

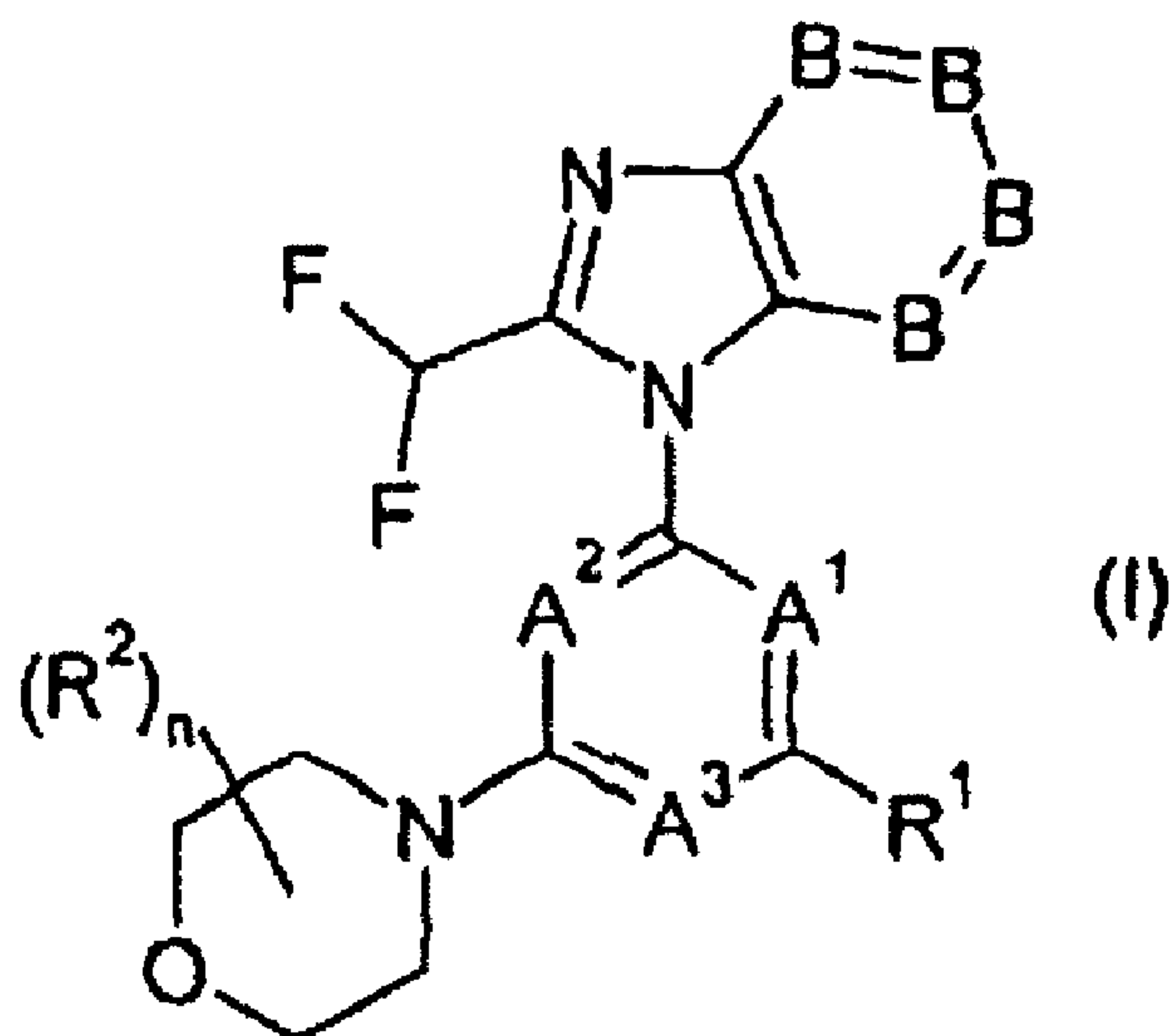


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(54) Titre : COMPOSE HETEROCYCLIQUE
(54) Title: HETEROCYCLIC COMPOUND



(57) Abrégé/Abstract:

[Problem]

A novel and excellent compound which is useful as an agent for preventing and/or treating rejection reactions in various ocean transplantations, allergy diseases, autoimmune diseases, and hematologic tumor. and based on a PI3K δ selective inhibitory action

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

and/or an IL-2 production inhibitory action and/or a B cell proliferation inhibitory action (including an activation inhibitory action),
[Means for Solution]

The present inventors have investigated a compound having a PI3K δ selective inhibitory action and/or an IL-2 production inhibitory action and/or a B cell proliferation inhibitory action (including an activation inhibitory action), and have found that the heterocyclic compound of the present invention has a PI3K δ selective inhibitory action and/or and IL-2 production inhibitory, action and/or a B cell proliferation inhibitory action (including an activation inhibitory action), thereby completing the present invention.

(see formula I)

Abstract

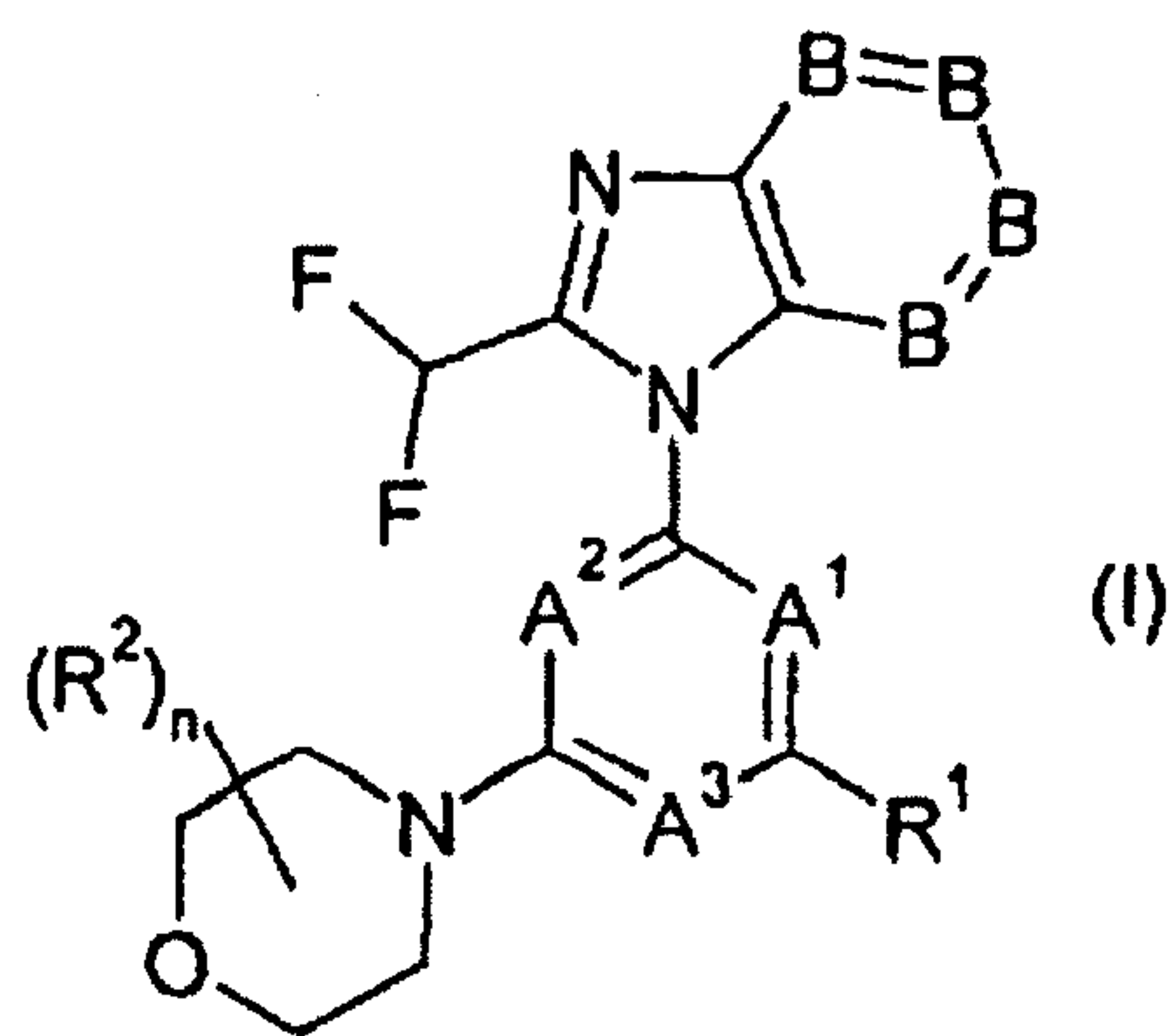
[Abstract]

[Problem]

A novel and excellent compound which is useful as an agent for preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor. and based on a PI3K δ selective inhibitory action and/or an IL-2 production inhibitory action and/or a B cell proliferation inhibitory action (including an activation inhibitory action),

[Means for Solution]

The present inventors have investigated a compound having a PI3K δ selective inhibitory action and/or an IL-2 production inhibitory action and/or a B cell proliferation inhibitory action (including an activation inhibitory action), and have found that the heterocyclic compound of the present invention has a PI3K δ selective inhibitory action and/or and IL-2 production inhibitory, action and/or a B cell proliferation inhibitory action (including an activation inhibitory action), thereby completing the present invention.



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JUMBO APPLICATIONS / PATENTS

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

THIS IS VOLUME __1__ OF __2__

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DESCRIPTION

Title of Invention: HETEROCYCLIC COMPOUND

5 Technical Field

[0001]

The present invention relates to a heterocyclic compound which is useful as an active ingredient of a pharmaceutical composition, for example, a pharmaceutical composition for preventing and/or treating phosphatidylinositol-3-kinase δ (PI3K δ)-related diseases.

10

Background Art

[0002]

Phosphatidylinositol-3-kinase (PI3K) is a lipid signaling kinase, which is present universally throughout species, ranging from plants or yeasts to mammals including humans.

15 PI3K is an enzyme for phosphorylating the hydroxyl group at the 3-position of phosphatidylinositol, phosphatidylinositol-4-phosphate, and phosphatidylinositol-4,5-diphosphate, which are cell membrane phospholipids, and from each of these substrates, phosphatidylinositol-3-phosphate, phosphatidylinositol-3,4-diphosphate, and phosphatidylinositol-3,4,5-triphosphate (PIP3) are produced. These phosphorylated
20 phosphatidylinositols thus produced act as an intracellular second messenger. Particularly, PIP3 causes migration of various molecules having pleckstrin homology (PH) domains to a position near the cell membrane to induce activation of the molecules, and thus it is considered to be the most important phosphorylated phosphatidylinositol ("The Journal of Biological Chemistry", 1999, Vol. 274, p. 8347-8350).

25 [0003]

PI3K is divided into three classes, Classes I, II, and III, according to various characteristics, and from the viewpoints that the only enzyme producing PIP3 in vivo is Class I PI3K, the Class I PI3K is considered to be the most important class ("Biochimica et Biophysica Acta", 2008, Vol. 1784, p. 159-185). The Class I PI3K is subdivided into IA and
30 IB. The Class IA PI3K consists of heterodimers including a combination of a 110-kDa catalytic subunit (p110 α , β , or δ) and a 50- to 85-kDa regulatory subunit (p85 α , p85 β , p55 α , p55 γ , or p50 α), and the Class IB PI3K is a heterodimer of a 110-kDa catalytic subunit (p110 γ) and a 101-kDa regulatory subunit (p101) ("Nature Immunology", 2003, No. 4, p. 313-319). Hereinafter, the respective names of PI3K are referred to as PI3K α , β , δ , and γ , corresponding
35 to catalytic subunits included therein.

[0004]

PI3K α and β are widely present in a biological body and deficiency of PI3K α and β in mice has been reported to be fetally lethal in both cases (“The Journal of Biological Chemistry”, 1999, Vol. 274, p. 10963-10968; and “Mammalian Genome”, 2002, Vol. 13, p. 169-172). As a result of studies using subtype selective compounds, it has been reported that PI3K α plays an important role in insulin signaling and a PI3K α inhibitor causes insulin resistance (“Cell”, 2006, Vol. 125, p. 733-747). Further, it has been reported that PI3K β is involved in platelet aggregation and a PI3K β inhibitor has an antithrombotic effect (“Nature Medicine”, 2005, Vol. 11, p. 507-514). On the other hand, mice deficient in PI3K δ or γ are all born normally, and no problems concerning growth, life span, reproduction, or the like have been found (“Science”, 2000, Vol. 287, p. 1040-1046; and “Molecular and Cellular Biology”, 2002, Vol. 22, p. 8580-8591). In particular, expression of PI3K δ is significantly limited to hemocytes and lymphoid tissues, and mice deficient in PI3K δ have been found to have significant damage in activation of lymphocytes. A close relationship between the activation of lymphocytes and immunity/inflammation is well known, and compounds selectively inhibiting PI3K δ have a potential to be immunity/inflammatory inhibitors having both a potent inhibitory action on the activation of lymphocytes and safety.

[0005]

Interleukin-2 (IL-2) is a kind of cytokine which is mainly produced from activated T cells. IL-2 induces proliferation and activation of lymphocytes via an IL-2 receptor which is a receptor for IL-2. IL-2 is a very important molecule in signaling the activation of an immune system, and its production inhibitors (for example, Tacrolimus and Cyclosporin A) have been used clinically as immunosuppressing agents. In addition, anti-IL-2 receptor monoclonal antibodies such as Basiliximab and Daclizumab have been used clinically as immunosuppressing agent.

[0006]

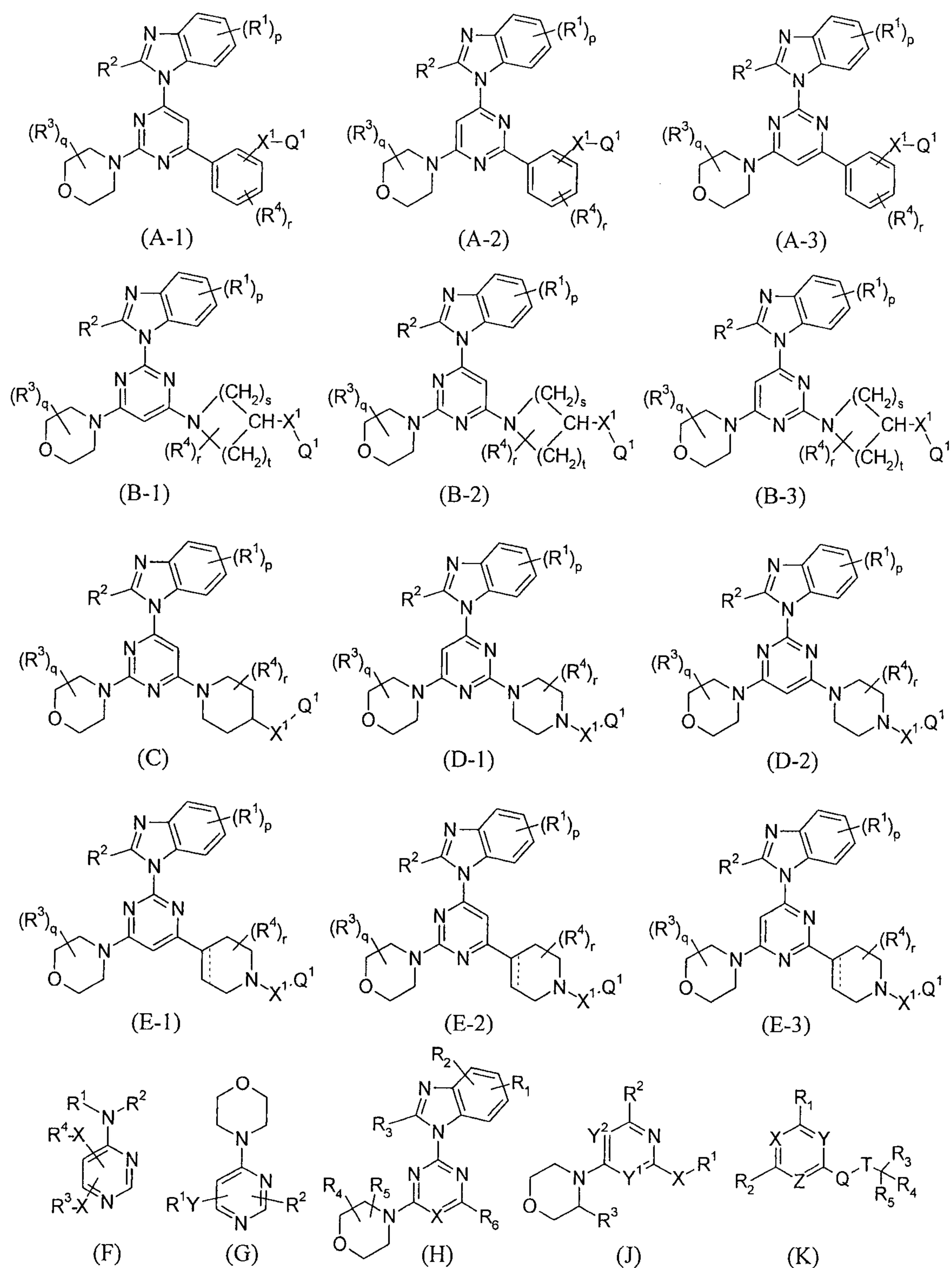
B cells are one of the main subsets of lymphocytes, along with T cells, and are cells which is a main actor of humoral immunity. It is known that humoral immunity plays an extremely important role in preventing infection from pathogens or the like, but in autoimmune diseases such as rheumatoid arthritis and the like, abnormal activation of humoral immunity occurs, which is deeply involved in the pathogenesis. In fact, an anti-CD20 antibody, Rituximab, has been used clinically as a drug for treating rheumatoid arthritis.

[0007]

As the compound having a PI3K inhibitory action, for example, the compounds of the formula (A-1) (Patent Document 1), the formula (A-2) (Patent Document 2), the formula (A-3) (Patent Document 3), the formula (B-1) (Patent Document 4), the formula (B-2) (Patent Document 5), the formula (B-3) (Patent Document 6), the formula (C) (Patent Document 7), the formula (D-1) (Patent Document 8), the formula (D-2) (Patent Document 9), the formula

(E-1) (Patent Document 10), the formula (E-2) (Patent Document 11), the formula (E-3) (Patent Document 12), the formula (F) (Patent Document 13), the formula (G) (Patent Document 14), the formula (H) (Patent Document 15 and Non-Patent Document 1), the formula (J) (Patent Document 16), and the formula (K) (Patent Document 17) described below have been reported. However, the compound of the formula (I) of the present application as described later is different in the structure of the group R^1 of the formula (I) from the compounds of the formulae (A-1) to (E-3), (H), and (K). It is different in structure from the compounds of the formulae (F) and (G), in that it has a benzimidazolyl-1-yl group. As the group R^2 of the formula (J), a heteroaryl group has been disclosed, but there is no specific disclosure of the benzimidazolyl-1-yl group, and there is no disclosure of the compound of the formula (I) of the present invention in Patent Document 16. Further, there is no description of a PI3K δ selective inhibitory action in any documents.

[Chem. 1]



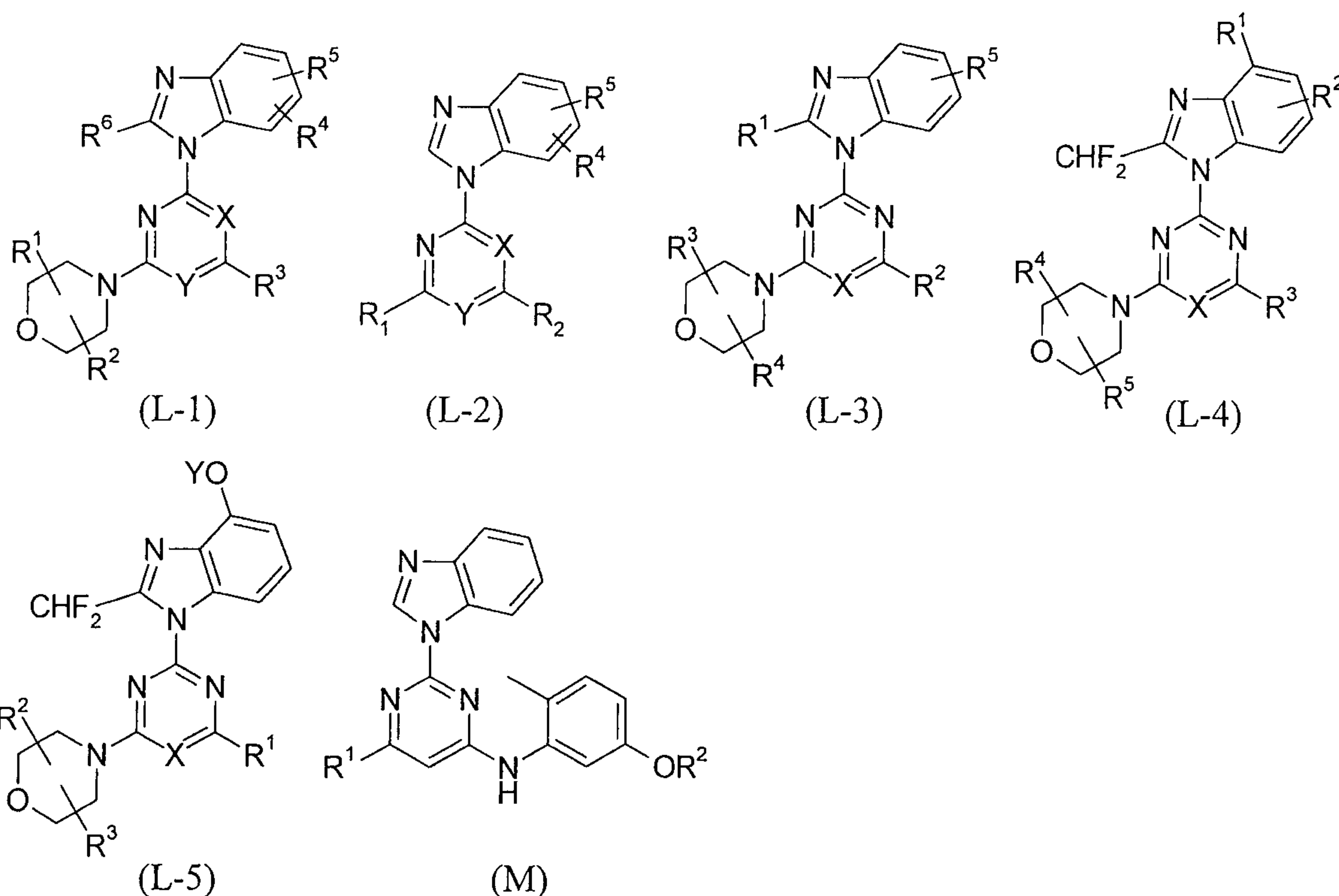
5 (wherein R^2 in the formulae (A-1) to (E-3) represents a difluoromethyl group or the like. R^1 and R^2 in the formula (F) are combined with each other to form an unsubstituted or

substituted morpholino group, together with N to which they are bonded, X represents a bond or the like, and R^3 represents an unsubstituted or substituted indolyl group. R^2 in the formula (G) represents a substituted indol-4-yl group at the position 5 or 6. R^3 in the formula (H) represents a difluoromethyl group or the like, and R^6 represents a morpholino group which
 5 may be substituted, or the like. In the formula (J), Y^1 and Y^2 represent N, CH, or the like, X represents $NR^4CR^6R^7$ or the like, R^1 represents a heterocyclic group or the like, and R^2 represents a heteroaryl group or the like. In the formula (K), X, Y, and Z represent N or CH, provided that at least two of X, Y, and Z represent N, R^1 represents heteroaryl or the like, R^2 represents a heterocycle or the like, Q represents a bond, azetidinylen-4-amino, or the like, T
 10 represents $-C(O)-$, $-C(=S)-$, or $-S(O)_2-$, and R^5 represents halogen or $-O-S(O)_2-R^7$. For the other symbols, reference may be made to the publication.)

[0008]

It has been reported that the compounds of the formula (L-1) (Patent Document 18), the formula (L-2) (Patent Document 19), the formula (L-3) (Patent Document 20), the formula
 15 (L-4) (Patent Document 21), and the formula (L-5) (Patent Document 22) described below have an anti-tumor activity. Further, in Non-Patent Document 2, it has been suggested that a secondary amine compound of the formula (M) has an Lck inhibitory action and an IL-2 production inhibitory action, and is applied for autoimmune diseases and rejection reaction in organ transplantation. However, the compound of the formula (I) of the present invention
 20 essentially has a difluoromethyl group, which is different in the structure from the compounds of the formulae (L-1), (L-2), and (M). It is also different in the structure of the group of R^1 of the formula (I) from the compounds of the formulae (L-3) and (L-5). In addition, it is different in the structure of the substituent on a benzimidazole ring from the compound of the formulae (L-4). Further, there is no description of a PI3K δ selective inhibitory action in any
 25 literature.

[Chem. 2]



(in the formula (L-1), both of X and Y represent N, or one of X and Y represents N and the other represents CR⁷, and R⁶ represents H or C₁₋₆ alkyl; in the formula (L-2), both of X and Y represent N, or one of X and Y represents N and the other represents CR³, and R¹ represents a morpholino group or the like; in the formula (L-3), X represents N or CH, R¹ represents CHF₂ (n is 1 or 2), and R² represents morpholino which may be substituted, or the like; in the formula (L-4), X represents N or CH, and R¹ represents halogen or a hydroxyl group; in the formula (L-5), X represents N or CH, R¹ represents a morpholino group which may be substituted with 1 to 4 C₁₋₆ alkyl groups, and Y represents C₁₋₆ alkyl; and in the formula (M), R¹ represents a morpholino group or the like. For the other symbols, reference may be made to the publication.)

[0009]

Furthermore, a quinazolin-4-one derivative (Patent Documents 23 to 25) has been reported as a PI3K δ selective inhibitor, and its usability in inflammation, immune diseases, or hematologic tumors (leukemia and the like) is indicated. As other PI3K δ selective inhibitors, a thiazolylurea derivative (Patent Document 26) has been reported together with its usability in inflammation, immune diseases, or the like.

[0010]

Furthermore, the invention relating to a triazine or pyrimidine derivative having a PI3K δ selective inhibitory action, which is an invention in the prior art by the present inventors, has been disclosed after the priority date of the present application (Patent Document 27). The compound of the present invention is different in the structure of the group R¹ in the formula (I) from the compound disclosed in the prior application.

Related Art

Patent Documents

[0011]

[Patent Document 1] Pamphlet of International Publication WO 2008/032027

[Patent Document 2] Pamphlet of International Publication WO 2008/032077

[Patent Document 3] Pamphlet of International Publication WO 2008/032086

[Patent Document 4] Pamphlet of International Publication WO 2008/032028

[Patent Document 5] Pamphlet of International Publication WO 2008/032036

[Patent Document 6] Pamphlet of International Publication WO 2008/032041

[Patent Document 7] Pamphlet of International Publication WO 2008/032033

[Patent Document 8] Pamphlet of International Publication WO 2008/032060

[Patent Document 9] Pamphlet of International Publication WO 2008/032064

[Patent Document 10] Pamphlet of International Publication WO 2008/032072

[Patent Document 11] Pamphlet of International Publication WO 2008/032089

[Patent Document 12] Pamphlet of International Publication WO 2008/032091

[Patent Document 13] Pamphlet of International Publication WO 2007/042810

[Patent Document 14] Pamphlet of International Publication WO 2008/125839

[Patent Document 15] Specification of European Patent Application Publication No.

1864665

[Patent Document 16] Pamphlet of International Publication WO 2009/007751

[Patent Document 17] Pamphlet of International Publication WO 2009/120094

[Patent Document 18] Specification of European Patent Application Publication No.

1020462

[Patent Document 19] International Publication WO 00/43385

[Patent Document 20] Pamphlet of European Patent Application Publication No.

1389617

[Patent Document 21] Pamphlet of European Patent Application Publication No.

1557415

[Patent Document 22] Pamphlet of European Patent Application Publication No.

1741714

[Patent Document 23] Pamphlet of International Publication WO 01/81346

[Patent Document 24] Pamphlet of International Publication WO 03/035075

[Patent Document 25] Pamphlet of International Publication WO 2005/113556

[Patent Document 26] Pamphlet of International Publication WO 2008/000421

[Patent Document 27] Pamphlet of International Publication WO 2010/092962

5 Non-Patent Documents

[0012]

[Non-Patent Document 1] Journal of the National Cancer Institute, 2006, Vol. 98, p. 545-556

10 [Non-Patent Document 2] Bioorganic & Medicinal Chemistry Letters, 2006, Vol. 16, p. 5973-5977

Disclosure of Invention

Problems to Be Solved by the Invention

[0013]

15 A pharmaceutical composition, for example, a pharmaceutical composition having a PI3K δ inhibitory action, in particular, a pharmaceutical composition for preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumors, and a heterocyclic compound which is useful as an active ingredient of the pharmaceutical composition, are provided.

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Means for Solving the Problems

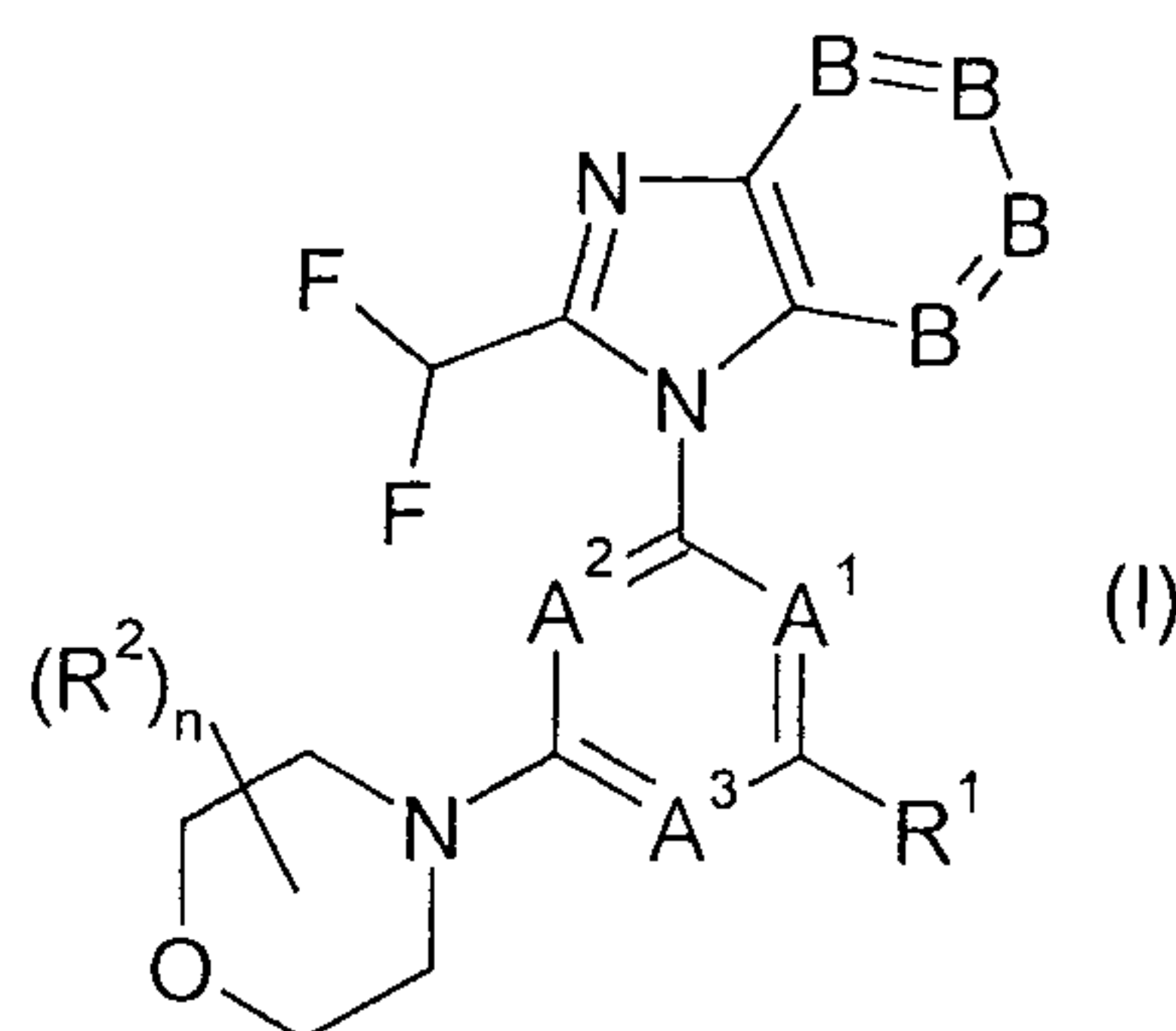
[0014]

The present inventors have extensively studied a PI3K δ selective inhibitory action and/or an IL-2 production inhibitory action and/or a B cell proliferation inhibitory action
25 (including an activation inhibitory action), and as a result, they have found that a novel triazine or pyrimidine derivative has an excellent PI3K δ selective inhibitory action and/or IL-2 production inhibitory action and/or B cell proliferation inhibitory action (including an activation inhibitory action), and can be an agent for preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and
30 hematologic tumor, thereby completing the present invention.

[0015]

That is, the present invention relates to a compound of the formula (I) or a salt thereof, and a pharmaceutical composition comprising the compound or a salt thereof and an excipient.

[Chem. 3]



(wherein

5 A^1 , A^2 , and A^3 are the same as or different from each other and are CH or N, provided that at least two of A^1 to A^3 are N,

B 's are the same as or different from each other and are CR^3 or N, provided that at least three of four B 's are CR^3 ,

R^1 is -NH-lower alkylene-C(O)-OH or $-L^1-L^2-Y$,

10 R^2 's are the same as or different from each other and are halogen, -OH, -O-lower alkyl, -CN, or lower alkyl which may be substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-lower alkyl, and -CN,

n is an integer of 0 to 8,

15 R^3 's are the same as or different from each other and are H, -O-lower alkyl, cyano, $-N(R^4)_2$, -C(O)-OH, -C(O)-O-lower alkyl, -C(O)- $N(R^4)_2$, or lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, $-N(R^4)_2$, -C(O)-OH, -C(O)-O-lower alkyl, -C(O)- $N(R^4)_2$, and halogen,

20 R^4 's are the same as or different from each other and are H, or lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, cycloalkyl, and phenyl,

L^1 is -lower alkynylene-, $-NR^5$ -, $-NR^5-S(O)_2$ -, $-NR^5-C(O)$ -, -O-, -S-, or $-S(O)_m$ -,

m 's are the same as or different from each other and are 1 or 2,

L^2 is a bond, $-ALK-X^2$ -, $-ALK-NR^6-C(O)$ -, $-ALK-NR^6-C(O)-O-ALK$ -, $-ALK-S(O)_m-X^1$ -, or $-ALK-C(O)-X^2$ -,

25 ALK 's are the same as or different from each other and are lower alkylene which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, cycloalkyl, and phenyl,

X^1 is a bond, $-NR^6$ -, or $-NR^6-ALK$ -,

30 X^2 's are the same as or different from each other and are a bond, $-NR^6$ -, $-NR^6-ALK$ -, -O-, -S-, $-NR^6-ALK-O$ -, $-NR^6-ALK-C(O)-NR^6$ -, or $-NR^6-ALK-C(O)$ -,

R^5 's are the same as or different from each other and are $-R^4$, lower alkenyl, or cycloalkyl,

R^6 's are the same as or different from each other and are H, cycloalkyl, phenyl, a non-aromatic heterocycle which may be substituted with lower alkyl, or lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, $-N(R^4)_2$, cycloalkyl, phenyl, and a non-aromatic heterocycle,

Y is lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, $-N(\text{lower alkyl})_2$ and $-C(O)-N(\text{lower alkyl})_2$, cycloalkyl which may be substituted with one or more substituents selected from a Group D1, aryl which may be substituted with one or more substituents selected from the Group D1, an aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1, or a non-aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1,

the Group D1 consists of:

- (1) halogen,
- (2) $-O-R^8$,
- (3) $-S-R^8$,
- (4) -CN,
- (5) $-NO_2$,
- (6) $-NR^4R^7$, in which R^7 is $-R^8$, $-C(O)-R^8$, $-C(O)-C(O)-N(R^8)_2$, $-C(O)-O-R^8$, and $-S(O)_2-R^8$,
- (7) $-C(O)-R^8$,
- (8) $-S(O)_2-R^8$ and $-S(O)_2-N(R^8)_2$,
- (9) $-C(O)-O-R^8$,
- (10) $-C(O)-N(R^8)_2$,
- (11) $-C(O)-C(O)-N(R^8)_2$,
- (12) $-O-C(O)-R^8$, $-O-C(O)-NH-C(=NH)-NH_2$, and $-O-C(O)-N(R^8)_2$,
- (13) $-L^3$ -cycloalkyl, $-L^3$ -aryl, $-L^3$ -aromatic heterocycle, and $-L^3$ -non-aromatic heterocycle, in which the cycloalkyl, aryl, aromatic heterocycle, and non-aromatic heterocycle may be each substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with one or more substituents selected from the group consisting of $-O-R^6$, -CN, halogen, $-N(R^6)_2$, $-C(O)-R^6$, $-C(O)-O-R^6$, $-C(O)-N(R^6)_2$, $-N(R^6)-C(O)-O-R^6$, $-S(O)_2$ -lower alkyl, cycloalkyl, phenyl, and a non-aromatic heterocycle; oxo; cycloalkyl, aryl, aromatic heterocycle, and a non-aromatic heterocycle, each of which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen; and the substituents of (1) to (12),
- (14) oxo, and

(15) lower alkyl, -O-lower alkyl, and lower alkenyl, each of which may be substituted with one or more substituents selected from the substituents described in (1) to (14),

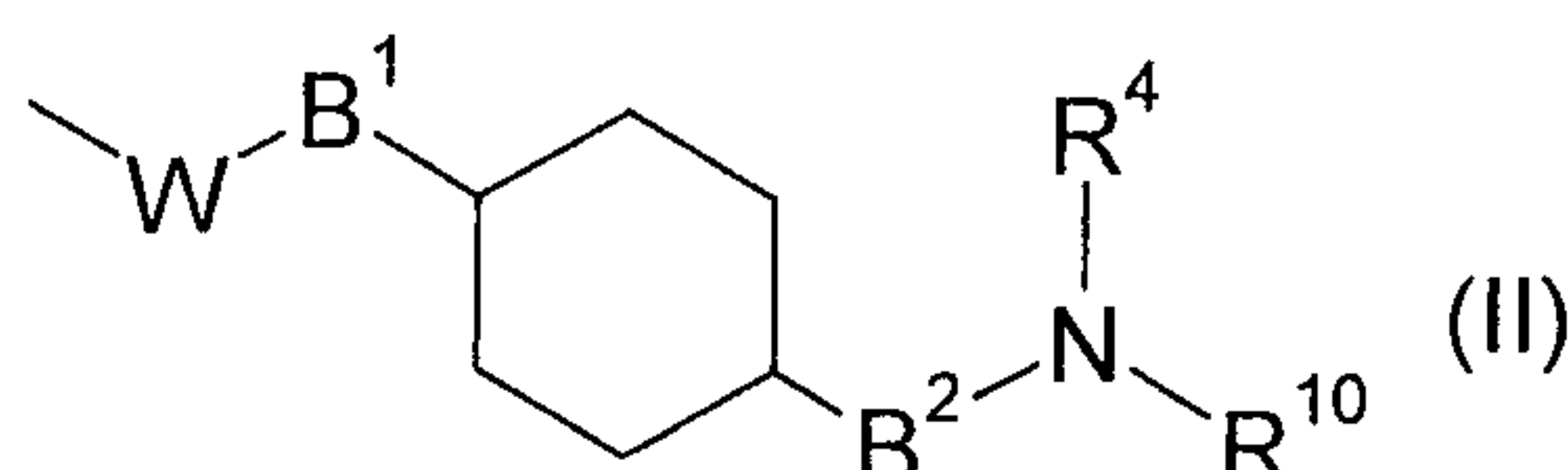
L^3 's are the same as or different from each other and are -a bond, -O-, -S-, -NR⁵-, -NR⁵-S(O)₂-, -NR⁵-C(O)-, -C(O)-NR⁵-, -S(O)_m-, -ALK-, -O-ALK-, -ALK-O-, -O-ALK-O-, -S-ALK-, -ALK-S-, -ALK-S(O)_m-, -S(O)_m-ALK-, -NR⁵-ALK-, -ALK-NR⁵-, -C(O)-NR⁵-ALK-, -C(O)-NR⁵-ALK-C(O)-, -C(O)-NR⁵-ALK-O-ALK-, -NR⁵-C(O)-ALK-, -NR⁵-C(O)-ALK-C(O)-, -NR⁵-C(O)-ALK-O-ALK-, -ALK-C(O)-NR⁵-, -ALK-NR⁵-C(O)-, -C(O)-O-, -ALK-C(O)-O-, -C(O)-O-ALK-, -C(O)-ALK-, -ALK-C(O)-, -NR⁵-C(O)-ALK-NR⁵-, or -C(O)-,

R^8 's are the same as or different from each other and are H; cycloalkyl, phenyl, pyridyl, or a non-aromatic heterocycle, each of which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen; -R⁹ or -ALK-L⁴-R⁹, in which R⁹ is lower alkyl which may be substituted with one or more substituents selected from the group consisting of -O-R⁶, -S-R⁶, -CN, -N(R⁶)₂, -C(O)-R⁶, -C(O)-O-R⁶, -C(O)-N(R⁶)₂, -N(R⁶)-C(O)-O-R⁶, -cycloalkyl, phenyl, and a non-aromatic heterocycle, and

L^4 is -C(O)-, -C(O)-NR⁵-, -NR⁵-, -NR⁵-S(O)₂-, -NR⁵-C(O)-, -NR⁵-C(O)-O-, -O-, -S-, or -S(O)_m-,

provided that in a case where R¹ has the following formula (II), all of B's are CH, W is NH or O, B¹ is a bond or lower alkylene, and B² is a bond or lower alkylene,

[Chem. 4]



R¹⁰ is -C(O)-(lower alkylene substituted with -NH-C(O)-O-lower alkyl)-S-lower alkyl, -C(O)-non-aromatic heterocycle, -C(O)-lower alkylene-NH-lower alkylene-(cycloalkyl which may be substituted with -OH), -C(O)-lower alkylene-NH-(cycloalkyl which may be substituted with a group selected from the group consisting of lower alkyl and -OH), -C(O)-lower alkylene-NH-non-aromatic heterocycle, -C(O)-lower alkylene-NH-(lower alkyl substituted with -OH), or -C(O)-(cycloalkyl substituted with one or more substituents selected from the group consisting of -NH₂, -N(lower alkyl)₂, and -NH-C(O)-O-lower alkyl), or

R⁴ and R¹⁰ form a 4- to 8-membered monocyclic heterocyclic group containing 1 to 4 hetero atoms selected from O, S, and N, together with N to which they are bonded, and are further substituted with at least one substituent selected from a Group D2,

in which the Group D2 consists of:

- (a) -O-(lower alkyl substituted with one or more substituents selected from the group consisting of -O-R⁶, -S-R⁶, -CN, -N(R⁶)₂, -C(O)-R⁶, -C(O)-O-R⁶, -C(O)-N(R⁶)₂, -N(R⁶)-C(O)-O-R⁶, cycloalkyl, and a non-aromatic heterocycle), -O-(cycloalkyl, phenyl, pyridyl, or a non-aromatic heterocycle, each of which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen), and -O-ALK-L⁴-R⁹,
- (b) -SR⁸,
- (c) -NO₂,
- (d) -NR¹¹R⁷, in which R⁷ is -R⁸, -C(O)-R⁸, -C(O)-C(O)-N(R⁸)₂, -C(O)-O-R⁸, and -S(O)₂-R⁸, and R¹¹ is lower alkyl substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, cycloalkyl, and phenyl,
- (e) -C(O)-R⁸,
- (f) -S(O)₂-R⁸ and -S(O)₂-N(R⁸)₂,
- (g) -C(O)-O-(lower alkyl substituted with one or more substituents selected from the group consisting of -O-R⁶, -S-R⁶, -CN, -N(R⁶)₂, -C(O)-R⁶, -C(O)-O-R⁶, -C(O)-N(R⁶)₂, -N(R⁶)-C(O)-O-R⁶, cycloalkyl, phenyl, and a non-aromatic heterocycle), -C(O)-O-(cycloalkyl, phenyl, pyridyl, or a non-aromatic heterocycle, each of which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen), and -C(O)O-ALK-L⁴-R⁹,
- (h) -C(O)-N(R⁸)₂,
- (i) -C(O)-C(O)-N(R⁸)₂,
- (j) -O-C(O)-(lower alkyl substituted with one or more substituents selected from the group consisting of -O-R⁶, -S-R⁶, -CN, -N(R⁶)₂, -C(O)-R⁶, -C(O)-O-R⁶, -C(O)-N(R⁶)₂, -N(R⁶)-C(O)-O-R⁶, cycloalkyl, phenyl, and a non-aromatic heterocycle), -O-C(O)-(cycloalkyl, phenyl, pyridyl, or a non-aromatic heterocycle, each of which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen), -O-C(O)-ALK-L⁴-R⁹, -O-C(O)-NH-C(=NH)-NH₂, and -O-C(O)-N(R⁸)₂,
- (k) lower alkyl substituted with one or more substituents selected from the group consisting of -CN, -N(R⁶)₂, -C(O)-R⁶, -C(O)-O-R⁶, -C(O)-N(R⁶)₂, -N(R⁶)-C(O)-O-R⁶, -S(O)₂-lower alkyl, cycloalkyl, and phenyl,
- (l) cycloalkyl which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen,
- (m) aryl which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen,
- (n) an aromatic heterocycle substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen, and

(o) a non-aromatic heterocycle substituted with one or more substituents selected from the group consisting of lower alkyl, -OH, -O-lower alkyl, -CN, and halogen.)

Unless specified otherwise, in the case where the symbols of the chemical formulae in the present specification are also used in other chemical formulae, the same symbols denote
5 the same meanings.

[0016]

Furthermore, the present invention relates to a pharmaceutical composition for preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor, which comprises the compound of the
10 formula (I) or a salt thereof as an active ingredient. Further, the pharmaceutical composition includes an agent for preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor, which comprises the compound of the formula (I) or a salt thereof. In a certain embodiment, the present invention relates to an agent for preventing and/or treating rejection reactions in
15 kidney, liver, and heart transplantations, in another embodiment, an agent for preventing and/or treating chronic rejection and acute rejection, and in still another embodiment, an agent for preventing and/or treating antibody-related rejection.

Furthermore, the present invention relates to use of the compound of the formula (I) or a salt thereof in the manufacture of a pharmaceutical composition for preventing and/or
20 treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor, and use of the compound of the formula (I) or a salt thereof in preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor, the compound of the formula (I) or a salt thereof for preventing and/or treating rejection reactions in various organ transplantations,
25 allergy diseases, autoimmune diseases, and hematologic tumor, and a method for preventing or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor, including administering to a subject an effective amount of the compound of the formula (I) or a salt thereof. Here, the "subject" is a human or any of other animals in need of prevention or treatment thereof, and in a certain embodiment, a
30 human in need of prevention or treatment thereof.

[0017]

Furthermore, the present invention relates to a PI3K δ selective inhibitor and/or an IL-2 production inhibitor and/or a B cell proliferation inhibitor, each of which contains the compound of the formula (I) or a salt thereof.

Effects of the Invention

[0018]

The compound of the formula (I) has a PI3K δ selective inhibitory action and/or an IL-2 production inhibitory action and/or a B cell proliferation inhibitory action (including an activation inhibitory action), and can therefore be used as an agent for preventing or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor.

Embodiments for Carrying Out the Invention

[0019]

Hereinbelow, the present invention will be described in detail.

[0020]

The “lower alkyl” is linear or branched alkyl having 1 to 6 carbon atoms (which is hereinafter simply referred to as C₁₋₆), and examples thereof include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, and the like. In another embodiment, the lower alkyl is C₁₋₄ alkyl, in still another embodiment, methyl, ethyl, or tert-butyl, and in a further still other embodiment, methyl.

[0021]

The “lower alkenyl” is linear or branched C₂₋₆ alkenyl, and examples thereof include vinyl, propenyl, butenyl, pentenyl, 1-methylvinyl, 1-methyl-2-propenyl, 1,3-butadienyl, 1,3-pentadienyl, and the like. In another embodiment, the lower alkenyl is C₂₋₄ alkenyl, and in still another embodiment, propenyl.

[0022]

The “lower alkylene” is a divalent group formed by the removal of any hydrogen atom of the “lower alkyl”. Accordingly, the “C₁₋₆ alkylene” is linear or branched alkylene having 1 to 6 carbon atoms, and examples thereof include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylenemethylene, dimethylenemethylene, ethylenemethylene, dimethylethylene, ethylethylene, and the like. In another embodiment, the lower alkylene is methylene, ethylene, and in still another embodiment, methylene.

[0023]

The “lower alkenylene” is linear or branched C₂₋₆ alkenylene, and examples thereof include vinylene, ethylidene, propenylene, butenylene, pentenylene, hexenylene, 1,3-butadienylene, 1,3-pentadienylene, and the like. In another embodiment, the lower alkenylene is C₂₋₄ alkenylene, and in still another embodiment, propenylene.

[0024]

The “lower alkynylene” is linear or branched C₂₋₆ alkynylene, and examples thereof include ethynylene, propynylene, butynylene, pentynylene, hexynylene, 1,3-butadiynylene,

1,3-pentadiynylene, and the like. In another embodiment, the lower alkynylene is C₂₋₄ alkynylene, and in still another embodiment, propynylene.

[0025]

The “halogen” is F, Cl, Br, or I, in another embodiment, F, and in still another
5 embodiment, Cl.

[0026]

The “cycloalkyl” is C₃₋₁₀ saturated hydrocarbon ring group, which may have a bridge and may be combined with a non-aromatic heterocyclic group to form a spiro ring. Specific examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
10 cyclohexenyl, cyclooctyl, bicyclo[3.3.0]octane, hexahydro-1'H-spiro-1,3-dioxane-2,2'-pentalene, 1,4-dioxaspiro[4.5]decane, bicyclo[2.2.2]octyl, adamantyl, azaspiro[5.5]undecanyl, octahydrocyclopenta[c]pyrrole, indanyl, and the like. In another embodiment, the cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, octahydropentalene, bicyclo[2.2.2]octyl, or adamantyl, in still another embodiment, C₃₋₈ cycloalkyl, in further still another
15 embodiment, C₃₋₆ cycloalkyl, in further still another embodiment, cyclohexyl, in further still another embodiment, octahydropentalene, and in further still another embodiment, adamantyl.

[0027]

The “aryl” is C₆₋₁₄ monocyclic to tricyclic aromatic hydrocarbon ring group, and examples thereof include phenyl, naphthyl, and the like. In another embodiment, the aryl is
20 phenyl.

[0028]

The “aromatic heterocycle” is an aromatic heterocycle having 5 to 6 ring members, containing at least one hetero atom selected from O, N, and S as a ring-constituting atom, and may be fused with a benzene ring or an aromatic heterocycle. Examples thereof include
25 pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, triazolyl, triazinyl, tetrazolyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thienyl, furyl, indolyl, isoindolyl, benzoimidazolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, benzoxazolyl, benzoisoxazolyl, benzofuranyl, benzothienyl, carbazolyl, dibenzo[b,d]furanyl,
30 dibenzo[b,d]thienyl, thienopyridyl, thienopyrimidinyl, thienopyrazyl, 1,4-benzodioxin-2-yl, [1,2,4]triazolo[4,3-a]pyridyl, imidazo[1,2-a]pyridyl, and the like. In another embodiment, the aromatic heterocycle is imidazolyl, pyridyl, pyrazinyl, indolyl, indazolyl, benzoimidazolyl, or benzothiazolyl.

[0029]

35 The “non-aromatic heterocycle” is a non-aromatic heterocycle having 4 to 8 ring members, containing at least one hetero atom selected from O, N, and S as a ring-constituting atom, which may have unsaturated bonds in a part of the ring and may be bridged. The non-

aromatic heterocycle may be fused with a benzene ring or an aromatic heterocycle. Further, the sulfur atom that is a ring-constituting atom may be oxidized. Examples of the non-aromatic heterocycle include azetidiny, pyrrolidiny, piperidiny, piperaziny, azepany, diazepany, morpholiny, thiomorpholiny, quinuclidiny, 1,1-dioxidethiomorpholiny, tetrahydropyridiny, oxetany, tetrahydrofurany, tetrahydropyrany, tetrahydrothieny, 4,5-dihydrothiazoly, dioxolany, dioxany, tetrahydrothiopyrany, tetrahydroisoquinoly, oxazolidiny, tropane, 3,9-diazaspiro[5.5]undecany, 2,8-diazaspiro[4.5]decany, octahydropyrrolo[1,2-a]pyrazyl, 5,6,7,8-tetrahydro-1,7-naphthalidyl, 3,4-dihydro-2H-1,4-benzoxaziny, 1,3-benzodioxoly, chromeny, 1,4-benzothiaziny, 4,5-dihydro-1,3-thiazoly, and the like. In another embodiment, the non-aromatic heterocycle is azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, tetrahydrofurany, tetrahydropyrany, or azepany, in still another embodiment, pyrrolidiny, piperidiny, tetrahydropyrany, or azepany, in further still another embodiment, piperidiny, and in further still another embodiment, pyrrolidiny.

[0030]

The “cyclic amino” is a non-aromatic heterocyclic group having a nitrogen atom-containing group and has a bonding position on the nitrogen atom, among the above “non-aromatic heterocycles” and may form a spiro ring, and specific examples thereof include pyrrolidin-1-yl, piperidin-1-yl, azepan-1-yl, piperazin-1-yl, 1,3-oxazolidin-2-one, morpholin-4-yl, thiomorpholin-4-yl, 1,1-dioxidethiomorpholin-4-yl, 2-oxa-6-azaspiro[3.3]hept-6-yl, 1-oxa-3-azaspiro[4.5]decan-2-one, 2,5-diazabicyclo[2.2.1]heptane, 2-oxa-5-azaspiro[3.4]octane, 2-oxa-5-azabicyclo[2.2.1]heptane, and the like. In another embodiment, the cyclic amino is pyrrolidin-1-yl.

[0031]

Furthermore, the monocyclic heterocyclic group in the expression “R¹⁰ and R⁴ form a 4- to 8-membered monocyclic heterocyclic group containing 1 to 4 hetero atoms selected from O, S, and N, together with N to which they are bonded” is a 4- to 8-membered monocyclic group containing 1 to 4 hetero atoms selected from O, S, and N in the “aromatic heterocycle” and the “cyclic amino” above.

[0032]

In the present specification, the expression “which may be substituted” means non-substitution or substitution with 1 to 5 substituents. In a certain embodiment, it is unsubstitution or substitutions with 1 to 3 substituents, in another embodiment, unsubstitution or substitution with 1 substituent, and in still another embodiment, unsubstitution. Further, in a case of having a plurality of substituents, the substituents may be the same as or different from each other.

[0033]

In a certain embodiment, the Group D1 consists of:

(1) halogen,

(2) -OH,

(3) -O-lower alkyl,

5 (4) -CN,

(5) -NO₂,

(6) -NR^{4a}R⁷, in which R^{4a} is H or lower alkyl, R⁷ is lower alkyl which may be substituted with one or more substituents selected from the group consisting of halogen, -OH, -O-lower alkyl, and aryl, -C(O)-lower alkyl, -C(O)-lower alkylene-N(lower alkyl)₂, lower
10 alkenyl, -C(O)-lower alkylene-NH-(lower alkyl substituted with cycloalkyl), -C(O)-lower alkylene-NH-(cycloalkyl which may be substituted with lower alkyl), -C(O)O-lower alkyl or H,

(7) -C(O)-lower alkyl,

(8) -C(O)-lower alkylene-N(R⁴)₂,

15 (9) -C(O)O-lower alkyl,

(10) -C(O) OH,

(11) -C(O)-N(R⁴)₂,

(12) -O-C(O)-NH-C(=NH)-NH₂,

(13) -L⁵-cycloalkyl, -L⁵-aryl, -L⁵-aromatic heterocycle, and -L⁵-non-aromatic
20 heterocycle, in which the cycloalkyl, aryl, aromatic heterocycle, and non-aromatic heterocycle may be each substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, halogen, -O-lower alkyl, and a non-aromatic heterocycle, -OH, -O-lower alkyl, -NH₂, halogen, -C(O)O-lower alkyl, -C(O)-lower alkyl, oxo, -NH-S(O)₂-lower alkyl,
25 -NH-S(O)₂-cycloalkyl, -NH-C(O)-lower alkyl, -NR⁴-C(O)-O-(lower alkyl which may be substituted with -OH), -S(O)₂-lower alkyl, -NH-(lower alkyl which may be substituted with -OH), cycloalkyl which may be substituted with -OH, and a non-aromatic heterocycle, in which L⁵'s are the same as or different from each other and are a bond, -O-, -lower alkylene, -O-lower alkylene, -O-lower alkylene-O-, -C(O)-NH-, -NH-C(O)-, -C(O)-lower alkylene-, or
30 -C(O)-;

in another embodiment, the cycloalkyl may be substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with one or more substituents selected from the group consisting of halogen, -OH, and -O-lower alkyl, halogen, -OH, -O-lower alkyl, -NH-lower alkylene-OH, -NH₂, -NH-C(O)-O-lower alkyl,
35 -NH-lower alkyl, and -C(O)-O-lower alkyl; the aryl may be substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, -O-lower alkyl, and

-C(O)-O-lower alkyl; the aromatic heterocycle may be substituted with one or more substituents selected from the group consisting of lower alkyl and -NH₂; and the non-aromatic heterocycle may be substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, halogen, -O-lower alkyl, and a non-aromatic heterocycle, -NH₂, halogen, -C(O)-O-lower alkyl, -C(O)-lower alkyl, oxo, -NH-S(O)₂-lower alkyl, -NH-S(O)₂-cycloalkyl, -NH-C(O)-lower alkyl, -NR⁴-C(O)-O-(lower alkyl which may be substituted with -OH), -S(O)₂-lower alkyl, -NH-(lower alkyl substituted with -OH), cycloalkyl which may be substituted with -OH, and a non-aromatic heterocycle,

(14) oxo, and

(15) lower alkyl, -O-lower alkyl, and lower alkenyl, each of which may be substituted with one or more substituents selected from the substituents described in (1) to (14) above.

[0034]

In another embodiment, the Group D1 consists of:

(1) halogen,

(2) -OH,

(3) -O-lower alkyl,

(4) -NR^{4a}R⁷, in which R^{4a} represents H or lower alkyl, R⁷ represents lower alkyl which may be substituted with -OH, -C(O)-lower alkylene-N(lower alkyl)₂, -C(O)-lower alkylene-NH-(lower alkyl substituted with cycloalkyl), -C(O)-(cycloalkyl substituted with -NH₂), -C(O)-lower alkylene-NH-tetrahydropyran, -C(O)-lower alkylene-N(lower alkyl)-(cycloalkyl which may be substituted with lower alkyl) or -C(O)-lower alkylene-NH-(cycloalkyl which may be substituted with lower alkyl),

(5) -C(O)-lower alkylene-N(R⁴)₂,

(6) -C(O)O-lower alkyl,

(7) -L⁵-(aryl which may be substituted with one or more substituents selected from the group consisting of lower alkyl, halogen, and -O-lower alkyl),

(8) -L⁵-(non-aromatic heterocycle which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -NH-C(O)-O-lower alkyl, -NH-C(O)-lower alkyl, -C(O)-O-lower alkyl, -C(O)-lower alkyl, -S(O)₂-lower alkyl, oxo, and -NH-lower alkyl),

(9) -L⁵-(cycloalkyl which may be substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with one or more groups selected from the group consisting of halogen and -OH, halogen, -OH, -O-lower alkyl, and -C(O)O-lower alkyl), and

(10) lower alkyl which may be each substituted with one or more substituents selected from the substituents described in (1) to (9) above.

[0035]

In still another embodiment, the Group D1 consists of:

(1) -OH,

(2) -O-lower alkyl,

5 (3) -NR^{4a}R⁷, in which R^{4a} represents H or lower alkyl, R⁷ represents lower alkyl which may be substituted with -OH, -C(O)-(cycloalkyl substituted with -NH₂), -C(O)-lower alkylene-NH-tetrahydropyran, -C(O)-lower alkylene-N(lower alkyl)-(cycloalkyl which may be substituted with lower alkyl), or -C(O)-lower alkylene-NH-(cycloalkyl which may be substituted with lower alkyl),

10 (4) -L^{5a}-(non-aromatic heterocycle which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -NH-C(O)-O-lower alkyl, -NH-C(O)-lower alkyl, -C(O)-O-lower alkyl, -C(O)-lower alkyl, and oxo), in which L^{5a} represents a bond, -C(O)-lower alkylene-, or -C(O)-, and

15 (5) -L^{5b}-(cycloalkyl which may be substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with -OH, halogen, -OH, and -O-lower alkyl), in which L^{5b} represents a bond or -C(O)-.

[0036]

In further still another embodiment, the Group D1 consists of:

20 (1) -L^{5a}-(non-aromatic heterocycle which may be substituted with one or more substituents selected from the group consisting of lower alkyl, -NH-C(O)-O-lower alkyl, -C(O)O-lower alkyl, -C(O)-lower alkyl, and oxo), in which L^{5a} represents a bond, -C(O)-lower alkylene-, or -C(O)-, and

25 (2) -C(O)-(cycloalkyl which may be substituted with one or more substituents selected from the group consisting of lower alkyl which may be substituted with -OH, -OH, and -O-lower alkyl).

[0037]

Certain embodiments of the compound of the formula (I) of the present invention are shown below.

30 (1) In a certain embodiment of A¹, A² and A³, any one of A¹, A² and A³ is CH, in another embodiment, A¹ and A³ are N and A² is CH, and in still another embodiment, A² and A³ are N and A¹ is CH.

35 (2) In a certain embodiment of B, all of B's are CR³, in which R³ is H, lower alkyl which may be substituted with halogen, or -O-lower alkyl, in another embodiment, R³ is H or lower alkyl, in still another embodiment, R³ is lower alkyl, in further still another embodiment, R³ is H, in further still another embodiment, one of B's is N and the others are CH, and in further still another embodiment, all of B's are CH.

(3) In a certain embodiment of R¹, R¹ is -L¹-L²-Y.

(4) In a certain embodiment of L^1 , L^1 is $-NR^5-$, $-NR^5-S(O)_2-$, $-NR^5-C(O)-$, or $-O-$, in another embodiment, L^1 is $-NH-$, $-N(\text{lower alkyl})-$, or $-O-$, in still another embodiment, $-NH-$ or $-O-$, in further still another embodiment, $-NH-$, and in further still another embodiment, $-O-$.

5 (5) In a certain embodiment, L^2 is a bond, $-ALK-$, $-ALK-S-$, $-ALK-S(O)_m-X^1-$, or $-ALK-C(O)-X^2-$, in which X^1 is a bond or $-NR^6-$, X^2 is a bond, $-NR^6-$, $-NR^6-ALK-$, or $-O-$, ALK is lower alkylene, and R^6 is H or lower alkyl, in another embodiment, L^2 is a bond, lower alkylene, or $-lower\ alkylene-C(O)NH-$, in still another embodiment, a bond or lower alkylene, in further still another embodiment, a bond, in further still another embodiment, 10 lower alkylene, and in further still another embodiment, methylene.

(6) In a certain embodiment, Y is cycloalkyl which may be substituted with one or more substituents selected from the Group D1, aryl which may be substituted with one or more substituents selected from the Group D1, an aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1, or a non-aromatic 15 heterocycle which may be substituted with one or more substituents selected from the Group D1, in another embodiment, cycloalkyl which may be substituted with one or more substituents selected from the Group D1 or a non-aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1, in still another embodiment, cycloalkyl which may be substituted with one or more substituents selected from 20 the Group D1, in further still another embodiment, a non-aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1, in further still another embodiment, cyclohexyl or cyclic amino, in further still another embodiment, cyclohexyl, in further still another embodiment, cyclic amino, in further still another embodiment, piperidinyl, pyrrolidinyl, or azetidiny, and in further still another embodiment, pyrrolidinyl or 25 azetidiny.

(7) In a certain embodiment, n is an integer of 0 or 1 to 2, and in another embodiment, 0.

(8) In a certain embodiment, R^2 's are the same as or different from each other and are lower alkyl which may be substituted with halogen.

30 (9) The compound or a salt thereof, which is a combination of any two or more of the embodiments of (1) to (8) as described above.

[0038]

The compound or a salt thereof, which is a combination of any two or more of the embodiments of (1) to (8) as described above, is also included in the present invention, as 35 described in (9) above, and the specific examples thereof also include the following embodiments.

(10) The compound or a salt thereof, wherein R^1 is $-NH-$ lower alkylene- $C(O)-OH$ or

-L¹-L²-Y, L¹ is -lower alkynylene-, -NR⁵-, -NR⁵-S(O)₂-, -NR⁵-C(O)-, -O-, -S-, or -S(O)_m-, m is 1 or 2, L² is a bond, -ALK-X²-, -ALK-NR⁶-C(O)-, -ALK-NR⁶-C(O)-O-ALK-, -ALK-S(O)_m-X¹-, or -ALK-C(O)-X²-, ALK's are the same as or different from each other and are lower alkylene which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, and cycloalkyl, X¹ is a bond, -NR⁶-, or -NR⁶-ALK-, X²'s are the same as or different from each other and are a bond, -NR⁶-, -NR⁶-ALK-, -O-, -S-, -NR⁶-ALK-O-, -NR⁶-ALK-C(O)-NR⁶-, or -NR⁶-ALK-C(O)-, R⁴'s are the same as or different from each other and are H, or lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, and cycloalkyl, R⁵'s are the same as or different from each other and are -R⁴, lower alkenyl, or cycloalkyl, R⁶'s are the same as or different from each other and are H, cycloalkyl, a non-aromatic heterocycle which may be substituted with lower alkyl, or lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -CN, halogen, -N(R⁴)₂, cycloalkyl, and a non-aromatic heterocycle, Y is lower alkyl which may be substituted with one or more substituents selected from the group consisting of -OH, -O-lower alkyl, -N(lower alkyl)₂ and -C(O)-N(lower alkyl)₂, cycloalkyl which may be substituted with one or more substituents selected from the Group D1, or a non-aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1, provided that L² is -ALK-X^{2a}-, -ALK-NR⁶-C(O)-, -ALK-NR⁶-C(O)-O-ALK-, -ALK-S(O)_m-X¹-, or -ALK-C(O)-X²-, in which in a case where X^{2a} is -NR⁶-, -NR⁶-ALK-, -O-, -S-, -NR⁶-ALK-O-, -NR⁶-ALK-C(O)-NR⁶-, or -NR⁶-ALK-C(O)-, Y is aryl which may be substituted with one or more substituents selected from the Group D1 or an aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1.

(11) The compound or a salt thereof as described in (10), wherein R¹ is -L¹-L²-Y, L¹ is -NR⁵-, -NR⁵-S(O)₂-, -NR⁵-C(O)-, or -O-, in which R⁵ is H or lower alkyl, L² is a bond, -ALK-, -ALK-S-, -ALK-S(O)_m-X¹-, or -ALK-C(O)-X²-, in which X¹ is a bond or -NR⁶-, X² is a bond, -NR⁶-, -NR⁶-ALK-, or -O-, ALK is lower alkylene, R⁶ is H or lower alkyl, and Y is cycloalkyl which may be substituted with one or more substituents selected from the Group D1, or a non-aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1.

(12) The compound or a salt thereof as described in (11), wherein -L¹-L²- is -NH- or -O-.

(13) The compound or a salt thereof as described in (12), wherein B's are all CH and n is 0.

(14) The compound or a salt thereof as described in (13), wherein A¹ and A³ are N and A² is CH.

(15) The compound or a salt thereof as described in (13), wherein A² and A³ are N and A¹ is CH.

[0039]

Examples of the specific compounds included in the compound of the formula (I) or a salt thereof include the following compounds:

methyl {(3S)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]-2-oxopyrrolidin-3-yl} carbamate,

methyl {(3R)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]-2-oxopyrrolidin-3-yl} carbamate,

ethyl {(3R)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]-2-oxopyrrolidin-3-yl} carbamate,

[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl][(2R)-tetrahydrofuran-2-yl]methanone,

[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl](tetrahydro-2H-pyran-4-yl)methanone,

methyl {(3S)-1-[trans-4-({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)cyclohexyl]-2-oxopyrrolidin-3-yl} carbamate,

methyl {(3R)-1-[trans-4-({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)cyclohexyl]-2-oxopyrrolidin-3-yl} carbamate,

methyl {(3R)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)cyclohexyl]-2-oxopyrrolidin-3-yl} carbamate,

1-[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl]-2-(tetrahydrofuran-2-yl)ethanone,

1-[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl]-2-(tetrahydro-2H-pyran-4-yl)ethanone,

1-[3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)azetidin-1-yl]-2-(tetrahydrofuran-2-yl)ethanone,

methyl 4-{[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl]carbonyl}piperidine-1-carboxylate,

[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)pyrrolidin-1-yl](tetrahydrofuran-3-yl)methanone,

4-{[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)pyrrolidin-1-yl]carbonyl}-1-methylpyrrolidin-2-one,

2-(1-acetylpiperidin-4-yl)-1-[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl]ethanone,

[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl](tetrahydrofuran-3-yl)methanone,

4-{[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl]carbonyl}-1-methylpyrrolidin-2-one,
 1-[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl]-2-(piperidin-1-yl)ethanone,
 5 (5S)-5-{[3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)azetidin-1-yl]carbonyl}pyrrolidin-2-one,
 (5S)-5-{[3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)azetidin-1-yl]carbonyl}pyrrolidin-2-one,
 2-(1-acetylpiperidin-4-yl)-1-[3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)azetidin-1-yl]ethanone,
 10 [3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)azetidin-1-yl](tetrahydrofuran-3-yl)methanone,
 4-{[3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)azetidin-1-yl]carbonyl}-1-methylpyrrolidin-2-one,
 15 [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl][cis-4-(hydroxymethyl)cyclohexyl]methanone, and
 [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)pyrrolidin-1-yl][trans-4-(hydroxymethyl)cyclohexyl]methanone, and salts thereof.
 [0040]

20 The compound of the formula (I) may exist in the form of tautomers or geometrical isomers depending on the kind of substituents. In the present specification, the compound of the formula (I) shall be described in only one form of isomer, yet the present invention includes other isomers, isolated forms of the isomers, or a mixture thereof.

In addition, the compound of the formula (I) may have asymmetric carbon atoms or axial asymmetry in some cases, and correspondingly, it may exist in the form of optical isomers based thereon. The present invention includes both an isolated form of the optical isomers of the compound of the formula (I) or a mixture thereof.

[0041]

Moreover, the present invention also includes a pharmaceutically acceptable prodrug of the compound represented by the formula (I). The pharmaceutically acceptable prodrug is a compound having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like through solvolysis or under physiological conditions. Examples of the group forming the prodrug include the groups described in Prog. Med., 5, 2157-2161 (1985) and "Pharmaceutical Research and Development" (Hirokawa Publishing Company, 1990), Vol. 7, Molecular Design, 163-198.

[0042]

Furthermore, the salt of the compound of the formula (I) may form an acid addition salt or a salt with a base depending on the kind of substituents, and such salts are included in the present invention as long as they are pharmaceutically acceptable salts. Specific examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, and with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, and glutamic acid, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum, or organic bases such as methylamine, ethylamine, ethanolamine, lysine, and ornithine, salts with various amino acids such as acetylleucine, and amino acid derivatives, as well as ammonium salts.

[0043]

In addition, the present invention also includes various hydrates or solvates, and polymorphic crystalline substances of the compound of the formula (I) and pharmaceutically acceptable salts thereof. In addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

[0044]

The "PI3K δ selective inhibitor" means an inhibitor exhibiting a potent activity, in which the inhibitory activity of PI3K δ is 10-times or more, in another embodiment, 30-times or more, and in still another embodiment, 100-times or more than the inhibitory activity of PI3K α in terms of the IC₅₀ value.

[0045]

(Preparation Methods)

The compound of the formula (I) and a pharmaceutically acceptable salt thereof can be prepared by applying various known synthesis methods on the basis of characteristics derived from their skeletal structure or the type of their substituents. During the preparation, replacement of the relevant functional group with a suitable protective group (a group that can be easily converted into the relevant functional group) at the stage from starting material to an intermediate may be effective depending on the type of the functional group in the production technology in some cases. Examples of such the functional group include an amino group, a hydroxyl group, and a carboxyl group, and such the protective group for such a functional group may include, for example, the protective groups described in Greene and Wuts, "Protective Groups in Organic Synthesis (3rd edition, 1999)", which may be selected and used as appropriate, depending on reaction conditions. In such a method, after introduction of the

protective group and a subsequent reaction, the protective group may be removed, if necessary to obtain a desired compound.

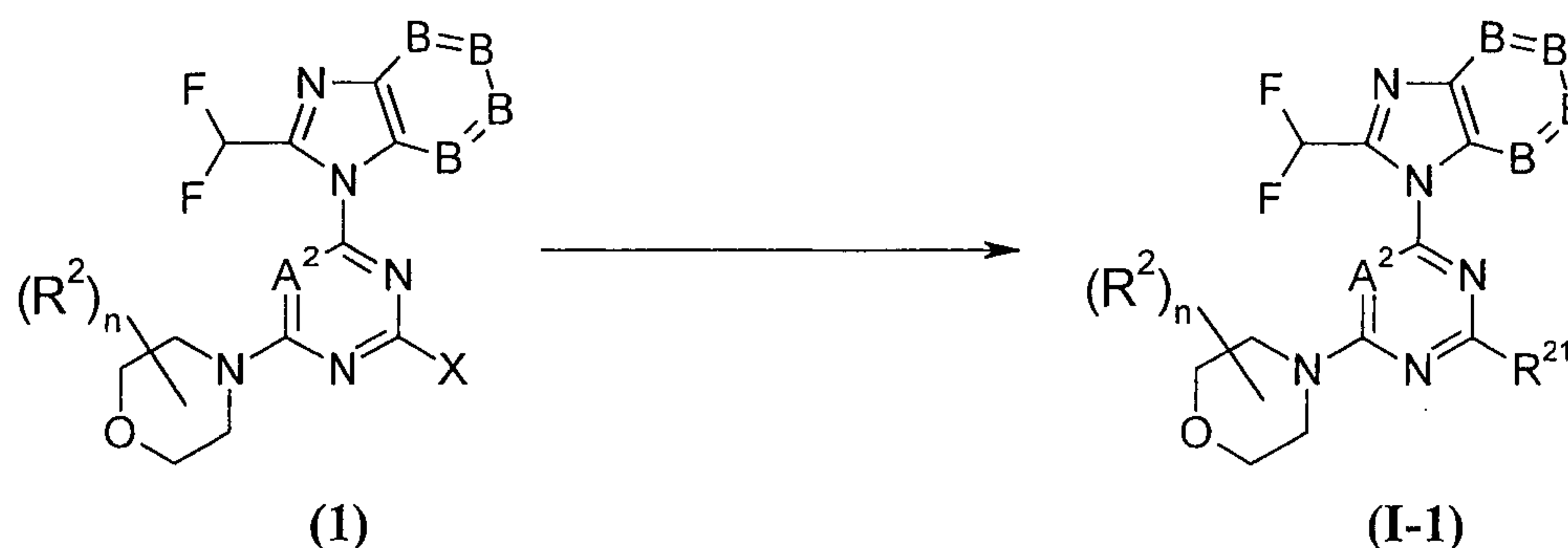
In addition, the prodrug of the compound of the formula (I) can be prepared by introducing a specific group at the stage from a starting material to an intermediate, or by carrying out the reaction using the obtained compound of the formula (I), as in the case of the above-mentioned protective group. The reaction can be carried out using methods known to those skilled in the art, such as ordinary esterification, amidation, dehydration, and the like.

Hereinbelow, the representative preparation methods for the compound of the formula (I) will be described. Each of the production processes may also be carried out with reference to the References appended in the present description. Further, the preparation methods of the present invention are not limited to the examples as shown below.

[0046]

(Production Process 1)

[Chem. 5]



(wherein X represents a leaving group, R^{21} represents $-NH$ -lower alkylene- $C(O)-OH$ or $-L^1-L^2-Y$, and L^1 represents $-NR^5-$, $-NR^5-S(O)_2-$, $-NR^5-C(O)-$, $-O-$, $-S-$, or $-S(O)_m-$. The same shall apply hereinafter.)

[0047]

The compound (I-1) of the present invention can be obtained by the ipso substitution reaction of the compound (1) with, for example, $-L^1-L^2-Y$.

Examples of the leaving group X include halogen, methylsulfinyl, methylsulfonyl groups, and the like.

The present reaction is carried out by using the compound (1) and, for example, a compound $-L^1-L^2-Y$ in equivalent amounts, or either thereof in an excess amount, and stirring a mixture thereof in a solvent which is inert to the reaction, or in the absence of a solvent, in a range of from cooling to heating and refluxing, preferably at $0^\circ C$ to $100^\circ C$, usually for 0.1 hours to 5 days. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as diethyl

ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, ethyl acetate, acetonitrile, and a mixture thereof. It is preferable in some cases for the smooth progress of the reaction to use organic bases such as triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, and the like, or inorganic bases such as potassium carbonate, sodium carbonate, cesium carbonate, potassium hydroxide, and the like. It may be advantageous in some cases for the smooth progress of the reaction to carry out the reaction by heating the reaction mixture by microwave irradiation.

[Documents]

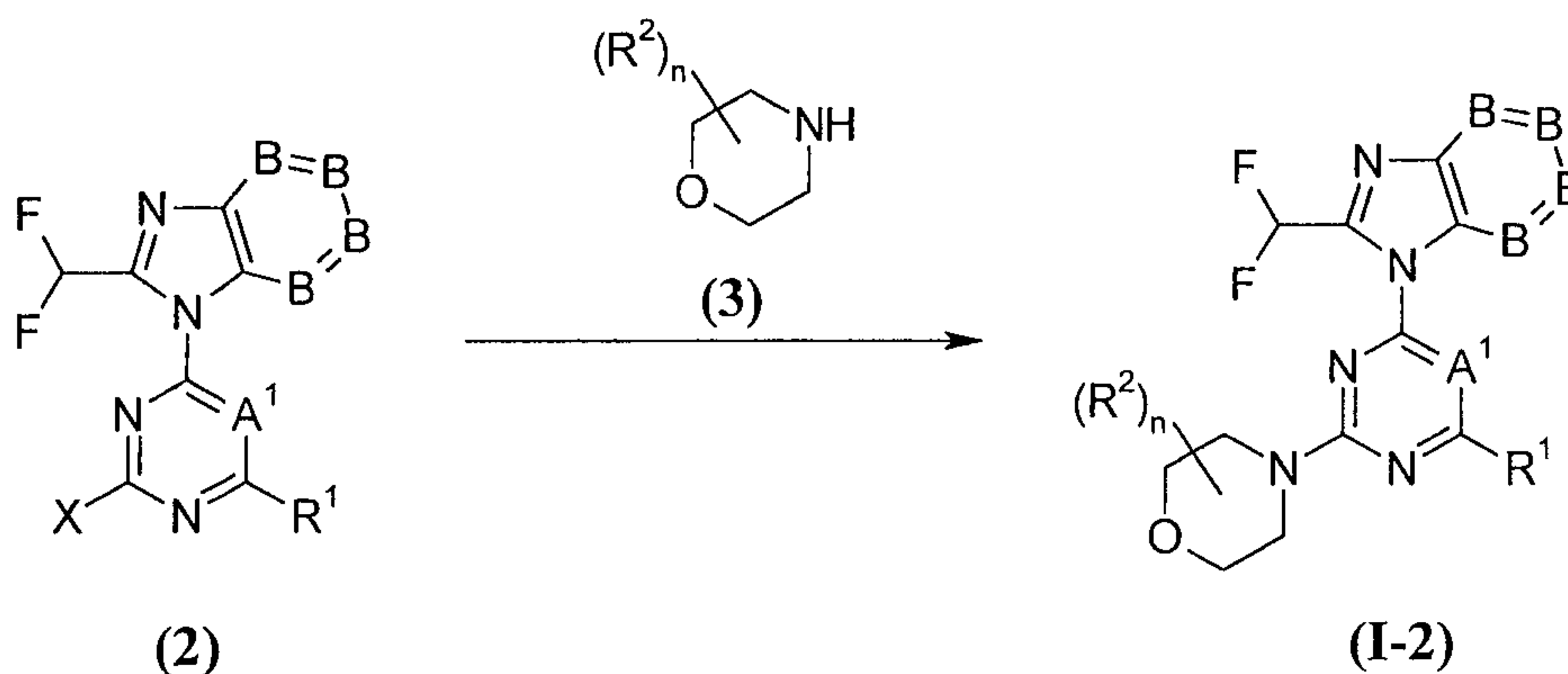
S. R. Sandler and W. Karo, "Organic Functional Group Preparations", 2nd edition, Vol. 1, Academic Press Inc., 1991

"Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th Edition) (Vol. 14)", edited by The Chemical Society of Japan, Maruzen, 2005

[0048]

(Production Process 2)

[Chem. 6]



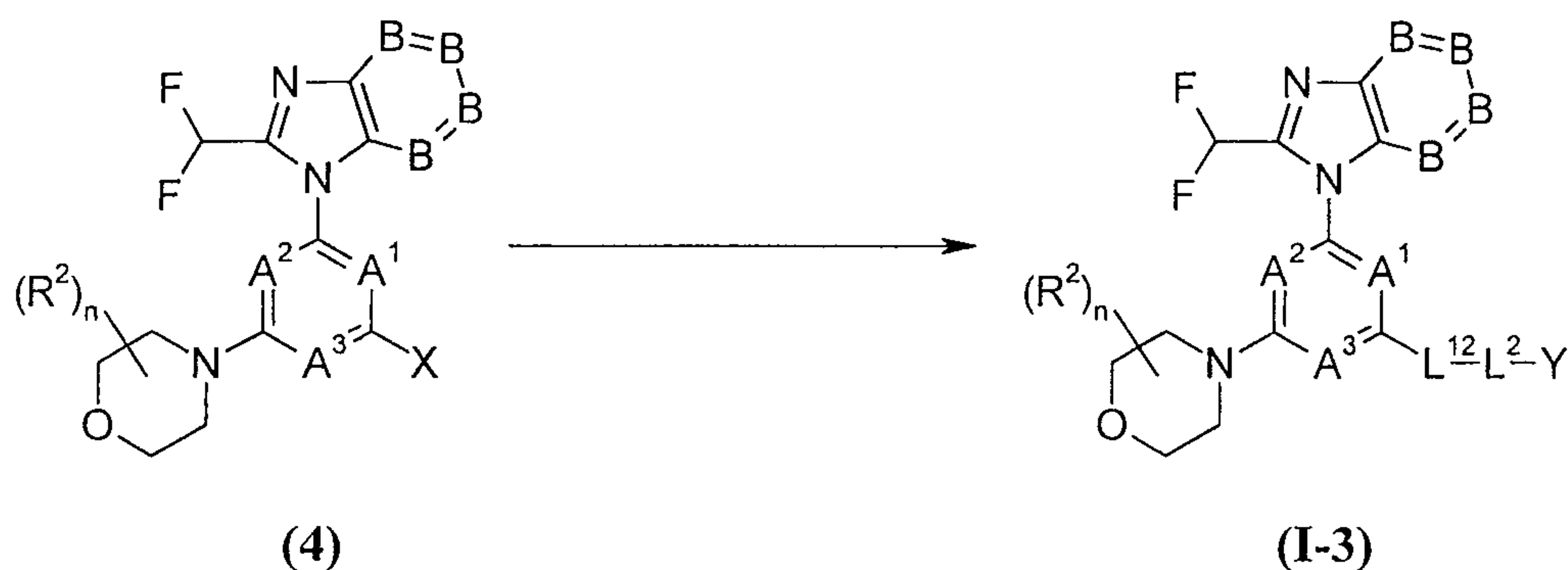
[0049]

The compound of the formula (I-2) can be obtained by the reaction of a compound (2) and a compound (3). The reaction conditions are the same as in the Production Process 1.

[0050]

(Production Process 3)

[Chem. 7]



(wherein L¹² represents -lower alkynylene.)

[0051]

The compound (I-3) of the present invention can be obtained by a Sonogashira coupling reaction of a compound (4) and a terminal alkyne derivative.

Examples of the leaving group X include halogen, and the like.

The present reaction is carried out by using the compound (4) and the terminal alkyne derivative in equivalent amounts, or either thereof in an excess amount, and stirring a mixture thereof in a solvent which is inert to the reaction, under the temperature condition ranging from room temperature to heating and refluxing, usually for 0.1 hours to 5 days, in the presence of a base and a palladium catalyst. The present reaction is preferably carried out under inert gas atmosphere. Examples of the solvent used herein are not particularly limited, but include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, alcohols such as methanol, ethanol, 2-propanol, butanol, and the like, N,N-dimethylformamide, dimethylsulfoxide, and a mixed solvent thereof. As the base, inorganic bases such as potassium carbonate, sodium carbonate, cesium carbonate, potassium hydroxide, and the like are preferable. As the palladium catalyst, tetrakis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, palladium-1,1'-bis(diphenylphosphino)ferrocene chloride, and the like are preferred. Further, it may be advantageous in some cases for the smooth progress of the reaction to heat the reaction mixture by microwave irradiation.

[Documents]

“Metal-Catalyzed Cross-Coupling Reactions”, edited by A. d. Meijere and F. Diederich, Vol. 1, VCH Publishers Inc., 1997

“Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th Edition)”, edited by The Chemical Society of Japan, Vol. 13 (2005) (Maruzen)

[0052]

Various substituents on R^1 in the compound of the formula (I) can be easily converted into other functional groups by using the compound of the formula (I) as a starting material by means of the reactions described in Examples as described later, the reactions apparent to a person skilled in the art, or modified methods thereof. For example, the steps that can be usually employed by a person skilled in the art, such as O-alkylation, N-alkylation, oxidation, reduction, reductive alkylation, ring formation, hydrolysis, amidation, acylation, deprotection, epoxylation, and the like can be arbitrarily combined and performed.

[0053]

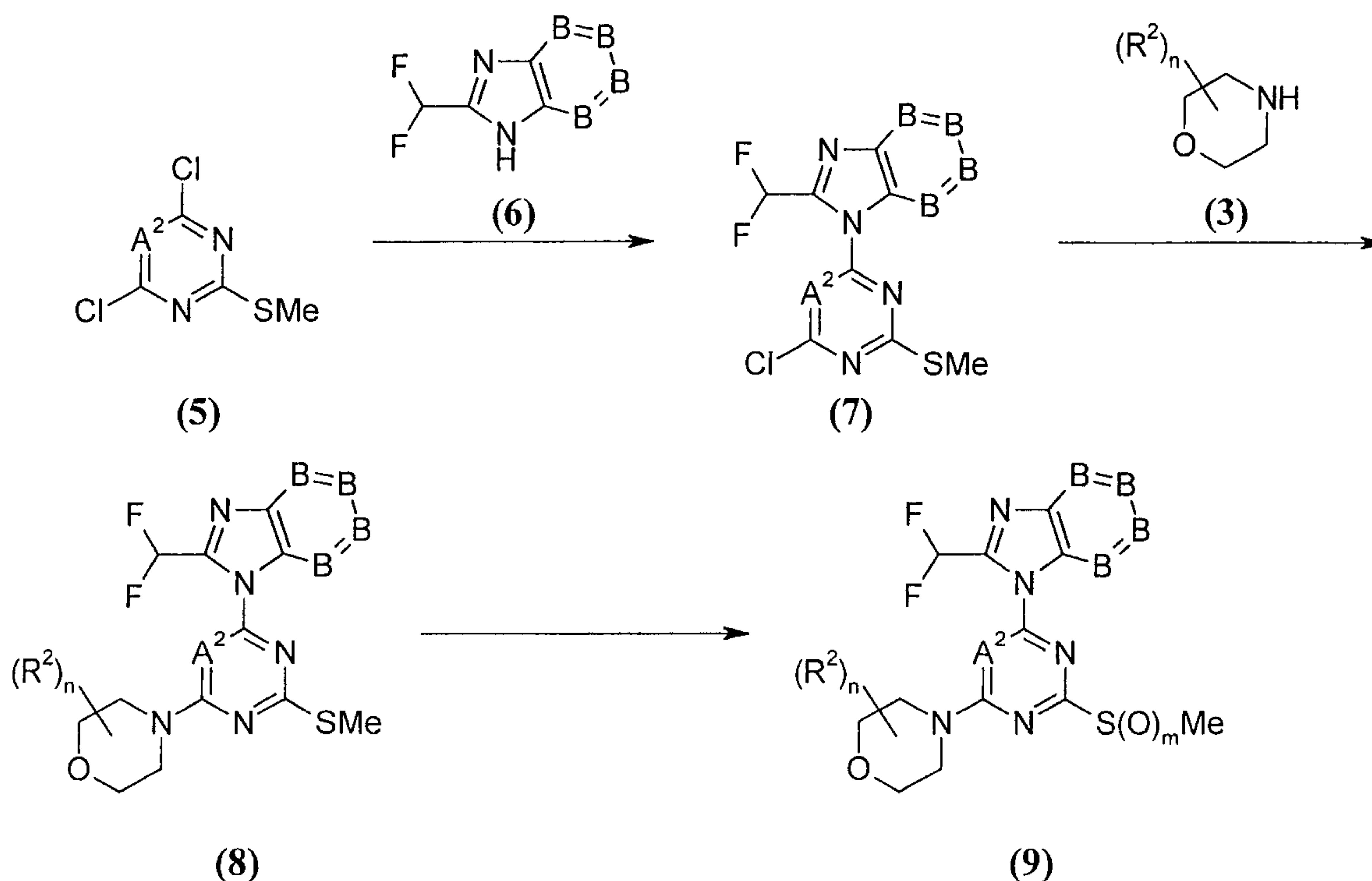
(Preparation of Starting Compound)

In the preparation method above, the starting compound can be prepared by using any of, for example, the methods below, the methods described in Preparation Examples as described later, known methods, or modified methods thereof.

[0054]

(Starting Material Synthesis 1)

[Chem. 8]



[0055]

The present production process is a method for preparing a compound (9), in which X is -S(O)_m-methyl in (1) which is the starting compound in Production Process 1.

[0056]

A compound (7) can be obtained by the reaction of a compound (5) with a compound (6).

The reaction condition is the same as in Production Process 1.

[0057]

A compound (8) can be obtained by the reaction of the compound (7) with the compound (3).

The reaction condition is the same as in Production Process 1.

[0058]

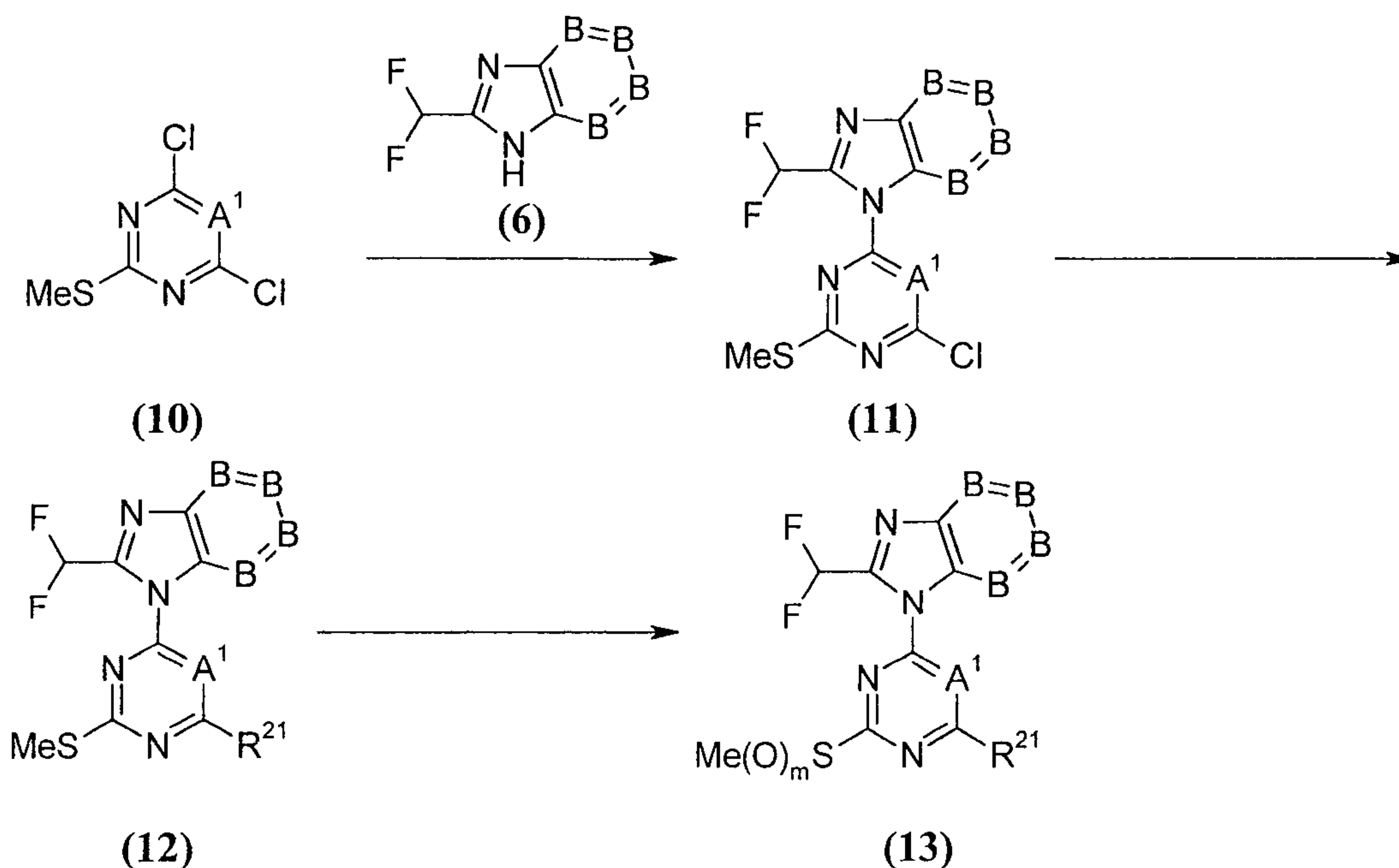
A compound (9) can be obtained by the oxidation reaction of the compound (8).

The present reaction can be carried out by using the compound (9) in an equivalent amount or an excess amount, in a range of from cooling to heating. As the solvent, solvents such as aromatic hydrocarbons and halogenated hydrocarbons may be used singly or in a mixture of two or more kinds thereof. Examples of the oxidant include m-chloroperbenzoic acid, peracetic acid, and a hydrogen peroxide solution.

[0059]

(Starting Material Synthesis 2)

[Chem. 9]



[0060]

The present production process is a method for preparing a compound (13), in which X is -S(O)_m-methyl and R¹ is R²¹, in (2) which is the starting compound in Production Process 2.

[0061]

A compound (11) can be obtained by the reaction of the compound (10) with the compound (6).

The reaction conditions are the same as in Production Process 1.

5 [0062]

A compound (12) can be obtained by the ipso substitution reaction of the compound (11) with, for example, $-L^1-L^2-Y$.

The reaction conditions are the same as in Production Process 1.

[0063]

10 A compound (13) can be obtained by the oxidation reaction of the compound (12).

The reaction conditions are the same as in the oxidation reaction described in Starting Material Synthesis 1.

[0064]

15 Other starting compounds (1), (2), and (4) can be prepared by, for example, the methods described in the following documents: WO2002/088112, EP1389617, WO2008/032033, WO2008/032036, WO2008/032041, or WO2008/032060.

[0065]

20 The compounds of the formula (I) can be isolated and purified as their free compounds, pharmaceutically acceptable salts, hydrates, solvates, or polymorphic crystalline substances thereof. The pharmaceutically acceptable salts of the compound of the formula (I) can be prepared by carrying out the treatment of a conventional salt forming reaction.

Isolation and purification are carried out by employing ordinary chemical operations such as extraction, fractional crystallization, various types of fractional chromatography, and the like.

25 Various isomers can be prepared by selecting an appropriate starting compound or separated by using the difference in the physicochemical properties between the isomers. For example, the optical isomers can be obtained by means of a general method for designing optical resolution of racemates (for example, fractional crystallization for inducing diastereomer salts with optically active bases or acids, chromatography using a chiral column or the like, and others), and further, the isomers can also be prepared from an appropriate optically active starting compound.

[0066]

The pharmacological activity of the compound of the formula (I) was confirmed by the tests shown below.

35 1. PI3K δ Enzyme Inhibitory Activity

For the experiment, a PI3-Kinase HTRF Assay kit (Millipore® Corporation, Catalogue No. 33-016) and a human PI3K δ enzyme (Millipore® Corporation, Catalogue No. 14-604) were

used. The measurement method was in accordance with the appended instructions. The overview thereof is as follows.

PI3K δ (10 ng/well), phosphatidylinositol-4,5-bisphosphate (10 μ M), ATP (30 μ M), and the test compound were mixed in a 384-well plate (total 20 μ L), and incubated at room temperature for 30 minutes. EDTA and biotinylated phosphatidylinositol-3,4,5-triphosphate were added thereto to stop the reaction. Thereafter, a Europium labeled anti-GST antibody, a GST bond GRP1 PH domain, and streptavidin-APC were added thereto, followed by incubation overnight. An HTRF ratio was measured using an HTRF plate reader. The IC₅₀ value of the compound was calculated, taking the inhibition rate without addition of the enzyme as 100% and the inhibition rate without addition of the test compound and with addition of an enzyme as 0%, by means of a logistic method.

[0067]

2. PI3K α Enzyme Inhibitory Activity

Human PI3K α (12 ng/well, Millipore Corporation, Catalogue No. 14-602), phosphatidylinositol (0.2 μ g/well), and the test compound were mixed in a 384-well plate in a reaction buffer (50 mM Hepes, 10 mM NaCl, 10 mM MgCl₂, 2 mM EGTA, 2 mM DTT, pH 7.3) (total 10 μ L), and incubated at 37°C for 3 hours. After the reaction, 10 μ L of a Kinase-Glo Plus reagent (Promega, Catalogue No. V3772) was added thereto, and a luminescence was measured with a luminometer. The IC₅₀ value of the compound was calculated, taking the inhibition rate without addition of the enzyme as 100% and the inhibition rate without addition of the test compound as 0%, by a logistic method.

The results of the IC₅₀ values (nM) of several representative compounds are shown in Table 1. In the Table, Ex represents Example Compound No. as described later of the test compounds.

[0068]

[Table 1]

Ex	PI3K δ	PI3K α
1	29	2800
4	60	>3000
10	5.8	>3000
13	36	980
16	69	>10000
18	50	7700
20	19	1800
25	69	6200
28	35	>3000
29	45	>3000
30	12	>3000
33	11	>3000
34	14	>3000
35	18	4200
36	17	6700
37	20	1900
38	23	2200
39	27	3900
40	20	>10000
43-1	8	13000
43-2	8.6	8000
44	14	5000
45	56	6800
67	47	990
69	22	10000
75	25	5400
77	18	5400
78	8.5	2900
85	21	5500
87	4.9	>10000
99	16	>10000
100	5.7	>3000
120	27	6400
121	13	4900
123	4.5	>3000
132	12	>10000
133	5.2	5900

Ex	PI3K δ	PI3K α
134	4.7	6600
135	3.0	8000
136	4.0	>10000
137	5.2	>10000
158	11	6700
193	4.9	8200
194	5.8	3300
195	4.1	>10000
196	4.8	>10000
215	13	>10000
216	13	>10000
224	3.3	7300
248	34	720
371	35	5000
389	11	>10000
423	24	>10000
441	48	1400
A4	31	730
A290	7.4	3800
A293	19	3200
A298	28	3500
A299	26	4900
A300	26	6500
A449	20	1400
A451	35	2200
A463	27	3100
A464	10	2200
A466	15	2000
A475	25	1400
A561	14	2900
A564	19	3000
A567	11	1600

For the experiment, male LEW/CrlCrlj rats (Charles River Laboratories, Japan, Inc.) (6-week old, body weight 130 to 180 g) were used. The test compound was suspended in a 0.5% methyl cellulose solution and orally administered at 5 mL/kg. IL-2 production was induced by tail vein injection of Concanavalin A (Funakoshi Corporation, Catalogue No. L-1000) at a dose of 15 mg/kg.

The test was carried out according to the protocol shown below. At 2 hours or 16 hours before administration of Concanavalin A, the test compound was orally administered to rats. At 3 hours after administration of Concanavalin A, blood was collected. The IL-2 concentration in blood was quantified using an ELISA kit (R&D Systems, Inc., Catalogue No. DY502E). An inhibition rate was calculated from the amount of IL-2 produced in a group administered with the test compound with respect to the amount of the IL-2 produced in a control group administered with a vehicle.

[0070]

As a result, it was confirmed that when the test compounds (10 mg/kg) were administered, for example, 2 hours before the administration of Concanavalin A, the several representative compounds of Examples 10, 29, 33, 34, 37, 43-1, and A4 exhibited inhibitory activities of 77%, 51%, 75%, 72%, 81%, 73%, and 58%, respectively, and had excellent IL-2 production inhibitory activities.

[0071]

4. Rat B Cell Proliferation Inhibition Test

Spleen cells (1.0×10^5 cells/well) prepared from male LEW/CrlCrlj rats (Charles River Laboratories, Japan, Inc.), mouse F(ab')₂ fragment anti-rat IgM (3 µg/well, SouthernBiotech Associates, Inc., Catalogue No. 3082-14) and the test compound dissolved in DMSO (final DMSO concentration 0.1%) were mixed in a 96-well plate using a 10% FCS-containing RPMI-1640 culture medium (total 200 µL). They were cultured in a CO₂ incubator for 48 hours and [³H]thymidine (925 GBq/mmol, Moravek Biochemicals, Inc., Catalogue No. MT6038) was added thereto at 0.037 MBq/well at 4 hours before completion of culture. Cells were harvested in a GF/C glass filter using a cell harvester, and a radioactivity on the filter was measured using a liquid scintillation counter. The IC₅₀ value of the compound was calculated, taking the dpm (disintegration per minute) without addition of IgM as an inhibition rate of 100% and the dpm without addition of the test compound as an inhibition rate of 0%, by a logistic method.

The results of several representative compounds are shown in Table 2.

[0072]

[Table 2]

Ex	IC ₅₀ (nM)
10	2.9
36	6.8
37	1.52
38	2.9
40	9.0
43-1	2.1
43-2	3.1
85	2.6
87	3.5
99	2.5

Ex	IC ₅₀ (nM)
121	2.0
132	1.5
134	3.4
135	2.5
136	1.7
137	4.6
158	10
193	4.1
195	3.0
196	3.6

Ex	IC ₅₀ (nM)
215	6.7
216	5.7
224	1.5
248	1.4
389	4.4
423	3.1
441	1.8
A290	2.2
A293	2.6
A298	1.2

Ex	IC ₅₀ (nM)
A299	2.5
A300	2.6
A449	0.4
A451	1.2
A463	1.4
A466	1.8
A475	1.1
A561	3.9
A564	2.2
A567	1.8

[0073]

As shown in the tests above, it was confirmed that several representative compounds have excellent PI3K δ selective inhibitory action, and/or IL-2 production inhibitory action, and/or B cell proliferation inhibitory action (including an activation inhibitory action). Accordingly, the compound of the formula (I) can be used as an agent for preventing or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and/or hematologic tumor.

[0074]

Furthermore, since the compound of the formula (I) is a PI3K δ inhibitor having a significantly potent PI3K δ inhibitory action than a PI3K α inhibitory action, it can be an excellent immunosuppressing agent which does not cause insulin resistance based on the PI3K α inhibitory action.

[0075]

The various types of organs include the kidney, liver, and heart. The rejection reaction in organ transplantation involves chronic rejection and acute rejection, and its mechanism is largely classified into antibody-related rejection and T cell-related rejection. The compound of the formula (I) or a salt thereof is useful particularly as an agent for preventing and/or treating antibody-related rejection.

[0076]

A pharmaceutical composition containing one or two or more kinds of the compound of the formula (I) or a salt thereof as an active ingredient can be prepared using excipients that are usually used in the art, that is, excipients for pharmaceutical preparations, carriers for pharmaceutical preparations, and the like according to the methods usually used.

Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, or the like, or parenteral administration, such as use

of injections such as intraarticular, intravenous, and intramuscular injections, suppositories, eye drops, eye ointments, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalers, and the like.

[0077]

5 The solid composition for use in the oral administration is used in the form of tablets, powders, granules, or the like. In such a solid composition, one or more active ingredient(s) are mixed with at least one inactive excipient such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, and/or magnesium aluminometasilicate. In an ordinary method, the composition may
10 contain inactive additives, such as a lubricant such as magnesium stearate, a disintegrating agent such as sodium carboxymethyl starch, a stabilizer, or a solubilization assisting agent. If necessary, tablets or pills may be coated with sugar or a film of a gastric-soluble or enteric coating substance.

 The liquid composition for oral administration contains pharmaceutically
15 acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and also contains generally used inert diluents, for example, purified water and ethanol. In addition to the inert diluent, the liquid composition may also contain auxiliary agents such as a solubilization assisting agent, a moistening agent, and a suspending agent, sweeteners, flavors, aromatics, or antiseptics.

20 [0078]

 The injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. The aqueous solvent includes, for example, distilled water for injection and physiological saline. Examples of the non-aqueous solvent include propylene glycol, polyethylene glycol, plant oils such as olive oil, alcohols
25 such as ethanol, Polysorbate 80 (Japanese Pharmacopeia), and the like. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizer, or a solubilizing assisting agent. These are sterilized, for example, by filtration through a bacteria retaining filter, blending of a bactericide, or irradiation. In addition, these can also be used by preparing a sterile solid
30 composition, and dissolving or suspending it in sterile water or a sterile solvent for injection prior to its use.

[0079]

 The agent for external use includes ointments, plasters, creams, jellies, poultices, sprays, lotions, eye drops, and eye ointments. The agents contain generally used ointment
35 bases, lotion bases, aqueous or non-aqueous liquid preparations, suspensions, and emulsions. Examples of the ointment bases or the lotion bases include polyethylene glycol, propylene glycol, white vaseline, bleached beeswax, polyoxyethylene hydrogenated

castor oil, glyceryl monostearate, stearyl alcohol, cetyl alcohol, laurmacrogol, and sorbitan sesquioleate.

[0080]

As the transmucosal agents such as an inhaler and a transnasal agent, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with a conventionally known method. For example, a known excipient, and also a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizer, a thickening agent, or the like may be appropriately added thereto. For their administration, an appropriate device for inhalation or blowing can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier, using a known device or sprayer, such as a measured administration inhalation device. A dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a powder-containing capsule may be used. Alternatively, this may be in a form such as a pressurized aerosol spray which uses an appropriate propellant, for example, a suitable gas such as chlorofluoroalkane, hydrofluoroalkane, and carbon dioxide.

[0081]

Typically, in oral administration, the daily dose is appropriately from about 0.001 to 100 mg/kg, preferably from 0.1 to 30 mg/kg, and more preferably 0.1 to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 separate portions. In the case of intravenous administration, the daily dose is suitably administered from about 0.0001 to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 to 100 mg/kg per body weight, once a day or two or more times a day. The dose is appropriately decided in response to the individual case by taking the symptoms, the age, and the gender, and the like into consideration.

[0082]

Although varying depending on administration routes, dosage forms, administration sites, or the types of excipients and additives, the pharmaceutical composition of the present invention contains 0.01 to 100% by weight, and in a certain embodiment, 0.01 to 50% by weight of one or more kinds of the compound of the formula (I) or a salt thereof, which is an active ingredient.

[0083]

The compound of the formula (I) can be used in combination with various agents for treating or preventing the diseases, in which the compound of the formula (I) is considered effective. In such use in combination, drugs may be administered simultaneously or separately in succession or at desired time intervals. Formulations for simultaneous administration may be in either mixed or have separate forms.

(Examples)

[0084]

Hereinbelow, the preparation methods for the compound of the formula (I) and the starting compounds thereof will be described in more detail with reference to Examples, but the present invention is not limited to the compounds described in the Examples below. Further, the production processes for the starting compounds will be each described in Preparation Examples. In addition, the preparation methods for the compound of the formula (I) are not limited to the preparation methods of the specific Examples shown below, but the compound of the formula (I) can be prepared by a combination of the preparation methods or a method that is apparent to a person skilled in the art.

[0085]

Furthermore, the following abbreviations may be used in some cases in Preparation Examples, Examples, and Tables below.

PEx: Preparation Example No., Ex: Example No., Syn: Example No. prepared by the same method, PSyn: Preparation Example No. prepared by the same method, Str: Structural formula, DAT: Physicochemical data, ESI+: m/z values in mass spectroscopy (Ionization ESI, representing $(M+H)^+$ unless otherwise specified), ESI-: m/z values (Ionization ESI, representing $(M-H)^-$ unless otherwise specified), NMR1: δ (ppm) in ^1H NMR in DMSO- d_6 , NMR2: δ (ppm) in ^1H NMR in $CDCl_3$, s: singlet (spectrum), d: doublet (spectrum), t: triplet (spectrum), q: quartet (spectrum), br: broad line (spectrum) (e.g.: br-s), RT: retention time (min) in HPLC, [M] in Preparation Examples and Examples: [mol/L], SFC preparative: preparative supercritical fluid chromatography, DEA: diethylamine.

Furthermore, for example, a description of "26+44" in Syn of Example Tables indicates that preparation is performed by the same method as in Example 26, and subsequently the product is prepared by the same method as in Example 44 as a starting material. Further, in Preparation Example Tables, there is, for example, a description of Syn. 87 in the PSyn column of Preparation Example 148, indicating that Preparation Example 148 is prepared by the same method as in Example 87. In Example Tables, there is, for example, a description of PSyn. 8 in the Syn column of Example 295, indicating that Example 295 is prepared by the same method as in Preparation Example 8. HCl in the structural formula denotes hydrochloride and the numeral before HCl denotes a molar ratio. For example, 2HCl means dihydrochloride. Further, Me in the structural formula denotes a methyl group, Et denotes an ethyl group, Ph denotes a phenyl group, iBu denotes an isobutyl group, tBu denotes a tert-butyl group, and Boc denotes a tert-butoxycarbonyl group. The compound having "*" in the structure indicates that the compound is an optically active substance.

[0086]

Preparation Example 1

To a solution of 4,6-dichloro-2-(methylsulfanyl)pyrimidine (5 g) in N,N-dimethylformamide (50 mL) were added potassium carbonate (5.3 g) and 2-(difluoromethyl)-1H-benzimidazole (3.9 g), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by silica gel column chromatography (hexane:ethyl acetate) to obtain 1-[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]-2-(difluoromethyl)-1H-benzimidazole (5.49 g) as a white powder.

[0087]

Preparation Example 2

To a solution of 1-[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]-2-(difluoromethyl)-1H-benzimidazole (2.2 g) in N,N-dimethylformamide (11 mL) were added potassium carbonate (1.4 g) and morpholine (0.88 mL), and the mixture was stirred at room temperature for 1 hour. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by silica gel column chromatography (hexane:ethyl acetate) to obtain 2-(difluoromethyl)-1-[2-(methylsulfanyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (2.1 g) as a white powder.

[0088]

Preparation Example 3

To a solution of 2-(difluoromethyl)-1-[2-(methylsulfanyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (3 g) in dichloromethane (60 mL) was added m-chloroperbenzoic acid (75% wet) (1.9 g) under ice-cooling, and the mixture was stirred at 0°C for 15 minutes. To the reaction mixture was added a saturated aqueous sodium bicarbonate solution, followed by extraction with dichloromethane. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by silica gel column chromatography (chloroform:methanol) to obtain 2-(difluoromethyl)-1-[2-(methylsulfinyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (2.8 g) as a pale yellow amorphous substance.

[0089]

Preparation Example 4

To a solution of 2-(difluoromethyl)-1-[2-(methylsulfanyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (2.1 g) in dichloromethane (21 mL) was added m-chloroperbenzoic acid (75% wet) (2.7 g) under ice-cooling and the mixture was stirred at

0°C for 15 minutes. To the reaction mixture was added a saturated aqueous sodium bicarbonate solution, followed by extraction with dichloromethane. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by silica gel column chromatography (chloroform:methanol) to obtain 2-(difluoromethyl)-1-[2-(methylsulfonyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (2.27 g) as a pale yellow amorphous substance.

[0090]

Preparation Example 5

To a mixture of 1-[6-chloro-2-(methylsulfonyl)pyrimidin-4-yl]-2-(difluoromethyl)-1H-benzimidazole (1 g) and N,N-dimethylacetamide (10 mL) were added tert-butyl 4-(hydroxymethyl)piperidine-1-carbamate (1 g) and cesium carbonate (3 g), and the mixture was stirred at 120°C for 3 hours. The reaction mixture was poured into water, followed by extraction with hexane-ethyl acetate (1:1). The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by silica gel column chromatography (hexane:ethyl acetate) to obtain tert-butyl 4-[(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(methylsulfonyl)pyrimidin-4-yl}oxy)methyl]piperidine-1-carbamate (680 mg) as a white amorphous substance.

[0091]

Preparation Example 6

N-(2-{[6-Chloro-2-(methylsulfonyl)pyrimidin-4-yl]amino}-5-methylphenyl)acetamide (270 mg) was dissolved in a mixed solvent of ethanol (2.8 mL) and 1,4-dioxane (2.8 mL), and 6 M hydrochloric acid (9.6 mL) was added thereto, followed by heating and refluxing for 3 hours. After air-cooling to room temperature, the pH was adjusted to 6 to 7 using saturated aqueous sodium bicarbonate, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to obtain N¹-[6-chloro-2-(methylsulfonyl)pyrimidin-4-yl]-4-methylbenzene-1,2-diamine (230 mg).

[0092]

Preparation Example 7

A mixture of 2-(methylsulfonyl)-6-(morpholin-4-yl)pyrimidin-4-amine (500 mg), 2-bromo-1-methyl-3-nitrobenzene (1 g), tris(dibenzylideneacetone)dipalladium (0) (202 mg), (9,9-dimethyl-9H-xanthen-4,5-diyl)bis(diphenylphosphine) (192 mg), and cesium carbonate (1.0 g) in toluene was stirred in a microwave reactor at 140°C for 1 hour. The reaction mixture was filtered through celite and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate) to

obtain N-(2-methyl-6-nitrophenyl)-2-(methylsulfanyl)-6-(morpholin-4-yl)pyrimidin-4-amine (756 mg) as a yellow powder.

[0093]

Preparation Example 8

5 N-(2-Methyl-6-nitrophenyl)-2-(methylsulfanyl)-6-(morpholin-4-yl)pyrimidin-4-amine (750 mg) was dissolved in ethanol (22.5 mL), and iron chloride (III) hexahydrate (56 mg) and activated carbon (75 mg) were added thereto, followed by stirring at 80°C. Hydrazine monohydrate was added dropwise thereto, followed by heating and refluxing overnight. The reaction mixture was cooled to room temperature and filtered through
10 celite®. The mother liquid was concentrated and the residue was purified using silica gel column chromatography (hexane:ethyl acetate) to obtain 3-methyl-N²-[2-(methylsulfanyl)-6-(morpholin-4-yl)pyrimidin-4-yl]benzene-1,2-diamine (544 mg) as a pale yellow powder.

[0094]

Preparation Example 9

15 To tert-butyl [(2S)-1-{{[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]amino}-4-(methylsulfanyl)-1-oxobutan-2-yl]carbamate (760 mg) was added methyl iodide (3.5 mL), followed by stirring at room temperature overnight. Methyl iodide was evaporated under reduced pressure to obtain a desired compound [(3S)-3-[(tert-butoxycarbonyl)amino]-4-{{[trans-4-({6-[2-
20 (difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]amino}-4-oxobutyl](dimethyl)sulfonium iodide (919 mg).

[0095]

Preparation Example 10

25 4,6-Dichloro-2-(methylsulfanyl)pyrimidine (50 mg) and tert-butyl (2-amino-4-methylphenyl)carbamate (57 mg) were dissolved in dimethylacetamide (250 µL), and N,N-diisopropyl ethylamine (69 µL) was added thereto, followed by stirring at 100°C for 7 hours. After the completion of the reaction, the mixture was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The extracts were washed with saturated brine, the organic layer was dried over anhydrous magnesium
30 sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane) to obtain a desired compound tert-butyl (2-{{[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]amino}-4-methylphenyl)carbamate (50 mg) as a white powder.

[0096]

35 Preparation Example 11

tert-Butyl (2-{{[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]amino}-4-methylphenyl)carbamate (8.5 g) was dissolved in 1,4-dioxane (85 mL), and a 4 M solution (56 mL) of hydrogen chloride in 1,4-dioxane was added thereto, followed by stirring at

room temperature for 8 hours. After the completion of the reaction, a saturated aqueous sodium bicarbonate solution and a 4 M aqueous sodium hydroxide solution were added thereto. The mixture was quenched, made free, and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to obtain N²-[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]-4-methylbenzene-1,2-diamine (6 g) as a yellow powder.

[0097]

Preparation Example 12

N²-[6-Chloro-2-(methylsulfanyl)pyrimidin-4-yl]-4-methylbenzene-1,2-diamine (6 g) and difluoroacetic anhydride (7.4 g) were dissolved in acetonitrile (60 mL), followed by stirring at room temperature for 1 hour. After confirming that the starting material had been disappeared, a 4 M solution (53 mL) of hydrogen chloride in 1,4-dioxane was added thereto, followed by stirring at 100°C for 10 hours. After the completion of the reaction, the mixture was cooled to room temperature, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine. The obtained organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:hexane) to obtain 1-[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]-2-(difluoromethyl)-6-methyl-1H-benzimidazole (2.9 g) as a white powder.

[0098]

Preparation Example 13

(3a'R,5'S,6a'S)-5,5-Dimethylhexahydro-1'H-spiro[1,3-dioxane-2,2'-pentalen]-5'-ol (1.0 g) and 1H-isoindole-1,3(2H)-dione (780 mg) and triphenylphosphine (1.39 g) were dissolved in tetrahydrofuran (17 mL), and a 2.2 M solution (2.41 mL) of ethyl azodicarbonate in tetrahydrofuran was added dropwise thereto at 0°C, followed by stirring at 0°C for 1 hour and at room temperature for 4 hours. To the reaction solution was added silica gel, followed by concentrating and purifying using silica gel column chromatography (hexane:ethyl acetate) to obtain 2-[(3a'R,5'r,6a'S)-5,5-dimethylhexahydro-1'H-spiro[1,3-dioxane-2,2'-pentalen]-5'-yl]-1H-isoindole-1,3(2H)-dione (1.1 g) as a white powder.

[0099]

Preparation Example 14

To a mixture of ethyl-4-(4-cyanophenyl)-1-piperazine carboxylate (10 g), sodium borohydride (3.4 g), and tetrahydrofuran (50 mL) was added a mixture of iodine (9.8 g) and tetrahydrofuran (50 mL) under a nitrogen gas flow while ice-cooling, followed by stirring at the same temperature for 1 hour, and then further heating and refluxing for 3 hours. The reaction solution was ice-cooled and a 6 M hydrochloric acid solution was added thereto to adjust the pH to 1. The reaction solution was stirred at 70°C for 30

minutes. After leaving to be cooled, sodium hydroxide was added thereto to adjust the pH to 10, followed by extraction with ethyl acetate. The extracts were washed with saturated brine, the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was made into powder using
 5 tetrahydrofuran, ethyl acetate, and diisopropyl ether, to obtain ethyl-4-[4-(aminomethyl)phenyl]-1-piperazine carboxylate (5.2 g).

[0100]

Preparation Example 15

2-(Difluoromethyl)-1-[2-(methylsulfanyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-
 10 benzimidazole (2.1 g) was dissolved in methylene chloride (21 mL), and m-chloroperbenzoic acid (75% wet) (2.7 g) was added thereto under ice-cooling, followed by stirring at 0°C for 15 minutes. Saturated aqueous sodium bicarbonate was added thereto, followed by extraction with methylene chloride. The extracts were washed with water and saturated brine, the organic layer was dried over anhydrous magnesium sulfate, and the
 15 solvent was evaporated under reduced pressure. The residue was purified using silica gel column chromatography (chloroform:methanol) to obtain 2-(difluoromethyl)-1-[2-(methylsulfonyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (2.27 g) as a pale yellow amorphous substance.

[0101]

20 Preparation Example 16

To a mixture of 2-[(3a'R,5'r,6a'S)-5,5-Dimethylhexahydro-1'H-spiro[1,3-dioxane-2,2'-pentalen]-5'-yl]-1H-isoindole-1,3(2H)-dione (1.1 g), tetrahydrofuran (22 mL) and ethanol (22 mL) was added hydrazine monohydrate (0.75 mL), followed by heating and refluxing for 2 hours. The insoluble matter was removed by filtration through celite and
 25 concentrated under reduced pressure. To the residue was added chloroform, followed by drying over sodium sulfate, and then the solvent was evaporated under reduced pressure to obtain (3a'R,5's,6a'S)-5,5-dimethylhexahydro-1'H-spiro[1,3-dioxane-2,2'-pentalen]-5'-amine (0.74 g) as a white powder.

[0102]

30 Preparation Example 17

Benzyl 9-oxo-3-azaspiro[5.5]undecane-3-carboxylate (230 mg) was dissolved in methanol (4.5 mL) and methylene chloride (1.5 mL), and ammonium acetate (1.47 g) was added thereto, followed by stirring at room temperature for 10 minutes. Subsequently, sodium triacetoxyborohydride (323 mg) was added thereto, followed by stirring at room
 35 temperature overnight. To the reaction solution was added saturated aqueous sodium bicarbonate, followed by extraction with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated

under reduced pressure to obtain benzyl 9-amino-3-azaspiro[5.5]undecane-3-carboxylate (255 mg).

[0103]

Preparation Example 80

5 trans-4-(Dibenzylamino)cyclohexanol (200 mg), 2-(3-bromopropoxy)tetrahydro-2H-pyran (604 mg), powder potassium hydroxide (179 mg), and tetrabutylammonium bromide (44 mg) were suspended in xylene (2 mL), followed by stirring at room temperature for 2 hours. To the reaction mixture were added ethyl acetate and water, and the organic layer was extracted and washed with saturated brine and dried over anhydrous
10 magnesium sulfate. The solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=100:0-80:20) to obtain trans-N,N-dibenzyl-4-[3-(tetrahydro-2H-pyran-2-yloxy)propoxy]cyclohexanamine (174 mg).

[0104]

15 Preparation Example 81

trans-N,N-Dibenzyl-4-[3-(tetrahydro-2H-pyran-2-yloxy)propoxy]cyclohexanamine (170 ml) was dissolved in methanol (1 mL), and a 4 M solution (972 μ L) of hydrogen chloride in 1,4-dioxane was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was neutralized with a
20 saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 3-{{trans-4-(dibenzylamino)cyclohexyl}oxy}propan-1-ol (110 mg).

[0105]

25 Preparation Example 82

To 3-{{trans-4-(dibenzylamino)cyclohexyl}oxy}propan-1-ol (110 mg) were added tosyl chloride (60 mg) and pyridine (51 μ L) under ice-cooling, followed by stirring at room temperature for 1 hour. To the reaction mixture were added N,N-dimethylformamide (1.1 mL), potassium carbonate (43 mg), and pyrrolidine (26 μ L), followed by stirring at room
30 temperature overnight. The reaction mixture were added ethyl acetate and water, and the organic layer was extracted, washed with saturated brine, and then dried over anhydrous magnesium sulfate. Then, the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=90:10-70:30) to obtain trans-N,N-dibenzyl-4-[3-(pyrrolidin-1-yl)propoxy]cyclohexanamine (70 mg).

[0106]

Preparation Example 83

trans-N,N-Dibenzyl-4-[3-(pyrrolidin-1-yl)propoxy]cyclohexanamine (115 mg) was dissolved in ethanol (2.3 ml), and 20% palladium hydroxide/carbon 50% wet was added thereto, followed by catalytic reduction at room temperature for 4 hours at 3 atm under a hydrogen atmosphere. The catalyst was removed by filtration after nitrogen
 5 substitution, and then concentrated under reduced pressure to obtain trans-4-[3-(pyrrolidin-1-yl)propoxy]cyclohexanamine (48 mg).

[0107]

Preparation Example 84

Triethyl phosphonoacetate (107 mg) was dissolved in tetrahydrofuran (1 mL), and
 10 60% sodium hydride (19 mg) was added thereto, followed by stirring at room temperature for 30 minutes. A solution of tert-butyl (trans-4-formylcyclohexyl)carbamate (90 mg) in tetrahydrofuran (1 mL) was added dropwise thereto, followed by stirring at room temperature for 2 hours. Ethyl acetate and water were added thereto, followed by extraction with ethyl acetate. The extracts were washed with saturated brine and then
 15 dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-50:50) to obtain ethyl (2E)-3-{trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}acrylate (100 mg).

[0108]

20 Preparation Example 85

60% Sodium hydride (394 mg) was suspended in 1,2-dimethoxyethane (20 mL), and tert-butyl 4-hydroxybenzylcarbamate (1 g) and 15-crown-5-ether (1.09 g) were added thereto, followed by stirring at room temperature for 30 minutes. 4,6-Dichloro-2-(methylsulfonyl)pyrimidine was added thereto, followed by stirring at 80°C overnight.
 25 The reaction solution was cooled to room temperature and then an aqueous ammonium chloride solution (50 mL) was added thereto, followed by extraction with ethyl acetate. The extracts were washed with water and saturated brine, and the organic layer was dried over anhydrous magnesium sulfate. The desiccant was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified using silica gel
 30 column chromatography (hexane:ethyl acetate=95:5-85:15) to obtain tert-butyl{4-[(4,6-dichloropyrimidin-2-yl)oxy]benzyl}carbamate (762 mg).

[0109]

Preparation Example 86

A mixture of 4,6-dichloro-2-(methylsulfonyl)pyrimidine (700 mg), 2-
 35 (difluoromethyl)-4-ethoxy-1H-benzimidazole (761 mg), potassium carbonate (744 mg), and N,N-dimethylformamide (7 mL) was stirred at room temperature overnight. To the mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The desiccant

was removed by filtration and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-80:20) to obtain 1-[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]-2-(difluoromethyl)-4-ethoxy-1H-benzimidazole (464 mg) (Preparation Example 86-1) and 1,1'-[2-(methylsulfanyl)pyrimidine-4,6-diyl]bis[2-(difluoromethyl)-4-ethoxy-1H-benzimidazole]. 1,1'-[2-(Methylsulfanyl)pyrimidine-4,6-diyl]bis[2-(difluoromethyl)-4-ethoxy-1H-benzimidazole] was suspended in ethyl acetate and warmed. After leaving to be cooled, the insoluble matter was collected by filtration to obtain 1,1'-[2-(methylsulfanyl)pyrimidine-4,6-diyl]bis[2-(difluoromethyl)-4-ethoxy-1H-benzimidazole] (275 mg) (Preparation Example 86-2).

[0110]

Preparation Example 87

To a mixture of trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexanamine (700 mg) and N,N-dimethylformamide (7.0 mL) were added N-(tert-butoxycarbonyl)-N-methyl-L-methionine (622 mg), 1H-benzotriazol-1-ol (319 mg), and N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (452 mg), followed by stirring at room temperature overnight. After the completion of the reaction, water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate. The desiccant was removed by filtration and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane:ethyl acetate=90:10-40:60) to obtain tert-butyl [(2S)-1-{{[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]amino}-4-(methylsulfanyl)-1-oxobutan-2-yl]methylcarbamate (859 mg).

[0111]

Preparation Example 88

To a mixture of methyl[(2S)-1-({trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}amino)-4-(methylsulfanyl)-1-oxobutan-2-yl]carbamate (1.5 g), methylene chloride (15 mL) and methanol (15 mL) was added methyl iodide (11.6 mL), followed by stirring at room temperature overnight. The solvent was evaporated under reduced pressure, and to a mixture of the residue and dimethylformamide (7.5 mL) was added cesium carbonate (3.6 g), followed by stirring overnight. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine. The organic layer was dried over anhydrous sodium sulfate, the desiccant was removed by filtration, and then the solvent was evaporated under reduced pressure. To the residue was added ethanol, and the resulting solid was collected

by filtration and dried under reduced pressure to obtain methyl[(3S)-1-{trans-4-[(tert-butoxycarbonyl)amino]cyclohexyl}-2-oxopyrrolidin-3-yl]carbamate (0.88 g).

[0112]

Preparation Example 89

To a solution of 1,1'-[2-(methylsulfanyl)pyrimidine-4,6-diyl]bis[2-(difluoromethyl)-1H-benzimidazole] (2 g) in N,N-dimethylacetamide (10 mL) were added tert-butyl (3S)-3-(hydroxymethyl)pyrrolidine-1-carboxylate (965 mg) and cesium carbonate (2.1 g), followed by stirring at 60°C for 5 hours. After the completion of the reaction, to the reaction solution was added ice water and the precipitated solid was collected by filtration. After drying, the resultant was dissolved in dichloromethane and purified by silica gel column chromatography (hexane:ethyl acetate=90:10-65:35) to obtain tert-butyl (3S)-3-[(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(methylsulfanyl)pyrimidin-4-yl}oxy)methyl]pyrrolidine-1-carboxylate (2.01 g).

[0113]

Preparation Example 90

A mixture of 1-[6-chloro-2-(methylsulfanyl)pyrimidin-4-yl]-2-(difluoromethyl)-1H-benzimidazole (350 mg), methyl[(3R)-1-(trans-4-aminocyclohexyl)-2-oxopyrrolidin-3-yl]carbamate hydrochloride (344 mg), potassium carbonate (178 mg), N-ethyl-N-isopropylpropan-2-amine (1.1 mL), and N,N-dimethylacetamide (1.75 mL) was stirred at 60°C overnight. To the reaction solution were added water and ethyl acetate. The insoluble matter was collected by filtration, followed by extraction with ethyl acetate. The solvent was evaporated under reduced pressure, and then the residue and the insoluble matter were combined. Ethyl acetate was added thereto, and the mixture was suspended, stirred, and then collected by filtration. The resultant was washed with water and dried to obtain methyl{(3R)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(methylsulfanyl)pyrimidin-4-yl}amino)cyclohexyl]-2-oxopyrrolidin-3-yl}carbamate (446 mg).

[0114]

Example 1

A mixture of 2-difluoromethyl-1-[2-(methylsulfonyl)-6-morpholin-4-yl]pyrimidin-4-yl]-1H-benzimidazole (770 mg), tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (525 mg), potassium carbonate (390 mg), and N,N-dimethylacetamide (19 mL) was stirred in a microwave reactor at 100°C for 1 hour. The reaction mixture was cooled to room temperature and then poured into water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=80:20-50:50) to obtain tert-butyl (3S)-3-({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-

ylpyrimidin-2-yl}amino)pyrrolidine-1-carboxylate (310 mg) as a pale yellow amorphous substance.

[0115]

Example 22

5 A mixture of 2-(difluoromethyl)-1-[2-(methylsulfonyl)-6-morpholin-4-ylpyrimidin-4-yl]-1H-benzimidazole (100 mg), 1-benzyl-3-(methylamino)pyrrolidine (93 mg), potassium carbonate (50 mg), and N,N-dimethylacetamide (2.5 mL) was stirred in a microwave reactor at 100°C for 1 hour. The reaction mixture was cooled to room temperature and then poured into water, followed by extraction with ethyl acetate. The
10 organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=80:20-50:50). Desired fractions were combined and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane, and a 4 M solution (61 µL) of hydrogen chloride in 1,4-
15 dioxane was added thereto. Further, diisopropyl ether (10 mL) was added thereto. The resulting powder was collected by filtration, washed with diisopropyl ether, and dried under reduced pressure to obtain N-(1-benzylpyrrolidin-3-yl)-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-morpholin-4-ylpyrimidin-2-amine hydrochloride (28 mg) as a pale yellow powder.

20 [0116]

Example 26

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-[(3S)-pyrrolidin-3-yl]pyrimidin-2-amine dihydrochloride (58 mg) and N,N-dimethylformamide (1.2 mL) were added phenylacetaldehyde (21 mg), sodium
25 triacetoxyborohydride (75 mg), and acetic acid (0.29 mL), and the mixture was stirred at room temperature overnight. To the reaction mixture was added a saturated aqueous sodium bicarbonate solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino
30 silica gel column chromatography (hexane:ethyl acetate=80:20-50:50, and then chloroform:methanol=100:0-80:20) to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-[(3S)-1-(2-phenylethyl)pyrrolidin-3-yl]pyrimidin-2-amine (30 mg) as a white powder.

[0117]

35 Example 43

To a solution of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-(piperidin-4-ylmethyl)pyrimidin-2-amine (400 mg) in 1,2-dichloroethane (8 mL) was added 4-fluorocyclohexanone (210 mg), and the mixture was stirred at room temperature

for 10 minutes. Subsequently sodium triacetoxyborohydride (382 mg) was added thereto, followed by stirring at room temperature overnight. To the reaction mixture was added a saturated aqueous sodium bicarbonate solution, followed by extraction with chloroform. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=70:30-40:60) to obtain two types of compounds below, each as a white powder.

4-[2-(Difluoromethyl)-1H-benzimidazol-1-yl]-N-[[1-(trans-4-fluorocyclohexyl)piperidin-4-yl]methyl]-6-(morpholin-4-yl)pyrimidin-2-amine (109 mg)

The R_f value in amino silica gel TLC (hexane:ethyl acetate=50:50) of the present compound was 0.35.

4-[2-(Difluoromethyl)-1H-benzimidazol-1-yl]-N-[[1-(cis-4-fluorocyclohexyl)piperidin-4-yl]methyl]-6-(morpholin-4-yl)pyrimidin-2-amine (87 mg)

The R_f value in amino silica gel TLC (hexane:ethyl acetate=50:50) of the present compound was 0.28.

The 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[[1-(trans-4-fluorocyclohexyl)piperidin-4-yl]methyl]-6-(morpholin-4-yl)pyrimidin-2-amine (80 mg) obtained above was dissolved in a mixed solvent of chloroform (1.5 mL) and methanol (0.3 mL), and a 4 M solution (0.37 mL) of hydrogen chloride in 1,4-dioxane was added thereto. The mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[[1-(trans-4-fluorocyclohexyl)piperidin-4-yl]methyl]-6-(morpholin-4-yl)pyrimidin-2-amine dihydrochloride (Example 43-1, 87 mg) as a white powder.

In the similar manner, 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[[1-(cis-4-fluorocyclohexyl)piperidin-4-yl]methyl]-6-(morpholin-4-yl)pyrimidin-2-amine dihydrochloride (Example 43-2, 70 mg) was obtained as a white powder from the 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[[1-(cis-4-fluorocyclohexyl)piperidin-4-yl]methyl]-6-(morpholin-4-yl)pyrimidin-2-amine (62 mg) obtained above.

[0118]

Example 44

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-N-[(1-phenylpiperidin-4-yl)methyl]pyrimidin-2-amine (38 mg), chloroform (0.75 mL), and methanol (0.35 mL) was added a 4 M solution (0.2 mL) of hydrogen chloride in 1,4-dioxane, and the mixture was stirred at room temperature for 10 minutes. The reaction mixture was concentrated under reduced pressure to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-N-[(1-phenylpiperidin-4-yl)methyl]pyrimidin-2-amine dihydrochloride (43 mg) as a white powder.

[0119]

Example 45

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-[(3S)-pyrrolidin-3-yl]pyrimidin-2-amine dihydrochloride (75 mg) and N,N-dimethylformamide (1.5 mL) were added 2-(dimethylamino)ethyl bromide (26 mg) and potassium carbonate (85 mg), and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=50:50-0:100, and subsequently chloroform:methanol=100:0-80:20). Desired fractions are combined and concentrated under reduced pressure. The residue was dissolved in 1,4-dioxane (0.5 mL) and a 4 M solution (80 μ L) of hydrogen chloride in 1,4-dioxane was added thereto. Diisopropyl ether (10 mL) was further added thereto. The resulting powder was collected by filtration, washed with diisopropyl ether, and dried under reduced pressure to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-{(3S)-1-[2-(dimethylamino)ethyl]pyrrolidin-3-yl}-6-morpholin-4-ylpyrimidin-2-amine dihydrochloride (10 mg) as a white powder.

[0120]

Example 52

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-(piperidin-4-ylmethyl)pyrimidin-2-amine (100 mg) and ethanol (2 mL) were added 2-(fluoromethyl)oxirane (19 μ L) and N,N-diisopropyl ethylamine (79 μ L), and the mixture was stirred in a microwave reactor at 120°C for 1 hour. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino silica gel column chromatography (ethyl acetate:hexane) to obtain 1-{4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl]amino)methyl]piperidin-1-yl}-3-fluoropropan-2-ol (81 mg) as a white powder.

[0121]

Example 53

To a mixture of tert-butyl (3S)-3-({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-ylpyrimidin-2-yl}amino)pyrrolidine-1-carboxylate (300 mg) and 1,4-dioxane (3 mL) was added a 4 M solution (1.5 mL) of hydrogen chloride in 1,4-dioxane, and the mixture was stirred at room temperature for 2 hours. To the reaction mixture was added diisopropyl ether (10 mL). The resulting powder was collected by filtration, washed with diisopropyl ether, and dried under reduced pressure to obtain 4-[2-

(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-[(3S)-pyrrolidin-3-yl]pyrimidin-2-amine dihydrochloride (354 mg) as a pale yellow powder.

[0122]

Example 54

5 To a mixture of tert-butyl 4-({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-ylpyrimidin-2-yl}amino)piperidine-1-carboxylate (42 mg) and methanol (0.84 mL) were added a 4 M solution of hydrogen chloride in 1,4-dioxane, and the mixture was stirred at room temperature for 4 hours. The reaction mixture was neutralized by the addition of saturated aqueous sodium bicarbonate solution, and extracted with chloroform.
10 The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=50:50) to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-piperidin-4-ylpyrimidin-2-amine (27 mg) as a pale yellow powder.

15 [0123]

Example 66

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-piperidin-4-ylpyrimidin-2-amine (18 mg) and N,N-dimethylformamide (0.36 mL) were added N,N-dimethylglycine (4.8 mg), 1-hydroxybenzotriazole (6.2 mg), and N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride (8.8 mg), and the mixture
20 was stirred at room temperature for 6 hours. To the reaction mixture was added water, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by amino silica gel column chromatography (ethyl acetate, and
25 subsequently chloroform:methanol=96:4). Desired fractions were combined and concentrated under reduced pressure. The residue was solidified by the addition of a small amount of diisopropyl ether to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-{1-[(dimethylamino)acetyl]piperidin-4-yl]-6-morpholin-4-ylpyrimidin-2-amine (9 mg) as a white powder.

30 [0124]

Example 71

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-(piperidin-4-ylmethyl)-1,3,5-triazin-2-amine (50 mg) and pyridine (2 mL) was added acetic anhydride (14 μ L), and the mixture was stirred at room temperature overnight. To
35 the reaction mixture was added toluene, followed by concentrating under reduced pressure. The residue was dissolved in dichloromethane, and silica gel was added thereto, followed by concentrating under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate, and subsequently chloroform:methanol) to obtain

N-[(1-acetylpiperidin-4-yl)methyl]-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-amine (44 mg) as a white powder.

[0125]

Example 74

5 To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl-N-(piperidin-4-ylmethyl)pyrimidin-2-amine (50 mg) and 1,2-dimethoxyethane (1 mL) were added bromobenzene (24 μ L), tris(dibenzylideneacetone)dipalladium (0) (6.5 mg), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (11 mg), and potassium phosphate (96 mg), and the mixture was stirred in a microwave reactor at 130°C for 1 hour.

10 The reaction mixture was filtered through celite, and to the filtrate was added silica gel, followed by concentrating under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate) to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-N-[(1-phenylpiperidin-4-yl)methyl]pyrimidin-2-amine (39 mg) as a white powder.

15 [0126]

Example 80

A mixture of tert-butyl 4-[(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(methylsulfinyl)pyrimidin-4-yl}oxy)methyl]piperidine-1-carbamate (240 mg), morpholine (0.3 mL), and N,N-dimethylacetamide (2 mL) was stirred at room temperature for 1 hour.

20 To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and then the residue was purified by silica gel column chromatography (hexane:ethyl acetate=70:30-50:50) to obtain tert-butyl 4-[(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)methyl]piperidine-1-carbamate (246 mg) as a white powder.

25

[0127]

Example 82

1-[4-Chloro-6-(morpholin-4-yl)pyrimidin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (100 mg) was dissolved in dimethylformamide (1 mL), and 3-methoxyprop-1-yne (45 μ L), tetrakis(triphenylphosphine)palladium (0) (16 mg), copper (I) iodide (1.3 mg), and potassium carbonate (227 mg) were added thereto, followed by stirring in a microwave reactor at 80°C for 1 hour. An aqueous ammonium chloride solution and chloroform were added thereto, and the organic layer was extracted, washed with saturated

35 brine, and then dried over anhydrous magnesium sulfate. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=60:40). A mixed solvent of diisopropyl ether and hexane was added thereto, and the resulting solid was collected by filtration and further

washed with hexane to obtain 2-(difluoromethyl)-1-[4-(3-methoxyprop-1-yn-1-yl)-6-(morpholin-4-yl)pyrimidin-2-yl]-1H-benzimidazole (10 mg) as a yellow powder.

[0128]

Example 83

5 Methyl trans-4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl]amino)methyl]cyclohexane carboxylate (150 mg) was dissolved in a mixed solvent of methanol (750 μ L) and tetrahydrofuran (750 μ L), and a 1 M aqueous sodium hydroxide solution (899 mL) was added thereto, followed by stirring at room temperature for 2 hours. After the completion of the reaction, 1 M hydrochloric acid was
10 added thereto under ice-cooling until the reaction solution became weakly acidic, followed by stirring at 0°C for 1 hour. The resulting solid was collected by filtration and washed with hexane to obtain trans-4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl]amino)methyl]cyclohexanecarboxylic acid (74 mg) as a white powder.

15 [0129]

Example 84

[(3S)-3-[(tert-Butoxycarbonyl)amino]-4-{[trans-4-(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl]oxy)cyclohexyl]amino}-4-oxobutyl](dimethyl)sulfonium iodide (919 mg) was dissolved in tetrahydrofuran (1.4 mL),
20 and cooled to 0°C under a nitrogen air flow, and a 1.6 M solution (0.7 mL) of hexamethyldisilazanelithium in tetrahydrofuran was added dropwise thereto, followed by stirring at 0°C for 2 hours. A 1.6 M solution (0.7 mL) of hexamethyldisilazanelithium in tetrahydrofuran was further added dropwise thereto, followed by stirring at 0°C for 1 hour. A saturated aqueous ammonium chloride solution was added thereto, followed by
25 extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=70:30-0:100) to obtain tert-butyl{(3S)-1-[trans-4-(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyridin-4-yl]oxy)cyclohexyl]-2-oxopyrrolidin-3-yl}carbamate (154 mg).
30

[0130]

Example 85

N-[(4-Aminobicyclo[2.2.2]oct-1-yl)methyl]-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-amine (150 mg) was dissolved in
35 ethanol (3 mL), and N,N-diisopropyl ethylamine (81 μ L) and 2,2-dimethyloxirane (36 μ L) were added thereto, followed by stirring at 120°C for 1 hour and at 140°C for 1 hour using a microwave reactor. The reaction solution was concentrated and the residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=20:80, and subsequently

chloroform:methanol=98:2) to obtain 1-({4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)methyl]bicyclo[2.2.2]oct-1-yl}amino)-2-methylpropan-2-ol (148 mg) as a white amorphous substance.

[0131]

5 Example 86

1-({trans-4-[(4-[2-(Difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl}amino)methyl]cyclohexyl}amino)-2-methylpropan-2-ol (100 mg) was dissolved in tetrahydrofuran (2 mL), and di-1H-imidazol-1-ylmethanone (131 mg) and triethylamine (50 μ L) were added thereto, followed by stirring
 10 for 3 hours while heating and refluxing. After the completion of the reaction, water was added thereto, followed by extraction with ethyl acetate. The extracts were washed with saturated brine and dried over anhydrous magnesium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=60:40) to obtain 3-{trans-4-[(4-[2-
 15 (difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl}amino)methyl]cyclohexyl}-5,5-dimethyl-1,3-oxazolidin-2-one (100 mg) as a white powder.

[0132]

Example 87

20 To (3S)-3-amino-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]pyrrolidin-2-one (75 mg), triethylamine (22 μ L), and dichloromethane (750 μ L) was added methylchlorocarbonate (12 μ L), followed by stirring at room temperature for 1 hour. After the completion of the reaction, a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction
 25 with chloroform. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol) to obtain methyl{(3S)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]-2-oxopyrrolidin-3-yl}carbamate (55 mg)
 30 as a white powder.

[0133]

Example 88

To (3S)-3-amino-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]pyrrolidin-2-one (75 mg), N-ethyl-N-isopropylpropan-2-amine (73 μ L), and 1,2-dichloroethane (750 μ L) was added
 35 methanesulfonyl chloride (17 μ L), followed by stirring at room temperature for 1 hour. After the completion of the reaction, a saturated aqueous sodium bicarbonate solution was added thereto, followed by extraction with chloroform. The organic layer was washed

with saturated brine and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol) to obtain N-((3S)-1-[trans-4-((6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl)oxy)cyclohexyl]-2-oxopyrrolidin-3-yl)methanesulfonamide (82 mg) as a pale yellow powder.

[0134]

Example 89

2-Bromo-N-[trans-4-((6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl)oxy)cyclohexyl]acetamide (100 mg) was suspended in dimethylformamide (2 mL), and potassium carbonate (30 mg) and cyclobutylamine (60 µL) were added thereto, followed by stirring at room temperature overnight. To the reaction solution was added water, followed by extraction with ethyl acetate. The extracts were washed with water and saturated brine, the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel chromatography (hexane:ethyl acetate=40:60-10:90) to obtain N²-cyclobutyl-N-[trans-4-((6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl)oxy)cyclohexyl]glycinamide (79 mg).

[0135]

Example 90

trans-4-((6-[2-(Difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl)oxy)cyclohexanamine (200 mg) was dissolved in ethanol (4 mL), and acetaldehyde (28 µL) was added thereto, followed by stirring at room temperature for 5 hours. Sodium borohydride (34 mg) was added thereto, followed by further stirring at room temperature for 1 hour. Water and ethyl acetate were added thereto, the organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=50:50-0:100, and subsequently chloroform:methanol=100:0-98:2) to obtain trans-4-((6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl)oxy)-N-ethylcyclohexanamine (84 mg).

[0136]

Example 91

N-[2-(Cyclopentylsulfanyl)ethyl]-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-1,3,5-triazin-2-amine (60 mg) was dissolved in methylene chloride (1.2 mL), and m-chloroperbenzoic acid (75% wet) (32 mg) was added thereto at 0°C, followed by stirring for 10 minutes. Water was added thereto, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the

solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=20:80, and subsequently methanol:chloroform=98:2-90:10) to obtain N-[2-(cyclopentyl sulfinyl)ethyl]-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-1,3,5-triazin-2-amine (53 mg) as a white powder.

[0137]

Example 92

2-(Difluoromethyl)-1-[6-(1,4-dioxaspiro[4.5]deca-8-ylmethoxy)-2-(methylsulfonyl)pyrimidin-4-yl]-1H-benzimidazole (1.3 g) was dissolved in dichloromethane (20 mL), and m-chloroperbenzoic acid (75% wet) (712 mg) was added thereto at 0°C, followed by stirring for 30 minutes. To the reaction solution was added a saturated aqueous sodium bicarbonate, followed by extraction with chloroform. The extracts were washed with water and saturated brine, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was dissolved in dimethylformamide (10 mL), and morpholine (1.22 mL) was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was poured into water, followed by extraction with ethyl acetate. The extracts were washed with water and saturated brine, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5-80:20) to obtain 2-(difluoromethyl)-1-[6-(1,4-dioxaspiro[4.5]deca-8-ylmethoxy)-2-(morpholin-4-yl)pyrimidin-4-yl]-1H-benzimidazole (1.21 g) as a white powder.

[0138]

Example 93

2-(Difluoromethyl)-1-[6-(1,4-dioxaspiro[4.5]deca-8-ylmethoxy)-2-(morpholin-4-yl)pyrimidin-4-yl]-1H-benzimidazole (1.2 g) was dissolved in a mixed solvent of tetrahydrofuran (12 mL) and water (12 mL), and 4-methylbenzene sulfonic acid monohydrate (2.27 g) was added thereto, followed by stirring at room temperature for 3 hours. To the reaction solution was added saturated aqueous sodium bicarbonate, followed by extraction with ethyl acetate. The extracts were washed with water and saturated brine, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20-40:60) to obtain 4-[(6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)methyl]cyclohexanone (941 mg) as a white powder.

[0139]

Example 94

N-[2-(Cyclopentylsulfanyl)ethyl]-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-1,3,5-triazin-2-amine (60 mg) was dissolved in methylene chloride (1.2 ml), and m-chloroperbenzoic acid (75% wet) (73 mg) was added thereto at 0°C, followed by stirring for 10 minutes. Water was added thereto, followed by extraction with
 5 chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=50:50-0:100) to obtain N-[2-(cyclopentylsulfonyl)ethyl]-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-1,3,5-triazin-2-amine (58 mg) as a white powder.

10 [0140]

Example 237

To a solution of [3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)azetidin-1-yl](cis-4-hydroxycyclohexyl)methanone (60 mg) in methylene chloride (1.2 mL) was added a Dess-Martin reagent (53 mg) under ice-cooling,
 15 followed by stirring at room temperature overnight. To the reaction mixture were added ethyl acetate and a saturated aqueous sodium bicarbonate solution, the organic layer was extracted, washed with saturated brine, and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10) to obtain 4-{[3-
 20 ({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)azetidin-1-yl]carbonyl}cyclohexanone (20 mg).

[0141]

Example 238

4-(Morpholin-4-ylmethyl)benzenesulfonamide (35 mg) was dissolved in N,N-
 25 dimethylacetamide (1.25 mL), and 60% sodium hydride (24 mg) was added thereto, followed by stirring at room temperature for 30 minutes. To the reaction mixture was added 1-[6-chloro-2-(morpholin-4-yl)pyrimidin-4-yl]-2-(difluoromethyl)-1H-benzimidazole (50 mg), followed by stirring at 120°C for 1 hour. The mixture was cooled to room temperature, and then a saturated aqueous sodium chloride solution, ethyl acetate,
 30 and tetrahydrofuran were added thereto, followed by neutralization with a 10% aqueous potassium hydrogen sulfate solution, and then the organic layer was extracted. The organic layer was washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The desiccant was removed by filtration and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel
 35 column chromatography (hexane:ethyl acetate=20:80-0:100 and subsequently chloroform:methanol=100:0-80:20) to obtain N-{6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}-4-(morpholin-4-ylmethyl) benzenesulfonamide (13 mg).

[0142]

Example 239

trans-4-({6-[2-(Difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)cyclohexanecarboxylic acid (232 mg) was dissolved in tetrahydrofuran (2.3 mL), and isobutyl chloroformate (70 μ L) and 4-methylmorpholine (60 μ L) were added thereto at 0°C, followed by stirring at 0°C for 30 minutes and at room temperature for 2 hours. Subsequently, 28% aqueous ammonia (300 μ L) was added thereto at 0°C, followed by stirring for 2 hours. The solvent was evaporated under reduced pressure and purified by silica gel chromatography (hexane:ethyl acetate=40:60-0:100 and chloroform:methanol=100:0-95:5) to obtain trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)cyclohexanecarboxamide (230 mg).

[0143]

Example 240

To a solution of N-{4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}cyclohexane-1,3-diamine (70 mg) in dimethylacetamide (1.4 mL) were added triethylamine (56 μ L) and bis(2-bromomethyl)ether (31 μ L), followed by stirring at 120°C for 2 hours using a microwave reactor. To the reaction solution was added water, followed by extraction with ethyl acetate. The extracts were washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate, the desiccant was removed by filtration, and then the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=60:40-20:80) to obtain 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-N-[3-(morpholin-4-yl)cyclohexyl]pyrimidin-2-amine (42 mg).

[0144]

Example 241

To a mixture of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-morpholin-4-yl)-N-[(3S)-pyrrolidin-3-yl]pyrimidin-2-amine dihydrochloride (100 mg) and methylene chloride (1 mL) were added triethylamine (0.1 mL) and benzoyl chloride (28.5 μ L) under a nitrogen air flow while ice-cooling, followed by stirring at the same temperature for 4 hours. To the reaction mixture was added water (30 mL), followed by extraction with ethyl acetate (100 mL). The organic layer was washed with saturated brine (50 mL) and dried over anhydrous sodium sulfate. The desiccant was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol=100:0-90:10). This was solidified with ethyl acetate and diisopropyl ether, then collected by filtration, and dried to obtain [(3S)-3-({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)pyrrolidin-1-yl](phenyl)methanone (66 mg) as a white powder.

[0145]

Example 242

To a solution of trans-N-{4-[2-(difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}cyclohexane-1,4-diamine (150 mg) in ethanol (3 mL) was added 1H-1,2,3-benzotriazol-1-ylmethanol (59 mg), followed by stirring at room temperature for 5 hours. To this mixture was added sodium borohydride (25 mg), followed by further stirring at room temperature for 1 hour. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The desiccant was removed by filtration and then the solvent was evaporated under reduced pressure. The residue was separated and purified by amino silica gel column chromatography (hexane:ethyl acetate=50:50-0:100 and chloroform:methanol=100:0-98:2) to obtain trans-N'-{4-[2-(difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}-N,N-dimethylcyclohexane-1,4-diamine (50 mg) (Example 242-1) and trans-N-{4-[2-(difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}-N'-methylcyclohexane-1,4-diamine (100 mg) (Example 242-2).

[0146]

Example 243

To a solution of trans-N-{4-[2-(difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}cyclohexane-1,4-diamine (50 mg) in methylene chloride (1 mL) were added triethylamine (46 μ L) and 4-chlorobutyryl chloride (16 μ L), followed by stirring for 1 hour in a water bath. The reaction solution was concentrated under reduced pressure and to the residue were added tetrahydrofuran (5 mL) and 60% sodium hydride (13 mg), followed by stirring at 0°C for 30 minutes and at room temperature for 1 hour. To the reaction solution was added water, followed by extraction with ethyl acetate, and the extracts were washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The desiccant was removed by filtration and then the solvent was evaporated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=50:50-0:100 and chloroform:methanol=100:0-90:10) to obtain 1-[trans-4-({4-[2-(difluoromethyl)-6-methyl-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)cyclohexyl]pyrrolidin-2-one (40 mg).

[0147]

Example 244

To a mixture of tert-butyl N-{4-[2-(difluoromethyl)-1H-benzimidazo-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}-L-alaninate (80 mg) and methylene chloride (3 mL) were added a 4 M solution of hydrogen chloride in 1,4-dioxane (0.84 mL), followed by stirring for 4 hours. After the completion of the reaction, the solvent was evaporated under

reduced pressure and then dried to obtain N-{4-[2-(difluoromethyl)-1H-benzimidazo-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}-L-alanine hydrochloride (83 mg).

[0148]

Example 245

To a solution of 2-(benzyloxy)ethyl{(3S)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]-2-oxopyrrolidin-3-yl}carbamate (84 mg) in methanol (1 mL) was added 10% palladium-carbon (50% wet) (84 mg), followed by stirring at room temperature overnight at 3 atm under a hydrogen atmosphere. The catalyst was removed and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (chloroform:methanol=100:0-92:8) to obtain 2-hydroxyethyl{(3S)-1-[trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexyl]-2-oxopyrrolidin-3-yl}carbamate (30 mg).

[0149]

Example 246

To a mixture of methyl 2-{4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)methyl]piperidin-1-yl}cyclopentane carboxylate (50 mg) and tetrahydrofuran (1 mL) were added a 1.06 M solution of methyllithium in diethyl ether at 0°C, followed by stirring at the same temperature for 4 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by amino silica gel column chromatography (hexane:ethyl acetate=1:2-0:100) to obtain 2-(2-{4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)methyl]piperidin-1-yl}cyclopentyl)propan-2-ol (11.1 mg).

[0150]

Example 247

trans-4-({6-[2-(Difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexanol (100 mg) was suspended in N,N-dimethylformamide (4 mL), and 1,1'-carbonyldiimidazole (73 mg) was added thereto, followed by stirring at 60°C for 2 hours. Further, 1,1'-carbonyldiimidazole (182 mg) was added thereto, followed by stirring at 60°C for 2 hours. To this mixture was added guanidine carbonate (405 mg) at room temperature, followed by stirring at room temperature overnight. Water was added thereto, followed by extraction with ethyl acetate, the organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (10% MeOH/chloroform: chloroform=10:90-90:10) to obtain

trans-4-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}oxy)cyclohexylcarbamimidylcarbamate (103 mg).

[0151]

Example 248

5 A mixture of 2-(difluoromethyl)-1-[2-(methylsulfonyl)-6-(morpholin-4-yl)pyrimidin-4-yl]-1H-benzimidazole (200 mg) and methyl[(3S)-1-(trans-4-aminocyclohexyl)-2-oxopyrrolidin-3-yl]carbamate hydrochloride (214 mg), potassium carbonate (135 mg), N-ethyl-N-diisopropylpropan-2-amine (0.38 mL) and N,N-dimethylacetamide (3 mL) was stirred at 100°C for 6 hours. After leaving to be cooled,
10 to the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The desiccant was removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol=100:0-80:20) to obtain methyl{(3S)-1-[trans-4-({4-[2-
15 (difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)cyclohexyl]-2-oxopyrrolidin-3-yl}carbamate (102 mg) as a white powder.

[0152]

Example 249

20 N-(Azetidin-3-yl)-6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-amine (100 mg) was dissolved in N,N-dimethylformamide (1 ml), and 4-methoxycyclohexanecarboxylic acid (43 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (142 mg), and N,N-diisopropyl ethylamine (213 µL) were added thereto, followed by stirring at room temperature for 3 hours. The reaction mixture was added water (100 ml), followed by extraction with ethyl
25 acetate (100 ml). The extracts were washed with water and saturated brine, and then dried over anhydrous magnesium sulfate. The desiccant was removed by filtration and then the solvent was evaporated under reduced pressure. The residue was separated/purified by silica gel column chromatography (from hexane:ethyl acetate=50:50-0:100 to chloroform:methanol=100:0-80:20) to obtain [3-({6-[2-(difluoromethyl)-1H-
30 benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)azetidin-1-yl](cis-4-methoxycyclohexyl)methanone (26 mg) (Example 249-1) and [3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}amino)azetidin-1-yl](trans-4-methoxycyclohexyl)methanone (7.1 mg) (Example 249-2).

[0153]

35 Example 422

To a mixture of methyl 2-{4-[({4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl}amino)methyl]piperidin-1-yl}cyclopentane carboxylate (50 mg) and tetrahydrofuran (1 mL) were added a 1.01 M solution of (240 µL)

diisobutylaluminum in toluene at 0°C, followed by stirring at the same temperature for 6 hours. To the reaction mixture were added methanol and sodium sulfate decahydrate, followed by stirring at room temperature for 1 hour. The insoluble matter was removed by filtration and then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=50:50-0:100) to obtain desired (2-{4-[(4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)pyrimidin-2-yl]amino)methyl]piperidin-1-yl}cyclopentyl)methanol (33 mg).

[0154]

Example 432

10 Racemic N-{6-[2-(Difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}-1-(tetrahydro-2H-pyran-4-yl)azepan-4-amine (300 mg) was optically resolved using supercritical fluid chromatography to obtain optically active substance, N-{6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl}-1-(tetrahydro-2H-pyran-4-yl)azepan-4-amines (135 mg (RT 6.76 min) and 137 mg (RT 8.03 min)) as white amorphous substances, respectively.

SFC fractionation: AD-H/4.6×250 mm /CO₂ 75%, MeOH (0.1% DEA) 25%/Flow 3 ml/min/Conc. 2 mg/mL/rt=6.76 min, 8.03 min

[0155]

Example A1

20 To a solution of 1-methylpiperidin-4-amine (4.6 mg) in N,N-dimethylformamide (200 µL) were added a solution of N,N-diisopropyl ethylamine (8.7 µL) in N,N-dimethylformamide (50 µL) and a solution of 1-[4-chloro-6-(morpholin-4-yl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (9.2 mg) in N,N-dimethylformamide (300 µL), followed by stirring at 80°C overnight. To the reaction mixture were added a saturated aqueous sodium bicarbonate solution and chloroform at room temperature, followed by liquid-liquid phase separation, and the organic layer was concentrated under reduced pressure. The residue was purified by preparative HPLC to obtain 4-[2-(difluoromethyl)-1H-benzimidazolyl]-N-(1-methylpiperidin-4-yl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine (11.1 mg).

30 [0156]

Example B1

To a solution of 1-(4-hydroxyphenyl)ethanone (5.4 mg) in N,N-dimethylformamide (200 µL) were added potassium carbonate (6.9 mg) and a solution of 1-[4-chloro-6-(morpholin-4-yl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (9.2 mg) in N,N-dimethylformamide (300 µL), followed by stirring at 80°C overnight. To the reaction solution were added water and chloroform at room temperature, followed by liquid-liquid phase separation, and the organic layer was evaporated under reduced pressure. The residue was purified by preparative HPLC to obtain 1-[4-(4-[2-

(difluoromethyl)-1H-benzimidazol-1-yl]-6-(morpholin-4-yl)-1,3,5-triazin-2-yl}oxy)phenyl]ethanone (1.4 mg).

[0157]

5 The conditions for HPLC carried out to determine RT in Examples A1 and B1 are shown below.

Columns: Wakosil-II 5 C18AR (Wako Pure Chemical Industries, Ltd.) (particle diameter: 5 μ m, internal diameter: 2.0 mm, length: 30 mm)

Mobile phase: A Solution 5 mM aqueous trifluoroacetic acid solution, B Solution methanol

10 Flow rate: 1.2 mL/min; detection wavelength: 254 nm; column temperature: 35.0°C; injection amount: 5 μ L

[0158]

[Table 3]

Time (min)	A sol (%)	B sol (%)	Elution
0-4	95→0	5→100	Gradient
4-4.5	0	100	Isocratic

15 [0159]

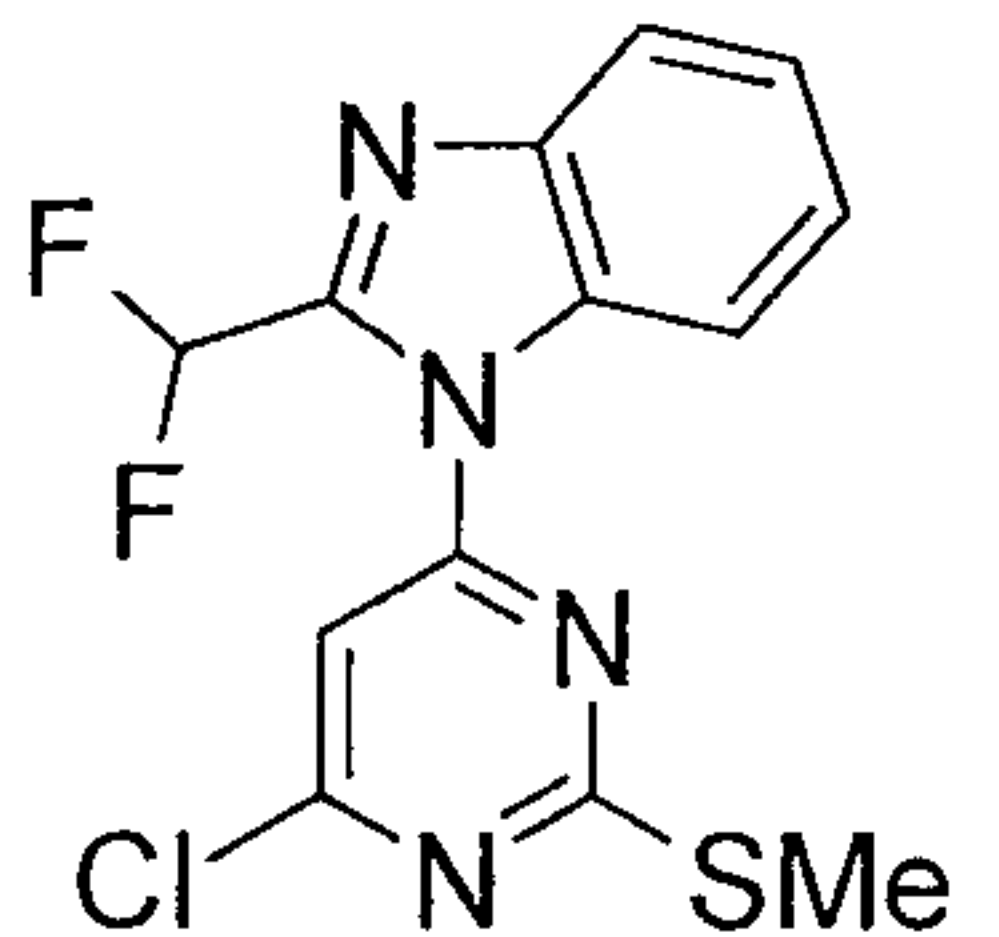
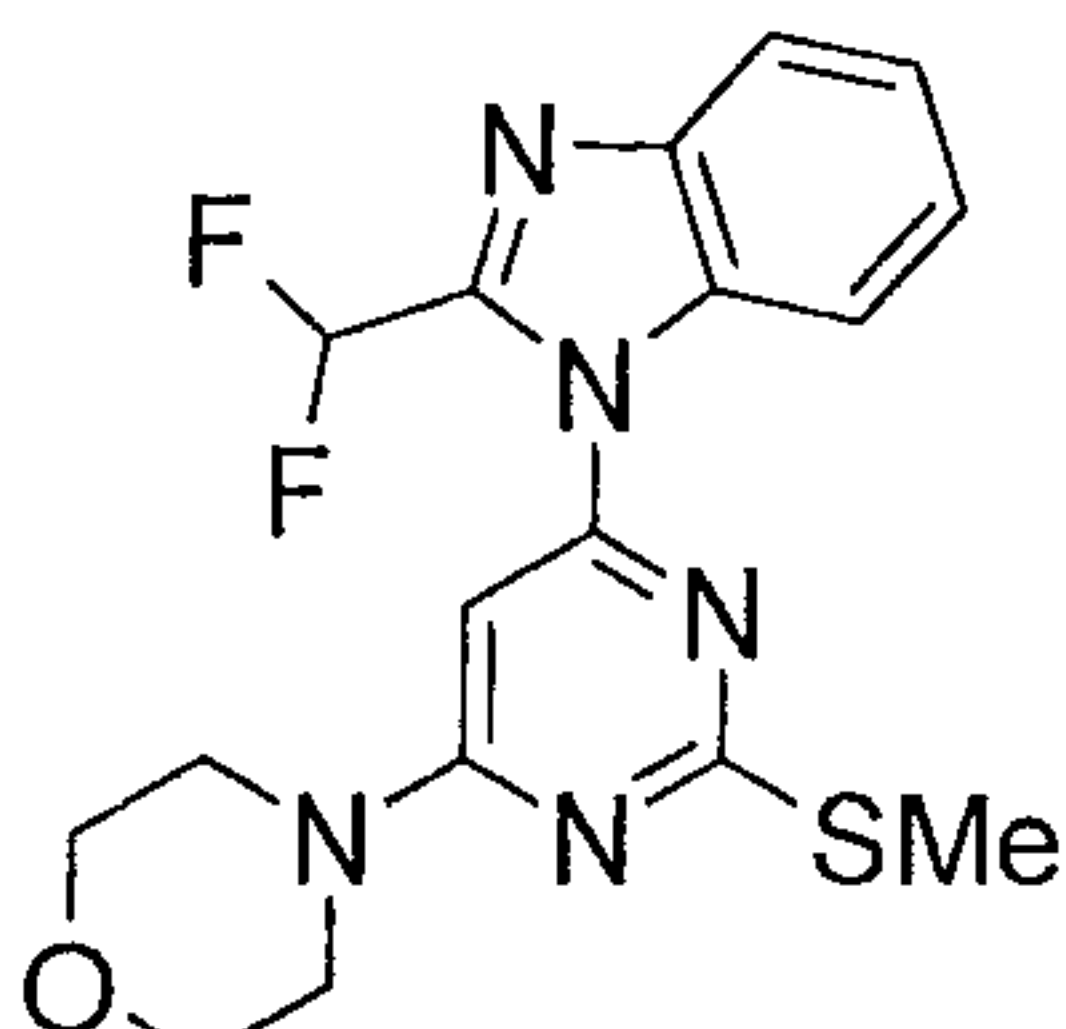
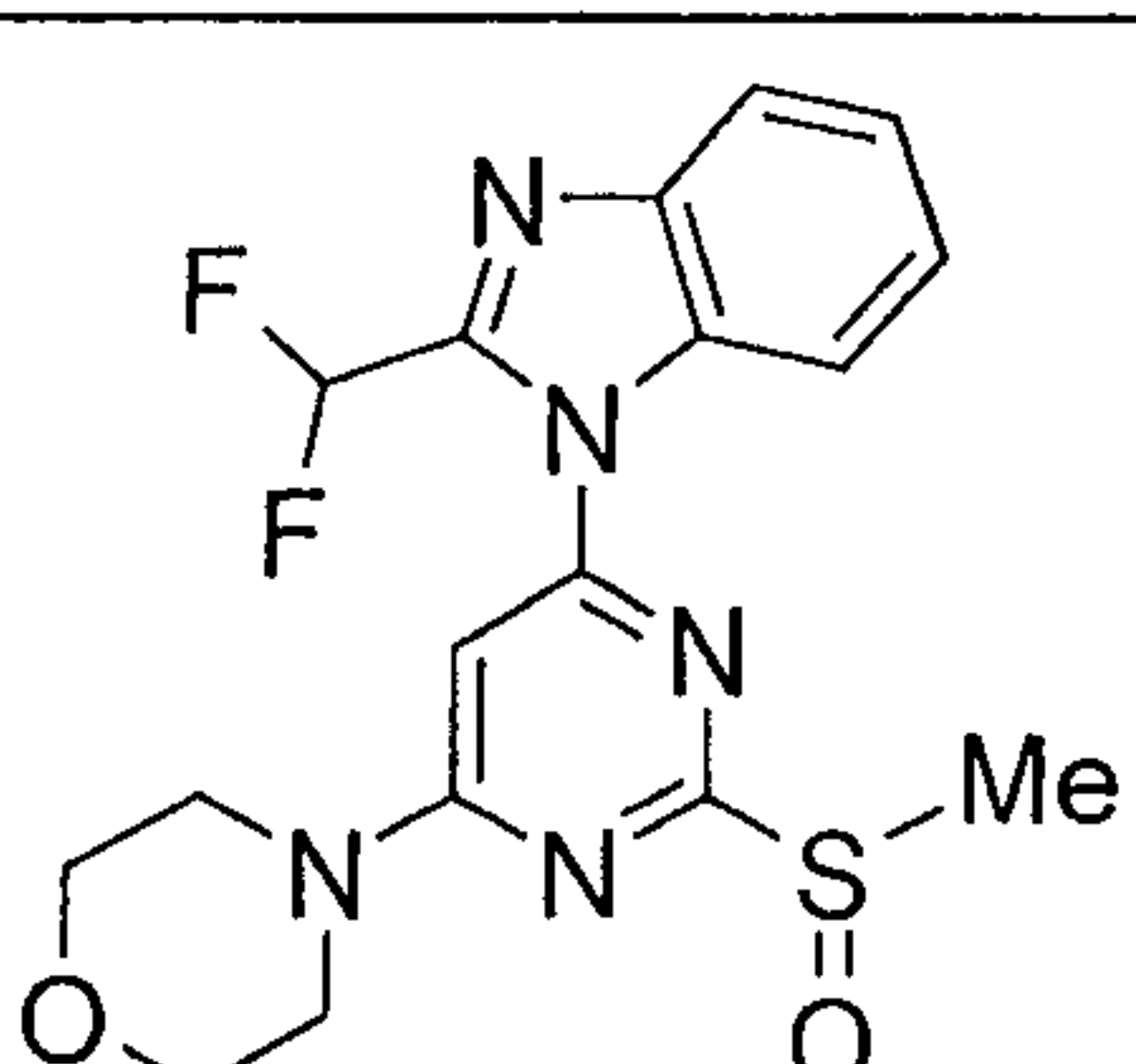
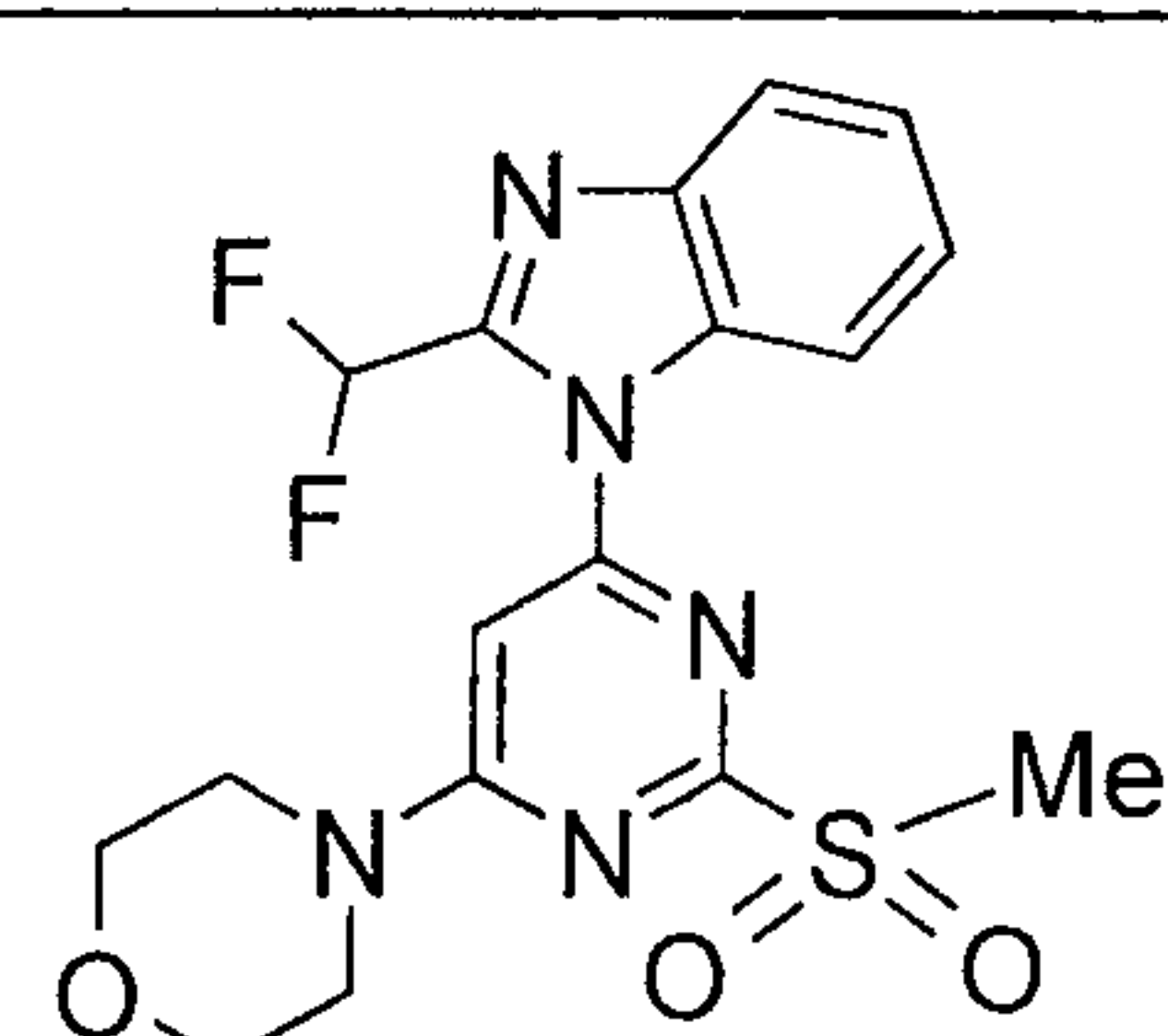
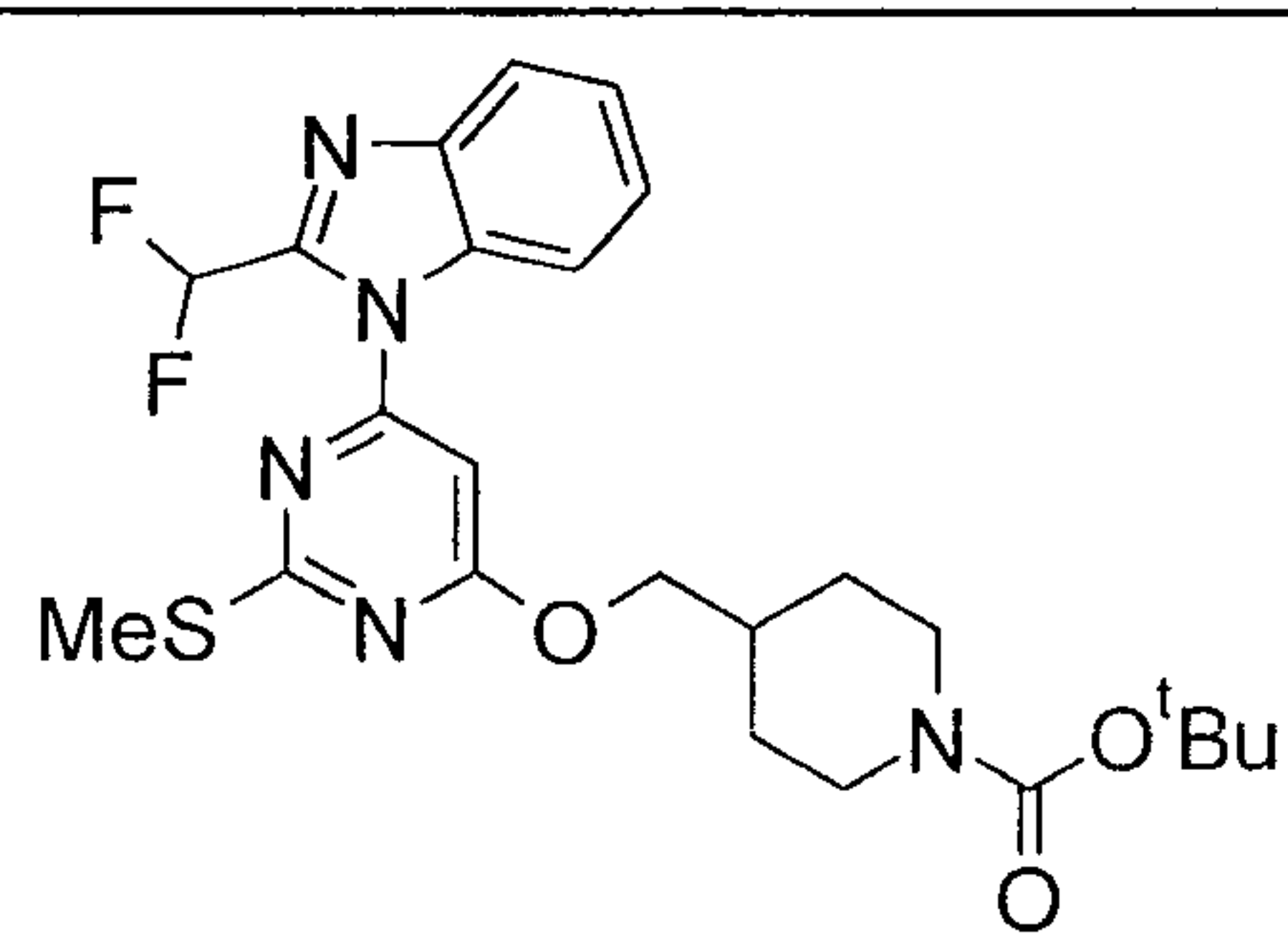
The compounds of Preparation Examples and Examples shown in Tables below were prepared in the same manner as in Preparation Examples and Examples as described above.

20 The chemical structural formulae, the preparation methods, and the physicochemical data of the compounds of Preparation Examples are shown in Tables 4 to 34. Further, the chemical structural formulae of the compounds of Examples are shown in Tables 35 to 139, and the preparation methods and the physicochemical data of the compounds of Examples are shown in Tables 140 to 161.

25 Furthermore, the structures and the physicochemical data of the compounds of Examples prepared in the same manner as the method of Example A1 are shown in Tables 162 to 306, and the structures and the physicochemical data of the compounds of Examples prepared in the same manner as the method of Example B1 are shown in Tables 307 to 337.

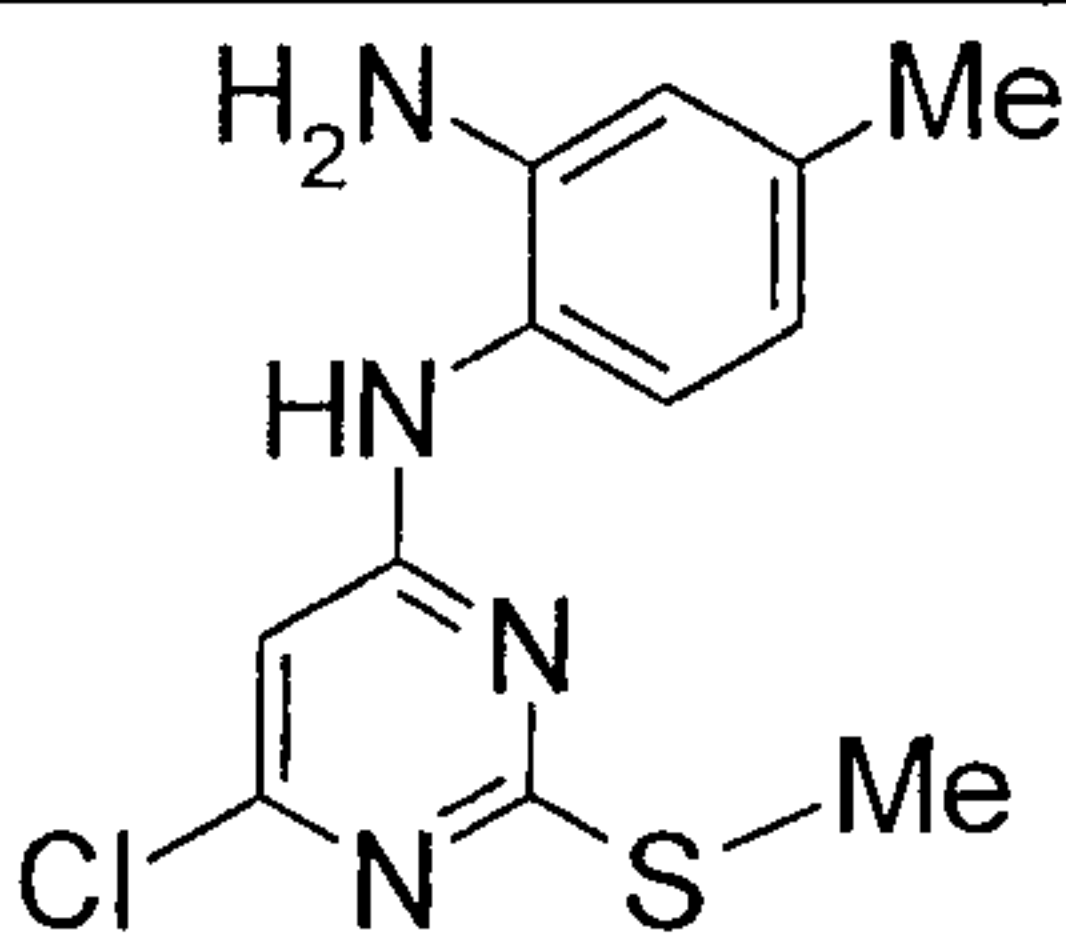
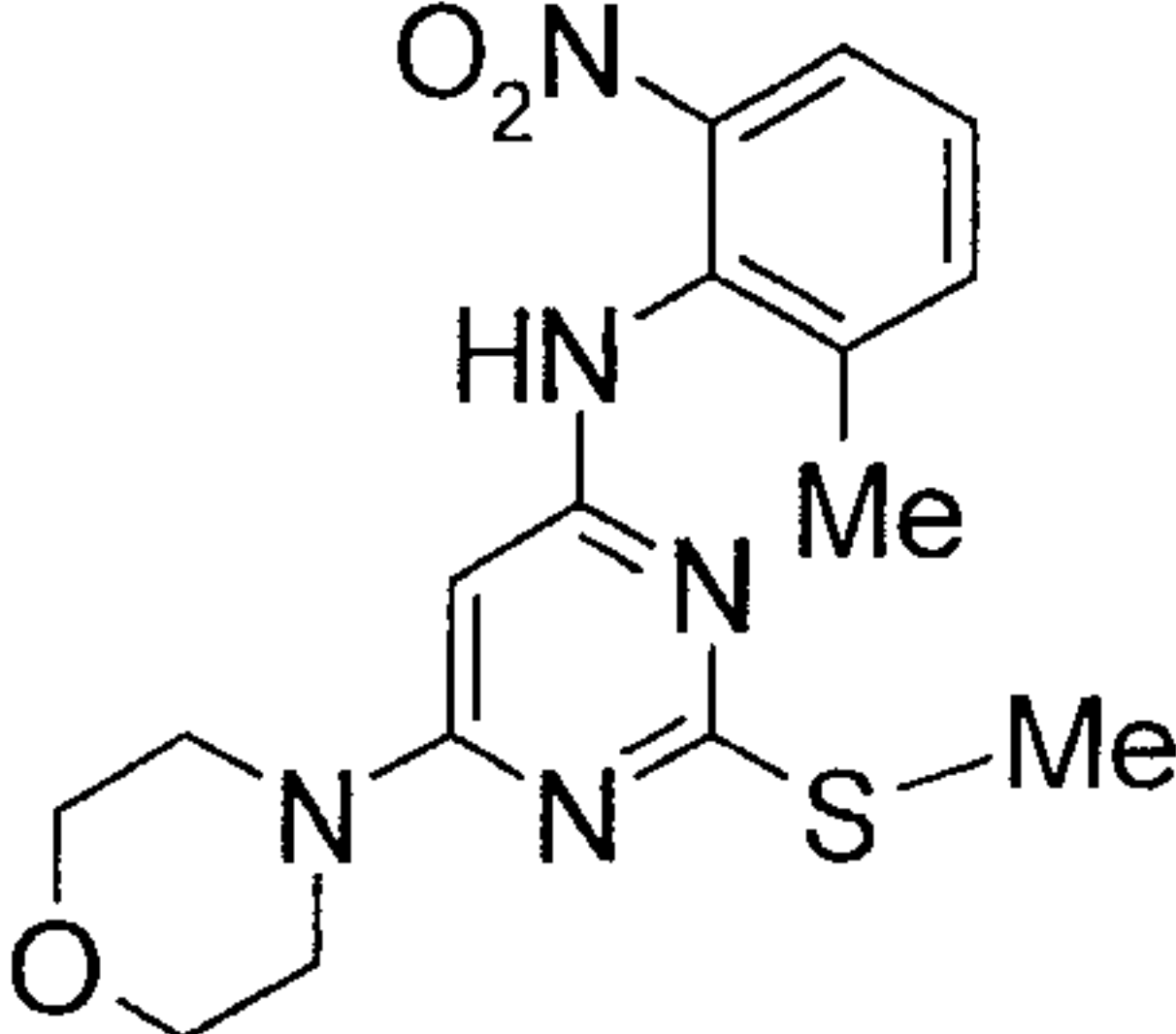
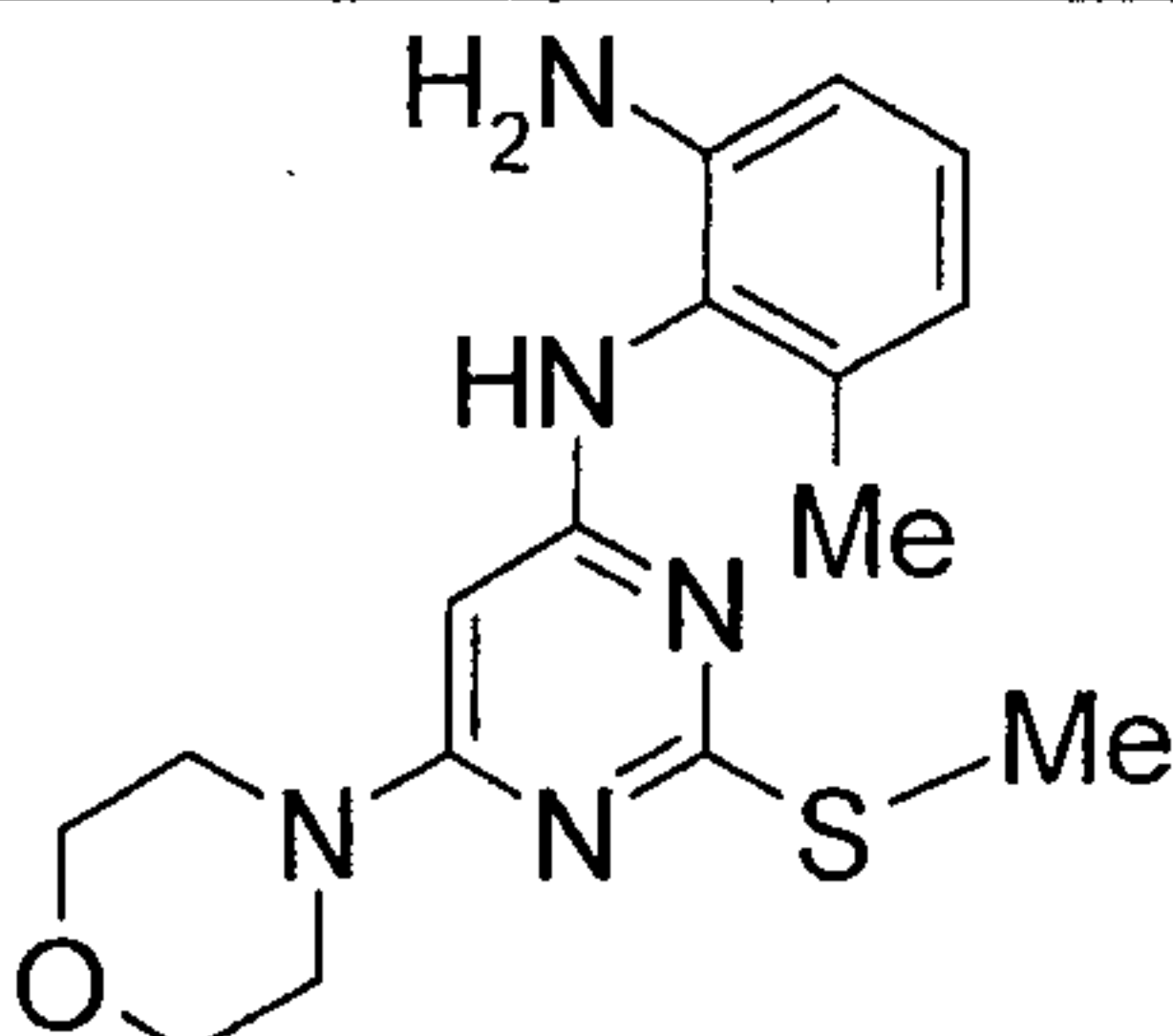
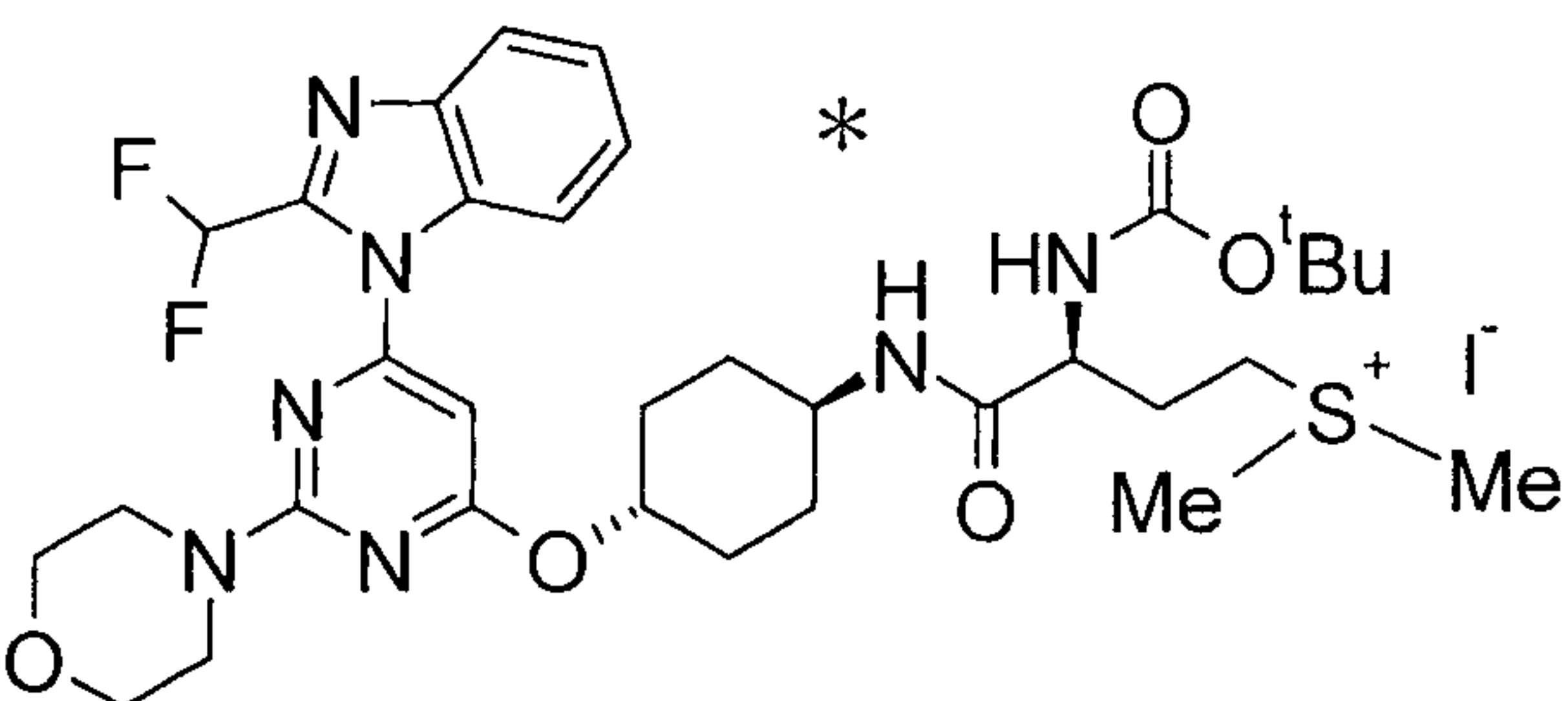
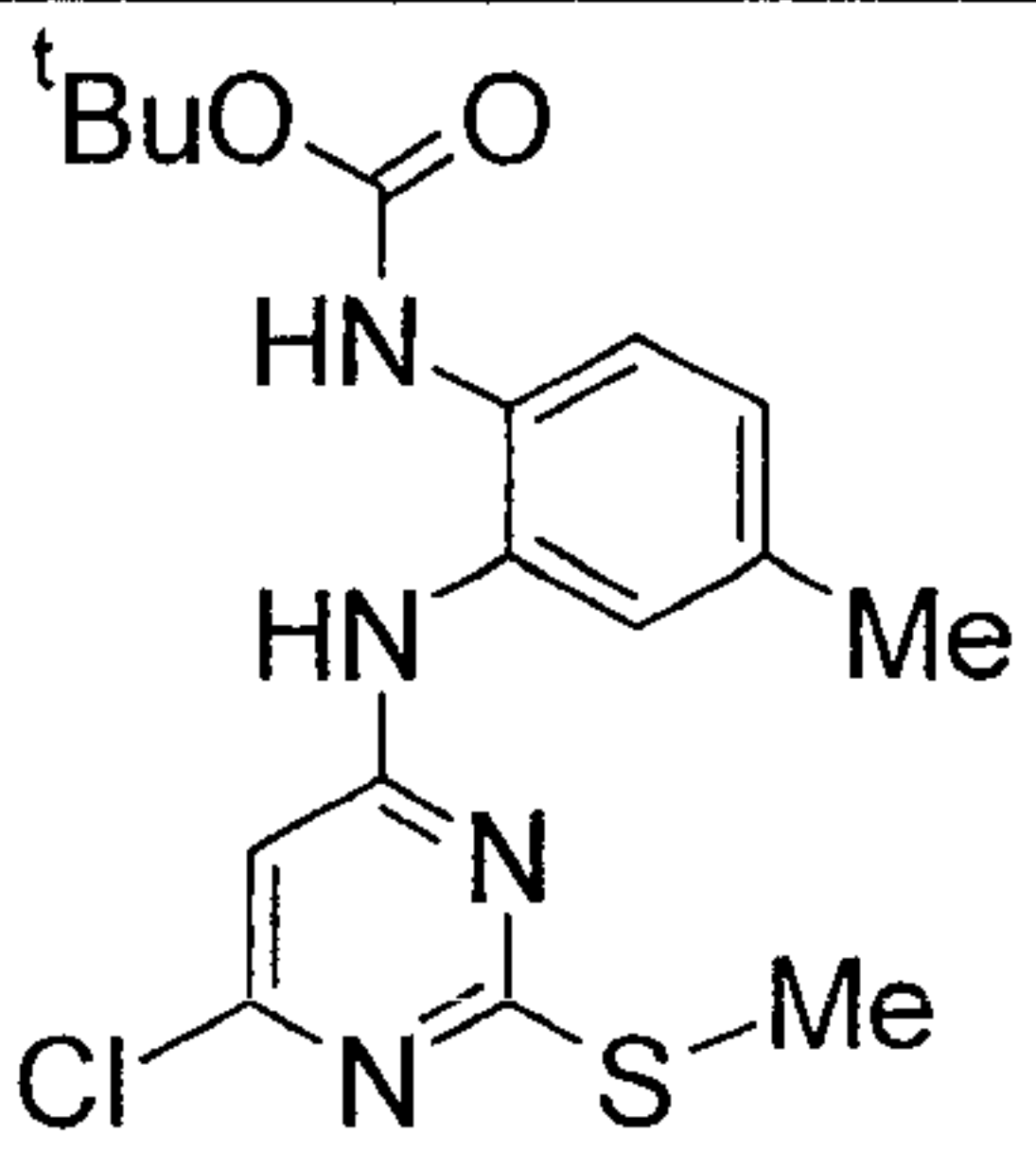
[0160]

[Table 4]

PEx	PSyn	Str	DAT
1	1		ESI+: 327
2	2		ESI+: 378
3	3		ESI+: 394
4	4		ESI+: 410
5	5		ESI+: 506

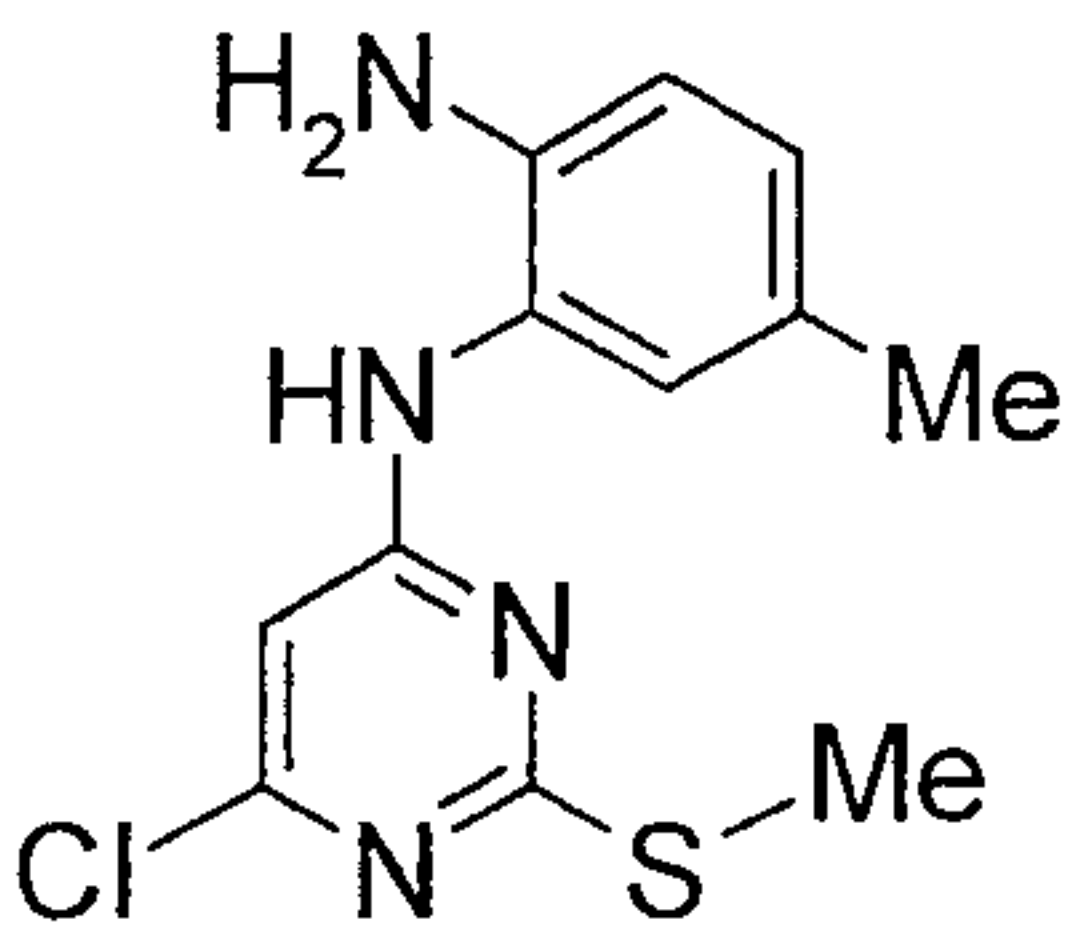
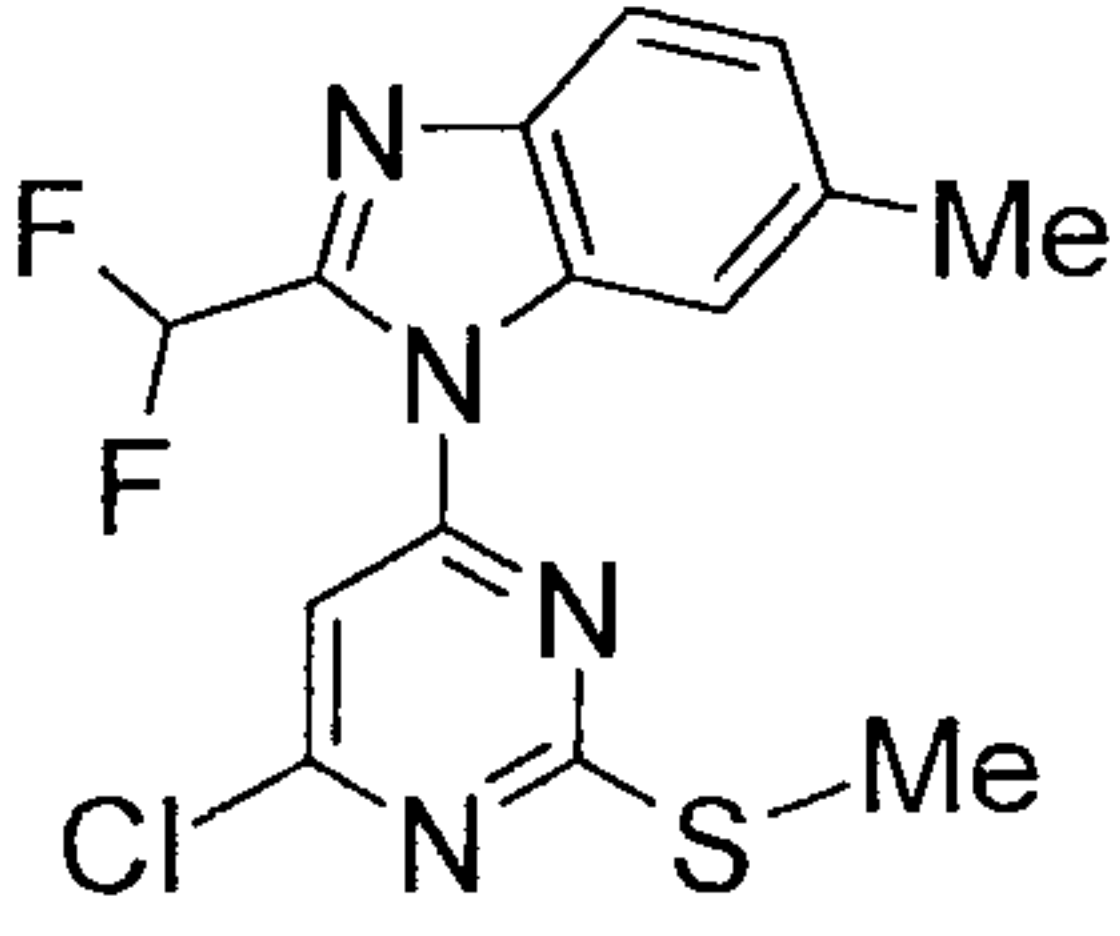
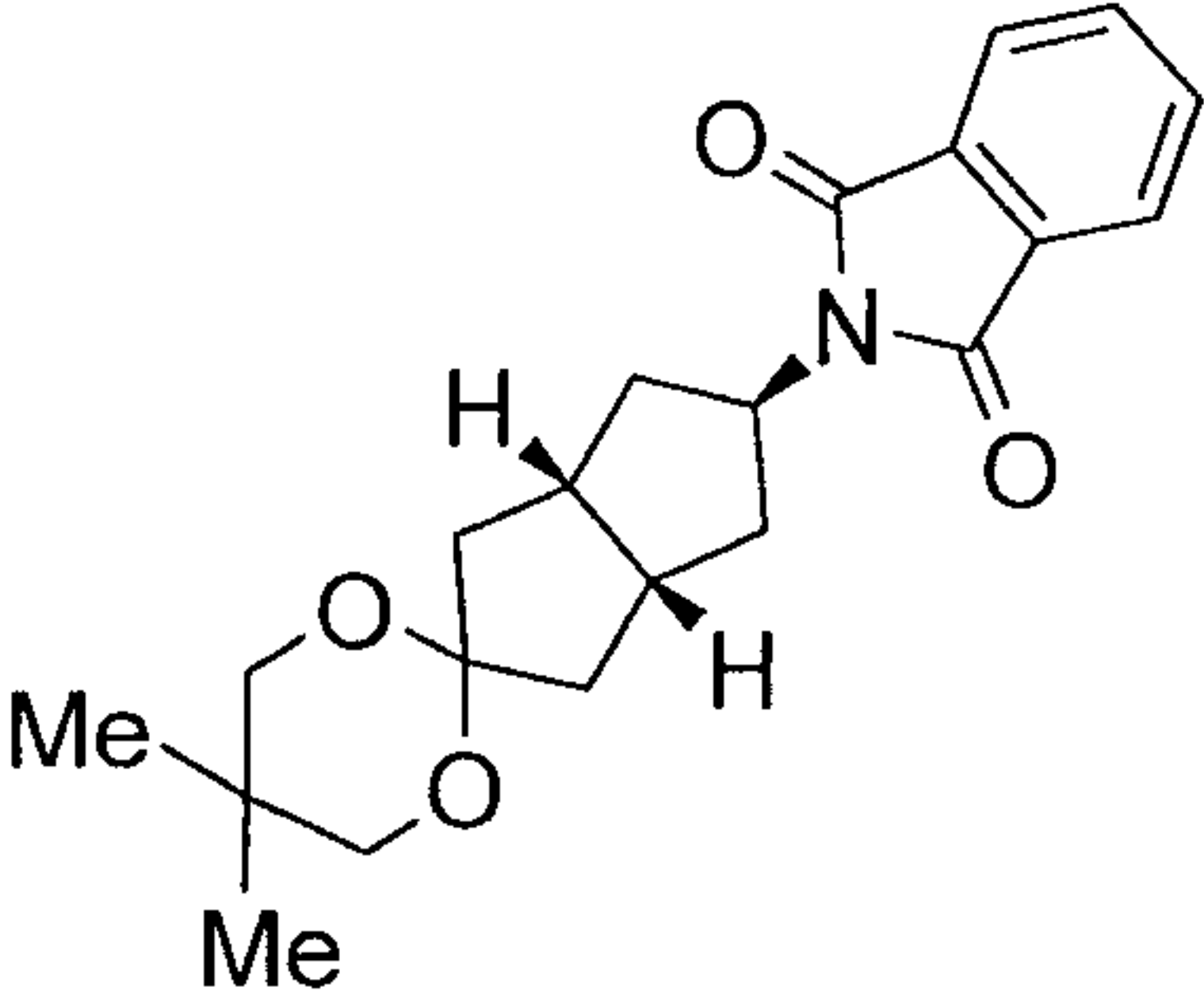
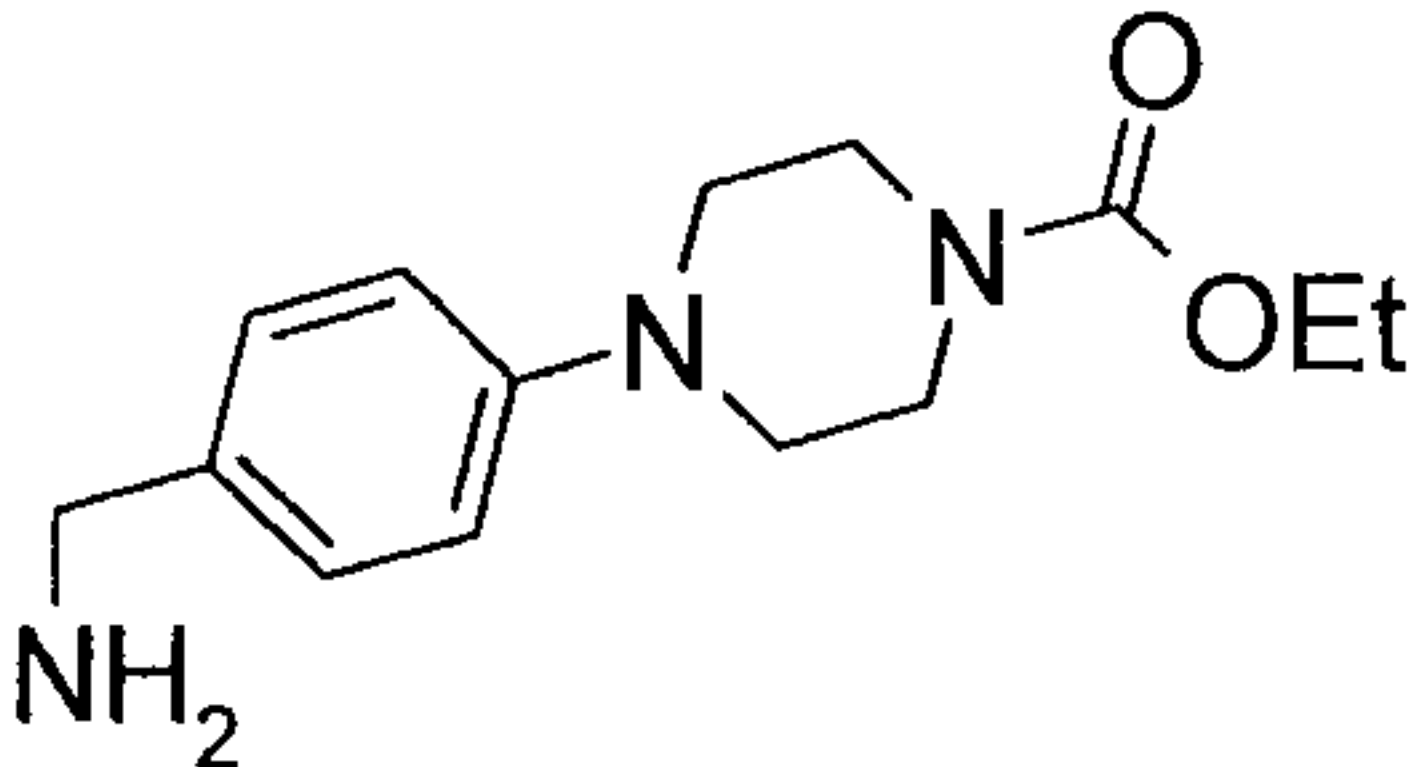
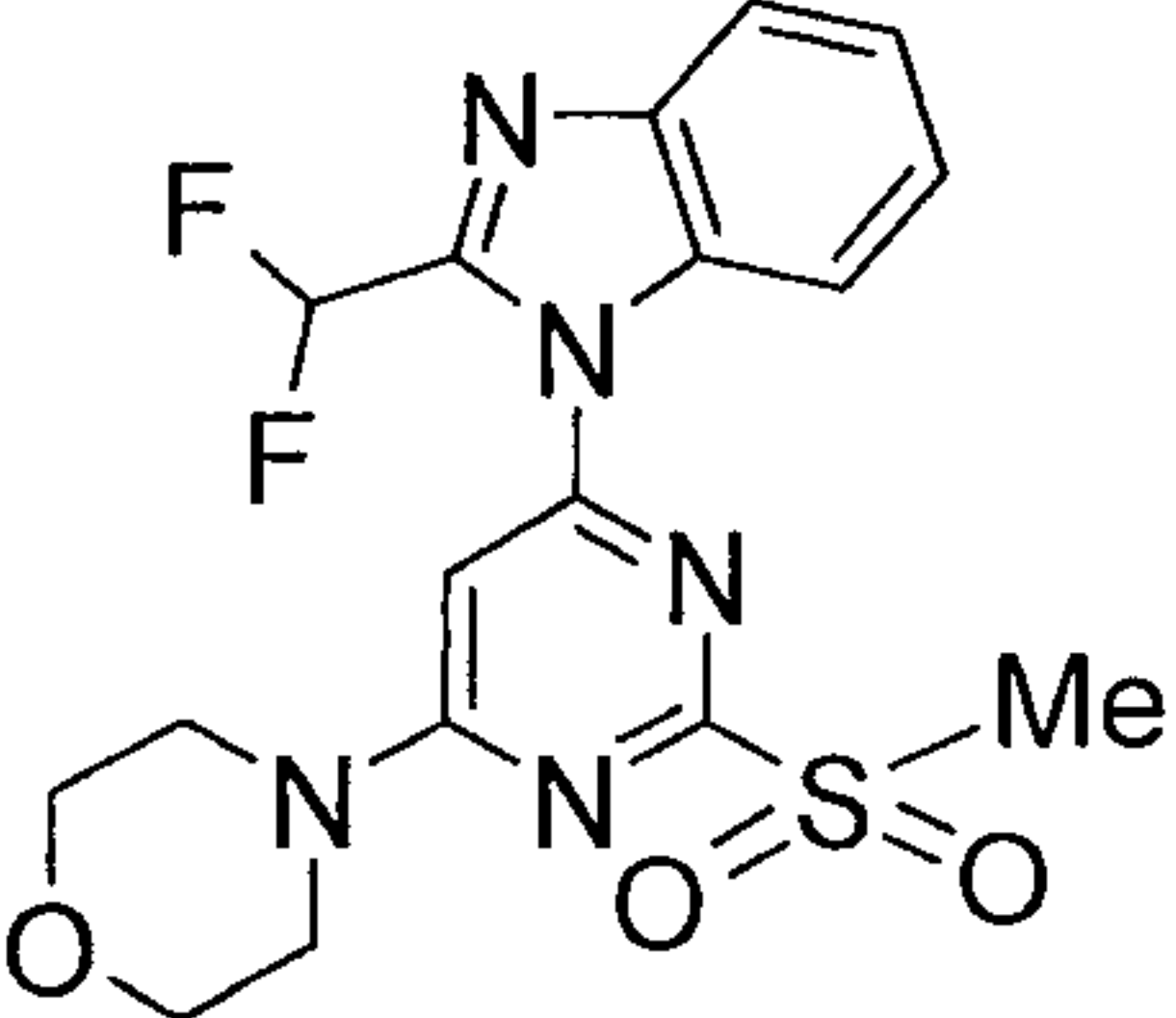
[0161]

