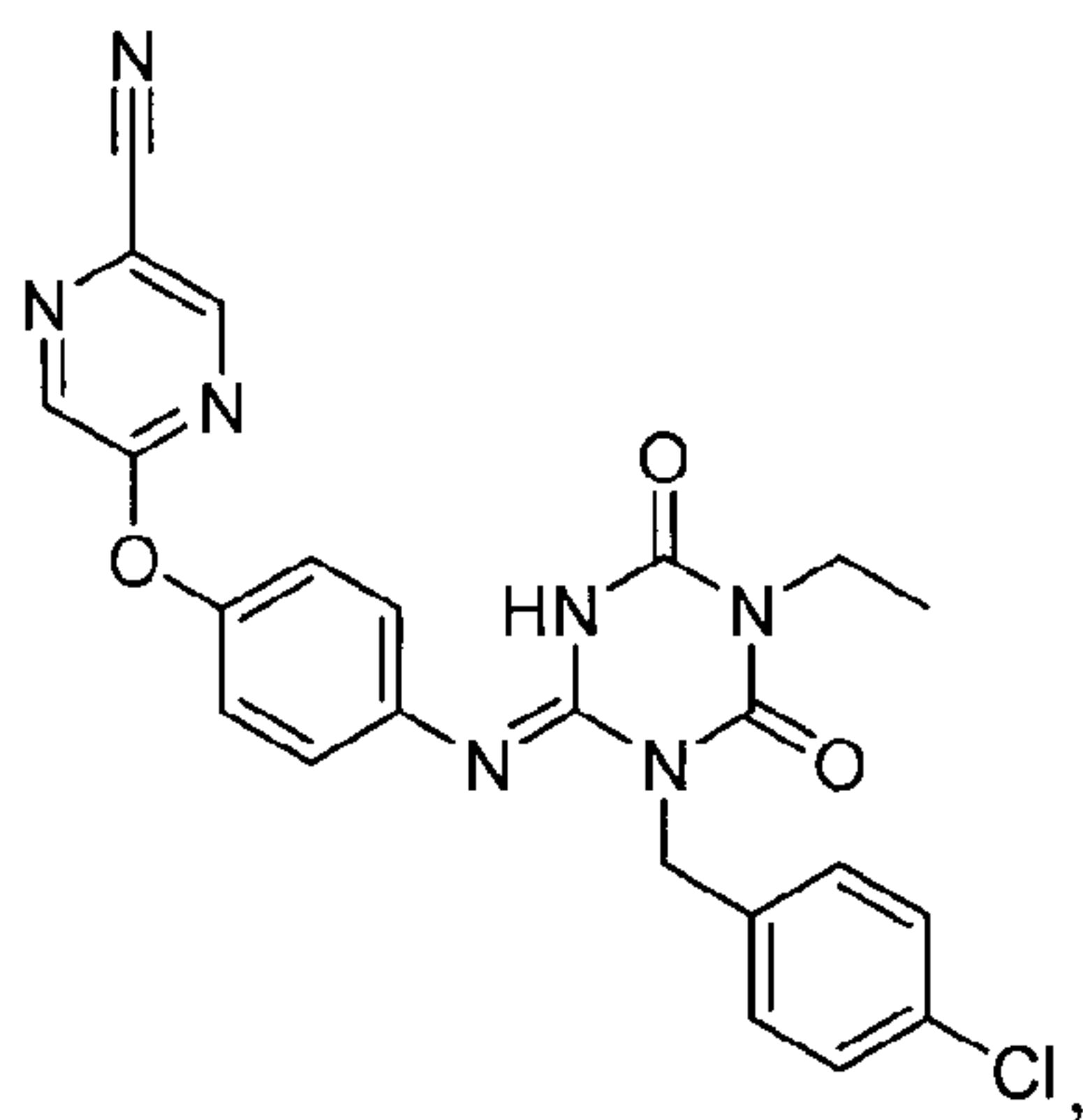
or a pharmaceutically-acceptable salt thereof.

