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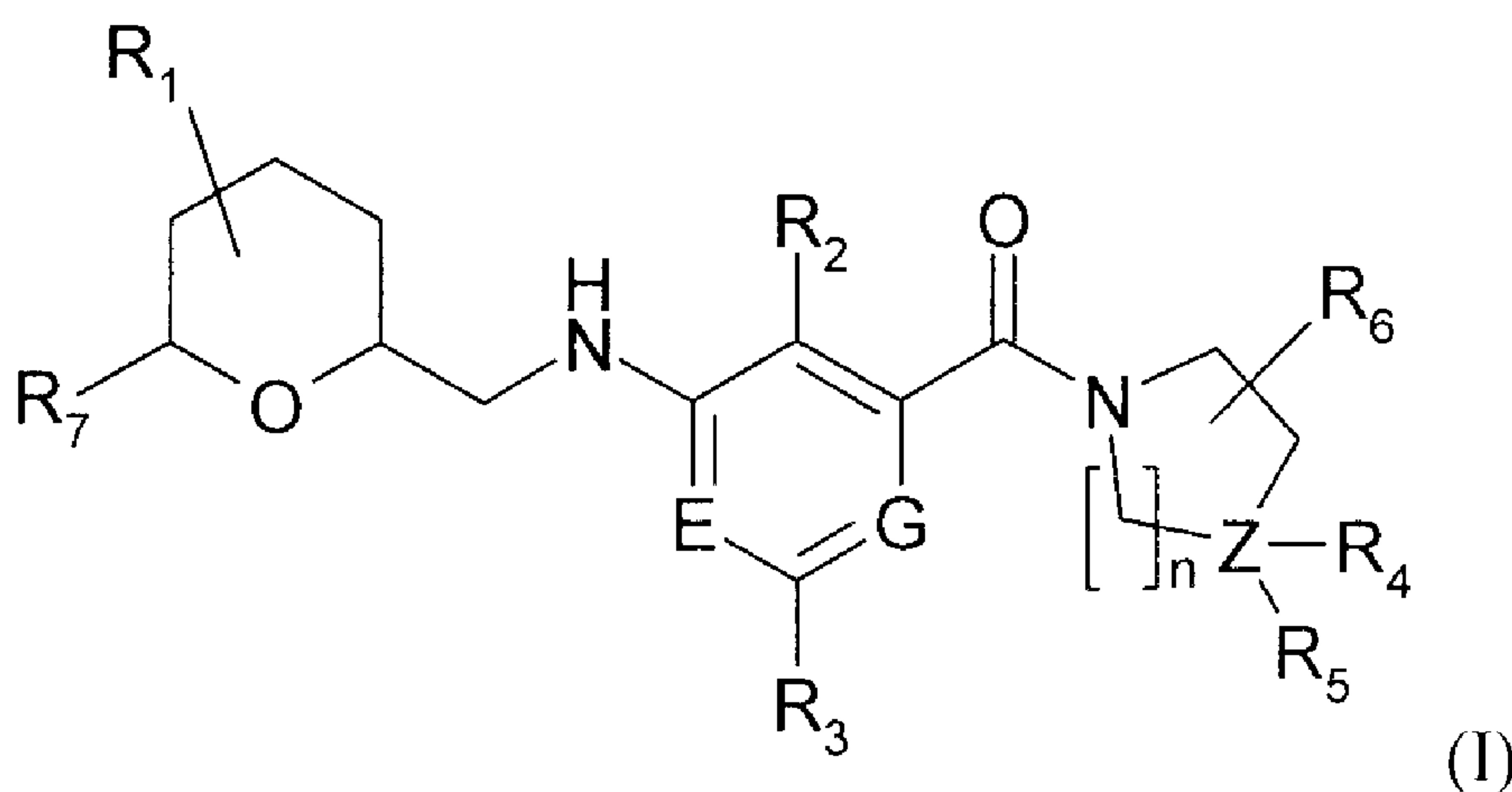
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(54) **Titre : NOUVEAUX ANTAGONISTES DU RECEPTEUR CCR2**
(54) **Title: NEW CCR2 RECEPTOR ANTAGONISTS**



(57) **Abrégé/Abstract:**

The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2) of Formula (I)

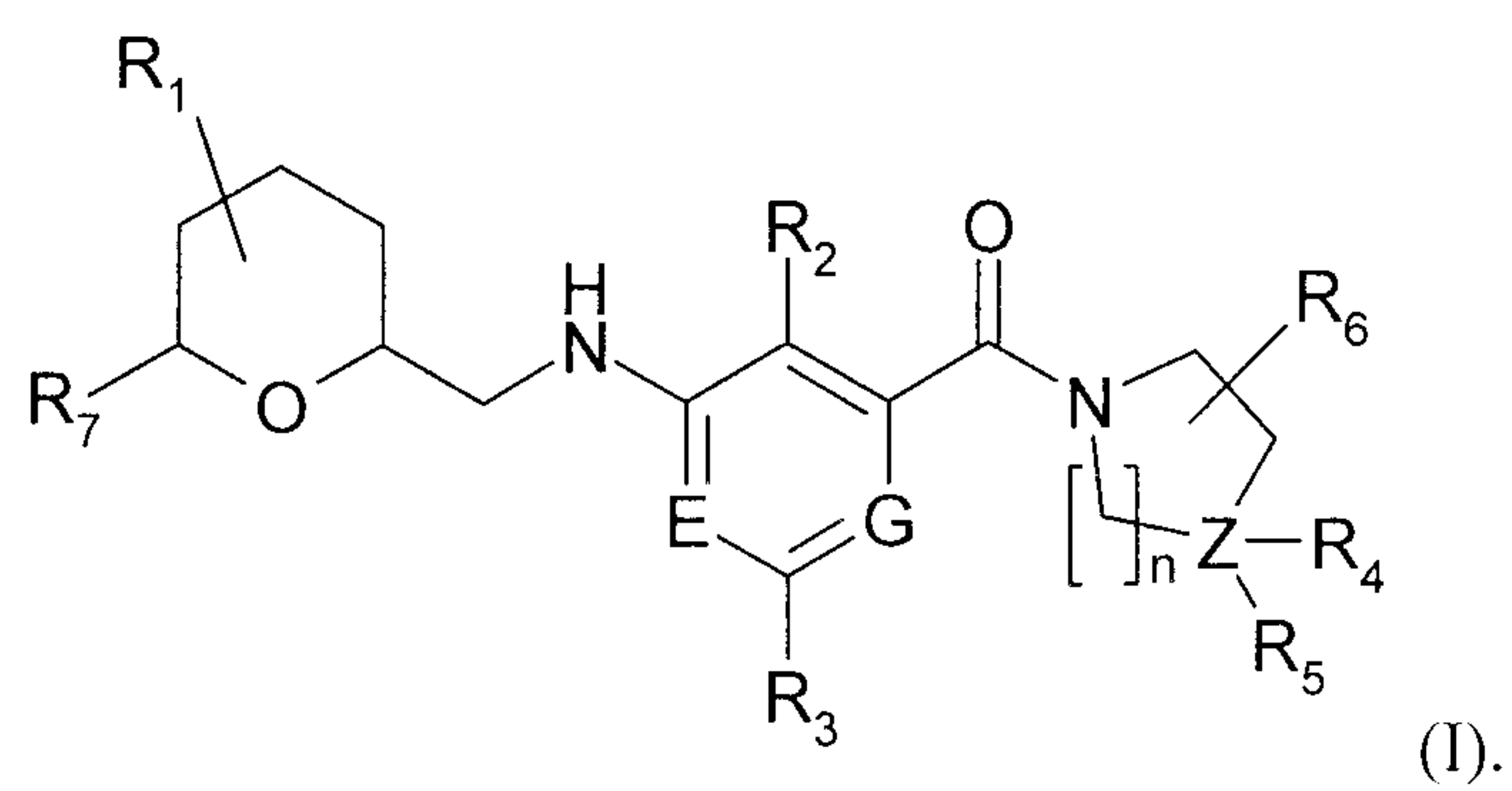
(see formula I).

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Abstract

The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2) of Formula (I)



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New CCR2 receptor antagonists**Field of invention**

The present invention relates to novel antagonists for CCR2 (CC chemokine receptor 2)

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Background of the invention

The chemokines are a family of small, proinflammatory cytokines, with potent chemotactic activities. Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract various cells, such as monocytes, macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation.

Chemokine receptors, such as CCR2 or CCR5 have been implicated as being important mediators of inflammatory and immunoregulatory disorders and diseases as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. Accordingly, agents which modulate chemokine receptors such as the CCR2 and CCR5 receptor may be useful in such disorders and diseases.

In particular it is widely accepted that numerous conditions and diseases involve inflammatory processes. Such inflammations are critically triggered and / or promoted by the activity of macrophages, which are formed by differentiation out of monocytes. It has further been found that monocytes are characterized by, e.g., a high expression of membrane-resident CCR2, whereas the CCR2 expression in macrophages is lower. CCR2 is a critical regulator of monocytes trafficking, which can be described as the movement of the monocytes towards an inflammation along a gradient of monocyte chemoattractant proteins (MCP-1, MCP-2, MCP-3, MCP-4).

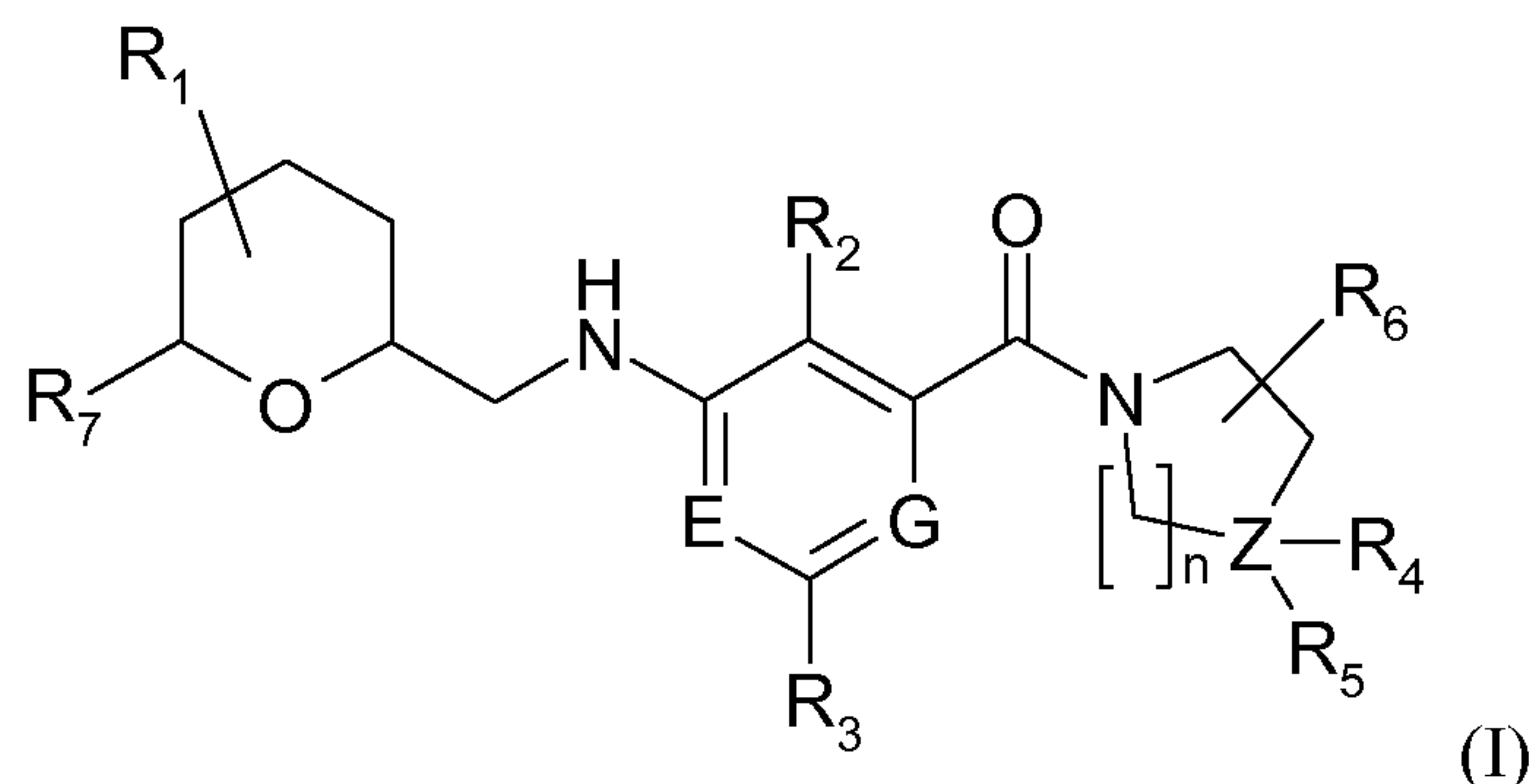
Therefore, in order to reduce macrophage-induced inflammation, it would be desirable to block the monocyte CCR2 by an antagonist, so that the monocytes can be less triggered to move towards an inflammation area for conversion into macrophages.

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Based on the aforesaid there is a need for providing effective antagonists for CCR2, which are pharmacologically acceptable.

Description of the invention

It has now been found that such effective CCR2 inhibitors can be provided by compounds according to general formula (I),



wherein R₁ is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₇ is a ring selected from among -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, and -C₅-C₁₀-heteroaryl,

wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -C₁-C₆-alkyl, -C(CH₃)₂-CN, and -halogen,

or wherein the ring R₇ is optionally substituted with one or more groups selected from among -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₂-C₆-alkenyl, and -C₂-C₆-alkynyl, optionally being substituted by one or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, -methyl, and =O,

or wherein the ring R₇ is optionally further bi-valently substituted on two neighbouring ring atoms, such that an annellated ring is formed by one or more groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene and -C₄-C₆-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O;

wherein R₂ is selected from among -H, -halogen, -CN, -O-C₂-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₃ is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

wherein n is 1, 2 or 3;

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wherein G and E are independently selected from among C-H or N;

wherein Z is C,

- 5 and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R_{8'}), with R₈ and R_{8'} independently being selected from among -H, and -C₁-C₆-alkyl, or wherein Z is N,

- 10 and R₄ denotes an electron pair and R₅ is selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R_{8'}), with R₈ and R_{8'} independently being selected from among -H, and -C₁-C₆-alkyl

- and wherein R₄ if different from an electron pair or -H and R₅ if different from -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R₉,R_{9'}), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R_{11'}), -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R_{13'}), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene(R₂₀,R_{20'}), -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),
- 15 20 25

wherein Q is selected from among -C(O)-, and -SO₂-,

wherein R₁₀, R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

- 30 wherein R₉, R_{9'}, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a -C₂-C₆-alkylene group,

- wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,
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and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl,

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wherein R_{20} and $R_{20'}$ together form a spiro- C_3 - C_8 -cycloalkylcycle or spiro- C_3 - C_8 -heterocycle comprising one or more group selected from O in the ring, and wherein said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from among - C_1 - C_6 -alkylene, - C_2 - C_6 -alkenylene, and - C_4 - C_6 -alkynylene and wherein said
 5 spirocycle is optionally further substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen,

or wherein Z is C,

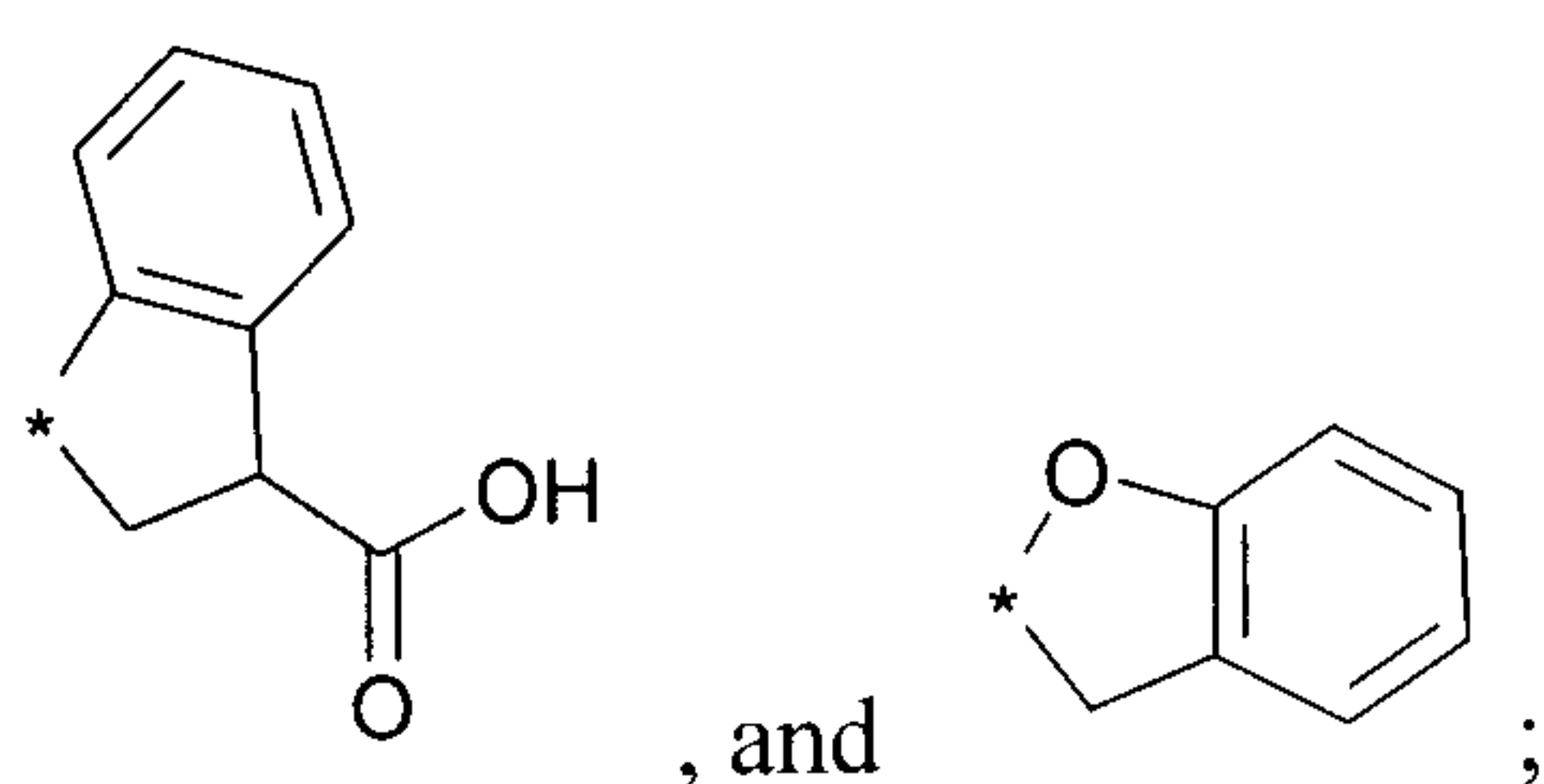
and R_4 denotes -H, and R_5 is selected from a group of the structure - L_1 - R_{18} ,
 10 wherein L_1 is selected from among -NH- and -N(C_1 - C_4 -alkyl)-, and a bond,
 wherein R_{18} is selected from among - C_5 - C_{10} -aryl, - C_5 - C_{10} -heteroaryl, - C_3 - C_8 -cycloalkyl, and - C_3 - C_8 -heterocyclyl,
 wherein R_{18} is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O- C_1 - C_4 -alkyl, - C_1 - C_6 -alkyl, -NH-C(O)- C_1 - C_6 -alkyl,
 15 -N(C_1 - C_4 -alkyl)-C(O)- C_1 - C_6 -alkyl, -C(O)- C_1 - C_6 -alkyl, -S(O)₂- C_1 - C_6 -alkyl,
 -NH-S(O)₂- C_1 - C_6 -alkyl, -N(C_1 - C_4 -alkyl)-S(O)₂- C_1 - C_6 -alkyl, and -C(O)-O- C_1 - C_6 -alkyl,
 and wherein R_5 and R_{18} are optionally further substituted by spiro- C_3 - C_8 -cycloalkyl or spiro- C_3 - C_8 -heterocyclyl such that together with R_4 , R_5 and/or R_{18} a spirocycle is formed,
 wherein said spiro- C_3 - C_8 -heterocyclyl optionally comprises one or more groups selected from
 20 among nitrogen, -C(O)-, -SO₂-, and -N(SO₂- C_1 - C_4 -alkyl)- in the ring,
 or wherein R_5 and R_{18} are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among - C_1 - C_6 -alkylene, - C_2 - C_6 -alkenylene, and - C_4 - C_6 -alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may
 25 optionally be substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among -OH, -NH₂, - C_1 - C_3 -alkyl, -O- C_1 - C_6 -alkyl, -CN, -CF₃, -OCF₃, and halogen;

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or wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R_{19'}), wherein R₁₉ and R_{19'} together form a -C₂-C₆-alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, -(C₆-aryl)-COOH, -C(O)-O-C₂H₅,



wherein R₆ is selected from among H, -C₁-C₄-alkyl, OH, -O-C₁-C₄-alkyl, -halogen, -CN, -CF₃, and -OCF₃;

as well as in form of their acid addition salts with pharmacologically acceptable acids, as well as in form of their solvates and/or hydrates.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₈, R₁₉, R_{19'}, L₁, E, G, Z, Q, and n as herein before or below defined, wherein R₇ is a ring selected from among -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, and -C₅-C₁₀-heteroaryl,

wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, -C₁-C₆-alkyl, -C(CH₃)₂-CN, and -halogen,

or wherein the ring R₇ is optionally substituted with one or more groups selected from among -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-heterocyclyl, -C₂-C₆-alkenyl, and -C₂-C₆-alkynyl, optionally being substituted by one or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, -methyl, and =O,

or wherein the ring R₇ is optionally further bi-valently substituted on two neighbouring ring atoms, such that an annellated ring is formed by one or more groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene and -C₄-C₆-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, R₁₉, R_{19'}, E, G, Q, and n as herein before or below defined, wherein Z is C,

and R₄ and R₅ are independently selected from -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R_{8'}), with R₈ and R_{8'} independently being selected from among -H, and -C₁-C₆-alkyl,

and wherein R₄ and R₅ if different from -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R₉,R_{9'}), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R_{11'}), -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R_{13'}), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),

wherein Q is selected from among -C(O)-, and -SO₂-,

wherein R₁₀, R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

wherein R₉, R_{9'}, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a -C₂-C₆-alkylene group,

wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-

heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,

and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl, or wherein Z is C,

and R₄ denotes -H and R₅ is selected from a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(C₁-C₄-alkyl)-,

wherein R₁₈ is selected from among -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl,

wherein R₁₈ is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl, -NH-C(O)-C₁-C₆-alkyl, -N(C₁-C₄-

alkyl)-C(O)-C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, -NH-S(O)₂-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-S(O)₂-C₁-C₆-alkyl, and -C(O)-O-C₁-C₆-alkyl,

and wherein R₄, R₅ and R₁₈ are optionally further substituted by spiro-C₃-C₈-cycloalkyl or spiro-C₃-C₈-heterocyclyl such that together with R₄, R₅ and/or R₁₈ a spirocycle is formed,

wherein said spiro-C₃-C₈-heterocyclyl optionally comprises one or more groups selected from among nitrogen, -C(O)-, -SO₂-, and -N(SO₂-C₁-C₄-alkyl)- in the ring,

or wherein R₄, R₅ and R₁₈ are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may

optionally be substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, and halogen.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂,

R₃, R₆, R₇, R₁₉, R_{19'}, E, G, Q, and n as herein before or below defined, wherein

Z is N, and R₄ denotes an electron pair, and R₅ is a group selected from among -H,

-C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R_{8'}), with R₈ and R_{8'} independently being selected from among -H, and -C₁-C₆-alkyl,

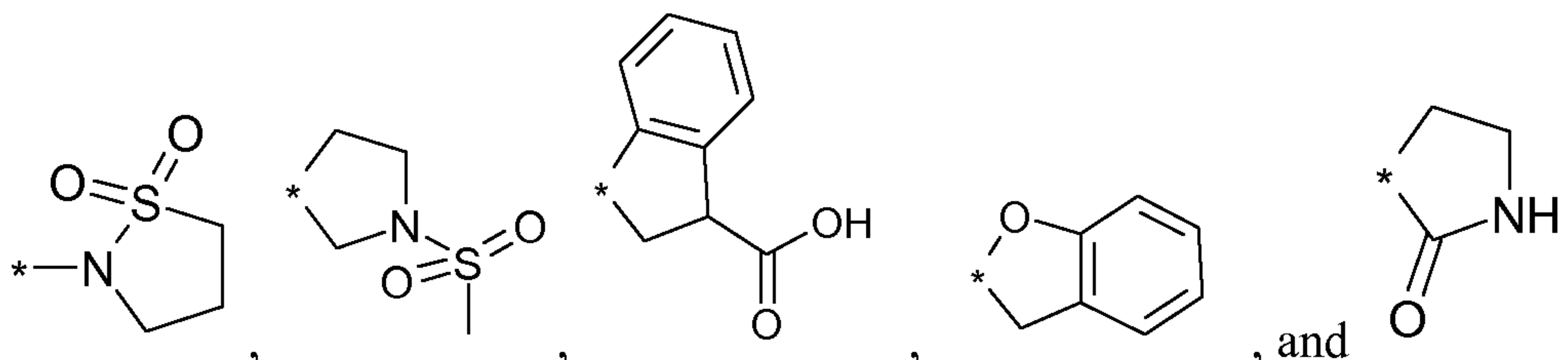
and wherein R₅ if different from an -H is optionally substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-

- C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R₉,R_{9'}), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-cycloalkyl,
 -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R_{11'}), -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R_{13'}), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene-Q-C₁-C₆-alkyl,
 -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and
 -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),
 wherein Q is selected from among -C(O)-, and -SO₂-,
 wherein R₁₀, R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,
 wherein R₉, R_{9'}, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,
 or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a
 -C₂-C₆-alkylene group,
 wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,
 and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from
 among -OH, -OCH₃, -CF₃, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl.

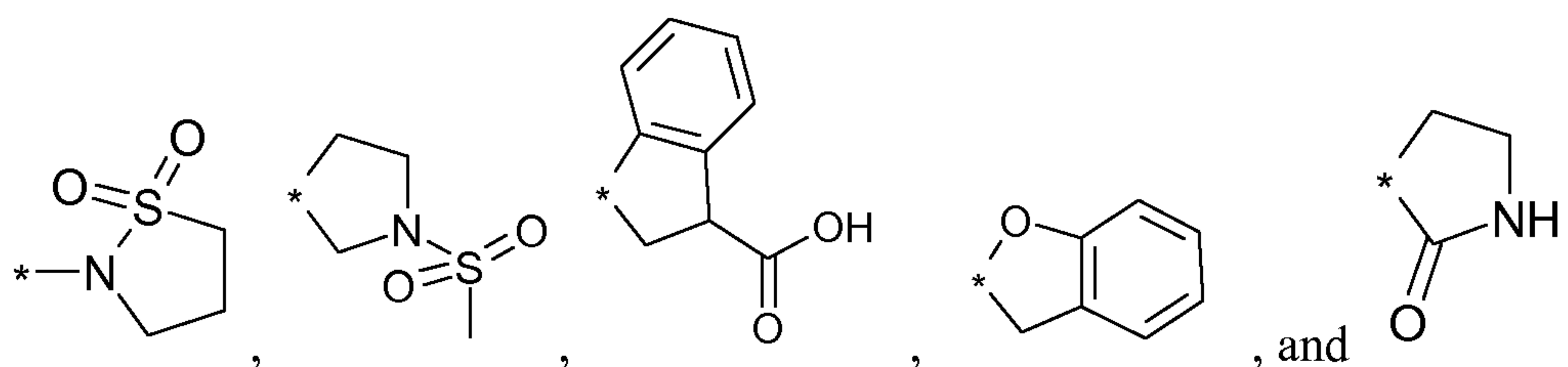
Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, E, G, Q, and n as herein before or below defined,
 wherein Z is C,

- and R₄ and R₅ are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R₈,R_{8'}), with R₈ and R_{8'} independently being selected from among -H and -C₁-C₆-alkyl,
 wherein R₄ and R₅ if different from -H are optionally independently substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF₃, -OCF₃, -CN, -O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇, -N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₂H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅,

-NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉,
 5 -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -(C₆-aryl)-COOH, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



- 10 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, E, G, Q, and n as herein before or below defined, wherein Z is N, and R₄ denotes an electron pair, and R₅ is a group selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -
 15 tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H and -C₁-C₆-alkyl, wherein R₅ if different from -H is optionally substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -
 20 -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇, -N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-
 25 C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₂H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅,
 30 -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -(C₆-aryl)-COOH, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,

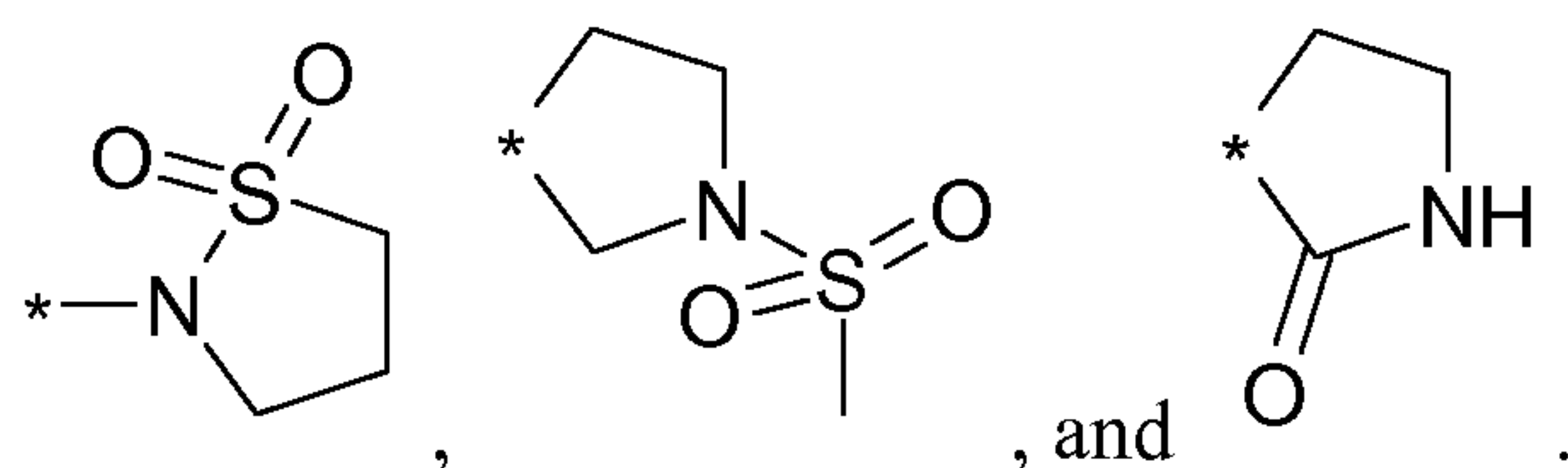


Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Q , and n as herein before or below defined, wherein Z is C ,

and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R_8 , R_8'), with R_8 and R_8'

independently being selected from among -H and -C₁-C₆-alkyl,

wherein R_4 and R_5 if different from -H are optionally independently substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF₃, -OCF₃, -CN, -O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇, -N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₃H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Q , and n as herein before or below defined,

wherein Z is N,

and R₄ denotes an electron pair, and R₅ is a group selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R₈,R₈'), with R₈ and R₈'

5 independently being selected from among -H and -C₁-C₆-alkyl,

wherein R₅ if different from an -H is optionally substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -

CF₃, -OCF₃, -CN, -O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃,

-C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂,

10 -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇,

-N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-

CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅,

-NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-

C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₂H₅, -CH₂-NH-SO₂-CH₃,

15 -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇,

-CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂,

-N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂,

-N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅,

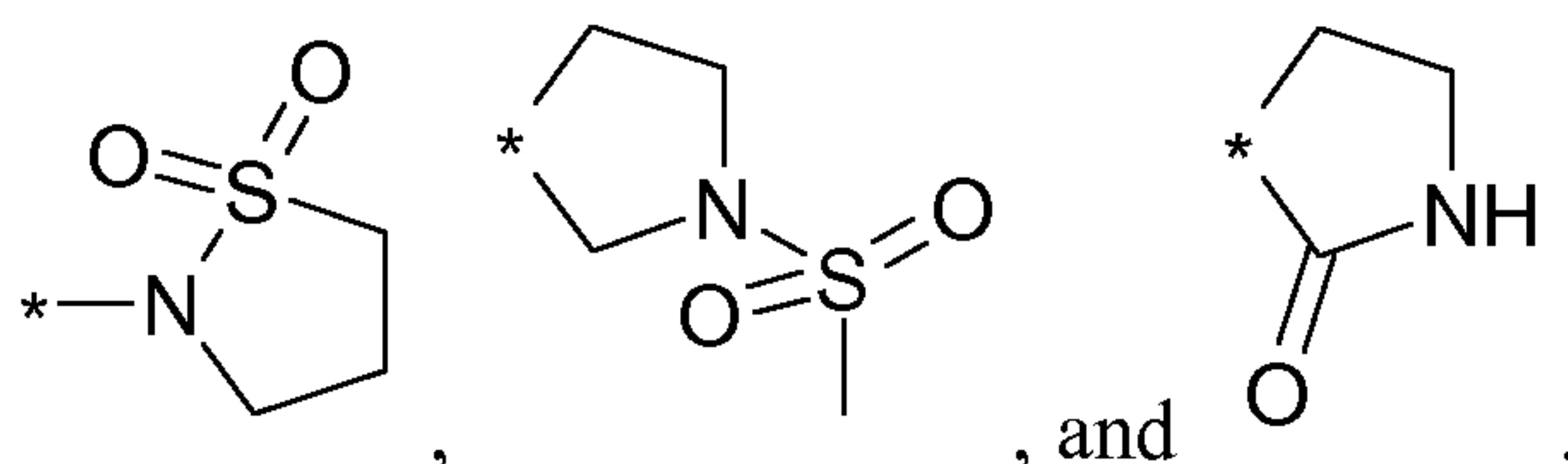
-C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅,

20 -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂,

-N(CH₃)-SO₂-N(CH₃)₂, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl,

-O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl,

-3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



25

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Q, and n as herein before or below defined,

wherein Z is C,

30 and R₄ denotes -H and R₅ is a group selected from among , -i-propyl, -amino, -pyrrolidinyl,

-piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny,

-tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R₈,R₈'), with R₈ and R₈'

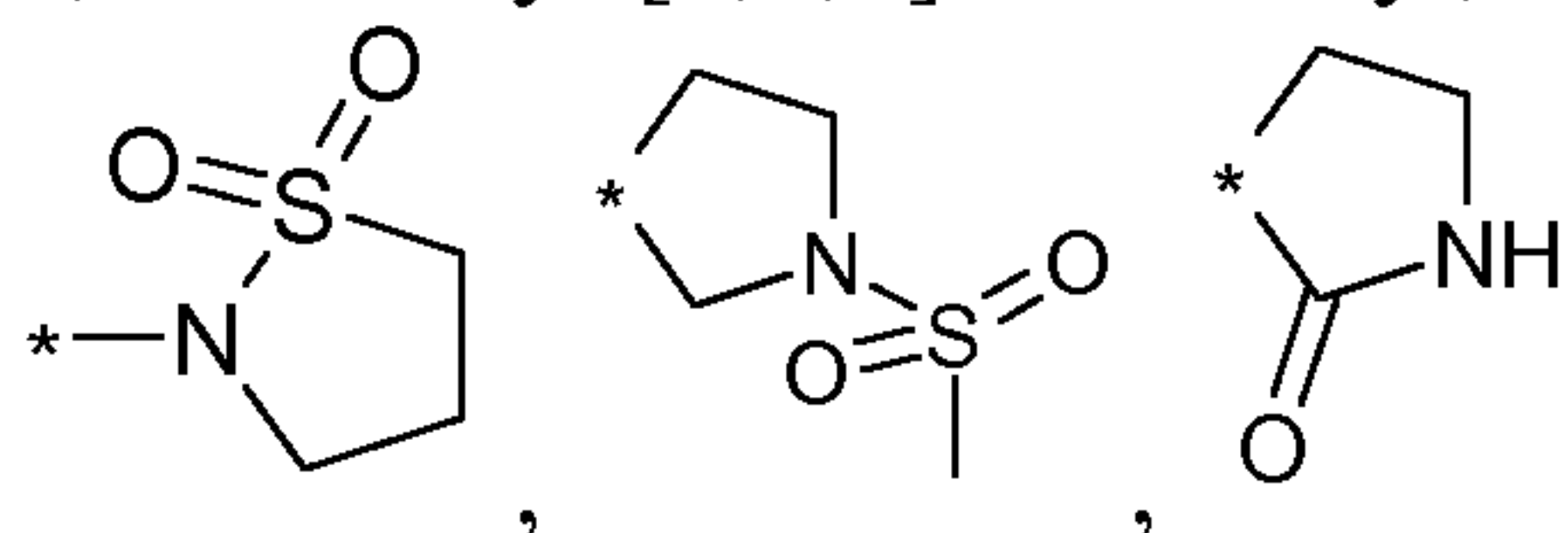
independently being selected from among -H and -C₁-C₆-alkyl,

wherein R₅ is optionally substituted with one or more groups selected from among -fluoro,

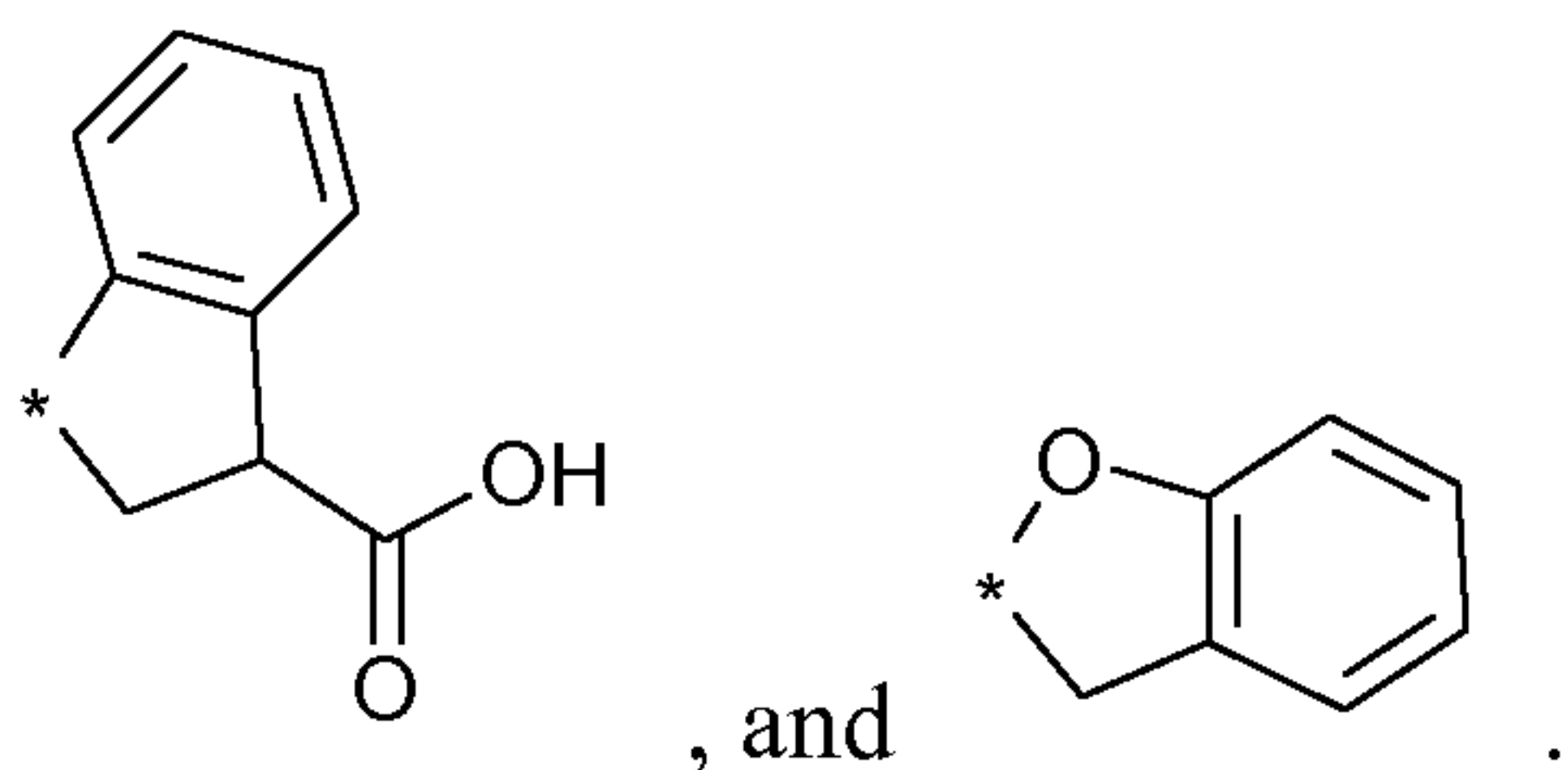
35 -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF₃, -OCF₃, -CN,

-O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-

C_2H_5 , $-C(O)-C_3H_7$, $-COOH$, $-C(O)-NH_2$, $-C(O)-NH-CH_3$, $-C(O)-N(CH_3)_2$, $-NH-C(O)-CH_3$,
 $-N(CH_3)C(O)-CH_3$, $-NH-C(O)-C_2H_5$, $-N(CH_3)-C(O)-C_2H_5$, $-NH-C(O)-C_3H_7$, $-N(CH_3)-C(O)-$
 C_3H_7 , $-NH-SO_2-CH_3$, $-N(CH_3)-SO_2-CH_3$, $-N(C_2H_5)-SO_2-CH_3$, $-N(C_3H_7)-SO_2-CH_3$, $-NH-SO_2-$
 C_2H_5 , $-N(CH_3)-SO_2-C_2H_5$, $-N(C_2H_5)-SO_2-C_2H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-NH-SO_2-C_3H_7$,
5 $-N(CH_3)-SO_2-C_3H_7$, $-N(C_2H_5)-SO_2-C_3H_7$, $-N(C_3H_7)-SO_2-C_3H_7$, $-NH-SO_2-C_3H_5$,
 $-N(CH_3)-SO_2-C_3H_5$, $-N(C_2H_5)-SO_2-C_3H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-CH_3$,
 $-CH_2-N(CH_3)-SO_2-CH_3$, $-CH_2-NH-SO_2-C_2H_5$, $-CH_2-N(CH_3)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-C_3H_7$,
 $-CH_2-N(CH_3)-SO_2-C_3H_7$, $-CH_2-NH-SO_2-C_3H_5$, $-CH_2-N(CH_3)-SO_2-C_3H_5$, $-NH-C(O)-NH_2$,
 $-N(CH_3)-C(O)-NH_2$, $-NH-C(O)-NH-CH_3$, $-N(CH_3)-C(O)-NH-CH_3$, $-NH-C(O)-N(CH_3)_2$,
10 $-N(CH_3)-C(O)-N(CH_3)_2$, $-SO_2-NH_2$, $-SO_2-NH(CH_3)$, $-SO_2-N(CH_3)_2$, $-C(O)-NH-C_2H_5$,
 $-C(O)-N(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-C_3H_7$, $-C(O)-N(CH_3)-C_4H_9$, $-C(O)-NH-CH(CH_3)-C_2H_5$,
 $-C(O)-N(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-C(O)-NH_2$, $-CH_2-C(O)-NH-CH_3$, $-CH_2-C(O)-N(CH_3)_2$,
 $-N(CH_3)-SO_2-N(CH_3)_2$, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl,
-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl,
15 -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



or wherein R_5 is optionally substituted with one or more groups selected from among $-(C_6\text{-aryl})-COOH$,

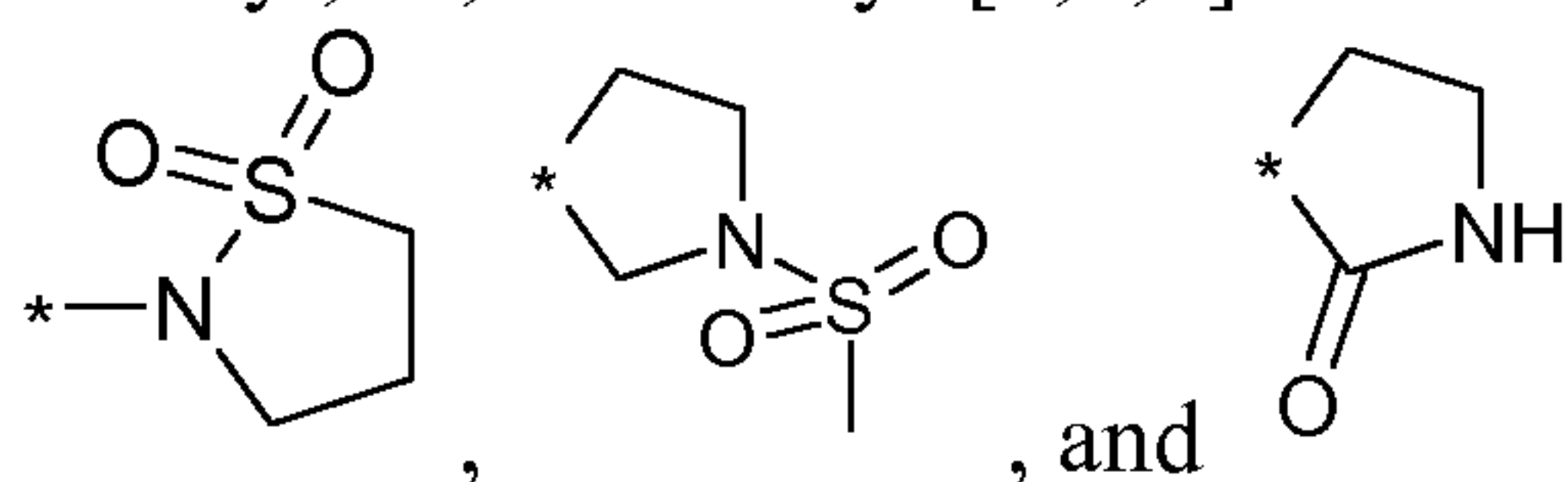


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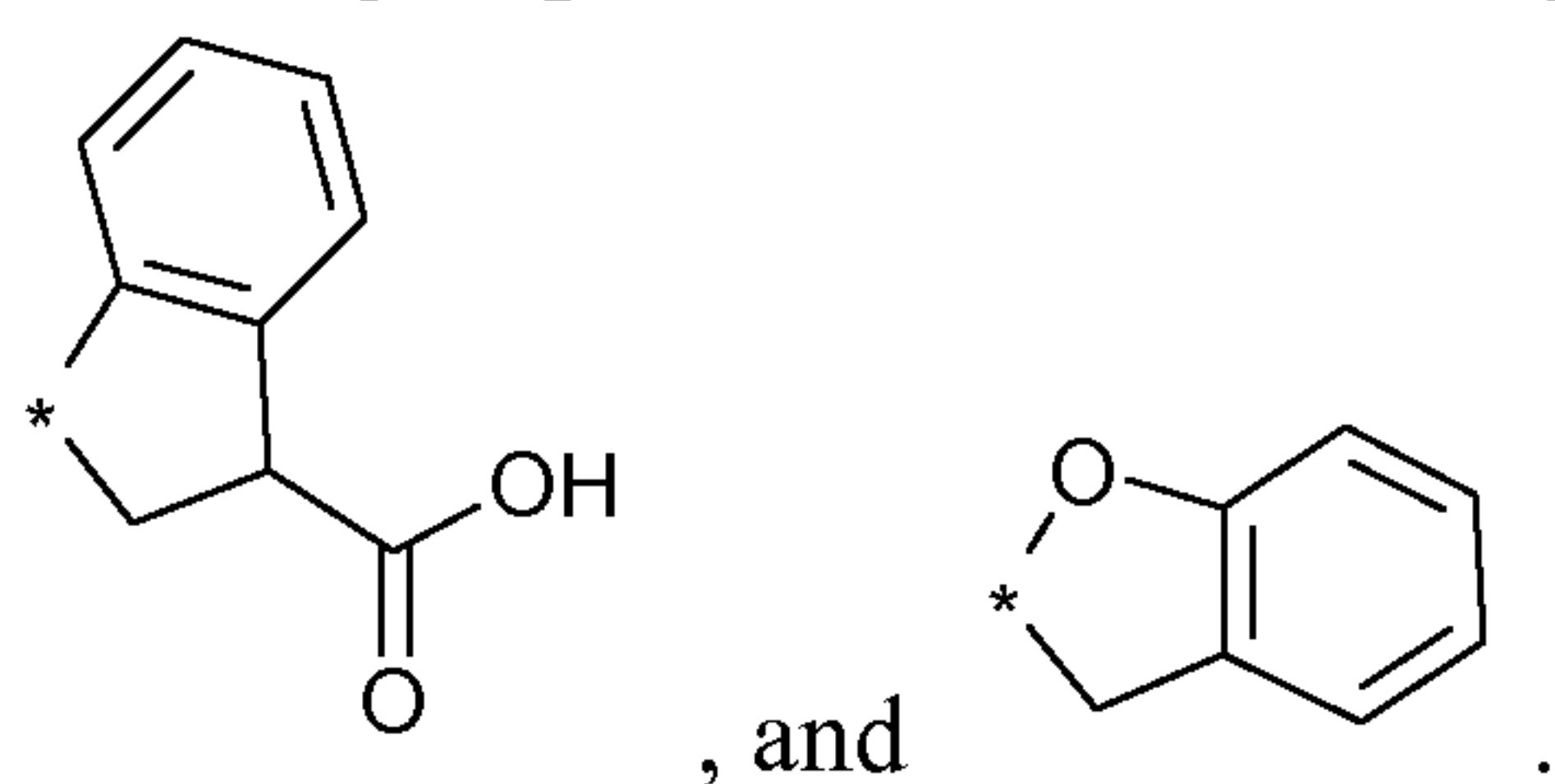
Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Q , and n as herein before or below defined, wherein Z is C ,

25 and R_4 and R_5 are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and $-C(O)-N(R_8, R_8')$, with R_8 and R_8' independently being selected from among -H and $-C_1-C_6\text{-alkyl}$,
wherein R_4 and R_5 if different from -H are optionally independently substituted with one or
30 more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, $-CF_3$, $-CN$, $-CH_2-CN$, $-CH_2-O-CH_3$, $-(CH_2)_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)-C_2H_5$, $-C(O)-C_3H_7$, $-COOH$, $-C(O)-NH_2$, $-C(O)-NH-CH_3$, $-C(O)-N(CH_3)_2$, $-NH-C(O)-CH_3$, $-N(CH_3)C(O)-CH_3$, $-NH-C(O)-C_2H_5$, $-N(CH_3)-C(O)-C_2H_5$, $-NH-C(O)-C_3H_7$, $-N(CH_3)-C(O)-$

C_3H_7 , $-NH-SO_2-CH_3$, $-N(CH_3)-SO_2-CH_3$, $-N(C_2H_5)-SO_2-CH_3$, $-N(C_3H_7)-SO_2-CH_3$, $-NH-SO_2-$
 C_2H_5 , $-N(CH_3)-SO_2-C_2H_5$, $-N(C_2H_5)-SO_2-C_2H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-NH-SO_2-C_3H_7$,
 $-N(CH_3)-SO_2-C_3H_7$, $-N(C_2H_5)-SO_2-C_3H_7$, $-N(C_3H_7)-SO_2-C_3H_7$, $-NH-SO_2-C_3H_5$,
 $-N(CH_3)-SO_2-C_3H_5$, $-N(C_2H_5)-SO_2-C_3H_5$, $-N(C_3H_7)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-CH_3$,
5 $-CH_2-N(CH_3)-SO_2-CH_3$, $-CH_2-NH-SO_2-C_2H_5$, $-CH_2-N(CH_3)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-C_3H_7$,
 $-CH_2-N(CH_3)-SO_2-C_3H_5$, $-CH_2-NH-SO_2-C_3H_5$, $-CH_2-N(CH_3)-SO_2-C_3H_5$, $-NH-C(O)-NH_2$,
 $-N(CH_3)-C(O)-NH_2$, $-NH-C(O)-NH-CH_3$, $-N(CH_3)-C(O)-NH-CH_3$, $-NH-C(O)-N(CH_3)_2$,
 $-N(CH_3)-C(O)-N(CH_3)_2$, $-SO_2-NH_2$, $-SO_2-NH(CH_3)$, $-SO_2-N(CH_3)_2$, $-C(O)-NH-C_2H_5$,
 $-C(O)-N(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-C_3H_7$, $-C(O)-N(CH_3)-C_4H_9$, $-C(O)-NH-CH(CH_3)-C_2H_5$,
10 $-C(O)-N(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-C(O)-NH_2$, $-CH_2-C(O)-NH-CH_3$, $-CH_2-C(O)-N(CH_3)_2$,
 $-N(CH_3)-SO_2-N(CH_3)_2$, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -pyrrolidine-2-
one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



or wherein R_4 and R_5 if different from $-H$ are optionally independently substituted with one
 15 or more groups selected from among $-(C_6\text{-aryl})-COOH$,

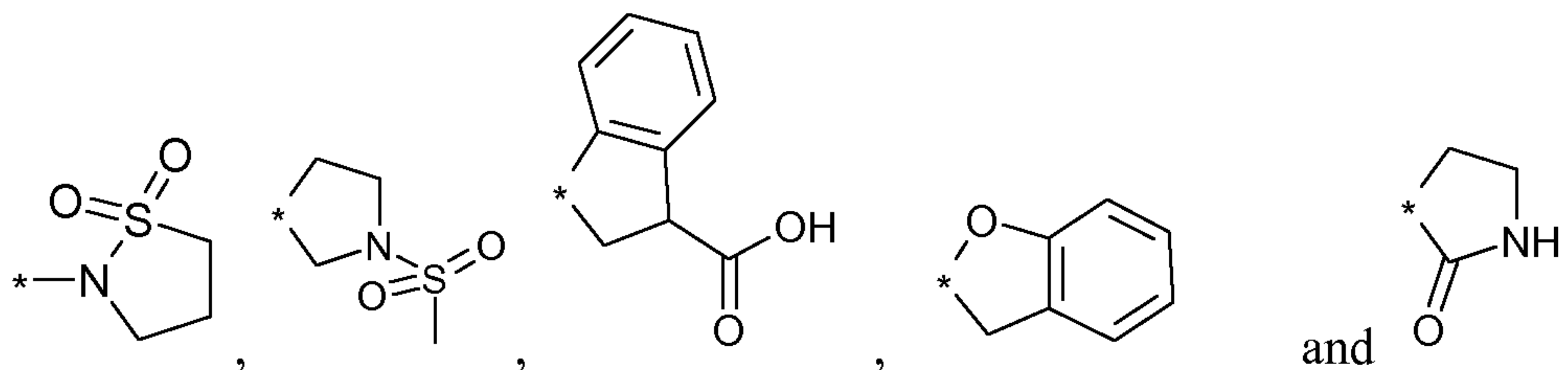


Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,
 R_3 , R_6 , R_7 , E , G , Q , and n as herein before or below defined,
 20 wherein Z is C ,

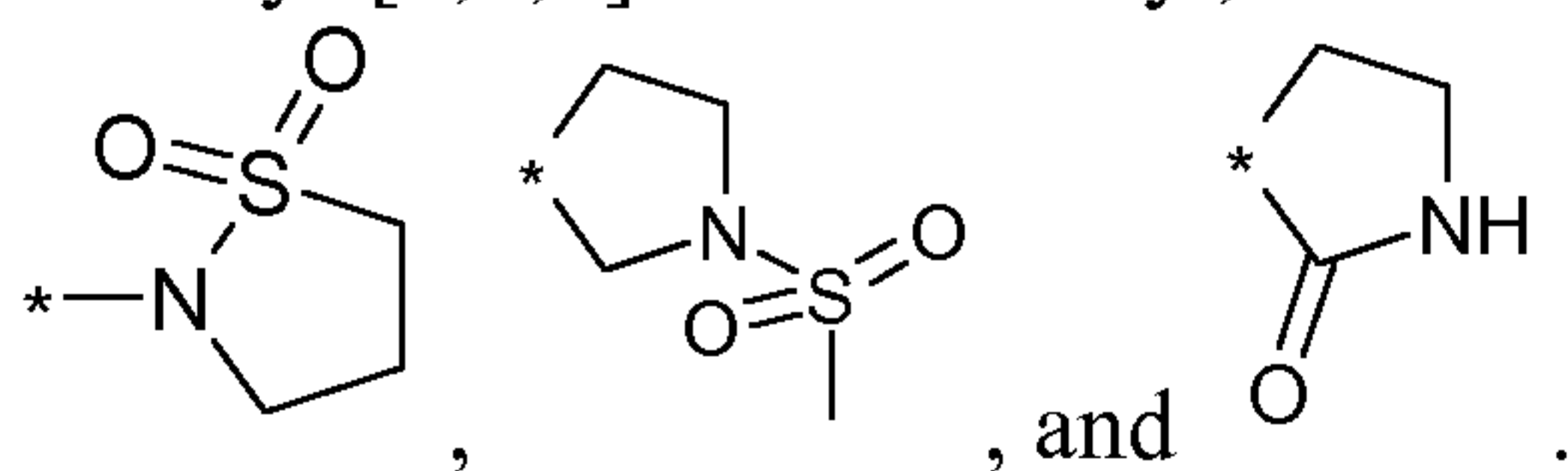
and R_4 and R_5 are independently selected from among $-H$, $-i$ -propyl, $-amino$, $-pyrrolidinyl$, $-$
 $piperidinyl$, $-morpholinyl$, $-azepanyl$, $-oxazepanyl$, $-piperazinyl$, $-azetidiny$, $-$
 $tetrahydropyranyl$, $-cyclopentyl$, $-cyclohexyl$, and $-C(O)-N(R_8, R_8)$, with R_8 and R_8
 independently being selected from among $-H$ and $-C_1-C_6$ -alkyl,

25 wherein R_4 and R_5 if different from $-H$ are optionally independently substituted with one or
 more groups selected from among $-fluoro$, $-methyl$, $-ethyl$, $propyl$, $-i$ -propyl, $-butyl$, $-i$ -butyl,
 $-t$ -butyl, $-hydroxy$, $-CF_3$, $-CN$, $-CH_2-CN$, $-CH_2-O-CH_3$, $-(CH_2)_2-O-CH_3$, $-C(O)-CH_3$, $-C(O)-$
 C_2H_5 , $-C(O)-C_3H_7$, $-COOH$, $-C(O)-NH_2$, $-C(O)-NH-CH_3$, $-C(O)-N(CH_3)_2$, $-CH_2-NH-SO_2-$
 CH_3 , $-CH_2-N(CH_3)-SO_2-CH_3$, $-CH_2-NH-SO_2-C_2H_5$, $-CH_2-N(CH_3)-SO_2-C_2H_5$, $-CH_2-NH-SO_2-$
 30 C_3H_7 , $-CH_2-N(CH_3)-SO_2-C_3H_7$, $-CH_2-NH-SO_2-C_3H_5$, $-CH_2-N(CH_3)-SO_2-C_3H_5$, $-C(O)-NH-$
 C_2H_5 , $-C(O)-N(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-C_3H_7$, $-C(O)-N(CH_3)-C_4H_9$,
 $-C(O)-NH-CH(CH_3)-C_2H_5$, $-C(O)-N(CH_3)-CH(CH_3)-C_2H_5$, $-CH_2-C(O)-NH_2$, $-CH_2-C(O)-NH-$
 CH_3 , $-CH_2-C(O)-N(CH_3)_2$, $-N(CH_3)-SO_2-N(CH_3)_2$, $-(C_6\text{-aryl})-COOH$, -phenyl, -pyridin-4-yl,

-CH₂-3-methyl-oxetan-3-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl,
3-methyl-[1,2,4]oxadiazol-5-yl,



- 5 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Q, and n as herein before or below defined, wherein Z is C,
and R₄ and R₅ are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl,
10 -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H and -C₁-C₆-alkyl,
wherein R₄ and R₅ if different from -H are optionally independently substituted with one or more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl,
15 -t-butyl, -hydroxy, -CF₃, -CN, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉,
20 -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -phenyl, -pyridin-4-yl, -CH₂-3-methyl-oxetan-3-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



25

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, E, G, Q, and n as herein before or below defined, wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

- 30 wherein L₁ is selected from among -NH-, -N(CH₃)-, -N(C₂H₅)-, and a bond
and wherein R₁₈ is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl,

-morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl, -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl, wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃,
 5 -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-C₂H₅, more preferred wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -O-CH₃, -N(CH₃)-S(O)₂-CH₃, most preferred wherein R₁₈ is optionally substituted by -O-CH₃.

10 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined, wherein R₁₈ is optionally substituted by one or more groups selected from among -F, and -O-CH₃,

15 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, E, G, Q, and n as herein before or below defined, wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(CH₃)-, -N(C₂H₅)-, and a bond

20 and wherein R₁₈ is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl, -morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl, -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl, wherein R₁₈ is optionally substituted by -F.

25 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₉, R₁₉', E, G, Q, and n as herein before or below defined, wherein Z is C,

30 and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(CH₃)-, and -N(C₂H₅)-,

and wherein R₁₈ is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl, -morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl,

35 -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl, wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-C₂H₅.

5 and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,
wherein L₁ is selected from among -NH-, -N(CH₃)-, -N(C₂H₅)-, and a bond,
and wherein R₄, R₅ and R₁₈ are optionally further bi-valently substituted by one or more
groups selected from among



15 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₉, R_{19'}, E, G, Q, and n as herein before or below defined, wherein Z is C,

20 wherein L₁ is selected from among -NH-, -N(CH₃)-, and -N(C₂H₅)-,
and wherein R₄, R₅ and R₁₈ are optionally further bi-valently substituted by one or more
groups selected from among



Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃,
30 R₄, R₅, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, R₁₈, R₁₉,
R_{19'}, R₂₀, R_{20'}, L₁, E, G, Z, Q, and n as herein before or below defined,

wherein R₁ is a group selected from among -H, -halogen, -CN, -C₁-C₃-alkyl, -CH=CH₂, -C≡CH, and -CF₃, more preferred wherein R₁ is a group selected from among -H, -halogen, and -methyl.

- 5 Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Z, Q, and n as herein before or below defined,
 wherein R₁ is a group selected from among -H, -halogen, -CN, -C₁-C₃-alkyl, -CH=CH₂, -C≡CH, and -CF₃, more preferred wherein R₁ is a group selected from among -H, -halogen,
 10 and -methyl.

- Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined,
 15 wherein R₇ is selected from among -C₅-C₆-aryl, -C₅-C₆-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl,
 and wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -methyl, -C(CH₃)₂-CN, and -halogen.

- 20 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Z, Q, and n as herein before or below defined,
 wherein R₇ is selected from among -C₅-C₆-aryl, -C₅-C₆-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl,
 25 and wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, -methyl, -C(CH₃)₂-CN, and -halogen.

- Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined,
 30 wherein R₇ is selected from among -C₅-C₆-aryl, and -C₅-C₆-heteroaryl,
 wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -methyl, -F, -Cl, -C(CH₃)₂-CN, and -Br.

- 35 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Z, Q, and n as herein before or below defined,
 wherein R₇ is selected from among -C₅-C₆-aryl, and -C₅-C₆-heteroaryl,

wherein the ring R₇ is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, -methyl, -F, -Cl, -C(CH₃)₂-CN, and -Br.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂,

5 R₃, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₉, R₁₉', R₂₀, R₂₀', E, G, Q, and n as herein before or below defined,

wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(CH₃)-, -N(C₂H₅)-, and optionally a bond

10 and wherein R₁₈ is selected from among -C₆-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O,

and wherein R₁₈ is optionally substituted by one or more groups selected from among among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-

15 C₂H₅, more preferred wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -O-CH₃, -N(CH₃)-S(O)₂-CH₃, more preferred wherein R₁₈ is optionally substituted by one or more groups selected from among -O-CH₃, -N(CH₃)-S(O)₂-CH₃, more preferred wherein R₁₈ is optionally substituted by one or more groups selected from among -F, and -O-CH₃, most preferred wherein R₁₈ is optionally substituted by -O-CH₃.

20

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂,

R₃, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₉, R₁₉', E, G, Q, and n as herein before or below defined,

wherein Z is C,

25 and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(CH₃)-, and -N(C₂H₅)-,

and wherein R₁₈ is selected from among -C₆-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O,

and wherein R₁₈ is optionally substituted by one or more groups selected from among among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-

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C₂H₅, more preferred wherein R₁₈ is optionally substituted by one or more groups selected from among -O-CH₃, -N(CH₃)-S(O)₂-CH₃, most preferred wherein R₁₈ is optionally substituted by -O-CH₃.

35

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂,

R₃, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁', R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, E, G, Q, and n as herein before or below defined,

wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R_{19'}), wherein R₁₉ and R_{19'} together form a -C₂-C₆-alkylene group, preferably a -C₄-C₅-alkylene group, more preferably a -C₅-alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among

among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -(C₆-aryl)-COOH, -C(O)-O-C₂H₅, more preferred wherein such ring is optionally substituted

by one or more groups selected from among -O-CH₃, -NH-S(O)₂-CH₃, -(C₆-aryl)-COOH, and -N(CH₃)-S(O)₂-CH₃, more preferred wherein such ring is optionally substituted by one or

more groups selected from among -O-CH₃, -NH-S(O)₂-CH₃, and -N(CH₃)-S(O)₂-CH₃, more preferred wherein such ring is optionally substituted by one or more groups selected from among -(C₆-aryl)-COOH, and -N(CH₃)-S(O)₂-CH₃, most preferred wherein such ring is optionally substituted by -N(CH₃)-S(O)₂-CH₃.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, E, G, Q, and n as herein before or below defined,

wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R_{19'}),

wherein R₁₉ and R_{19'} together form a -C₂-C₆-alkylene group, preferably a -C₄-C₅-alkylene group, more preferably a -C₅-alkylene group such that a ring is formed, wherein such ring is optionally substituted by -(C₆-aryl)-COOH.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂,

R₃, R₆, R₇, R₈, R_{8'}, R₉, R_{9'}, R₁₀, R₁₁, R_{11'}, R₁₂, R₁₃, R_{13'}, R₁₄, R₁₅, R_{15'}, R₁₆, R₁₇, E, G, Q, and n as herein before or below defined,

wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R_{19'}),

wherein R₁₉ and R_{19'} together form a -C₂-C₆-alkylene group, preferably a -C₅-C₆-alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among

among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-C₂H₅, more preferred wherein such ring is optionally substituted by one or more

groups selected from among -O-CH₃, -NH-S(O)₂-CH₃, and -N(CH₃)-S(O)₂-CH₃, most preferred wherein such ring is optionally substituted by -N(CH₃)-S(O)₂-CH₃.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Z , Q , and n as herein before or below defined,

wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, -CH=CH₂, and -C≡CH, more preferred wherein R_2 is selected from among -H, -Methyl, -Ethyl, and -Br, more preferred wherein R_2 is selected from among -H, and -Methyl, most preferred wherein R_2 denotes -Methyl.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Z , Q , and n as herein before or below defined,

wherein R_2 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, -CH=CH₂, and -C≡CH, more preferred wherein R_2 is selected from among -H, -Methyl, -Ethyl, and -Br, more preferred wherein R_2 is selected from among -H, and -Methyl, most preferred wherein R_2 denotes -Methyl.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Z , Q , and n as herein before or below defined, wherein R_2 denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Z , Q , and n as herein before or below defined, wherein R_2 denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Z , Q , and n as herein before or below defined, wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Z , Q , and n as herein before or below defined, wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Z , Q , and n as herein before or below defined,

wherein R_3 is selected from among $-\text{OCH}_3$, $-\text{H}$, $-\text{CF}_3$, and $-\text{methyl}$, more preferred wherein R_3 is selected from among $-\text{H}$, and $-\text{methyl}$, more preferred wherein R_3 denotes $-\text{H}$.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,
 5 R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} ,
 R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Z , Q , and n as herein before or below defined,
 wherein R_3 denotes $-\text{OCH}_3$.

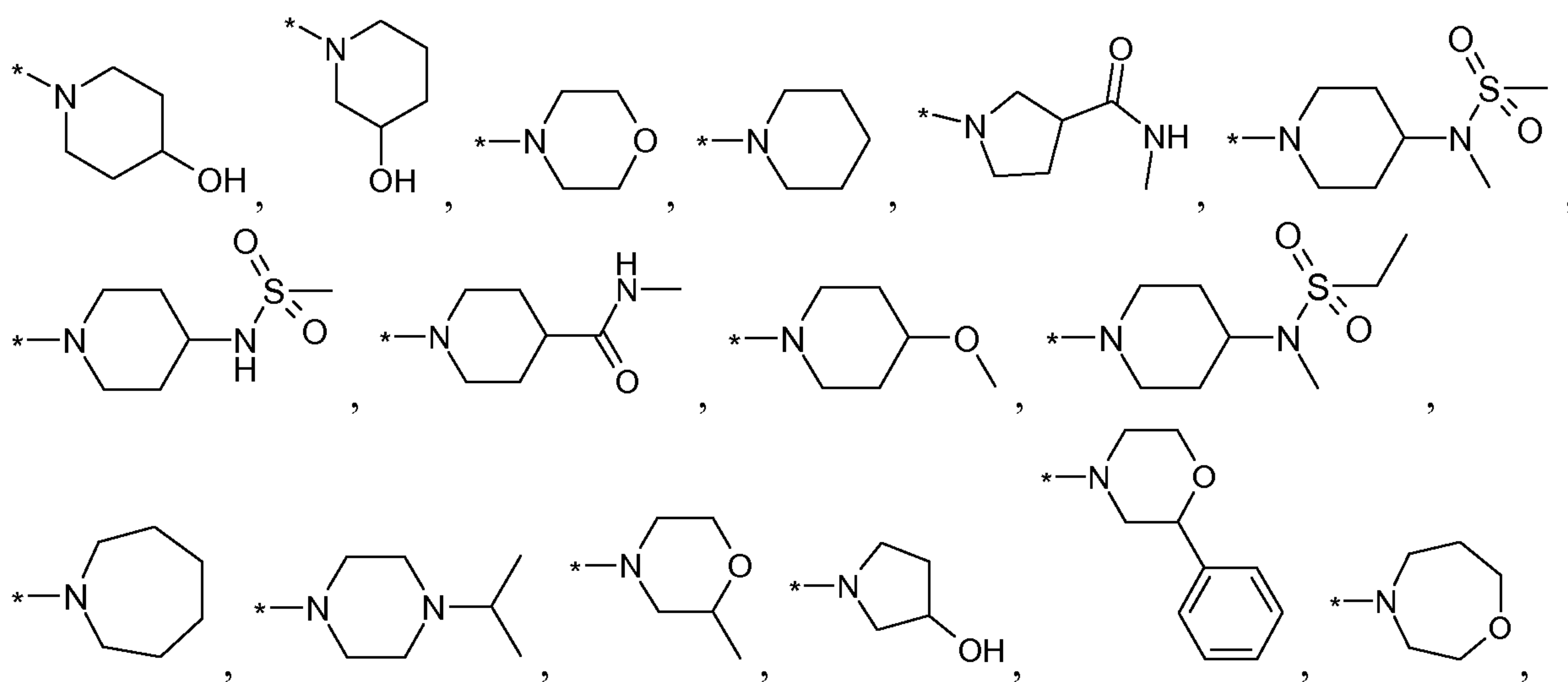
Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,
 10 R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} ,
 R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Z , Q , and n as herein before or below defined,
 wherein R_3 denotes $-\text{CF}_3$.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,
 15 R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} ,
 R_{19} , R_{19}' , L_1 , E , G , Z , Q , and n as herein before or below defined,
 wherein R_3 is selected from among $-\text{H}$, $-\text{CF}_3$, and $-\text{methyl}$, more preferred wherein R_3 is
 selected from among $-\text{H}$, and $-\text{methyl}$, more preferred wherein R_3 denotes $-\text{H}$.

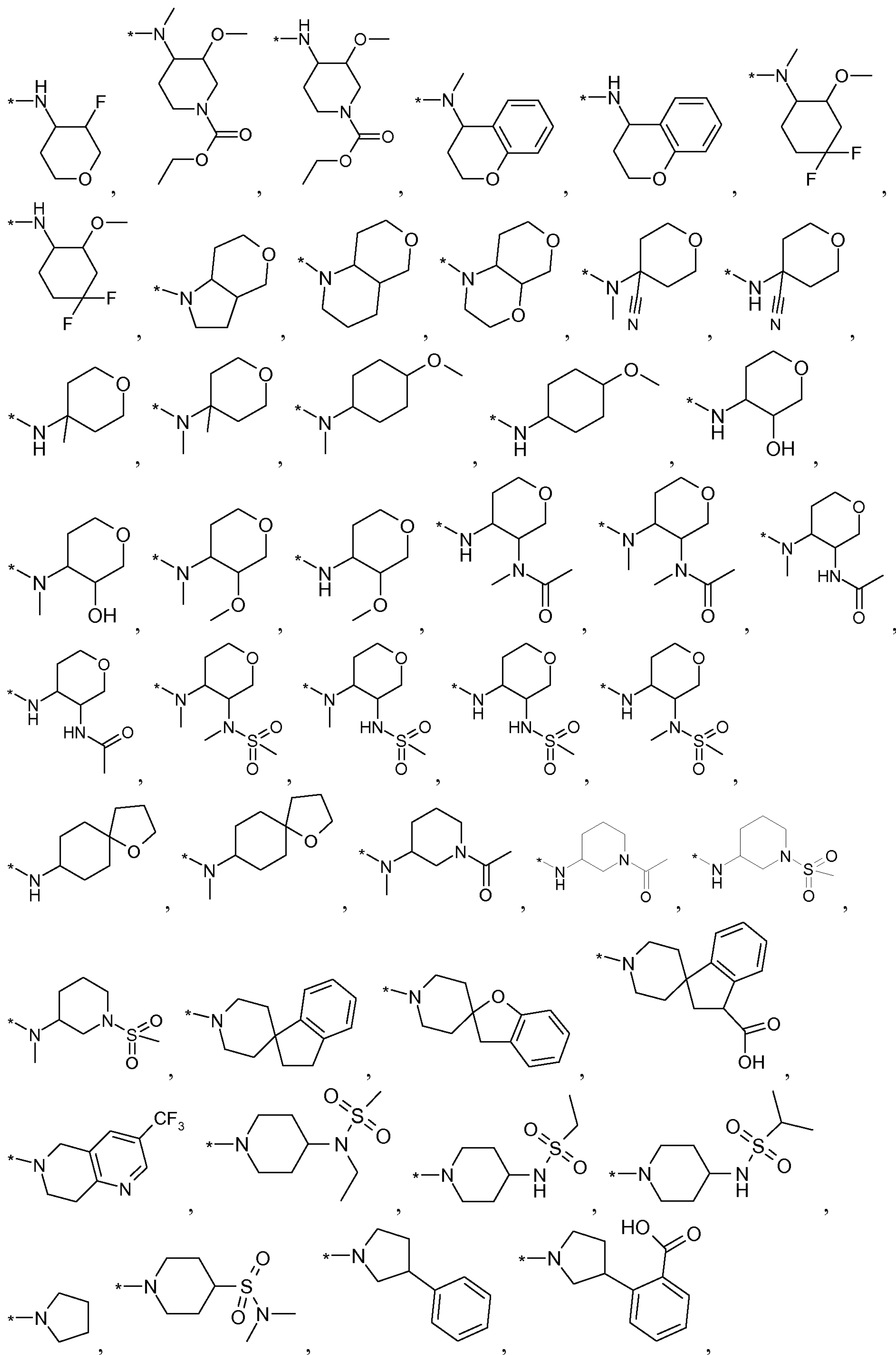
20 Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,
 R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' ,
 R_{20} , R_{20}' , L_1 , E , G , Q , and n as herein before or below defined,
 wherein Z is C ,

R_4 denotes $-\text{H}$, and R_5 is selected from among

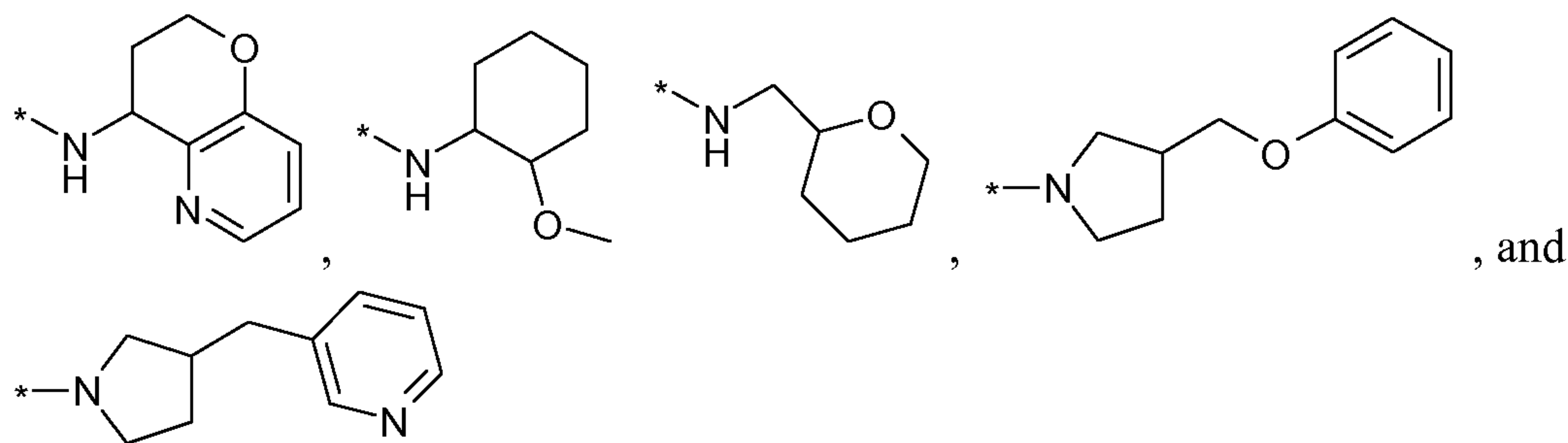
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Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,

R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , E , G , Q , and n as herein before or below defined,

wherein Z is C ,

and R_4 denotes $-H$, and R_5 denotes $-N(R_{19}, R_{19}')$, wherein R_{19} and R_{19}' together form a $-C_2-$ C_6 -alkylene group such that a ring is formed, more preferred wherein R_{19} and R_{19}' together

form a $-C_4-C_5$ -alkylene group such that a ring is formed, most preferred wherein R_{19} and R_{19}' together form a $-C_5$ -alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among among $-F$, $-CF_3$, $-OCF_3$, $-CN$, $-OH$, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-(C_6\text{-aryl})-COOH$,

$-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$, more preferred wherein such ring is optionally substituted by one or more groups selected from among $-O-CH_3$, $-NH-S(O)_2-CH_3$, $-(C_6\text{-aryl})-COOH$, and $-N(CH_3)-S(O)_2-CH_3$, more preferred wherein such ring is optionally substituted by one or more groups selected from among $-(C_6\text{-aryl})-COOH$, and

$-N(CH_3)-S(O)_2-CH_3$, most preferred wherein such ring is optionally substituted by

$-N(CH_3)-S(O)_2-CH_3$.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 ,

R_3 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Q , and n as herein before or below defined,

wherein Z is C ,

and R_4 denotes $-H$, and R_5 denotes $-N(R_{19}, R_{19}')$, wherein R_{19} and R_{19}' together form a $-C_2-$ C_6 -alkylene group such that a ring is formed, more preferred wherein R_{19} and R_{19}' together

form a $-C_5-C_6$ -alkylene group such that a ring is formed, most preferred wherein R_{19} and R_{19}' together form a $-C_5$ -alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among among $-F$, $-CF_3$, $-OCF_3$, $-CN$, $-OH$, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$,

$-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, and $-C(O)-O-C_2H_5$, more preferred wherein such ring is optionally substituted by one or more

groups selected from among $-O-CH_3$, $-NH-S(O)_2-CH_3$, and $-N(CH_3)-S(O)_2-CH_3$, most

preferred wherein such ring is optionally substituted by $-N(CH_3)-S(O)_2-CH_3$.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined,

5 wherein R₄ is selected from among -H, and -C(O)-NH₂, more preferred wherein R₄ denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined,

10 wherein R₅ is selected from among -H, and -C(O)-NH₂, more preferred wherein R₅ denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Z, Q, and n as herein before or below defined,

15 wherein R₅ is selected from among -H, and -C(O)-NH₂, more preferred wherein R₅ denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', E, G, Z, Q, and n as herein before or below defined,

20 wherein L₁ denotes a bond.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined, wherein R₆ is selected from among -H, -CH₃, -C₂H₅, -O-CH₃, -O-C₂H₅, -F, -CF₃, and -OCF₃, more preferred wherein R₆ is -H or -O-CH₃, most preferred wherein R₆ denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Z, Q, and n as herein before or below defined, wherein R₆ is selected from among -H, -CH₃, -C₂H₅, -O-CH₃, -O-C₂H₅, -F, -CF₃, and -OCF₃, more preferred wherein R₆ is -H or -O-CH₃, most preferred wherein R₆ denotes -H.

Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, Q, and n as herein before or below defined, wherein R₁ is -H.

Preferred compounds of formula (I) according to the invention are compounds with R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, E, G, Z, Q, and n as herein before or below defined, wherein R₁ is -H.

5 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Z, and Q, as herein before or below defined, wherein n is 2.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈,
10 R₁₉, R₁₉', L₁, E, G, Z, and Q, as herein before or below defined, wherein n is 2.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, Z, Q, and n as herein before or below defined, wherein G and E are N.

15 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, Z, Q, and n as herein before or below defined, wherein G and E are N.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂,
20 R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, Z, Q, and n as herein before or below defined, wherein G is C-H, and E is N.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈,
25 R₁₉, R₁₉', L₁, Z, Q, and n as herein before or below defined, wherein G is C-H, and E is N.

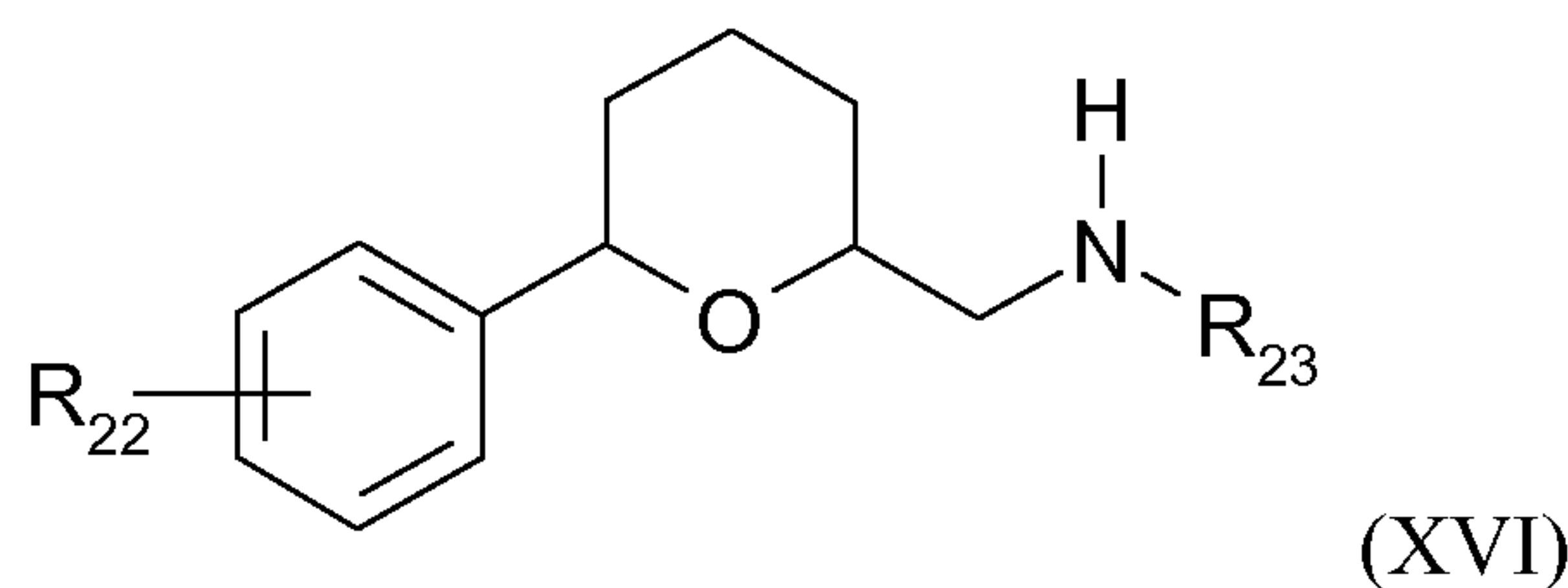
Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, Z, Q, and n as herein before or below defined, wherein E is C-H, and
30 G is N.

Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', L₁, Z, Q, and n as herein before or below defined, wherein E is C-H, and G is N.

35 Preferred compounds of formula (I) according to the invention are compounds with R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₈', R₉, R₉', R₁₀, R₁₁, R₁₁' R₁₂, R₁₃, R₁₃', R₁₄, R₁₅, R₁₅', R₁₆, R₁₇, R₁₈, R₁₉, R₁₉', R₂₀, R₂₀', L₁, E, G, Q, and n as herein before or below defined, wherein Z is C.

Preferred compounds of formula (I) according to the invention are compounds with R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , L_1 , E , G , Q , and n as herein before or below defined, wherein Z is C .

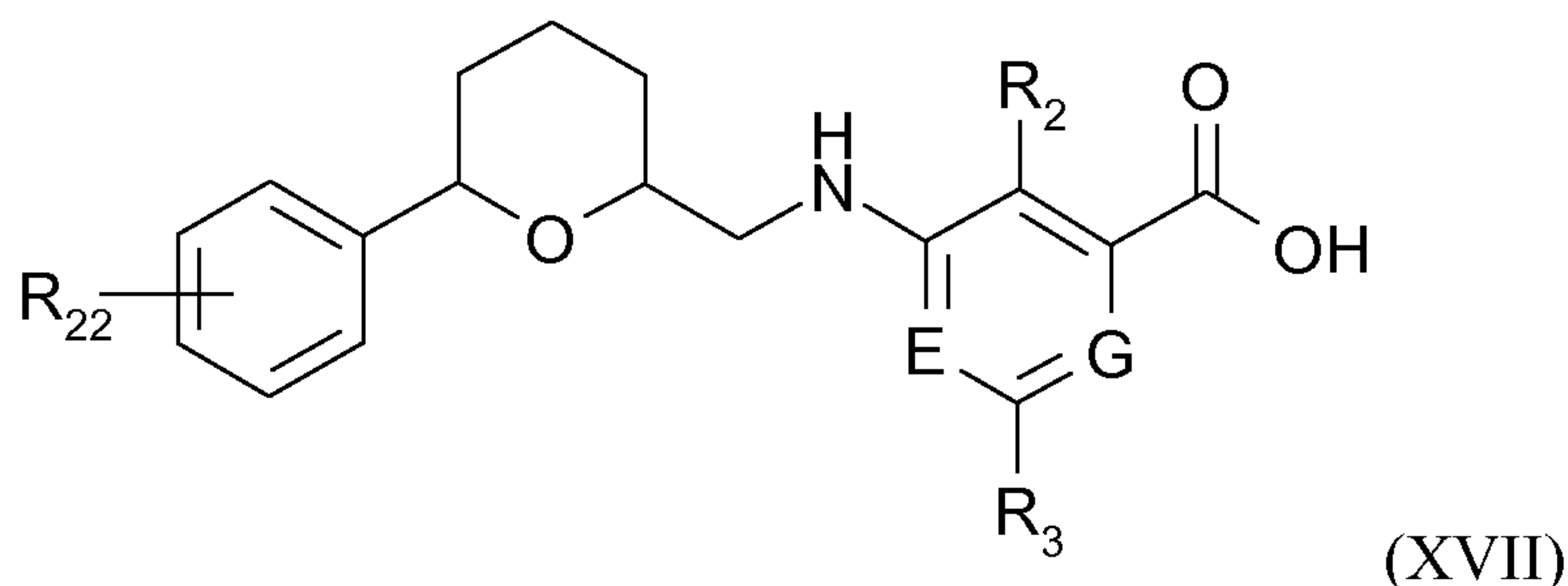
- 5 The present invention also relates to process for preparing a compound of formula (I) as herein before or below defined, wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , L_1 , Z , E , G , Q , and n have the meanings defined hereinbefore.
- 10 The present invention also relates to the following intermediate products for synthesizing the compounds of formula (I) according to the invention:
- compounds according to formula (II) according to preparation method A,
 - compounds according to formula (III) according to preparation method A,
 - compounds according to formula (V) according to preparation method B,
 - 15 - compounds according to formula (VI) according to preparation method B,
 - compounds according to formula (VIII) according to preparation method C,
 - compounds according to formula (X) according to preparation method D,
 - compounds according to formula (XI) according to preparation method D,
 - compounds according to formula (XIII) according to preparation method E,
 - 20 - compounds according to formula (XIV) according to preparation method E,
- wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_8' , R_9 , R_9' , R_{10} , R_{11} , R_{11}' , R_{12} , R_{13} , R_{13}' , R_{14} , R_{15} , R_{15}' , R_{16} , R_{17} , R_{18} , R_{19} , R_{19}' , R_{20} , R_{20}' , R_{21} , R_{21}' , L_1 , E , G , Q , Z , CYC , and n have the meanings defined hereinbefore.
- 25 The present invention also relates to the following intermediate products according to general formula (XVI) for synthesizing the compounds of formula (I) according to the invention



- wherein R_{22} is a group selected from among $-H$, $-CF_3$, $-O-CF_3$, $-S-CF_3$, $-CN$, $-C_1-C_6$ -alkyl, $-C(CH_3)_2-CN$, and $-halogen$
- 30 or wherein R_{22} is a group selected from among $-C_1-C_6$ -alkyl, $-O-C_1-C_6$ -alkyl, $-C_5-C_{10}$ -aryl, $-C_5-C_{10}$ -heteroaryl, $-C_3-C_8$ -cycloalkyl, $-C_3-C_8$ -heterocyclyl, $-C_2-C_6$ -alkenyl, and $-C_2-C_6$ -alkynyl, optionally being substituted by one or more groups selected from among $-OH$, $-NH_2$, $-C_1-C_3$ -alkyl, $-O-C_1-C_6$ -alkyl, $-CN$, $-CF_3$, $-OCF_3$, halogen, $-methyl$, and $=O$,

more preferred wherein R_{22} is a group selected from among $-\text{CF}_3$, $-\text{O}-\text{CF}_3$, $-\text{S}-\text{CF}_3$, $-\text{CN}$,
 $-\text{methyl}$, $-\text{C}(\text{CH}_3)_2-\text{CN}$, and $-\text{halogen}$, more preferred wherein R_{22} is a group selected from
among $-\text{CF}_3$, $-\text{O}-\text{CF}_3$, $-\text{S}-\text{CF}_3$, $-\text{CN}$, $-\text{methyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{C}(\text{CH}_3)_2-\text{CN}$, and $-\text{Br}$,
and wherein R_{23} is a group selected from among $-\text{H}$ and $-\text{C}_1-\text{C}_3-\text{alkyl}$, more preferred
5 wherein R_{23} denotes $-\text{H}$.

The present invention also relates to the following intermediate products according to general
formula (XVII) for synthesizing the compounds of formula (I) according to the invention



wherein R_{22} is a group selected from among $-\text{H}$, $-\text{CF}_3$, $-\text{O}-\text{CF}_3$, $-\text{S}-\text{CF}_3$, $-\text{CN}$, $-\text{C}_1-\text{C}_6-\text{alkyl}$,
 $-\text{C}(\text{CH}_3)_2-\text{CN}$, and $-\text{halogen}$, or wherein R_{22} is a group selected from among $-\text{C}_1-\text{C}_6-\text{alkyl}$, $-\text{O}-\text{C}_1-\text{C}_6-\text{alkyl}$, $-\text{C}_5-\text{C}_{10}-\text{aryl}$, $-\text{C}_5-\text{C}_{10}-\text{heteroaryl}$, $-\text{C}_3-\text{C}_8-\text{cycloalkyl}$, $-\text{C}_3-\text{C}_8-\text{heterocyclyl}$, $-\text{C}_2-$
 $\text{C}_6-\text{alkenyl}$, and $-\text{C}_2-\text{C}_6-\text{alkynyl}$, optionally being substituted by one or more groups selected
15 from among $-\text{OH}$, $-\text{NH}_2$, $-\text{C}_1-\text{C}_3-\text{alkyl}$, $-\text{O}-\text{C}_1-\text{C}_6-\text{alkyl}$, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{halogen}$, $-\text{methyl}$,
and $=\text{O}$, more preferred wherein R_{22} is a group selected from among $-\text{CF}_3$, $-\text{O}-\text{CF}_3$, $-\text{S}-\text{CF}_3$, $-\text{CN}$, $-\text{methyl}$, $-\text{C}(\text{CH}_3)_2-\text{CN}$, and $-\text{halogen}$, more preferred wherein R_{22} is a group selected
from among $-\text{CF}_3$, $-\text{O}-\text{CF}_3$, $-\text{S}-\text{CF}_3$, $-\text{CN}$, $-\text{methyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{C}(\text{CH}_3)_2-\text{CN}$, and $-\text{Br}$,
and wherein R_2 is a group selected from among $-\text{H}$, $-\text{halogen}$, $-\text{CN}$, $-\text{O}-\text{C}_2-\text{C}_4-\text{alkyl}$, $-\text{C}_1-\text{C}_4-$
20 alkyl , $-\text{CH}=\text{CH}_2$, $-\text{C}\equiv\text{CH}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCF}_2\text{H}$, and $-\text{OCFH}_2$, more preferred wherein R_2 is
a group selected from among $-\text{H}$, $-\text{methyl}$, $-\text{ethyl}$, $-\text{propyl}$, $-\text{i-propyl}$, $-\text{butyl}$, $-\text{i-butyl}$, $-\text{t-butyl}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{CN}$, $-\text{CH}=\text{CH}_2$, and $-\text{C}\equiv\text{CH}$, more preferred wherein R_2 is a group selected
from among $-\text{H}$, $-\text{Methyl}$, $-\text{Ethyl}$, and $-\text{Br}$, more preferred wherein R_2 is selected from among
 $-\text{H}$, and $-\text{Methyl}$, most preferred wherein R_2 denotes $-\text{Methyl}$ or wherein R_2 denotes $-\text{H}$;
25 and wherein R_3 is a group selected from among $-\text{H}$, $-\text{methyl}$, $-\text{ethyl}$, $-\text{propyl}$, $-\text{i-propyl}$,
 $-\text{cyclopropyl}$, $-\text{OCH}_3$, $-\text{CF}_3$, and $-\text{CN}$, more preferred wherein R_3 is a group selected from
among $-\text{H}$, $-\text{CF}_3$, $-\text{O}-\text{CH}_3$, and $-\text{methyl}$, more preferred wherein R_3 is selected from among
 $-\text{H}$, $-\text{O}-\text{CH}_3$, and $-\text{methyl}$, more preferred wherein R_3 denotes $-\text{H}$, or wherein R_3 denotes
 $-\text{O}-\text{CH}_3$, or wherein R_3 denotes $-\text{CF}_3$; and wherein G and E are independently selected from
30 among $\text{C}-\text{H}$ or N , more preferred wherein G denotes $\text{C}-\text{H}$ and E denotes N , more preferred
wherein G denotes N and E denotes $\text{C}-\text{H}$, most preferred wherein G and E are N .

The present invention also relates to process for preparing a compound

of formula (II) according to preparation method A wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.

- 5 The present invention also relates to process for preparing a compound of formula (III) according to preparation method A wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.
- 10 The present invention also relates to process for preparing a compound of formula (V) according to preparation method B wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.
- 15 The present invention also relates to process for preparing a compound of formula (VI) according to preparation method B wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.
- 20 The present invention also relates to process for preparing a compound of formula (VIII) according to preparation method C wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.
- 25 The present invention also relates to process for preparing a compound of formula (X) according to preparation method D wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.
- 30 The present invention also relates to process for preparing a compound of formula (XI) according to preparation method D wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', R_{21}, R_{21}', L_1, L_2, E, G, Z, Y_1, Q$, and n have the meanings defined hereinbefore.
- 35 The present invention also relates to process for preparing a compound of formula (XIII) according to preparation method E wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n have the meanings defined hereinbefore.
- 40 The present invention also relates to process for preparing a compound

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of formula (XIV) according to preparation method E wherein $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', R_{21}, R_{21}', L_1, E, G, Z, Q, CYC$, and n have the meanings defined hereinbefore.

5 All of the above embodiments under formula (I) have to be understood to optionally be present in form of their individual optical isomers, mixtures of their individual optical isomers, or racemates, as well as in form of their acid addition salts with pharmacologically acceptable acids, as well as in form of their solvates and/or hydrates.

It has been found that such compounds as herein before or below defined could be used for the treatment of inflammatory and neuropathic pain disease.

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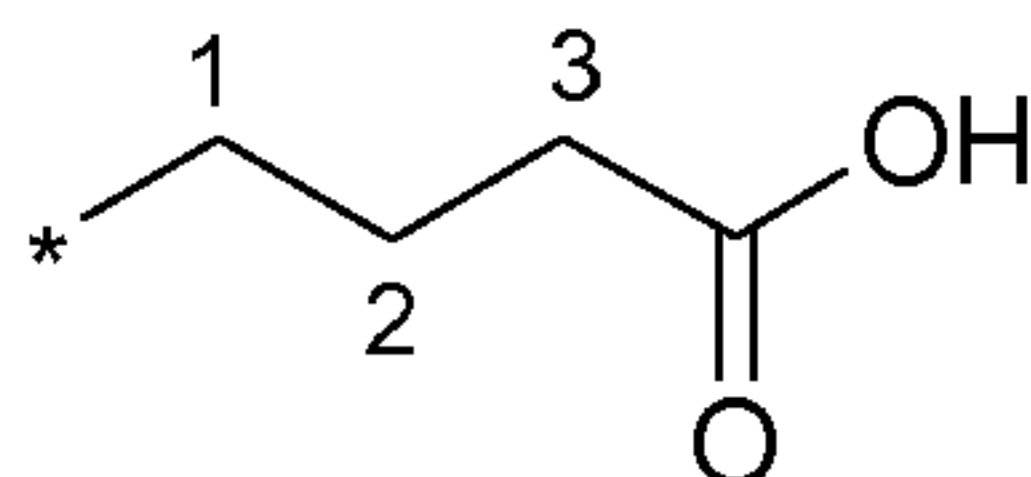
Definitions

Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. As used in the specification, however, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, -C₁-C₆-alkyl means an alkyl group or radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named subgroup is the radical attachment point, for example, the substituent "aryl-C₁-C₃-alkyl-" means an aryl group which is bound to a C₁-C₃-alkyl-group, the latter of which is bound to the core or to the group to which the substituent is attached.

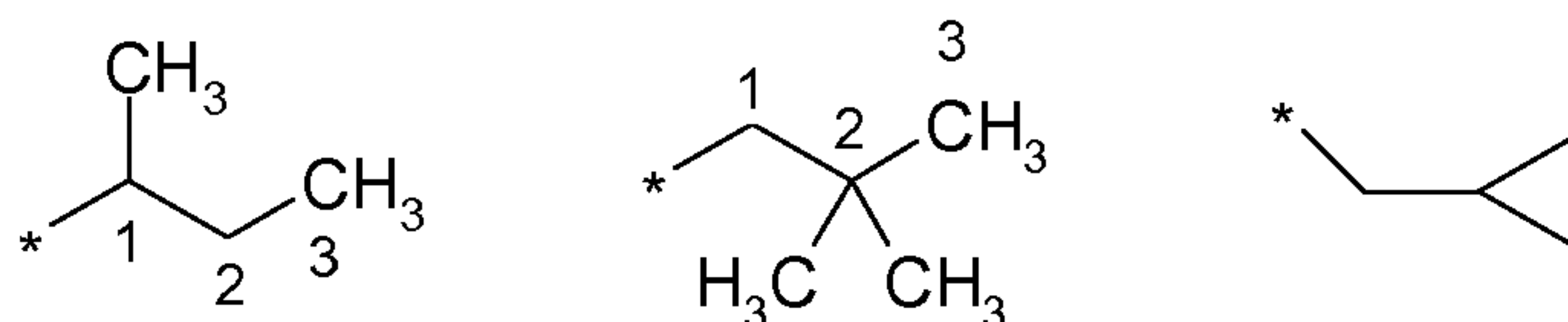
In case a compound of the present invention is depicted in form of a chemical name and as a formula in case of any discrepancy the formula shall prevail. An asterisk is may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

For example, the term "3-carboxypropyl-group" represents the following substituent:



5

wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms "1-methylpropyl-", "2,2-dimethylpropyl-" or "cyclopropylmethyl-" group represent the following groups:



10

The asterisk may be used in sub-formulas to indicate the bond which is connected to the core molecule as defined.

Many of the following terms may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one another.

15

Unless otherwise stated, all the substituents are independent of one another. If for example there might be a plurality of C₁-C₆-alkyl groups as substituents in one group, in the case of three substituents C₁-C₆-alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

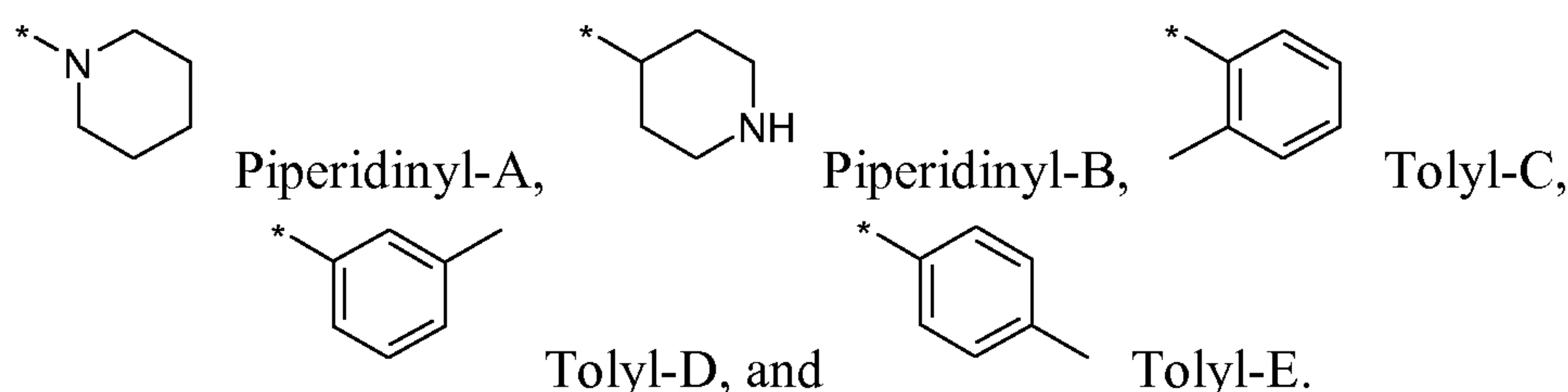
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Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule.

Moreover, the atom of the substituent which follows the linking point is referred to as the atom in position number 1. Thus, for example, the groups *N*-piperidiny (Piperidin-A),

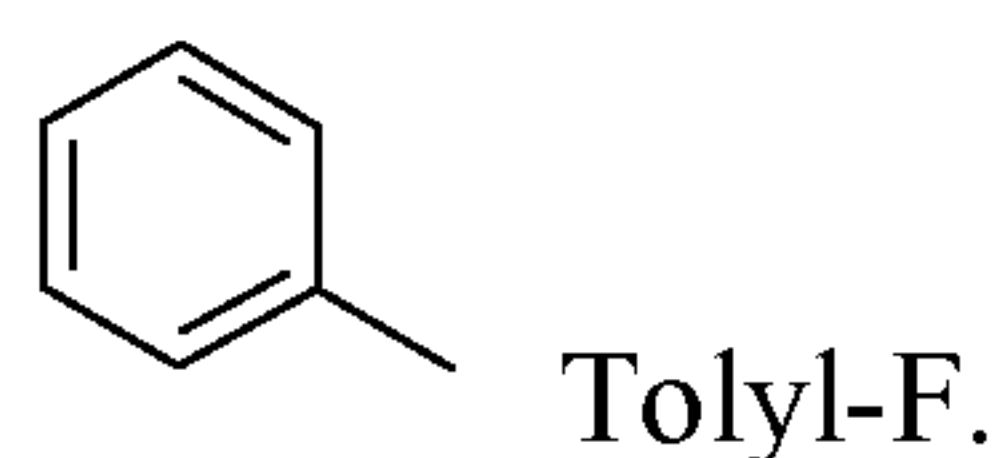
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4-piperidiny (Piperidin-B), 2-tolyl (Tolyl-C), 3-tolyl (Tolyl-D), and 4-tolyl (Tolyl-E) are shown as follows:



If there is no asterisk (*) in the structural formula of the substituent, each hydrogen atom may be removed from the substituent and the valency thus freed may act as a binding site to the rest of a molecule. Thus, for example, (Tolyl-F) may represent 2-tolyl, 3-tolyl, 4-tolyl, and benzyl

30



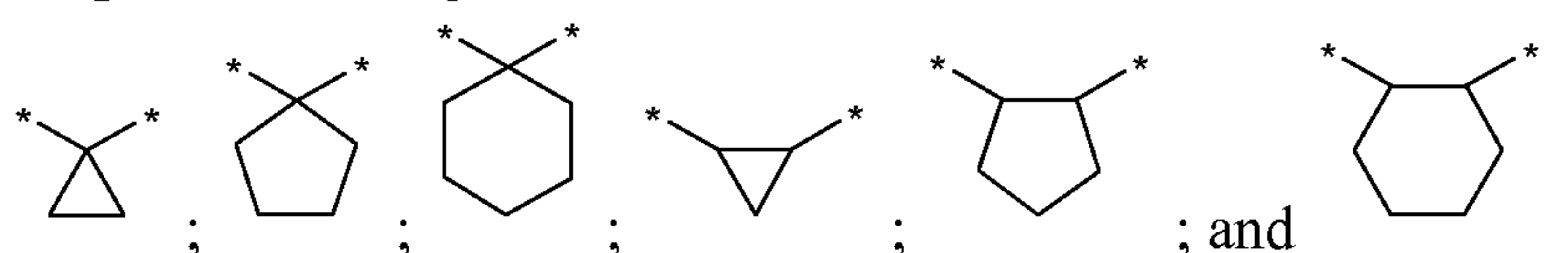
The term "substituted" as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound.

By the term "optionally substituted" is meant within the scope of the invention the above-mentioned group, optionally substituted by a lower-molecular group. Examples of lower-molecular groups regarded as chemically meaningful are groups consisting of 1-200 atoms. Preferably such groups have no negative effect on the pharmacological efficacy of the compounds. For example the groups may comprise:

- Straight-chain or branched carbon chains, optionally interrupted by heteroatoms, optionally substituted by rings, heteroatoms or other common functional groups.
- Aromatic or non-aromatic ring systems consisting of carbon atoms and optionally heteroatoms, which may in turn be substituted by functional groups.
- A number of aromatic or non-aromatic ring systems consisting of carbon atoms and optionally heteroatoms which may be linked by one or more carbon chains, optionally interrupted by heteroatoms, optionally substituted by heteroatoms or other common functional groups.

By the term "branched or unbranched, saturated or unsaturated C₁-C₆-carbon chain" it is meant a chain of carbon atoms, which is constituted by 1 to 6 carbon atoms arranged in a row and which can optionally further comprise branches or one or more hetero atoms selected from N, O or S. Said carbon chain can be saturated or unsaturated by comprising double or triple bonds.

If the carbon chain is to be substituted by a group which together with one or two carbon atoms of the alkylene chain forms a carbocyclic ring with 3, 5 or 6 carbon atoms, this includes the following examples of the rings:



The term "C₁-C_n-alkyl", wherein n is an integer from 2 to n, either alone or in combination with another radical denotes an acyclic, saturated, branched or linear hydrocarbon radical with 1 to n C atoms. For example the term C₁-C₅-alkyl embraces the radicals H₃C-, H₃C-CH₂-,

H₃C-CH₂-CH₂-, H₃C-CH(CH₃)-, H₃C-CH₂-CH₂-CH₂-, H₃C-CH₂-CH(CH₃)-,
 H₃C-CH(CH₃)-CH₂-, H₃C-C(CH₃)₂-, H₃C-CH₂-CH₂-CH₂-CH₂-, H₃C-CH₂-CH₂-CH(CH₃)-,
 H₃C-CH₂-CH(CH₃)-CH₂-, H₃C-CH(CH₃)-CH₂-CH₂-, H₃C-CH₂-C(CH₃)₂-,
 H₃C-C(CH₃)₂-CH₂-, H₃C-CH(CH₃)-CH(CH₃)- and H₃C-CH₂-CH(CH₂CH₃)-

- 5 By the term "C₁-C₆-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C₁-C₄-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. By the term "C₁-C₃-alkyl" are meant branched and unbranched alkyl groups with 1 to 3 carbon atoms and by the term
- 10 "C₂-C₄-alkyl" are meant branched and unbranched alkyl groups with 2 to 4 carbon atoms. Examples for alkyl groups with 1-6 carbon atoms include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl or hexyl. Optionally the abbreviations Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc. may also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl, butyl, pentyl and hexyl
- 15 include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

- The term "C₁-C_n-alkylene" wherein n is an integer 2 to n, either alone or in combination with another radical, denotes an acyclic, straight or branched chain divalent alkyl radical
- 20 containing from 1 to n carbon atoms. For example the term C₁-C₄-alkylene includes -CH₂-, -CH₂-CH₂-, -CH(CH₃)-, -CH₂-CH₂-CH₂-, -C(CH₃)₂-, -CH(CH₂CH₃)-, -CH(CH₃)-CH₂-, -CH₂-CH(CH₃)-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH(CH₃)-, -CH(CH₃)-CH₂-CH₂-, -CH₂-CH(CH₃)-CH₂-, -CH₂-C(CH₃)₂-, -C(CH₃)₂-CH₂-, -CH(CH₃)-CH(CH₃)-, -CH₂-CH(CH₂CH₃)-, -CH(CH₂CH₃)-CH₂-, -CH(CH₂CH₂CH₃)-, -CH(CH(CH₃))₂- and
- 25 -C(CH₃)(CH₂CH₃)-

- By the term "C₁-C₈-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 8 carbon atoms. By the term "C₂-C₈-alkylene" are meant branched and unbranched alkylene groups with 2 to 8 carbon atoms. By the term "C₂-C₆-alkylene" are meant branched and unbranched alkylene groups
- 30 with 2 to 6 carbon atoms. By the term "C₁-C₄-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms. By the term "C₁-C₂-alkylene" are meant branched and unbranched alkylene groups with 1 to 2 carbon atoms. By the term "C₀-C₄-alkylene" are meant branched and unbranched alkylene groups with 0 to 4 carbon atoms, thus also a single bond is encompassed. By the term "C₁-C₃-alkylene" are meant branched and unbranched
- 35 alkylene groups with 1 to 3 carbon atoms. Examples for C₁-C₈-alkylene include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene, hexylene, heptylene or octylene. Unless stated otherwise, the definitions propylene, butylene, pentylene, hexylene, heptylene and

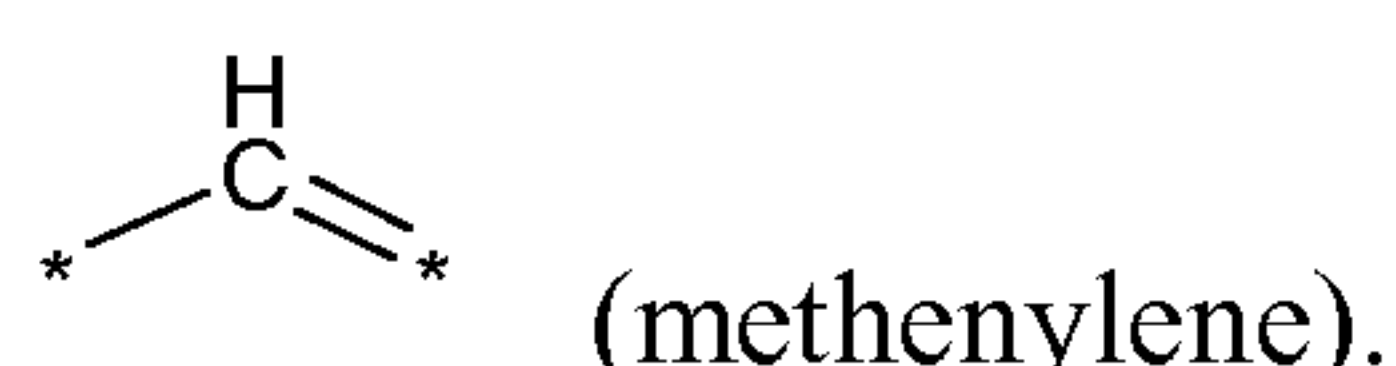
octylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

5 The term "C₂-C_n-alkenyl", is used for a group as defined in the definition for "C₁-C_n-alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond.

By the term "C₂-C₆-alkenyl" (including those which are part of other groups) are meant branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term

10 "C₂-C₄-alkenyl" are meant branched and unbranched alkenyl groups with 2 to 4 carbon atoms, provided that they have at least one double bond. Alkenyl groups with 2 to 4 carbon atoms are preferred. Examples for C₂-C₆-alkenyls include: ethenyl or vinyl, propenyl, butenyl, pentenyl, or hexenyl. Unless stated otherwise, the definitions propenyl, butenyl, pentenyl and hexenyl include all the possible isomeric forms of the groups in question. Thus, for example,
15 propenyl includes 1-propenyl and 2-propenyl, butenyl includes 1-, 2- and 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl etc.

By the term "methenylene" is meant a group with 1 carbon atom, provided that it is linked by a single bond as well as on the other side by a double bond. The asterisks (*) in the structural
20 formula is to be understood as being the linking points to the rest of the molecule, whereas the valency of the rest of the molecule be freed thus a single and a double bond can be formed by replacement of further hydrogens at the binding site if applicable:



25

The term "C₂-C_n-alkenylene" is used for a group as defined in the definition for "C₁-C_n-alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a double bond.

By the term "C₂-C₈-alkenylene" (including those which are part of other groups) are meant
30 branched and unbranched alkenylene groups with 2 to 8 carbon atoms and by the term "C₂-C₆-alkenylene" are meant branched and unbranched alkenylene groups with 2 to 6 carbon atoms. By the term "C₁-C₂-alkenylene" are meant alkenylene groups with 1 to 2 carbon atoms, provided that they have at least one double bond, whereas by the term "C₁-alkenylene" is meant "methenylene". Examples for C₂-C₈-alkenylenes include: ethenylene, propenylene,
35 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene, 2,2-dimethylpropenylene, 1,2-dimethylpropenylene, 1,3-dimethylpropenylene, hexenylene, heptenylene or octenylene. Unless stated otherwise, the definitions propenylene, butenylene, pentenylene and hexenylene

include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propenyl also includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene.

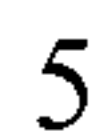
5 The term "C₂-C_n-alkynyl", is used for a group as defined in the definition for "C₁-C_n-alkyl" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond.

By the term "C₂-C₆-alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term
 10 "C₂-C₄-alkynyl" are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Examples for C₂-C₆-alkynyls include: ethynyl, propynyl, butynyl, pentynyl or hexynyl. Unless stated otherwise, the definitions propynyl, butynyl, pentynyl and hexynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes
 15 1-, 2-, and 3-butynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl etc.

The term "C₂-C_n-alkynylene" is used for a group as defined in the definition for "C₁-C_n-alkylene" with at least two carbon atoms, if at least two of those carbon atoms of said group are bonded to each other by a triple bond.

20 By the term "C₂-C₈-alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 8 carbon atoms and by the term "C₂-C₆-alkynylene" are meant branched and unbranched alkynylene groups with 2 to 6 carbon atoms. Examples of C₂-C₈-alkynylenes include: ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene,
 25 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2 -dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene, hexynylene, heptynylene or octynylene. Unless stated otherwise, the definitions propynylene, butynylene, pentynylene and hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and
 30 butynylene includes 1-methylpropynylene, 1, 1-dimethylethynylene, 1, 2-dimethylethynylene.

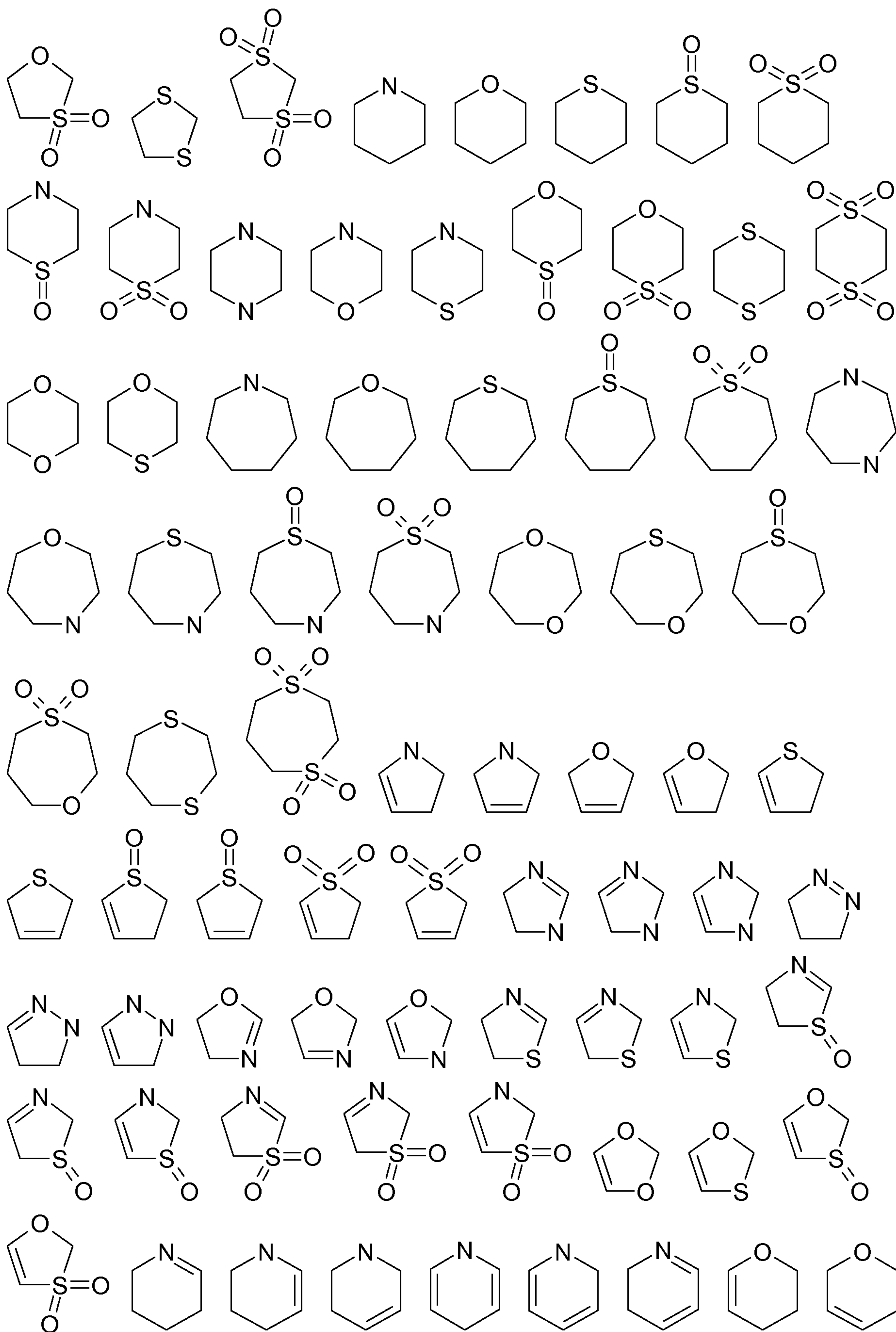
The term "carbocyclyl" as used either alone or in combination with another radical, means a mono- bi- or tricyclic ring structure consisting of 3 to 14 carbon atoms. The term "carbocycle" refers to fully saturated and aromatic ring systems and partially saturated ring systems. The
 35 term "carbocycle" encompasses fused, bridged and spirocyclic systems:



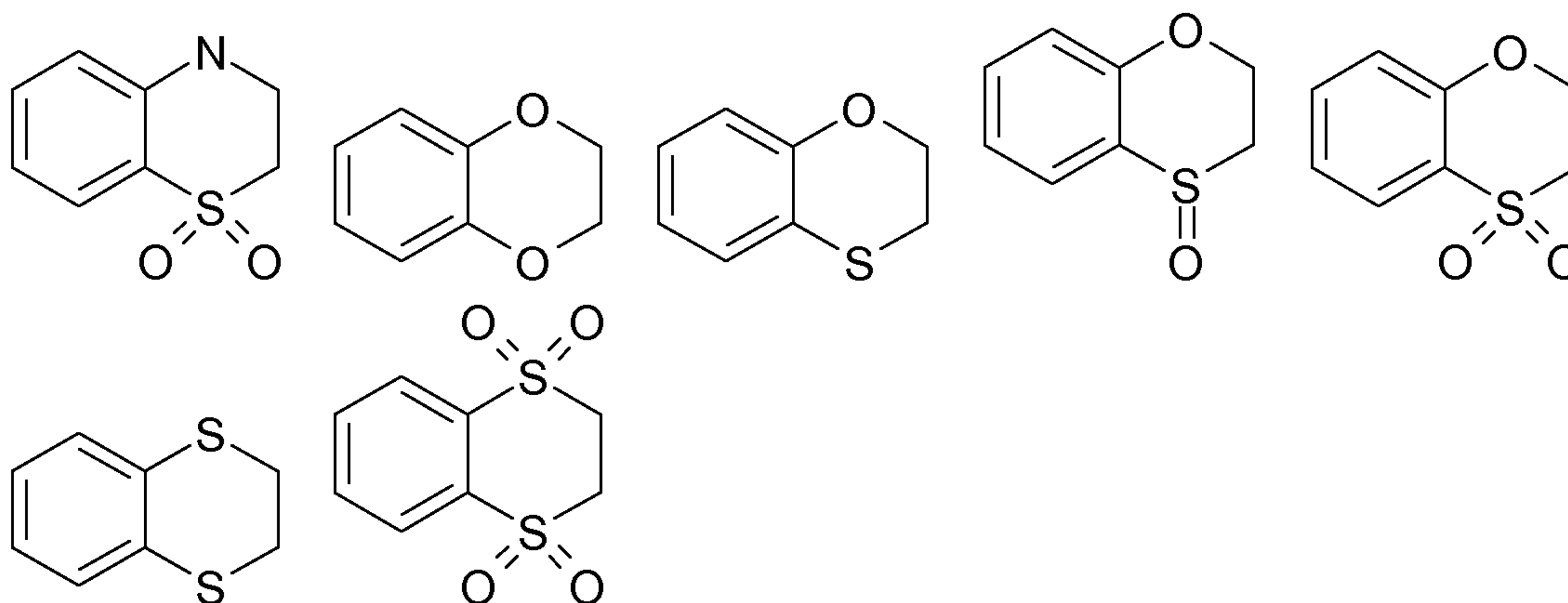
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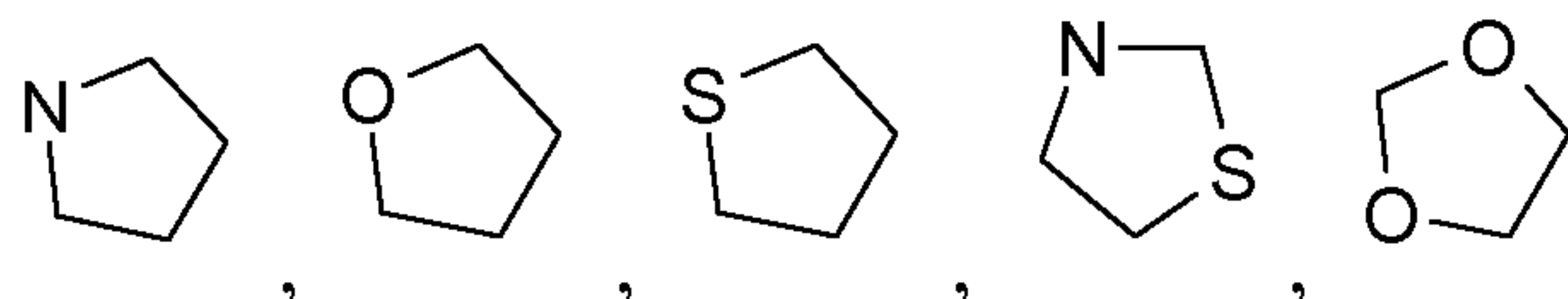
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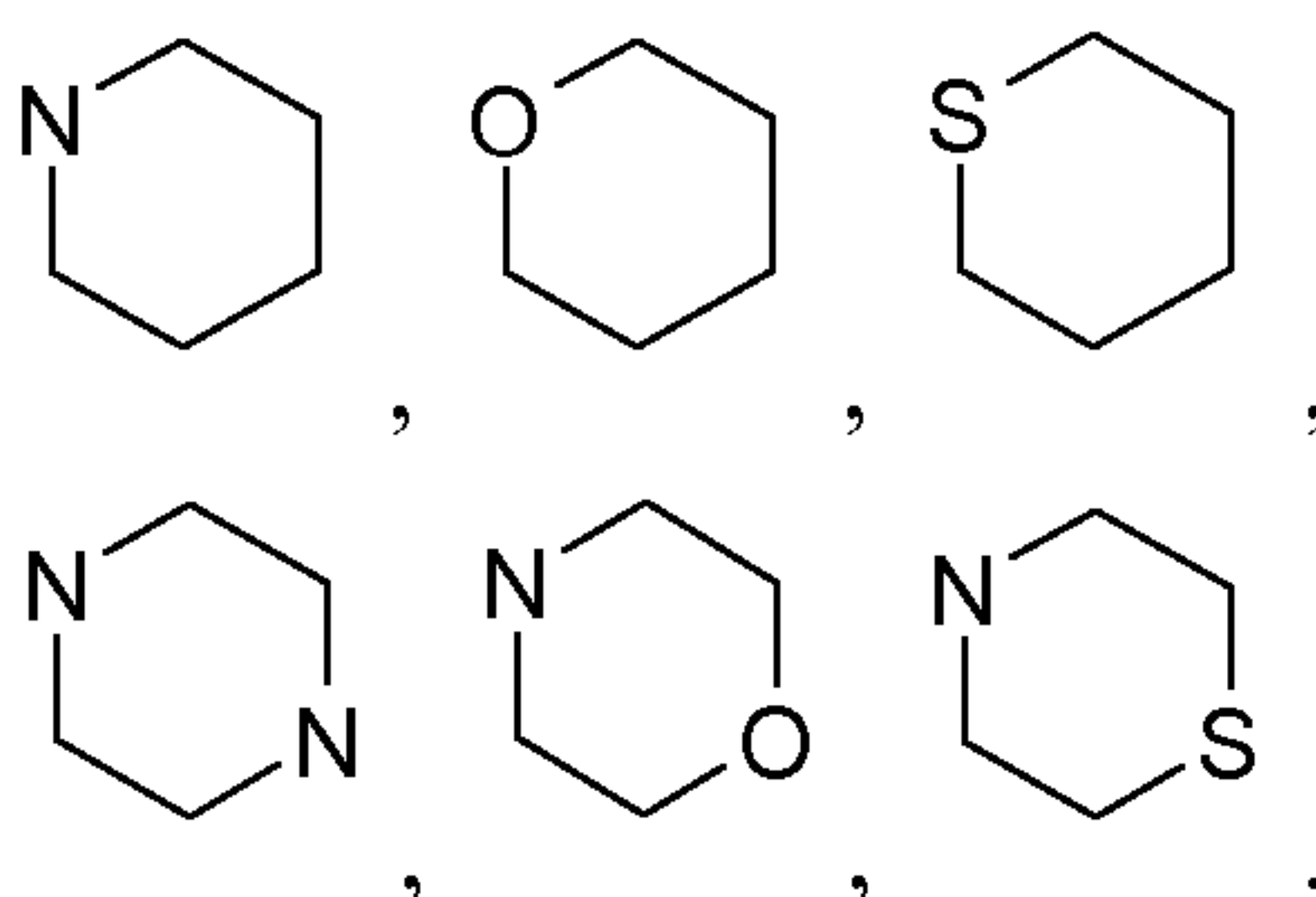




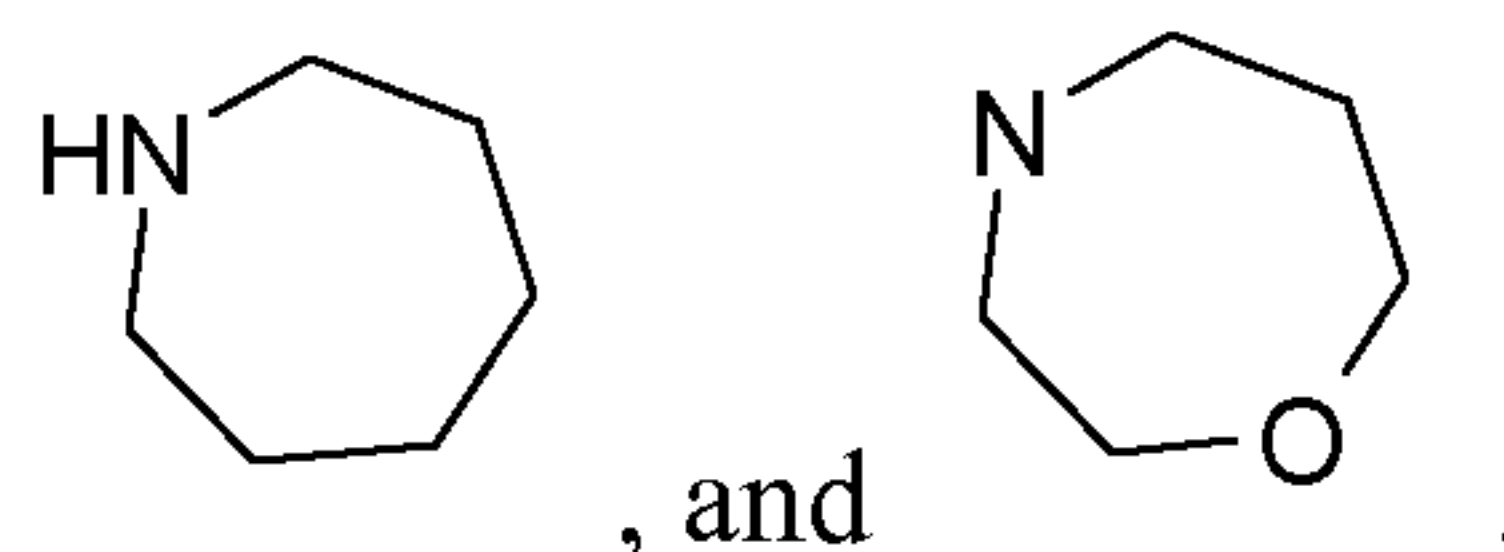
By the term “-C₃-C₈-heterocyclyl” are meant three-, four-, five-, six-, seven, or eight-membered, saturated or unsaturated heterocyclic rings which may contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be replaced by such heteroatoms. The ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. By the term “-C₅-C₈-heterocyclyl” are meant five-, six-, seven or eight-membered, saturated or unsaturated heterocyclic rings which may contain one, two, or three heteroatoms, selected from among oxygen, sulfur, and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. Examples for C₅-heterocyclyl include:



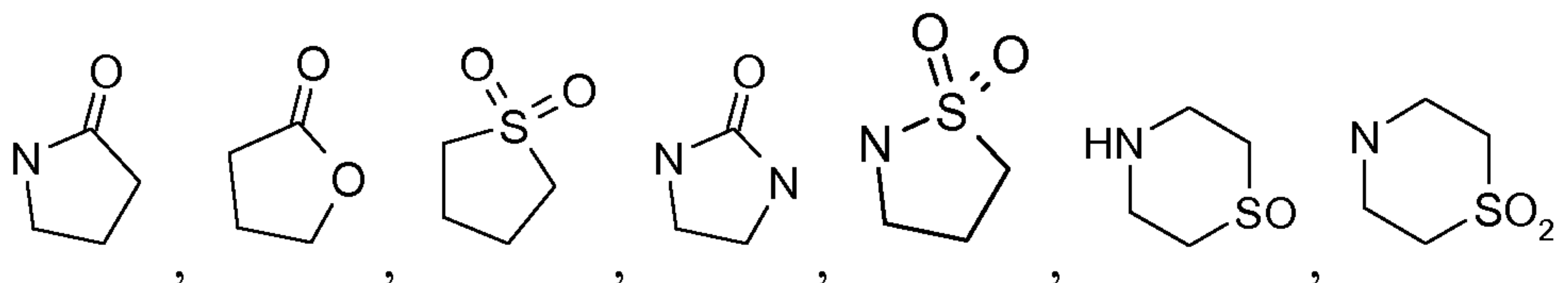
Examples for C₆-heterocyclyl include:

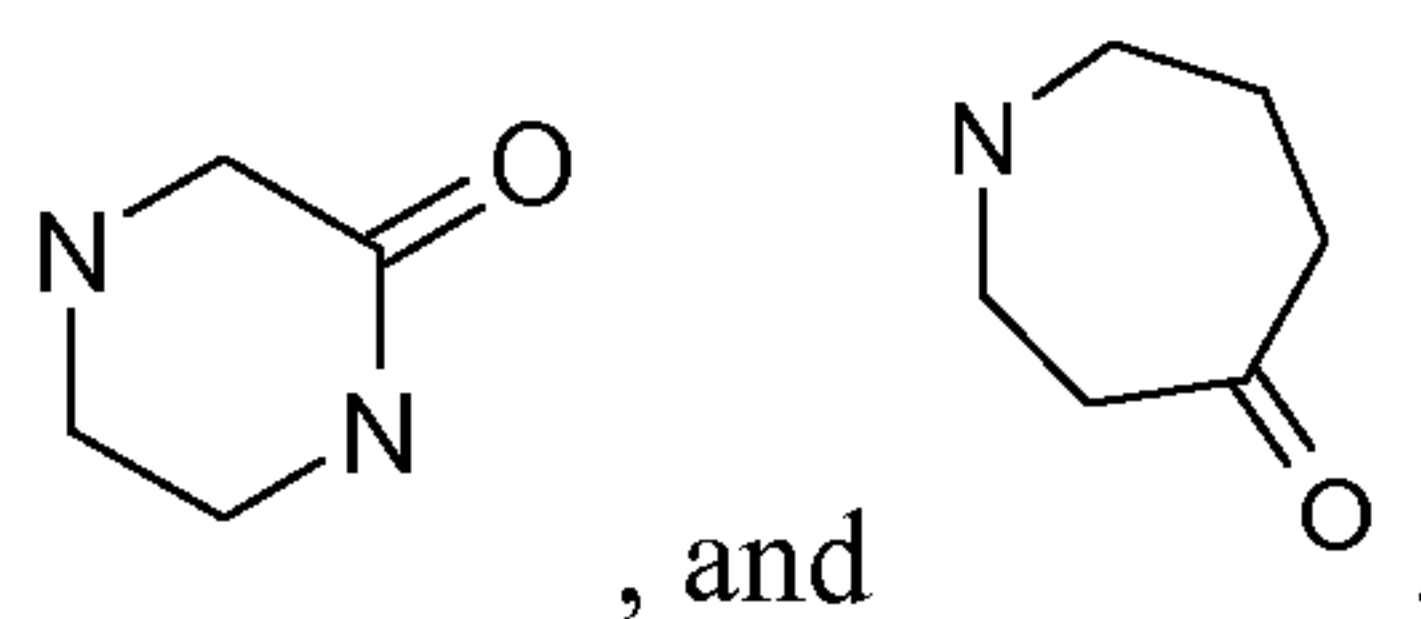


Examples for C₇-heterocyclyl include:



Unless otherwise mentioned, a heterocyclic ring (or “heterocycle”) may be provided with a keto group. Examples include:





The term "C₃-C_n-cycloalkyl", wherein n is an integer from 3 to n, either alone or in
 5 combination with another radical denotes a cyclic, saturated, unbranched hydrocarbon radical
 with 3 to n C atoms. For example the term C₃-C₇-cycloalkyl includes cyclopropyl, cyclobutyl,
 cyclopentyl, cyclohexyl and cycloheptyl.

By the term "C₃-C₈-cycloalkyl" (including those which are part of other groups) are meant
 cyclic alkyl groups with 3 to 8 carbon atoms. Likewise, by the term "C₃-C₆-cycloalkyl" are
 10 meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples of C₃-C₈-cycloalkyls include:
 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. Unless otherwise
 stated, the cyclic alkyl groups may be substituted by one or more groups selected from among
 methyl, ethyl, isopropyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

15 The term "C₃-C_n-cycloalkenyl", wherein n is an integer from 3 to n, either alone or in
 combination with another radical, denotes an cyclic, unsaturated but nonaromatic, unbranched
 hydrocarbon radical with 3 to n C atoms, at least two of which are bonded to each other by a
 double bond. For example the term C₃-C₇-cycloalkenyl includes cyclopropenyl, cyclobutenyl,
 cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl
 20 cycloheptadienyl and cycloheptatrienyl.

By the term "aryl" (including those which are part of other groups) are meant aromatic ring
 systems.

The term "aryl" as used herein, either alone or in combination with another radical, denotes a
 25 carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further
 fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or
 unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, naphthyl,
 anthracenyl, phenanthrenyl, tetrahydronaphthyl and dihydronaphthyl.

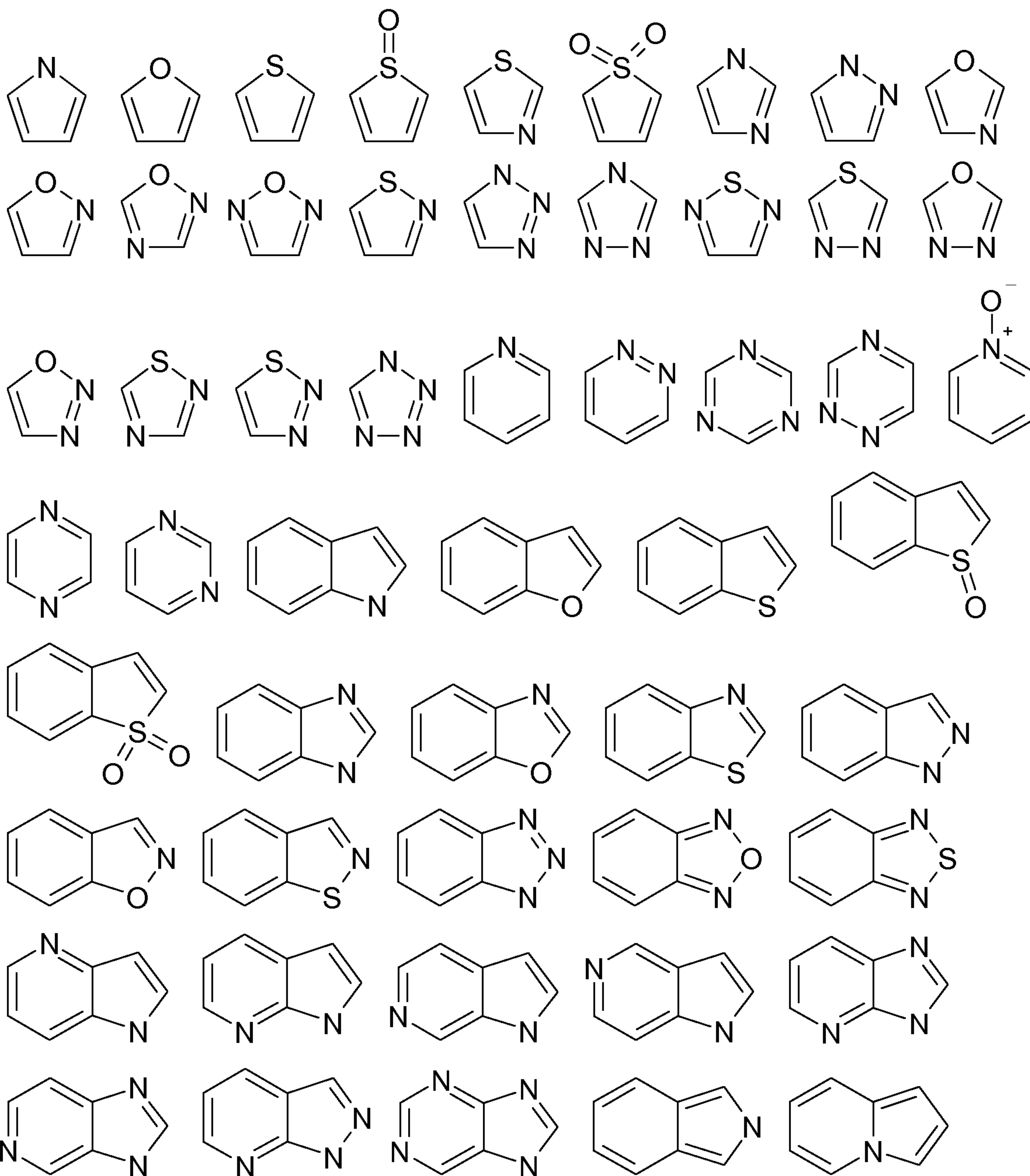
By the term "C₅-C₁₀-aryl" (including those which are part of other groups) are meant aromatic
 30 ring systems with 5 to 10 carbon atoms. Preferred are "C₆-C₁₀-aryl" groups whereas aromatic
 rings are meant with 6 to 10 carbon atoms. Examples include: phenyl or naphthyl. Also
 preferred are "C₅-C₆-aryl" groups whereas aromatic rings are meant with 5 to 6 carbon atoms.
 Further preferred are "C₆-aryl" groups whereas a aromatic ring is meant with 6 carbon
 atoms. Unless otherwise stated, the aromatic ring systems may be substituted by one or more
 35 groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine,
 bromine and iodine.

The term "heteroaryl" means a mono- or polycyclic-ring systems containing one or more heteroatoms selected from N, O or S(O)_r, wherein r = 0, 1 or 2, consisting of 5 to 14 ring atoms wherein at least one of the heteroatoms is part of aromatic ring. The term "heteroaryl" is intended to include all the possible isomeric forms.

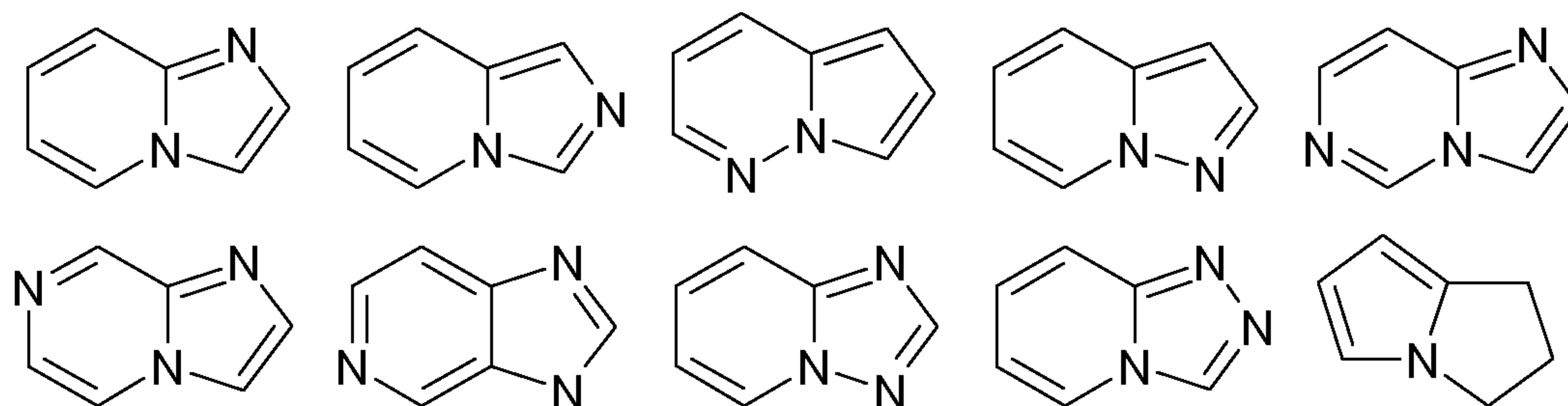
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Thus, the term "heteroaryl" includes the following exemplary structures which are not depicted as radicals as each form may be attached through a covalent bond to any atom so long as appropriate valences are maintained:

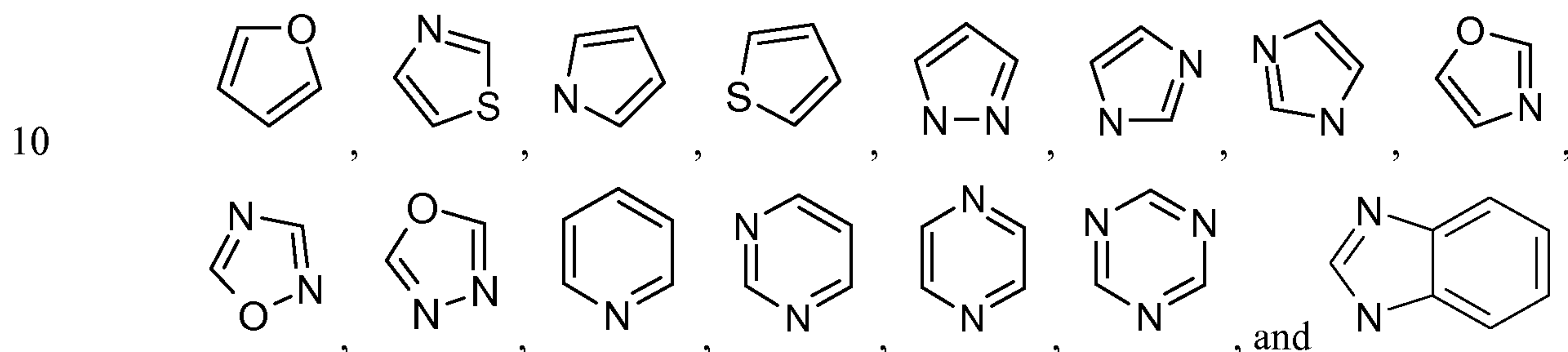
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By the term "C₅-C₁₀-heteroaryl" (including those which are part of other groups) are meant five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be replaced by such heteroatoms, and whereas the rings contain so many conjugated double bonds that an aromatic system is formed. The following are examples of five- or six- or nine-membered heterocyclic aromatic groups:

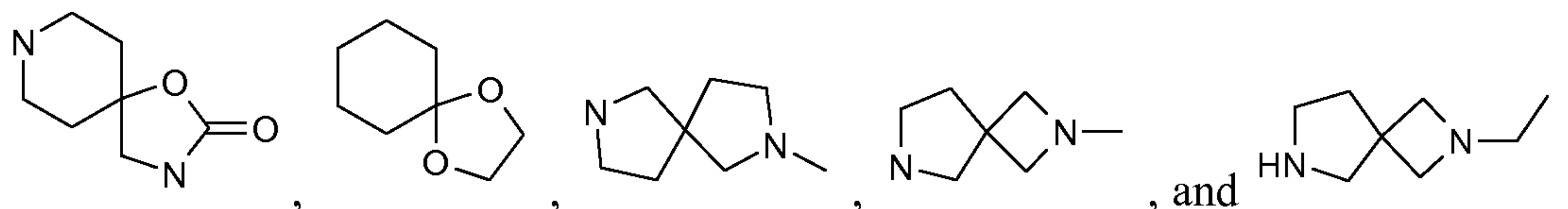


Preferred are "C₅-C₆-heteroaryl" groups whereas aromatic rings are meant five- or six-membered heterocyclic aromatic groups. Unless otherwise stated, these heteroaryls may be substituted by one or more groups selected from among methyl, ethyl, isopropyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine, and iodine.

When a generic combined groups are used, for example -X-C₁-C₄-alkyl- with X being a functional group such as -CO-, -NH-, -C(OH)- and the like, the functional group X can be located at either of the ends of the -C₁-C₄-alkyl chain.

By the term "spiro-C₃-C₈-cycloalkyl" (spiro) are meant 3-8 membered, spirocyclic rings while the ring is linked to the molecule through a carbon atom. By the term "spiro-C₃-C₈-heterocyclyl" (spiro) are meant 3-8 membered, spirocyclic rings which may contain one, two, or three heteroatoms selected from among oxygen, sulfur, and nitrogen, whereas carbon atoms be replaced by such heteroatoms. The ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one.

Unless otherwise mentioned, a spirocyclic ring may be provided with an oxo, methyl, or ethyl group. Examples include:



"Halogen" within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated to the contrary, fluorine, chlorine and bromine are regarded as preferred
5 halogens.

"Linker" within the scope of the present invention denominates a bivalent group or a bond.

The above listed groups and residues can be combined to form more complex structures
10 composed from carbon chains and rings or the like.

Compounds of general formula (I) may have acid groups, chiefly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula (I) may therefore occur as internal salts, as salts with pharmaceutically useable inorganic acids such as
15 hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine *inter alia*.

20 The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, and
25 commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or
30 organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include salts from ammonia, L-arginine, betaine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine (2,2'-iminobis(ethanol)), diethylamine, 2-(diethylamino)-ethanol, 2-aminoethanol, ethylenediamine, N-ethyl-glucamine, hydrabamine, 1H-imidazole, lysine,
35 magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine (2,2',2"-nitrilotris(ethanol)), tromethamine, zinc hydroxide, acetic acid, 2,2-dichloro-acetic acid, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 2,5-dihydroxybenzoic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, carbonic acid,

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cinnamic acid, citric acid, cyclamic acid, decanoic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethylenediaminetetraacetic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycine, glycolic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, lysine, maleic acid, (-)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, galactaric acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid (embonic acid), phosphoric acid, propionic acid, (-)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like.

(also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

As mentioned hereinbefore, the compounds of formula (I) may be converted into the salts thereof, particularly into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand be in the form of the physiologically and pharmacologically acceptable acid addition salts of the compounds of formula (I) with inorganic or organic acids. On the other hand, if R is hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use mixtures of the above-mentioned acids. The alkali and alkaline earth metal salts of the compound of formula (I) are preferably prepared using the alkali and alkaline earth metal hydroxides and hydrides thereof, of which the hydroxides and hydrides of the alkaline earth metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are particularly preferred.

If desired, the compounds of general formula (I) may be converted into the salts thereof, particularly into the pharmacologically acceptable acid addition salts

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with an inorganic or organic acid. Suitable acids include for example succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid or citric acid. It is also possible to use mixtures of the above-mentioned acids.

5

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers etc...) and racemates thereof as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist, as well as salts, including pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates including solvates of the free compounds or solvates of a salt of the compound.

10

Hence the invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids - such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

15

20

The compounds according to the invention may optionally occur as racemates, but they may also be obtained as pure enantiomers / diastereomers.

The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids - such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

25

30

The compounds according to formula (I) according to the invention have the meanings hereinbefore whereas in particular the preferred embodiments defined by $R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_8', R_9, R_9', R_{10}, R_{11}, R_{11}', R_{12}, R_{13}, R_{13}', R_{14}, R_{15}, R_{15}', R_{16}, R_{17}, R_{18}, R_{19}, R_{19}', R_{20}, R_{20}', L_1, E, G, Z, Q$, and n in each case are independently selected of one another.

35

The above exemplary substances have been tested for binding to CCR2 using a binding assay as outlined herein below:

Cell culture:

THP-1 cells (human acute monocytic leukaemia cells) were cultured under standardized conditions at 37 °C and 5 % CO₂ in a humidified incubator. THP-1 cells were cultivated in RPMI 1640 medium (Gibco 21875) containing 1 % MEM-NEAA (Gibco 11140) 2 mM L-glutamine, 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES and 1.0 mM sodium pyruvate, 90 %; 10 % fetal calf serum (FCS Gibco 10500-064).

Membranes were prepared from THP-1 cells. THP-1 cells were centrifuged at 300xg at 4°C for 10 min. The cell pellet was resuspended in Phosphate Buffer Saline (PBS, including 10 µM Pefabloc and a protease inhibitor mix 'complete', Boehringer Mannheim (1 tablet/ 50 ml)), to a concentration of 80 cells/ ml. The membrane preparation was performed by disrupting the cells by nitrogen decomposition (at 50 bar, for 1h) in a "Nitrogen Bombe" (Parr Instrument). Cell debris was removed by centrifugation (800xg at 4°C, 1 min). The supernatant was centrifuged at 80000xg, 4°C for 30 min to sediment the cell membranes. Usually 50 mg of protein (Bradford assay) were yielded from 1x10⁹ cells. The membranes were resuspended in 25 mM HEPES, 25 mM MgCl₂, 1 mM CaCl₂, 10 % Glycerine for storage in aliquots at -80 °C in 25 mM HEPES, 25 mM MgCl₂, 1 mM CaCl₂, 10 % Glycerine and stored at -80°C.

Receptor membrane binding assay:

Perkin Elmer NEX 332 Jod 125 MCP-1, Stock: 2200 Ci/mmol solved in 2000 µl assay buffer, stored at -20°C. THP-1 membrane were adjusted with 25 mM HEPES, pH 7.2; 5 mM MgCl₂; 0.5 mM CaCl₂; 0.2 % BSA assay buffer to a concentration of 2.5 µg/15 µl. Amersham Biosciences PVT-WGA Beads (RPNQ0001) were adjusted with assay buffer to a concentration of 0.24 mg/30 µl. For preparation of the membrane-bead-suspension membranes and beads were incubated for 30 min at RT under rotation (60 rpm) with a ratio of 1:2. Test compounds dissolved in 100 % DMSO to a concentration of 10 mM and are further diluted with 100 % DMSO to 1 mM. All additional compound dilutions were obtained with assay buffer, final 1% DMSO. Compounds, membrane-bead-suspension and [125I]MCP-1 (ca. 25000 cpm/10 µl) were incubated. Bound radioactivity was determined by scintillation counter after 8h. Determination of affinity of test compounds (dissociation constant hKi) is calculated by iterative fitting of experimental data using the "easy sys" program, which is based on law of mass action (Schittkowski K. (1994), Numerische Mathematik, Vol. 68, 129-142).

All of the referenced examples have been found to have an activity in this assay of 10 µM or less.

Example	hKi
1	8 [nM]

Example	hKi
15	24 [nM]

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2	151 [nM]
3	203 [nM]
4	26 [nM]
5	237 [nM]
6	190 [nM]
7	36 [nM]
8	185 [nM]
9	13 [nM]
10	142 [nM]
11	53 [nM]
12	27 [nM]
13	486 [nM]
14	479 [nM]

16	11 [nM]
17	11 [nM]
18	10 [nM]
19	162 [nM]
20	11 [nM]
21	11 [nM]
22	11 [nM]
23	494 [nM]
24	4 [nM]
25	418 [nM]
26	6 [nM]
27	12 [nM]
28	658 [nM]

Example	hKi
29	4 [nM]
30	5 [nM]
31	276 [nM]
32	333 [nM]
33	148 [nM]
34	63 [nM]
35	96 [nM]
36	51 [nM]
37	25 [nM]
38	6 [nM]
39	287 [nM]
40	26 [nM]
41	3 [nM]
42	8 [nM]

Example	hKi
43	39 [nM]
44	166 [nM]
45	6 [nM]
46	302 [nM]
47	94 [nM]
48	7 [nM]
49	4 [nM]
50	9 [nM]
51	8 [nM]
52	1 [nM]
53	2 [nM]
54	28 [nM]

Example	hKi
28a	45 [nM]
28b	0.5 [nM]

Example	hKi
53a	7 [nM]
53b	20 [nM]

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28c	0.4 [nM]
28d	12 [nM]
28e	20 [nM]
28f	78 [nM]
28g	8 [nM]
28h	4 [nM]
28i	221 [nM]
28j	1 [nM]
28k	3 [nM]

53c	98 [nM]
53d	19 [nM]
53e	16 [nM]
53f	12 [nM]
53g	16 [nM]
53h	2 [nM]
53i	2 [nM]
53j	21 [nM]
53k	9 [nM]
53l	0.5 [nM]
53m	0.3 [nM]

Example	hKi
54a	5 [nM]
28l	2 [nM]
28m	1 [nM]
28n	38 [nM]
53n	5 [nM]
53o	1 [nM]
53p	0.8 [nM]
53q	1 [nM]
53r	0.8 [nM]
53s	0.2 [nM]
53t	0.4 [nM]
53u	3 [nM]
53v	7 [nM]
53w	0.6 [nM]
53x	9 [nM]
53y	16 [nM]
53z	3 [nM]

Example	hKi
53aa	2 [nM]
53ab	1 [nM]
53ac	0.8 [nM]
53ad	0.3 [nM]
53ae	0.4 [nM]
53af	8 [nM]
53ag	5 [nM]
53ah	0.8 [nM]
53ai	1.1 [nM]
53aj	0.7 [nM]
53ak	0.8 [nM]
53al	0.4 [nM]
53am	0.3 [nM]
55	311 [nM]
56	802 [nM]
57	1802 [nM]
58	1134 [nM]
59	263 [nM]
60	733 [nM]

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The present invention provides a method for modulating or treating inflammatory pain, or neuropathic pain such as low back pain.

The method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CCR2 antagonist to a cell,
5 tissue, organ, animal or patient in need of such modulation, treatment or therapy.

Pharmaceutical formulations

Suitable forms for potential administration are for example tablets, capsules, solutions, syrups, emulsions or inhalable powders or aerosols. The content of the compound(s) in each case should be in the range from 0.1 to 90 wt.%, preferably 0.5 to 50 wt.% of the total composition, i.e. in
10 amounts which are sufficient to achieve the dosage range specified hereinafter.

The preparations may be administered orally in the form of a tablet, as a powder, as a powder in a capsule (e.g. a hard gelatine capsule), as a solution or suspension. When administered by inhalation the active substance may be given as a powder, as an aqueous or aqueous-ethanolic solution or using a propellant gas formulation.

15 Preferably, therefore, pharmaceutical formulations are characterised in that they contain one or more compounds of formula (I) according to the preferred embodiments above.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such
20 as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core
25 may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

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Syrups containing the active substances according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example,
 5 condensation products of fatty alcohols with ethylene oxide, or preservatives such as *p*-hydroxybenzoates.

Capsules containing one or more active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

10 Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or poly functional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral
 15 powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For potential oral administration the tablets may, of course, contain, apart from the
 20 abovementioned carriers, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like.

Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active substances
 25 may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free

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inhalable solutions, which are optionally present in admixture with conventional physiologically acceptable excipients.

Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile ready-to-use inhalable solutions. The preparations which may
 5 be used according to the invention are described in more detail in the next part of the specification.

Inhalable powders

If the active substances of formula (I) are present in admixture with physiologically
 10 acceptable excipients, the following physiologically acceptable excipients may be used to prepare the inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or
 15 disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred. Methods of preparing the inhalable powders according to the invention by grinding and micronising and by finally mixing the components together are known from the prior art.

20

Propellant-containing inhalable aerosols

The propellant-containing inhalable aerosols which may be used according to the invention may contain the active substances of formula (I) dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols
 25 according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as preferably fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are fluorinated alkane derivatives
 30 selected from TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof. The propellant-driven inhalation aerosols used within the scope of the use according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

35

Propellant-free inhalable solutions

The compounds of formula (I) according to the invention are preferably used to prepare propellant-free inhalable solutions and inhalable suspensions. Solvents used for this purpose include aqueous or alcoholic, preferably ethanolic solutions. The solvent may be water on its

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- own or a mixture of water and ethanol. The solutions or suspensions are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid.
- 5 Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If
- 10 desired, mixtures of the above acids may also be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.
- Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions
- 15 used for the purpose according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance
- 20 which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example,
- 25 surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents. The preferred
- 30 excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins occurring in the human body. Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic
- 35 acid or benzoates such as sodium benzoate in the concentration known from the prior art.

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Experimental procedures and synthetic examples**LIST of ABBREVIATIONS**

	ACN	acetonitrile
5	APCI	atmospheric pressure chemical ionization (in MS)
	Ctrl	control
	DAD	diode array detector
	DMA	<i>N,N</i> -dimethylacetamide'
	DMF	<i>N,N</i> -dimethylformamide
10	DMSO	dimethyl sulfoxide
	EI	electron impact (in MS)
	ESI	electrospray ionization (in MS)
	ex	example
	GC/MS	gas chromatography with mass spectrometric detection
15	h	hour(s)
	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluoro-phosphate
	HPLC	high performance liquid chromatography
	HPLC/MS	coupled high performance liquid chromatography-mass spectrometry
20	min	minutes
	MS	mass spectrometry
	NMR	nuclear magnetic resonance
	NMP	<i>N</i> -Methyl-2-pyrrolidinone
	R_t	retention time (in HPLC)
25	sec	secondary
	TBTU	<i>O</i> -(1 <i>H</i> -benzo-1,2,3-triazol-1-yl)- <i>N,N,N',N'</i> - tetramethyluronium tetrafluoroborate
	tert	tertiary
	TFA	trifluoroacetic acid
30	THF	tetrahydrofuran
	TLC	thin-layer chromatography
	UV	ultraviolet absorption

ANALYTICAL METHODS35 **HPLC methods****Methods:**• **1E**Column: Symmetry C8, 5 μ m, 3 x 150 mm

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	Mobile phase:	A = (10 nM aqueous solution of NH_4COOH) + 10% ACN; B = ACN + 10% (10 nM aqueous solution of NH_4COOH).
	Flow rate:	1200 $\mu\text{L}/\text{min}$
	Gradient:	A (100%) for 1.5 min then to B (100%) in 10 min for 3 min
5		
	• <u>1E (Hydro)</u>	
	Column:	Synergy Hydro RP80A, 4 μm , 4.6 x 100 mm
	Mobile phase:	A = (10 nM aqueous solution of NH_4COOH) + 10% ACN; B = ACN + 10% (10 nM aqueous solution of NH_4COOH).
10	Flow rate:	1200 $\mu\text{L}/\text{min}$
	Gradient:	A (100 %) for 1.5 min then to B (100 %) in 10 min for 3 min
	<u>Equipment:</u>	
	Instrument:	HPLC/MS ThermoFinnigan HPLC Surveyor DAD,
15	Detection:	UV @ 254nm
	Detection:	Finnigan MSQ, quadrupole
	Ion source:	APCI
	<u>Methods:</u>	
20	• <u>2F</u>	
	Column:	Symmetry Shield RP8, 5 μm , 4.6 x 150 mm
	Mobile phase:	A = (H_2O + HCOOH 0.1%) + 10% ACN B = ACN + 10% (H_2O + 0.1% HCOOH)
	Flow rate:	1000 $\mu\text{L}/\text{min}$
25	Gradient:	A/B (95/5 %) for 1.5 min then to A/B (5/95 %) in 10 min for 1.5 min
	• <u>2M</u>	
	Column:	Symmetry Shield RP8, 5 μm , 4.6 x 150 mm
30	Mobile phase:	A = (H_2O + HCOOH 0.1%) + 10% ACN B = ACN + 10% (H_2O + 0.1% HCOOH)
	Flow rate:	1200 $\mu\text{L}/\text{min}$
	Gradient:	A/B (90/10 %) for 1.5 min then to A/B (5/95 %) in 10 min for 2 min
35		
	<u>Equipment:</u>	
	Instrument:	HPLC/MS ThermoFinnigan HPLC Surveyor DAD, LCQDuo Ion Trap
	Detection:	UV λ 254 nm

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Detection: Finnigan LCQDuo Ion Trap
Ion source: ESI

Method:5 • **2FF**

Column: Symmetry Shield RP8, 5 μ m, 4.6 x 150 mm

Mobile phase: A = (H₂O + HCOOH 0.1%) + 10% ACN

B = ACN + 10% (H₂O + 0.1% HCOOH)

Flow rate: 1000 μ L/min

10 Gradient: A/B (95/5 %) for 1.5 min then to A/B (5/95 %) in 10 min for 1.5 min

Equipment:

Instrument: HPLC/MS ThermoFinnigan HPLC Surveyor DAD,
 LCQFLEET Ion Trap

15 **Detection:** UV λ 254 nm

Detection: Finnigan LCQDuo Ion Trap

Ion source: ESI

Methods:20 • **2Ia (isocratic)**

Column: DAICEL Chiralpack AS-H 5 μ m, 4.6x250 mm

Mobile phase: A = Hexane; B = EtOH

A/B = 98/2%

Flow rate: 1 ml/min

25

• **2Ib (isocratic)**

Column: DAICEL Chiralpack AS-H 5 μ m, 4.6x250 mm

Mobile phase: A = Hexane; B = EtOH

A/B = 95/5%

30 Flow rate: 1 ml/min

• **2Ic (isocratic)**

Column: DAICEL Chiralpack AS-H 5 μ m, 4.6x250 mm

Mobile phase: A = Hexane; B = EtOH

35 A/B = 70/30%

• **2J (isocratic)**

Column: DAICEL Chiralpack AD-H 5 μ m, 4.6x250 mm

Mobile phase: A = Hexane; B = Isopropanol

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A/B = 98/2%

Flow rate: 1 ml/min

- **2Ja (isocratic)**

5 Column: DAICEL Chiralpack AD-H 5 µm, 4.6x250 mm

Mobile phase: A = Hexane; B = Isopropanol

A/B = 80/20%

Flow rate: 1 ml/min

10

- **2K (isocratic)**

Column: DAICEL Chiralcel OJ-H 5 µm, 4.6x250 mm

Mobile phase: A = Hexane; B = EtOH

A/B = 85/15%

Flow rate: 1 ml/min

15

- **2Ka (isocratic)**

Column: DAICEL Chiralcel OJ-H 5 µm, 4.6x250 mm

Mobile phase: A = Hexane; B = EtOH

A/B = 98/2%

20 Flow rate: 1 ml/min

Equipment**Instrument:** LC Agilent Technologies. HPLC 1100 Serie, DAD Version A.**Detection:** UV 220 - 300nm

25

Method:

- **2Ha**

Column: MERCK; Chromolith Flash; RP18e; 25x4.6 mm

Mobile phase: A = Water + 0.1% HCOOH; B = ACN + 0.1% HCOOH

30 Flow rate: 1.6 µL/min

Gradient:

% B	Minutes
10	0.00
90	2.70
90	3.00
10	3.30

Equipment:**Instrument:** Agilent Technology; HP 1100 Series , DAD35 **Detection:** UV 190 - 400 nm

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Detection: Agilent Technology; HP 1100 MSD
Ion source: ESI +

Methods:5 • **2Ga**

Column: ACQUITY UPLC BEH C18, 1.7 μ m, 2.1 x 50 mm
 Mobile phase: A = (NH₄COOH 5mM) + 10% ACN B = ACN + 10% water
 Flow rate: 700 μ L/min
 Gradient: from A/B (100/0 %) to A/B (0/100 %) in 2.4 min, then A/B
 (0/100 %) for 0.3 min

10

• **2Gb**

Column: ACQUITY UPLC HSS C18, 1.7 μ m, 2.1 x 50 mm
 Mobile phase: A = Water + 0.05% TFA; B = ACN + 0.1% water
 Flow rate: 700 μ L/min
 Gradient: from A/B (100/0 %) to A/B (0/100 %) in 2.4 min, then A/B
 (0/100 %) for 0.3 min

15

Equipment:

Instrument: Acquity UPLC/MS WATERS
 20 Detection: Waters PDA (total scan)
 Detection: Waters ELSD
 Detection: Waters SQD
 Ion source: ESI

25 **GC-MS methods:****Methods:**• **3A**

Column: Agilent DB-5MS, 25m x 0.25mm x 0.25 μ m
 Carrier gas: Helium, 1 ml/min constant flow
 30 Oven Program: 50°C (hold 1 min.), to 100°C in 10°C / min, to 200°C in 20°C /
 min, to 300°C in 30°C / min

• **3B**

Column: Agilent DB-5MS, 25m x 0.25mm x 0.25 μ m
 35 Carrier gas: Helium, 1 ml/min constant flow
 Oven Program: 80°C to 110°C in 10°C / min (hold 40 min), to 280°C in 30°C /
 min

Equipment

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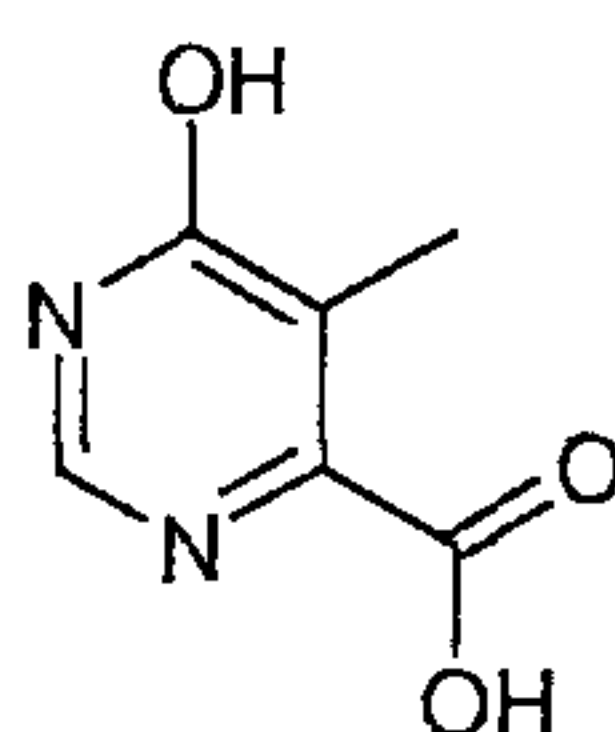
Instrument: GC/MS Finnigan TRACE GC, TRACE MS quadrupole
Detection: TRACE MS quadrupole
Ion source: EI

5 MICROWAVE HEATING:

- Discover® CEM instruments, equipped with 10 and 35 mL vessels.

SYNTHESIS OF INTERMEDIATES

Intermediate 1a

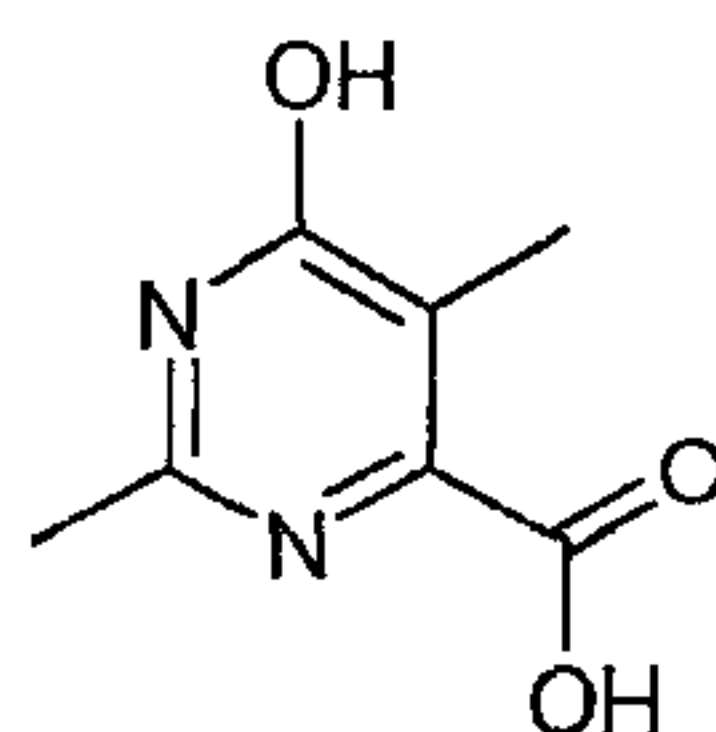


10

Potassium hydroxide (37.9 g, 0.67 mol) was suspended in 200 ml of dry ethanol, formamidine acetate (28.1 g, 0.27 mol) and commercially available diethyl oxalpropionate (50 ml, 0.27 mol) were added and the reaction mixture was stirred under reflux overnight. The reaction mixture was cooled to room temperature and the precipitate formed was filtered, washed with ethanol and diethyl ether, dissolved in 200 ml of water and the solution obtained acidified by a 37% aqueous solution of hydrochloric acid until pH=2. The acidic aqueous solution was concentrated under vacuum and the residue obtained was suspended and stirred in 100 ml of methanol. The insoluble inorganic salts were filtered off. The solution was concentrated. 15 g (97.4 mmol) of the desired compound were obtained.

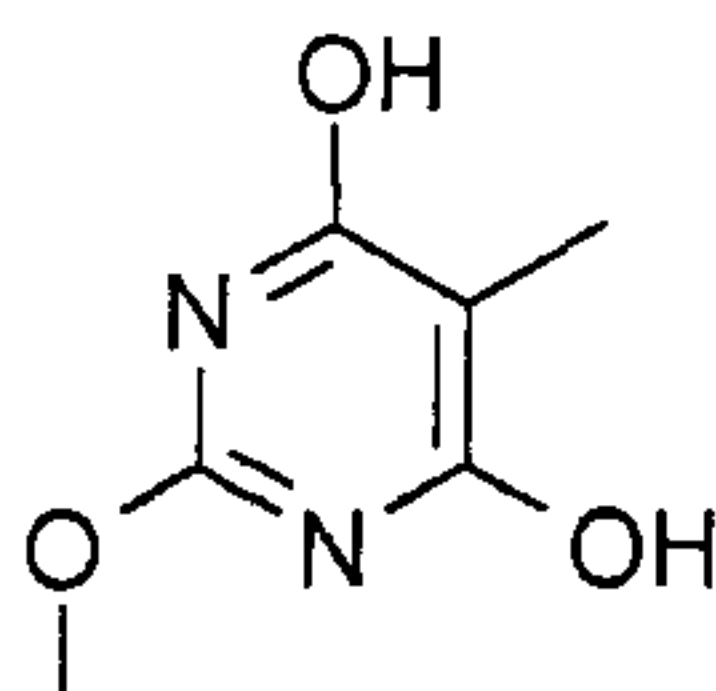
20

Intermediate 1b



was synthesized in analogy to Intermediate 1a, starting from acetamidine hydrochloride.

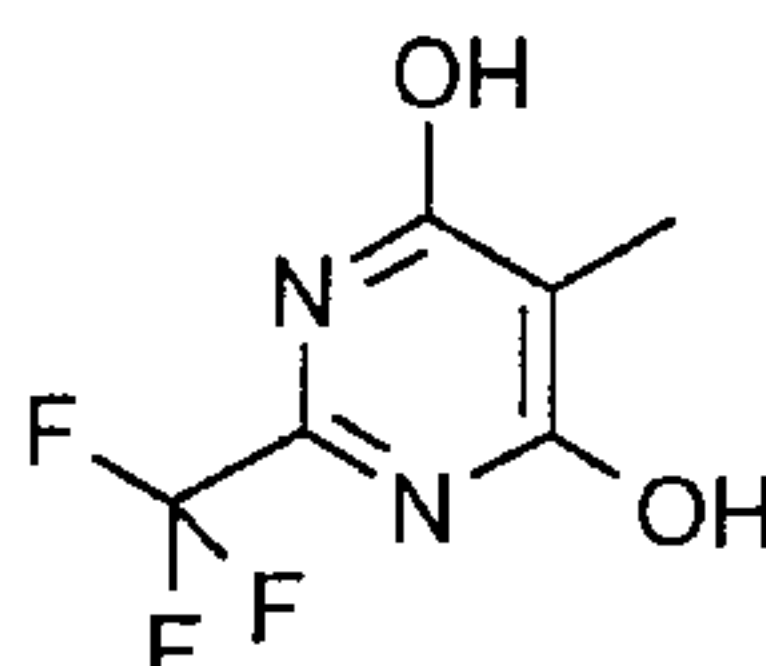
25 Intermediate 1c



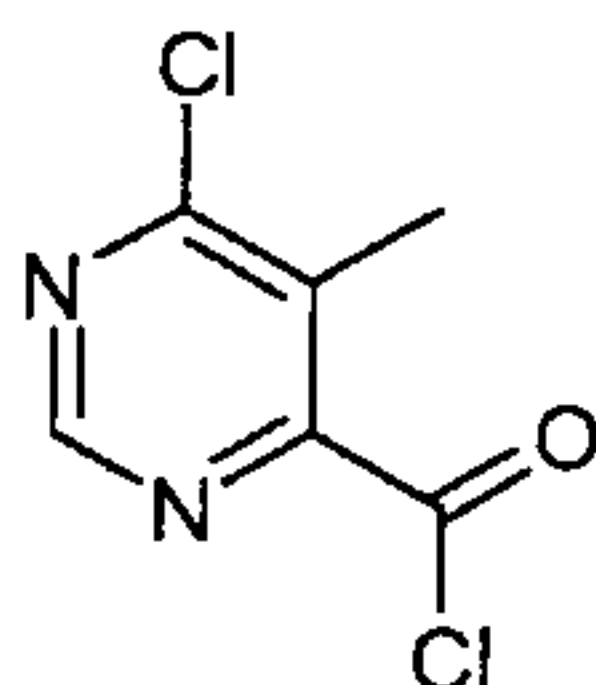
Diethylmethyl malonate (17 ml, 107 mmol) was added to sodium methoxide (30% in methanol, 101 ml, 547 mmol) and stirred for 15 min at 0°C. A solution of commercially

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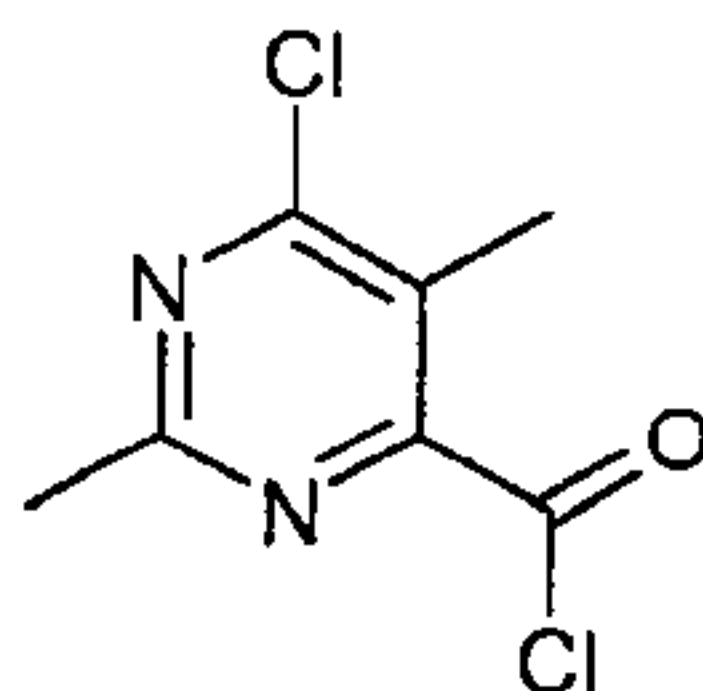
- available *O*-methylisourea hydrochloride (14.5 g, 131 mmol) in 20 ml MeOH was added dropwise to the reaction mixture. The reaction mixture was stirred for 1 h at 0°C. Then, the reaction was heated for 2 h at 65°C. The solvent was removed under vacuum. Water was added to the residue and heated for 10 min at 50°C. The mixture was acidified by addition of acetic acid until pH 4 and then cooled in an ice bath. The formed precipitate was filtered and washed with ice water to give the desired product (13.8 g).

Intermediate 1d

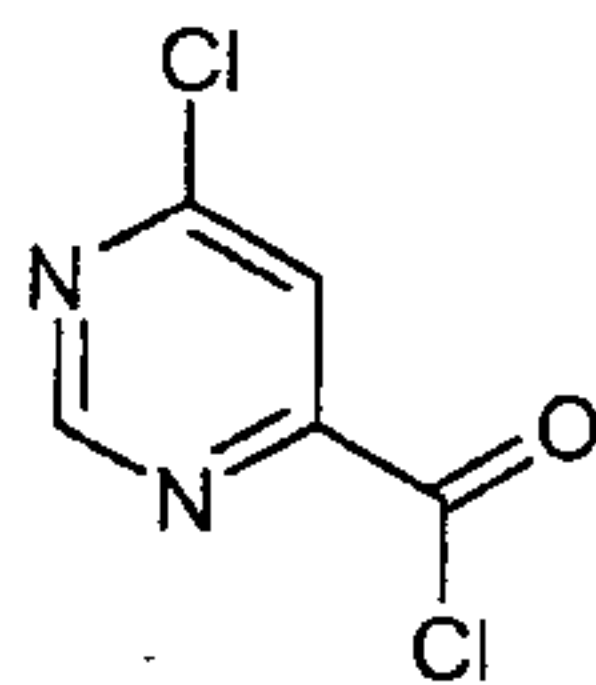
- was synthesized in analogy to intermediate 1c starting from commercially available 2,2,2,-trifluoro-acetamidine.

Intermediate 2a

- Intermediate 1a (7.0 g, 45.4 mmol) was suspended in 35 ml of thionyl chloride (0.45 mol), 0.10 ml of DMF was added and the reaction mixture was refluxed for 1h. The reaction mixture was concentrated in vacuum. 8.6 g (45 mmol) of the desired product were obtained and used in the next steps without further purification.

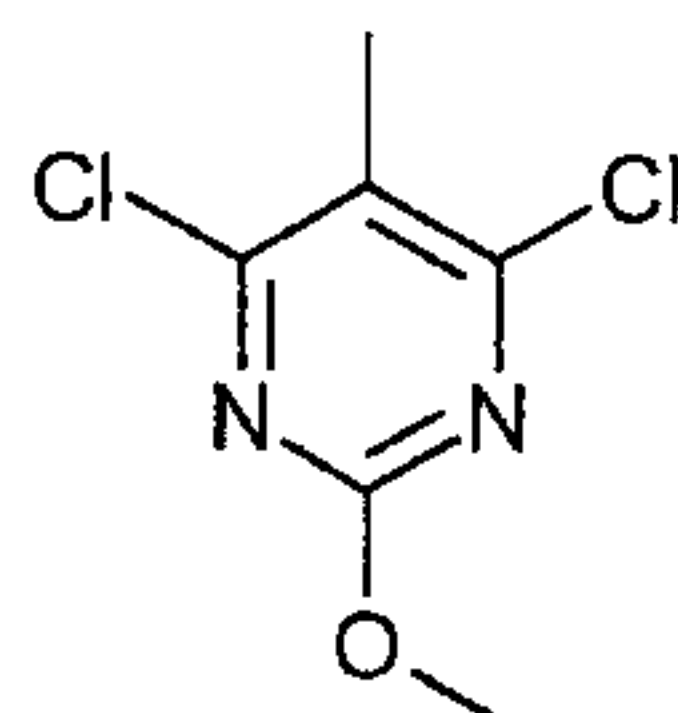
Intermediate 2b

was synthesized in analogy to Intermediate 2a, starting from Intermediate 1b.

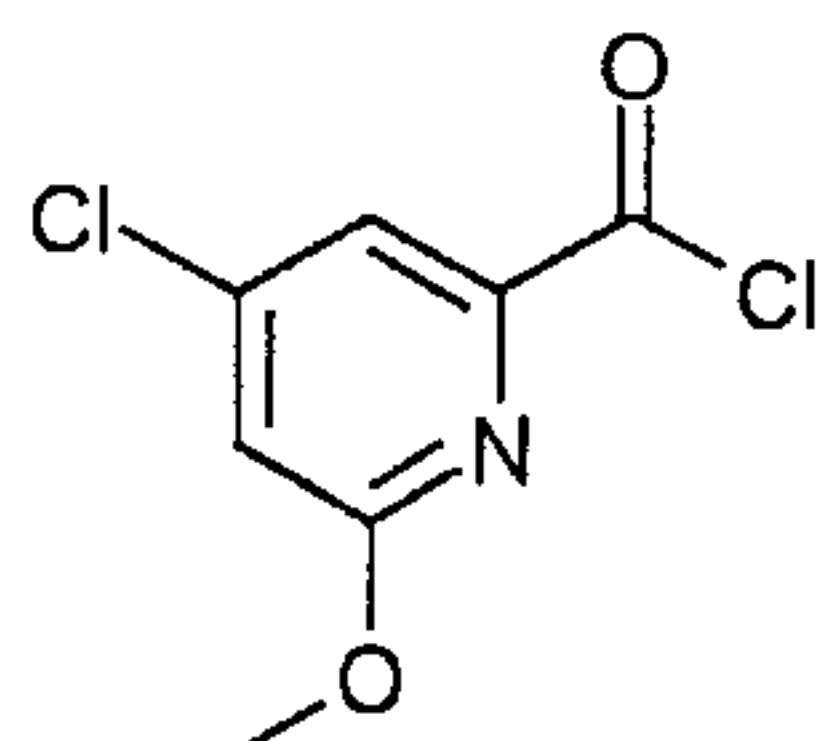
Intermediate 2c

- was synthesized in analogy to Intermediate 2a starting from commercially available 6-hydroxypyrimidine-4-carboxylic acid.