[Table 5]

PEx	PSyn	Str	DAT
6	6		ESI+: 281
7	7		ESI+: 362
8	8		ESI+: 332
9	9		ESI+: 690(M ⁺)
10	10		ESI+: 381

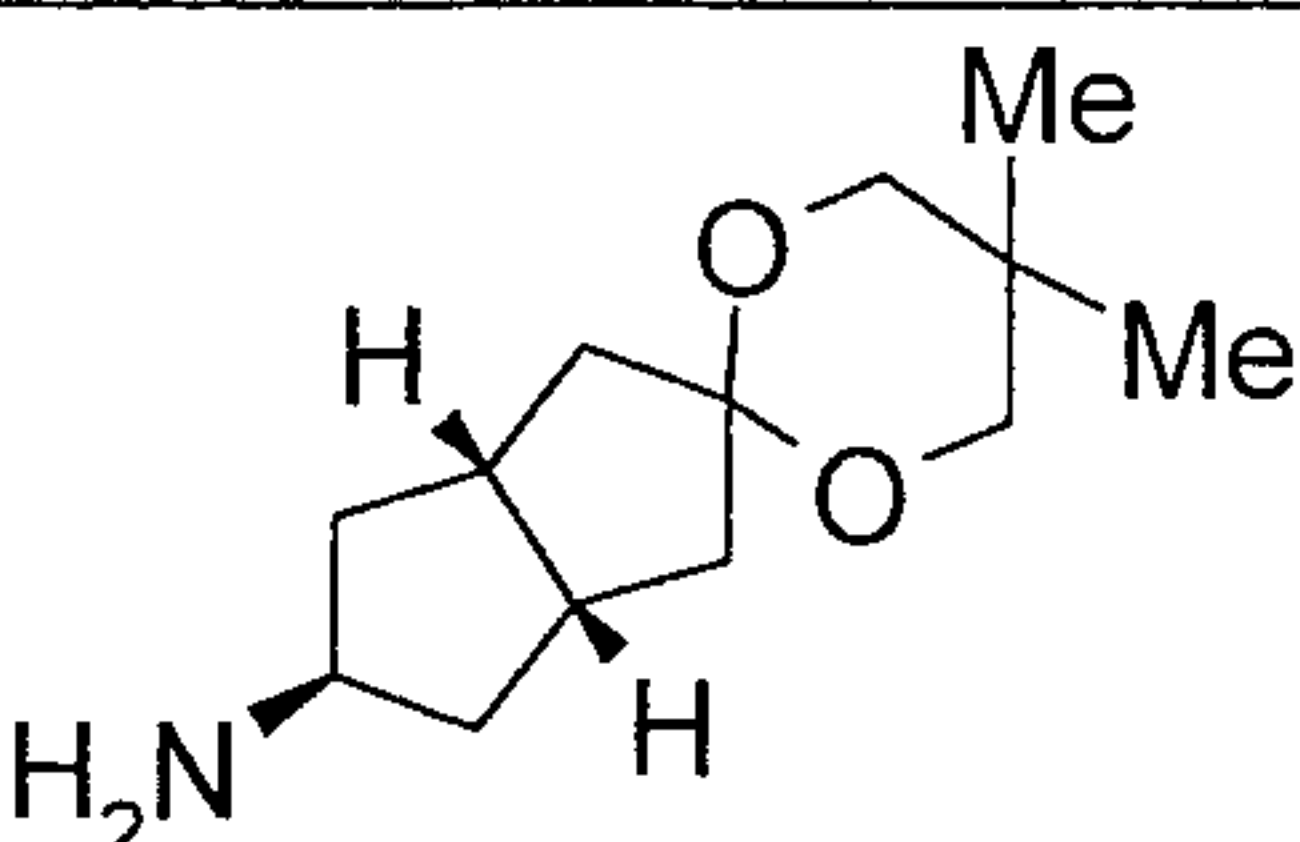
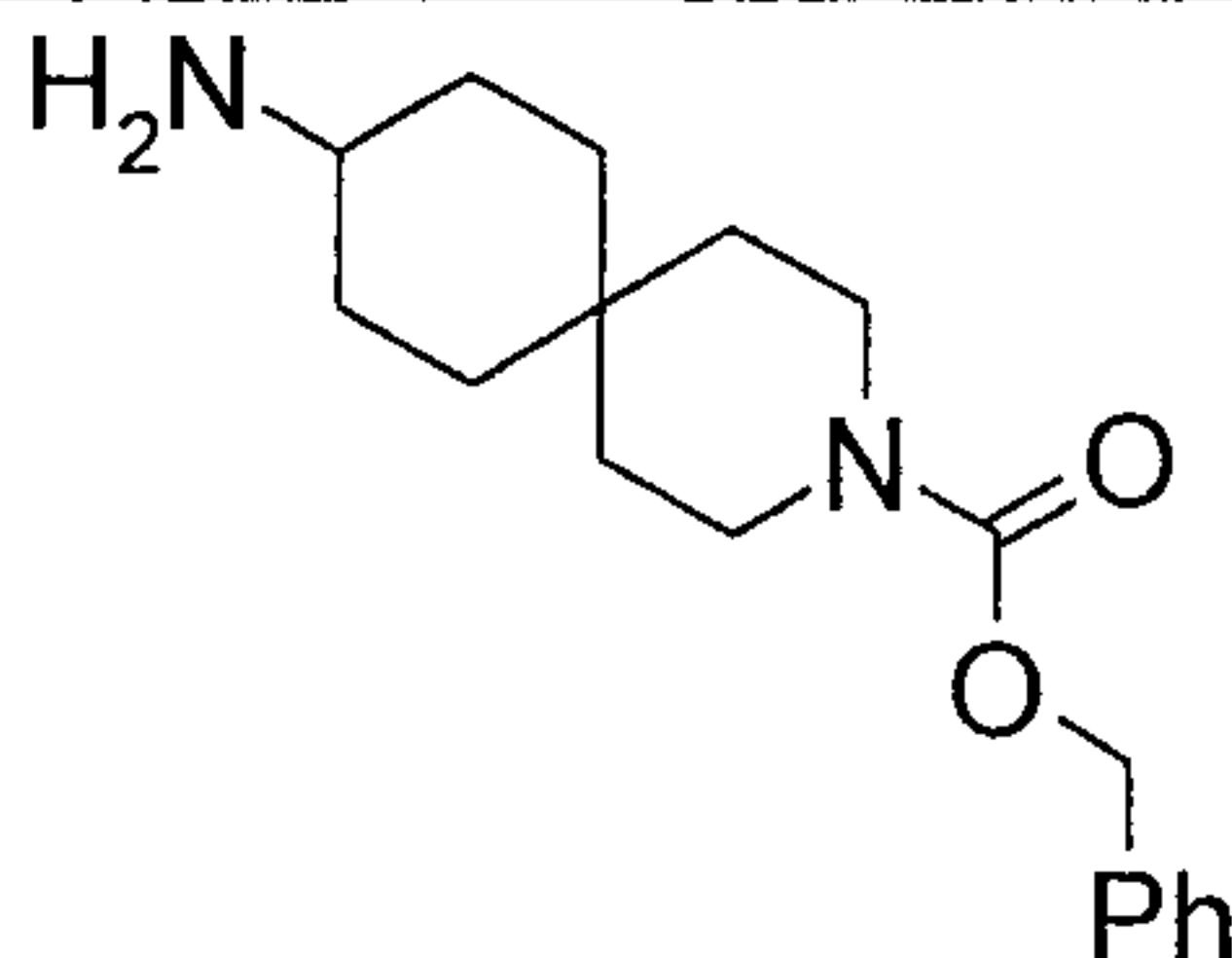
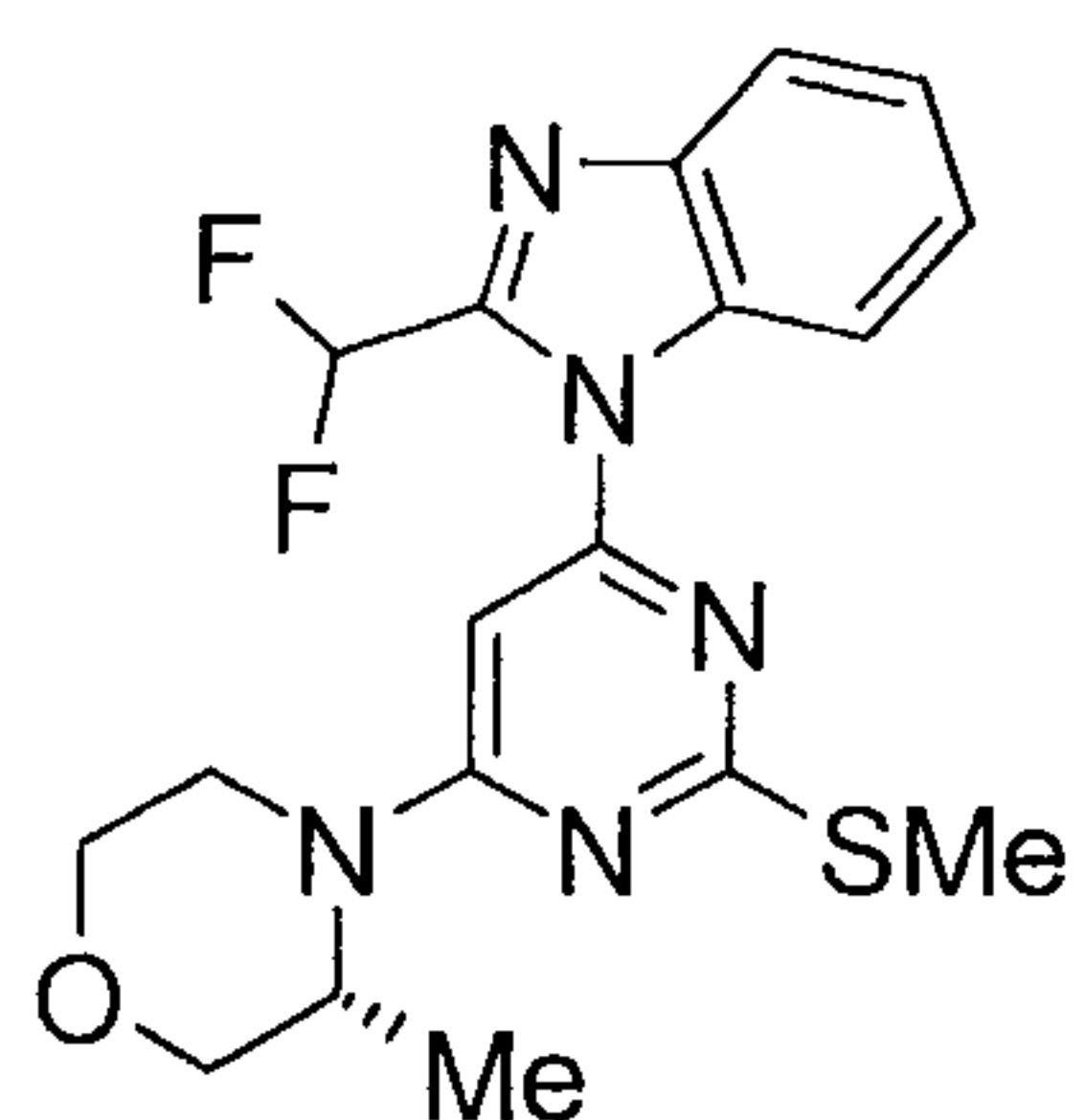
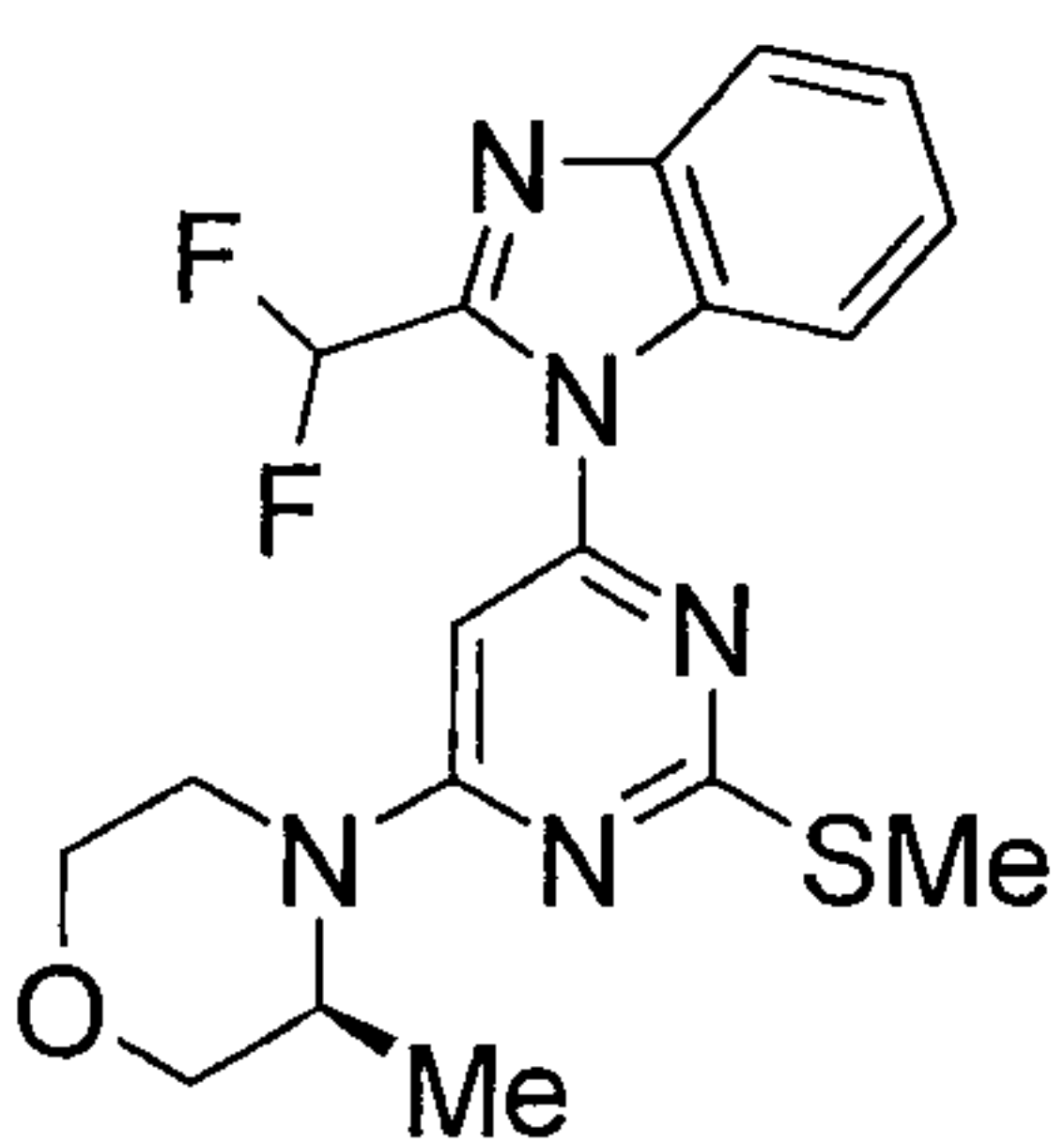
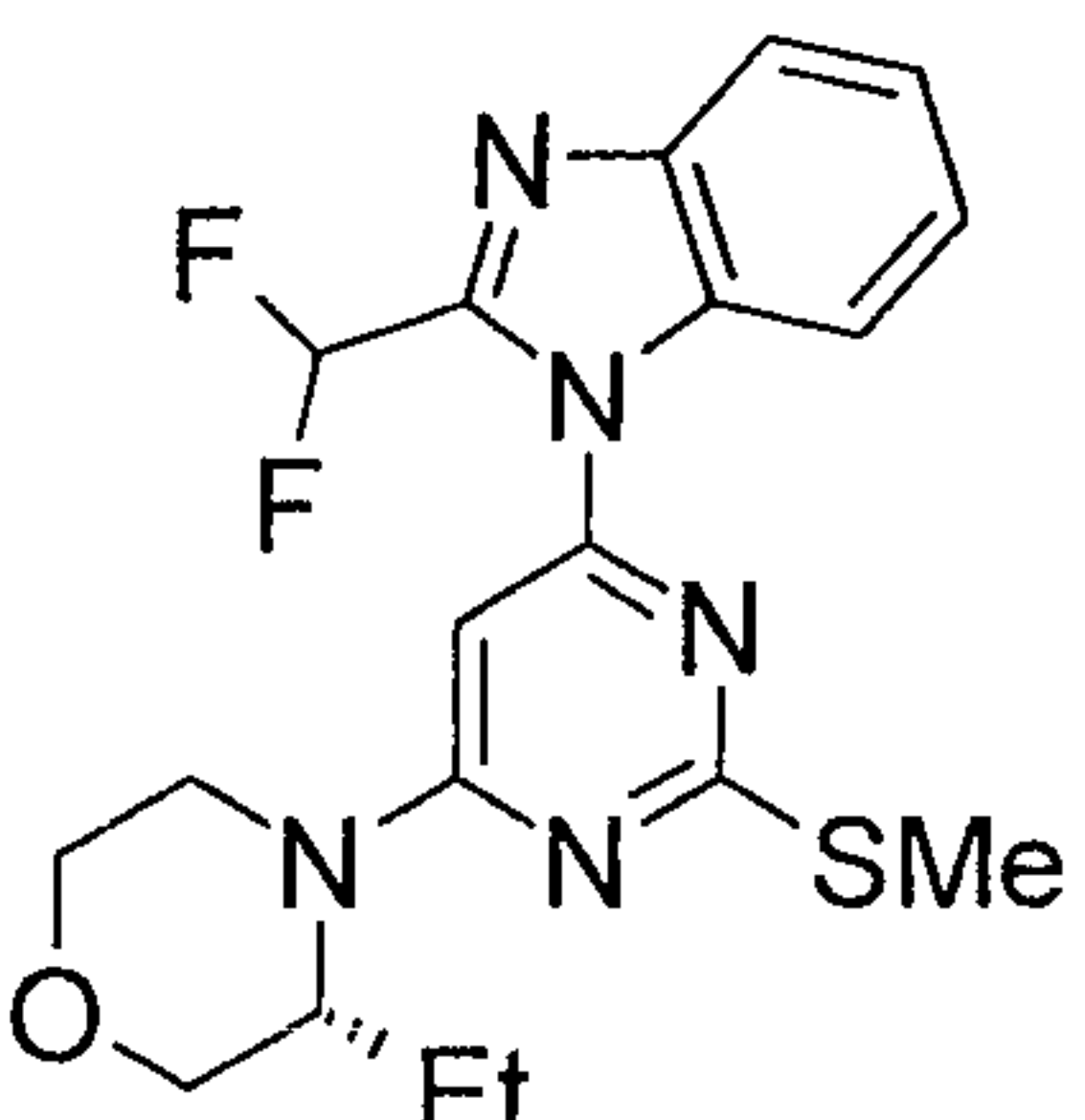
[0162]

[Table 6]

PEX	PSyn	Str	DAT
11	11		ESI+: 281
12	12		ESI+: 341
13	13		ESI+: 356
14	14		ESI+: 264
15	15		ESI+: 410

[0163]

[Table 7]

PEx	PSyn	Str	DAT
16	16		ESI+: 226
17	17		ESI+: 303
18	2		ESI+: 392
19	2		ESI+: 392
20	2		ESI+: 406

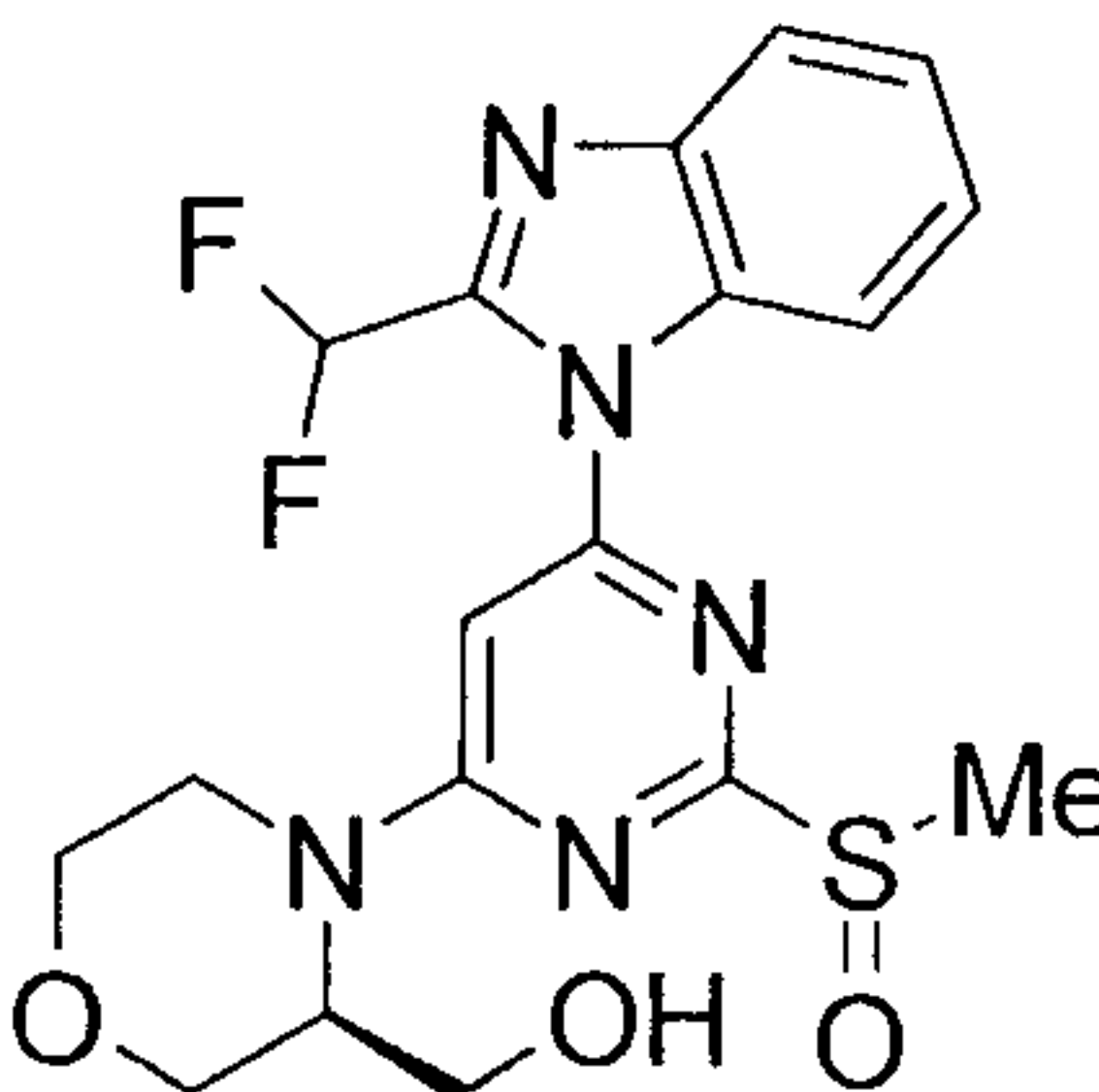
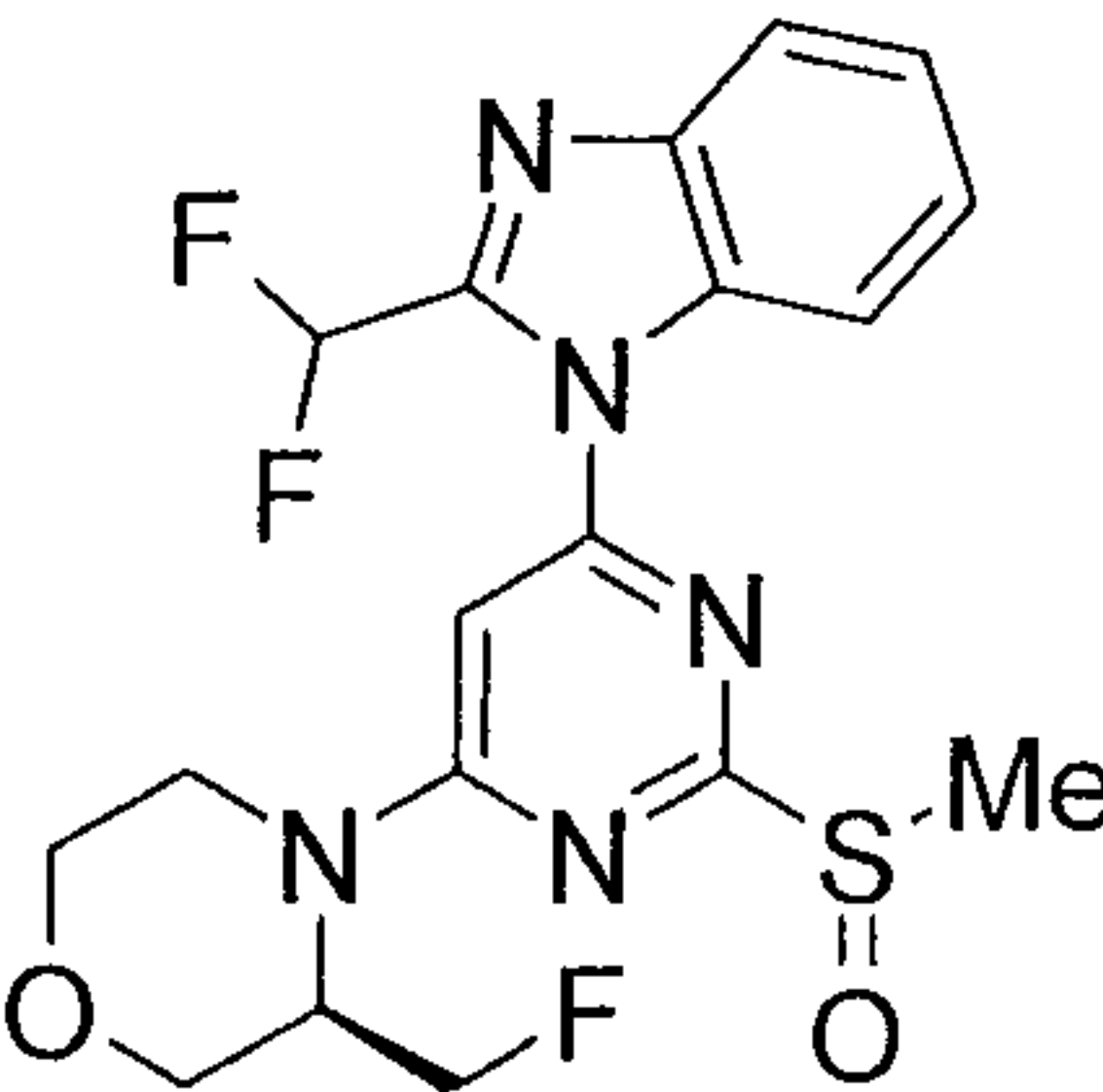
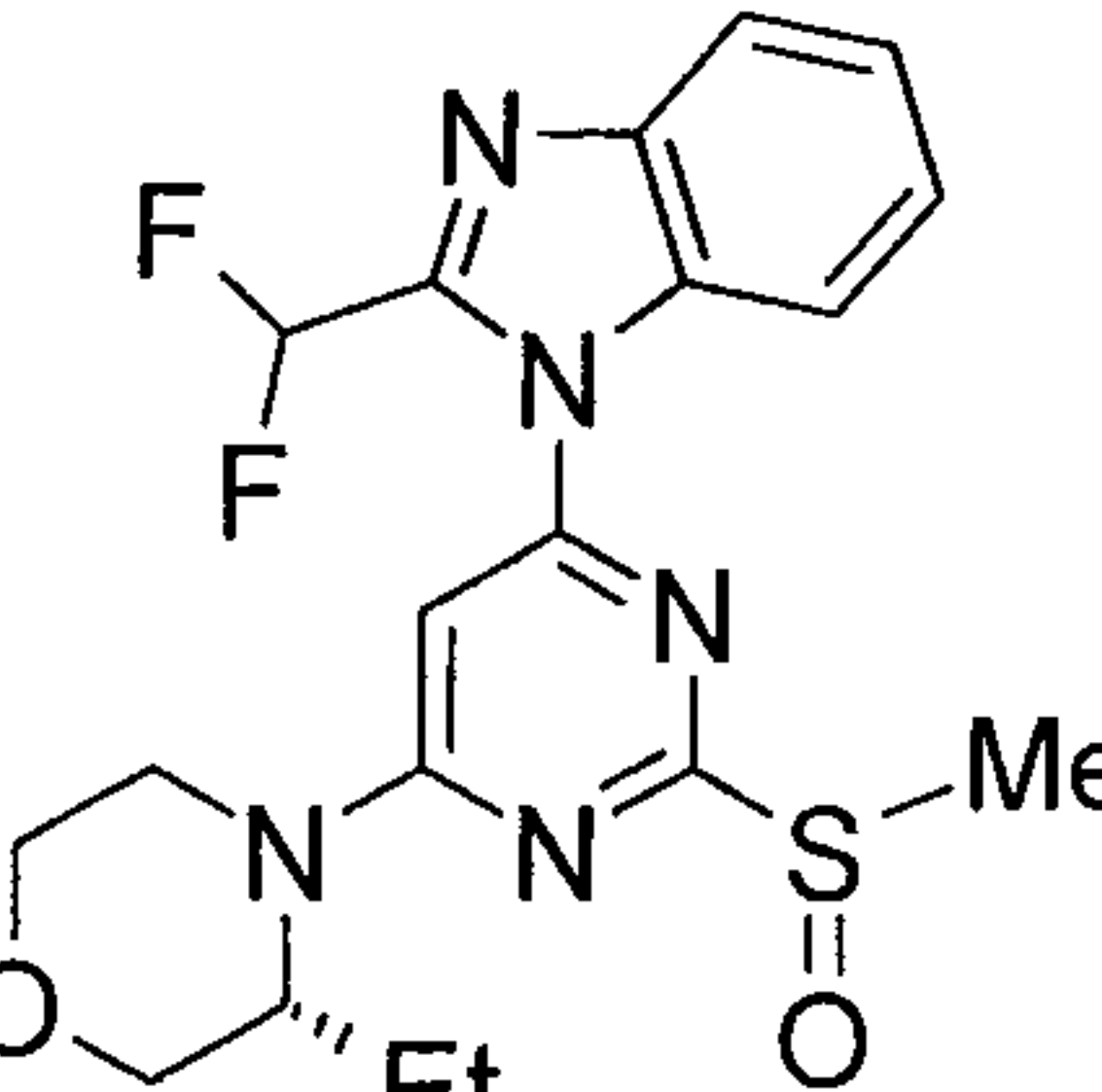
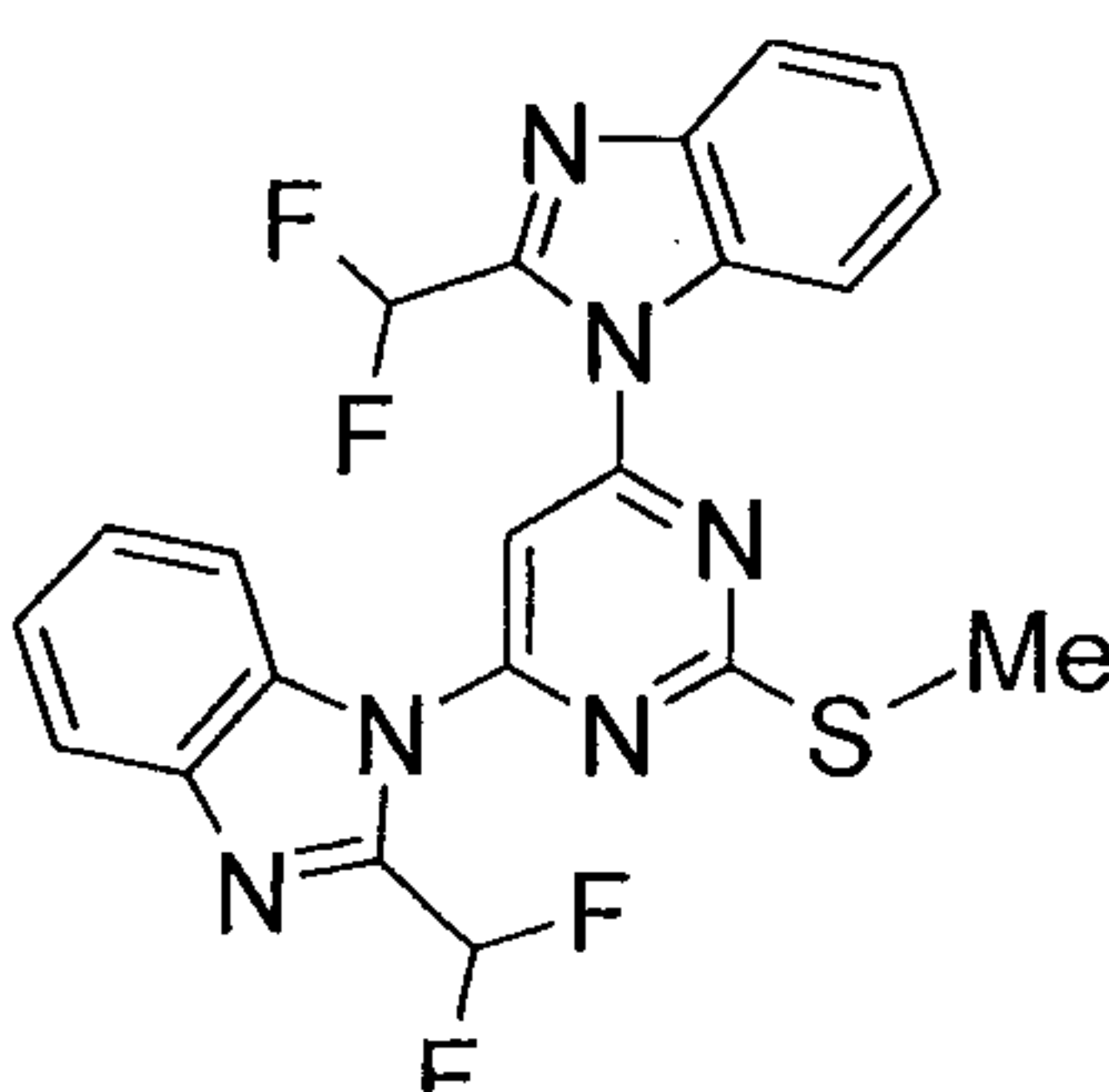
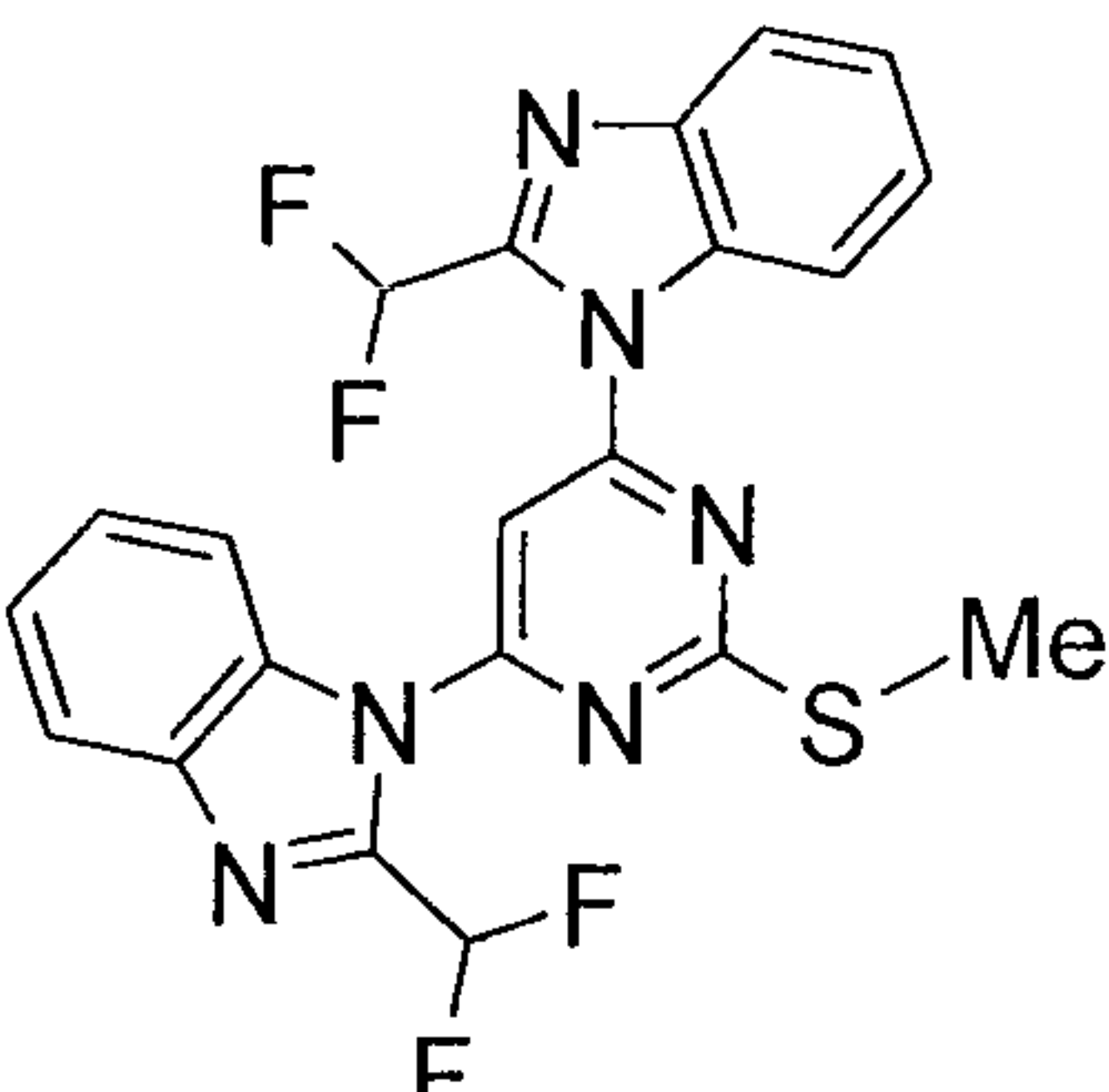
[0164]

[Table 8]

PEx	PSyn	Str	DAT
21	2		ESI+: 410
22	2		ESI+: 408
23	3		ESI+: 522
24	3		ESI+: 408
25	3		ESI+: 408

[0165]

[Table 9]

PEx	PSyn	Str	DAT
26	3		ESI+: 424
27	3		ESI+: 426
28	3		ESI+: 422
29	1		ESI+: 459
30	1		ESI+: 459

[0166]

[Table 10]

PEx	PSyn	Str	DAT
31	1		ESI+: 378
32	4		ESI+: 394
33	1		ESI+: 580(M+Na)
34	1		ESI+: 477
35	1		ESI+: 505

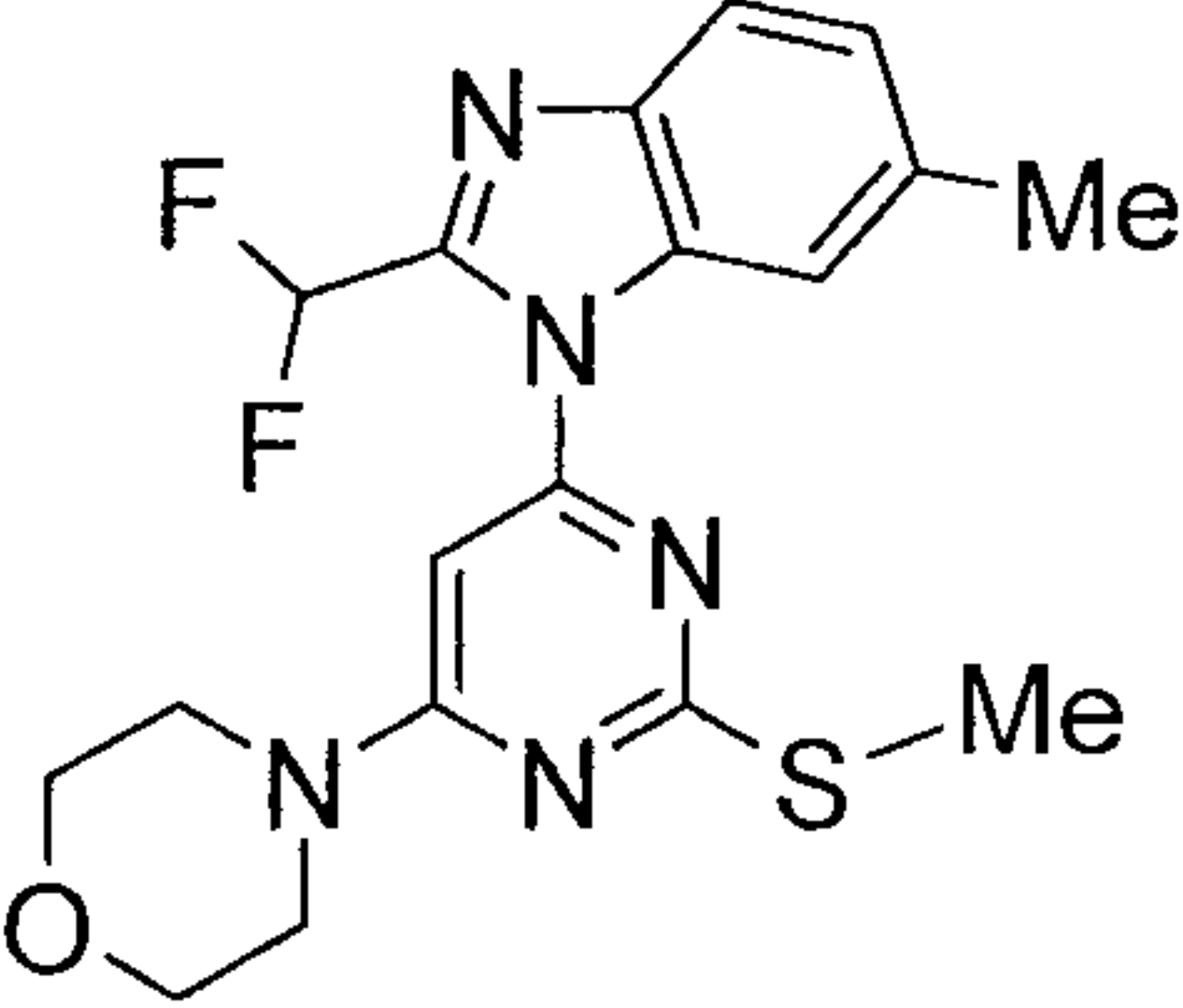
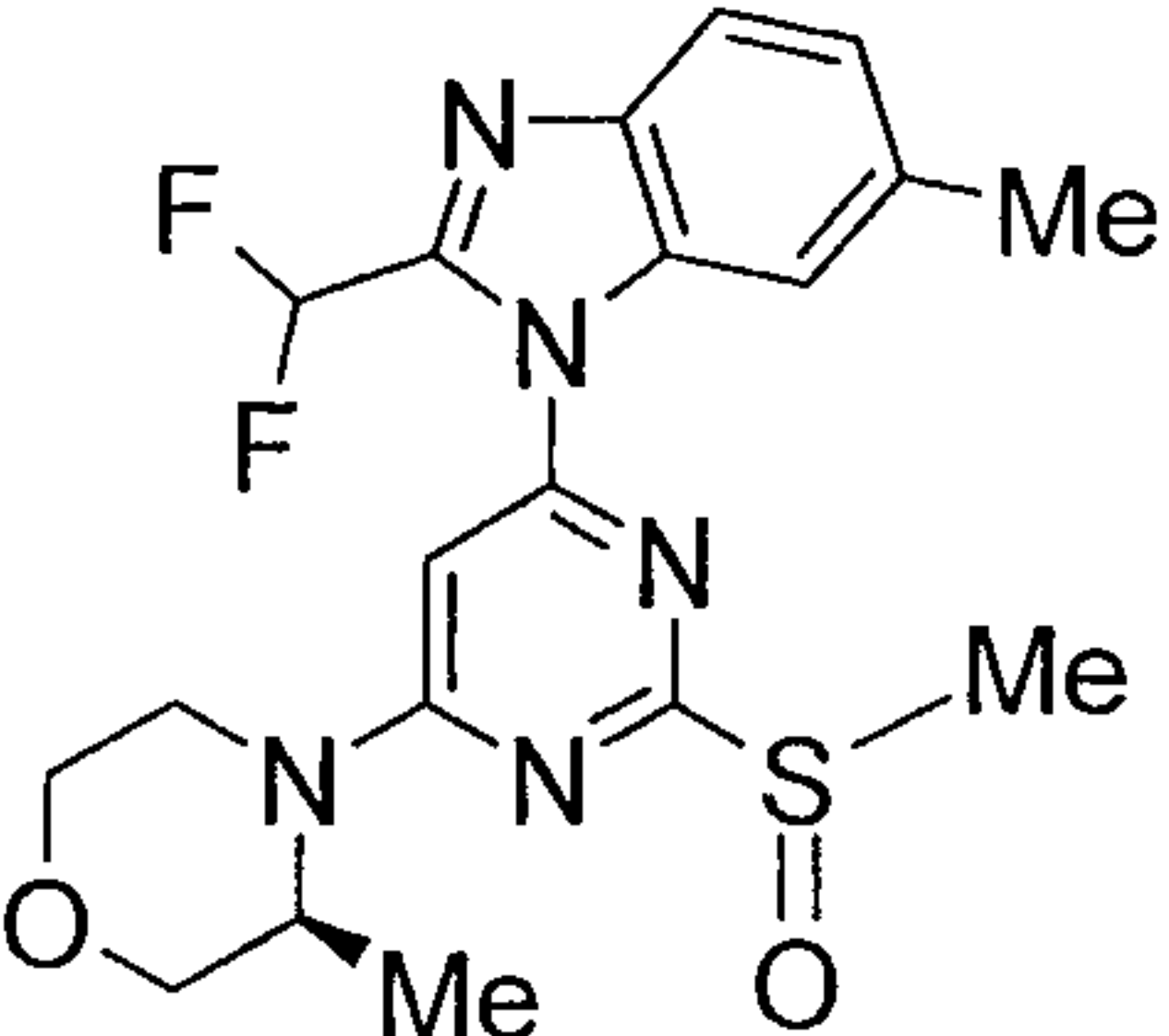
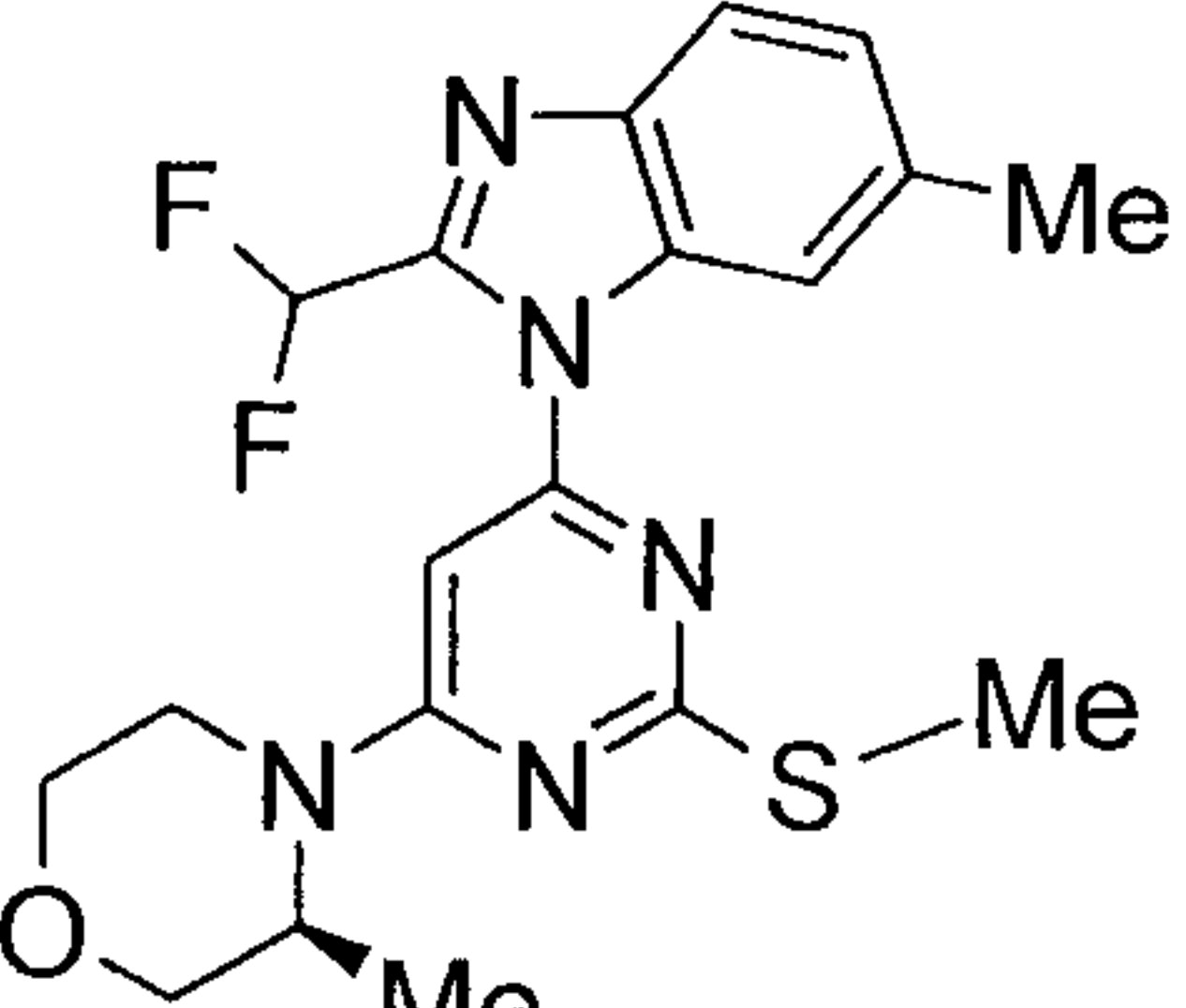
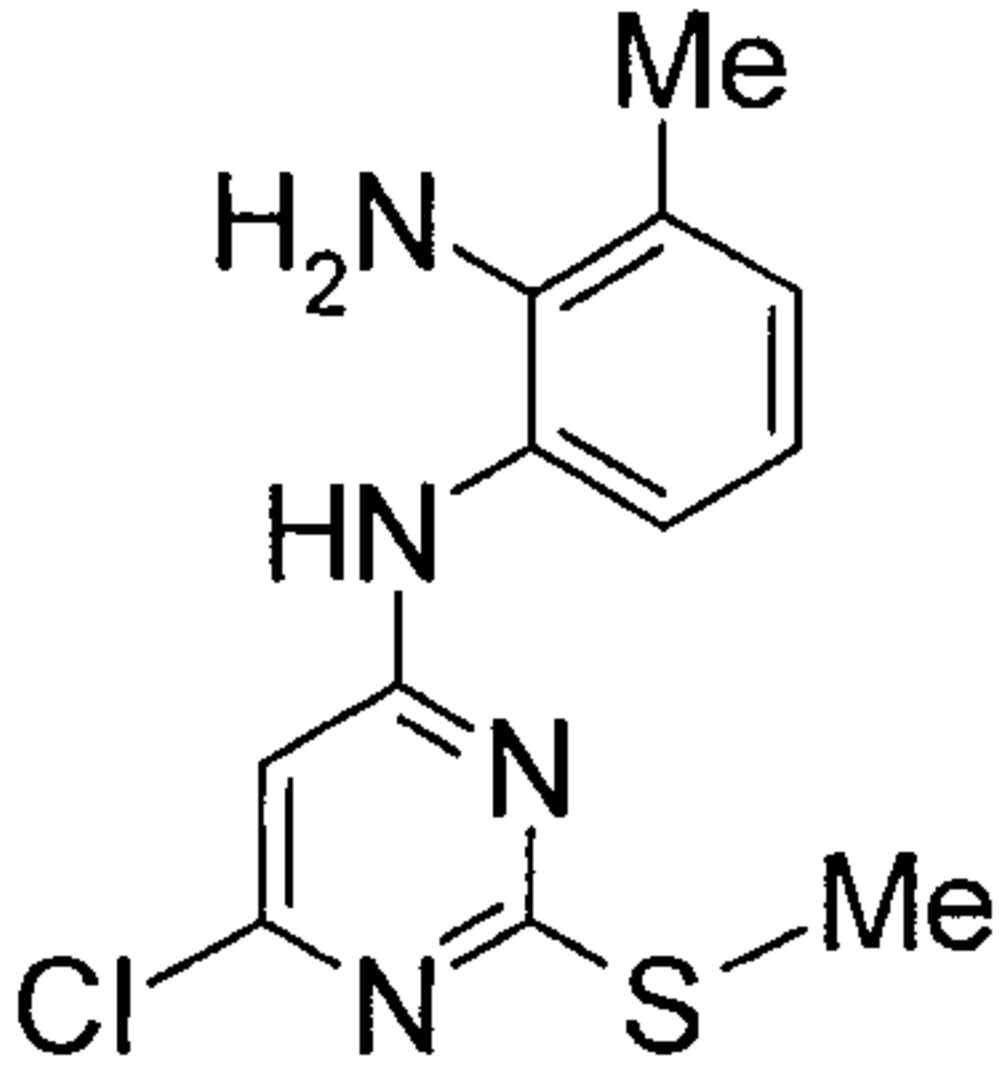
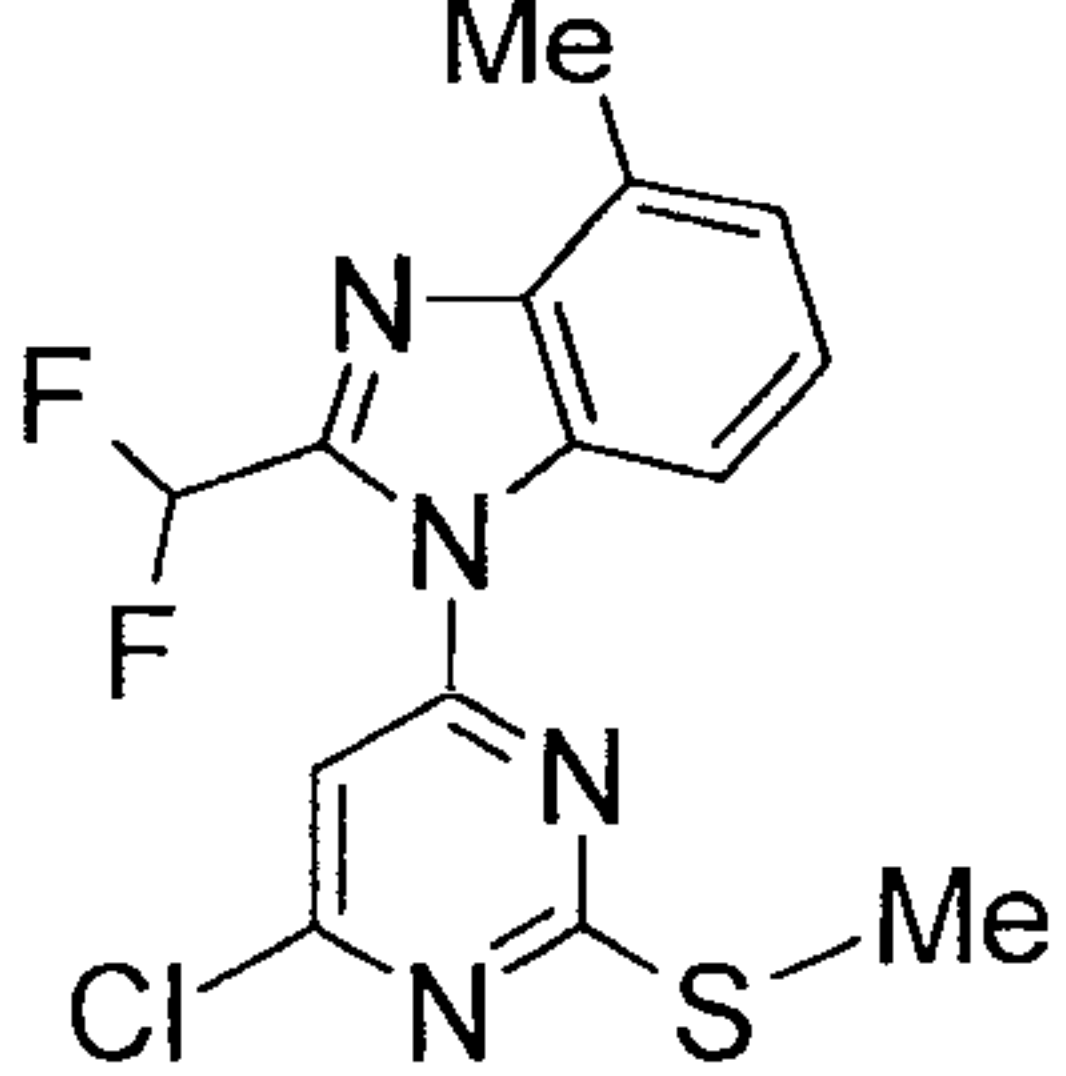
[0167]

[Table 11]

PEx	PSyn	Str	DAT
36	3		ESI+: 408
37	1		ESI+: 392
38	12		ESI+: 341
39	1		ESI+: 323
40	3		ESI+: 408

[0168]

[Table 12]

PEx	PSyn	Str	DAT
41	1		ESI+: 392
42	3		ESI+: 422
43	1		ESI+: 406
44	10		ESI+: 281
45	12		ESI+: 341

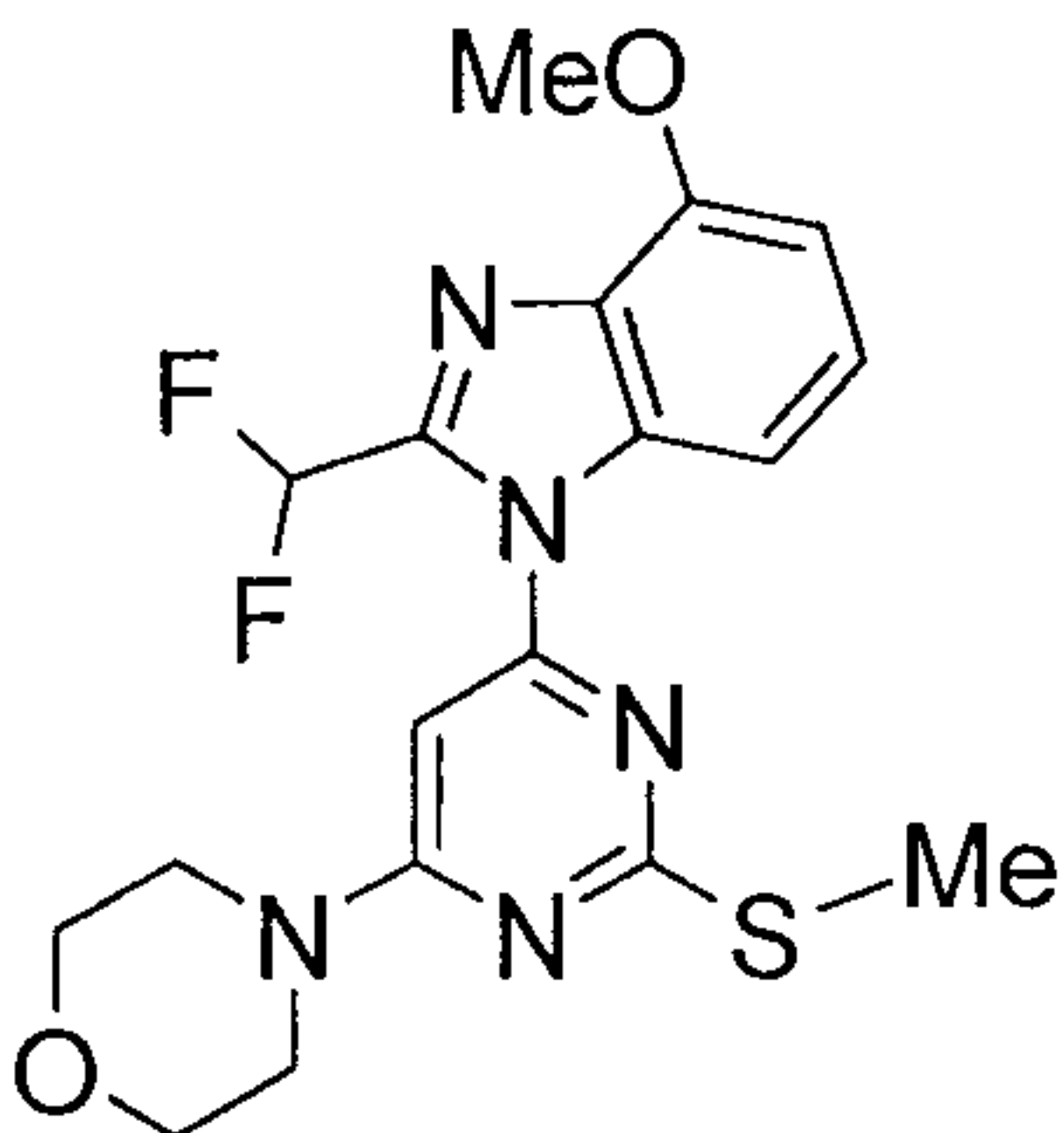
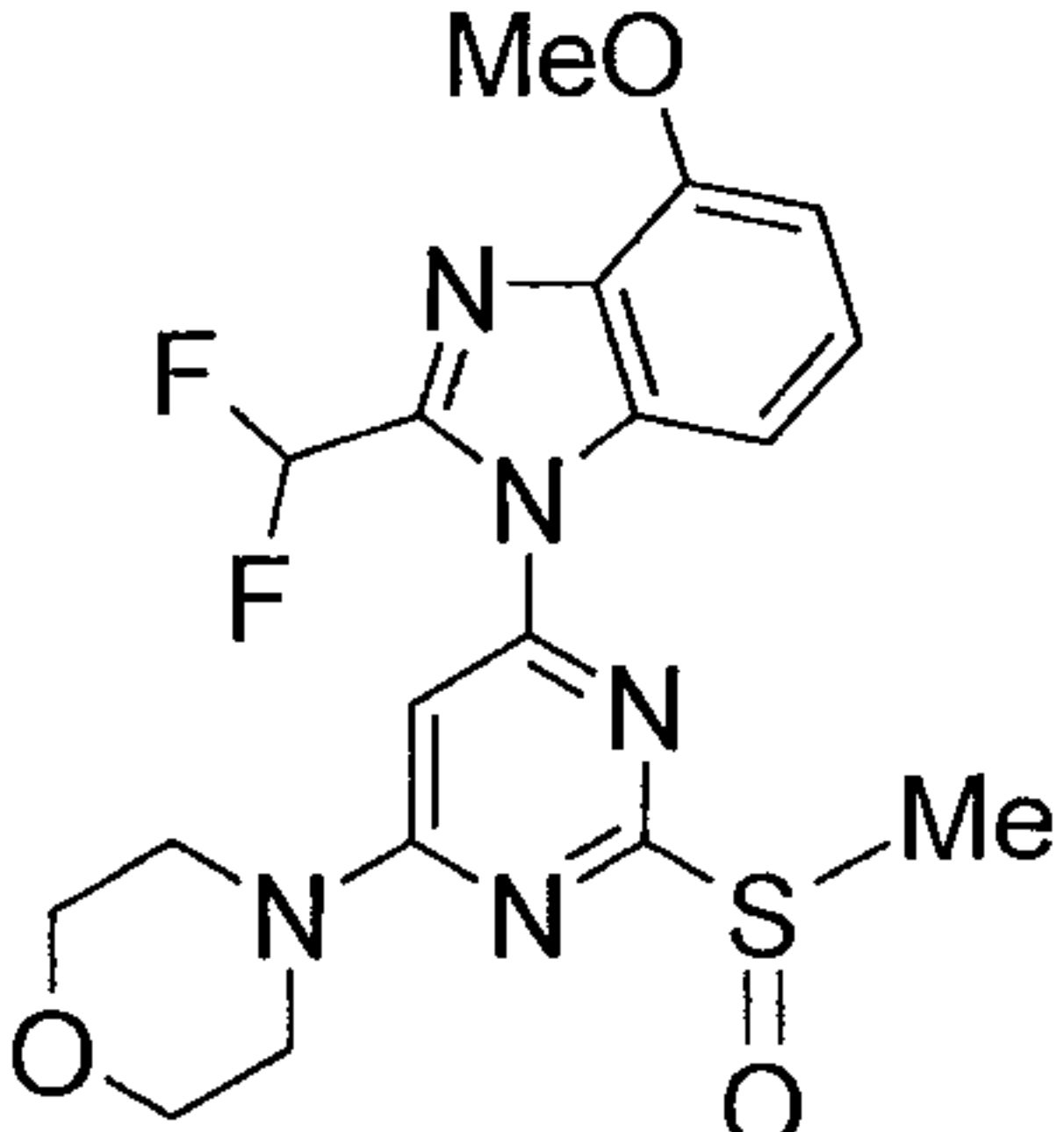
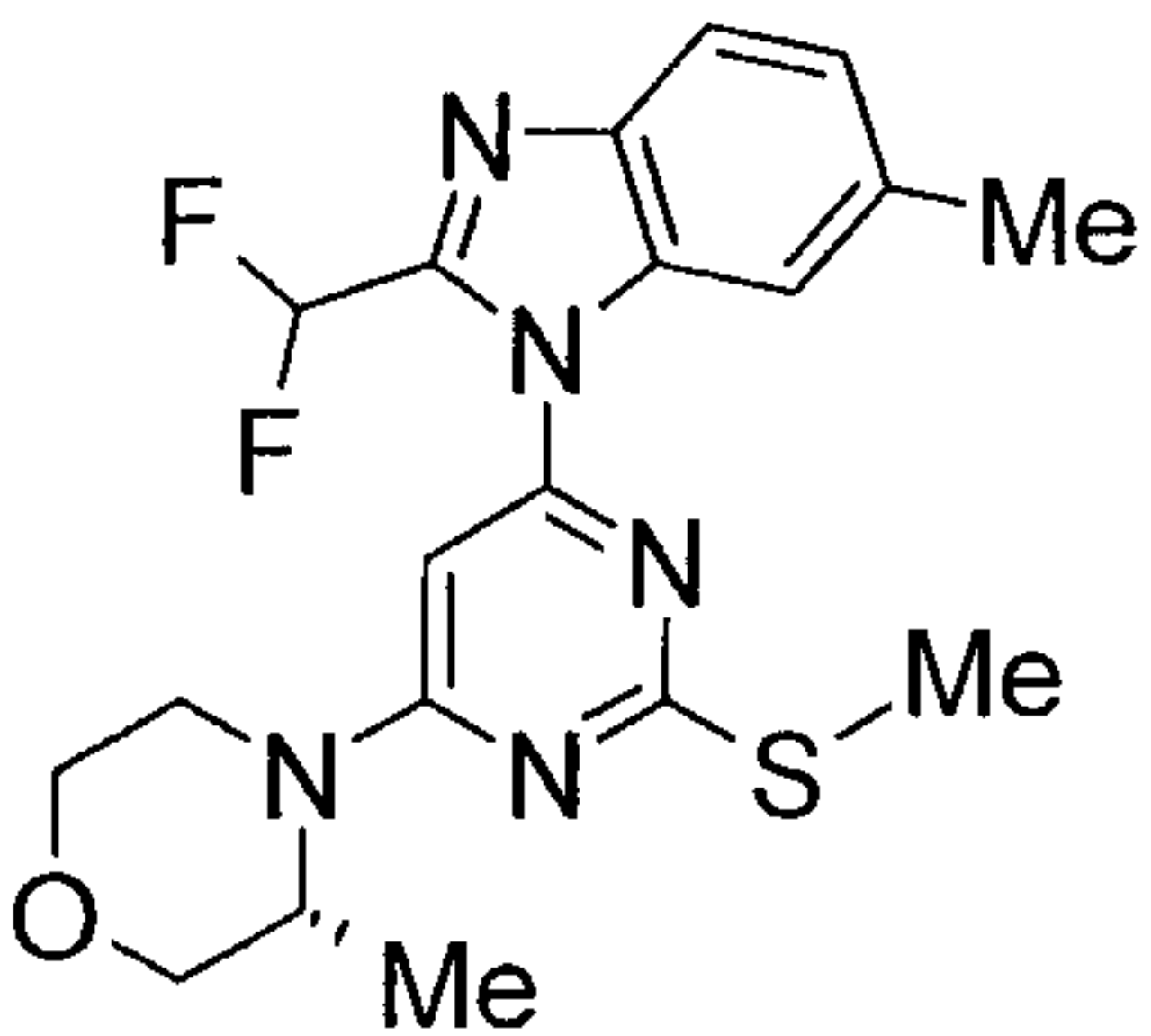
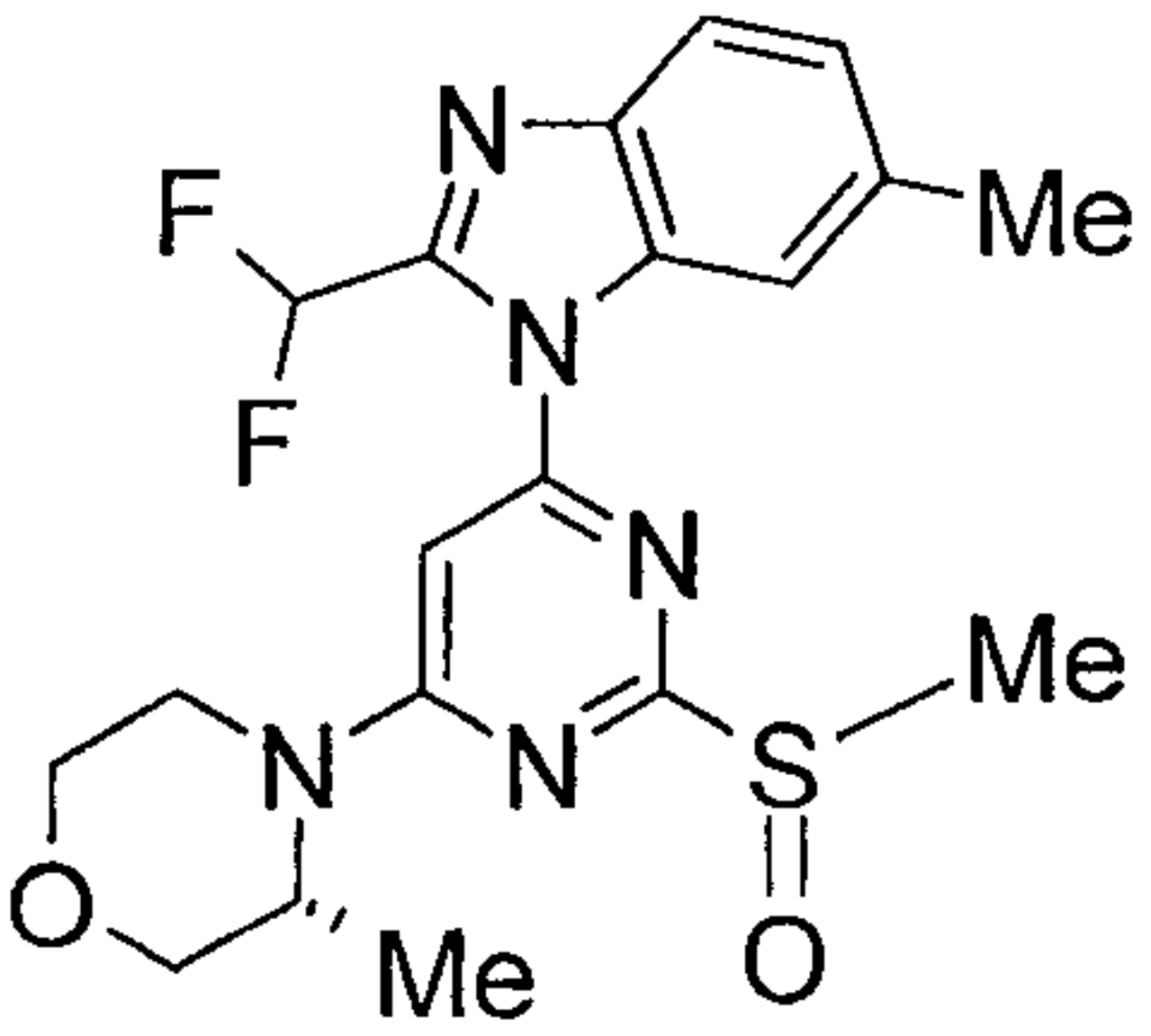
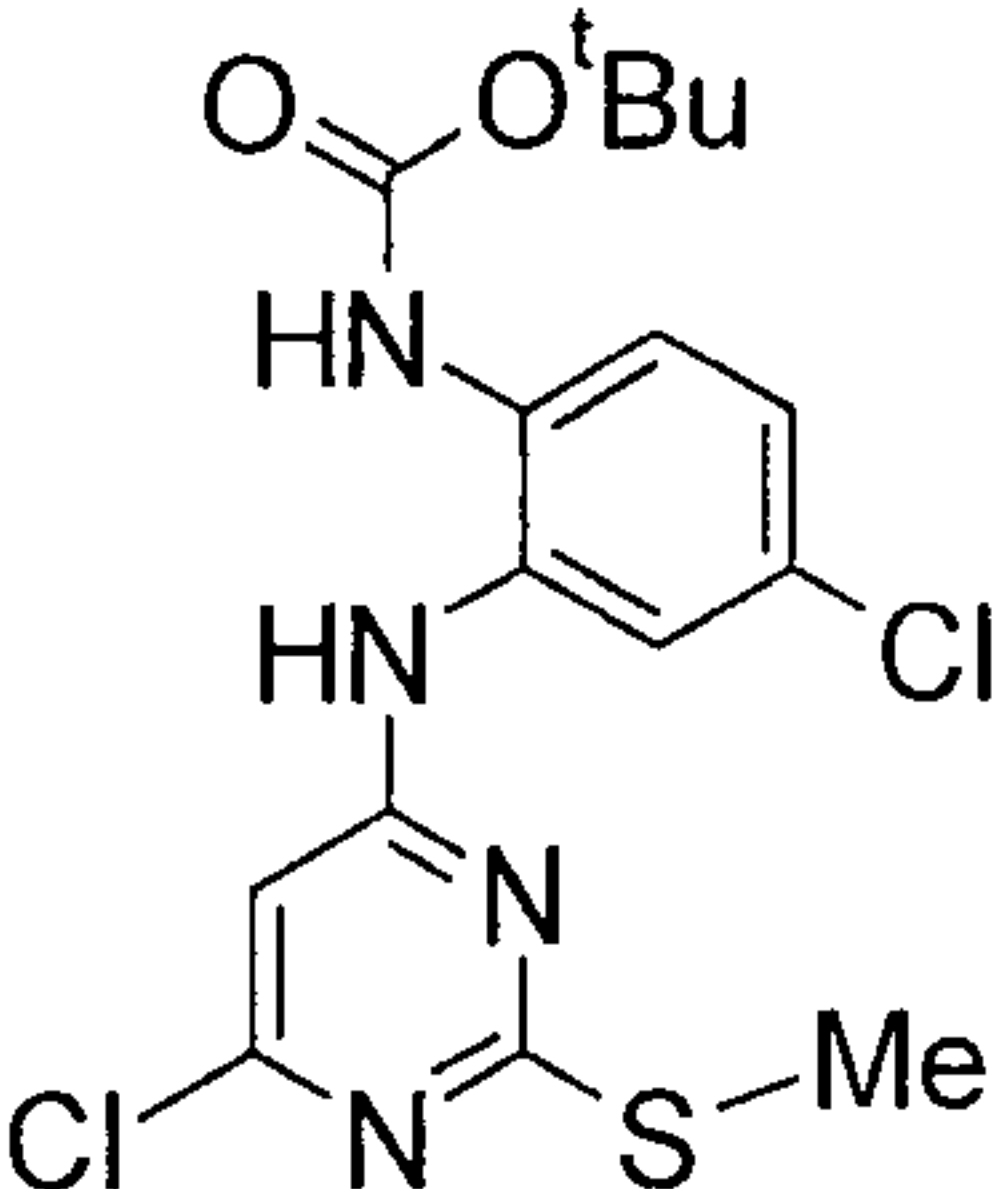
[0169]

[Table 13]

PEX	PSyn	Str	DAT
46	1		ESI+: 392
47	4		ESI+: 408
48	12		ESI+: 392
49	15		ESI+: 424
50	1		ESI+: 357

[0170]

[Table 14]

PEx	PSyn	Str	DAT
51	1		ESI+: 408
52	3		ESI+: 424
53	1		ESI+: 406
54	3		ESI+: 422
55	10		ESI+: 401/403

[0171]

[Table 15]

PEx	PSyn	Str	DAT
56	10		ESI+: 435
57	11		ESI+: 301
58	5		ESI+: 492
59	5		ESI+: 492
60	1		ESI+: 279
61	12		ESI+: 361/363

[0172]

[Table 16]

PEx	PSyn	Str	DAT
62	11		ESI+: 335
63	12		ESI+: 395
64	1		ESI+: 412
65	1		ESI+: 446
66	3		ESI+: 428
67	Syn.53		ESI+: 179

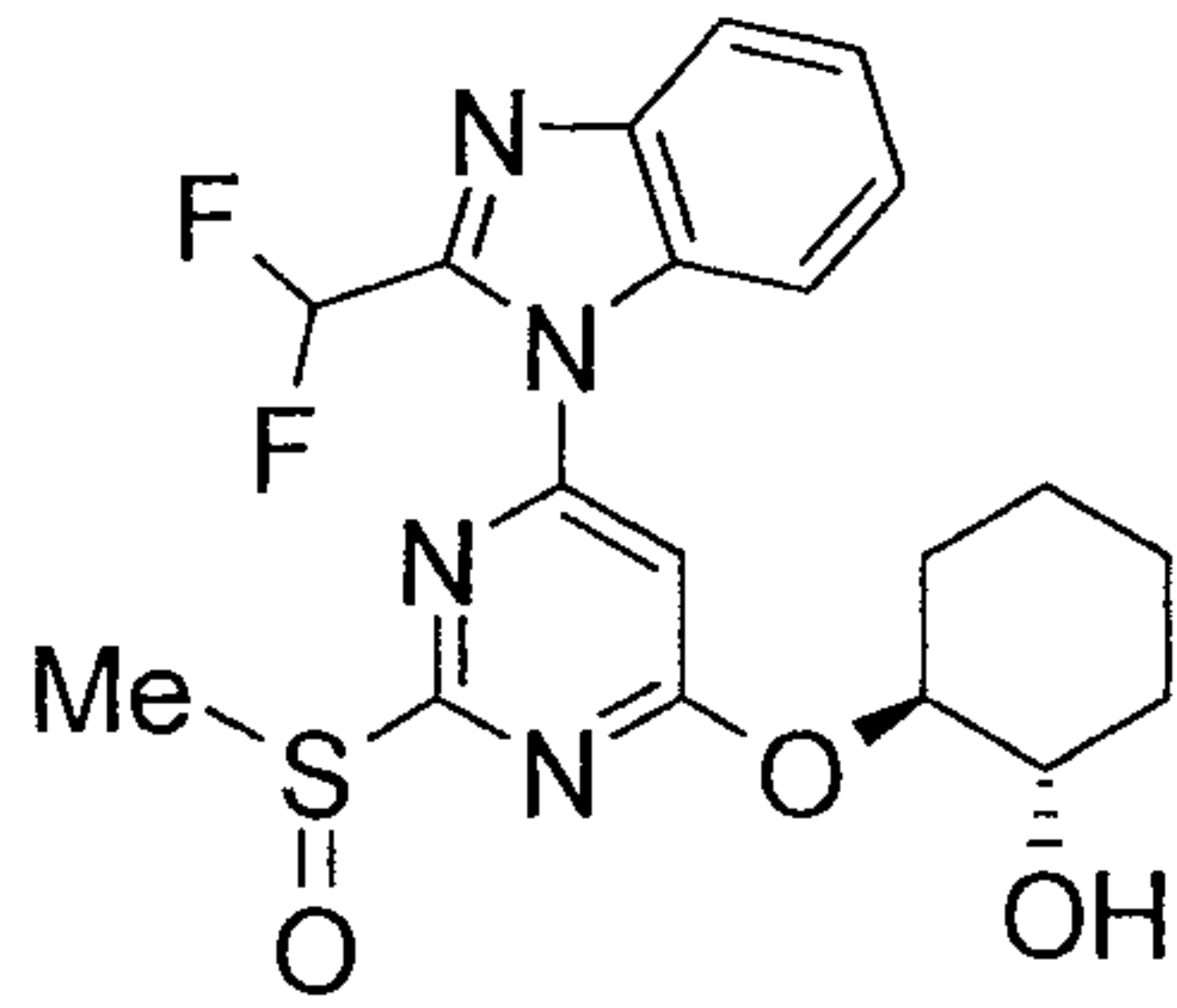
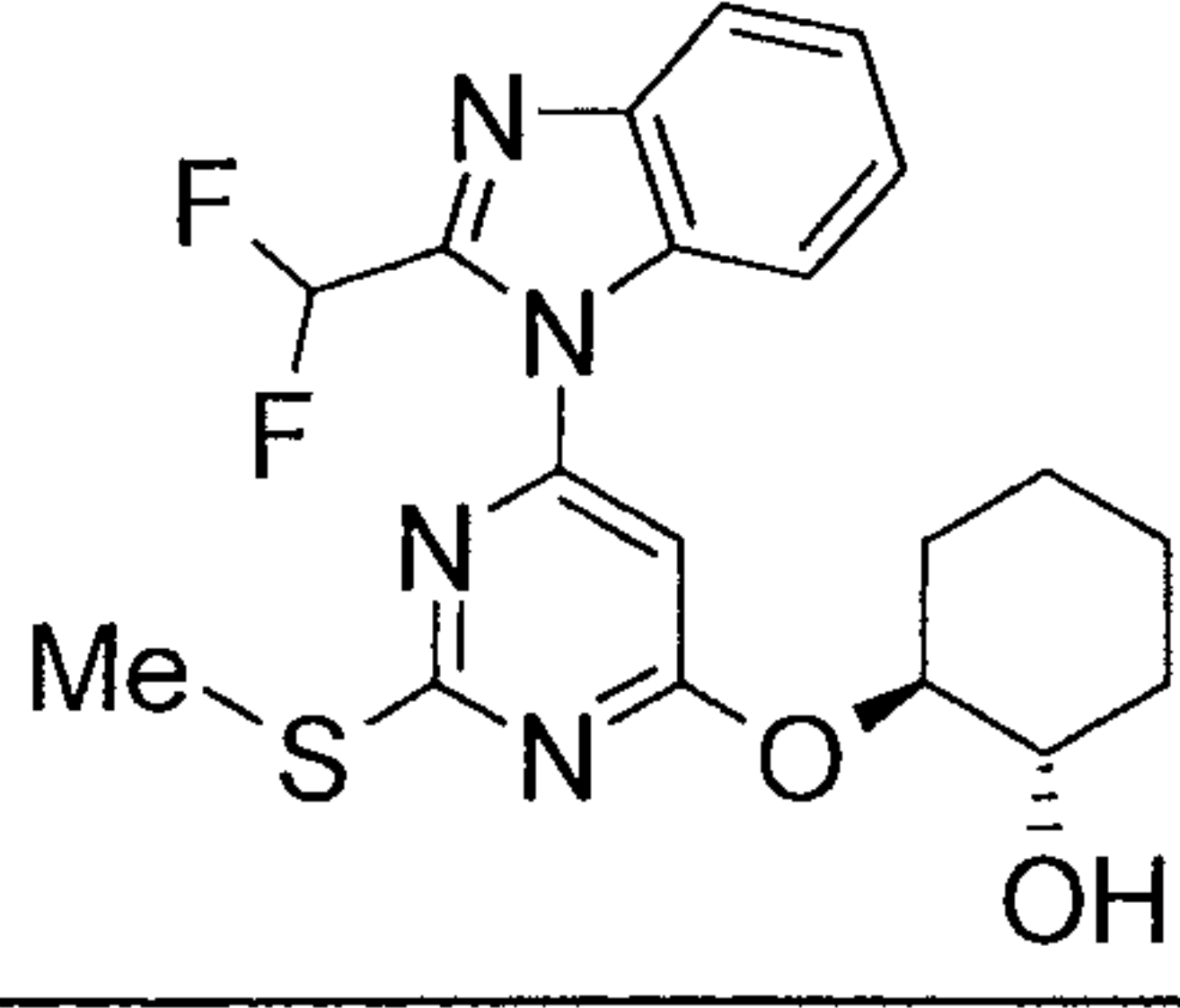
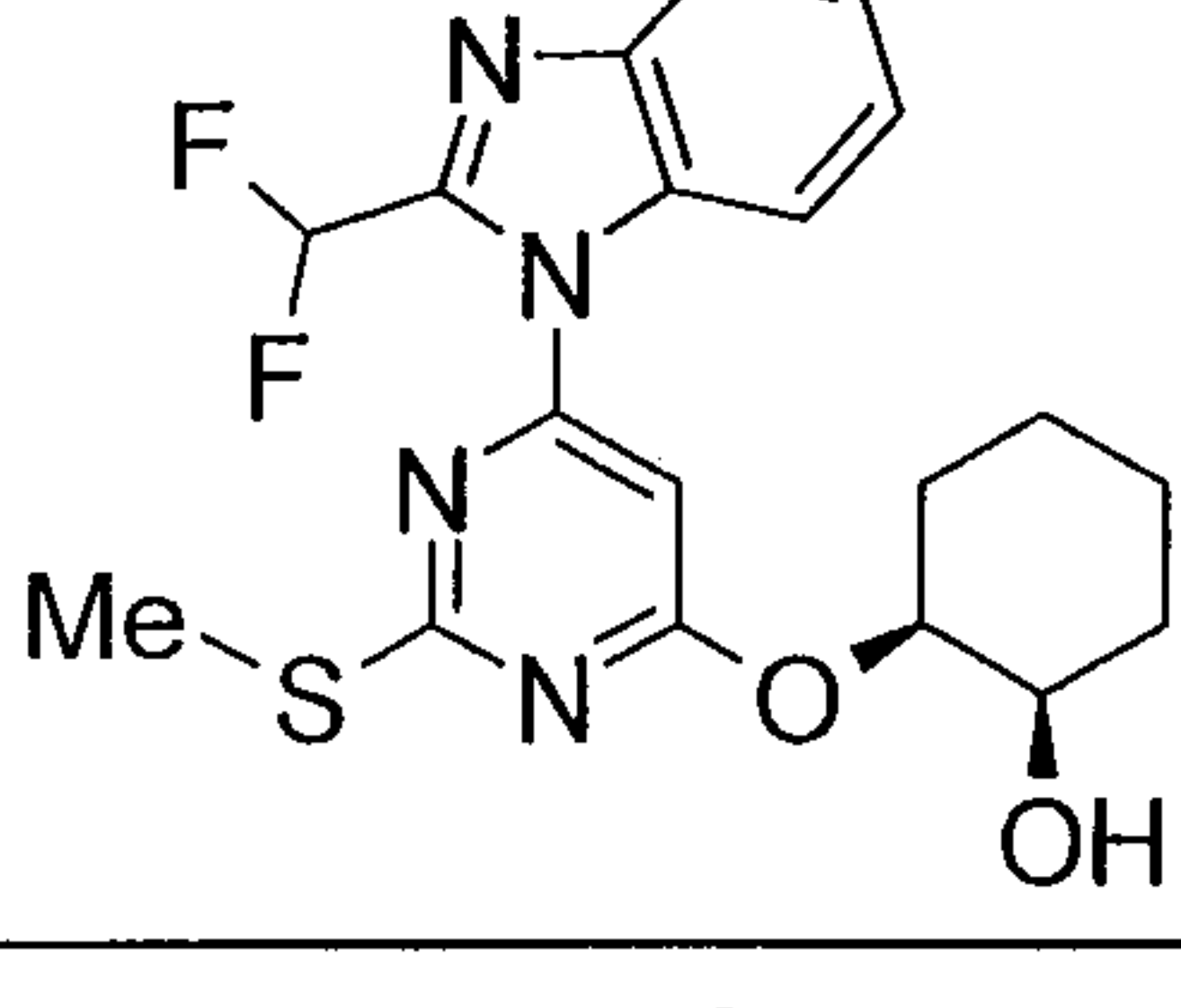
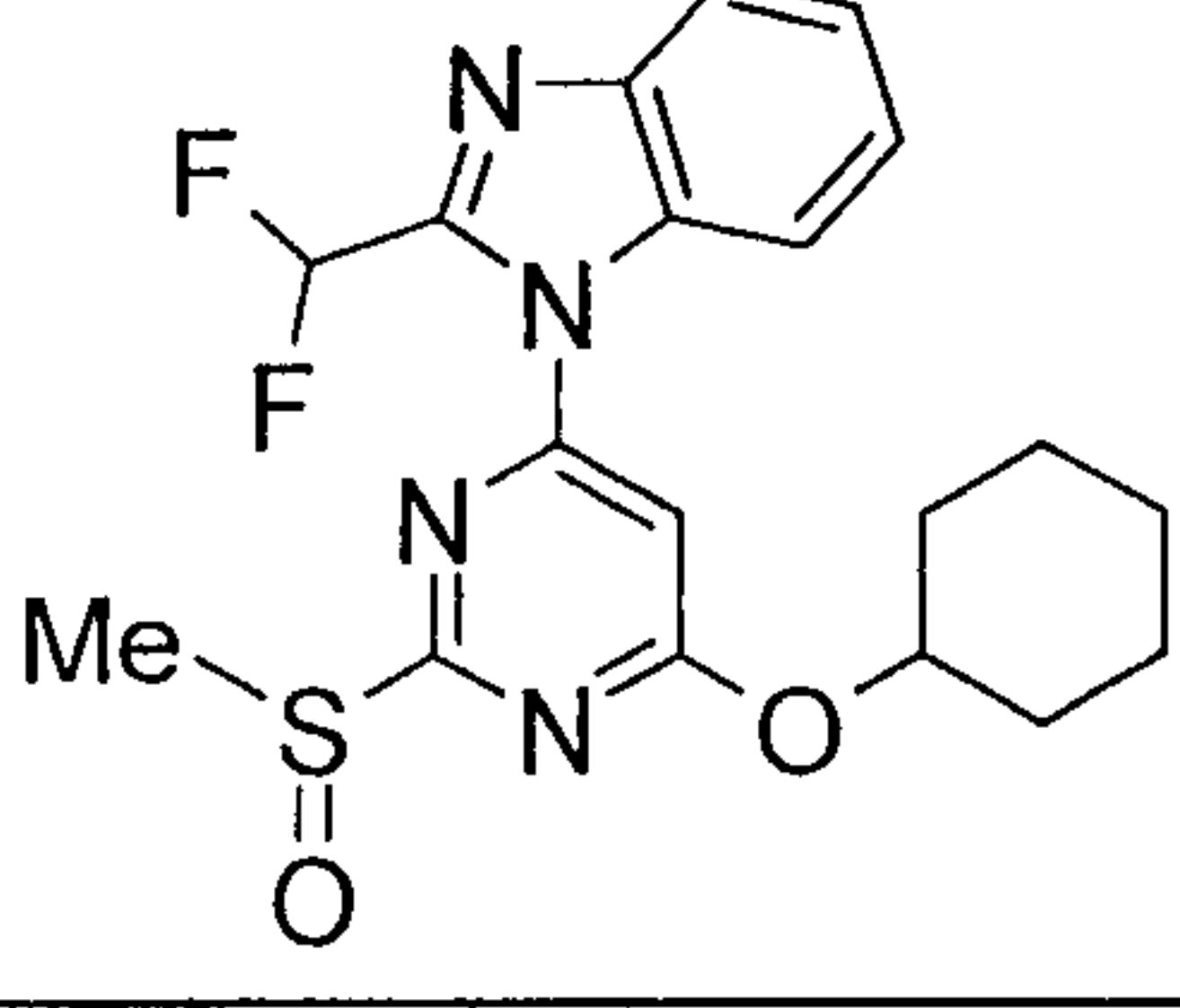
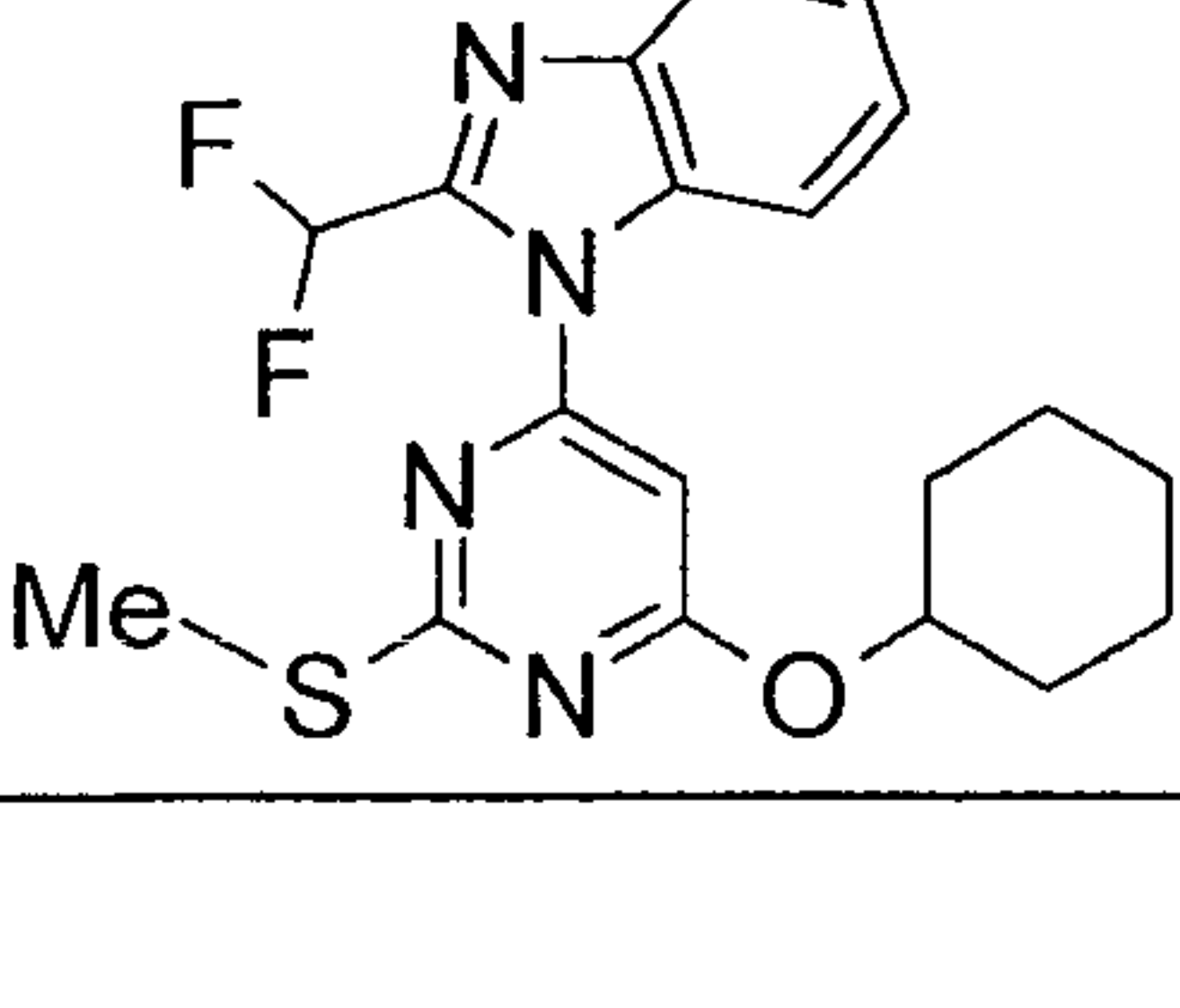
[0173]

[Table 17]

PEx	PSyn	Str	DAT
68	3		ESI+: 462
69	89		ESI+: 407
70	3		ESI+: 423
71	3		ESI+: 423
72	1		ESI+: 516

[0174]

[Table 18]

PEx	PSyn	Str	DAT
73	3		ESI+: 423
74	89		ESI+: 407
75	89		ESI+: 407
76	3		ESI+: 407
77	5		ESI+: 391

[0175]

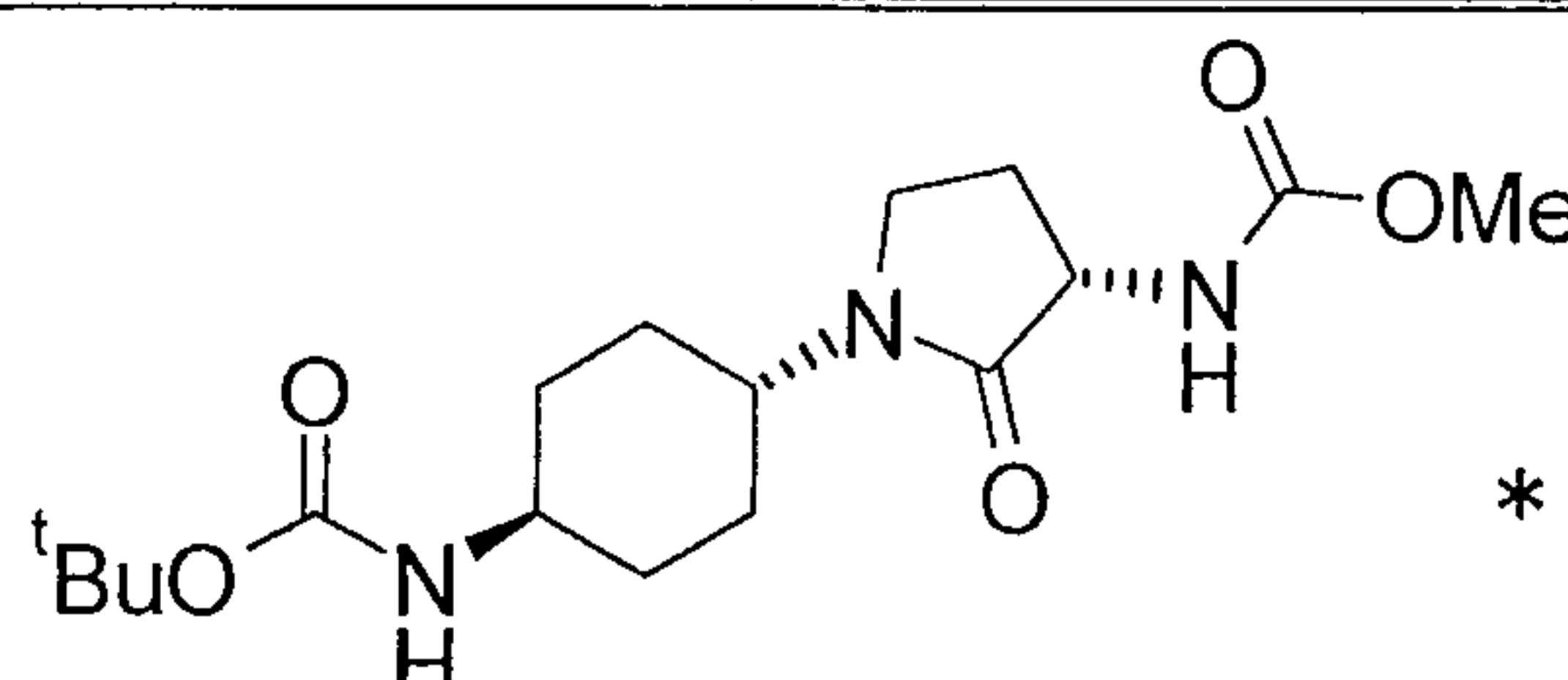
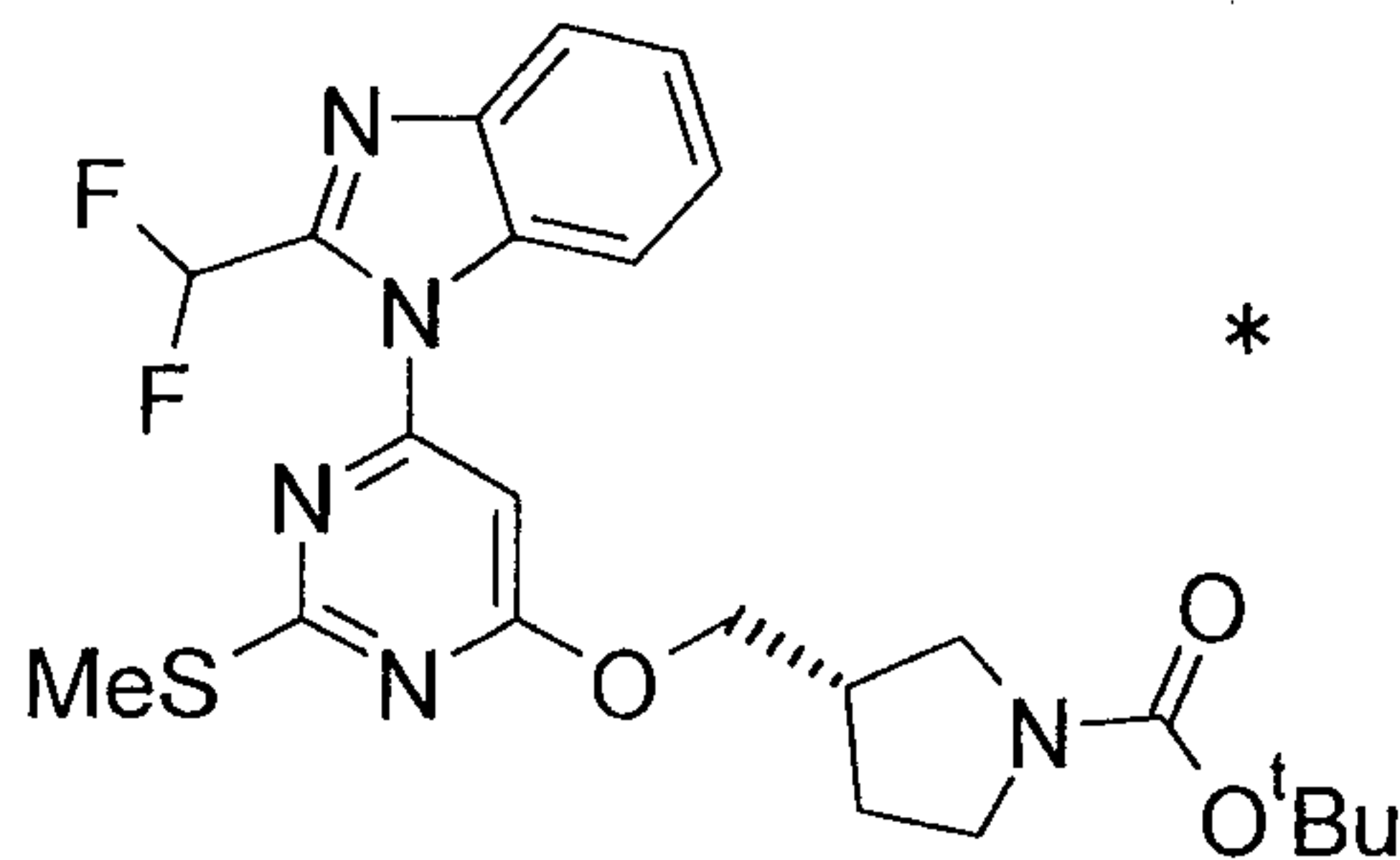
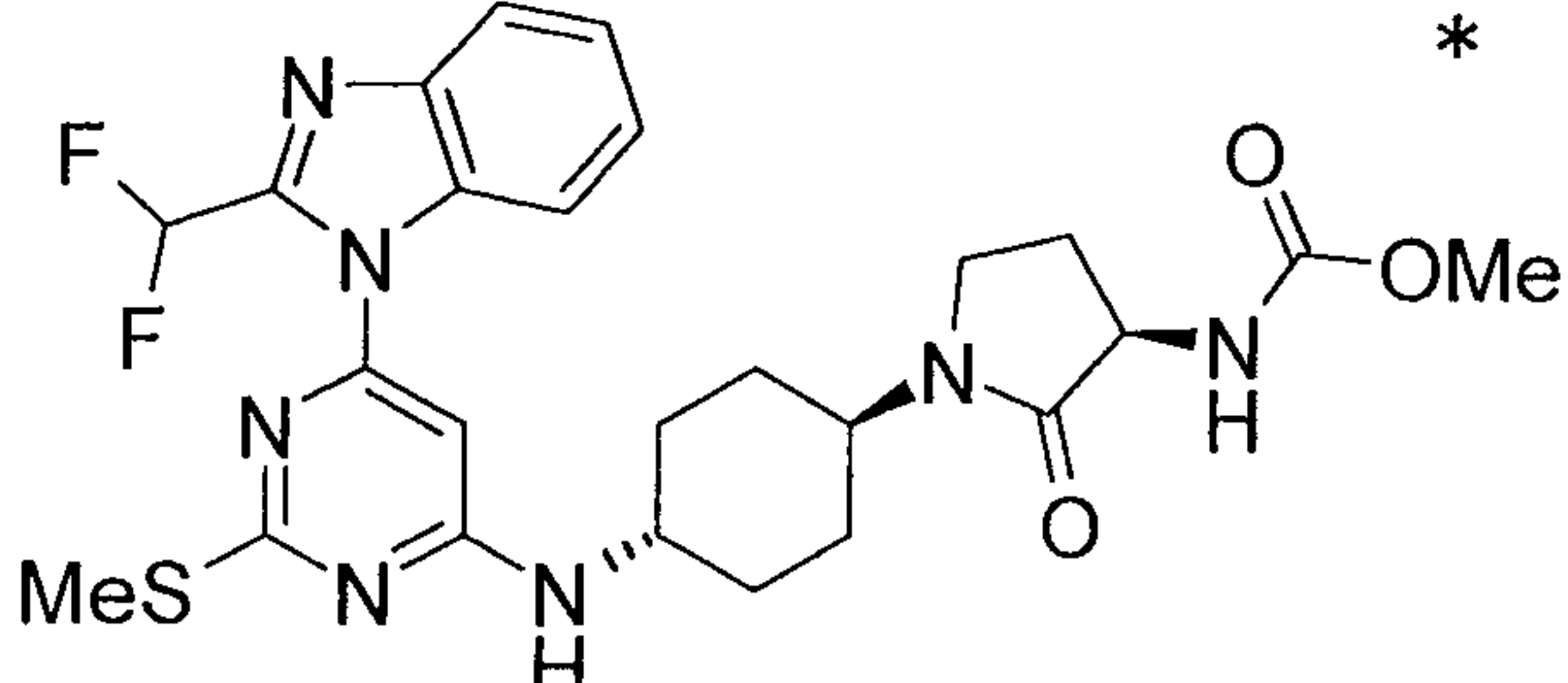
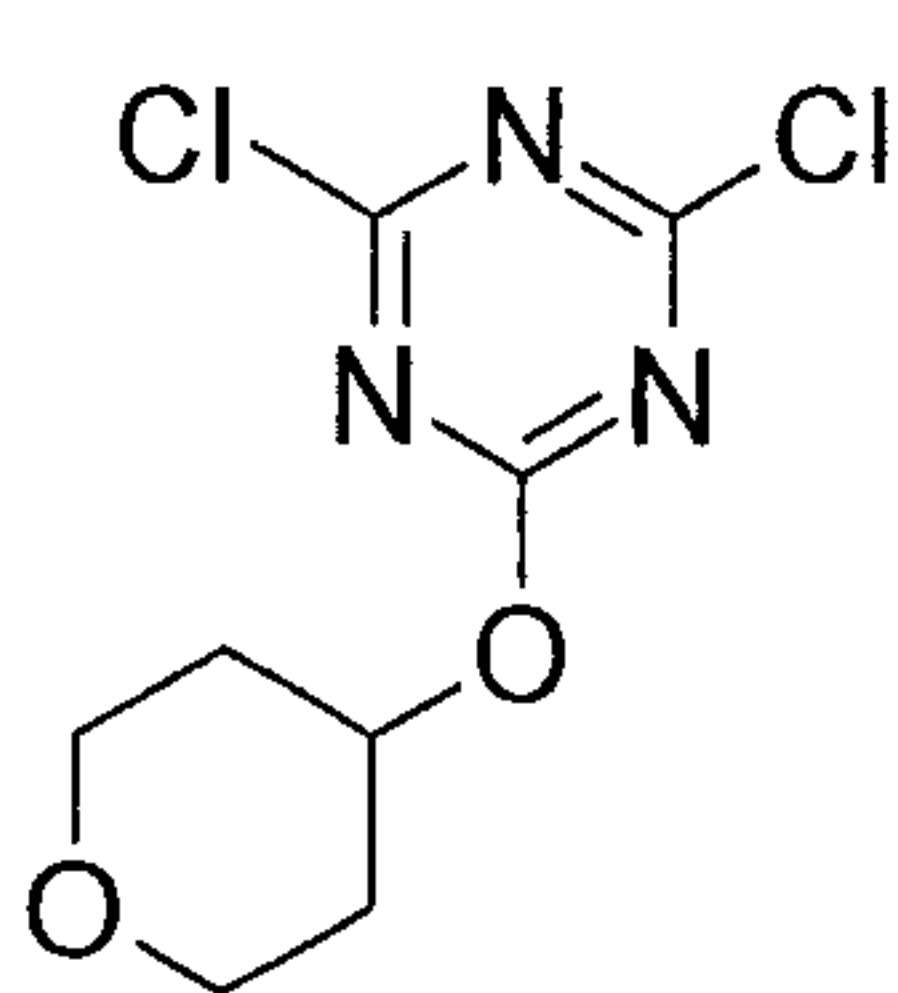
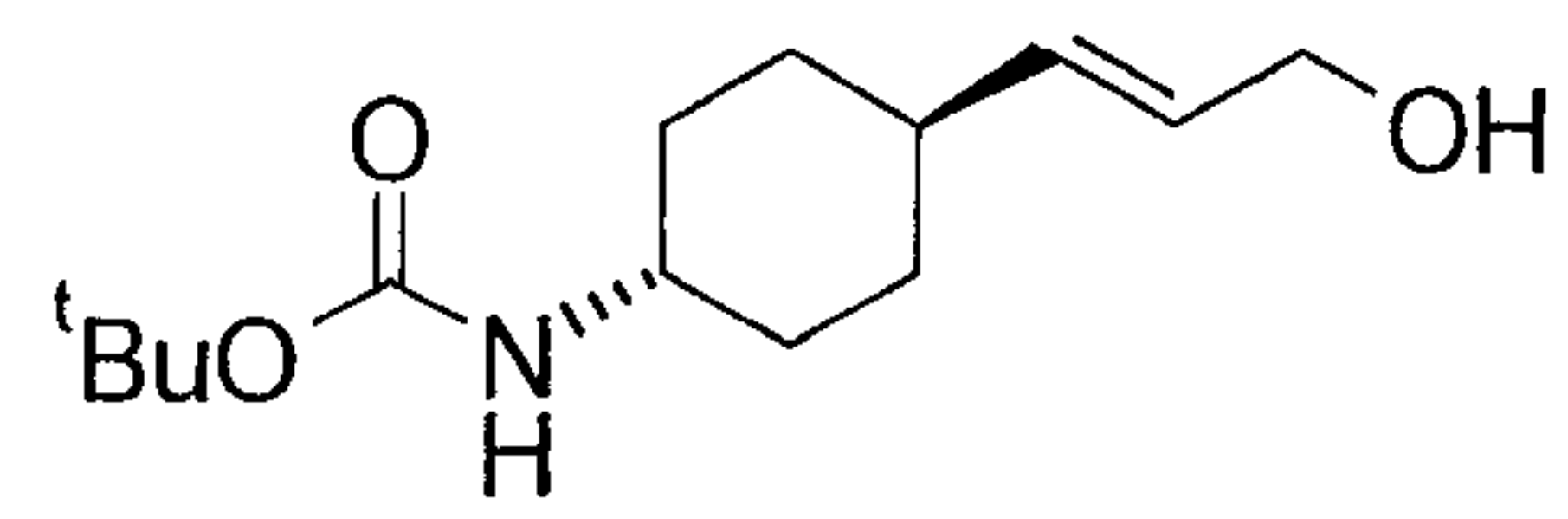
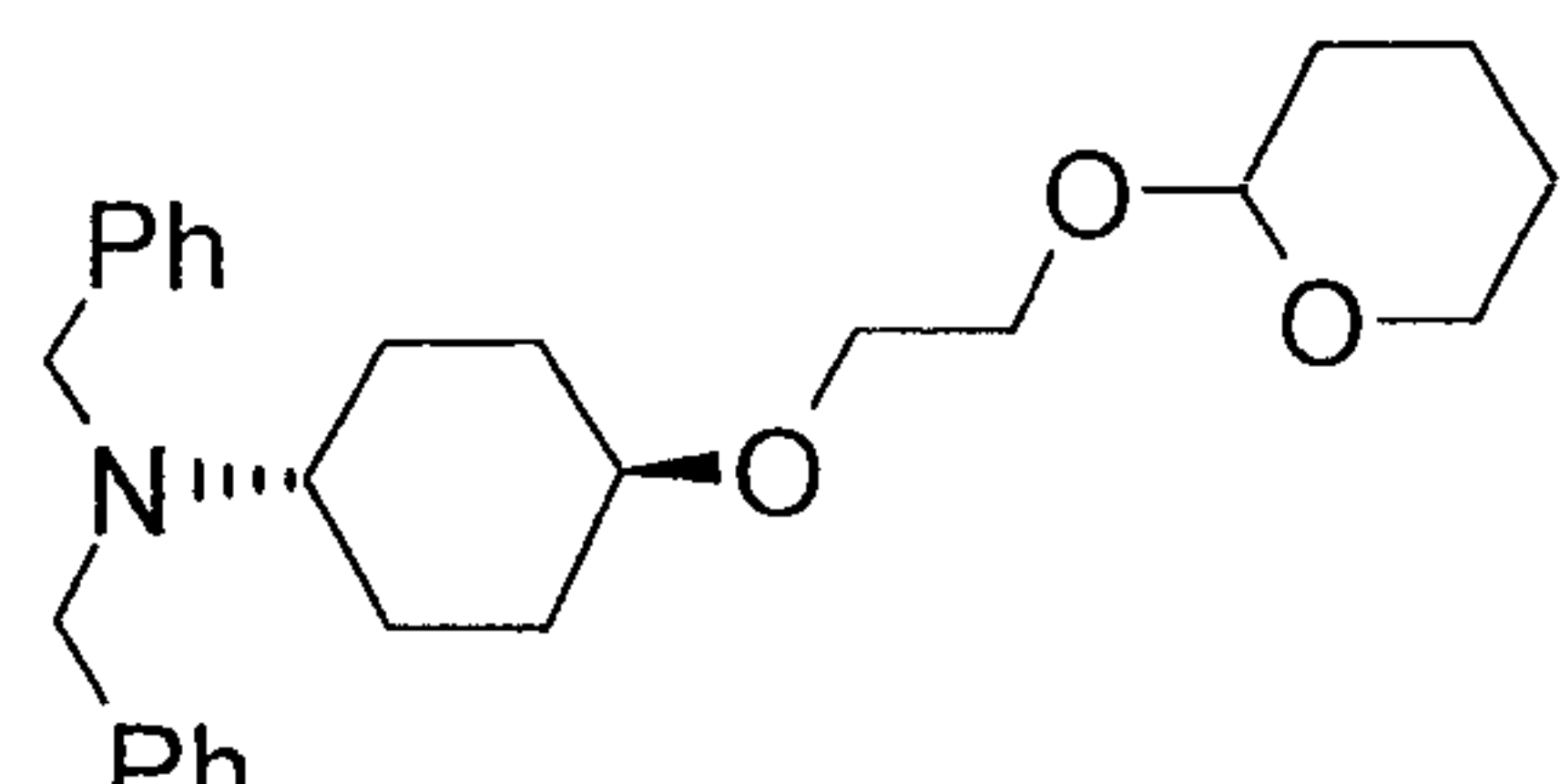
[Table 19]

PEx	PSyn	Str	DAT
78	1		ESI+: 505
79	11		ESI+: 458 NMR1:0.82-1.03(4H,m),1.35-2.60(2H,m),1.65-1.82(4H,m),2.99-3.03(2H,m),3.56-3.75(8H,m),6.23-6.37(1H,m),7.09-7.17(1H,m),7.37-7.48(2H,m),7.75-7.79(1H,m),7.82-7.88(1H,m)
80	80		ESI+: 438
81	81		ESI+: 354
82	82		ESI+: 407
83	83		ESI+: 227

[0176]

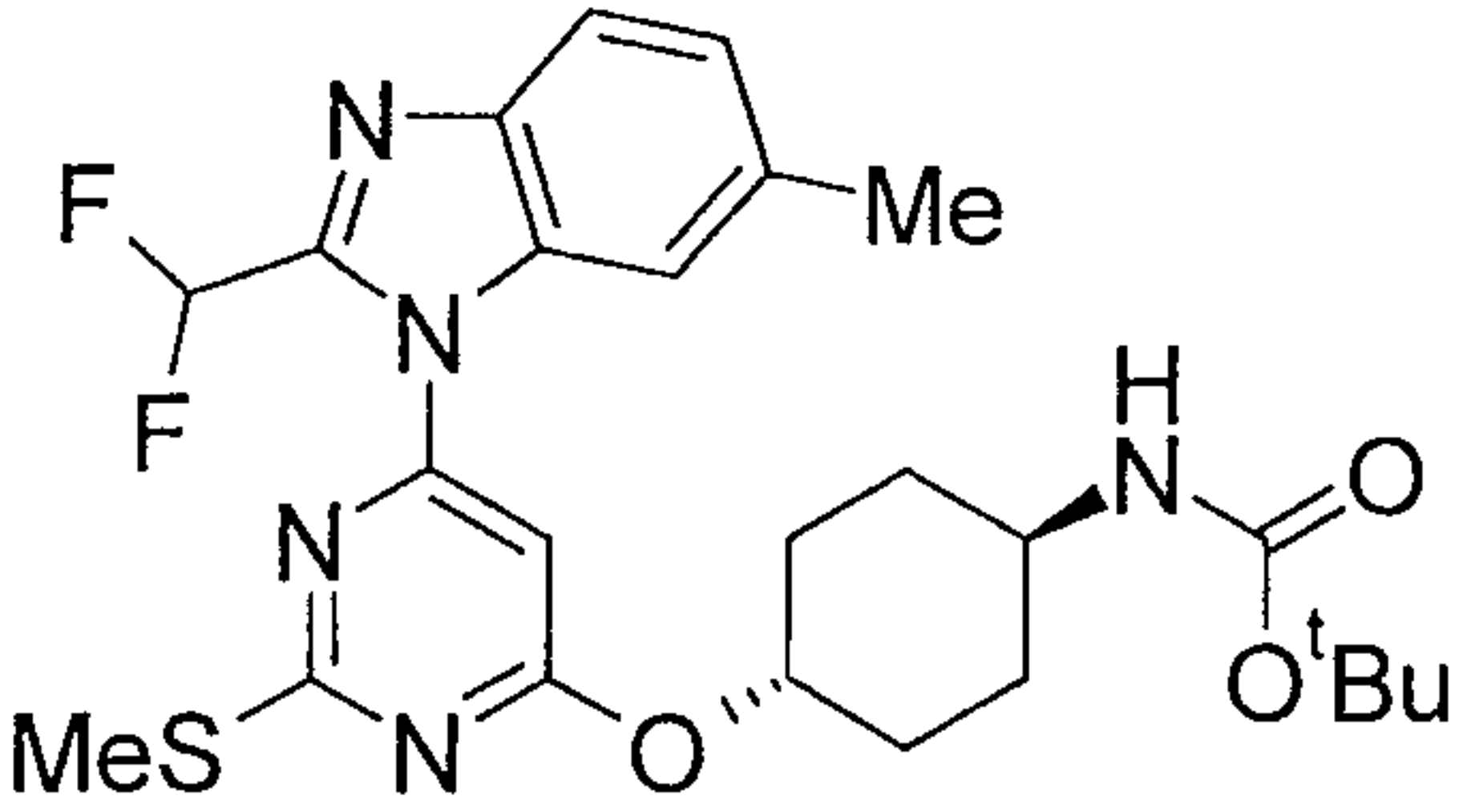
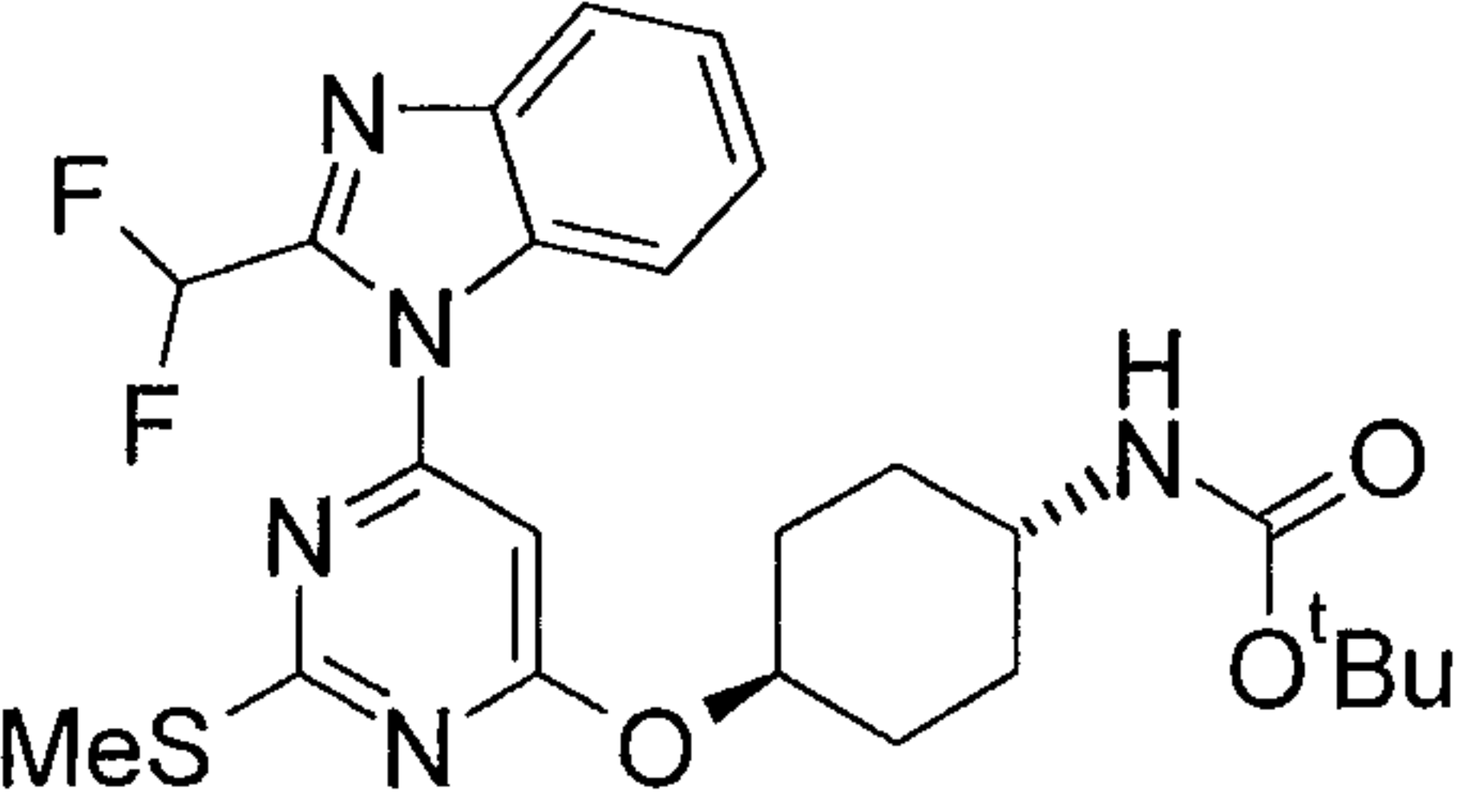
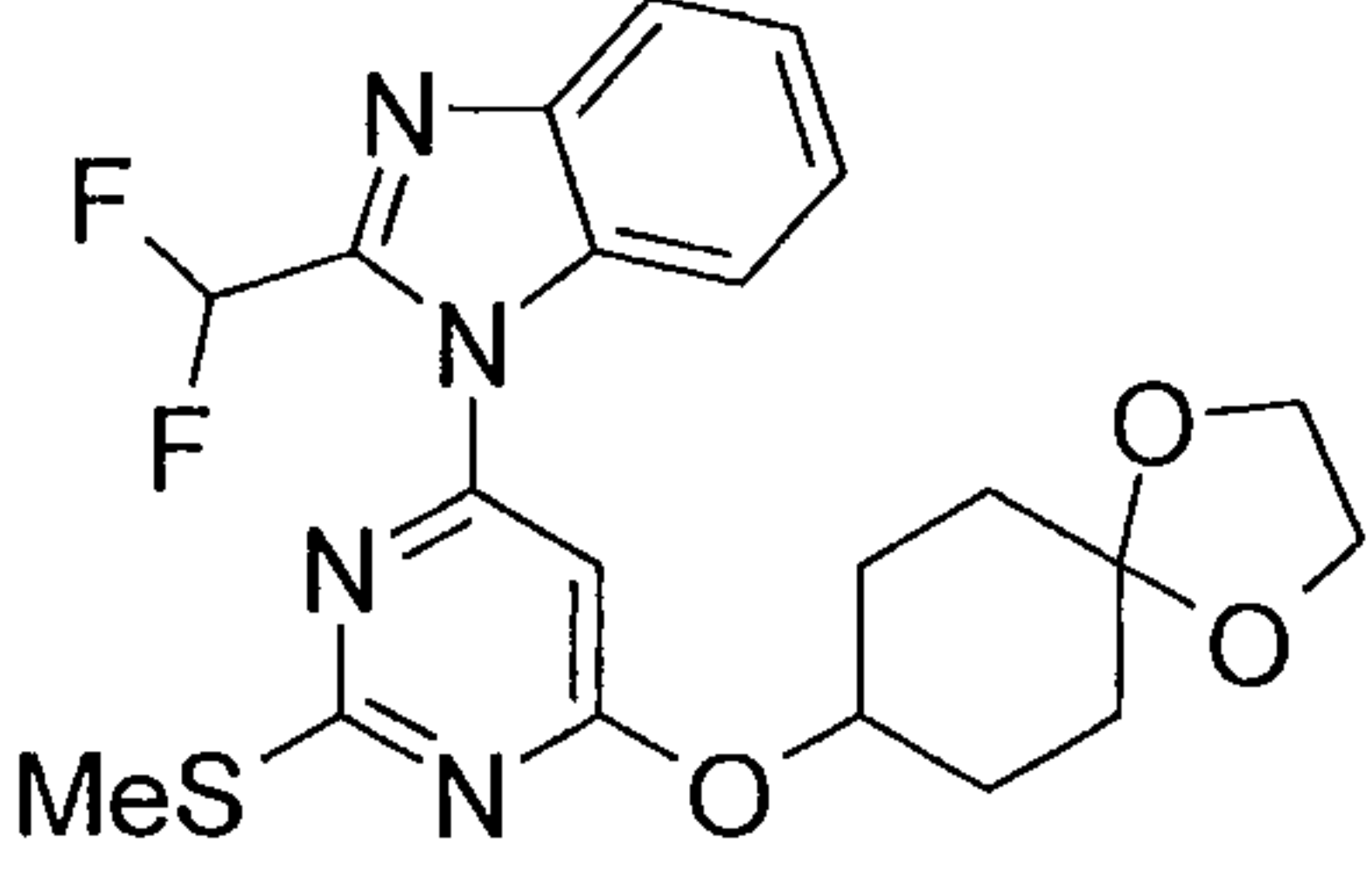
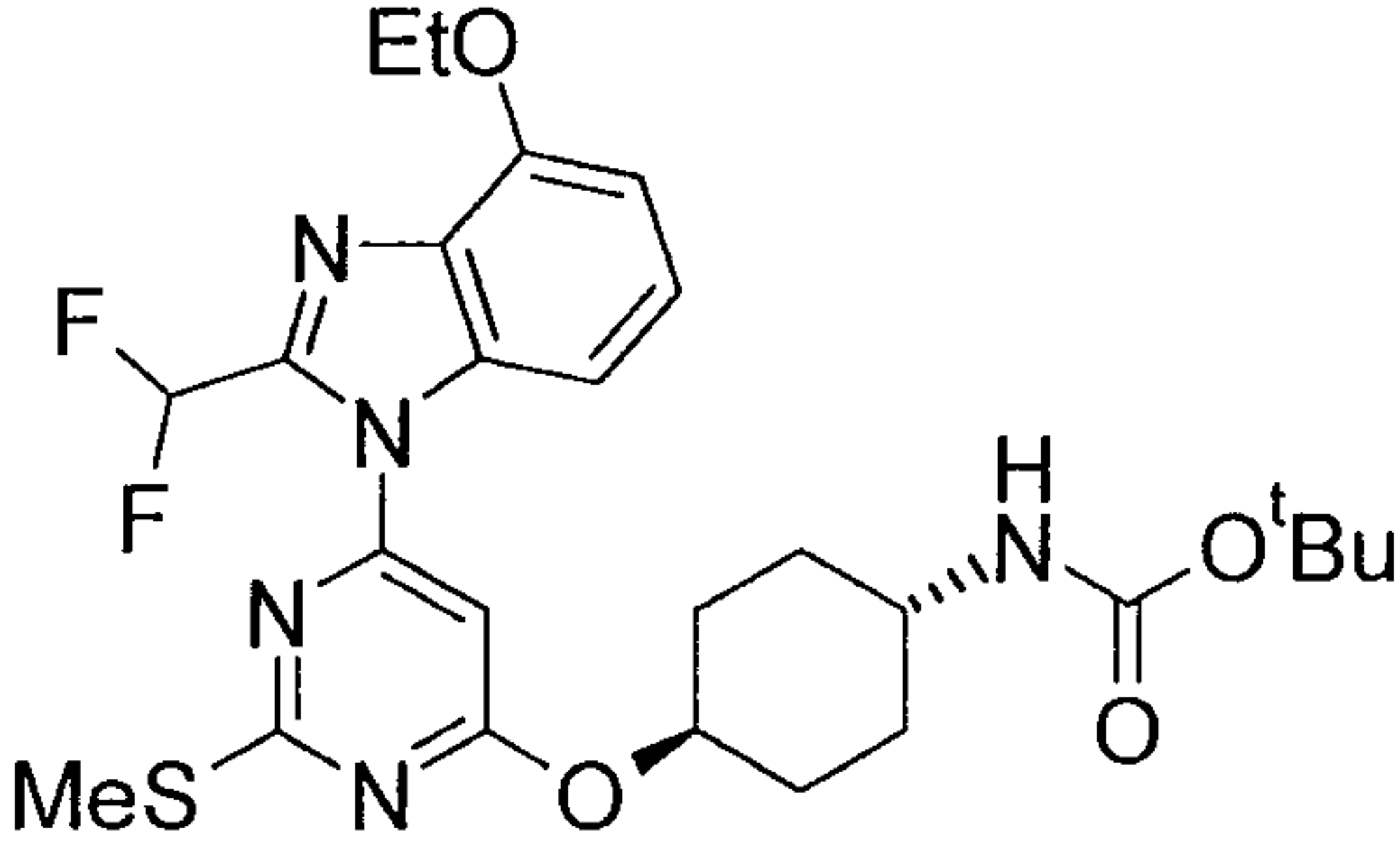
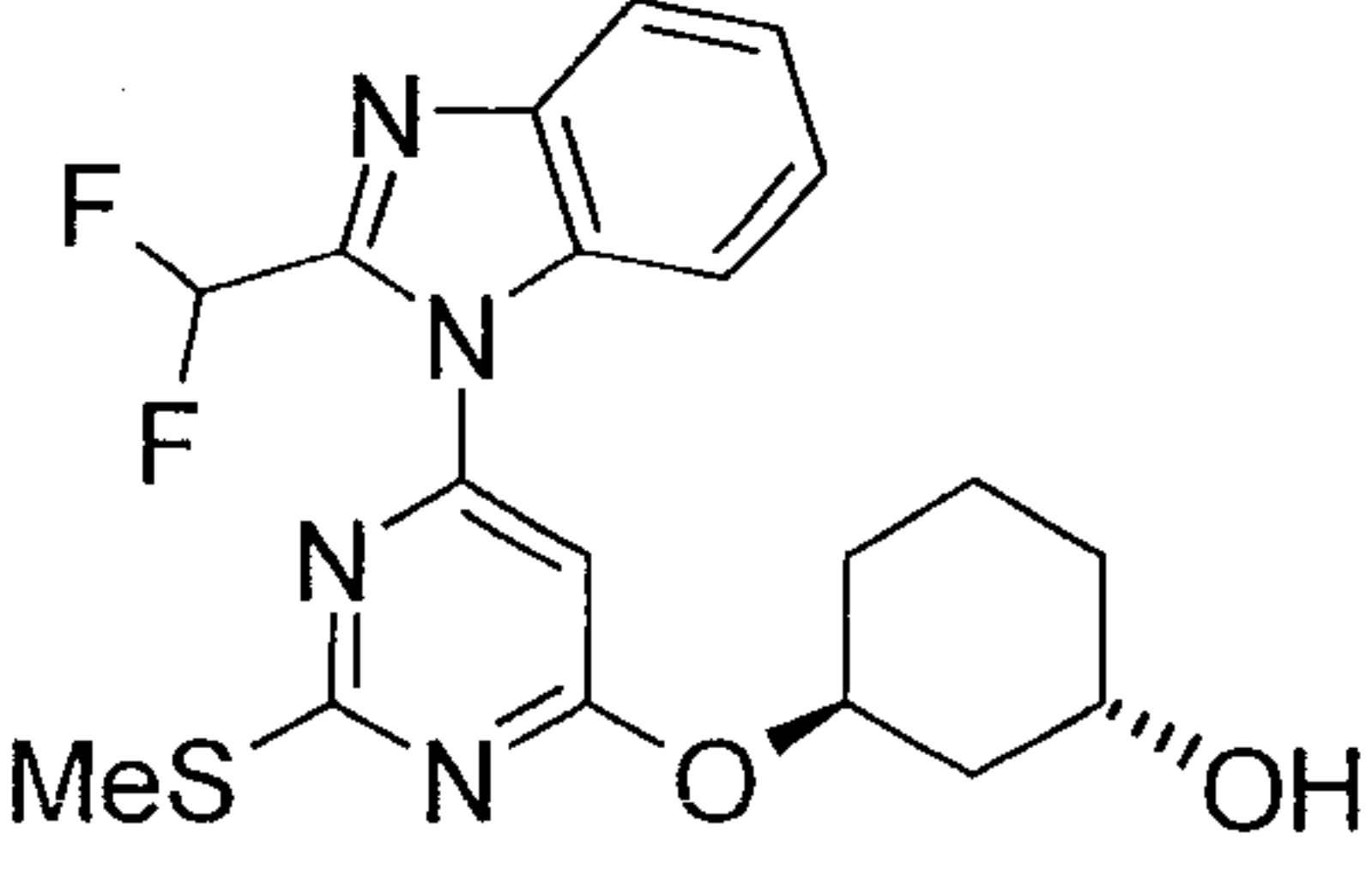
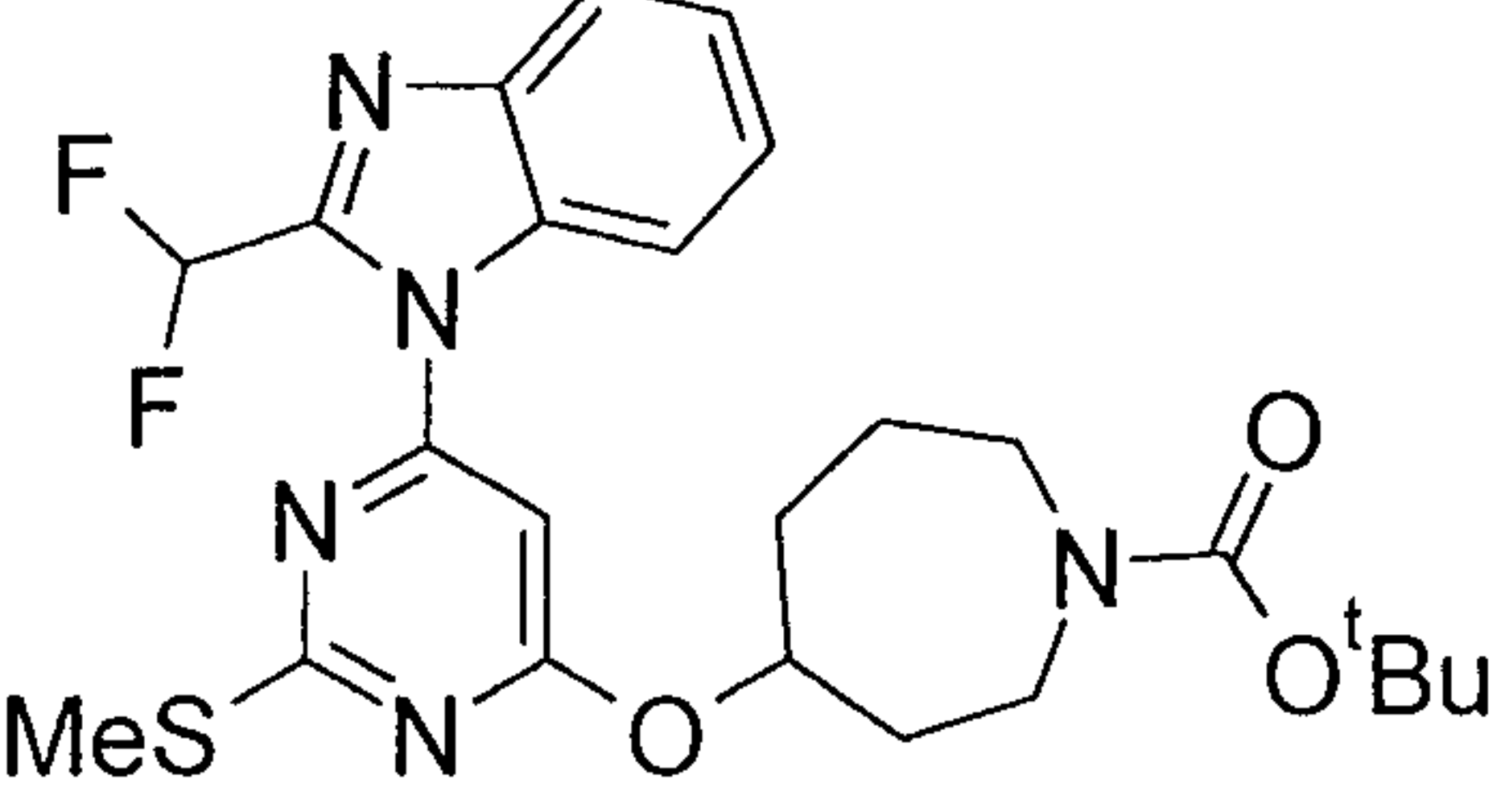
[Table 20]

PEx	PSyn	Str	DAT
84	84		ESI+: 320(M+Na)+
85	85		NMR1:1.40(9H,s), 4.08- 4.19(2H,m),7.09- 7.34(4H,m),7.37- 7.47(1H,m)
86-1	86		ESI+: 371
86-2	86		ESI+: 547
87	87		ESI+: 690

PE _x	PSyn	Str	DAT
88	88		ESI+: 356
89	89		ESI+: 492
90	90		ESI+: 546
91	5		NMR2:1.83-1.95(2H,m),2.04-2.14(2H,m),3.58-3.67(2H,m),3.95-4.03(2H,m),5.32-5.40(1H,m)
92	Syn.422		ESI+: 256
93	80		ESI+: 424

[0178]

[Table 22]

PEx	PSyn	Str	DAT
94	5		not found
95	89		ESI+: 506
96	89		ESI+: 449
97	89		ESI+: 550
98	89		ESI+: 407
99	89		ESI+: 506

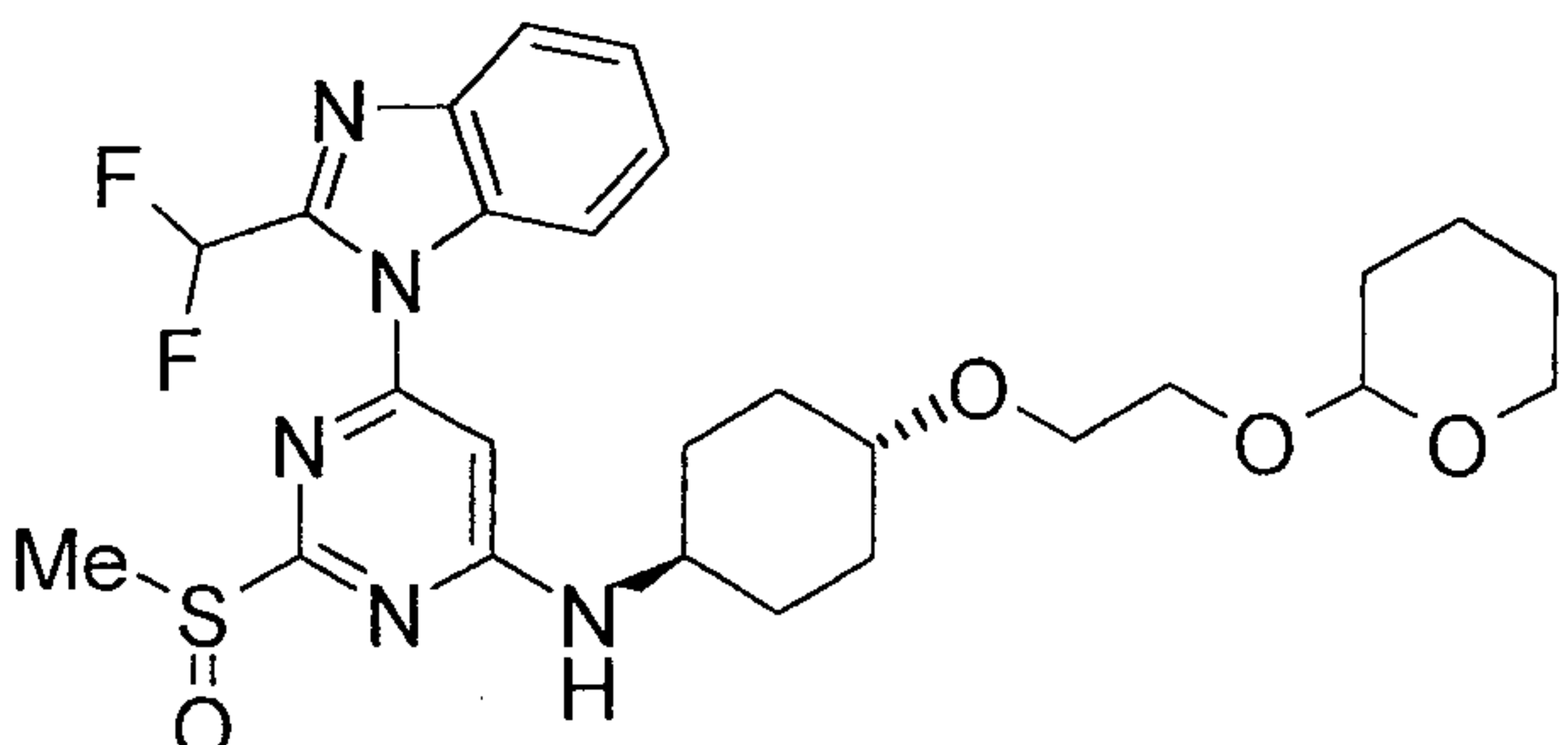
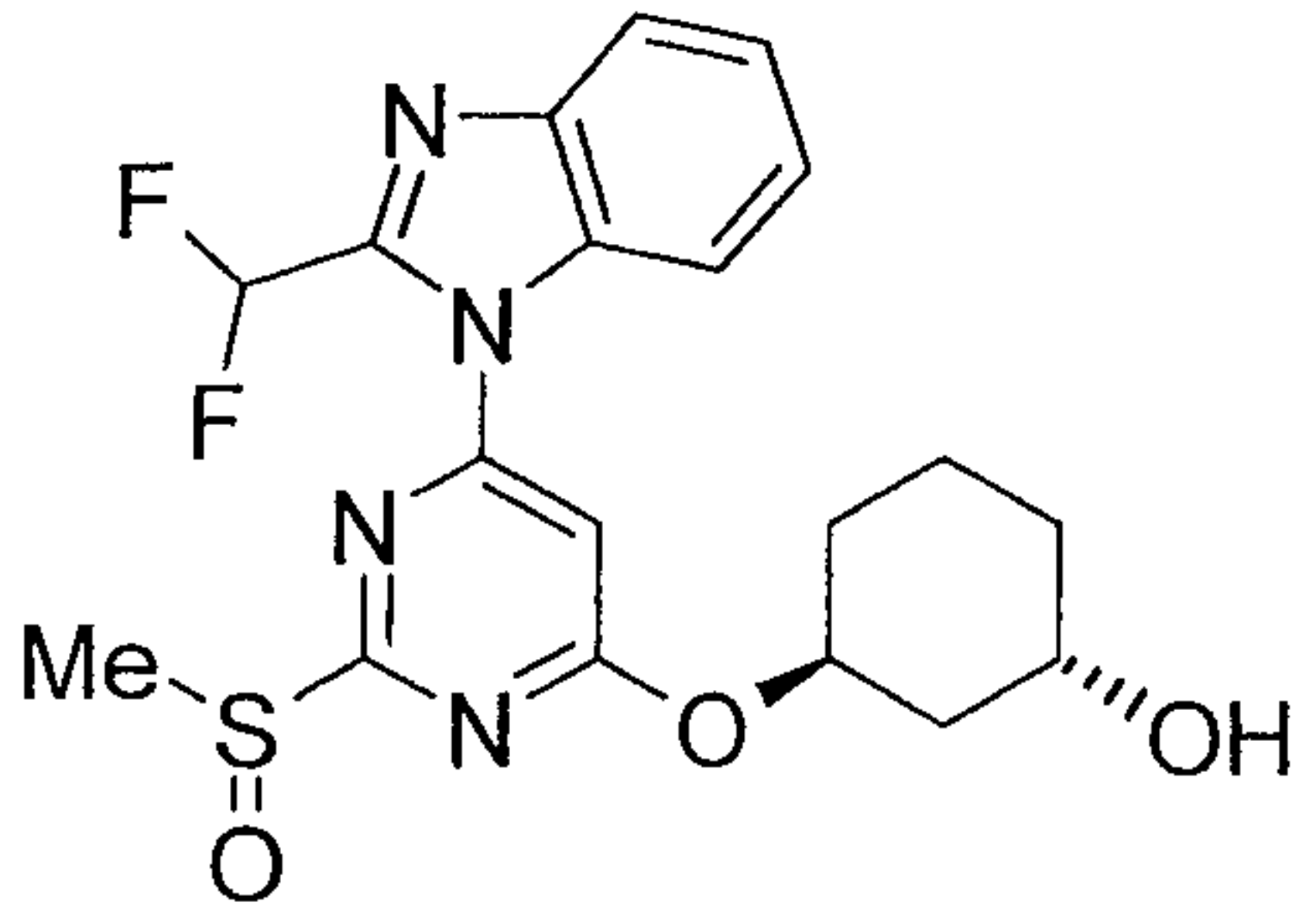
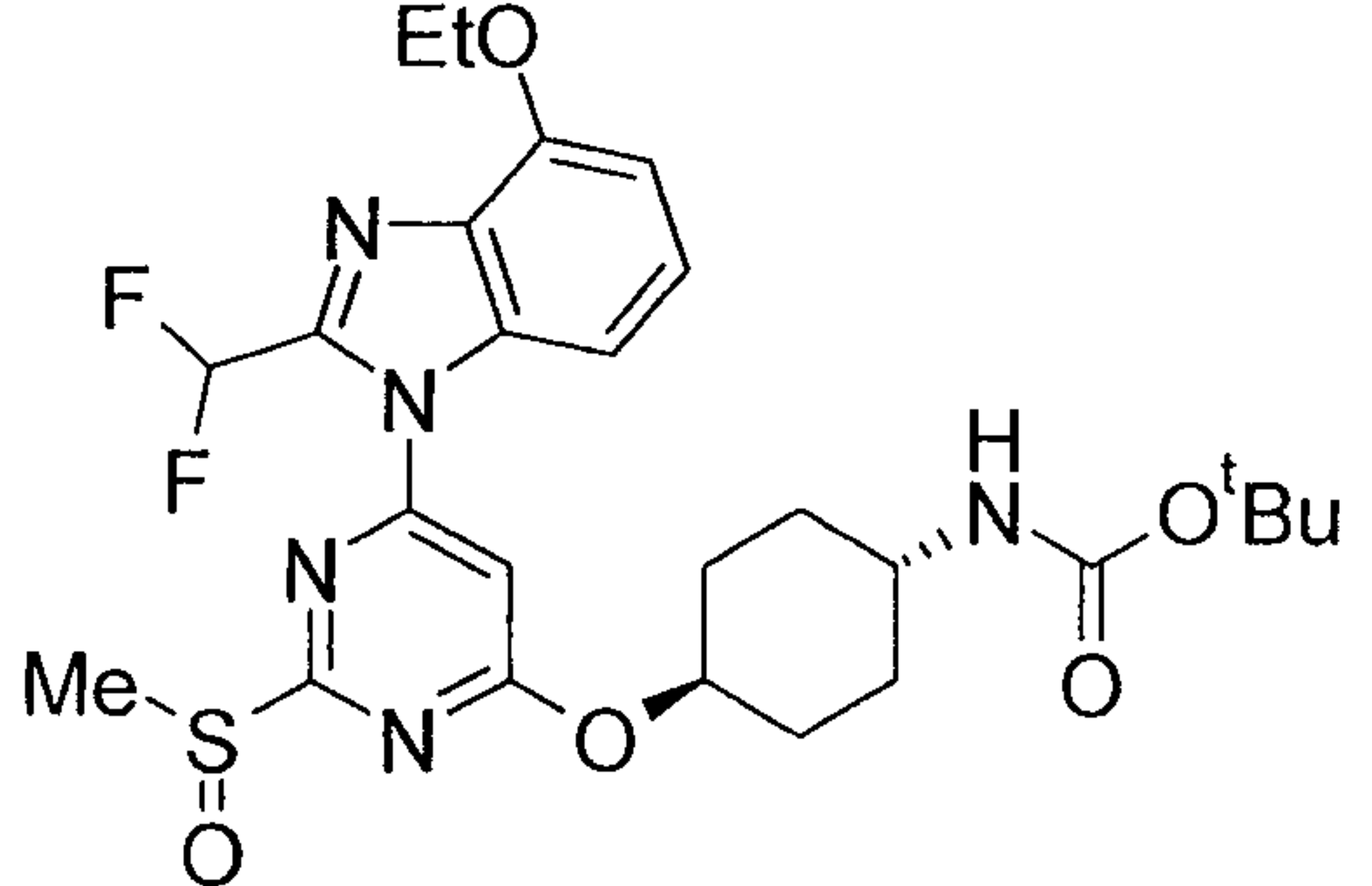
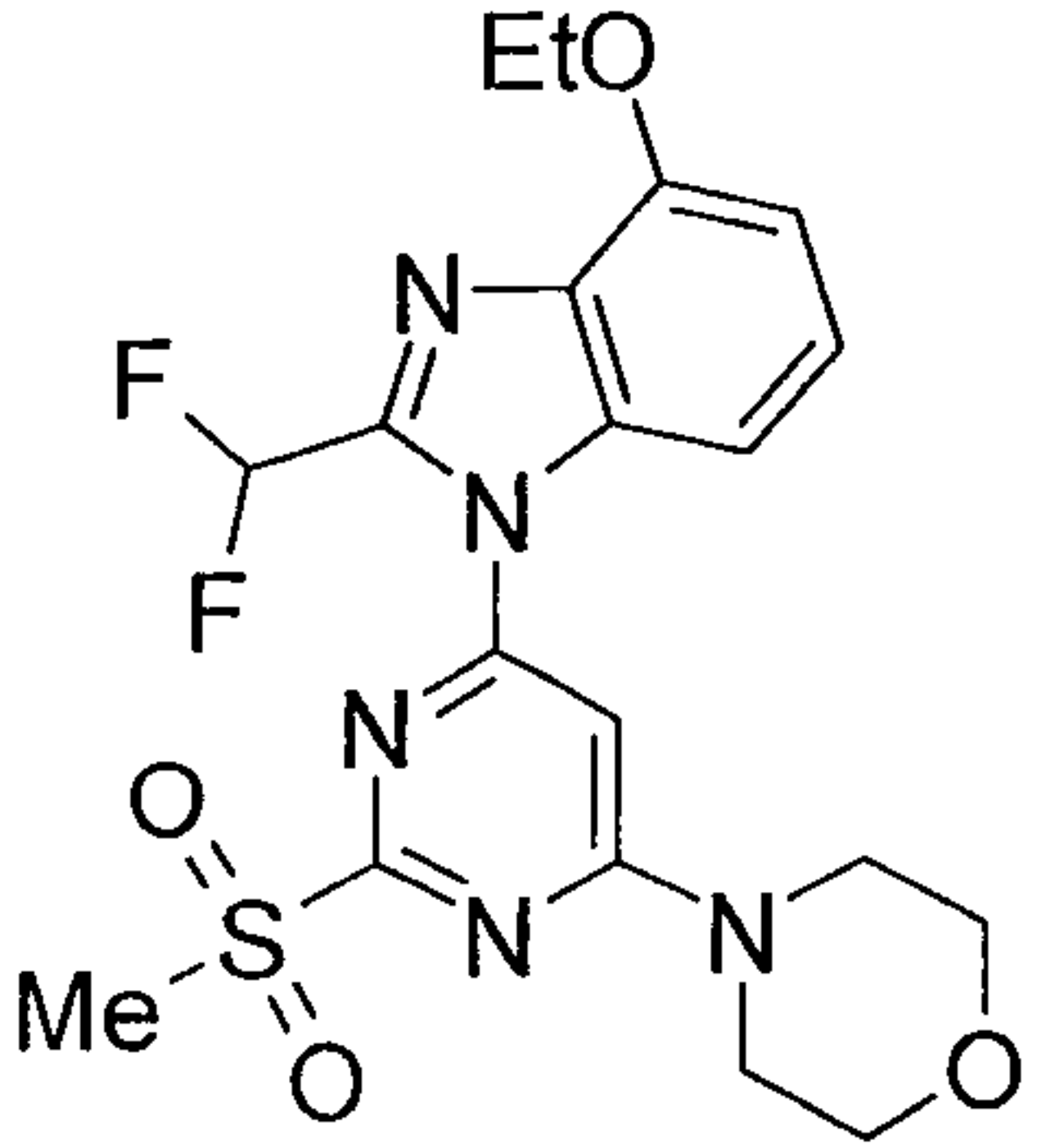
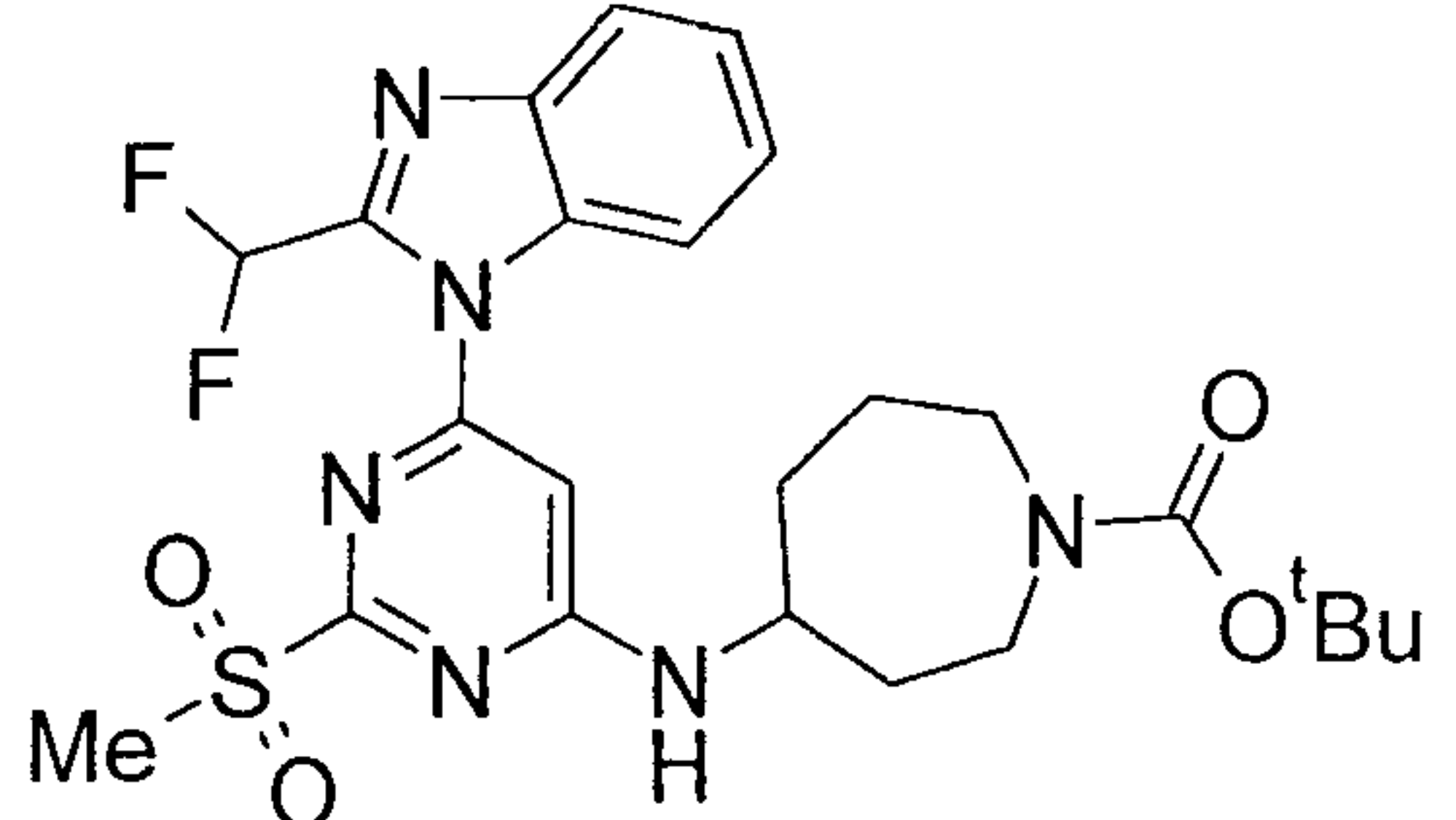
[0179]

[Table 23]

PEX	PSyn	Str	DAT
100	89		ESI+: 478
101	89		ESI+: 407
102	9		ESI+: 690
103	9		ESI+: 704
104	3		ESI+: 564

[0180]

[Table 24]

PEx	PSyn	Str	DAT
105	3		ESI+: 550
106	3		ESI+: 423
107	3		ESI+: 566
108	4		ESI+: 454
109	4		ESI+: 537

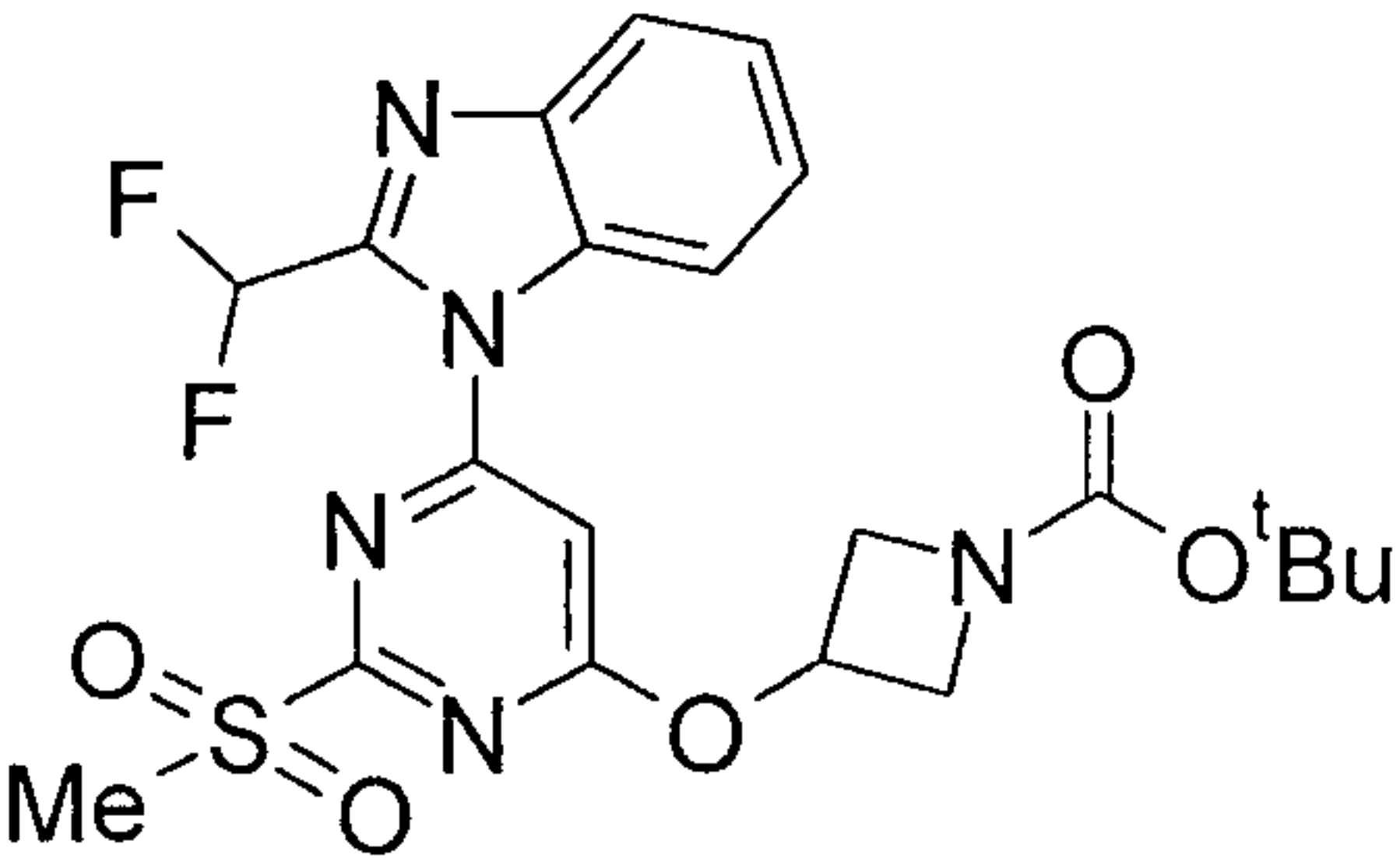
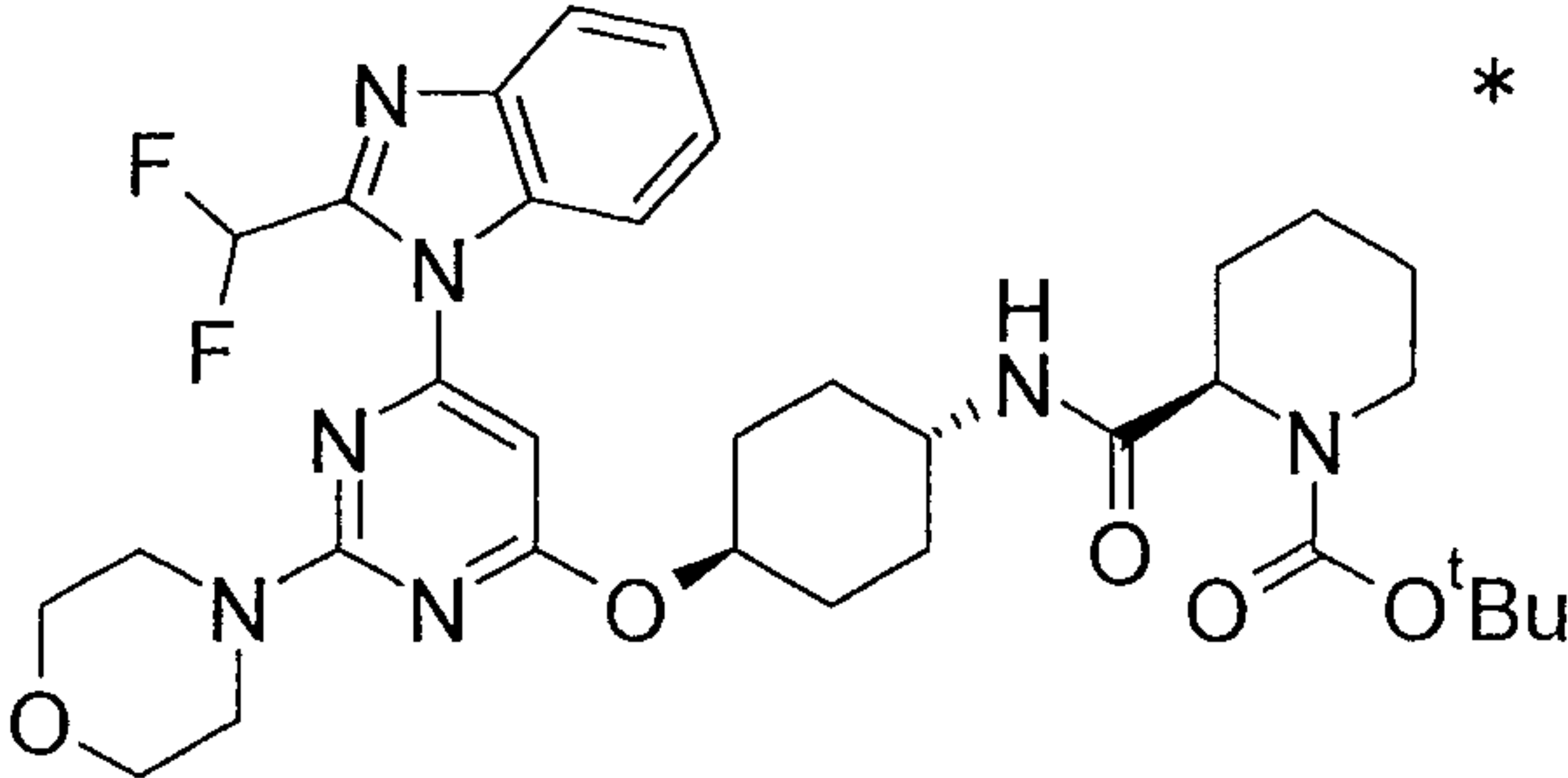
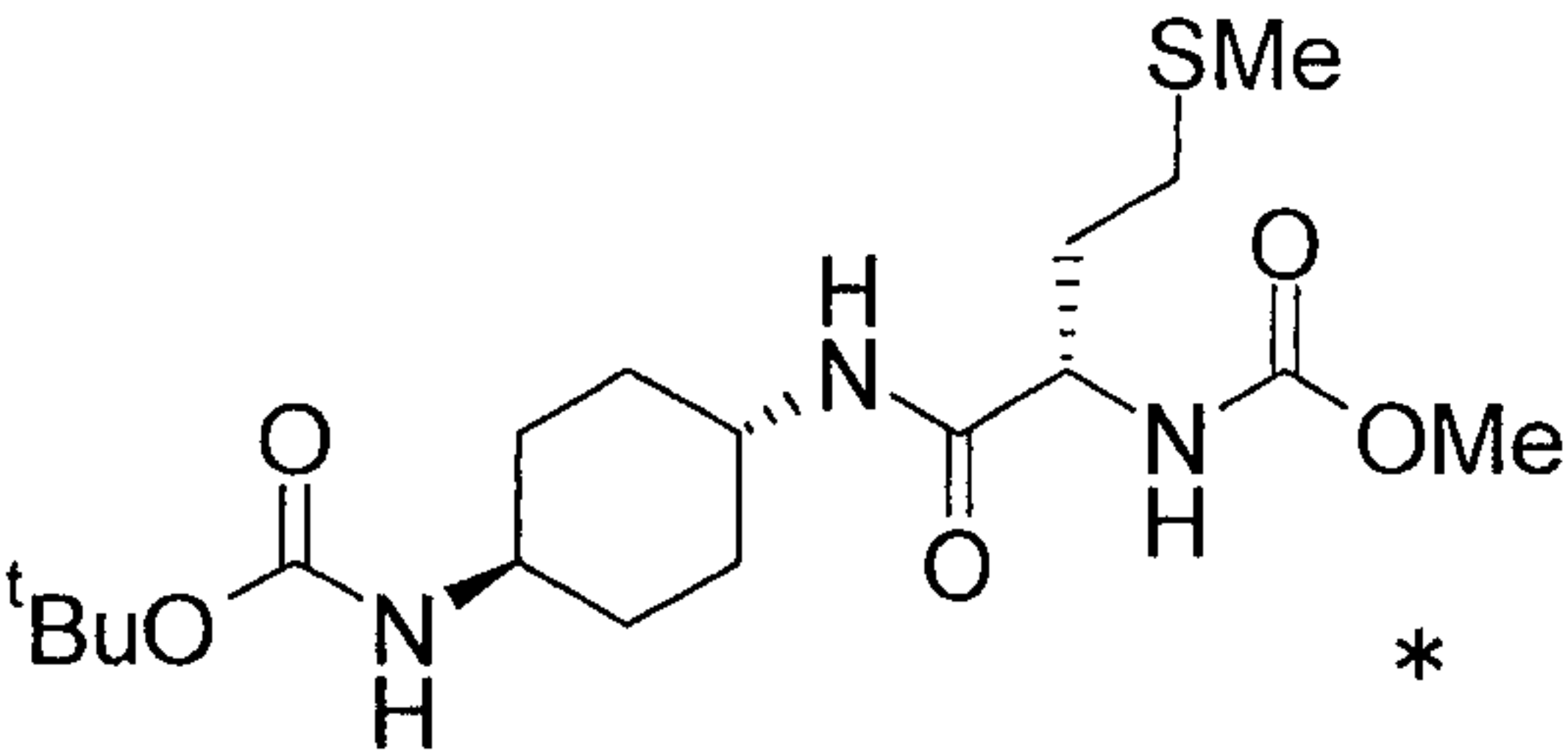
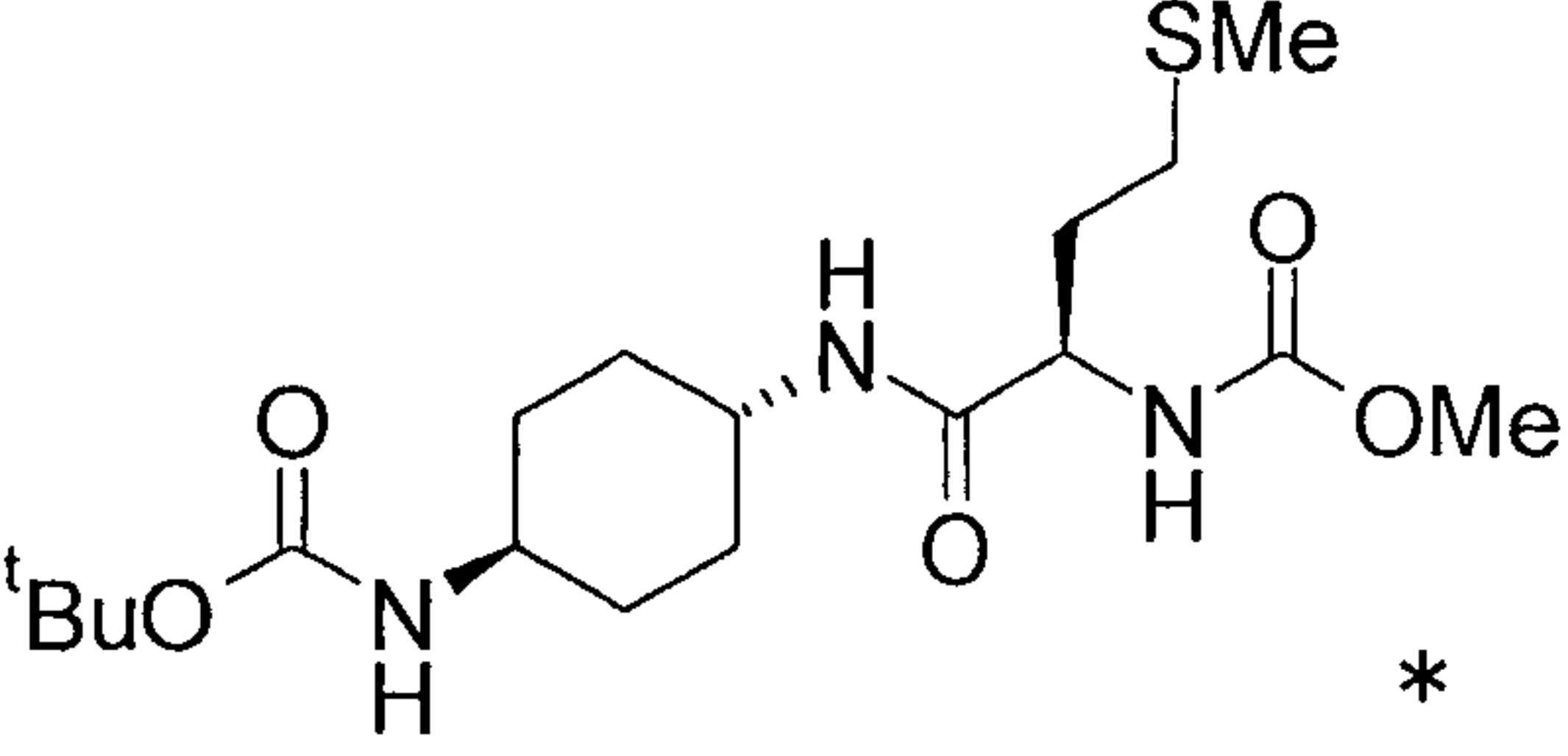
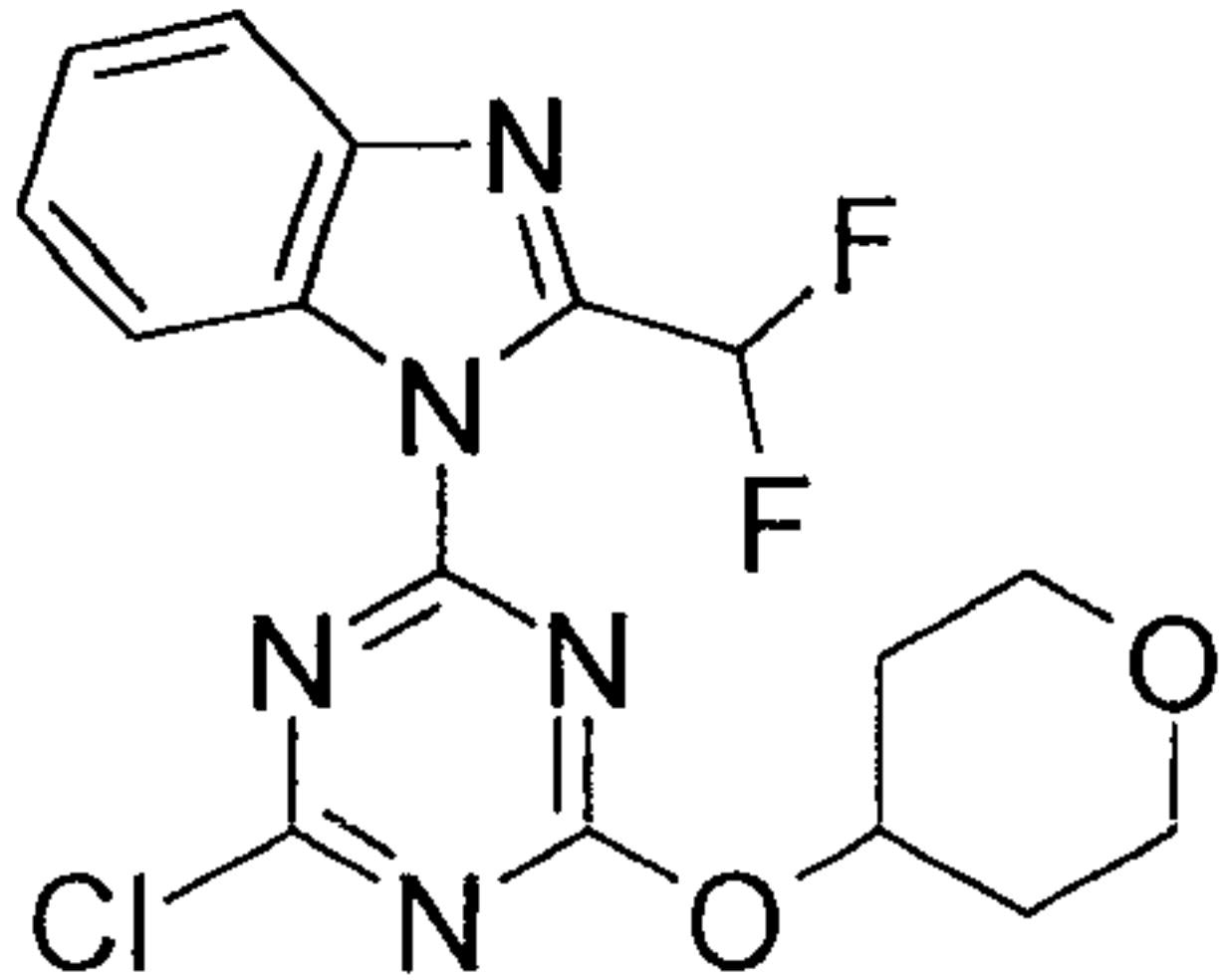
[0181]

[Table 25]

PEx	PSyn	Str	DAT
110	4		ESI+: 529
111	4		ESI+: 440
112	4		ESI+: 577
113	4		ESI+: 538
114	4		ESI+: 510

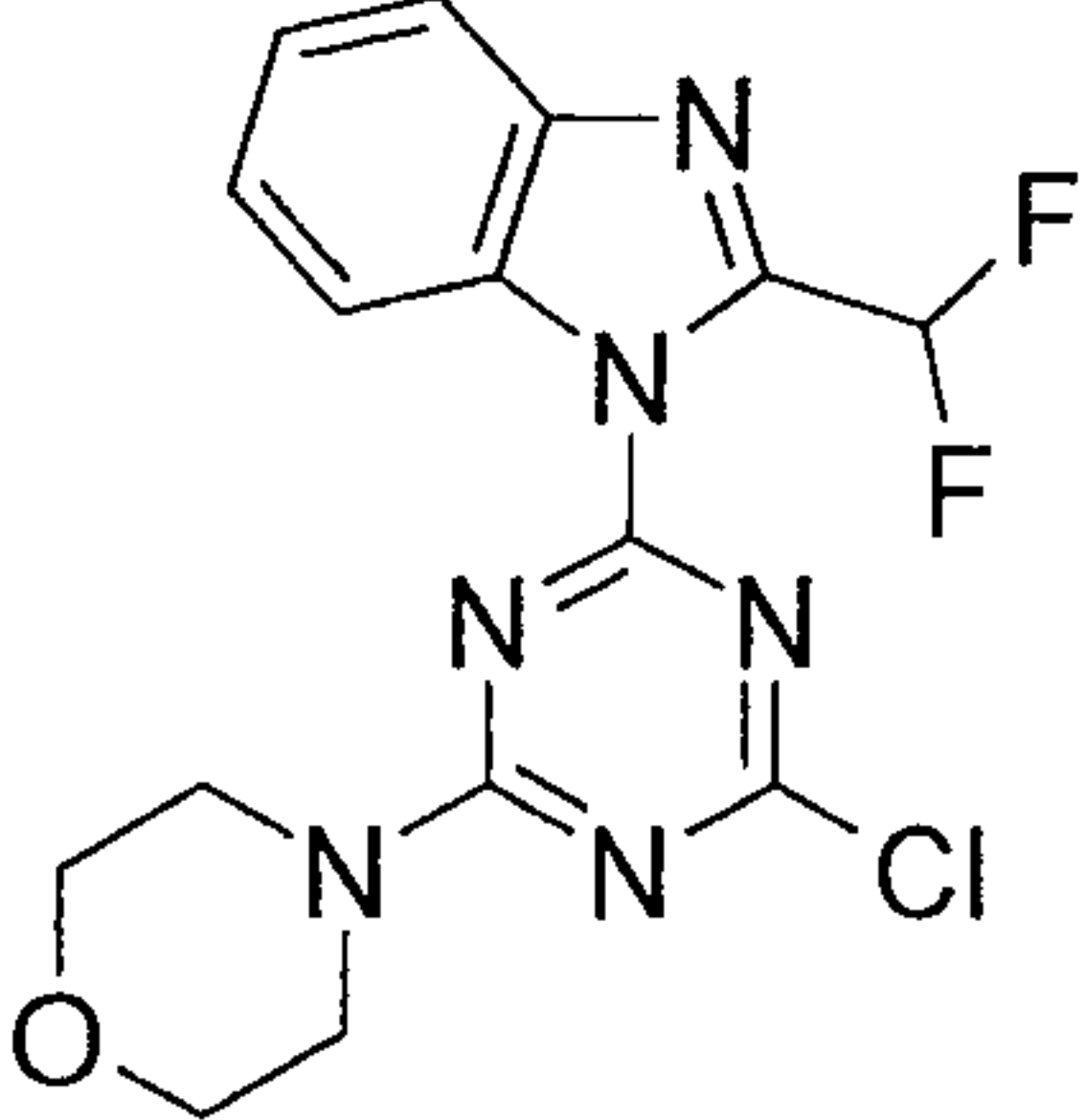
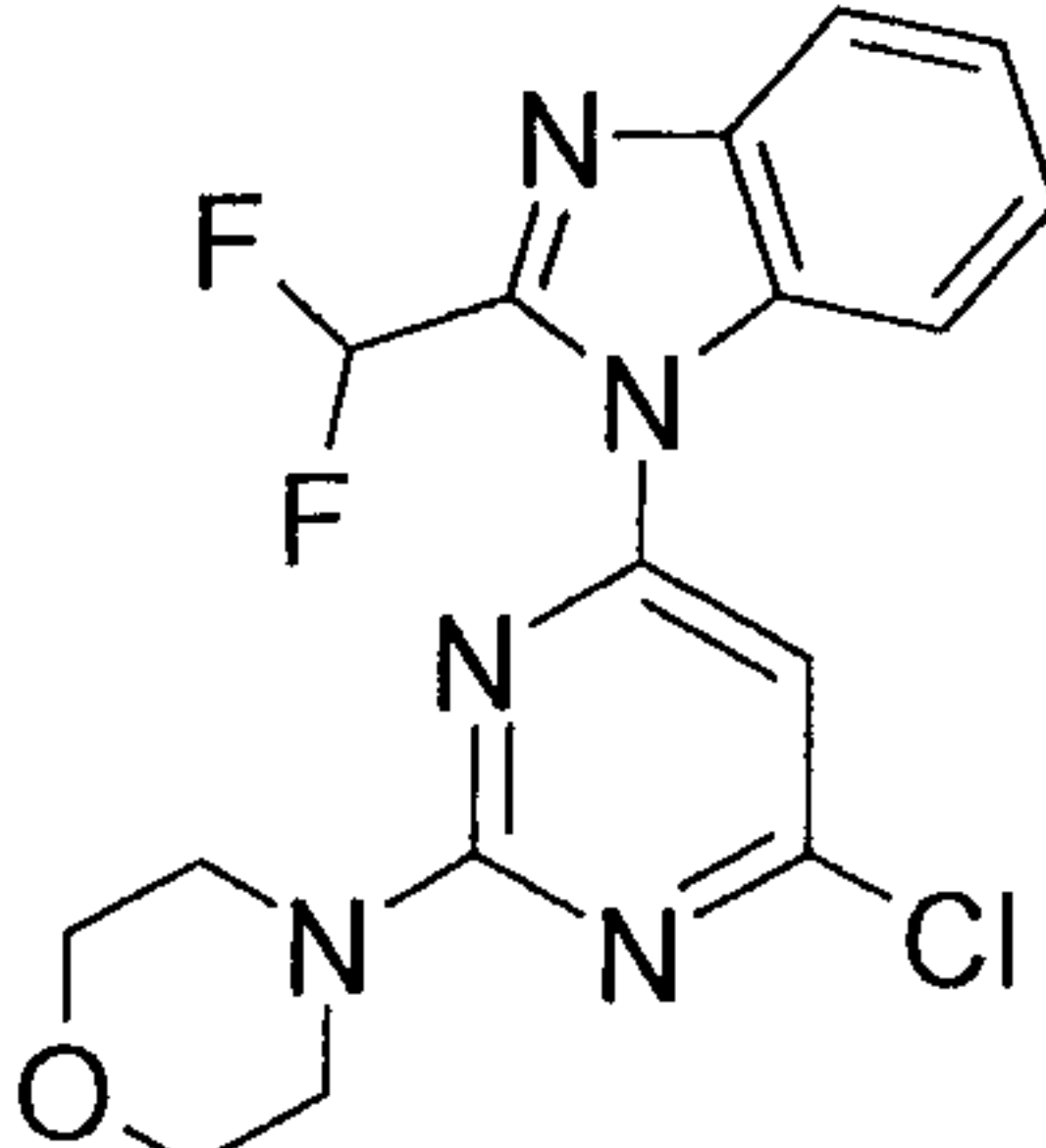
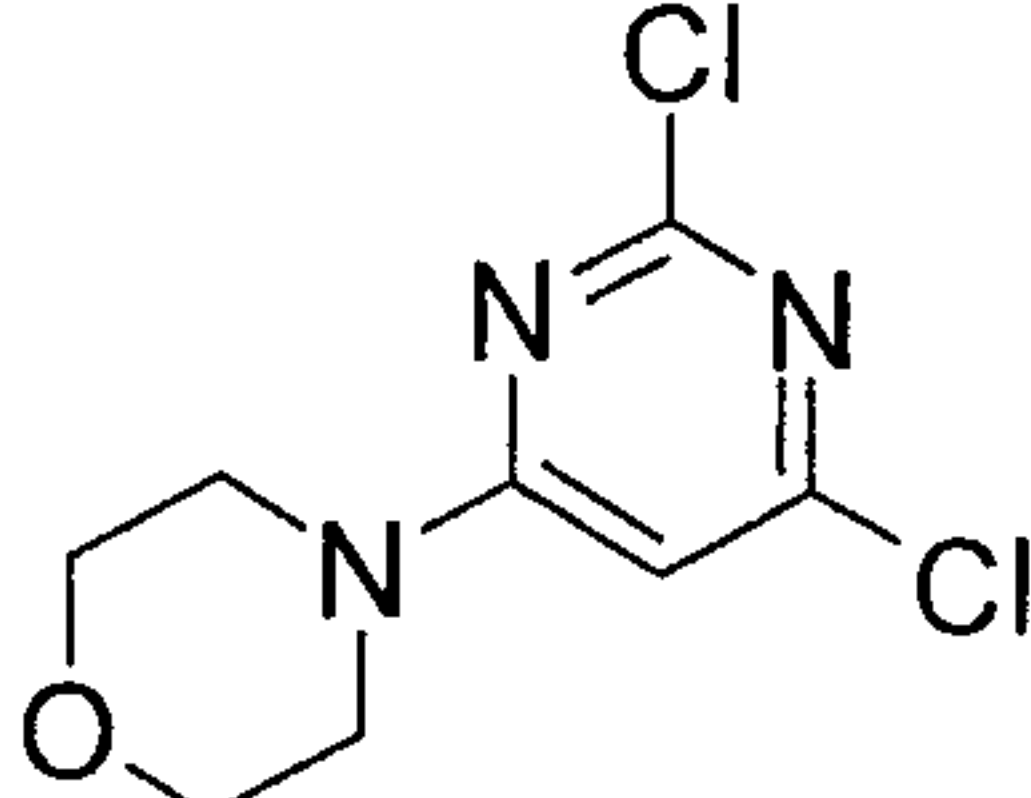
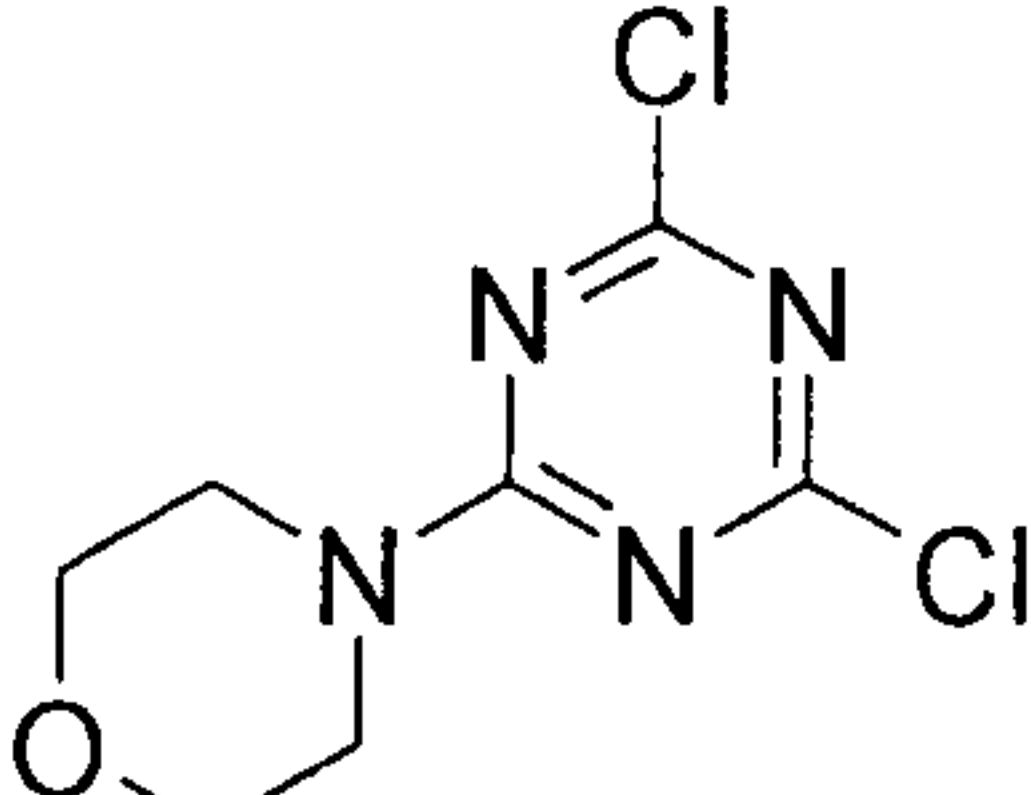
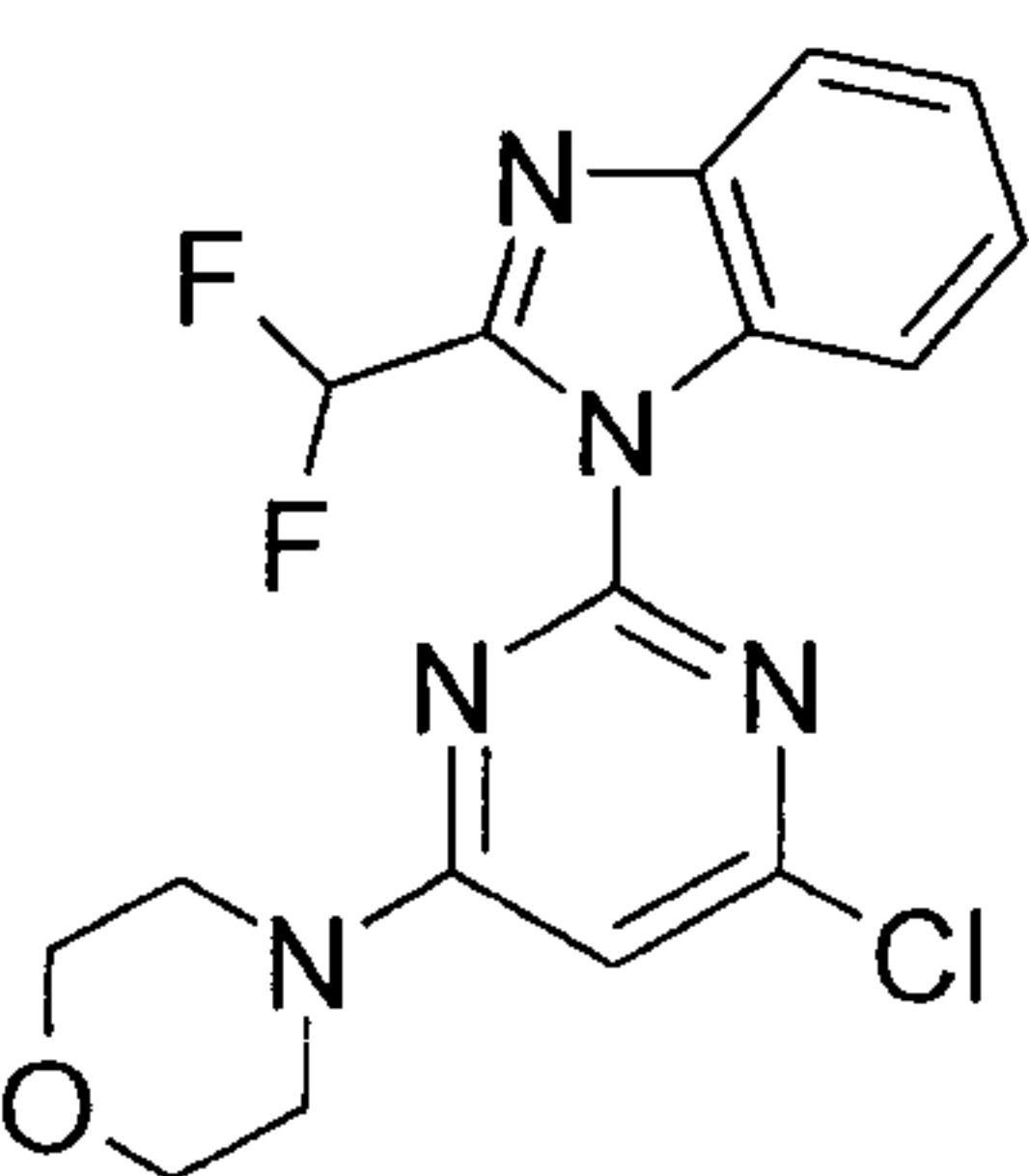
[0182]

[Table 26]

PEx	PSyn	Str	DAT
115	4		ESI+: 496
116	87		ESI+: 656
117	87		ESI+: 404
118	87		ESI+: 404
119	1		ESI+: 382

[0183]

[Table 27]

PEX	PSyn	Str	DAT
120	1		ESI+: 367
121	1		NMR1:3.66-3.79(8H,m),7.40-7.69(3H,m),7.8-7.85(1H,d),7.87-7.92(1H,d)
122	1		ESI+: 234
123	1		ESI+: 236
124	1		ESI+: 366

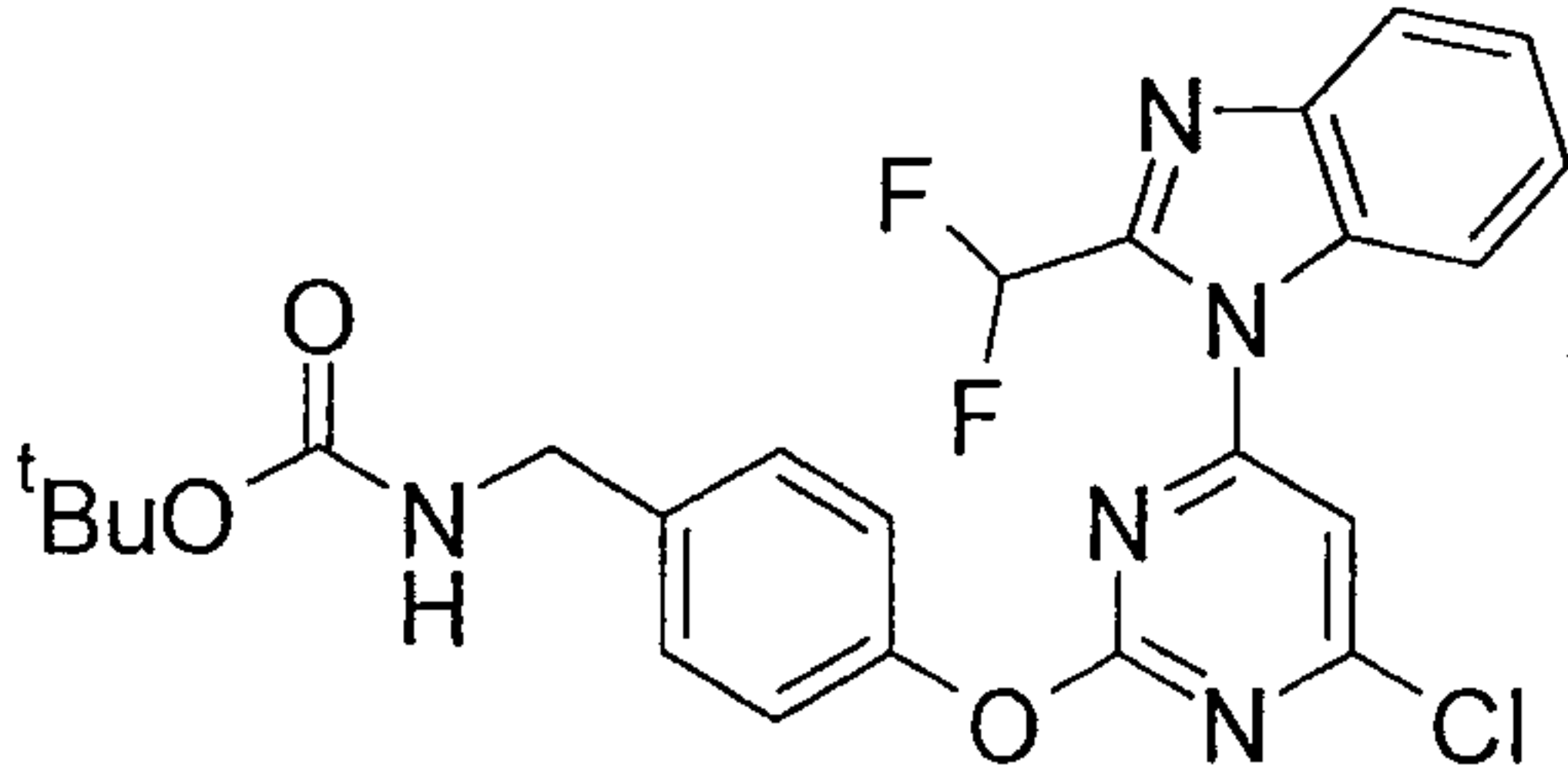
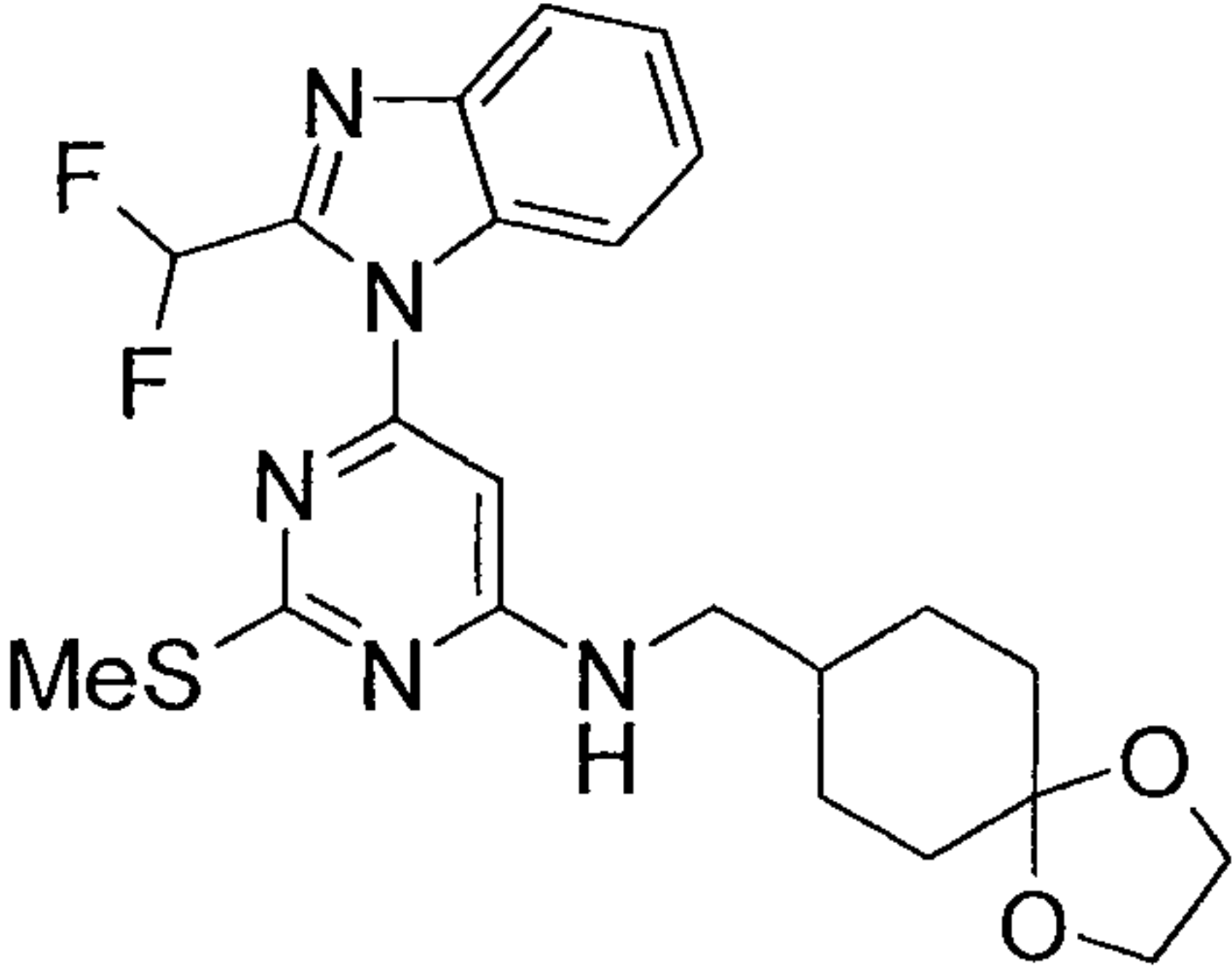
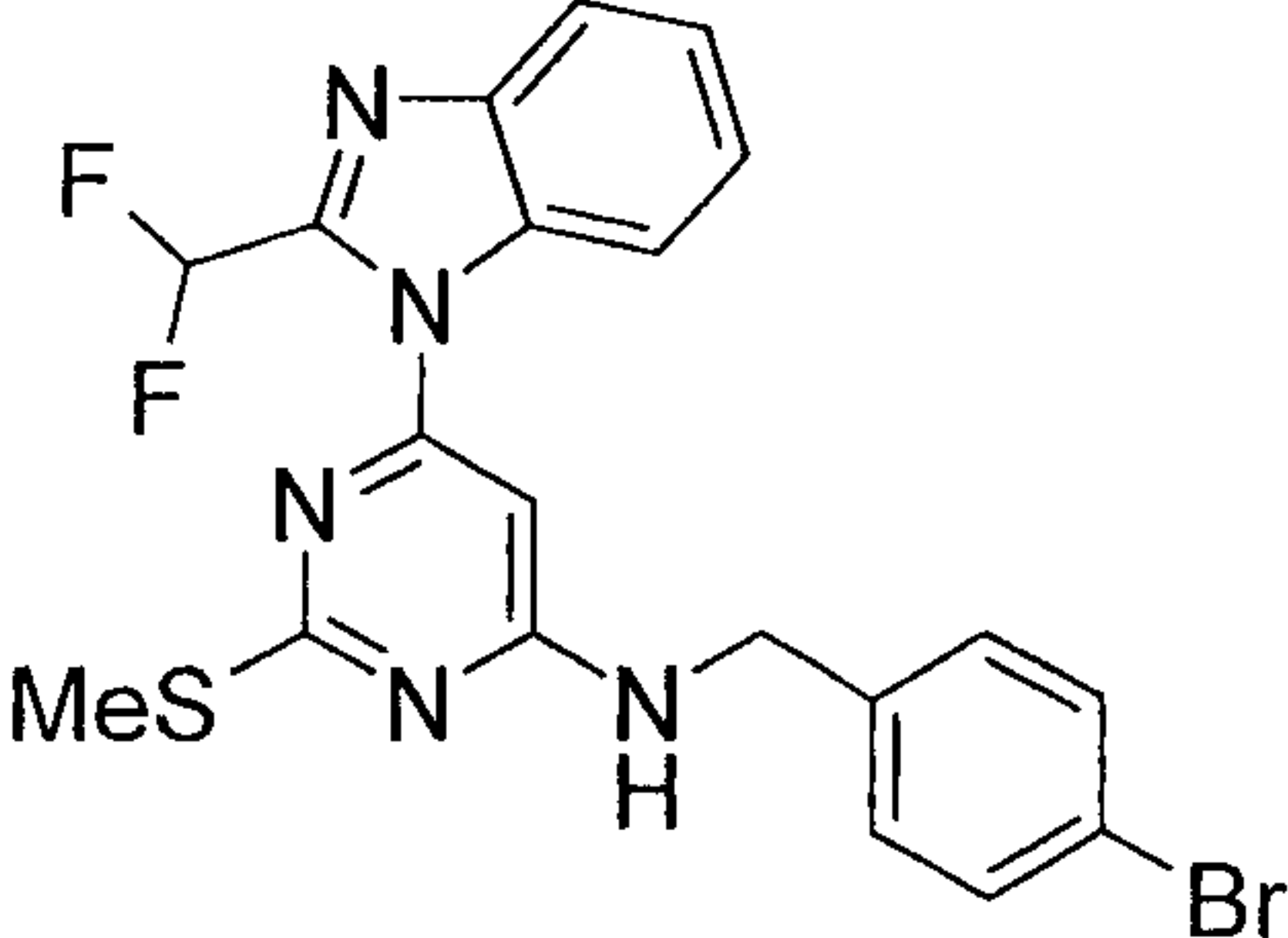
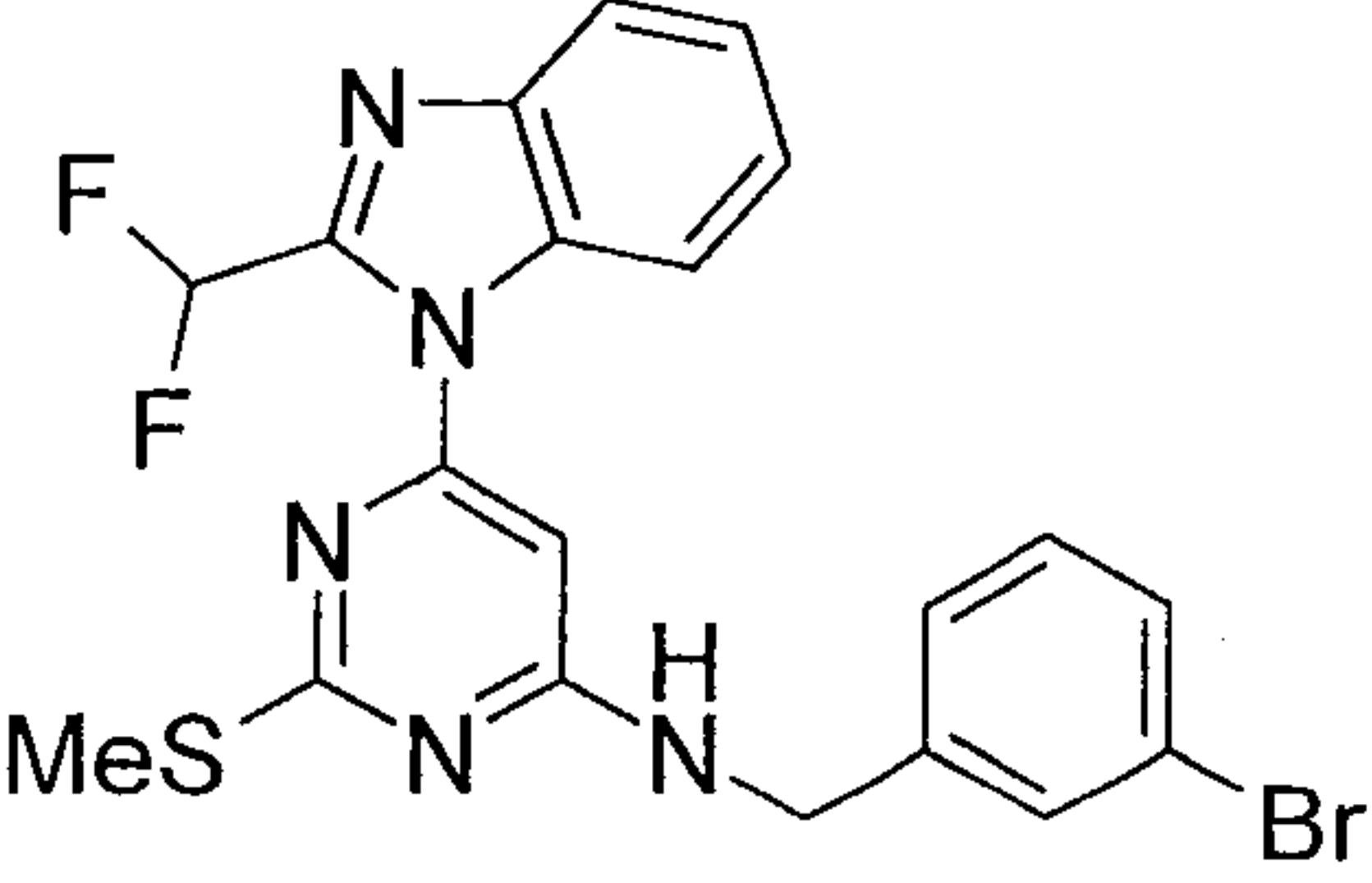
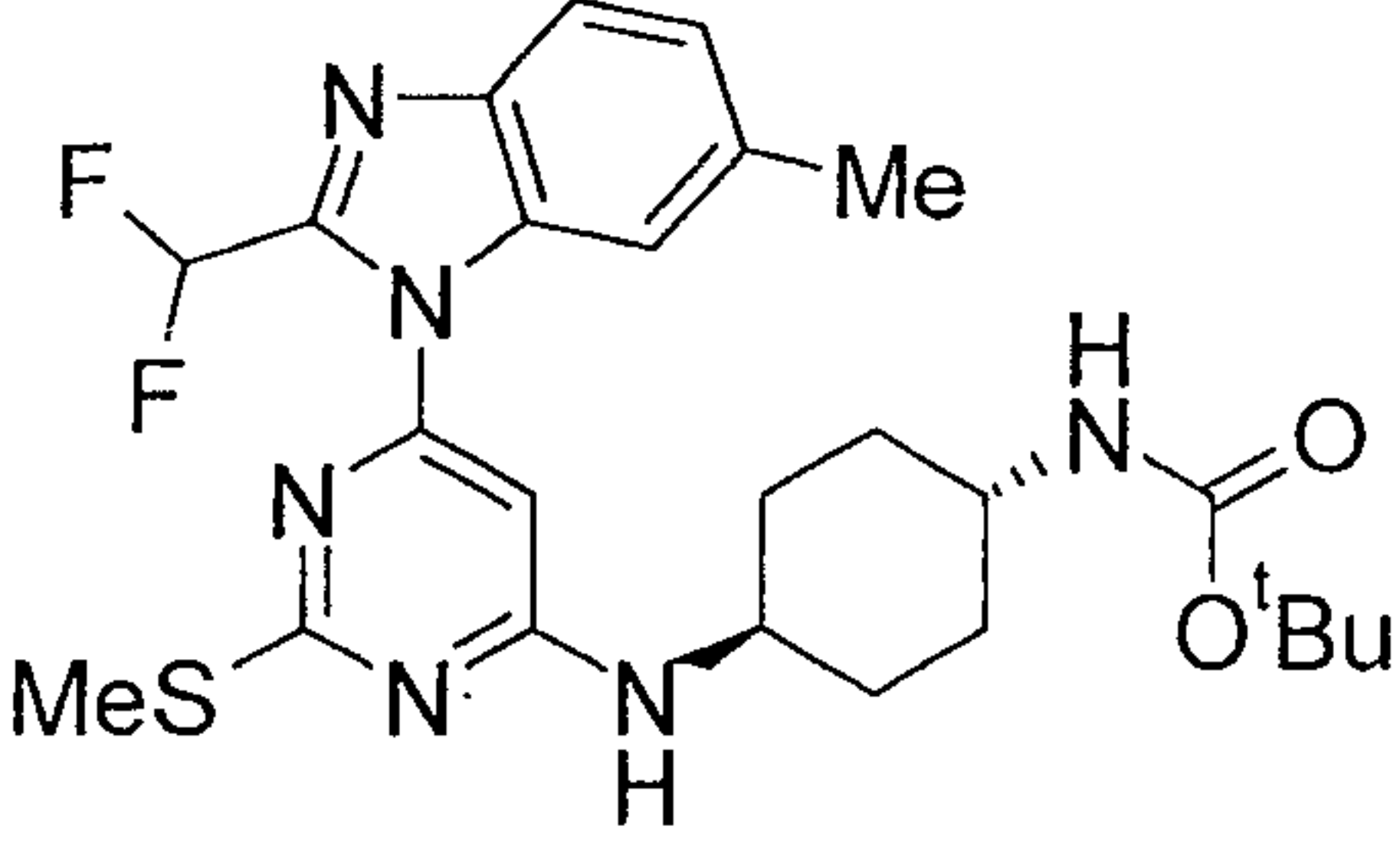
[0184]

