



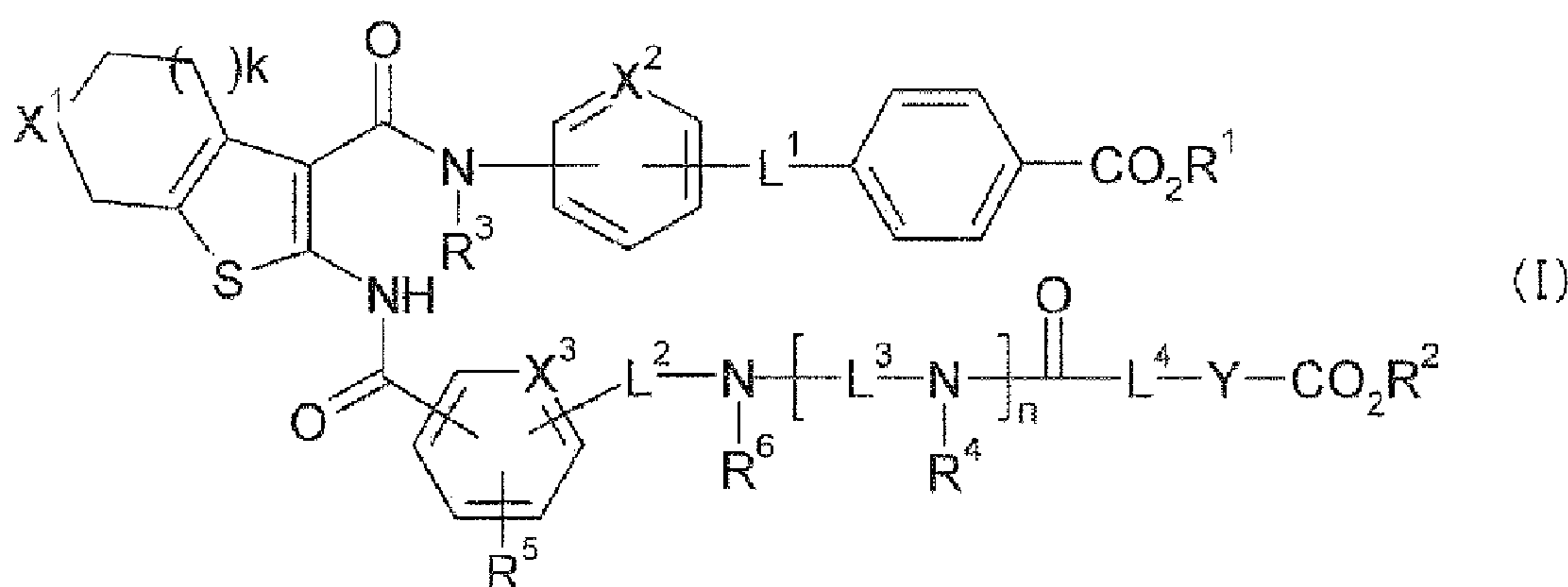
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(54) Titre : DERIVE DE N-THIENYL BENZAMIDE SUBSTITUE AVEC UN AMINOALKYLE
(54) Title: AMINOALKYL-SUBSTITUTED N-THIENYLBENZAMIDE DERIVATIVE



(57) Abrégé/Abstract:

The objective of the present invention is to provide a compound having inhibitory activity against an intestinal phosphate transporter (NPT-IIb), and useful as an active ingredient in a hyperphosphatemia therapeutic agent and/or preventive. A thiophene compound represented by formula (I) may be used as a hyperphosphatemia therapeutic agent and/or preventive having NPT-IIb inhibitory activity. (In the formula, R¹⁻⁶ each represent H or a lower alkyl or the like, L¹⁻⁴ each represent a lower alkyl or the like, X¹ represents CH² or O, X²⁻³ each represent CH or N, k is 1-3, and n is 0-1.)



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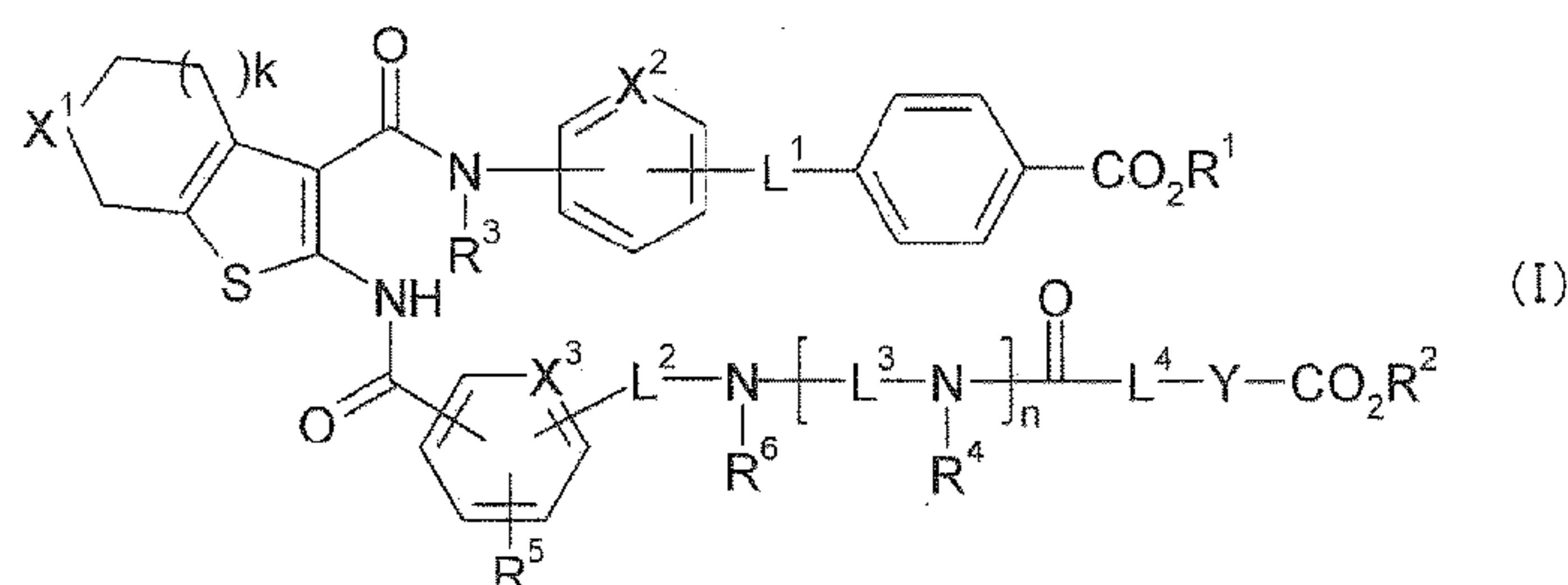
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(54) Title: AMINOALKYL-SUBSTITUTED N-THIENYL BENZAMIDE DERIVATIVE

(54) 発明の名称: アミノアルキル置換 N-チエニルベンズアミド誘導体



(57) **Abstract:** The objective of the present invention is to provide a compound having inhibitory activity against an intestinal phosphate transporter (NPT-IIb), and useful as an active ingredient in a hyperphosphatemia therapeutic agent and/or preventive. A thiophene compound represented by formula (I) may be used as a hyperphosphatemia therapeutic agent and/or preventive having NPT-IIb inhibitory activity. (In the formula, R¹⁻⁶ each represent H or a lower alkyl or the like, L¹⁻⁴ each represent a lower alkyl or the like, X¹ represents CH₂ or O, X²⁻³ each represent CH or N, k is 1-3, and n is 0-1.)

(57) **要約:** 腸管リン酸トランスポーター (NPT-IIb) 阻害作用を有し、高リン血症の治療剤及び／又は予防剤の有効成分として有用な化合物を提供することを目的とする。下記式 (I) で表されるチオフェン化合物は、NPT-IIb 阻害作用を有し、高リン血症の予防及び／又は治療剤として使用し得る。(式中、R¹⁻⁶ は H 又は低級アルキル等であり、L¹⁻⁴ は低級アルキレン等であり、X¹ は CH₂ 又は O であり、X²⁻³ は CH 又は N であり、k は 1 ~ 3 であり、n は 0 ~ 1 である。)

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DESCRIPTION

Title of Invention: AMINOALKYL-SUBSTITUTED N-THIENYLBENZAMIDE
DERIVATIVE

Technical Field

[0001]

The present invention relates to an aminoalkyl-substituted N-thienylbenzamide derivative useful as an active ingredient of a pharmaceutical composition, for example, a pharmaceutical composition for treating hyperphosphatemia.

Background Art

[0002]

Phosphorus is an essential element in the maintenance of life and plays very important roles in various physiological functions. Phosphorus is taken up in the form of phosphate through the gastrointestinal tract from food, and most of the phosphorus is excreted by incorporation into urine, whereby its total amount in a living is maintained and regulated. It is known that in the process of formation of urine, substantially most of phosphate is filtered at the glomerulus and only a necessary amount thereof is reabsorbed in the tubules. Accordingly, if the filtration ability of the glomerulus decreases as renal failure progresses, excretion of phosphorus becomes insufficient, and abnormal increase in the serum phosphorus level, that is, hyperphosphatemia is caused. Thus, hyperphosphatemia that induces various complications of renal failure is considered to be a factor for reducing the QOL of a patient with renal failure through fractures and bone pain, or a factor of death of a patient with renal failure through cardiovascular diseases resulting from cardiovascular calcification. Consequently, hyperphosphatemia is a very major issue in clinical practice ("KDIGO Clinical Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)", *Kidney International*, 76, Supplement 113 (2009)).

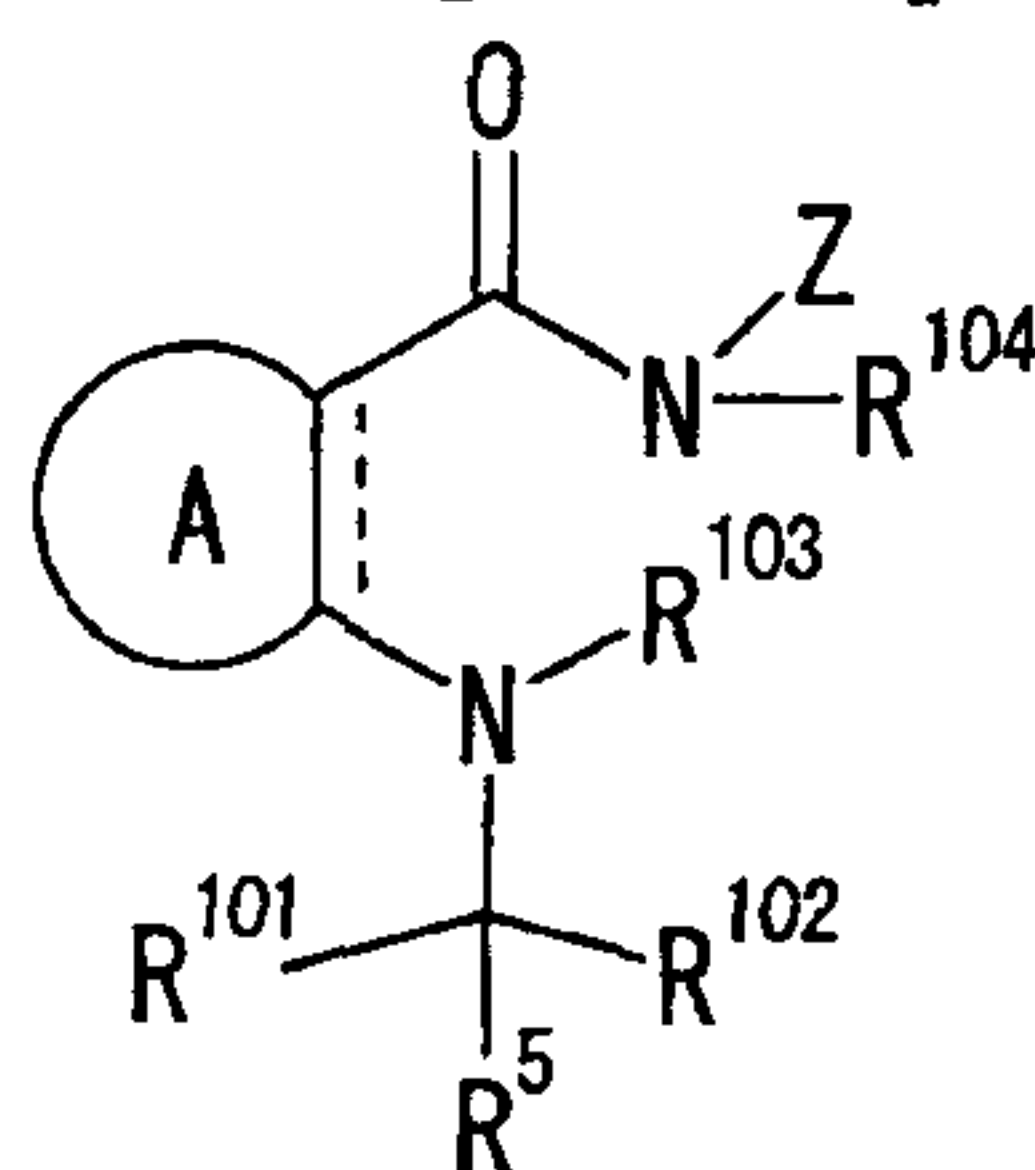
Currently, for the treatment of hyperphosphatemia, phosphate binders are used, for example, various calcium salt preparations represented by precipitated calcium carbonate, polymers represented by sevelamer hydrochloride, or metal salt preparations such as lanthanum carbonate, aluminum hydroxide, and iron preparations. However, these drugs have various problems, such as poor dose adherence due to the requirement for several grams per day, gastrointestinal symptoms such as constipation and diarrhea, increase in serum calcium levels, and accumulation of various metals. Therefore, development of a novel agent for treating hyperphosphatemia that improves the above factors is required (*ibid*).

Phosphate transporters present in the brush-border membrane of the gastrointestinal tract and renal tubules are considered to be involved in the absorption and excretion of phosphorus. So far, a large number of phosphate transporters have been reported. Among these, NPT-IIb plays a main role in phosphate absorption in the gastrointestinal tract, and NPT-IIa plays a main role in phosphate reabsorption in the kidneys. In addition, these molecules have been reported to be cotransporters of sodium and phosphate. In this respect, it has been pointed out that if the function of the NPT-IIb is inhibited, phosphorus absorption from the gastrointestinal tract can be suppressed (Journal of the American Society of Nephrology, 20: p 2348-2358 (2009)).

[0003]

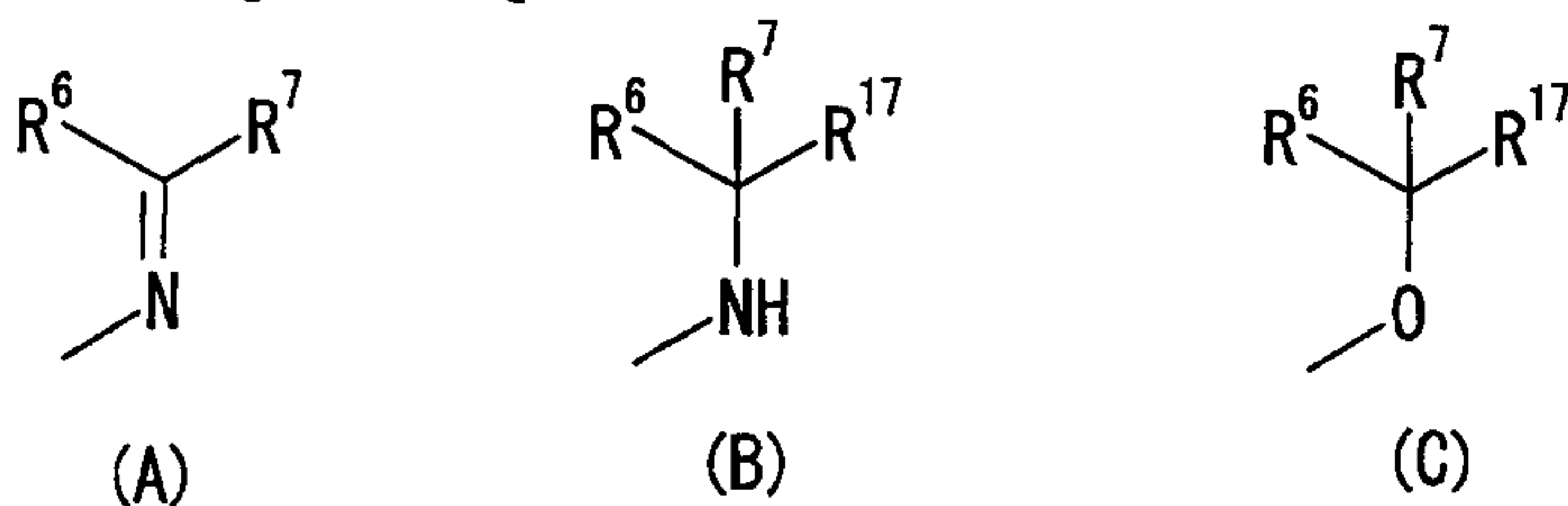
A drug for treating hyperphosphatemia based on this mechanism of action is being studied, and for example, a compound represented by the following general formula has been reported to be a compound having NPT-IIb inhibitory action (Patent Document 1).

[Chem. 1]



(In the formula, A represents a 5- to 9- membered unsaturated carbocycle portion or unsaturated heterocycle portion; when the carbocycle portion or the heterocycle portion represented by A is substituted with two C₁₋₆ alkyl groups or C₂₋₆ alkenyl groups, these alkyl groups or alkenyl groups may form a 5- to 7-membered unsaturated carbocycle in combination with the carbon atoms to which these groups bind; R⁵ represents an aryl group or the like which may be substituted; R¹⁰¹ and R¹⁰² in combination represent =O, R¹⁰³ and R¹⁰⁴ represent a hydrogen atom or the like; and Z represents the following Formula (A), (B), or (C) in which R⁶ and R⁷ may be the same as or different from each other and represent a hydrogen atom, an aryl group, or the like, and R¹⁷ represents a hydrogen atom. Regarding other symbols in the formula, see the corresponding gazette.)

[Chem. 2]



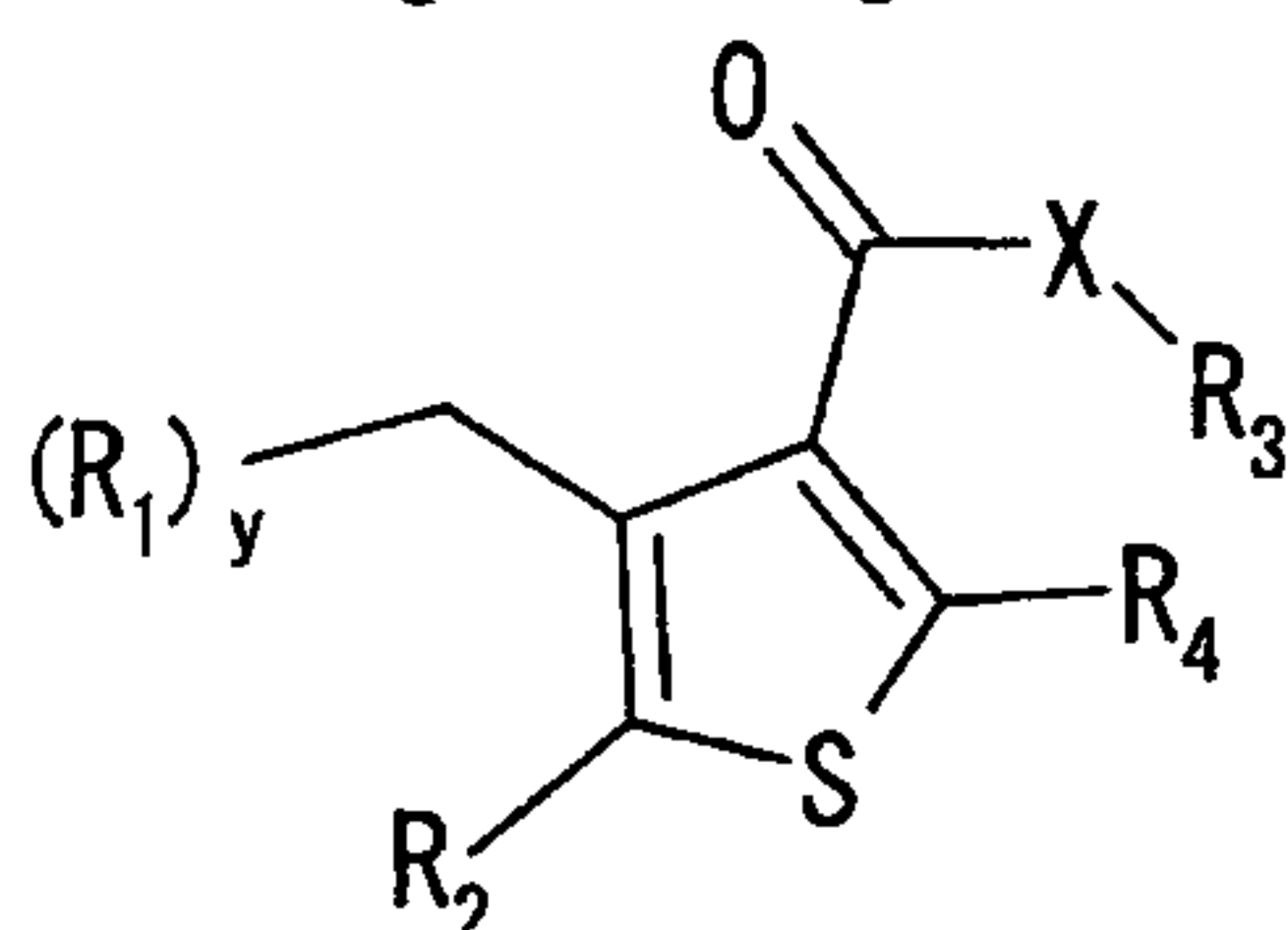
[0004]

In addition, as compounds that have the NPT-IIb inhibitory action and are used for preventing or treating hyperphosphatemia, a triazole compound (Patent Document 2) and a quinazolone compound (Patent Document 3) have been disclosed.

[0005]

Moreover, a tetrahydrobenzothiophene derivative that has a carbonylamino group at a 2-position and a carbamoyl group at a 3-position has been reported. For example, a tetrahydrobenzothiophene compound represented by the following general formula is reported to have an antiviral action (Patent Document 4).

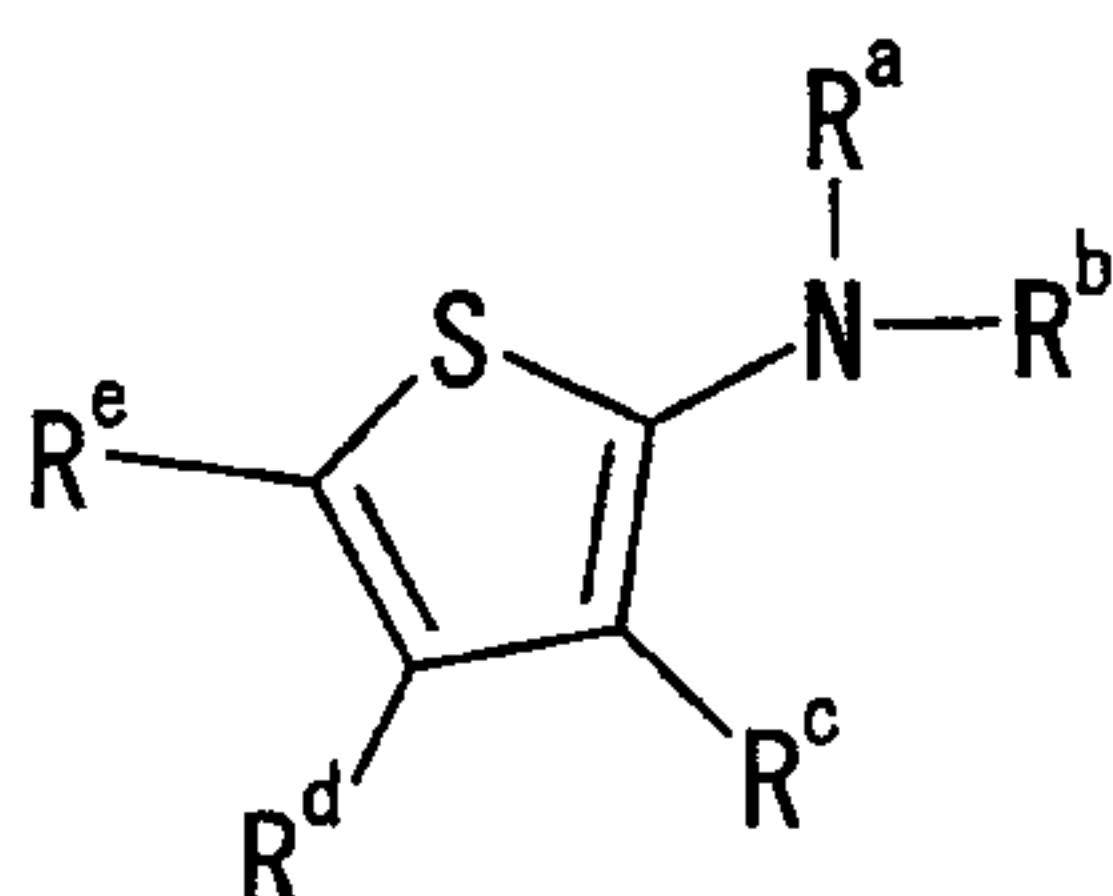
[Chem. 3]



(In the formula, X represents N(R') or an oxygen atom, R₁ and R₂ form a ring in combination with atoms bonded thereto, y represents 0 to 3, R₃ represents a substituted carbocycle or heterocycle, or the like, R₄ represents -N(R')-C(O)-R₇ or the like, R₇ represents a substituted carbocycle or heterocycle, or the like, and R' represents a hydrogen atom or lower alkyl. Regarding other symbols in the formula, see the corresponding gazette.)

A tetrahydrobenzothiophene compound represented by the following general formula is reported to have an antiviral action (Patent Document 5).

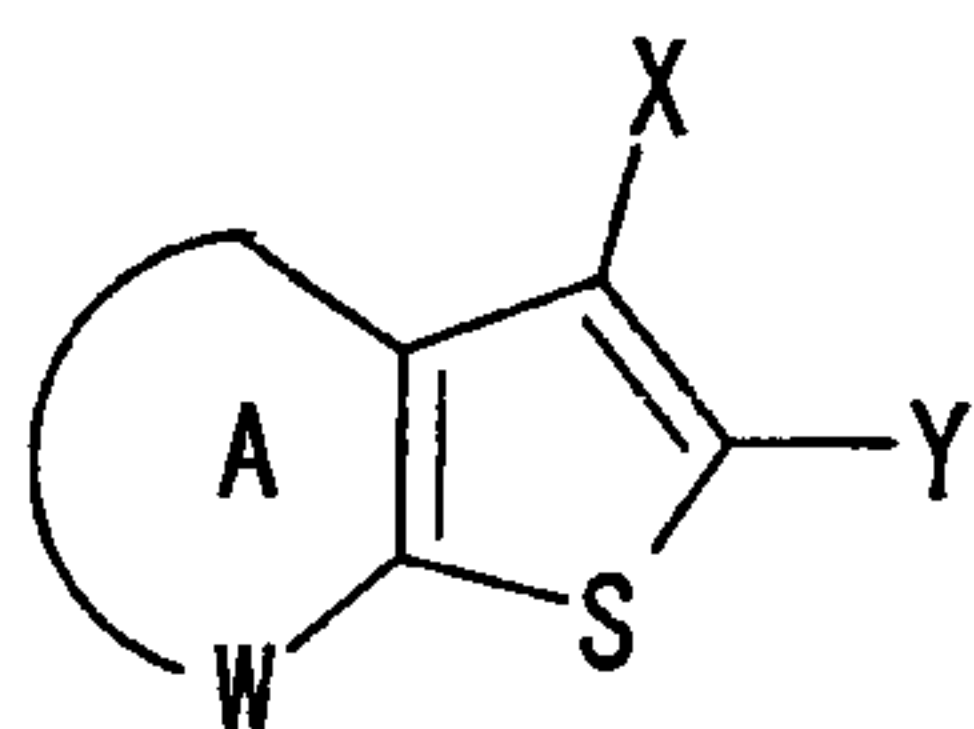
[Chem. 4]



(In the formula, R^a represents a hydrogen atom, an alkyl group, or the like which may be substituted, R^b represents -C(O)-R^{b1} or the like which may be substituted, R^{b1} represents amino, aminoalkyl, a carbocycle, a heterocycle, or the like which may be substituted, R^c represents -C(O)-R^{b1} or the like which may be substituted, and R^d and R^e represent a carbocycle, a heterocycle, formed in combination with atoms bonded thereto or the like which may be substituted. Regarding other symbols in the formula, see the corresponding gazette.)

A tetrahydrobenzothiophene compound represented by the following general formula is reported to have an antitumor action (Patent Document 6).

[Chem. 5]



(In the formula, W represents a carbon atom or a nitrogen atom, A represents 5- to 14-membered cycloalkyl, heteroaryl, or the like which may be substituted, Y represents -NR¹R² or the like, X represents -C(O)NR⁵R⁶ or the like, R¹ represents a hydrogen atom or lower alkyl, R² represents -C(O)R¹⁰ or the like, R¹⁰ represents aryl, heteroaryl, or the like which may be substituted, R⁵ represents aryl, heteroaryl, or the like which may be substituted, and R⁶ represents a hydrogen atom or the like. Regarding other symbols in the formula, see the corresponding gazette.)

However, none of Patent Documents 4 to 6 disclose or suggest that these compounds have an NPT-IIb inhibitory action or can be used for preventing or treating hyperphosphatemia.

Related Art

Patent Document

[0006]

- | | |
|---------------------|---|
| [Patent Document 1] | Pamphlet of International Publication WO2004/085382 |
| [Patent Document 2] | Pamphlet of International Publication WO2003/048134 |
| [Patent Document 3] | JP-A-2007-131532 |
| [Patent Document 4] | Pamphlet of International Publication WO2006/026619 |
| [Patent Document 5] | Pamphlet of International Publication WO2006/093518 |
| [Patent Document 6] | Pamphlet of International Publication WO2006/044826 |

Disclosure of Invention

Problems to Be Solved by the Invention

[0007]

The present invention provides an aminoalkyl-substituted N-thienylbenzamide derivative useful as an active ingredient of a pharmaceutical composition, for example, a pharmaceutical composition for treating hyperphosphatemia.

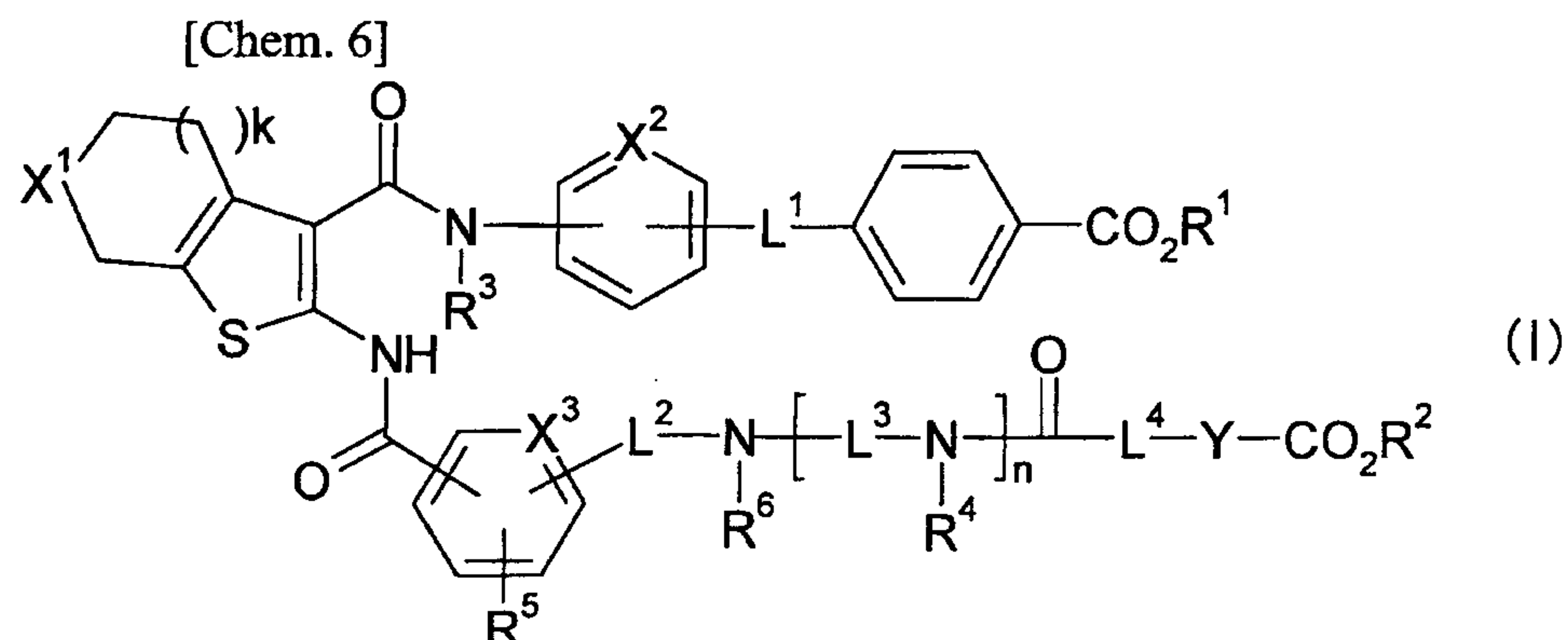
Means for Solving the Problems

[0008]

The present inventors conducted thorough research aiming at creating a compound having an NPT-IIb inhibitory action. As a result, they found that an N-thienylbenzamide compound having a characteristic substituent on an aromatic ring of benzamide has an

NPT-IIb inhibitory action and an action of inhibiting phosphorus absorption from the intestinal tract, thereby completing the present invention.

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



(In formula,

X^1 represents CH_2 or O,

k represents 1, 2, or 3,

R^3 represents H or lower alkyl,

X^2 represents CH or N,

L^1 represents lower alkylene,

R^1 represents H or lower alkyl,

X^3 represents CH or N,

L^2 represents lower alkylene,

R^5 represents H or lower alkyl,

R^6 represents H, lower alkyl, lower alkyl substituted with one to two of $-OR^0$, $-C(O)$ -lower alkyl, $-S(O)_m$ -lower alkyl, $-lower\ alkylene-N(lower\ alkyl)_2$, $-R^{00}$ -heterocycle, $-R^{00}$ -phenyl, or $-R^{00}$ -cycloalkyl, wherein the heterocycle, phenyl, and cycloalkyl may be substituted with one to two lower alkyl or $C(O)$ -lower alkyl, and $-R^{00}$ may be substituted with one $-OR^0$,

R^{00} represents a bond or lower alkylene,

R^0 represents H or lower alkyl,

m represents 0, 1, or 2,

L^3 represents lower alkylene,

n represents 0 or 1,

R^4 represents H, lower alkyl, $-lower\ alkylene-COO-R^0$, $-lower\ alkylene-OR^0$, $-lower\ alkylene-NHR^0$, $-lower\ alkylene-N(lower\ alkyl)_2$, or cycloalkyl,

L^4 represents a bond, O, or $-NR^0-$,

Y represents $-R^{00}$ -monocyclic heterocycle- R^{00} -, $-R^{00}$ -phenyl- R^{00} -, -lower alkylene- NR^0 -lower alkylene-, lower alkylene-O-lower alkylene-, or lower alkylene which may be substituted with a hydroxyl group, and,
 R^2 represents H or lower alkyl.)

In addition, unless otherwise specified, when symbols in a certain chemical formula in the present specification are also used in another chemical formula, the same symbol represents the same meaning.

[0009]

The present invention also relates to a pharmaceutical composition containing the compound of Formula (I) or a salt thereof, particularly, to a pharmaceutical composition for treating or preventing hyperphosphatemia. Moreover, the pharmaceutical composition includes an agent for treating hyperphosphatemia containing the compound of Formula (I) or a salt thereof.

In addition, the present invention relates to use of the compound of Formula (I) or a salt thereof for the manufacture of a pharmaceutical composition for treating or preventing hyperphosphatemia, use of the compound of Formula (I) or a salt thereof for treating or preventing hyperphosphatemia, the compound of Formula (I) or a salt thereof for treating or preventing hyperphosphatemia, and a method of treating hyperphosphatemia including administering an effective amount of the compound of Formula (I) or a salt thereof to a subject. In addition, the “subject” refers to a human being or other animals that require the treatment or prevention of hyperphosphatemia, and as a certain embodiment, the “subject” refers to a human being that requires the prevention or treatment of hyperphosphatemia.

Effects of the Invention

[0010]

The compound of Formula (I) or a salt thereof has an NPT-IIb inhibitory action and can be used as an agent for preventing and/or treating hyperphosphatemia, renal insufficiency, or abnormality in bone metabolism caused by renal insufficiency.

Embodiments for Carrying Out the Invention

[0011]

Hereinafter, the present invention will be described in detail.

In the present specification, “lower alkyl” refers to linear or branched alkyl having 1 to 6 carbon atoms (herebelow, abbreviated to C_{1-6}), for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 1-ethylpropyl, n-hexyl, or the like. As another embodiment, the alkyl is methyl, ethyl, n-propyl, isopropyl, tert-butyl, or 1-ethylpropyl, and as still another embodiment, the alkyl is methyl or 1-ethylpropyl.

[0012]

“Lower alkylene” refers to linear or branched C₁₋₆ alkylene, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, methylenemethylene, ethylethylene, 1,2-dimethylethylene, 1,1,2,2-tetramethylethylene, or the like. As another embodiment, the lower alkylene is methylene, ethylene, trimethylene, tetramethylene, or pentamethylene, and as still another embodiment, the lower alkylene is methylene, ethylene, or trimethylene.

[0013]

“Cycloalkyl” refers to a saturated C₃₋₁₀ hydrocarbon ring group which may have bridge(s), for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, or the like. As another embodiment, the cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0014]

A “heterocyclic” group refers to a 3- to 15-membered, or, as another embodiment, 5- to 10-membered mono- to tricyclic heterocyclic group containing 1 to 4 hetero atoms selected from oxygen, sulfur, and nitrogen. The heterocyclic group includes a saturated ring, an aromatic ring, and a partially hydrogenated aromatic ring. Sulfur or nitrogen as a ring atom may be oxidized to form oxide or dioxide. The heterocyclic group is specifically monocyclic heteroaryl such as pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, triazolyl, triazinyl, tetrazolyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thienyl, or furyl; bicyclic heteroaryl such as indolyl, isoindolyl, benzimidazolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, benzothiazolyl, benzisothiazolyl, benzothiadiazolyl, benzoxazolyl, benzisoxazolyl, benzofuranyl, or benzothieryl; tricyclic heteroaryl such as carbazolyl, dibenzo[b,d]furanyl, or dibenzo[b,d]thienyl; a non-aromatic monocyclic heterocycle such as azetidyl, pyrrolidinyl, piperidyl, piperazinyl, azepanyl, diazepanyl, morpholinyl, thiomorpholinyl, tetrahydropyridinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, dioxolanyl, dioxanyl, or tetrahydrothiopyranyl; a non-aromatic bicyclic heterocycle such as indolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydrobenzimidazolyl, tetrahydrobenzimidazolyl, tetrahydroquinoxalinyl, dihydroquinoxalinyl, dihydrobenzoxazolyl, dihydrobenzoxazinyl, dihydrobenzofuryl, chromanyl, chromenyl, methylenedioxyphenyl, or ethylenedioxyphenyl; or a bridged heterocycle such as quinuclidinyl. As another embodiment, the heterocyclic group is pyridyl, thiazolyl, pyrazinyl, pyrimidinyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, thienyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, or quinuclidinyl. As still another embodiment, the heterocyclic group is pyridyl, tetrahydrofuranyl, tetrahydropyranyl, or piperazinyl.