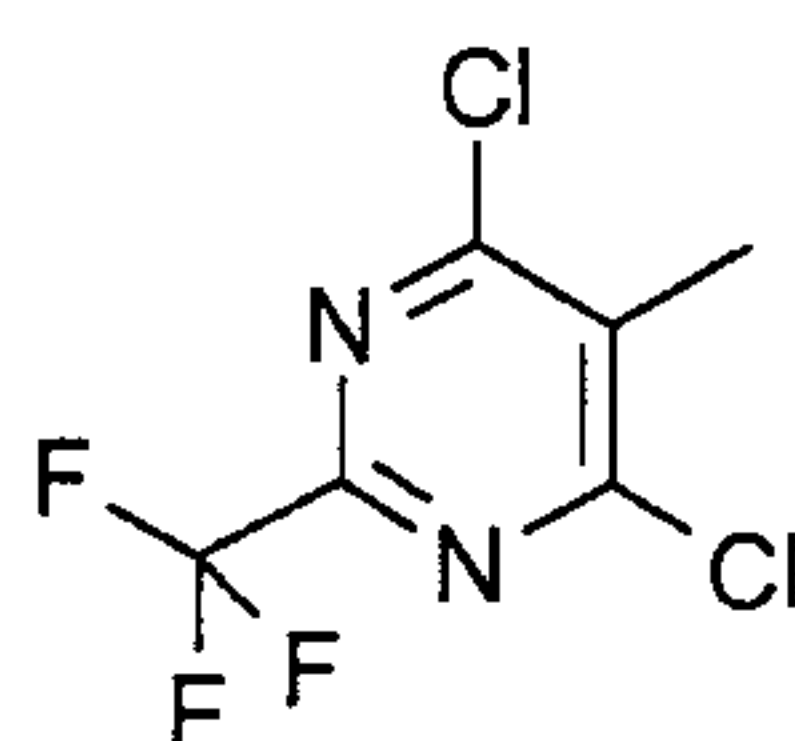
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Intermediate 2d

Intermediate 1c (1.9 g, 12.2 mmol) was added to phosphoryl chloride (17 ml) and the reaction mixture was stirred overnight at 60°C. The reaction mixture was cooled to 0°C and quenched with 4 N NaOH. Then, the crude mixture was extracted with dichloromethane. The combined organic layers were concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product.

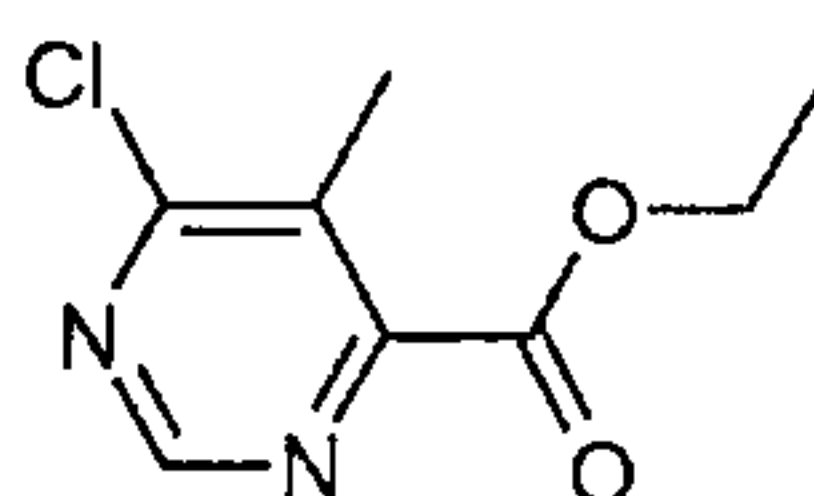
10 **Intermediate 2e**

Commercially available 1-chloro-*N,N*,2-trimethylpropenylamine (70.5 μ l, 533 μ mol) was slowly added to a solution of commercially available 4-chloro-6-methoxy-pyridine-2-carboxylic acid (50 mg, 267 μ mol) in 3 ml dichloromethane at 0°C, and the reaction mixture was stirred for 3 h at room temperature. The solvent was removed in vacuum to give the desired product (55 mg) which was used in the next step without purification.

Intermediate 2f

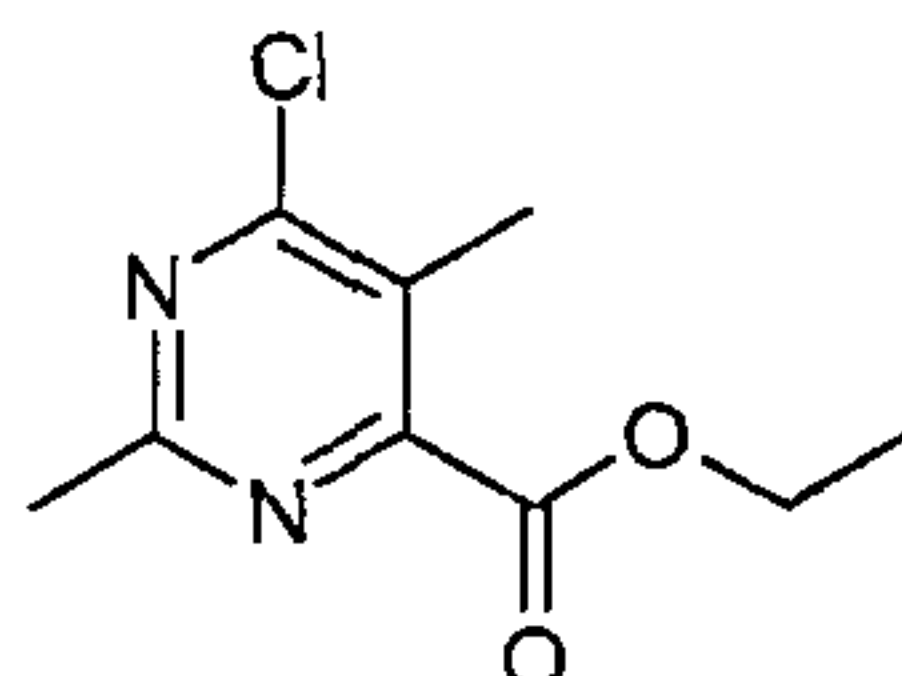
20 Thionylchloride (11.2 ml, 155 mmol) and DMF (250 μ l) were added to a solution of intermediate 1d (3.0 g, 15.5 mmol) in 9 ml dichloromethane and the reaction mixture was refluxed for 4 h. The reaction mixture was cooled to 0°C and quenched with 4 N NaOH. Then, the crude mixture was extracted with dichloromethane. The combined organic layers were concentrated under vacuum to give the desired product (2.7 g).

25

Intermediate 3a

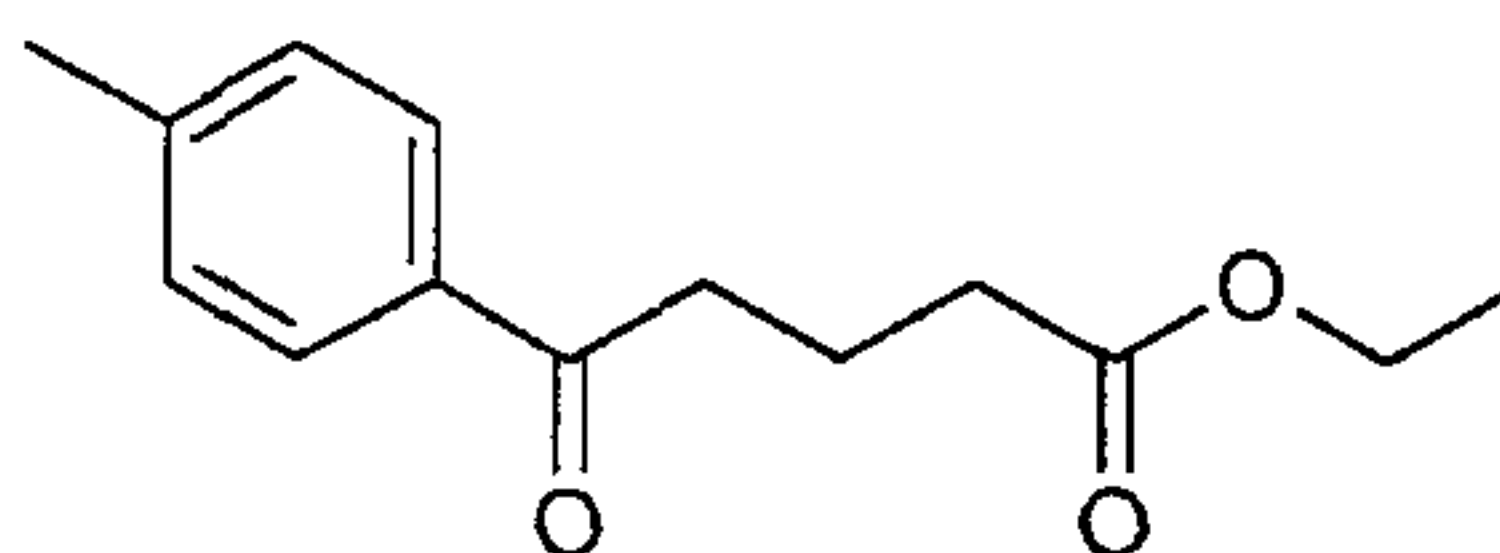
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Potassium carbonate (43.34 g, 0.31 mol) was suspended in 350 ml of dry ethanol. A solution of Intermediate 2a (20 g, 0.10 mol) in 10 ml of dichloromethane was added slowly at 0°C. The reaction mixture was allowed to reach room temperature and stirred for 1h. Potassium carbonate was filtered off and the solvent was removed under vacuum. The crude product was purified by flash chromatography (BIOTAGE SP1; silica gel cartridge: 65i; eluent: dichloromethane/ethyl acetate=95/5%). 5.3 g (26 mmol) of the desired compound were obtained.

Intermediate 3b

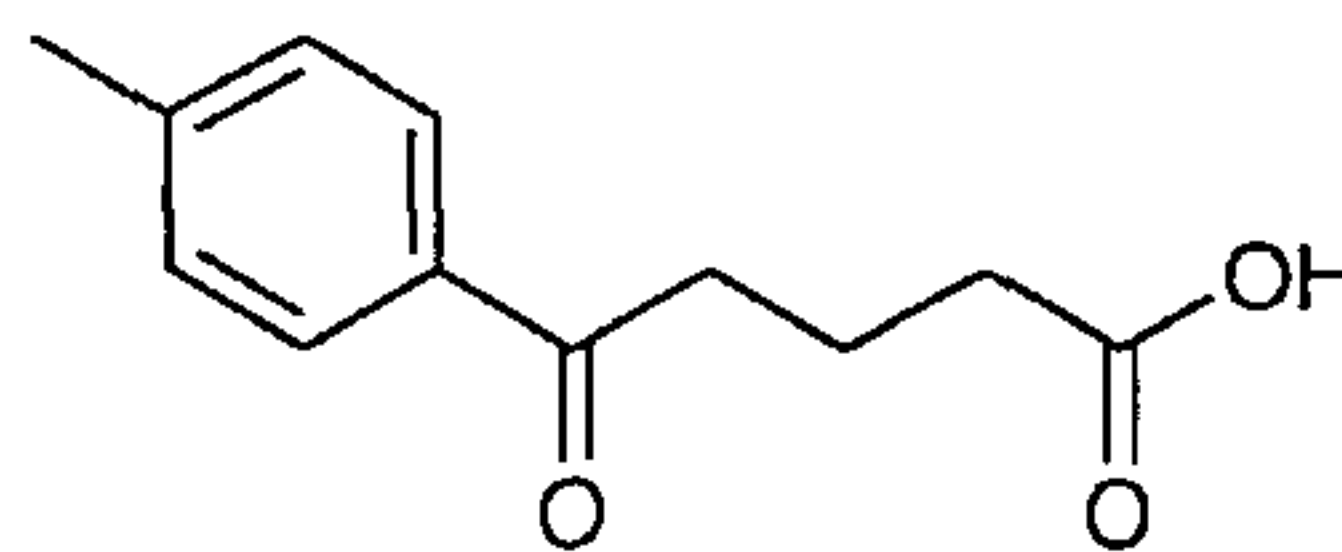
10

was synthesized in analogy to Intermediate 3a, starting from Intermediate 2b.

Intermediate 4a

To a solution of lithium bromide (24 g, 277.06 mmol) in 500 ml of dry tetrahydrofuran, stirred under nitrogen atmosphere, copper(I) bromide (19,87 g, 138,52 mmol) was added. The reaction mixture was stirred at room temperature until a solution was obtained. Then, the reaction mixture was cooled to 0°C and a 0.5M solution of commercially available 4-tolyl magnesium bromide in THF (277.05 ml, 138,52 mmol) was added. Then, commercially available 4-chlorocarbonyl-butyric acid ethyl ester (19 g, 115,44 mmol) was added and the reaction mixture was stirred at 0°C for 18h.

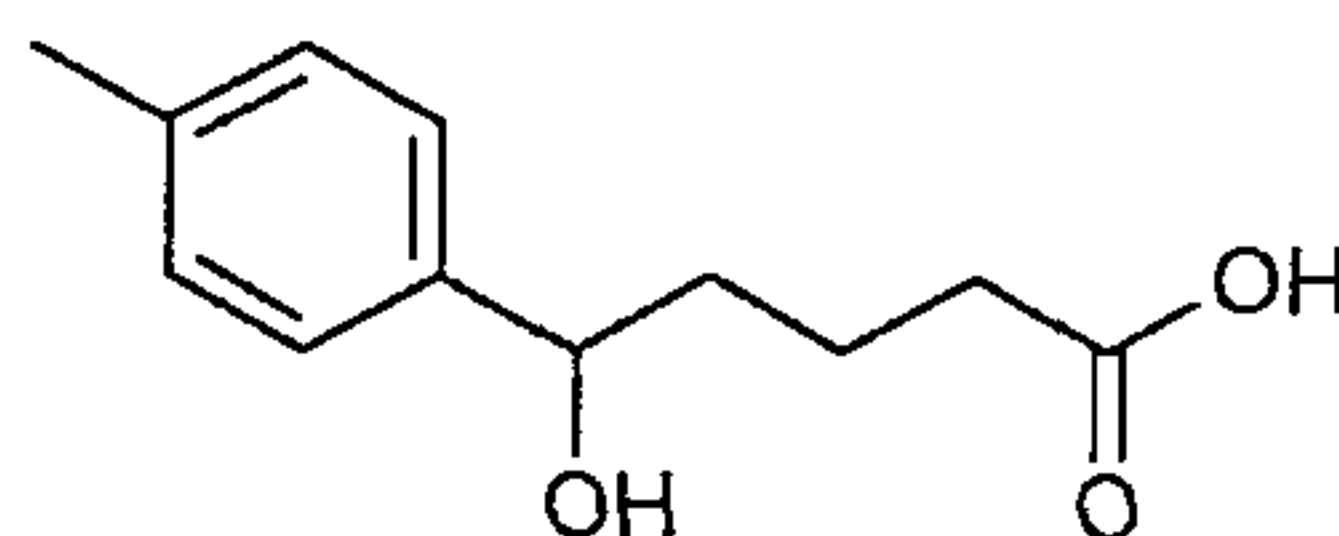
500 ml of a saturated aqueous ammonium chloride solution was added and the reaction mixture was extracted twice with dichloromethane. The organic phase was washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulphate and concentrated under vacuum. The crude product (20 g) was used in the next step without any purification.

Intermediate 5a

To a solution of intermediate 4a (20 g, 90,80 mmol) in 50 ml of tetrahydrofuran 50 ml of water and lithium hydroxide monohydrate (11,43 g, 274,40 mmol) were added and the reaction mixture was stirred at 50°C for 1h.

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The reaction mixture was extracted with ethyl acetate and the layers were separated. The water phase was acidified with aqueous HCl (37%) until pH 1 and then extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was triturated with diisopropyl ether. The solvent was removed by filtration yielding the desired product (13g, 63.10 mmol).

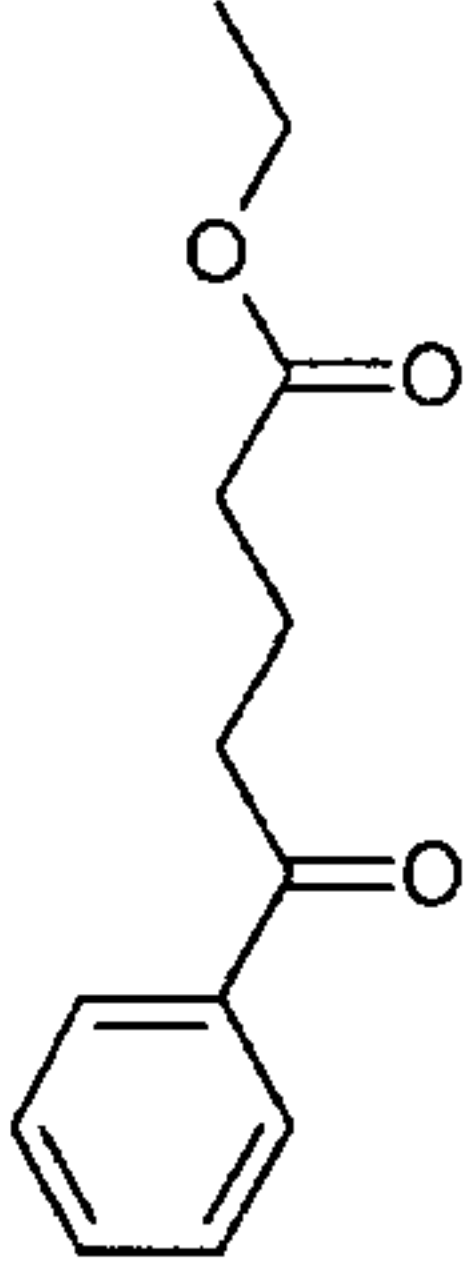
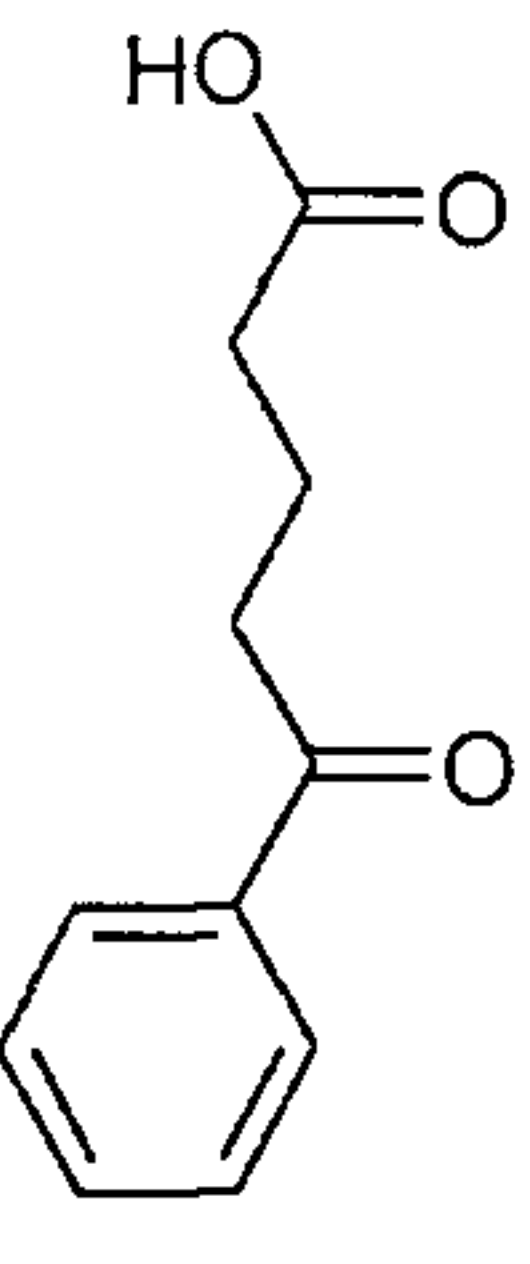
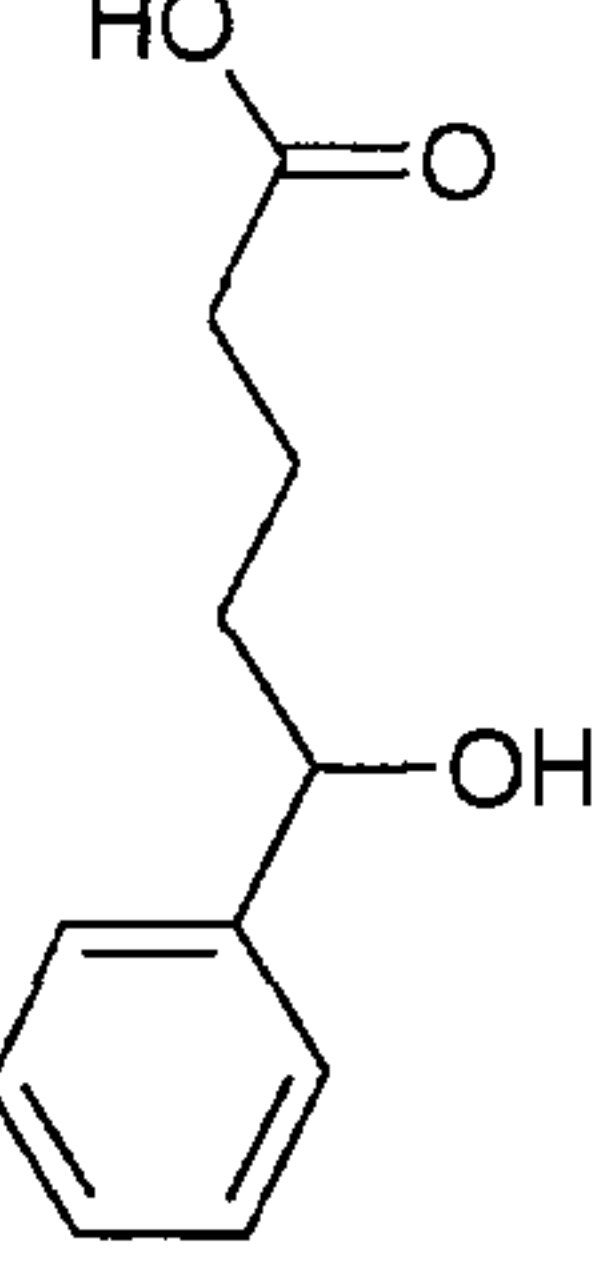
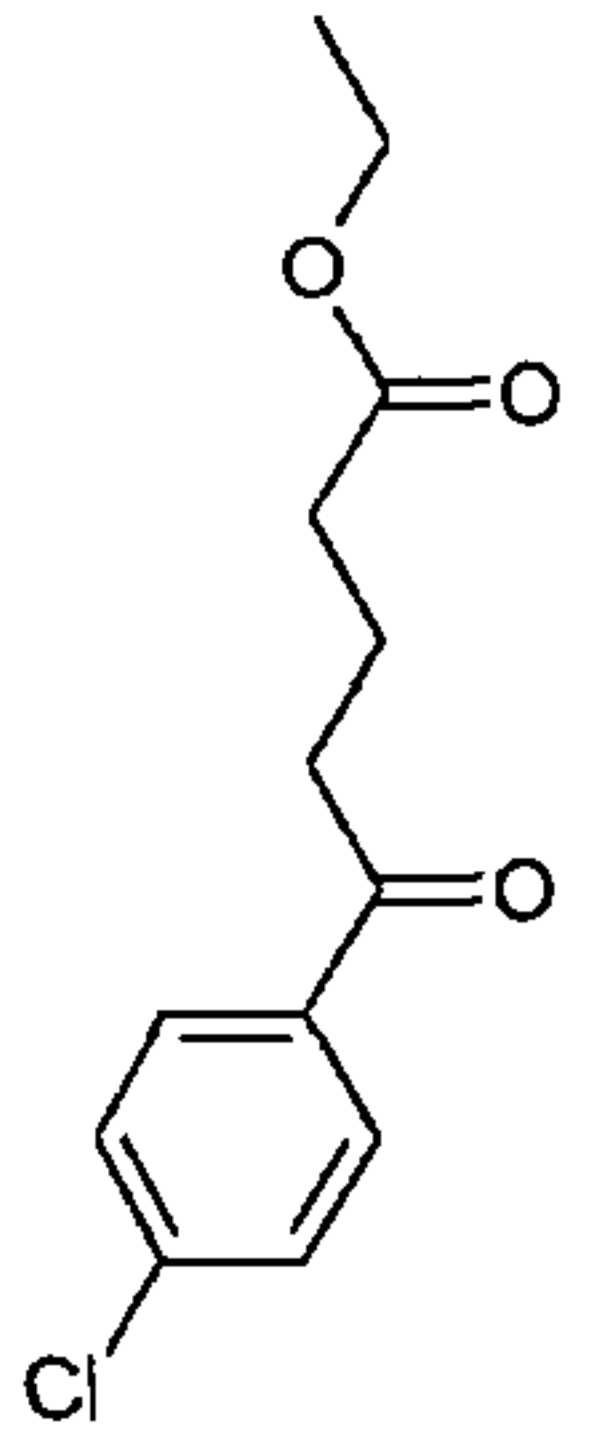
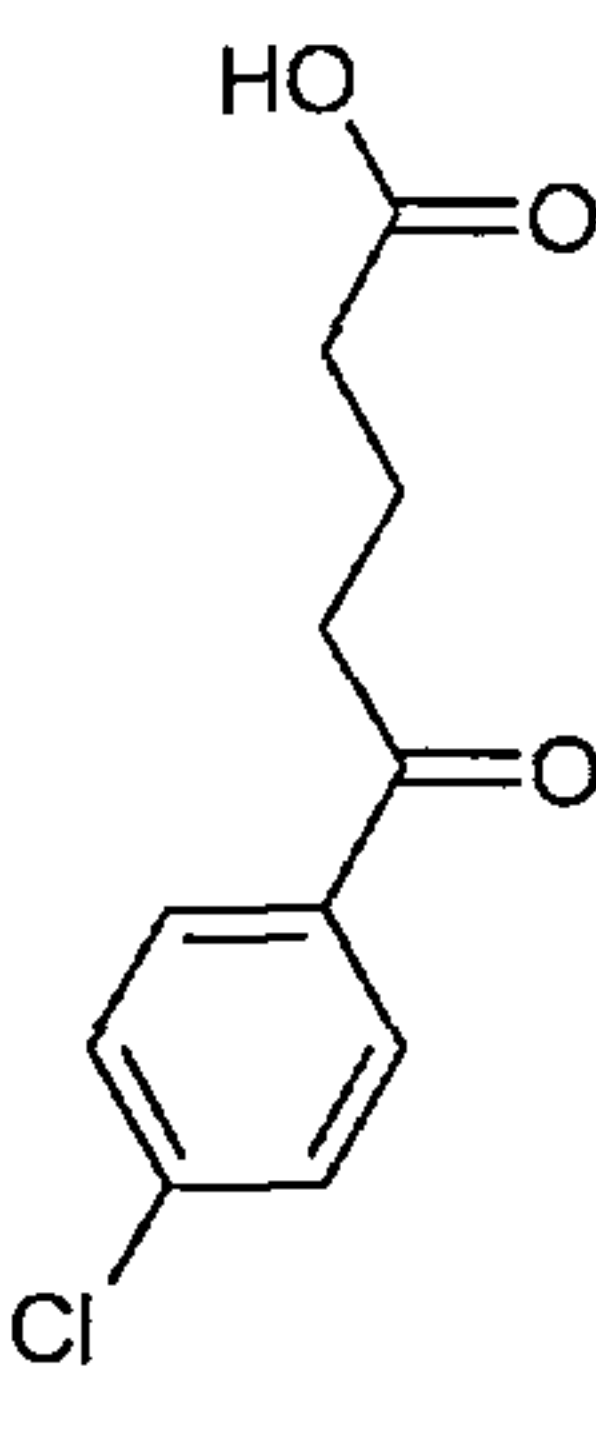
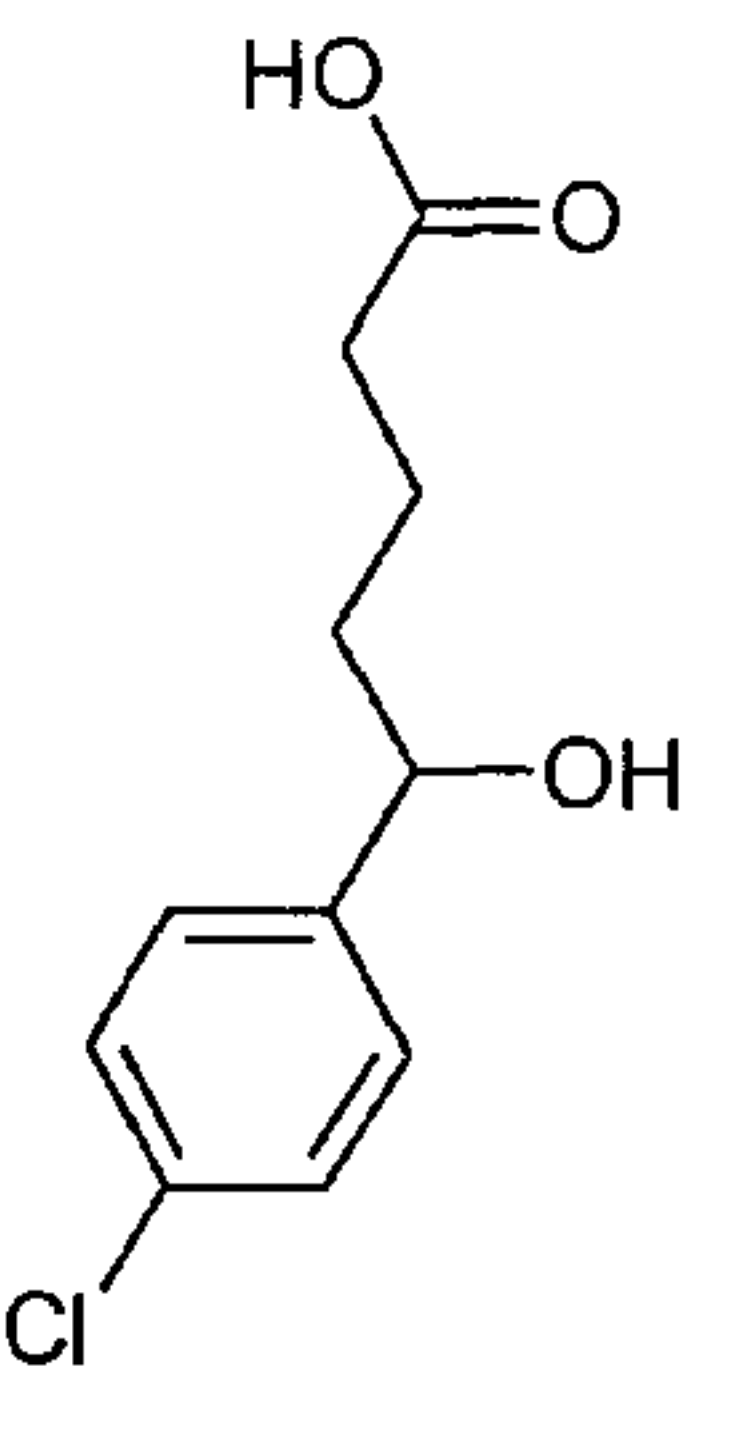
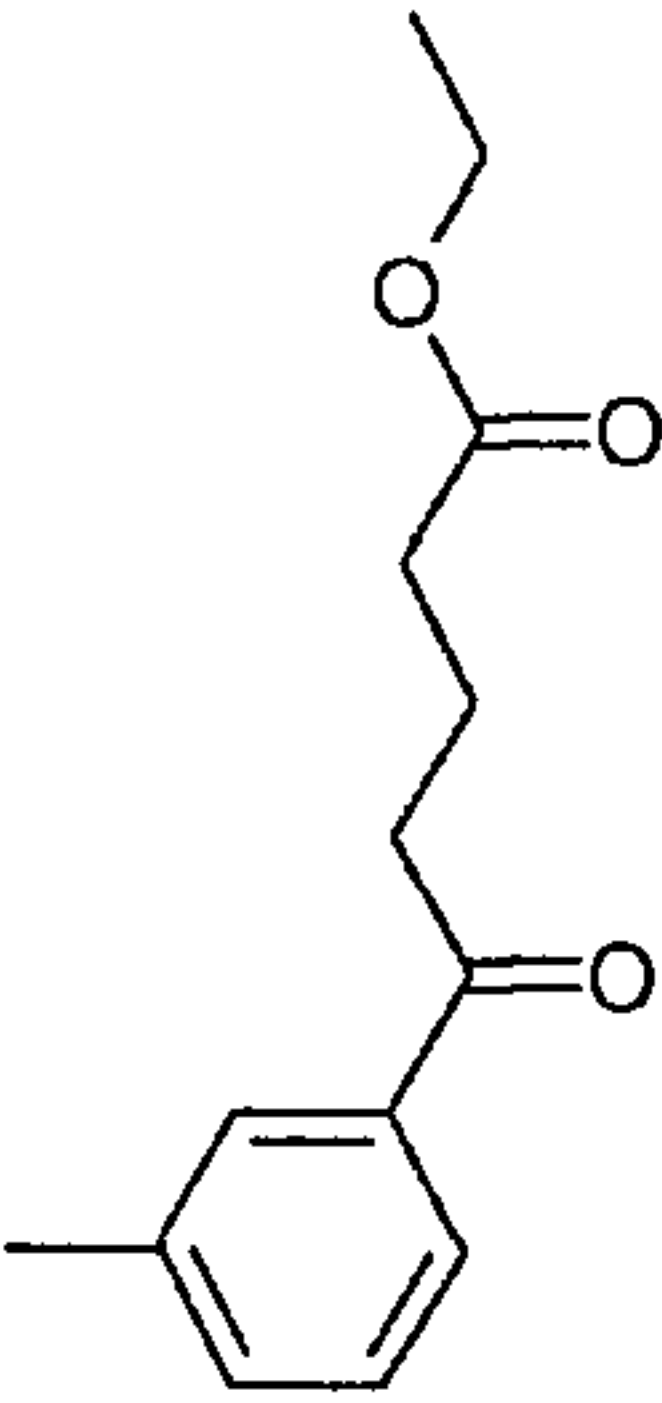
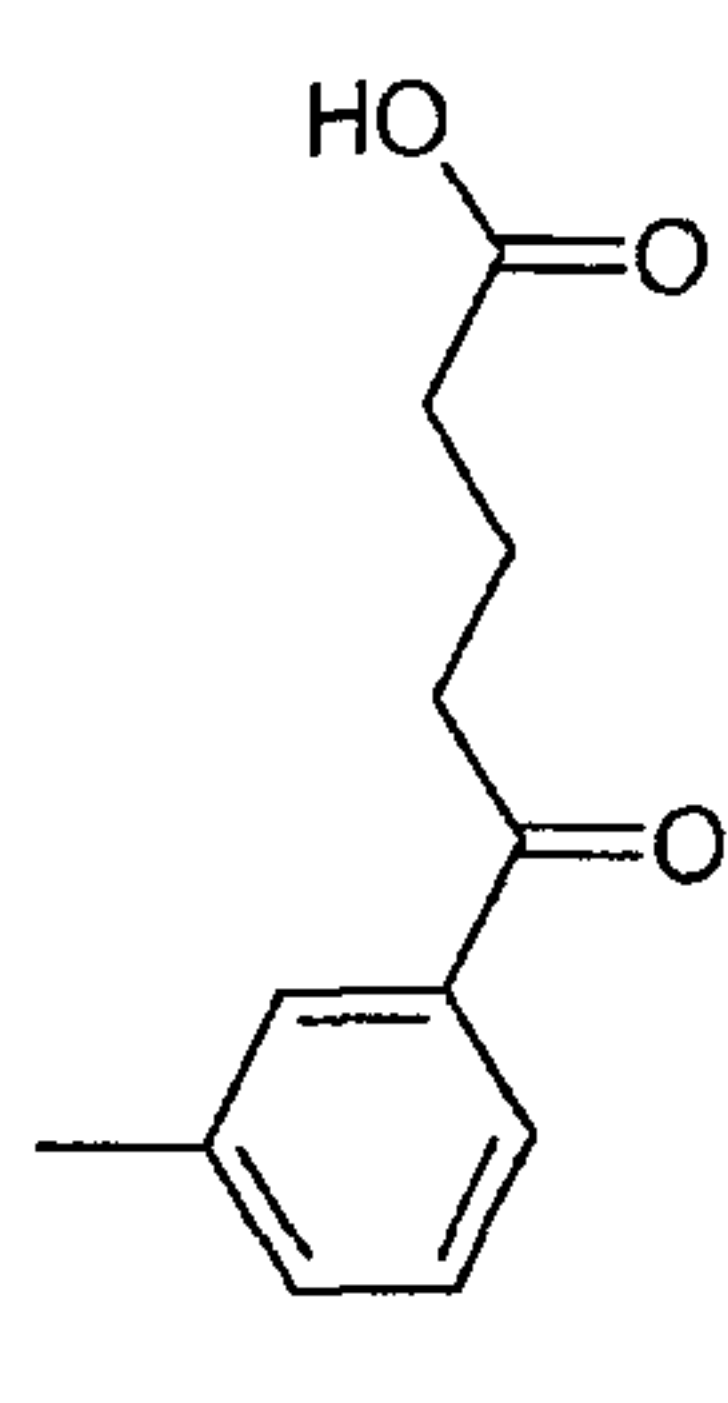
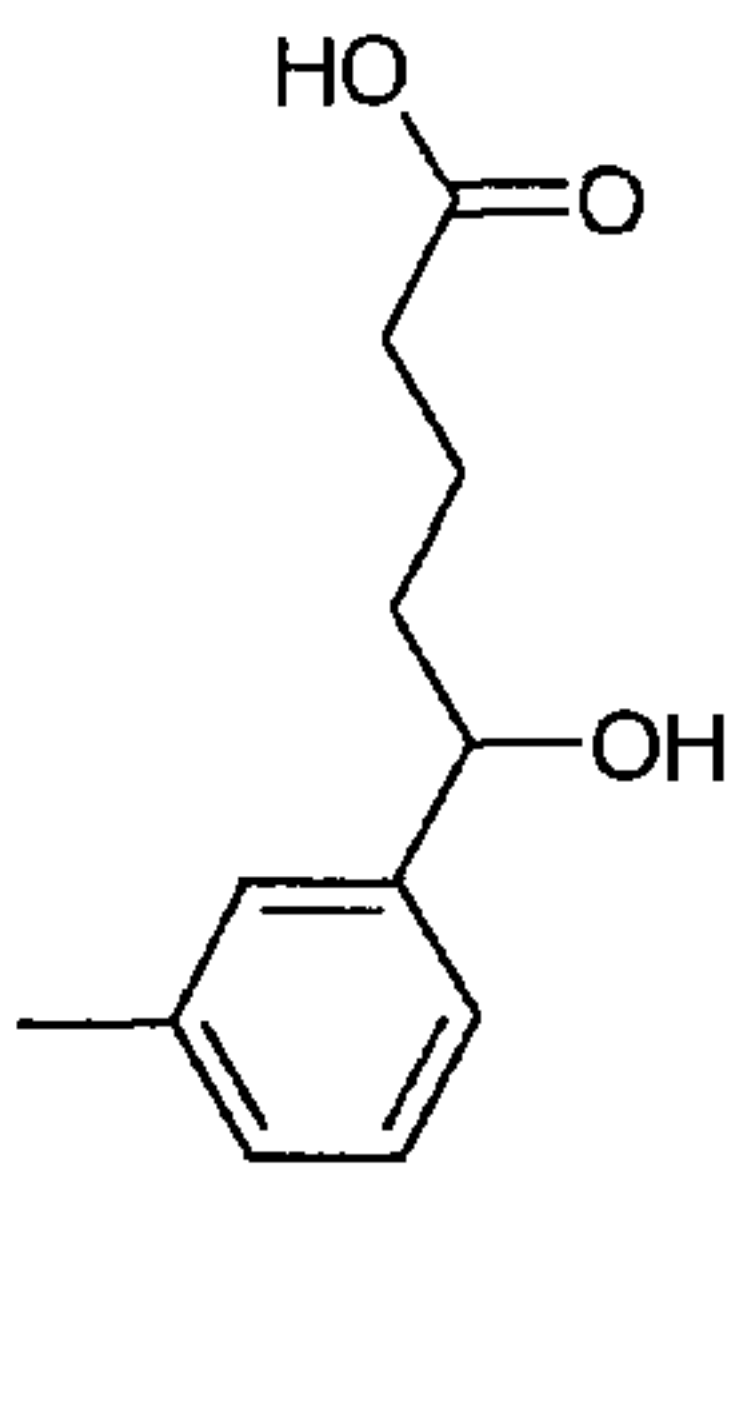
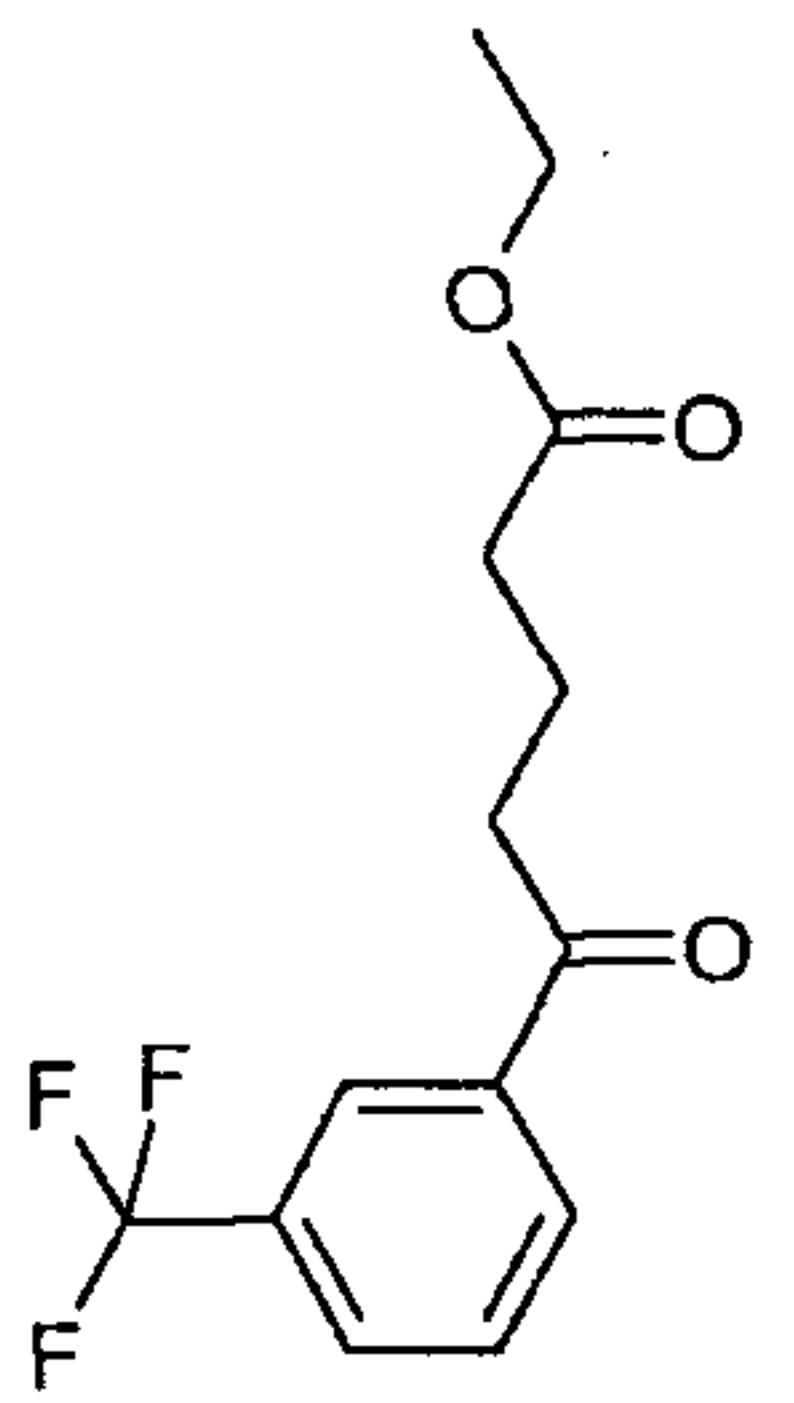
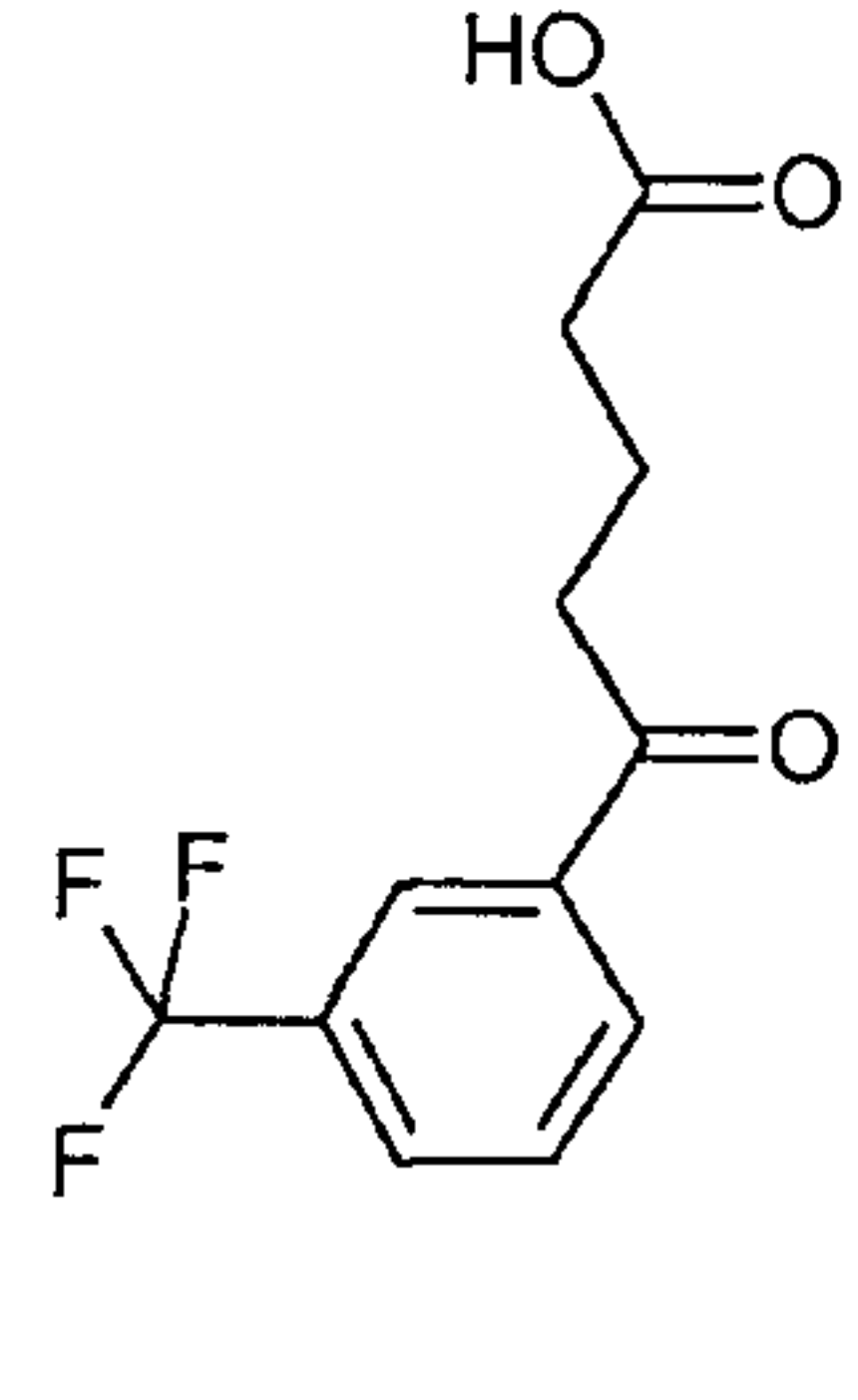
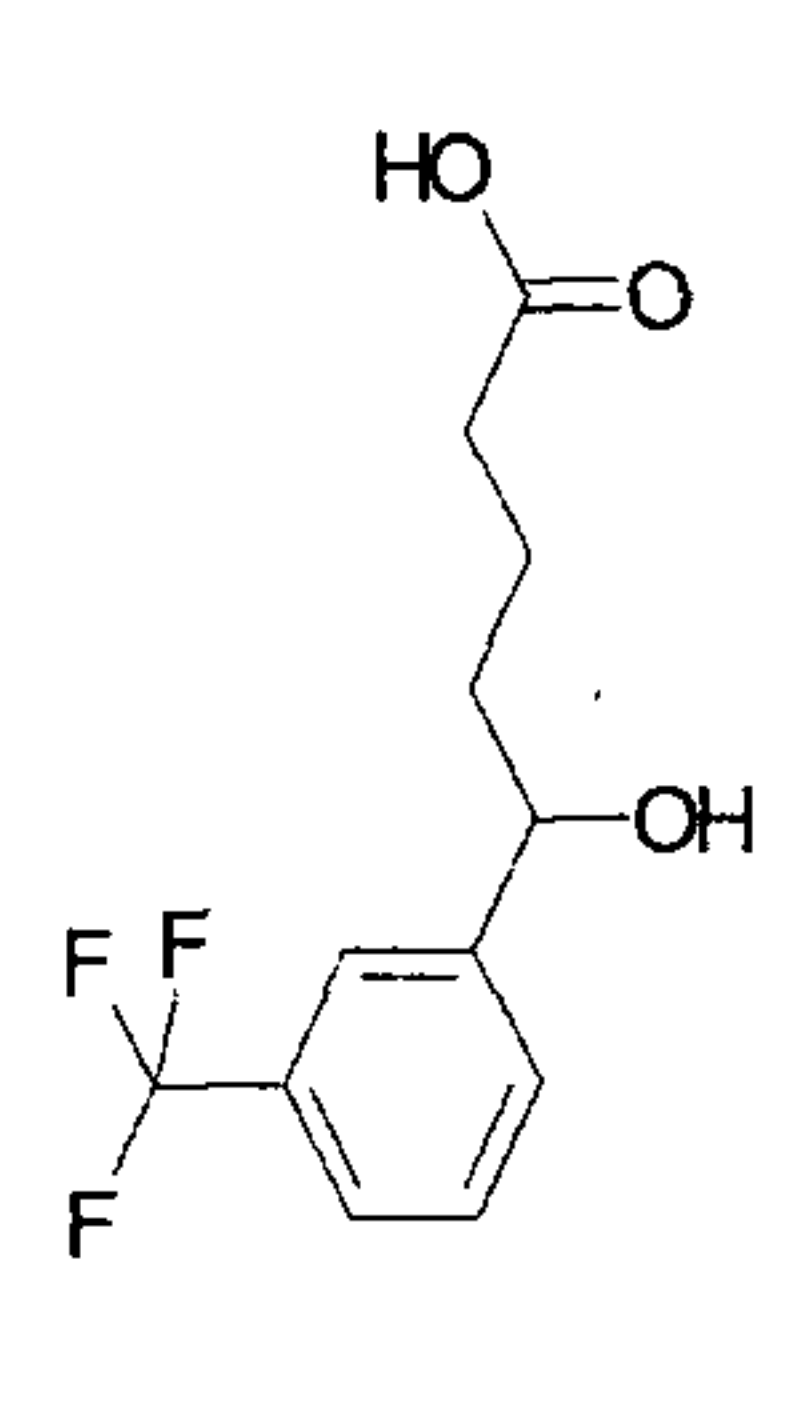
Intermediate 6a

A suspension of Intermediate 5a (11.5 g, 55.76 mmol) in 250 ml of water was cooled to 10°. Then, potassium hydroxide (7.82 g, 139.4 mmol) and sodium borohydride (1.83 g, 48.51 mmol) were added and the reaction mixture was allowed to reach room temperature and stirred for 2h. 13 ml of a 12M aqueous hydrochloric acid was added and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum to give the crude product (11 g, 52.82 mmol).

The following intermediates were synthesized in analogy to Intermediates 4a, 5a and 6a.

<i>synthesis in analogy to intermediate 4a</i>				<i>synthesis in analogy to intermediate 5a</i>		<i>synthesis in analogy to intermediate 6a</i>	
Starting Grignard	Source/Reference	Keto-ester Intermediate	STRUCTURE	Keto-acid Intermediate	STRUCTURE	Hydroxy-acid Intermediate	STRUCTURE
4-((Trifluoro-methyl)-phenyl)-magnesium bromide	WO2009/73203	4b		5b		6b	

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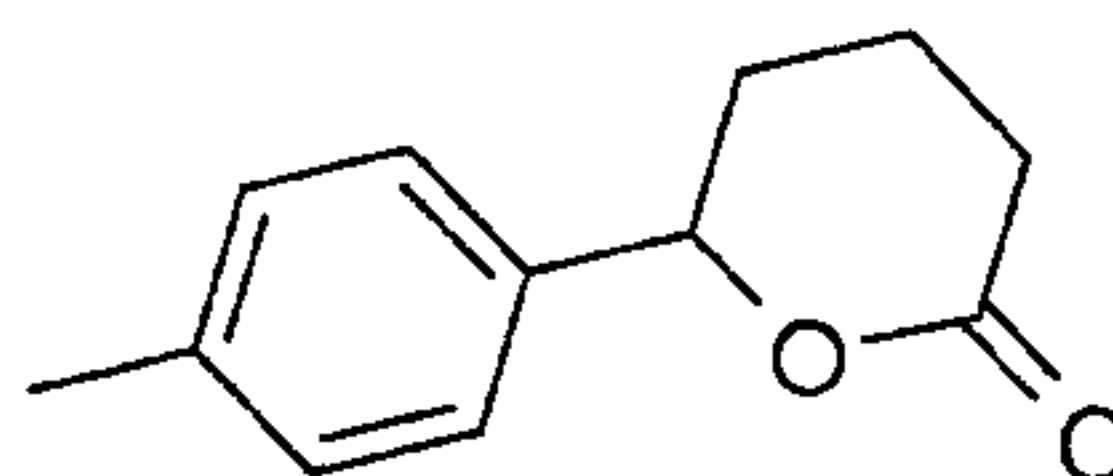
Phenyl magnesium bromide	Commercially available	4c		5c		6c	
4-Chloro-phenyl magnesium bromide	Commercially available	4d		5d		6d	
3-Tolyl-magnesium bromide	Commercially available	4e		5e		6e	
3-((Trifluoro-methyl)-phenyl)-magnesium bromide	WO2009/73203	4f		5f		6f	

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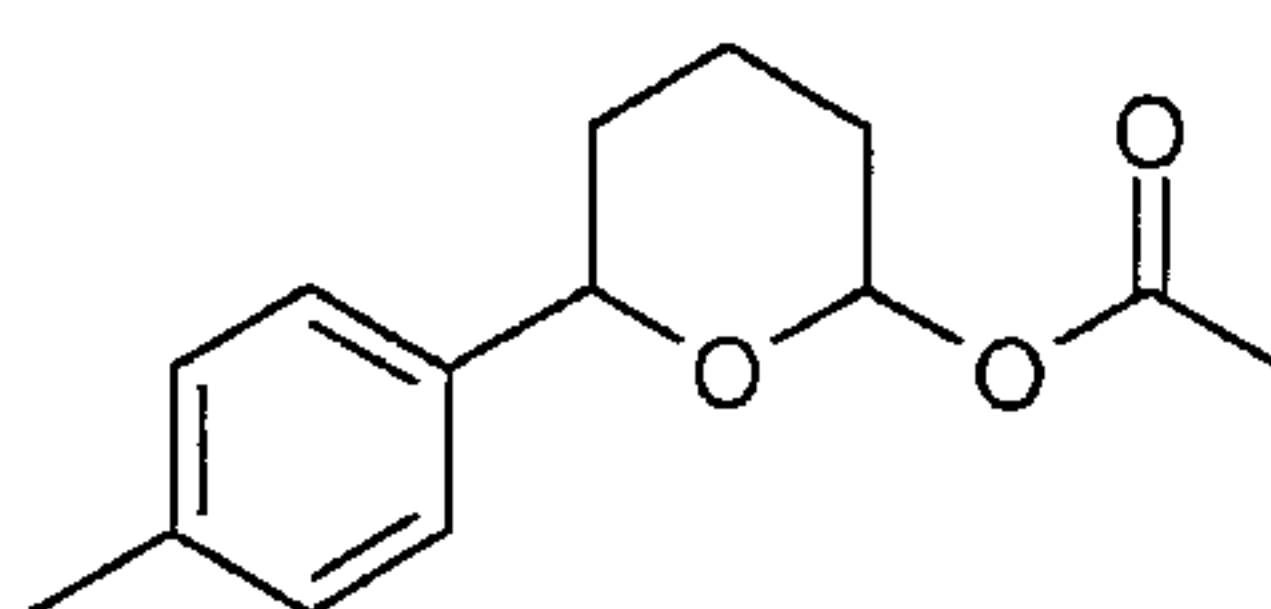
(6-(Trifluoro-methyl)pyridin-3-yl)magnesium bromide	*)	4g		5g		6g	
4-((Trifluoro-methoxy)-phenyl)-magnesium bromide	Commercially available	4h		5h		6h	
4-Fluoro-phenyl-magnesium bromide	Commercially available	4i		5i		6i	

*) 6-(Trifluoro-methyl)pyridin-3-yl)magnesium bromide was prepared by adding 5 ml of dry tetrahydrofurane and 0.061 ml (0.061 mmol) of a 1M solution of diisobutyl aluminium hydride in hexane to magnesium turnings (3.9 g, 160 mmol) and of lithium chloride (6.27 g, 148 mmol). The reaction mixture was stirred at 0°C for 5 min, then a solution of (6-(trifluoro-methyl)pyridin-3-yl)-bromide (7.5g, 32.2 mmol) in 30 ml of dry tetrahydrofurane was added dropwise. The reaction mixture was allowed to reach room temperature, stirred for 30 min and used directly.

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Intermediate 7a

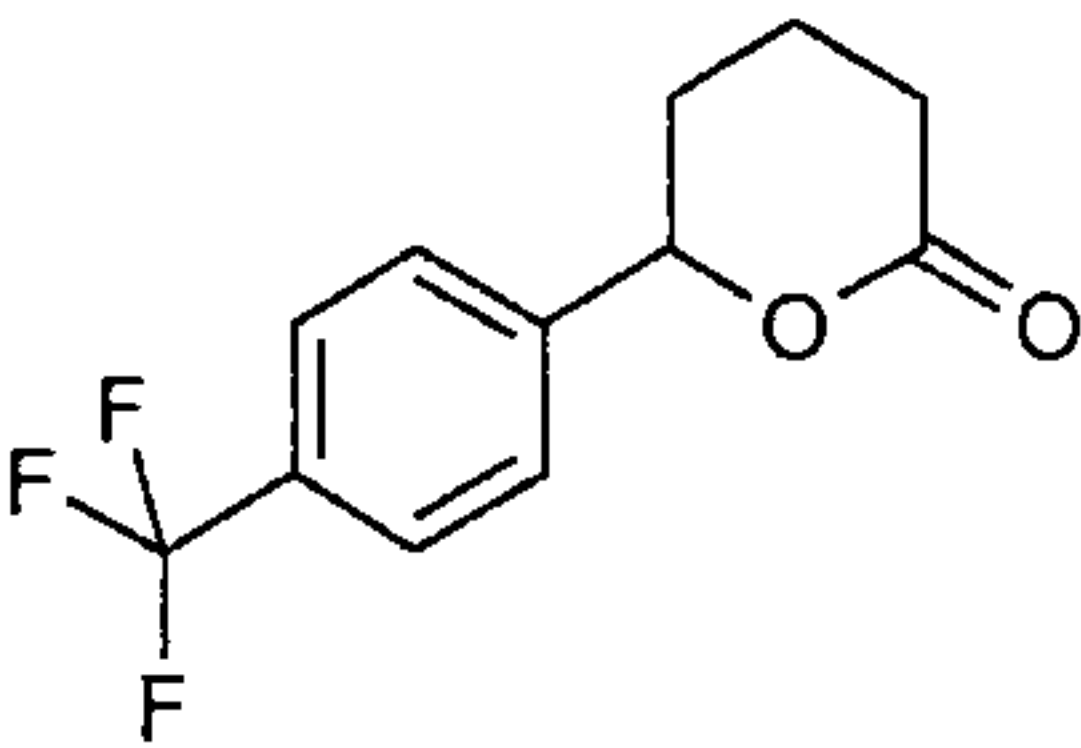
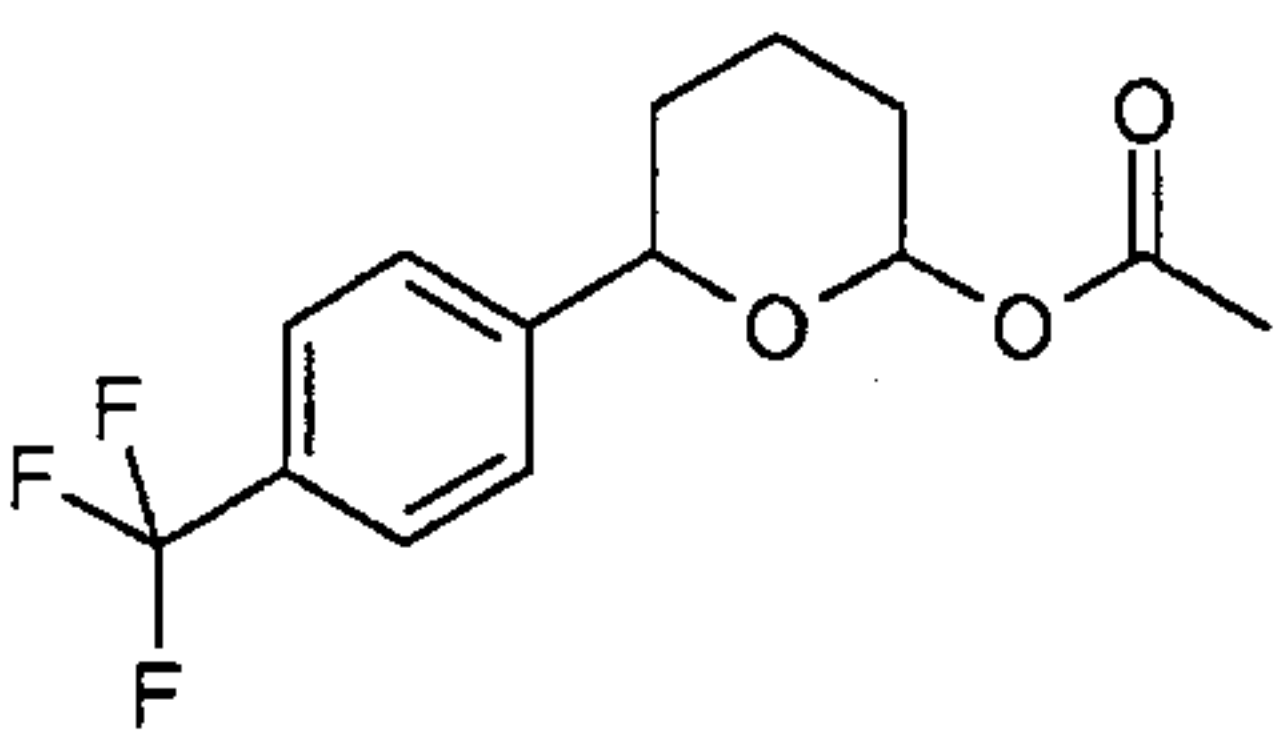
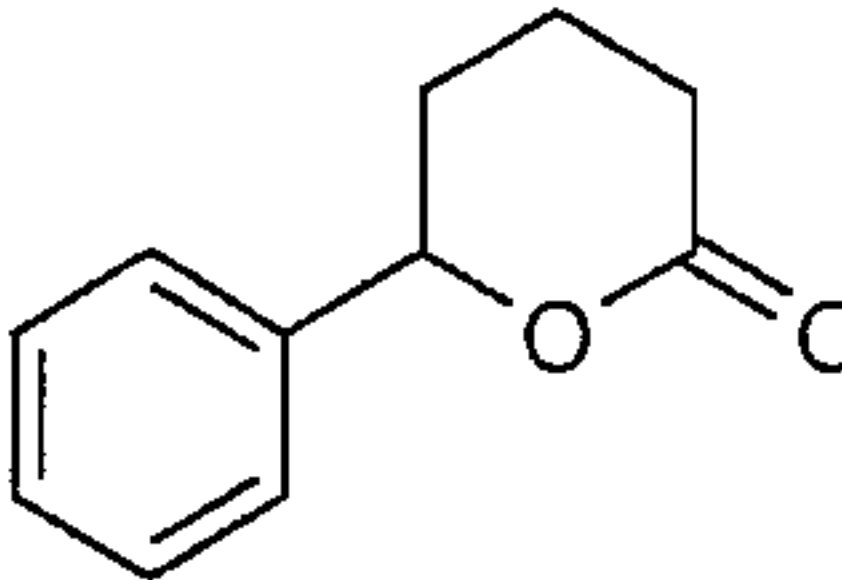
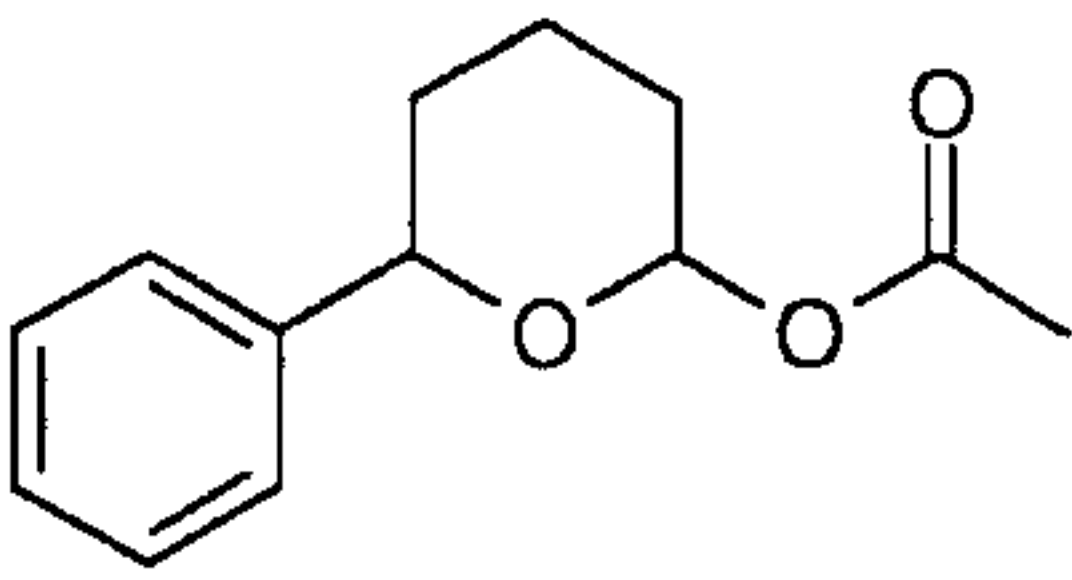
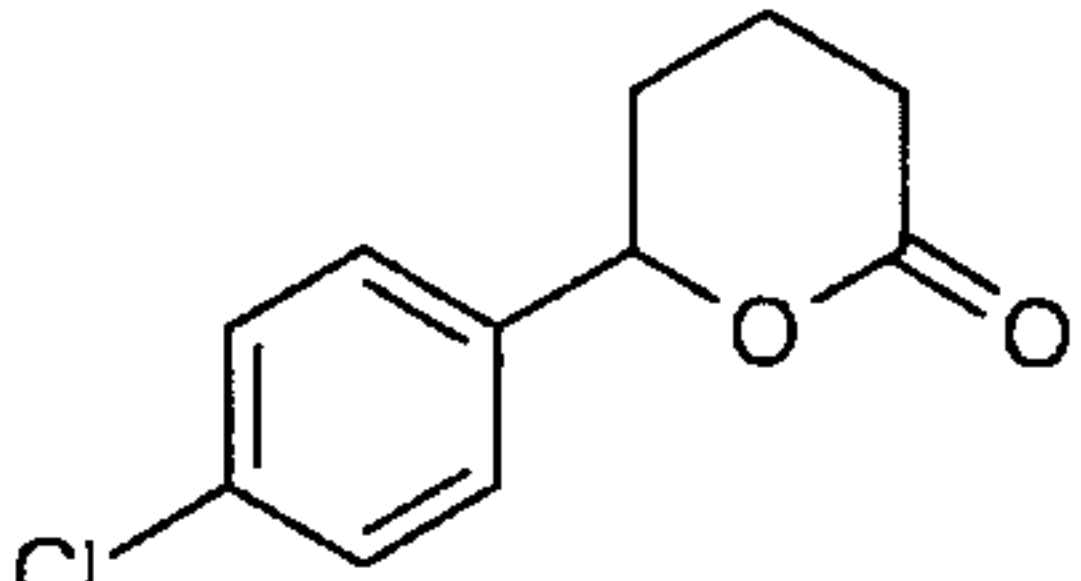
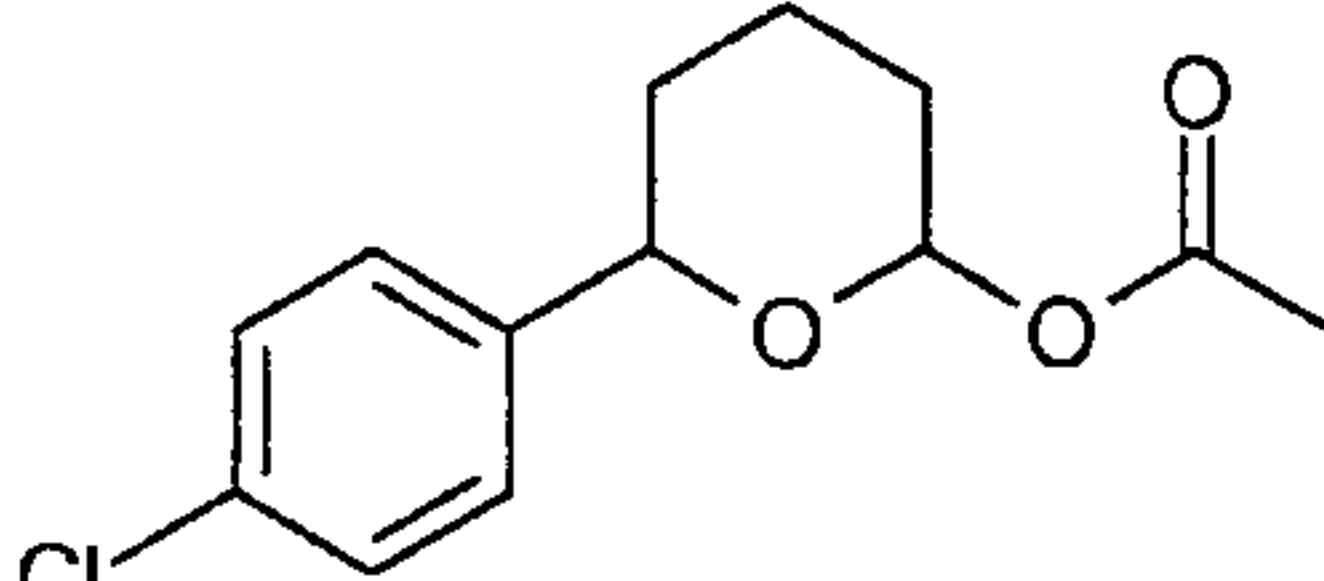
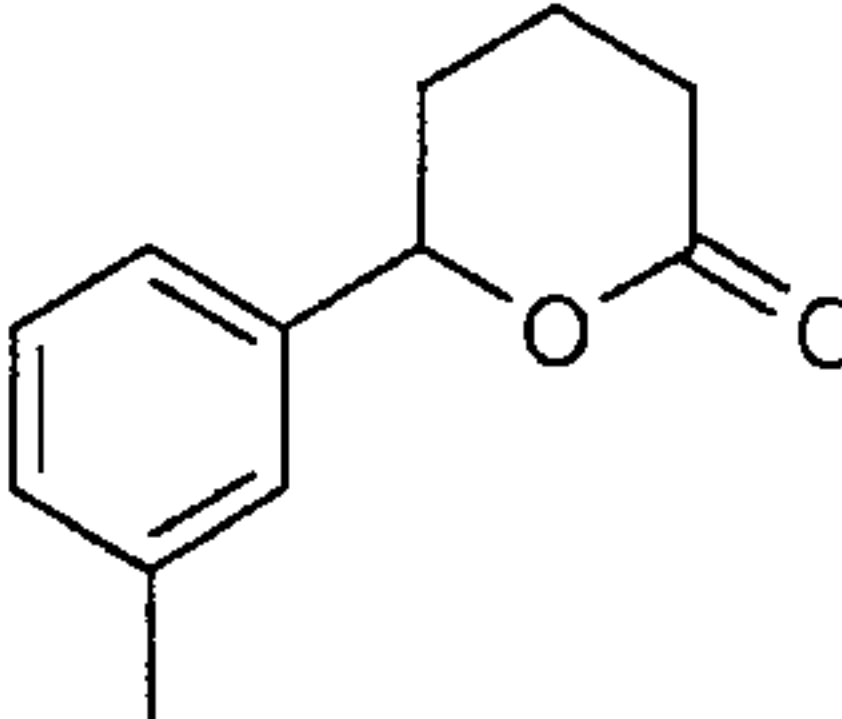
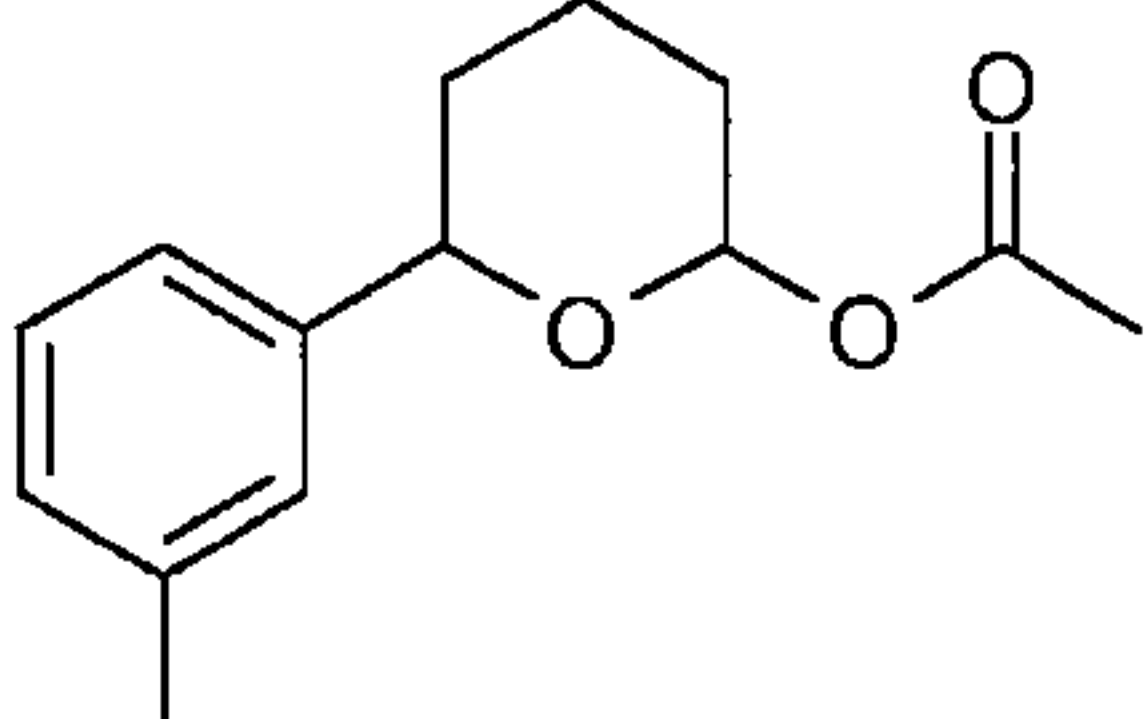
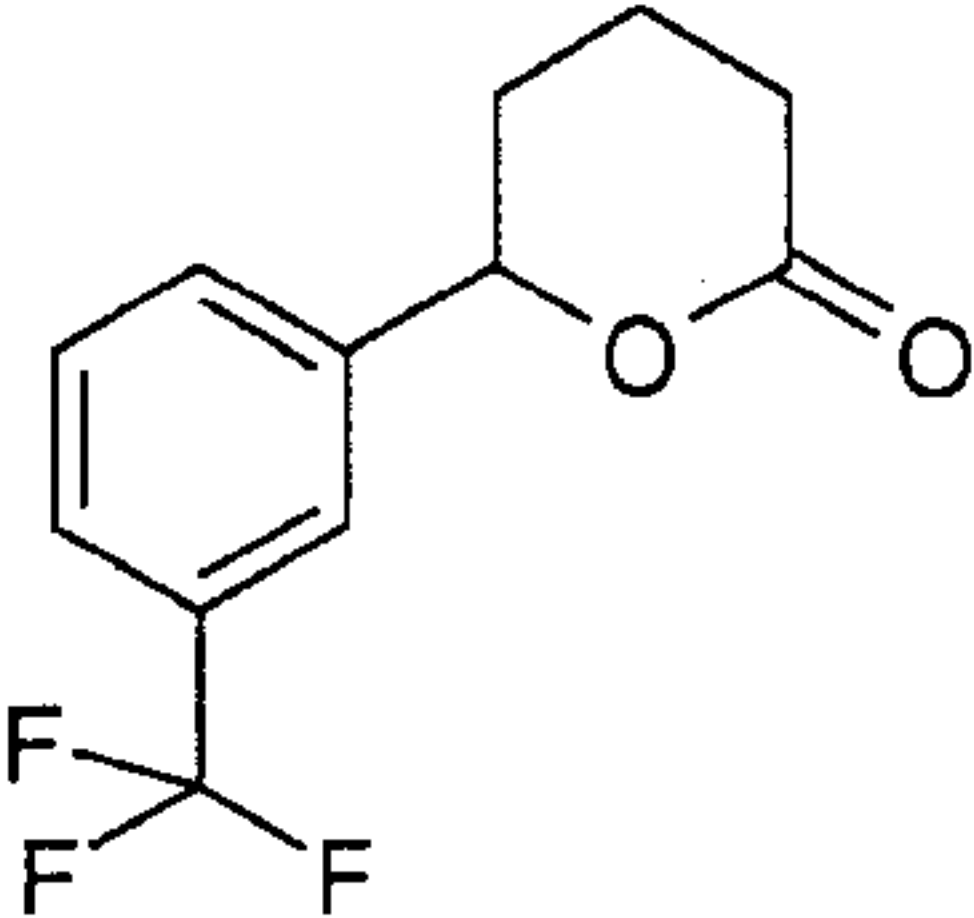
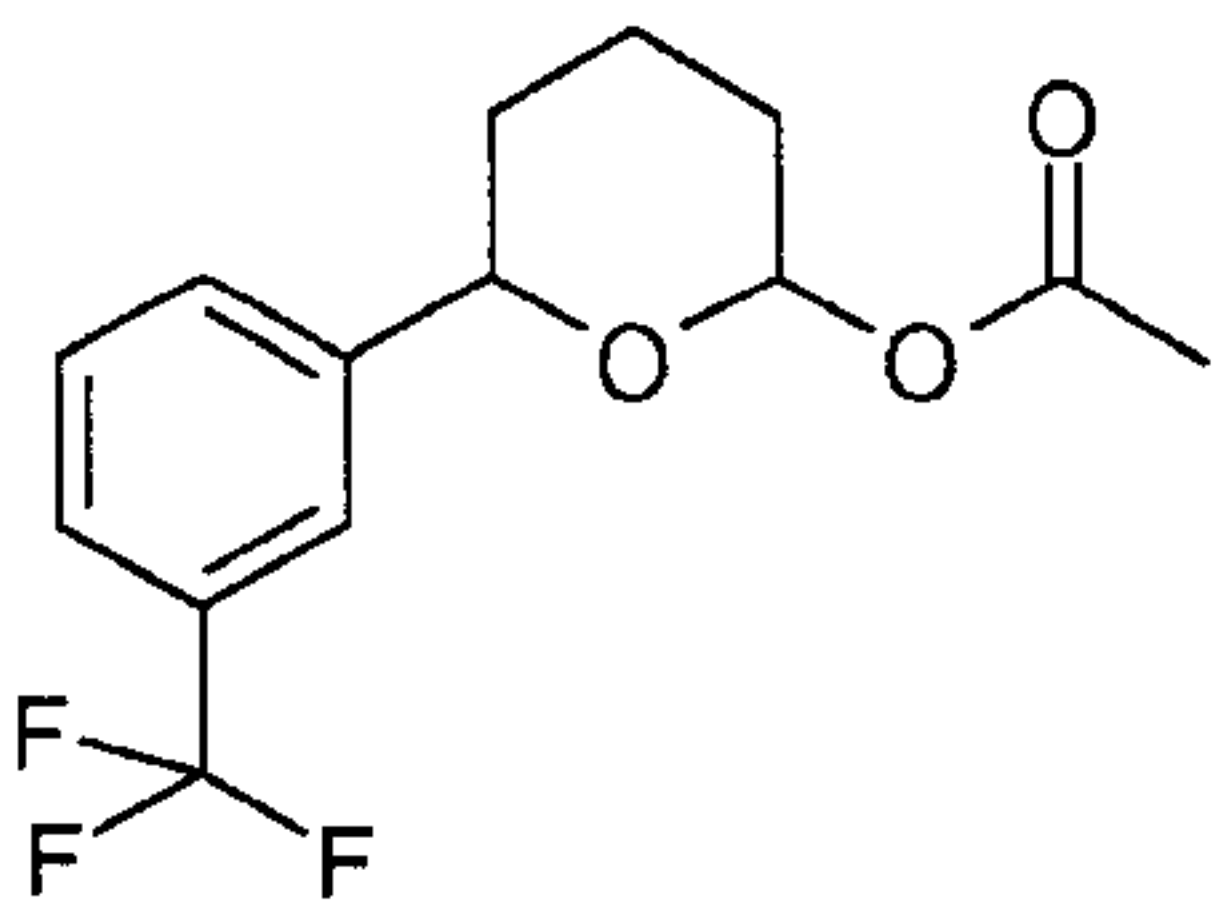
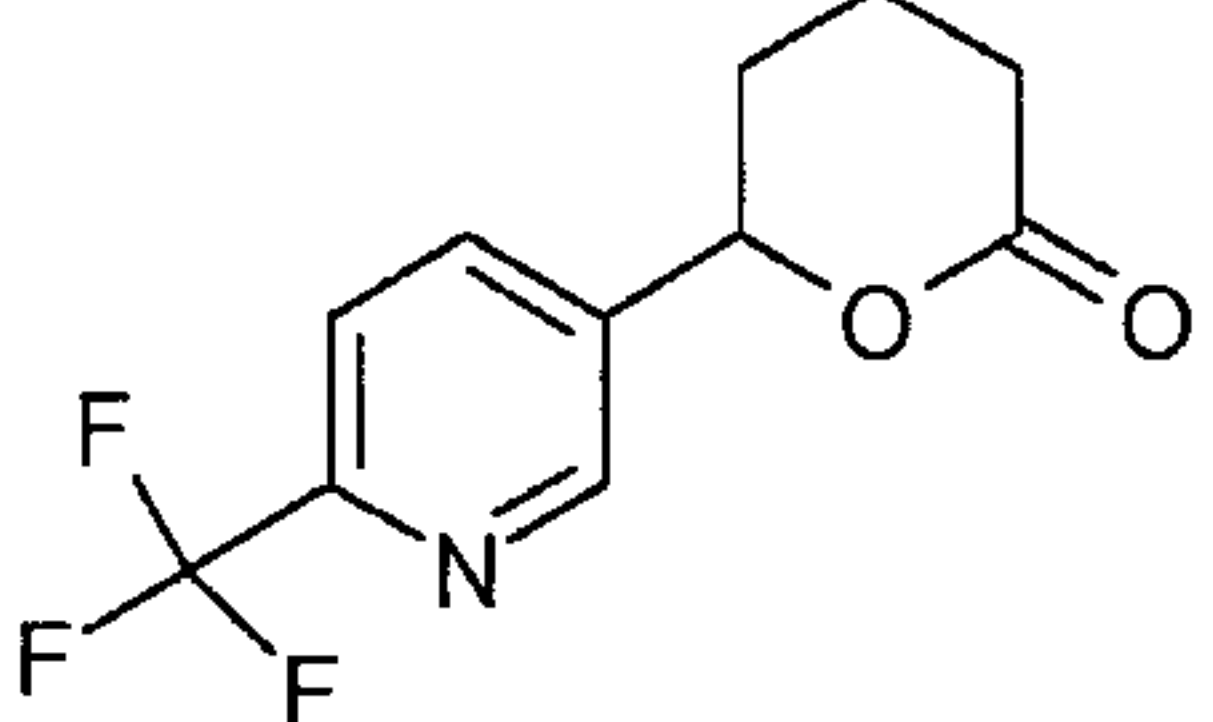
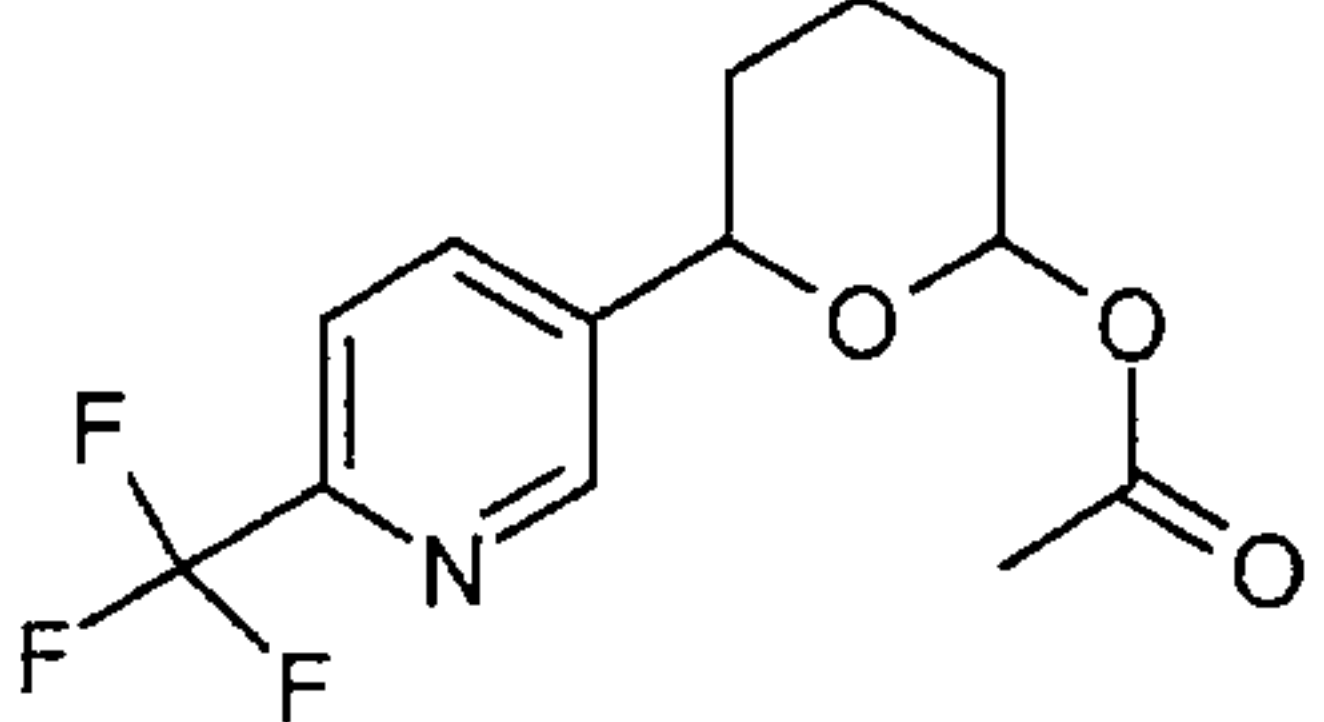
Intermediate 6a (6 g, 28.81 mmol) was dissolved in 100 ml of dichloromethane. 1.5 ml of trifluoroacetic acid was added and the reaction mixture was stirred at room temperature for 18h. The reaction mixture was diluted with 50 ml of dichloromethane and washed with 50 ml of a saturated aqueous sodium bicarbonate solution and water. The organic layer was dried over sodium sulfate and removed under vacuum to give the desired product (4.38 g (23.0 mmol)).

10 **Intermediate 8a**

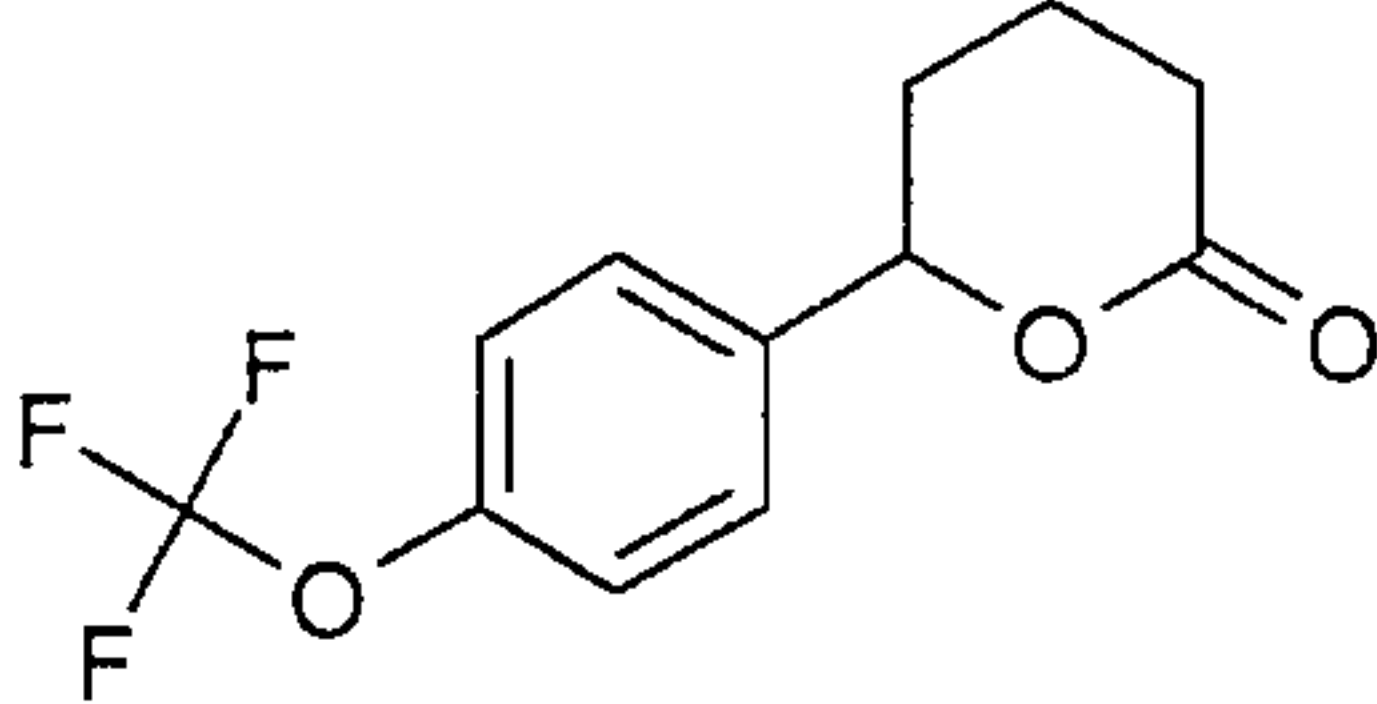
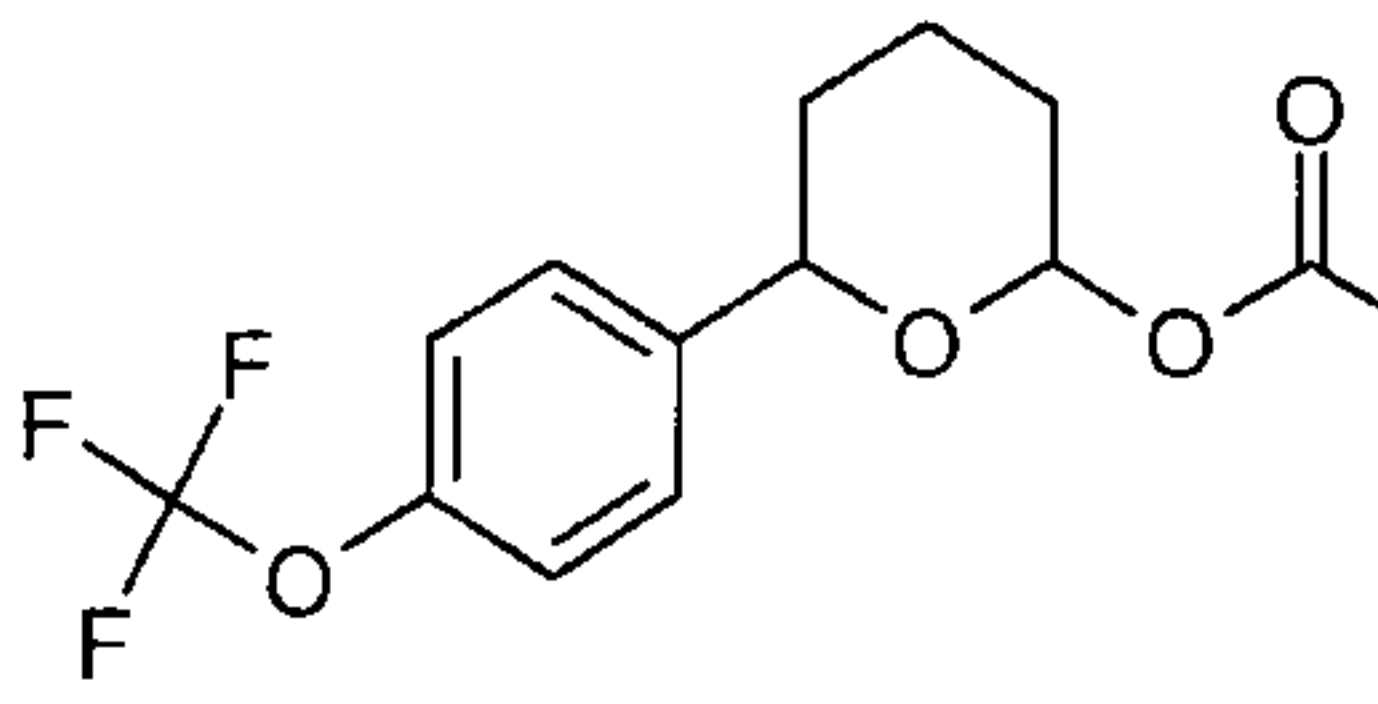
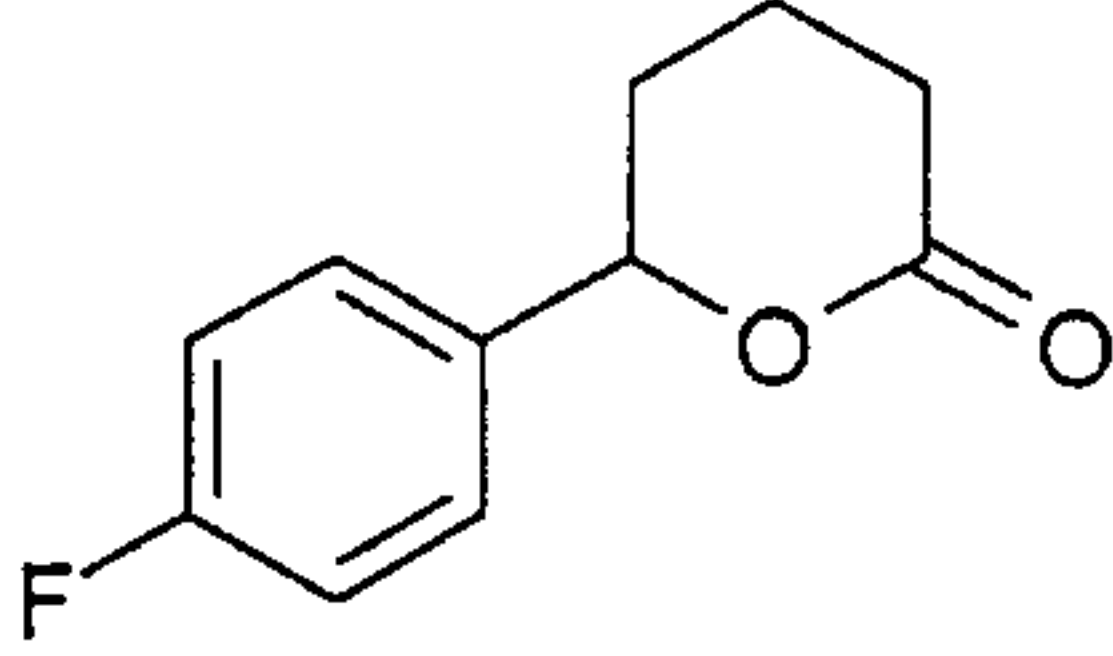
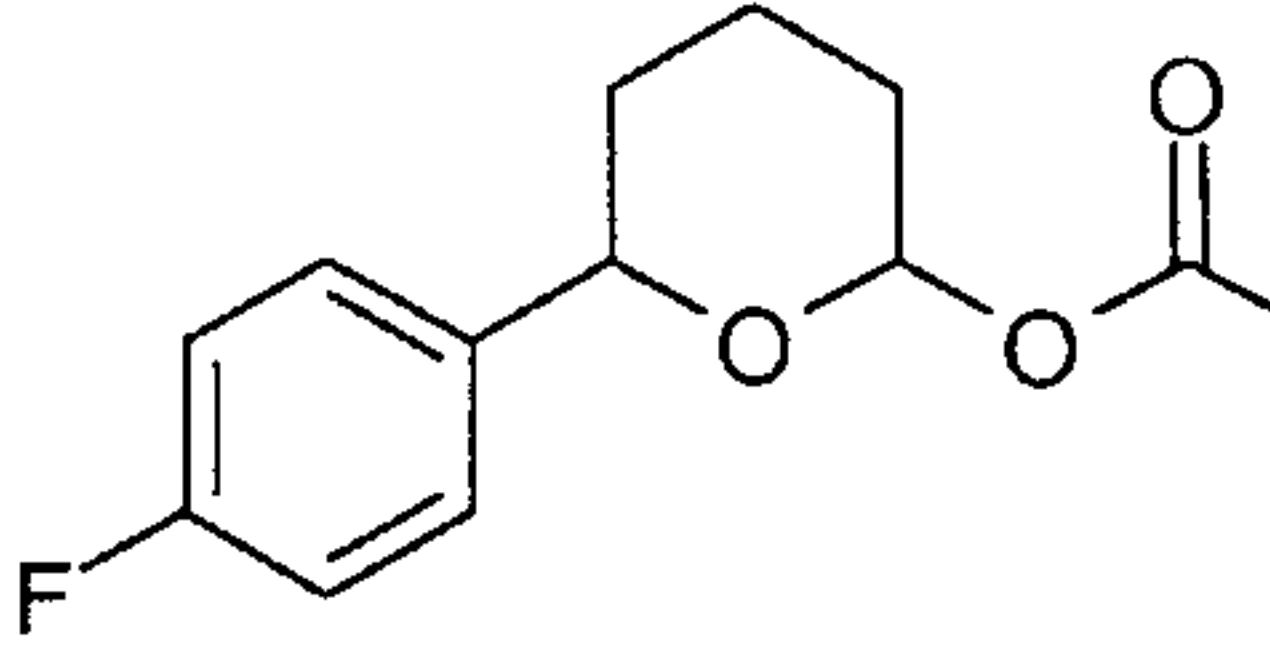
A solution of intermediate 7a (4.38 mg, 3.94 mmol) in 110 ml of dichloromethane was cooled to -78°C. Then, a 1M solution of diisobutylaluminumhydride (46.15 ml, 46.15 mmol) in dichloromethane was added dropwise. The reaction mixture was stirred at -78°C for 120 min. The conversion into the lactol intermediate was confirmed by GC-MS analysis of a sample of the reaction mixture treated with water and extracted with dichloromethane. 100 ml of methanol was added at -78°C and the reaction mixture was allowed to reach room temperature. The reaction mixture was concentrated under vacuum and the crude product obtained was triturated with ethyl ether. The precipitate was filtered off and washed with ethyl ether. The organic layer was removed under vacuum to give the crude lactol (4.4g, 22.9 mmol). The lactol was dissolved in 80 ml of dry dichloromethane and cooled to 0°C. Then triethylamine (4.96 ml, 34.33 mmol), acetic anhydride (2.54 ml, 27.46 mmol) and 4-dimethylaminopyridine (279.59 mg, 2.29 mmol) were added. The reaction mixture was allowed to reach room temperature and stirred for 1h. A saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with dichloromethane. The organic phase was dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (Biotage SP1 cartridge 50g, eluent: cyclohexane/ethyl acetate=95/5) to give desired product (4 g, 17.1 mmol).

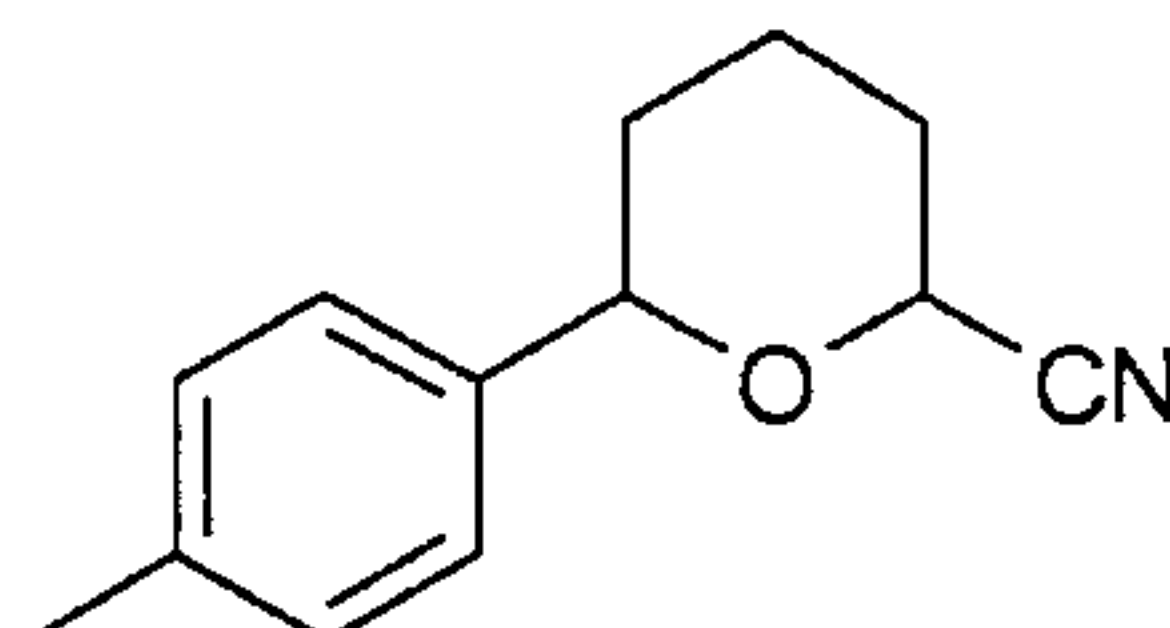
The following intermediates were synthesized in analogy to Intermediates 7a and 8a.

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<i>synthesis in analogy to intermediate 7a</i>			<i>synthesis in analogy to intermediate 8a</i>	
Starting Hydroxy-acid Intermediate	Lactone Intermediate	STRUCTURE	Lactol-acetate Intermediate	STRUCTURE
6b	7b		8b	
6c	7c		8c	
6d	7d		8d	
6e	7e		8e	
6f	7f		8f	
6g	7g		8g	

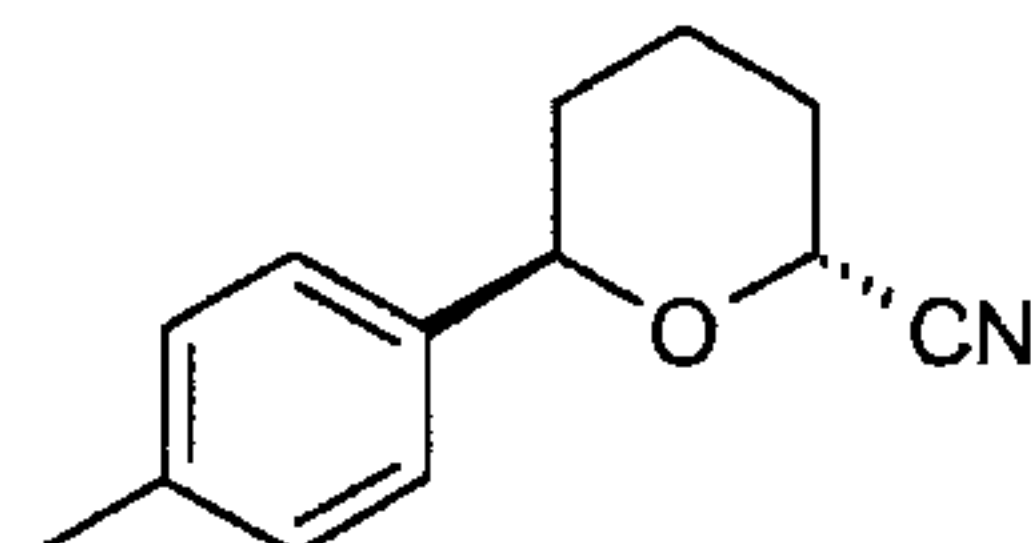
31214-7

6h	7h		8h	
6i	7i		8i	

Intermediate 9a

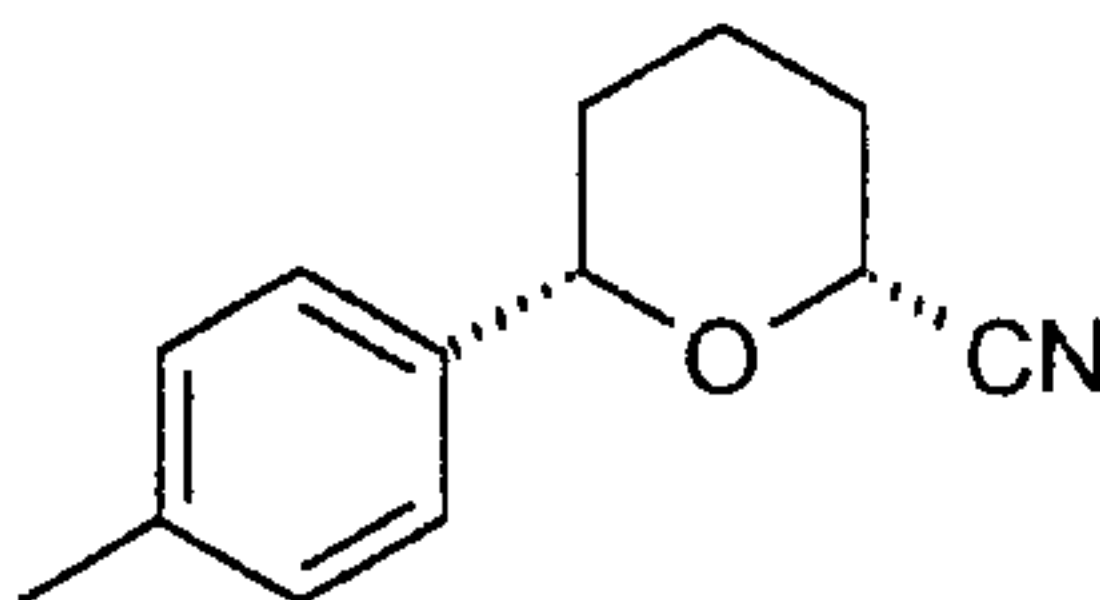
Trimethylsilylcyanide (0.52 ml, 4.16 mmol) and borontrifluoride etherate (0.27 ml, 2.22 mmol) were added to a solution of Intermediate 8a (650 mg, 2.77 mmol) in 50 ml of acetonitrile under nitrogen atmosphere at room temperature. The reaction mixture was stirred for 18h. The reaction mixture was concentrated under vacuum to give the desired product (mixture of diastereoisomers).

GC/MS (method 3A) R_t = 10.47 min and 10.68 min (diastereoisomeric mixture, ratio trans/cis = 8/2)

Intermediate 10a

Intermediate 9a was purified by flash chromatography (Biotage SP1 cartridge 25g, eluent: cyclohexane/ethyl acetate=99/1). 400 mg of diastereomerically pure trans stereoisomer was obtained (racemate, relative configuration assigned by NMR).

GC/MS (method 3A) R_t = 10.47 min

Intermediate 11a

Further elution of the column gave 100 mg of the diastereomerically pure cis stereoisomer (racemate, relative configuration assigned by NMR).

GC/MS (method 3A) R_t = 10.68 min

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Intermediate 11a was also obtained by epimerization of Intermediate 10a: Intermediate 10a (3.2 g, 15 mmol) was dissolved in 40 ml of tetrahydrofurane. Potassium tert-butoxide (178 mg, 1 mmol) was added and the reaction mixture was stirred at room temperature for 0.5h. The solid was removed by filtration and the reaction mixture was concentrated under vacuum.

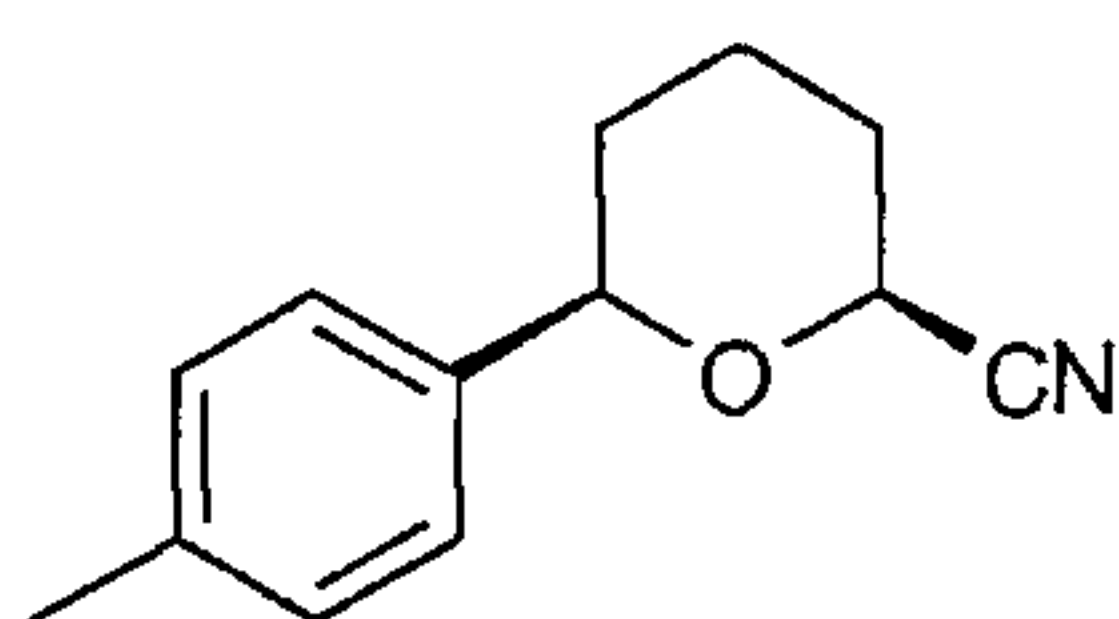
- 5 The crude product was purified by flash chromatography (Biotage SP1 cartridge 50g, eluent: cyclohexane/ethyl acetate=99/1). 1.45 g of the desired cis diastereoisomer was obtained.

The following intermediates were synthesized in analogy to Intermediates 9a, 10a and 11a.

<i>synthesis in analogy to intermediate 9a</i>			<i>synthesis in analogy to intermediate 10a</i>		<i>synthesis in analogy to intermediate 11a</i>	
Starting Lactol-acetate Intermediate	Intermediate	STRUCTURE	Intermediate	STRUCTURE	Intermediate	STRUCTURE
8b	9b		10b		11b	
8c	9c		10c		11c	
8d	9d		10d		11d	
8e	9e		10e		11e	

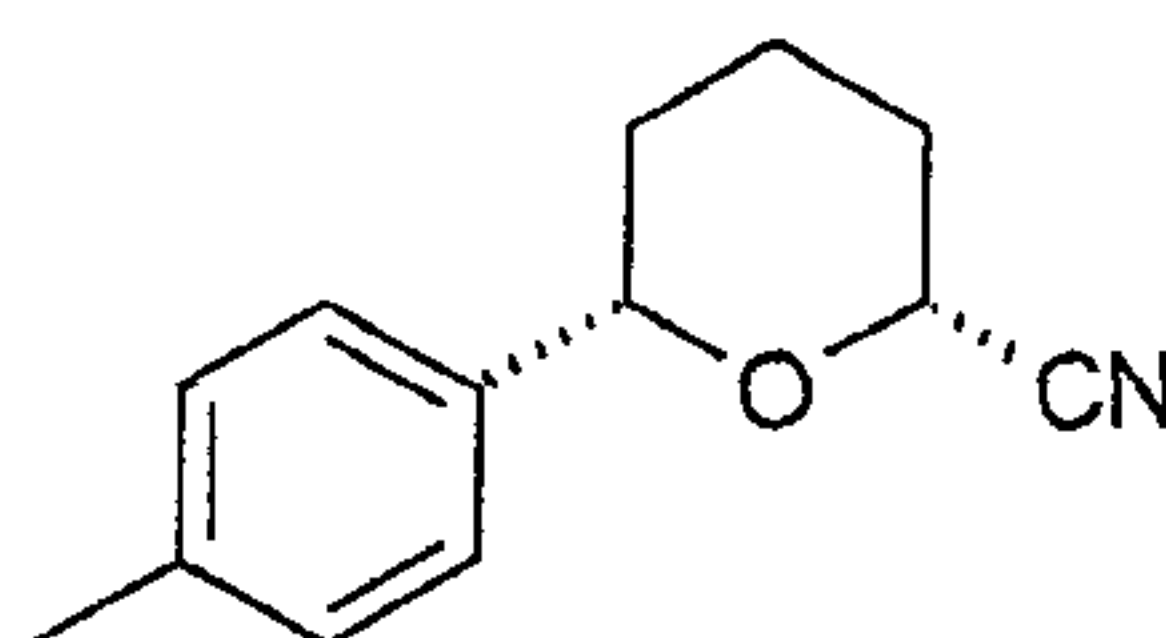
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8f	9f		10f		11f	
8g	9g		10g		11g	
8h	9h		10h		11h	
8i	9i					

Intermediate 12a

5 Racemic Intermediate 11a (1.17 g, 2.06 mmol) was separated by chiral HPLC (semi-preparative column). 400 mg (1.99 mmol) were obtained as single stereoisomer.

Chiral HPLC (method 2Ia isocratic): $R_t = 8.74$ min

Intermediate 13a

10 Further elution of the column gave 390 mg (1.94) of the corresponding single enantiomer.

Chiral HPLC (method 2Ia isocratic): $R_t = 9.06$ min

Absolute stereochemistry was determined by X-ray crystallography :

Absolute stereochemistry was derived from the refinement of anomalous dispersion data.

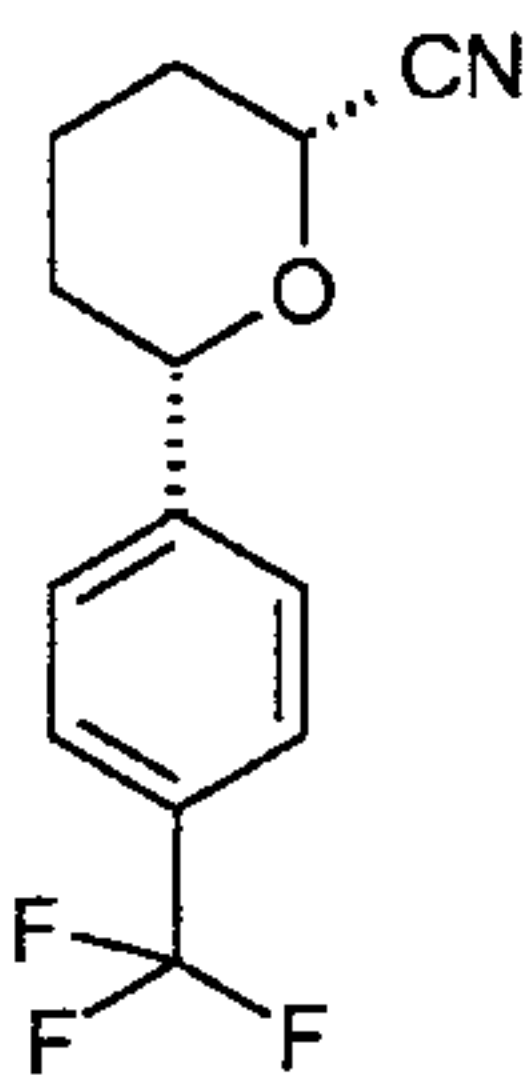
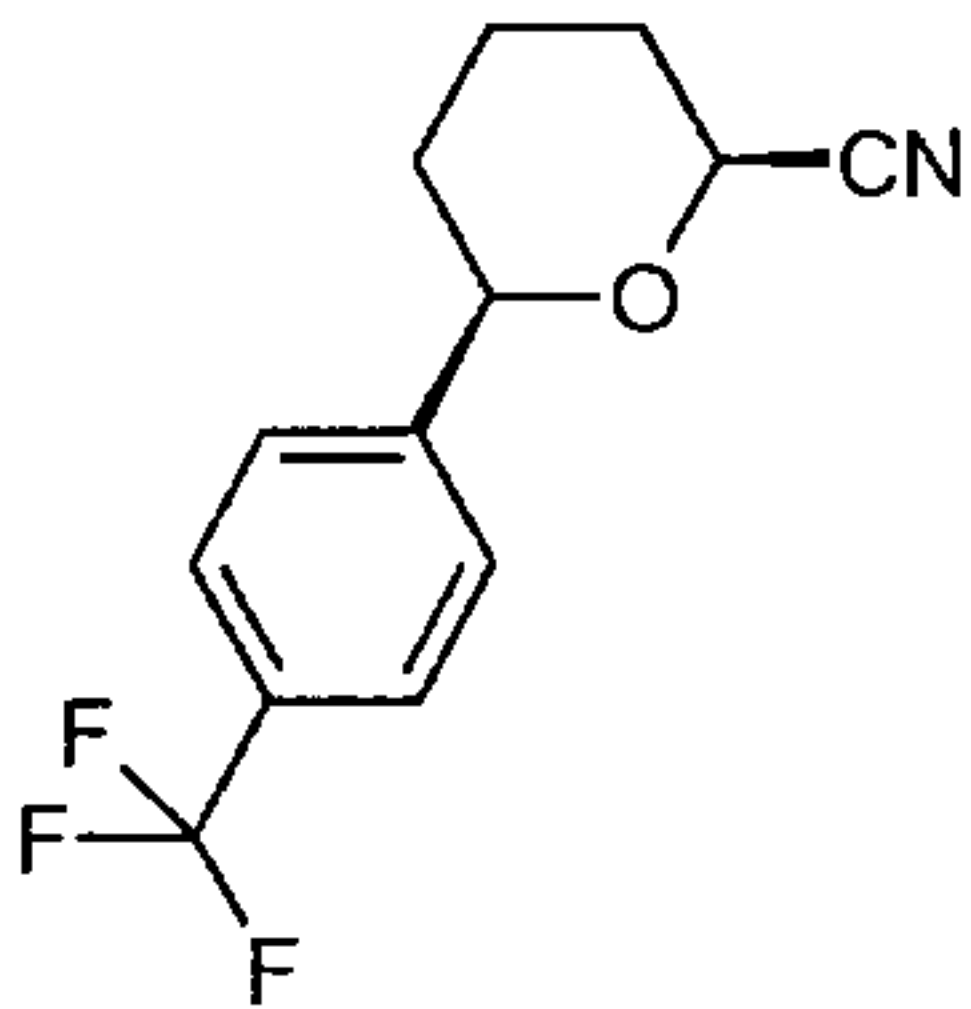
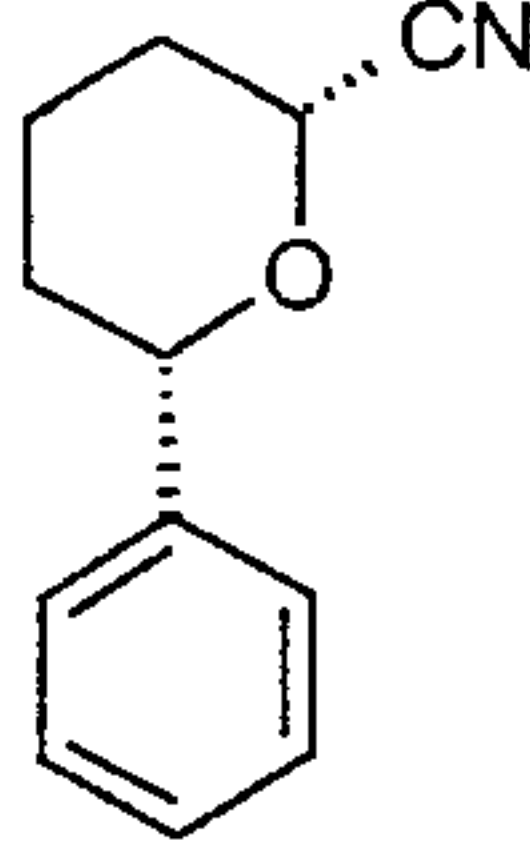
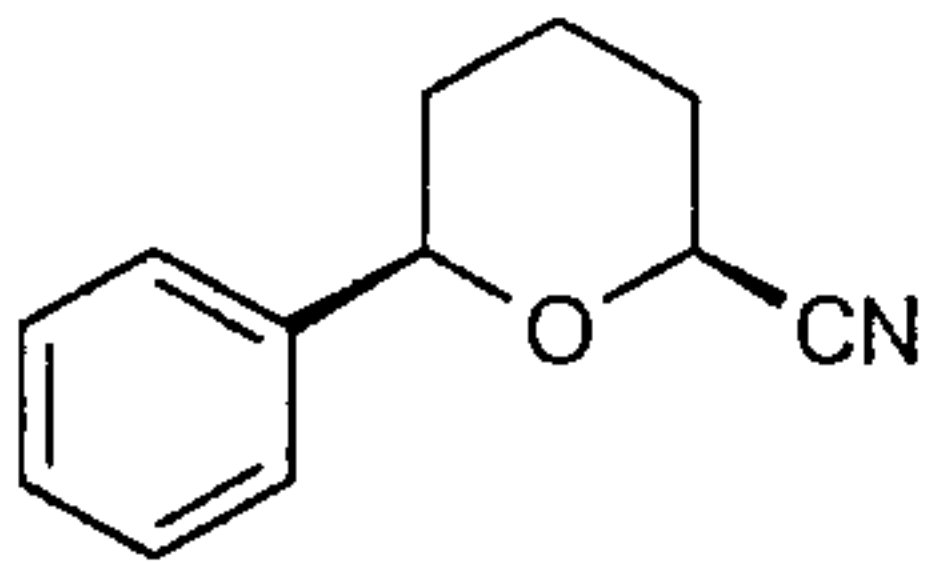
15 While an unambiguous assignment is not possible due to the lack of heavy atoms, the Flack parameter gave a clear tendency toward the indicated chiral configuration.

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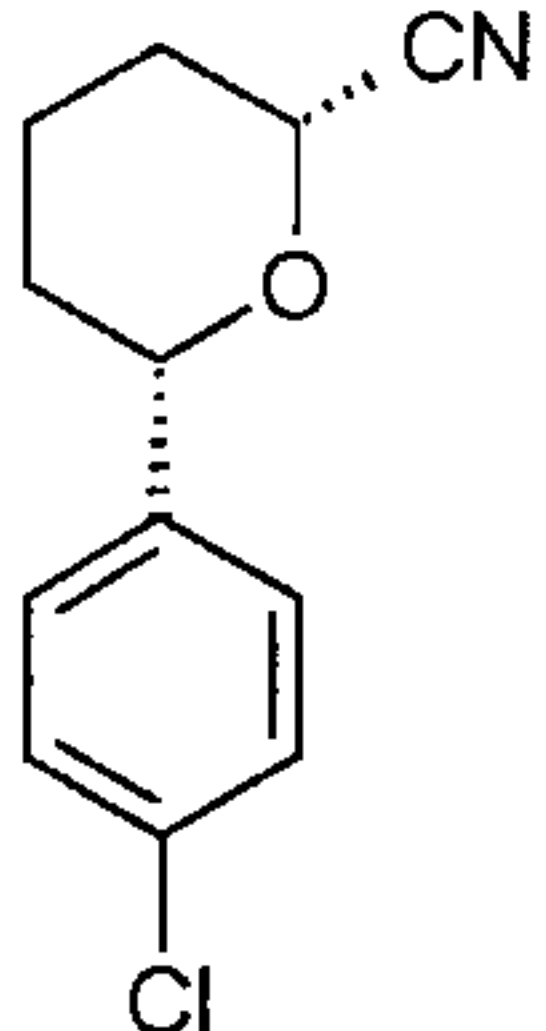
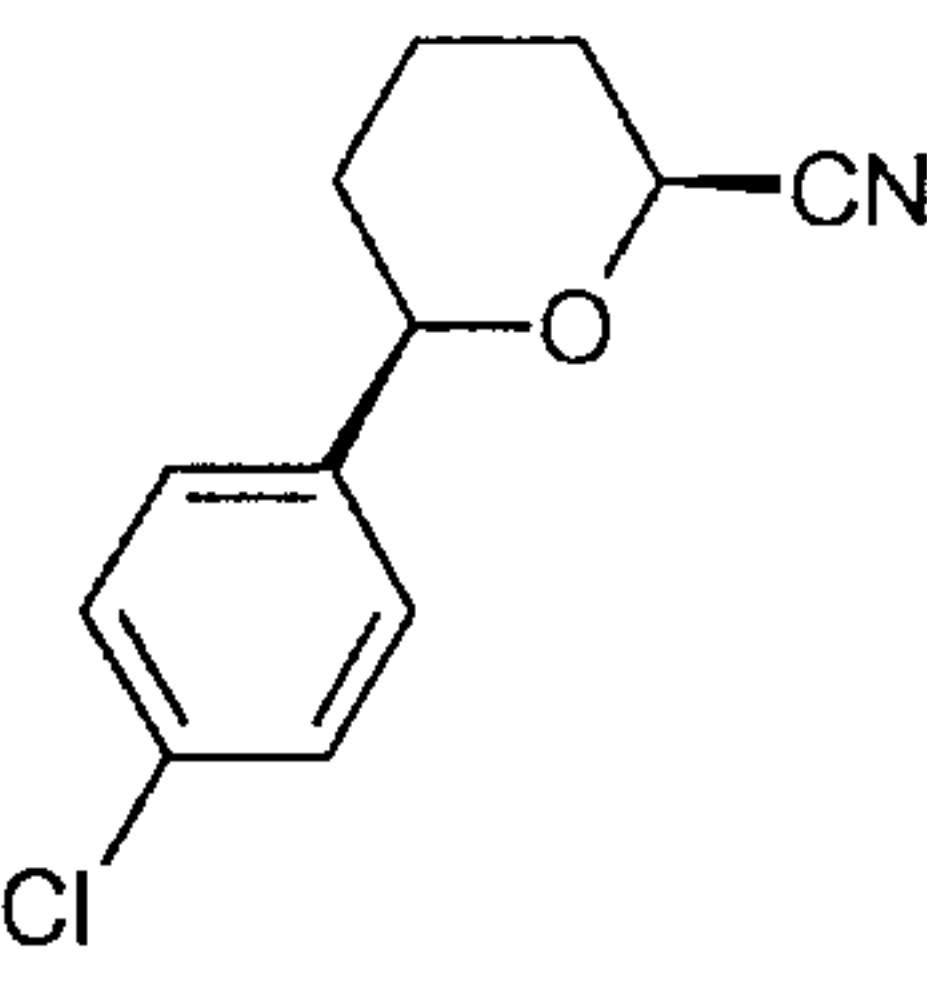
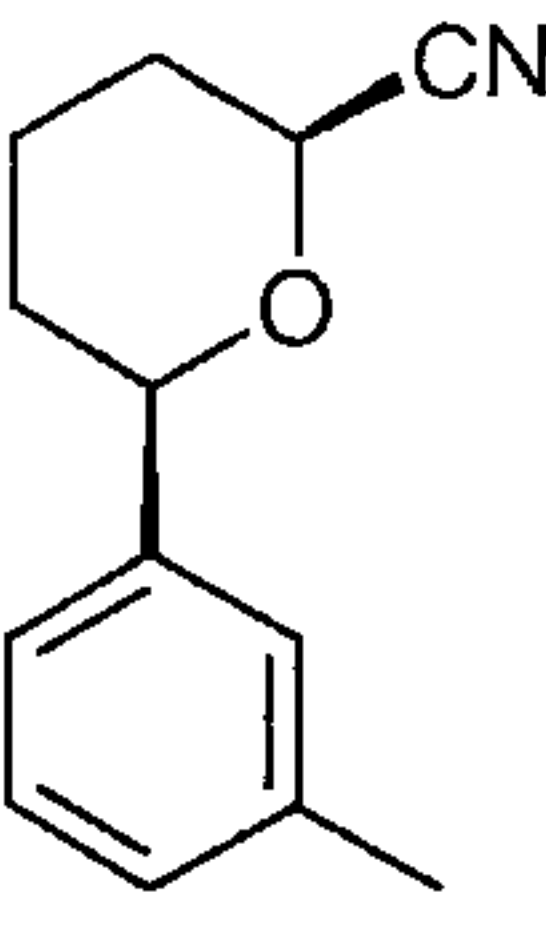
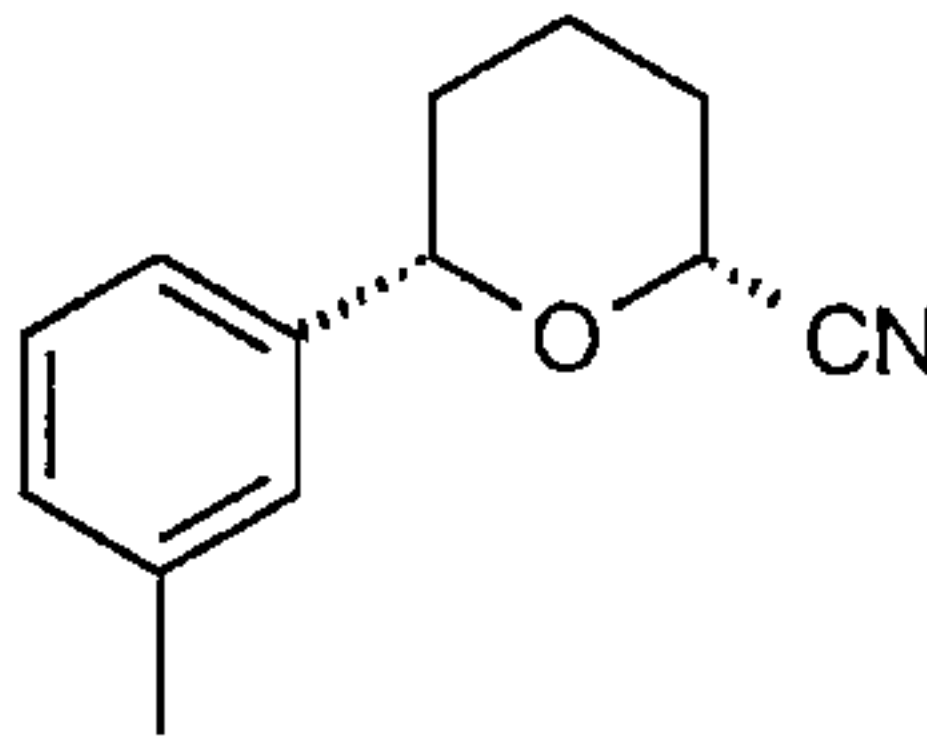
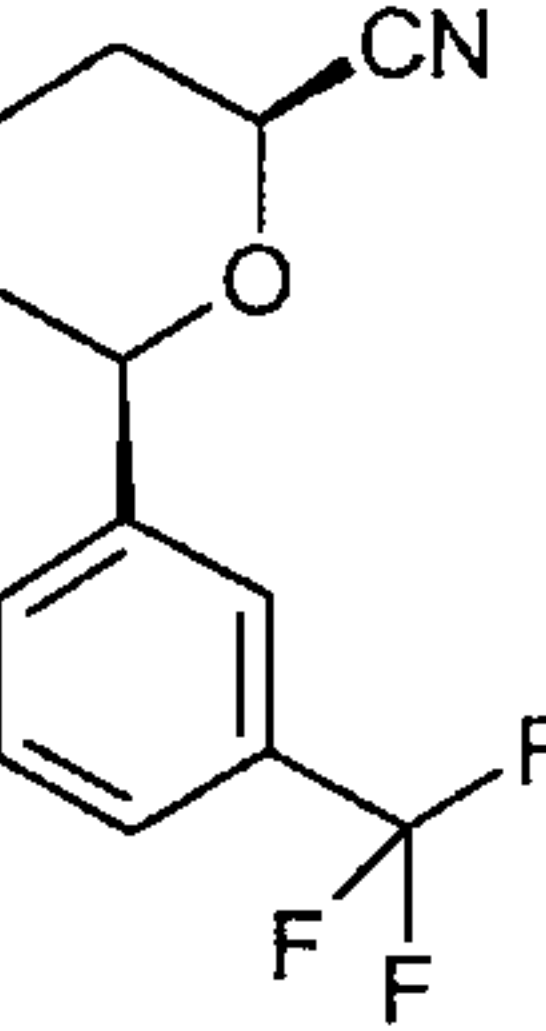
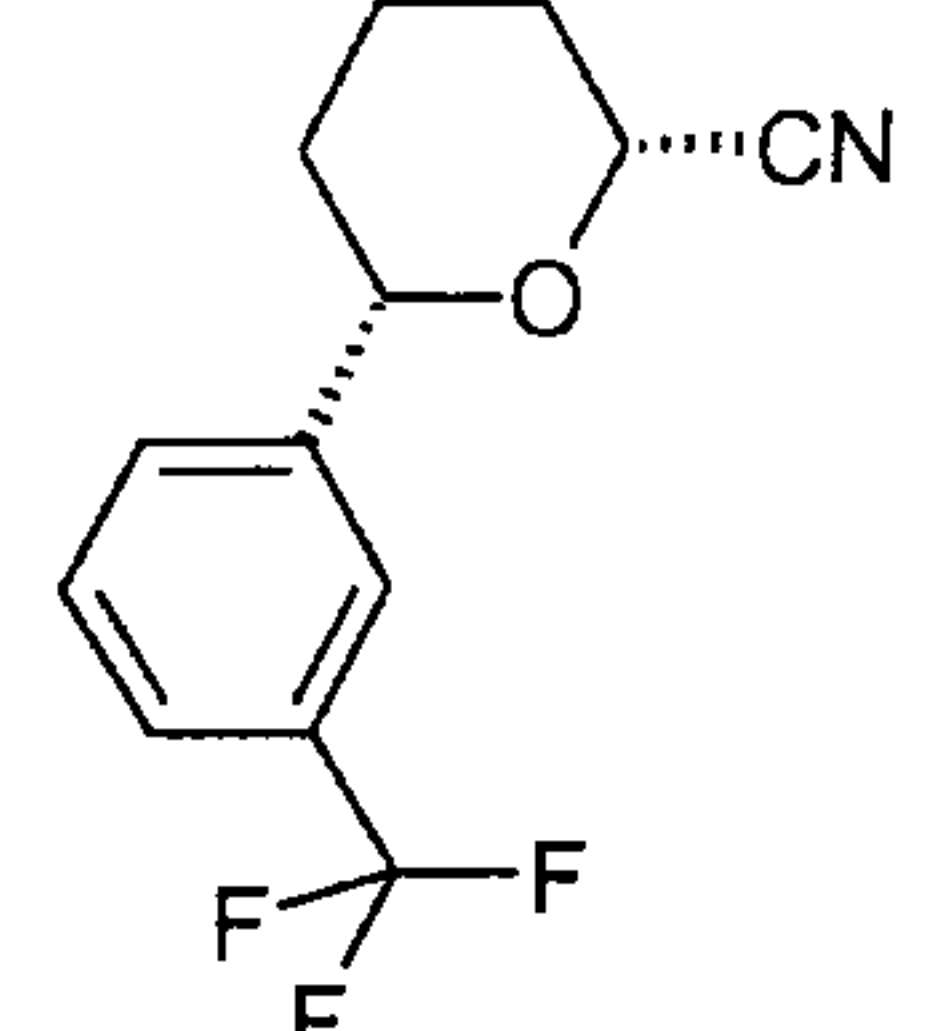
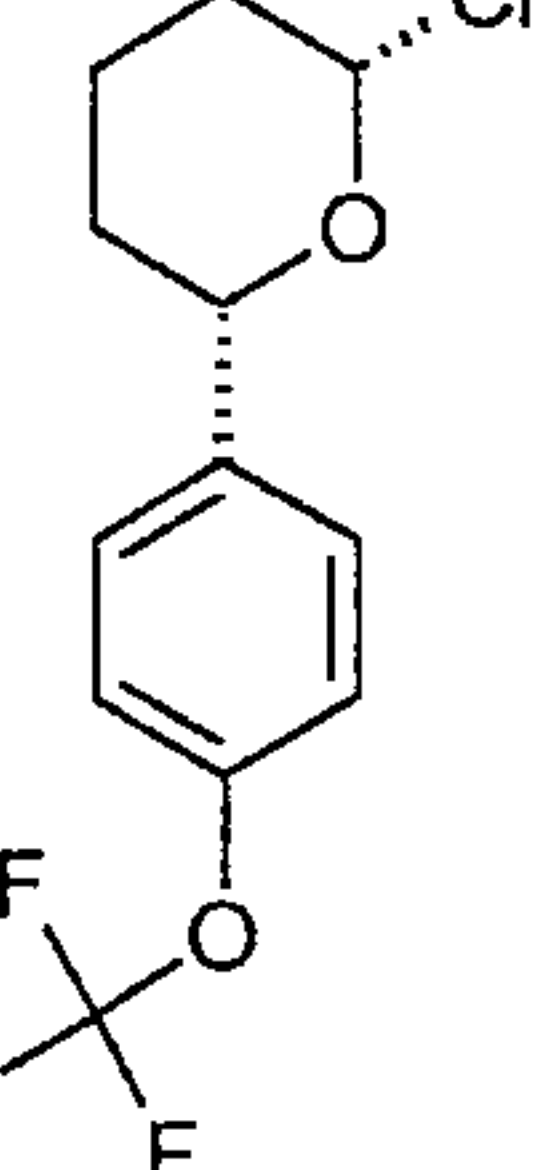
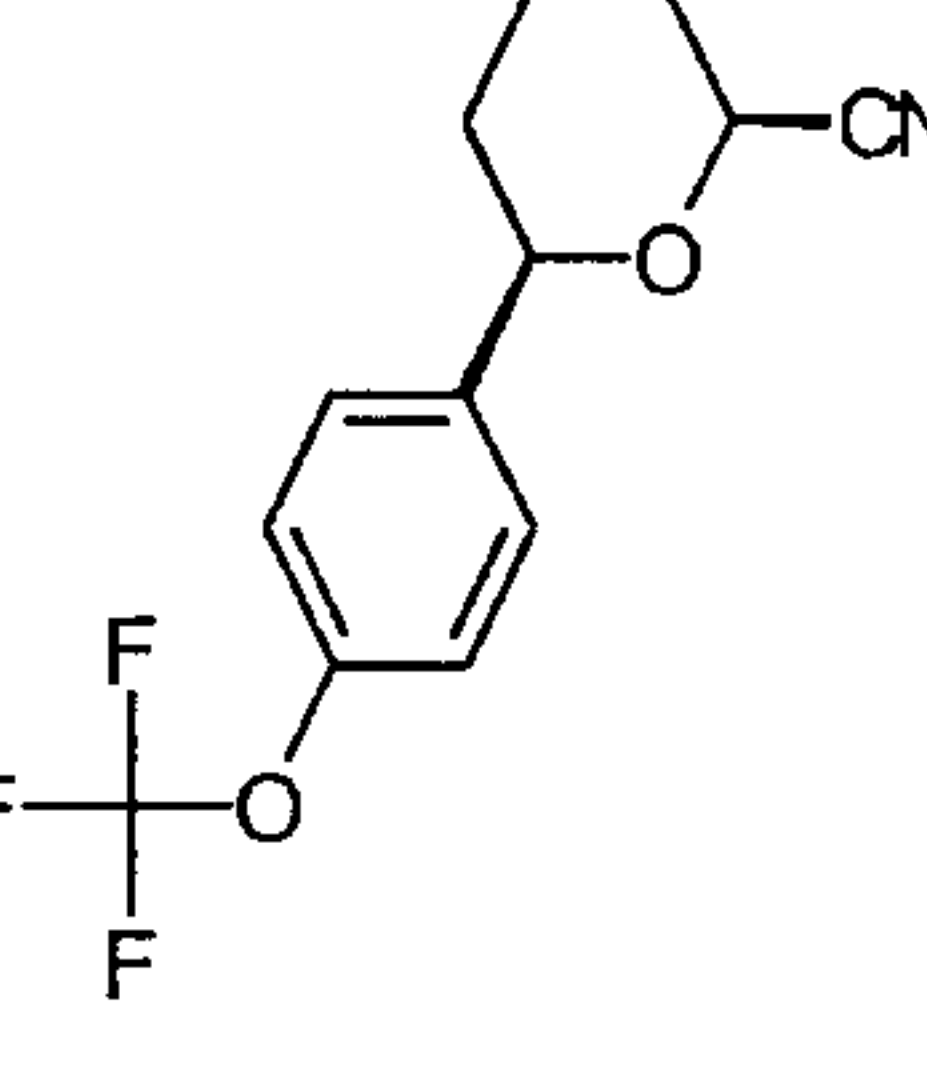
Crystal Data: $C_{13}H_{15}N_1O_1$ $M_r = 201.26$, orthorhombic, $P2_12_12_1$, $a=8.0519(16)\text{\AA}$, $b=11.185(2)\text{\AA}$, $c=12.637(3)\text{\AA}$, $V = 1138.2(4)\text{\AA}^3$, $Z = 4$, $D_x = 1.175\text{g/cm}^3$, $\mu = 1.542\text{\AA}$, $m = 0.58\text{mm}^{-1}$, $F(000) = 423$, $T = 100(1)\text{ K}$. Data Collection: 12235 measured reflections, 1888/1130 unique, $R_{\text{int}} = 0.079$. Refinement: 138 parameters; hydrogen atoms were included as riding atoms, $S = 1.02$, $R1 = 0.052$ for 1393 reflections with $F_o > 4\text{sig}(F_o)$, $wR = 0.128$ (Weight $w=1/[s^2(F_o^2)+(0.0864P)^2+0.0P]$ where $P=(F_o^2+2F_c^2)/3$, largest difference peak: $0.31\text{ e/\AA}^3$; largest difference hole $-0.22\text{ e/\AA}^3$, Flack= 0.2(5).

The following intermediates were separated in analogy to Intermediates 12a and 13a.

10

Starting syn-racemate	Chiral HPLC Method	First Single syn-stereoisomer	R_t (min)	STRUCTURE	Second Single syn-stereoisomer	R_t (min)	STRUCTURE	Stereochemistry
11b	2Ia	12b	13.25		13b	14.33		Absolute stereochemistry as shown*
11c	2J	12c	9.94		13c	10.84		relative stereochemistry cis

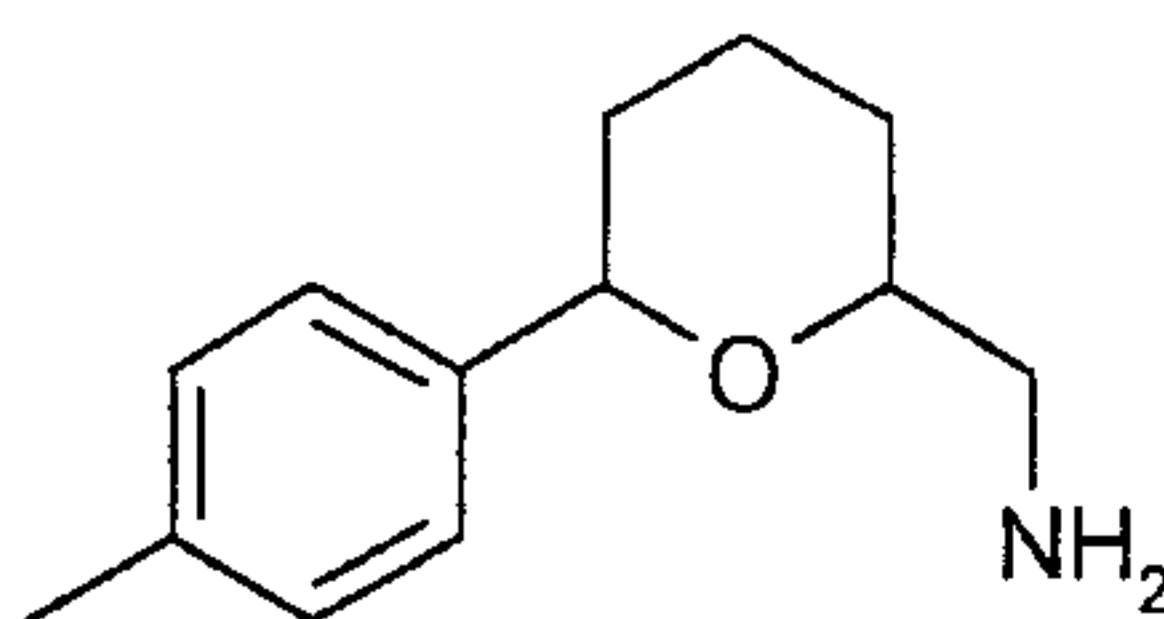
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11d	2K	12d	9.09		13d	9.76		relative stereochemistry cis
11e	2Ib	12e	7.23		13e	8.24		relative stereochemistry cis
11f	2K	12f	6.03		13f	6.67		relative stereochemistry cis
11h	2Ka	12h	13.65		13h	14.53		relative stereochemistry cis

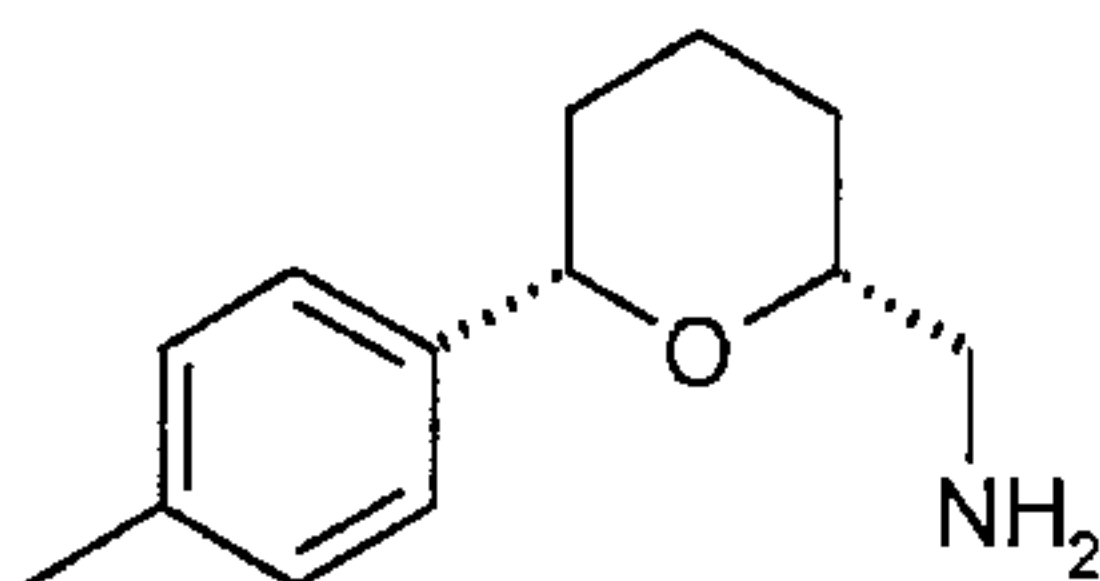
*Absolute stereochemistry for intermediate 12b was derived from the refinement of anomalous dispersion data for Intermediate 12b. While an unambiguous assignment is not possible due to the lack of heavy atoms, the Flack parameter gave a clear tendency toward the indicated chiral configuration.

Crystal Data: C₁₃ H₁₂ N₁ O₁ F₃, M_r = 255.24, orthorhombic, P2₁2₁2₁, a = 7.5726(15) Å, b = 11.053(2) Å, c = 14.173(3) Å, V = 1186.3(4) Å³, Z = 4, D_x = 1.429 g/cm³, μ = 1.542 Å⁻¹, m = 1.061 mm⁻¹, F(000) = 528, T = 100(1) K. Data Collection: 8980 measured reflections, 1900/1131 unique, R_{int} = 0.045. Refinement: 164 parameters; hydrogen atoms were included as riding atoms, S = 1.10, R₁ = 0.065 for 1710 reflections with Fo > 4sig(Fo), wR = 0.167 (Weight w = 1/[s²(Fo²) + (0.1147P)² + 1.0917P] where P = (Fo² + 2Fc²)/3, largest difference peak: 0.43 e/Å³; largest difference hole -0.39 e/Å³, Flack = 0.2(3).

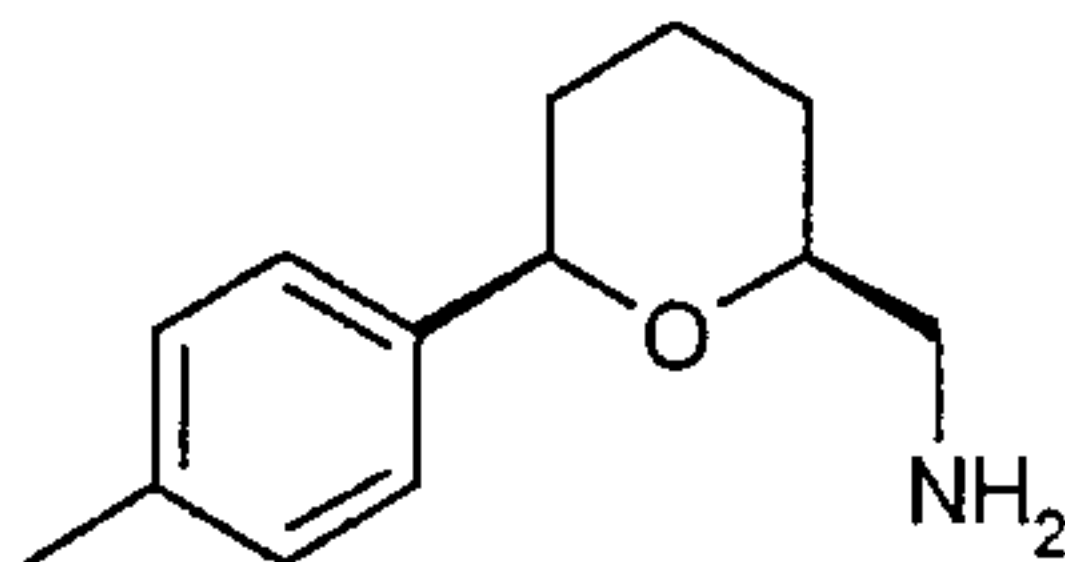
31214-7

Intermediate 14a

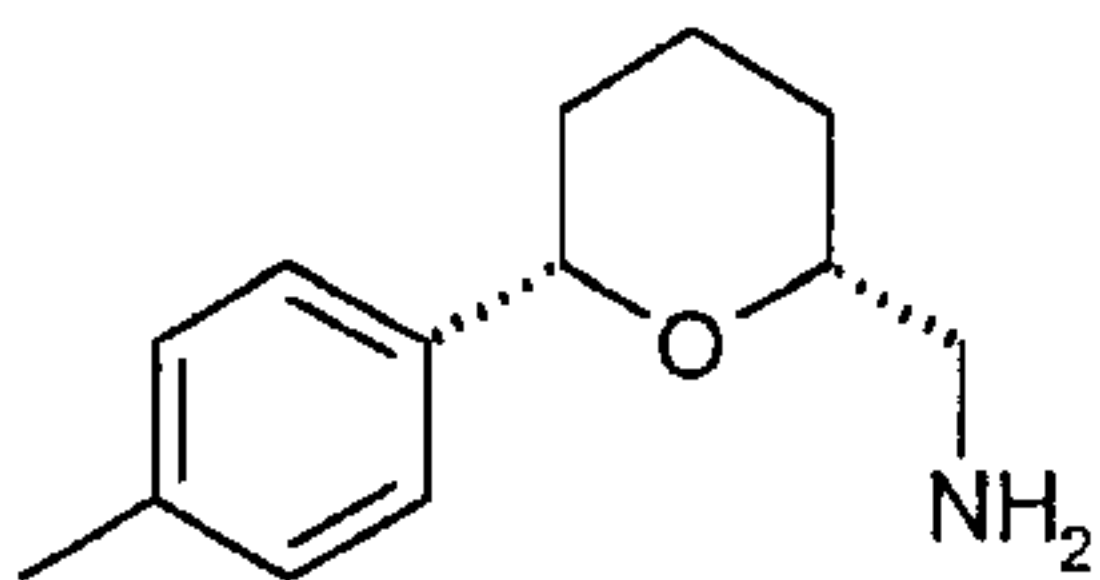
Intermediate 9a was dissolved in 20 ml of tetrahydrofurane, a 1M solution of borane-
 5 tetrahydrofurane complex (3.28 ml, 3.28 mmol) was added and the reaction mixture was
 stirred at room temperature for 18h. 20 ml of a saturated aqueous sodium bicarbonate solution
 and 50 ml of dicholometane were added. The organic layer was dried over magnesium sulfate
 and concentrated under vacuum. 90 mg (0.44 mmol) of the desired product were obtained.

Intermediate 15a

was synthesized in analogy to Intermediates 14a starting from intermediate 11a

Intermediate 16a

15 was synthesized in analogy to Intermediates 14a starting from intermediate 12a. Absolute
 stereochemistry known.

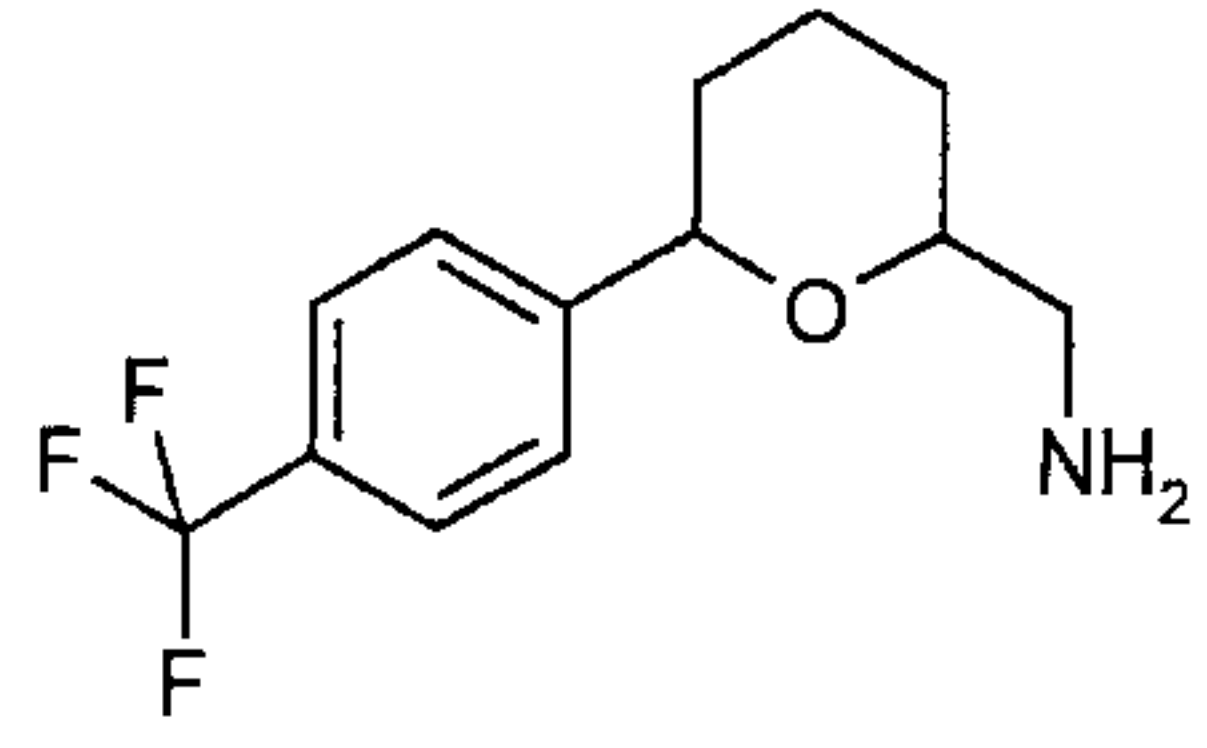
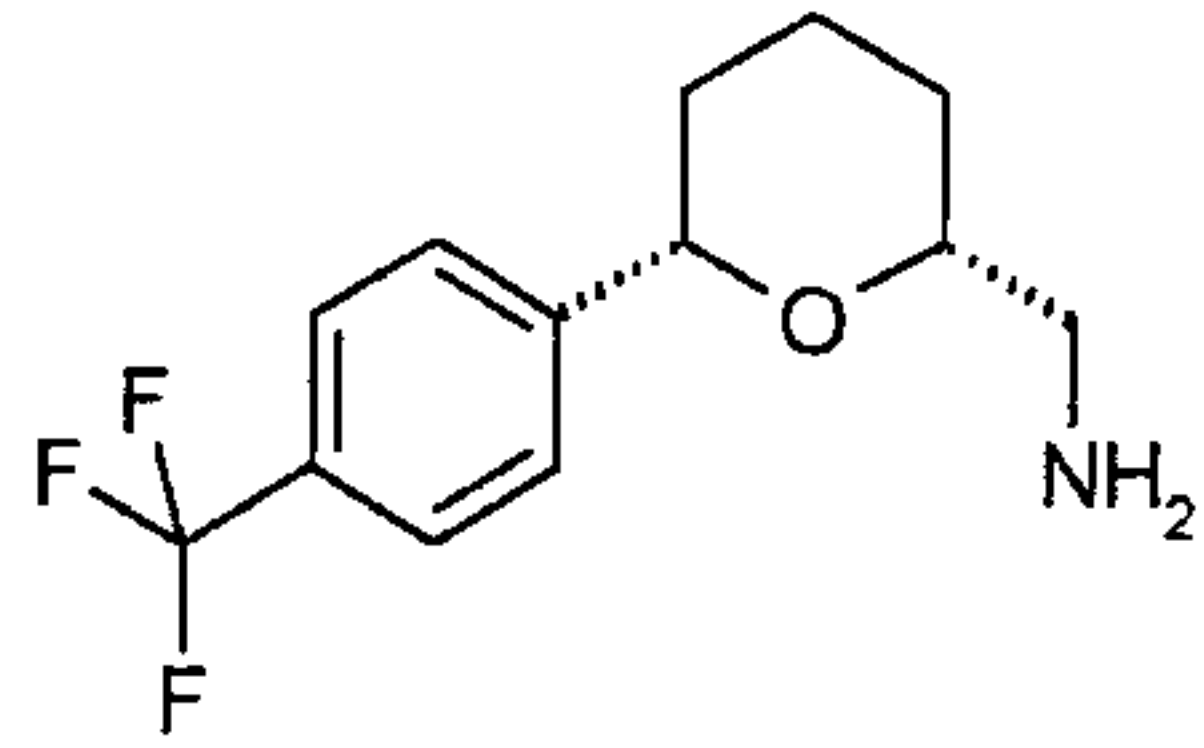
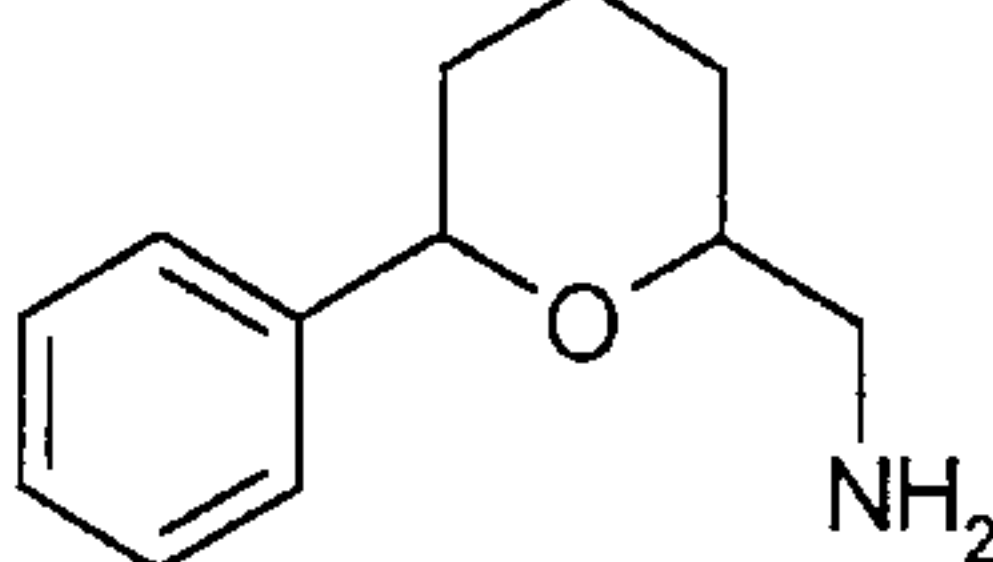
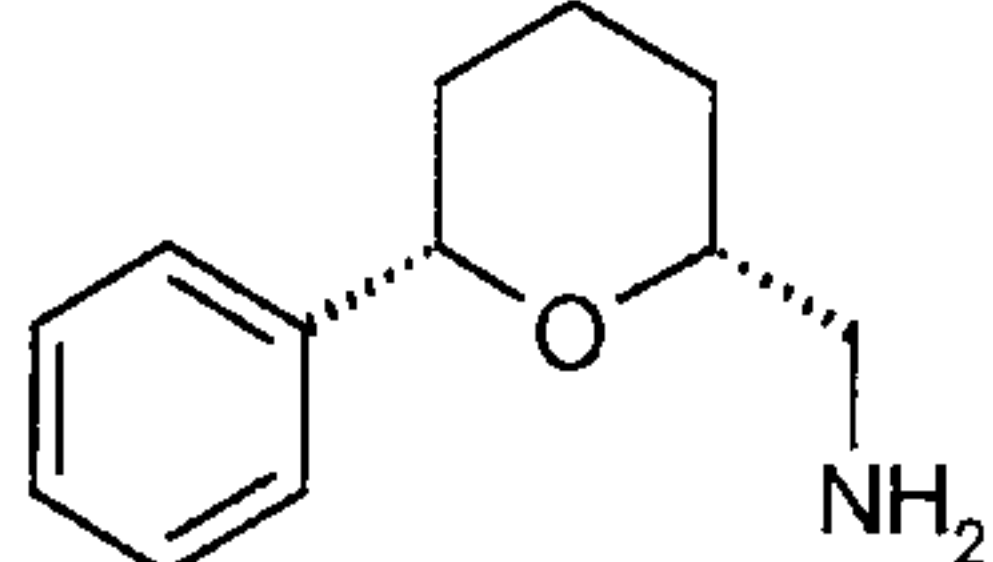
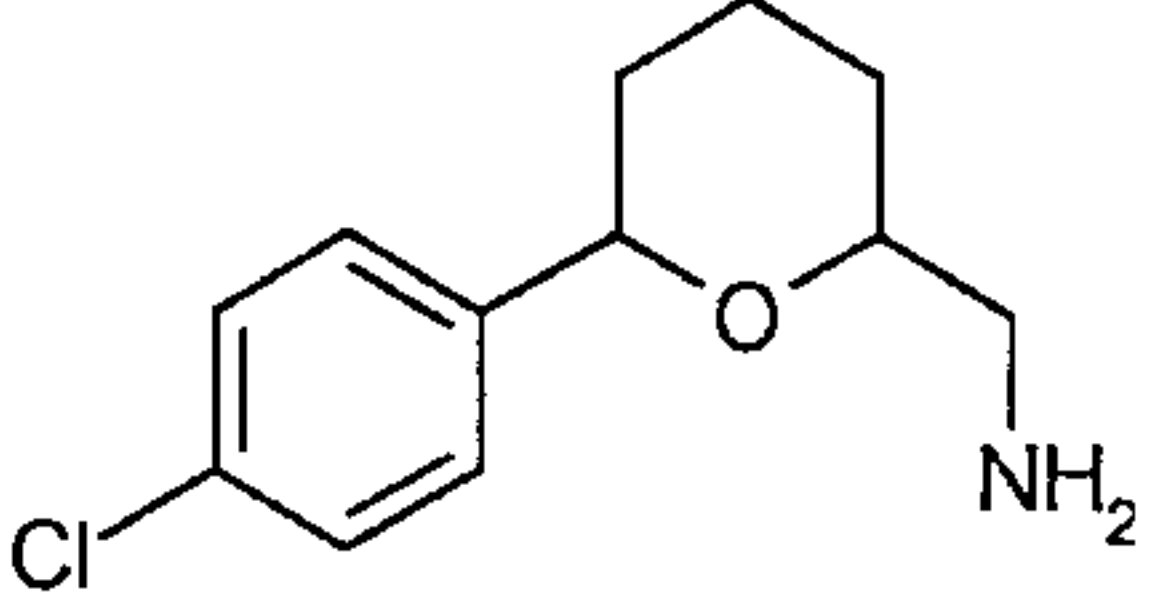
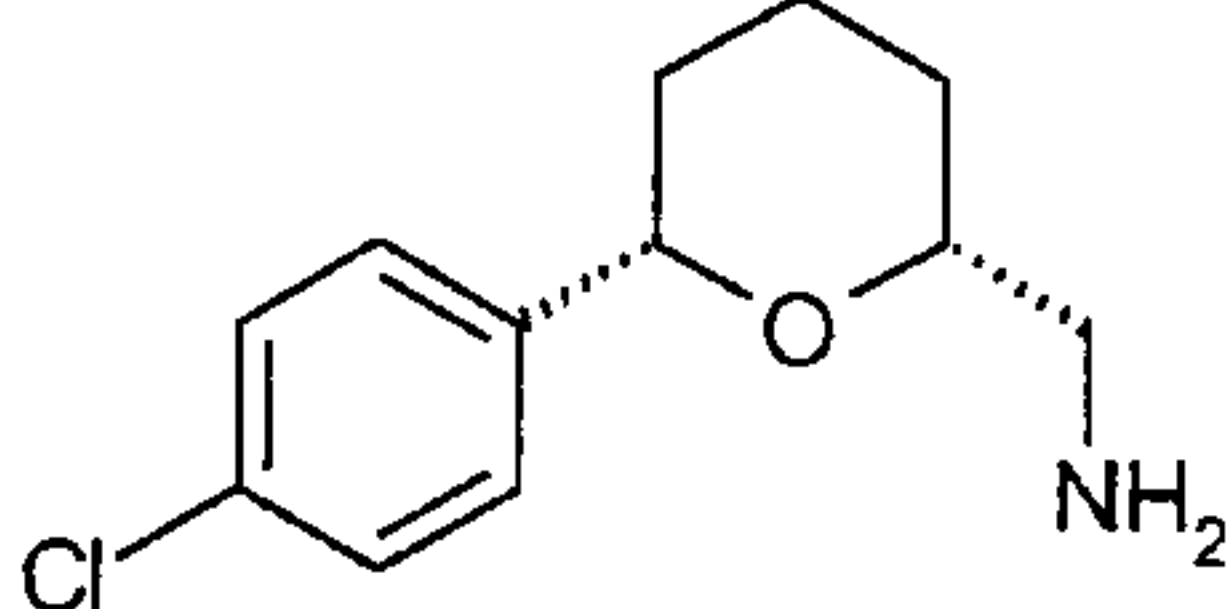
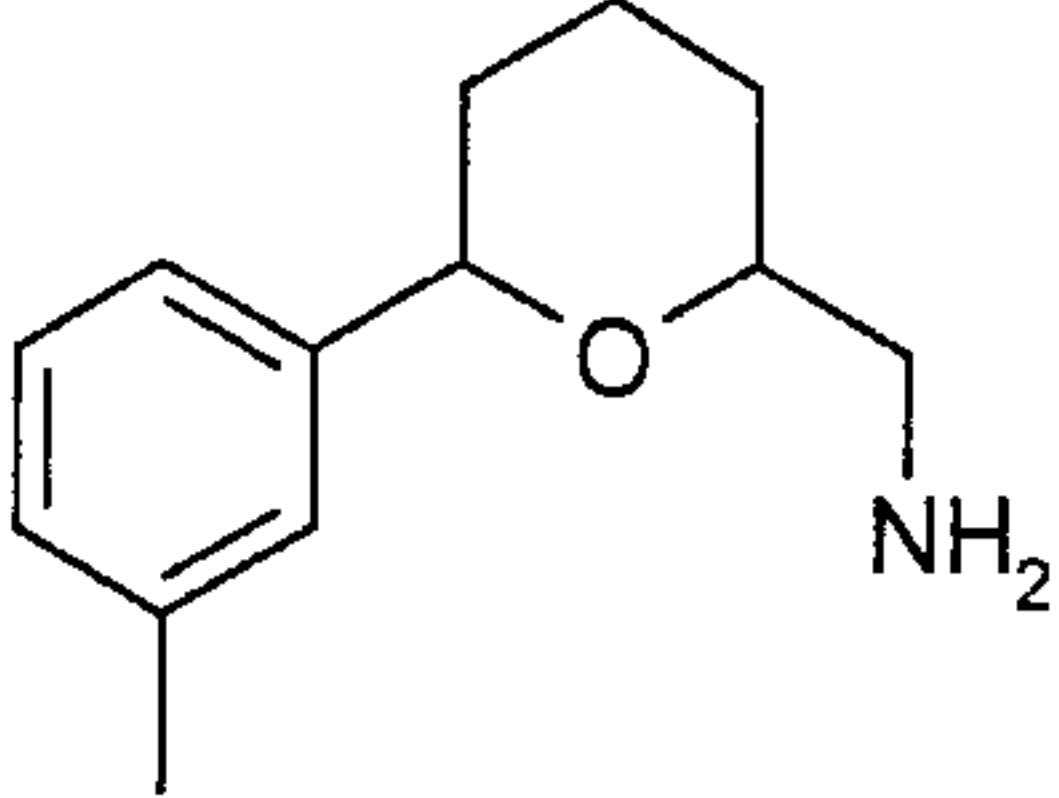
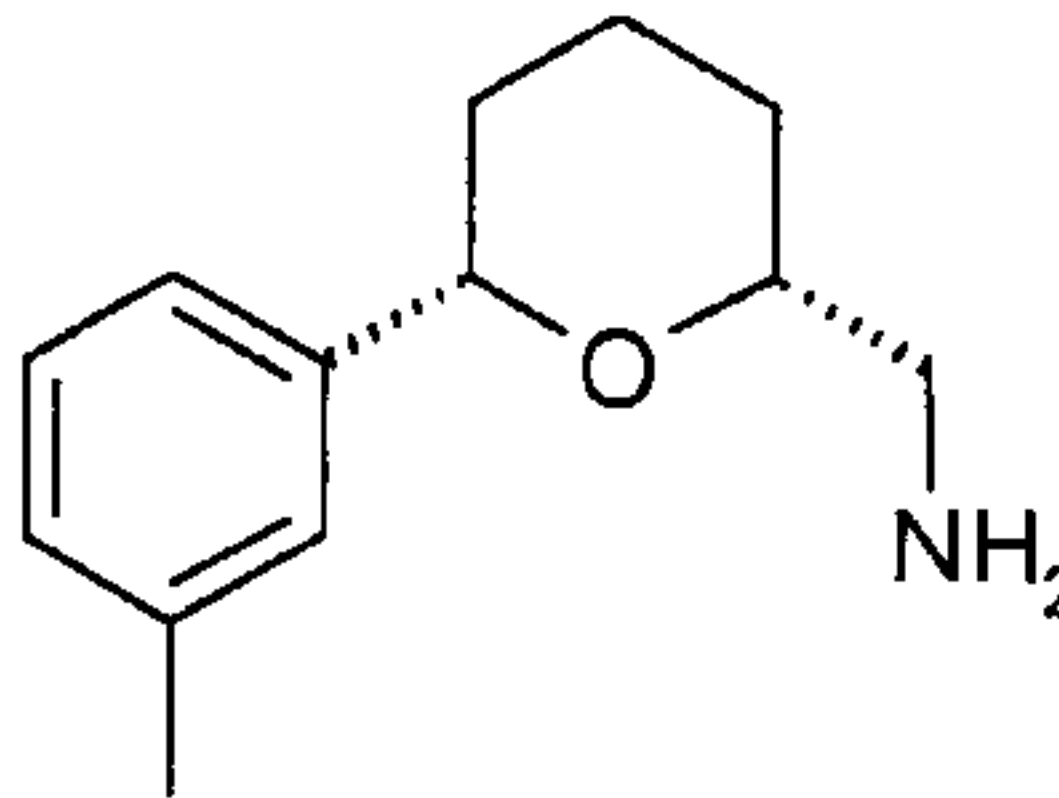
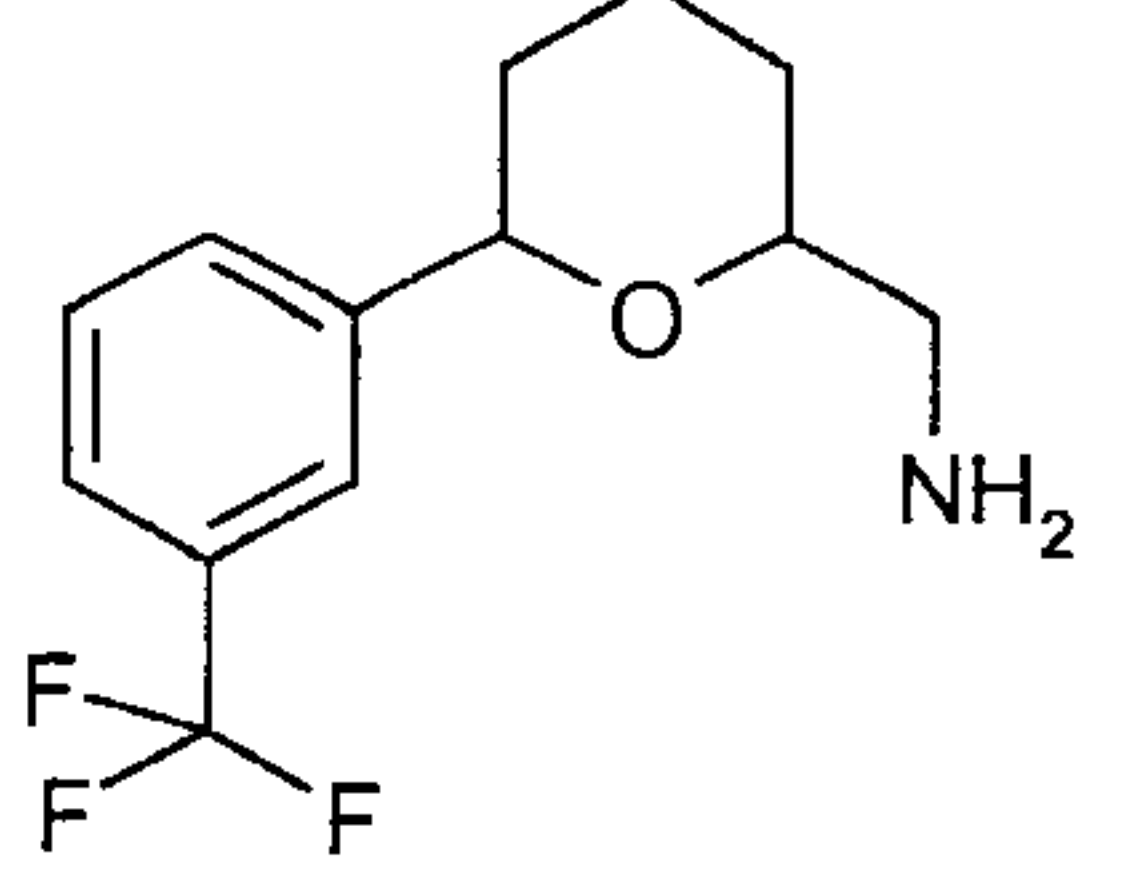
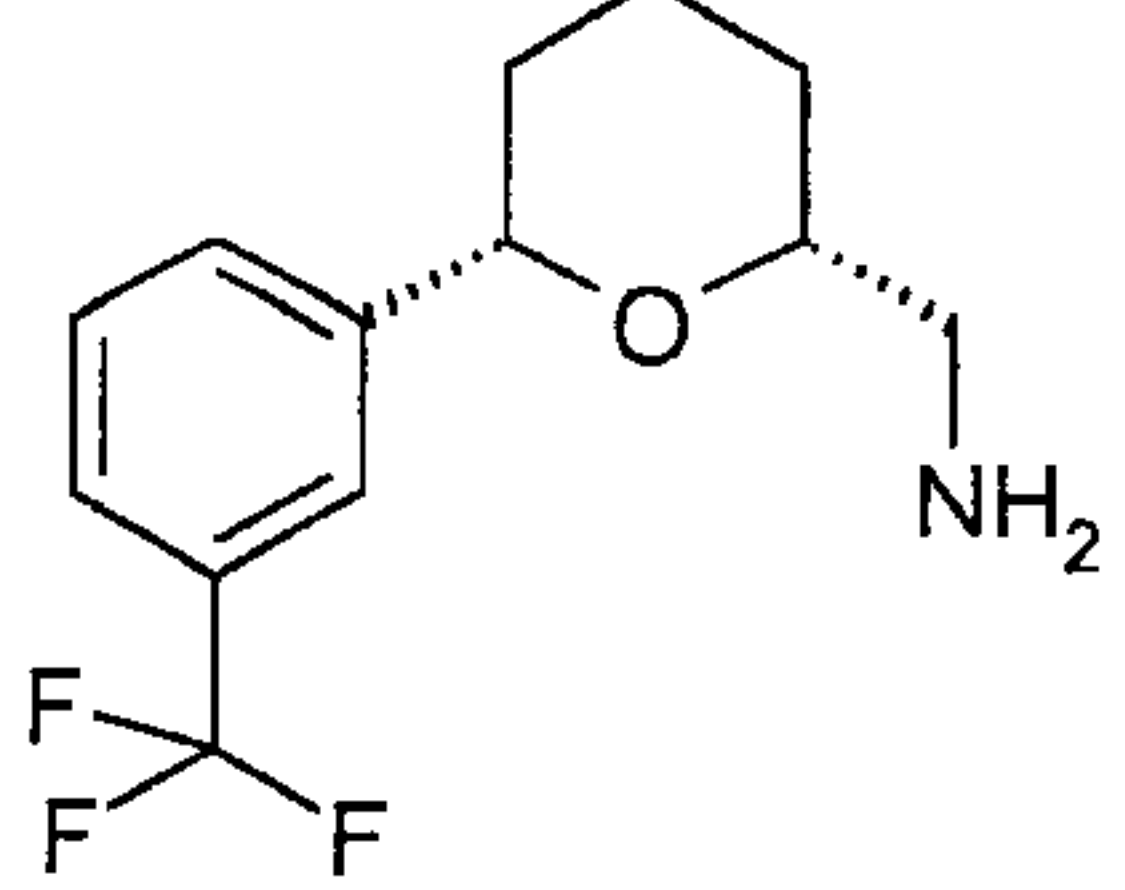
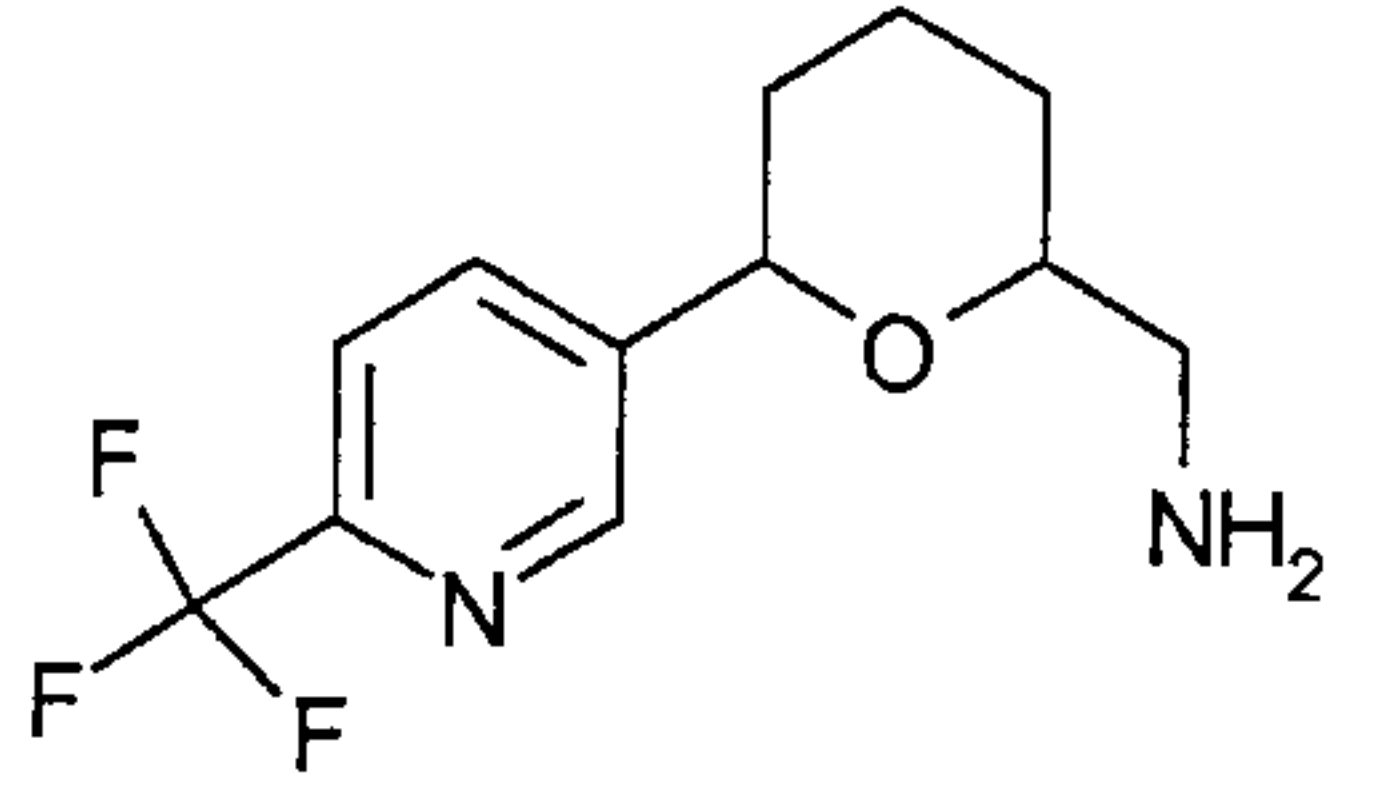
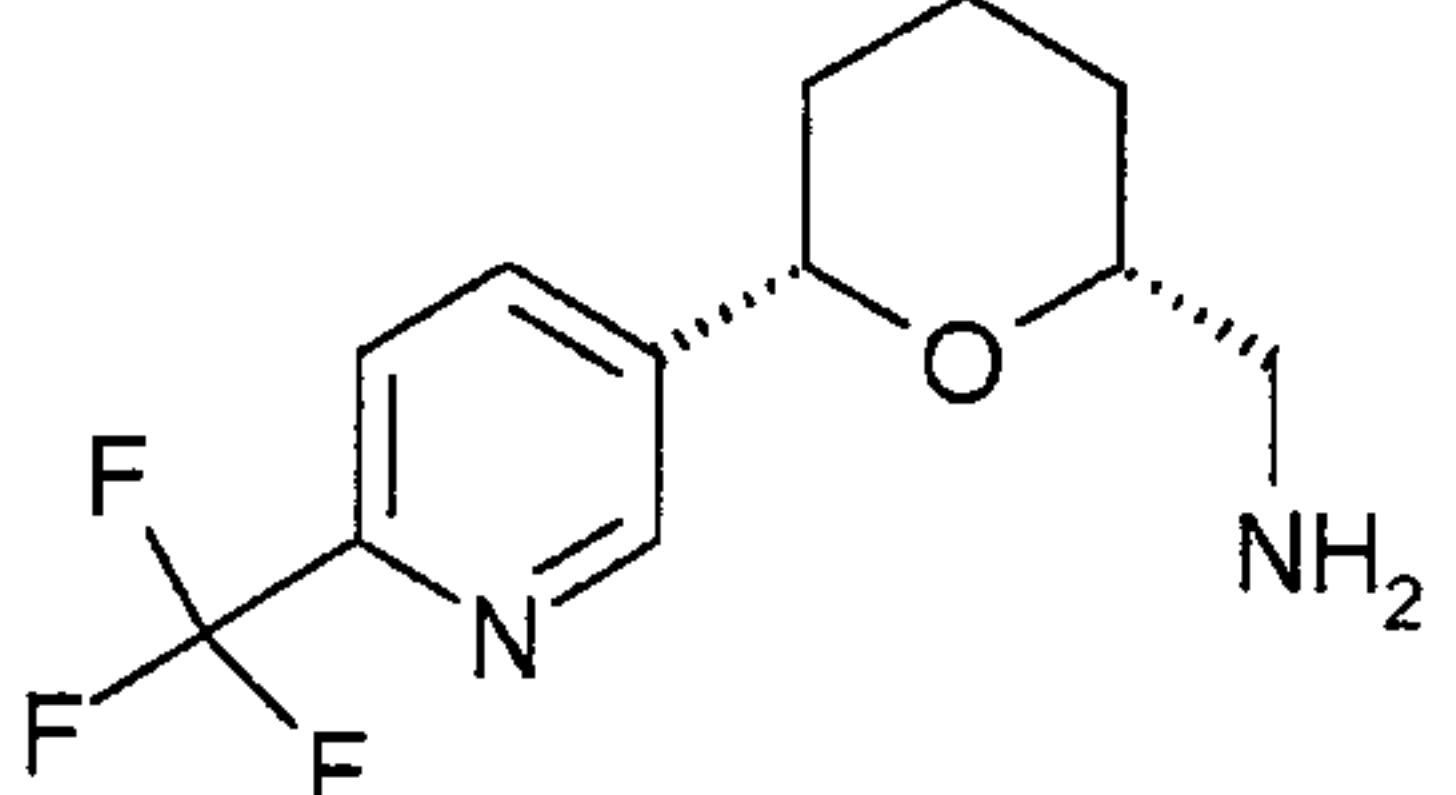
Intermediate 17a

20 was synthesized in analogy to intermediate 14a starting from intermediate 13a. Absolute
 stereochemistry known.