[Table 28]

PEx	PSyn	Str	DAT
125	1		ESI+: 422
126	1		ESI+: 527(M+Na)+
127	1		ESI+: 548
128	1		ESI+: 534
129	1		ESI+: 469

[0185]

[Table 29]

PEX	PSyn	Str	DAT
130	1		not found
131	1		ESI+: 462
132	1		ESI+: 476
133	1		ESI+: 476
134	1		Not found

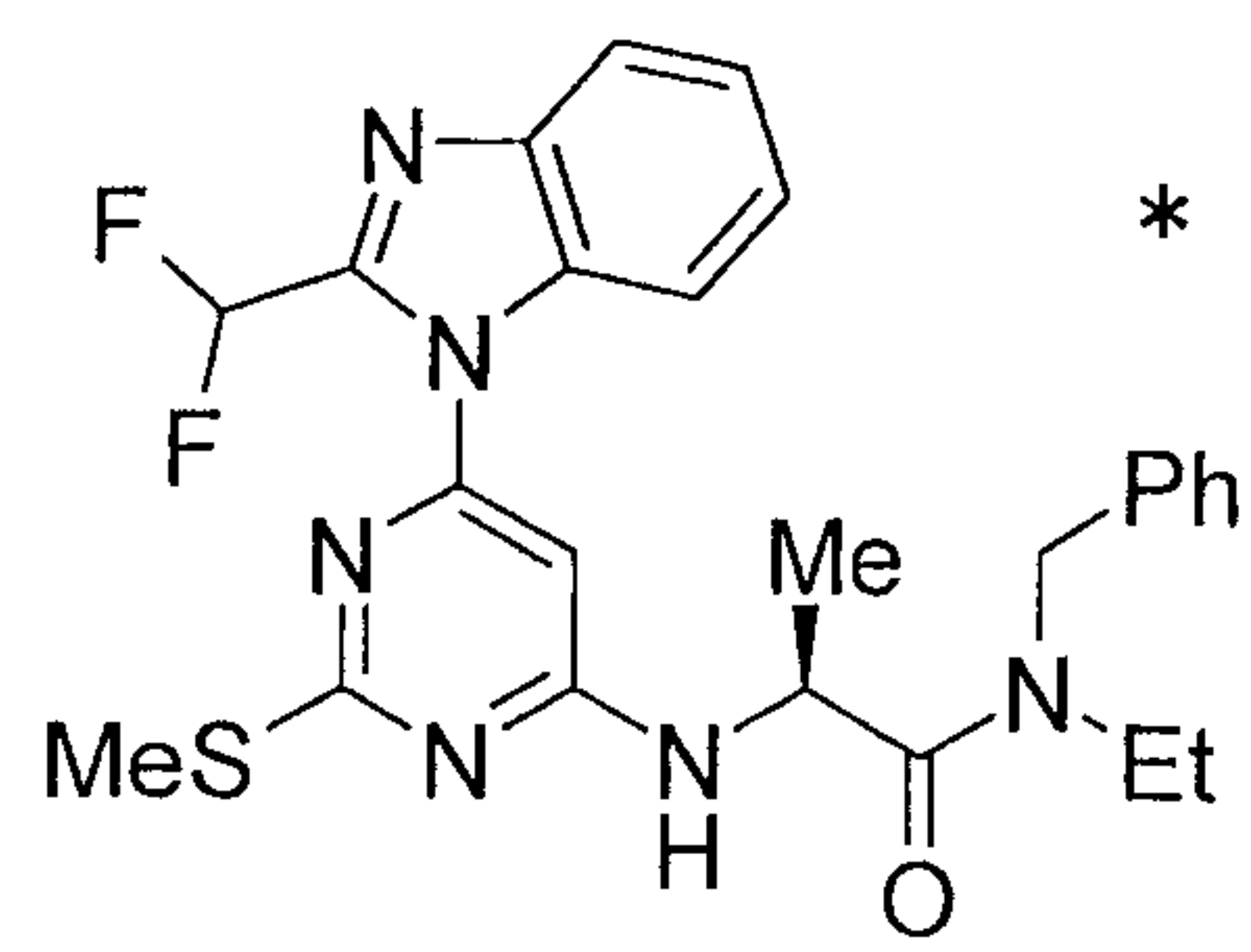
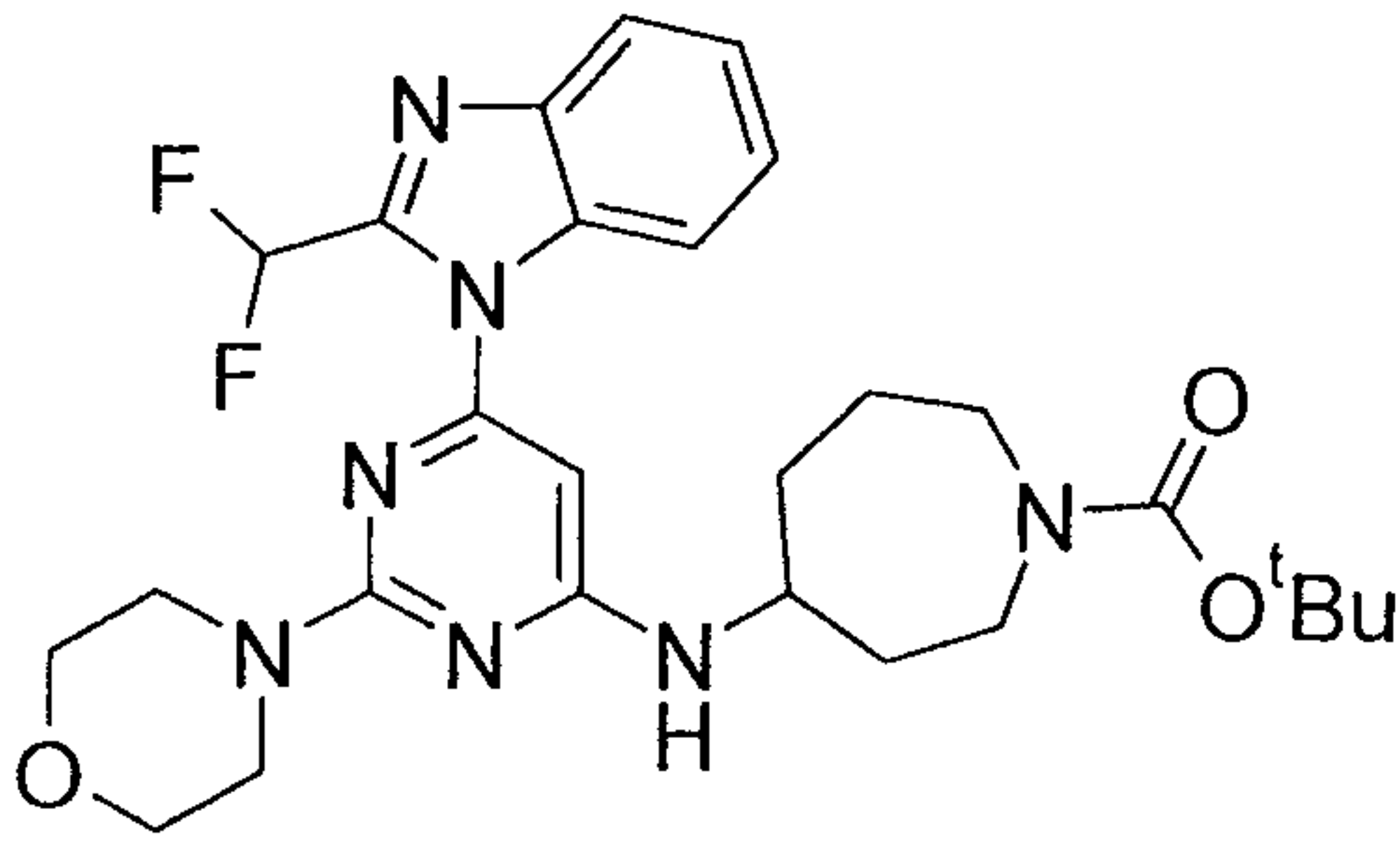
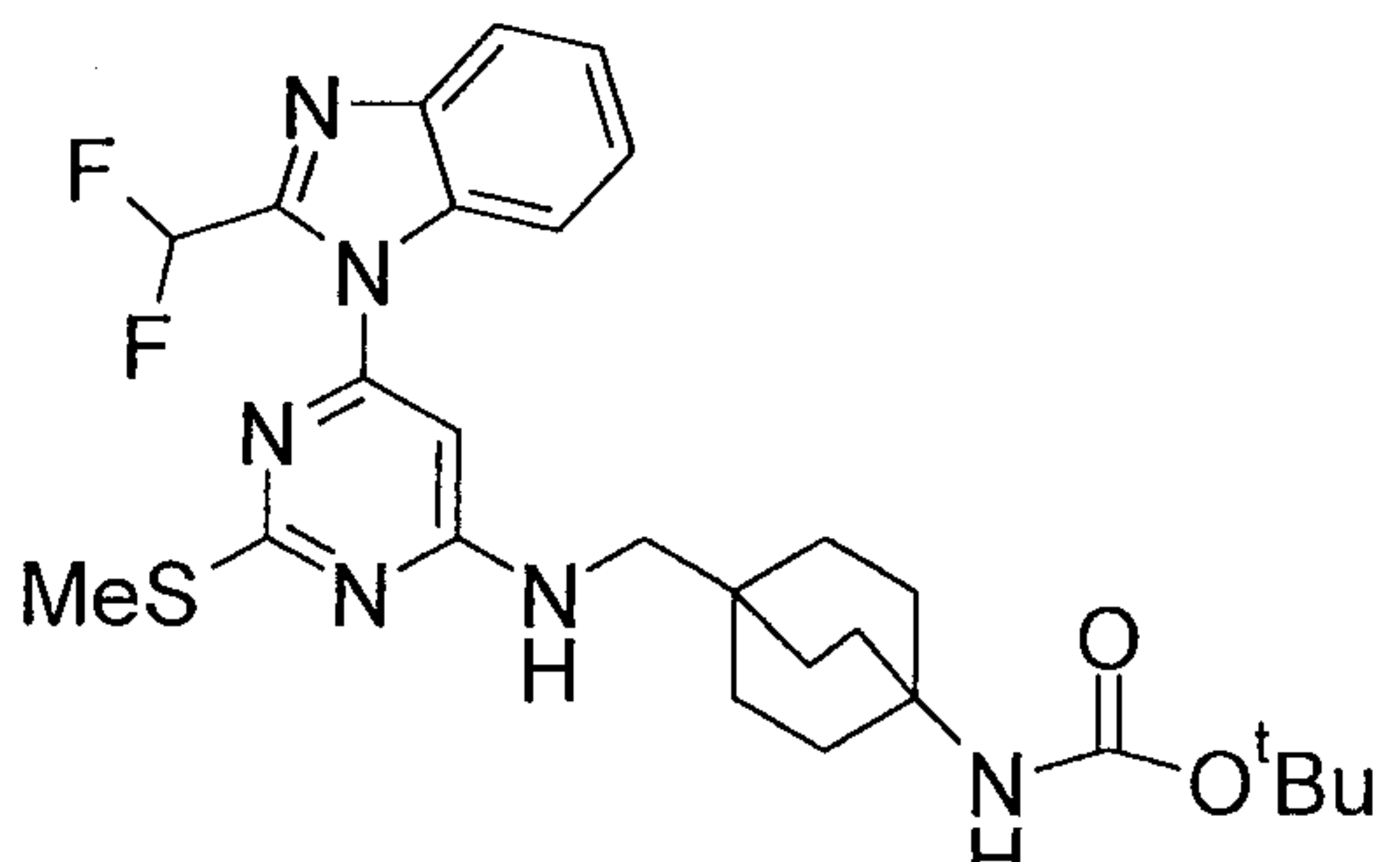
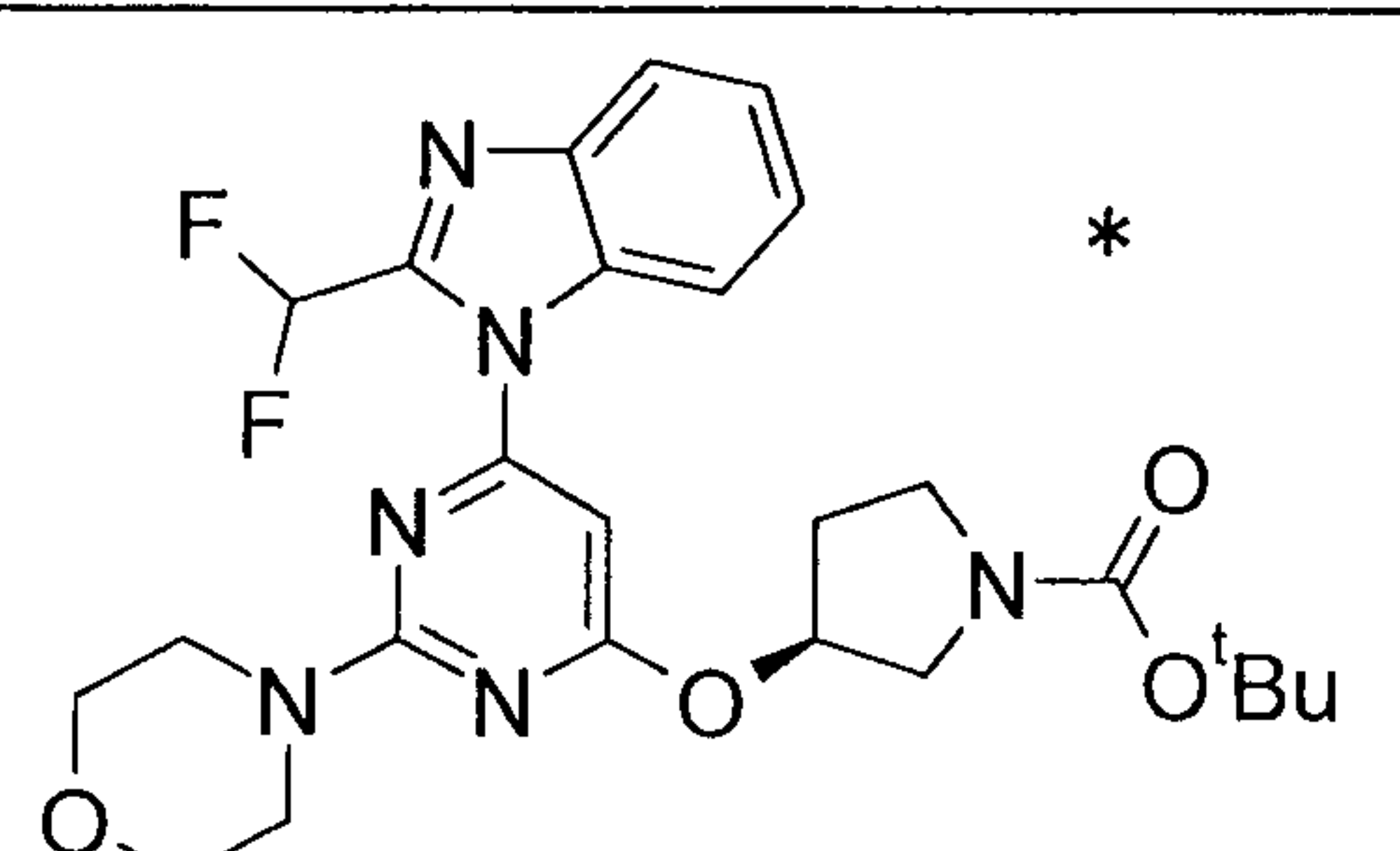
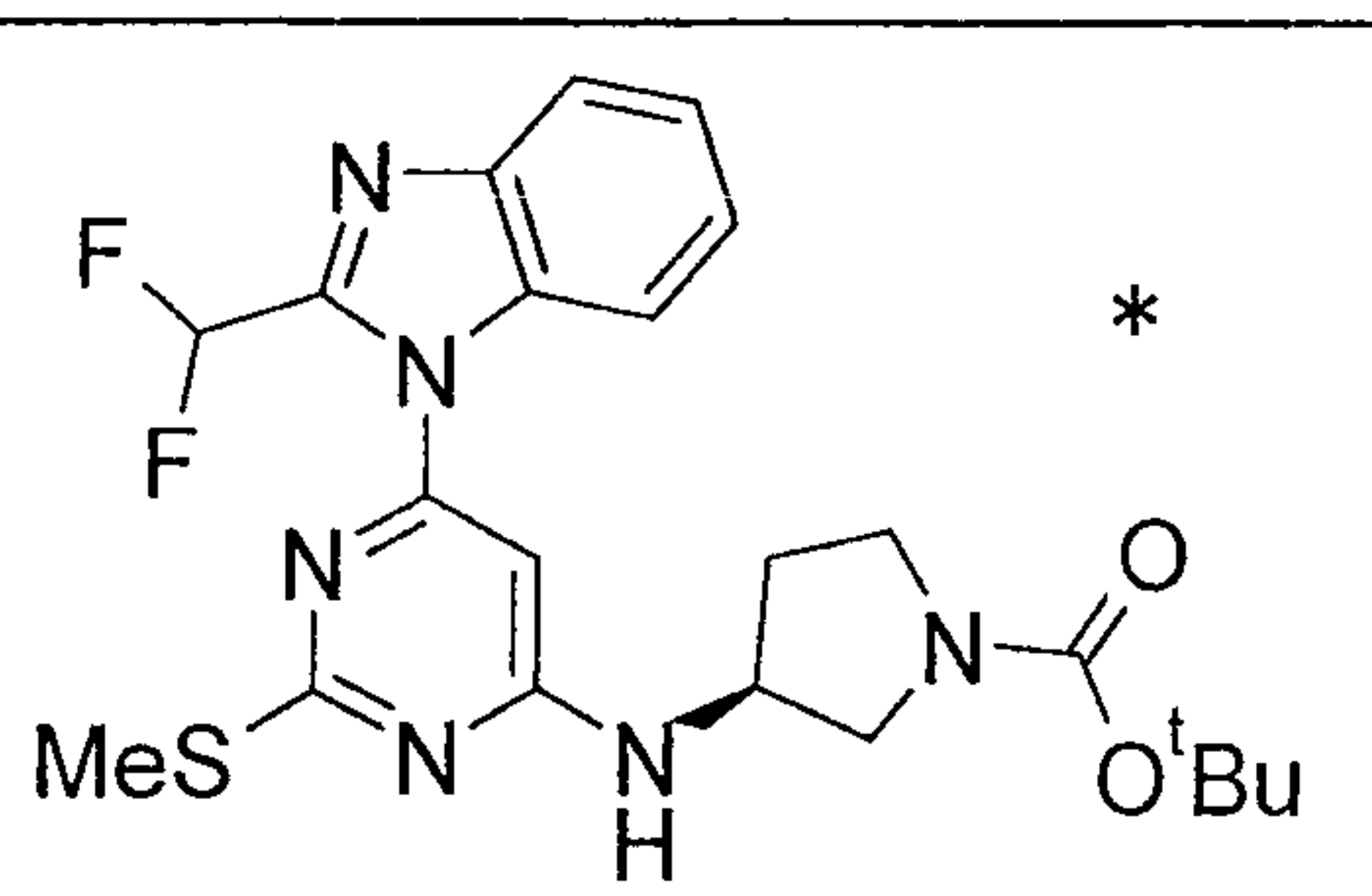
[0186]

[Table 30]

PEx	PSyn	Str	DAT
135	1		ESI+: 490
136	1		ESI+: 516
137	1		ESI+: 422
138	1		ESI+: 505
139	1		ESI+: 505

[0187]

[Table 31]

PEx	PSyn	Str	DAT
140	1		ESI+: 497
141	1		ESI+: 544
142	1		ESI+: 545
143	1		ESI+: 517
144	1		ESI+: 477

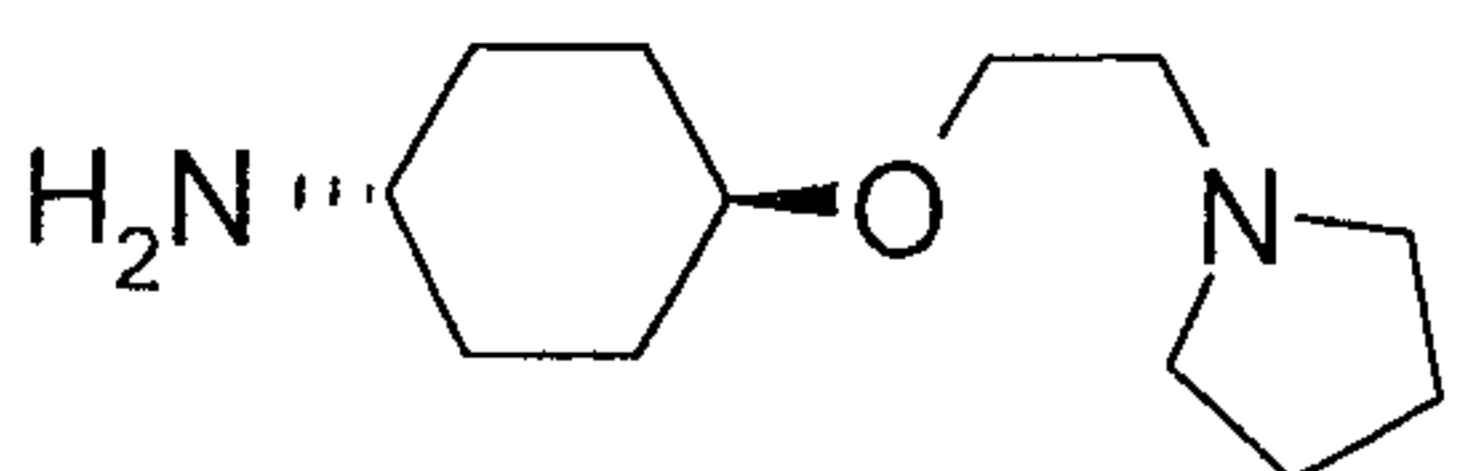
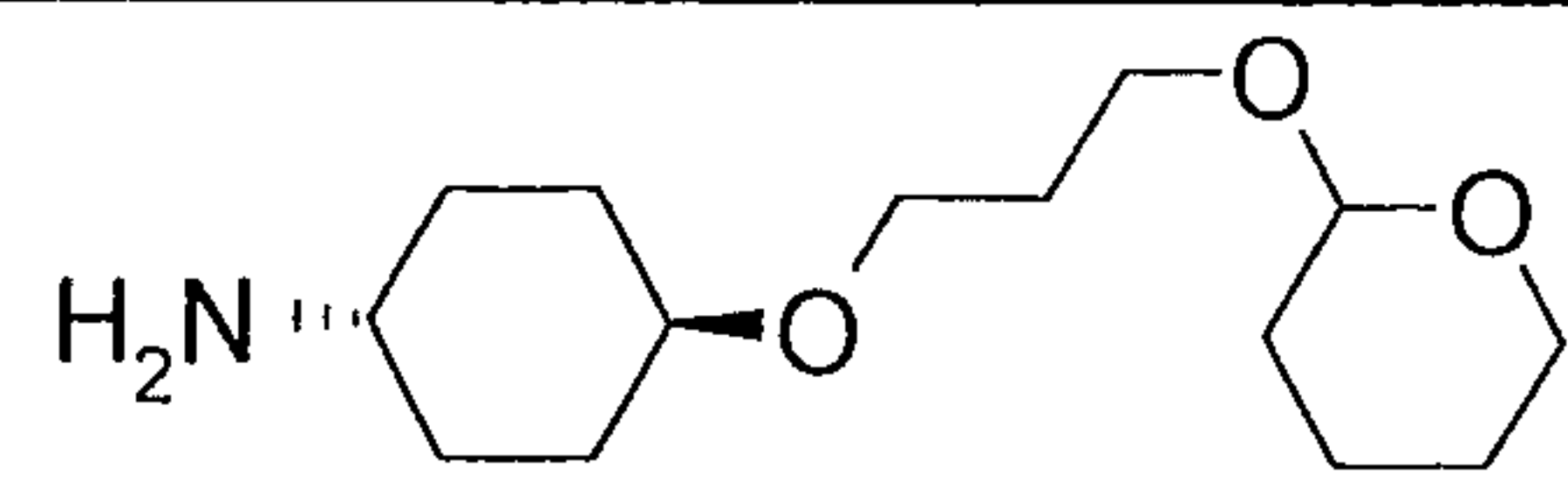
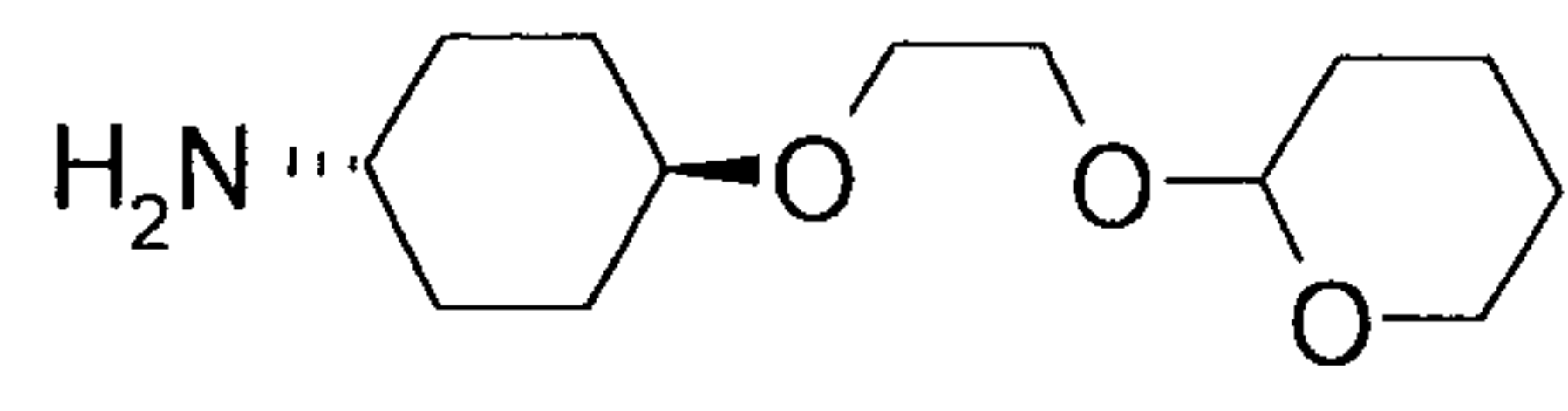
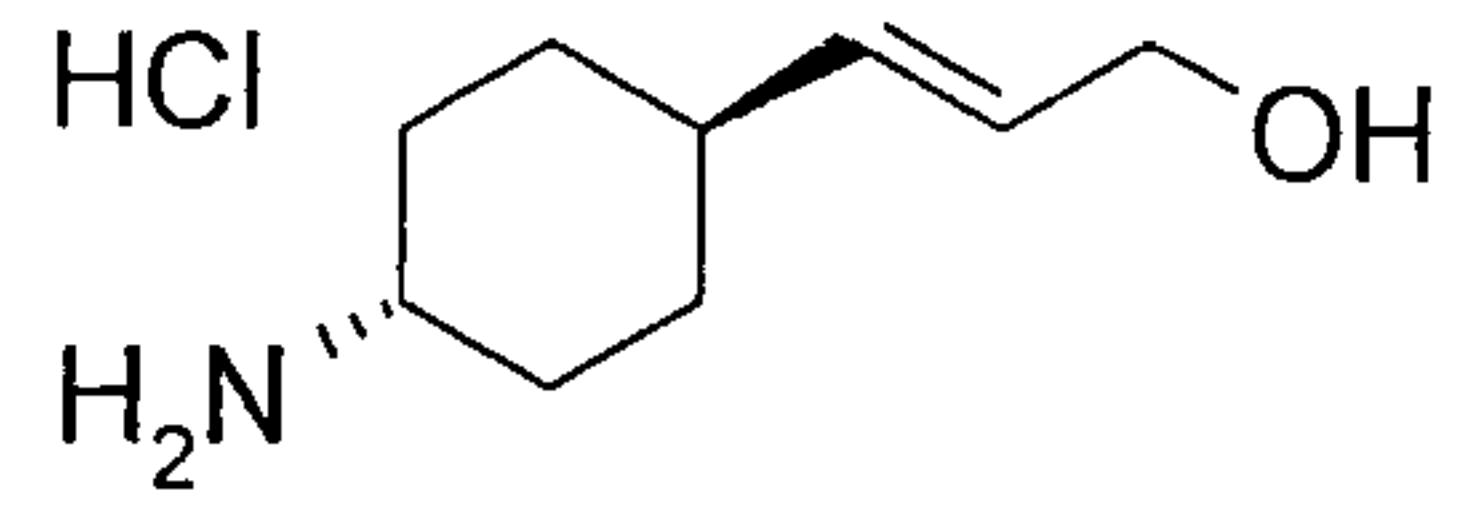
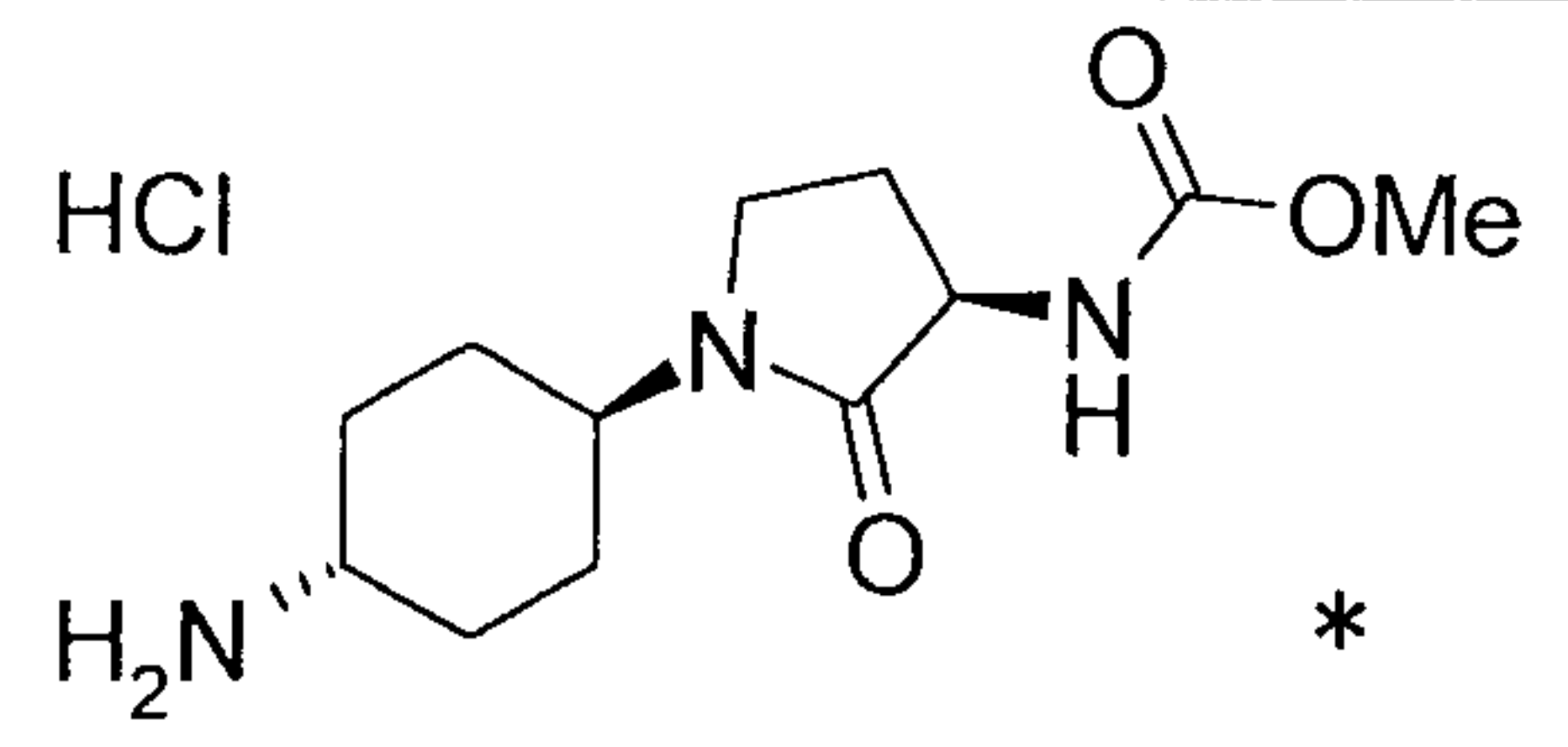
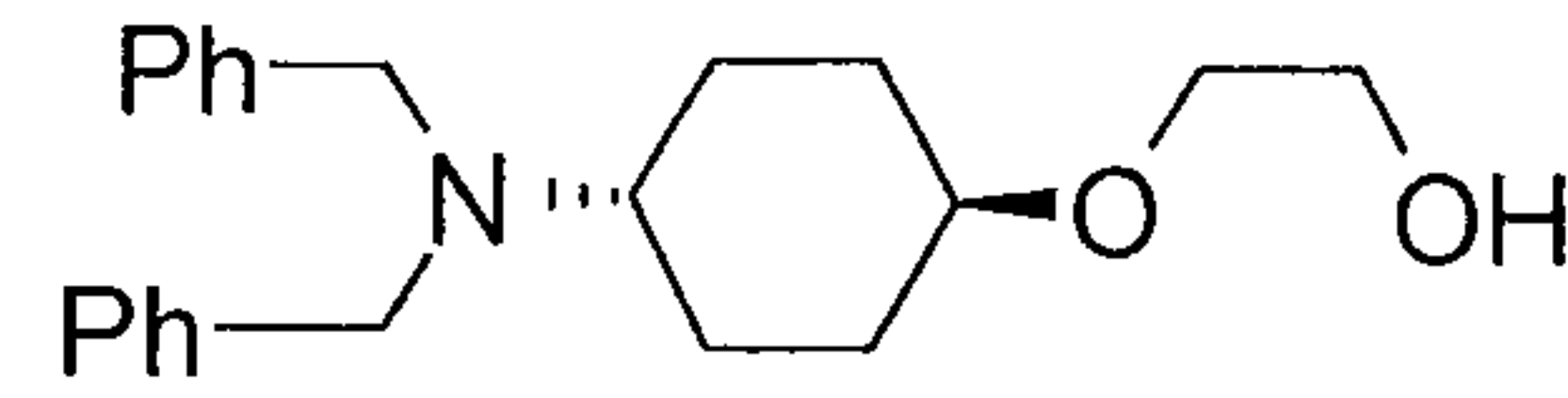
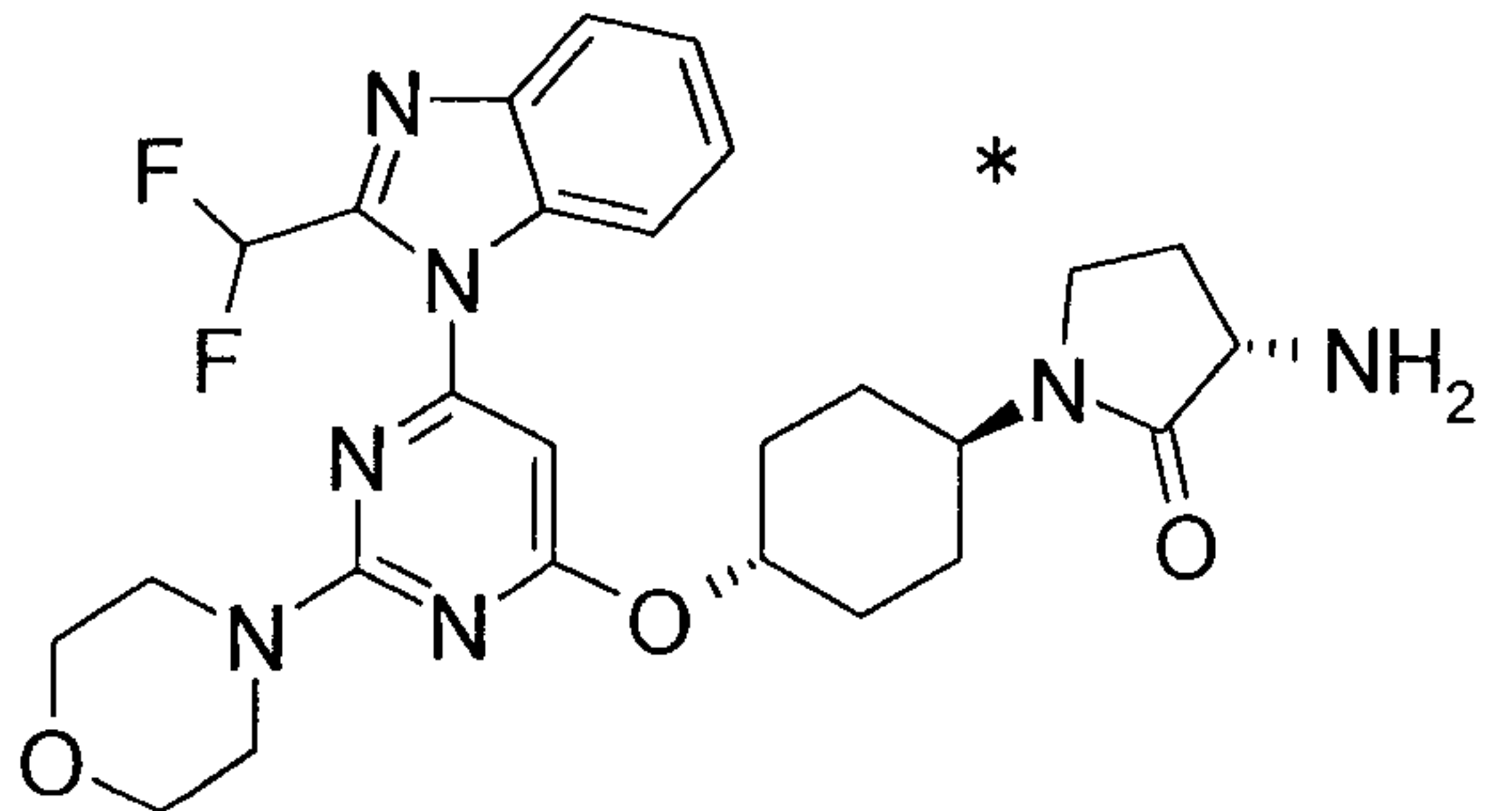
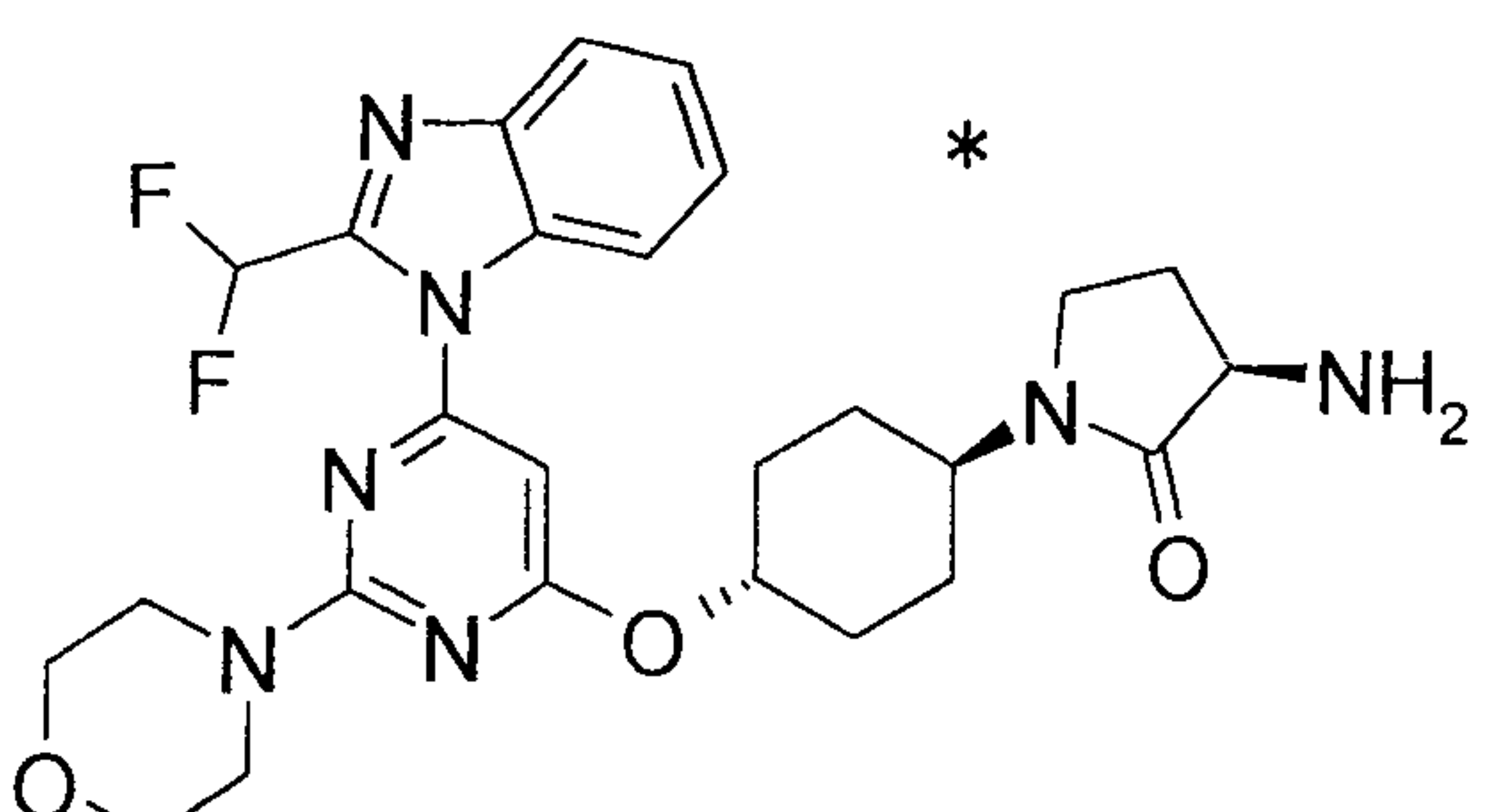
[0188]

[Table 32]

PEx	PSyn	Str	DAT
145	1		ESI+: 491
146	1		ESI+: 477
147	90		ESI+: 546
148	Syn.87		ESI+: 706
149	82		ESI+: 393

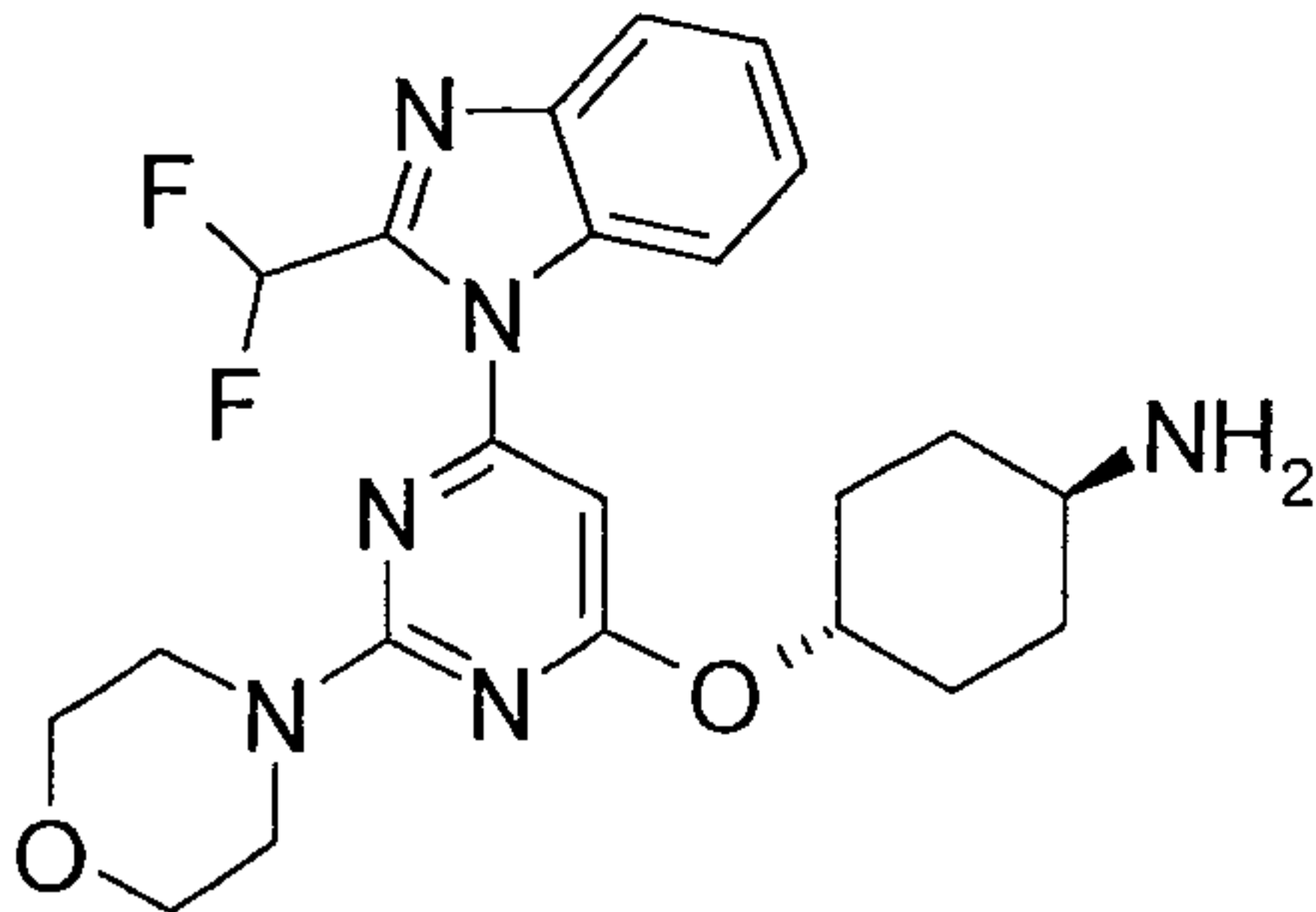
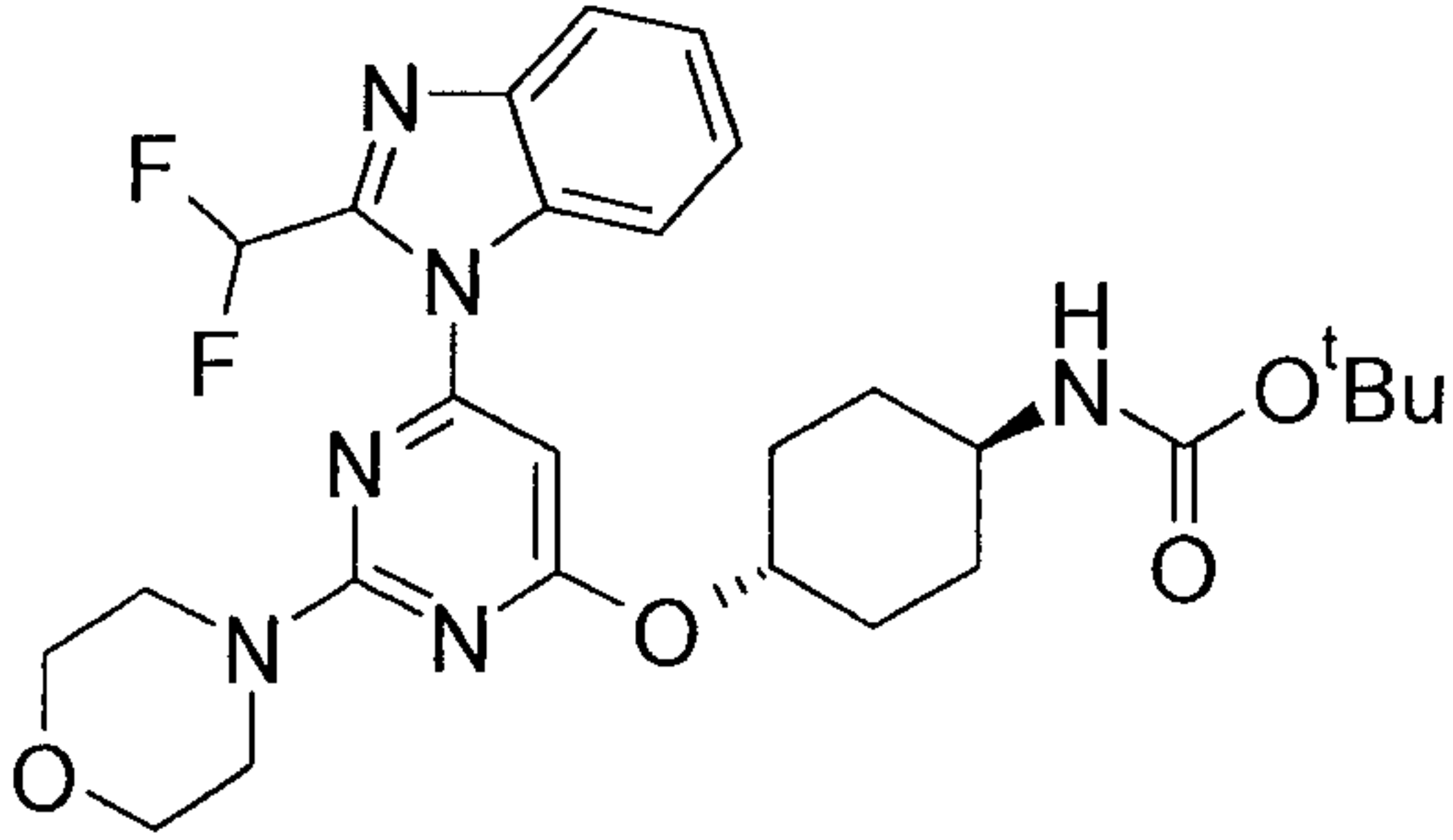
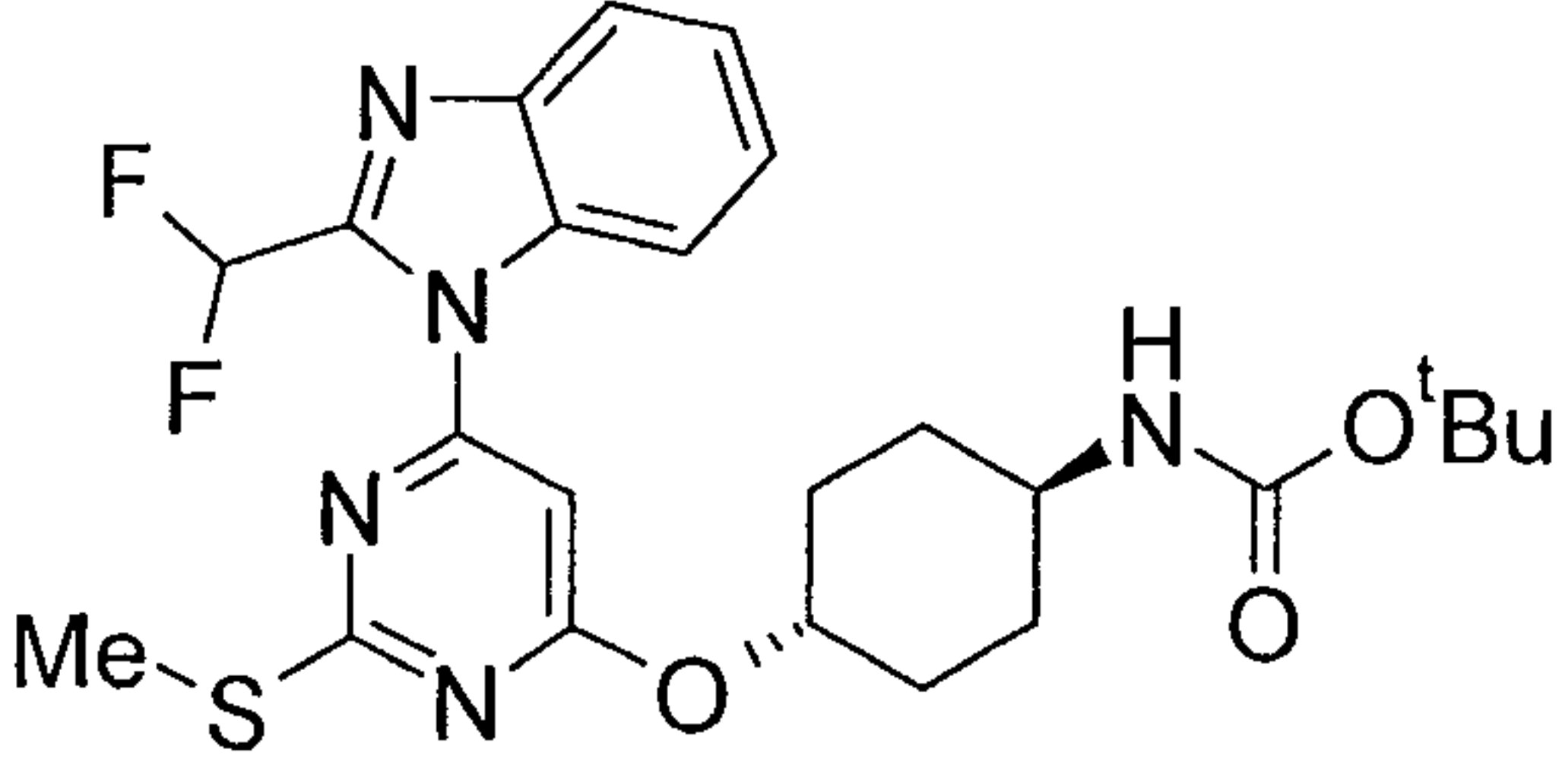
[0189]

[Table 33]

PEX	PSyn	Str	DAT
150	83		ESI+: 213
151	83		ESI+: 258
152	83		ESI+: 244
153	11		ESI+: 156
154	11		ESI+: 256
155	81		ESI+: 340
156	Syn.54		ESI+: 528
157	Syn.54		ESI+: 528

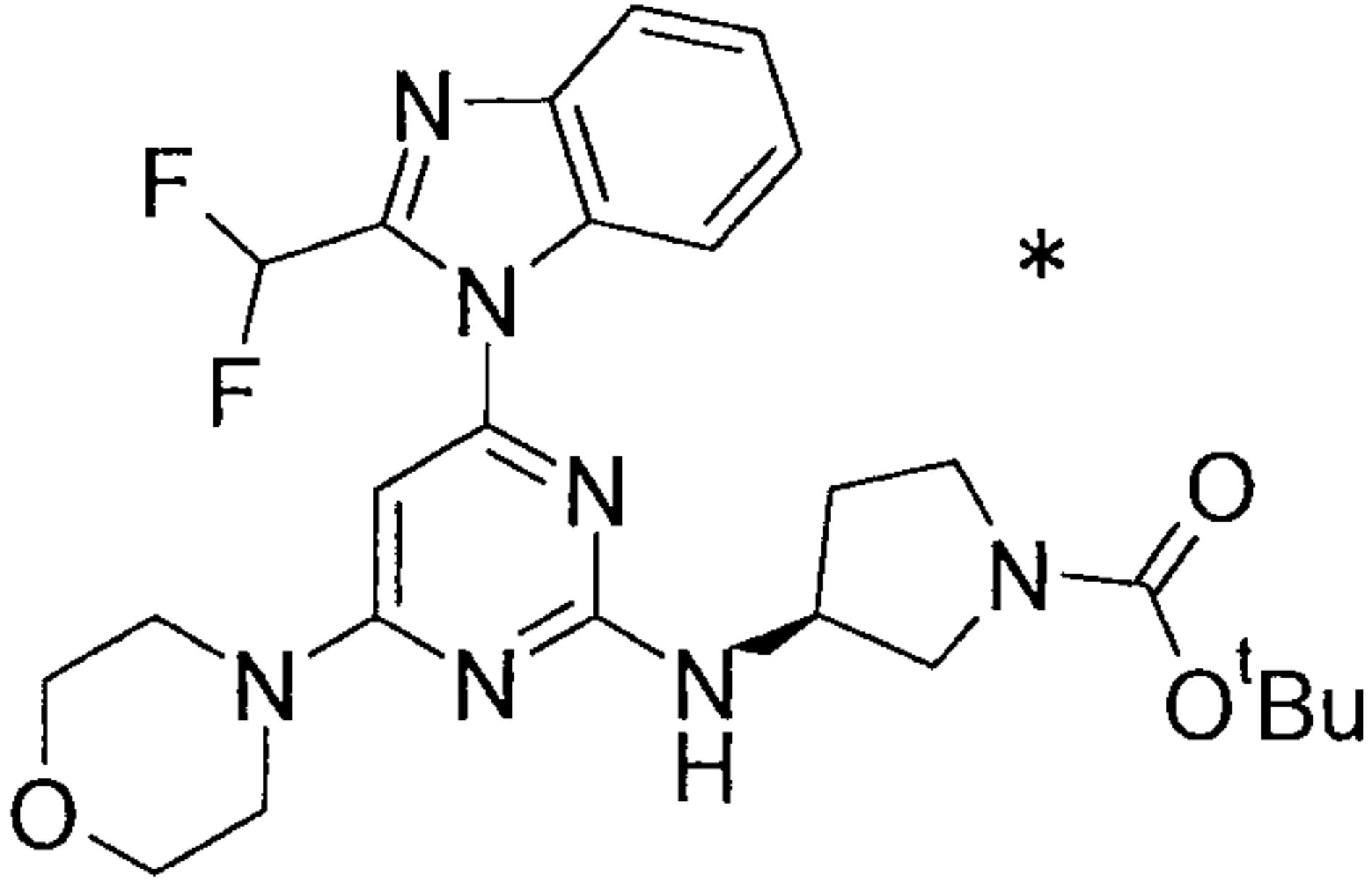
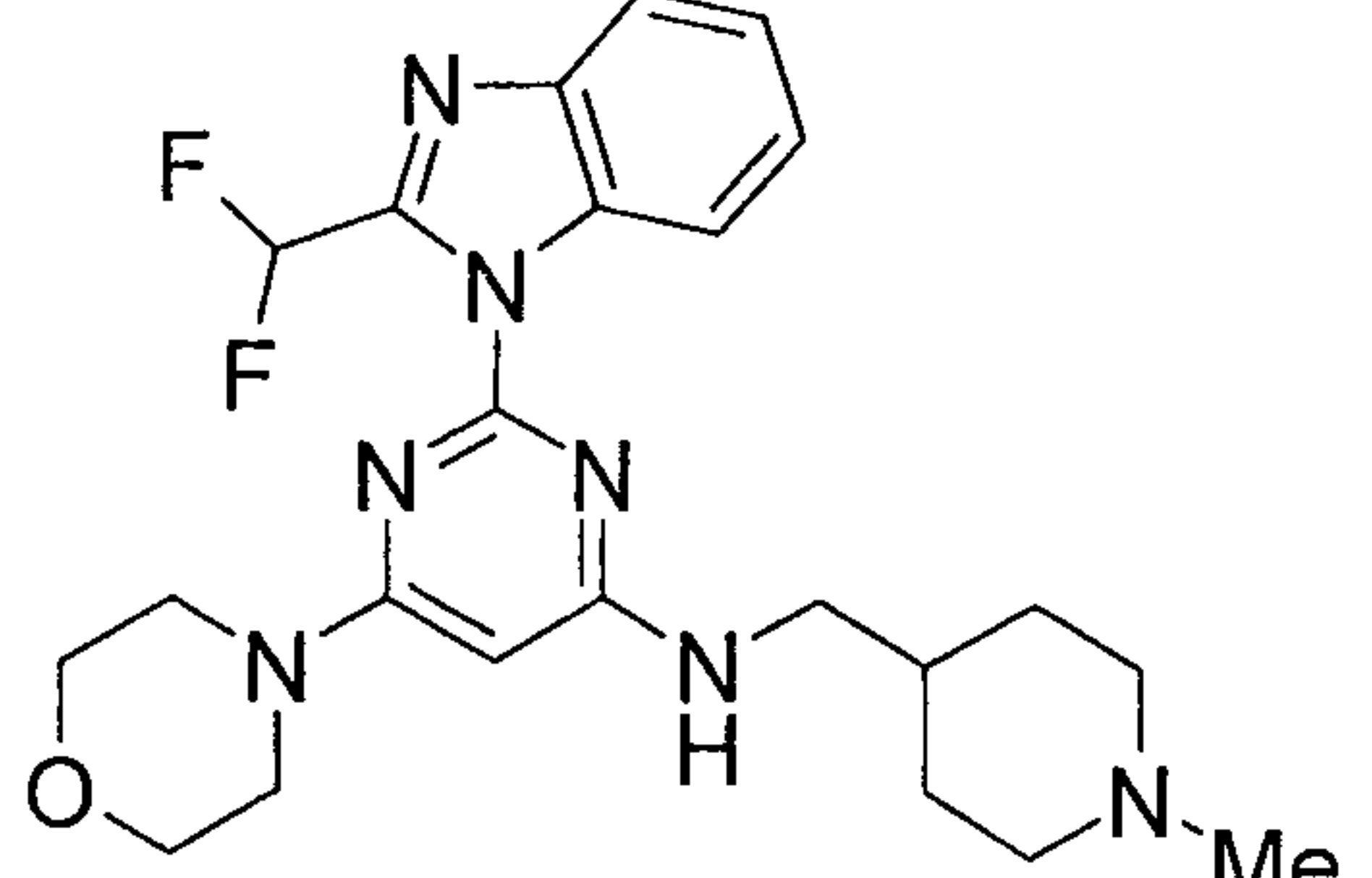
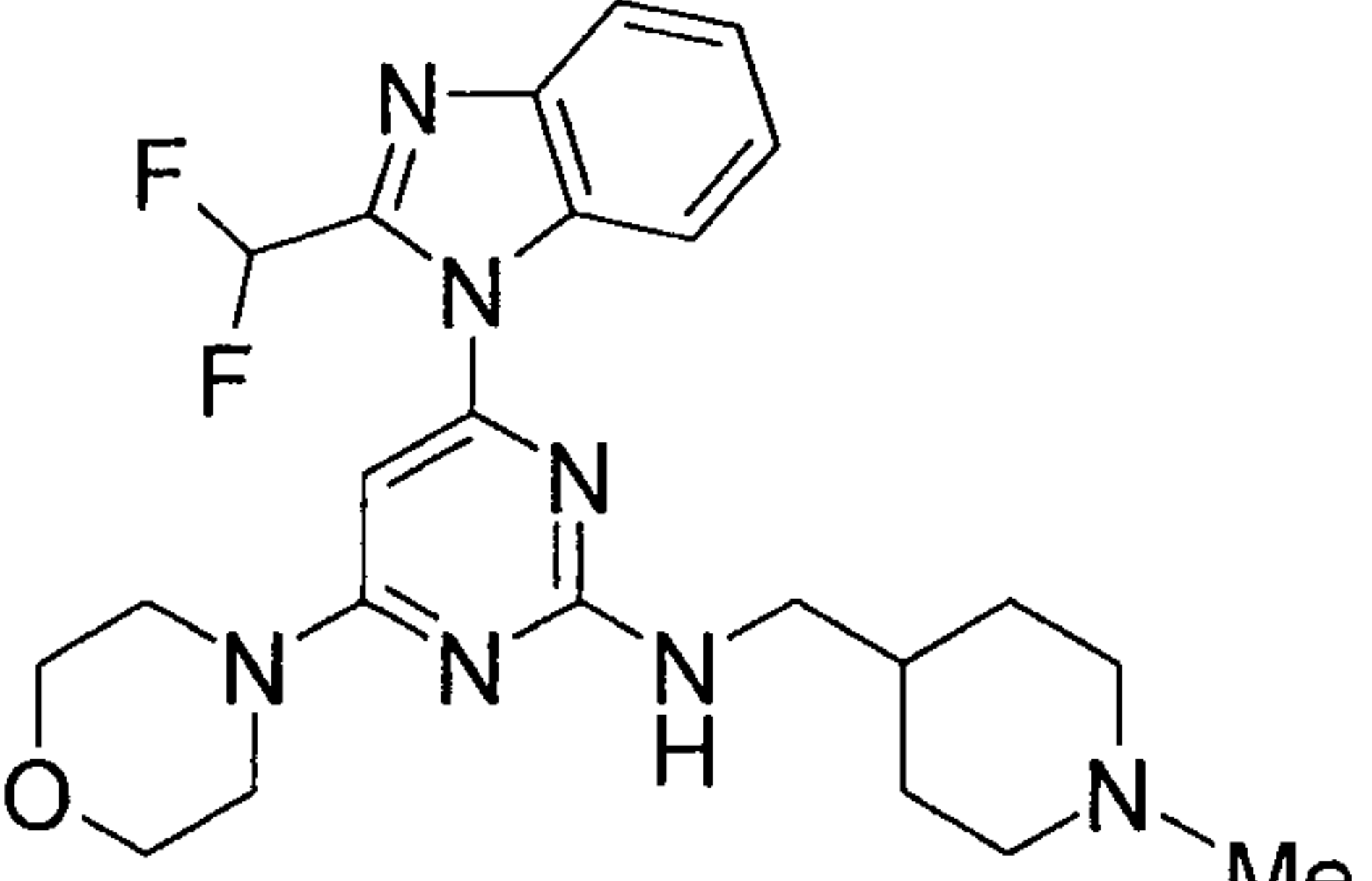
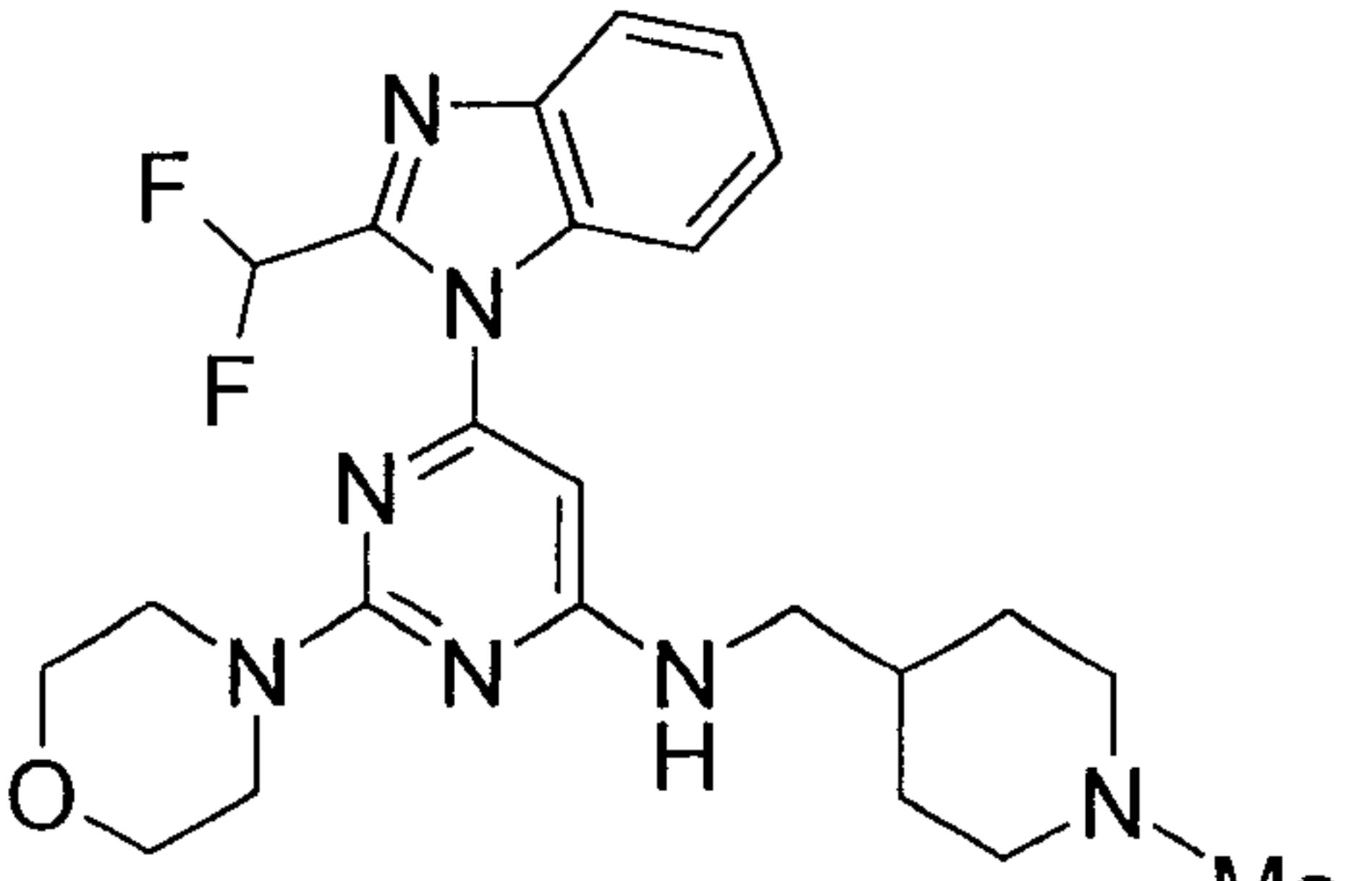
[0190]

[Table 34]

PEX	PSyn	Str	DAT
158	Syn.54		ESI+: 445
159	2		ESI+: 567[M+Na]
160	5		ESI+: 528[M+Na]

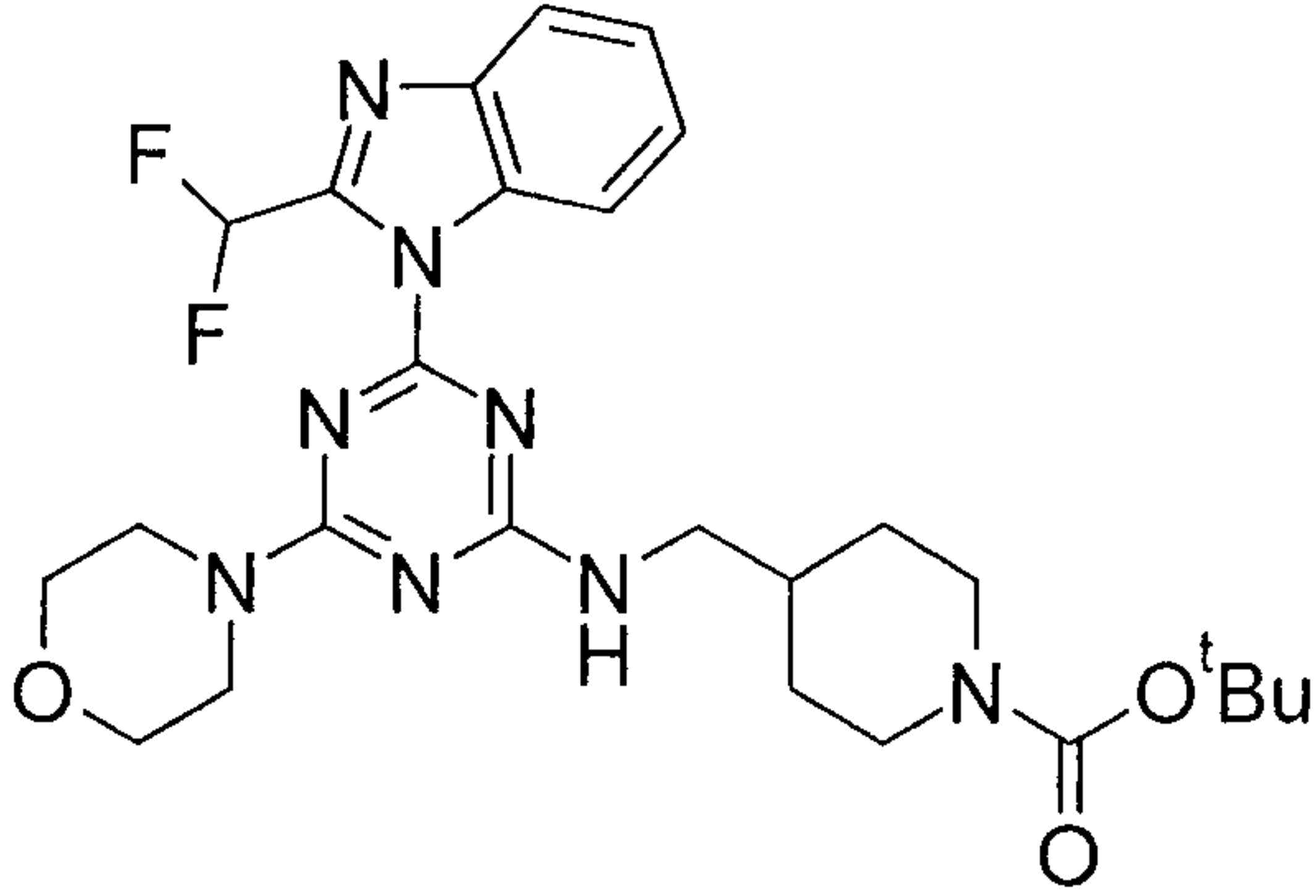
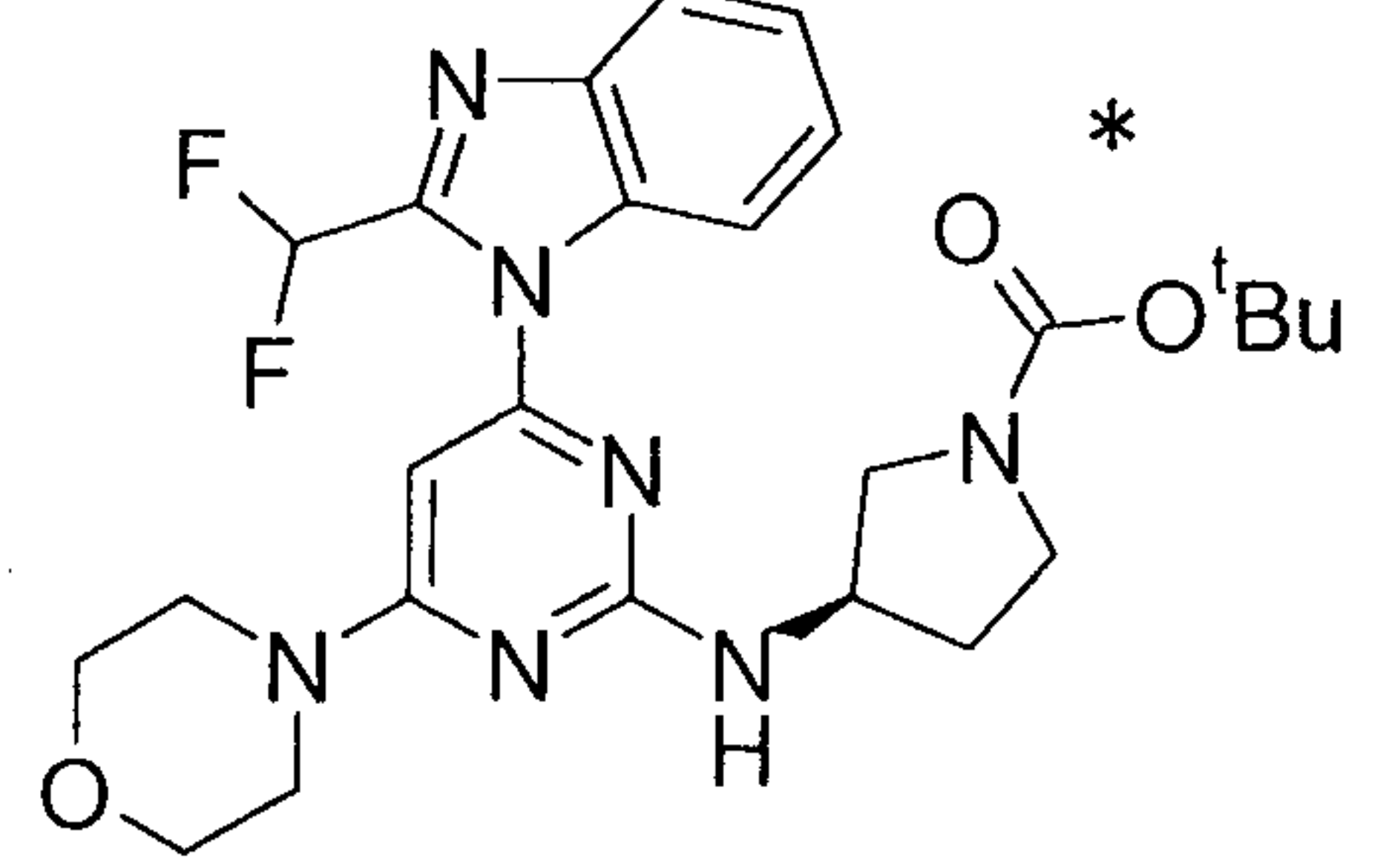
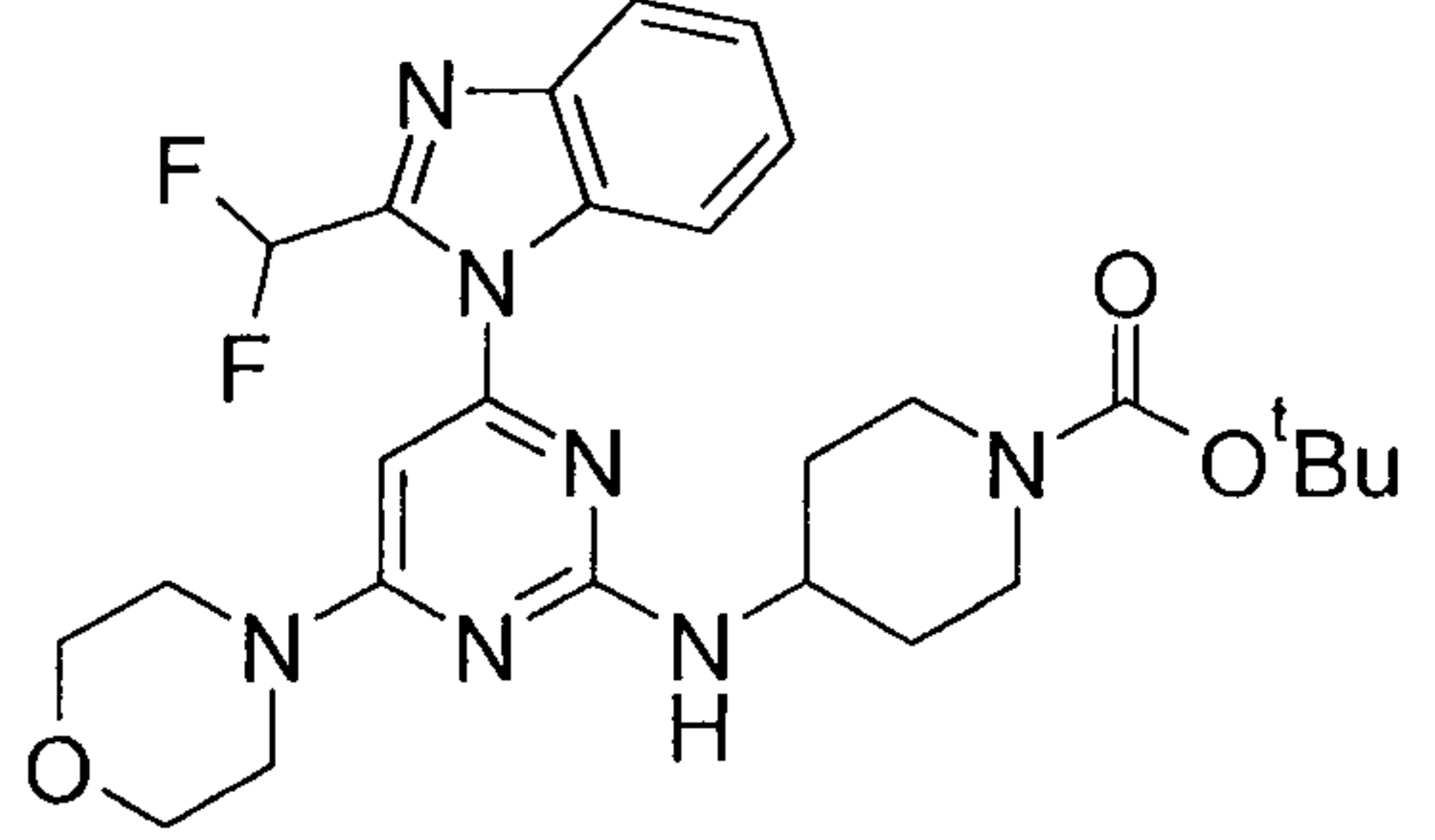
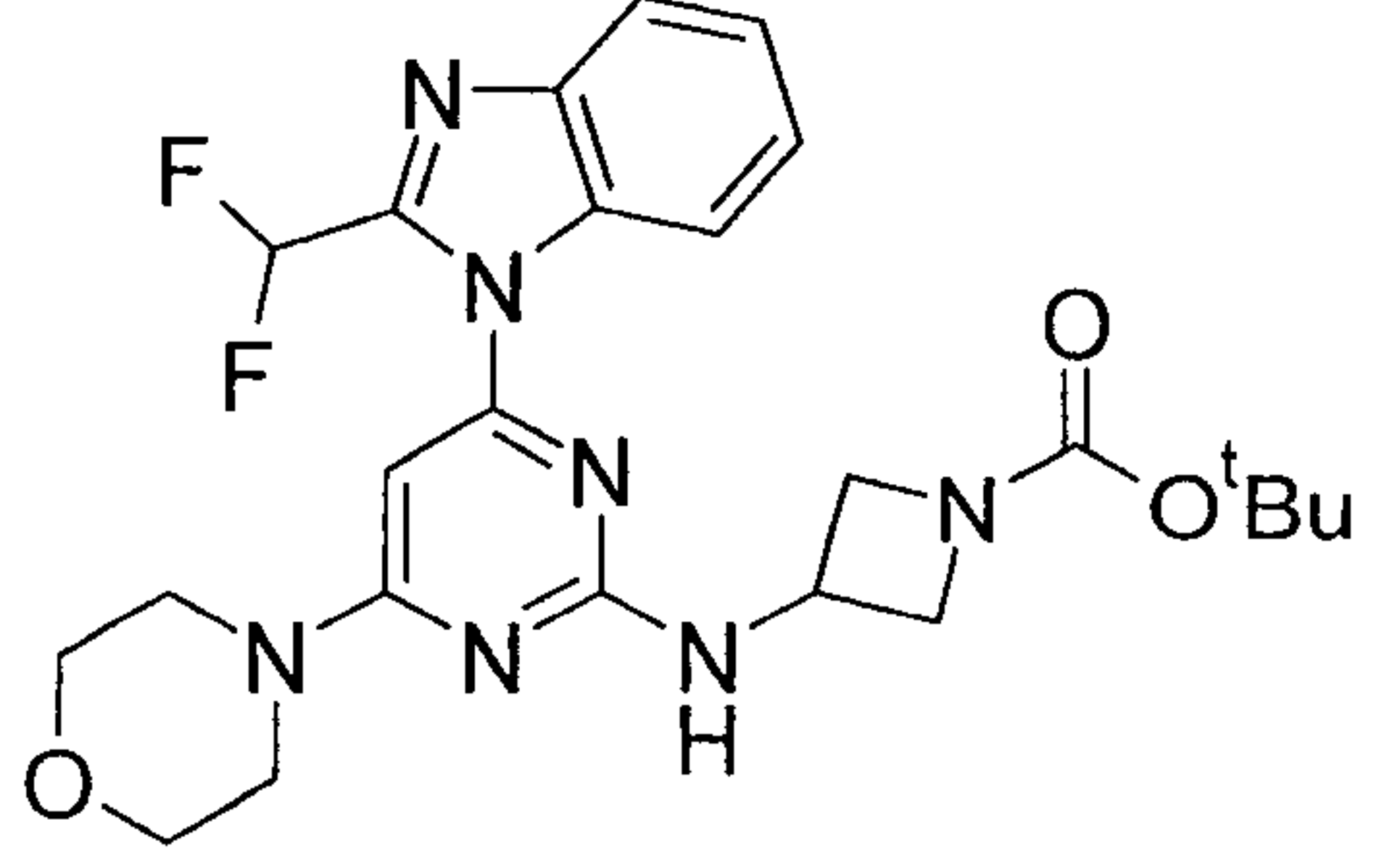
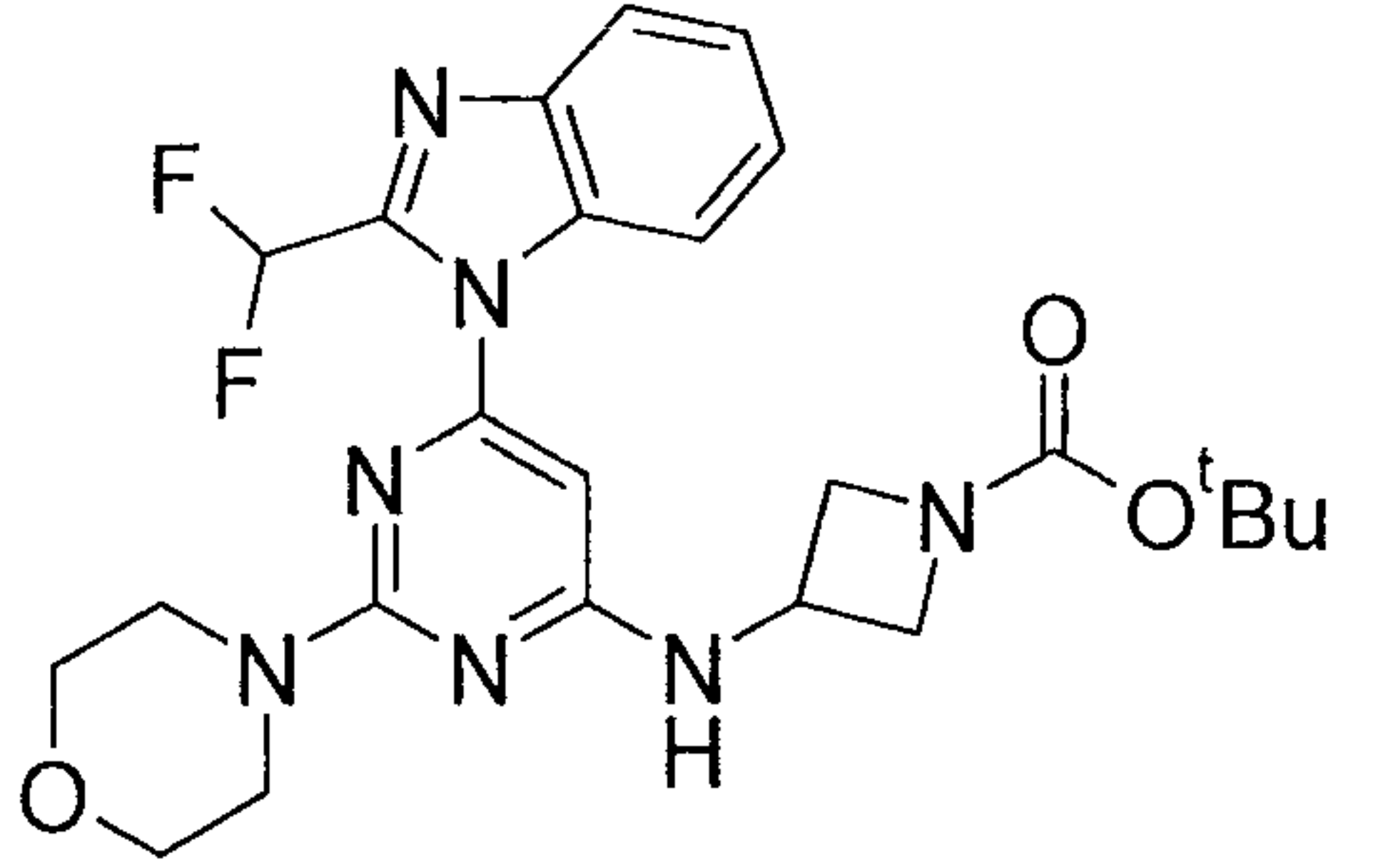
[0191]

[Table 35]

Ex	Str
1	
2	
3	
4	

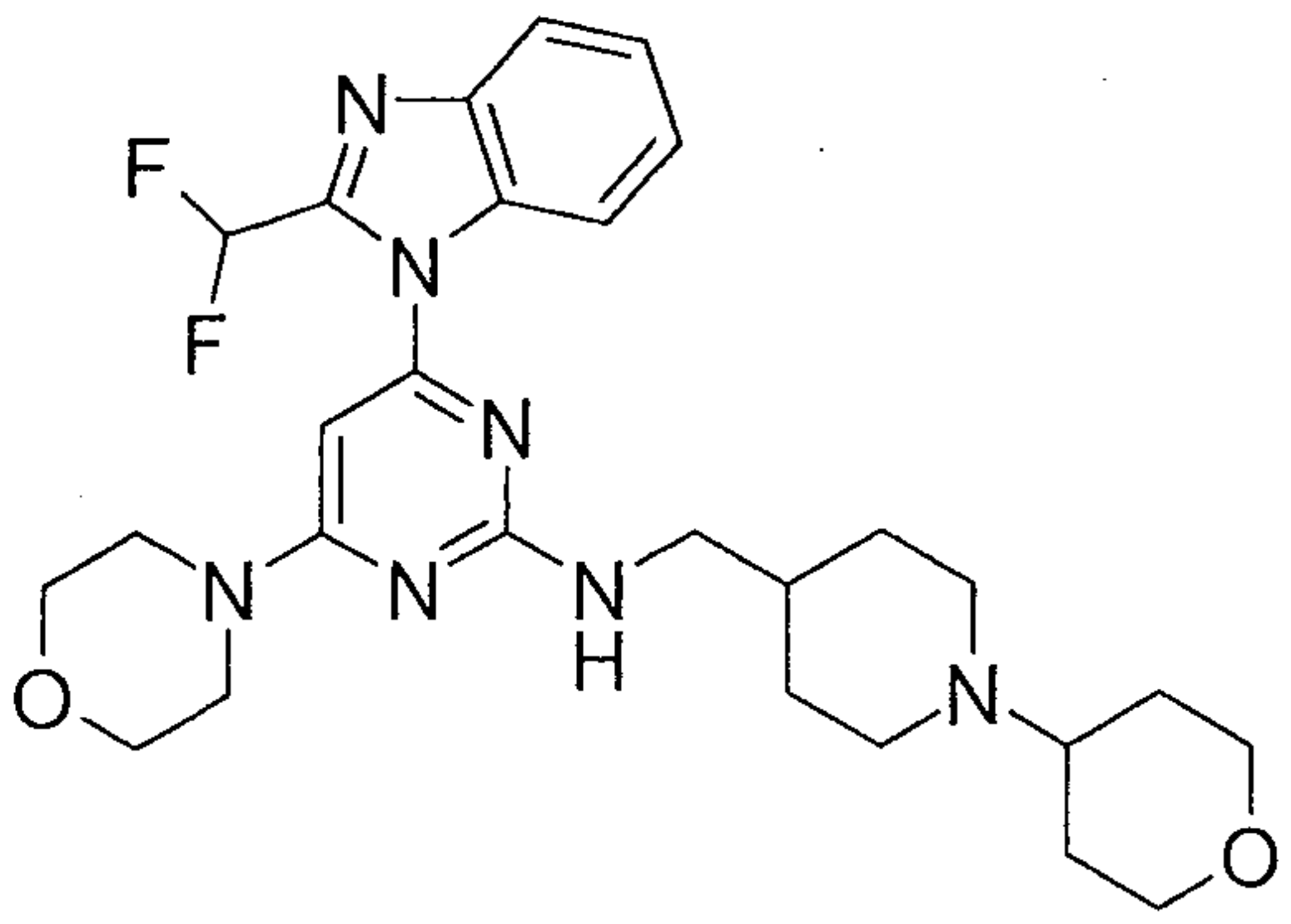
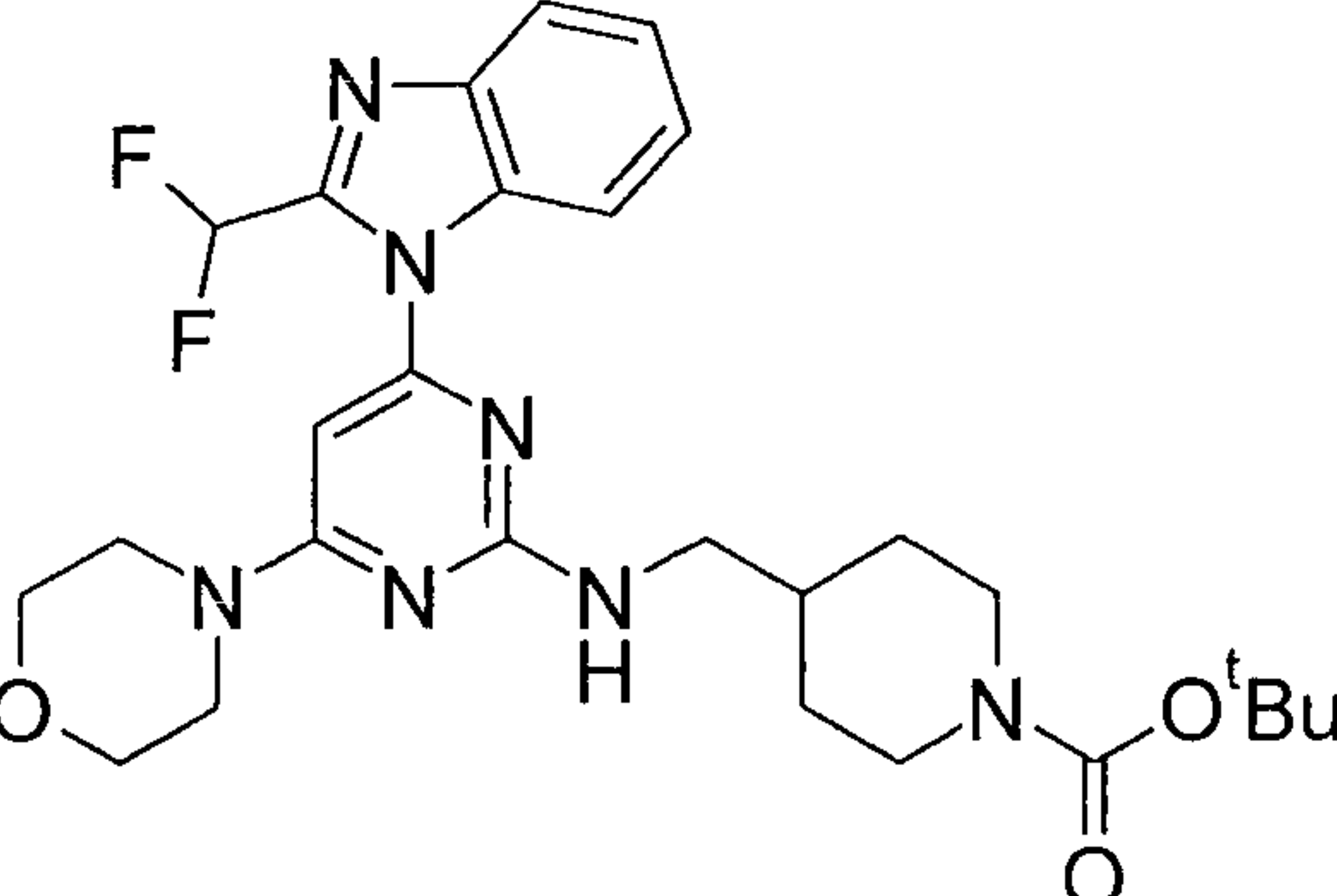
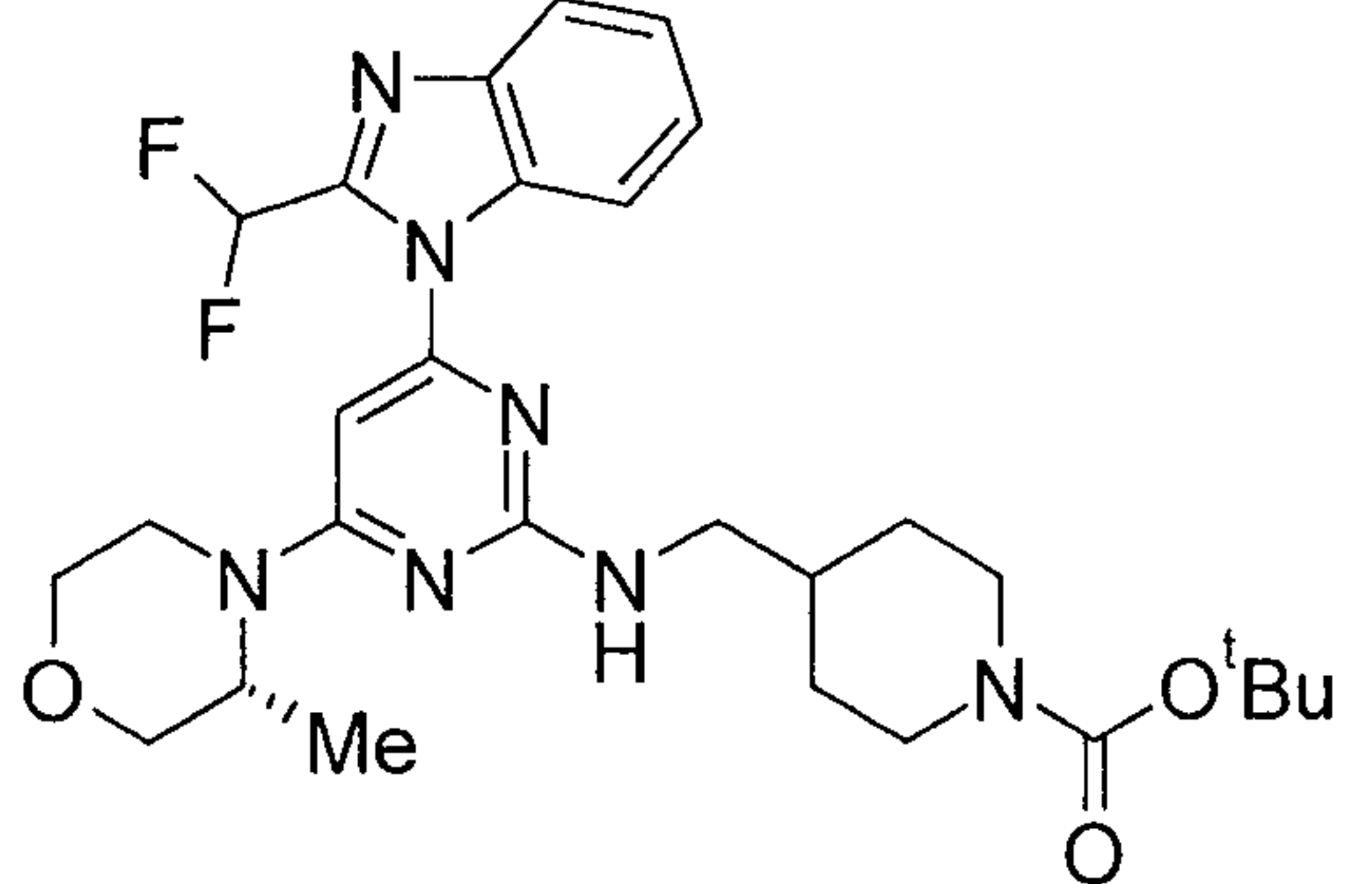
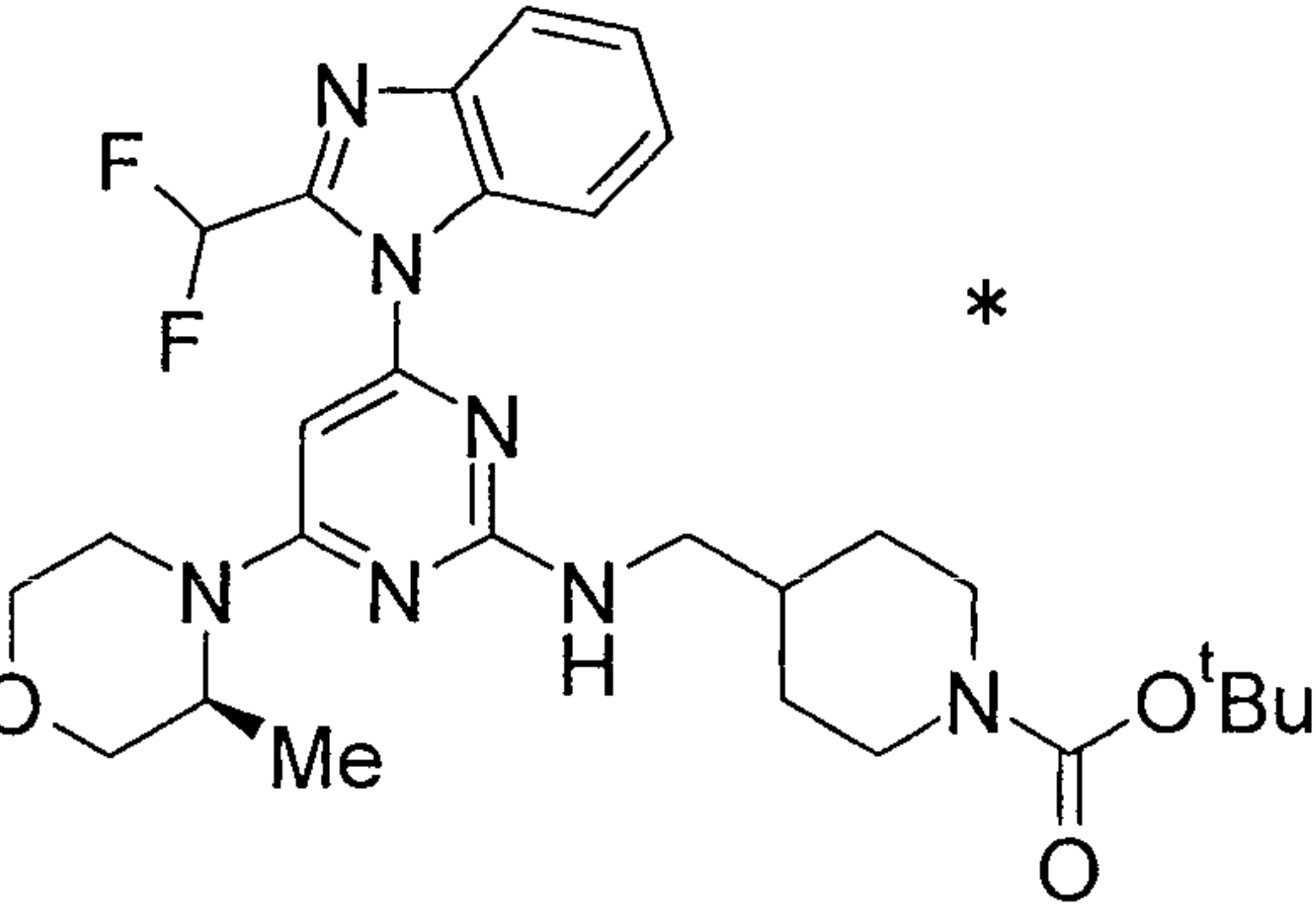
[0192]

[Table 36]

Ex	Str
5	
6	
7	
8	
9	

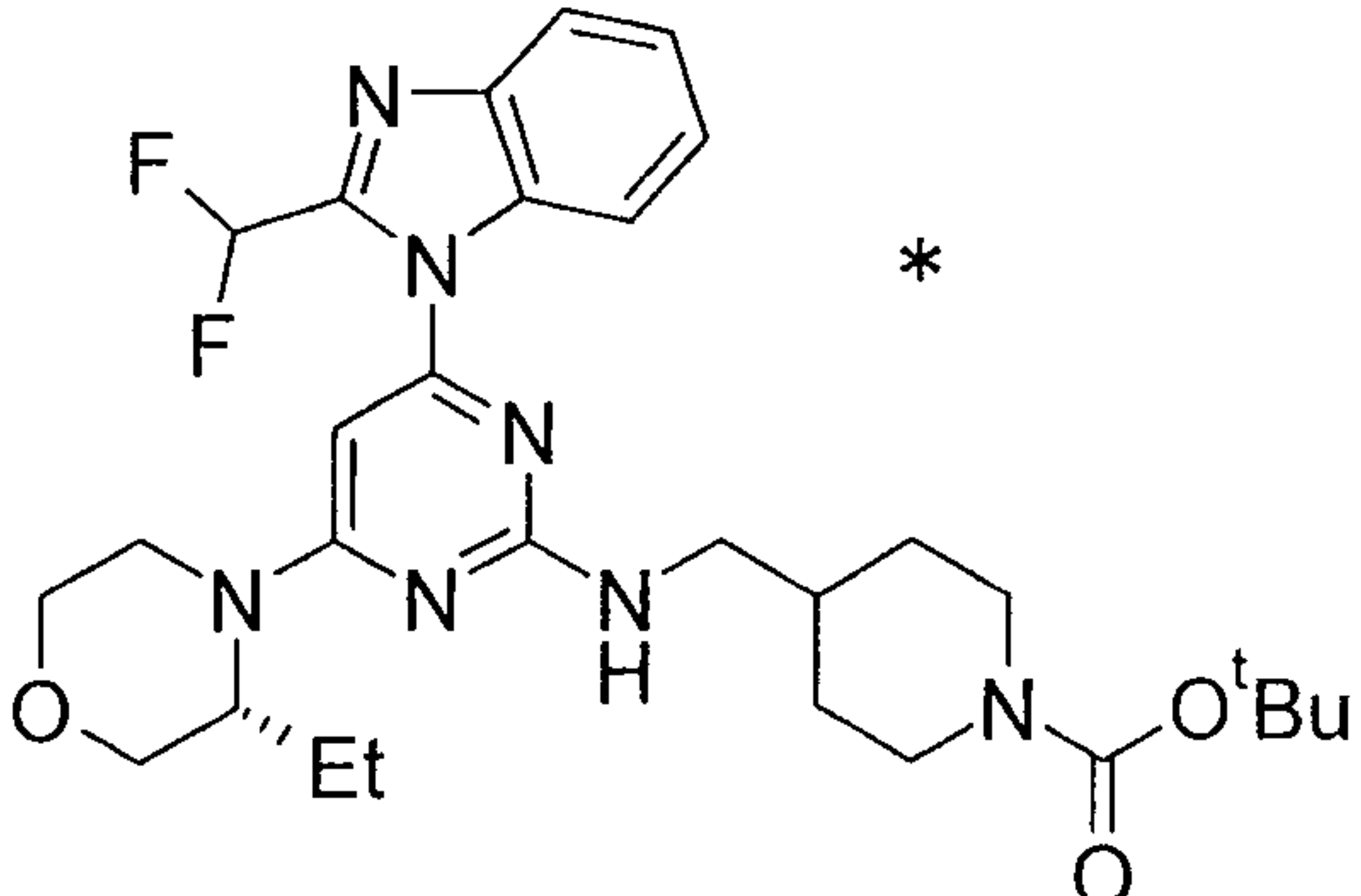
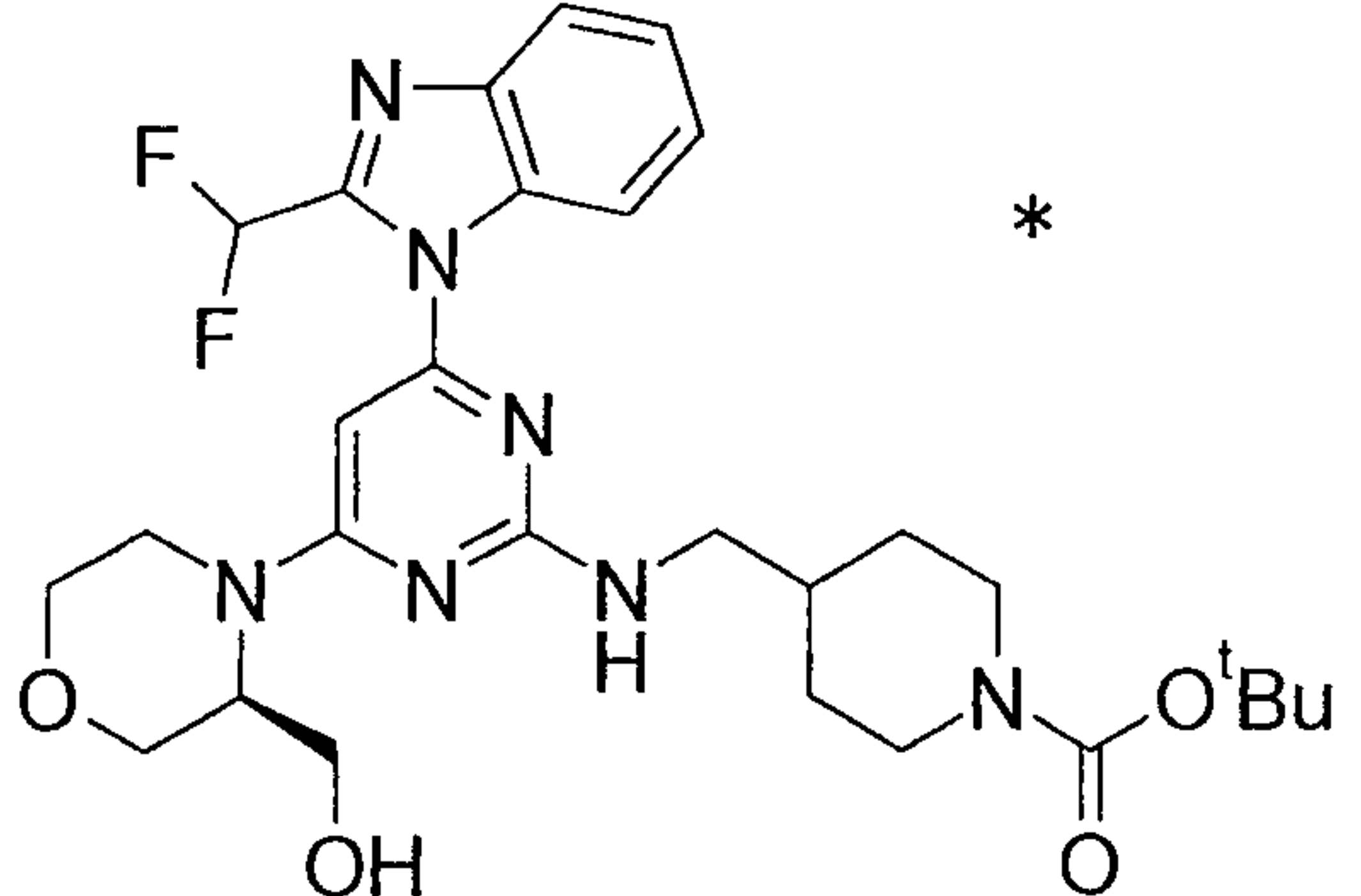
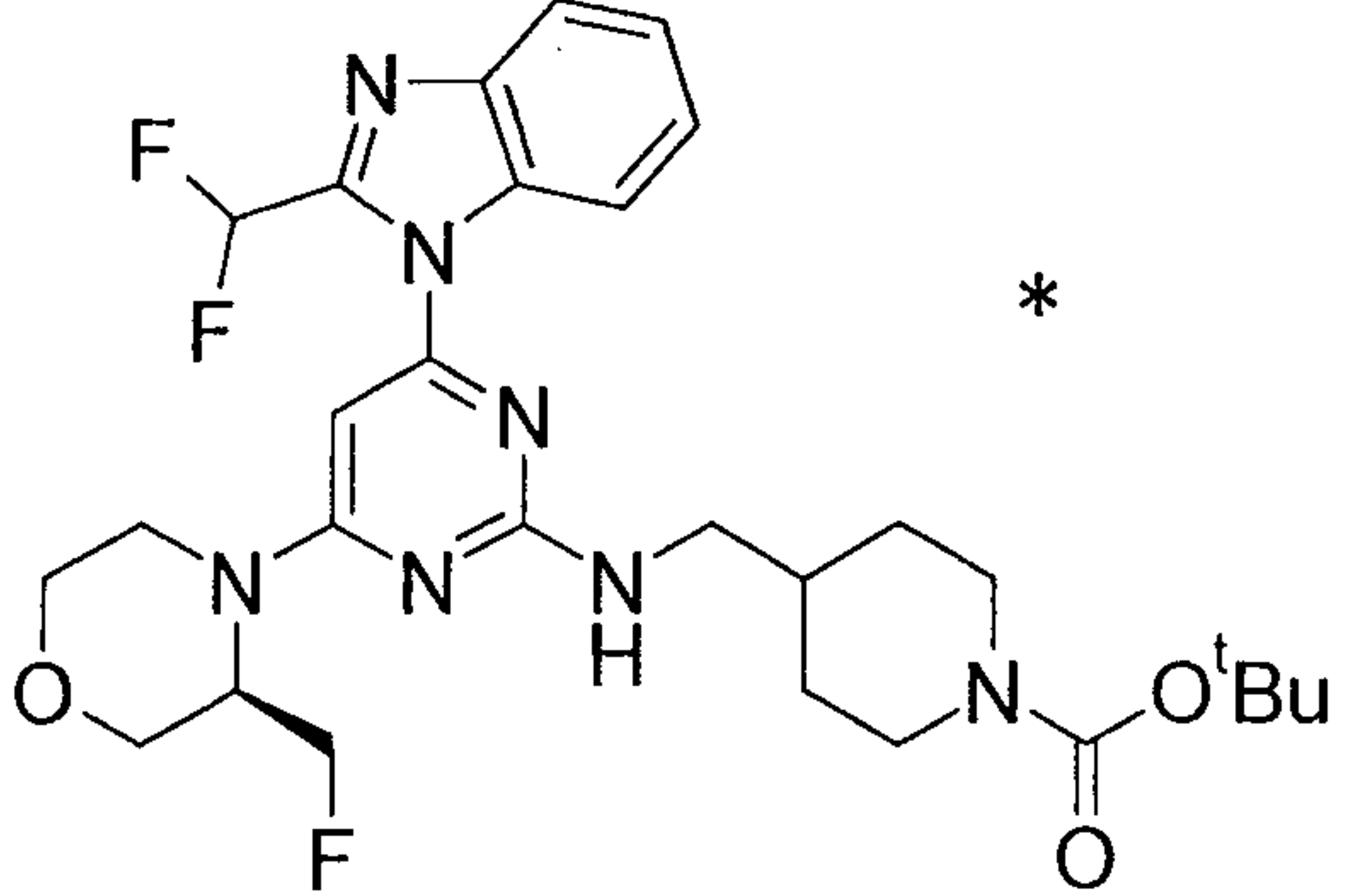
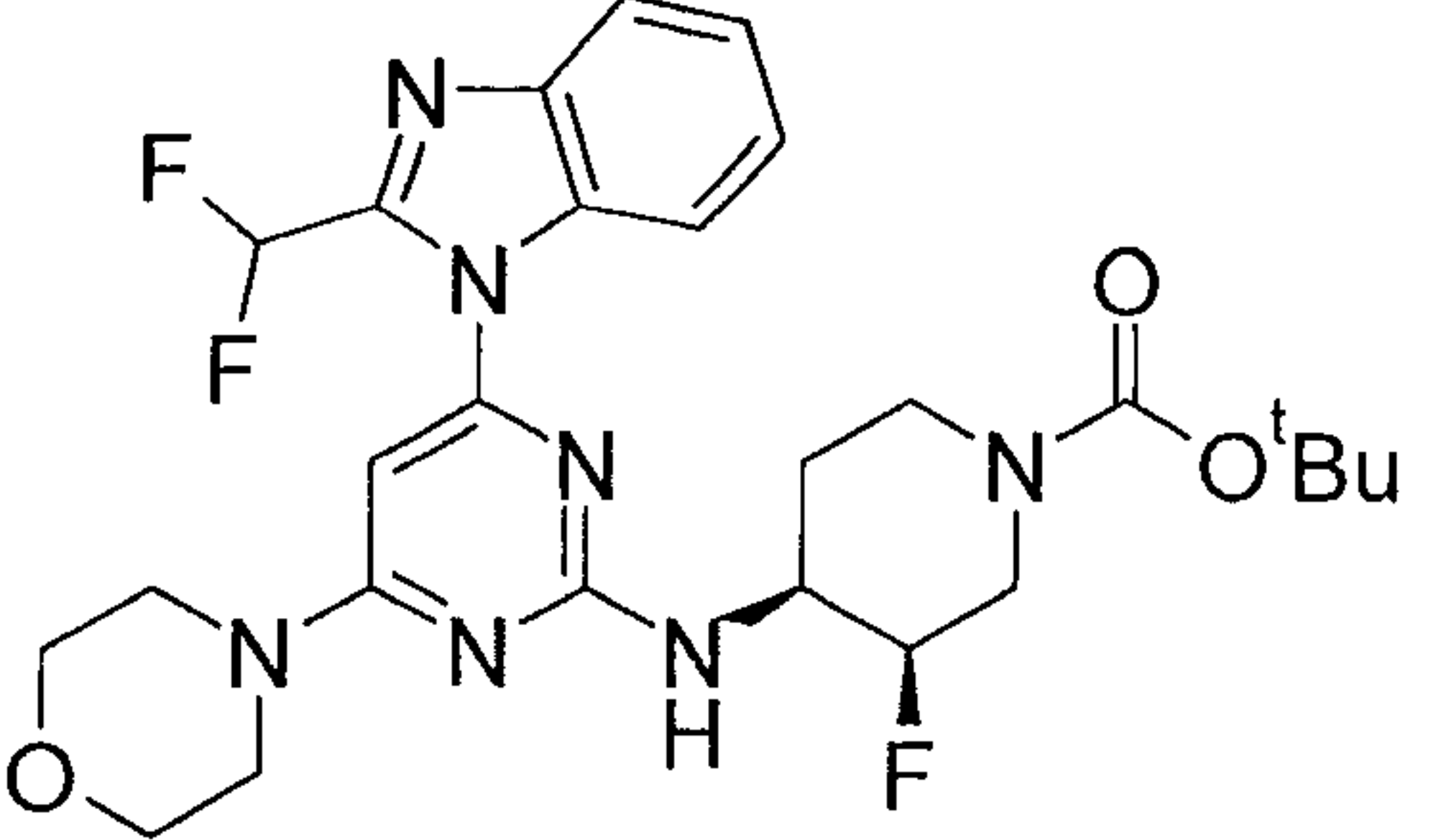
[0193]

[Table 37]

Ex	Str
10	
11	
12	
13	

[0194]

[Table 38]

Ex	Str
14	
15	
16	
17	

[0195]

[Table 39]

Ex	Str
18	
19	
20	
21	
22	

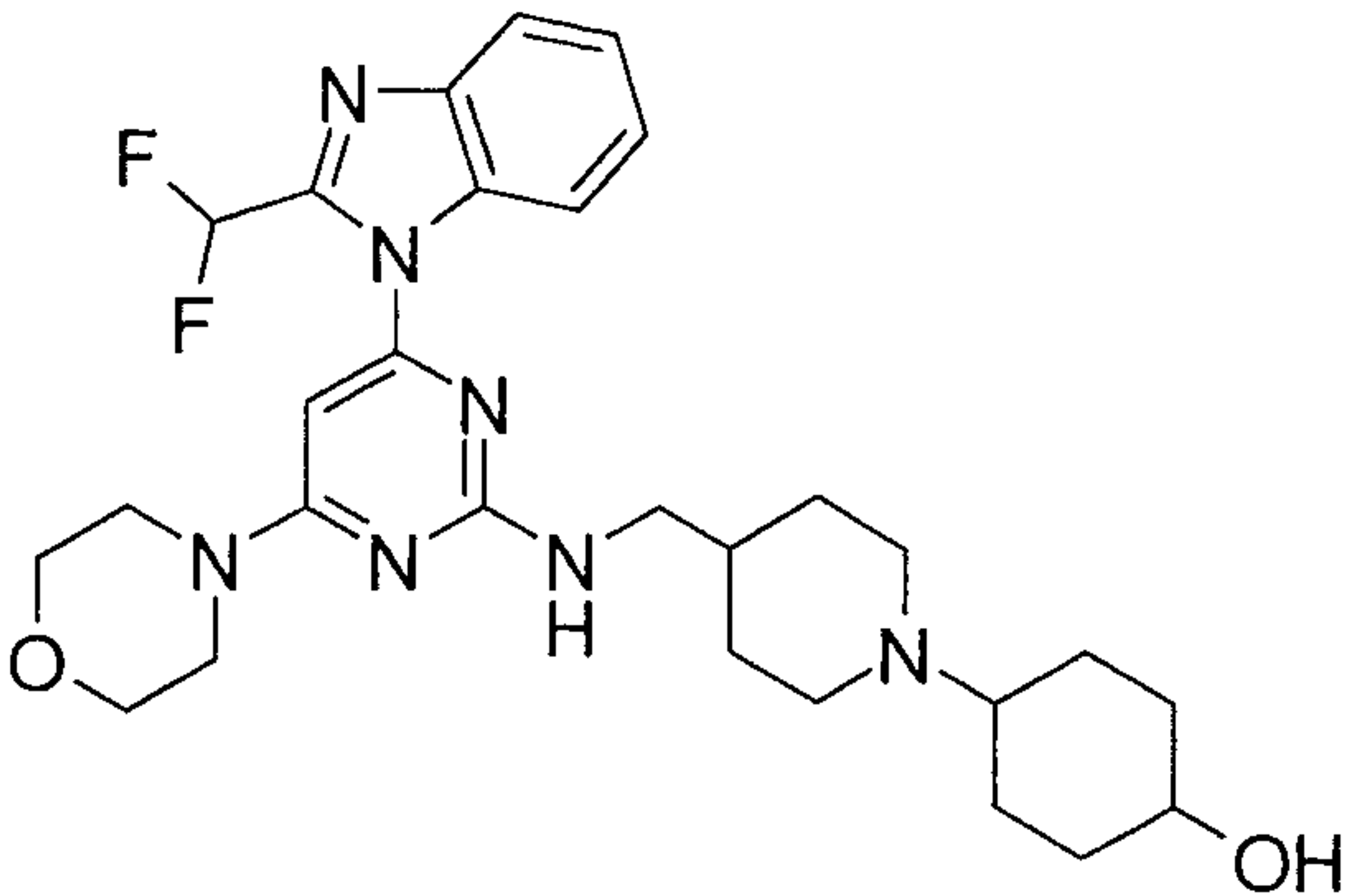
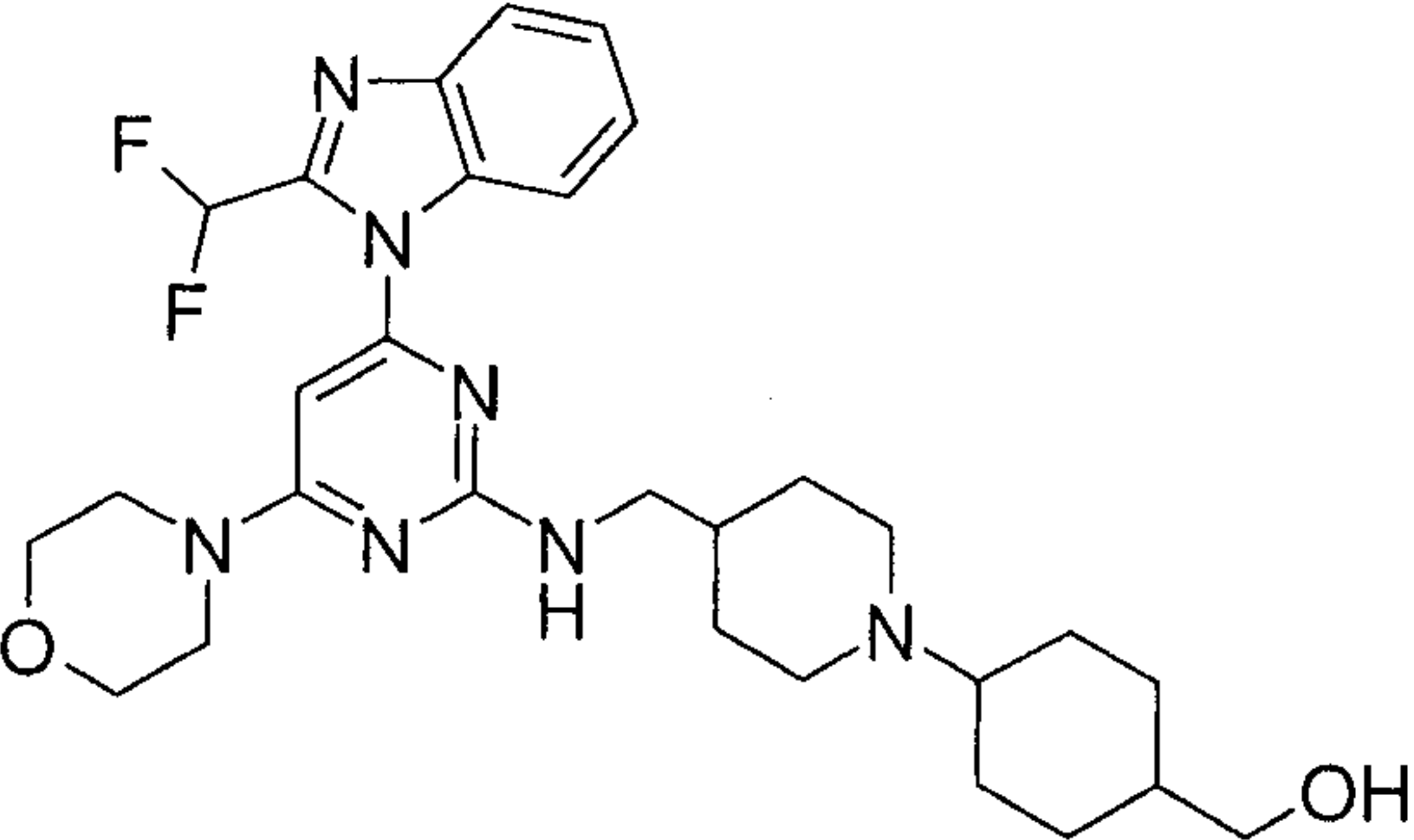
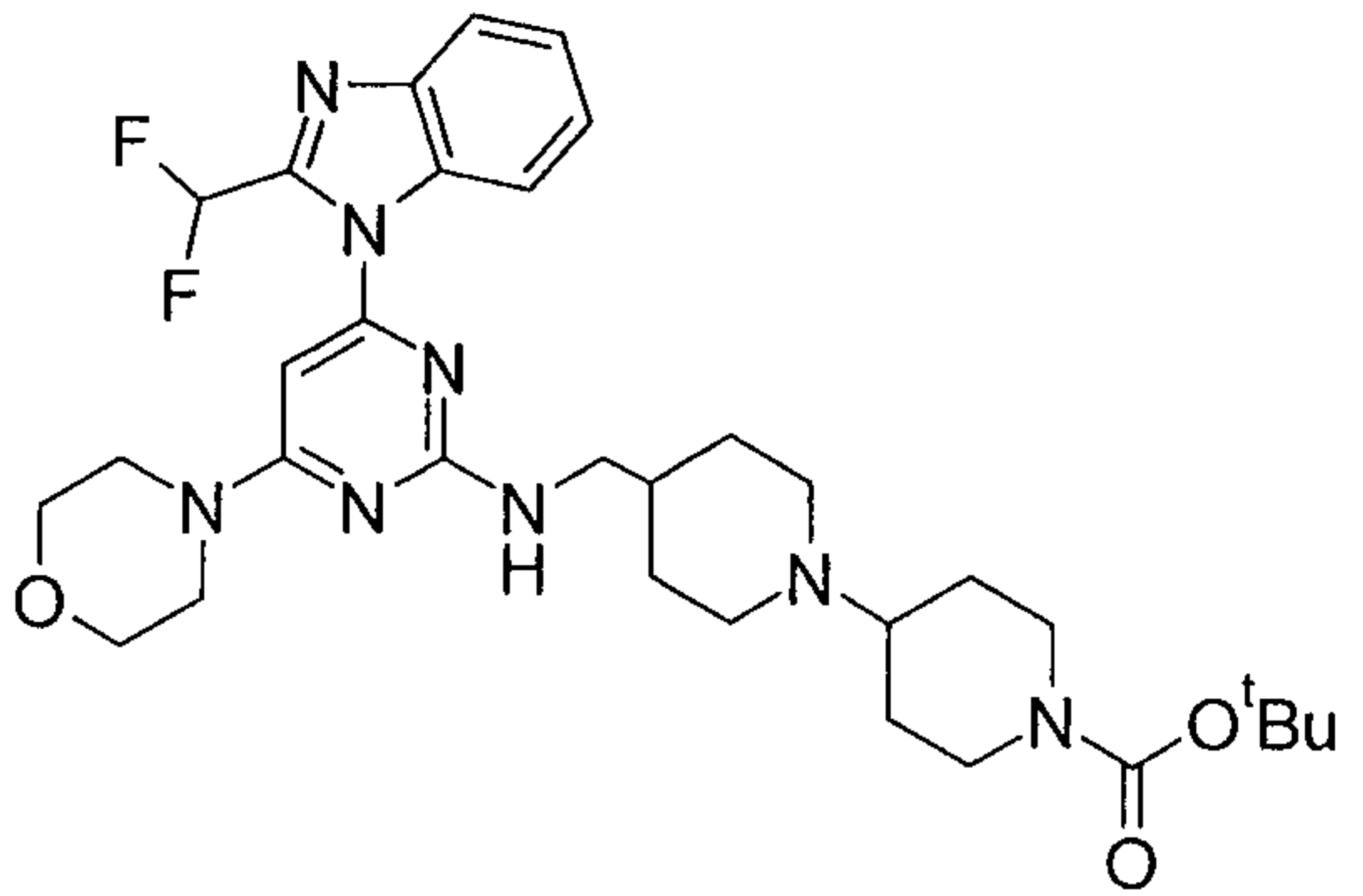
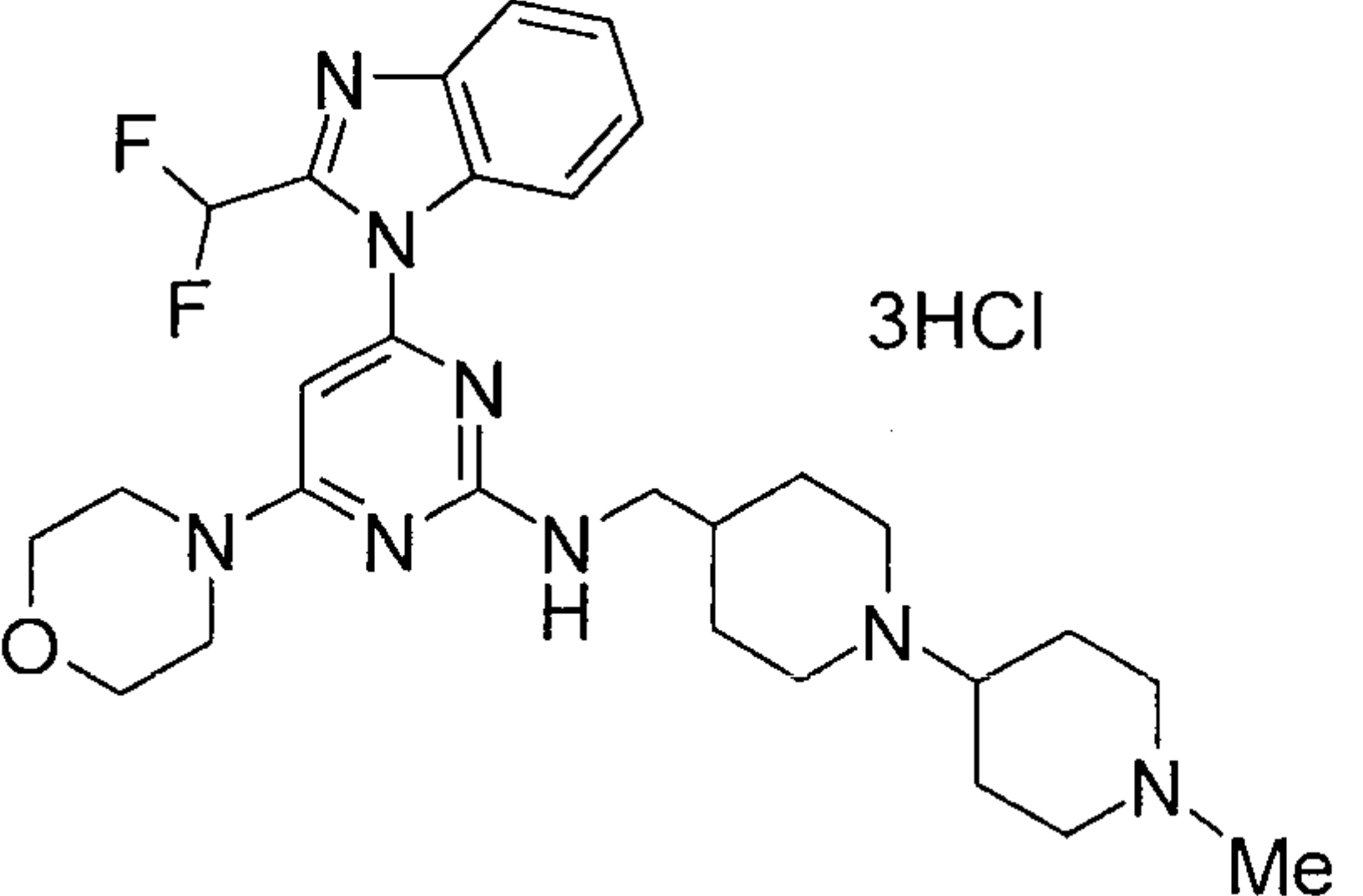
[0196]

[Table 40]

Ex	Str
23	
24	
25	
26	
27	

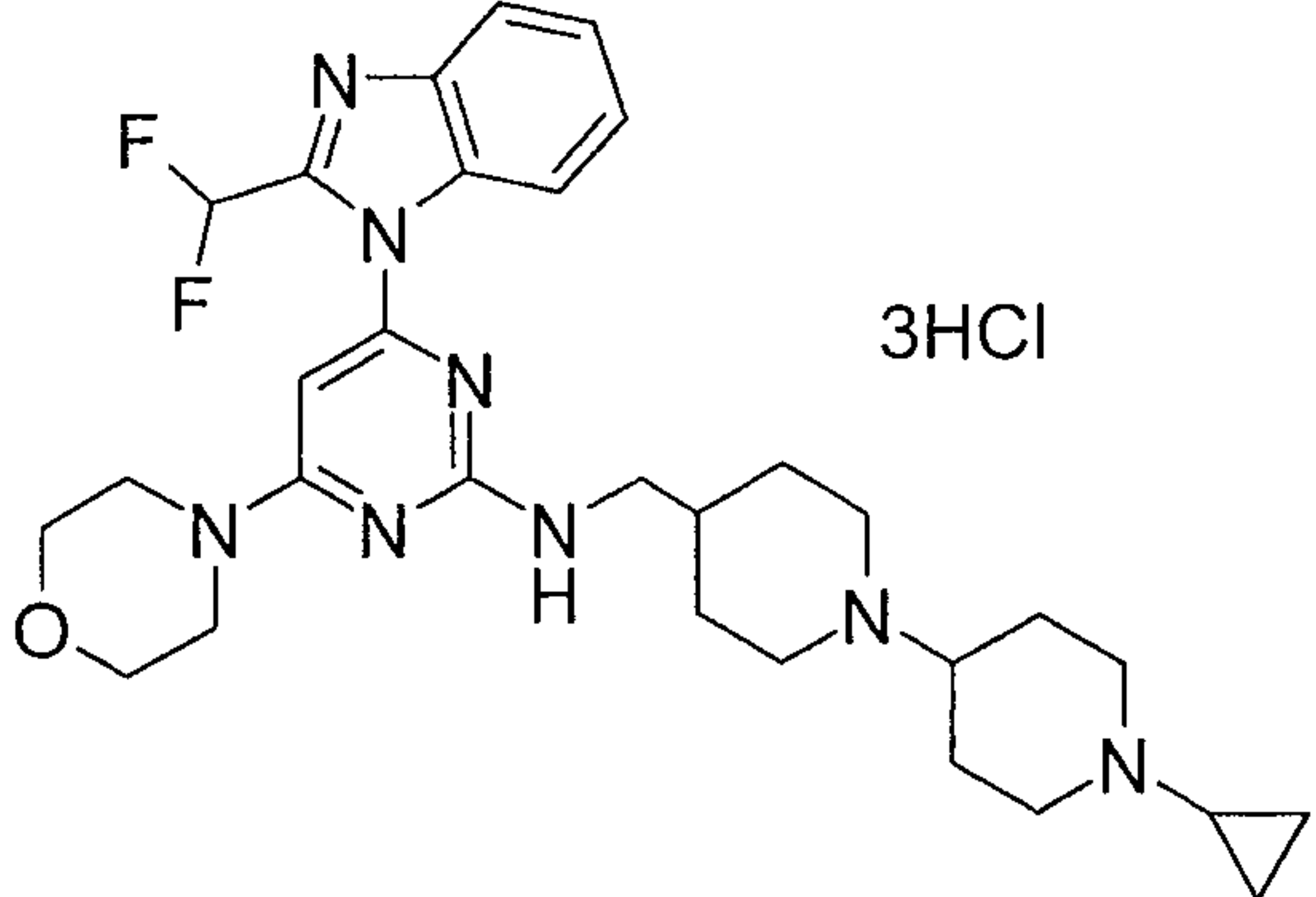
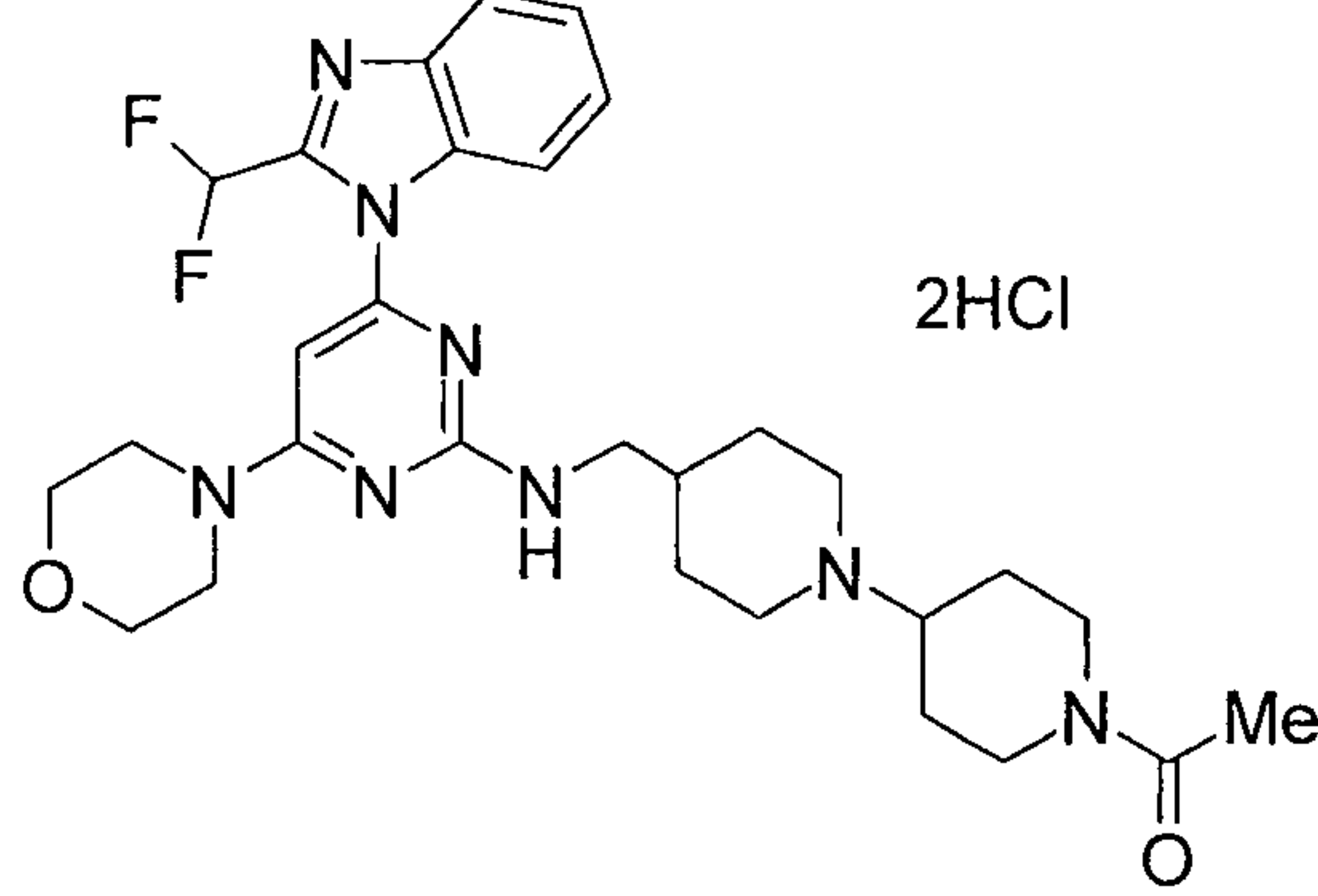
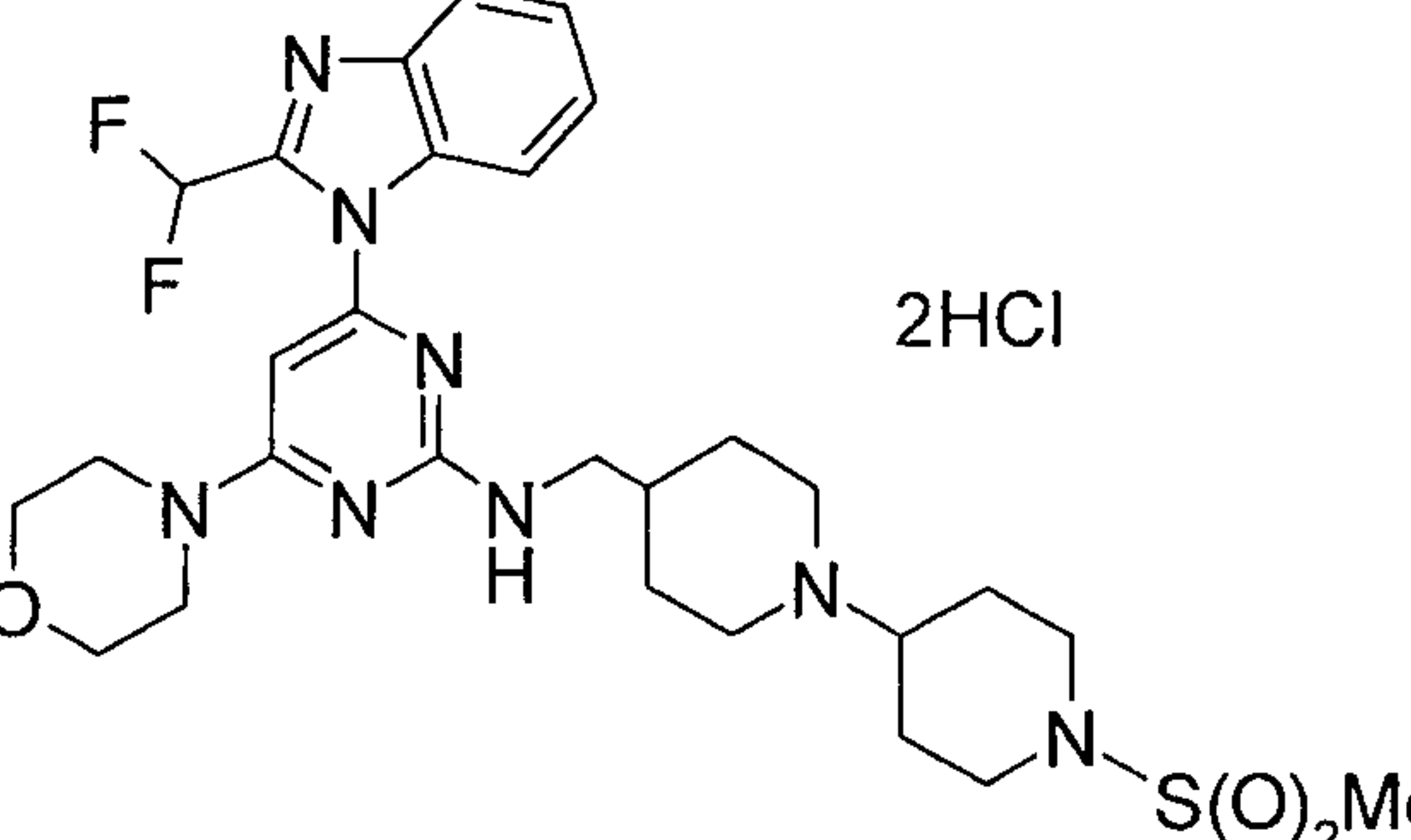
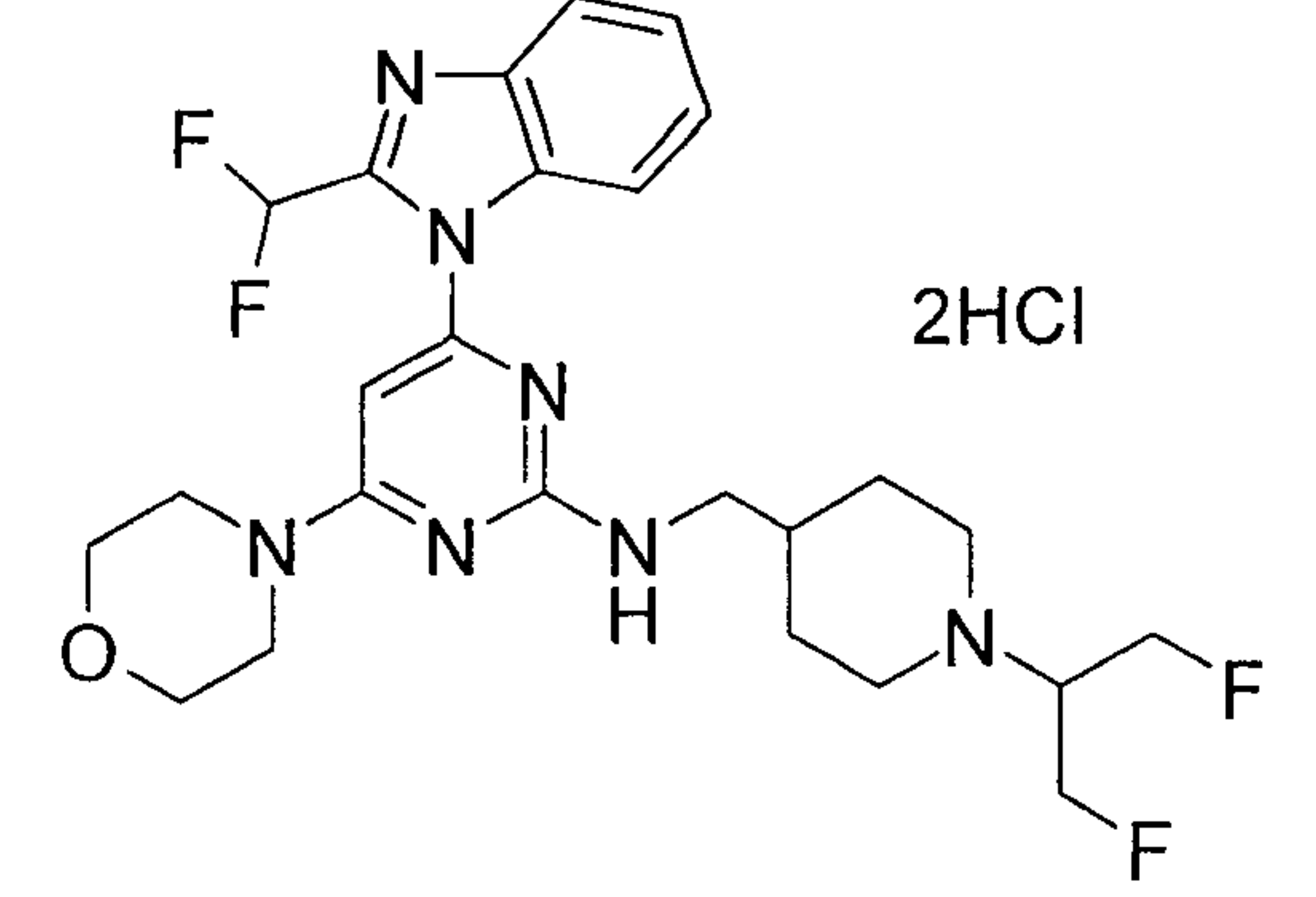
[0197]

[Table 41]

Ex	Str
28	
29	
30	
31	 3HCl

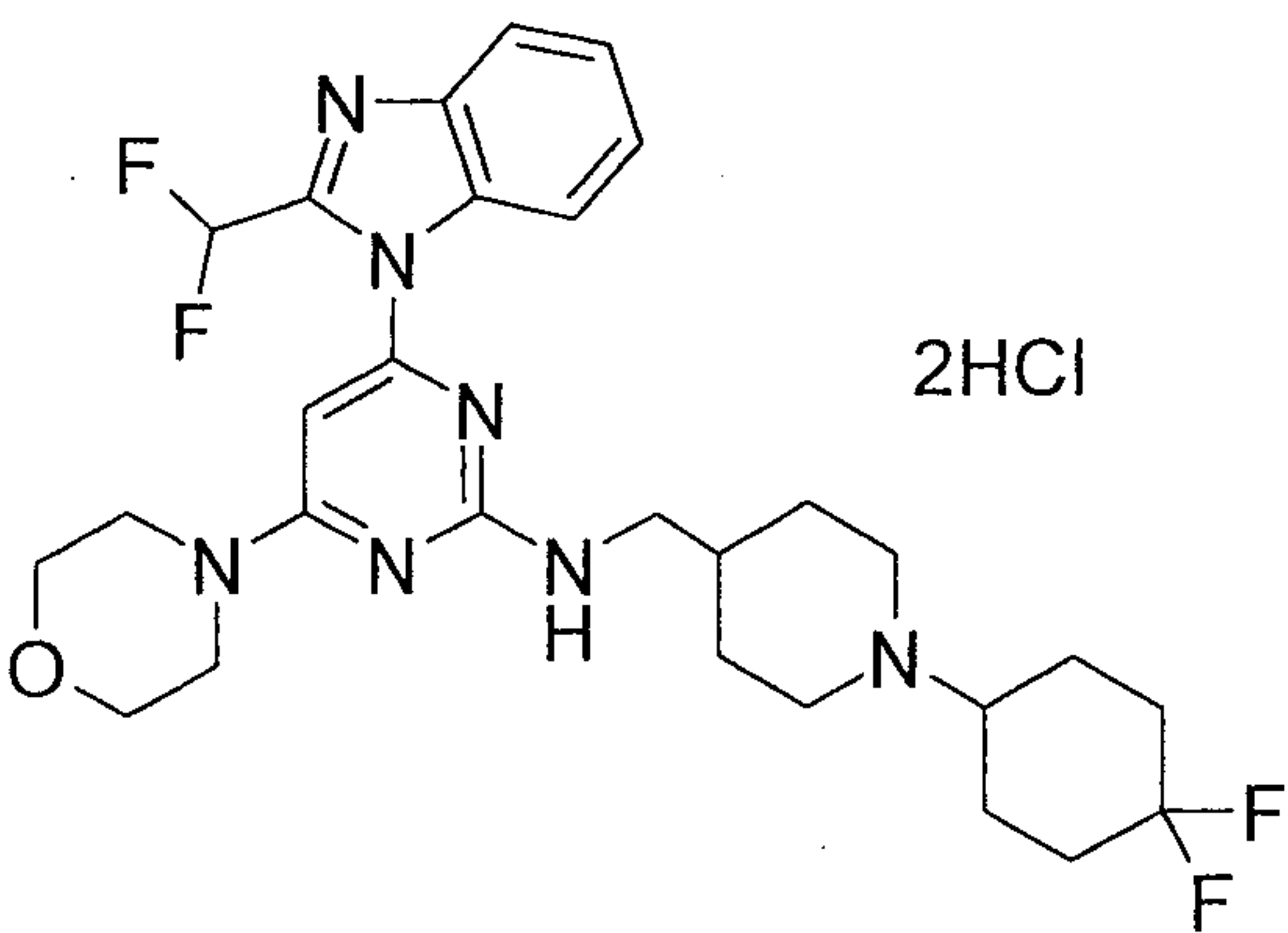
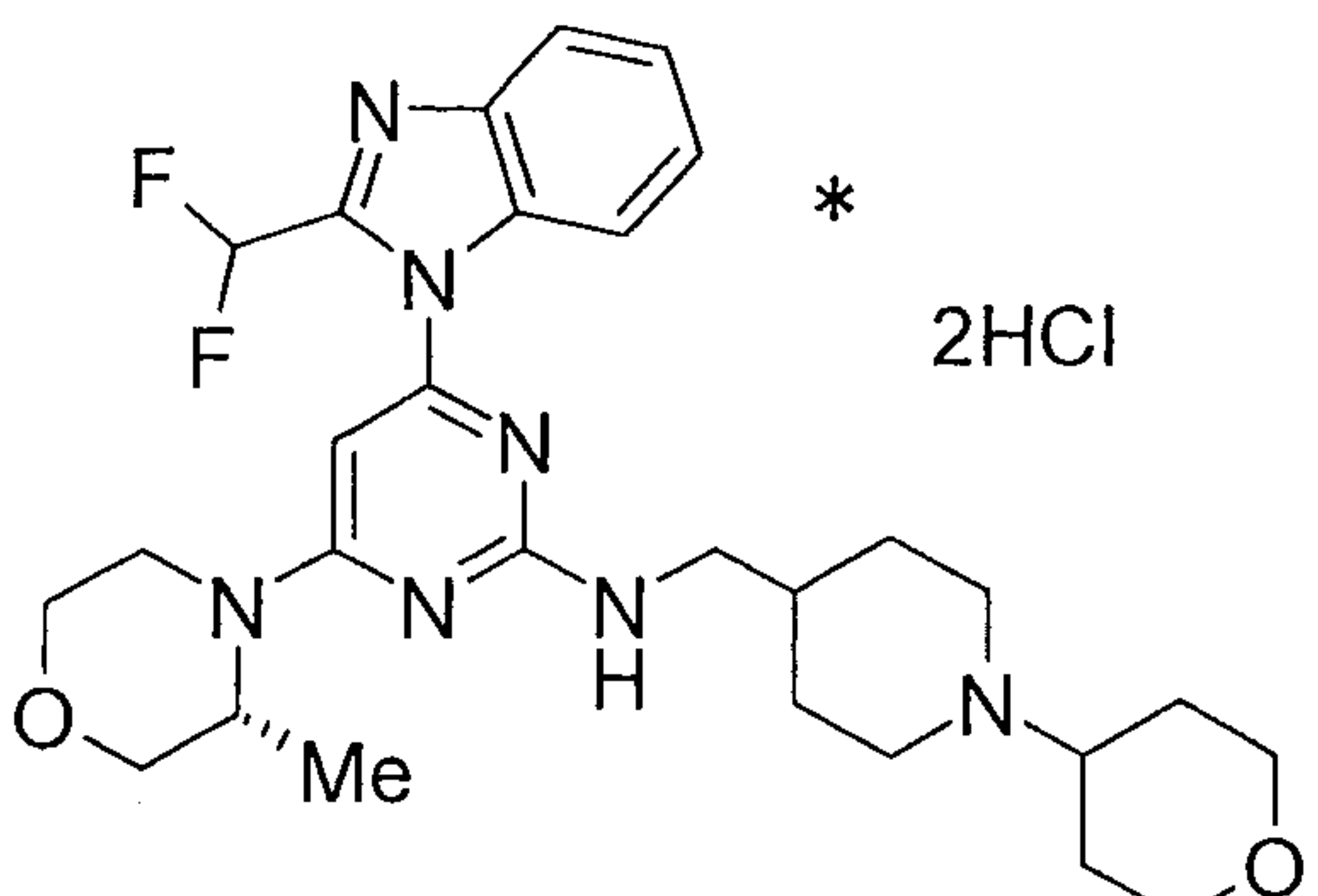
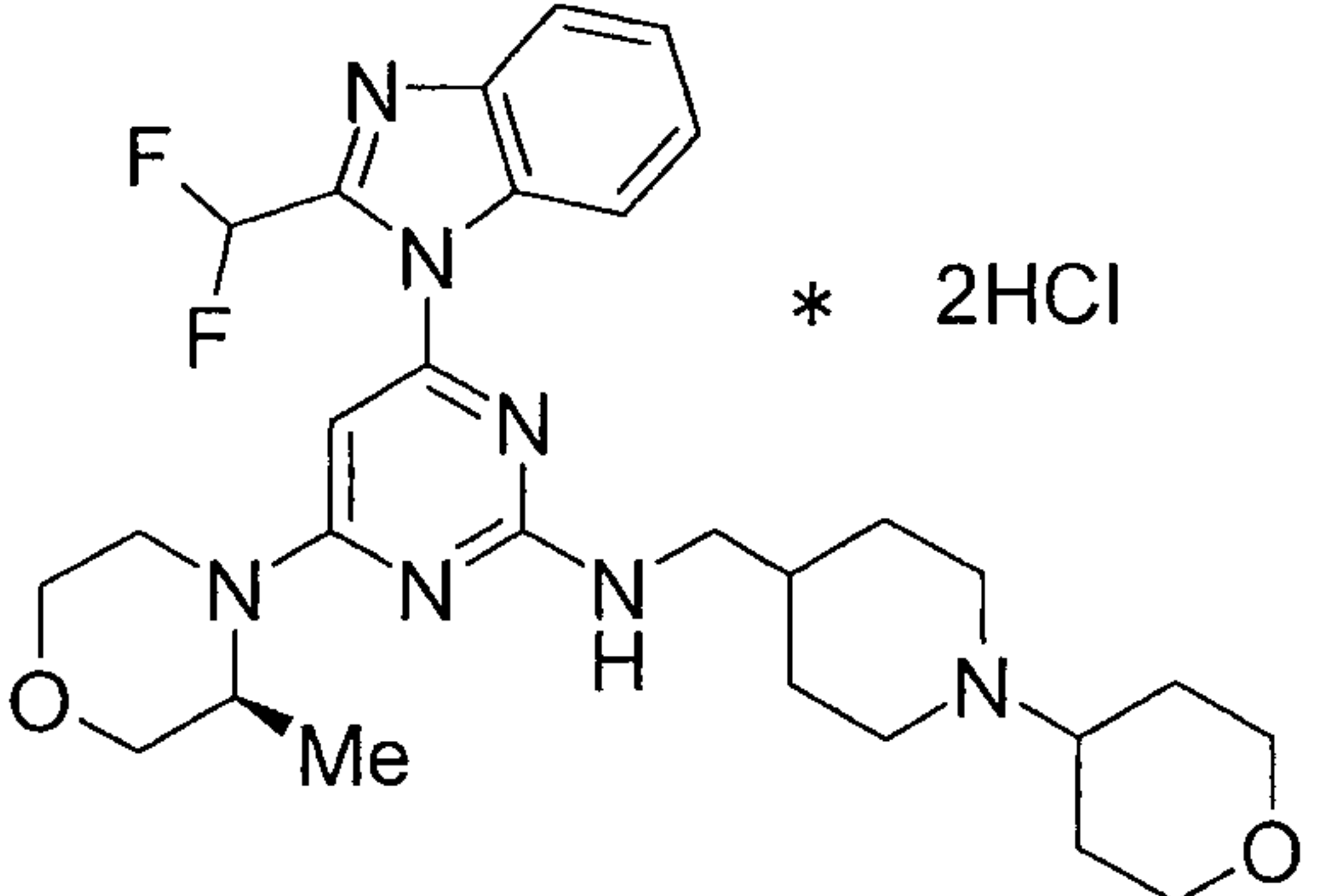
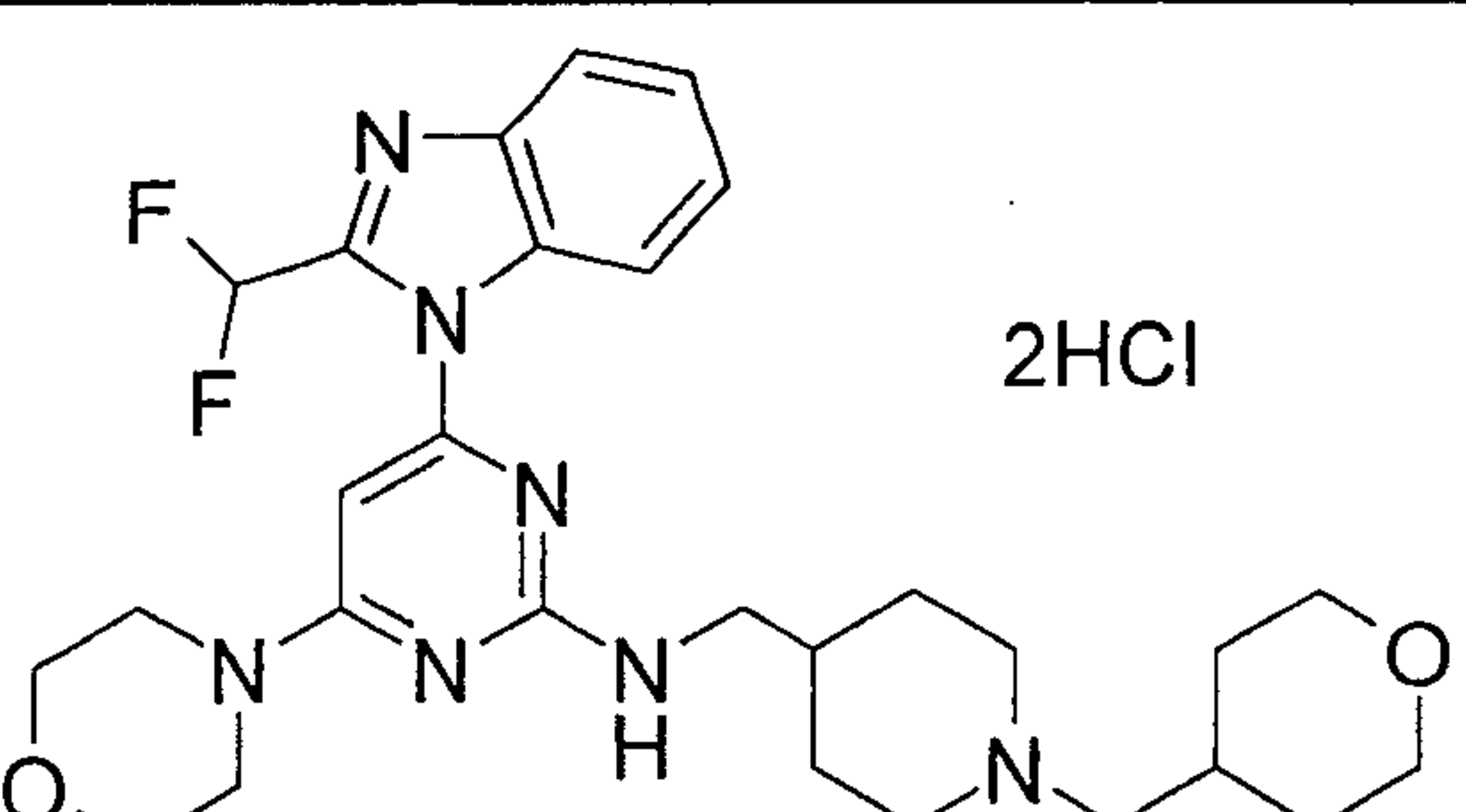
[0198]

[Table 42]

Ex	Str
32	
33	
34	
35	

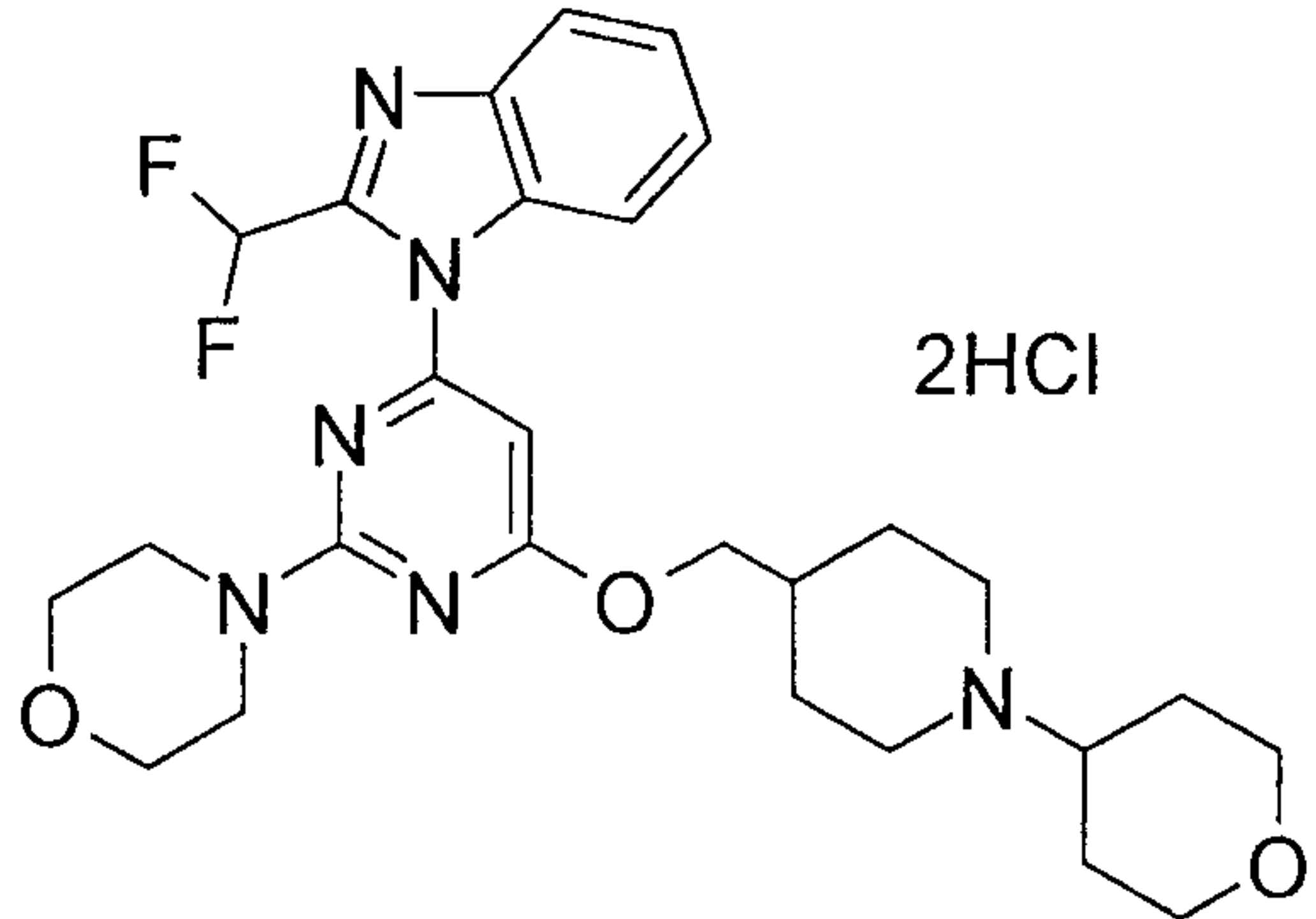
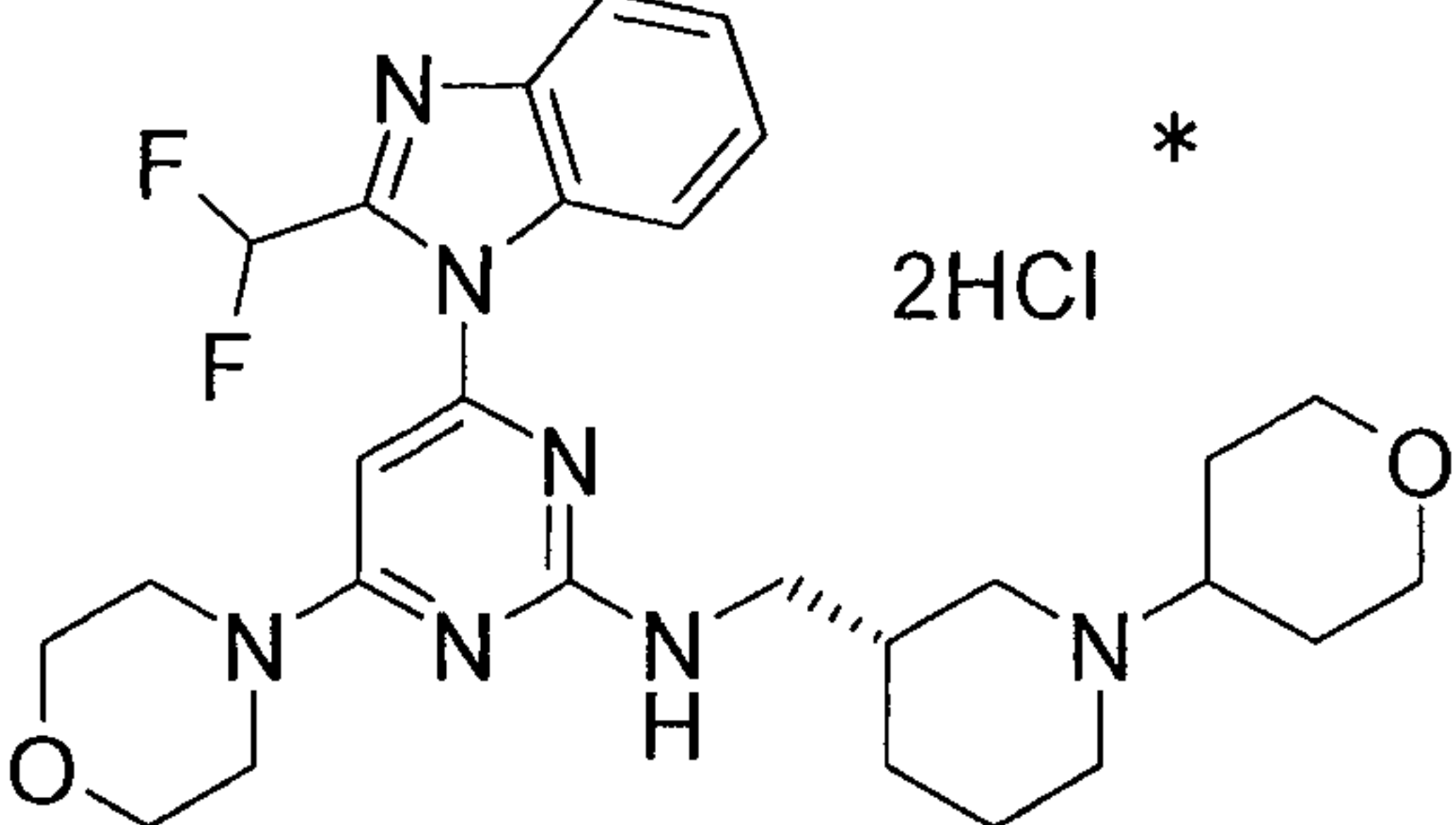
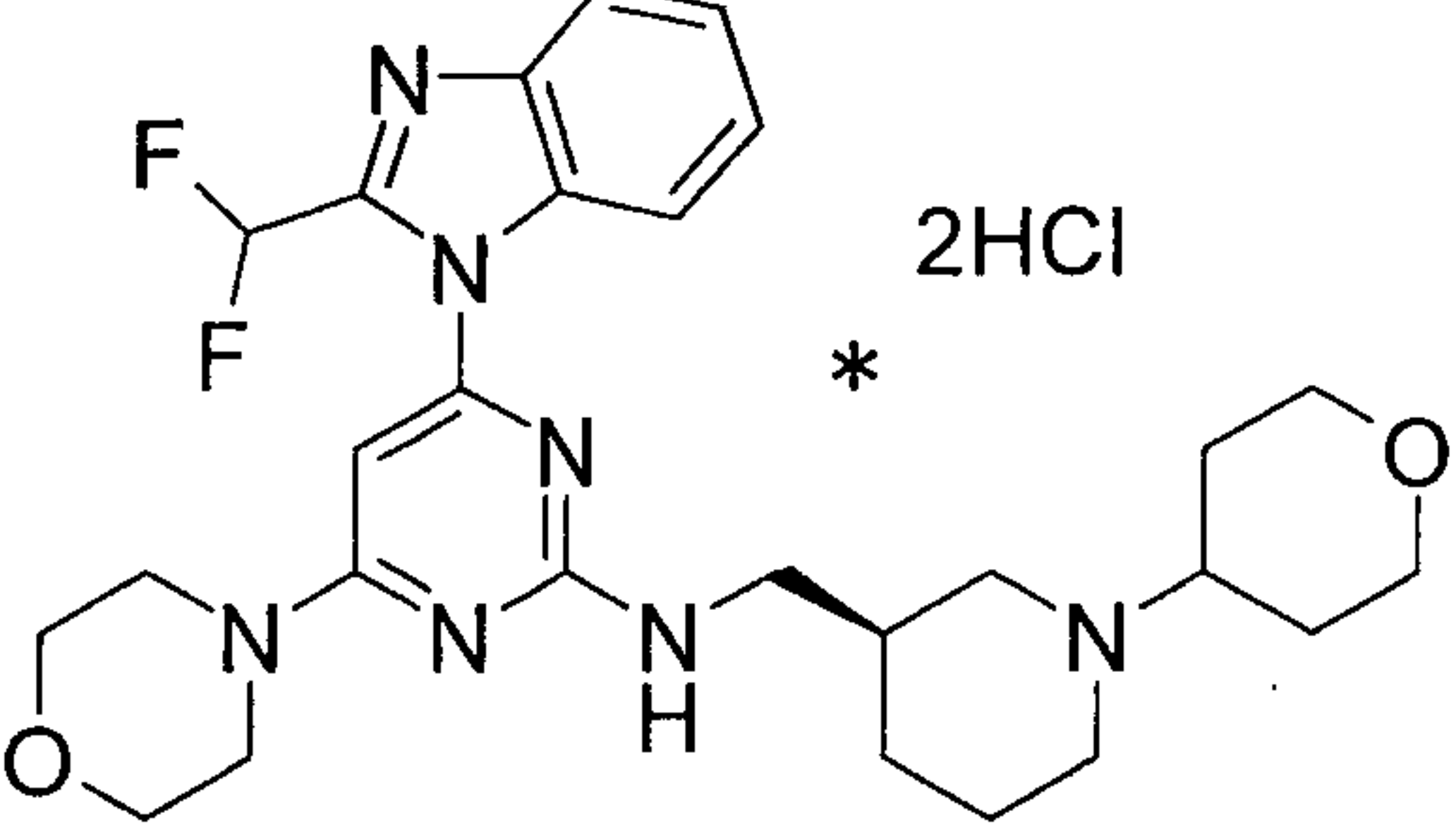
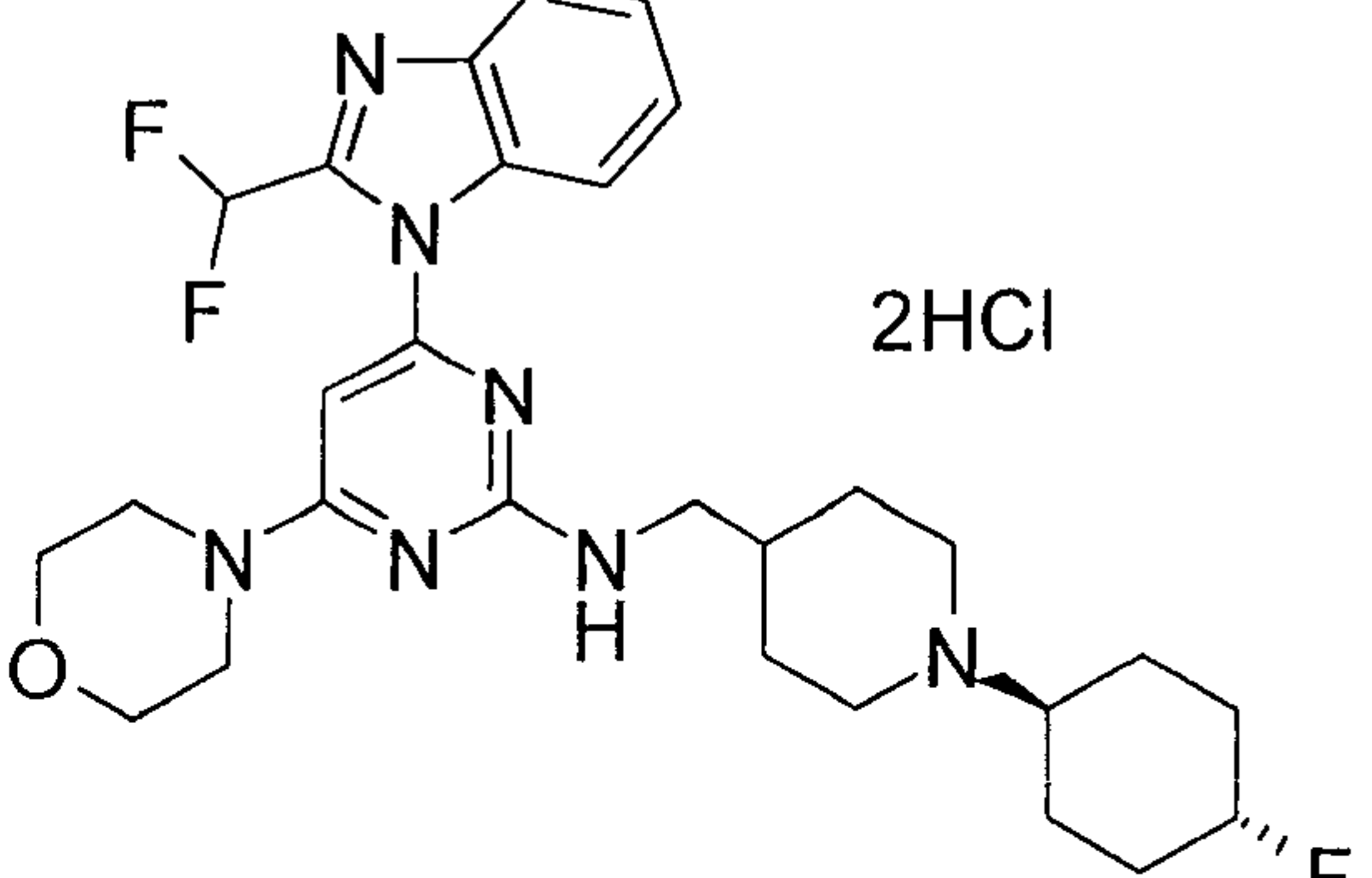
[0199]

[Table 43]

Ex	Str
36	
37	
38	
39	

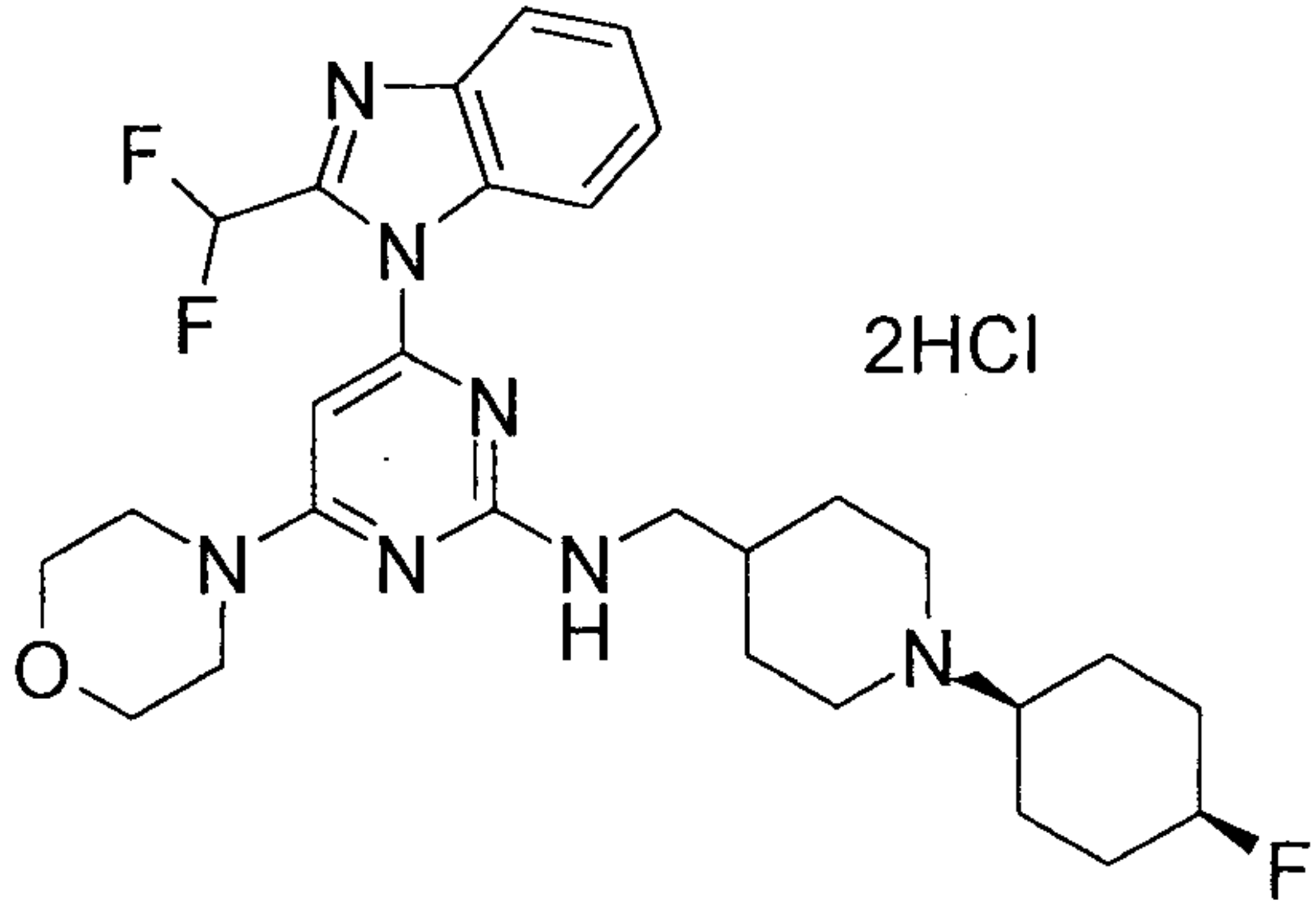
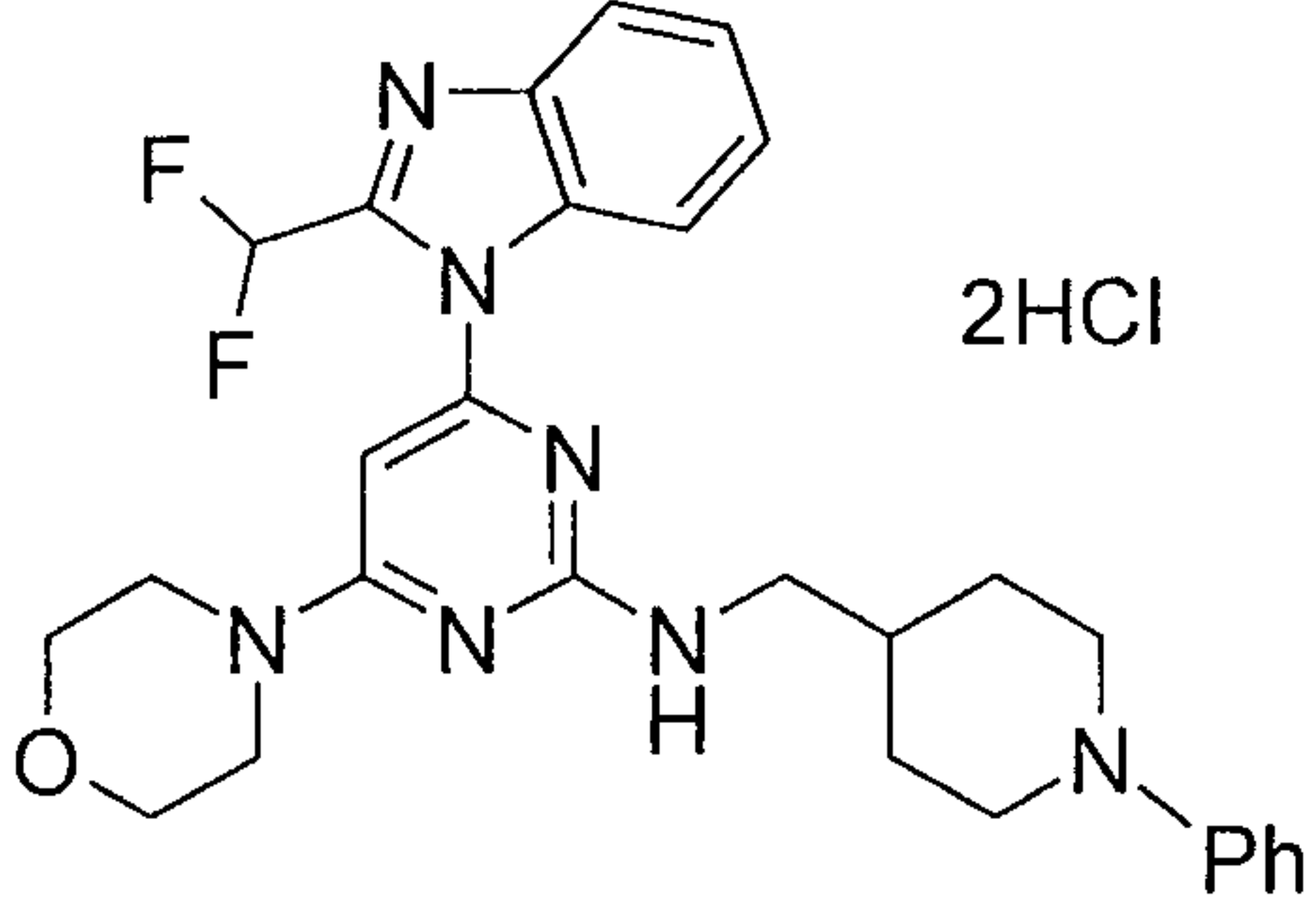
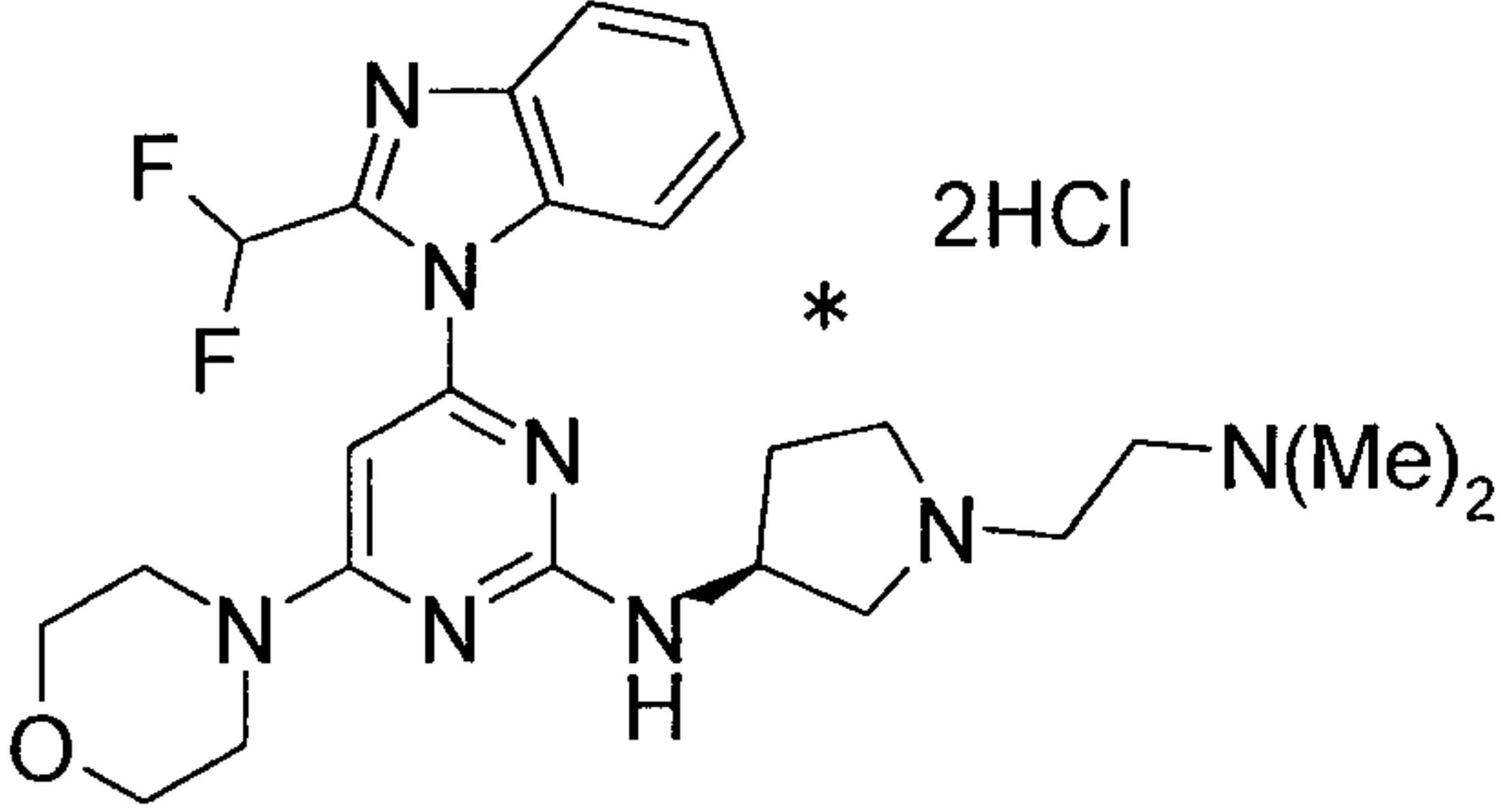
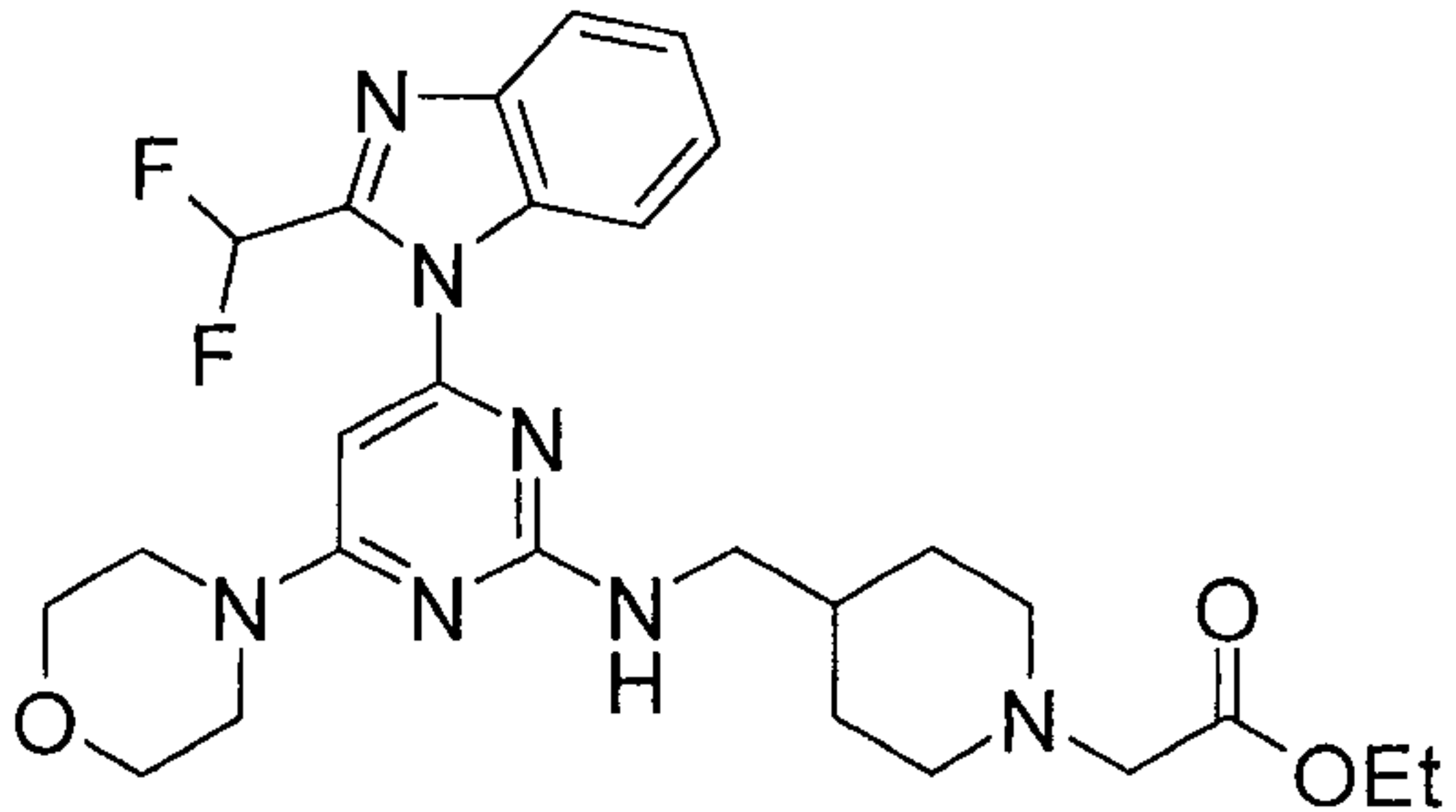
[0200]

[Table 44]

Ex	Str
40	
41	
42	
43-1	

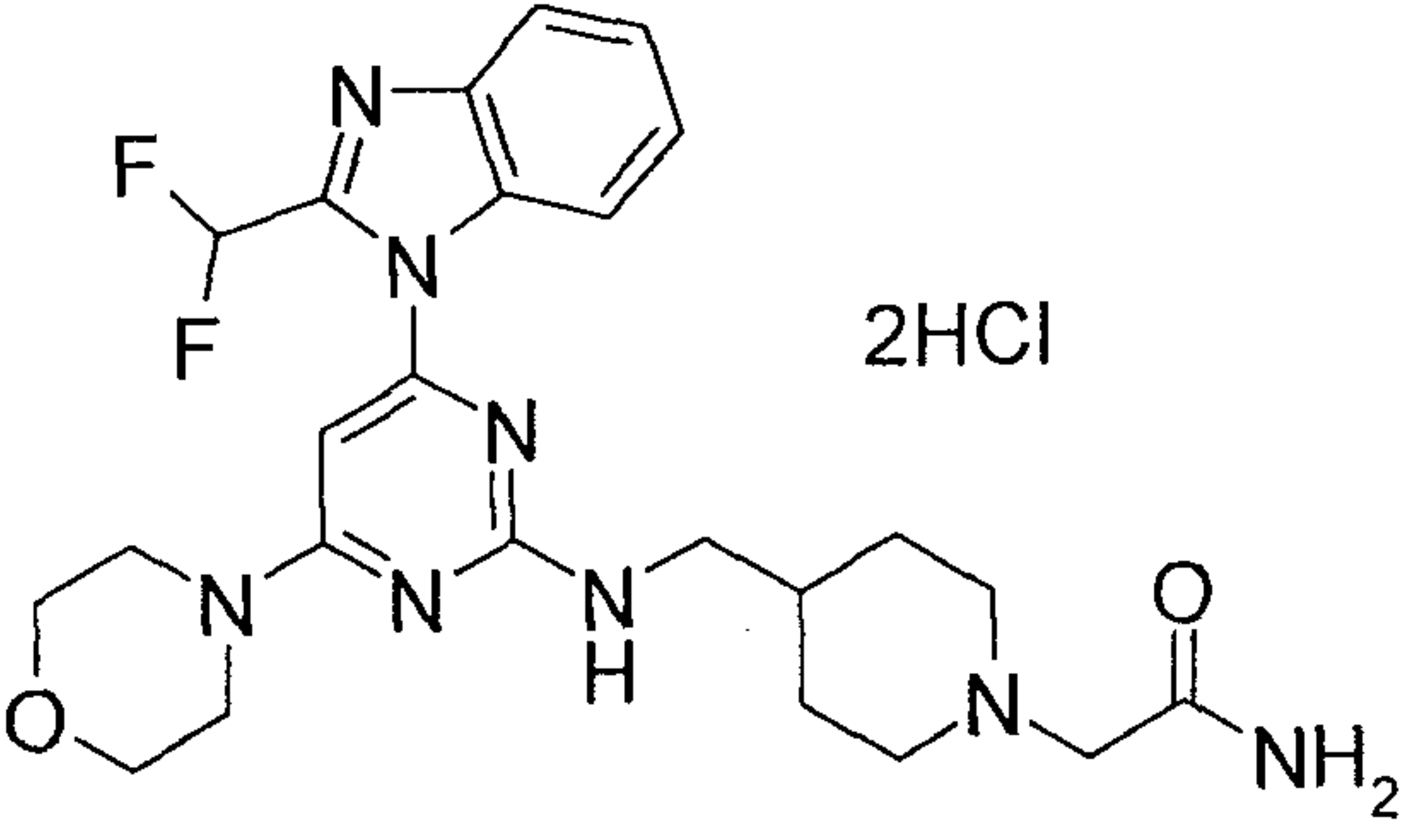
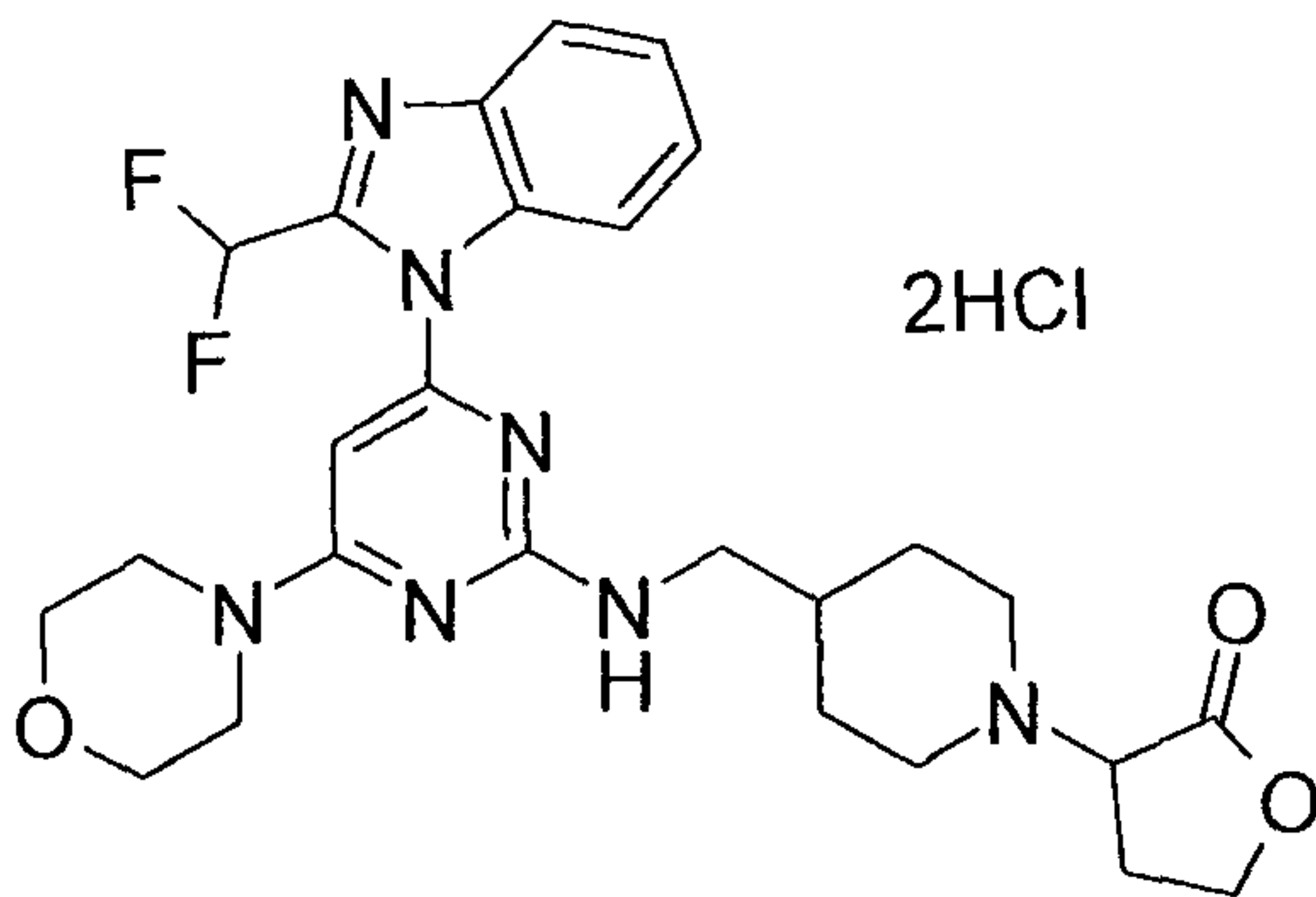
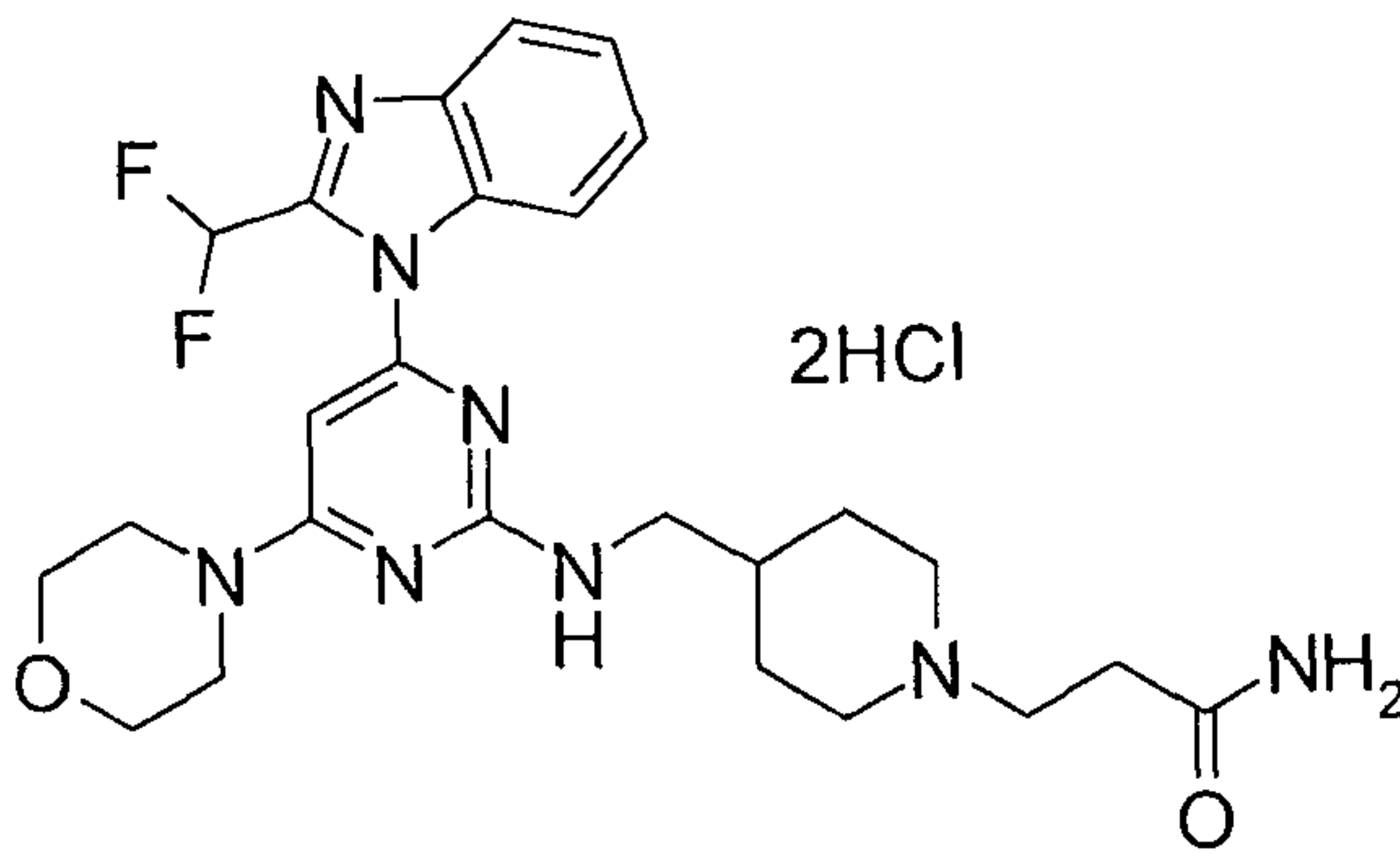
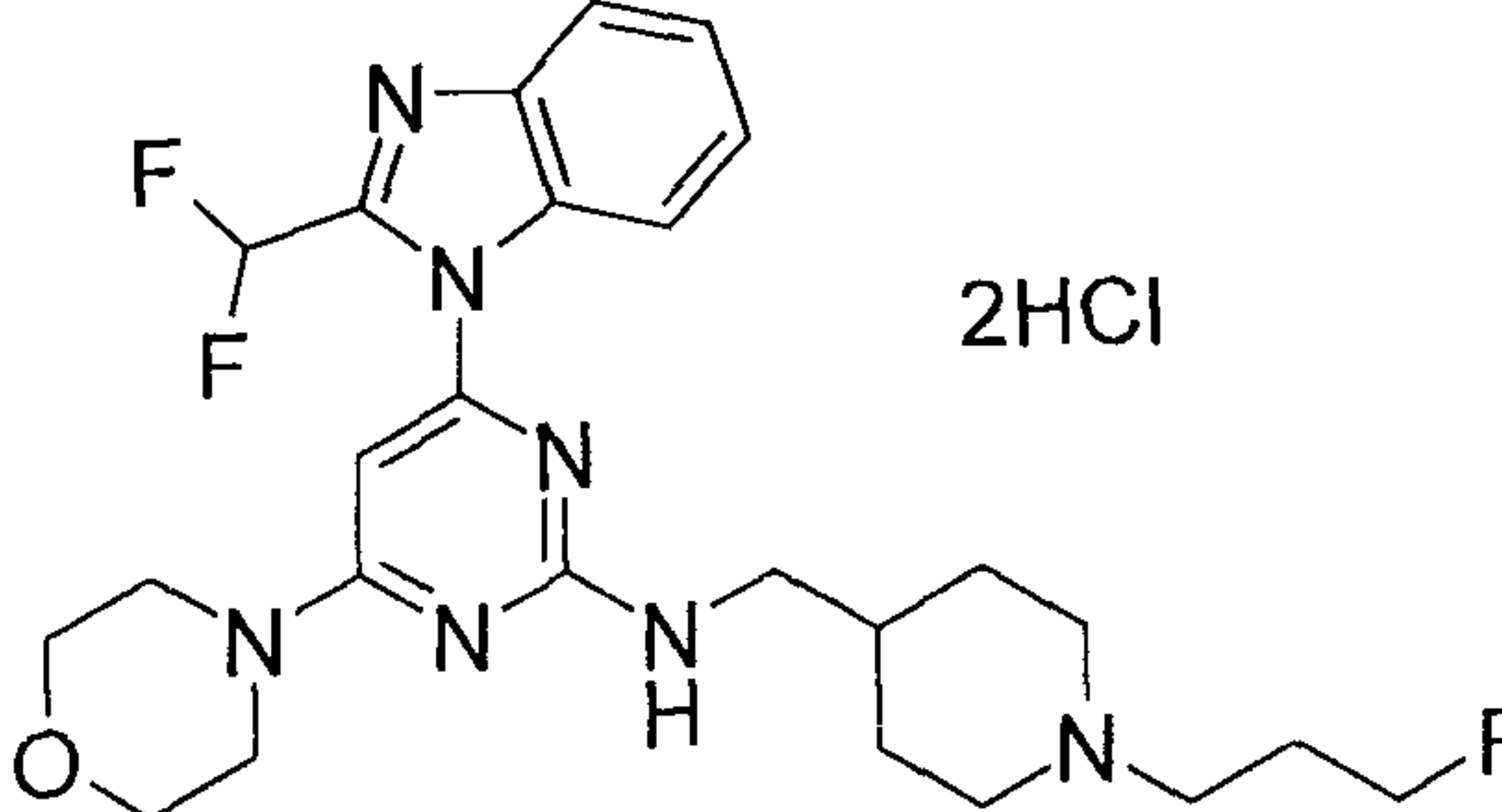
[0201]

[Table 45]