[0015]

In the present specification, for convenience, a divalent or multivalent cyclic group, that is the group which has a plurality of substituents, is also expressed as a monovalent group such as aryl, cycloalkyl, or a heterocycle.

[0016]

Some embodiments of the present invention contain the compounds of Formula (I) described below or a salt thereof:

- (1) A compound of Formula (I) in which X^1 represents CH_2 , as another embodiment, a compound in which X^1 represents O,
- (2) A compound of Formula (I) in which k represents 1, and as another embodiment, k represents 2 or 3,
- (3) A compound of Formula (I) in which R^3 represents H,
- (4) A compound of Formula (I) in which X^2 represents CH,
- (5) A compound of Formula (I) in which L^1 represents ethylene or trimethylene, and as another embodiment, L^1 represents ethylene,
- (6) A compound of Formula (I) in which R^1 represents H,
- (7) A compound of in Formula (I) in which X^3 represents CH,
- (8) A compound of Formula (I) in which R^5 represents H,
- (9) A compound of Formula (I) in which L^2 represents methylene,
- (10) A compound of Formula (I) in which R^6 represents H, lower alkyl, lower alkyl substituted with one to two of $-OR^0$, $-N(\text{lower alkyl})_2$, $-C(O)\text{-lower alkyl}$, $-S(O)_2\text{-lower alkyl}$, $\text{-lower alkylene-}N(\text{lower alkyl})_2$, $-R^{00}\text{-heterocycle}$, $-R^{00}\text{-phenyl}$, or $-R^{00}\text{-cycloalkyl}$, wherein the heterocycle, phenyl, and cycloalkyl may be substituted with one to two lower alkyl or $C(O)\text{-lower alkyl}$; as another embodiment, a compound in which R^6 represents lower alkyl or cycloalkyl; as still another embodiment, a compound in which R^6 represents 1-ethylpropyl or cyclopropyl; an embodiment of the above heterocycle consists of morpholinyl, tetrahydrofuranyl, tetrahydropyranyl, quinuclidinyl, pyridyl, piperidyl, or piperazinyl,
- (11) A compound of Formula (I) in which L^3 represents ethylene or trimethylene,
- (12) A compound of Formula (I) in which R^4 represents H, lower alkyl, $\text{-lower alkylene-}OR^0$, or $\text{-lower alkylene-COO-}R^0$; as another embodiment, a compound in which R^4 represents H, lower alkyl or lower alkylene- OR^0 ,
- (13) A compound of Formula (I) in which n represents 0; as another embodiment, a compound in which n represents 1,
- (14) A compound of Formula (I) in which L^4 represents a bond or O,
- (15) A compound of Formula (I) in which Y represents $-R^{00}\text{-phenyl-}R^{00}\text{-}$; as another embodiment, a compound in which Y represents lower alkylene which may be substituted with a hydroxyl group, $-R^{00}\text{-monocyclic heterocycle-}R^{00}\text{-}$, $\text{-lower alkylene-NR}^0\text{-lower alkylene-}$, or lower alkylene-O-lower alkylene-; as still another embodiment, a

compound in which Y represents lower alkylene which may be substituted with a hydroxyl group, or -lower alkylene-NR⁰-lower alkylene-; as another embodiment, a compound in which Y represents lower alkylene which may be substituted with a hydroxyl group; an embodiment of the above monocyclic heterocycle consists of piperazinyl, pyridyl or piperidyl,

(16) A compound of in Formula (I) in which R² represents H,

(17) A compound which has one of the groups according to the above embodiments (1) to (16) or is a combination of two or more of the groups.

[0017]

In regard to the above embodiment (17), some embodiments of the present invention relating to Formula (I) are exemplified below:

(18) A compound of Formula (I) in which R⁶ represents lower alkyl or cycloalkyl,

(19) The compound according to embodiment (18), in which n represents 1, and R⁴ represents H, lower alkyl or lower alkylene-OR⁰,

(20) The compound according to embodiment (19), in which Y represents lower alkylene which may be substituted with a hydroxyl group,

(21) The compound according to embodiment (20), in which X¹ represents CH₂ and k represents 1,

(22) The compound according to embodiment (21) in which both the X² and X³ are CH,

(23) The compound according to embodiment (18), in which n represents 0.

[0018]

Specific examples of the compounds included in the present invention are exemplified below.

4-(2-{4-[(2-[(3-{[2-[(3-carboxypropanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-[(3-{[2-[(carboxymethoxy)carbonyl](methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-[(3-{[2-[(4-carboxy-4-methylpentanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-[(3-{[3-[(3-carboxypropanoyl)(methyl)amino]propyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-[(3-{[2-(3-carboxypropanoyl)(2-methoxyethyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-[(3-{[(4-carboxy-4-methylpentanoyl)(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-[(3-{[(4-carboxy-3,3-dimethylbutanoyl)(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

or a salt thereof.

[0019]

The compound of Formula (I) has a tautomer or a regio isomer depending on the type of substituents. In the present specification, when a compound of the Formula (I) is described in only one form of its isomers, the present invention includes other isomers, separated form of these isomers, or a mixture thereof.

In addition, the compound of Formula (I) has asymmetric carbon atoms or axis chirality in some cases, and there may be optical isomers based on these chiralities. The present invention includes separated optical isomers of the compound of Formula (I) or a mixture thereof.

[0020]

Moreover, the present invention includes pharmaceutically acceptable prodrugs of the compound represented by Formula (I). The pharmaceutically acceptable prodrugs refer to compounds having a group that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like by solvolysis or under physiological conditions. Examples of the groups that form the prodrugs include the groups disclosed in Prog. Med., 5, 2157-2161 (1985) or in "Pharmaceutical Research and Development", (Hirokawa Publishing Company, 1990), Vol. 7, Drug Design 163-198.

[0021]

The salt of the compound of Formula (I) refers to a pharmaceutically acceptable salt of the compound of Formula (I), and an acid addition salt or a salt with a base is formed depending on the type of substituents. Specific examples of the salt include acid addition salts with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid or phosphoric acid, or with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid or glutamic acid, inorganic salts with a metal such as lithium, sodium, potassium, magnesium, calcium or aluminum, or

with an organic base such as methylamine, ethylamine, ethanolamine, lysine, arginine, histidine, meglumine, tromethamine, or ornithine, salts with various amino acids and amino acid derivatives such as acetylleucine, ammonium salts, and the like.

[0022]

The present invention also includes various hydrates or solvates and polymorphic substances of the compound of Formula (I) and a salt thereof. In addition, the present invention includes compounds labeled with various radioisotopes or non-radioactive isotopes.

[0023]

(Preparation process)

The compound of Formula (I) or a salt thereof can be prepared by applying various known synthesis processes, by using characteristics based on the basic structure thereof or the type of substituents. At this time, depending on the type of functional groups, it is in some cases effective to change the functional group to advance with an appropriate protective group (group that can be easily converted into said functional group) at some stage between a starting material and a final intermediate. Examples of the protective group include those disclosed in Wuts (P. G. M. Wuts) and Greene (T. W. Greene), "Greene's Protective Groups in Organic Synthesis (4th edition, 2006)", and the like. The protective group may be appropriately selected and used according to the reaction conditions of the target reaction. After the protective group is introduced as described above, the reaction is performed, and then the protective group is appropriately removed, whereby a desired compound can be obtained.

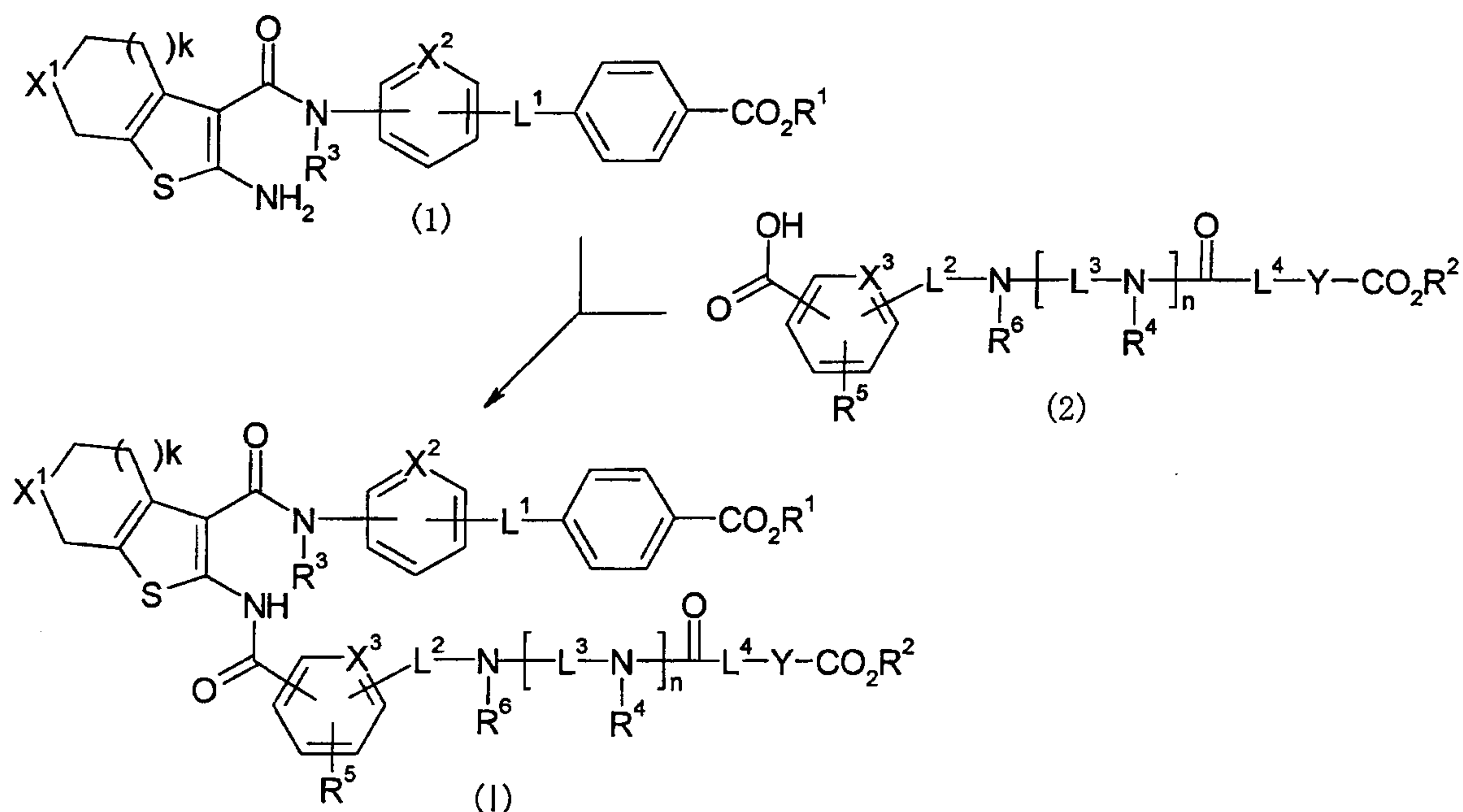
In addition, a prodrug of the compound of Formula (I) can be prepared by introducing a specific group at some stage between a starting material and an intermediate in a similar manner as described in the above protective group, or by introducing such group to the obtained compound of Formula (I). The reaction can be performed by applying methods known to a person skilled in the art, such as esterification, amidation, and dehydration.

Hereinafter, a typical preparation process of the compound of Formula (I) will be described. Each preparation process can be performed with reference to the literatures cited in the corresponding description. Moreover, the preparation process of the present invention is not limited to the following examples.

[0024]

Preparation process 1

[Chem. 7]



In the following reaction scheme, a compound (I) is simply described as (I).

The compound (I) of the present invention can be obtained from a reaction between a compound (1) and a compound (2).

In this reaction, both the compounds (1) and (2) are used in an equal amount, or one of the compounds is used in an excessive amount than the other. A mixture of these compounds is stirred generally for 0.1 hours to 5 days under cooling to heating preferably at -20°C to 60°C in a solvent inactive to the reaction in the presence of a condensing agent. Though not particularly limited, examples of the solvent used herein include aromatic hydrocarbons such as benzene, toluene, and xylene, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, and chloroform, ethers such as diethylether, tetrahydrofuran (THF), dioxane, and dimethoxyethane, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, water, and a mixture of these. Examples of the condensing agent include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole, diphenylphosphoryl azide and phosphorus oxychloride, but the present invention is not limited thereto. It is preferable to use an additive (for example, 1-hydroxybenzotriazole (HOBt)) in some cases for the reaction. It is advantageous to perform the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, or N-methylmorpholine, or an inorganic base such as potassium carbonate, sodium carbonate, or potassium hydroxide, in terms of causing the reaction to proceed smoothly.

In addition, it is also possible to use a method of converting carboxylic acid (2) into a reactive derivative and then reacting this with amine (1). Examples of the reactive derivative of carboxylic acid include acid halides obtained when the carboxylic acid reacts with a halogenating agent such as phosphorus oxychloride or thionyl chloride, mixed acid

anhydrides obtained when the carboxylic acid reacts with isobutyl chloroformate or the like, and active esters obtained when the carboxylic acid is condensed with 1-hydroxybenzotriazole or the like. The reaction between these reactive derivatives and the compound (1) can be performed in a solvent inactive to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, or ethers, under cooling to heating preferably at -20°C to 60°C.

[Document]

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

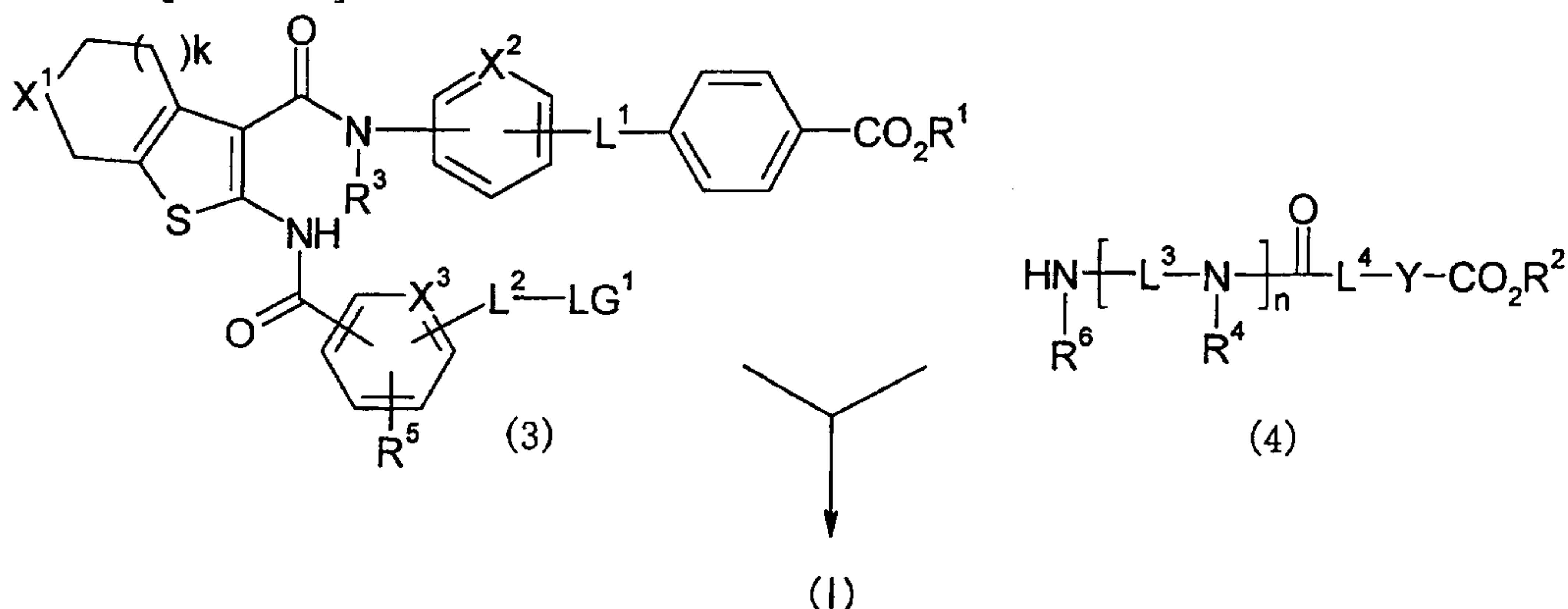
The Chemical Society of Japan., "Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th edition)", Vol. 16, (2005) (MARUZEN Co., Ltd.)

In Formula (I), the compound having a bond at L⁴ can be prepared by a similar amidation reaction by using a corresponding carboxylic acid and an amine compounds as starting materials.

[0025]

Preparation process 2

[Chem. 8]



(In the formula, LG¹ represents an leaving group.)

The compound (I) of the present invention can be obtained from a reaction between a compound (3) and a compound (4). Herein, examples of the leaving group include halogen, methanesulfonyloxy, p-toluenesulfonyloxy groups and the like.

In this reaction, both the compounds (3) and (4) are used in an equal amount, or one of the compounds used in an excessive amount than the other. A mixture of these is stirred generally for 0.1 hours to 5 days under cooling to heating under reflux preferably at 0°C to 80°C in a solvent inactive to the reaction or without using a solvent. Though not particularly limited, examples of the solvent used herein include aromatic hydrocarbons, ethers, halogenated hydrocarbons, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, and a mixture of these. It is advantageous to perform the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, or N-

methyldmorpholine, or an inorganic base such as potassium carbonate, sodium carbonate, or potassium hydroxide, in terms of causing the reaction to proceed smoothly.

[Document]

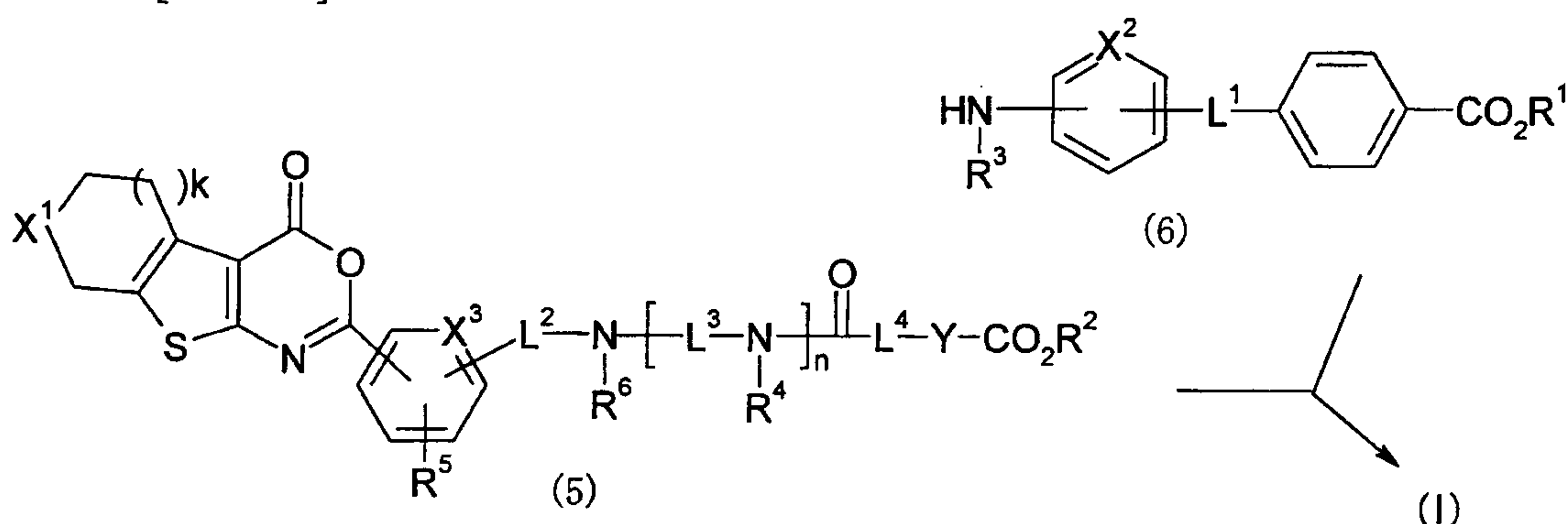
S. R. Sandler and W. Karo, "Organic Functional Group Preparations", 2nd edition, Vol. 1, Academic Press Inc. 1991

The Chemical Society of Japan., "Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th edition)", Vol. 14, (2005) (MARUZEN Co., Ltd.)

[0026]

Preparation process 3

[Chem. 9]



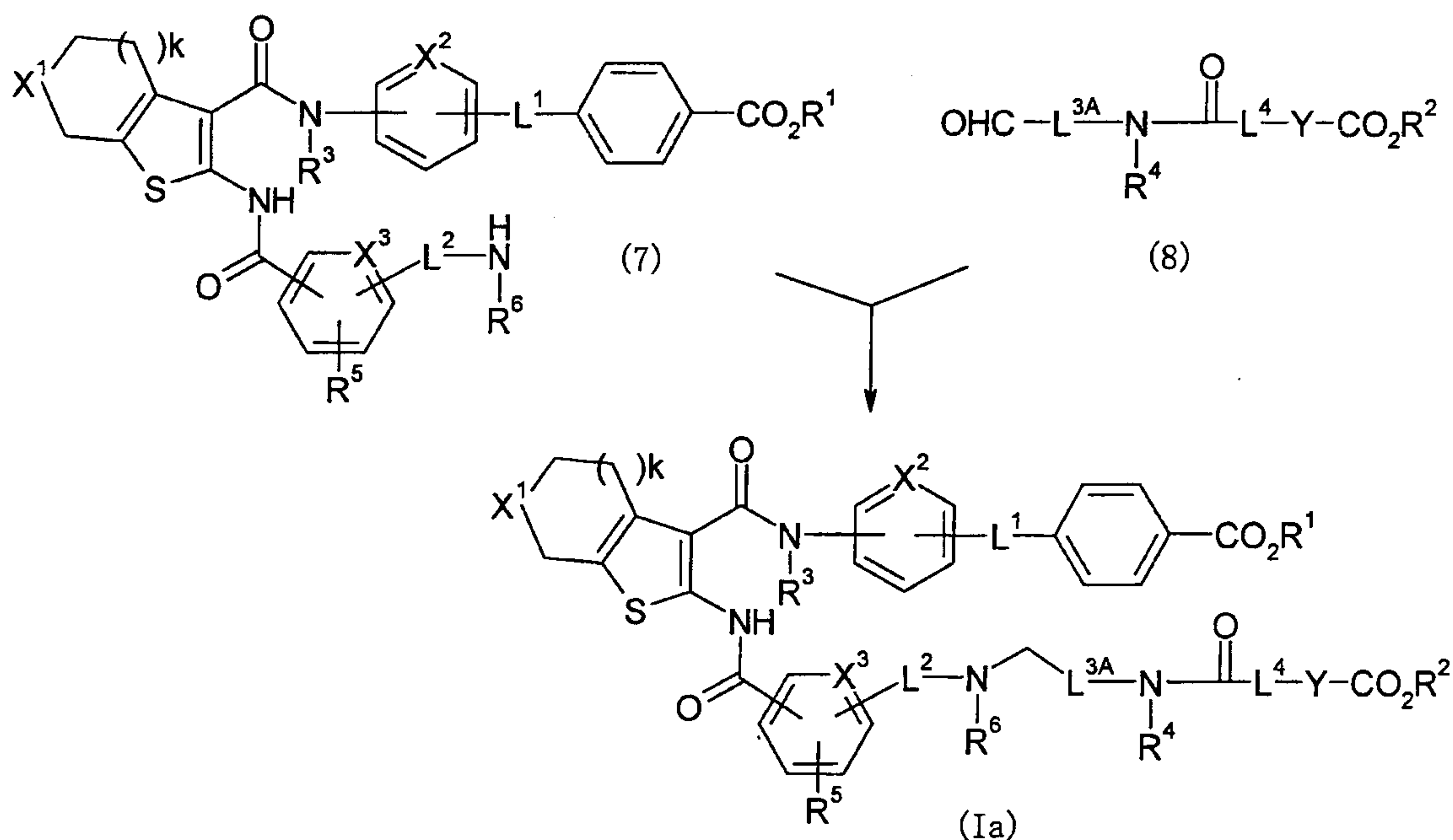
The compound (I) of the present invention can be obtained from a reaction between a compound (5) and a compound (6).

In this reaction, both the compounds (5) and (6) are used in an equal amount, or one of the compounds used in an excessive amount than the other. A mixture of these is stirred generally for 0.1 hours to 5 days under cooling to heating under reflux preferably at -78°C to 60°C in a solvent inactive to the reaction or without using a solvent in the presence of a base. Though not particularly limited, examples of the solvent used herein include aromatic hydrocarbons, ethers, and a mixture of these. As the base, butyllithium, lithium diisopropylamide, lithium hexamethyldisilazide, potassium hexamethyldisilazide, sodium hexamethyldisilazide, diisobutylaluminium hydride or pyridine can be used.

[0027]

Preparation process 4

[Chem. 10]



(In the formula, L^{3A} represents lower alkylene that is a group forming L^3 of Formula (I) together with an adjacent methylene group in Formula (Ia).)

A compound (Ia) in which n represents 1 and L^3 represents $-\text{CH}_2-L^{3A}$ in the compound (I) of the present invention can be obtained from a reaction between a compound (7) and a compound (8).

In this reaction, both the compounds (7) and (8) are used in an equal amount, or one of the compounds used in an excessive amount than the other. A mixture of these is stirred generally for 0.1 hours to 5 days from -45°C to heating under reflux preferably at 0°C to room temperature in a solvent inactive to the reaction in the presence of a reducing agent. Though not particularly limited, examples of the solvent used herein include alcohols, ethers, halogenated hydrocarbons, and a mixture of these. Examples of the reducing agent include sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, and the like. It is preferable to perform the reaction in the presence of a dehydrating agent such as molecular sieves or an acid such as acetic acid, hydrochloric acid, or a titanium(IV) isopropoxide complex in some cases. Depending on the reaction, an imine generates by the condensation of the compounds (7) and (8) and can be isolated as a stable intermediate in some cases. In this case, the compound (Ia) can be obtained by a reduction reaction of the imine intermediate. In addition, instead of treating the compounds with the reducing agent, it is possible to perform the reaction in a solvent such as methanol, ethanol, or ethyl acetate in the presence or absence of an acid such as acetic acid or hydrochloric acid by using a reduction catalyst (for example, palladium carbon or Raney nickel). In this case, it is preferable to perform the reaction in a hydrogen atmosphere under normal pressure to 50 atm, under cooling to heating.

[Document]

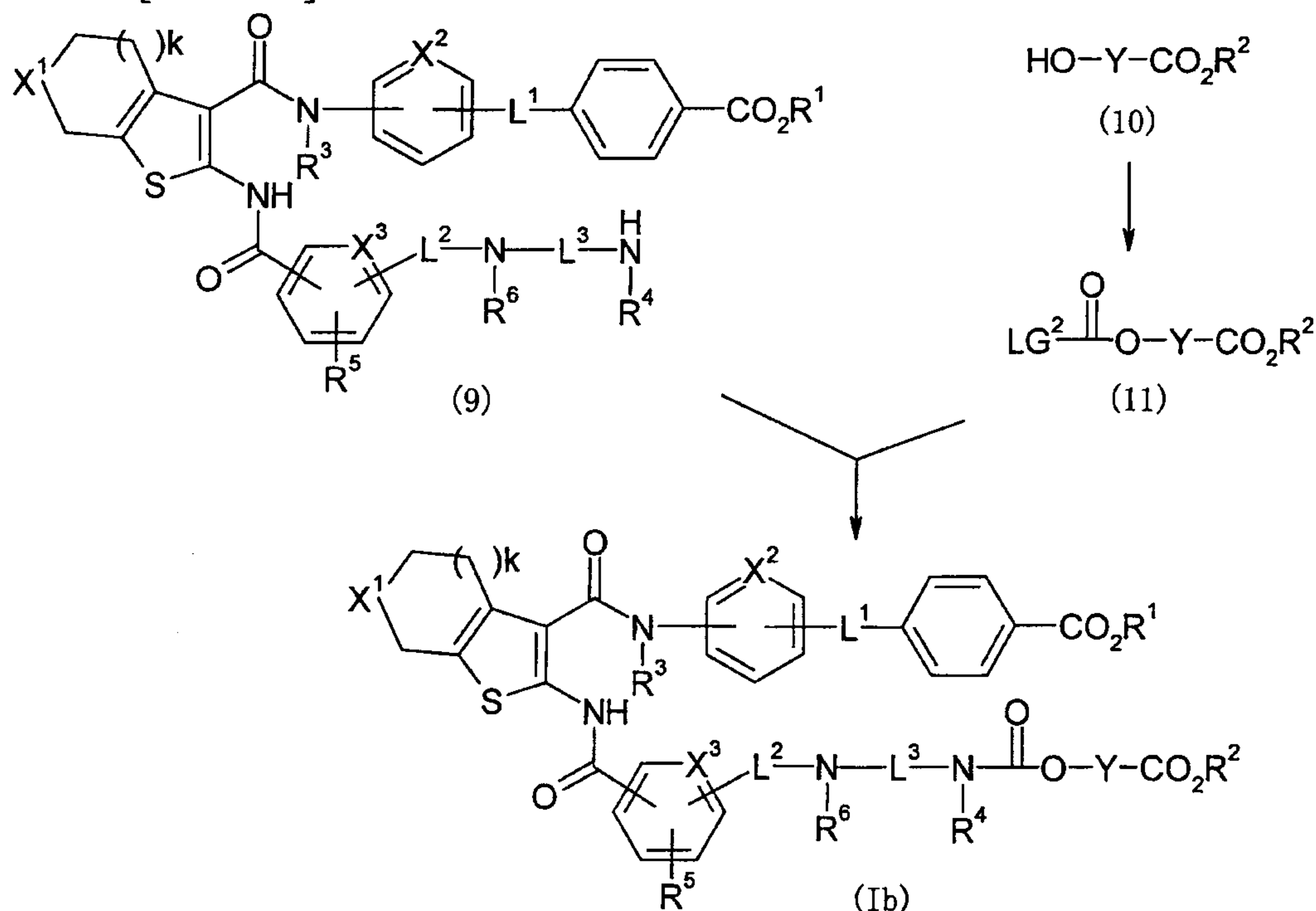
A. R. Katritzky and R. J. K. Taylor, "Comprehensive Organic Functional Group Transformations II", Vol. 2, Elsevier Pergamon, 2005

The Chemical Society of Japan., "Jikken Kagaku Koza (Courses in Experimental Chemistry) (5th edition)", Vol. 14, (2005) (MARUZEN Co., Ltd.)

[0028]

Preparation process 5

[Chem. 11]



(In the formula, LG² represents an leaving group.)

A compound (Ib) in which n represents 1 and L⁴ represents 0 in the compound (I) of the present invention can be obtained by converting a compound (10) into a carbonate ester derivative (11) and then reacting it with an amine compound (9). Examples of the leaving group include Cl, imidazolyl, phenoxy, and 4-nitrophenoxy groups.

The first step is performed by reacting the compound (10) with a carbonylating reagent in an equal amount or with a carbonylating reagent that is used in an excessive amount than the compound (10) generally for about 0.1 hours to 1 day under cooling to heating preferably at -20°C to 80°C in a solvent inactive to the reaction in the presence of a base. In the next step, without quenching the first step reaction, equimolar amount or excess amount of the amine compound (9) is added to the reaction mixture, and this mixture is stirred for about 0.1 hours to 1 day under cooling to heating preferably from -20°C to 80°C. Though not particularly limited, examples of the solvent used herein include halogenated hydrocarbons, aromatic hydrocarbons, ethers, N,N-dimethylformamide, dimethyl sulfoxide, ethyl acetate, acetonitrile, and a mixture of these. Examples of the carbonylating reagent include diphosgene, triphosgene, 1,1'-

carbonyldiimidazole, 4-nitrophenyl chloroformate, and phenyl chloroformate. In case a phenylcarbonate intermediate is stable, this may be isolated first, and then the next reaction may be performed.

[Document]

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

A compound of Formula (I) in which n represents 1 and L^4 represents $-NR^0-$ can also be prepared by ureation reaction using the compound (9) and a compound ($HNR^0-Y-CO_2R^2$) corresponding to the compound (10) as starting materials under the conditions similar to those described above.

[0029]

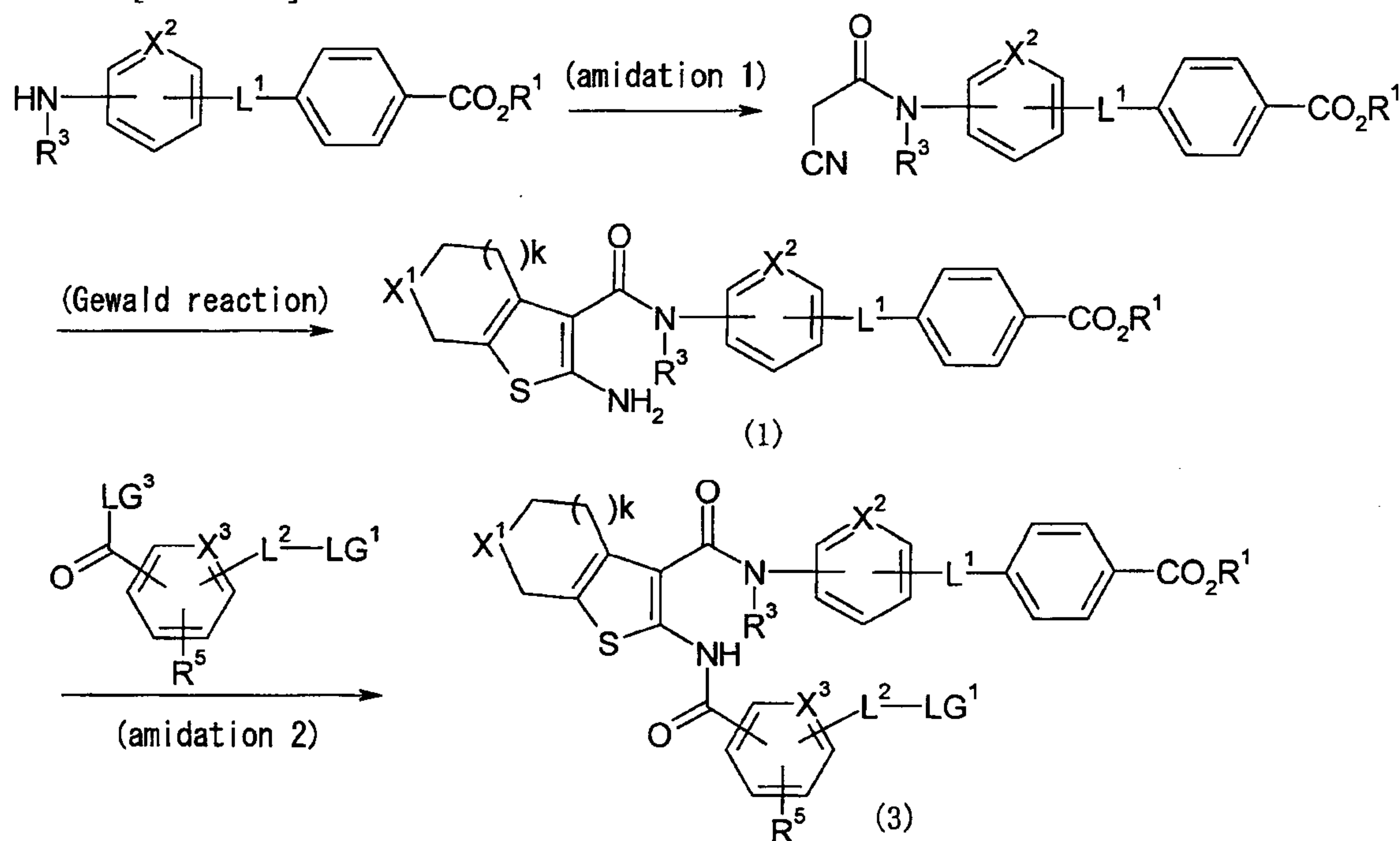
Preparation process 6

In the compound (I) of the present invention, a compound having a carboxyl group in a molecule can be prepared by preparing a precursor in which the carboxyl was protected in the method described above followed by deprotection of the precursor. This reaction can be performed with reference to Greene and Wuts, "Protective Groups in Organic Synthesis" 3rd edition, John Wiley & Sons Inc, 1999.

[0030]

Preparation process of Starting Compound

[Chem. 12]



(In the formula, LG^3 represents halogen.)

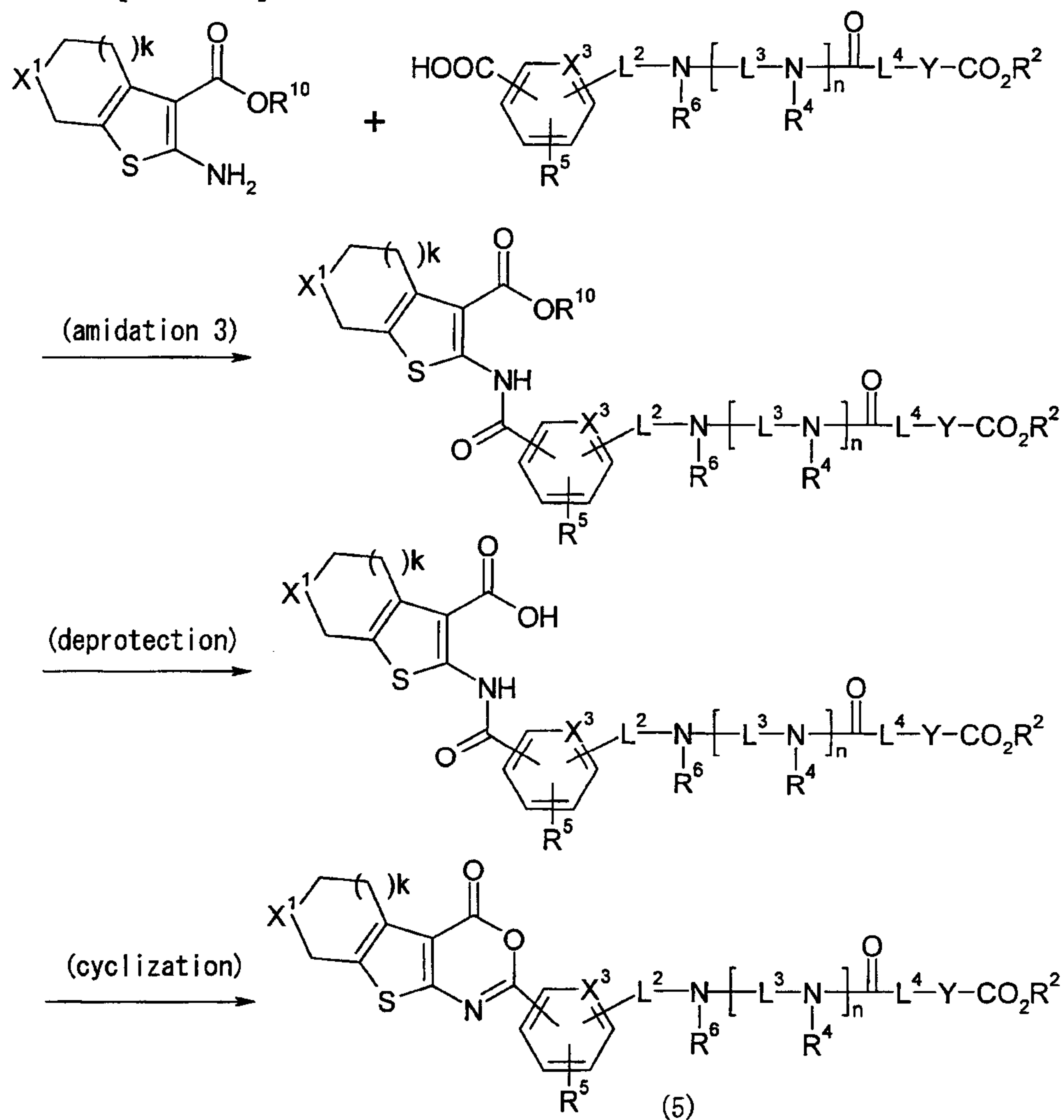
The starting compounds (1) and (3) in the Preparation processes 1 and 2 can be prepared by the reaction described above. In the above description, amidation 1 can be

particularly performed by a method using a condensing agent in the conditions of the Preparation process 1. Amidation 2 can be performed by using the conditions similar to a certain case of Preparation process 1 in which a carboxylic acid compound is transformed into a reactive derivative, and then the derivative is reacted with an amine compound. Gewald reaction can be performed with reference to K. Gewald, "Chem. Ber., 98 (1965), 3571".