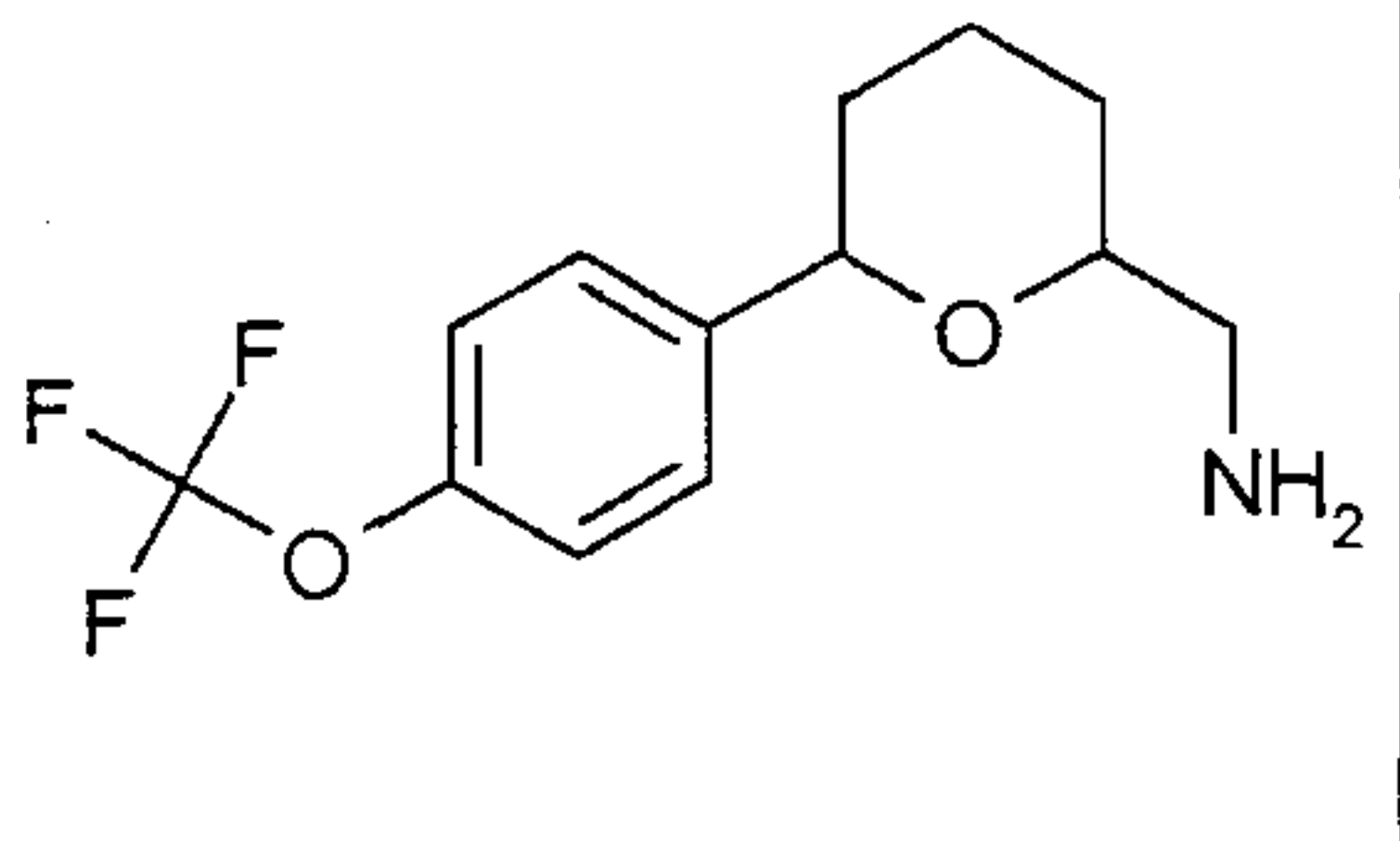
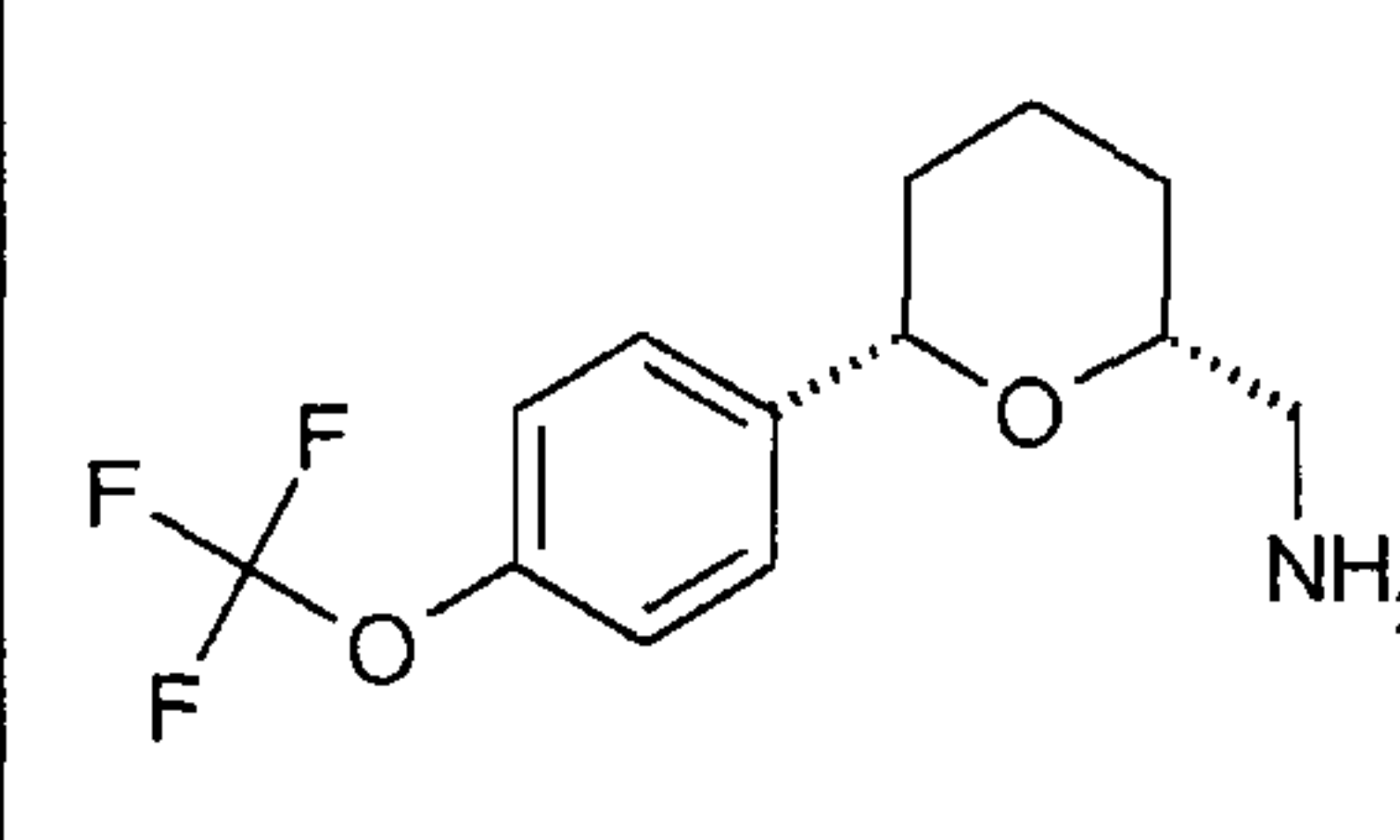
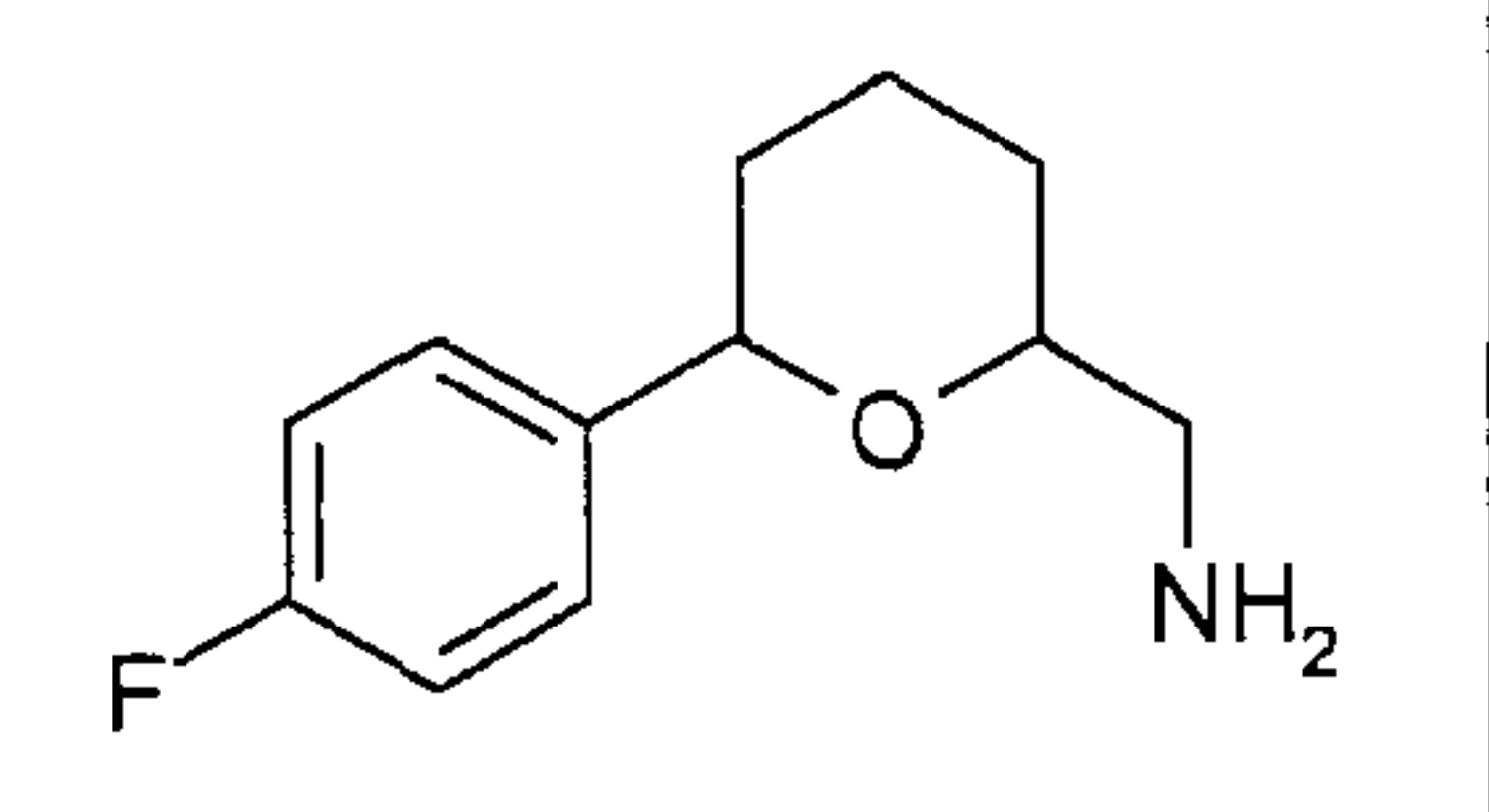
The following intermediates were synthesized in analogy to Intermediates 14a and 15a.

25

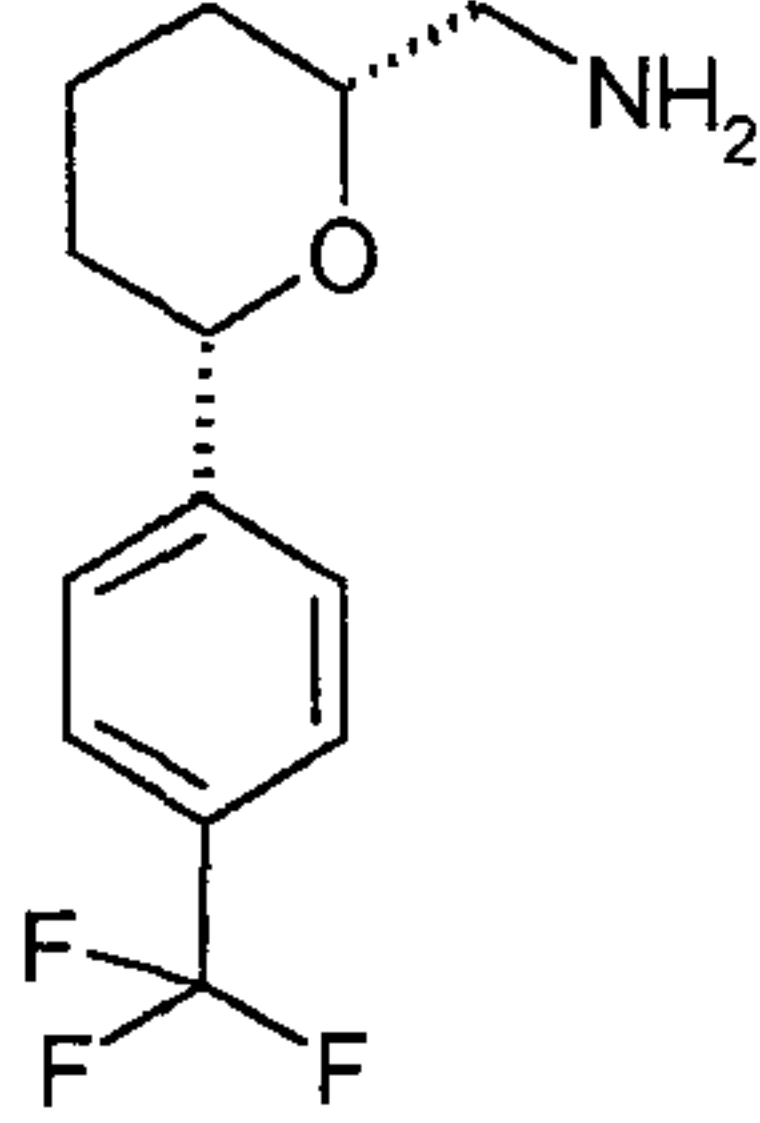
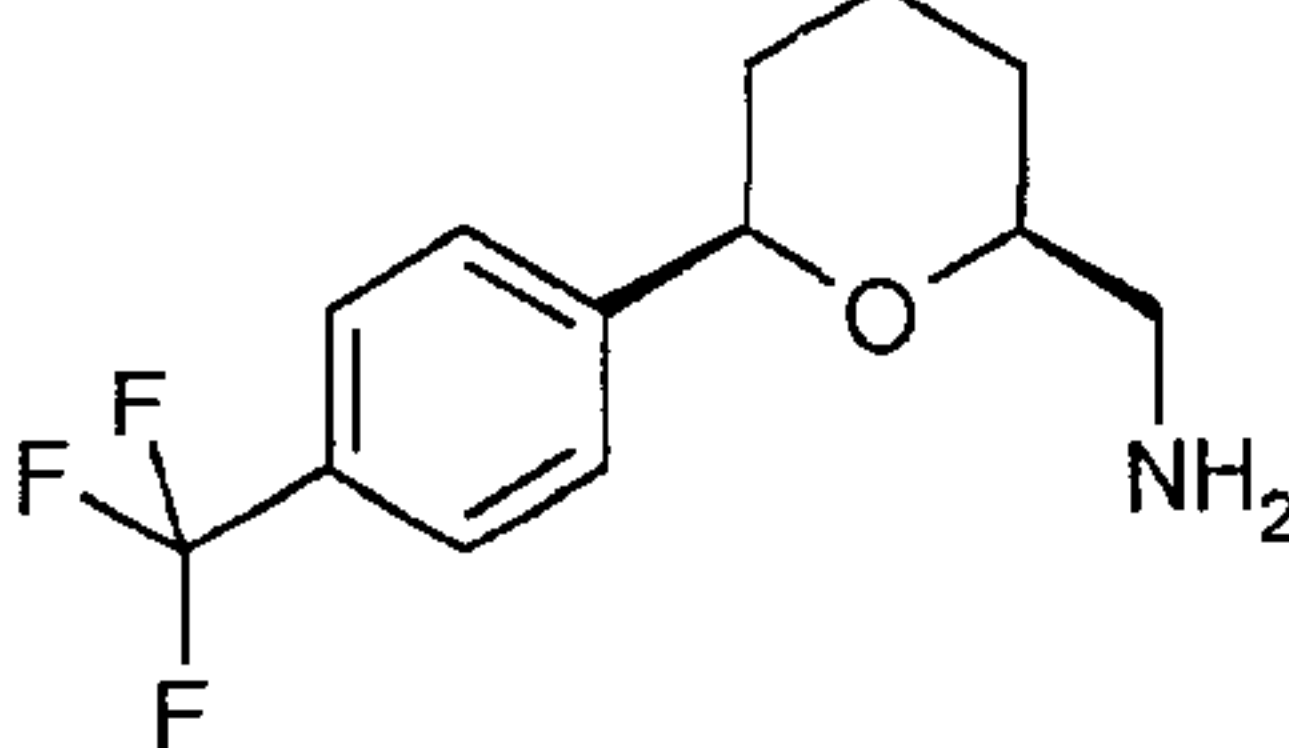
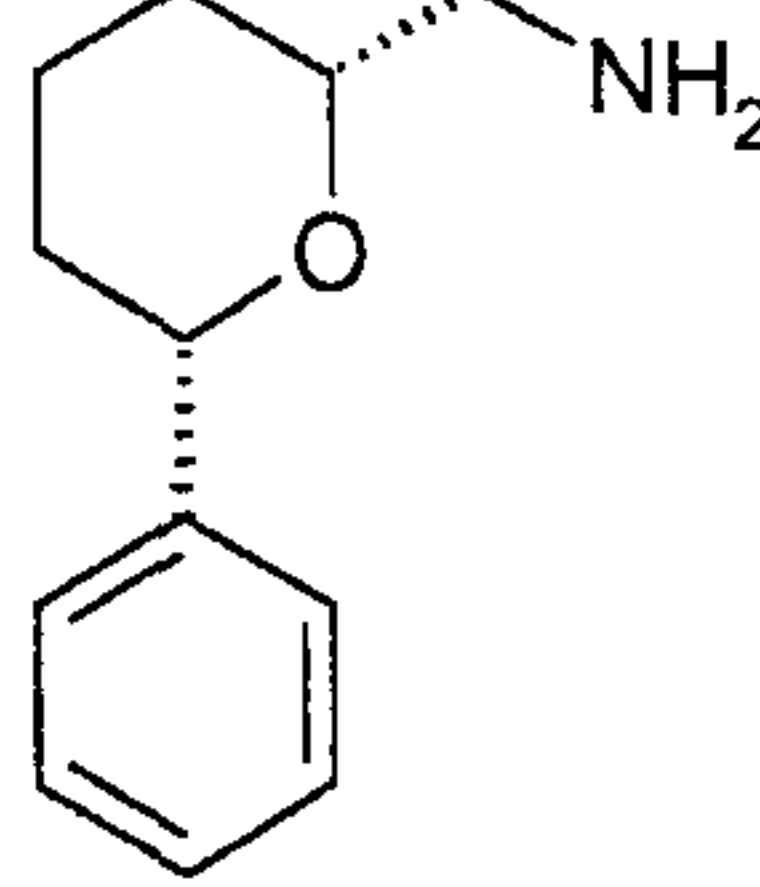
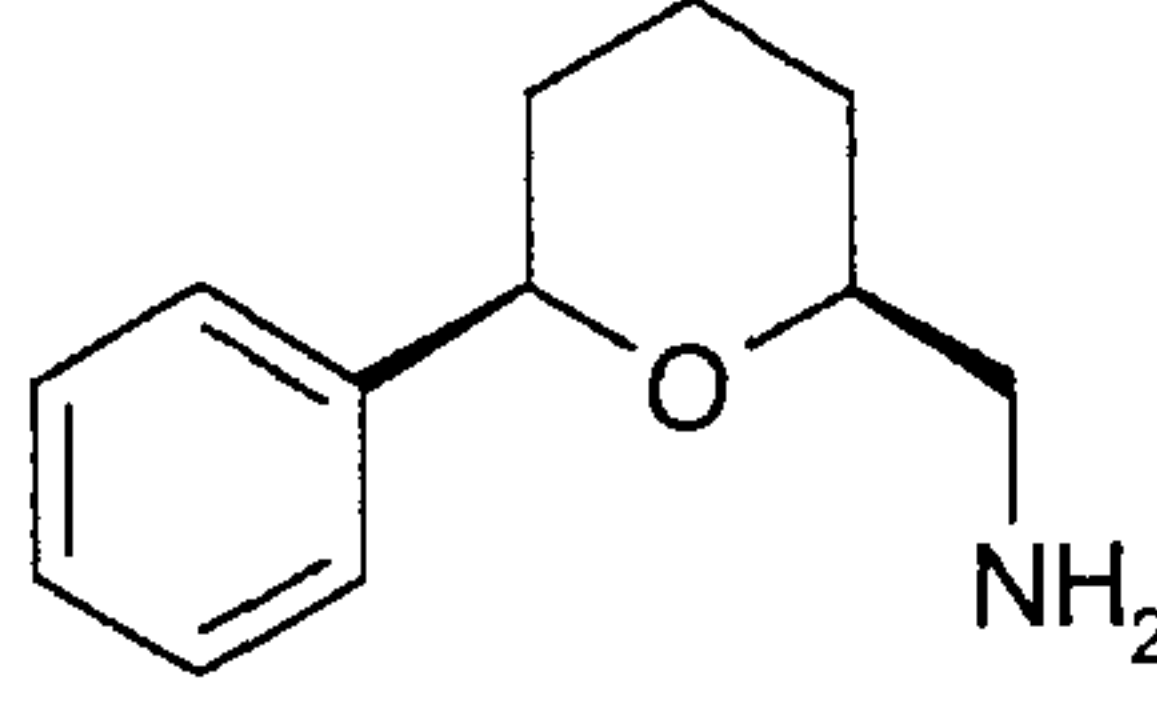
31214-7

<i>synthesis in analogy to intermediate 14a</i>			<i>synthesis in analogy to intermediate 15a</i>		
Starting Intermediate	Intermediate	STRUCTURE	Starting intermediate	Intermediate	STRUCTURE
9b	14b		11b	15b	
9c	14c		11c	15c	
9d	14d		11d	15d	
9e	14e		11e	15e	
9f	14f		11f	15f	
9g	14g		11g	15g	

31214-7

9h	14h		11h	15h	
9i	14i				

The following intermediates were synthesized in analogy to Intermediates 16a and 17a.

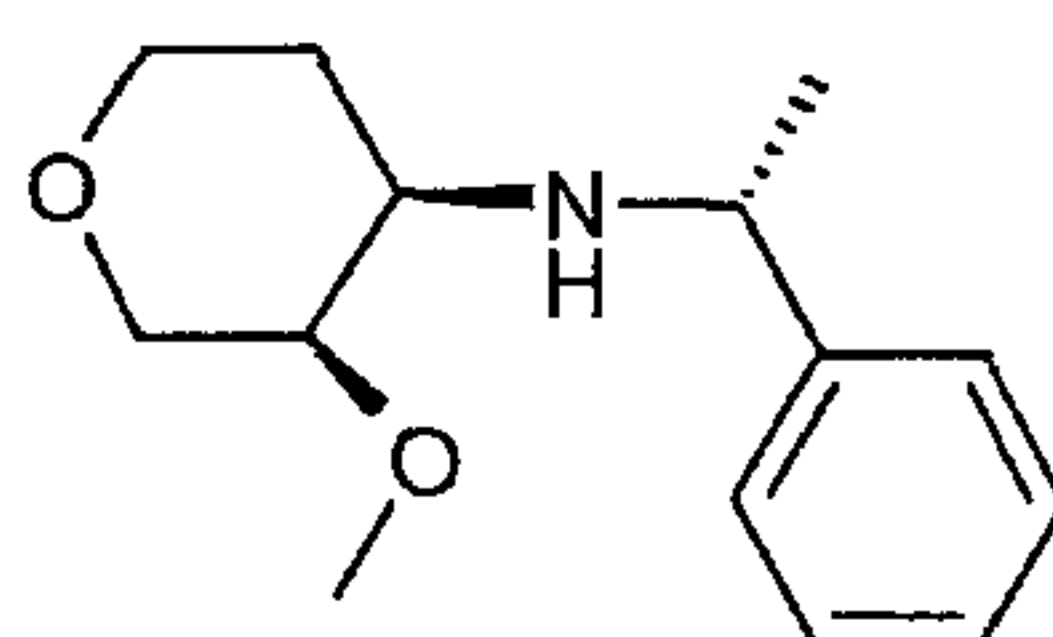
<i>synthesis in analogy to intermediate 16a</i>			<i>synthesis in analogy to intermediate 17a</i>			
Starting Intermediate	Intermediate	STRUCTURE	Starting intermediate	Intermediate	STRUCTURE	Stereochemistry
12b	16b		13b	17b		absolute stereochemistry as shown
12c	16c		13c	17c		relative stereochemistry cis *

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12d	16d		13d	17d		relative stereochemistry cis
12e	16e		13e	17e		relative stereochemistry cis
12f	16f		13f	17f		relative stereochemistry cis
12h	16h		13h	17h		relative stereochemistry cis

* Shown stereochemistry corresponds to stereoselective synthesis of intermediate 39d using (S,S)-teth-TsDpen ruthenium chloride (Johnson Matthey Catalysts).

Intermediate 18a



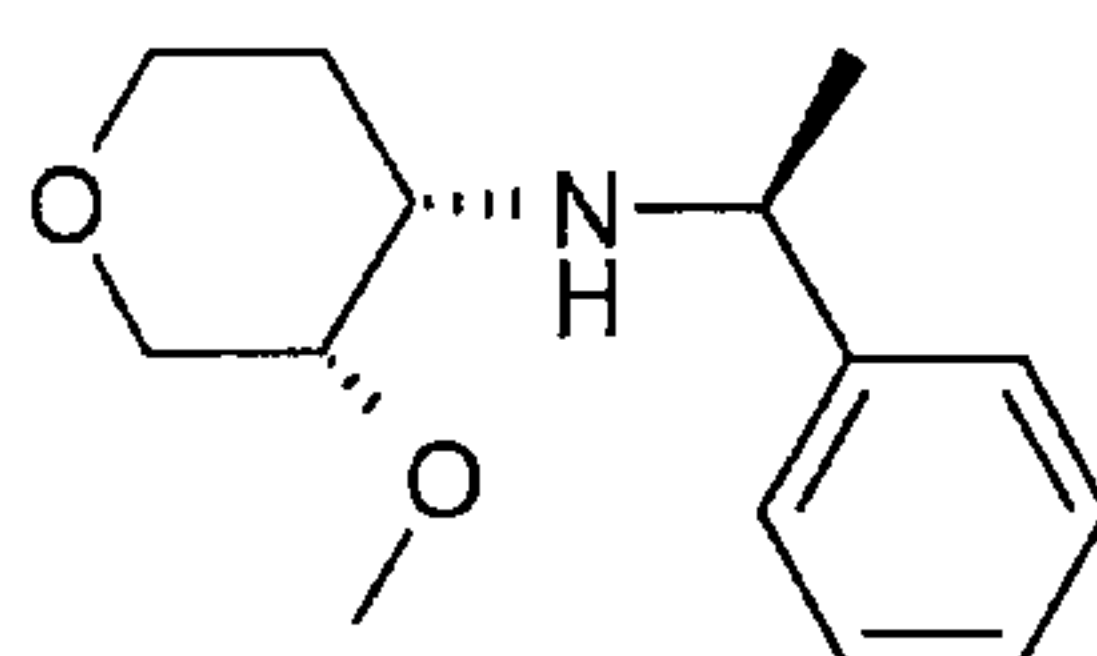
• 31214-7

3-Methoxy-tetrahydro-pyran-4-one* (1 g, 7.68 mmol), commercially available (R)-(+)-1-phenylethylamine (0.99 ml, 7.68 mmol) and Raney-Nickel (200 mg) in 10 ml of dry ethanol were stirred under a hydrogen atmosphere (5 bar) for 15 days. The reaction mixture was diluted with 20 ml of methanol and 20 ml of tetrahydrofuran, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum. The crude product was loaded on a SCX cartridge (50g). The cartridge was washed with methanol and the desired product was eluted with a 7 M solution of ammonia in methanol. The basic organic phase was concentrated under vacuum and the crude product was purified by flash chromatography (dichloromethane/methanol= 98/2%) to obtain 710 mg (3.02 mmol) of the desired product as single stereoisomer (diastereoisomeric purity confirmed and relative cis stereochemistry assigned by NMR).

GC/MS (method 3B) R_t = 35.04 min

* Tetrahedron Letters, **2005** , 447 - 450

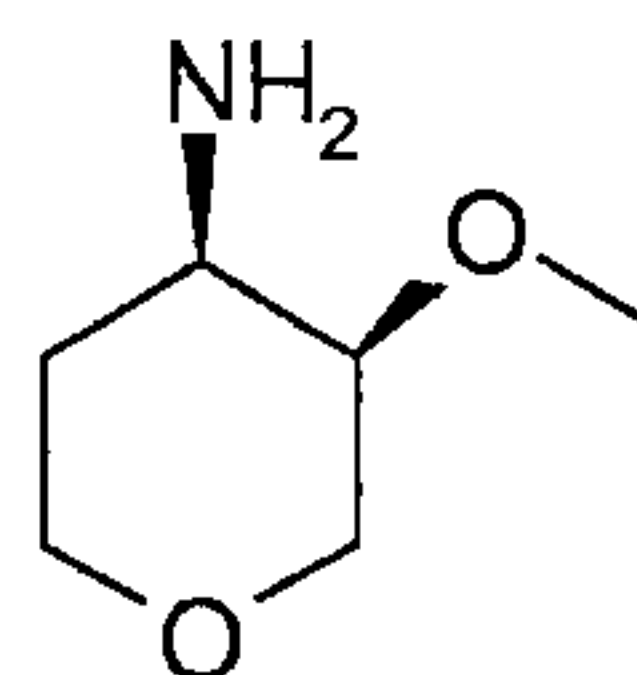
15 Intermediate 18b



was synthesised in analogy to Intermediate 18a, starting from 3-Methoxy-tetrahydro-pyran-4-one and commercially available (S)-(-)-1-phenylethylamine (diastereoisomeric purity confirmed and relative cis configuration assigned by NMR).

20 GC/MS (method 3B) R_t = 35.04 min

Intermediate 19a

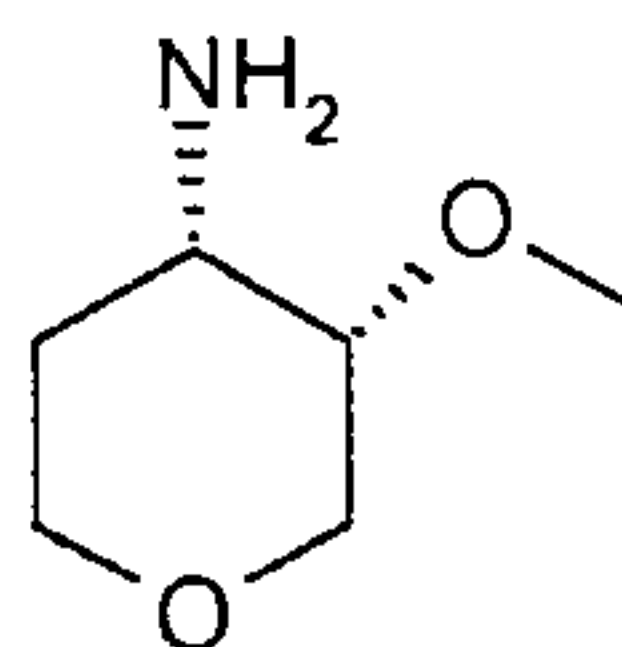


Intermediate 18a (1.18 g, 5.01 mmol), Pd/C 10% (200 mg) and acetic acid (0.3 ml, 5.01 mmol) in 20 ml of methanol were stirred under a hydrogen atmosphere (5 bar) for 18h. The reaction mixture was diluted with 20 ml of methanol, stirred for 15 minutes, filtered on a celite pad and concentrated under vacuum. The crude product was loaded on a SCX cartridge (50g). The cartridge was wash with methanol and the desired product was eluted with a 7 M

31214-7

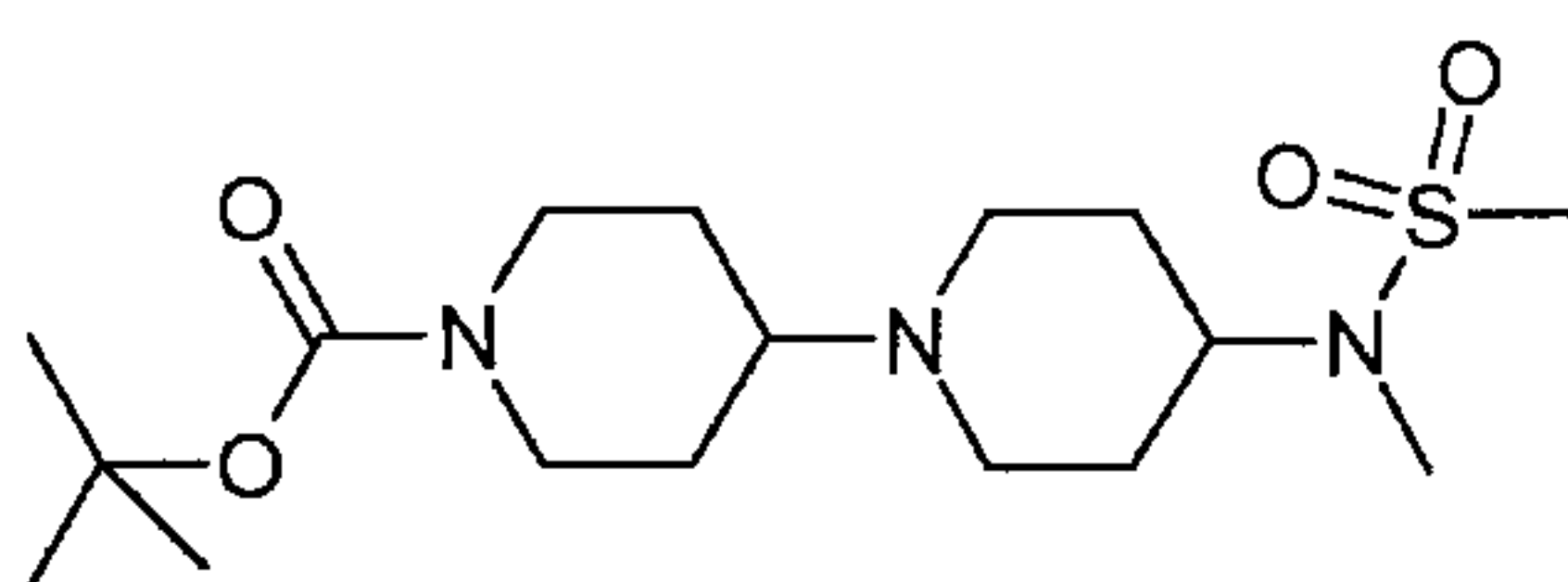
solution of ammonia in methanol. The basic organic phase was concentrated under vacuum and 513 mg (3.91 mmol) of the desired product were obtained as single stereoisomer

Intermediate 19b



5 was synthesised in analogy to Intermediate 19a, starting from Intermediate 18b.

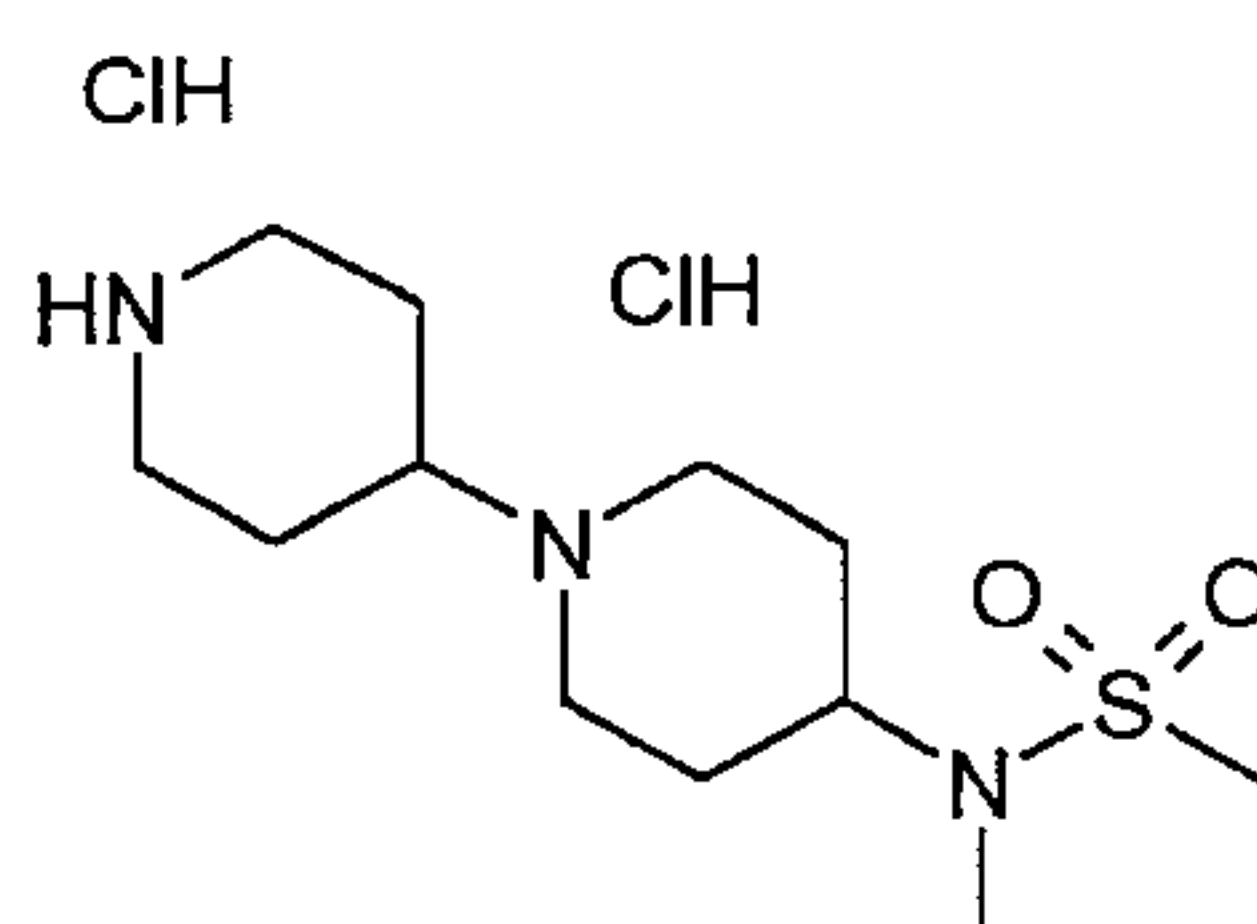
Intermediate 20a



10 N-methyl-N-piperidin-4-yl-methanesulfonamide hydrochloride (11 g, 47.91 mmol; WO2009/47161) was suspended in 200 ml of 1,2-dichloroethane, N,N-diisopropylethylamine (17,12 ml, 96.17 mmol) and commercially available 1-(tert-butoxycarbonyl)-piperidin-4-one (9.58 g, 48.08 mmol) were added and the reaction mixture was stirred at room temperature for 30 min. Sodium triacetoxyborohydride (12.23 g, 57.50 mmol) was added and the reaction
15 mixture was stirred at room temperature for 72h. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Biotage SP1; silica gel cartridge: 65i; eluent: ethyl acetate/methanol=50/50%) to obtain 7.2 g (19.2 mmol) of the desired compound.

20

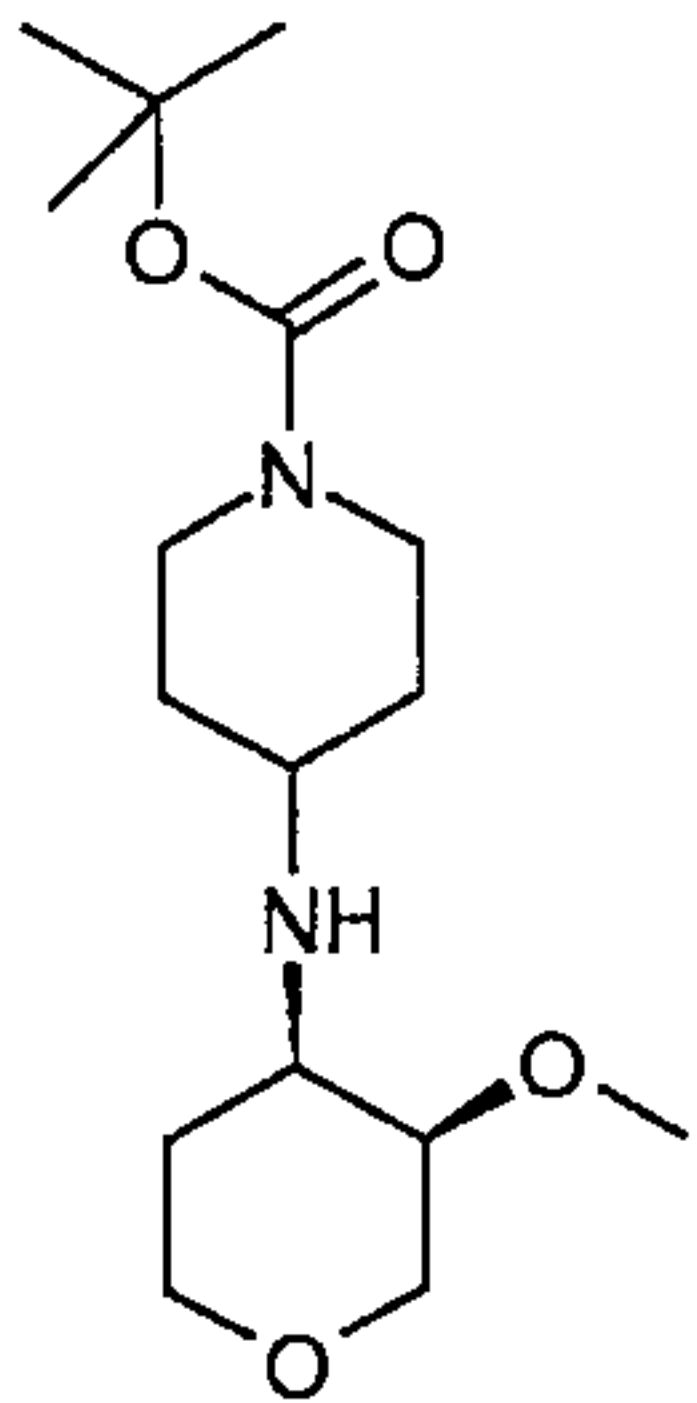
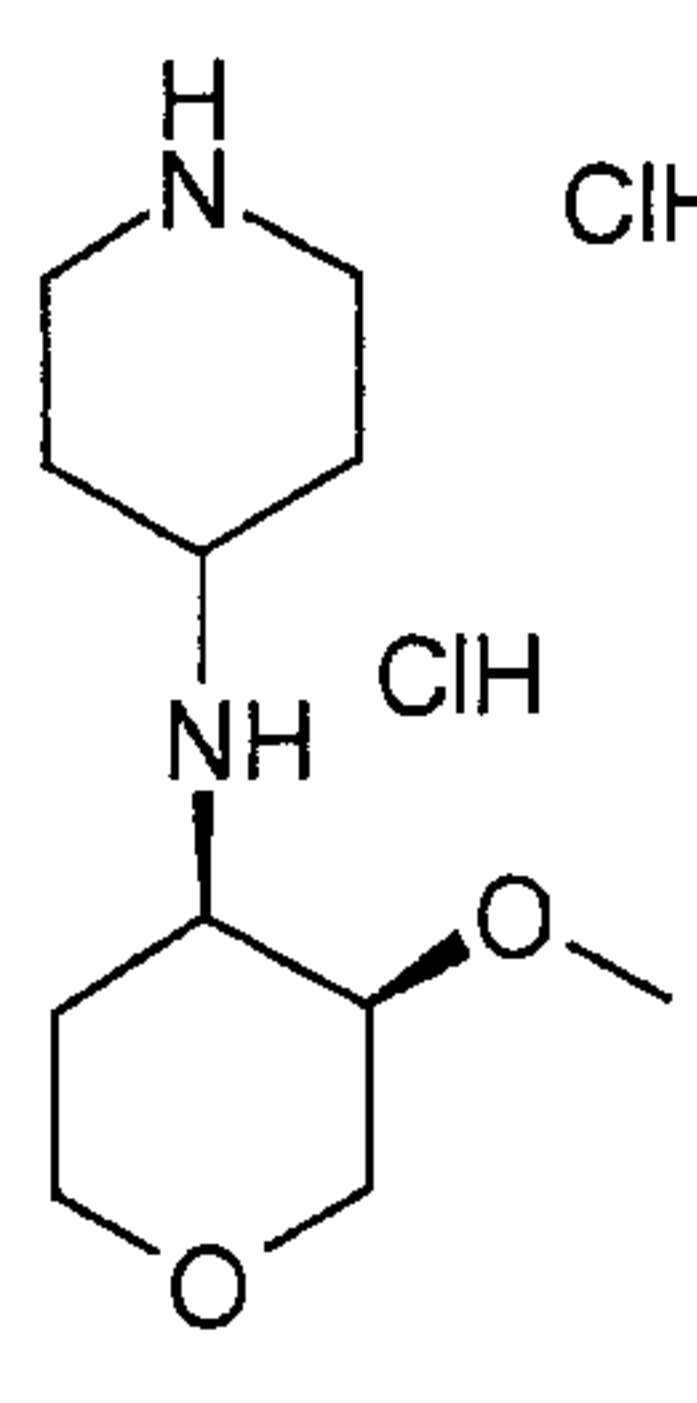
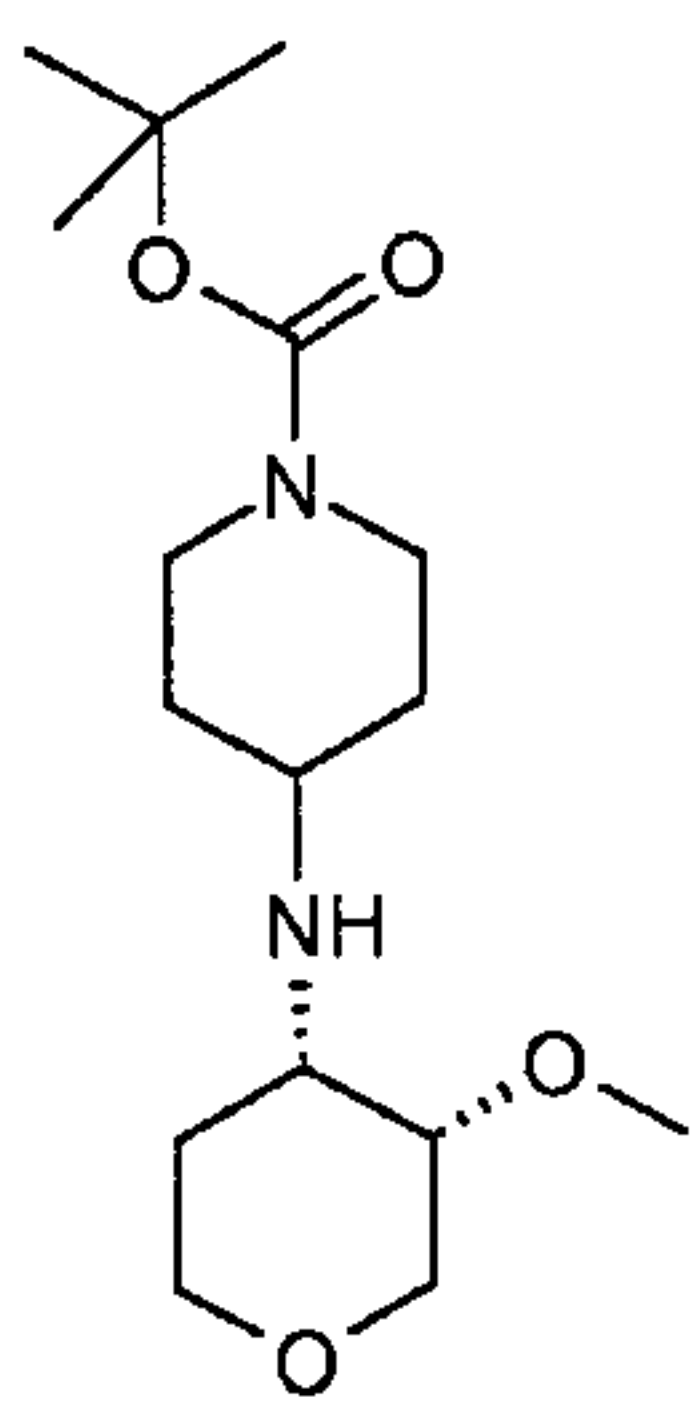
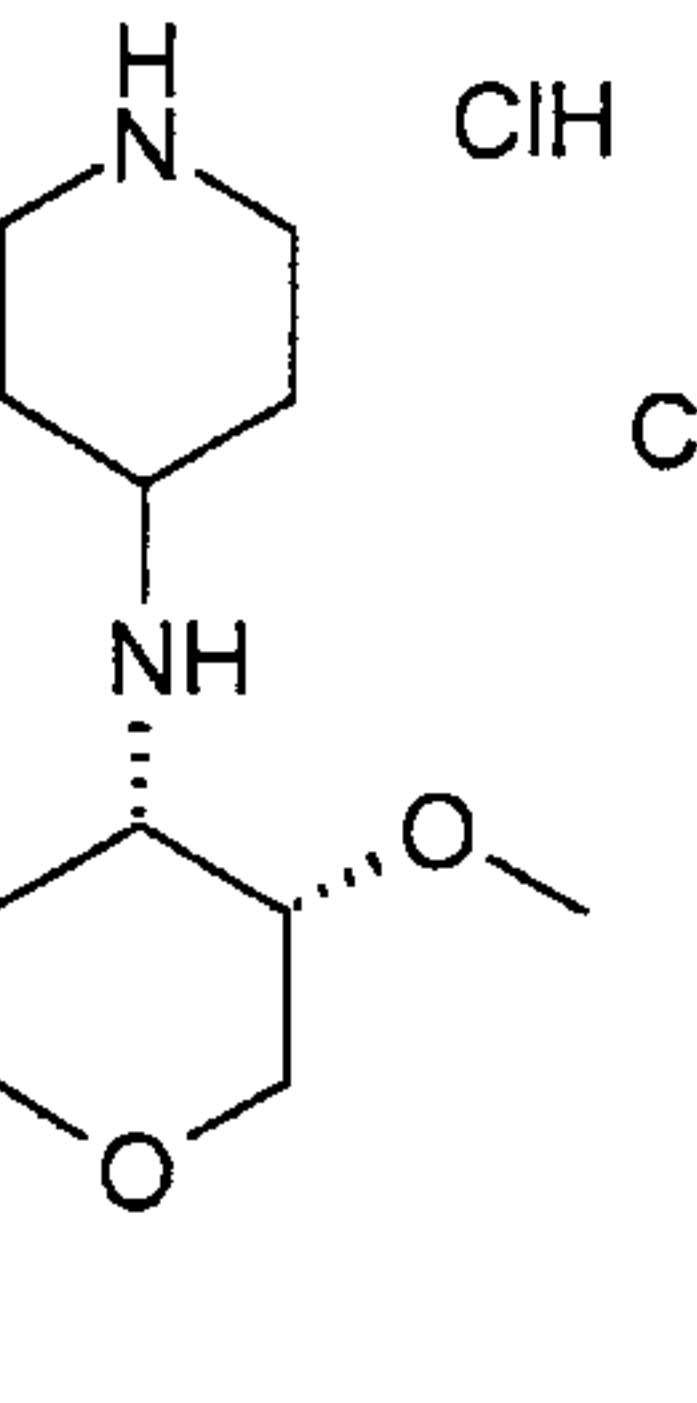
Intermediate 21a



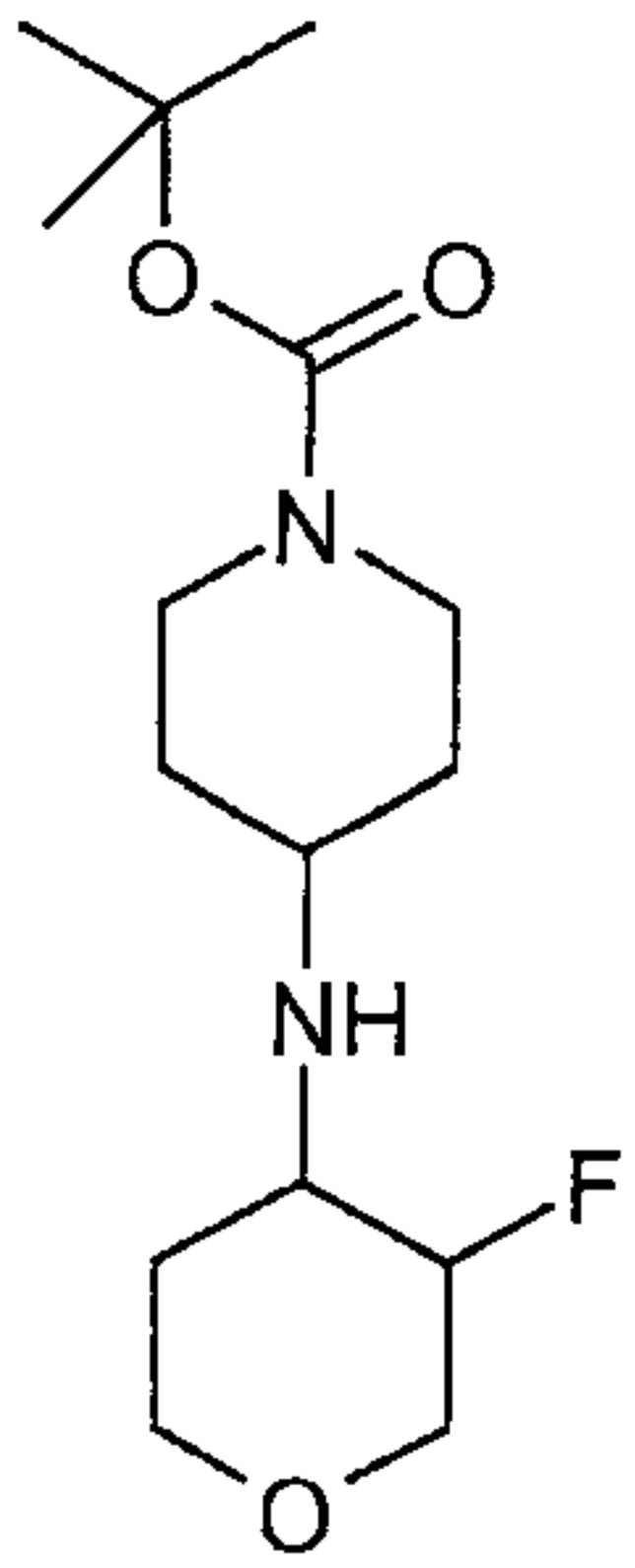
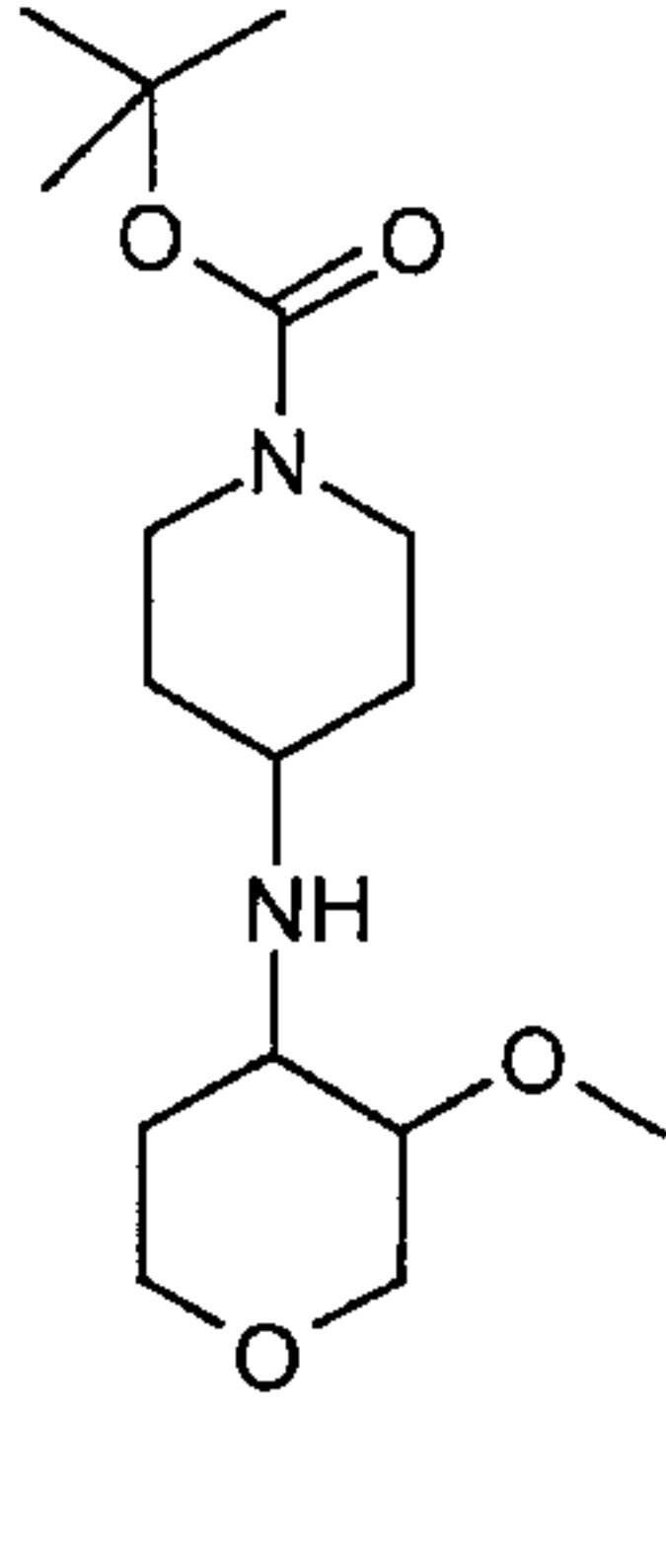
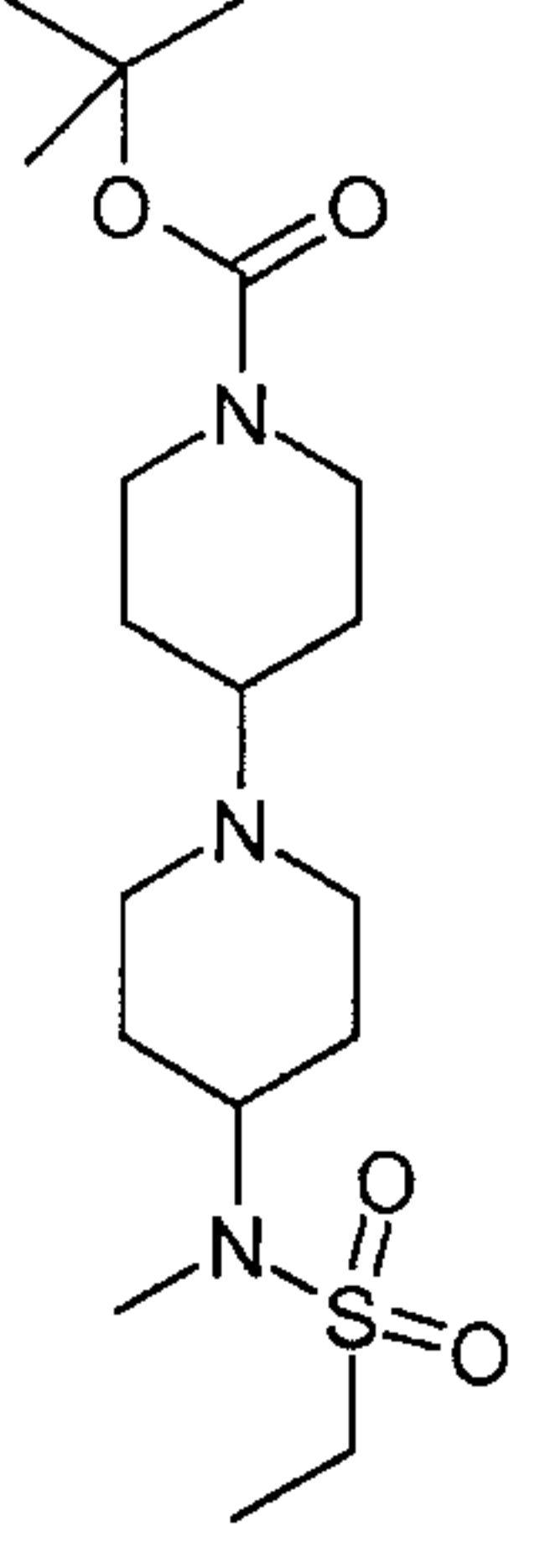
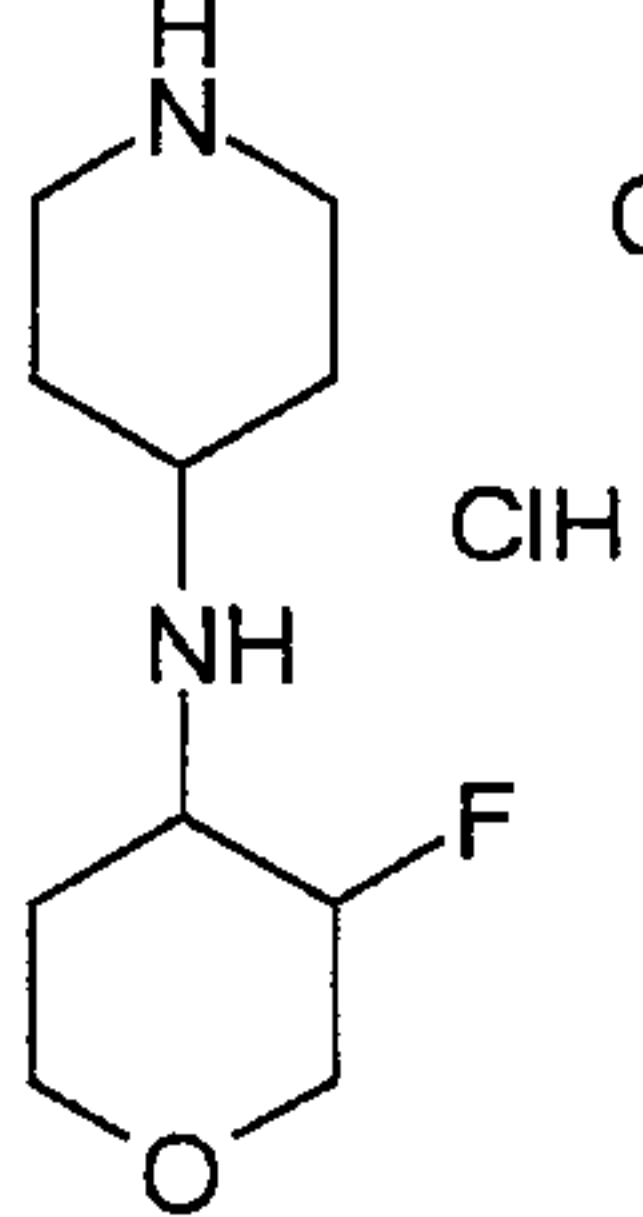
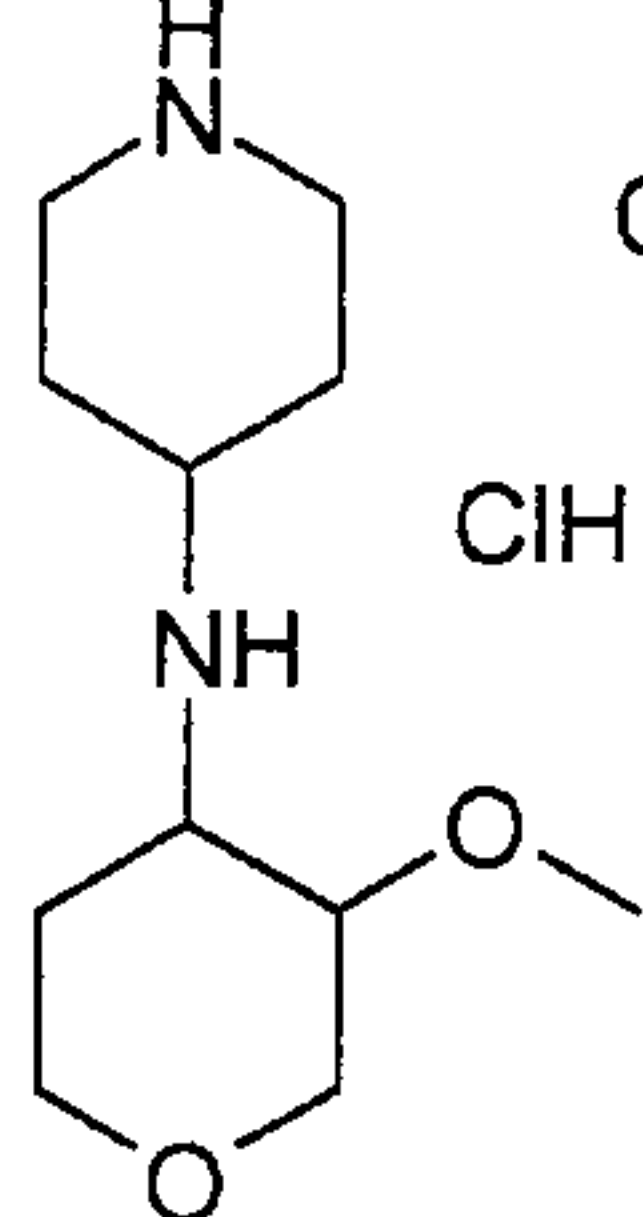
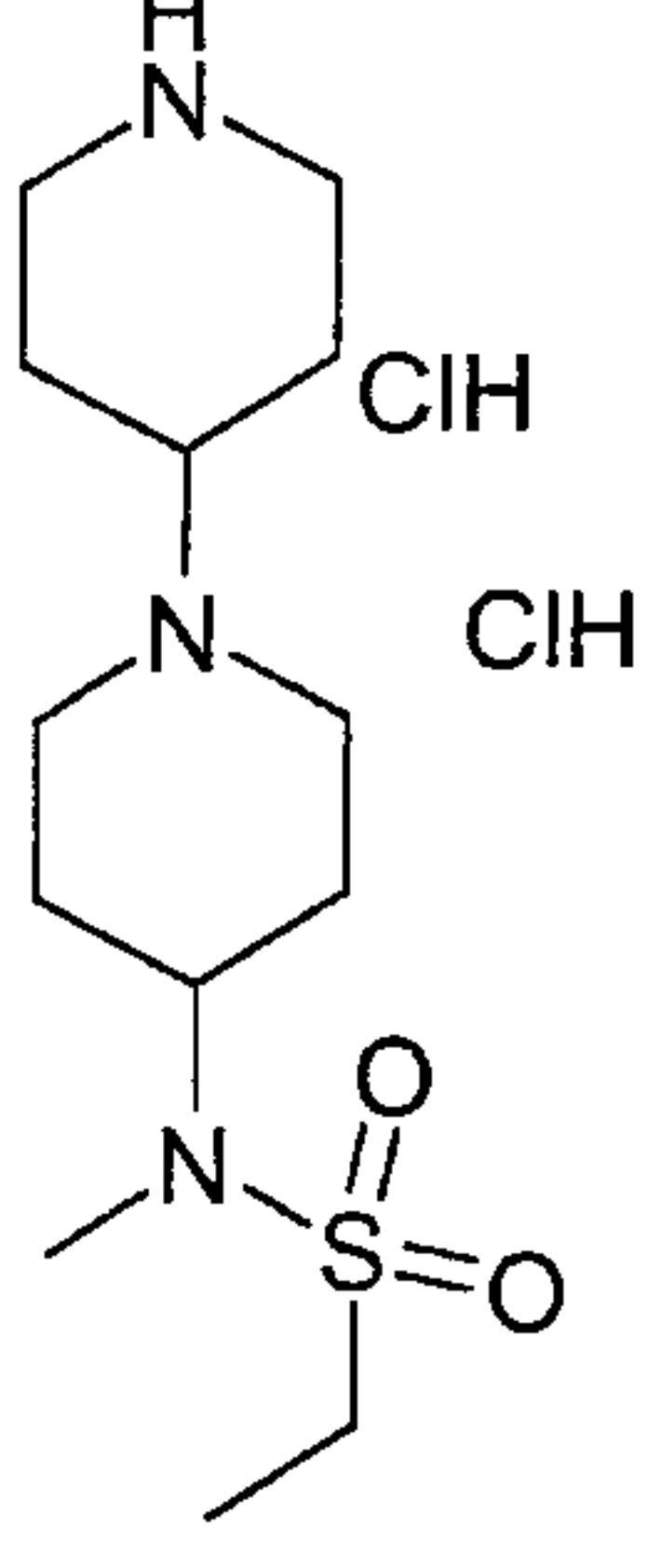
Intermediate 20a (7.2 g, 19.2 mmol) was suspended in 20 ml of 1,4-dioxane, a 4M solution of hydrochloric acid (48 ml, 192 mmol) in 1,4-dioxane was added dropwise. The reaction
25 mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. 6.3 g (18 mmol) of the desired compound were obtained.

The following intermediates were synthesized in analogy to Intermediates 20a and 21a.

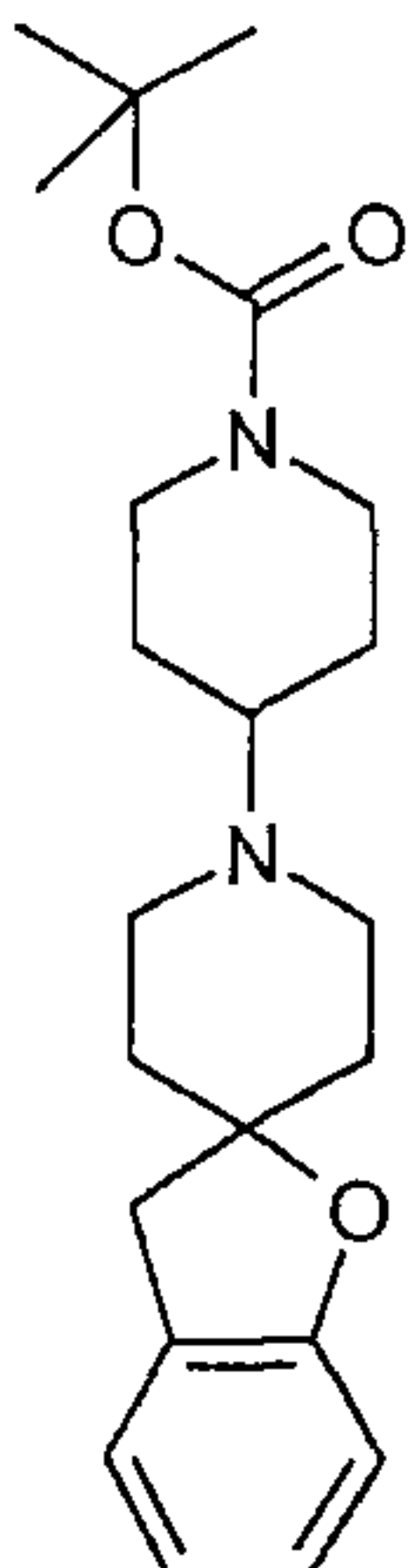
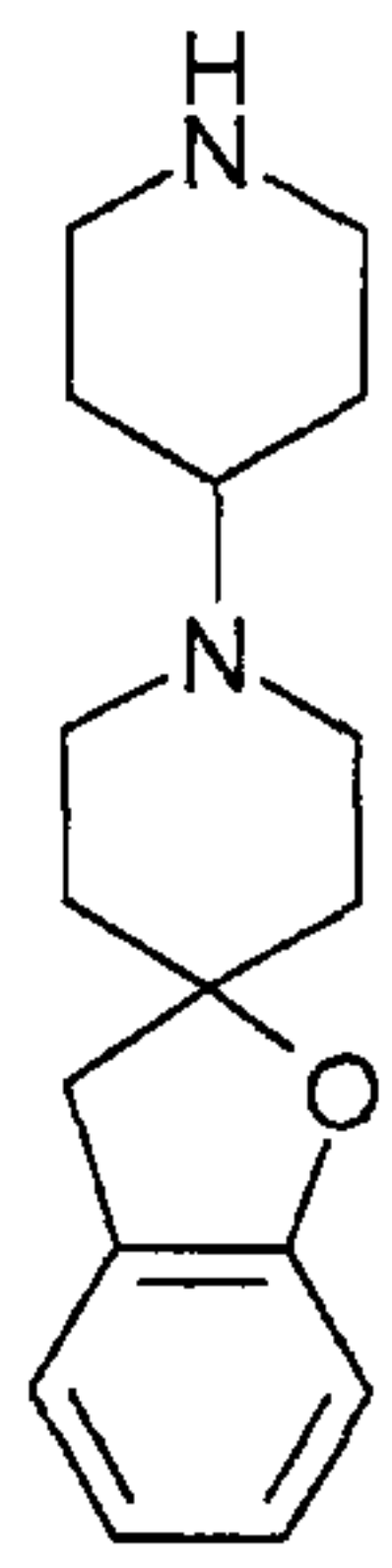
31214-7

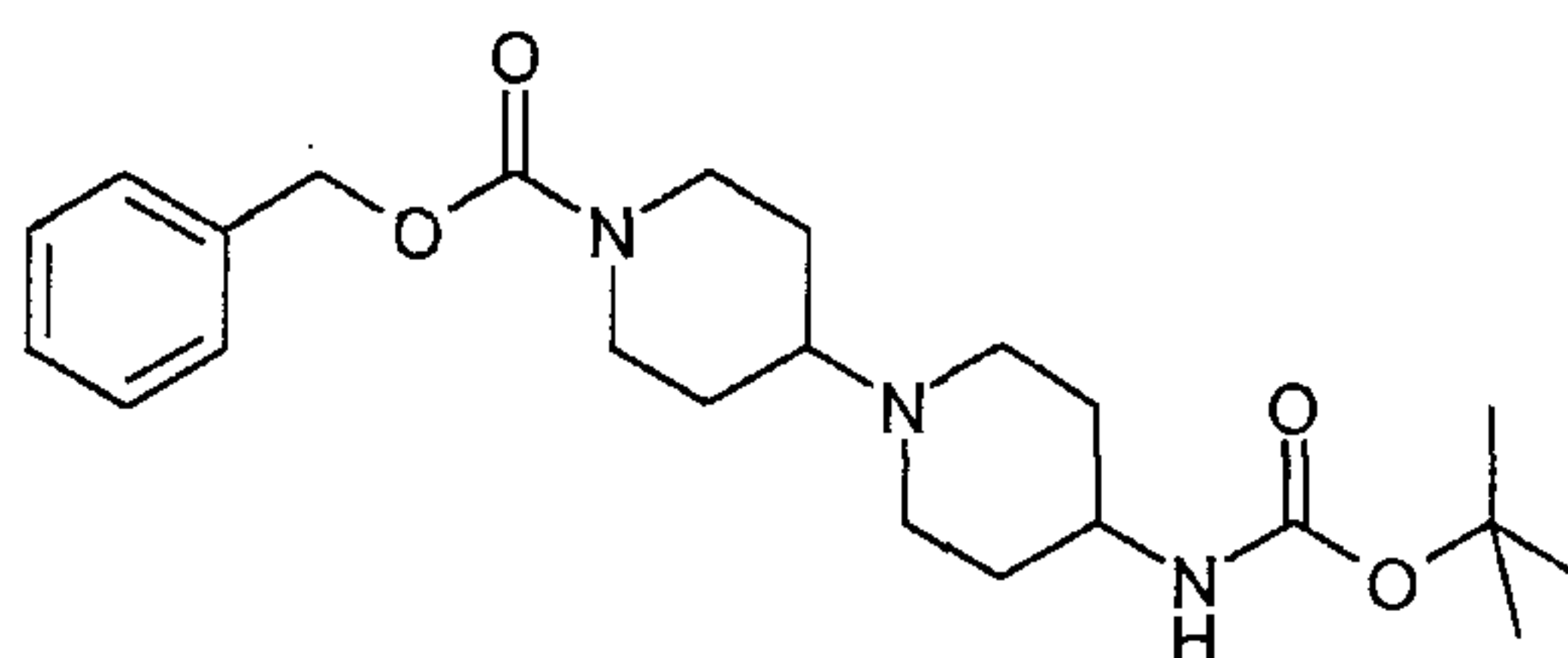
synthesis in analogy to intermediate 20a						synthesis in analogy to intermediate 21a	
Starting intermediate	Source/Reference	Starting intermediate	Source/Reference	Carbamate Intermediate	STRUCTURE	Diamino Intermediate	STRUCTURE
1-(tert-butoxycarbonyl)-4-oxopiperidine	commercially available	19a	-	20b		21b	
1-(tert-butoxycarbonyl)-4-oxopiperidine	commercially available	19b	-	20c		21c	

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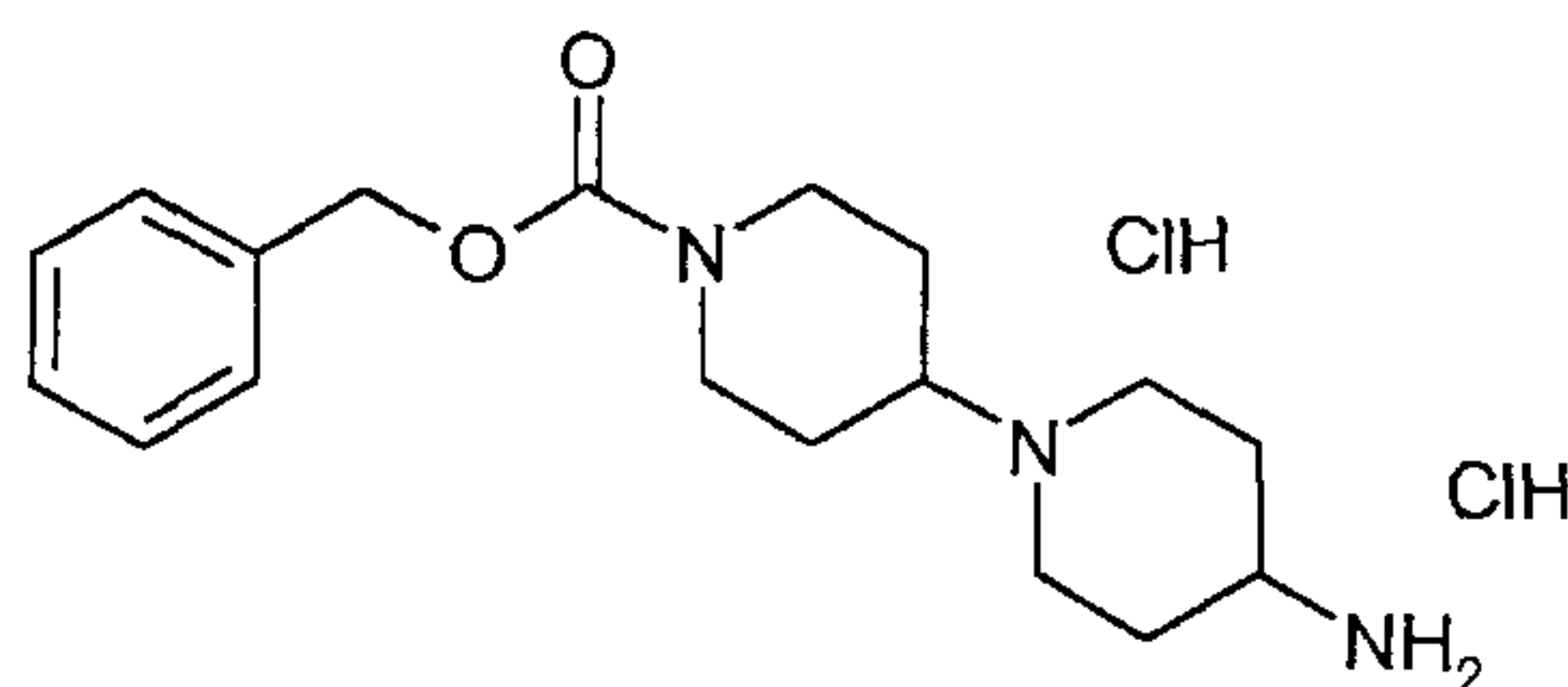
3-Fluoro-tetrahydro-pyran-4-one	3-Methoxy-tetrahydro-pyran-4-one	1-(tert-butoxycarbonyl)-4-oxopiperidine
WO2003/93231	Tetrahedron Letters, 2005 , 447 - 450	Commercially available
4-amino-piperidine-1-carboxylic acid tert-butyl-ester	4-amino-piperidine-1-carboxylic acid tert-butyl-ester	N-methyl-N-piperidin-4-yl-ethanesulfonamide
Commercially available	Commercially available	Prepared in analogy to N-methyl-N-piperidin-4-yl-methanesulfonamide starting from ethanesulfonyl chloride (see intermediate 20a)
20f	20e	20d
		
21f	21e	21d
		

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3H-spiro[1-benzofuran-2,4'-piperidine]	Commericly available	1-(tert-butoxycarbonyl)-piperidin-4-one	Commericly available	20g		21g		ClH ClH
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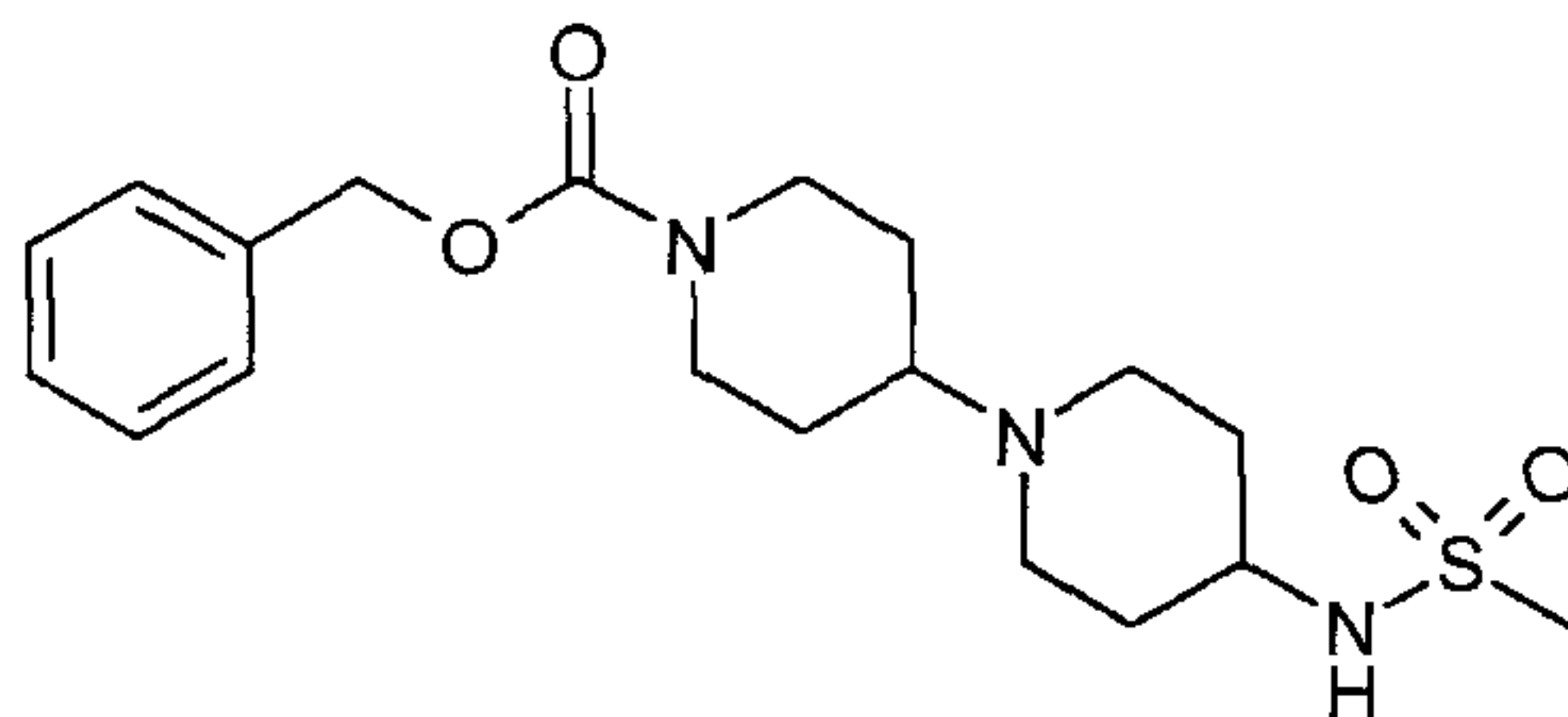
Intermediate 22

- Commercially available piperidin-4-yl-carbamic acid tert-butyl ester (6 g, 30 mmol) and commercially available 1-(benzyloxycarbonyl)-4-oxopiperidine (9.6 g, 48 mmol) were dissolved in 50 ml of dichloromethane and the reaction mixture was stirred at room temperature for 30 min; sodium triacetoxyborohydride (12.23 g, 57.5 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was dried over sodium sulfate and concentrated under vacuum. The crude product was treated with acetone/isopropyl ether and the precipitate obtained was filtered off. 8.4g (20 mmol) of the desired product were obtained.

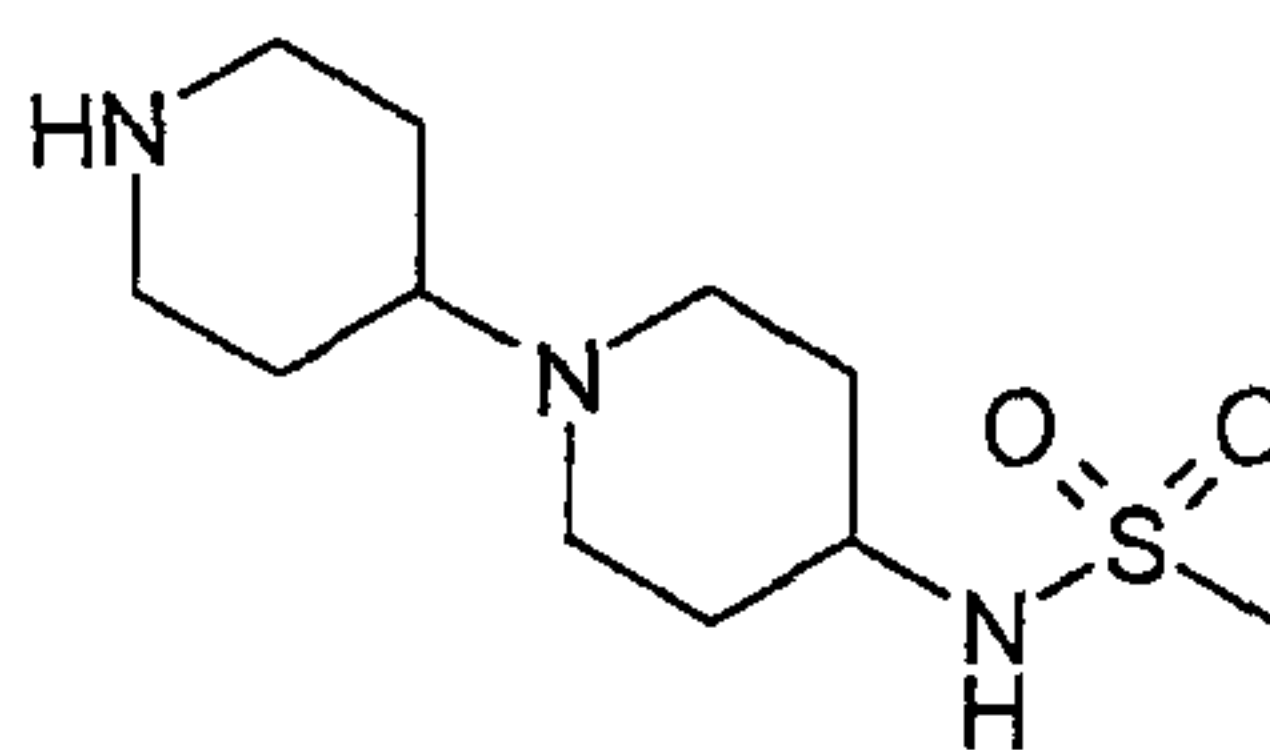
Intermediate 23

- A solution of intermediate 22 (8.4 g, 20 mmol) in 150 ml of 1,4-dioxane was cooled to 0°C. Then, 12.6 ml (50 mmol) of a 4M solution of hydrochloric acid in 1,4-dioxane were added dropwise; the reaction mixture was allowed to warm to room temperature and stirred overnight. The precipitate was filtered off and dried at 50°C under vacuum to give the desired product (6g, 15 mmol).

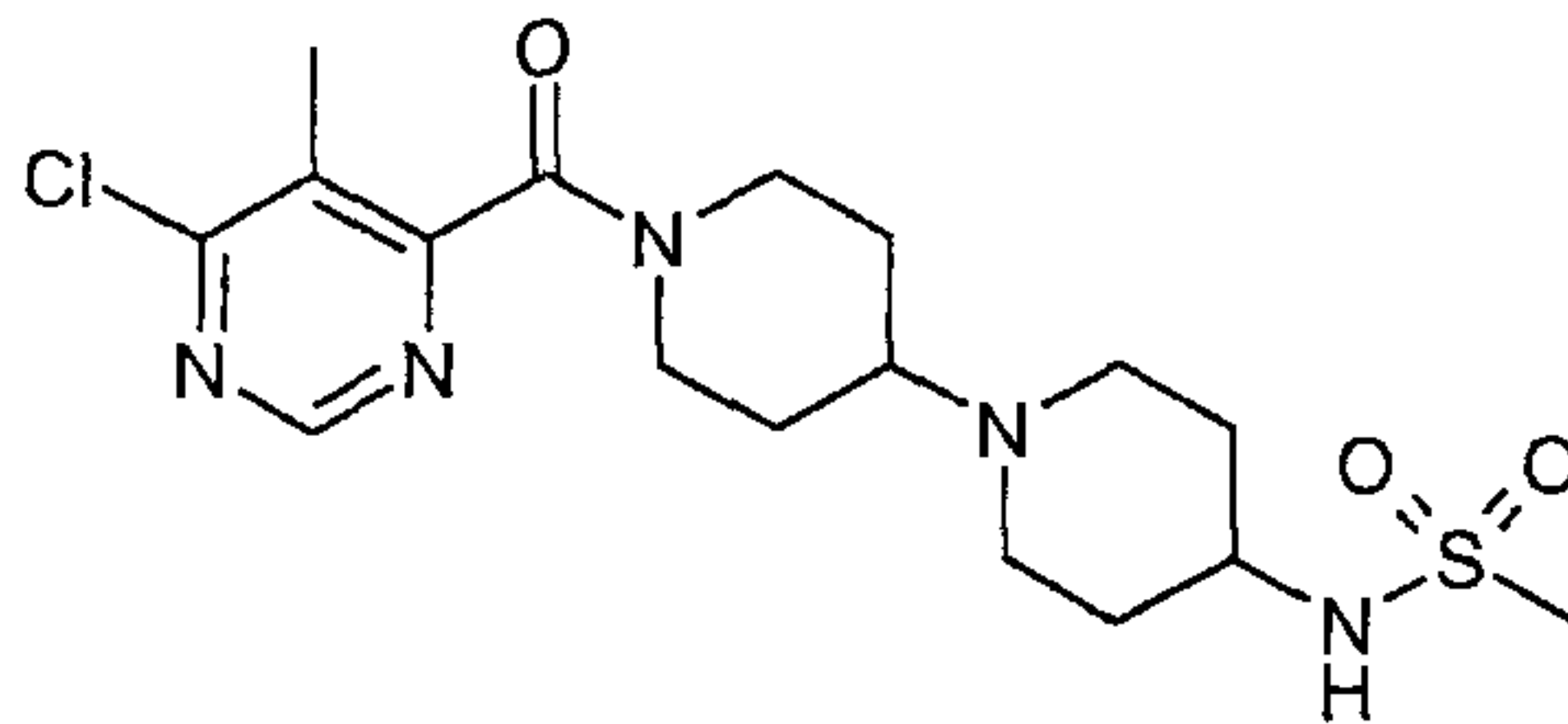
31214-7

Intermediate 24

- 5 Intermediate 23 (6.0 g, 15 mmol) was suspended in 55 ml of dichloromethane; triethylamine (6.43 ml, 46 mmol) was added and the reaction mixture was cooled to 0°C and stirred for 30 min. Methanesulfonyl chloride (1.43 ml, 18 mmol) in 5 ml of dichloromethane was added dropwise. The reaction mixture was stirred at 0°C for 1h; then water was added and the reaction mixture was extracted with dichloromethane. The organic phase was washed with an
- 10 aqueous saturated sodium bicarbonate solution, with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was treated with diisopropyl ether, the precipitate was filtered off and dried. 5 g (13 mmol) of the desired product were obtained.

Intermediate 25

- 15 Intermediate 24 (5 g, 13 mmol) was dissolved in 50 ml of methanol; acetic acid (1.5 ml, 25.3 mmol) and Pd/C 10% (500 mg) were added in sequence and the reaction mixture was stirred under a hydrogen atmosphere (3 bar) at room temperature for 5 days. The reaction mixture was filtered on a celite pad and the organic phase was loaded on a SCX cartridge (10g). After
- 20 washing with methanol, the desired compound was eluted with a 2M solution of ammonia in methanol. 3.7 g (4.6 mmol) of the desired product were obtained.

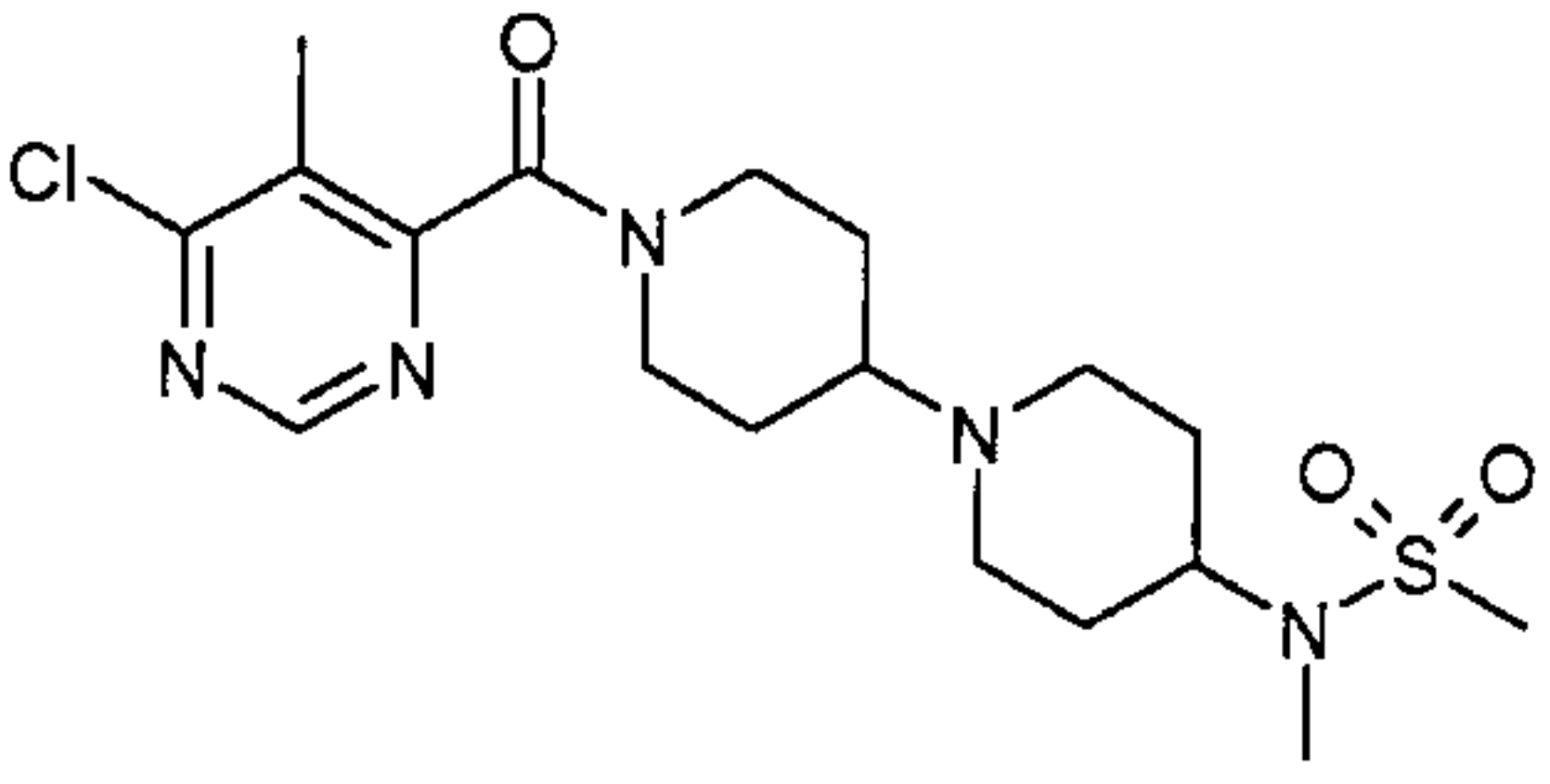
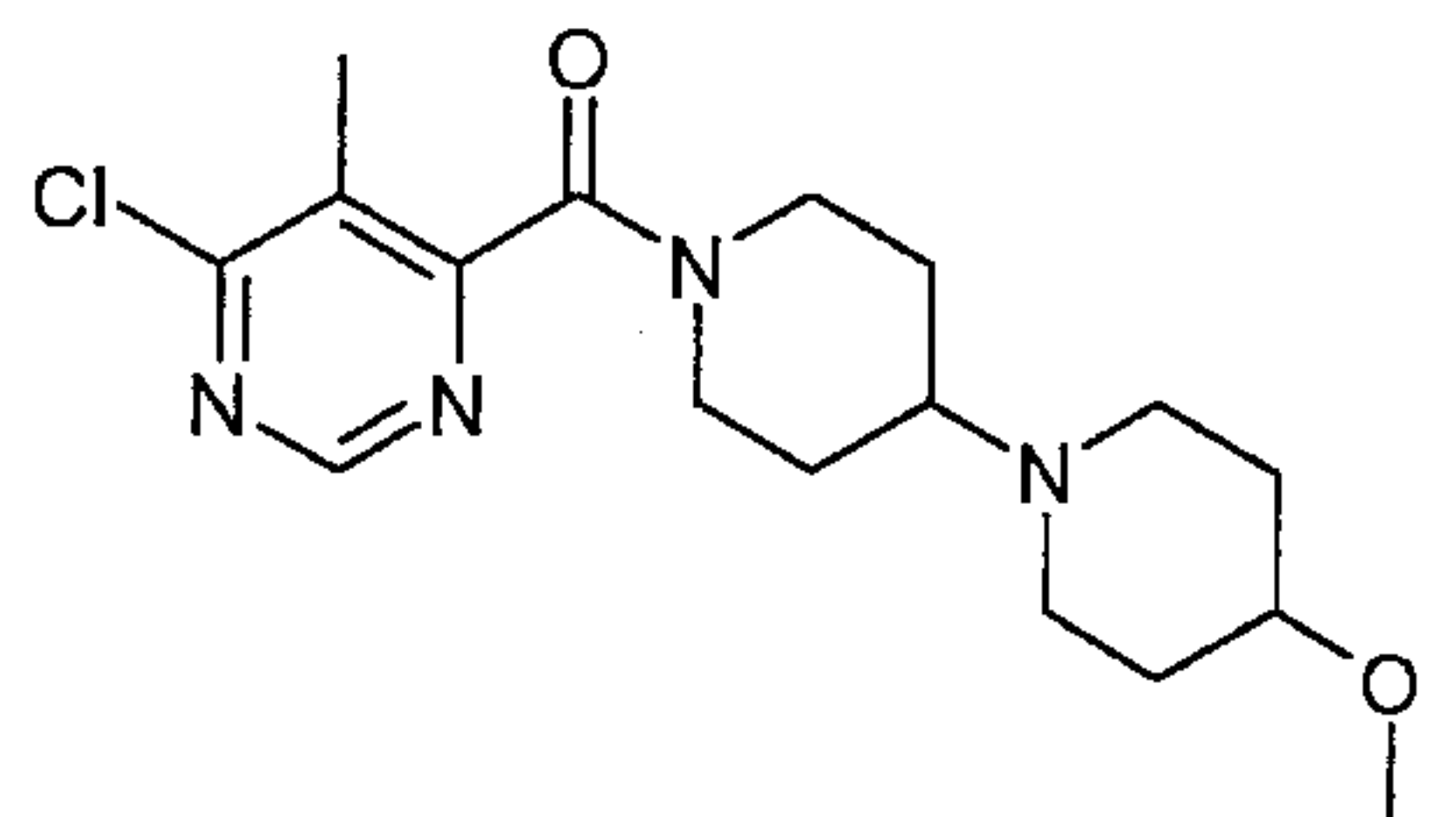
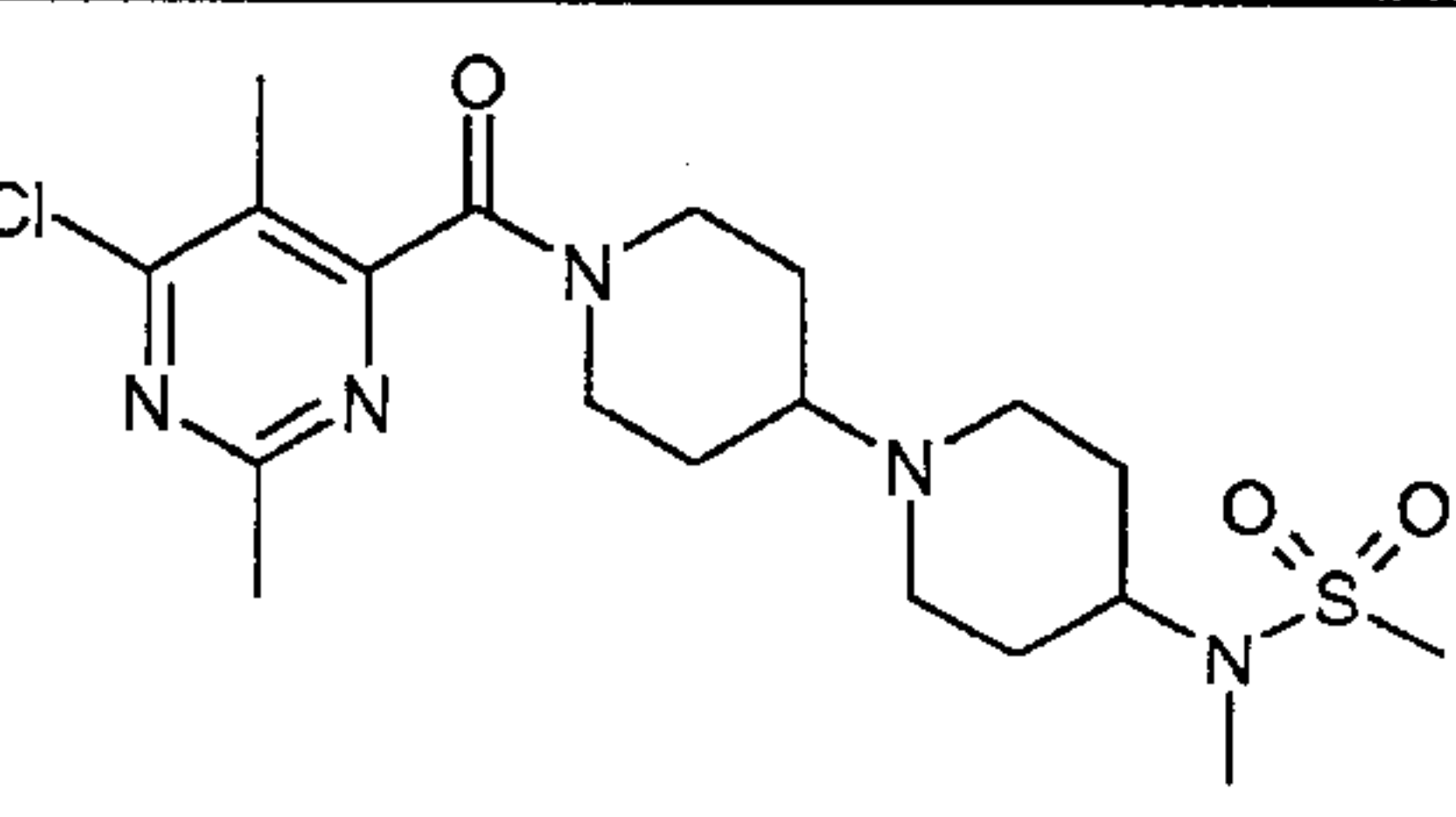
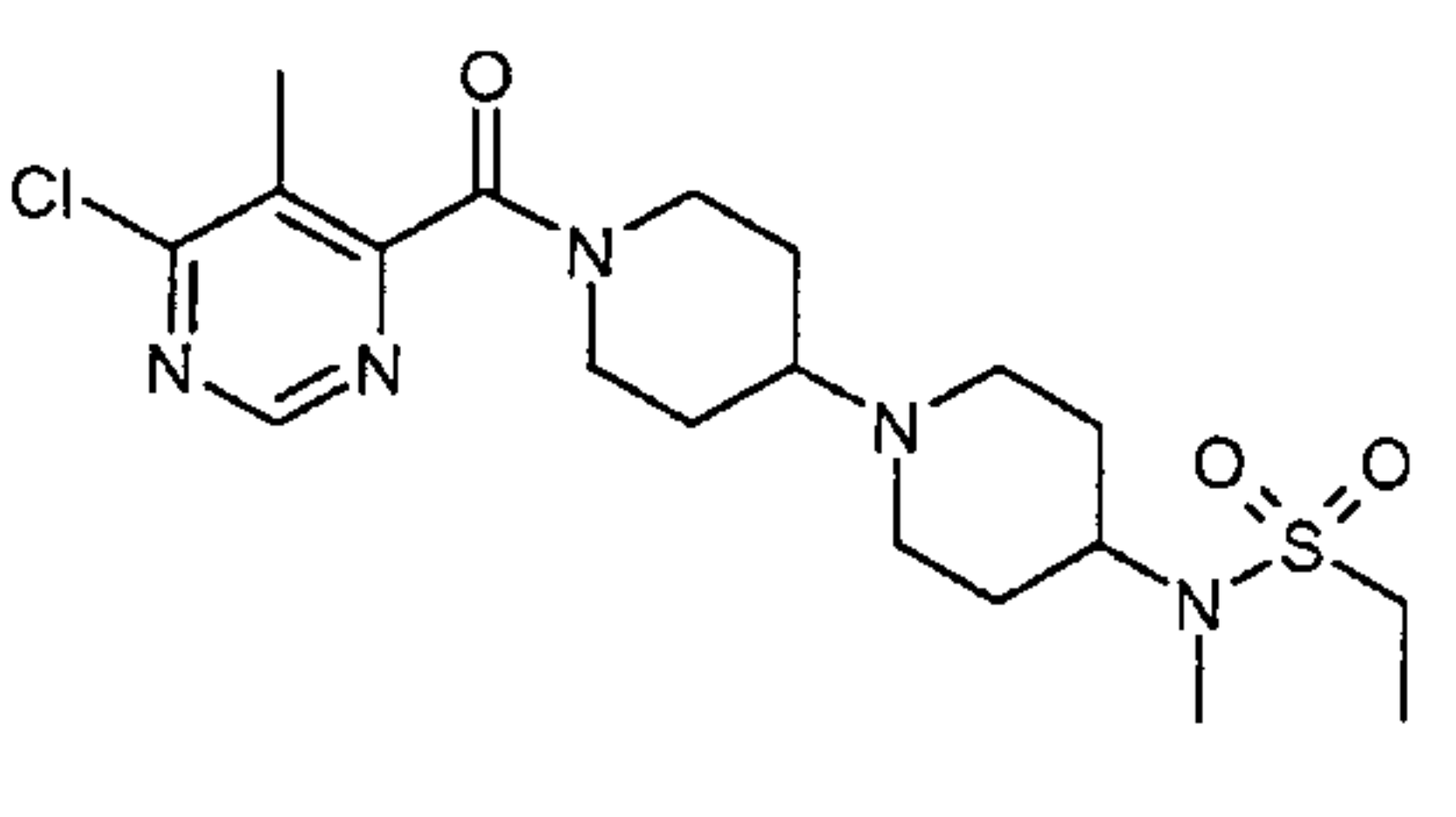
Intermediate 26a

- 25 Intermediate 25 (1.1 g, 4.21 mmol) was suspended in 20 ml of dry dichloromethane, N,N-diisopropylethylamine (1.47 ml, 8.42 mmol) and DMF (137 µl, 1.67 mmol) were added and the reaction mixture was stirred under nitrogen atmosphere and cooled to 0°C. Intermediate 2a (812 mg, 4.21 mmol) in 5 ml of dichloromethane was added dropwise and the reaction

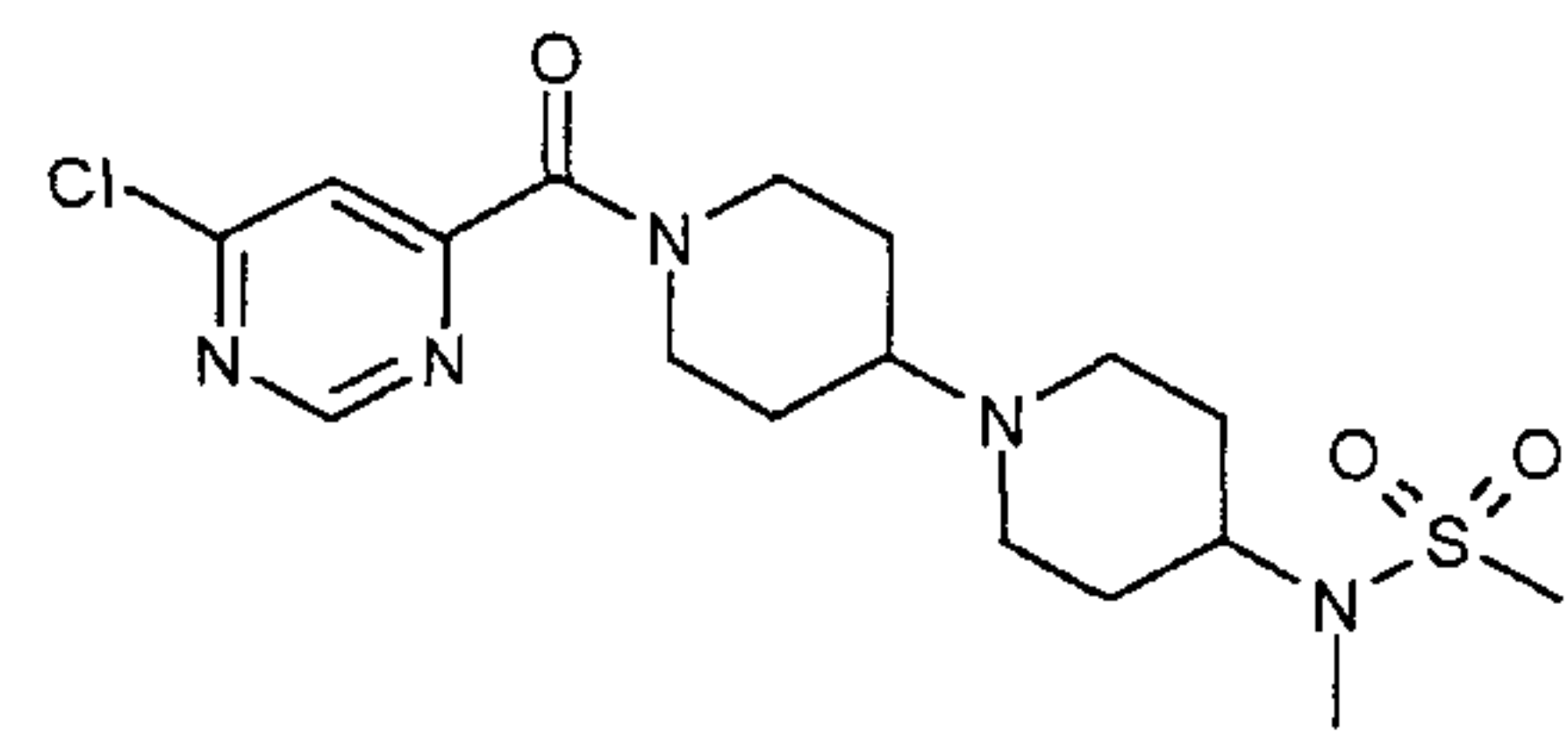
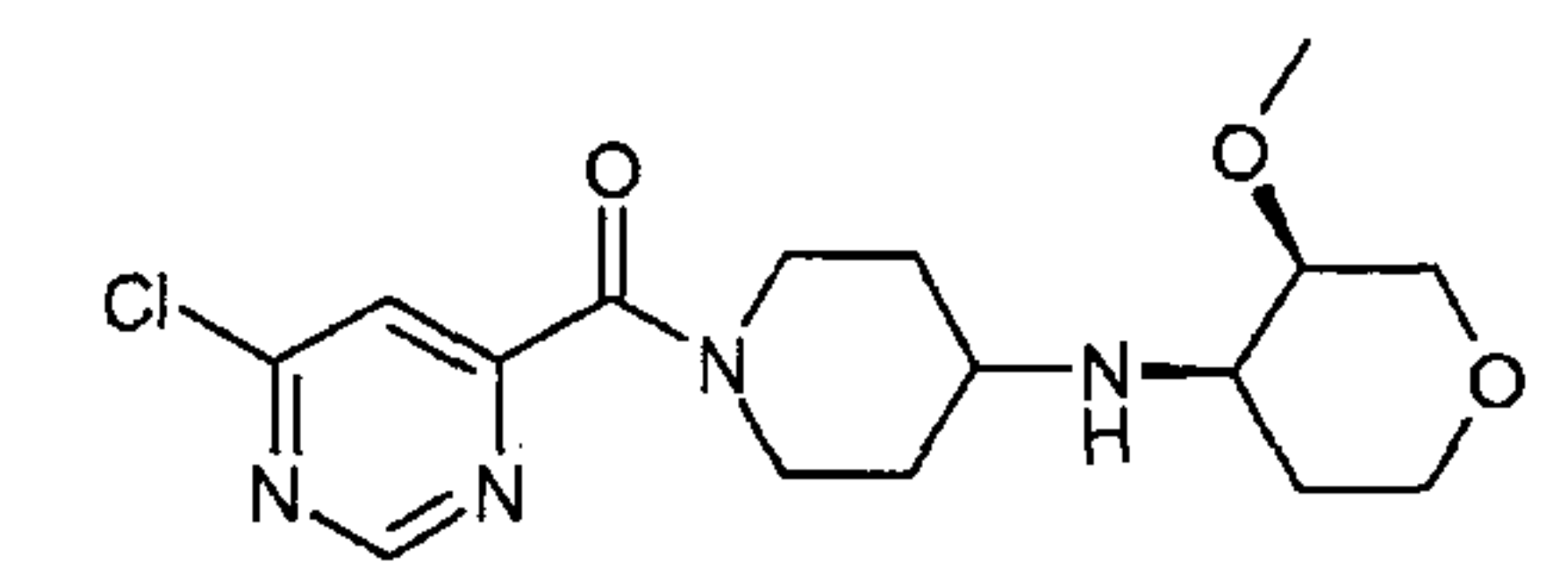
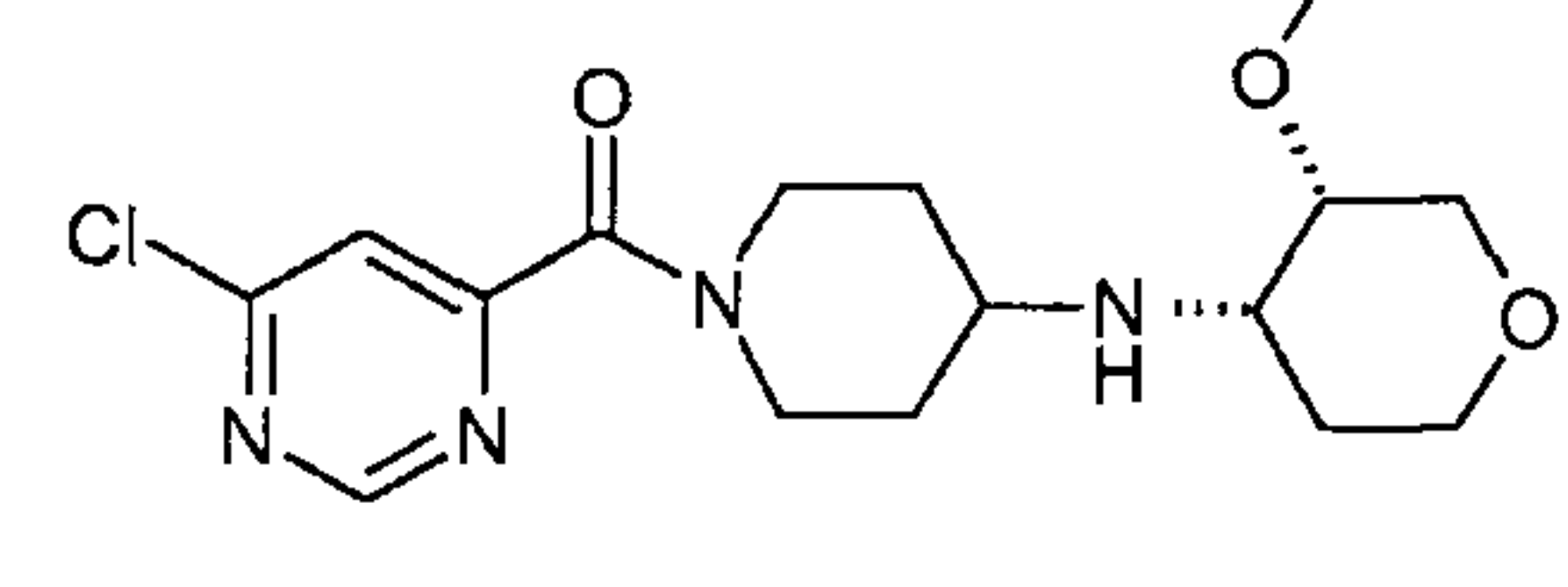
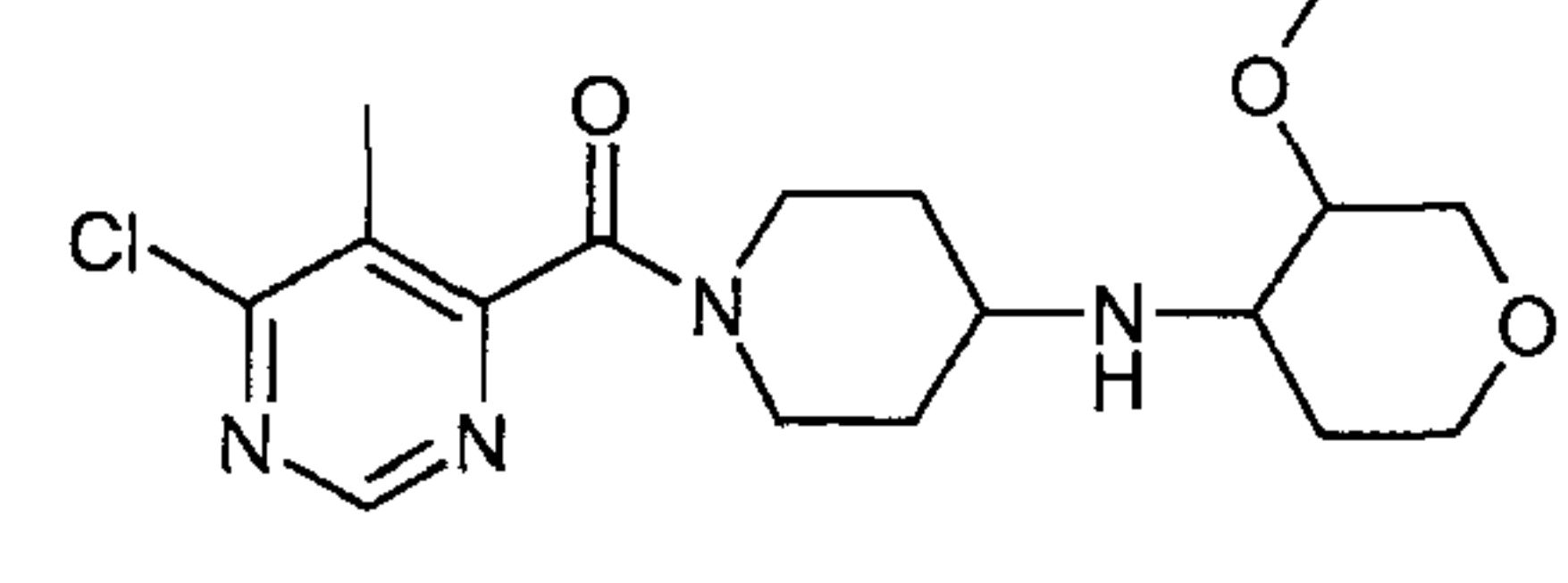
31214-7

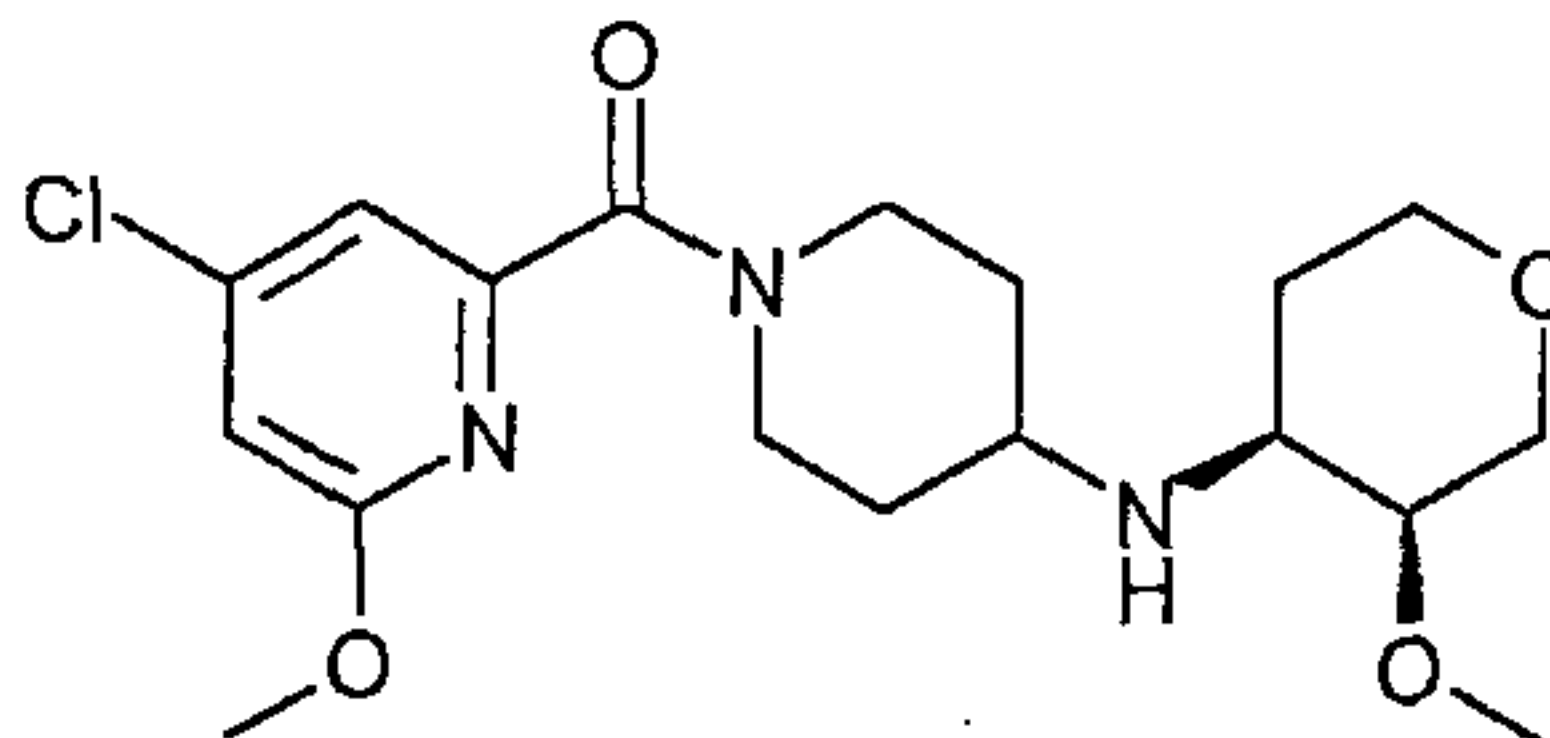
mixture was allowed to warm to room temperature and stirred for 1.5h; the reaction mixture was diluted with dichloromethane and washed with an aqueous saturated sodium bicarbonate solution. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge: 10g; eluent: dichloromethane/methanol=95/5%). 1.0 g (2.41 mmol) of the title compound were obtained.

The following intermediates were synthesized in analogy to Intermediate 26a.

Core Intermediate	Piperidine Intermediate	Chloro-pyrimidine Intermediate	STRUCTURE
2a	21a	26b	
2a	4-Methoxy-[1,4']bi piperidinyl (commercially available)	26c	
2b	21a	26d	
2a	21d	26e	

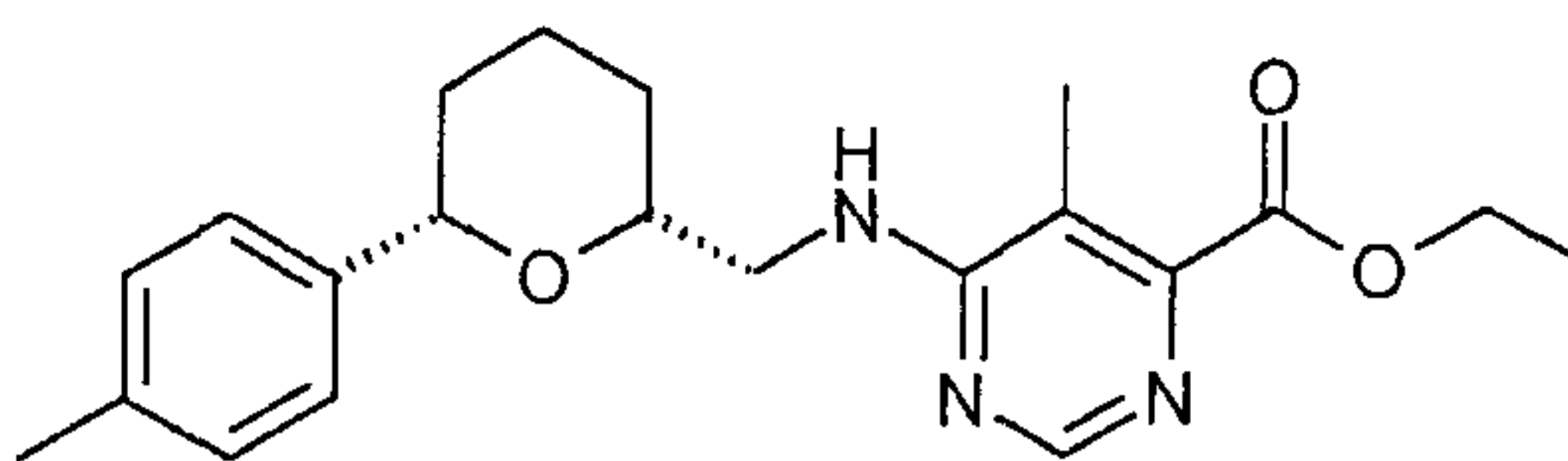
312r4-7

2c	21a	26f	
2c	21b	26g	
2c	21c	26h	
2a	21e	26i	

Intermediate 26j

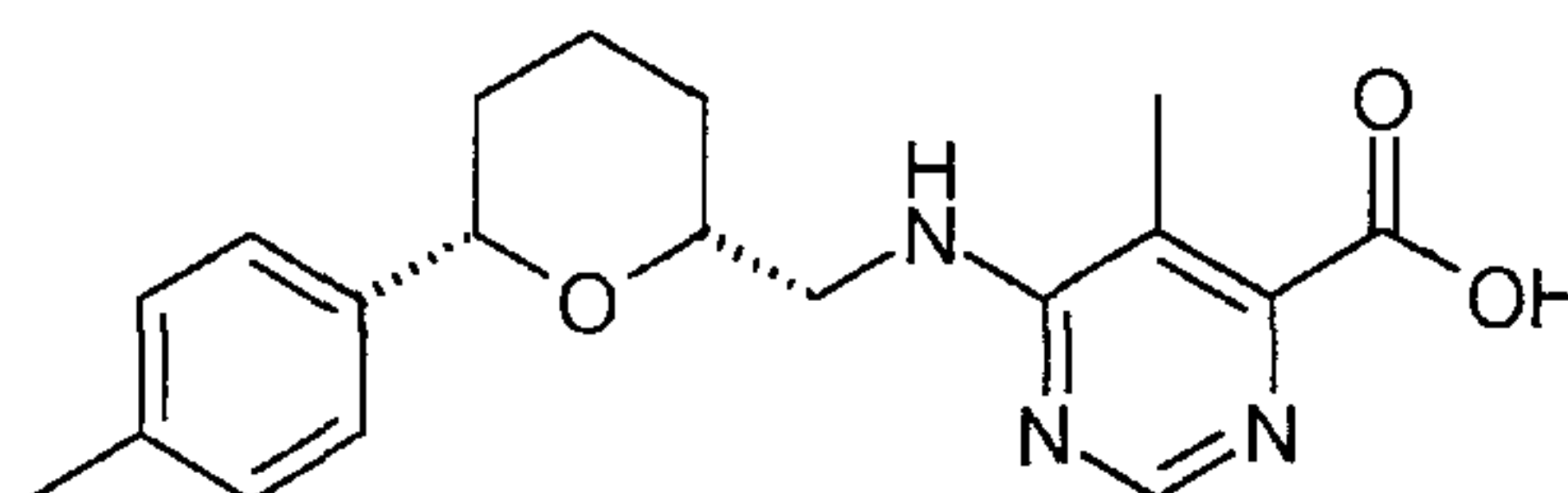
Intermediate 2e (55 mg, 267 μmol) was added to a solution of triethylamine (111 μl ,
 5 800 μmol) and Intermediate 21c (73 mg, 291 μmol) in 2.5 ml dichloromethane, and the
 reaction mixture was stirred for 15 min at room temperature. The reaction mixture was diluted
 with dichloromethane, washed with a saturated aqueous sodium bicarbonate solution, dried
 over sodium sulfate and concentrated under vacuum. The residue was purified by reversed
 phase HPLC to give the desired product (133 mg).

10

Intermediate 27a

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Intermediate 3a (976 mg, 4.6 mmol) and N,N-diisopropylethylamine (0.9 ml, 5.24 mmol) were dissolved in 15 ml of dry 1,4-dioxane; intermediate 17a (430 mg, 2.09 mmol) was added and the reaction mixture was refluxed for 6h. The reaction mixture was cooled to room temperature, water was added and the reaction mixture was extracted with dichloromethane; the organic phase was washed with an aqueous saturated sodium bicarbonate solution and concentrated under vacuum. 770 mg (2.08 mmol) of the desired compound were obtained as crude product. Absolute stereochemistry known.

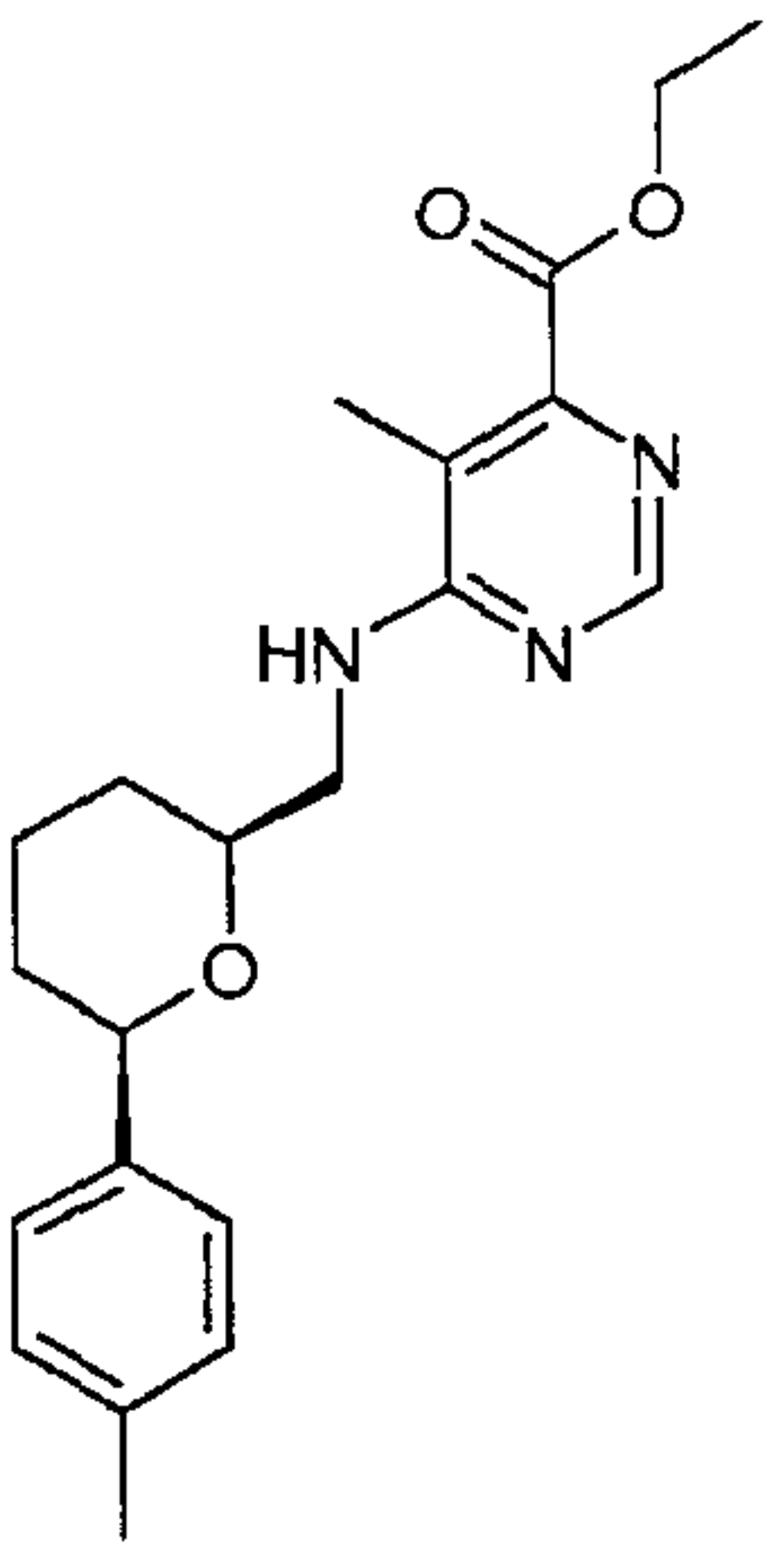
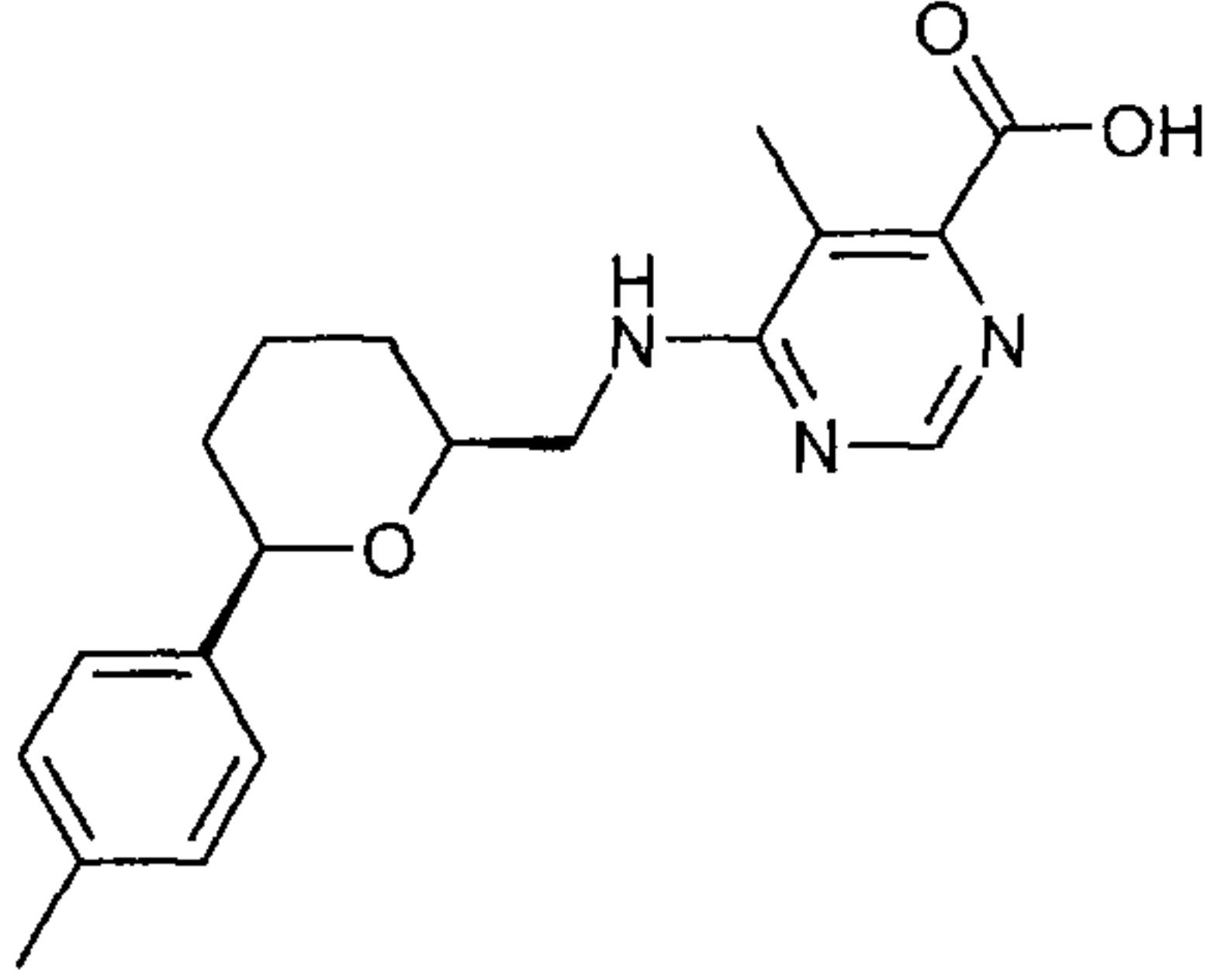
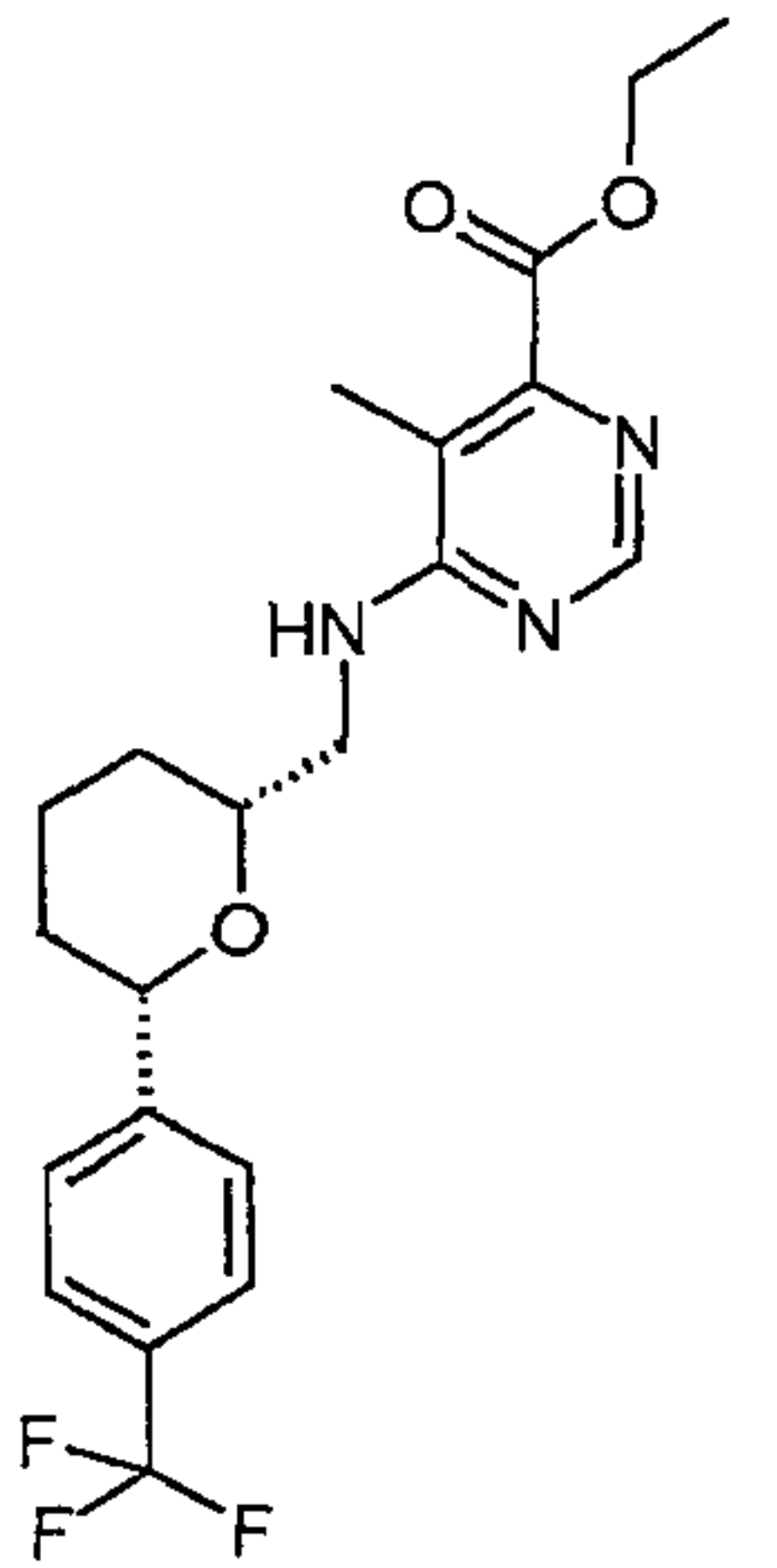
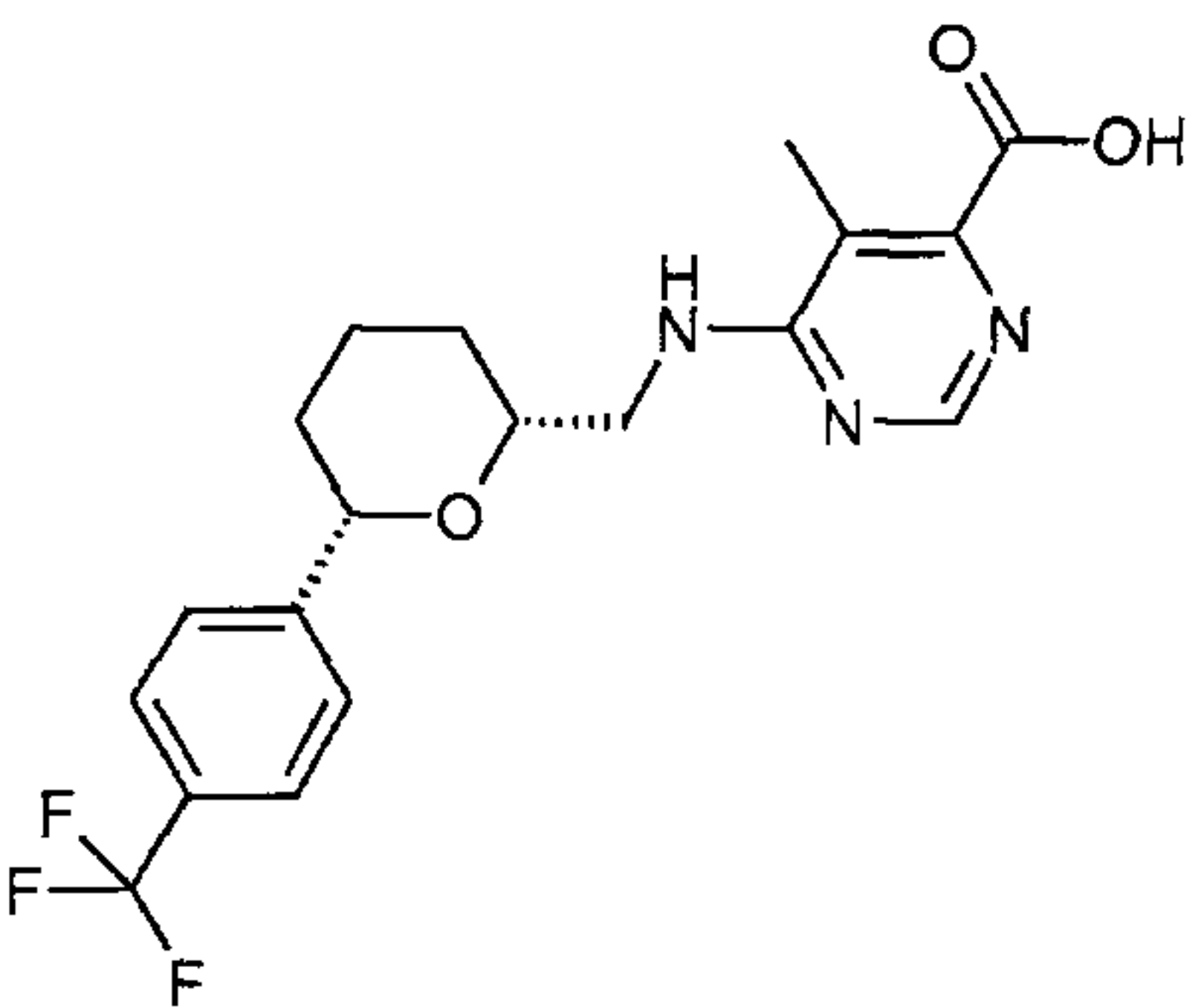
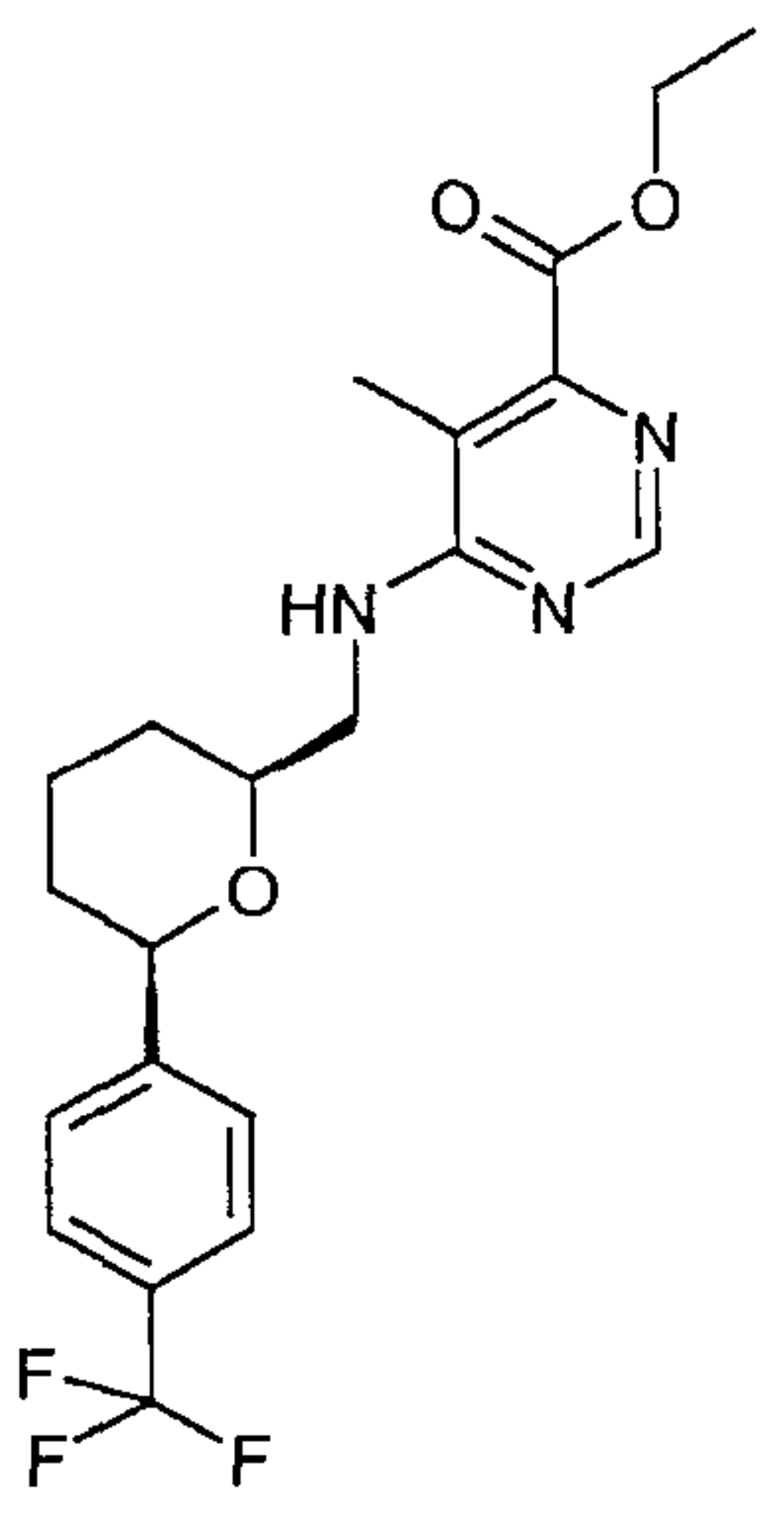
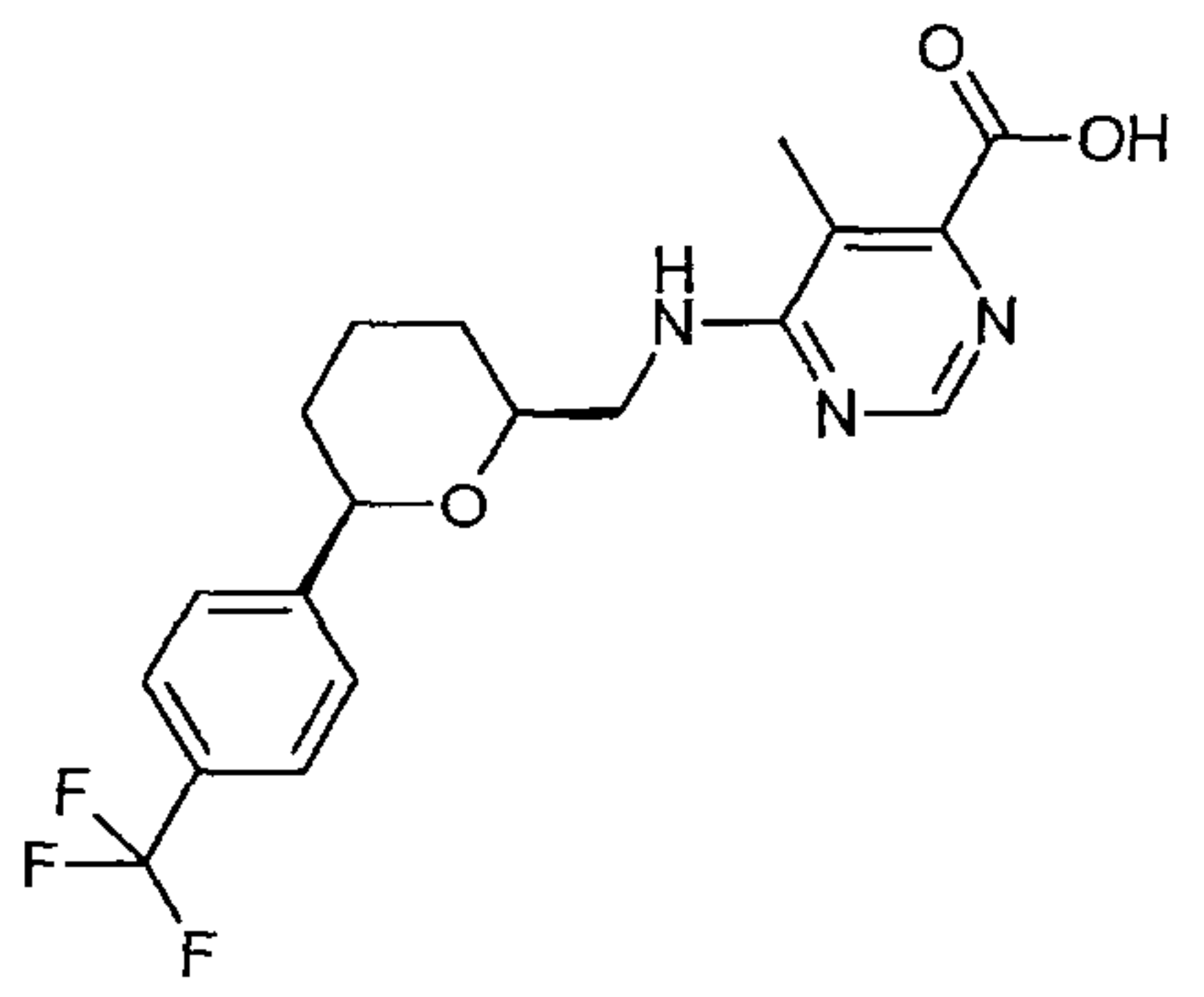
Intermediate 28a

Intermediate 27a (770 mg, 2.08 mmol) was dissolved in 8 ml of tetrahydrofuran and a solution of LiOH (262 mg, 6.24 mmol) in 8 ml of water was added. The reaction mixture was stirred at 70°C for 1 hour and then concentrated under vacuum. 20 ml of water was added and the reaction mixture was acidified with 5 ml of a 4M solution of hydrochloric acid in water. The aqueous phase was extracted with dichloromethane (2x20ml). The organic phase was dried over sodium sulfate and removed under vacuum. 670 mg (1.96 mmol) of the desired product were obtained. Absolute stereochemistry known.

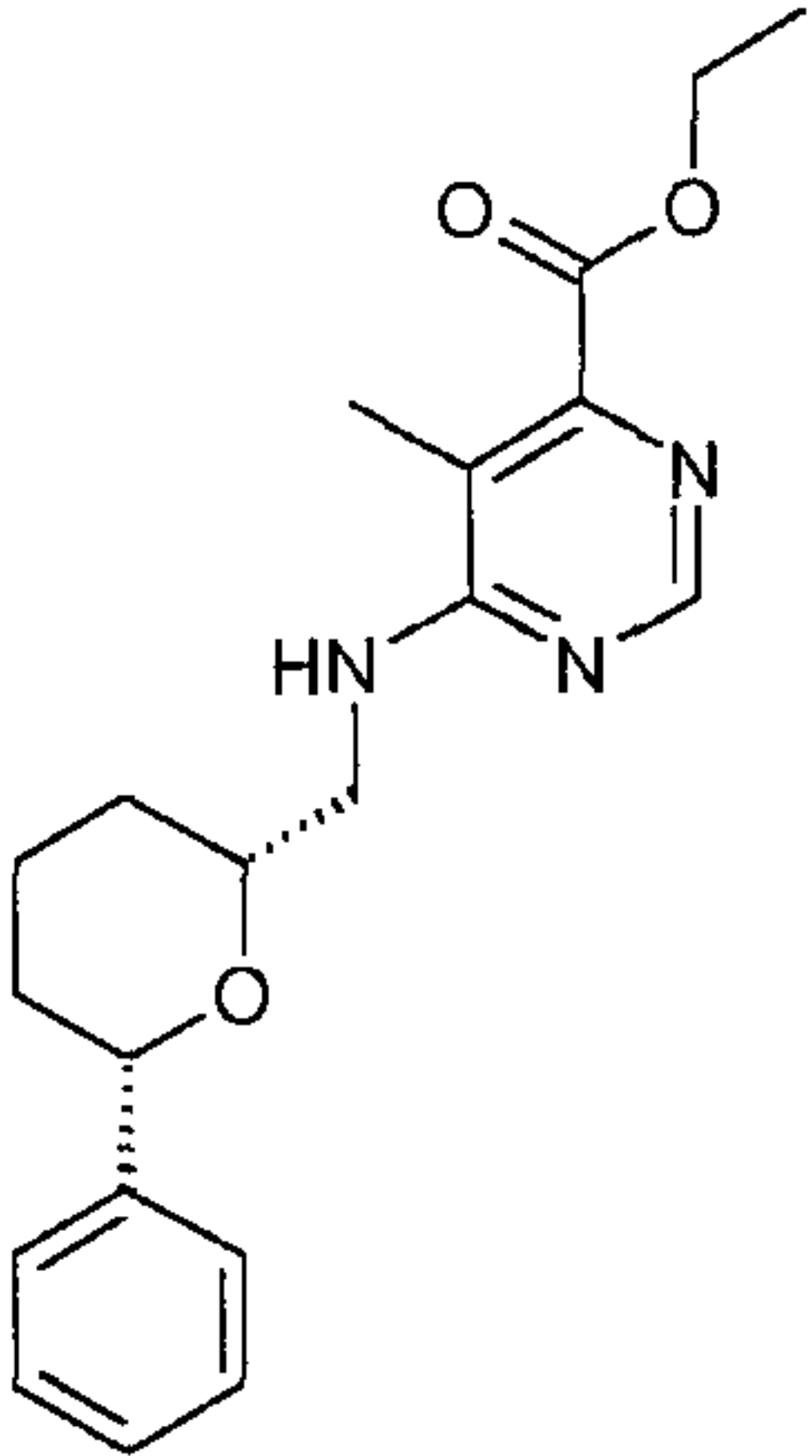
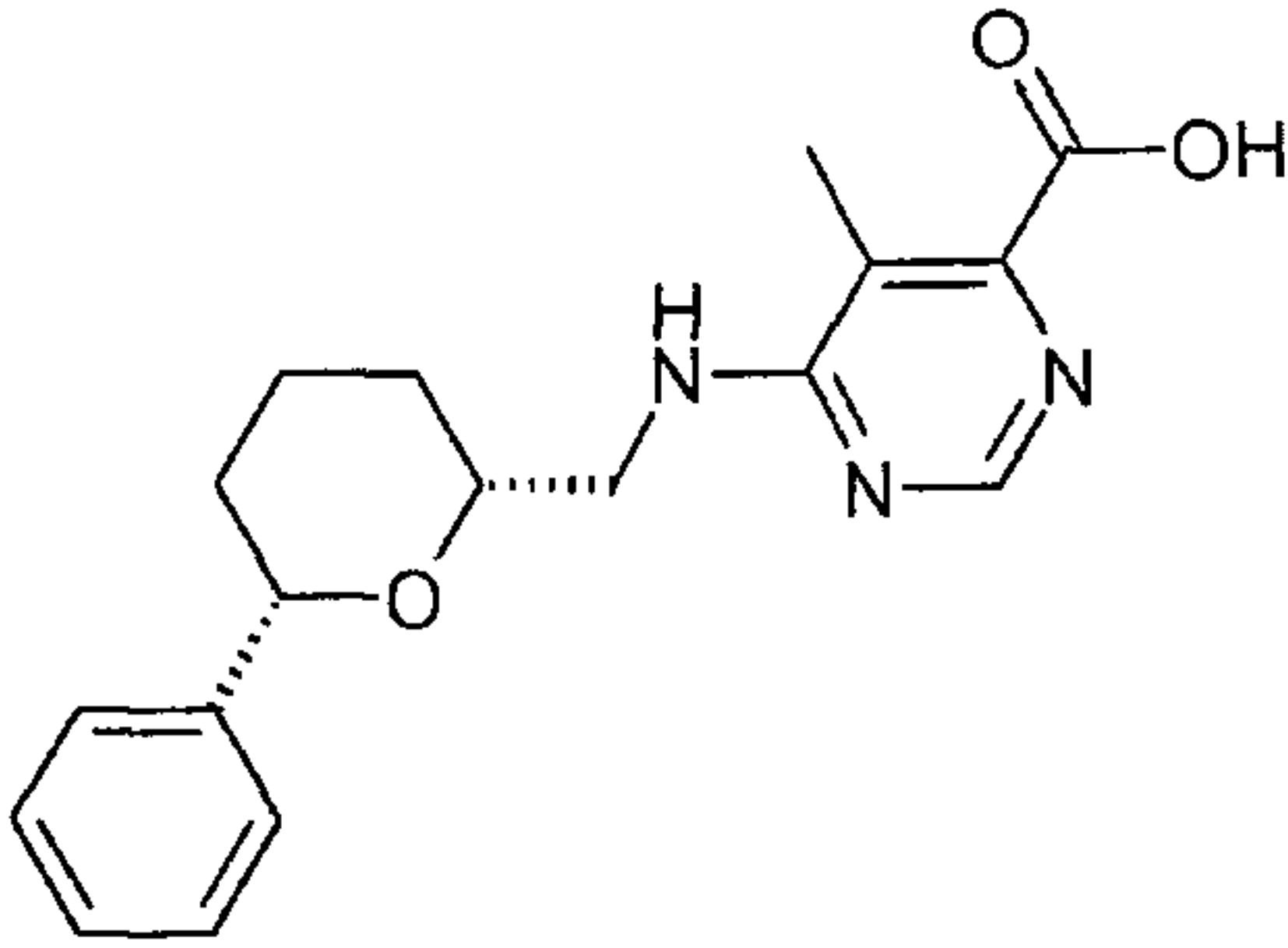
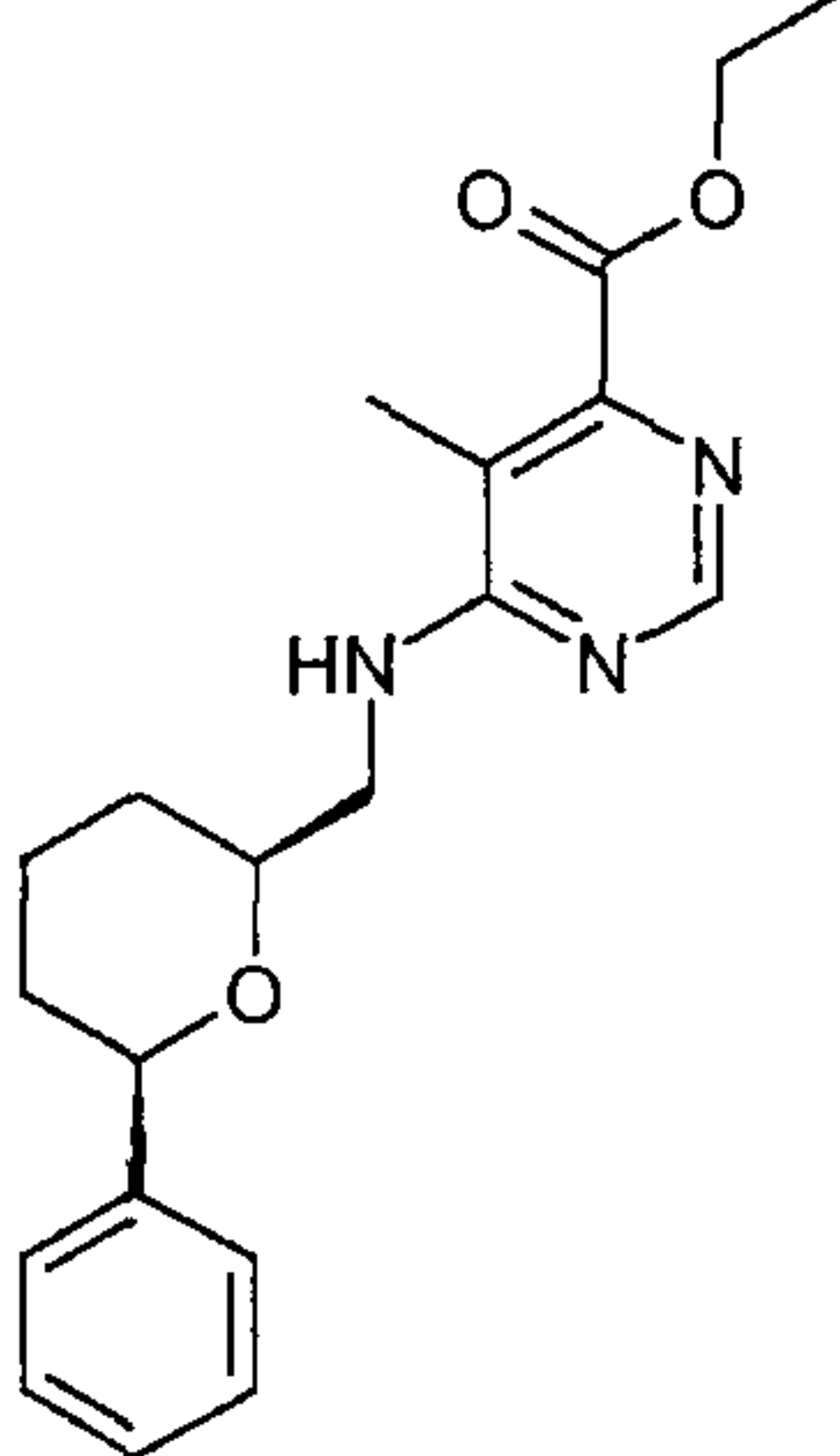
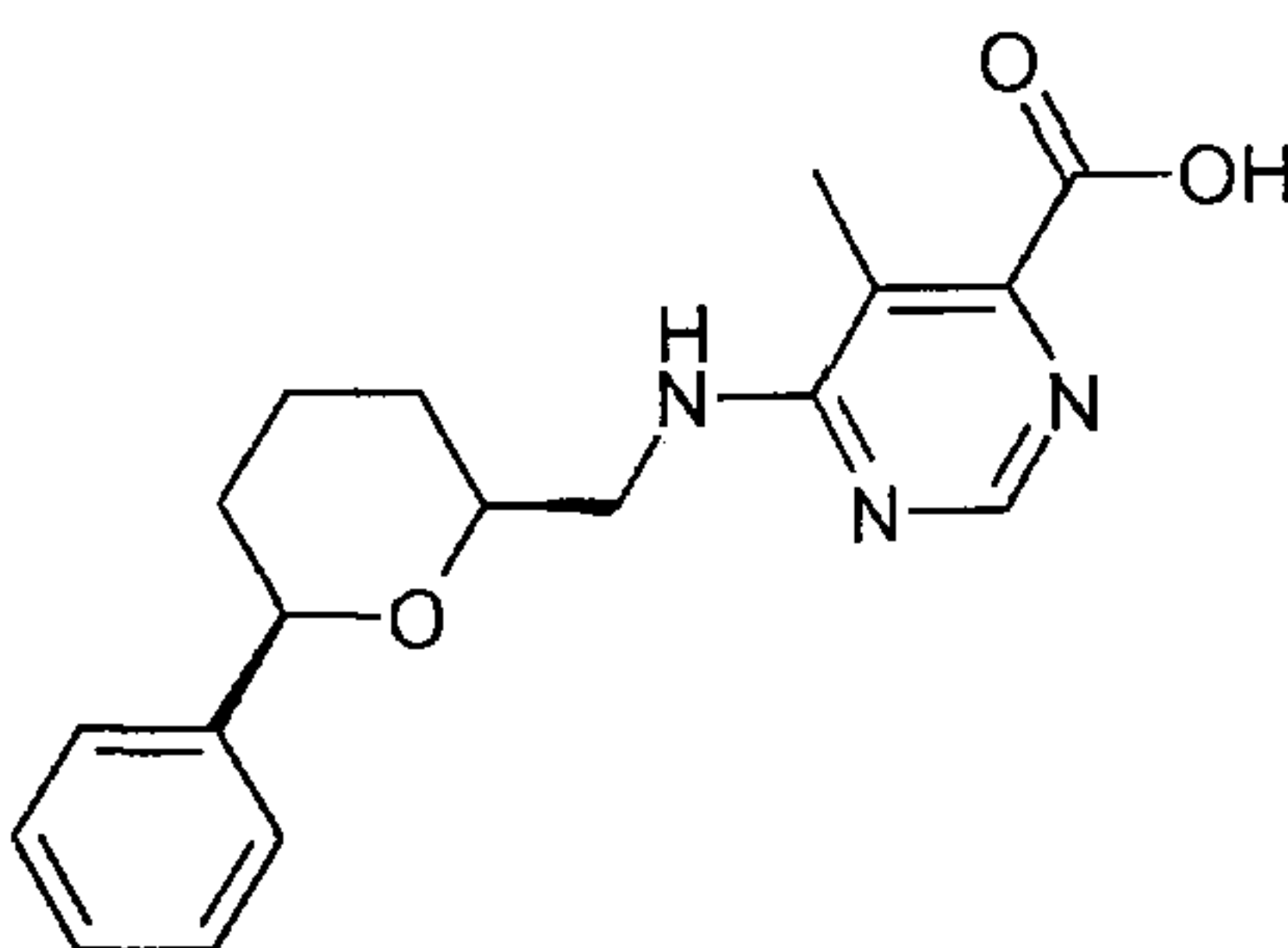
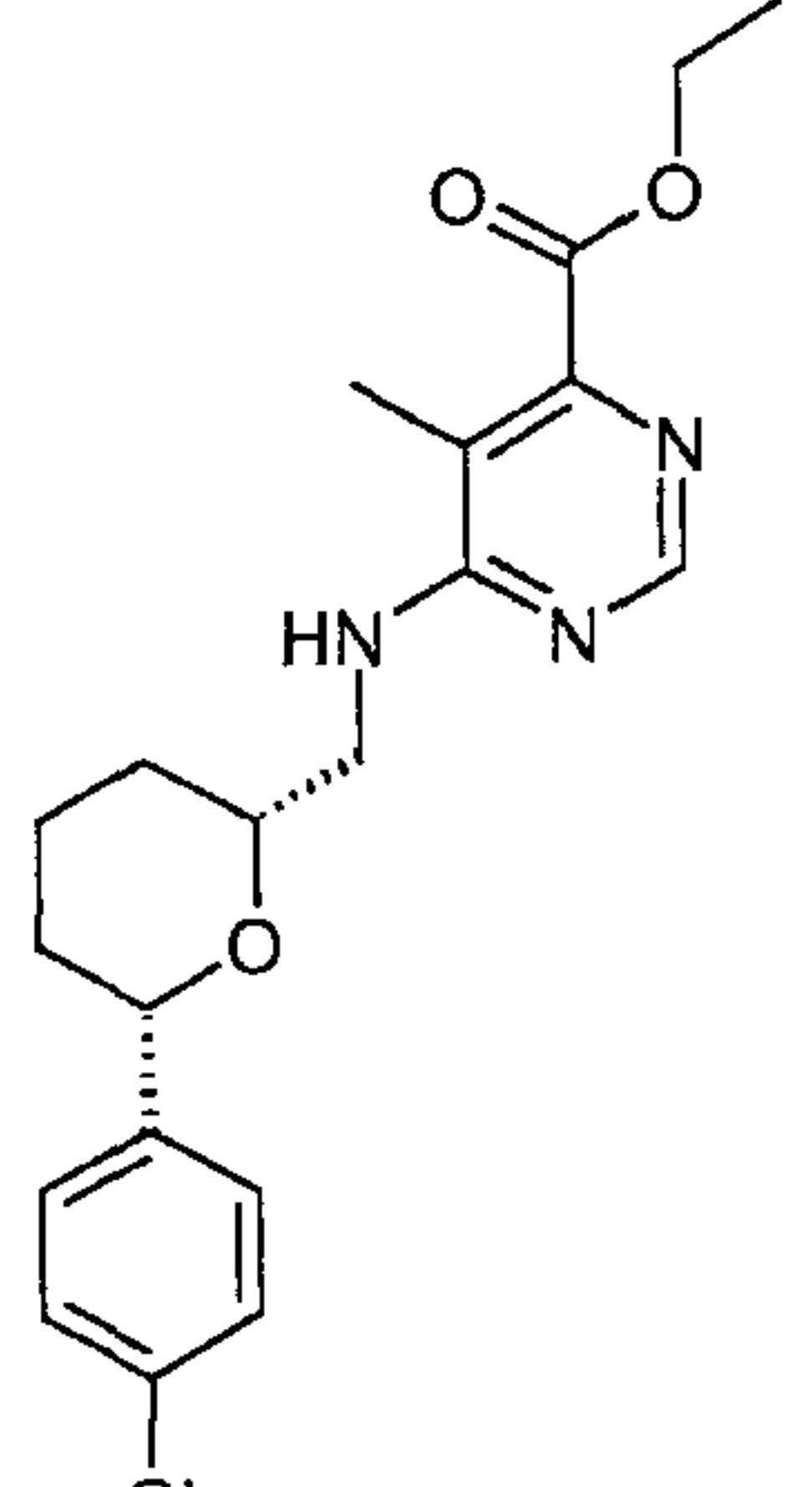
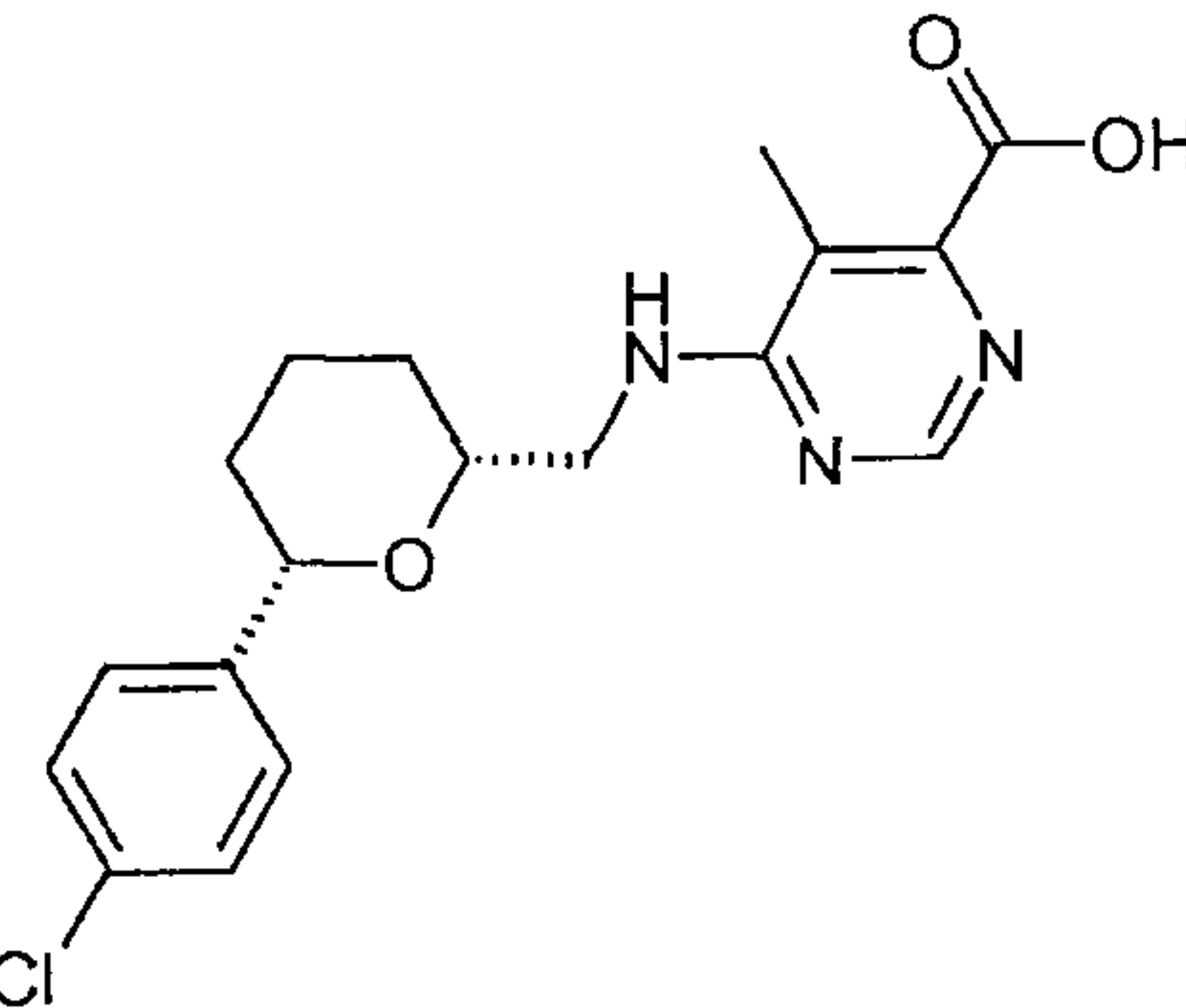
The following intermediates were synthesized in analogy to Intermediates 27a and 28a .