2. The compound according to claim 1, which is:



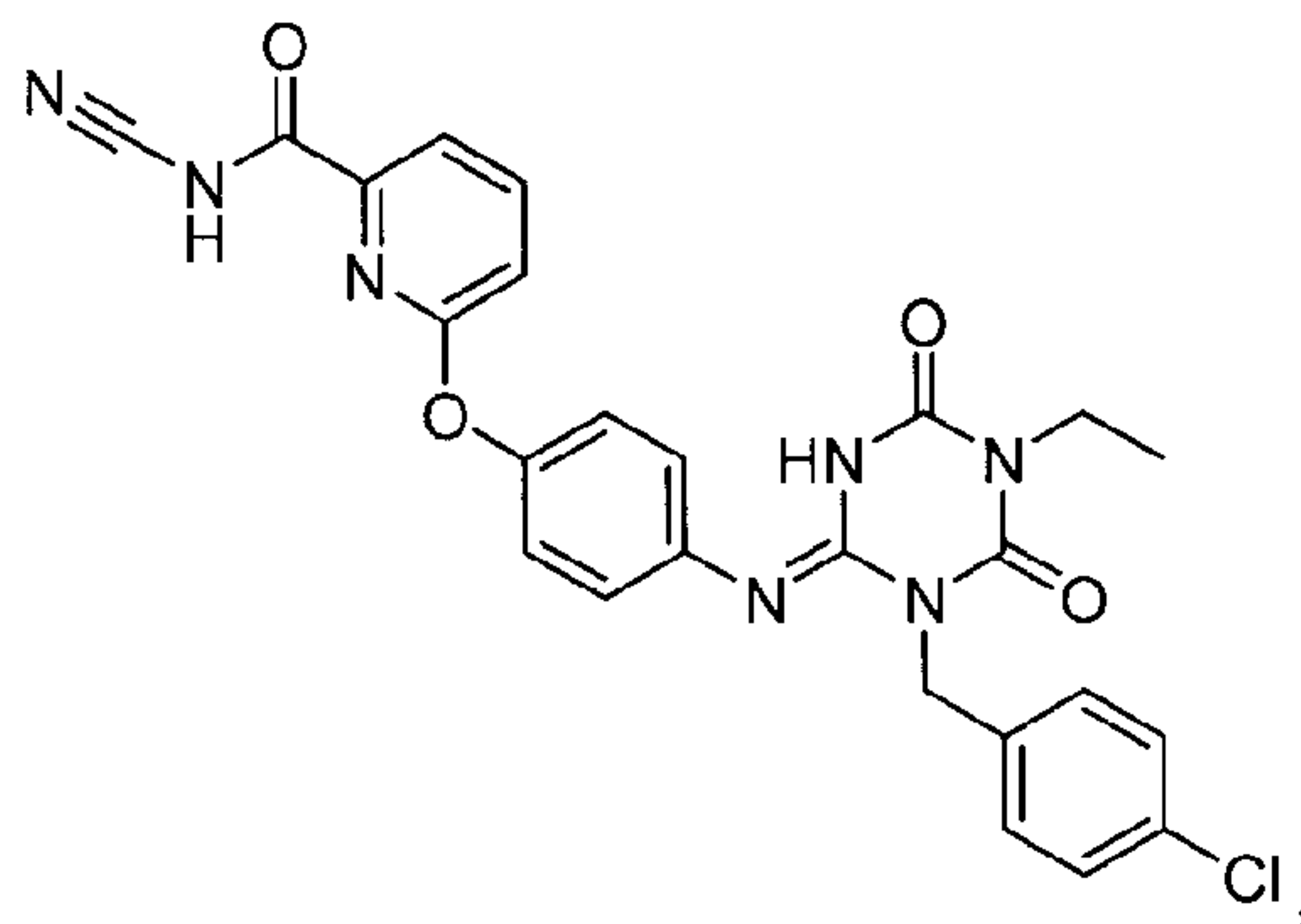
or the pharmaceutically-acceptable salt thereof.