The starting compounds of the aforementioned Preparation processes 4 to 6 can also be prepared by the above preparation process, otherwise, in some cases, by combining the Preparation processes 1 and 2. For example, the starting compound (7) of the Preparation process 4 can be prepared using the starting material (3) and R^6NH_2 , under the conditions similar to the Preparation process 2.

[0031]

[Chem. 13]



(In the formula, R^{10} represents a protective group of a carboxyl group.)

The starting compound (5) in the Preparation process 3 can be prepared by the above reaction. In the above formula, amidation 3 can be performed using the conditions

of the Preparation process 1. Deprotection can be performed with reference to Greene and Wuts, "Protective Groups in Organic Synthesis", 3rd edition, John Wiley & Sons Inc, 1999. Cyclization can be performed with reference to I. A. Kharizomenova, "Chemistry of Heterocyclic Compounds, 1980, vol. 16, 36".

[0032]

The compound of Formula (I) is isolated and purified as a free compound, a salt thereof, hydrate, solvate, or polymorphic substance. The salt of the compound of Formula (I) can be prepared by a salt preparation reaction using a common method.

Isolation and purification are performed by applying standard chemical operations such as extraction, fractionated crystallization, and various types of fractionation chromatography.

Various isomers can be prepared by selecting appropriate starting compounds, or can be separated using differences in physicochemical characteristics between isomers. For example, an optical isomer is obtained by general optical resolution of a racemate (for example, fractionated crystallization of diastereomeric salt with a chiral base or acid, otherwise chromatography using a chiral column), or can be prepared from an appropriate starting compound that is optically active.

[0033]

The pharmacological activity of the compound of Formula (I) was confirmed by the following test.

Test example 1: Inhibitory action against ³³P- phosphate uptake into rat NPT-IIb expression cell

(1) Preparation of rat NPT-IIb expression cell

A rat small intestine cDNA library was used as a template, and rat NPT-IIb ORF was cloned into p3×FLAG-CMV-10 by PCR according to the prescribed method. Thereafter, 293 cells were transfected with the cloned rat NPT-IIb expression plasmid, thereby obtaining a rat NPT-IIb stable expression cell line by using G418.

(2) Evaluation system for inhibition of phosphate uptake into rat NPT-IIb expression cell

The rat NPT-IIb expression cells were seeded to a 96-well plate, followed by incubation overnight. Thereafter, the culture medium was removed, the plate was washed with buffer A (137 mM N-methyl-D-glucamine, 5.4 mM KCl, 2.8 mM CaCl₂, 1.2 mM MgCl₂, and 10 mM HEPES (adjusted to pH 7.4 using HCl)), and then buffer B (137 mM NaCl, 5.4 mM KCl, 2.8 mM CaCl₂, 1.2 mM MgCl₂, 0.1 mM KH₂PO₄, and 10 mM HEPES (adjusted to pH 7.4 using KOH)) was added thereto. Subsequently, a compound with a concentration of 10 times the evaluation concentration was prepared by dilution with the buffer B and added thereto. After the resultant was incubated in a CO₂ incubator, the buffer B supplemented 50 μCi/mL of ³³P was added thereto, and then the

resultant was incubated again in a CO₂ incubator. After the reaction, the buffer was removed, the plate was washed with buffer C (137 mM NaCl, 10 mM Tris/HCl, pH 7.2). Thereafter, MicroScint-20 was added thereto, and ³³P uptake was measured using TopCount. An inhibition rate was calculated by the following formula.

$$\text{Inhibition rate (\%)} = (1 - (^{33}\text{P uptake of well treated with chemical}) / (^{33}\text{P uptake of DMSO-added well})) \times 100$$

[0034]

Table 1 illustrates examples of the inhibition rate (Int. 1) of the ³³P-phosphate uptake into the rat NPT-IIb in some of the compounds of the present invention at a concentration of drug efficacy evaluation of 1 μM. Here, Ex represents the number of example compounds described later (the same shall apply hereinafter).

[Table 1]

Ex	Int. 1 (%)
2	87
4	77
3 1	87
3 7	77
3 8	61
4 1	73
4 3	65
5 3	85
6 0	86

Ex	Int. 1 (%)
6 6	76
6 7	89
7 0	60
7 9	75
9 6	70
9 9	71
1 0 9	86
1 2 1	79
1 7 2	48

[0035]

Test example 2: Action of inhibiting increase in blood radioactivity in rat orally loaded with ^{32}P phosphate (phosphate absorption inhibitory action)

Male Wistar rats (6- to 7-week old) were fasted for 24 hours and then used as experimental animals. The compound was suspended or dissolved with a solvent, and was used at a concentration of 0.6 mg/mL. The compound was forcibly orally administered at a dose of 3 mg/kg to the animals of a compound-administered group. Control-group animals were administered a solvent containing no compound at a dose of 5 mL/kg. After 5 minutes from administration of the compound or the solvent, a ^{32}P -containing phosphate solution (8.3 mM NaH_2PO_4) was orally administered thereto at a dose of 7.2 mL/kg. After 15 minutes and 30 minutes, the blood was taken from the orbital venous plexus and the serum was collected. Radioactivity in 0.1 mL of the serum was measured by a liquid scintillation counter. $\text{AUC}_{0-30 \text{ min}}$ calculated from the measured counts was considered as a phosphate absorption amount. The phosphate absorption inhibitory rate was determined from the $\text{AUC}_{0-30 \text{ min}}$ value according to the following formula.

Inhibition rate of phosphate absorption (%) = $(1 - \text{phosphate absorption count of compound-administered group} / \text{phosphate absorption count of standard group}) \times 100$

[0036]

Table 2 illustrates examples of the inhibition rate (Int. 2) of phosphate absorption in regard to some of the compounds of Formula (I).

[Table 2]

Ex	Int. 2 (%)
2	>60
4	53
6 0	56
6 6	59

[0037]

As described above, it was found that the compound of the present invention has an action of inhibiting NPT-IIb-mediated phosphate uptake and exhibits action of inhibiting phosphate absorption from the intestinal tract even in vivo. Consequently, the compound of Formula (I) can be used for the treatment and the like of hyperphosphatemia and the like.

[0038]

The pharmaceutical composition containing one or two or more kinds of the compound of Formula (I) or a salt thereof as an active ingredient can be prepared using excipients generally used in the related art, that is, using excipients or carriers for medications, by methods generally used.

The composition can be administered in any forms such as oral administration by using a tablet, a pill, a capsule, granules, powder, or liquid, and parenteral administration by using a preparation for injection such as intra-articular injection, intravenous injection, and intramuscular injection, a suppository, an eye drop, an eye ointment, a transdermal liquid, an ointment, a transdermal patch, a transmucosal liquid, a transmucosal patch, or an inhalation.

[0039]

As a solid composition for oral administration, a tablet, powder, granules, and the like are used. In such a solid composition, one or two or more kinds of active ingredients are mixed with at least one kind of inactive excipient. The composition may contain inactive additives, for example, a lubricant, a disintegrating agent, a stabilizer, and a dissolution adjuvant according to common methods. The tablet or pill may optionally be coated with sugar or with film of a gastric or enteric material.

A liquid composition for oral administration includes a pharmaceutically acceptable emulsion, solution, suspension, syrup, elixir, or the like, and contains a generally used inactive diluent, for example, purified water or ethanol. The liquid composition may contain an auxiliary agent such as a solubilizer, a moisturizer, or a suspension, a sweetener, a flavor, an aromatic, and a preservative, in addition to the inactive diluent.

[0040]

The injection preparation for parenteral administration contains a sterile aqueous or non-aqueous solution, a suspension, or an emulsion. Examples of the aqueous solution include distilled water for injection and physiological saline. Examples of the non-aqueous solution include alcohols such as ethanol. These compositions may further contain a tonicity agent, a preservative, a moisturizer, an emulsifier, a dispersant, a stabilizer, or a solubilizer. These are sterilized by, for example, filtering in which they are filtered through a bacteria retentive filter, by being mixed with a germicide, or by irradiation. Moreover, these can be used by being prepared as a sterile solid composition and dissolved or suspended in sterile water or a sterile vehicle for injection before use.

[0041]

Examples of agents for external use include an ointment, a plaster, a cream, a jelly, a cataplasm, a spray, a lotion, eye drops, an eye ointment, and the like. The agent for external use contains generally used substrates of ointments and lotions, an aqueous or non-aqueous liquid formulation, a suspension, an emulsion, and the like.

[0042]

Transmucosal agents such as an inhalation and a transnasal agent are used in the form of a solid, a liquid or a semisolid, and can be prepared according to methods known in the related art. For example, a known excipient, a pH adjustor, a preservative, a surfactant, a lubricant, a stabilizer, a thickener or the like may be appropriately added thereto. For administration, appropriate devices for inhalation or insufflation can be used. For example,

by using a known device such as a metered dose inhaler or an atomizer, the compound can be administered alone or administered as powder of a formulated mixture or as a solution or suspension which is a combination of the compound with a pharmaceutically acceptable carrier. A dry powder inhaler and the like may be for single administration or multiple administration, and dry powder or powder-containing capsules can be used. Alternatively, the compound may be administered in the form of a pressurized aerosol spray using an appropriate ejection agent, for example, a suitable gas such as a chlorofluoroalkane, or carbon dioxide.

[0043]

Generally, in the case of oral administration, an appropriate daily dose is about 0.001 mg/kg to 100 mg/kg in terms of body weight, preferably 0.1 mg/kg to 30 mg/kg, and more preferably 0.1 mg/kg to 10 mg/kg, which is administered once or two to four times in separate doses. In the case of intravenous administration, an appropriate daily dose is about 0.0001 mg/kg to 10 mg/kg in terms of body weight, which is administered once or plural times in separate doses. In addition, the transmucosal agent is administered once a day or plural times a day in separate doses, in a dose of about 0.001 mg/kg to 100 mg/kg in terms of body weight. The dose is appropriately determined case by case in consideration of the symptoms, age, gender, and the like.

[0044]

The pharmaceutical composition of the present invention contains one or more kinds of the compound of Formula (I) and a salt thereof as an active ingredient, in an amount of 0.01% by weight to 100% by weight, and 0.01% by weight to 50% by weight as an embodiment, even though the amount varies with the route of administration, dosage forms, site of administration, and the type of excipient or additive.

[0045]

The compound of Formula (I) can be used concurrently with an agent for treating or preventing various diseases considered to be diseases for which the compound of Formula (I) is effective. In concurrent use, the compound and the agent may be administered simultaneously, administered sequentially one by one, or administered at a desired time interval. The preparation for simultaneous administration may be a combination drug or individual preparations.

[Examples]

[0046]

Hereinafter, the preparation process of the compound of Formula (I) will be described in detail based on examples, but the present invention is not limited to the compound described in the following examples. In addition, the preparation process of starting compounds will be shown respectively in preparation examples. The preparation process of the compound of Formula (I) is not limited to the preparation processes of the specific

examples shown below. The compound of Formula (I) can be prepared by combining those preparation processes, or by a method that is clearly known to a person skilled in the art.

[0047]

In addition, in examples, preparation examples, and tables described later, the following abbreviation will be used in some cases.

Pr: preparation example number, Ex: example number, Str: structural formula (in the structural formula, a compound to which “*” is attached is a chiral compound in which the corresponding carbon atom is the chiral center; in the structural formula, if a certain bond of a compound is represented by two cross lines, the bond is a double bond, and the compound is a mixture of an E-isomer and a Z-isomer.), Syn: preparation process (the number means that the corresponding example compound is prepared in a preparation process similar to that of the compound with the example number), PSy: preparation method (the number means that the compound of the corresponding preparation example is prepared in a preparation process similar to that of the compound with the preparation example number; in addition, in case the compounds have more than one preparation example numbers which are separated by “,”, this means that the compound is prepared by a successive preparation processes similar to said preparation examples starting from the left), Dat: physicochemical data, ESI+: a value of m/z in mass spectrometry (ionization ESI, $(M+H)^+$ unless otherwise specified), ESI-: a value of m/z in mass spectrometry (ionization ESI, $(M-H)^-$ unless otherwise specified), EI: a value of m/z in mass spectrometry (ionization EI, $(M)^+$ unless otherwise specified), FAB+: a value of m/z in mass spectrometry (ionization FAB, $(M+H)^+$ unless otherwise specified), FAB-: a value of m/z in mass spectrometry (ionization FAB, $(M-H)^-$ unless otherwise specified), APCI/ESI+: a value of m/z in mass spectrometry (ionization APCI and ESI are performed at the same time, $(M+H)^+$ unless otherwise specified), CI+: a value of m/z in mass spectrometry (ionization CI, $(M+H)^+$ unless otherwise specified), NMR: δ (ppm) of the characteristic peaks of ^1H NMR spectrum measured in DMSO- d_6 . ^1H NMR spectrum of Example 60 was measured at 80°C.

[0048]

HCl in the structural formula means that the compound is isolated as a hydrochloride.

In addition, a concentration mol/L is represented by M for convenience. For example, a 1M aqueous sodium hydroxide solution means a 1 mol/L aqueous sodium hydroxide solution.

[0049]

Preparation Example 1

To a mixture of 6.2 mL of 2-(methylamino)ethanol, 6.48 g of sodium hydrogen carbonate, 60 mL of THF, and 30 mL of water was added dropwise 10 mL of ethyl succinyl chloride over 30 minutes under ice cooling, followed by stirring for 3 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel

column chromatography (hexane:ethyl acetate=1:4), thereby obtaining 12.0 g of ethyl 4-[(2-hydroxyethyl)(methyl)amino]-4-oxobutanoate.

[0050]

Preparation Example 2

To a mixture of 11.9 g of ethyl 4-[(2-hydroxyethyl)(methyl)amino]-4-oxobutanoate and 120 mL of methylene chloride was added slowly 26.0 g of Dess-Martin Periodinane under ice cooling, and the mixture was allowed to warm to room temperature over 3 hours. An aqueous sodium hydrogen carbonate solution and an aqueous sodium thiosulfate solution were added to the reaction mixture, followed by stirring for 30 minutes at room temperature. An aqueous layer was extracted with methylene chloride, the organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:4), thereby obtaining 4.48 g of ethyl 4-[methyl(2-oxoethyl)amino]-4-oxobutanoate.

[0051]

Preparation Example 3

By using 2.55 g of 2-(cyclopropylamino)ethanol hydrobromide and 3.54 g of sodium hydrogen carbonate, 0.60 g of ethyl 4-[cyclopropyl(2-hydroxyethyl)amino]-4-oxobutanoate was obtained by the method similar to Preparation Example 1.

[0052]

Preparation Example 4

To a mixture of 1.0 g of N'-(2,2-dimethoxyethyl)-N,N-diethylethane-1,2-diamine, 0.84 mL of N-ethyl-N-isopropylpropan-2-amine, and 10 mL of methylene chloride was added 0.70 mL of ethyl succinyl chloride under ice cooling, followed by stirring for 1 hour under ice cooling. The reaction mixture was concentrated under reduced pressure, ethyl acetate and water were added thereto, and extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine and dried over anhydrous sodium sulfate, followed by concentration under reduced pressure, thereby obtaining 1.2 g as oily product. A mixture of 1.2 g of the obtained oily product, 12 mL of methylene chloride, and 12 mL of trifluoroacetic acid (TFA) was stirred for 4 hours at room temperature. The reaction mixture was concentrated under reduced pressure, an aqueous sodium hydrogen carbonate solution and ethyl acetate were added thereto, and extracted with ethyl acetate. The organic layer was washed sequentially with water and saturated brine and dried over anhydrous sodium sulfate, followed by concentration under reduced pressure, thereby obtaining 0.78 g of ethyl 4-{[2-(diethylamino)ethyl](2-oxoethyl)amino}-4-oxobutanoate.

[0053]

Preparation Example 5

To a mixture of 50.1 g of methyl 4-[(E)-2-(4-nitrophenyl)vinyl]benzoate, 600 mL of THF, and 200 mL of N,N-dimethylformamide (DMF) was added 10.3 g of 10% palladium

carbon (wetted with 55% H₂O), followed by stirring for 8 hours at room temperature in a hydrogen atmosphere (1 atm). The inside of the reaction vessel was purged with argon, and then the insoluble material was removed by filtration by using celite. The filtrate was concentrated under reduced pressure, and 1000 mL of water was added to the residue, followed by stirring for 30 minutes at room temperature. The precipitate was collected by filtration, thereby obtaining 44.0 g of methyl 4-[2-(4-aminophenyl)ethyl]benzoate.

[0054]

Preparation Example 6

To a mixture of 43.9 g of methyl 4-[2-(4-aminophenyl)ethyl]benzoate, 22.3 g of cyanoacetic acid, and 150 mL of DMF was added 49.5 g of WSC·hydrochloride under ice cooling. After the reaction mixture was stirred for 24 hours at room temperature, 450 mL of water was added thereto at room temperature, followed by stirring for 30 minutes at room temperature. Thereafter, the precipitate was collected by filtration, thereby obtaining 54.2 g of methyl 4-(2-{4-[(cyanoacetyl)amino]phenyl}ethyl)benzoate.

[0055]

Preparation Example 7

To a mixture of 54.0 g of methyl 4-(2-{4-[(cyanoacetyl)amino]phenyl}ethyl)benzoate, 50.0 mL of cyclohexanone, and 300 mL of toluene was added dropwise 15.0 mL of morpholine at room temperature. A Dean-Stark type dehydrating tube was attached to the reactor, and the reaction mixture was stirred for 3 hours with oil bath heated at 120°C. Thereafter, the reaction mixture was heated to reflux and further stirred for 1 hour. The reaction mixture was cooled to room temperature, followed by concentration under reduced pressure. 200 mL of diisopropylether was further added thereto, followed by stirring for 14 hours. The precipitated solid was collected by filtration, thereby obtaining 53.2 g of methyl 4-[2-(4-{[(cyano(cyclohexylidene)acetyl]amino}phenyl)ethyl]benzoate. To a mixture of this solid, 4.5 g of sulfur and 80 mL of DMF was added dropwise 12.0 mL of morpholine at room temperature, and the reaction mixture was stirred for 1 hour at 50°C. Saturated brine was added to the reaction mixture, followed by extraction with ethyl acetate, and then the organic layer was washed with water and saturated brine. The organic layer was dried over anhydrous sodium sulfate, followed by filtration, and then the solvent was removed under reduced pressure. Isopropanol was added to the thus obtained residue, and the precipitated solid was collected by filtration, thereby obtaining 43.1 g of methyl 4-[2-(4-{[(2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate.

[0056]

Preparation Example 8

To a mixture of 6.9 g of methyl 4-[2-(4-{[(2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate, 1.5 mL of pyridine and 69 mL of methylene chloride was added dropwise 3.27 g of 3-(chloromethyl)benzoyl chloride, followed

by stirring for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure, ethanol was added thereto, and the precipitated solid was collected by filtration, thereby obtaining 9.27 g of methyl 4-[2-(4-{{(2-{{(3-(chloromethyl)benzoyl}amino)}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate.

[0057]

Preparation Example 9

A mixture of 8.00 g of methyl 4-[2-(4-{{(2-{{(3-(chloromethyl)benzoyl}amino)}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate, 4.8 mL of pentan-3-amine, 3.5 mL of N-ethyl-N-isopropylpropan-2-amine, and 80 mL of DMF was stirred for 13 hours at 80°C. Ethyl acetate and water were added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed sequentially with water and saturated brine and dried over anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (2% methanol/chloroform), thereby obtaining 6.57 g of methyl 4-{2-[4-{{(2-{{(3-[(pentan-3-ylamino)methyl]benzoyl}amino)}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl}benzoate.

[0058]

Preparation Example 10

By using 250 mg of methyl 4-[2-(4-{{(2-{{(3-(chloromethyl)benzoyl}amino)}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate and 0.25 mL of N,N'-diisopropylethylenediamine as starting materials, the reaction similar to Preparation Example 9 was performed, thereby obtaining 220 mg of methyl 4-[2-(4-{{(2-{{(3-{{(isopropyl[2-(isopropylamino)ethyl]amino}methyl)benzoyl}amino)}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate.

[0059]

Preparation Example 11

By using 1.0 g of tert-butyl (2-bromoethyl)carbamate, 2.5 mL of pentan-3-amine, and 10 mL of acetonitrile as starting materials, the reaction similar to Preparation Example 9 was performed, thereby obtaining 890 mg of tert-butyl [2-(pentan-3-ylamino)ethyl]carbamate.

[0060]

Preparation Example 12

To a mixture of 240 mg of methyl 4-(2-{4-[[{2-[(3-{{2-[(tert-butoxycarbonyl)amino]ethyl})(pentan-3-yl)amino]methyl}benzoyl]amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl)ethyl)benzoate and 5.0 mL of methylene chloride was added 3.0 mL of TFA under ice cooling, followed by stirring for 1 hour at the same temperature and then stirring for 5 hours at room temperature. The reaction mixture was concentrated under reduced pressure, chloroform and a saturated aqueous sodium hydrogen carbonate solution were added thereto, followed by extraction with chloroform.

The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure, thereby obtaining 210 mg of methyl 4-(2-{4-[(2-{(3-{(2-aminoethyl)(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0061]

Preparation Example 13

To a mixture of 210 mg of methyl 4-(2-{4-[(2-{(3-{(2-aminoethyl)(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate, 0.10 mL of triethylamine, and 10 mL of methylene chloride was added 70 mg of ethyl succinyl chloride under ice cooling, and then the mixture was stirred for 1 hour at the same temperature and then stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, chloroform and water were added to the reaction mixture, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol/chloroform), thereby obtaining 170 mg of methyl 4-(2-{4-[(2-{(3-{(2-{(4-ethoxy-4-oxobutanoyl)amino)ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0062]

Preparation Example 14

To a mixture of 800 mg of methyl 4-{2-[4-({2-[(3-{(pentan-3-ylamino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino)phenyl]ethyl}benzoate, 257 mg of tert-butyl methyl(2-oxoethyl)carbamate, 7.5 mg of acetic acid and 16 mL of dichloroethane was added 372 mg of sodium triacetoxyborohydride followed by stirring for 15 hours at room temperature. An aqueous sodium hydrogen carbonate solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1), thereby obtaining 908 mg of methyl 4-(2-{4-[(2-{(3-{(2-{(tert-butoxycarbonyl)(methyl)amino)ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0063]

Preparation Example 15

To a mixture of 250 mg of methyl 4-[2-(4-{(2-{(3-{(2-(methylamino)ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl)amino}phenyl)ethyl]benzoate, 0.20 mL of N-ethyl-N-isopropylpropan-2-amine and 10 mL of THF under ice cooling was added 70 mg of methyl (S)-(-)-2-

isocyanatopropionate, followed by stirring for 1 hour at the same temperature and then for 2 hours at room temperature. Ethyl acetate and an aqueous sodium hydrogen carbonate solution were added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol/chloroform), thereby obtaining 290 mg methyl 4-{2-[4-({[2-({3-[(4S)-4,7-dimethyl-3,6-dioxo-10-(pentan-3-yl)-2-oxa-5,7,10-triazaundecan-11-yl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate.

[0064]

Preparation Example 16

To a mixture of 100 mg of (2R)-4-methoxy-2-methyl-4-oxobutanoic acid and 10 ml of methylene chloride were added 0.10 mL of oxalyl chloride and 0.020 mL of DMF in this order under ice cooling. The reaction mixture was stirred for 1 hour at room temperature and then concentrated under reduced pressure. 5.0 ml of the methylene chloride solution was added to a mixture of 200 mg of methyl 4-[2-(4-{[(2-{[3-({[2-(methylamino)ethyl](pentan-3-yl)amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate, 0.10 mL of triethylamine, and 5.0 ml of methylene chloride under ice cooling, followed by stirring for 1 hour at the same temperature and then for 4 days at room temperature. The reaction mixture was concentrated under reduced pressure, chloroform and water were added thereto, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol/chloroform), thereby obtaining 230 mg of methyl 4-(2-{4-[(2-{[3-({[(2R)-4-methoxy-2-methyl-4-oxobutanoyl](methyl)amino}ethyl)(pentan-3-yl)amino]methyl}benzoyl]amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0065]

Preparation Example 17

To a mixture of 220 mg of methyl 4-[2-(4-{[(2-{[3-({[2-(methylamino)ethyl](pentan-3-yl)amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate, 0.20 mL of N-ethyl-N-isopropylpropan-2-amine and 5.0 mL of methylene chloride was added 100 mg of 2,2-dimethylglutaric anhydride under ice cooling, followed by stirring for 1 hour at the same temperature and then for a day at room temperature, and the reaction mixture was concentrated under reduced pressure. 200 mg of potassium carbonate and 10 mL of DMF were added to the obtained residue, 150 mg of methyl iodide was further added thereto under ice cooling, and the reaction mixture was stirred for 1 hour under ice cooling and then for a day at room temperature. Ethyl acetate and water

were added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol/chloroform), thereby obtaining 260 mg of methyl 4-(2-{4-[(2-[(3-{[2-[(5-methoxy-4,4-dimethyl-5-oxopentanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0066]

Preparation Example 18

To a mixture of 1.0 g of 3-(methylamino)propan-1-ol and 10 mL of methanol was added 3.0 g of di-tert-butyl dicarbonate under ice cooling, followed by stirring for 5 days at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:7), thereby obtaining 2.05 g of tert-butyl (3-hydroxypropyl)methylcarbamate.

[0067]

Preparation Example 19

To a mixture of 1.5 g of 2-(3-bromophenyl)ethanol, 1.0 g of imidazole and 15 mL of DMF was added 2.8 g of tert-butyl(chloro)diphenylsilane under ice cooling, and the followed by stirring for 1 hour at the same temperature then for a day at room temperature. Diethyl ether and water were added to the reaction mixture, followed by extraction with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:3), thereby obtaining 3.27 g of [2-(3-bromophenyl)ethoxy](tert-butyl)diphenylsilane.

[0068]

Preparation Example 20

To a mixture of 3.27 g of [2-(3-bromophenyl)ethoxy](tert-butyl)diphenylsilane and 50mL of THF was slowly added 5.5 mL of butyllithium (1.62 M hexane solution) at -78°C, followed by stirring for 30 minutes at -78°C. In addition, carbon dioxide was blown into the reaction mixture at -78°C, and the temperature thereof was slowly increased to room temperature, followed by stirring for 1 hour at room temperature. Water was added to the reaction mixture, and the mixture was neutralized with 9.0 ml of 1.0 M hydrochloric acid. Ethyl acetate was added thereto to separate the organic layer, the organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and then the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:6), thereby obtaining 1.45 g of 3-(2-{[tert-butyl(diphenyl)silyl]oxy}ethyl)benzoic acid.

[0069]

Preparation Example 21

To a mixture of 480 mg of 3-(2-{{tert-butyl(diphenyl)silyl}oxy}ethyl)benzoic acid and 10 ml of methylene chloride was added 160 mg of 1-chloro-N,N,2-trimethylpropenylamine under ice cooling, followed by stirring for 1 hour at room temperature. 10 ml of a methylene chloride solution containing 450 mg of methyl 4-[2-(4-{{(2-amino-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate and 0.20 mL of pyridine was added to the reaction mixture under ice cooling, followed by stirring for 1 hour under ice cooling and then for 4 days at room temperature. The reaction mixture was concentrated under reduced pressure, ethyl acetate and water were added thereto, and the organic layer was separated. The organic layer was washed with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and saturated brine in this order and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1), thereby obtaining 830 mg of methyl 4-[2-(4-{{(2-{{3-(2-{{tert-butyl(diphenyl)silyl}oxy}ethyl)benzoyl}amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate.

[0070]

Preparation Example 22

To a mixture of 830 mg of methyl 4-[2-(4-{{(2-{{3-(2-{{tert-butyl(diphenyl)silyl}oxy}ethyl)benzoyl}amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate and 10 mL of THF was added 1.5 mL of tetrabutylammonium fluoride (TBAF) (1.0 M THF solution) under ice cooling, followed by stirring for 4 hours at room temperature and then overnight at 50°C. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (10% methanol/chloroform), thereby obtaining 540 mg of methyl 4-[2-(4-{{(2-{{3-(2-hydroxyethyl)benzoyl}amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate.

[0071]

Preparation Example 23

By using 250 mg of methyl 4-[2-(4-{{(2-{{3-(2-hydroxyethyl)benzoyl}amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoate and 450 mg of Dess-Martin Periodinane, the reaction similar to Preparation Example 2 was performed, and then the reaction similar to Preparation Example 14 was performed, thereby obtaining 260 mg of methyl 4-{{2-[4-{{2-{{3-[2-(pentan-3-ylamino)ethyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino}phenyl)ethyl}benzoate.

[0072]

Preparation Example 24

A mixture of 640 mg of methyl glycolate, 0.60 mL of pyridine, and 10 mL of methylene chloride was added to 10 mL of a methylene chloride solution including 1.44 g of 4-nitrophenyl chloroformate at room temperature, followed by stirring for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and diethyl ether and water were added to the residue and an organic layer was separated. The organic layer was sequentially washed with water and saturated brine and dried over anhydrous sodium sulfate, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (using chloroform only), thereby obtaining 320 mg of methyl {[4-(4-nitrophenoxy)carbonyl]oxy}acetate.

[0073]

Preparation Example 25

To a mixture of 16.5 g of 1-(4-nitrophenyl)ethanone, 16.4 g of methyl 4-formylbenzoate and 100 mL of ethanol was added dropwise 4.0 mL of piperidine at room temperature, followed by heating under reflux for 8 hours. The precipitate was collected by filtration, thereby obtaining 24.6 g of a crude product. The crude product was suspended in 100 mL of ethanol, followed by heating under reflux for 6 hours. The precipitate was collected by filtration, thereby obtaining 24.0 g of methyl 4-[3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]benzoate.

[0074]

Preparation Example 26

To a mixture of 5.0 g of methyl 4-[3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]benzoate and 150 mL of methanol was added dropwise 5.0 mL of concentrated sulfuric acid under ice cooling. In an argon atmosphere, 500 mg of 10% palladium carbon was added to the reaction mixture. After hydrogen (3 atm) purging was performed at room temperature, the mixture was stirred for 24 hours. The insoluble material was removed by filtration by using celite, and then the filtrate was concentrated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution was added to the residue under ice cooling to neutralize the residue, and then extraction was performed using ethyl acetate. The organic layer was washed with water and saturated brine and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (chloroform), thereby obtaining 2.9 g of methyl 4-[3-(4-aminophenyl)propyl]benzoate.

[0075]

Preparation Example 27

A mixture of 194 mg of methyl 4-[2-(4-{{(2-{{3-({cyclopropyl[2-(methylamino)ethyl]amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate, 0.050 mL of (2-methoxyethoxy)acetic acid, 84 mg of WSC·hydrochloride, and 5.0 mL of DMF was stirred for 15 hours at room temperature.

Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol/chloroform), thereby obtaining 200 mg of methyl 4-[2-(4-{{(2-{{(3-(11-cyclopropyl-8-methyl-7-oxo-2,5-dioxa-8,11-diazadodecan-12-yl)benzoyl]amino}}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate.

[0076]

Preparation Example 28

By using 1.4 mL of (2-methoxyethoxy)acetic acid and 1.0 g of 3-(methylamino)propan-1-ol as starting materials, the reaction similar to Preparation Example 16 was performed, thereby obtaining 2.19 g of N-(3-hydroxypropyl)-2-(2-methoxyethoxy)-N-methylacetamide.

[0077]

Preparation Example 29

By using 2.0 g of methyl 4-[2-(4-{{(2-{{(3-(chloromethyl)benzoyl]amino}}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate, 1.0 g of tert-butyl [2-(cyclopropylamino)ethyl]carbamate, 0.76 g of potassium carbonate, and 40 mL of DMF, 2.5 g of methyl 4-(2-{4-[(2-[(3-{{(2-[(tert-butoxycarbonyl)amino]ethyl}(cyclopropyl)amino)methyl}benzoyl]amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate was obtained by the method similar to Preparation Example 9.

[0078]

Preparation Example 30

A mixture of 1.0 g of methyl 4-(2-{4-[(2-[(3-{{(2-aminoethyl)(cyclopropyl)amino)methyl}benzoyl]amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate, 0.20 mL of ethyl bromoacetate, 212 mg of potassium carbonate, and 20 mL of DMF was stirred overnight at room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, thereby obtaining 140 mg of methyl 4-{2-[4-({[2-({3-[(cyclopropyl{2-[(2-ethoxy-2-oxoethyl)amino]ethyl}amino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate.

[0079]

Preparation Example 31

By using 200 mg of tert-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate and 421 mg of Dess-Martin Periodinane, a reaction was performed by the method similar to

Preparation Example 2. Thereafter, the reaction product was reacted with 300 mg of methyl 4-{2-[4-({[2-({3-[(pentan-3-ylmino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate by the method similar to Preparation Example 14, thereby obtaining 350 mg of tert-butyl (2S)-2-({[3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl](pentan-3-yl)amino}methyl)pyrrolidine-1-carboxylate.

[0080]

Preparation Example 32

To a mixture of 200 mg of methyl 4-[2-(4-{{[2-{{[3-{{[2-(methylamino)ethyl](pentan-3-yl)amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl]amino}phenyl)ethyl]benzoate, 48 mg of N-ethyl-N-isopropylpropan-2-amine and 4 mL of dioxane was added 44 mg of 3,3-dimethyldihydrofuran-2,5-dione, followed by stirring overnight at 65°C. The reaction mixture was concentrated under reduced pressure, ethyl acetate and water were added to the residue, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, thereby obtaining 200 mg of 4-[(2-{{[3-{{[3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl](pentan-3-yl)amino}ethyl)(methyl)amino]-2,2-dimethyl-4-oxobutanoic acid.

[0081]

Preparation Example 33

By using 200 mg of methyl 4-[2-(4-{{[2-{{[3-{{[2-(methylamino)ethyl](pentan-3-yl)amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl]amino}phenyl)ethyl]benzoate, 60 mg of monoethyl adipate, and 0.10 mL of N-ethyl-N-isopropylpropan-2-amine as starting materials, and using 142 mg of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) as a condensing agent, the reaction similar to Preparation Example 27 was performed, thereby obtaining 200 mg of methyl 4-(2-{4-[(2-{{[3-{{[2-[(6-ethoxy-6-oxohexanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl}benzoyl]amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0082]

Preparation Example 34

By using 220 mg of methyl 4-(2-{4-[(2-{{[3-{{[2-[(chloroacetyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl}benzoyl]amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate, 60 mg of sarcosine ethyl ester hydrochloride, and 120 mg of potassium carbonate, 200 mg of methyl 4-{2-[4-({[2-({3-[5,8-dimethyl-6,10-dioxo-2-(pentan-3-yl)-11-oxa-2,5,8-triazatridec-1-yl]benzoyl}amino)-

4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate was obtained by the method similar to Preparation Example 9.

[0083]

Preparation Example 35

To 4.8 g of tert-butyl ethyl 2,2'-piperazine-1,4-diyl diacetate was added 20 mL of a 4M hydrogen chloride/ethyl acetate solution, followed by stirring for 2 hours at room temperature. The generated insoluble material was collected by filtration, thereby obtaining 4.0 g of [4-(2-ethoxy-2-oxoethyl)piperazin-1-yl]acetic acid dihydrochloride.

[0084]

Preparation Example 36

By using 200 mg of methyl 4-[2-(4-{[(2-{[3-({[2-(methylamino)ethyl](pentan-3-yl)amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate and 79 mg of methyl 3-(bromomethyl)benzoate, the reaction similar to Preparation Example 30 was performed, thereby obtaining 220 mg of methyl 3-{[(2-{[3-({[3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl](pentan-3-yl)amino}ethyl)(methyl)amino]methyl}benzoate.

[0085]

Preparation Example 37

To 1.0 g of ethyl 2-(hydroxymethyl)isonicotinate was added 3.0 mL of thionyl chloride, followed by stirring overnight. The reaction mixture was concentrated under reduced pressure, and 4.0 mL of pentan-3-amine and 20 mL of DMF were added to the obtained residue, followed by stirring overnight at 70°C. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, thereby obtaining 1.3 g of ethyl 2-[(pentan-3-ylamino)methyl]isonicotinate.

[0086]

Preparation Example 38

A mixture of 1.9 g of ethyl 2-[[{2-[(4-tert-butoxy-4-oxobutanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl]isonicotinate, 8.2 mL of a 1.0 M aqueous sodium hydroxide solution, 8.0 mL of methanol, and 16 mL of THF was stirred overnight at room temperature. The mixture was neutralized using 1.0 M hydrochloric acid, water was added thereto, followed by extraction with chloroform-methanol. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure, thereby obtaining 1.5 g of 2-[[{2-[(4-tert-butoxy-4-oxobutanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl]isonicotinic acid.

[0087]

Preparation Example 39

To 20 mL of a dioxane solution including 2.0 g of 2-bromo-5-nitropyridine were added 1.58 g of methyl 4-ethynylbenzoate, 4.1 mL of N-isopropylpropan-2-amine and 281 mg of copper (I) iodide, and 504 mg of bis(tri-tert-butylphosphine)palladium(0) was further added thereto in an argon atmosphere, followed by stirring for 1 hour at room temperature. 50 ml of ethyl acetate was added to the reaction mixture, the precipitated insoluble material was collected by filtration, thereby obtaining 2.45 g of methyl 4-[(5-nitropyridin-2-yl)ethynyl]benzoate.

[0088]

Preparation Example 40

By using 120 mg of 2-({3-[(cyclopropylamino)methyl]benzoyl}amino)-N-[4-(pyridin-4-ylmethynyl)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 120 mg of ethyl 5-chloro-5-oxopentanoate, the reaction similar to Preparation Example 13 was performed, thereby obtaining 105 mg of ethyl 5-(cyclopropyl{3-[(3-{[4-(pyridin-4-ylmethynyl)phenyl]carbamoyl}-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)carbamoyl]benzyl}amino)-5-oxopentanoate.