<i>Synthesis in analogy to intermediate 27a</i>				<i>Synthesis in analogy to intermediate 28a</i>		
Core Intermediate	Amine	Ester Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE	Stereochemistry

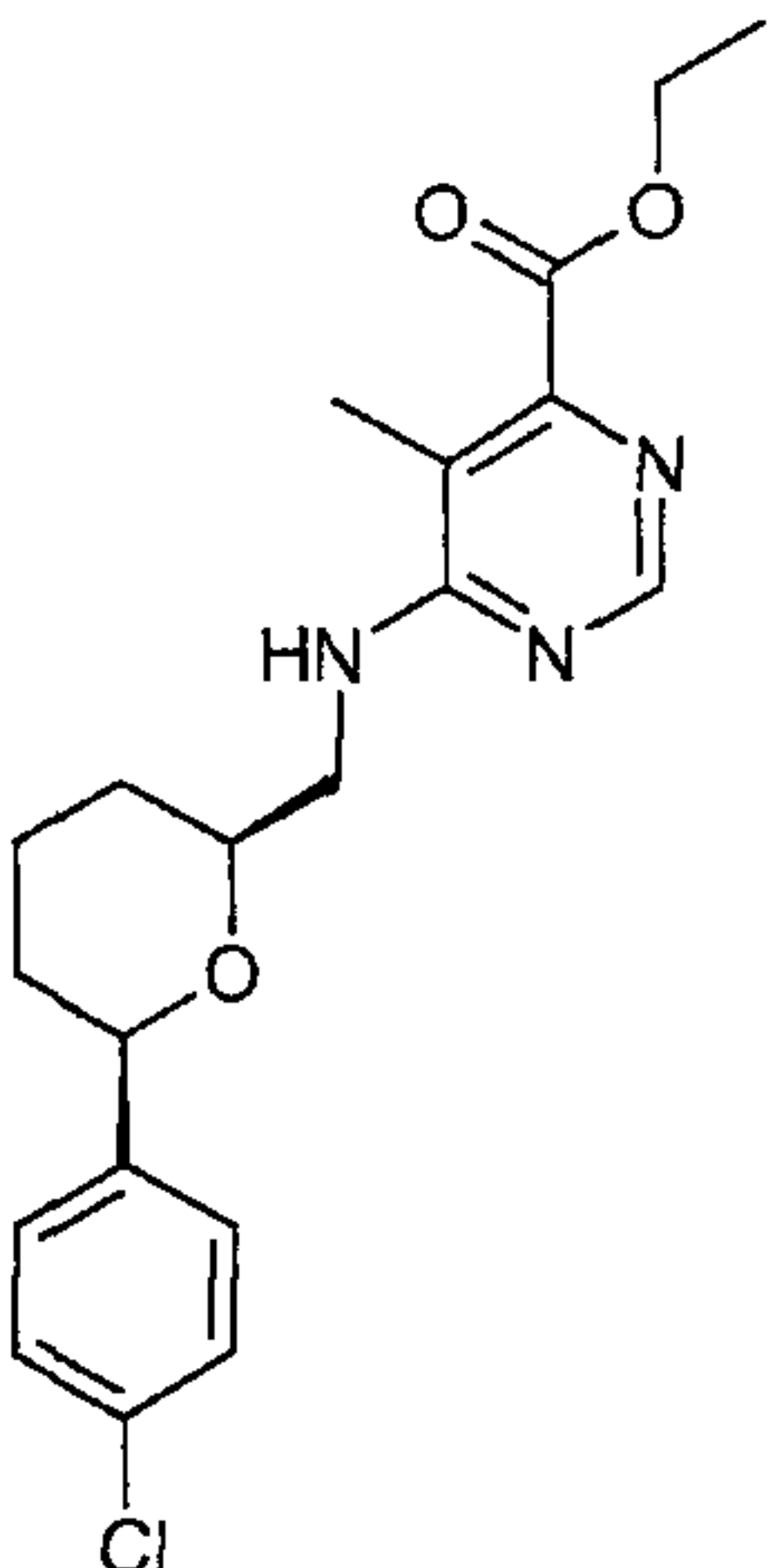
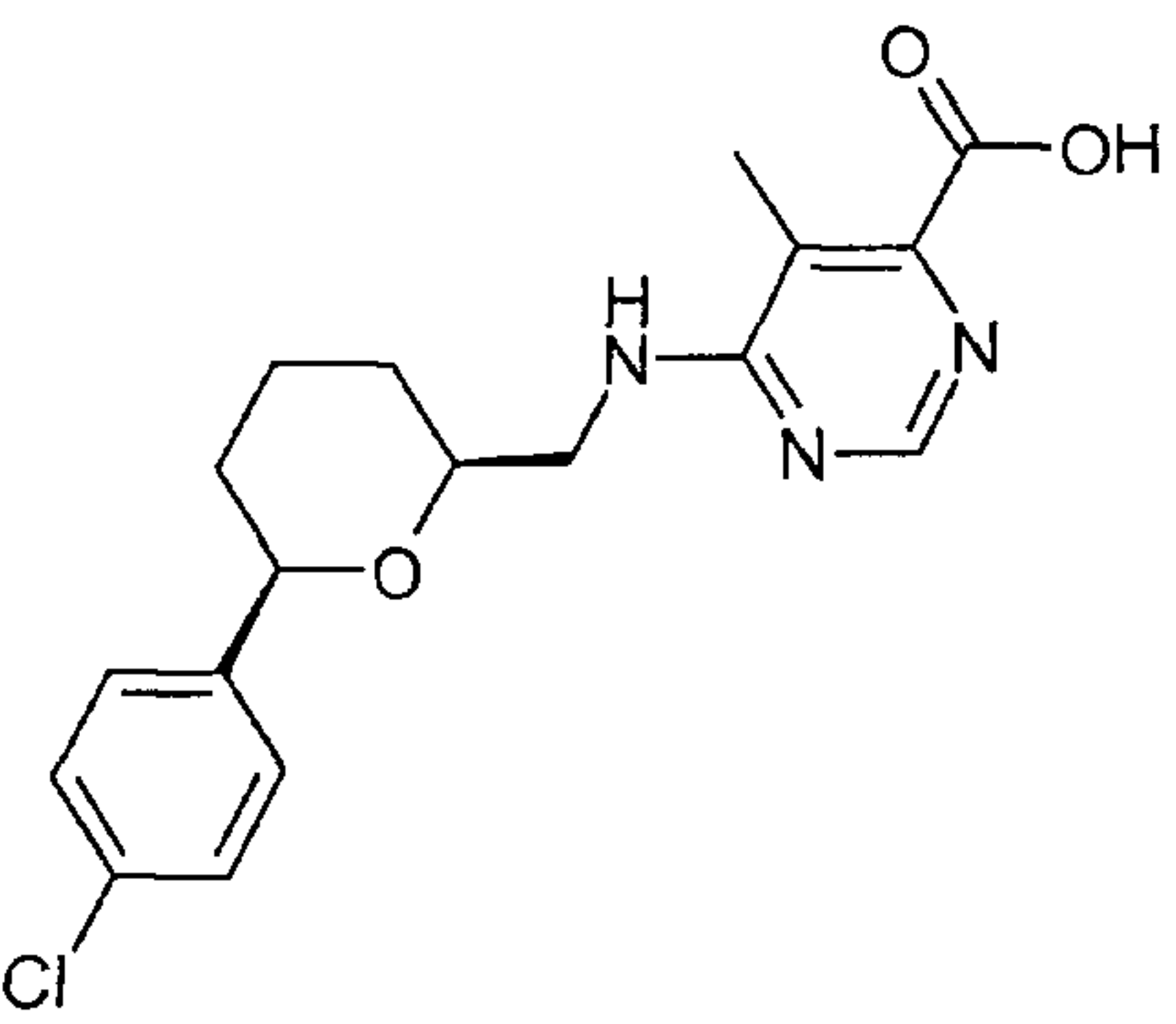
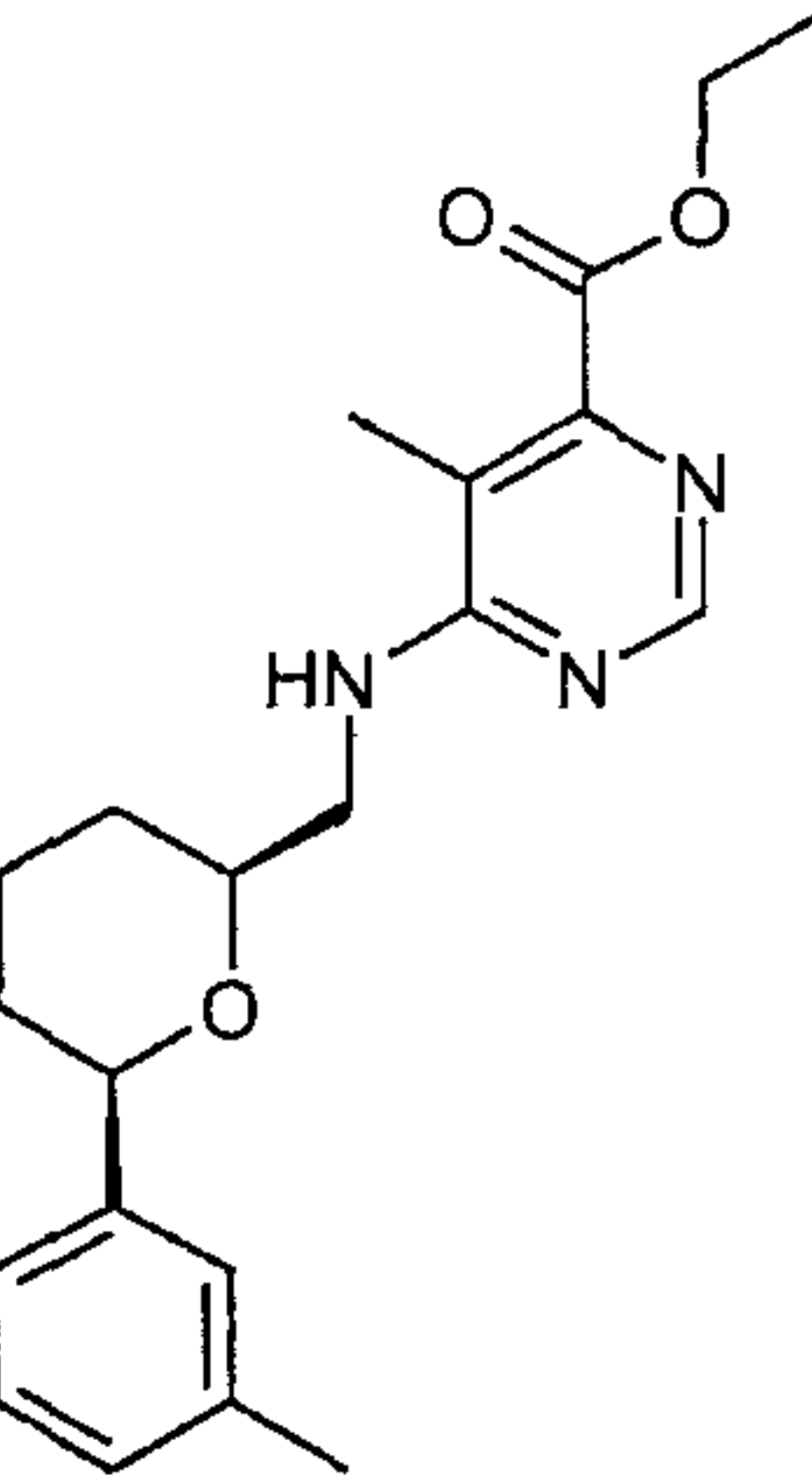
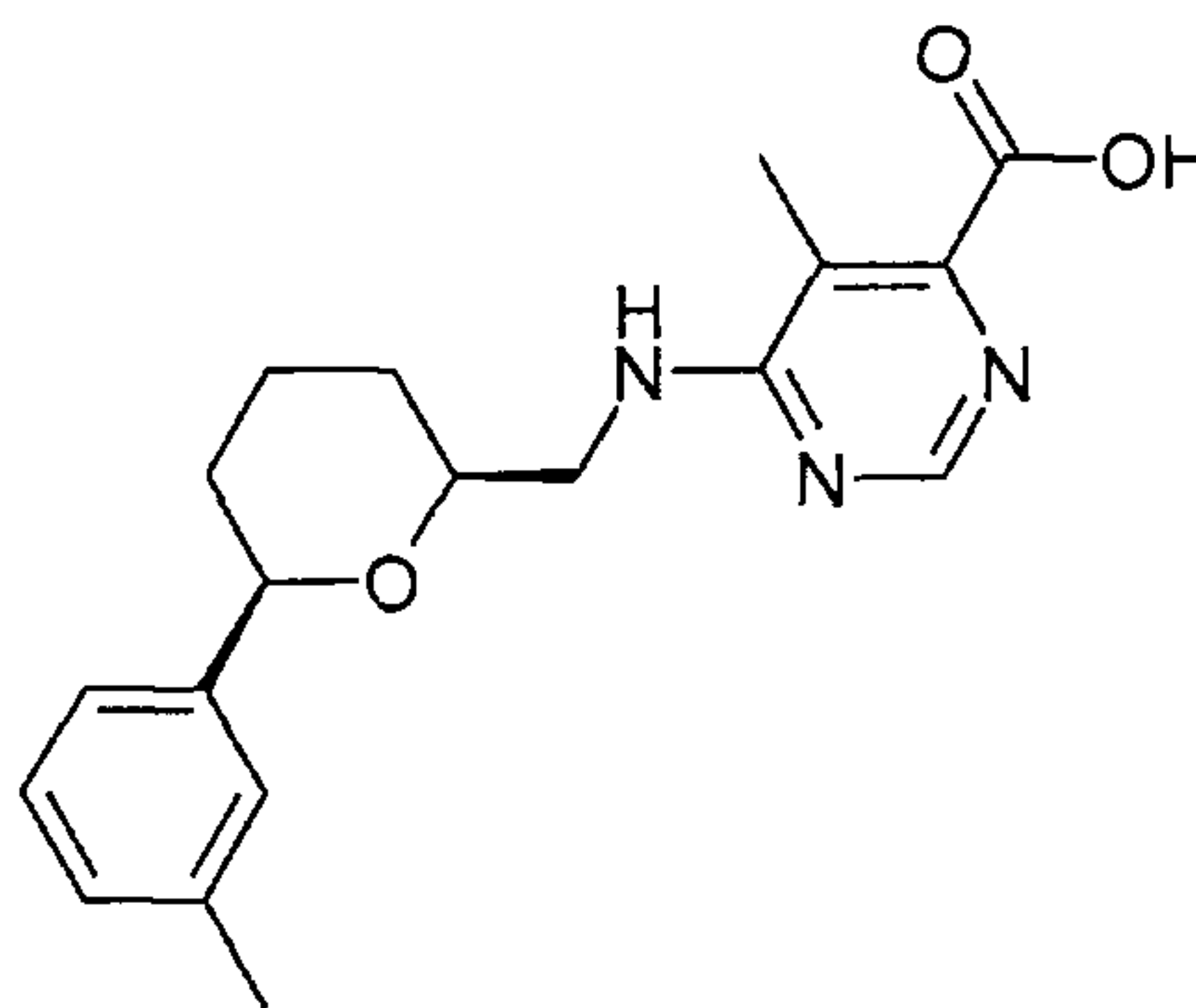
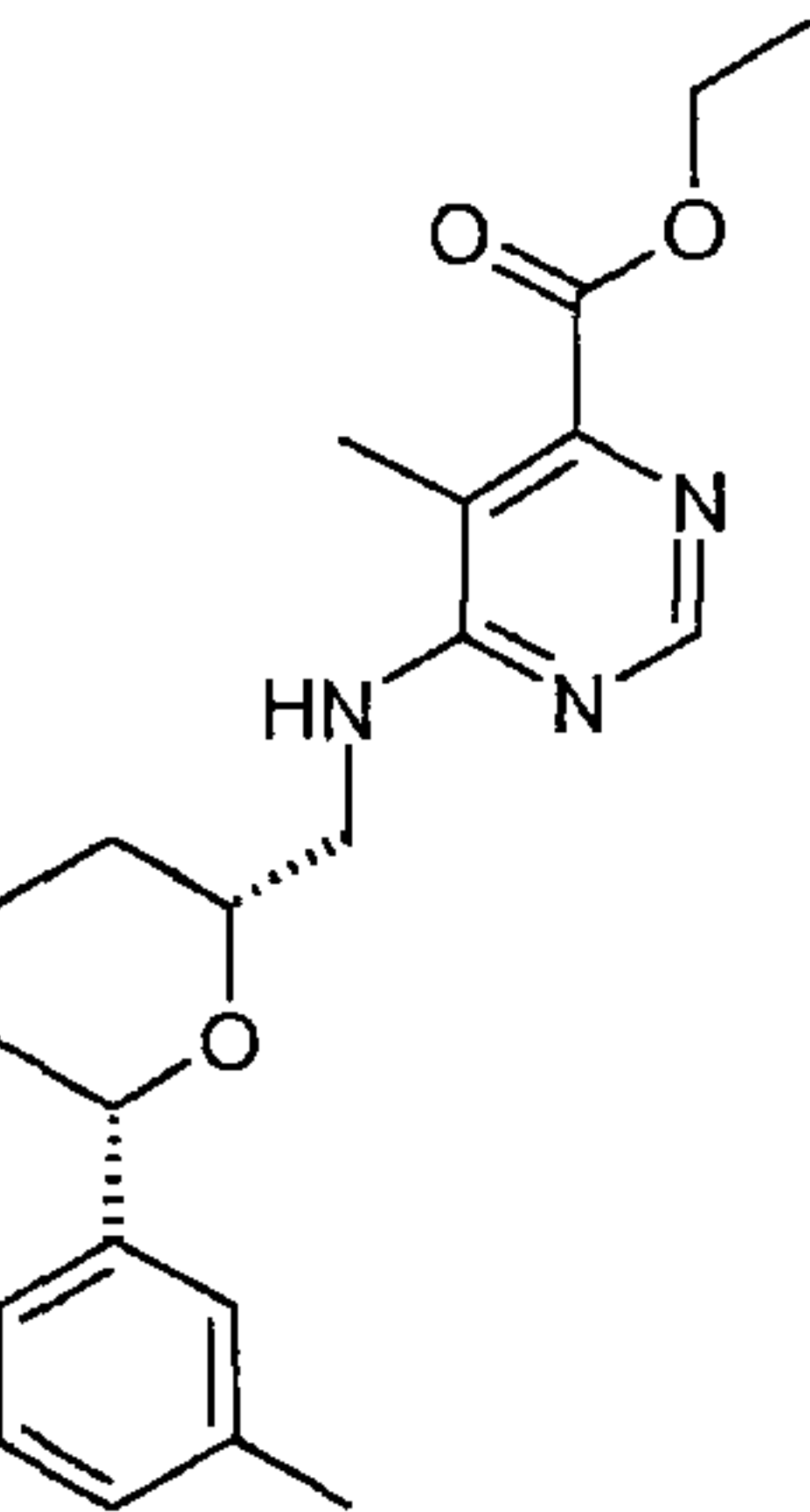
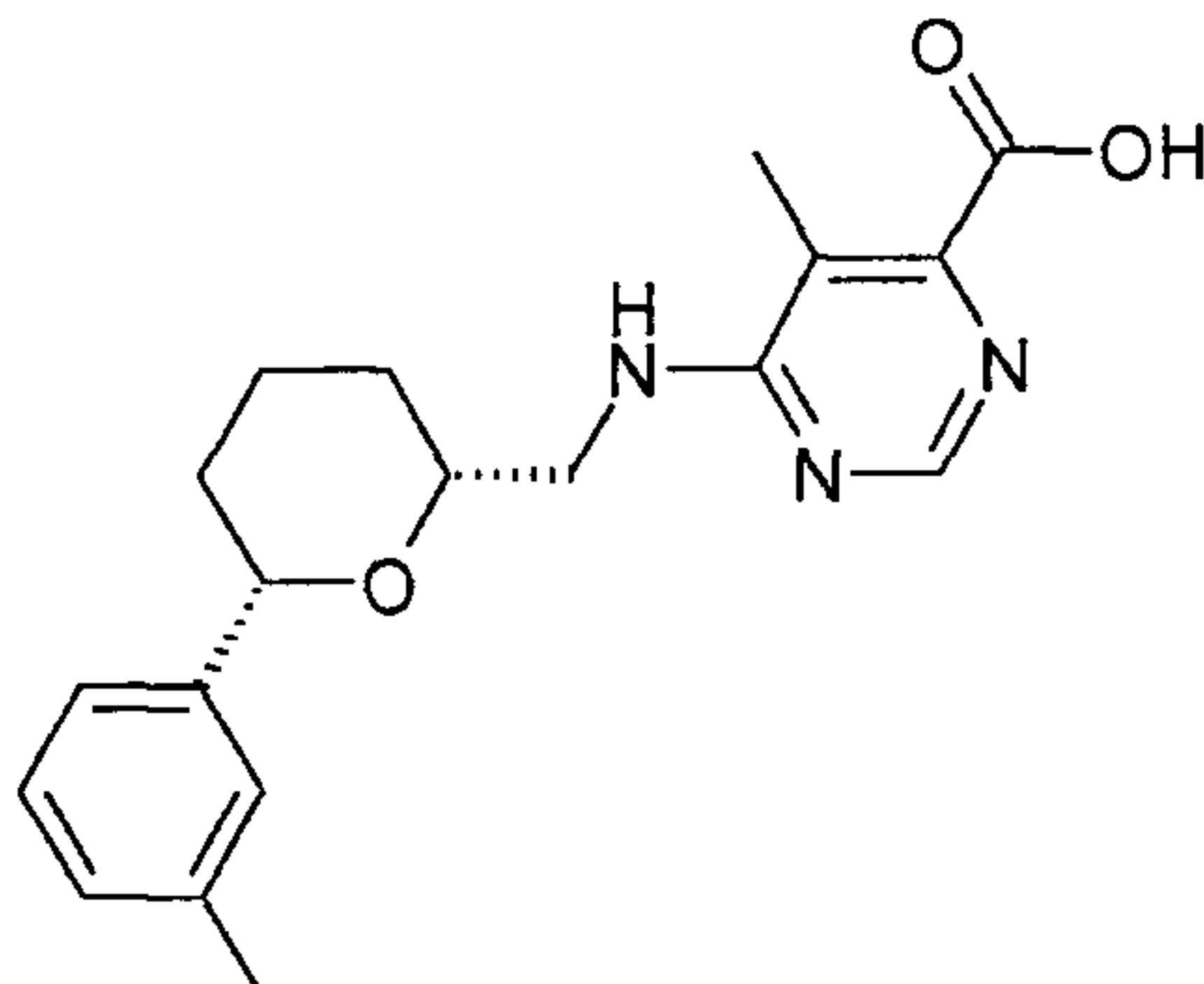
31214-7

3a	16a	27b		28b		absolute stereochemistry as shown
3a	16b	27c		28c		absolute stereochemistry as shown
3a	17b	27d		28d		absolute stereochemistry as shown

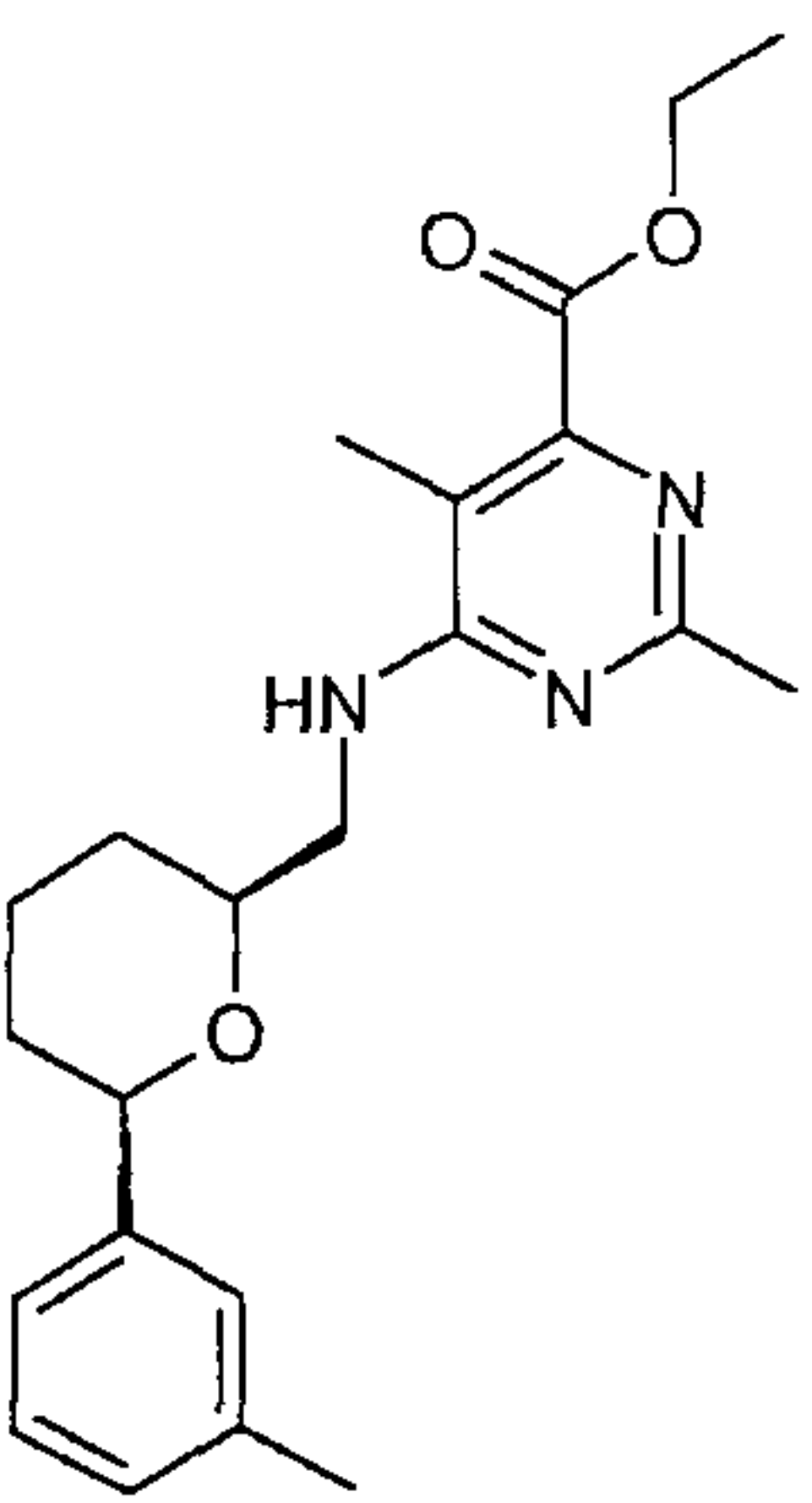
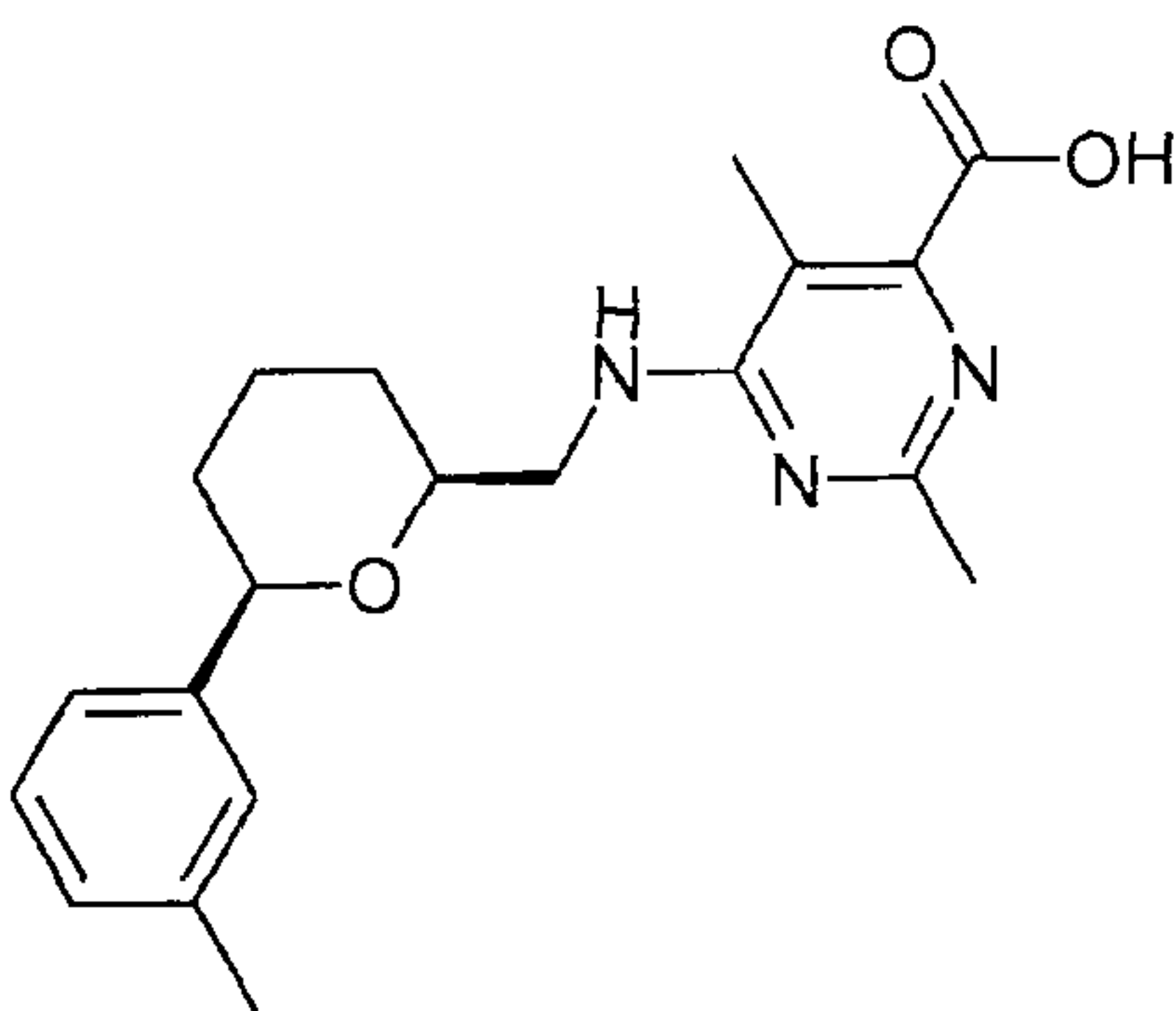
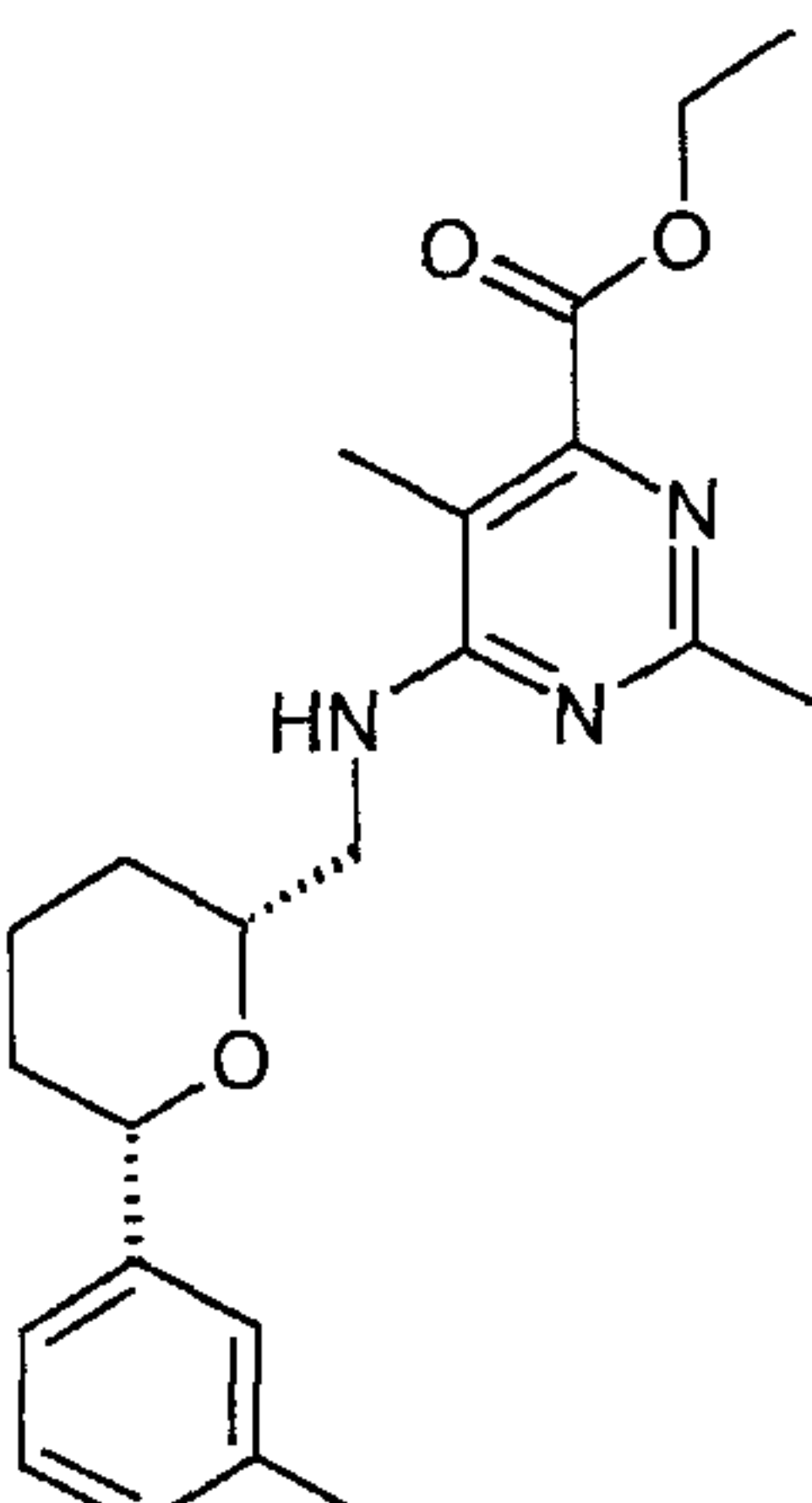
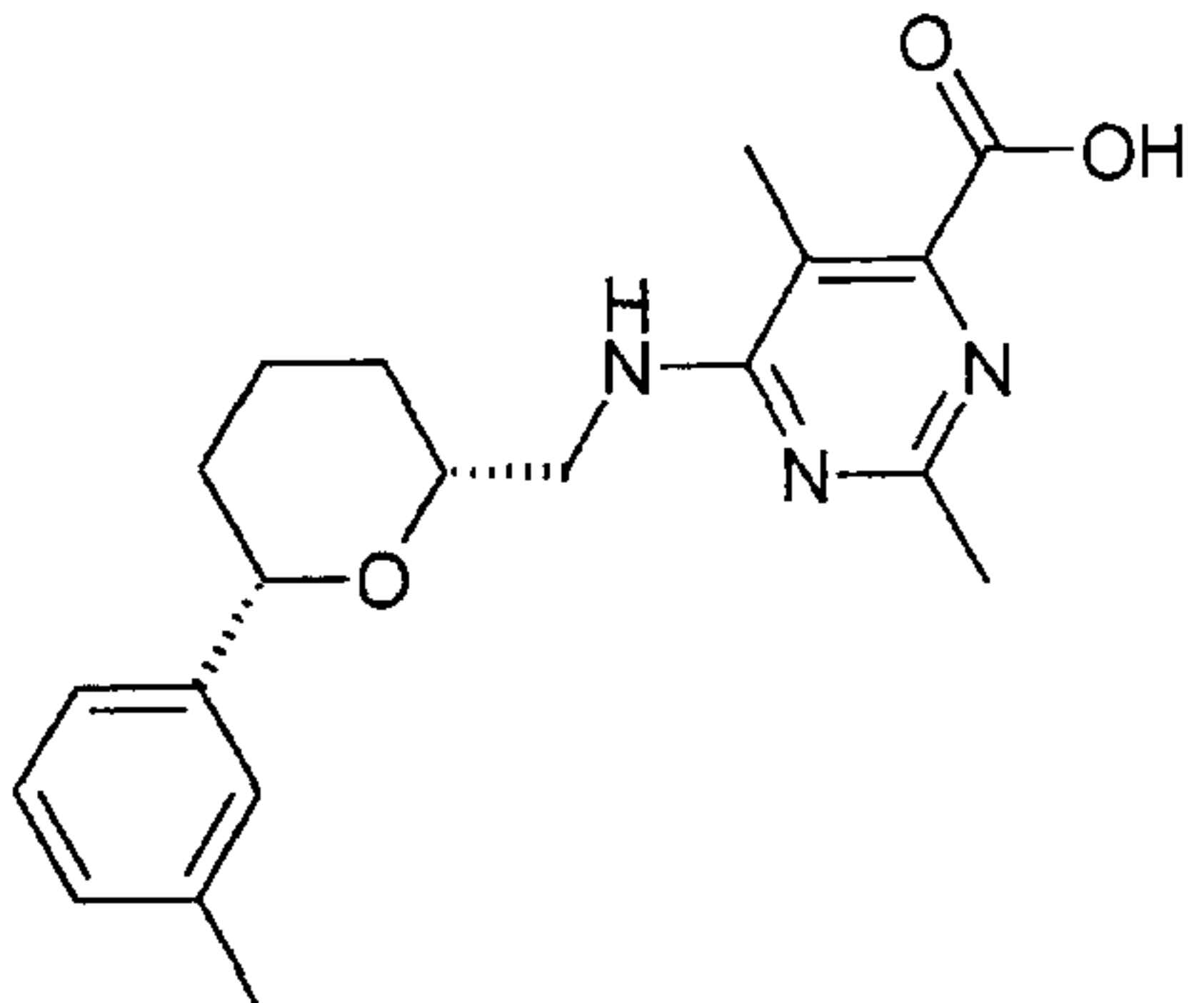
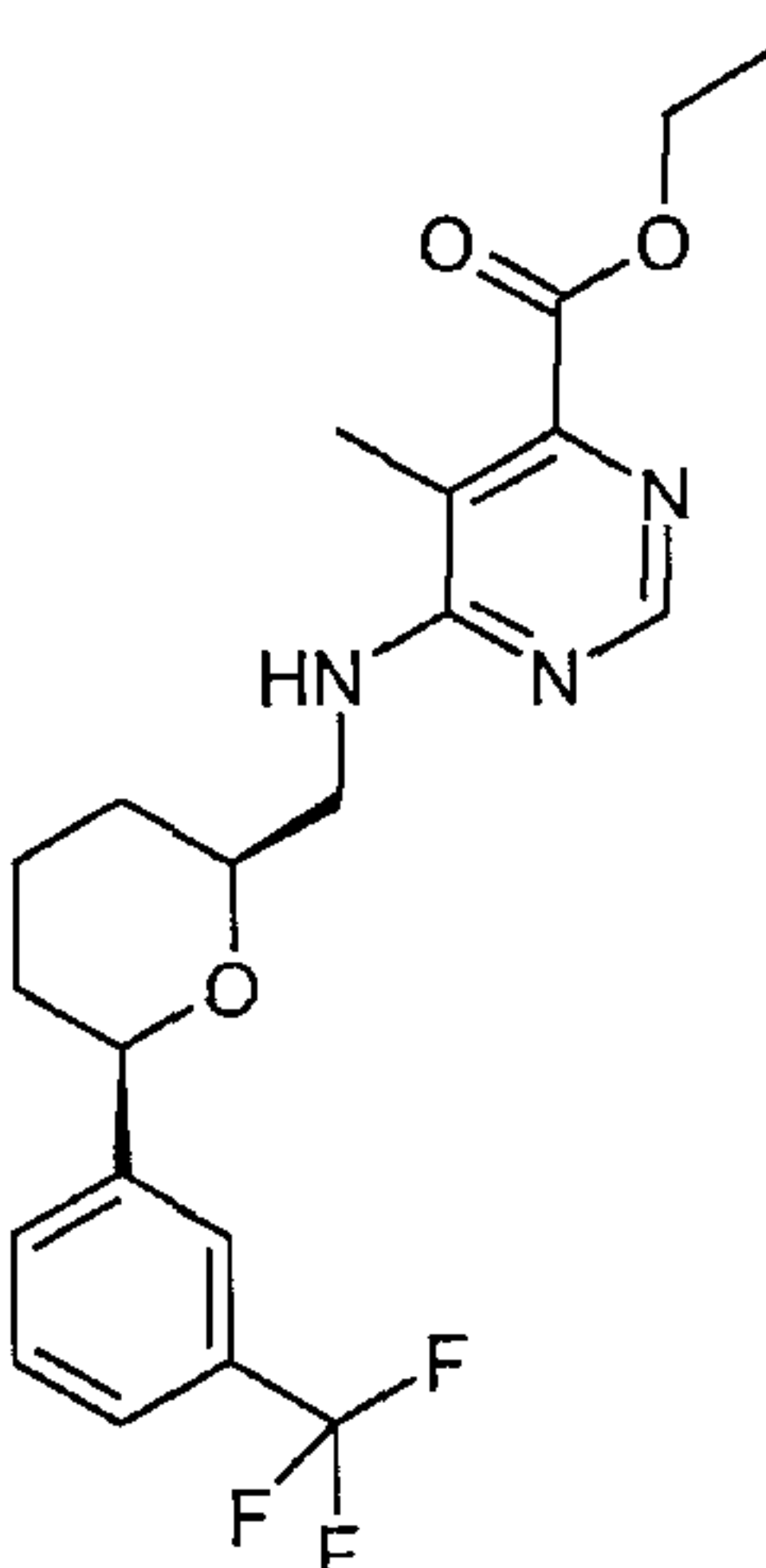
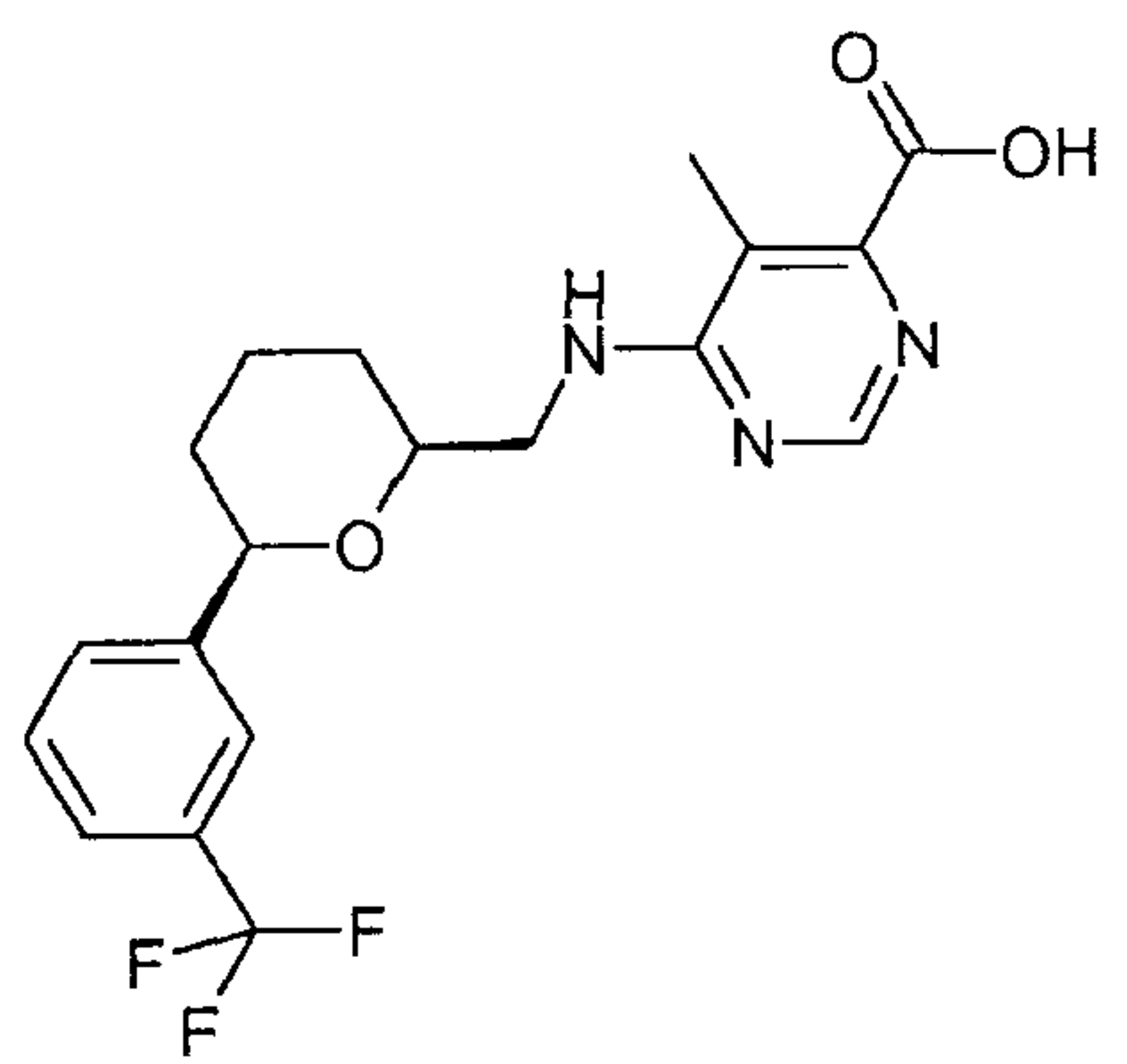
31214-7

3a	16c	27e		28e		relative stereochemistry cis
3a	17c	27f		28f		relative stereochemistry cis
3a	16d	27g		28g		relative stereochemistry cis

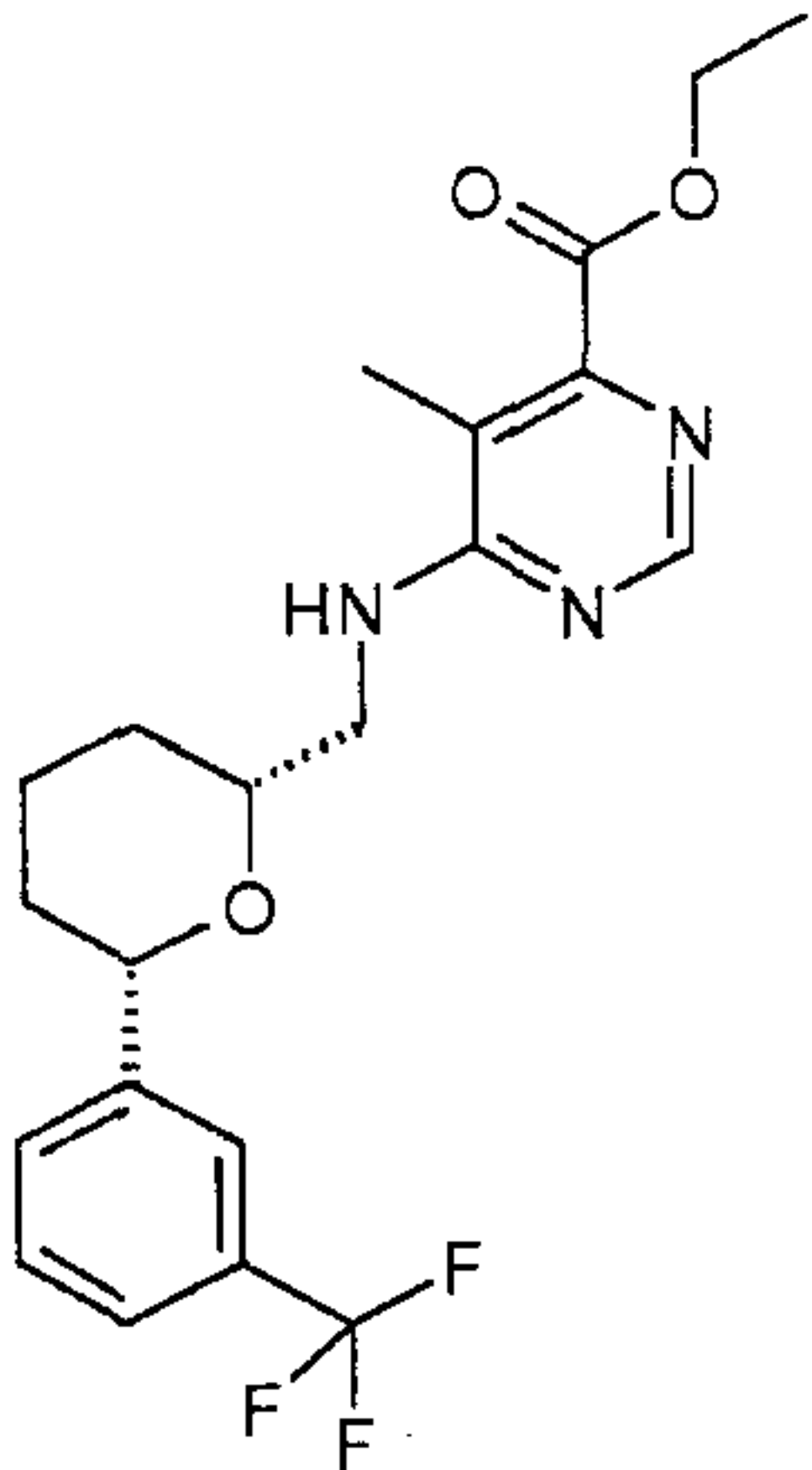
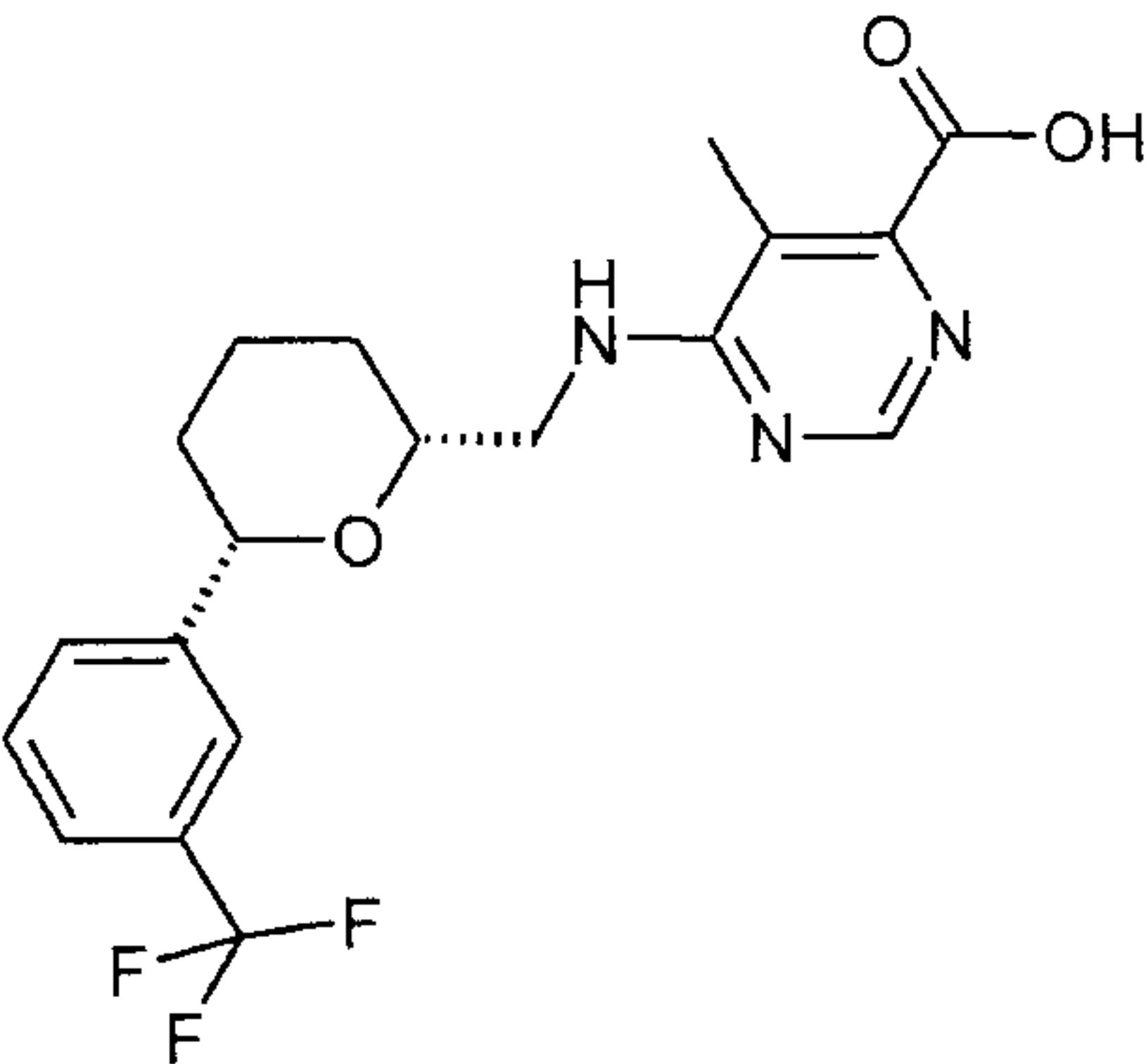
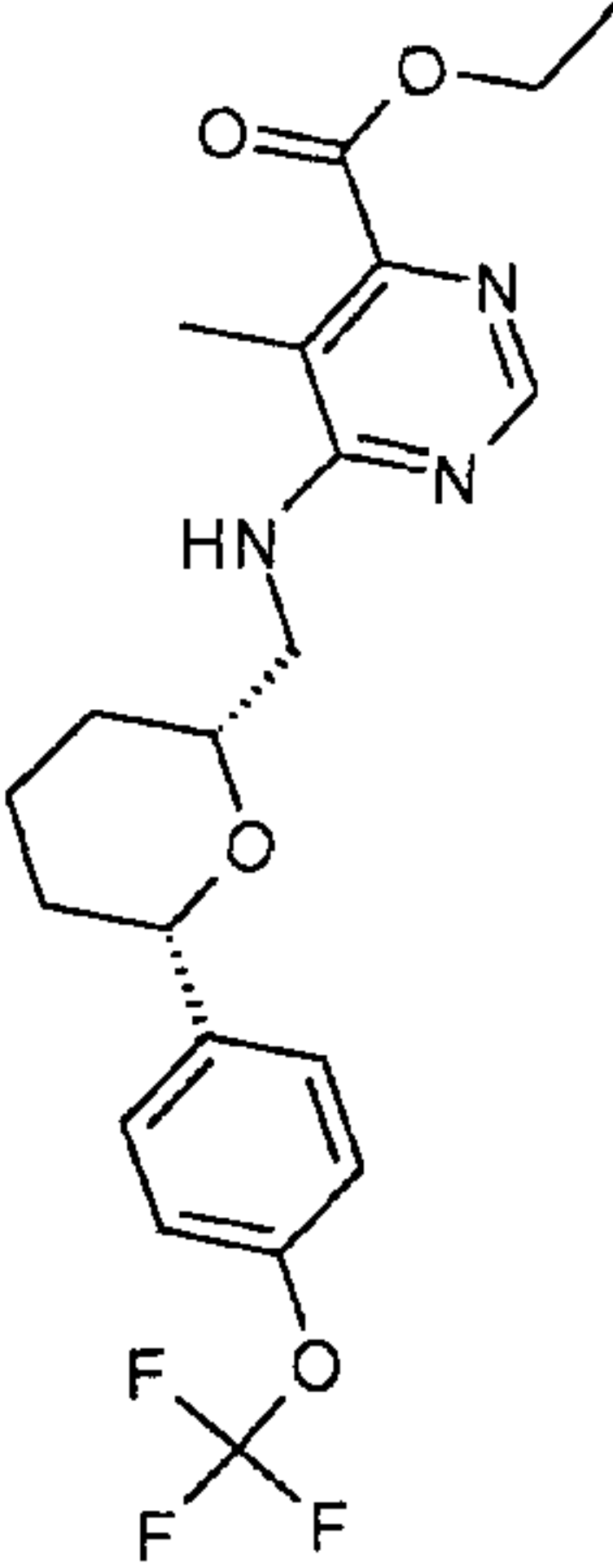
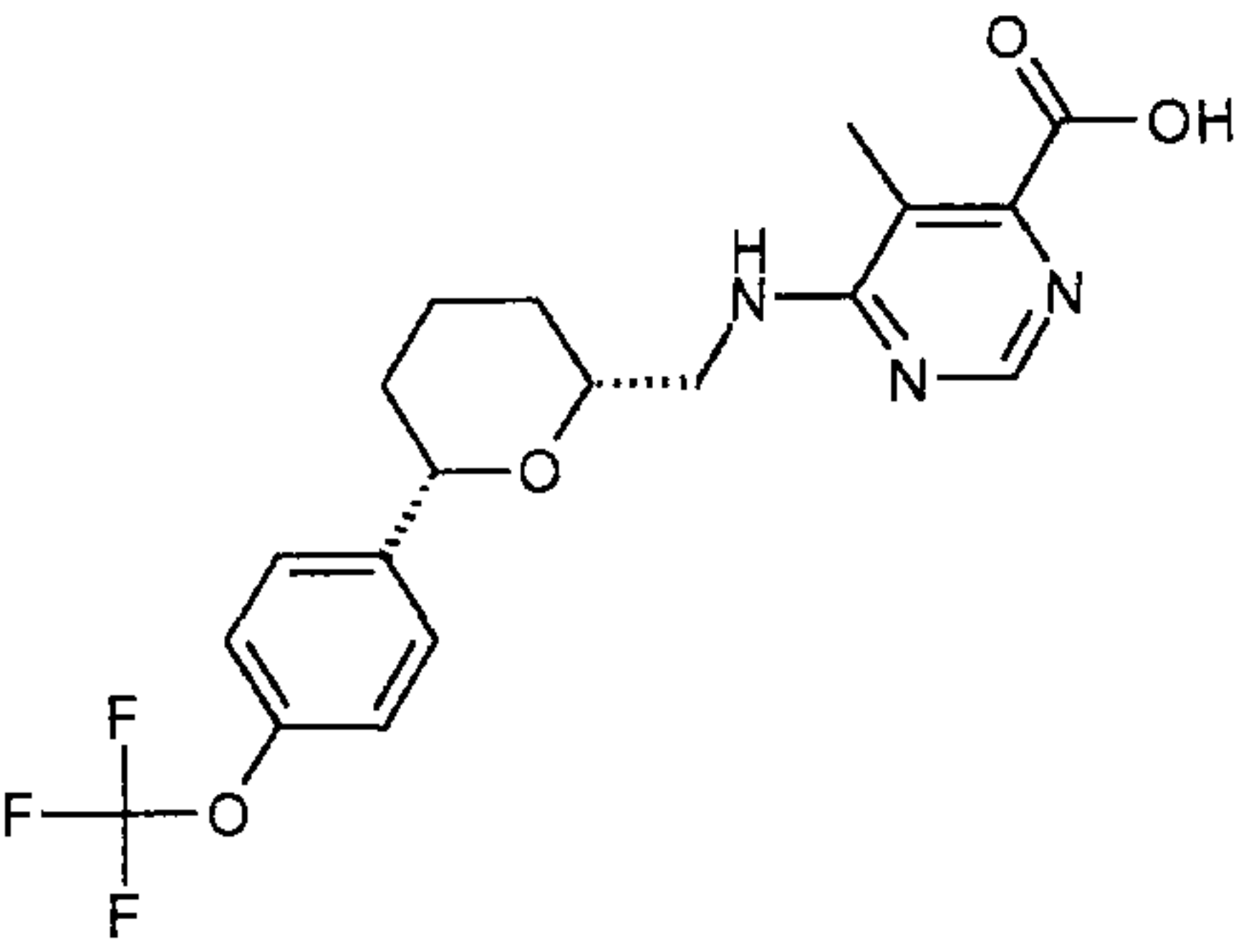
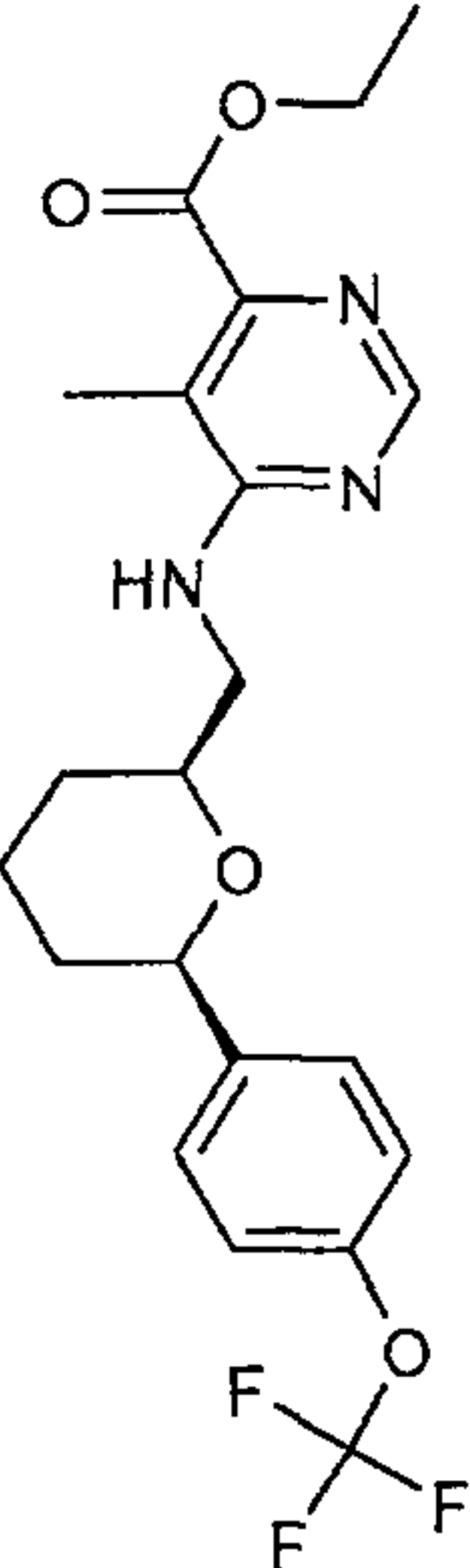
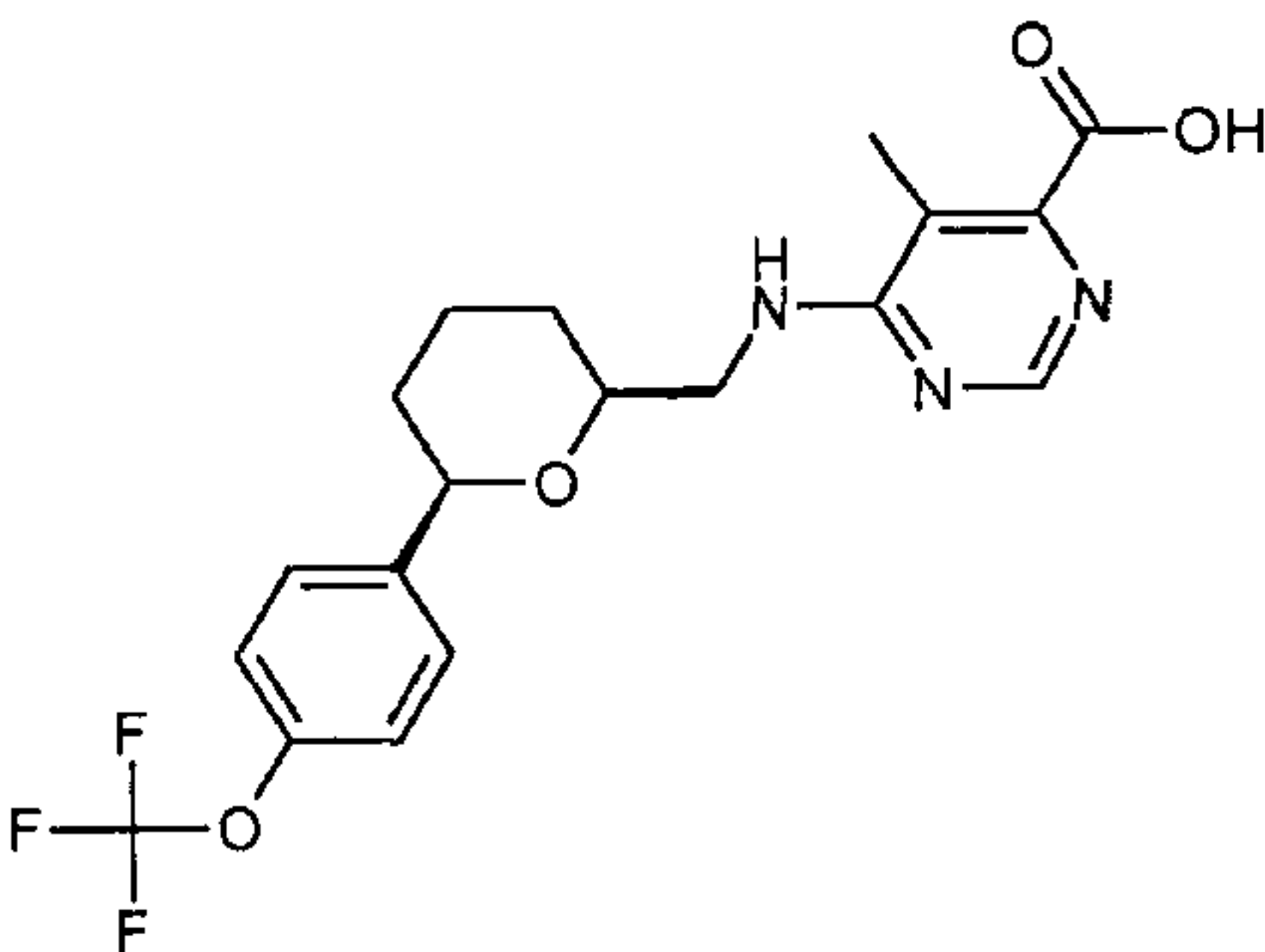
31214-7

3a	17d	27h		28h		relative stereochemistry cis
3a	16e	27i		28i		relative stereochemistry cis
3a	17e	27j		28j		relative stereochemistry cis

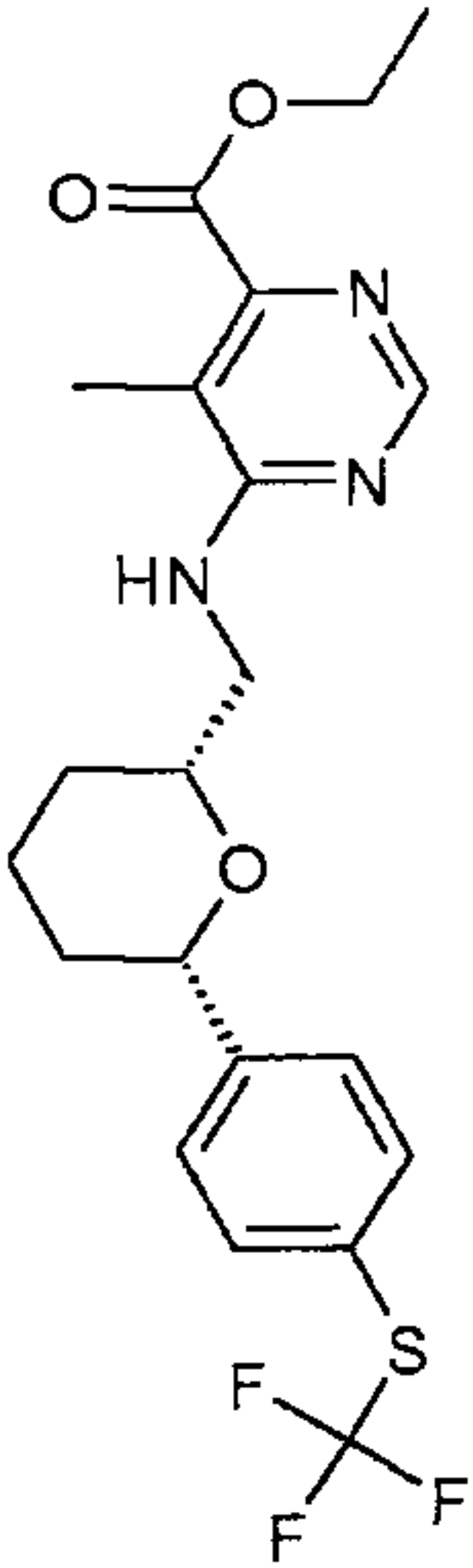
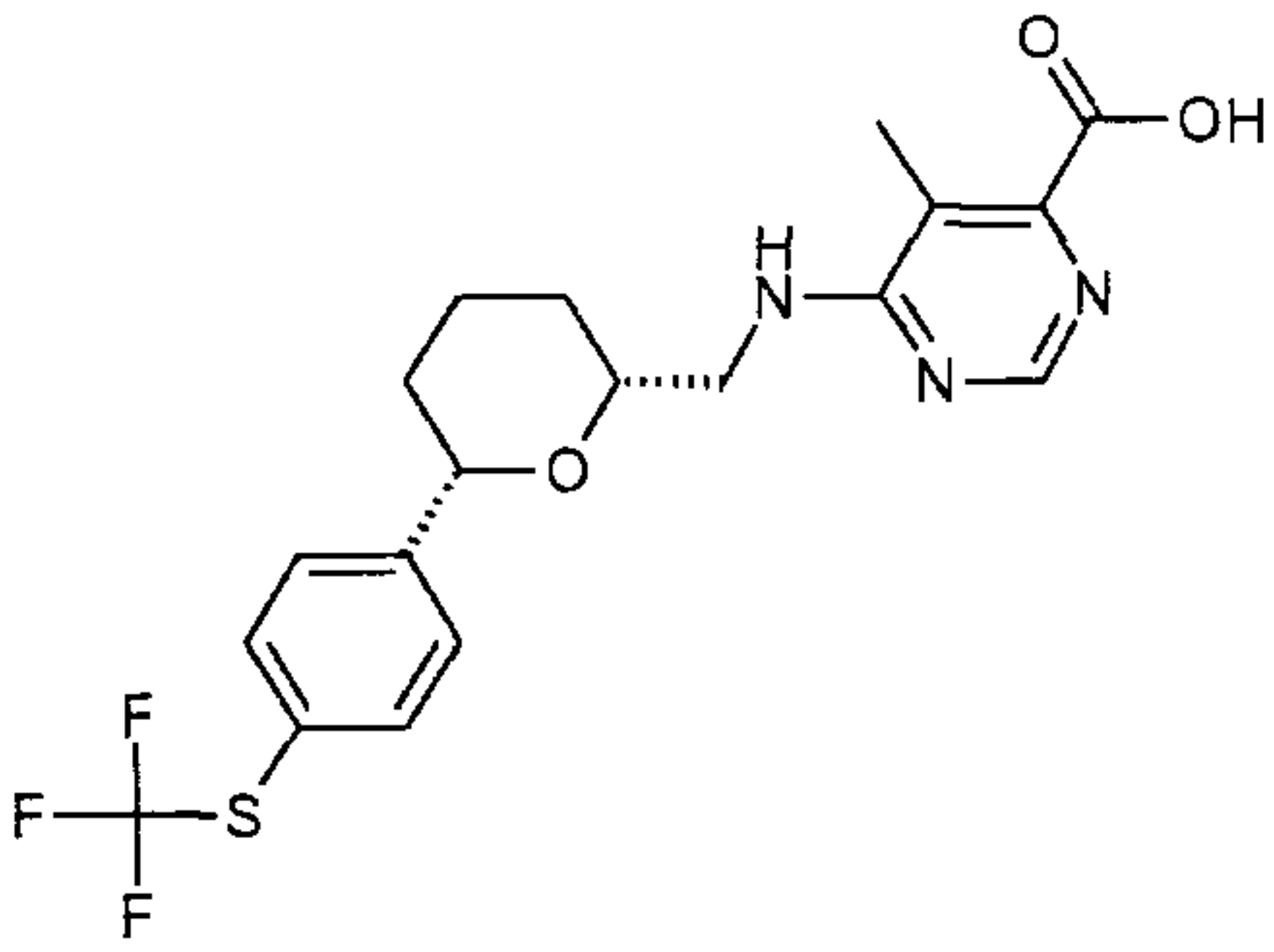
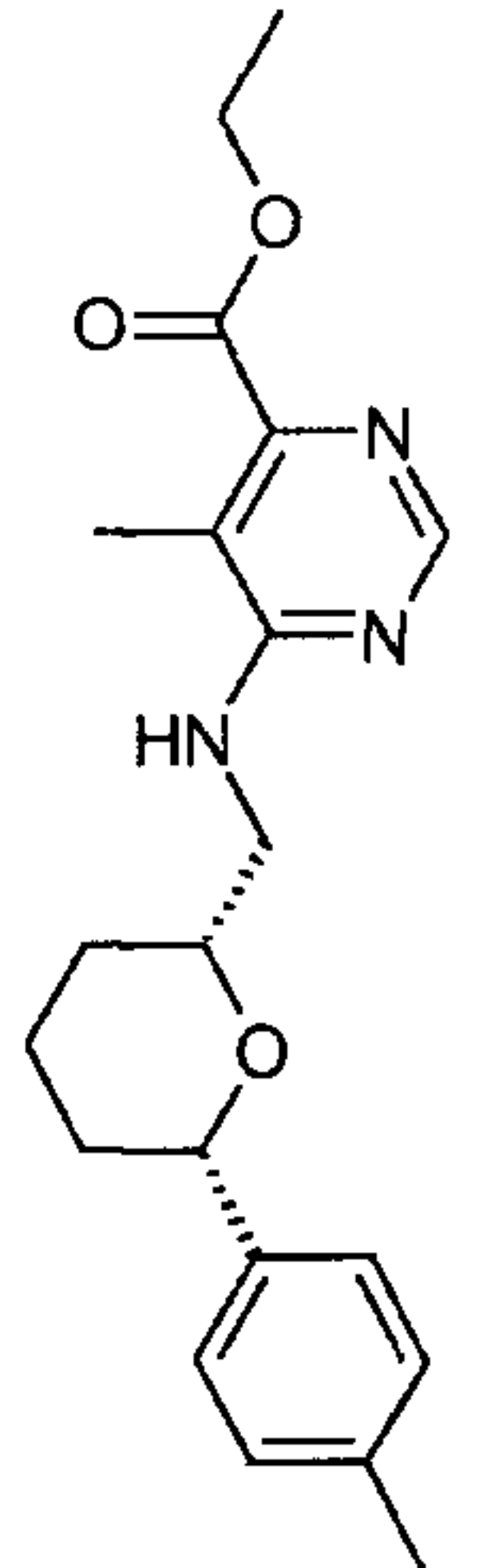
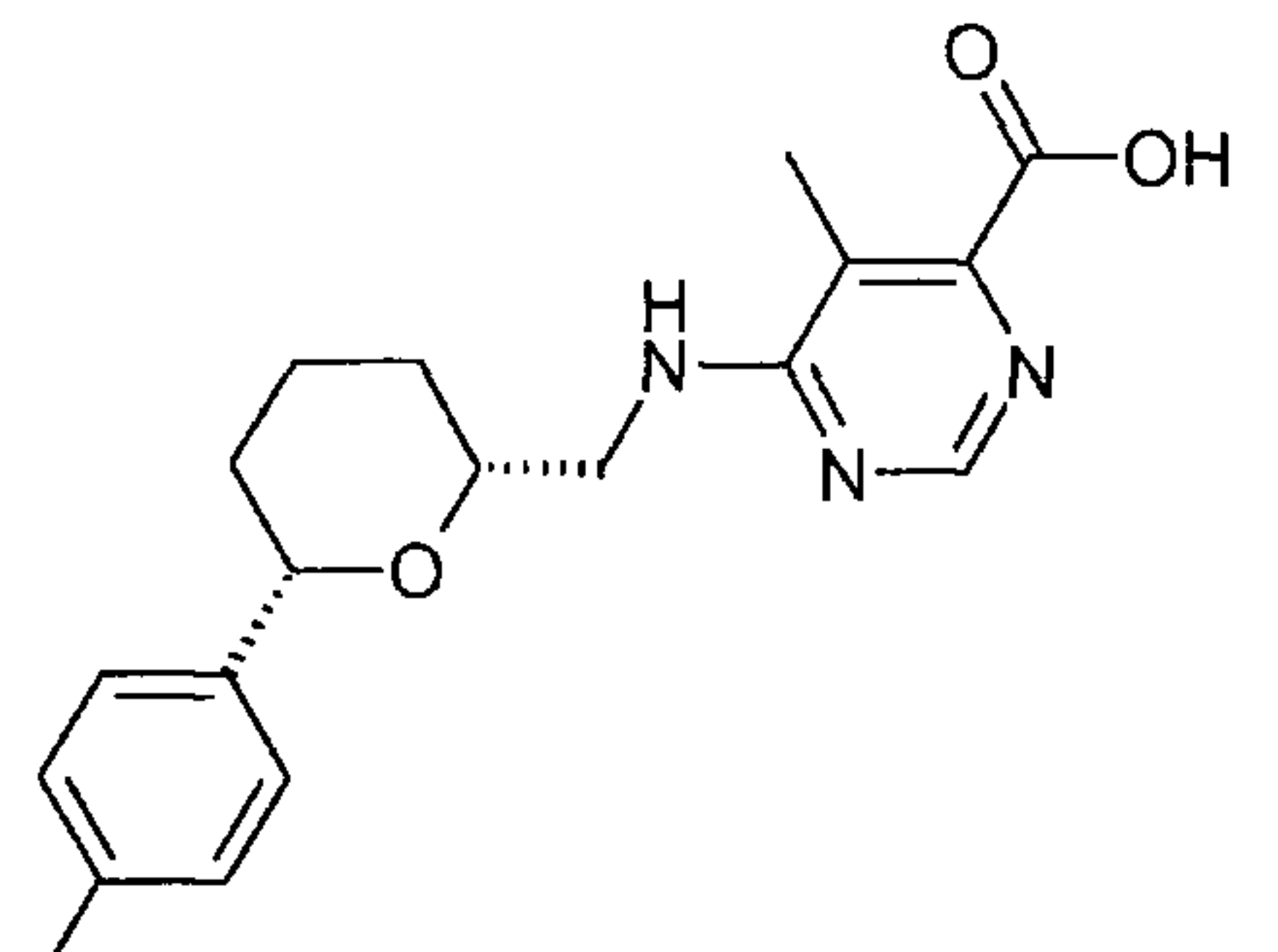
31214-7

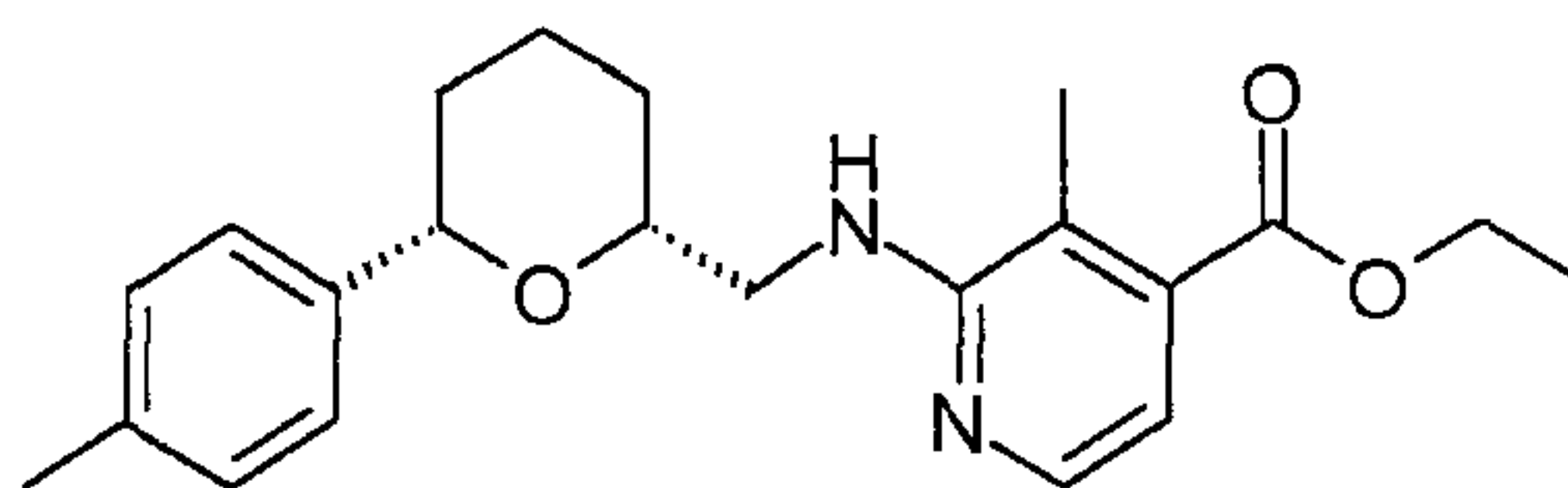
3b	16e	27k		28k		relative stereochemistry cis
3b	17e	27l		28l		relative stereochemistry cis
3a	16f	27m		28m		relative stereochemistry cis

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3a	17f	27n		28n		relative stereochemistry cis
3a	16h	27o		28o		relative stereochemistry cis
3a	17h	27p		28p		relative stereochemistry cis

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3a	42	27pa		28pa		relative stereochemistry cis
3a	15a	27pb		28pb		relative stereochemistry cis

Intermediate 27q

5

Commercially available 2-chloro-3-methylpyridine-4-carboxylic acid ethyl ester (243 mg, 1.22 mmol), Intermediate 17a (250 mg, 1.22 mmol), palladium (II) acetate (27 mg, 0.12 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (379 mg, 0.61 mmol) and sodium tert-butoxide (163 mg, 1.07 mmol) were suspended in 20 ml of 1,2-dimethoxyethane and refluxed for 12h. The reaction mixture was diluted with dichloromethane, washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (isolute silica gel cartridge:

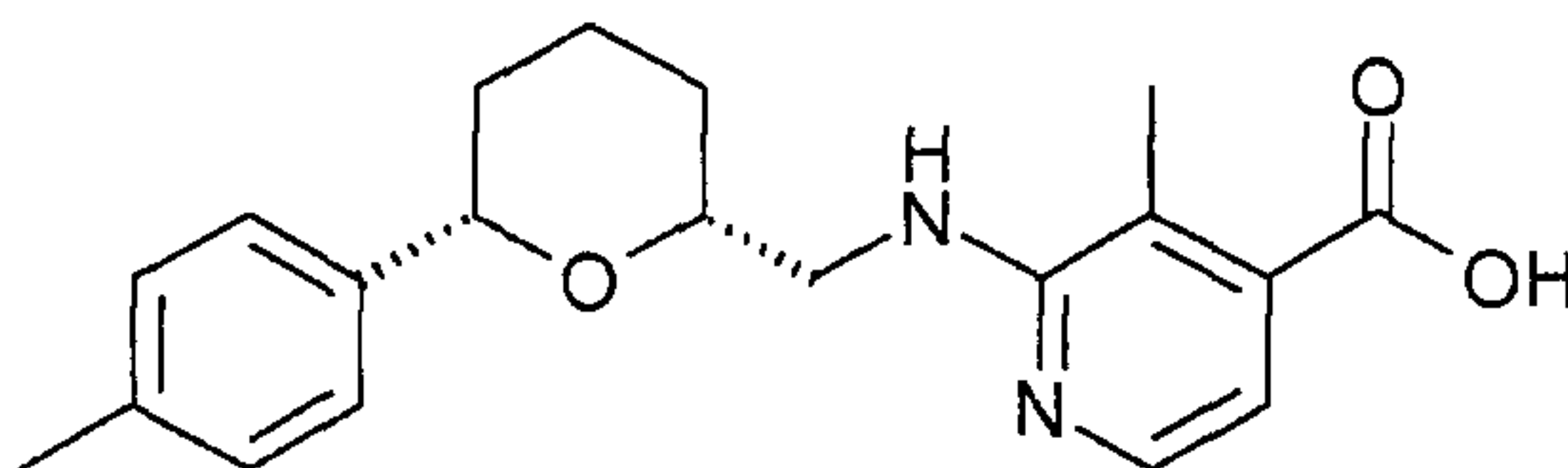
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31214-7

10g; eluent: cyclohexane/ethyl acetate=90/10%). 70 mg (0.19 mmol) of the desired product were obtained. Absolute stereochemistry known.

Intermediate 28q

5



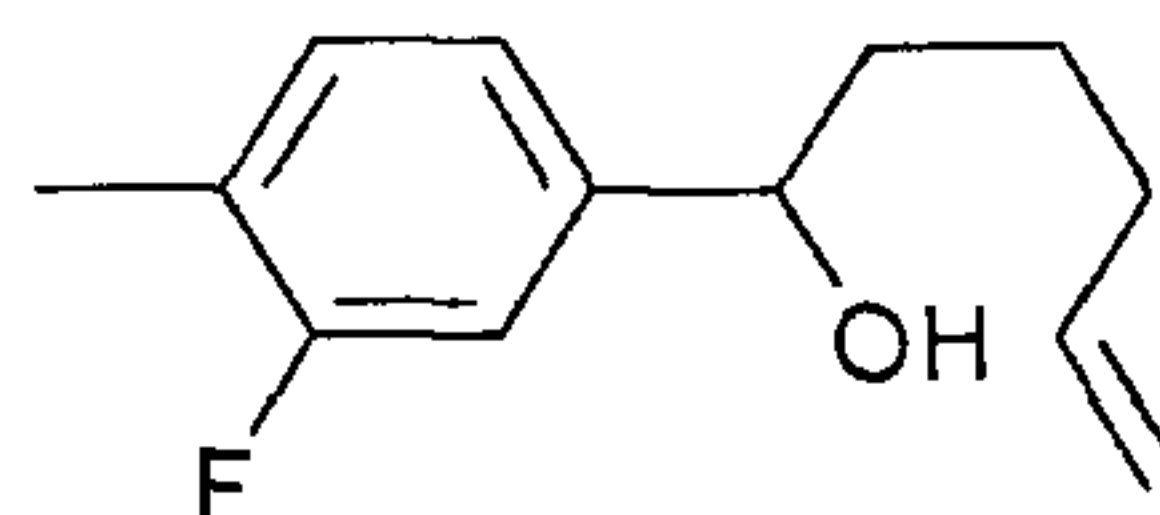
was synthesized in analogy to Intermediates 28a starting from intermediate 27q

The following intermediates were synthesized in analogy to Intermediates 27q and 28q.

10

<i>Synthesis in analogy to intermediate 27q</i>				<i>Synthesis in analogy to intermediate 28q</i>		
Core Intermediate	Amine	Ester Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE	Stereochemistry
3a	16c	27r		28r		relative stereochemistry cis

31214-7

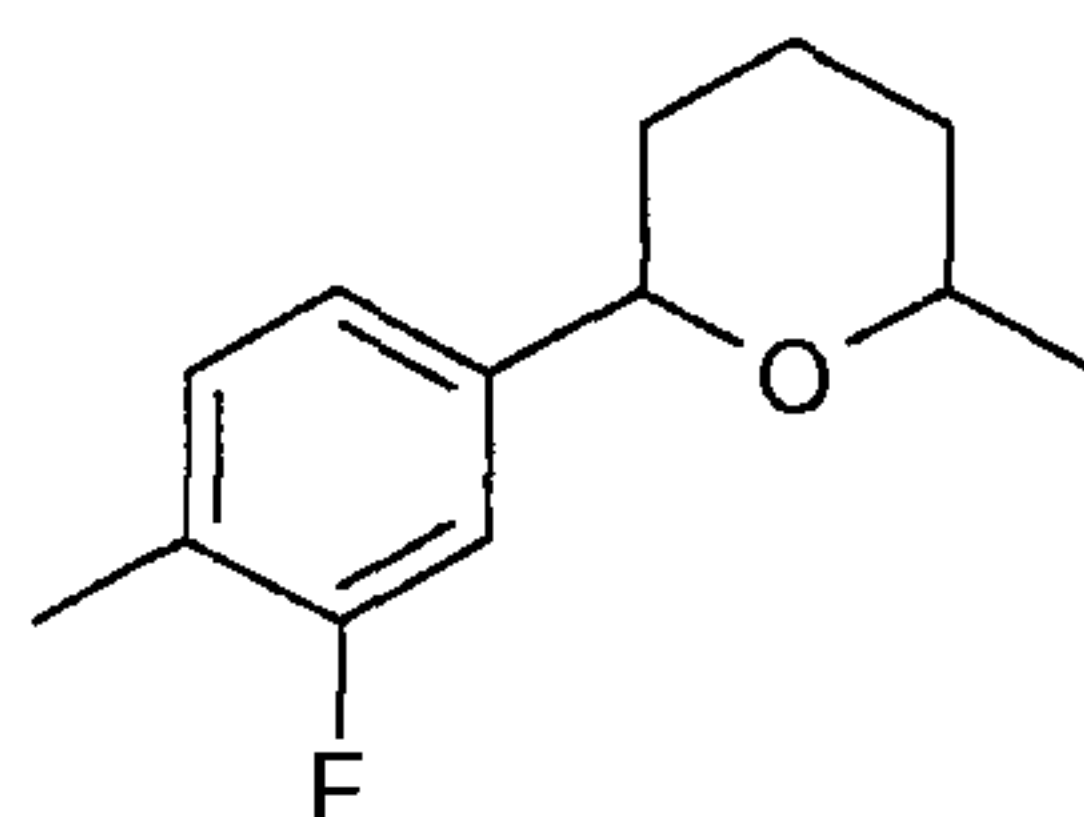
Intermediate 29a

Commercially available 3-fluoro-4-methylbenzaldehyde (2.6g, 18.82 mmol) was dissolved in 30ml of tetrahydrofuran and the reaction mixture was cooled to -78°C under nitrogen atmosphere. 60 ml of a cooled 0.5 M solution of (pent-4-enyl)magnesium bromide (Liebigs Annalen der Chemie **1982**, 1478) was added and the reaction was stirred at -78°C for 1h. The reaction mixture was quenched with an saturated aqueous ammonium chloride solution and extracted with dichloromethane. The organic phase was separated, dried on sodium sulfate and concentrated under vacuum. 3.9 g of a crude oil were obtained.

The following intermediates were synthesized in analogy to intermediate 29a.

Aldehyde	Source/Reference	Intermediate	STRUCTURE
2-(4-formyl-phenyl)-2-propionitrile	Commercially available	29b	
5-trifluoromethyl-furan-2-carbaldehyde	Commercially available	29c	

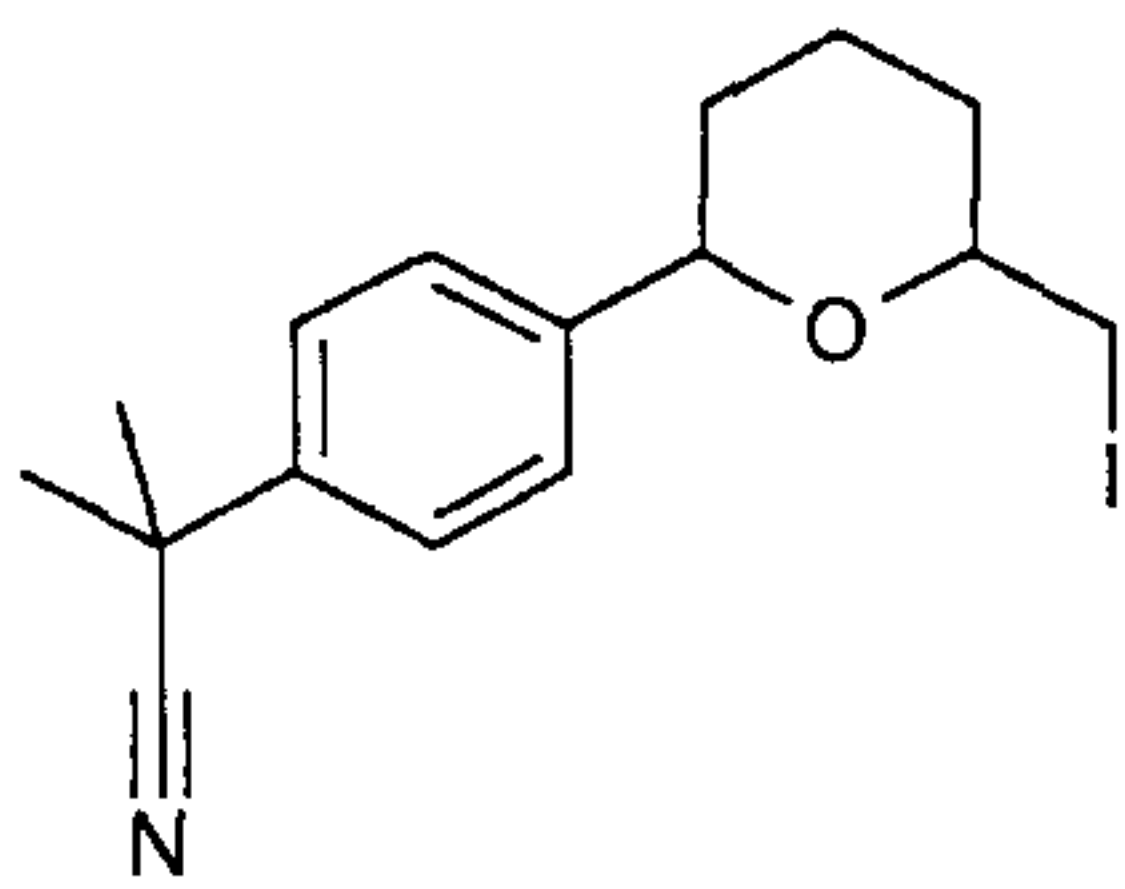
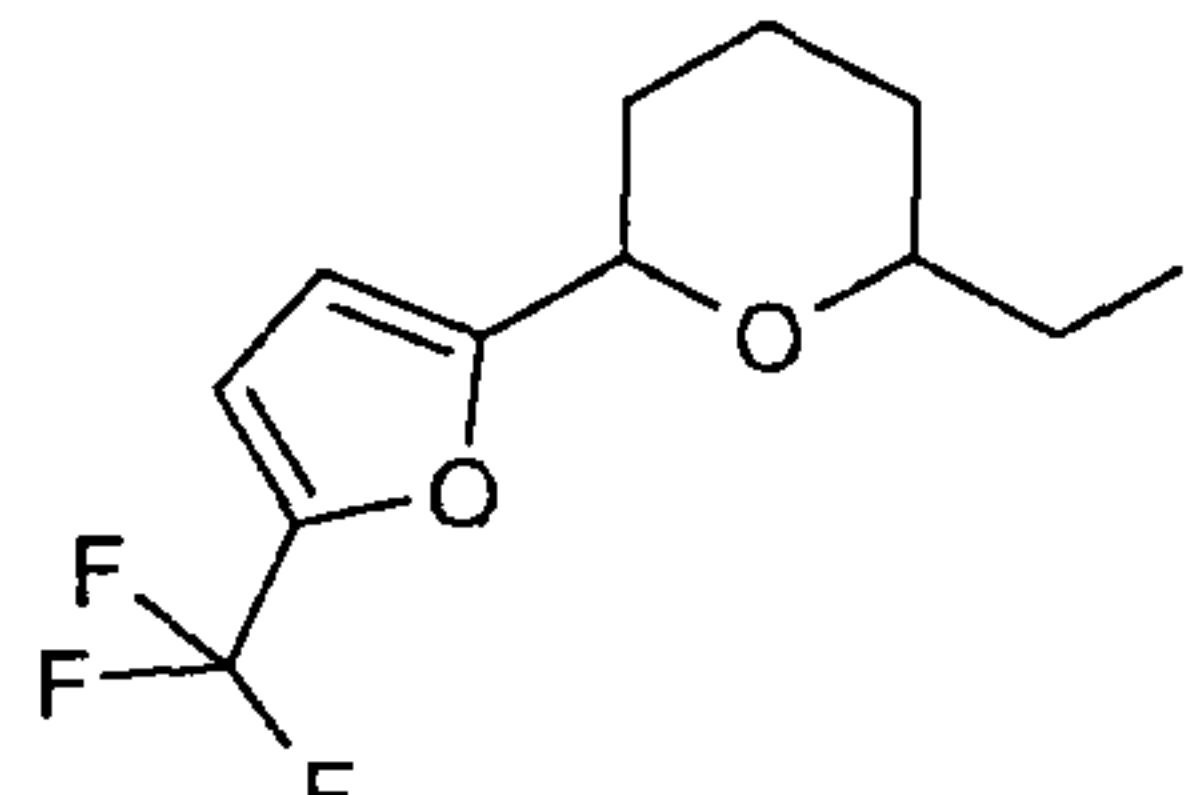
15

Intermediate 30a

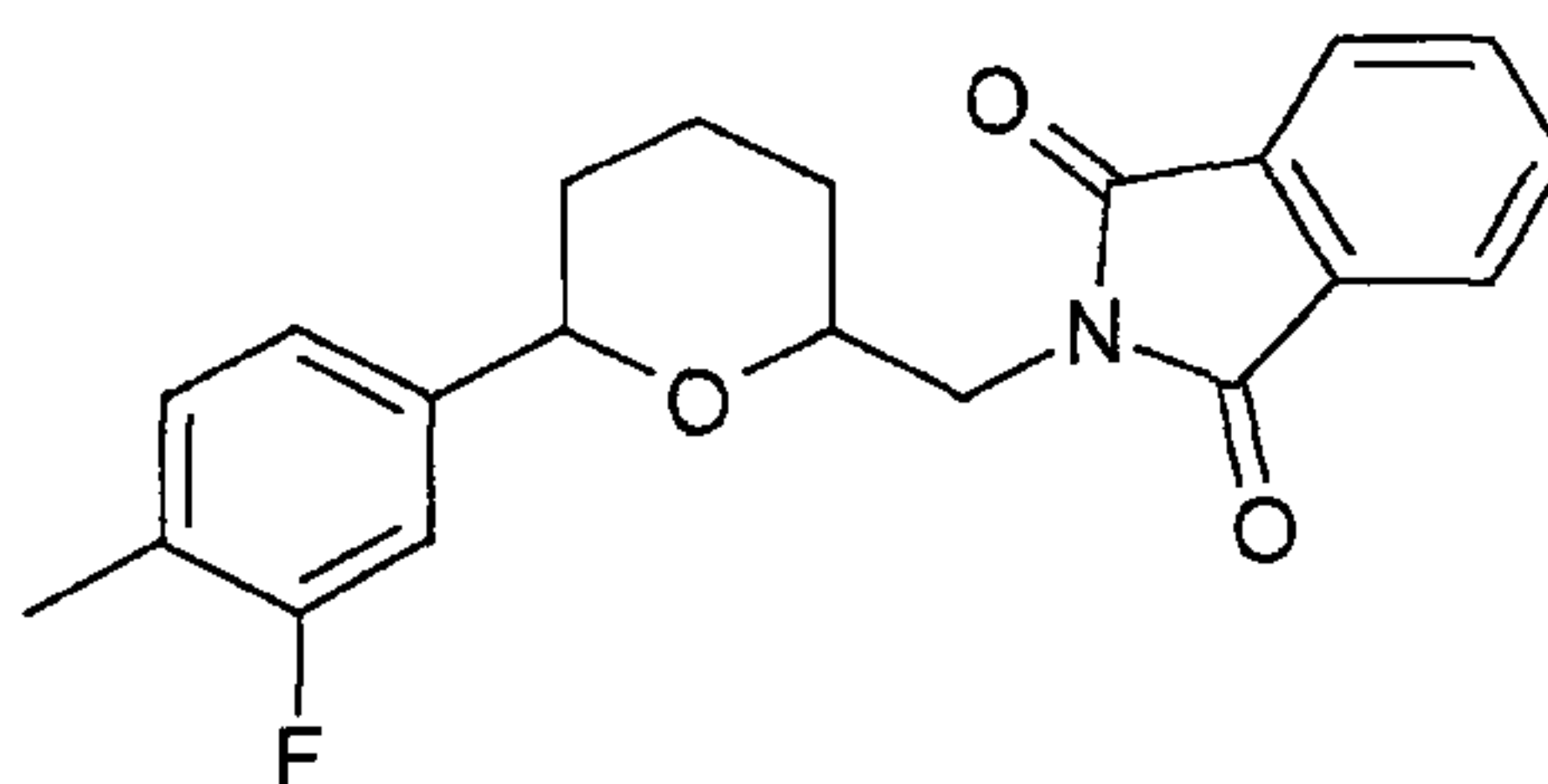
31214-7

Sodium bicarbonate (4.72g, 56.18 mmol) was suspended in 100 ml of acetonitrile and, under nitrogen atmosphere, intermediate 29a (3.9g, 18.73 mmol) and iodine (14.26g, 56.18 mmol) were added. The reaction mixture was stirred at room temperature for 30 minutes, then a 10% water solution of sodium thiosulfate was added. The reaction mixture was extracted with diethyl ether and the organic phase was separated, dried on sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (SP1 SNAP cartridge 50g; eluent: cyclohexane/dichloromethane=95/5%). 2.5g (7.48 mmol) of the desired product were obtained.

10 The following intermediates were synthesized in analogy to intermediate 30a.

Starting intermediate	Intermediate	STRUCTURE
29b	30b	
29c	30c	

Intermediate 31a

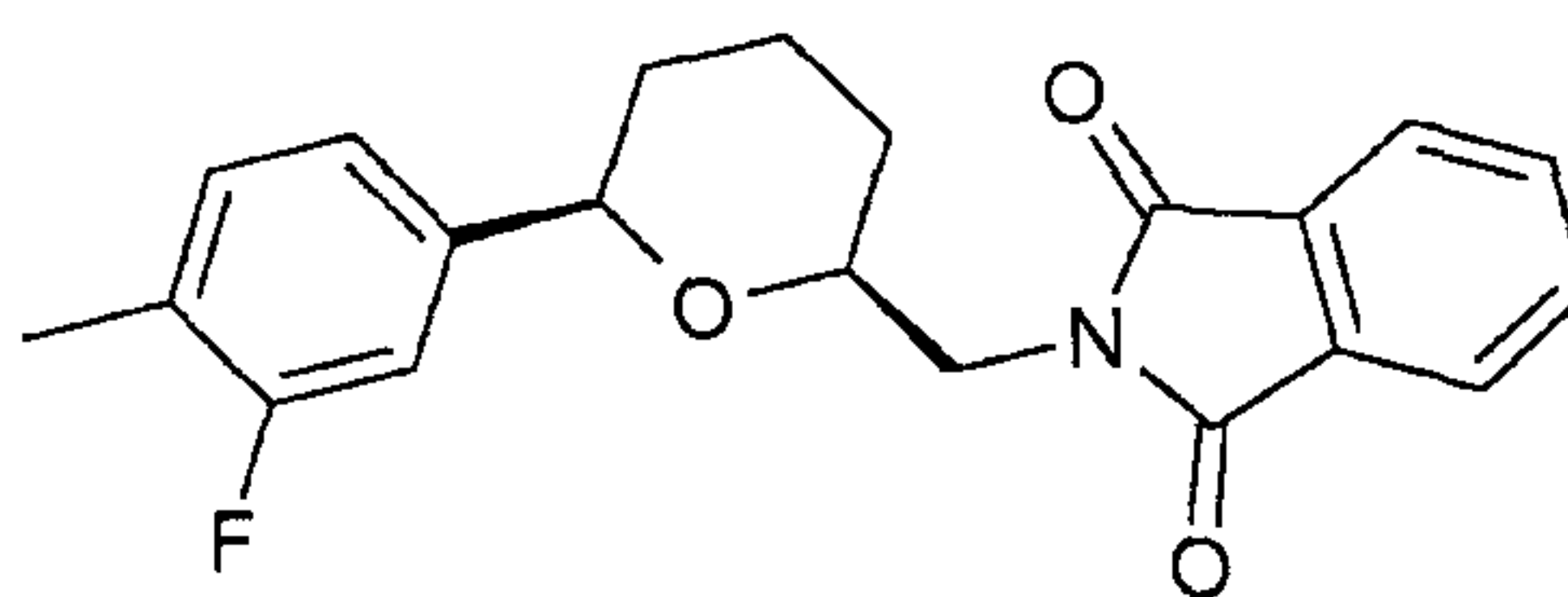


15

Intermediate 30a (2.5g, 7.48 mmol) was dissolved in 40 ml of DMF and, under nitrogen atmosphere, potassium phthalimide (1.66g, 8.98 mmol) was added. The reaction mixture was warmed to 90°C for 4h, then cooled to room temperature and diluted with 100 ml of a saturated aqueous sodium bicarbonate solution. The reaction mixture was extracted with diethyl ether and the organic phase was separated, dried on sodium sulfate and concentrated under vacuum. 2.2 g of the crude product were obtained,

20

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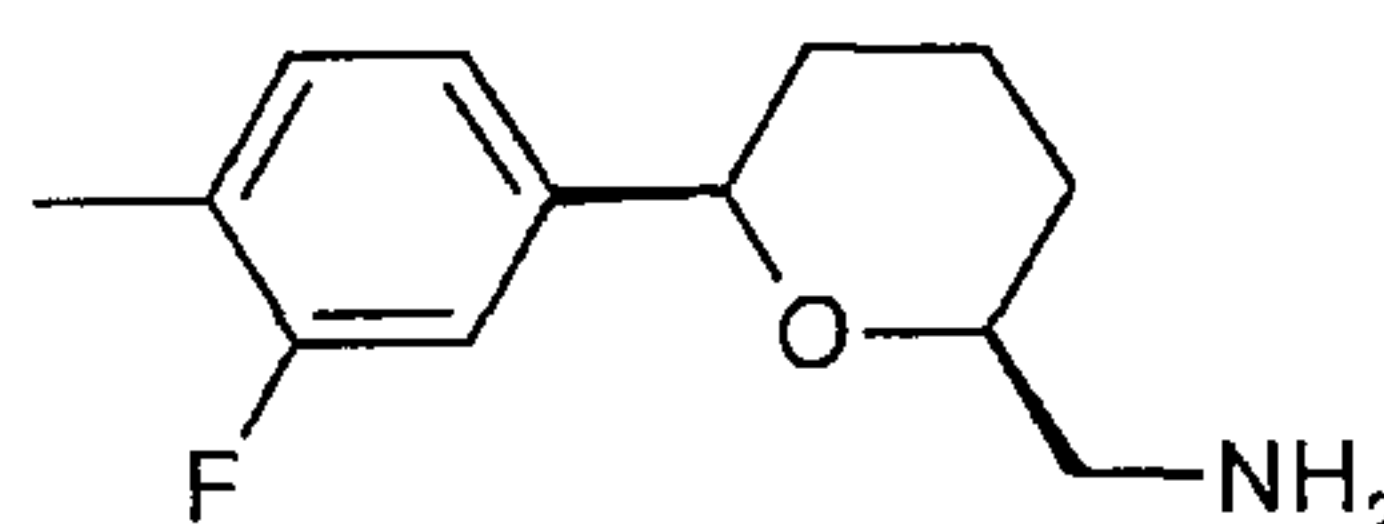
Intermediate 32a

- 5 The crude product (2.2 g) was precipitated with 100 ml of a cyclohexane/ethyl acetate=50/50% solution and 1.8 g (5.06 mmol) of the desired cis racemate were obtained (stereochemistry assigned by ¹H-NMR).

The following intermediates were synthesized in analogy to intermediate 31a and 32a.

10

<i>Synthesis in analogy to intermediate 31a</i>			<i>Synthesis in analogy to intermediate 32a</i>	
Starting intermediate	Intermediate	STRUCTURE	Intermediate	STRUCTURE
30b	31b		32b	
30c	31c			

Intermediate 33a

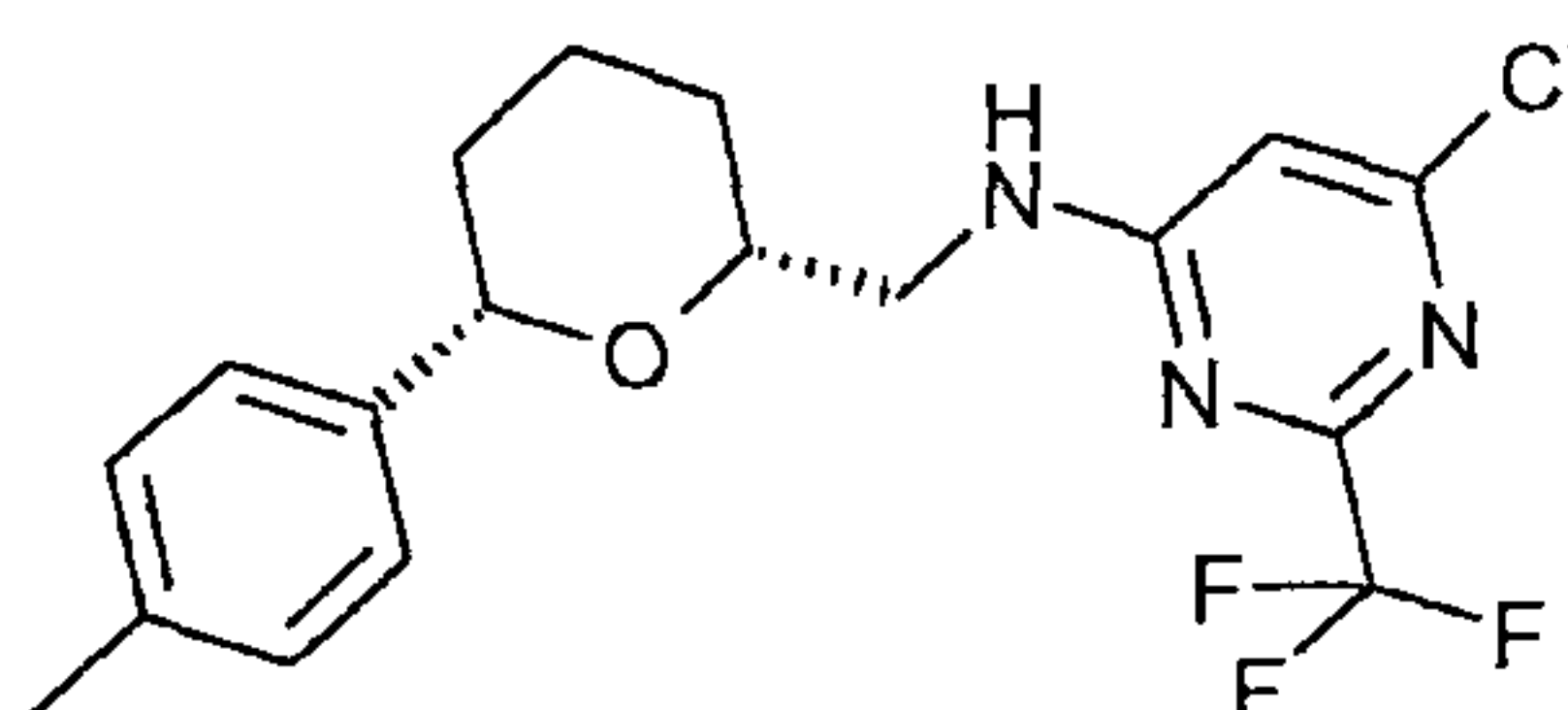
31214-7

Intermediate 32a (200 mg, 0.57 mmol) was suspended in 5 ml of methanol and hydrazine hydrate (0.21 ml, 4.41 mmol) was added. The reaction mixture was stirred at room temperature for 2h, then it was concentrated under vacuum. The residue was treated with dichloromethane, the solid residue was filtered off and the filtrate was concentrated under vacuum to yield 120 mg of the crude amine.

The following intermediates were synthesized in analogy to intermediate 33a.

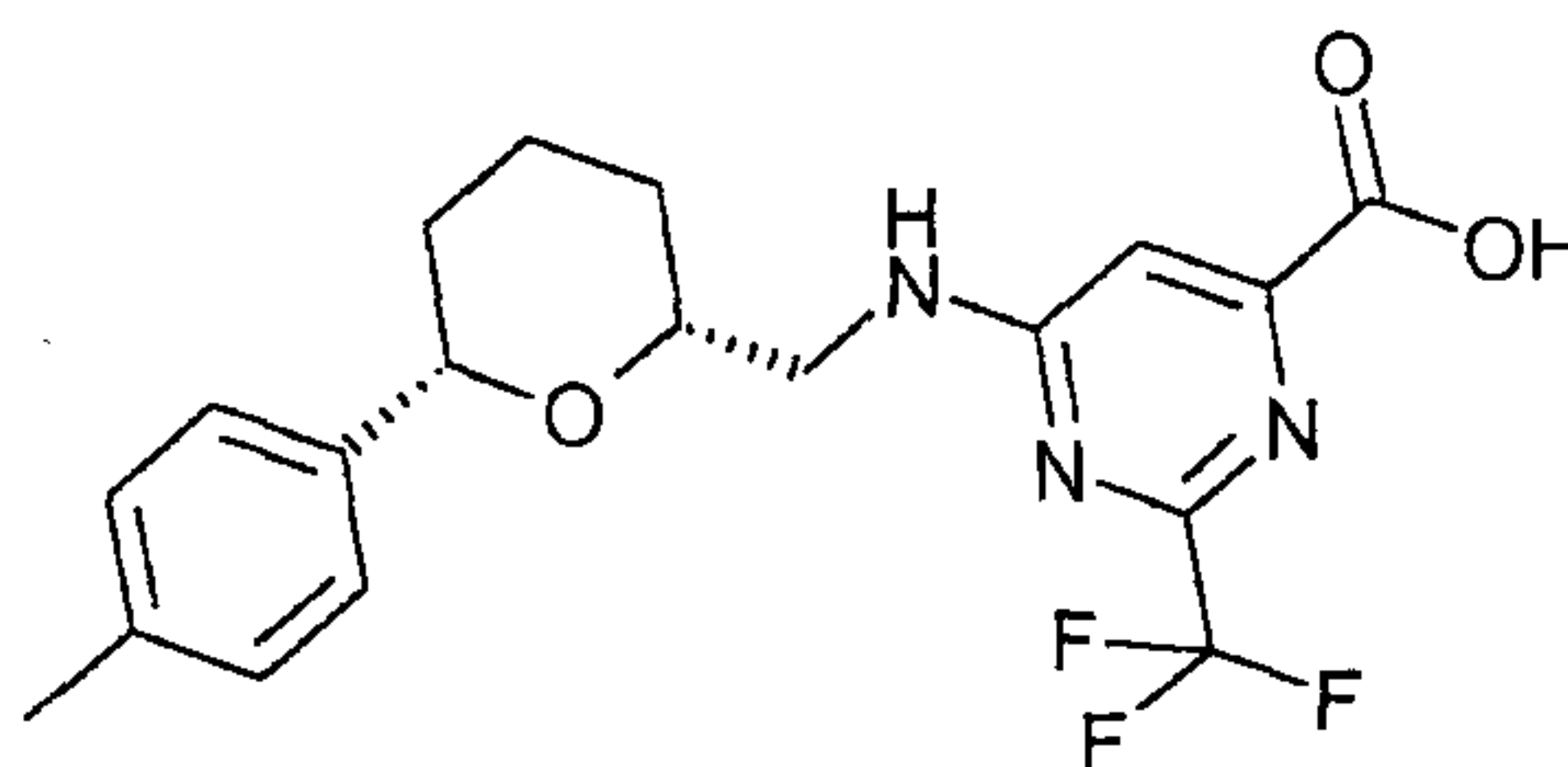
Starting intermediate	Intermediate	STRUCTURE
32b	33b	
31c	33c	

10 Intermediate 34



N,N-diisopropylethylamine (213 μ l, 1.15 mmol) was added to a mixture of intermediate 15a (94 mg, 461 μ mol) and commercially available 4,6-dichloro-2-trifluoromethyl-pyrimidine (100 mg, 461 μ mol) in 2 ml NMP. The reaction mixture was heated in the microwave for 1 h at 120°C. The mixture was purified by reversed phase HPLC to give the desired product (95 mg).

Intermediate 35

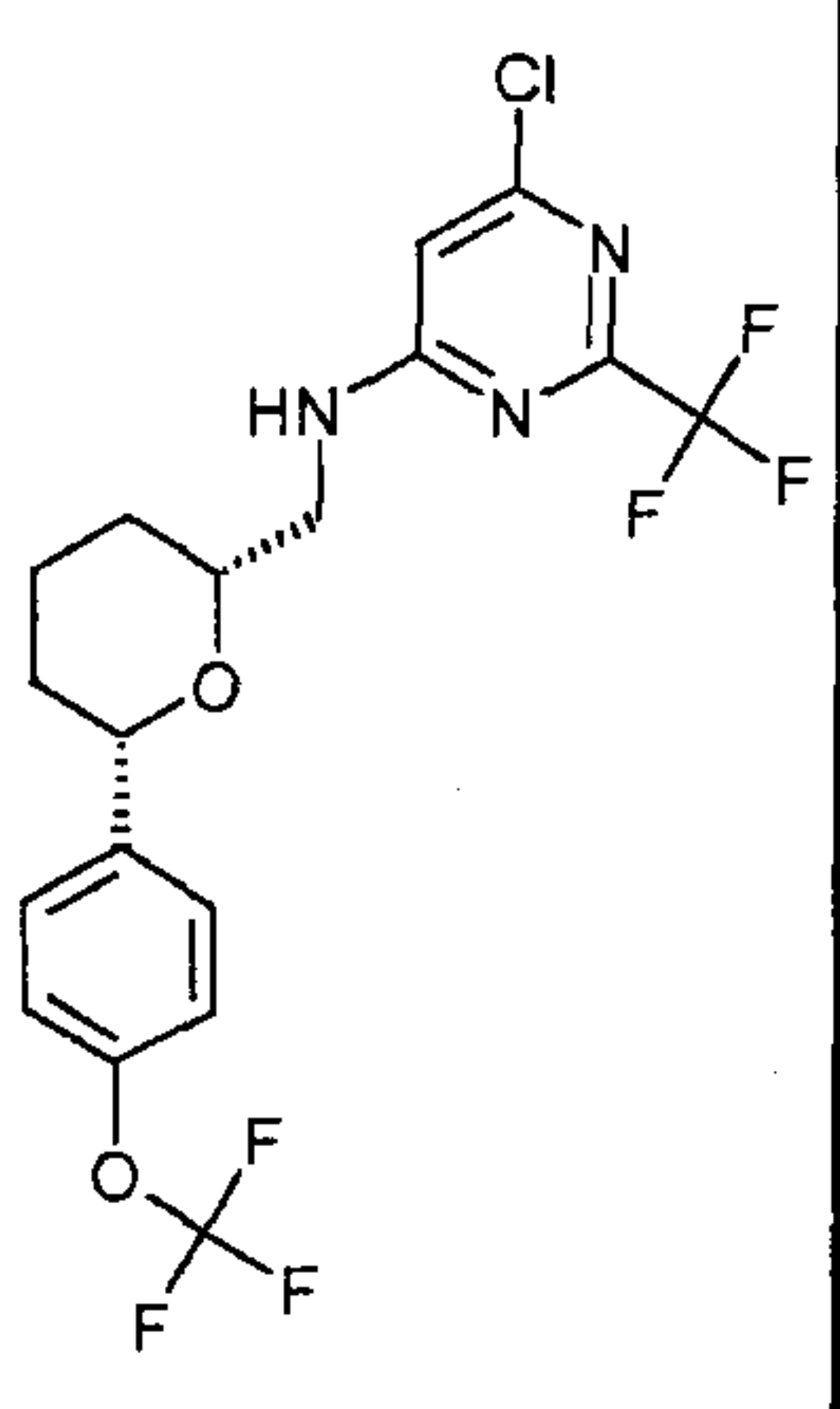
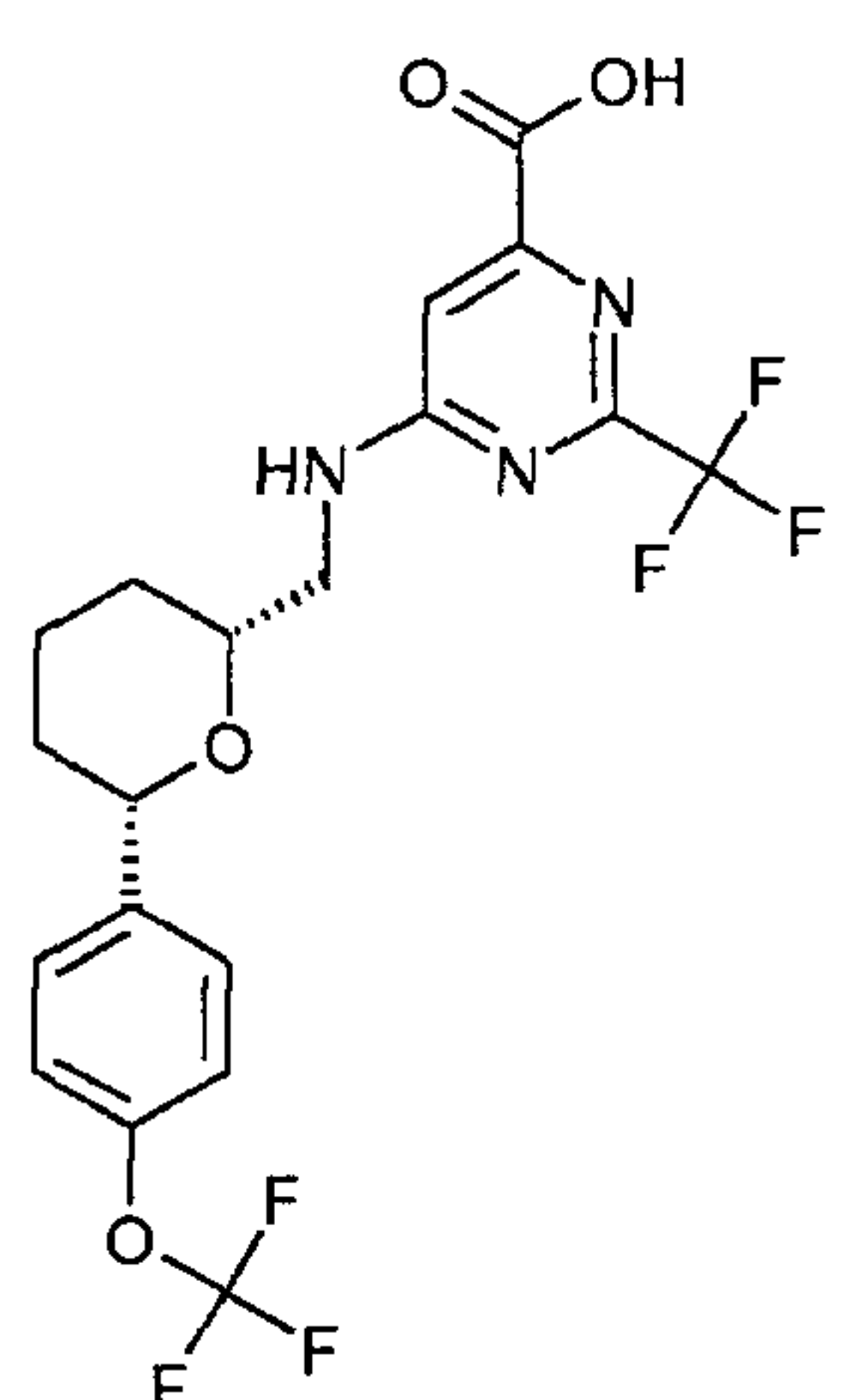


31214-7

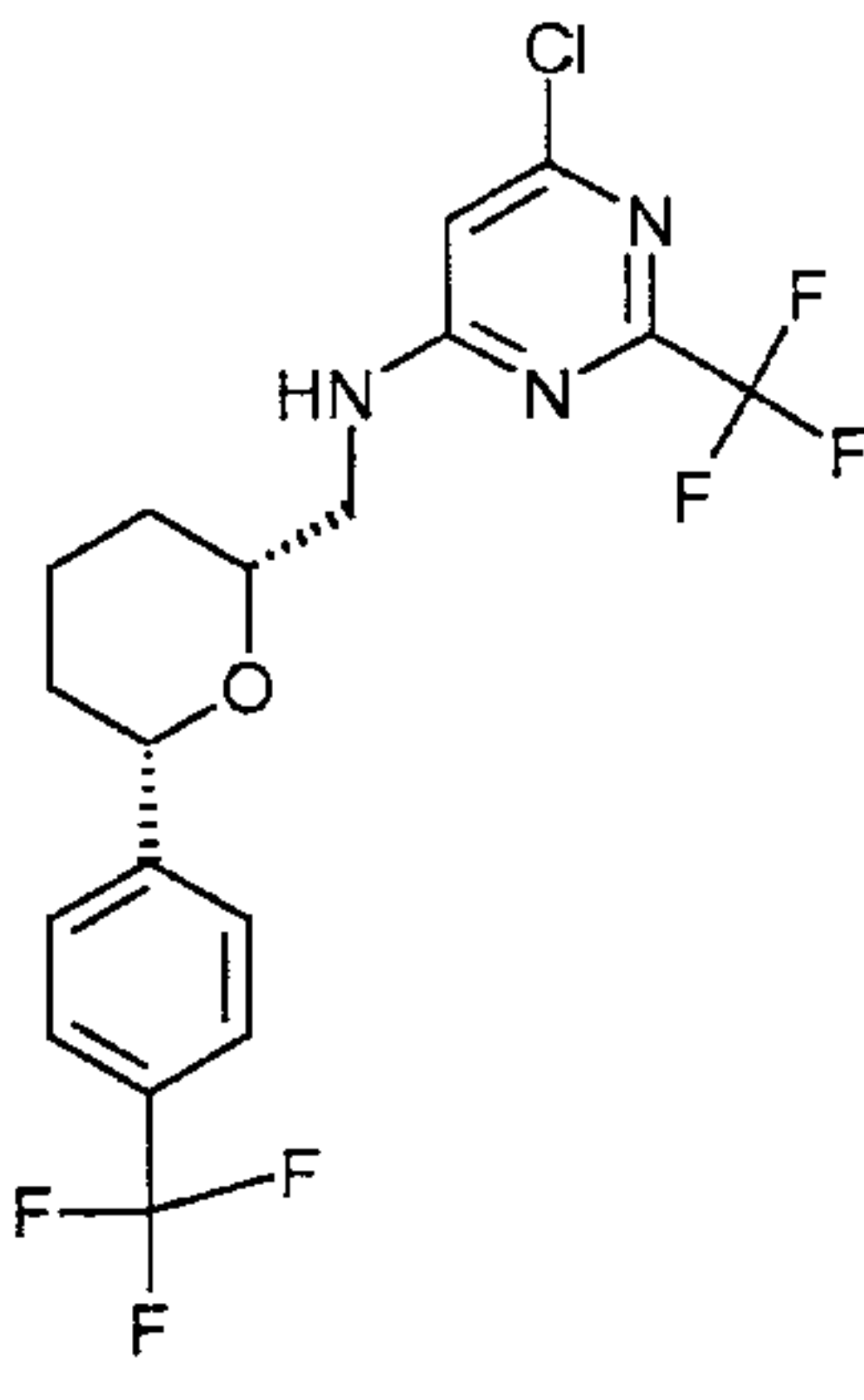
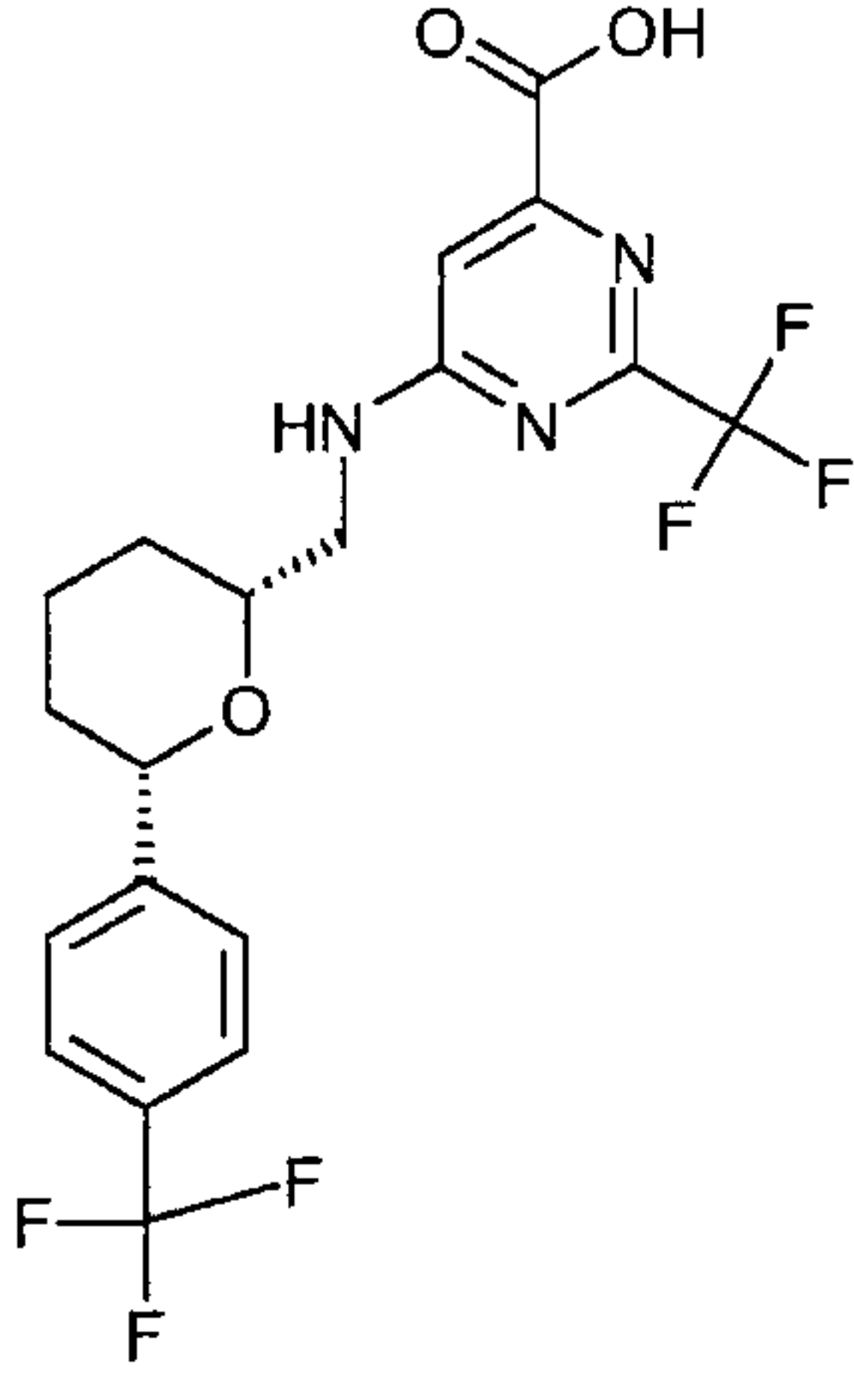
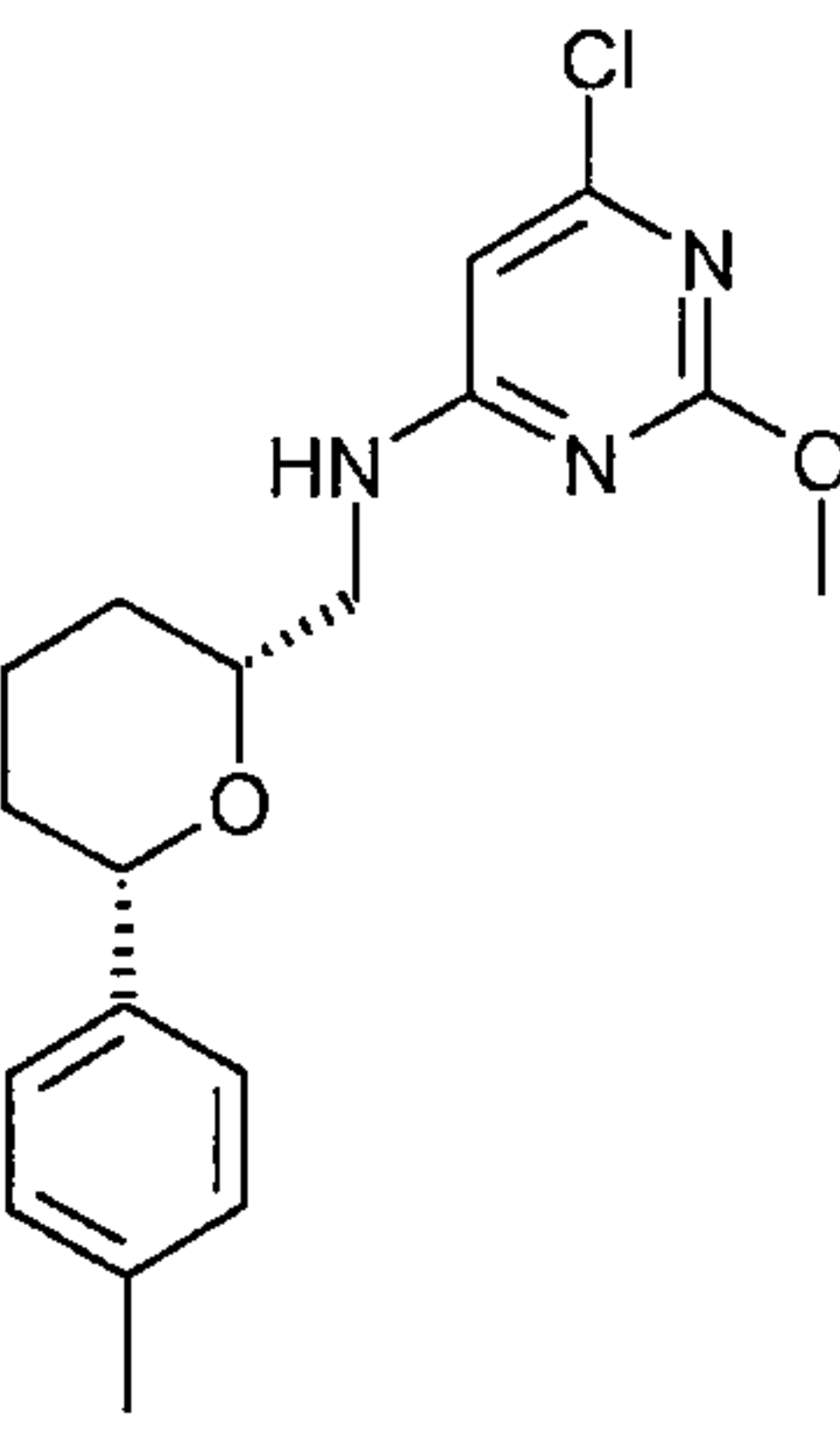
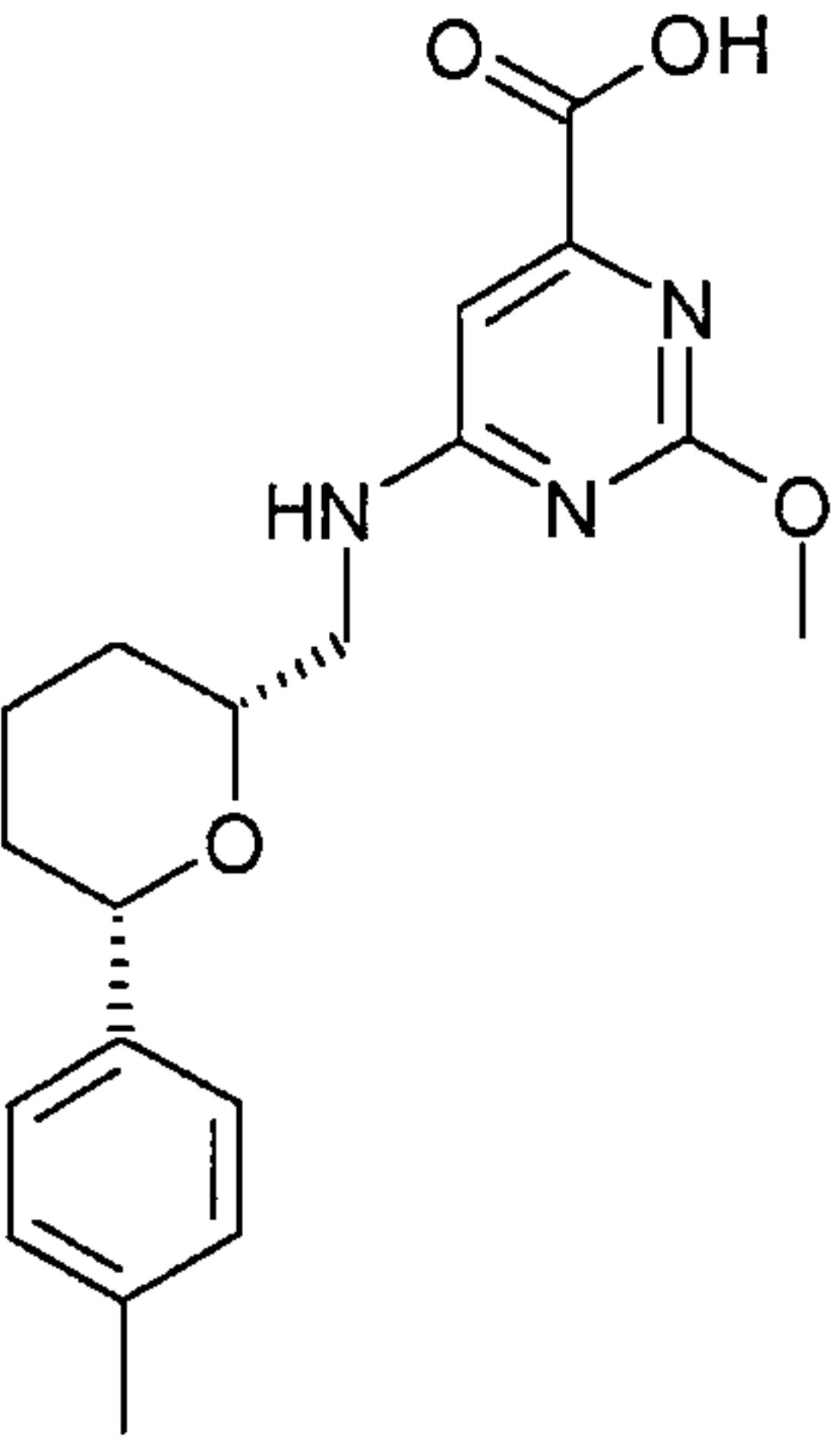
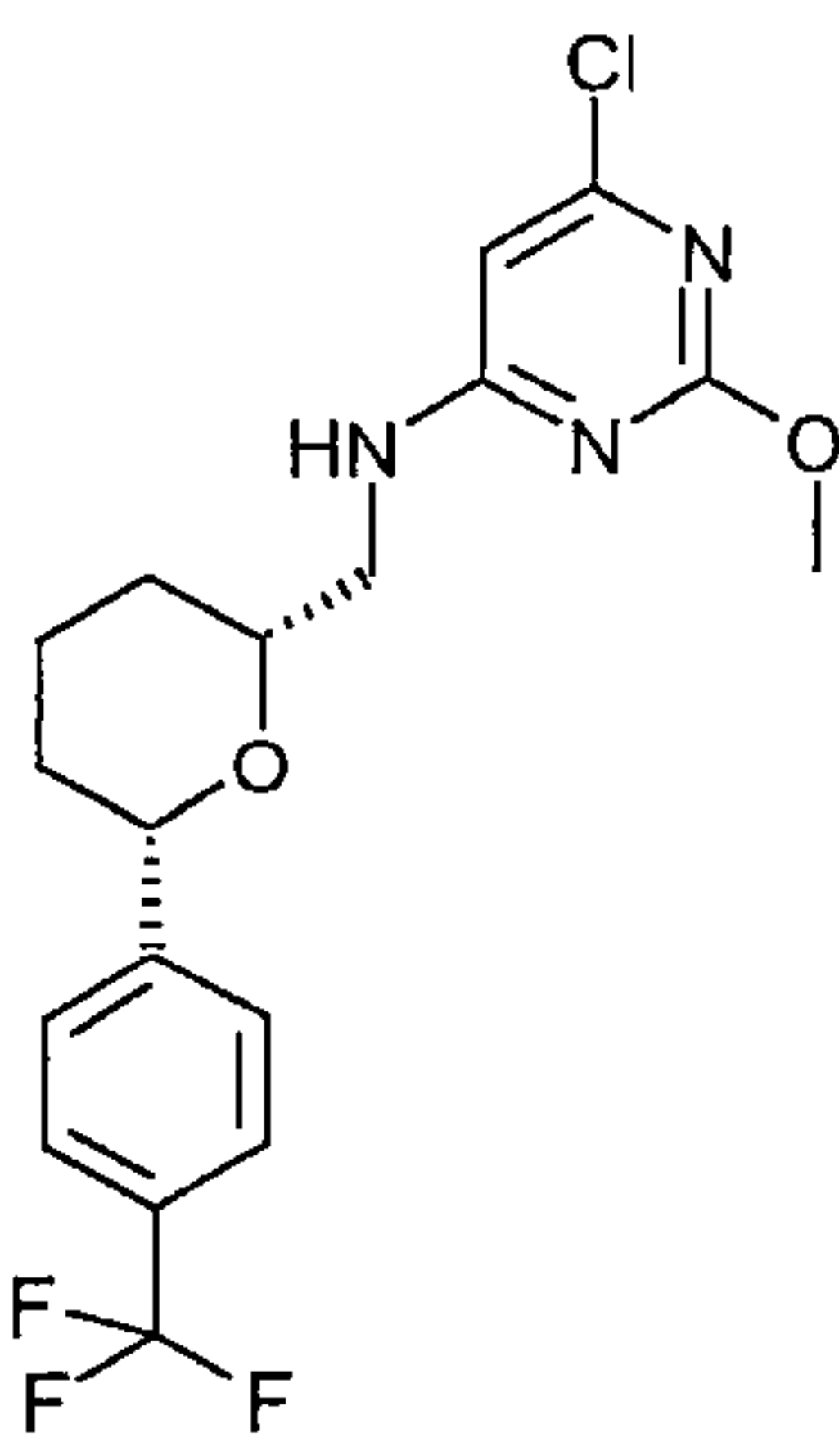
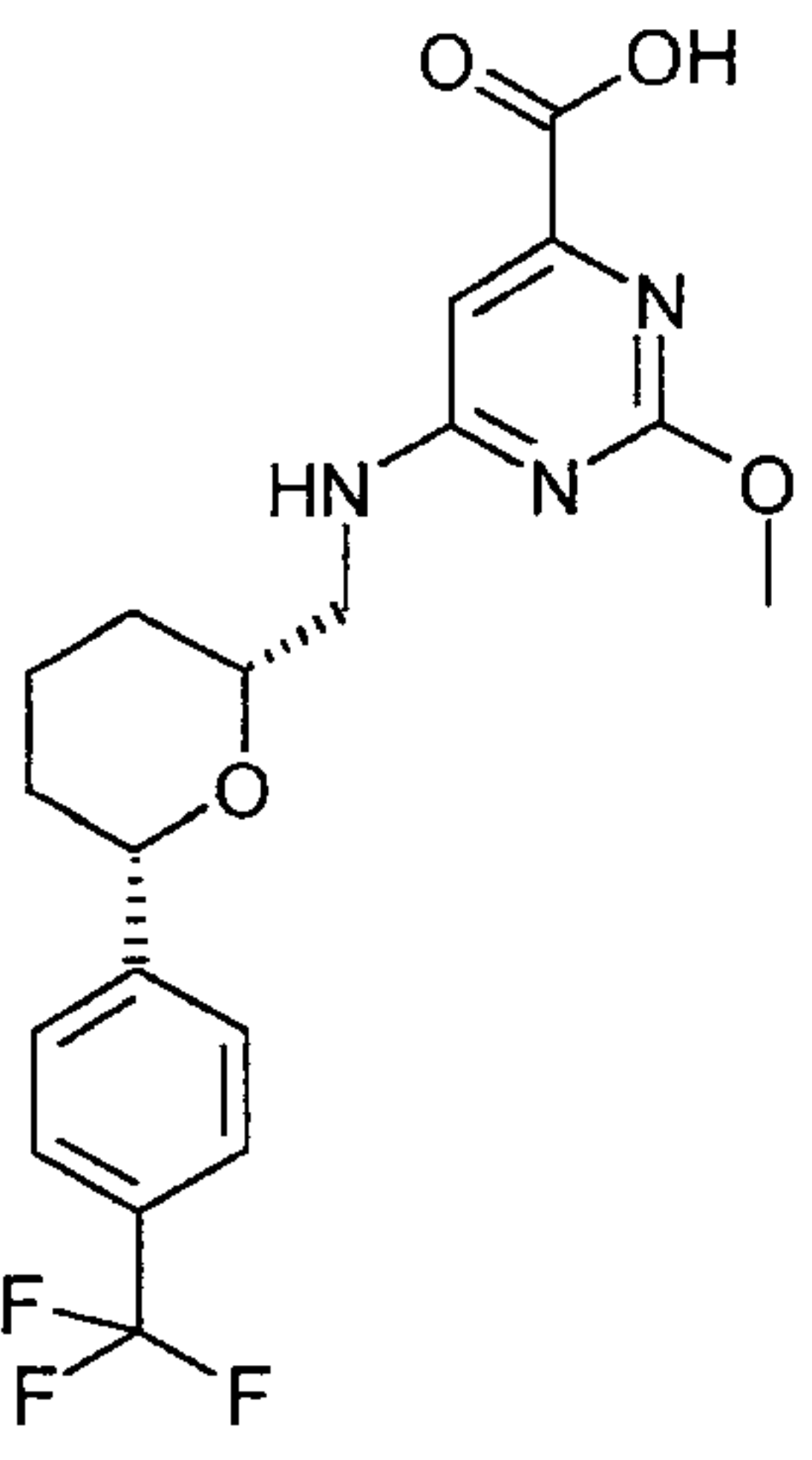
- A mixture of intermediate 34 (95 mg, 246 μmol), palladium acetate (5.5 mg, 25 μmol), 1,1'-bis(diphenylphosphino)-ferrocene (13 mg, 25 μmol), sodium acetate (60 mg, 739 μmol) in 5 ml methanol and 5 ml DMF was stirred under a carbon monoxide atmosphere (5 bar) over night at 70°C. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase HPLC to give the corresponding ester (88 mg, 168 μmol).
- Lithium hydroxide (28 mg, 672 μmol) was added to a solution of the ester (88 mg, 168 μmol) in 3 ml THF and 3 ml water. The reaction mixture was heated for 15 min at 100°C. Then, the solvent was removed in vacuum and the residue was purified by reversed phase HPLC to give the desired product (61 mg).

10

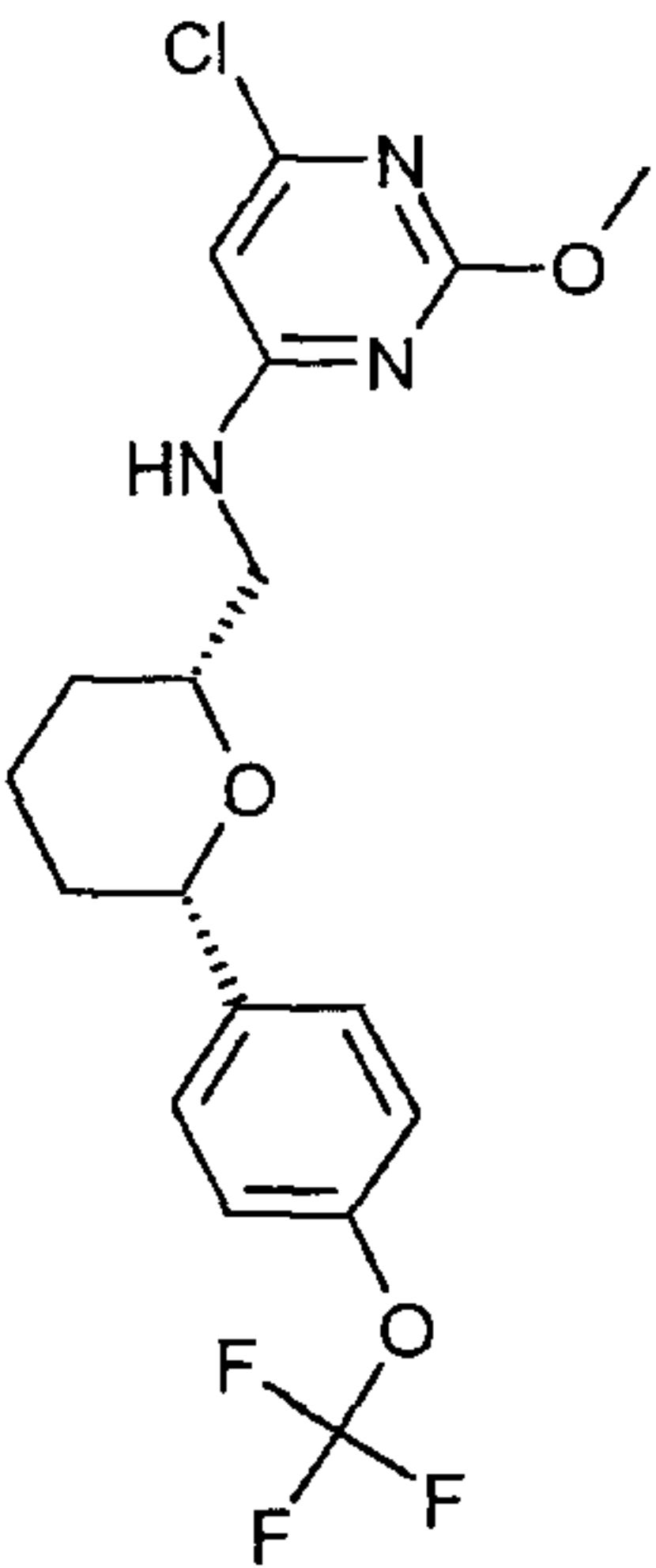
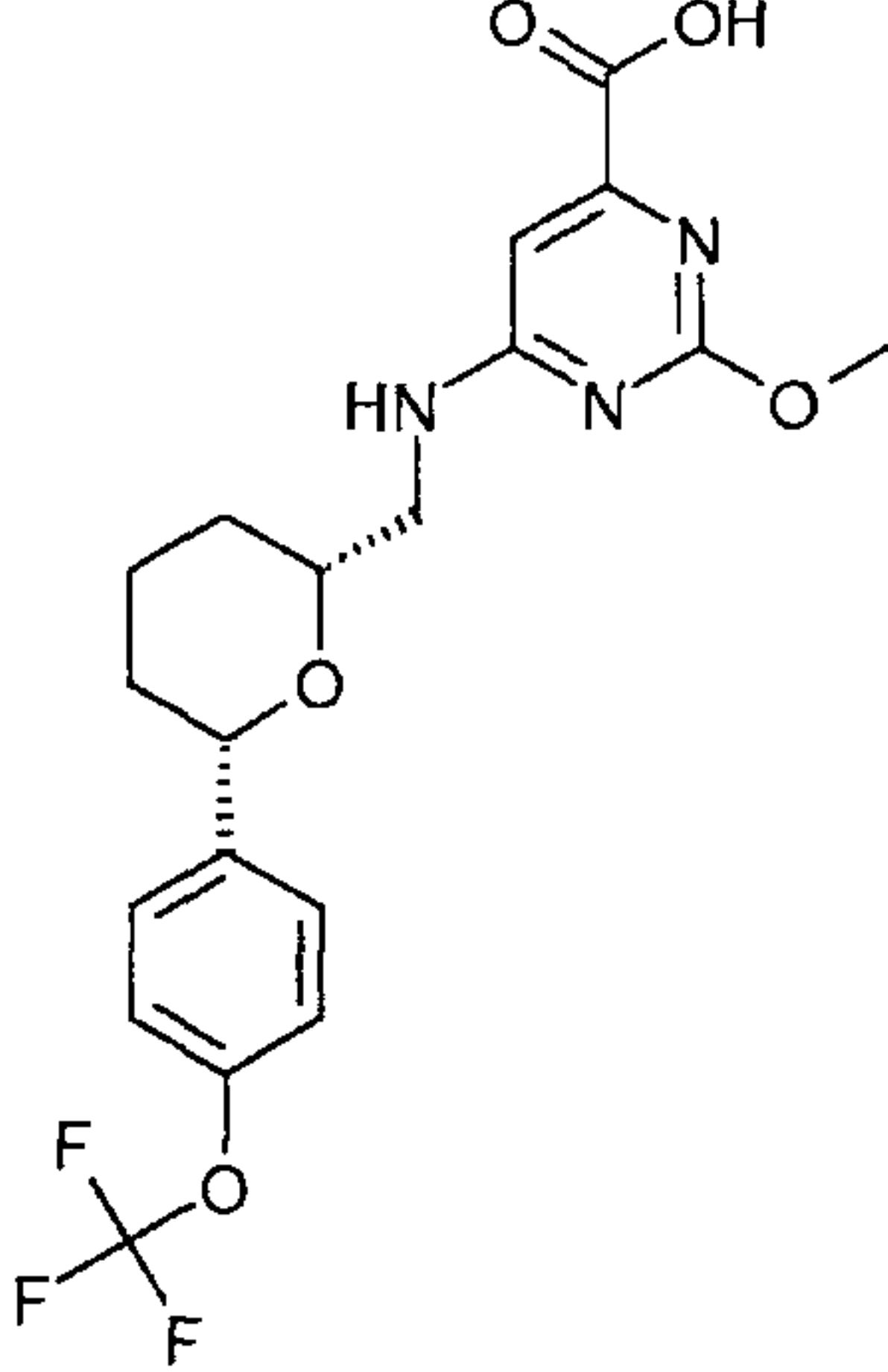
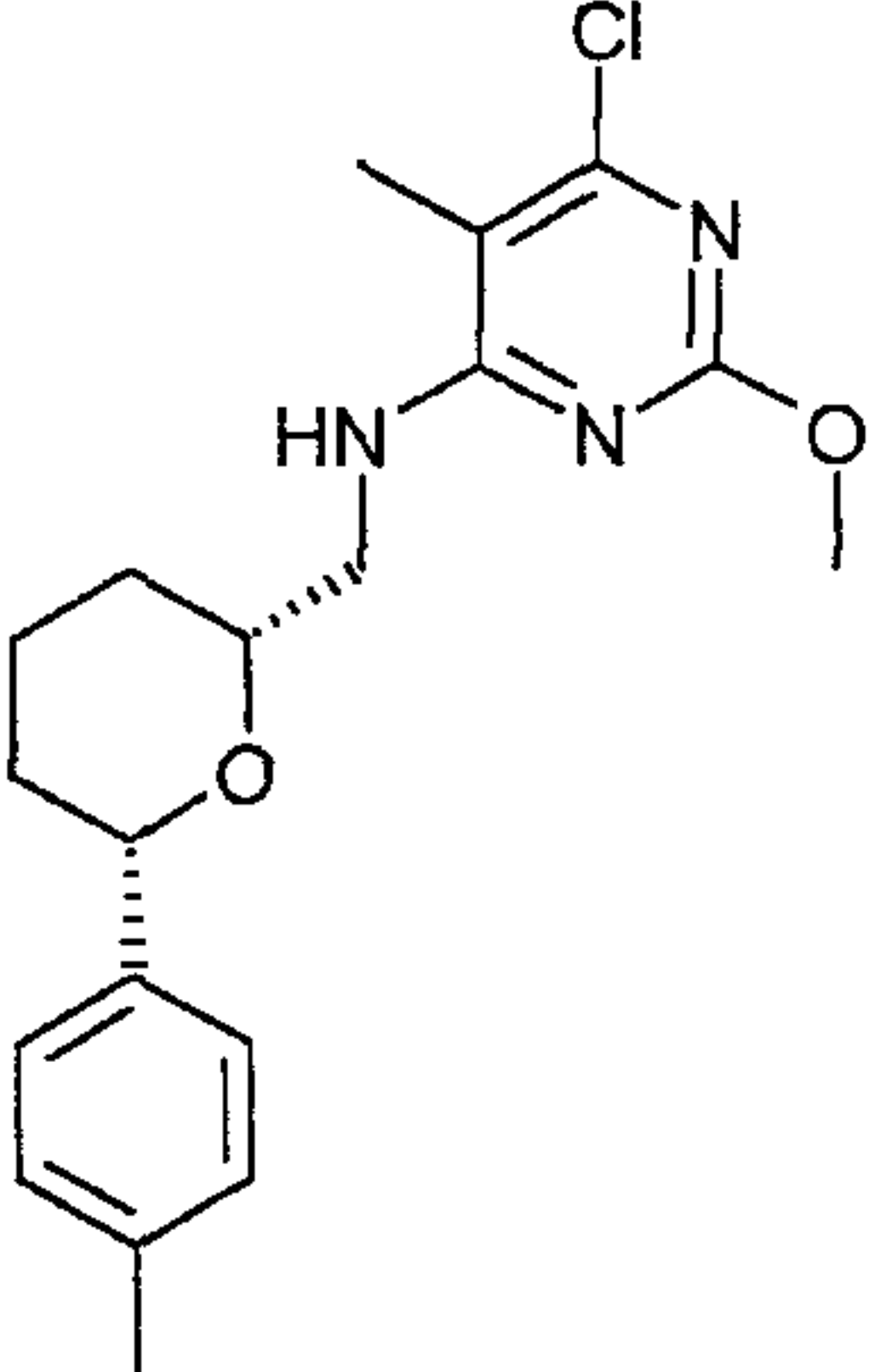
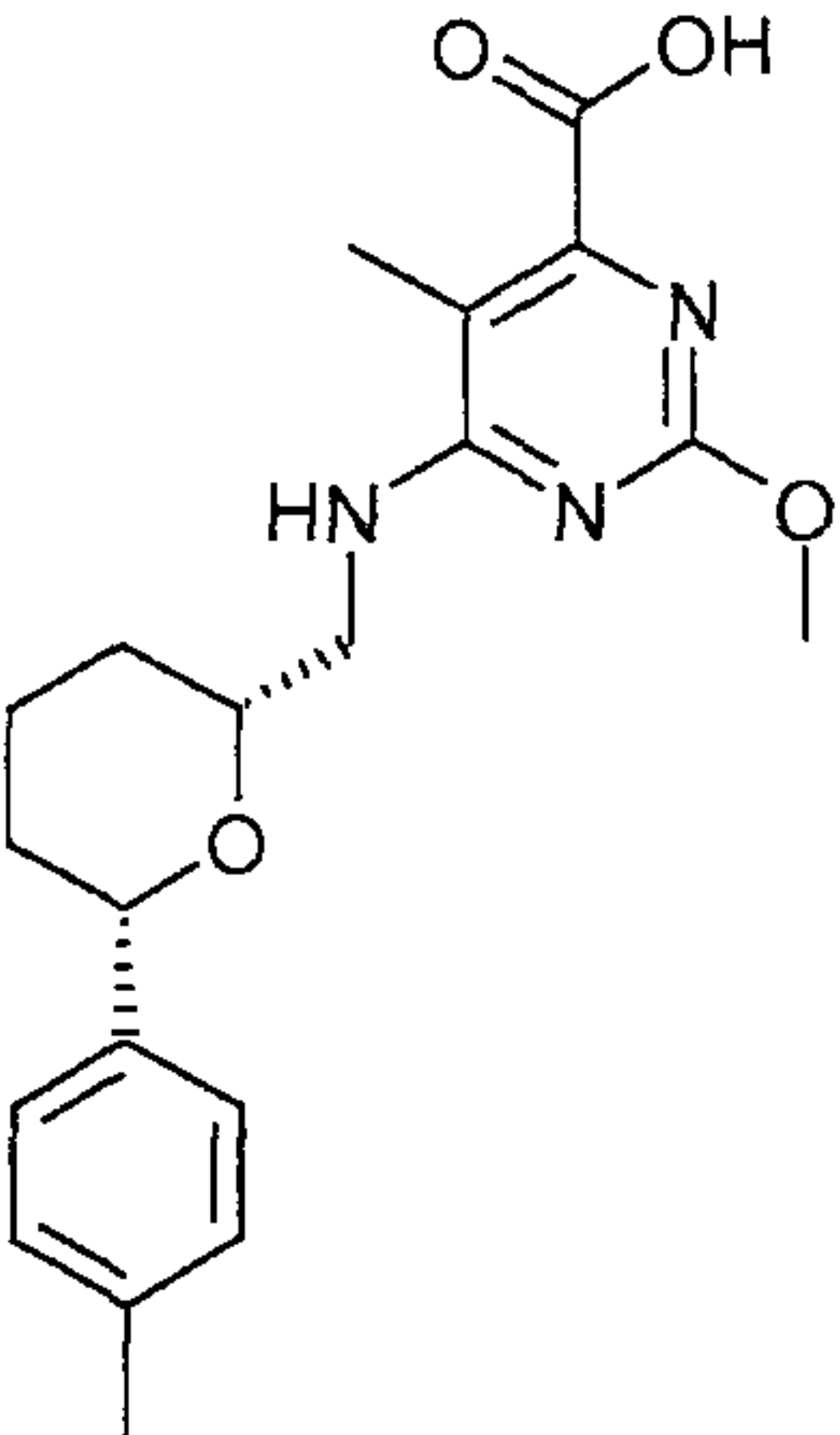
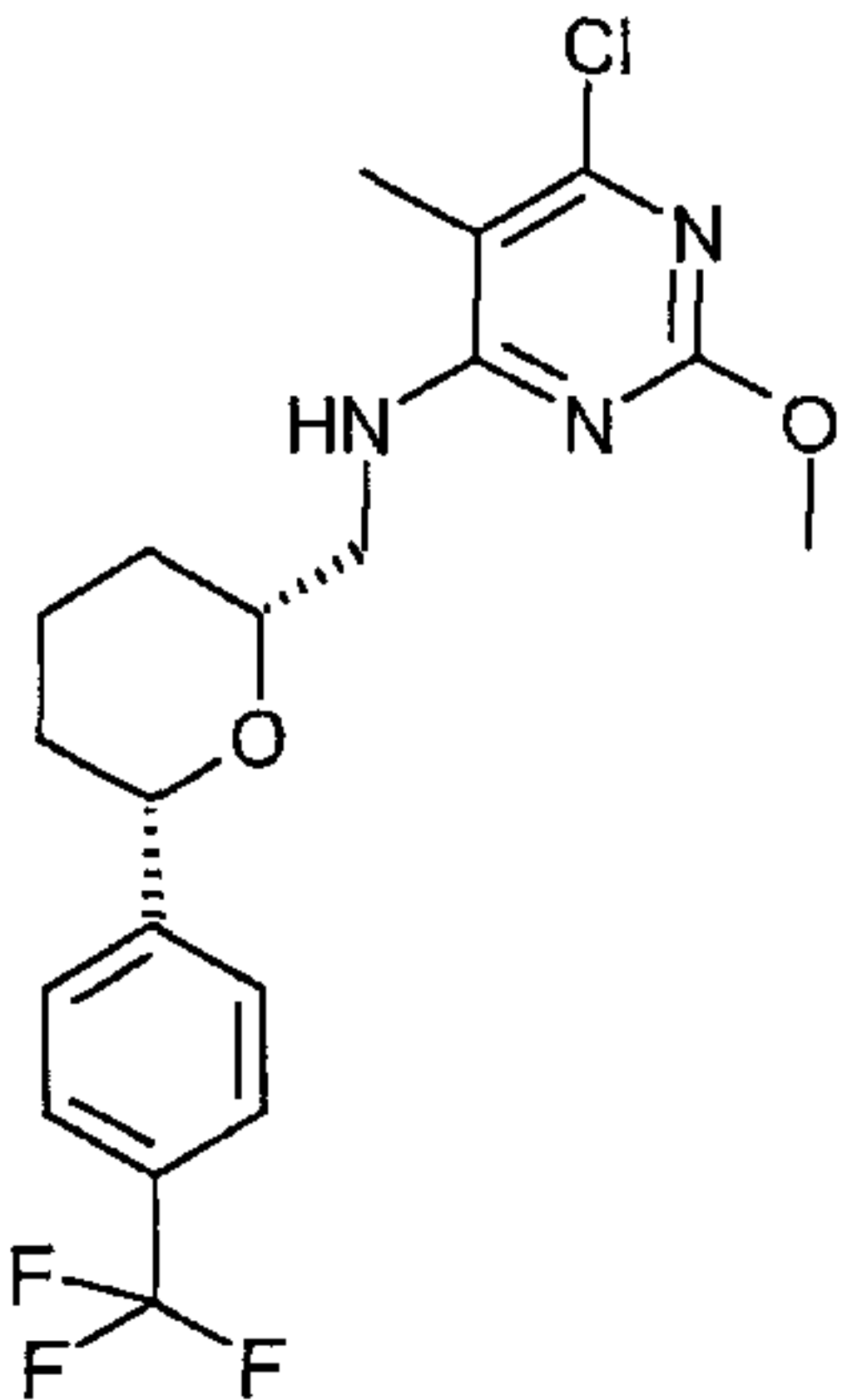
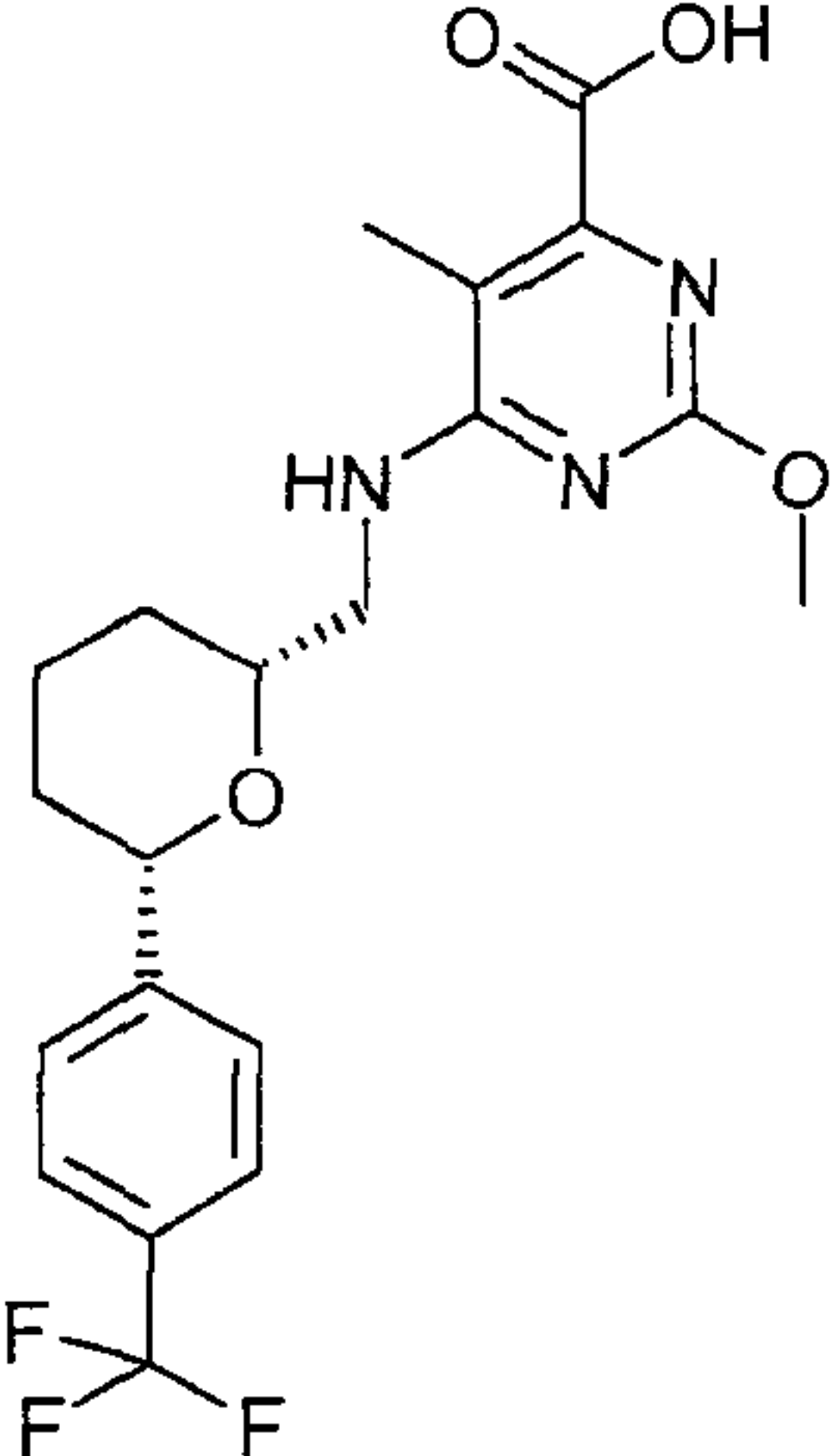
The following intermediates were synthesised in analogy to Intermediate 34 and 35.

<i>Synthesis in analogy to intermediate 34</i>					<i>Synthesis in analogy to intermediate 35</i>		
Core Intermediate	Source/Reference	Amine	Chloro Intermediate	STRUCTURE	Acid Intermediate	STRUCTURE	Stereochemistry
4,6-dichloro-2-trifluoromethyl-pyrimidine	Commercially available	16h	34a		35a		relative stereochemistry cis

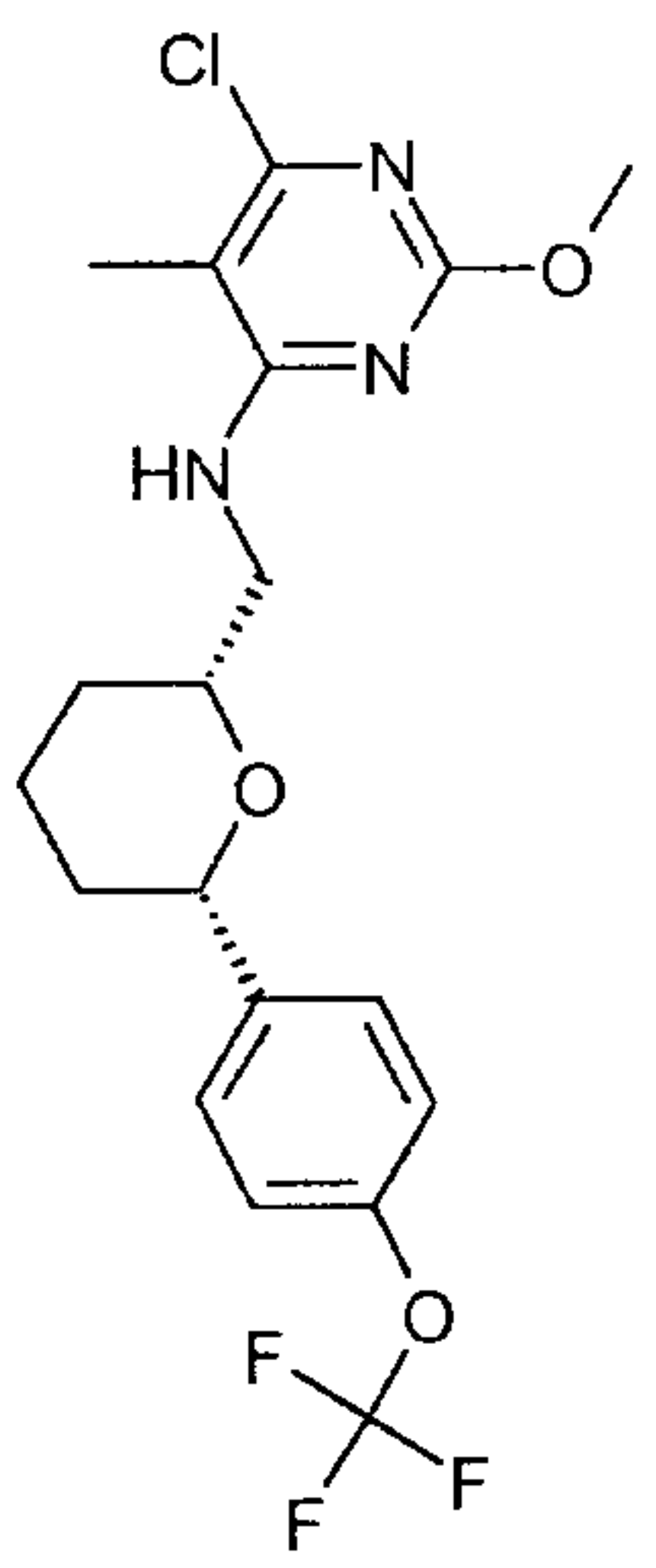
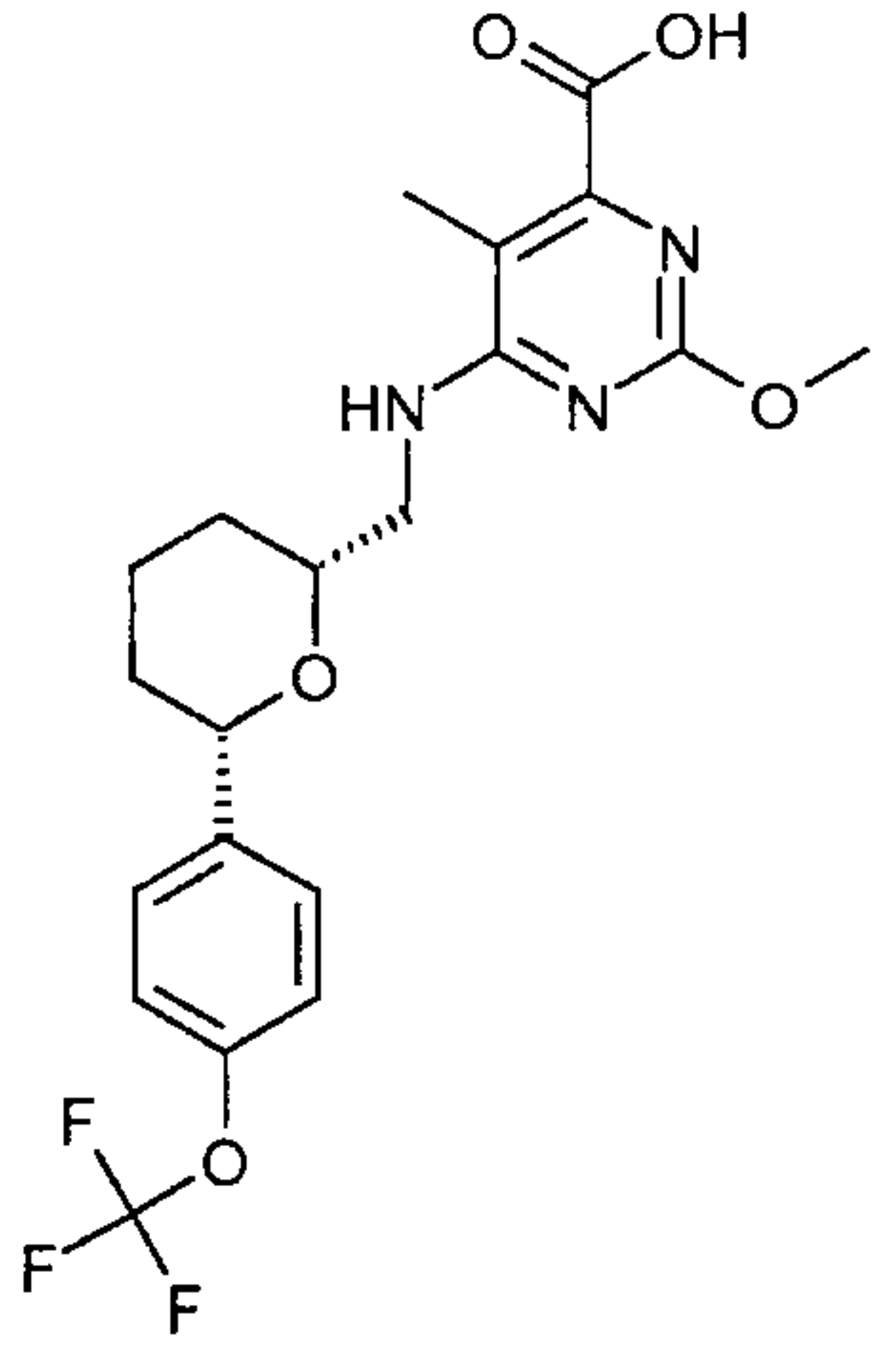
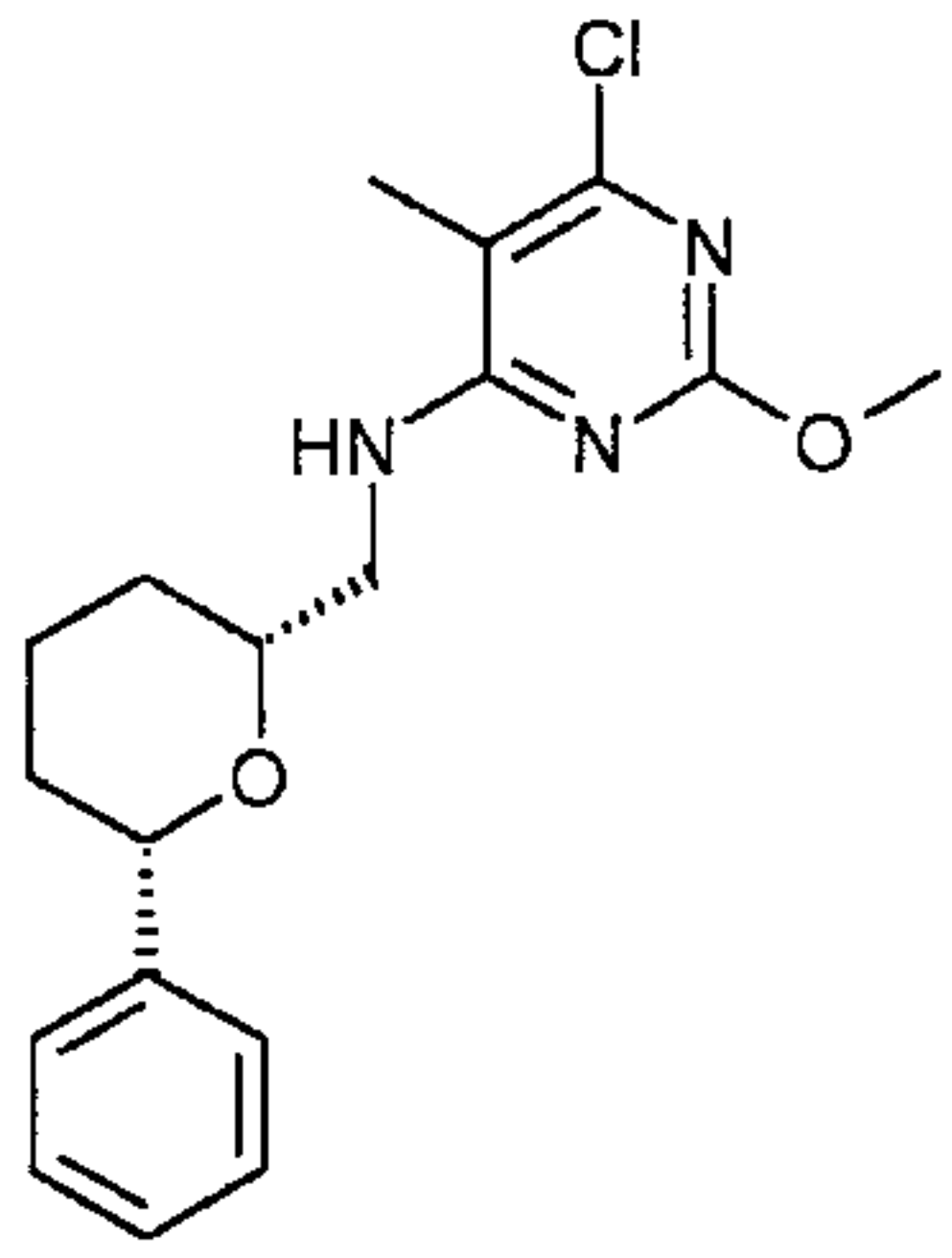
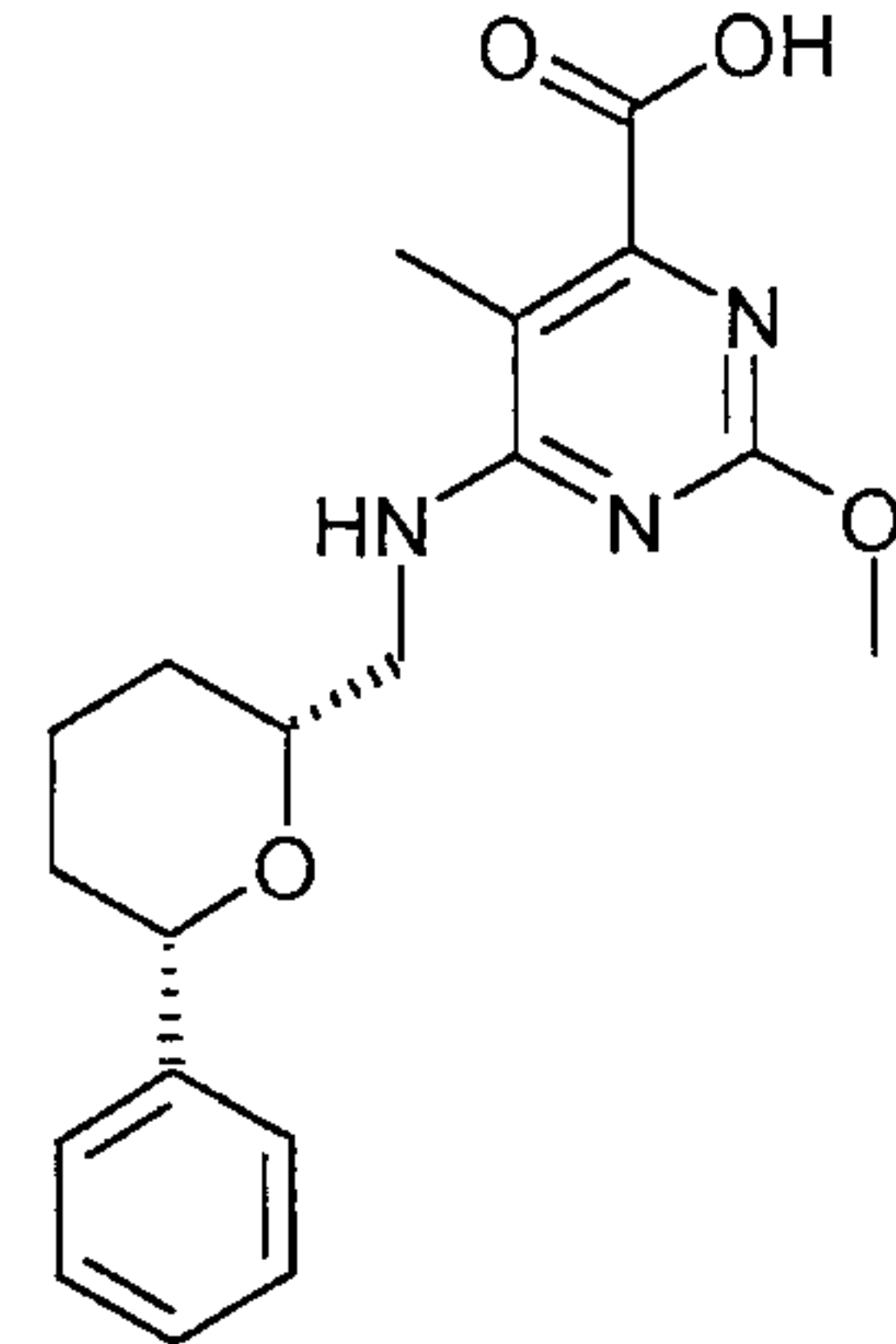
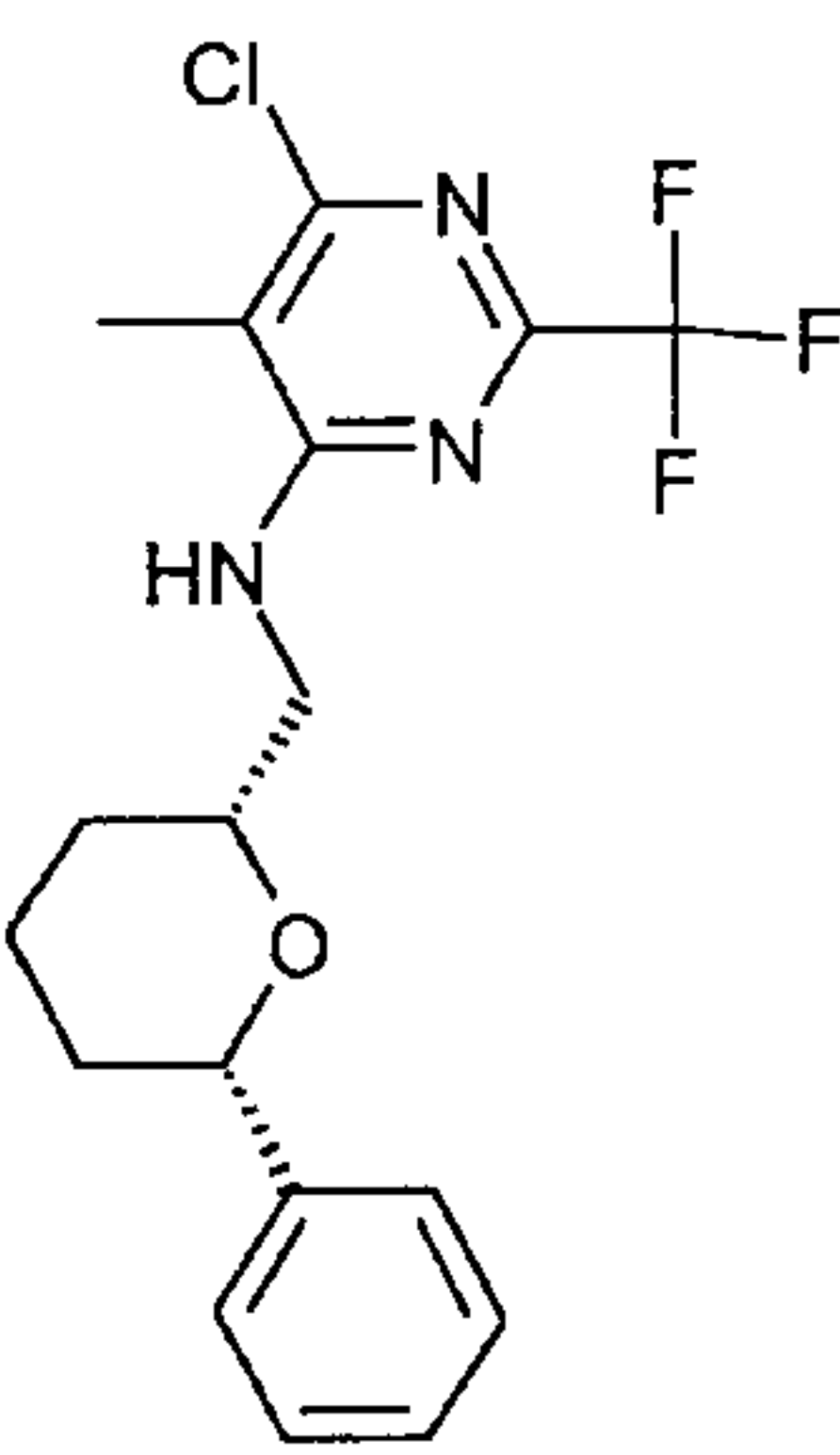
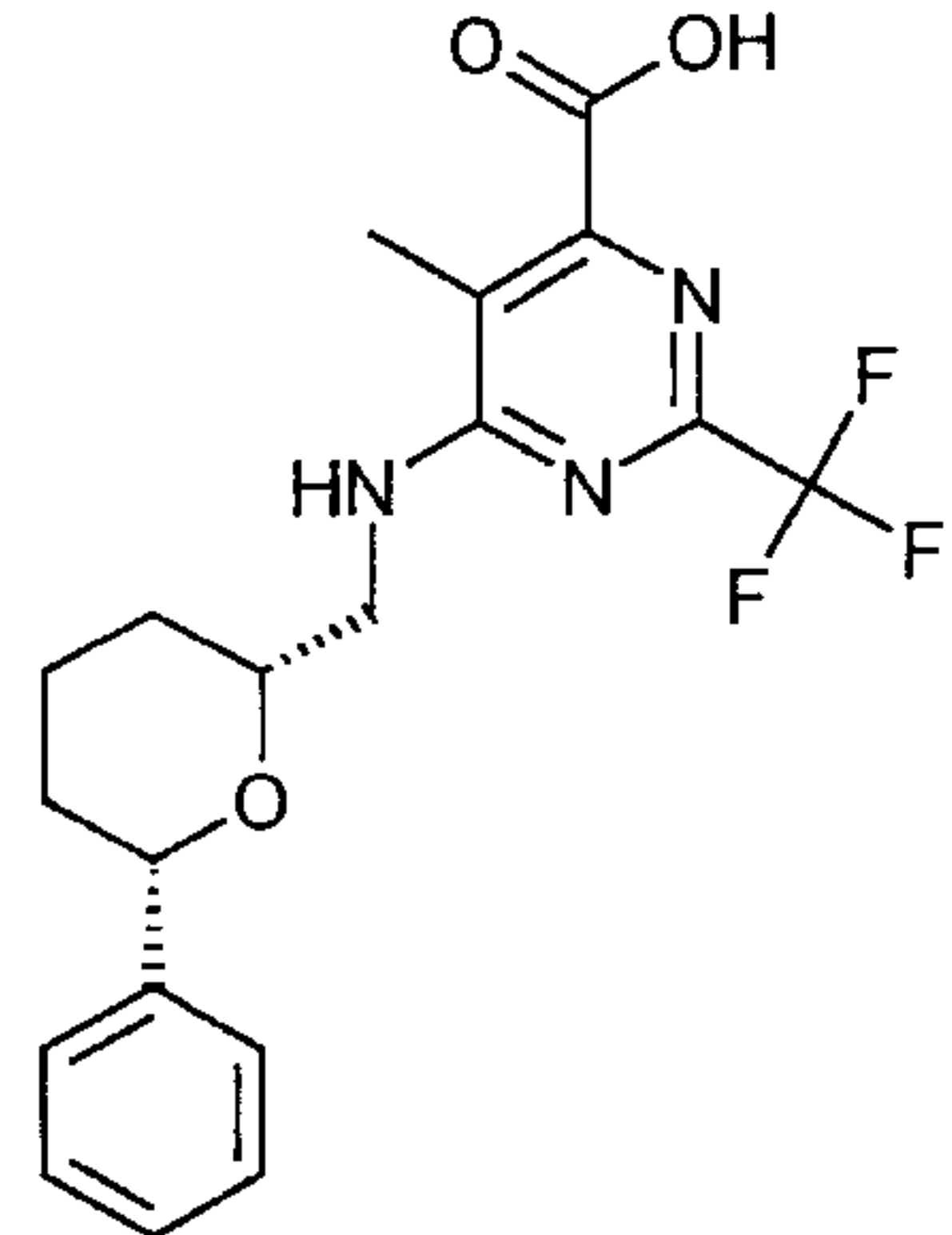
31214-7

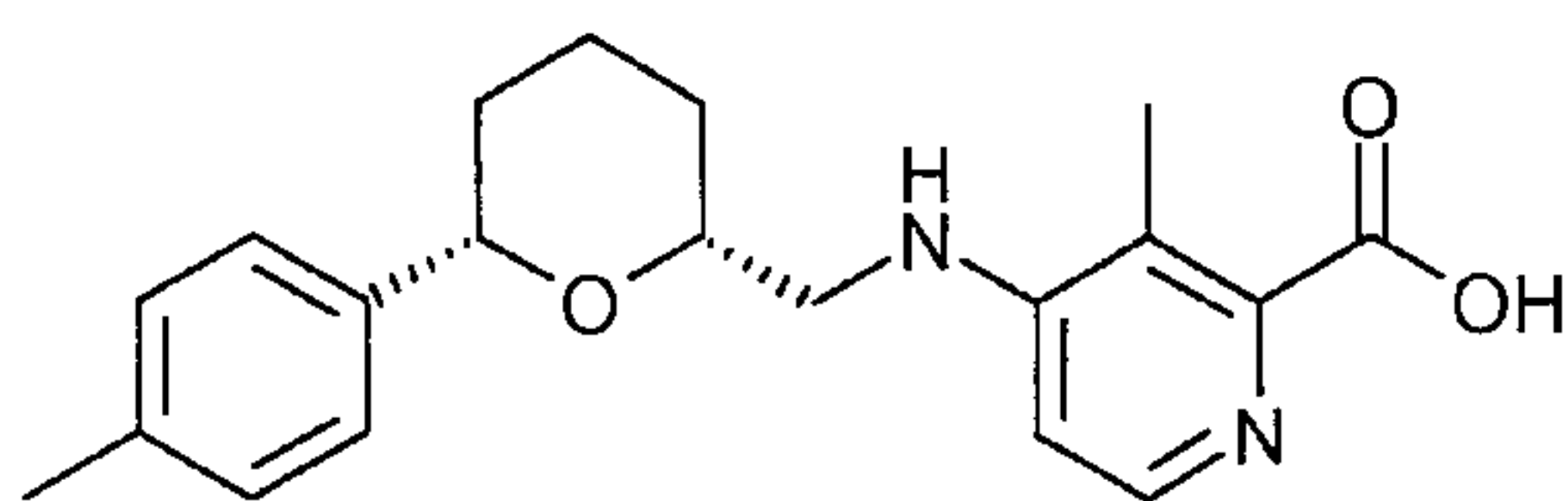
4,6-dichloro-2-trifluoromethylpyrimidine	Commercially available	16b	34b		35b		absolute stereochemistry as shown
4,6-dichloro-2-methoxypyrimidine	Commercially available	17a	34c		35c		absolute stereochemistry as shown
4,6-dichloro-2-methoxypyrimidine	Commercially available	16b	34d		35d		absolute stereochemistry as shown

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4,6-dichloro-2-methoxypyrimidine	Commercially available	16h	34e		35e		relative stereochemistry cis
2d	-	17a	34f		35f		absolute stereochemistry as shown
2d	-	16b	34g		35g		absolute stereochemistry as shown

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2d	-	16h	34h		35h		relative stereochemistry cis
2d	-	16c	34i		35i		relative stereochemistry cis
2f	-	16c	34j		35j		relative stereochemistry cis

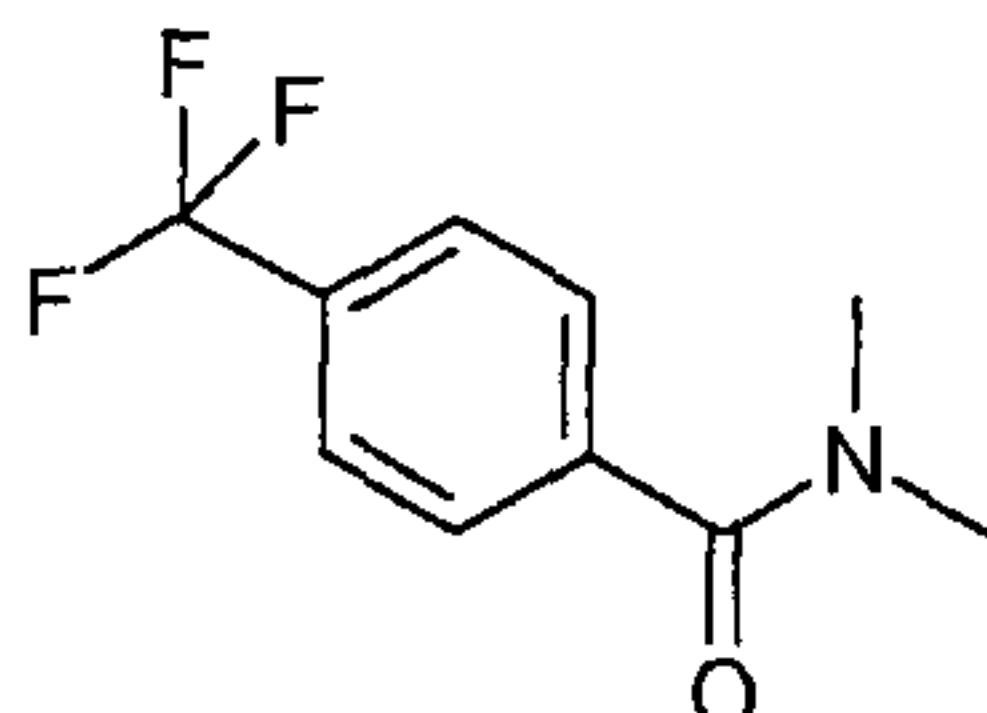
Intermediate 36

31214-7

Commercially available 4-chloro-3-methyl-picolinate (100mg, 0.5 mmol), Intermediate 17a (205 mg, 1 mmol) and N,N-diisopropyl-ethyl-amine (0.18 ml, 1 mmol) were dissolved in 3 ml of N,N-dimethylacetamide and refluxed overnight. The reaction mixture was purified by preparative LC/MS (reverse phase). 120 mg (0.35 mmol) of the desired product were obtained. Absolute stereochemistry known.