3. The compound according to claim 1, which is:



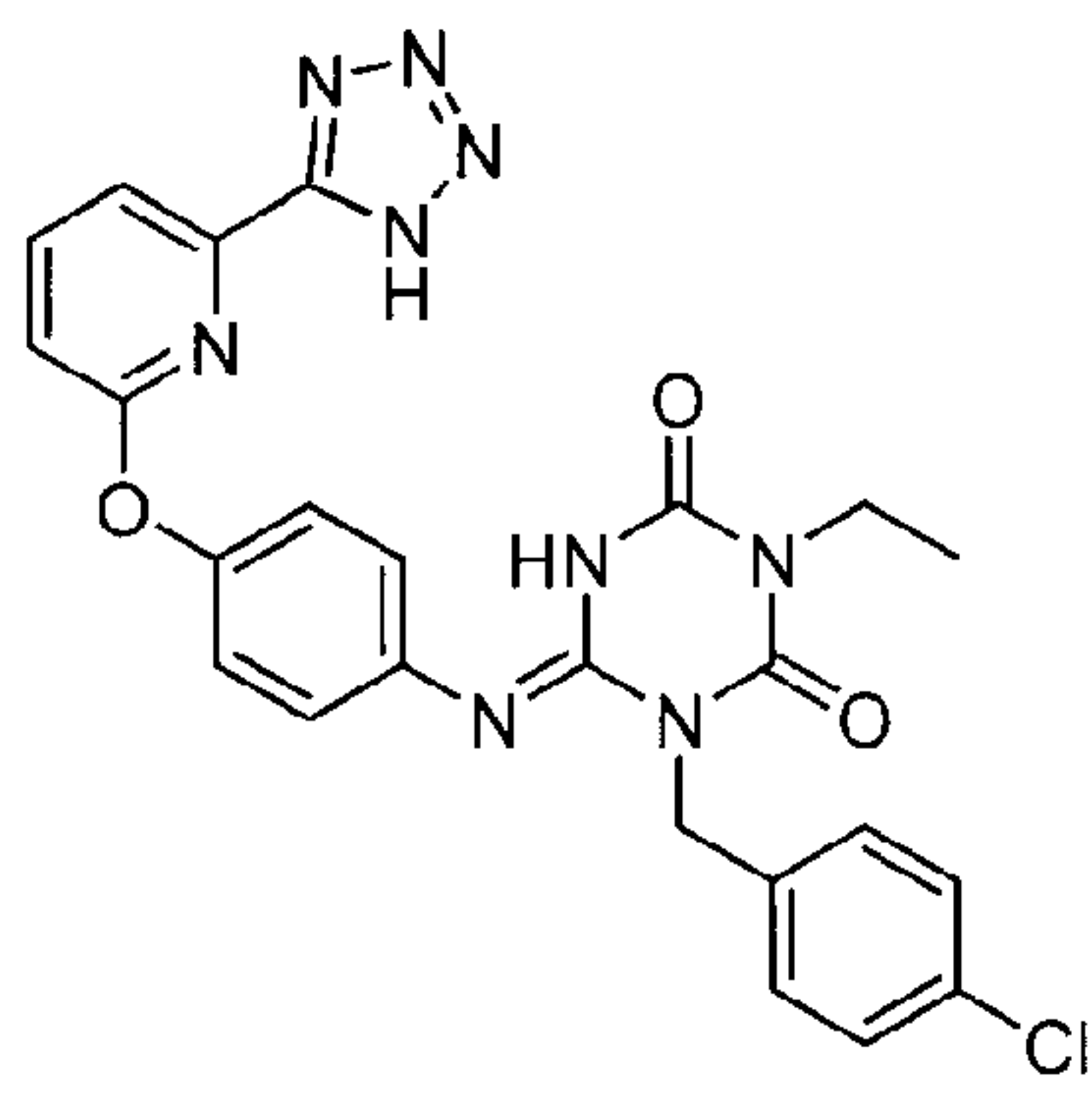
or the pharmaceutically-acceptable salt thereof.