[0089]

Preparation Example 41

By using 300 mg of methyl 4-{2-[4-({2-({3-[(cyclopropylamino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate, 198 mg of 5-{cyclopropyl[3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]amino}-3,3-dimethyl-5-oxopentanoic acid was obtained by the method similar to Preparation Example 32.

[0090]

Preparation Example 42

To a mixture of 150 mg of methyl 4-{3-[4-({2-({3-[(isopropylamino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]propyl}benzoate and 3.5 mL of THF was added 0.045 mL of triethylamine and 28 mg of triphosgene under ice cooling, followed by stirring for 3 hours at room temperature. Thereafter, 0.080 mL of ethyl isonipecotatate was added to the reaction mixture, followed by stirring for 18 hours at room temperature. An aqueous sodium hydrogen carbonate solution was added to the reaction mixture, followed by stirring for 1 hour at room temperature, and then extraction was performed using chloroform. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by basic silica gel column chromatography(NH silica gel manufactured by FUJI SILYSIA CHEMICAL LTD. (amino type silica gel (treated with aminopropyl)), (hexane:ethyl acetate=1:1)), thereby obtaining 178

mg of ethyl 1-{isopropyl[3-({3-[(4-{3-[4-(methoxycarbonyl)phenyl]propyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]carbamoyl}piperidine-4-carboxylate.

[0091]

Preparation Example 43

By using 116 mg of methyl 4-{3-[4-({[2-({3-[(isopropylamino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]propyl}benzoate and 50 mg of 6-(methoxycarbonyl)pyridine-2-carboxylic acid as starting materials, the reaction similar to Preparation Example 33 was performed, thereby obtaining 115 mg of methyl 6-{isopropyl[3-({3-[(4-{3-[4-(methoxycarbonyl)phenyl]propyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]carbamoyl}pyridine-2-carboxylate.

[0092]

Preparation Example 44

By using 550 mg of methyl 4-{2-[4-({[2-({3-[(isopropylamino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate and 200 mg of 4-(diethoxyphosphoryl)butanoic acid as starting materials, the reaction similar to Preparation Example 27 was performed, thereby obtaining 600 mg of methyl 4-[2-(4-{[(2-({[3-({4-(diethoxyphosphoryl)butanoyl](isopropyl)amino}methyl)benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl]amino}phenyl)ethyl]benzoate.

[0093]

Preparation Example 45

By using 1.0 g of methyl 4-[2-(4-{[(2-({[3-(chloromethyl)benzoyl]amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl]amino}phenyl)ethyl]benzoate and 1.8 mL of 28% aqueous ammonia, 900 mg of methyl 4-[2-(4-{[(2-({[3-(aminomethyl)benzoyl]amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl]amino}phenyl)ethyl]benzoate by the method similar to Preparation Example 9.

[0094]

Preparation Example 46

By using 370 mg of methyl 4-(2-{4-[(2-({[3-((chloroacetyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate and 400 mg of ethyl isonipecotate, the reaction similar to Preparation Example 30 was performed, thereby obtaining 380 mg of ethyl 1-(2-({[3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl](pentan-3-yl)amino}-2-oxoethyl)piperidine-4-carboxylate.

[0095]

Preparation Example 47

To a mixture of 3.0 g of 3-formylbenzoic acid and 30 ml of methylene chloride were added 1.7 mL of oxalyl chloride and 0.020 mL of DMF in this order under ice cooling. The reaction mixture was stirred for 5 hours at room temperature and concentrated under reduced pressure. A mixture of the resultant and 30 ml of methylene chloride was added to a mixture of 2.8 mL of 2-(trimethylsilyl)ethanol, 1.6 mL of pyridine, and 30 ml of methylene chloride, followed by stirring for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure, water was added thereto, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1), thereby obtaining 3.5 g of 2-(trimethylsilyl)ethyl 3-formylbenzoate.

[0096]

Preparation Example 48

By using 500 mg of 2-(trimethylsilyl)ethyl 3-formylbenzoate and 188 mg of 3-aminopyridine, the reaction similar to Preparation Example 14 was performed, thereby obtaining 505 mg of 2-(trimethylsilyl)ethyl 3-[(pyridin-3-ylamino)methyl]benzoate.

[0097]

Preparation Example 49

By using 375 mg of 2-(trimethylsilyl)ethyl 3-{[(5-ethoxy-5-oxopentanoyl)(pyridin-3-yl)amino]methyl}benzoate and 1.0 mL of 1.0 M TBAF (THF solution), 160 mg of 3-{[(5-ethoxy-5-oxopentanoyl)(pyridin-3-yl)amino]methyl}benzoic acid was obtained by the method similar to Preparation Example 22.

[0098]

Preparation Example 50

To a mixture of 8.99 g of tert-butyl 2-({3-[(pentan-3-ylamino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate and 100 mL of methylene chloride was added 30 mL of TFA, followed by stirring for 15 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and azeotropy was performed using toluene. 4.3 mL of thionyl chloride and 50 mL of toluene were added to the residue, and 0.10 mL of DMF was added dropwise thereto, followed by stirring for 1 hour at 60°C. The reaction mixture was concentrated under reduced pressure, a saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:2), thereby obtaining 7.05 g of 2-{3-[(pentan-3-ylamino)methyl]phenyl}-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-4-one.

[0099]

Preparation Example 51

To a mixture of 4.81 g of 2,2-dimethyl-5-oxo-5-{[3-(4-oxo-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-2-yl)benzyl](pentan-3-yl)amino}pentanoic acid and 50 mL of DMF were added 2.59 g of methyl iodide and 3.16 g of potassium carbonate, followed by stirring for 1 hour at room temperature. Water was added to a reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol, thereby obtaining 3.24 g of methyl 2,2-dimethyl-5-oxo-5-{[3-(4-oxo-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-2-yl)benzyl](pentan-3-yl)amino}pentanoate as a yellowish white solid.

[0100]

Preparation Example 52

Lithium hexamethyldisilazide (1.0 M in THF) 1.1 mL was added dropwise to a mixture of 200 mg of methyl 2,2-dimethyl-5-oxo-5-{[3-(4-oxo-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-2-yl)benzyl](pentan-3-yl)amino}pentanoate, 90 mg of 4-[2-(morpholin-4-yl)ethyl]aniline, and 5.0 mL of THF under ice cooling, followed by stirring for 30 minutes at the same temperature. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1), thereby obtaining 164 mg of methyl 2,2-dimethyl-5-[(3-{[3-({4-[2-(morpholin-4-yl)ethyl]phenyl}carbamoyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]carbamoyl}benzyl)(pentan-3-yl)amino]-5-oxopentanoate.

[0101]

Preparation Example 53

A borane-THF complex (1.08 M THF solution) 23 mL was added dropwise to a mixture of 3.02 g of tert-butyl 4-[3-(4-nitrophenyl)propanoyl]piperazine-1-carboxylate and THF 40 mL under ice cooling in an argon atmosphere, followed by stirring for 10 minutes at room temperature, and then heating under reflux was performed for 2 hours. The reaction mixture was cooled with ice, and 30 mL of methanol was added dropwise thereto, followed by stirring for 3 hours at 50°C. The reaction mixture was concentrated under reduced pressure, water and ethyl acetate were added to the residue, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (5% methanol/chloroform), thereby obtaining 2.78 g of tert-butyl 4-[3-(4-nitrophenyl)propyl]piperazine-1-carboxylate.

[0102]

Preparation Example 54

By using 180 mg of methyl 2,2-dimethyl-5-oxo-5-[pentan-3-yl(3-{[3-({4-[3-(piperazin-1-yl)propyl]phenyl} carbamoyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]carbamoyl}benzyl)amino]pentanoate and 0.06 mL of a 37% aqueous formalin solution, the reaction similar to Preparation Example 14 was performed, thereby obtaining 152 mg of methyl 2,2-dimethyl-5-[(3-{[3-({4-[3-(4-methylpiperazin-1-yl)propyl]phenyl} carbamoyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]carbamoyl}benzyl)(pentan-3-yl)amino]-5-oxopentanoate.

[0103]

Preparation Example 55

To a mixture of 680 mg of tert-butyl (5-nitropyridin-2-yl)acetate and 10 mL of DMF was added 373 mg of sodium hydride (55%, dispersion in paraffin liquid) under ice cooling in an argon atmosphere, followed by stirring for 30 minutes at room temperature. In addition, 0.62 mL of methyl iodide was added dropwise thereto under ice cooling, followed by stirring for 5 hours at room temperature. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1), thereby obtaining 582 mg of tert-butyl 2-methyl-2-(5-nitropyridin-2-yl)propanoate.

[0104]

Preparation Example 56

To a mixture of 200 mg of N-[4-(benzyloxy)phenyl]-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 6.0 mL of TFA was added 255 mg of 1,2,3,4,5-pentamethylbenzene, followed by stirring overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution were added thereto, followed by extraction using ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (3% methanol/chloroform), thereby obtaining 169 mg of N-(4-hydroxyphenyl)-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide.

[0105]

Preparation Example 57

By using 169 mg of N-(4-hydroxyphenyl)-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 95 mg of methyl 4-(bromomethyl)benzoate, 193 mg of methyl 4-[(4-{[(2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-

yl)carbonyl]amino}phenoxy)methyl]benzoate was obtained by the method similar to Preparation Example 30.

[0106]

Preparation Example 58

By using 610 mg of methyl 4-(2-{4-[(2-[(3-[[1-[N-(tert-butoxycarbonyl)-N-methylglycyl]piperidin-4-yl}(cyclopropyl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate and 5.0 mL of TFA as starting materials, the deprotection reaction similar to Preparation Example 12 and the amidation reaction similar to Preparation Example 32 were performed sequentially, thereby obtaining 240 mg of 4-{[2-(4-{cyclopropyl[3-((3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]amino}piperidin-1-yl)-2-oxoethyl](methyl)amino}-4-oxobutanoic acid.

[0107]

Preparation Example 59

By using 250 mg of methyl 4-{2-[4-((2-((3-[(cyclopropylamino)methyl]benzoyl)amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl)amino)phenyl]ethyl}benzoate and 153 mg of ethyl 2-chloropyrimidine-5-carboxylate as starting materials, the reaction similar to Preparation Example 30 was performed, thereby obtaining 307 mg of ethyl 2-{cyclopropyl[3-((3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]amino}pyrimidine-5-carboxylate.

[0108]

Preparation Example 60

A mixture of 22.2 g of 2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylic acid and 230 mL of toluene was heated at 60°C, and 20 mL of thionyl chloride was added thereto, followed by stirring for 1 hour at 60°C. The insoluble material was collected by filtration and washed with toluene. A saturated aqueous sodium hydrogen carbonate solution and ethyl acetate were added to the material collected by filtration, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was washed with ethanol, thereby obtaining 18.9 g of 2-[3-(morpholin-4-ylmethyl)phenyl]-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-4-one.

[0109]

Preparation Example 61

By using 300 mg of methyl 4-{2-[4-((2-((3-[(cyclopropylamino)methyl]benzoyl)amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl)amino)phenyl]ethyl}benzoate and 289 mg of ethyl 4-bromobutyrate, the reaction

similar to Preparation Example 30 was performed, thereby obtaining 201 mg of methyl 4-(2-{4-[(2-[(3-{[cyclopropyl(4-ethoxy-4-oxobutyl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0110]

Preparation Example 62

To a mixture of 5.27 g of benzyl 5-methylthiophene-2-carboxylate and 100 mL of carbon tetrachloride were added 4.18 g of N-bromosuccinimide (NBS) and 142 mg of azobisisobutyronitrile (AIBN), followed by stirring overnight at 80°C. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=7:3), thereby obtaining 4.44 g of benzyl 5-(bromomethyl)thiophene-2-carboxylate.

[0111]

Preparation Example 63

To a mixture of 2.18 g of benzyl 5-(bromomethyl)thiophene-2-carboxylate and 26 mL of toluene was added 1.86 g of triphenylphosphine, followed by stirring overnight at 80°C. The insoluble material was collected by filtration, thereby obtaining 2.89 g of ({5-[(benzyloxy)carbonyl]-2-thienyl}methyl)(triphenyl)phosphonium bromide.

[0112]

Preparation Example 64

A mixture of 3.01 g of methyl 5-(morpholin-4-ylmethyl)thiophene-2-carboxylate and 30 mL of 6.0 M hydrochloric acid was subjected to heating under reflux overnight at 100°C. The reaction mixture was concentrated under reduced pressure, and the residue was washed with acetonitrile, thereby obtaining 3.05 g of 5-(morpholin-4-ylmethyl)thiophene-2-carboxylic acid hydrochloride.

[0113]

Preparation Example 65

By using 3.42 g of methyl 6-methylpyrazine-2-carboxylate and 4.40 g of NBS, a bromination reaction was performed by the method similar to Preparation Example 62. Thereafter, by using 10 mL of morpholine as amine, the reaction similar to Preparation Example 9 was performed, thereby obtaining 987 mg of methyl 6-(morpholin-4-ylmethyl)pyrazine-2-carboxylate.

[0114]

Preparation Example 66

By using 1.2 g of tert-butyl 4-(4-ethoxy-4-oxobutanoyl)piperazine-1-carboxylate and 1.0 mL of 4.0 M hydrogen chloride/ethyl acetate solution, the reaction similar to Preparation Example 35 was performed, thereby obtaining 900 mg of ethyl 4-oxo-4-(piperazin-1-yl)butanoate hydrochloride.

[0115]

Preparation Example 67

To a mixture of 306 mg of N-cyclopropyl-N-[3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]glycine hydrochloride and 5.0 mL of dichloromethane were added 0.182 mL of triethylamine, 91 mg of methyl N-methylglycinate hydrochloride, 125 mg of WSC-hydrochloride and 88 mg of HOBt, followed by stirring for 15 hours at room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and then dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, thereby obtaining 152 mg of methyl N-cyclopropyl-N-[3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]glycyl-N-methylglycinate.

[0116]

Preparation Example 68

By a method similar to Preparation Example 37, 197 mg of methyl 4-(2-{4-[(2-{3-[(2-hydroxyethyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate was reacted with 0.10 mL of thionyl chloride, and then the resultant was reacted with 325 mg of ethyl isonipecotate, thereby obtaining 206 mg of ethyl 1-(2-{3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl](pentan-3-yl)amino}ethyl)piperidine-4-carboxylate.

[0117]

Preparation Example 69

To a mixture of 2.88 g of ({5-[(benzyloxy)carbonyl]-2-thienyl}methyl)(triphenyl)phosphonium bromide, 823 mg of 4-nitrobenzaldehyde and 30 mL of THF was added dropwise 1.0 mL of a 5.0 M sodium methoxide/methanol solution, followed by stirring overnight at room temperature. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed sequentially with 1.0 M hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution, and saturated brine and then dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:6). 10 mL of methanol and 10 mL of THF were added to the obtained residue, and 98 mg of 10% palladium carbon was added thereto under an argon flow, followed by stirring overnight at room temperature in a hydrogen atmosphere. The reaction mixture was filtered using celite, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1), thereby obtaining 765 mg of methyl 5-[2-(4-aminophenyl)ethyl]thiophene-2-carboxylate.

[0118]

Compounds of Preparation Examples 70 to 315 shown in the following table were prepared in the similar manner as in Preparation Examples 1 to 69. The following table shows the structure, physicochemical data, and preparation process of the compounds of preparation examples.

[0119]

Example 1

To a mixture of 1.00 g of methyl 4-{2-[4-({2-({3-[(pentan-3-ylamino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl}amino)phenyl]ethyl}benzoate, 1.00 g of sodium triacetoxyborohydride, 0.50 mL of acetic acid and 20 mL of methylene chloride was added 473 mg of ethyl 4-[methyl(2-oxoethyl)amino]-4-oxobutanoate, followed by stirring for 1 hour at room temperature. 498 mg of sodium triacetoxyborohydride and 237 mg of ethyl 4-[methyl(2-oxoethyl)amino]-4-oxobutanoate were further added to the reaction mixture, followed by stirring for 2 hours at room temperature. An aqueous sodium hydrogen carbonate solution was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by basic silica gel column chromatography (ethyl acetate), thereby obtaining 1.19 g of methyl 4-(2-{4-[(2-[(3-[[2-[(4-ethoxy-4-oxobutanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0120]

Example 2

A mixture of 1.18 g of methyl 4-(2-{4-[(2-[(3-[[2-[(4-ethoxy-4-oxobutanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate, 5.0 mL of a 1.0 M aqueous sodium hydroxide solution, and 24 mL of ethanol was subjected to heating under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure, and 4 mL of 1.0 M hydrochloric acid was added thereto. Then, 600 mg of lactobionic acid was added thereto to neutralize the mixture, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol/chloroform) to afford 1.10 g of a product. 3.0 mL of acetonitrile and 0.40 mL of 1.0 M hydrochloric acid were added to 300 mg of this product, and the reaction mixture was purified by ODS column chromatography (50% acetonitrile/0.01 M hydrochloric acid), followed by lyophilization, thereby obtaining 253 mg of 4-(2-{4-[(2-[(3-[[2-[(3-carboxypropanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid hydrochloride.

[0121]

Example 2A

To a mixture of 100 mg of the 4-(2-{4-[(2-{3-[(2-{3-carboxypropanoyl})(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid which was obtained by the chromatographic purification as described in Example 2, 3.0 mL of ethanol, 1.5 mL of water and 0.26 mL of an 1.0 M aqueous sodium hydroxide solution was added dropwise 1.3 mL of a 0.1 M aqueous magnesium chloride solution. The reaction mixture was stirred overnight with heating under reflux, and then the precipitated solid was collected by filtration, thereby obtaining 89 mg of a hydrate of magnesium 4-(2-{4-[(2-{3-[(2-{3-carboxylatopropanoyl})(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate as the crystal. ESI+:781.

[0122]

Example 3

A mixture of 100 mg of methyl {[(4-nitrophenoxy)carbonyl]oxy}acetate and 5.0 mL of THF was added to a mixture of 180 mg of methyl 4-[2-(4-{[(2-{[3-[(2-(methylamino)ethyl](pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl]amino}phenyl)ethyl]benzoate, 0.15 mL of N-ethyl-N-isopropylpropan-2-amine, and 5.0 mL of THF under ice cooling, followed by stirring for 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution were added to the residue, followed by extraction with ethyl acetate. The organic layer was washed sequentially with a saturated aqueous sodium hydrogen carbonate solution, water, and saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by basic silica gel column chromatography (hexane:chloroform=4:6), thereby obtaining 204 mg of methyl 4-{2-[4-({[2-({3-[7-methyl-3,6-dioxo-10-(pentan-3-yl)-2,5-dioxa-7,10-diazaundecan-11-yl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate.

[0123]

Example 4

To a mixture of 203 mg of methyl 4-{2-[4-({[2-({3-[7-methyl-3,6-dioxo-10-(pentan-3-yl)-2,5-dioxa-7,10-diazaundecan-11-yl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl]carbonyl}amino)phenyl]ethyl}benzoate, 4.0 mL of methanol and 4.0 mL of THF was added 1.5 mL of a 1.0 M aqueous sodium hydroxide solution at room temperature, followed by stirring for 14 hours at 60°C. 1.5 mL of 1.0 M hydrochloric acid was added to the reaction mixture under ice cooling, followed by concentration under reduced pressure. A mixed solvent (methanol/chloroform=15/85) was added to the residue, the insoluble material was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% methanol/chloroform). A mixed solvent

(acetonitrile/water=90/10) was added to the obtained product, 0.5 mL of 1.0 M hydrochloric acid was added thereto under ice cooling, and the solvent was removed under reduced pressure. The residue was subjected to lyophilization, thereby obtaining 186 mg of 4-(2-{4-[(2-{3-[(2-{[(carboxymethoxy)carbonyl](methyl)amino}ethyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid hydrochloride.

[0124]

Example 4A

To a mixture of 100 mg of the 4-(2-{4-[(2-{3-[(2-{[(carboxymethoxy)carbonyl](methyl)amino}ethyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid which was obtained by the chromatographic purification as described in Example 4 and 0.5 mL of ethanol was added 0.26 mL of a 1.0 M aqueous sodium hydroxide solution at room temperature, followed by stirring for 15 minutes at 80°C. 1.3 mL of a 0.1 M aqueous magnesium chloride solution was added dropwise to the reaction mixture, and the reaction mixture was stirred for 30 minutes with heating under reflux. 0.49 mL of water was added to the reaction mixture, followed by heating under reflux for additional 1 hour. 1.5 mL of ethanol was added to the reaction mixture, followed by stirring for additional 1 hour with heating under reflux, and then the mixture was cooled to room temperature. The precipitated solid was collected by filtration, thereby obtaining 105 mg of a hydrate of magnesium 4-(2-{4-[(2-{3-[(2-{[(carboxylatomethoxy)carbonyl](methyl)amino}ethyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate as the crystal.

ESI+: 783.

[0125]

Example 5

A mixture of 195 mg of methyl 4-[2-(4-{[(2-{[3-(11-cyclopropyl-8-methyl-7-oxo-2,5-dioxa-8,11-diazadodecan-12-yl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate, 1.0 mL of a 1.0 M aqueous sodium hydroxide solution, and 5.0 mL of methanol was stirred for 15 hours at 60°C. The reaction mixture was concentrated under reduced pressure, 1.0 mL of 1.0 M hydrochloric acid was added to the residue, and extraction was performed by using chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol/chloroform). The obtained foam-like material was dissolved in 5.0 mL of ethyl acetate, and 0.13 mL of 4.0 M hydrogen chloride/ethyl acetate solution was added thereto under ice cooling, followed by stirring for 2 hours at room temperature. The precipitated solid was collected by filtration

and washed with ethyl acetate, followed by drying under reduced pressure, thereby obtaining 108 mg of 4-[2-(4-{{(2-{{(3-(11-cyclopropyl-8-methyl-7-oxo-2,5-dioxo-8,11-diazadodecan-12-yl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoic acid hydrochloride.

[0126]

Example 6

A mixture of 140 mg of methyl 4-{2-[4-{{(2-{{(3-{{(cyclopropyl{2-[(2-ethoxy-2-oxoethyl)amino]ethyl}amino)methyl]benzoyl}amino)-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl}amino)phenyl]ethyl}benzoate, 1.0 mL of a 1.0M aqueous sodium hydroxide solution, 1.0 mL of methanol, and 2.0 mL of THF was stirred overnight at room temperature. To the reaction mixture was added 1.0 mL of 1.0 M hydrochloric acid. The precipitated solid was collected by filtration, thereby obtaining 113 mg of 4-(2-{4-[[{2-[(3-{{[2-[(carboxymethyl)amino]ethyl}(cyclopropyl)amino]methyl}benzoyl}amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl]amino]phenyl}ethyl)benzoic acid.

[0127]

Example 7

By using 160 mg of methyl 4-[2-(4-{{(2-{{(3-{{(cyclopropyl[2-(methylamino)ethyl]amino}methyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate and 70 mg of methyl 3-(bromomethyl)benzoate as starting materials, the similar alkylation as in Preparation Example 30 and the hydrolysis similar to Example 2 were sequentially performed, thereby obtaining 69 mg of 3-{{[2-[(3-{{[3-{{(4-[2-(4-carboxyphenyl)ethyl]phenyl}carbamoyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]carbamoyl}benzyl)(cyclopropyl)amino]ethyl}(methyl)amino]methyl}benzoic acid dihydrochloride.

[0128]

Example 8

By using 320 mg of methyl 4-(2-{5-[[{2-[(2-{{[2-[(4-tert-butoxy-4-oxobutanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl}isonicotinoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]pyridin-2-yl}ethyl)benzoate as a starting material, removal of a tert-butyl group with 3.0 mL of TFA under the conditions similar to Example 10 as described later, and the hydrolysis similar to Example 2 were performed, thereby obtaining 279 mg of 4-(2-{5-[[{2-[(2-{{[2-[(3-carboxypropanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino]methyl}isonicotinoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl]amino]pyridin-2-yl}ethyl)benzoic acid trihydrochloride.

[0129]

Example 9

A mixture of 180 mg of 4-[2-(4-{{(2-{{(3-{{(4-(diethoxyphosphoryl)butanoyl}(isopropyl)amino)methyl)benzoyl}amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl}amino}phenyl)ethyl]benzoic acid, 0.040 mL of bromotrimethylsilane, and 3.6 mL of chloroform was stirred overnight at room temperature. Water was added to the reaction mixture, followed by extraction with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography, thereby obtaining 42 mg of 4-(2-{{4-{{(2-{{(3-{{(4-[ethoxy(hydroxy)phosphoryl]butanoyl}(isopropyl)amino)methyl}benzoyl}amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl}amino}phenyl}ethyl)benzoic acid.

[0130]

Example 10

A mixture of 675 mg of methyl 5-{{3-{{(3-{{(6-(1-tert-butoxy-2-methyl-1-oxopropan-2-yl)pyridin-3-yl]carbamoyl}-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)carbamoyl]benzyl}(pentan-3-yl)amino]-2,2-dimethyl-5-oxopentanoate, 10 mL of methylene chloride, and 1.3 mL of TFA was stirred 15 hours at room temperature. The reaction mixture was concentrated under reduced pressure, and a saturated aqueous sodium hydrogen carbonate solution was added to the residue, followed by extraction by using ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (10% methanol/chloroform), thereby obtaining 550 mg of 2-{{5-{{(2-{{(3-{{(5-methoxy-4,4-dimethyl-5-oxopentanoyl)(pentan-3-yl)amino)methyl}benzoyl}amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl}amino]pyridin-2-yl}-2-methylpropanoic acid.

[0131]

Example 11

To a mixture of 410 mg of 2-{{5-{{(2-{{(3-{{(5-methoxy-4,4-dimethyl-5-oxopentanoyl)(pentan-3-yl)amino)methyl}benzoyl}amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl}amino]pyridin-2-yl}-2-methylpropanoic acid, 75 mg of 4-methylmorpholine and 10 mL of THF was added 0.089 mL of isobutyl chloroformate under ice cooling, followed by stirring for 10 minutes at room temperature. The reaction mixture was filtered, and then the filtrate was cooled with ice. 65 mg of sodium borohydride and 1.0 mL of water were added thereto, followed by stirring for 10 minutes at room temperature. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:2), thereby obtaining 155 mg of methyl 5-{{3-{{(3-{{(6-(1-hydroxy-2-methylpropan-2-yl)pyridin-3-

yl]carbamoyl}-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)carbamoyl]benzyl}(pentan-3-yl)amino]-2,2-dimethyl-5-oxopentanoate.

[0132]

Example 12

A mixture of 150 mg of 4-{[(2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}benzoic acid, 57 mg of N,N-diethyl-p-phenylenediamine, 61 mg of WSC·hydrochloride, 42 mg of HOBt, and 1.5 mL of methylene chloride was stirred for 3 hours at room temperature. Water was added to the reaction mixture, followed by extraction with methylene chloride. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by basic silica gel column chromatography (2% methanol/chloroform), thereby obtaining an oily material. Methanol and 4.0 M hydrogen chloride/ethyl acetate solution were added to this material, and the solution was concentrated under reduced pressure. The residue was treated with ethyl acetate, thereby obtaining 85 mg of N-(4-{[4-(diethylamino)phenyl]carbamoyl}phenyl)-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide dihydrochloride.

[0133]

Example 13

By using 340 mg of 2-[(3-{[cyclopropyl(piperidin-4-yl)amino]methyl}benzoyl)amino]-N-[4-(diethylamino)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 99 mg of ethyl bromoacetate, a reaction was performed under the conditions similar to Preparation Example 30, thereby obtaining 310 mg of ethyl [4-(cyclopropyl{3-[(3-{[4-(diethylamino)phenyl]carbamoyl}-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)carbamoyl]benzyl}amino)piperidin-1-yl]acetate.

[0134]

Example 14

By using 1.71 g of tert-butyl 3-(hydroxymethyl)-4-[3-({3-[(4-{2-[4-(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]piperazine-1-carboxylate and 17 mL of TFA, a reaction was performed under the conditions similar to Preparation Example 12, thereby obtaining 1.38 g of methyl 4-(2-{4-[(2-{[3-{[2-(hydroxymethyl)piperazin-1-yl]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate.

[0135]

Example 15

To a mixture of 200 mg of 2-{[3-(chloromethyl)benzoyl]amino}-N-[4-(diethylamino)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 8 mL of DMF was added 1.0 mL of morpholine, followed by stirring for 3 days at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by

silica gel column chromatography (chloroform:methanol:aqueous ammonia solution=50:1:0.1). The obtained residue was dissolved in a mixed solution of ethyl acetate and ethanol (4:1), and 1.0 mL of 4.0 M hydrogen chloride/ethyl acetate solution was further added thereto. The precipitated solid was collected by filtration, thereby obtaining 183 mg of N-[4-(diethylamino)phenyl]-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide dihydrochloride.

[0136]

Example 16

By using 400 mg of 2-{[3-(chloromethyl)benzoyl]amino}-N-[4-(pyridin-4-ylmethyl)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 819 mg of ethyl 4-(cyclopropylamino)cyclohexanecarboxylate, the alkylation similar to Preparation Example 30 was performed, and then hydrolysis was performed under the conditions similar to Example 5, thereby obtaining 261 mg of 4-(cyclopropyl{3-[(3-{[4-(pyridin-4-ylmethyl)phenyl]carbamoyl}-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)carbamoyl]benzyl}amino)cyclohexane carboxylic acid dihydrochloride.

[0137]

Example 17

To a mixture of 350 mg of 2-[3-(morpholin-4-ylmethyl)phenyl]-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-4-one, 150 mg of 2-N,2-N-diethylpyrimidine-2,5-diamine and 5.0 mL of THF was added dropwise 1.0 mL of lithium hexamethyldisilazide (1.0 M in THF) under ice cooling, followed by stirring for 1 hour at the same temperature. A saturated aqueous ammonium chloride solution was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (methanol/chloroform). Ethyl acetate and 0.5 mL of 4.0 M hydrogen chloride/ethyl acetate solution were sequentially added to the residue, followed by stirring for 30 minutes at room temperature. The insoluble material was collected by filtration, thereby obtaining 174 mg of N-[2-(diethylamino)pyrimidin-5-yl]-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide dihydrochloride.

[0138]

Example 18

By using 250 mg of methyl 4-(2-{4-[(2-{3-[(4-{2-[(benzyloxy)carbonyl]cyclohexyl}(isopropyl)amino)methyl]benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino]phenyl)ethyl)benzoate and 10 mg of 10% palladium carbon, catalytic hydrogen reduction was performed under the conditions similar to Preparation Example 5, thereby obtaining 88 mg of cis-4-{isopropyl[3-[(3-[(4-{2-[(4-

(methoxycarbonyl)phenyl]ethyl}phenyl)carbamoyl]-4,5,6,7-tetrahydro-1-benzothiophen-2-yl}carbamoyl)benzyl]amino}cyclohexanecarboxylic acid.

[0139]

Example 19

By using 5.34 g of 2-{[3-(chloromethyl)benzoyl]amino}-N-[4-(diethylamino)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 13.1 g of 1-[4-(cyclopropylamino)piperidin-1-yl]ethanone as starting materials, a reaction was performed under the conditions similar to Preparation Example 29, thereby obtaining 5.37 g of 2-[(3-{[(1-acetylpiperidin-4-yl)(cyclopropyl)amino]methyl}benzoyl)amino]-N-[4-(diethylamino)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide.

[0140]

Example 20

By using 23 mg of methyl 4-[2-(4-{[(2-{[3-(chloromethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate and 19 mg of methyl [(1-ethylpropyl)amino]acetate as starting materials, alkylation was performed under the conditions similar to Preparation Example 30, and then hydrolysis was performed under the conditions similar to Example 6, thereby obtaining 6.7 mg of 4-(2-{4-[(2-{[3-{[(carboxymethyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid.

[0141]

Example 21

By using 250 mg of 2-amino-N-[4-(pyridin-4-ylmethyl)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide and 244 mg of 5-(morpholin-4-ylmethyl)-2-furoic acid as starting materials, a condensation reaction was performed under the conditions similar to Preparation Example 16, thereby obtaining 307 mg of 2-{[5-(morpholin-4-ylmethyl)-2-furoyl]amino}-N-[4-(pyridin-4-ylmethyl)phenyl]-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide dihydrochloride.

[0142]

Example 22

A mixture of 0.07 mL of lithium hexamethyldisilazide (1.0M in THF) and 0.2 mL of THF was added to a mixture of 11.5 mg of 2-[3-(morpholin-4-ylmethyl)phenyl]-5,6,7,8-tetrahydro-4H-[1]benzothieno[2,3-d][1,3]oxazin-4-one, 4.9 mg of 5-cyclopropyl-1,3,4-thiadiazol-2-amine, and 0.8 mL of THF, followed by stirring overnight at room temperature. Chloroform and a saturated aqueous ammonium chloride solution were added to the reaction mixture, and the organic layer was separated. After the solvent was removed under reduced pressure, the obtained residue was purified, thereby obtaining 11.4 mg of N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2-{[3-(morpholin-4-ylmethyl)benzoyl]amino}-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide.

[0143]

Example 67A

To a mixture of 90 mg of 4-(2-{4-[(2-{(3-{[2-(4-carboxy-4-methylpentanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid hydrochloride and 0.5 mL of ethanol was added 0.32 mL of a 1.0 M aqueous sodium hydroxide solution at room temperature, followed by stirring for 5 minutes at room temperature. 1.1 mL of a 0.1 M aqueous magnesium chloride solution was added dropwise to the reaction mixture at 80°C, and then 0.38 mL of water was added thereto, followed by stirring again for 30 minutes at 80°C. 0.4 mL of EtOH was added to the reaction mixture, followed by stirring again for 14 hours at 80°C. 0.9 mL of water was added to the reaction mixture, followed by stirring for additional 1 hour at 80°C. 1.8 mL of water was further added to the reaction mixture, followed by stirring again for 2 hours at 80°C. After the reaction mixture was cooled to room temperature, the precipitate was collected by filtration, thereby obtaining 86 mg of a hydrate of magnesium 4-(2-{4-[(2-{(3-{[2-(4-carboxylato-4-methylpentanoyl)(methyl)amino]ethyl}(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate as the crystal. ESI+:823

[0144]

Example 109A

To a mixture of 80 mg of 4-(2-{4-[(2-{(3-{[(4-carboxy-4-methylpentanoyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid and 0.4 mL of ethanol was added 0.21 mL of a 1.0 M aqueous sodium hydroxide solution at room temperature, followed by stirring for 5 minutes at room temperature. 1.0 mL of a 0.1 M aqueous magnesium chloride solution was added dropwise to the reaction mixture at 80°C, and then 0.39 mL of water was added to the reaction mixture, followed by stirring again for 30 minutes at 80°C. 0.4 mL of ethanol was added to the reaction mixture, followed by stirring again for 30 minutes at 80°C. 0.8 mL of water was added to the reaction mixture, followed by stirring for 14 hours at 80°C, and then 0.8 mL of water was further added thereto, followed by stirring again for 2 hours at 80°C. After the reaction mixture was cooled to room temperature, the precipitate was collected by filtration, thereby obtaining 74 mg of a hydrate of magnesium 4-(2-{4-[(2-{(3-{[(4-carboxylato-4-methylpentanoyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate as the crystal. ESI-:764.

[0145]

Example 121A

To a mixture of 80 mg of 4-(2-{4-[(2-{3-[(4-carboxy-3,3-dimethylbutanoyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid and 0.4 mL of ethanol was added 0.21 mL of a 1.0 M aqueous sodium hydroxide solution at room temperature, followed by stirring for 5 minutes at room temperature. 1.0 mL of a 0.1 M aqueous magnesium chloride solution was added dropwise to the reaction mixture at 80°C, and then 0.39 mL of water was added thereto, followed by stirring again for 30 minutes at 80°C. 0.4 mL of ethanol was added to the reaction mixture, followed by stirring again for 30 minutes at 80°C. 0.8 mL of water was added to the reaction mixture, followed by stirring for 14 hours at 80°C, and then 0.8 mL of water was further added thereto, followed by stirring again for 2 hours at 80°C. After the reaction mixture was cooled to room temperature, the precipitate was collected by filtration, thereby obtaining 77 mg of a hydrate of magnesium 4-(2-{4-[(2-{3-[(4-carboxylato-3,3-dimethylbutanoyl)(pentan-3-yl)amino]methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoate as the crystal. ESI-:764.

[0146]

Example 148

By using 29 mg of methyl 4-[2-(4-{[(2-{3-(chloromethyl)benzoyl)amino}-4,5,6,7-tetrahydro-1-benzothiophen-3-yl)carbonyl]amino}phenyl)ethyl]benzoate and 30 mg of methyl 3-(aminomethyl)benzoate hydrochloride as starting materials, amination was performed under the conditions similar to Preparation Example 30, thereafter alkylation with MP-Triacetoxyborohydride (Biotage) was performed under the conditions similar to Example 1, and then hydrolysis was performed under the conditions similar to Example 6, thereby obtaining 15 mg of 3-{[(3-{3-[(4-[2-(4-carboxyphenyl)ethyl]phenyl}carbamoyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]carbamoyl}benzyl)(isopropyl)amino]methyl}benzoic acid.