Ex	Str
43- 2	
44	
45	
46	

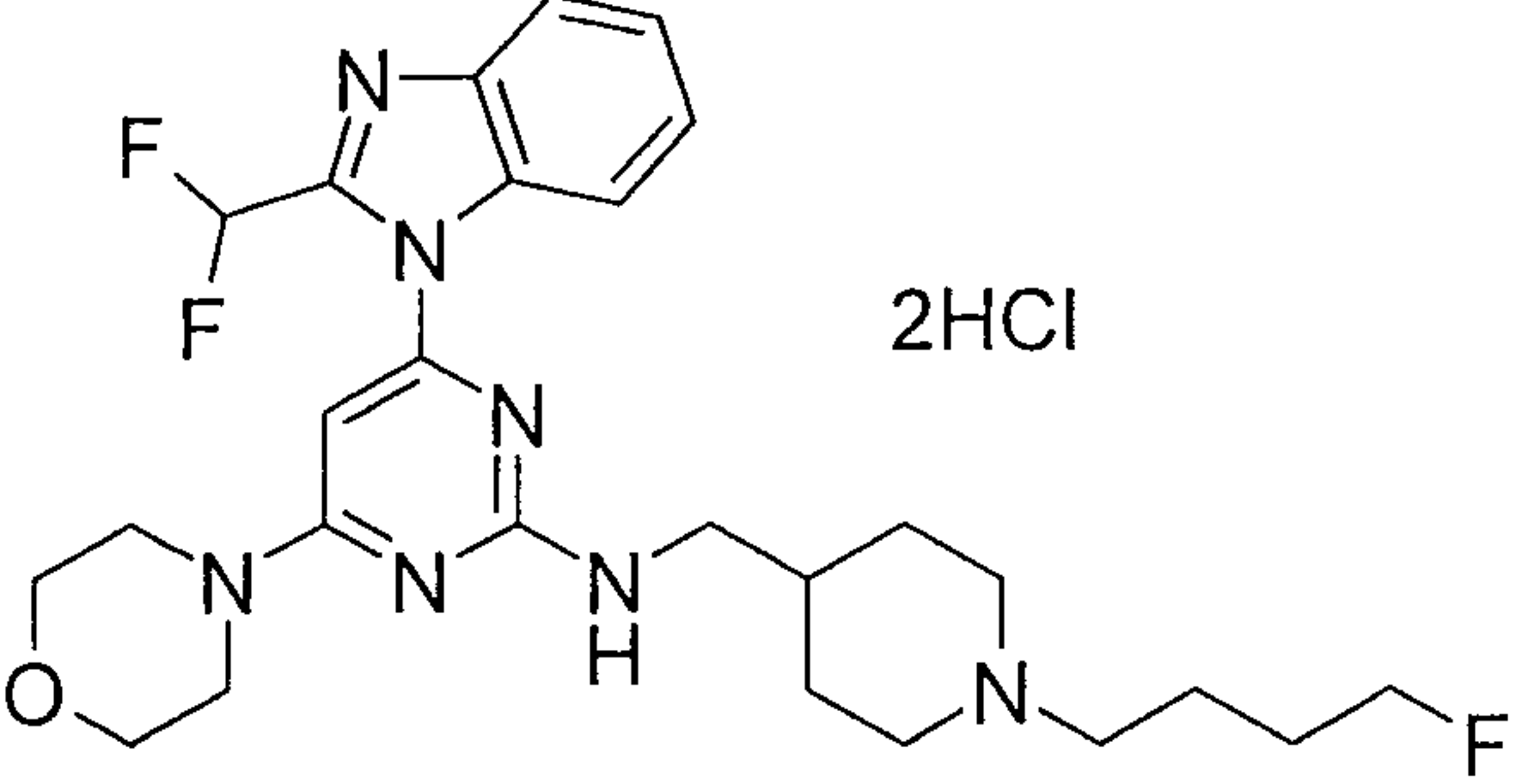
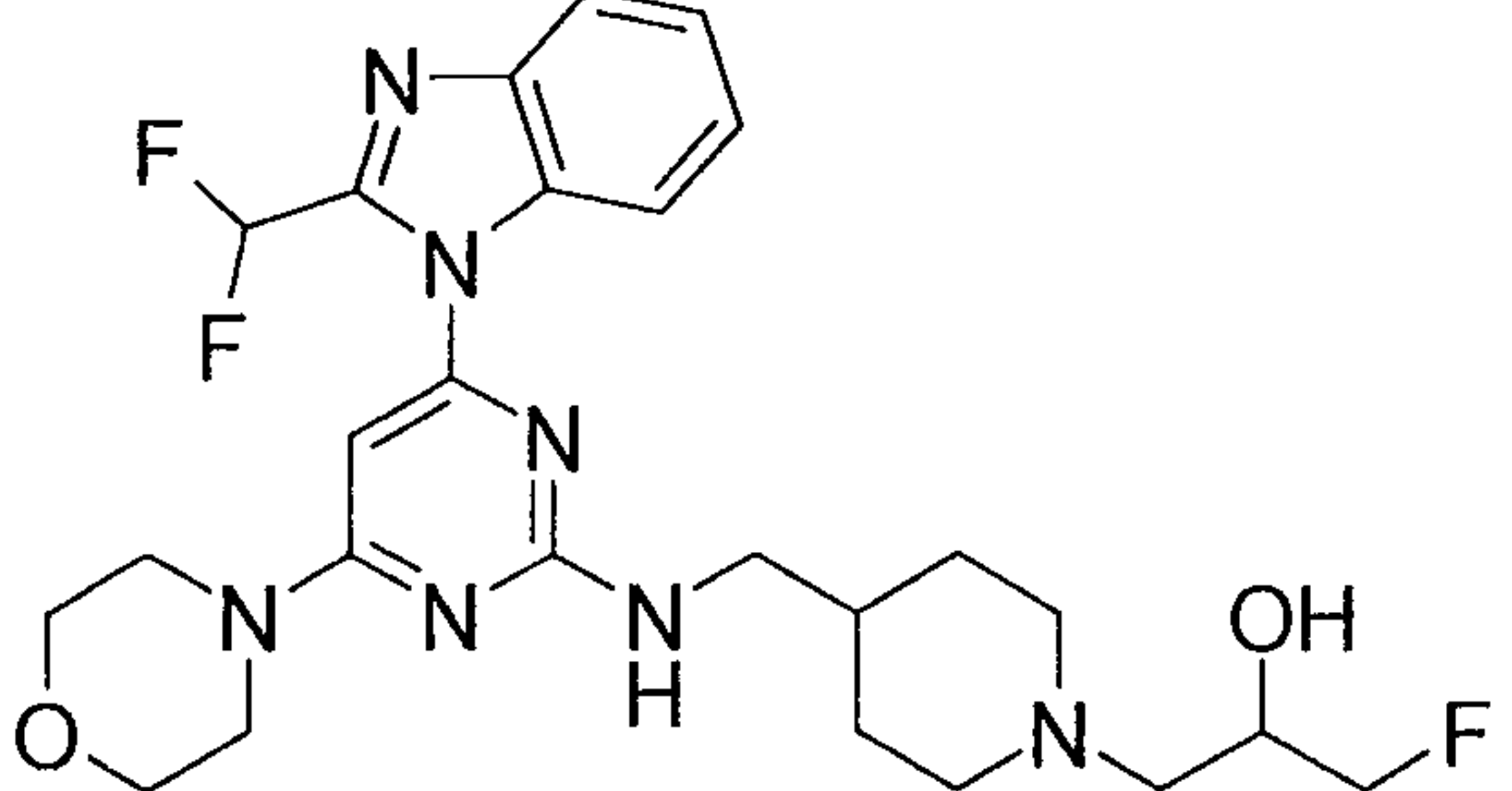
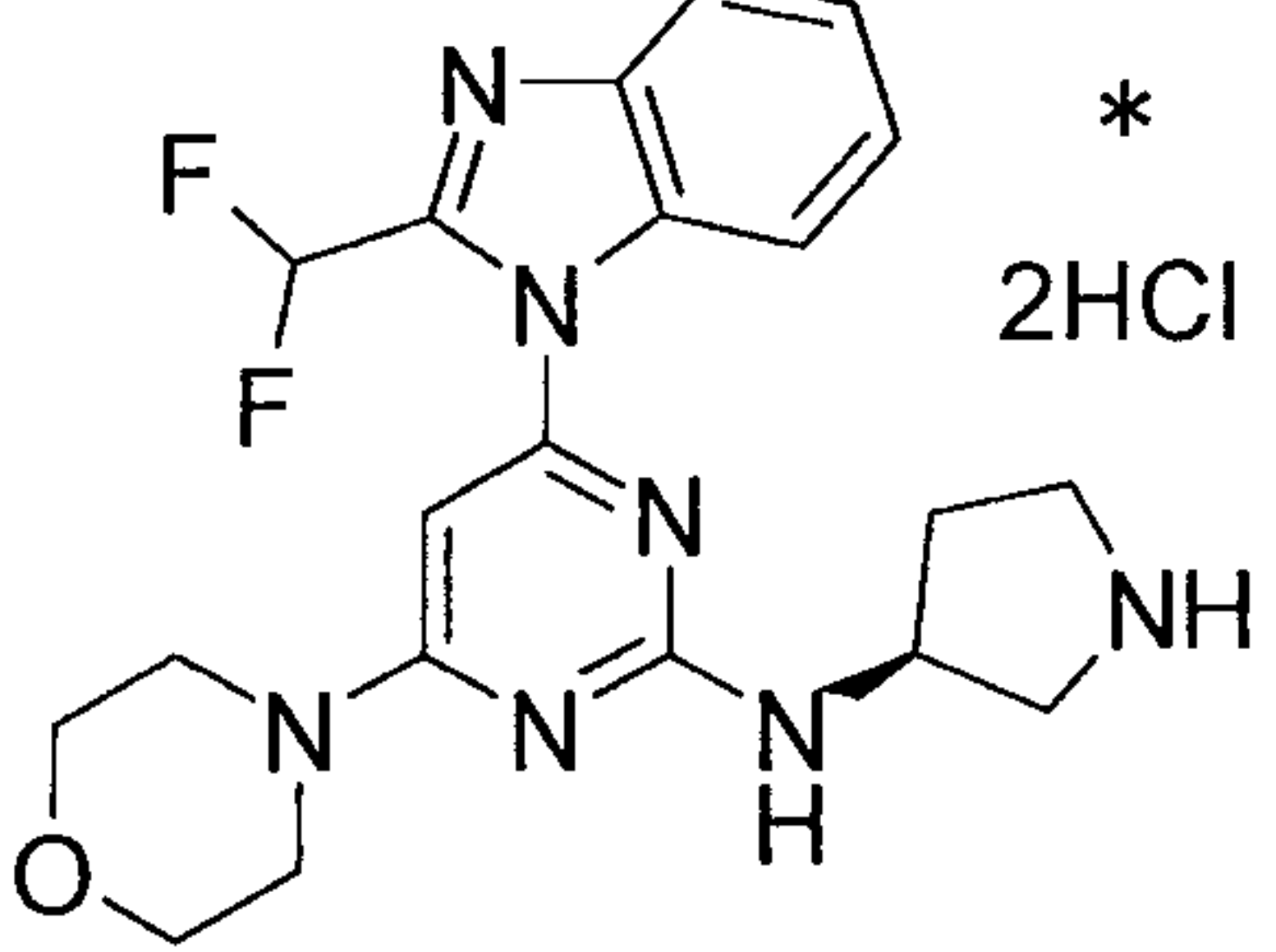
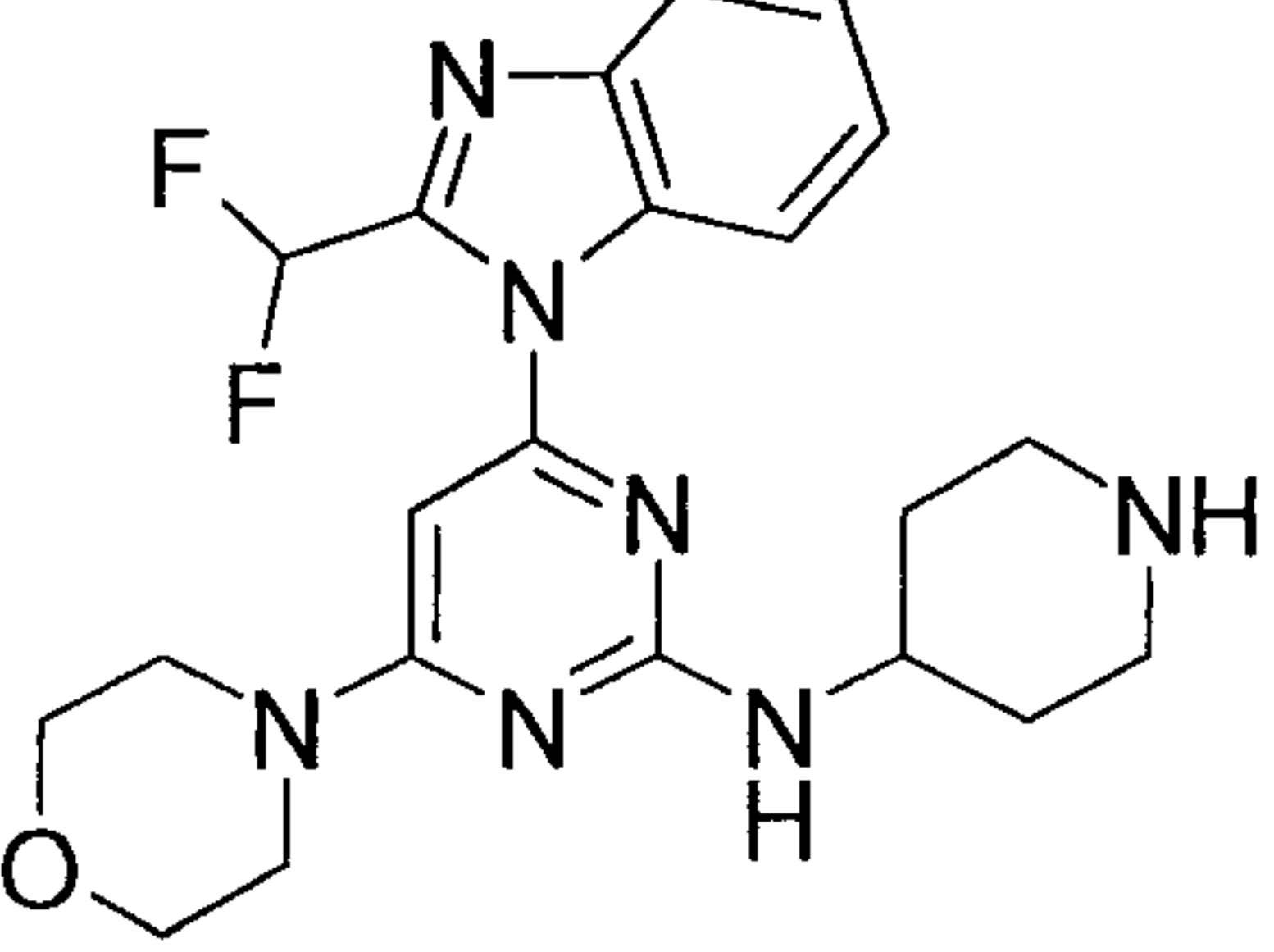
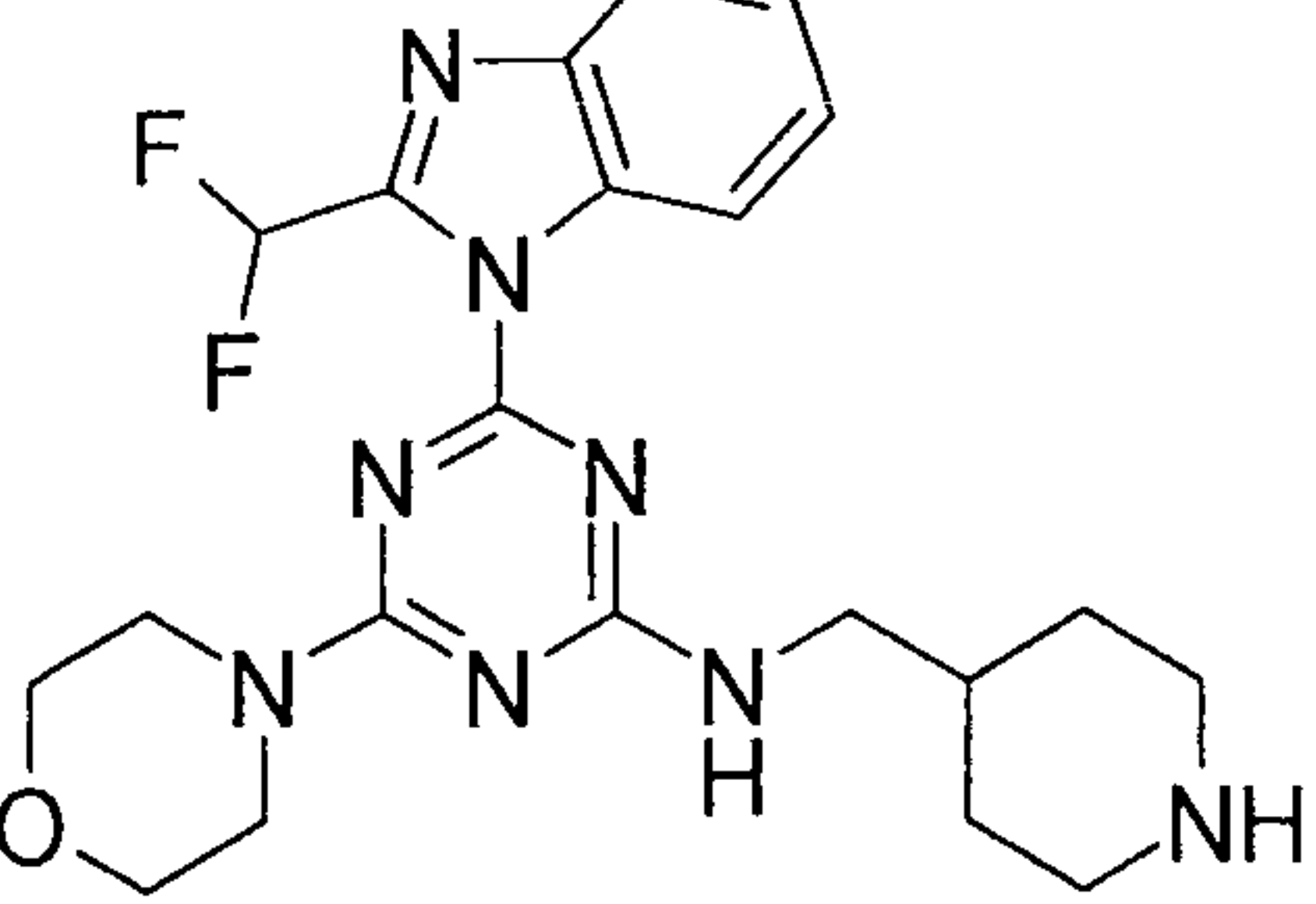
[0202]

[Table 46]

Ex	Str
47	
48	
49	
50	

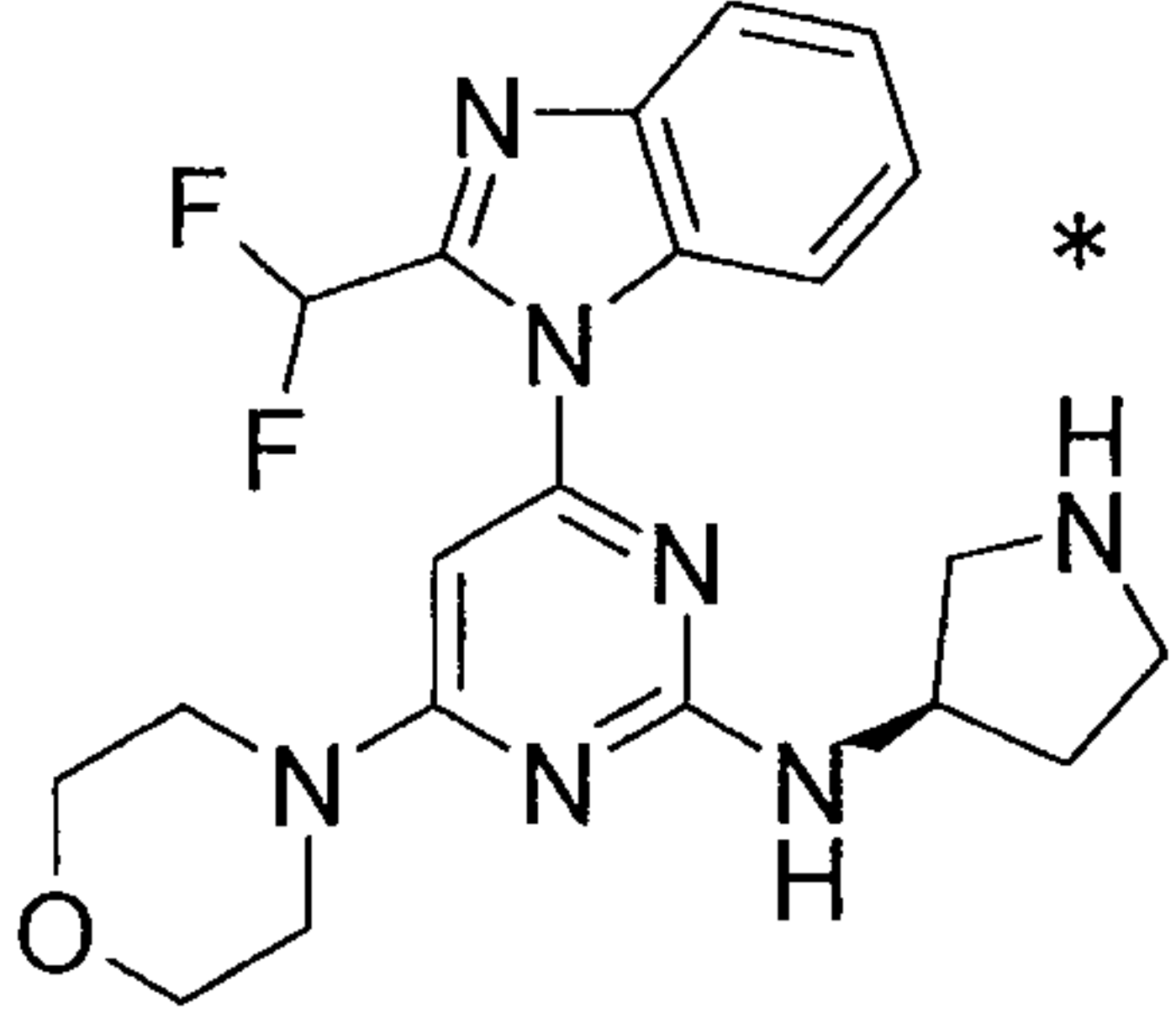
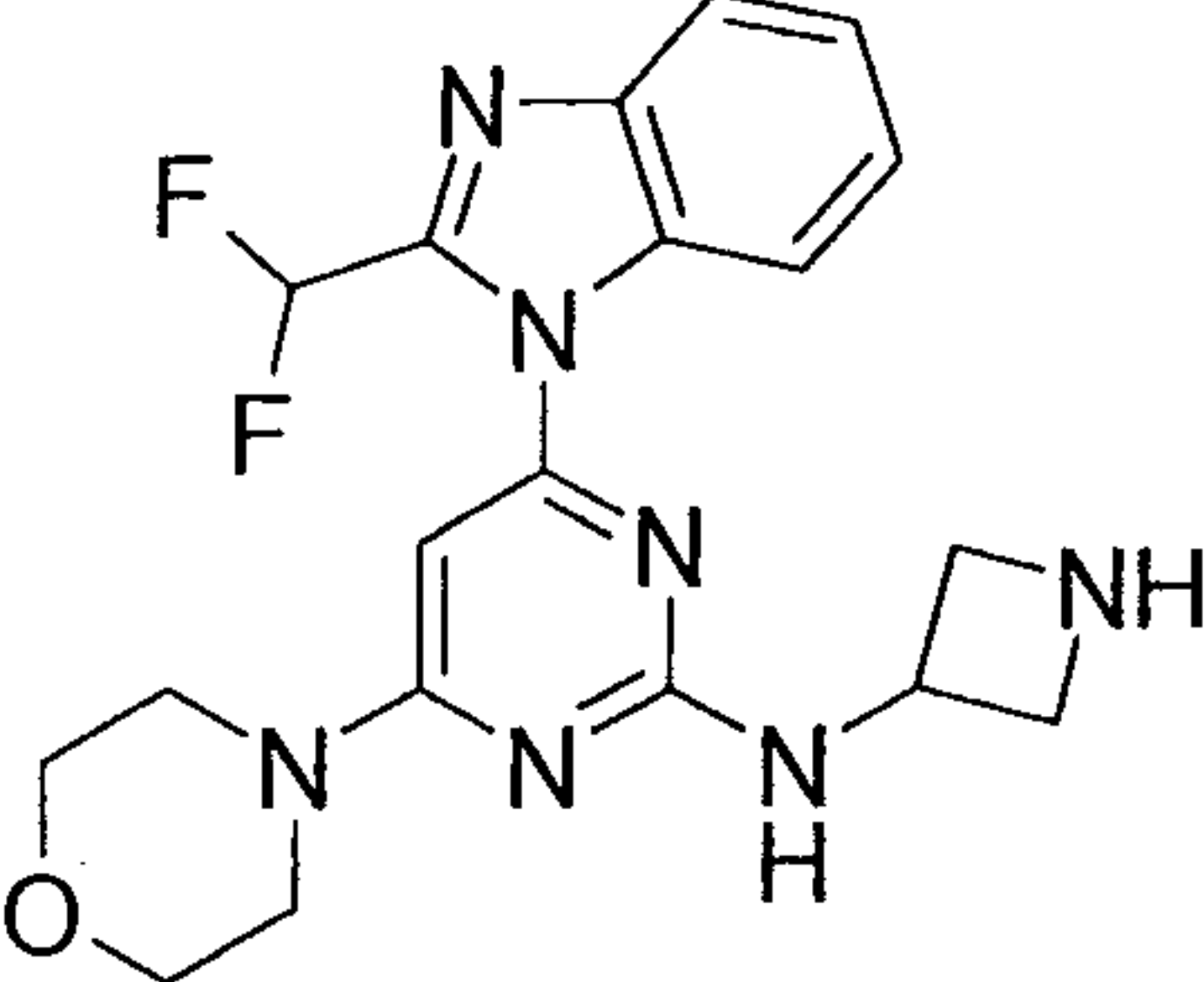
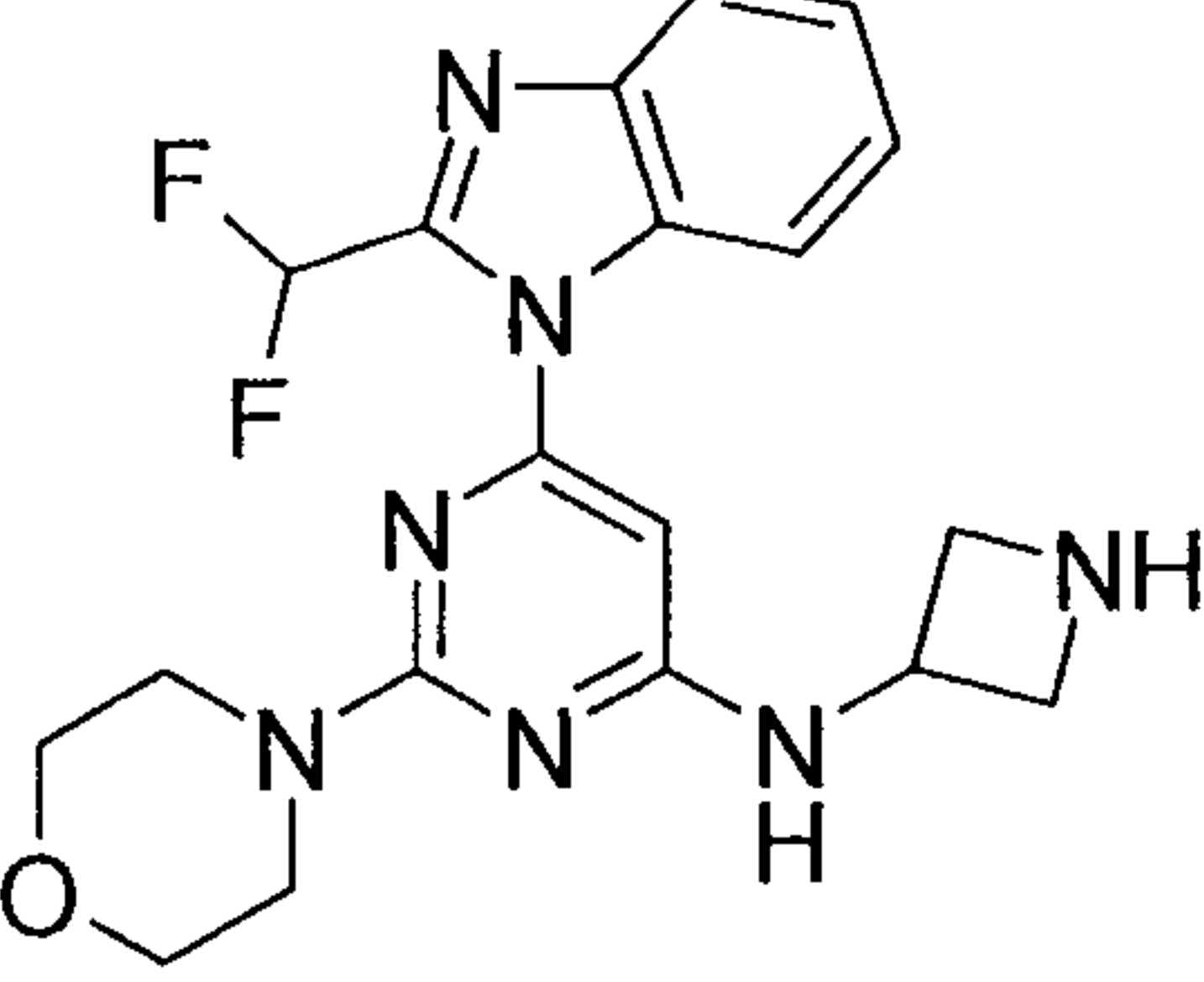
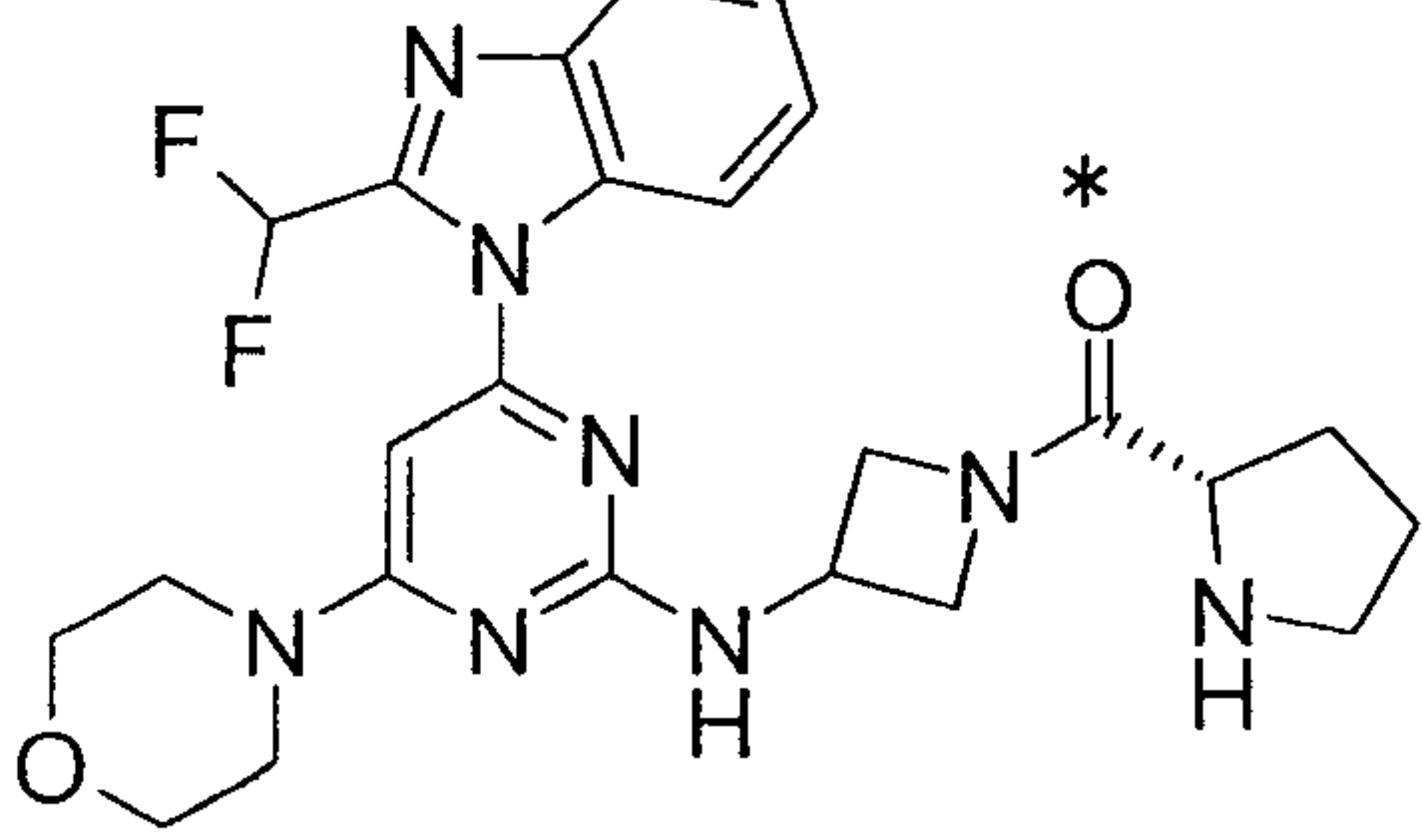
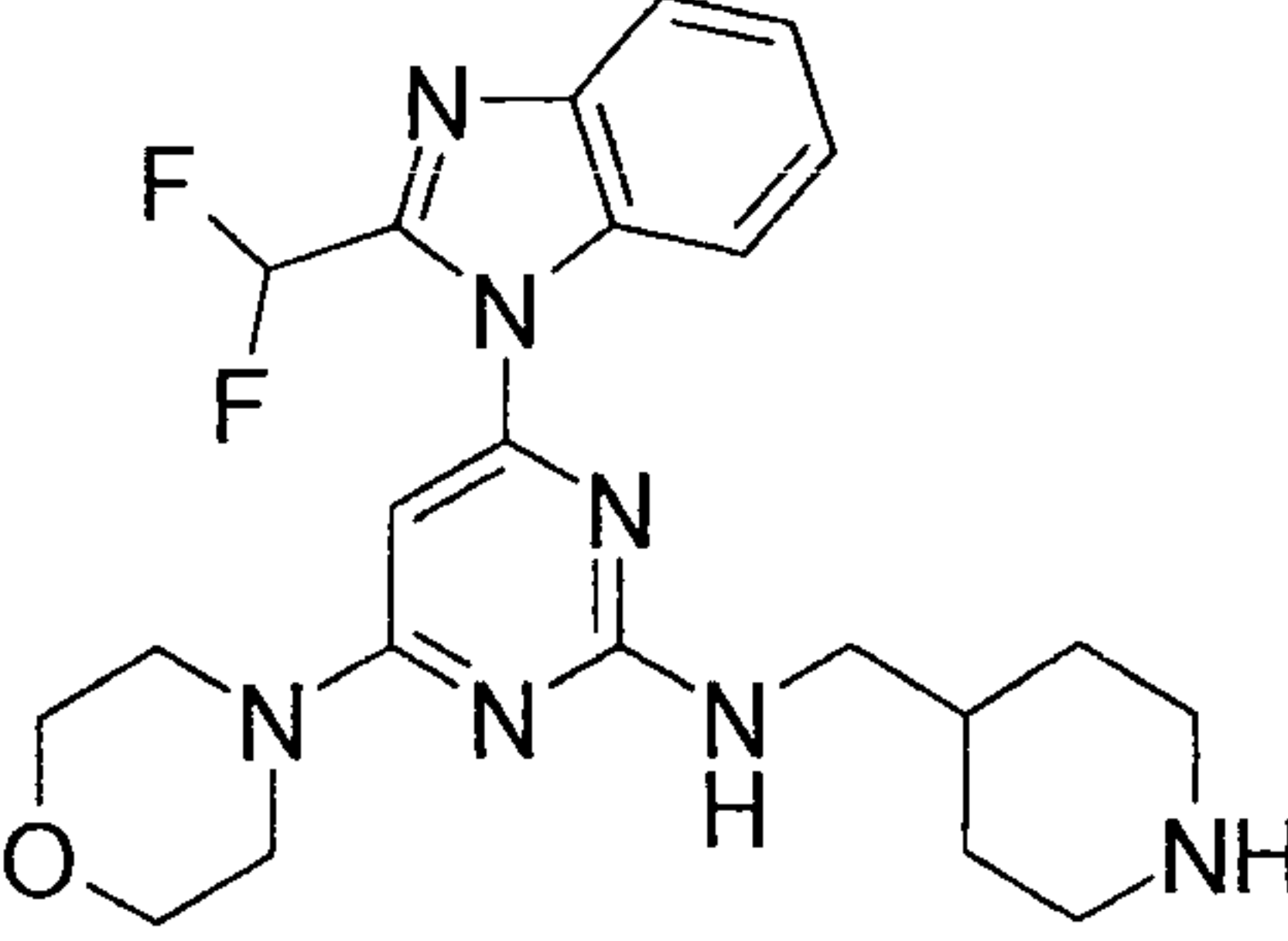
[0203]

[Table 47]

Ex	Str
51	
52	
53	
54	
55	

[0204]

[Table 48]

Ex	Str
56	
57	
58	
59	
60	

[0205]

[Table 49]

Ex	Str
61	
62	
63	
64	
65	

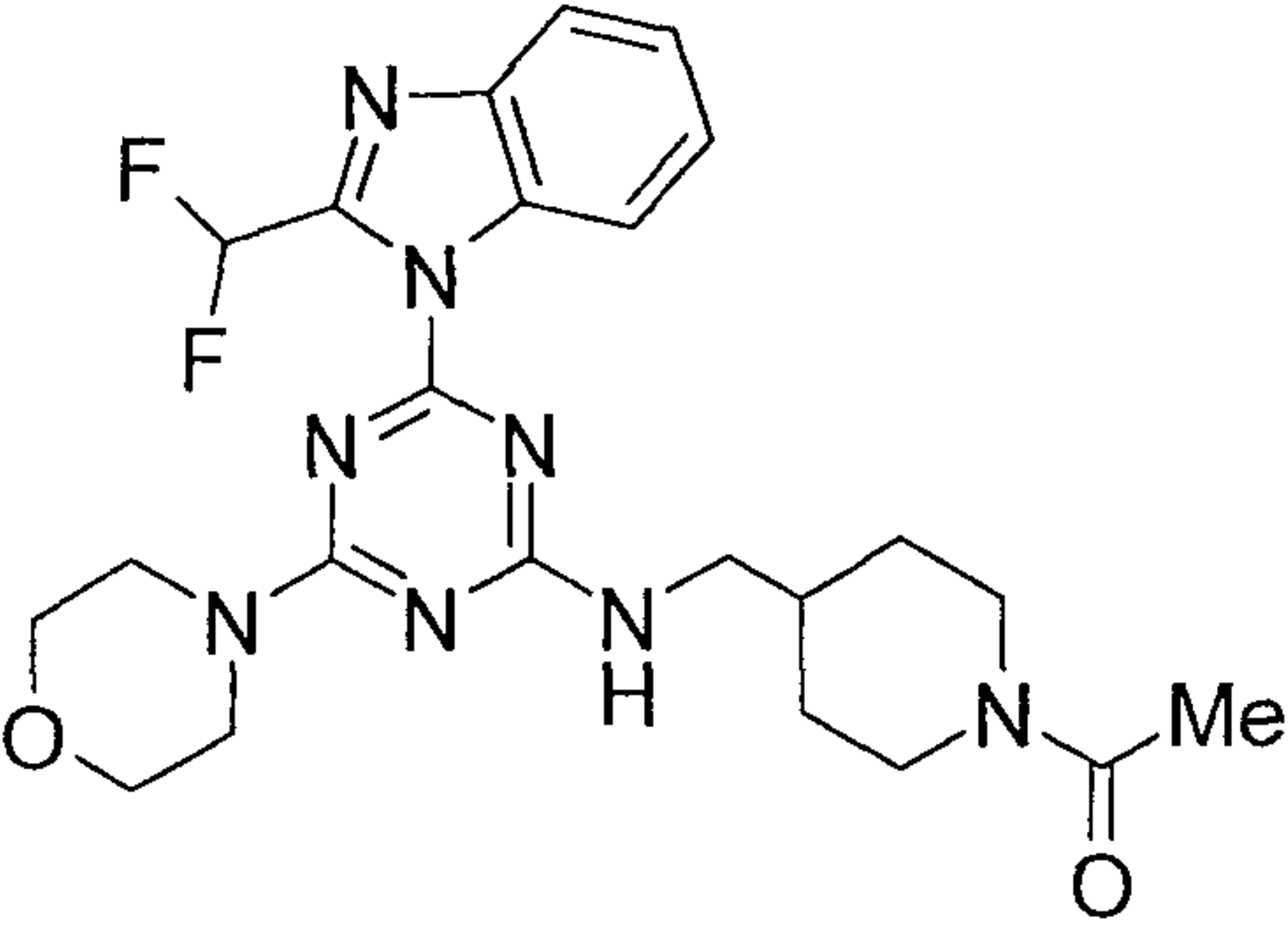
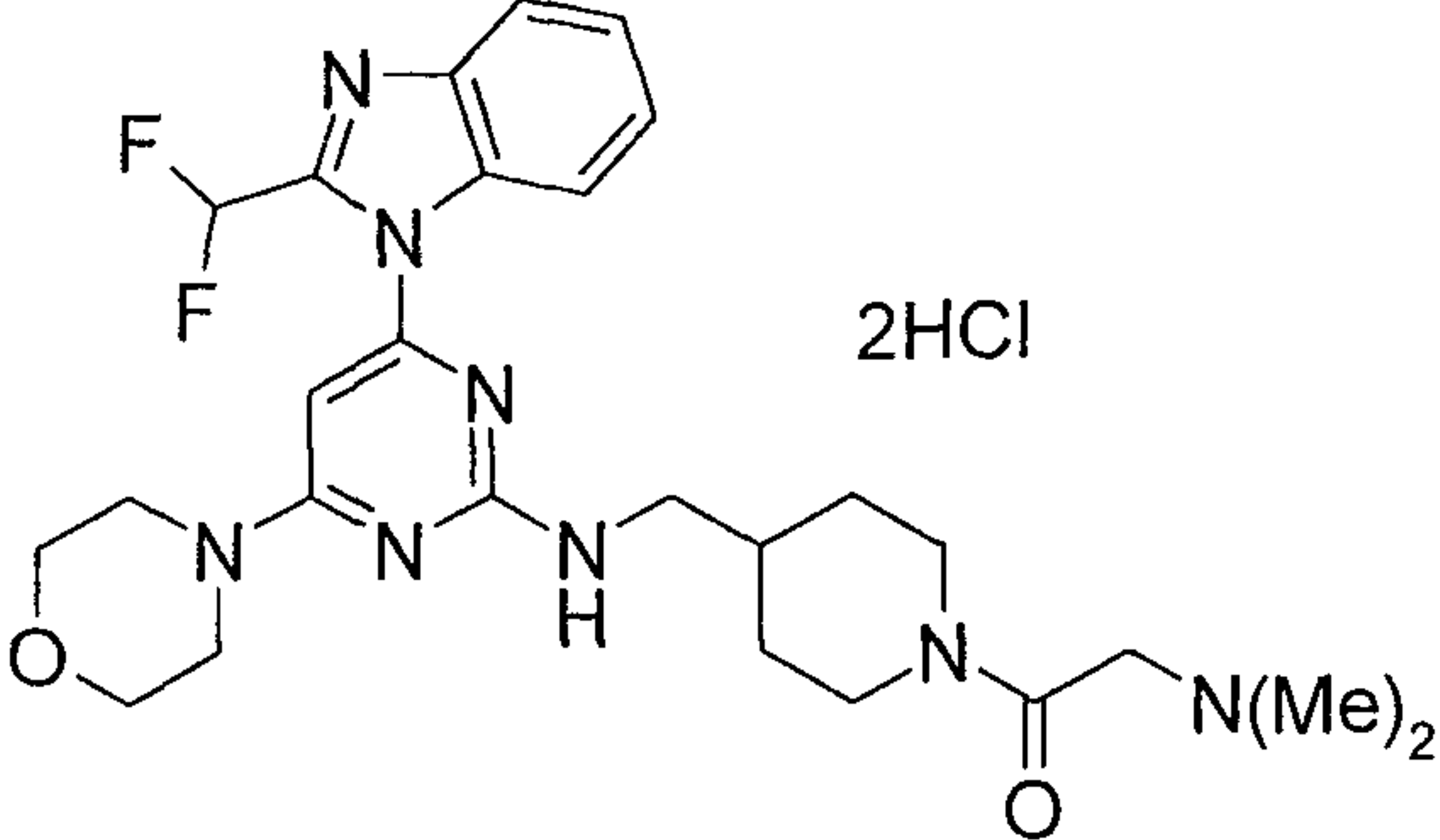
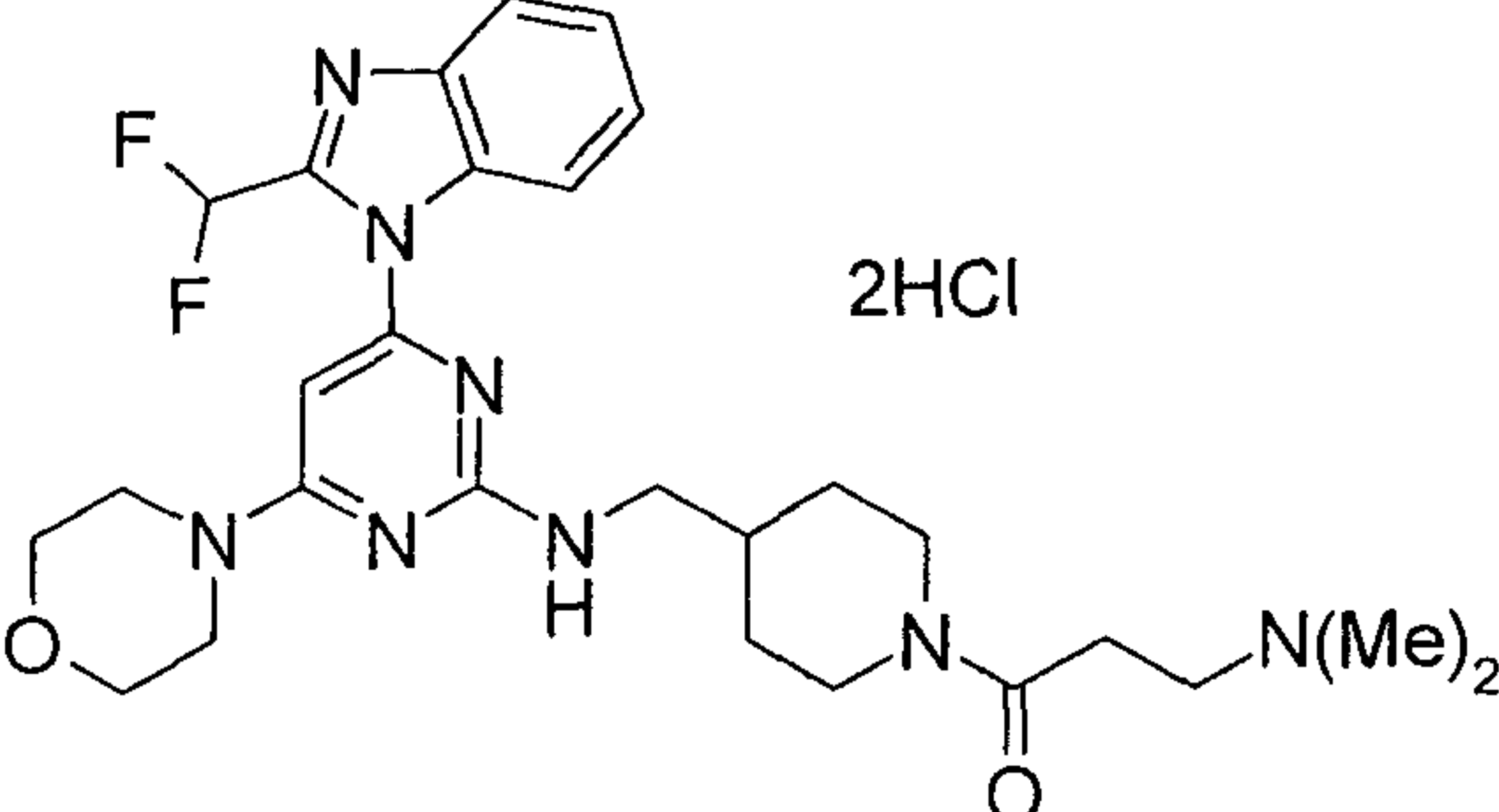
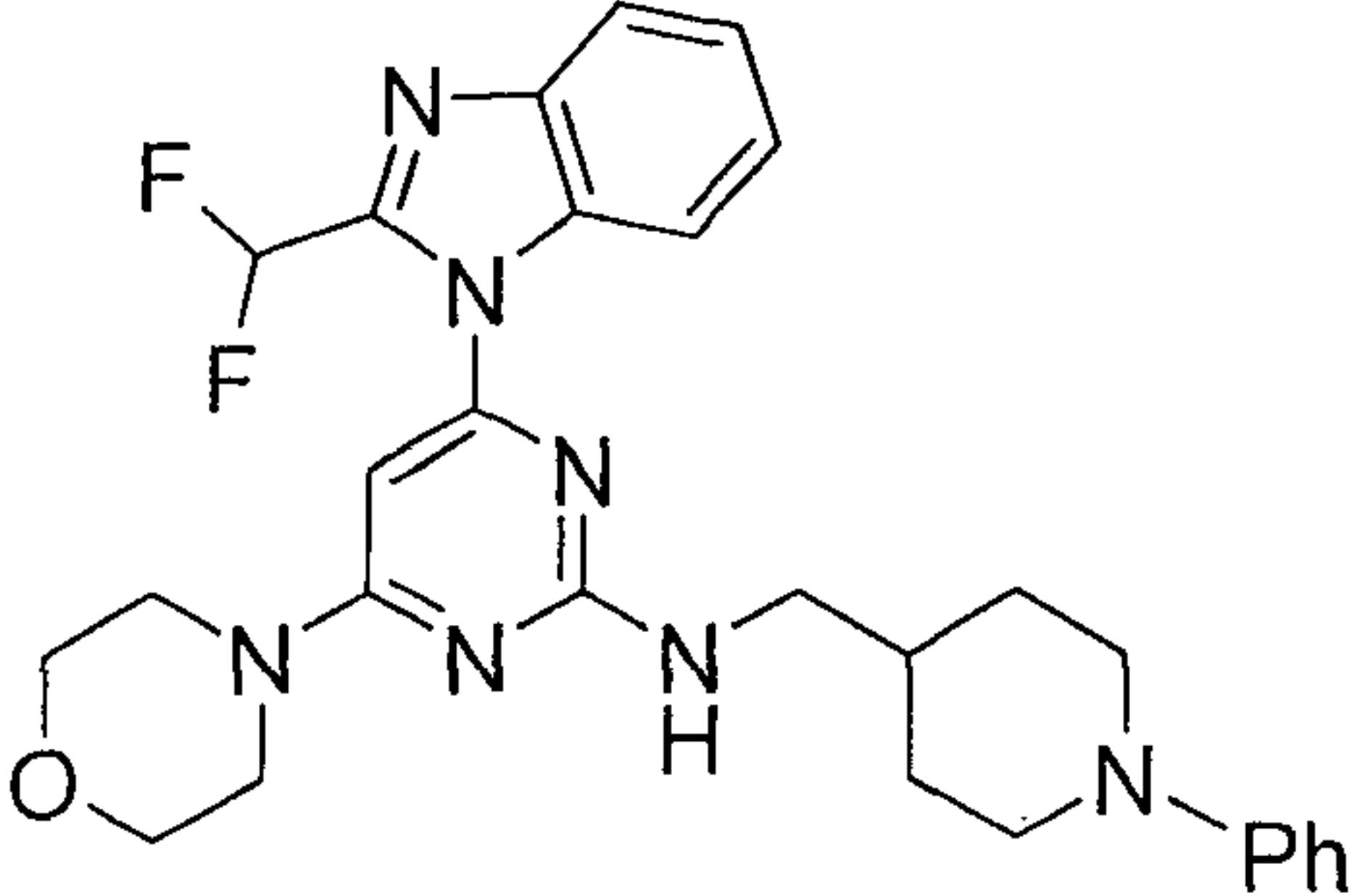
[0296]

[Table 50]

Ex	Str
66	
67	
68	
69	
70	

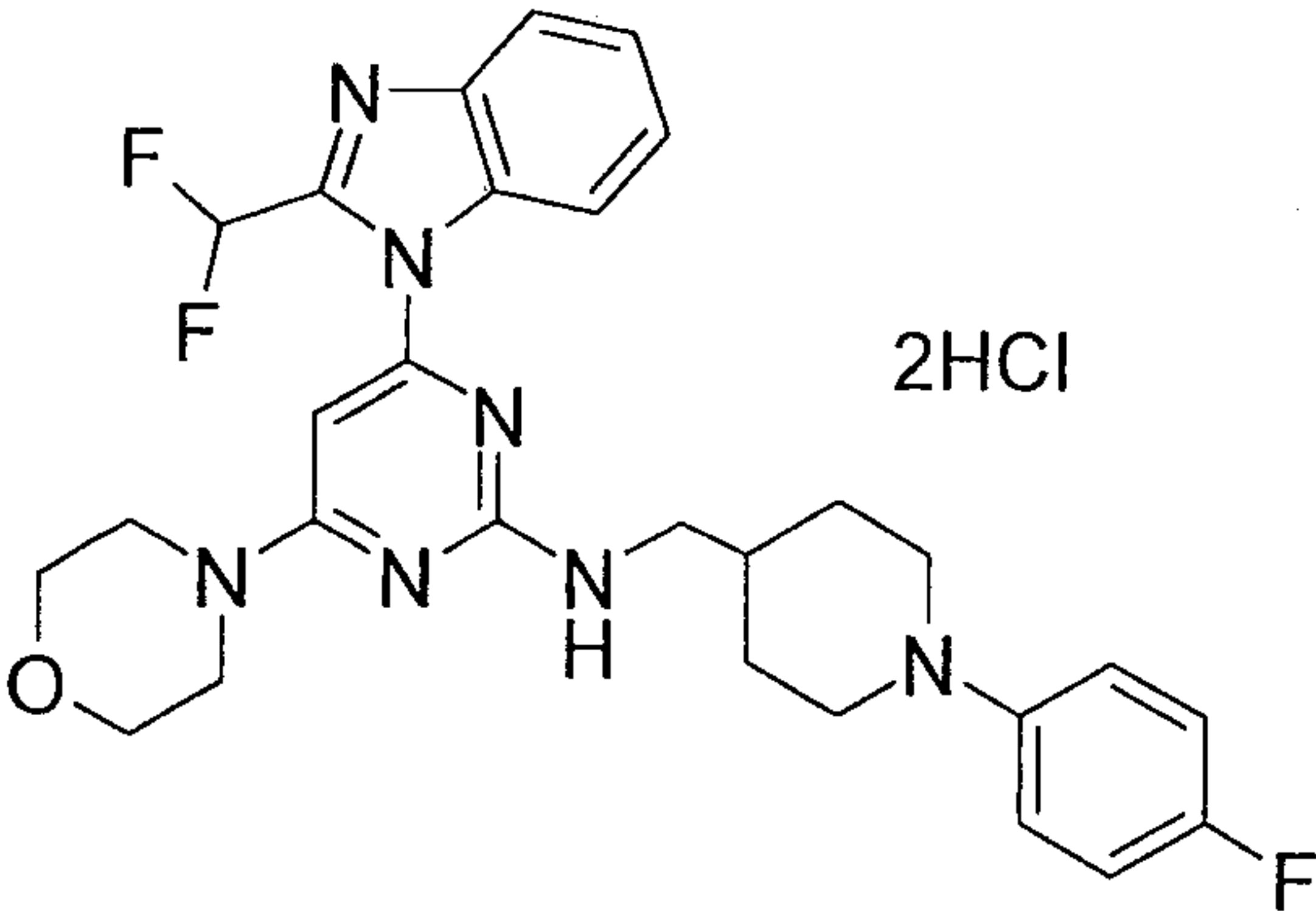
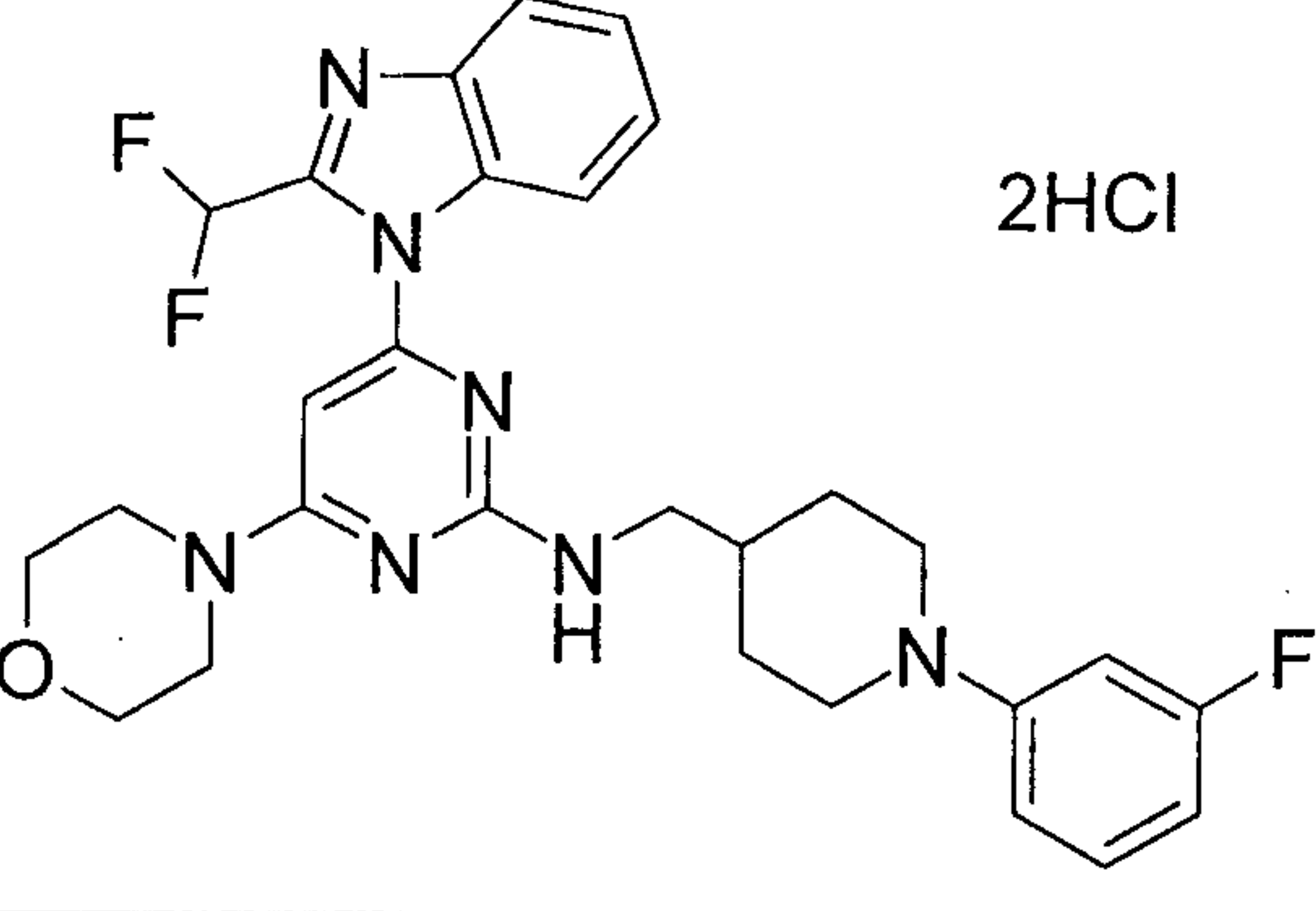
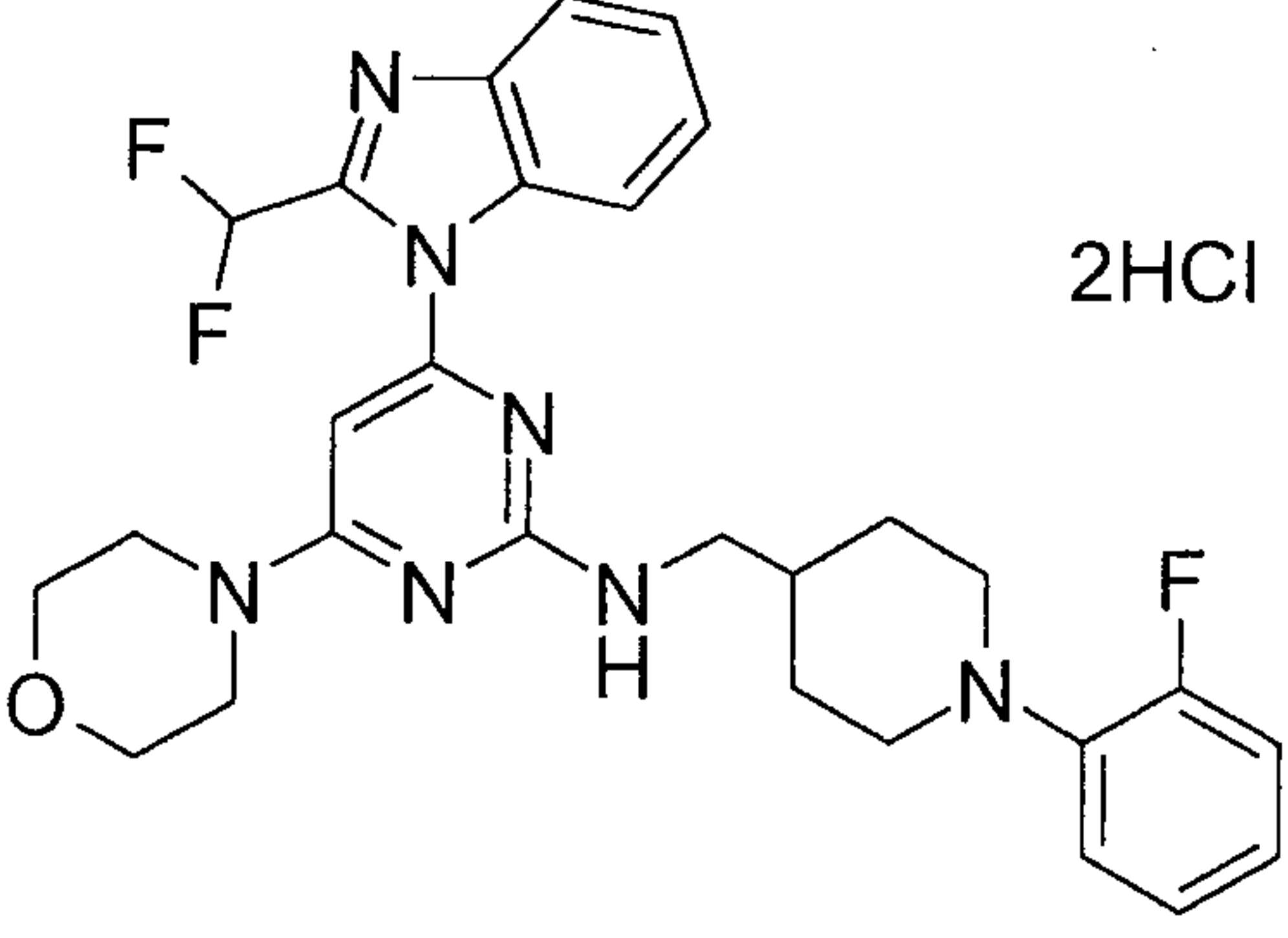
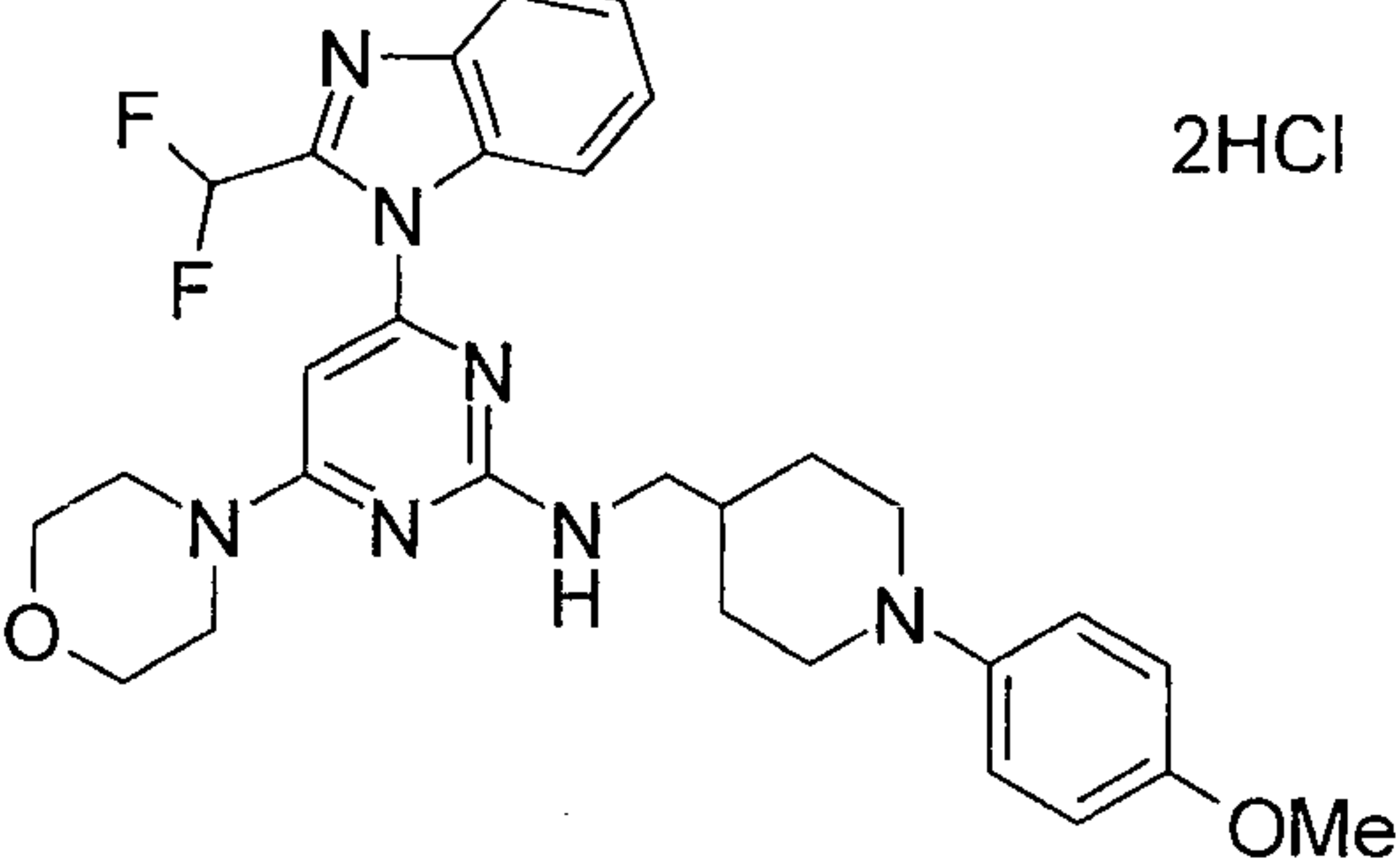
[0207]

[Table 51]

Ex	Str
71	
72	
73	
74	

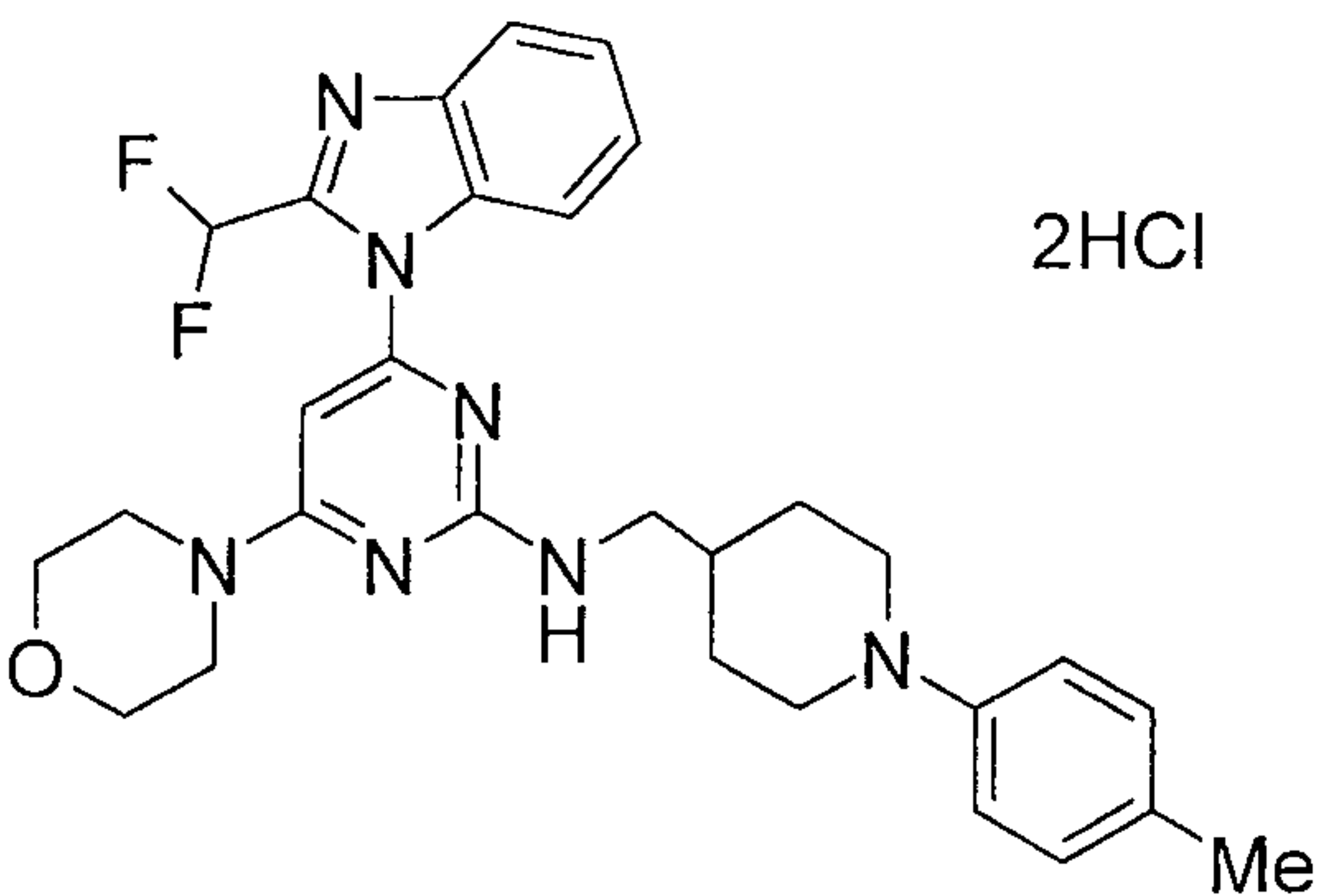
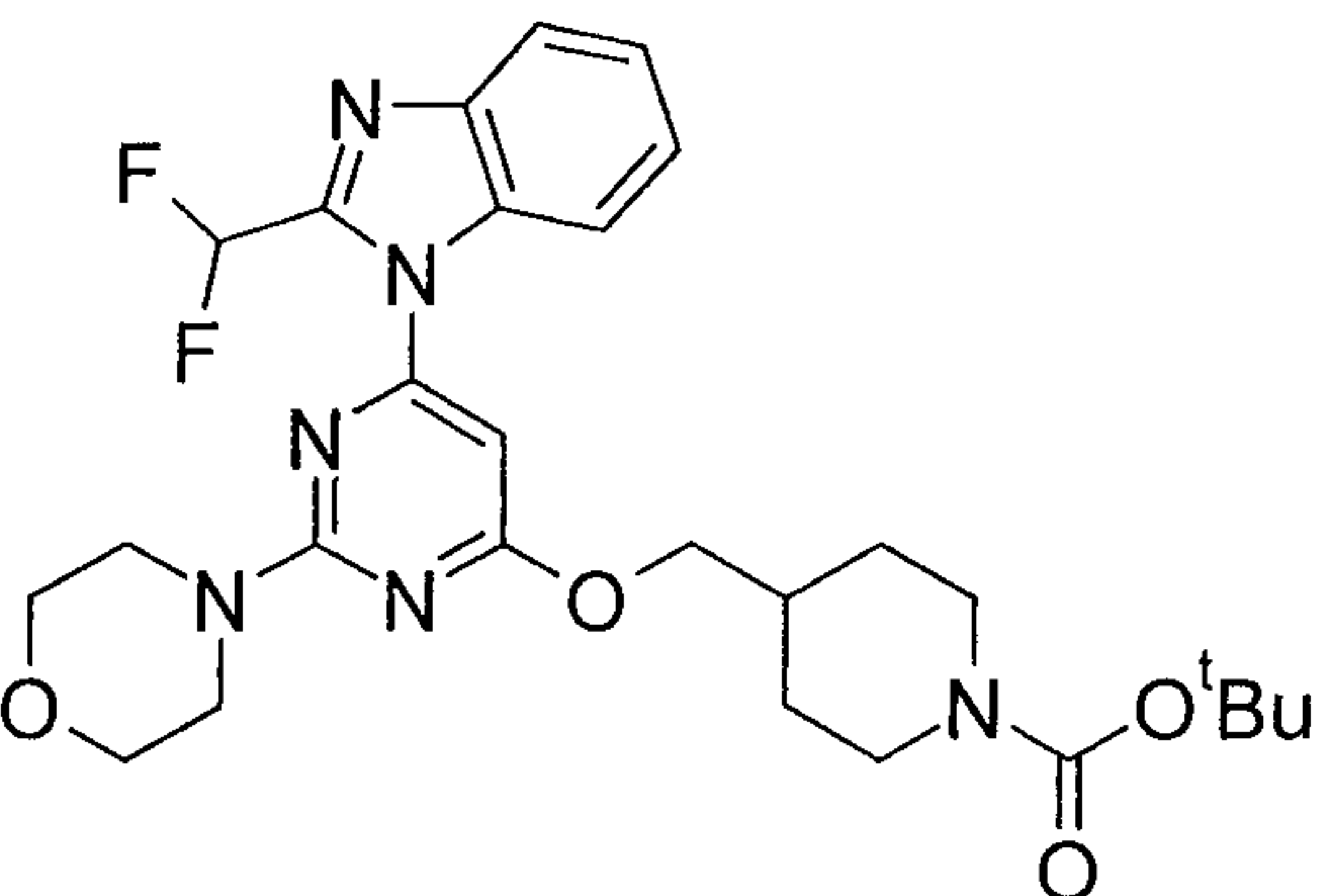
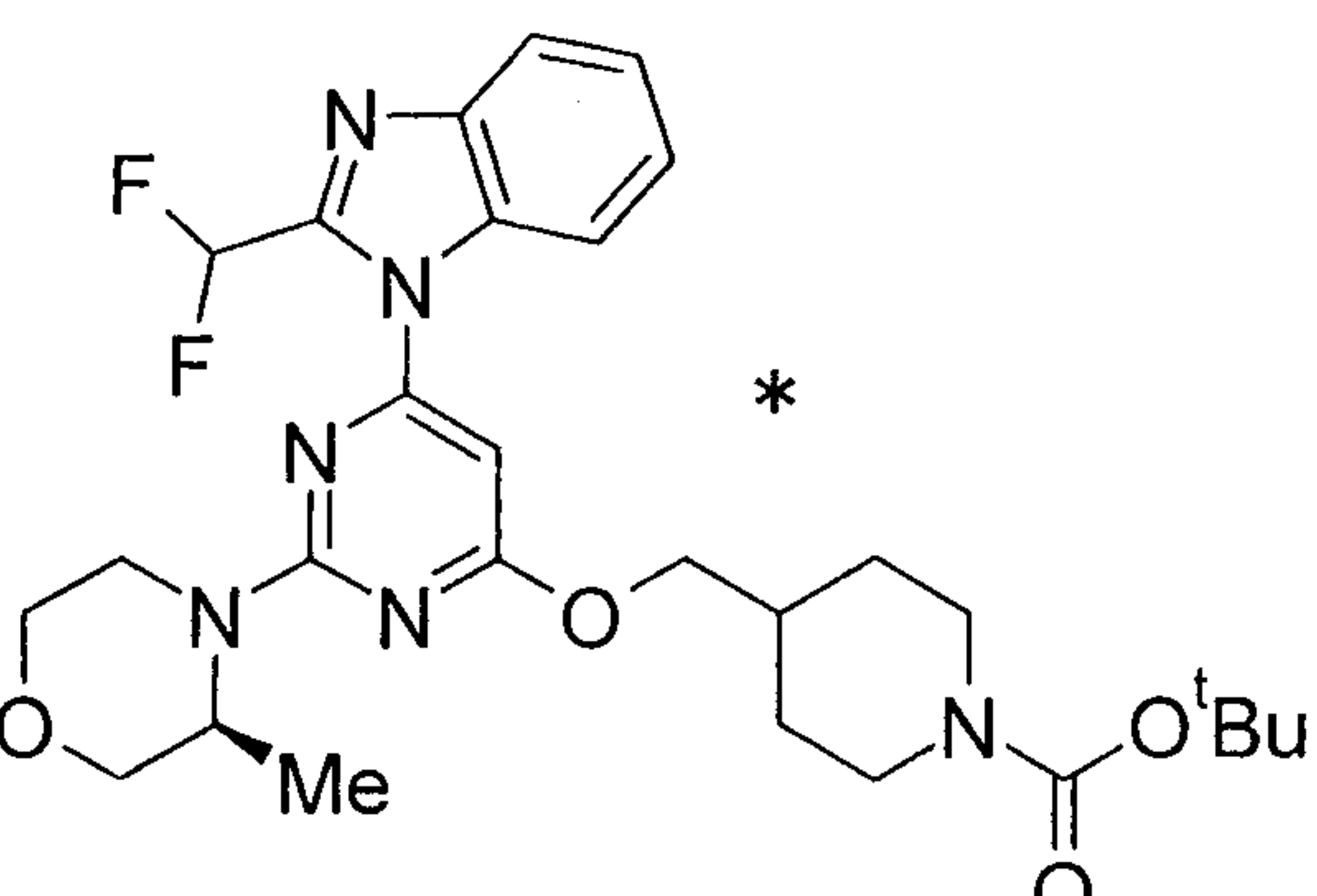
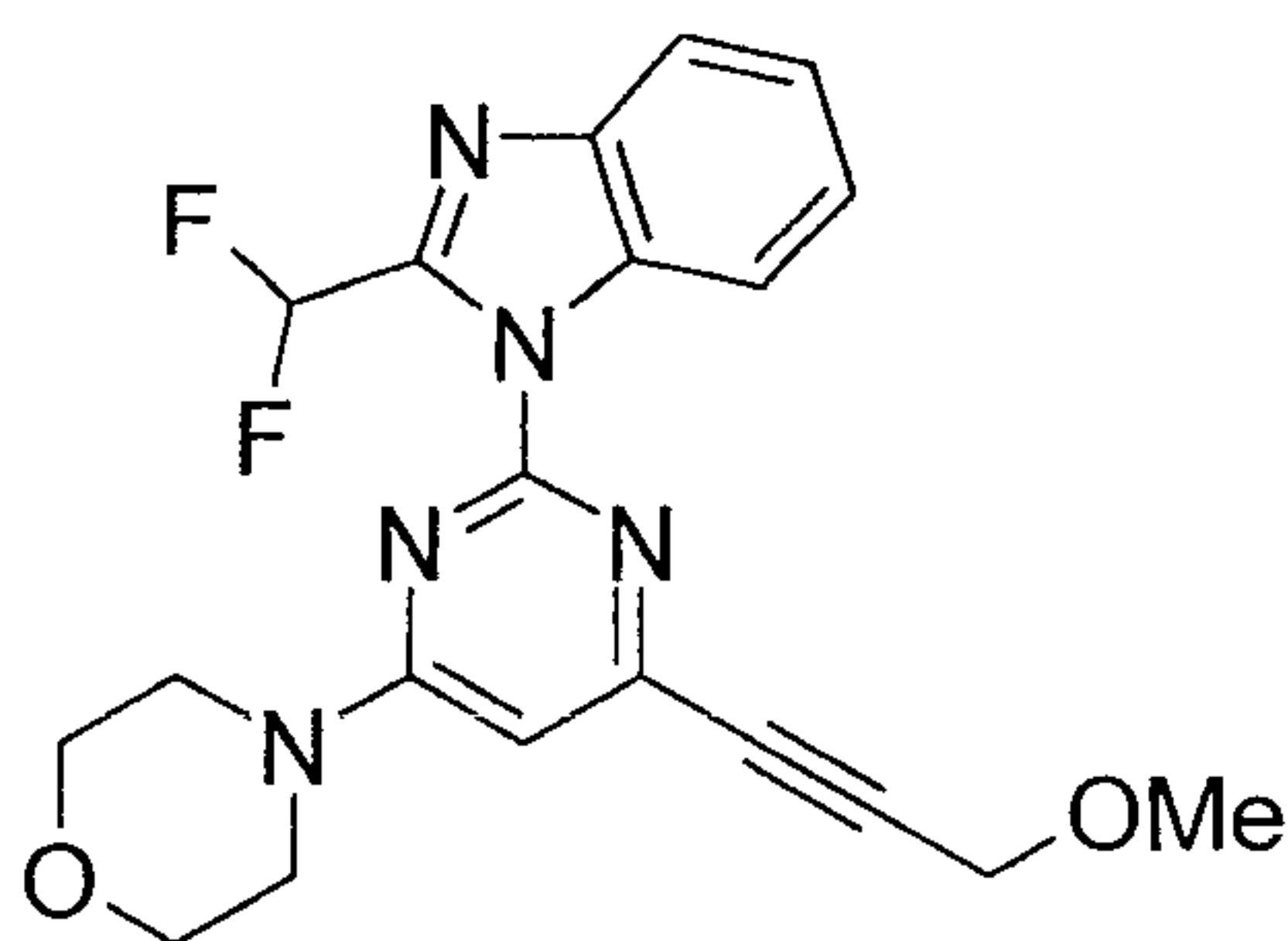
[0208]

[Table 52]

Ex	Str
75	
76	
77	
78	

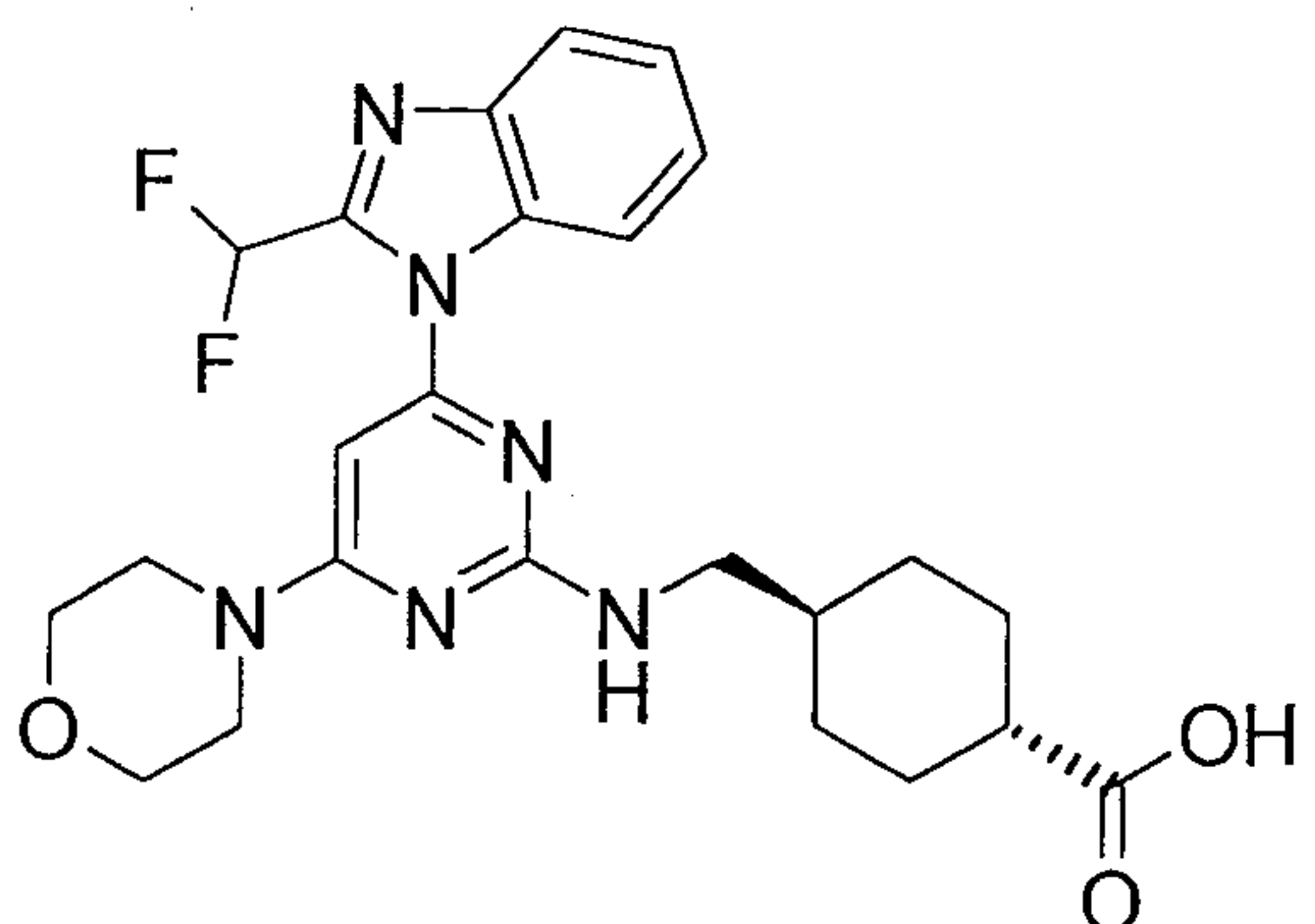
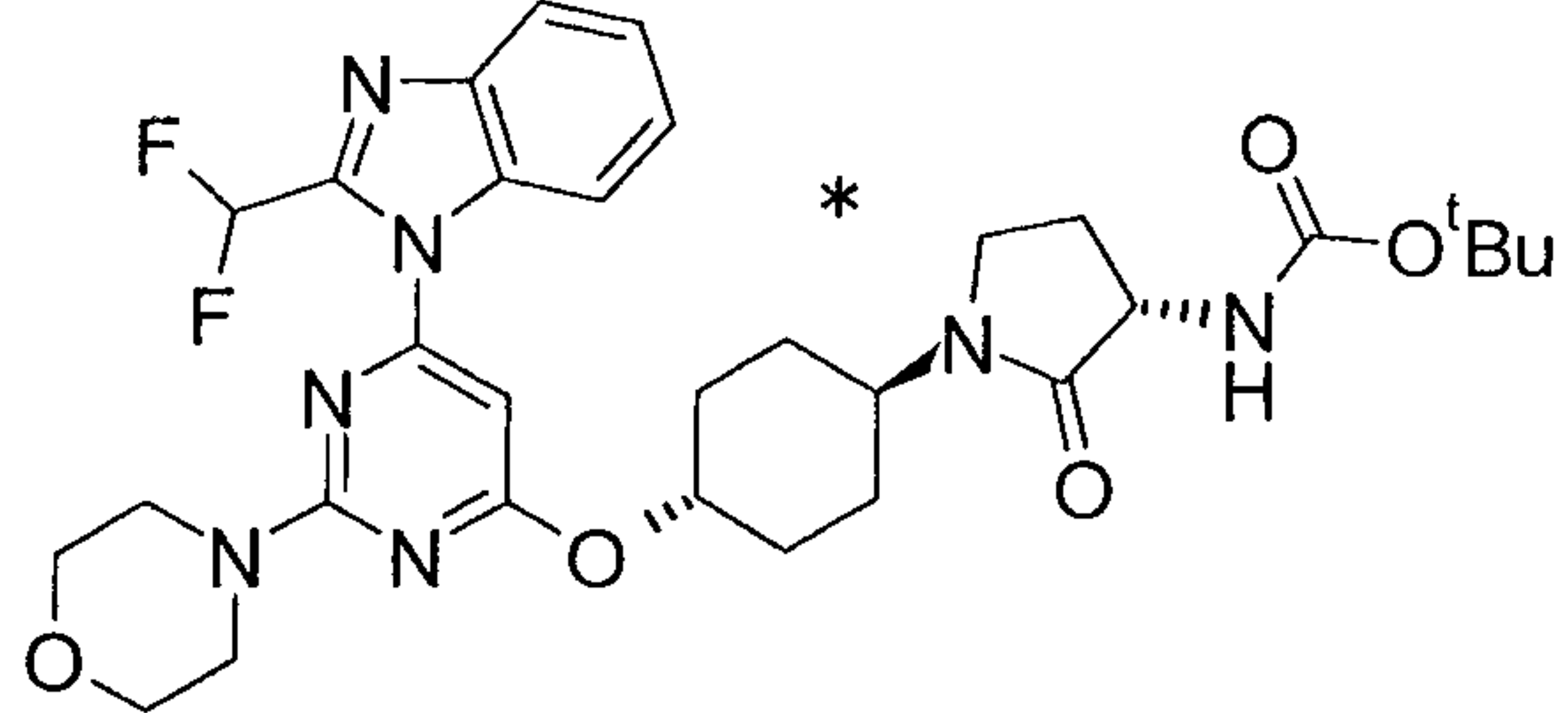
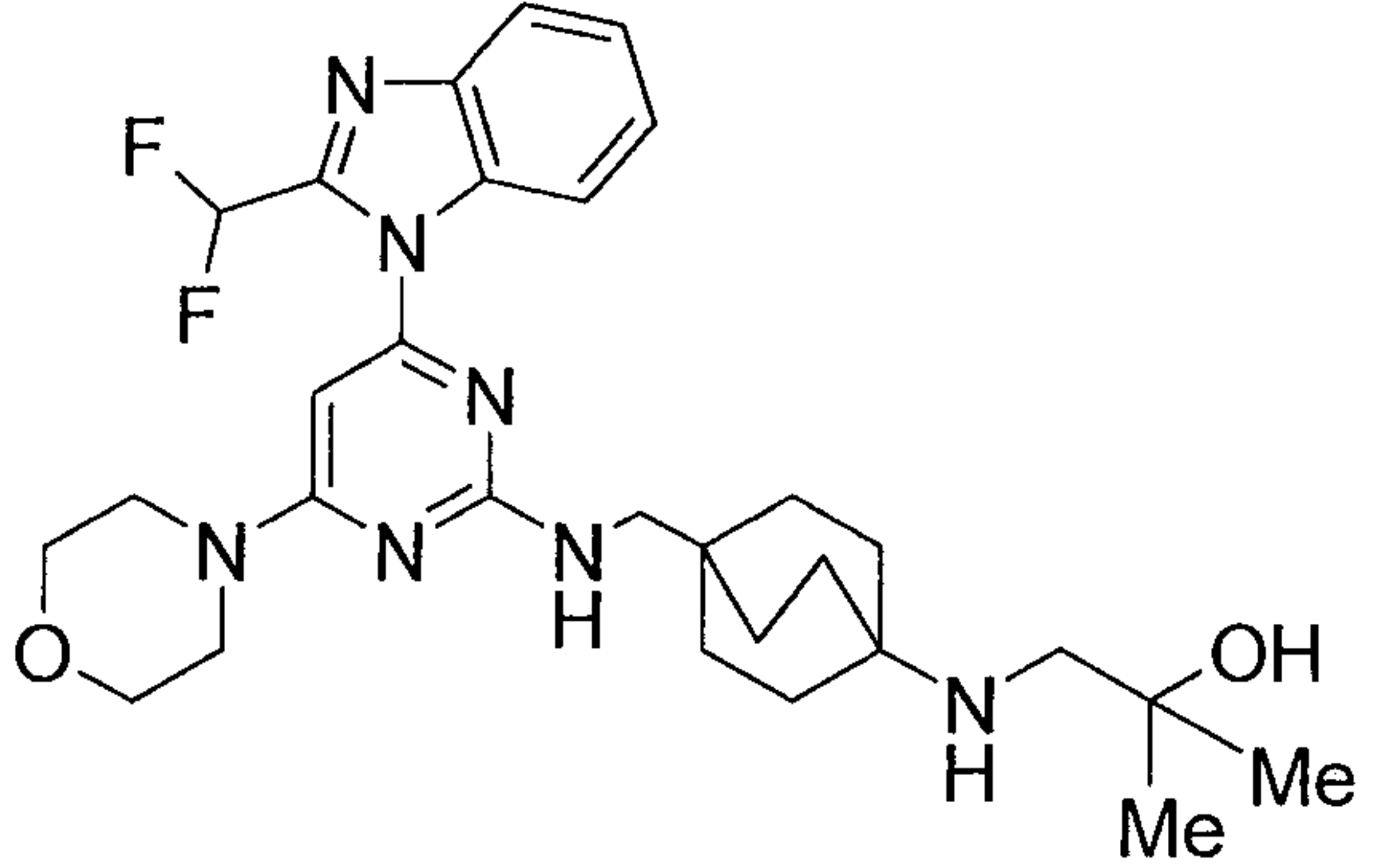
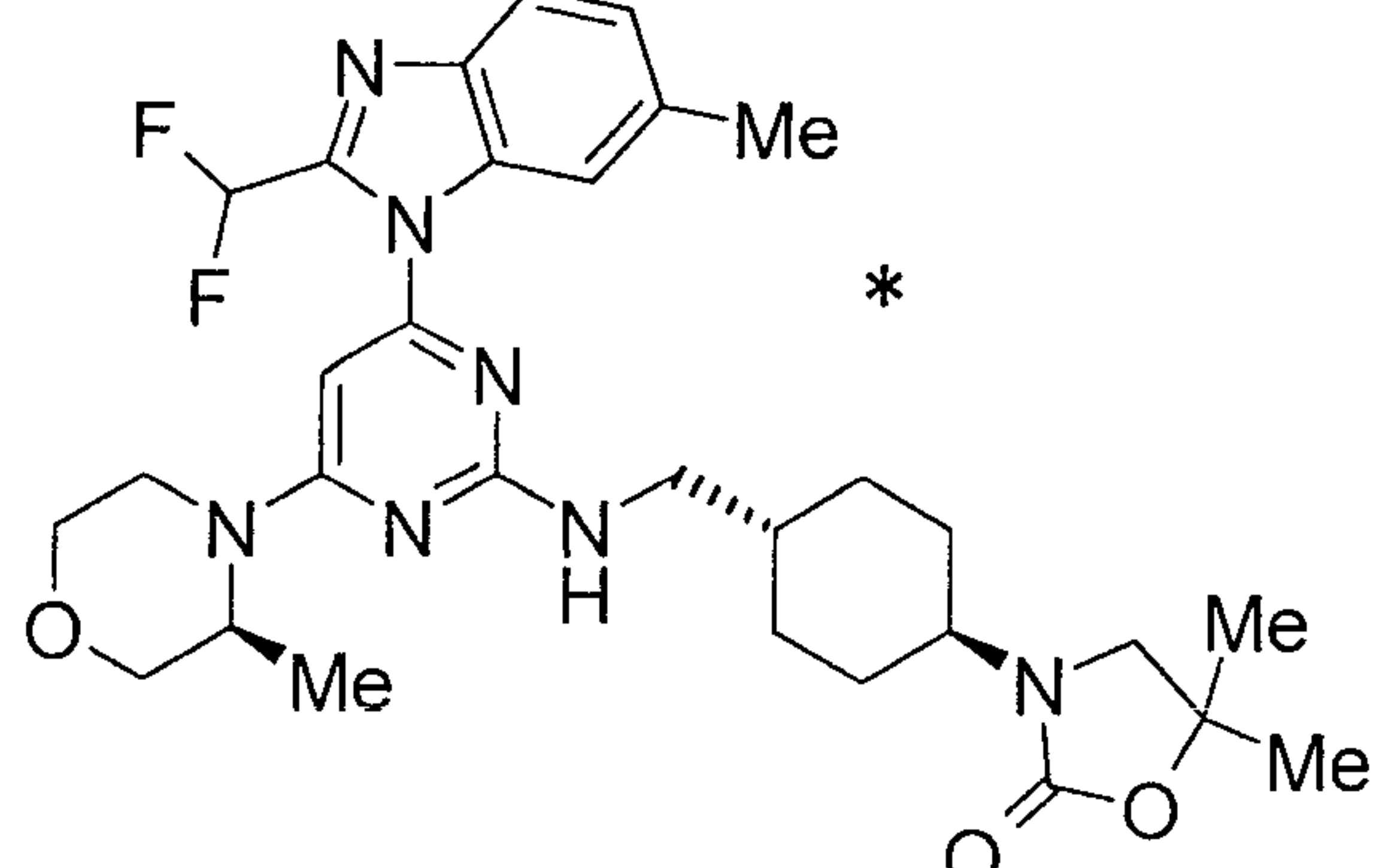
[0209]

[Table 53]

Ex	Str
79	
80	
81	
82	

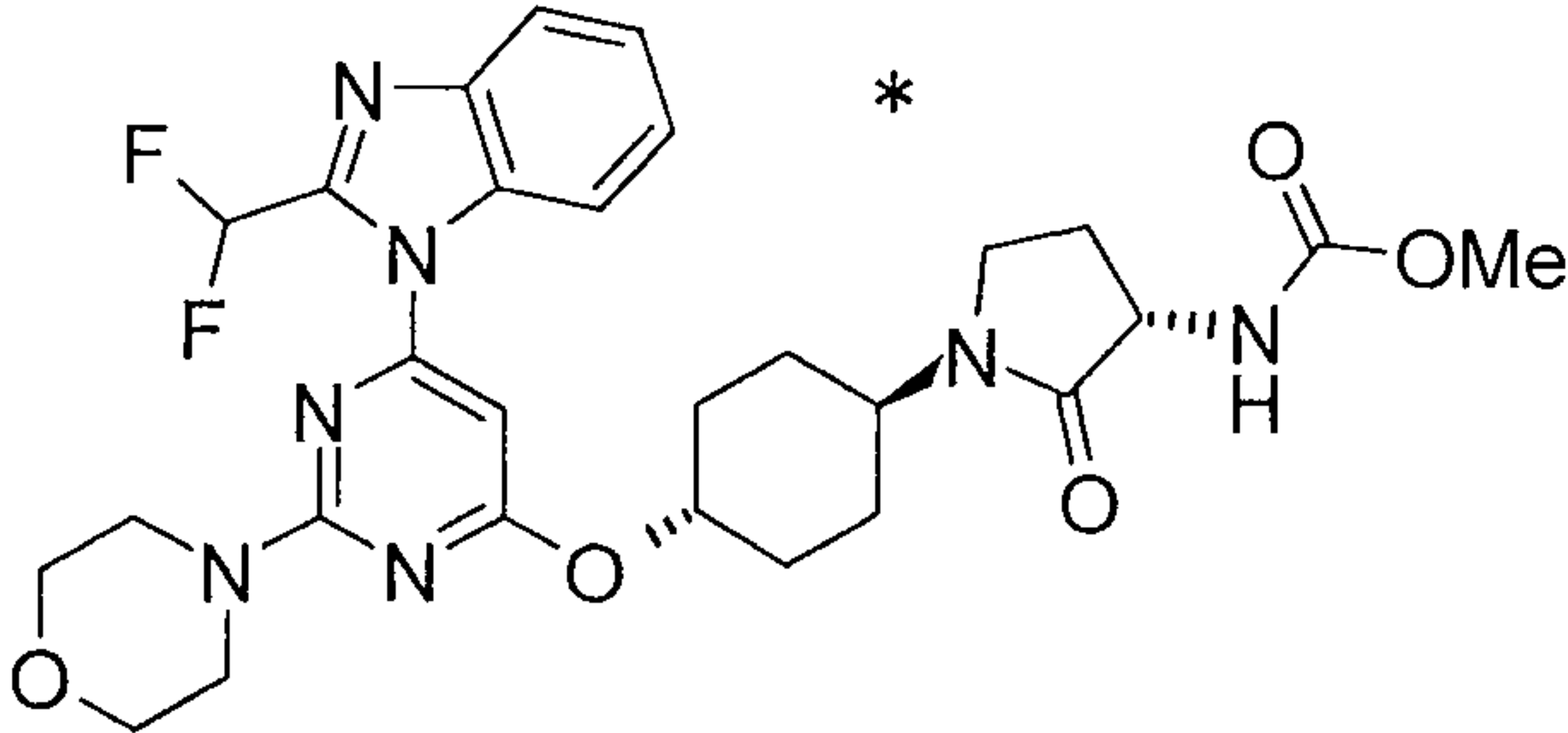
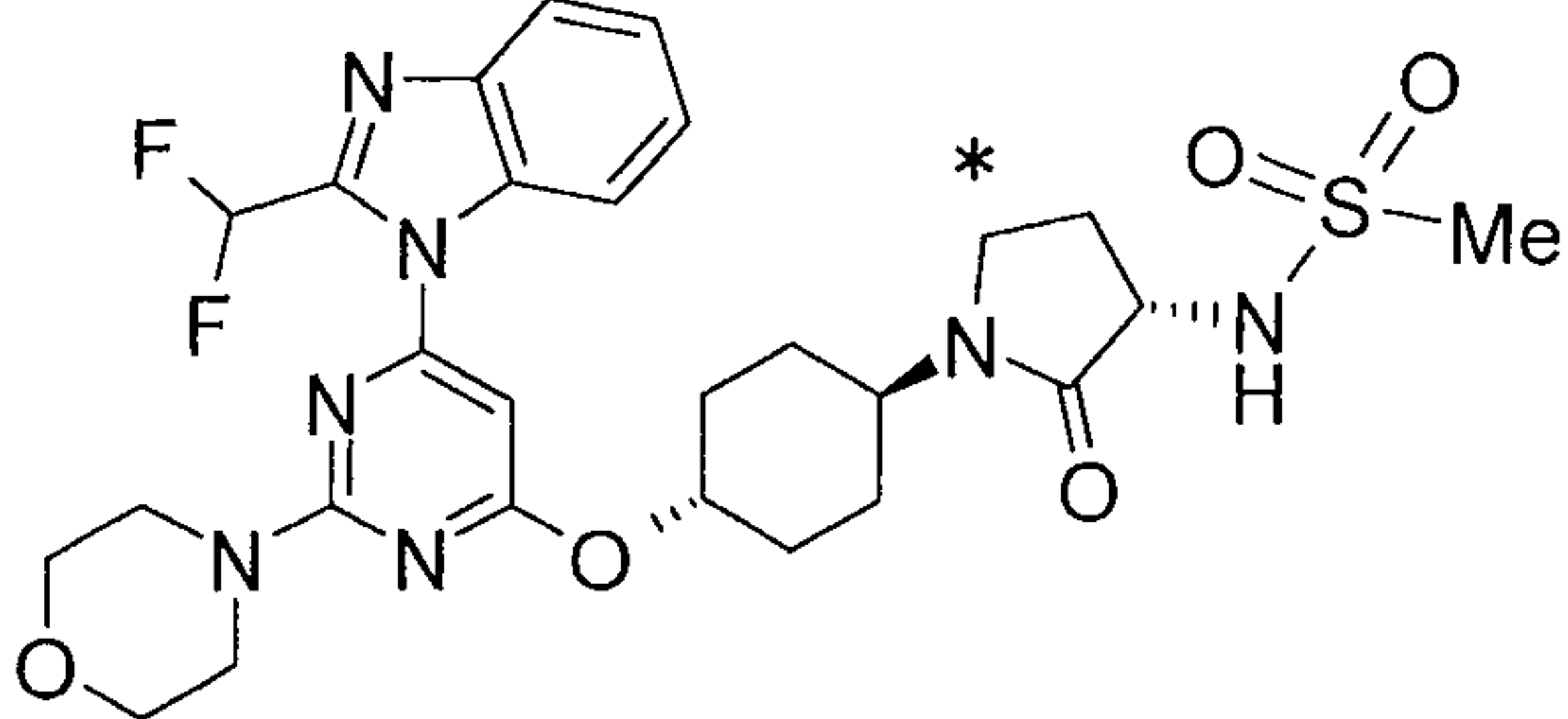
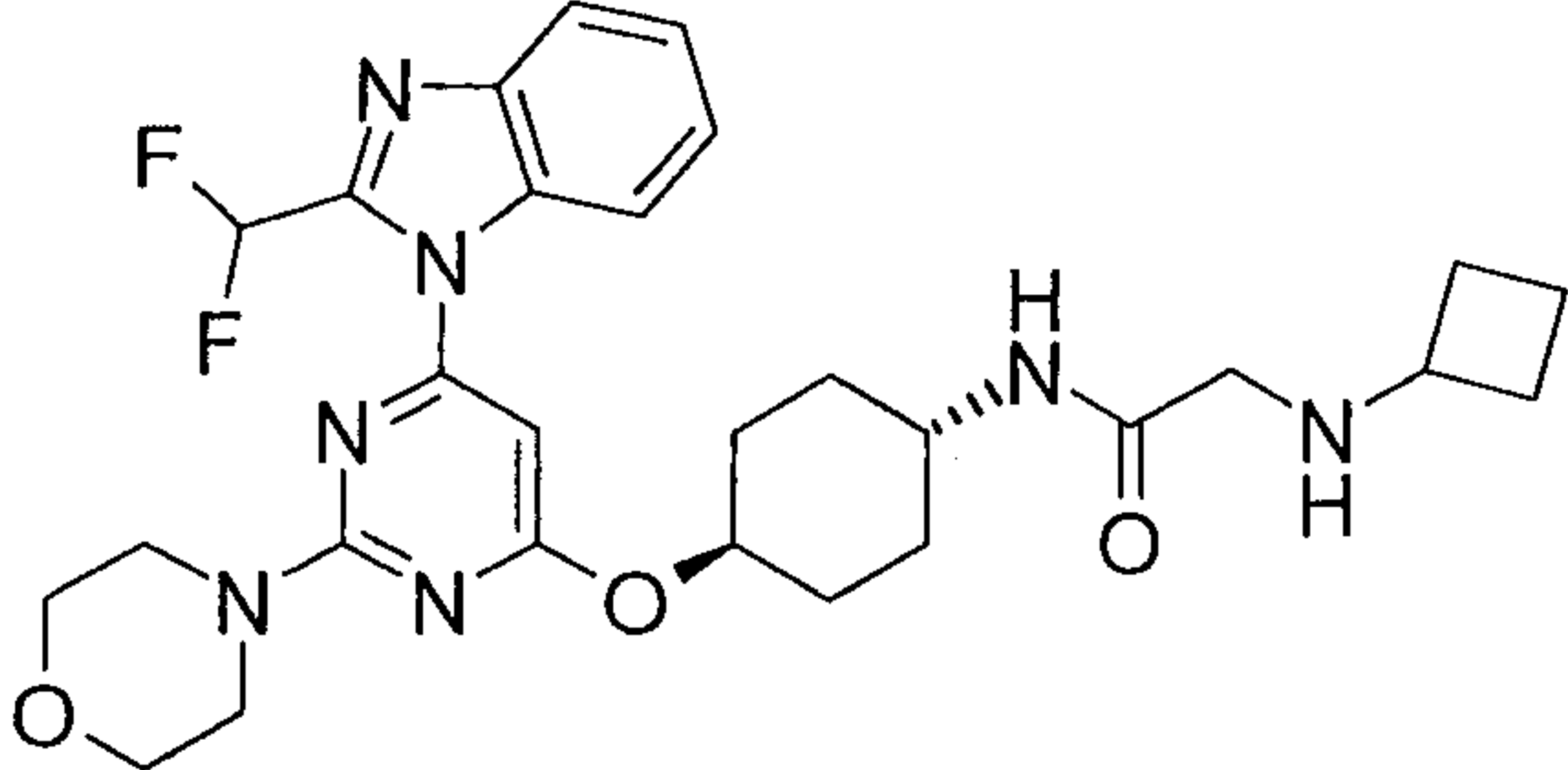
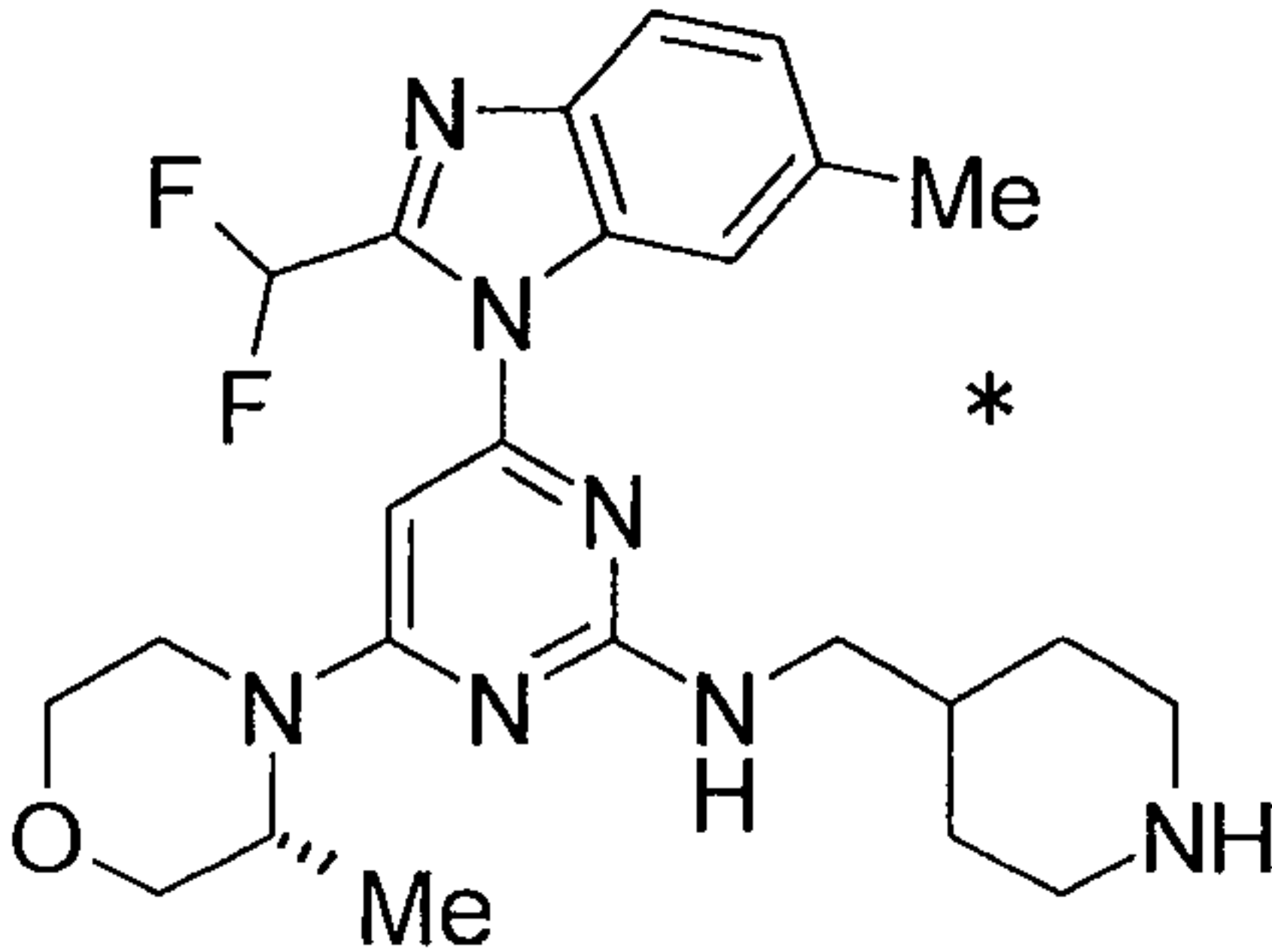
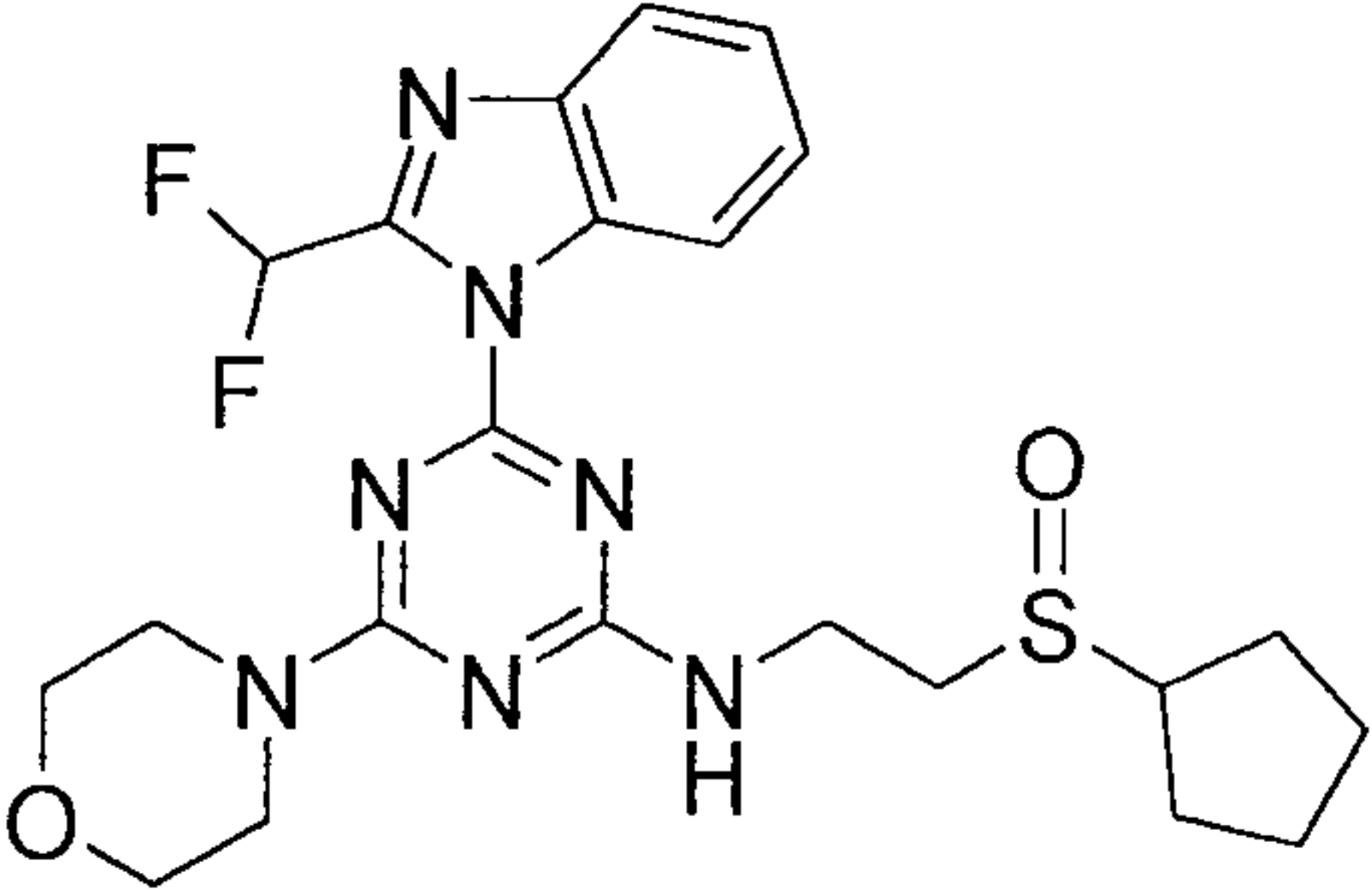
[0210]

[Table 54]

Ex	Str
83	
84	
85	
86	

[0211]

[Table 55]

Ex	Str
87	
88	
89	
90	
91	

[0212]

[Table 56]

Ex	Str
92	
93	
94	
95	
96	

[0213]

[Table 57]

Ex	Str
97	
98	
99	
100	
101	

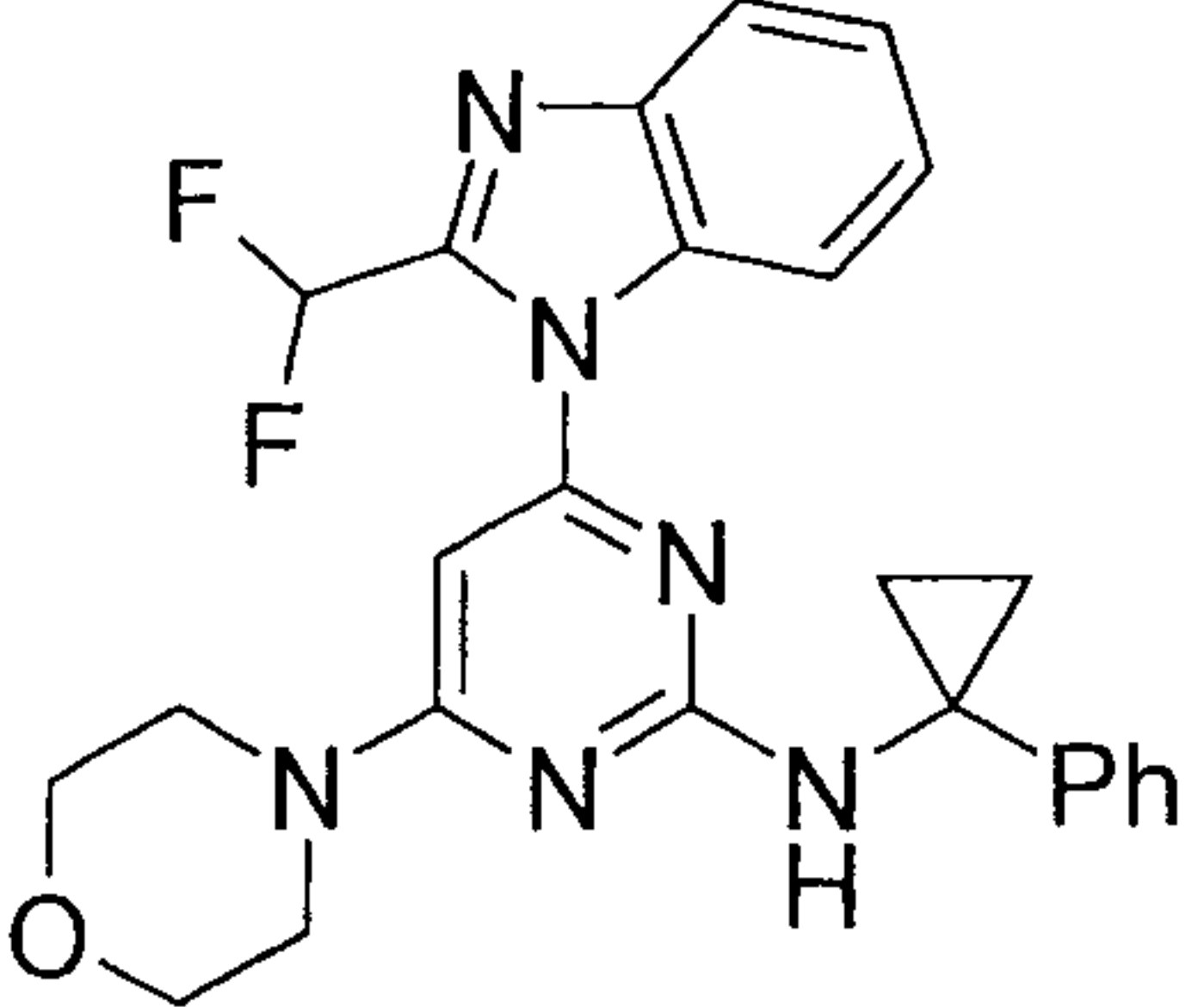
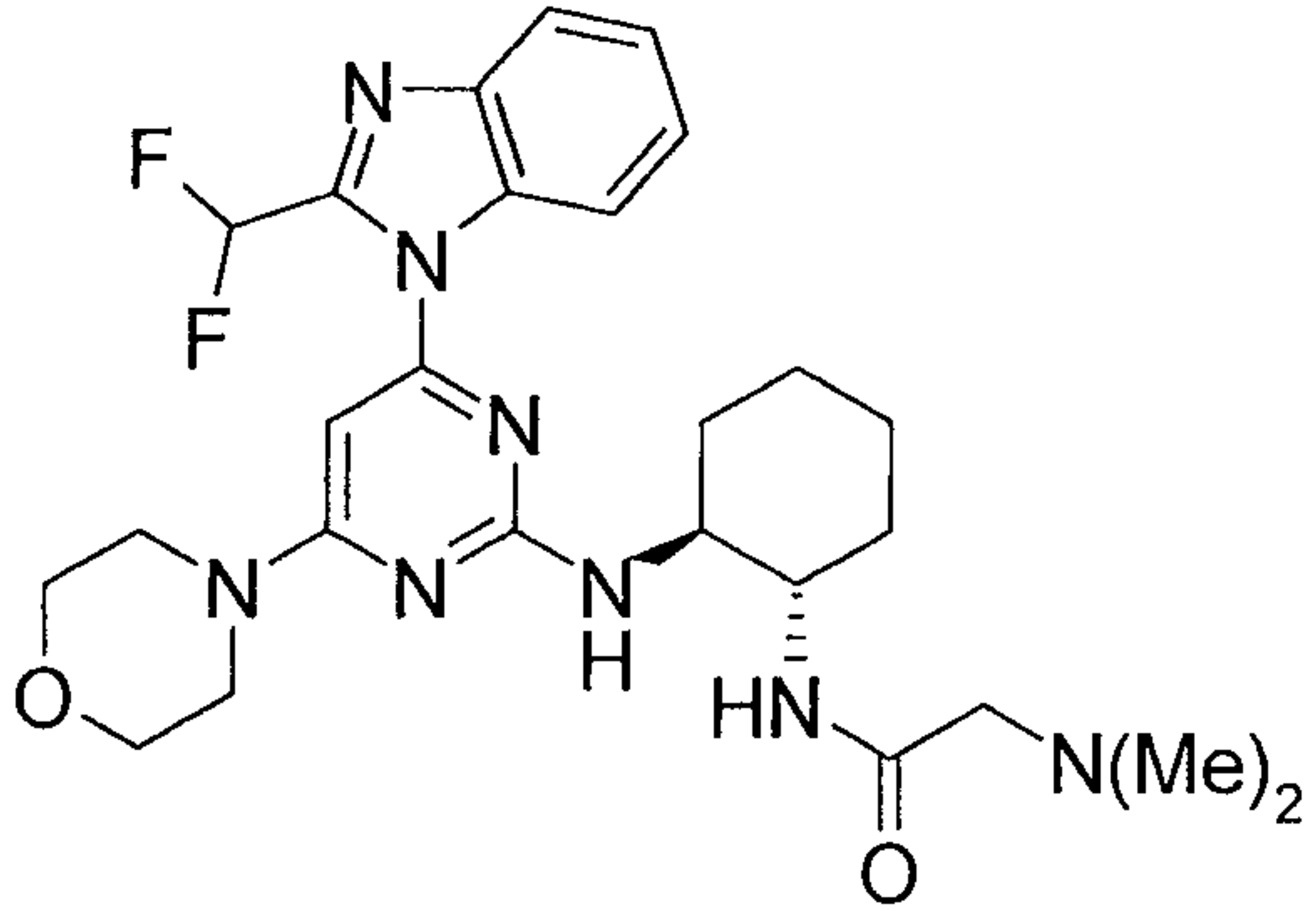
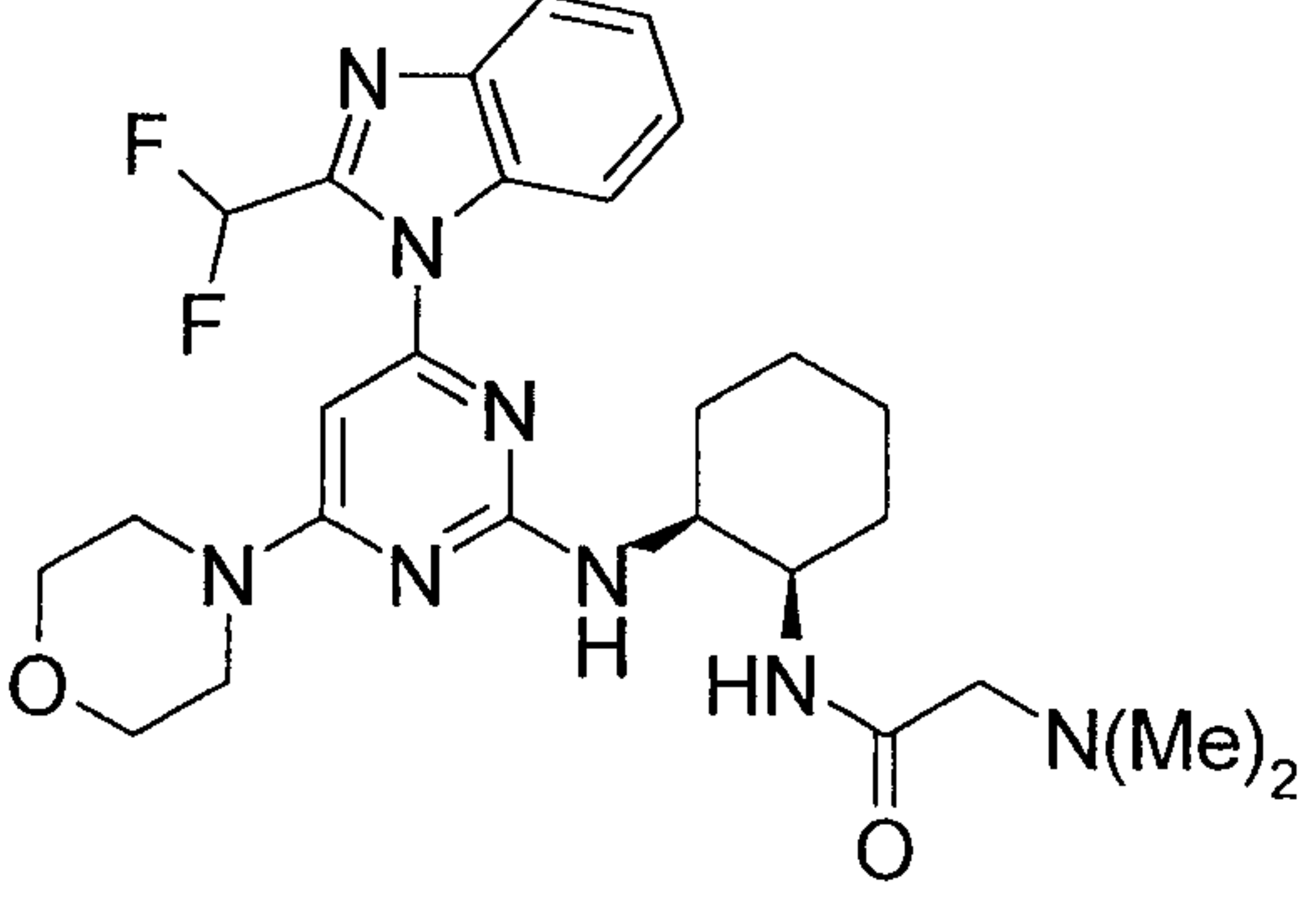
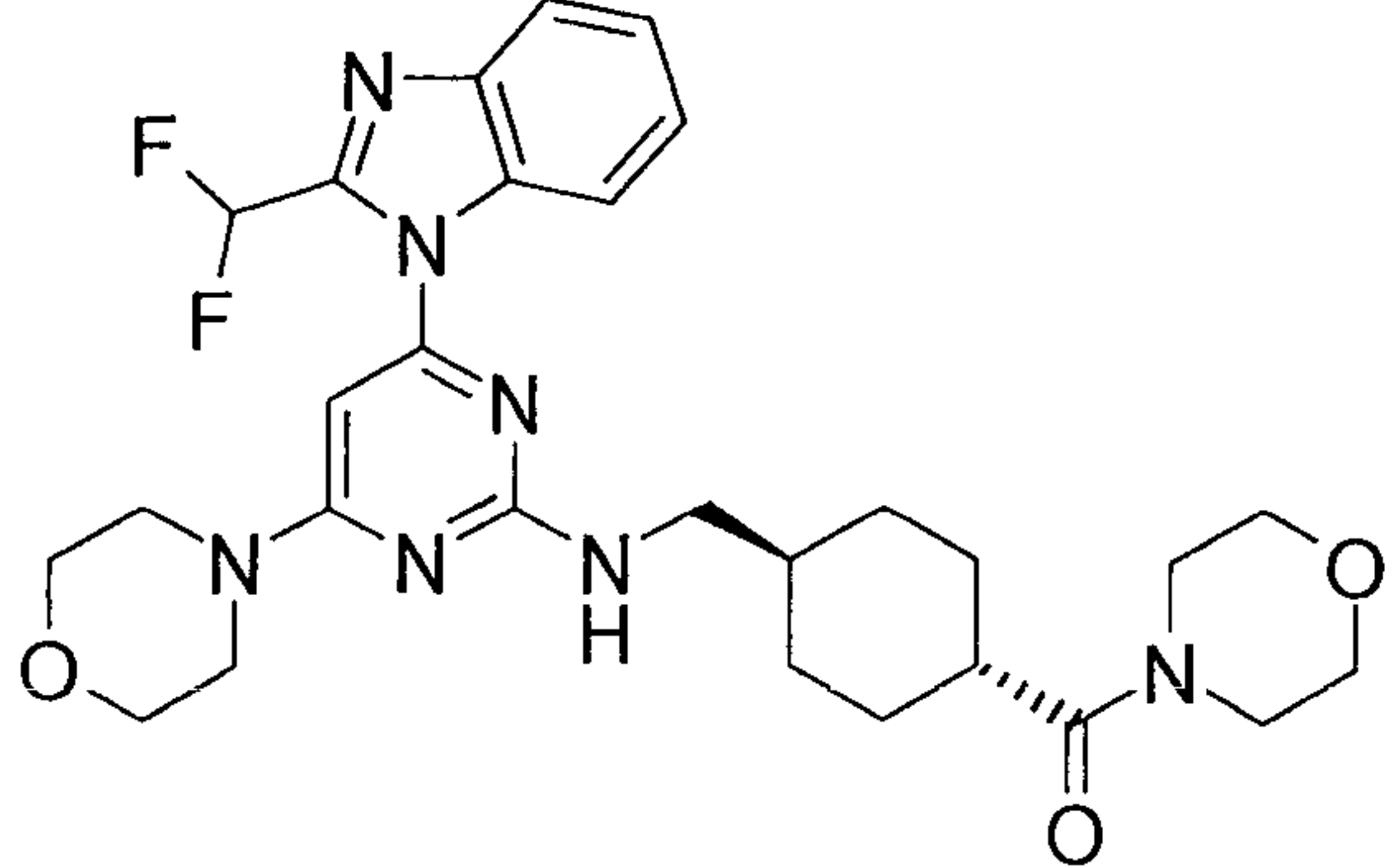
[0215]

[Table 59]

Ex	Str
107	
108	
109	
110	
111	

[0216]

[Table 60]

Ex	Str
112	
113	
114	
115	

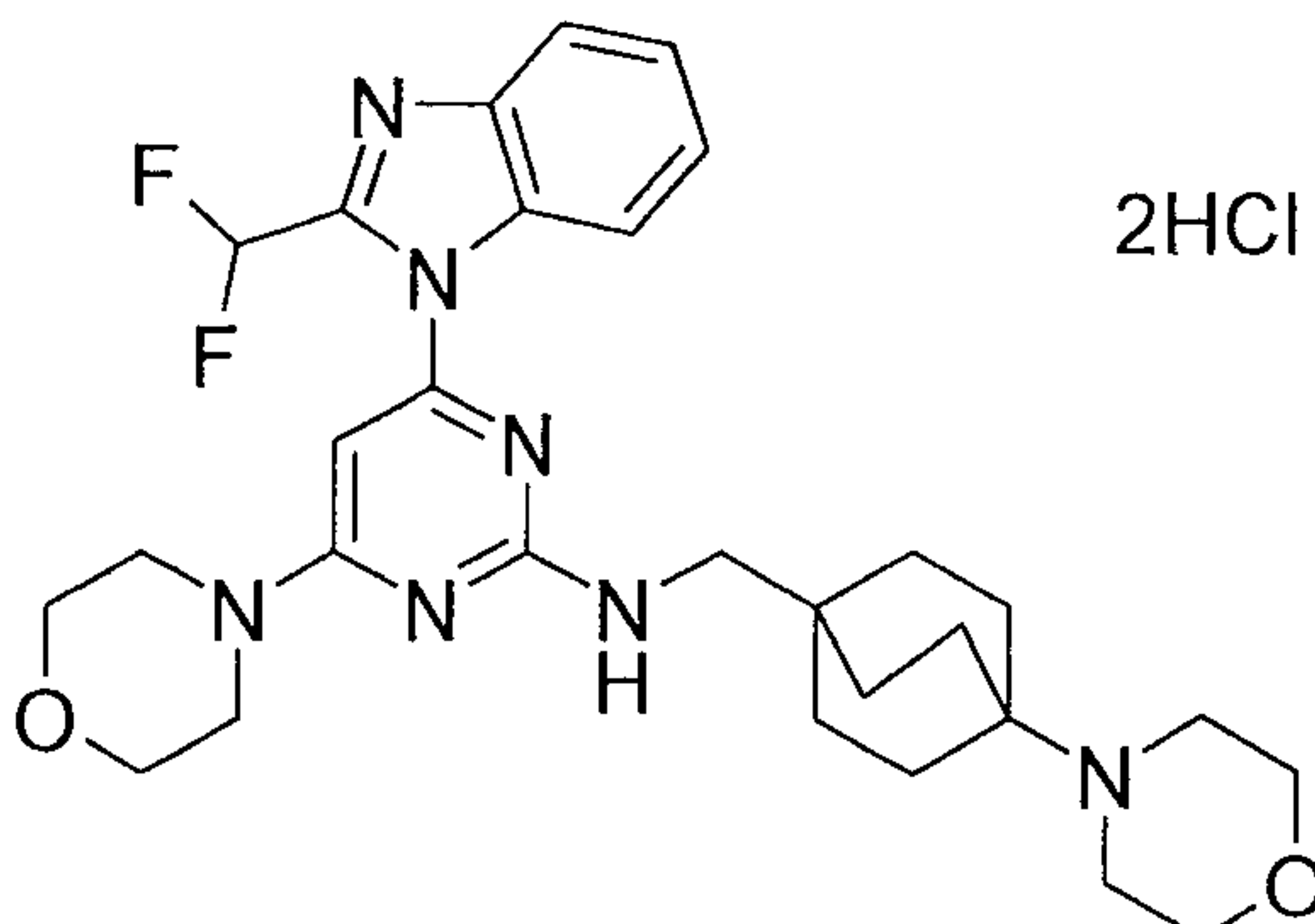
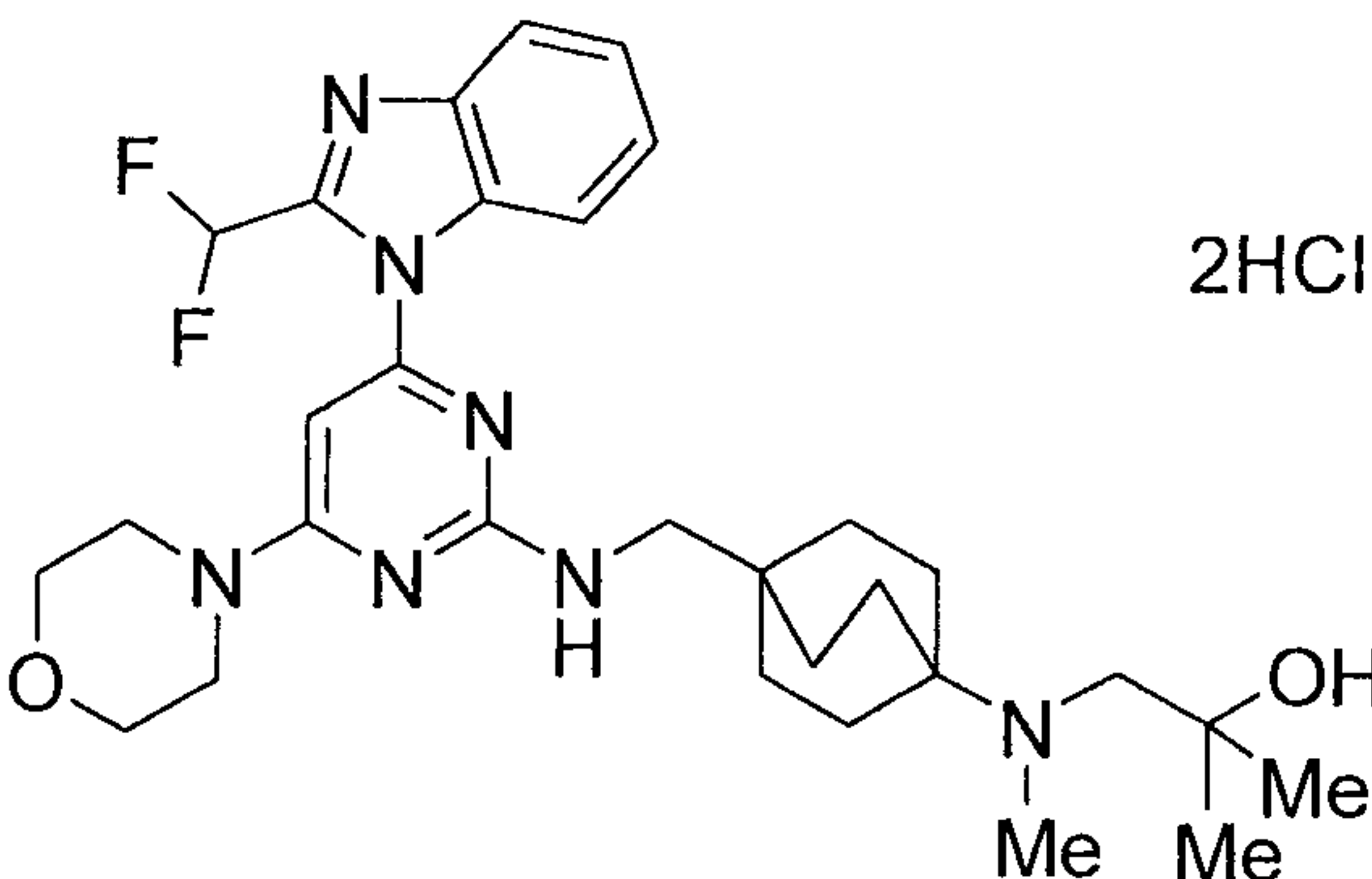
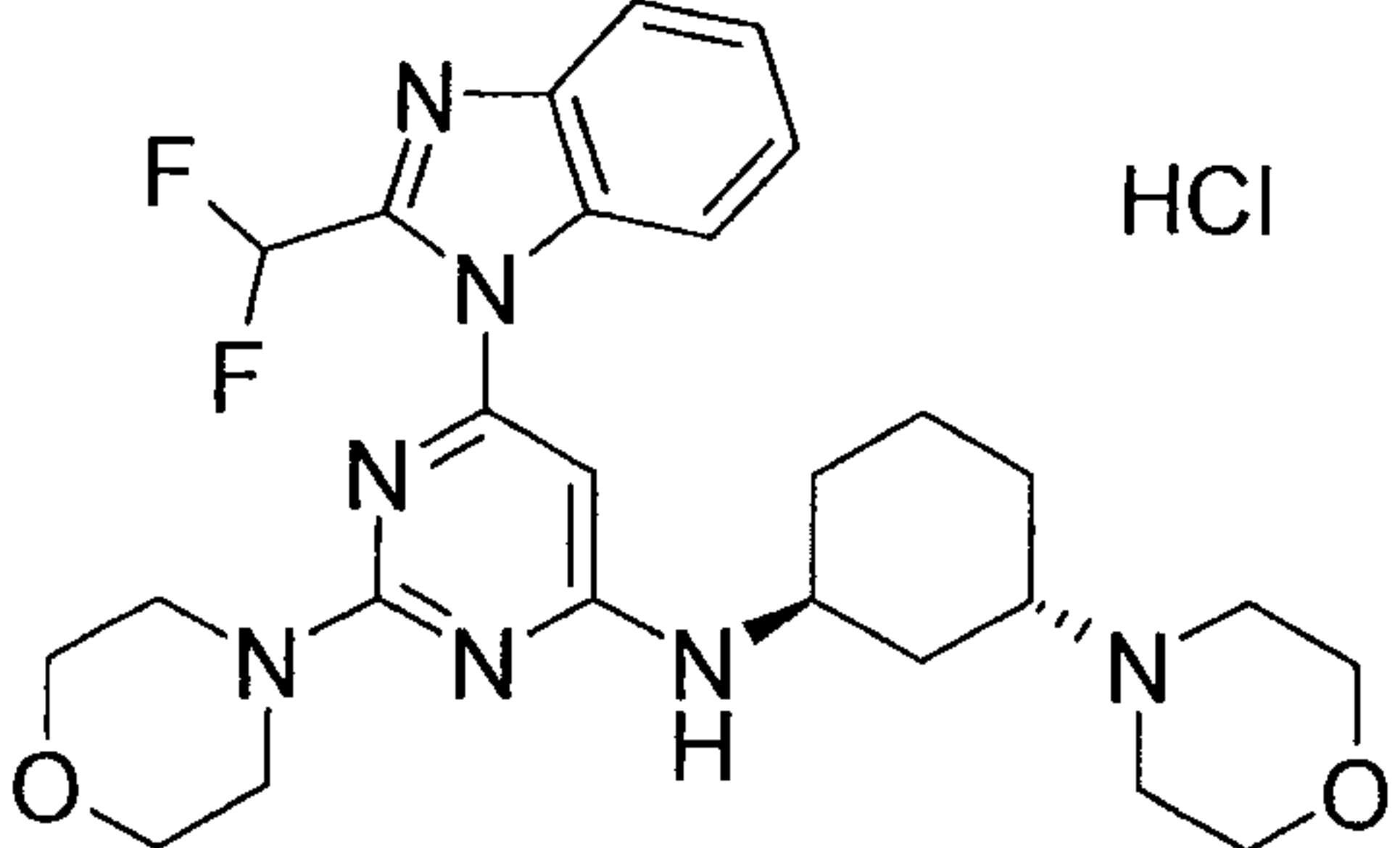
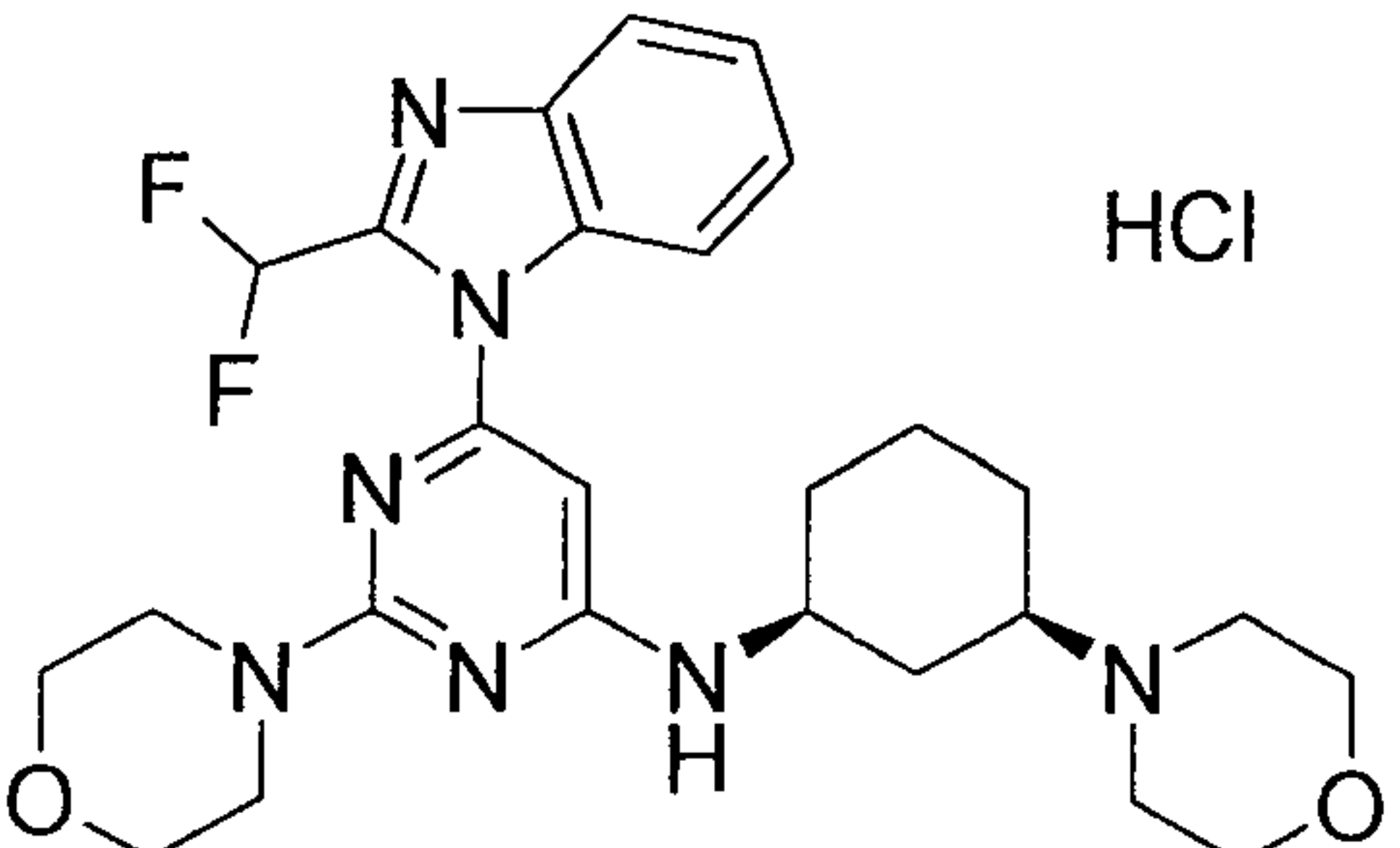
[0217]

[Table 61]

Ex	Str
116	
117	
118	
119	

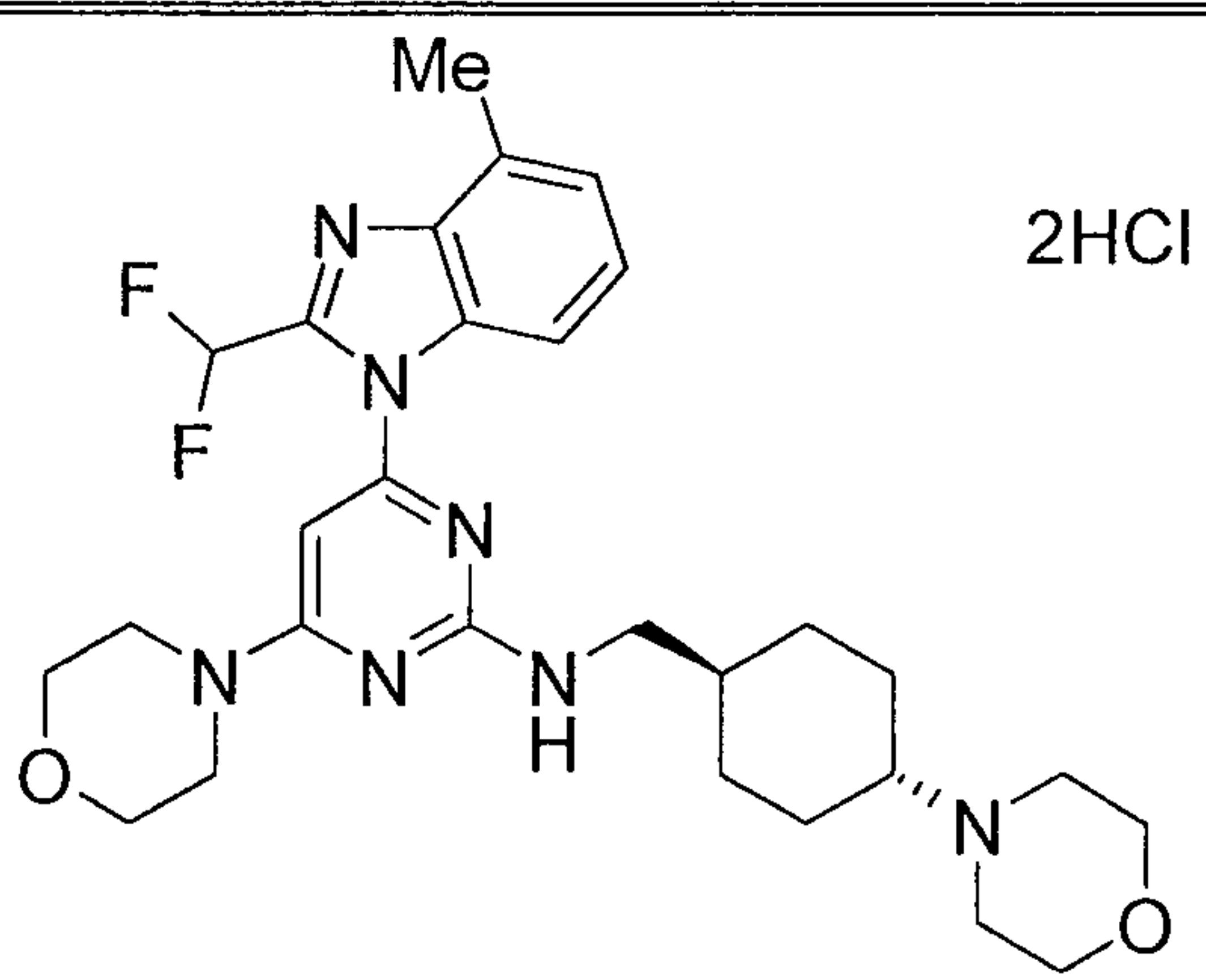
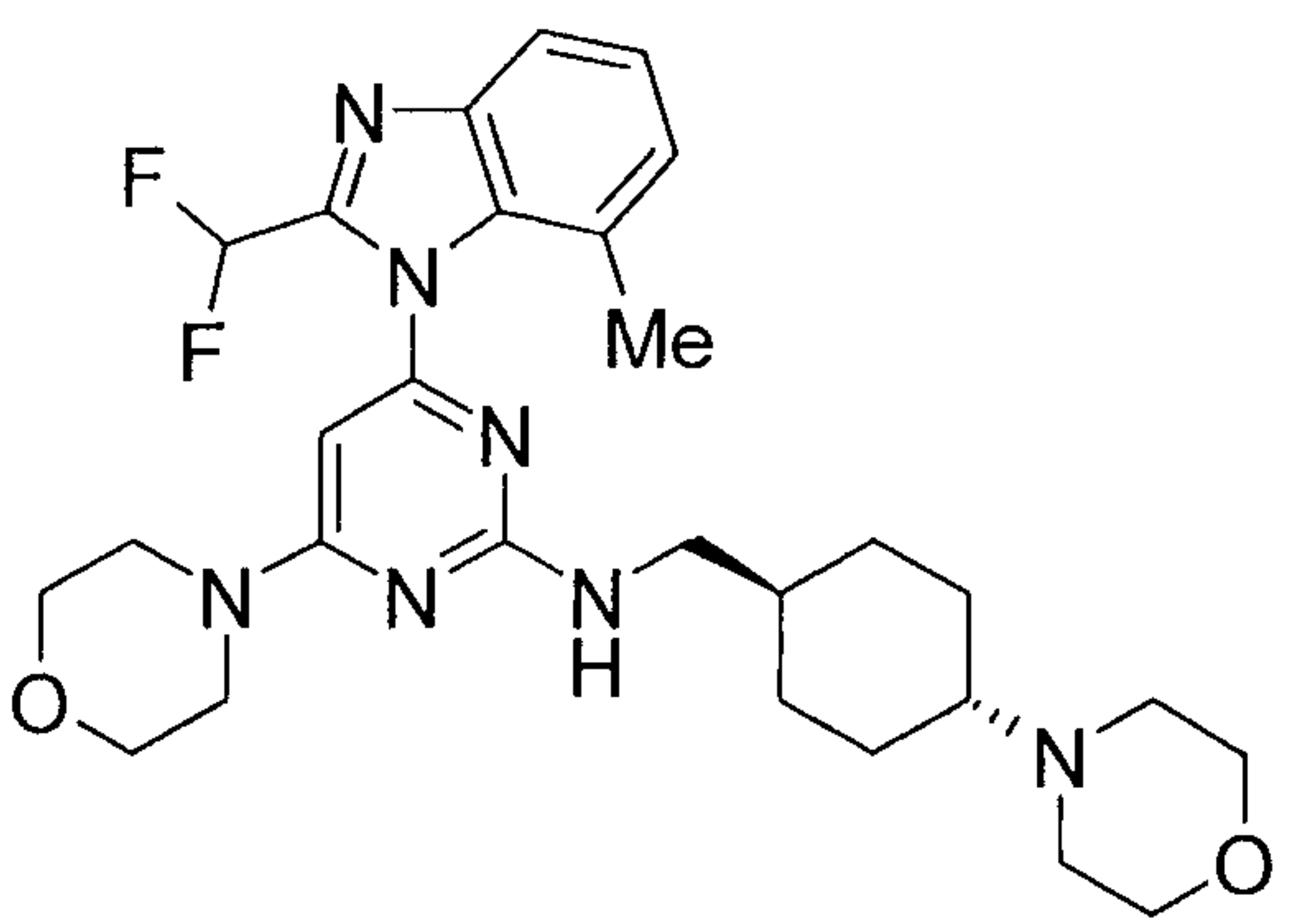
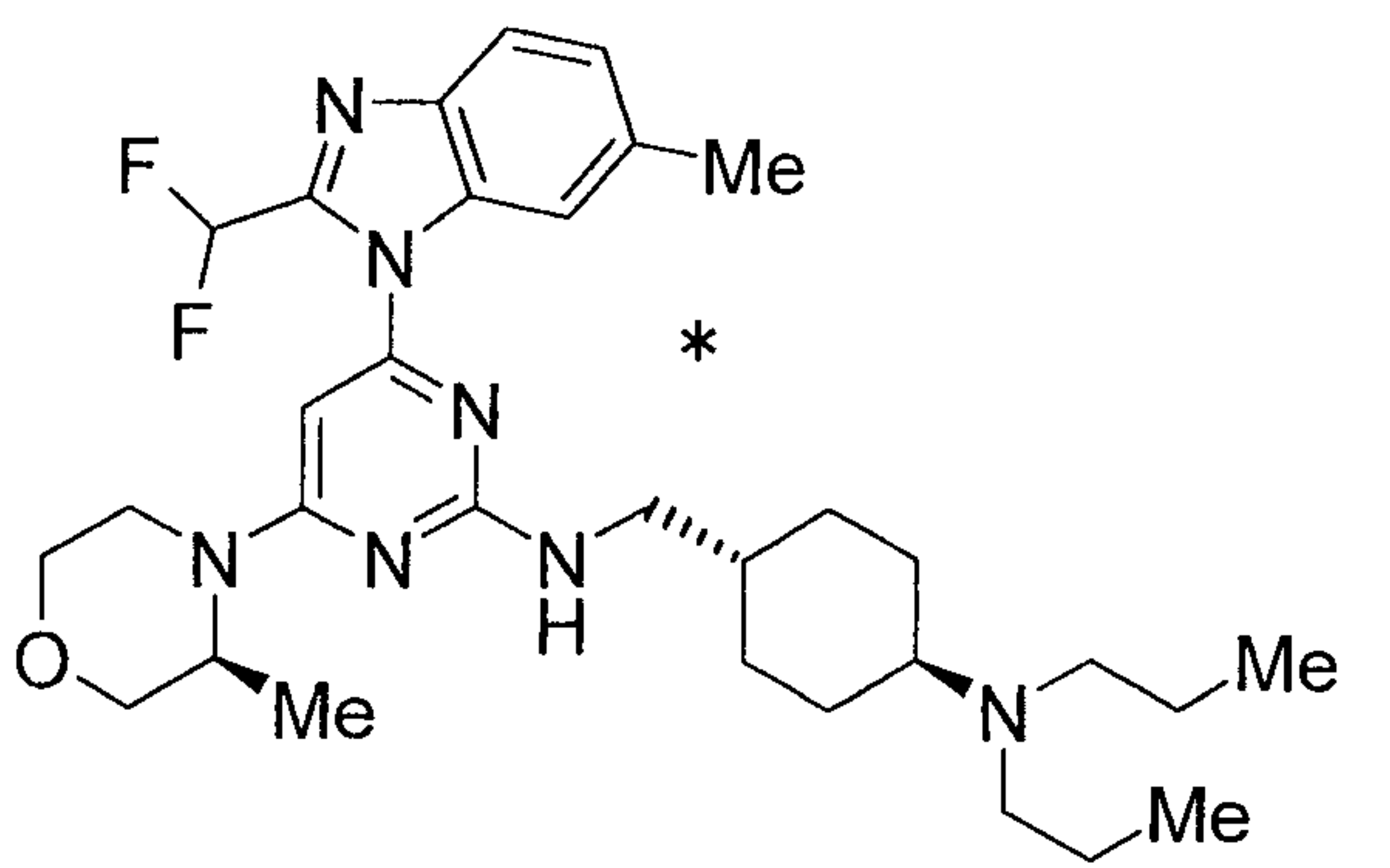
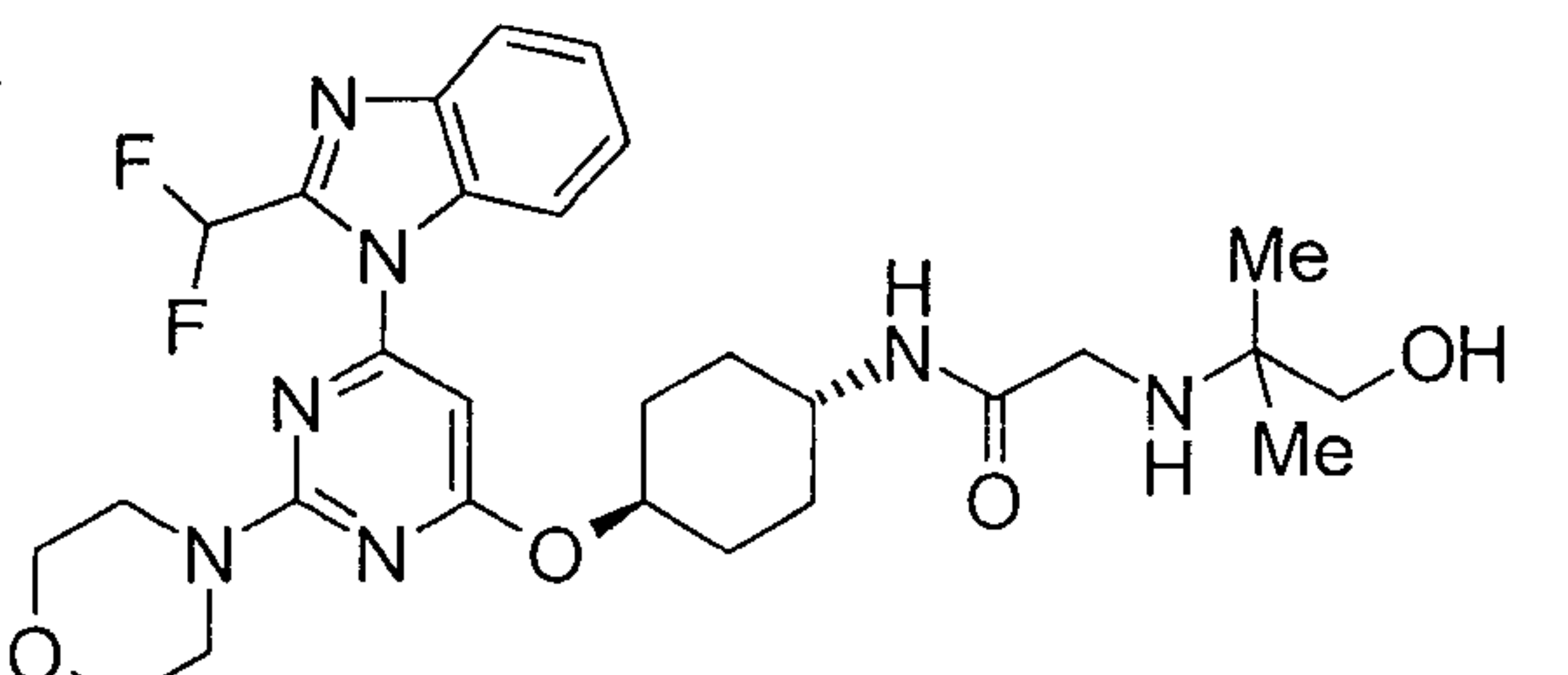
[0218]

[Table 62]

Ex	Str
120	
121	
122	
123	

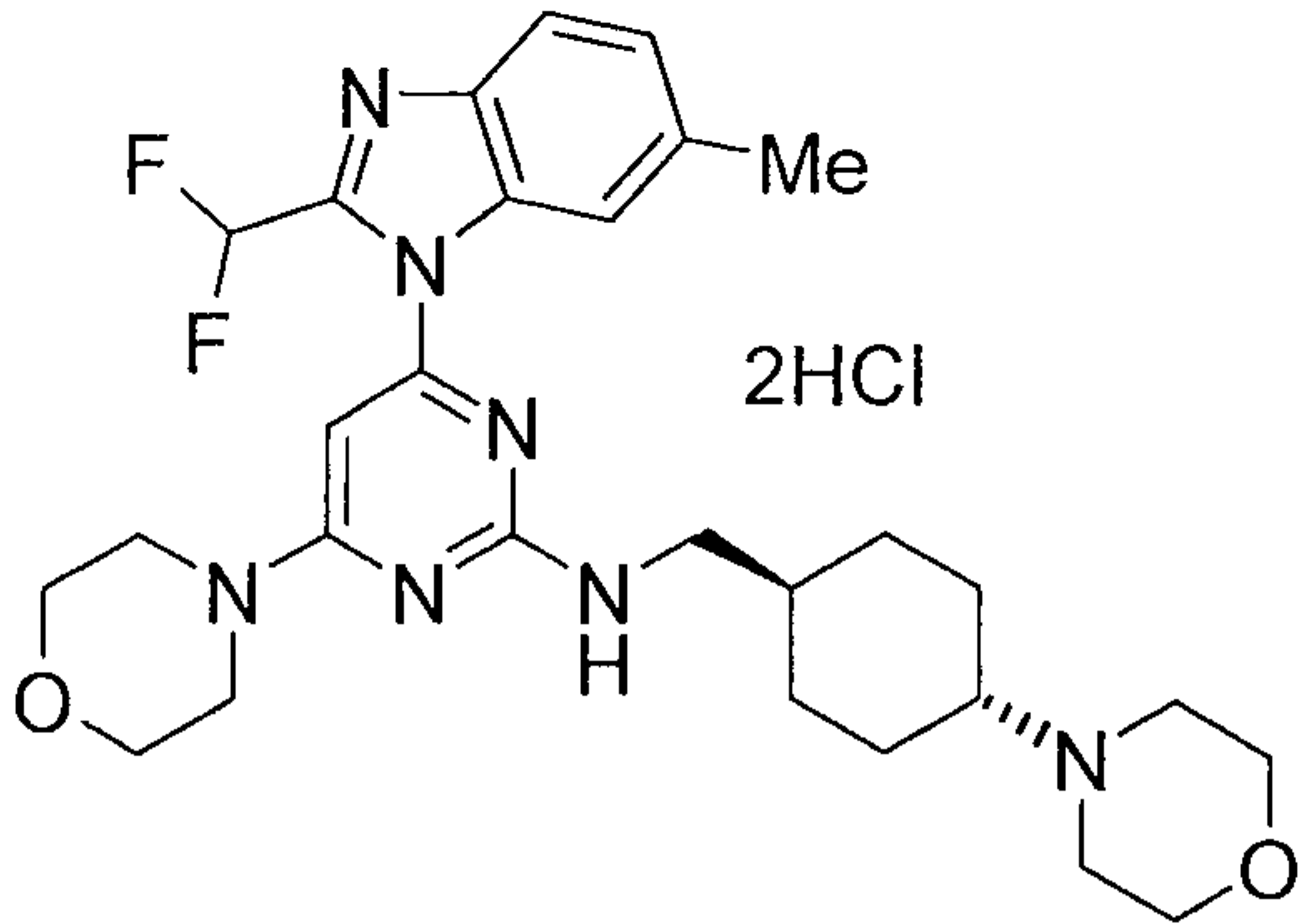
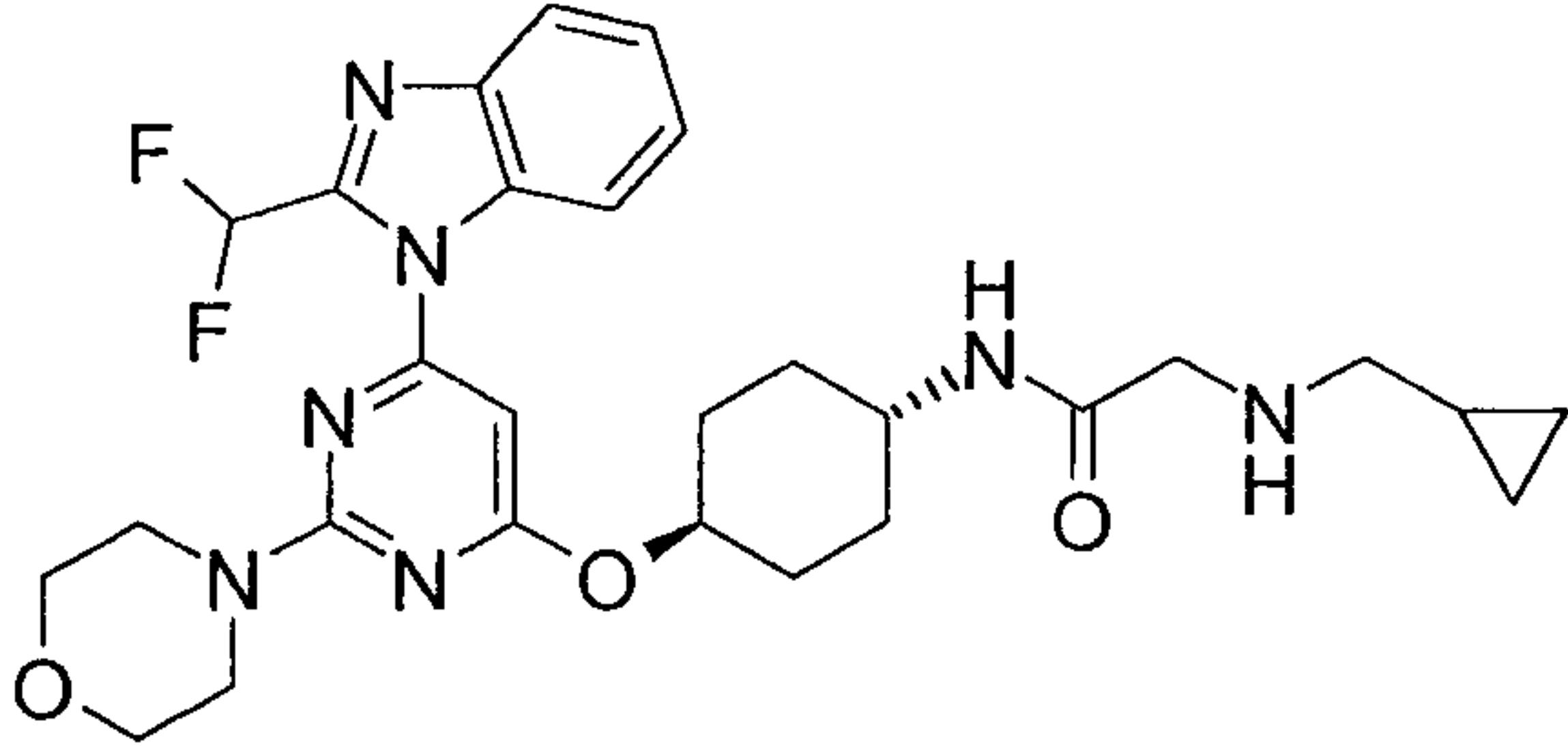
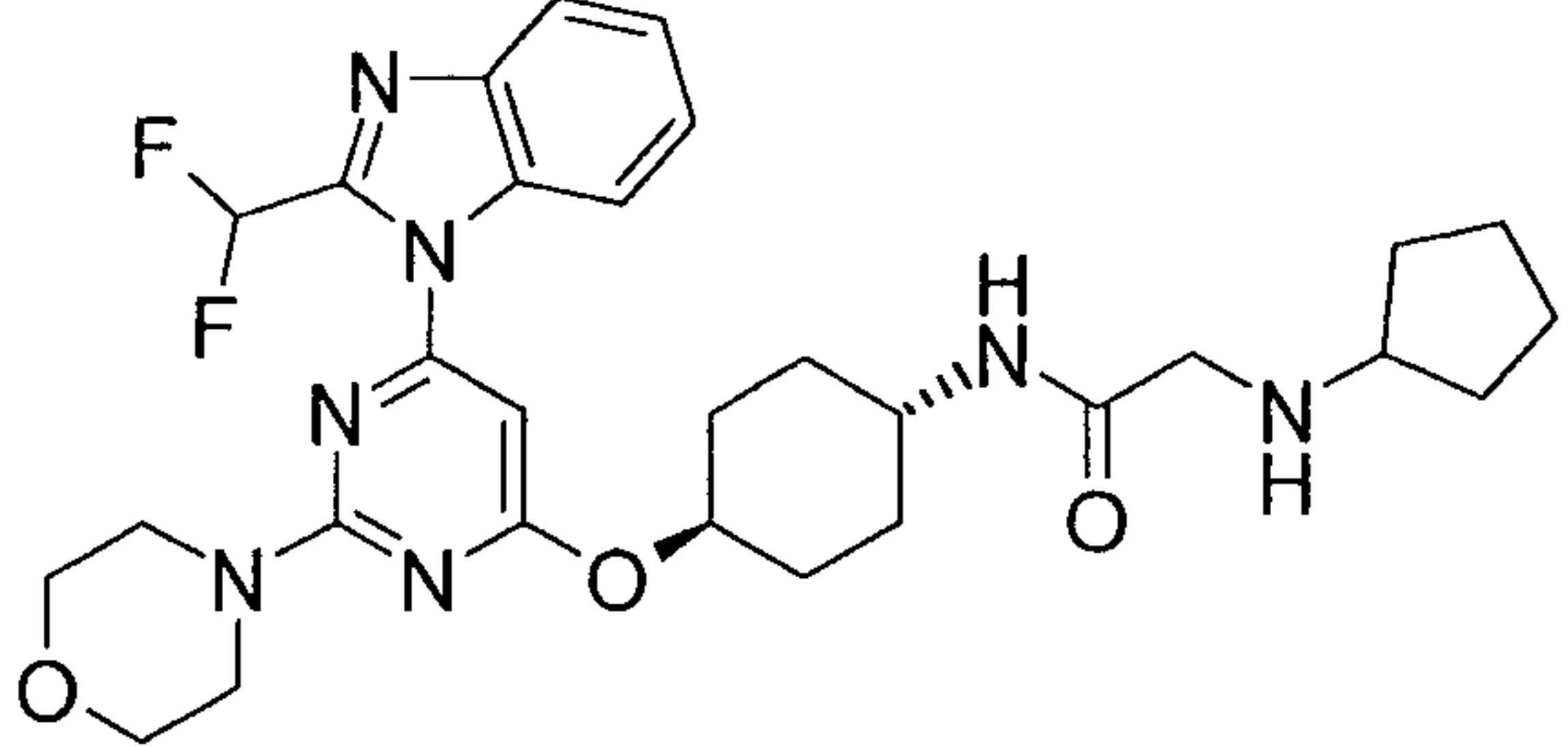
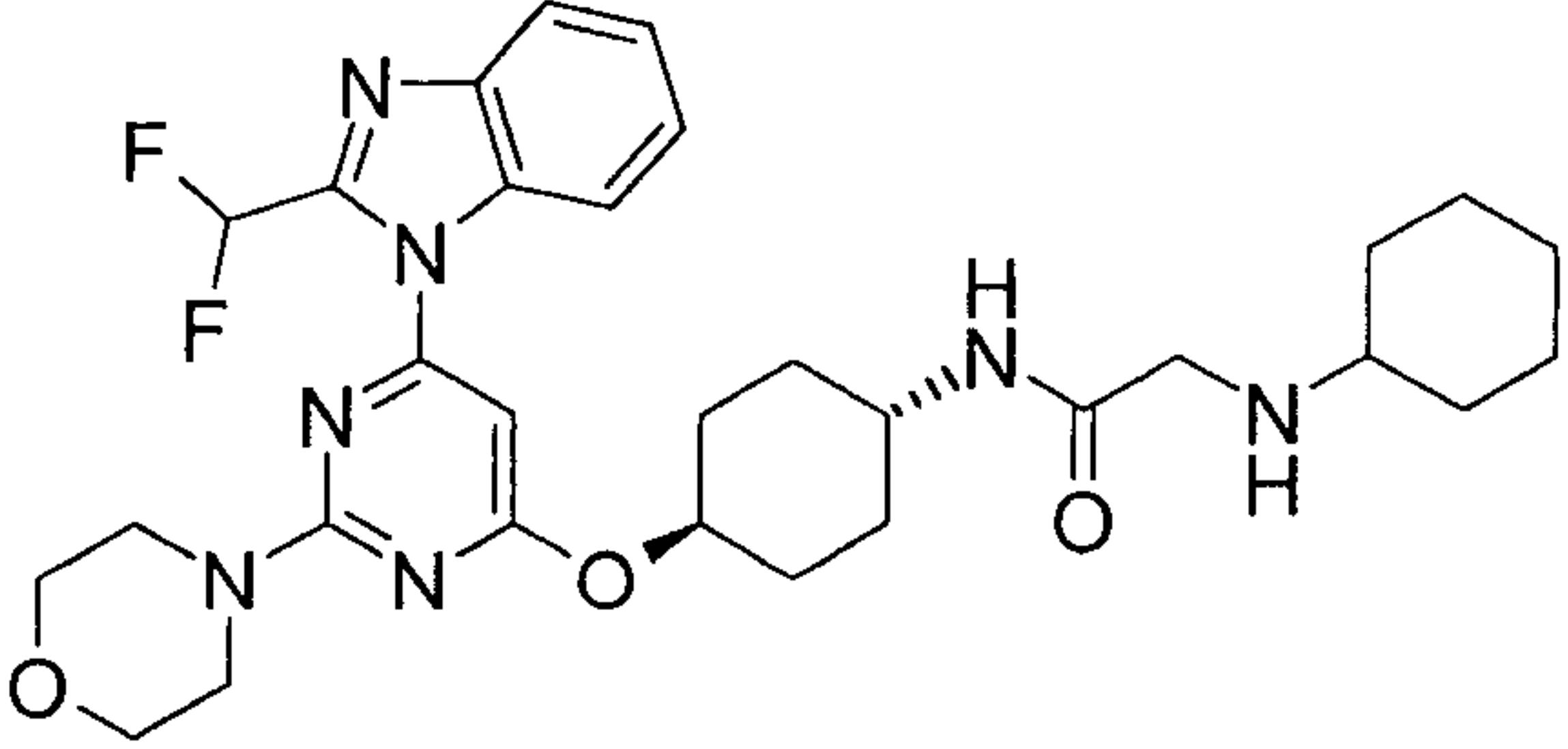
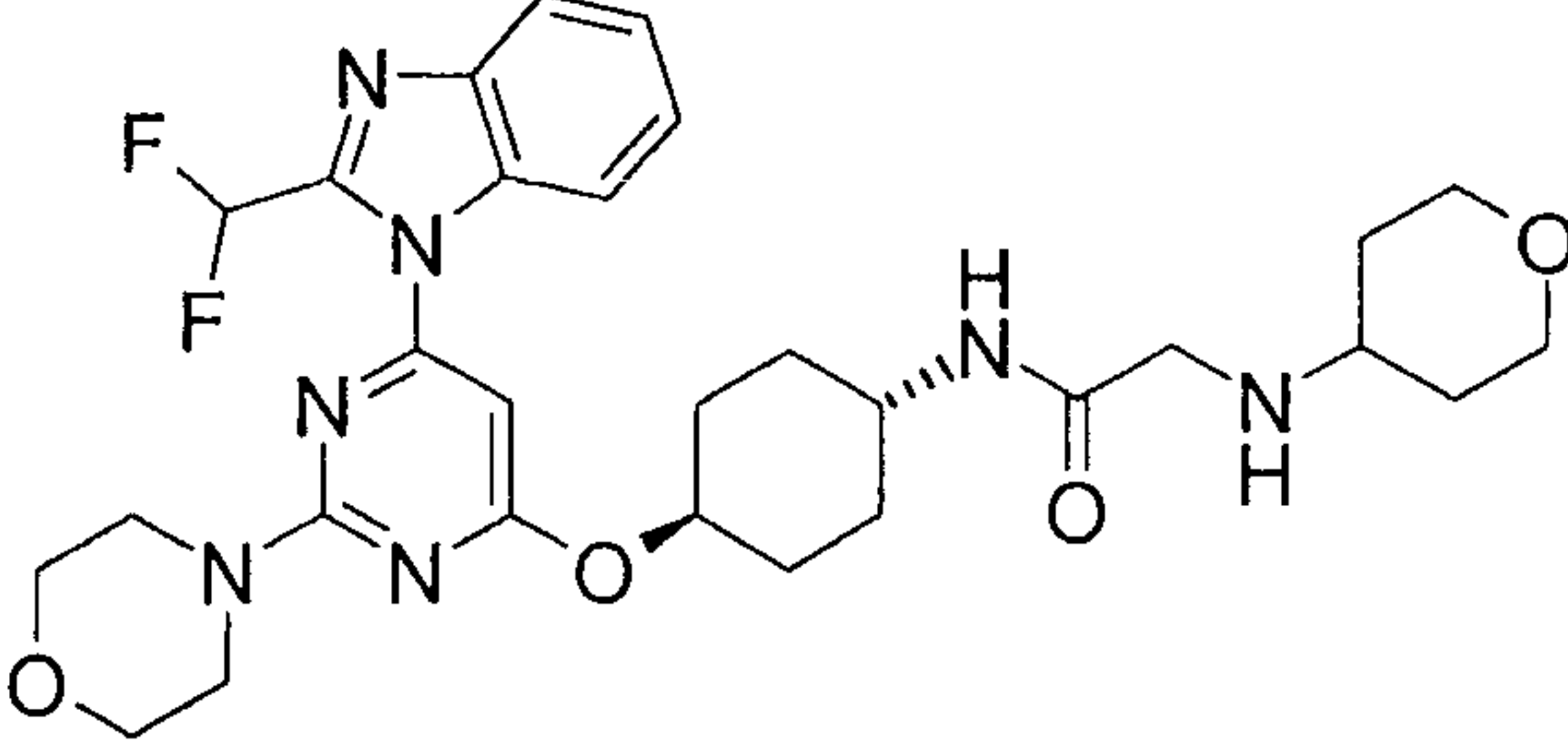
[0219]

[Table 63]

Ex	Str
124	
125	
126	
127	

[0221]

[Table 65]

Ex	Str
132	
133	
134	
135	
136	

[0222]

[Table 66]

Ex	Str
137	 <chem>C[C@H]1CC[C@@H](NC(=O)CC2=CN3C(=NC(=C3)C(F)F)N(C2)C4=CC=CC=C4)C[C@H](O[C@@H]5CCCC[C@H]5OC6=NC7=C(NC8=CC=CC=C8N(C7)C(F)F)N(C6)C9=CC=CC=C9N9)C6</chem>
138	 <chem>C1CC[C@H](O[C@@H]2CCCC[C@H]2OC3=NC4=C(NC5=CC=CC=C5N(C4)C(F)F)N(C3)C6=CC=CC=C6N6)C1C(=O)CC[C@H](N[C@@H]7CCOC7)N</chem>
139	 <chem>C1CC[C@H](O[C@@H]2CCCC[C@H]2OC3=NC4=C(NC5=CC=CC=C5N(C4)C(F)F)N(C3)C6=CC=CC=C6N6)C1C(=O)CC[C@H](N[C@@H]7CCOC7)N</chem>
140	 <chem>C1CC[C@H](O[C@@H]2CCCC[C@H]2OC3=NC4=C(NC5=CC=CC=C5N(C4)C(F)F)N(C3)C6=CC=CC=C6N6)C1C(=O)CC[C@H](N[C@@H]7C8=CC9CC1CC2C(C8)CC9)N7</chem>
141	 <chem>C1CC[C@H](O[C@@H]2CCCC[C@H]2OC3=NC4=C(NC5=CC=CC=C5N(C4)C(F)F)N(C3)C6=CC=CC=C6N6)C1C(=O)CC[C@H](N[C@@H]7C8=CC9CC1CC2C(C8)CC9)N7</chem>

[0223]

[Table 67]

Ex	Str
142	
143	
144	
145	
146	

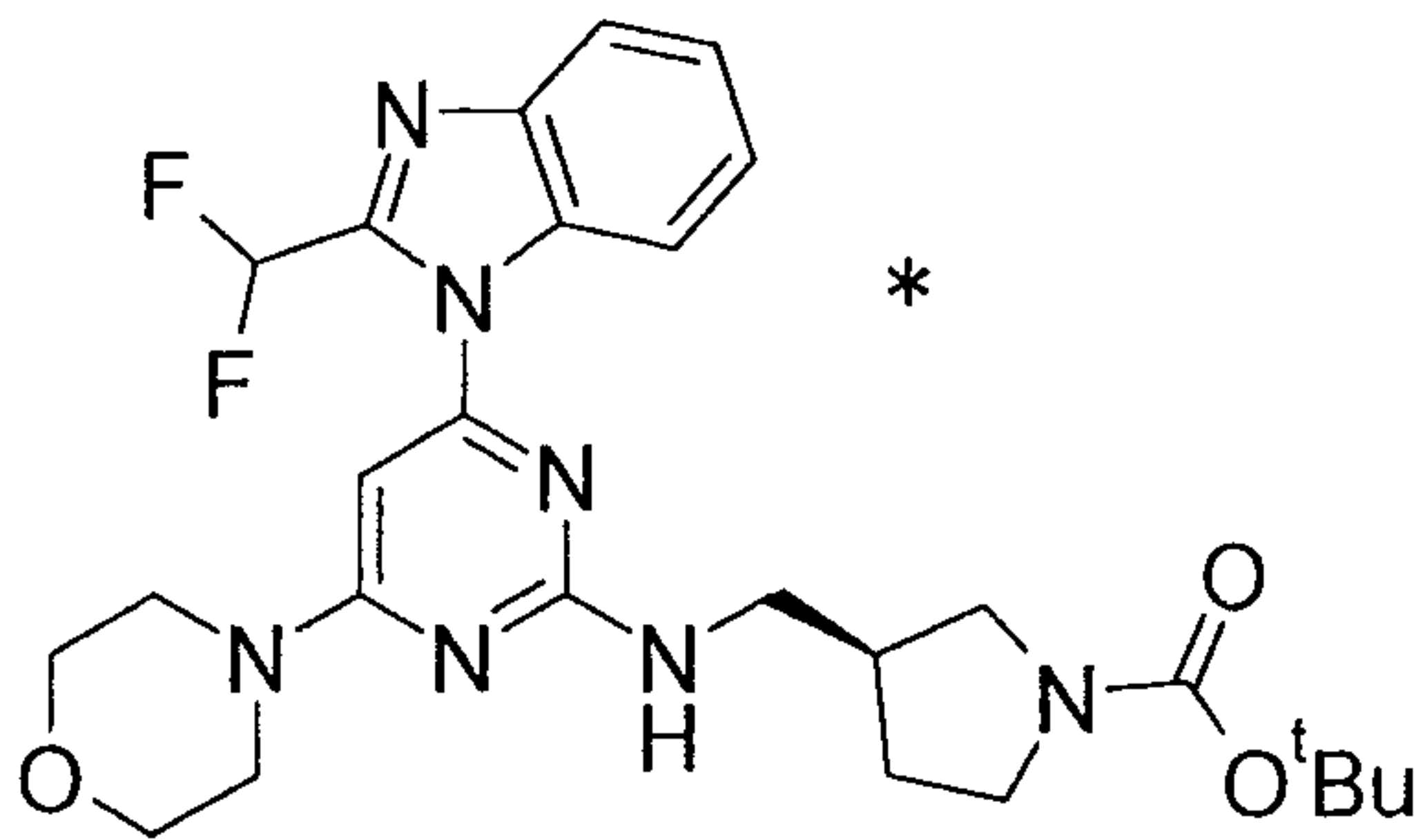
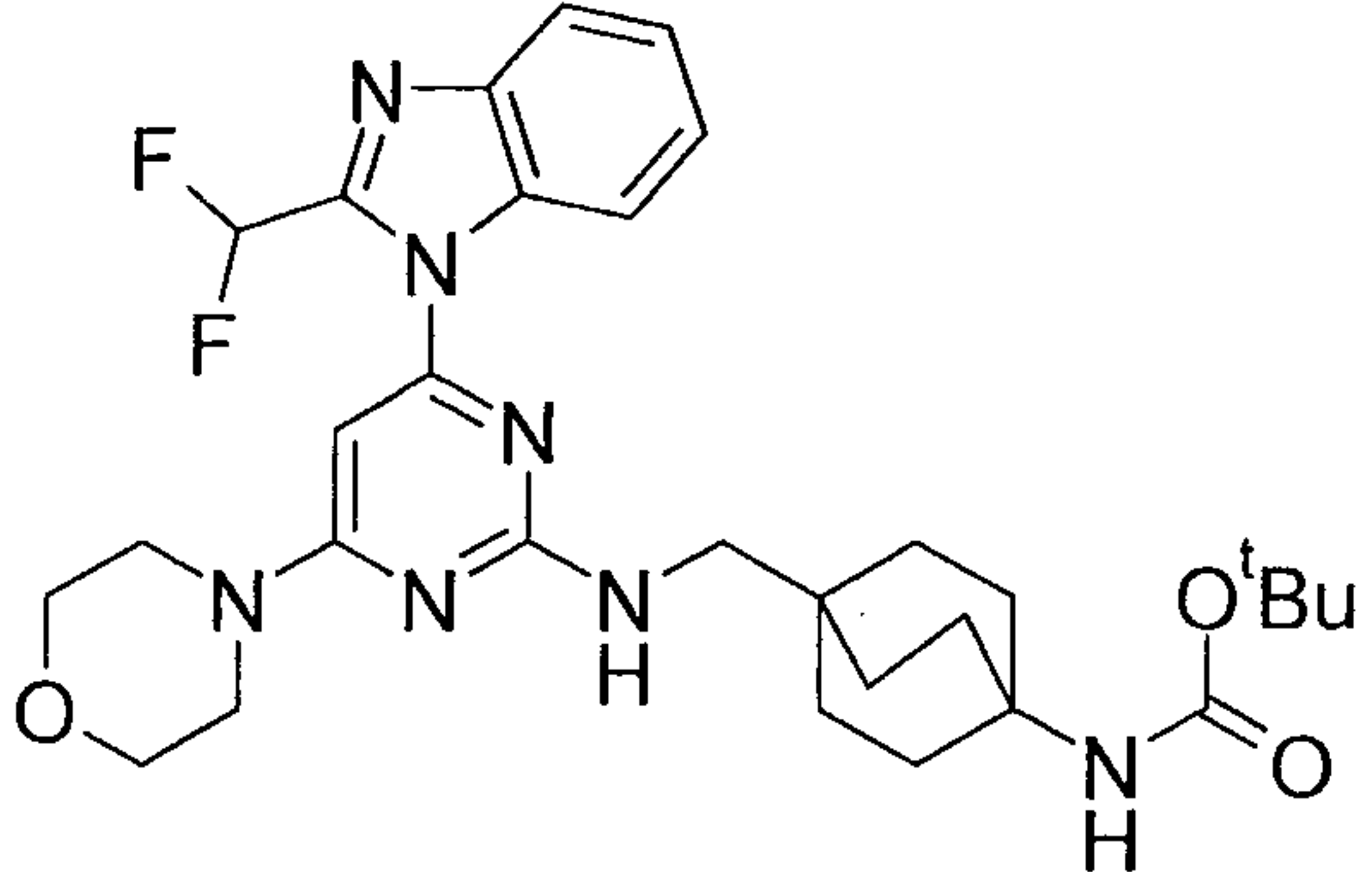
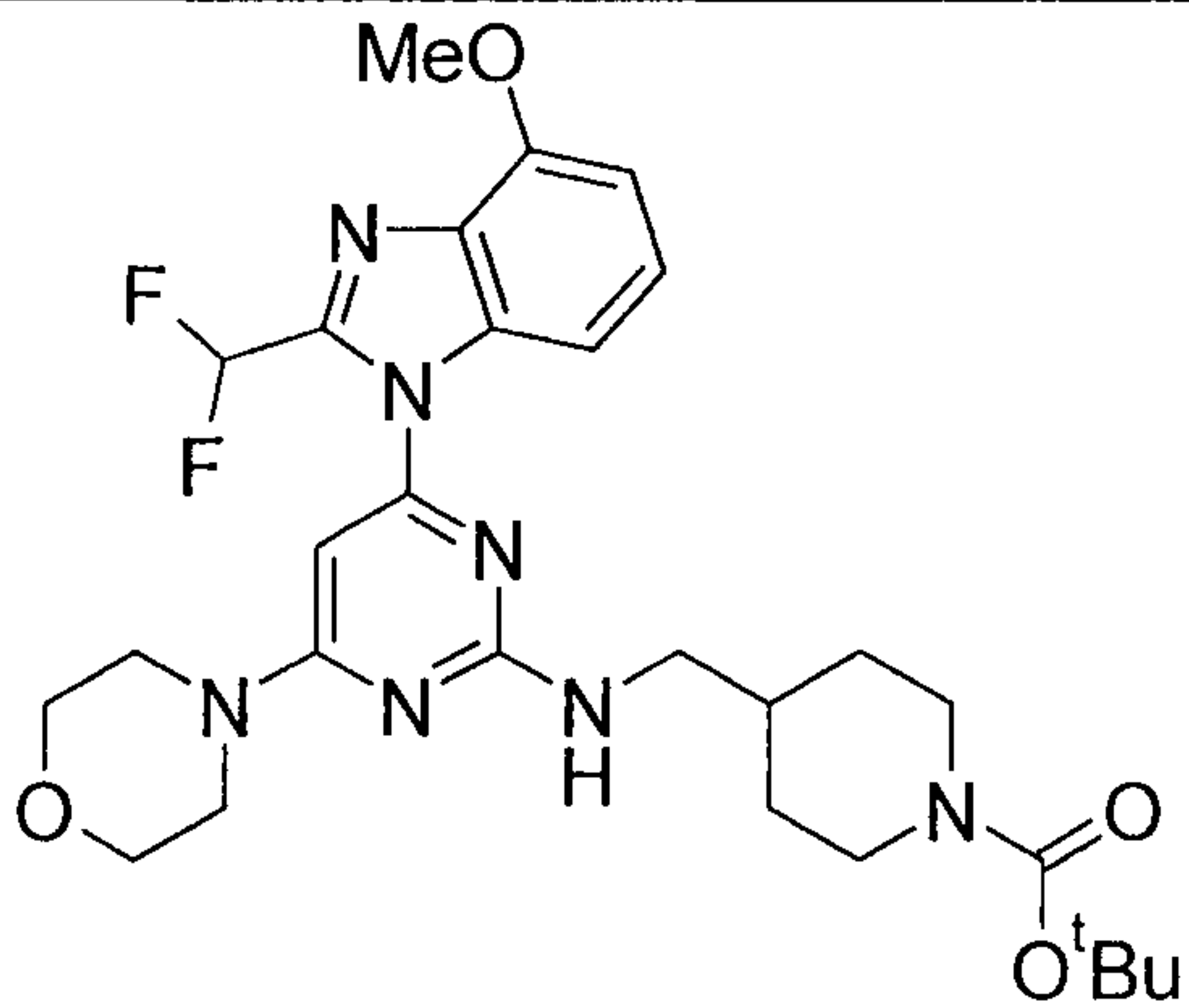
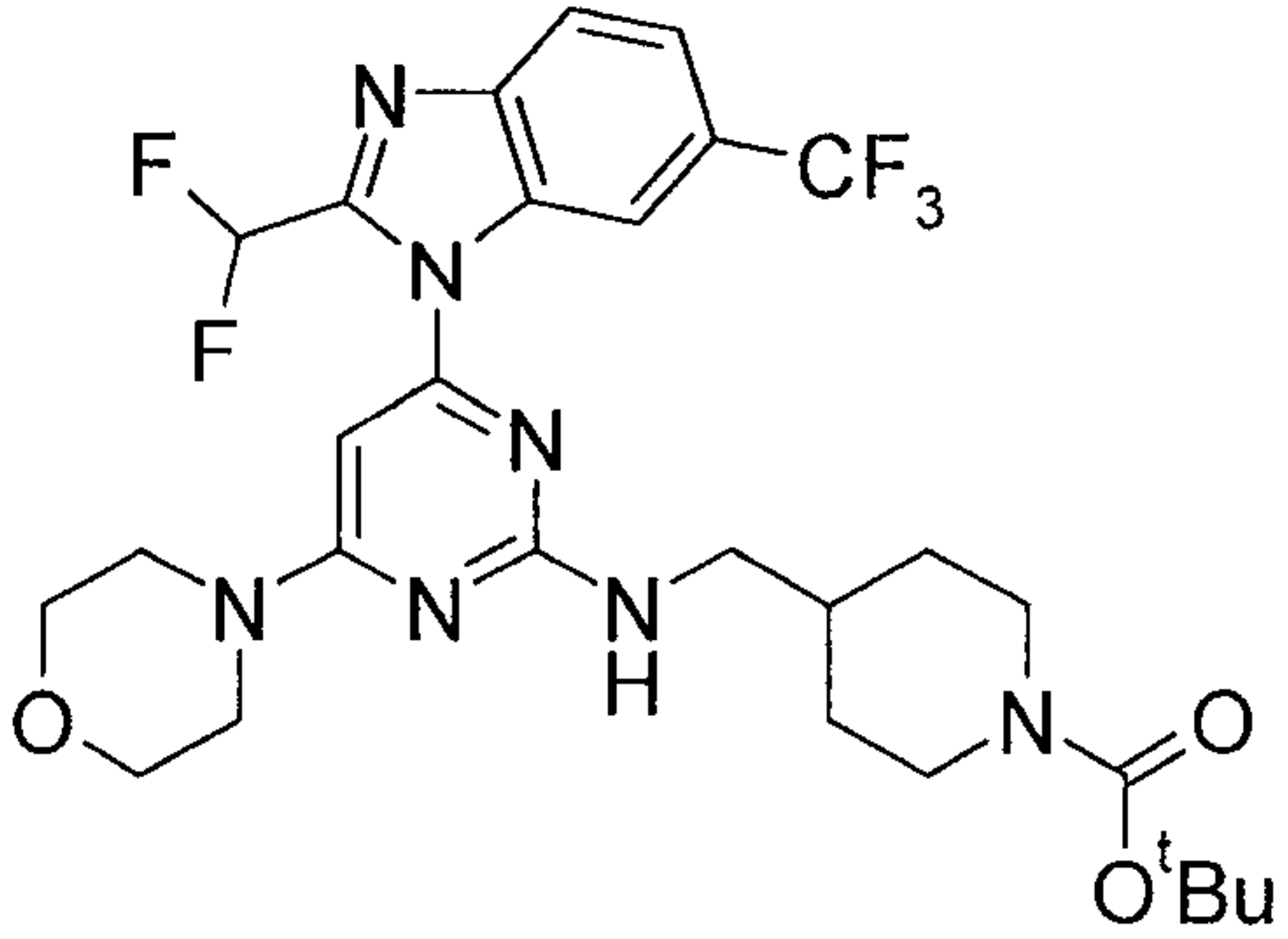
[0224]

[Table 68]

Ex	Str
147	
148	
149	
150	

[0225]

[Table 69]

Ex	Str
151	
152	
153	
154	

[0226]

[Table 70]

Ex	Str
155	<chem>Cc1ccnc(CNc2nc(N3C(=Nc4ccccc4N3C(F)F)nc5ccccc52)c6ccn6)c7ccn7</chem>
156	<chem>C1CCN(C1)c2cc(CNc3nc(N4C(=Nc5ccccc5N4C(F)F)nc6ccccc63)nc7ccn7)ccn2</chem>
157	<chem>CN1CCN(C1)c2cc(CNc3nc(N4C(=Nc5ccccc5N4C(F)F)nc6ccccc63)nc7ccn7)ccn2</chem>
158	<chem>CCOC(=O)N1CCN(C1)c2cc(CNc3nc(N4C(=Nc5ccccc5N4C(F)F)nc6ccccc63)nc7ccn7)ccn2</chem>

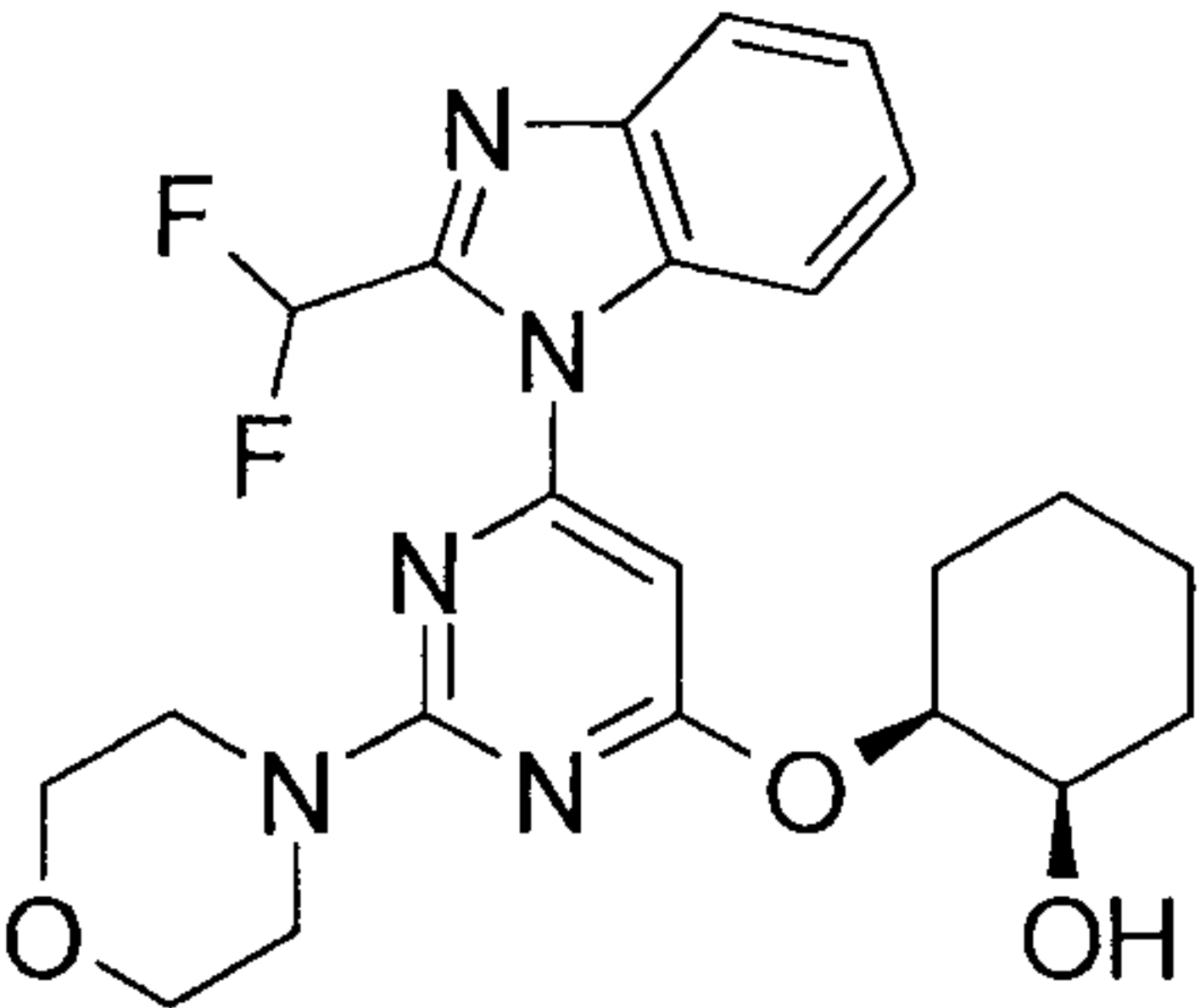
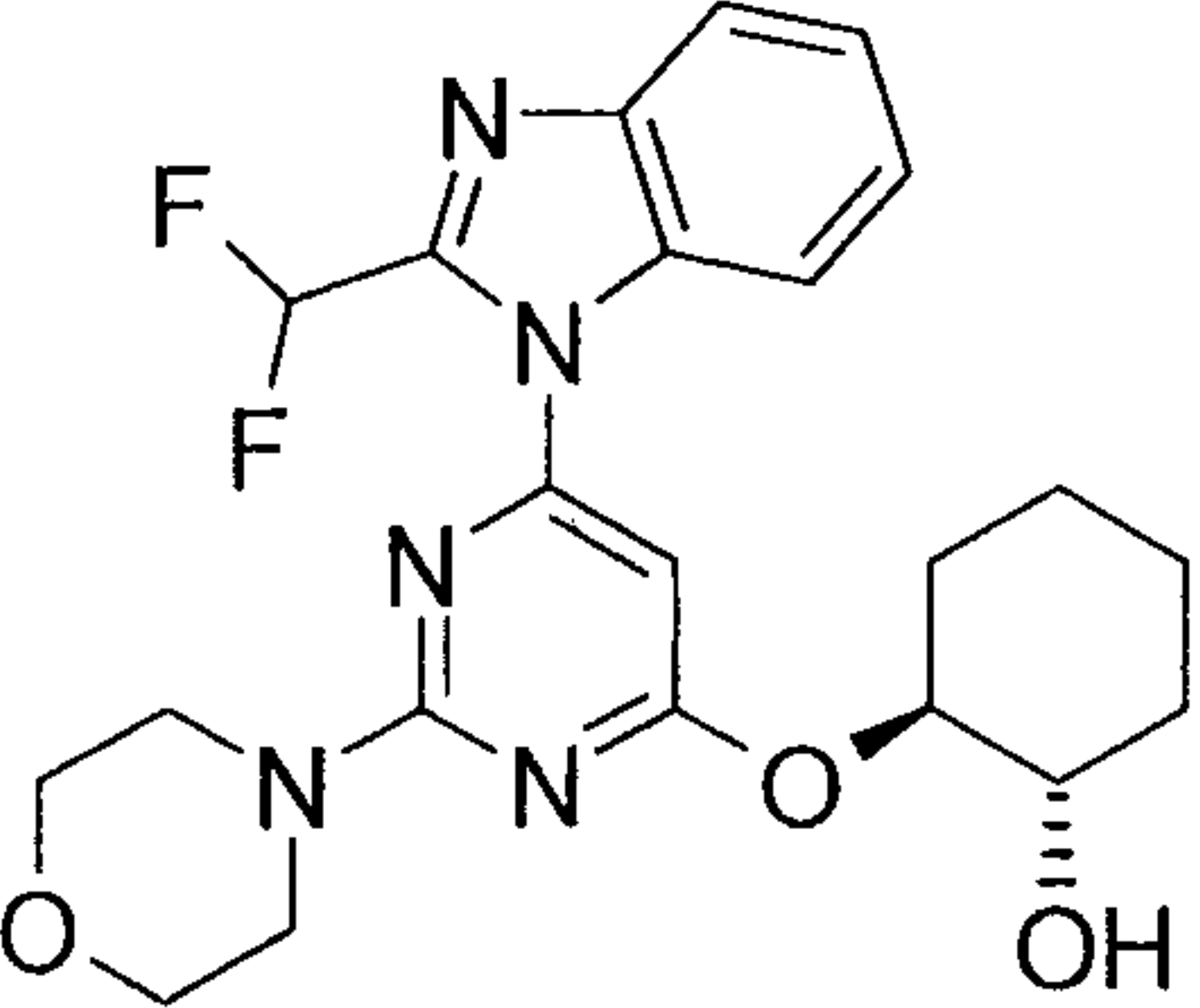
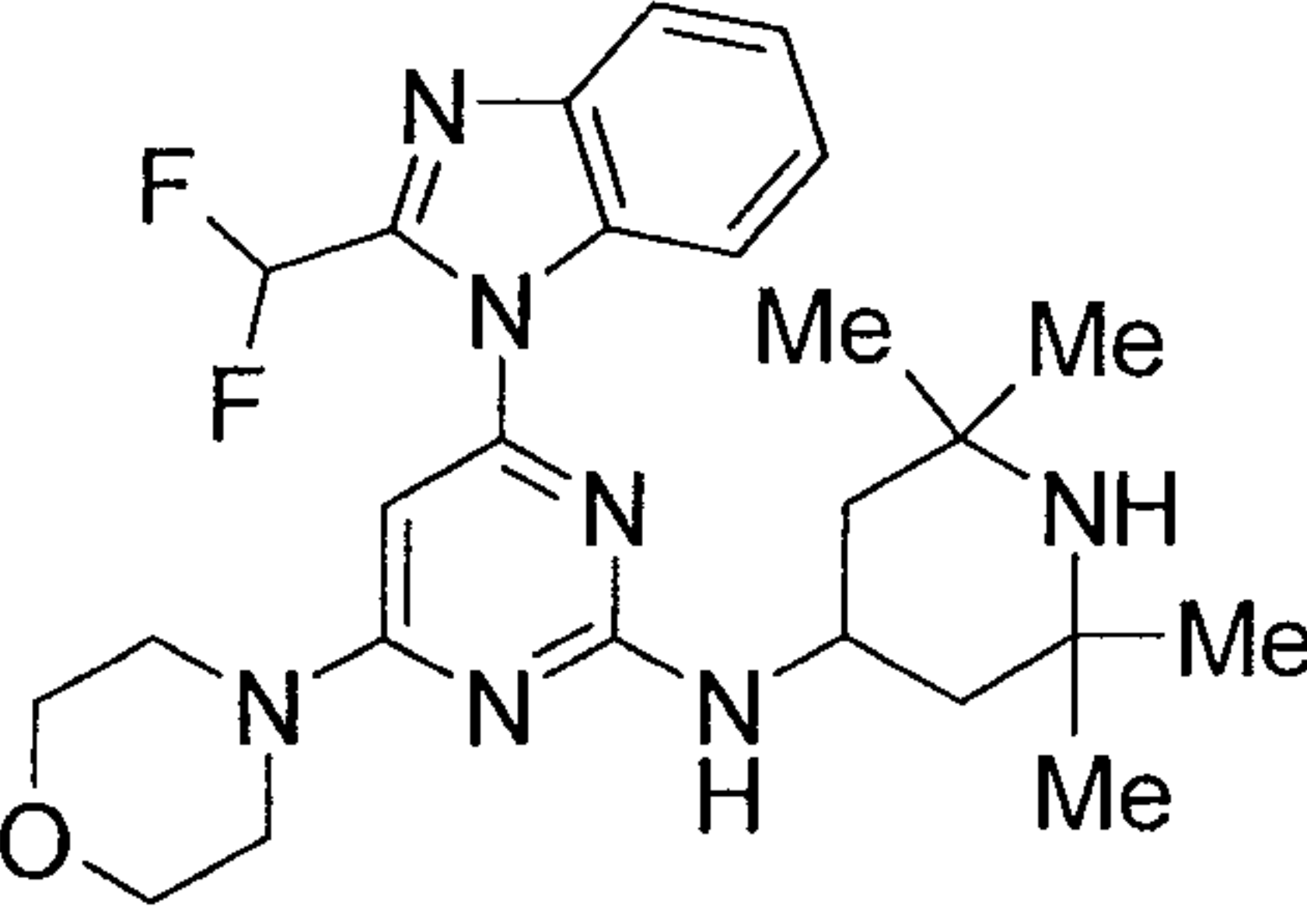
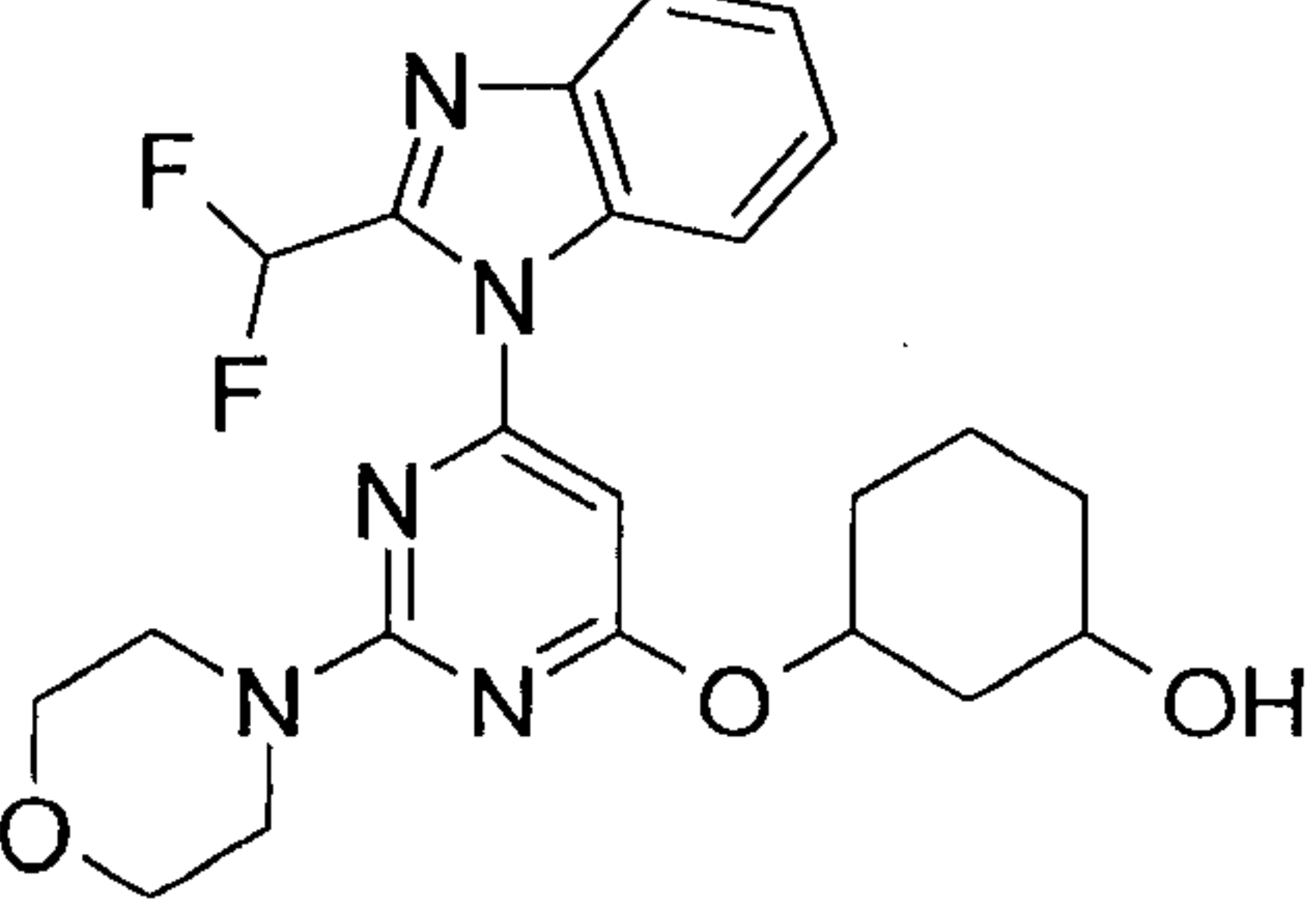
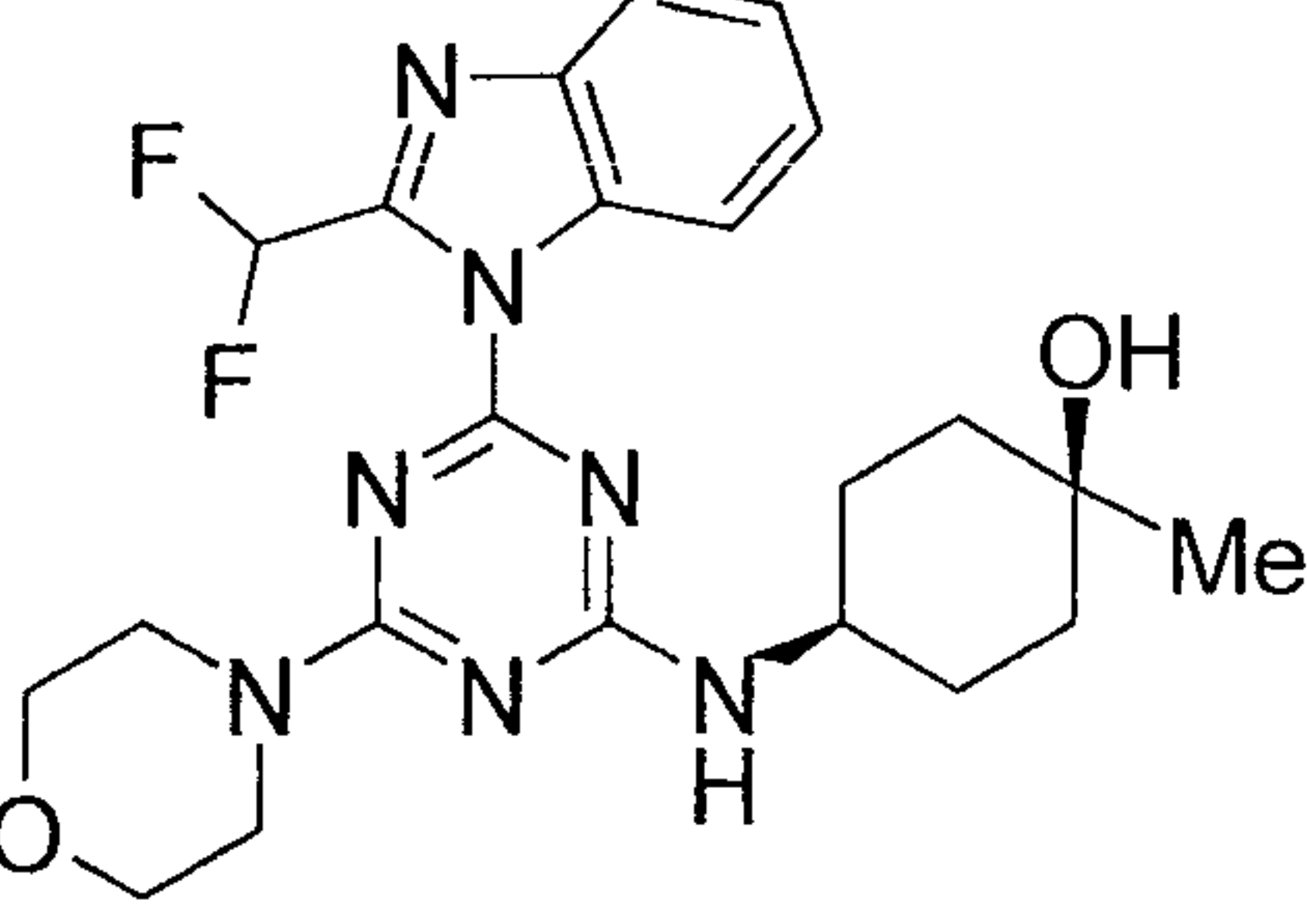
[0227]