The following synthesis sequence allows the preparation of Intermediates 16b, 16c, 16h, 17a, and preparation of Intermediate 42:

Intermediate 37a

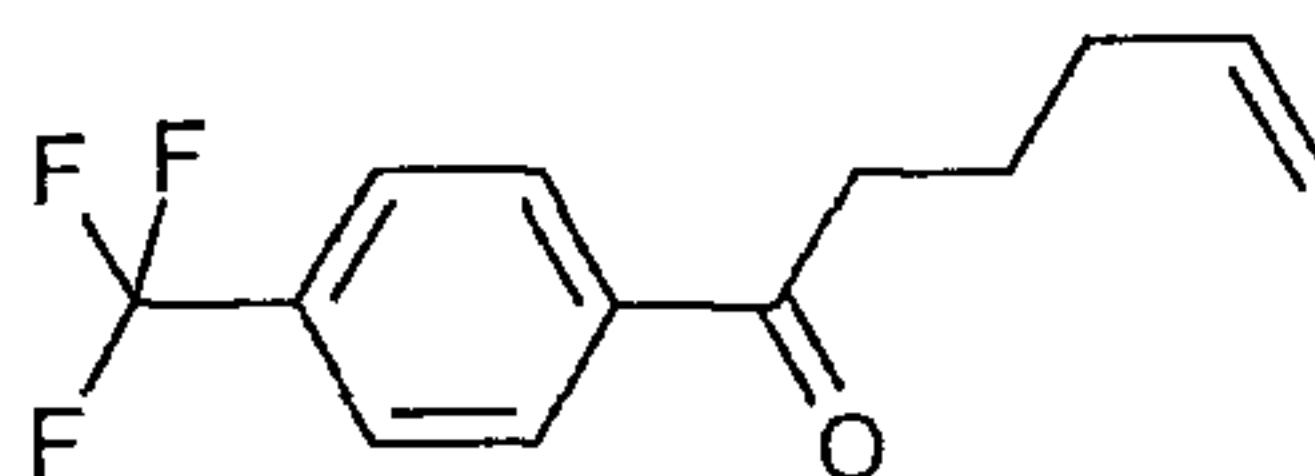


10

To a solution of commercially available 4-(trifluoromethyl)-benzoyl chloride (25 g, 112 mmol) in 250 ml dry tetrahydrofuran under nitrogen atmosphere, dimethylamine dihydrochloride (14.7 g, 180 mmol) and potassium carbonate (49.62 g, 360 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum, the crude product was dissolved in ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated under vacuum. The crude product was used in the next step without any purification.

15

Intermediate 38a

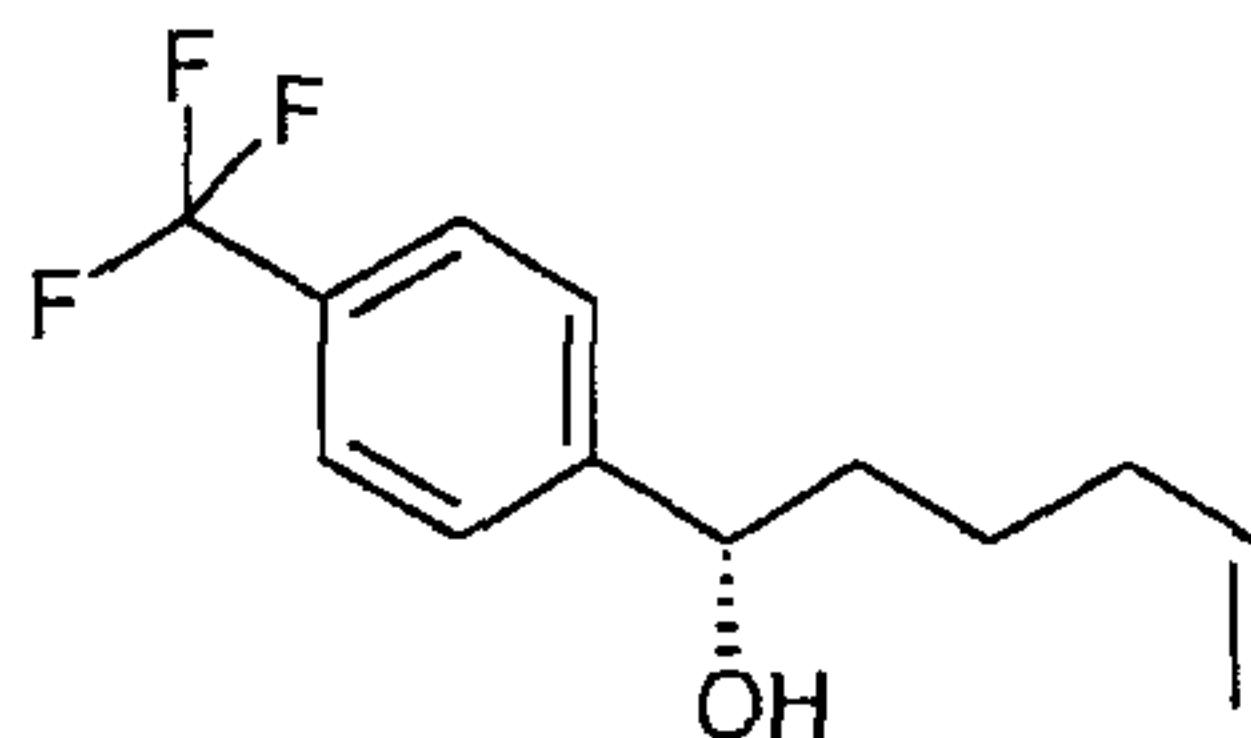


20

Intermediate 37a (25g) was dissolved in 125 ml of dry tetrahydrofuran and the reaction mixture was cooled to 0°C. 350 ml of a cooled 0.5 M solution of (pent-4-enyl)magnesium bromide (Liebigs Annalen der Chemie **1982**, 1478) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography to give 25g of the desired product.

25

Intermediate 39a



30

31214-7

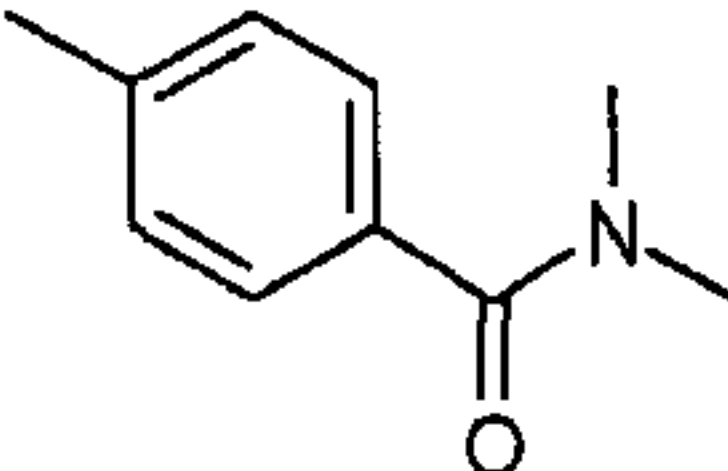
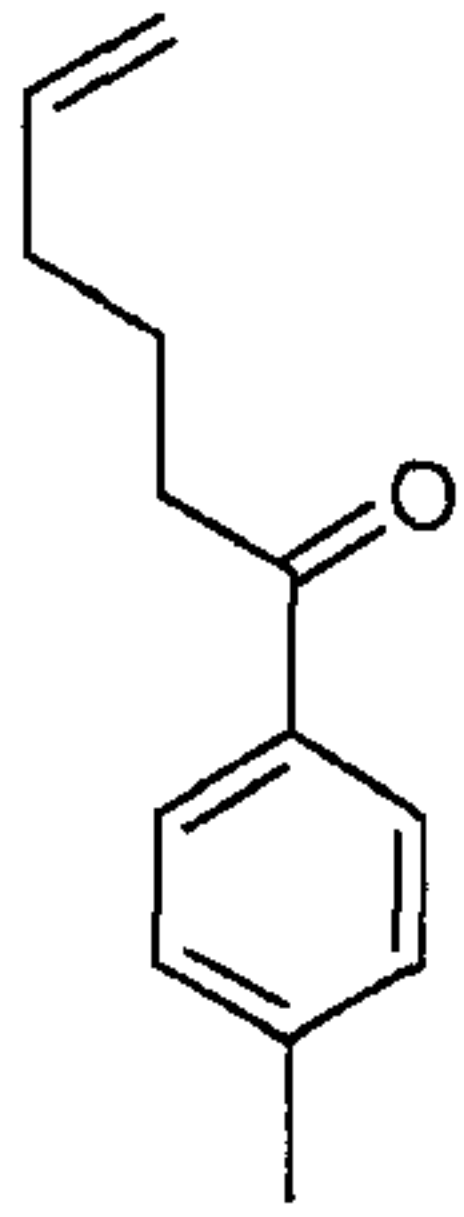
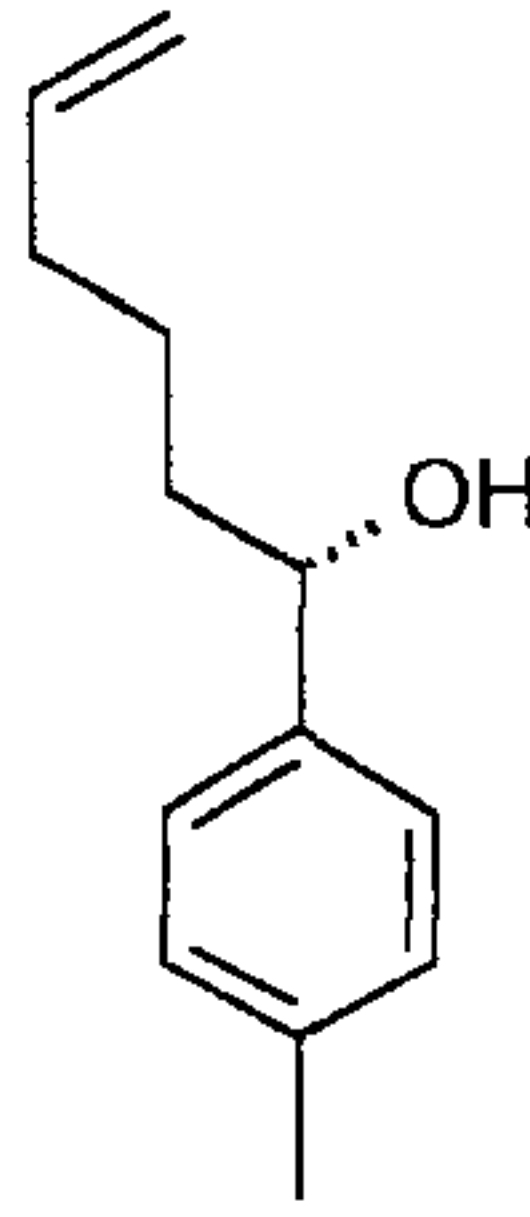
Intermediate 38a was added dropwise to a suspension of (S,S)-teth-TsDpen ruthenium chloride (20 mg, 0.032 mmol; Johnson Matthey Catalysts) in 200 ml formic acid/triethylamine complex under argon atmosphere.

- 5 The reaction mixture was warmed to 70°C for 18 h. Then, water was added and the reaction mixture was extracted with diethyl ether. The organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product (40 g) was used in the next step without any purification.

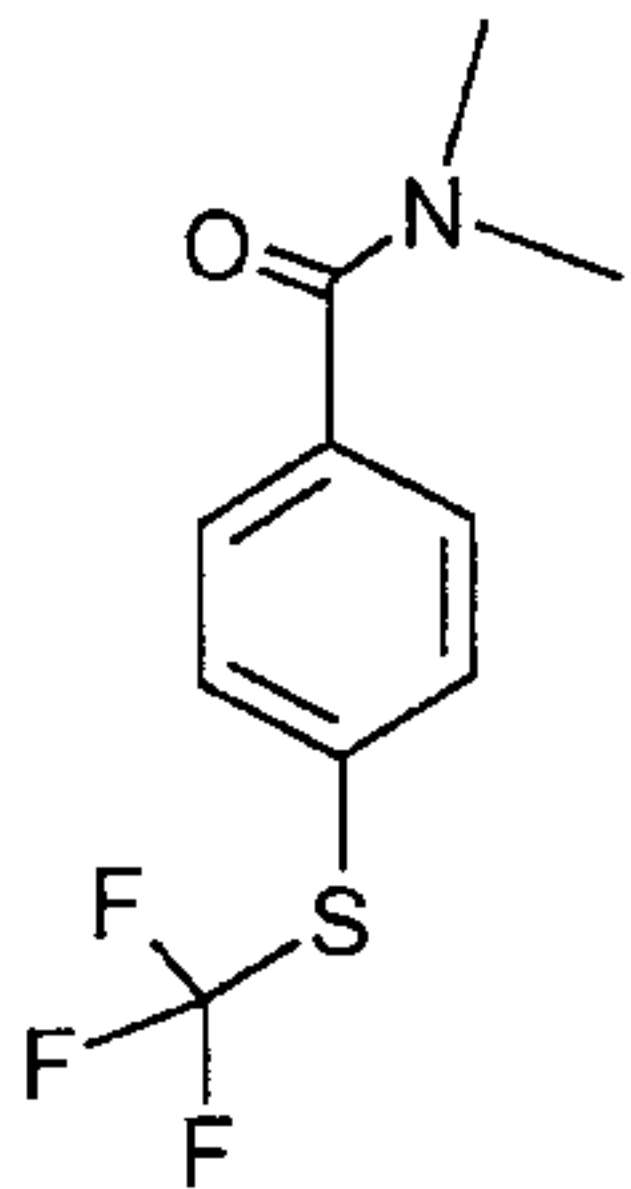
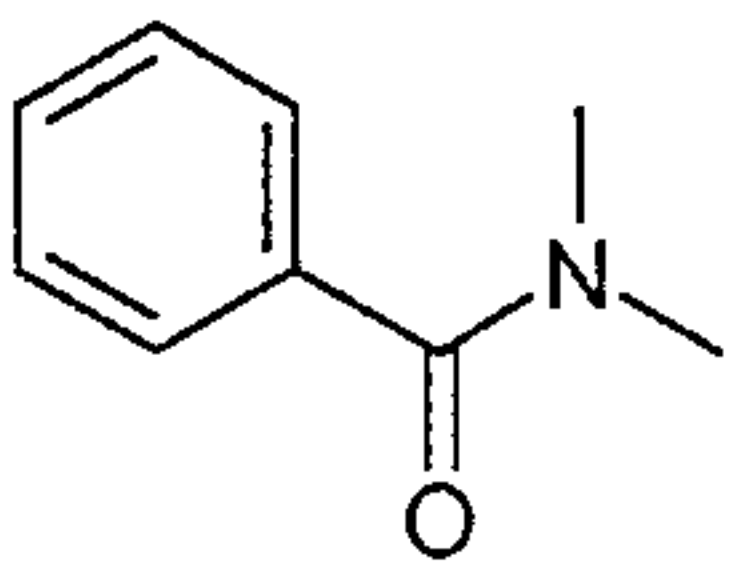
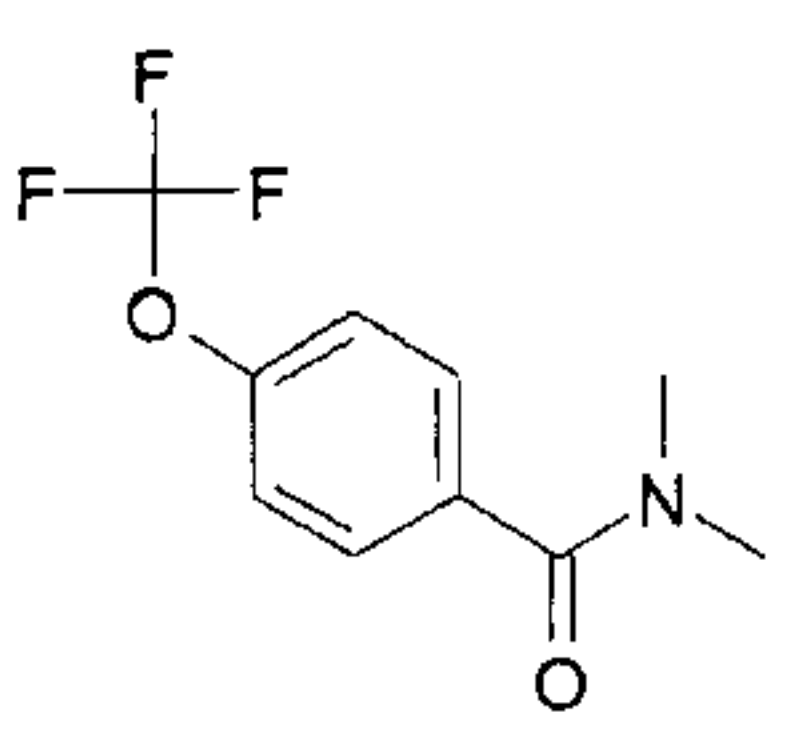
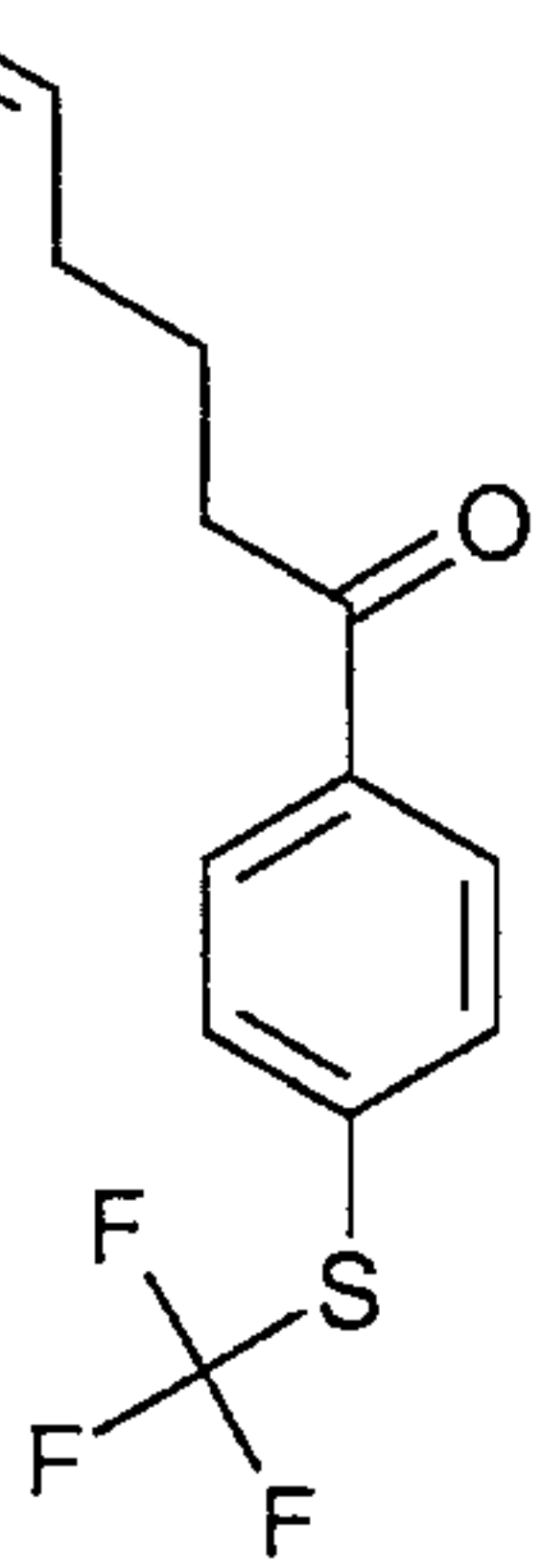
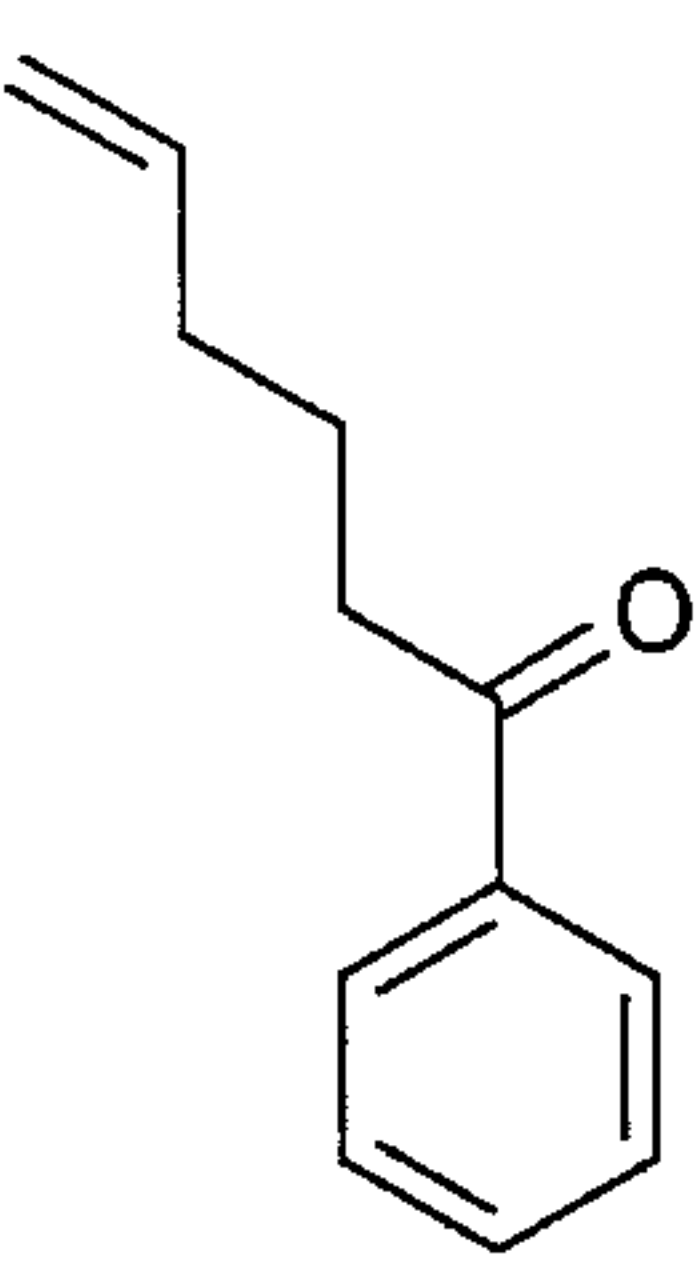
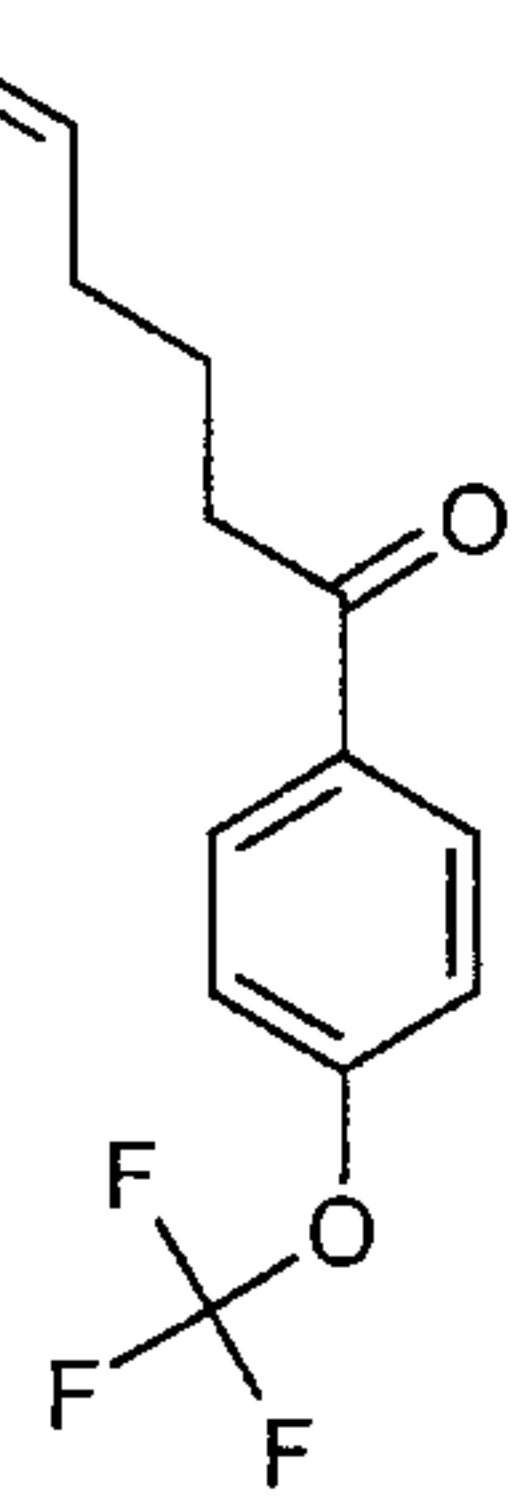
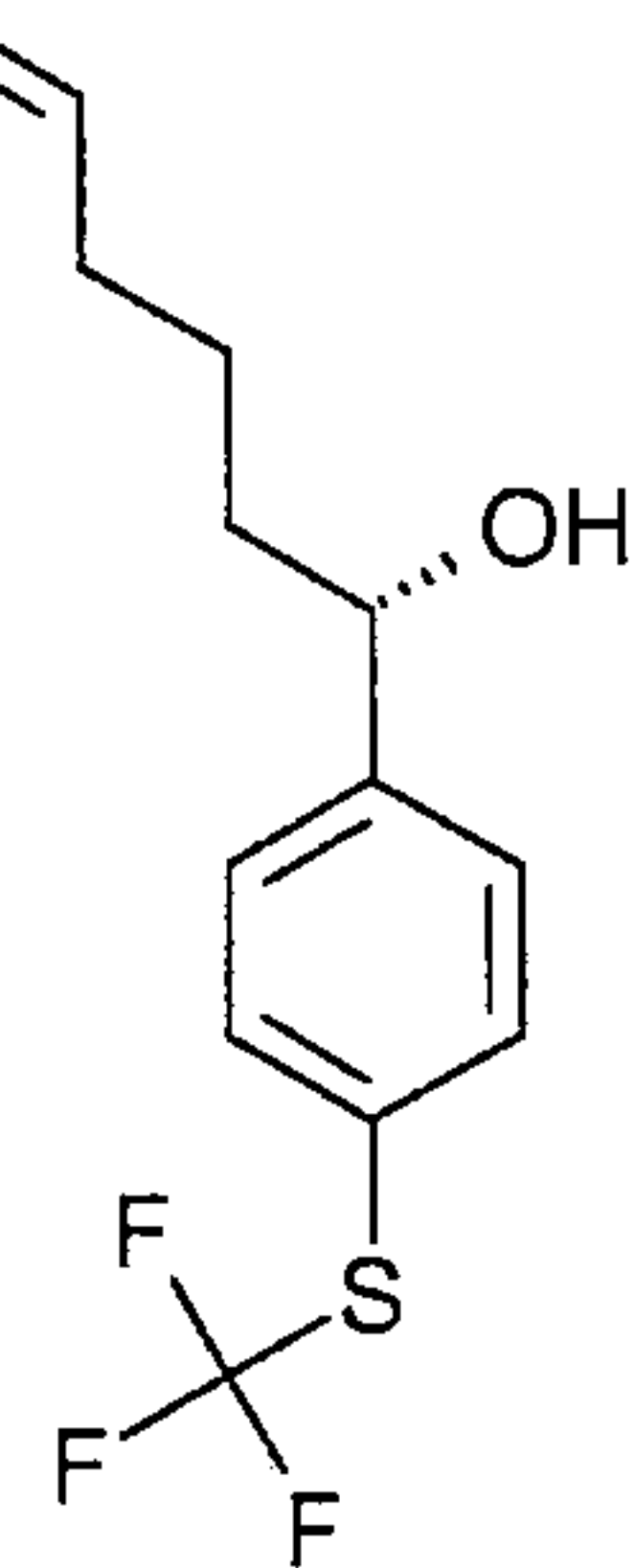
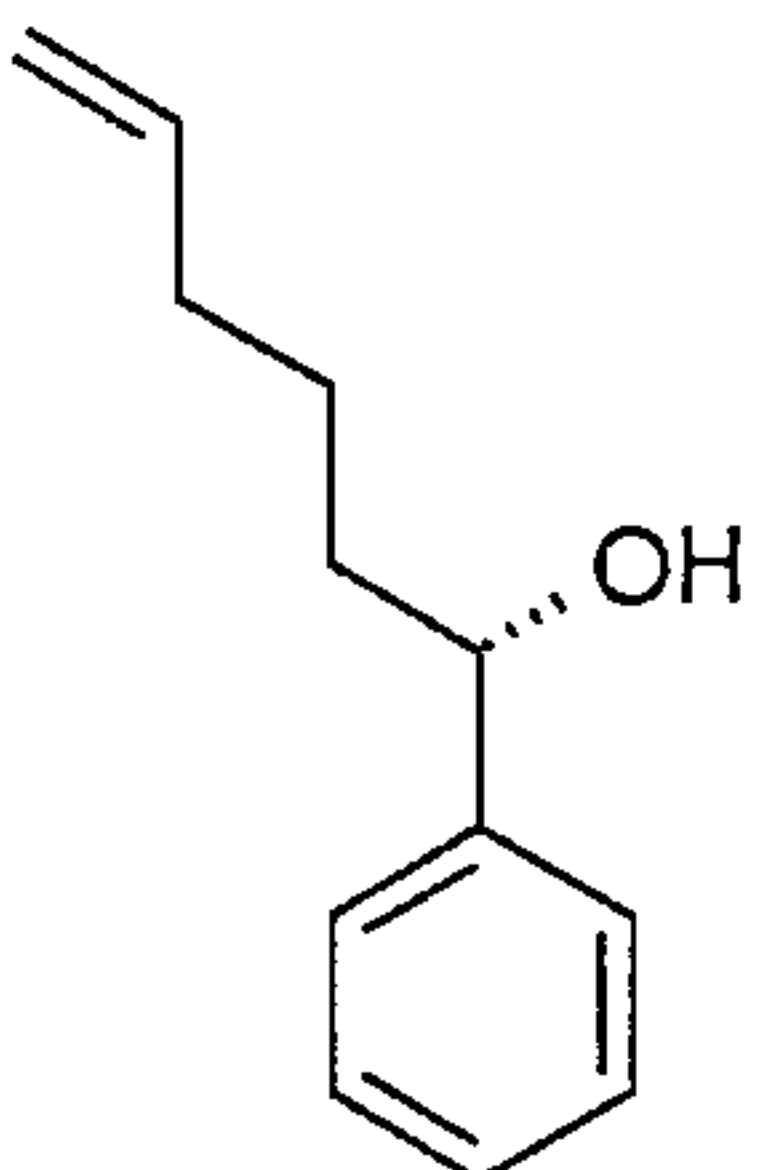
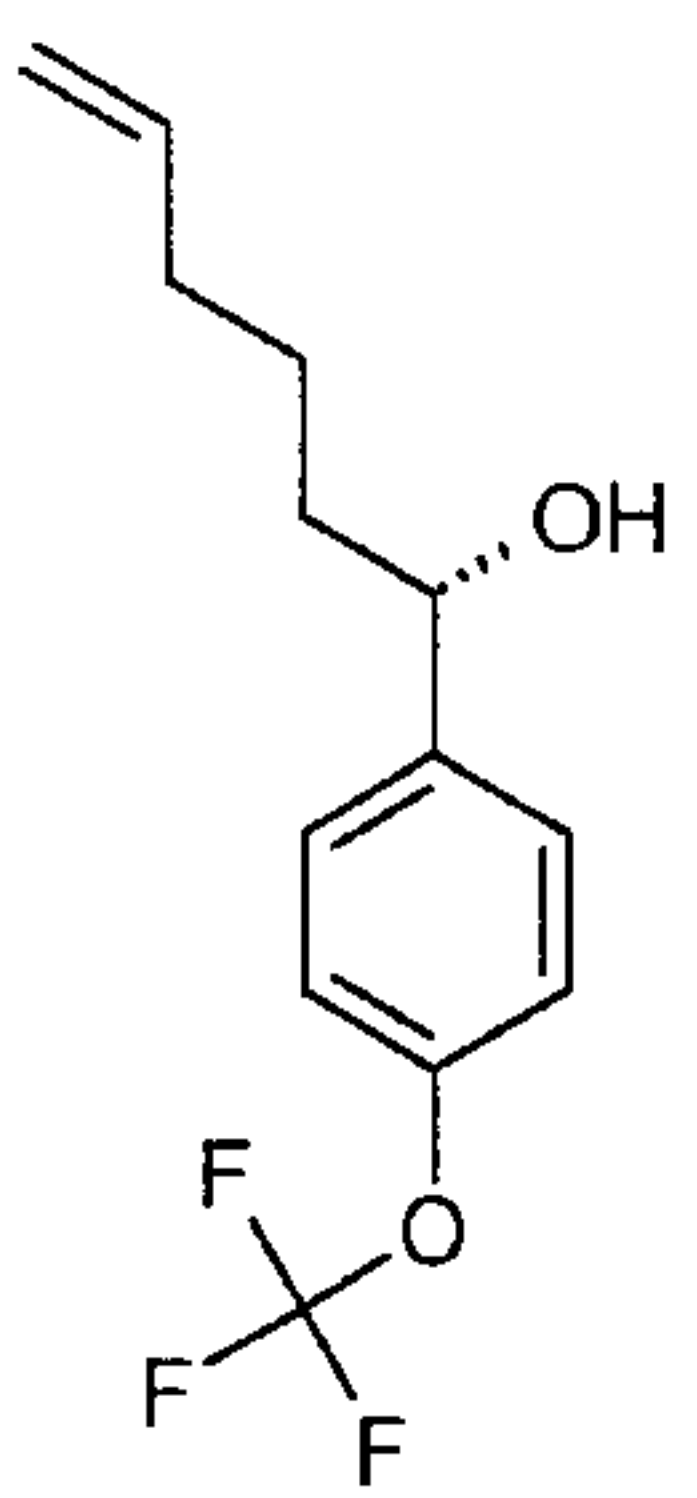
Stereochemistry in analogy to Organic Letters **2000**, 1749-51.

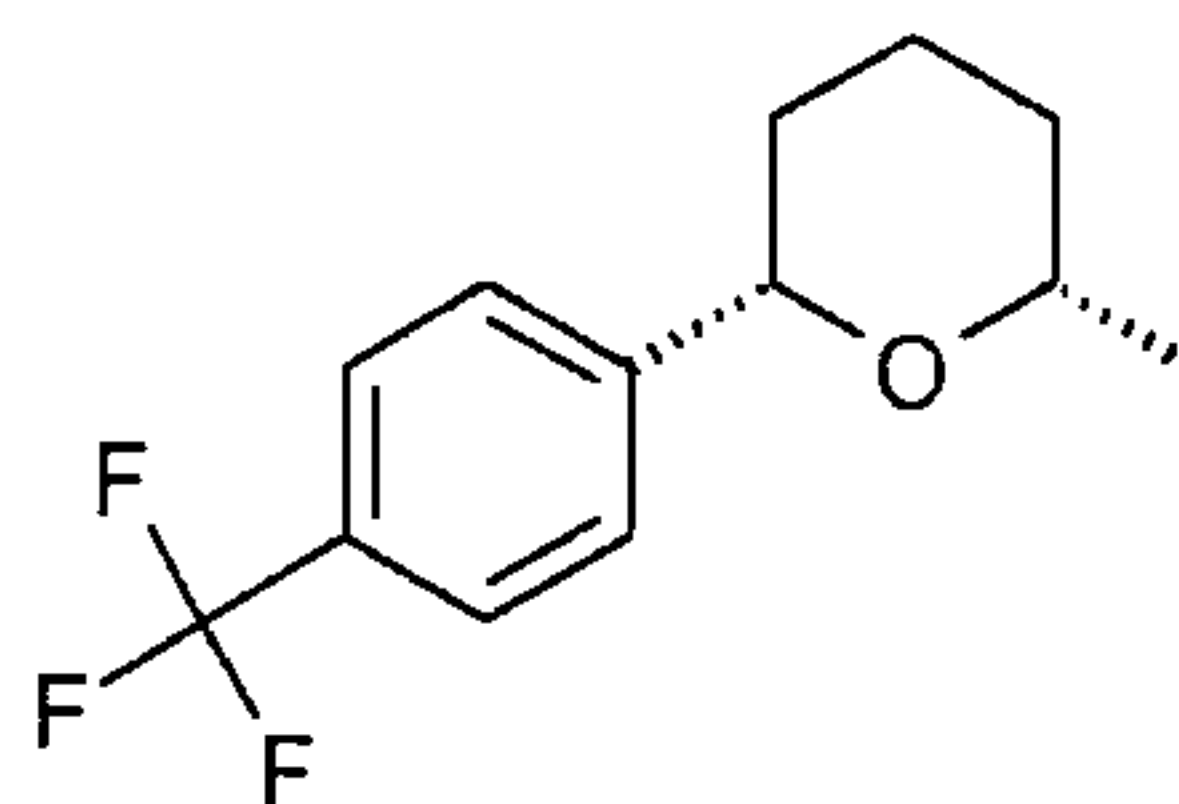
10

The following intermediates were synthesized in analogy to Intermediates 37a, 38a and 39a.

<i>synthesis in analogy to intermediate 37a</i>				<i>synthesis in analogy to intermediate 38a</i>		<i>synthesis in analogy to intermediate 39a</i>		
Starting Benzoyl chloride	Source	Amide Intermediate	STRUCTURE	Keton Intermediate	STRUCTURE	Alcohol Intermediate	STRUCTURE	Stereochemistry
4-methyl-benzoyl chloride	Commercially available	37b		38b		39b		in analogy to Organic Letters 2000 , 1749-51

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4-(trifluoromethylthio)benzoyl chloride	Benzoyl chloride	4-(trifluoromethoxy)benzoyl chloride
Chlorination of commercially available 4-(trifluoromethylthio) benzoic acid using thionylchloride	Commercially available	Commercially available
37e	37d	37c
		
38e	38d	38c
		
39e	39d	39c
		
in analogy to Organic Letters 2000, 1749-51	in analogy to Organic Letters 2000, 1749-51	in analogy to Organic Letters 2000, 1749-51

Intermediate 40a

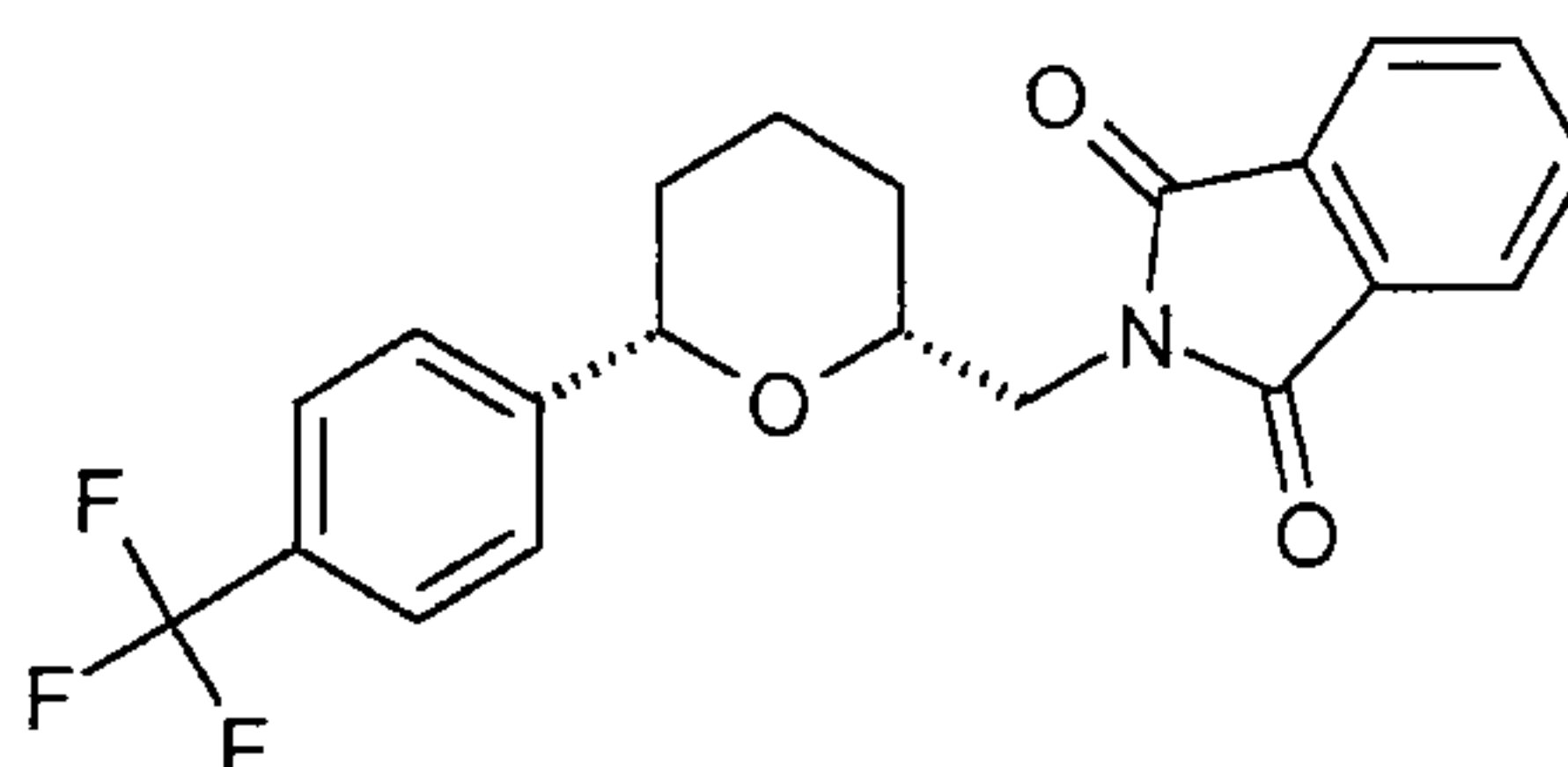
- 5 To a suspension of sodium bicarbonate (40.6 g, 482 mmol) in 600 ml of acetonitrile, a solution of Intermediate 39a (40 g) in 100 ml of acetonitrile was added, followed by the

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addition of iodine (122 g, 482 mmol). The reaction mixture was stirred at room temperature for 1 h, then 1000 ml of a saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution were added. The mixture was extracted with diethyl ether. Then, the organic phase was separated, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography to yield 29 g of the desired *cis* stereoisomer.

Relative stereochemistry was assigned by $^1\text{H-NMR}$.

Intermediate 41a



- 10 Commercially available phthalimide potassium salt (17.4 g, 94.0 mmol) was added to a solution of Intermediate 40a (29 g, 78.4 mmol) in 250 ml DMF. The reaction mixture was stirred at 90°C for 18 h. The reaction mixture was concentrated under vacuum, diethyl ether was added and the organic phase was washed with an aqueous 1 M sodium hydroxide solution. The organic layer was separated, dried over sodium sulfate and concentrated under vacuum. The crude product (28.7g) was re-crystallised using 350 ml of methylcyclohexane. 9.5 g of enantiomerically enriched product were obtained.

Enantiomeric purity was determined by chiral HPLC (Method 2Ja):

R_t (preferred stereoisomer) = 6.69 min

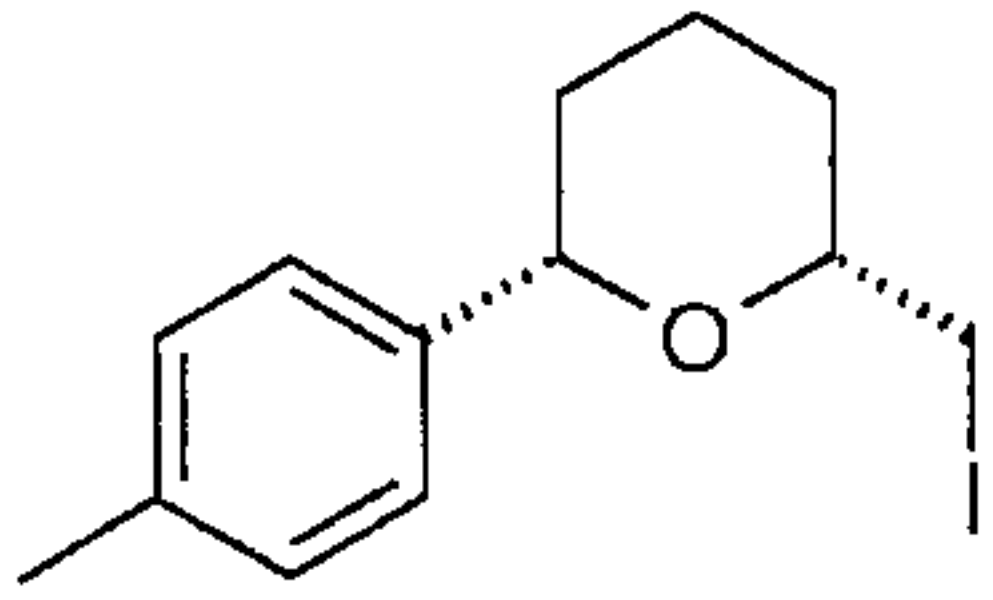
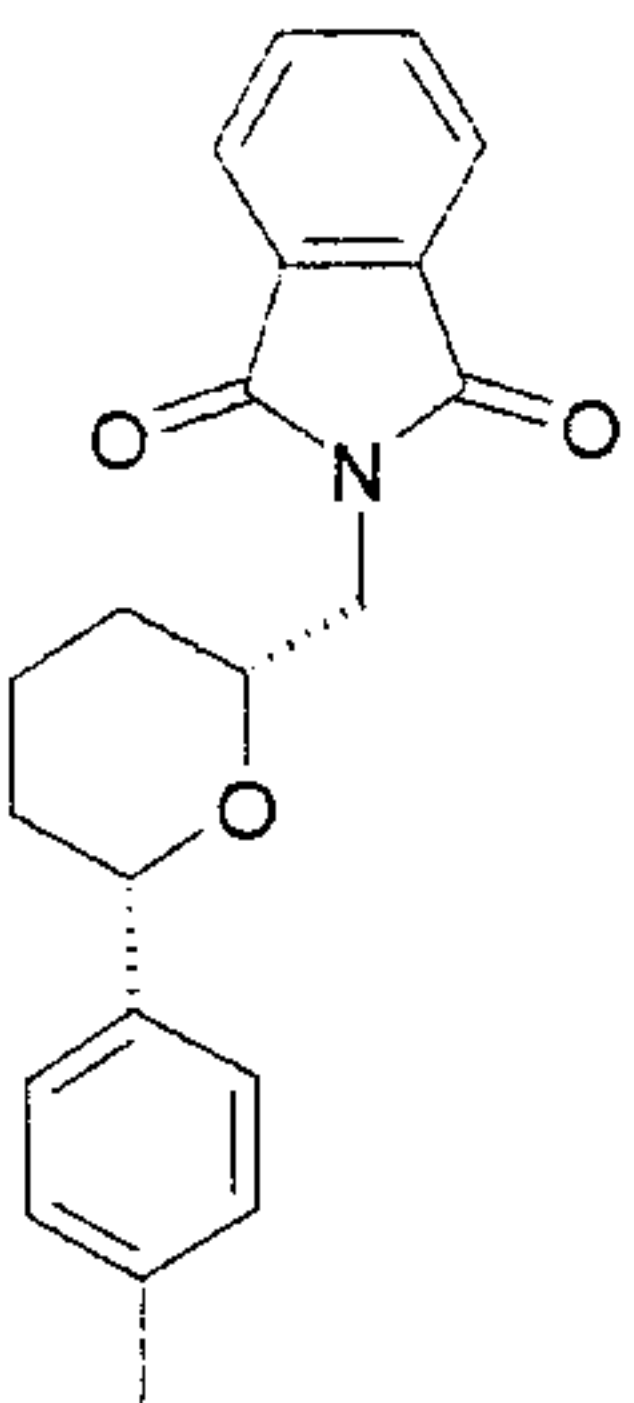
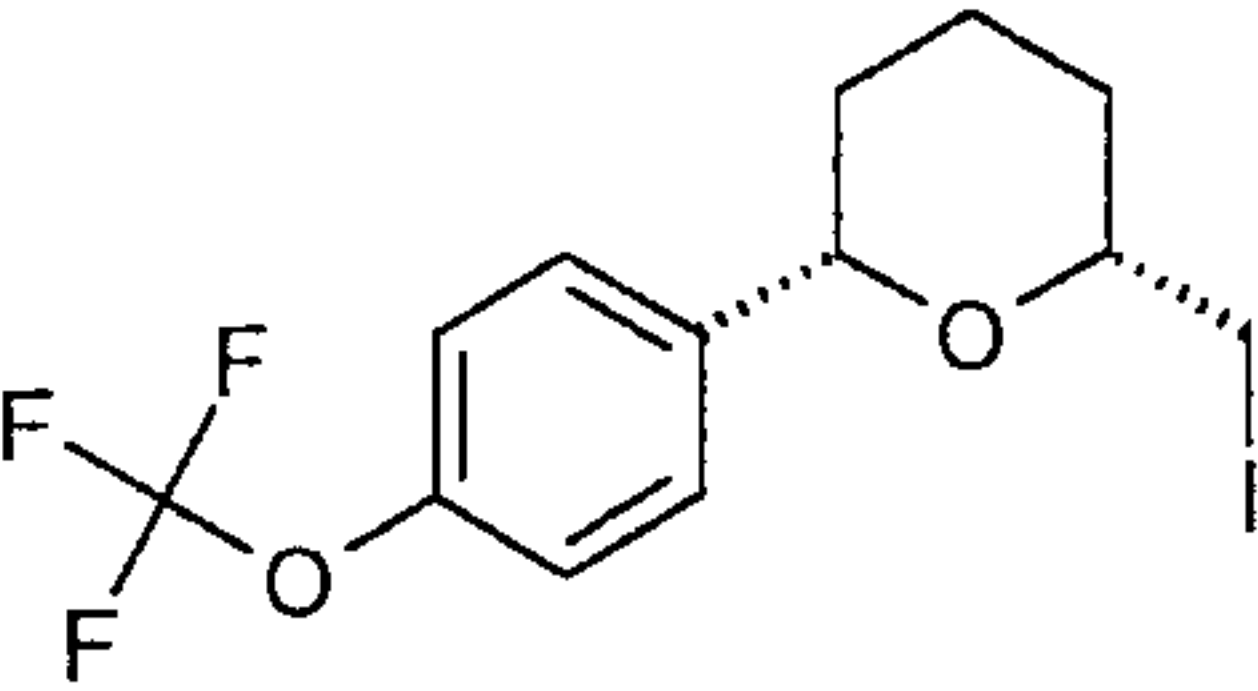
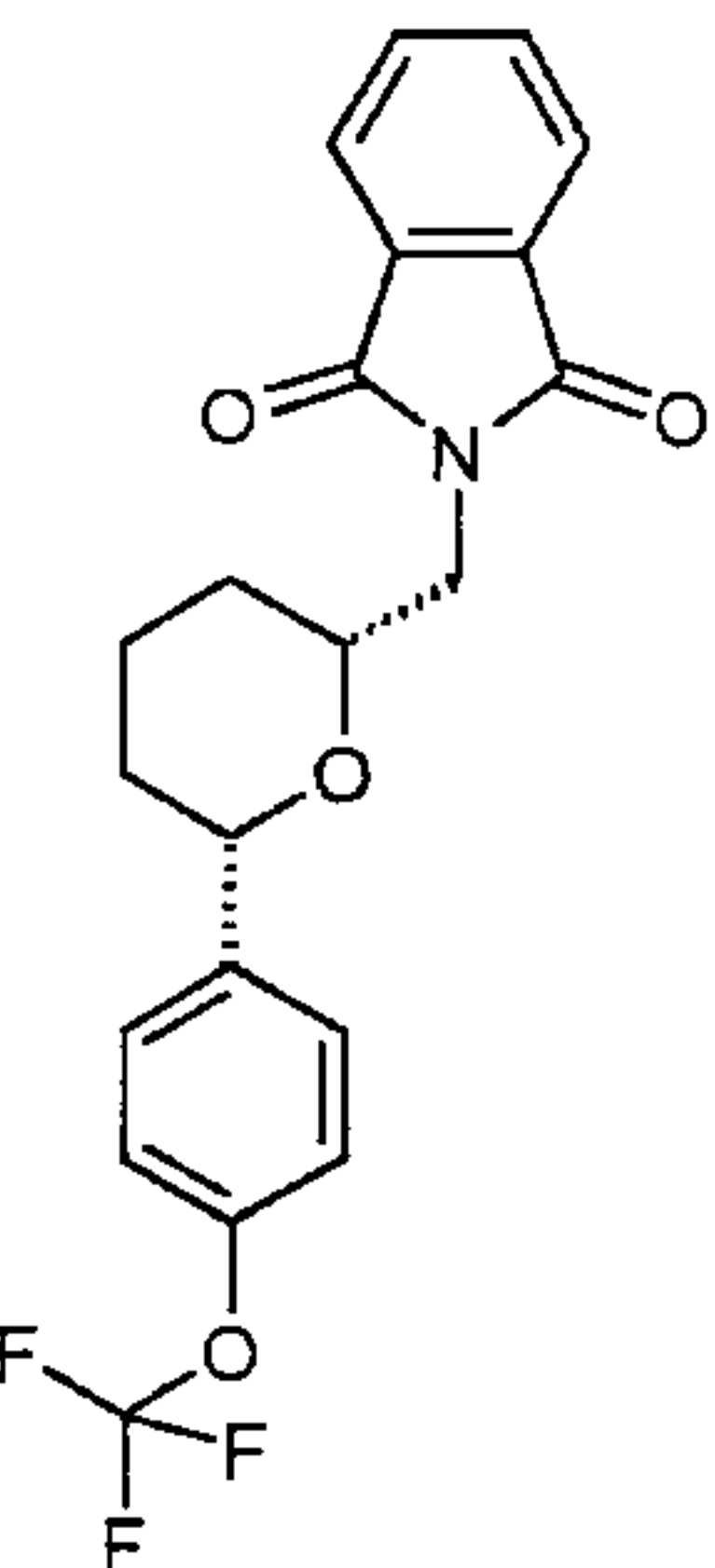
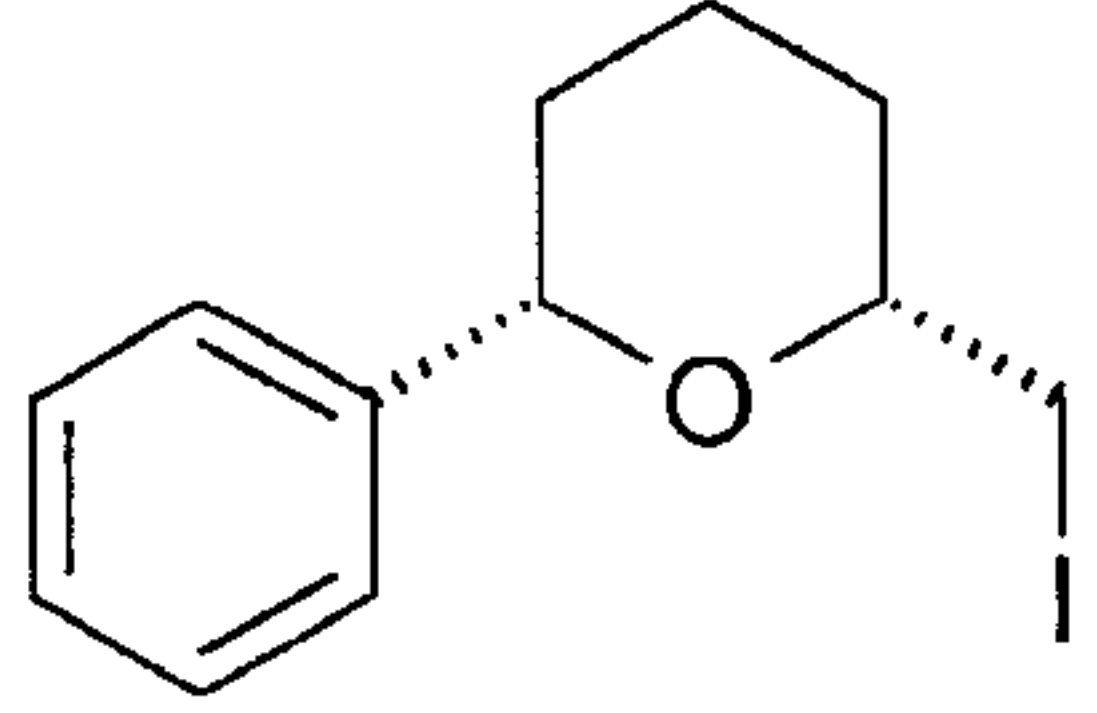
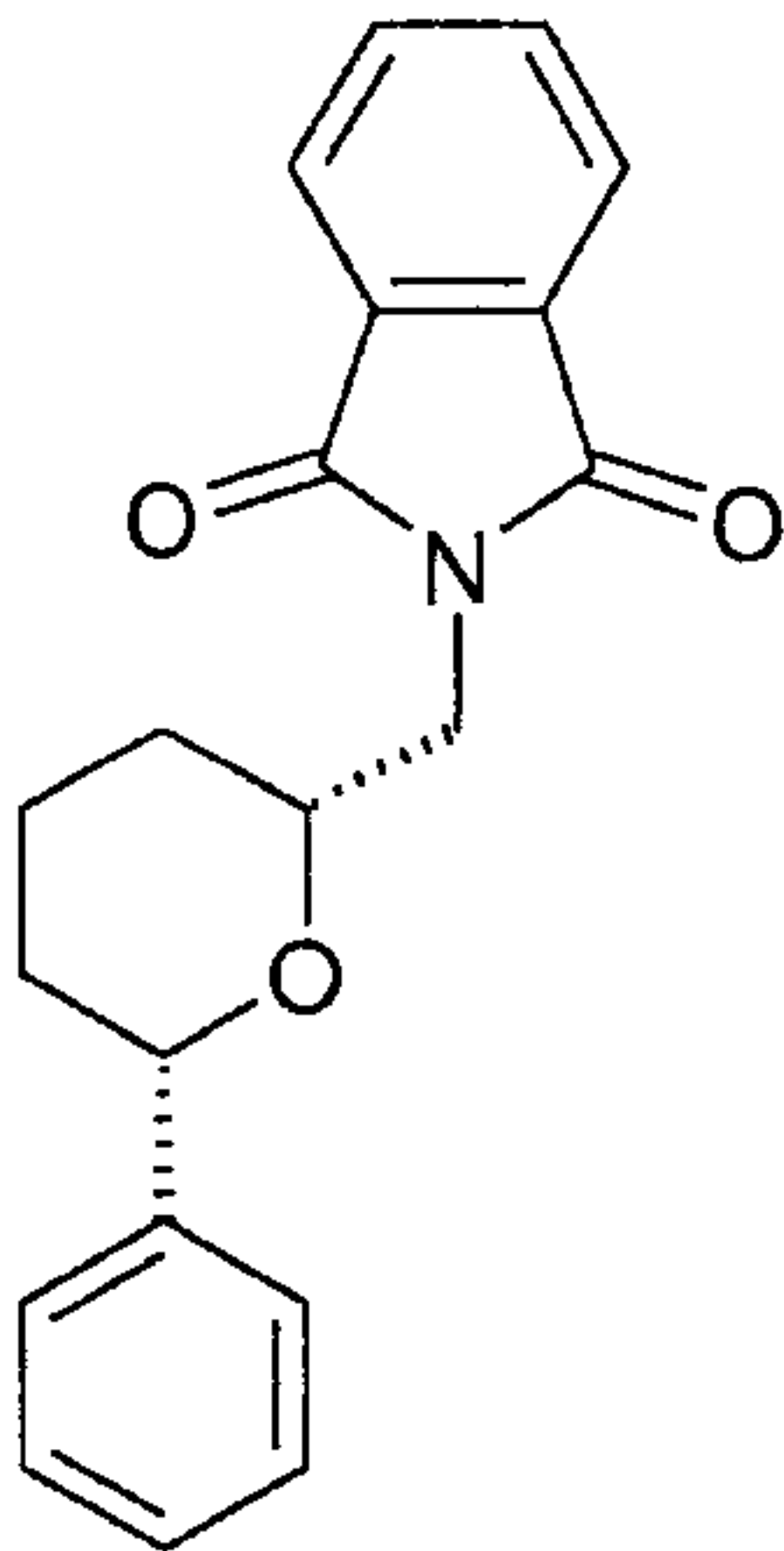
- 20 R_t (second stereoisomer) = 6.00 min

Repeated re-crystallisations with methylcyclohexane allowed to increase the yield of the enantiopure preferred stereoisomer.

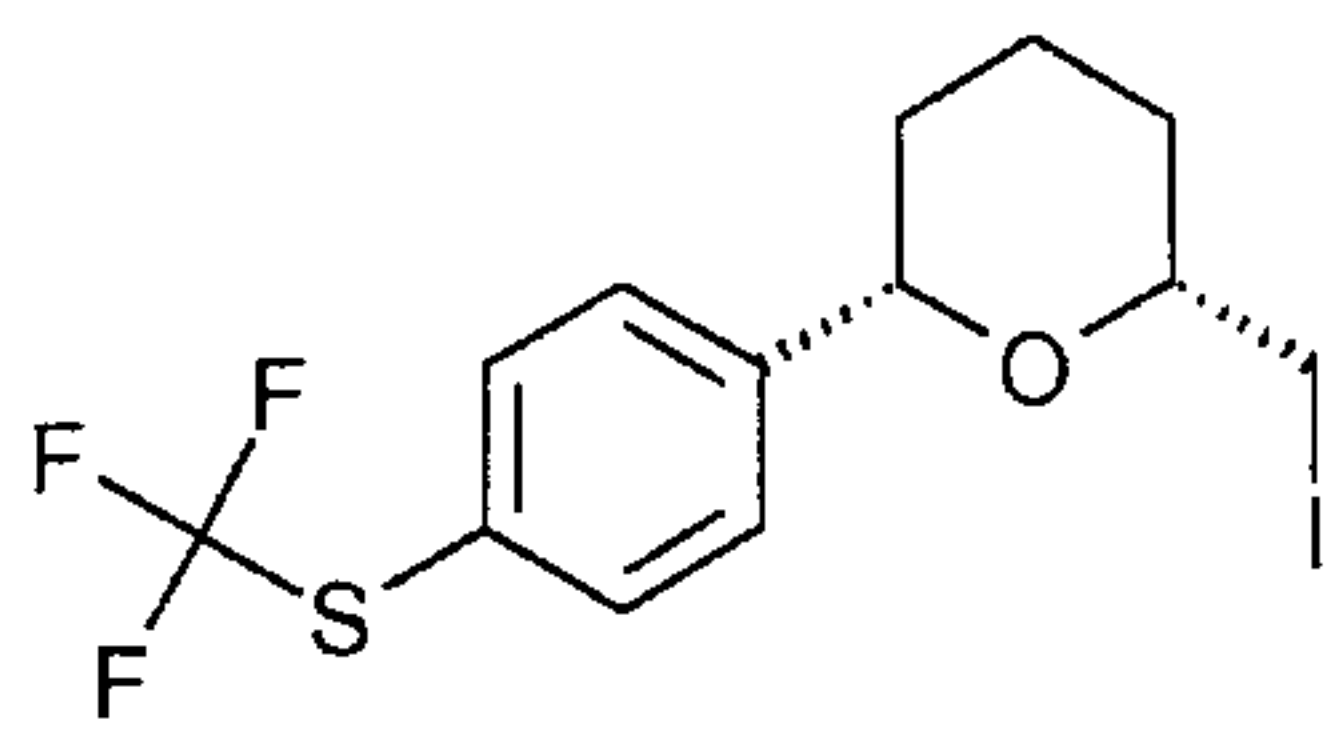
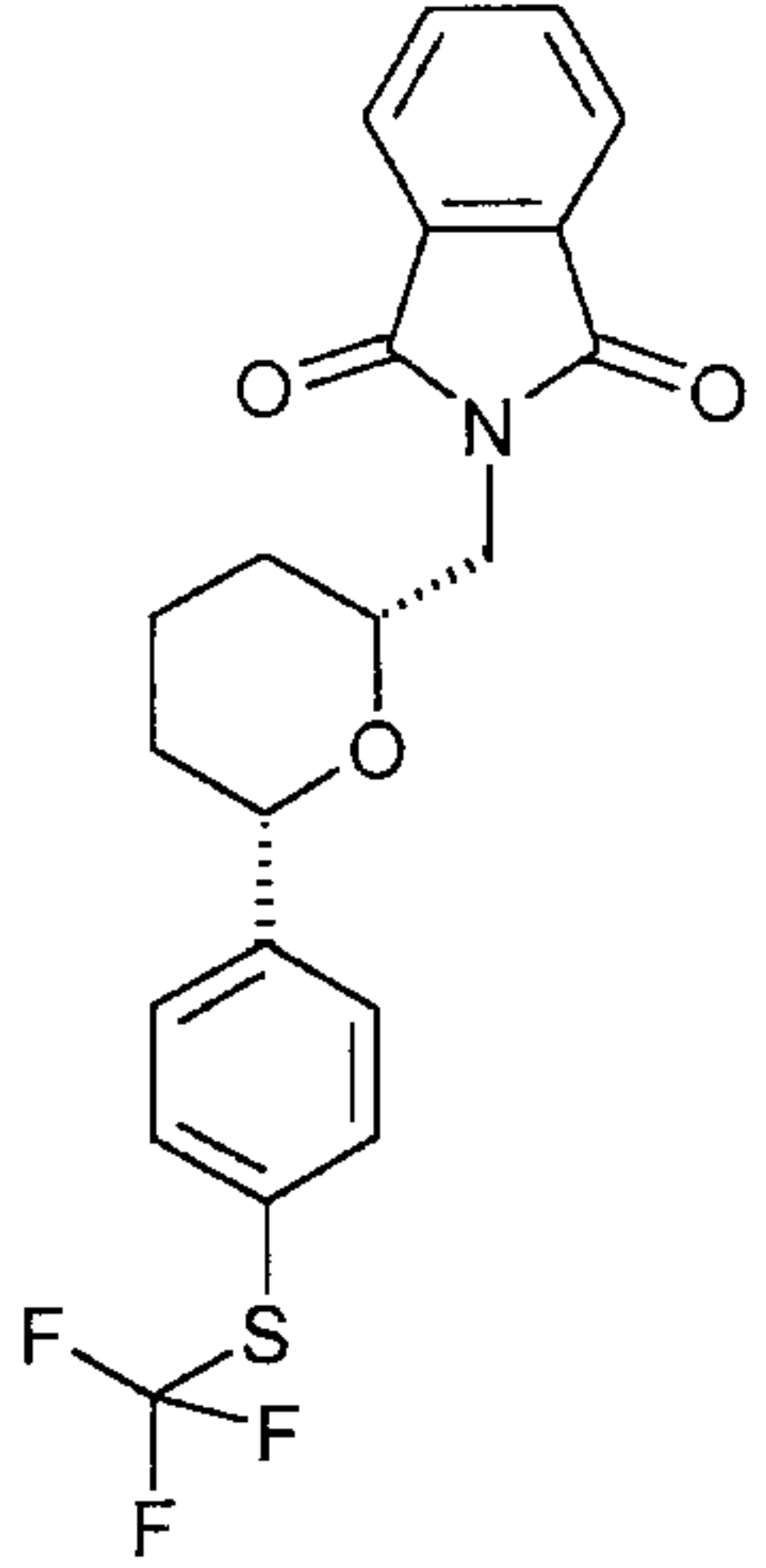
- 25 The following intermediates were synthesized in analogy to Intermediates 40a and 41a.

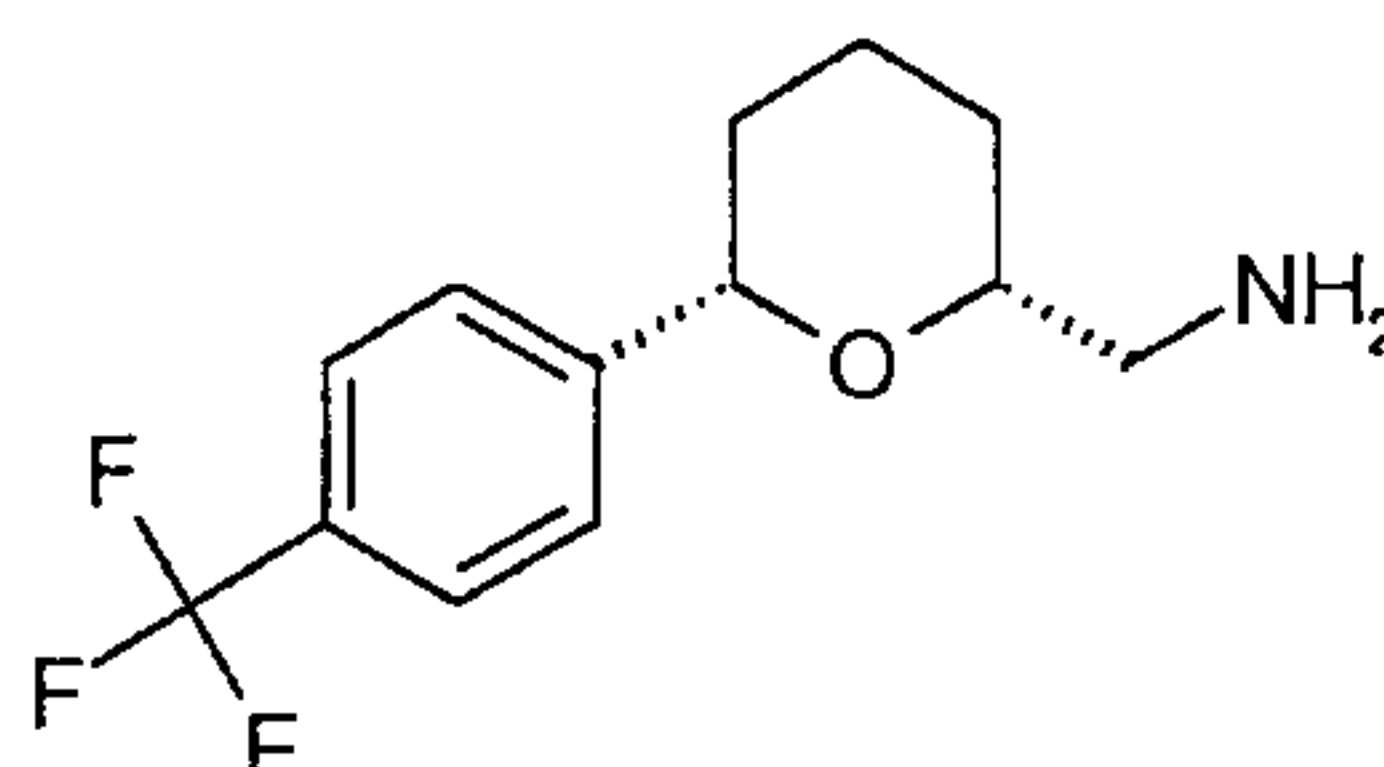
<i>synthesis in analogy to intermediate 40a</i>			<i>synthesis in analogy to intermediate 41a</i>			
Starting Intermediate	Iodo Intermediate	STRUCTURE	Fthalimide Intermediate	STRUCTURE	Chiral HPLC method	R_t (min)

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39b	40b		41b		Method 2Ja	R ₁ (preferred s stereoisomer)=6.27 R ₁ (second stereoisomer)=5.62
39c	40c		41c		Method 2Ja	R ₁ (preferred stereoisomer)=6.14 R ₁ (second stereoisomer)=5.64
39d	40d		41d		Method 2Ja	R ₁ (preferred stereoisomer)= 6.58 R ₁ (second stereoisomer)= 5.95

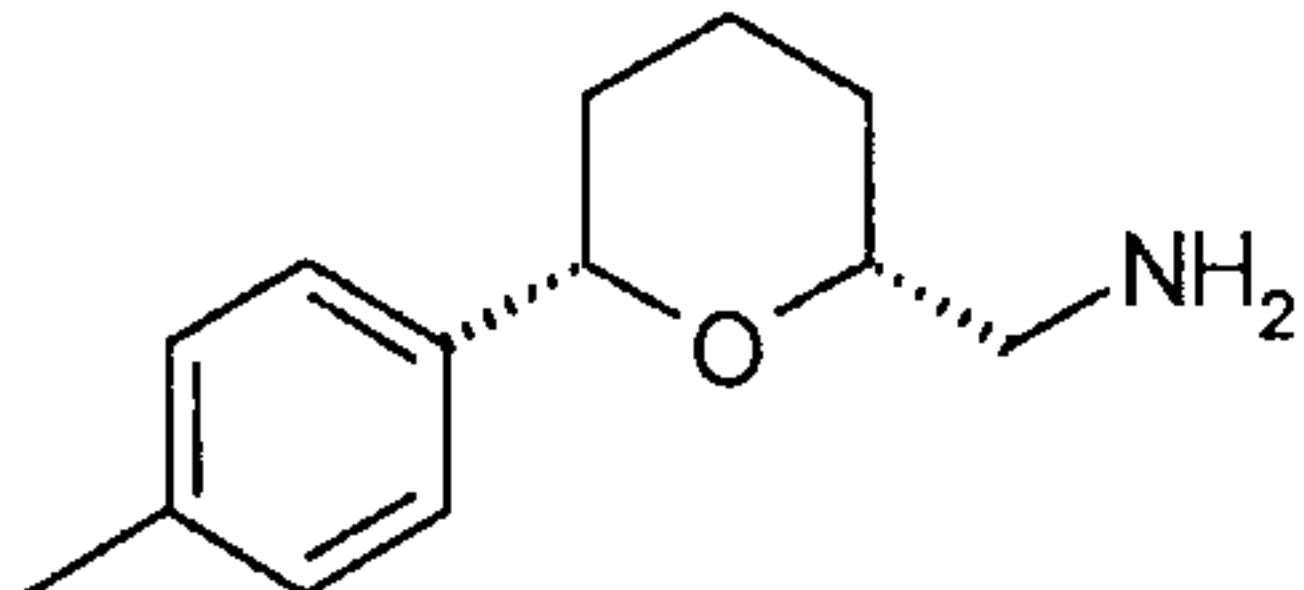
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39e	40e		41e		Method 2Ja	R_1 (preferred stereoisomer)= 6.73 R_1 (second stereoisomer)= 5.86
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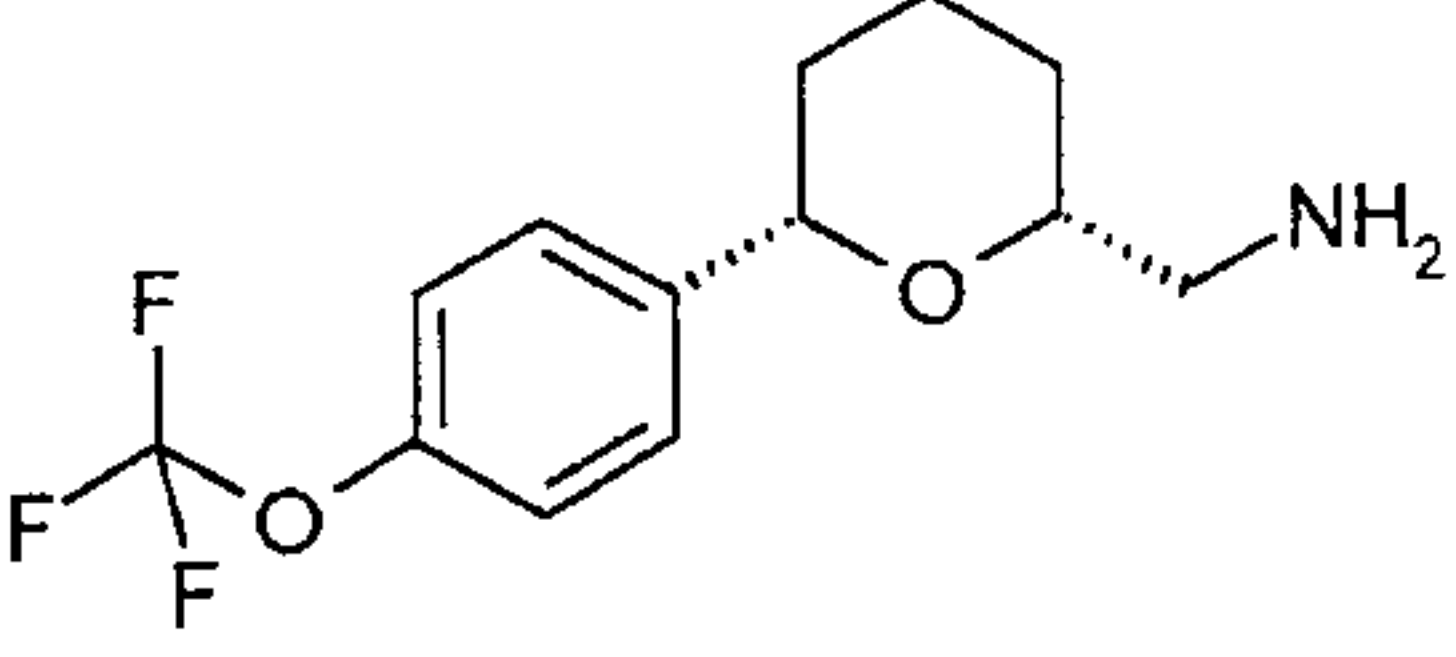
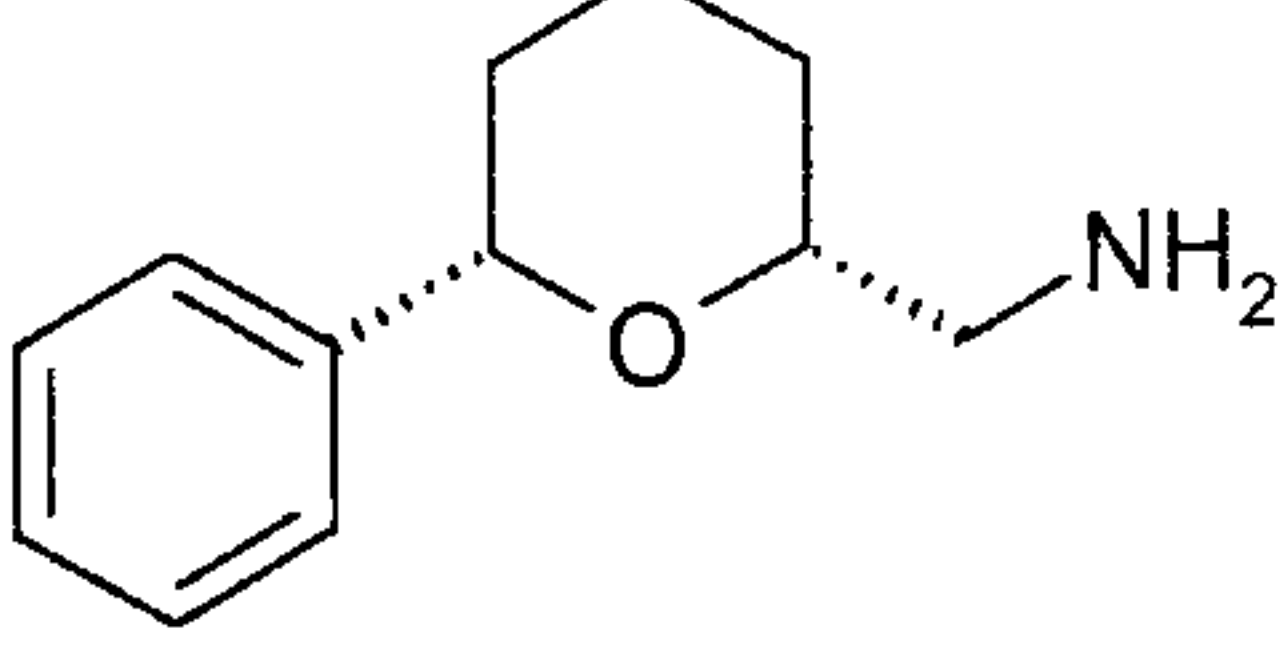
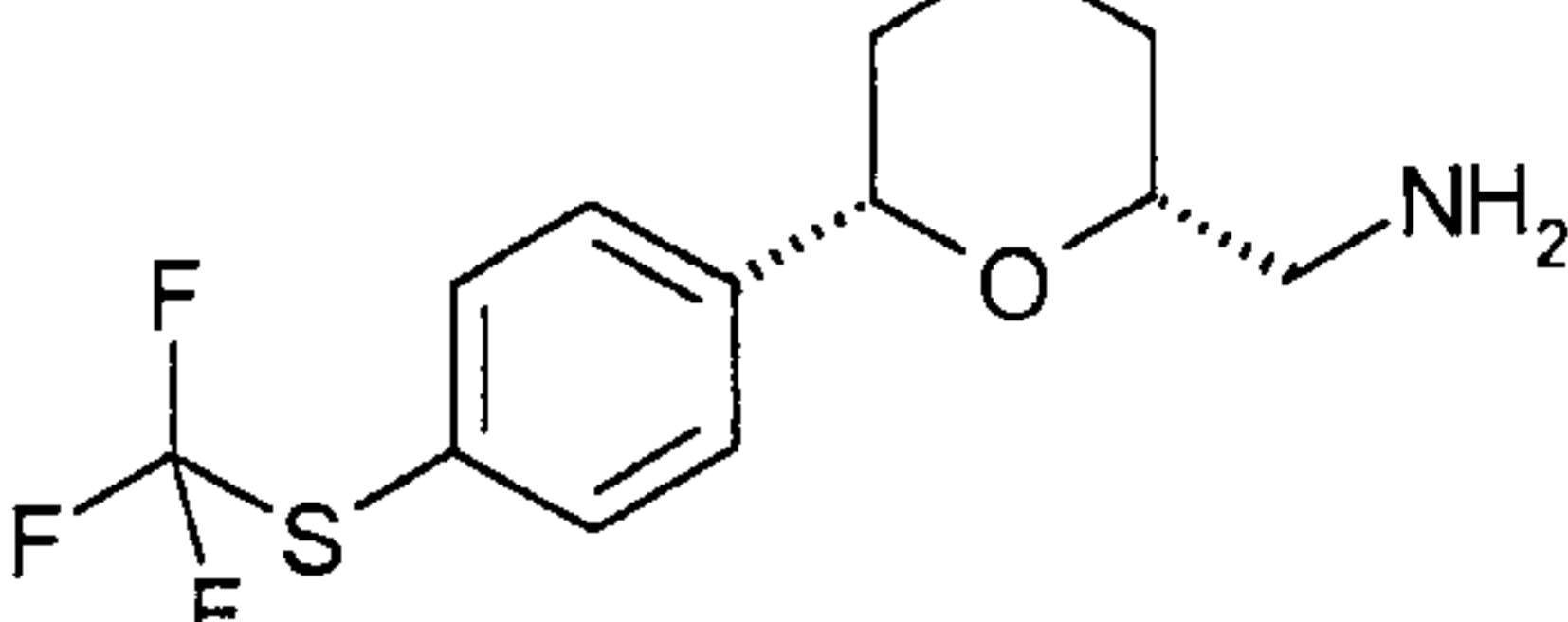
Intermediate 16b

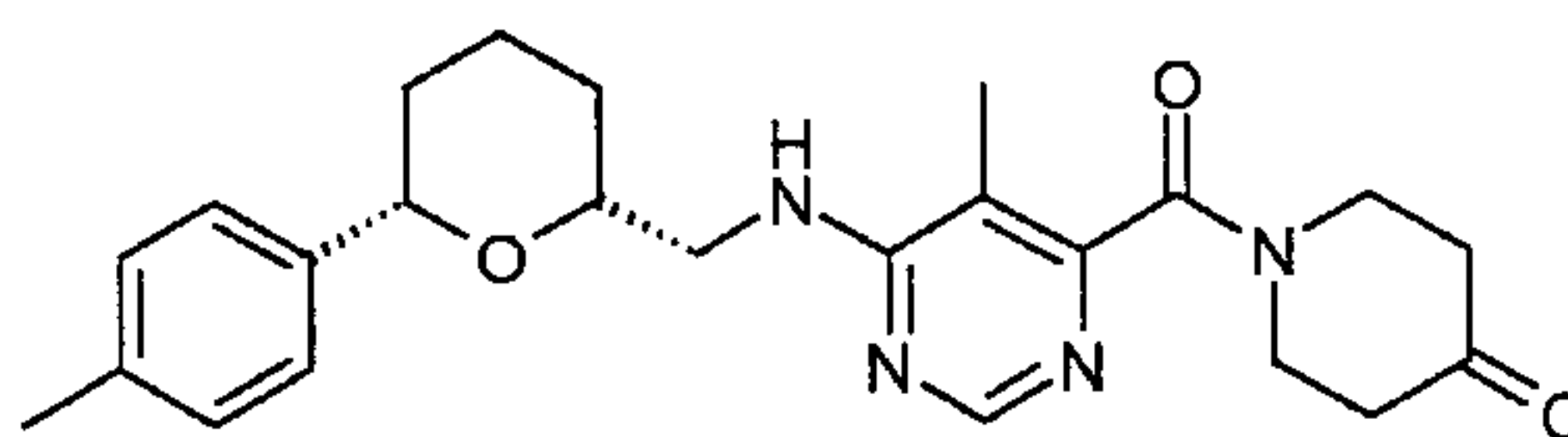
- 5 Ethanolamine (8.84 ml, 146.4 mmol) was added to a solution of Intermediate 41a (9.5 g, 24.4 mmol) in 100 ml of toluene. The reaction mixture was stirred at 70°C for 3 h. Then, the mixture was cooled to room temperature and diluted with water and ethyl acetate. The organic phase was separated and washed with an aqueous 1M solution of sodium hydroxide, dried over sodium sulfate and concentrated under vacuum to give the desired product (6.1 g). The
- 10 crude product was used in the next step without any purification.

The following intermediates were synthesized in analogy to Intermediate 16b.

Starting Intermediate	Amine Intermediate	STRUCTURE
41b	17a	

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41c	16h	
41d	16c	
41e	42	

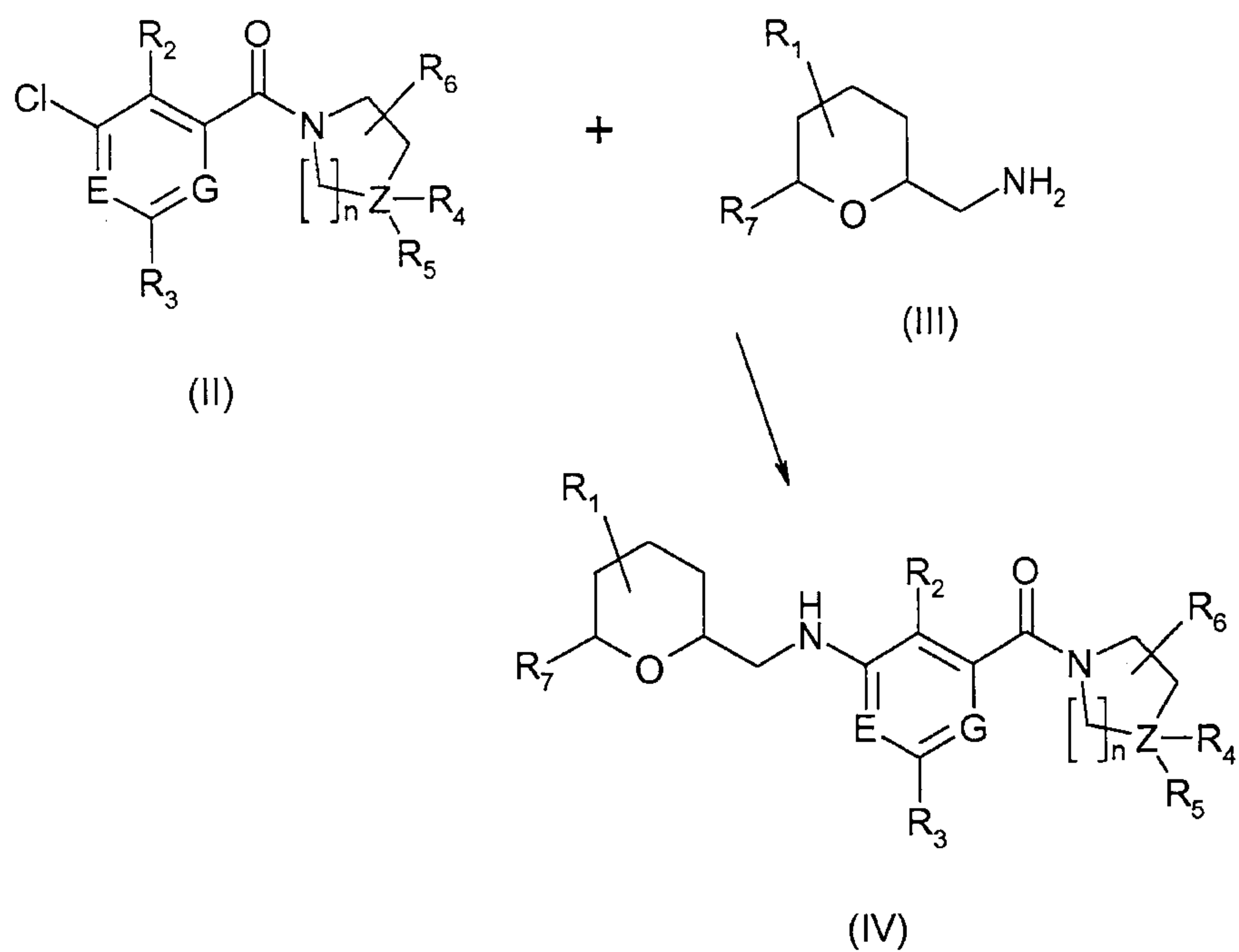
Intermediate 43

- 5 Intermediate 28pb (870 mg, 2.55 mmol), HATU (1.07 g, 2.8 mmol) and N,N-diisopropylethylamine (1.1 ml, 6.4 mmol) in 6 ml DMF were stirred at room temperature for 15 min. 4-Piperidone (345 mg, 2.6 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was treated with 80 ml of a 5% aqueous solution of sodium hydroxide and extracted with ethyl acetate. The organic phase was washed with
- 10 brine, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography to give 843 mg (2.0 mmol) of the desired product.

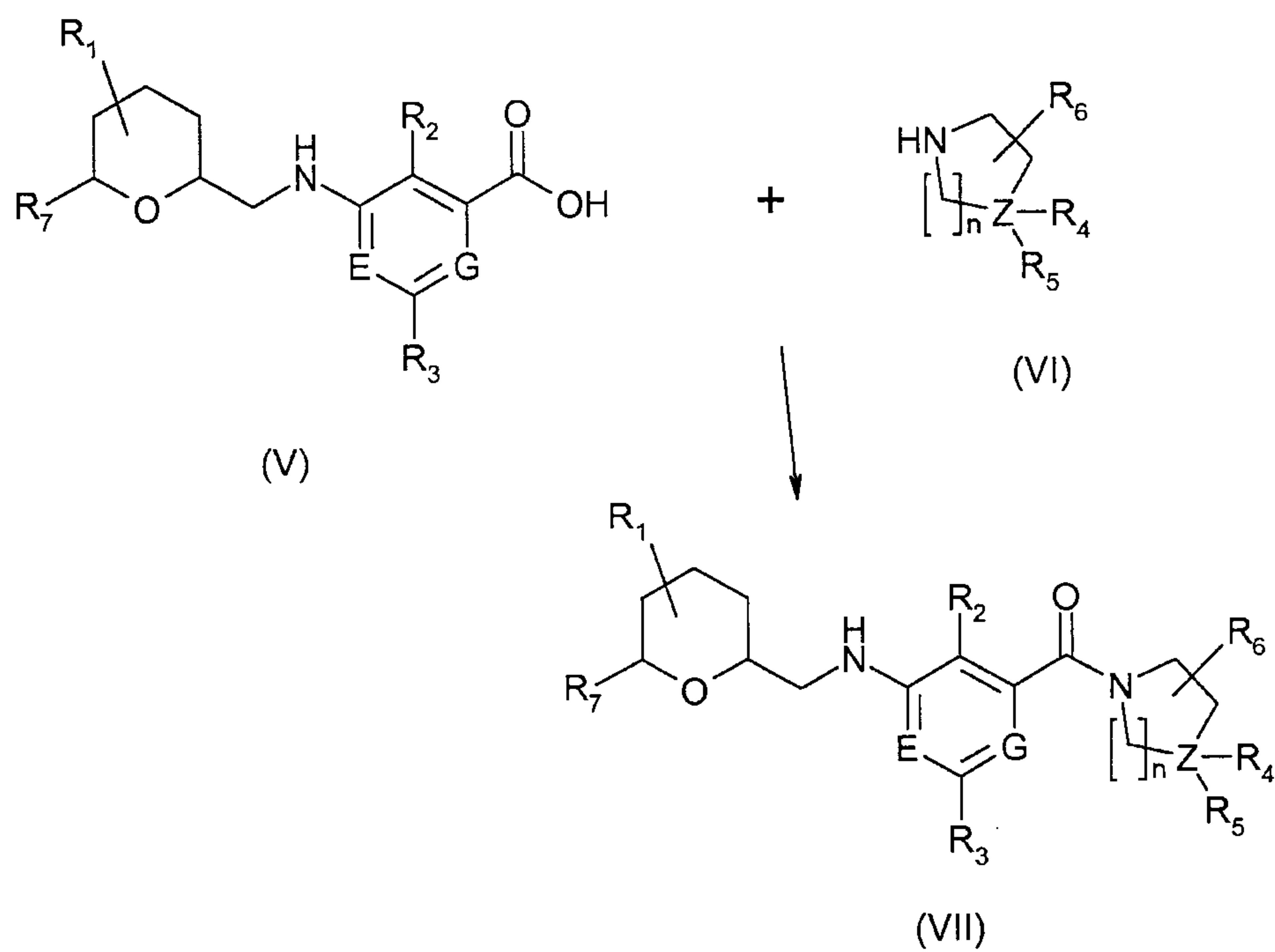
SYNTHESIS OF EXAMPLES

- 15 The examples of this invention are synthesized according to the following general synthetic procedures:

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Synthetic Procedure A:

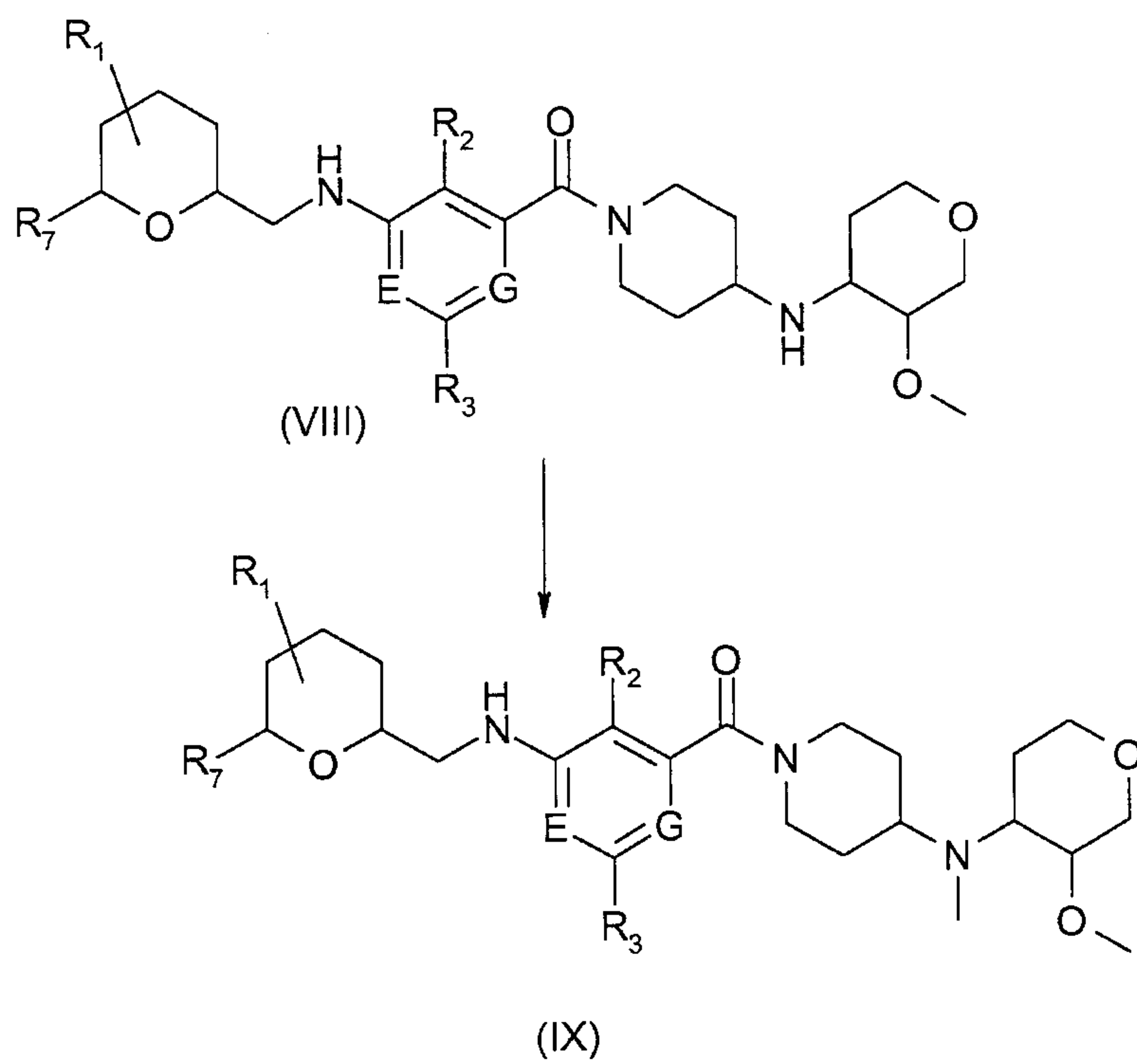
Examples: 1-28; 28a - 28n

Synthetic Procedure B:

5

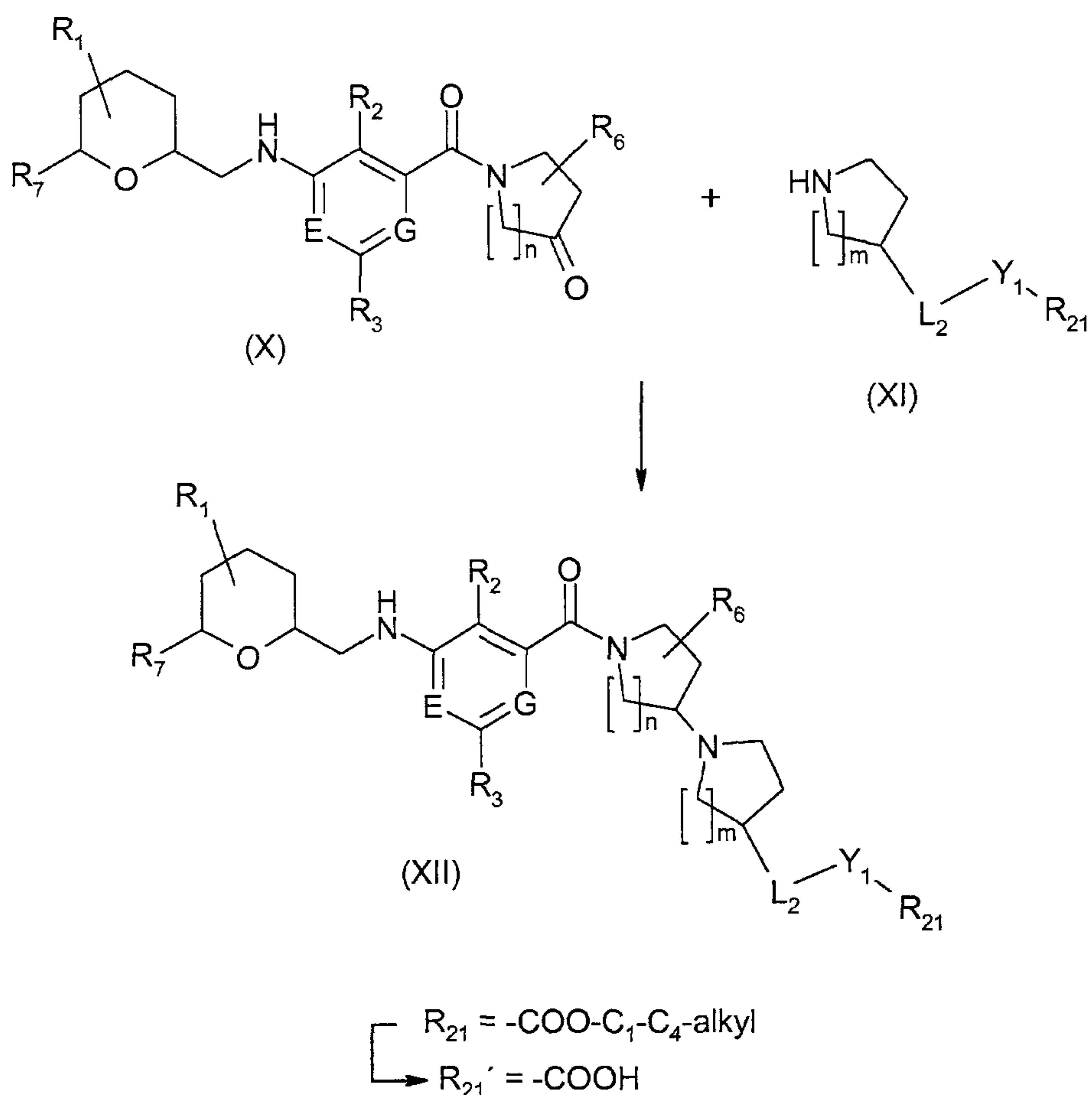
Examples: 29-53; 53a - 53z ; 53aa - 53am

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Synthetic Procedure C:

Examples: 54, 54a

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Synthetic Procedure D:

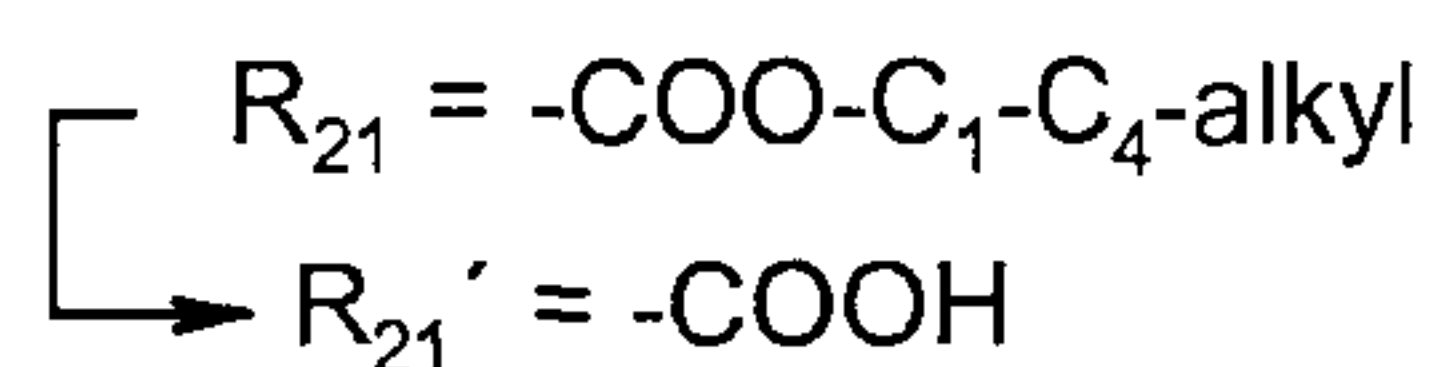
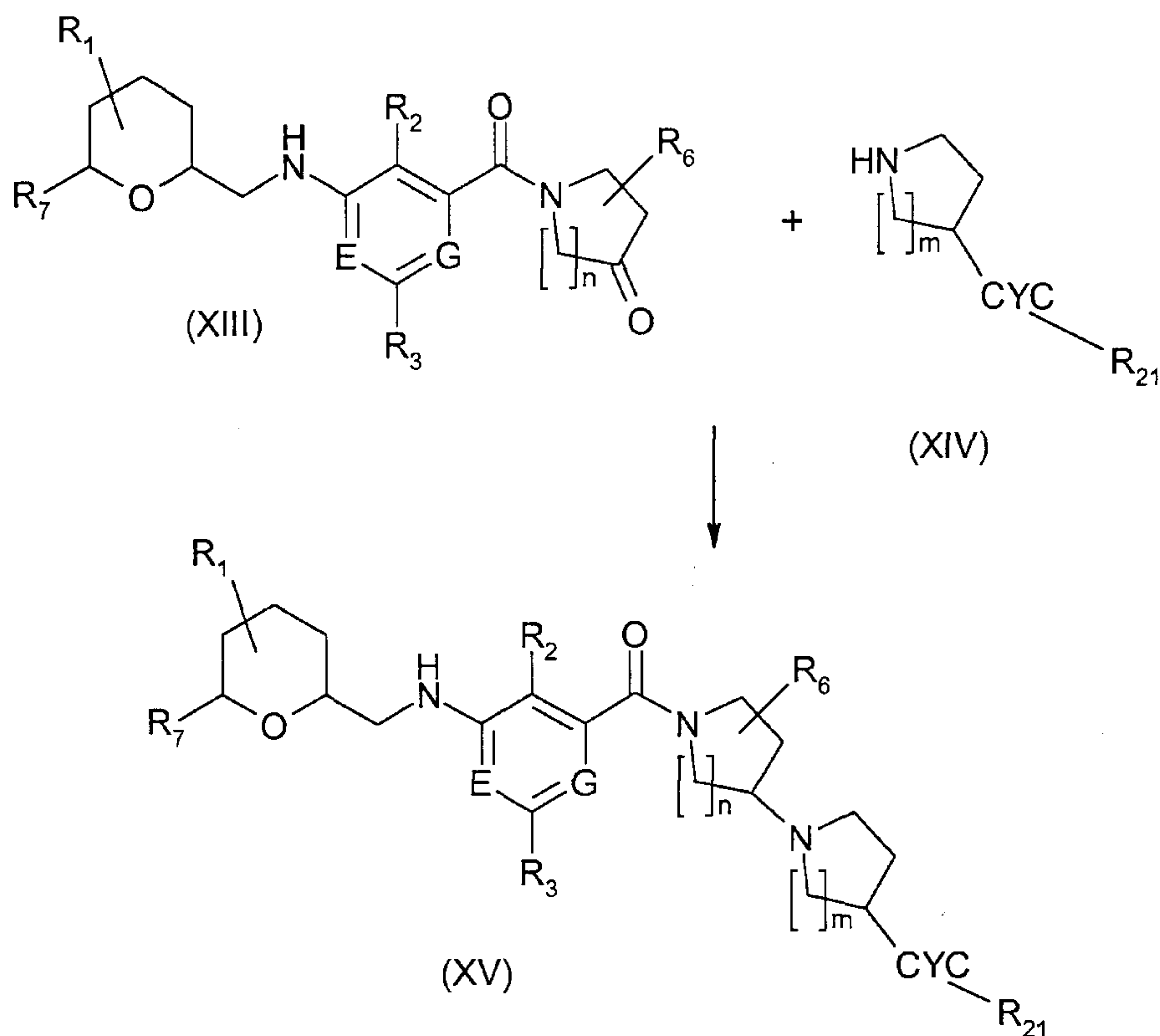
Examples: 55 – 59

- 5 For synthetic procedure D the L_2 group represents a linker wherein L_2 is a group selected from among $-\text{C}_0-\text{C}_4\text{-alkylene}$, preferred wherein L_2 is a group selected from among a bond, $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$, and $-(\text{CH}_2)_3-$, most preferred wherein L_2 denotes a bond (which reflects examples 55 to 59);
wherein m is 1 or 2;
- 10 wherein Y_1 is a group selected from among $-\text{H}$, $-\text{C}_1-\text{C}_6\text{-alkyl}$, $-\text{C}_5-\text{C}_{10}\text{-aryl}$, $-\text{C}_5-\text{C}_{10}\text{-heteroaryl}$, $-\text{C}_3-\text{C}_8\text{-cycloalkyl}$, and $-\text{C}_3-\text{C}_8\text{-heterocyclyl}$, wherein said $-\text{C}_3-\text{C}_8\text{-heterocyclyl}$ optionally comprises nitrogen and/or $-\text{SO}_2-$ in the ring, more preferred wherein Y_1 is a group selected from $-\text{C}_5-\text{C}_{10}\text{-aryl}$, $-\text{C}_5-\text{C}_{10}\text{-heteroaryl}$, $-\text{C}_3-\text{C}_8\text{-cycloalkyl}$, and $-\text{C}_3-\text{C}_8\text{-heterocyclyl}$, most preferred wherein Y_1 denotes $-\text{C}_6\text{-aryl}$ (which reflects examples 55 to 59);
- 15 and wherein the group Y_1 is optionally substituted with the group R_{21} , wherein R_{21} is selected from among $-\text{OH}$, $-\text{OCH}_3$, $-\text{CF}_3$, $-\text{COO}-\text{C}_1-\text{C}_4\text{-alkyl}$, $-\text{OCF}_3$, $-\text{CN}$, $-\text{halogen}$, $-\text{C}_1-\text{C}_4\text{-alkyl}$, $=\text{O}$, and $-\text{SO}_2-\text{C}_1-\text{C}_4\text{-alkyl}$, more preferred wherein R_{21} denotes $-\text{COO}-\text{C}_1-\text{C}_4\text{-alkyl}$. In the case that R_{21} denotes $-\text{COO}-\text{C}_1-\text{C}_4\text{-alkyl}$ the compound (XII) is modified by an additional step

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wich results in a transformation of R_{21} to R_{21}' , wherein R_{21}' denotes $-\text{COOH}$ (which reflects examples 55 to 59).

Synthetic Procedure E:



5

Example: 60

For synthetic procedure E the CYC group represents a group selected from among
 $-\text{C}_0-\text{C}_4\text{-alkylene}(R_{20}, R_{20}')$, more preferred wherein CYC is selected from among
 $-\text{C}_0\text{-alkylene}(R_{20}, R_{20}')$ whereas R_{20} and R_{20}' together form a spiro- $\text{C}_3-\text{C}_8\text{-carbocycle}$ or spiro-
 $\text{C}_3-\text{C}_8\text{-heterocycle}$ comprising one or more groups selected from O in the ring and wherein
said spirocycle is optionally further bi-valently substituted by an annellated ring forming
group selected from among $-\text{C}_1-\text{C}_6\text{-alkylene}$, $-\text{C}_2-\text{C}_6\text{-alkenylene}$, and $-\text{C}_4-\text{C}_6\text{-alkynylene}$ as
well as wherein said spirocycle is optionally further substituted by R_{21} , most preferred
wherein the CYC group denotes $-\text{C}_0\text{-alkylene}(R_{20}, R_{20}')$ whereas R_{20} and R_{20}' together form a
spiro- $\text{C}_5\text{-carbocycle}$ wherein said spirocycle is further bi-valently substituted by an annellated

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ring forming group selected from $-C_4$ -alkenylene and wherein said spirocycle is further substituted by R_{21} (which reflects examples 60);

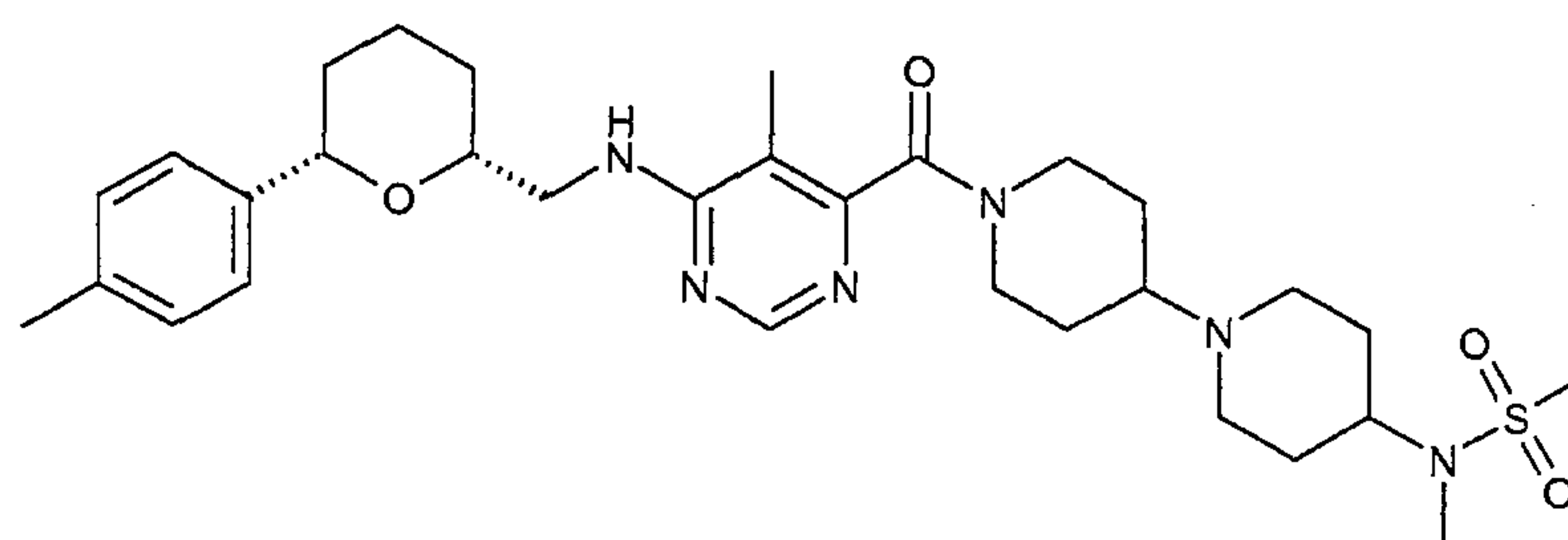
wherein m is 1 or 2, more preferred wherein m is 1;

and wherein R_{21} is selected from among $-H$, $-OH$, $-OCH_3$, $-CF_3$, $-COO-C_1-C_4$ -alkyl, $-OCF_3$,

- 5 $-CN$, $-halogen$, $-C_1-C_4$ -alkyl, $=O$, and $-SO_2-C_1-C_4$ -alkyl, more preferred wherein R_{21} denotes $-COO-C_1-C_4$ -alkyl. In the case that R_{21} denotes $-COO-C_1-C_4$ -alkyl the compound (XV) is modified by an additional step which results in a transformation of R_{21} to R_{21}' , wherein R_{21}' denotes $-COOH$ (which reflects example 60).

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Example 1



- Intermediate 26b (60 mg, 0.14 mmol), Intermediate 17a (28.6 mg, 0.14 mmol) and N,N -diisopropyl-ethyl amine (0.05 ml, 0.31 mmol) in 0.5 ml of dry 1,4-dioxane were mixed in a microwave vial and reacted in the following conditions: Power 100, Ramp 5 min, Hold 2h, Temperature 150°C, Pressure 150 psi, Stirring. The reaction mixture was concentrated under vacuum and diluted with dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase preparative HPLC. 40 mg (0.07 mmol) of the desired product were obtained.

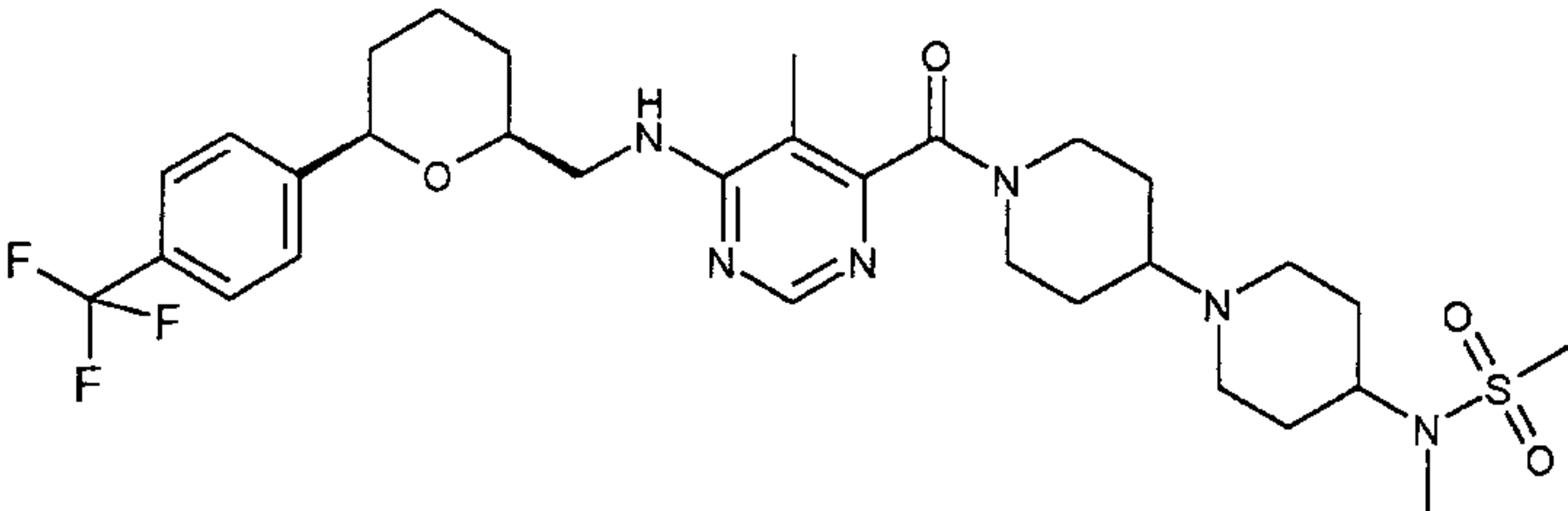
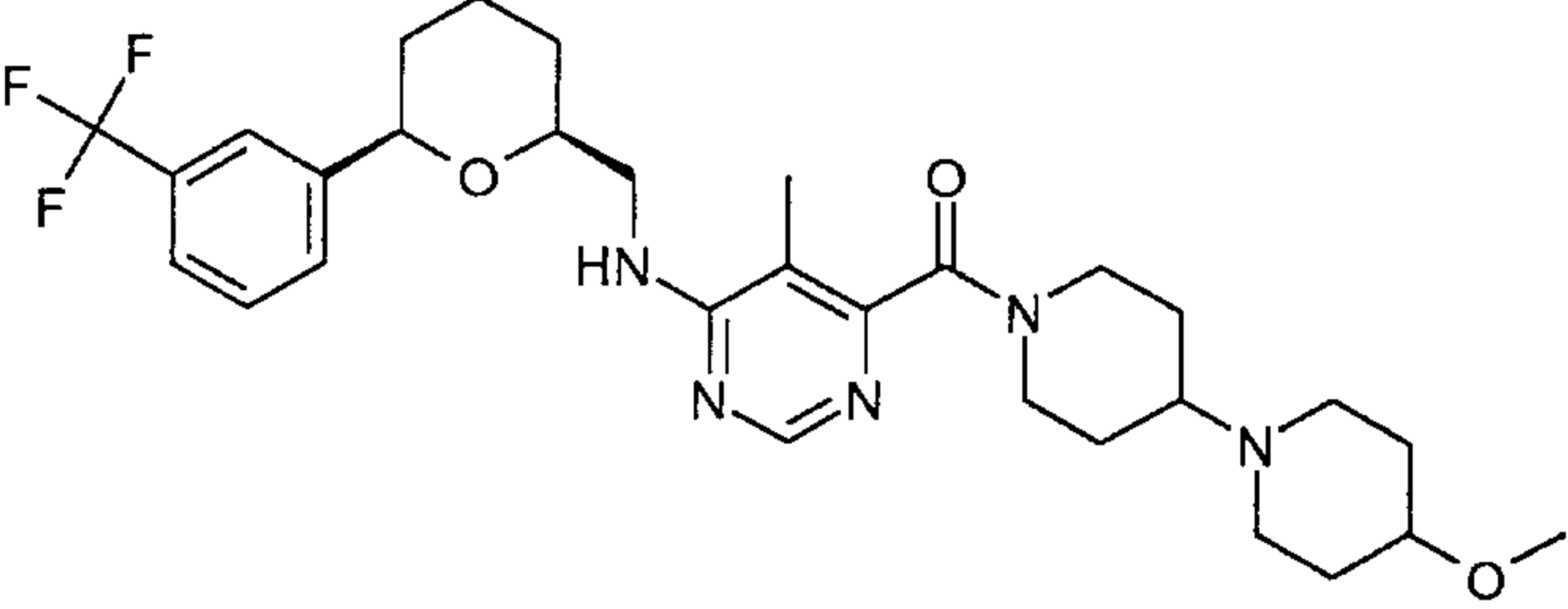
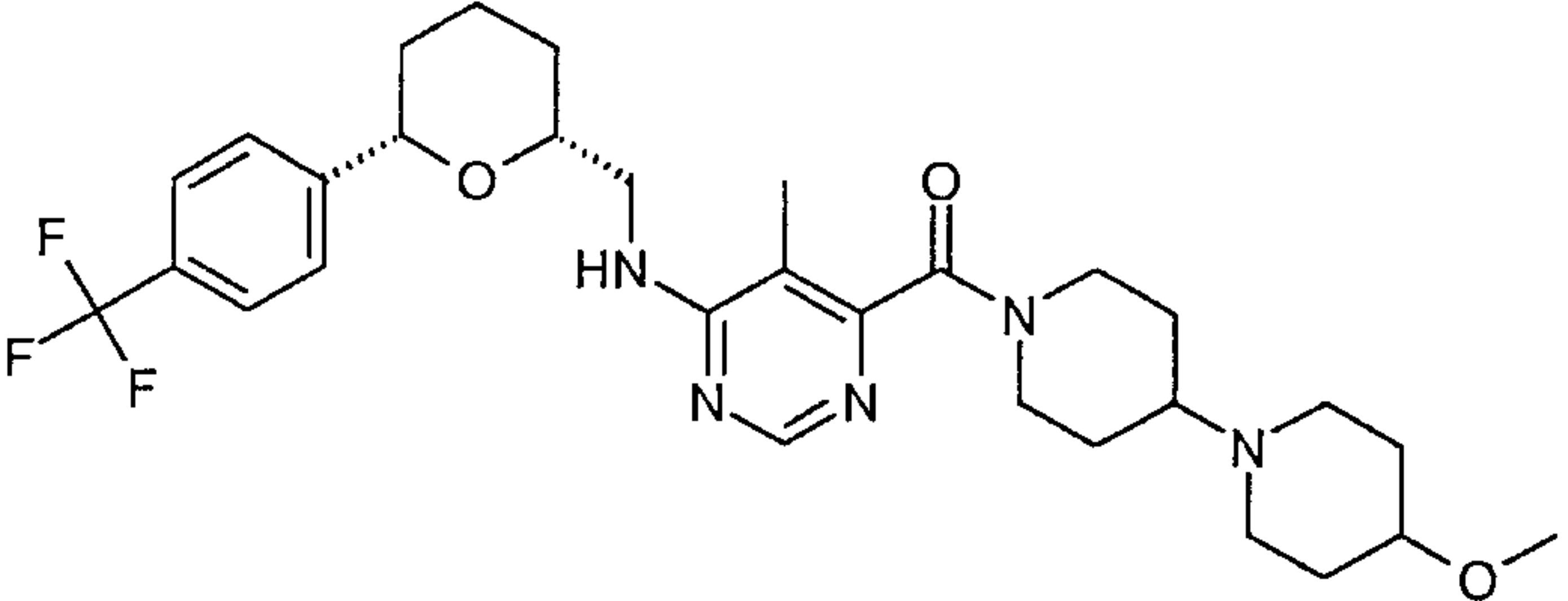
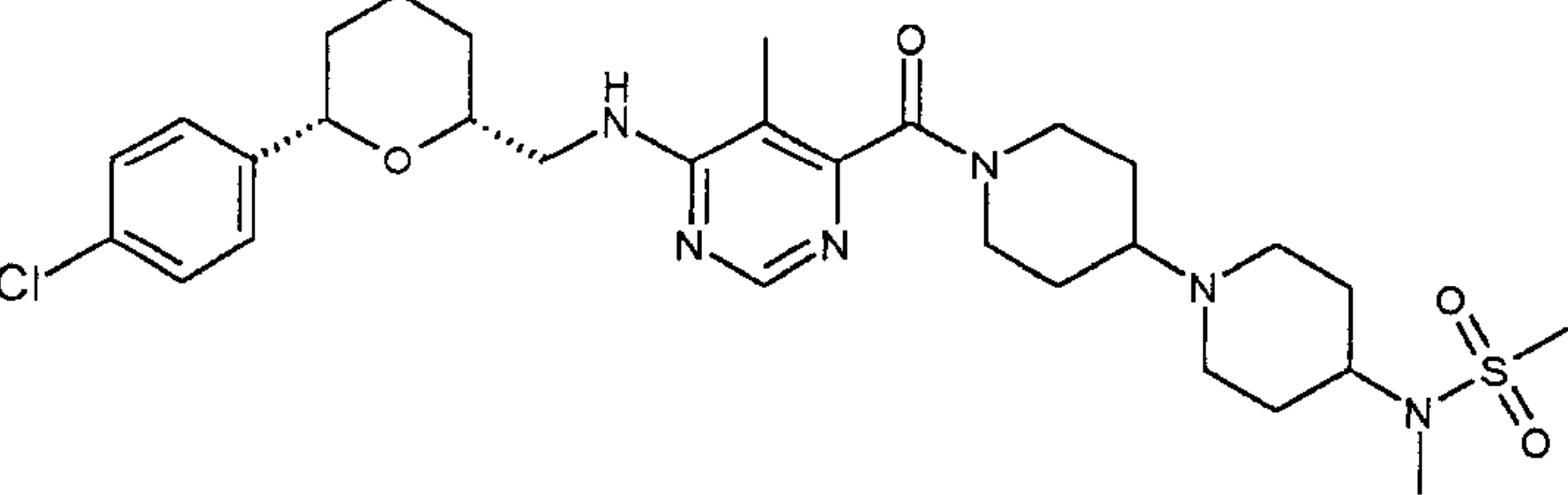
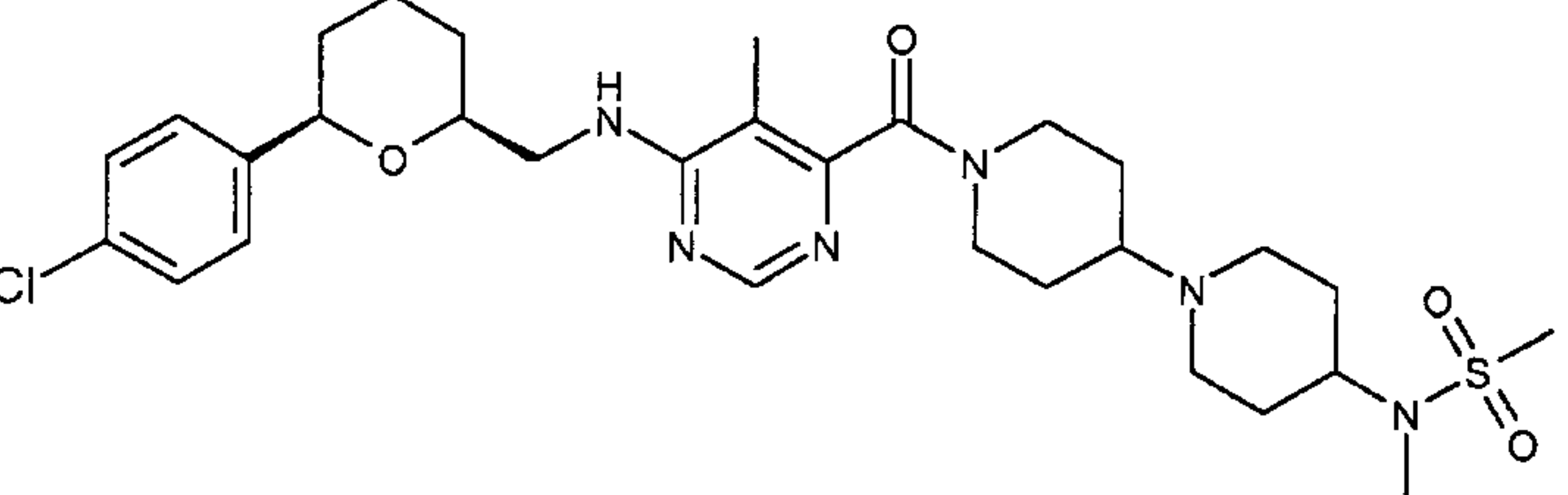
HPLC (Method 2M): R_t (min) = 6.00

$[M+H]^+ = 599$

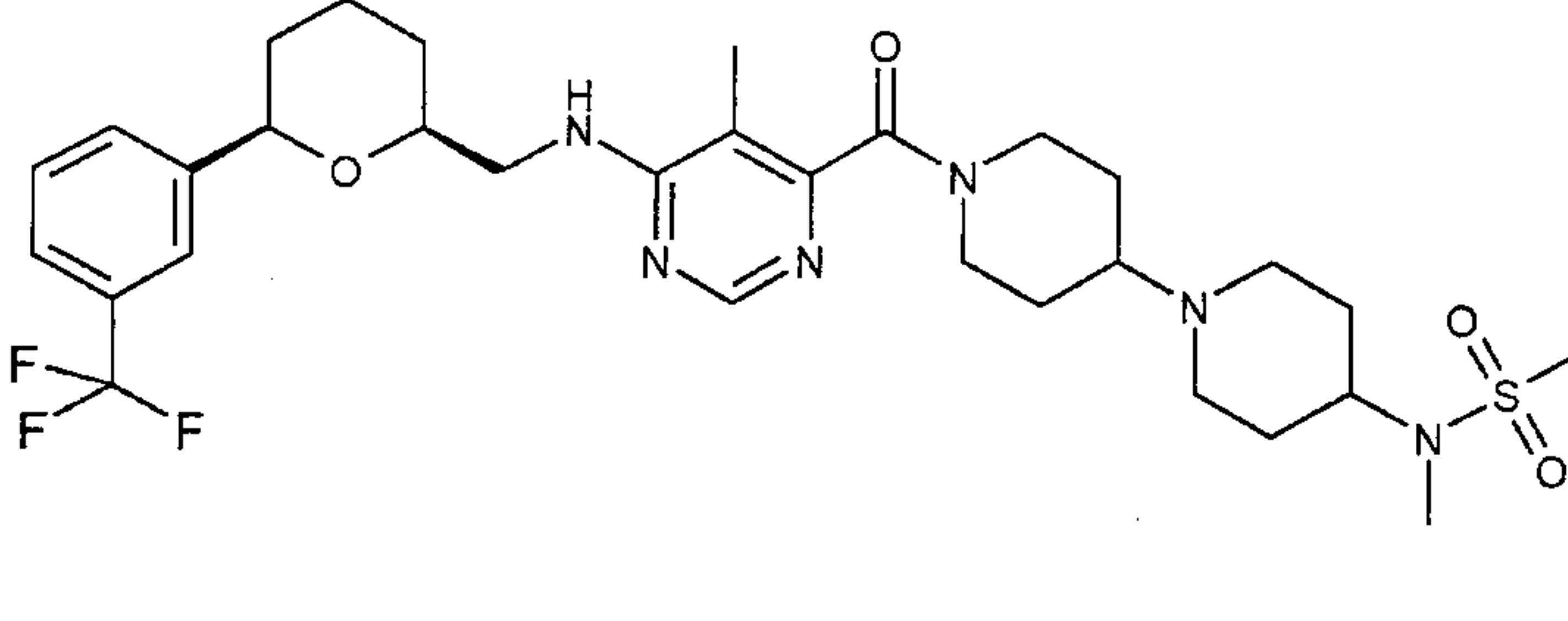
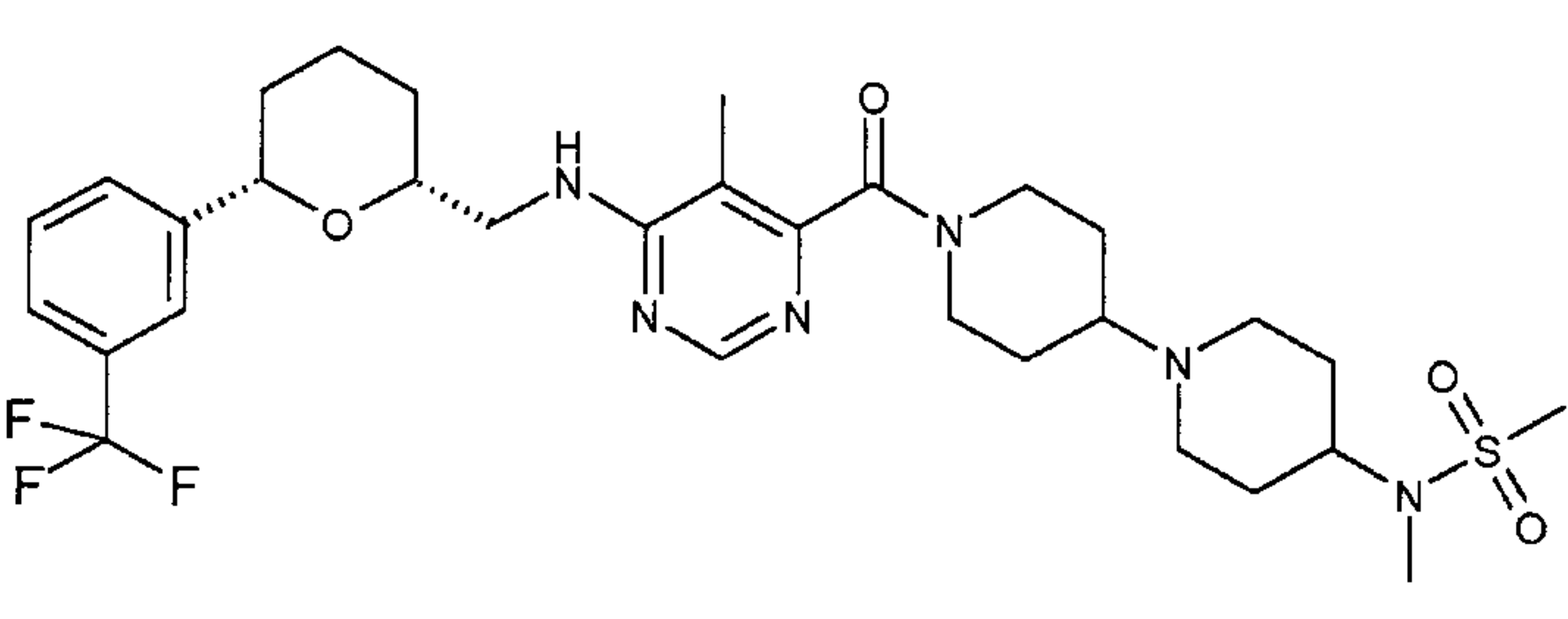
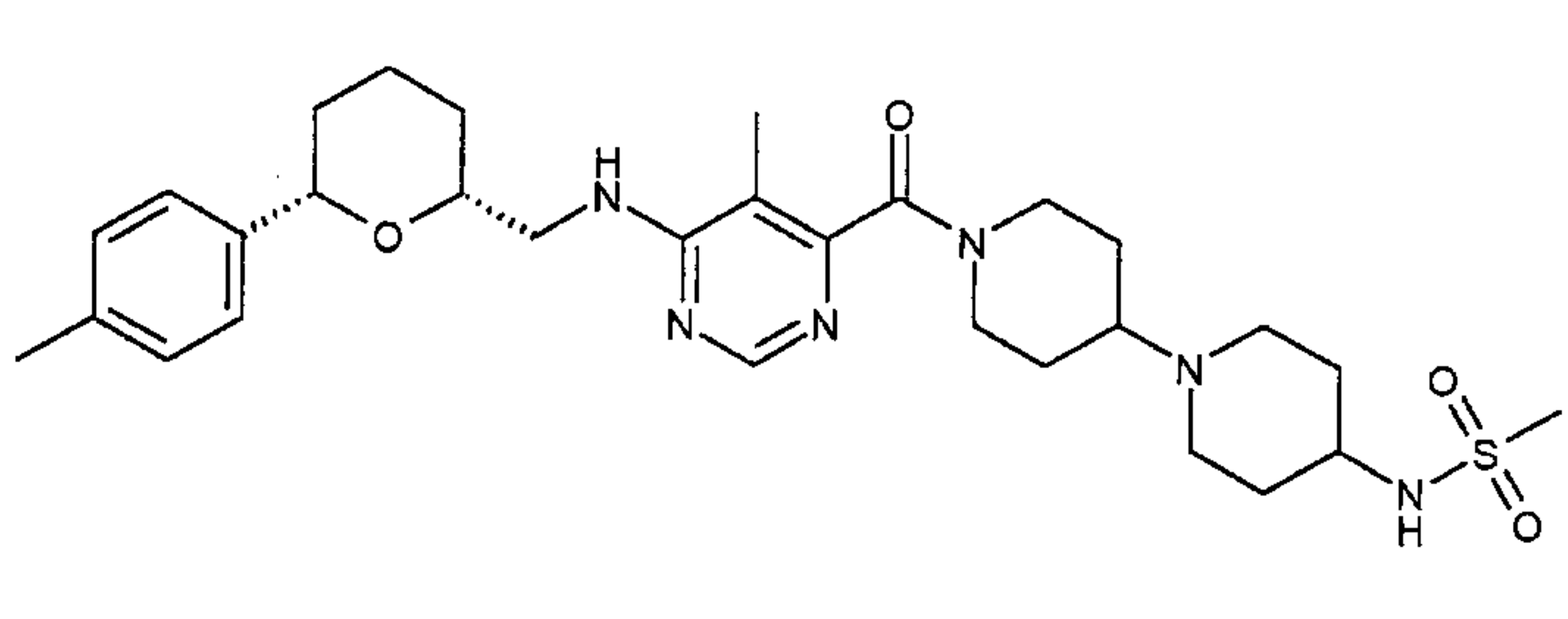
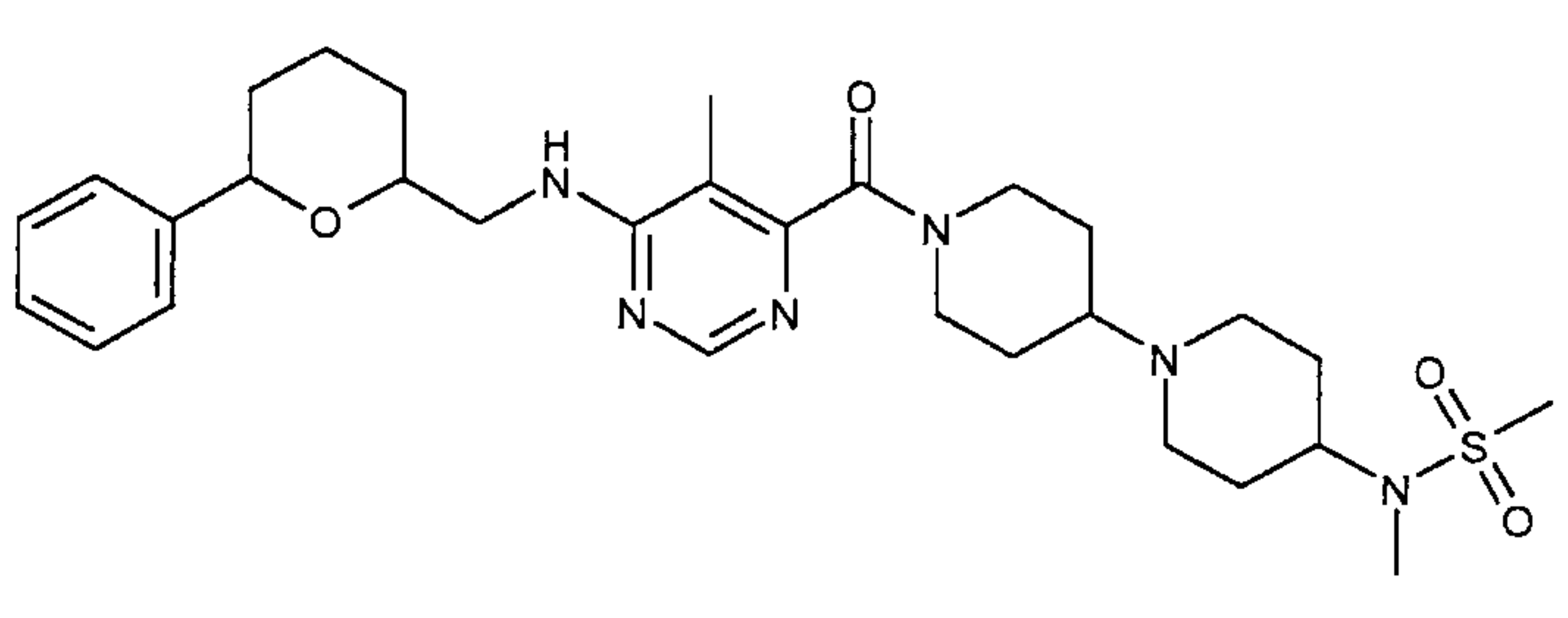
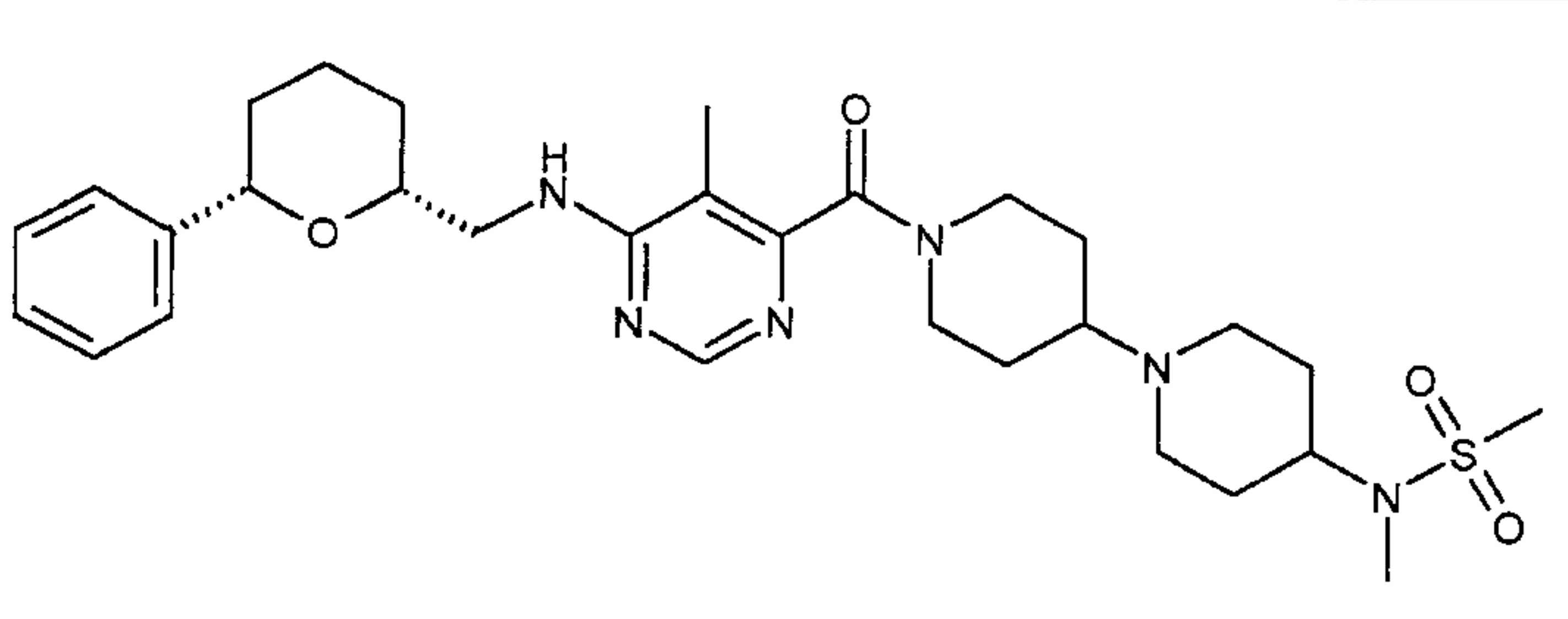
The following examples were synthesized in analogy to the preparation of Example 1

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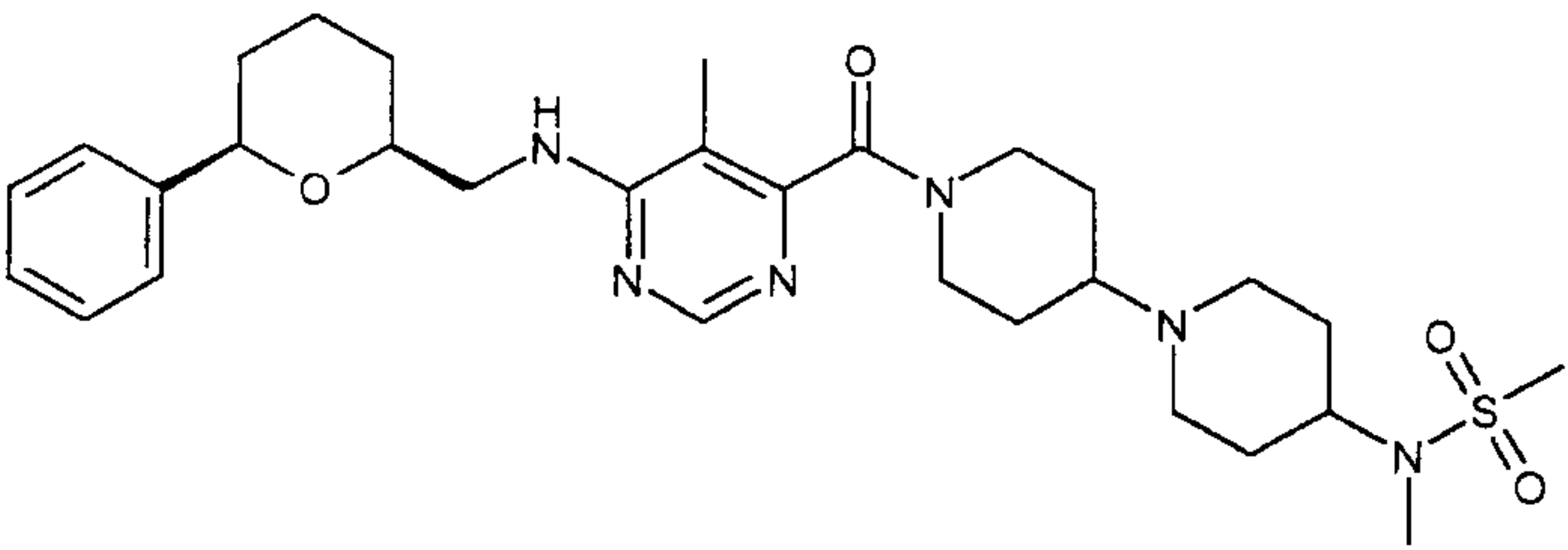
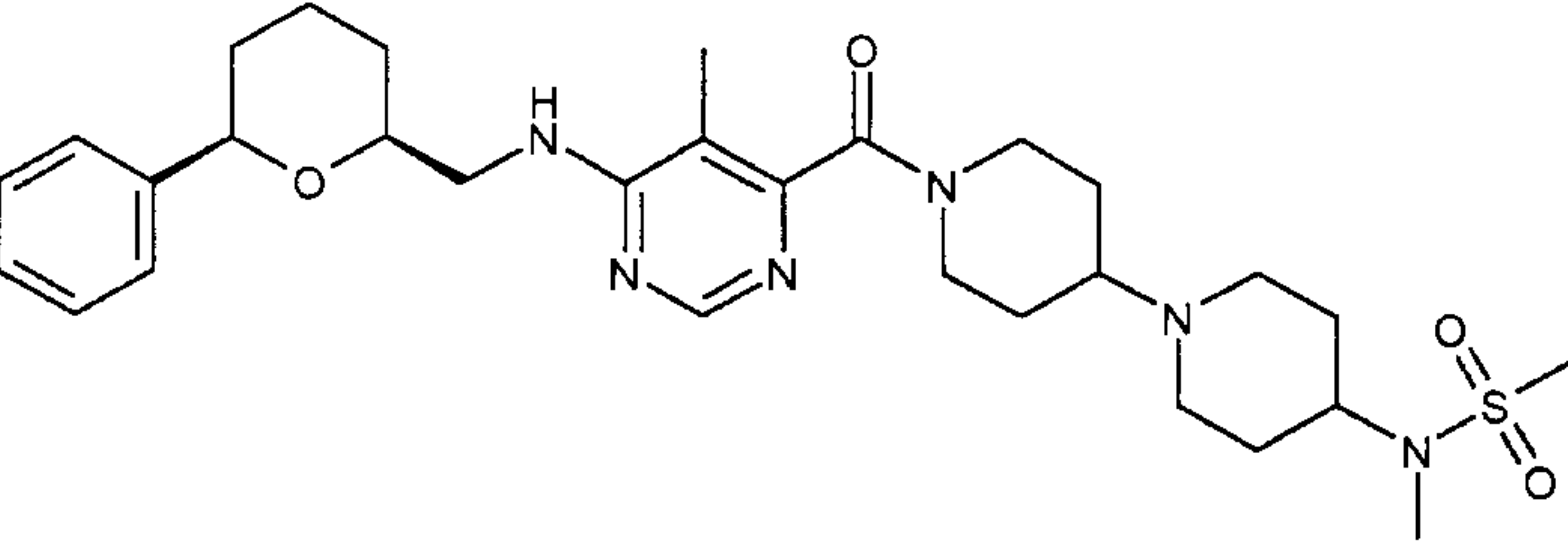
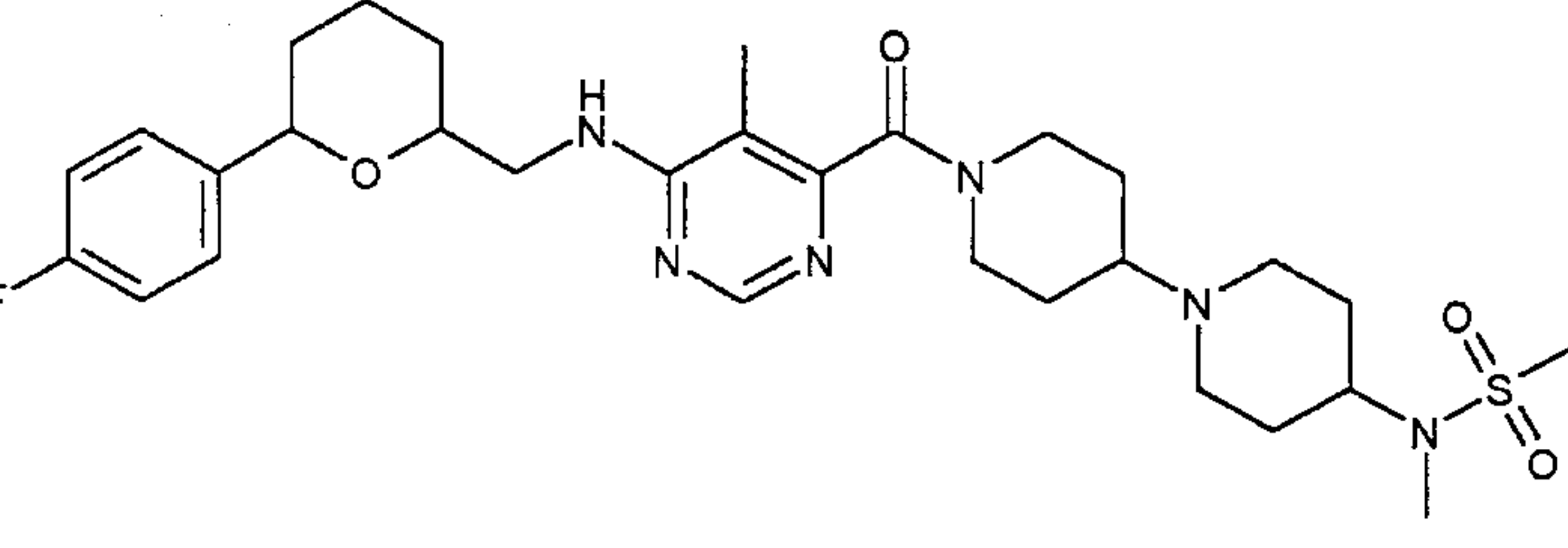
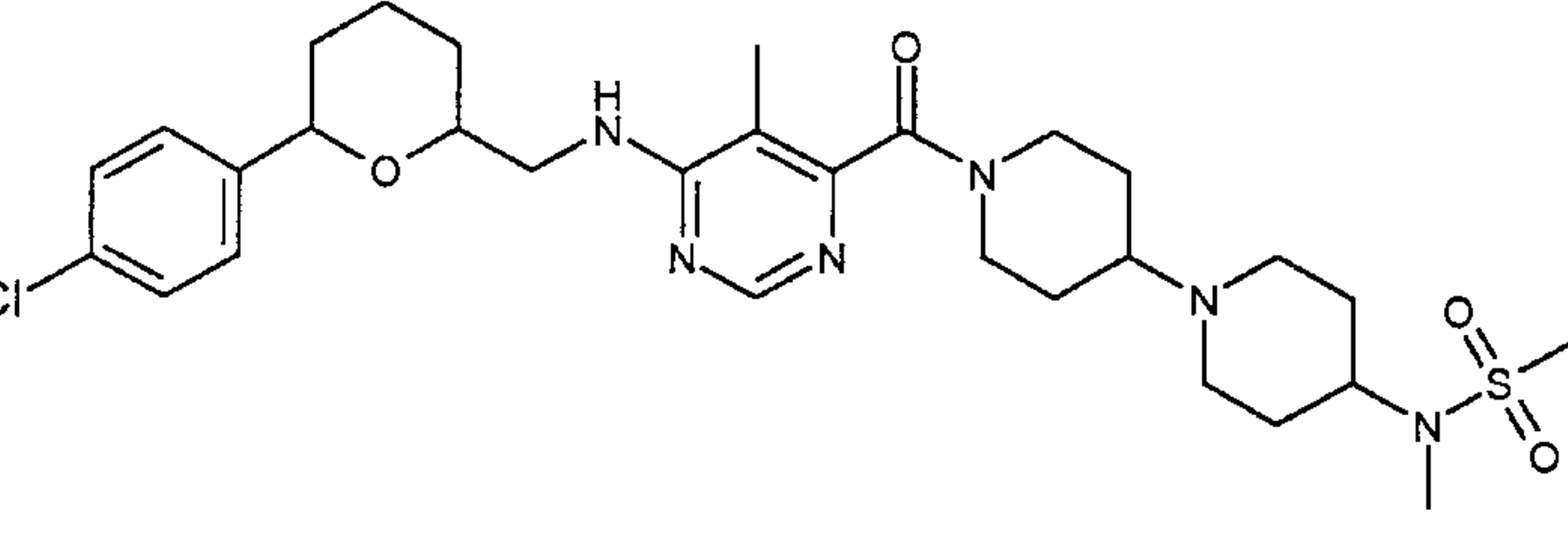
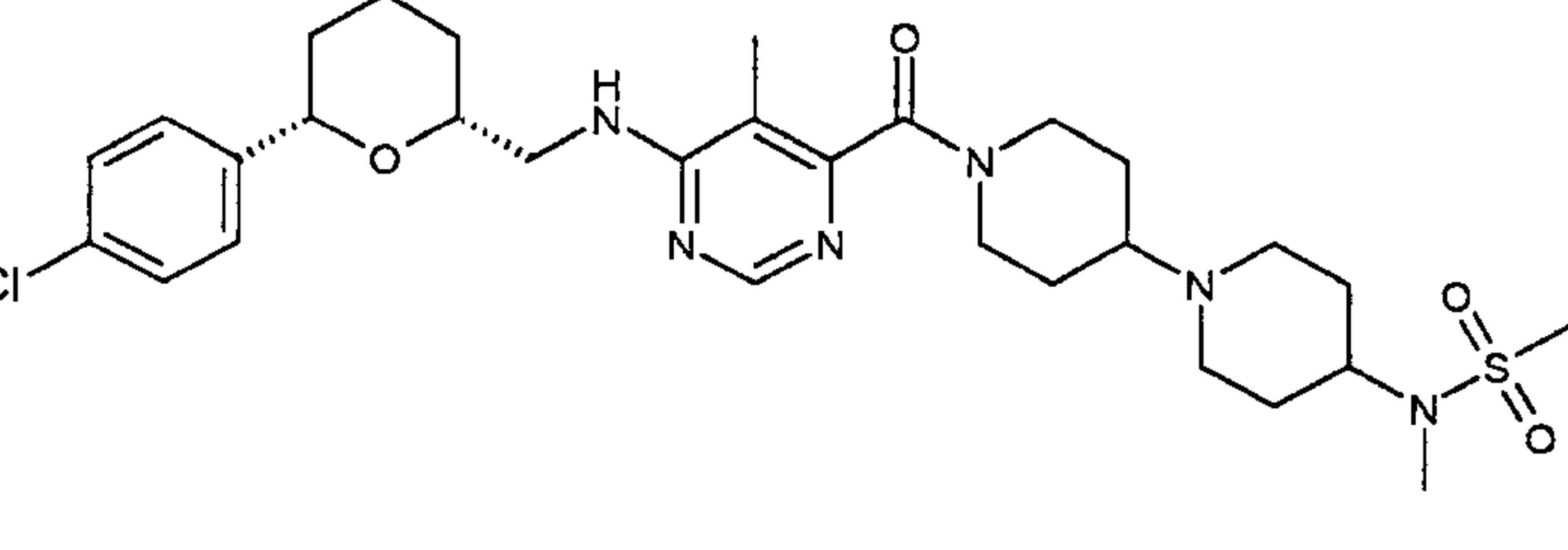
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Ex #	MOLSTRUCTURE	Intermediate	Amine	[M+H] ⁺	HPLC R _t (min)	Method
2		26b	17b	653	9.53	1E (Hydro)
3		26c	15f	576	10.62	1E (Hydro)
4		26c	15b	576	10.96	1E (Hydro)
5		26b	16d	619	9.81	1E (Hydro)
6		26b	17d	619	9.85	1E (Hydro)

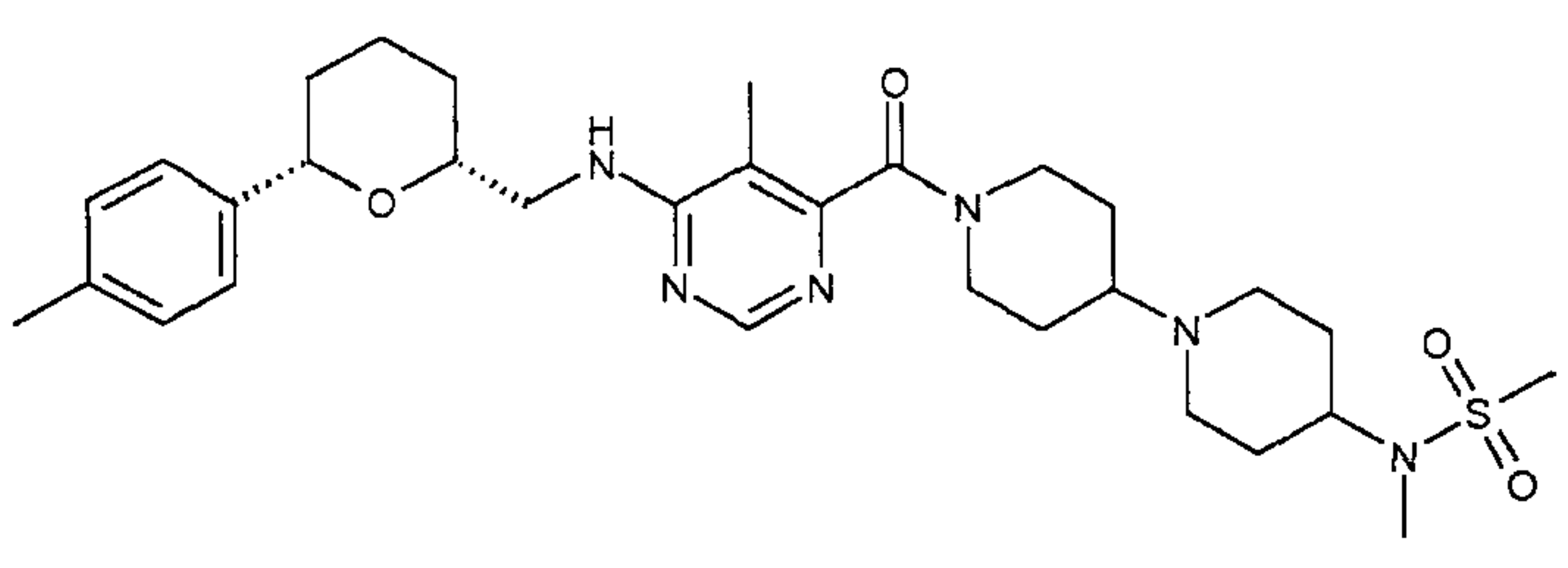
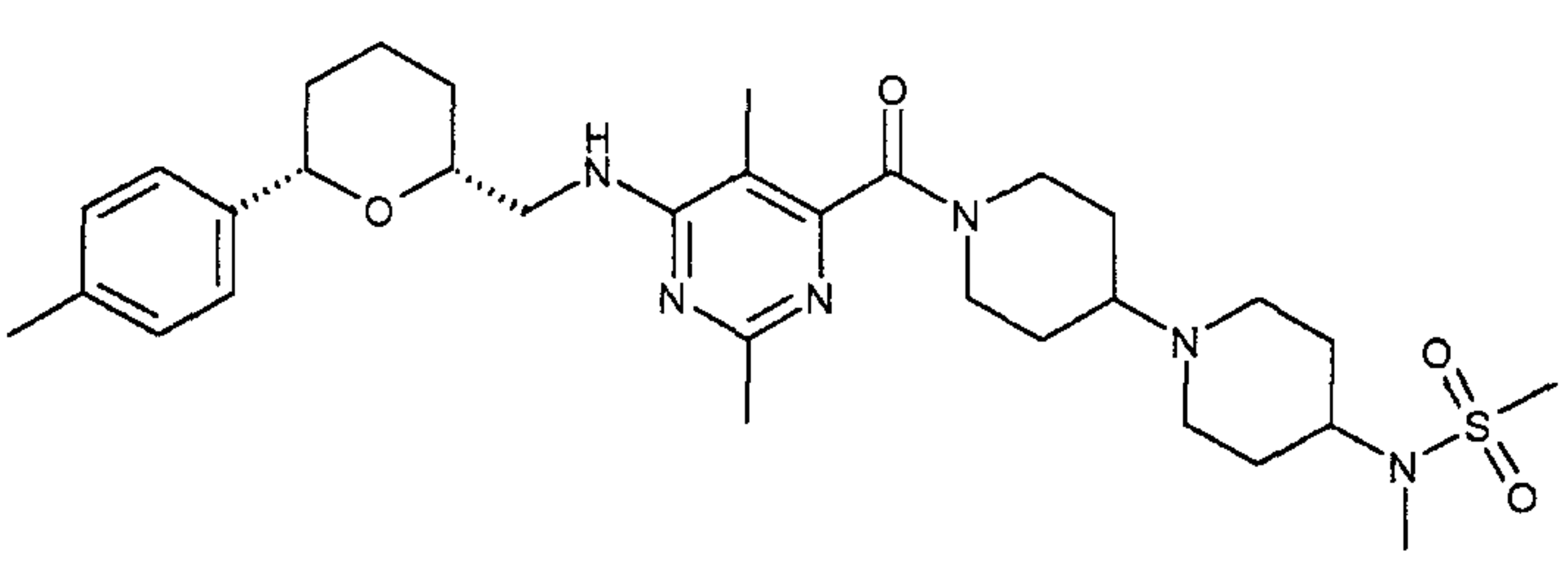
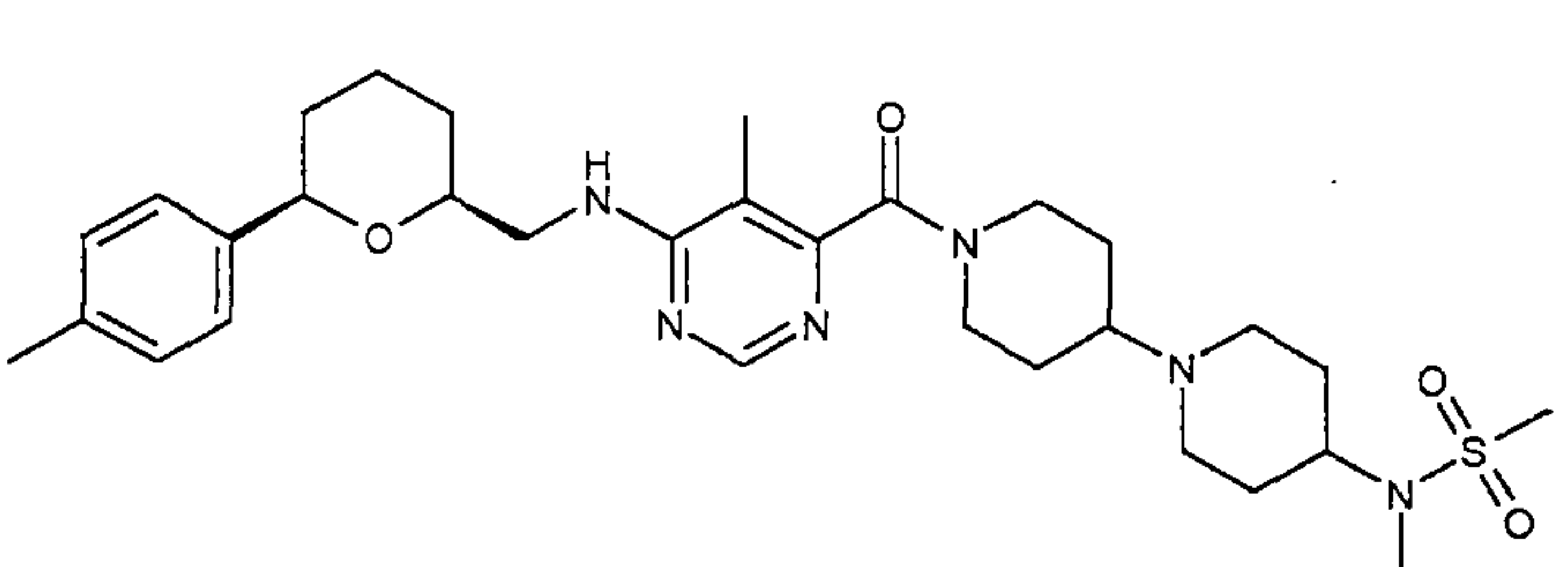
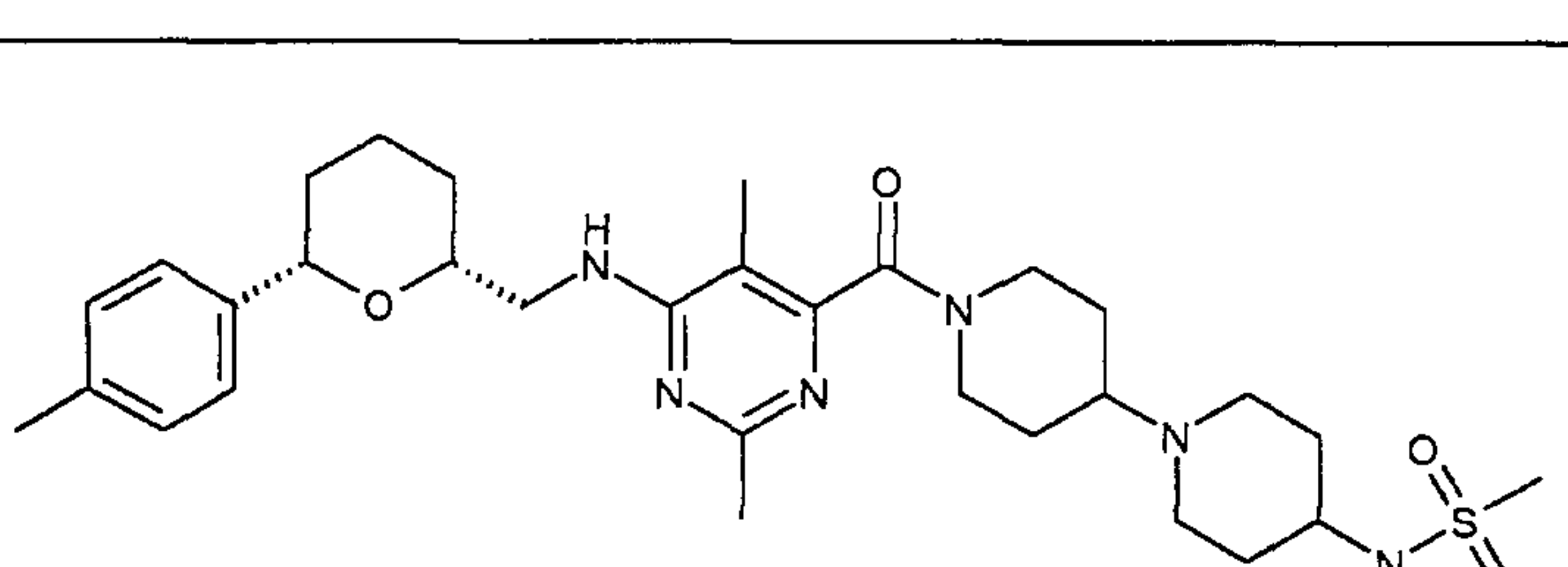
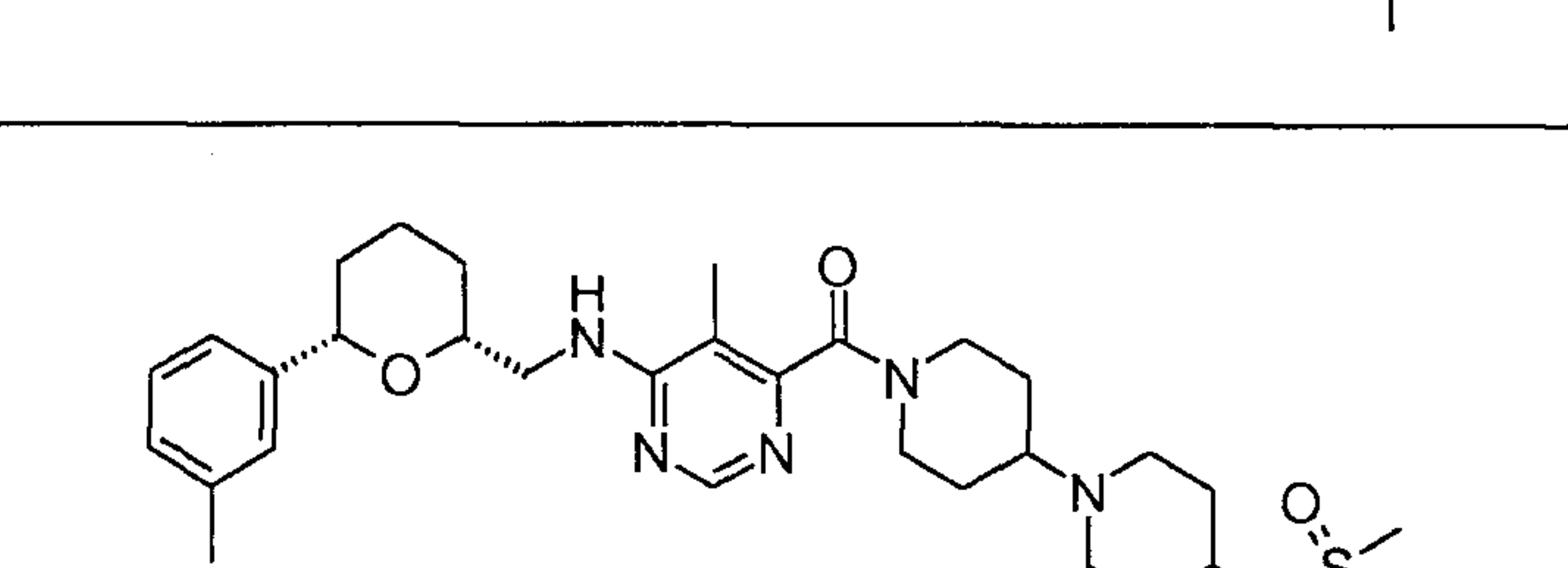
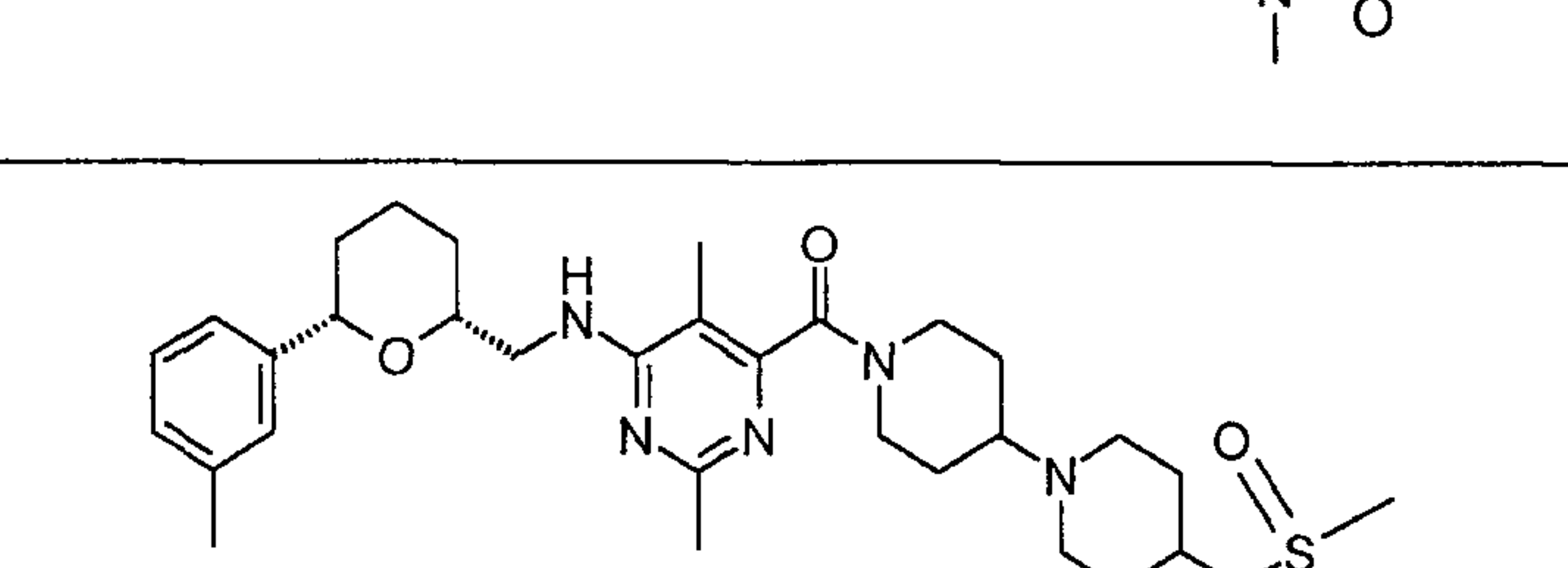
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7		26b	16f	653	7.21	2F
8		26b	17f	653	7.09	2F
9		26c	17a	585	9.24	1E (Hydro)
10		26b	14c	585	8.62 and 9.08	1E (hydro)
11		26b	15c	585	9.03	1E (Hydro)