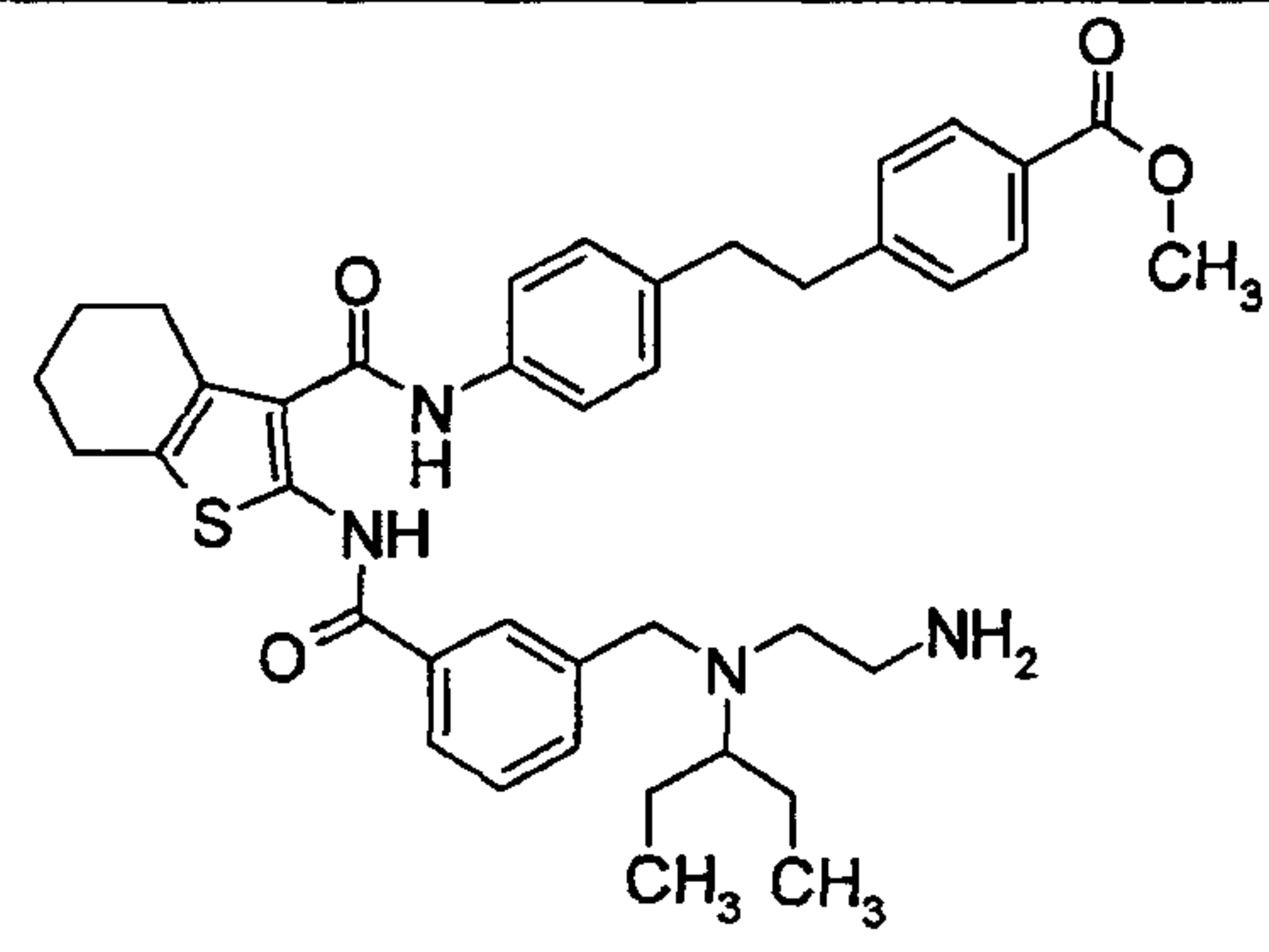
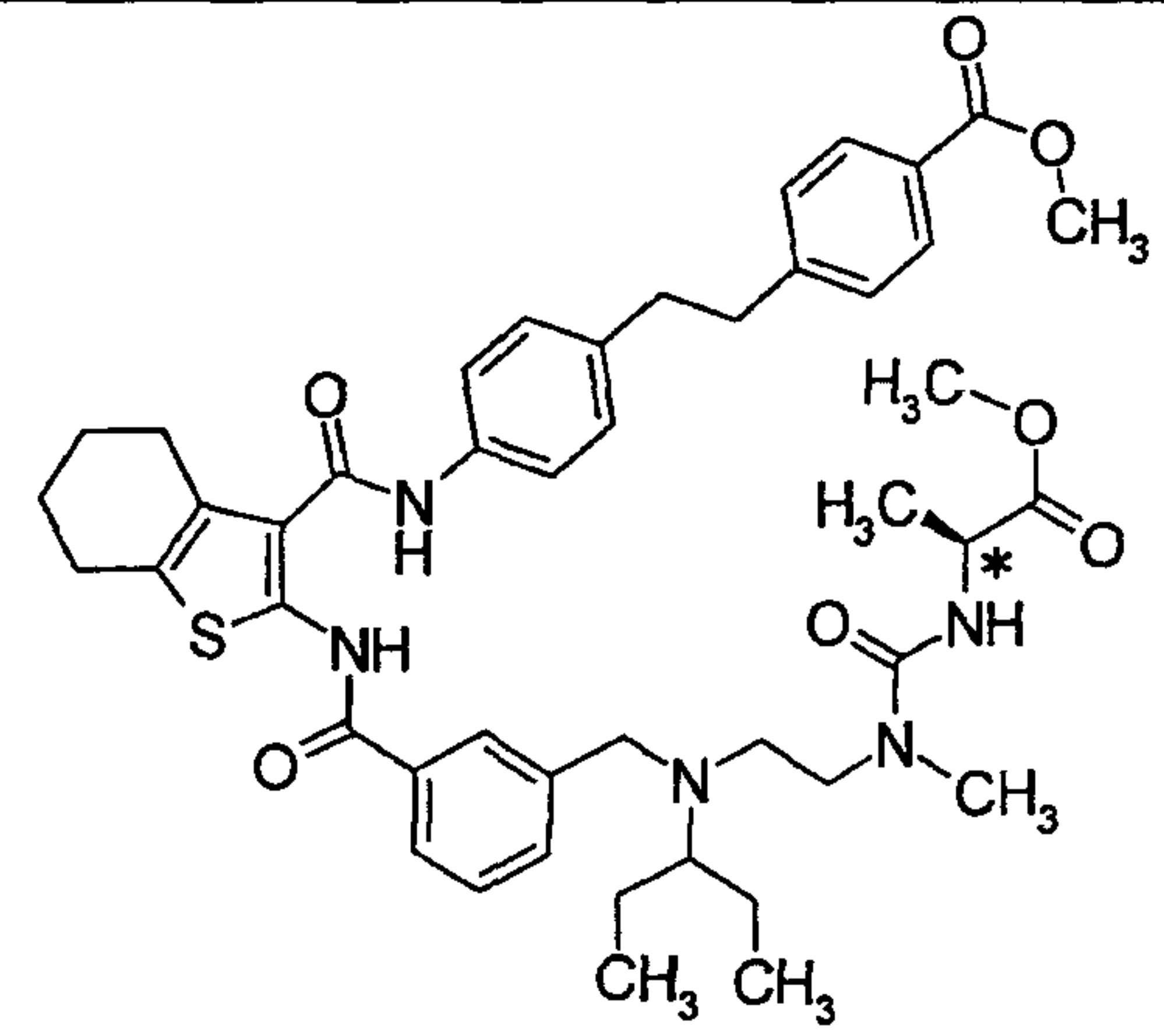
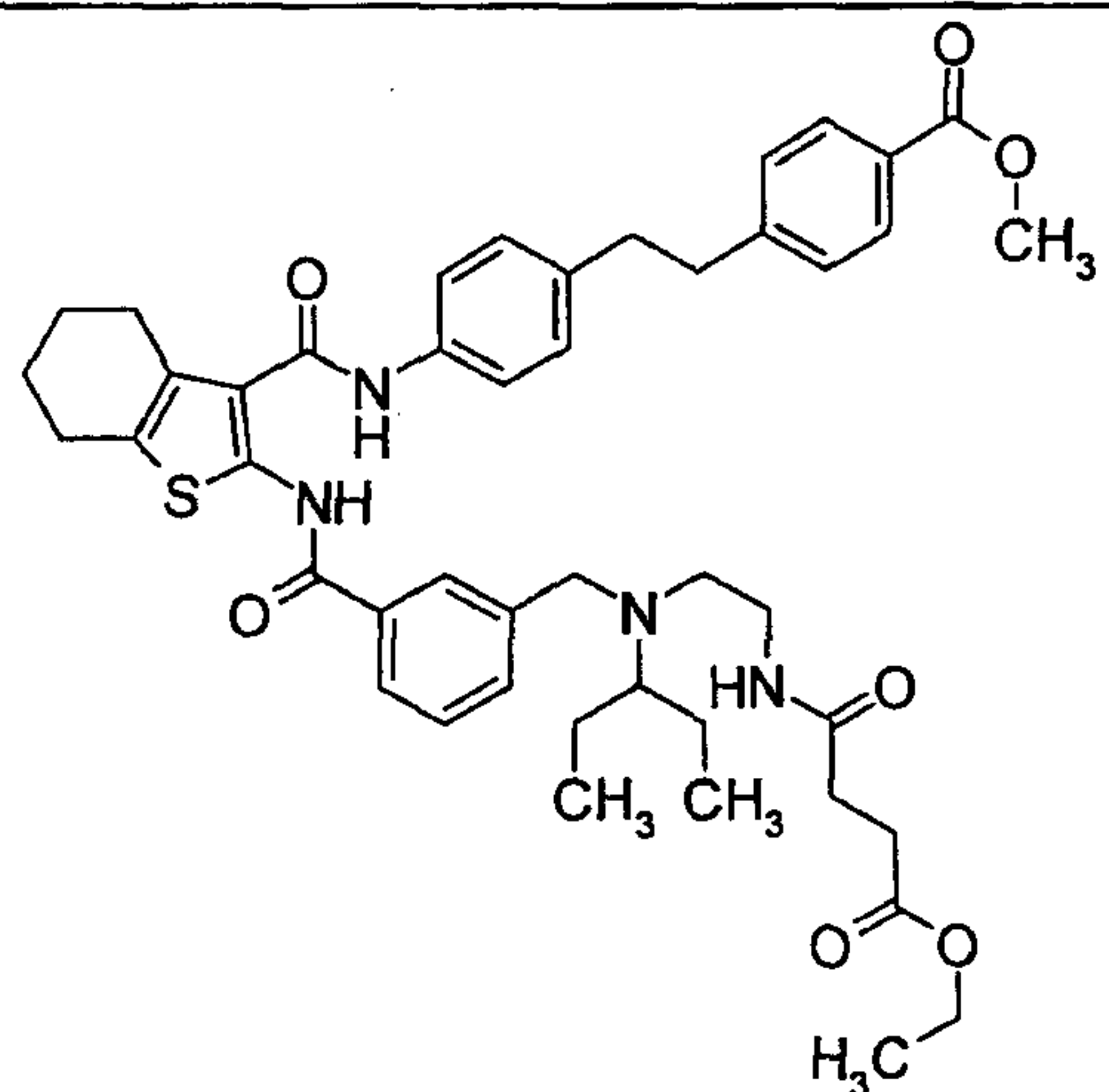
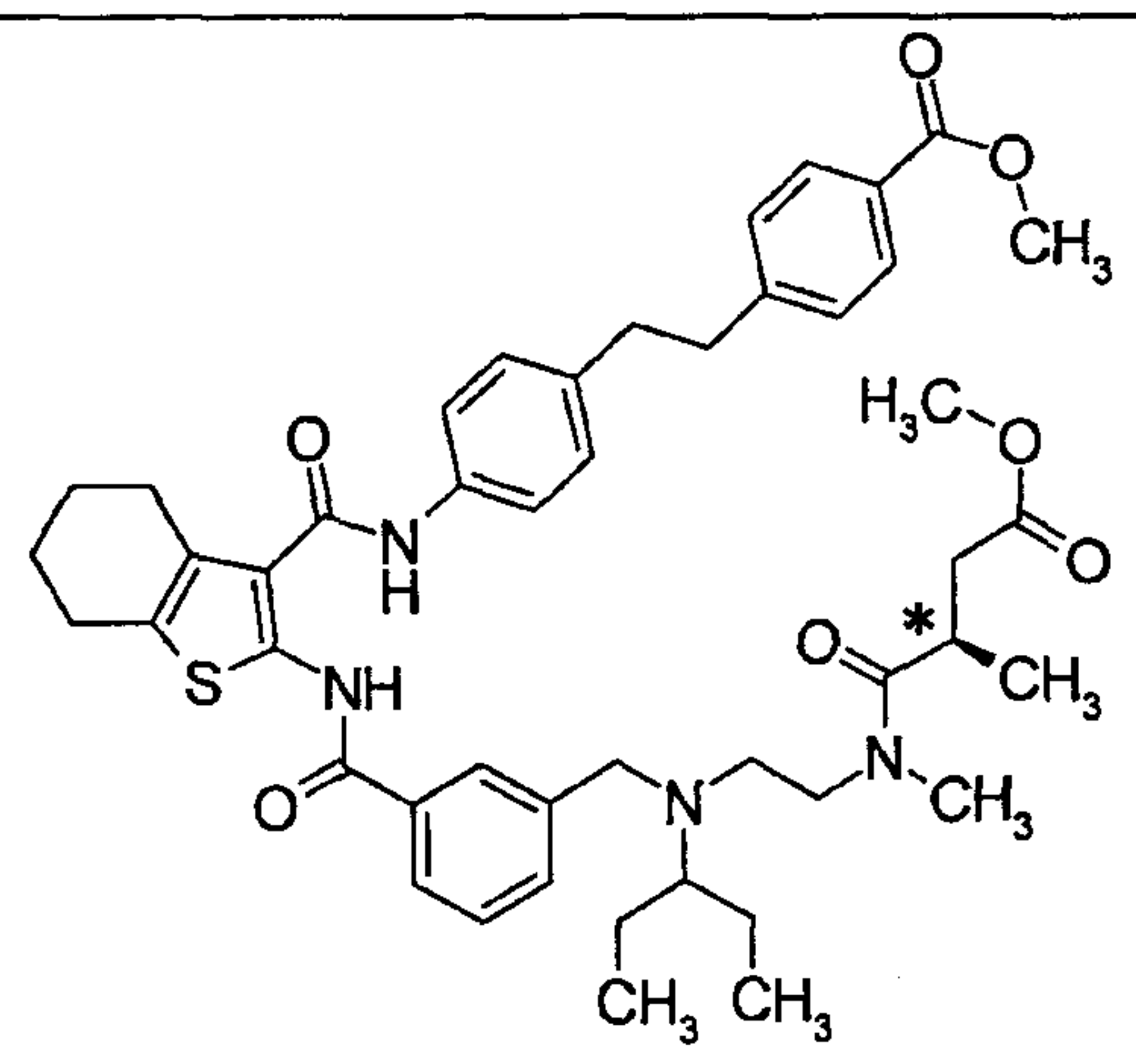
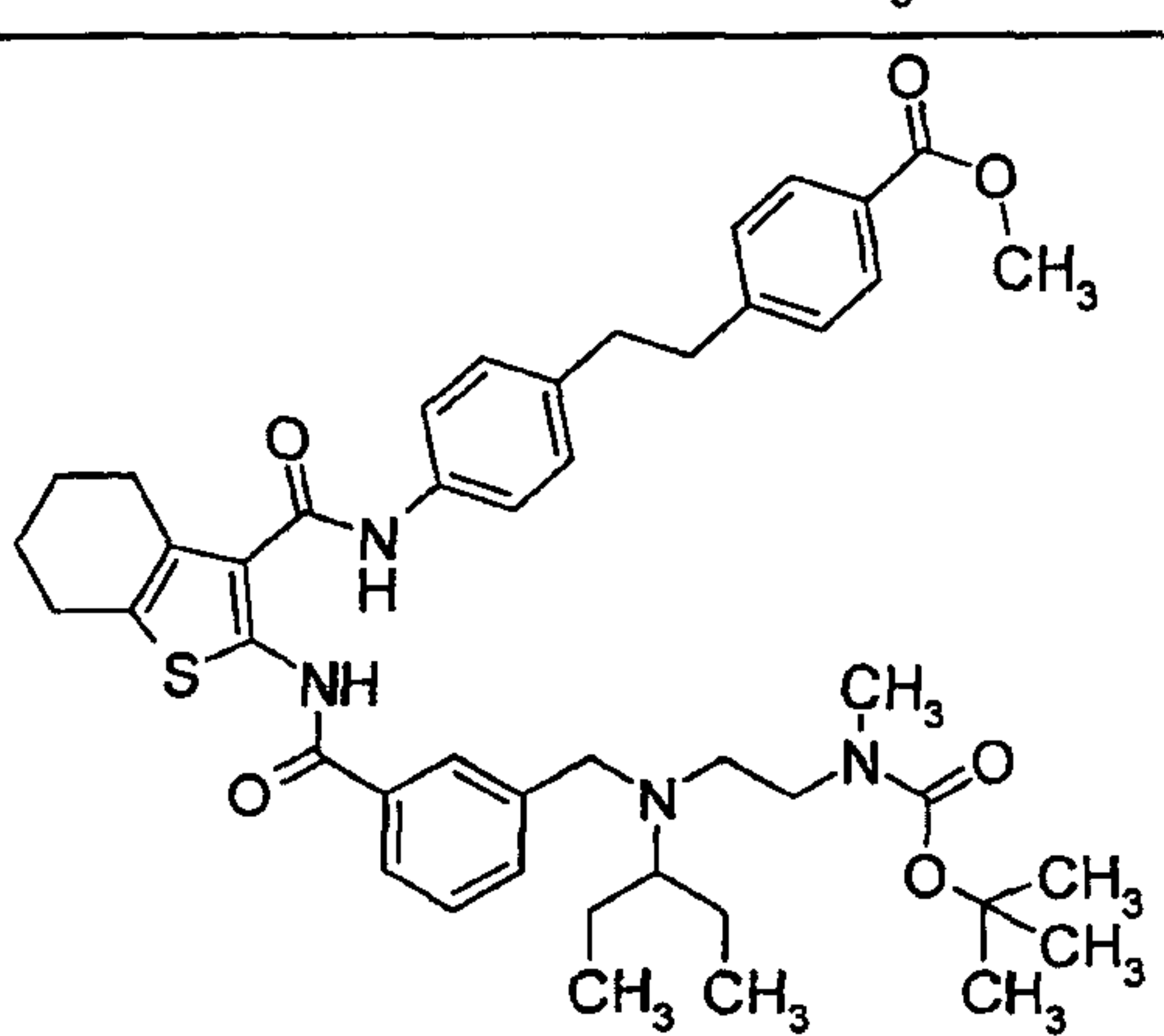
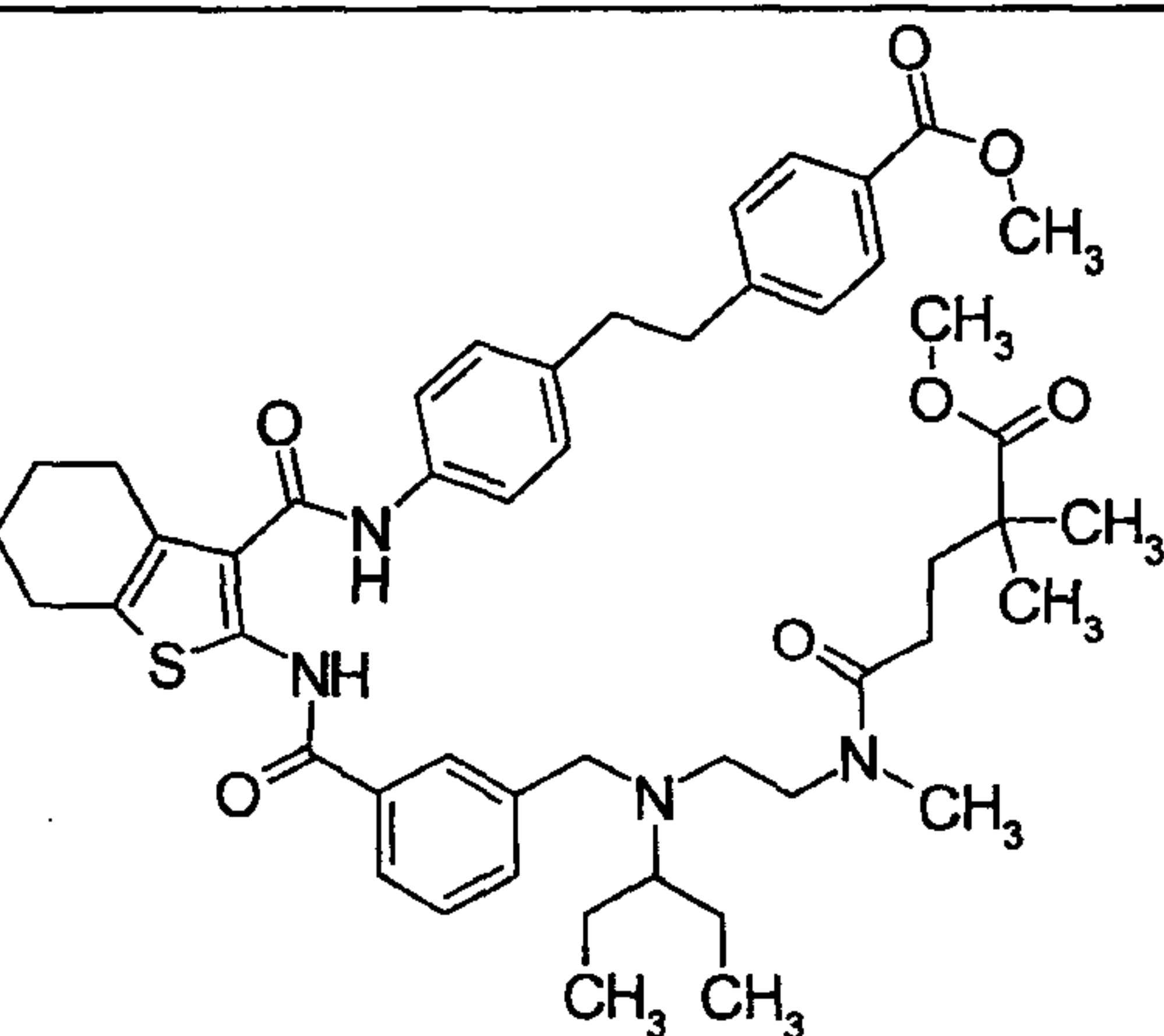
[0147]

Compounds of Examples 23 to 246 shown in the following table were prepared in the similar manner as in Examples 1 to 22. The following table shows the structure, physicochemical data, and preparation process of the example compounds.

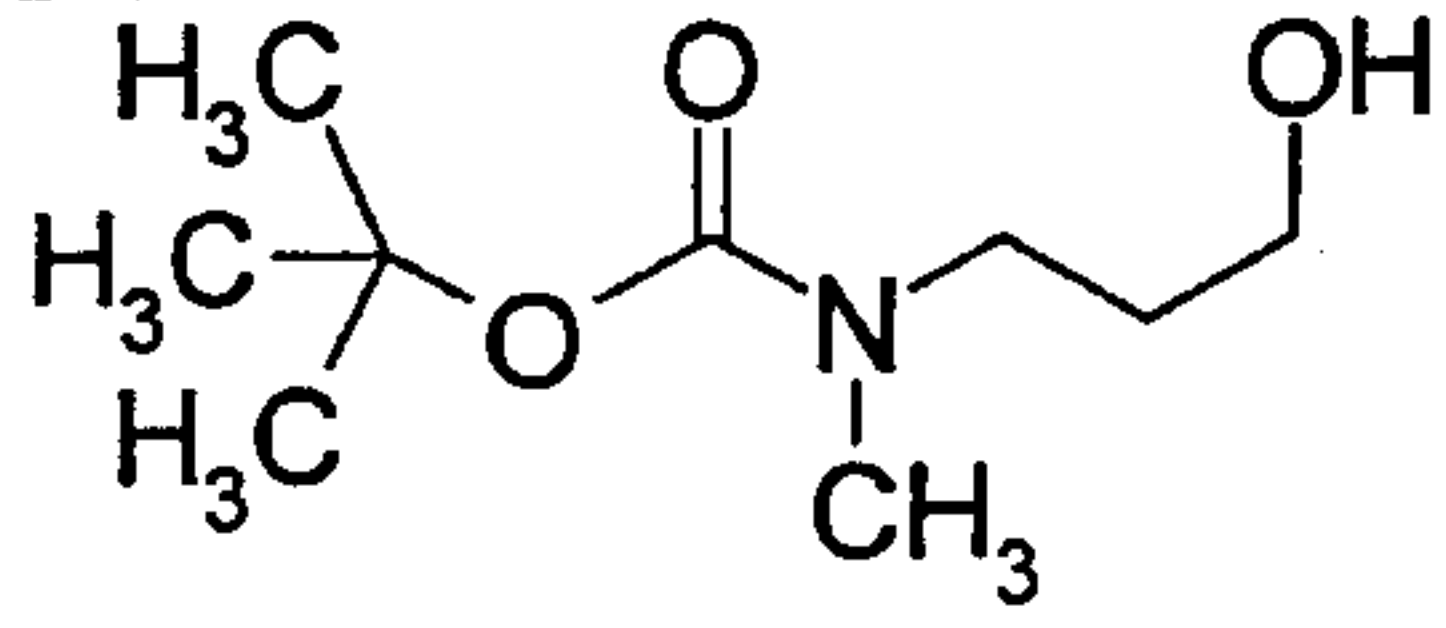
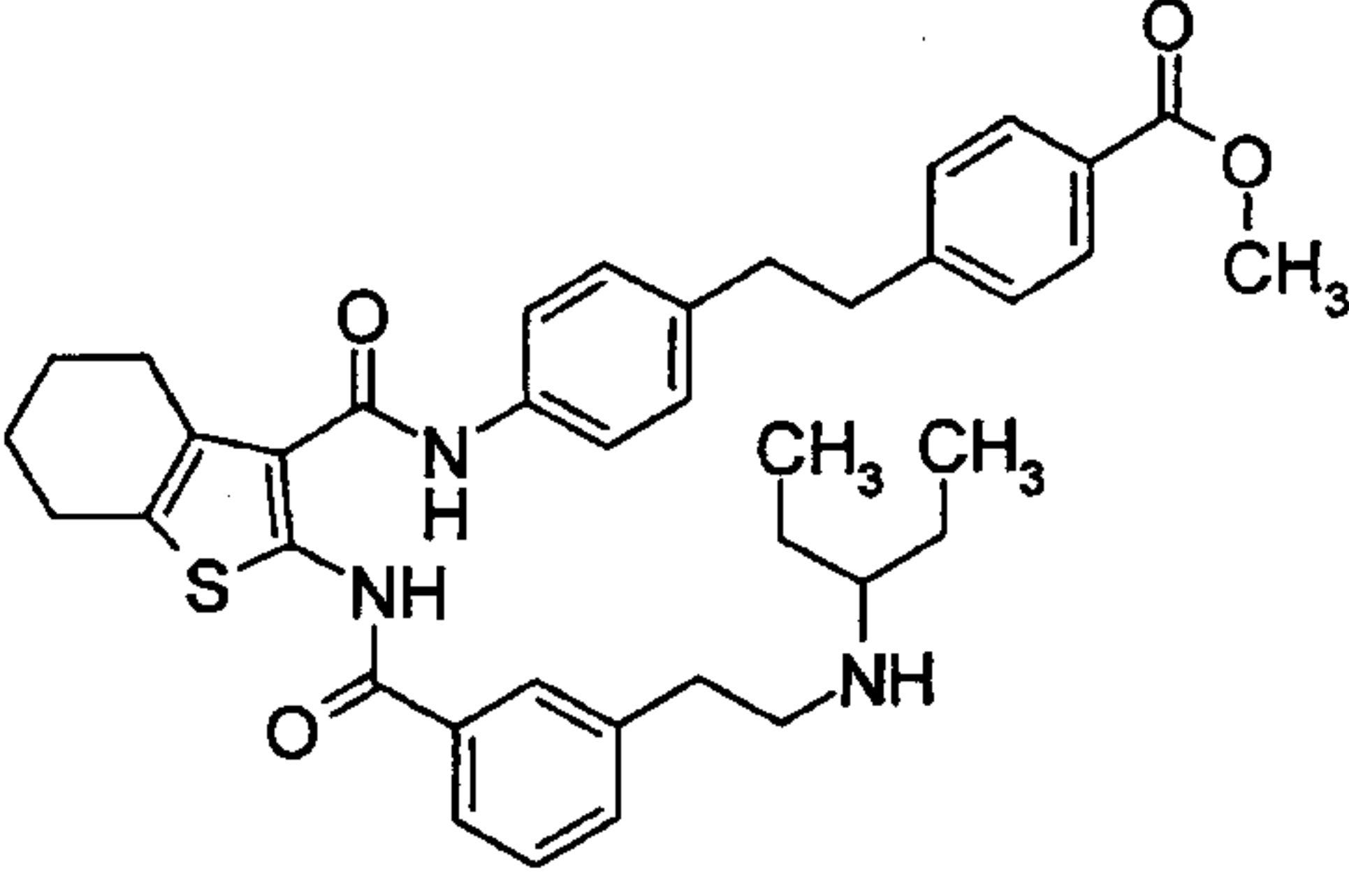
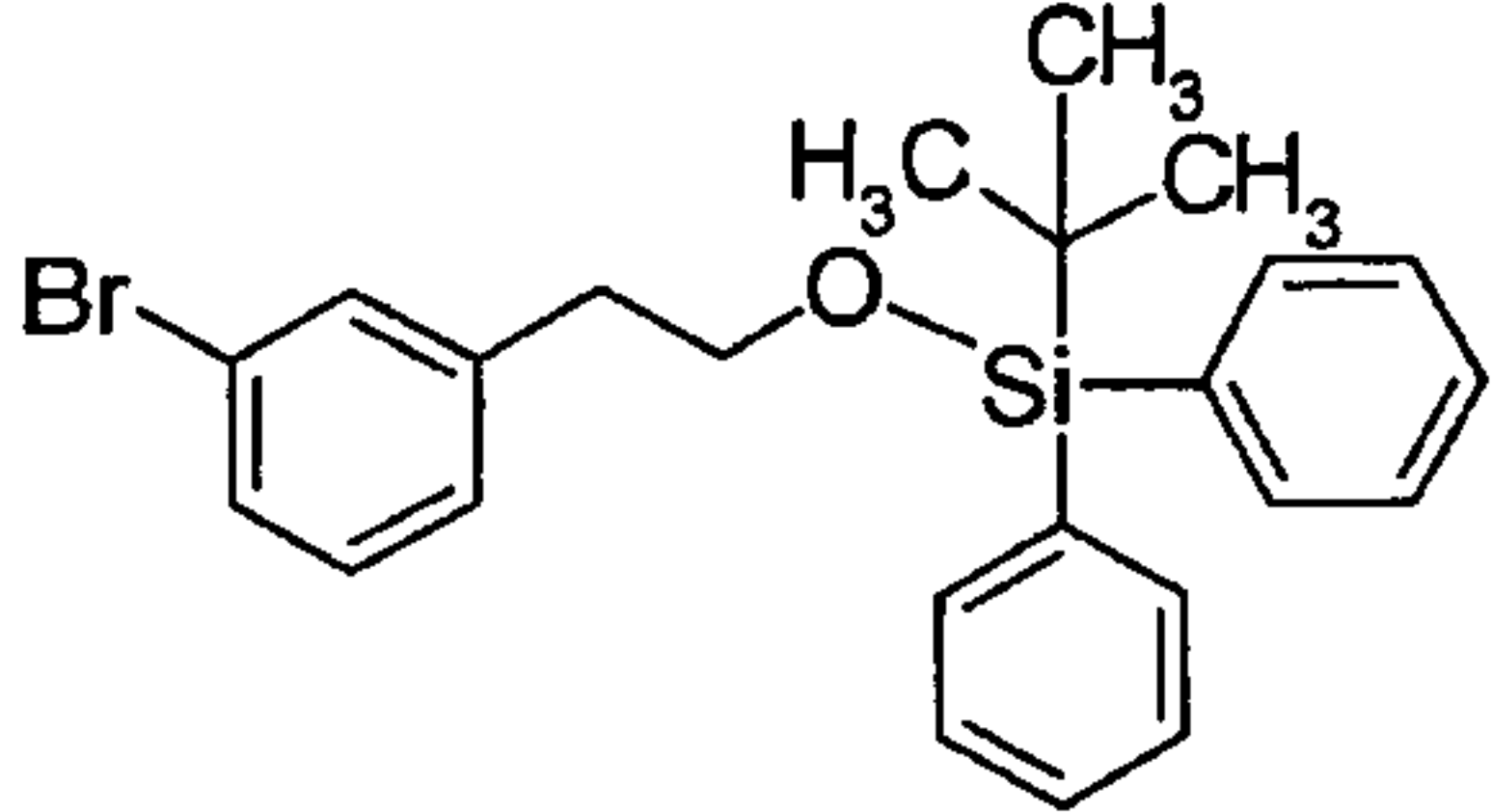
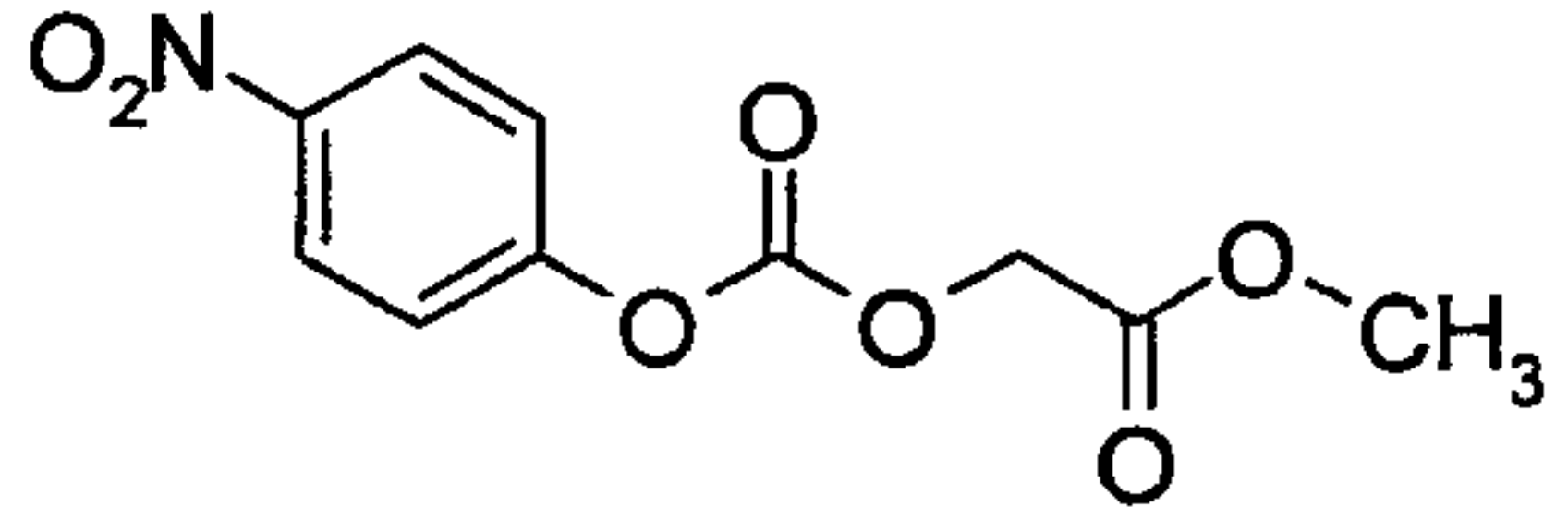
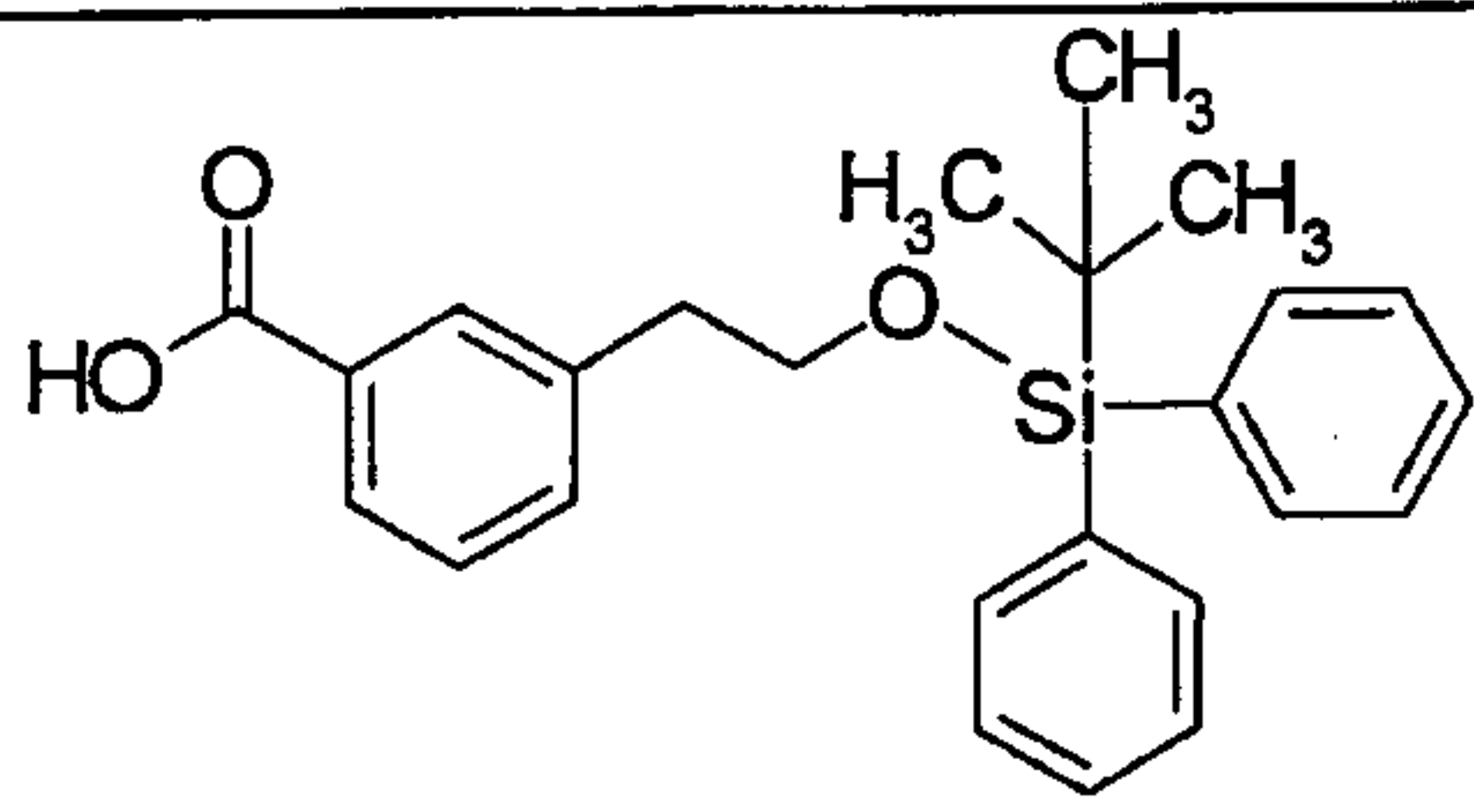
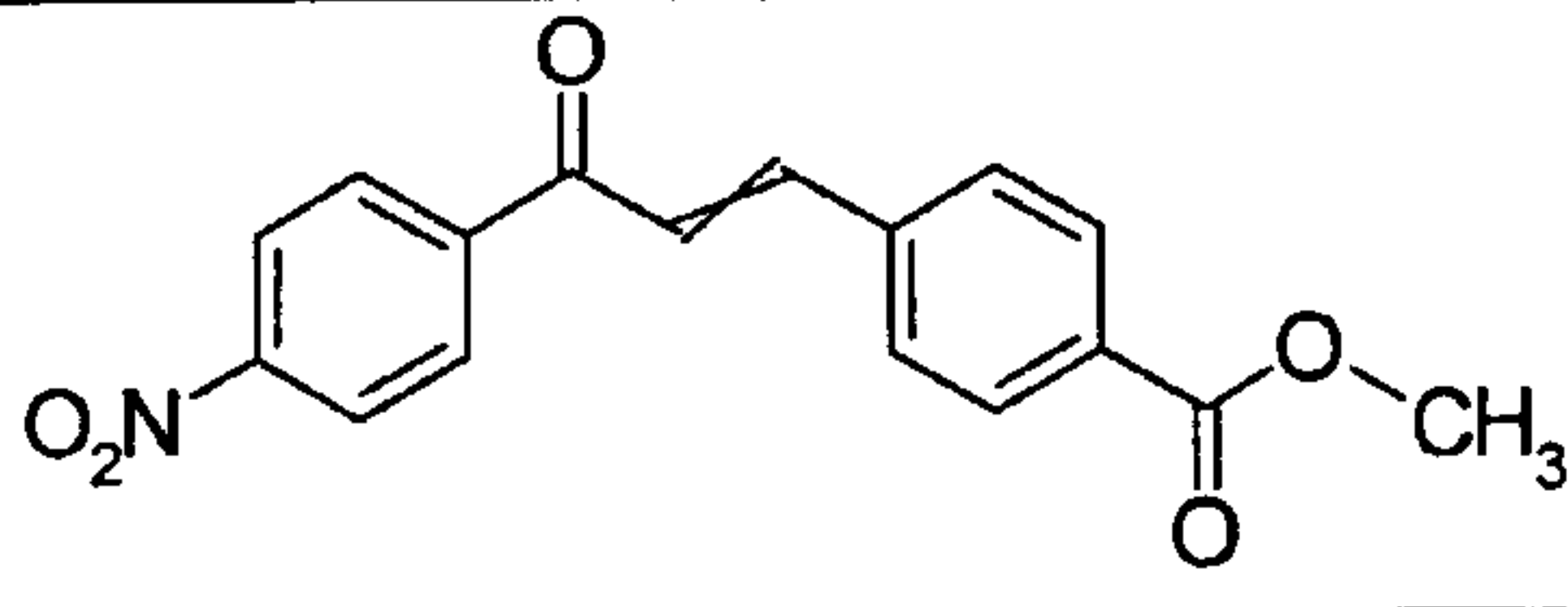
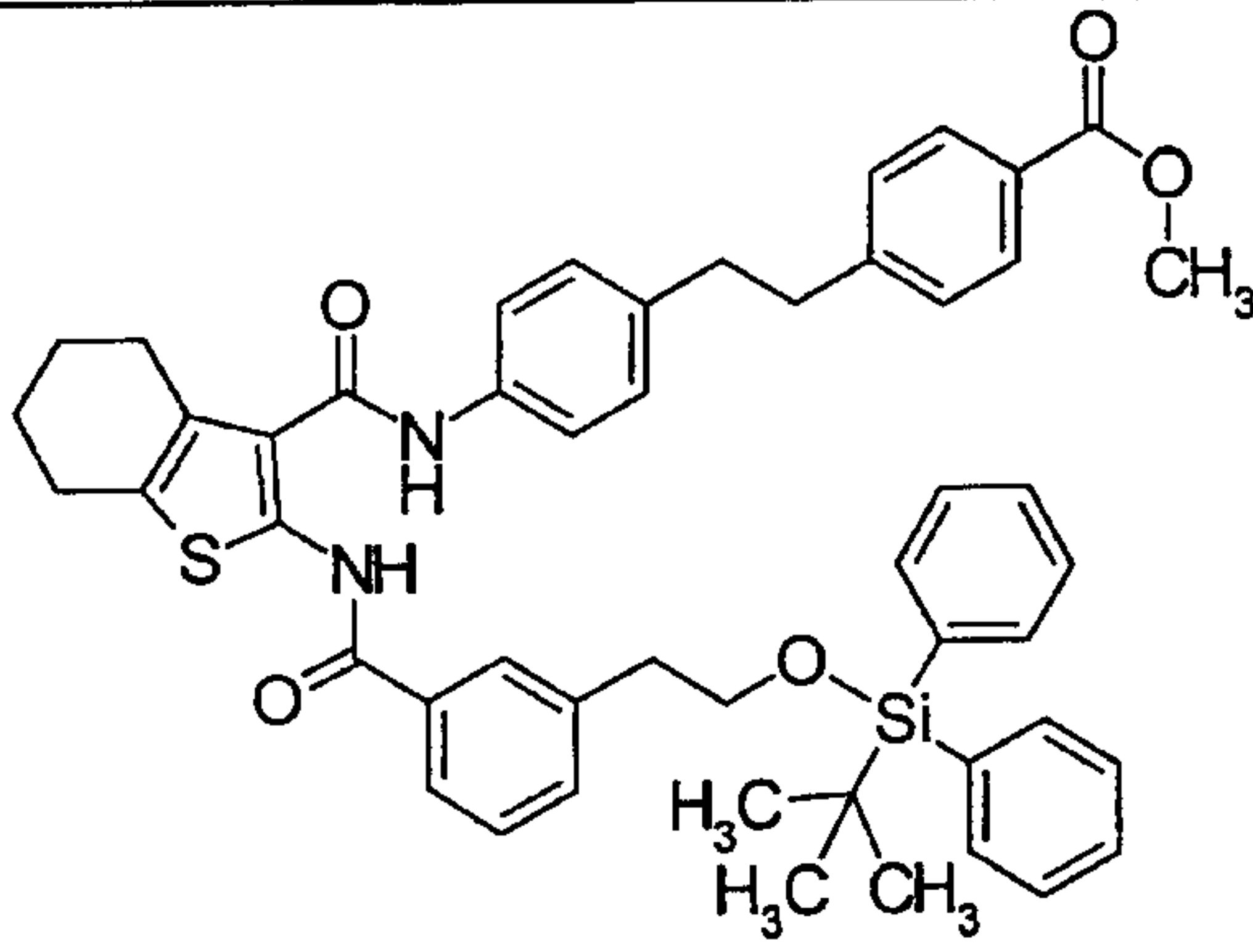
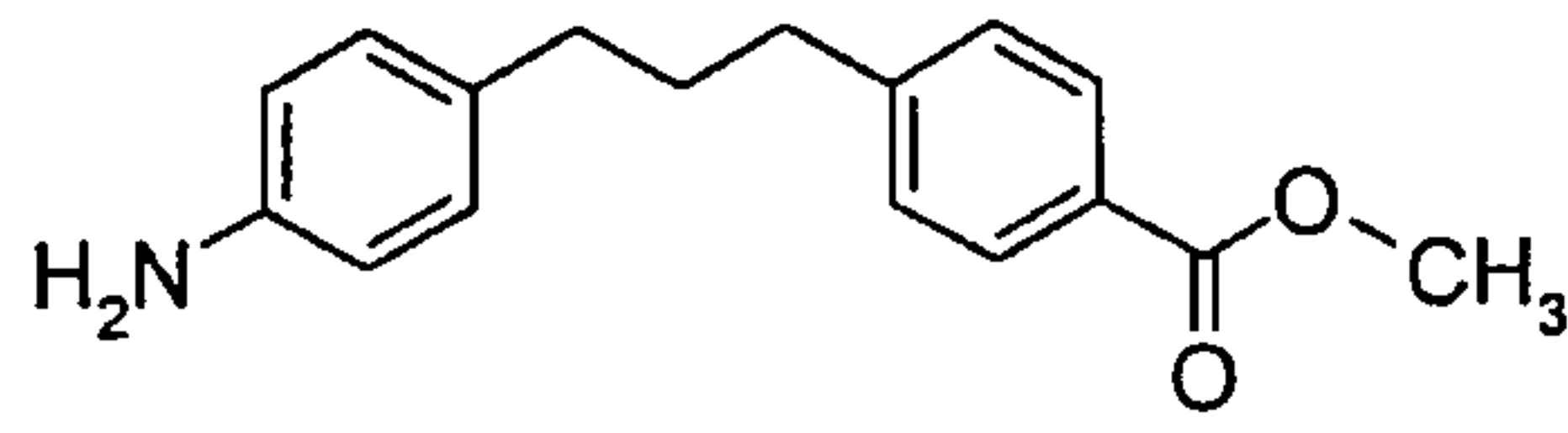
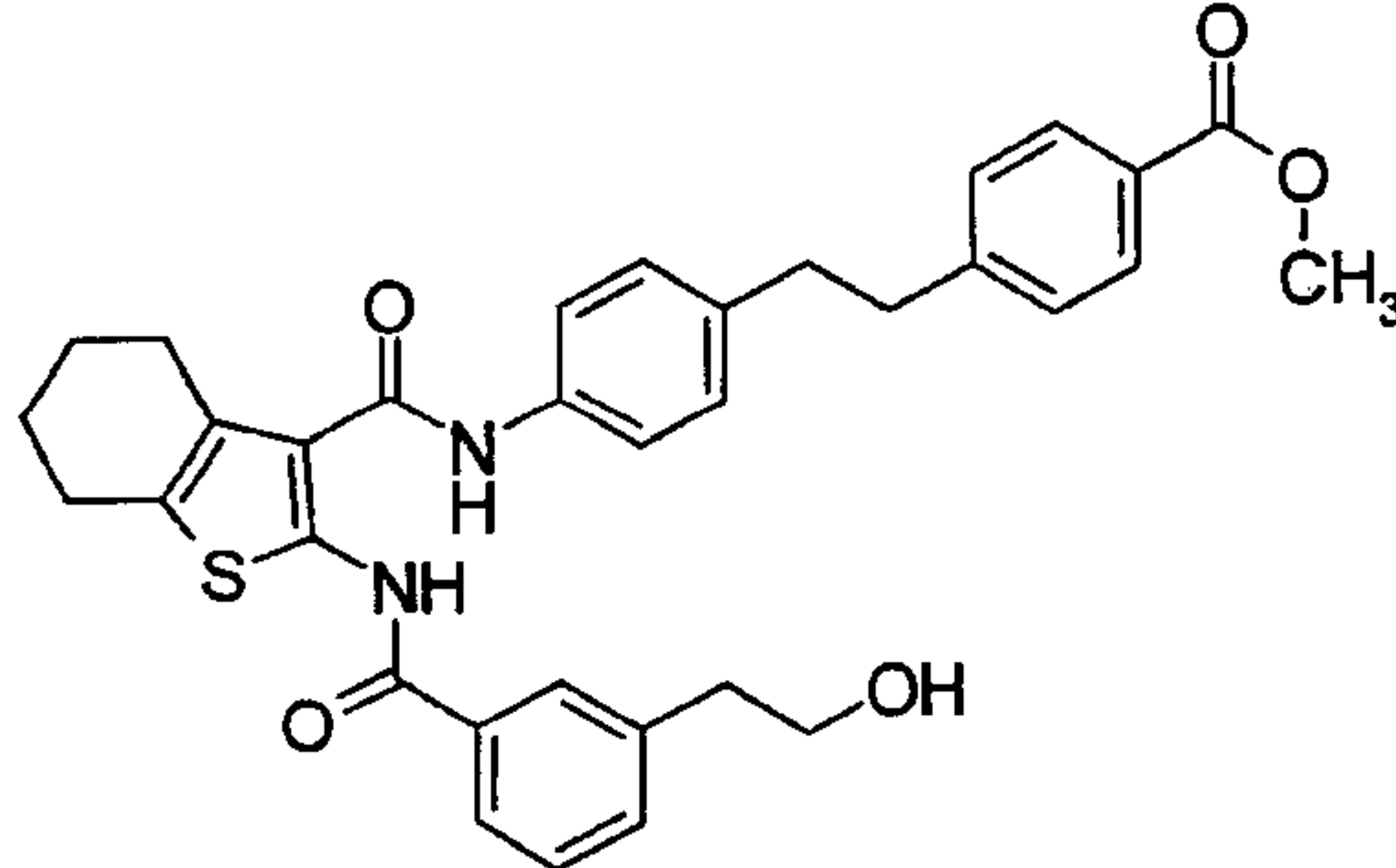
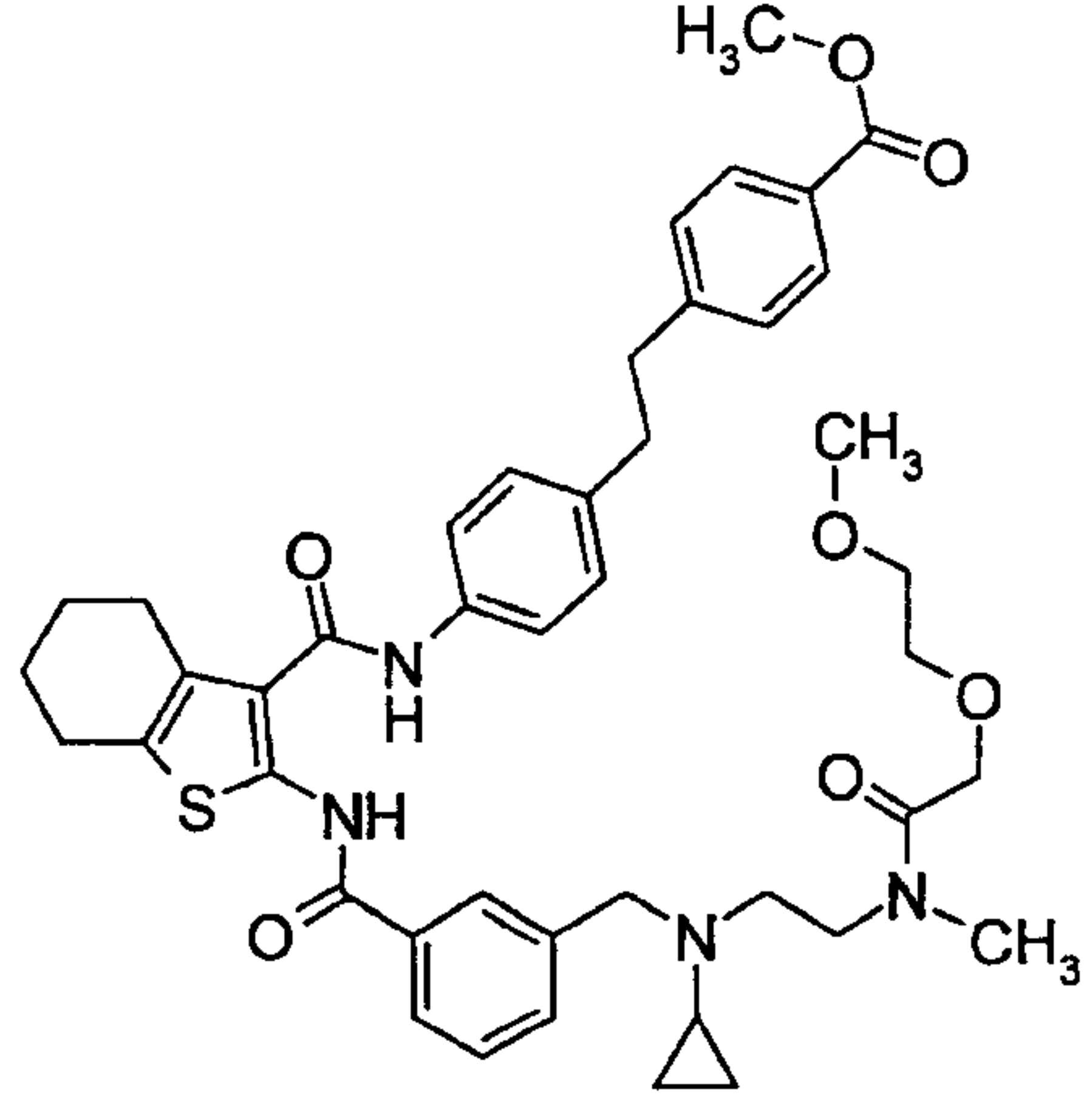
[0148]
[Table 3]