[Table 71]

Ex	Str
159	
160	
161	
162	
163	

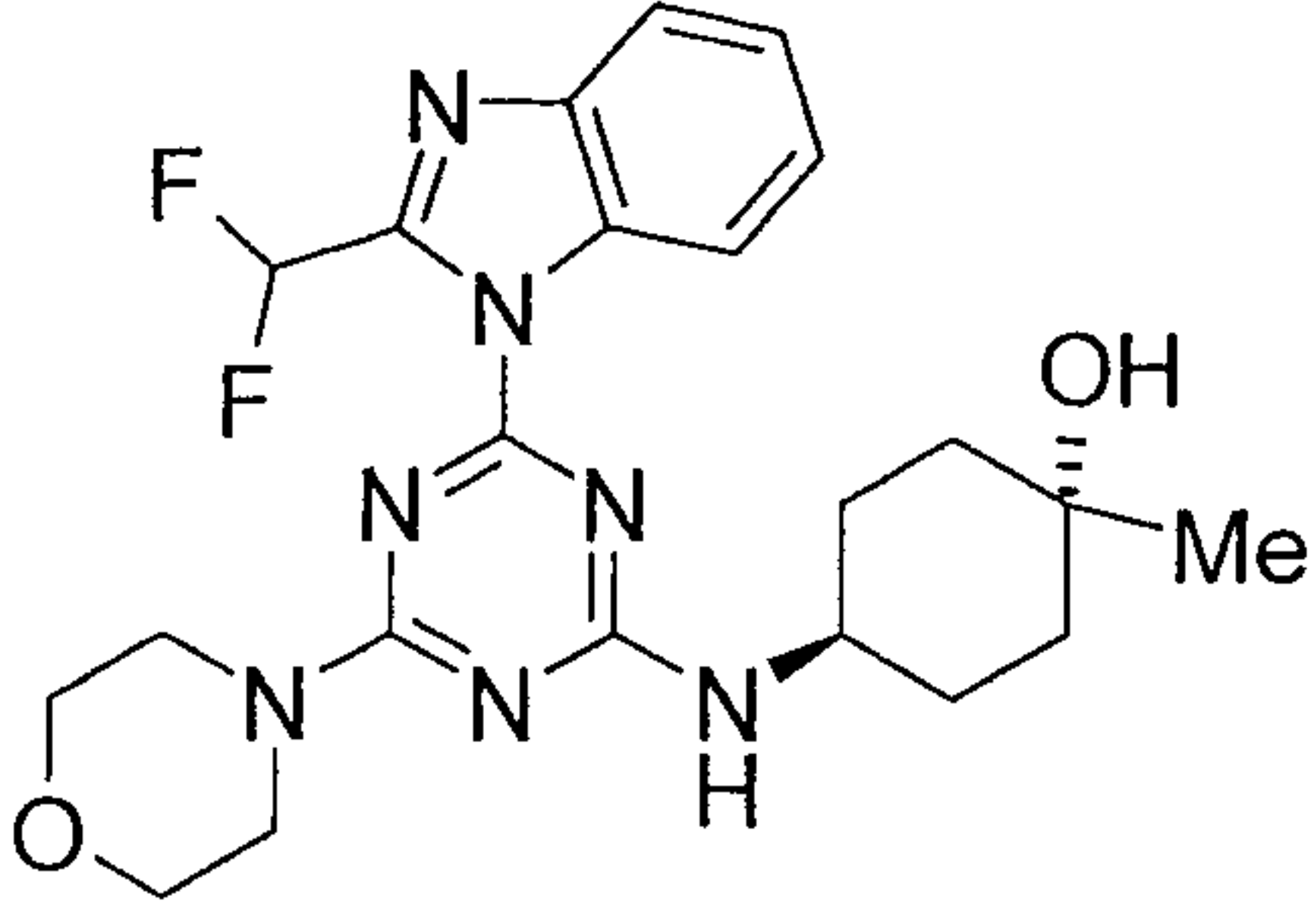
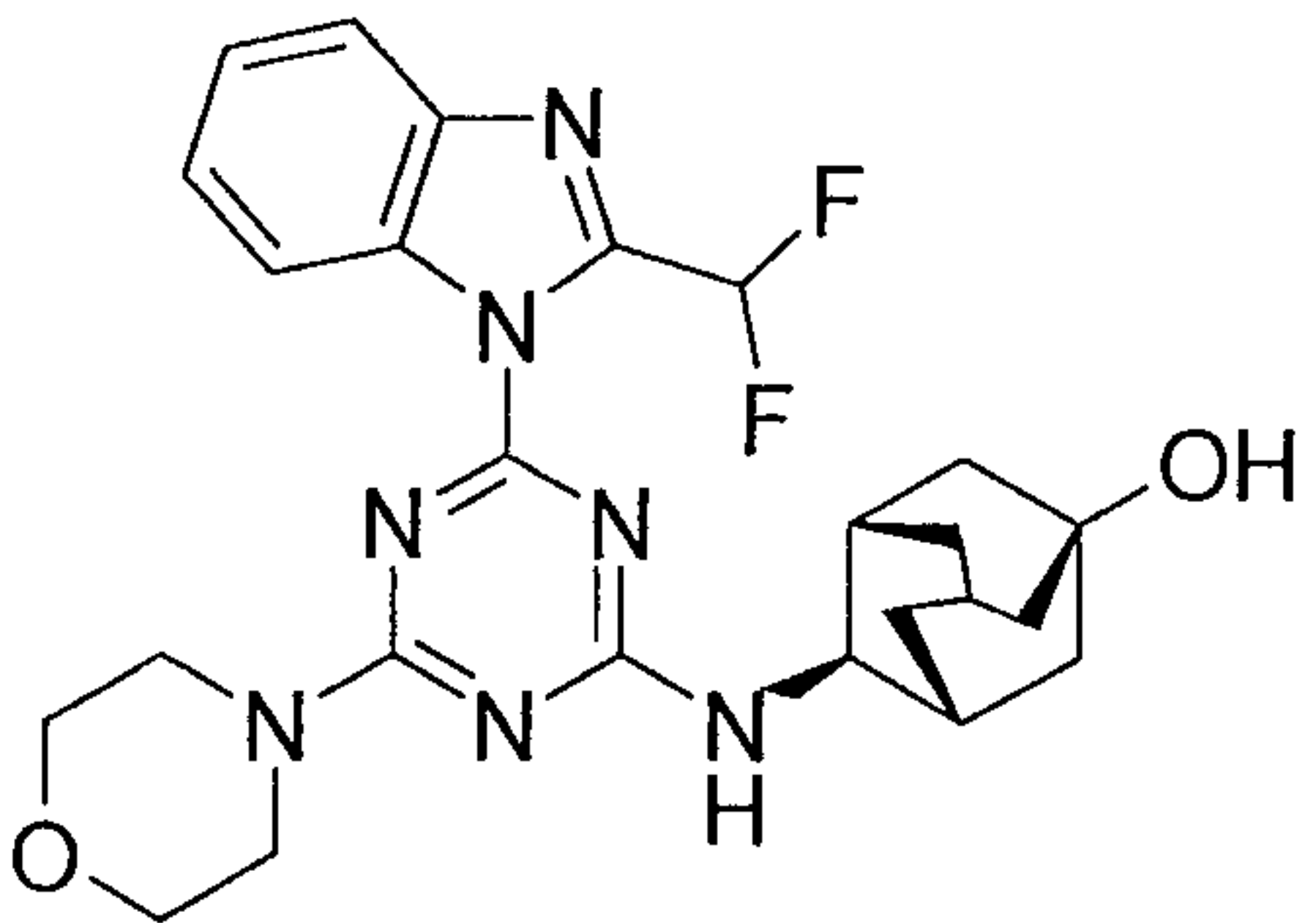
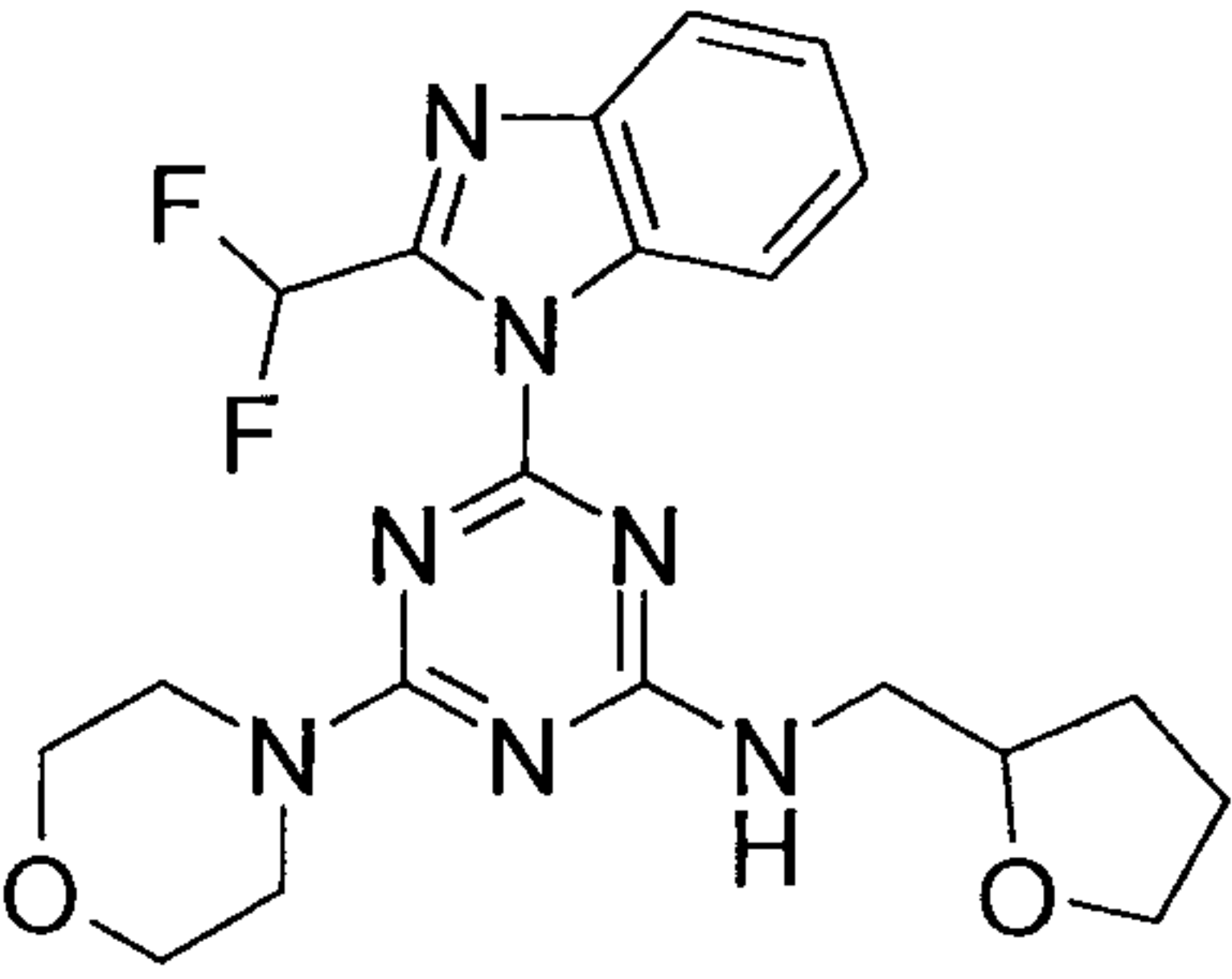
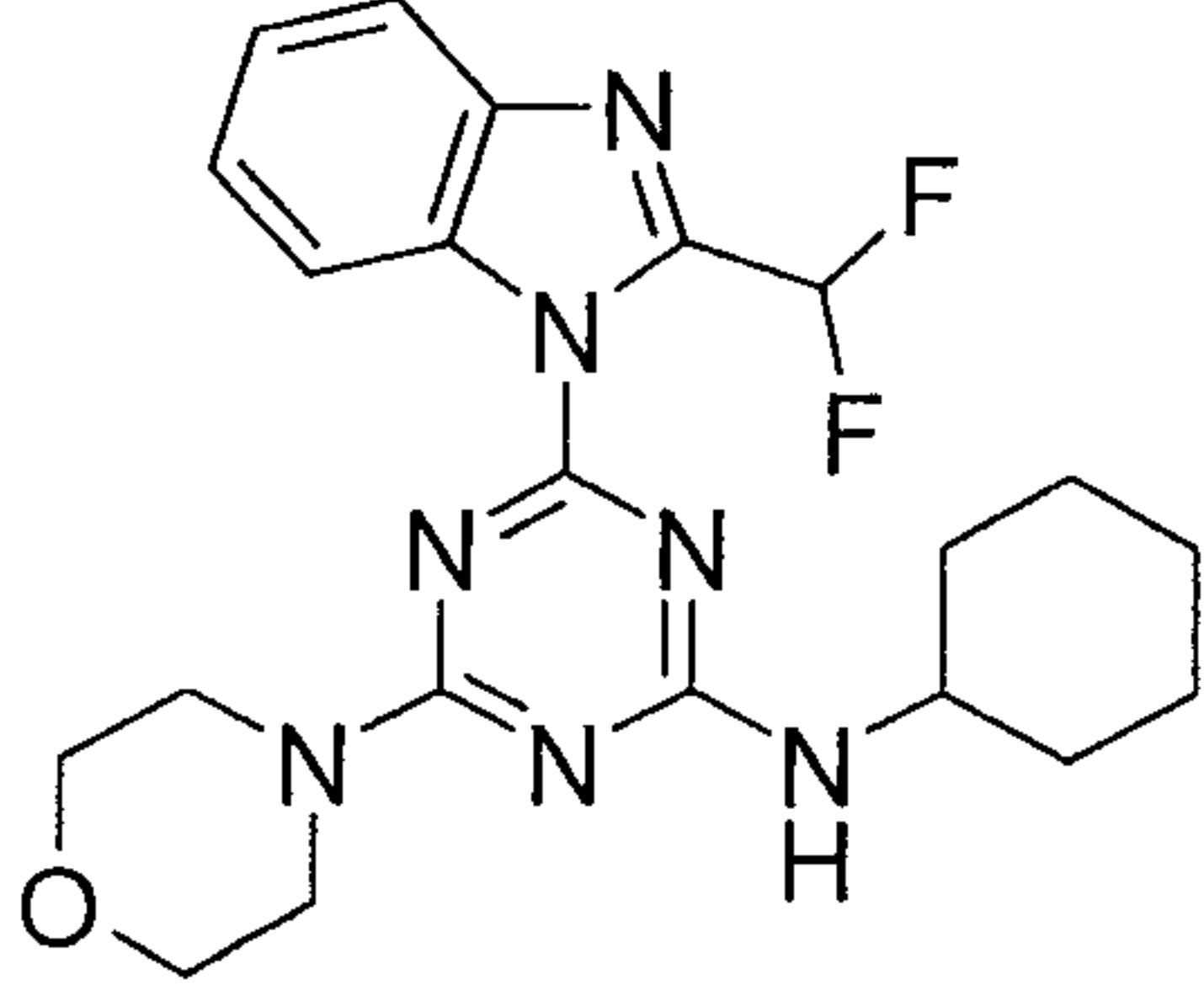
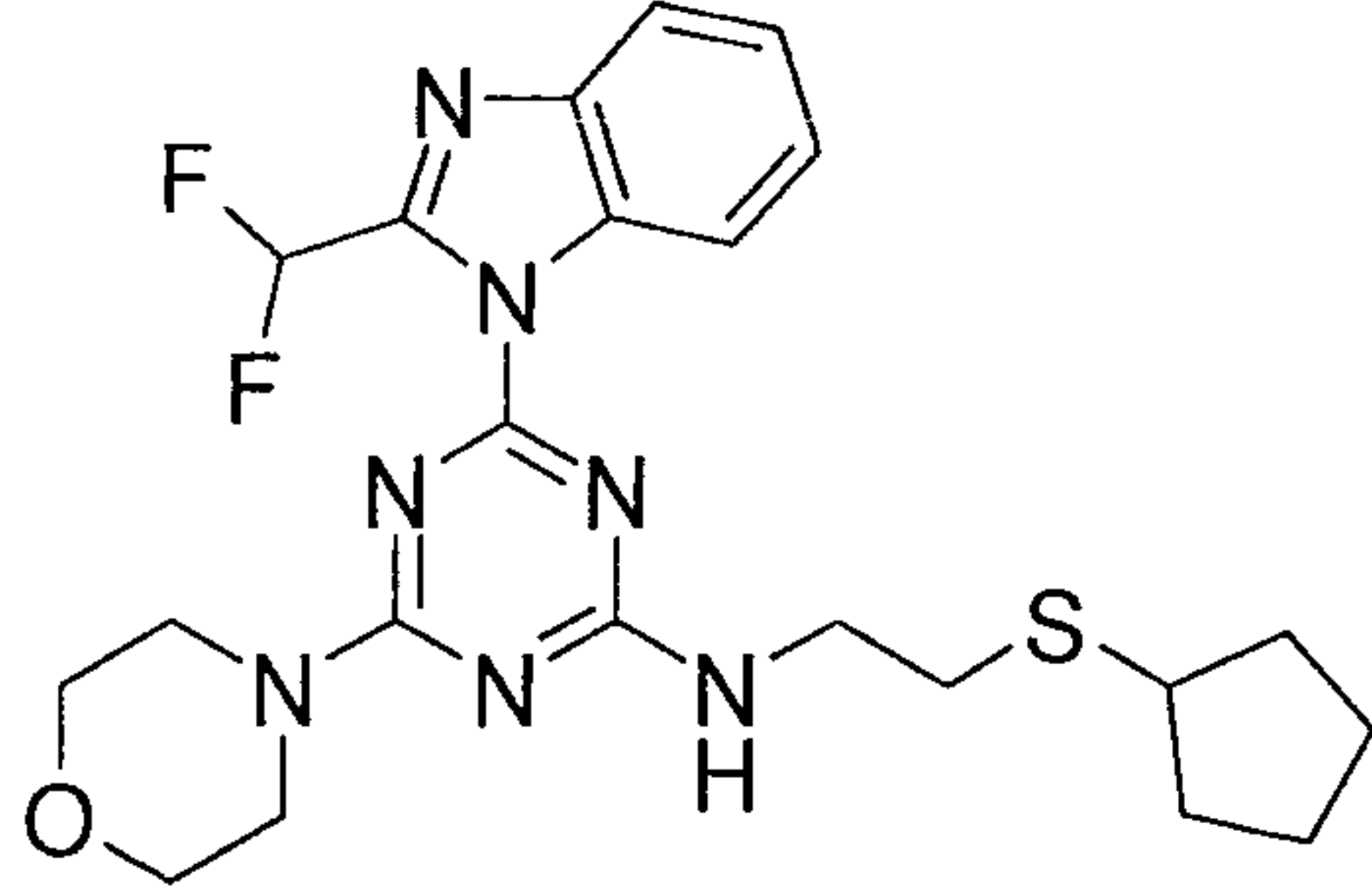
[0228]

[Table 72]

Ex	Str
164	
165	
166	
167	
168	

[0229]

[Table 73]

Ex	Str
169	 <chem>C[C@H]1CCCC[C@H]1NC2=NC3=C(N2)N(C3)N(C4=CC=CC=C4C(F)F)N5CCOCC5</chem>
170	 <chem>O[C@H]1C2CCC(CC2)C1NC3=NC4=C(N3)N(C4)N(C5=CC=CC=C5C(F)F)N6CCOCC6</chem>
171	 <chem>C1CCOC1CN2C3=NC4=C(N2)N(C3)N(C4)N(C5=CC=CC=C5C(F)F)N6CCOCC6</chem>
172	 <chem>C1CCC(CC1)NC2=NC3=C(N2)N(C3)N(C4=CC=CC=C4C(F)F)N5CCOCC5</chem>
173	 <chem>C1CCC(CC1)SCCN2C3=NC4=C(N2)N(C3)N(C4)N(C5=CC=CC=C5C(F)F)N6CCOCC6</chem>

[0230]

[Table 74]

Ex	Str
174	
175	
176	
177	
178	

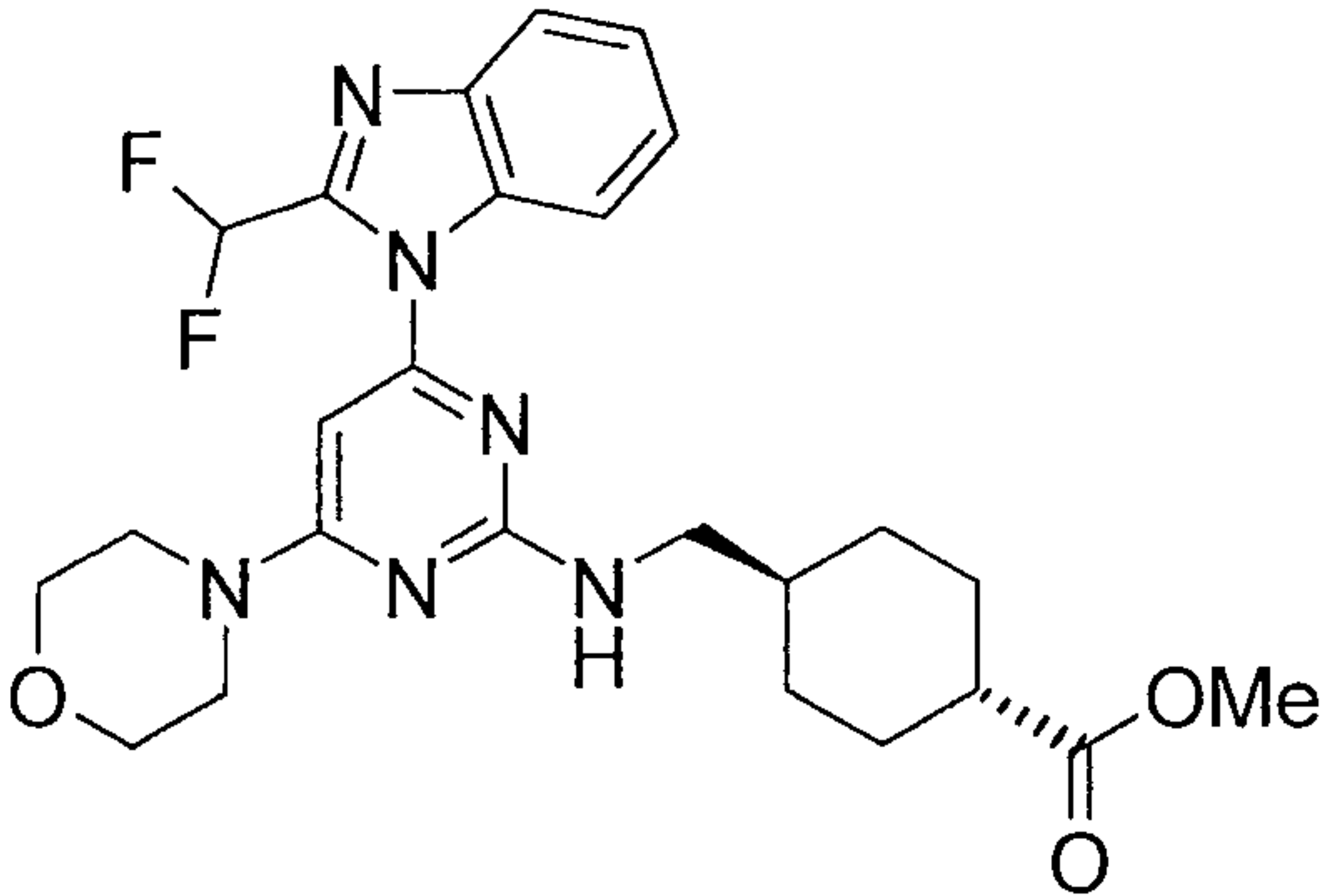
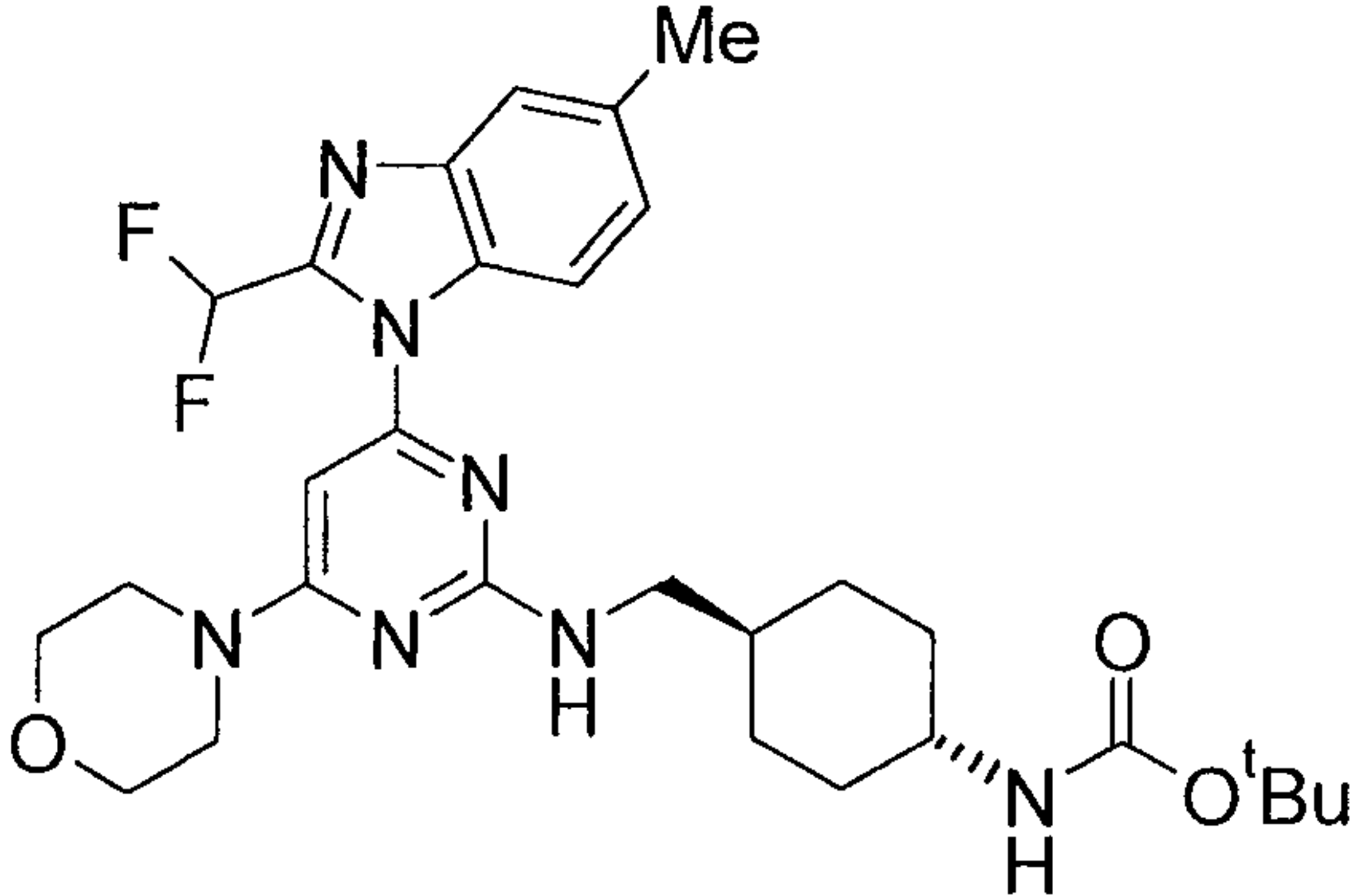
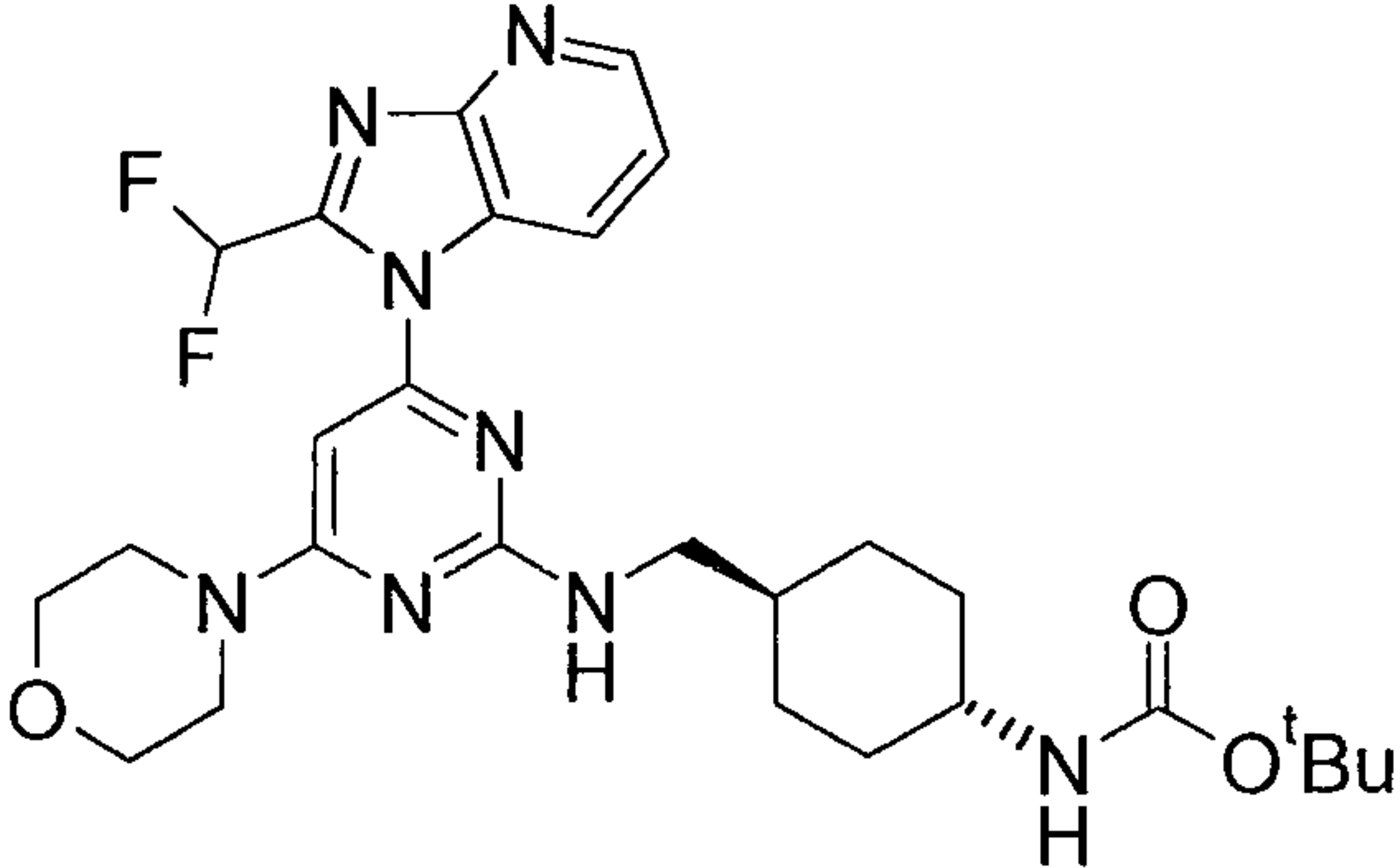
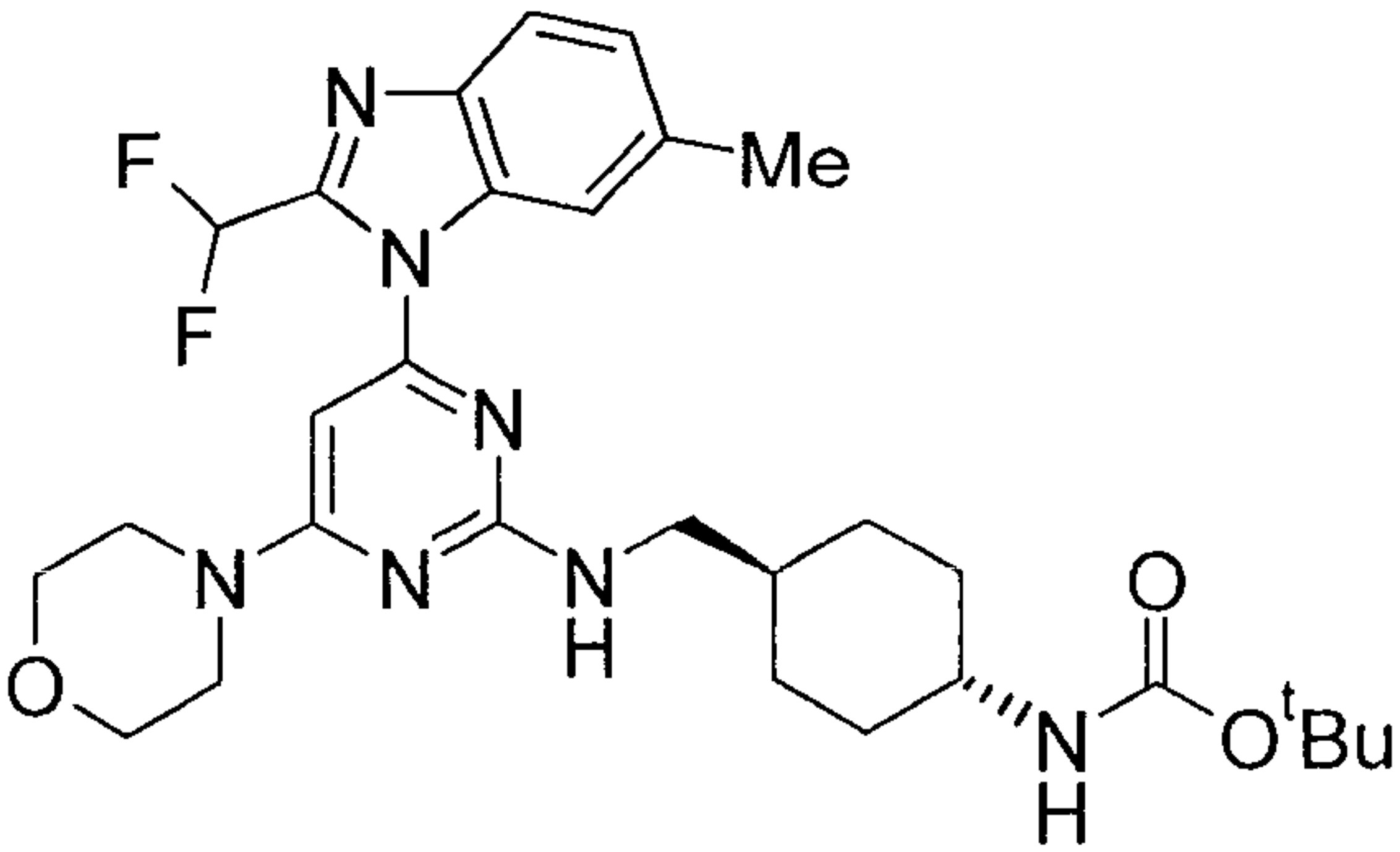
[0231]

[Table 75]

Ex	Str
179	
180	
181	
182	
183	

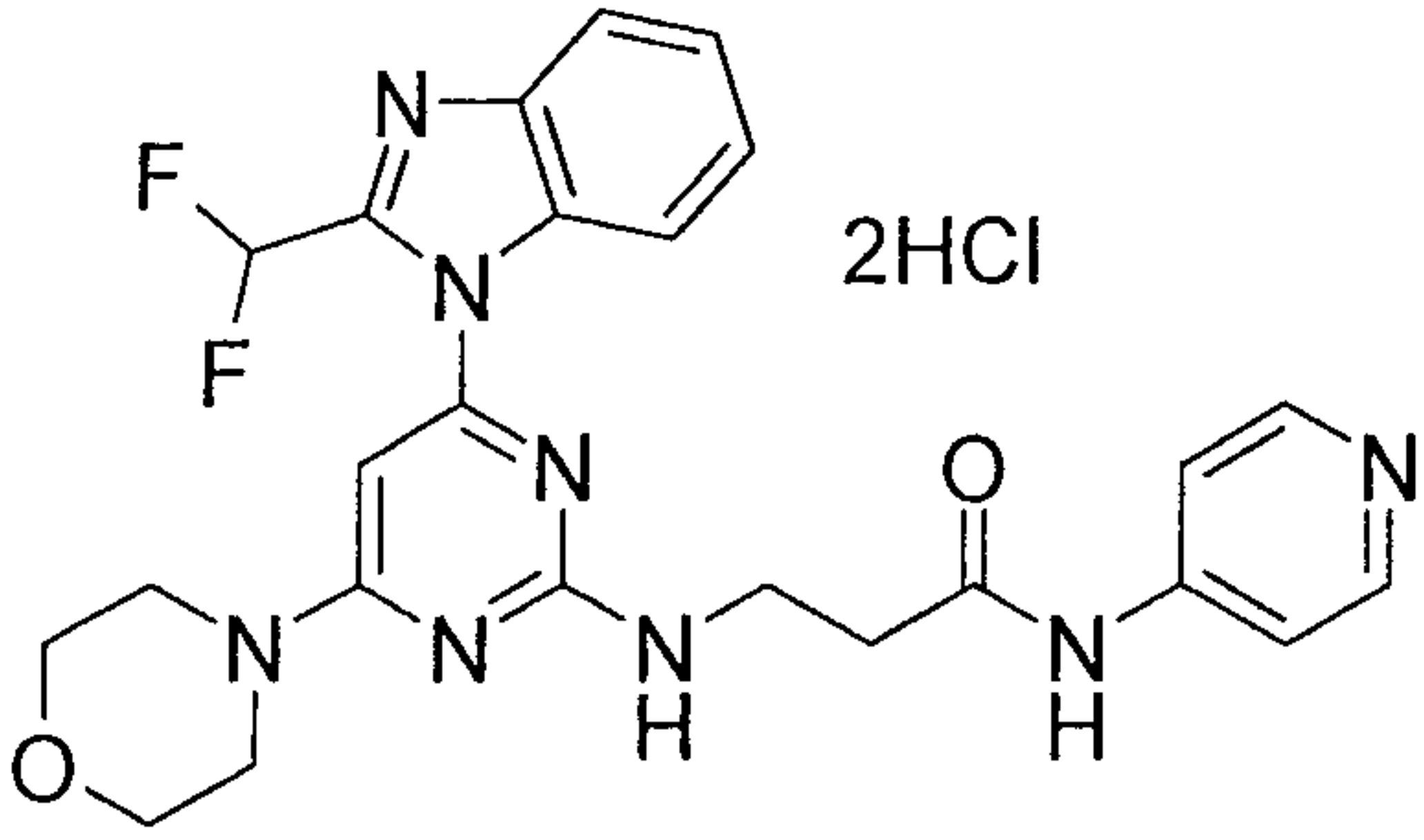
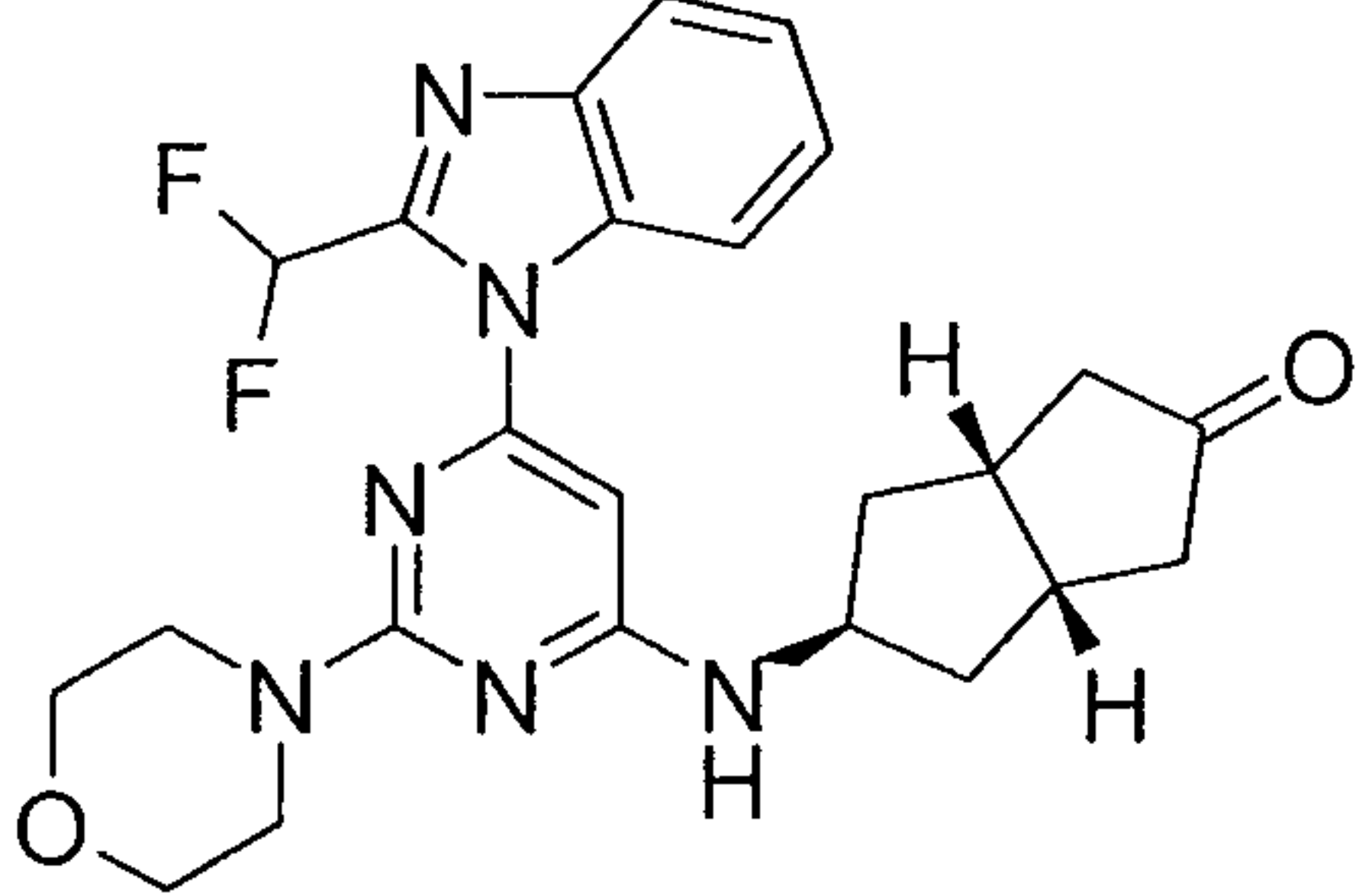
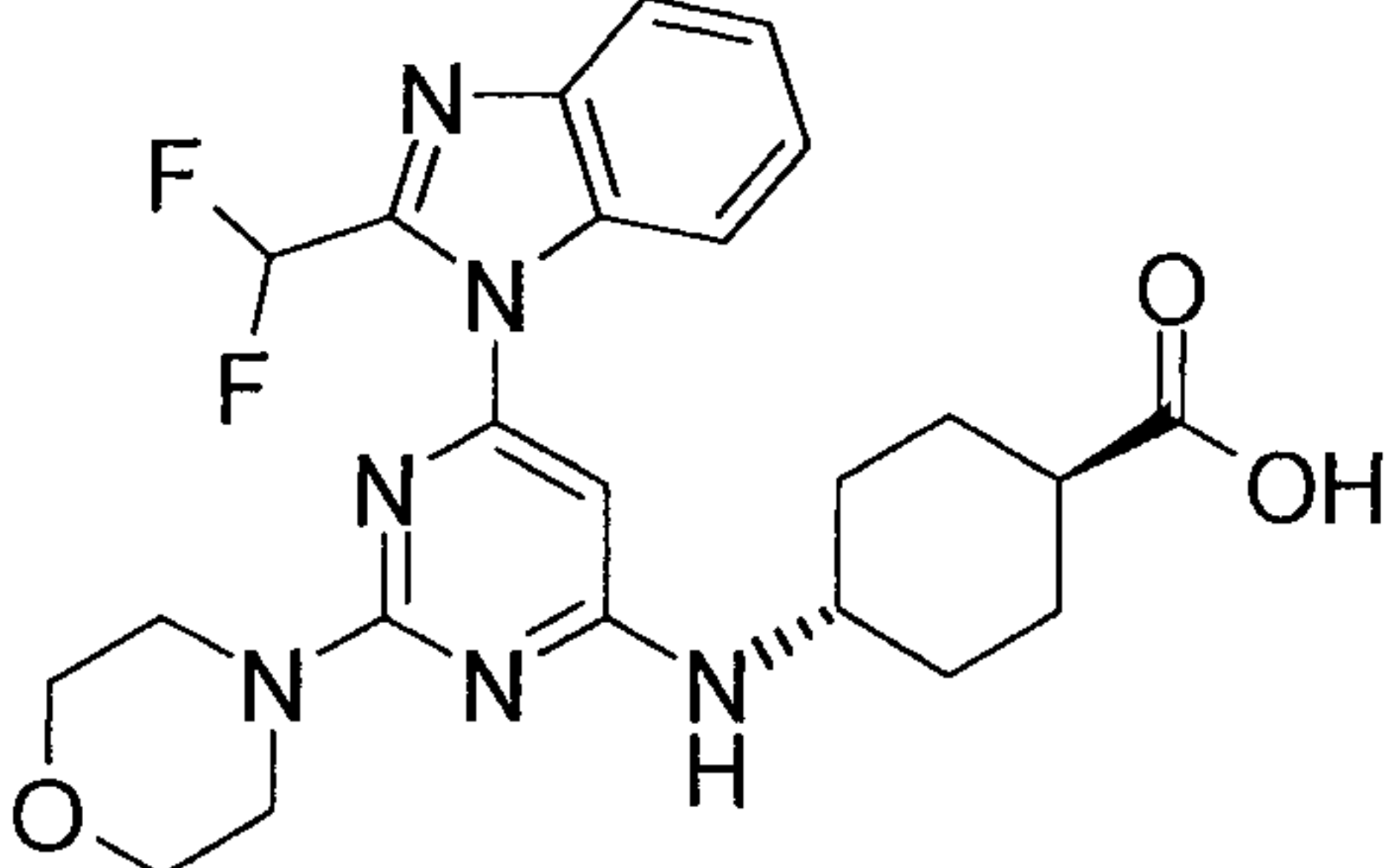
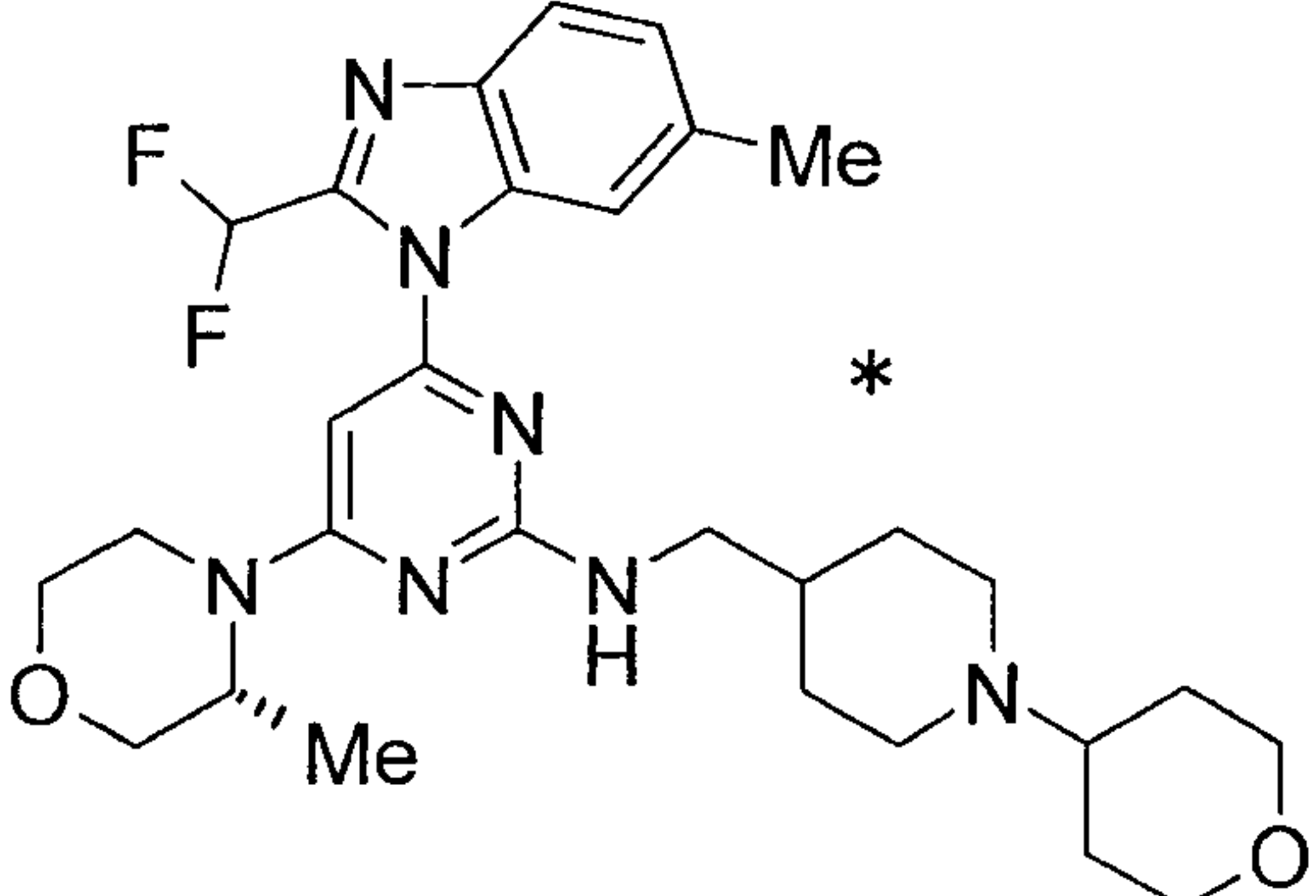
[0232]

[Table 76]

Ex	Str
184	
185	
186	
187	

[0233]

[Table 77]

Ex	Str
188	
189	
190	
191	

[0234]

[Table 78]

Ex	Str
192	
193	
194	
195	

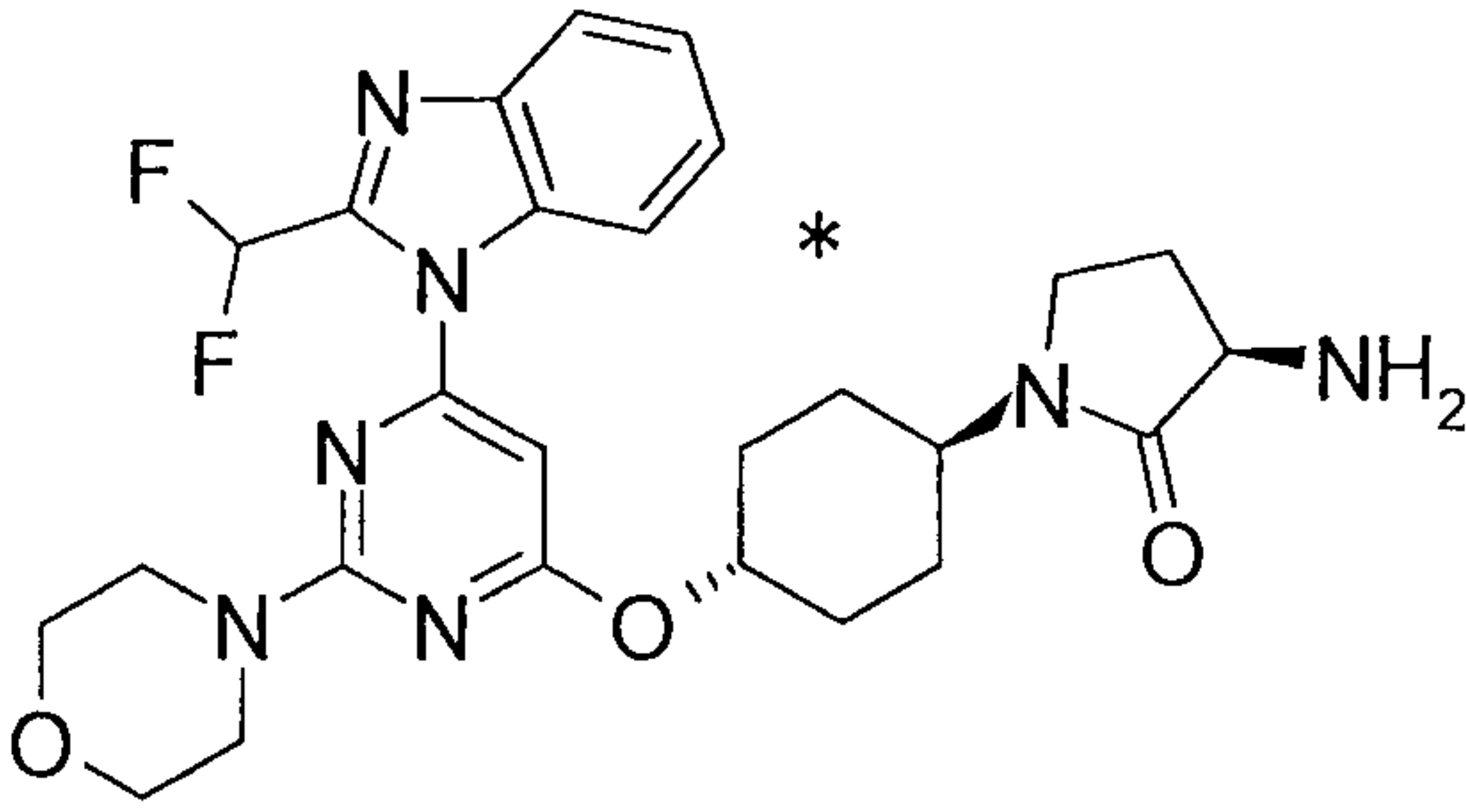
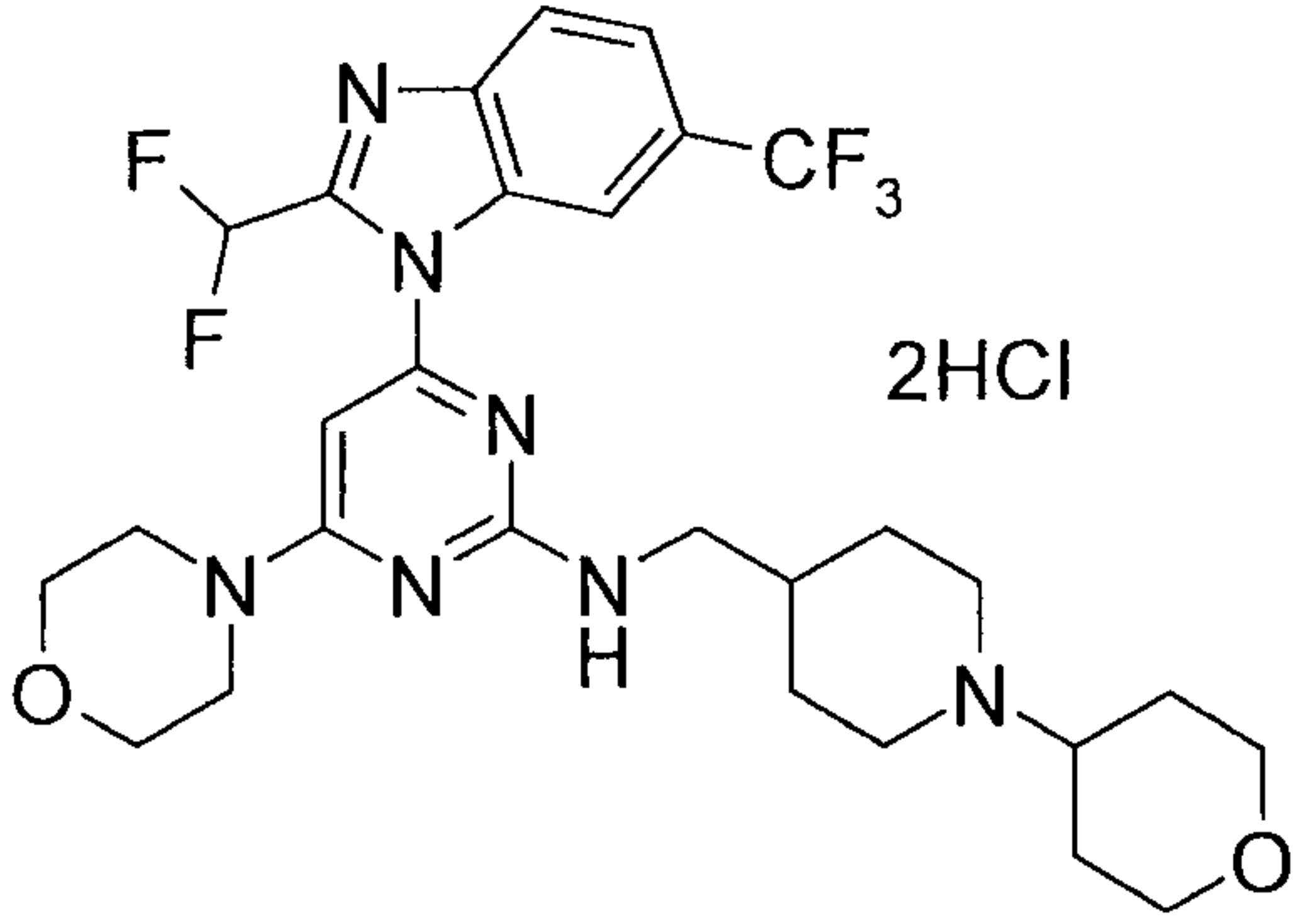
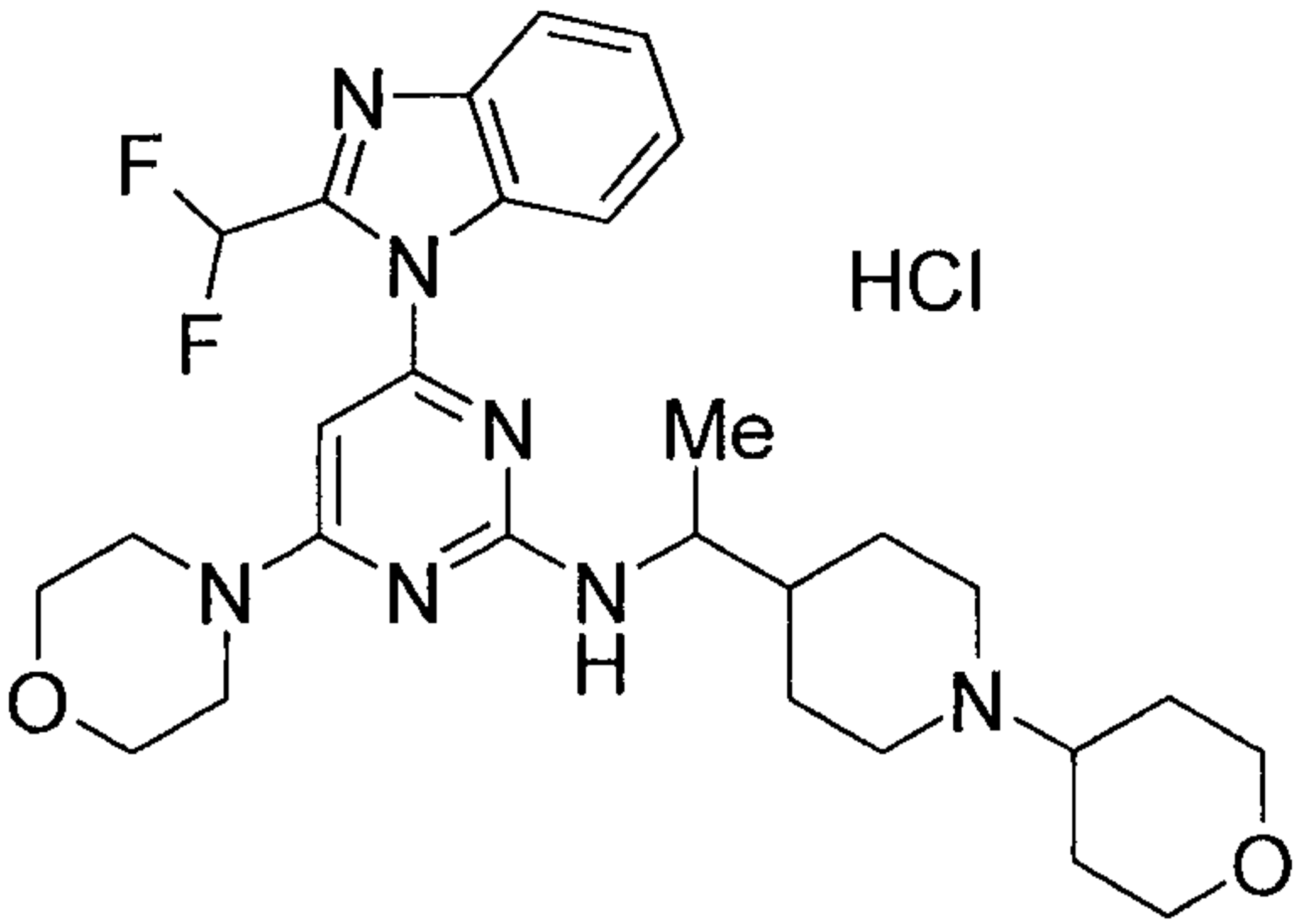
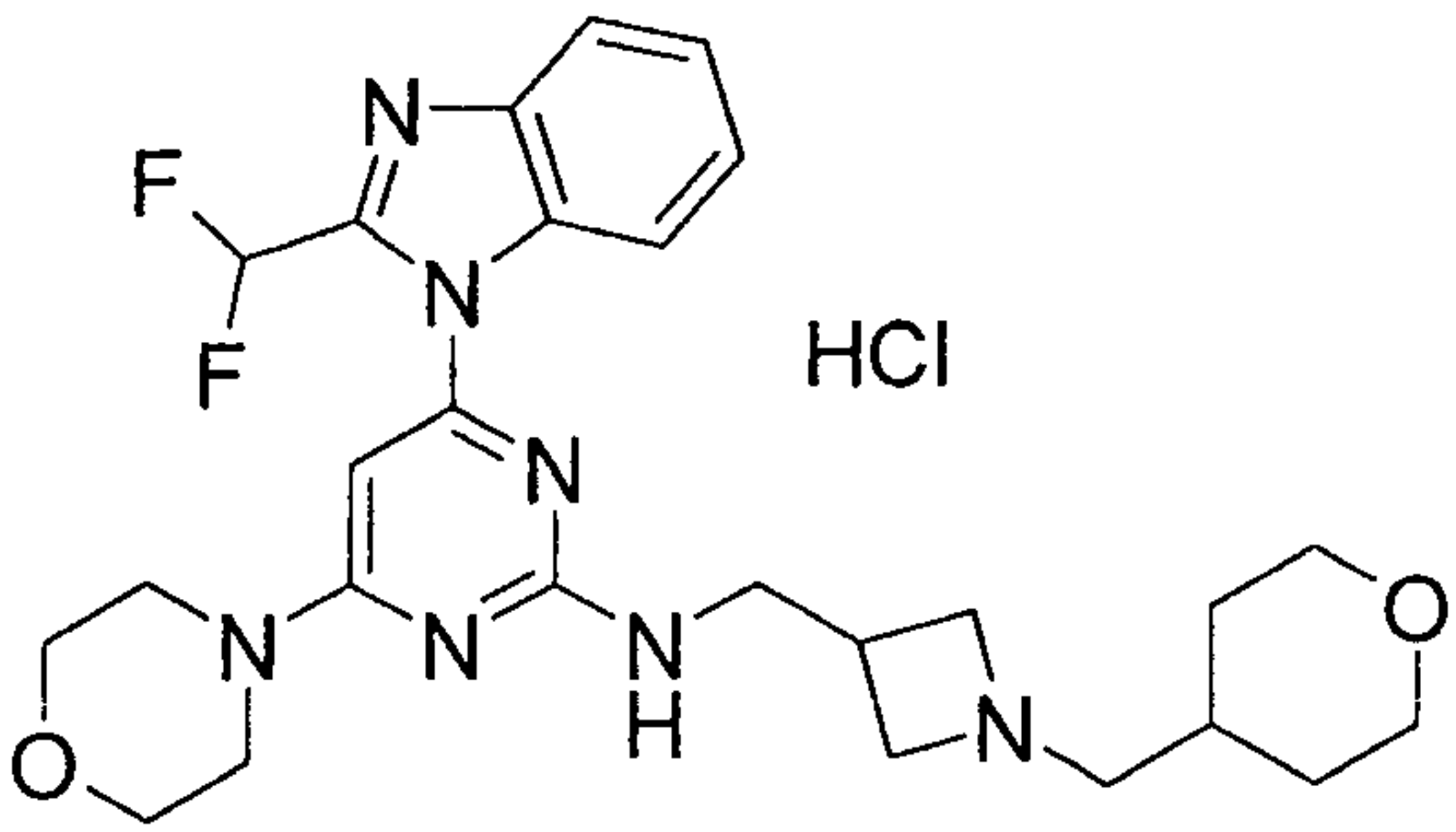
[0235]

[Table 79]

Ex	Str
196	
197	
198	
199	
200	

[0236]

[Table 80]

Ex	Str
201	
202	
203	
204	

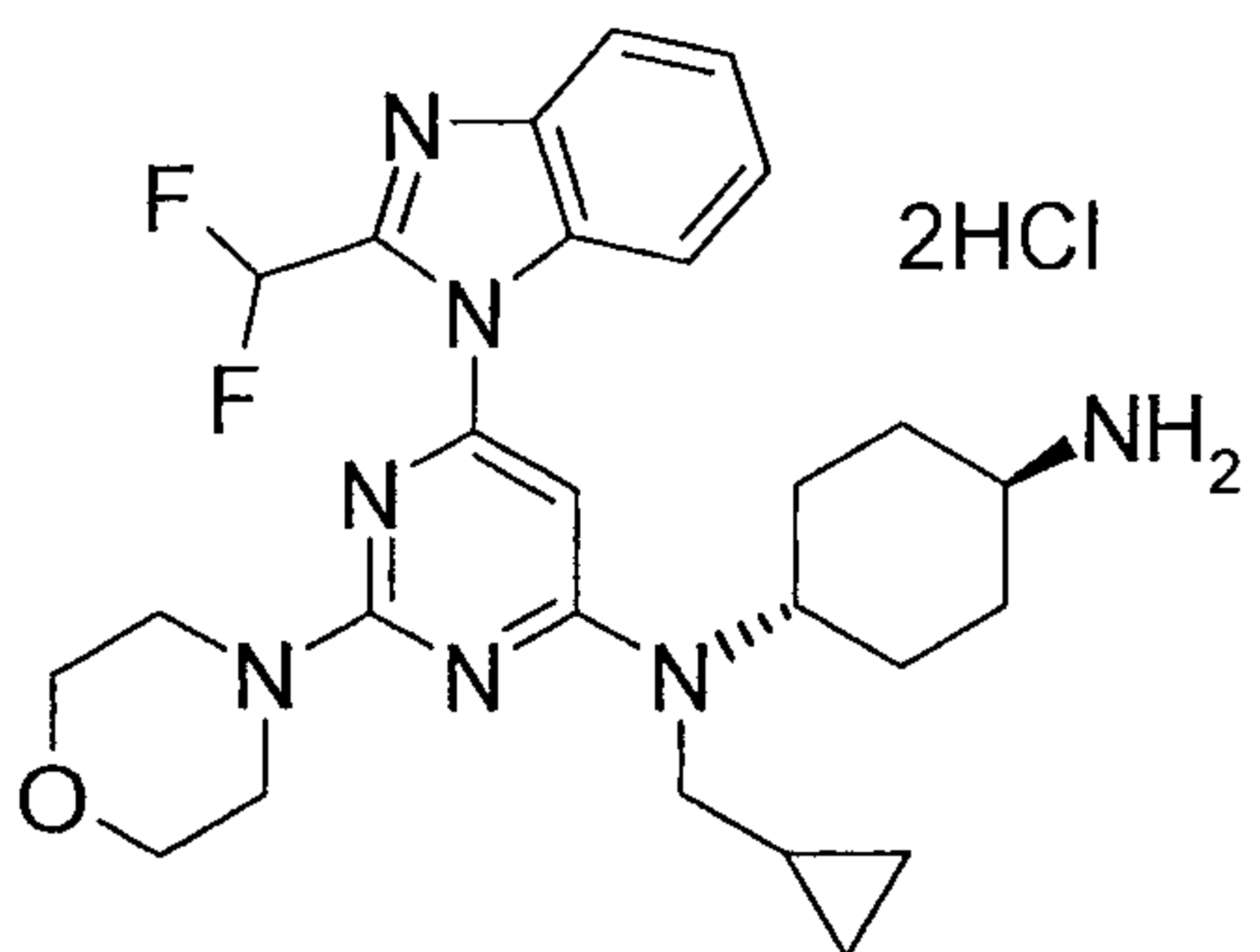
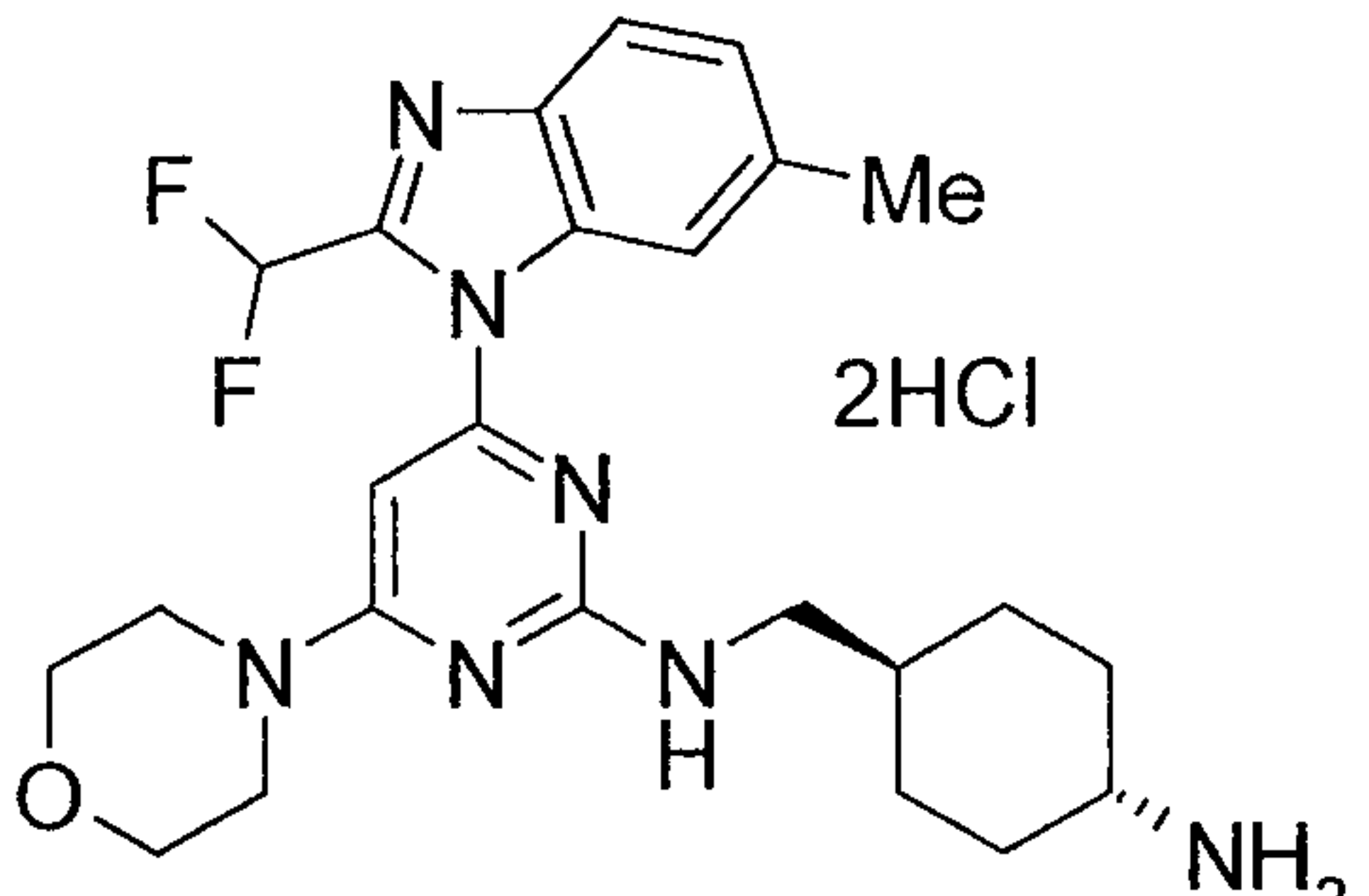
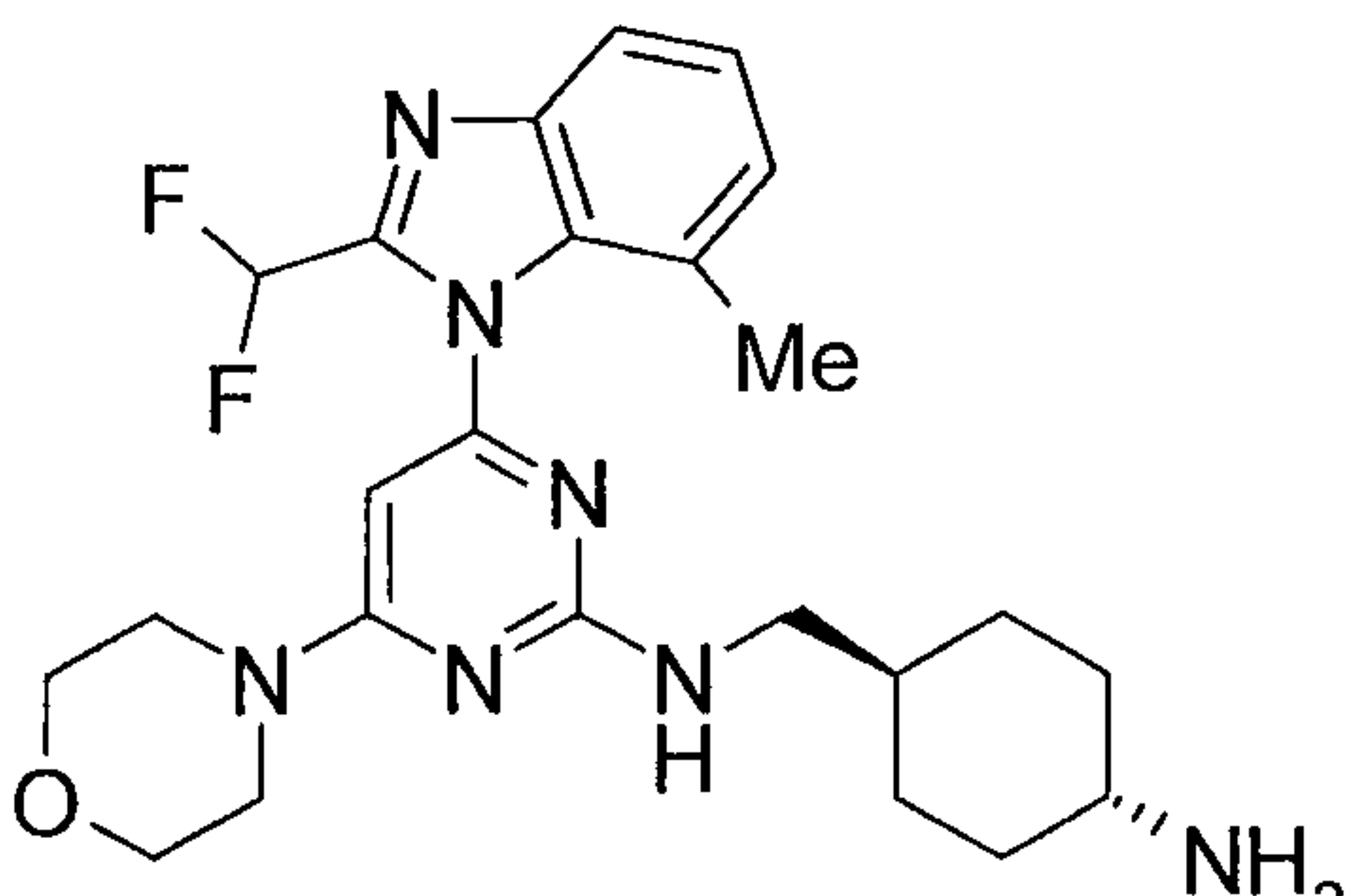
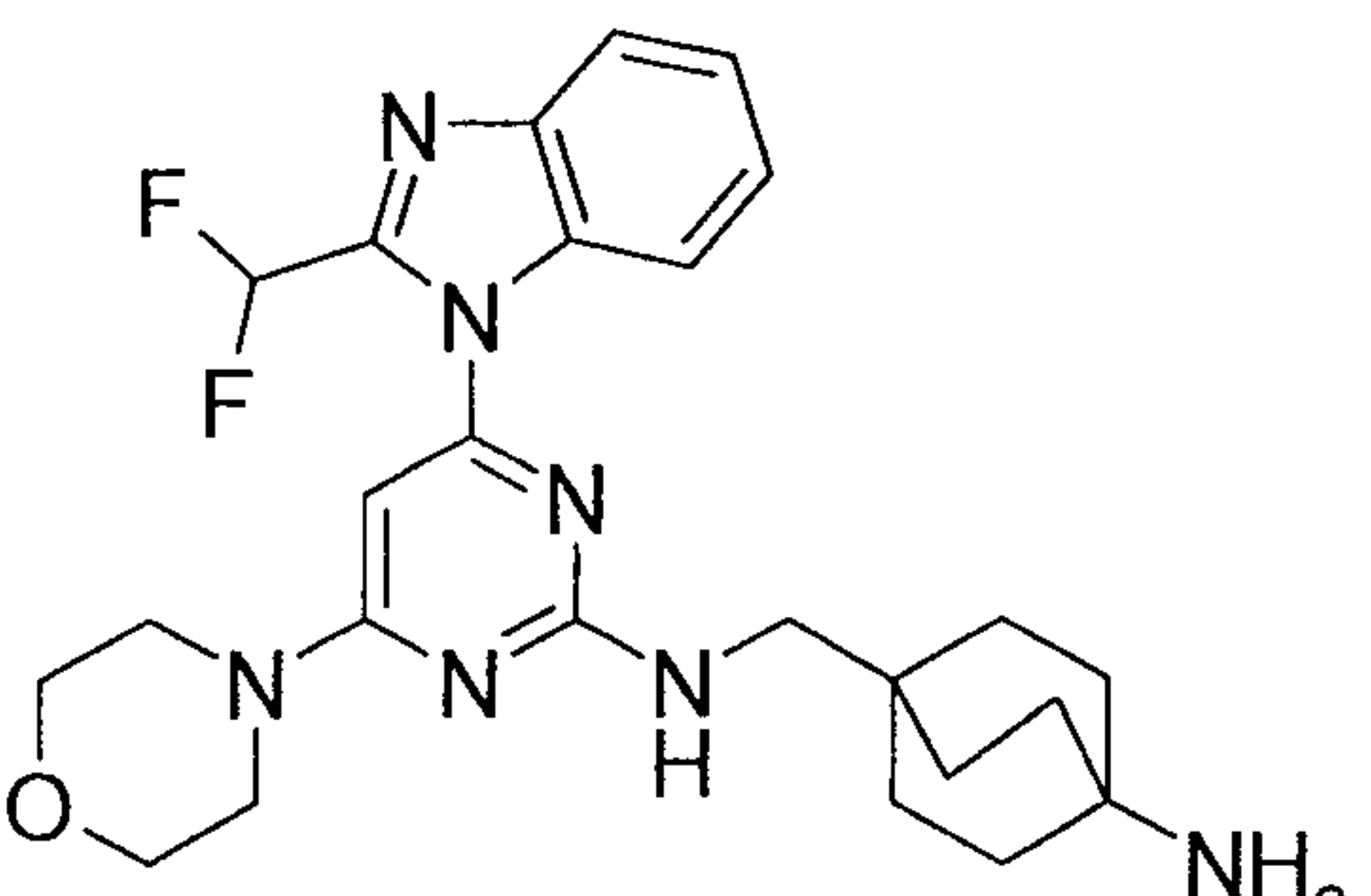
[0237]

[Table 81]

Ex	Str
205	
206	
207	
208	

[0238]

[Table 82]

Ex	Str
209	
210	
211	
212	

[0239]

[Table 83]

Ex	Str
213	
214	
215	
216	
217	

[0240]

[Table 84]

Ex	Str
218	
219	
220	
221	

[0241]

[Table 85]

Ex	Str
222	
223	
224	
225	

[0242]

[Table 86]

Ex	Str
226	
227	
228	
229	

[0243]

[Table 87]

Ex	Str
230	 <chem>Cc1ccc2nc(C(F)F)c3nc(NC4CCN(C4)C(=O)OC(C)(C)C)nc3n2C5=CC=CC=C5C6CCN(C6)C</chem>
231	 <chem>C1=CC=CC=C2N3C(=N1)C(F)F3N2C4=CC=CC=C4C5=CC=CC=C5C6CCN(C6)C(=O)OC(C)(C)C</chem>
232	 <chem>C1=CC=CC=C2N3C(=N1)C(F)F3N2C4=CC=CC=C4C5=CC=CC=C5C6CCN(C6)C(=O)OC(C)(C)C</chem>
233	 <chem>C1=CC=CC=C2N3C(=N1)C(F)F3N2C4=CC=CC=C4C5=CC=CC=C5C6CCN(C6)C</chem>

[0244]

[Table 88]

Ex	Str
234	
235	
236	
237	
238	

[0245]

[Table 89]

Ex	Str
239	
240	
241	
242 -1	
242 -2	

[0246]

[Table 90]

Ex	Str
243	
244	
245	
246	
247	

[0247]

[Table 91]

Ex	Str
248	
249 -1	
249 -2	
250	
251	

[0248]

[Table 92]

Ex	Str
252	
253	
254	
255	
256	

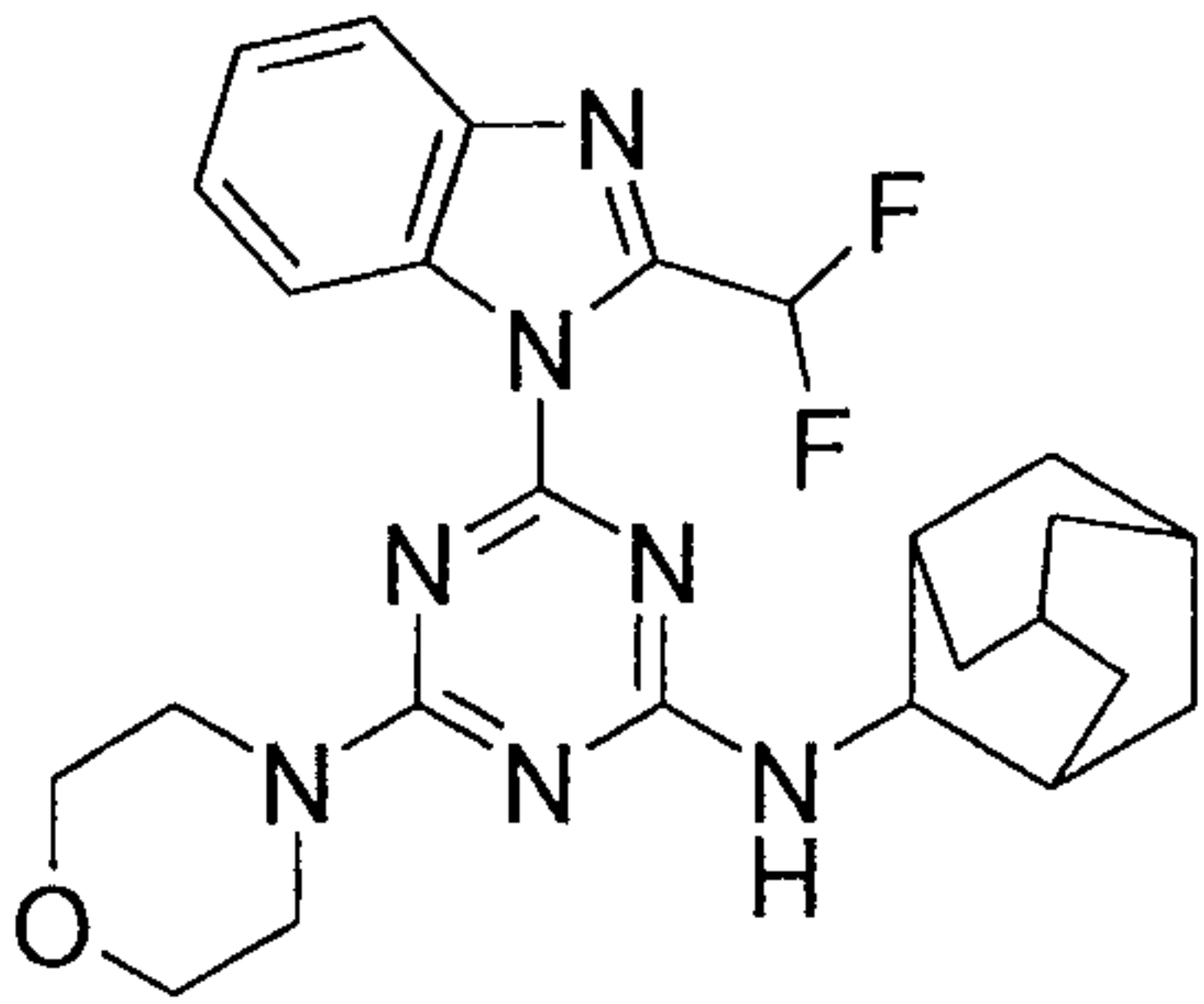
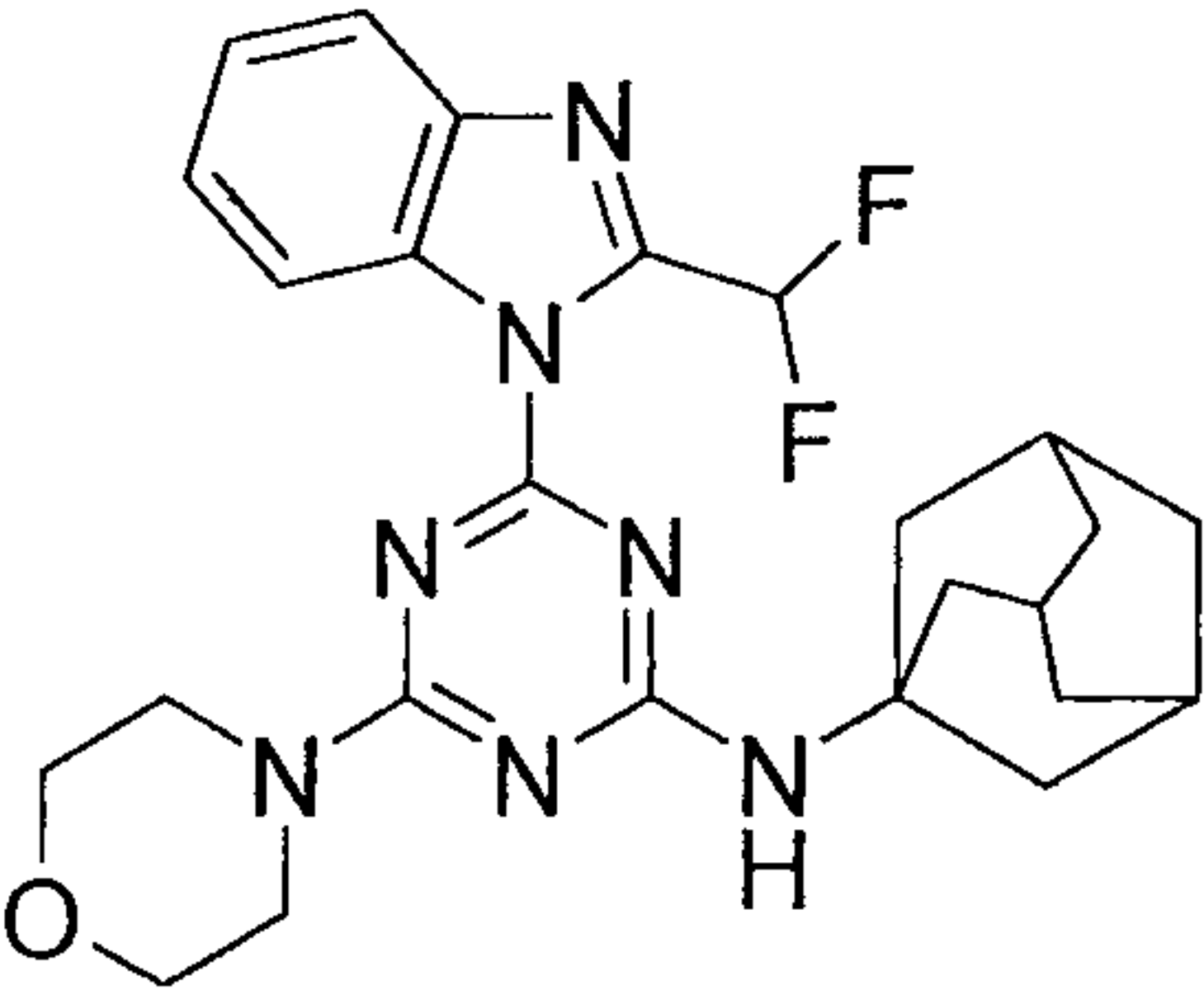
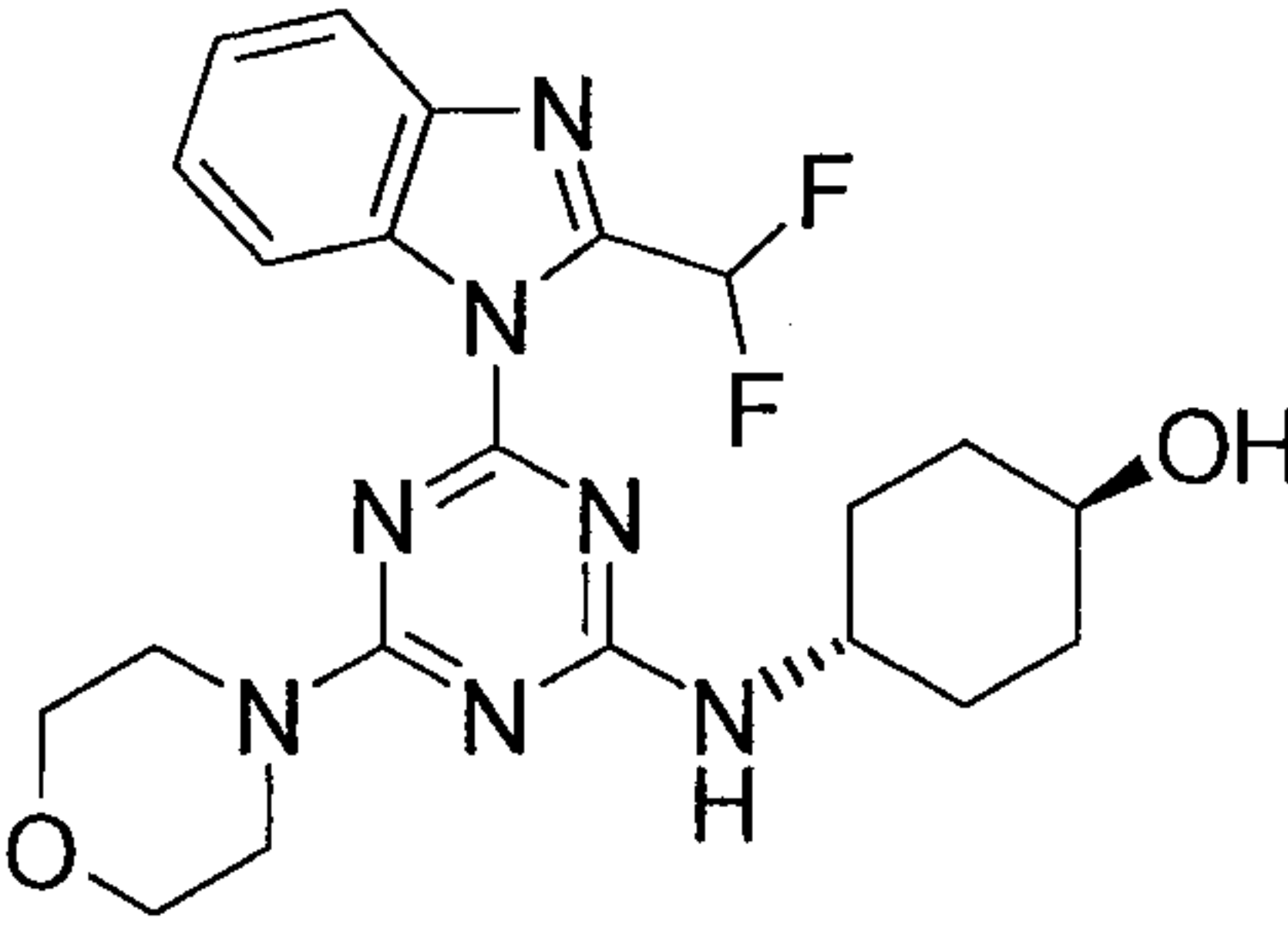
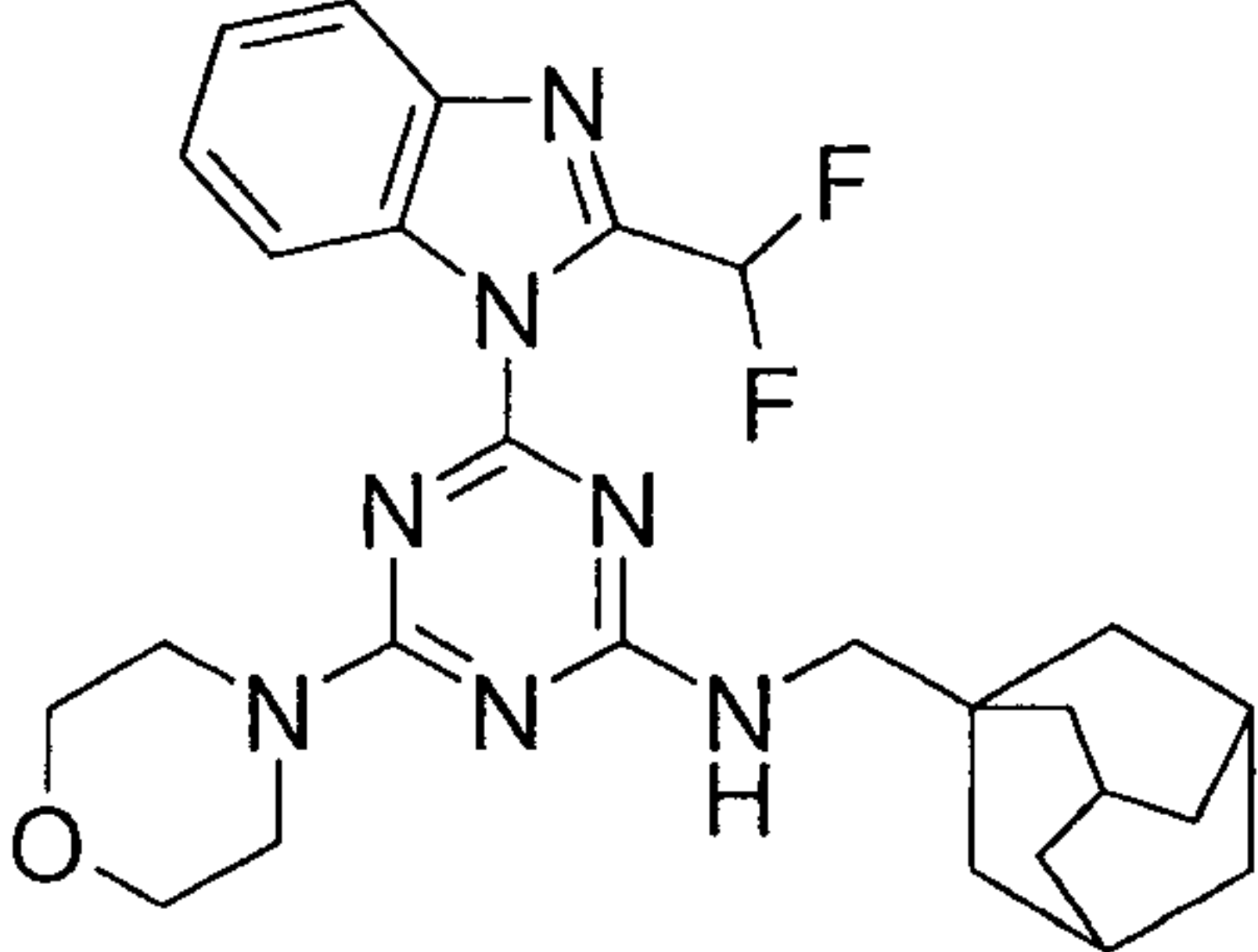
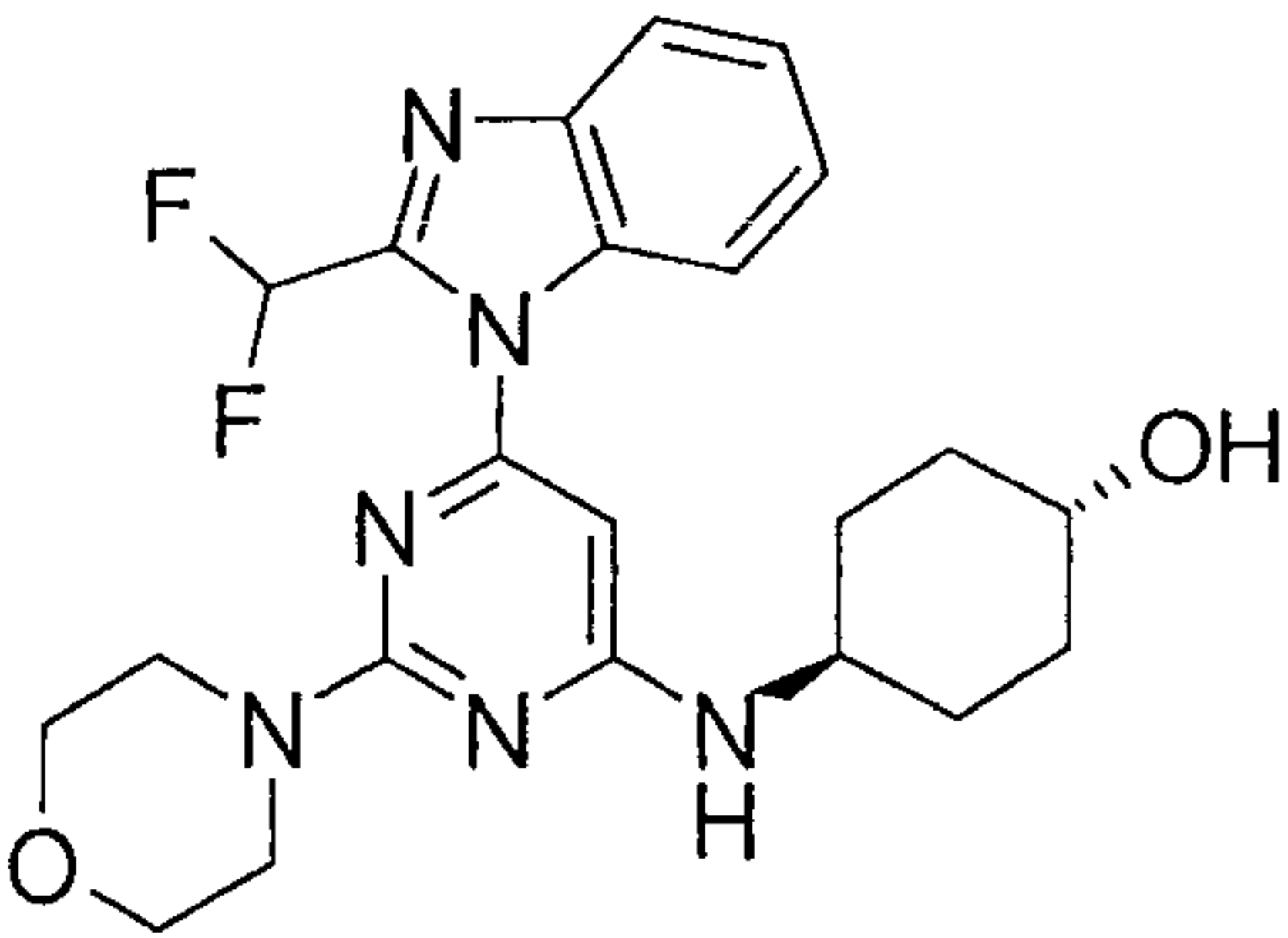
[0249]

[Table 93]

Ex	Str
257	
258	
259	
260	
261	

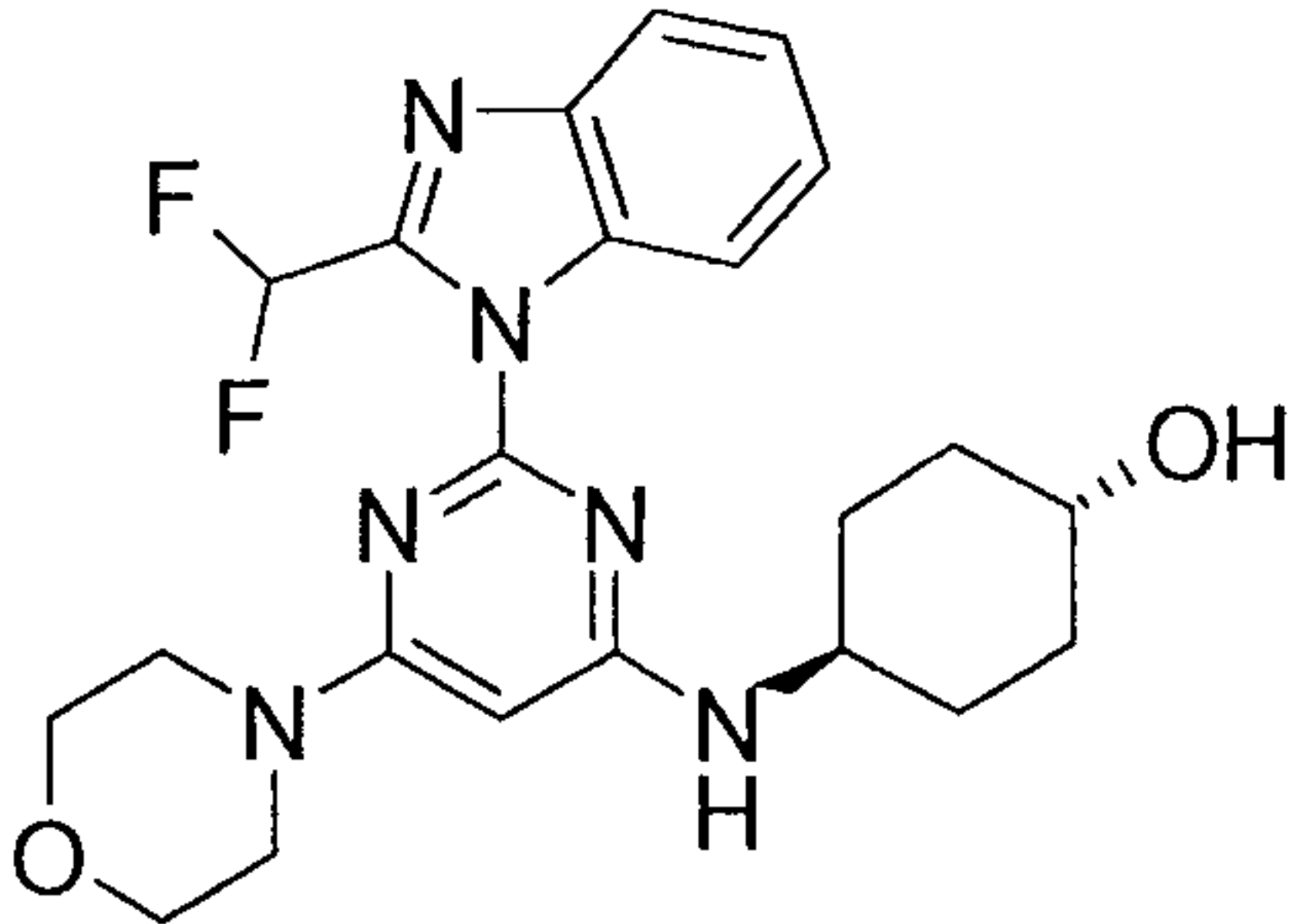
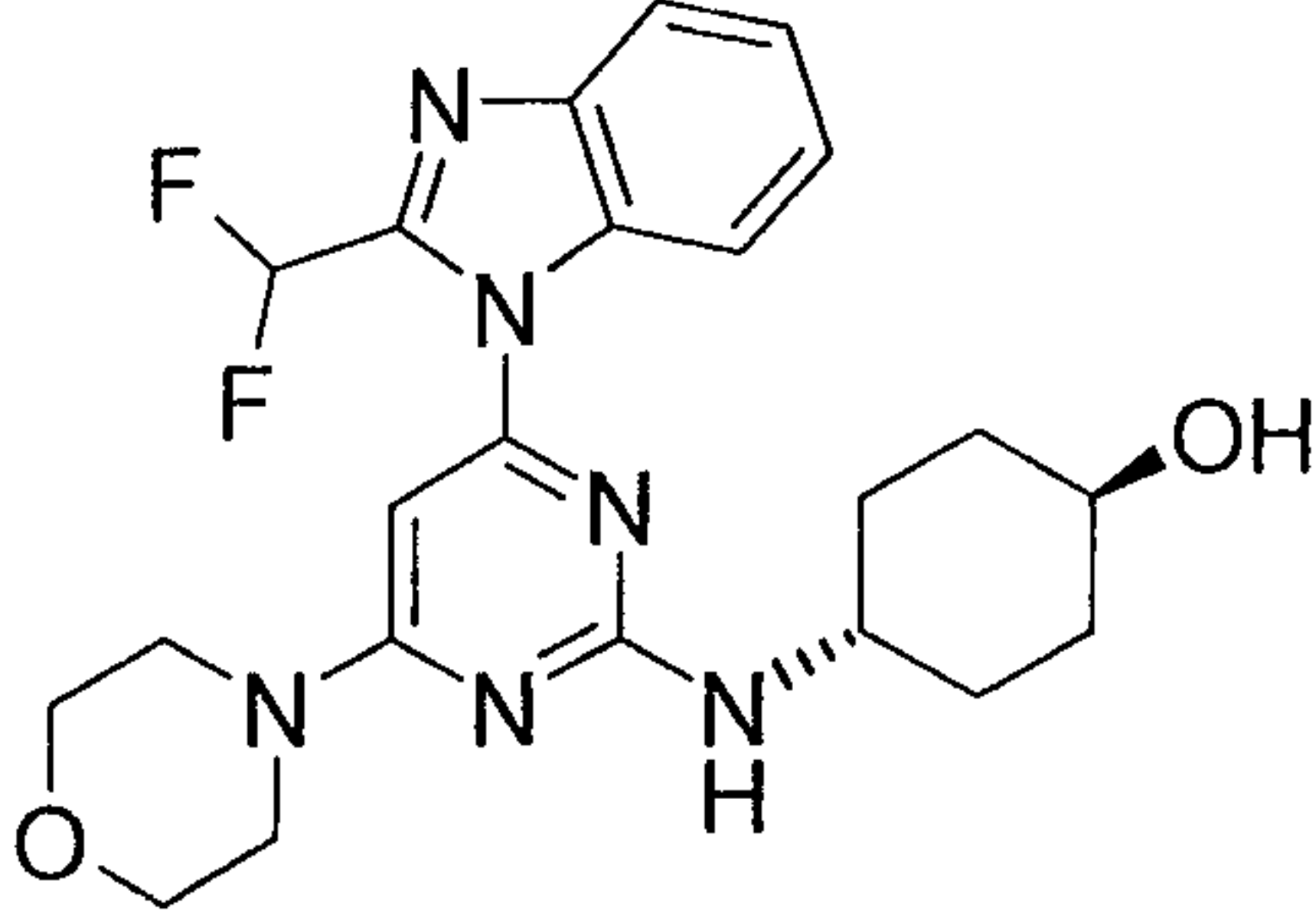
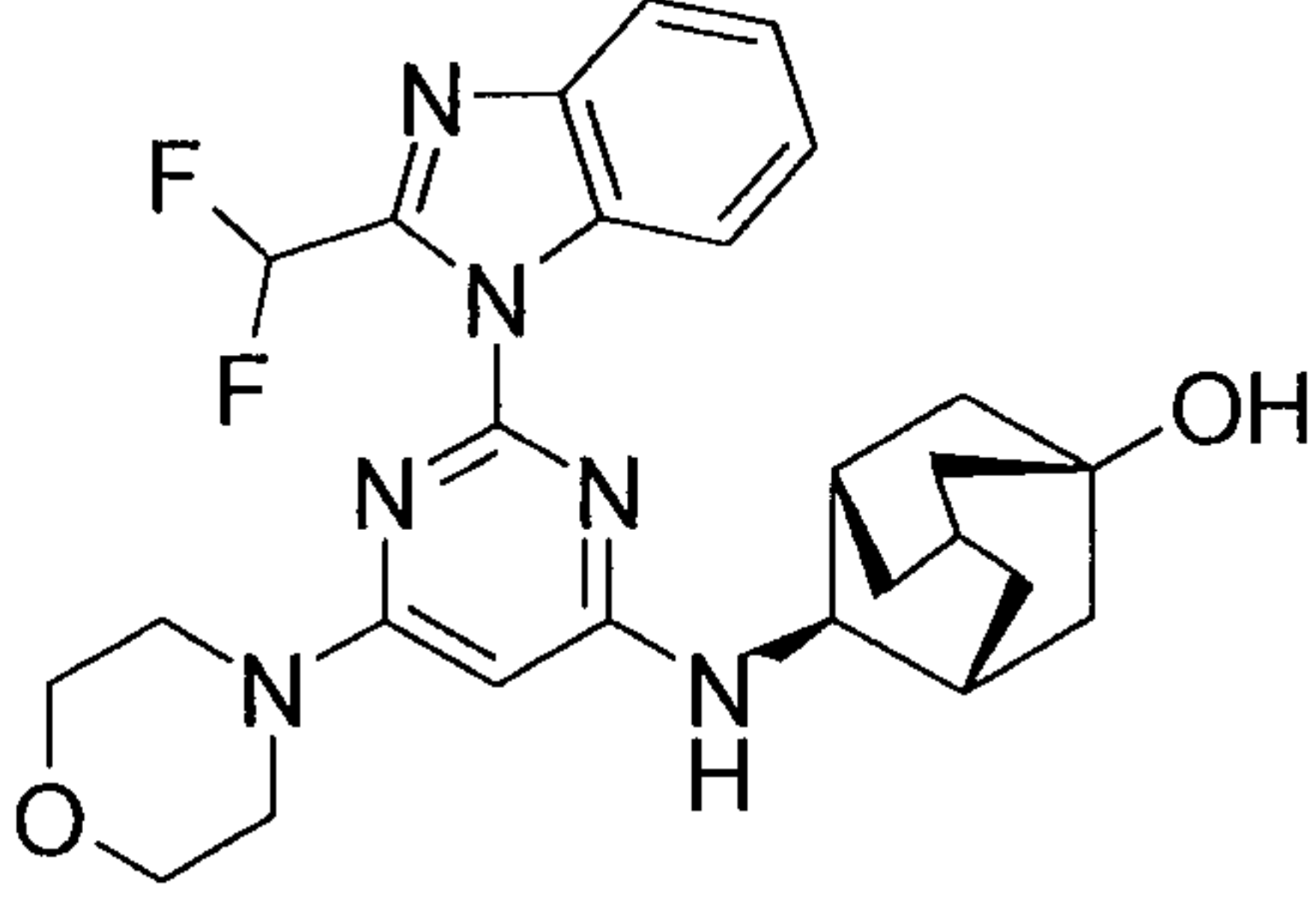
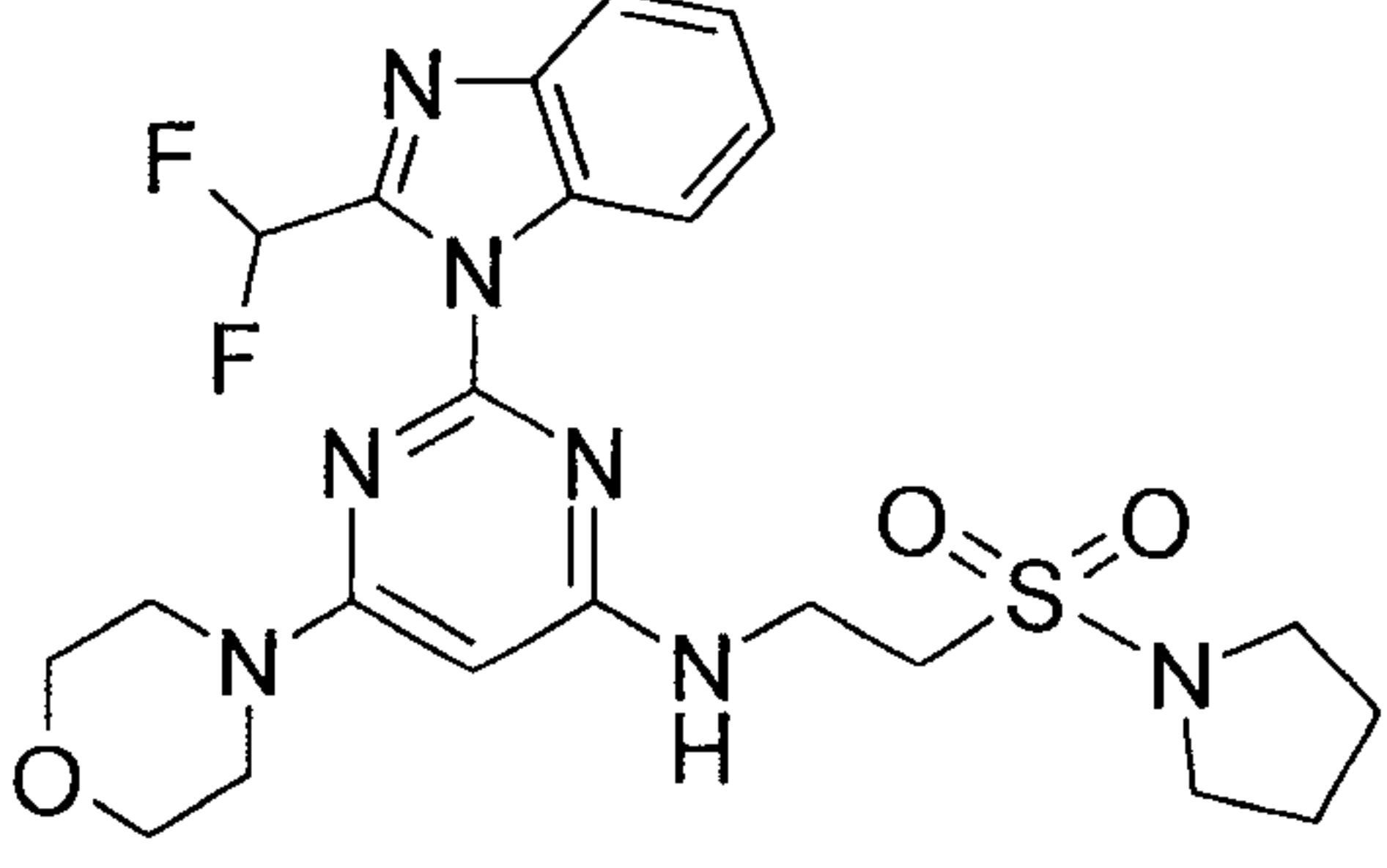
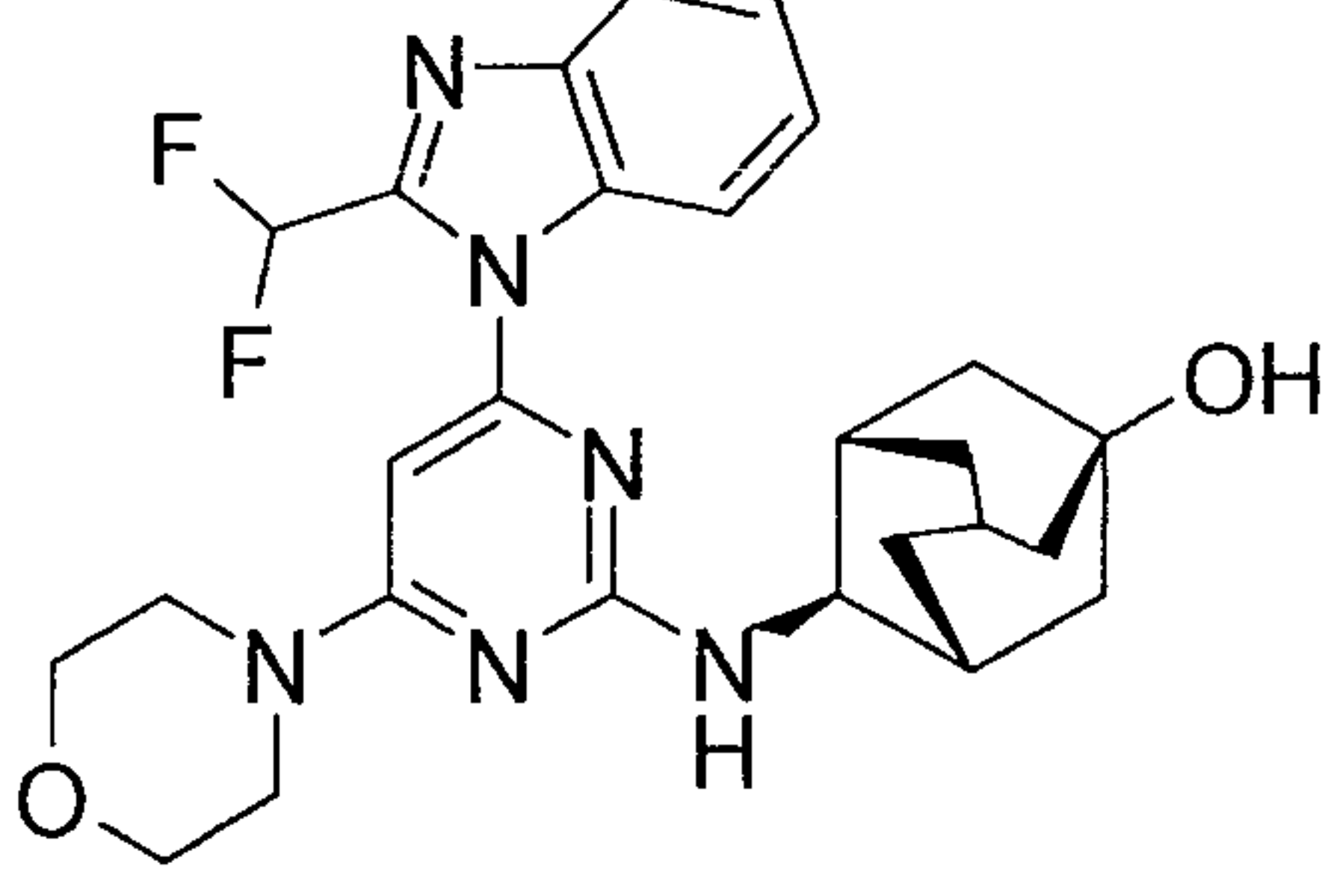
[0250]

[Table 94]

Ex	Str
262	
263	
264	
265	
266	

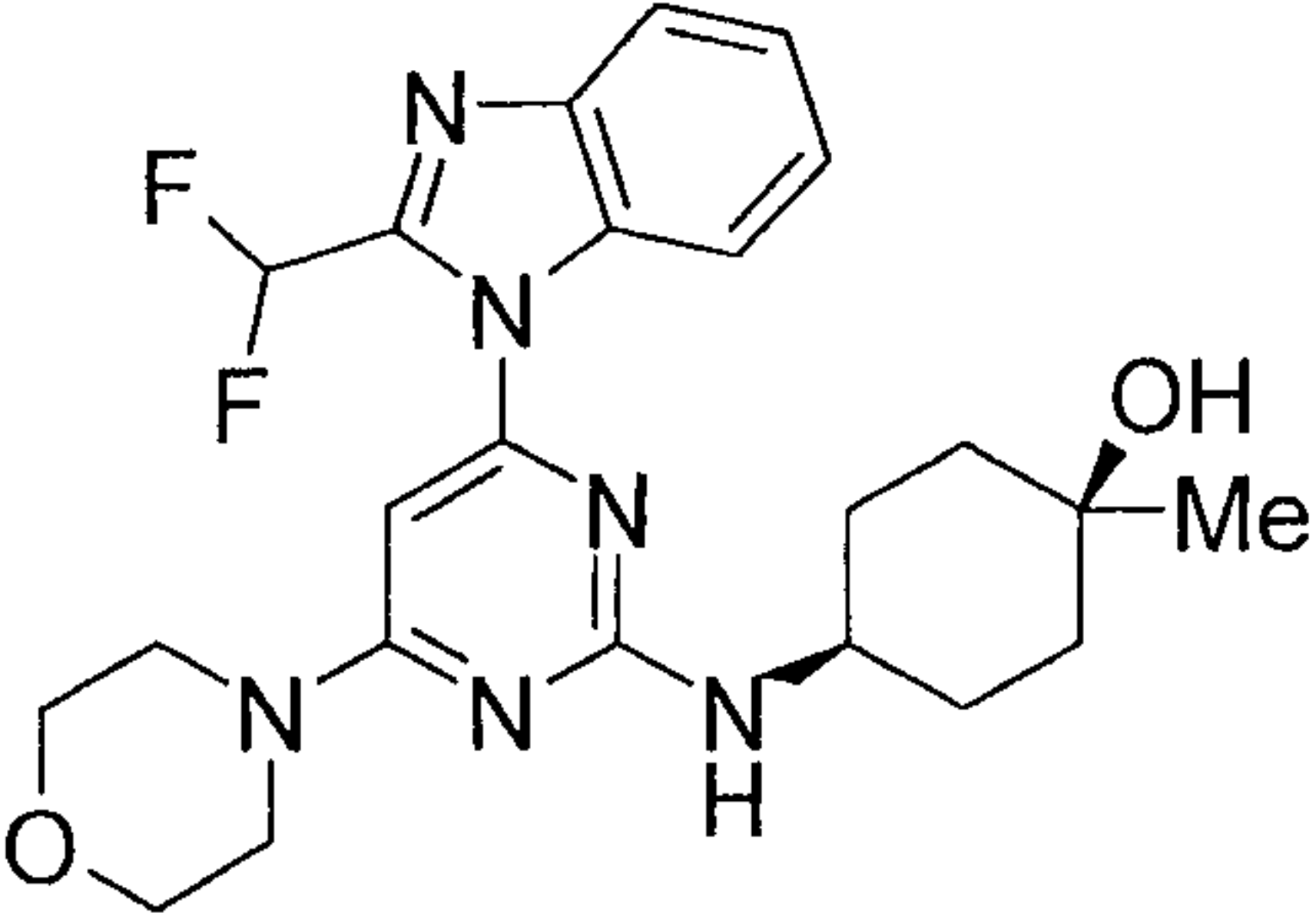
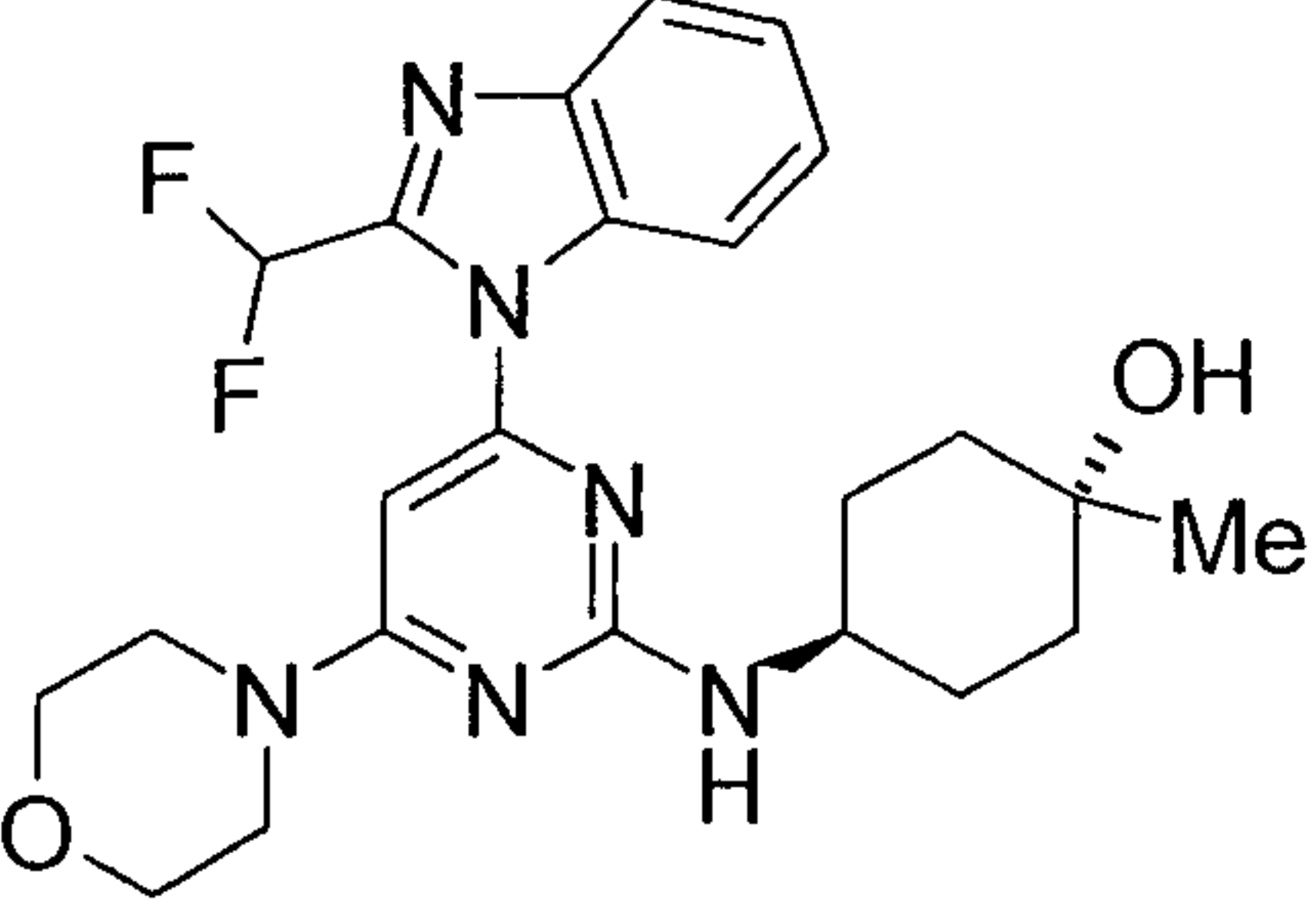
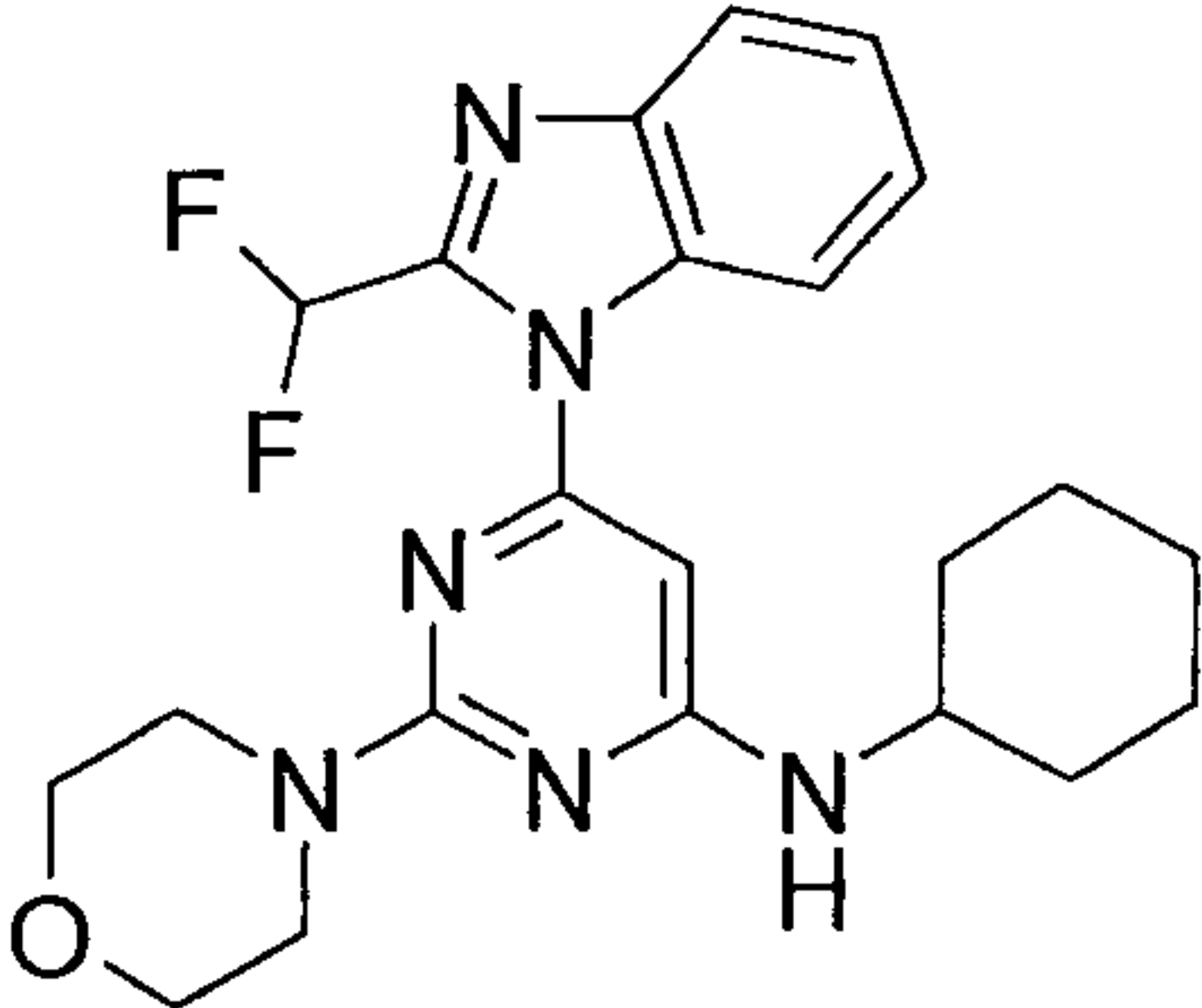
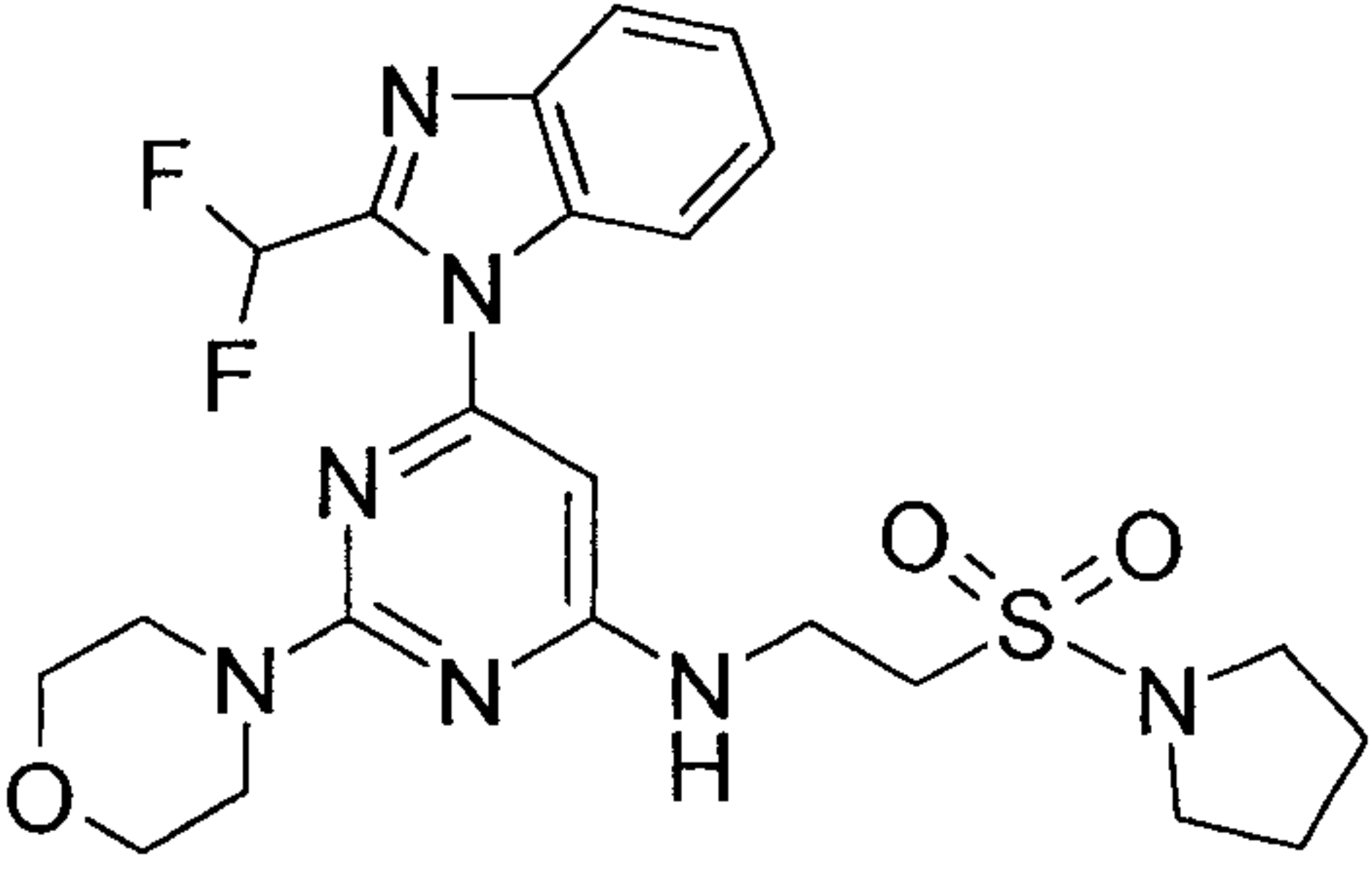
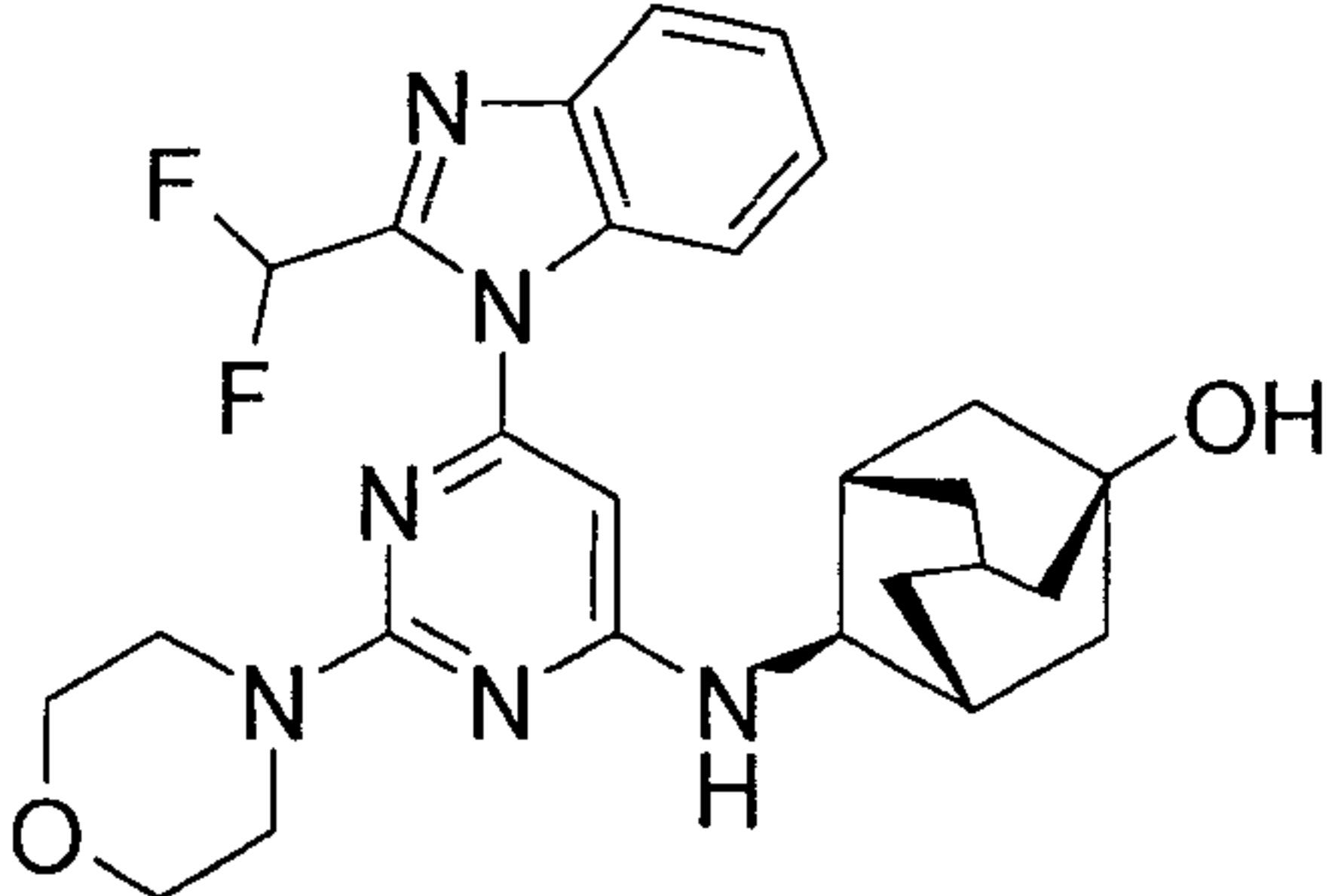
[0251]

[Table 95]

Ex	Str
267	
268	
269	
270	
271	

[0252]

[Table 96]

Ex	Str
272	
273	
274	
275	
276	

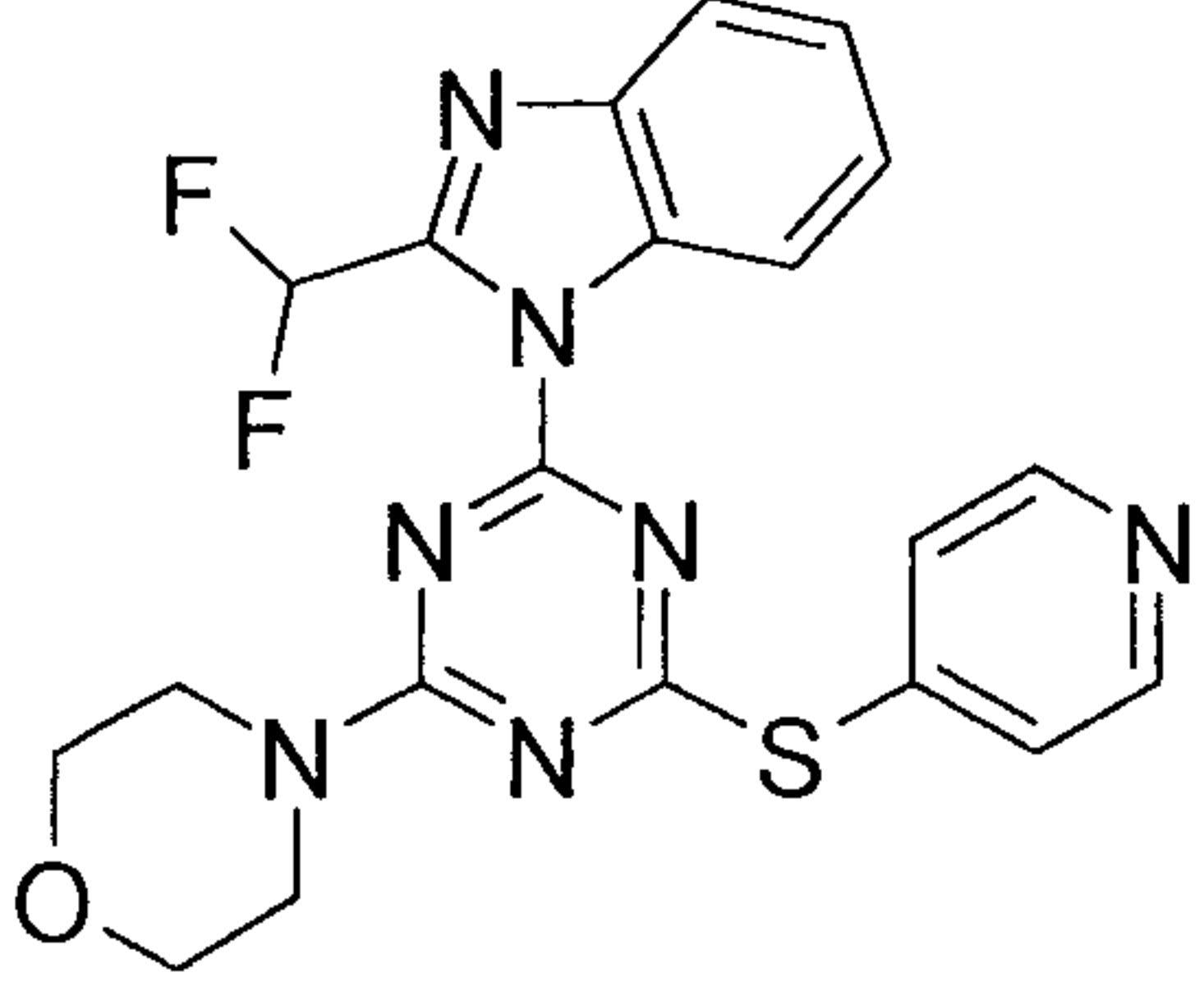
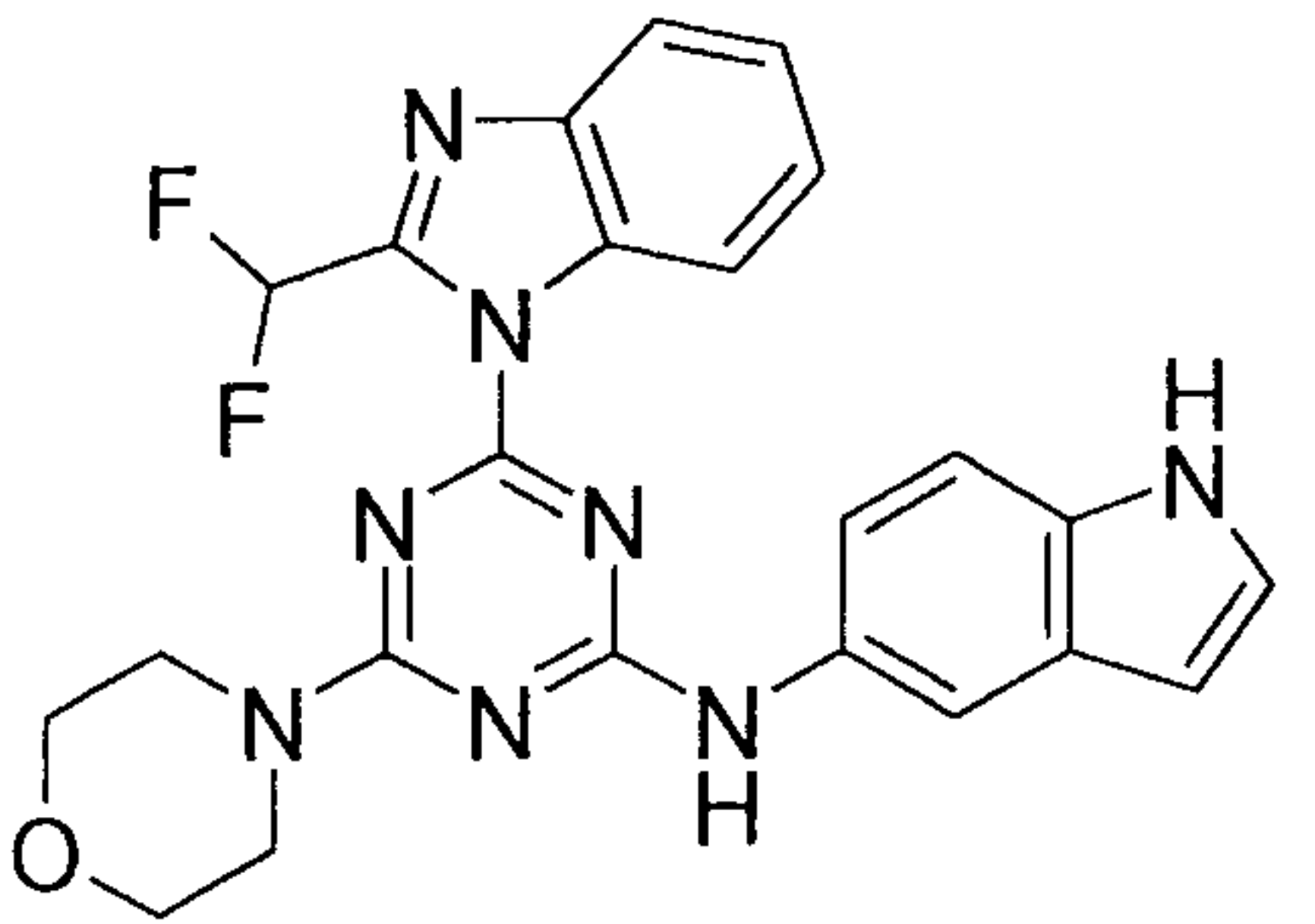
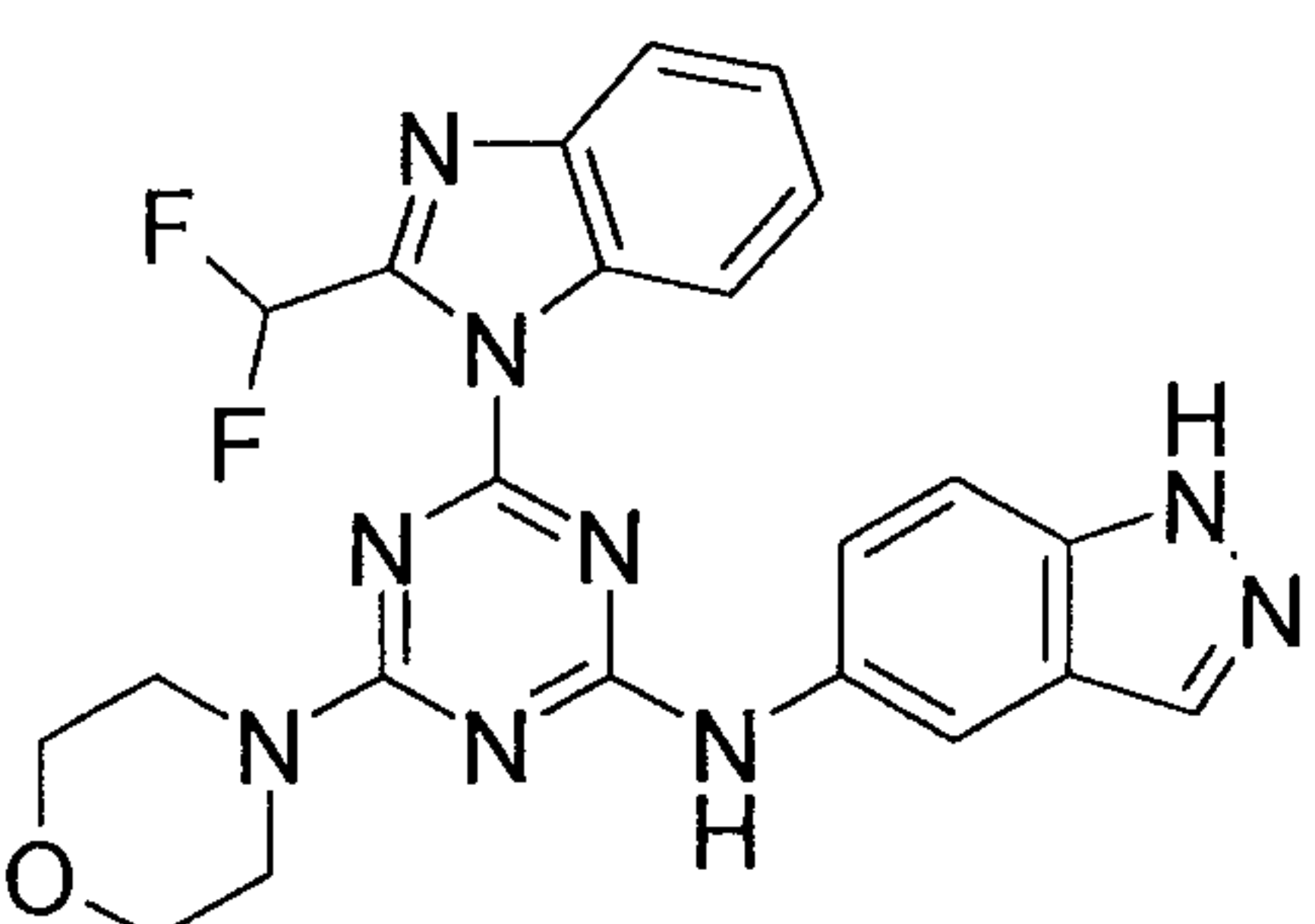
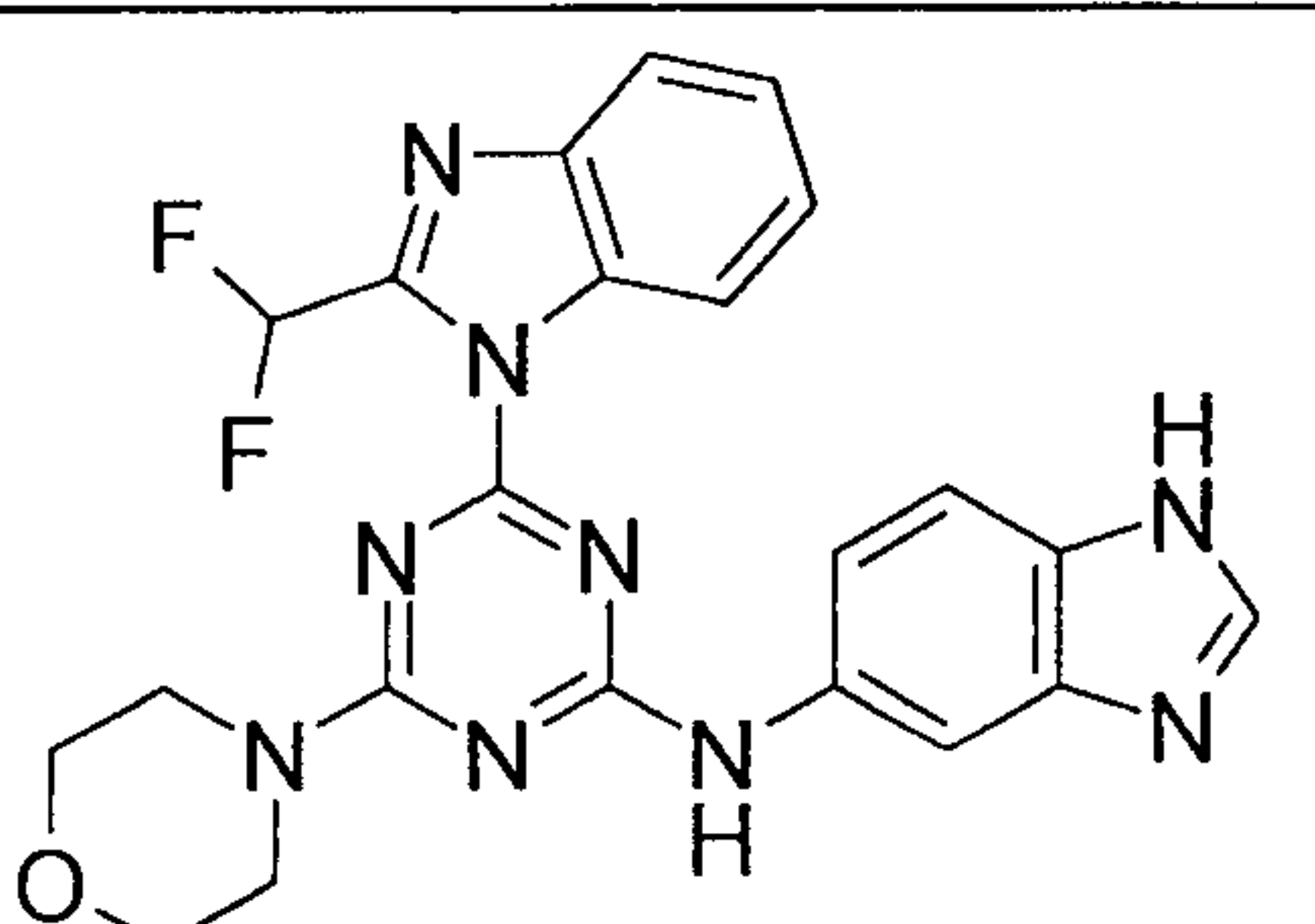
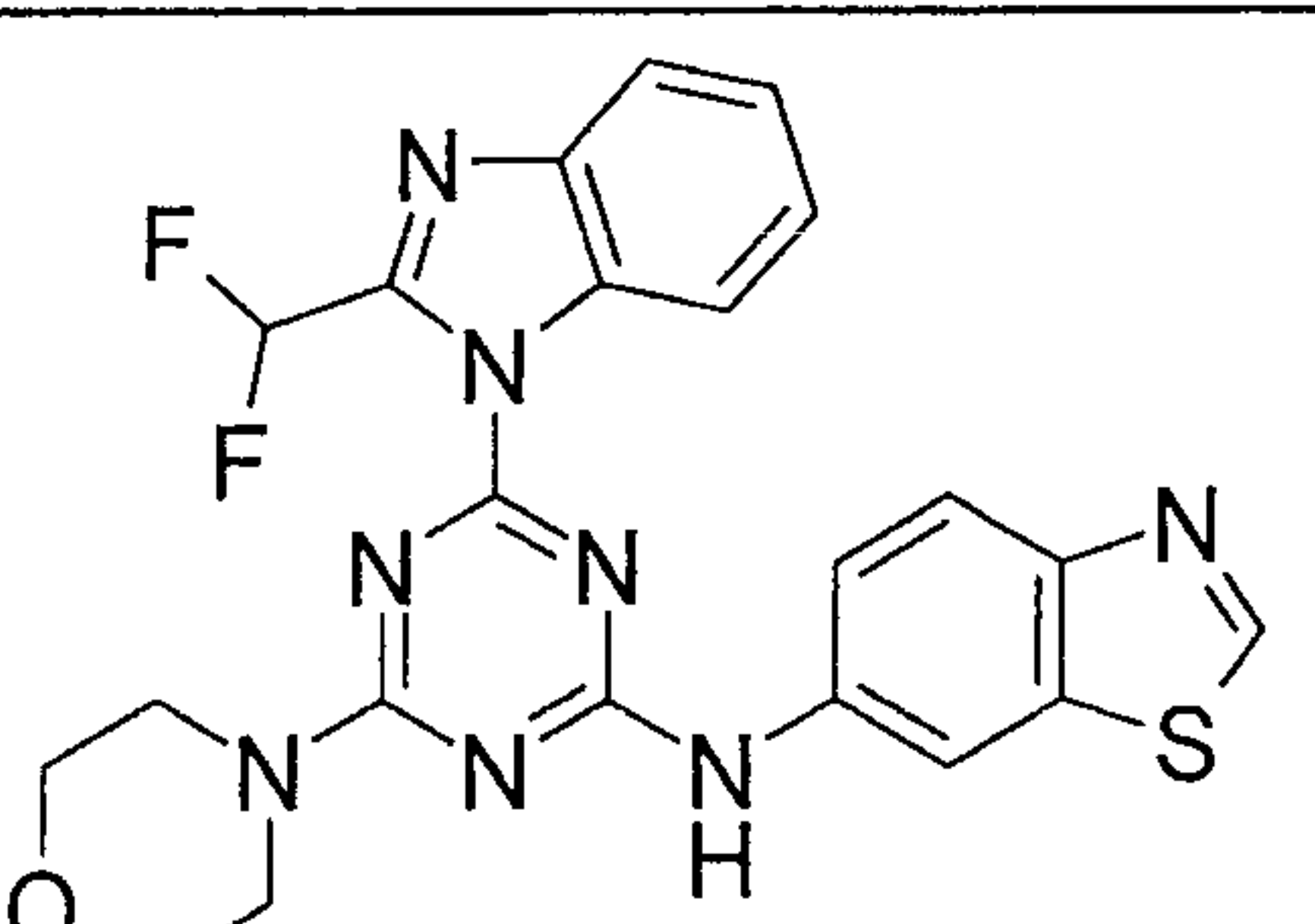
[0253]

[Table 97]

Ex	Str
277	
278	
279	
280	
281	

[0254]

[Table 98]

Ex	Str
282	 <chem>CC(F)(F)c1nc2c(ncn2C3CCOCC3)C4=CC=CC=C4SC5=CC=CC=N5</chem>
283	 <chem>CC(F)(F)c1nc2c(ncn2C3CCOCC3)C4=CC=CC=C4NC5=CC=C6C(=C5)C=CN6</chem>
284	 <chem>CC(F)(F)c1nc2c(ncn2C3CCOCC3)C4=CC=CC=C4NC5=CC=C6C(=C5)C=NN=N6</chem>
285	 <chem>CC(F)(F)c1nc2c(ncn2C3CCOCC3)C4=CC=CC=C4NC5=CC=C6C(=C5)N=CN6</chem>
286	 <chem>CC(F)(F)c1nc2c(ncn2C3CCOCC3)C4=CC=CC=C4NC5=CC=C6C(=C5)S=N6</chem>

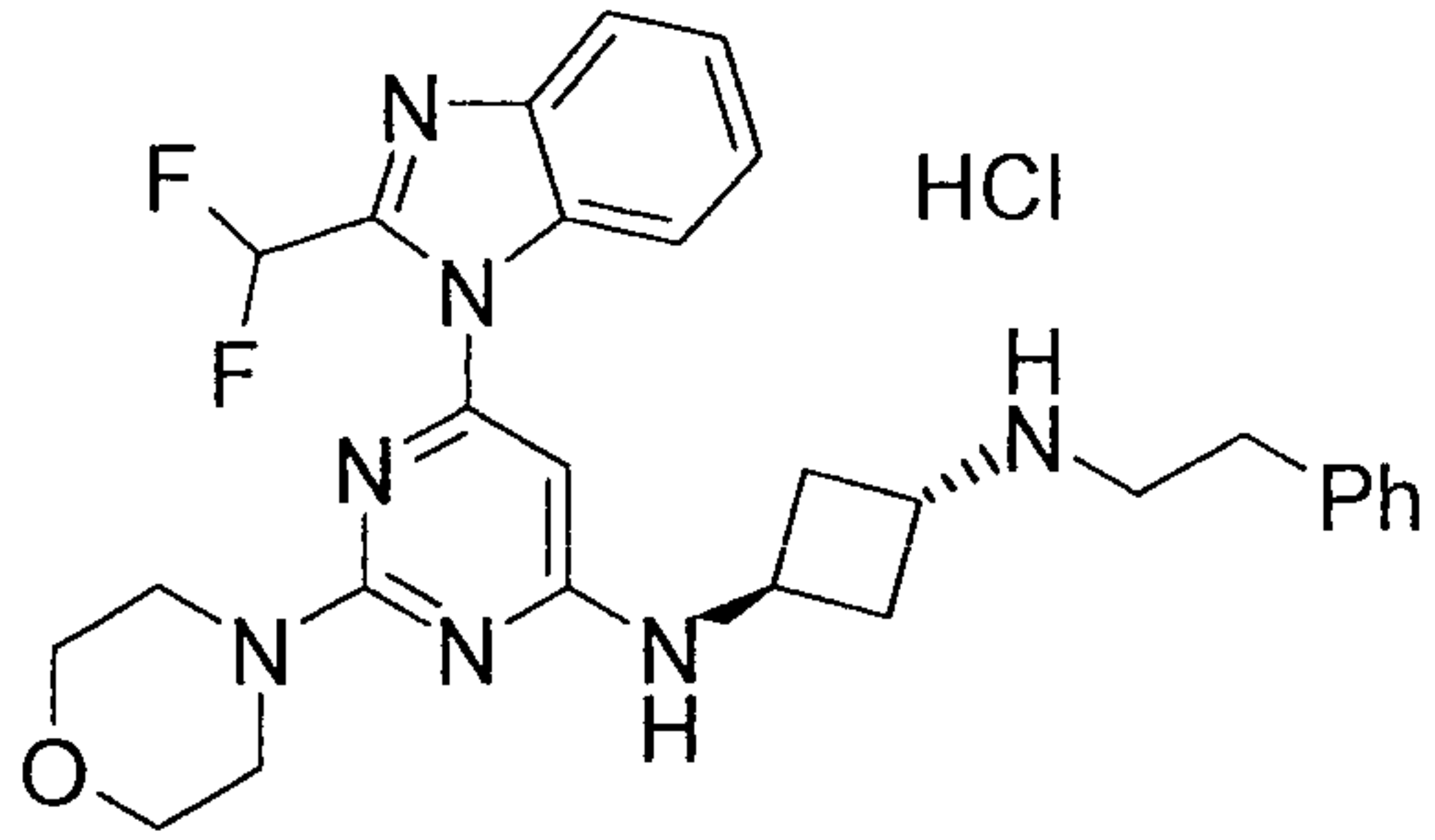
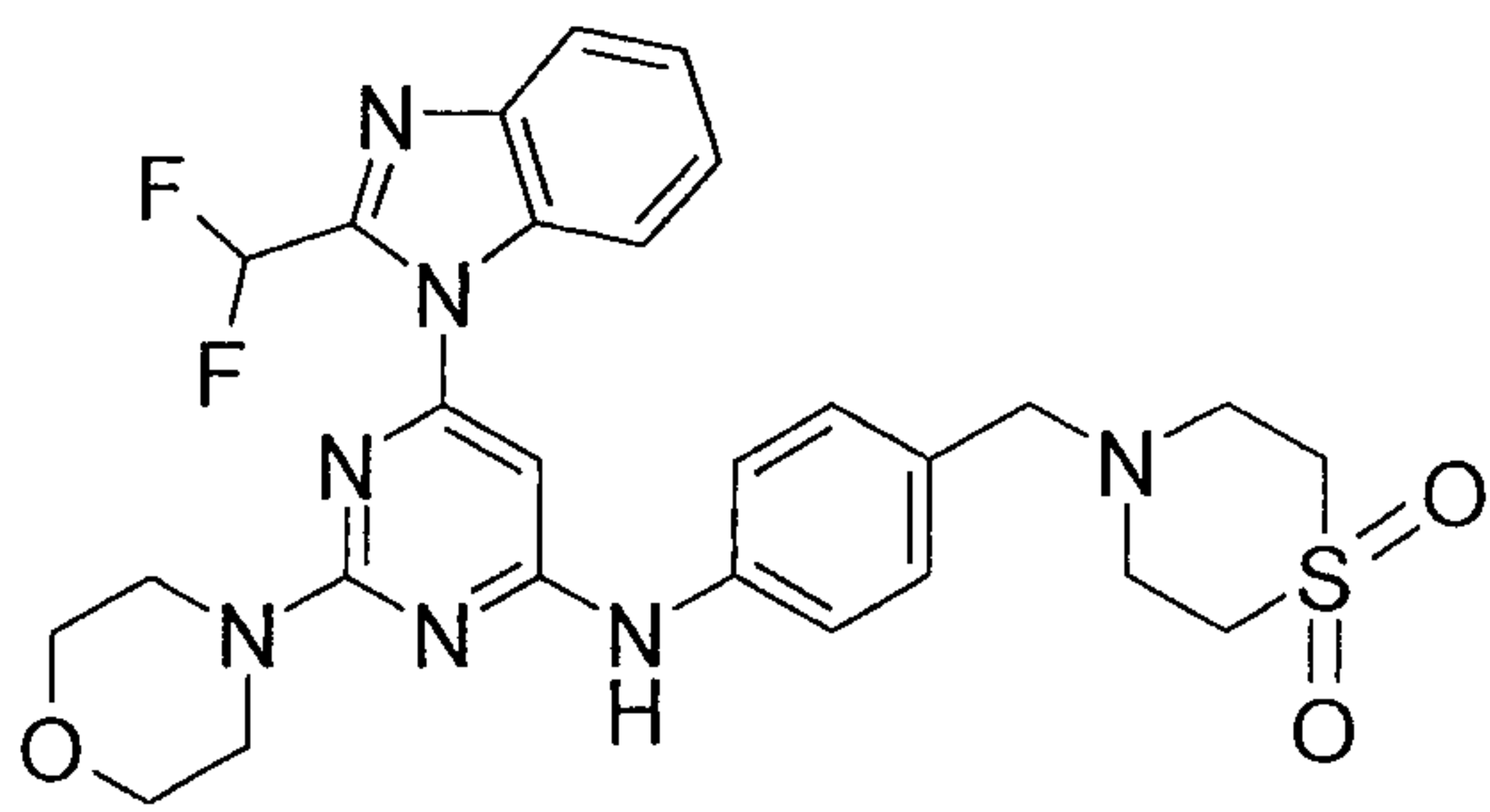
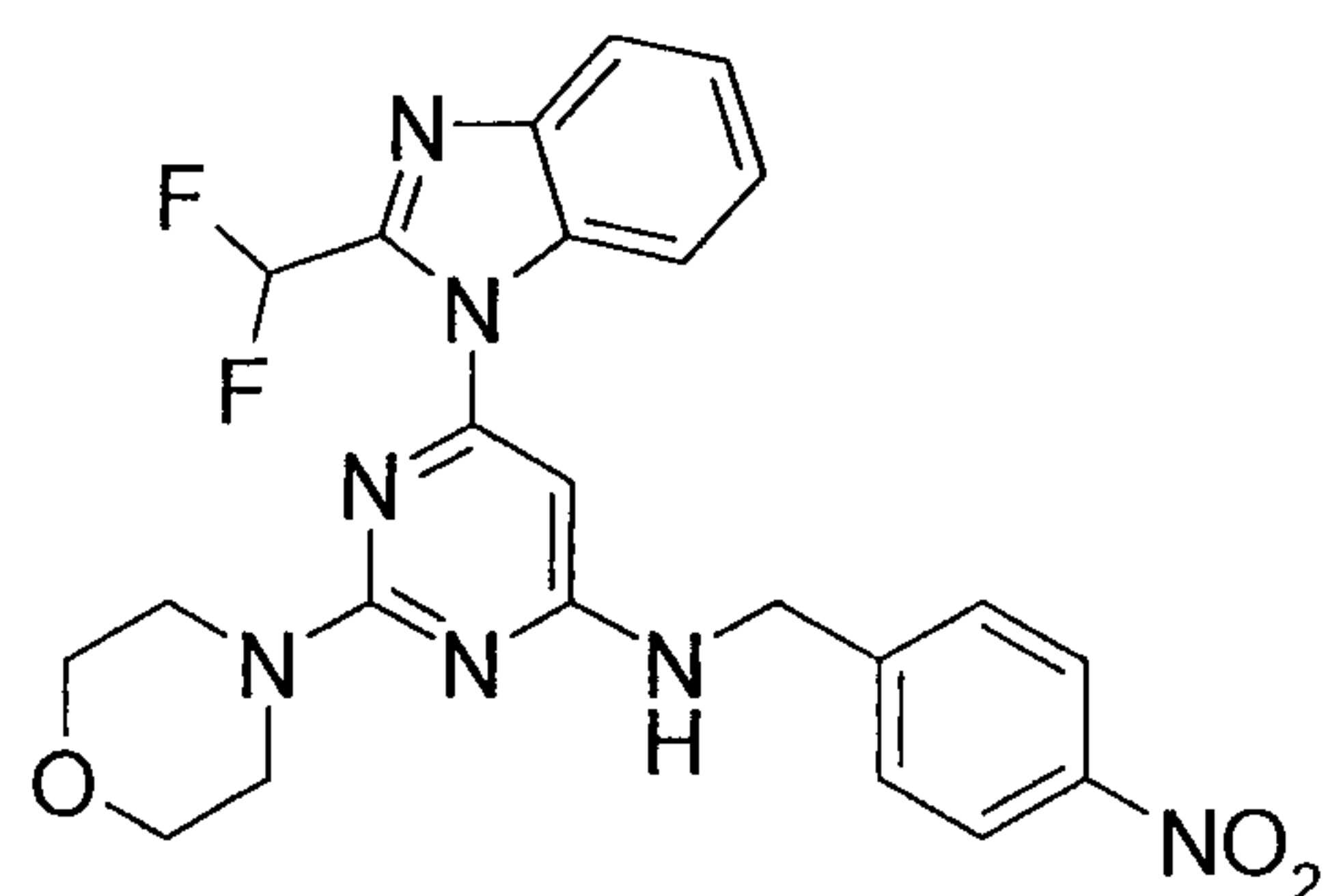
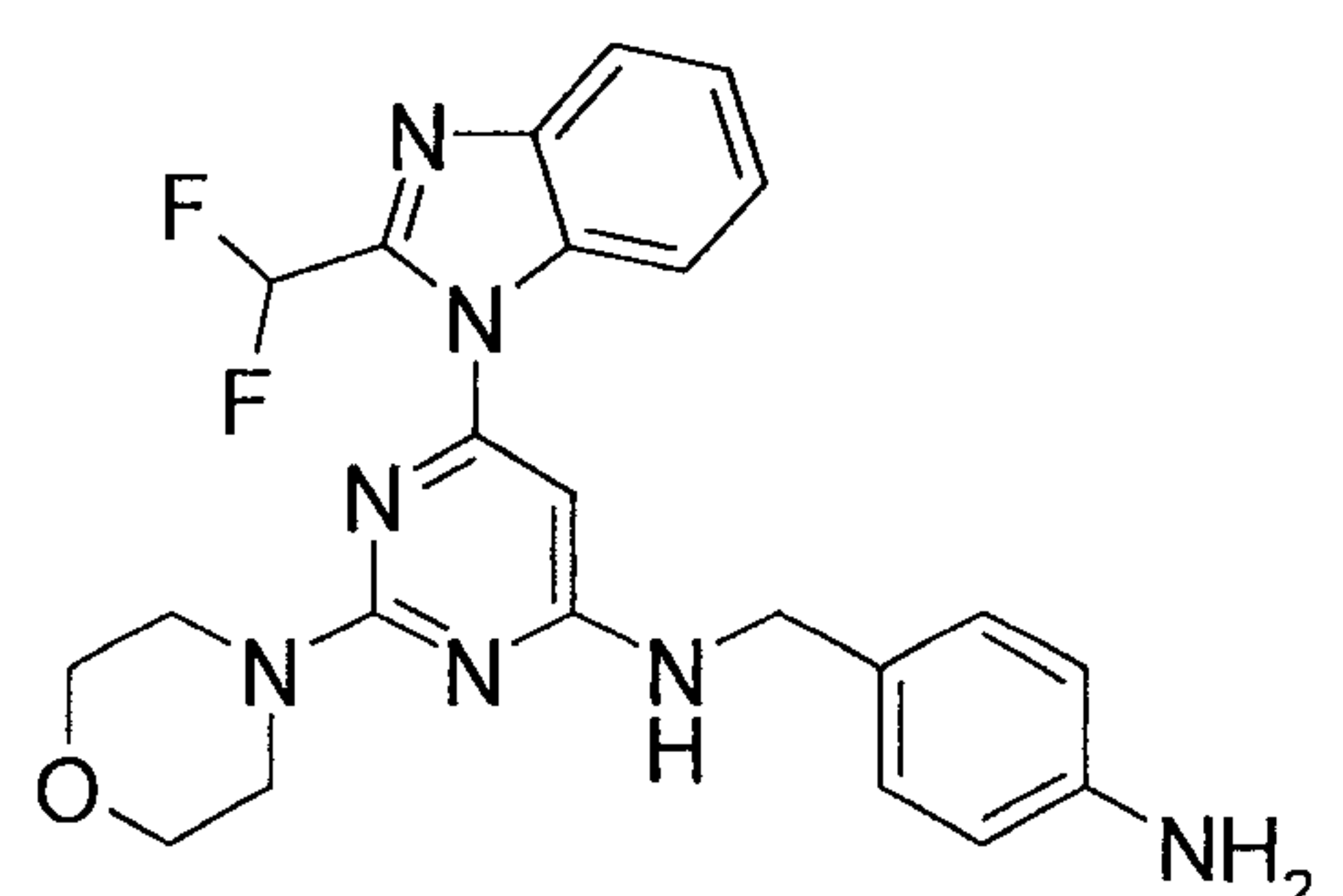
[0255]

[Table 99]

Ex	Str
287	<chem>Nc1nc(s1)-c2nc(NC3=NC4=C(N3)N(C4)N5CCOCC5)nc2</chem>
288	<chem>C1=NC2=CC=CC=C2S1N=C3C=CC(=N3)N4CCOCC4</chem>
289	<chem>C1CCN(CC1)Cc2ccc(NC3=NC4=C(N3)N(C4)N5CCOCC5)cc2</chem>
290	<chem>Cc1nc2ccccc2s1N=C3C=CC(=N3)N4CCOCC4</chem>
291	<chem>C1CCN(CC1)Cc2ccc(NC3=NC4=C(N3)N(C4)N5CCOCC5)cc2</chem>

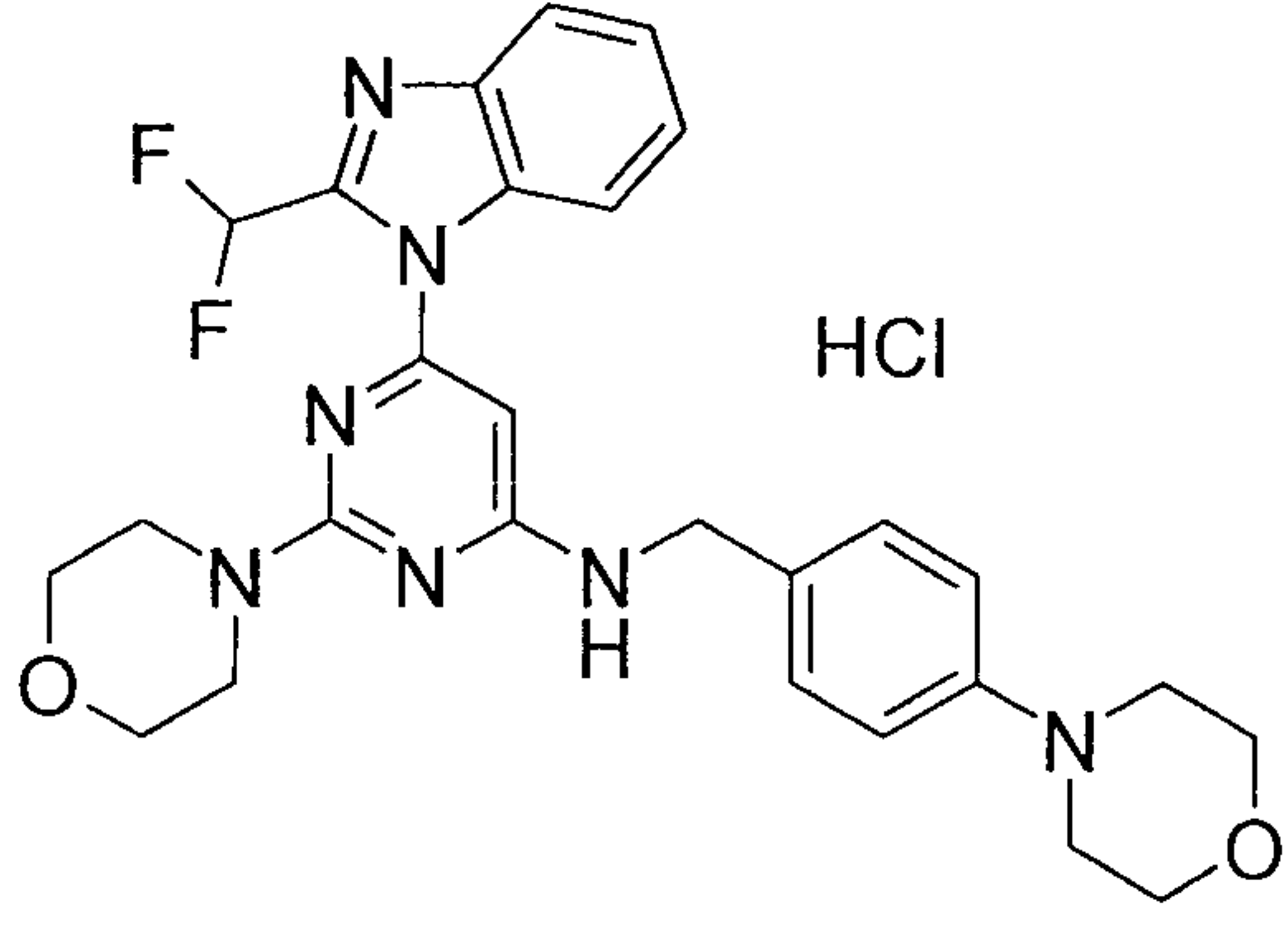
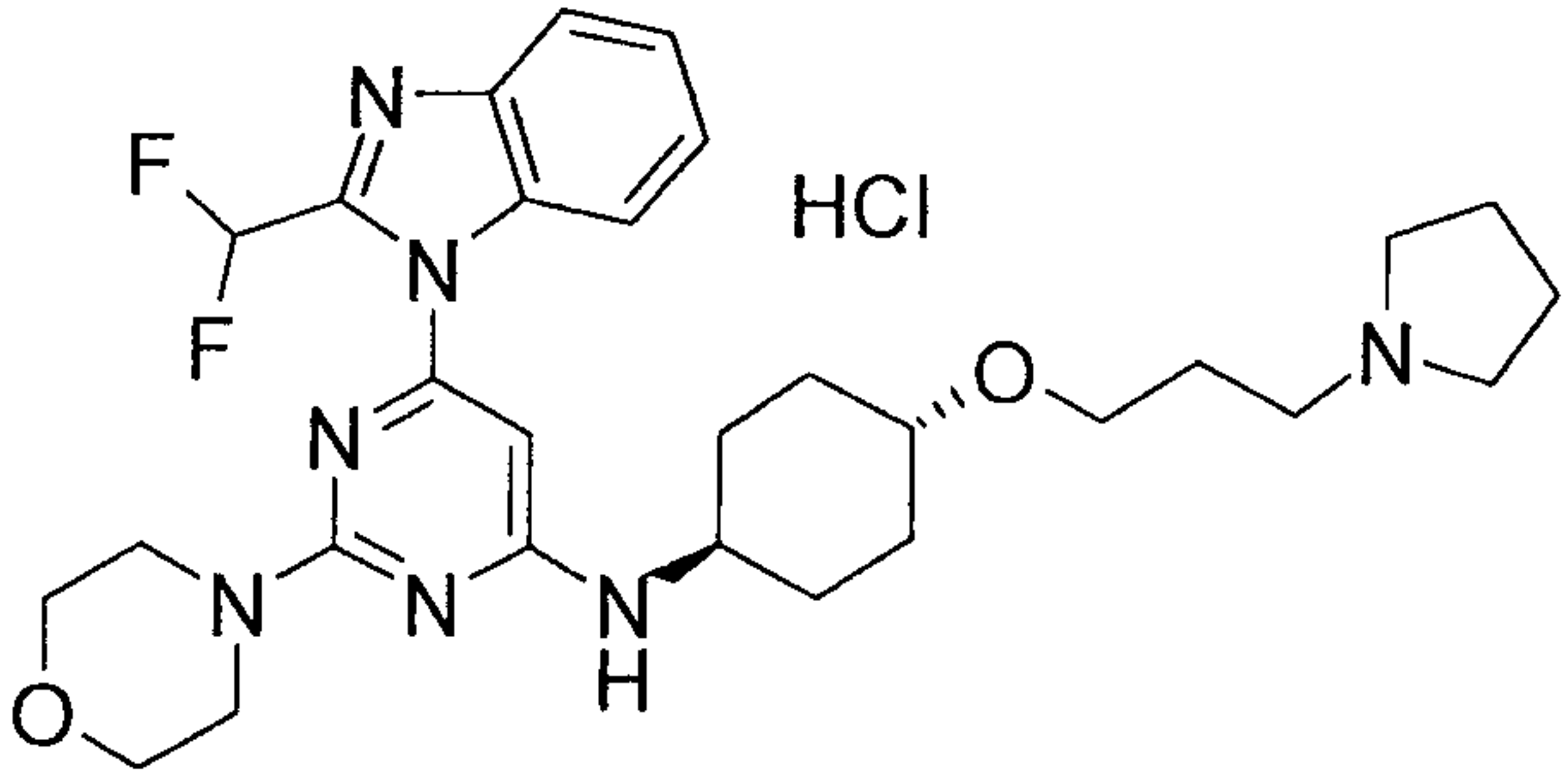
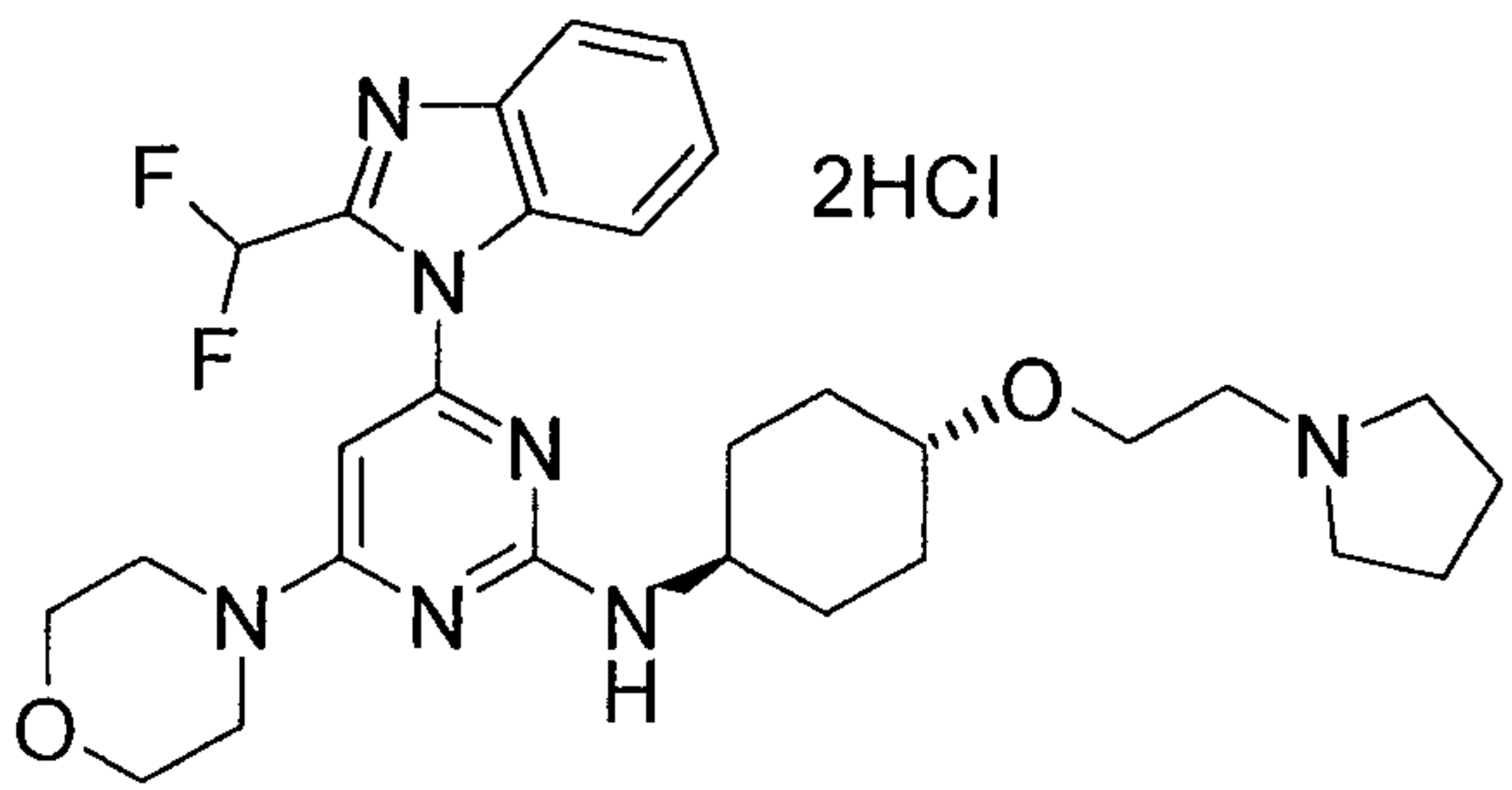
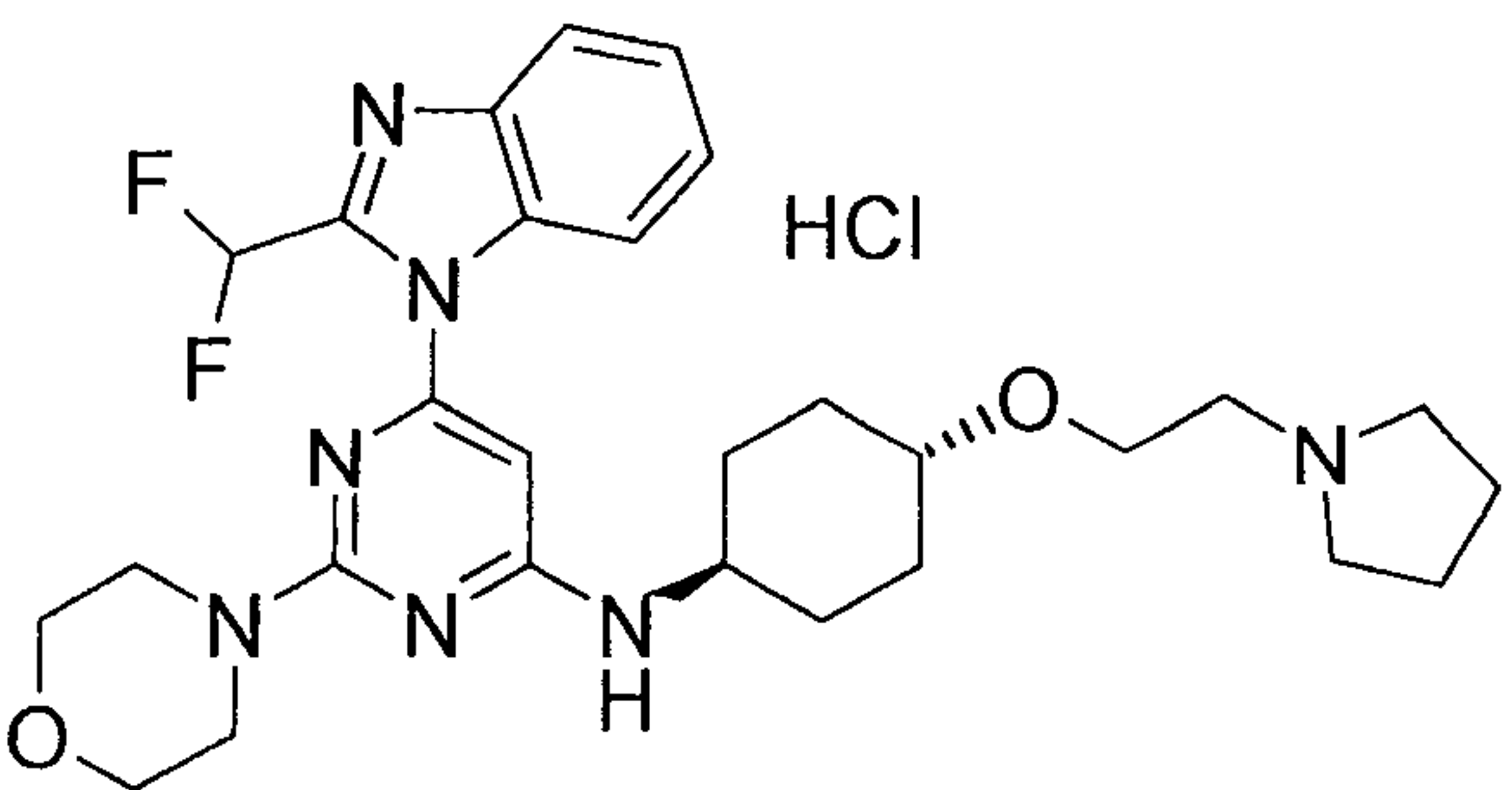
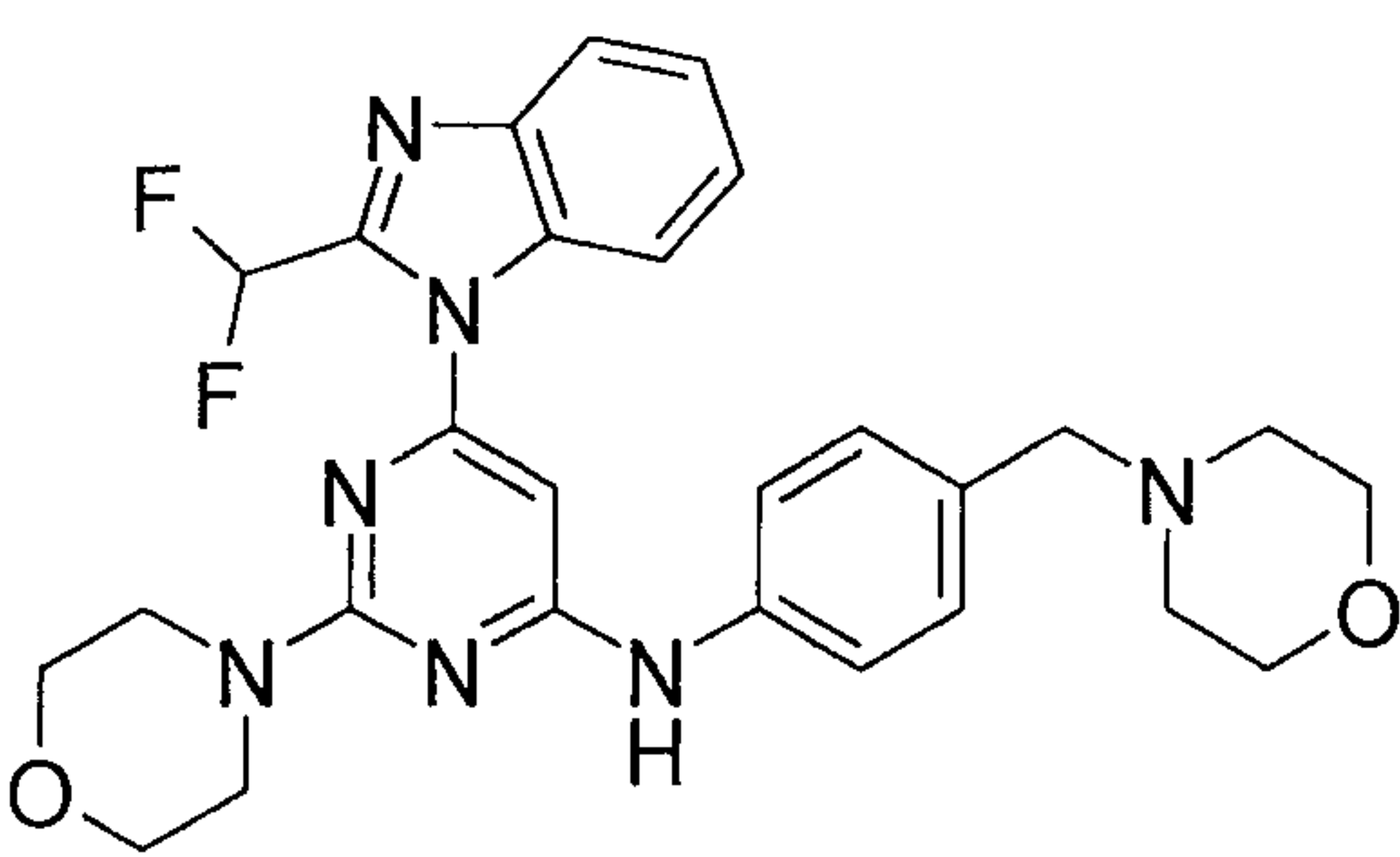
[0256]

[Table 100]

Ex	Str
292	
293	
294	
295	

[0257]

[Table 101]

Ex	Str
296	
297	
298	
299	
300	

[0258]

[Table 102]

Ex	Str
301	
302	
303	
304	
305	

[0259]

[Table 103]

Ex	Str
306	
307	
308	
309	
310	

[0260]

[Table 104]

Ex	Str
311	 <chem>COc1ccc(Nc2nc3c(ncn3C(F)F)c4ccccc42)c5ccccc5N6CCOCC6</chem>
312	 <chem>COc1ccc(Nc2nc3c(ncn3C(F)F)c4ccccc42)c5ccncc5N6CCOCC6</chem>
313	 <chem>COc1ccc(Nc2nc3c(ncn3C(F)F)c4ccccc42)c5cc(OC)cc5N6CCOCC6</chem>
314	 <chem>C1CCN(C1)Cc2cc(Nc3nc4c(ncn4C(F)F)c5ccccc53)ccn2N6CCOCC6</chem>
315	 <chem>O=C1NCCN1c2ccc(Nc3nc4c(ncn4C(F)F)c5ccccc53)cc2N6CCOCC6</chem>

[0261]

[Table 105]

Ex	Str
316	
317	
318	
319	
320	

[0262]

[Table 106]

Ex	Str
321	
322	
323	
324	
325	

[0263]

[Table 107]

Ex	Str
326	
327	
328	
329	
330	

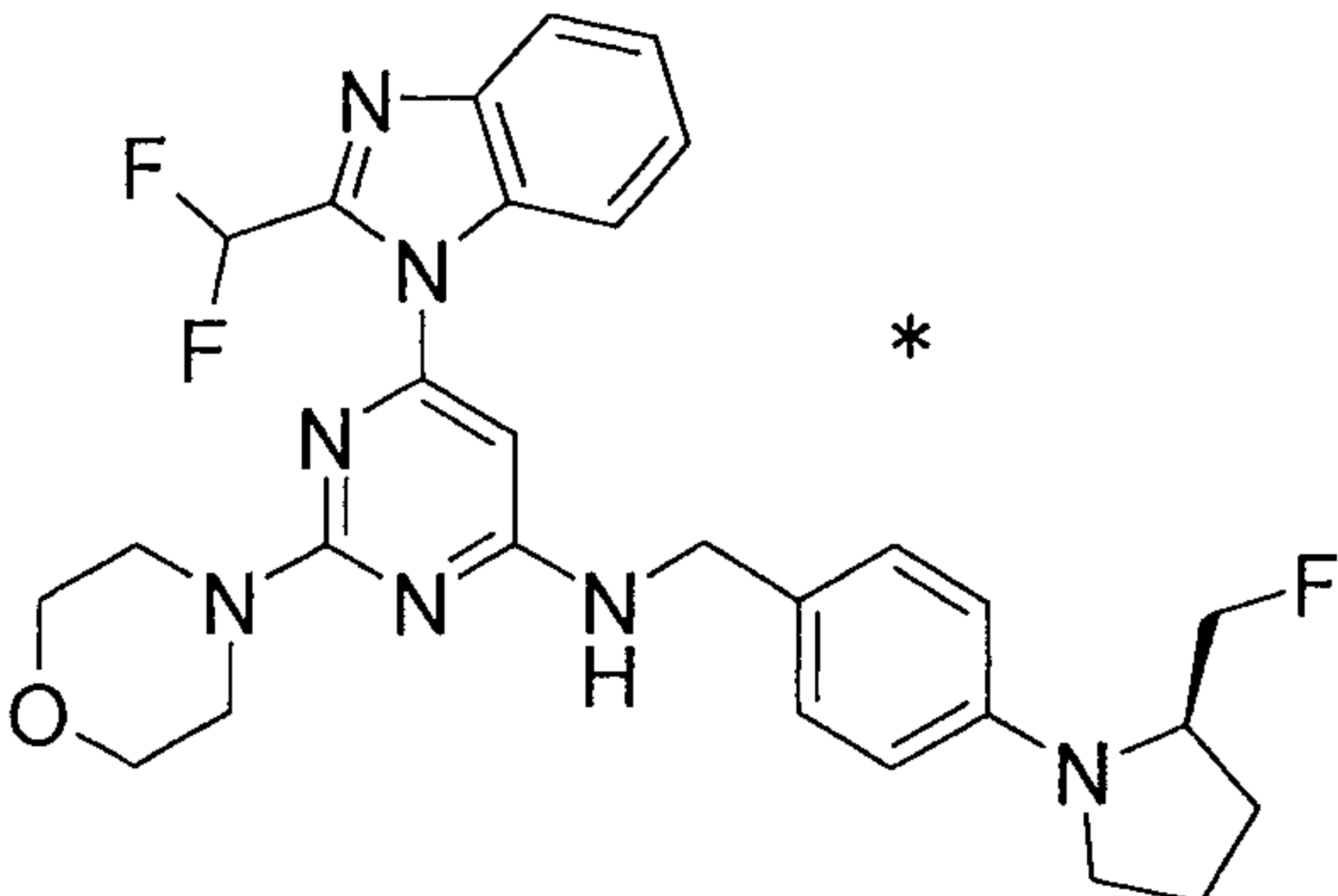
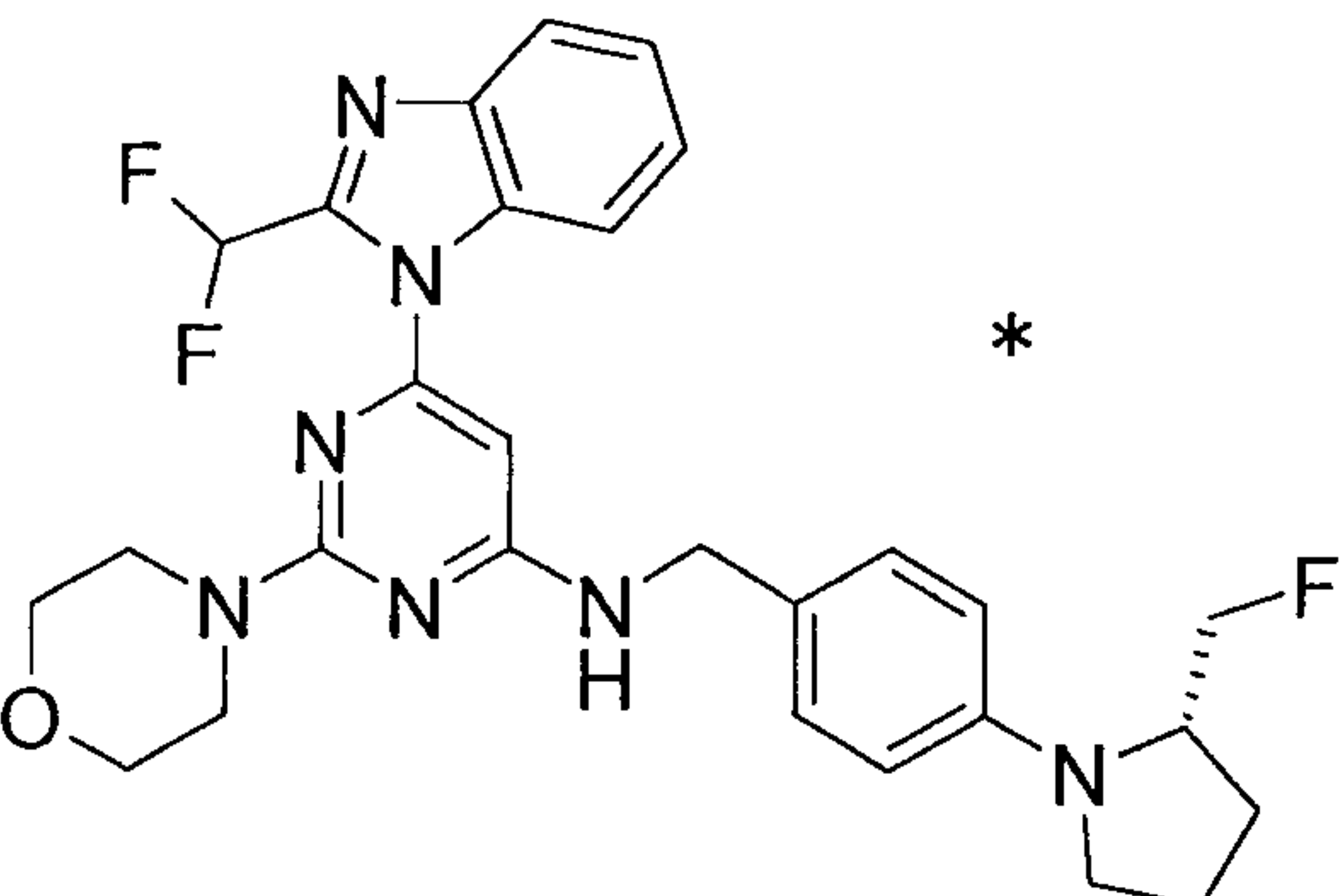
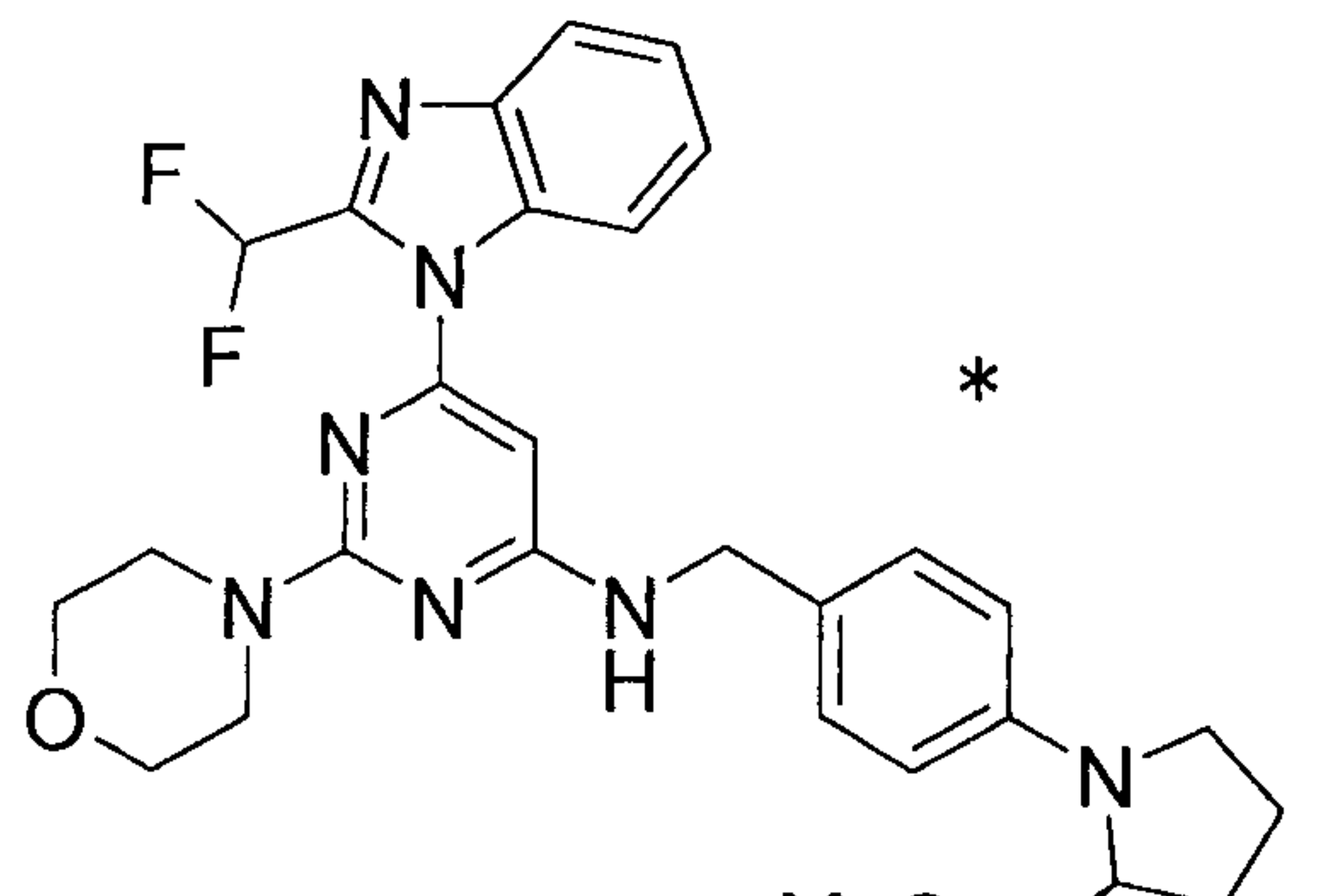
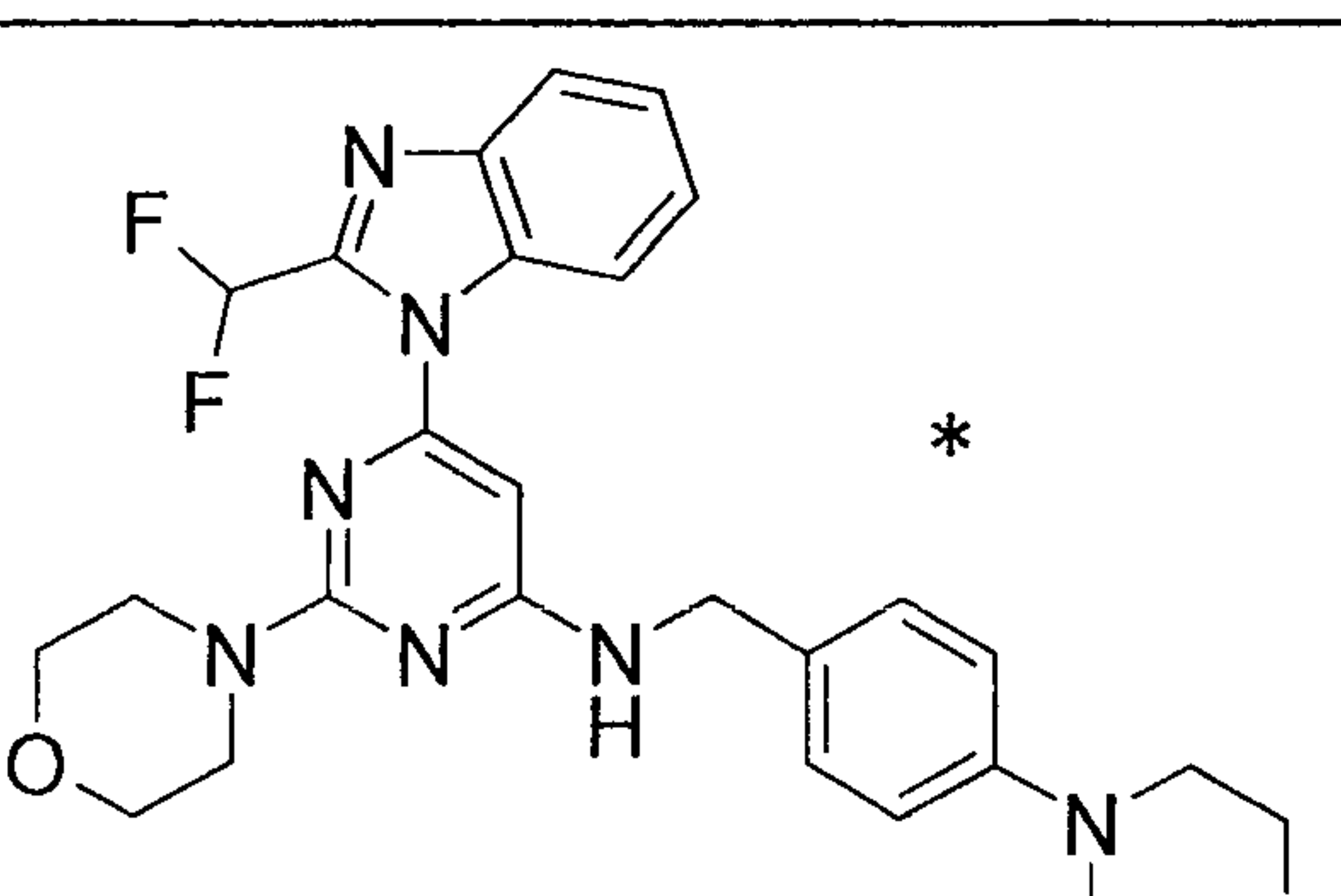
[0264]

[Table 108]