4. The compound according to claim 1, which is:



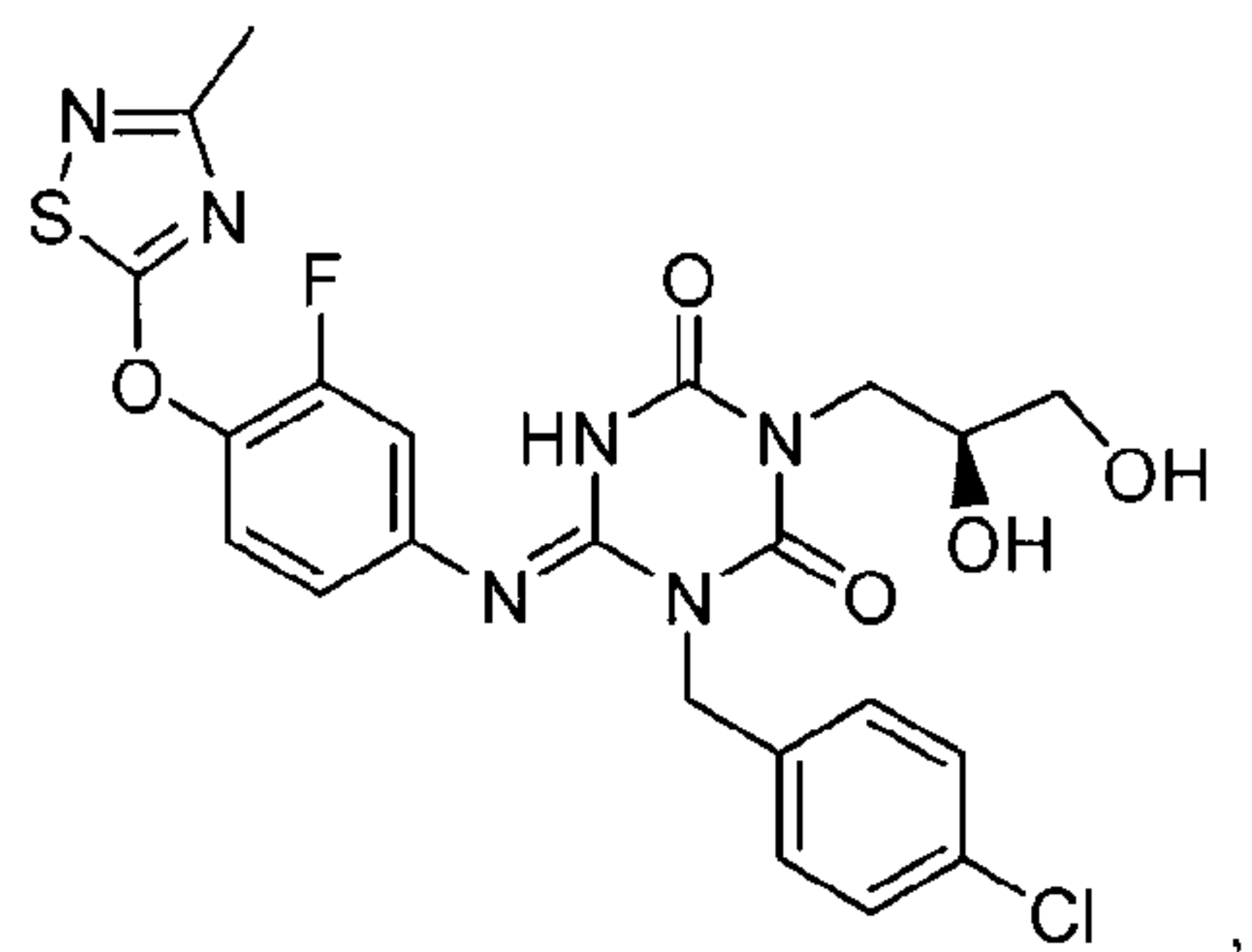
or the pharmaceutically-acceptable salt thereof.

5. The compound according to claim 1, which is:



or the pharmaceutically-acceptable salt thereof.

6. The compound according to claim 1, which is:



or the pharmaceutically-acceptable salt thereof.

7. A pharmaceutical composition comprising the compound according to any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof, and a pharmaceutical additive.

8. The pharmaceutical composition according to claim 7, wherein the composition has a P2X₃ and/or P2X_{2/3} receptor antagonistic effect.

9. A compound according to any one of claims 1 to 6, or the pharmaceutically-acceptable salt thereof, for use in treating and/or preventing a disease related to P2X₃ and/or P2X_{2/3} receptor.