Pr	Str	Pr	Str
1		8	
2		9	
3		10	
4		11	
5			
6			
7			

[0149]
[Table 4]

Pr	Str	Pr	Str
12		15	
13		16	
14		17	

[0150]
[Table 5]

Pr	Str	Pr	Str
18		23	
19		24	
20		25	
21		26	
22		27	

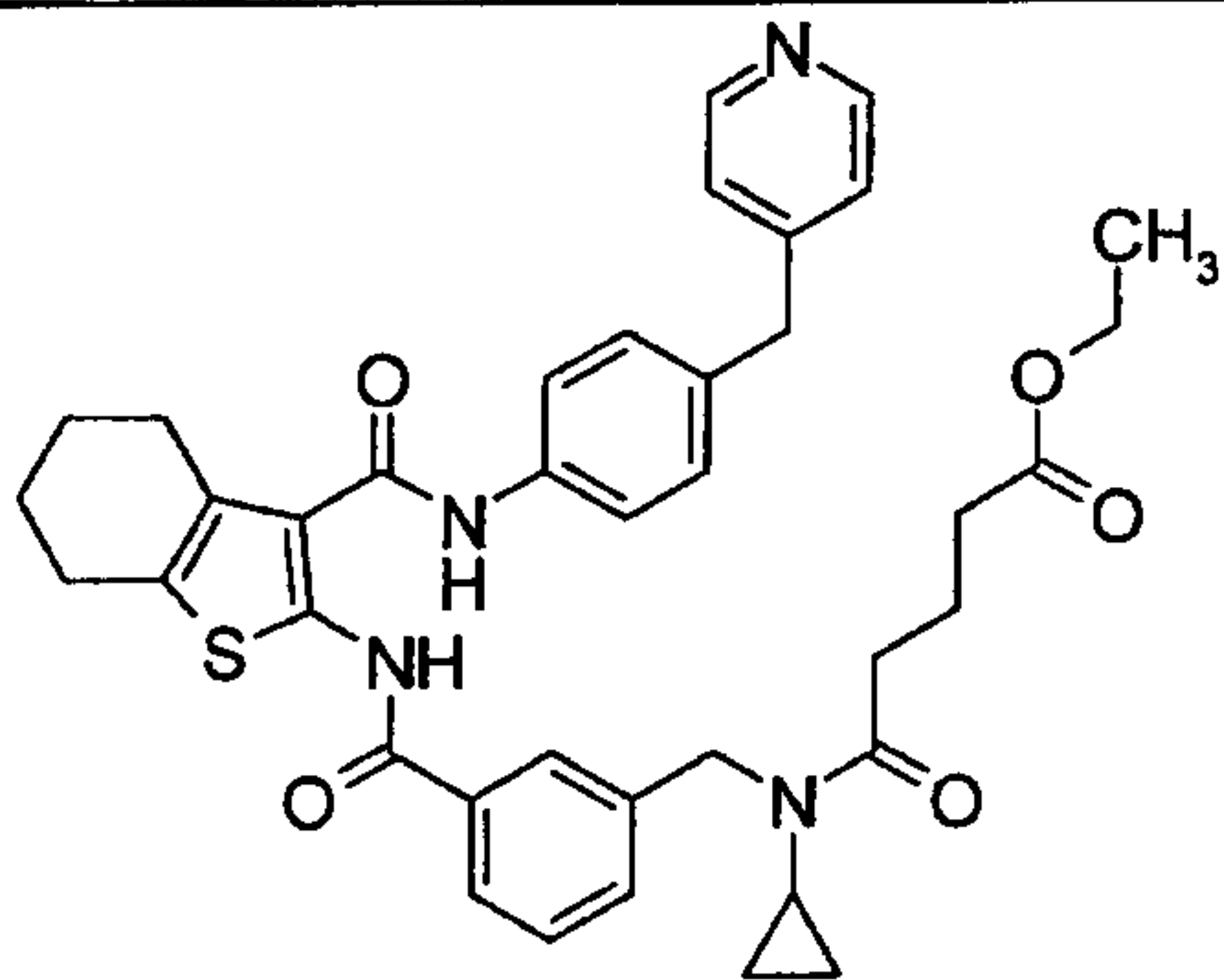
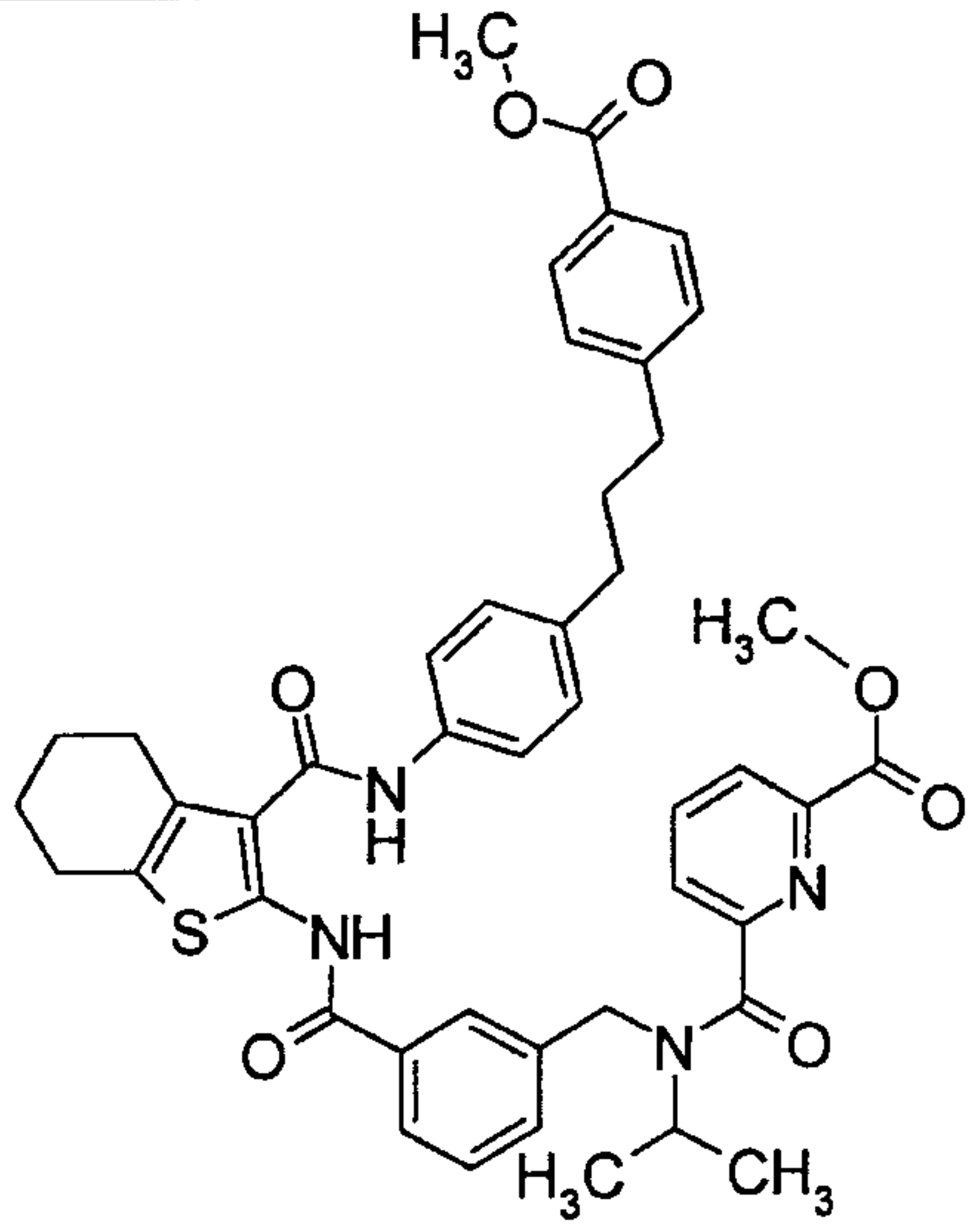
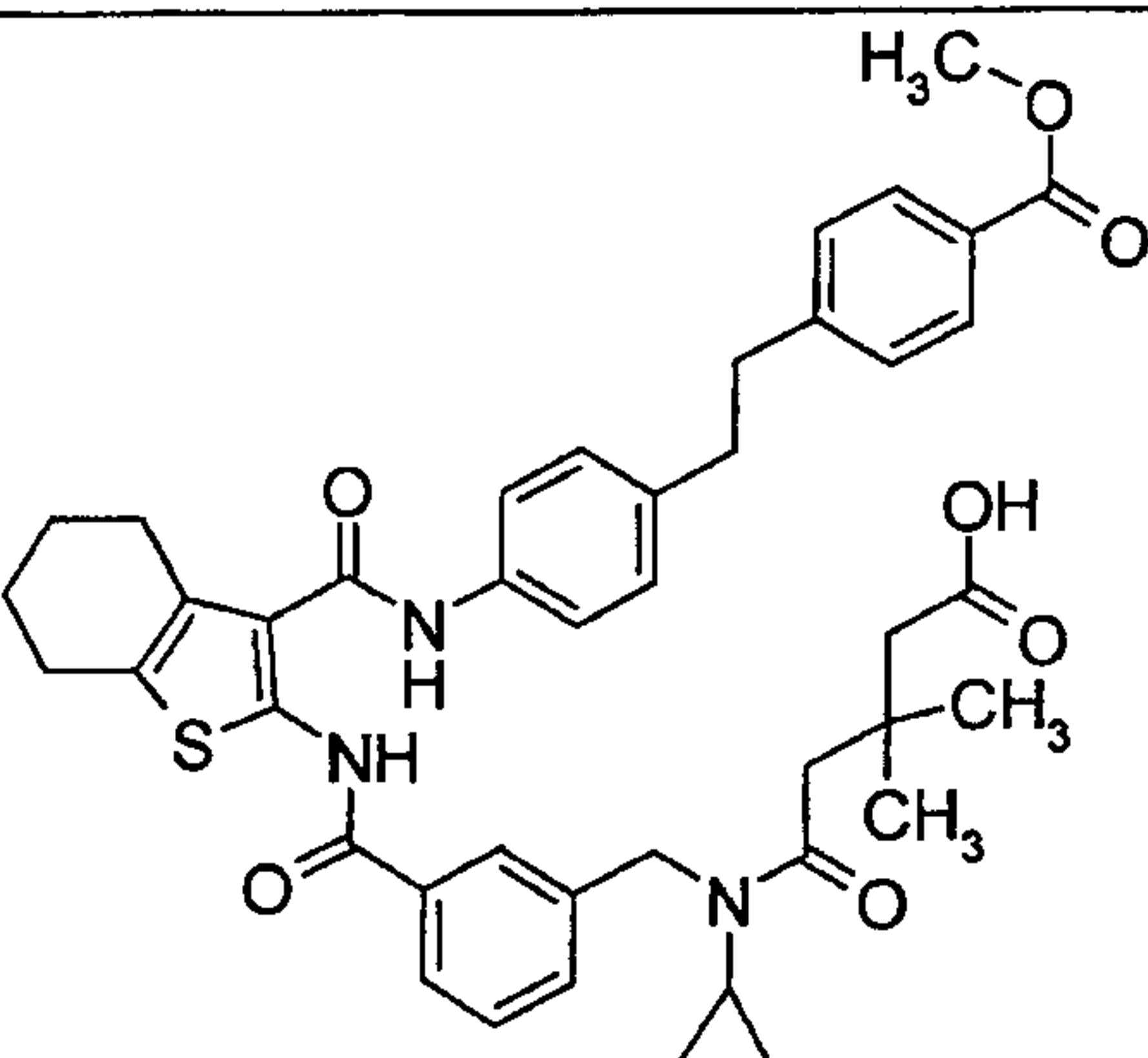
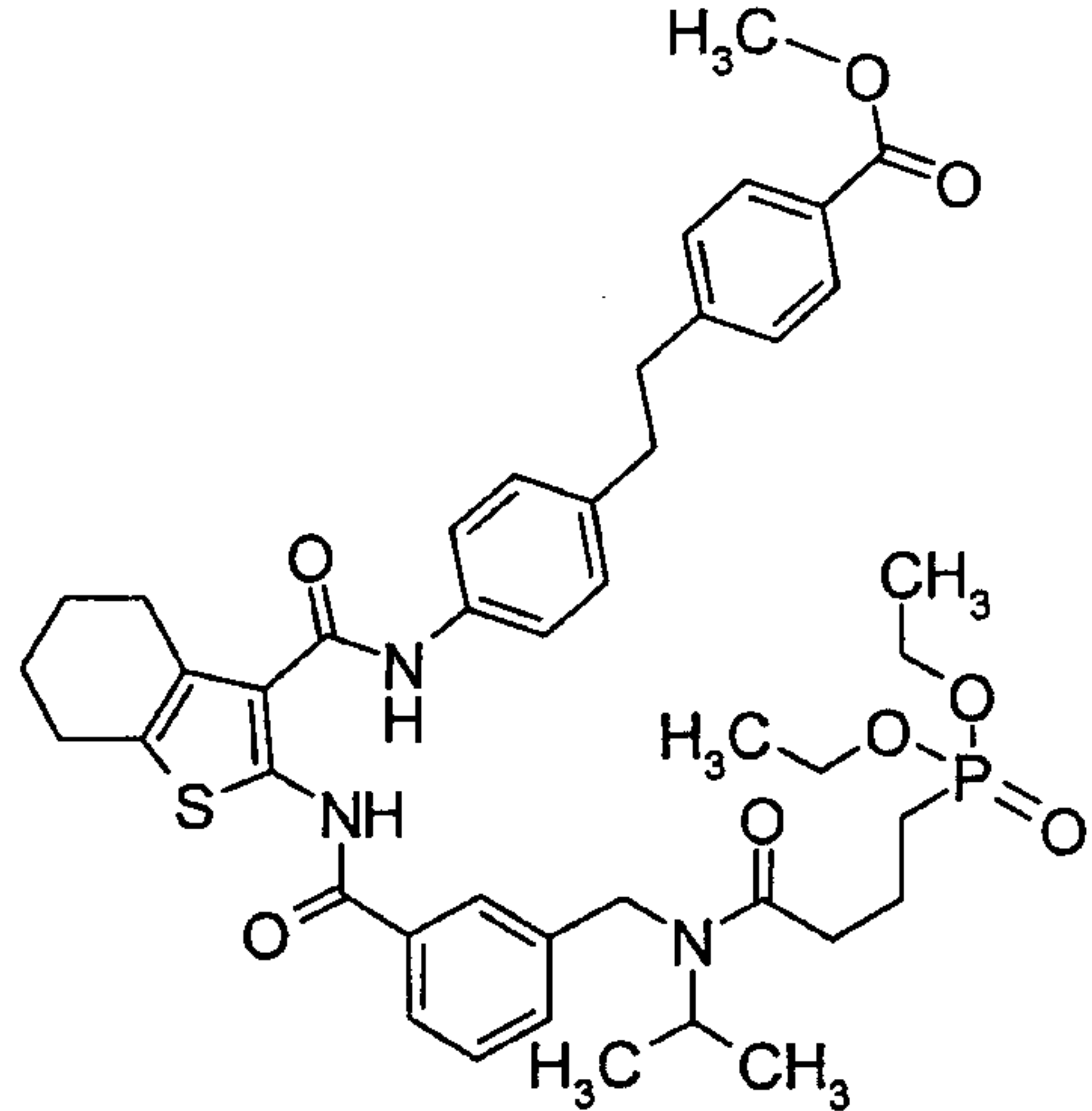
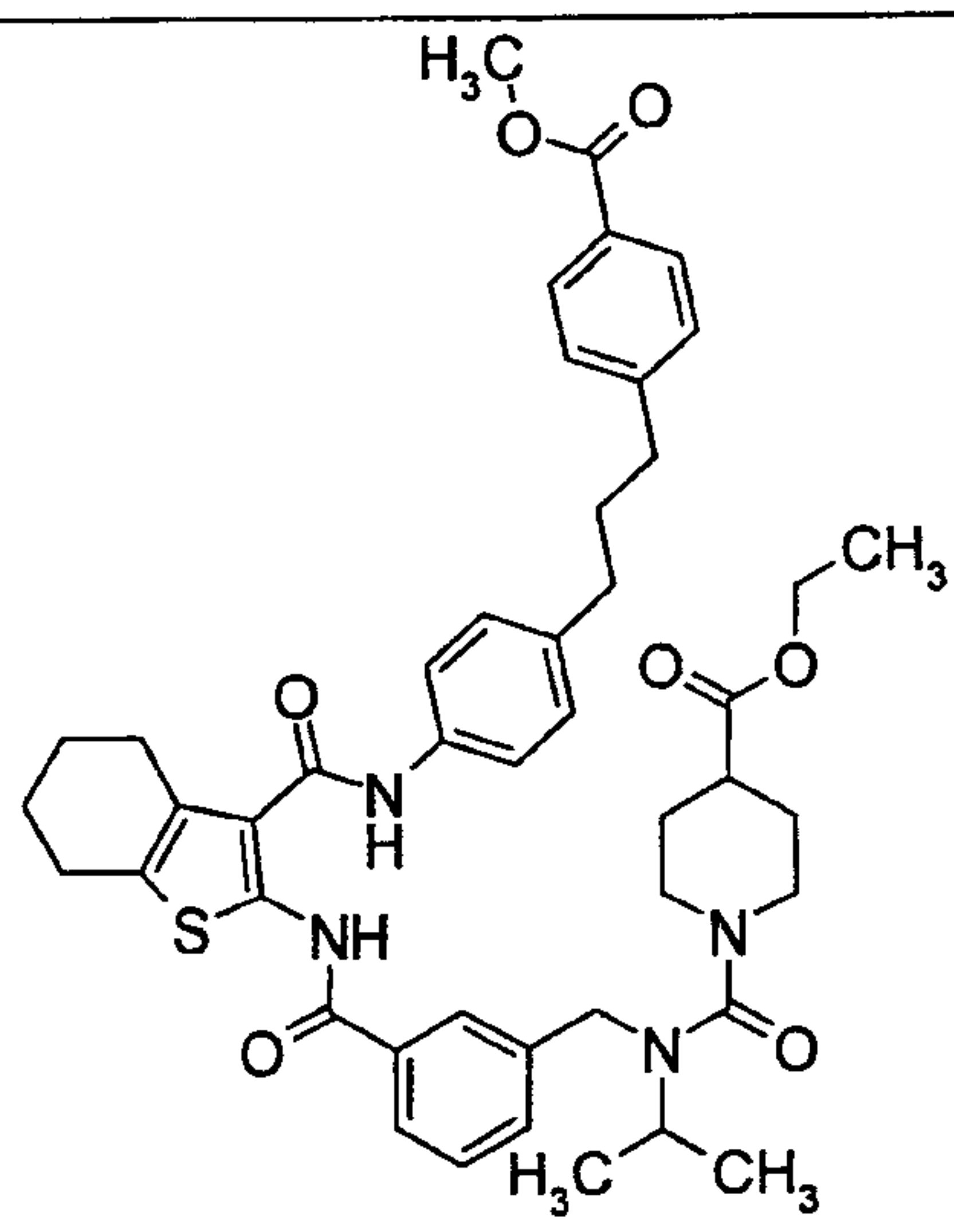
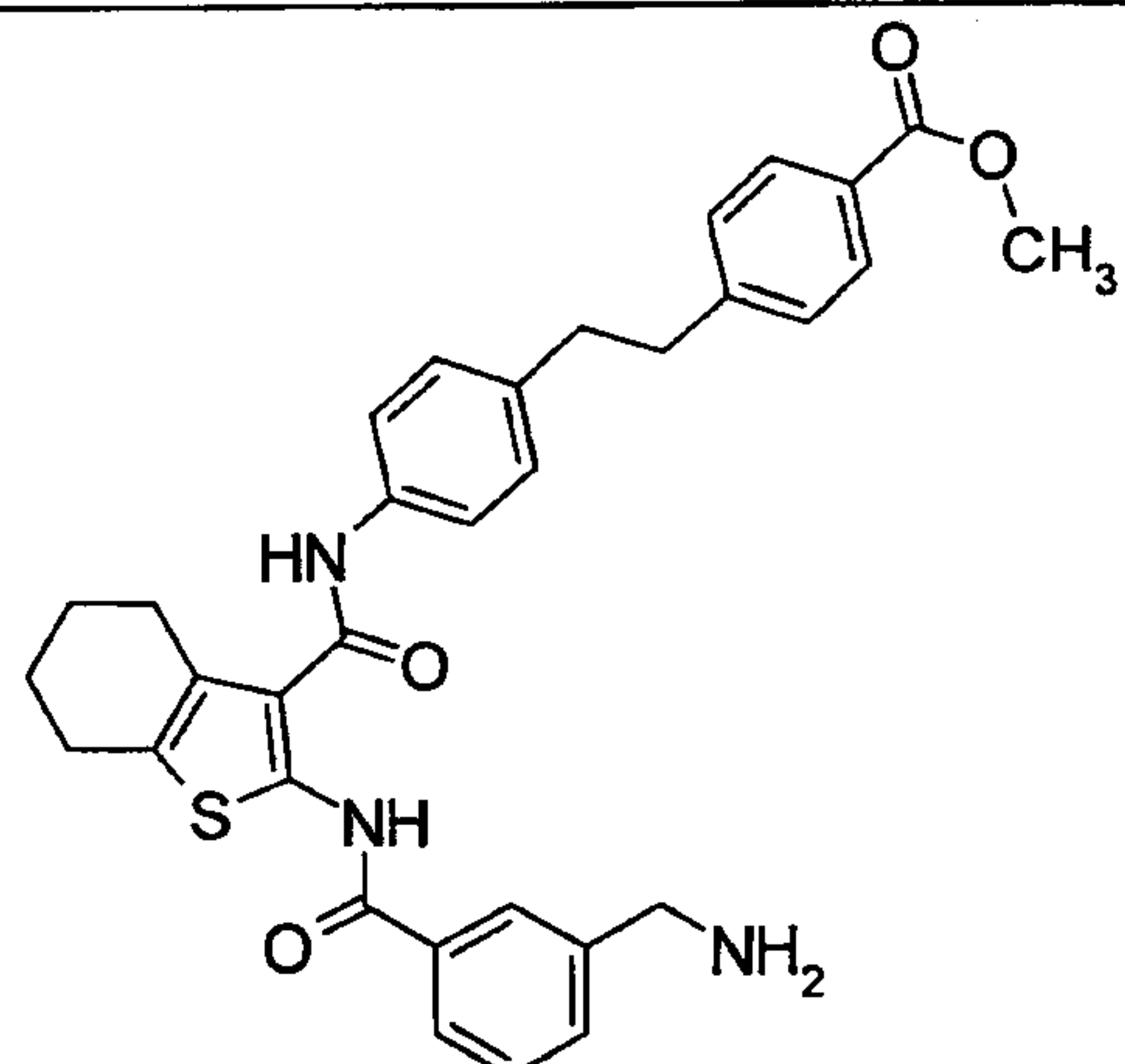
[0151]
[Table 6]