Ex	Str
331	
332	
333	
334	

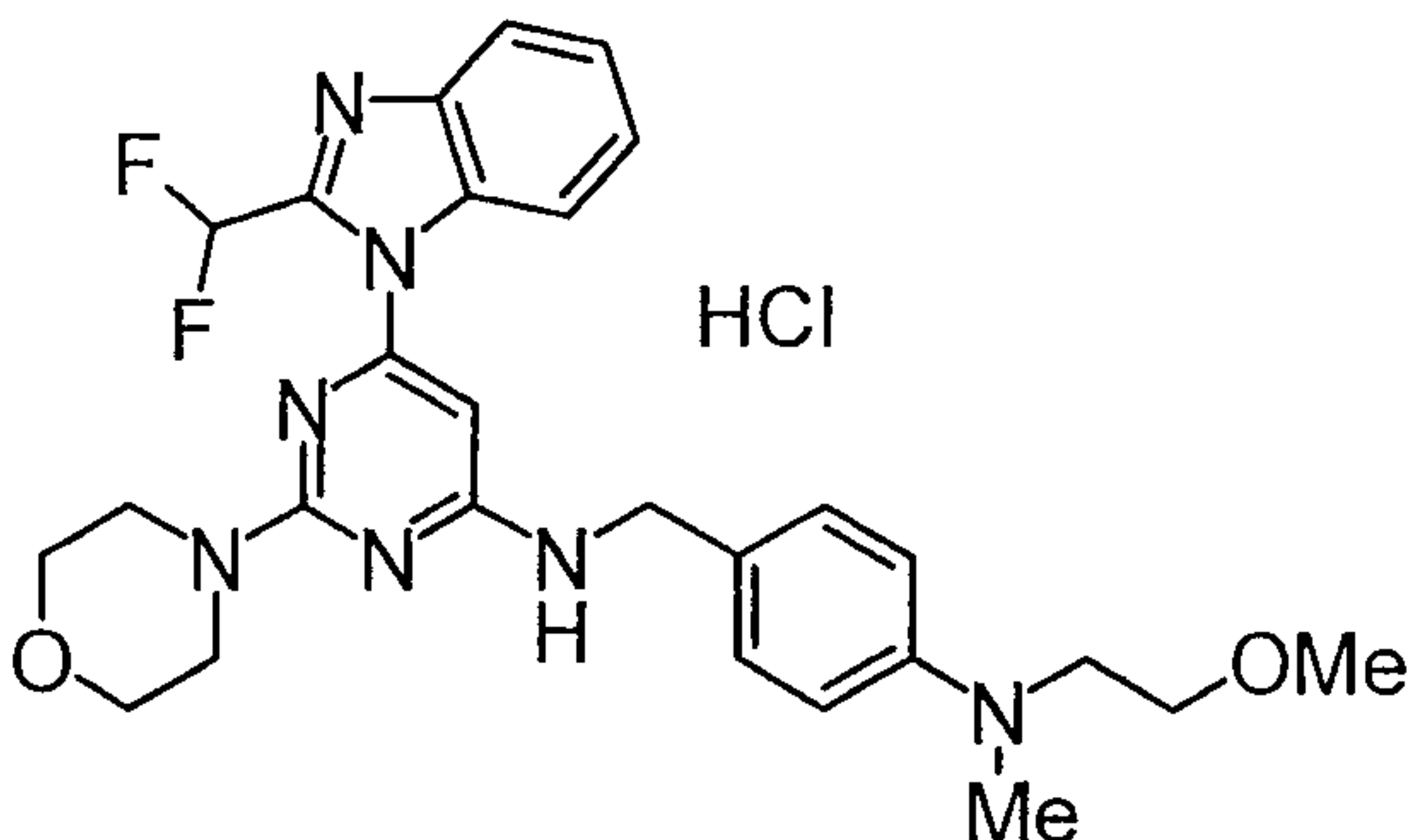
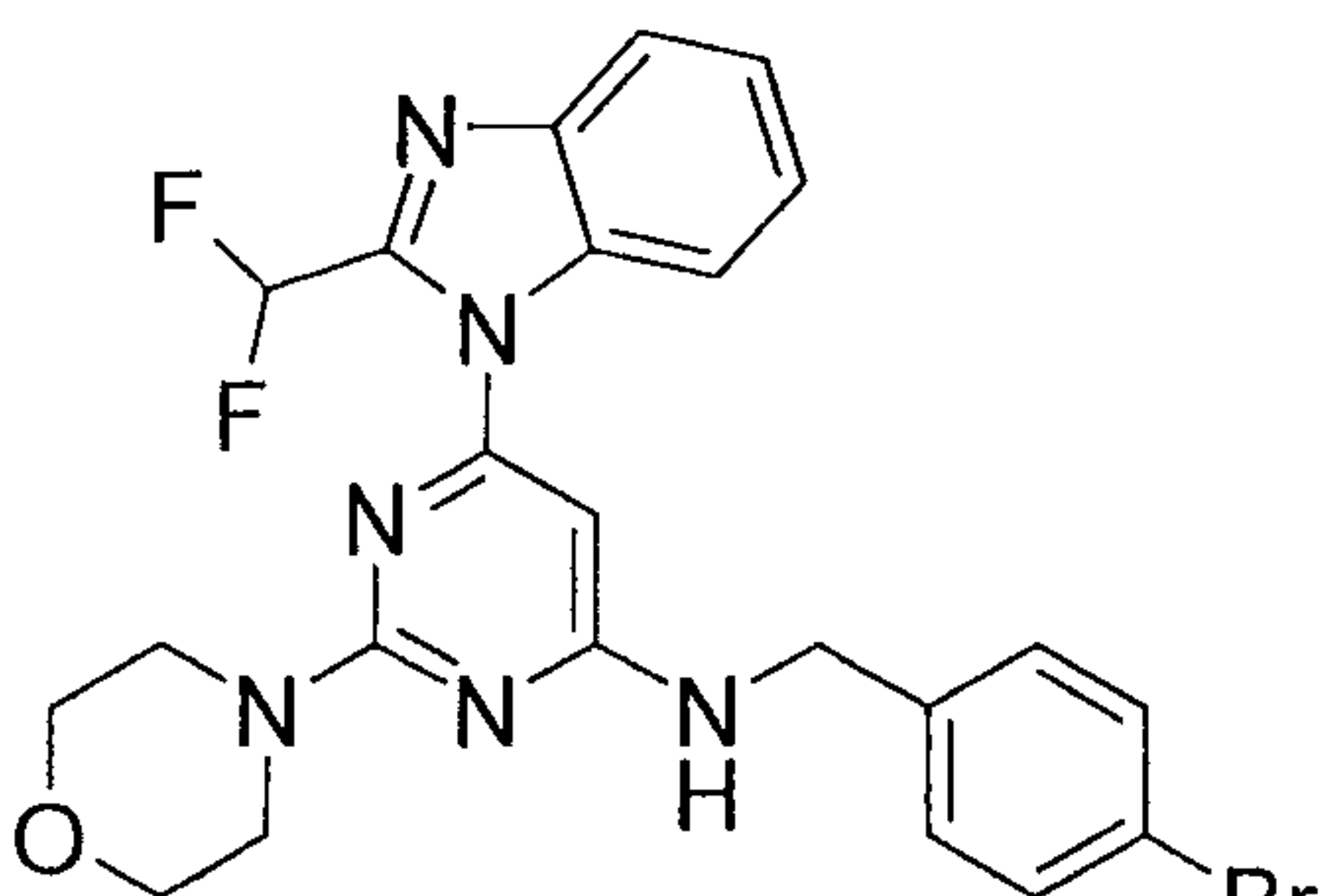
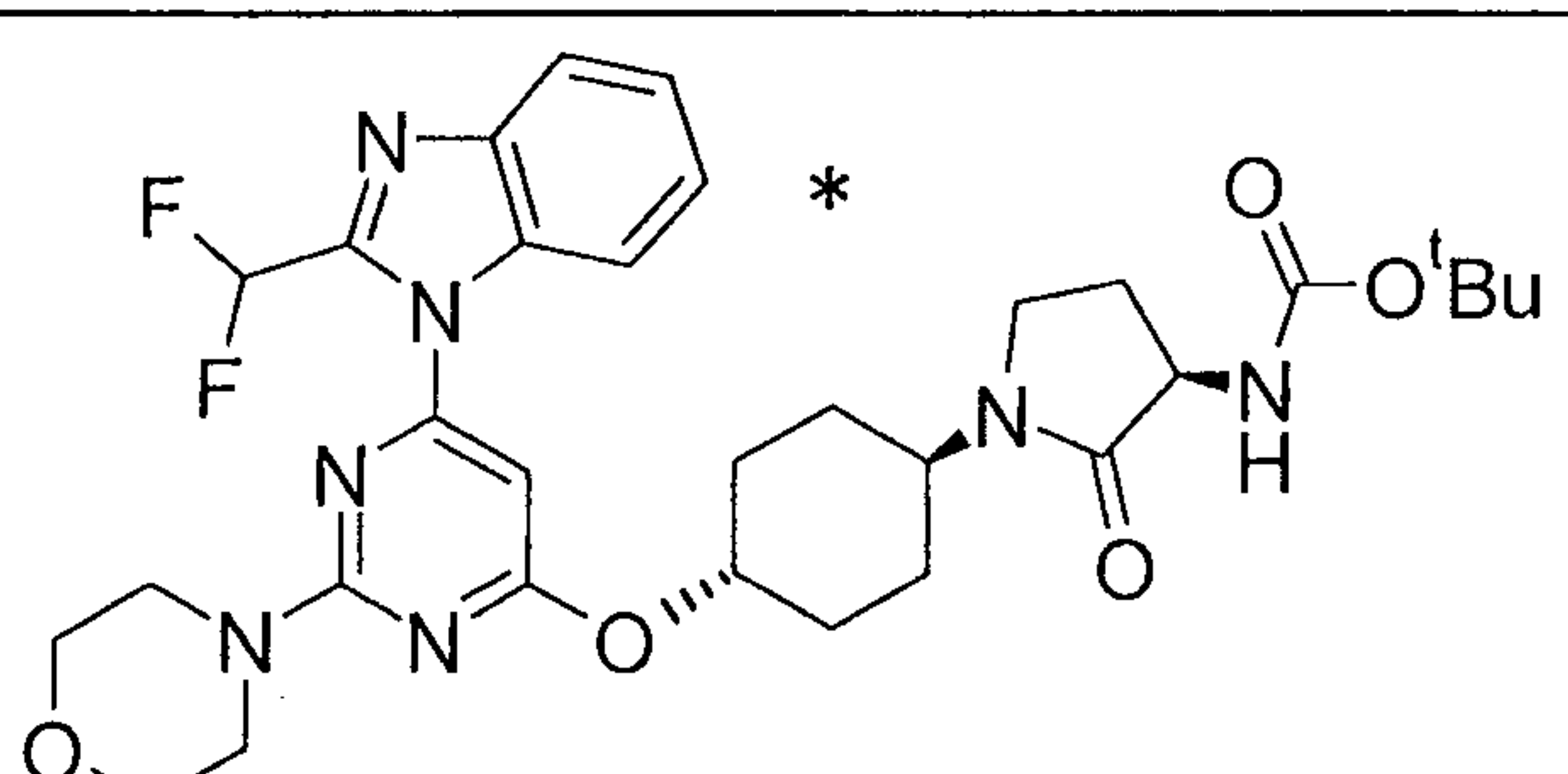
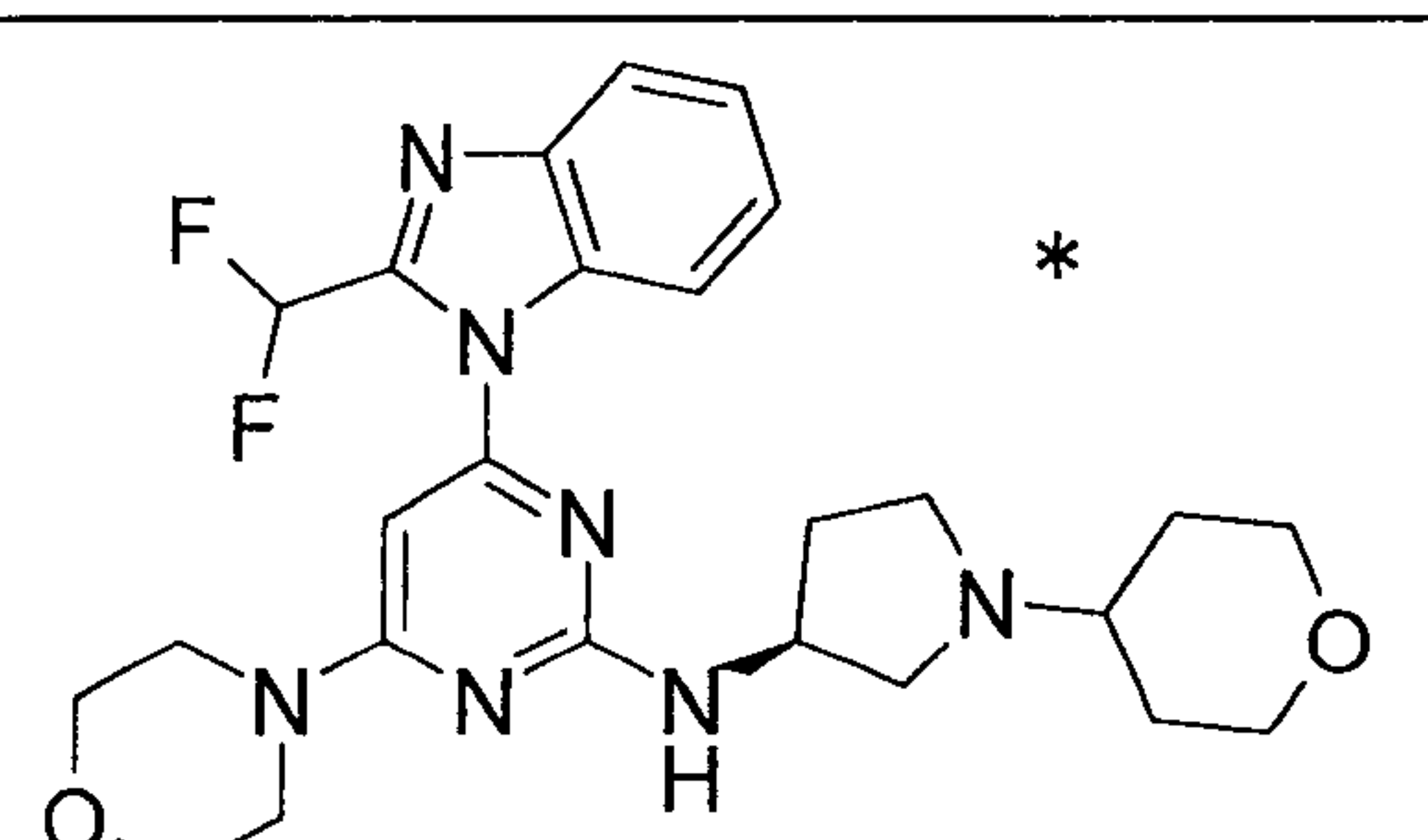
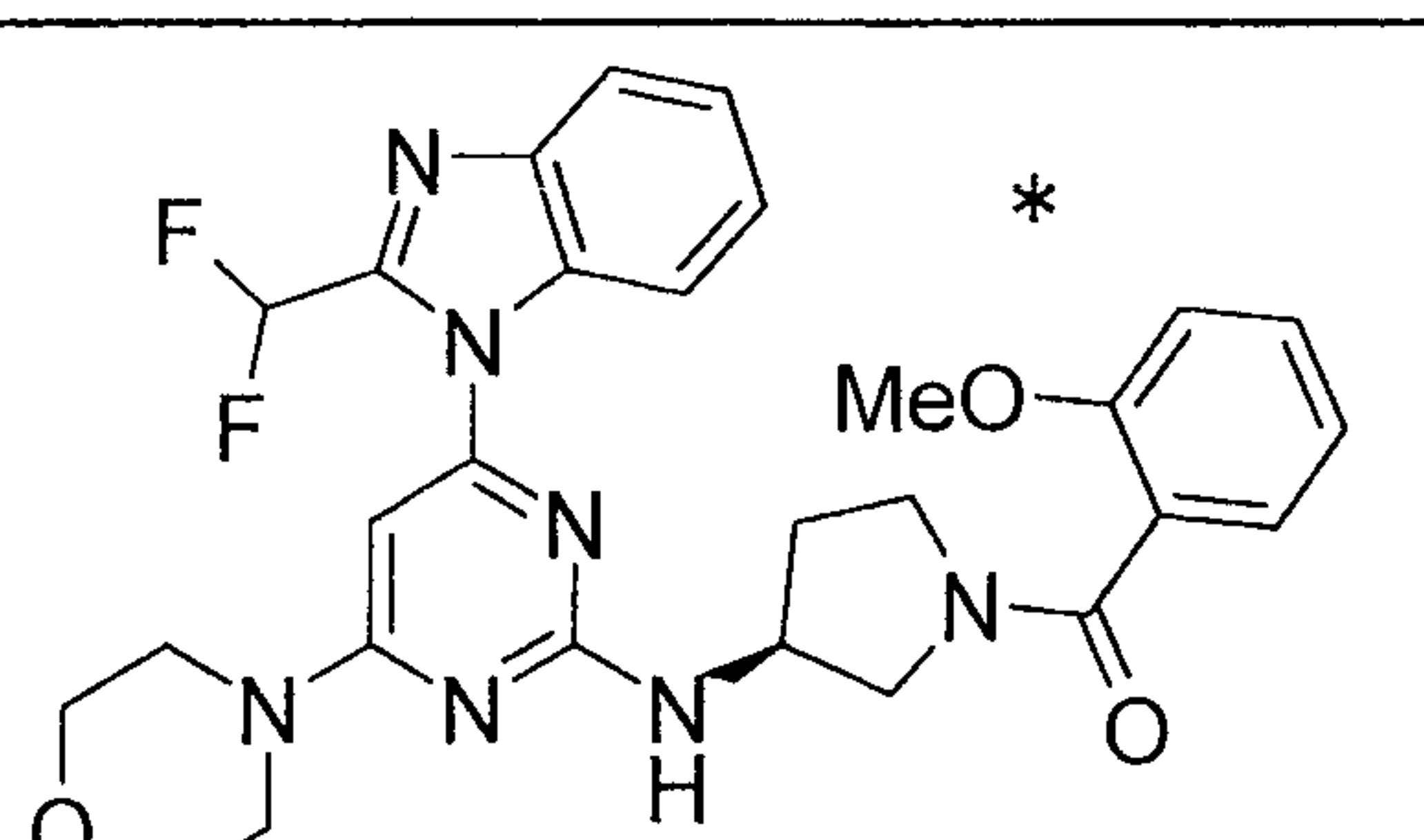
[0265]

[Table 109]

Ex	Str
335	
336	
337	
338	

[0266]

[Table 110]

Ex	Str
339	
340	
341	
342	
343	

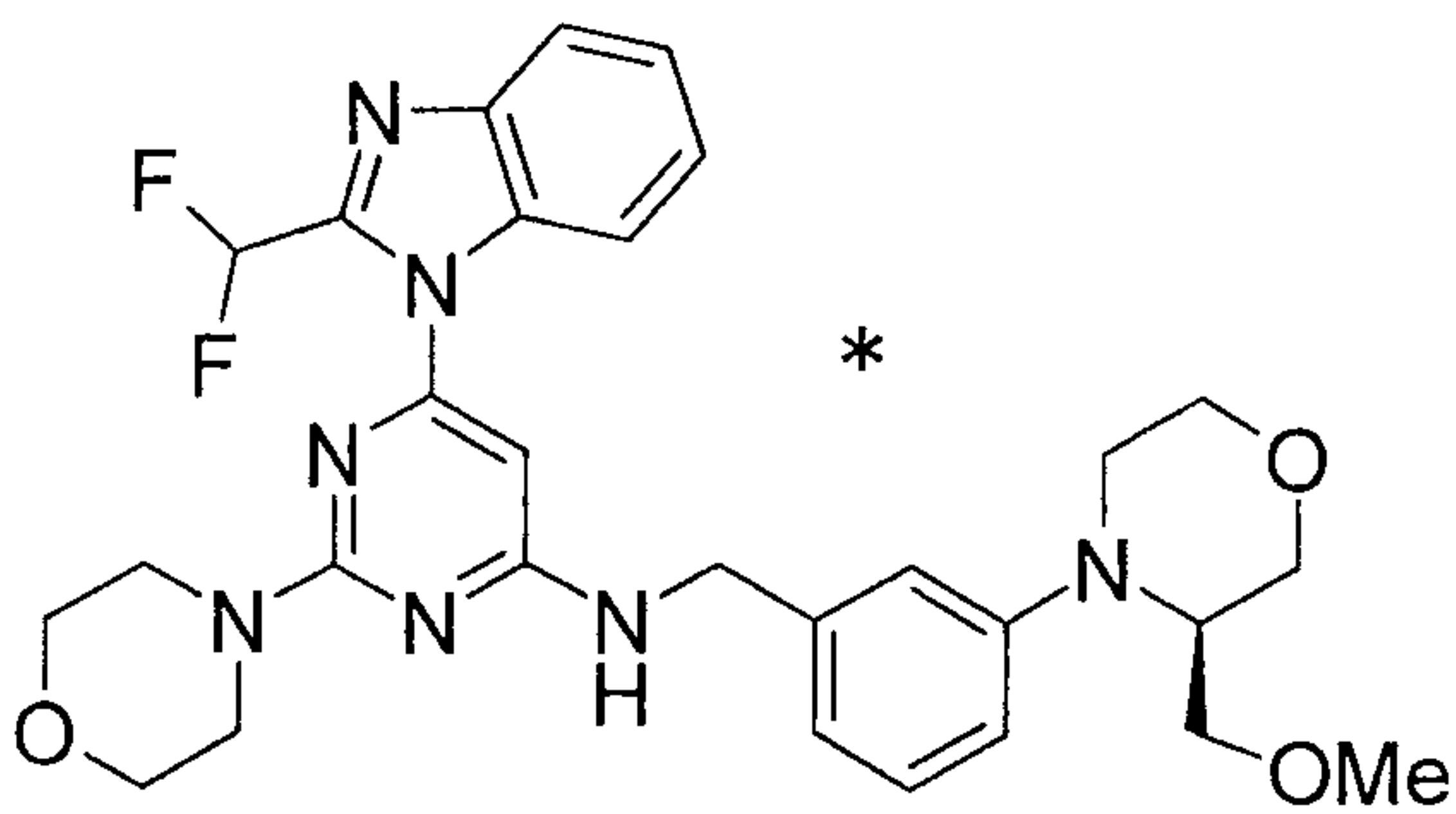
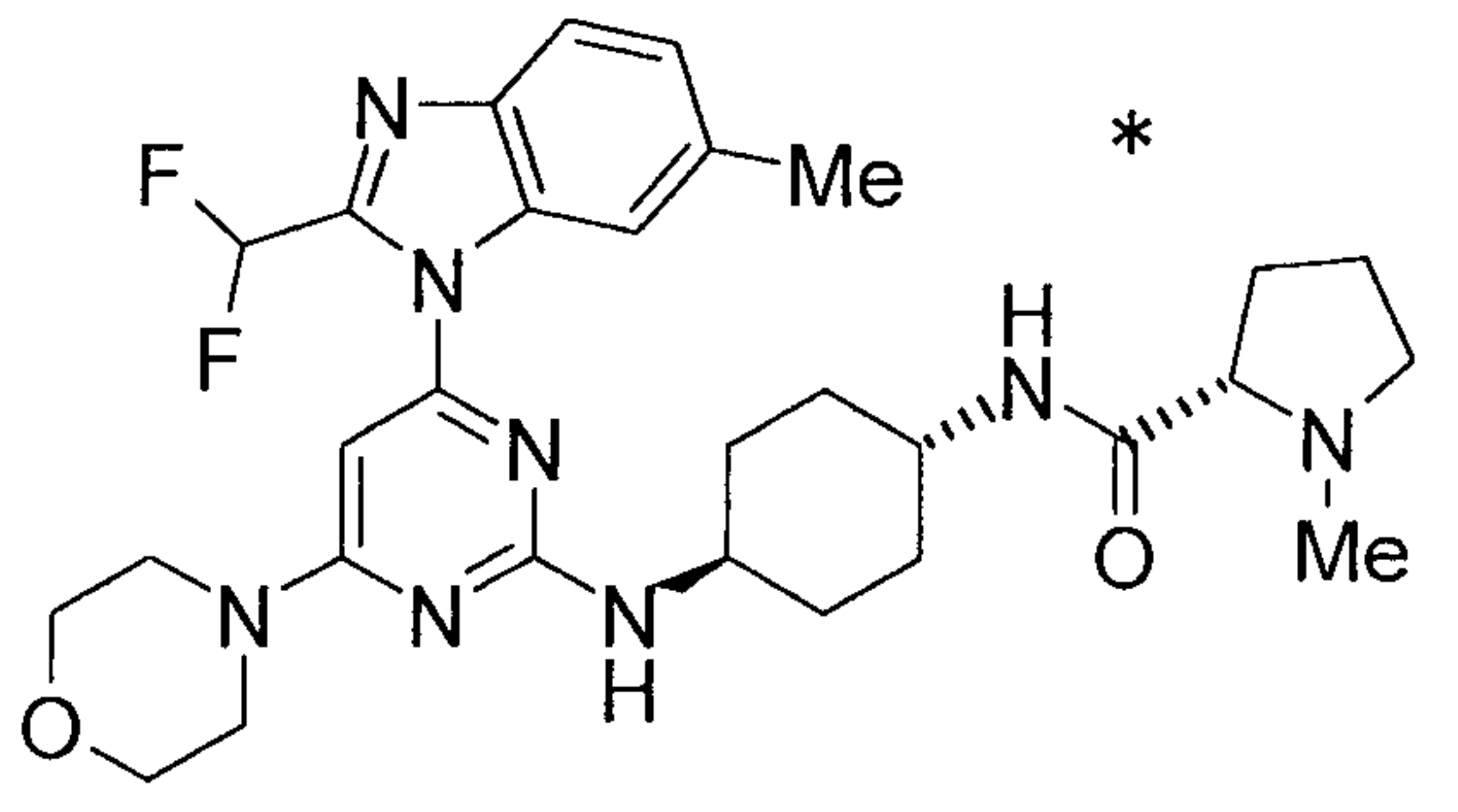
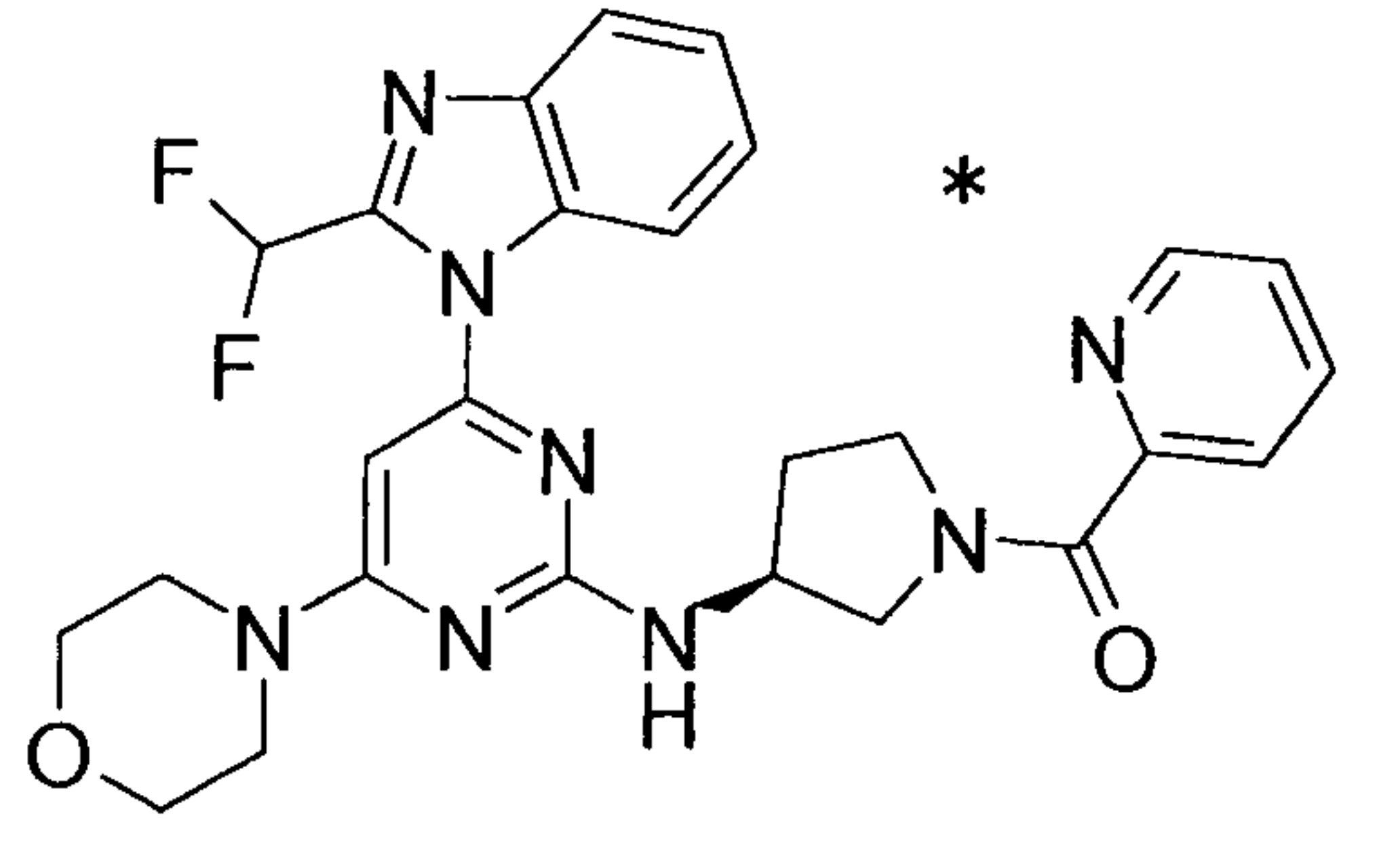
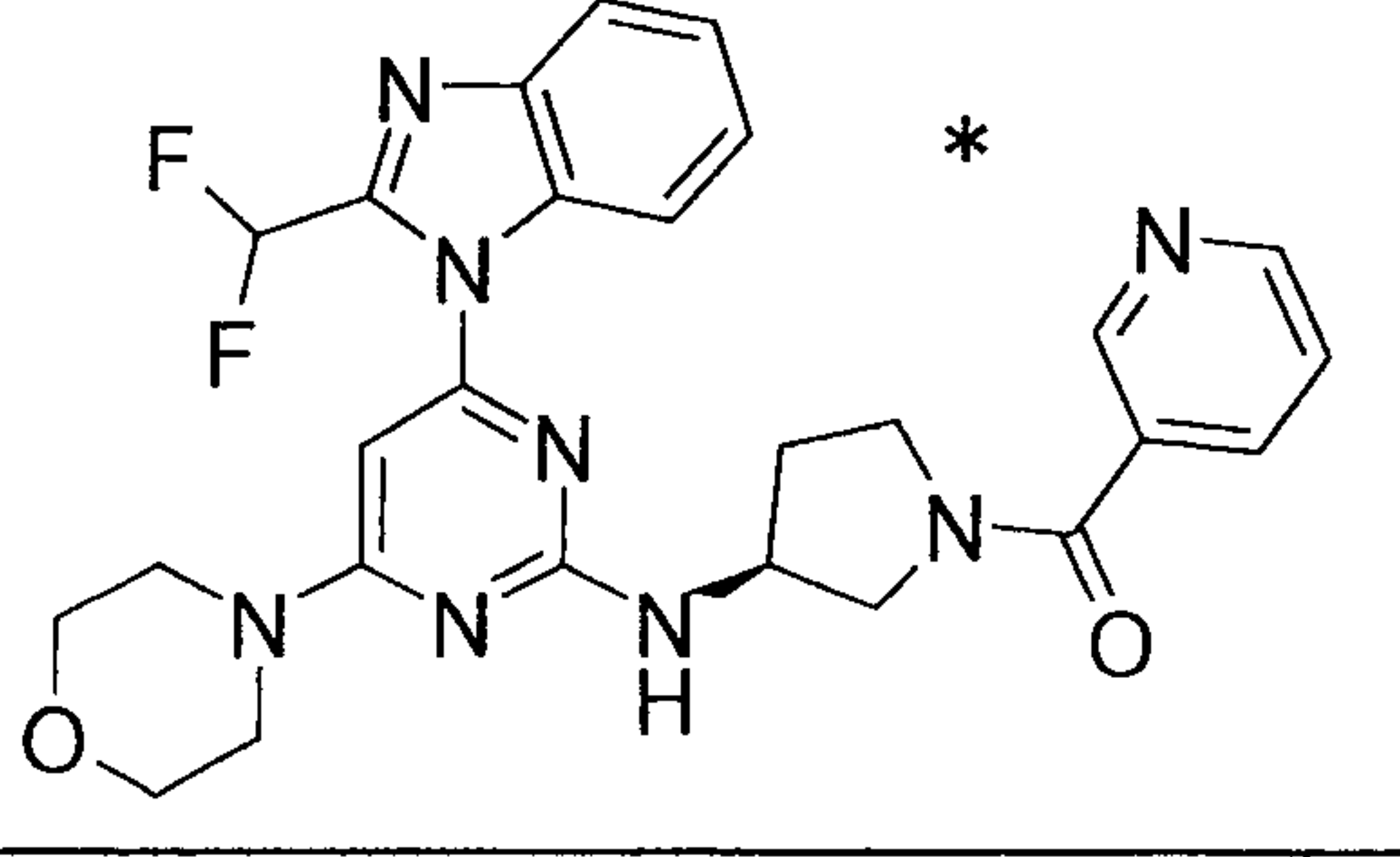
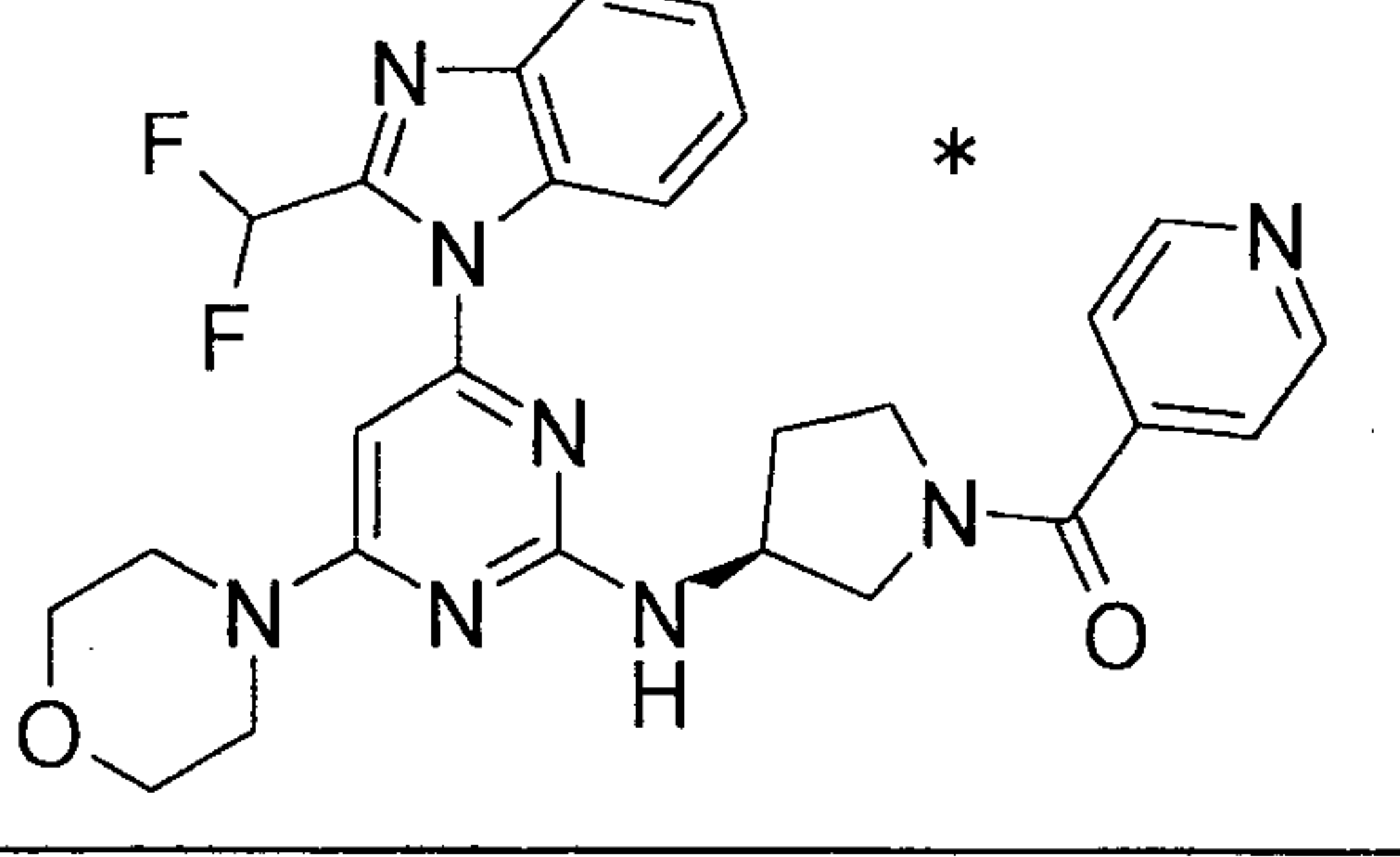
[0267]

[Table 111]

Ex	Str
344	
345	
346	
347	
348	

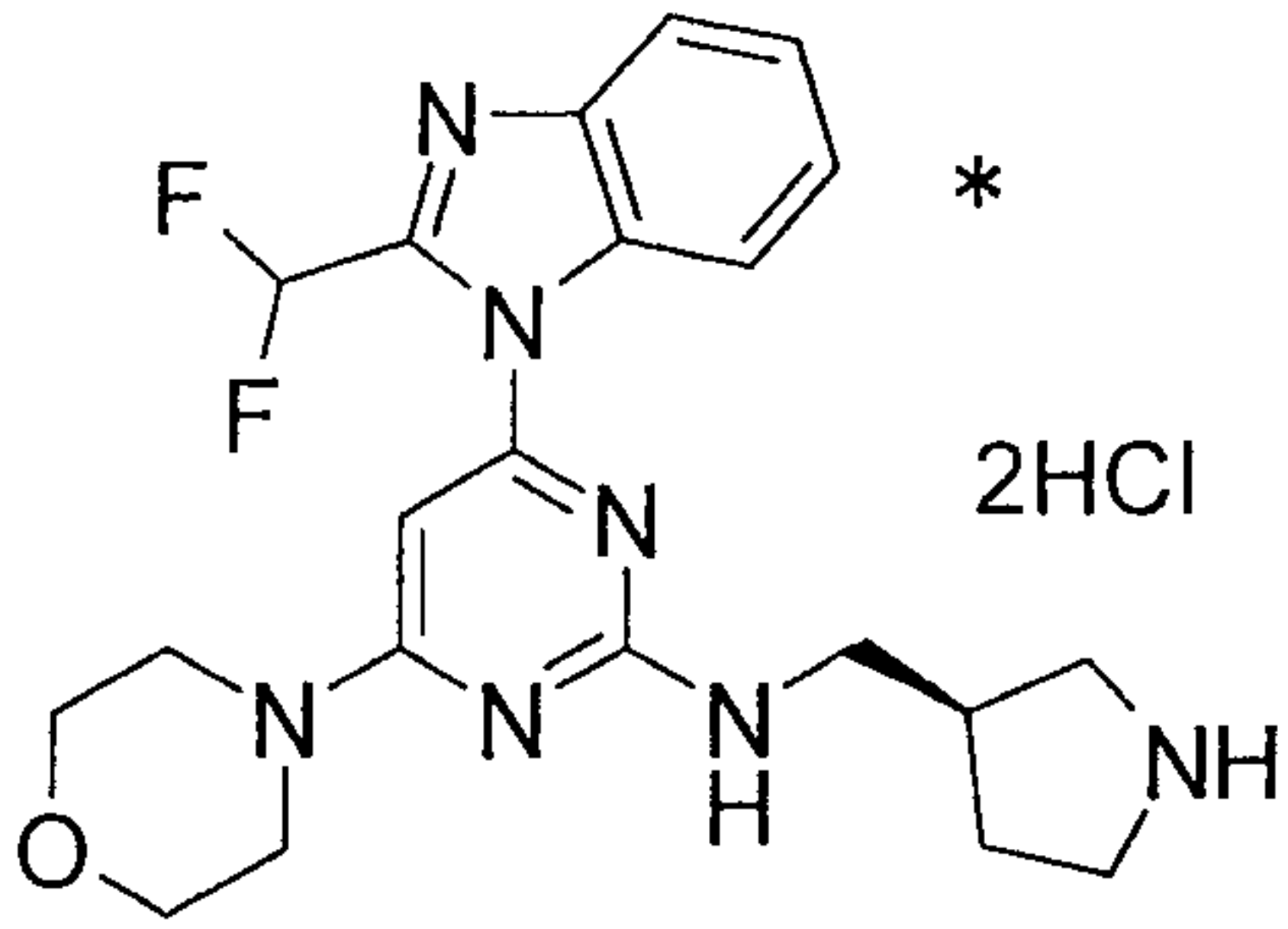
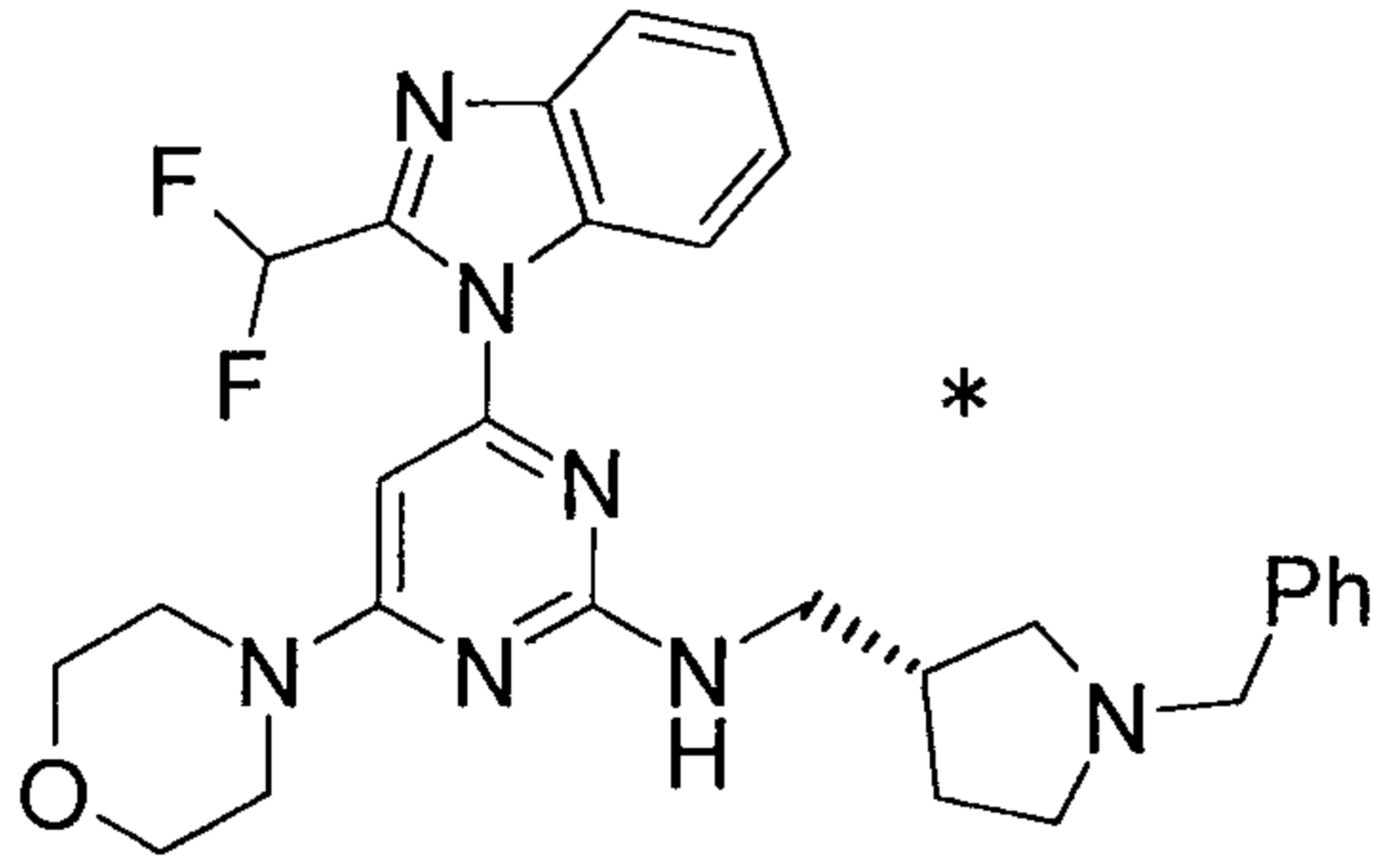
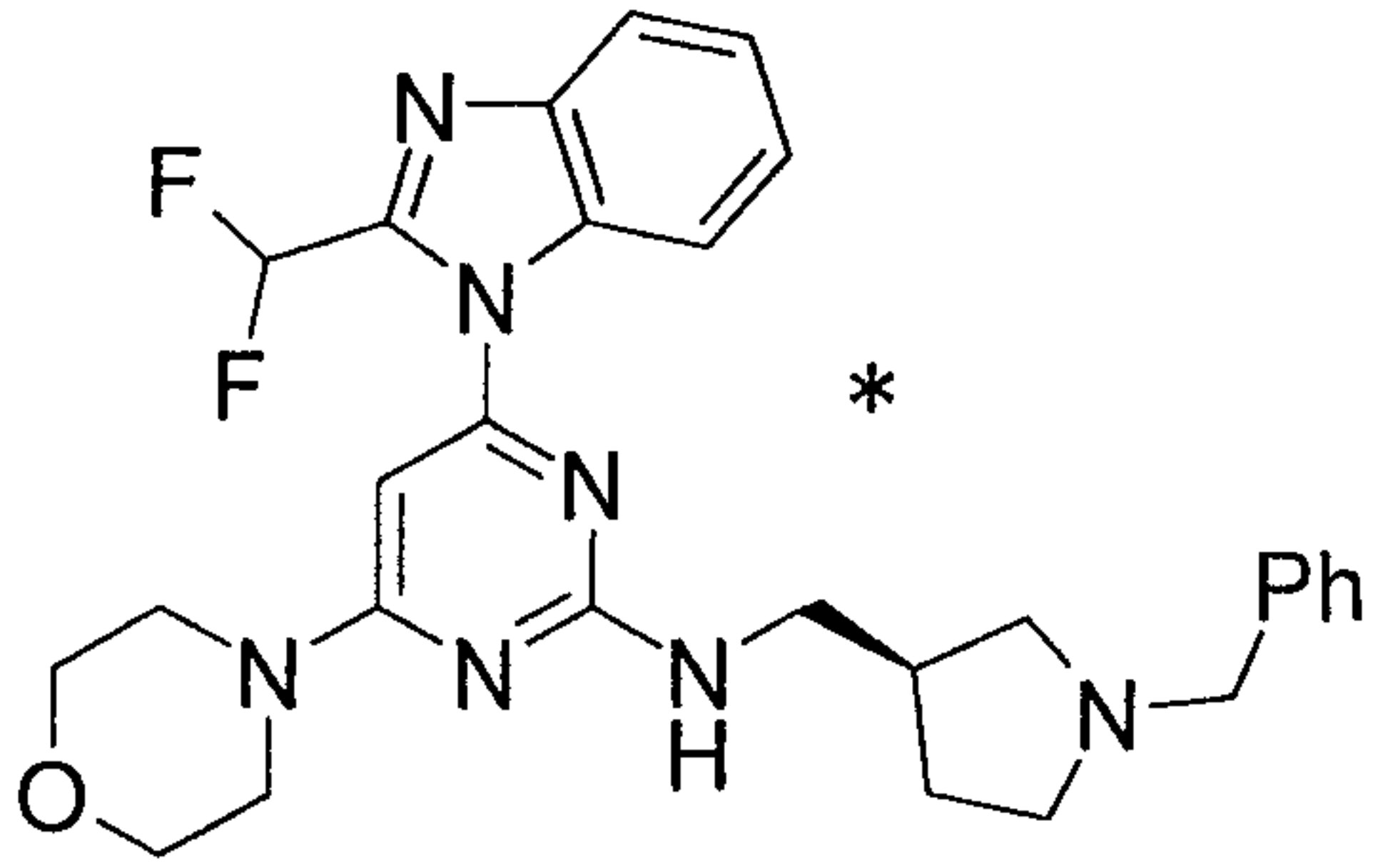
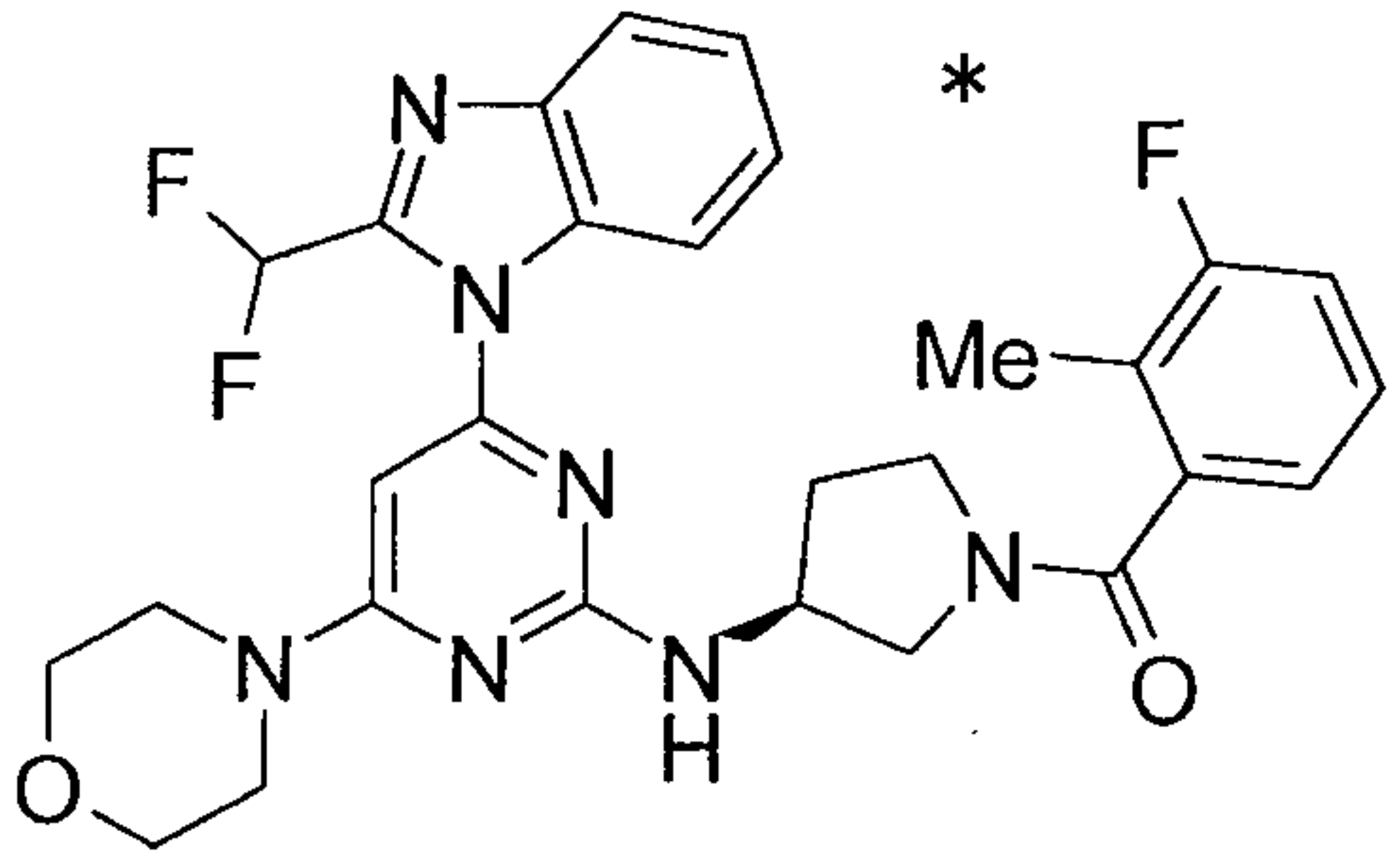
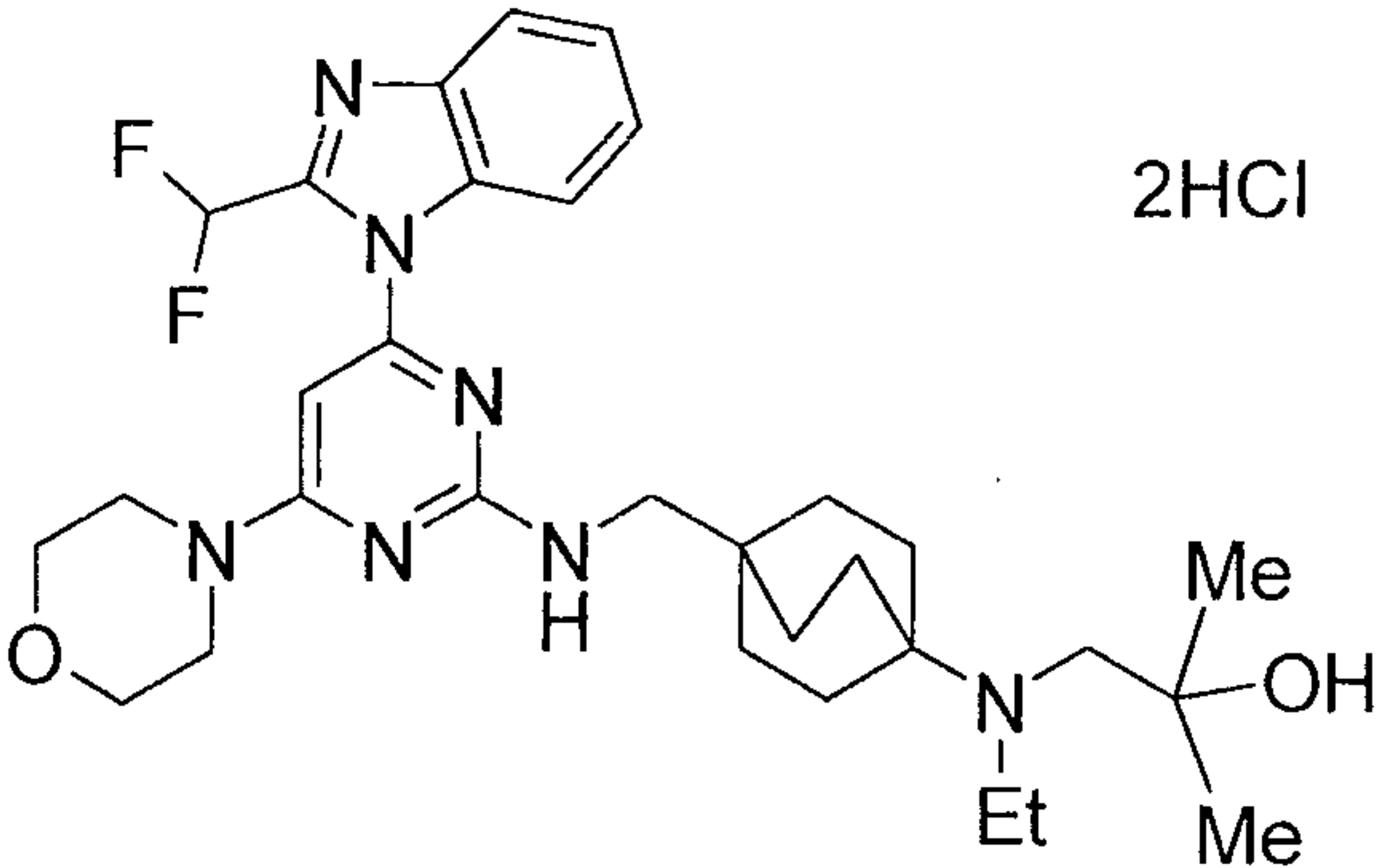
[0268]

[Table 112]

Ex	Str
349	
350	
351	
352	
353	

[0269]

[Table 113]

Ex	Str
354	
355	
356	
357	
358	

[0270]

[Table 114]

Ex	Str
359	
360	
361	
362	
363	

[0271]

[Table 115]

Ex	Str
364	
365	
366	
367	
368	

[0272]

[Table 116]

Ex	Str
369	
370	
371	
372	

[0273]

[Table 117]

Ex	Str
373	
374	
375	
376	

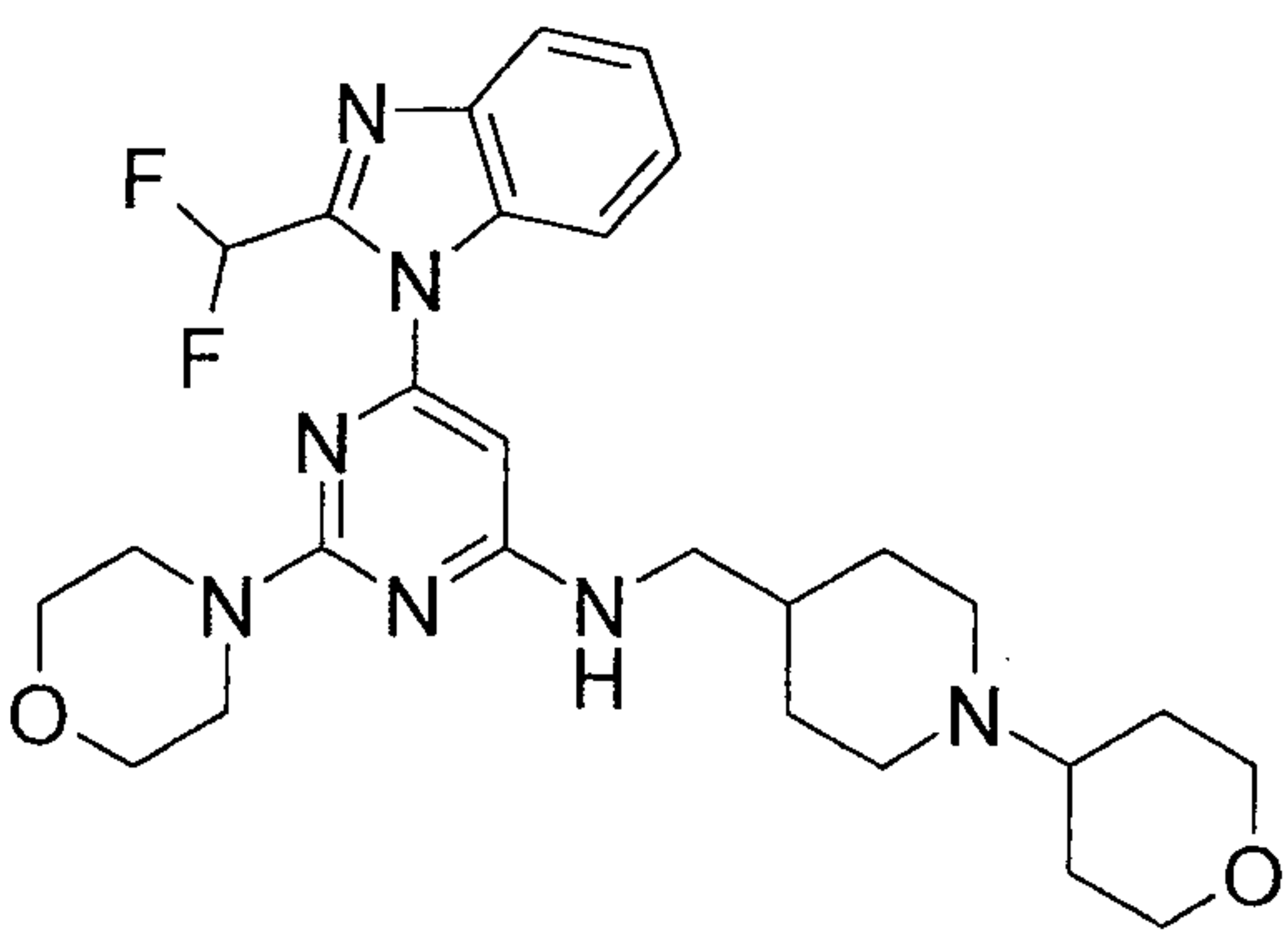
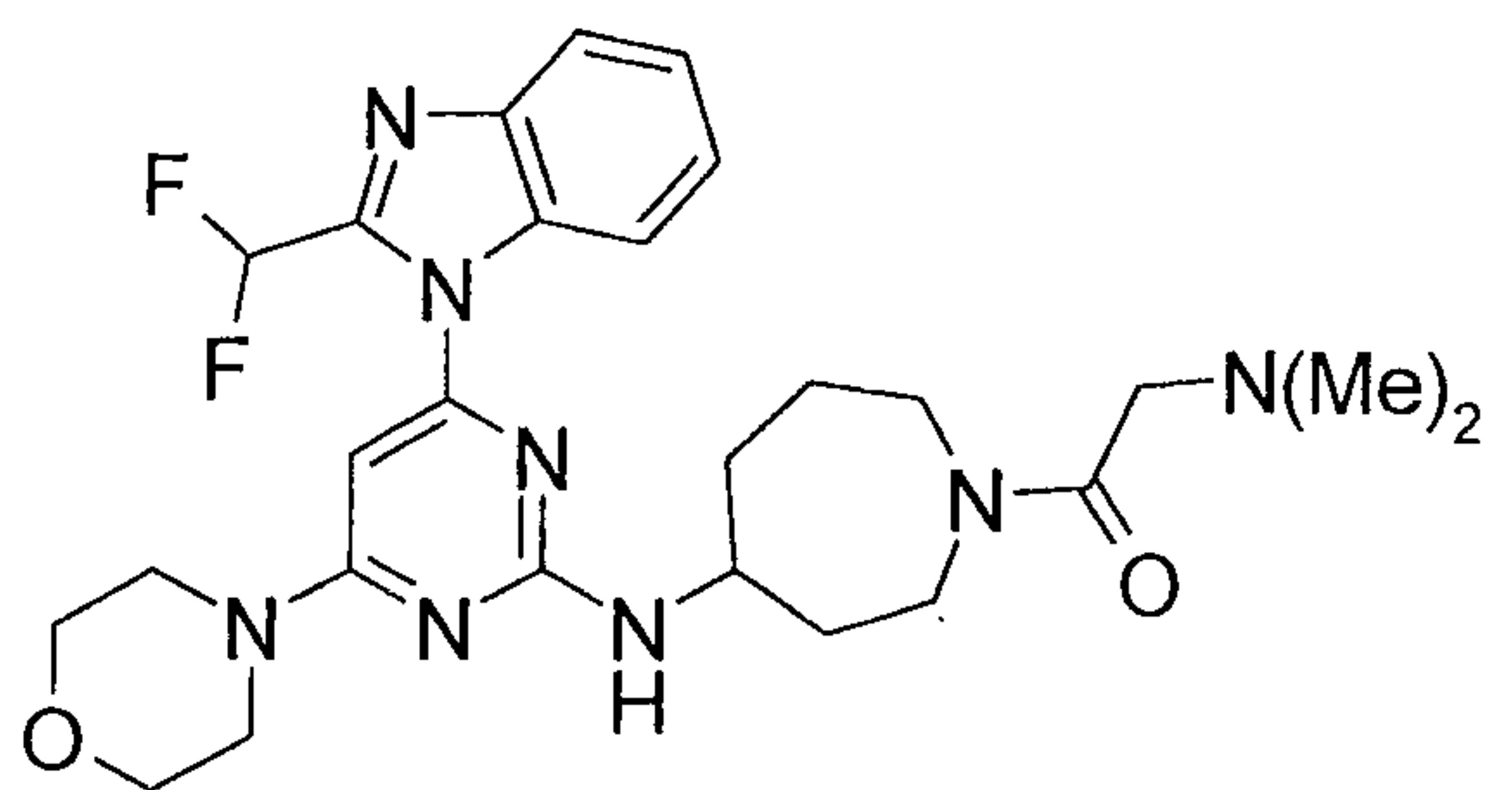
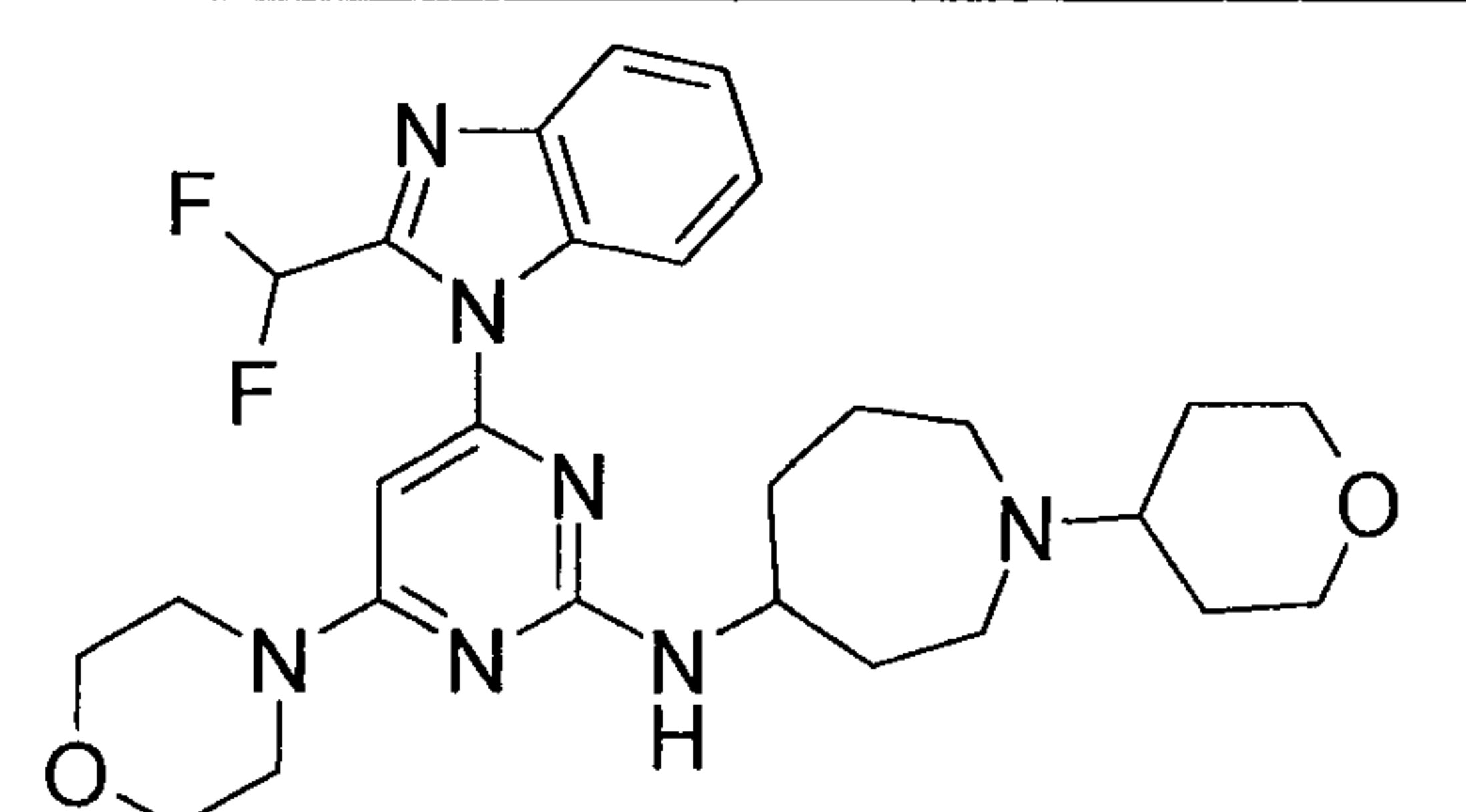
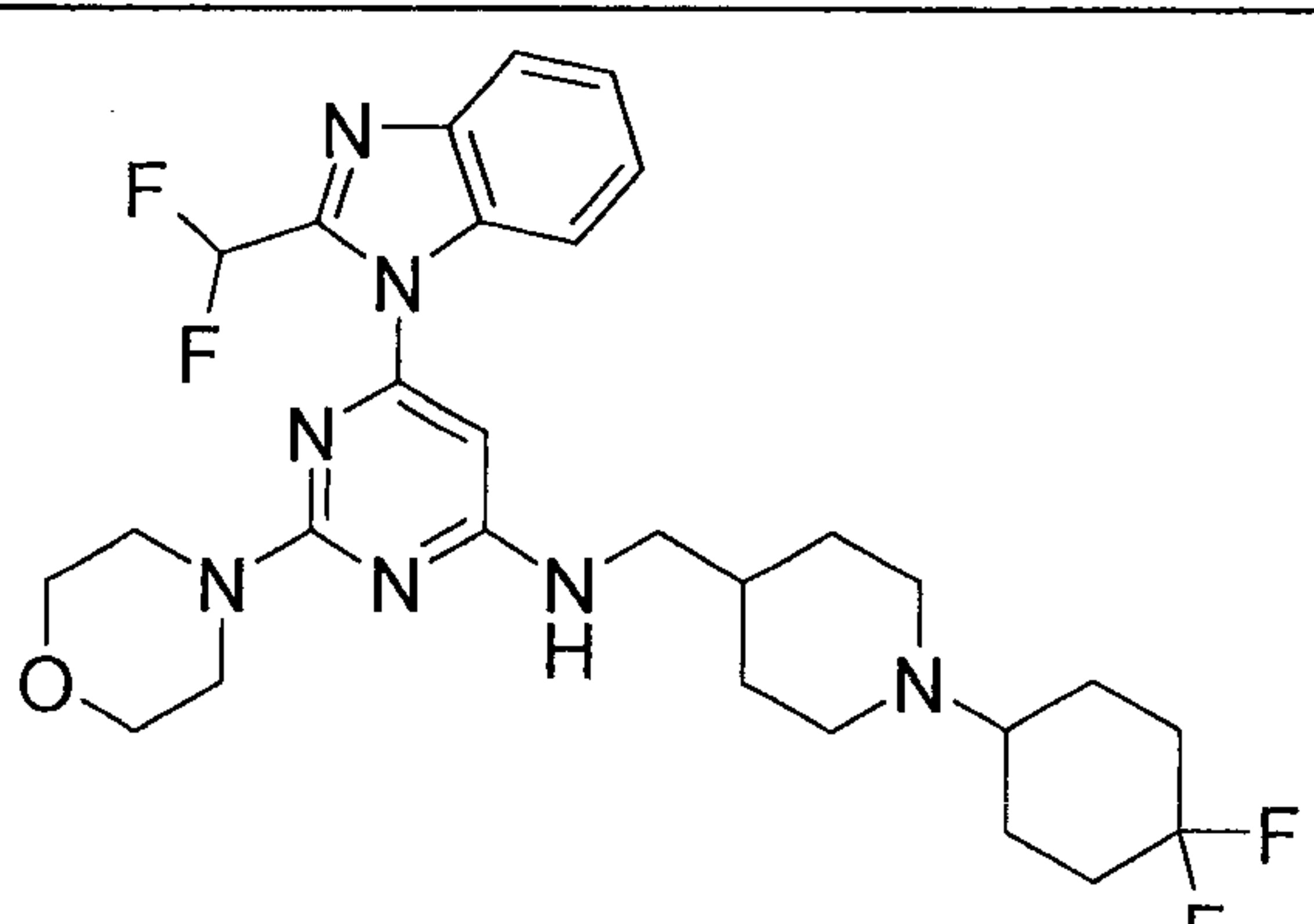
[0274]

[Table 118]

Ex	Str
377	 <chem>CC(C)(C)OC(=O)N1CCN(C1)CNC2=NC=NC(N2C3=CC=CC=C3N4C(=N5C(=C(C(=C5)F)F)N4)N6CCOCC6)C7=CC=CC=C7</chem>
378	 <chem>CC1CCN(C1)CNC2=NC=NC(N2C3=CC=CC=C3N4C(=N5C(=C(C(=C5)F)F)N4)N6CCOCC6)C7=CC=CC=C7</chem>
379	 <chem>CC(C)(C)OC(=O)N1CCN(C1)CCNC2=NC=NC(N2C3=CC=CC=C3N4C(=N5C(=C(C(=C5)F)F)N4)N6CCOCC6)C7=CC=CC=C7</chem>
380	 <chem>C1CCN(C1)CCNC2=NC=NC(N2C3=CC=CC=C3N4C(=N5C(=C(C(=C5)F)F)N4)N6CCOCC6)C7=CC=CC=C7</chem>

[0275]

[Table 119]

Ex	Str
381	
382	
383	
384	

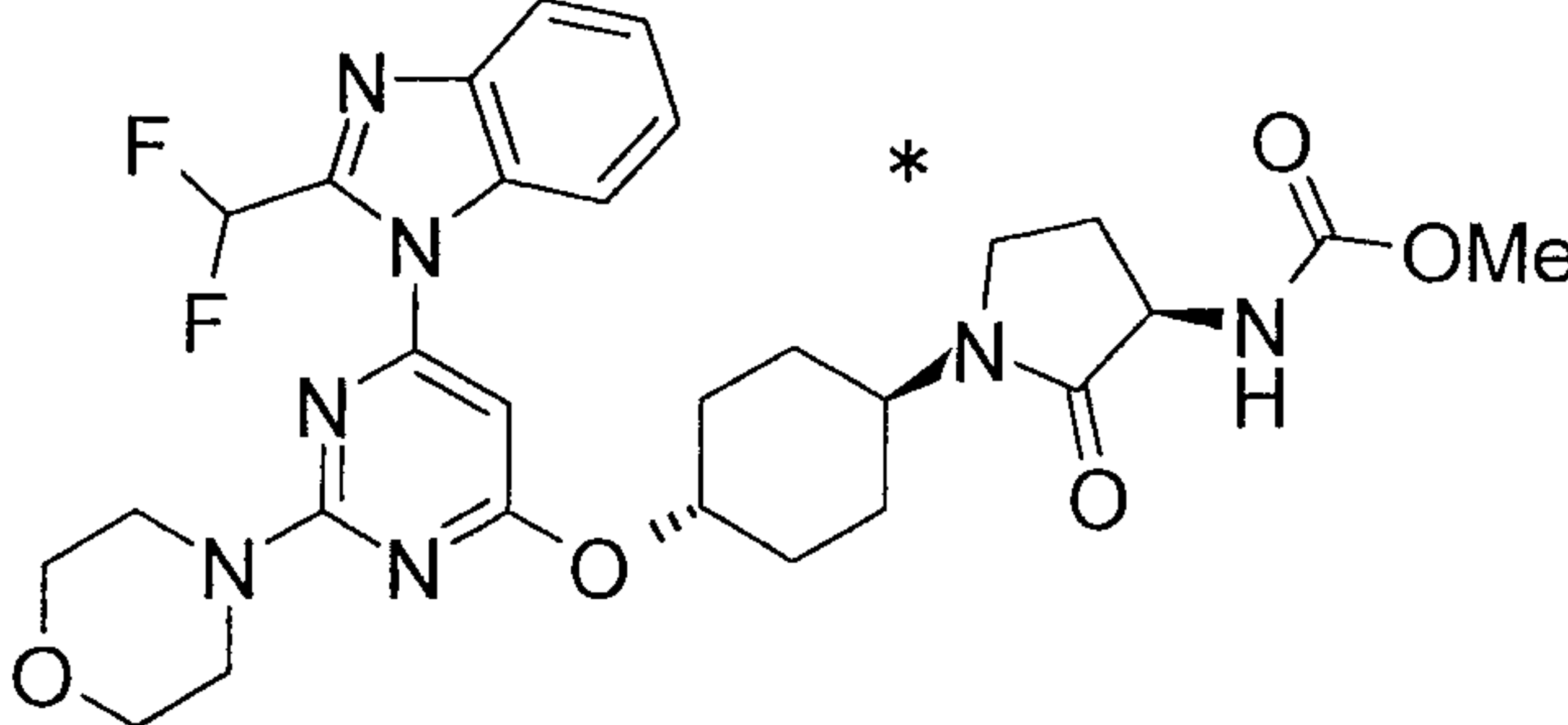
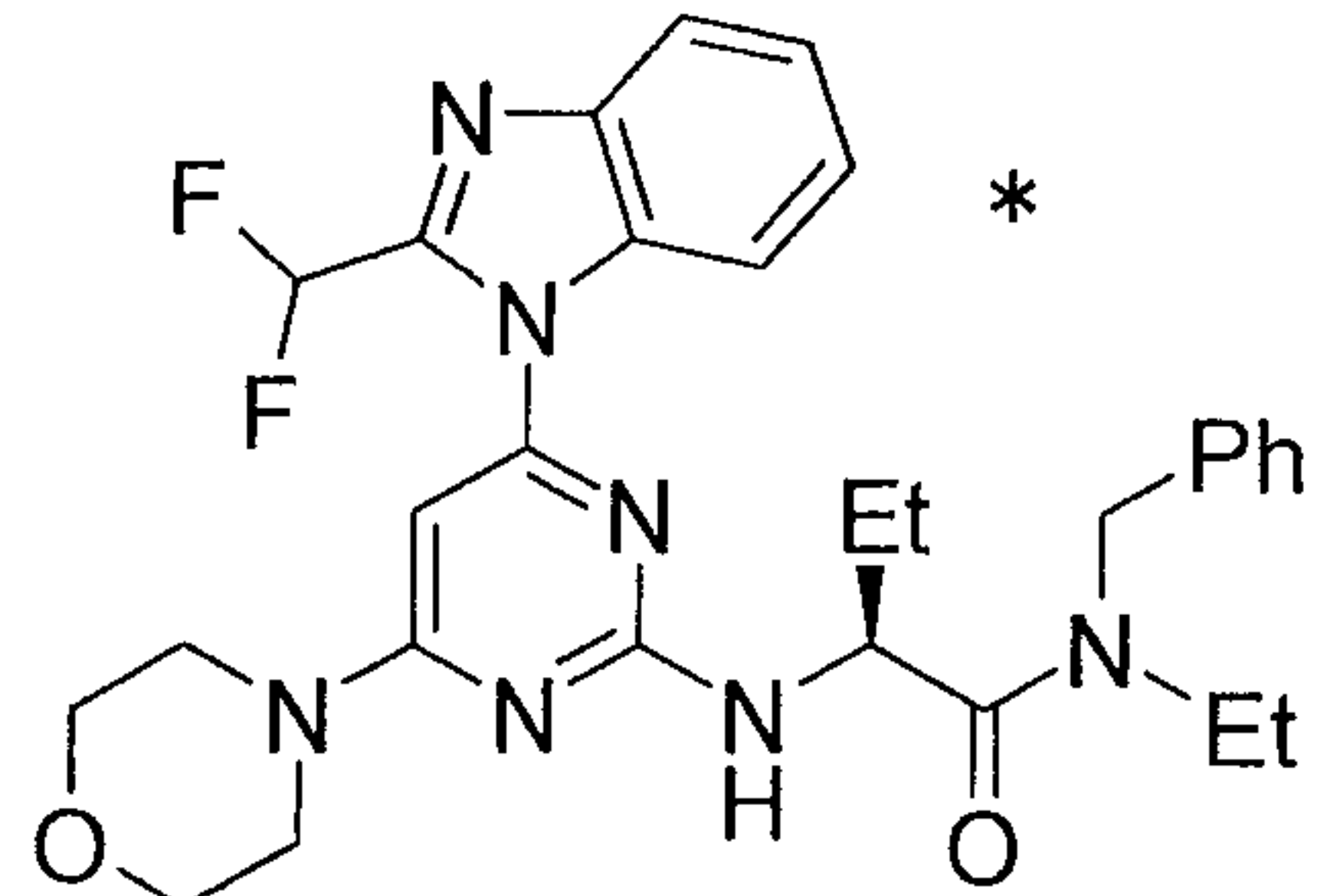
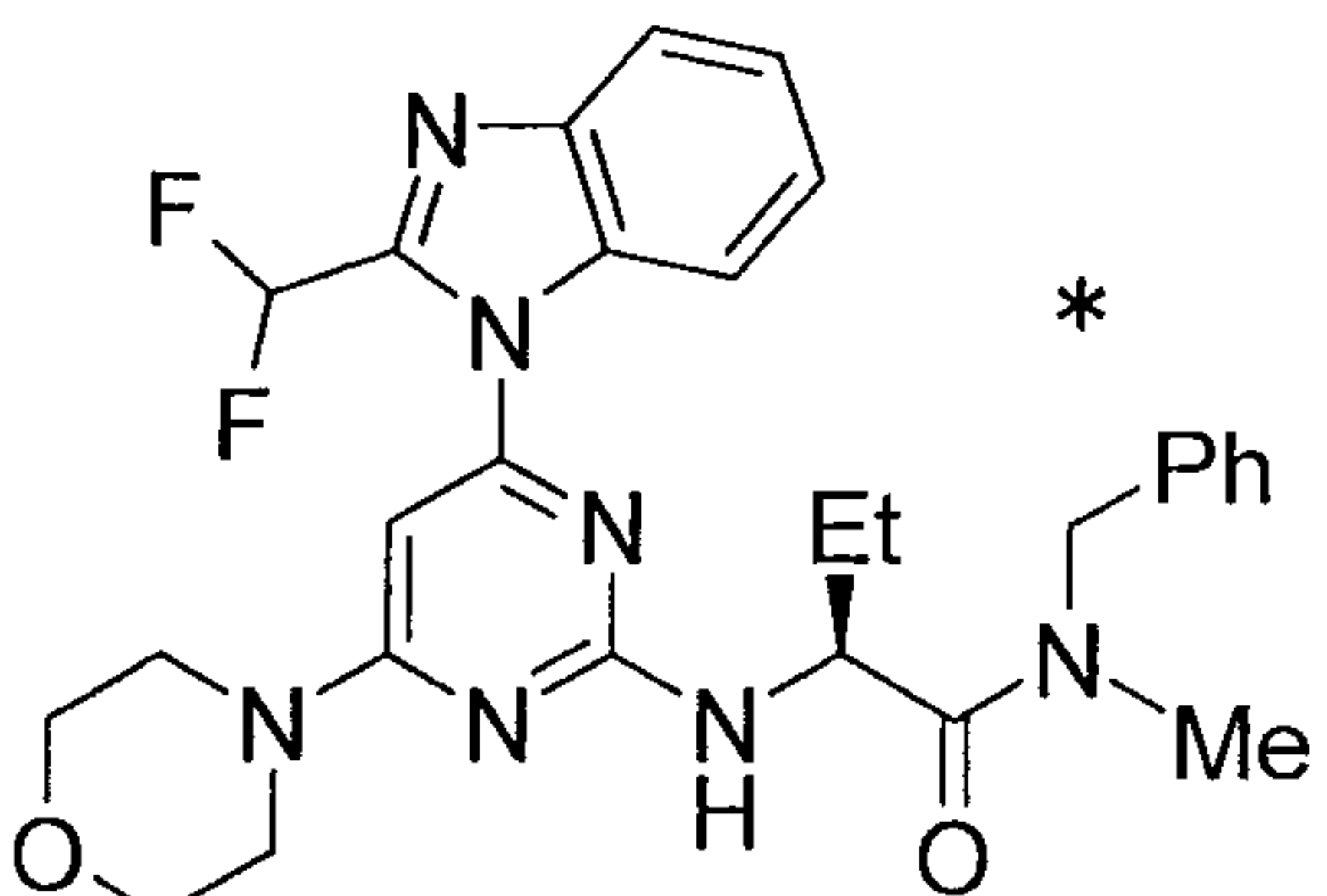
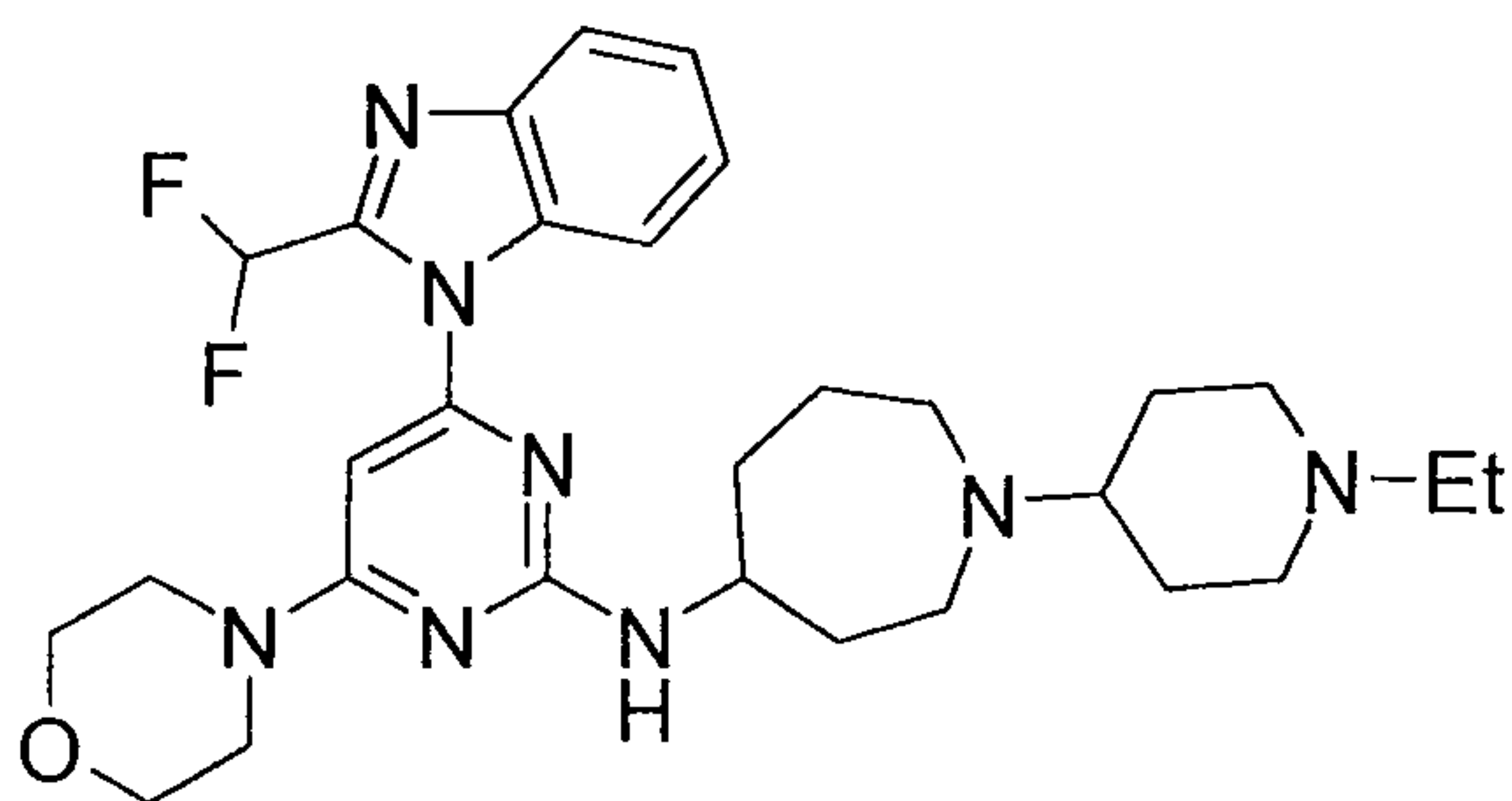
[0276]

[Table 120]

Ex	Str
385	
386	
387	
388	

[0277]

[Table 121]

Ex	Str
389	
390	
391	
392	

[0278]

[Table 122]

Ex	Str
393	 <chem>CC1(O)CCCC1N2CCCCC2NC3=NC(=NC(=N3)N4C(=CC=C4)N(C5CCOCC5)C6=CC=CC=C6C7C(F)(F)CC7=N2)C8=CC=CC=C8</chem>
394	 <chem>COC1CCCC1N2CCCCC2NC3=NC(=NC(=N3)N4C(=CC=C4)N(C5CCOCC5)C6=CC=CC=C6C7C(F)(F)CC7=N2)C8=CC=CC=C8</chem>
395	 <chem>C1CCOC1N2CCCCC2NC3=NC(=NC(=N3)N4C(=CC=C4)N(C5CCOCC5)C6=CC=CC=C6C7C(F)(F)CC7=N2)C8=CC=CC=C8</chem>
396	 <chem>CCOC(=O)C1(O)CCCC1N2CCCCC2NC3=NC(=NC(=N3)N4C(=CC=C4)N(C5CCOCC5)C6=CC=CC=C6C7C(F)(F)CC7=N2)C8=CC=CC=C8</chem>

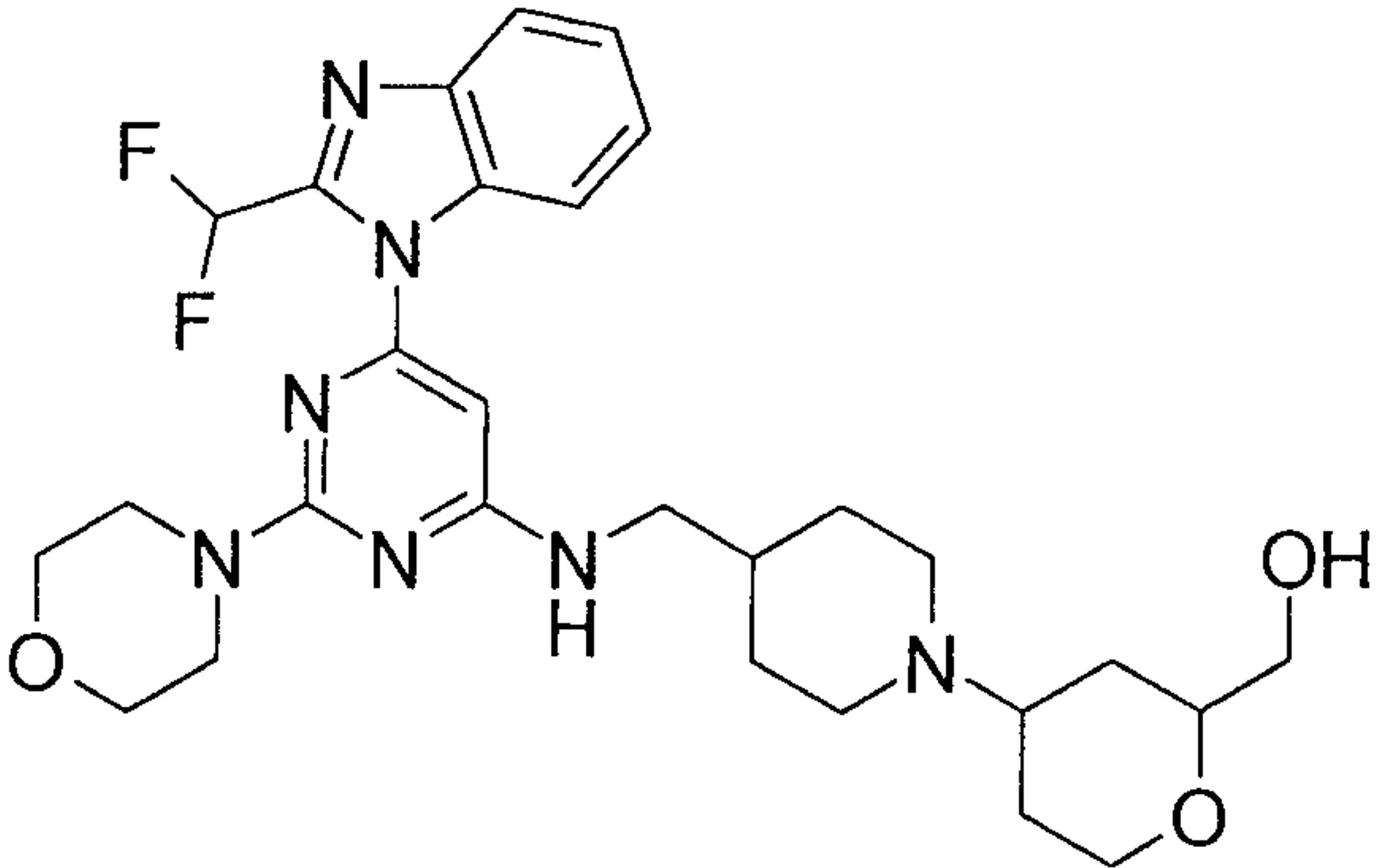
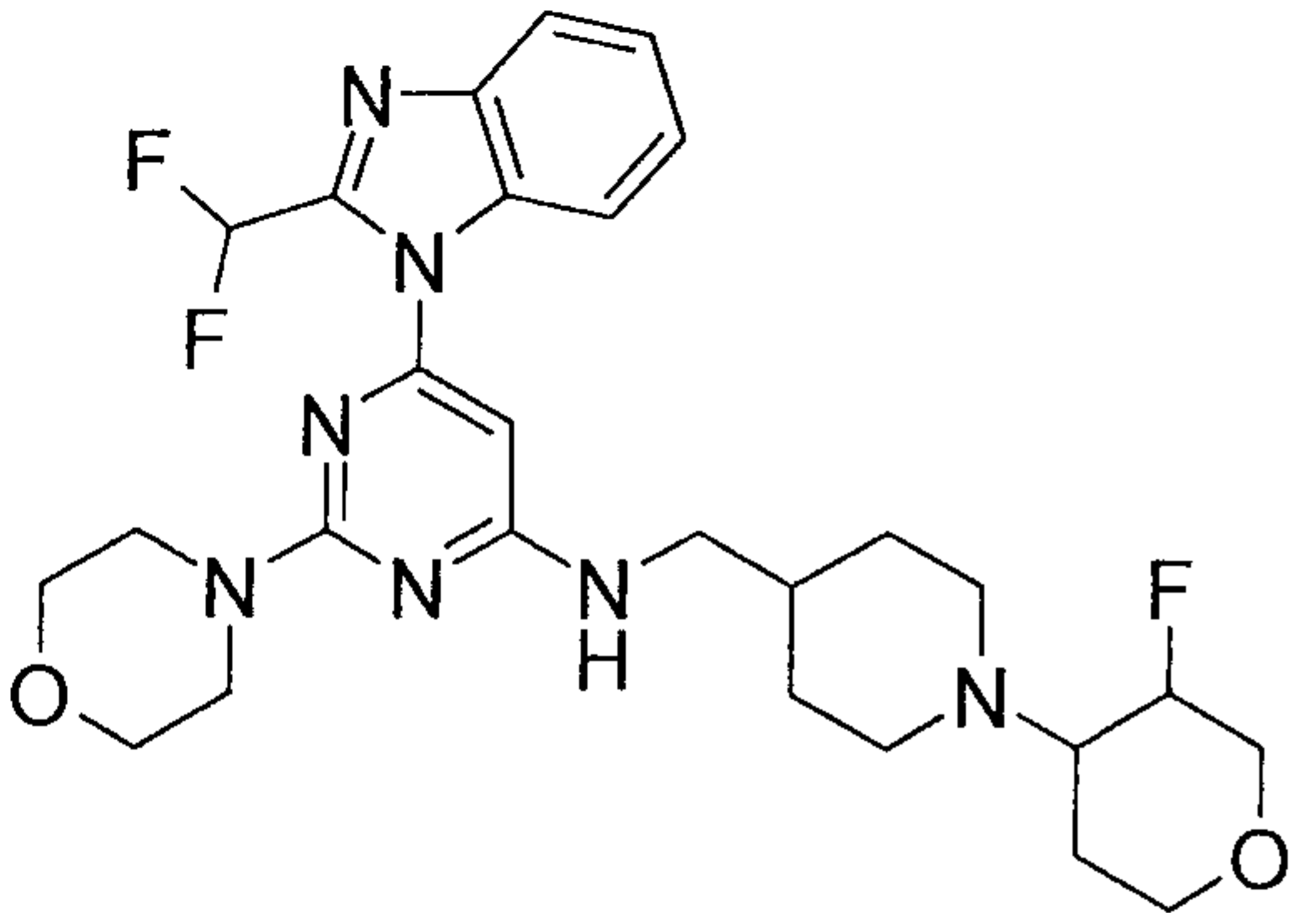
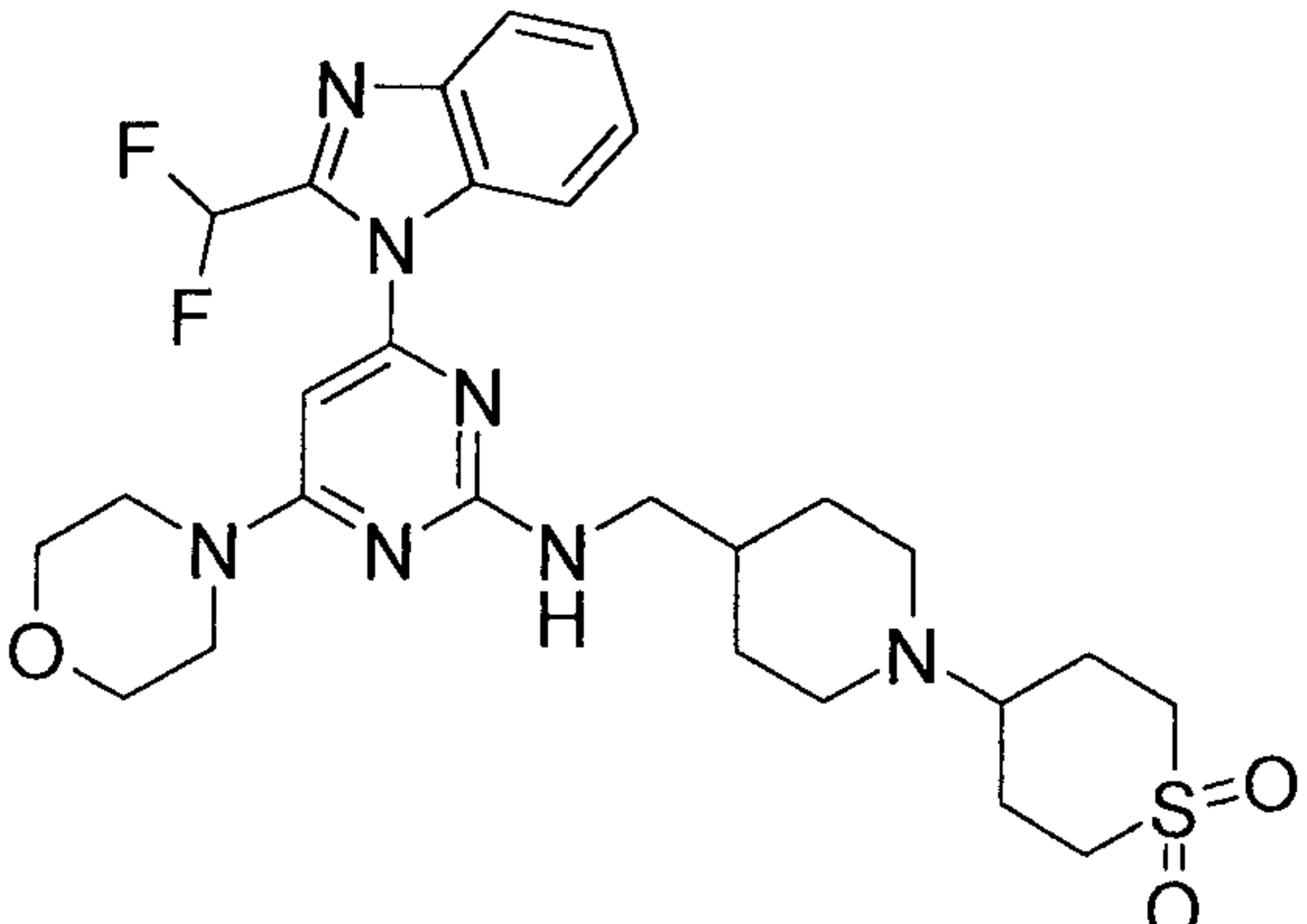
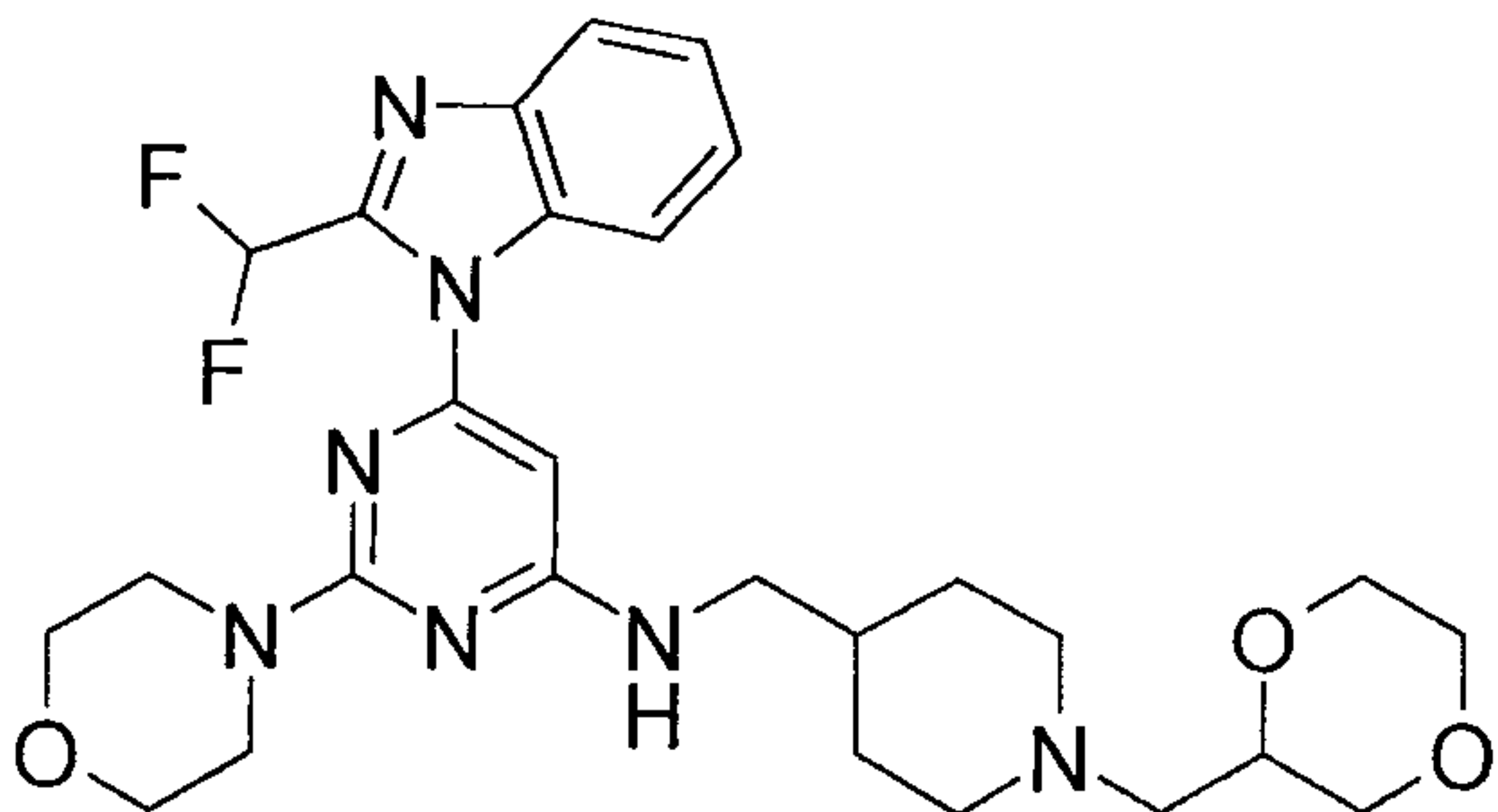
[0279]

[Table 123]

Ex	Str
397	
398	
399	
400	

[0280]

[Table 124]

Ex	Str
401	
402	
403	
404	

[0281]

[Table 125]

Ex	Str
405	
406	
407	
408	

[0282]

[Table 126]

Ex	Str
409	
410	
411	
412	

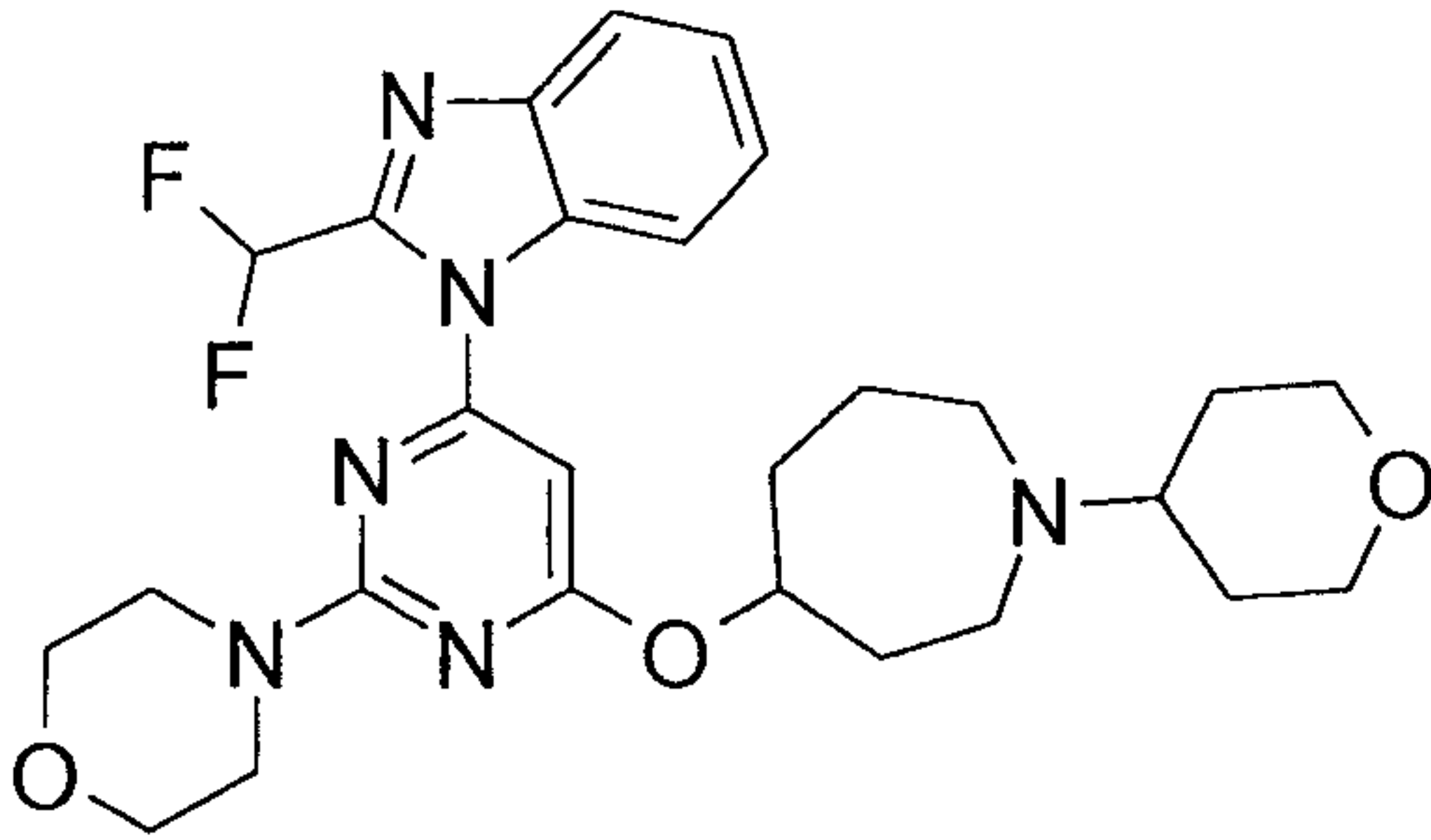
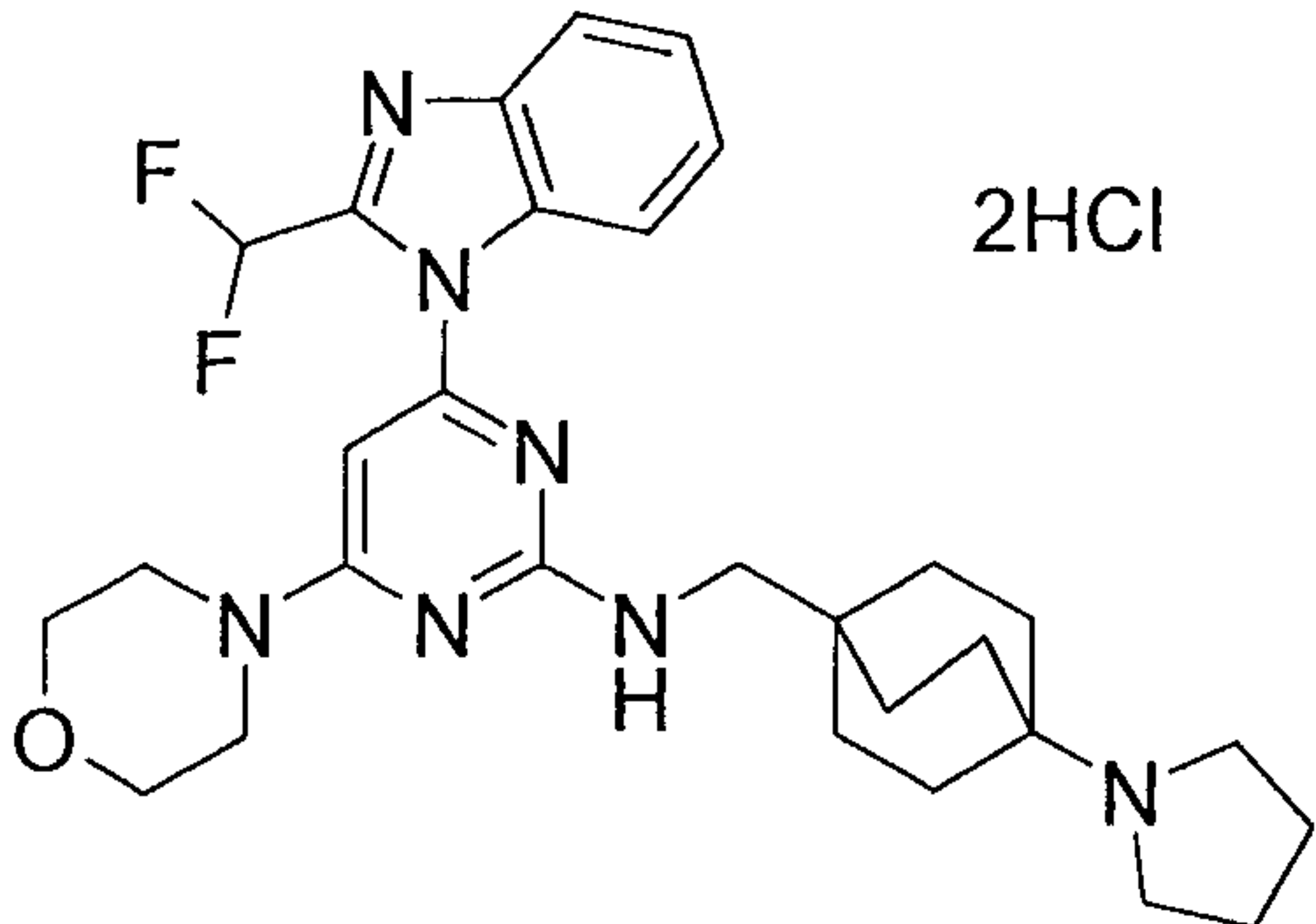
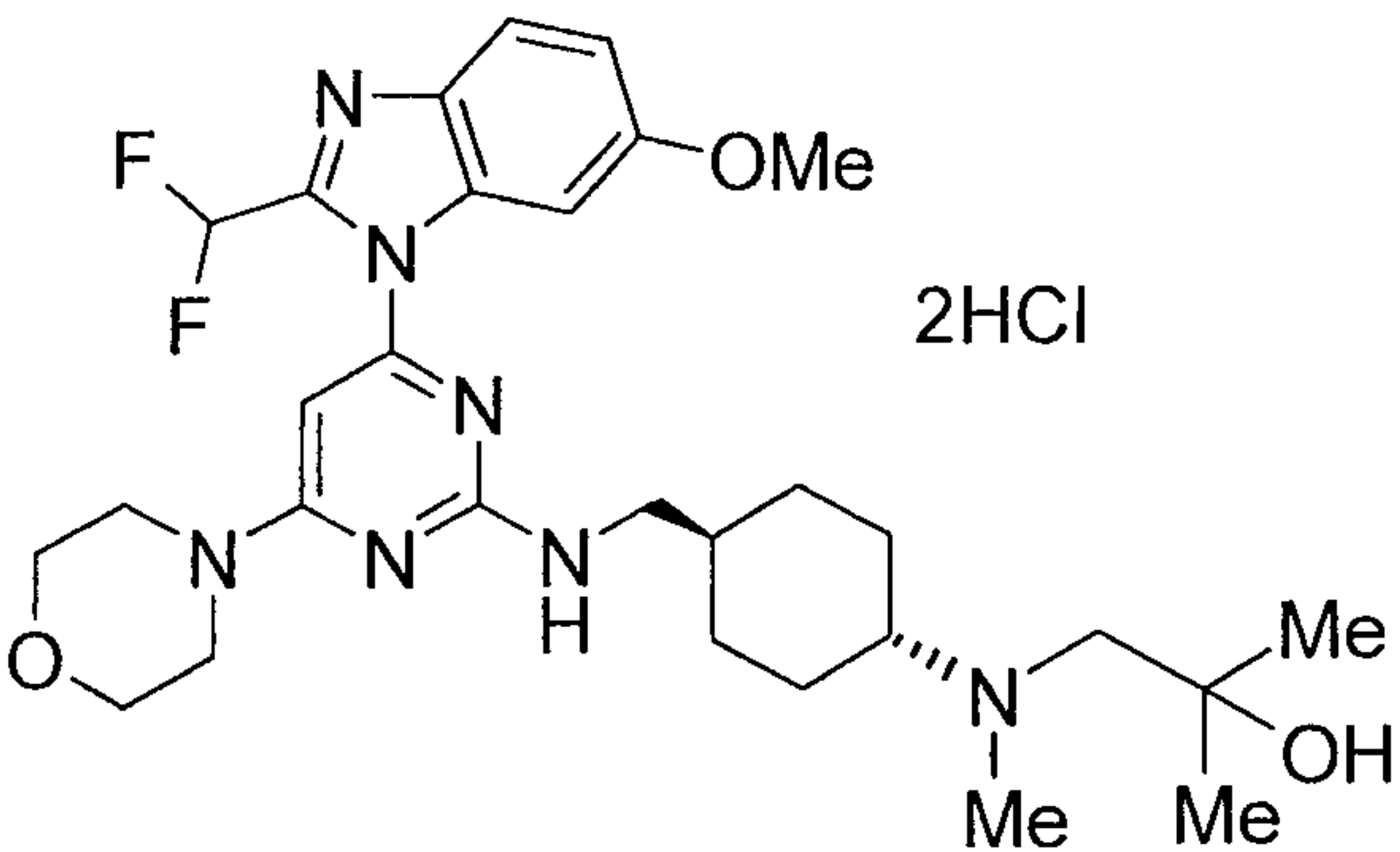
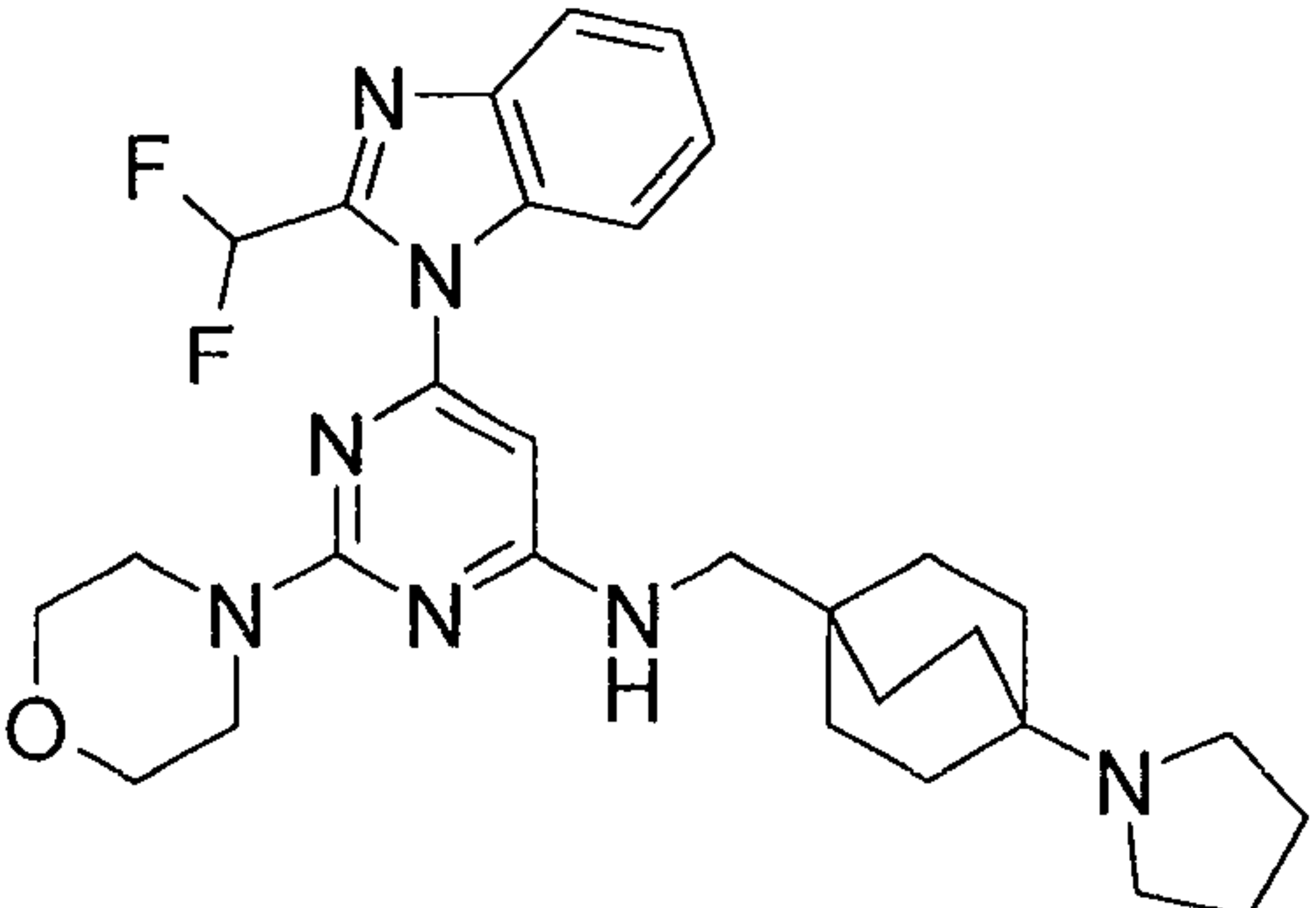
[0283]

[Table 127]

Ex	Str
413	 <chem>CC1(C)C(O)CN(C1Cc2nc3nc(NC4=CN=C(NC5=CC=CC=C5)C(F)(F)C5)C=C4)C6=CC=CC=C6</chem>
414	 <chem>CCN(C1Cc2nc3nc(NC4=CN=C(NC5=CC=CC=C5)C(F)(F)C5)C=C4)C6=CC=CC=C6</chem>
415	 <chem>CC(C)(C)C(=O)N1CCCCC1OC2=CN=C(NC3=CC=CC=C3)C=C2N(C4=CC=CC=C4)C5=CC=CC=C5</chem>
416	 <chem>C1CCN(C1OC2=CN=C(NC3=CC=CC=C3)C=C2N(C4=CC=CC=C4)C5=CC=CC=C5)C6=CC=CC=C6</chem>

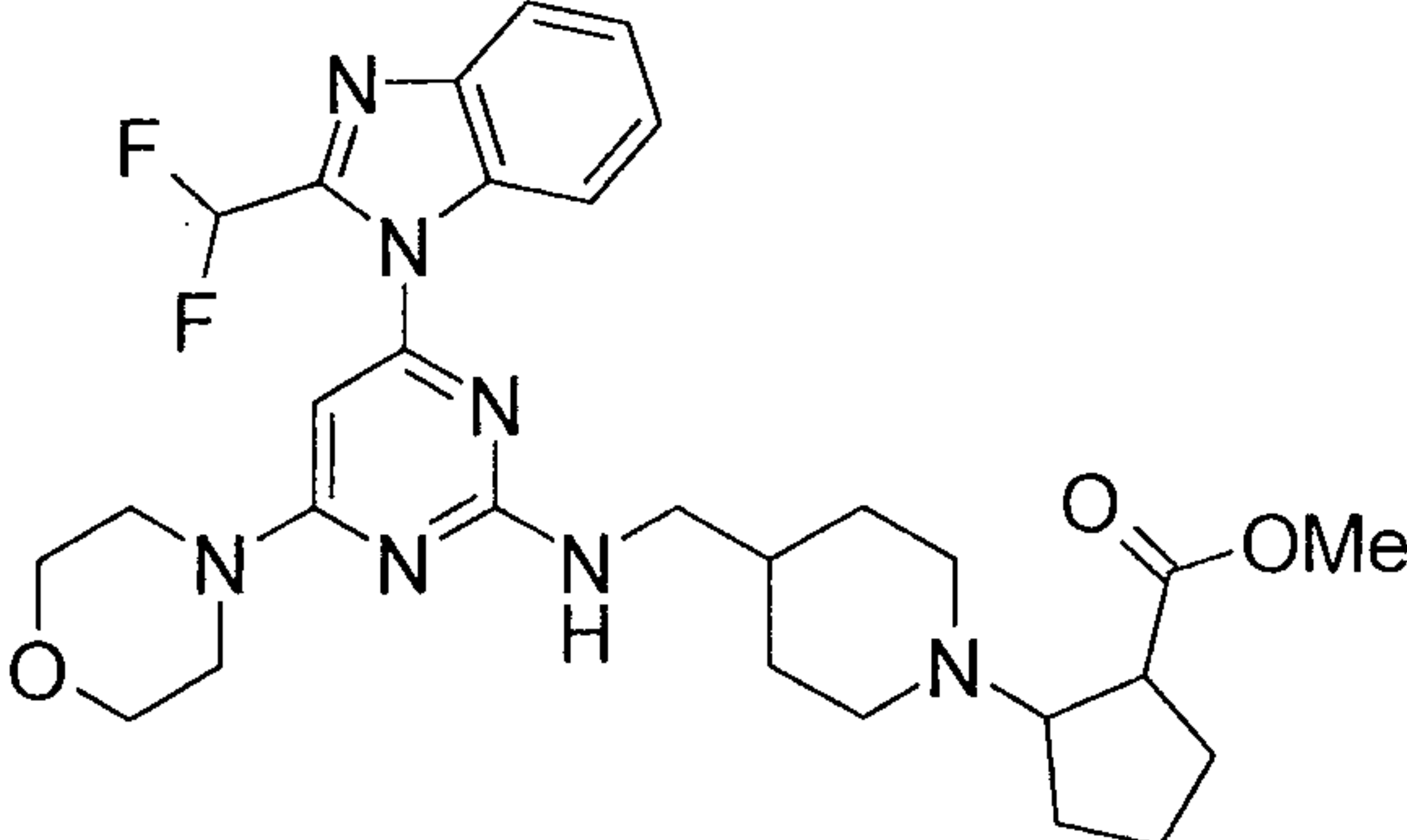
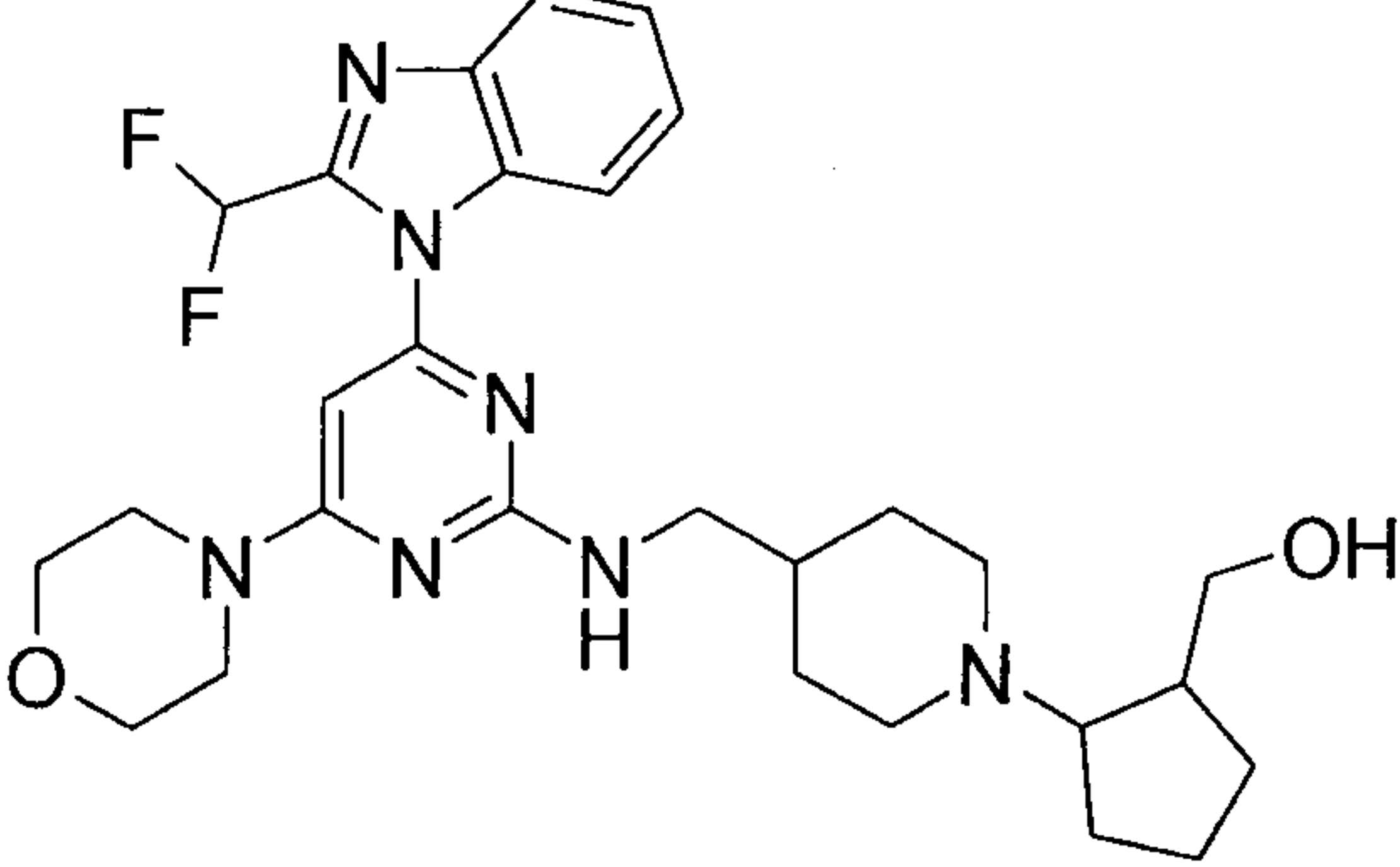
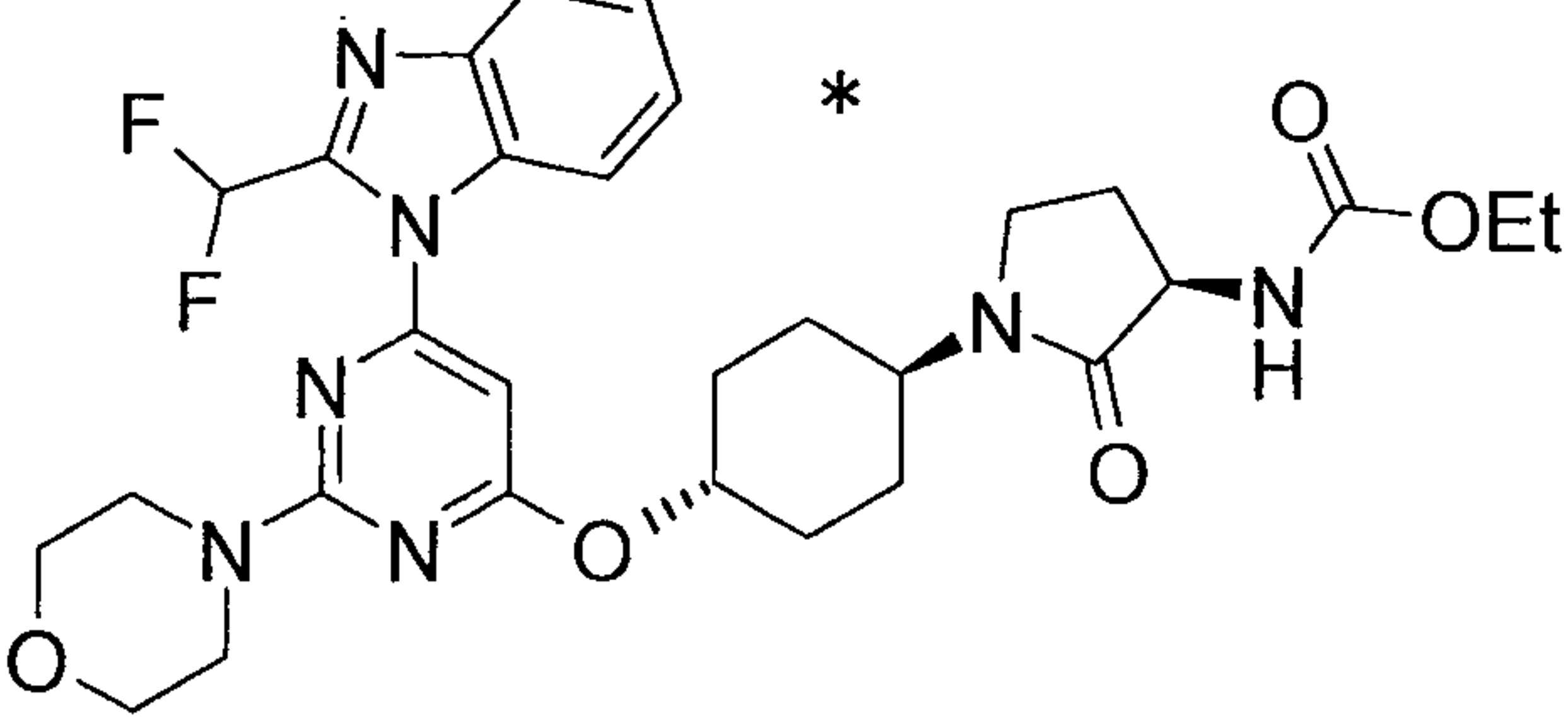
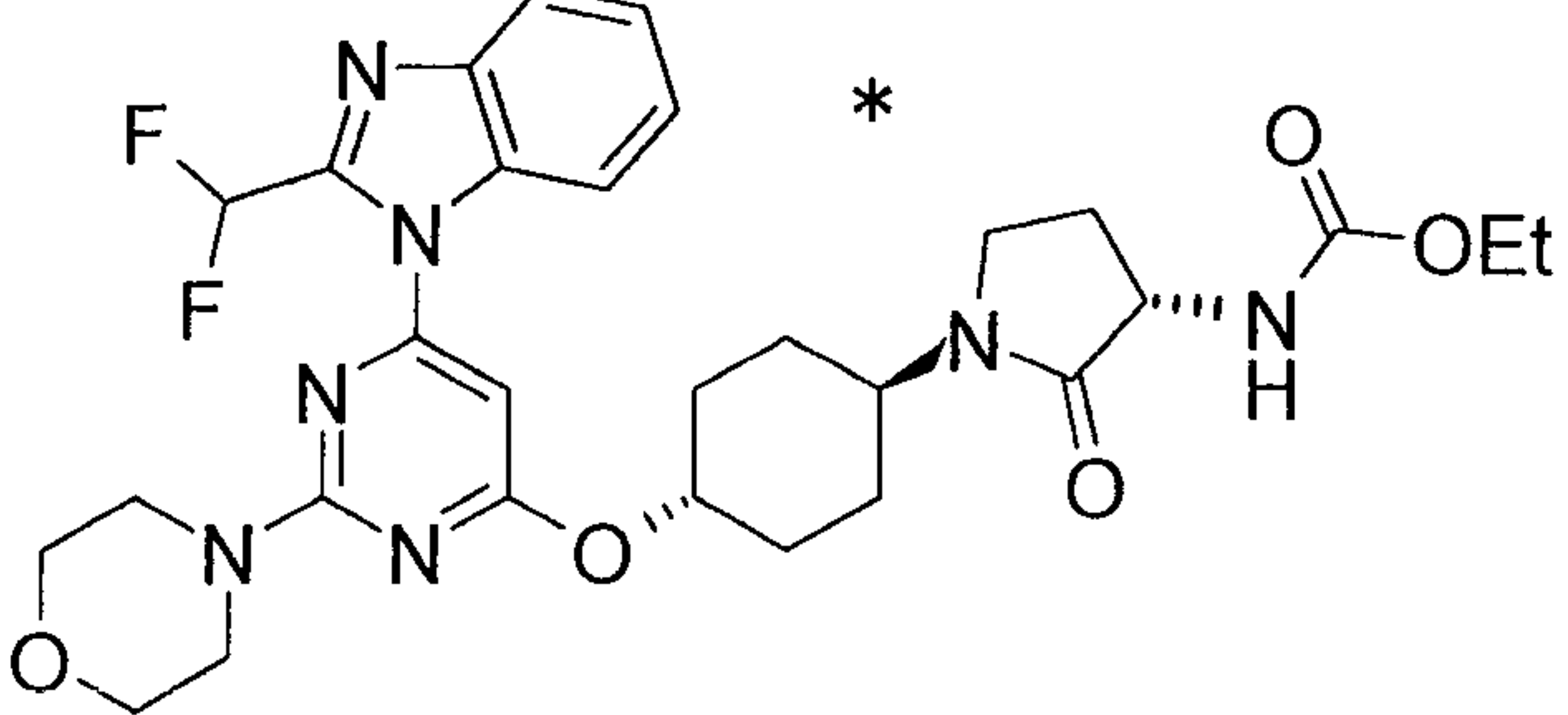
[0284]

[Table 128]

Ex	Str
417	
418	
419	
420	

[0285]

[Table 129]

Ex	Str
421	
422	
423	
424	

[0286]

[Table 130]

Ex	Str
425	
426	
427	
428	
429	

[0287]

[Table 131]

Ex	Str
430	
431	
432 -1	
432 -2	
433	

[0288]

[Table 132]

Ex	Str
434	
435	
436	
437	
438	

[0289]

[Table 133]

Ex	Str
439	
440	
441	
442	
443	

[0290]

[Table 134]

Ex	Str
444	
445	
446	
447	
448	

[0291]

[Table 135]

Ex	Str
449	
450	
451	
452	
453	

[0293]

[Table 137]

Ex	Str
459	
460	
461	
462	
463	

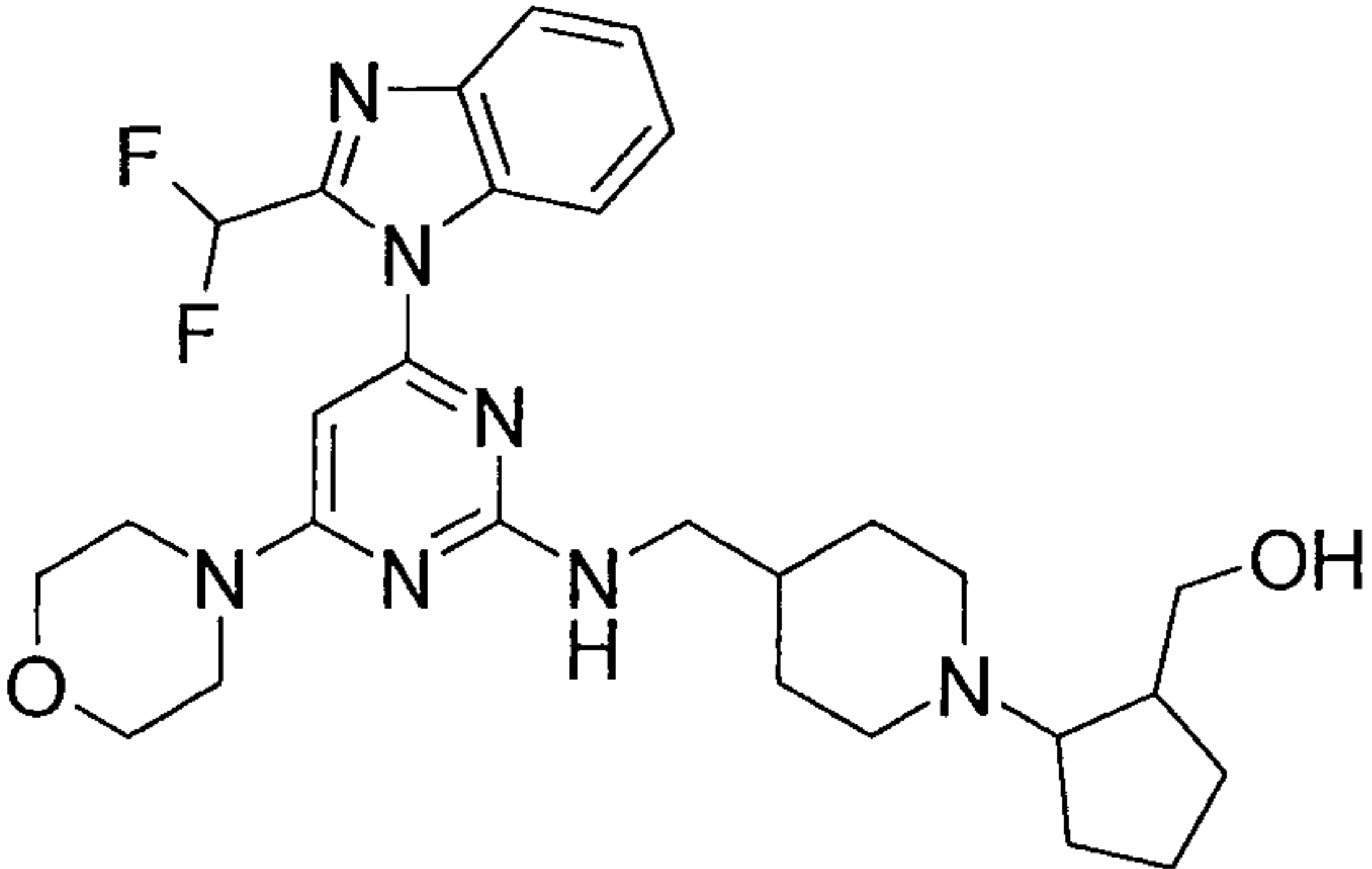
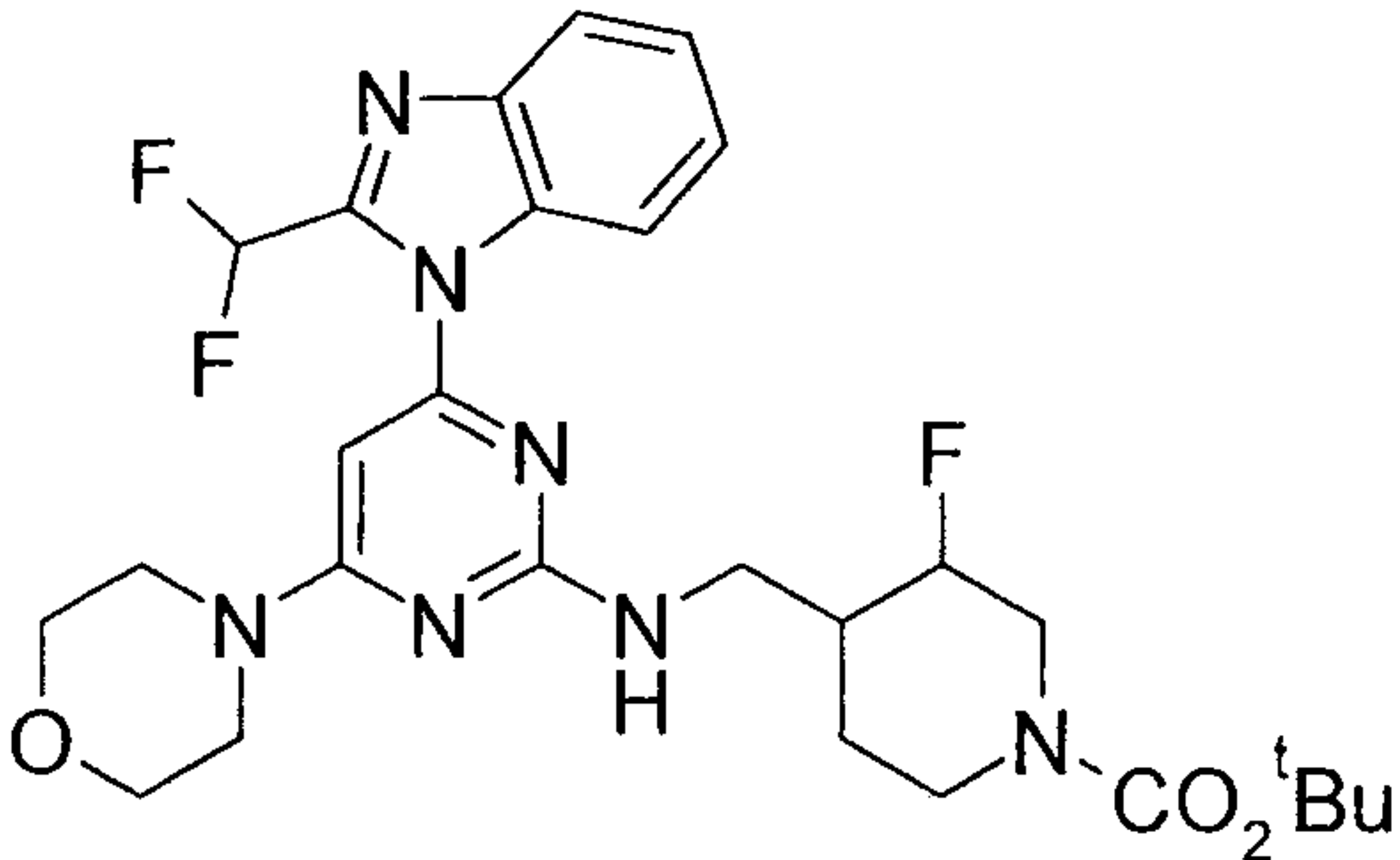
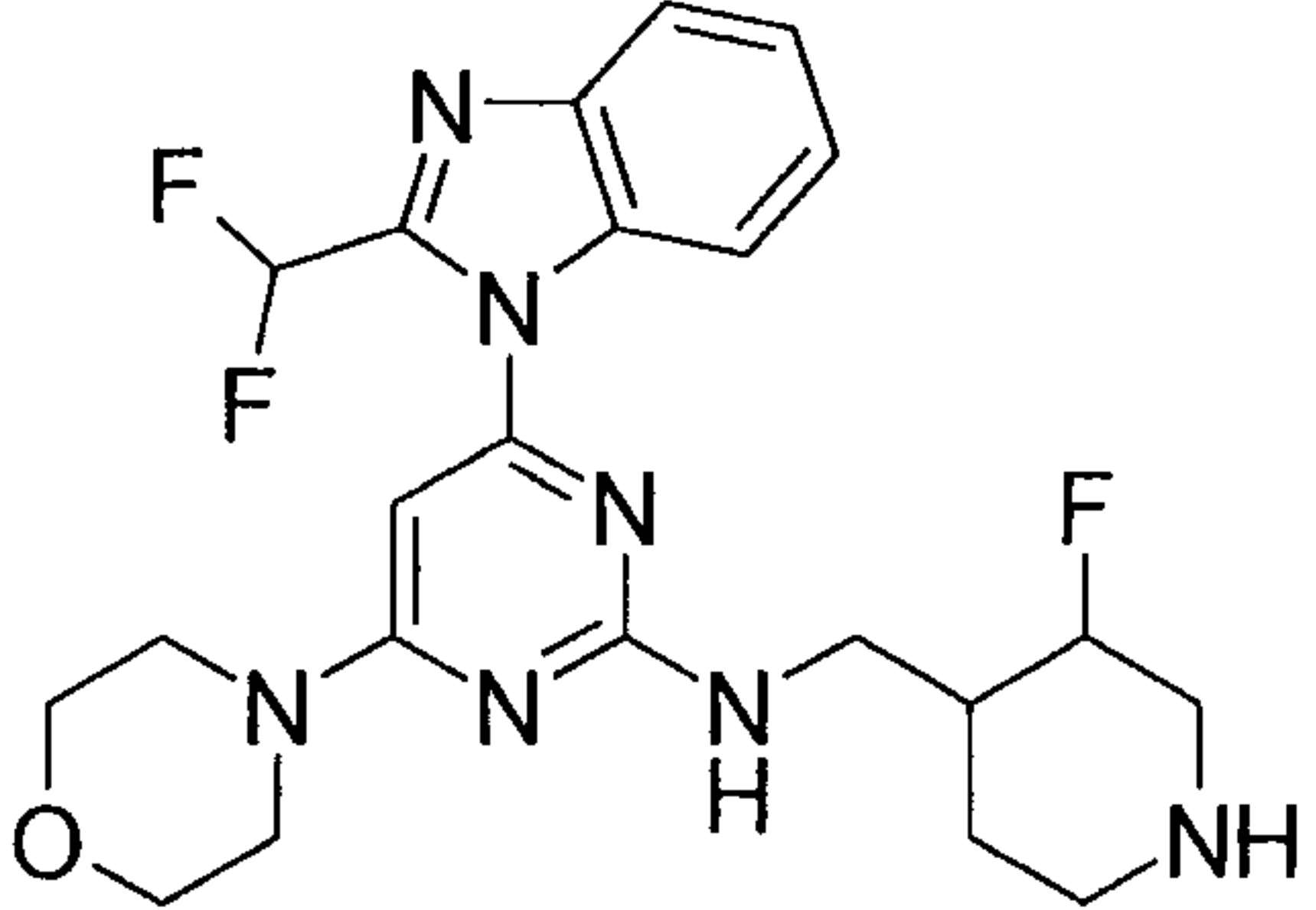
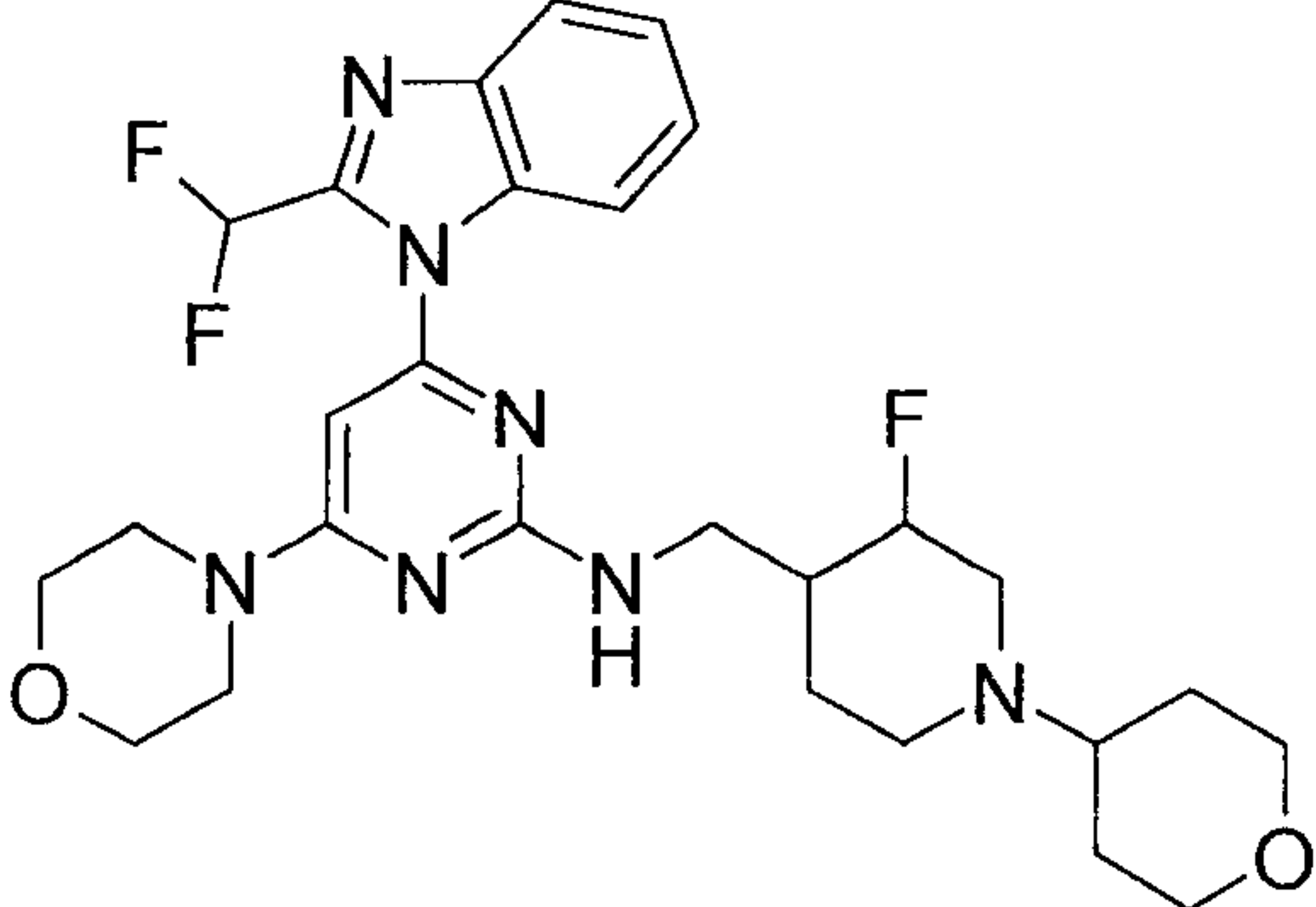
[0294]

[Table 138]

Ex	Str
464	
465	
466	
467	

[0295]

[Table 139]

Ex	Str
468	
469	
470	
471	

[0296]

[Table 140]

Ex	Syn	DAT
1	1	ESI+: 516 NMR1:1.39(9H,s),1.81-1.94(1H,m),2.02-2.16(1H,m),3.11-3.87(11H,m),4.27-4.43(2H,m),6.33-6.46(1H,m),7.29-7.87(6H,m)
2	1	ESI+: 458 NMR1:1.14-1.27(2H,m),1.46-1.58(1H,m),1.64-1.85(4H,m),2.13(3H,s),2.76(2H,m),3.06-3.34(2H,m),3.40-3.76(8H,m),5.64(1H,s),7.33-7.49(3H,m),7.79-7.86(1H,m),8.32-8.44(1H,m)
3	1	ESI+: 458 NMR1:0.79-1.84(8H,m),2.12(3H,s),2.67-2.71(2H,m),3.01-3.18(1H,m),3.63-3.68(8H,m),5.21-6.38(1H,m),7.13-7.19(1H,m),7.39-7.86(5H,m)
4	1	ESI+: 458 NMR1:1.12-1.30(2H,m),1.43-1.60(1H,m),1.63-1.72(2H,m),1.75-1.86(2H,m),2.14(3H,s),2.71-2.80(2H,m),3.21-3.32(2H,m),3.61-3.72(8H,m),6.14(1H,s),7.37-7.89(6H,m)
5	1	ESI+: 567[M+Na] NMR1:0.98-1.13(2H,m),1.36-1.40(9H,m),1.63-1.83(3H,m),2.57-2.80(2H,m),3.22-3.32(2H,m),3.62-3.84(8H,m),3.87-4.01(2H,m),7.39-8.07(5H,m),8.40-8.58(1H,m)
6	1	ESI+: 538[M+Na] NMR1:1.39(9H,s),1.60-2.16(2H,m),3.12-3.45(2H,m),3.59-3.76(9H,m),3.98-4.08(1H,m),4.31-4.40(1H,m),6.02-6.09(1H,m),6.34-6.45(1H,m),7.33-7.90(5H,m)
7	1	ESI+: 552[M+Na] NMR1:1.39(9H,s),1.66-1.98(4H,m),3.57-3.74(10H,m),3.74-3.94(3H,m),6.28-6.41(1H,m),6.99-7.13(1H,m),7.37-7.90(5H,m)
8	1	ESI+: 524[M+Na] NMR1:1.37(9H,s),3.57-4.17(12H,m),4.48-4.57(1H,m),6.37-6.47(1H,m),7.20-7.97(6H,m)
9	1	ESI+: 524[M+Na] NMR1:1.37-1.41(9H,m),3.60-3.72(8H,m),3.74-3.84(2H,m),4.13-4.26(2H,m),4.55-4.70(1H,m),6.11(1H,s),7.36-7.66(3H,m),7.70-7.89(2H,m),8.10-8.22(1H,m)
10	1	ESI+: 528 NMR1:0.79-1.75(9H,m),1.95-2.10(2H,m),2.26-2.45(1H,m),2.78-2.91(2H,m),3.03-3.42(4H,m),3.54-3.71(8H,m),3.79-3.92(2H,m),6.26-6.37(1H,m),7.13-7.18(1H,m),7.39-7.86(5H,m)
11	1	ESI+: 544 NMR1:0.90-1.12(2H,m),1.32-1.45(9H,m),1.58-1.81(3H,m),2.53-2.80(2H,m),3.06-3.26(2H,m),3.55-3.75(8H,m),3.83-4.00(2H,m),6.23-6.40(1H,m),7.18(1H,br-s),7.36-7.89(5H,m)

[0297]

[Table 141]

Ex	Syn	DAT
12	1	ESI+: 558 NMR1:0.91-1.12(2H,m),1.23(3H,d,J=6.8Hz),1.38(9H,s),1.60-1.82(3H,m),2.53-2.78(2H,m),3.06-3.29(3H,m),3.39-3.52(1H,m),3.57-3.66(1H,m),3.68-3.77(1H,m),3.85-4.16(4H,m),4.41(1H,br-s),6.20-6.35(1H,m),7.18(1H,br-s),7.40-7.90(5H,m)
13	1	ESI+: 558 NMR1:0.91-1.12(2H,m),1.23(3H,d,J=6.8Hz),1.38(9H,s),1.60-1.82(3H,m),2.53-2.78(2H,m),3.06-3.29(3H,m),3.39-3.52(1H,m),3.57-3.66(1H,m),3.68-3.77(1H,m),3.85-4.16(4H,m),4.41(1H,br-s),6.20-6.35(1H,m),7.18(1H,br-s),7.40-7.90(5H,m)
14	1	ESI+: 572 NMR1:0.90(3H,t,J=7.5Hz),0.92-1.11(2H,m),1.38(9H,s),1.60-1.87(5H,m),2.56-2.78(2H,m),3.06-4.44(11H,m),6.18-6.35(1H,m),7.07-7.23(1H,m),7.34-7.89(5H,m)
15	1	ESI+: 574 NMR1:0.91-1.11(2H,m),1.20-1.31(1H,m),1.32-1.41(9H,m),1.57-1.81(3H,m),2.59-2.80(2H,m),3.02-3.25(3H,m),3.37-3.62(3H,m),3.66-3.77(1H,m),3.81-4.44(5H,m),4.84-4.92(1H,m),6.20-6.36(1H,m),7.15(1H,br-s),7.35-7.89(5H,m)
16	1	ESI+: 576 NMR1:0.92-1.11(2H,m),1.20-1.30(1H,m),1.33-1.42(9H,m),1.54-1.80(3H,m),2.54-2.81(2H,m),3.06-4.30(10H,m),4.55-4.83(2H,m),6.29-6.40(1H,m),7.25(1H,br-s),7.36-7.90(5H,m)
17	1	ESI+: 548 NMR1:1.40(9H,s),1.56-1.82(2H,m),2.71-3.80(10H,m),3.91-4.31(3H,m),4.66-5.00(1H,m),6.31-6.48(1H,m),7.00-7.94(6H,m)
18	1	ESI+: 544 NMR1:0.99-1.43(11H,m),1.54-1.80(3H,m),2.69-2.85(1H,m),3.02-4.00(13H,m),6.25-6.42(1H,m),7.12-7.29(1H,m),7.35-7.89(5H,m)
19	1	ESI+: 544 NMR1:0.99-1.43(11H,m),1.54-1.80(3H,m),2.69-2.85(1H,m),3.02-4.00(13H,m),6.25-6.42(1H,m),7.12-7.29(1H,m),7.35-7.89(5H,m)
20	1	ESI+: 558 NMR1:1.00-1.42(14H,m),1.53-1.82(3H,m),2.69-2.85(1H,m),2.99-4.16(11H,m),4.32-4.51(1H,m),6.20-6.36(1H,m),7.11-7.28(1H,m),7.35-7.90(5H,m)
21	1	ESI+: 558 NMR1:1.00-1.41(14H,m),1.54-1.82(3H,m),2.68-2.85(1H,m),3.00-4.17(11H,m),4.42(1H,br-s),6.19-6.36(1H,m),7.10-7.27(1H,m),7.35-7.89(5H,m)
22	22	ESI+: 520 NMR1:2.06-2.27(3H,m),2.79-3.85(14H,m),4.27-4.48(2H,m),5.46-5.70(1H,m),7.35-7.89(11H,m)

[0298]

[Table 142]

Ex	Syn	DAT
23	22	ESI+: 506 NMR1:2.98-3.84(14H,m),4.36-4.63(3H,m),6.39-6.52(1H,m),7.21-7.88(11H,m)
24	22	ESI+: 506 NMR1:1.87-2.54(2H,m),2.96-3.85(12H,m),4.23-4.67(3H,m),6.32-6.53(1H,m),7.28-7.88(11H,m)
25	22	ESI+: 548 NMR1:1.33-1.96(8H,m),2.76-2.72(16H,m),6.25-6.42(1H,m),6.98-7.21(1H,m),7.38-7.89(9H,m)
26	26	ESI+: 520 NMR1:1.22-3.08(10H,m),3.57-3.71(8H,m),4.24-4.38(1H,m),6.30-6.42(1H,m),7.11-7.88(11H,m)
27	26	ESI+: 502 NMR1:0.79-0.89(1H,m),1.21-1.38(2H,m),2.62-2.71(2H,m),2.78-2.86(1H,m),3.45-3.61(4H,m),3.61-3.72(8H,m),4.32-4.45(1H,m),6.29-6.44(1H,m),7.36-7.93(6H,m)
28	26	ESI+: 542 NMR1:0.96-3.38(21H,m),3.56-3.78(8H,m),4.18-4.45(1H,m),6.23-6.37(1H,m),7.08-7.18(1H,m),7.36-7.89(5H,m)
29	26	ESI+: 556 NMR1:0.74-3.36(23H,m),3.55-3.75(8H,m),4.28-4.37(1H,m),6.24-6.37(1H,m),7.09-7.17(1H,m),7.36-7.90(5H,m)
30	26	ESI+: 627 NMR1:1.01-3.74(35H,m),3.85-4.01(2H,m),6.24-6.37(1H,m),7.11-7.19(1H,m),7.36-7.89(5H,m)
31	26+44	ESI+: 541 NMR1:1.44-3.76(31H,m),6.29-6.44(1H,m),7.28-7.89(6H,m)
32	26+44	ESI+: 567 NMR1:0.70-3.75(33H,m),6.29-6.44(1H,m),7.26-7.89(6H,m)
33	26+44	ESI+: 569 NMR1:1.35-4.70(31H,m),6.29-6.45(1H,m),7.28-7.89(6H,m)
34	26+44	ESI+: 605 NMR1:1.45-3.77(31H,m),6.30-6.44(1H,m),7.27-7.89(6H,m)
35	26+44	ESI+: 522 NMR1:1.49-2.11(5H,m),3.04-3.53(6H,m),3.59-3.75(8H,m),3.83-4.05(1H,m),4.80-5.15(4H,m),6.29-6.44(1H,m),7.25-7.89(6H,m)
36	26+44	ESI+: 562 NMR1:1.37-2.23(13H,m),2.83-3.49(7H,m),3.57-3.78(8H,m),6.28-6.43(1H,m),7.25-7.35(1H,m),7.37-7.89(5H,m)

[0299]

[Table 143]

Ex	Syn	DAT
37	26+44	ESI+: 542 NMR1:1.00-1.27(5H,m),1.30-1.74(7H,m),1.95-2.10(2H,m),2.30-2.42(1H,m),2.80-2.91(2H,m),3.05-3.34(5H,m),3.39-3.52(1H,m),3.56-3.65(1H,m),3.67-3.97(4H,m),4.00-4.14(1H,m),4.33-4.49(1H,m),6.18-6.32(1H,m),7.13(1H,br-s),7.35-7.89(5H,m)
38	26+44	ESI+: 542 NMR1:1.00-1.27(5H,m),1.30-1.74(7H,m),1.95-2.10(2H,m),2.30-2.42(1H,m),2.80-2.91(2H,m),3.05-3.34(5H,m),3.39-3.52(1H,m),3.56-3.65(1H,m),3.67-3.97(4H,m),4.00-4.14(1H,m),4.33-4.49(1H,m),6.18-6.32(1H,m),7.13(1H,br-s),7.35-7.89(5H,m)
39	26+44	ESI+: 542 NMR1:1.02-3.36(17H,m),3.42-3.54(2H,m),3.59-3.74(8H,m),3.77-3.89(3H,m),6.39(1H,br-s),7.25-7.89(6H,m)
40	26+44	ESI+: 529 NMR1:1.64-2.17(9H,m),2.90-3.03(2H,m),3.23-3.81(13H,m),3.93-4.01(2H,m),4.31(2H,d,J=6.3Hz),6.43(1H,s),7.39-7.68(3H,m),7.74-7.79(1H,m),7.85-7.90(1H,m)
41	26+44	ESI+: 528 NMR1:1.43-2.08(9H,m),2.74-2.94(2H,m),3.07-3.38(5H,m),3.40-3.52(2H,m),3.58-3.75(8H,m),3.88-4.01(2H,m),6.28-6.45(1H,m),7.24-7.90(6H,m)
42	26+44	ESI+: 528 NMR1:1.06-4.30(28H,m),6.30-6.45(1H,m),7.29(1H,br-s),7.27-7.88(5H,m)
43-1	43	ESI+: 544 NMR1:1.19-2.25(13H,m),2.79-3.43(7H,m),3.58-3.75(8H,m),4.39-4.62(1H,m),6.30-6.46(1H,m),7.25-7.90(6H,m)
43-2	43	ESI+: 544 NMR1:1.20-2.18(13H,m),2.82-3.46(7H,m),3.59-3.75(8H,m),4.72-4.91(1H,m),6.26-6.47(1H,m),7.19-7.89(6H,m)
44	44	ESI+: 520 NMR1:1.68-2.10(5H,m),3.18-3.95(14H,m),6.29-6.45(1H,m),7.31-7.96(11H,m)
45	45	ESI+: 487 NMR1:1.96-2.57(4H,m),2.75-4.07(20H,m),4.45-4.65(1H,m),6.41-6.59(1H,m),7.37-7.90(6H,m)
46	45	ESI+: 530 NMR1:1.07-1.30(5H,m),1.43-1.73(3H,m),2.03-2.18(2H,m),2.75-2.86(2H,m),3.07-3.23(4H,m),3.58-3.74(8H,m),4.02-4.11(2H,m),6.23-6.38(1H,m),7.09-7.18(1H,m),7.28-7.87(5H,m)
47	45+44	ESI+: 501 NMR1:1.36-2.01(5H,m),2.84-4.51(16H,m),6.27-6.45(1H,m),7.20-8.06(8H,m)

[0300]

[Table 144]

Ex	Syn	DAT
48	45+44	ESI+: 528 NMR1:1.42-2.03(5H,m),2.49-3.44(7H,m),3.56-4.60(12H,m),6.37(1H,br-s),7.23-7.88(6H,m)
49	45+44	ESI+: 515 NMR1:1.37-1.92(5H,m),2.55-2.95(4H,m),3.10-3.48(6H,m),3.60-3.75(8H,m),6.38(1H,br-s),6.98-7.89(8H,m)
50	45+44	ESI+: 504 NMR1:1.36-1.93(5H,m),2.01-2.20(2H,m),2.76-2.94(2H,m),3.03-3.54(6H,m),3.60-3.74(8H,m),4.42-4.63(2H,m),6.29-6.45(1H,m),7.24-7.90(6H,m)
51	45+44	ESI+: 518 NMR1:1.35-1.92(9H,m),2.74-3.53(8H,m),3.57-3.73(8H,m),4.36-4.57(2H,m),6.29-6.44(1H,m),7.23-7.34(1H,m),7.27-7.88(5H,m)
52	52	ESI+: 520 NMR1:1.09-1.31(2H,m),1.46-1.72(2H,m),1.87-1.98(2H,m),2.20-2.34(2H,m),2.77-2.91(2H,m),3.09-3.21(2H,m),3.60-3.73(8H,m),3.73-3.83(2H,m),4.17-4.47(2H,m),4.81-4.87(1H,m),6.26-6.37(1H,m),7.12-7.20(1H,m),7.38-7.90(5H,m)
53	53	ESI+: 416 NMR1:1.93-2.02(1H,m),2.11-2.23(1H,m),3.07-3.92(12H,m),4.42-4.53(1H,m),3.46(1H,br-s),7.39-7.87(7H,m),9.35(2H,br-s)
54	54	ESI+: 430 NMR1:1.27-1.38(2H,m),1.70-1.88(2H,m),2.86-2.98(2H,m),3.57-3.78(11H,m),6.28-6.38(1H,m),6.94-7.06(1H,m),7.36-7.87(6H,m)
55	54	ESI+: 445 NMR1:0.97-1.13(2H,m),1.57-1.73(3H,m),2.31-2.48(2H,m),2.86-2.96(2H,m),3.16-3.32(2H,m),3.62-3.86(8H,m),7.38-7.52(2H,m),7.63-8.08(3H,m),8.42-8.59(1H,m)
56	54	ESI+: 416 NMR1:1.57-1.65(1H,m),1.86-2.04(1H,m),2.59-2.78(2H,m),2.83-3.07(2H,m),3.58-3.72(8H,m),4.17-4.27(1H,m),6.28-6.43(1H,m),7.00-7.18(1H,m),7.37-7.87(5H,m)
57	54	ESI+: 402 NMR1:3.44-3.60(4H,m),3.62-3.75(8H,m),4.56-4.69(1H,m),6.30-6.42(1H,m),6.83(1H,s),7.37-7.93(5H,m),8.31(1H,s)
58	54	ESI+: 402 NMR1:3.41-3.49(2H,m),3.59-3.71(10H,m),4.70-4.81(1H,m),6.10(1H,s),7.36-7.65(3H,m),7.69-7.88(2H,m),7.98-8.06(1H,m)
59	54	ESI+: 499 NMR1:1.52-1.66(4H,m),2.62-2.69(1H,m),2.85-2.94(1H,m),3.39-3.53(4H,m),3.62-3.72(8H,m),4.52-4.63(2H,m),6.37-6.49(1H,m),7.37-7.97(6H,m)

[0301]

[Table 145]

Ex	Syn	DAT
60	54	ESI+: 444 NMR1:0.91-3.28(11H,m),3.55-3.76(8H,m),6.23-6.39(1H,m),7.07-7.19(1H,m),7.36-7.89(5H,m)
61	54	ESI+: 458 NMR1:0.91-1.11(2H,m),1.23(3H,d,J=6.7Hz),1.54-1.70(3H,m),2.31-2.44(2H,m),2.84-2.95(2H,m),3.03-3.52(5H,m),3.56-3.77(2H,m),3.88-3.98(1H,m),4.00-4.16(1H,m),4.33-4.50(1H,m),6.18-6.32(1H,m),7.05-7.19(1H,m),7.58-7.88(5H,m)
62	54	ESI+: 458 NMR1:0.91-1.11(2H,m),1.23(3H,d,J=6.7Hz),1.54-1.70(3H,m),2.31-2.45(2H,m),2.84-2.97(2H,m),3.03-3.53(5H,m),3.57-3.77(2H,m),3.88-3.98(1H,m),4.00-4.16(1H,m),4.33-4.50(1H,m),6.18-6.32(1H,m),7.05-7.19(1H,m),7.58-7.88(5H,m)
63	54	ESI+: 445 NMR1:1.09-1.23(2H,m),1.62-1.72(2H,m),1.78-1.91(1H,m),2.40-2.50(2H,m),2.91-2.98(2H,m),3.64-3.79(8H,m),4.22(2H,d,J=6.4Hz),6.42(1H,s),7.39-7.50(2H,m),7.54(1H,t,J=52.5Hz),7.74-7.89(2H,m)
64	54	ESI+: 444 NMR1:0.93-1.13(1H,m),1.19-1.37(2H,m),1.44-1.80(3H,m),2.07-2.45(2H,m),2.72-2.99(2H,m),3.02-3.20(2H,m),3.56-3.74(8H,m),6.22-6.39(1H,m),7.13(1H,br-s),7.36-7.89(5H,m)
65	54	ESI+: 444 NMR1:0.93-1.13(1H,m),1.19-1.37(2H,m),1.44-1.80(3H,m),2.07-2.45(2H,m),2.72-2.99(2H,m),3.02-3.20(2H,m),3.56-3.74(8H,m),6.22-6.39(1H,m),7.13(1H,br-s),7.36-7.89(5H,m)
66	66	ESI+: 515 NMR1:1.22-1.51(2H,m),1.77-2.00(2H,m),2.11-2.23(6H,s),2.63-2.83(1H,m),2.96-3.18(3H,m),3.56-3.75(8H,m),3.90-4.05(2H,m),4.18-4.31(1H,m),6.28-6.43(1H,m),7.04-7.17(1H,m),7.37-7.89(5H,m)
67	66	ESI+: 530 NMR1:0.95-1.31(2H,m),1.67-1.91(3H,m),2.11-2.21(6H,m),2.86-3.15(3H,m),3.22-3.33(2H,m),3.63-3.85(8H,m),3.99-4.09(1H,m),4.30-4.39(1H,m),7.39-7.53(2H,m),7.64-8.09(3H,m),8.41-8.59(1H,m)
68	66	ESI+: 501 NMR1:1.80-2.25(10H,m),2.92-3.01(2H,m),3.45-3.75(10H,m),4.32-4.45(1H,m),6.33-6.47(1H,m),7.31-7.88(6H,m)
69	66	ESI+: 487 NMR1:2.17(6H,s),2.83-2.96(2H,m),3.85-3.74(8H,m),3.79-3.85(1H,m),4.01-4.19(2H,m),4.39-4.61(2H,m),6.37-6.48(1H,m),7.37-7.89(6H,m)
70	66	ESI+: 599

[0302]

[Table 146]

Ex	Syn	DAT
71	71	ESI+: 509[M+Na] NMR1:0.96-1.21(4H,m),1.66-1.90(3H,m),1.95-1.99(3H,m),2.91-3.04(1H,m),3.23-3.32(2H,m),3.63-3.87(8H,m),4.32-4.41(1H,m),7.39-7.54(2H,m),7.63-8.09(3H,m),8.41-8.59(1H,m)
72	66+44	ESI+: 529 NMR1:0.92-1.28(2H,m),1.67-1.93(3H,m),2.59-2.86(7H,m),2.91-3.30(3H,m),3.54-4.41(12H,m),6.26-6.44(1H,m),7.27(1H,br-s),7.37-7.90(5H,m)
73	66+44	ESI+: 543 NMR1:0.89-1.28(2H,m),1.64-1.91(3H,m),2.45-3.28(15H,m),3.76-3.97(8H,m),4.31-4.41(1H,m),6.38(1H,br-s),7.25-7.99(6H,m)
74	74	ESI+: 520
75	74+44	ESI+: 538 NMR1:1.60-2.07(5H,m),3.17-3.95(14H,m),6.29-6.45(1H,m),7.29-7.97(10H,m)
76	74+44	ESI+: 538 NMR1:1.41-1.72(2H,m),1.79-1.95(3H,m),2.95-3.35(4H,m),3.59-3.76(10H,m),6.38(1H,br-s),6.80-7.91(10H,m)
77	74+44	ESI+: 538 NMR1:1.33-1.53(2H,m),1.68-1.88(3H,m),2.68-2.83(2H,m),3.18-3.32(2H,m),3.34-3.44(2H,m),3.61-3.73(8H,m),6.36(1H,br-s),6.97-7.90(10H,m)
78	74+44	ESI+: 550 NMR1:1.74-2.08(5H,m),3.18-3.78(17H,m),6.36(1H,br-s),7.02-7.13(2H,m),7.26-7.90(8H,m)
79	74+44	ESI+: 534 NMR1:1.67-2.08(5H,m),2.33(3H,s),3.16-3.77(14H,m),6.36(1H,br-s),7.25-7.89(10H,m)
80	80	ESI+: 545 NMR1:1.11-1.26(2H,m),1.40(9H,s),1.70-1.79(2H,m),1.89-2.03(1H,m),2.64-2.85(2H,m),3.63-3.80(8H,m),3.91-4.05(2H,m),4.27(2H,d,J=6.4Hz),6.43(1H,s),7.38-7.50(2H,m),7.54(1H,t,J=52.5Hz),7.73-7.89(2H,m)
81	80	ESI+: 559 NMR1:1.10-1.27(5H,m),1.40(9H,s),1.70-1.79(2H,m),1.91-2.03(1H,m),2.68-2.84(2H,m),3.17-3.29(1H,m),3.40-3.49(1H,m),3.55-3.62(1H,m),3.68-3.75(1H,m),3.89-4.04(3H,m),4.19-4.33(3H,m),4.56-4.64(1H,m),6.43(1H,s),7.39-7.50(2H,m),7.54(1H,t,J=52.5Hz),7.74-7.90(2H,m)
82	82	ESI+: 422[M+Na]
83	83	ESI+: 487
84	84	ESI+: 628

[0303]

[Table 147]

Ex	Syn	DAT
85	52	ESI+: 556 NMR1:1.03(6H,s),1.43(12H,brs),2.28(2H,brs),3.01-3.14(2H,m),3.57-3.72(8H,m),4.01(1H,brs),6.21-6.37(1H,m),6.76-7.02(1H,m),7.34-7.96(5H,m)
86	86	ESI+: 584
87	87	ESI+: 586 NMR1:1.50-1.81(7H,m),2.23(3H,br),3.16-3.25(1H,m),3.28-3.36(2H,m),3.54(3H,s),3.70(4H,br),3.74(4H,br),3.81(1H,br),4.08-4.18(1H,m),4.99-5.08(1H,m),6.40(1H,s),7.38-7.50(3H,m),7.53(1H,t,J=52.5Hz),7.75(1H,d,J=7.8Hz),7.86(1H,d,J=7.8Hz)
88	88	ESI+: 606
89	89	ESI+: 556 NMR1:1.36-1.73(8H,m),1.81-1.91(2H,m),1.97-2.21(4H,m),2.97(2H,s),3.05-3.16(1H,m),3.60-3.80(9H,m),5.00-5.10(1H,m),6.40(1H,s),7.38-7.68(4H,m),7.72-7.78(1H,m),7.83-7.89(1H,m)
90	54	ESI+: 472
91	91	ESI+: 514[M+Na] NMR1:1.44-1.67(5H,m),1.76-2.03(3H,m),2.76-2.87(1H,m),2.95-3.09(1H,m),3.12-3.23(1H,m),3.62-3.94(10H,m),7.39-7.52(2H,m),7.70-8.28(3H,m),8.43-8.58(1H,m)
92	92	ESI+: 502
93	93	ESI+: 458
94	94	ESI+: 530[M+Na] NMR1:1.47-1.73(4H,m),1.80-2.00(4H,m),3.29-3.92(13H,m),7.38-8.24(5H,m),8.43-8.56(1H,m)
95	92	ESI+: 531
96	92	ESI+: 516 NMR1:1.39(9H,s),2.15-2.34(4H,m),3.61-3.72(8H,m),3.99-4.13(1H,m),4.38-4.50(1H,m),6.09(1H,s),7.25-7.94(7H,m)
97	92	ESI+: 544
98	92	ESI+: 531 NMR1:1.38(9H,s),1.42-2.36(6H,m),3.54-4.12(9H,m),5.48(1H,m),6.97(1H,d,J=8Hz),7.18-7.93(5H,m)
99	71	ESI+: 570 NMR1:1.51-1.79(7H,m),1.84(3H,s),2.17-2.34(3H,m),3.17-3.26(1H,m),3.27-3.38(2H,m),3.70(4H,br),3.74(4H,br),3.82(1H,br),4.98-5.10(1H,m),6.40(1H,s),7.38-7.49(2H,m),7.54(1H,t,J=52.4Hz),7.74(1H,d,J=7.8Hz),7.86(1H,d,J=7.4Hz),8.15(1H,d,J=8.2Hz)
100	66+44	ESI+: 529 NMR1:1.20-1.90(8H,m),2.72-2.85(6H,m),3.58-4.38(13H,m),6.26(1H,s),7.39-7.69(4H,m),7.72-7.68(1H,m),7.84-7.89(1H,m),8.54-8.63(1H,m)
101	66	ESI+: 676

[0304]

[Table 148]

Ex	Syn	DAT
102	66	ESI+: 676
103	66	ESI+: 516
104	66	ESI+: 516
105	66	ESI+: 544
106	66	ESI+: 552
107	66	ESI+: 541
108	66	ESI+: 541
109	66	ESI+: 541
110	66	ESI+: 542
111	66	ESI+: 515
112	66	ESI+: 463 NMR1:1.23(4H,s),3.57(8H,s),6.21-8.09(12H,m)
113	66	ESI+: 529
114	66	ESI+: 529
115	66	ESI+: 556
116	66	ESI+: 583 NMR1:0.2-0.6(4H,m),0.65-2(12H,m),2.17(6H,s),2.80(2H,s),3.0-4.0(9H,m),6.30(1H,brs),7.0-8.0(5H,m)
117	66	ESI+: 585
118	66+44	ESI+: 529
119	66+44	ESI+: 501
120	45+44	ESI+: 554 NMR1:1.54(6H,brs),1.82(6H,brs),2.87-3.02(2H,m),3.07-3.20(2H,m),3.29-3.39(2H,m),3.57-3.76(8H,m),3.81-4.01(4H,m),6.27-6.46(1H,m),7.14(1H,brs),7.35-7.92(5H,m)
121	45+44	ESI+: 570 NMR1:1.25(6H,brs),1.44-2.97(15H,m),3.13(3H,brs),3.39-3.49(1H,m),3.58-3.76(8H,m),6.29-6.46(1H,m),7.08-7.91(6H,m)
122	45+44	ESI+: 514
123	45+44	ESI+: 514
124	45+44	ESI+: 542
125	45	ESI+: 542 NMR1:0.75-2.16(10H,m),2.22(3H,s),2.43(4H,brs),2.95-3.18(2H,m),3.42-3.72(12H,m),6.36(1H,brs),7.02-7.39(4H,m),7.61-7.71(1H,m)
126	45	ESI+: 570
127	45	ESI+: 574 NMR1:0.80-2.18(15H,m),3.02(2H,s),3.14(2H,d,J=5.2Hz),3.61-3.77(9H,m),4.48(1H,t,J=5.2Hz),5.01-5.10(1H,m),6.39(1H,s),7.39-7.66(4H,m),7.70-7.77(1H,m),7.84-7.88(1H,m)

[0305]

[Table 149]

Ex	Syn	DAT
128	45	ESI+: 600 NMR1:1.34-2.40(19H,m),3.05(2H,s),3.58-3.78(9H,m),4.29(1H,d,J=4.0Hz),5.0-5.15(1H,m),6.39(1H,s),7.39-7.66(4H,m),7.72-7.76(1H,m),7.84-7.88(1H,m)
129	45	ESI+: 600 NMR1:0.81-2.28(19H,m),3.05(2H,s),3.61-3.77(9H,m),4.45(1H,d,J=4.4Hz),5.0-5.15(1H,m),6.39(1H,s),7.39-7.66(4H,m),7.72-7.76(1H,m),7.84-7.88(1H,m)
130	45	ESI+: 598 NMR1:0.17-0.68(4H,m),0.76-2.13(22H,m),3.01-3.60(6H,m),6.31(1H,brs),6.73(1H,brs),7.25-8.03(5H,m)
131	45+44	ESI+: 542
132	45+44	ESI+: 542
133	89	ESI+: 556 NMR1:0.05-0.11(2H,m),0.36-0.44(2H,m),0.80-0.90(2H,m),1.37-1.63(4H,m),1.81-1.92(2H,m),2.09-2.19(2H,m),2.27-2.37(2H,m),3.06(2H,s),3.60-3.78(9H,m),5.00-5.10(1H,m),6.40(1H,s),7.38-7.68(4H,m),7.72-7.78(1H,m),7.83-7.88(1H,m)
134	89	ESI+: 570 NMR1:1.20-1.72(12H,m),1.82-1.92(2H,m),2.05-2.18(3H,m),2.89-2.98(1H,m),3.03(2H,s),3.60-3.80(9H,m),5.01-5.11(1H,m),6.40(1H,s),7.38-7.68(4H,m),7.72-7.77(1H,m),7.84-7.89(1H,m)
135	89	ESI+: 584 NMR1:0.79-2.35(20H,m),3.06(2H,m),3.60-3.77(9H,m),5.01-5.11(1H,m),6.40(1H,s),7.39-7.68(4H,m),7.72-7.78(1H,m),7.84-7.89(1H,m)
136	89	ESI+: 586 NMR1:1.18-1.31(2H,m),1.36-1.63(4H,m),1.65-1.75(2H,m),1.81-1.91(2H,m),2.08-2.18(2H,m),3.08(2H,s),3.21-3.34(4H,m),3.60-3.86(11H,m),5.01-5.11(1H,m),6.40(1H,s),7.38-7.68(4H,m),7.72-7.77(1H,m),7.84-7.89(1H,m)
137	89	ESI+: 556 NMR1:0.26-0.31(2H,m),0.46-0.52(2H,m),1.15(3H,s),1.37-1.62(4H,m),1.80-1.90(2H,m),2.07-2.18(2H,m),2.33-2.44(1H,m),3.06-3.11(2H,m),3.59-3.78(9H,m),5.00-5.11(1H,m),6.40(1H,s),7.38-7.68(4H,m),7.72-7.78(1H,m),7.83-7.89(1H,m)
138	89	ESI+: 572 NMR1:1.35-3.80(27H,m),5.00-5.11(1H,m),6.40(1H,s),7.38-7.69(4H,m),7.71-7.78(1H,m),7.83-7.90(1H,m)
139	89	ESI+: 572 NMR1:1.35-3.80(27H,m),5.00-5.11(1H,m),6.40(1H,s),7.37-7.69(4H,m),7.71-7.78(1H,m),7.82-7.89(1H,m)

[0306]

[Table 150]

Ex	Syn	DAT
140	89	ESI+: 596 NMR1:0.58-2.21(19H,m),2.81-3.06(3H,m),3.59-3.80(9H,m),5.00-5.12(1H,m),6.40(1H,s),7.39-7.69(4H,m),7.72-7.79(1H,m),7.84-7.89(1H,m)
141	89	ESI+: 636 NMR1:1.37-1.65(16H,m),1.80-1.90(2H,m),1.94-2.04(4H,m),2.08-2.18(2H,m),3.03(2H,s),3.59-3.79(9H,m),5.02-5.13(1H,m),6.40(1H,s),7.39-7.71(4H,m),7.72-7.78(1H,m),7.83-7.89(1H,m)
142	89	ESI+: 652 NMR1:1.35-1.62(16H,m),1.81-1.90(2H,m),2.05-2.19(5H,m),3.02(2H,s),3.59-3.79(9H,m),4.40(1H,s),5.02-5.12(1H,m),6.40(1H,s),7.38-7.70(4H,m),7.72-7.78(1H,m),7.83-7.89(1H,m)
143	89	ESI+: 614 NMR1:1.07(3H,s),1.15-2.22(18H,m),3.06(2H,s),3.59-3.80(9H,m),3.93(1H,s),5.01-5.12(1H,m),6.40(1H,s),7.38-7.69(4H,m),7.72-7.78(1H,m),7.83-7.89(1H,m)
144	89	ESI+: 614 NMR1:1.11-2.46(21H,m),3.10(2H,s),3.65-3.87(9H,m),4.17(1H,s),5.05-5.17(1H,m),6.46(1H,s),7.43-7.75(4H,m),7.77-7.84(1H,m),7.88-7.95(1H,m)
145	52	ESI+: 558
146	1	ESI+: 572
147	1	ESI+: 572
148	1	ESI+: 558
149	1	ESI+: 530
150	1	ESI+: 474[M+Na] NMR1:3.63-3.93(8H,m),7.41-8.76(10H,m)
151	1	ESI+: 530
152	1	ESI+: 584
153	1	ESI+: 574 NMR1:0.85-1.13(2H,m),1.38(9H,s),1.56-1.80(3H,m),2.57-2.76(2H,m),3.06-3.24(2H,m),3.51-3.75(8H,m),3.83-4.03(5H,m),6.20-6.35(1H,m),6.91(1H,d,J=8.0Hz),7.09-7.80(4H,m)
154	1	ESI+: 612
155	1	ESI+: 453 NMR1:2.45(3H,s),3.37-3.75(8H,m),4.53-4.61(2H,m),6.25-6.49(1H,m),7.10-7.91(6H,m),8.38-8.56(2H,m)
156	1	ESI+: 523
157	1	ESI+: 536
158	1	ESI+: 593 NMR1:1.19(3H,t,J=8.0Hz),3.01-3.13(4H,m),3.44-3.54(4H,m),3.56-3.94(8H,m),4.06(2H,q,J=8.0Hz),4.31-4.45(2H,m),6.25-6.40(1H,m),6.92(2H,d,J=12Hz),7.10-7.94(8H,m)

[0307]

[Table 151]

Ex	Syn	DAT
159	1	ESI+: 494 NMR1:1.41(3H,d,J=8.0Hz),3.40-3.78(8H,m),4.33-4.47(1H,m),6.29-6.47(1H,m),6.92-7.96(11H,m),9.84-10.17(1H,m)
160	1	ESI+: 511 NMR1:0.62-0.84(2H,m),0.86-1.03(2H,m),3.47-3.88(10H,m),6.18-6.42(1H,m),6.91-7.93(10H,m)
161	1	ESI+: 508
162	1	ESI+: 522 NMR1:2.73-2.92(4H,m),3.47-3.82(12H,m),4.48-4.65(2H,m),6.21-6.44(1H,m),6.86-7.98(10H,m)
163	1	ESI+: 430
164	1	ESI+: 446 NMR1:1.28-1.43(2H,m),1.50-1.69(4H,m),1.70-1.79(1H,m),1.92-2.03(1H,m),3.69(4H,d,J=4.7Hz),3.72(4H,d,J=4.7Hz),3.90(1H,br),4.70(1H,d,J=4.7Hz),5.15-5.22(1H,m),6.39(1H,s),7.39-7.52(2H,m),7.55(1H,t,J=52.5Hz),7.77(1H,d,J=7.9Hz),7.87(1H,d,J=7.9Hz)
165	1	ESI+: 446 NMR1:1.20-1.43(4H,m),1.67(2H,br),1.90(1H,br),2.12(1H,br),3.53-3.64(1H,m),3.69(4H,d,J=4.2Hz),3.73(4H,d,J=3.7Hz),4.86-4.95(1H,m),4.94(1H,d,J=4.7Hz),6.39(1H,s),7.40-7.50(2H,m),7.55(1H,t,J=52.5Hz),7.77(1H,d,J=7.9Hz),7.87(1H,d,J=7.9Hz)
166	1	ESI+: 486 NMR1:0.94-1.31(14H,m),1.72(1H,br),1.82(1H,br),3.64(4H,br),3.68(4H,br),4.19(1H,br),6.32(1H,br),6.96(1H,br),7.33-7.88(5H,m)
167	1	ESI+: 446
168	1	ESI+:482[M+Na] NMR1:1.02-1.16(3H,m),1.33-1.45(2H,m),1.55-1.79(6H,m),3.64-4.09(10H,m),7.37-8.10(5H,m),8.39-8.63(1H,m)
169	1	ESI+: 482[M+Na] NMR1:1.00-1.06(3H,m),1.35-1.92(8H,m),3.61-3.94(9H,m),4.26-4.33(1H,m),7.38-8.09(5H,m),8.40-8.63(1H,m)
170	1	ESI+: 498 NMR1:1.30-1.42(2H,m),1.60-1.71(4H,m),1.72-1.84(2H,m),1.94-2.08(3H,m),2.09-2.20(2H,m),3.63-3.88(8H,m),3.97-4.12(1H,m),4.40-4.50(1H,m),7.38-7.52(2H,m),7.62-8.20(3H,m),8.41-8.66(1H,m)
171	1	ESI+: 454[M+Na]
172	1	ESI+: 430
173	1	ESI+: 476 NMR1:1.34-1.74(6H,m),1.86-2.03(2H,m),2.69-2.77(2H,m),3.13-3.27(1H,m),3.48-3.88(10H,m),7.33-7.53(2H,m),7.62-8.18(3H,m),8.40-8.58(1H,m)
174	1	ESI+: 540

[0308]

[Table 152]

Ex	Syn	DAT
175	1	ESI+: 444 NMR1:0.99-1.38(4H,m),1.38-1.76(4H,m),1.76-2.10(2H,m),3.25-3.54(2H,m),3.54-3.75(8H,m),6.22-6.39(1H,m),6.87-7.02(1H,m),7.35-7.91(5H,m)
176	1	ESI+: 444 NMR1:1.13-1.85(10H,m),2.94-3.11(1H,m),3.51-3.76(8H,m),3.76-3.90(1H,m),6.24-6.44(1H,m),6.44-6.73(1H,m),7.35-7.91(5H,m)
177	1	ESI+: 503
178	1	ESI+: 498 NMR1:1.42-1.65(6H,m),1.92-2.07(6H,m),2.16-2.24(2H,m),3.64-3.83(8H,m),4.55-4.60(1H,m),7.38-8.15(5H,m),8.44-8.63(1H,m)
179	1	ESI+: 487
180	1	ESI+: 522[M+Na]
181	1+44	ESI+: 556
182	1	ESI+: 523
183	1	ESI+: 654[M+Na] NMR1:1.01-1.82(12H,m),3.31-3.45(4H,m),3.59-3.74(9H,m),5.06(2H,s),6.25-6.38(1H,m),6.89-7.04(1H,m),7.27-7.88(10H,m)
184	1	ESI+: 501
185	1	ESI+: 572
186	1	ESI+: 559
187	1	ESI+: 572
188	22	ESI+: 495
189	93	ESI+: 469
190	83	ESI+: 473 NMR1:1.18-1.35(2H,m),1.39-1.55(2H,m),1.85-2.10(4H,m),2.16-2.27(1H,m),3.60-3.87(9H,m),6.09(1H,s),7.35-7.66(4H,m),7.68-7.74(1H,m),7.82-7.87(1H,m),12.08(1H,brs)
191	26	ESI+: 556
192	26	ESI+: 558
193	26	ESI+: 526 NMR1:0.98-1.13(2H,m),1.19(6H,br),1.57(2H,d,J=11.2Hz),1.72(6H,br),2.13(2H,br),2.79(1H,br),3.16(2H,br),3.30(1H,br),3.64(4H,br),3.68(4H,br),6.31(1H,br),7.15(1H,br),7.37-7.47(2H,m),7.53(1H,br),7.76(1H,d,J=7.9Hz),7.85(1H,d,J=7.7Hz)
194	26	ESI+: 556 NMR1:0.92-1.02(2H,m),1.08(6H,d,J=6.1Hz),1.12(2H,br),1.50(1H,br),1.66(2H,br),1.68(2H,br),2.05(2H,br),2.45(1H,br),2.82(2H,br),3.14(1H,s),3.18(1H,s),3.28-3.38(2H,m),3.63(4H,br),3.68(4H,br),6.31(1H,br),7.13(1H,br),7.36-7.47(2H,m),7.50-7.72(1H,m),7.77(1H,d,J=7.6Hz),7.85(1H,d,J=7.6Hz)
195	26	ESI+: 540

[0309]

[Table 153]

Ex	Syn	DAT
196	26	ESI+: 570 NMR1:1.41-1.65(6H,m),1.72-2.00(6H,m),2.07(3H,s),2.10-2.19(2H,m),2.76(2H,s),2.87-2.97(1H,m),3.60-3.79(9H,m),5.00-5.10(1H,m),6.40(1H,s),7.38-7.68(4H,m),7.72-7.78(1H,m),7.83-7.89(1H,m)
197	26	ESI+: 500
198	26	ESI+: 584 NMR1:1.49-2.30(16H,m),2.66-2.71(6H,m),3.64-3.84(9H,m),4.98-5.11(1H,m),6.40(1H,s),7.39-7.69(3H,m),7.72-7.77(1H,m),7.84-7.89(1H,m),8.19-8.29(1H,m),10.75-1.88(1H,m)
199	26	ESI+: 598 NMR1:0.80-2.30(22H,m),3.08-3.17(1H,m),3.56-3.79(9H,m),5.01-5.11(1H,m),6.40(1H,s),7.38-7.70(4H,m),7.72-7.78(1H,m),7.84-7.89(1H,m)
200	26+44	ESI+: 542
201	26+44	ESI+: 562
202	26+44	ESI+: 596
203	26+44	ESI+: 542
204	26+44	ESI+: 514
205	53	ESI+: 472
206	53	ESI+: 458
207	53	ESI+: 430
208	53	ESI+: 474
209	53	ESI+: 498 NMR1:0.16-0.73(4H,m),1.02-2.20(10H,m),2.80-3.99(11H,m),6.33(1H,brs),7.24-8.01(5H,m),8.21(2H,brs)
210	53	ESI+: 472
211	54	ESI+: 472
212	54	ESI+: 484
213	54	ESI+: 478
214	54	ESI+: 512
215	54	ESI+: 542 NMR1:1.38-2.42(14H,m),3.55-3.78(9H,m),5.00-5.10(1H,m),6.40(1H,s),7.38-7.89(6H,m)
216	54	ESI+: 556 NMR1:1.35-2.18(16H,m),3.54-3.78(9H,m),5.02-5.11(1H,m),6.40(1H,s),7.39-7.88(6H,m)
217	54	ESI+: 444
218	54	ESI+: 444
219	54	ESI+: 472
220	54	ESI+: 486
221	54	ESI+: 431
222	54	ESI+: 431

[0310]

[Table 154]

Ex	Syn	DAT
223	53	ESI+: 500
224	26	ESI+: 556 NMR1:1.07(6H,d,J=6.2Hz),1.14(2H,br),1.16(2H,br),1.52(1H,br),1.70(2H,br),1.72-1.79(2H,m),1.86(2H,br),2.28(1H,br),3.02(2H,br),3.13(1H,br),3.20(1H,br),3.63(4H,br),3.68(4H,br),3.73(2H,br),6.31(1H,br),7.14(1H,t,J=5.7Hz),7.36-7.48(2H,m),7.49-7.73(1H,m),7.76(1H,d,J=7.7Hz),7.85(1H,d,J=7.7Hz)
225	92	ESI+: 544
226	92	ESI+: 555
227	66	ESI+: 642
228	66	ESI+: 656
229	1	ESI+: 586
230	1	ESI+: 572
231	1	ESI+: 516
232	1	ESI+: 516
233	54	ESI+: 416
234	54	ESI+: 416
235	54	ESI+: 458
236	1	ESI+: 558
237	237	ESI+: 527
238	238	ESI+: 586
239	239	ESI+: 472
240	240	ESI+: 514
241	241	ESI+: 520
242-1	242+44	ESI+: 472
242-2	242+44	ESI+: 486
243	243	ESI+: 526
244	244	ESI+: 419
245	245	ESI+: 616
246	246	ESI+: 570
247	247	ESI+: 531
248	248	ESI+: 585 NMR1:1.27-2.31(10H,m),3.06-3.38(2H,m),3.53(3H,s),3.56-3.92(10H,m),4.06-4.20(1H,m),6.22-6.43(1H,m),6.88-7.13(1H,m),7.34-7.96(6H,m)
249-1	249	ESI+: 542 NMR1:1.33-1.88(8H,m),2.21-2.30(1H,m),3.20(3H,s),3.60-3.71(8H,m),3.75-3.81(1H,m),4.01-4.06(1H,m),4.15-4.19(1H,m),4.48-4.50(1H,m),4.59-4.71(1H,m),6.12(1H,s),7.37-7.64(3H,m),7.12-7.74(1H,m),7.73(1H,d,J=8Hz),7.86(1H,d,J=7.6Hz),8.12-8.20(1H,m)

[0311]

[Table 155]

Ex	Syn	DAT
249-2	249	ESI+: 542 NMR1:1.07-2.21(8H,m),3.22(3H,s),3.62-3.71(8H,m),3.75-3.81(1H,m),4.02-4.06(1H,m),4.15-4.19(1H,m),4.49-4.53(1H,m),4.59-4.70(1H,m),6.12(1H,s),3.78-3.62(5H,m),7.73(1H,d,J=8.0Hz),7.86(1H,d,J=7.5Hz),8.13-8.19(1H,m)
250	1	ESI+: 438
251	1	ESI+: 439
252	1	ESI+: 439
253	1	ESI+: 439
254	1	ESI+: 452
255	1	ESI+: 498
256	1	ESI+: 432
257	1	ESI+: 424
258	1	ESI+: 454
259	1	ESI+: 426
260	1	ESI+: 425
261	1	ESI+: 433
262	1	ESI+: 504[M+Na]
263	1	ESI+: 504[M+Na]
264	1	ESI+: 468[M+Na]
265	1	ESI+: 496
266	1	ESI+: 445
267	1	ESI+: 445
268	1	ESI+: 445
269	1	ESI+: 497
270	1	ESI+: 508
271	1	ESI+: 497
272	1	ESI+: 459
273	1	ESI+: 481[M+Na]
274	1	ESI+: 429
275	1	ESI+: 530[M+Na]
276	1	ESI+: 497
277	1	ESI+: 547[M+Na]
278	1	ESI+: 553[M+Na]
279	1	ESI+: 567[M+Na]
280	94	ESI+: 454
281	1	ESI+: 440
282	1	ESI+: 442
283	1	ESI+: 463
284	1	ESI+: 464
285	1	ESI+: 464
286	1	ESI+: 481

[0312]

[Table 156]

Ex	Syn	DAT
287	1	ESI+: 496
288	1	ESI-:479
289	74	ESI+: 520
290	1	ESI+: 478
291	1	ESI+: 520
292	26+44	ESI+: 520
293	74	ESI+: 570
294	92	ESI+: 504[M+Na]
295	PSyn.8	ESI+: 452
296	240+44	ESI+: 522
297	22	ESI+: 556
298	22	ESI+: 542
299	22	ESI+: 542
300	74	ESI+: 522
301	74	ESI+: 480
302	1	ESI+: 520
303	1	ESI+: 544
304	54	ESI+: 444
305	1	ESI+: 573
306	1	ESI+: 587
307	66+44	ESI+: 529
308	PSyn.81	ESI+: 489
309	PSyn.81	ESI+: 503
310	1	ESI+: 497
311	74	ESI+: 453
312	74	ESI+: 454
313	74	ESI+: 453
314	74	ESI+: 521
315	74	ESI+: 520
316	1	ESI+: 575[M+Na]
317	54	ESI+: 453
318	240+44	ESI+: 523
319	1	ESI+: 485
320	54	ESI+: 458
321	54	ESI+: 458
322	26	ESI+: 542
323	26	ESI+: 542
324	26	ESI+: 528
325	1	ESI+: 532
326	66	ESI+: 529
327	1	ESI+: 520

[0313]

[Table 157]

Ex	Syn	DAT
328	1	ESI+: 520
329	66	ESI+: 501
330	PSyn.148	ESI+: 488
331	66	ESI+: 534
332	66	ESI+: 534
333	66	ESI+: 534
334	74	ESI+: 506
335	74	ESI+: 538
336	74	ESI+: 538
337	74	ESI+: 550
338	74	ESI+: 566
339	74	ESI+: 524
340	92	ESI+: 515
341	84	ESI+: 628
342	26	ESI+: 500
343	66	ESI+: 550
344	66	ESI+: 554
345	66	ESI+: 538
346	66	ESI+: 538
347	66	ESI+: 538
348	74	ESI+: 580
349	74	ESI+: 566
350	66	ESI+: 569
351	66	ESI+: 521
352	66	ESI+: 521
353	66	ESI+: 521
354	53	ESI+: 430
355	26	ESI+: 520
356	26	ESI+: 520
357	66	ESI+: 552
358	89+44	ESI+: 584
359	92	ESI+: 556
360	92	ESI+: 555
361	93	ESI+: 469
362	26+44	ESI+: 540
363	92	ESI+: 488
364	26	ESI+: 514
365	26	ESI+: 528
366	241	ESI+: 534
367	22	ESI+: 437
368	84	ESI+: 664[M+Na]

[0314]

[Table 158]

Ex	Syn	DAT
369	1	ESI+: 536
370	92	ESI+: 585 NMR1:1.33(3H,br),1.52-1.81(5H,m),2.10(2H,br),2.24(1H,br),3.15-3.25(1H,m),3.54(3H,s),3.67(8H,br),3.75(1H,br),4.06-4.18(1H,m),6.10(1H,s),7.35-7.50(5H,m),7.51(1H,t,J=52.7Hz),7.71(1H,d,J=7.9Hz),7.85(1H,d,J=7.9Hz)
371	92	ESI+: 585 NMR1:1.20-1.33(3H,m),1.50-1.83(5H,m),2.01-2.18(2H,m),2.17-2.31(1H,m),3.13-3.25(1H,m),3.54(3H,s),3.59-3.91(10H,m),4.05-4.19(1H,m),6.10(1H,s),7.34-7.54(5H,m),7.72(1H,d,J=8.2Hz),7.85(1H,d,J=7.7Hz)
372	1	ESI+: 588
373	1	ESI+: 446
374	53	ESI+: 488
375	26	ESI+: 572
376	1	ESI+: 536
377	1	ESI+: 544
378	54	ESI+: 444
379	92	ESI+: 544
380	54	ESI+: 444
381	26	ESI+: 528
382	66	ESI+: 529
383	26	ESI+: 528
384	26	ESI+: 562
385	43	ESI+: 556
386	43	ESI+: 556
387	88	ESI+: 632
388	85	ESI+: 600
389	87	ESI+: 586 NMR1:1.52-1.82(7H,m),2.23(3H,br),3.17-3.24(1H,m),3.28-3.36(1H,m),3.54(3H,s),3.70(4H,br),3.75(4H,br),3.81(1H,br),4.13(1H,q,J=9.3Hz),5.00-5.08(1H,m),6.40(1H,s),7.38-7.50(3H,m),7.53(1H,t,J=52.2Hz),7.75(1H,d,J=7.7Hz),7.86(1H,d,J=7.7Hz)
390	1	ESI+: 550
391	1	ESI+: 536
392	26	ESI+: 555
393	26	ESI+: 556
394	26	ESI+: 570
395	26	ESI+: 500
396	26	ESI+: 628
397	1	ESI+: 475

[0315]

[Table 159]

Ex	Syn	DAT
398	1	ESI+: 522
399	66	ESI+: 537
400	43	ESI+: 558
401	43	ESI+: 558
402	26	ESI+: 546
403	26	ESI+: 576
404	89	ESI+: 544
405	89	ESI+: 544
406	54	ESI+: 444
407	44	ESI+: 569
408	26	ESI+: 528
409	1	ESI+: 558
410	1	ESI+: 584
411	54	ESI+: 484
412	52	ESI+: 556
413	89	ESI+: 570
414	89	ESI+: 584
415	1	ESI+: 545
416	54	ESI+: 445
417	26	ESI+: 529
418	240+44	ESI+: 538
419	89	ESI+: 574
420	240	ESI+: 538
421	26	ESI+: 570
422	422	ESI+: 542
423	87	ESI+: 600 NMR1:1.16(3H,t,J=7.1Hz),1.50-1.83(7H,m),2.23(3H,br),3.15-3.25(1H,m),3.27-3.36(1H,m),3.70(4H,d,J=4.7Hz),3.74(4H,d,J=4.6Hz),3.77-3.86(1H,m),3.99(2H,q,J=7.1Hz),4.12(1H,q,J=9.1Hz),4.98-5.09(1H,m),6.40(1H,s),7.34-7.50(3H,m),7.53(1H,t,J=52.5Hz),7.75(1H,d,J=7.6Hz),7.86(1H,d,J=7.6Hz)
424	87	ESI+: 600
425	83	ESI-:474
426	92	ESI+: 531
427	1	ESI+: 503
428	1	ESI+: 517
429	54	ESI+: 417
430	54	ESI+: 431
431	54	ESI+: 403
432-1	432	ESI+: 528
432-2	432	ESI+: 528
433	54	ESI+: 417

[0316]

[Table 160]

Ex	Syn	DAT
434	92	ESI+: 446
435	92	ESI+: 516
436	54	ESI+: 416
437	92	ESI+: 530
438	54	ESI+: 430
439	92	ESI+: 516
440	54	ESI+: 416
441	248	ESI+: 585 NMR1:1.27-2.29(10H,m),3.07-3.21(2H,m),3.53(3H,s),3.57-3.83(10H,m),4.06-4.18(1H,m),6.22-6.41(1H,m),6.87-7.08(1H,m),7.31-7.92(6H,m)
442	66	ESI+: 529
443	66	ESI+: 529
444	66	ESI+: 528
445	66	ESI+: 528
446	66	ESI+: 542
447	66	ESI+: 542
448	52	ESI+: 560
449	54	ESI+: 488
450	1	ESI+: 588
451	249	ESI+: 543 NMR1:1.34-1.45(4H,m),1.53-1.65(2H,m),1.78-1.88(2H,m),2.25-2.35(1H,m),3.19(3H,s),3.66-3.76(8H,m),3.86-3.91(1H,m),4.19-4.34(2H,m),4.60-4.66(1H,m),5.44-5.50(1H,m),6.52(1H,s),7.41-7.67(4H,m),7.77-7.79(1H,m),7.86-7.88(1H,m)
452	249	ESI+: 543 NMR1:1.03-1.40(4H,m),1.67-1.75(2H,m),1.96-2.25(3H,m),3.00-3.12(1H,m),3.22(3H,s),3.66-3.76(8H,m),3.85-3.92(1H,m),4.18-4.33(2H,m),4.60-4.67(1H,m),5.43-5.51(1H,m),6.52(1H,s),7.42-7.67(3H,m),7.78(1H,d,J=7.4Hz),7.87(1H,d,J=7.4Hz)
453	66	ESI+: 556 NMR1:1.38-1.66(10H,m),1.81-2.02(1H,m),2.05-2.30(1H,m),3.31-3.40(2H,m),3.40-3.52(1H,m),3.56-3.63(2H,m),3.84-3.94(1H,m),3.66(4H,br),3.70(4H,br),4.37(1H,dt,J=1.4,5.2Hz),4.43-4.60(1H,m),6.14(1H,br),7.36-7.50(2H,m),7.52(1H,t,J=52.7Hz),7.73(1H,d,J=7.6Hz),7.75-7.88(1H,m),7.86(1H,d,J=7.8Hz)
454	66	ESI+: 556 NMR1:0.85-1.01(2H,m),1.33(4H,br),1.67-1.80(4H,m),1.82-2.03(1H,m),2.09-2.40(1H,m),3.17-3.23(2H,m),3.34-3.50(1H,m),3.57-3.63(2H,m),3.66(4H,br),3.70(4H,br),3.91(1H,br),4.36(1H,t,J=5.3Hz),4.44-4.60(1H,br),6.14(1H,d,J=4.8Hz),7.37-7.49(2H,m),7.52(1H,t,J=52.7Hz),7.72(1H,d,J=8.3Hz),7.75-7.88(1H,br),7.85(1H,d,J=7.9Hz)

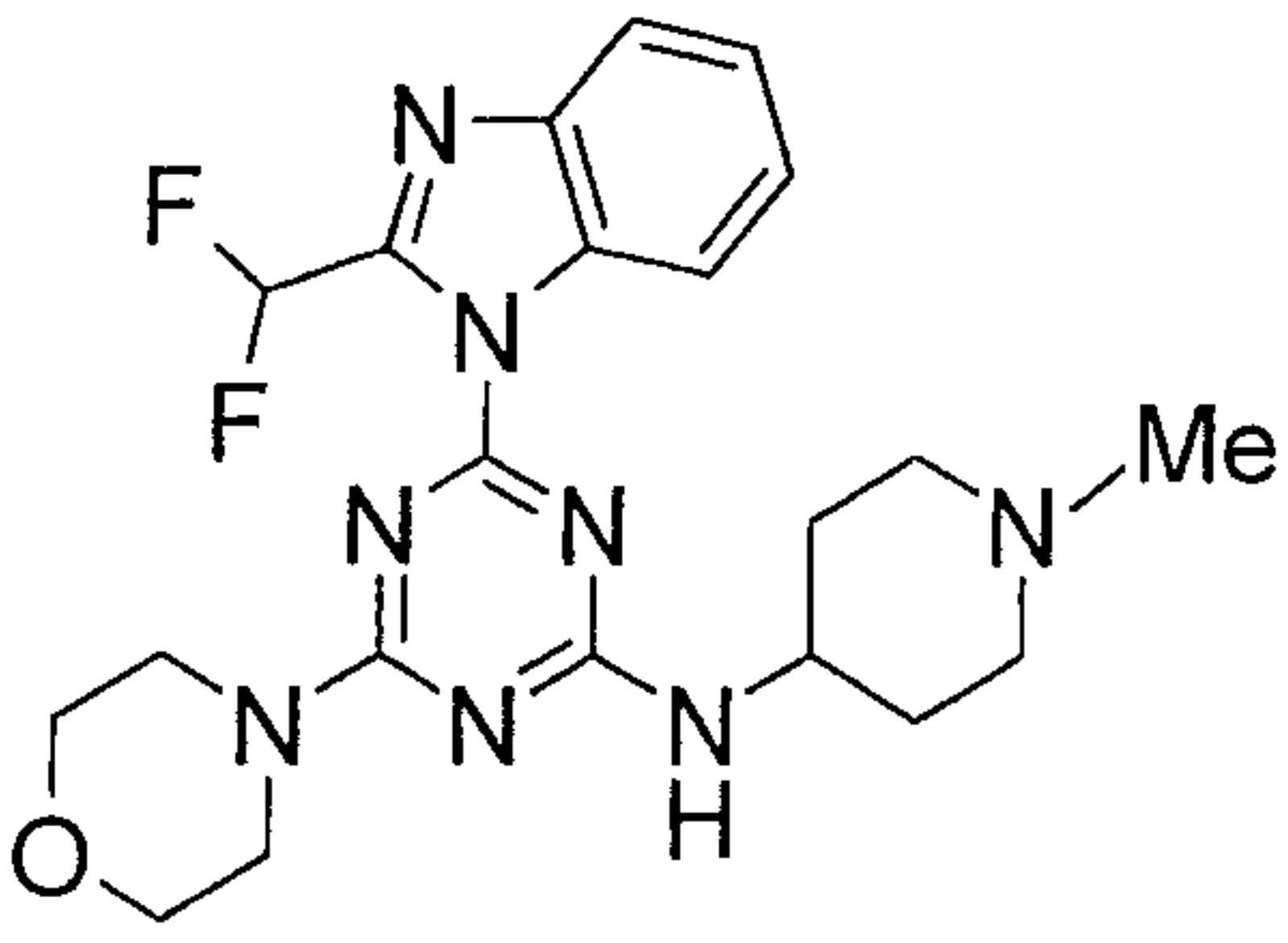
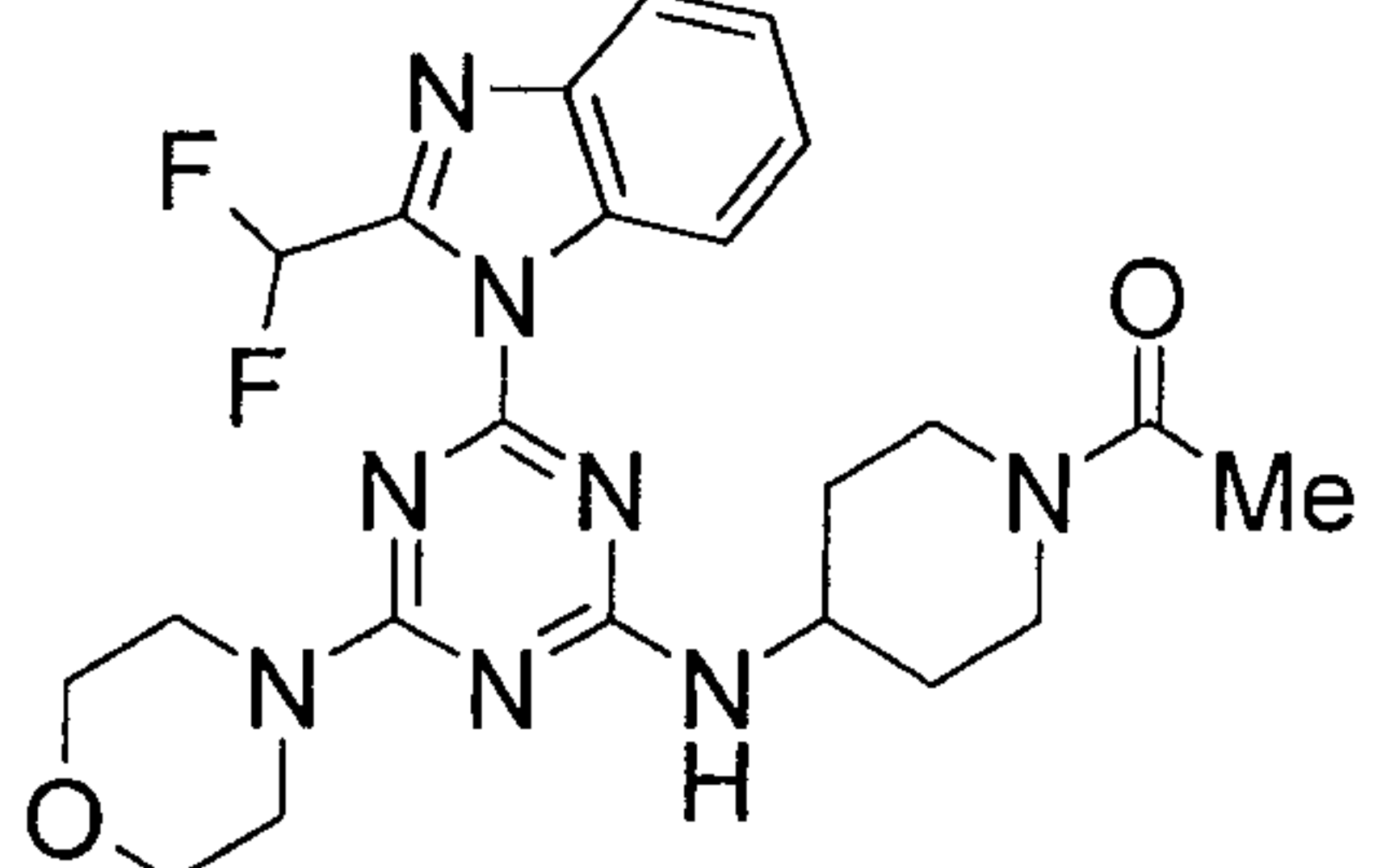
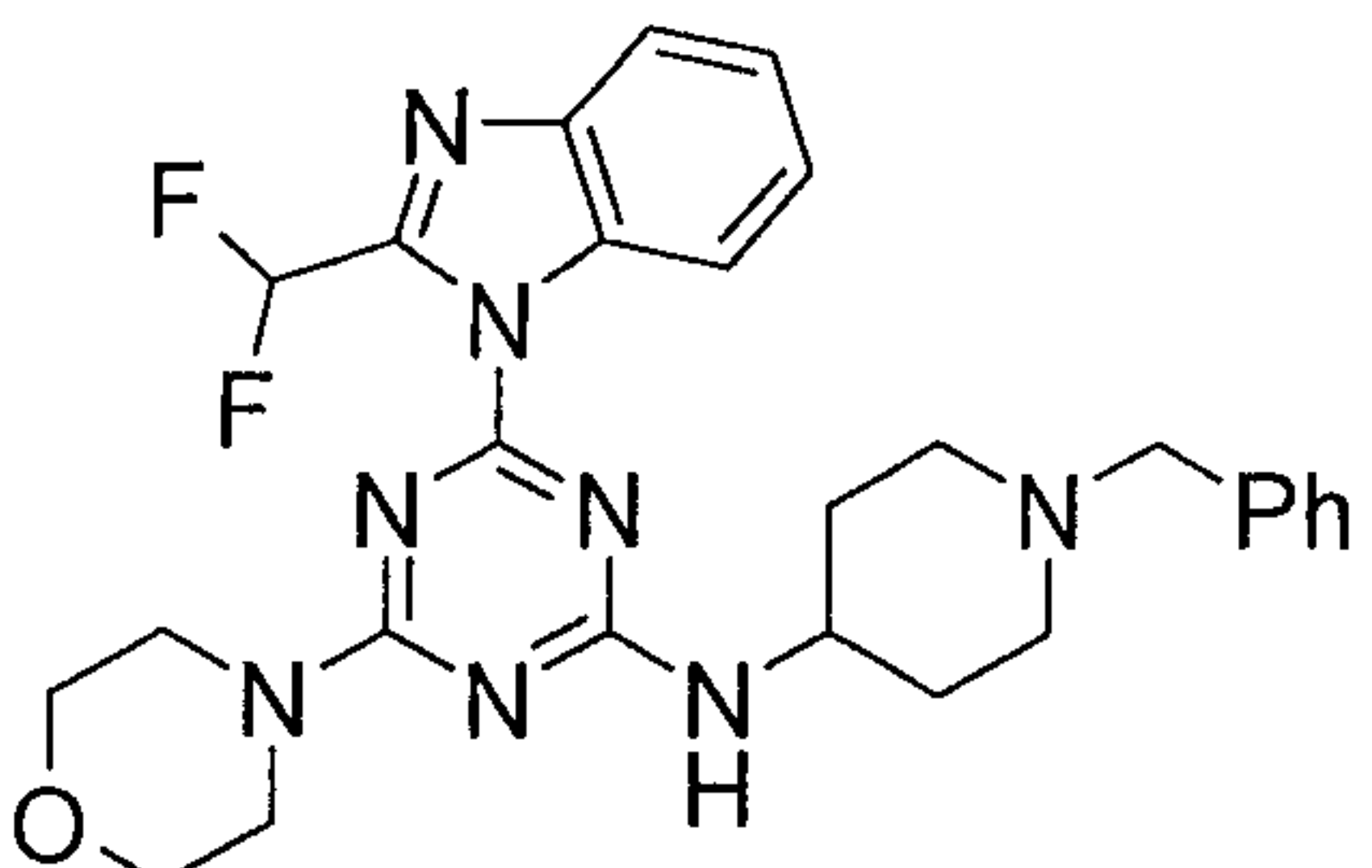
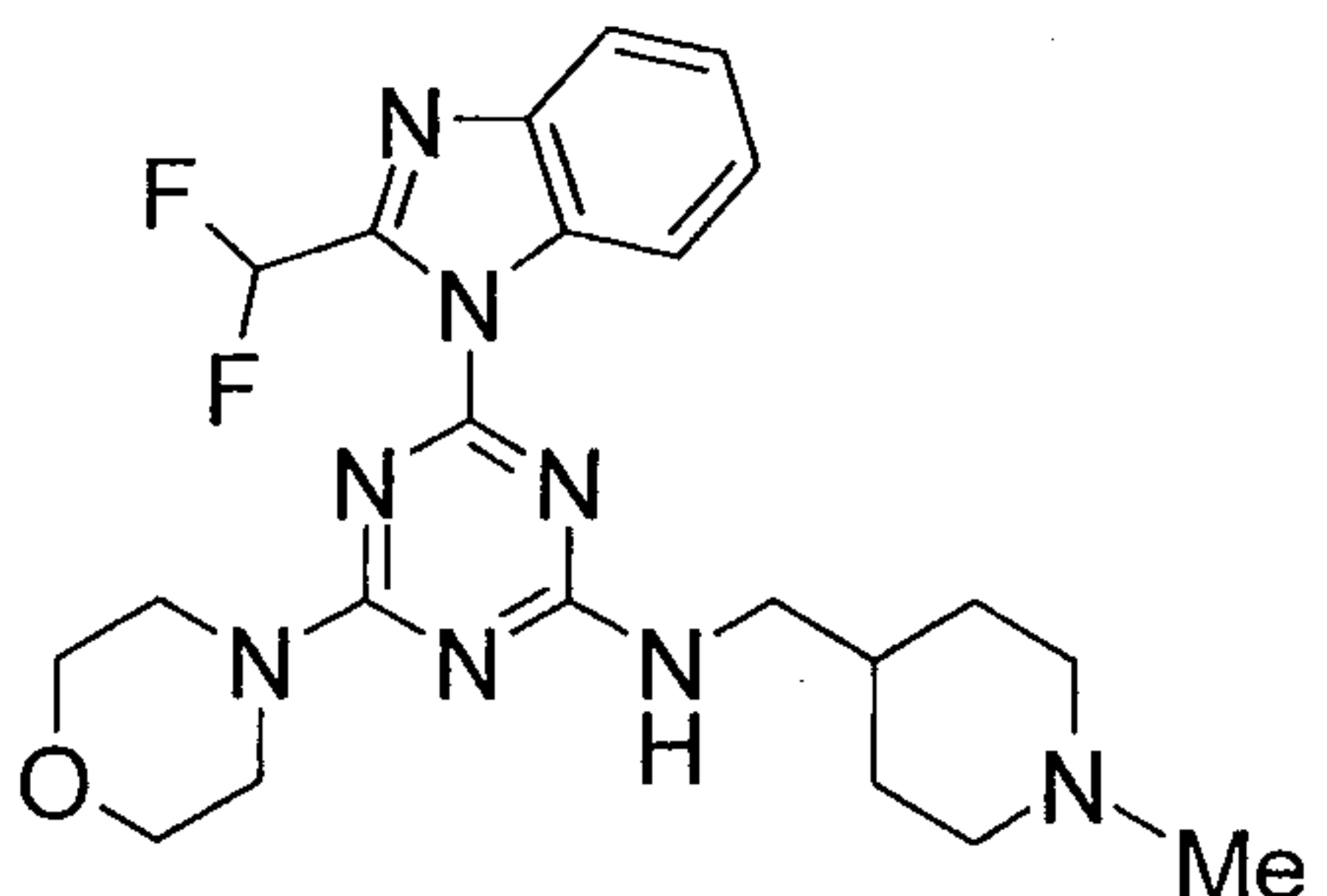
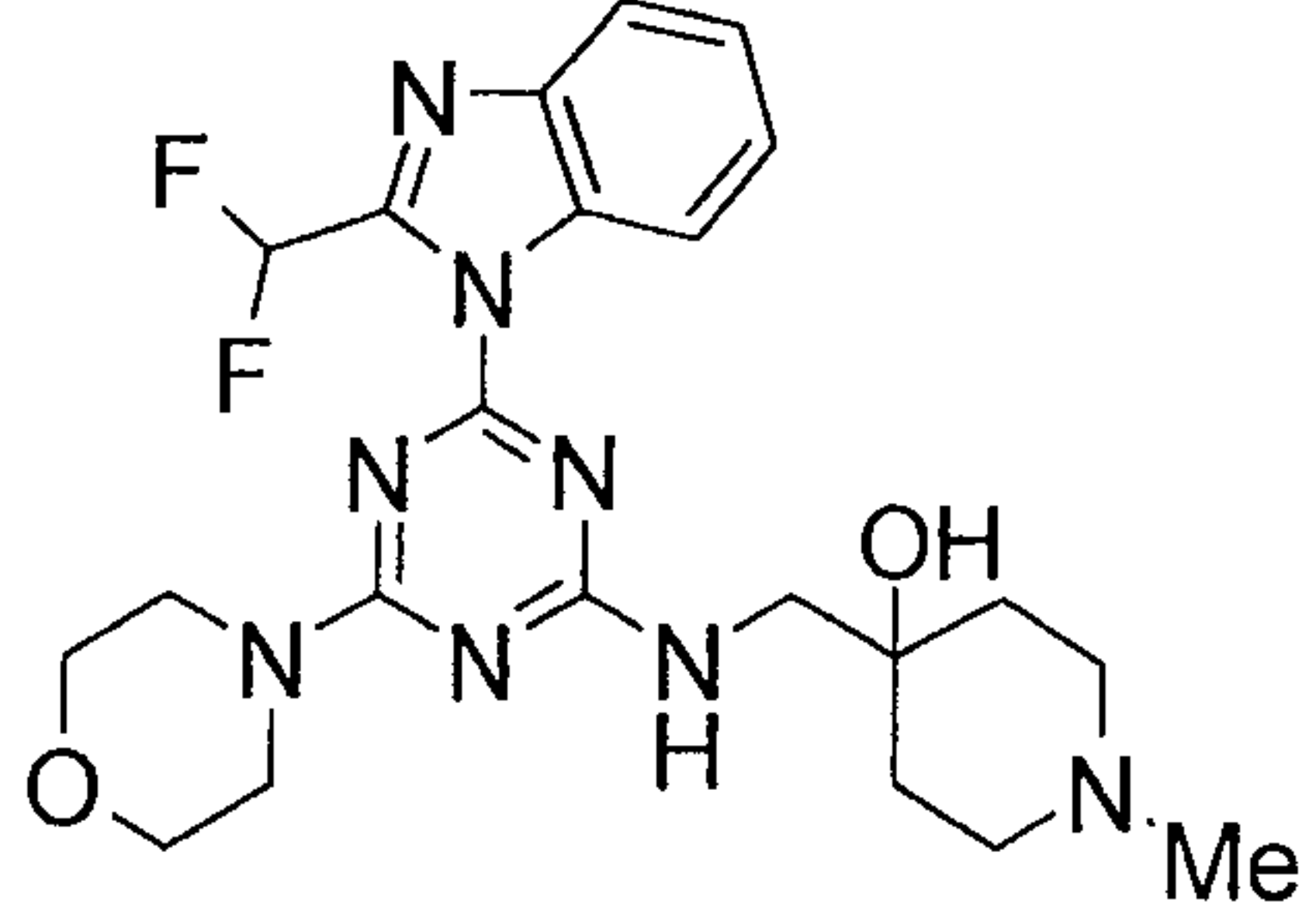
[0317]