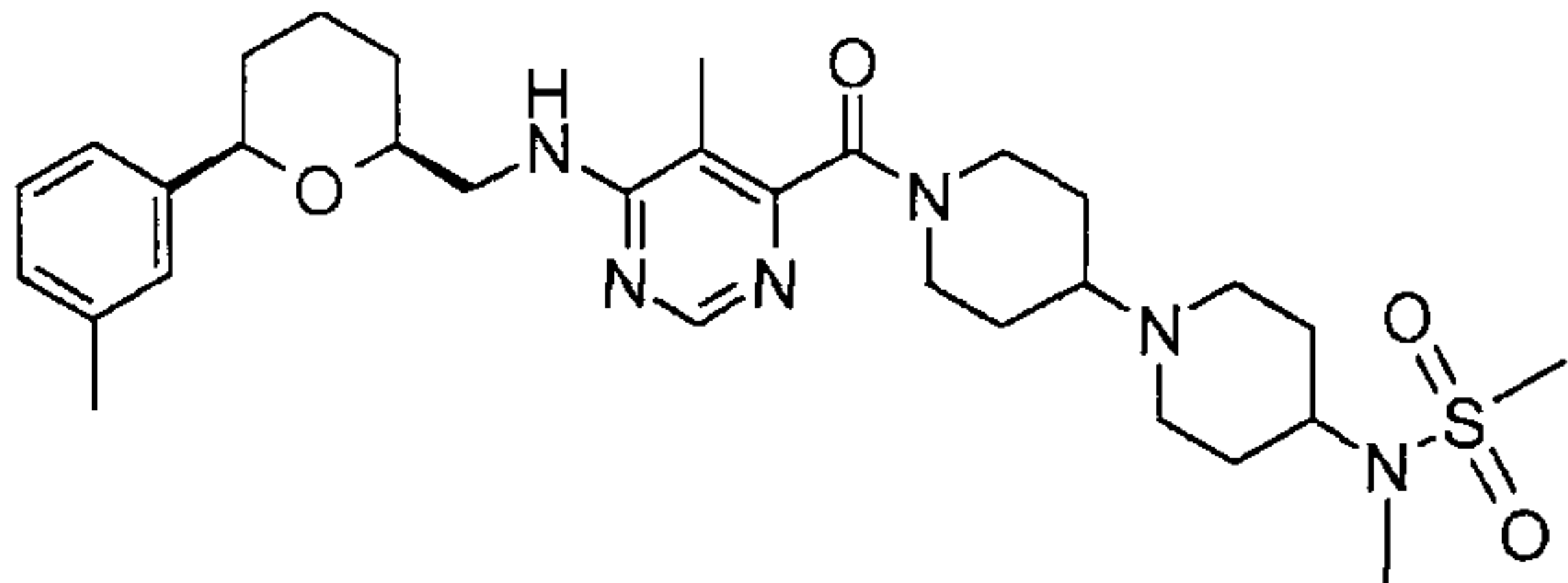
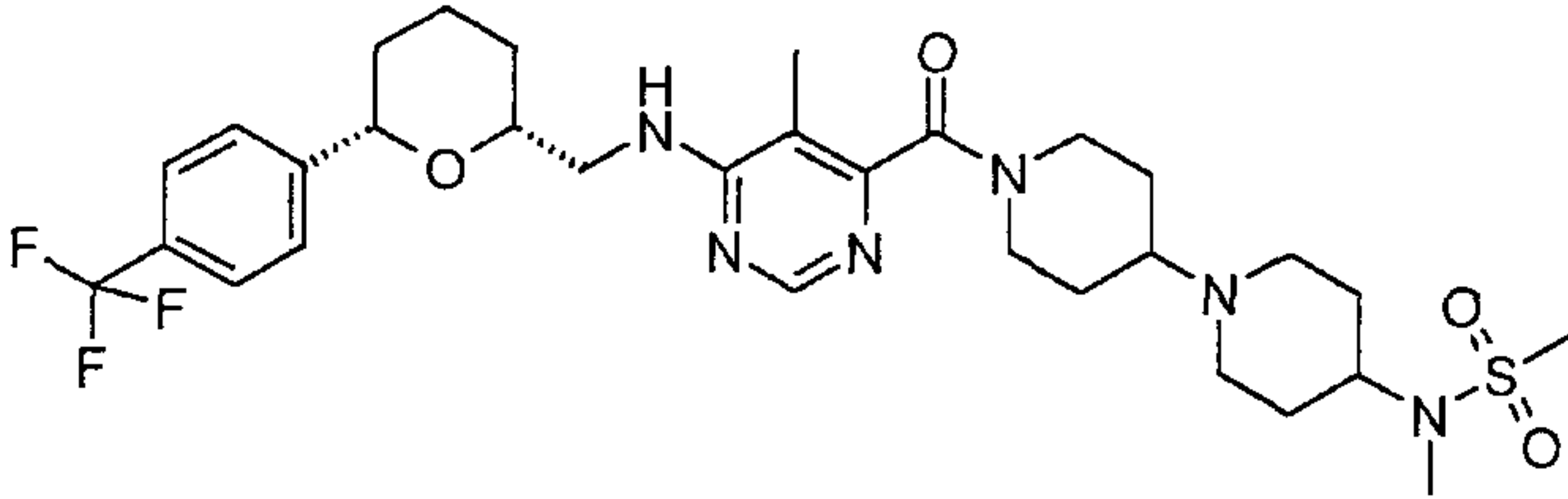
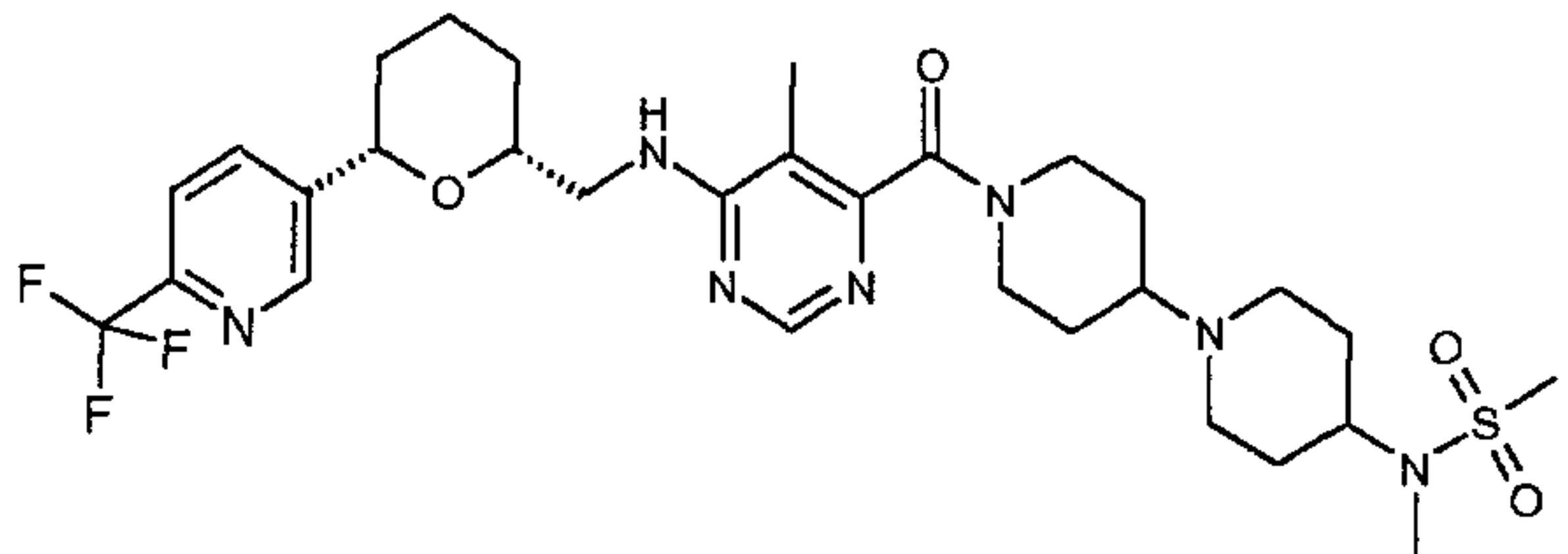
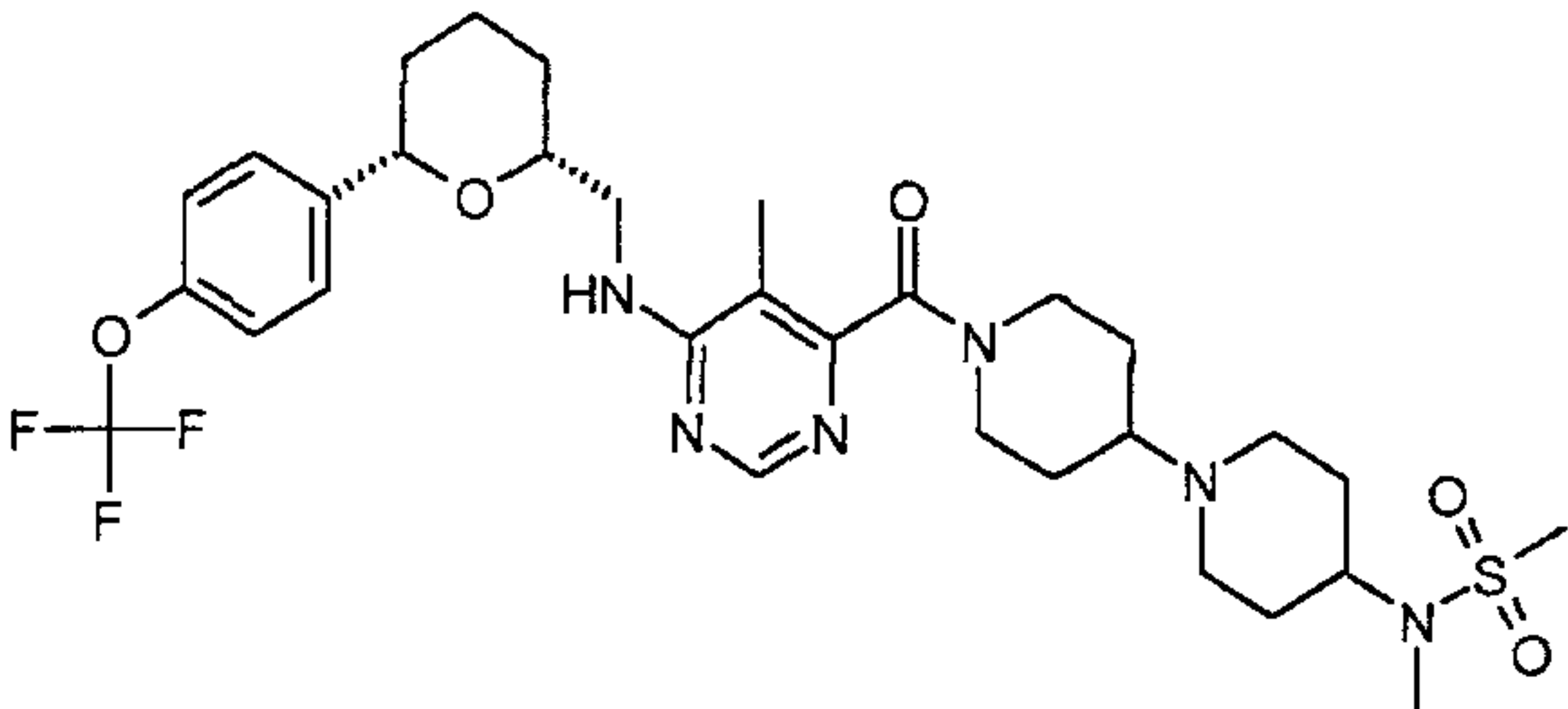
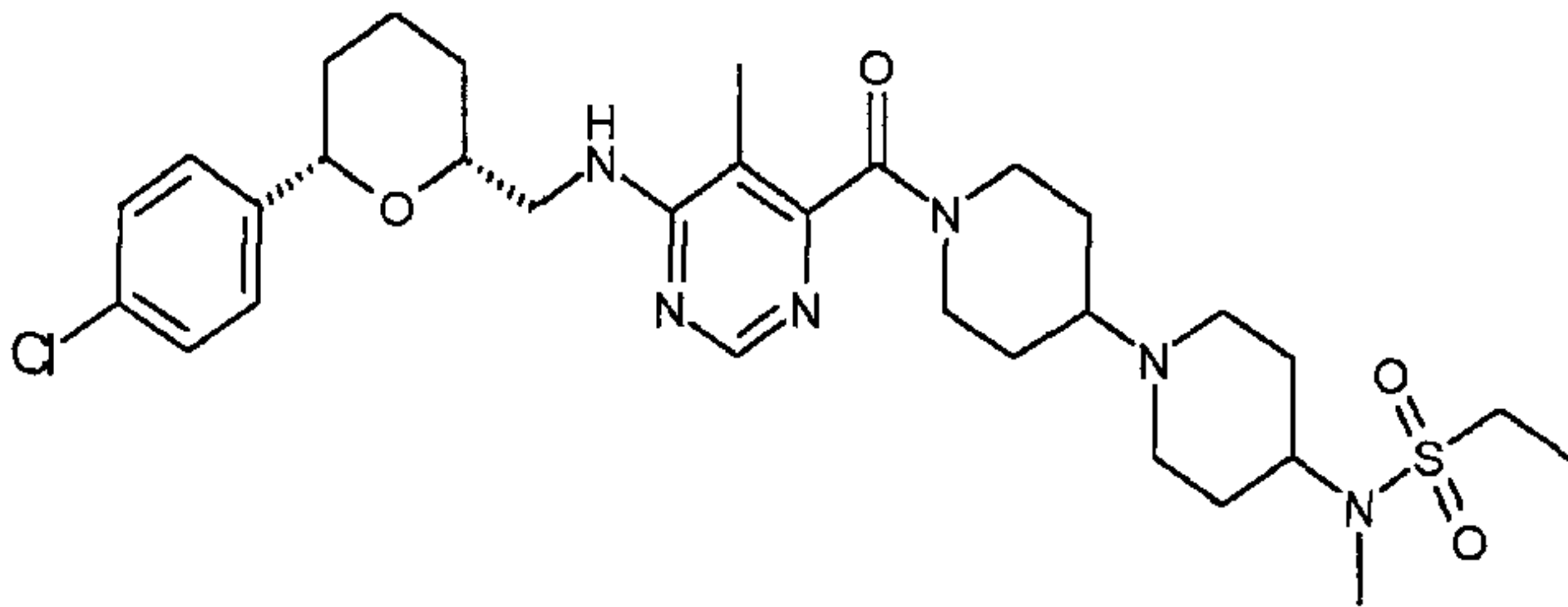
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12 *		26b	15c	585	8.95	1E (Hydro)
13 *		26b	15c	585	8.72	1E (Hydro)
14		26b	14i	603	8.6	1E (Hydro)
15		26b	14d	619	9.18 and 9.68	1E (Hydro)
16		26b	15d	619	9.77	1E (Hydro)

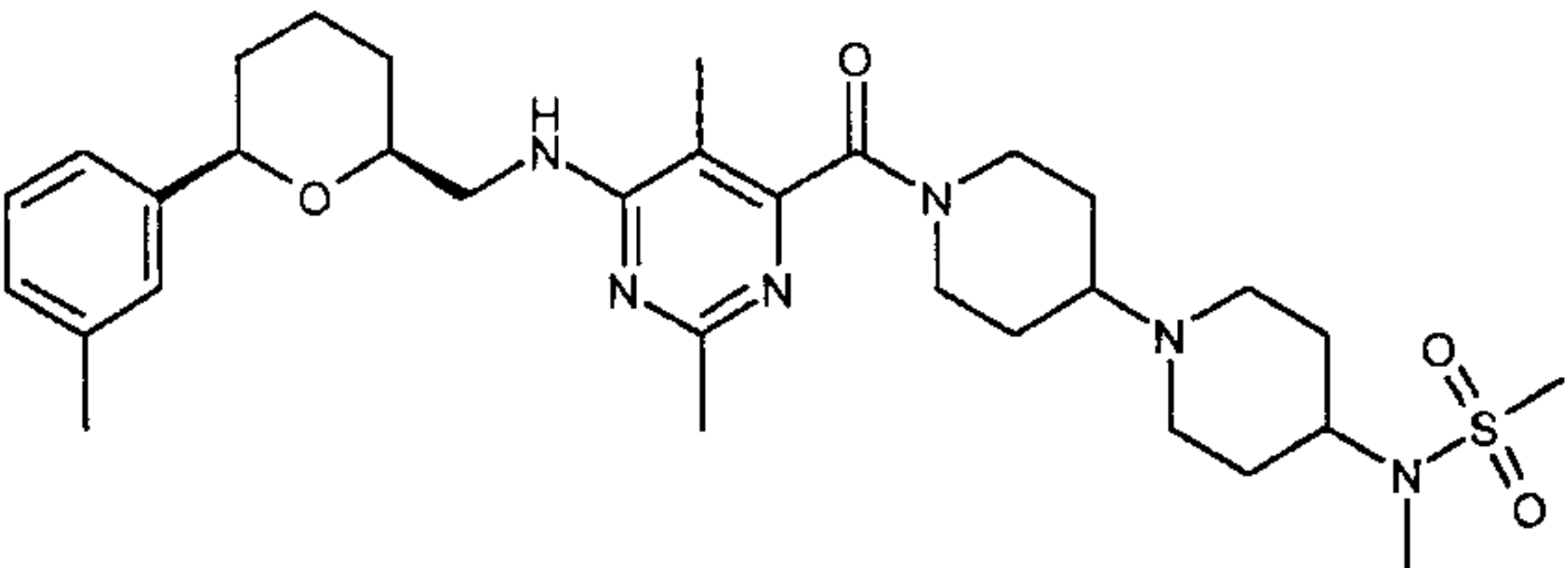
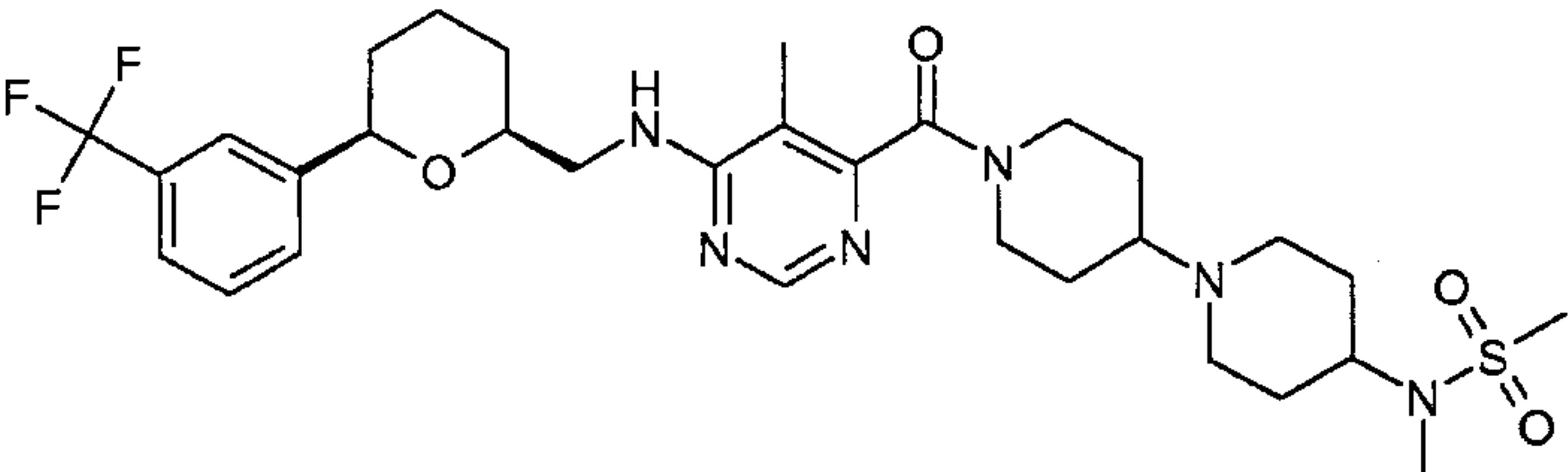
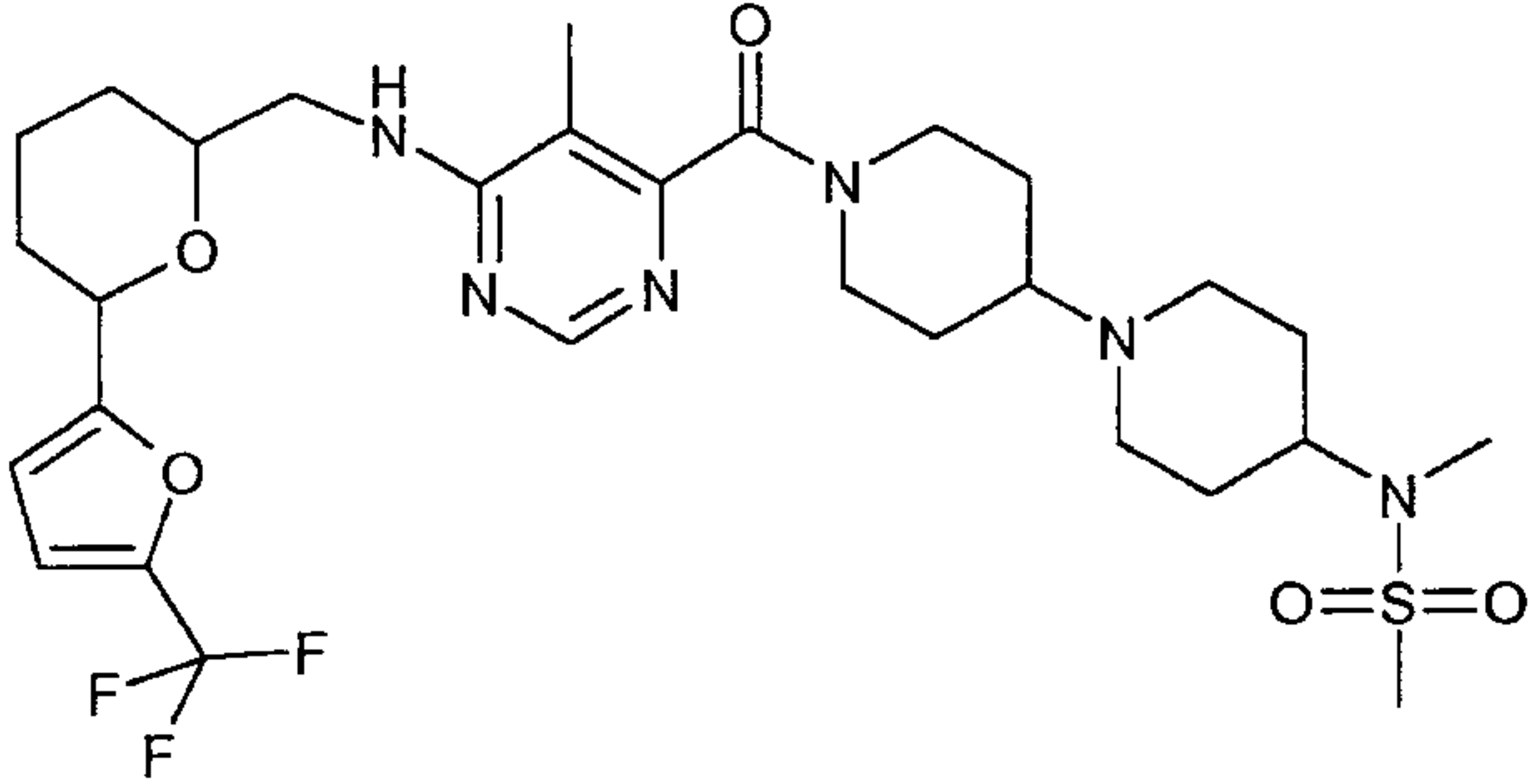
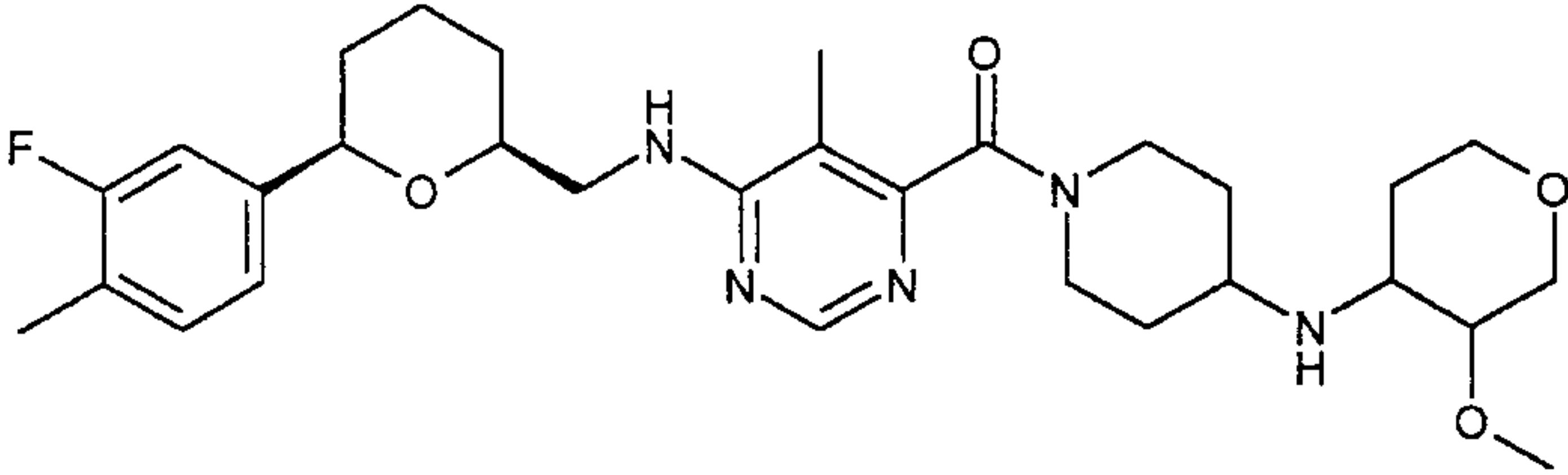
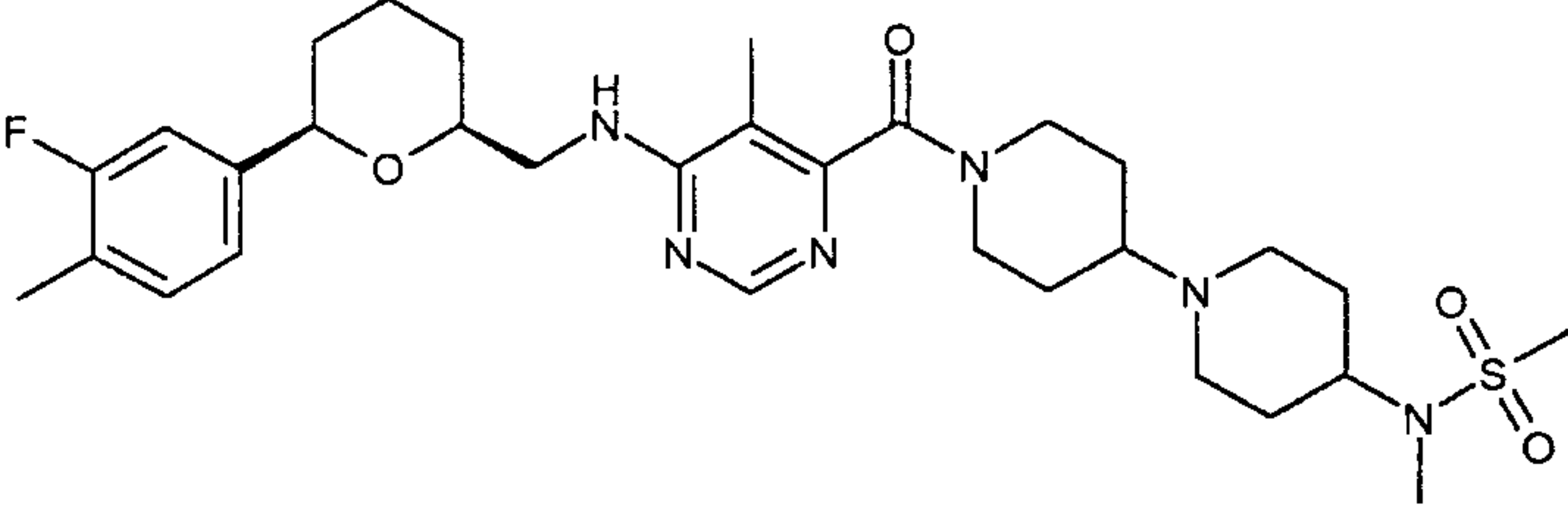
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17		26b	15a	599	8.98	1E (Hydro)
18		26d	15a	613	9.90	1E (Hydro)
19		26b	16a	599	9.4	1E (Hydro)
20		26d	17a	613	9.79	1E (Hydro)
21		26b	17e	599	9.48	1E (Hydro)
22		26d	17e	613	9.98	1E (Hydro)

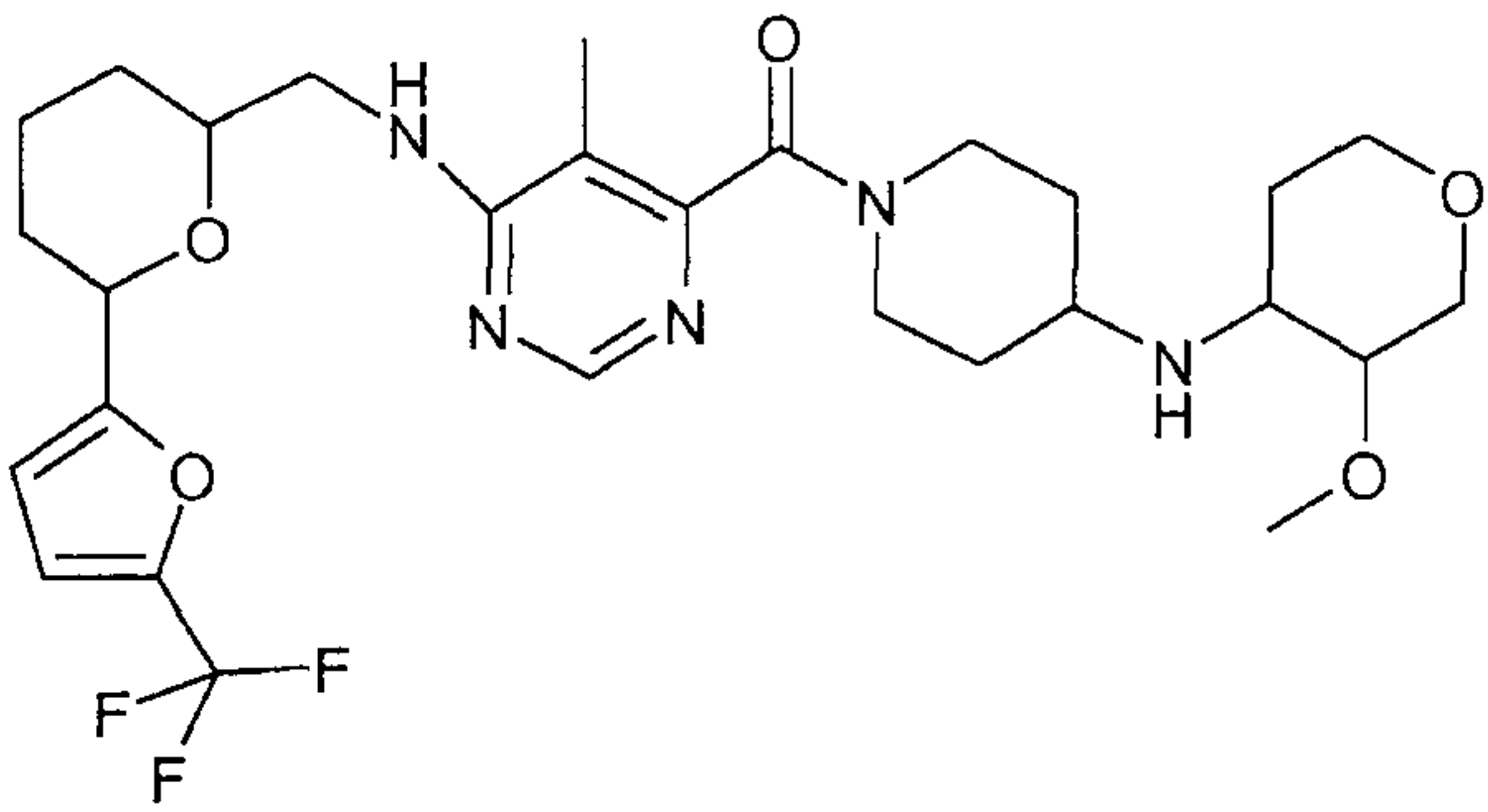
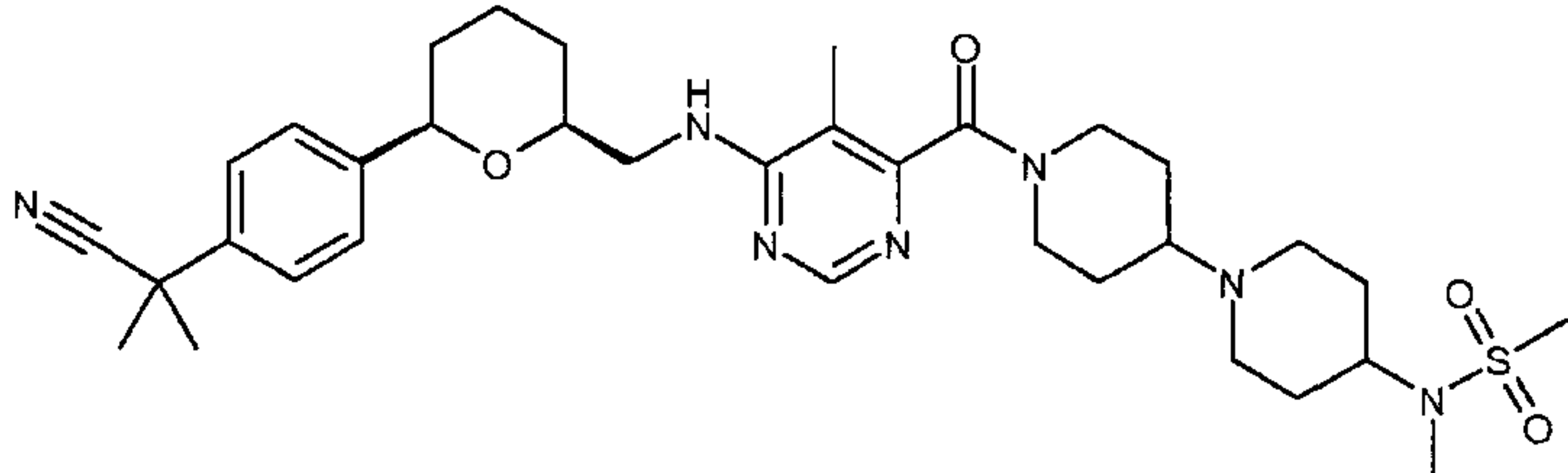
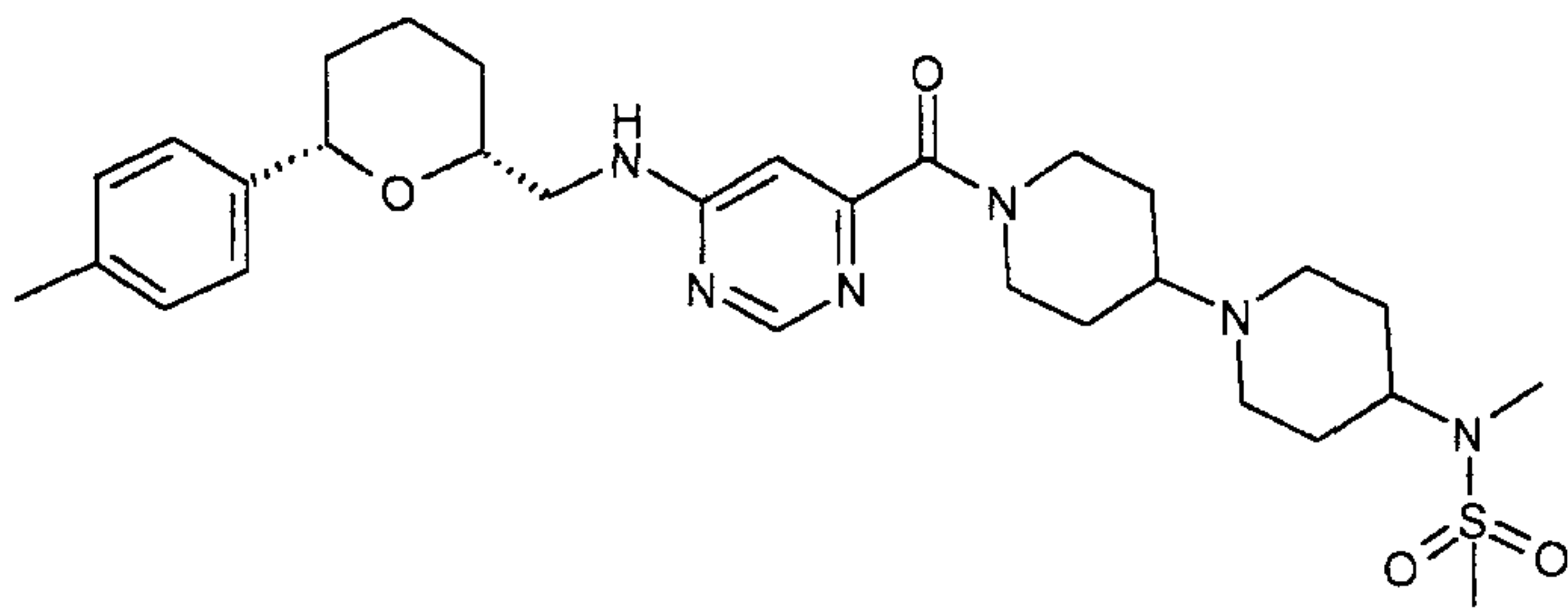
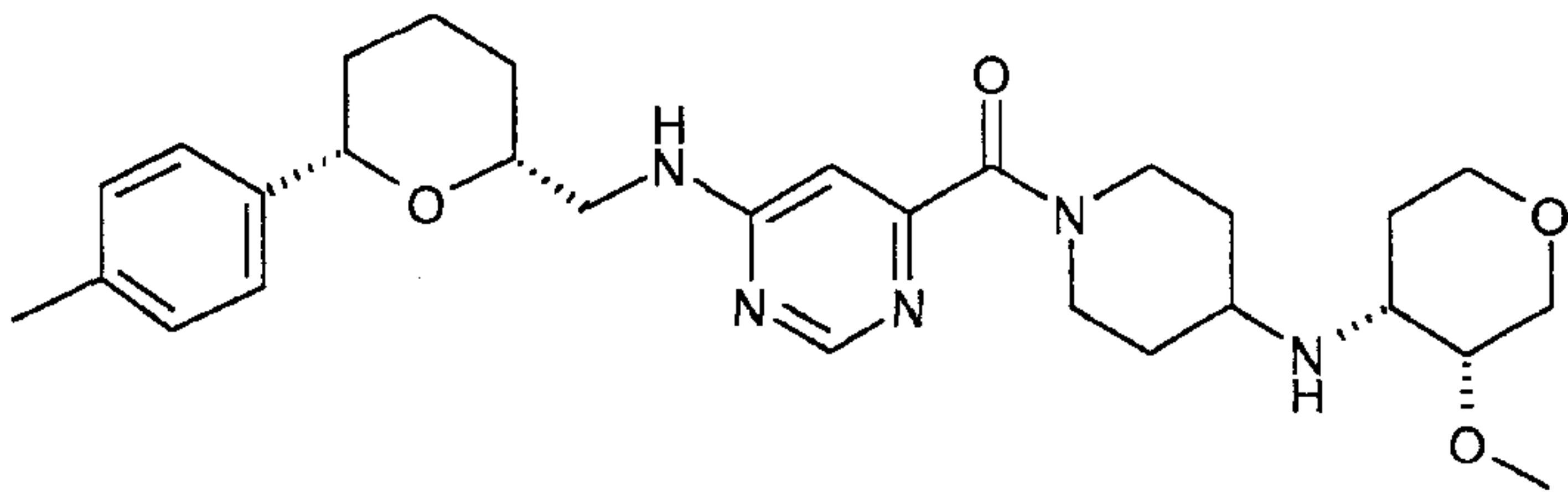
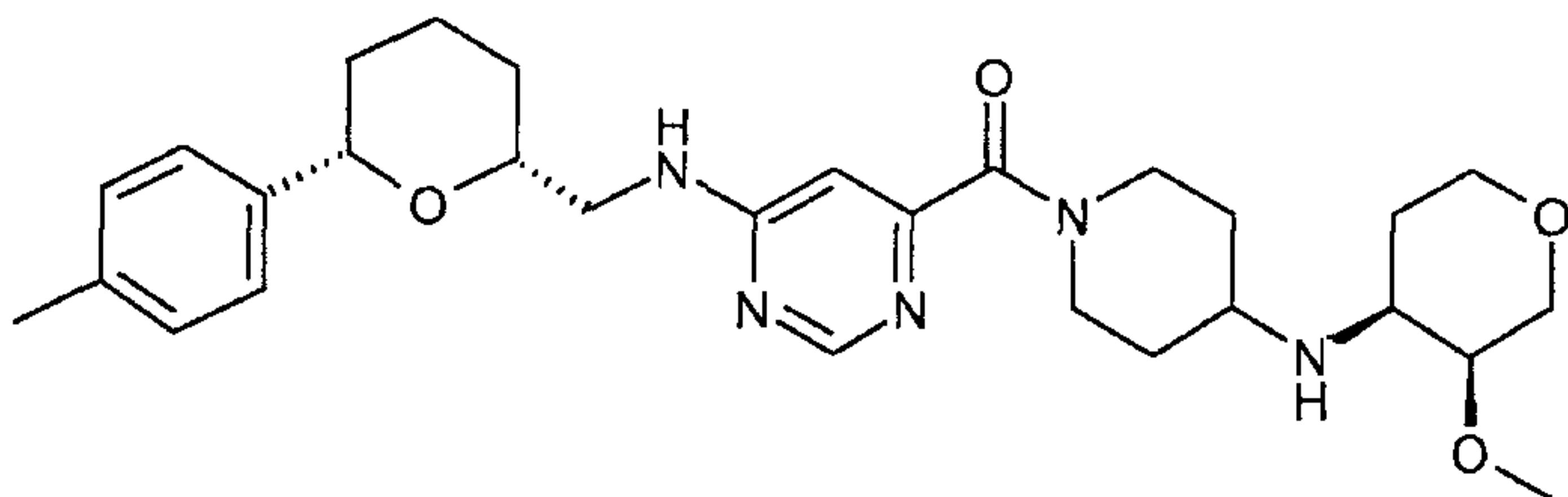
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23		26b	16e	599	9.53	1E (Hydro)
24		26b	16b	653	9.53	1E (Hydro)
25		26b	15g	654	8.83	1E (Hydro)
26		26b	15h	669	10.38	1E (Hydro)
27		26e	15d	633	9.47	1E (Hydro)

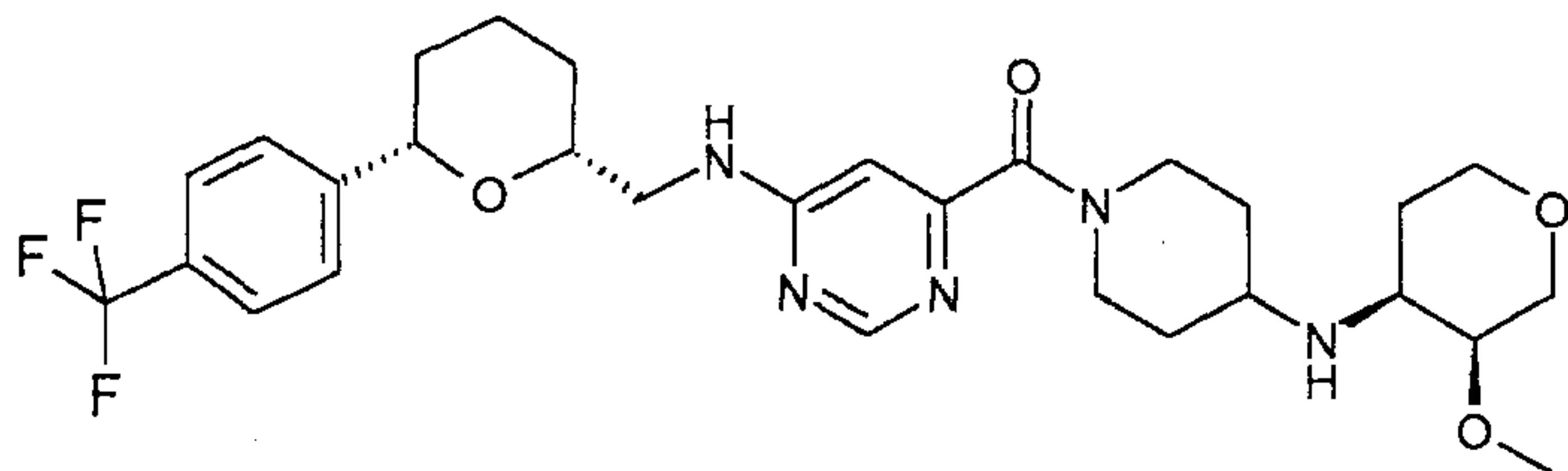
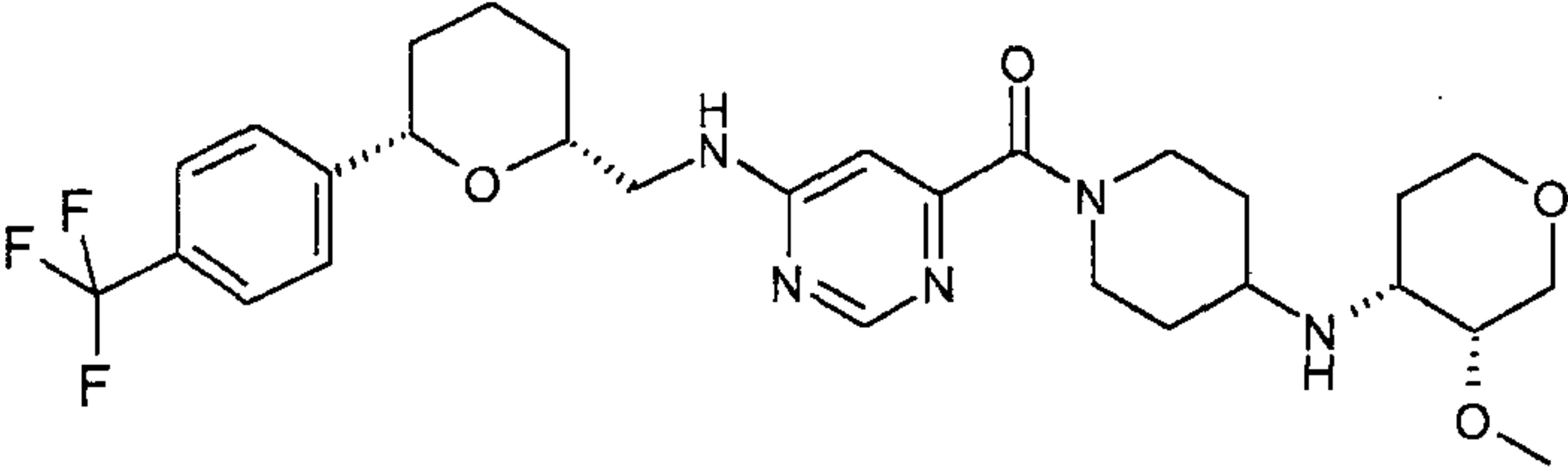
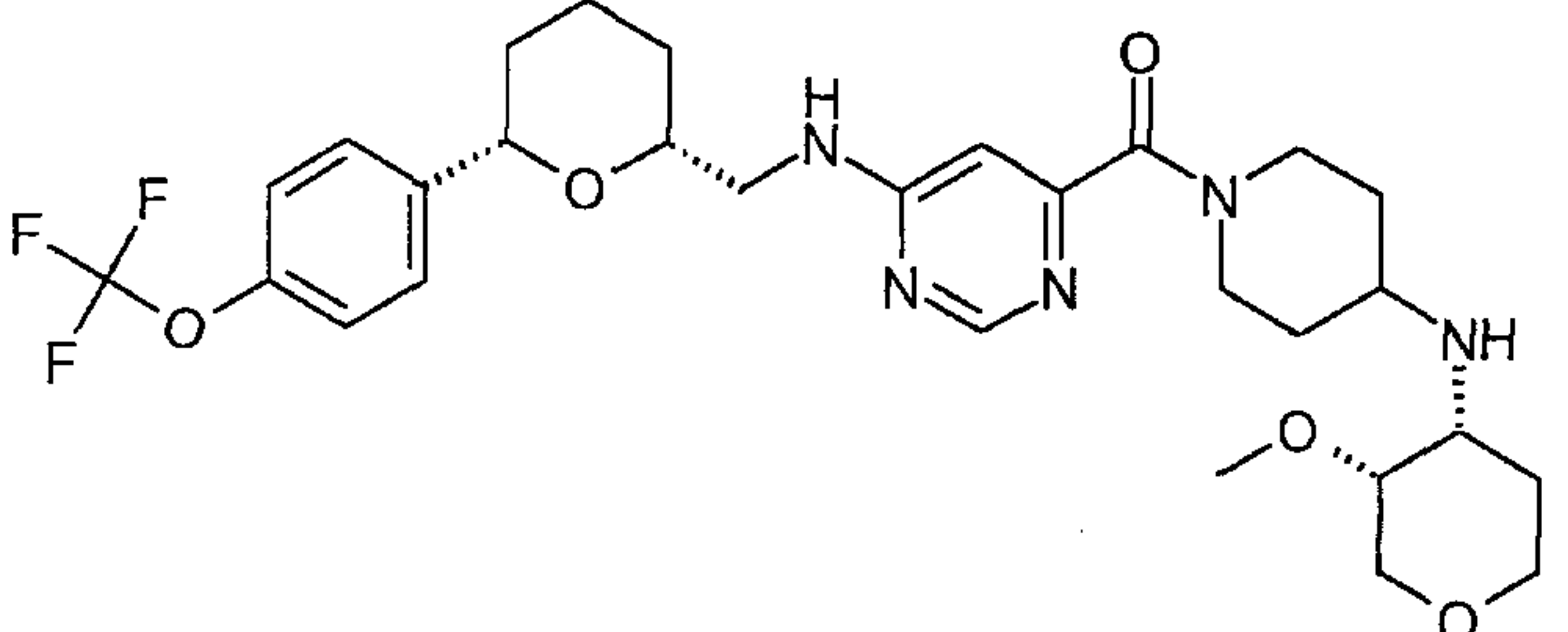
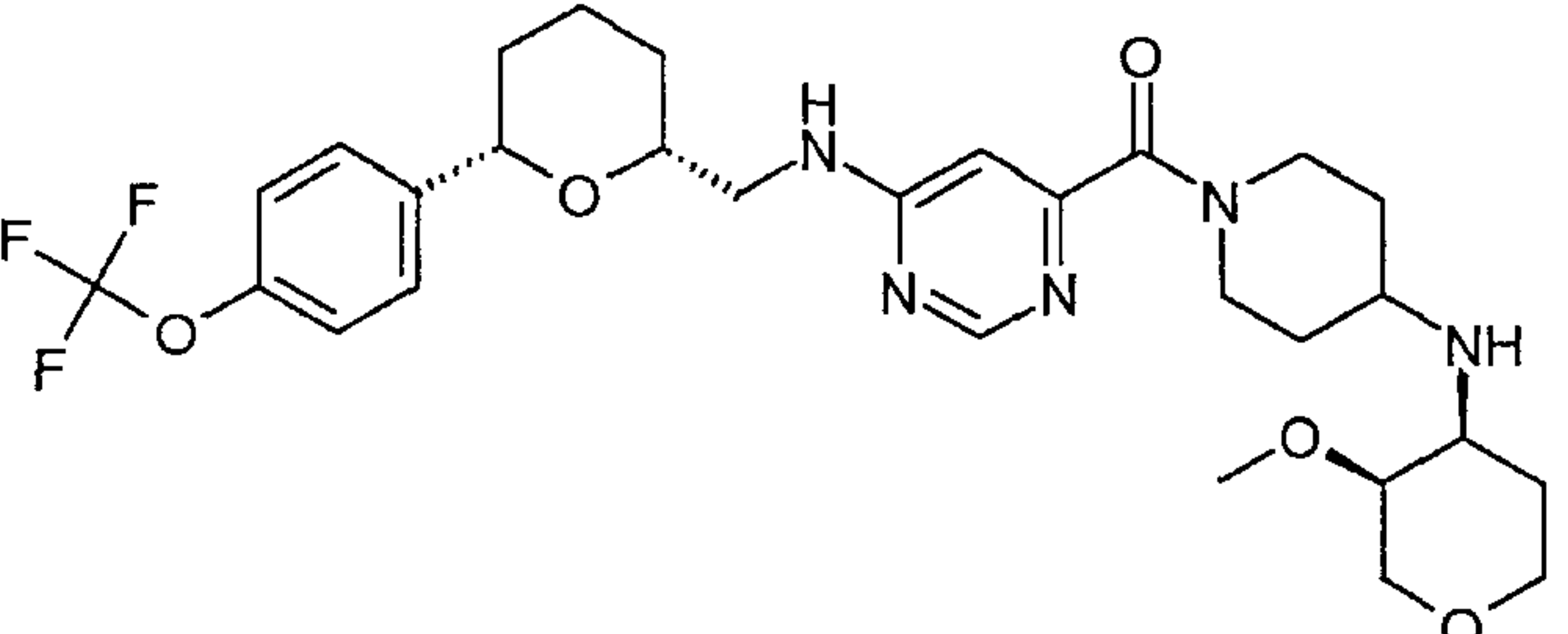
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28		26d	16e	613	9.98	1E (Hydro)
28 a		26b	15b	653	9.79	1E (Hydro)
28 b		26b	33c	643	8.95 and 9.28	1E (Hydro)
28 c		26i	33b	556	10.08	1E (Hydro)
28 d		26b	33b	617	10.05	1E (Hydro)

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28 e		26i	33c	582	8.70 and 9.07	1E (Hydro)
28 f		26b	33b	652	9.48	1E (Hydro)
28 g		26f	17a	585	1.83	2Ha
28 h		26g	17a	524	1.77	2Ha
28 i		26h	17a	524	1.78	2Ha

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28 j		26h	16b	578	1.91	2Ha
28 k		26g	16b	578	1.95	2Ha
28 l		26g	16h	594	1.96	2Ha
28 m		26h	16h	594	1.96	2Ha

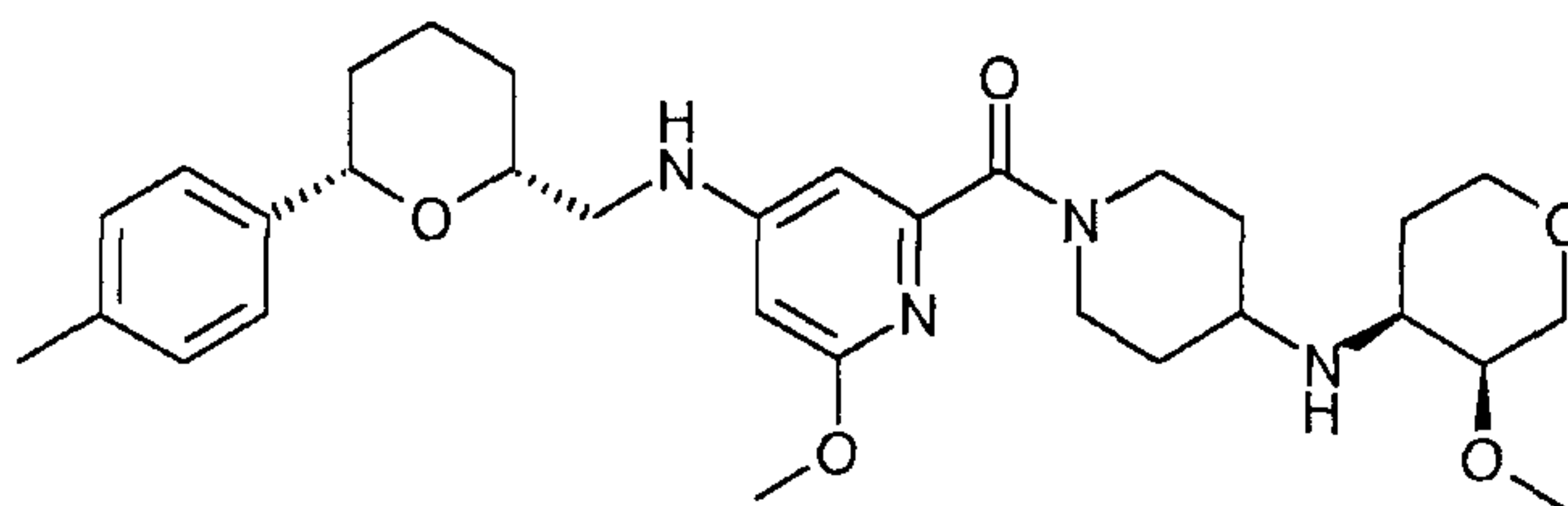
*Ex 12 and 13 were obtained by chiral HPLC separation of ex 11:

Ex 12: Chiral HPLC (method 2Ic isocratic): $R_t = 10.94$ min

Ex 13: Chiral HPLC (method 2Ic isocratic): $R_t = 12.93$ min

5

Example 28n



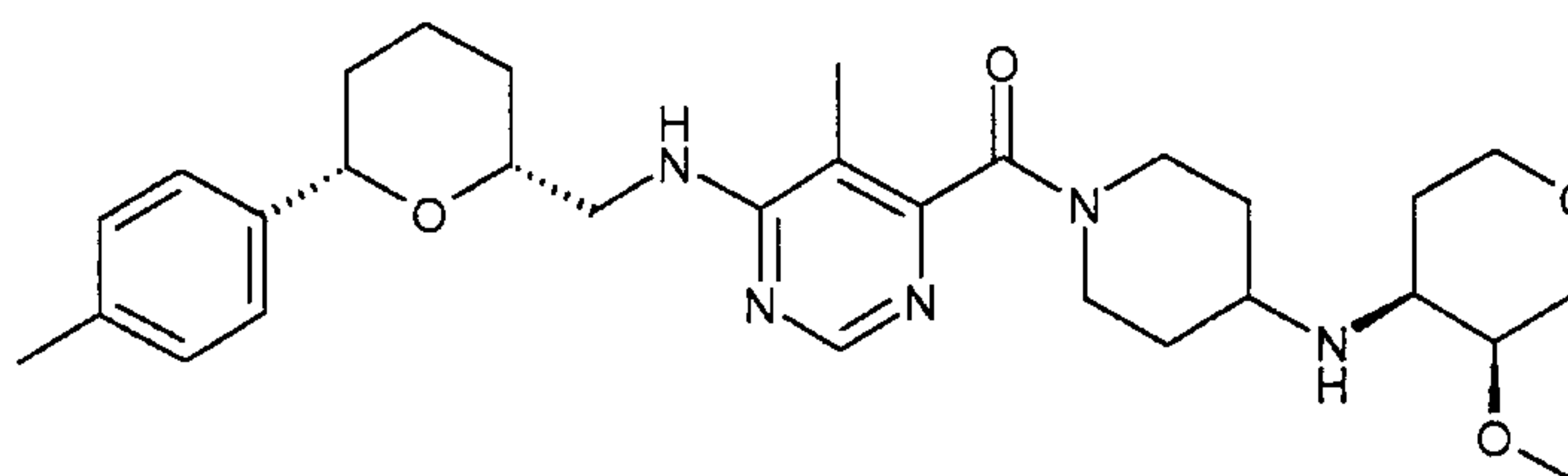
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Intermediate 17a (35 mg, 170 μ mol) and intermediate 26j (127 mg, 256 μ mol) were added to 1.5 ml toluene and 0.5 ml dioxane. Then, caesium carbonate (94 mg, 290 μ mol), tris(dibenzylideneacetone)dipalladium (15 mg, 17 μ mol) and XPhos (34 mg, 71 μ mol) were added and the reaction mixture was stirred over night at 110°C under argon atmosphere. The reaction mixture was diluted with ethyl acetate, washed with a saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The residue was purified by reversed phase HPLC to give the desired product (35 mg).

HPLC (Method 2HA): R_t (min) = 1.18

$[M+H]^+ = 553$

Example 29



Intermediate 28a (70 mg, 0.21 mmol), TBTU (65.8 mg, 0.20 mmol) and N,N-diisopropylethylamine (0.11 ml, 0.62 mmol) in 5 ml DMF were stirred at room temperature for 5 min.

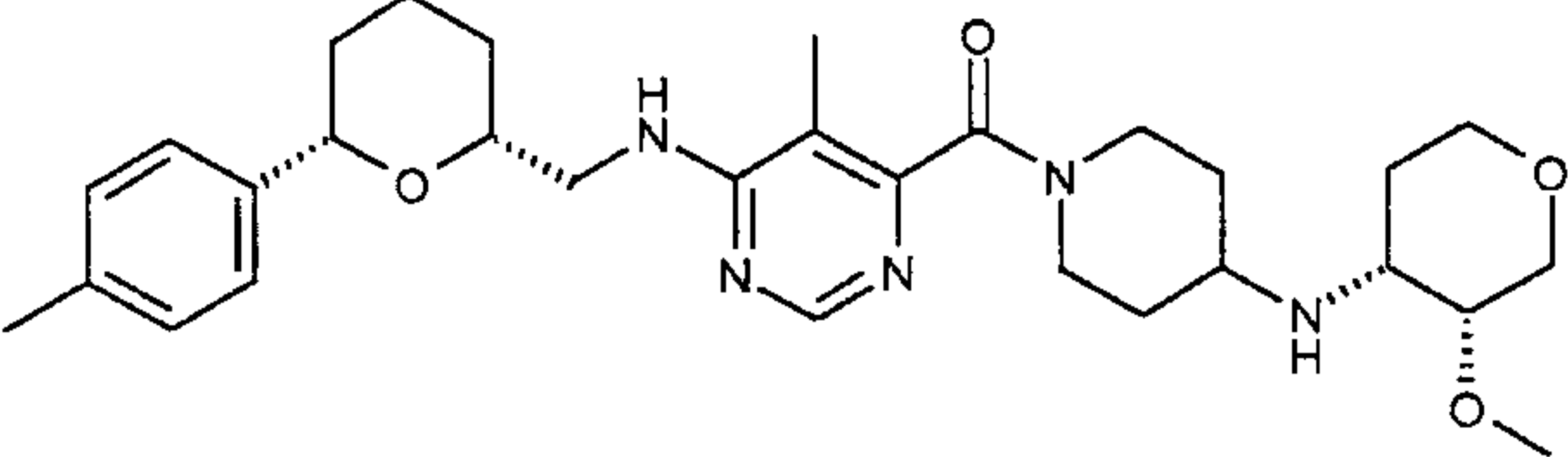
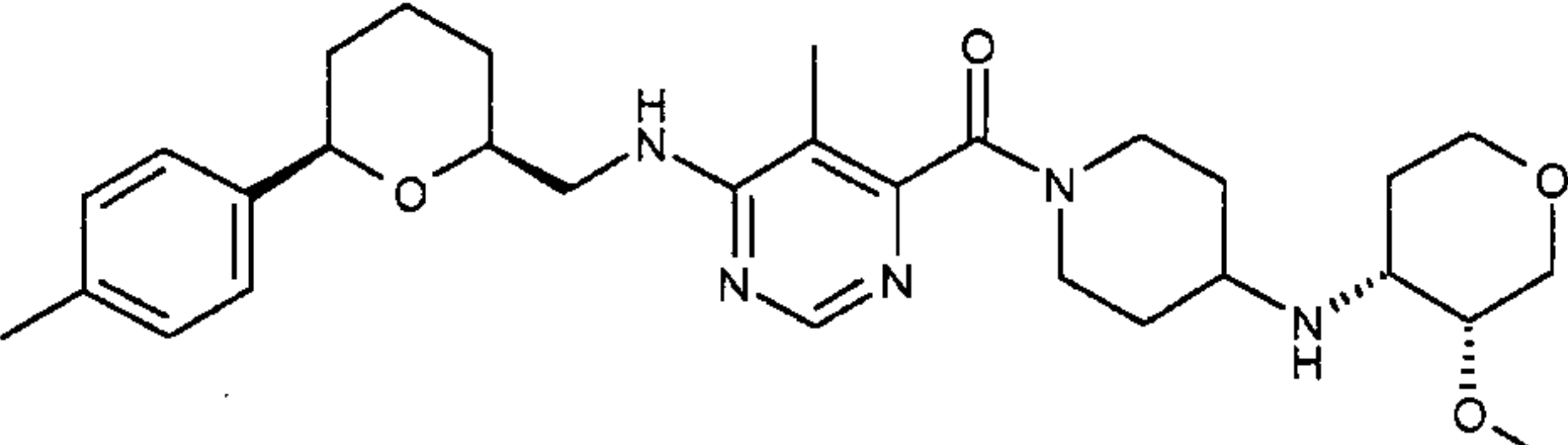
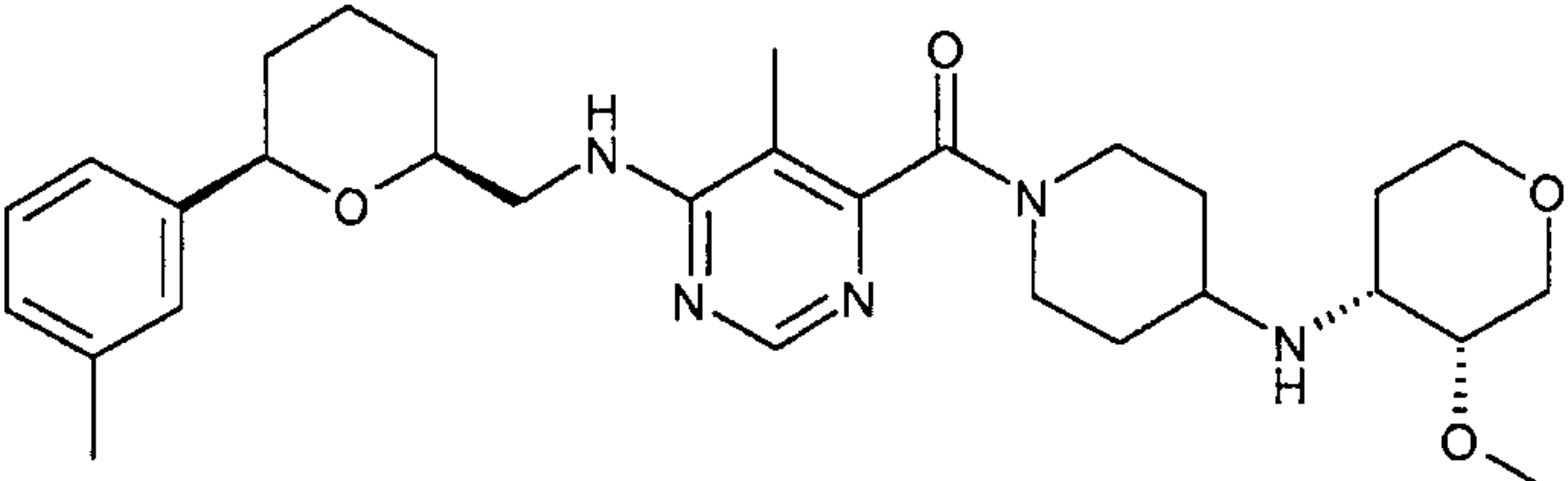
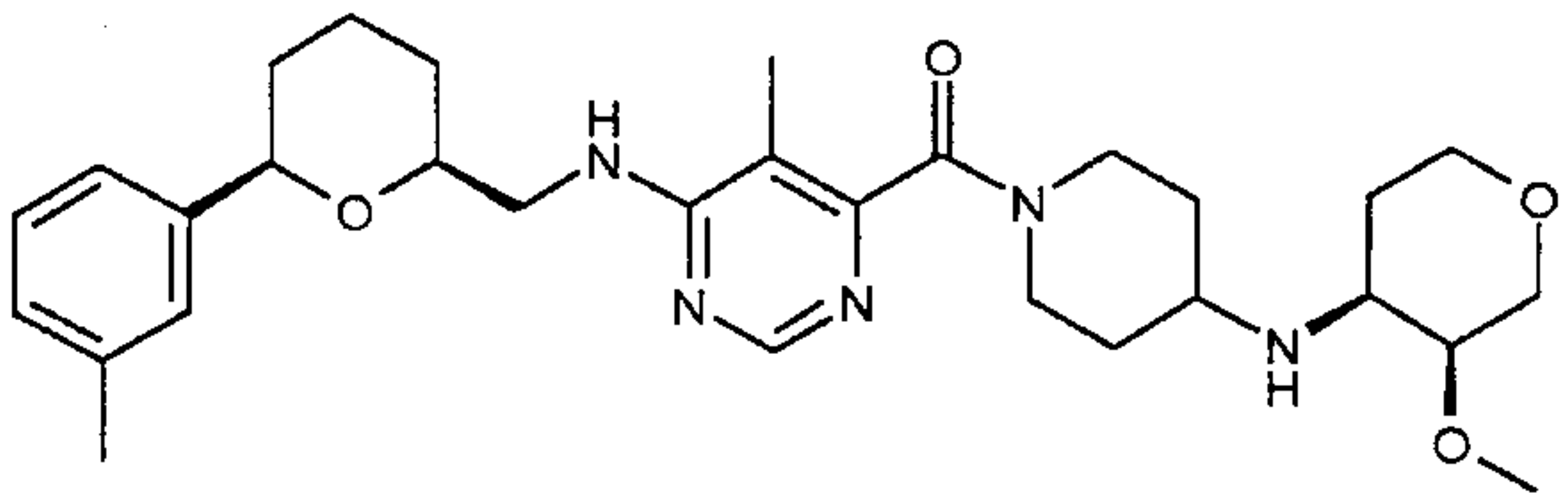
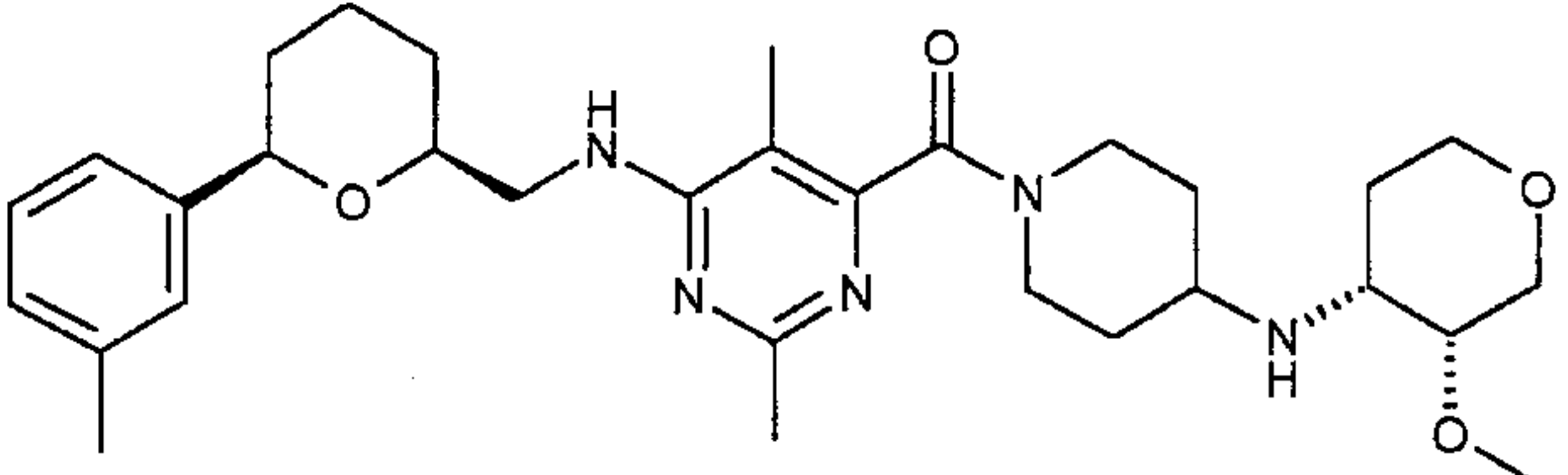
Intermediate 21c (59 mg, 0.21 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the crude product was dissolved in dichloromethane. The organic phase was washed with an aqueous saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under vacuum. The crude product was purified by flash chromatography (Si Isolute cartridge (5g); eluent: dichloromethane/MeOH=96/4%). 45 mg (0.08 mmol) of the desired product were obtained.

HPLC (Method 1E Hydro): R_t (min) = 8.50

$[M+H]^+ = 538$

The following examples were synthesized in analogy to the preparation of Example 29.

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Ex #	STRUCTURE	Intermediate	Amine	[M+H] ⁺	HPLC R _t (min)	Method
30		28a	21b	538	9.33	1E (Hydro)
31		28b	21b	538	9.55	1E (Hydro)
32		28i	21b	538	9.75	1E
33		28i	21c	538	9.76	1E
34		28k	21b	552	9.79	1E (Hydro)

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35		28k	21c	552	10.2	1E
36		28d	21b	592	9.27	1E (Hydro)
37		28d	21c	592	9.28	1E (Hydro)
38		28e	21c	524	8.64	1E (Hydro)
39		28f	21c	524	8.47	1E (Hydro)
40		28e	21b	524	8.66	1E (Hydro)

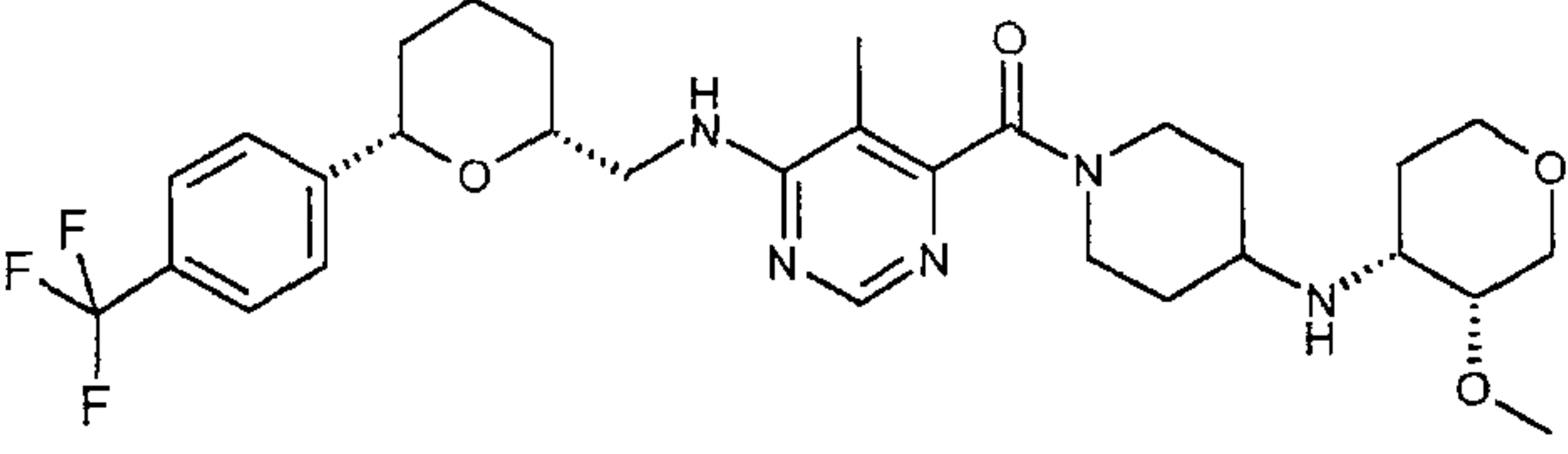
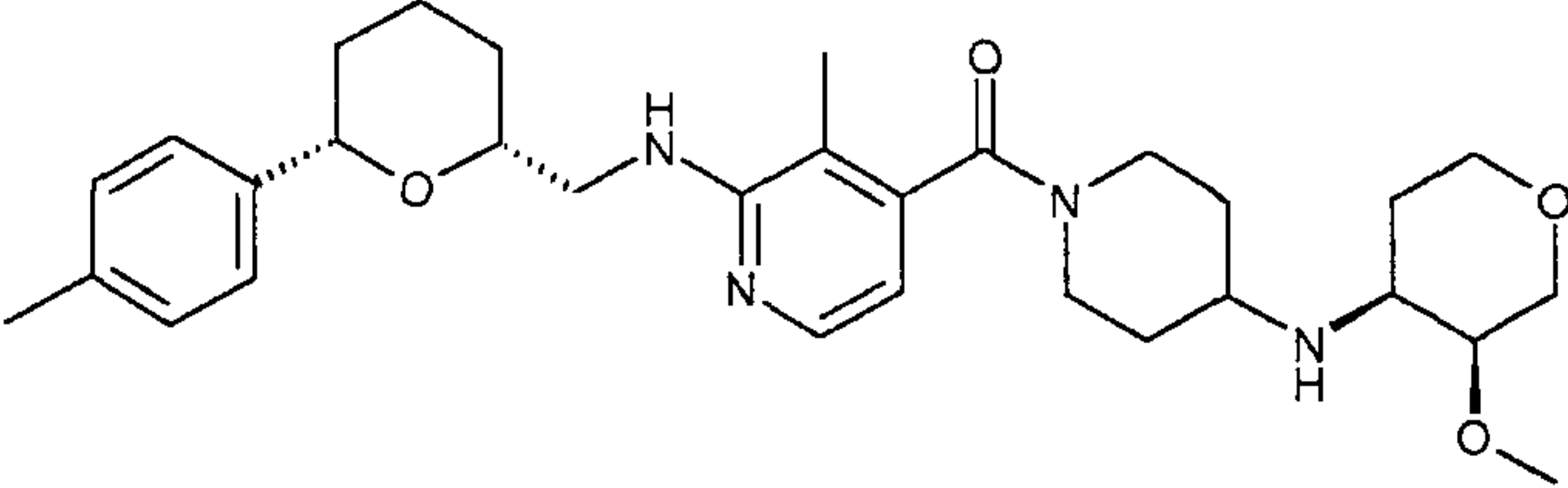
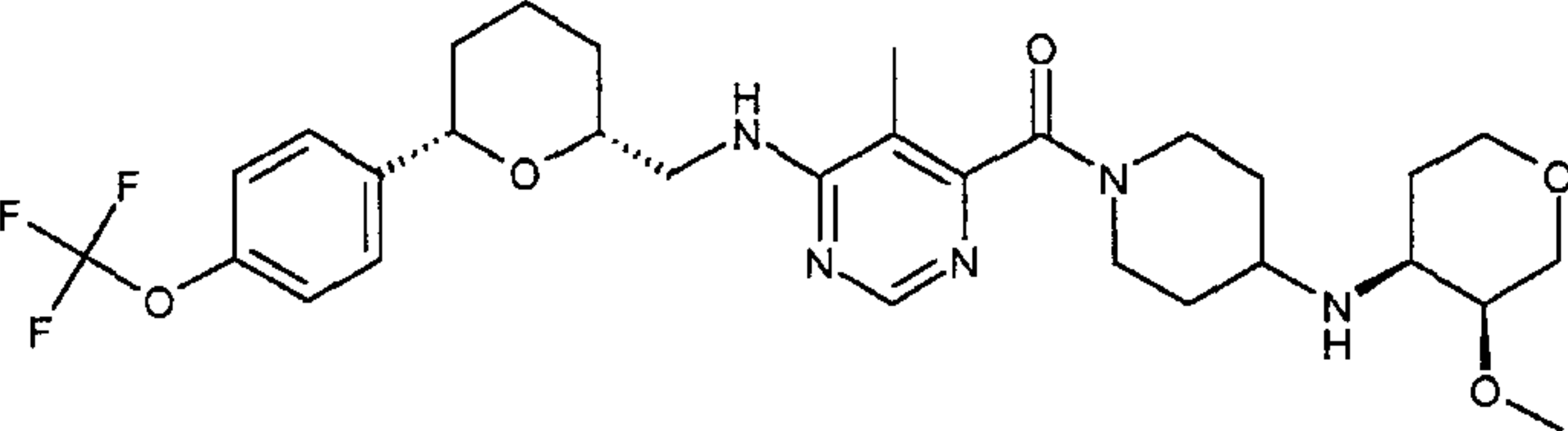
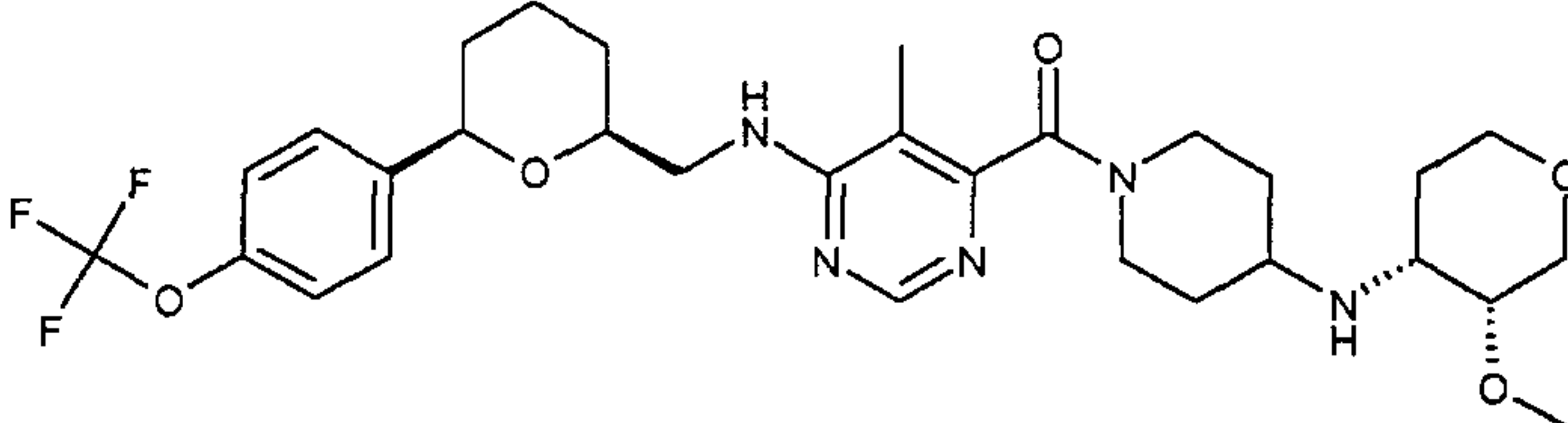
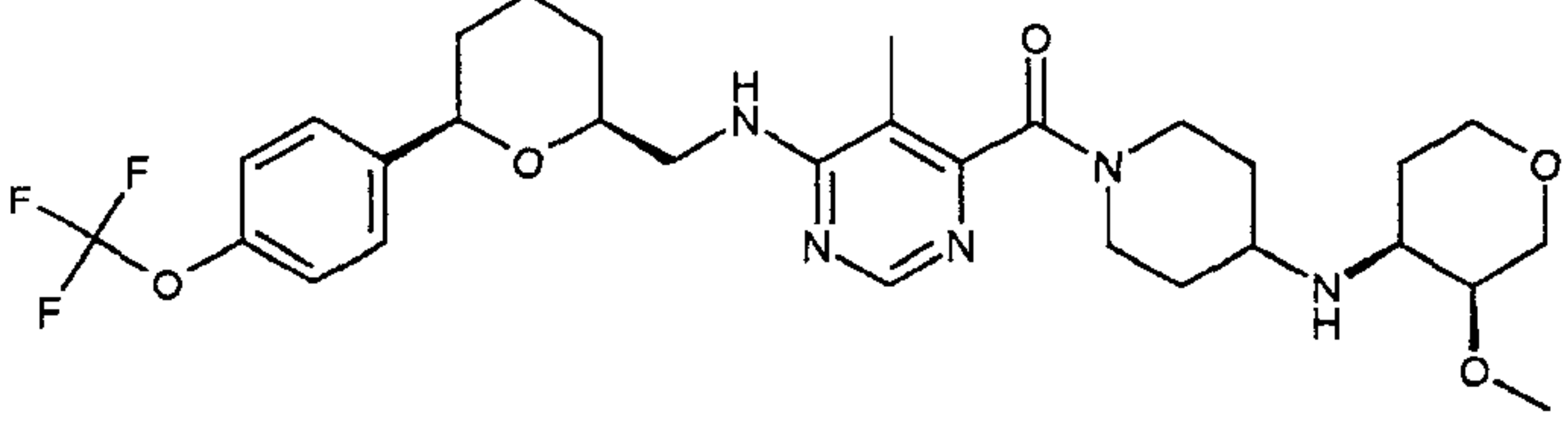
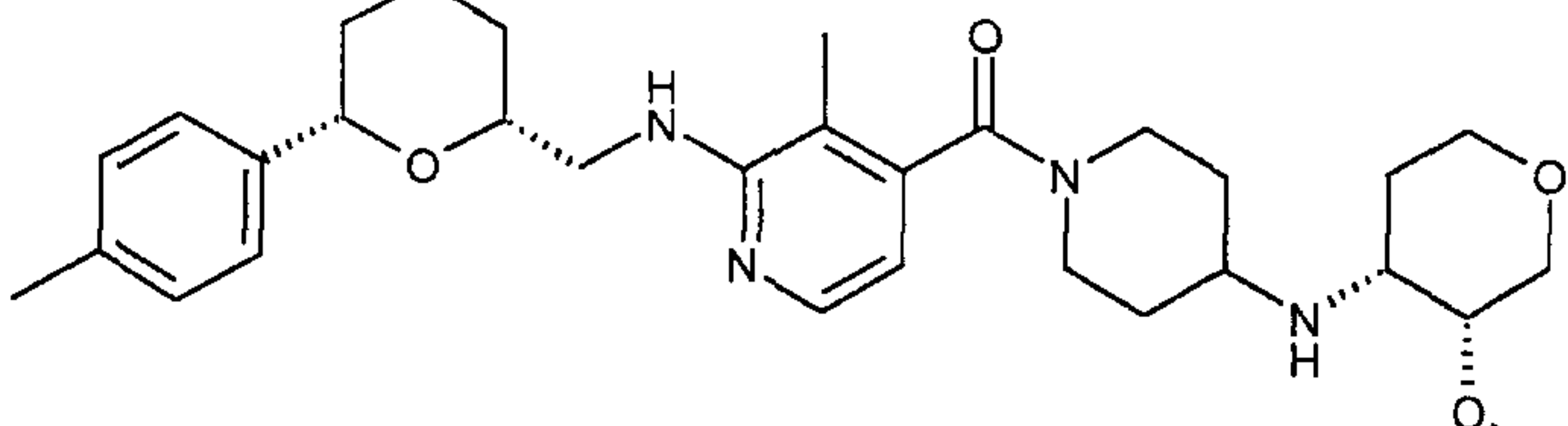
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41		28g	21c	558	7.14	2F
42		28g	21b	558	7.04	2F
43		28h	21c	558	7.17	2F
44		28h	21b	558	7.17	2F
45		28m	21c	592	9.89	1E (Hydro)
46		28m	21b	592	9.73	1E (Hydro)

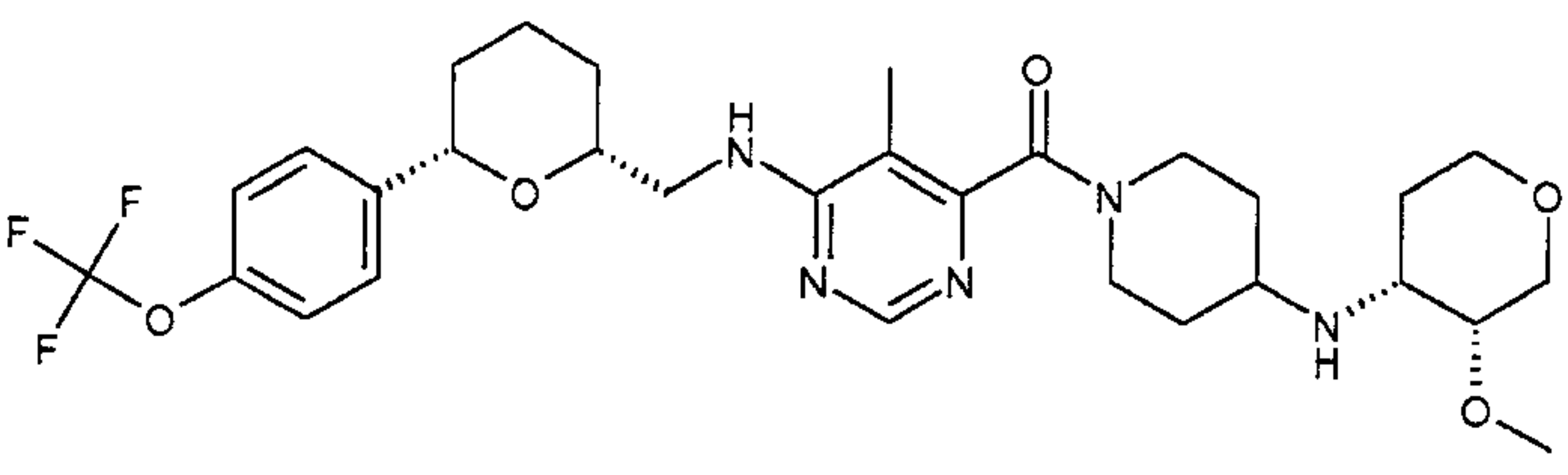
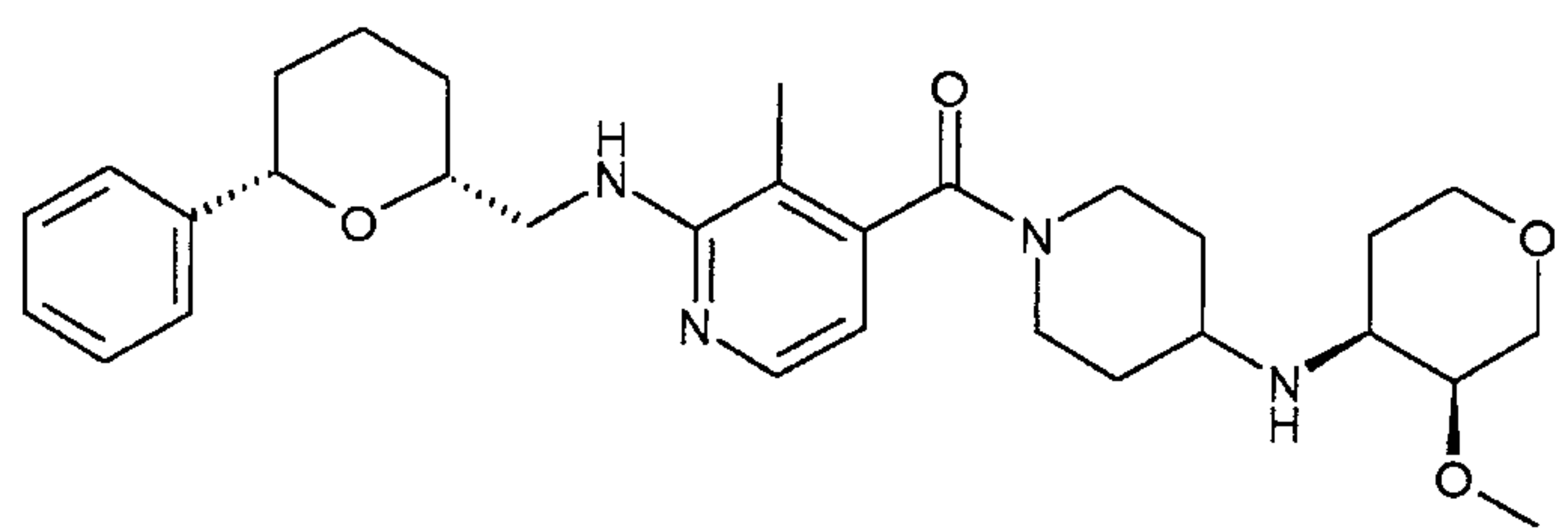
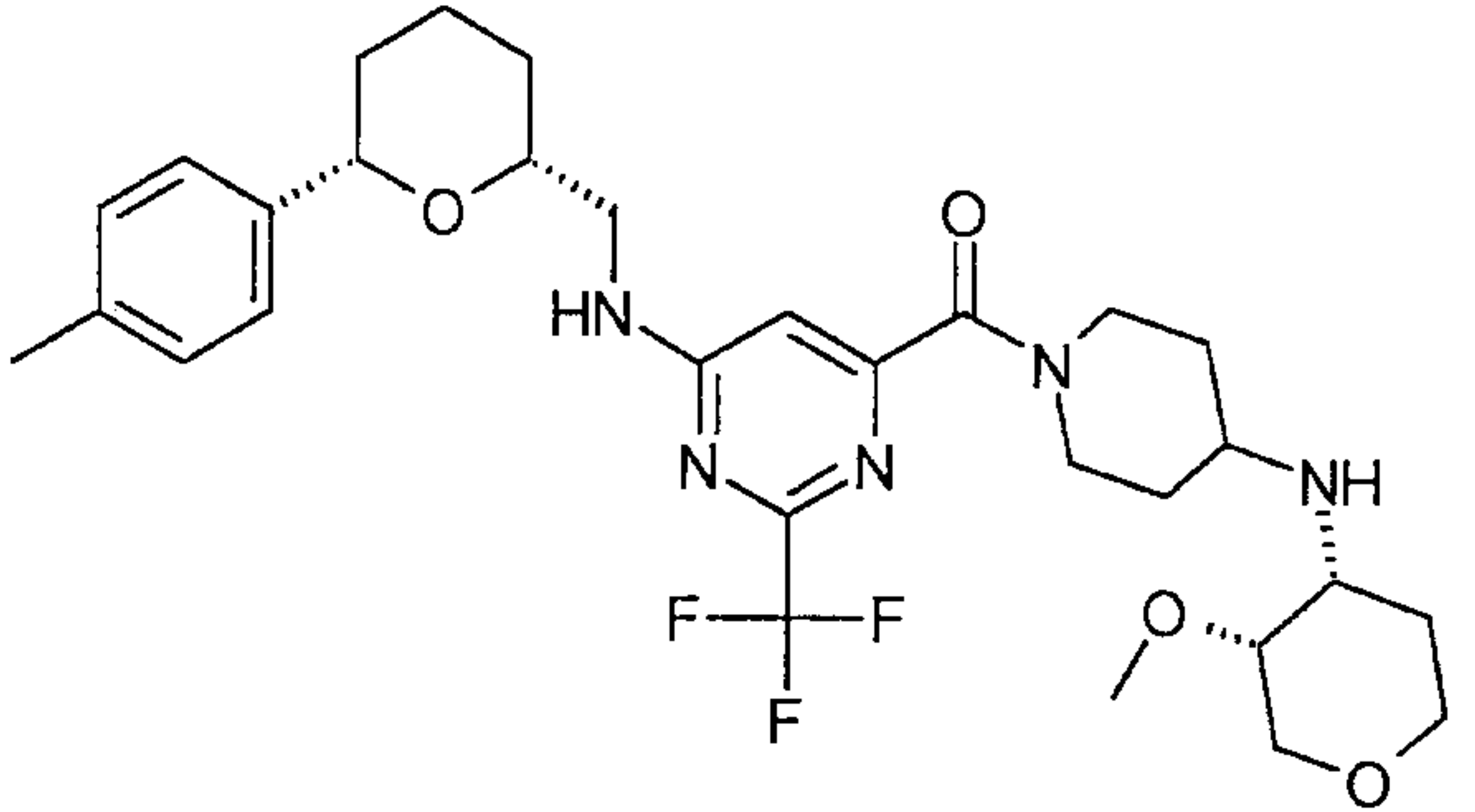
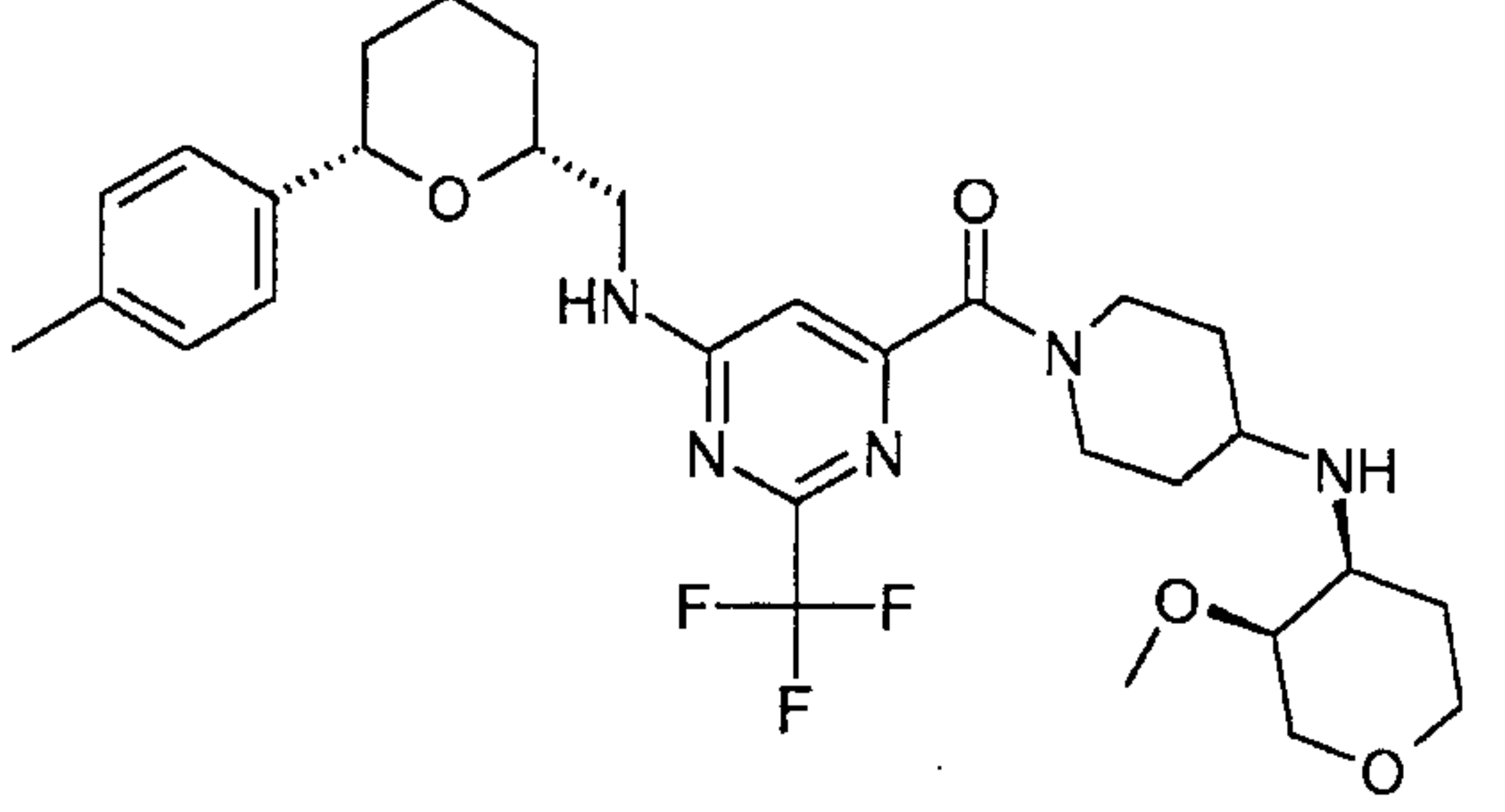
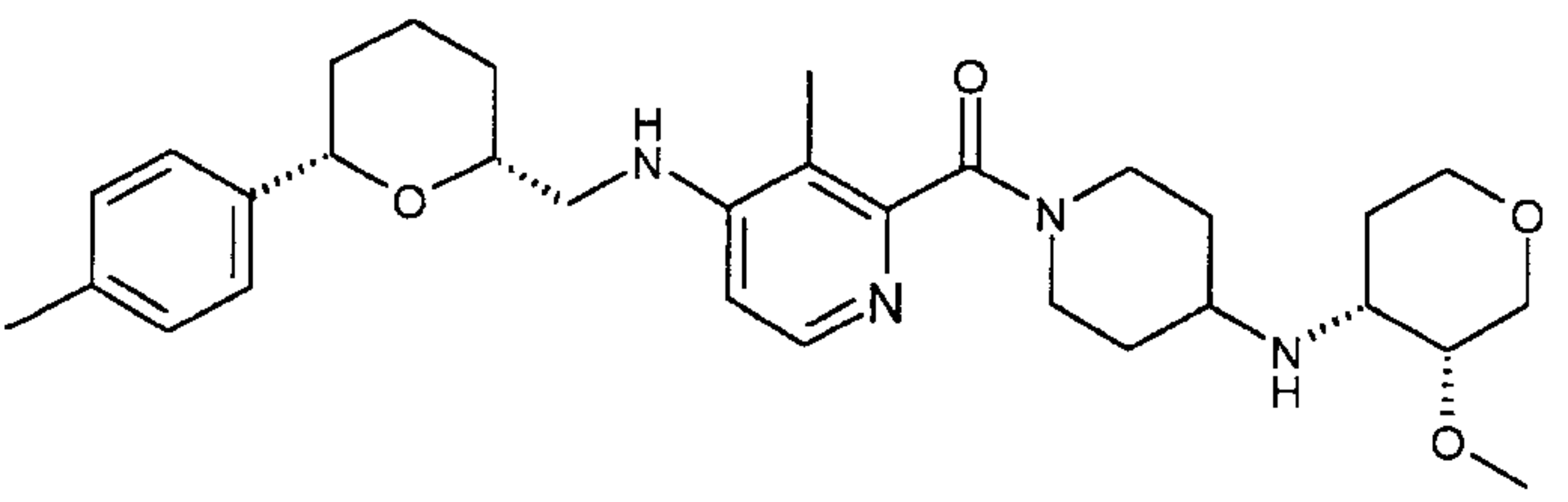
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47		28n	21c	592	9.65	1E (Hydro)
48		28j	21b	538	9.70	1E
49		28j	21c	538	9.63	1E
50		28l	21b	552	10.1	1E
51		28l	21c	552	10.18	1E
52		28c	21c	592	9.30	1E (Hydro)

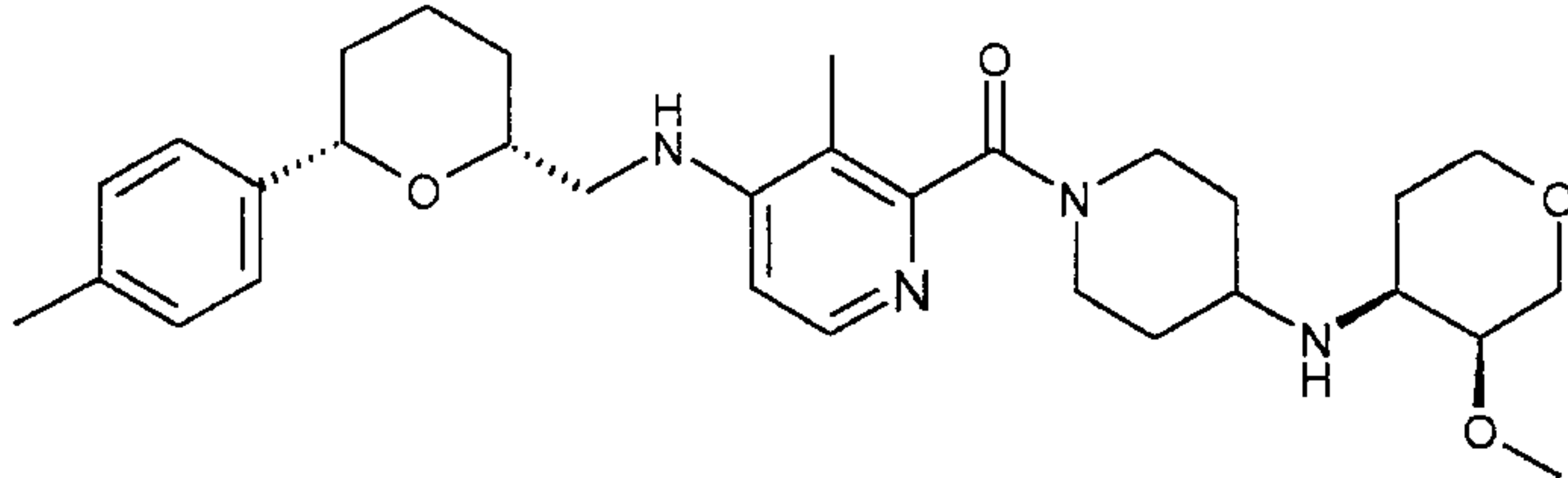
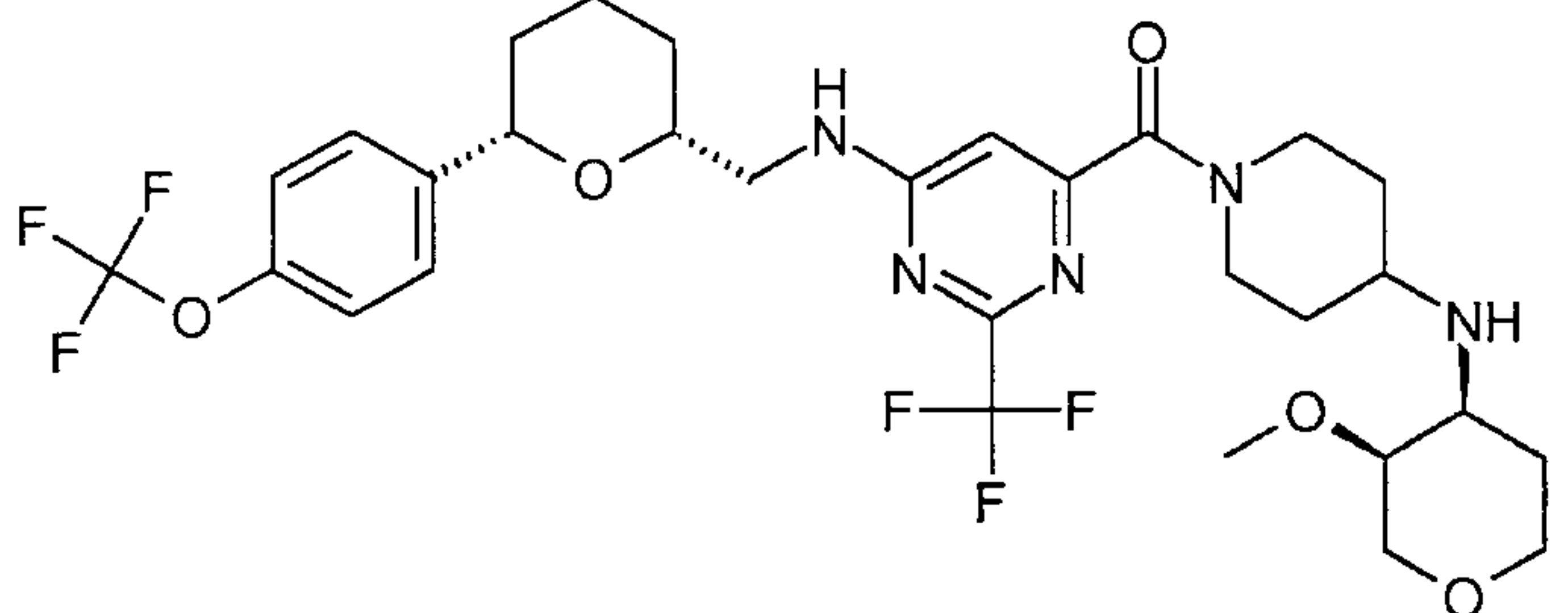
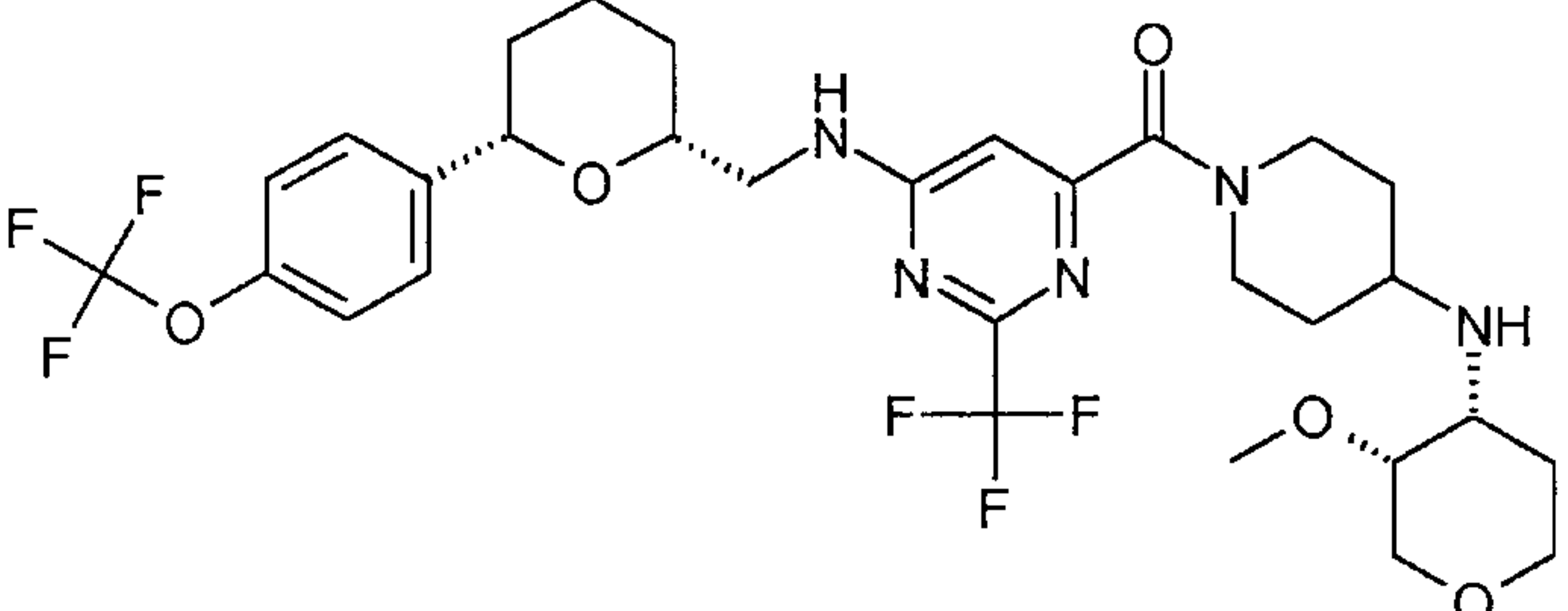
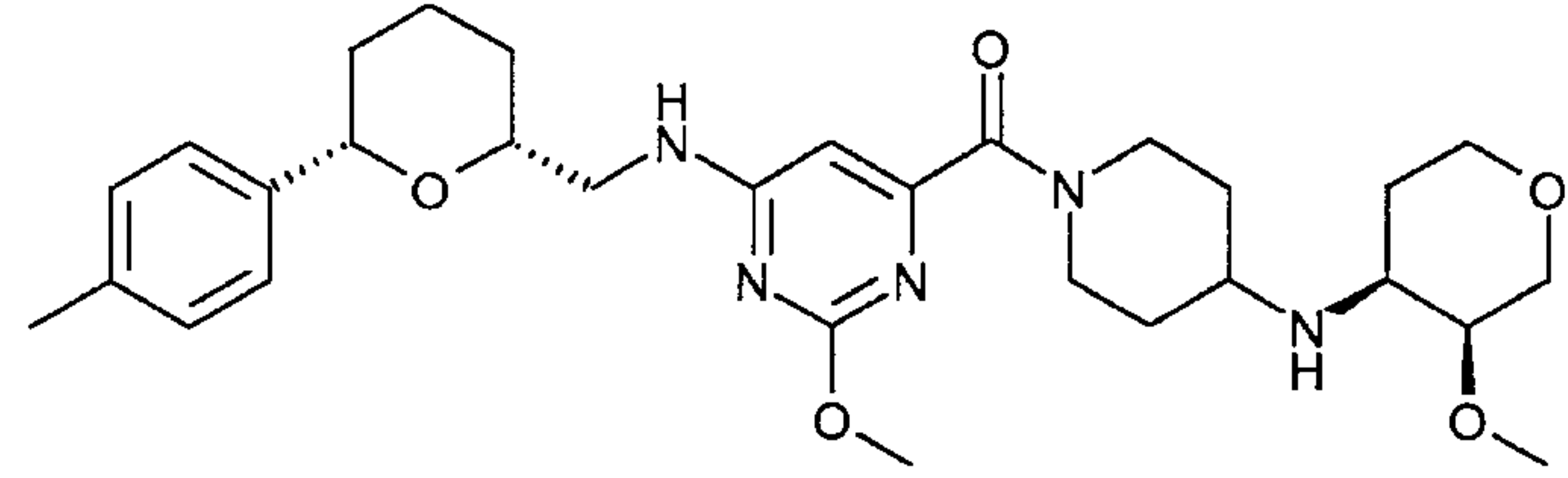
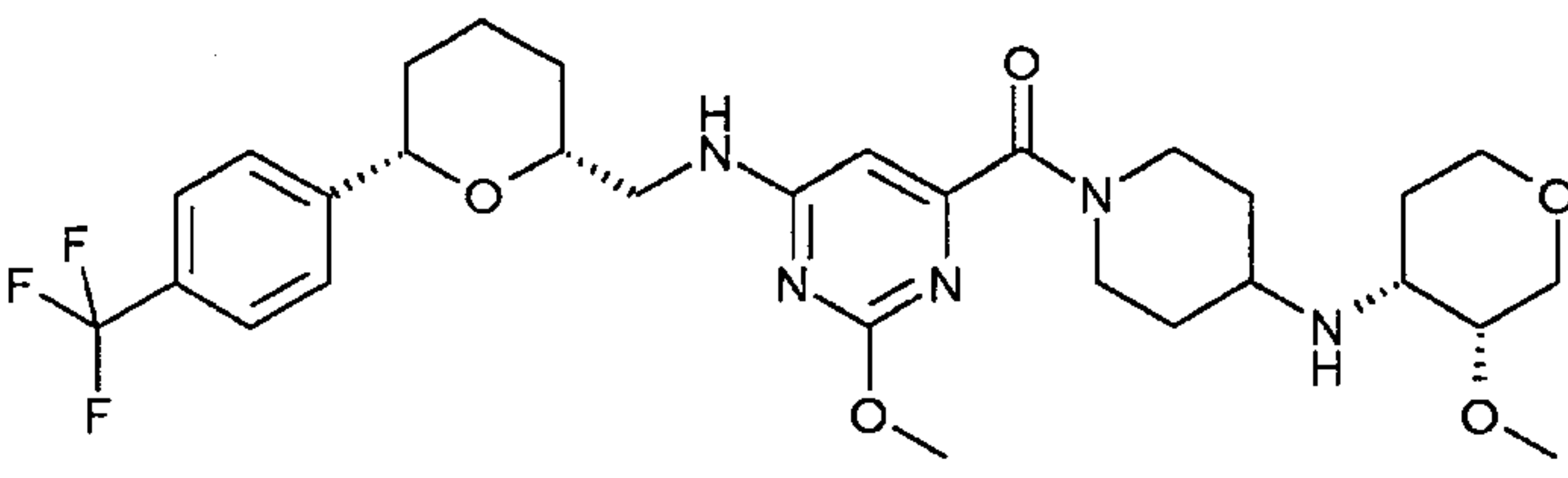
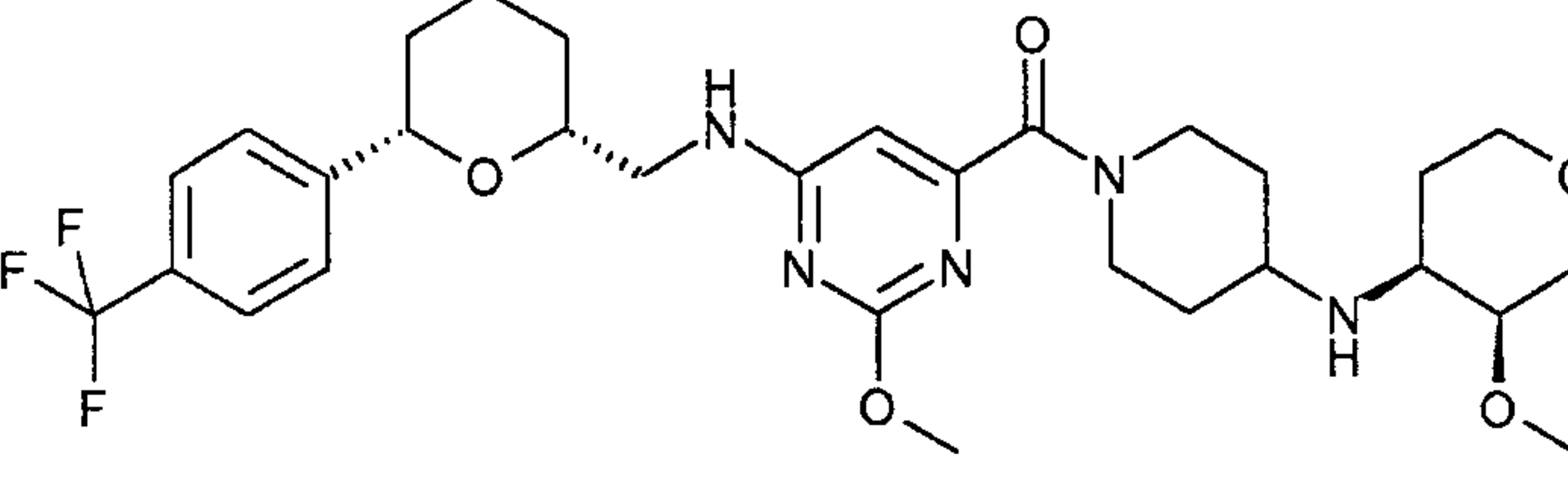
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53		28c	21b	592	9.30	1E (Hydro)
53a		28q	21c	537	10.28	1E
53b		28o	21c	607	7.59	2F
53c		28p	21b	608	7.47	2F
53d		28p	21c	608	7.59	2F
53e		28q	21b	537	10.32	1E

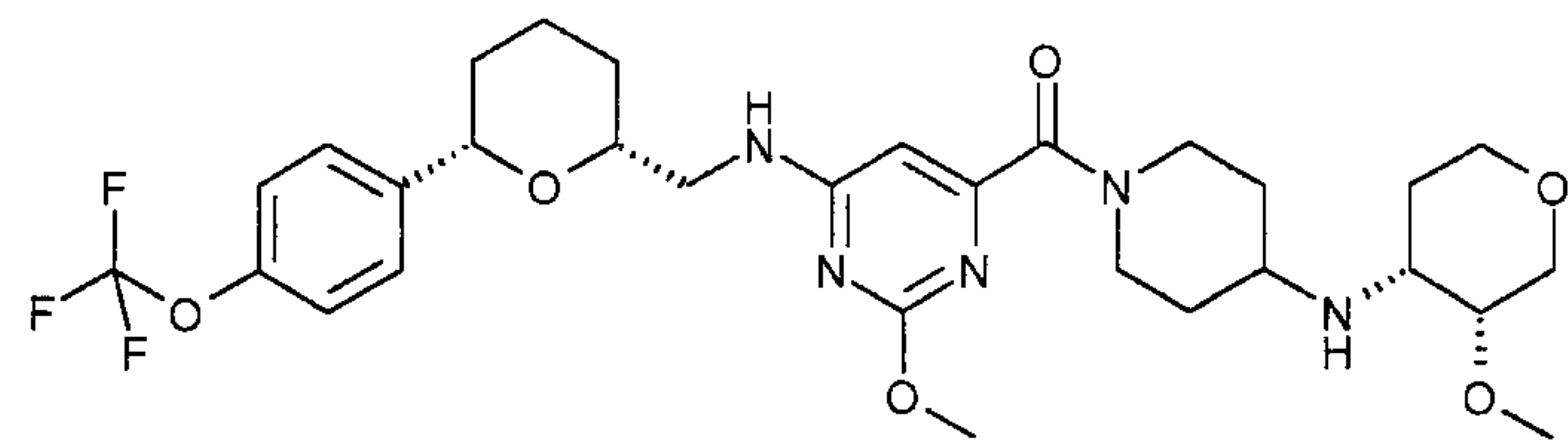
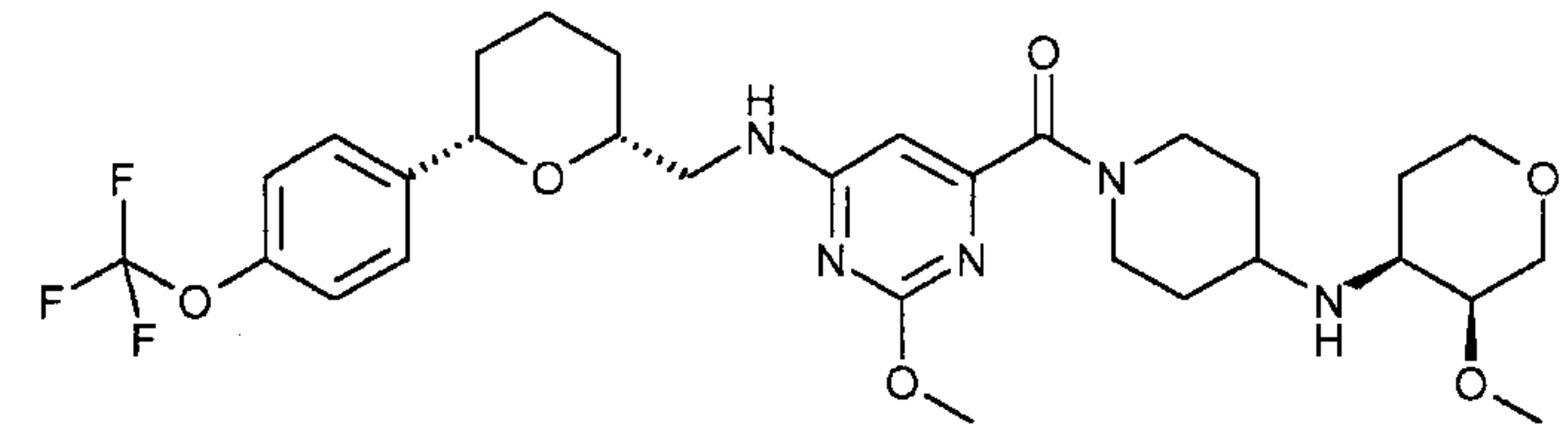
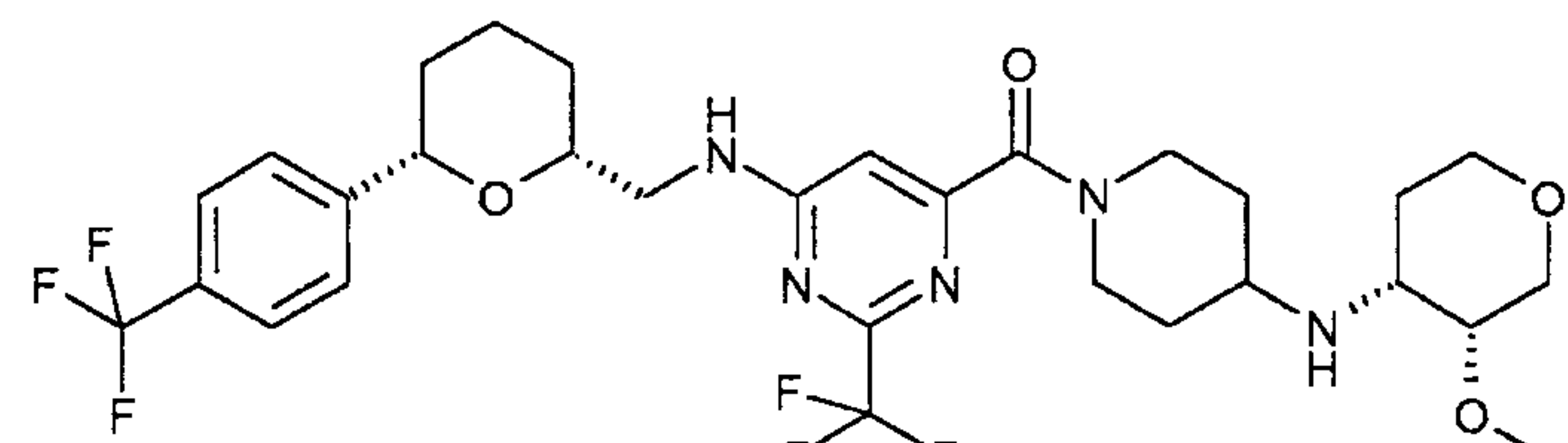
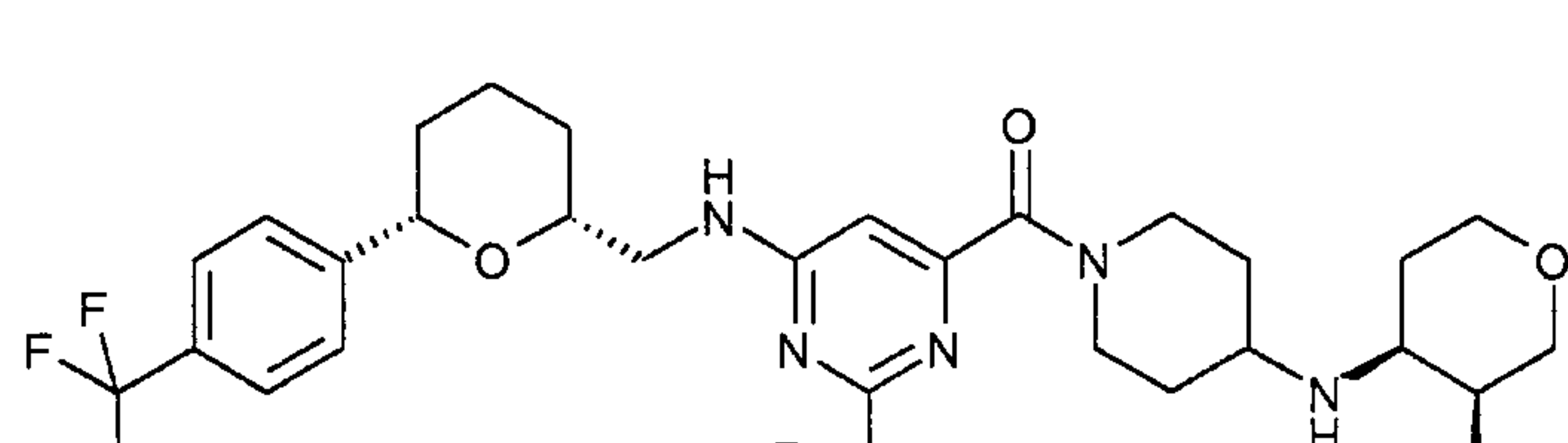
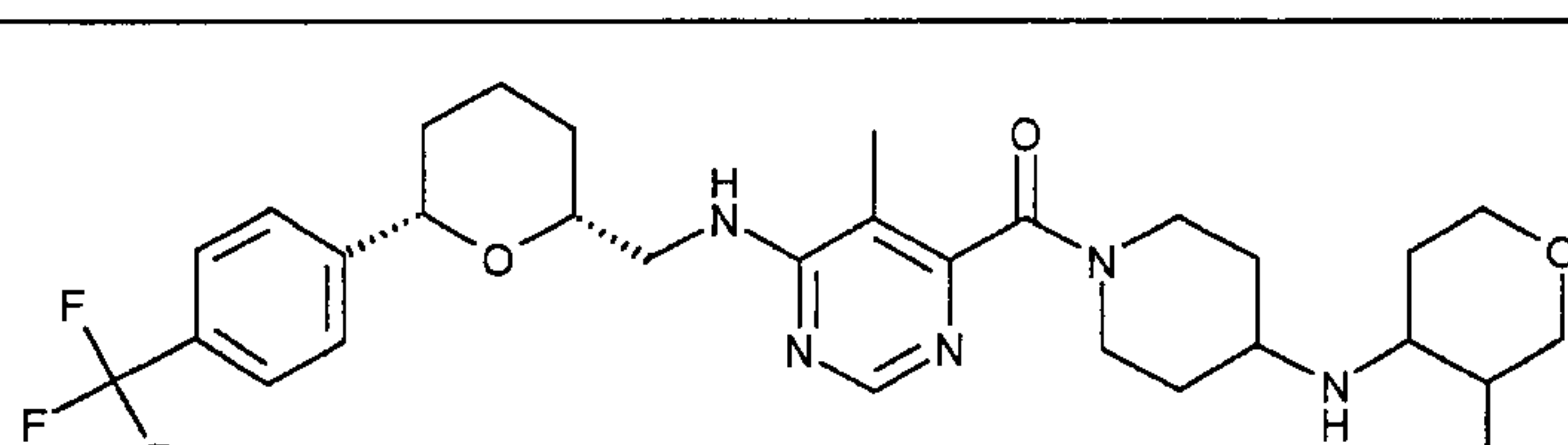
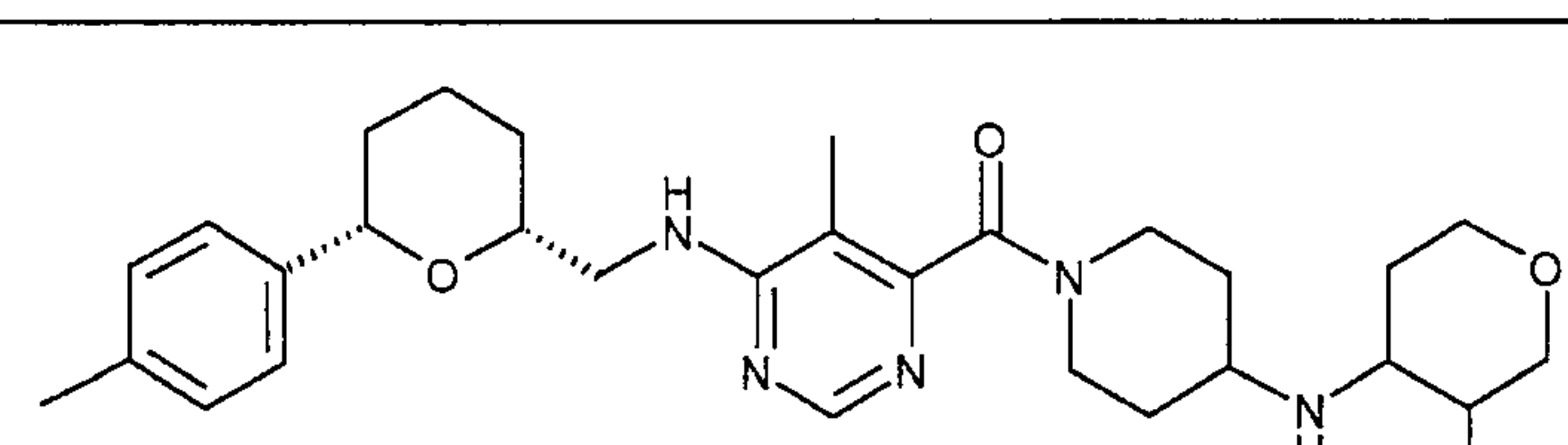
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53f		280	21b	608	7.59	2F
53g		28r	21c	523	9.18	1E (Hydro)
53h		35	21b	592	2.18	2Ha
53i		35	21c	592	2.17	2Ha
53j		36	21b	537	10.03	1E (Hydro)

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53k		36	21c	537	10.05	1E (Hydro)
53l		35a	21c	662	2.30	2Ha
53m		35a	21b	662	2.29	2Ha
53n		35c	21c	554	1.96	2Ha
53o		35d	21b	608	2.06	2Ha
53p		35d	21c	608	2.07	2Ha

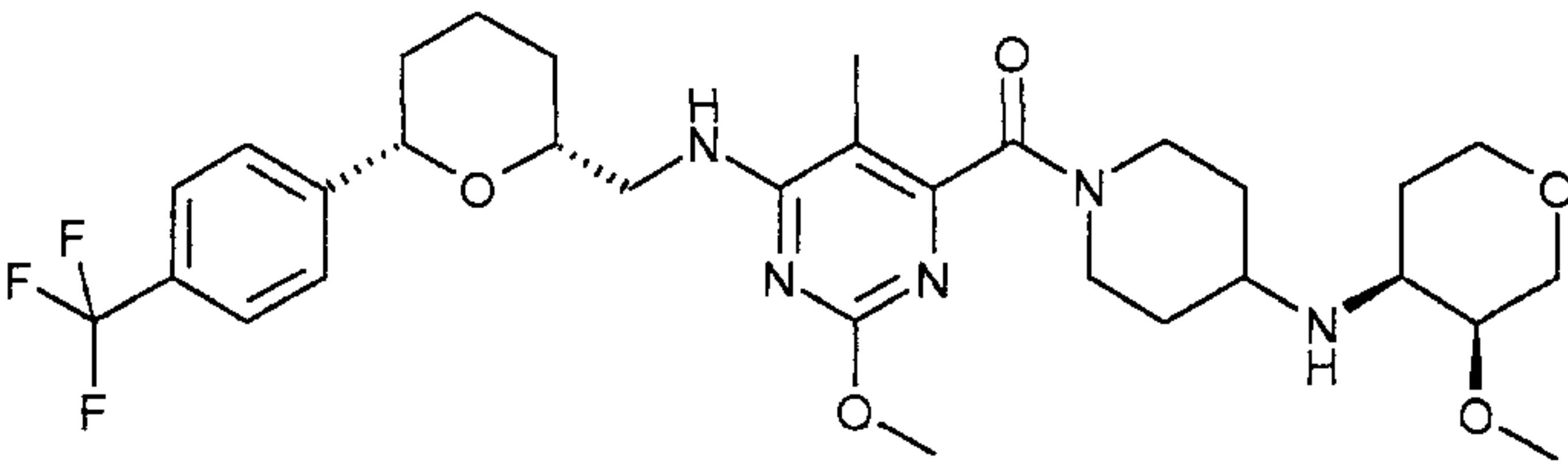
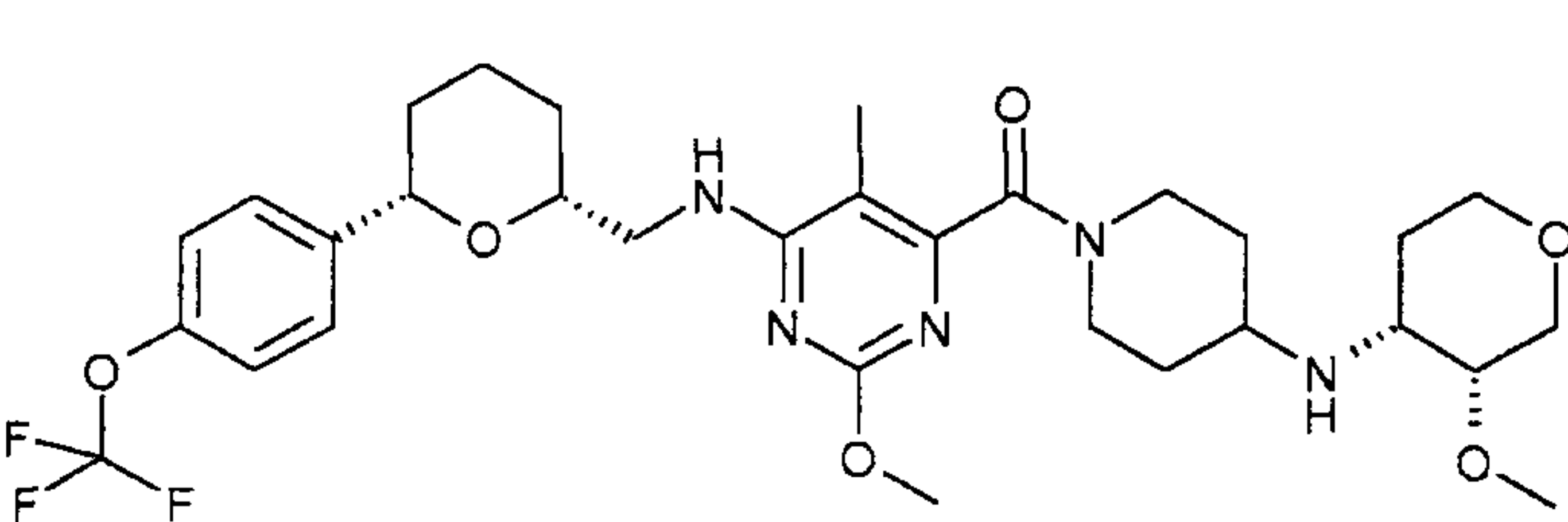
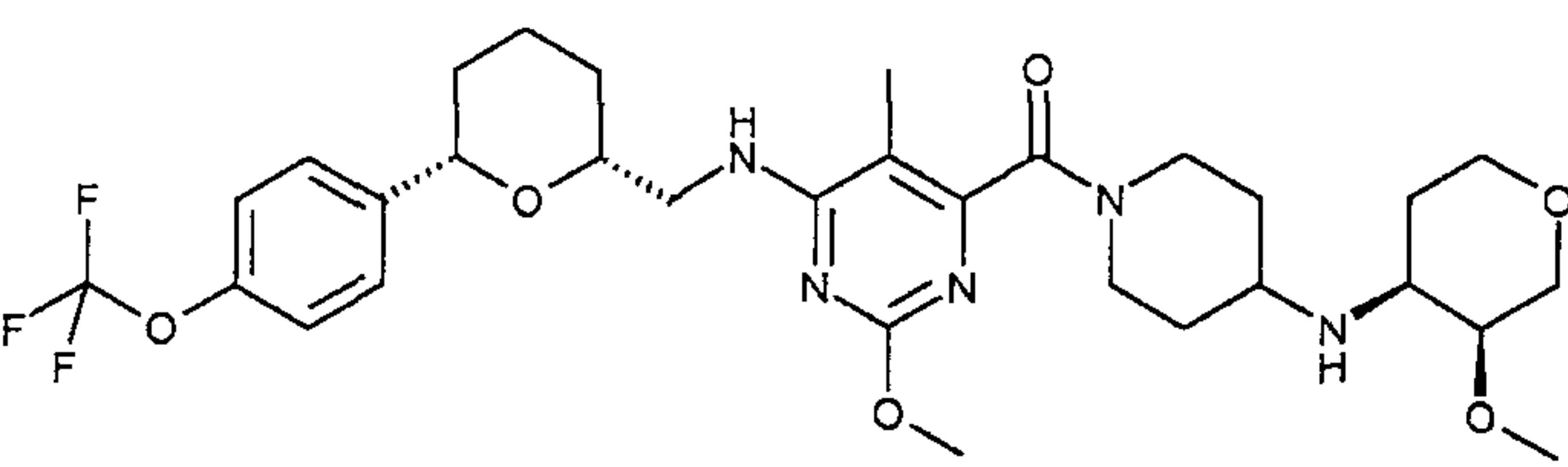
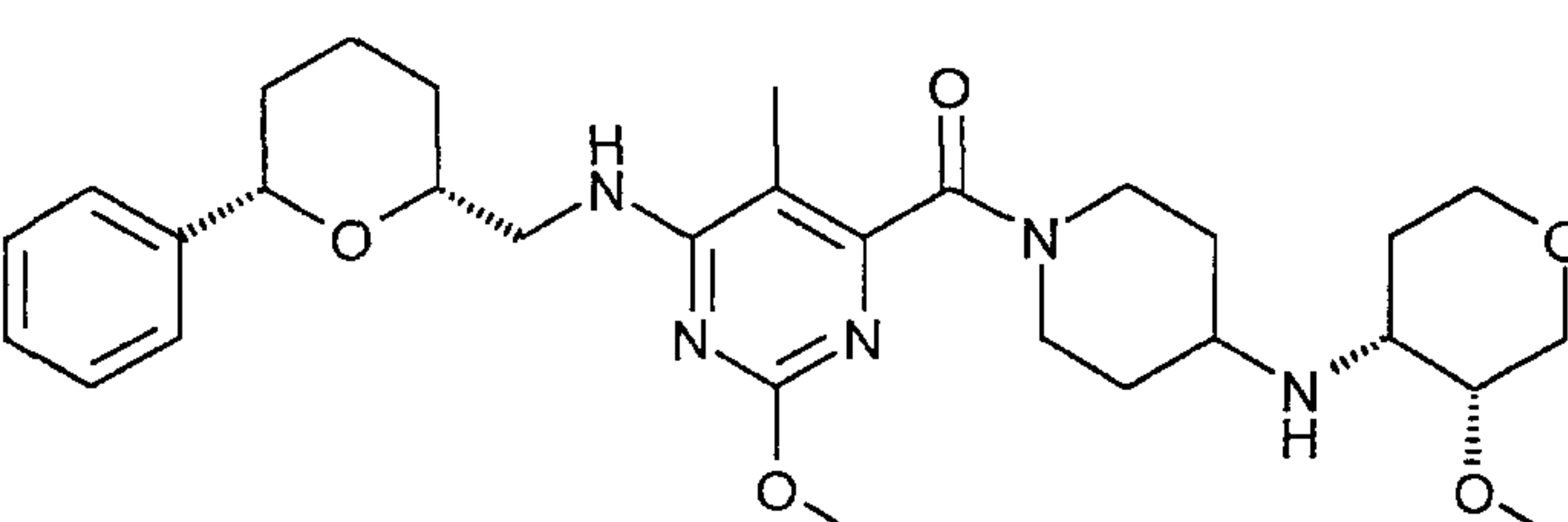
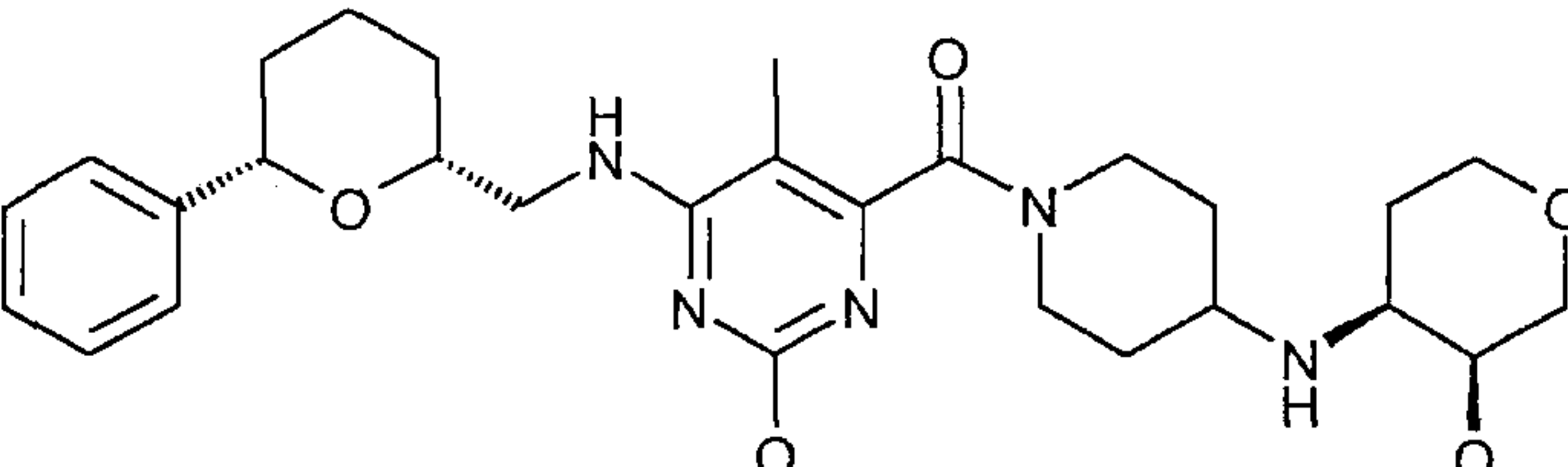
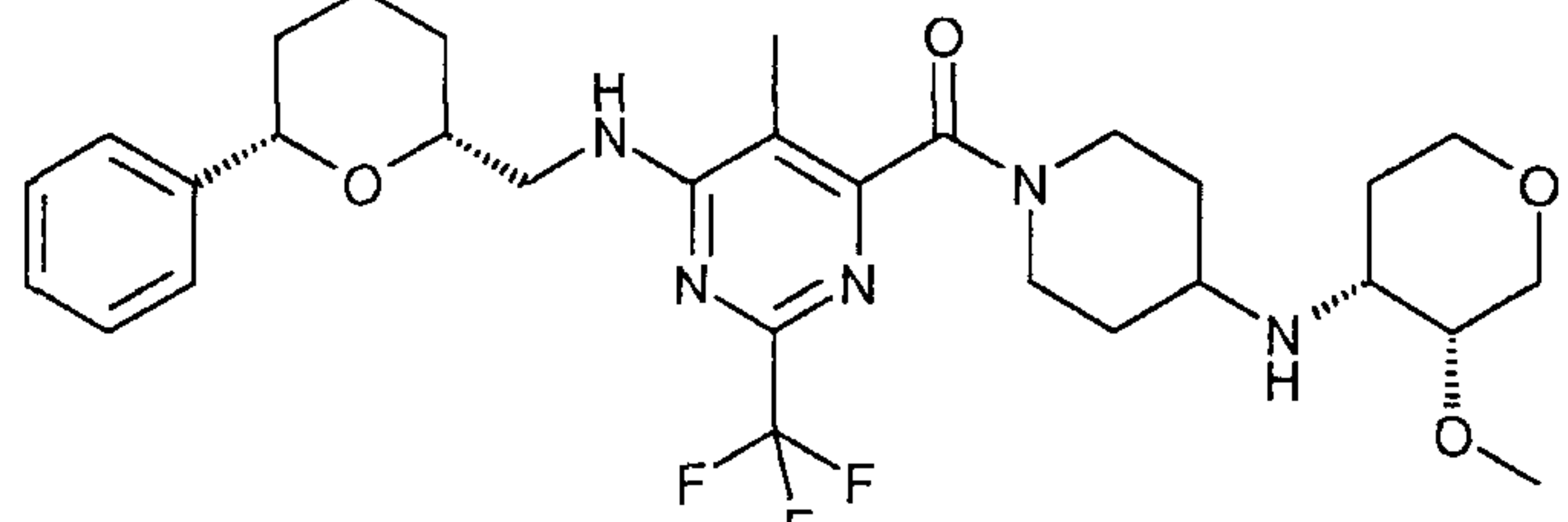
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53q		35e	21b	624	2.08	2Ha
53r		35e	21c	624	2.09	2Ha
53s		35b	21b	646	2.29	2Ha
53t		35b	21c	646	2.29	2Ha
53u		28c	21f	580	9.33	1E (Hydro)
53v		28a	21f	526	8.85	1E (Hydro)

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53w		280	21f	596	9.5	1E (Hydro)
53x		28a	21g	596	7.75	2FF
53y		28c	21g	650	8.14	2FF
53z		35f	21b	568	1.9	2Ha
53a a		35f	21c	568	1.88	2Ha
53a b		35g	21b	622	2.04	2Ha

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53a c		35g	21c	622	2.04	2Ha
53a d		35h	21b	638	2.06	2Ha
53a e		35h	21c	638	2.07	2Ha
53a f		35i	21b	554	1.77	2Ha
53a g		35i	21c	554	1.77	2Ha
53a h		35j	21b	592	2.03	2Ha

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53ai		35j	21c	592	2.03	2Ha
53a j *		-	-	596	9.52	1E (Hydro)
53a k *		-	-	596	9.53	1E (Hydro)
53al		28pa	21b	624	2.00	2Ha
53a m		28pa	21c	624	1.99	2Ha

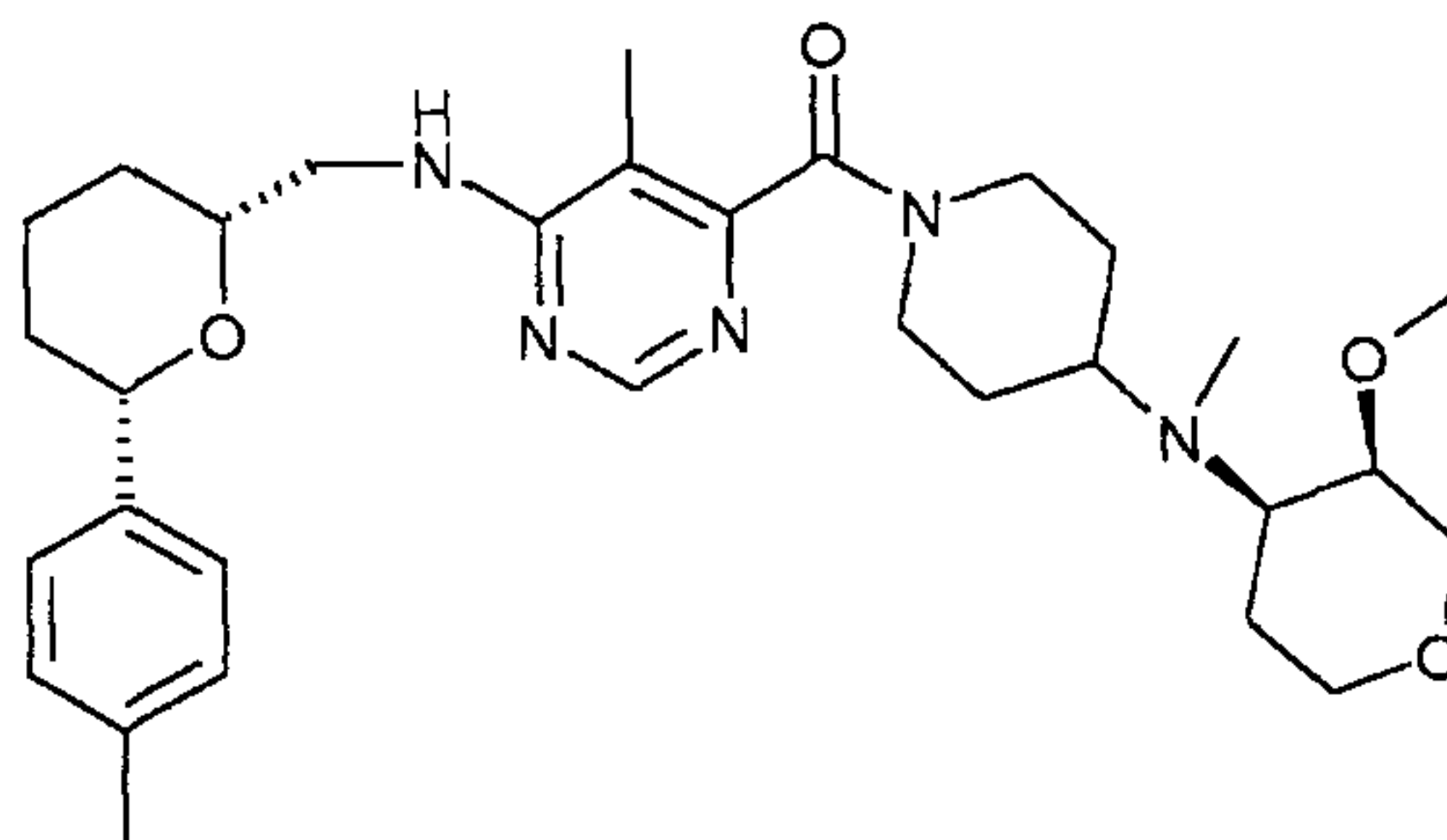
* Ex 53aj and 53ak were obtained by chiral HPLC separation of example 53w:

Ex 53aj: Chiral HPLC (method 2Ja): $R_t = 13.35$ min

Ex 53ak: Chiral HPLC (method 2Ja): $R_t = 15.28$ min

Relative stereochemistry of 3-fluoro-tetrahydro-pyran-4-ylamine assigned as cis by $^1\text{H-NMR}$.

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Example 54

Example 30 (95 mg, 0.14 mmol), formaldehyde (0.027 ml, 0.34 mmol), N,N-diisopropyl-ethylamine (0.034 ml, 0.2 mmol) and trifluoroacetic acid (0.017 ml, 0.22mmol) in 3 ml
 5 methanol were stirred at room temperature for 5 min. Sodium cyanoborohydride (43 mg, 0.68 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. 43 mg (0.08 mmol) of the desired product were obtained as solid.

HPLC (Method 1E Hydro): R_t (min) = 9.56

10 $[M+H]^+ = 552$

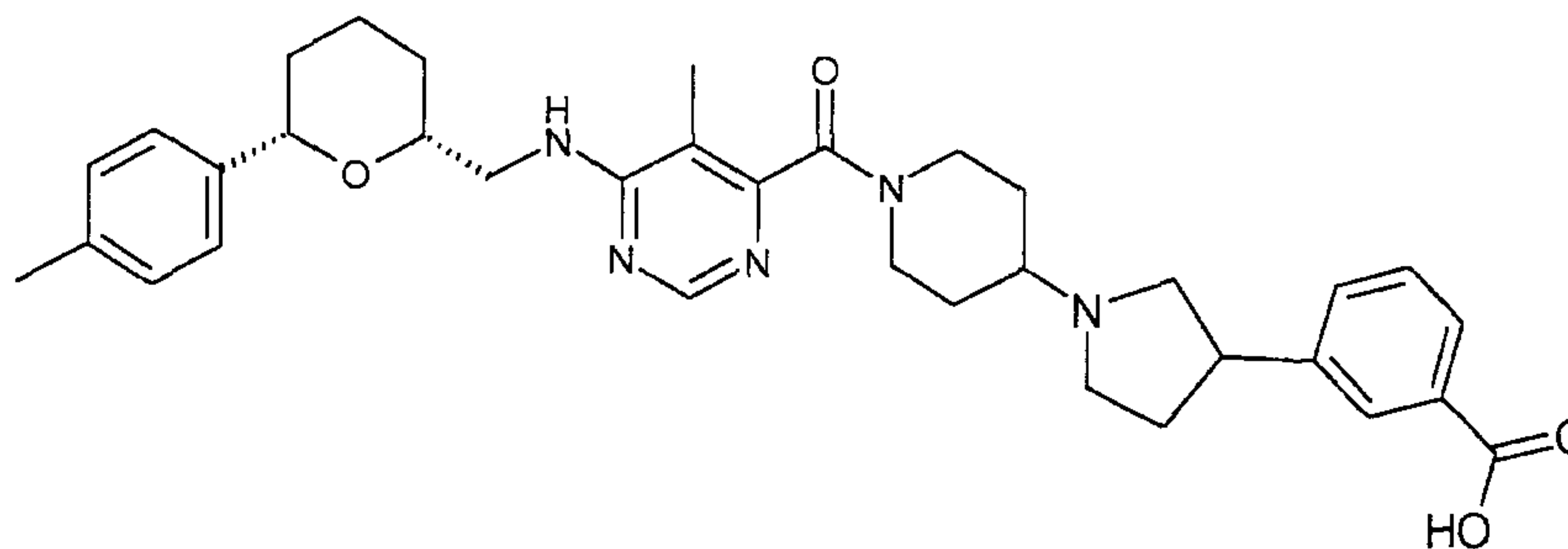
The following example was synthesized in analogy to the preparation of Example 54.

Ex #	STRUCTURE	Starting example	$[M+H]^+$	HPLC R_t (min)	Method
54a		53	606	7.53	2F

15

20

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Example 55

To a solution of commercially available 3-pyrrolidin-3-yl-benzoic acid ethyl ester (43.9 mg
 5 0.2 mmol) in 0.2 DMA, a solution of Intermediate 43 (40.7 mg, 0.1 mmol) in 0.3 ml of DMA
 and 0.08 ml of acetic acid were added. The reaction mixture was stirred at room temperature
 for 1h, then, sodium triacetoxyborohydride (25.4 mg, 0.12 mmol) was added. The reaction
 mixture was stirred at room temperature for 18h, then it was warmed at 65°C for 6h.
 0.4 ml of ethanol and 0.6 ml of an aqueous 10% sodium hydroxide solution were added and
 10 the reaction mixture was stirred at 65°C for 18h. 0.5 ml of trifluoroacetic acid were added and
 the reaction mixture was concentrated under vacuum. The mixture was purified by reverse
 preparative LC/MS. 23 mg (0.04 mmol) of the desired product were obtained.

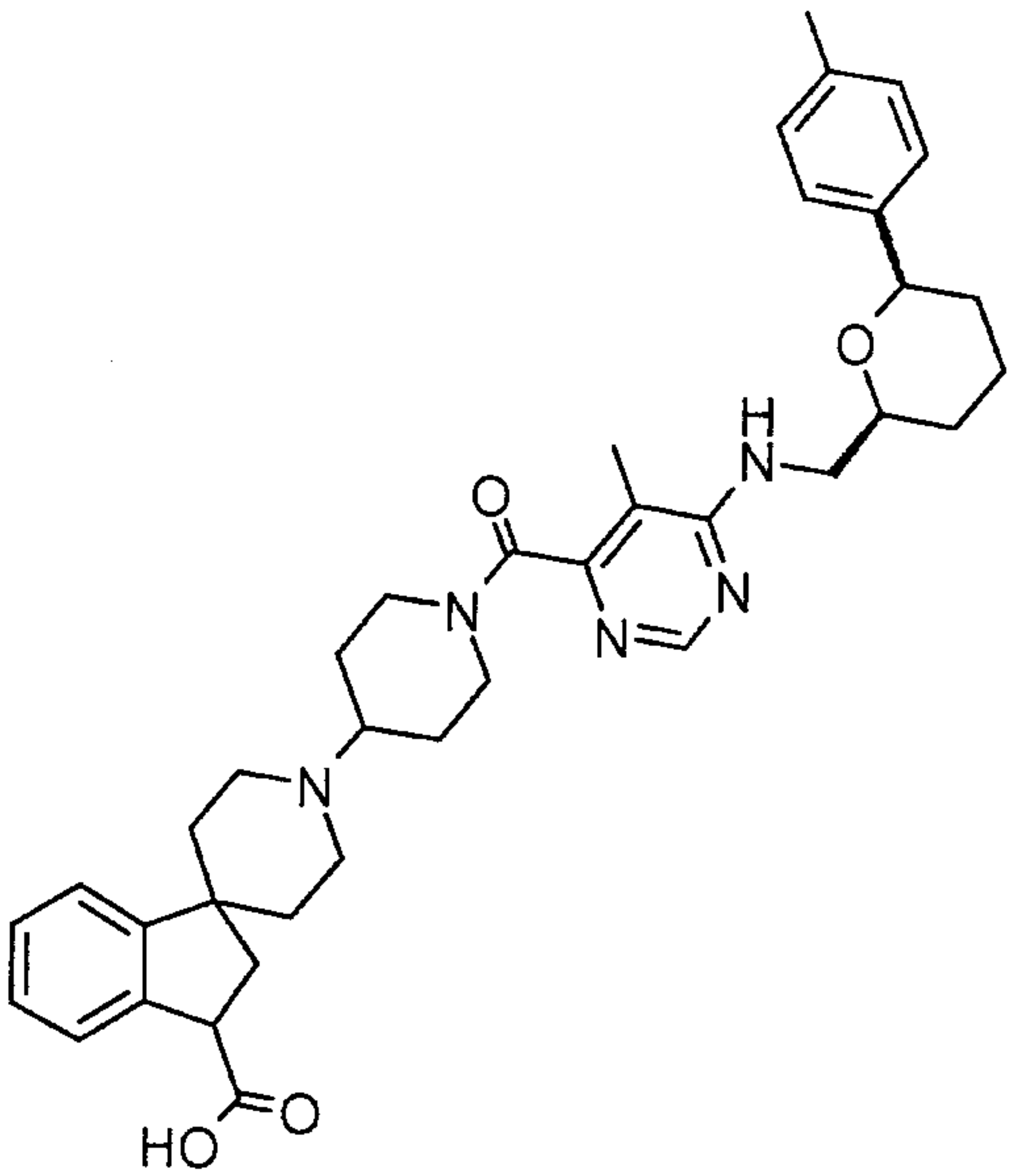
HPLC (Method 2Ga): R_t (min) = 1.34
 15 $[M+H]^+ = 598$

The following examples were synthesized in analogy to the preparation of Example 55

Ex #	STRUCTURE	Intermediate	Amino-ester	Source	$[M+H]^+$	HPLC R_t (min)	Method
56		43	3-piperidin-4-yl-benzoic acid methyl ester	Commercially available	612	1.37	2Ga

135

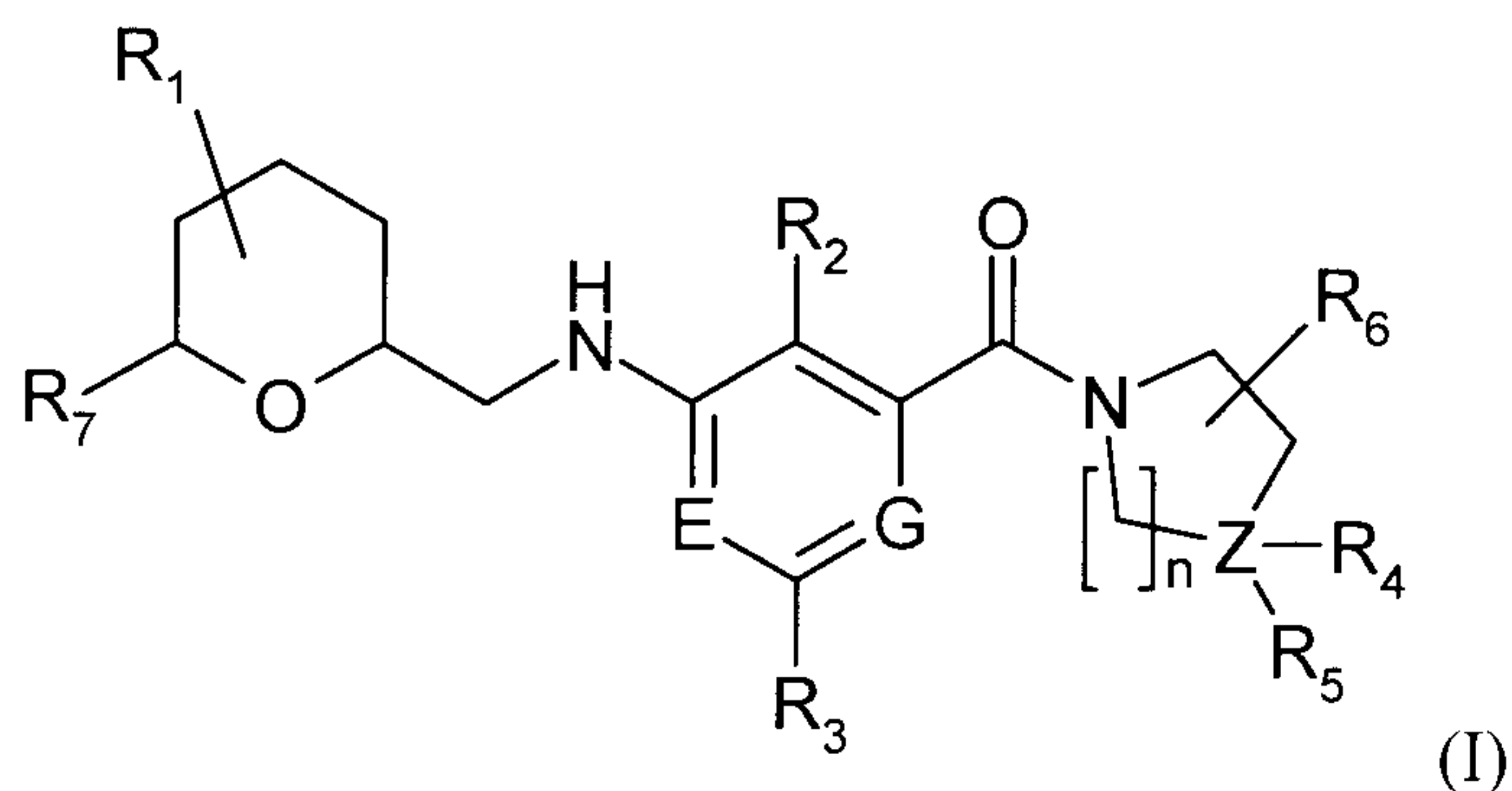
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60	
43	
2,3-dihydrospiro[indene-1,4'-piperidine]-3-carboxylic acid methyl ester	
Commercially available	
638	
1.36	
2Ga	

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CLAIMS:

1. A compound of formula (I),



wherein R_1 is a group selected from among -H, -halogen, -CN, -O- C_1 - C_4 -alkyl, - C_1 - C_4 -alkyl,
 5 -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R_7 is a ring selected from among - C_3 - C_8 -cycloalkyl, - C_3 - C_8 -heterocyclyl,
 - C_5 - C_{10} -aryl, and - C_5 - C_{10} -heteroaryl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among
 -CF₃, -O-CF₃, -S-CF₃, -CN, - C_1 - C_6 -alkyl, -C(CH₃)₂-CN, and -halogen,

10 or wherein the ring R_7 is optionally substituted with one or more groups selected from among
 - C_1 - C_6 -alkyl, -O- C_1 - C_6 -alkyl, - C_5 - C_{10} -aryl, - C_5 - C_{10} -heteroaryl, - C_3 - C_8 -cycloalkyl,
 - C_3 - C_8 -heterocyclyl, - C_2 - C_6 -alkenyl, and - C_2 - C_6 -alkynyl, optionally being substituted by one
 or more groups selected from among -OH, -NH₂, - C_1 - C_3 -alkyl, -O- C_1 - C_6 -alkyl, -CN, -CF₃,
 -OCF₃, halogen, -methyl, and =O,

15 or wherein the ring R_7 is optionally further bi-valently substituted on two neighbouring ring
 atoms, such that an annellated ring is formed by one or more groups selected from among
 - C_1 - C_6 -alkylene, - C_2 - C_6 -alkenylene and - C_4 - C_6 -alkynylene, in which one or two or three
 carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and
 S, the bivalent group being optionally substituted by one or more groups selected from -OH,
 20 -NH₂, - C_1 - C_3 -alkyl, -O- C_1 - C_6 -alkyl, -CN, -CF₃, -OCF₃, halogen, and =O;

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wherein R_2 is selected from among -H, -halogen, -CN, -O-C₂-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R_3 is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

5 wherein n is 1, 2 or 3;

wherein G and E are independently selected from among C-H or N;

wherein Z is C,

and R_4 and R_5 are independently selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R_8, R_8'), with

10 R_8 and R_8' independently being selected from among -H, and -C₁-C₆-alkyl,

or wherein Z is N,

and R_4 denotes an electron pair and R_5 is selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R_8, R_8'), with R_8 and R_8' independently being selected from among -H, and -C₁-C₆-alkyl,

15 and wherein R_4 if different from an electron pair or -H and R_5 if different from -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R_9, R_9'), -C₀-C₄-alkylene-N(R_{10})-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R_{10})-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R_{10})-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R_{10})-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R_{10})-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R_{11}, R_{11}'), -C₀-C₄-alkylene-N(R_{12})-Q-N(R_{13}, R_{13}'), -C₀-C₄-alkylene- R_{14} , -C₀-C₄-alkylene(R_{20}, R_{20}'),
20 -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q

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-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),

wherein Q is selected from among -C(O)-, and -SO₂-,

wherein R₁₀, R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and

5 -C₃-C₆-cycloalkyl,

wherein R₉, R_{9'}, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a -C₂-C₆-alkylene group,

10 wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,

and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and

15 -SO₂-C₁-C₄-alkyl,

wherein R₂₀ and R_{20'} together form a spiro-C₃-C₈-carbocycle or spiro-C₃-C₈-heterocycle comprising one or more group selected from O in the ring, and wherein said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene and wherein said

20 spirocycle is optionally further substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen,

or wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(C₁-C₄-alkyl)-, and a bond,

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wherein R_{18} is selected from among $-C_5-C_{10}$ -aryl, $-C_5-C_{10}$ -heteroaryl, $-C_3-C_8$ -cycloalkyl, and $-C_3-C_8$ -heterocyclyl,

wherein R_{18} is optionally substituted by one or more groups selected from among halogen, $-CF_3$, $-OCF_3$, $-CN$, $-OH$, $-O-C_1-C_4$ -alkyl, $-C_1-C_6$ -alkyl, $-NH-C(O)-C_1-C_6$ -alkyl, $-N(C_1-C_4$ -
 5 alkyl)- $C(O)-C_1-C_6$ -alkyl, $-C(O)-C_1-C_6$ -alkyl, $-S(O)_2-C_1-C_6$ -alkyl, $-NH-S(O)_2-C_1-C_6$ -alkyl, $-N(C_1-C_4$ -alkyl)- $S(O)_2-C_1-C_6$ -alkyl, and $-C(O)-O-C_1-C_6$ -alkyl,

and wherein R_5 and R_{18} are optionally further substituted by spiro- C_3-C_8 -cycloalkyl or spiro- C_3-C_8 -heterocyclyl such that together with R_4 , R_5 and/or R_{18} a spirocycle is formed, wherein
 10 said spiro- C_3-C_8 -heterocyclyl optionally comprises one or more groups selected from among nitrogen, $-C(O)-$, $-SO_2-$, and $-N(SO_2-C_1-C_4$ -alkyl)- in the ring,

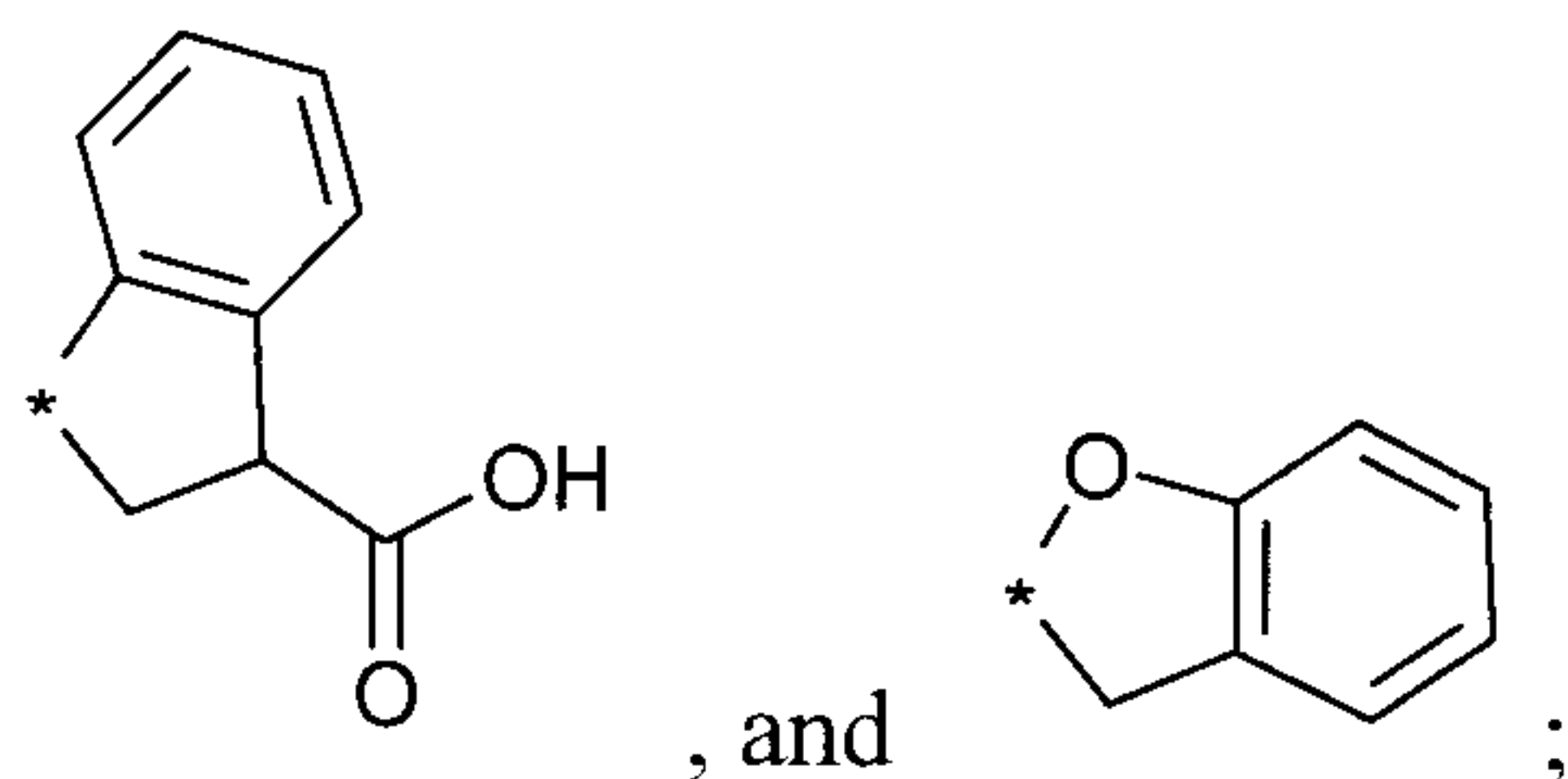
or wherein R_5 and R_{18} are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among $-C_1-C_6$ -alkylene, $-C_2-C_6$ -alkenylene, and $-C_4-C_6$ -alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be
 15 substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among $-OH$, $-NH_2$, $-C_1-C_3$ -alkyl, $-O-C_1-C_6$ -alkyl, $-CN$, $-CF_3$, $-OCF_3$, and halogen,

or wherein Z is C,

and R_4 and R_5 are independently selected from among $-H$, $-C_1-C_6$ -alkyl, and $-N(R_{19}, R_{19'})$,
 20 wherein R_{19} and $R_{19'}$ together form a $-C_2-C_6$ -alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among $-F$, $-CF_3$, $-OCF_3$, $-CN$, $-OH$, $-O-CH_3$, $-CH_3$, $-NH-C(O)-CH_3$, $-N(CH_3)-C(O)-CH_3$, $-C(O)-CH_3$, $-S(O)_2-CH_3$, $-NH-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_3$, $-N(CH_3)-S(O)_2-CH_2-CH_3$, $-(C_6$ -aryl)- $COOH$, $-C(O)-O-C_2H_5$,

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wherein R_6 is selected from among -H, -C₁-C₄-alkyl, -OH, -O-C₁-C₄-alkyl, -halogen, -CN, -CF₃, and -OCF₃;

as well as in form of their acid addition salts with pharmacologically acceptable acids.

5 2. The compound according to claim 1 or a pharmacologically acceptable acid addition salt thereof, wherein R_7 is selected from among -C₅-C₆-aryl, -C₅-C₆-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -methyl, -C(CH₃)₂-CN, and -halogen.

10 3. The compound according to claim 1 or a pharmacologically acceptable acid addition salt thereof, wherein R_7 is selected from among -C₅-C₆-aryl, and -C₅-C₆-heteroaryl, wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -methyl, -F, -Cl, -C(CH₃)₂-CN, and -Br.

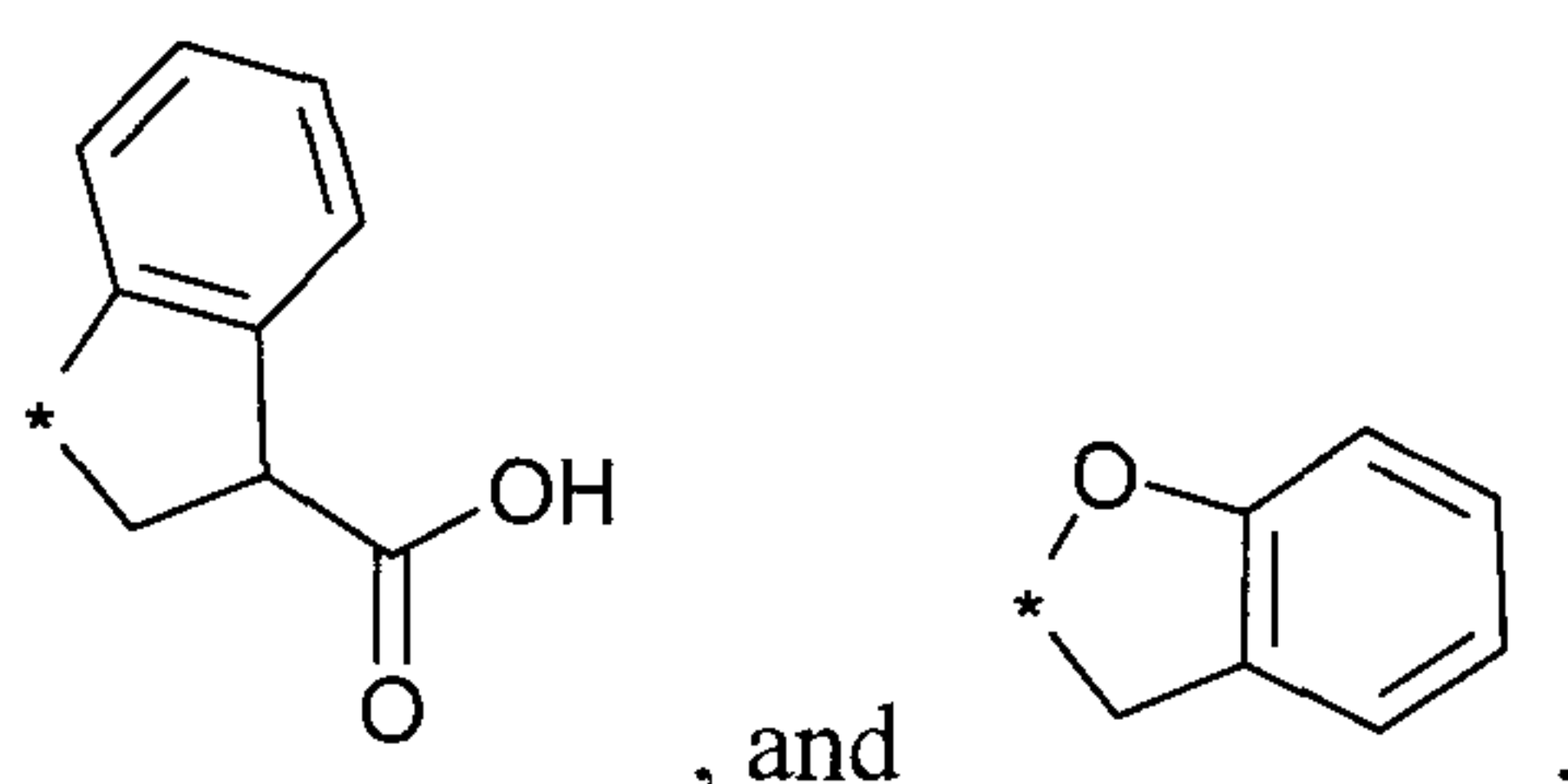
4. The compound according to claim 1, 2, or 3 or a pharmacologically acceptable
15 acid addition salt thereof,

wherein Z is C,

and R_4 and R_5 are independently selected from among -H, -C₁-C₆-alkyl, and -N(R_{19} , R_{19}), wherein R_{19} and R_{19} together form a -C₄-C₅-alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among
20 -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, -(C₆-aryl)-COOH, -C(O)-O-C₂H₅,

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5. The compound according to claim 1, 2, or 3 or a pharmacologically acceptable acid addition salt thereof,

wherein Z is C,

5 and R₄ and R₅ are independently selected from among -H, -i-propyl, -amino, -pyrrolidinyl, -piperidinyl, -morpholinyl, -azepanyl, -oxazepanyl, -piperazinyl, -azetidiny, -tetrahydropyranyl, -cyclopentyl, -cyclohexyl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H and -C₁-C₆-alkyl,

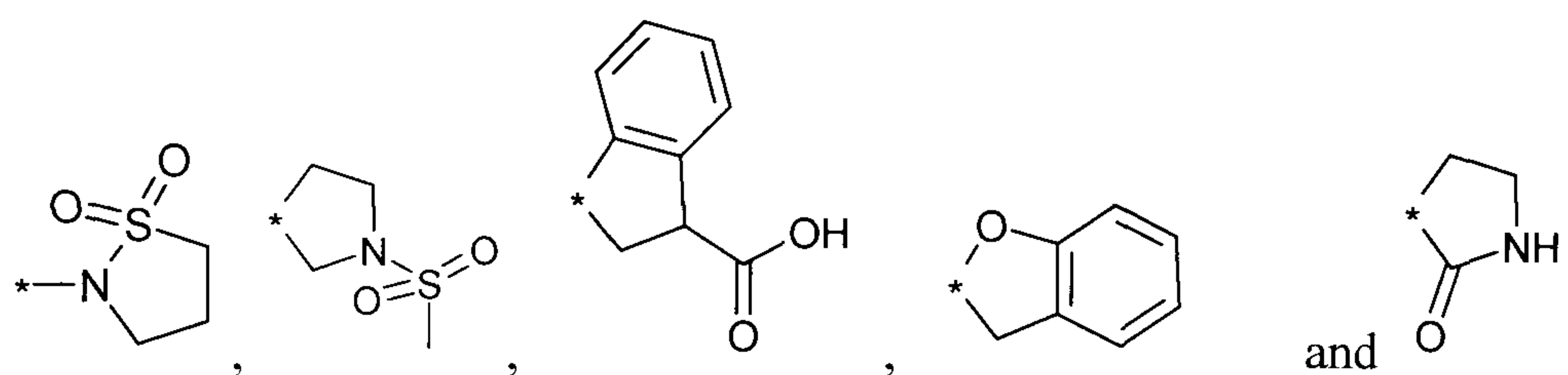
wherein R₄ and R₅ if different from -H are optionally independently substituted with one or

10 more groups selected from among -fluoro, -methyl, -ethyl, propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -hydroxy, -CF₃, -OCF₃, -CN, -O-CH₃, -O-C₂H₅, -O-C₃H₇, -CH₂-CN, -CH₂-O-CH₃, -(CH₂)₂-O-CH₃, -C(O)-CH₃, -C(O)-C₂H₅, -C(O)-C₃H₇, -COOH, -C(O)-NH₂, -C(O)-NH-CH₃, -C(O)-N(CH₃)₂, -NH-C(O)-CH₃, -N(CH₃)C(O)-CH₃, -NH-C(O)-C₂H₅, -N(CH₃)-C(O)-C₂H₅, -NH-C(O)-C₃H₇, -N(CH₃)-C(O)-C₃H₇, -NH-SO₂-CH₃, -N(CH₃)-SO₂-CH₃, -N(C₂H₅)-SO₂-CH₃, -N(C₃H₇)-SO₂-CH₃, -NH-SO₂-C₂H₅, -N(CH₃)-SO₂-C₂H₅, -N(C₂H₅)-SO₂-C₂H₅, -N(C₃H₇)-SO₂-C₂H₅, -NH-SO₂-C₃H₇, -N(CH₃)-SO₂-C₃H₇, -N(C₂H₅)-SO₂-C₃H₇, -N(C₃H₇)-SO₂-C₃H₇, -NH-SO₂-C₃H₅, -N(CH₃)-SO₂-C₃H₅, -N(C₂H₅)-SO₂-C₃H₅, -N(C₃H₇)-SO₂-C₂H₅, -CH₂-NH-SO₂-CH₃, -CH₂-N(CH₃)-SO₂-CH₃, -CH₂-NH-SO₂-C₂H₅, -CH₂-N(CH₃)-SO₂-C₂H₅, -CH₂-NH-SO₂-C₃H₇, -CH₂-N(CH₃)-SO₂-C₃H₇, -CH₂-NH-SO₂-C₃H₅, -CH₂-N(CH₃)-SO₂-C₃H₅, -NH-C(O)-NH₂, -N(CH₃)-C(O)-NH₂, -NH-C(O)-NH-CH₃, -N(CH₃)-C(O)-NH-CH₃, -NH-C(O)-N(CH₃)₂, -N(CH₃)-C(O)-N(CH₃)₂, -SO₂-NH₂, -SO₂-NH(CH₃), -SO₂-N(CH₃)₂, -C(O)-NH-C₂H₅, -C(O)-N(CH₃)-C₂H₅, -C(O)-N(CH₃)-C₃H₇, -C(O)-N(CH₃)-C₄H₉, -C(O)-NH-CH(CH₃)-C₂H₅, -C(O)-N(CH₃)-CH(CH₃)-C₂H₅, -CH₂-C(O)-NH₂, -CH₂-C(O)-NH-CH₃, -CH₂-C(O)-N(CH₃)₂, -N(CH₃)-SO₂-N(CH₃)₂, -(C₆-aryl)-COOH, -phenyl, -pyridin-4-yl,

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-CH₂-3-methyl-oxetan-3-yl, -O-1,2-difluoro-phen-5-yl, -O-pyridin-2-yl, -pyrrolidine-2-one-1-yl, -3,5-dimethyl-[1,2,4]triazol-4-yl, 3-methyl-[1,2,4]oxadiazol-5-yl,



or wherein Z is C,

5 and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(CH₃)-, and -N(C₂H₅)-,

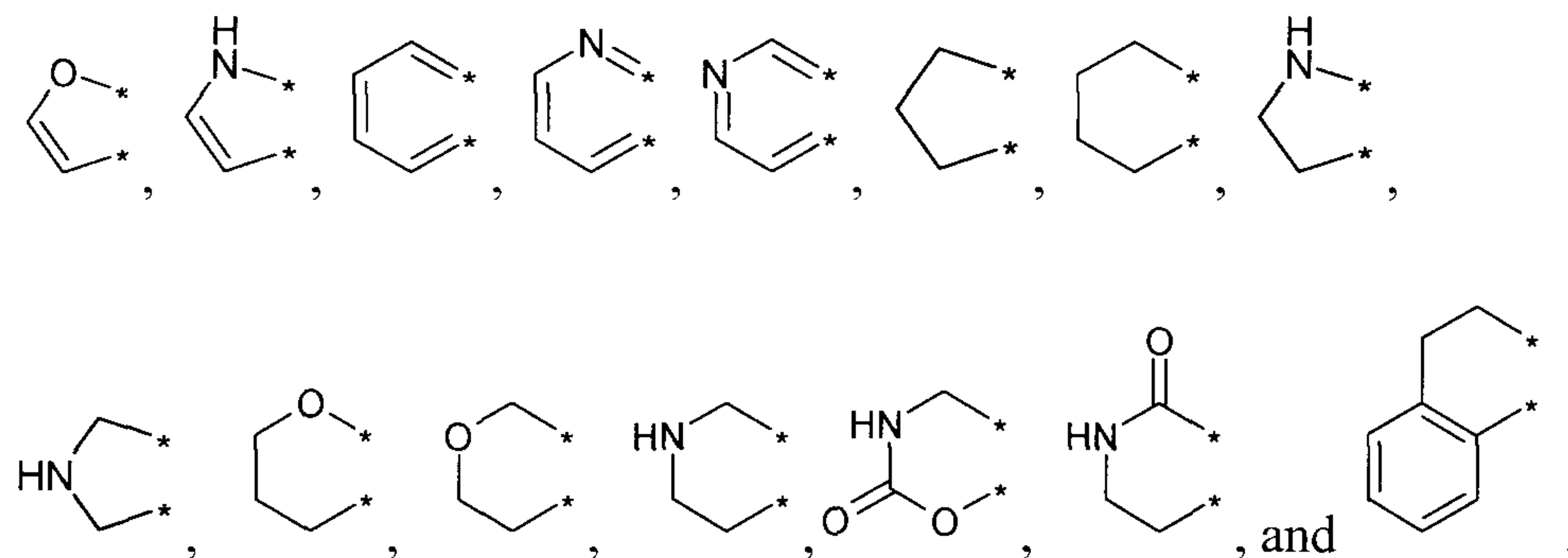
and wherein R₁₈ is selected from among -tetrahydropyranyl, -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -pyrrolidinyl, -piperidinyl, -piperazinyl, -morpholinyl, -chromanyl, -octahydro-pyrano-pyrrolyl, -octahydro-pyrano-pyridinyl,

10 -octahydro-pyrano-oxazinyl, -oxaspirodecanyl, and -tetrahydro-naphthyridinyl,

wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-C₂H₅,

and wherein R₄, R₅ and R₁₈ are optionally further bi-valently substituted by one or more

15 groups selected from among



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on one ring atom or on two neighboring ring atoms, such that spirocyclic or annellated rings are formed.