Pr	Str	Pr	Str
28		31	
29		32	
30			

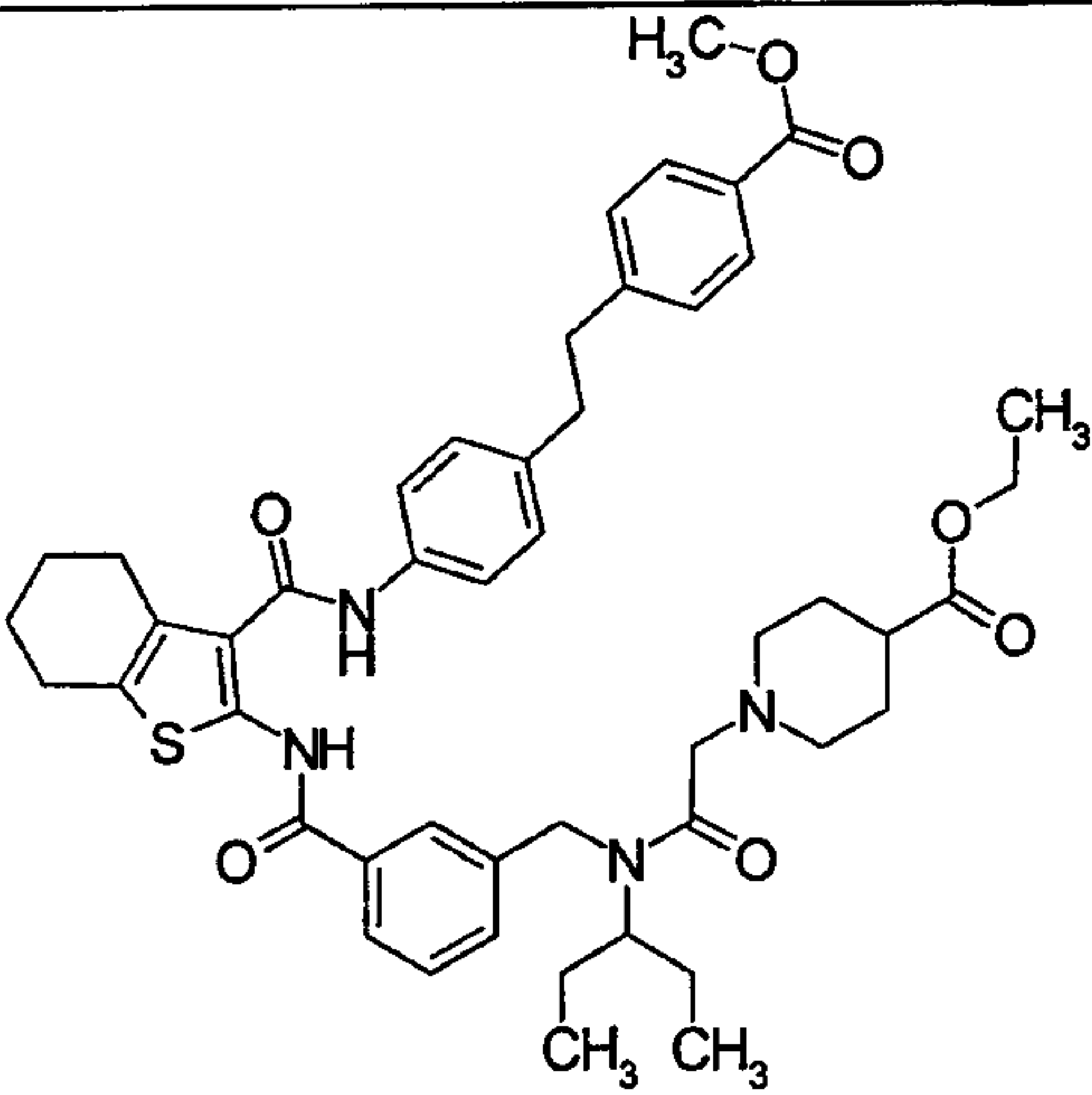
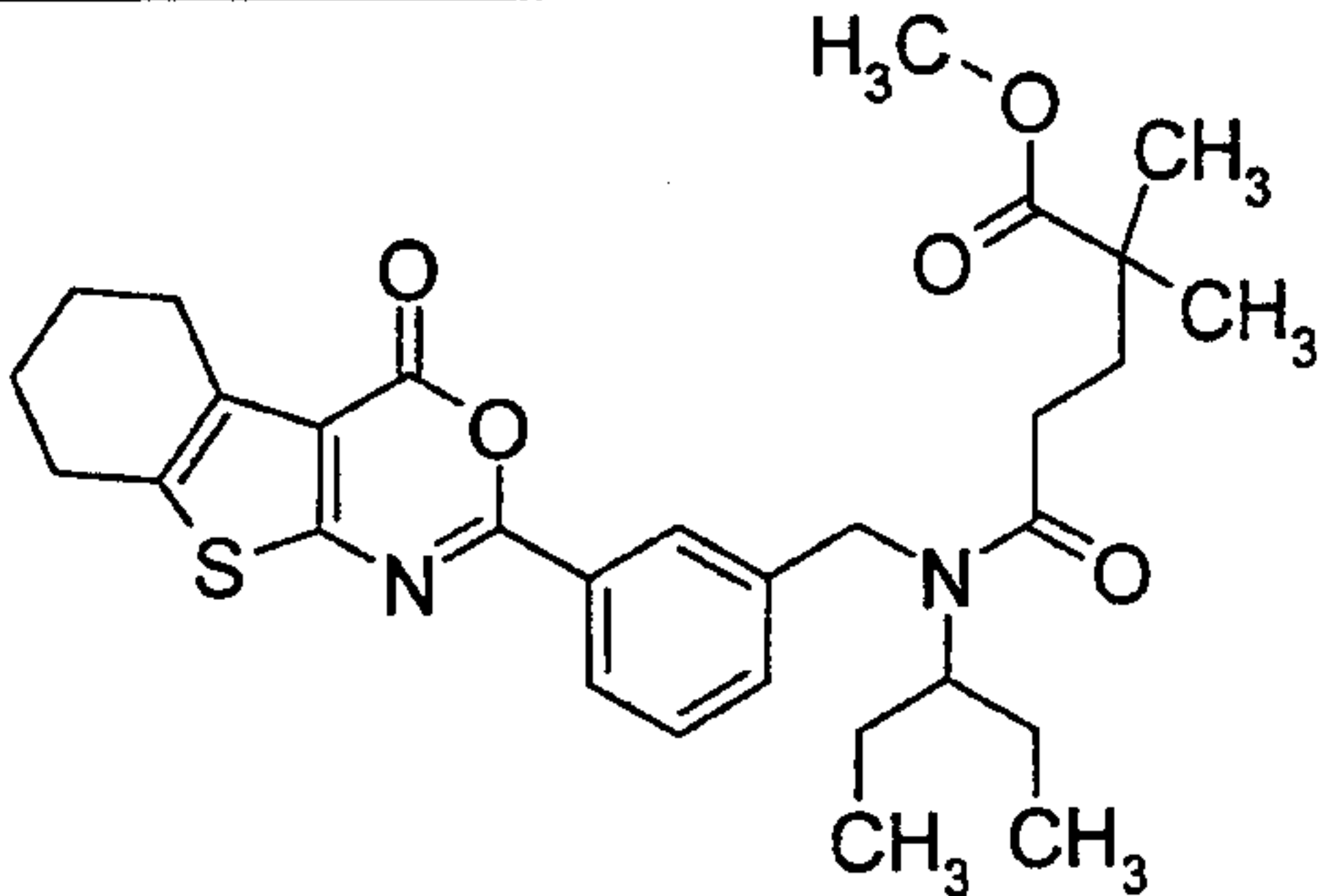
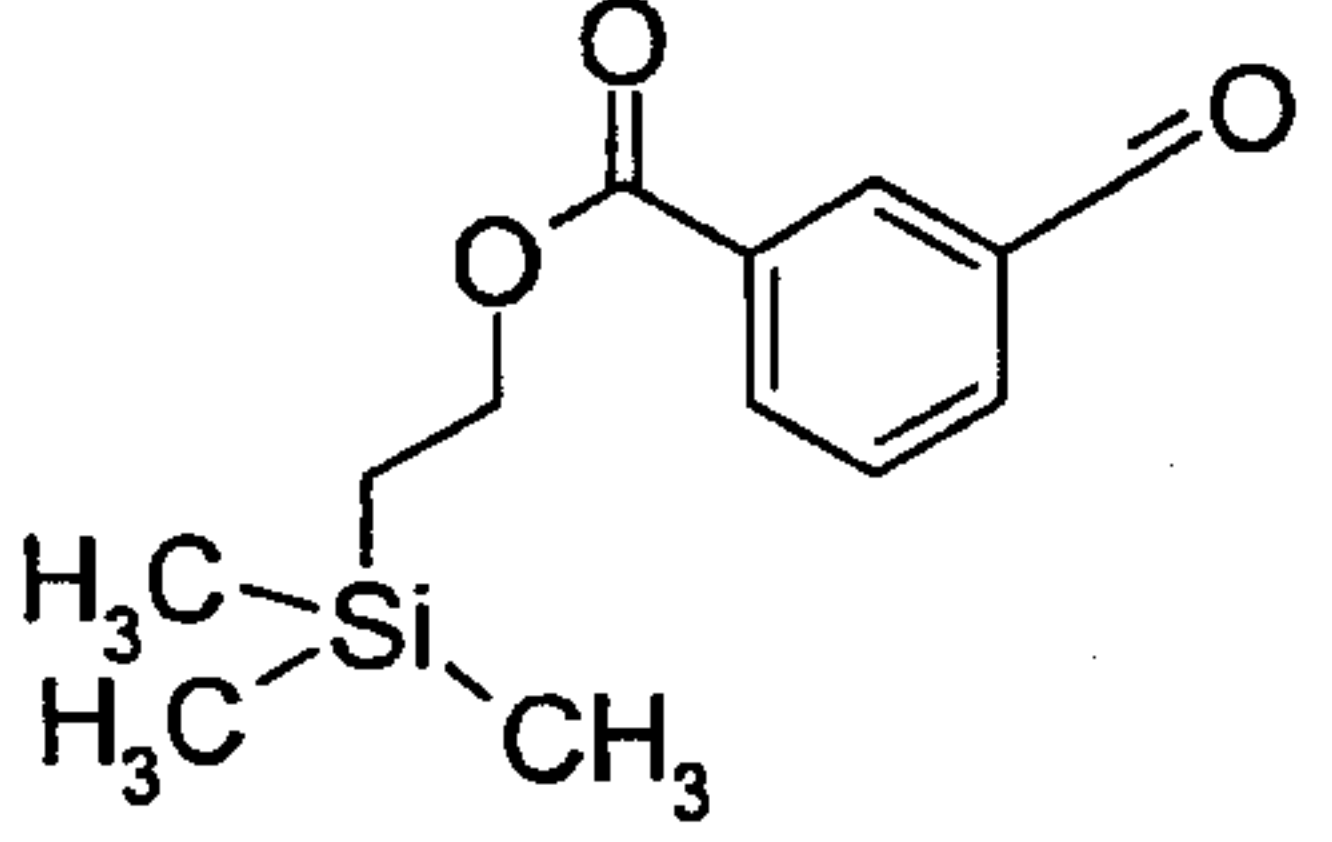
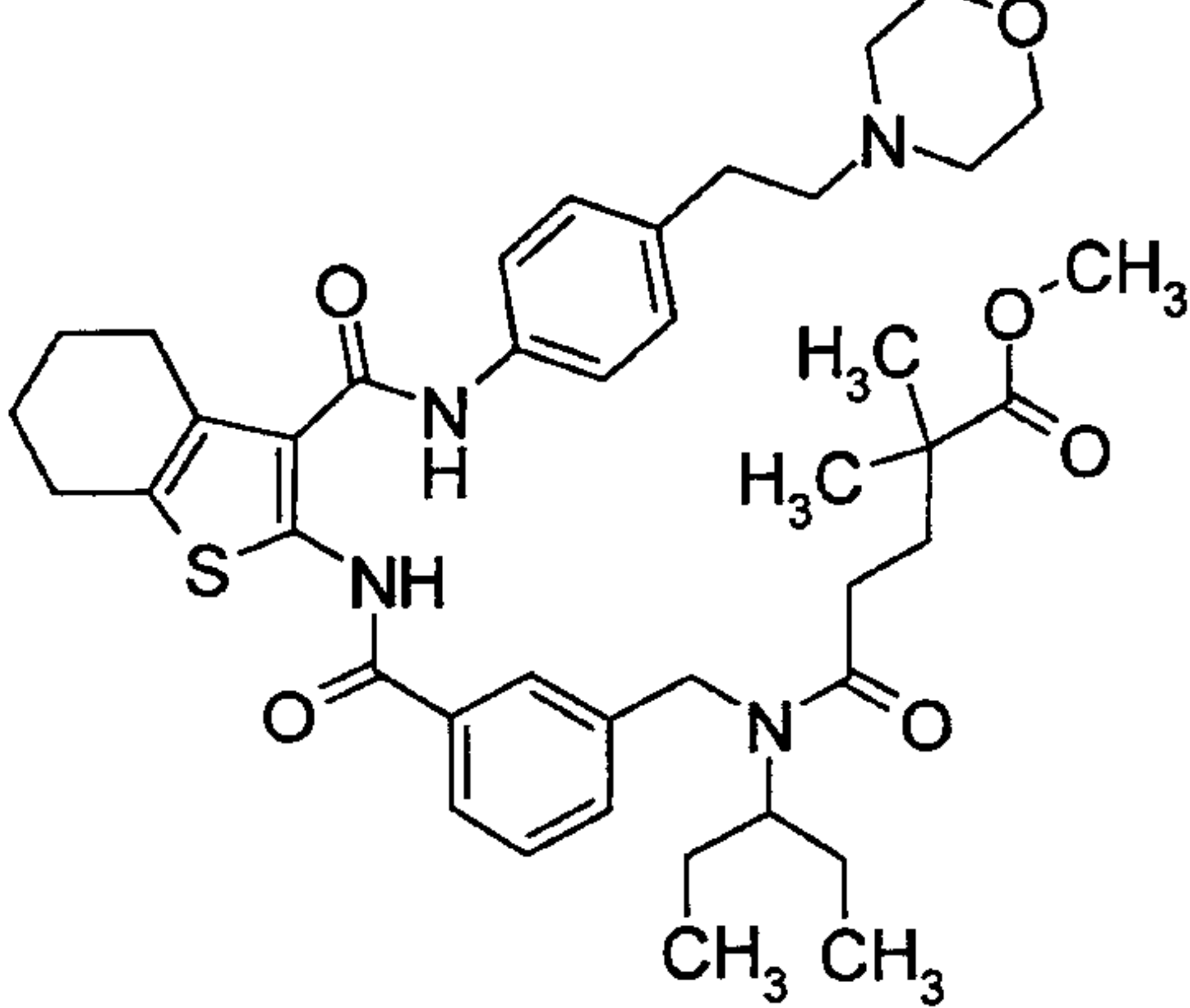
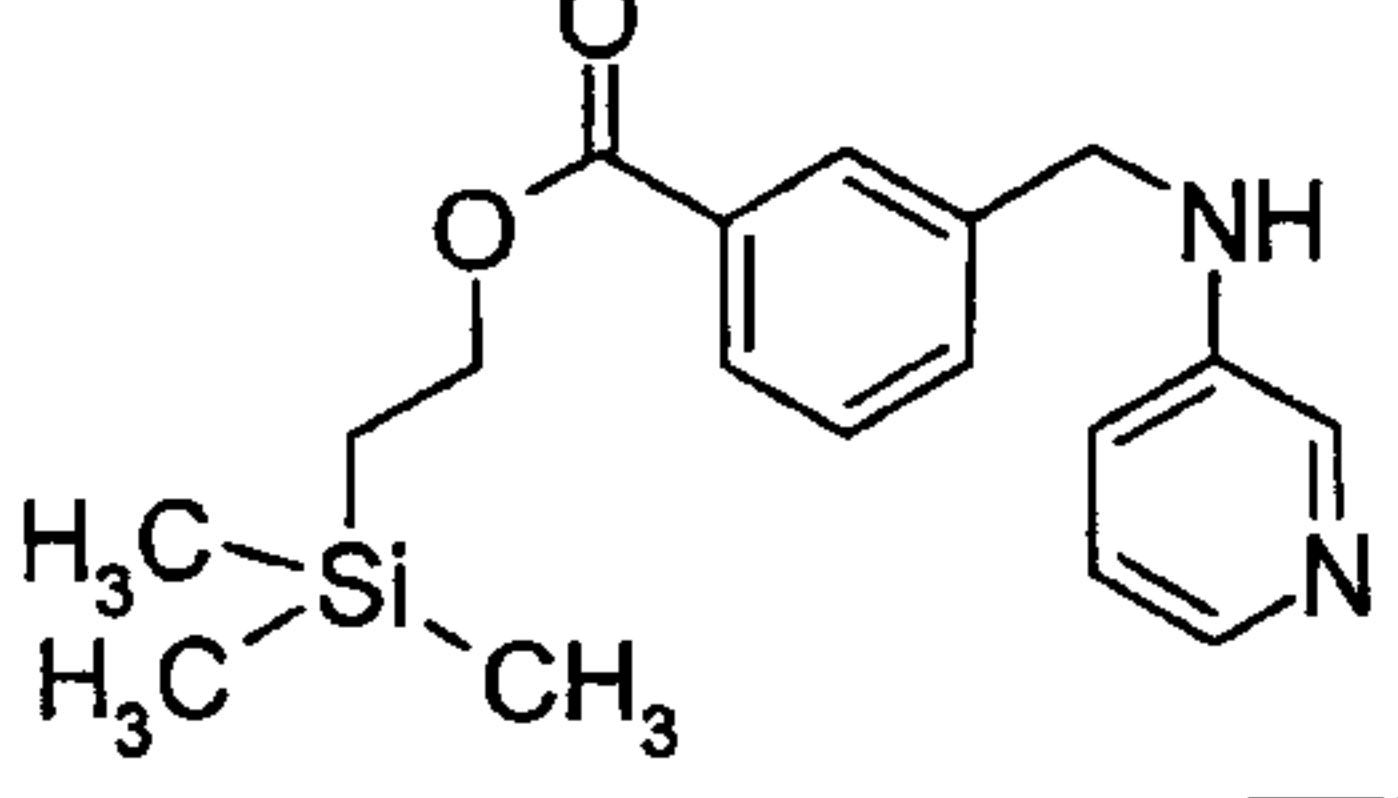
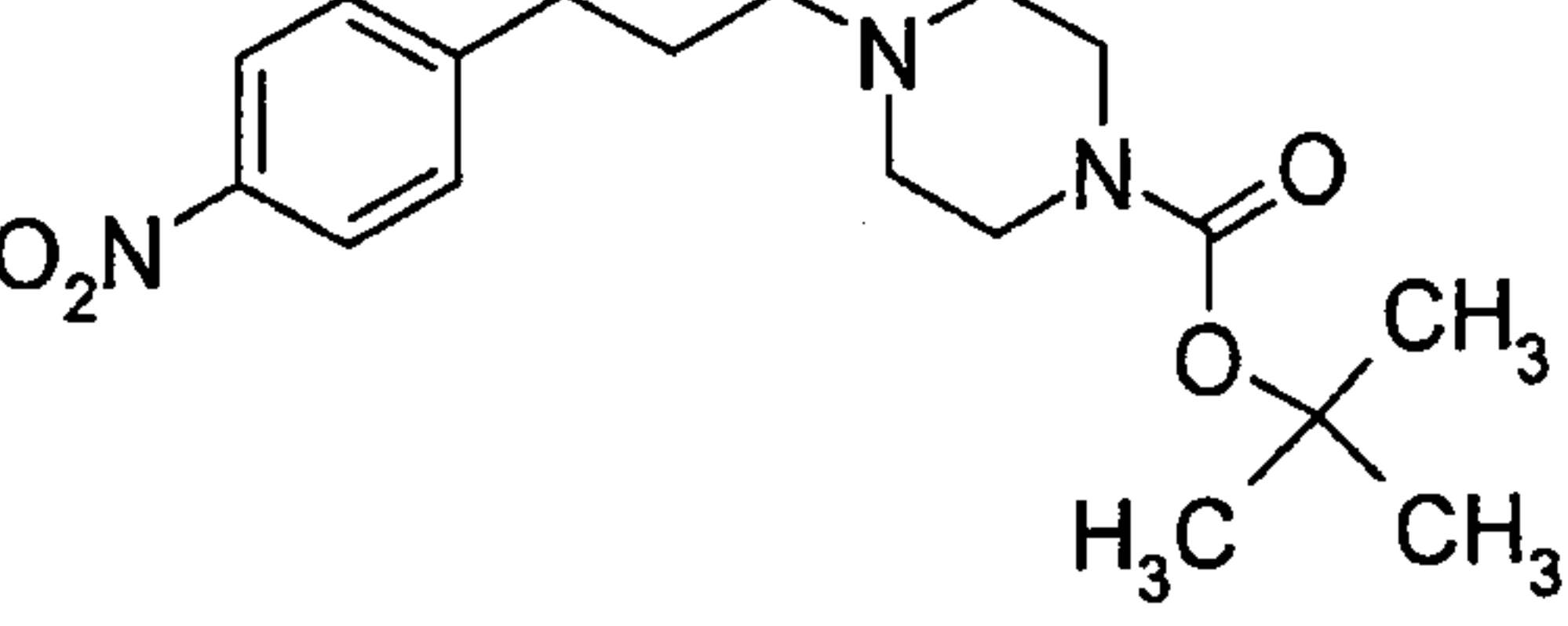
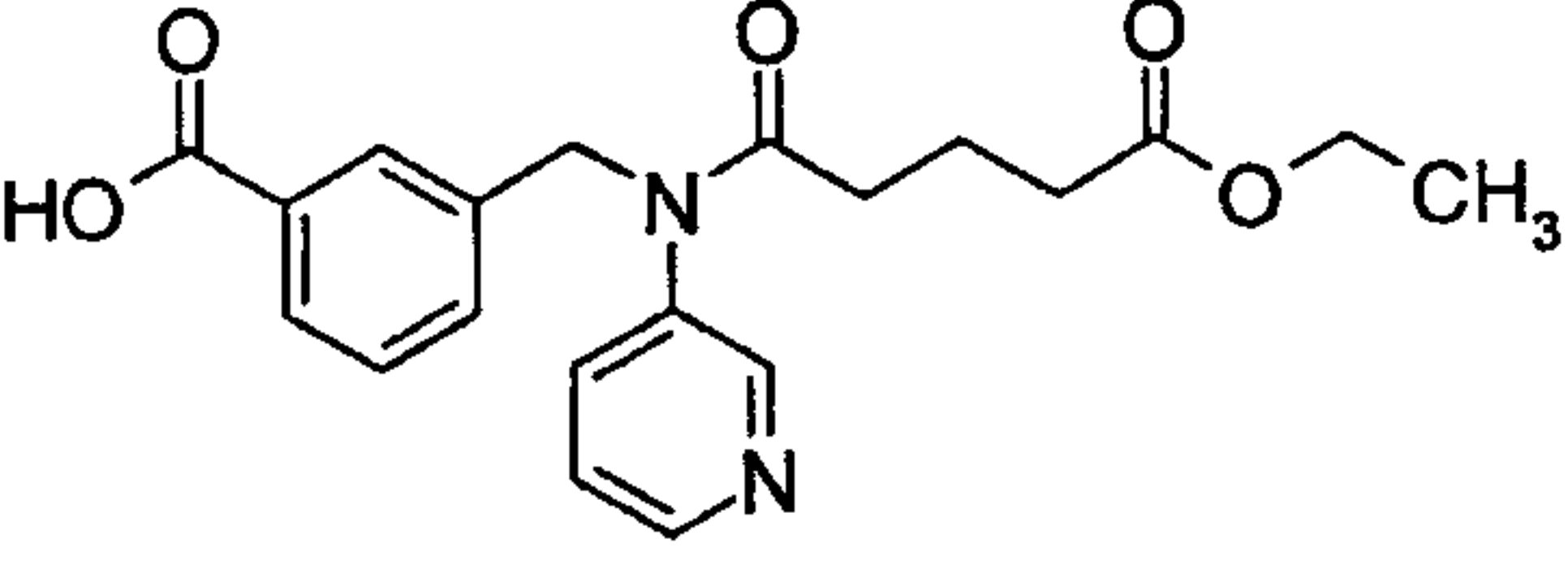
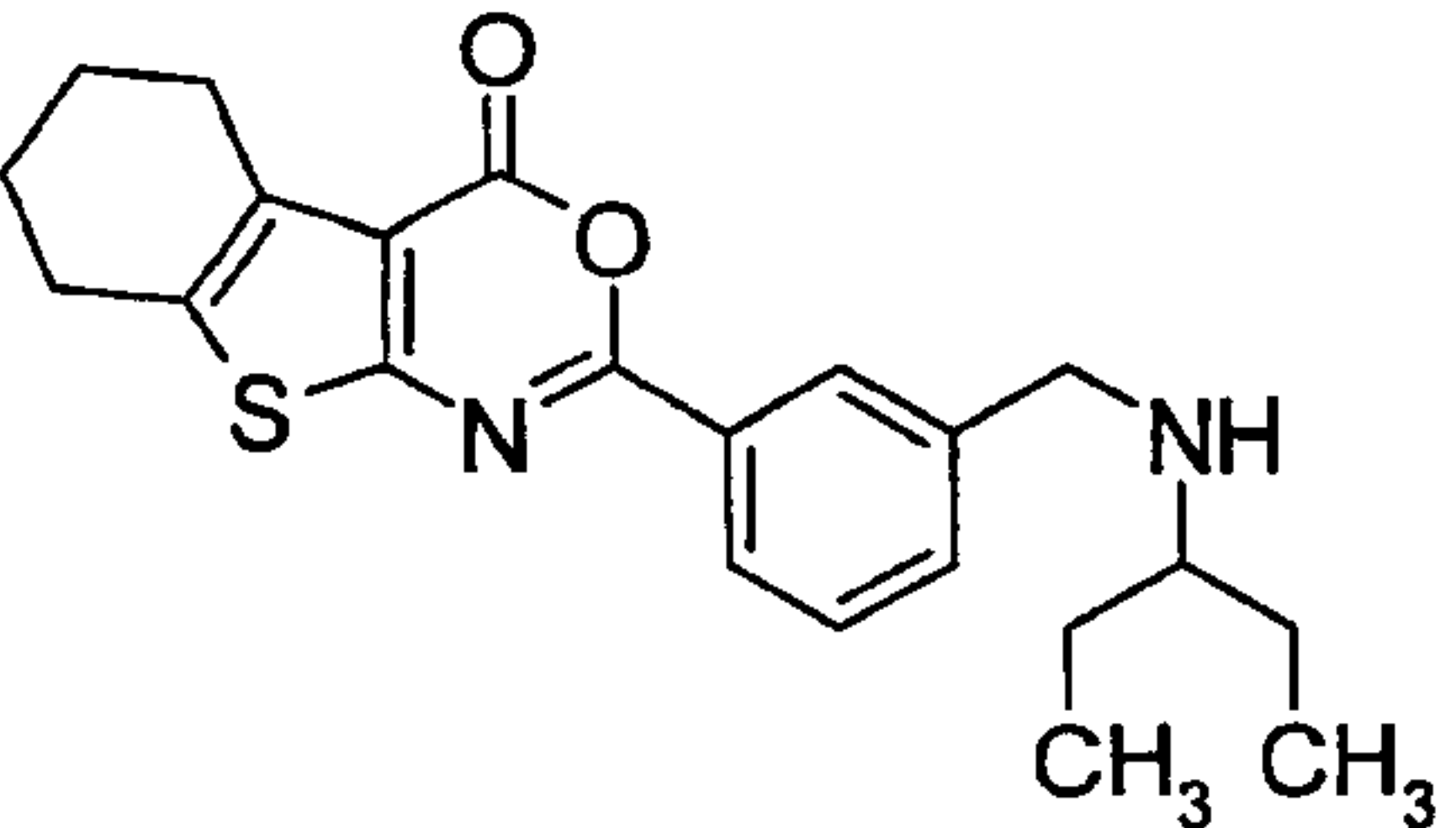
[0152]
[Table 7]

Pr	Str	Pr	Str
33		36	
34		37	
35		38	
	2HCl	39	

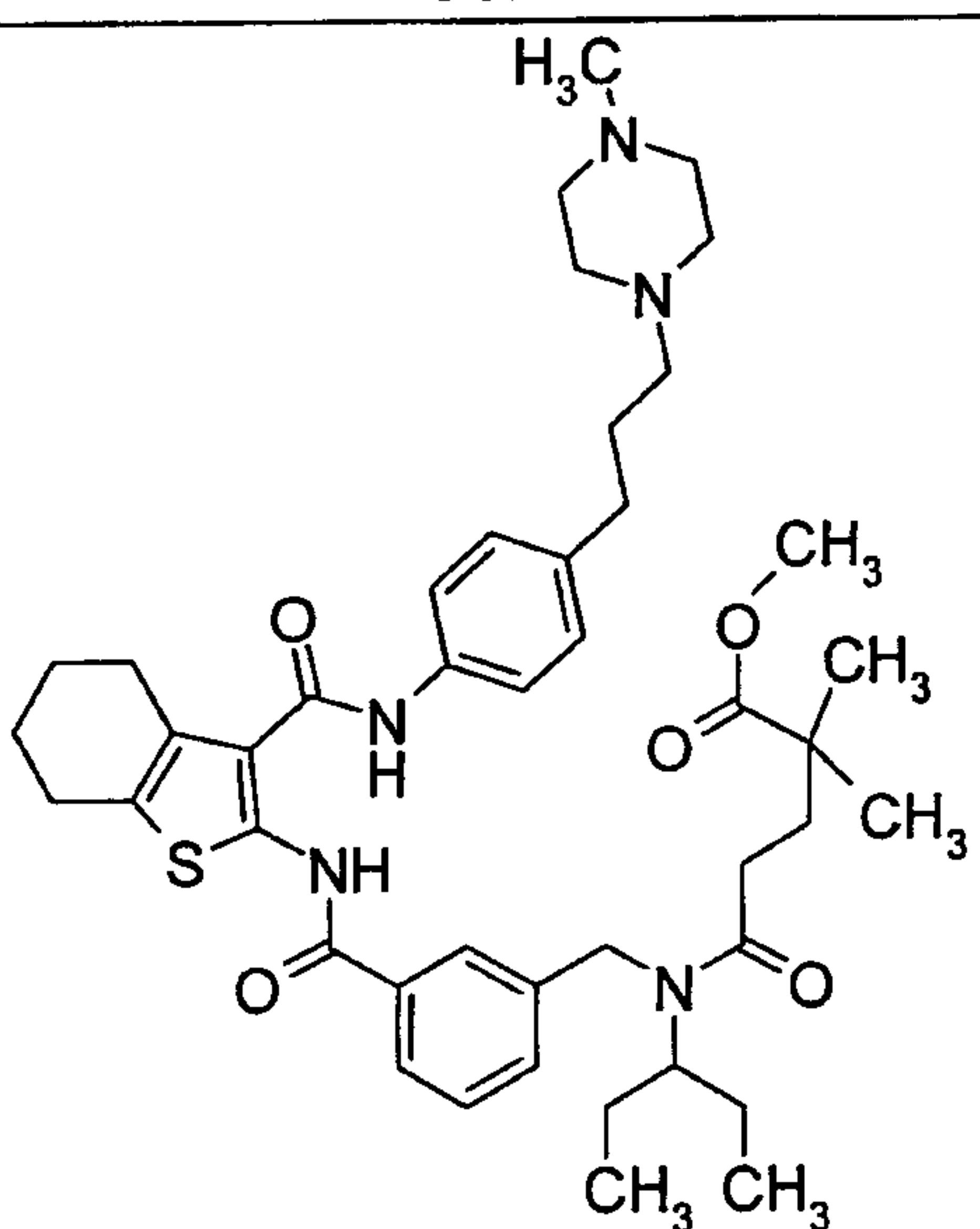
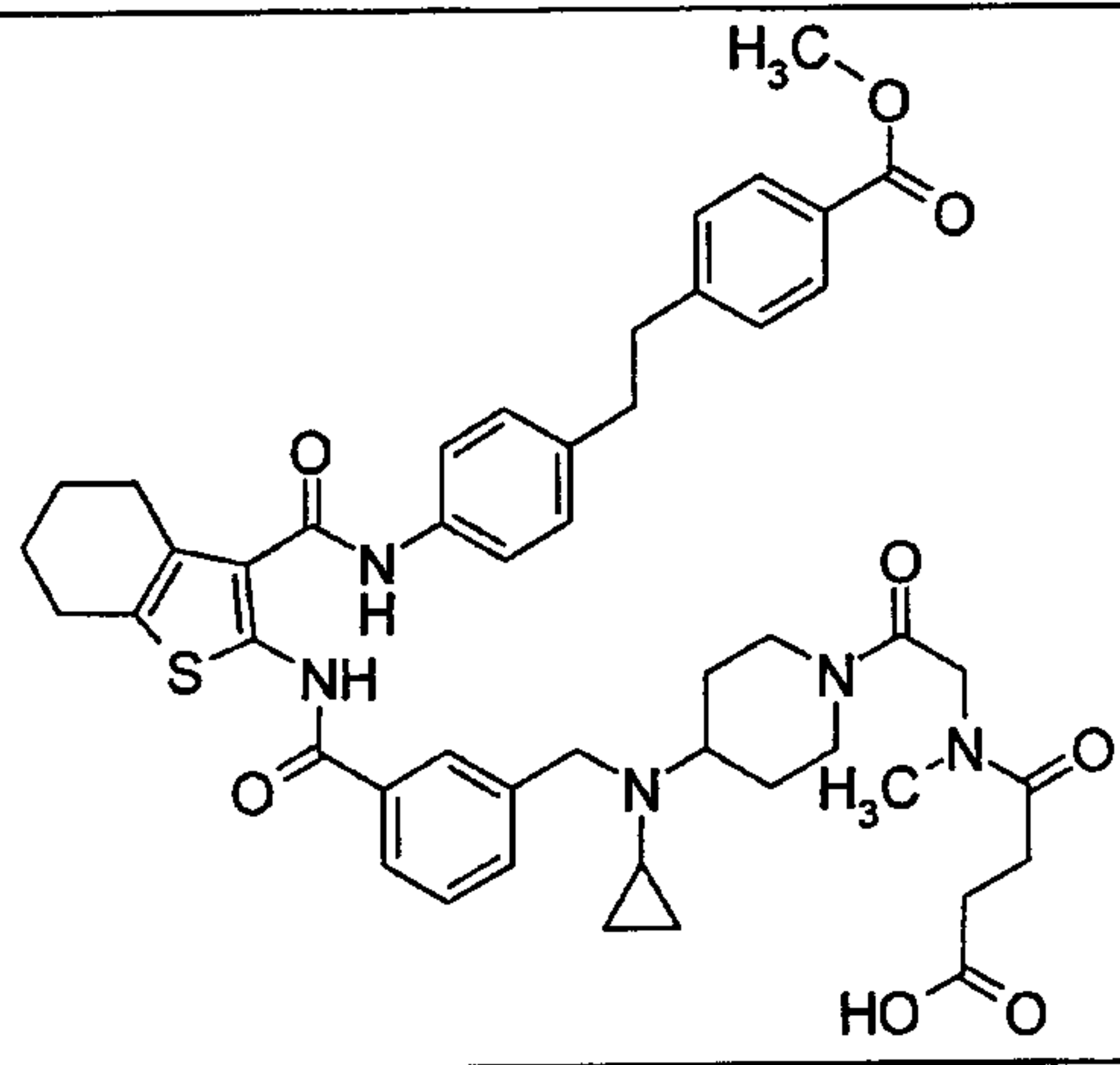
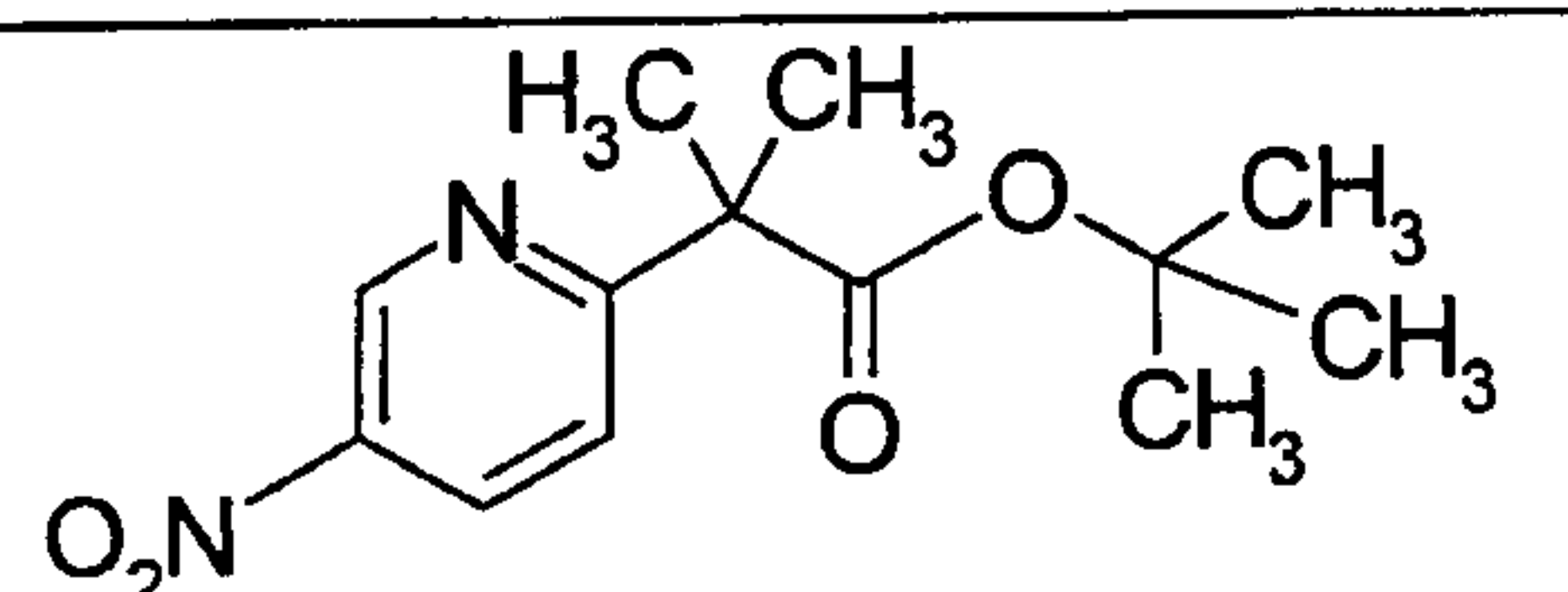
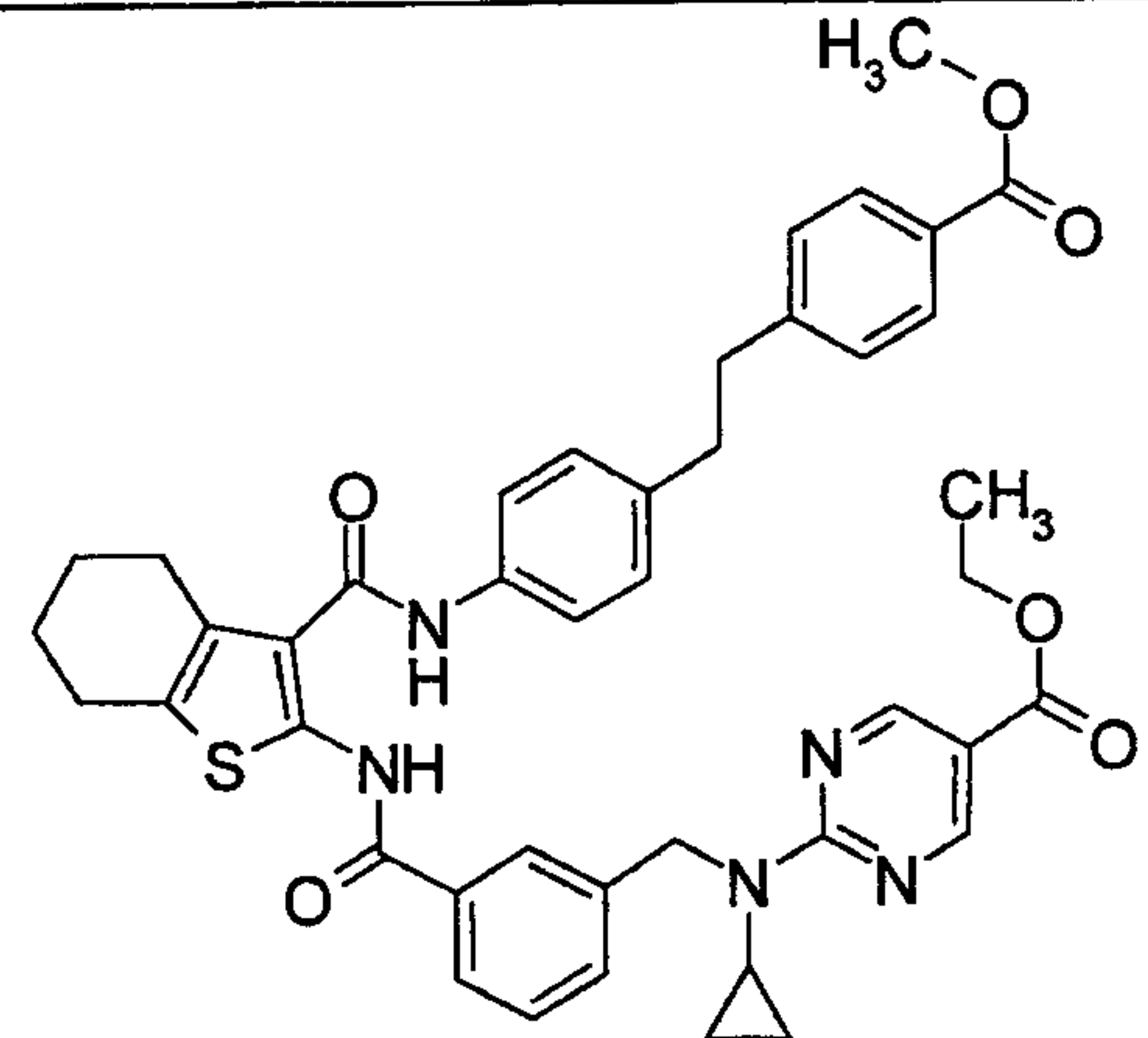
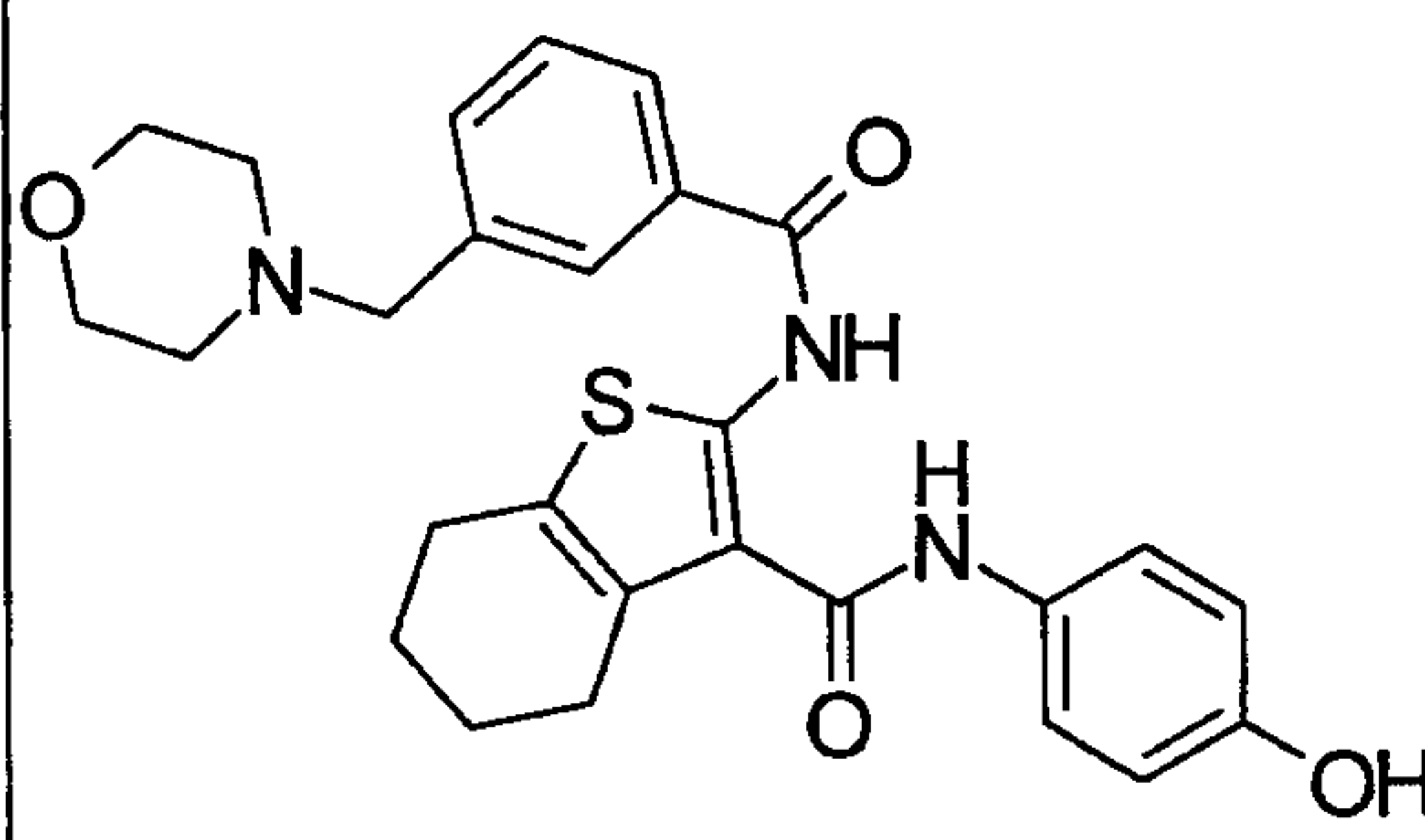
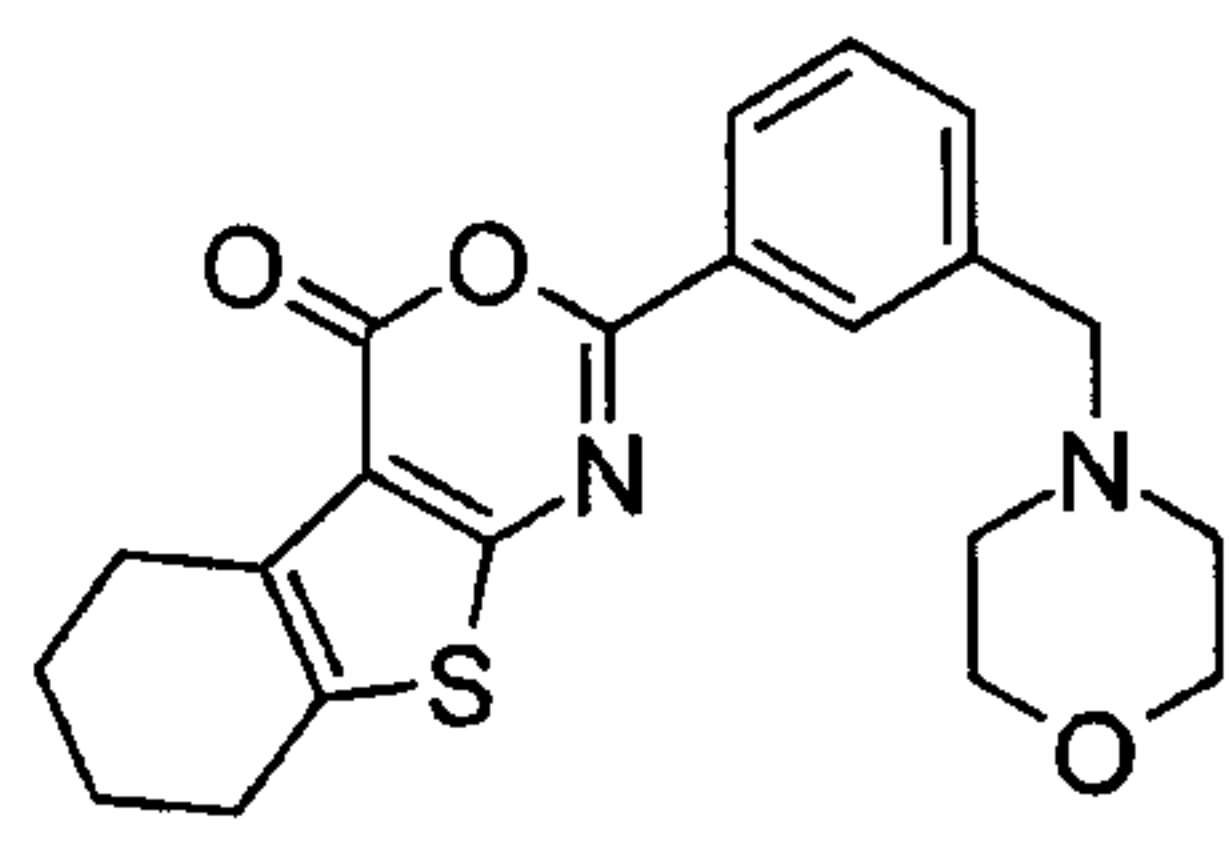
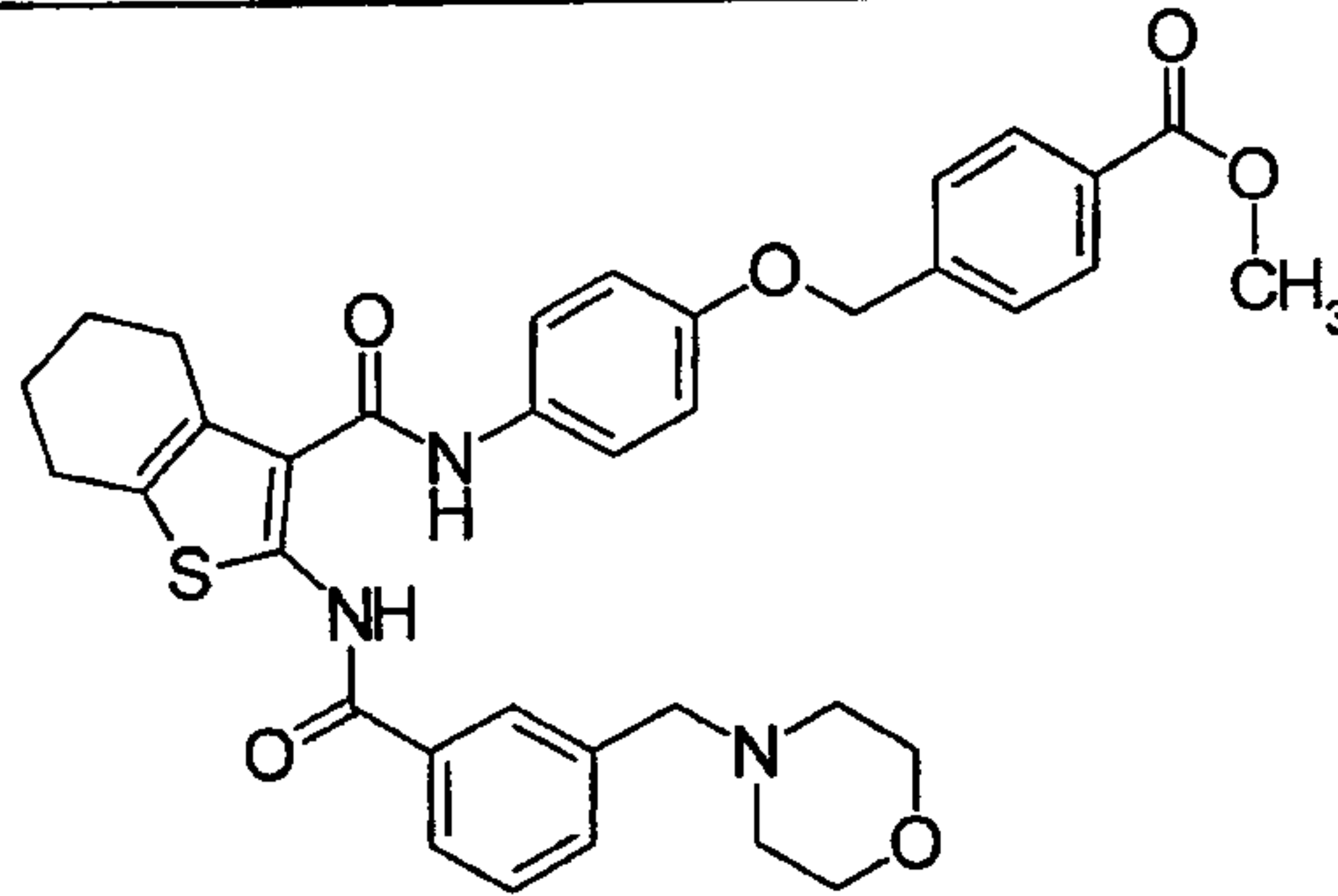
[0153]
[Table 8]