[Table 161]

Ex	Syn	DAT
455	66	ESI+: 544
456	1	ESI+: 458
457	66+44	ESI+: 543
458	71	ESI+: 500
459	54	ESI+: 458
460	92	ESI+: 558
461	66	ESI+: 543
462	66	ESI+: 557
463	71	ESI+: 514
464	1	ESI+: 589
465	53	ESI+: 489
466	85	ESI+: 586
467	66	ESI+: 574
468	422	ESI+: 593
469	1	ESI+: 562
470	54	ESI+: 462
471	26	ESI+: 546

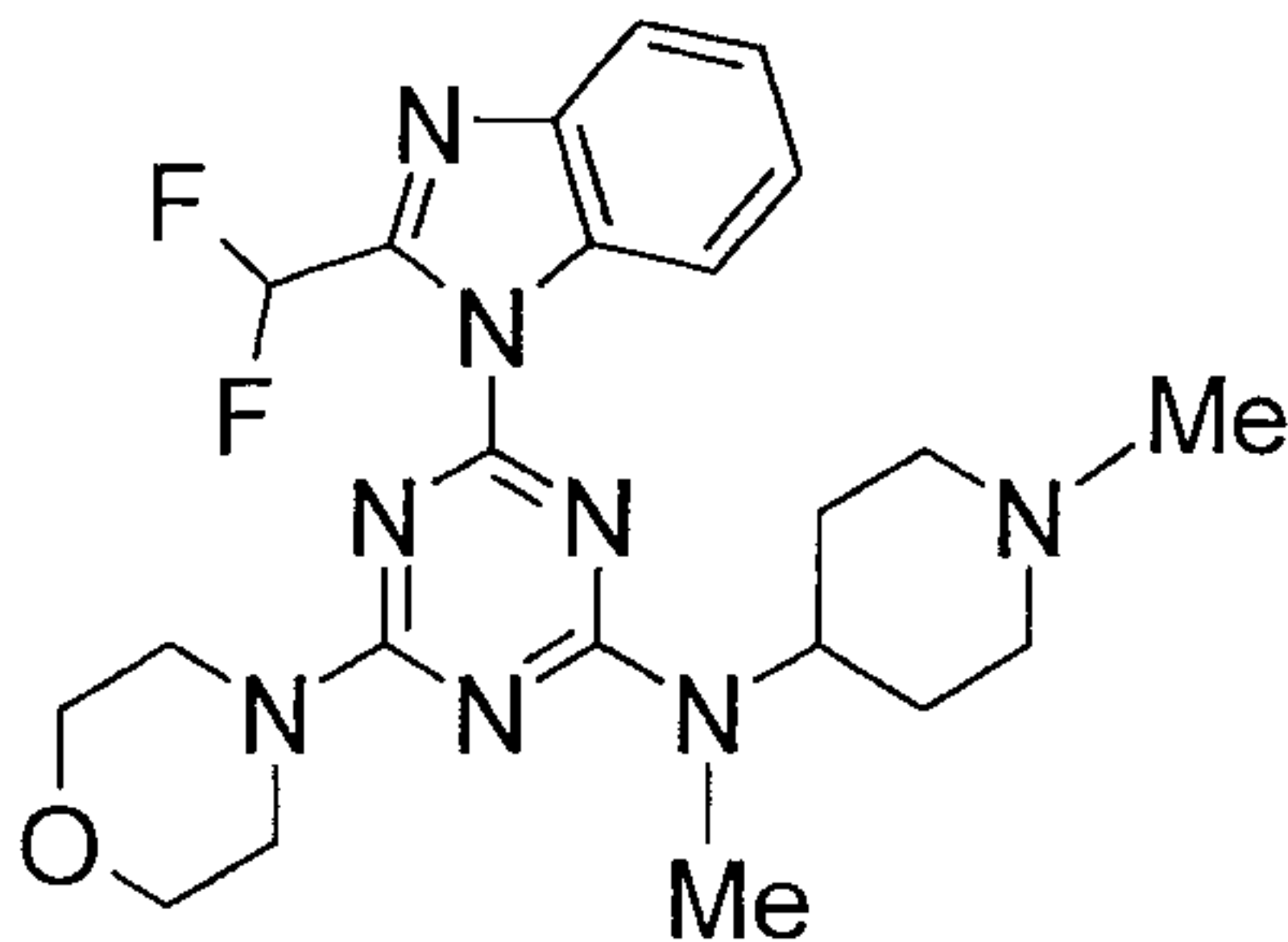
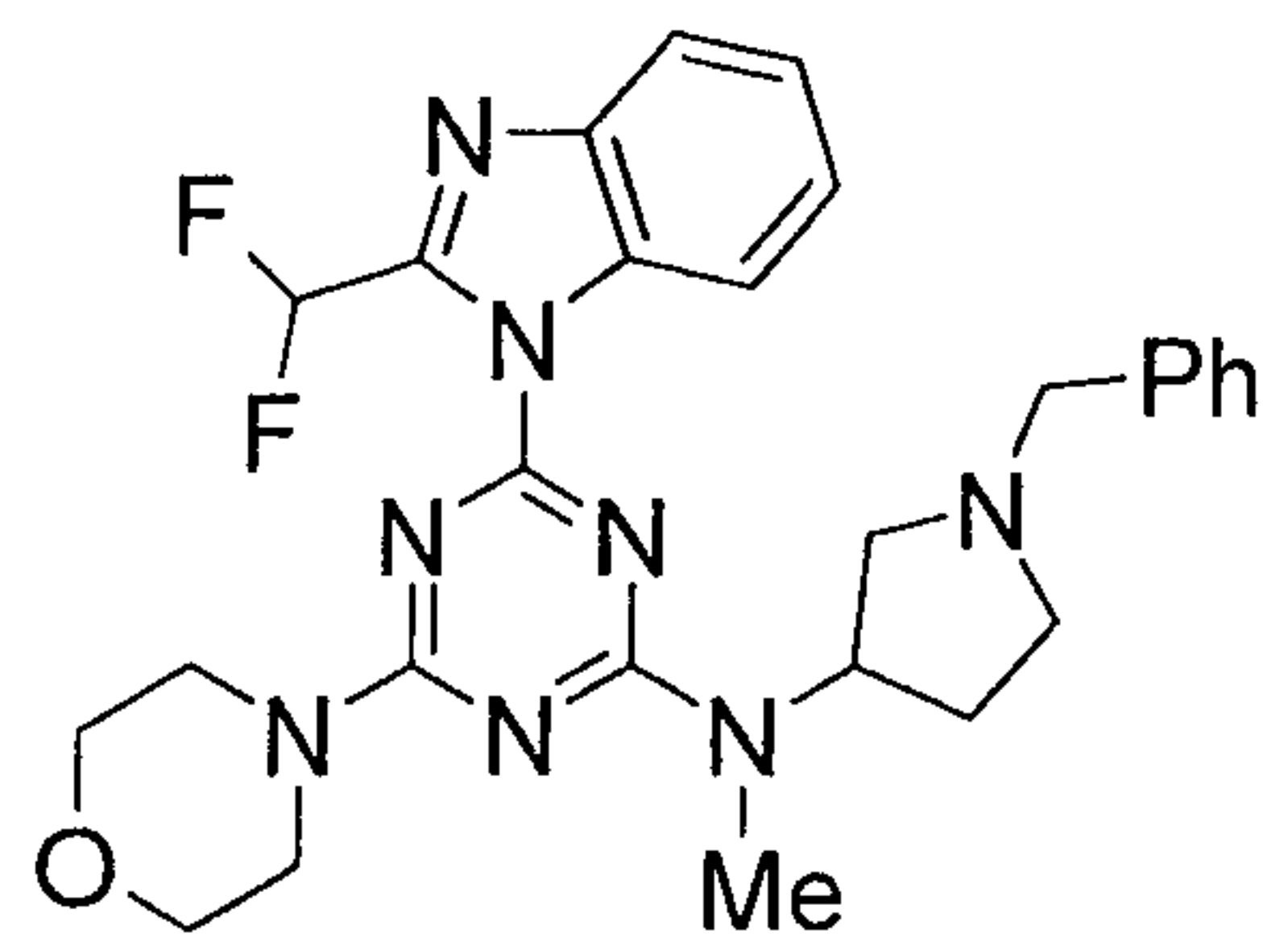
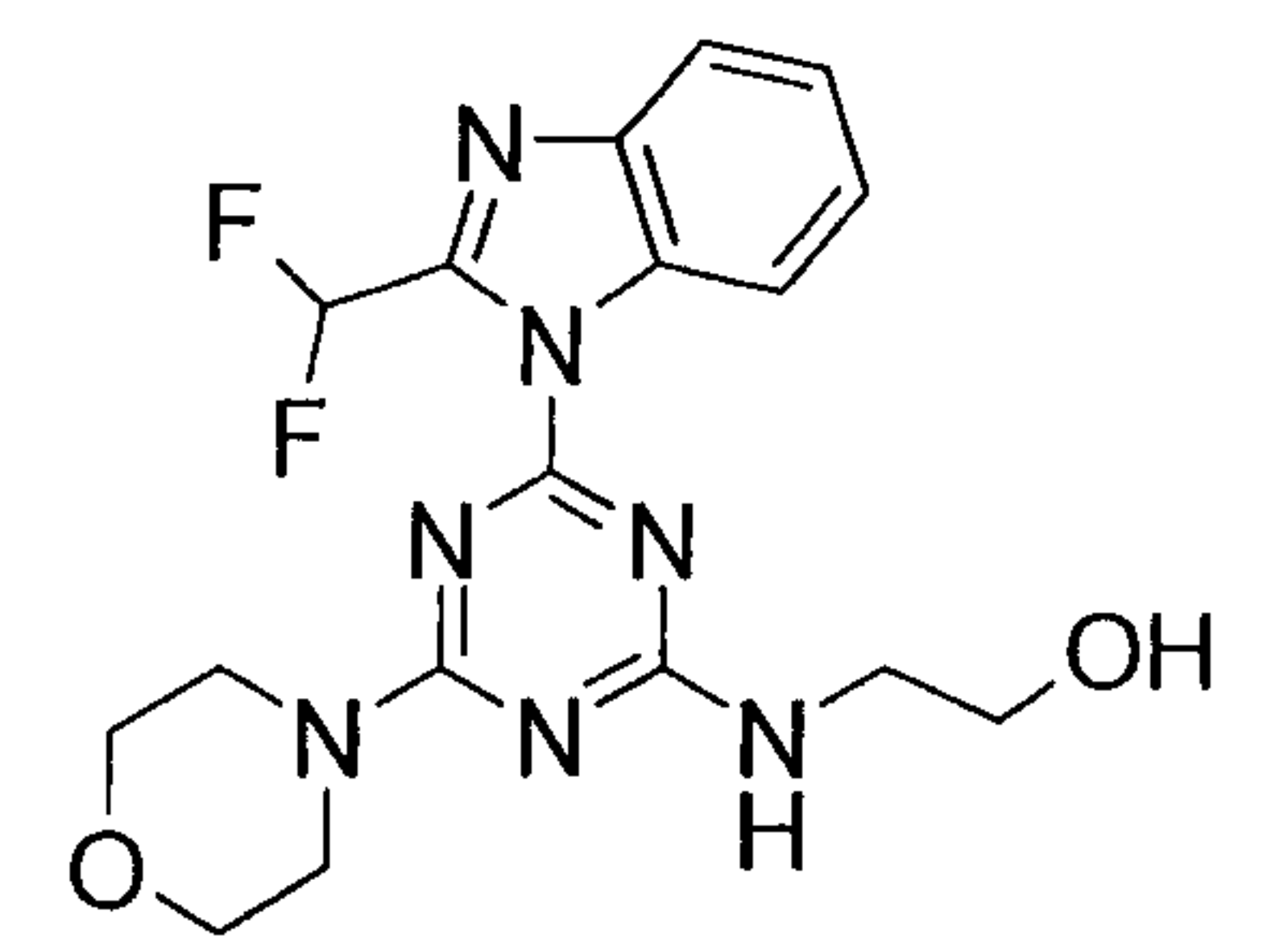
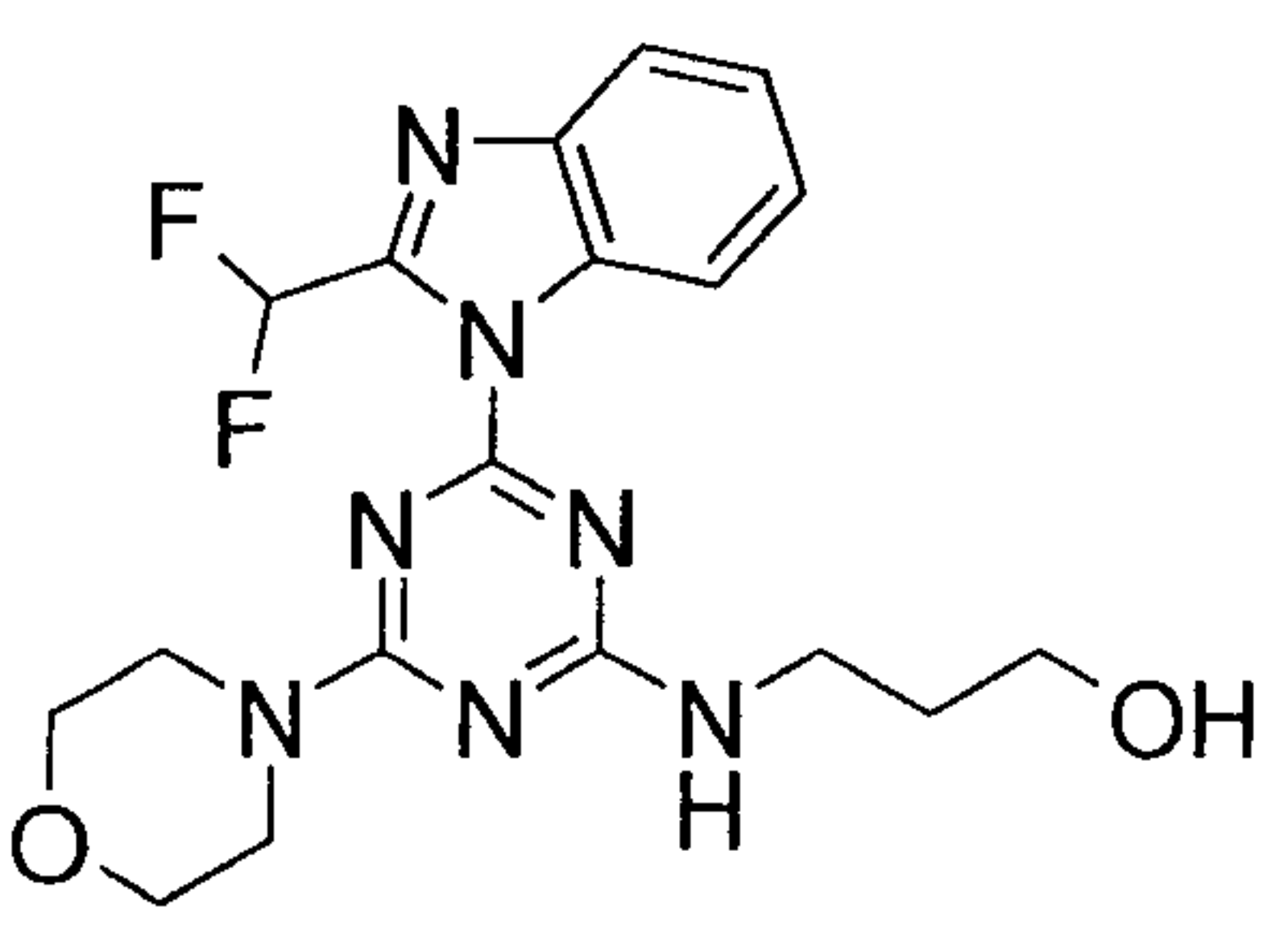
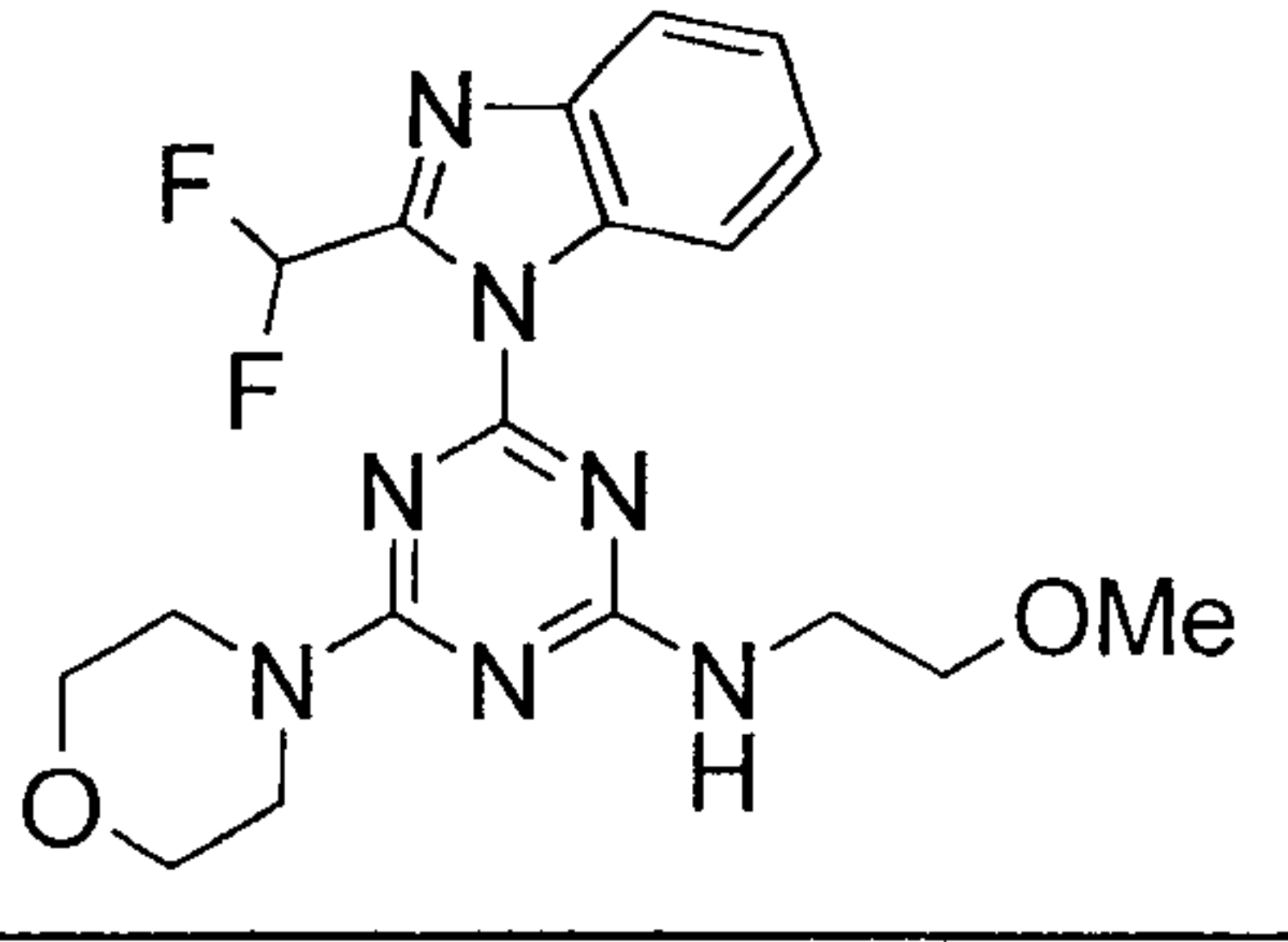
[0316]

[Table 162]

Ex	Str	ESI+	RT
A1		445	2.19
A2		473	2.81
A3		521	2.56
A4		459	2.28
A5		475	2.19

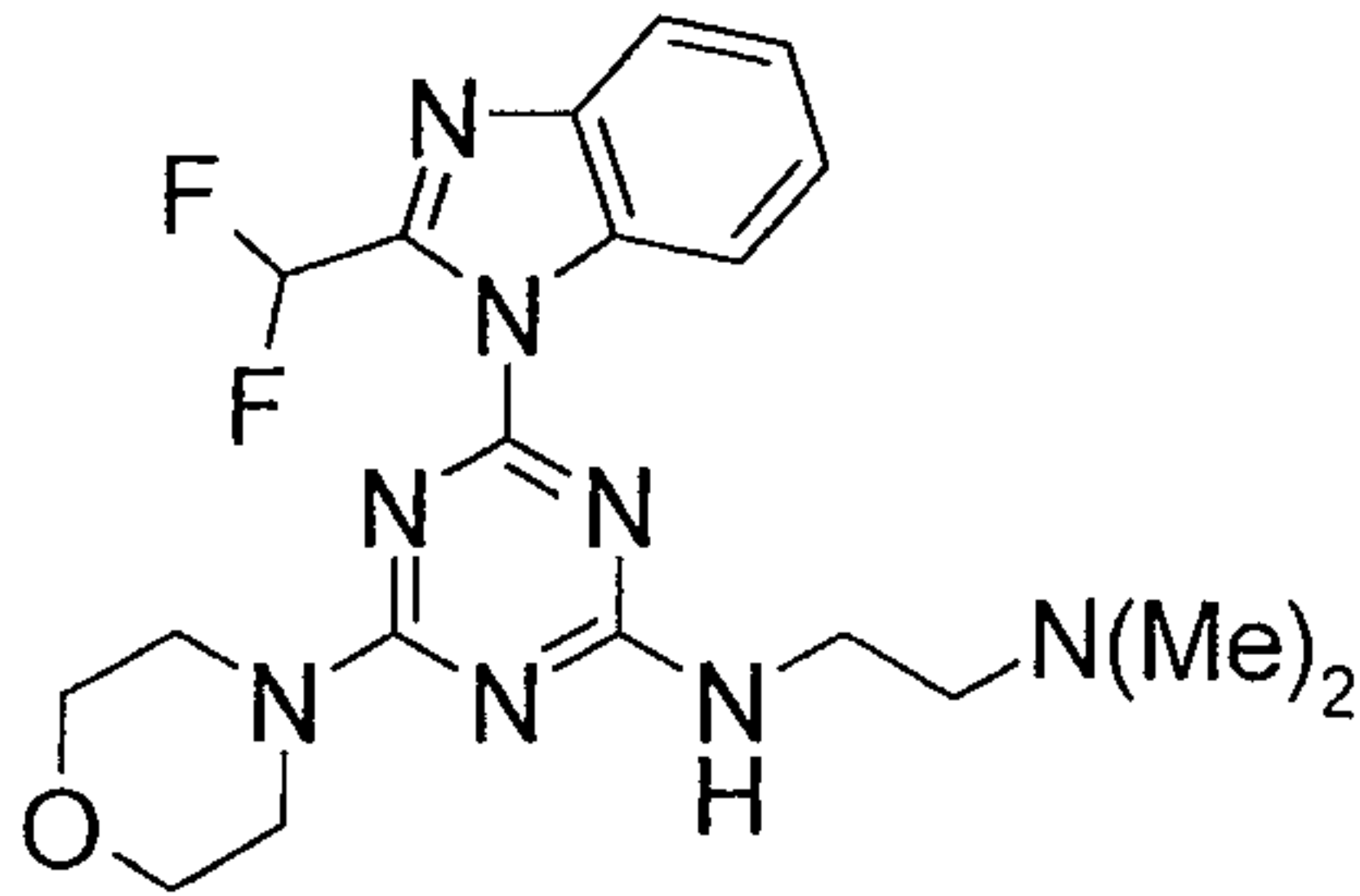
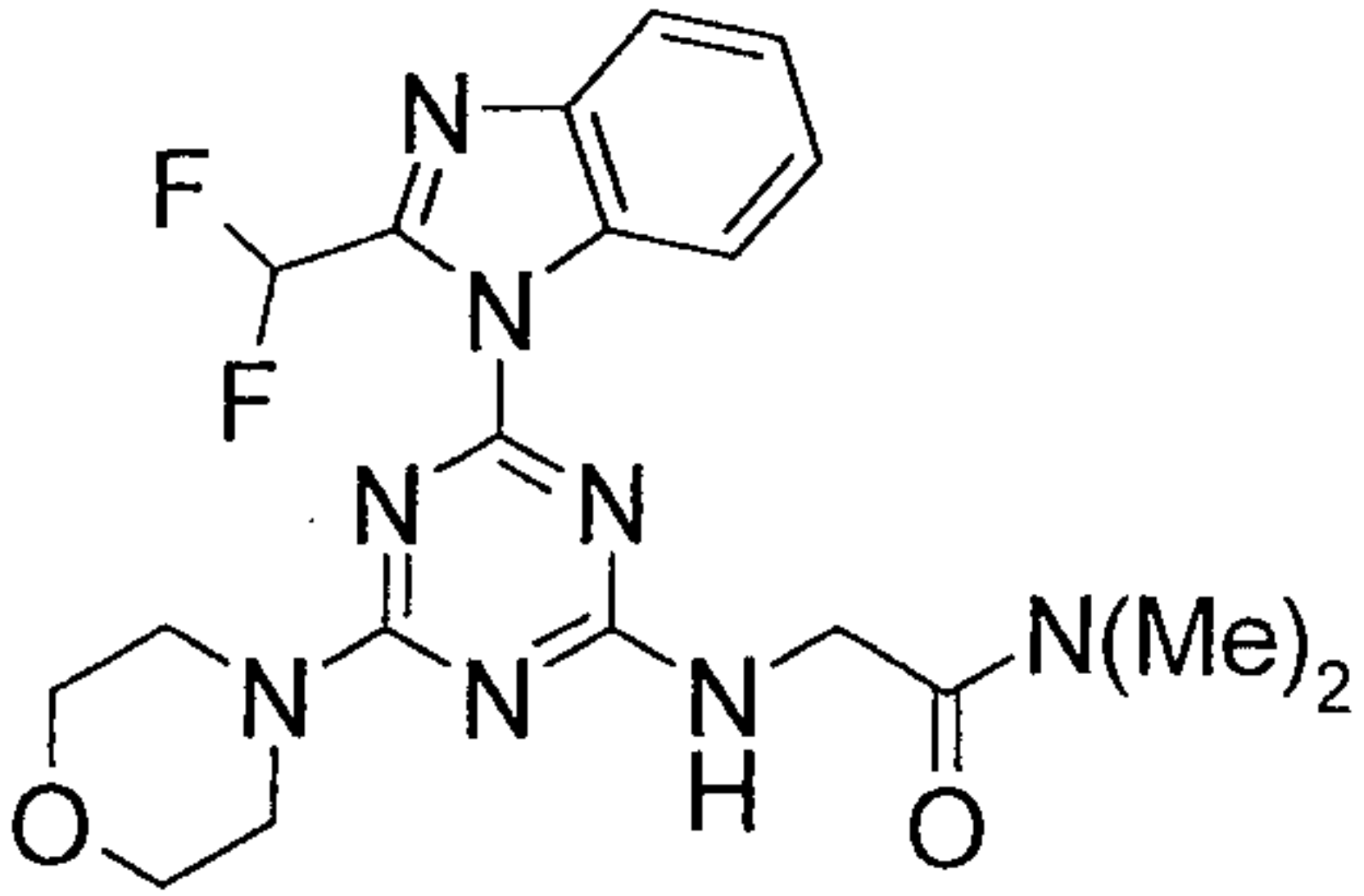
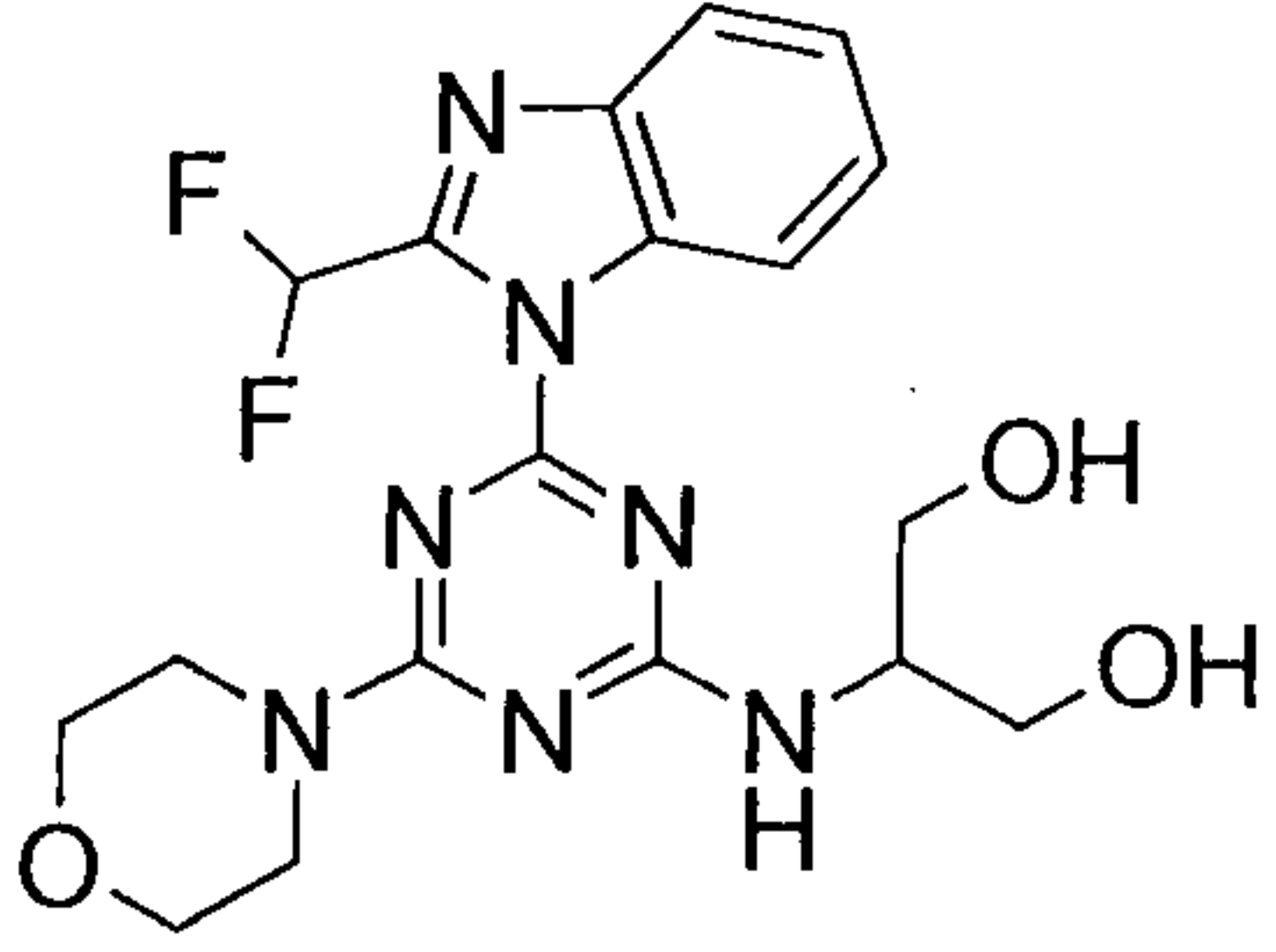
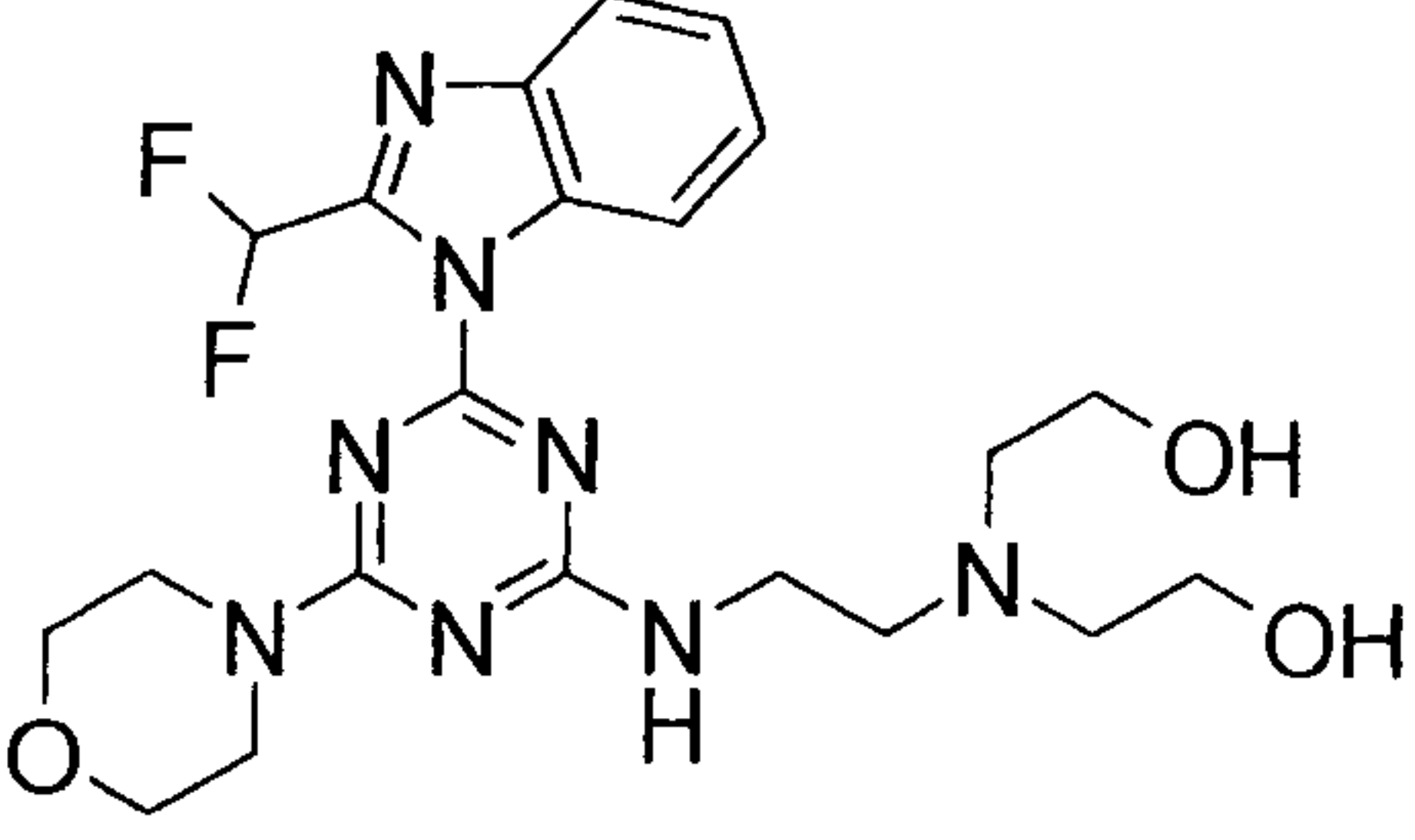
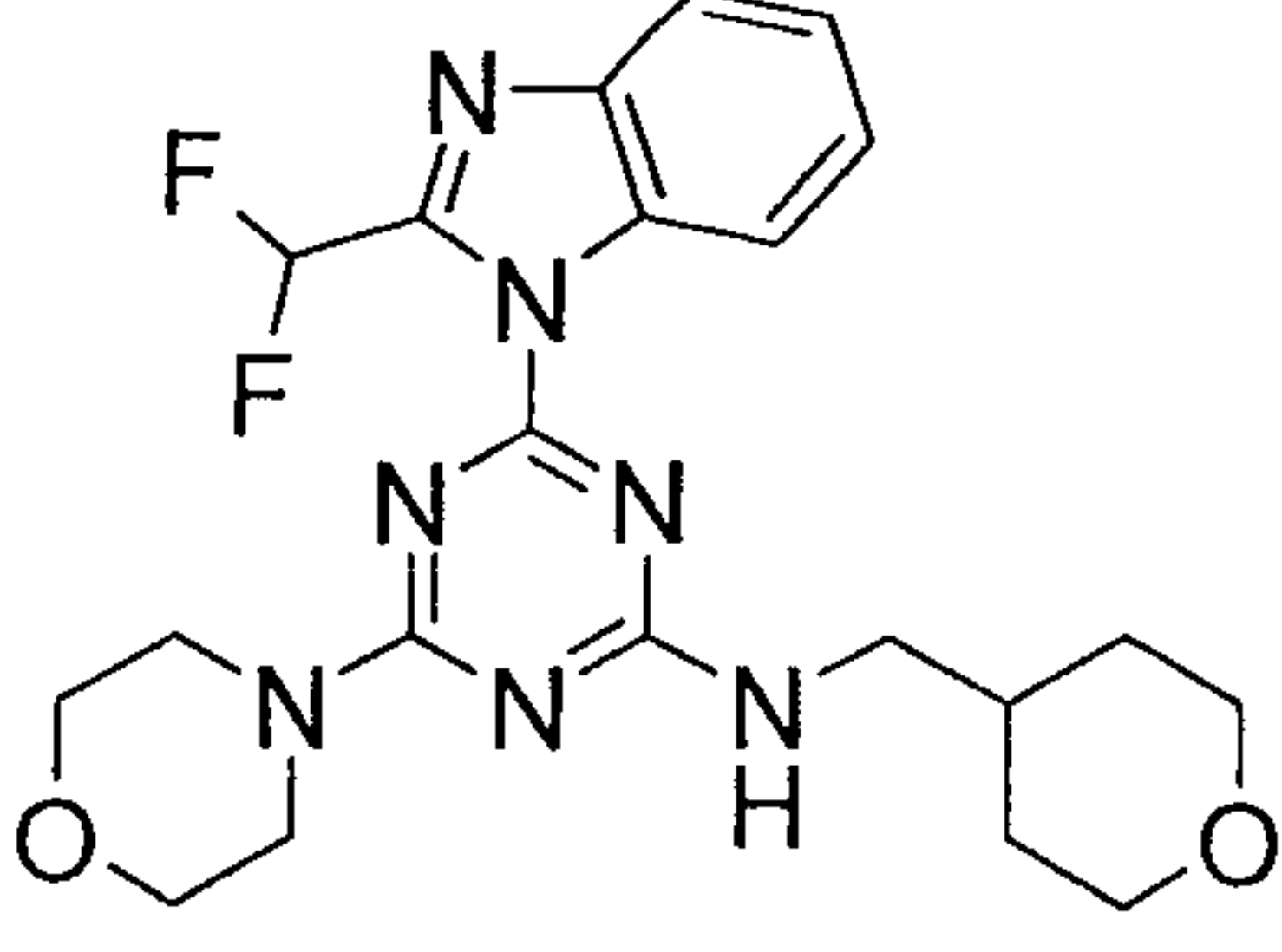
[0319]

[Table 163]

Ex	Str	ESI+	RT
A6		459	2.33
A7		521	2.61
A8		392	2.58
A9		406	2.67
A10		406	2.87

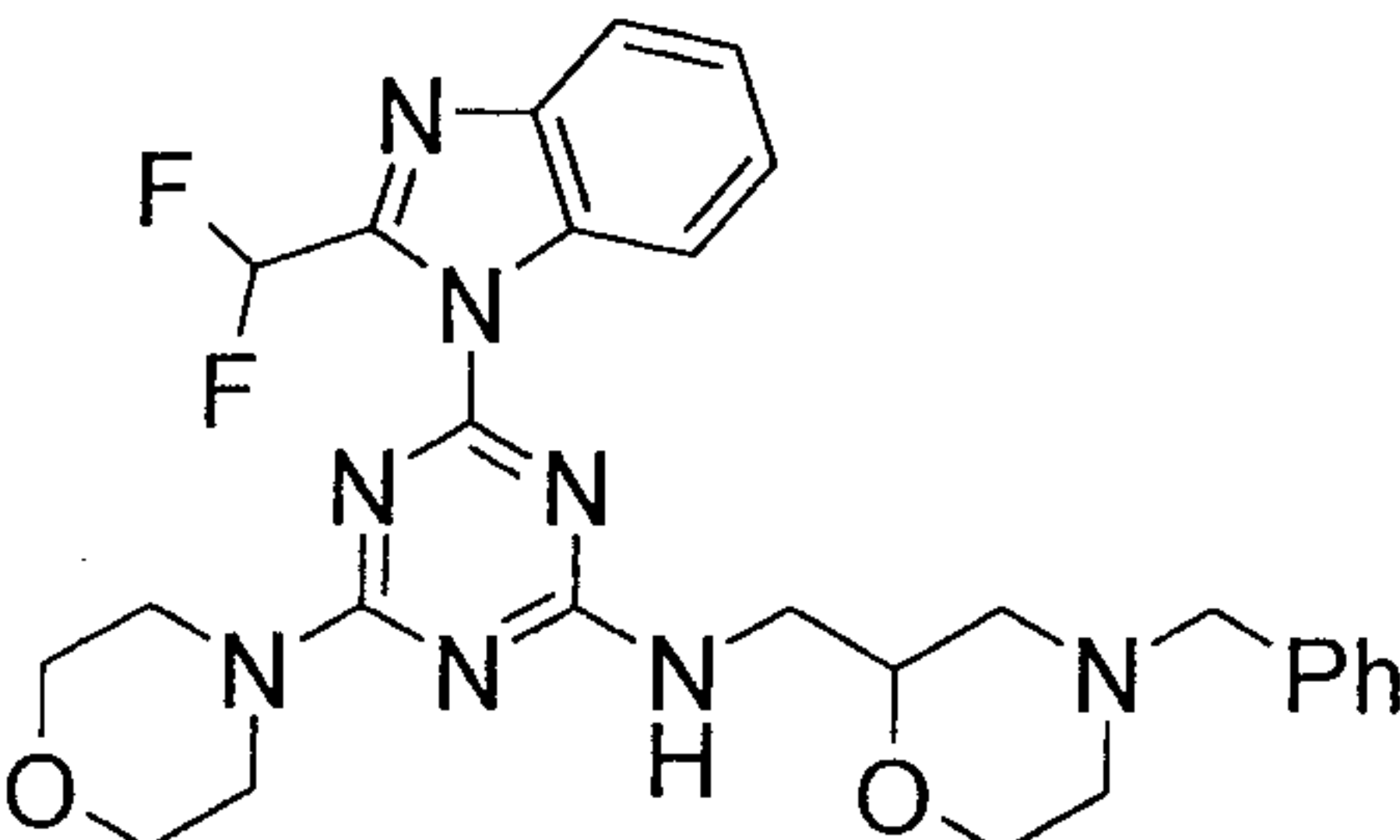
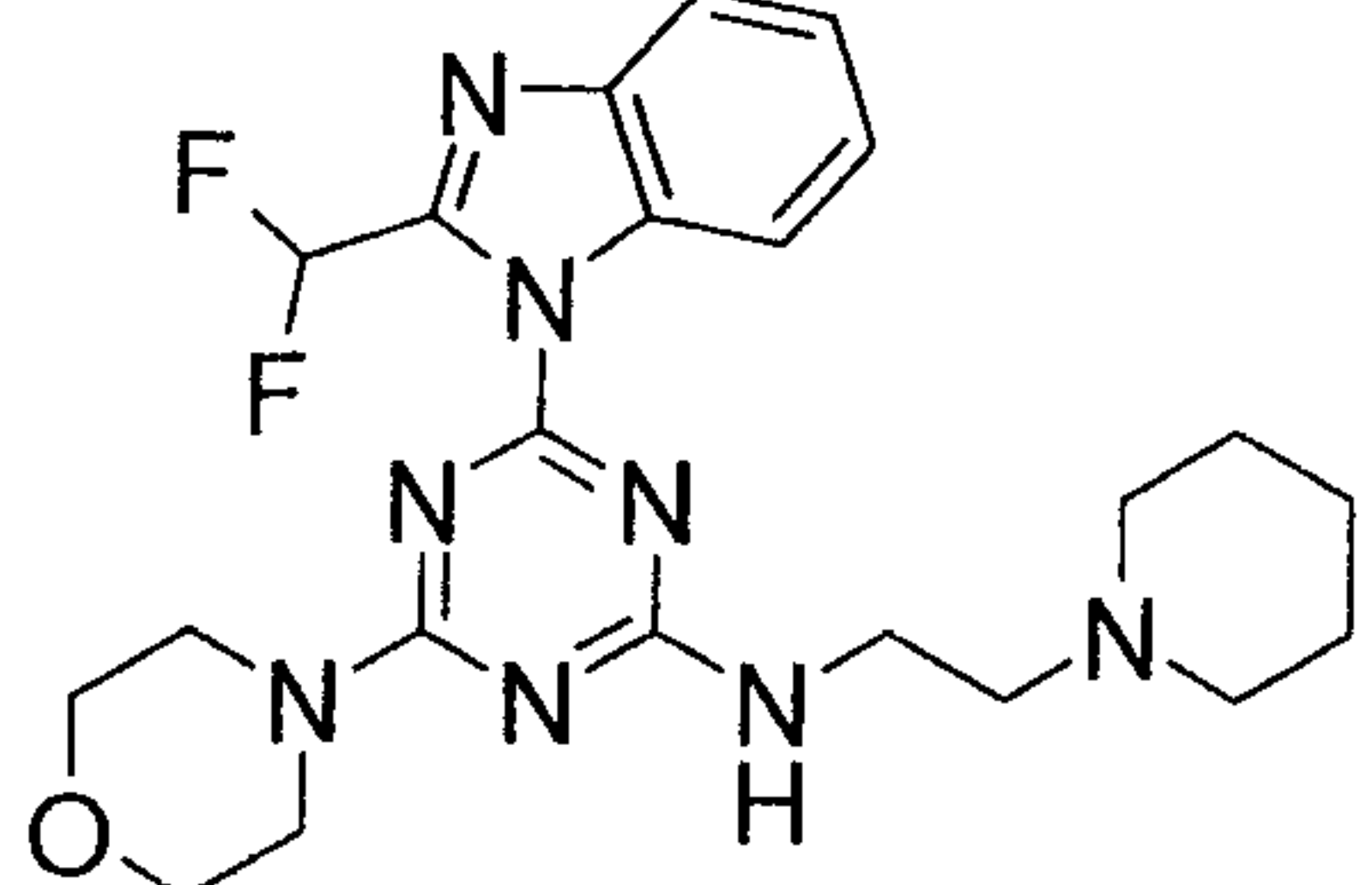
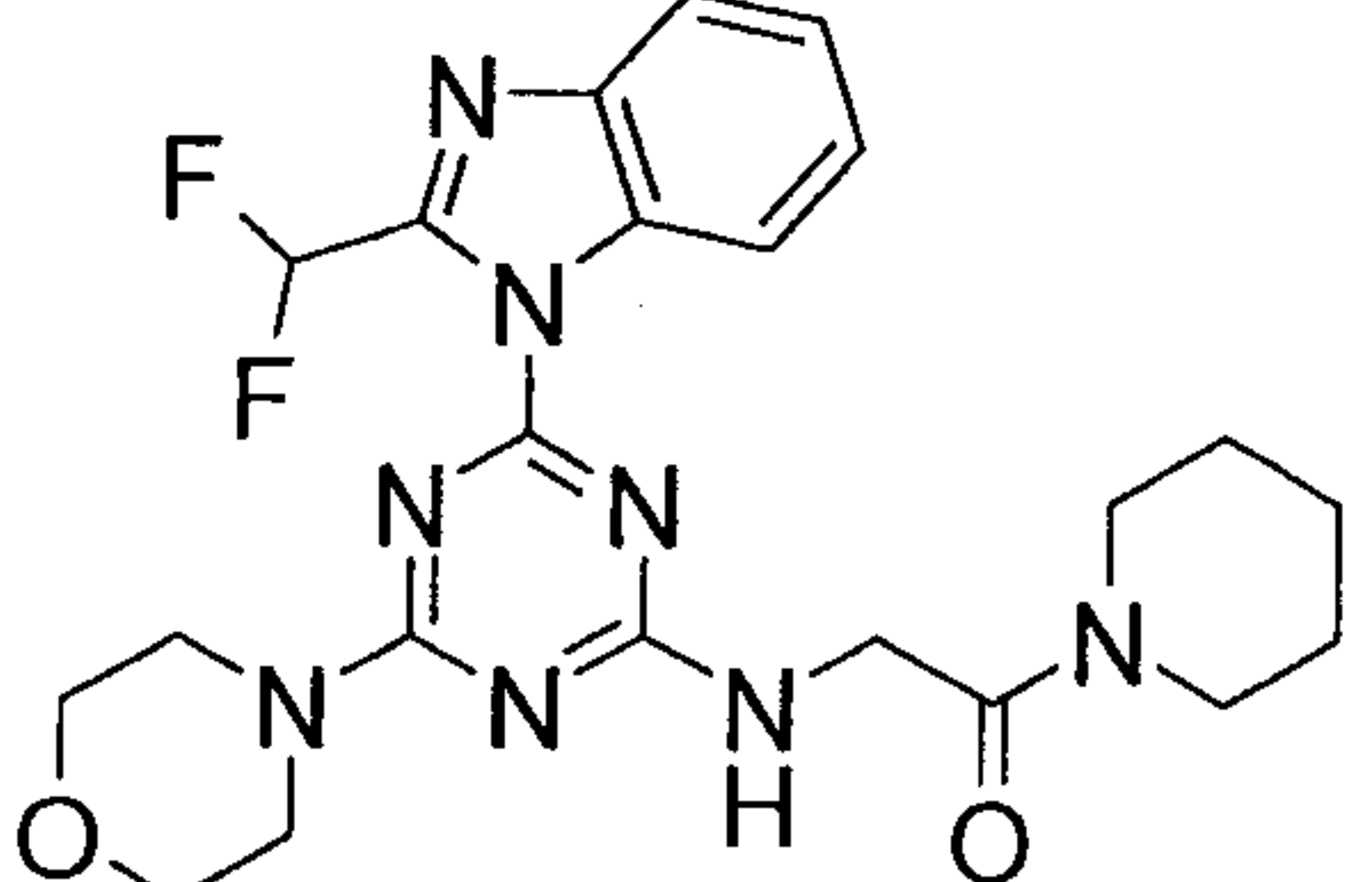
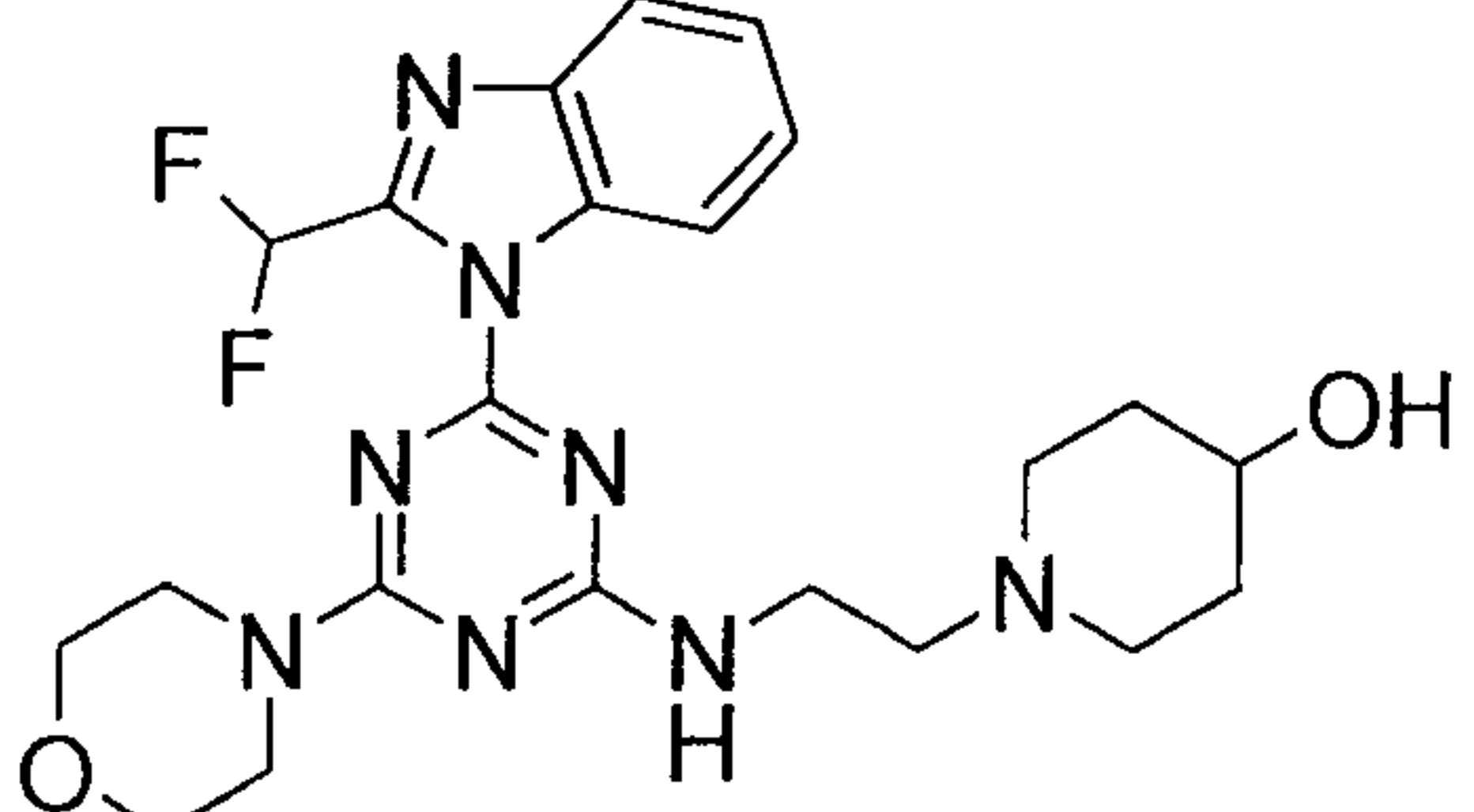
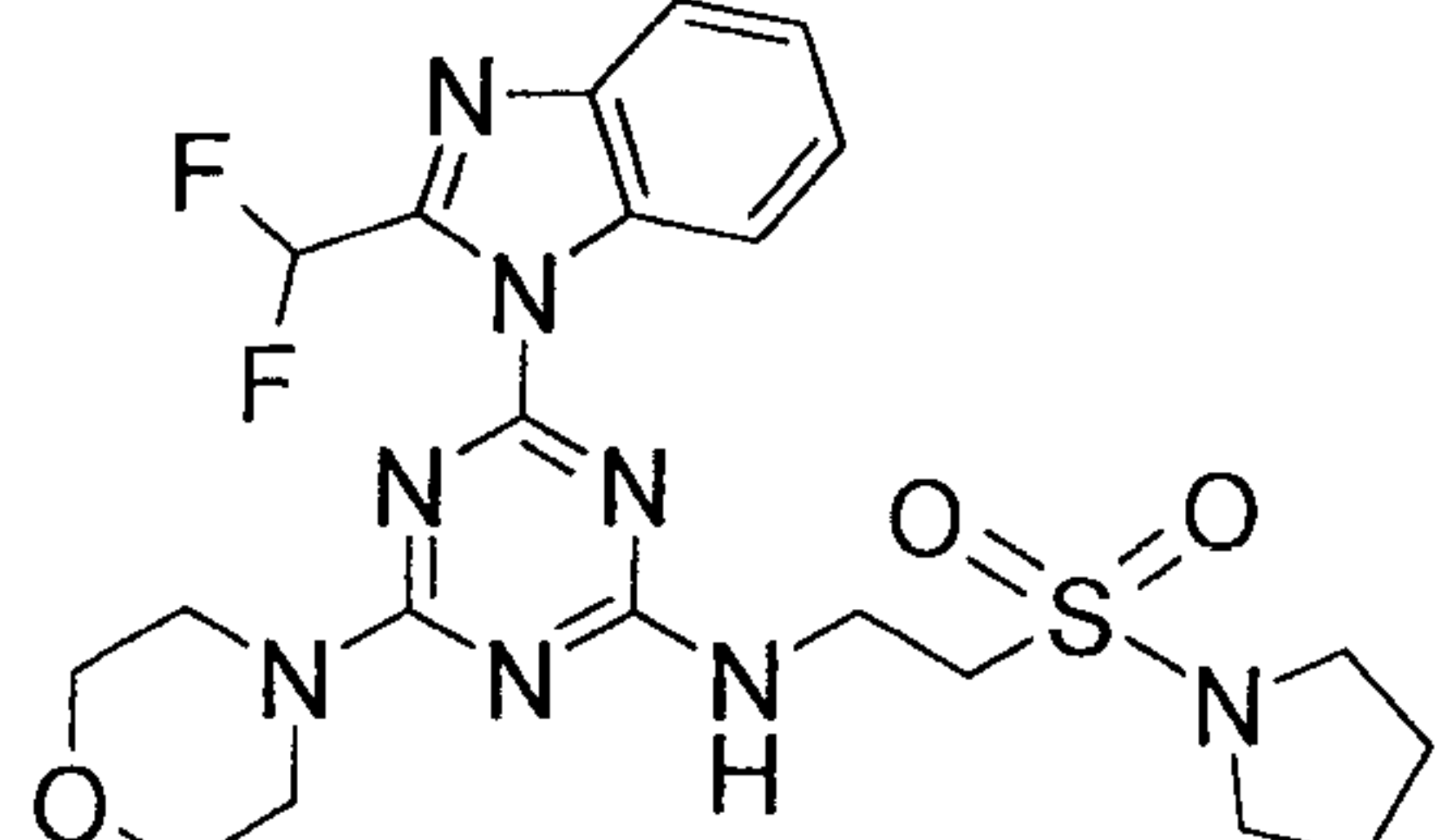
[0320]

[Table 164]

Ex	Str	ESI+	RT
A11		419	2.1
A12		433	2.59
A13		422	2.37
A14		479	2.06
A15		446	3.03

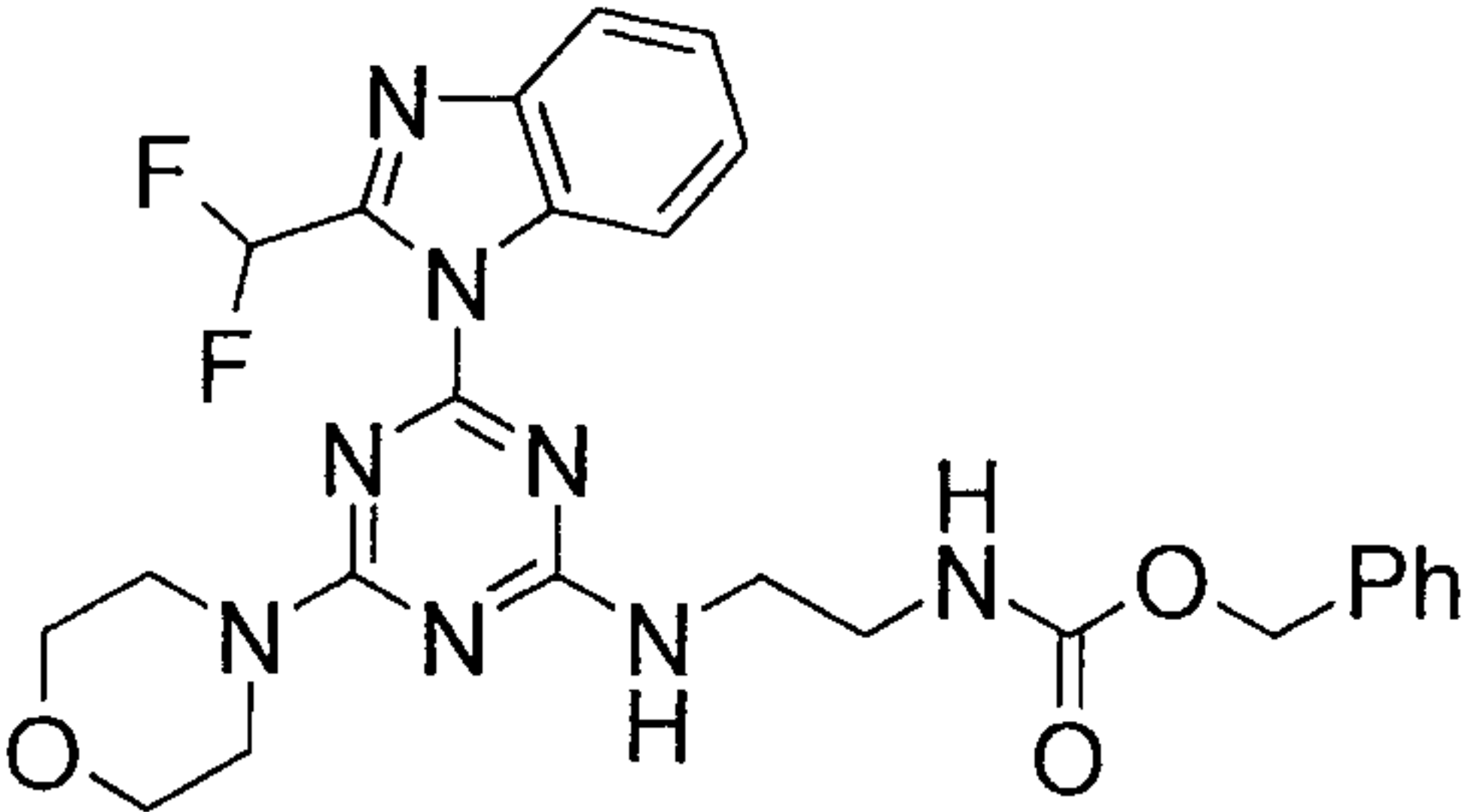
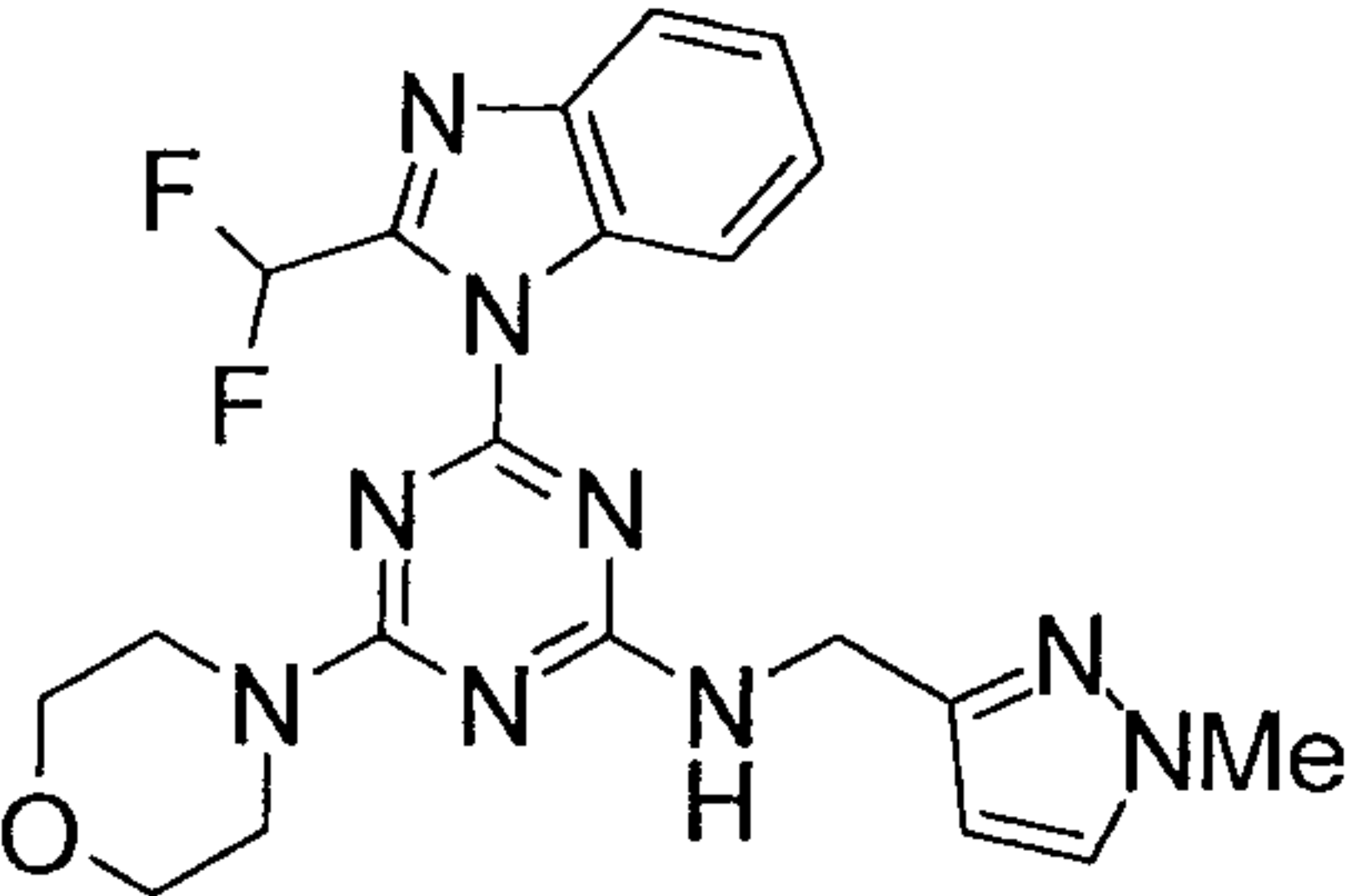
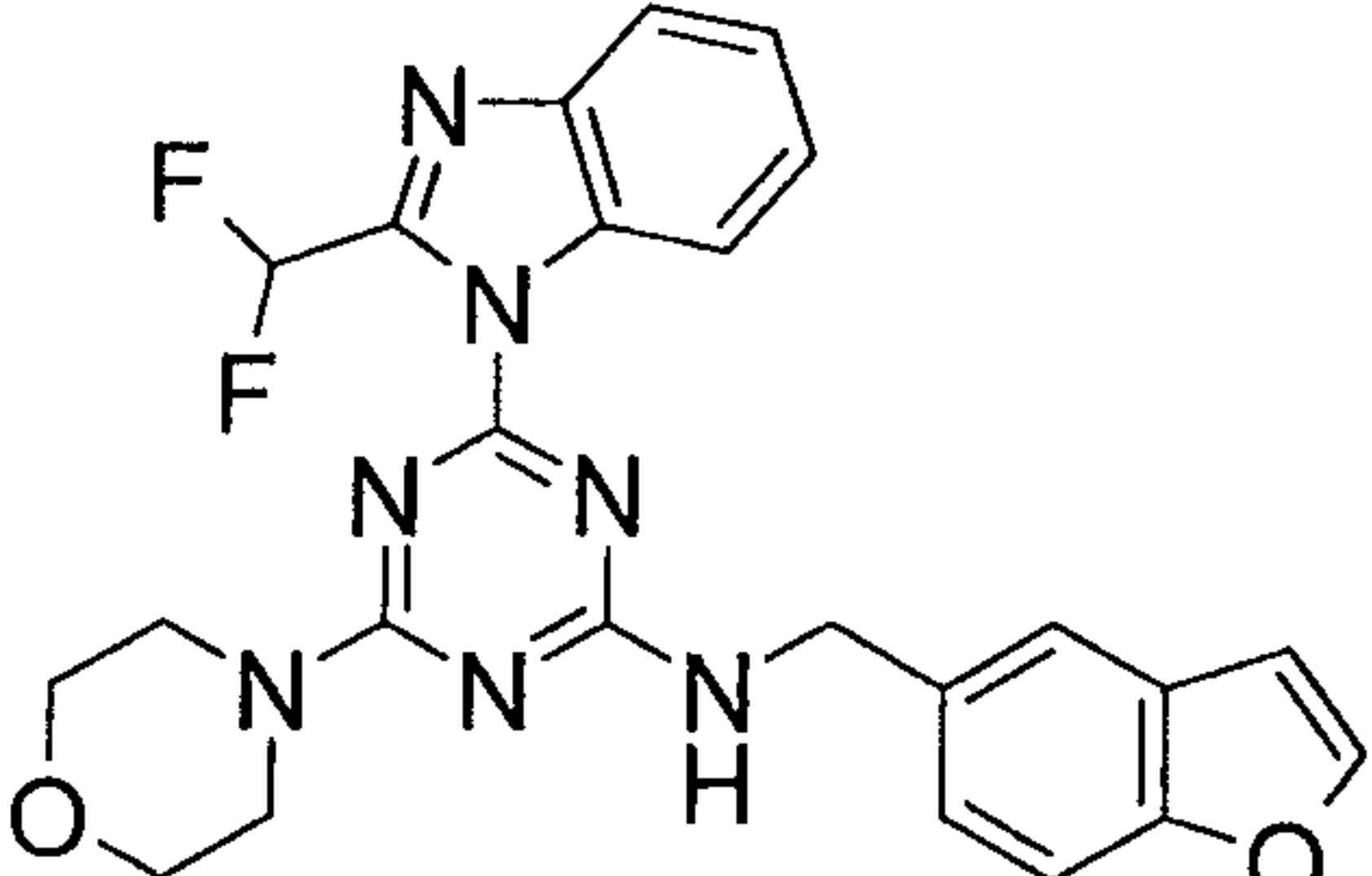
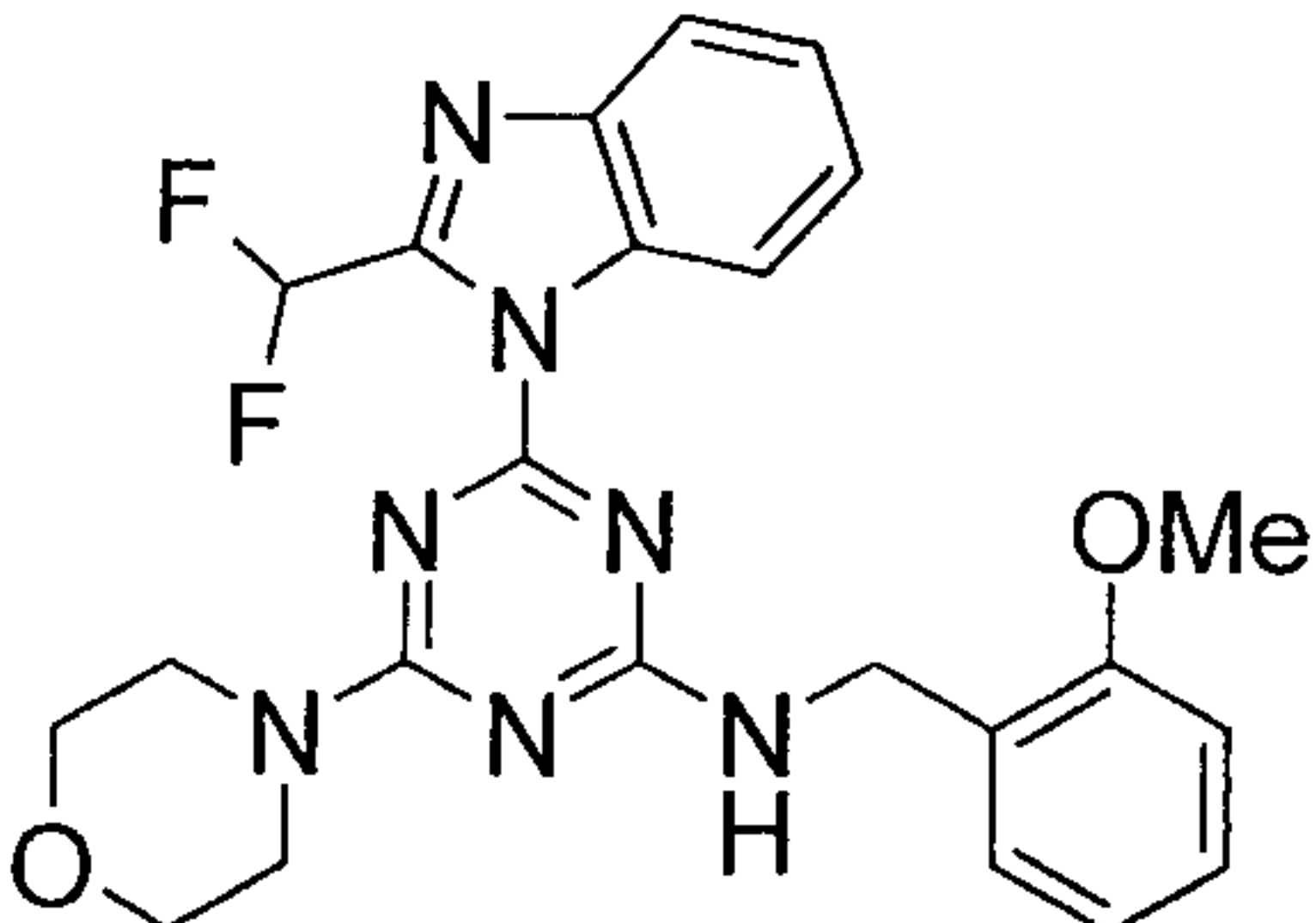
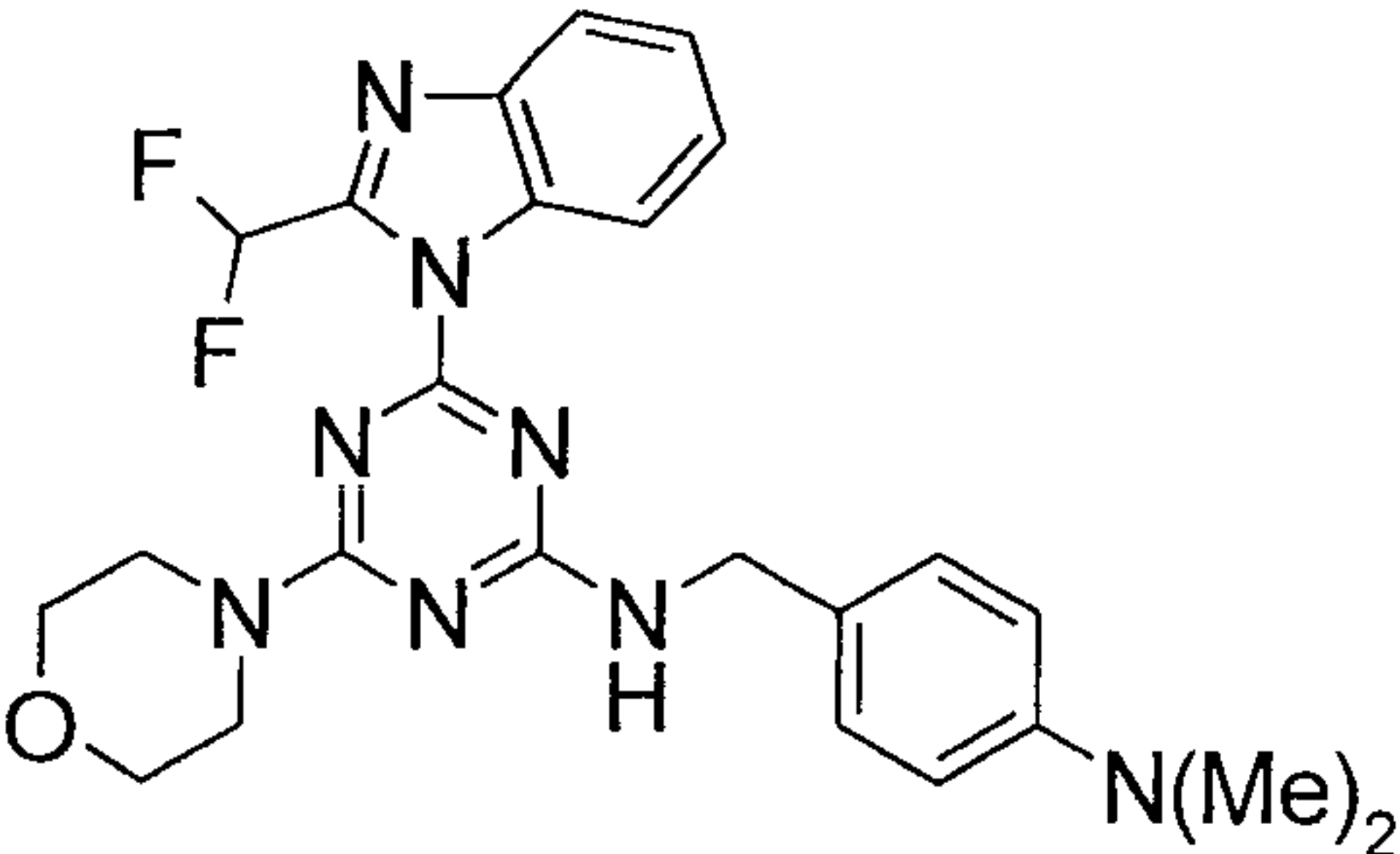
[0321]

[Table 165]

Ex	Str	ESI+	RT
A16		537	2.46
A17		459	2.16
A18		473	2.95
A19		475	2.09
A20		509	2.89

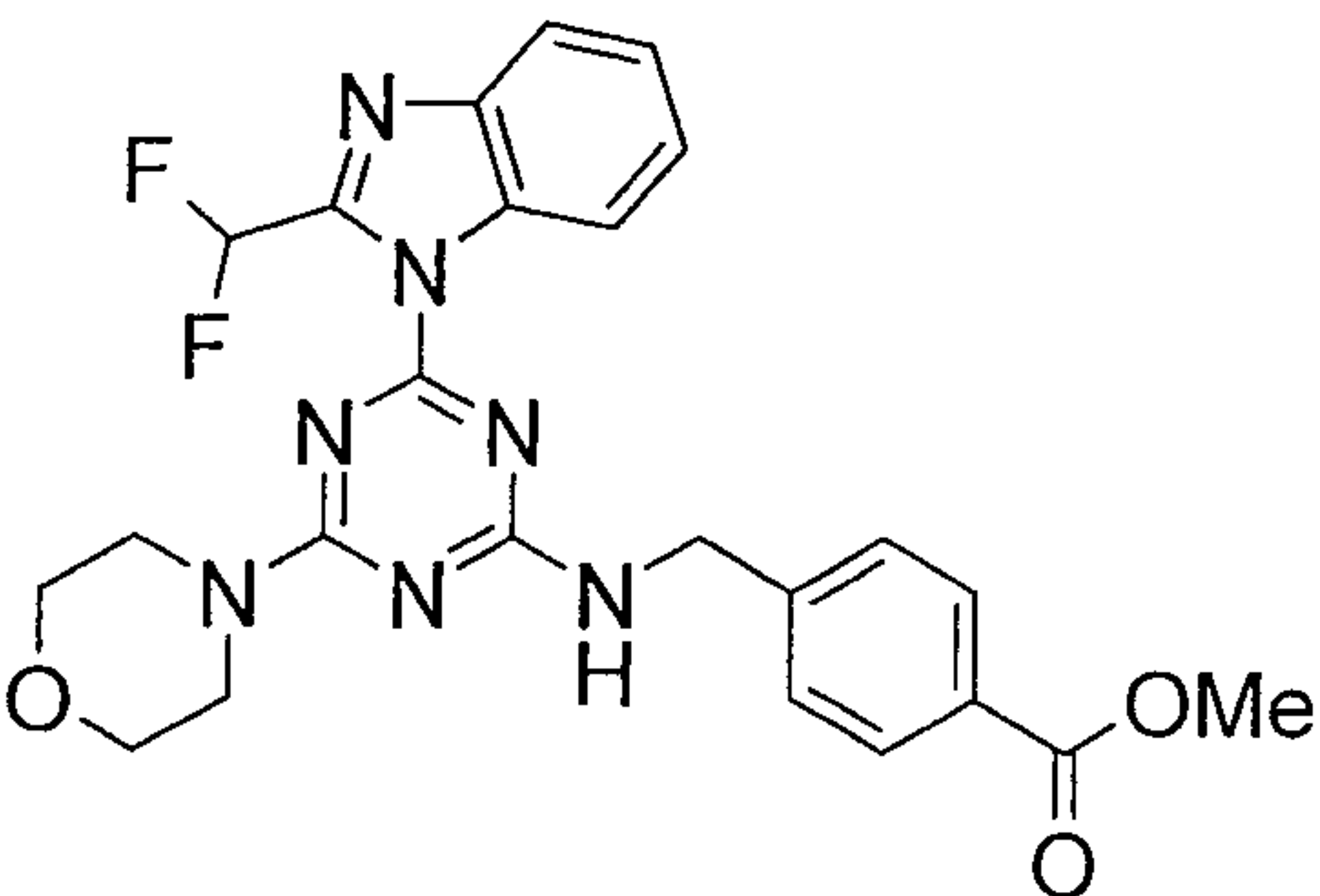
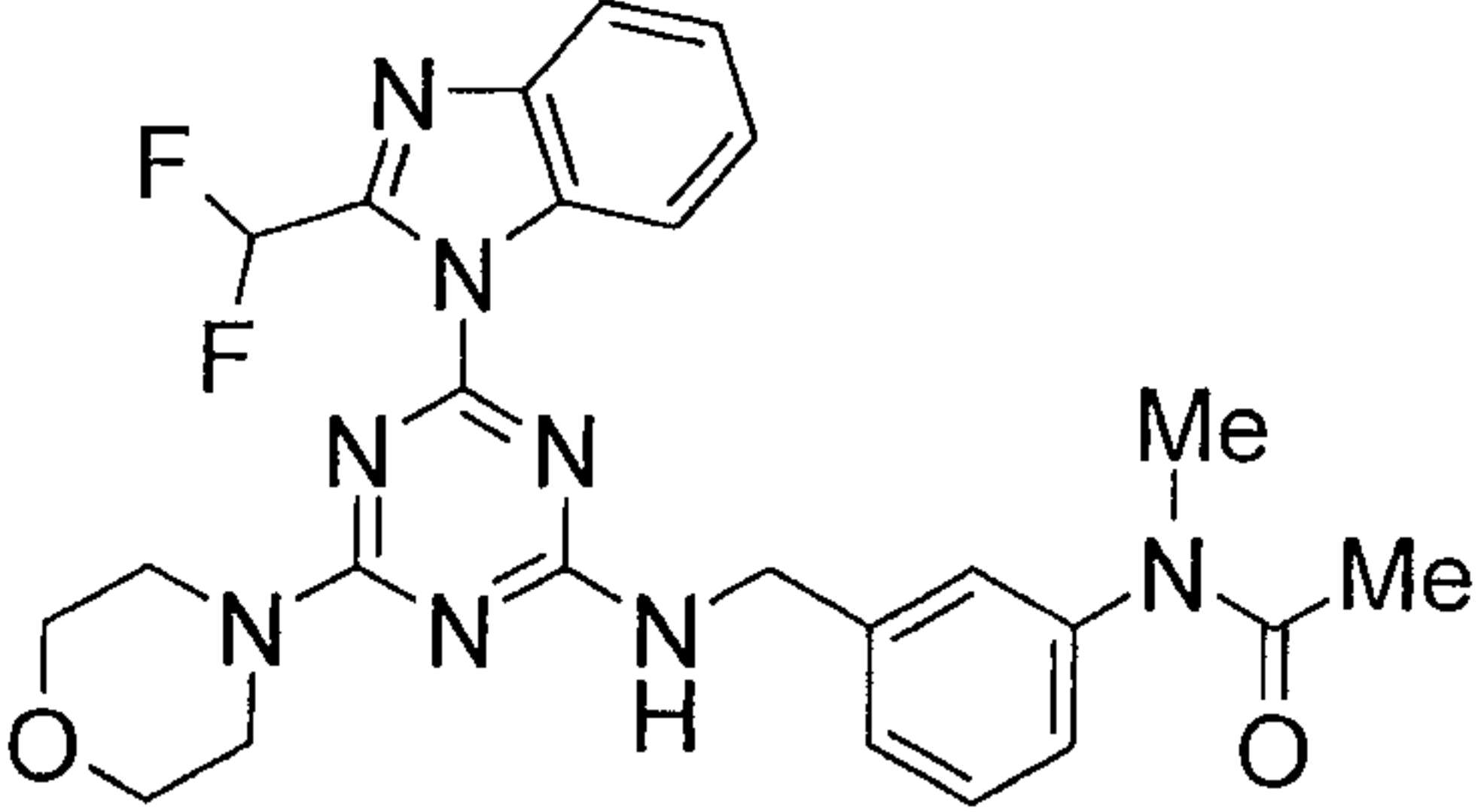
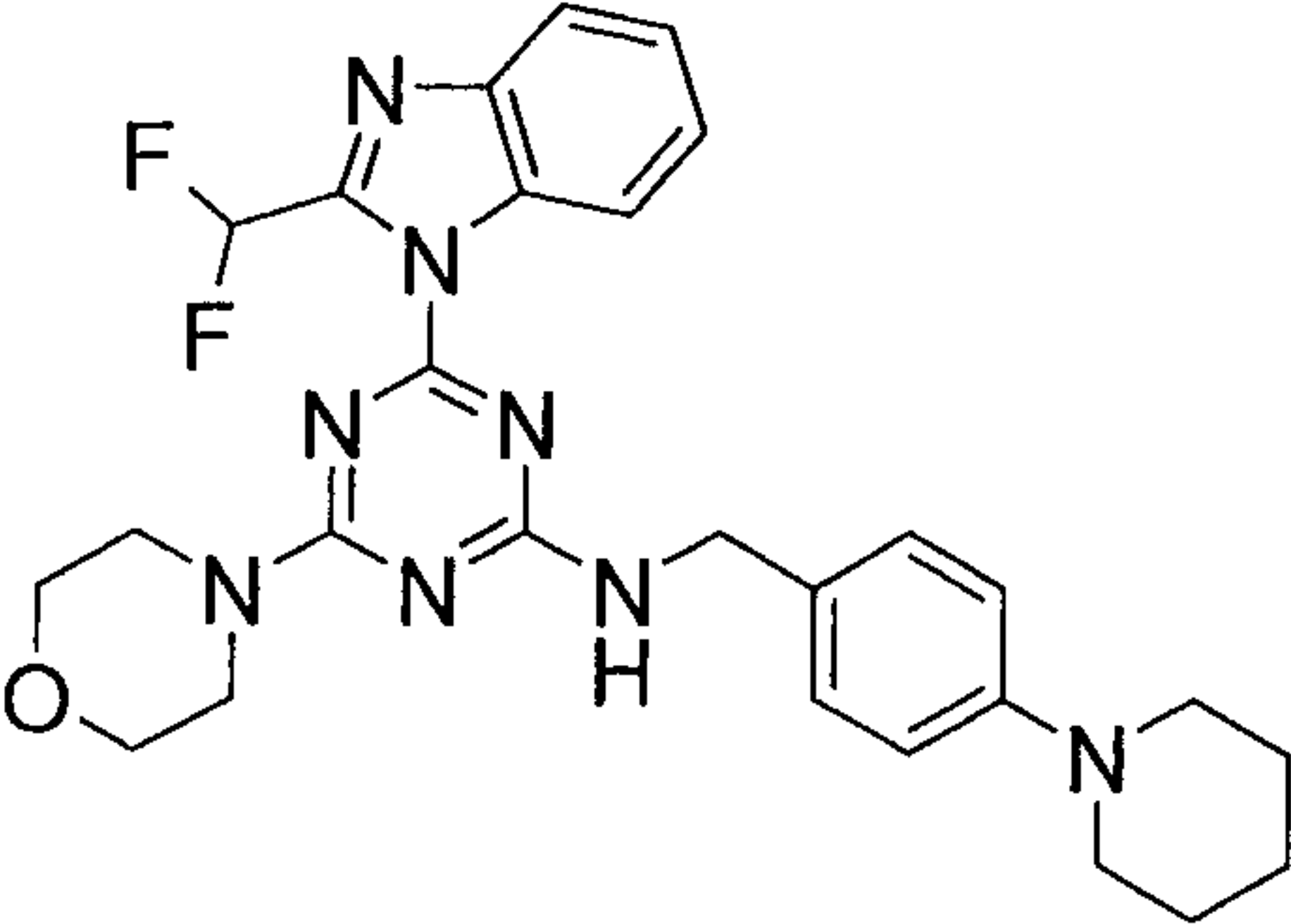
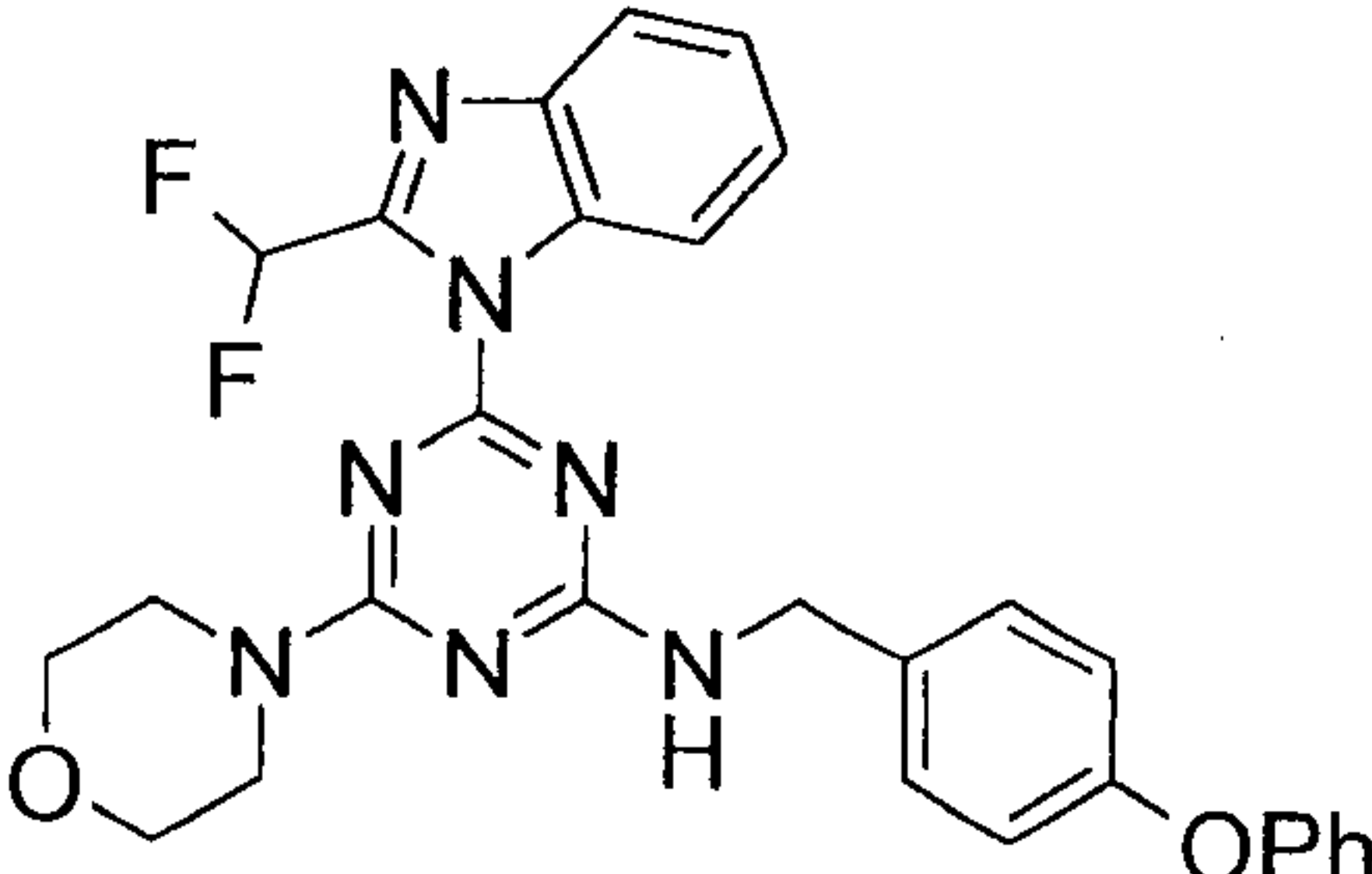
[0322]

[Table 166]

Ex	Str	ESI+	RT
A21		525	3.18
A22		442	2.8
A23		478	3.41
A24		468	3.39
A25		481	2.51

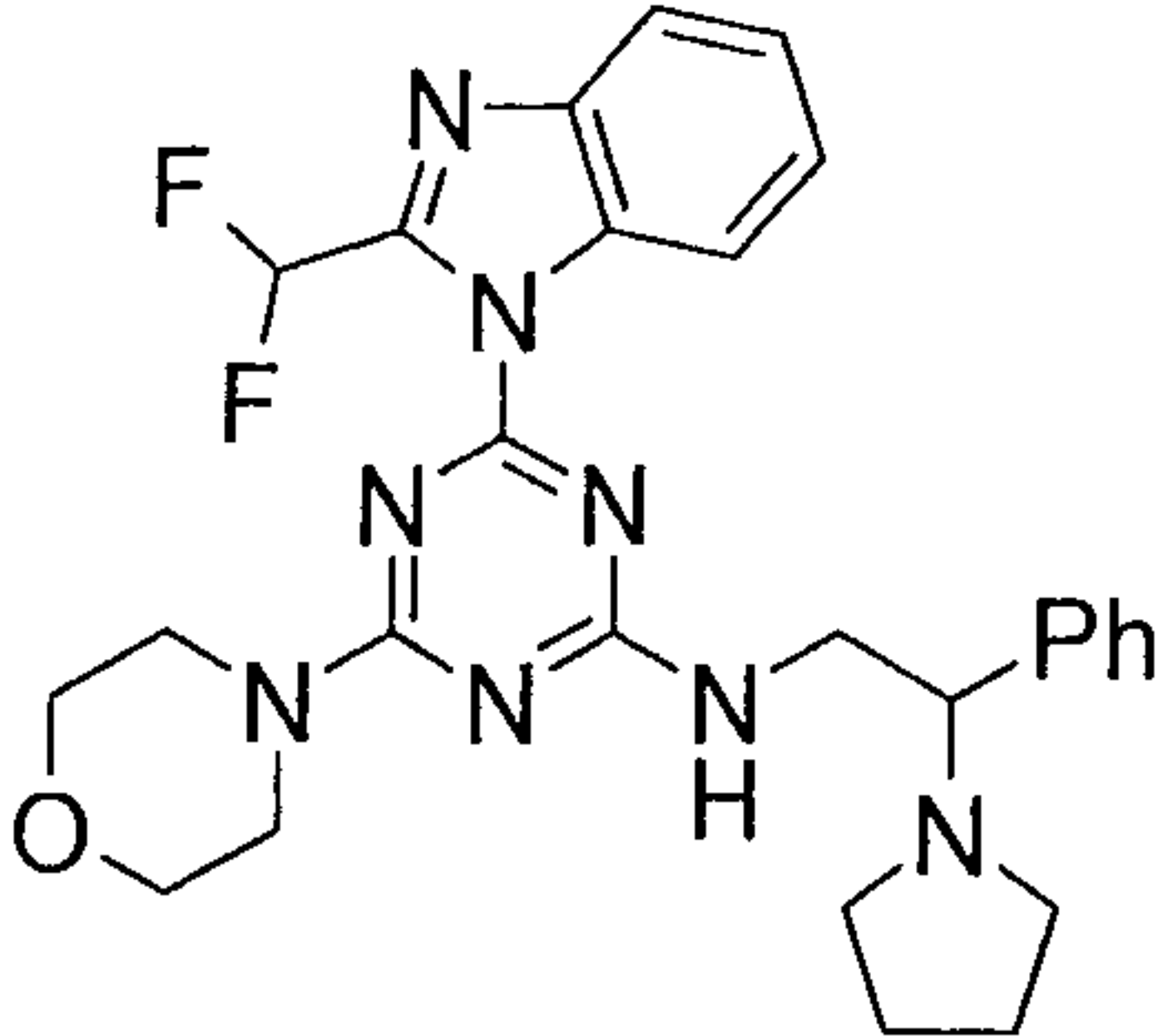
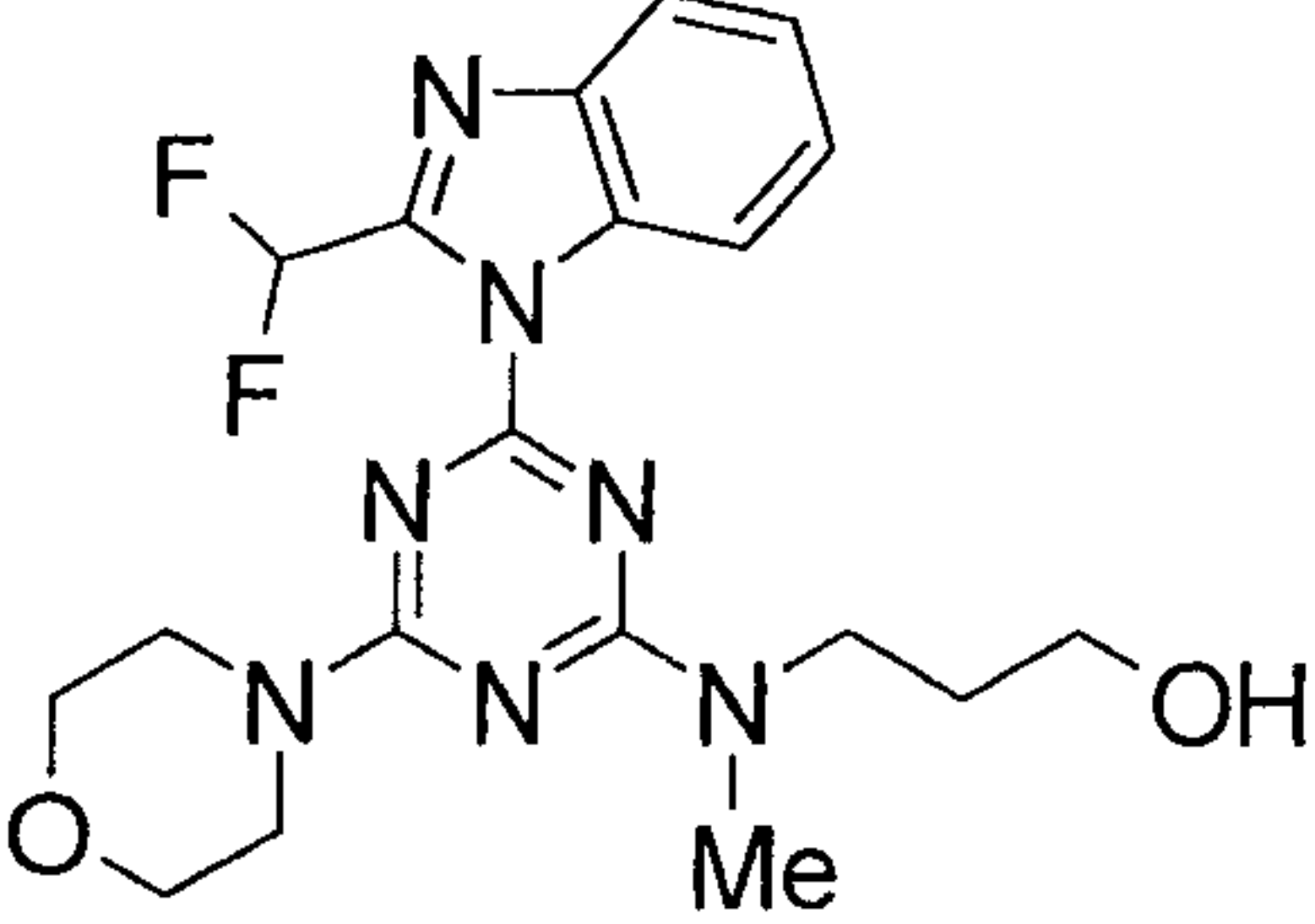
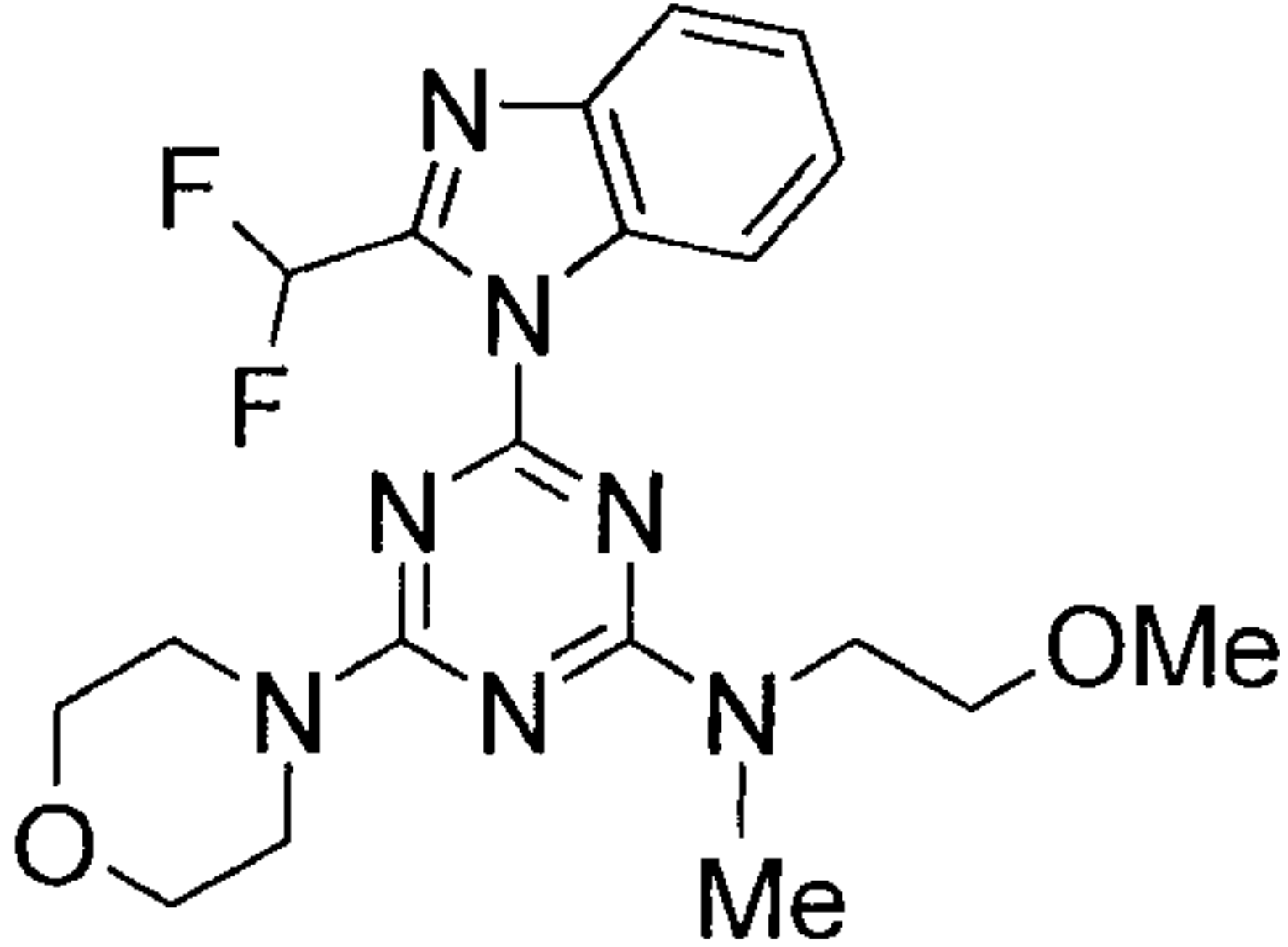
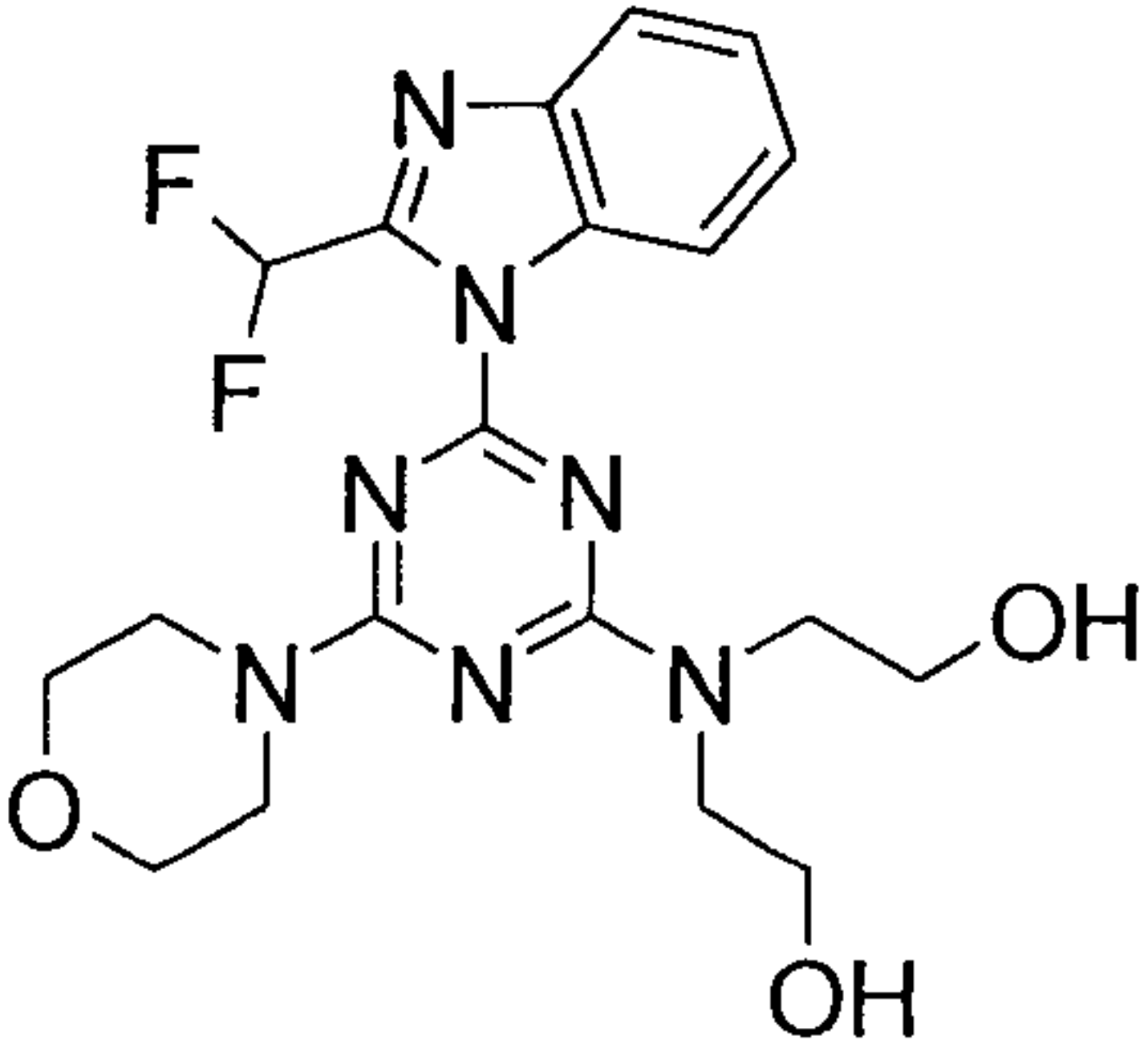
[0323]

[Table 167]

Ex	Str	ESI+	RT
A26		496	3.24
A27		509	3.01
A28		521	2.51
A29		530	3.74

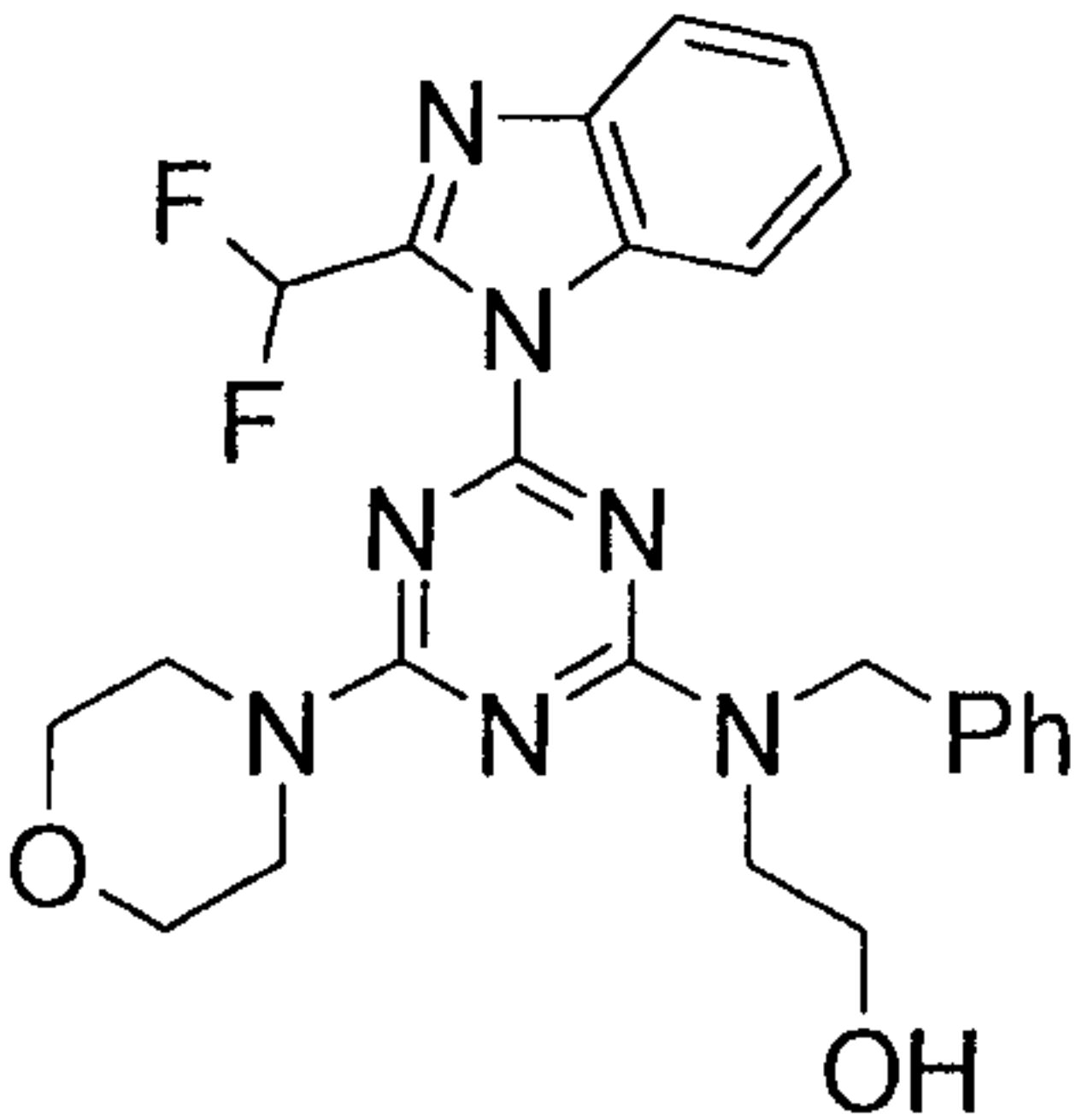
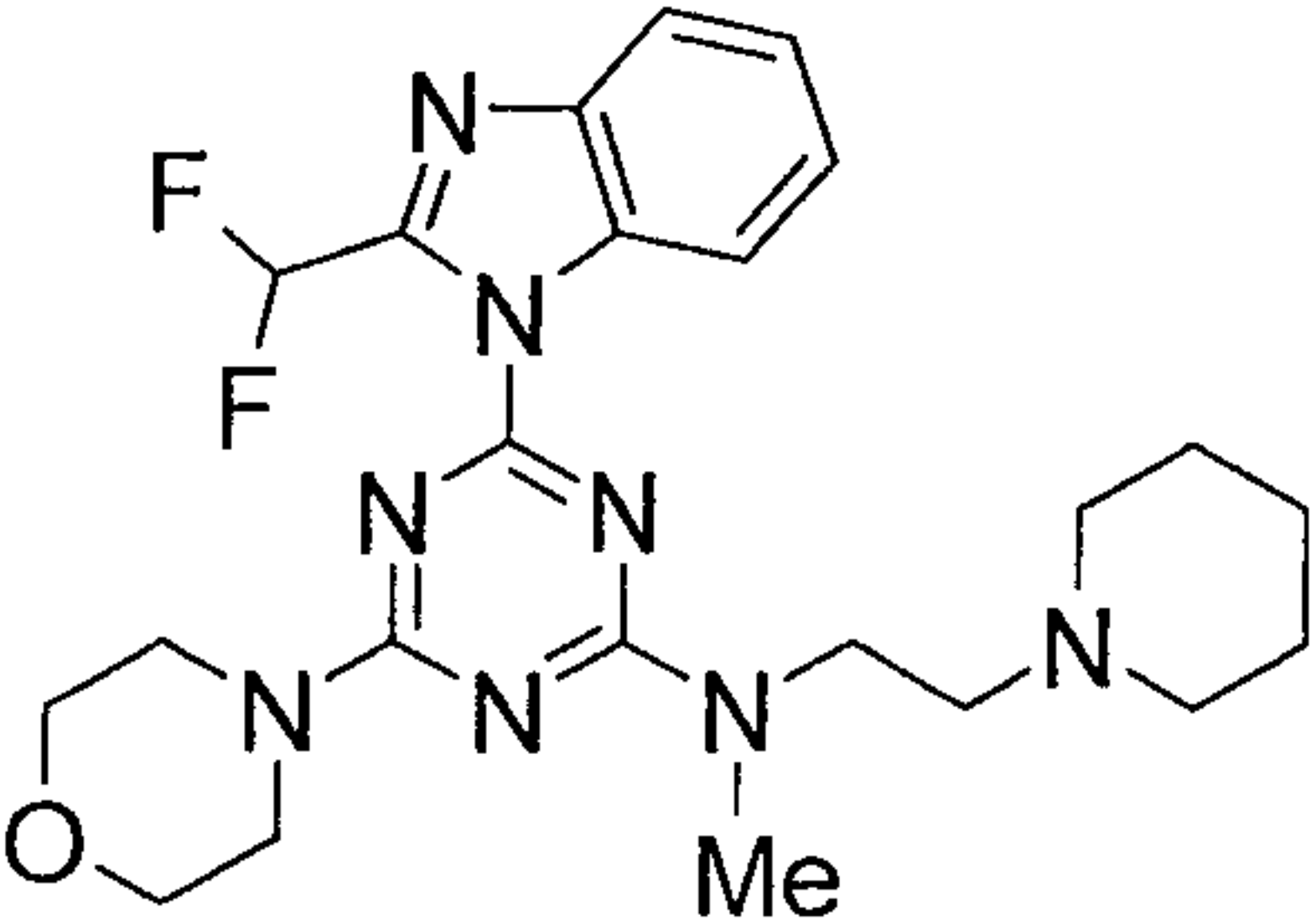
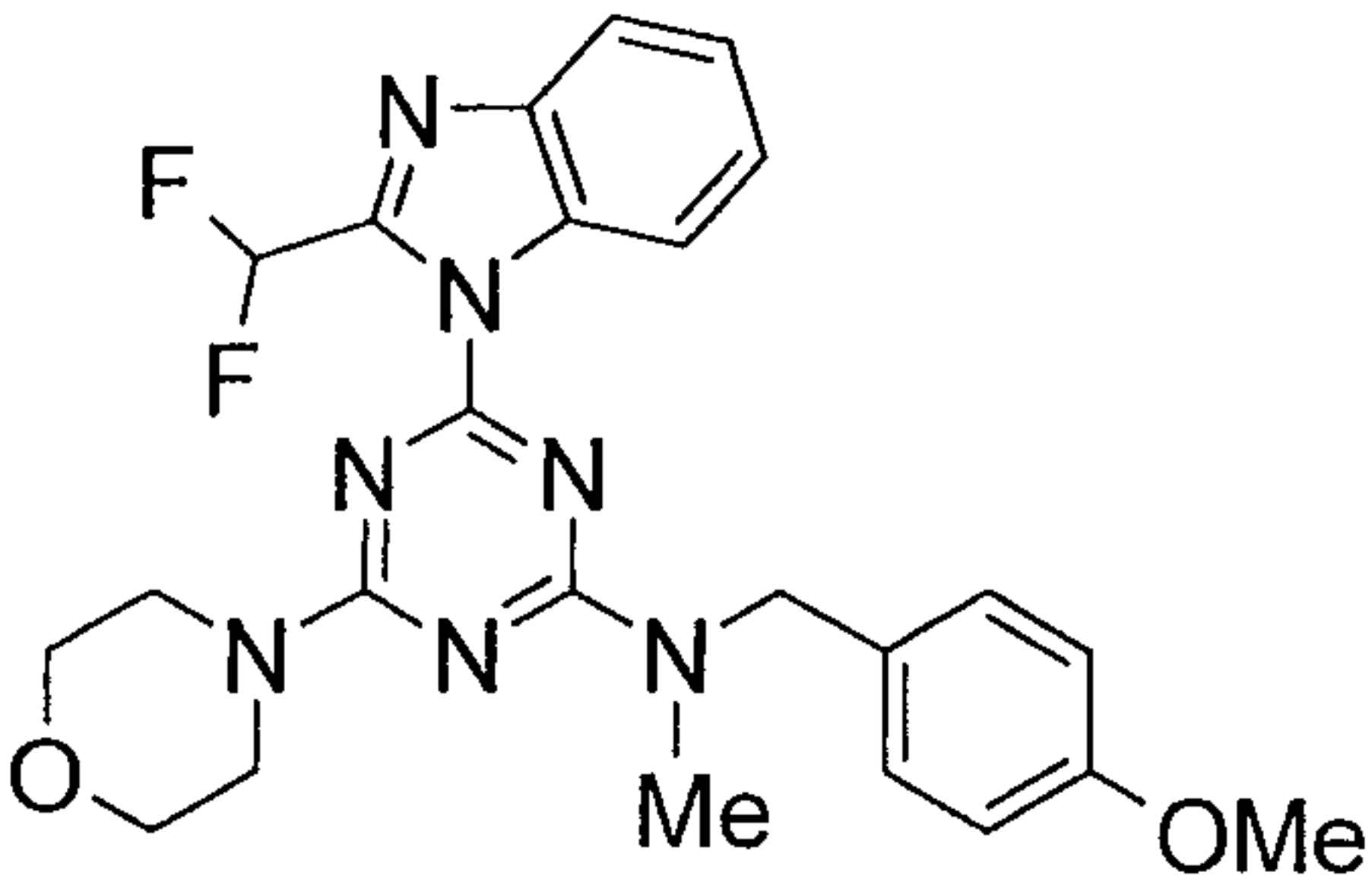
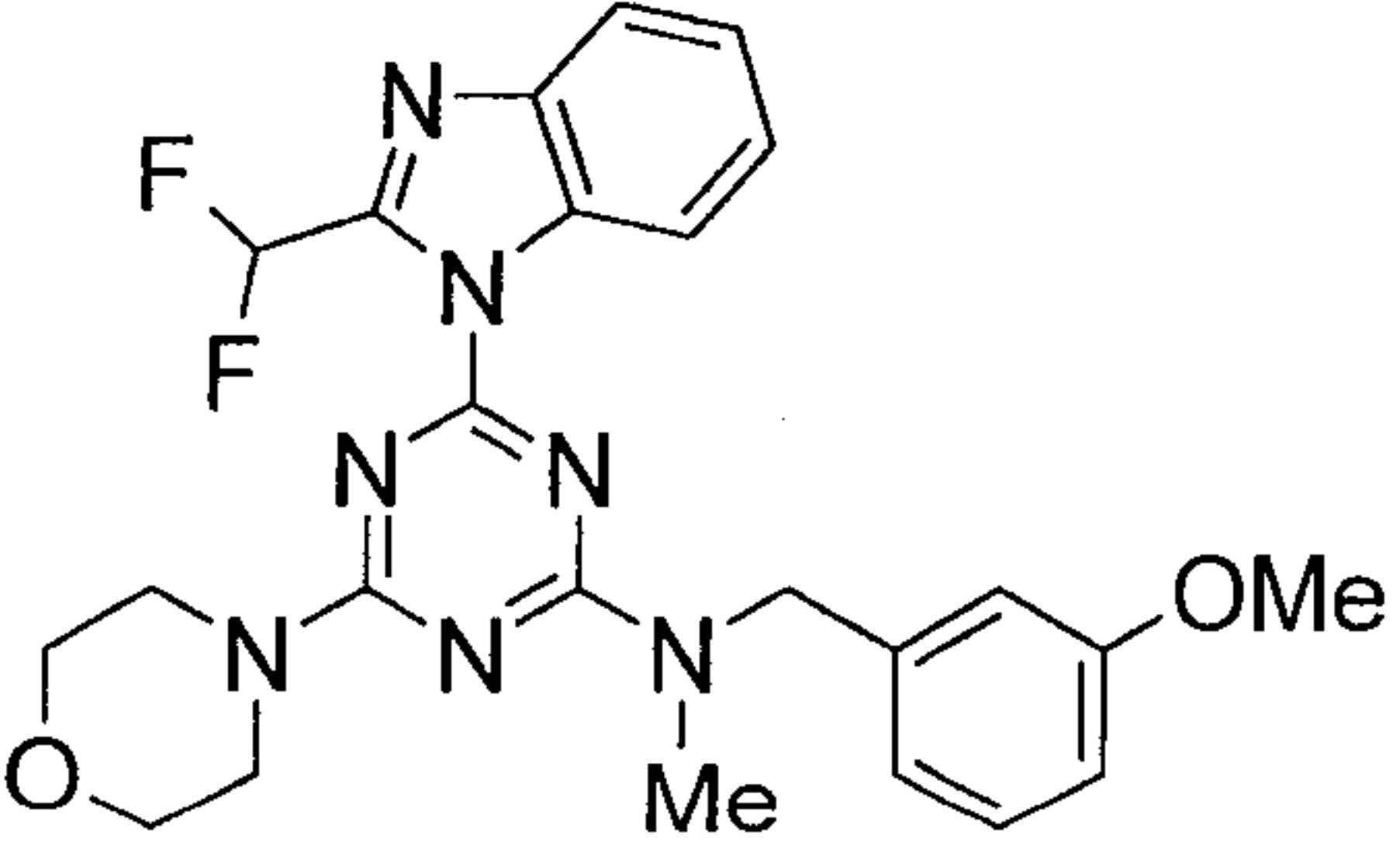
[0342]

[Table 168]

Ex	Str	ESI+	RT
A30		521	2.51
A31		420	2.92
A32		420	3.17
A33		436	2.58

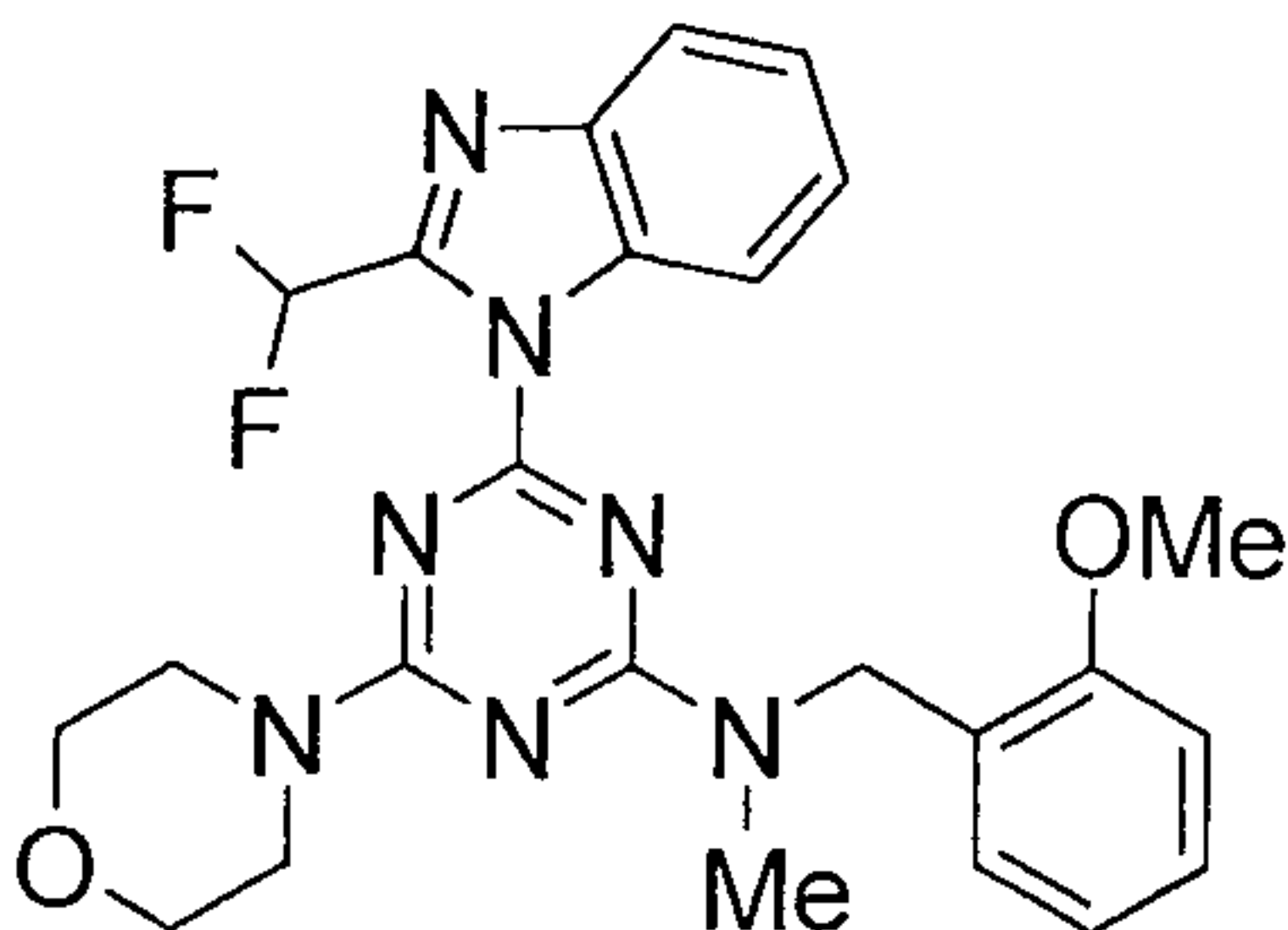
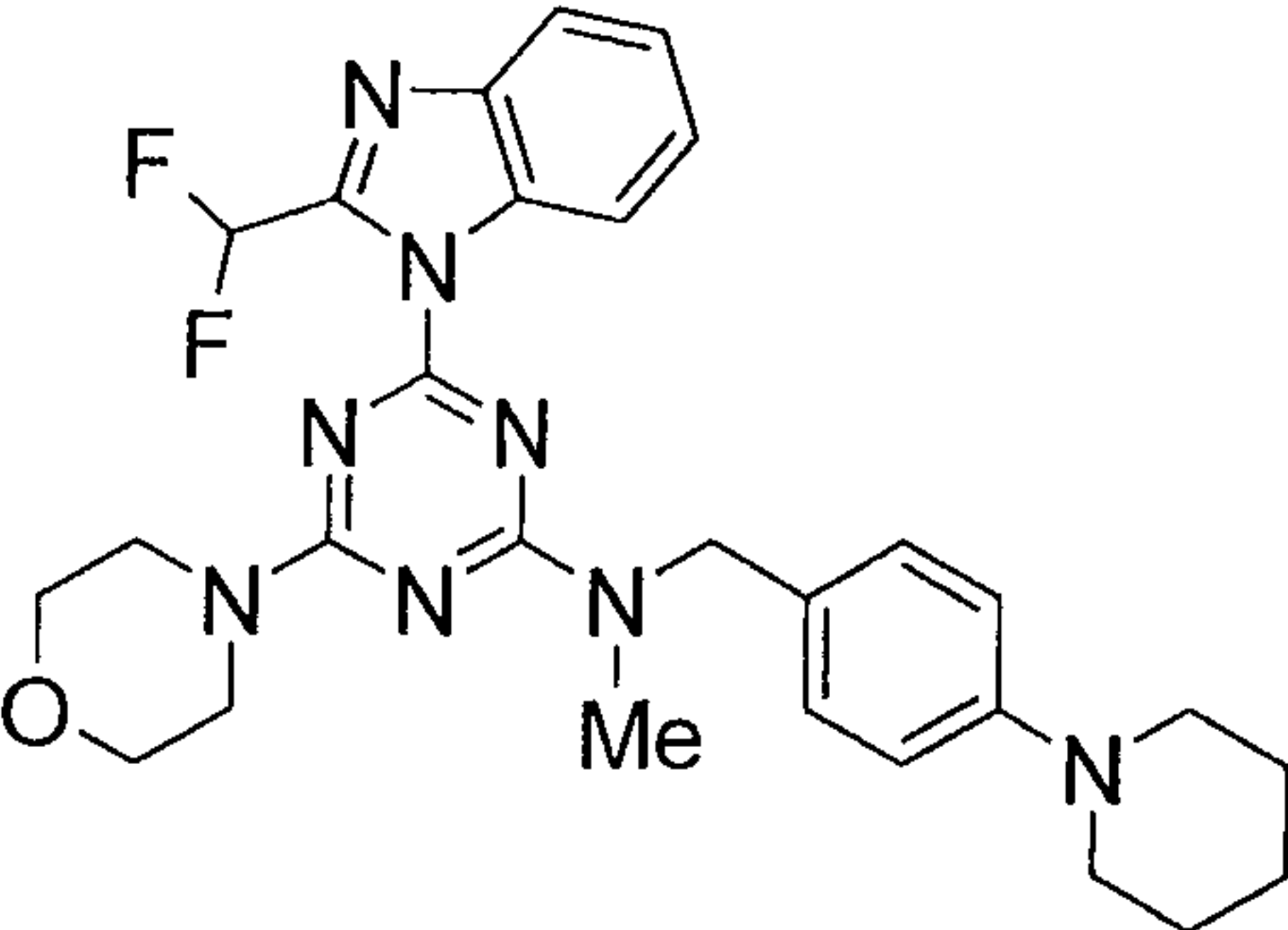
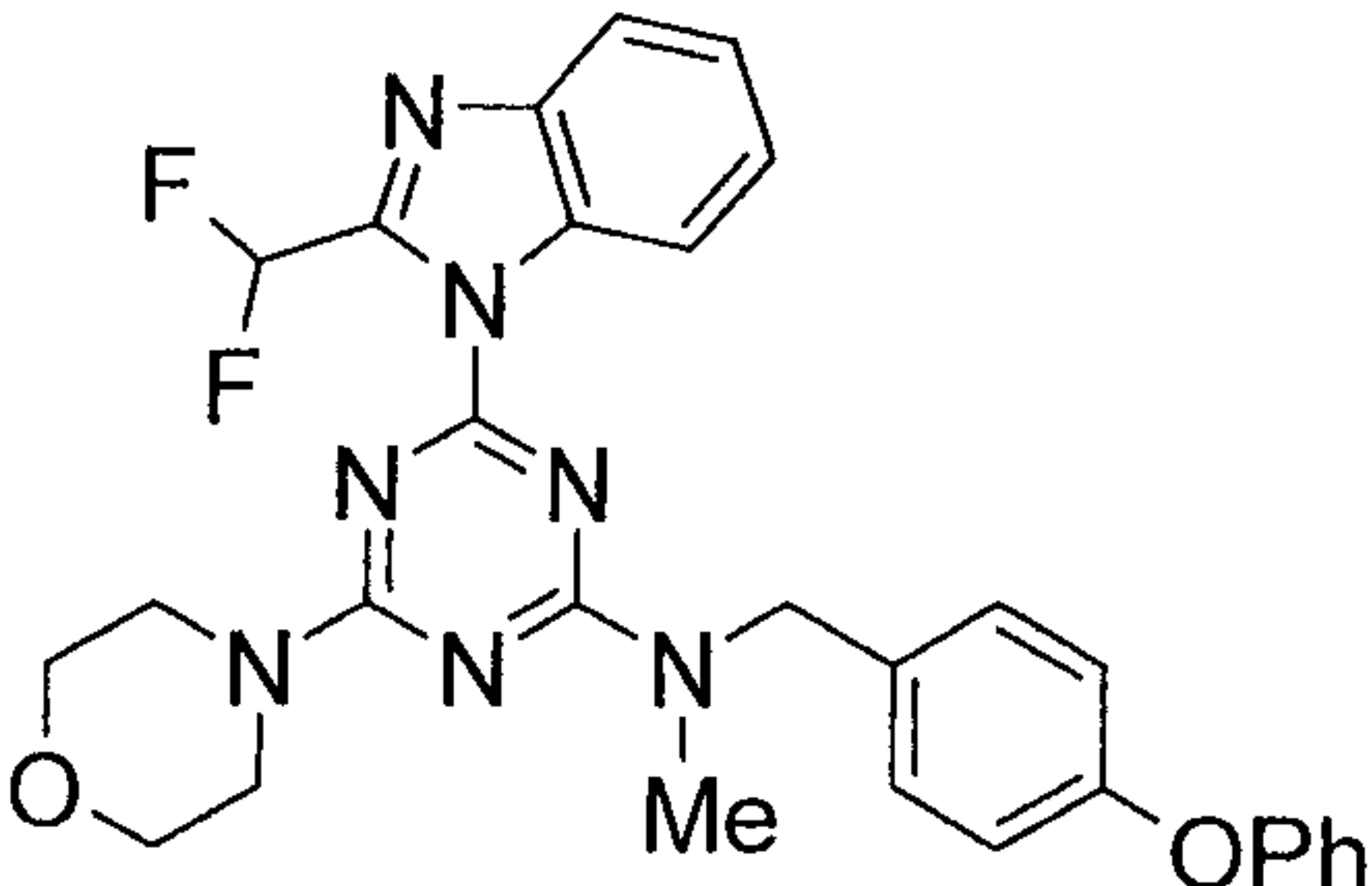
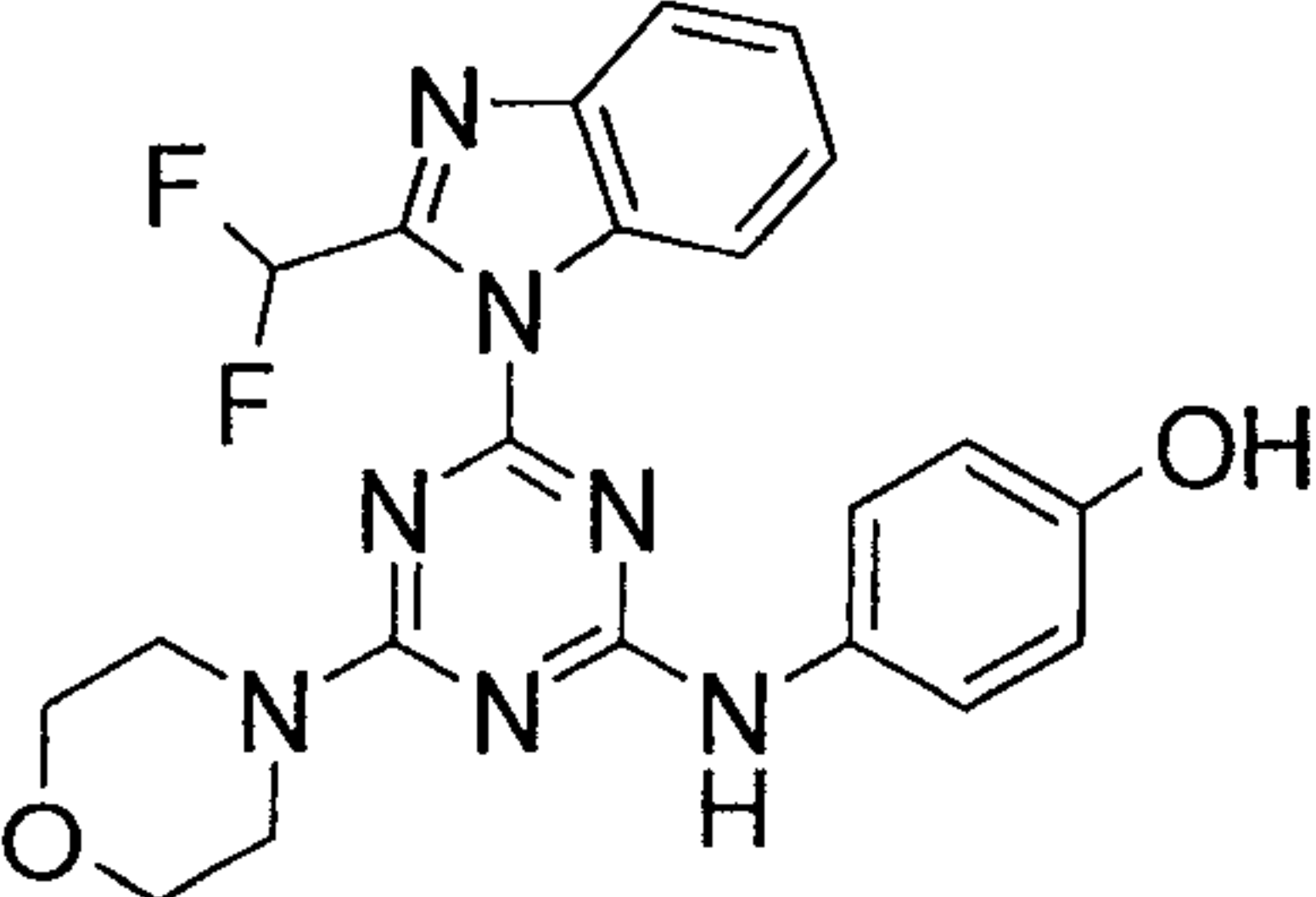
[0325]

[Table 169]

Ex	Str	ESI+	RT
A34		482	3.31
A35		473	2.29
A36		482	3.6
A37		482	3.59

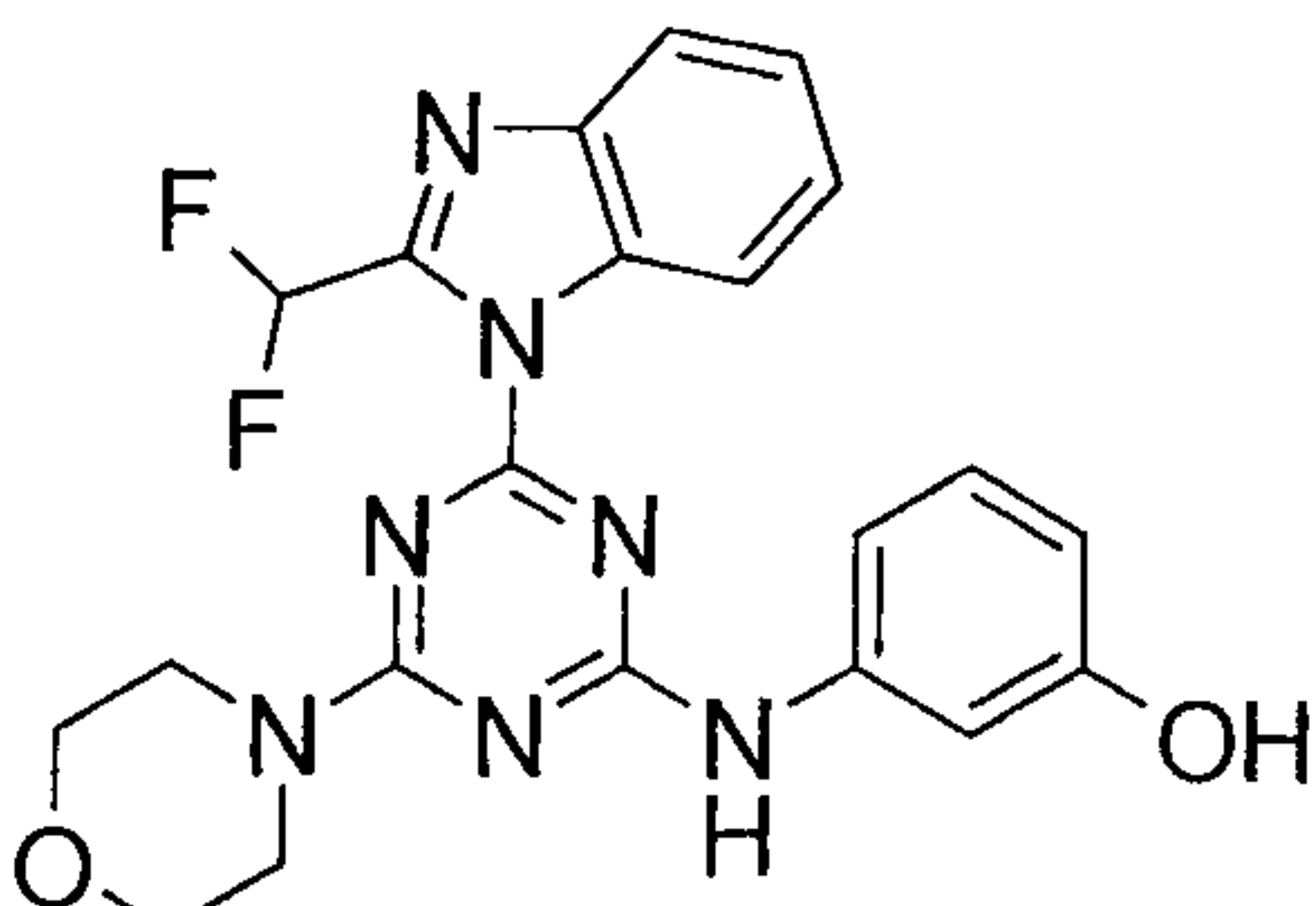
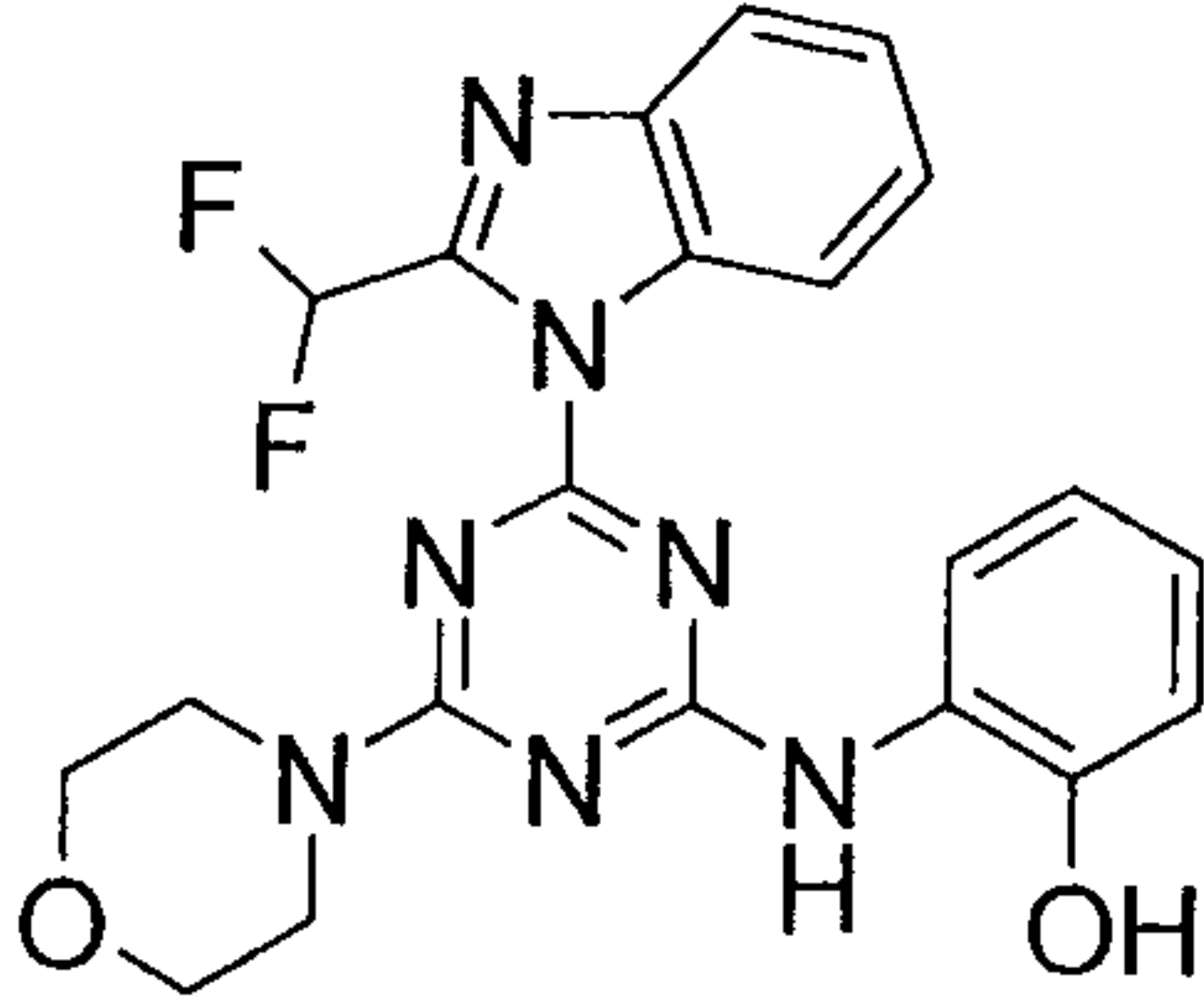
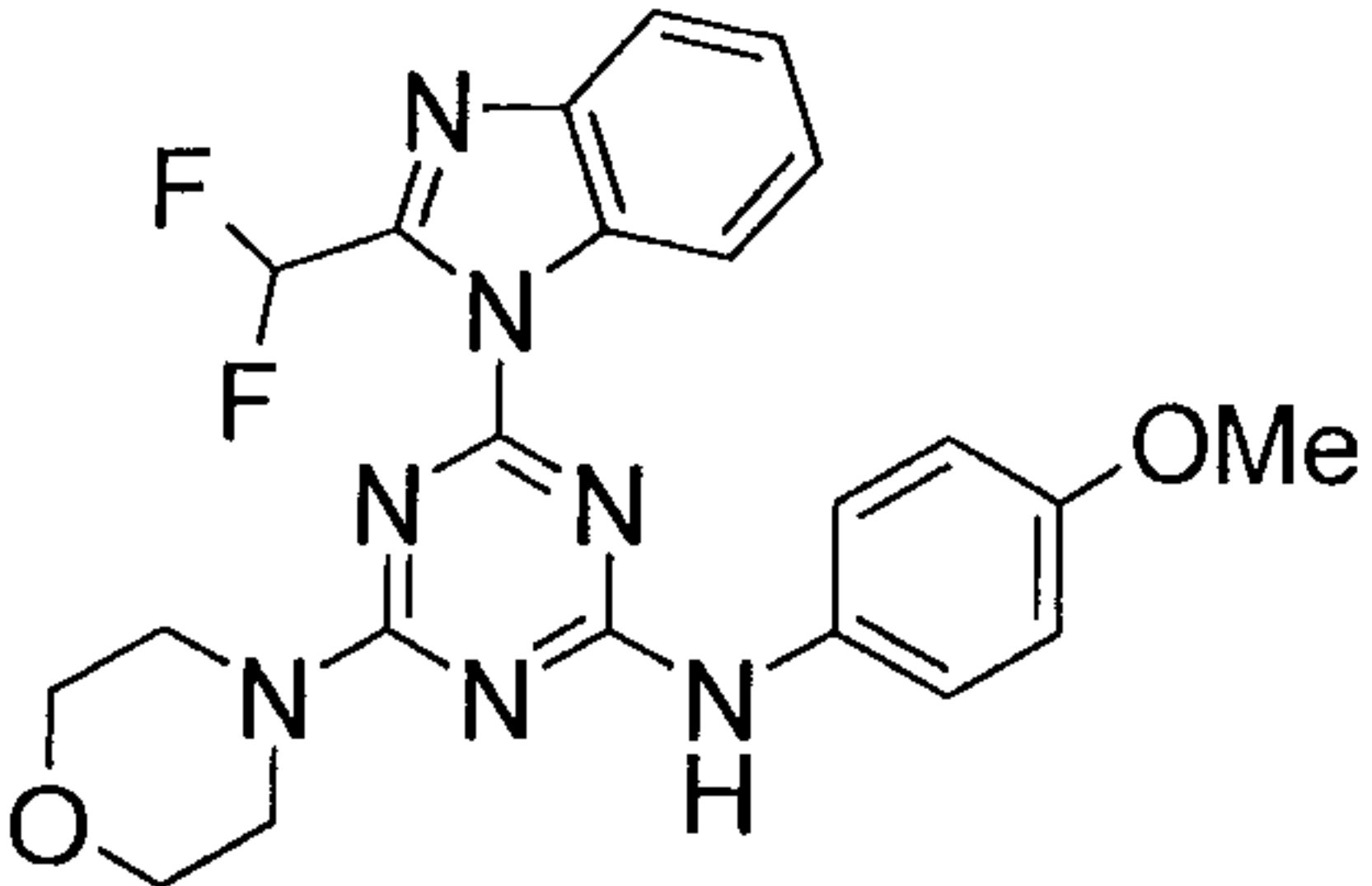
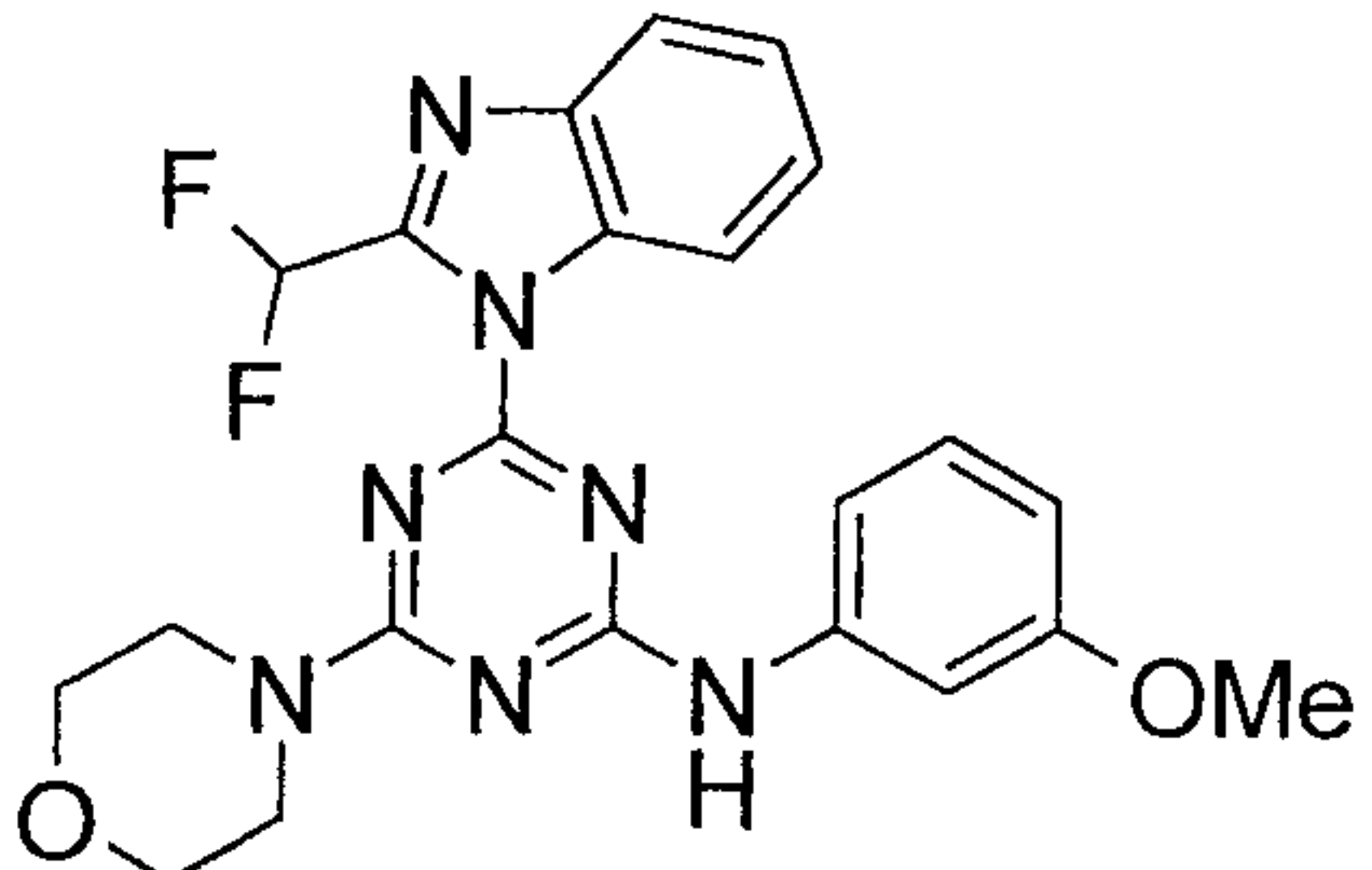
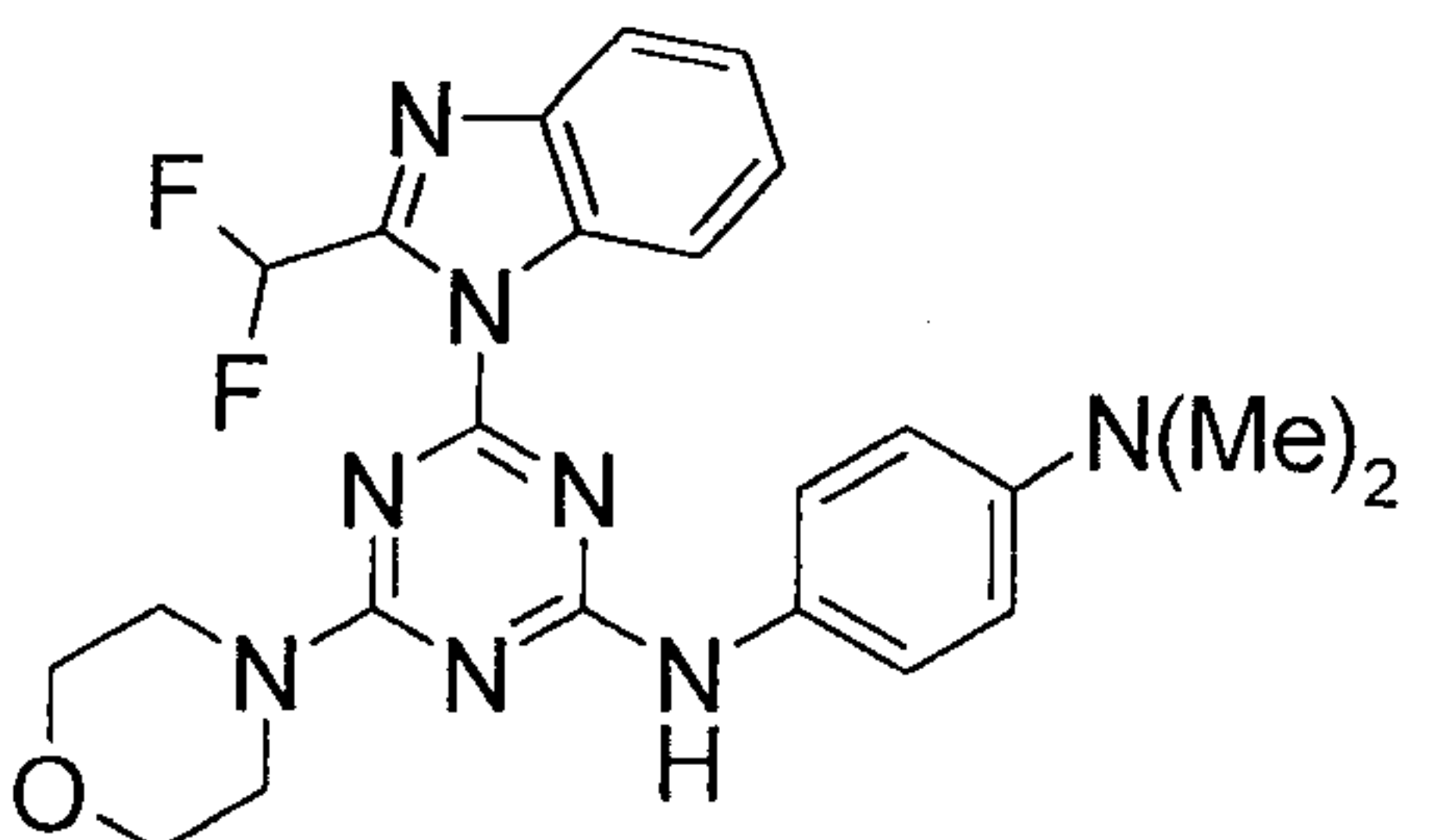
[0326]

[Table 170]

Ex	Str	ESI+	RT
A38		482	3.68
A39		535	2.76
A40		544	3.95
A41		440	2.94

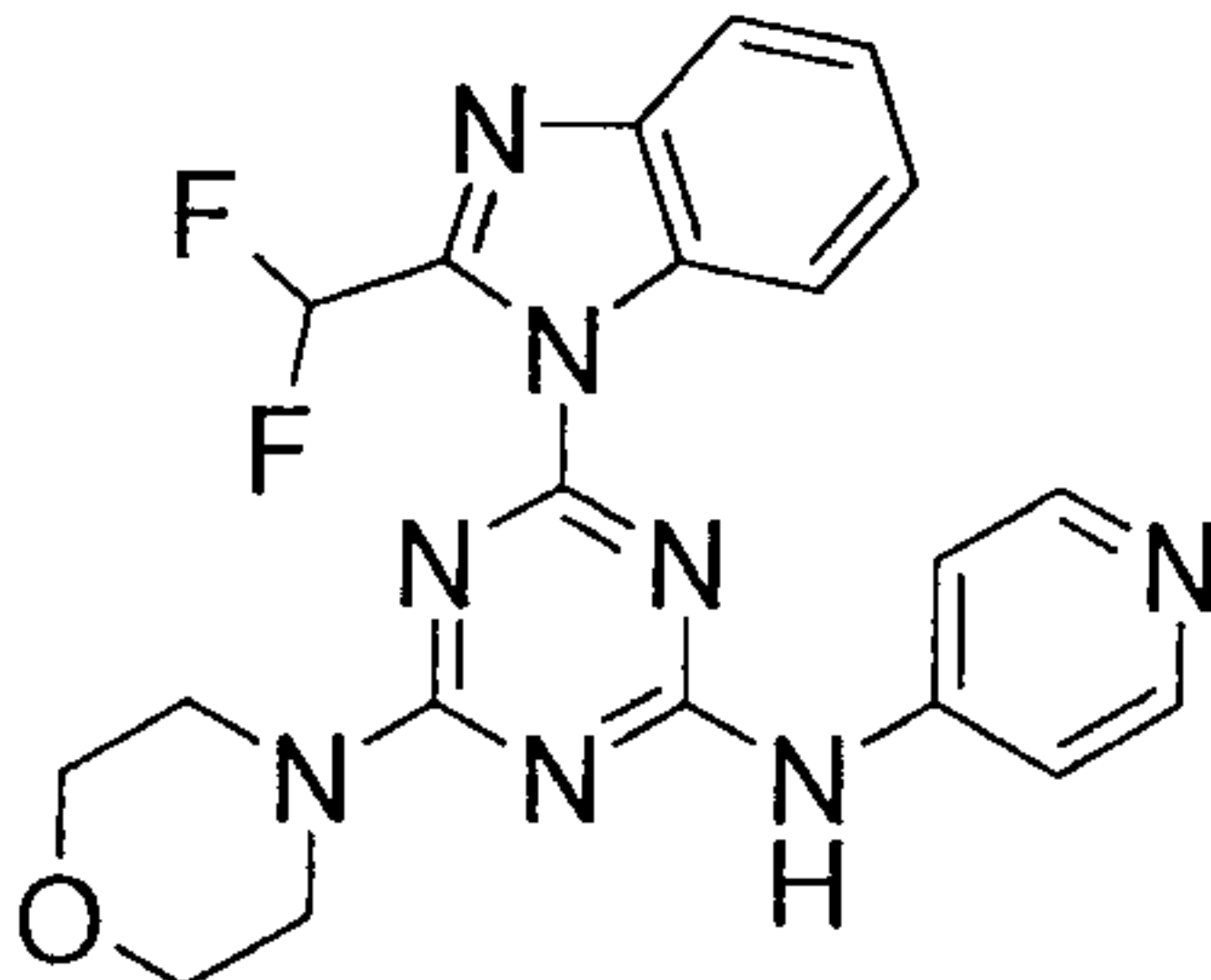
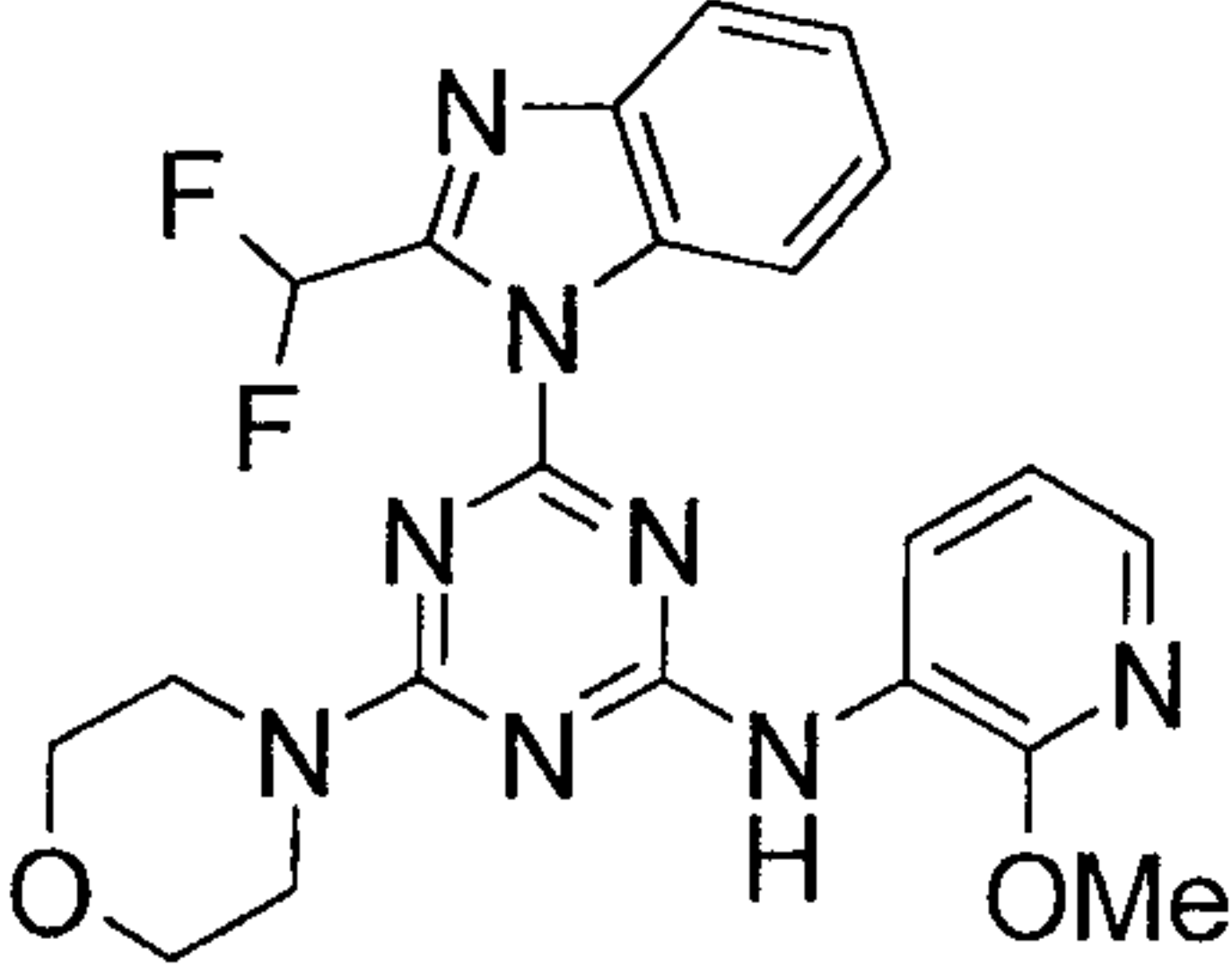
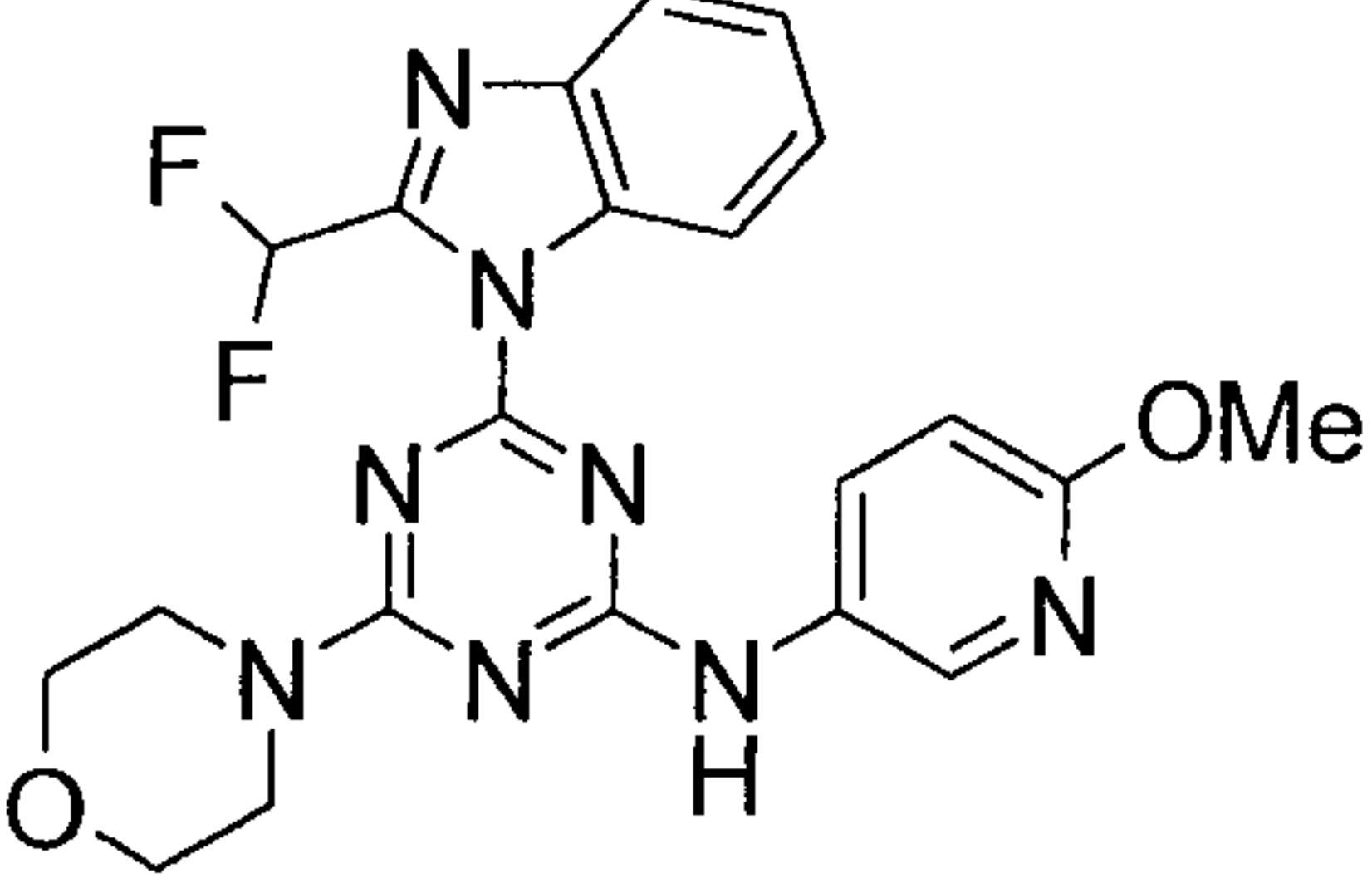
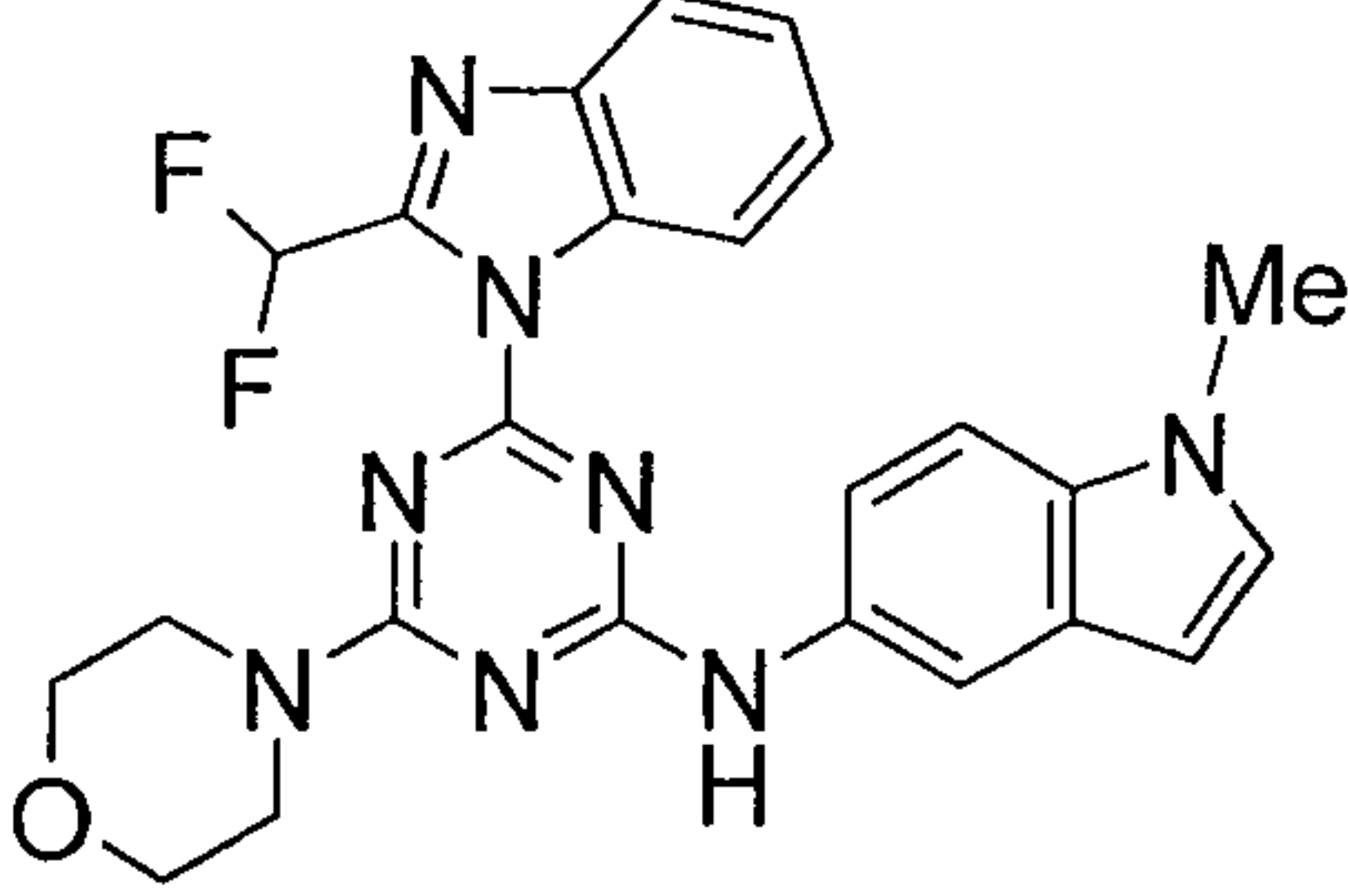
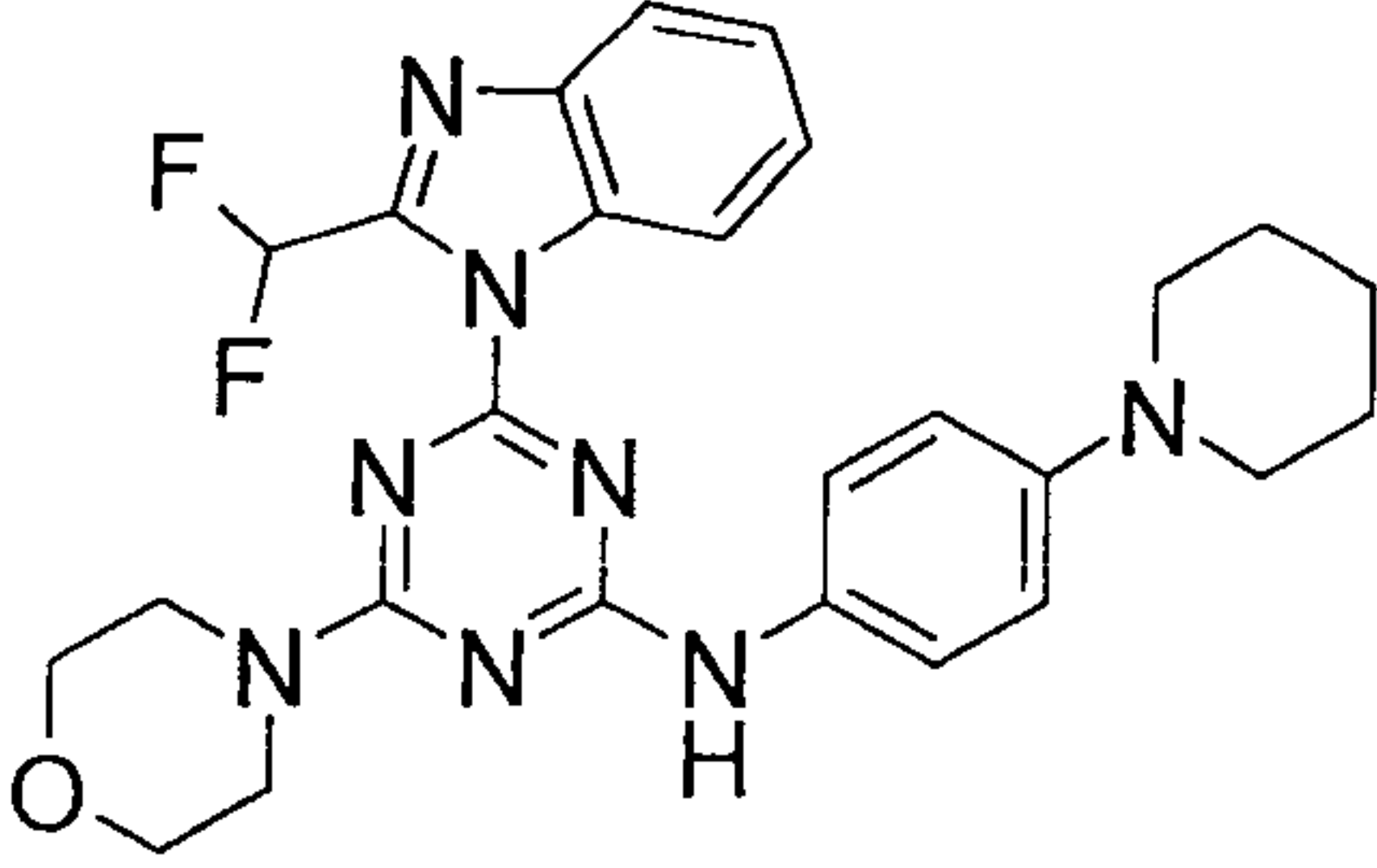
[0327]

[Table 171]

Ex	Str	ESI+	RT
A42		440	3.01
A43		440	3.16
A44		454	3.3
A45		454	3.36
A46		467	2.54

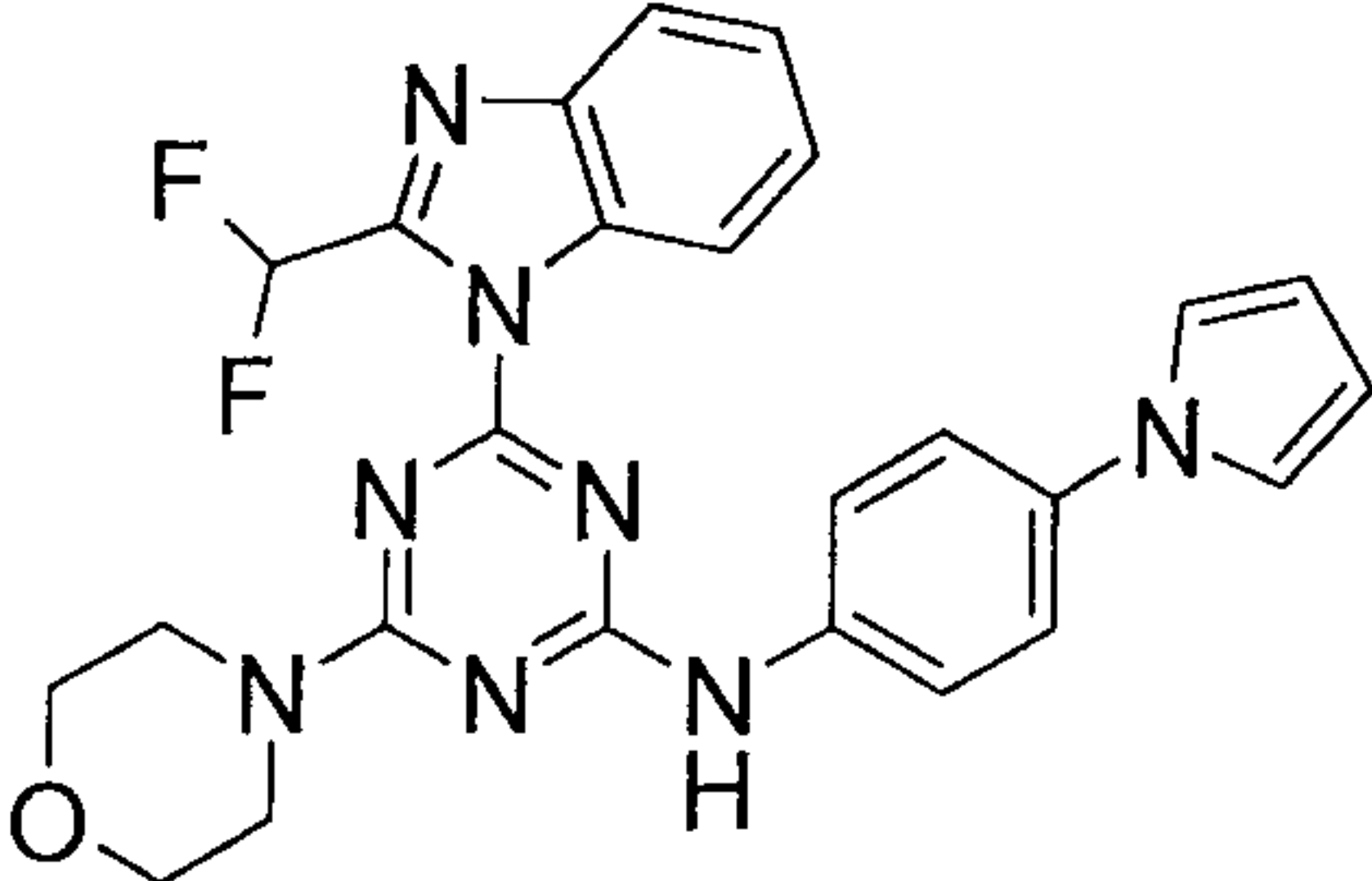
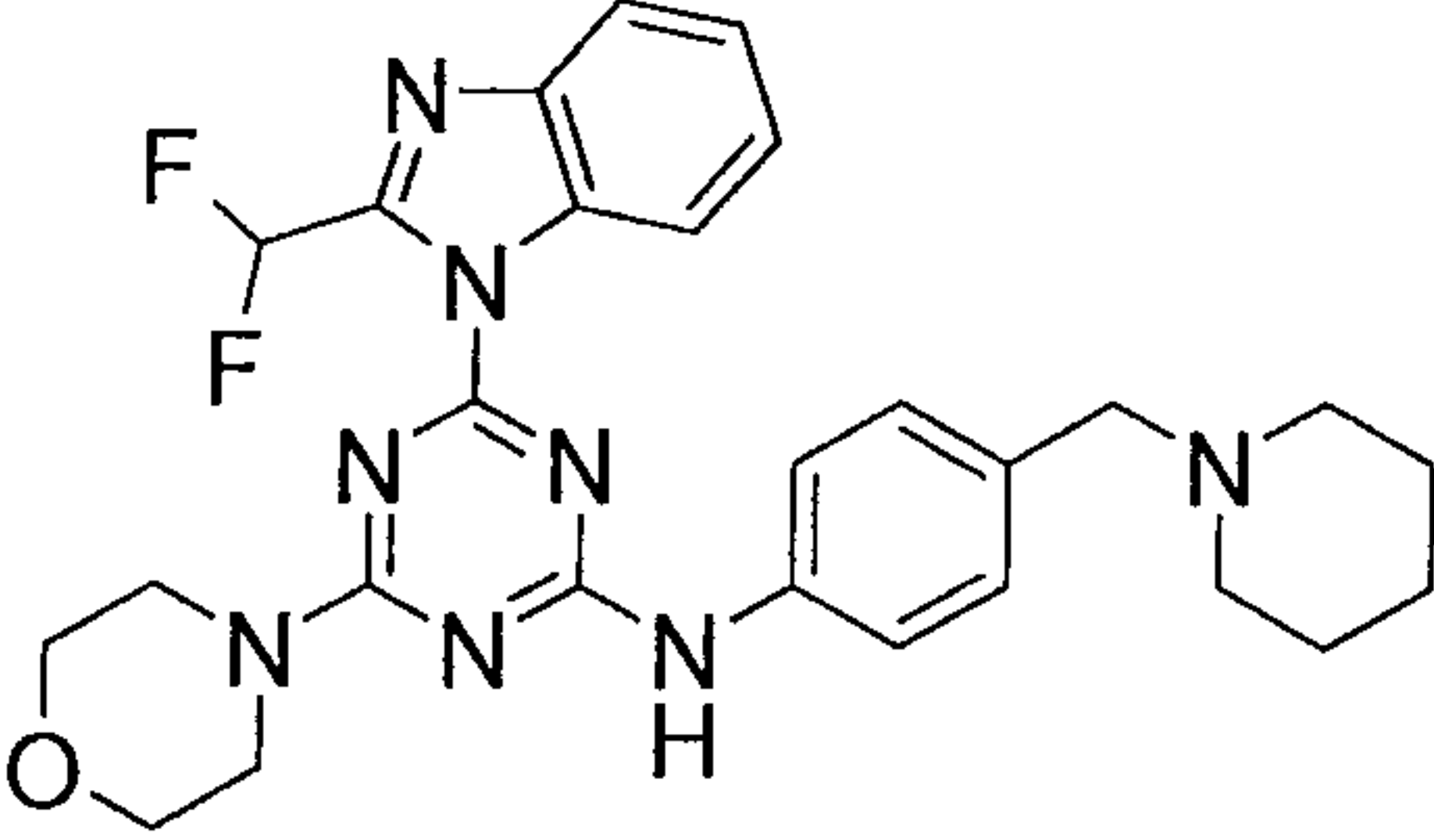
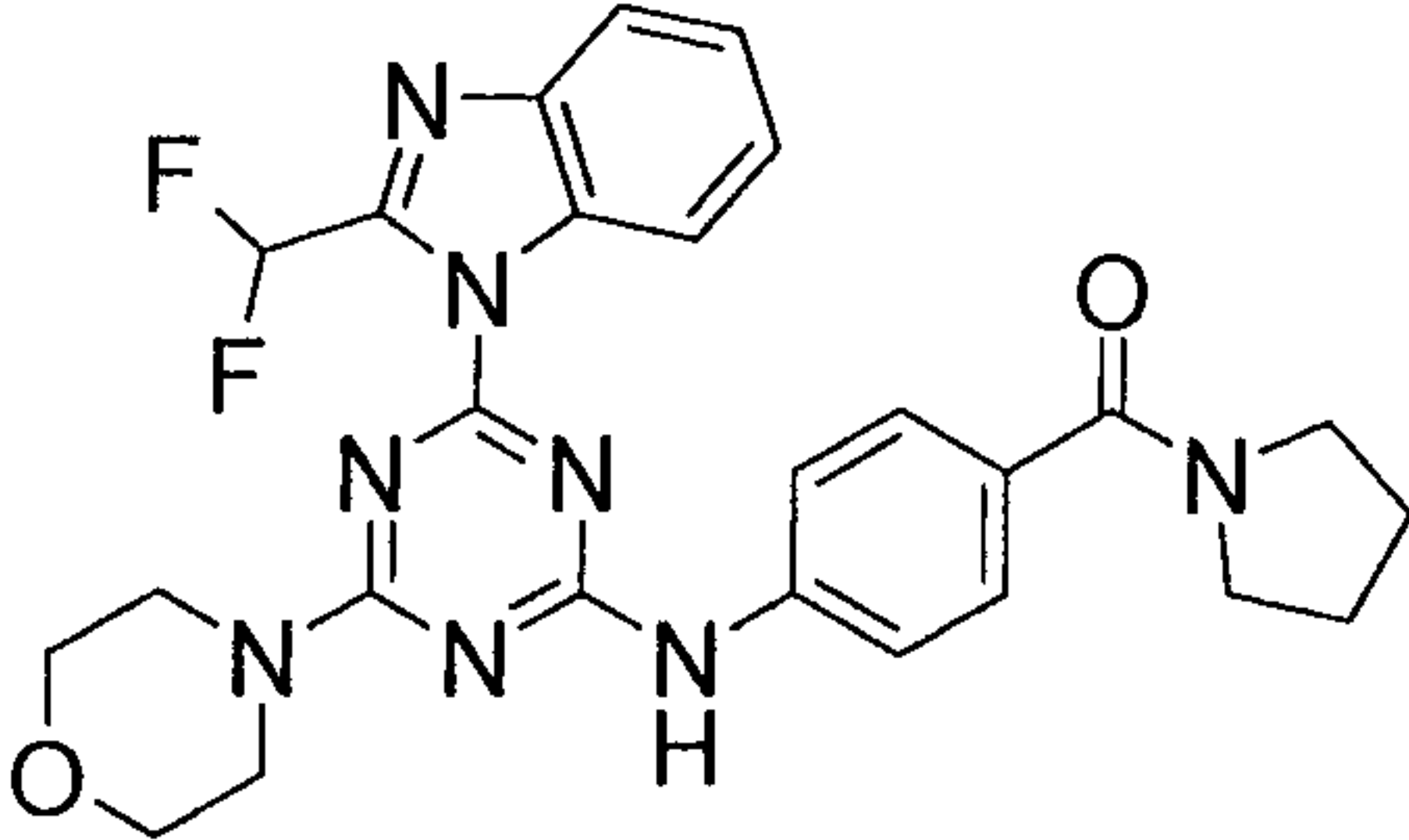
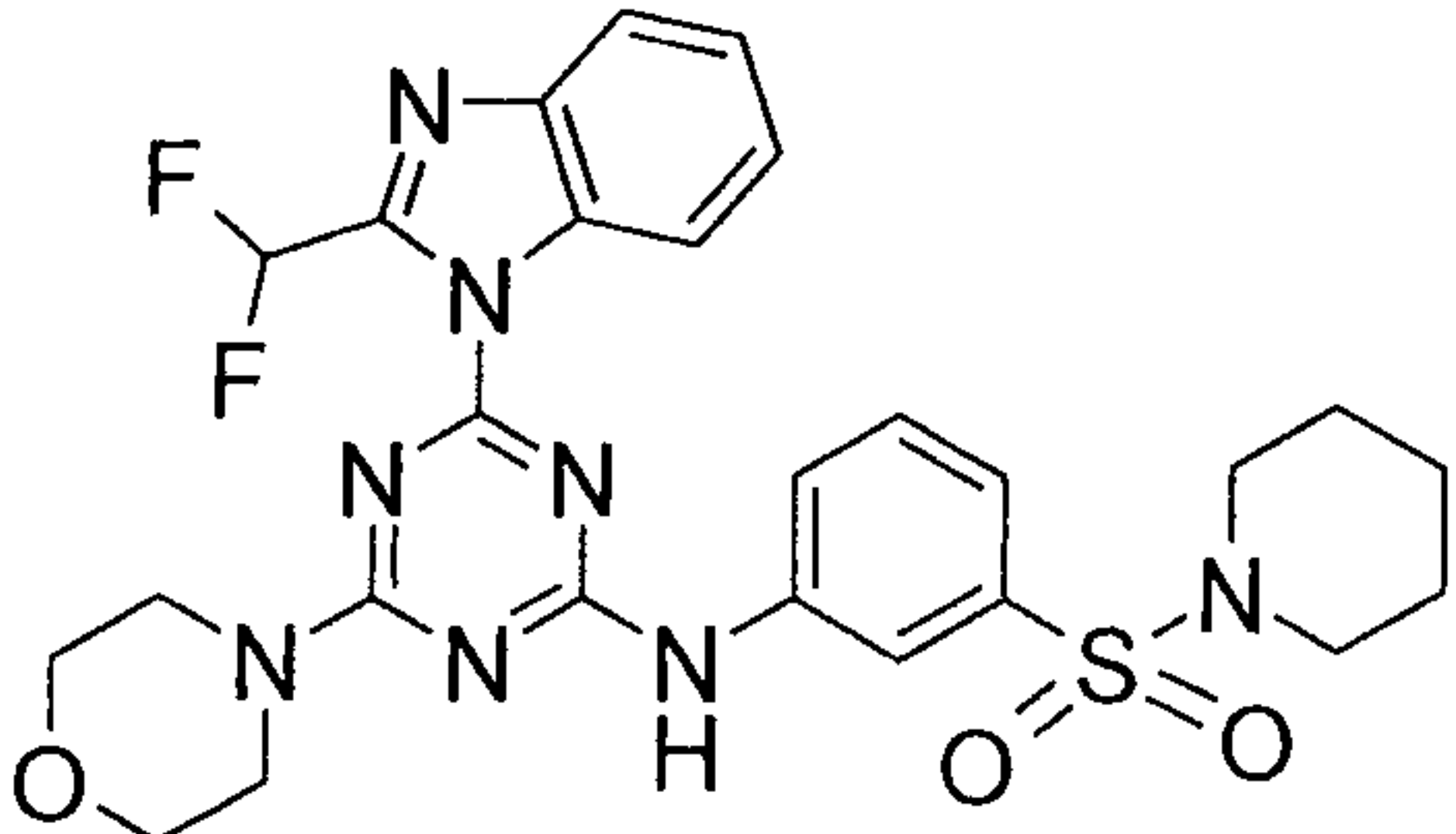
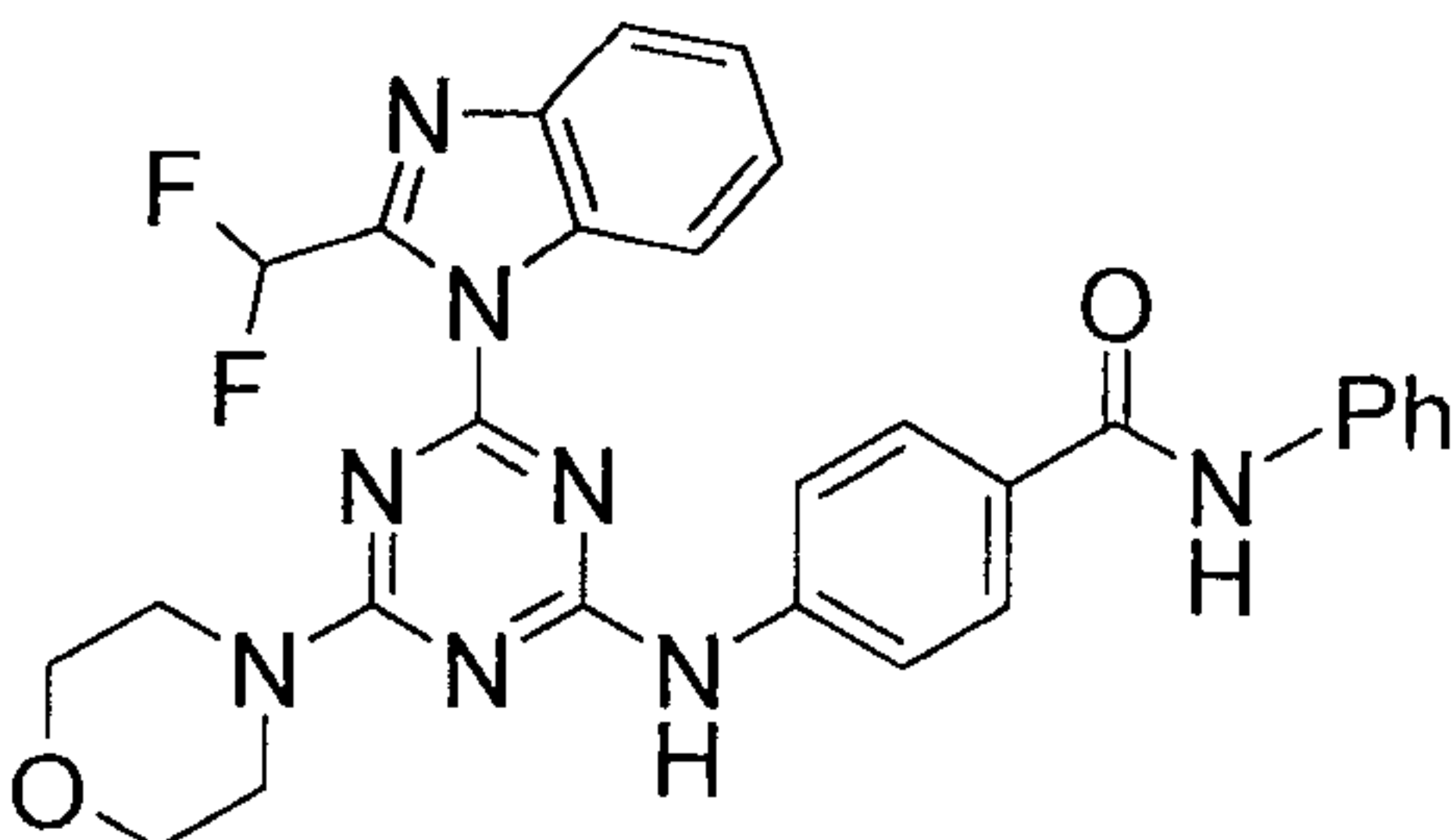
[0328]

[Table 172]

Ex	Str	ESI+	RT
A47		425	2.29
A48		455	3.24
A49		455	3.15
A50		477	3.37
A51		507	2.54

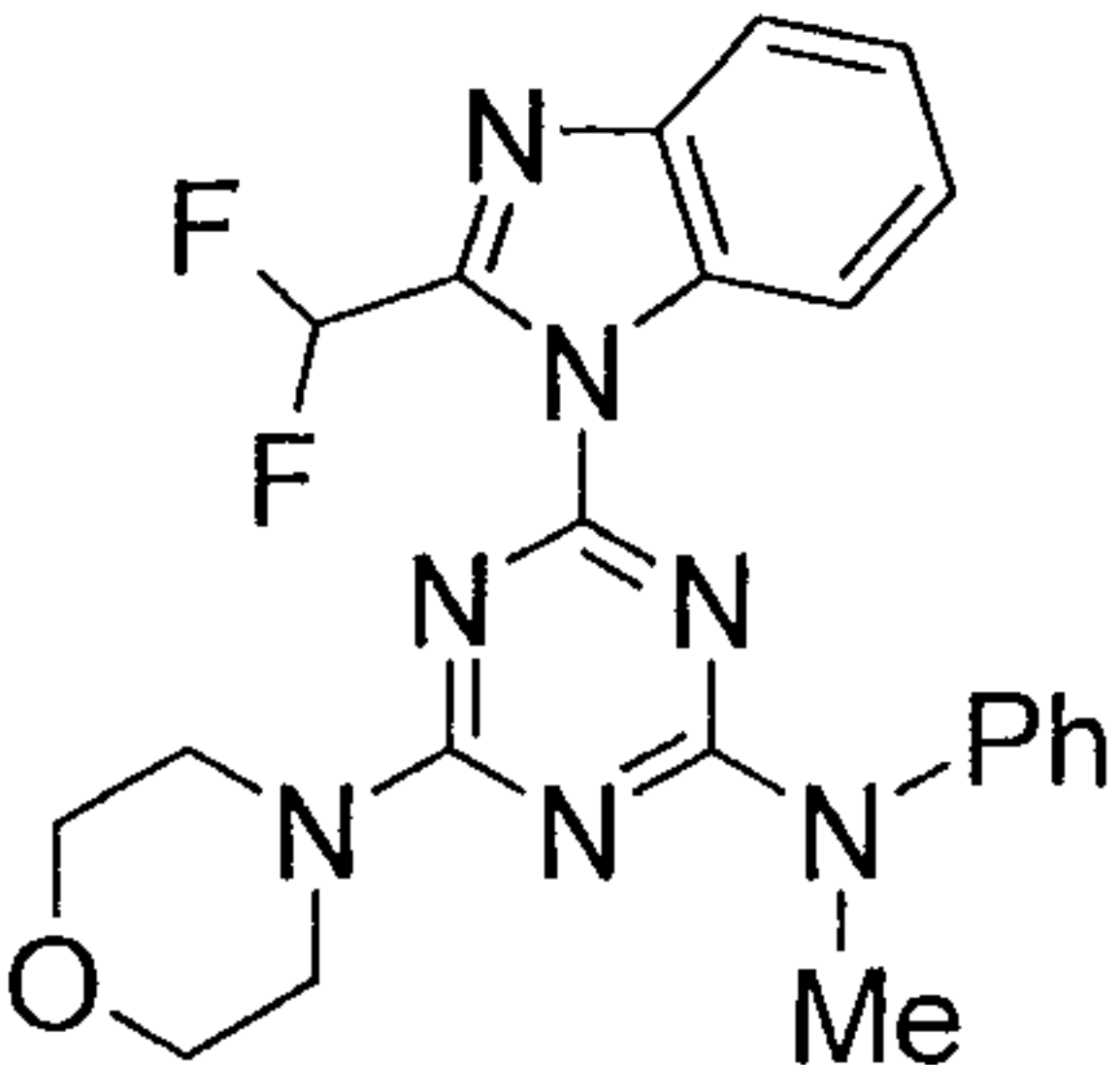
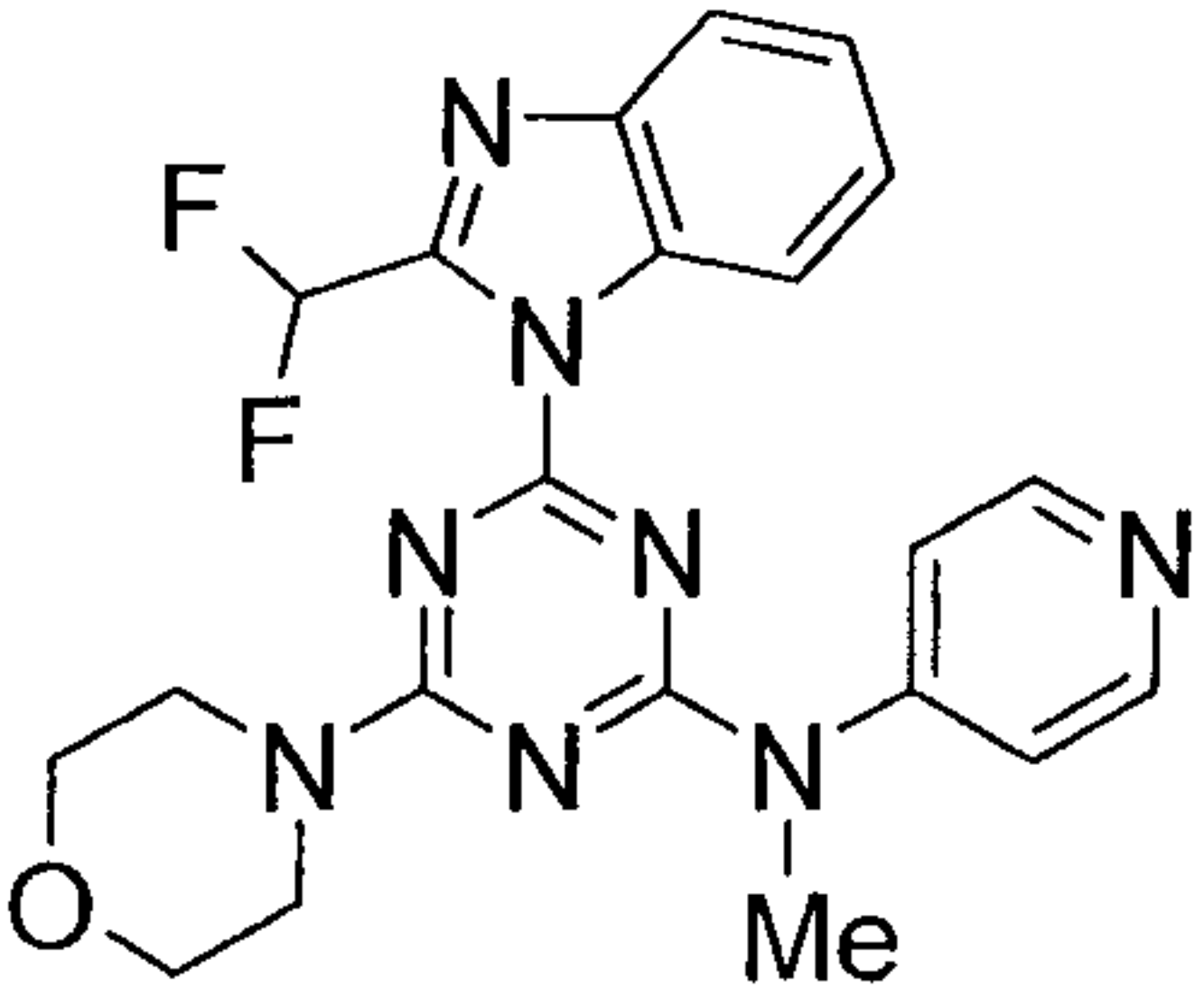
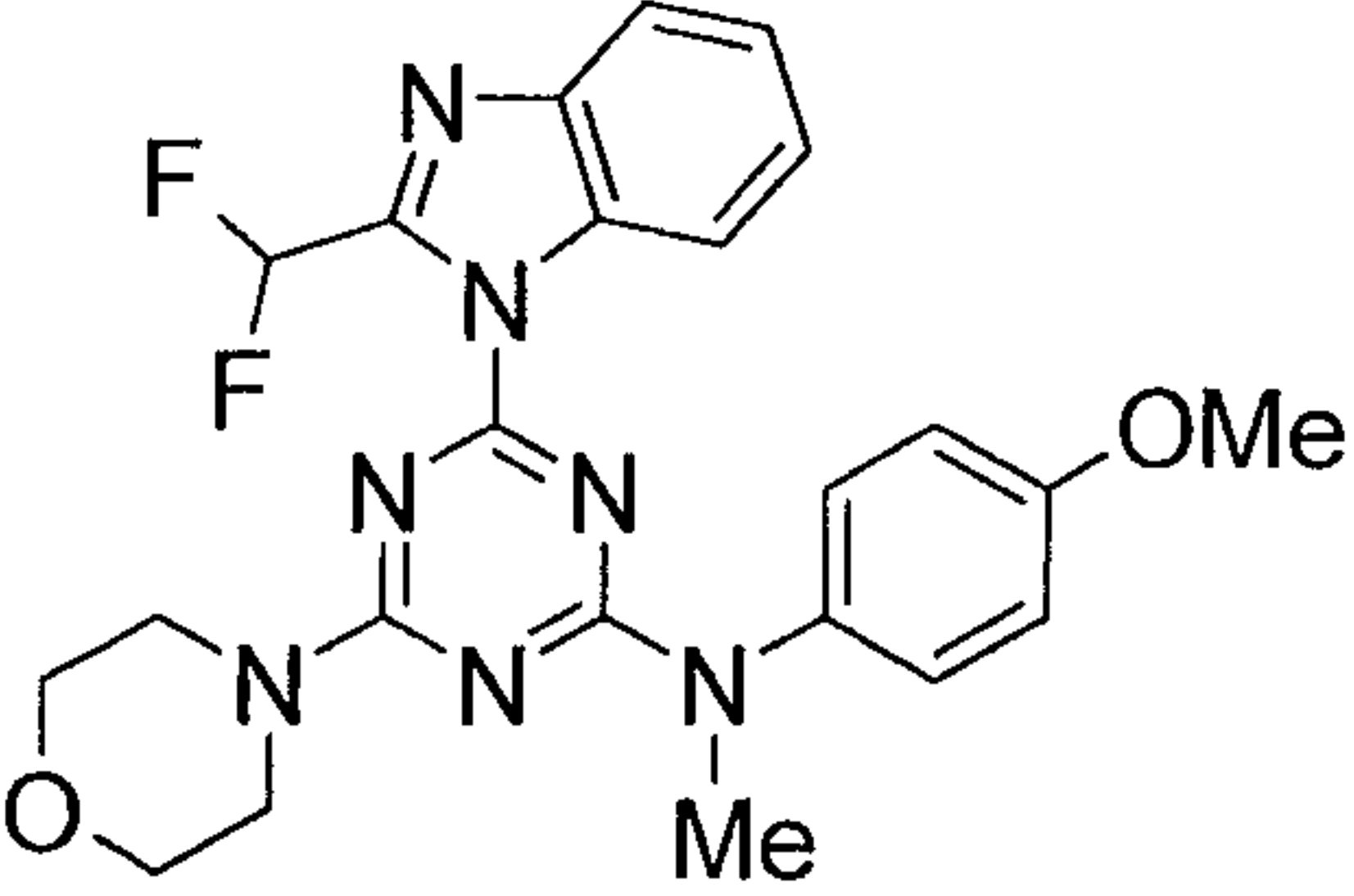
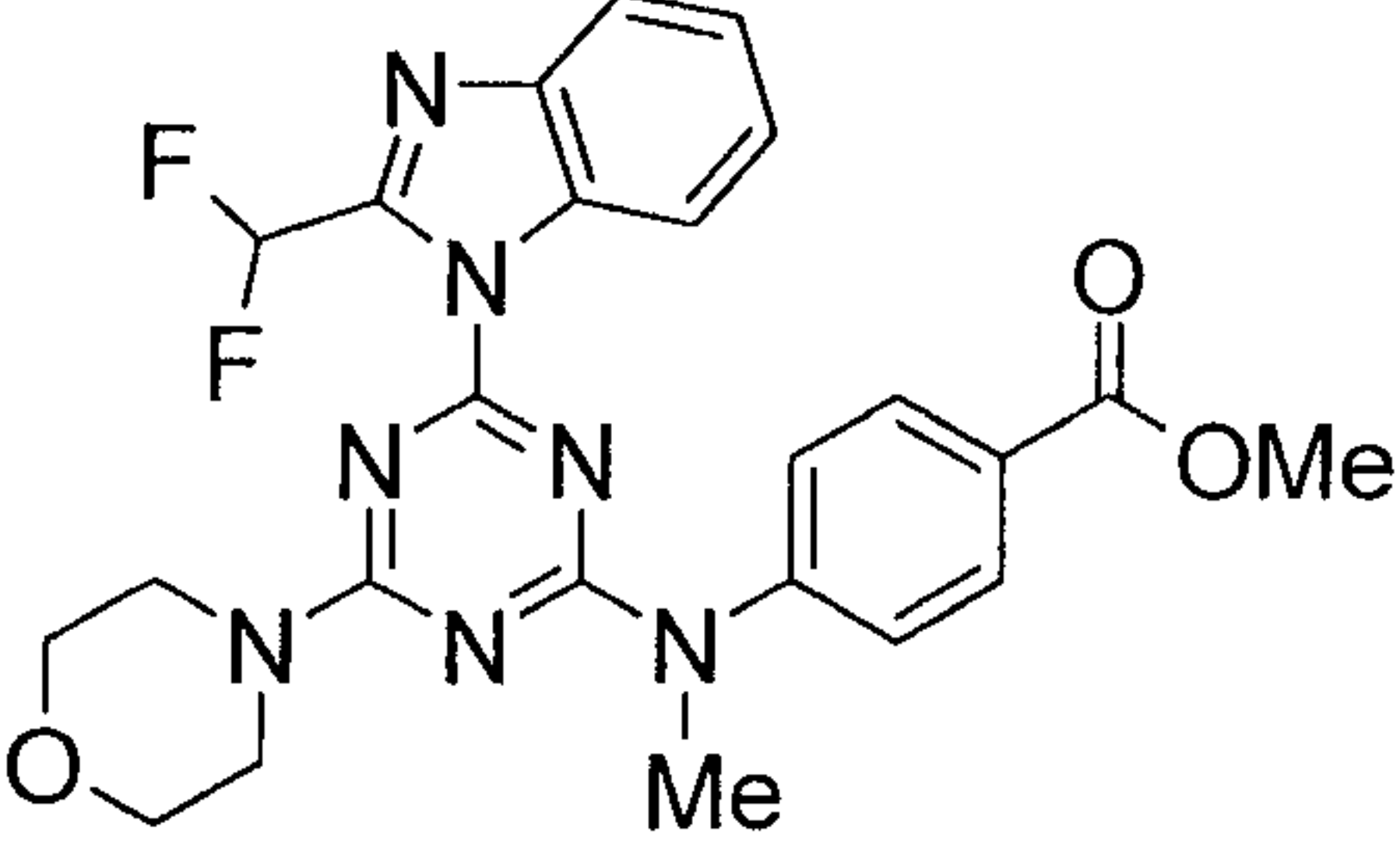
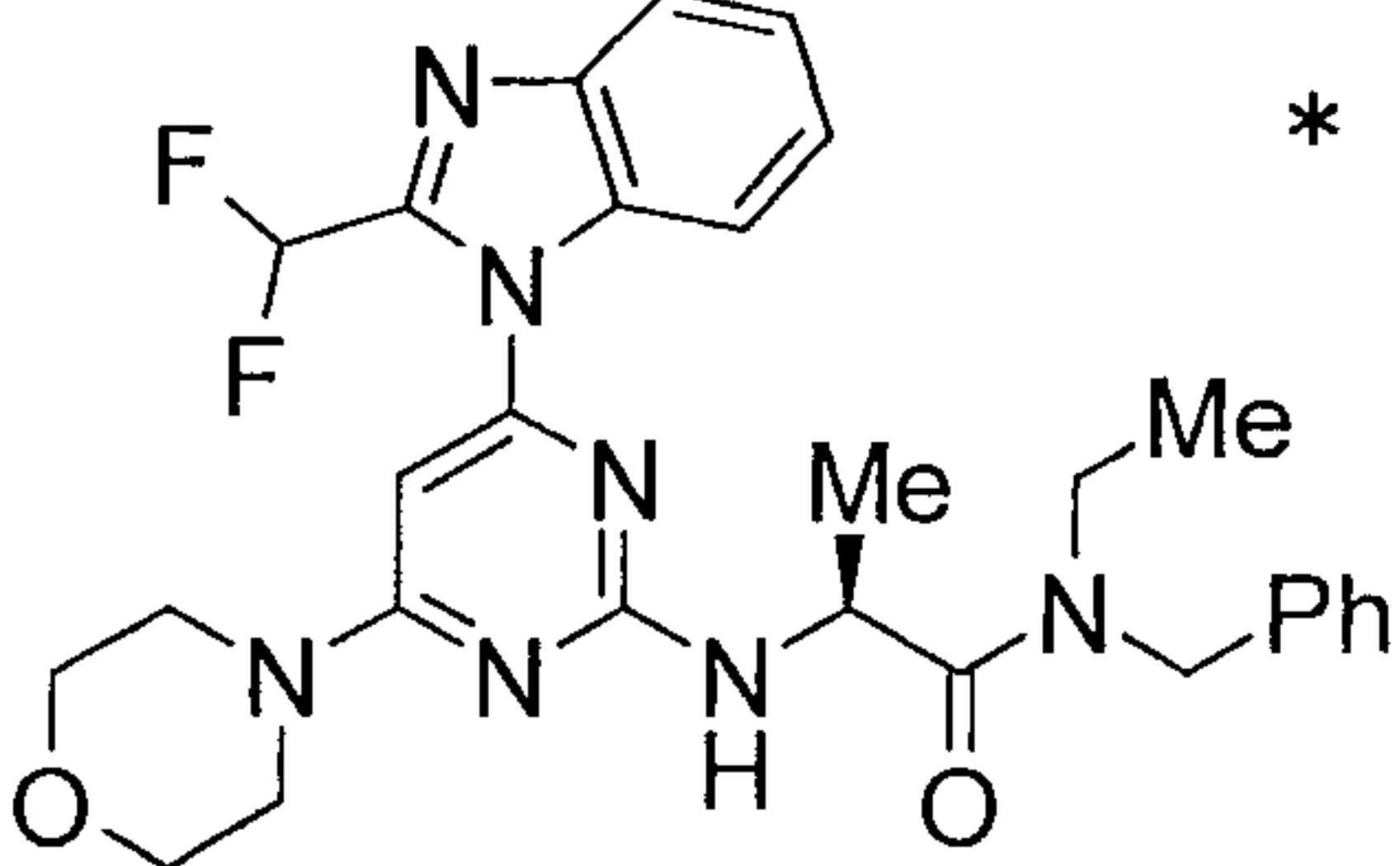
[0329]