6. The compound according to claim 1, 2, or 3 or a pharmacologically acceptable acid addition salt thereof,

5 wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(CH₃)-, -N(C₂H₅)-, and a bond,

and wherein R₁₈ is selected from among -C₆-heterocyclyl comprising 1 or 2 hetero atoms selected from among N, and O,

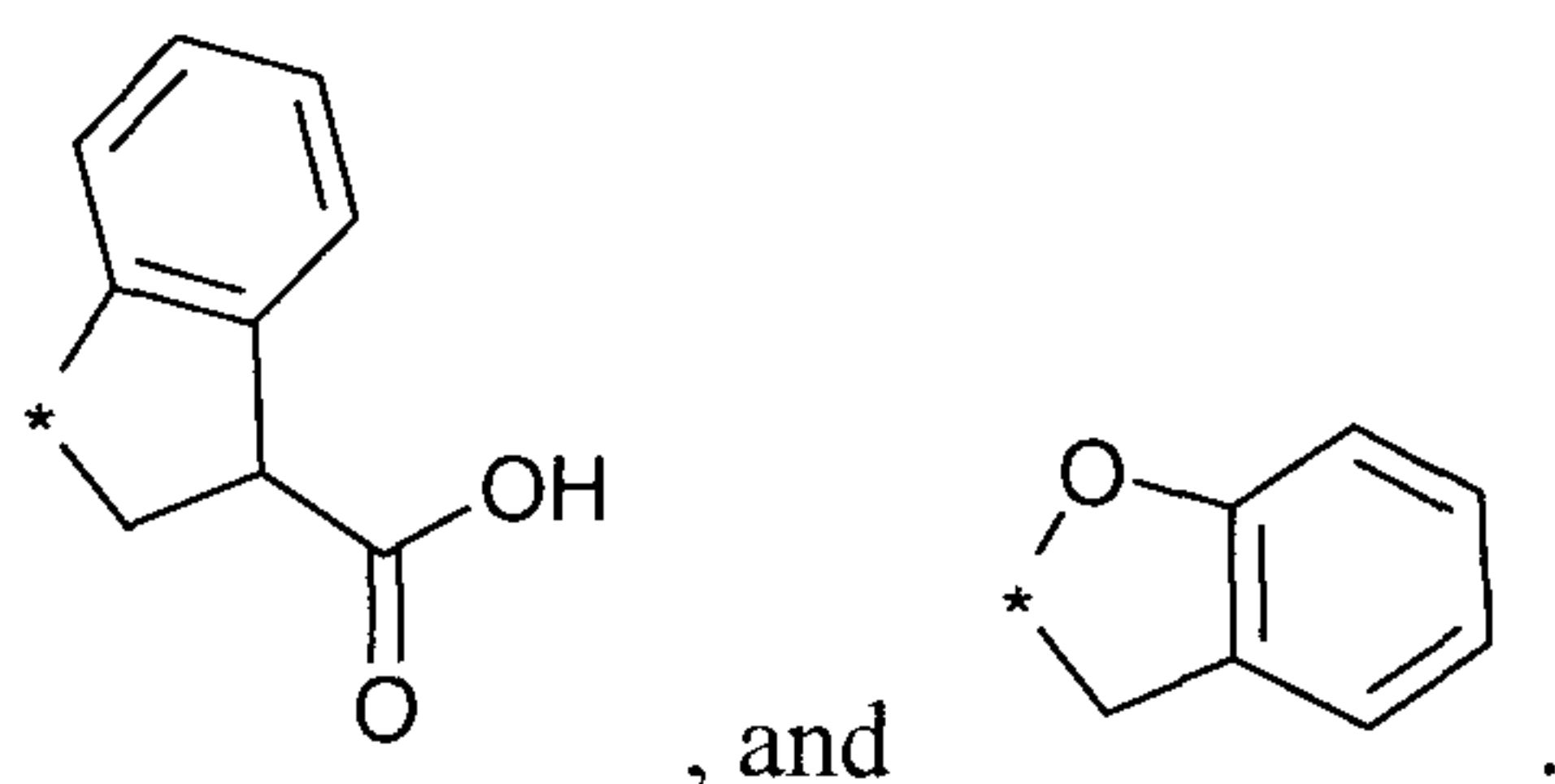
10 and wherein R₁₈ is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, and -C(O)-O-C₂H₅,

or wherein Z is C,

15 and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R₁₉'), wherein R₁₉ and R₁₉' together form a -C₂-C₆-alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃,

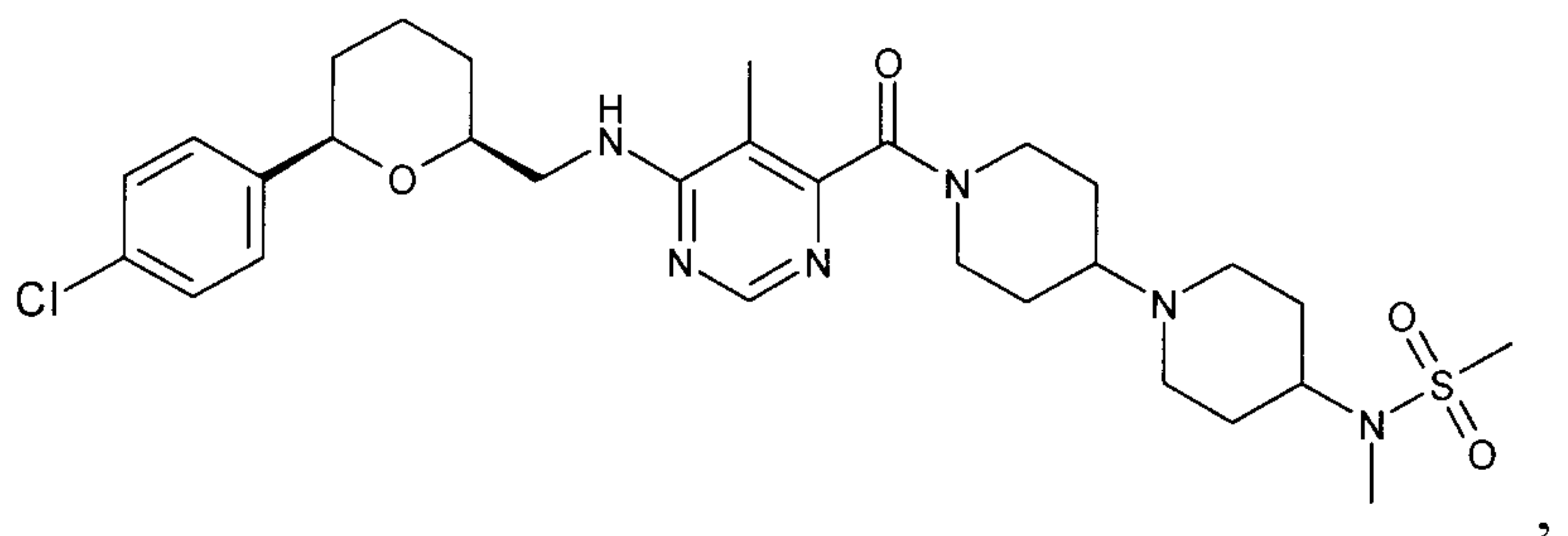
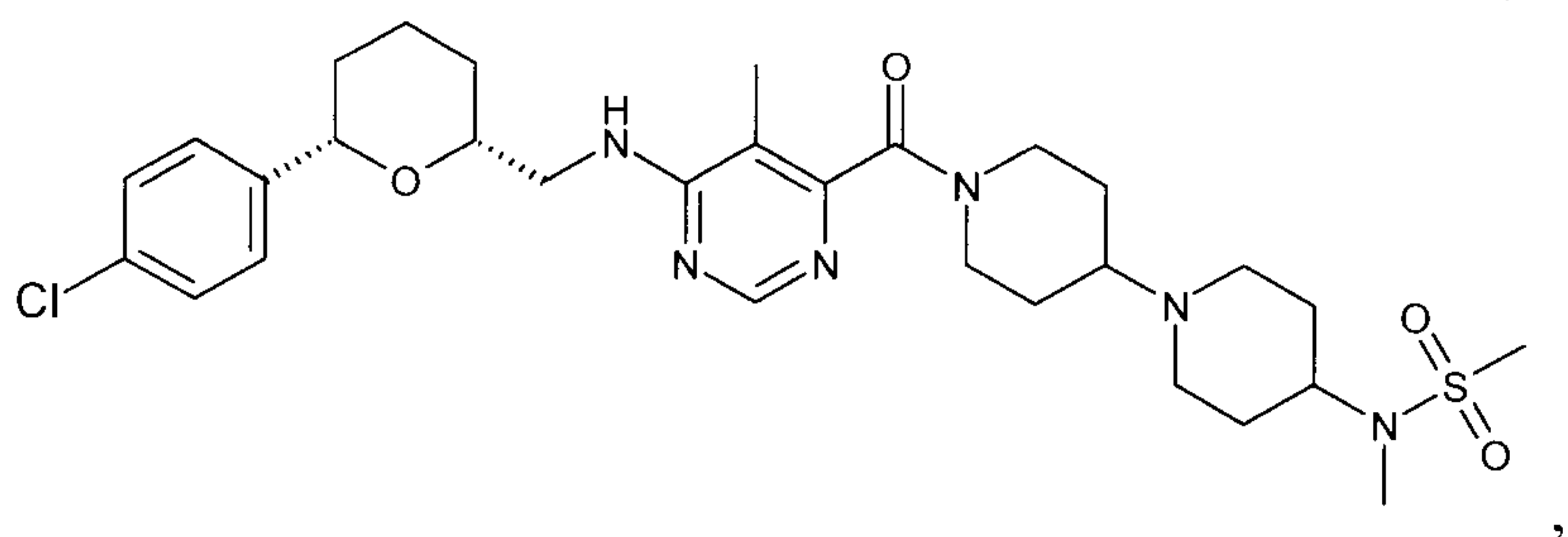
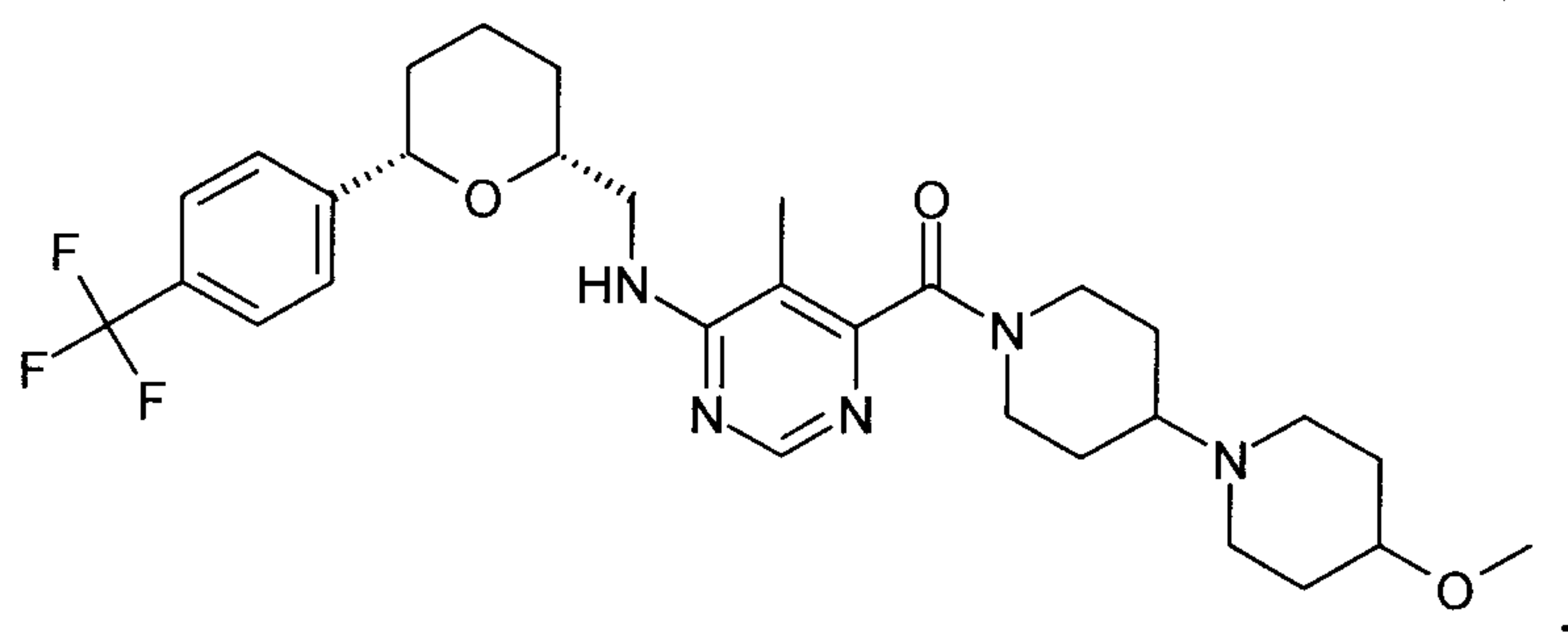
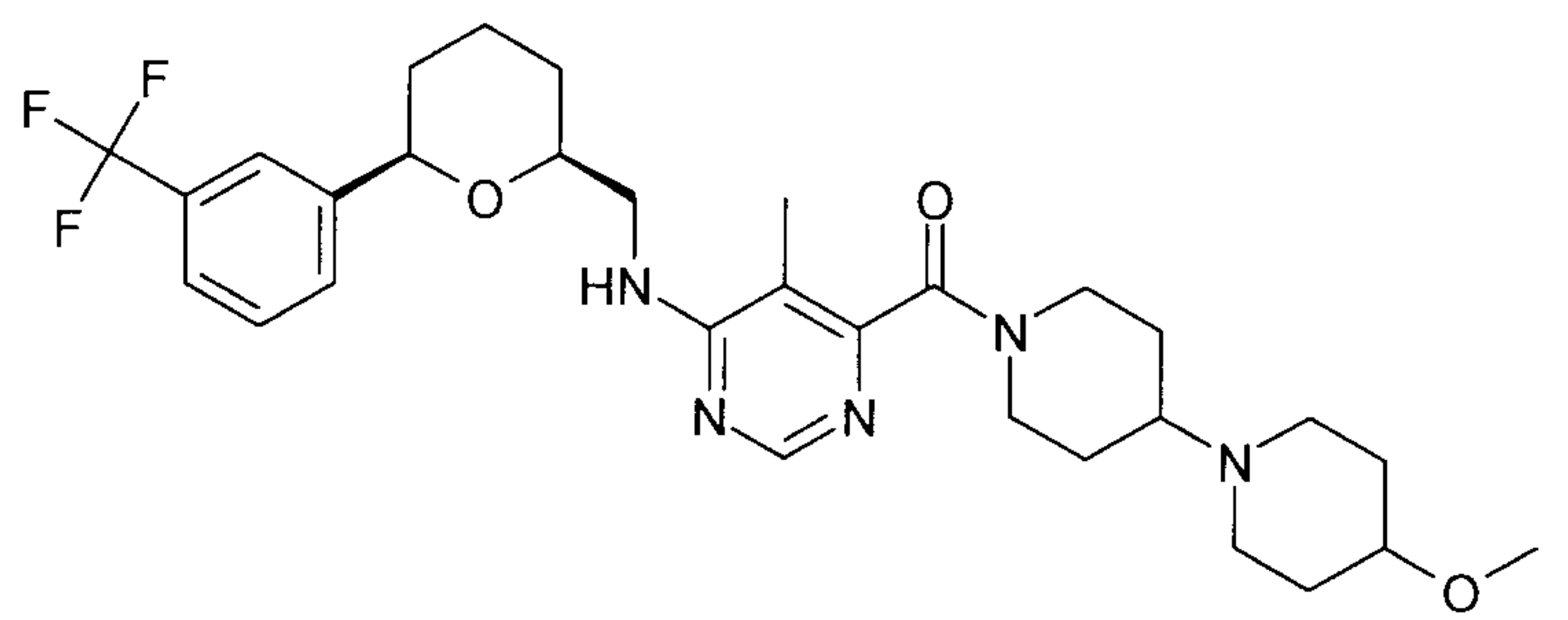
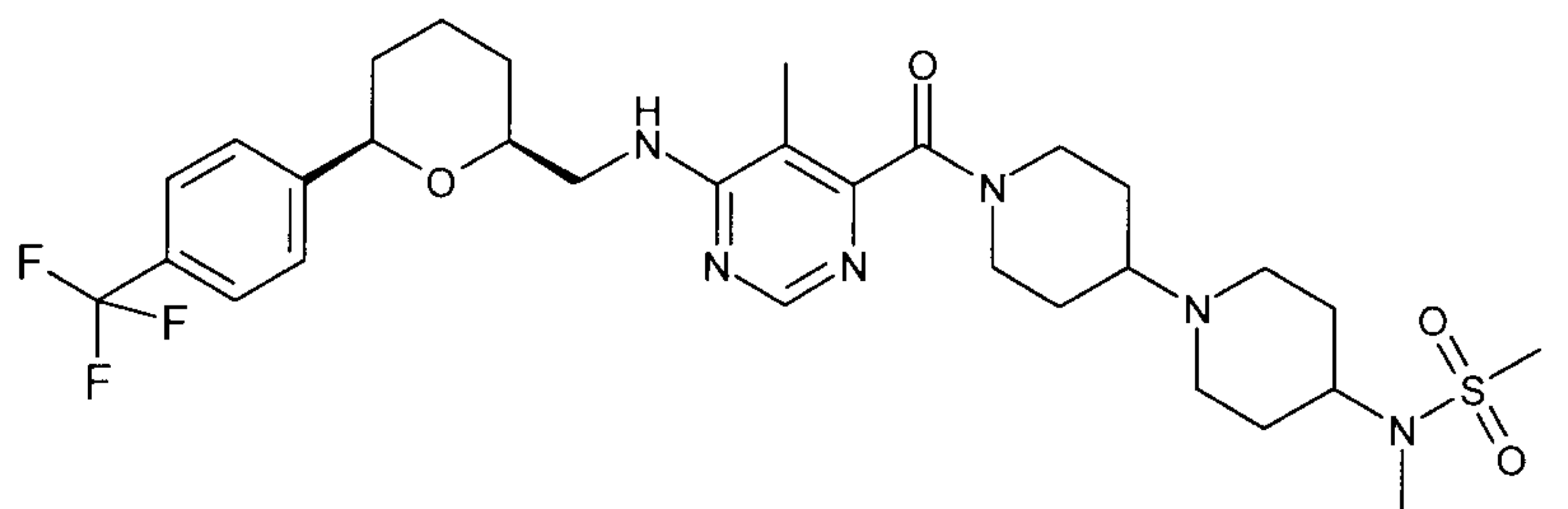
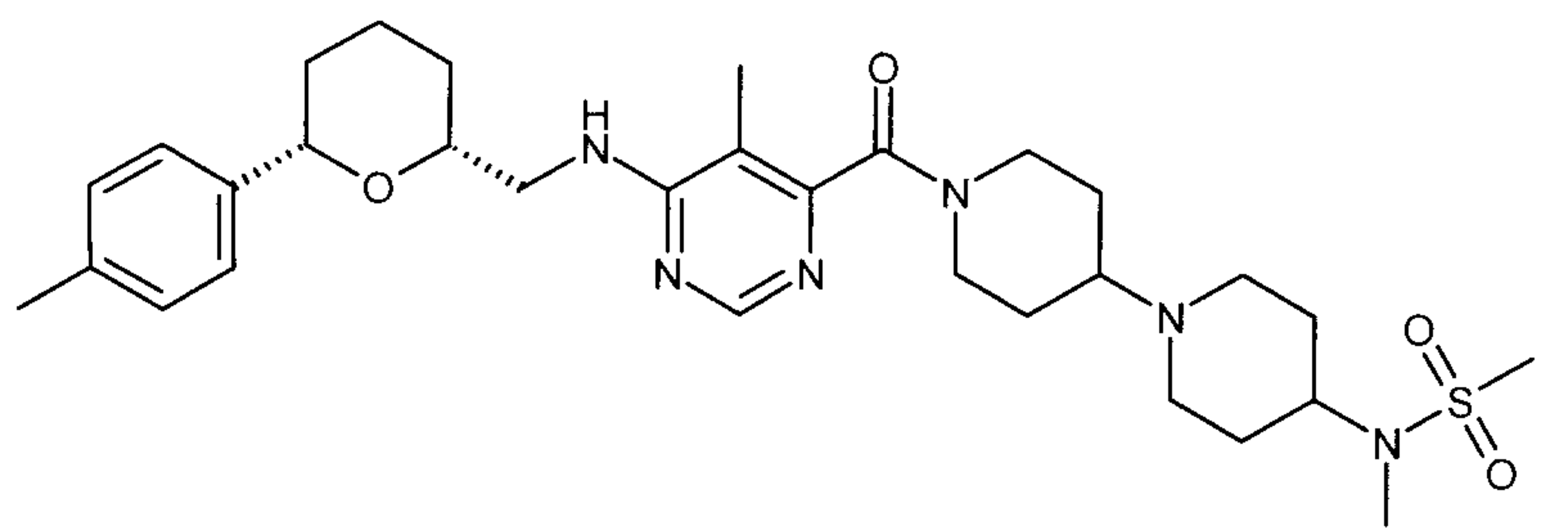
20 -(C₆-aryl)-COOH, -C(O)-O-C₂H₅,



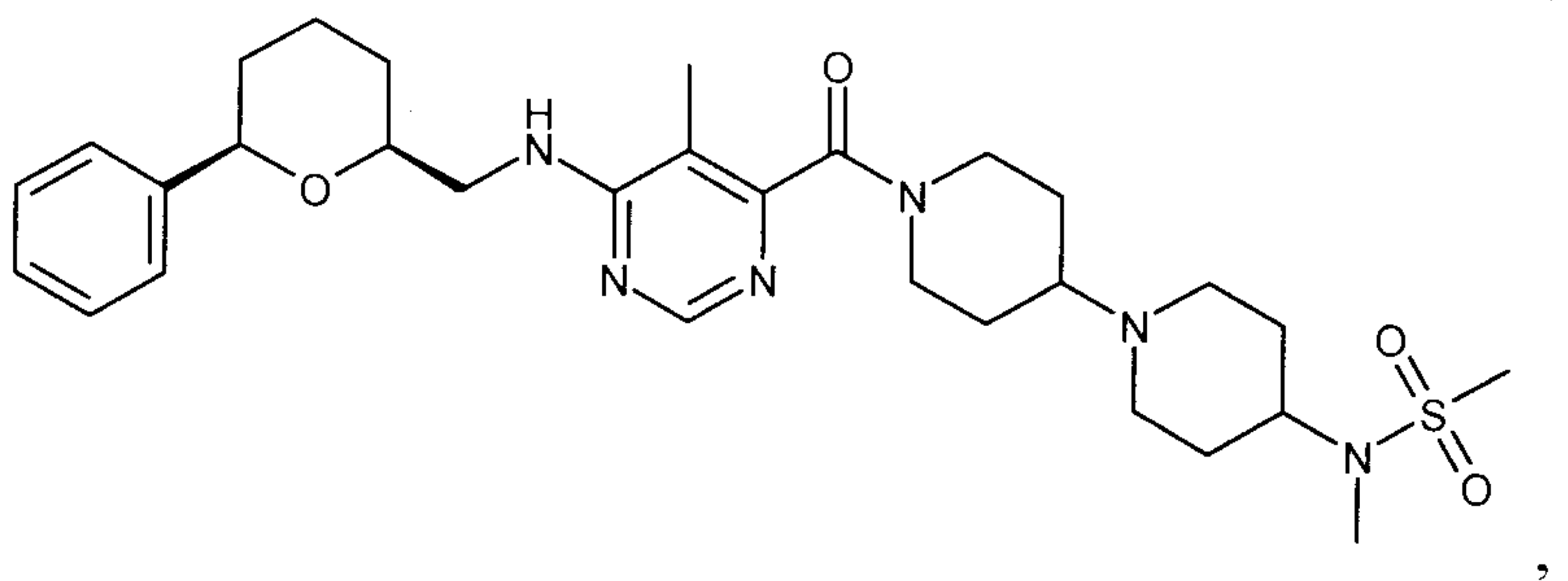
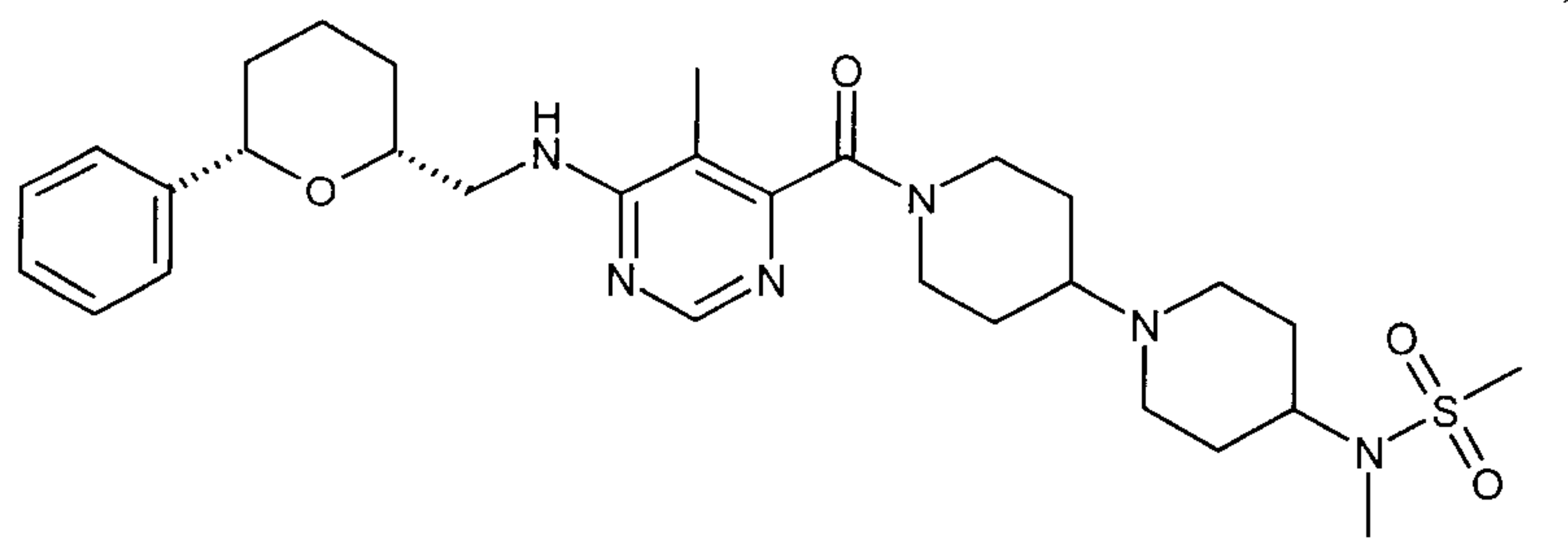
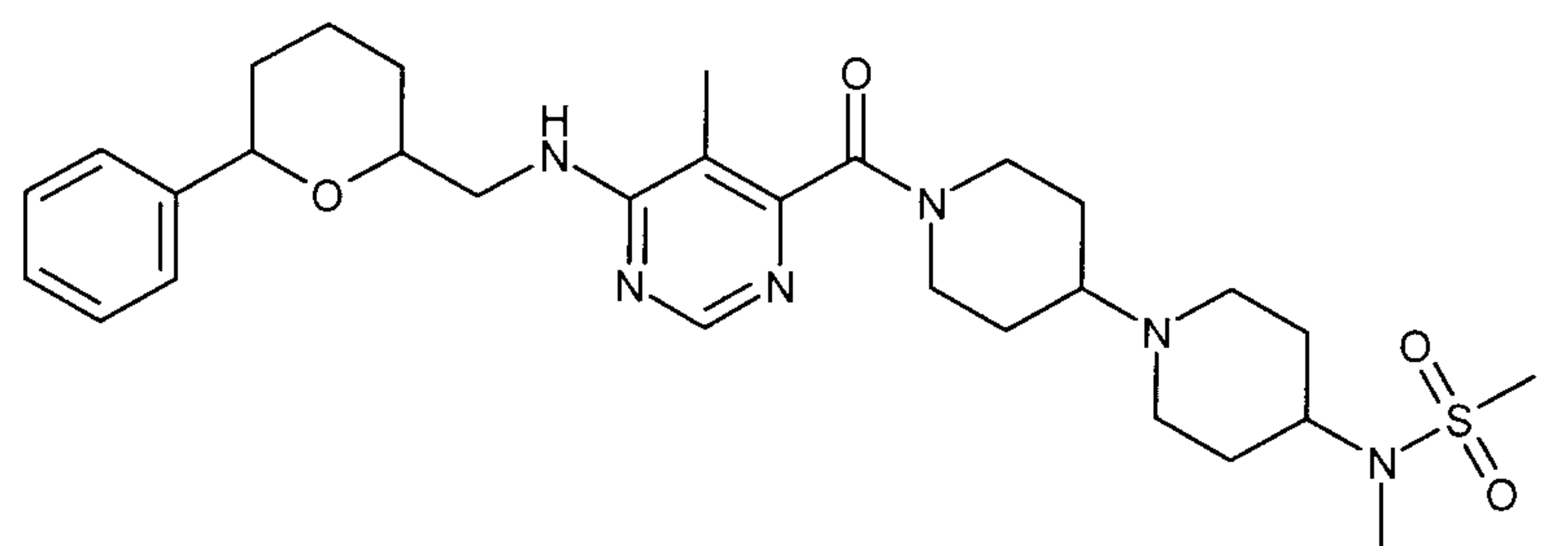
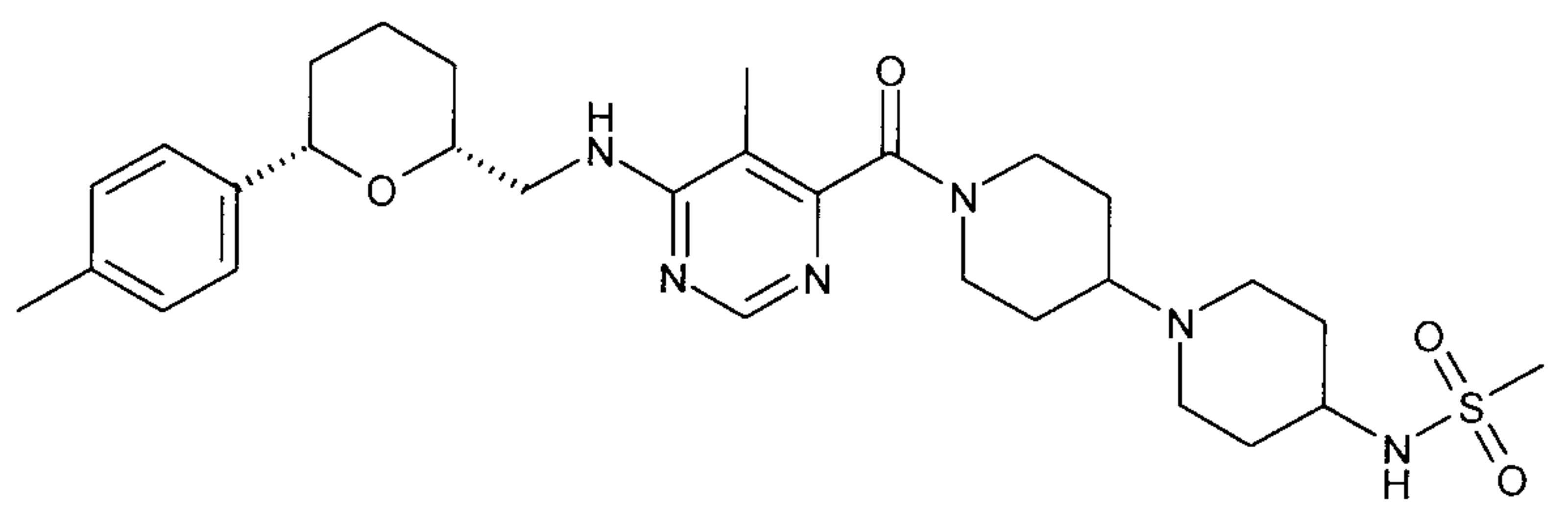
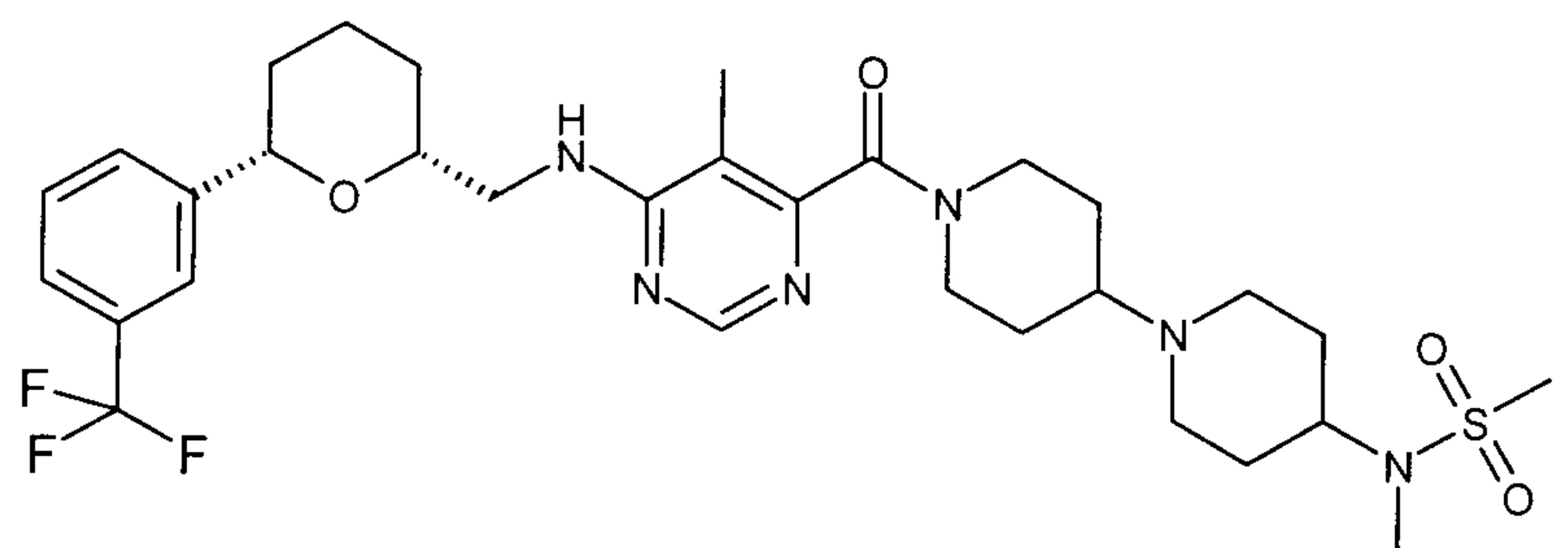
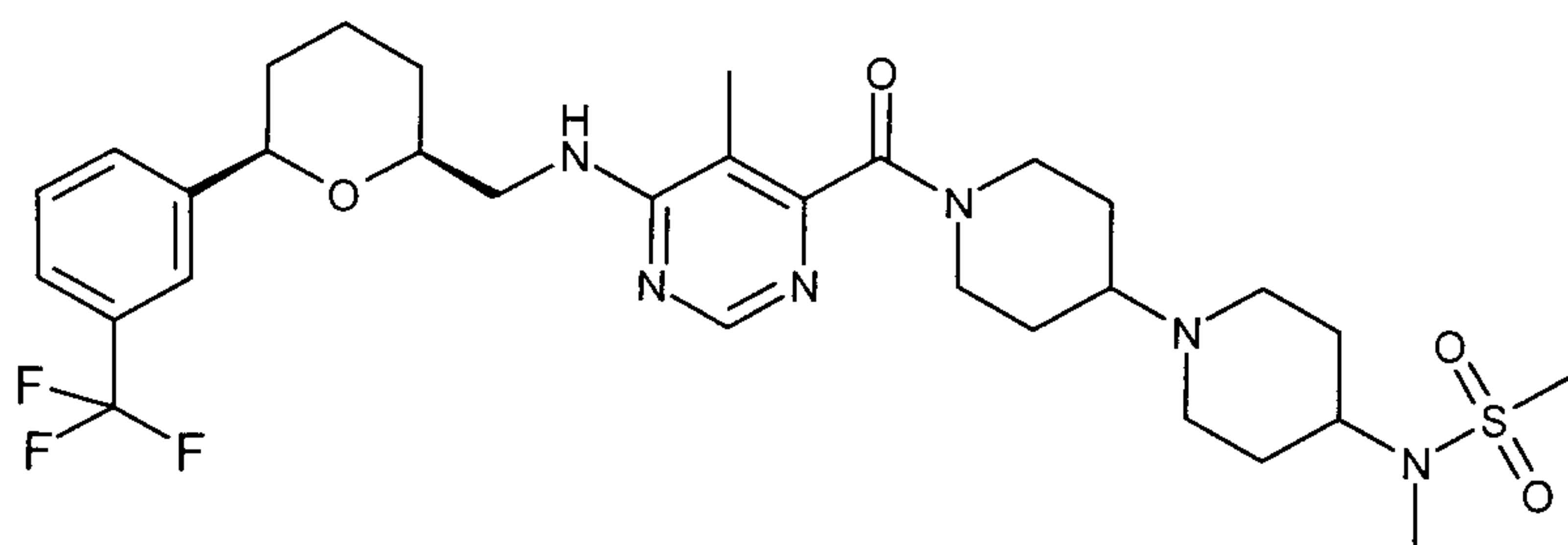
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7. The compound according to any one of claims 1 to 6 or a pharmacologically acceptable acid addition salt thereof, wherein R_2 is -H, -methyl, -ethyl, -propyl, -i-propyl, -butyl, -i-butyl, -t-butyl, -F, -Cl, -Br, -I, -CN, -CH=CH₂, or -C≡CH.
8. The compound according to any one of claims 1 to 7 or a pharmacologically acceptable acid addition salt thereof, wherein R_3 is -H, -CF₃, -O-CH₃, or -methyl.
9. The compound according to any one of claims 1 to 7 or a pharmacologically acceptable acid addition salt thereof, wherein R_3 is -H, -O-CH₃, or -methyl.
10. The compound according to any one of claims 1 to 7 or a pharmacologically acceptable acid addition salt thereof, wherein R_3 is -H.
11. The compound according to any one of claims 1 to 10 or a pharmacologically acceptable acid addition salt thereof, wherein R_6 is -H, -CH₃, -C₂H₅, -O-CH₃, -O-C₂H₅, -F, -CF₃, or -OCF₃.
12. The compound according to any one of claims 1 to 11 or a pharmacologically acceptable acid addition salt thereof, wherein R_6 is -H or -O-CH₃.
13. The compound according to any one of claims 1 to 12 or a pharmacologically acceptable acid addition salt thereof, wherein R_1 is -H.
14. The compound according to any one of claims 1 to 13 or a pharmacologically acceptable acid addition salt thereof, wherein n is 2.
15. The compound according to any one of claims 1 to 14 or a pharmacologically acceptable acid addition salt thereof, wherein G and E are N.
16. The compound according to any one of claims 1 to 15 or a pharmacologically acceptable acid addition salt thereof, wherein Z is C.
17. The compound according to claim 1, wherein the compound is:

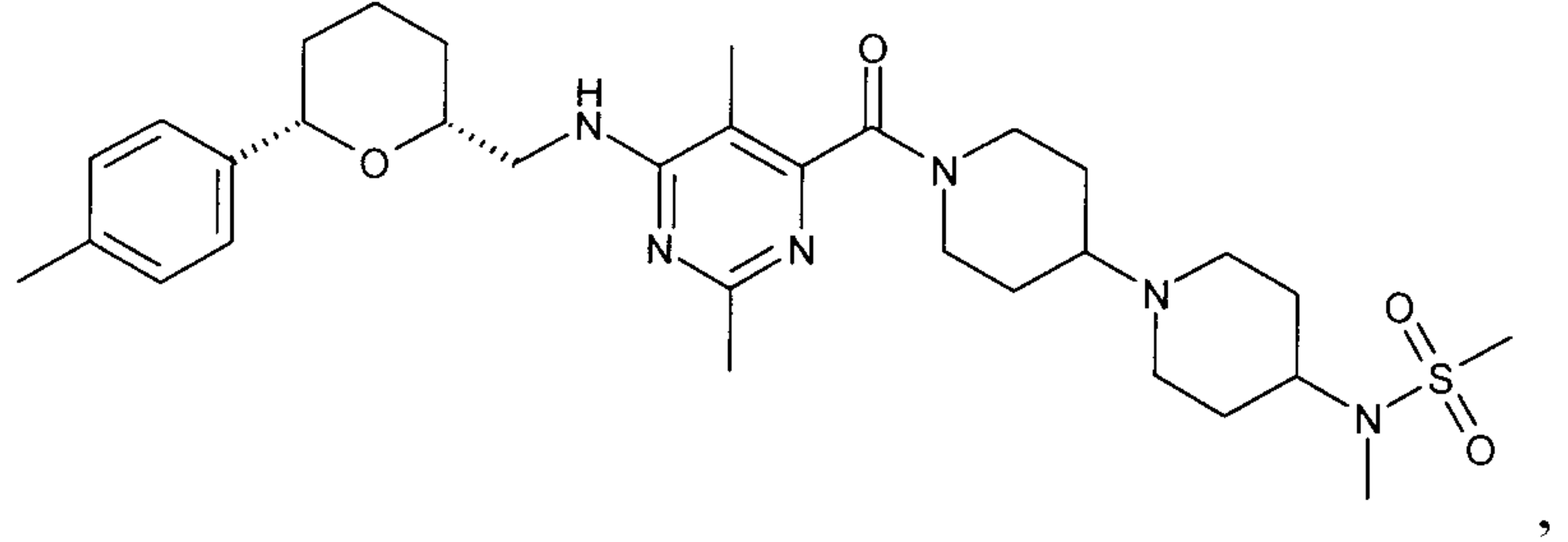
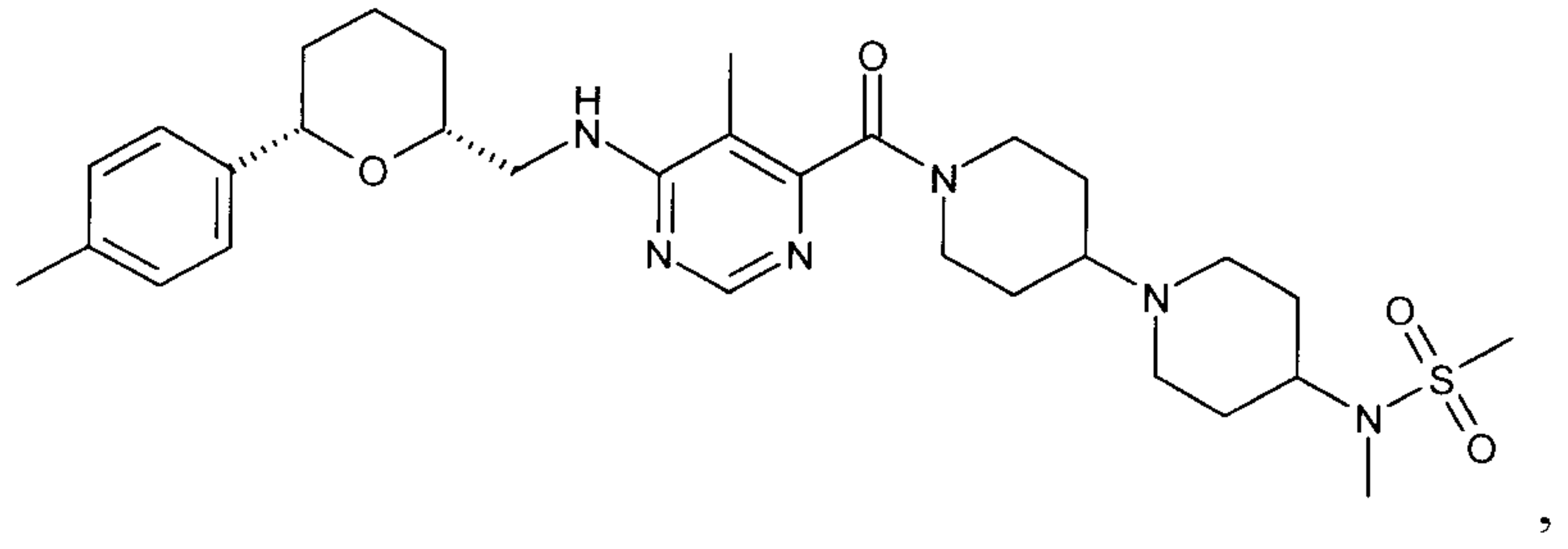
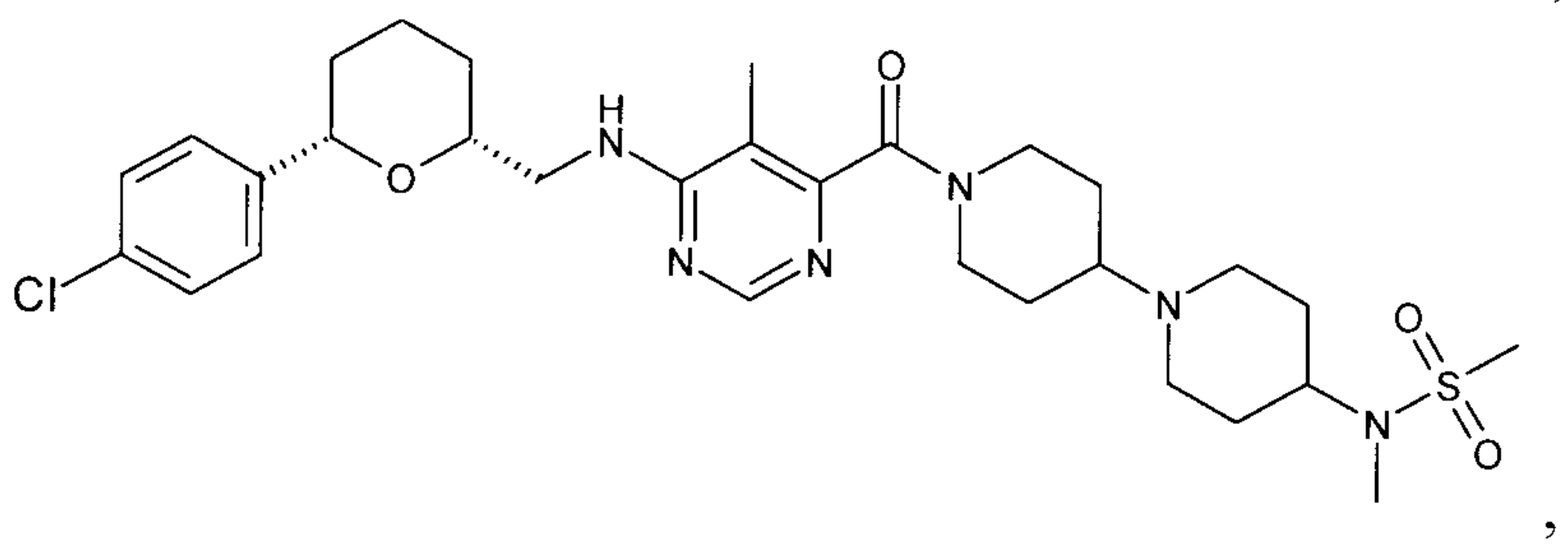
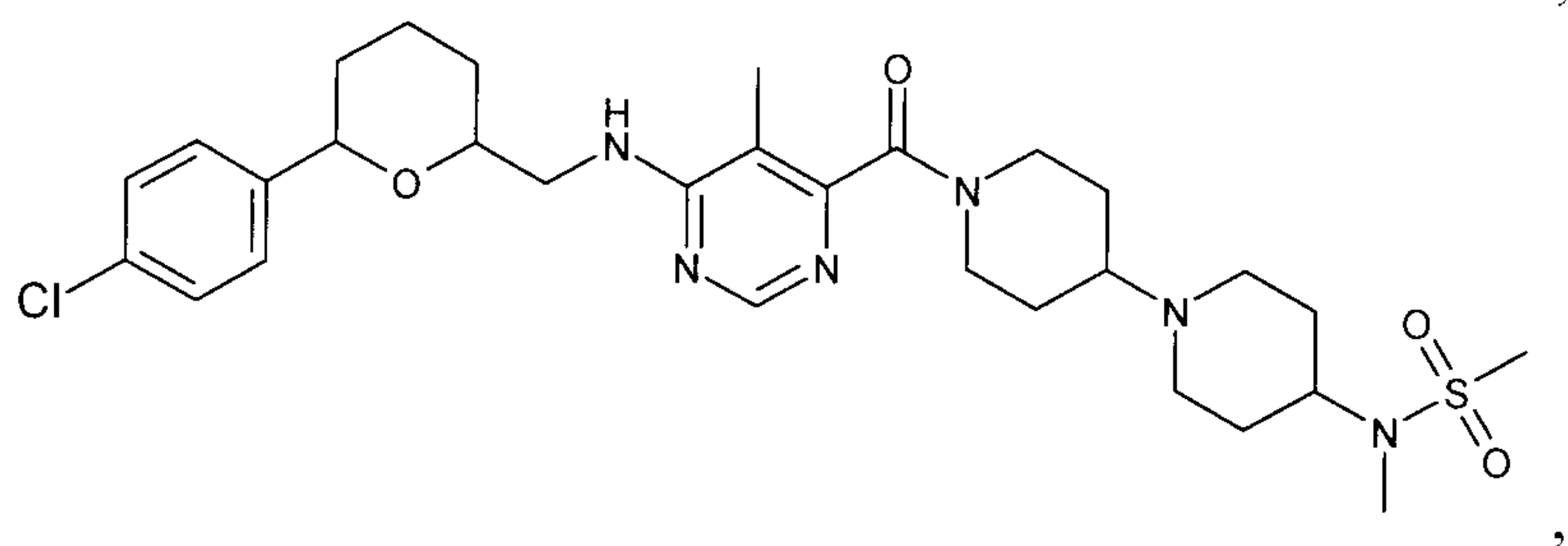
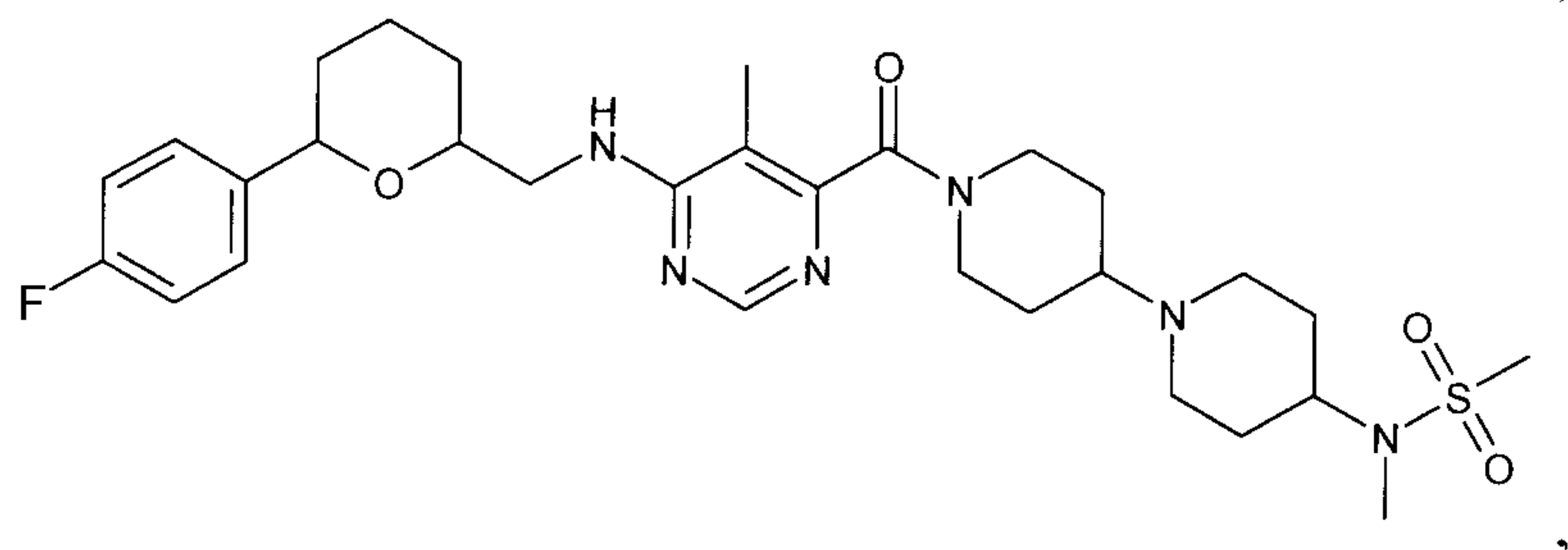
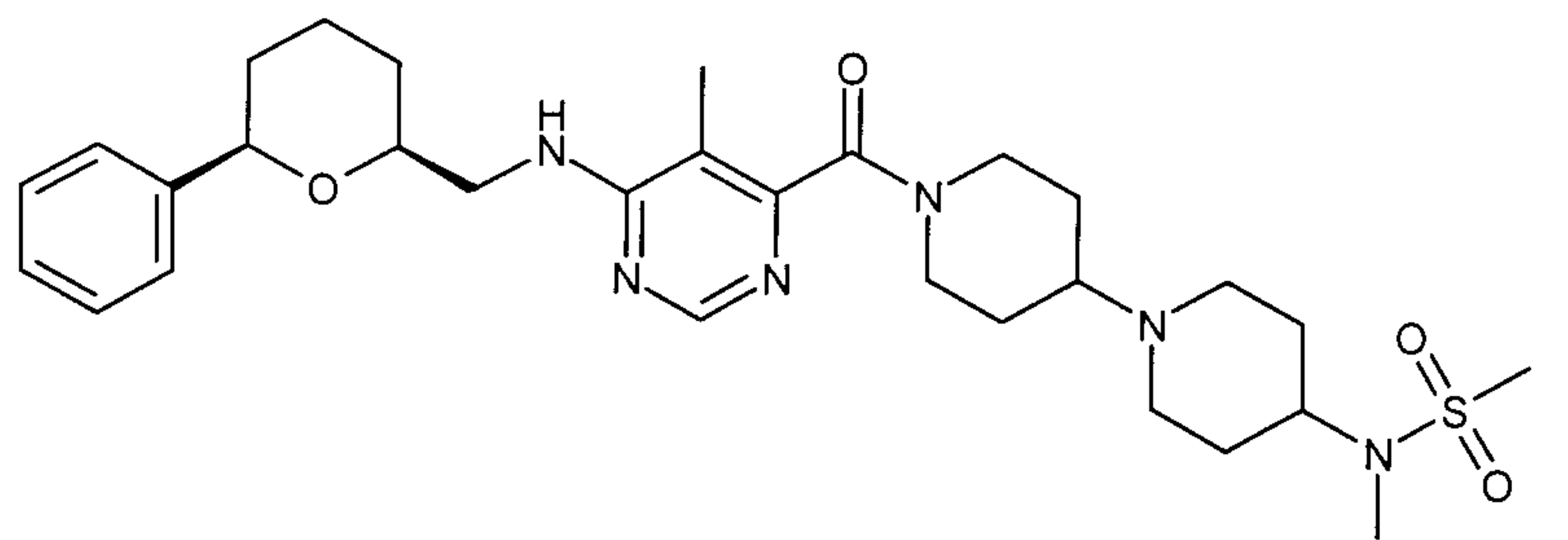
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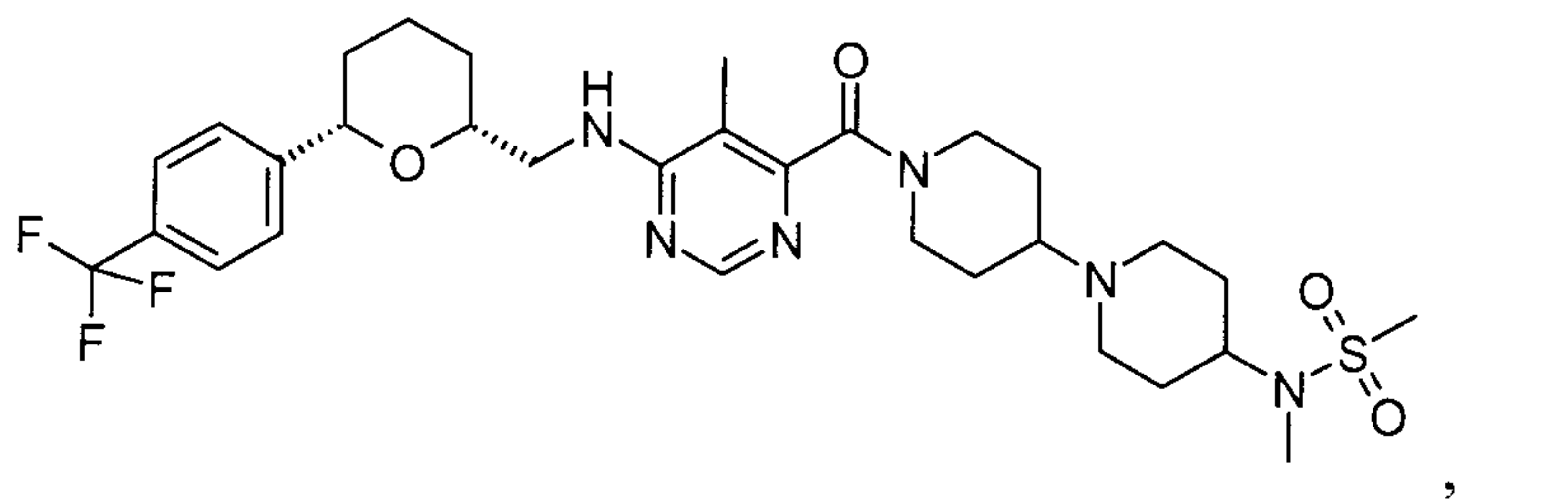
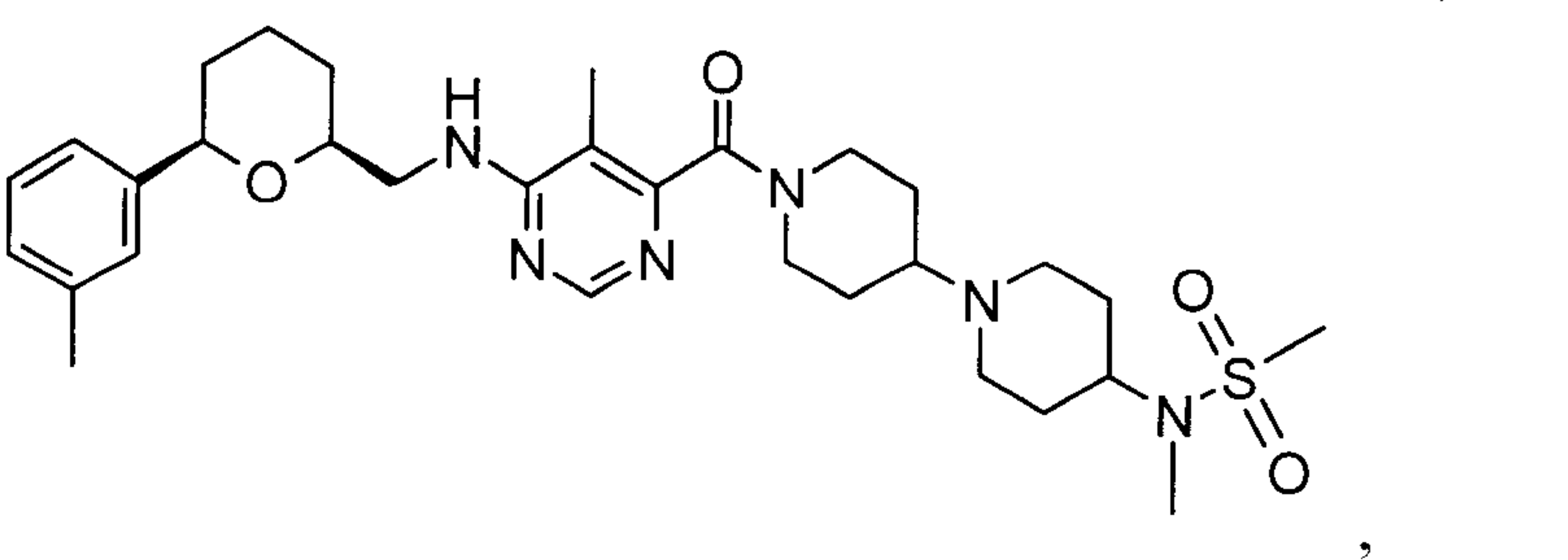
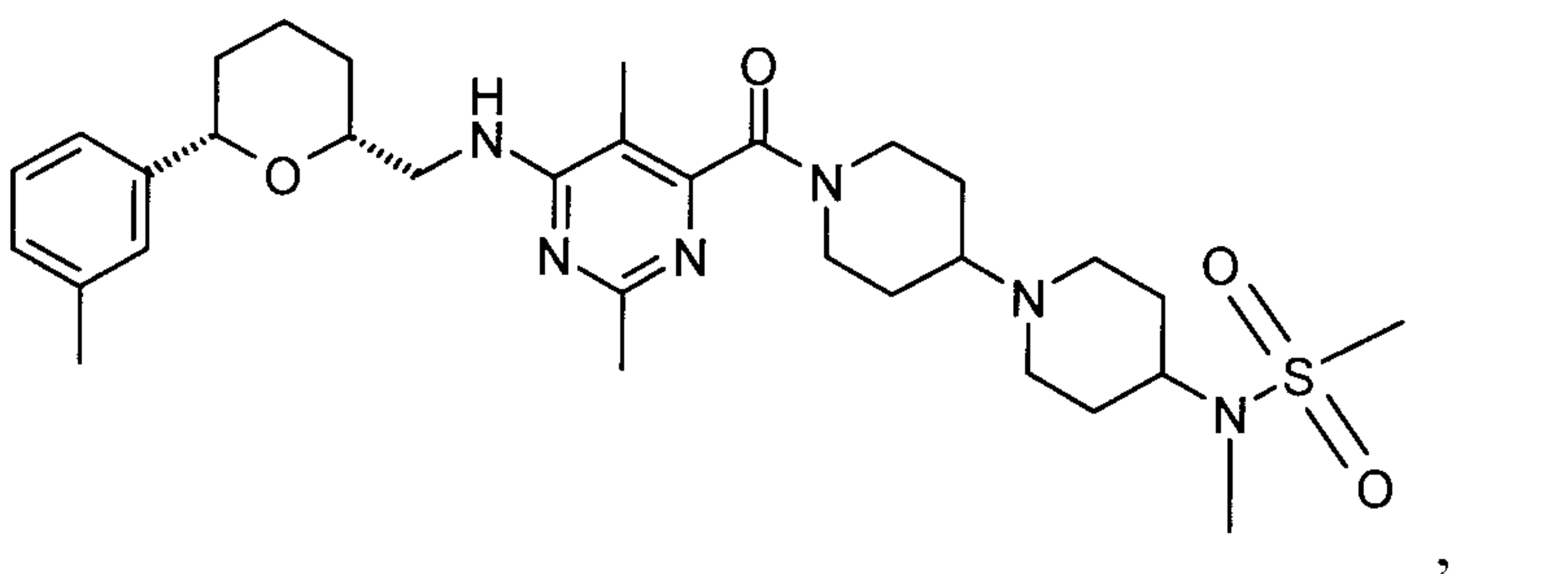
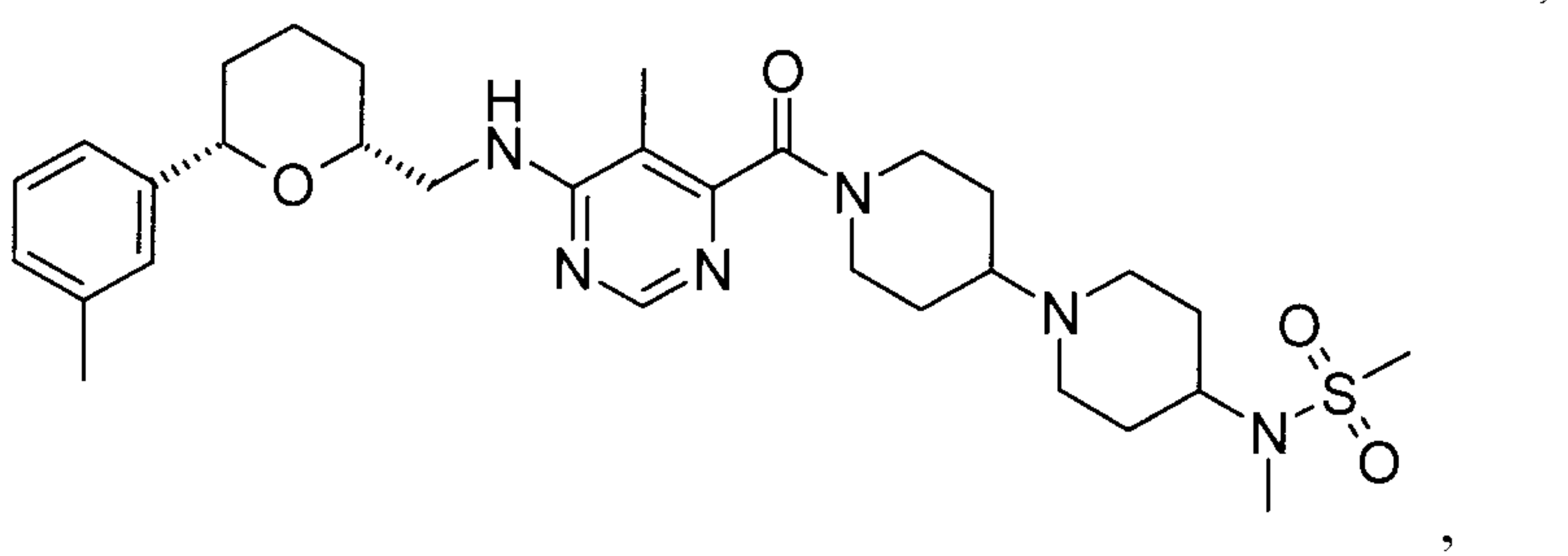
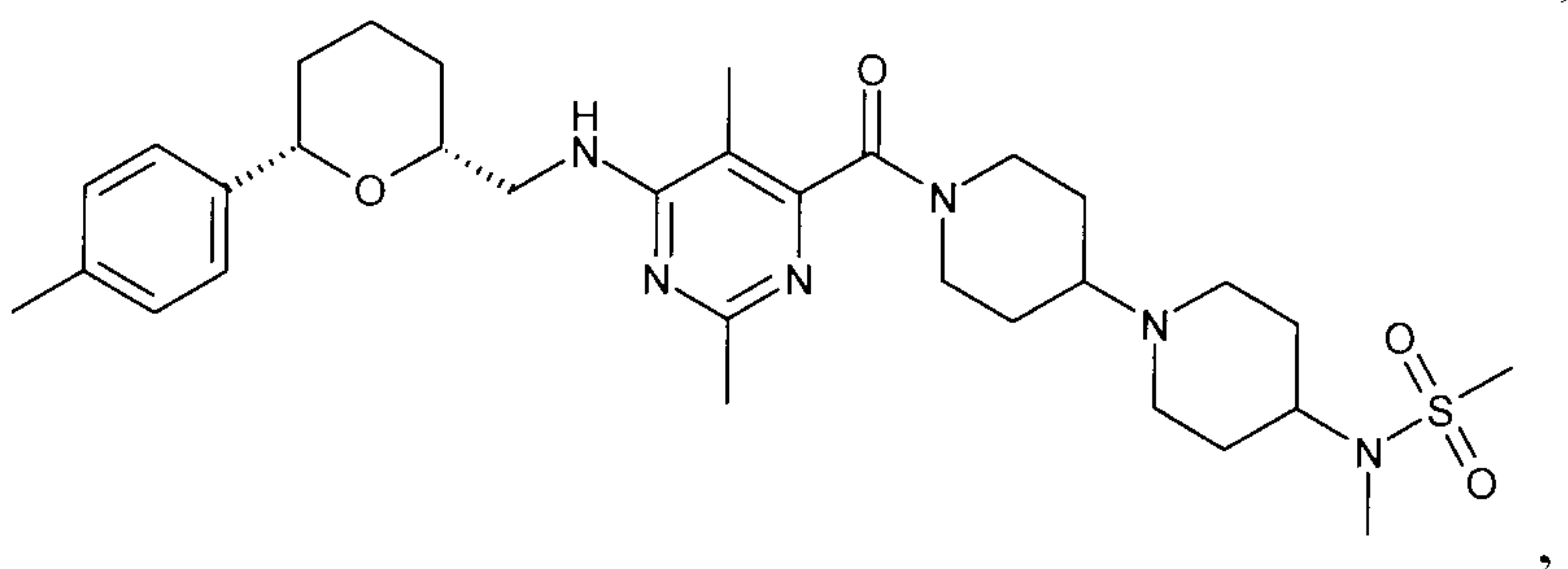
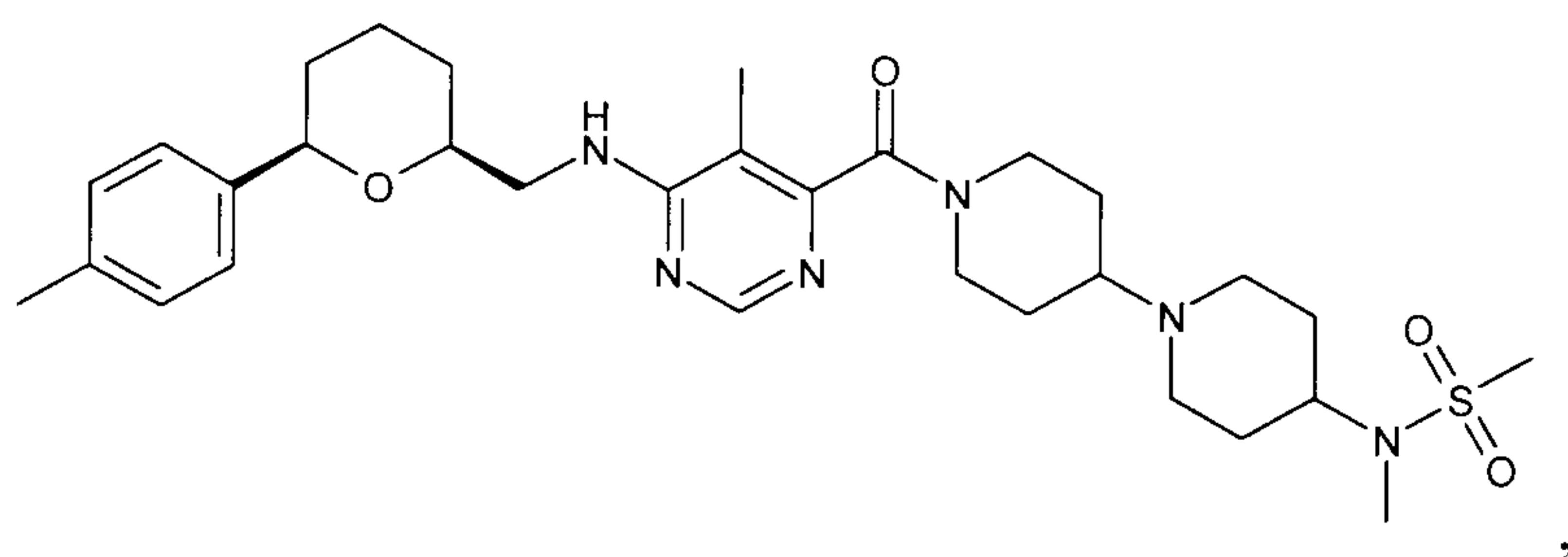
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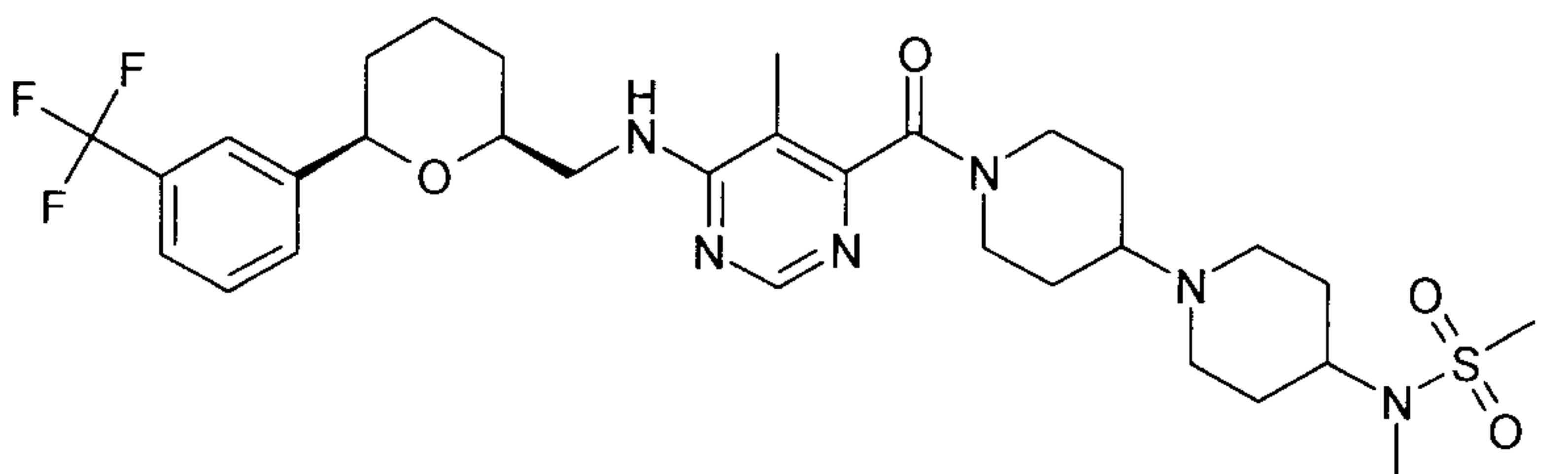
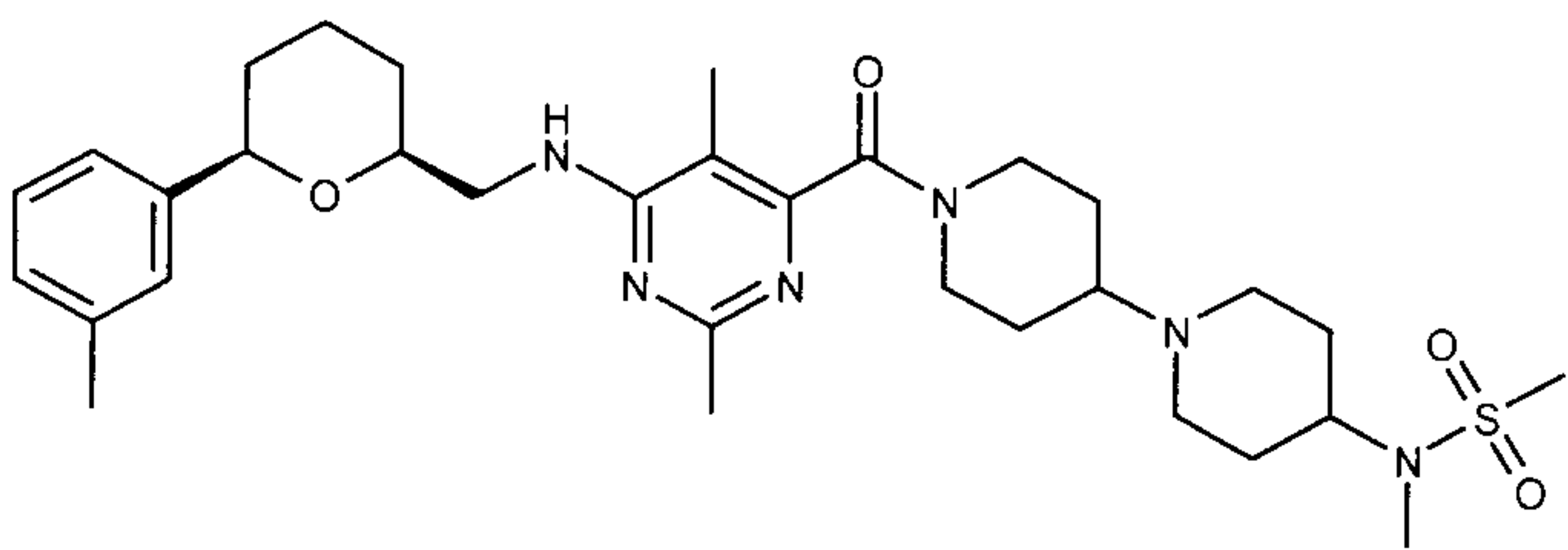
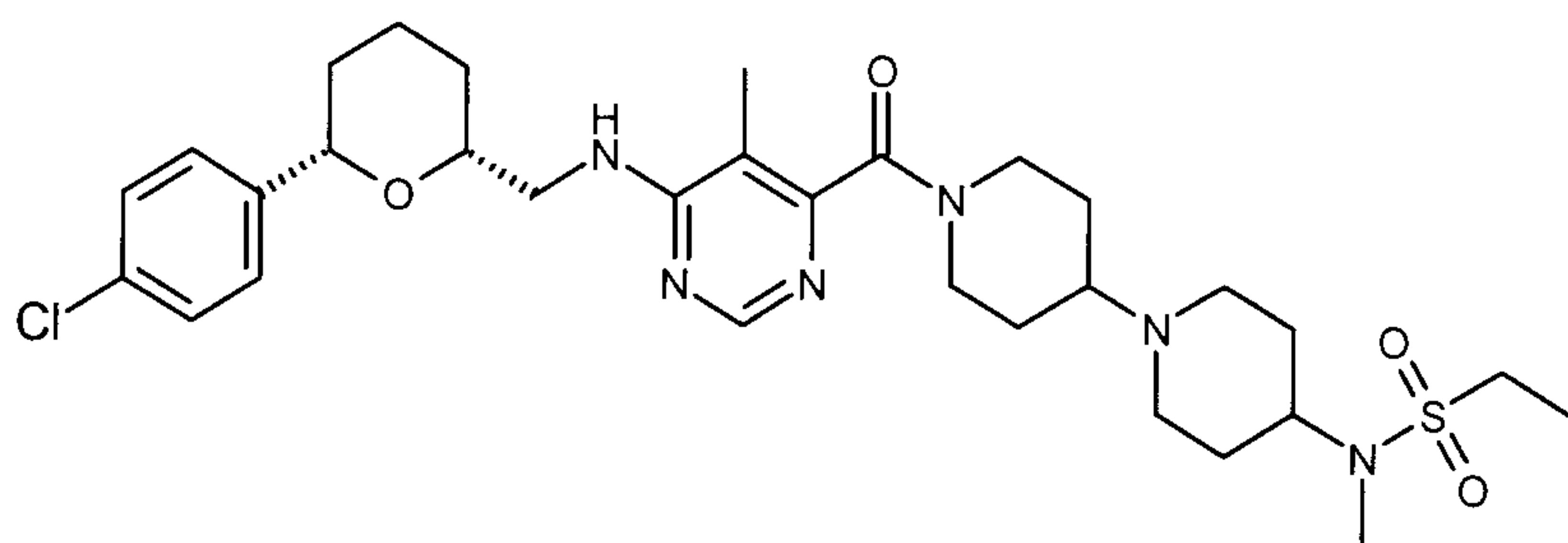
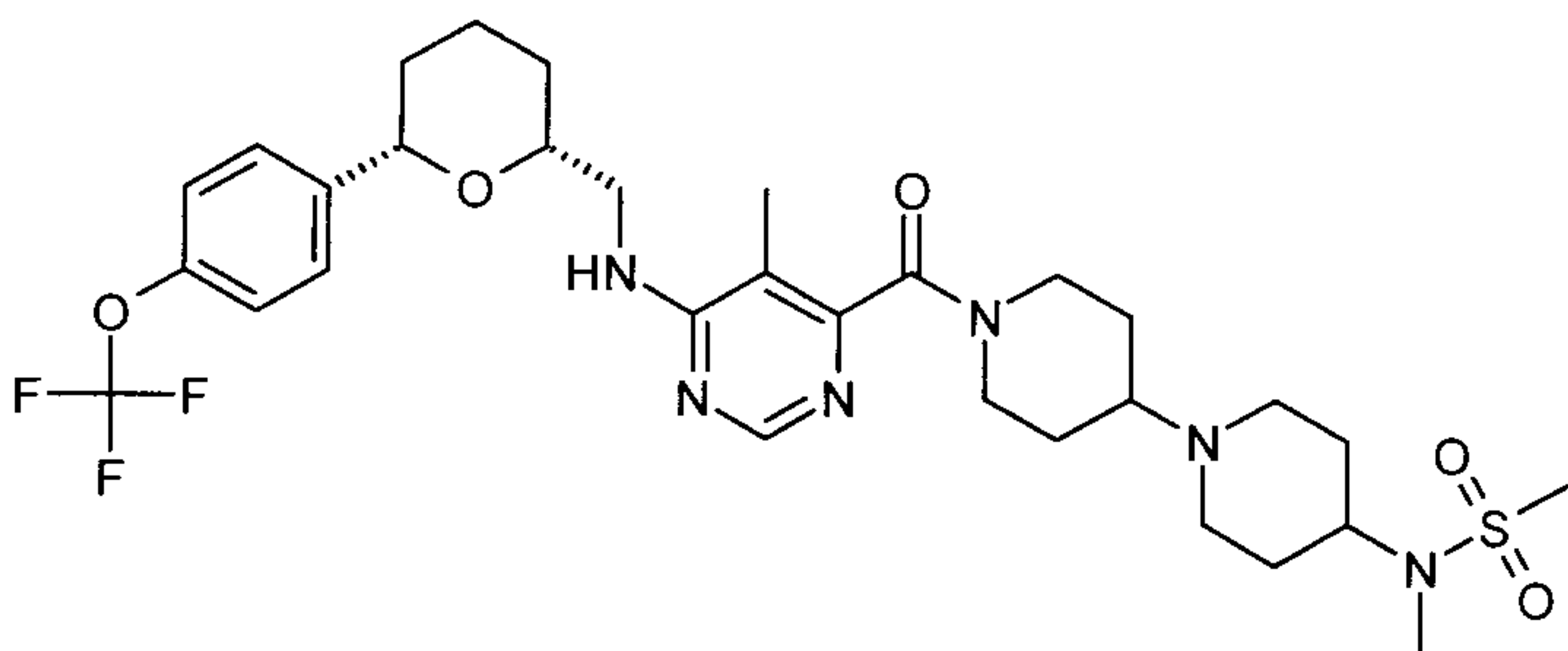
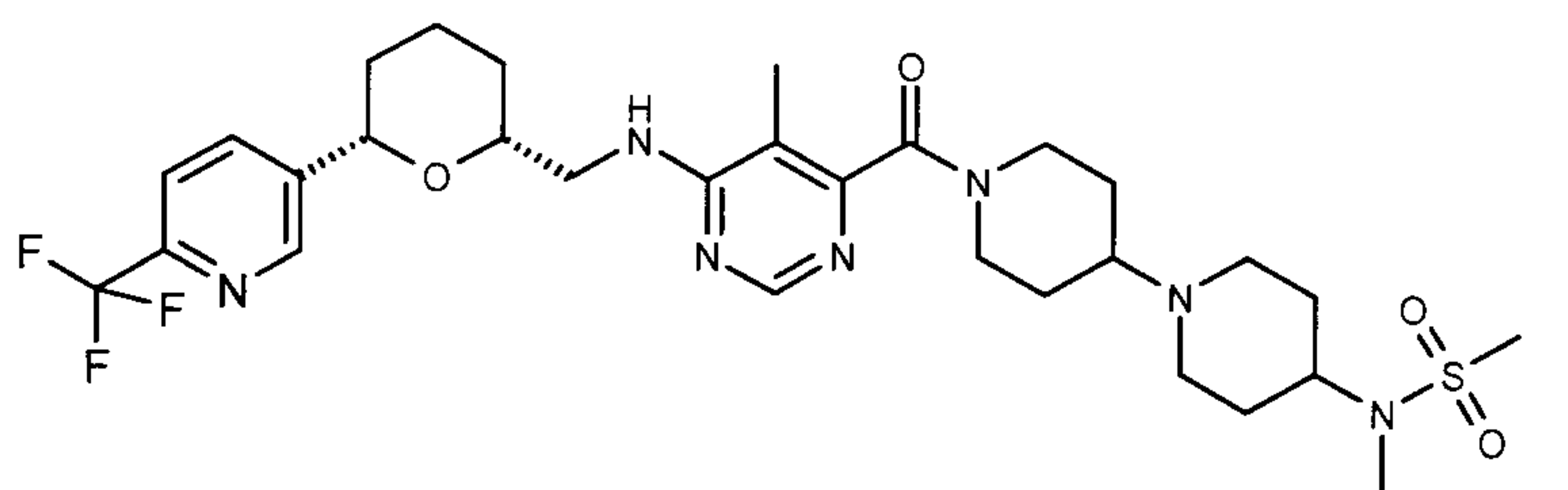
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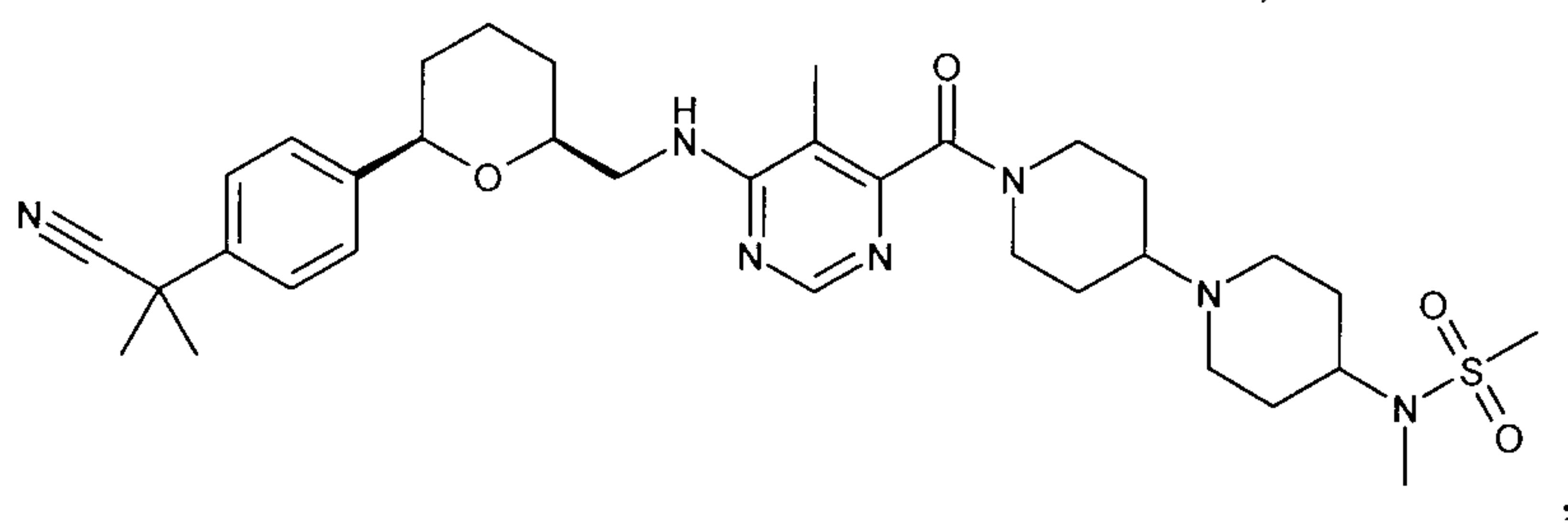
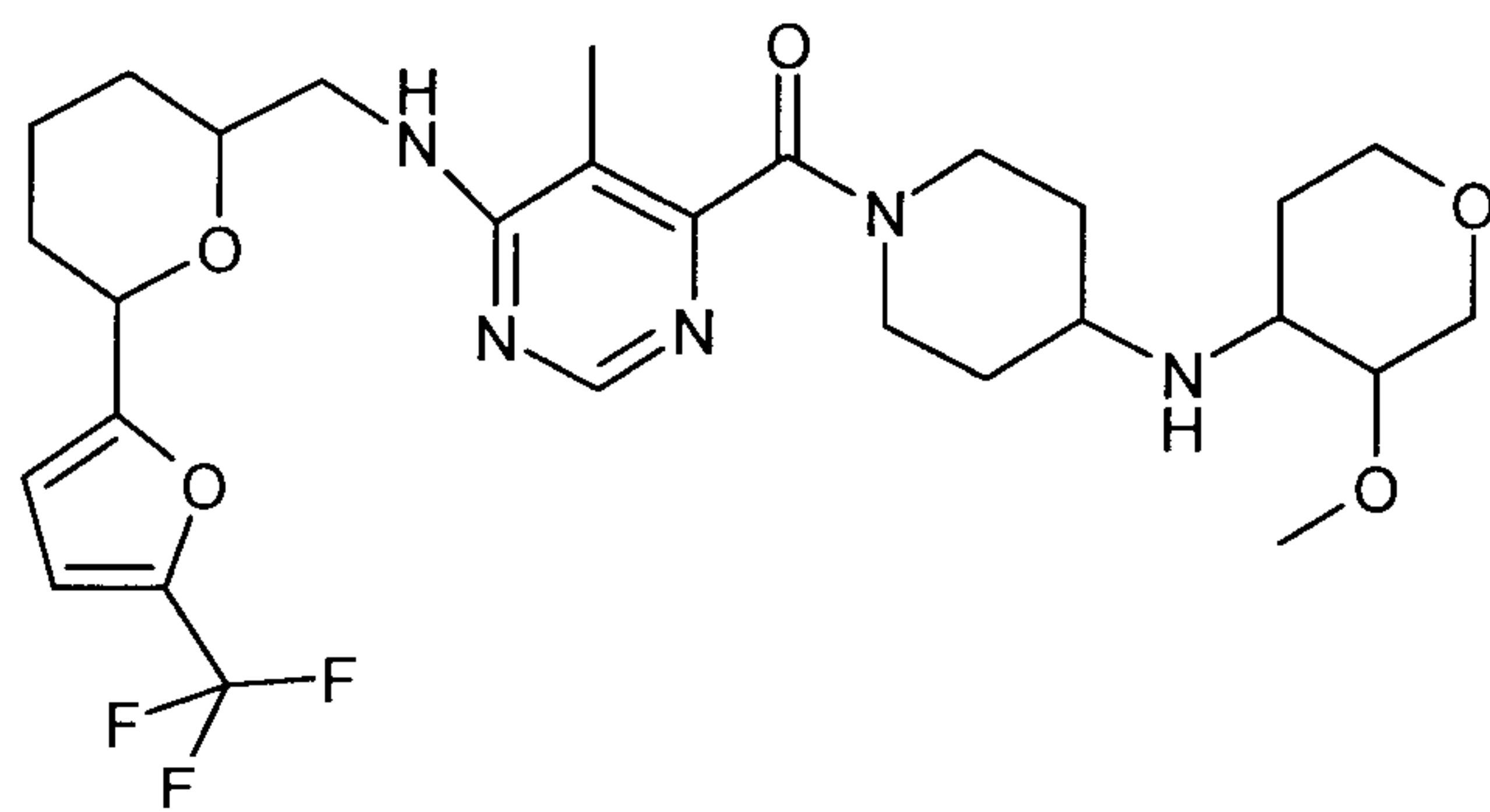
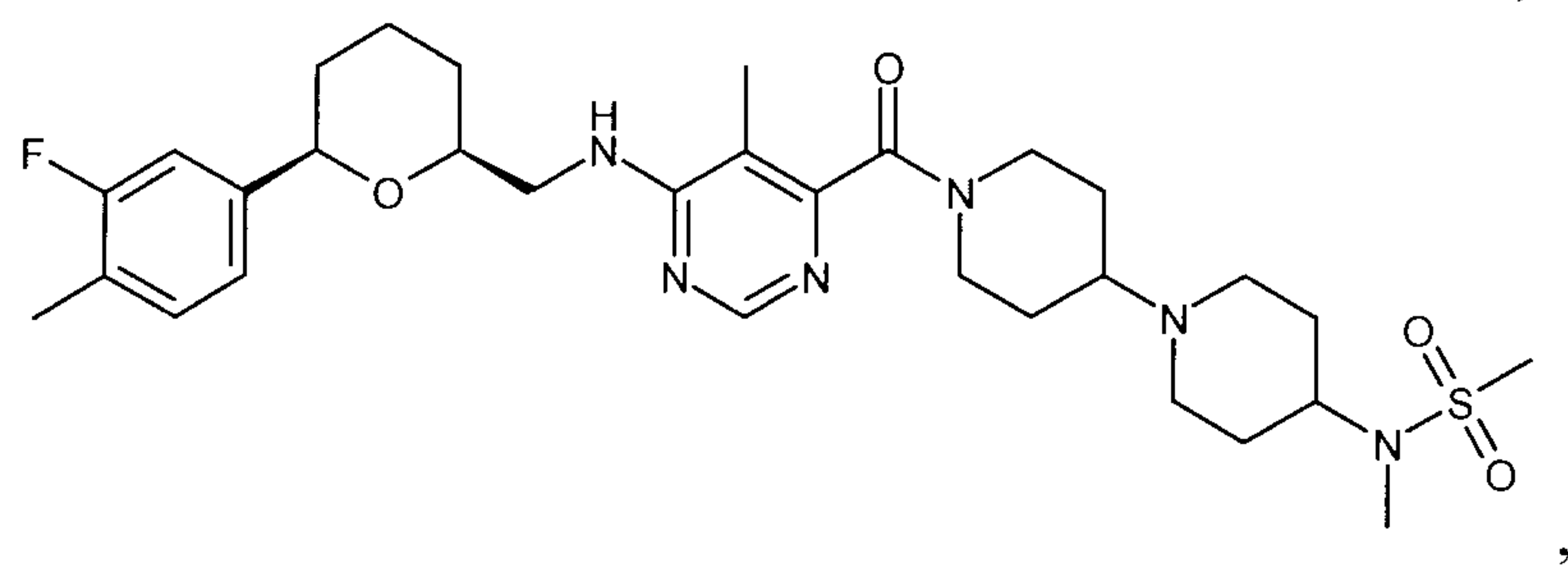
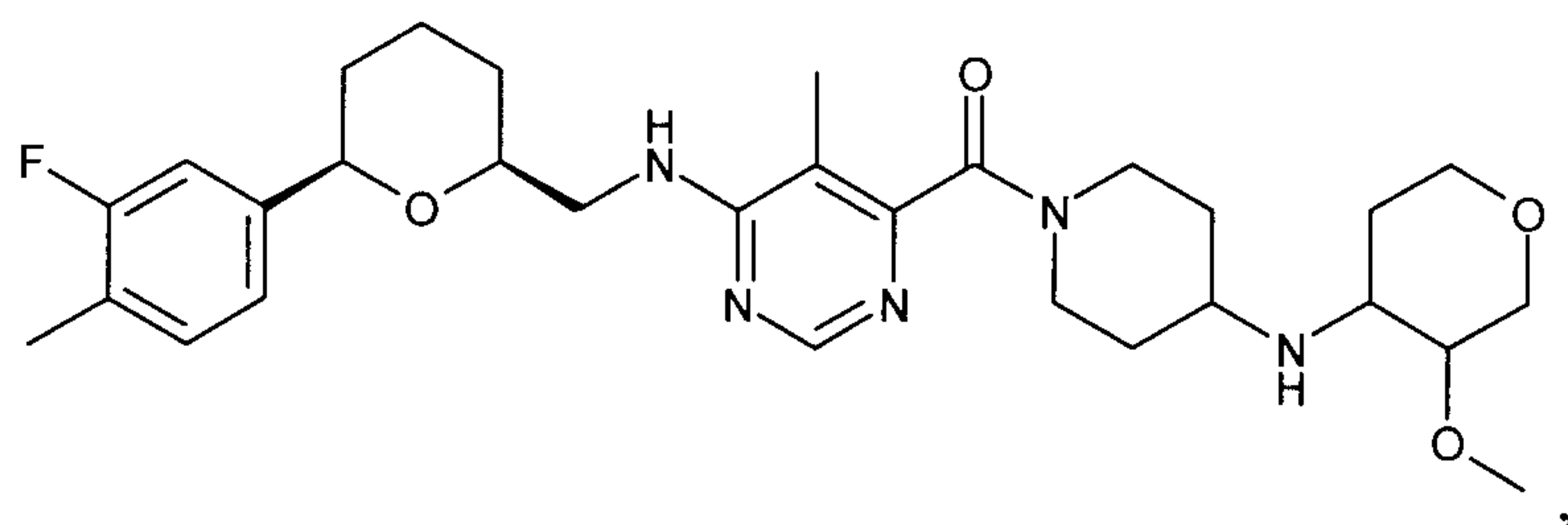
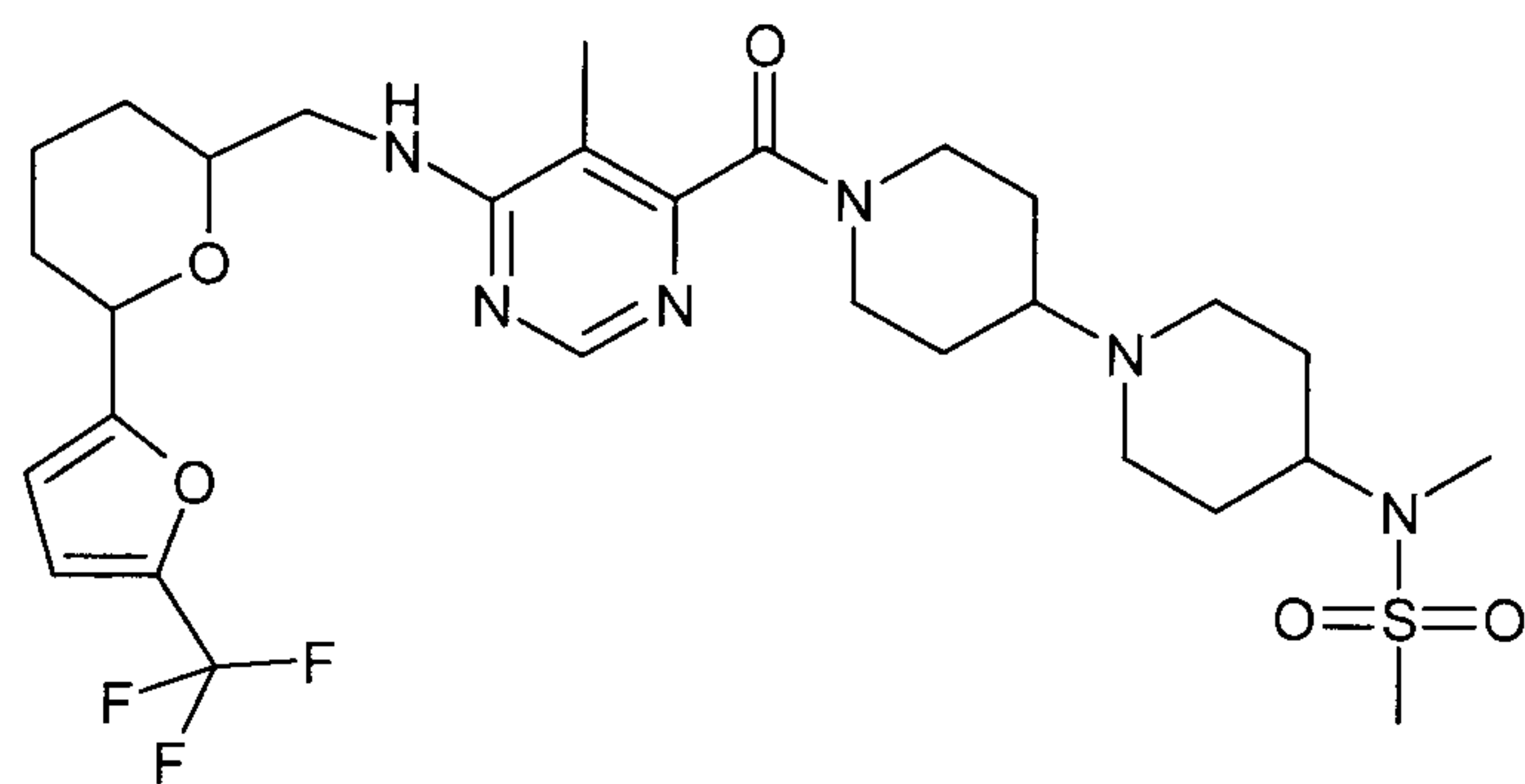
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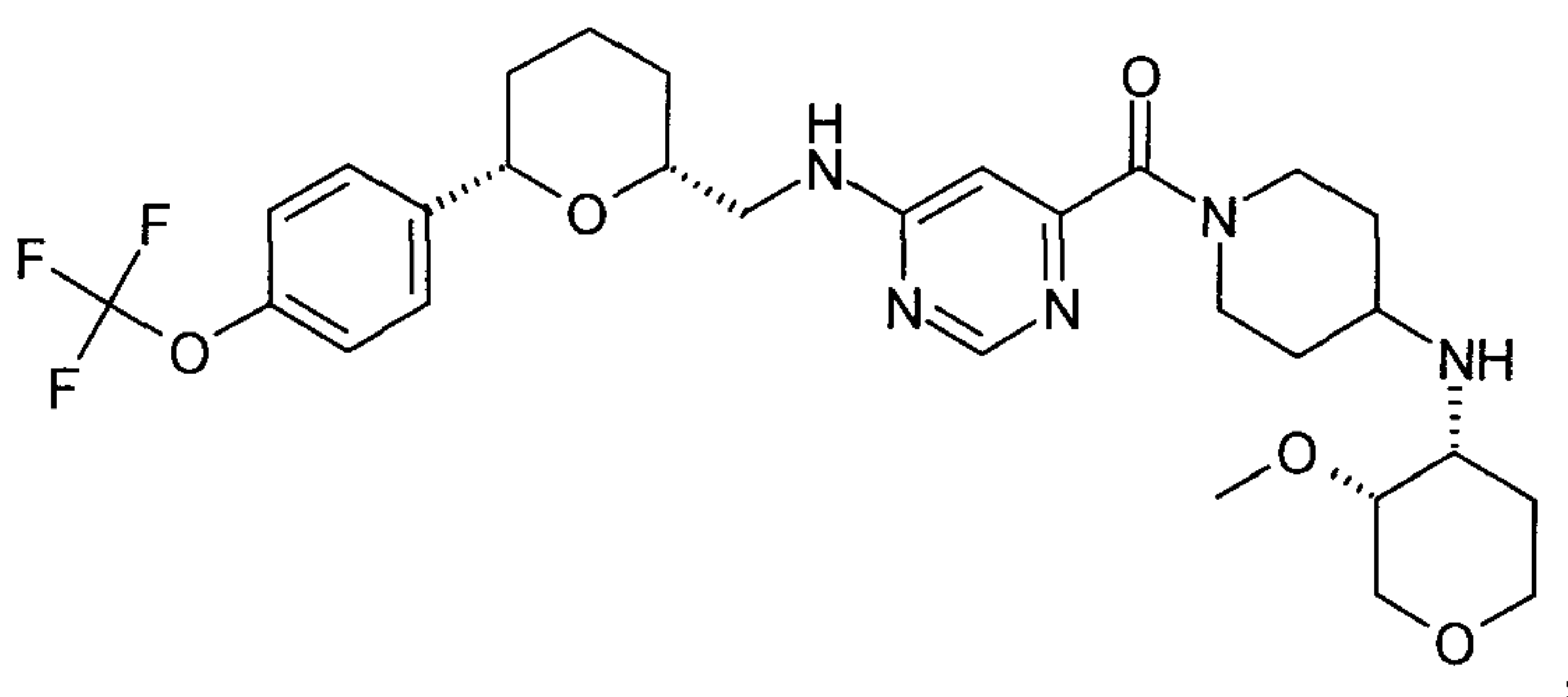
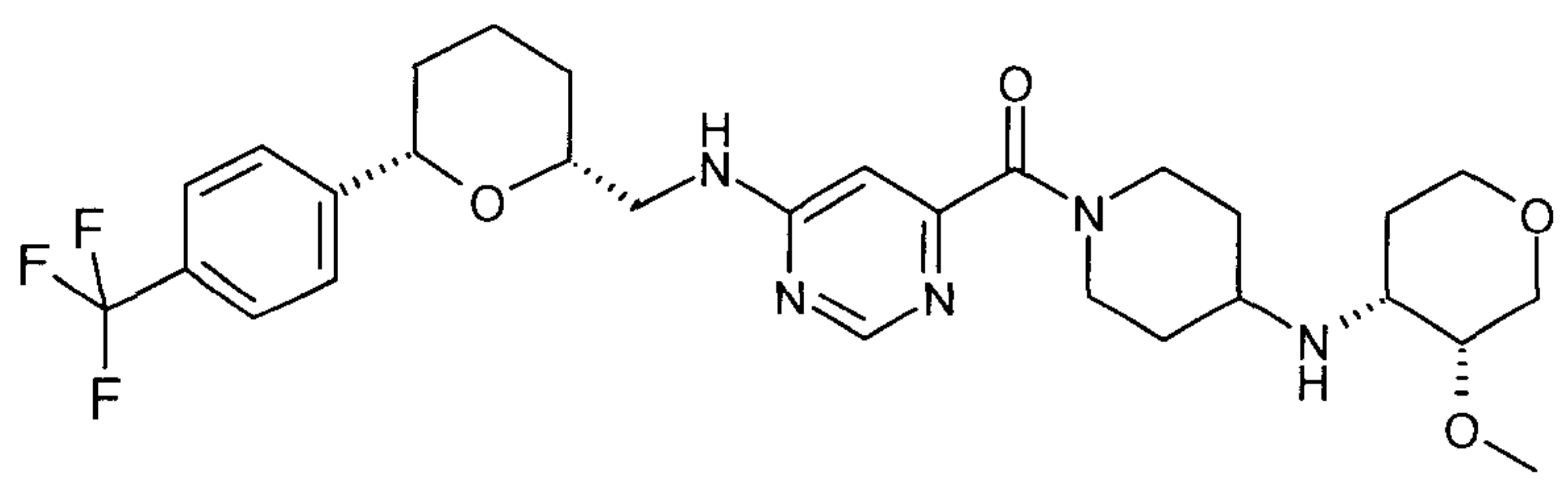
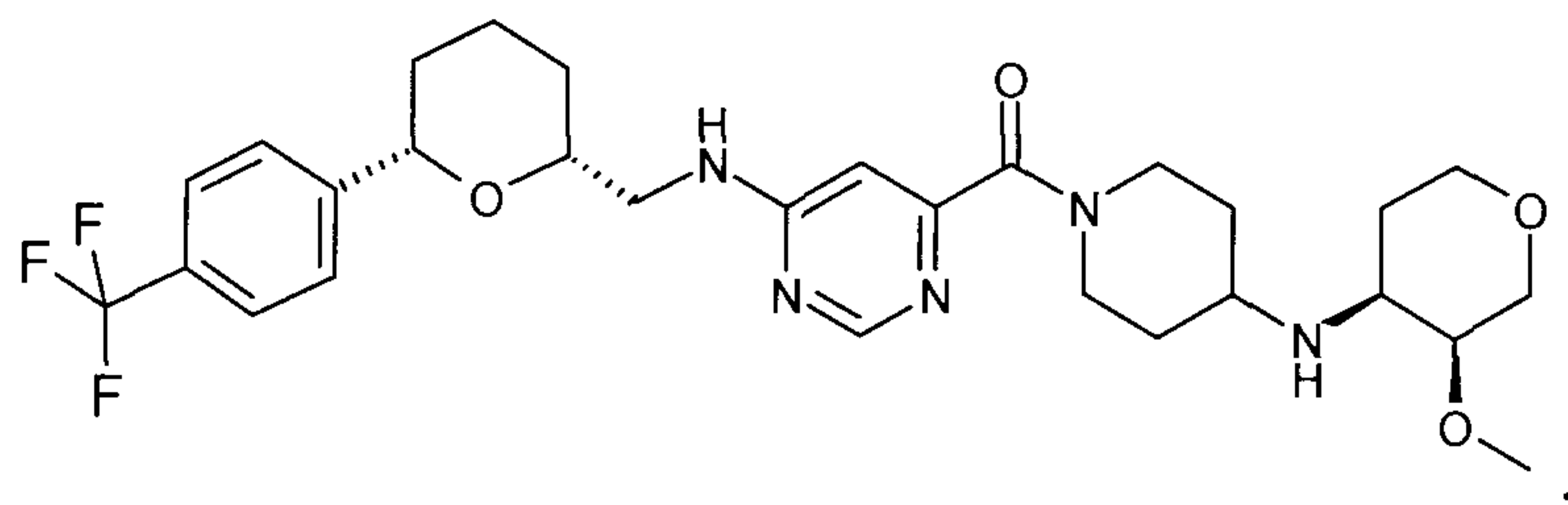
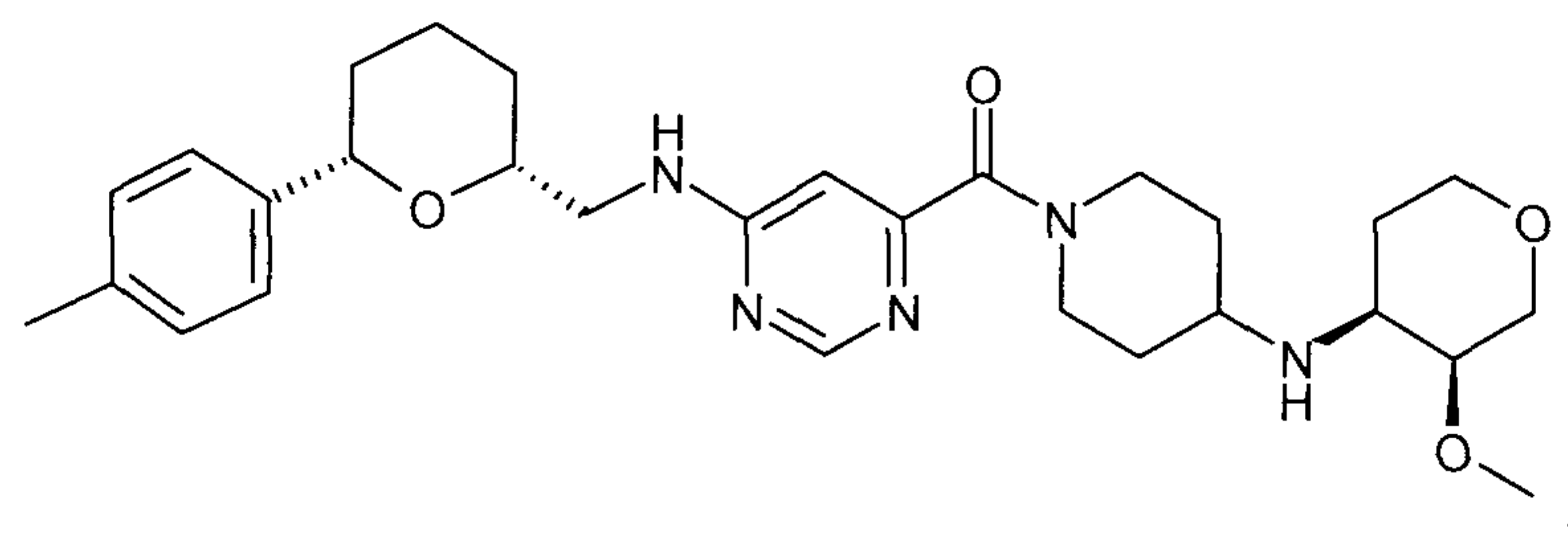
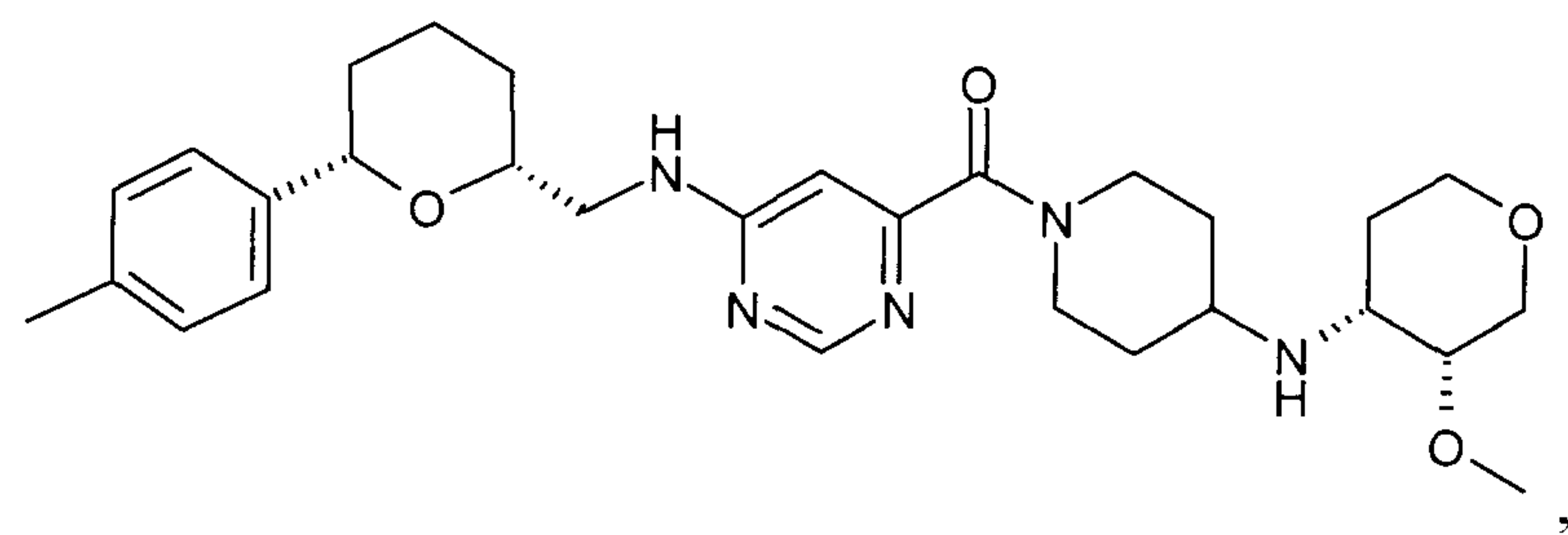
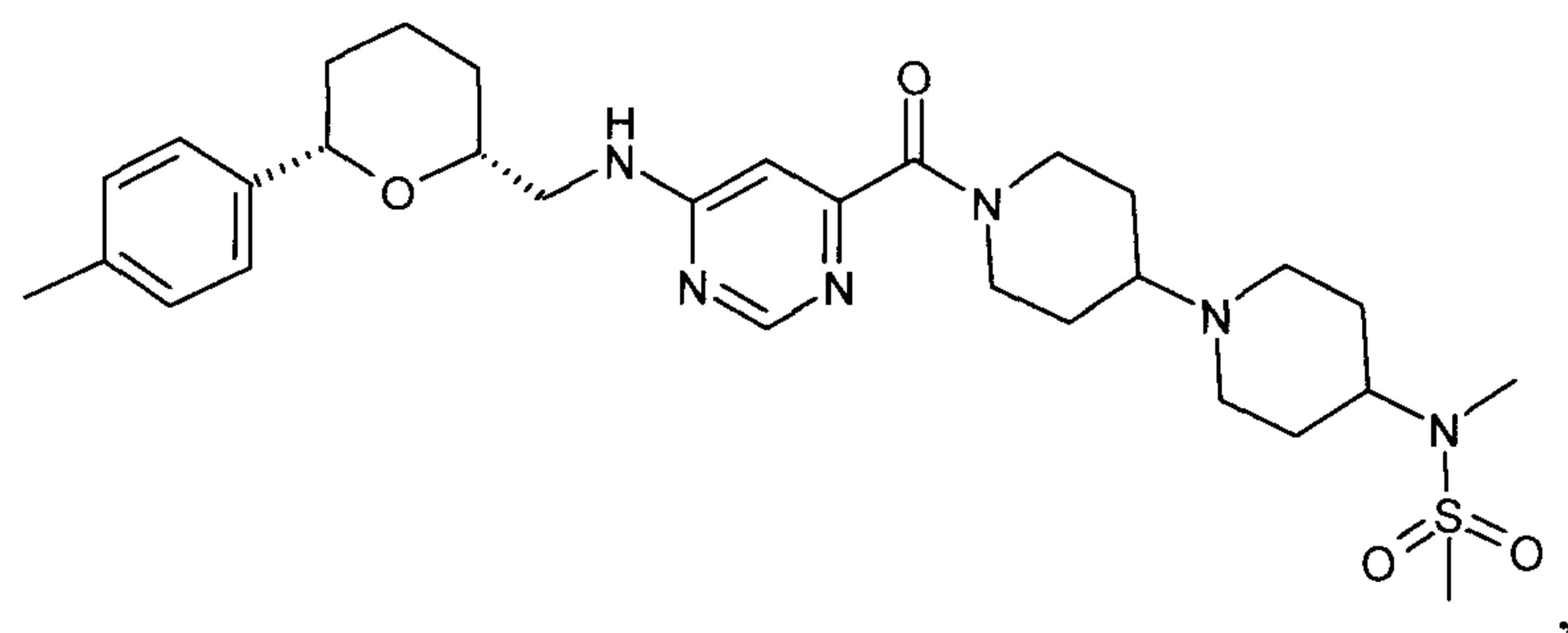
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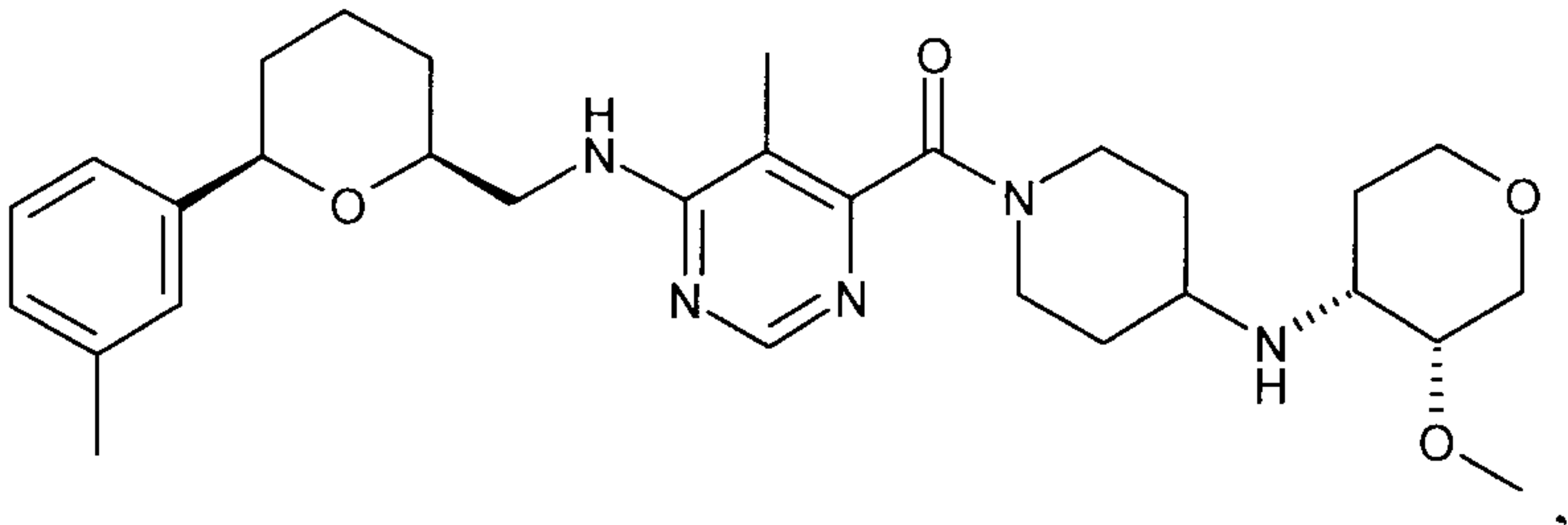
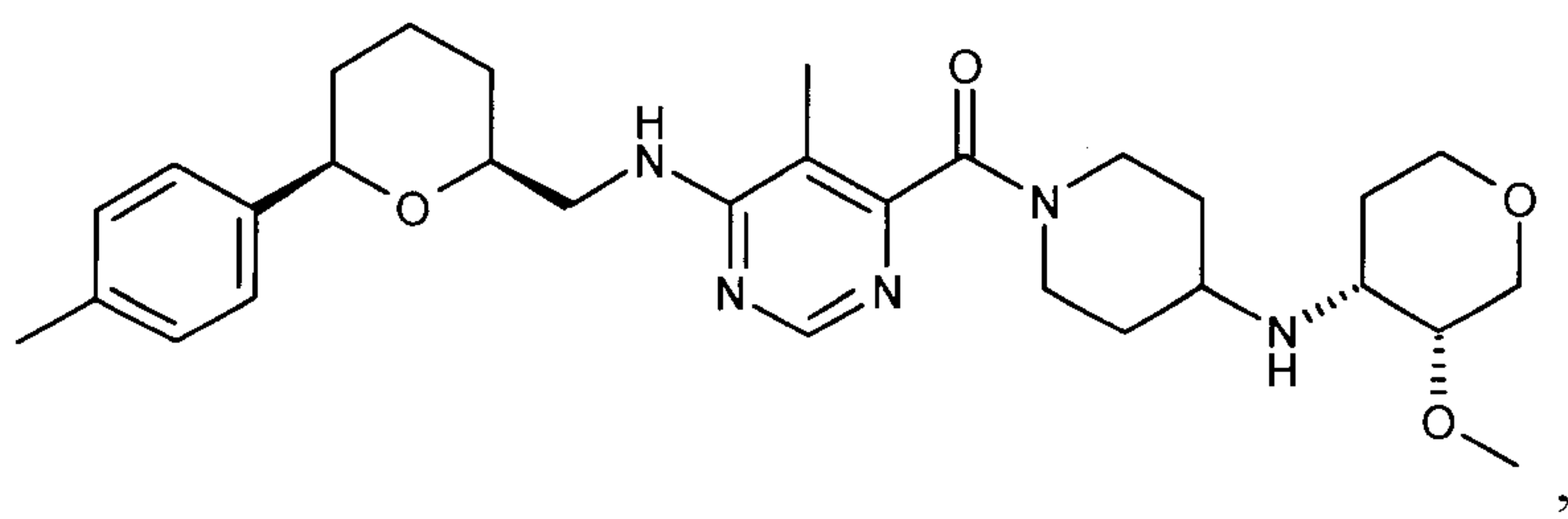
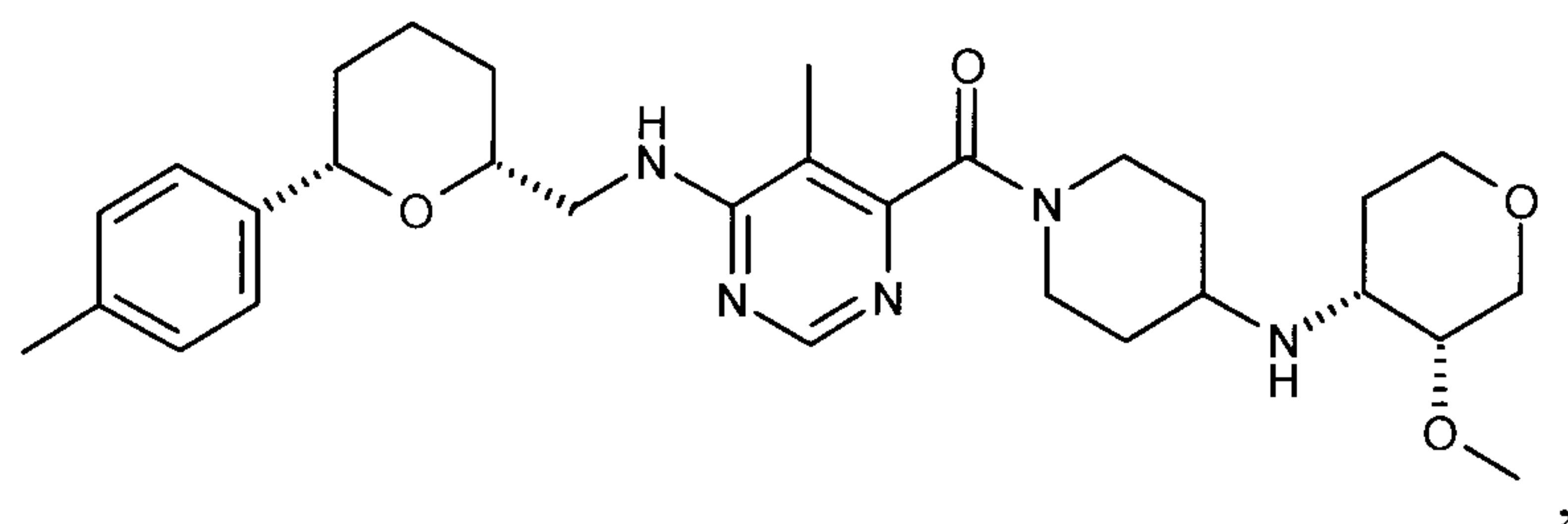
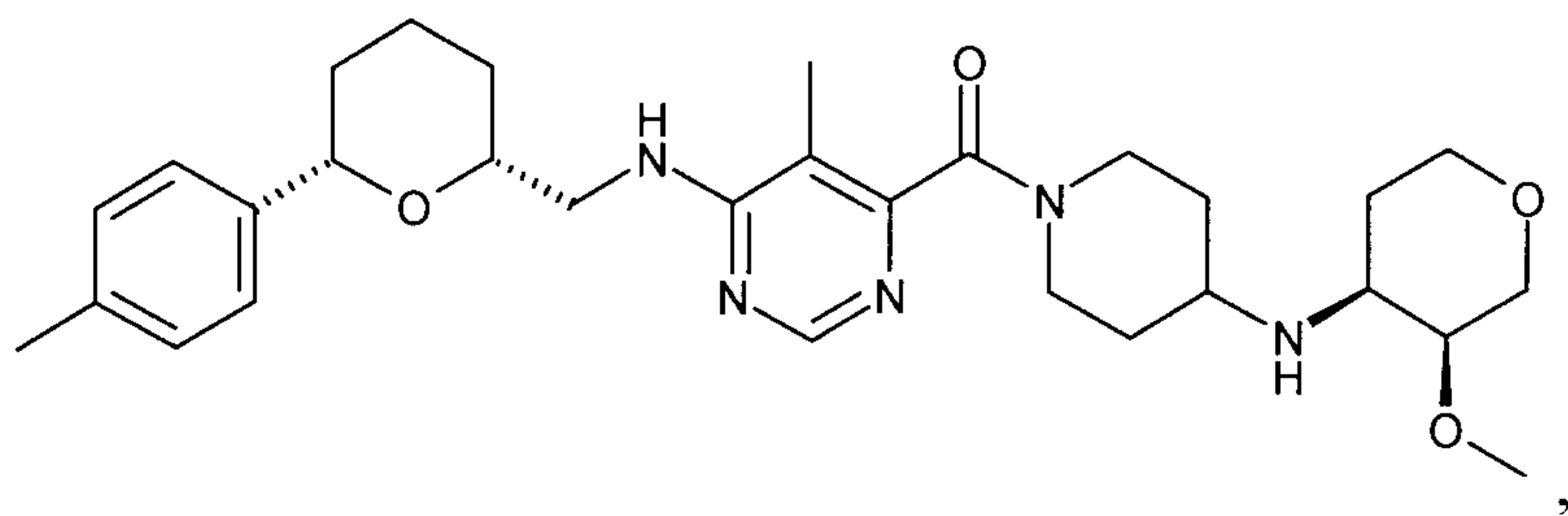
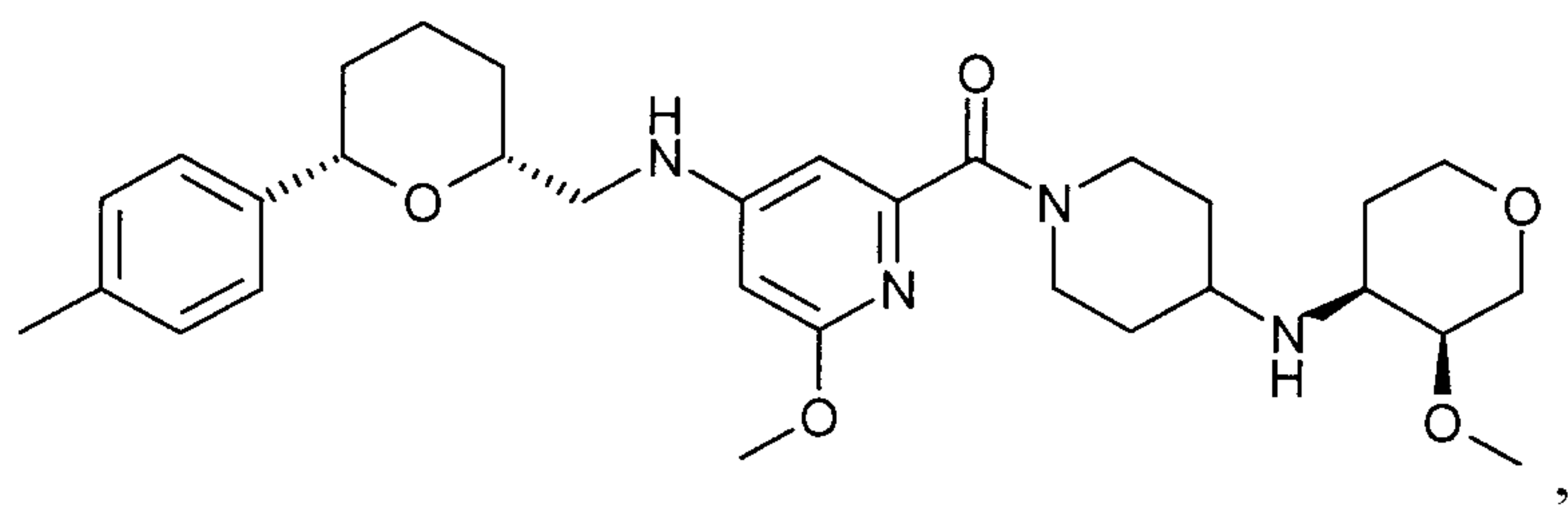
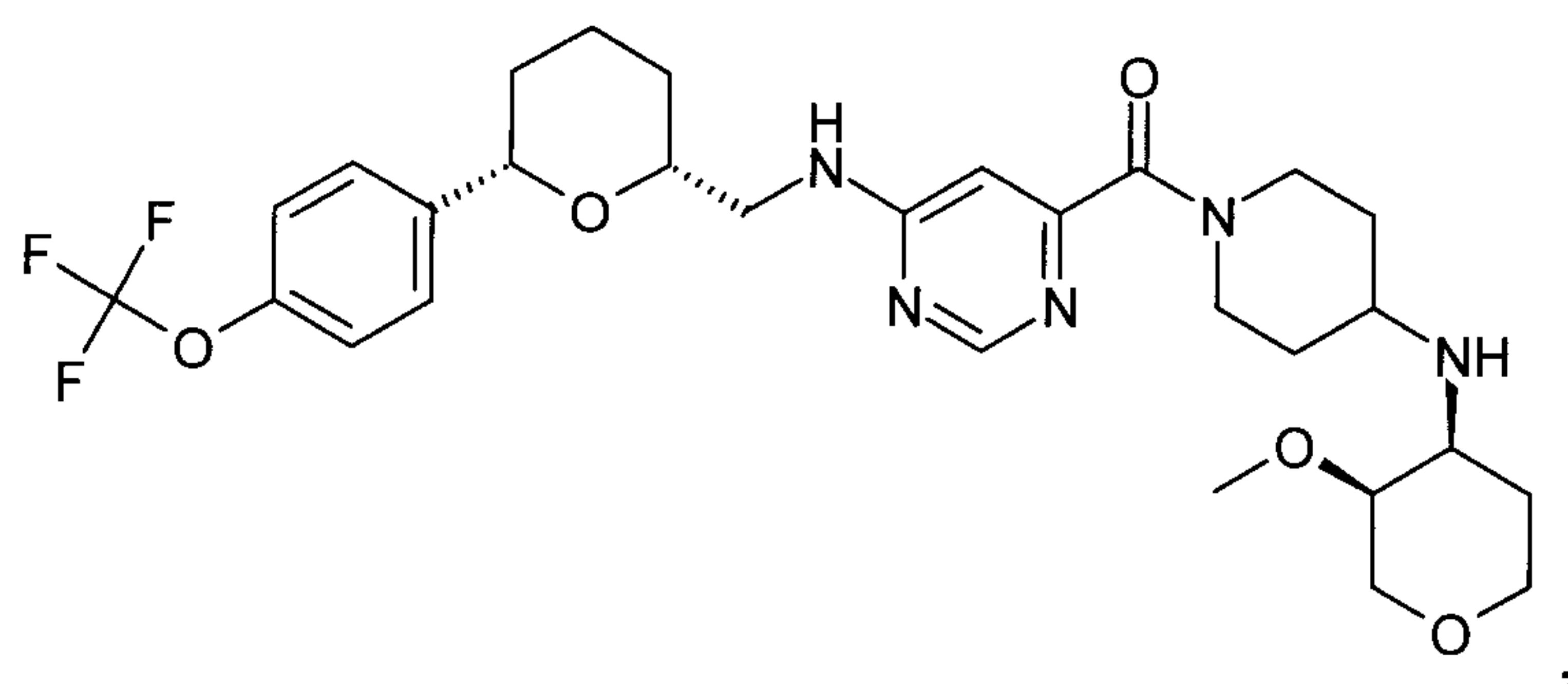
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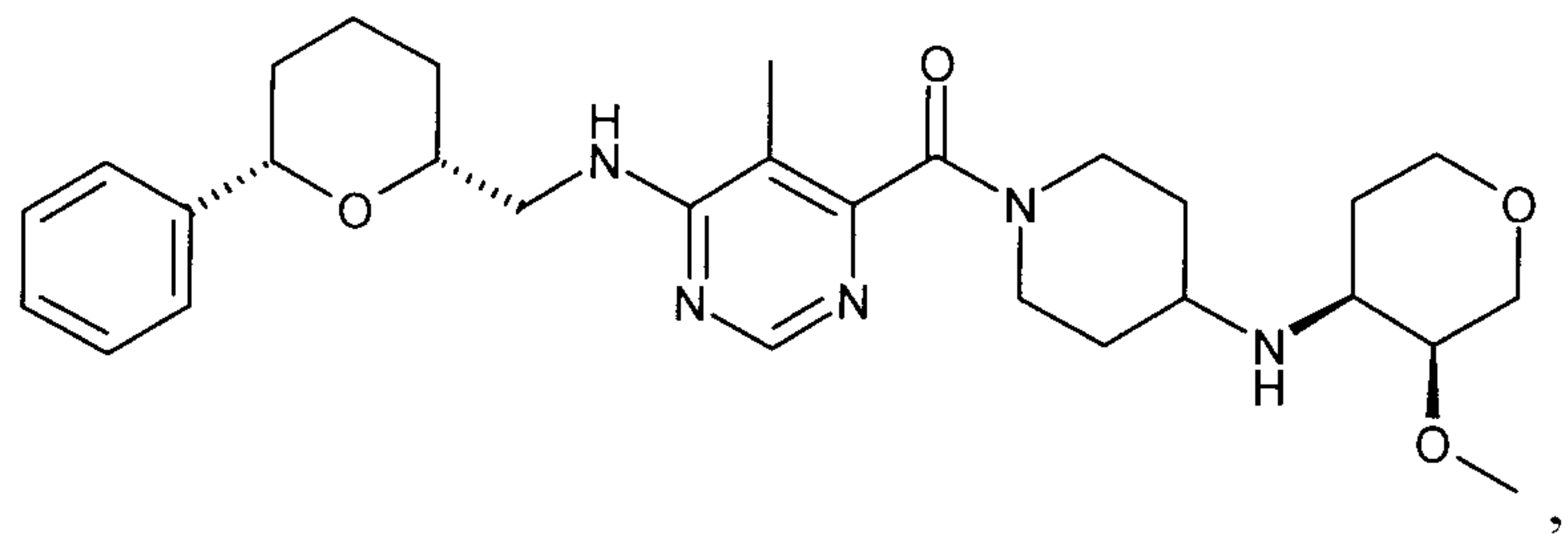
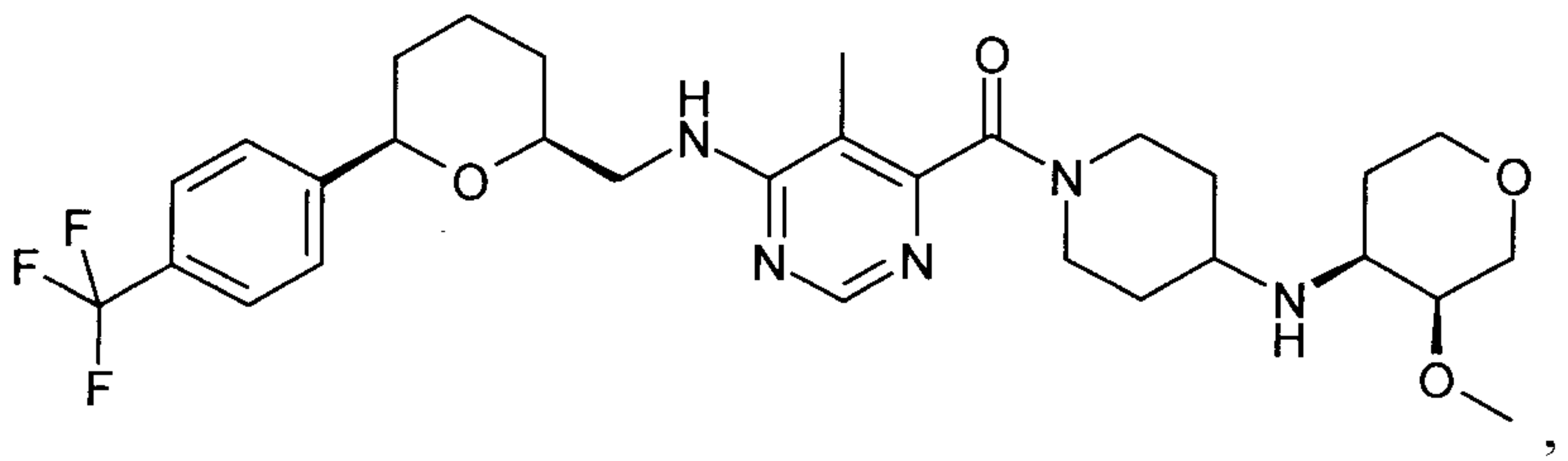
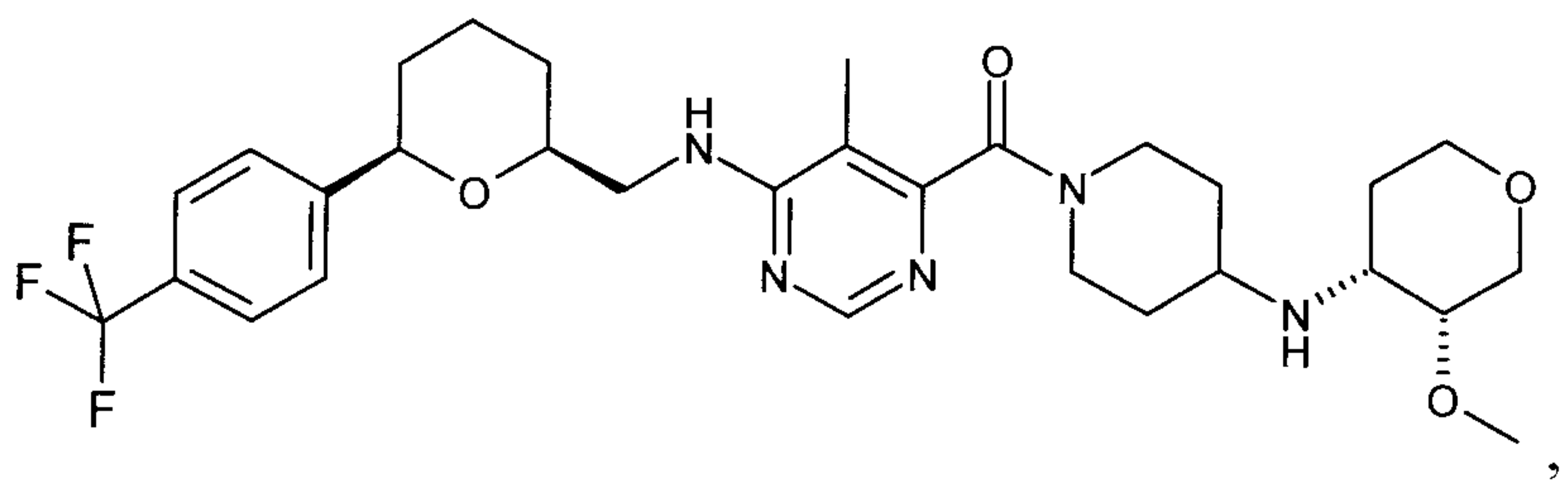
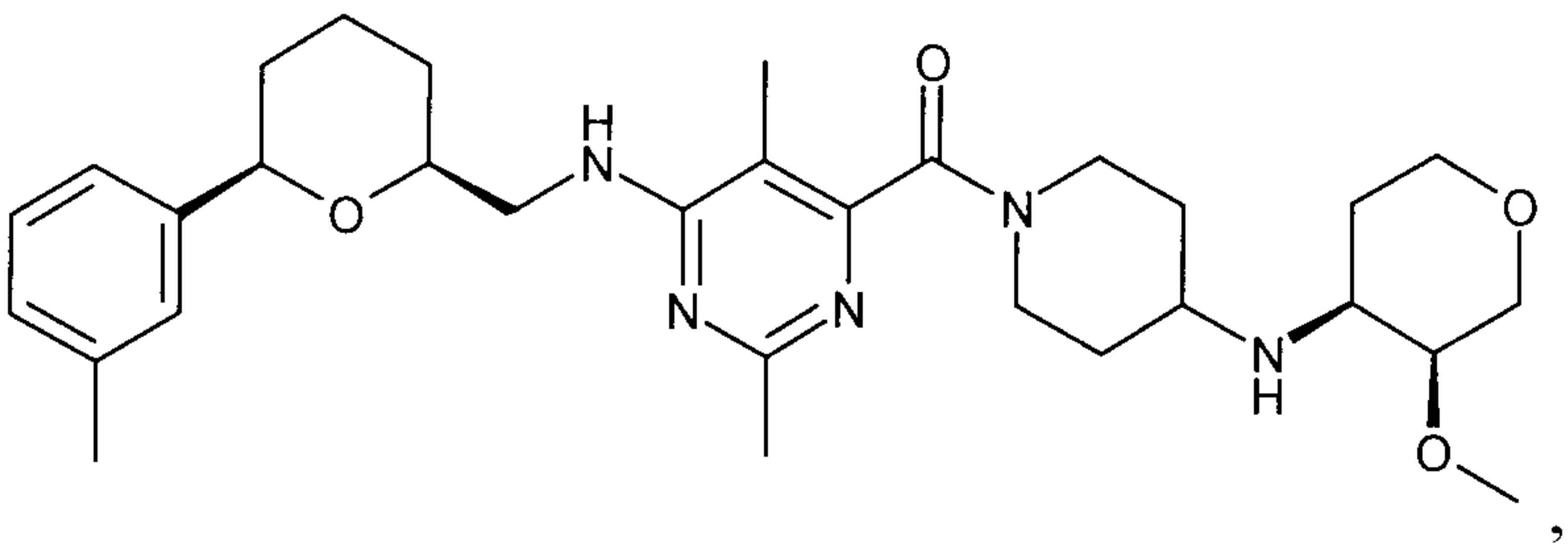
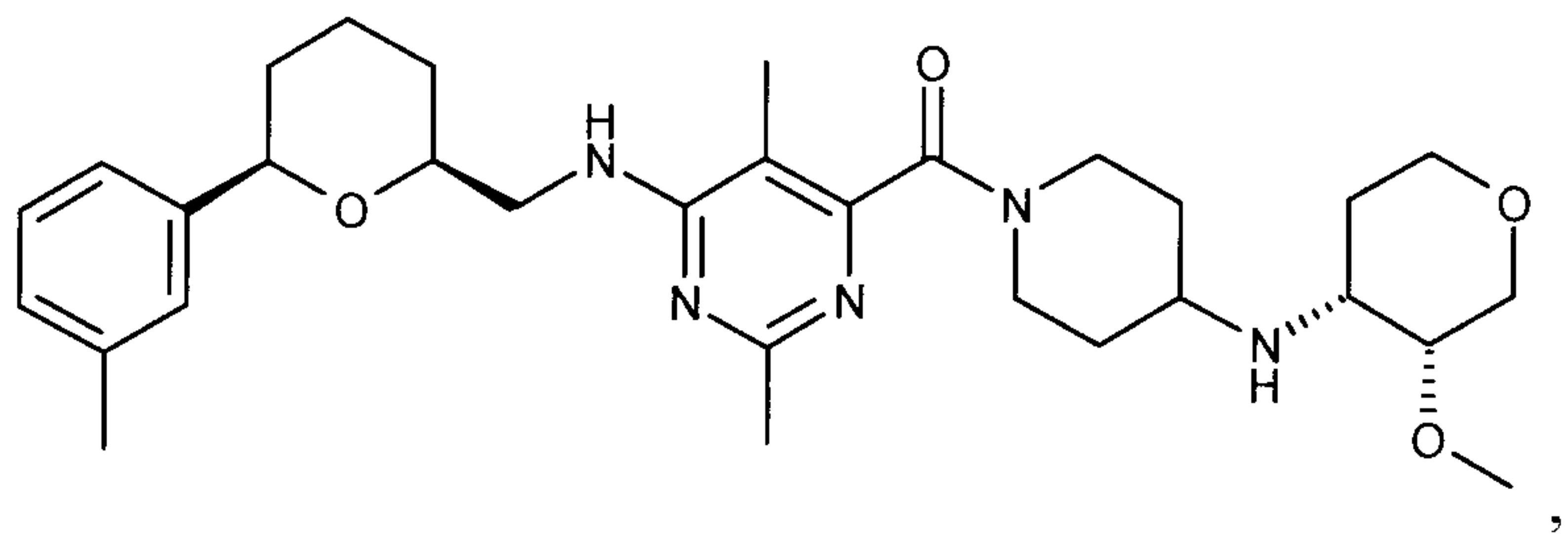
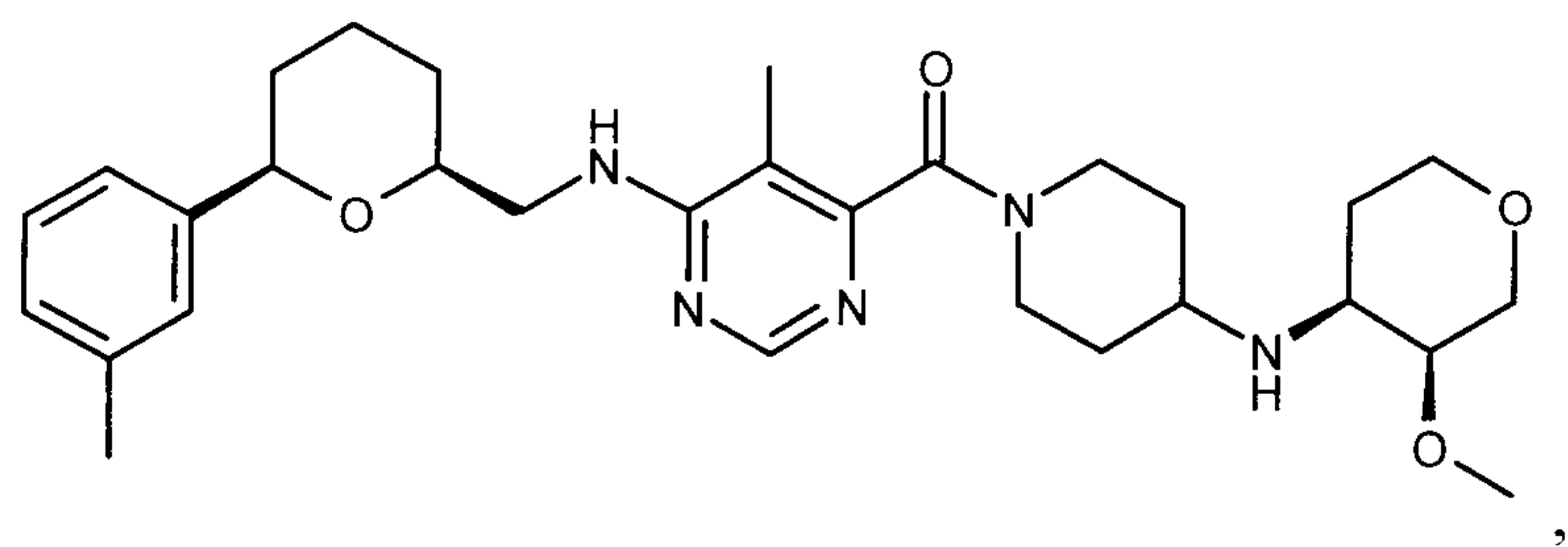
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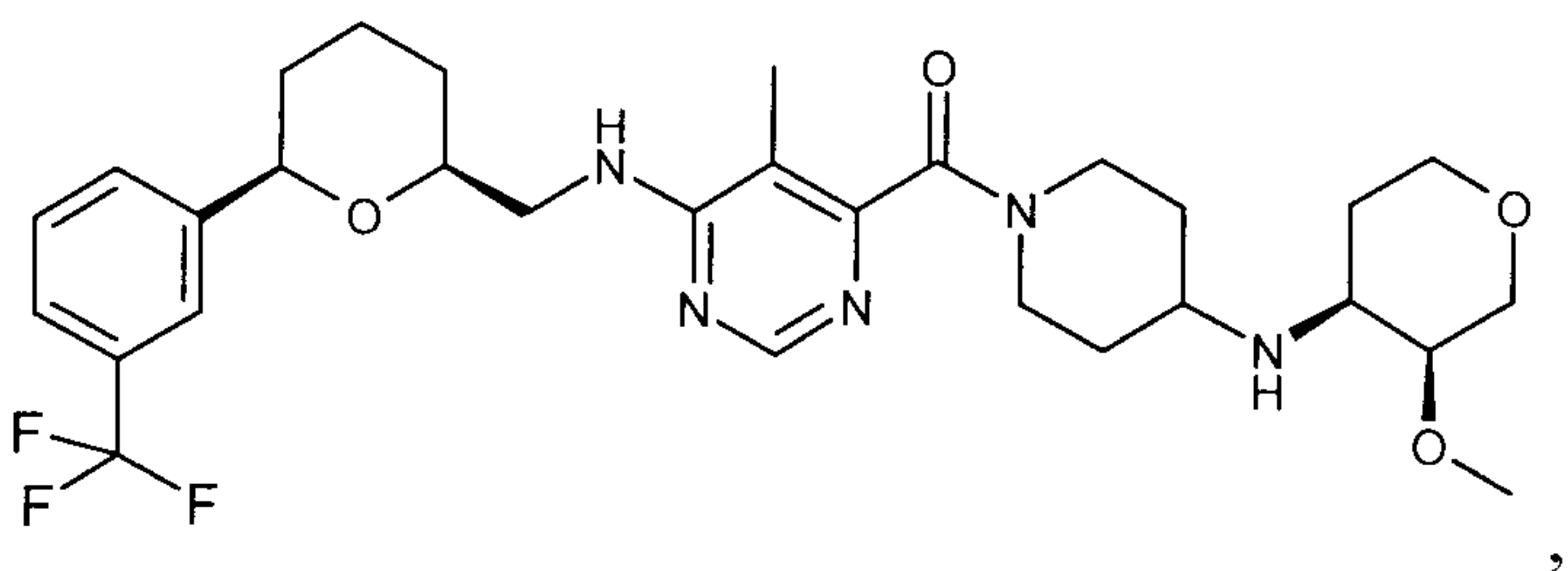
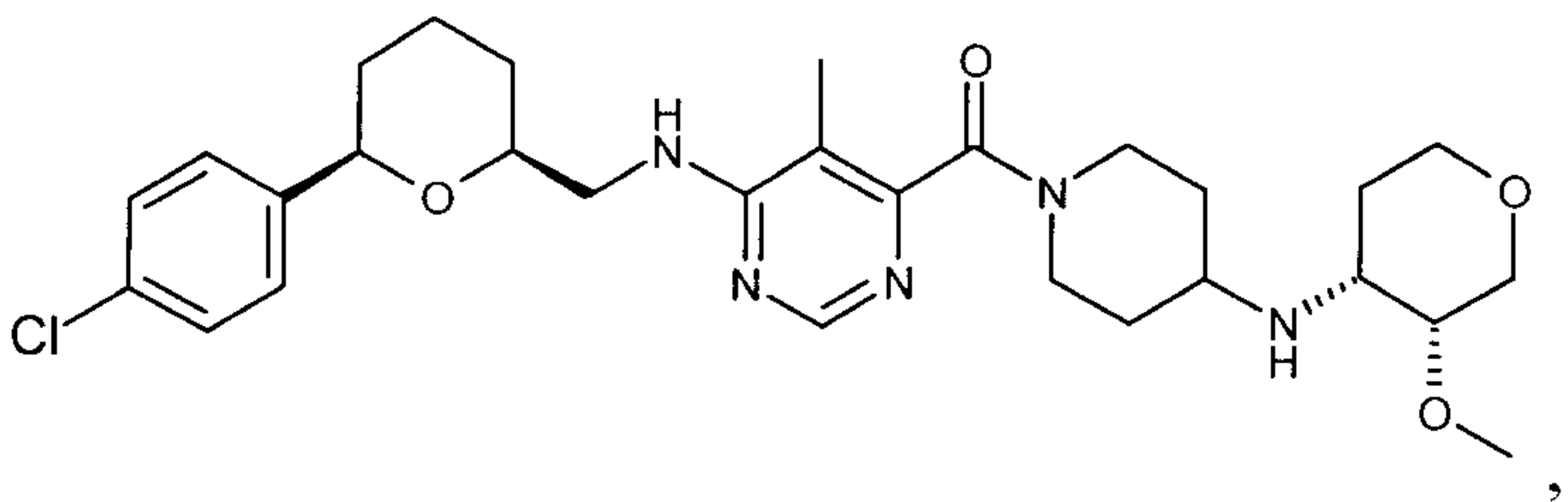
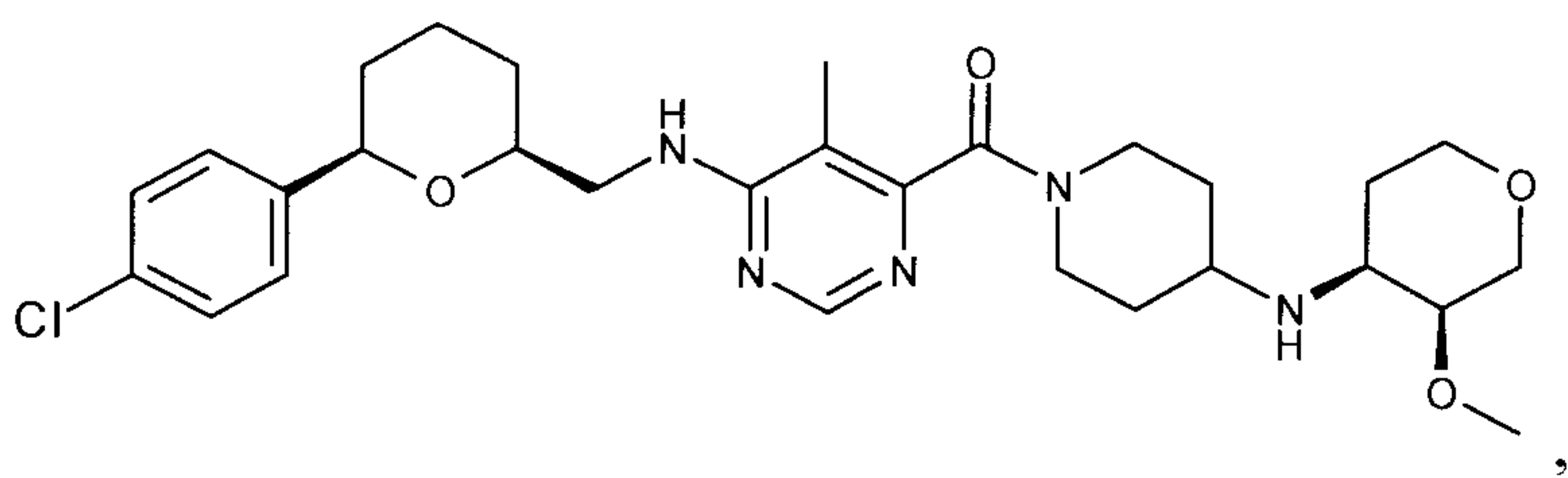
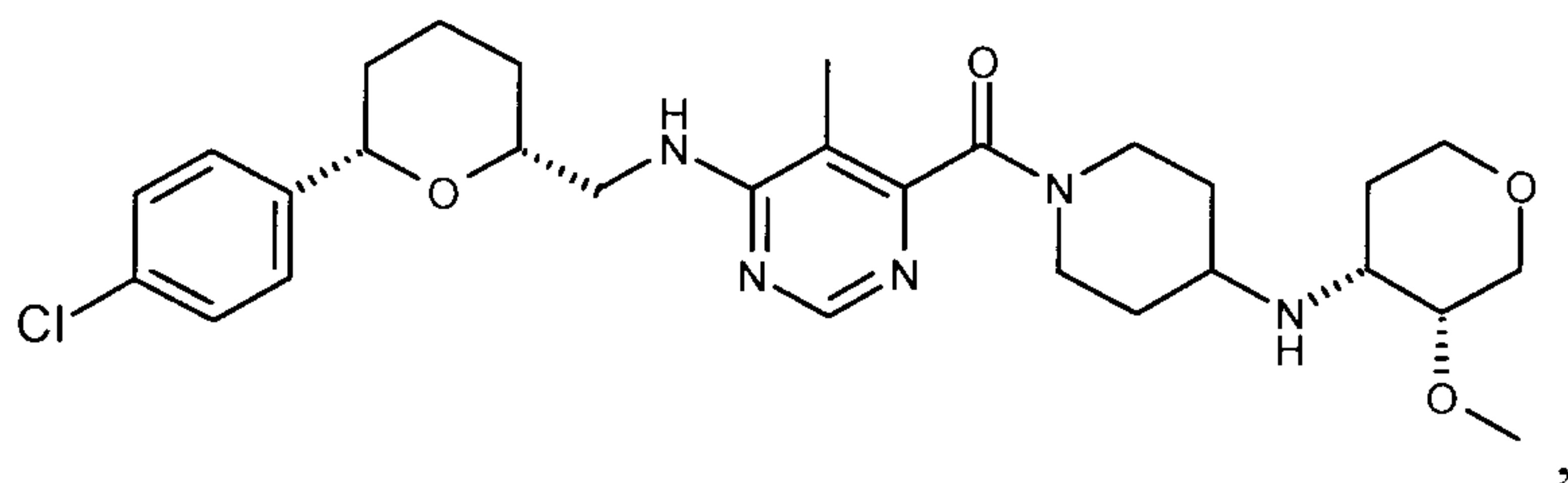
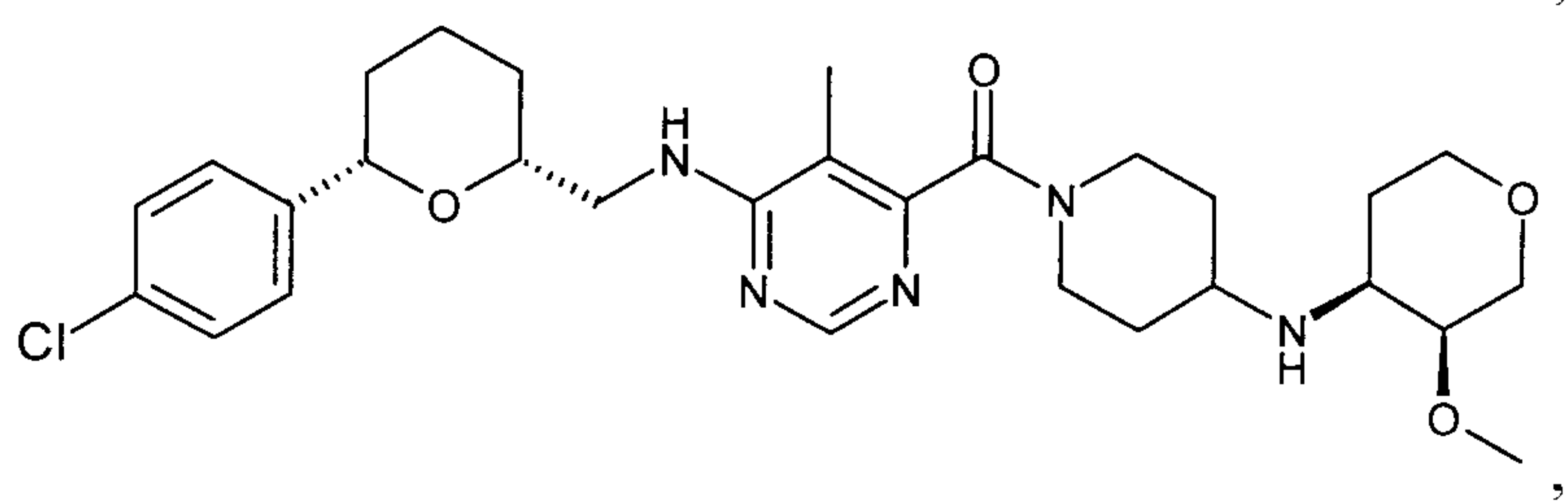
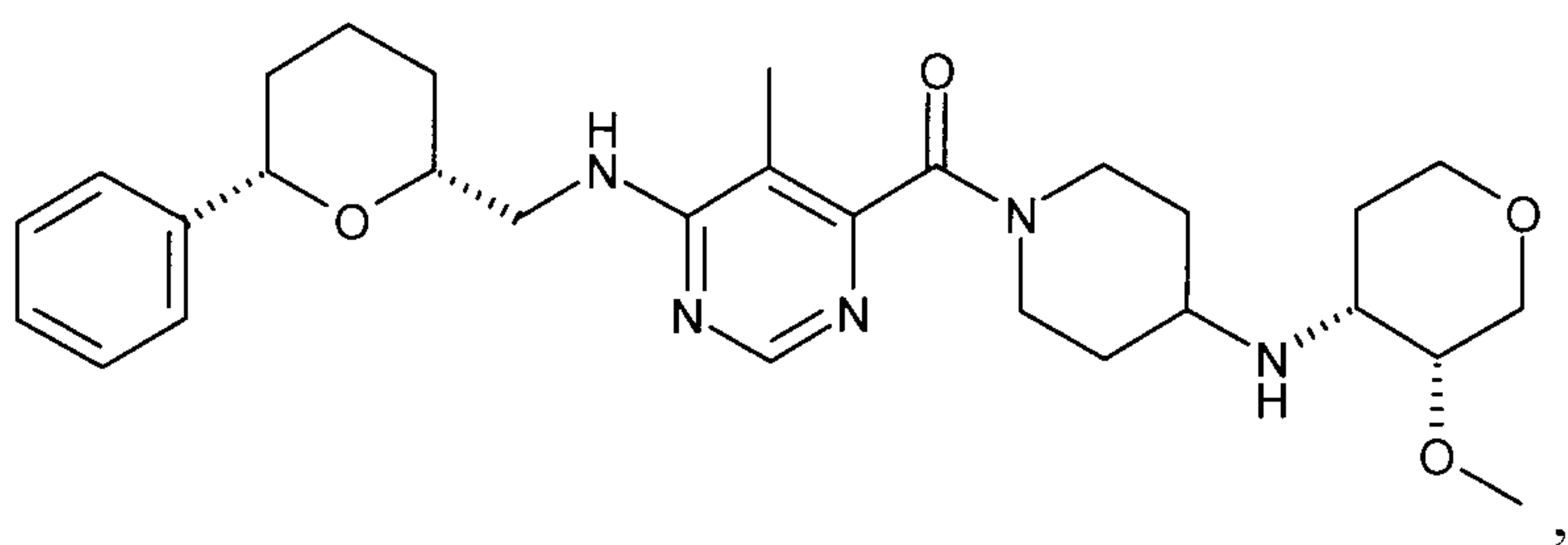
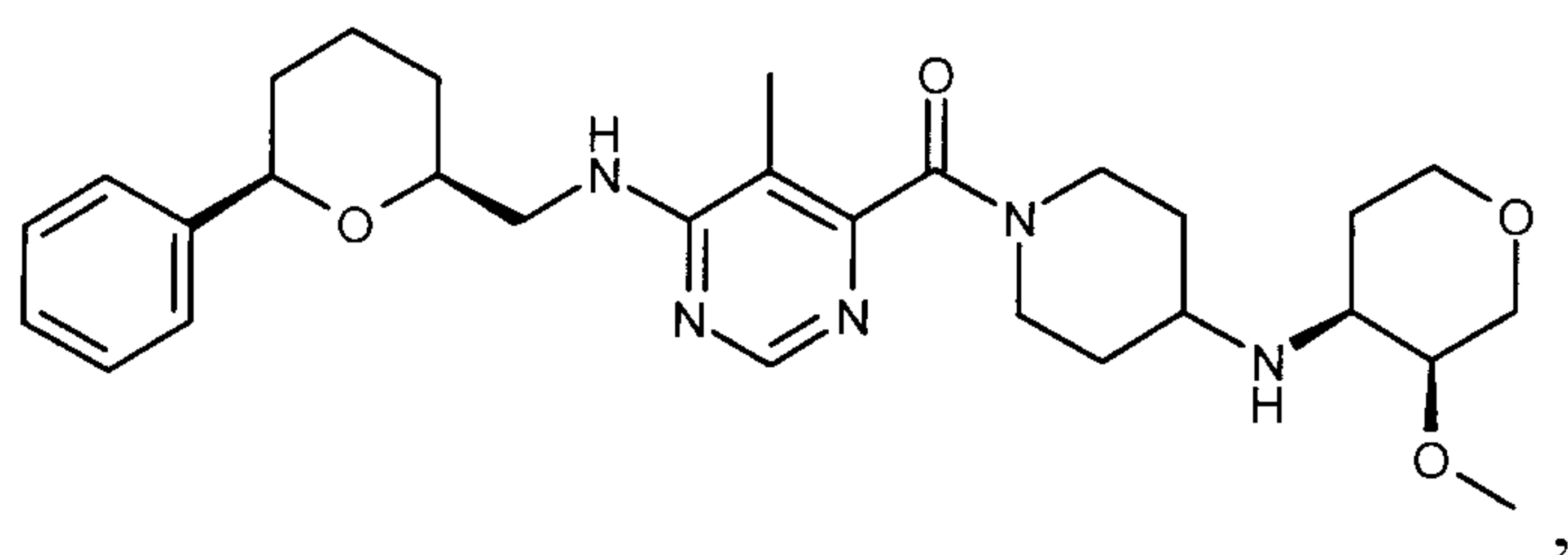
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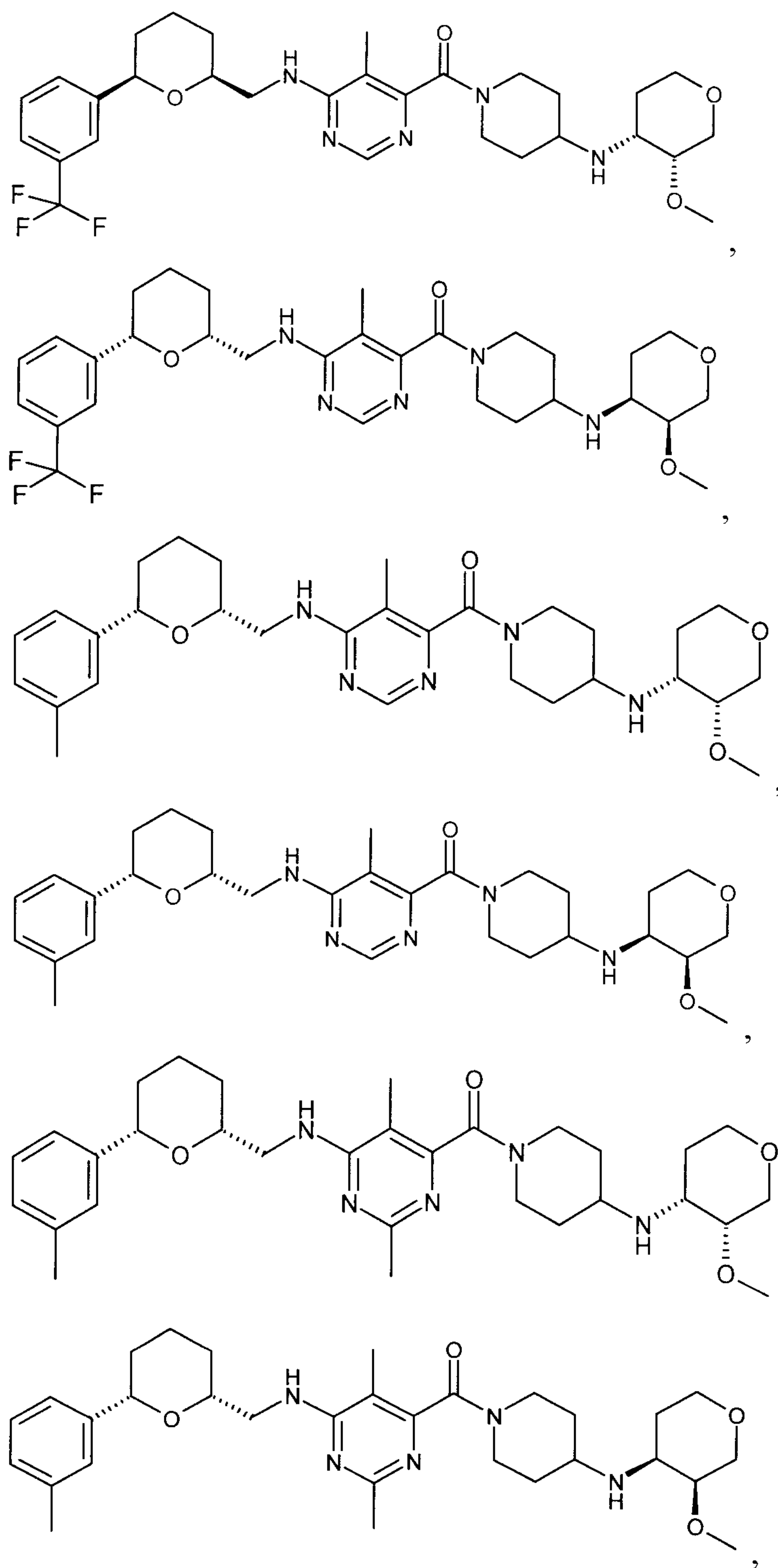
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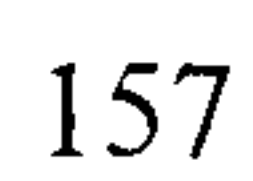


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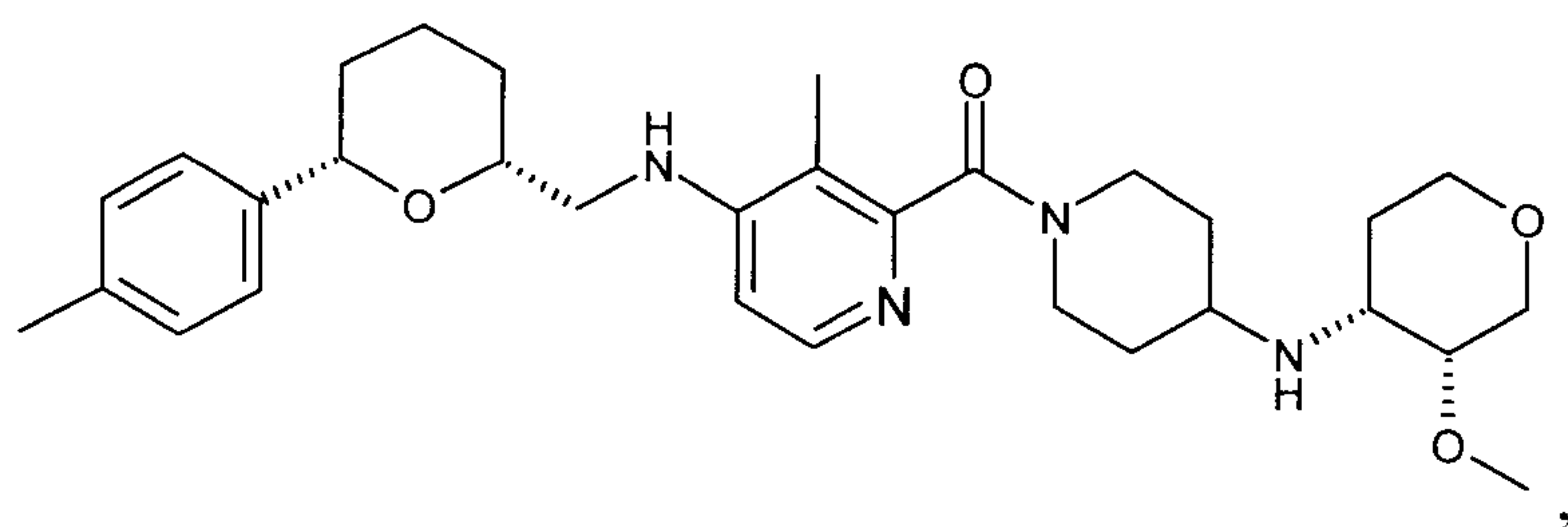
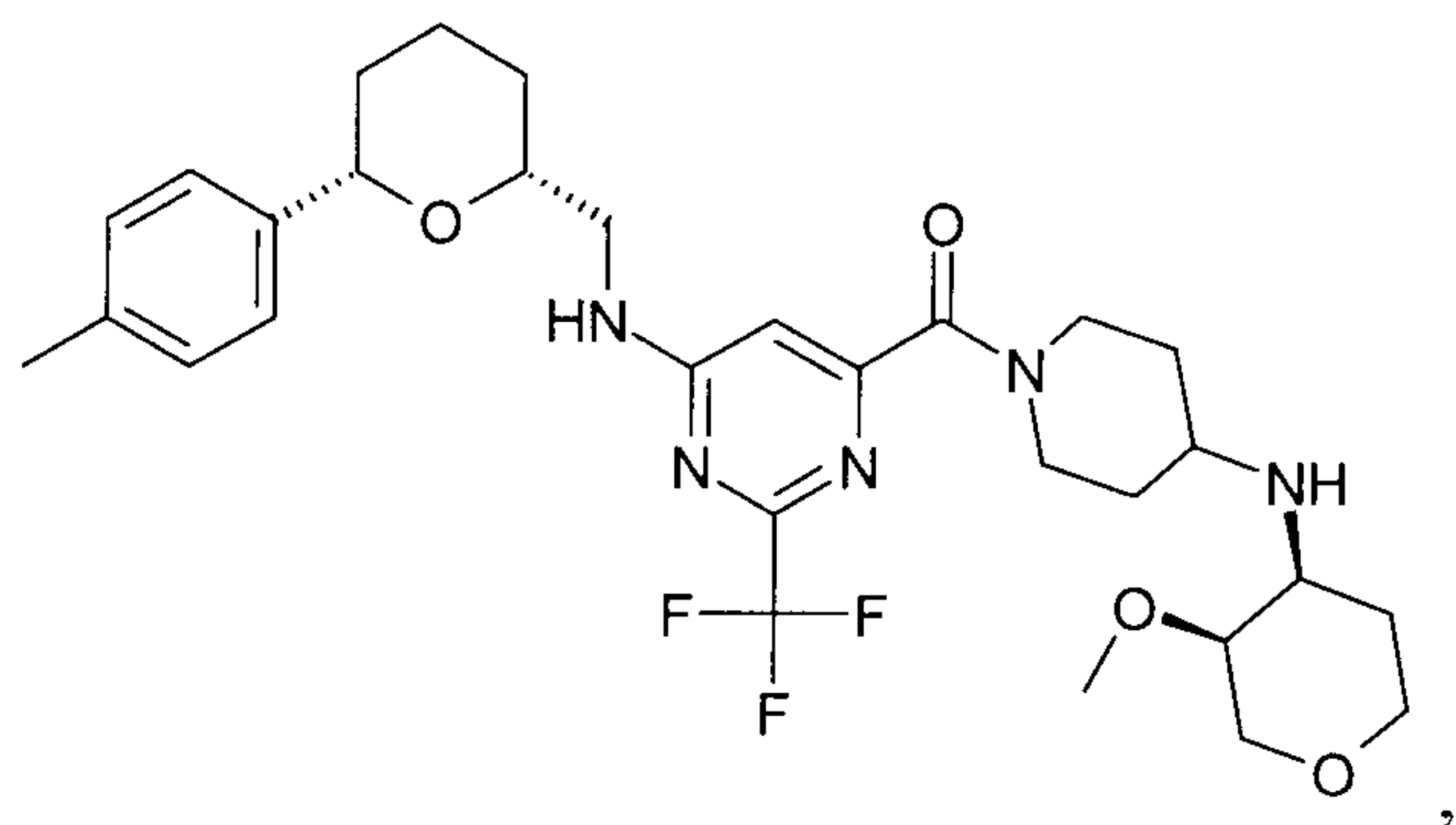
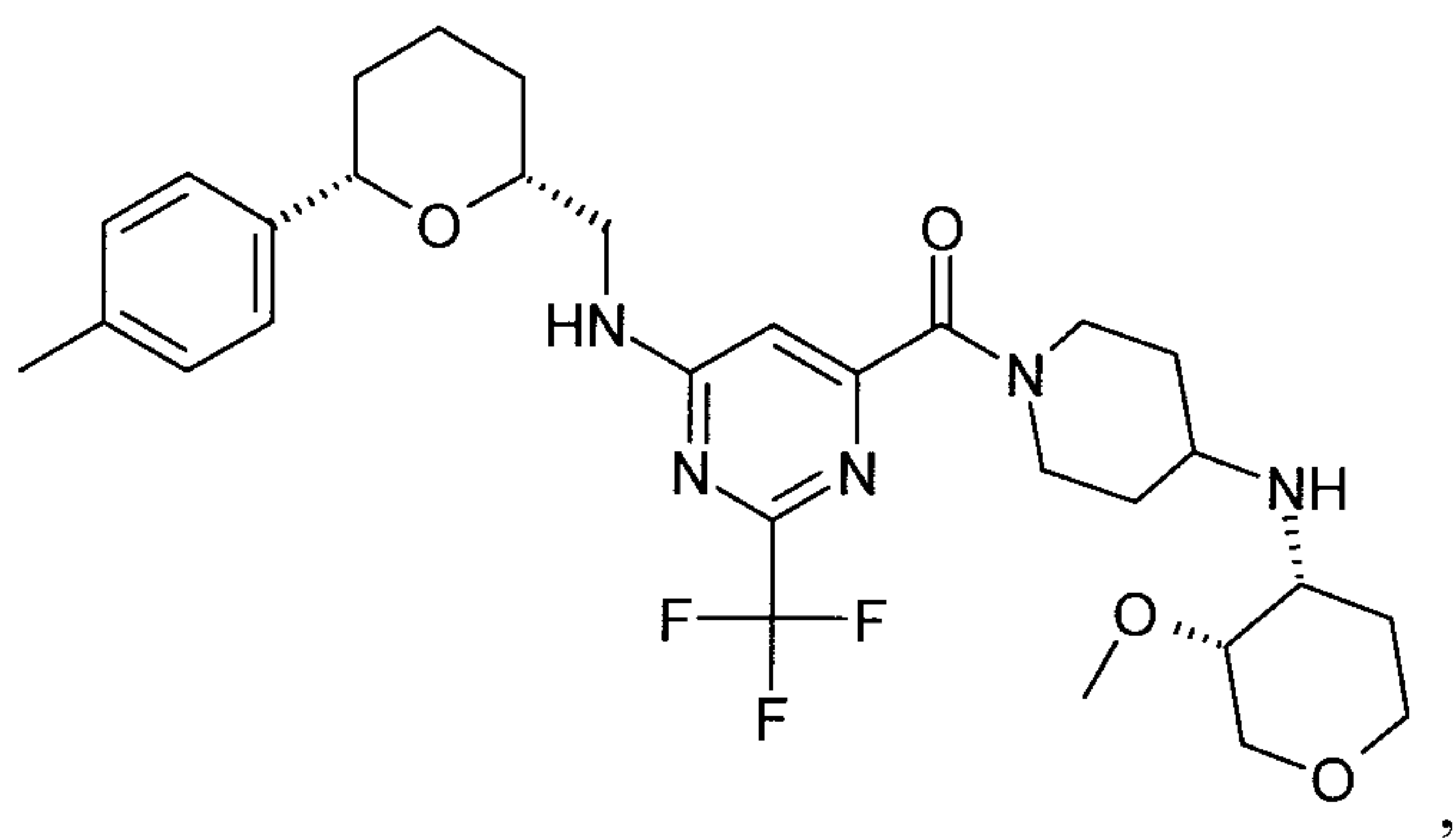
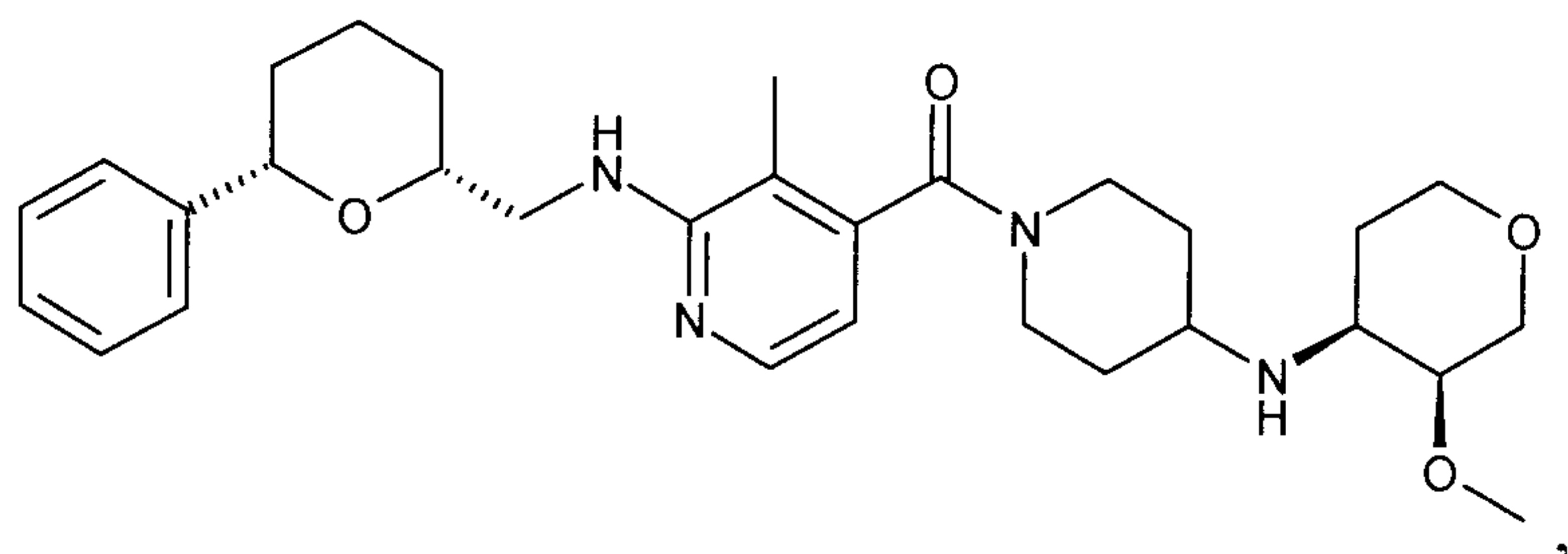
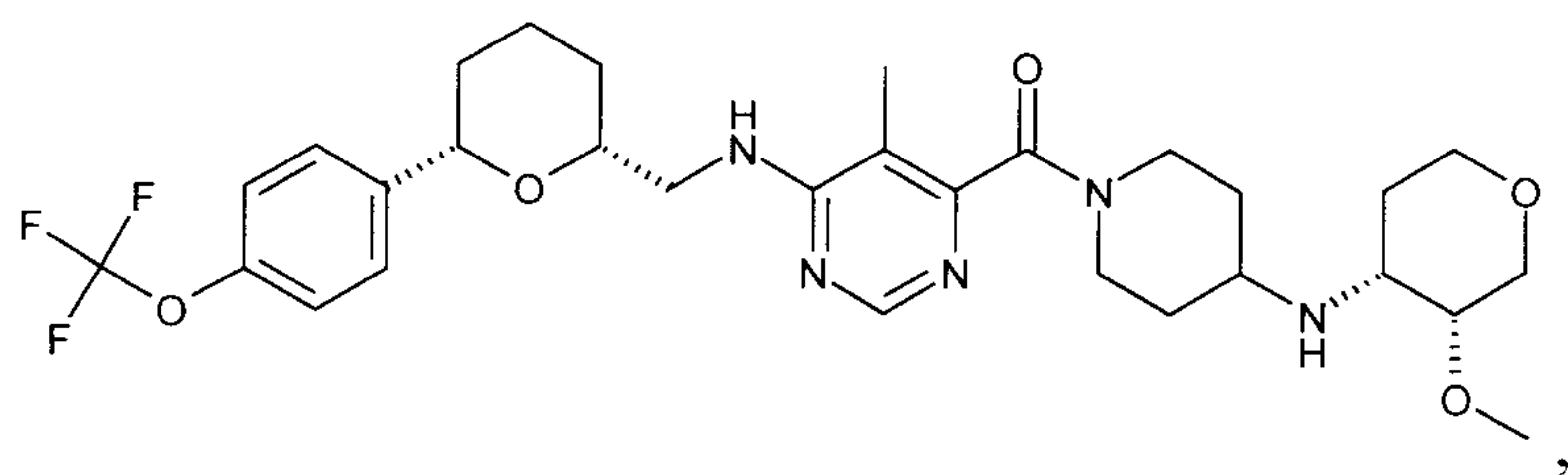


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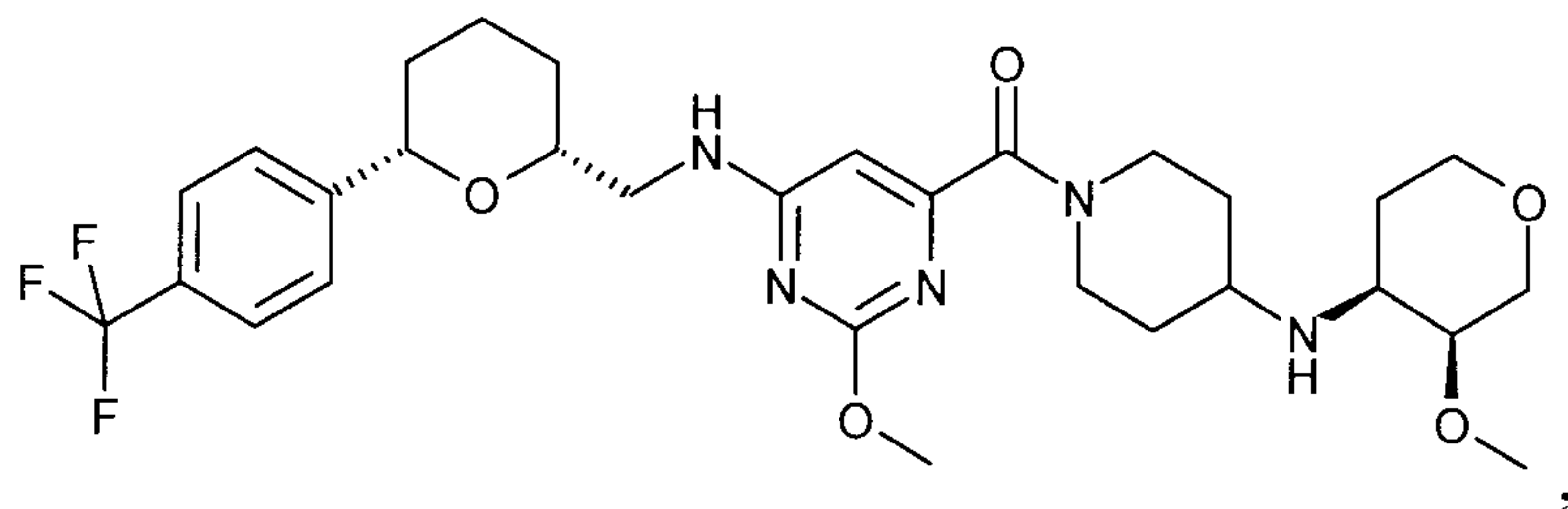
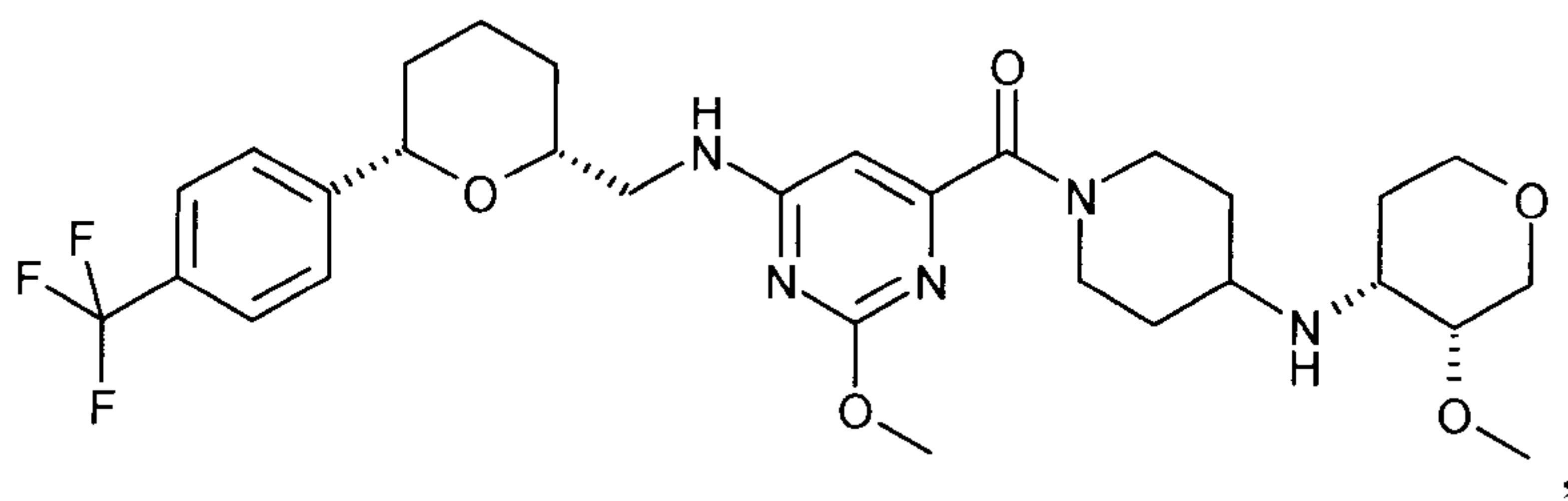
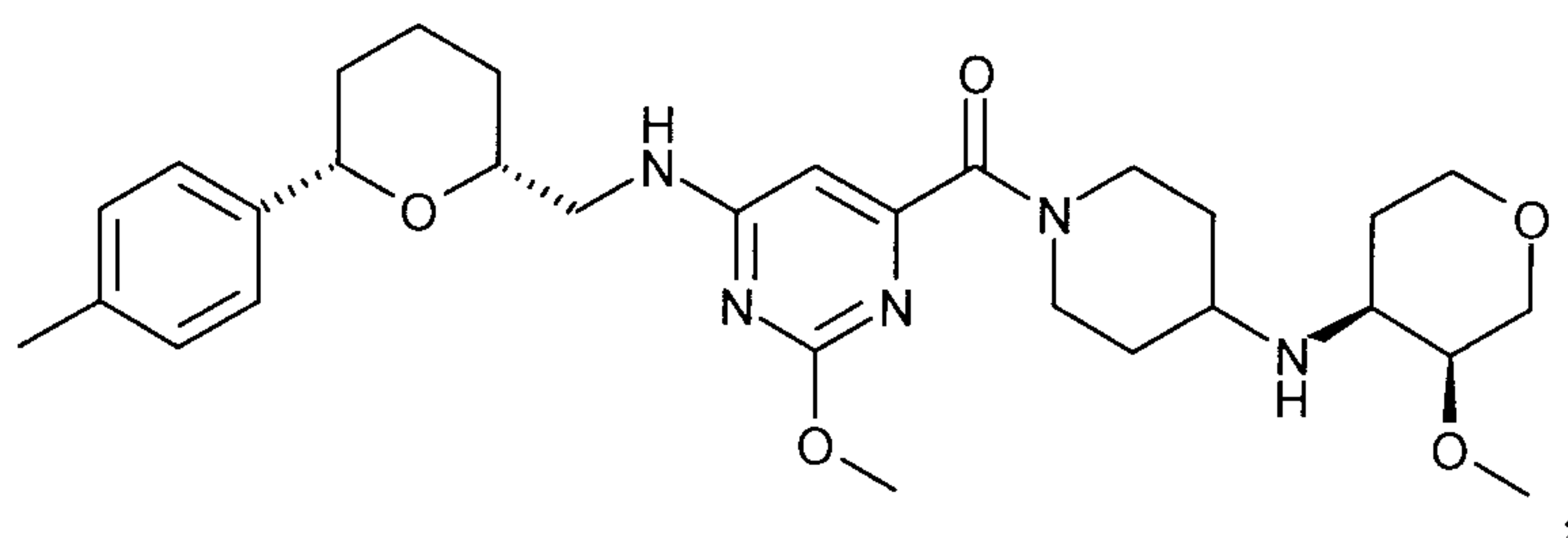
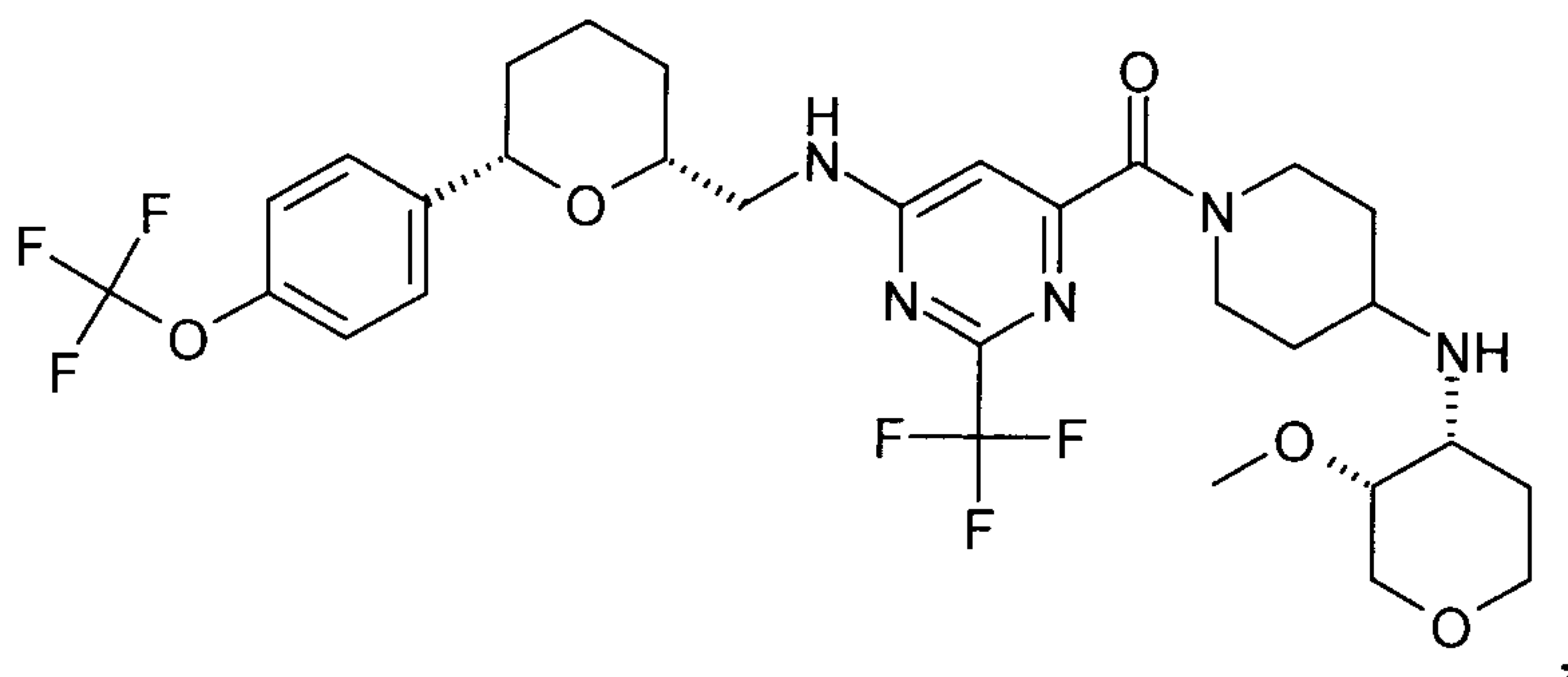
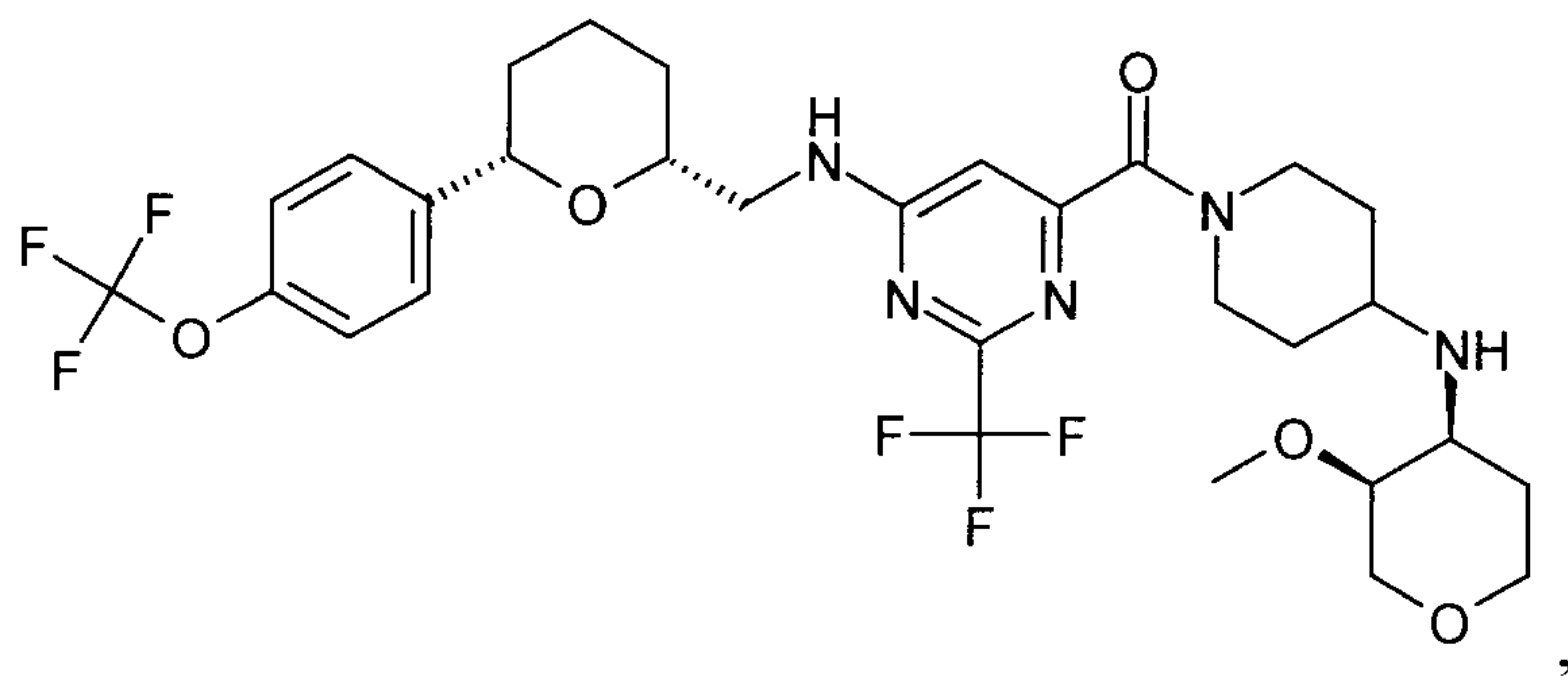
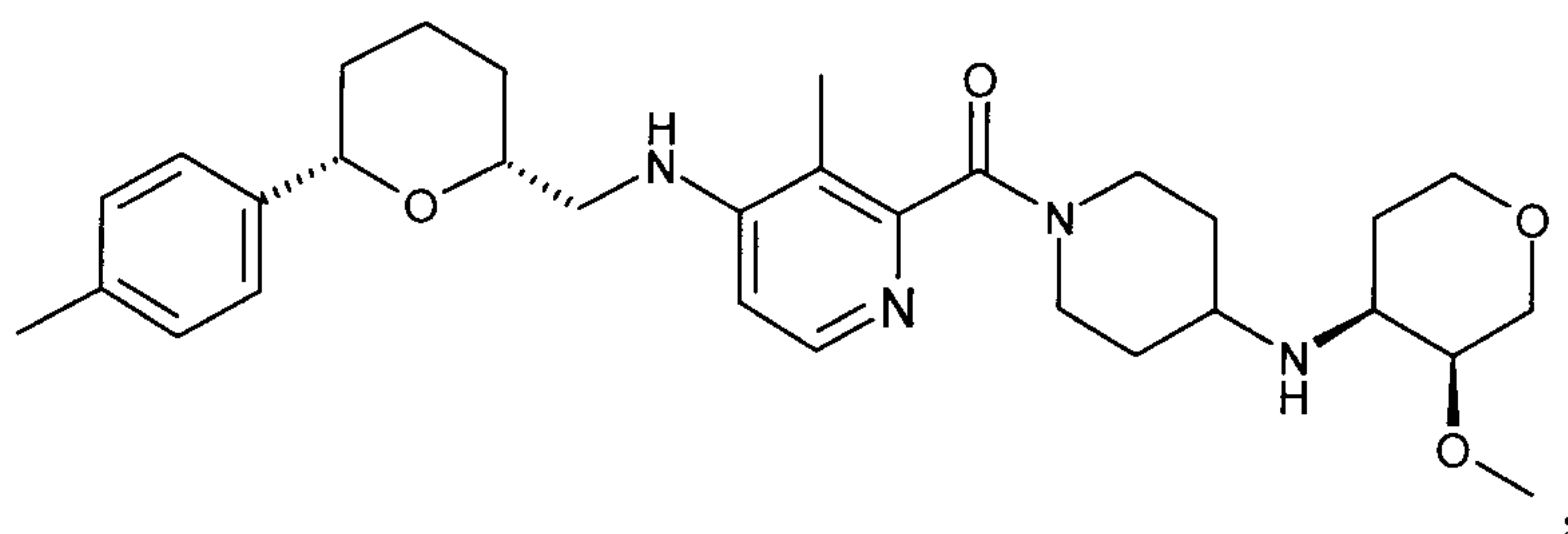




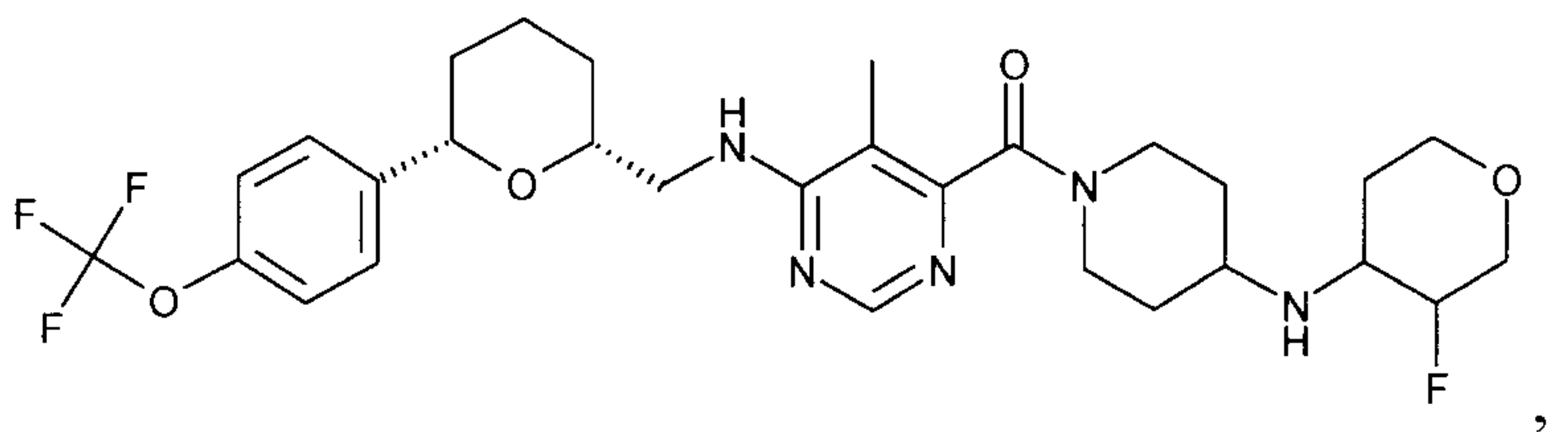
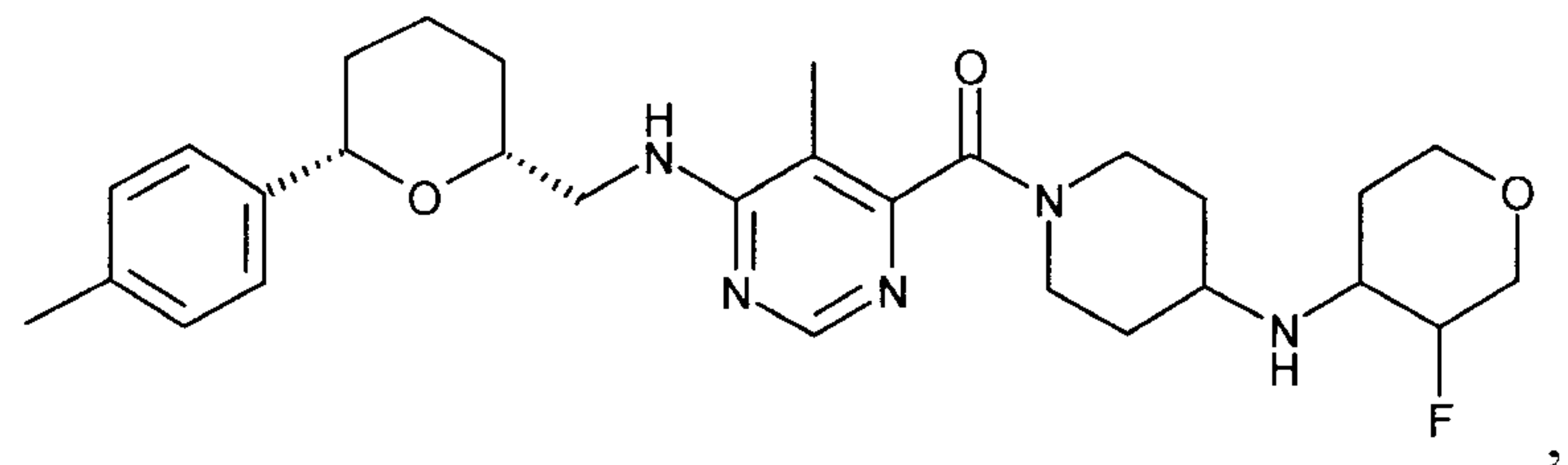
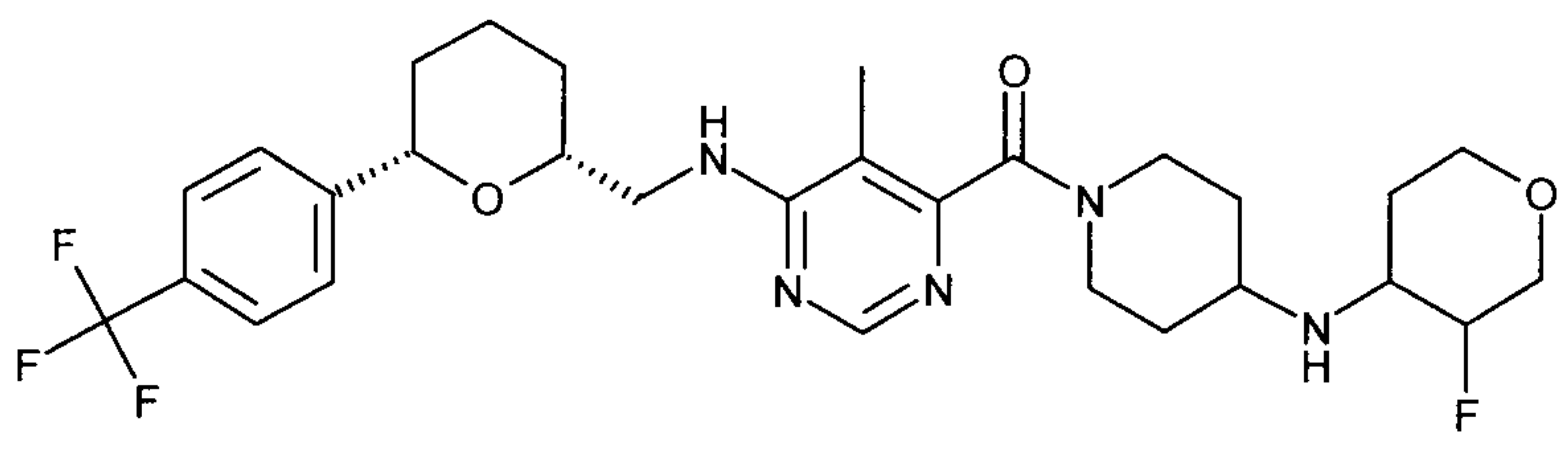
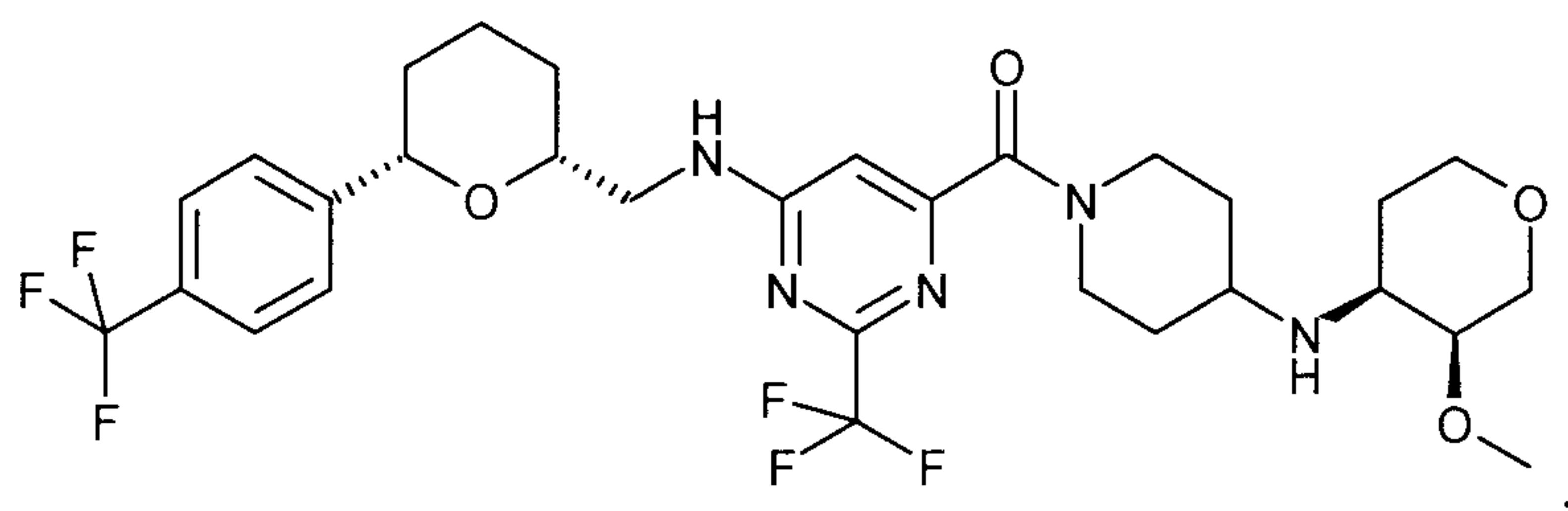
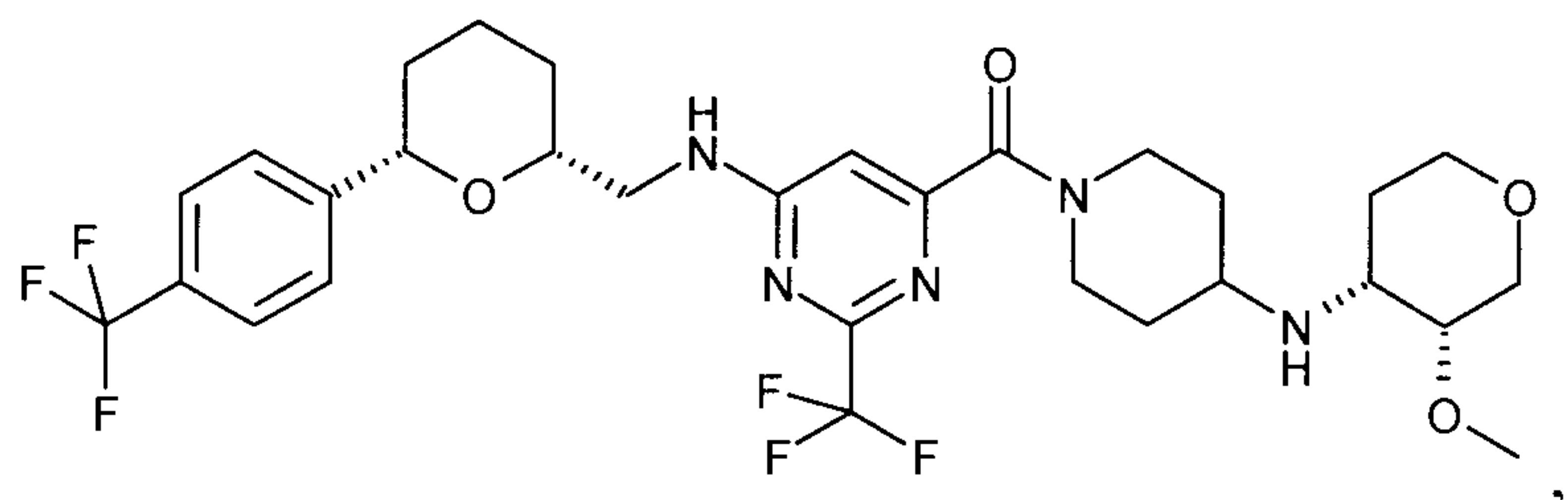
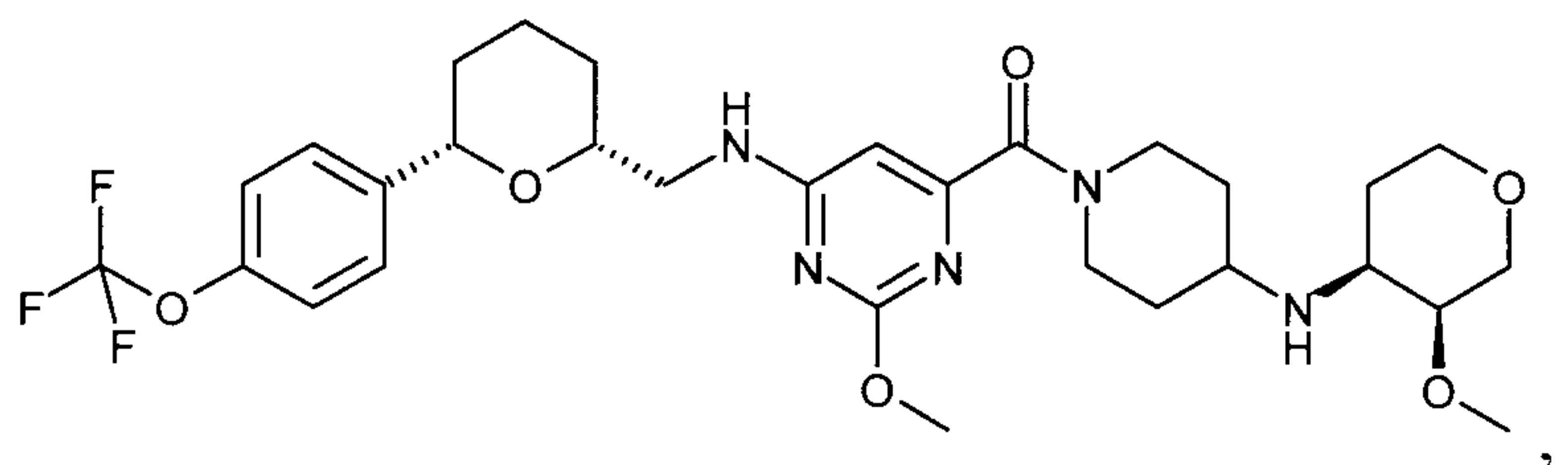
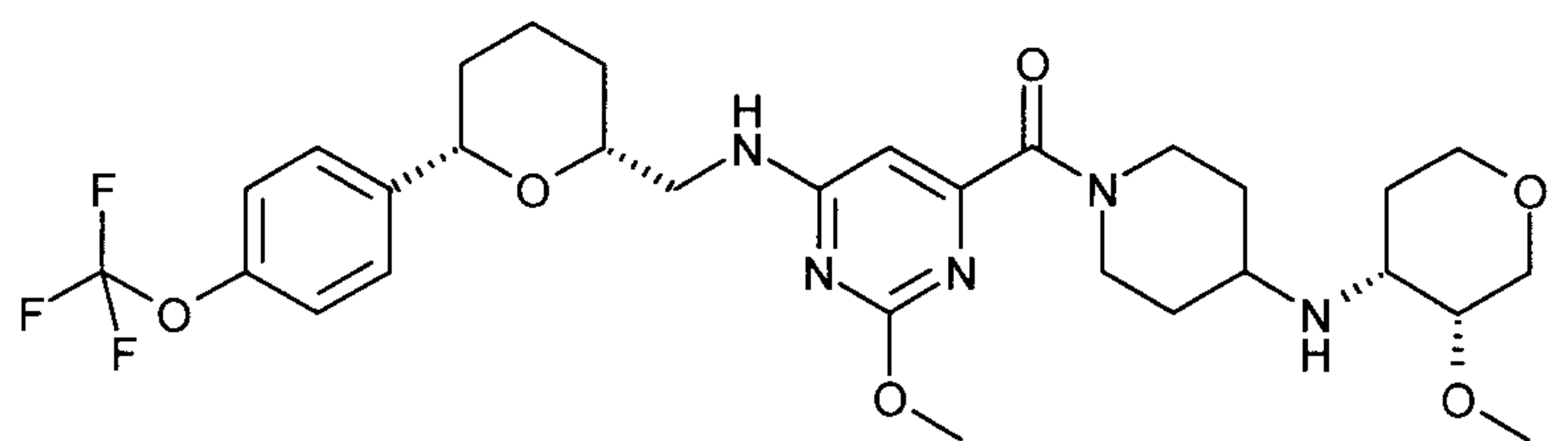
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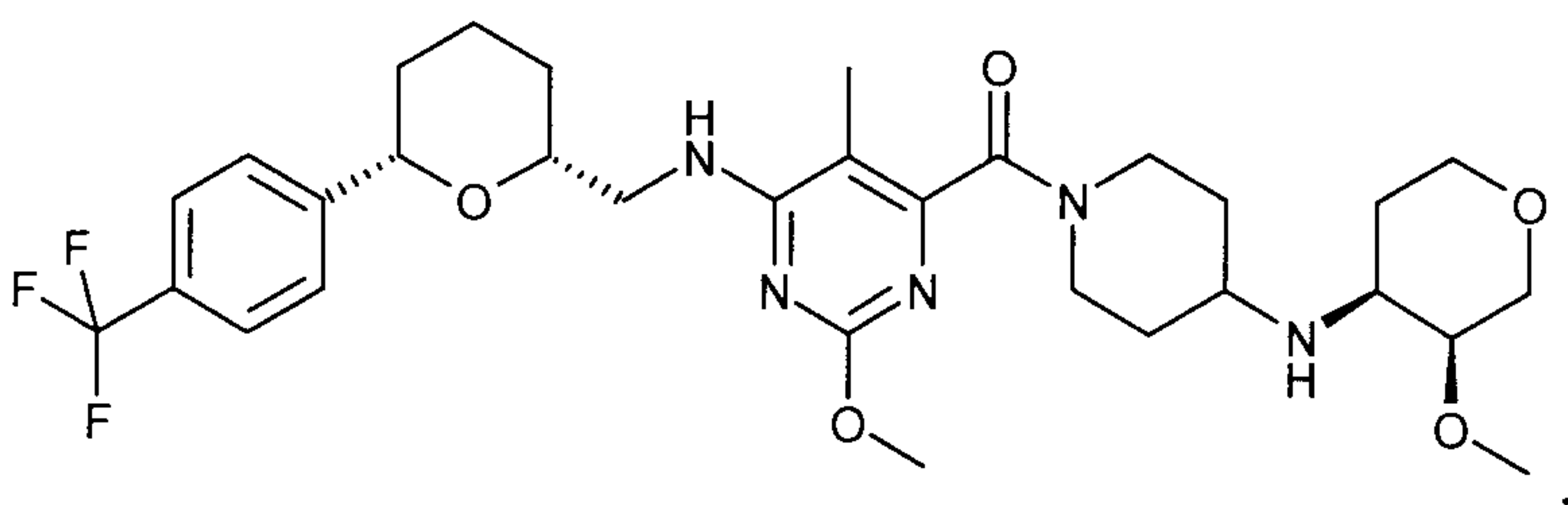
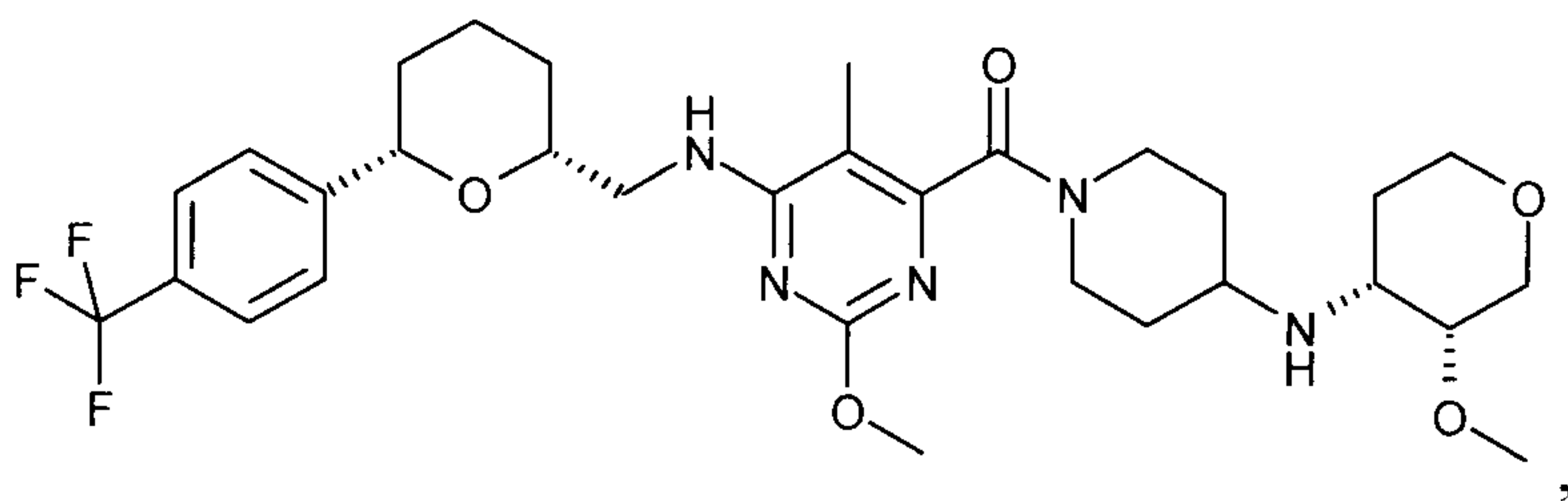
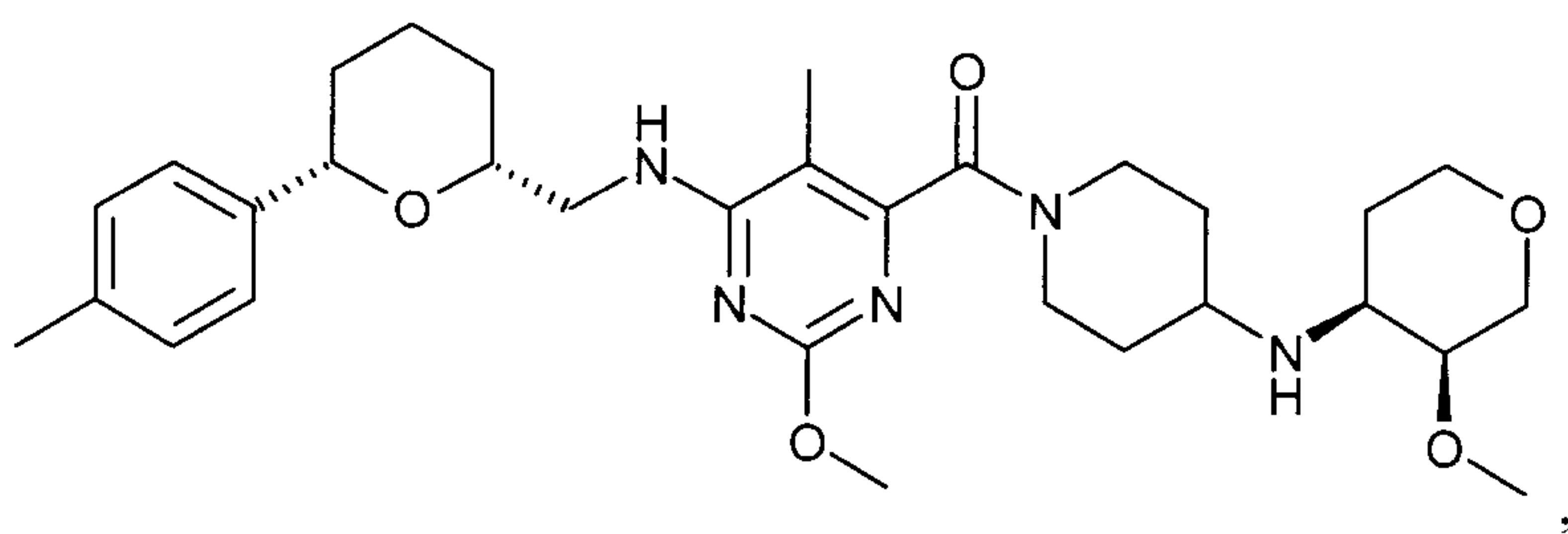
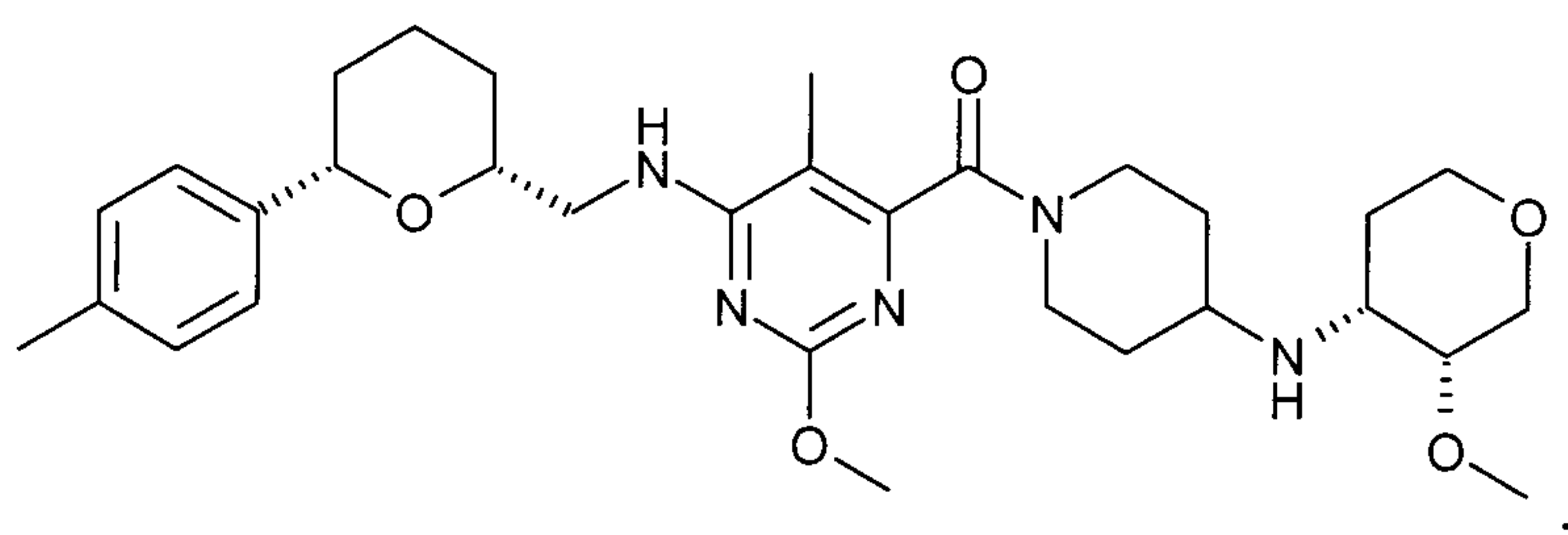
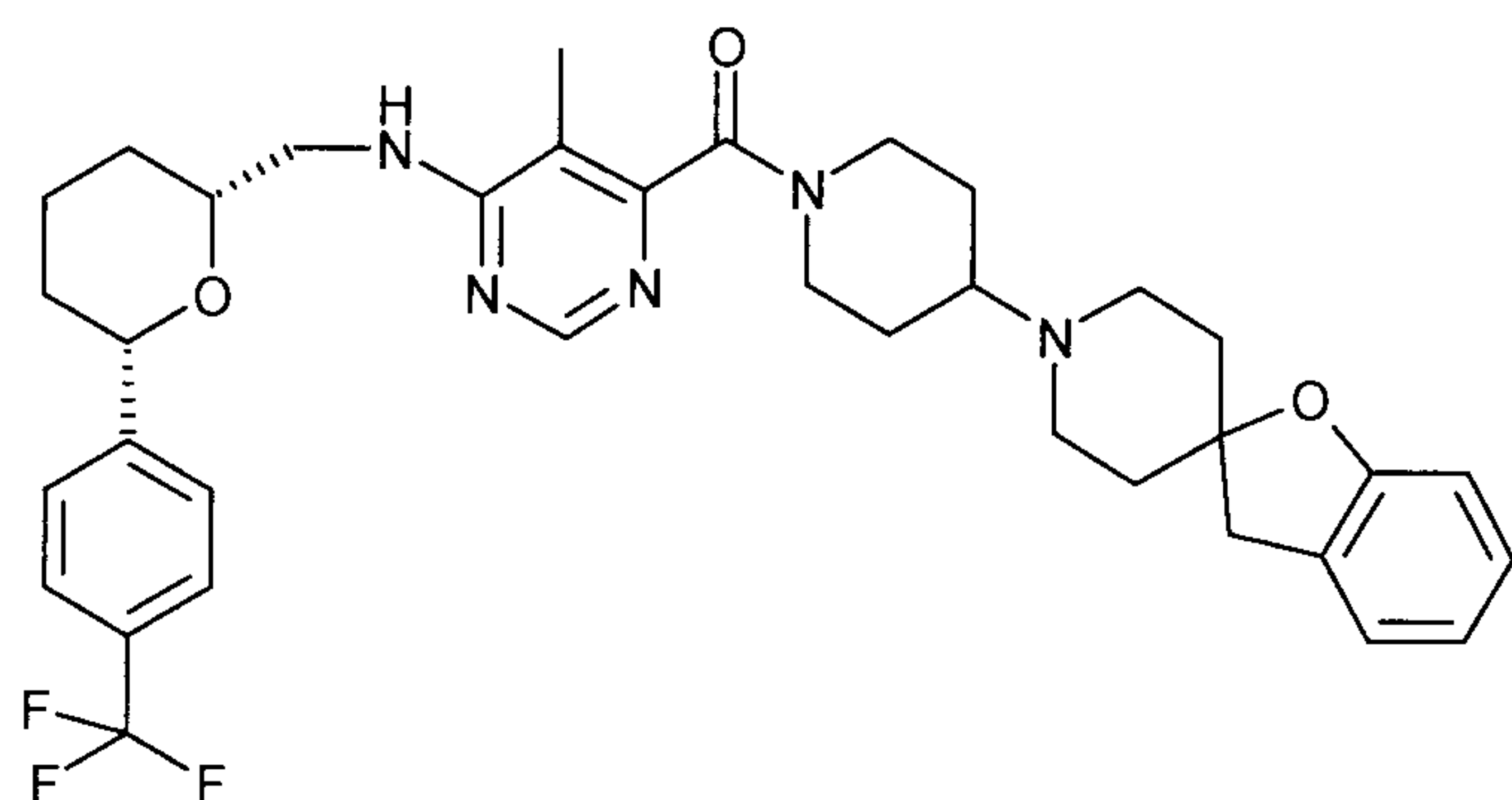
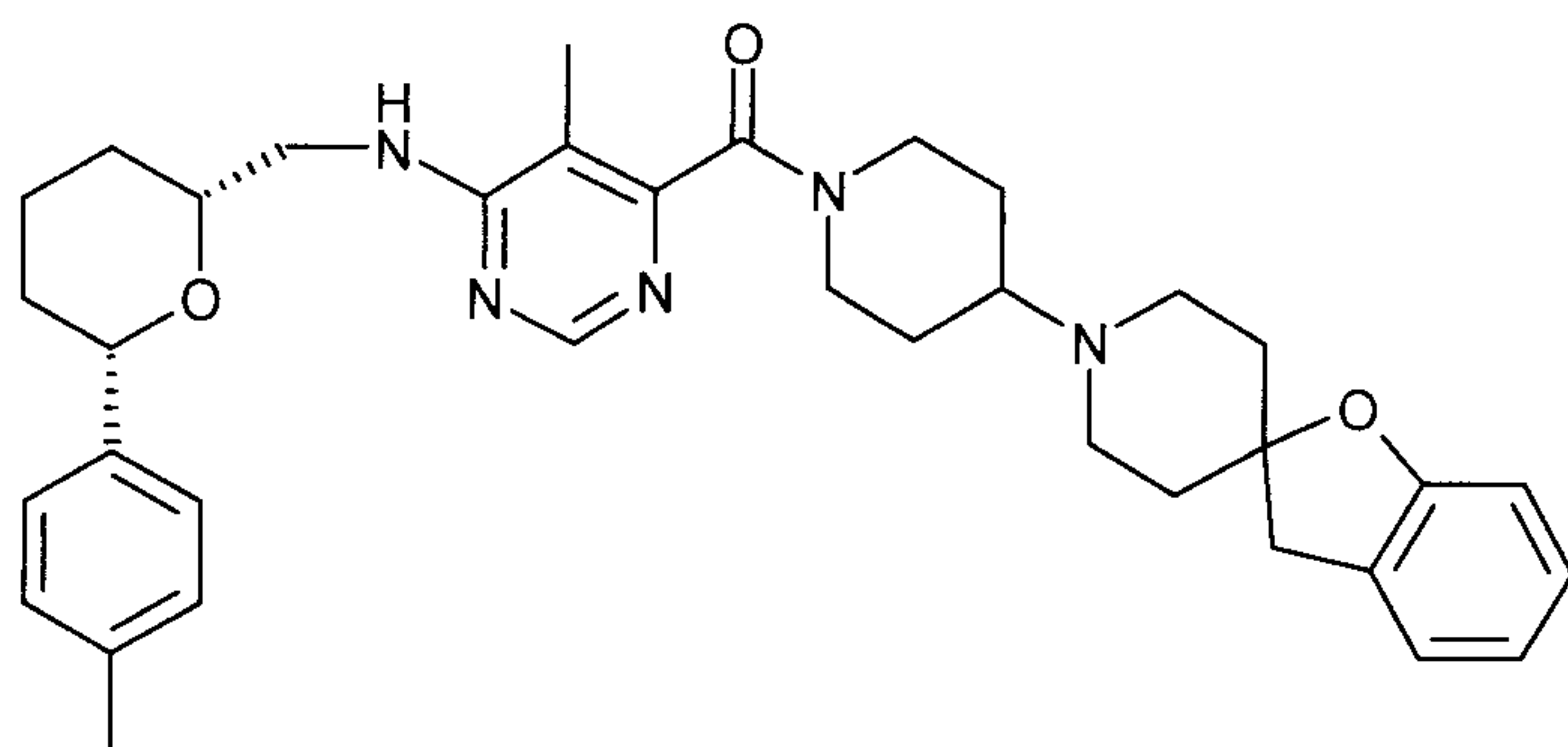
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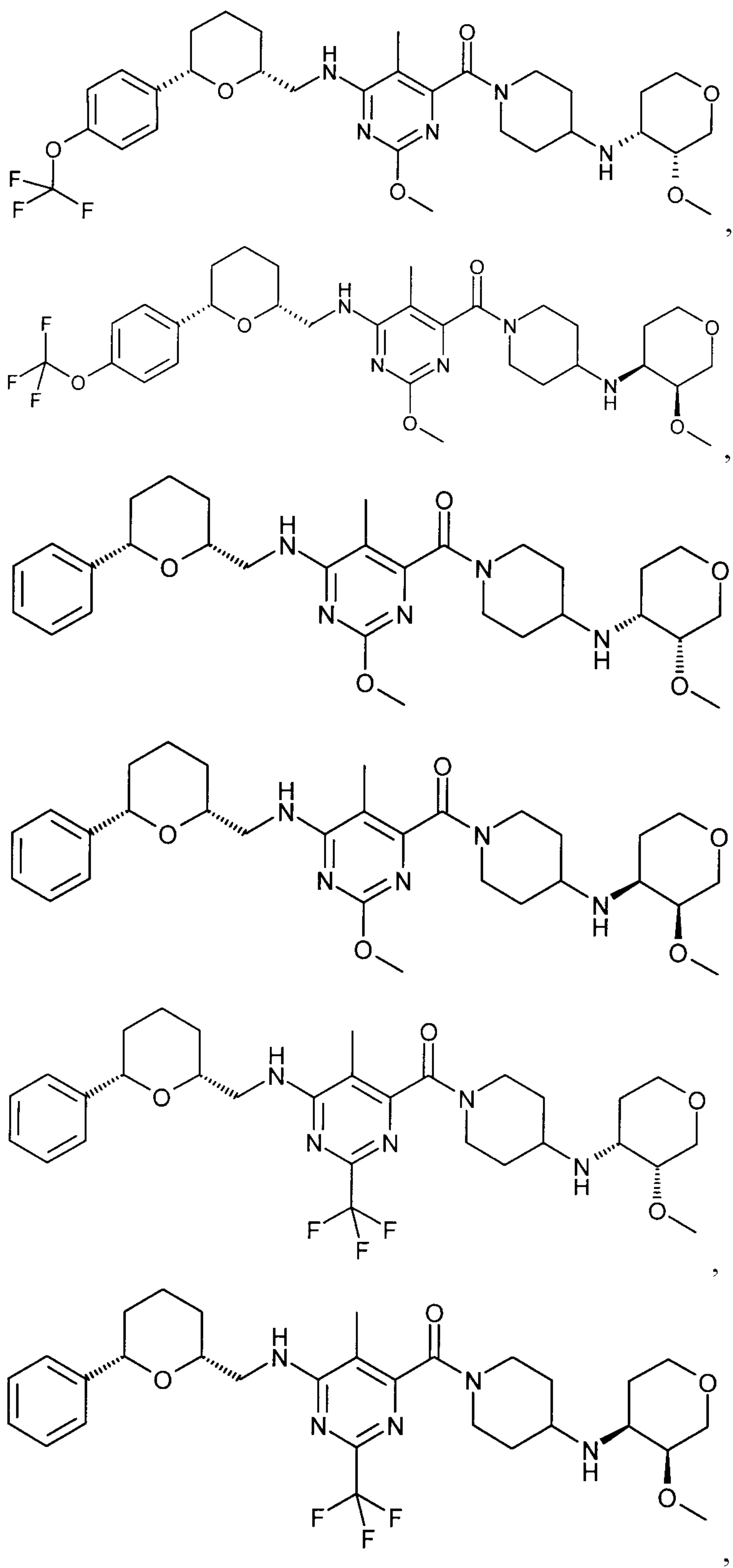
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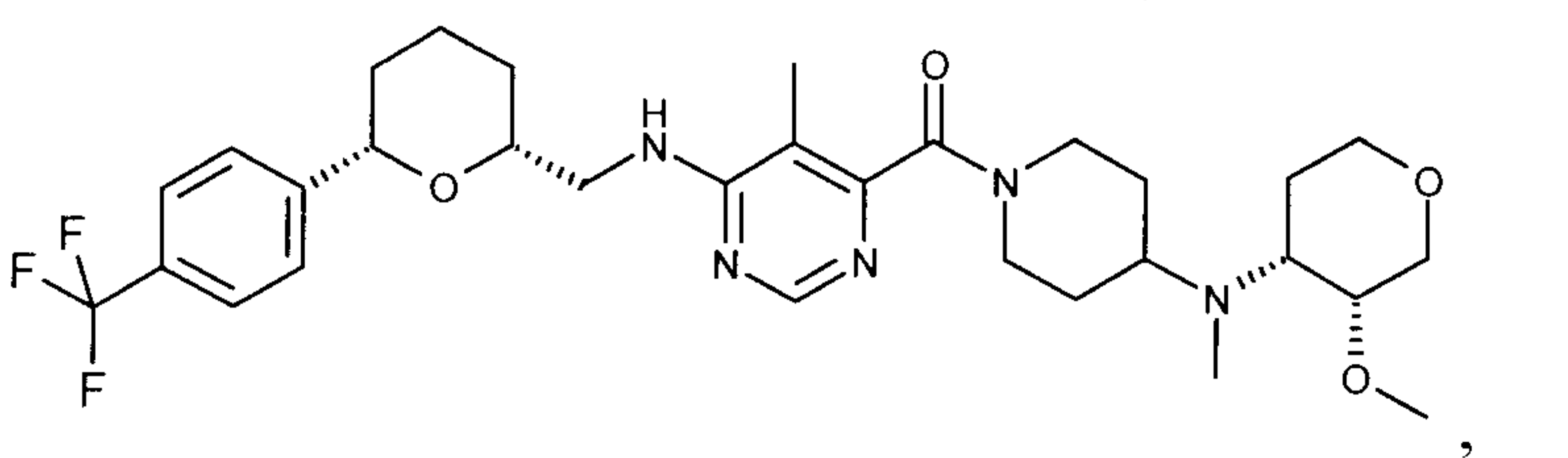
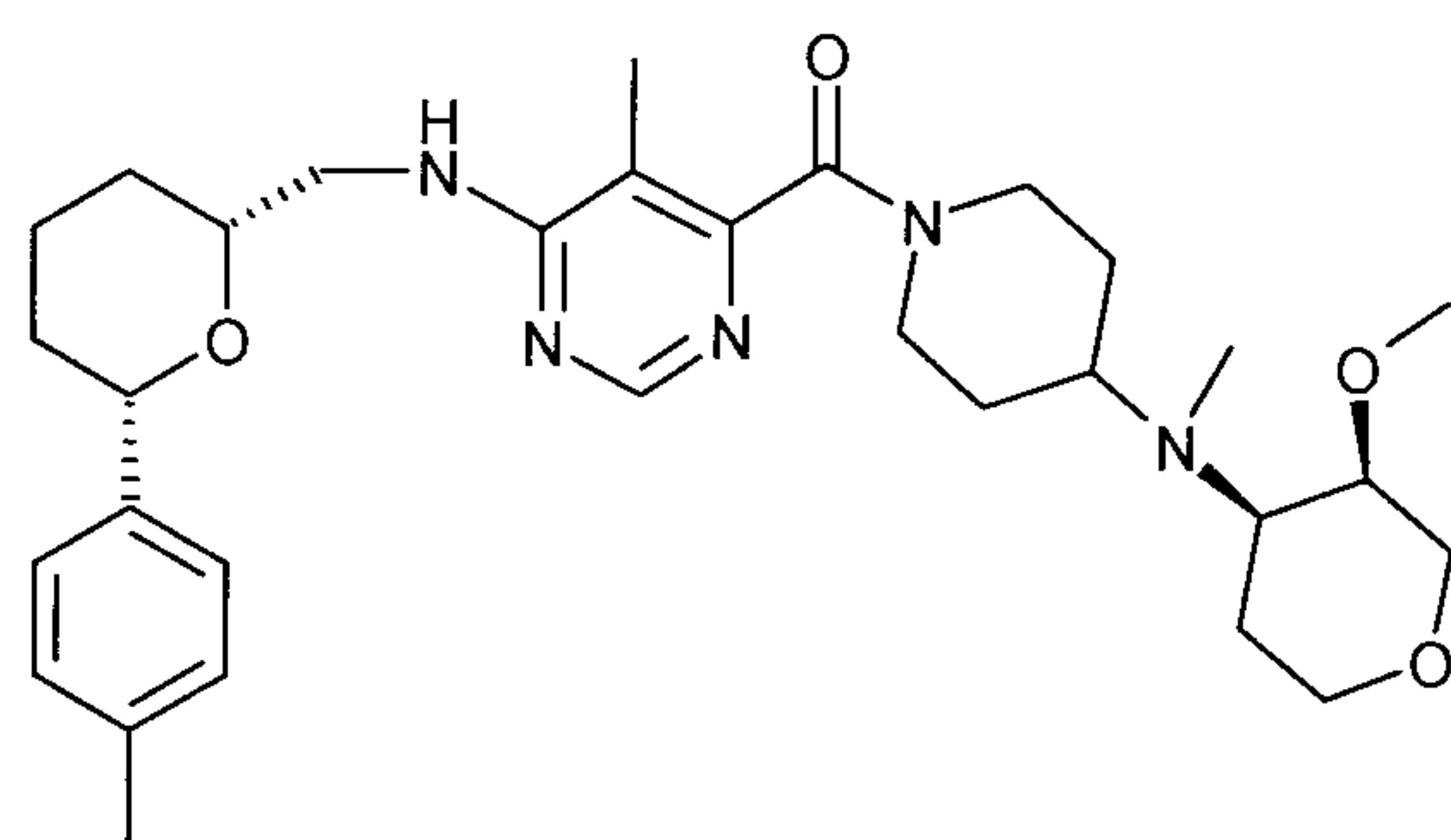
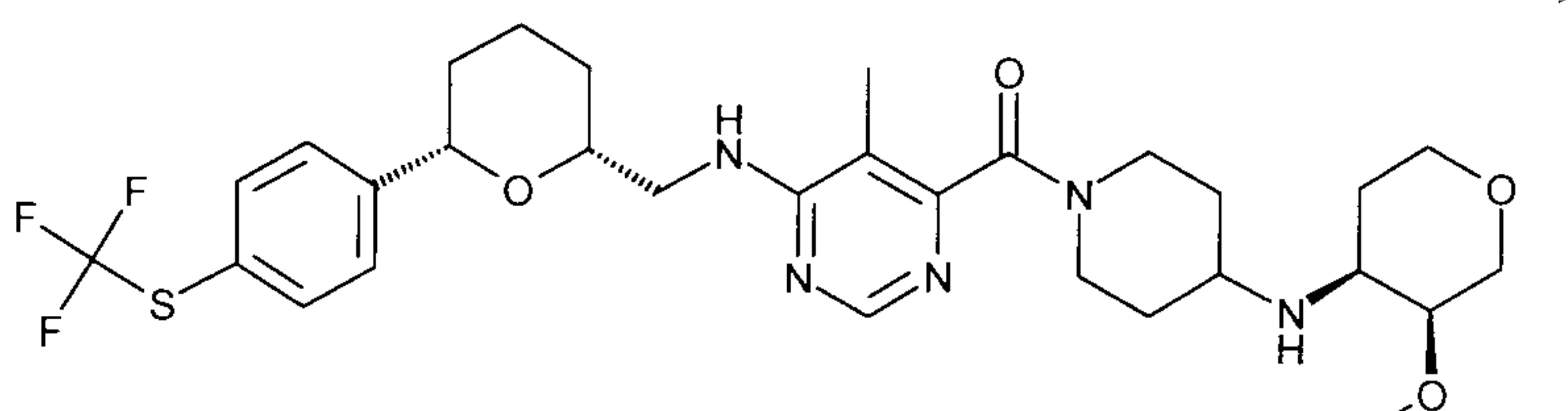
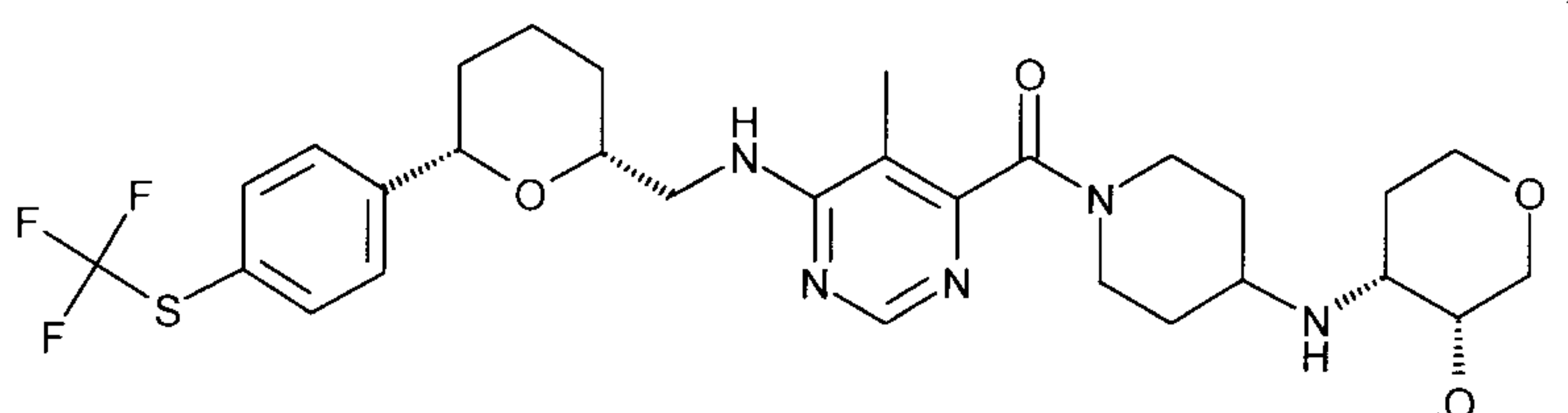
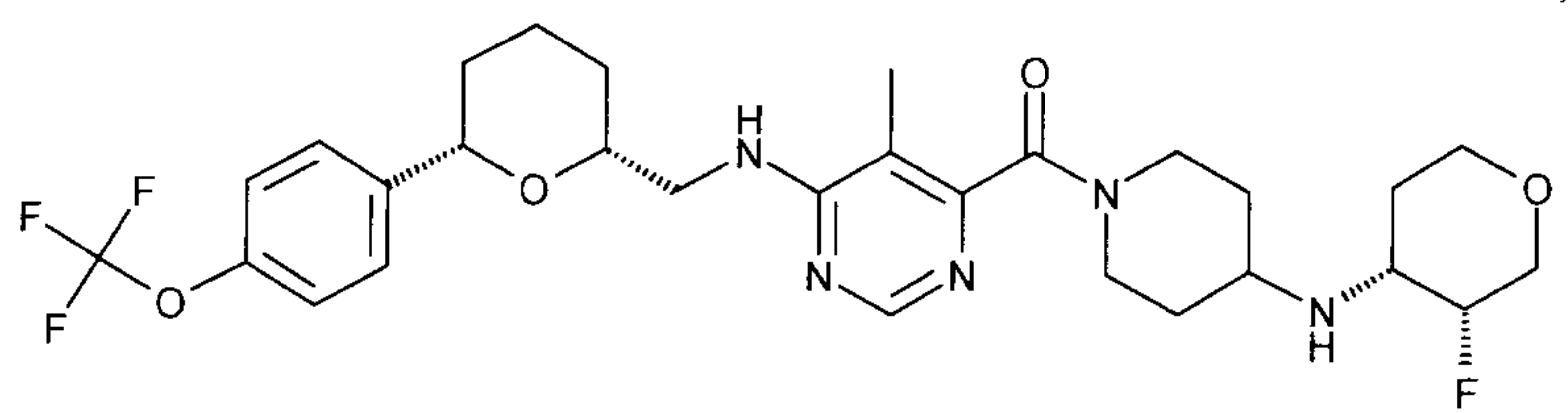
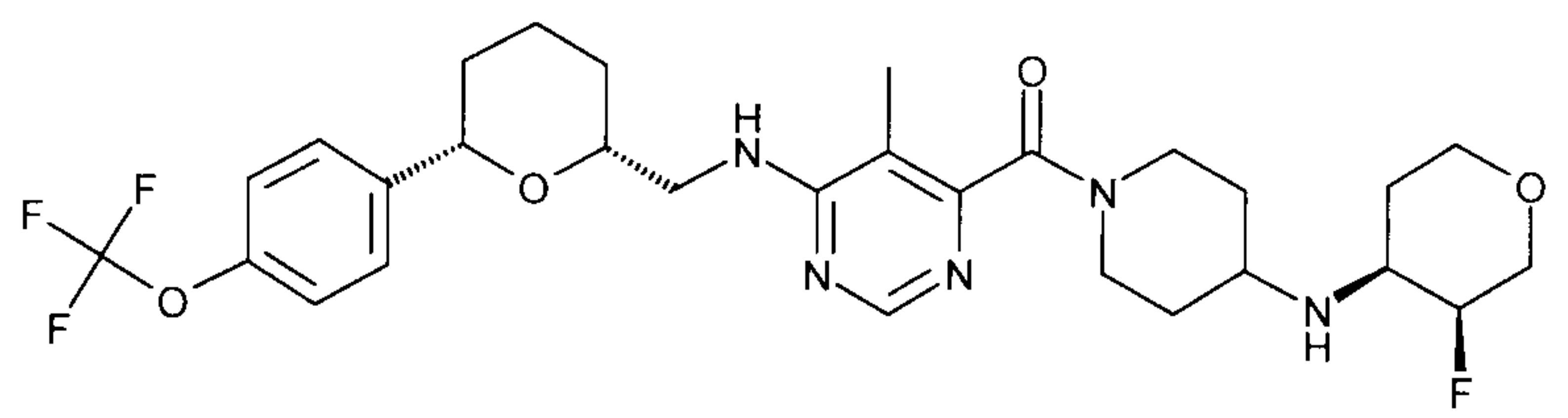
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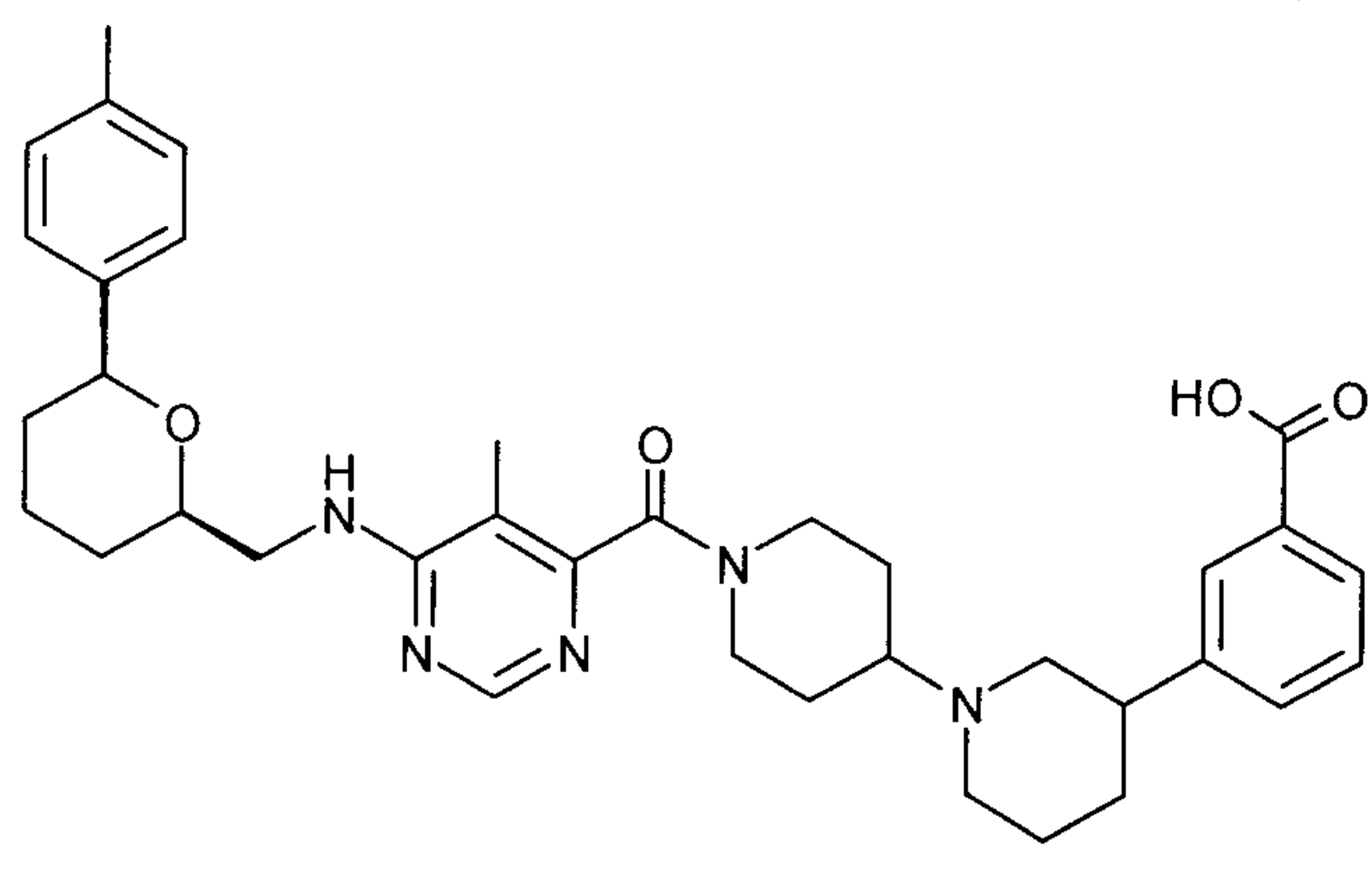
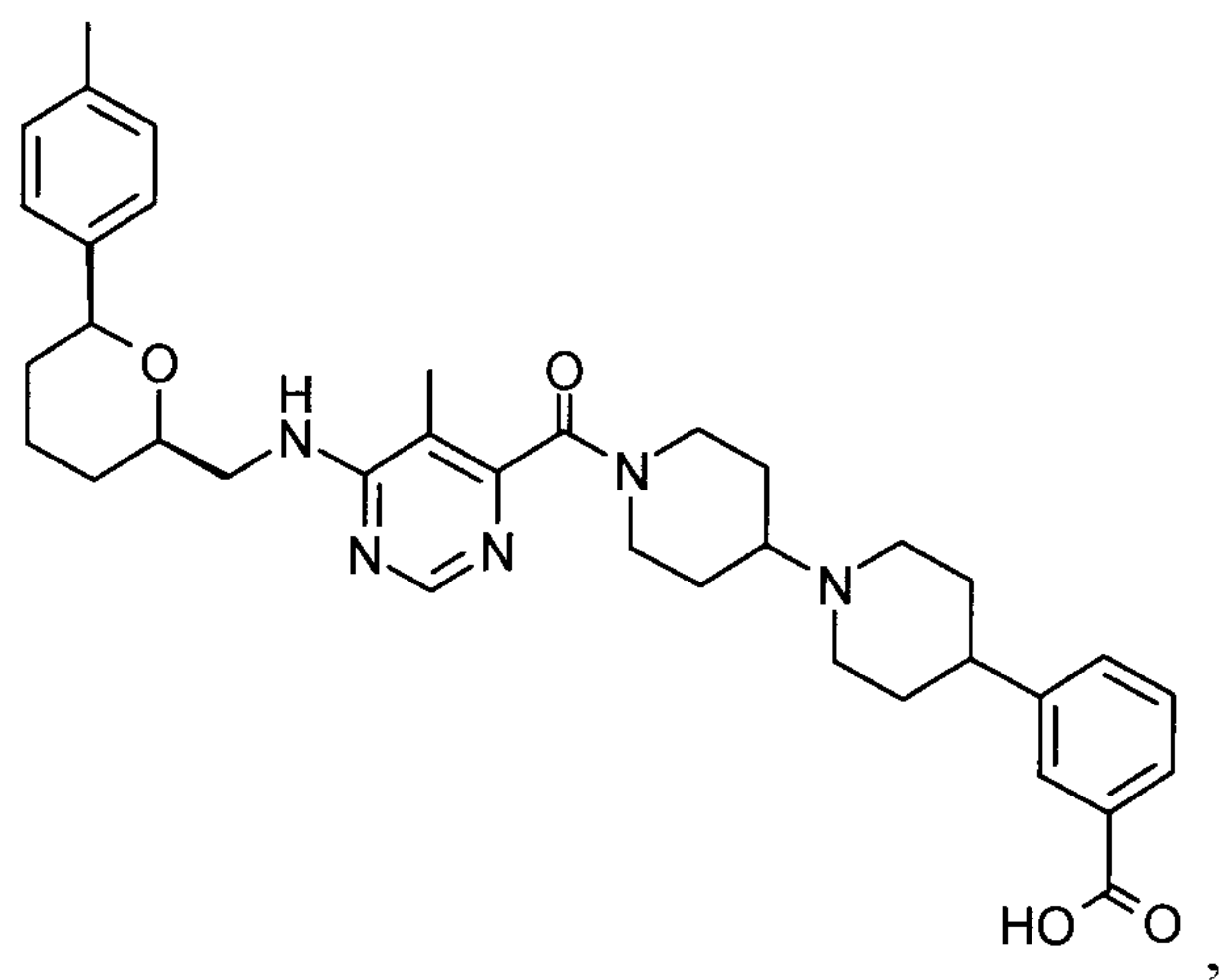
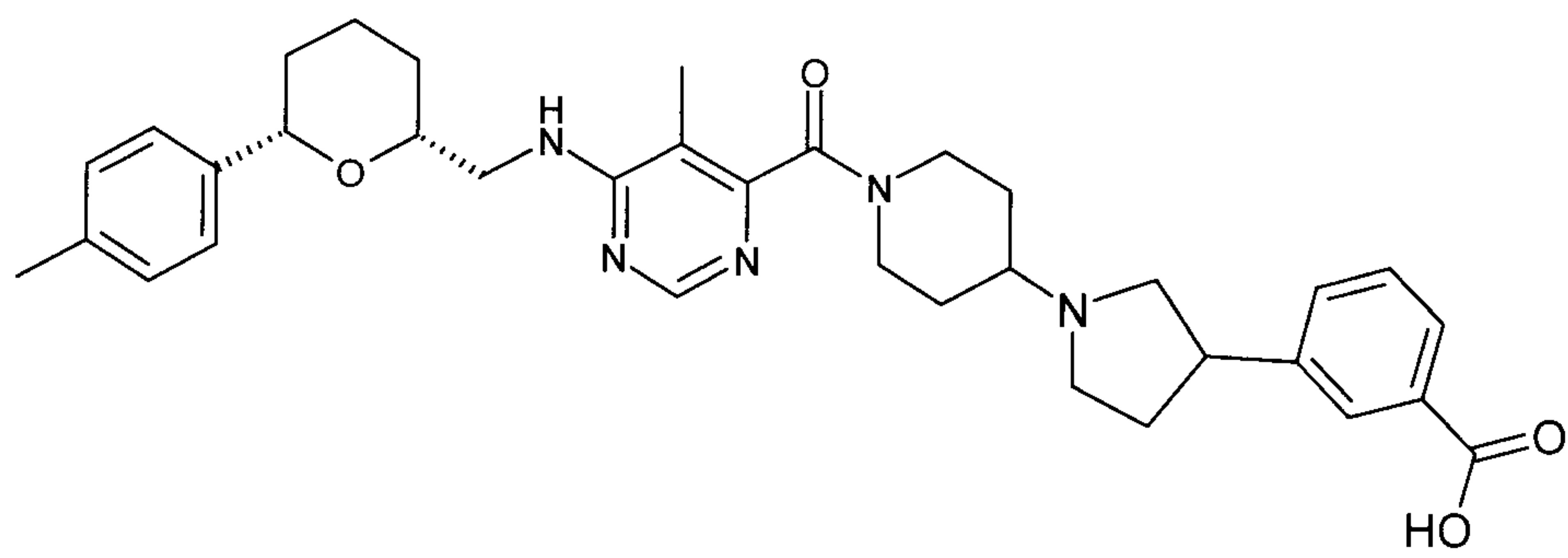
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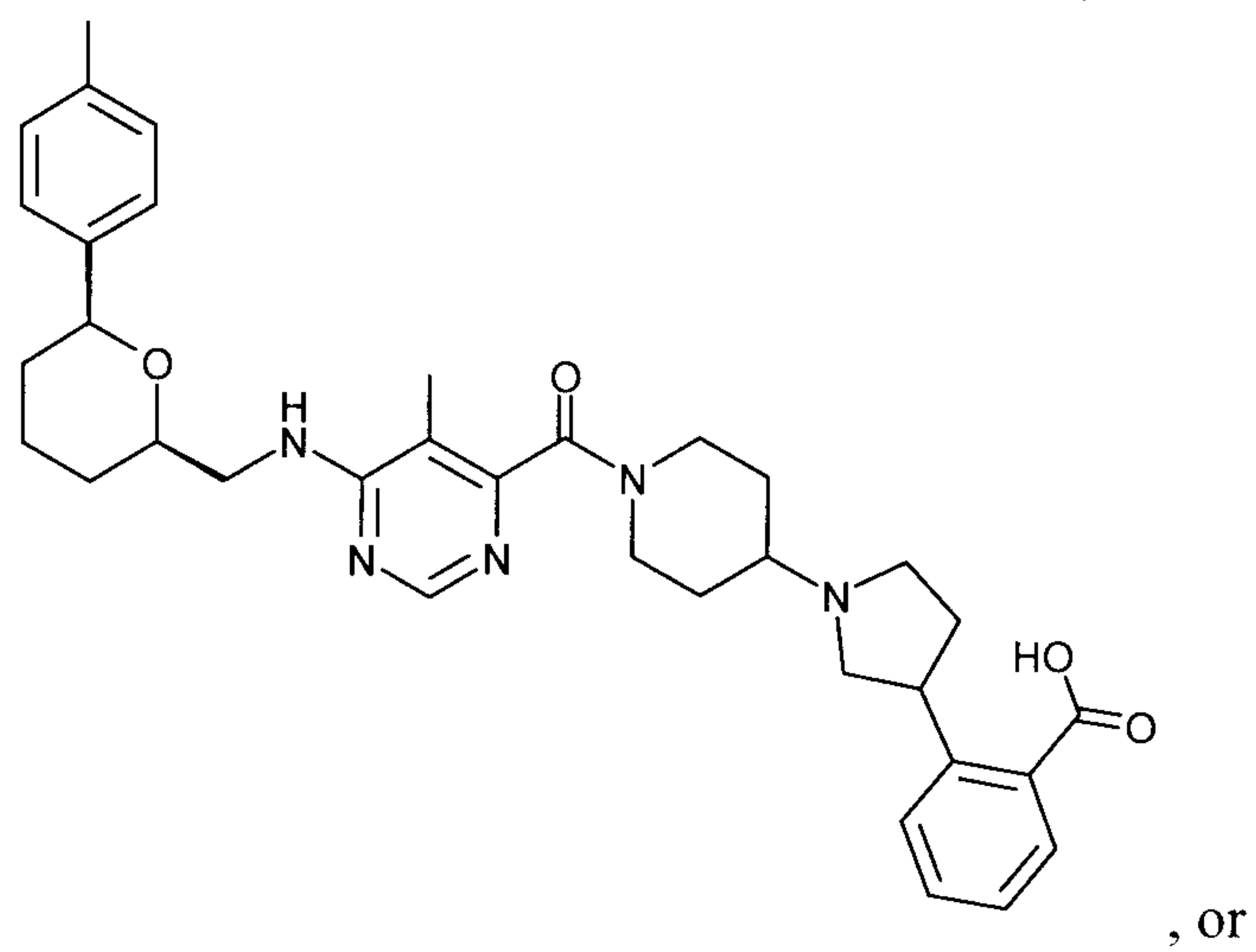
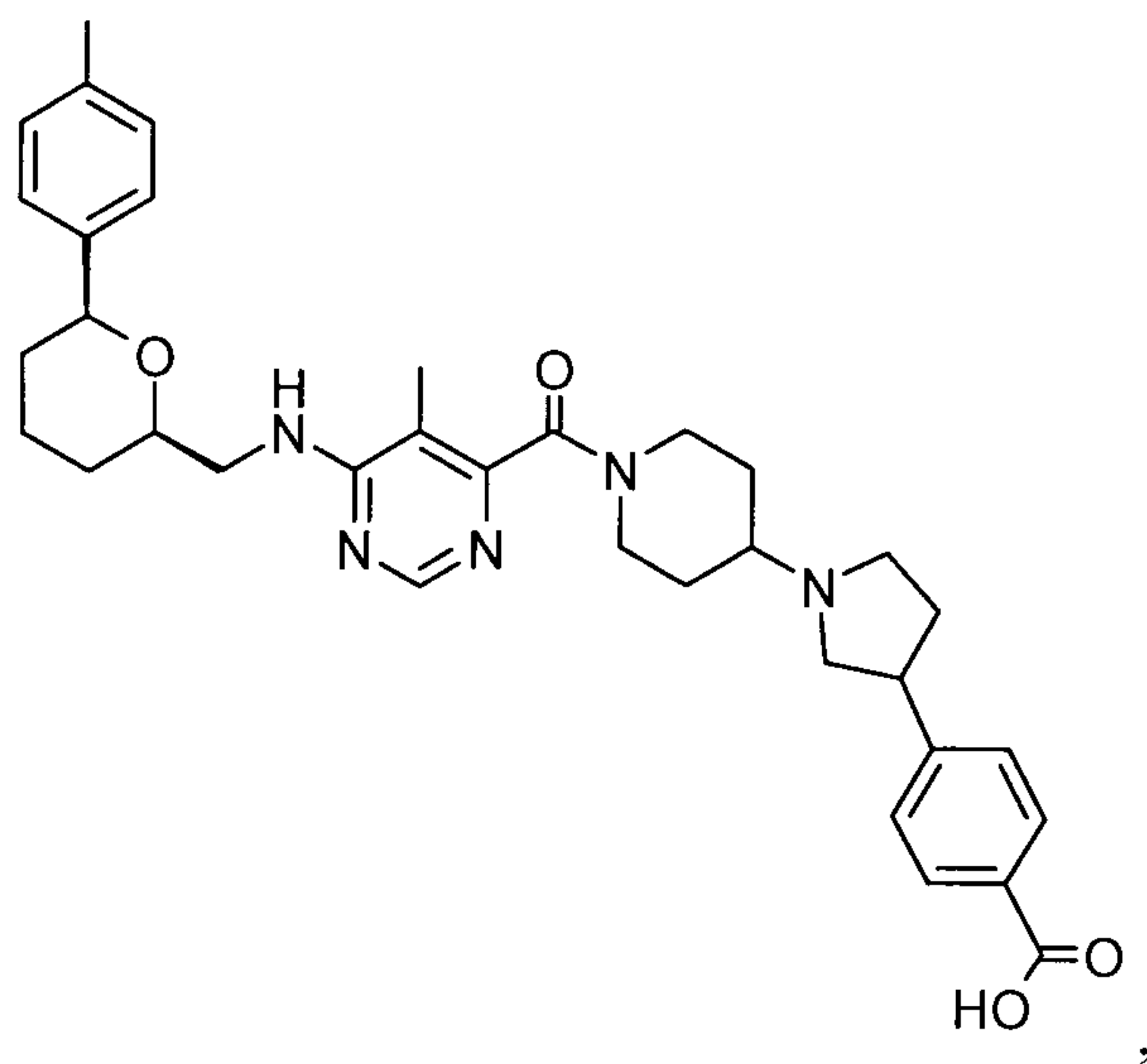
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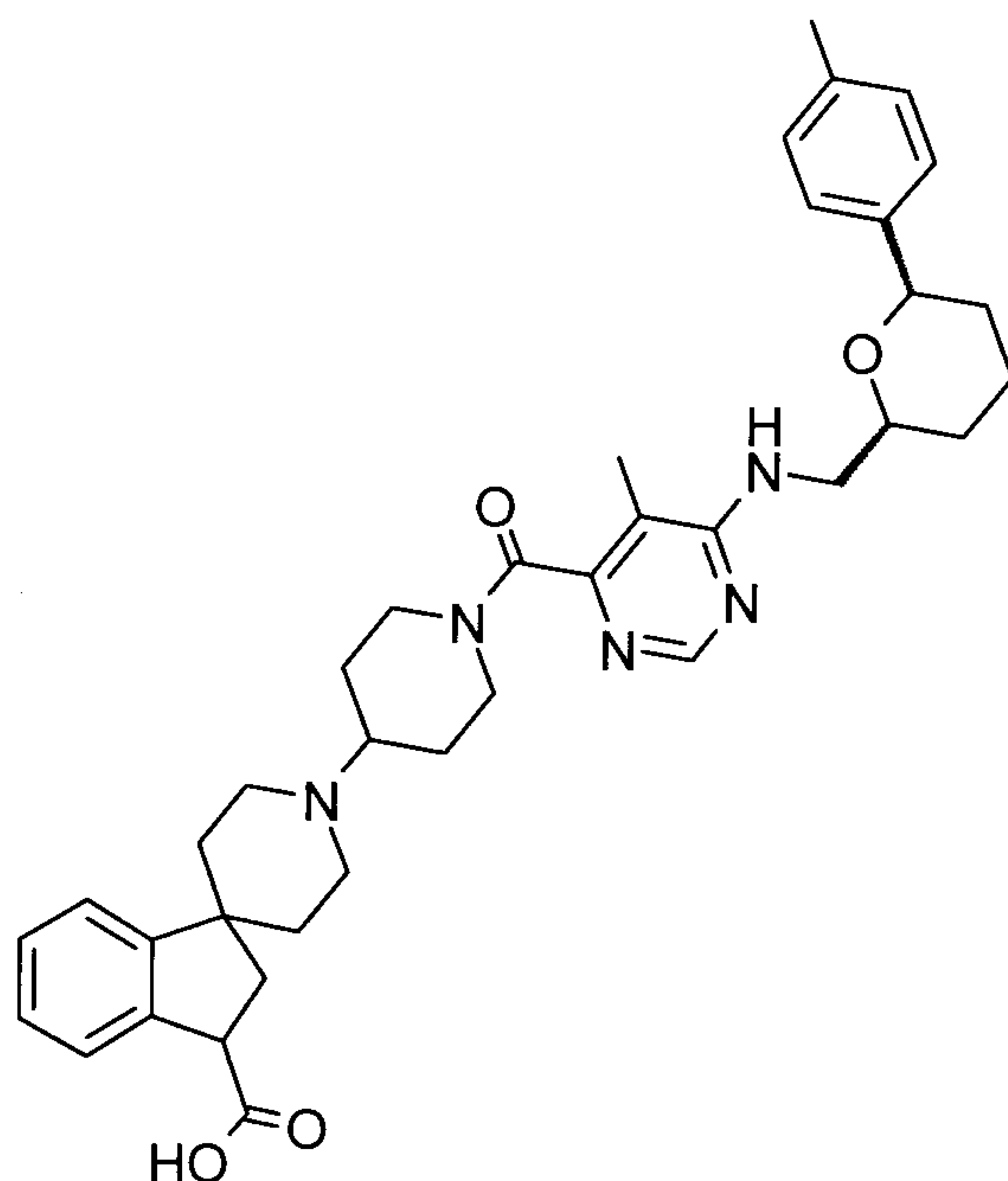


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, or

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or a pharmacologically acceptable acid addition salt thereof.

18. The compound according to claim 1 or a pharmacologically acceptable acid addition salt thereof, wherein R_4 denotes $-H$, R_5 is a group of the structure $-L_1-R_{18}$, and Z is C .

19. The compound according to claim 18 or a pharmacologically acceptable acid addition salt thereof, wherein G and E are N .

20. The compound according to claim 18 or 19 or a pharmacologically acceptable acid addition salt thereof, wherein n is 2.

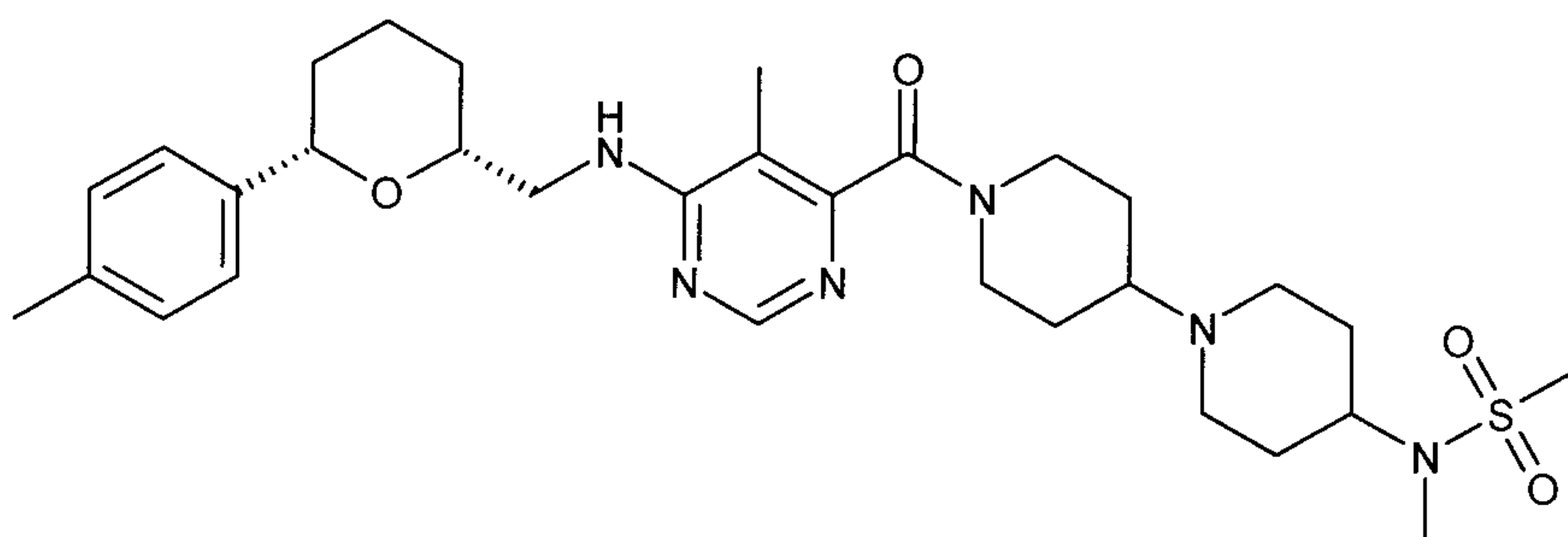
21. The compound according to any one of claims 18 to 20 or a pharmacologically acceptable acid addition salt thereof, wherein L_1 is $-NH-$.

22. The compound according to any one of claims 18 to 21 or a pharmacologically acceptable acid addition salt thereof, wherein R_{18} is $-C_3-C_8$ -heterocyclyl substituted by one or more groups selected from among halogen, $-CF_3$, $-OCF_3$, $-CN$, $-OH$, $-O-C_1-C_4$ -alkyl, $-C_1-C_6$ -alkyl, $-NH-C(O)-C_1-C_6$ -alkyl, $-N(C_1-C_4$ -alkyl) $-C(O)-C_1-C_6$ -alkyl, $-C(O)-C_1-C_6$ -alkyl, $-S(O)_2-C_1-C_6$ -alkyl, $-NH-S(O)_2-C_1-C_6$ -alkyl, $-N(C_1-C_4$ -alkyl) $-S(O)_2-C_1-C_6$ -alkyl, and $-C(O)-O-C_1-C_6$ -alkyl.

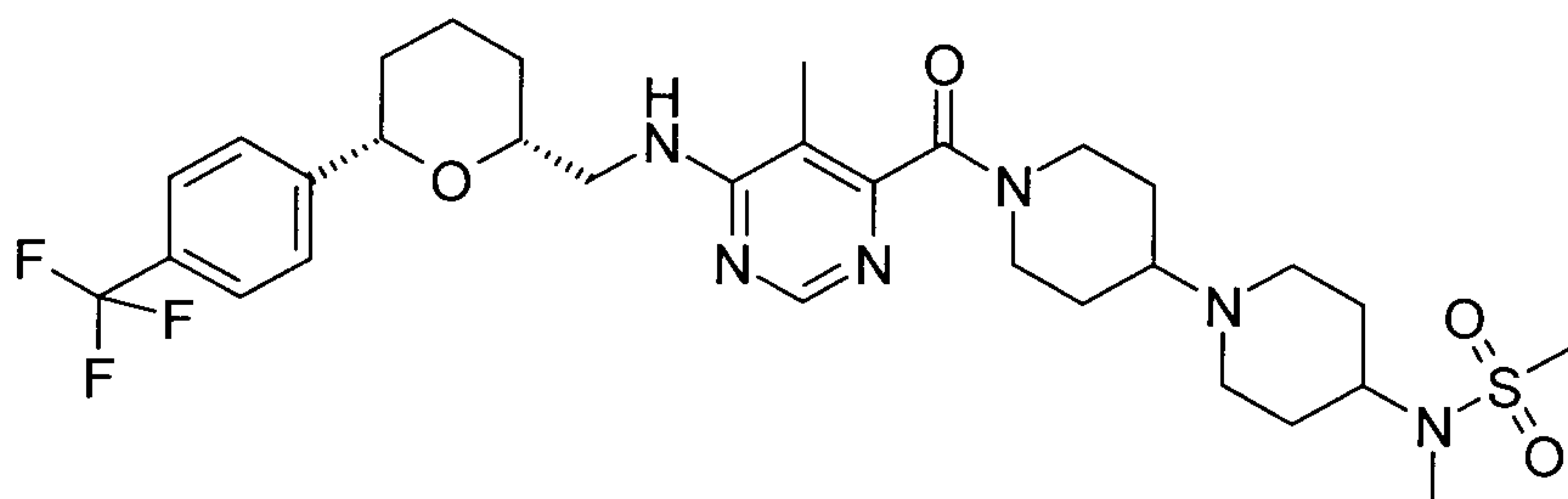
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23. The compound according to any one of claims 18 to 22 or a pharmacologically acceptable acid addition salt thereof, wherein R_7 is $-C_5-C_{10}$ -aryl optionally substituted with one or more groups selected from among $-CF_3$, $-O-CF_3$, $-CN$, $-C_1-C_6$ -alkyl, $-C(CH_3)_2-CN$, and halogen.

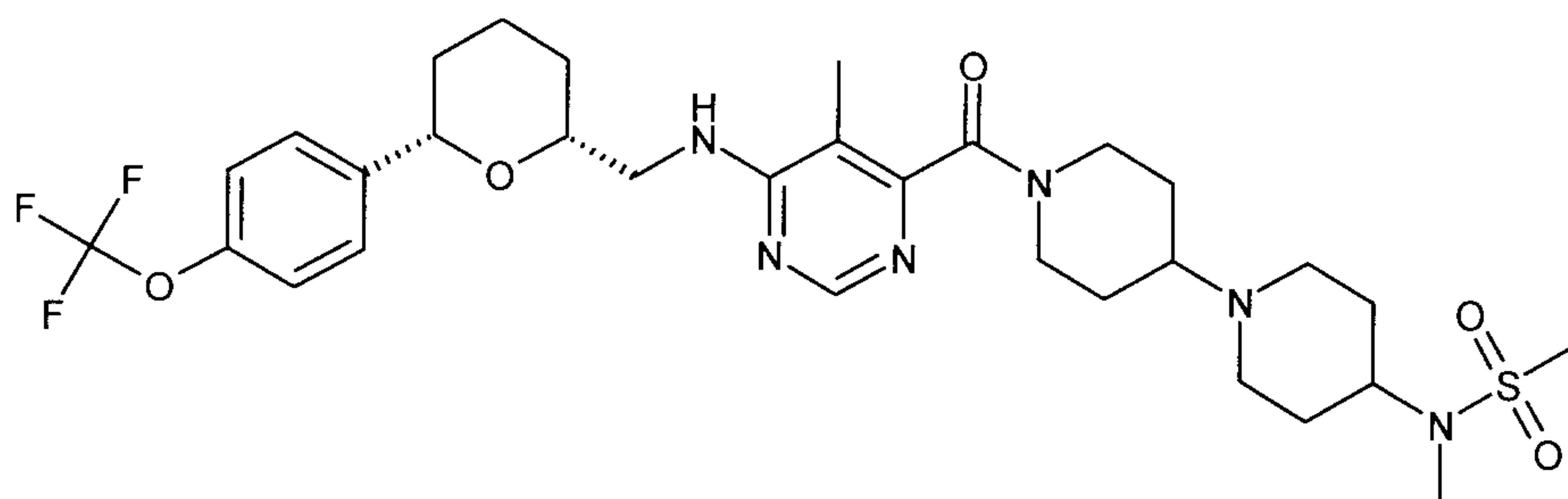
5 24. The compound:



25. The compound:

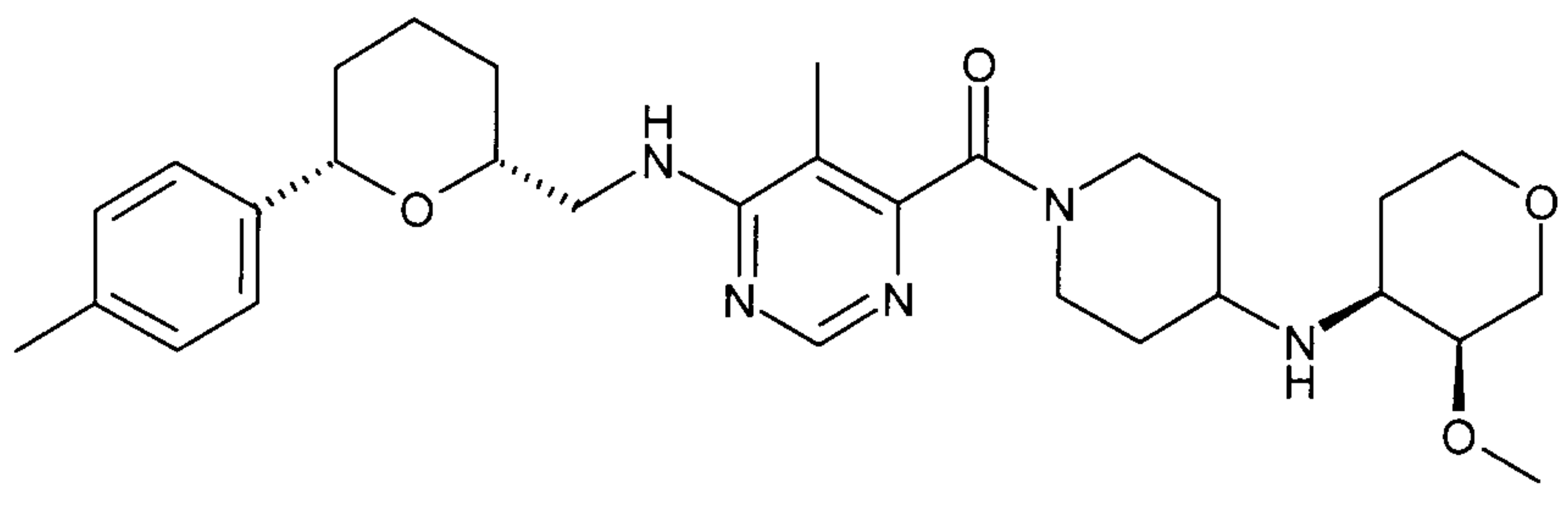


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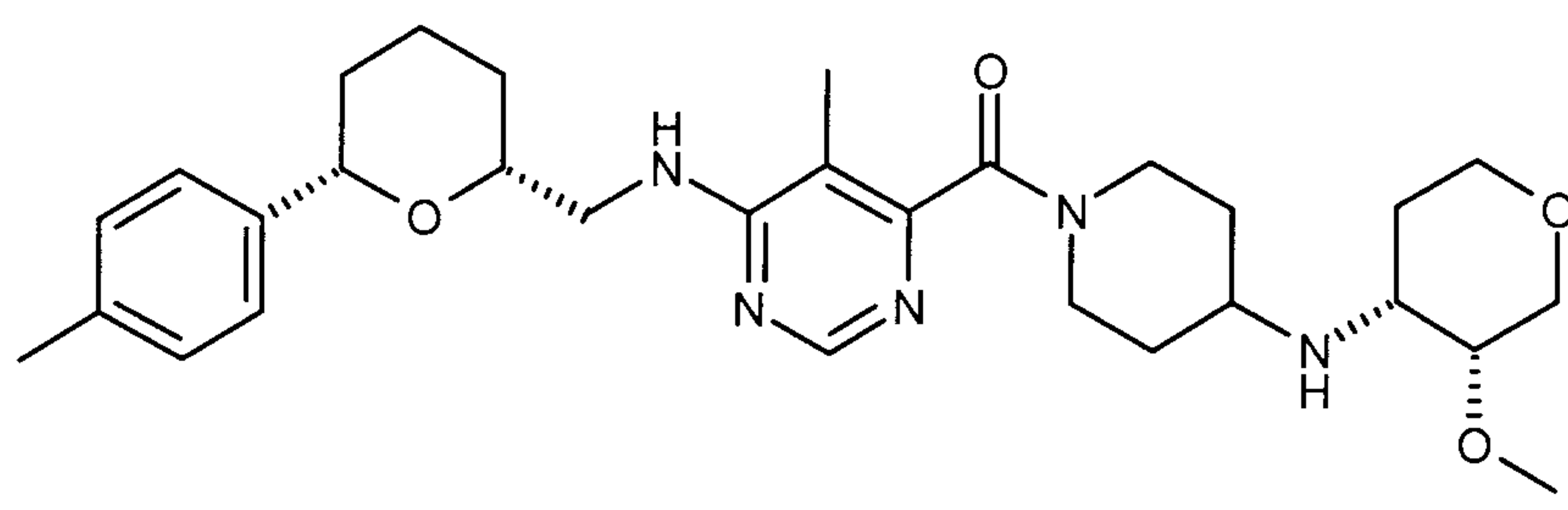


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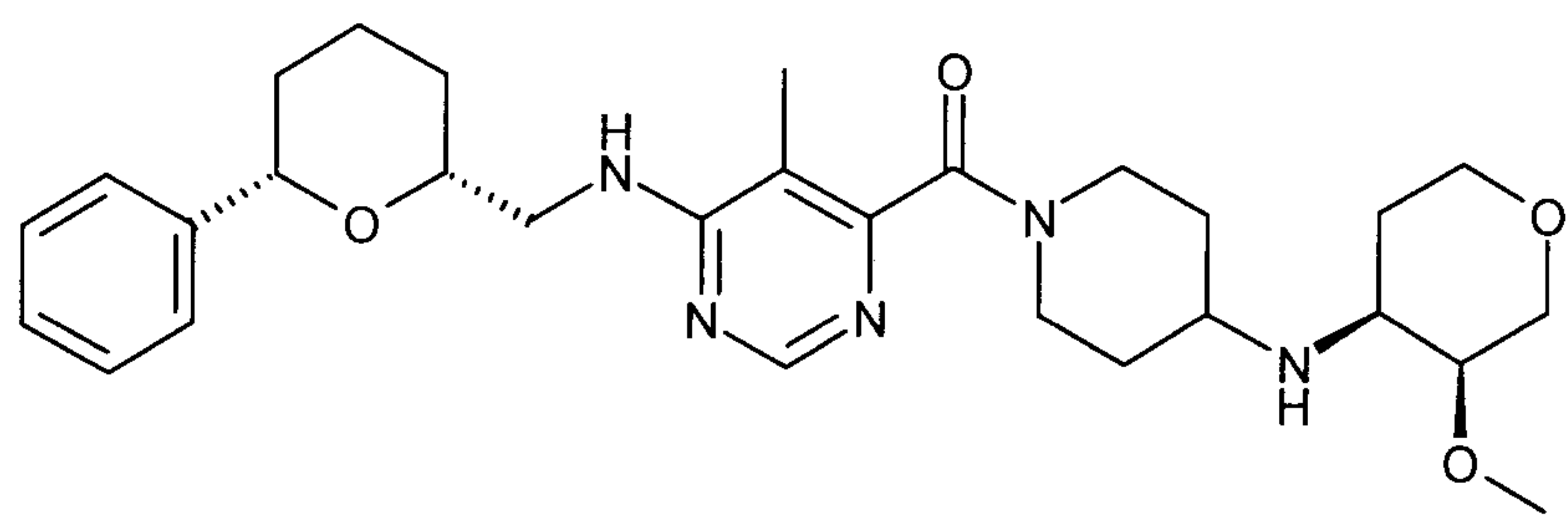
27. The compound:



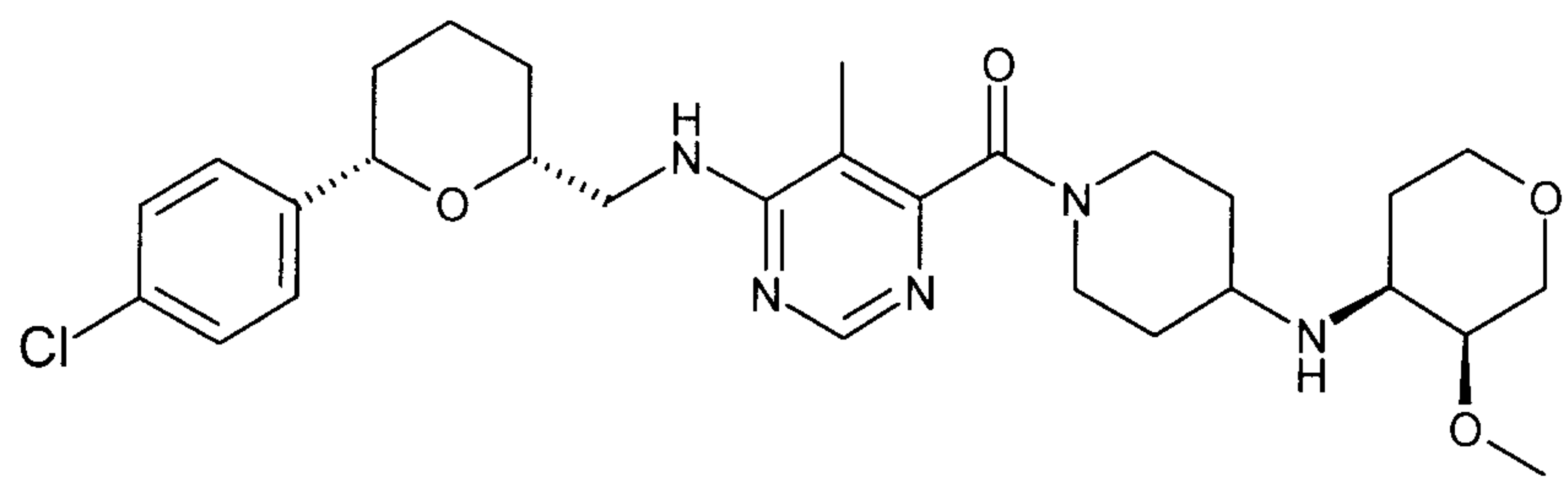
28. The compound:



29. The compound:

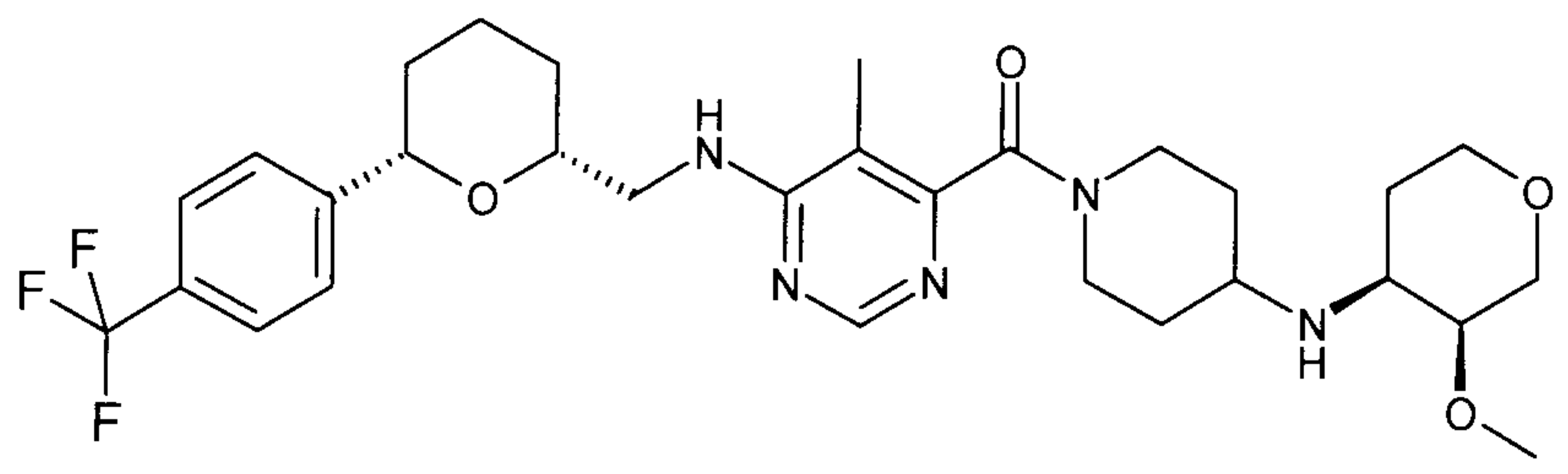


30. The compound:

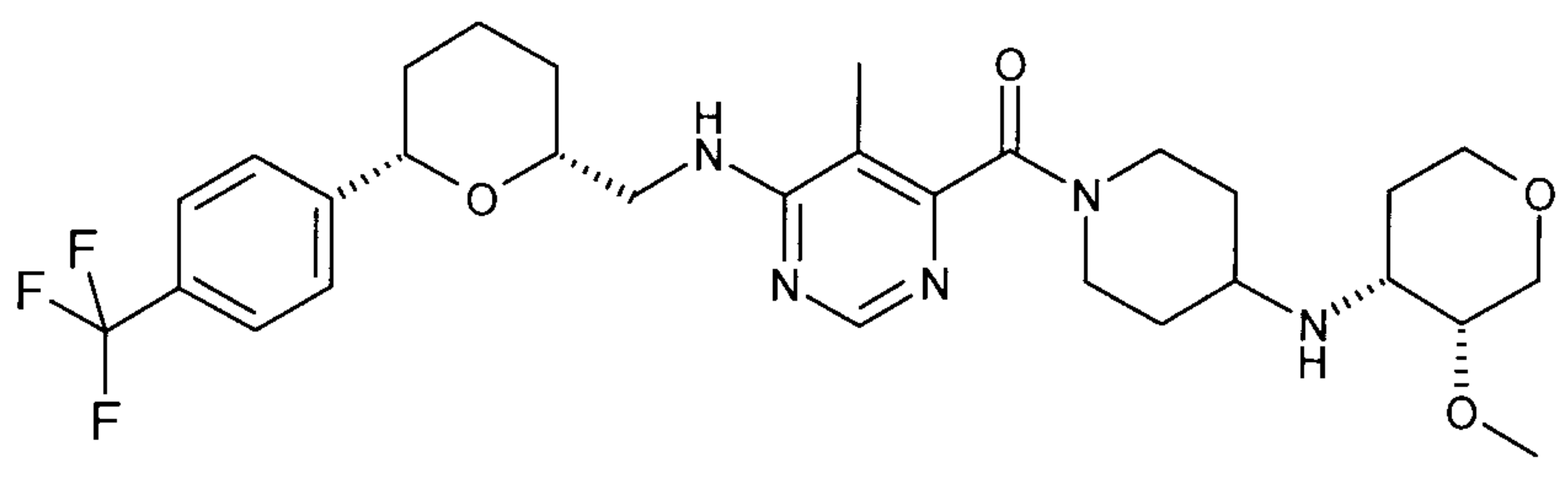


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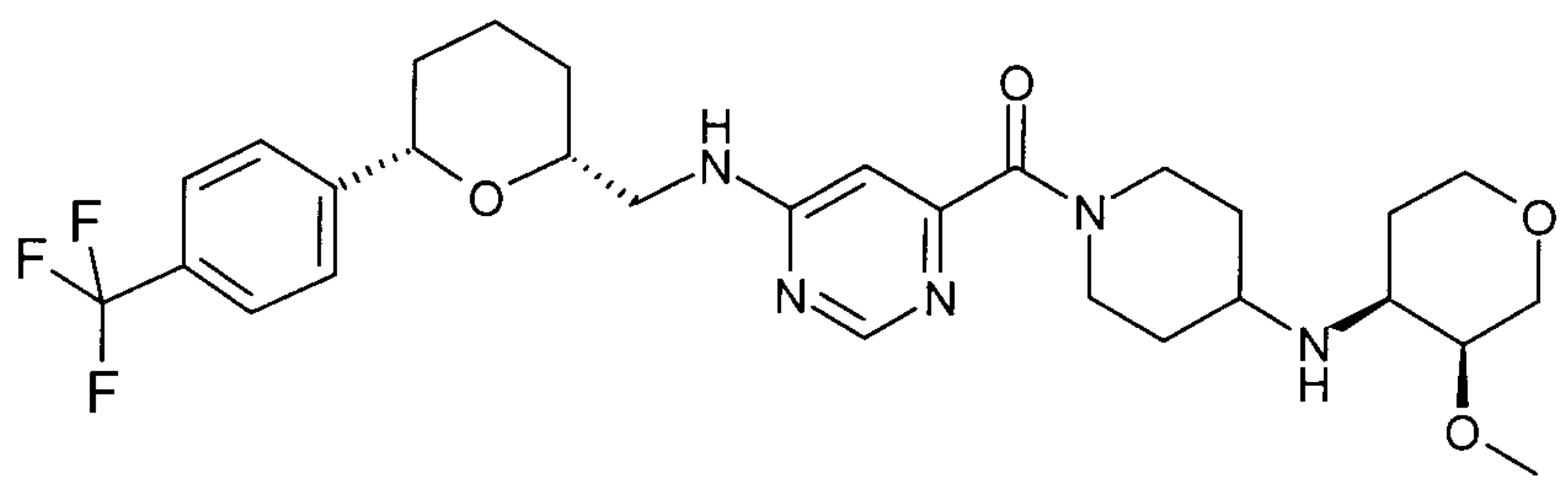
31. The compound:



32. The compound:

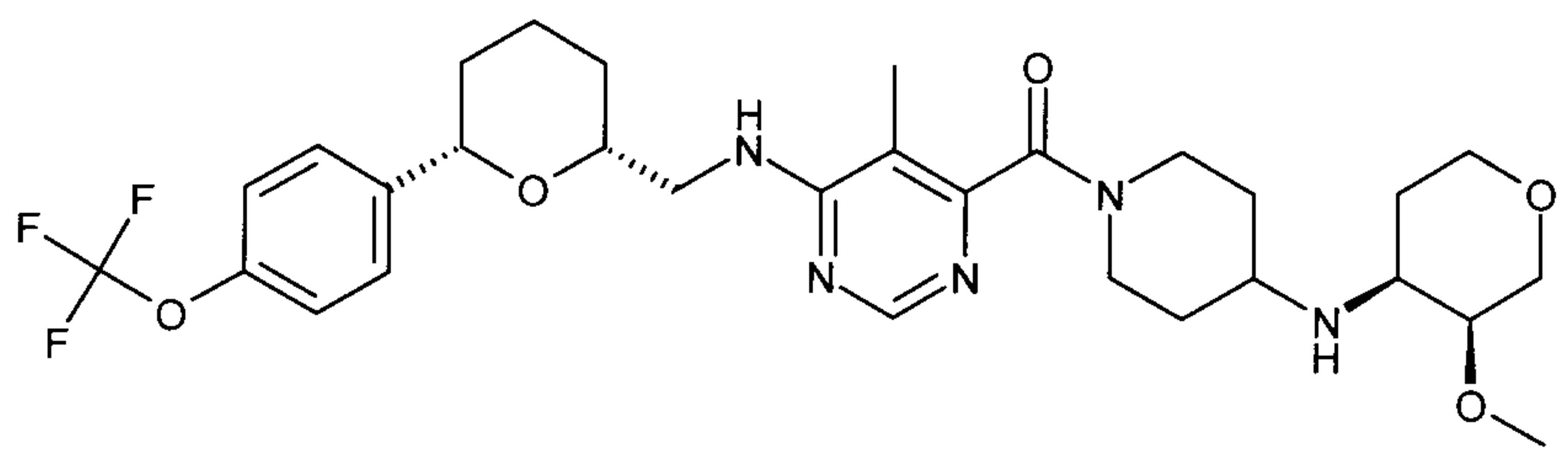


33. The compound:

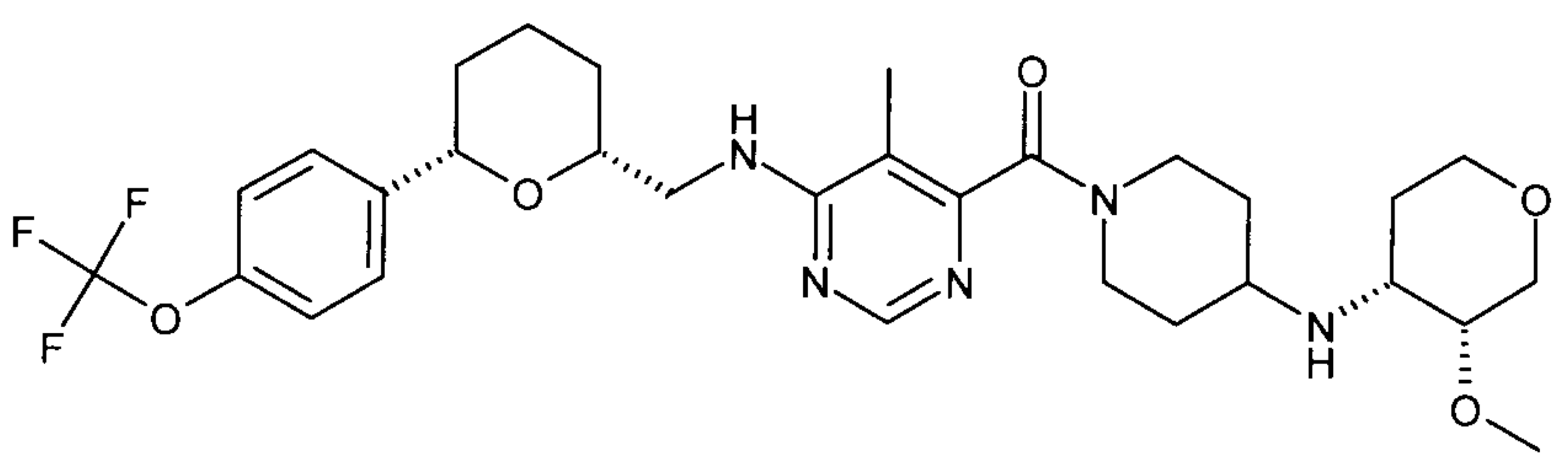


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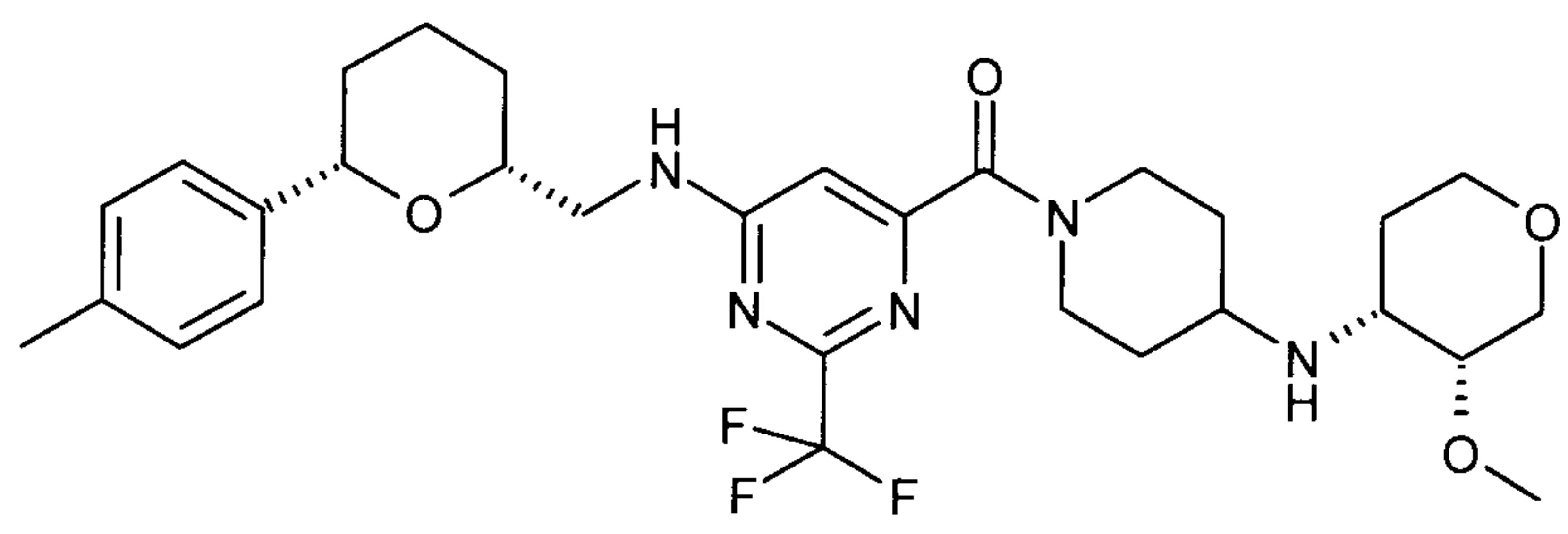
34. The compound:



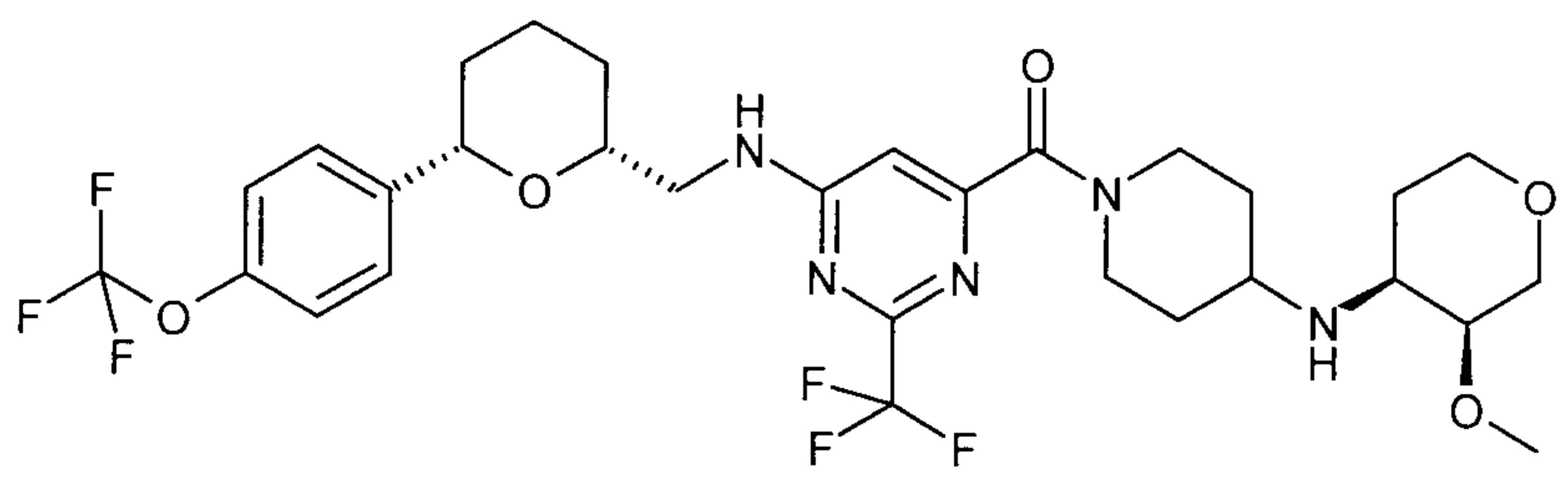
35. The compound:



5 36. The compound:

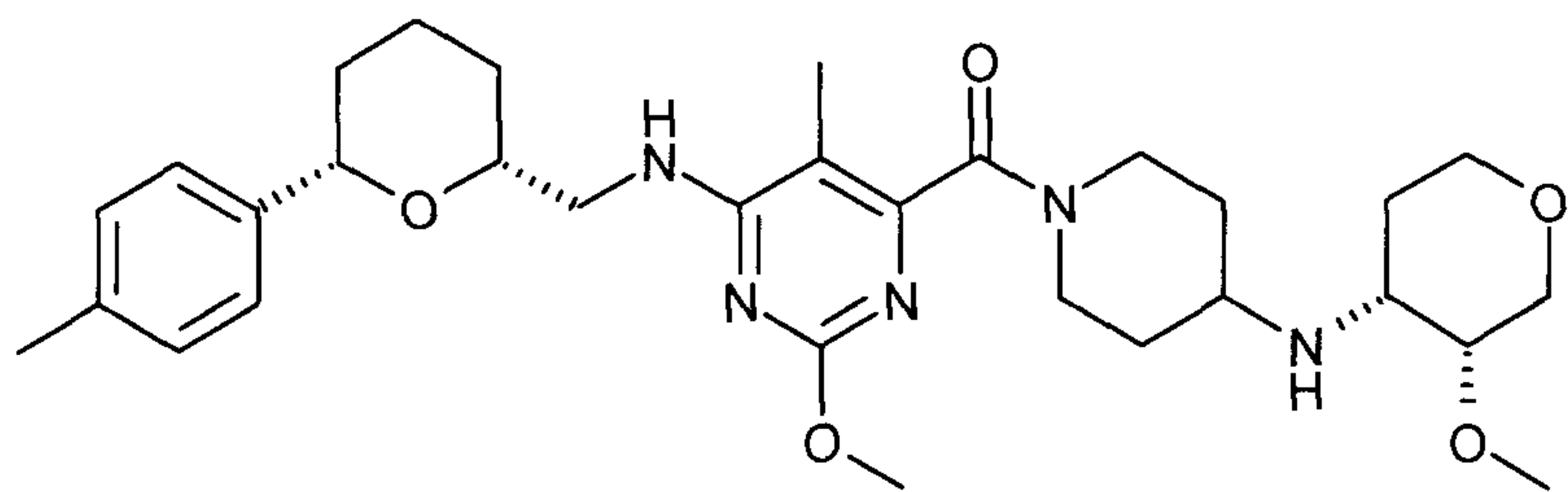


37. The compound:

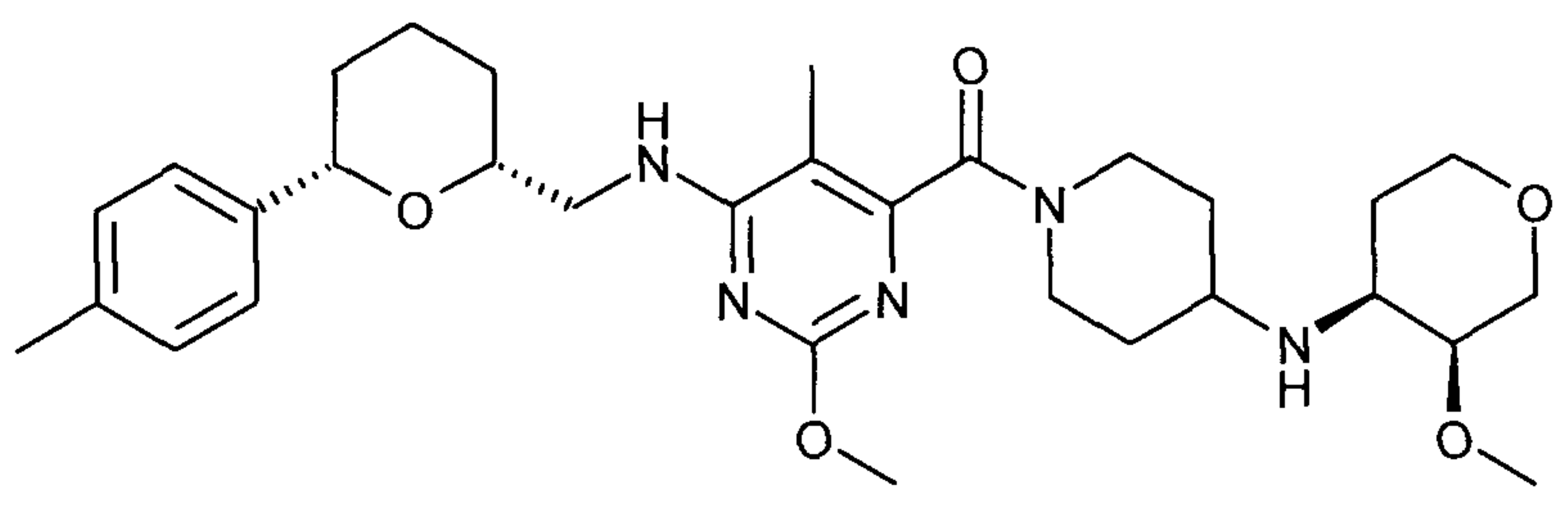


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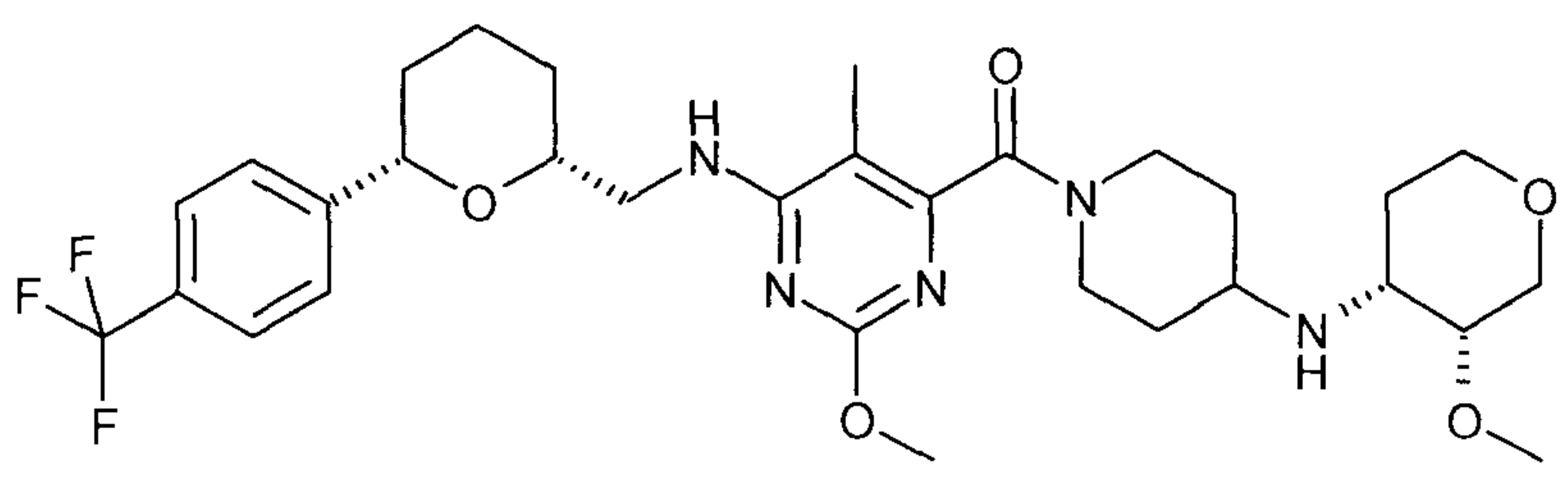
38. The compound:



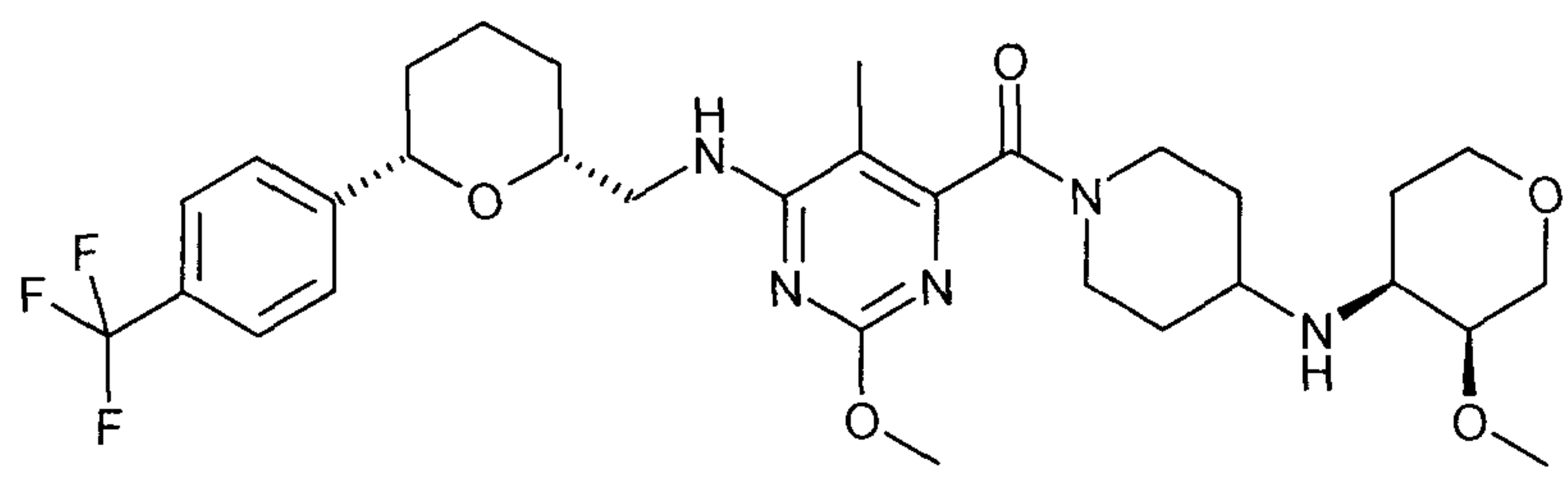
39. The compound:



5 40. The compound:

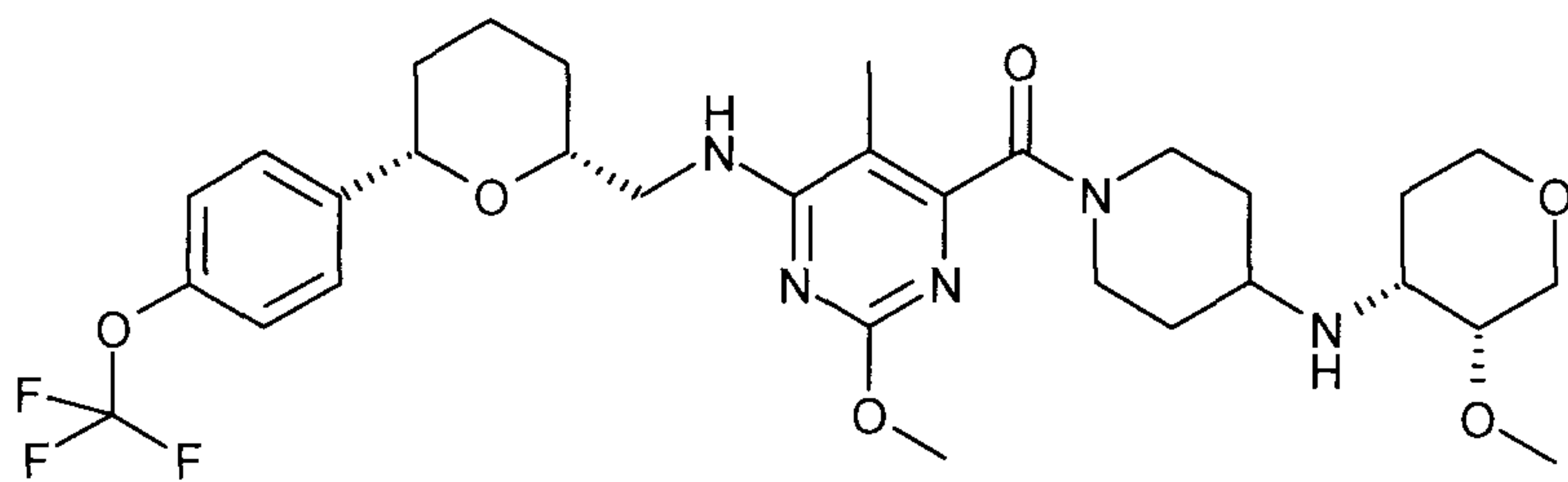


41. The compound:

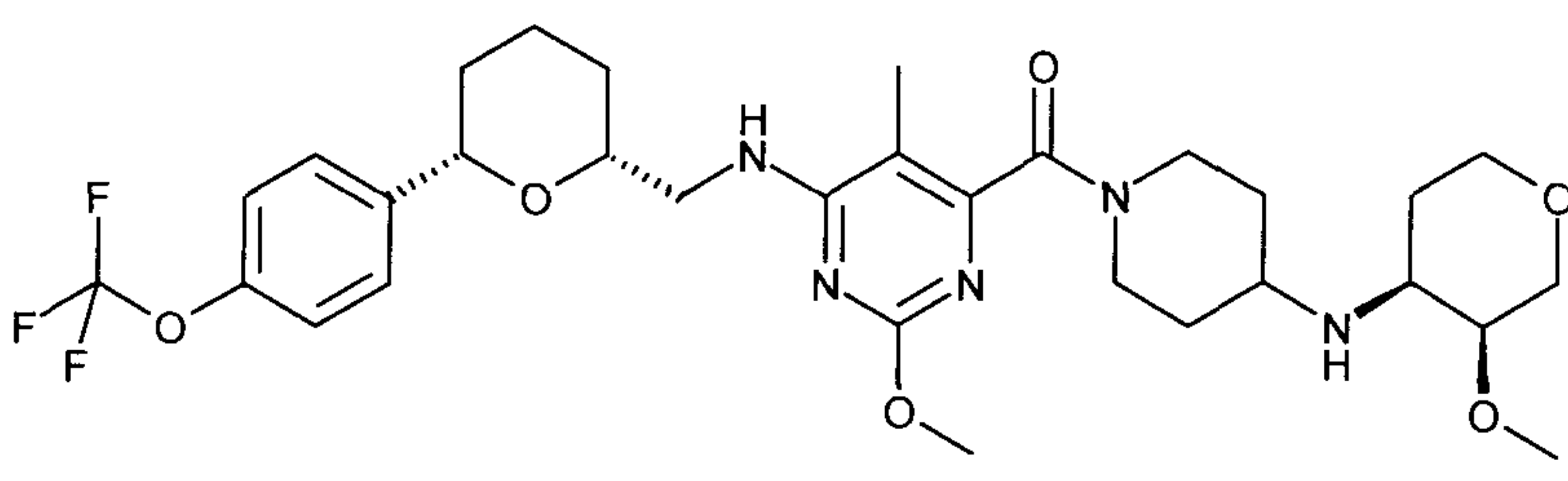


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42. The compound:



43. The compound:



5 44. Use of the compound according to any one of claims 1 to 43 or a pharmacologically acceptable acid addition salt thereof for binding CC chemokine receptor 2 (CCR2).

45. A pharmacologically acceptable acid addition salt of the compound according to any one of claims 24 to 27 and 29 to 43.

10 46. A pharmacologically acceptable acid addition salt of the compound according to claim 28.

47. A pharmaceutical formulation comprising a compound of claim 1 and an excipient.

48. A pharmaceutical formulation comprising a compound of claim 17 and an excipient.

15 49. A pharmaceutical formulation comprising a compound of claim 28 and an excipient.

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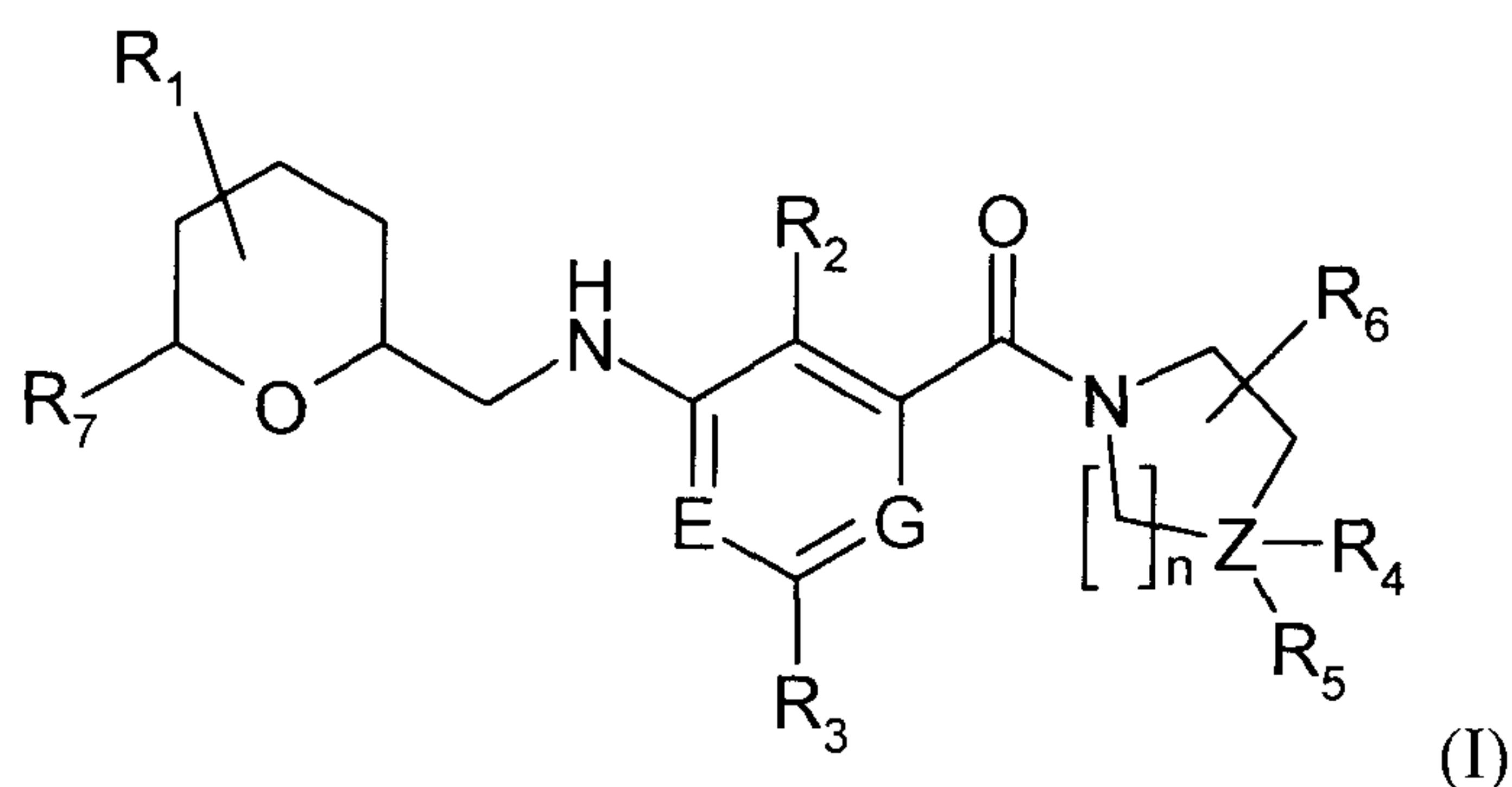
50. A pharmaceutical formulation comprising a pharmacologically acceptable acid addition salt of claim 46 and an excipient.

51. A pharmaceutical formulation comprising a compound of claim 19 and an excipient.

5 52. A pharmaceutical formulation comprising a compound of claim 21 and an excipient.

53. A pharmaceutical formulation comprising a compound of claim 23 and an excipient.

54. Use of a compound of formula (I) or a pharmacologically acceptable acid
10 addition salt thereof for treating neuropathic pain:



wherein R_1 is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

15 wherein R_7 is a ring selected from among -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, and -C₅-C₁₀-heteroaryl,

wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -C₁-C₆-alkyl, -C(CH₃)₂-CN, and -halogen,

or wherein the ring R_7 is optionally substituted with one or more groups selected from among -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl,
20 -C₃-C₈-heterocyclyl, -C₂-C₆-alkenyl, and -C₂-C₆-alkynyl, optionally being substituted by one

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or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, -methyl, and =O,

or wherein the ring R₇ is optionally further bi-valently substituted on two neighbouring ring atoms, such that an annellated ring is formed by one or more groups selected from among

- 5 -C₁-C₆-alkylene, -C₂-C₆-alkenylene and -C₄-C₆-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O;

- 10 wherein R₂ is selected from among -H, -halogen, -CN, -O-C₂-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₃ is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

wherein n is 1, 2 or 3;

wherein G and E are independently selected from among C-H or N;

- 15 wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H, and -C₁-C₆-alkyl,

or wherein Z is N,

- 20 and R₄ denotes an electron pair and R₅ is selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H, and -C₁-C₆-alkyl,

and wherein R₄ if different from an electron pair or -H and R₅ if different from -H are optionally independently substituted with one or more groups selected from among -halogen,

- 25 -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl,

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-O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl,
 -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-
 O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-
 N(R₉,R_{9'}), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-
 5 cycloalkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-
 C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R_{11'}),
 -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R_{13'}), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene(R₂₀,R_{20'}),
 -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q
 -C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl,
 10 -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),

wherein Q is selected from among -C(O)-, and -SO₂-,

wherein R₁₀, R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and
 -C₃-C₆-cycloalkyl,

wherein R₉, R_{9'}, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H,
 15 -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a
 -C₂-C₆-alkylene group,

wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl,
 -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-
 20 heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,

and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from
 among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and
 -SO₂-C₁-C₄-alkyl,

wherein R₂₀ and R_{20'} together form a spiro-C₃-C₈-carbocycle or spiro-C₃-C₈-heterocycle
 25 comprising one or more group selected from O in the ring, and wherein said spirocycle is
 optionally further bi-valently substituted by an annellated ring forming group selected from
 among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene and wherein said

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spirocycle is optionally further substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen,

or wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

5 wherein L₁ is selected from among -NH-, -N(C₁-C₄-alkyl)-, and a bond,

wherein R₁₈ is selected from among -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl,

wherein R₁₈ is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl, -NH-C(O)-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-C(O)-C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, -NH-S(O)₂-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-S(O)₂-C₁-C₆-alkyl, and -C(O)-O-C₁-C₆-alkyl,

and wherein R₅ and R₁₈ are optionally further substituted by spiro-C₃-C₈-cycloalkyl or spiro-C₃-C₈-heterocyclyl such that together with R₄, R₅ and/or R₁₈ a spirocycle is formed, wherein said spiro-C₃-C₈-heterocyclyl optionally comprises one or more groups selected from among
15 nitrogen, -C(O)-, -SO₂-, and -N(SO₂-C₁-C₄-alkyl)- in the ring,

or wherein R₅ and R₁₈ are optionally further bi-valently substituted by one or more spirocyclic or annellated ring forming groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be
20 substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, and halogen,

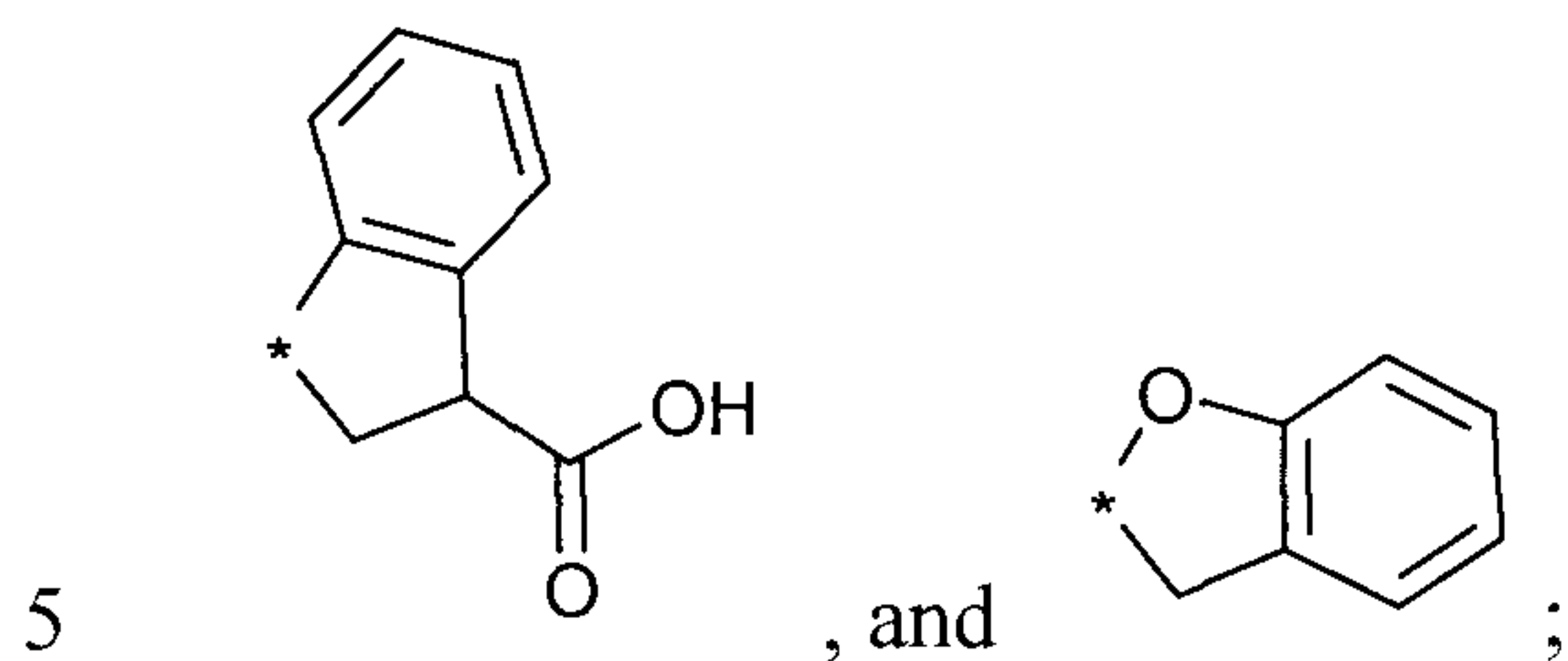
or wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R_{19'}),

25 wherein R₁₉ and R_{19'} together form a -C₂-C₆-alkylene group such that a ring is formed,

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wherein such ring is optionally substituted by one or more groups selected from among -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃, -S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃, -(C₆-aryl)-COOH, -C(O)-O-C₂H₅,



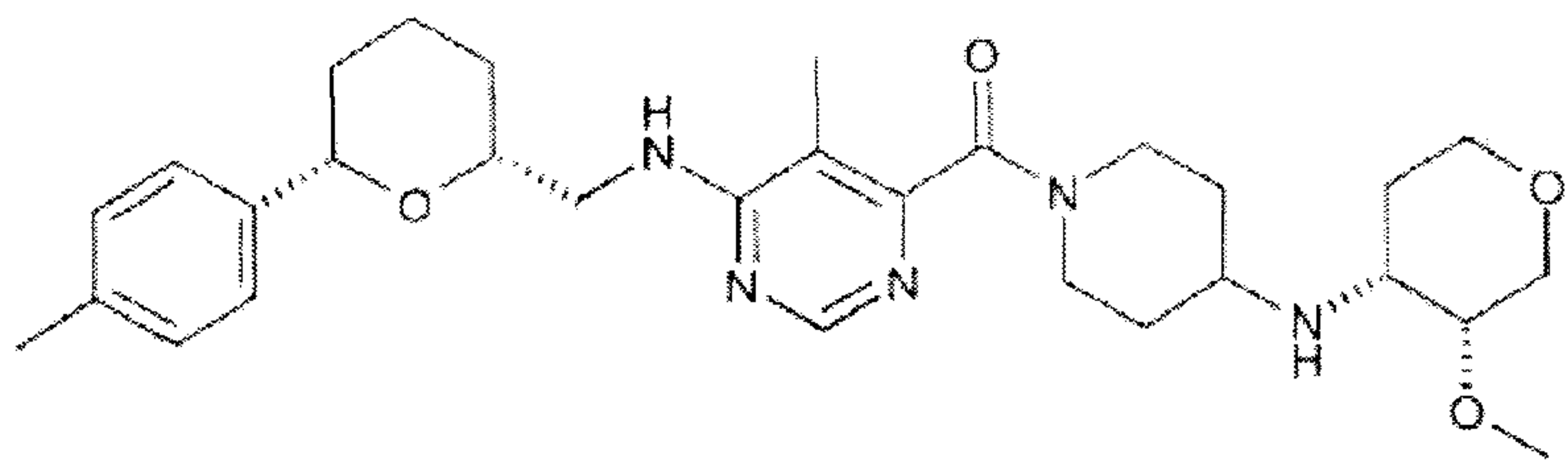
wherein R₆ is selected from among -H, -C₁-C₄-alkyl, -OH, -O-C₁-C₄-alkyl, -halogen, -CN, -CF₃, and -OCF₃.

55. The use of claim 54, wherein G and E are N.

56. The use of claim 54 or 55, wherein L₁ is -NH-.

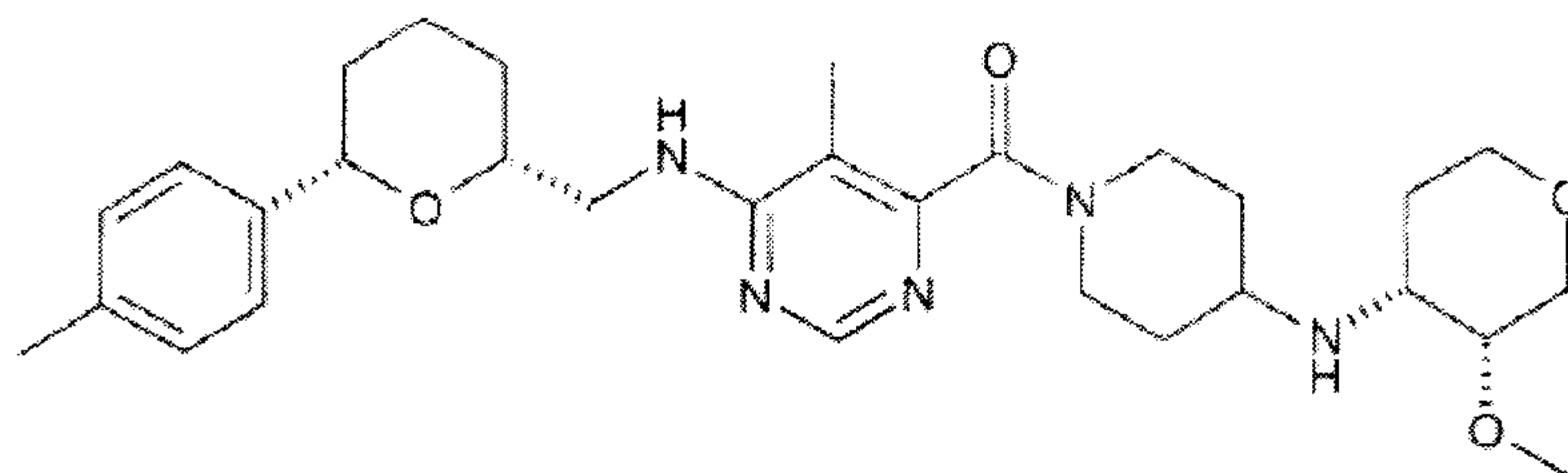
10 57. The use of any one of claims 54 to 56, wherein R₇ is -C₅-C₁₀-aryl optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, -C₁-C₆-alkyl, -C(CH₃)₂-CN, and halogen

58. The use of claim 54, wherein the compound is



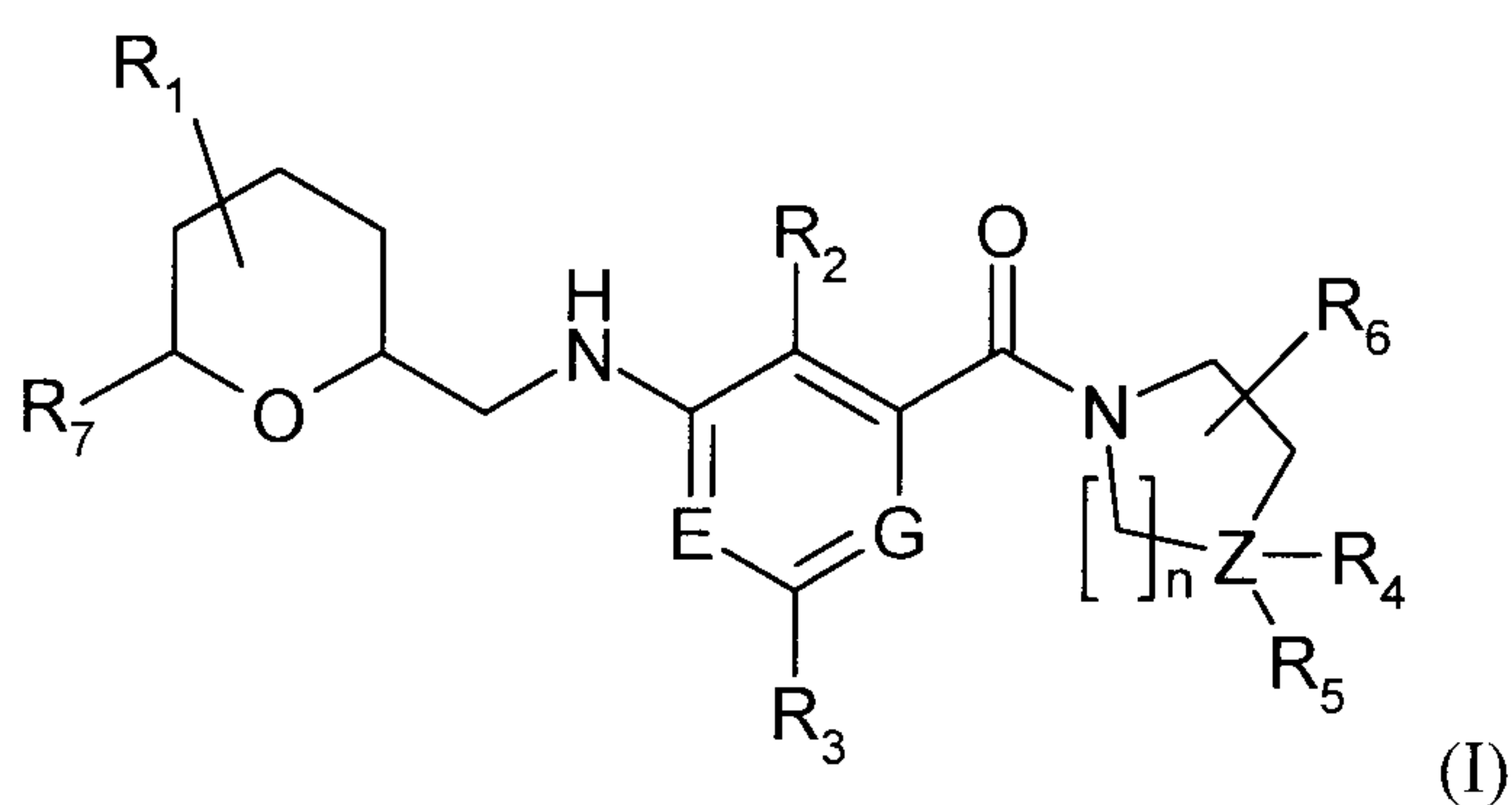
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59. The use of claim 54, wherein the compound is a pharmacologically acceptable



acid addition salt of

60. Use of a compound of formula (I) or a pharmacologically acceptable acid addition salt thereof for treating inflammatory pain:



wherein R_1 is a group selected from among -H, -halogen, -CN, -O-C₁-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R_7 is a ring selected from among -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, and -C₅-C₁₀-heteroaryl,

10 wherein the ring R_7 is optionally substituted with one or more groups selected from among -CF₃, -O-CF₃, -S-CF₃, -CN, -C₁-C₆-alkyl, -C(CH₃)₂-CN, and -halogen,

or wherein the ring R_7 is optionally substituted with one or more groups selected from among -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₂-C₆-alkenyl, and -C₂-C₆-alkynyl, optionally being substituted by one

15 or more groups selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, -methyl, and =O,

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or wherein the ring R₇ is optionally further bi-valently substituted on two neighbouring ring atoms, such that an annellated ring is formed by one or more groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene and -C₄-C₆-alkynylene, in which one or two or three carbon centers may optionally be replaced by 1 or 2 or 3 hetero atoms selected from N, O and S, the bivalent group being optionally substituted by one or more groups selected from -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, halogen, and =O;

wherein R₂ is selected from among -H, -halogen, -CN, -O-C₂-C₄-alkyl, -C₁-C₄-alkyl, -CH=CH₂, -C≡CH, -CF₃, -OCF₃, -OCF₂H, and -OCFH₂;

wherein R₃ is selected from among -H, -methyl, -ethyl, -propyl, -i-propyl, -cyclopropyl, -OCH₃, -CF₃, and -CN;

wherein n is 1, 2 or 3;

wherein G and E are independently selected from among C-H or N;

wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H, and -C₁-C₆-alkyl,

or wherein Z is N,

and R₄ denotes an electron pair and R₅ is selected from among -H, -C₁-C₆-alkyl, -NH₂, -C₃-C₈-cycloalkyl, -C₃-C₈-heterocyclyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, and -C(O)-N(R₈,R₈'), with R₈ and R₈' independently being selected from among -H, and -C₁-C₆-alkyl,

and wherein R₄ if different from an electron pair or -H and R₅ if different from -H are optionally independently substituted with one or more groups selected from among -halogen, -OH, -CF₃, -CN, -C₁-C₆-alkyl, -O-C₁-C₆-alkyl, -O-C₃-C₈-cycloalkyl, -O-C₃-C₈-heterocyclyl, -O-C₅-C₁₀-aryl, -O-C₅-C₁₀-heteroaryl, -C₀-C₆-alkylene-CN, -C₀-C₄-alkylene-O-C₁-C₄-alkyl, -C₀-C₄-alkylene-O-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-O-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-

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O-C₅-C₁₀-aryl, -C₀-C₄-alkylene-O-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-C₀-C₄-alkyl-N(R₉,R_{9'}), -C₀-C₄-alkylene-N(R₁₀)-Q-C₁-C₄-alkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-N(R₁₀)-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-Q-N(R₁₁,R_{11'}),
 5 -C₀-C₄-alkylene-N(R₁₂)-Q-N(R₁₃,R_{13'}), -C₀-C₄-alkylene-R₁₄, -C₀-C₄-alkylene(R₂₀,R_{20'}), -C₀-C₄-alkylene-Q-C₁-C₆-alkyl, -C₀-C₄-alkylene-Q-C₃-C₈-cycloalkyl, -C₀-C₄-alkylene-Q-C₃-C₈-heterocyclyl, -C₀-C₄-alkylene-Q-C₅-C₁₀-aryl, -C₀-C₄-alkylene-Q-C₅-C₁₀-heteroaryl, -C₀-C₄-alkylene-O-Q-N(R₁₅,R_{15'}), and -C₀-C₄-alkylene-N(R₁₆)-Q-O-(R₁₇),

wherein Q is selected from among -C(O)-, and -SO₂-,

10 wherein R₁₀, R₁₂, R₁₆, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

wherein R₉, R_{9'}, R₁₁, R_{11'}, R₁₃, R_{13'}, R₁₅, R_{15'}, are independently selected from among -H, -C₁-C₆-alkyl, and -C₃-C₆-cycloalkyl,

or wherein R₉ and R_{9'}, R₁₁ and R_{11'}, R₁₃ and R_{13'}, R₁₅ and R_{15'} together form a

15 -C₂-C₆-alkylene group,

wherein R₁₄ and R₁₇ are independently selected from among -H, -C₁-C₆-alkyl, -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and -C₃-C₈-heterocyclyl, wherein said -C₃-C₈-heterocyclyl optionally comprises nitrogen and/or -SO₂- in the ring,

and wherein R₁₄ and R₁₇ are optionally substituted with one or more groups selected from
 20 among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen, -C₁-C₄-alkyl, =O, and -SO₂-C₁-C₄-alkyl,

wherein R₂₀ and R_{20'} together form a spiro-C₃-C₈-carbocycle or spiro-C₃-C₈-heterocycle comprising one or more group selected from O in the ring, and wherein said spirocycle is optionally further bi-valently substituted by an annellated ring forming group selected from
 25 among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene and wherein said spirocycle is optionally further substituted with one or more groups selected from among -OH, -OCH₃, -CF₃, -COOH, -OCF₃, -CN, -halogen,

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or wherein Z is C,

and R₄ denotes -H and R₅ is a group of the structure -L₁-R₁₈,

wherein L₁ is selected from among -NH-, -N(C₁-C₄-alkyl)-, and a bond,

wherein R₁₈ is selected from among -C₅-C₁₀-aryl, -C₅-C₁₀-heteroaryl, -C₃-C₈-cycloalkyl, and

5 -C₃-C₈-heterocyclyl,

wherein R₁₈ is optionally substituted by one or more groups selected from among halogen, -CF₃, -OCF₃, -CN, -OH, -O-C₁-C₄-alkyl, -C₁-C₆-alkyl, -NH-C(O)-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-C(O)-C₁-C₆-alkyl, -C(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, -NH-S(O)₂-C₁-C₆-alkyl, -N(C₁-C₄-alkyl)-S(O)₂-C₁-C₆-alkyl, and -C(O)-O-C₁-C₆-alkyl,

10 and wherein R₅ and R₁₈ are optionally further substituted by spiro-C₃-C₈-cycloalkyl or spiro-C₃-C₈-heterocyclyl such that together with R₄, R₅ and/or R₁₈ a spirocycle is formed, wherein said spiro-C₃-C₈-heterocyclyl optionally comprises one or more groups selected from among nitrogen, -C(O)-, -SO₂-, and -N(SO₂-C₁-C₄-alkyl)- in the ring,

or wherein R₅ and R₁₈ are optionally further bi-valently substituted by one or more spirocyclic

15 or annellated ring forming groups selected from among -C₁-C₆-alkylene, -C₂-C₆-alkenylene, and -C₄-C₆-alkynylene, in which one or two carbon centers may optionally be replaced by one or two hetero atoms selected from among N, O and S and which may optionally be substituted by one or more groups on one ring atom or on two neighbouring ring atoms selected from among -OH, -NH₂, -C₁-C₃-alkyl, -O-C₁-C₆-alkyl, -CN, -CF₃, -OCF₃, and
20 halogen,

or wherein Z is C,

and R₄ and R₅ are independently selected from among -H, -C₁-C₆-alkyl, and -N(R₁₉,R_{19'}),

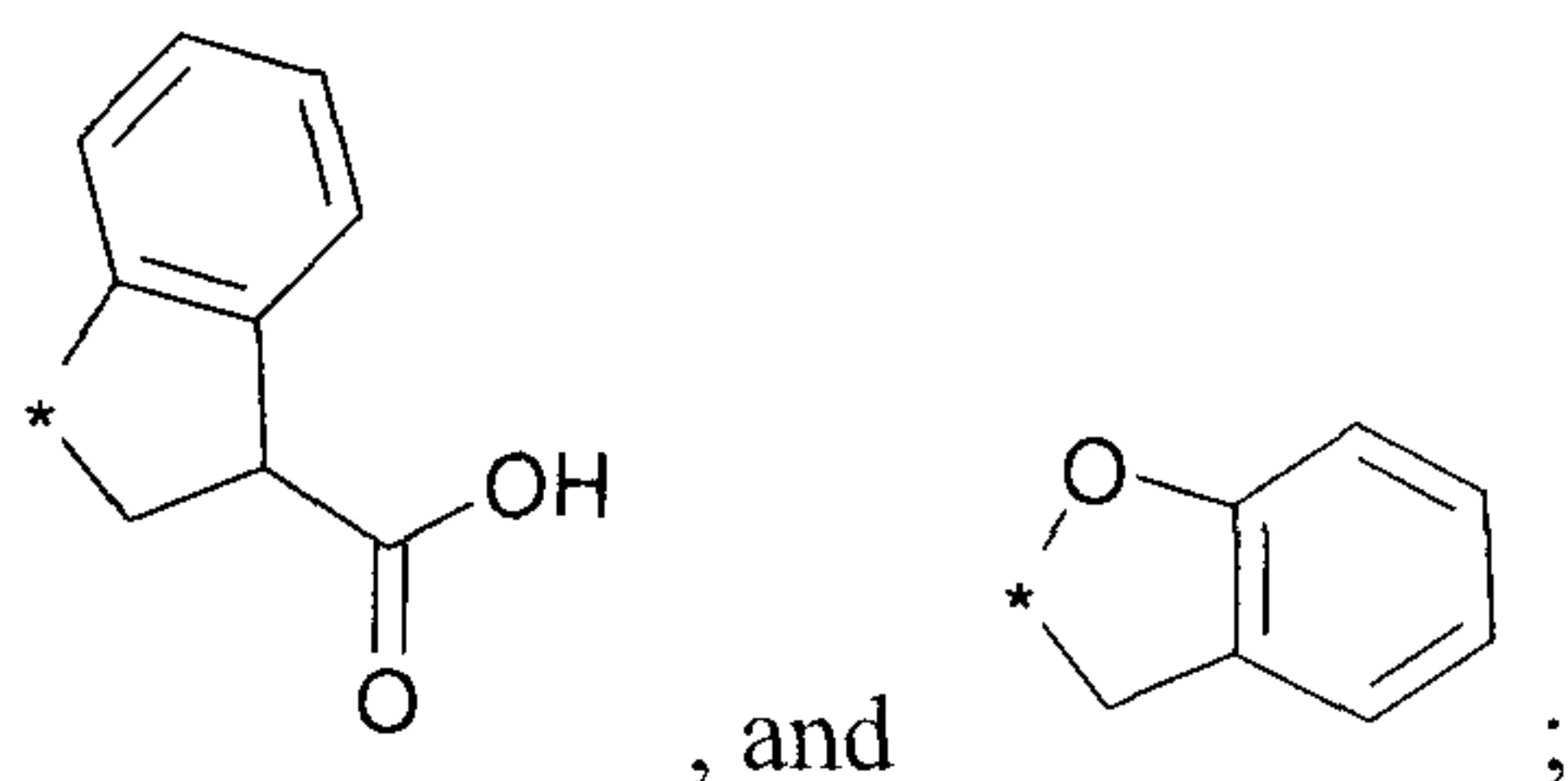
wherein R₁₉ and R_{19'} together form a -C₂-C₆-alkylene group such that a ring is formed,

wherein such ring is optionally substituted by one or more groups selected from among

25 -F, -CF₃, -OCF₃, -CN, -OH, -O-CH₃, -CH₃, -NH-C(O)-CH₃, -N(CH₃)-C(O)-CH₃, -C(O)-CH₃,

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-S(O)₂-CH₃, -NH-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₃, -N(CH₃)-S(O)₂-CH₂-CH₃,
 -(C₆-aryl)-COOH, -C(O)-O-C₂H₅,



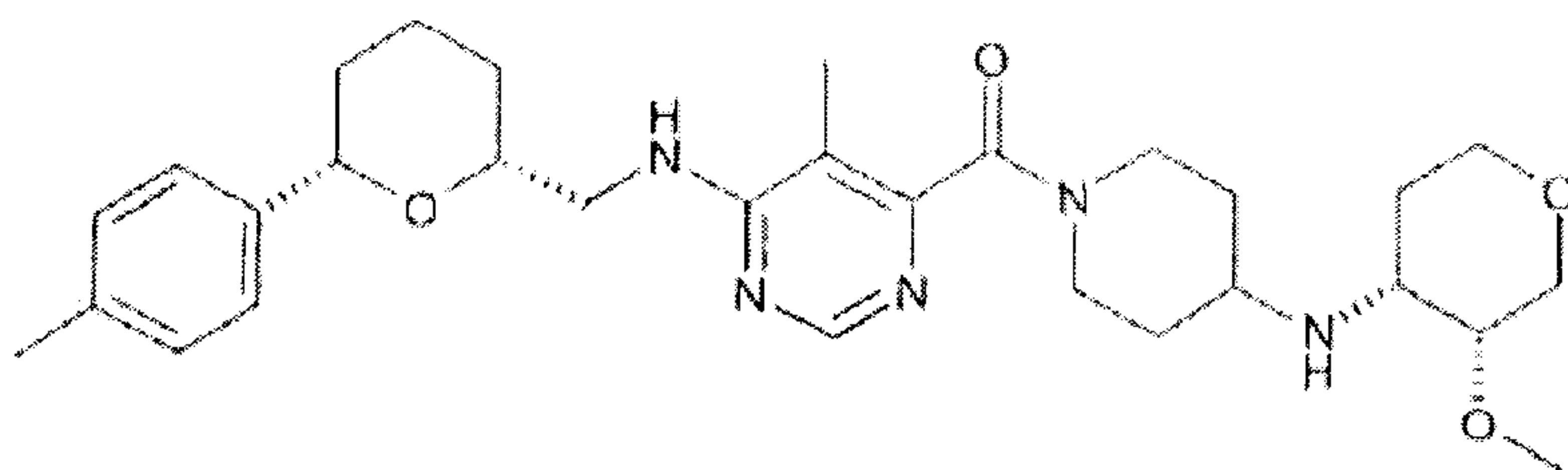
wherein R₆ is selected from among -H, -C₁-C₄-alkyl, -OH, -O-C₁-C₄-alkyl, -halogen, -CN,
 5 -CF₃, and -OCF₃.

61. The use of claim 60, wherein G and E are N.

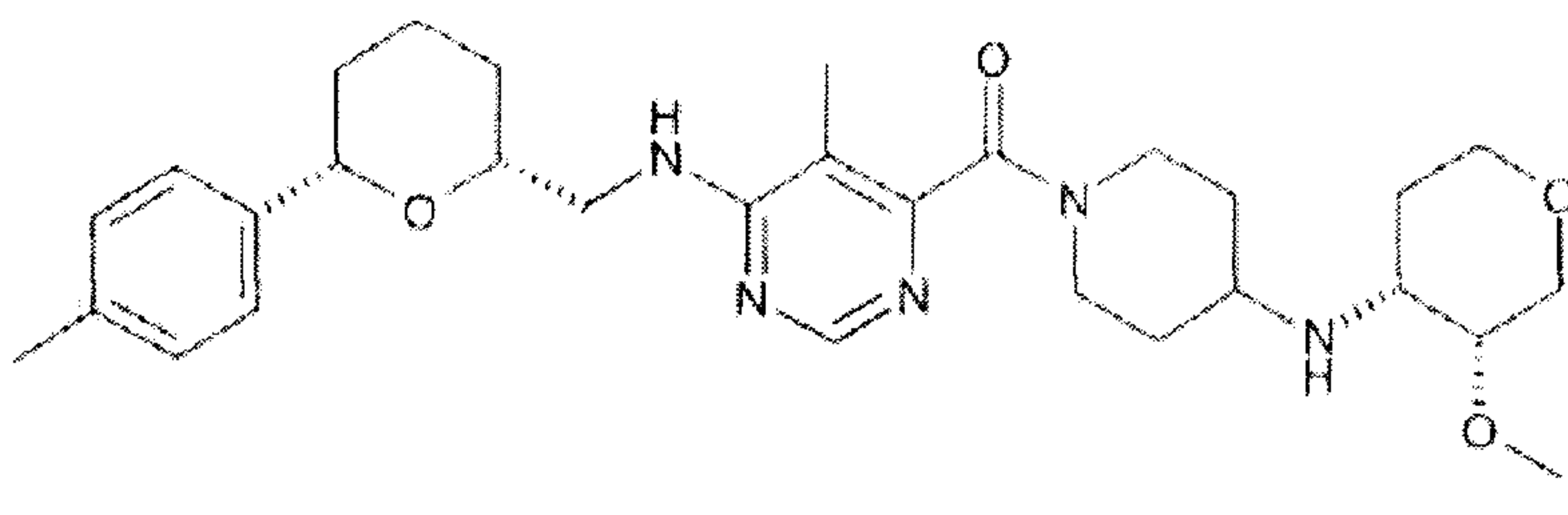
62. The use of claim 60 or 61, wherein L₁ is -NH-.

63. The use of any one of claims 60 to 62, wherein R₇ is -C₅-C₁₀-aryl optionally
 substituted with one or more groups selected from among -CF₃, -O-CF₃, -CN, -C₁-C₆-alkyl,
 10 -C(CH₃)₂-CN, and halogen

64. The use of claim 60, wherein the compound is



65. The use of claim 60, wherein the compound is a pharmacologically acceptable
 acid addition salt of



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