[Table 173]

Ex	Str	ESI+	RT
A52		489	3.63
A53		521	2.57
A54		521	3.16
A55		571	3.46
A56		543	3.31

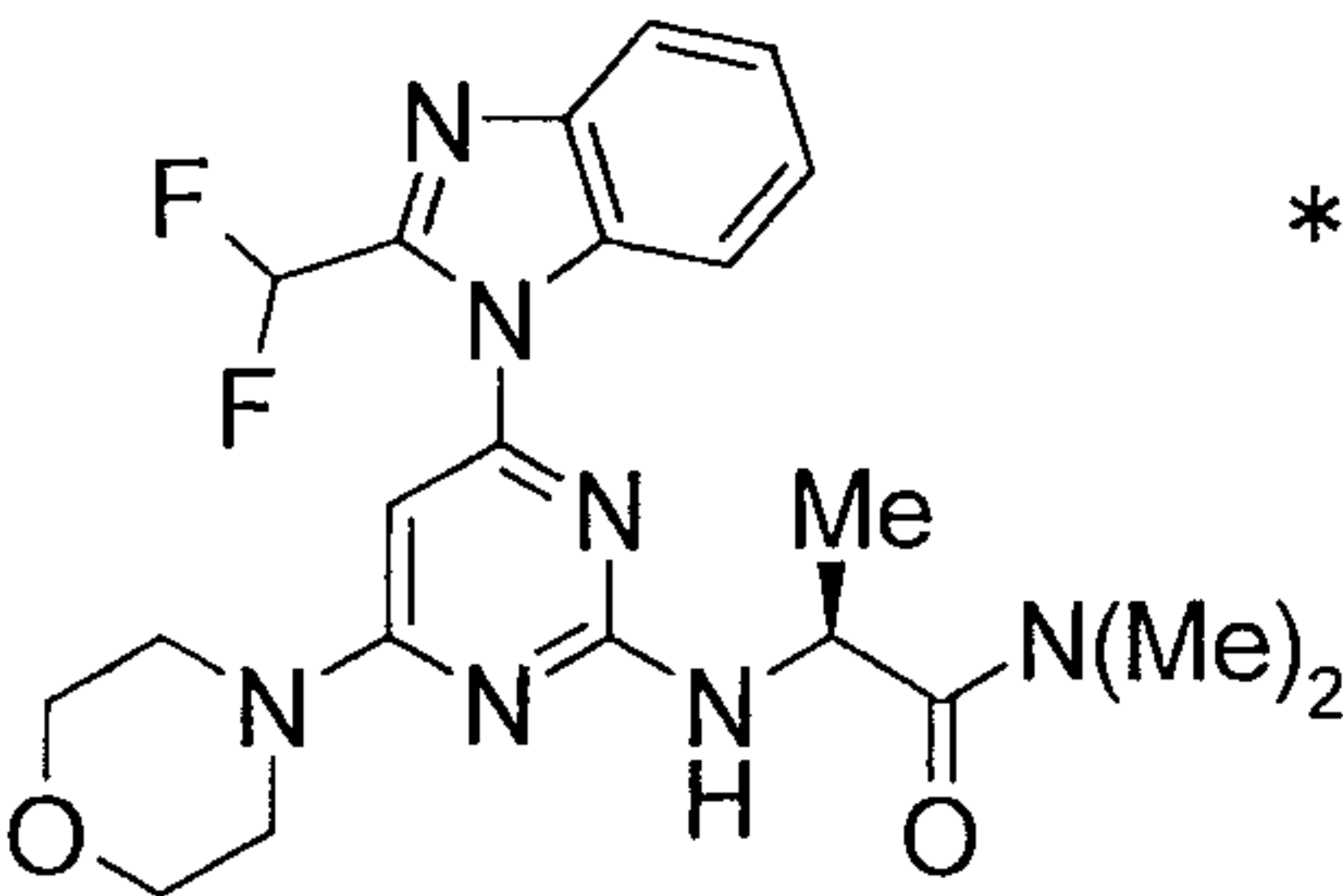
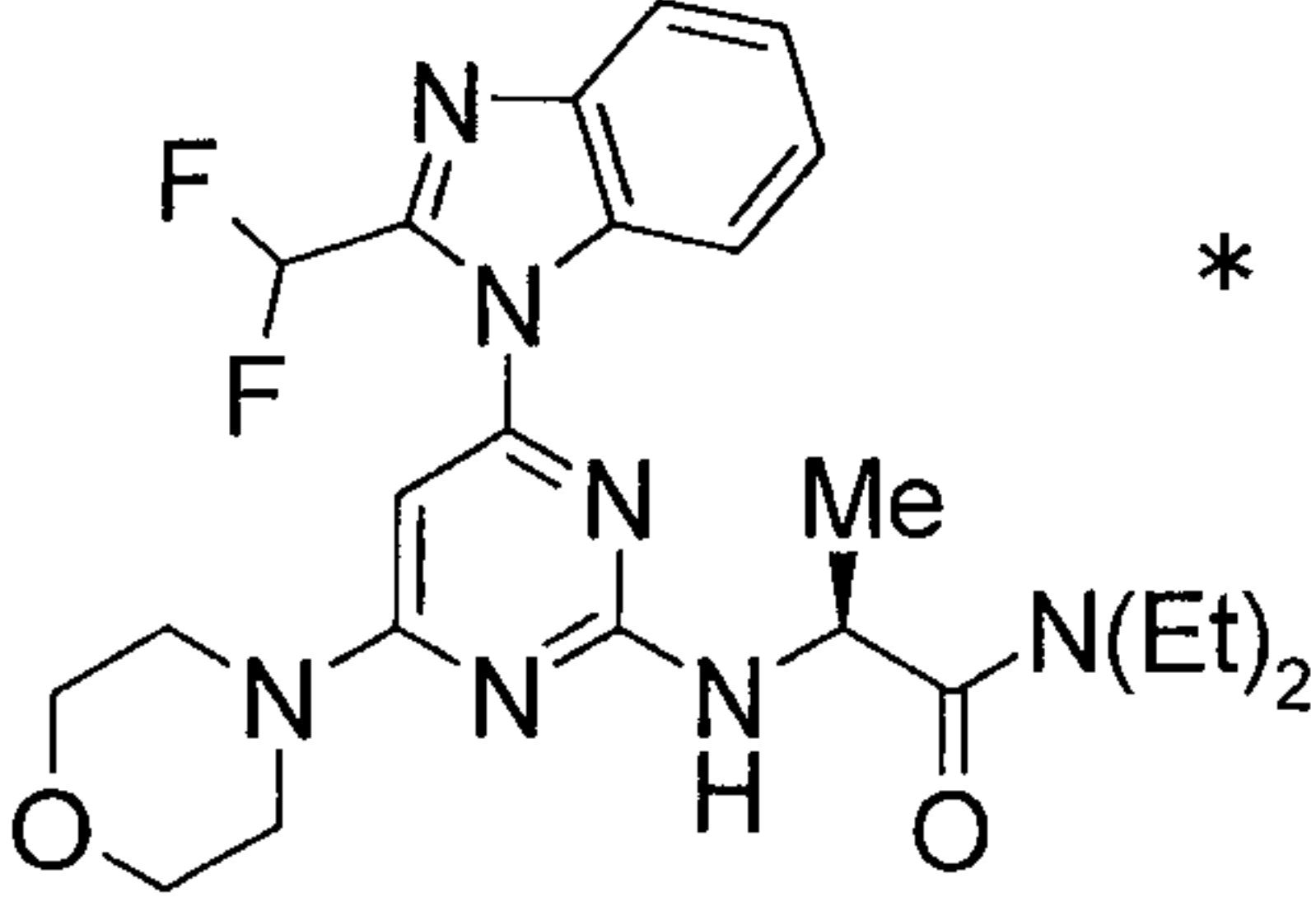
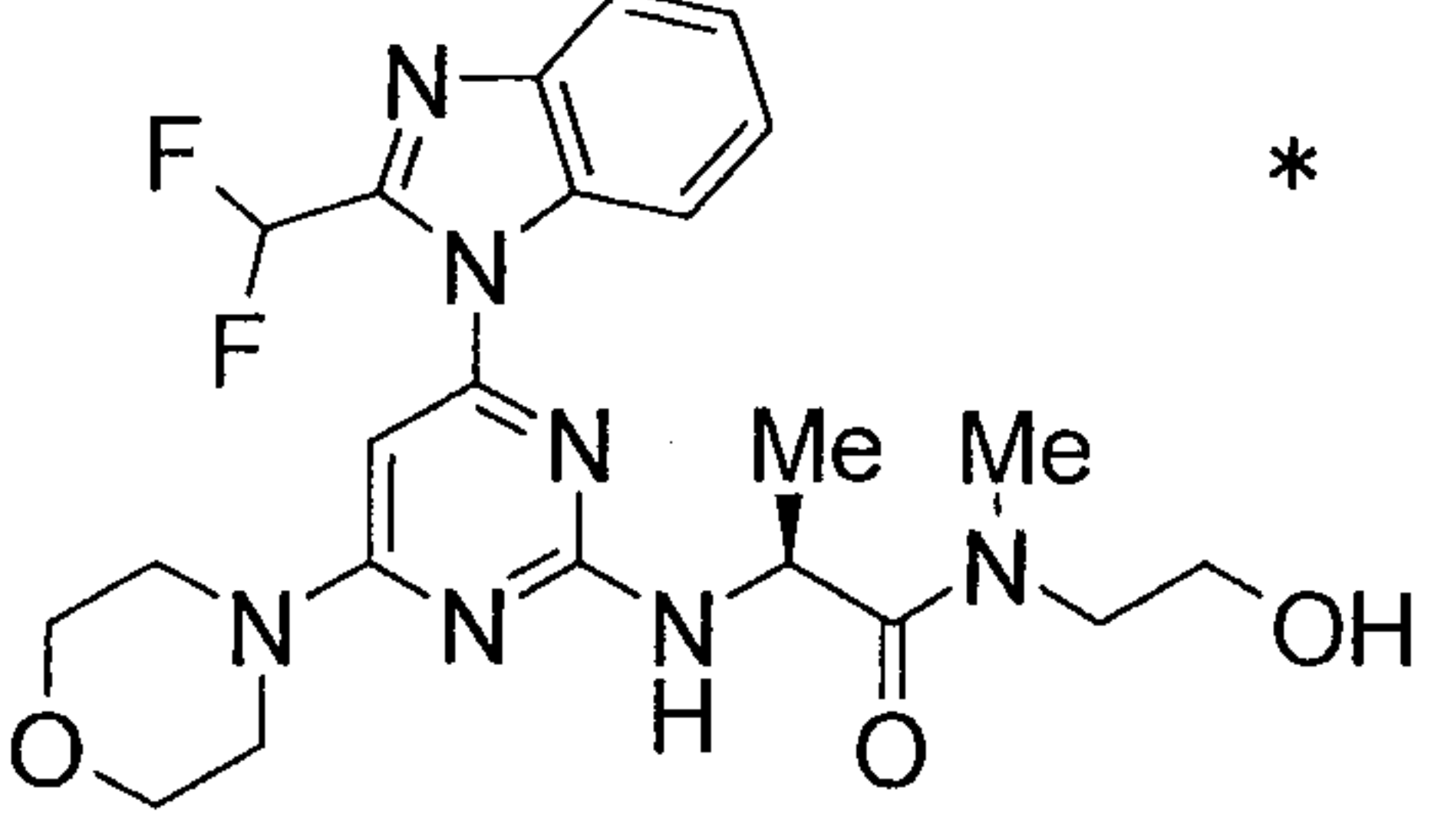
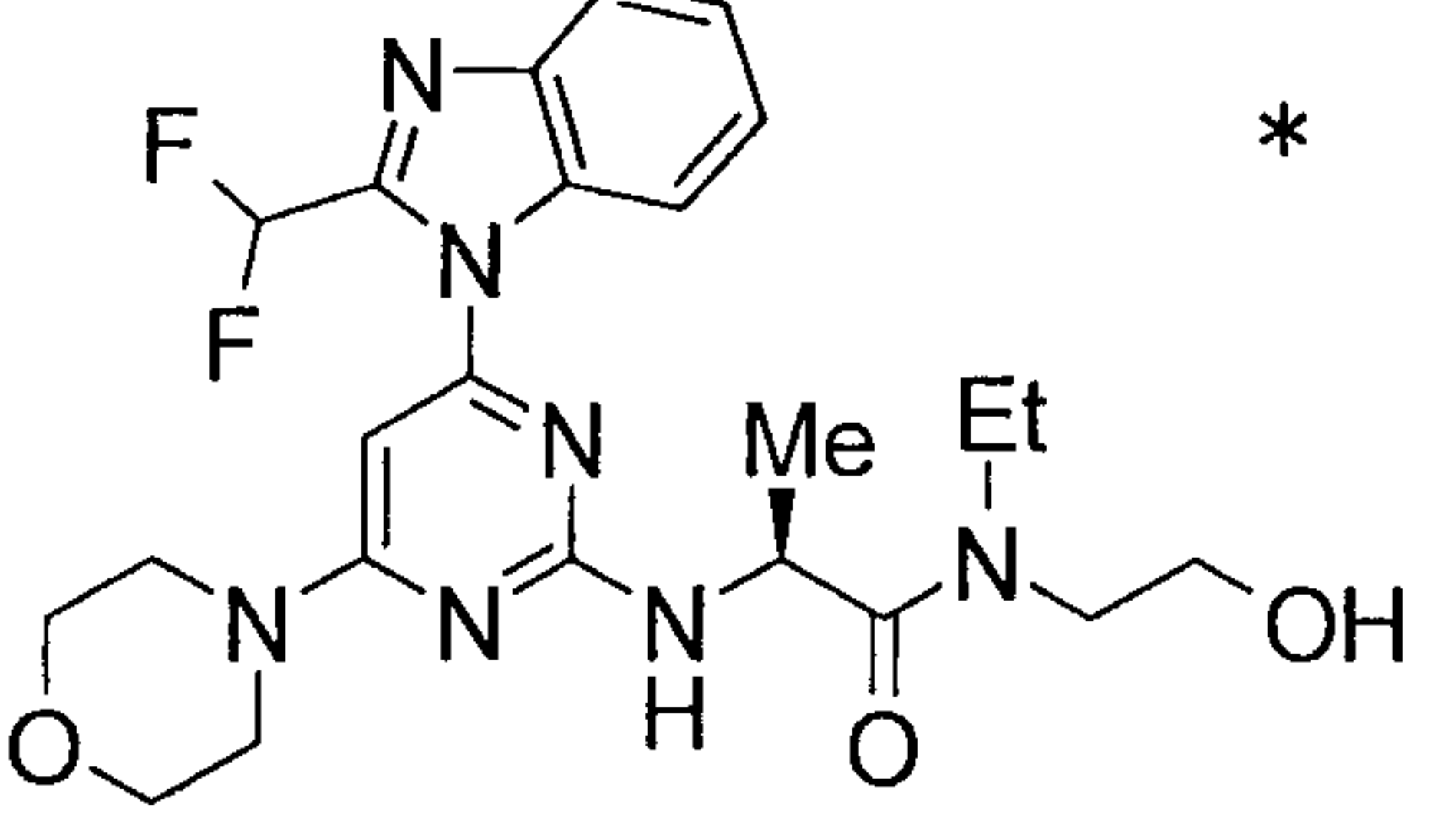
[0330]

[Table 174]

Ex	Str	ESI+	RT
A57		438	3.55
A58		439	2.25
A59		468	3.53
A60		496	3.47
A61		536	2.9

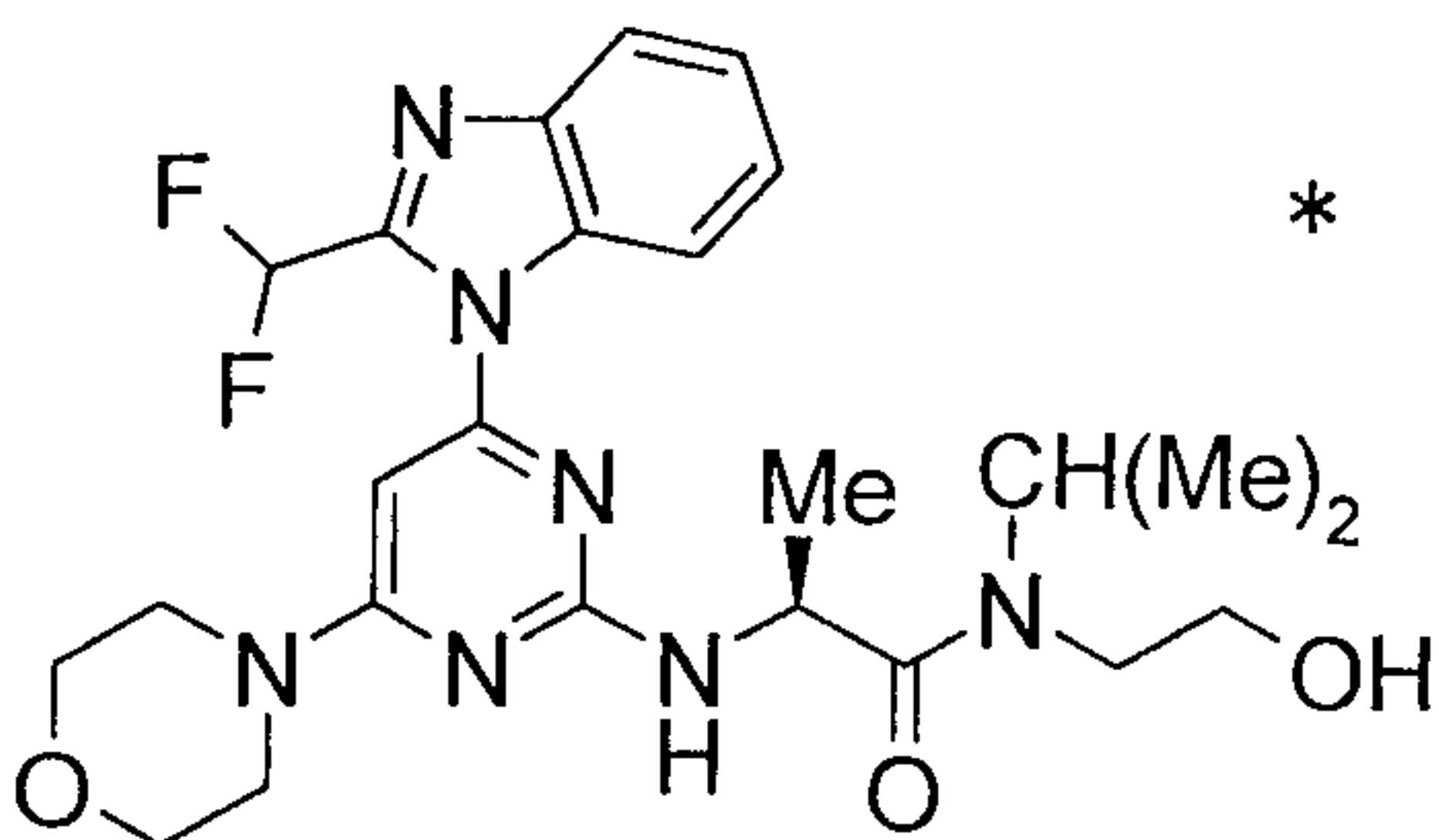
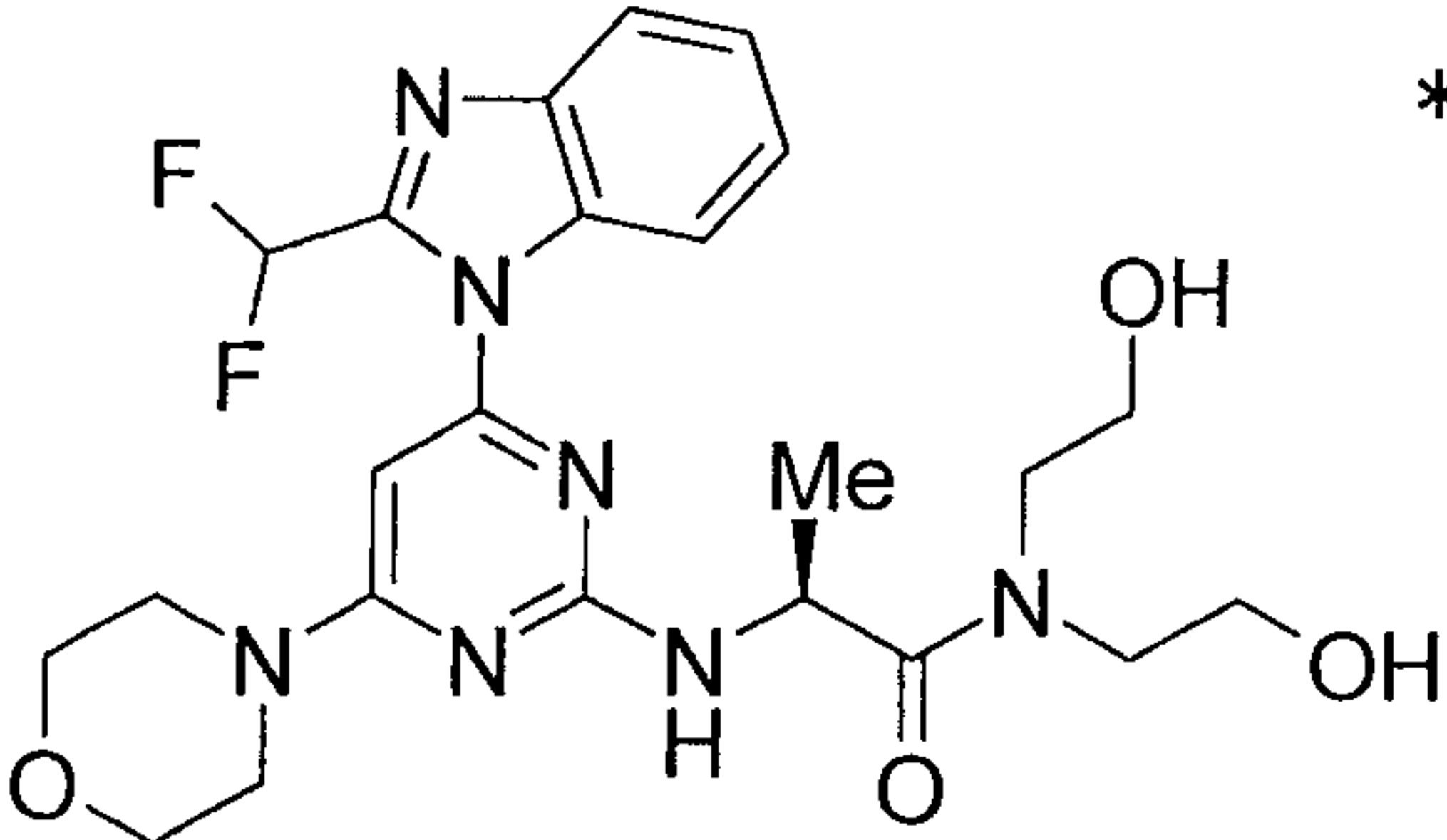
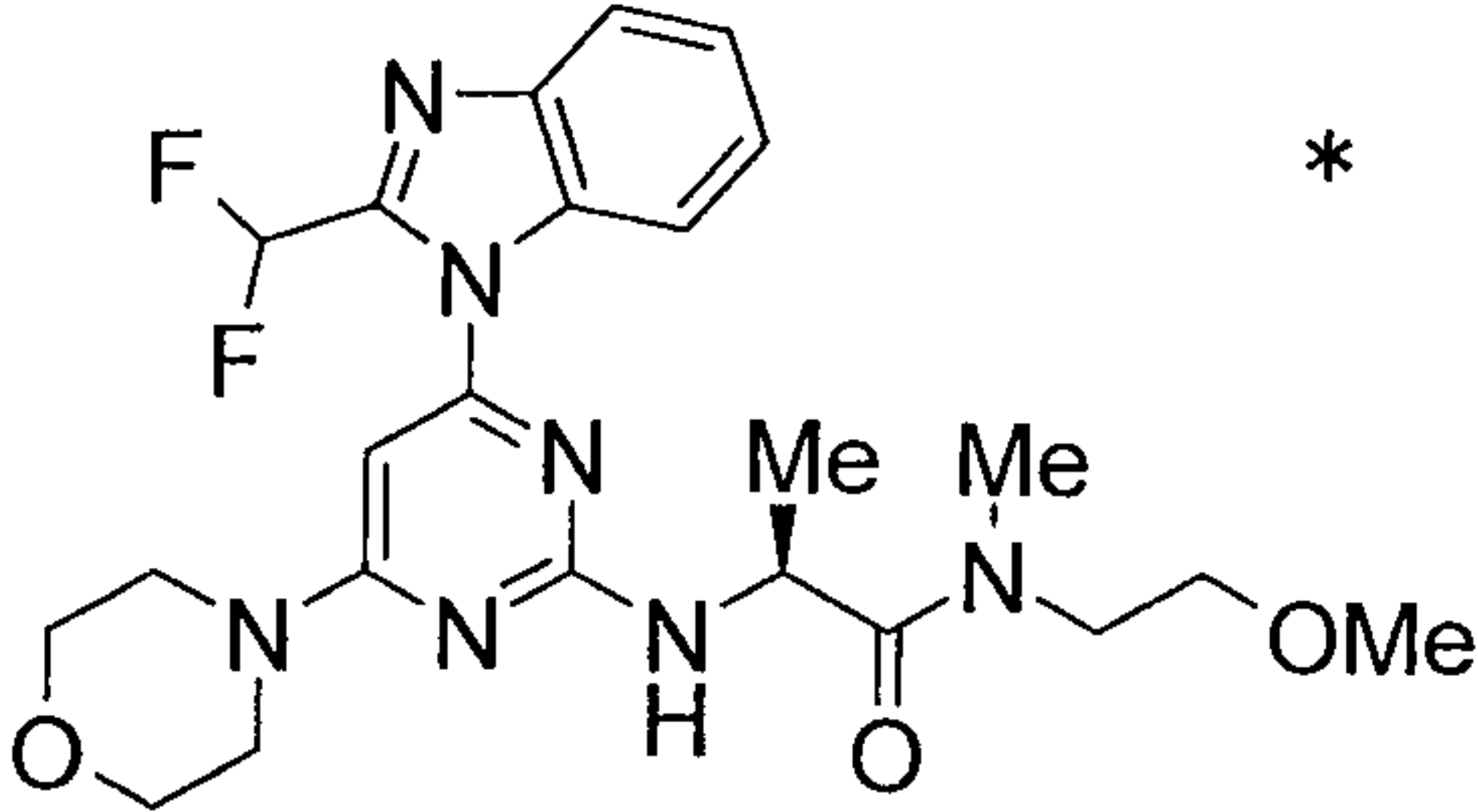
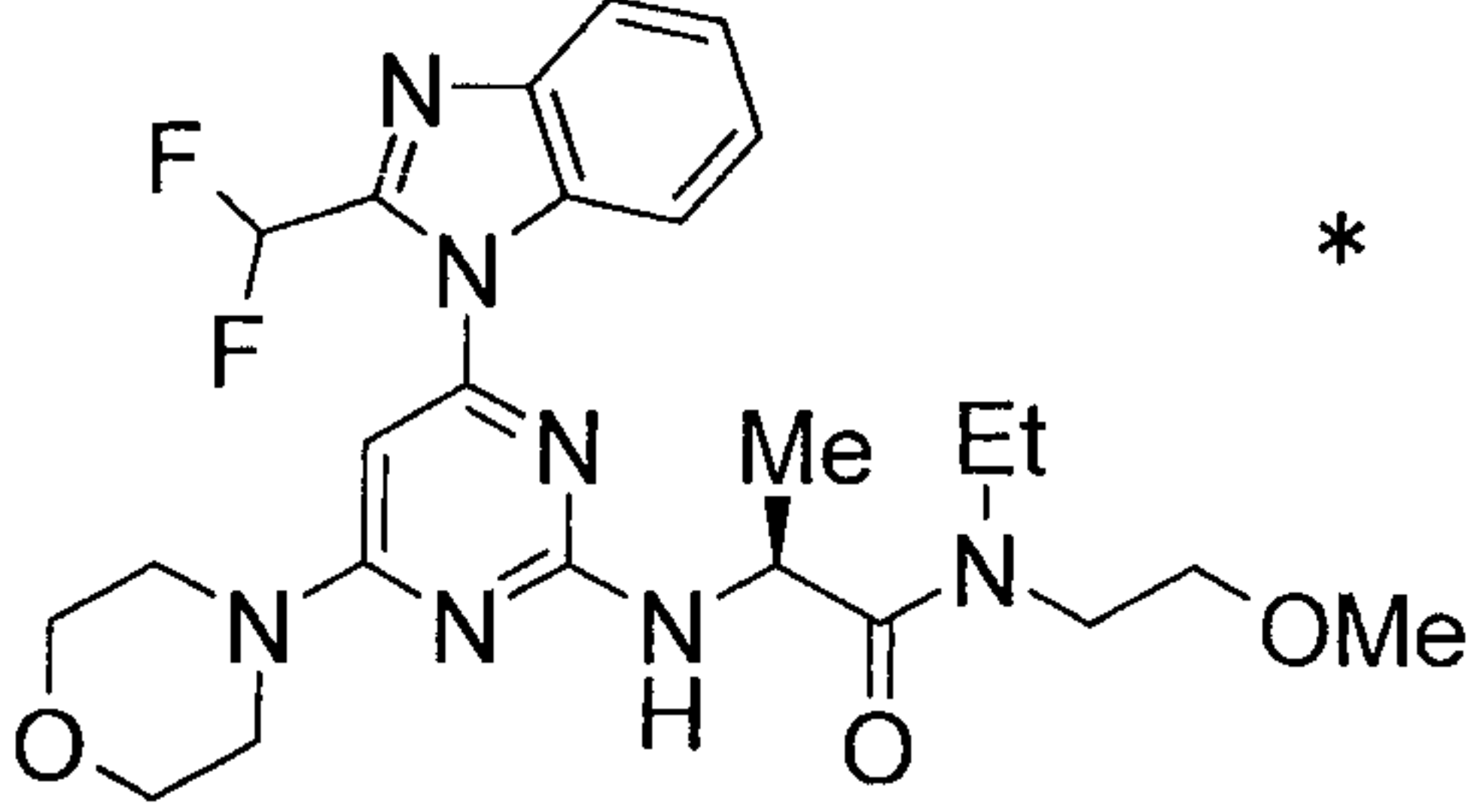
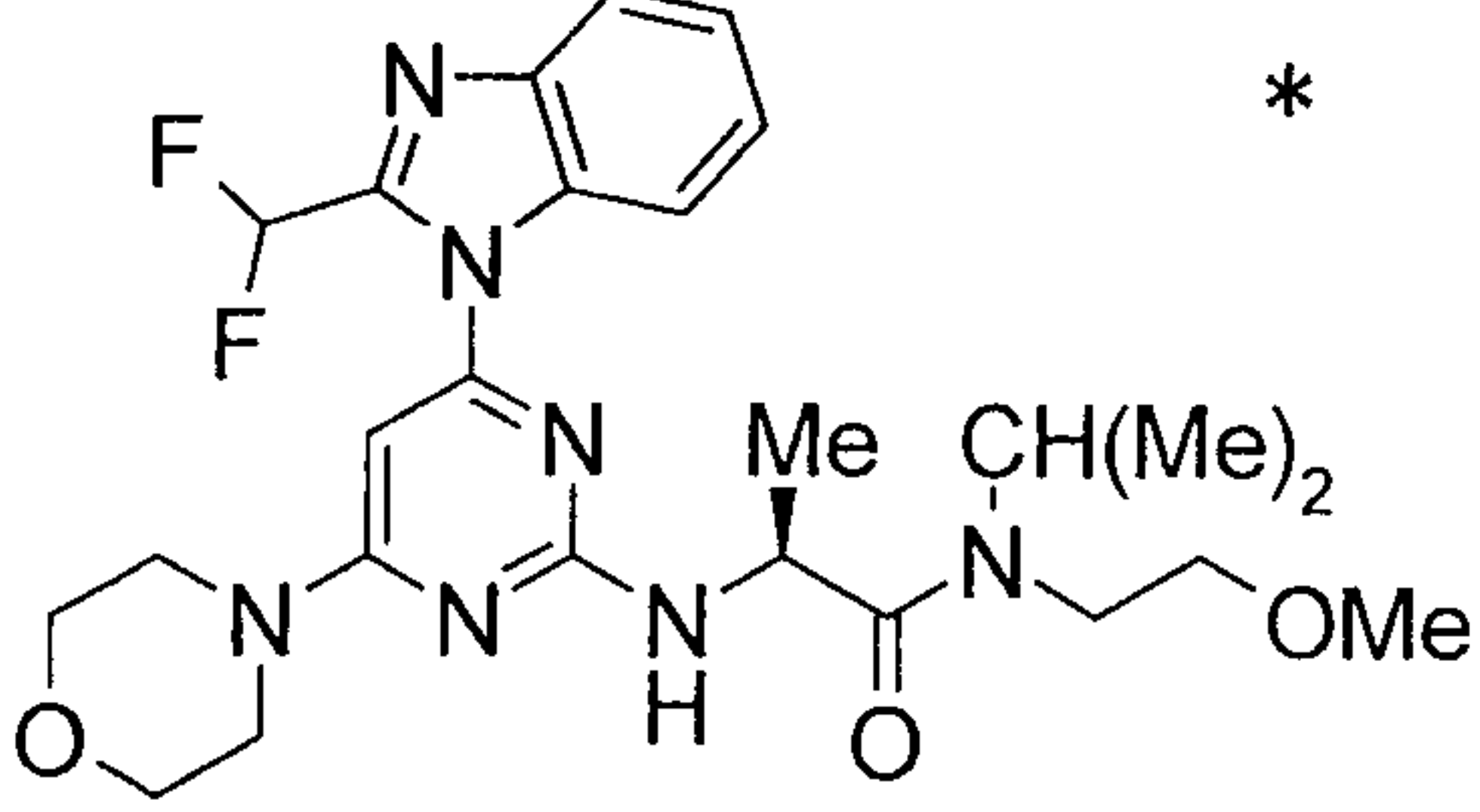
[0331]

[Table 175]

Ex	Str	ESI+	RT
A62		446	2.42
A63		474	2.67
A64		476	2.3
A65		490	2.41

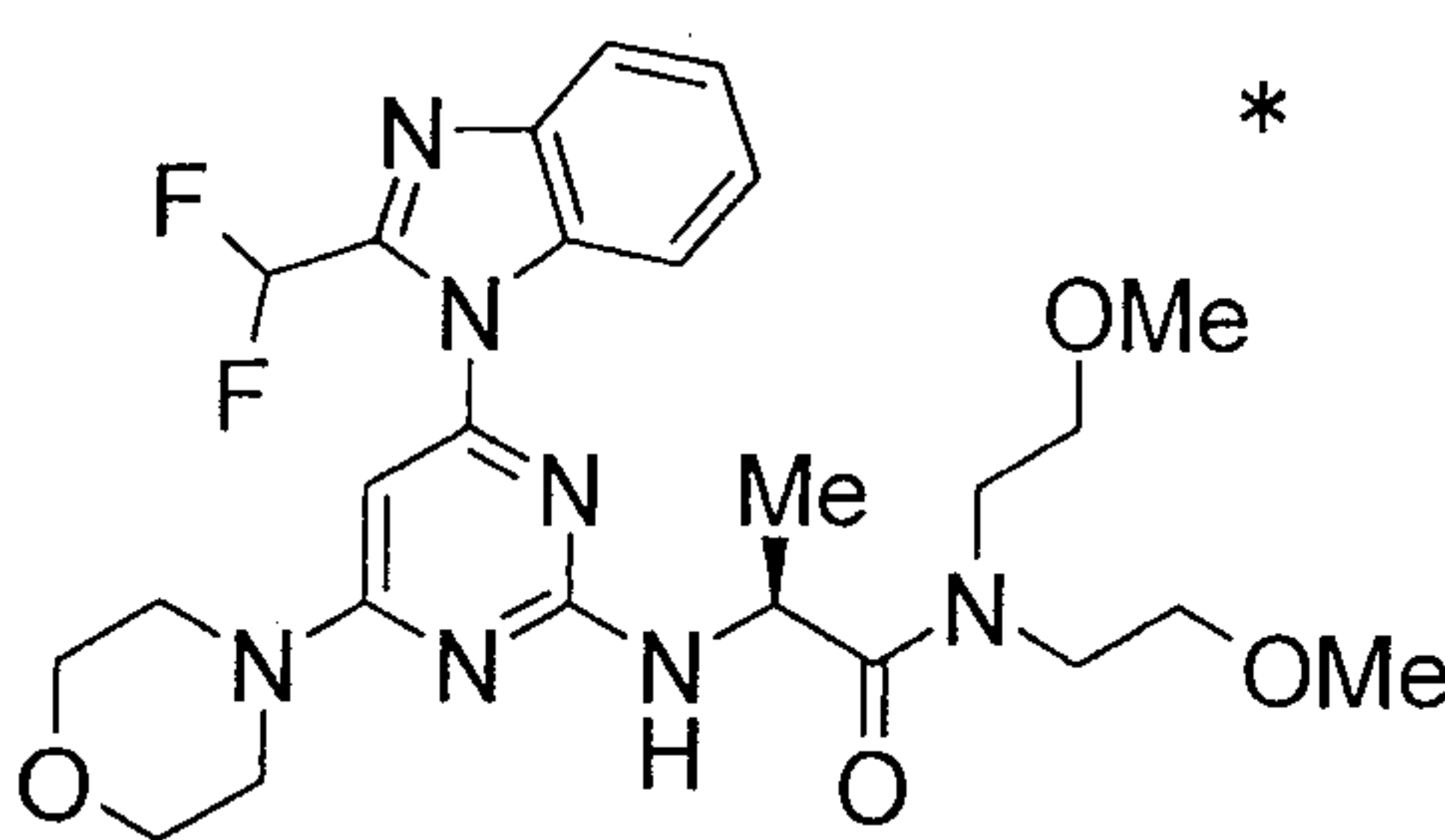
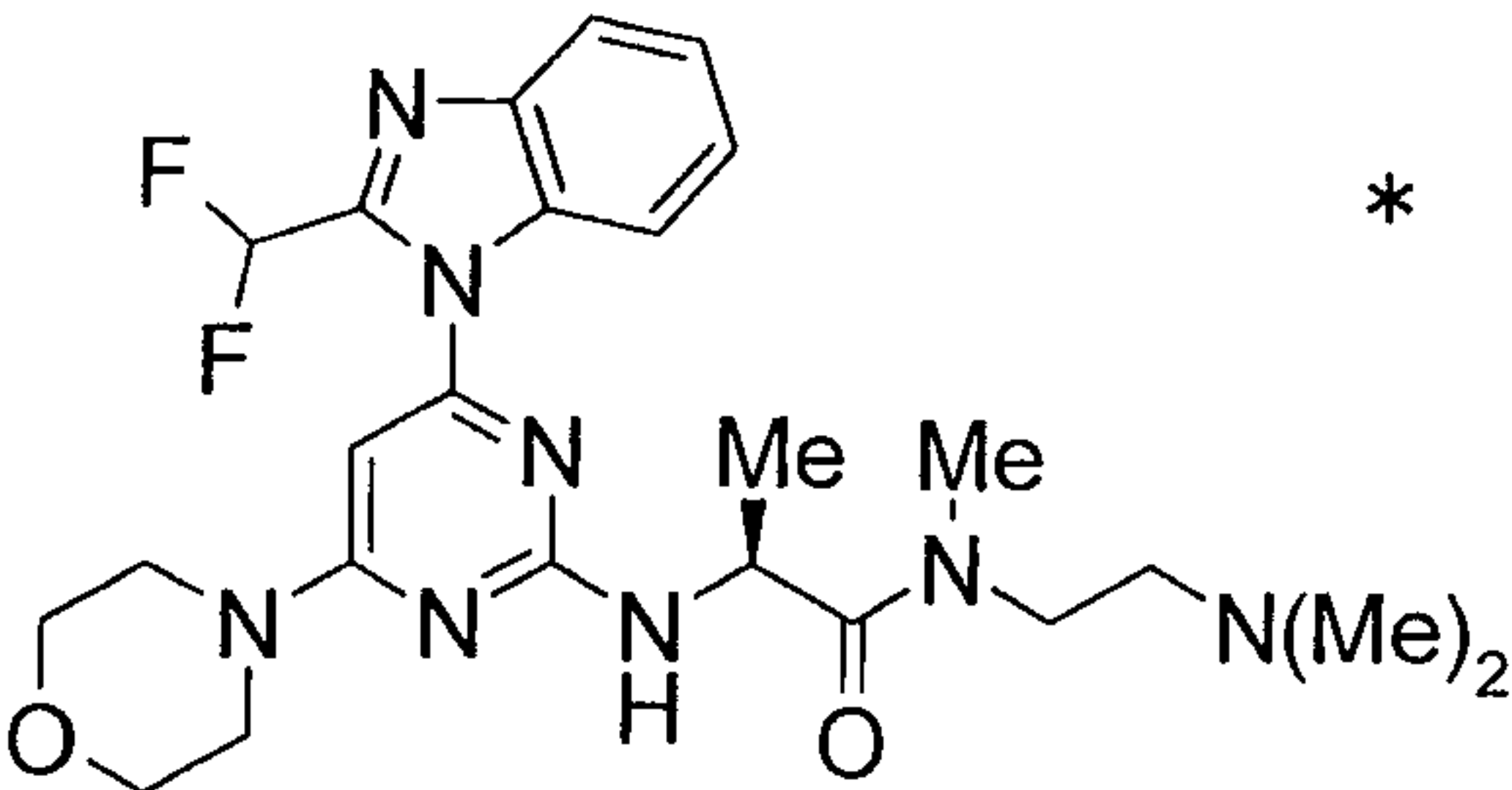
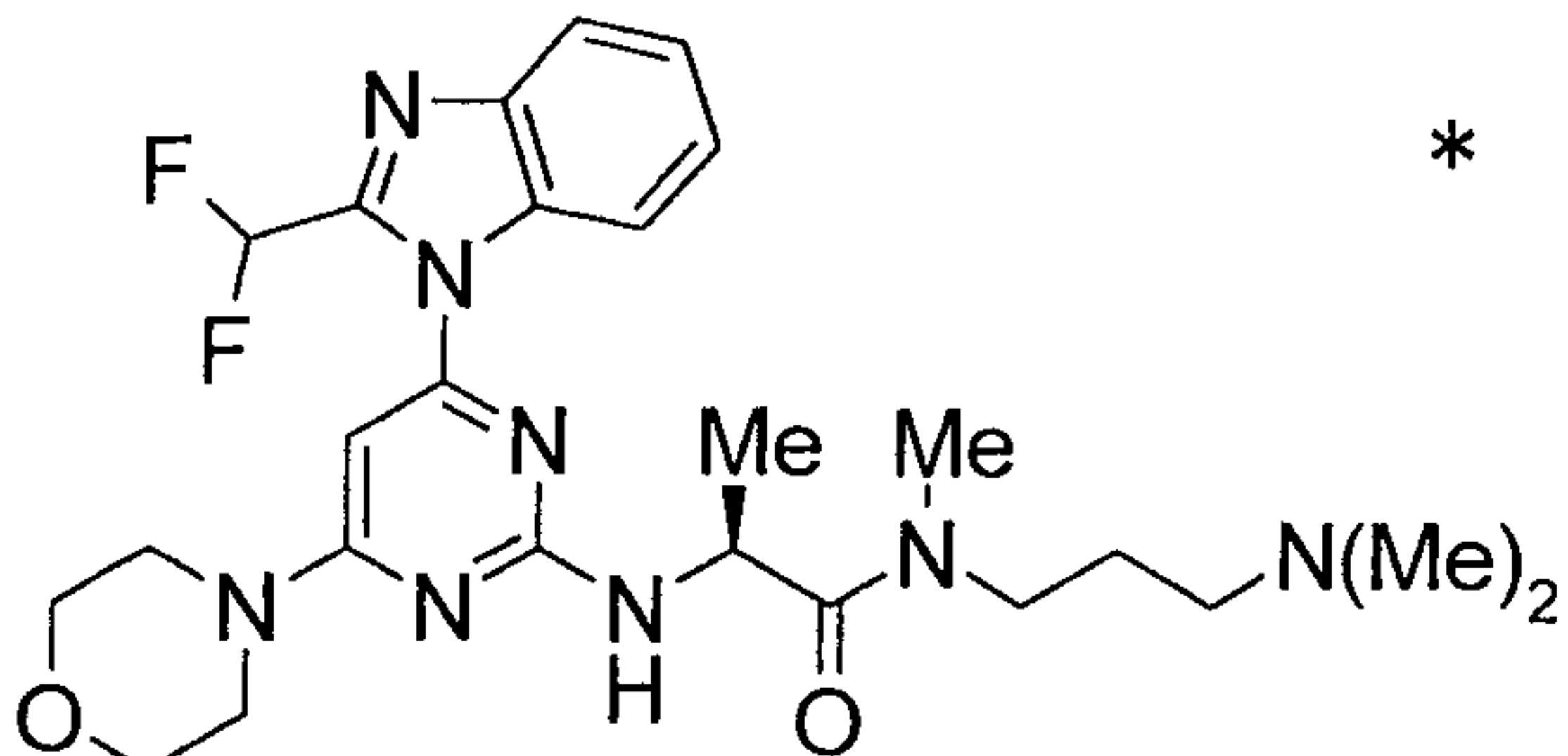
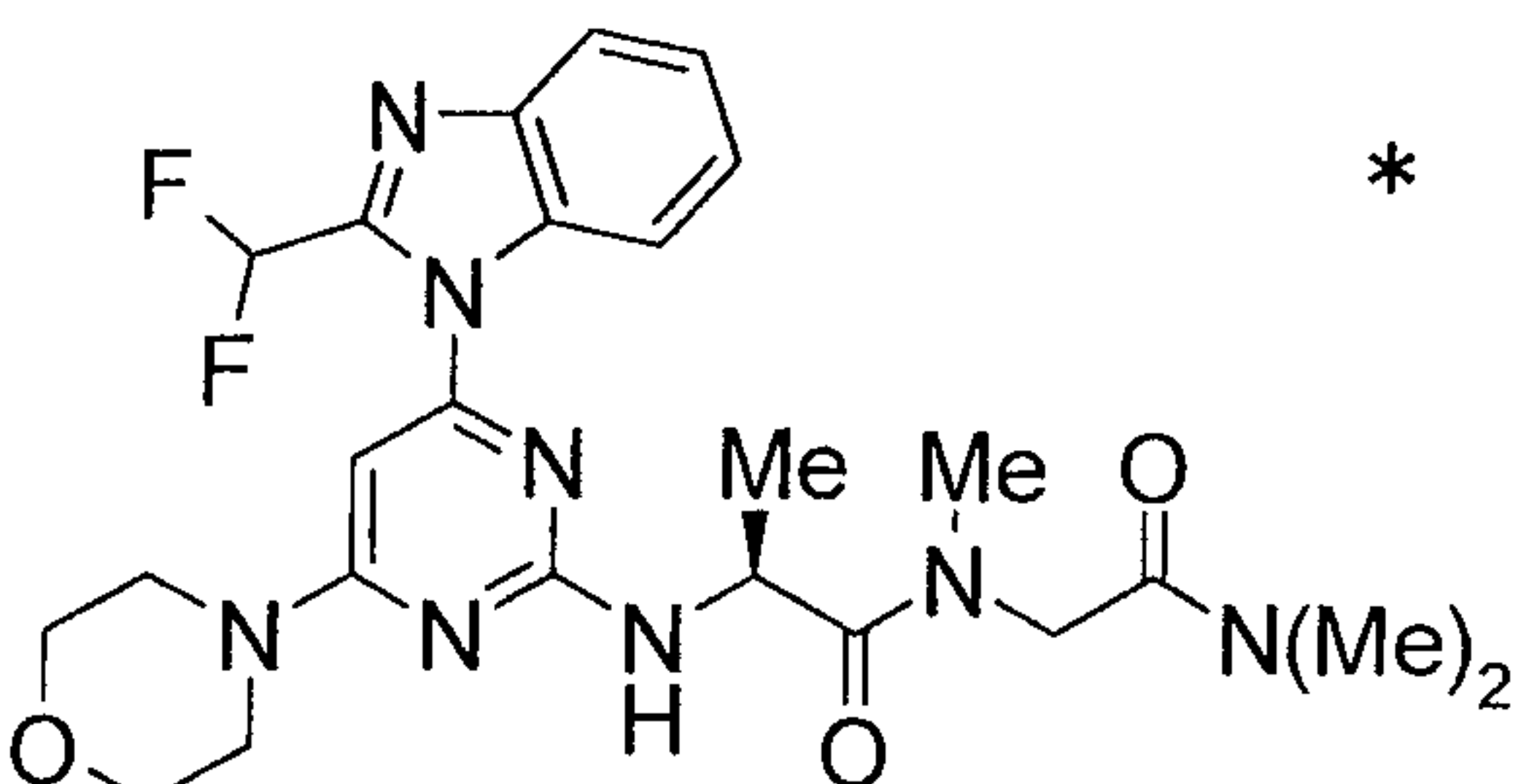
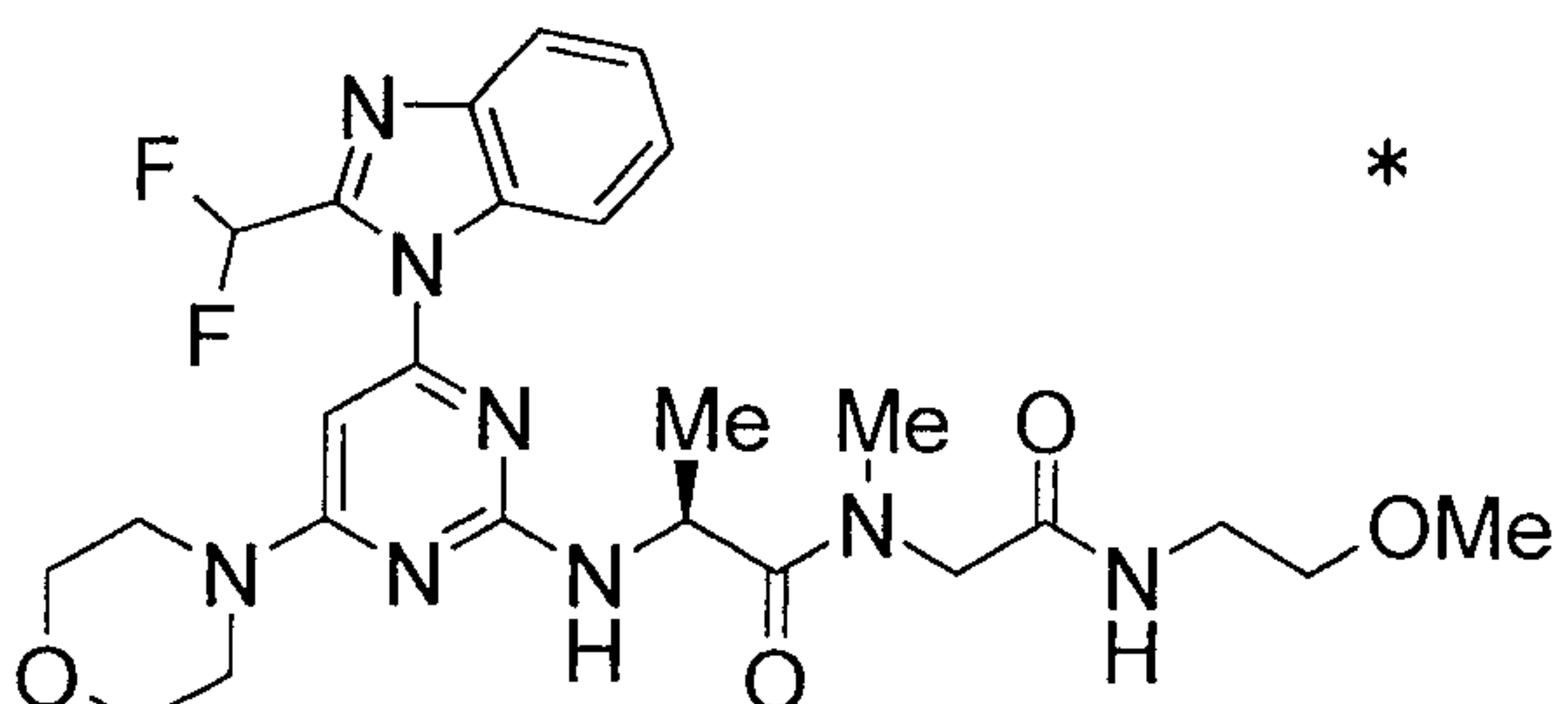
[0332]

[Table 176]

Ex	Str	ESI+	RT
A66		504	2.51
A67		506	2.18
A68		490	2.52
A69		504	2.64
A70		518	2.74

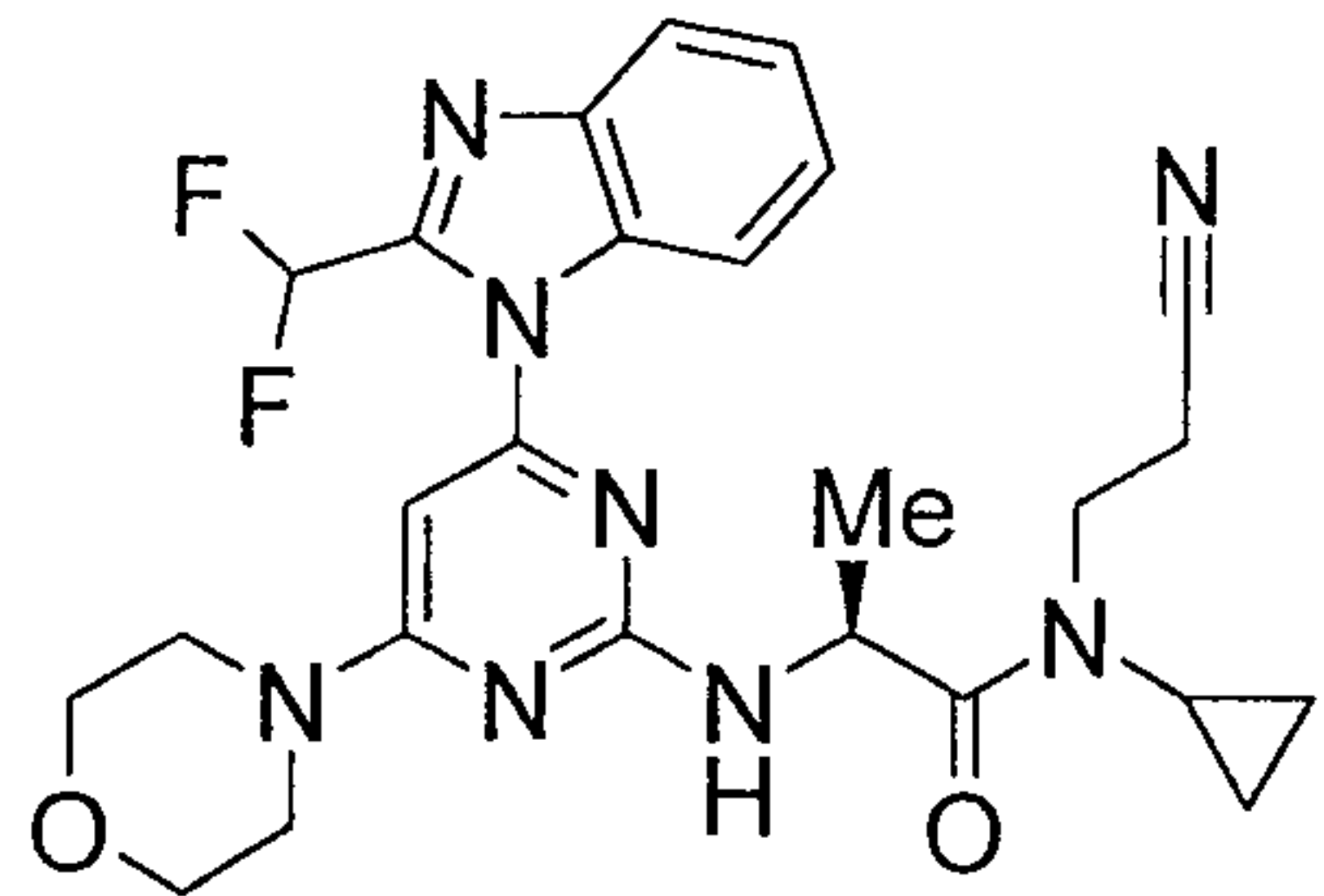
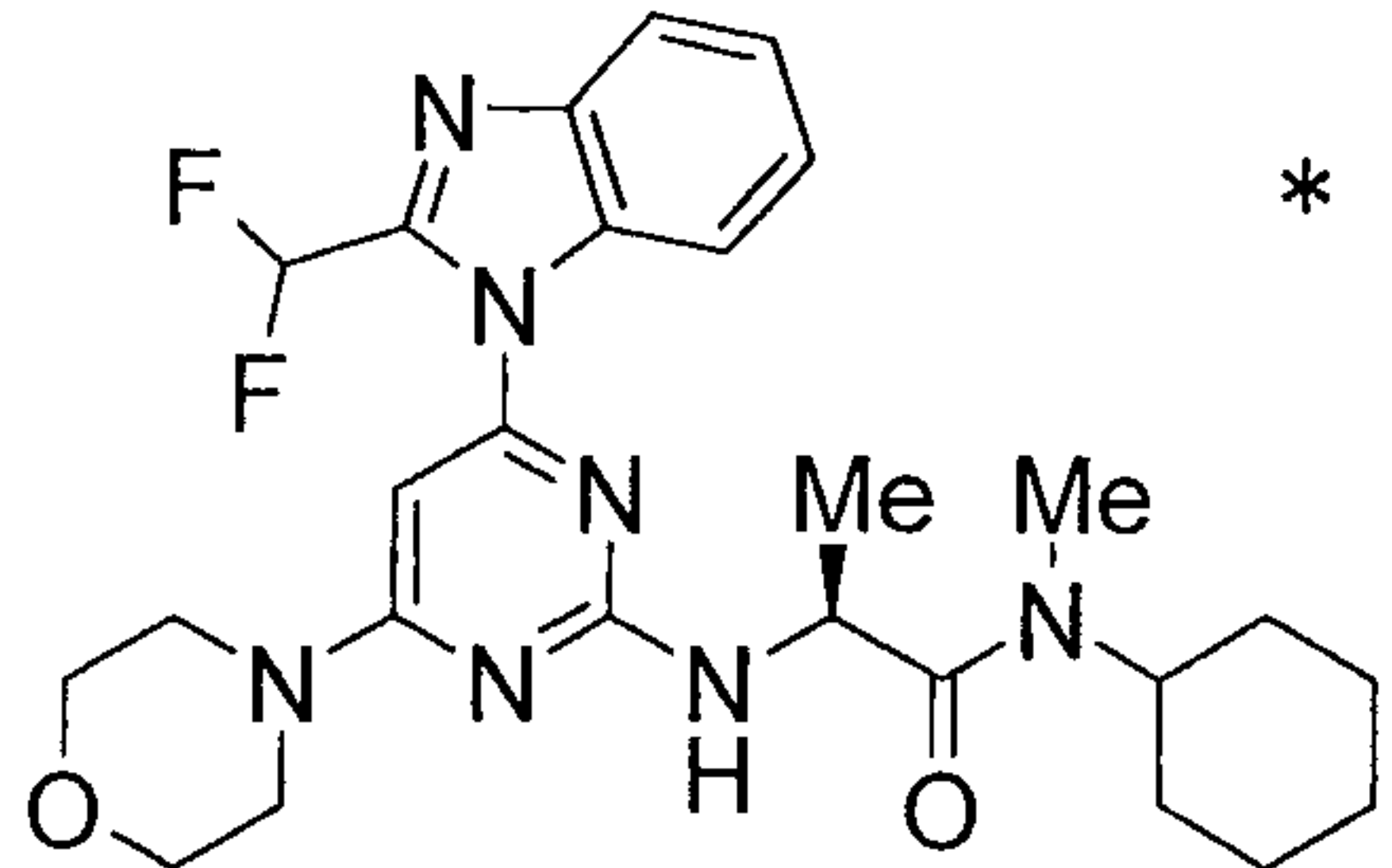
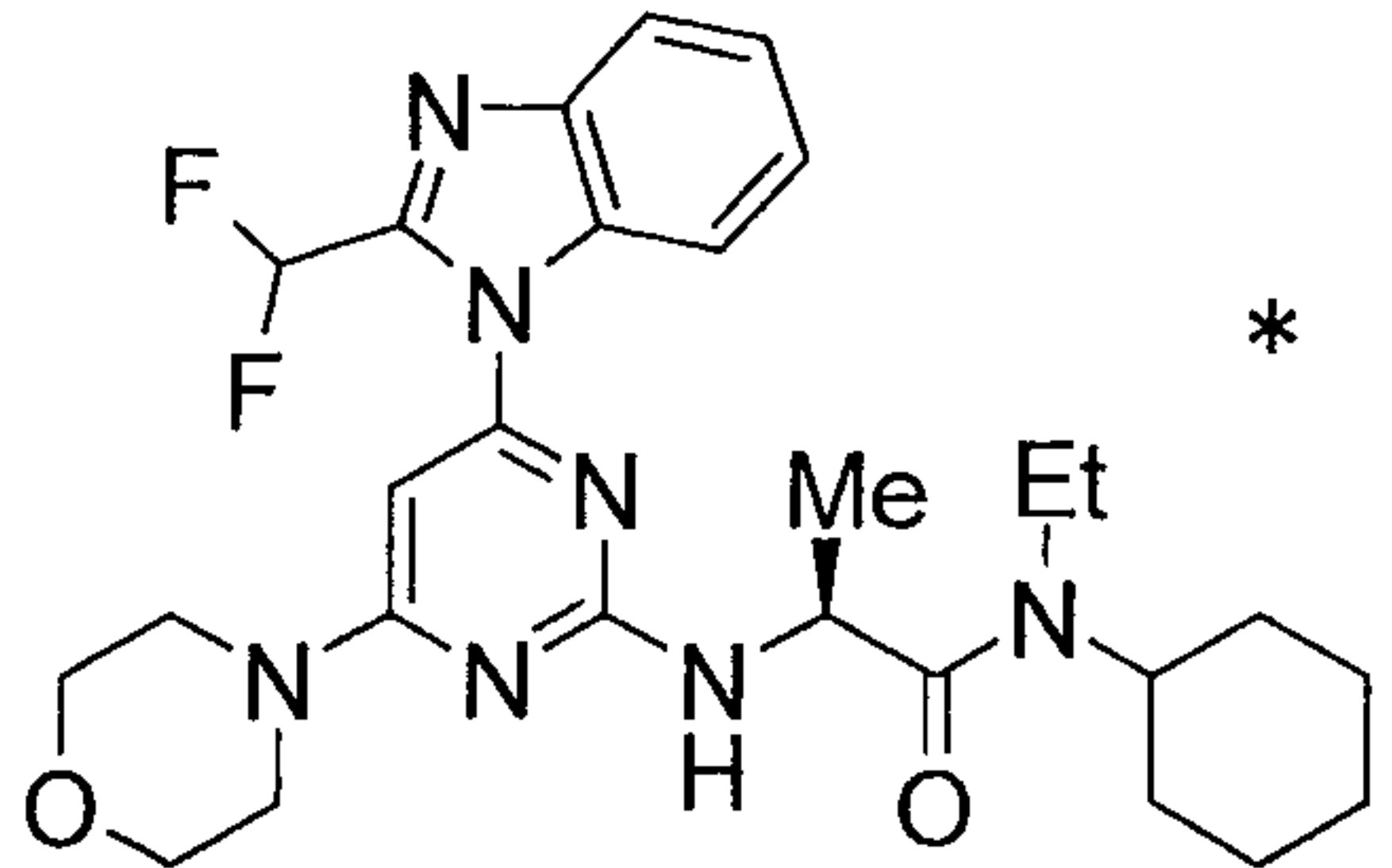
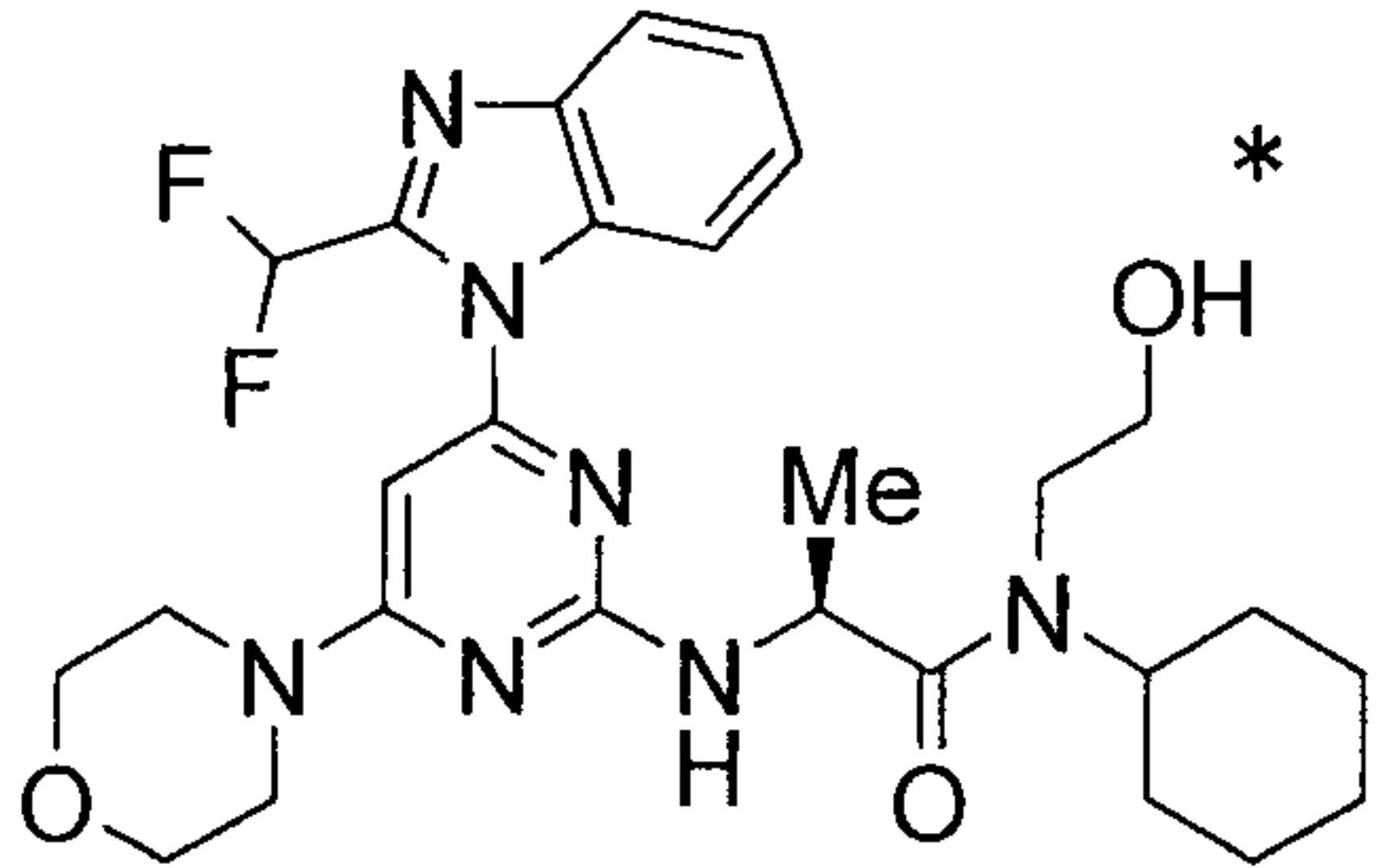
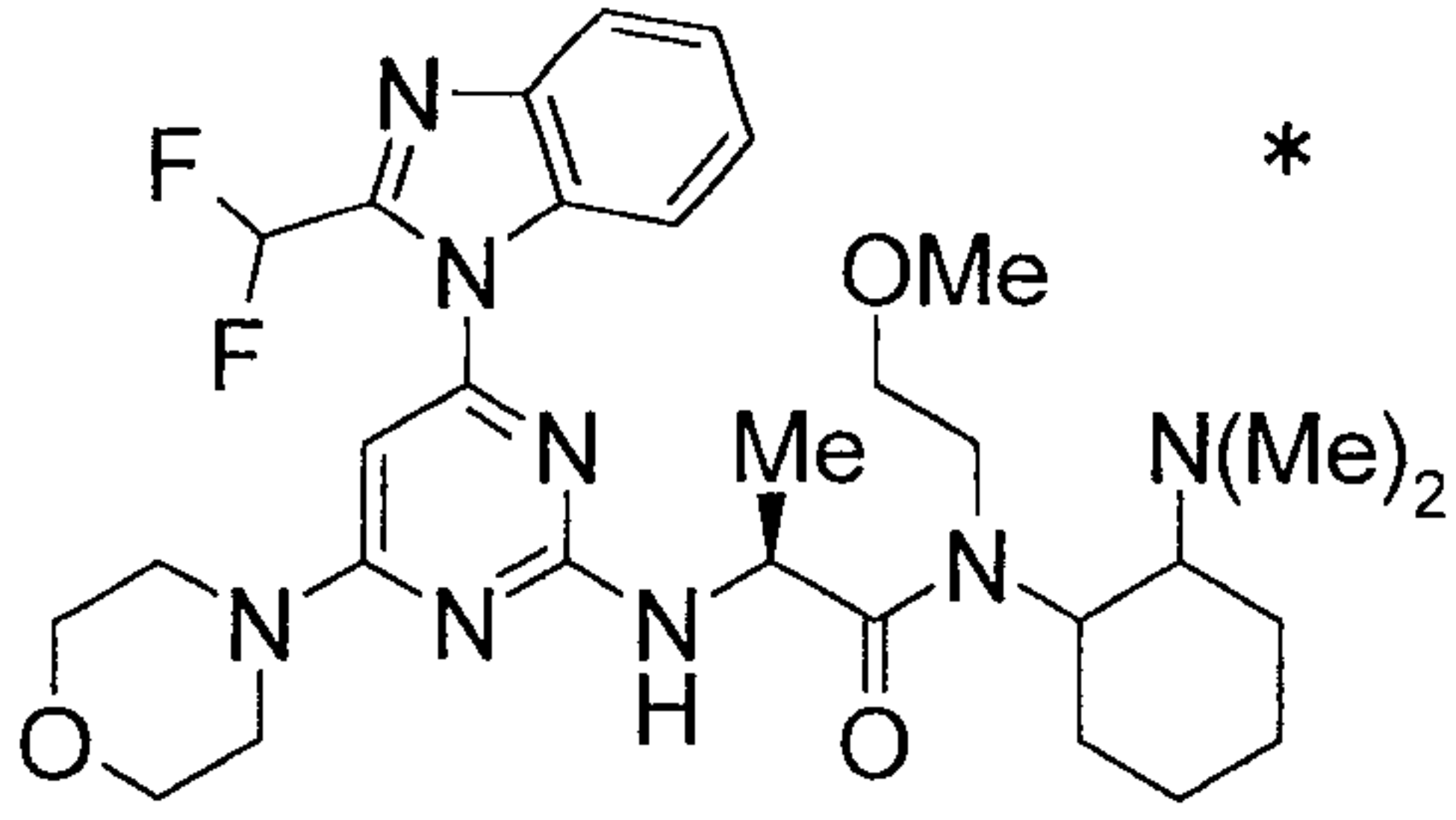
[0333]

[Table 177]

Ex	Str	ESI+	RT
A71		534	2.62
A72		503	1.87
A73		517	1.88
A74		517	2.35
A75		547	2.36

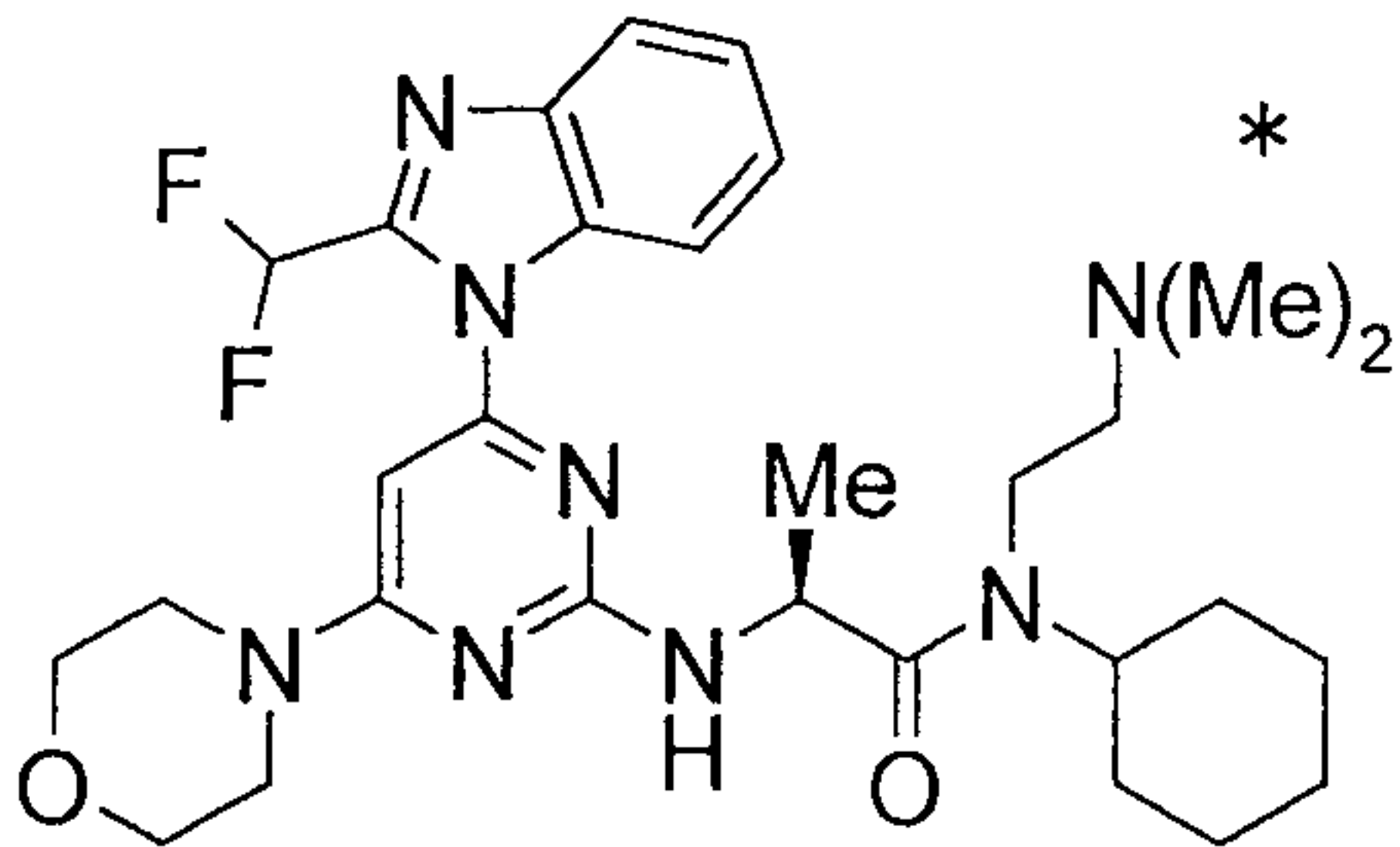
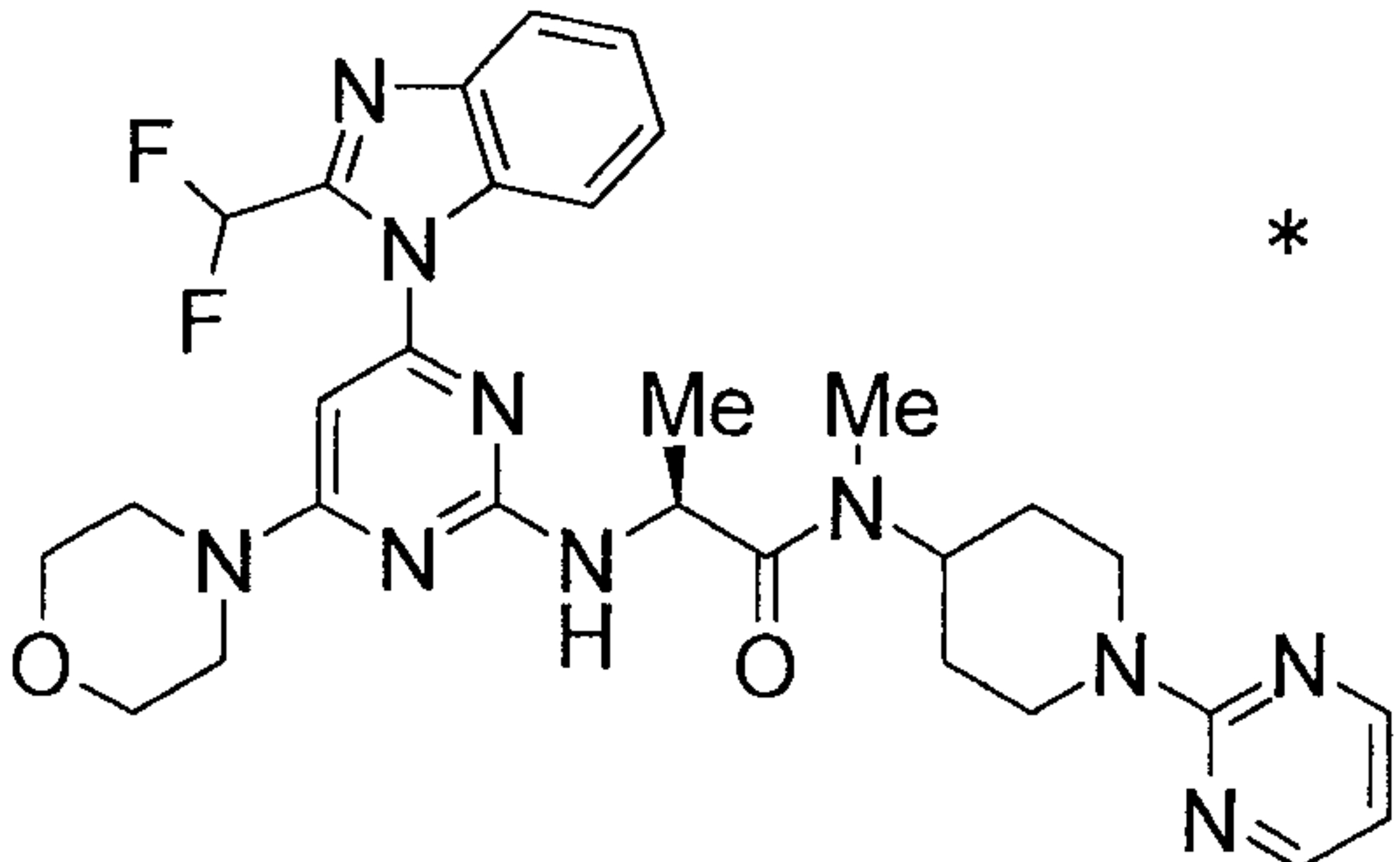
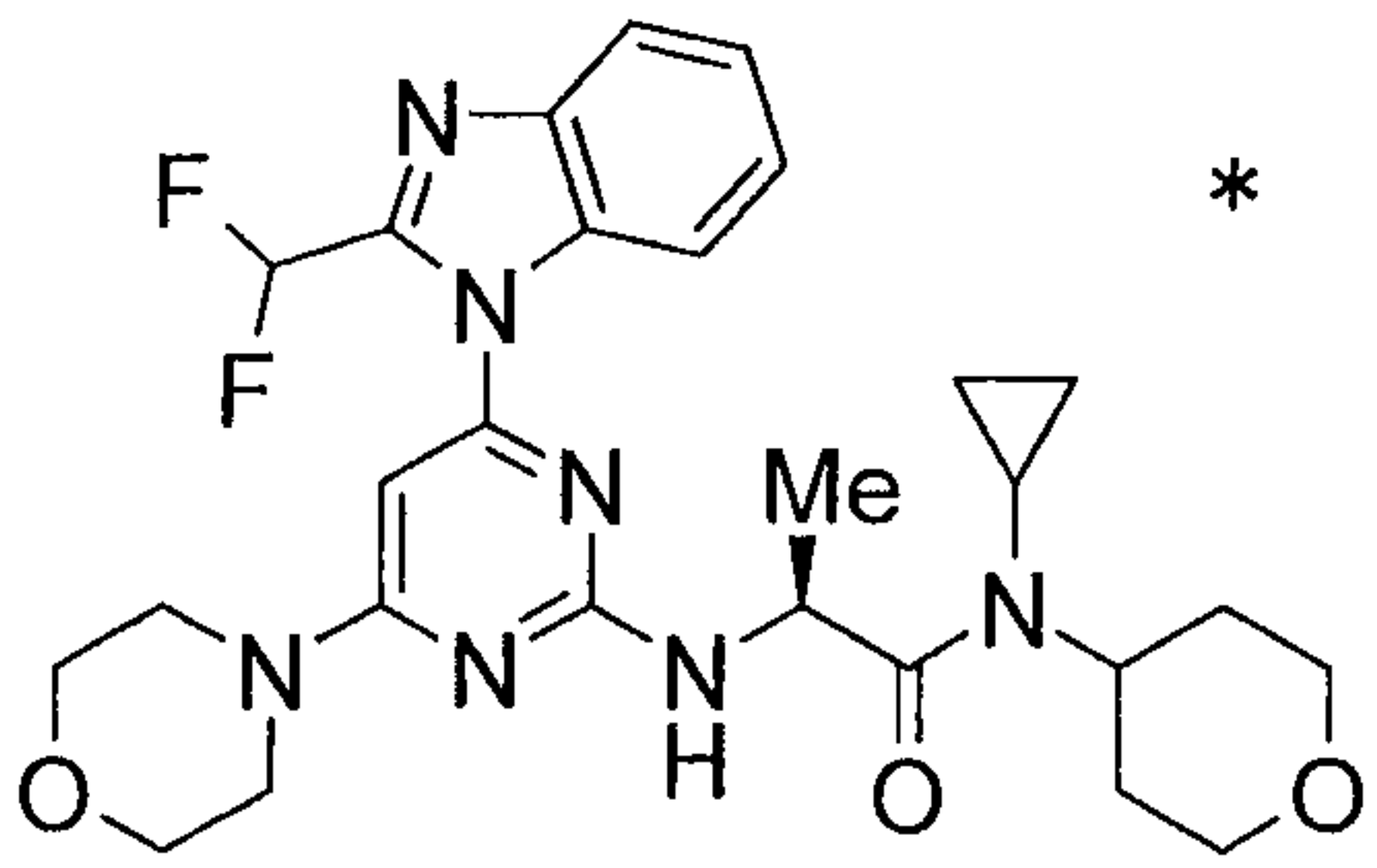
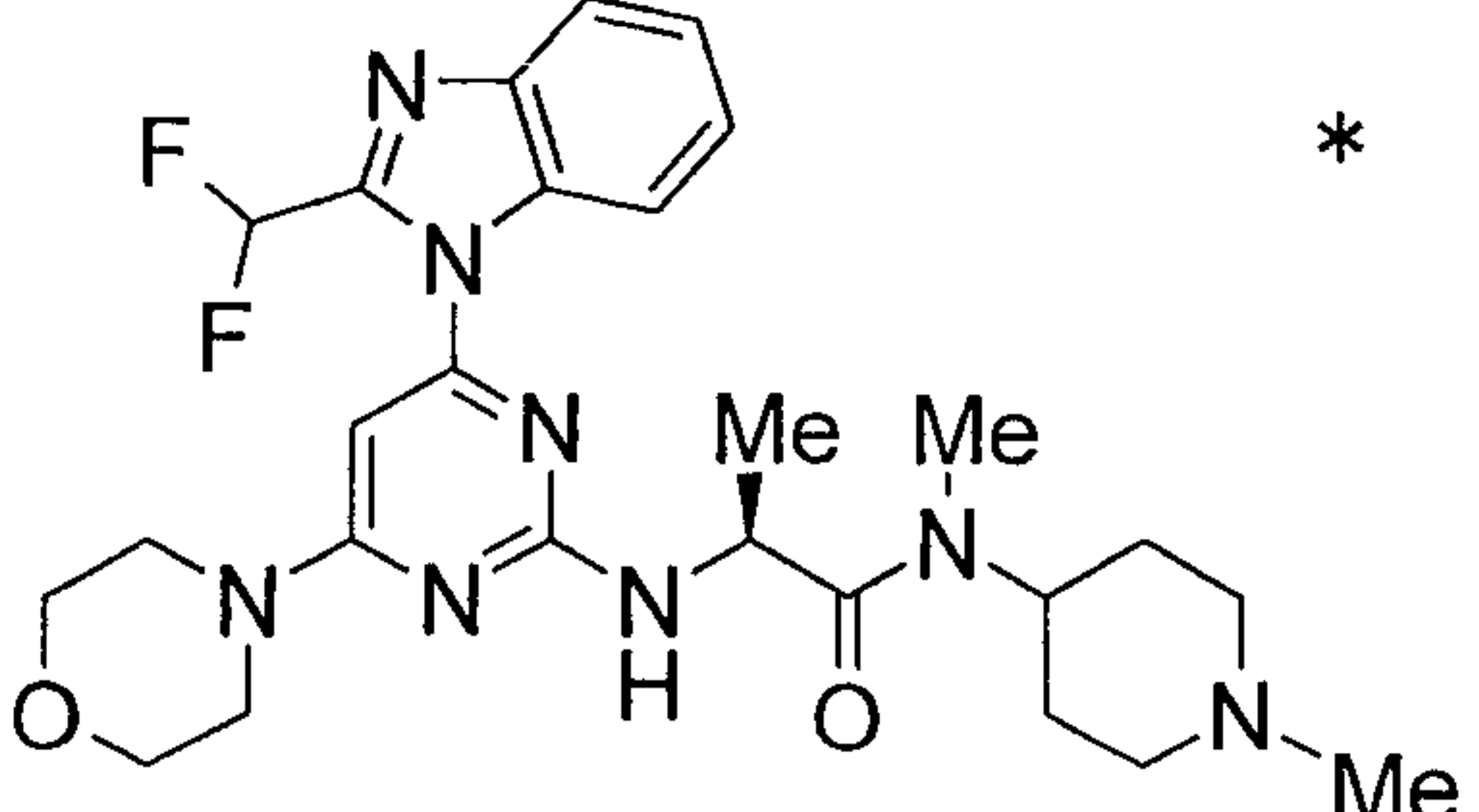
[0334]

[Table 178]

Ex	Str	ESI+	RT
A76		511	2.53
A77		514	2.94
A78		528	3.06
A79		544	2.79
A80		601	2.07

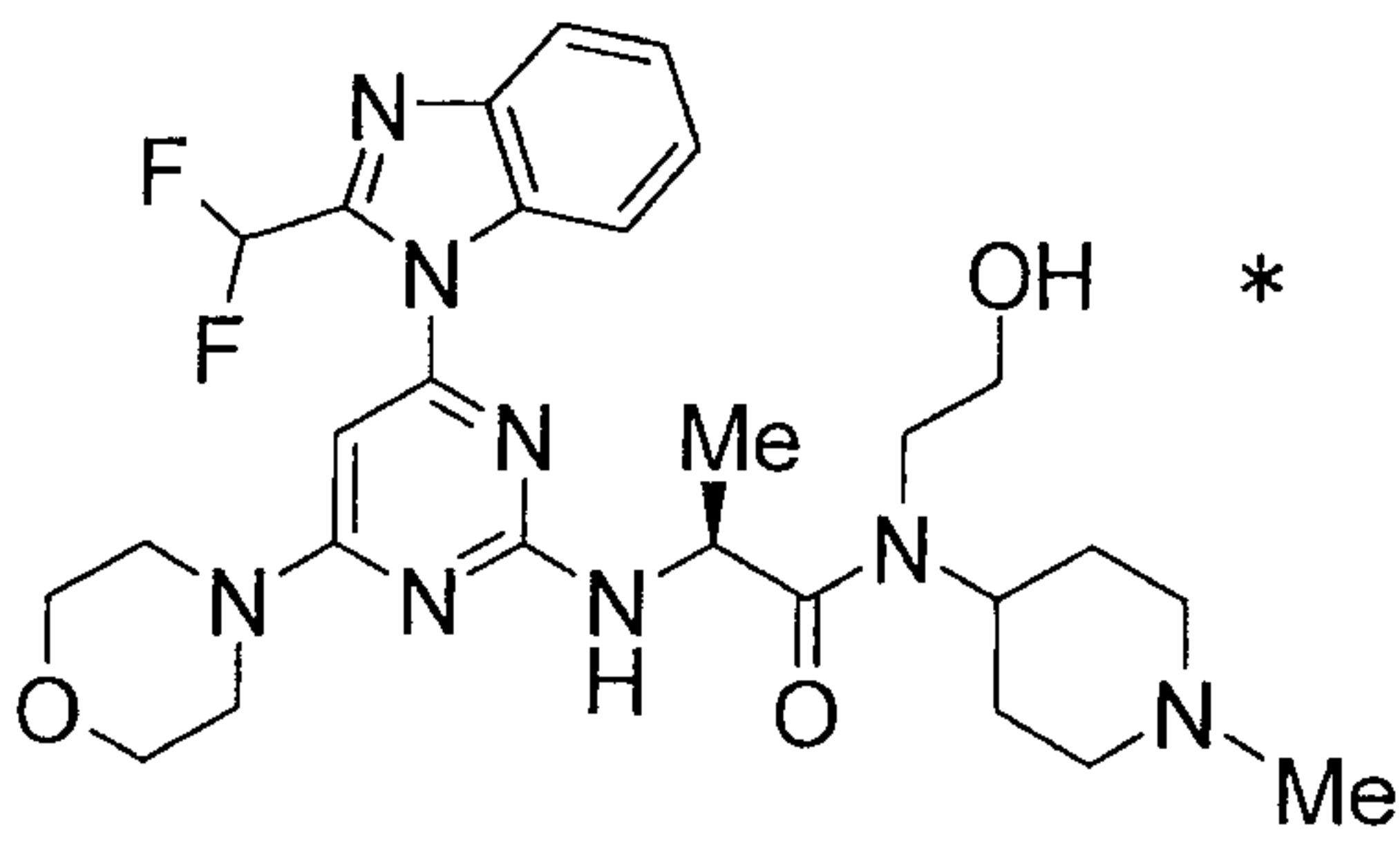
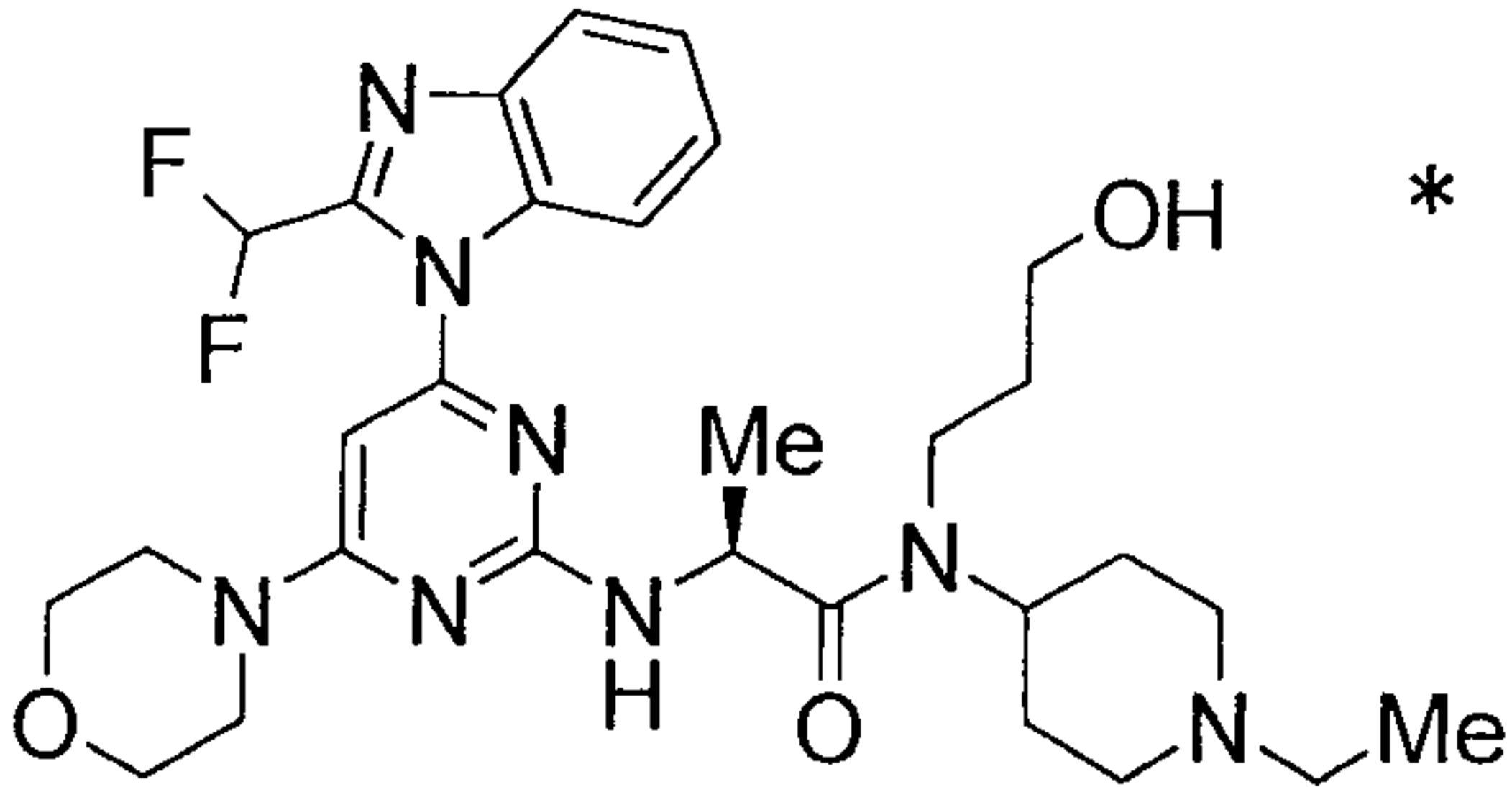
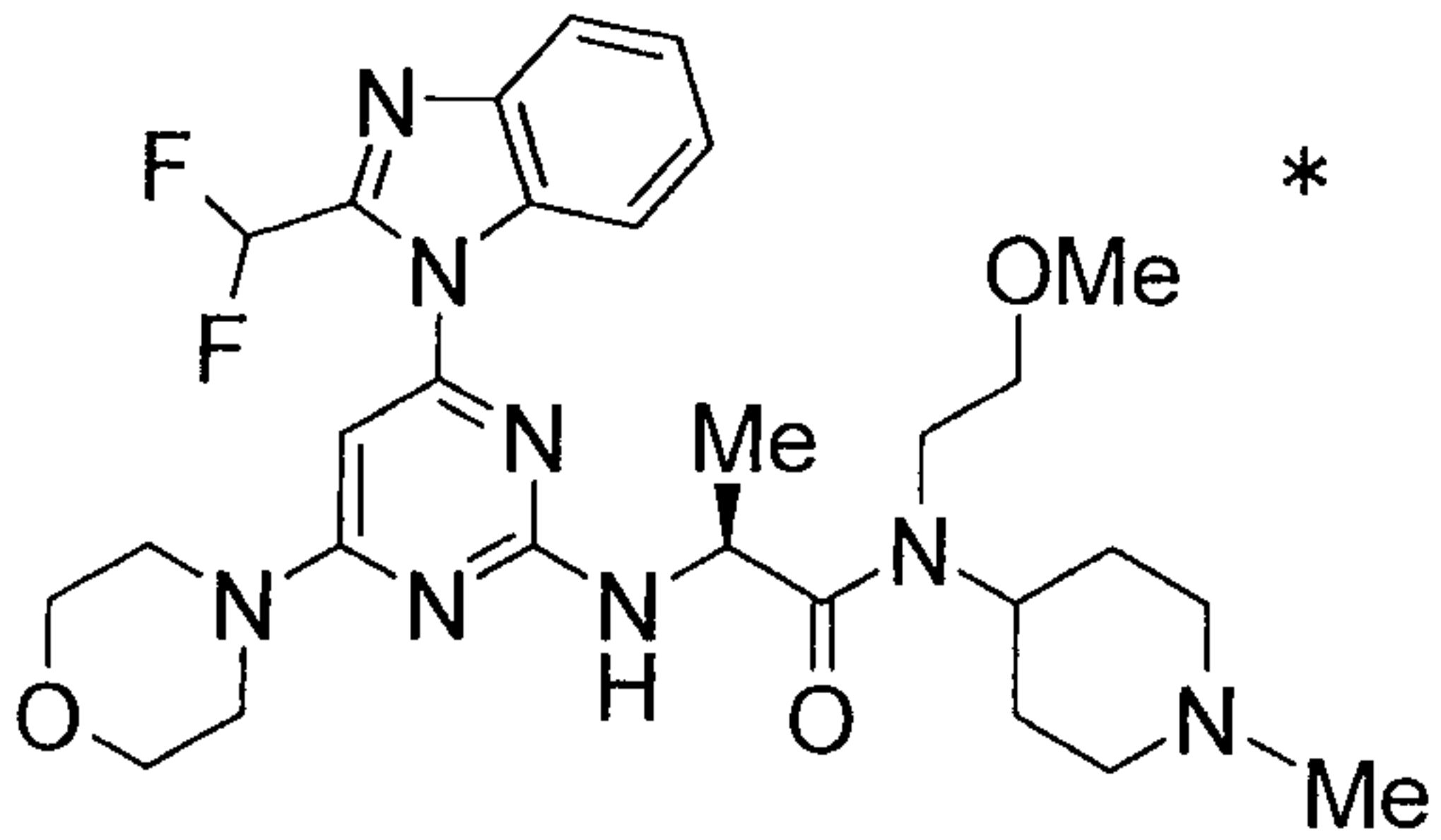
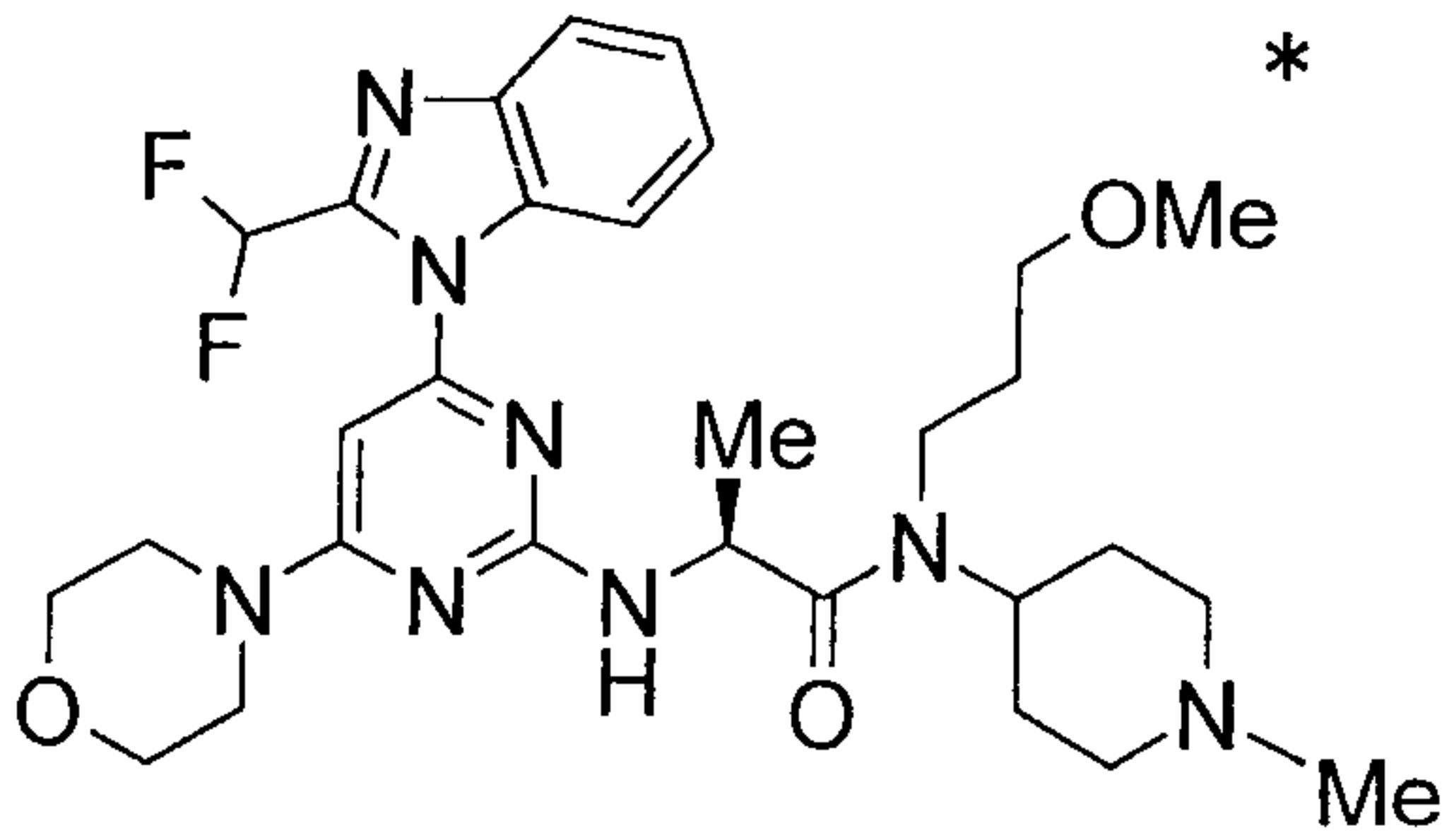
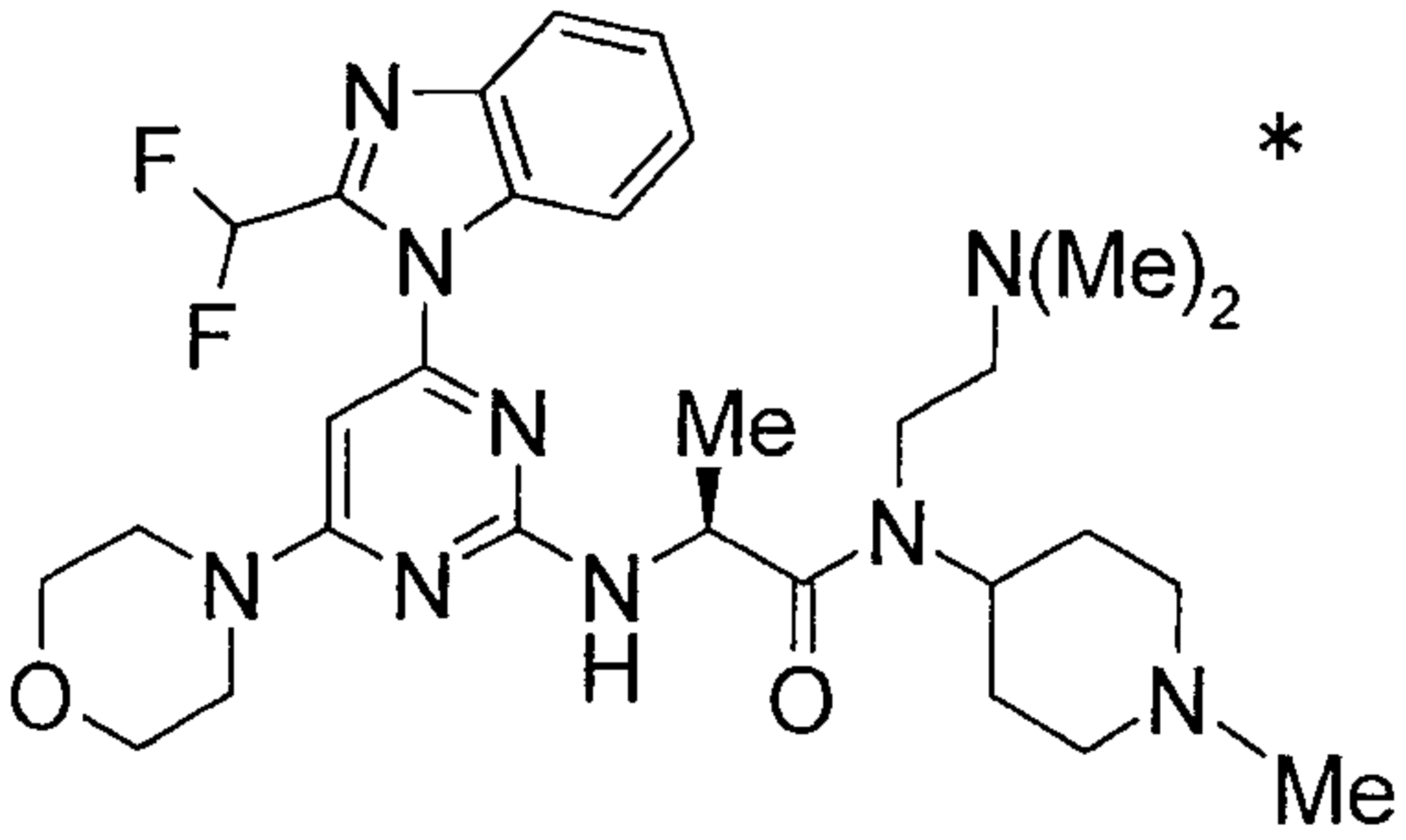
[0335]

[Table 179]

Ex	Str	ESI+	RT
A81		571	2.31
A82		593	2.73
A83		542	2.69
A84		529	1.88

[0336]

[Table 180]

Ex	Str	ESI+	RT
A85		559	1.84
A86		587	1.88
A87		573	2.02
A88		587	2.05
A89		586	1.41

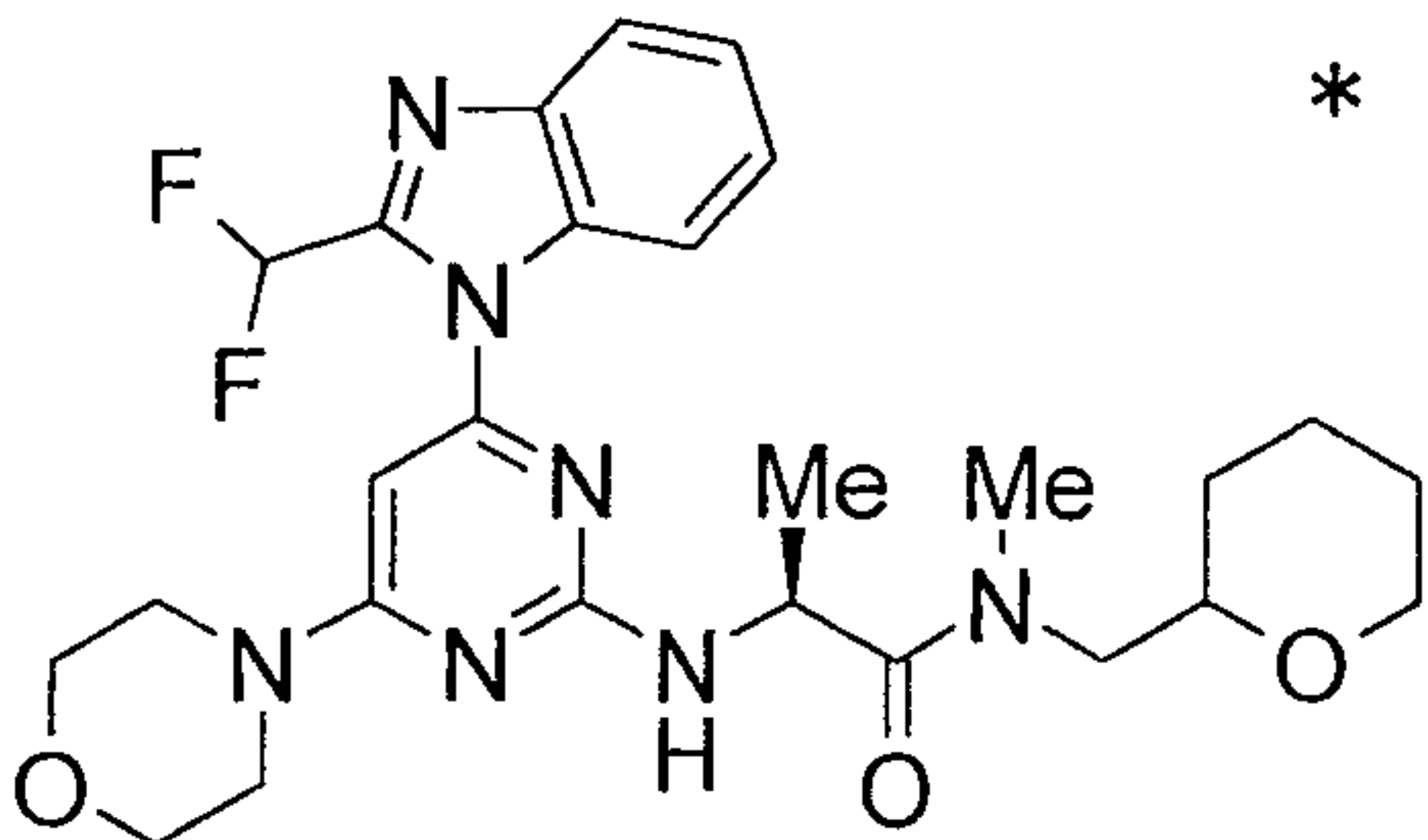
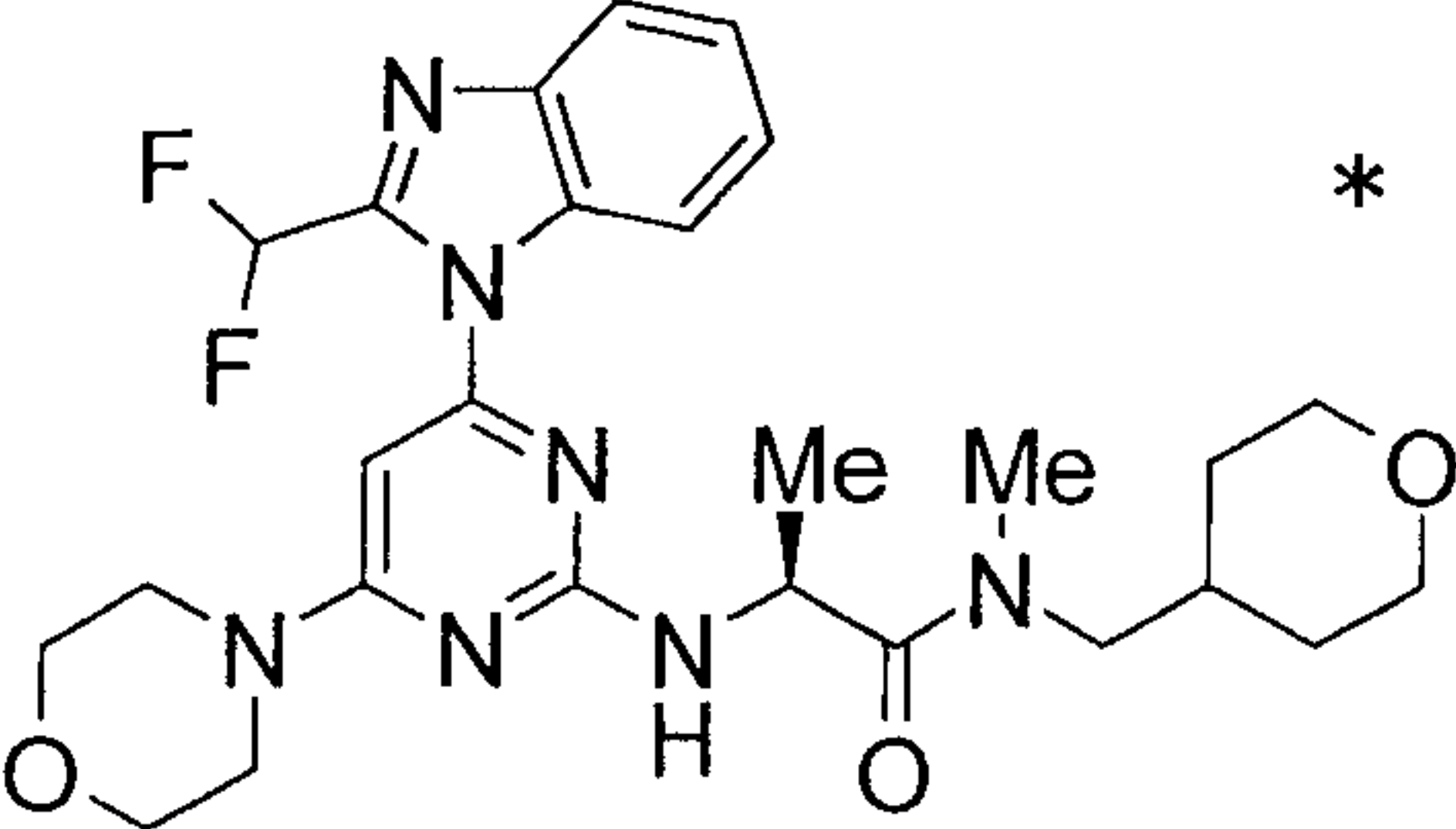
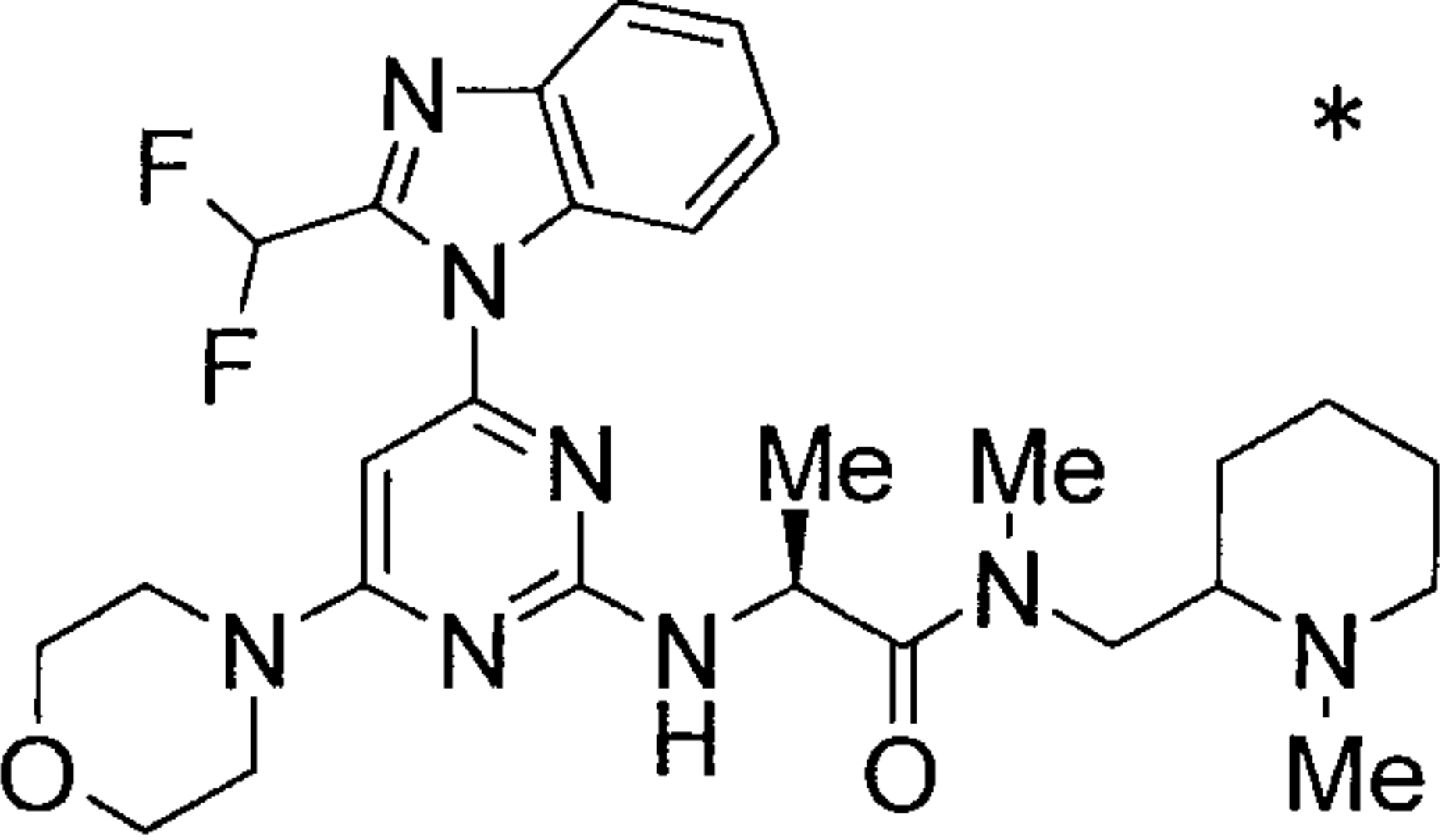
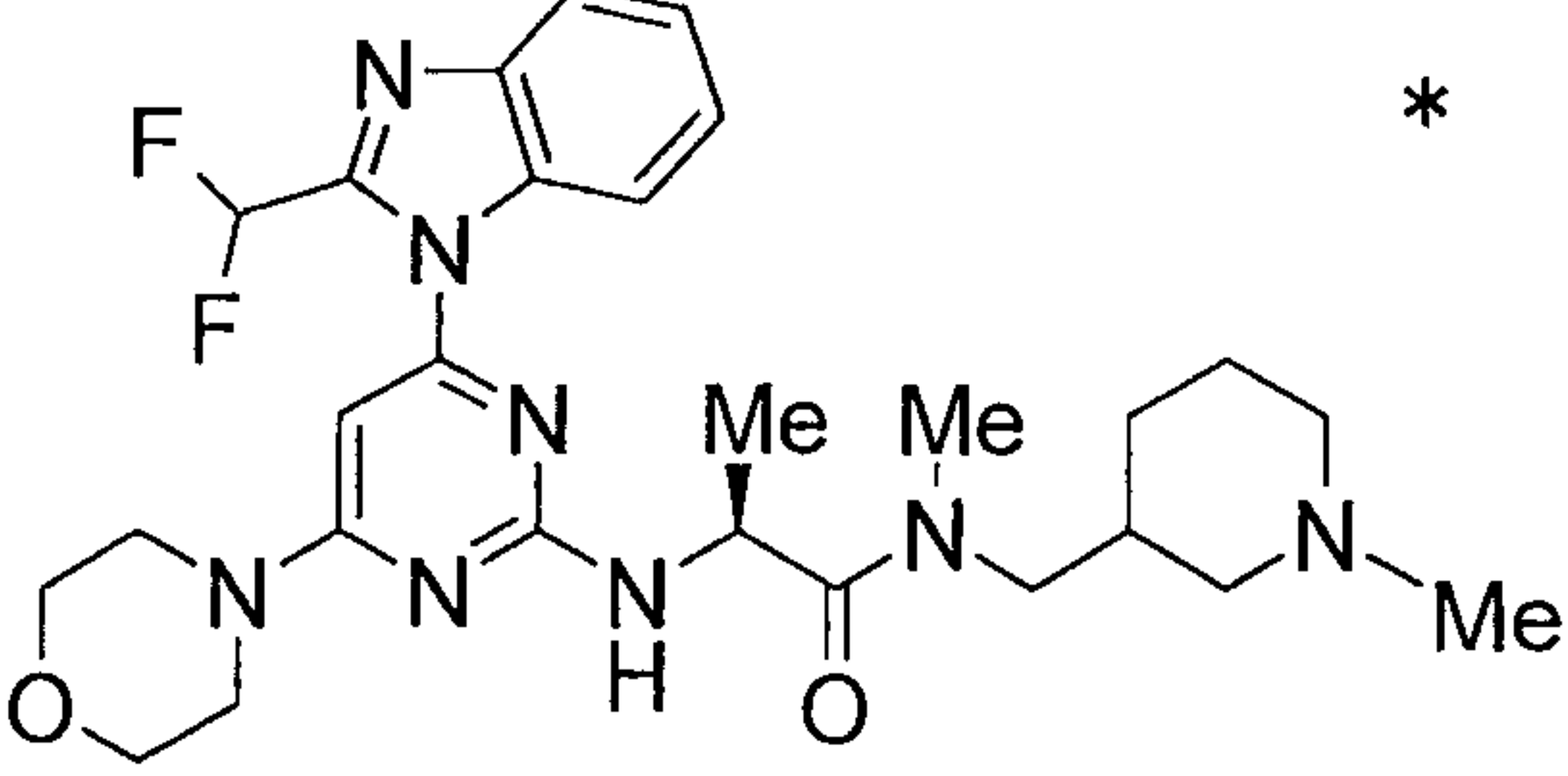
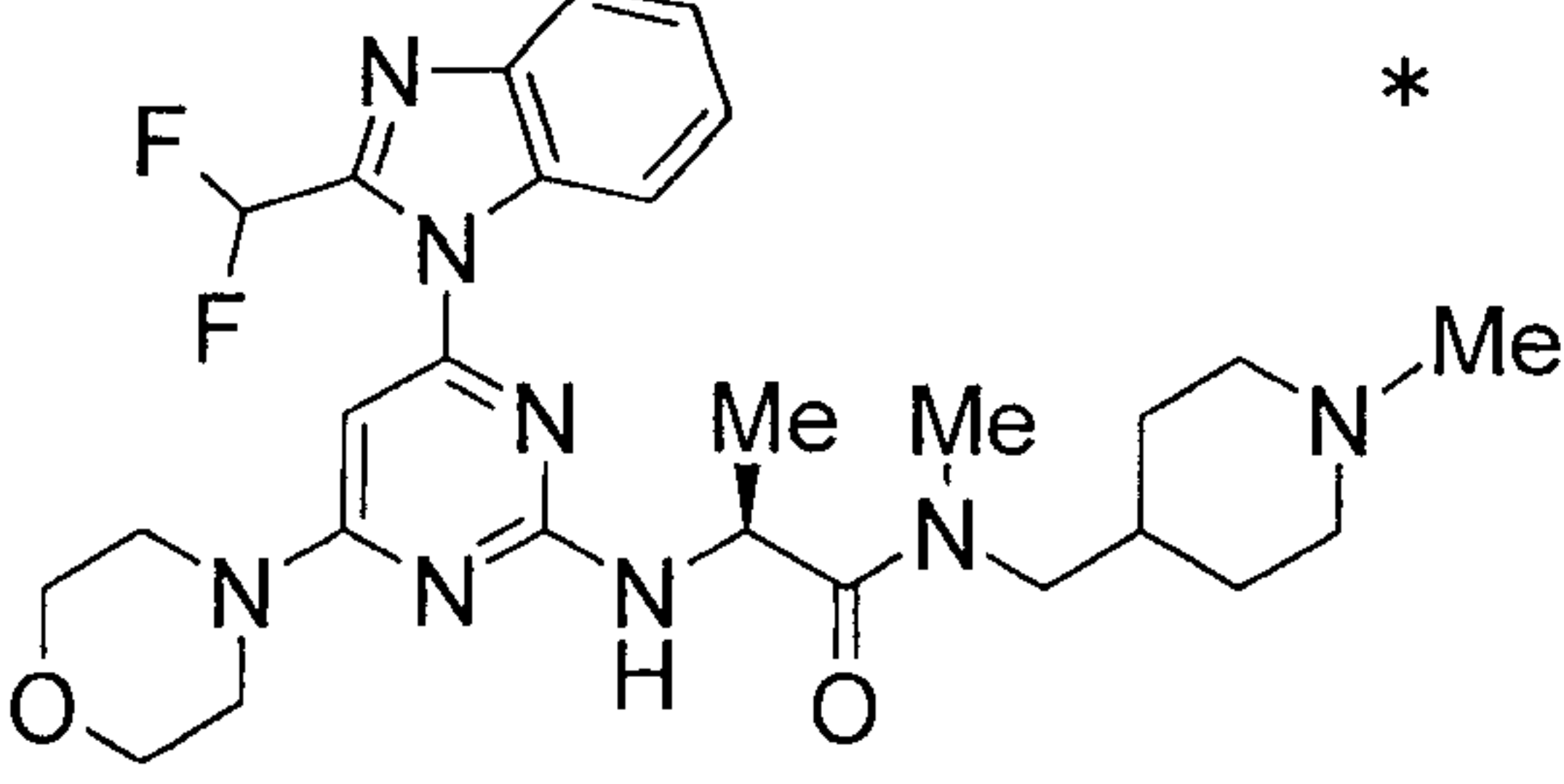
[0337]

[Table 181]

Ex	Str	ESI+	RT
A90		600	1.41
A91		583	2.58
A92		601	2.46
A93		587	2.69

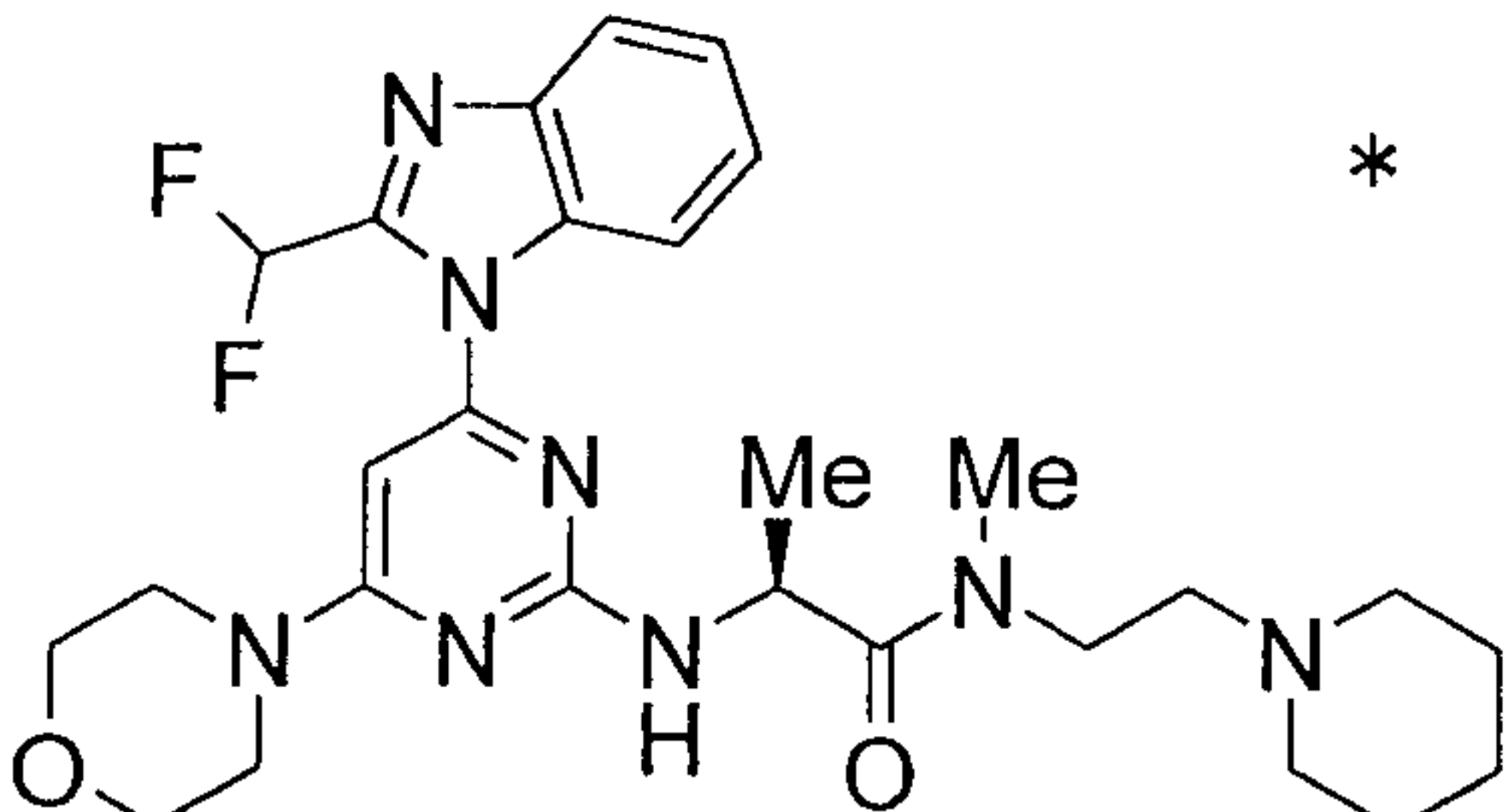
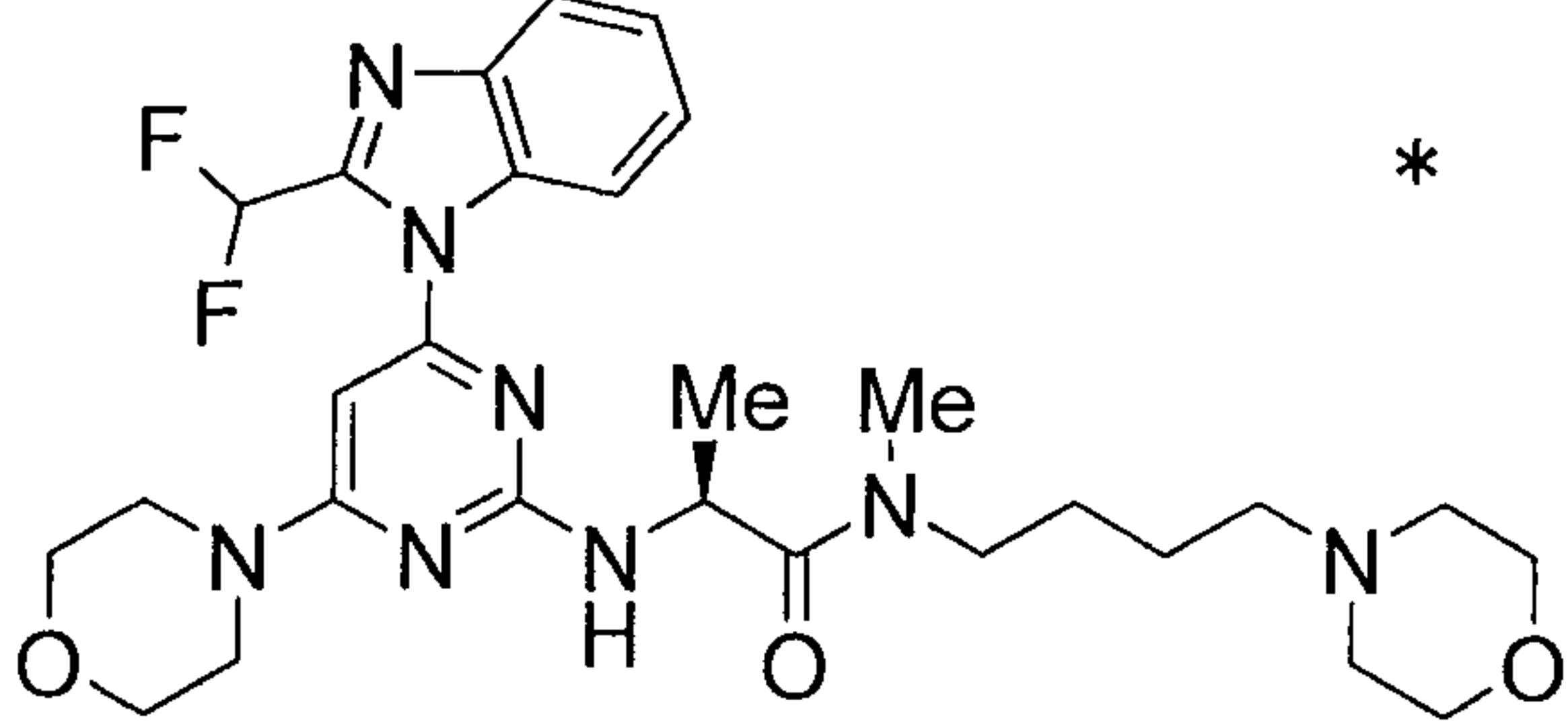
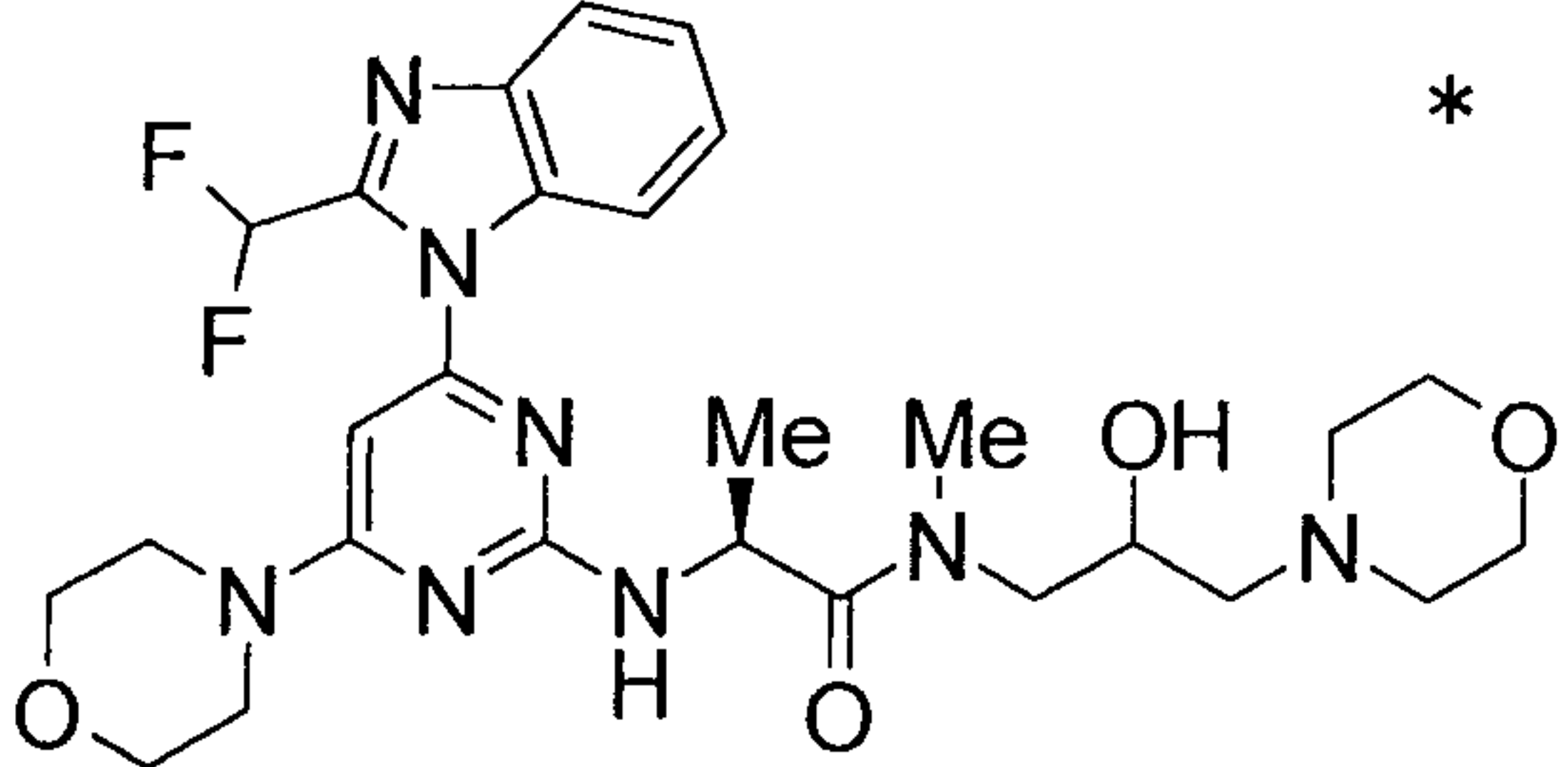
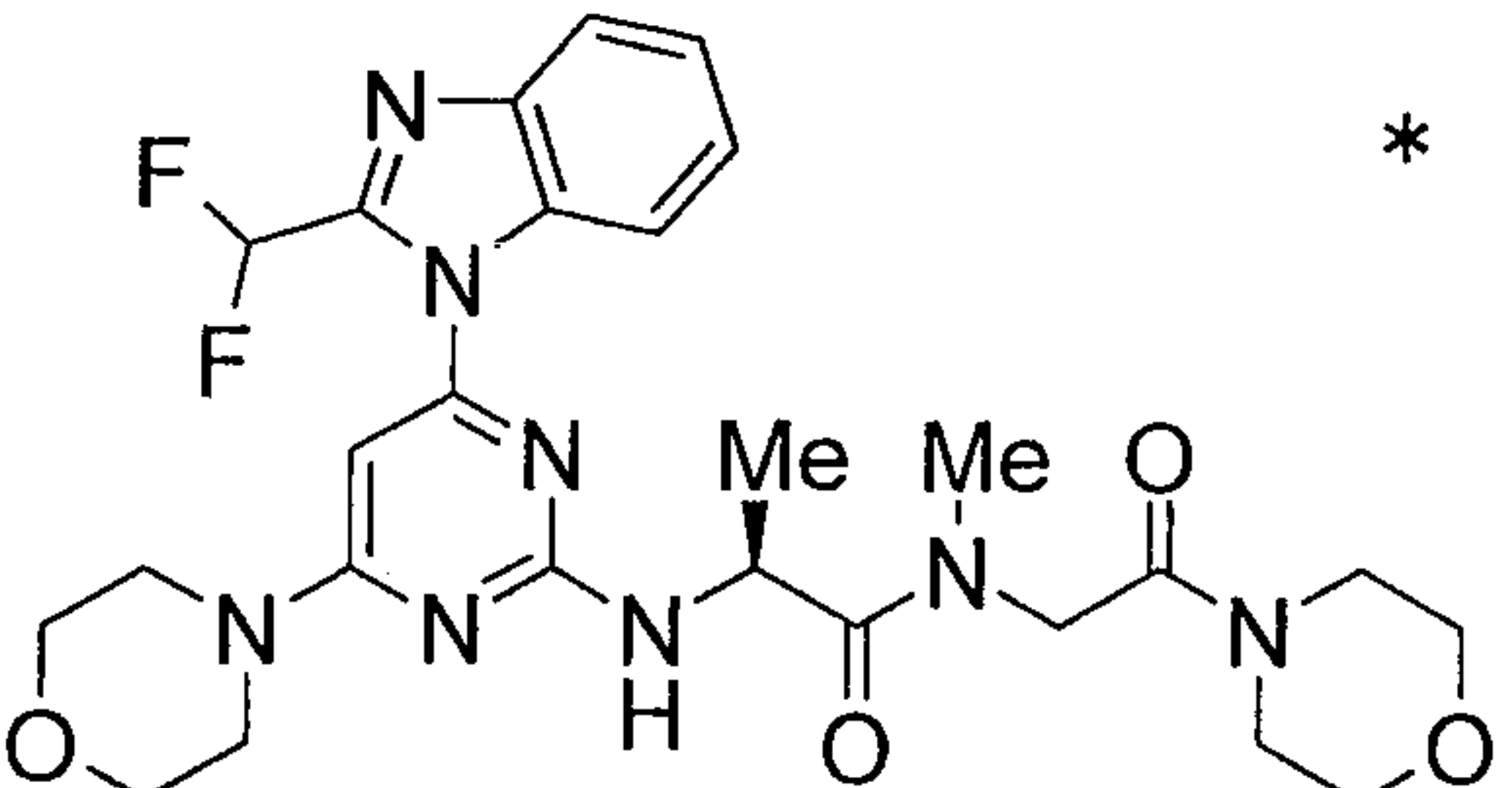
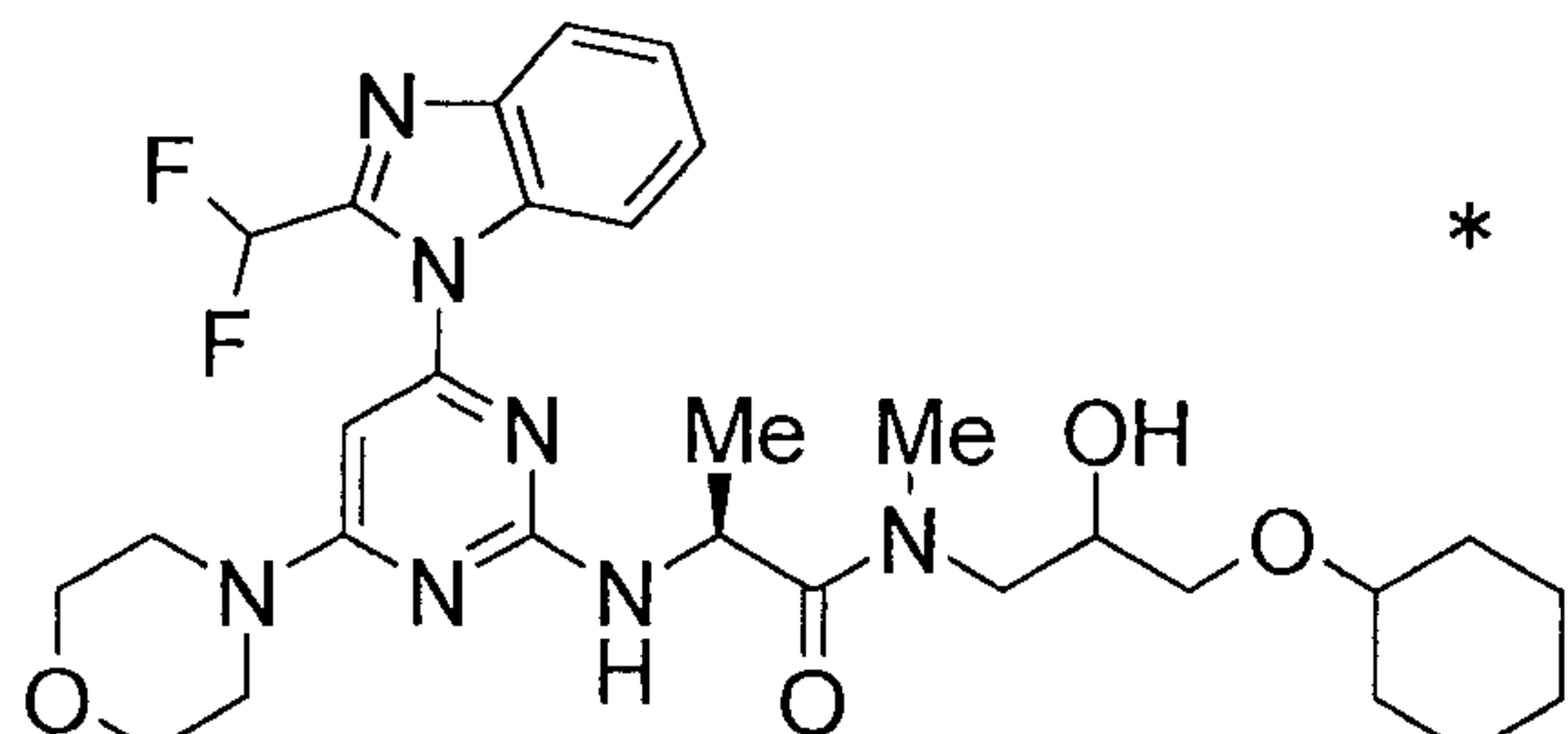
[0338]

[Table 182]

Ex	Str	ESI+	RT
A94		530	2.78
A95		530	2.52
A96		543	1.93
A97		543	1.93
A98		543	1.91

[0339]

[Table 183]

Ex	Str	ESI+	RT
A99		543	1.91
A100		573	1.93
A101		575	1.92
A102		559	2.35
A103		588	2.91

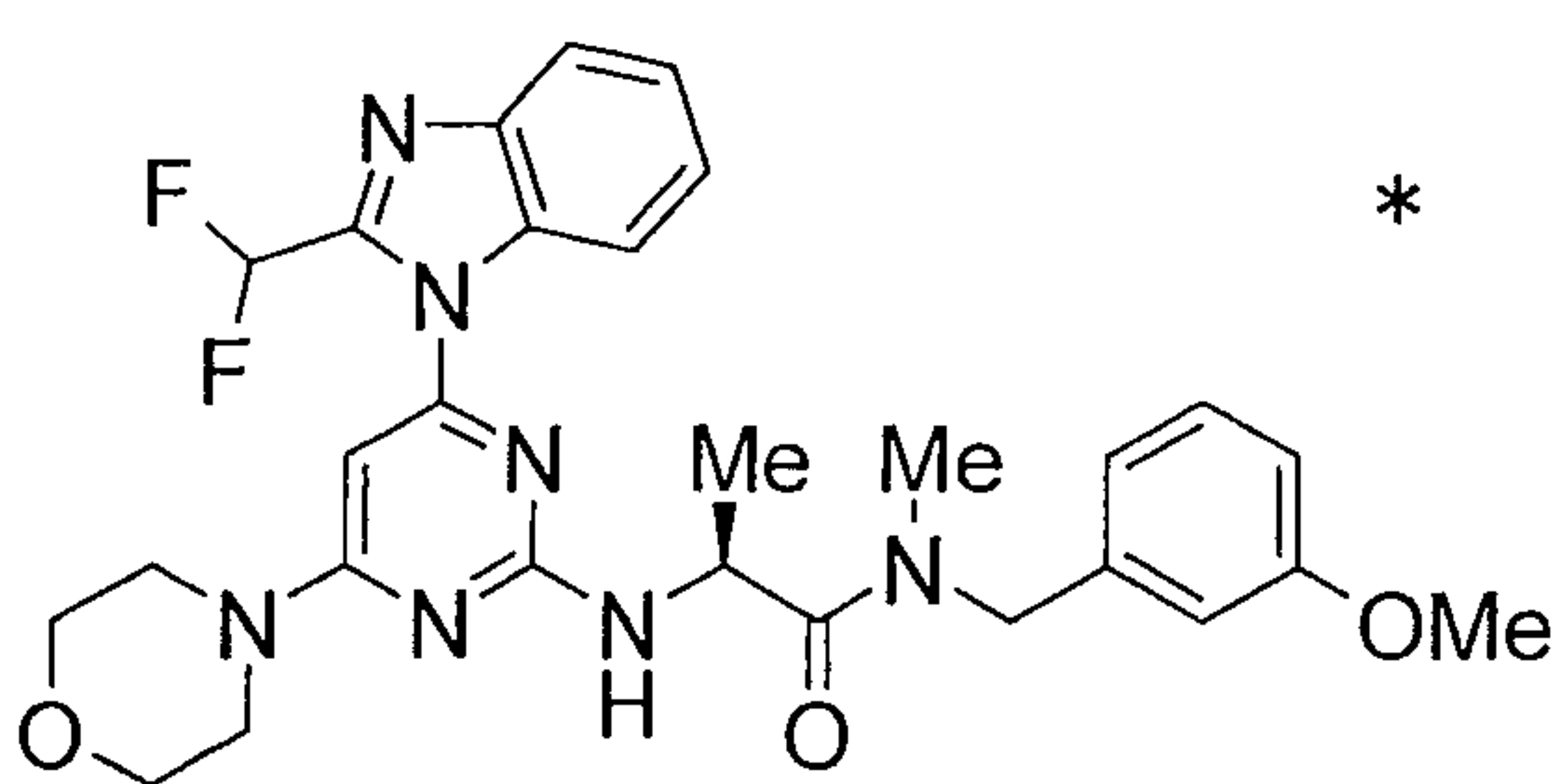
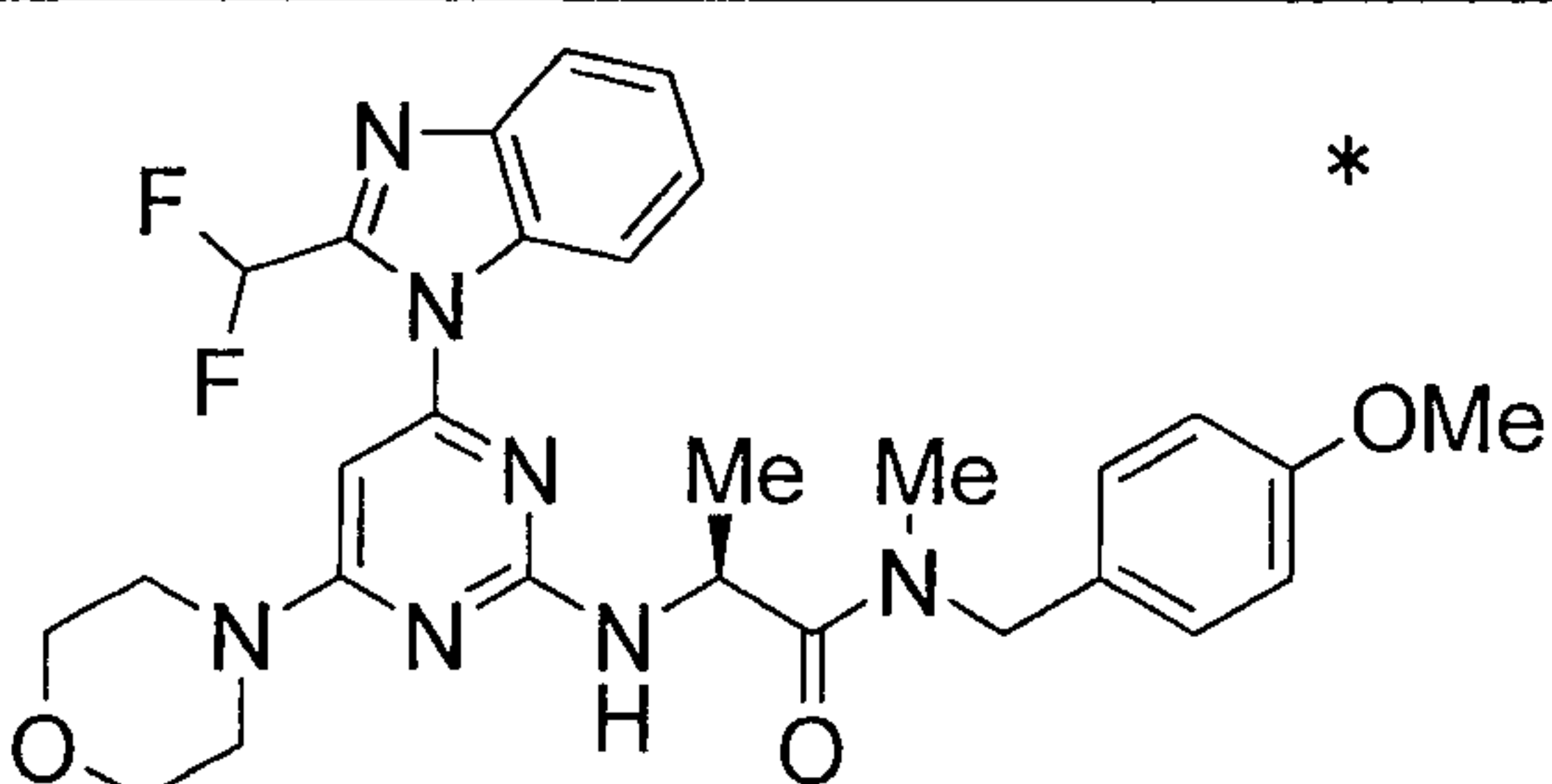
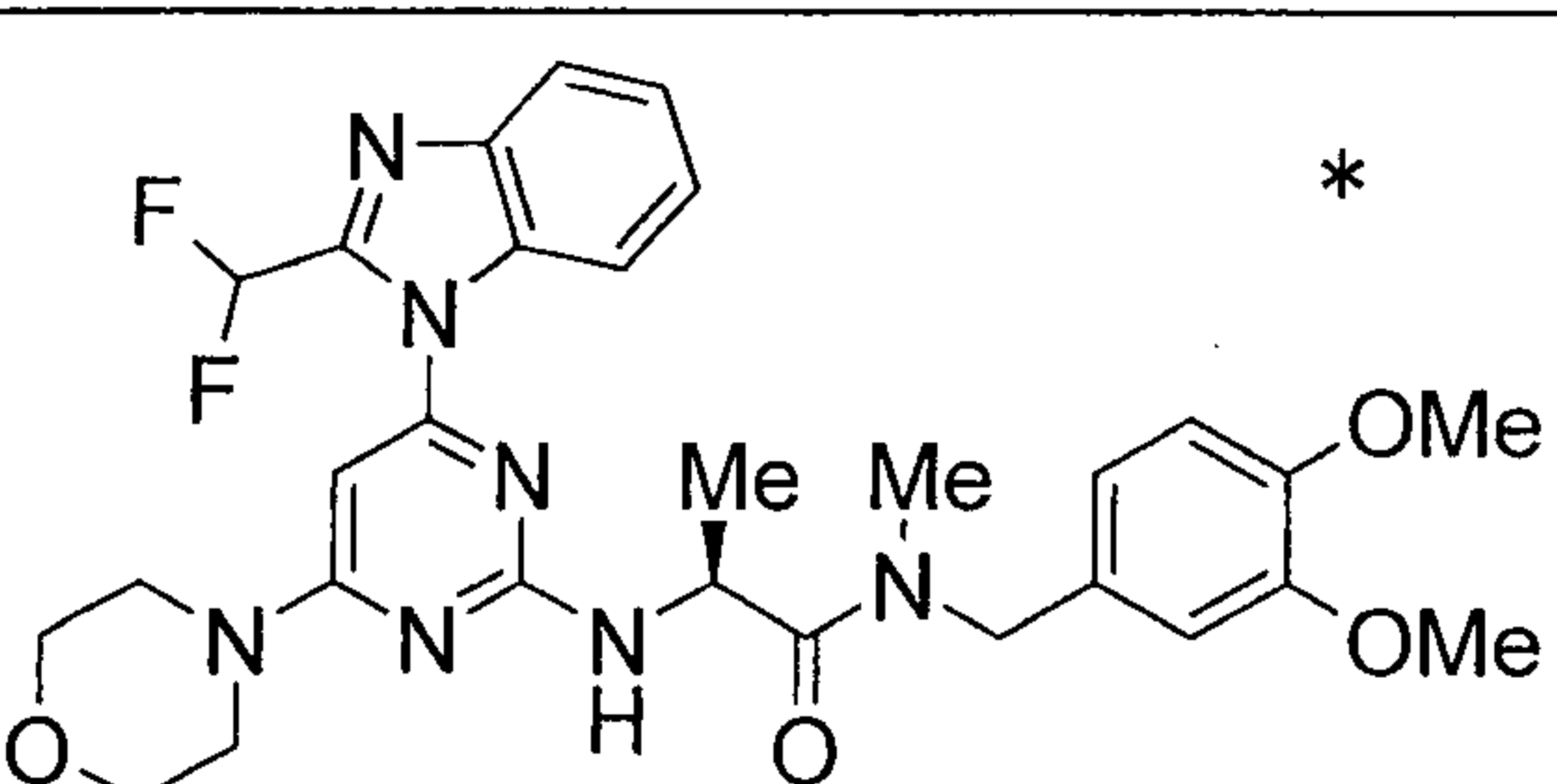
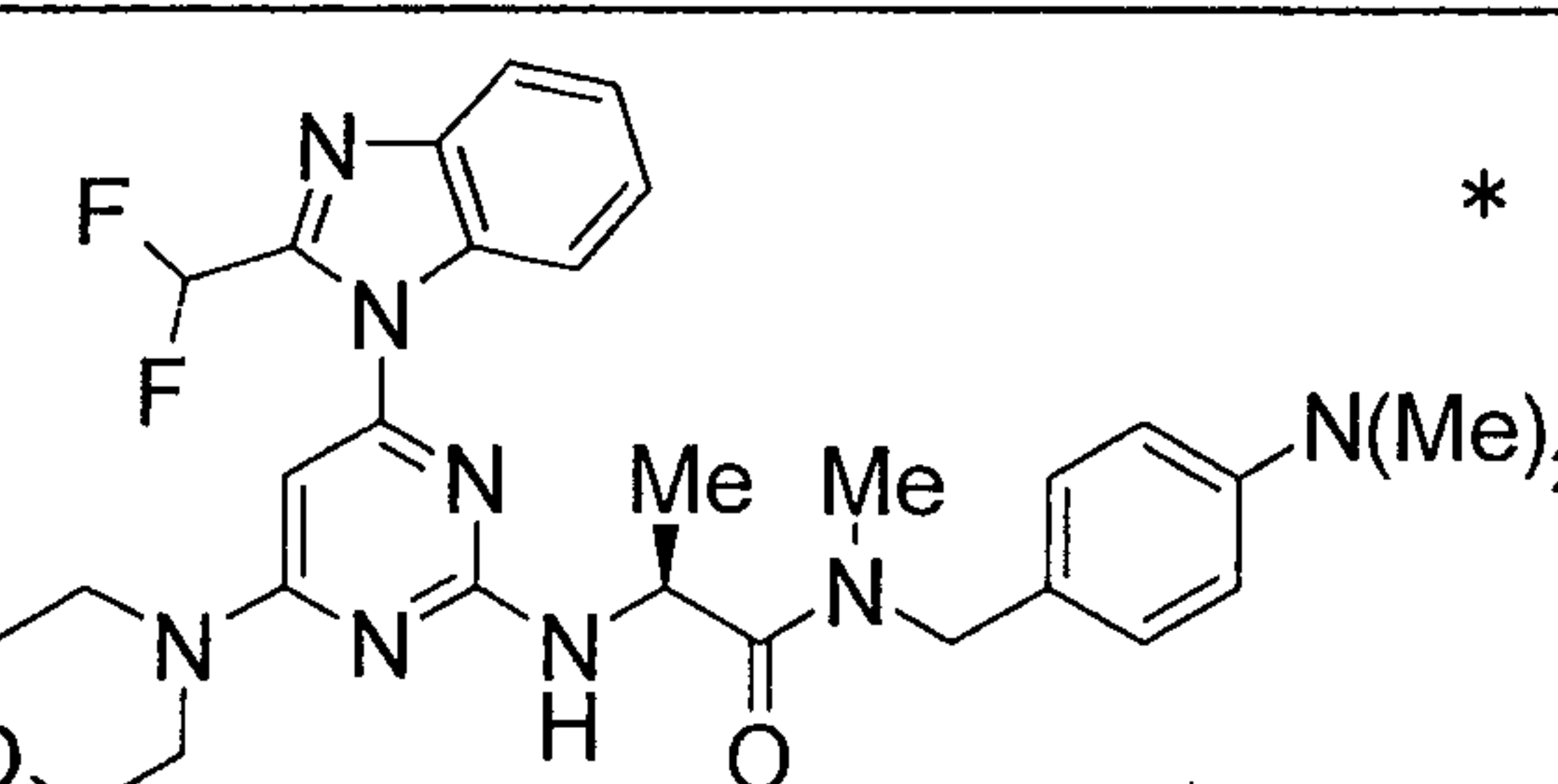
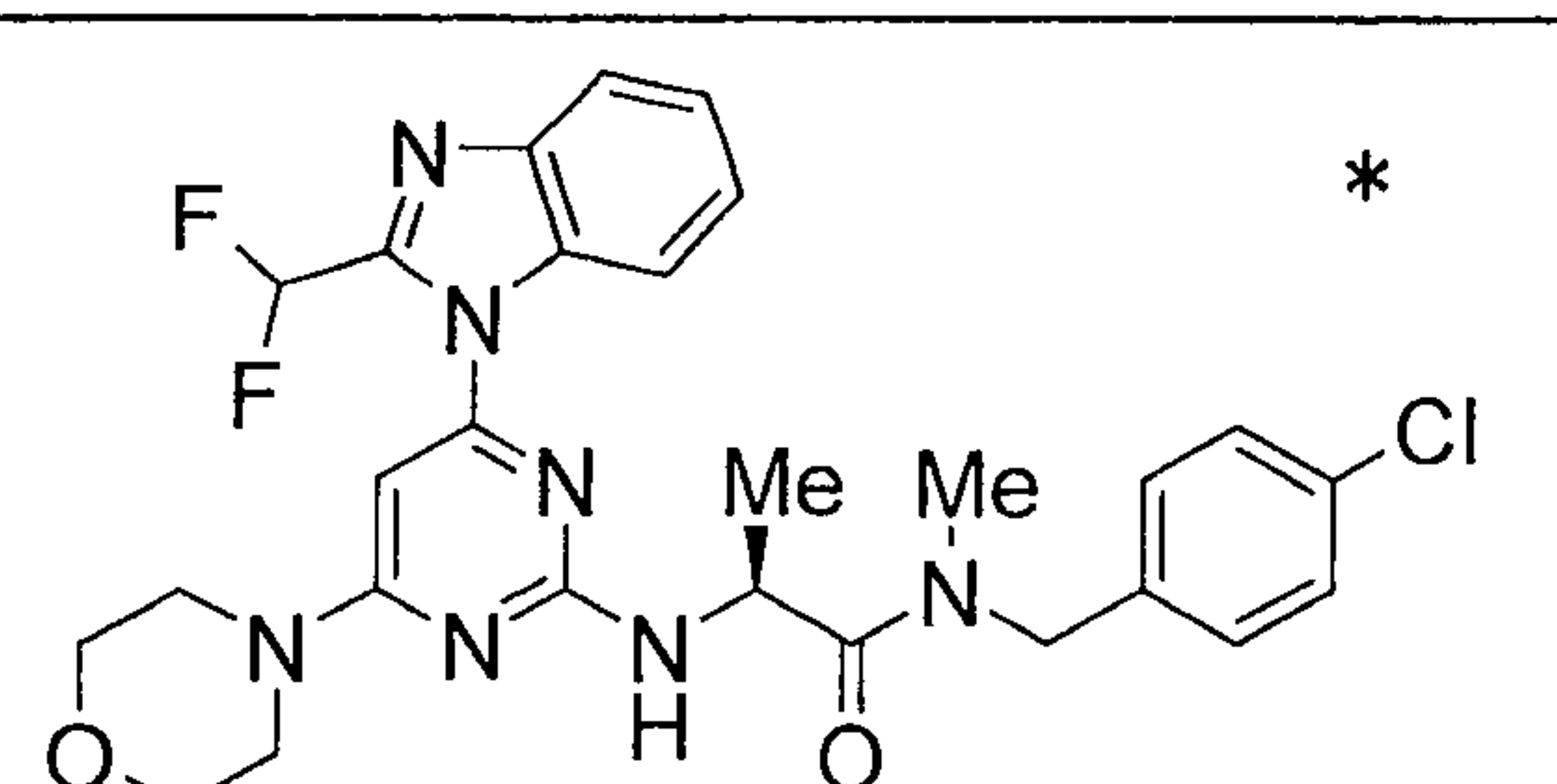
[0340]

[Table 184]

Ex	Str	ESI+	RT
A104		552	2.66
A105		566	2.69
A106		566	2.88
A107		579	2.21
A108		552	2.86

[0341]

[Table 185]

Ex	Str	ESI+	RT
A109		552	2.79
A110		552	2.78
A111		582	2.65
A112		565	2.62
A113		556	2.89

[0342]

[Table 186]

Ex	Str	ESI+	RT
A114		635	2.25
A115		523	2.39
A116		523	2.16
A117		523	2.02
A118		528	2.31

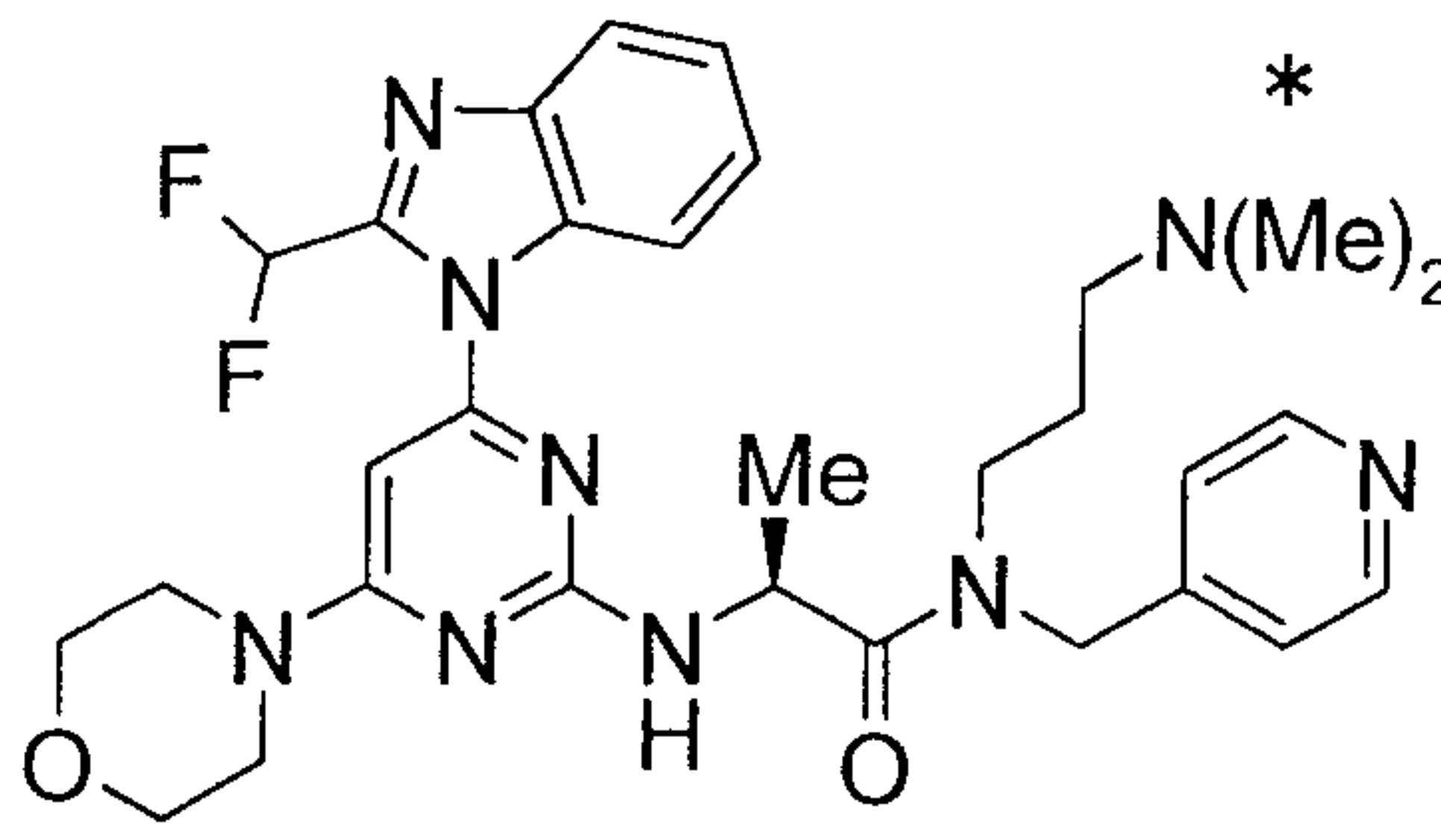
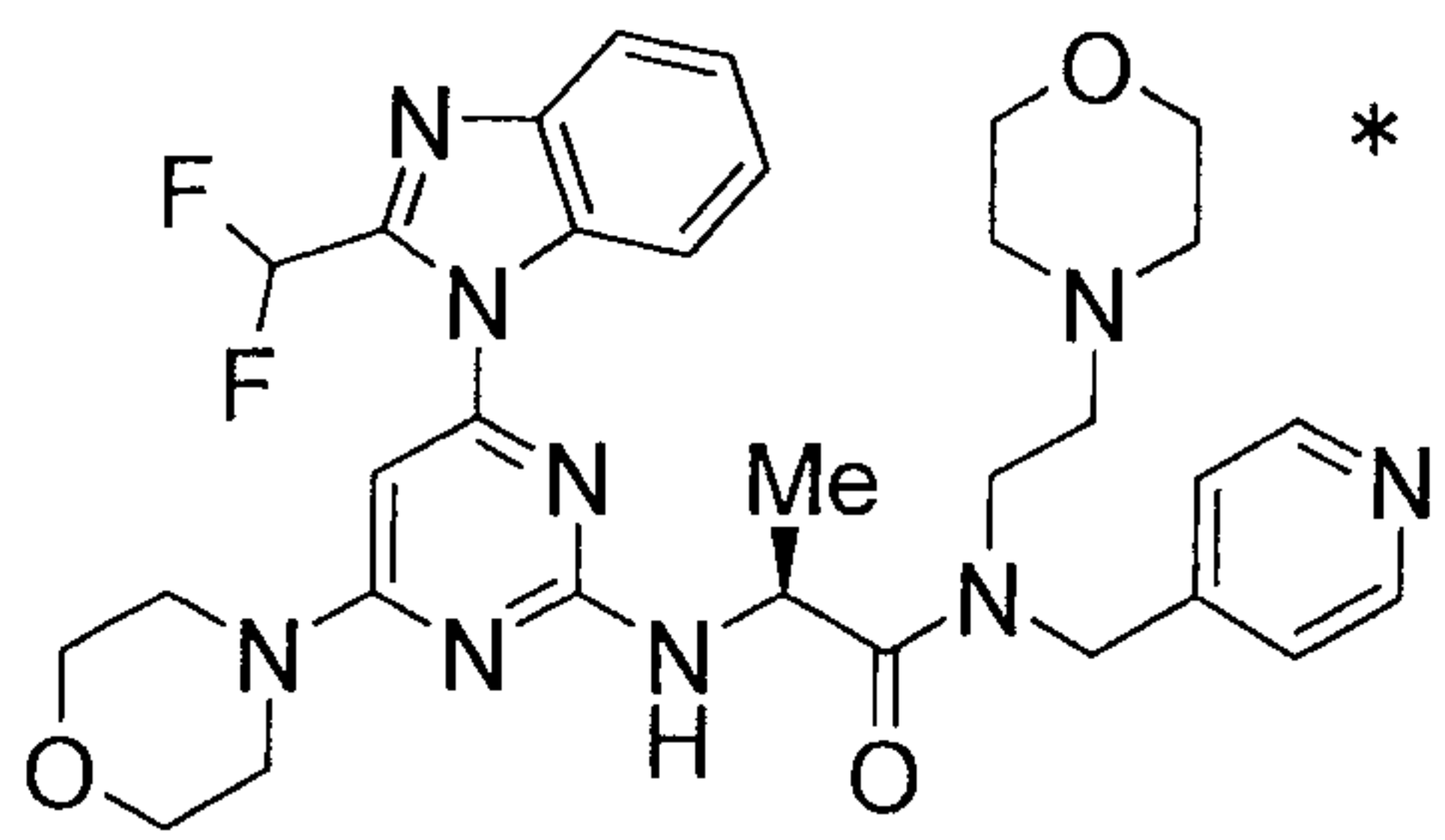
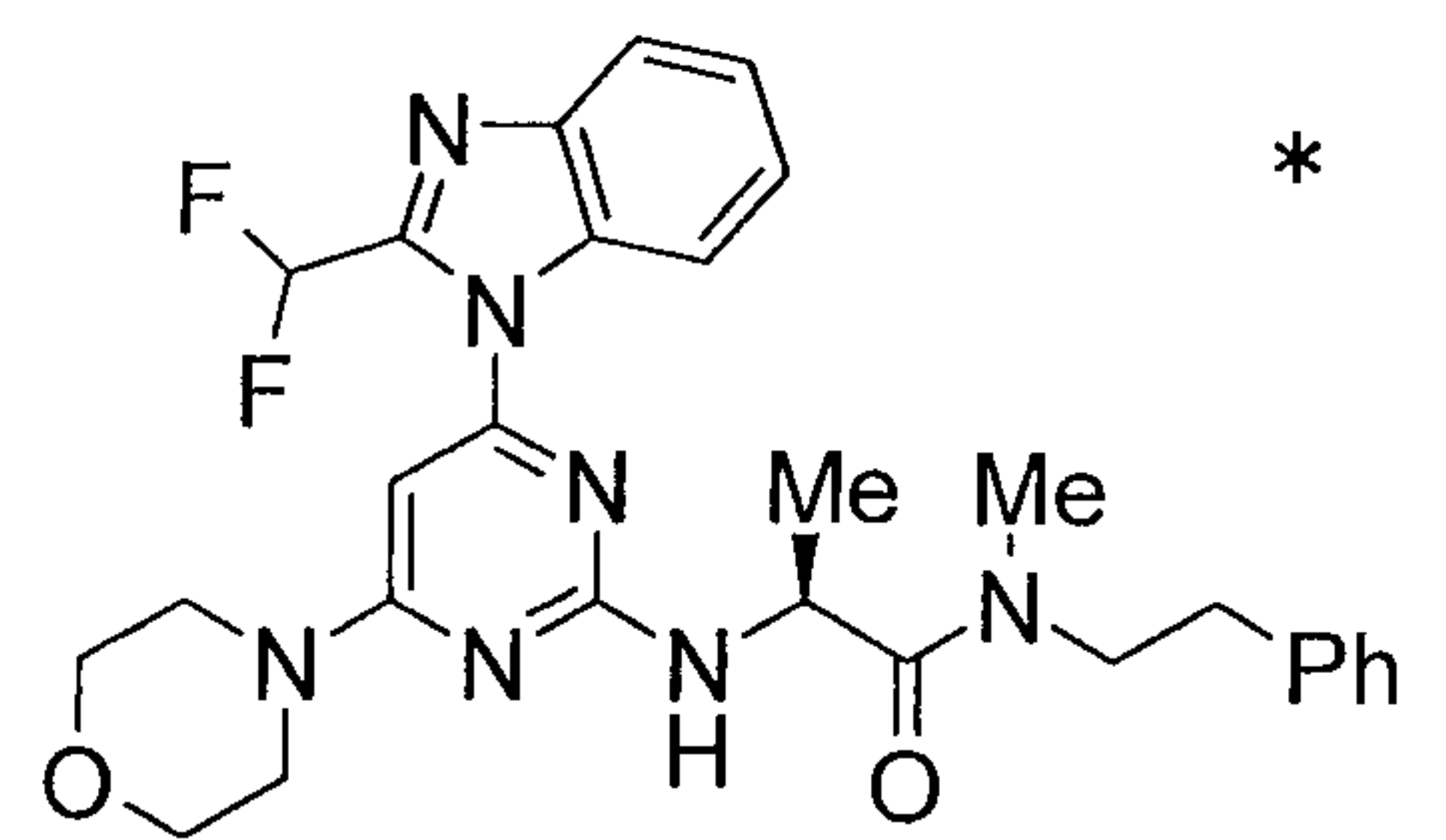
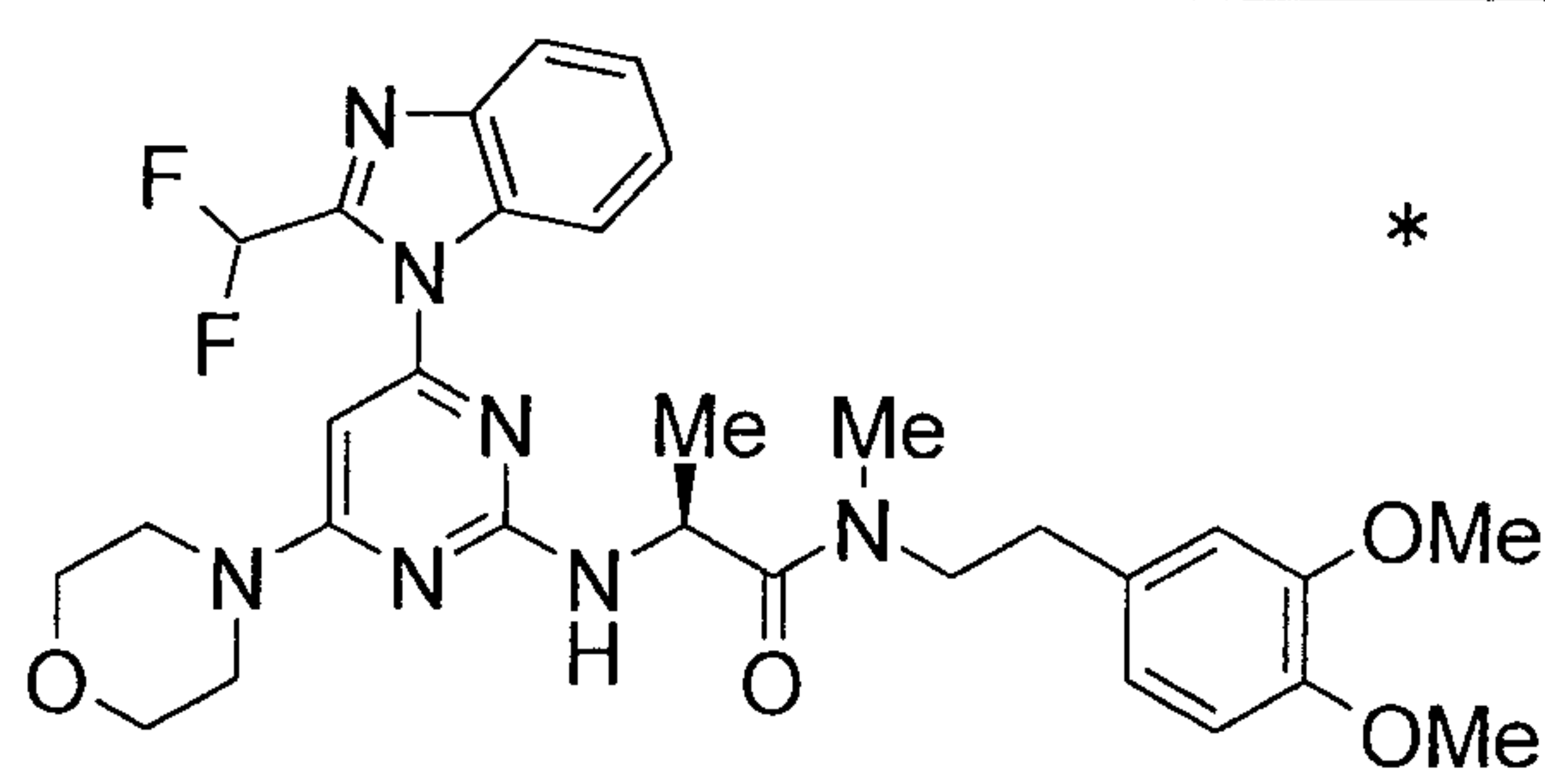
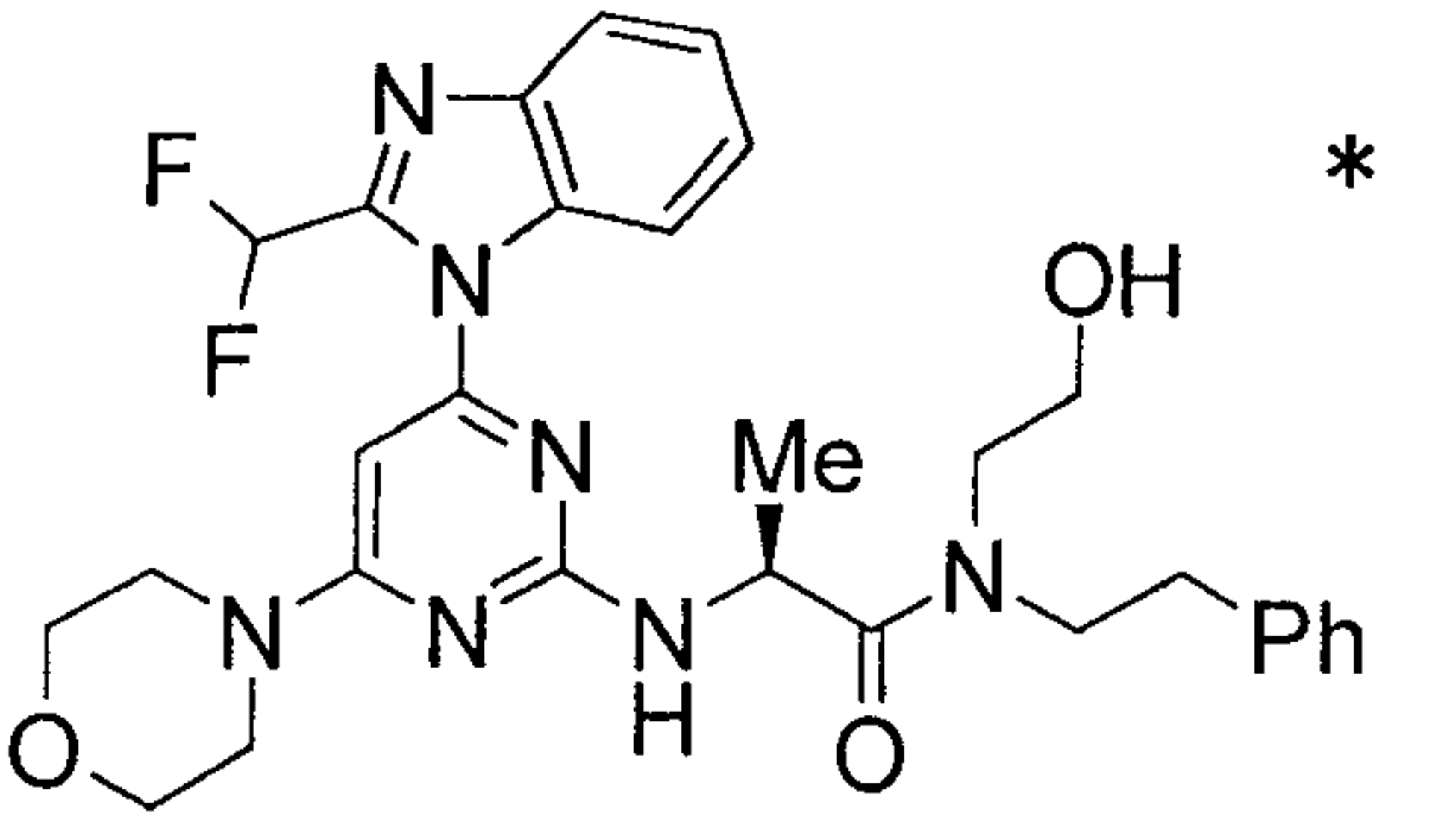
[0343]

[Table 187]

Ex	Str	ESI+	RT
A119		580	2.74
A120		553	1.93
A121		567	1.96
A122		581	2.34
A123		580	1.66

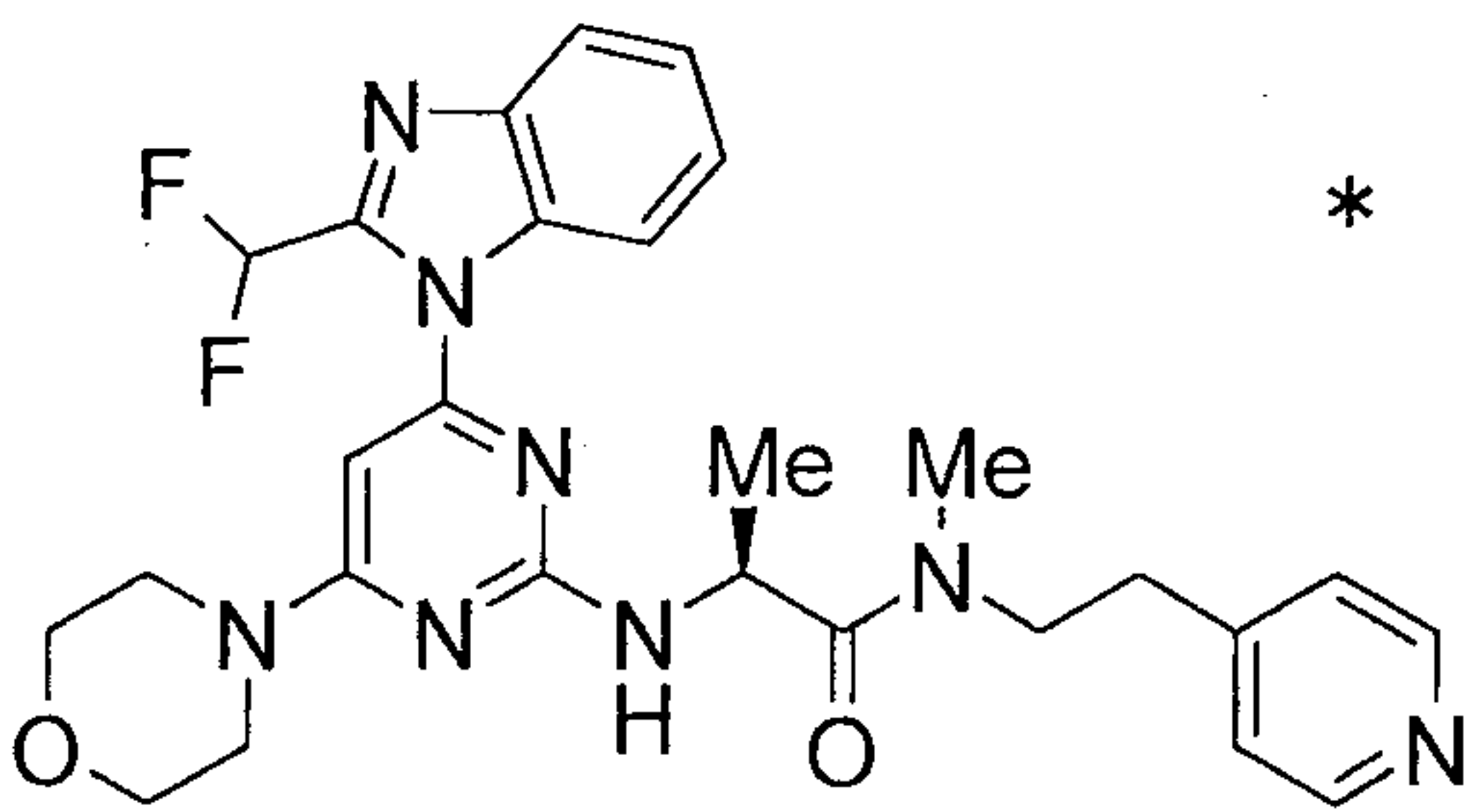
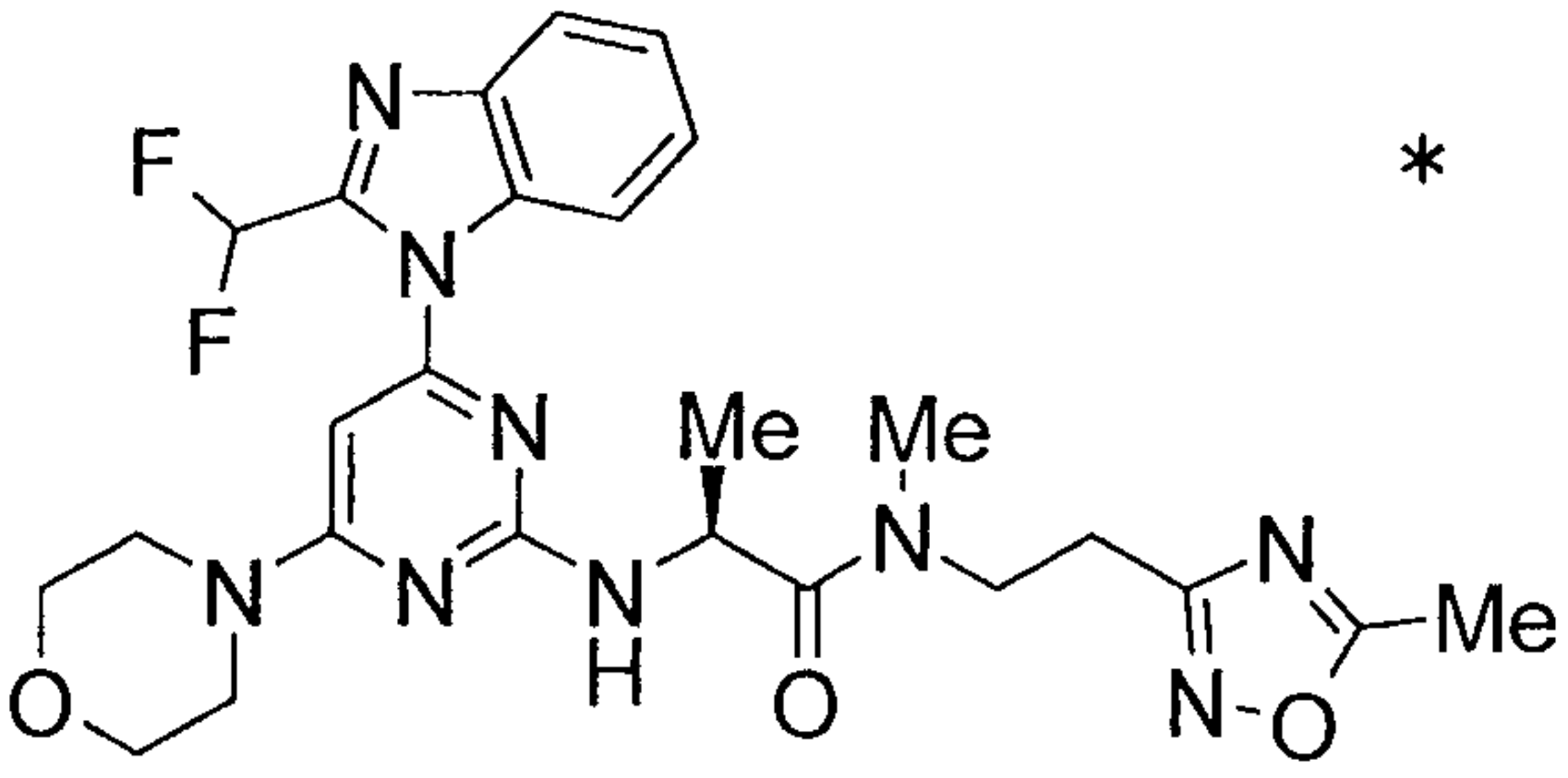
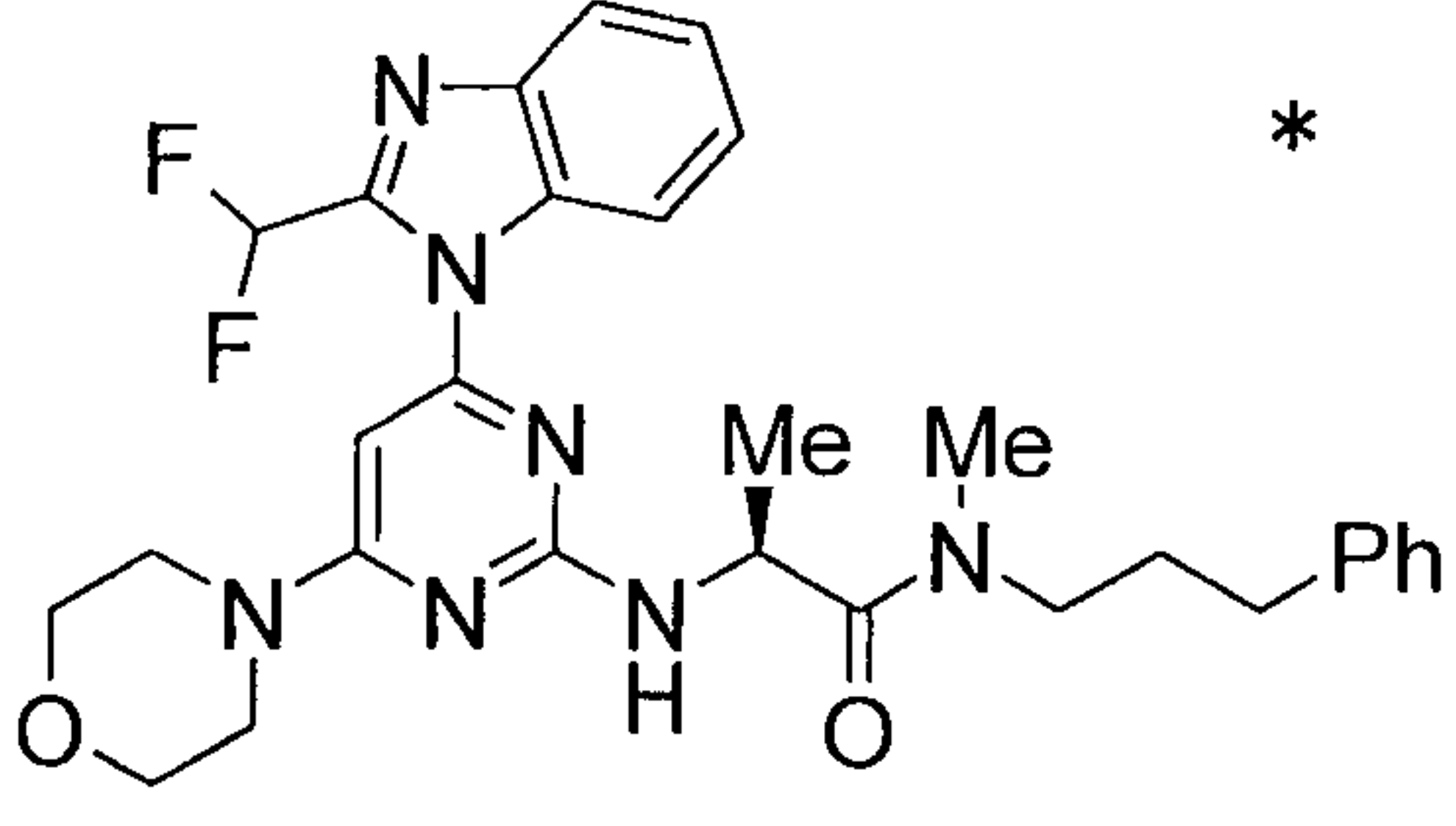
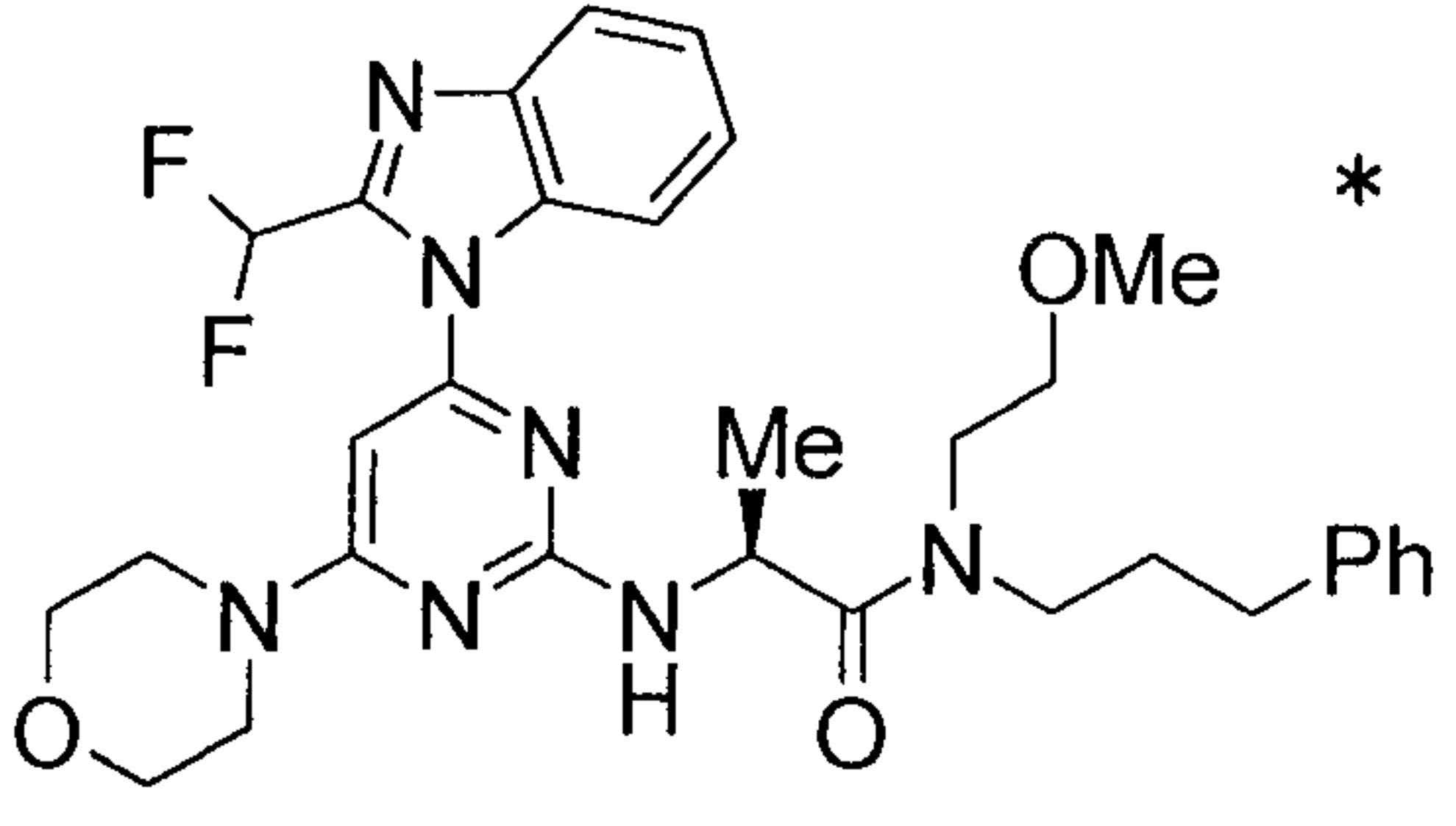
[0344]

[Table 188]

Ex	Str	ESI+	RT
A124		594	1.62
A125		622	1.69
A126		536	2.88
A127		596	2.72
A128		566	2.75

[0345]

[Table 189]

Ex	Str	ESI+	RT
A129		537	1.99
A130		542	2.5
A131		550	2.95
A132		594	3.01

DEMANDES OU BREVETS VOLUMINEUX

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

CECI EST LE TOME __1__ DE __2__

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__

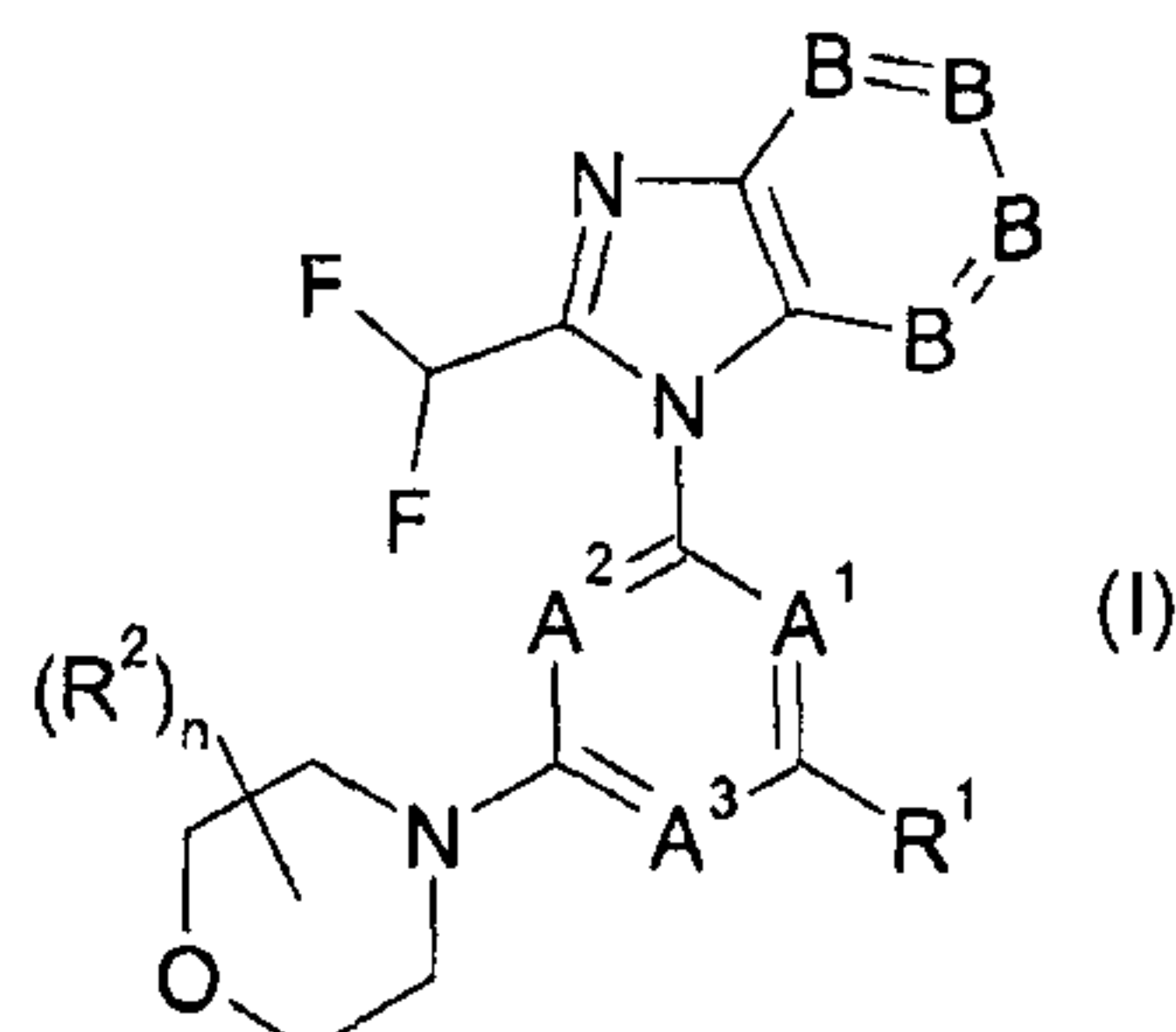
NOTE: For additional volumes please contact the Canadian Patent Office.

Claims

[Claim 1] A compound of the formula (I) or a salt thereof:

[Chem. 10]

5



wherein

A^2 and A^3 are N and A^1 is CH or A^1 and A^3 are N and A^2 is CH,

all B's are CH and n is 0,

10 R^1 is $-L^1-L^2-Y$, wherein $-L^1-L^2-$ is $-NH-$ or $-O-$,

Y is a non-aromatic heterocycle which may be substituted with one or more substituents selected from the Group D1, and

the Group D1 consists of:

15 (1) $-L^{5a}$ -(non-aromatic heterocycle which may be substituted with one or more substituents selected from the group consisting of linear or branched C_{1-6} alkyl, $-NH-C(O)-O$ -[linear or branched C_{1-6} alkyl], $-C(O)O$ -[linear or branched C_{1-6} alkyl], $-C(O)$ -[linear or branched C_{1-6} alkyl], and oxo), in which L^{5a} represents a bond, $-C(O)$ -[linear or branched C_{1-6} alkylene-], or $-C(O)-$, and

20 (2) $-C(O)$ -(cycloalkyl which may be substituted with one or more substituents selected from the group consisting of linear or branched C_{1-6} alkyl which may be substituted with $-OH$, $-OH$, and $-O$ -[linear or branched C_{1-6} alkyl].

[Claim 2] The compound or a salt thereof according to claim 1, wherein A^2 and A^3 are N and A^1 is CH.

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[Claim 3] The compound or a salt thereof according to claim 1, wherein $-L^1-L^2-$ is $-NH-$.

[Claim 4] The compound or a salt thereof according to claim 1, wherein Y is piperidinyl, pyrrolidinyl, or azetidinyl which may be respectively substituted with one or more substituents selected from the Group D1.

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[Claim 5] The compound or a salt thereof according to claim 1, wherein Group D1 consists of:

5 -L^{5a}-(non-aromatic heterocycle which may be substituted with one or more substituents selected from the group consisting of linear or branched C₁₋₆ alkyl, -C(O)O-[linear or branched C₁₋₆ alkyl], -C(O)-[linear or branched C₁₋₆ alkyl], and oxo), in which L^{5a} represents a bond or -C(O)-.

[Claim 6] The compound or a salt thereof according to claim 1, wherein the compound is

10 [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)pyrrolidin-1-yl][(2R)-tetrahydrofuran-2-yl]methanone,
[(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)pyrrolidin-1-yl](tetrahydro-2H-pyran-4-yl)methanone,
methyl 4-{{(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)pyrrolidin-1-yl}carbonyl} piperidine-1-carboxylate,
15 [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} oxy)pyrrolidin-1-yl](tetrahydrofuran-3-yl)methanone,
4-{{(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} oxy)pyrrolidin-1-yl}carbonyl}-1-methylpyrrolidin-2-one,
20 [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)pyrrolidin-1-yl](tetrahydrofuran-3-yl)methanone,
4-{{(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)pyrrolidin-1-yl}carbonyl}-1-methylpyrrolidin-2-one, or
4-{{3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)azetidin-1-yl}carbonyl}-1-methylpyrrolidin-2-one.
25

[Claim 7] The compound or a salt thereof according to claim 6, wherein the compound is [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} amino)pyrrolidin-1-yl](tetrahydro-2H-pyran-4-yl)methanone.
30

[Claim 8] The compound or a salt thereof according to claim 6, wherein the compound is [(3S)-3-({6-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-2-(morpholin-4-yl)pyrimidin-4-yl} oxy)pyrrolidin-1-yl](tetrahydrofuran-3-yl)methanone.

35 [Claim 9] A pharmaceutical composition comprising the compound or a salt thereof according to claim 6 and a pharmaceutically acceptable excipient.

[Claim 10] A pharmaceutical composition for preventing or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, or hematologic tumor, comprising the compound or a salt thereof according to claim 6 and a pharmaceutically acceptable excipient.

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[Claim 11] Use of the compound or a salt thereof according to claim 6 for the manufacture of a pharmaceutical composition for preventing or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, or hematologic tumor.

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[Claim 12] Use of the compound or a salt thereof according to claim 6 for preventing and/or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, and hematologic tumor.

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[Claim 13] The compound or a salt thereof according to claim 6 for preventing or treating rejection reactions in various organ transplantations, allergy diseases, autoimmune diseases, or hematologic tumor.