Pr	Str	Pr	Str
40		43	
41		44	
42		45	

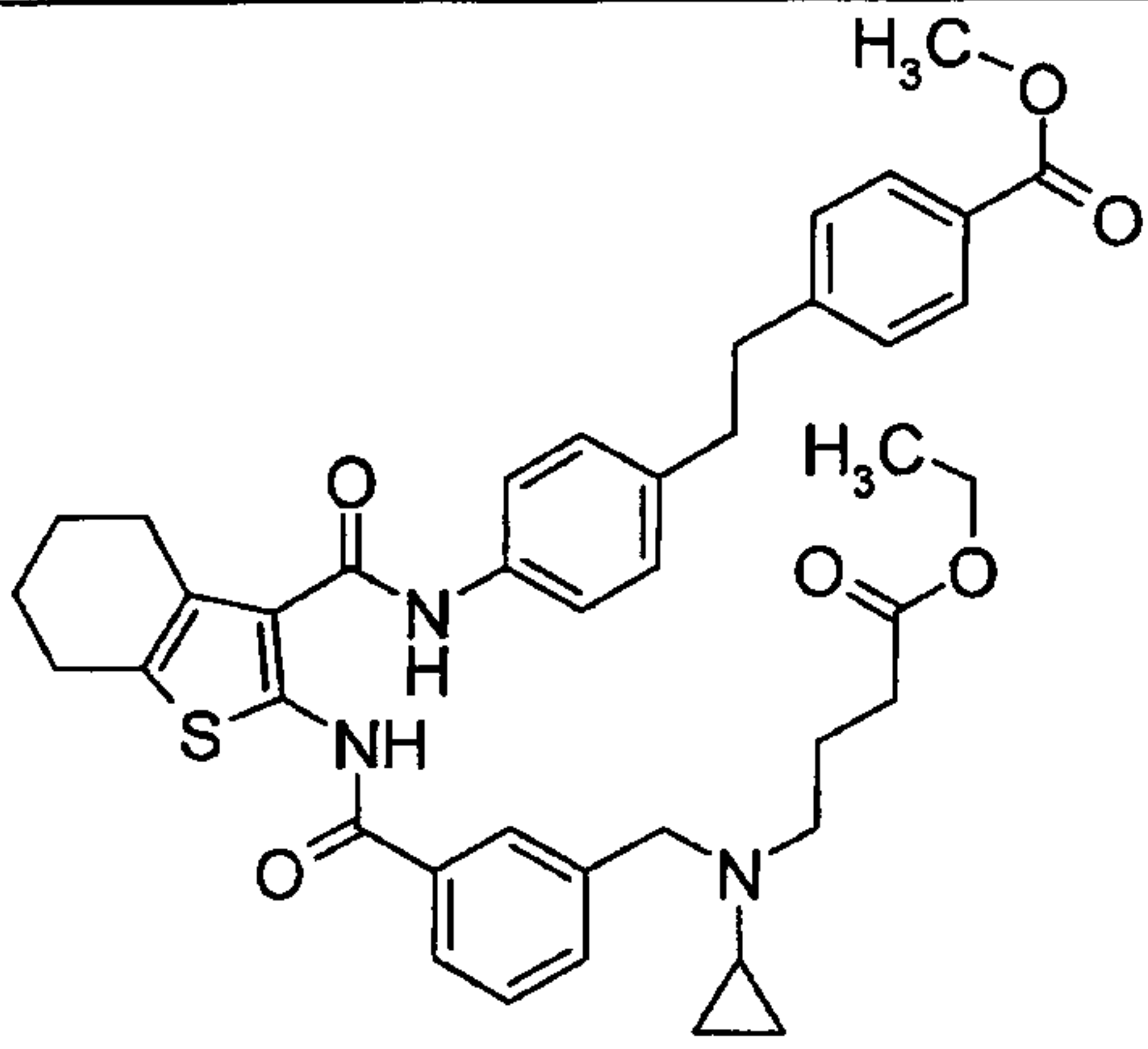
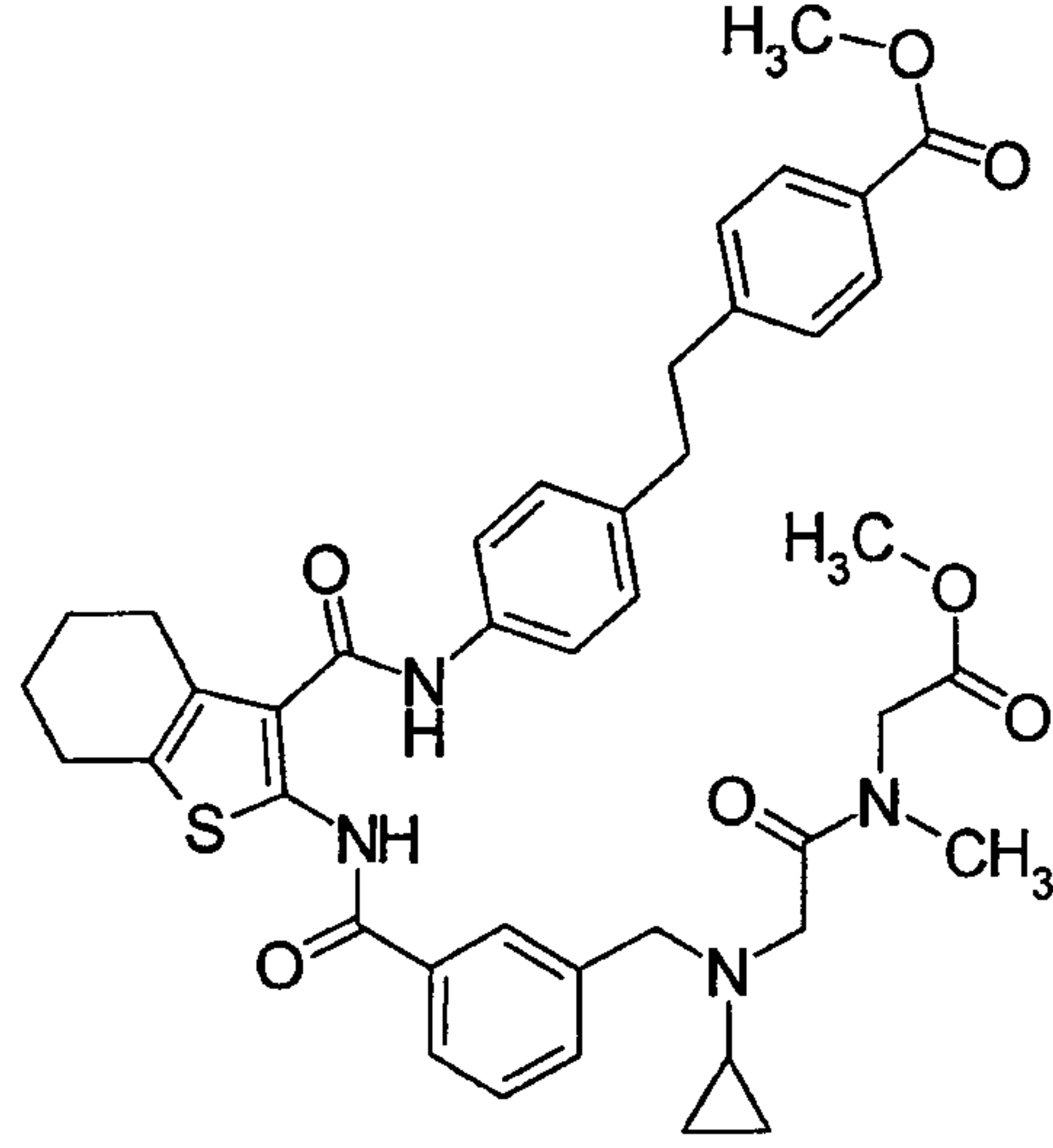
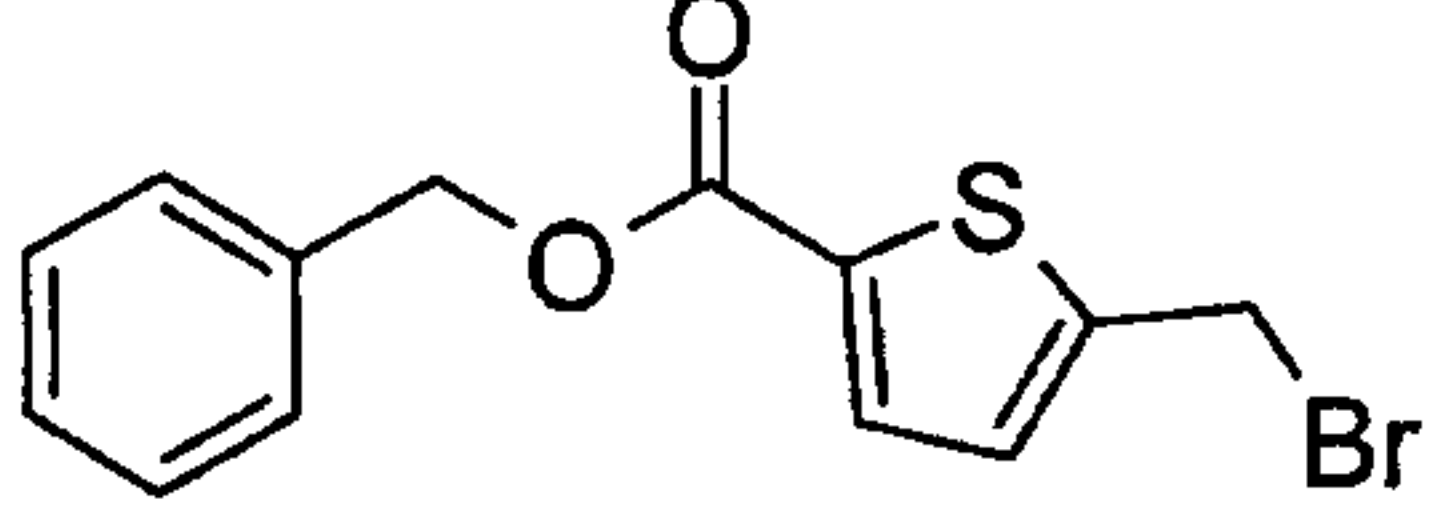
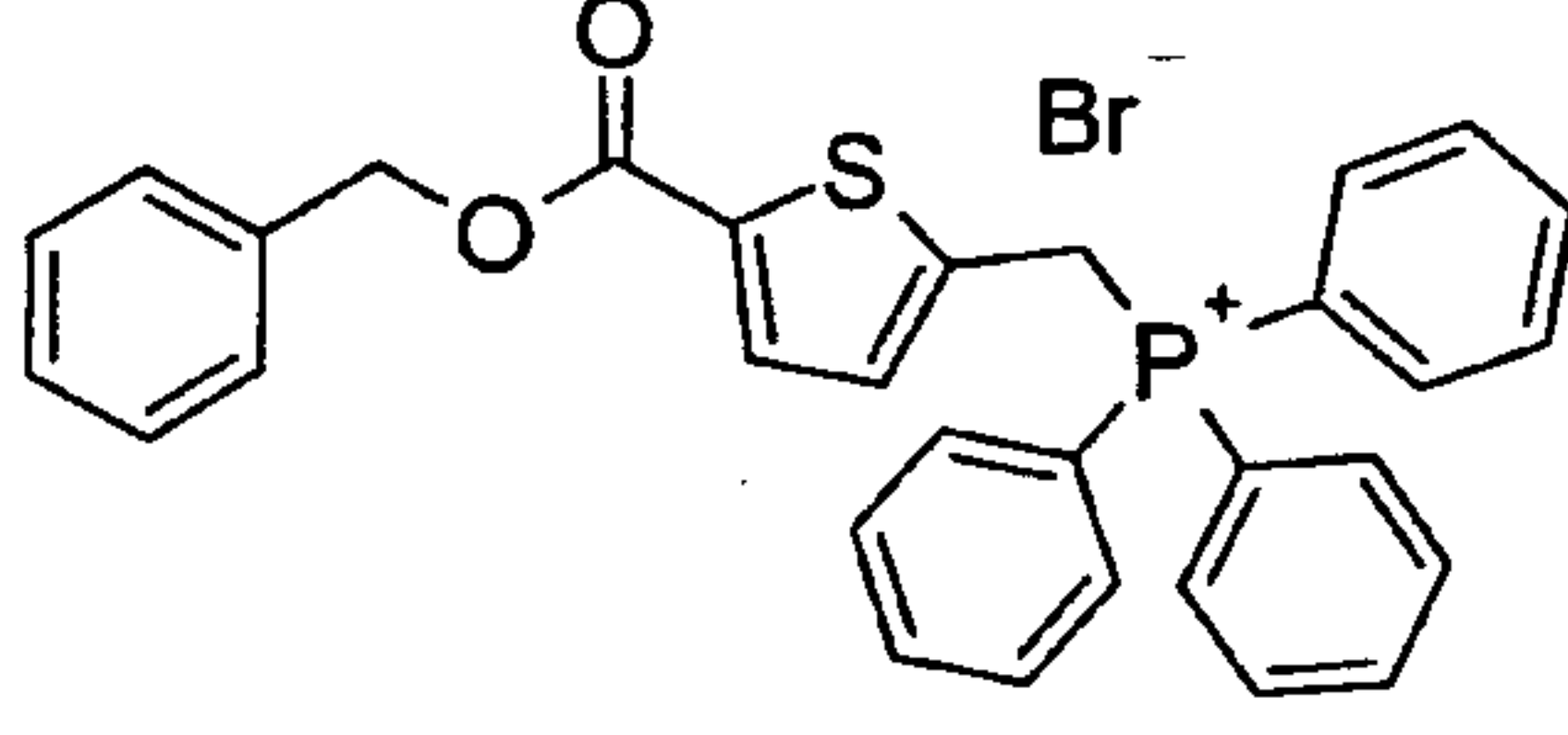
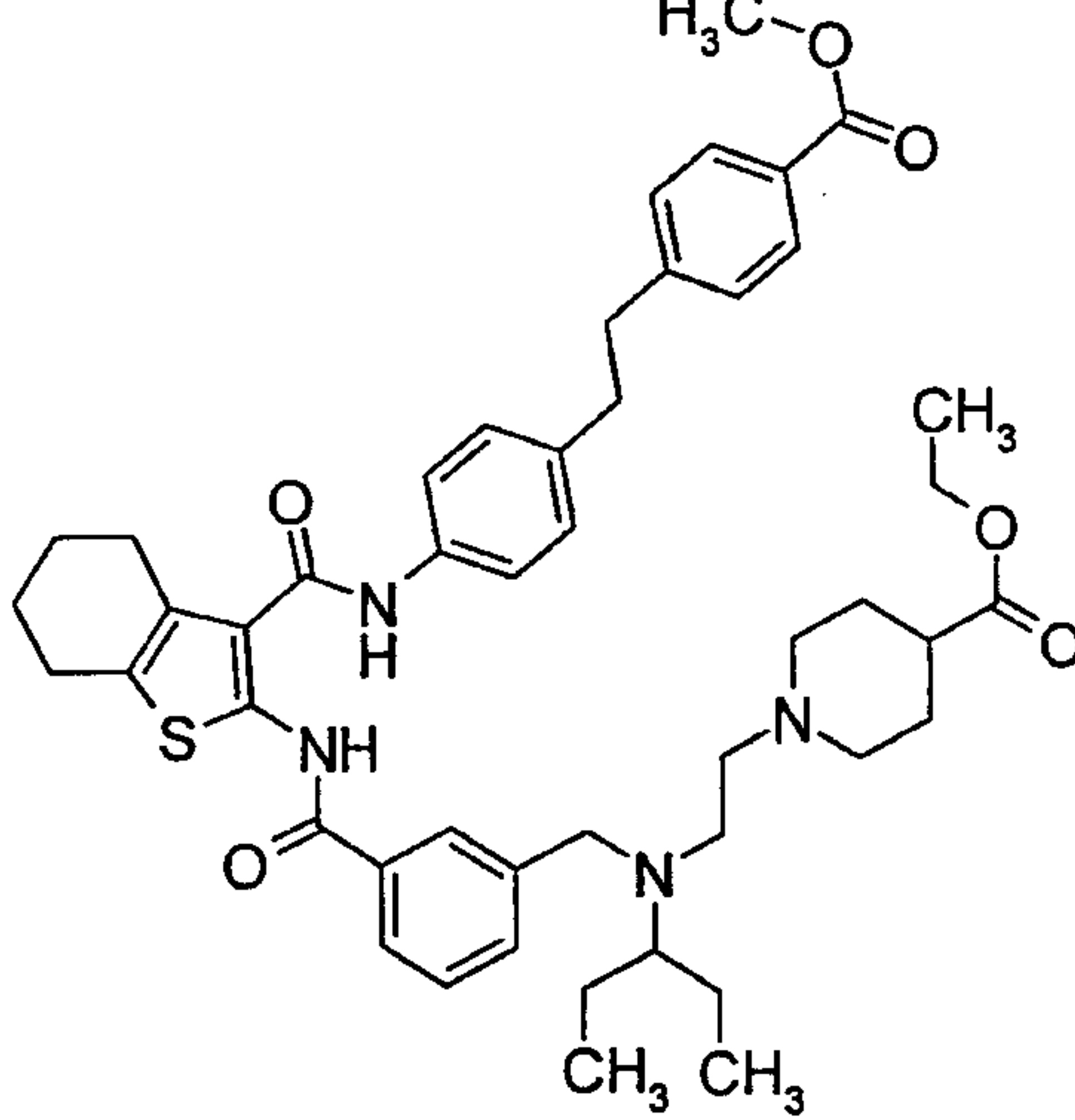
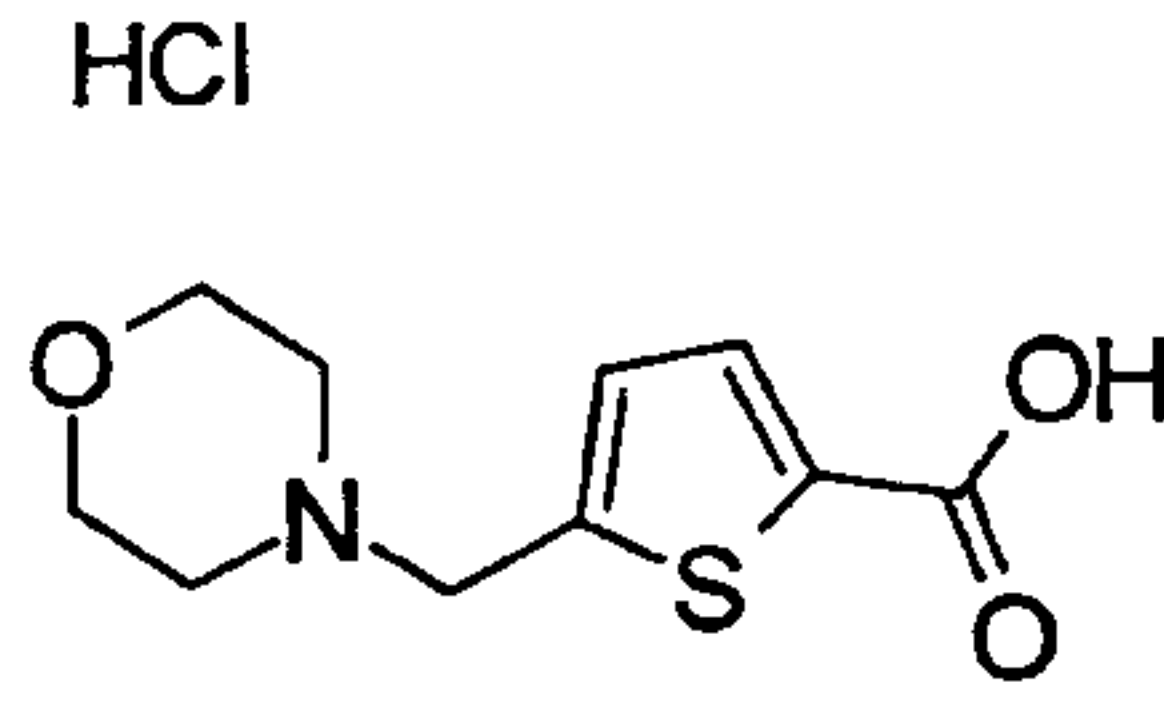
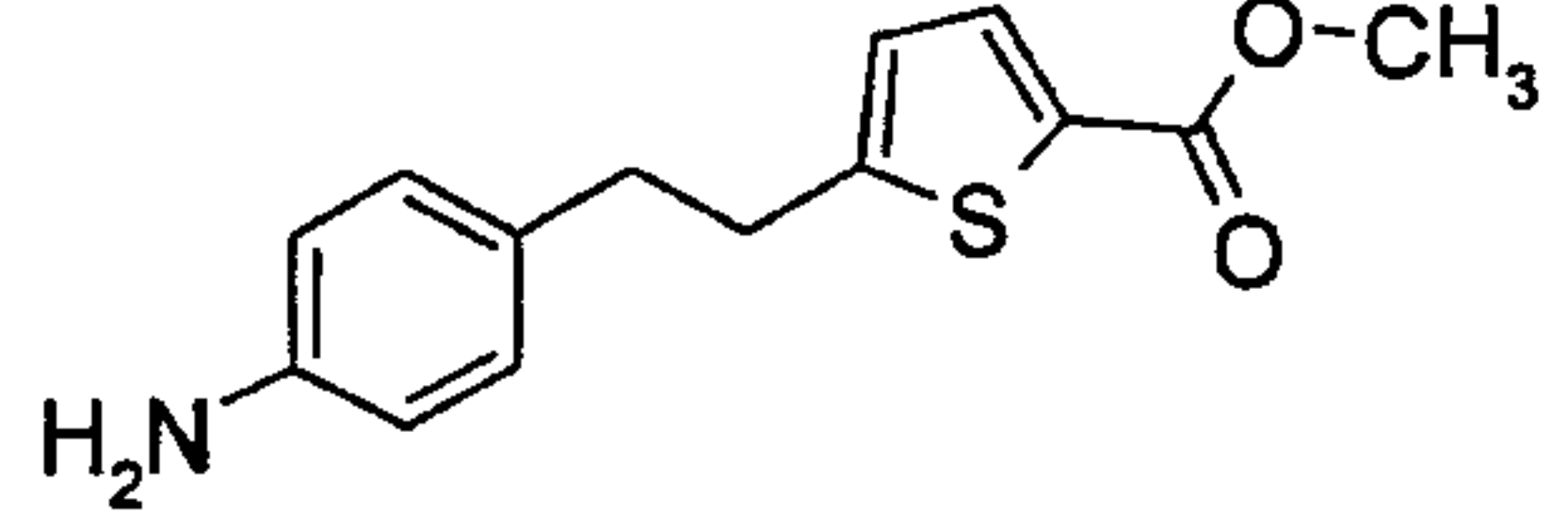
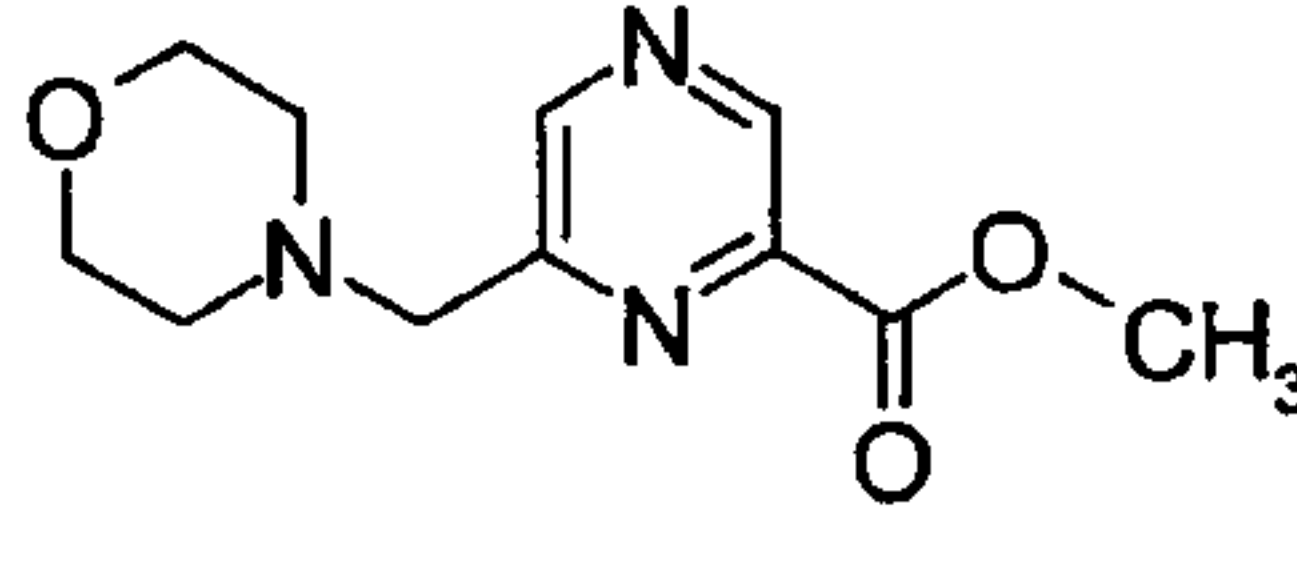
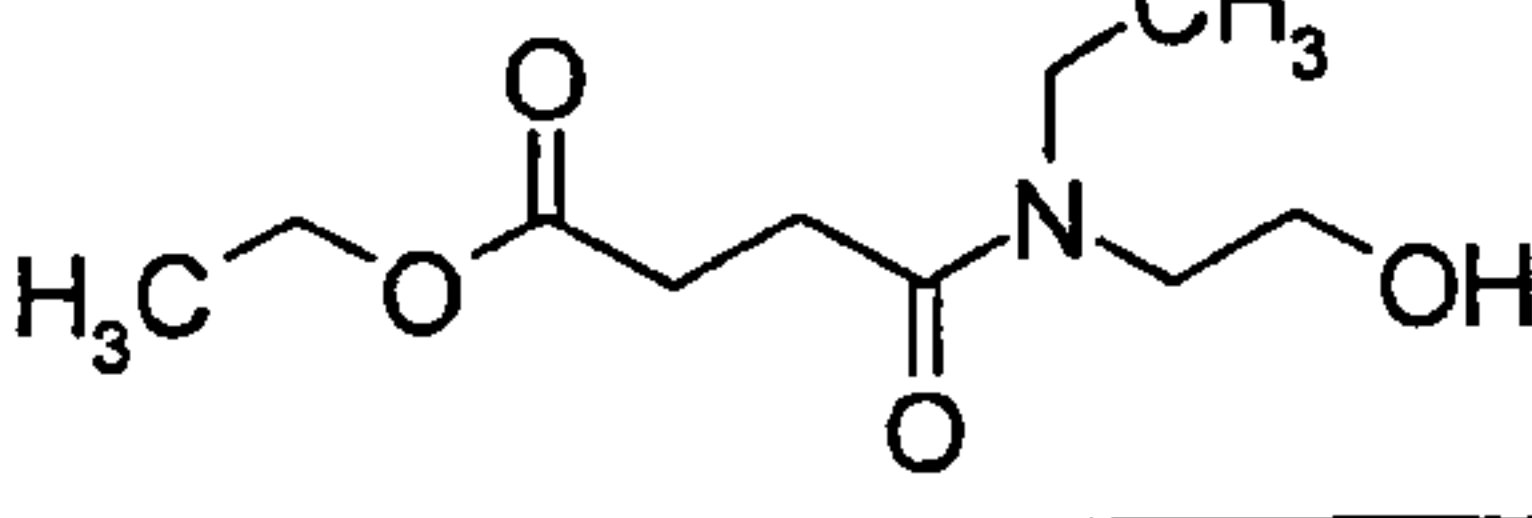
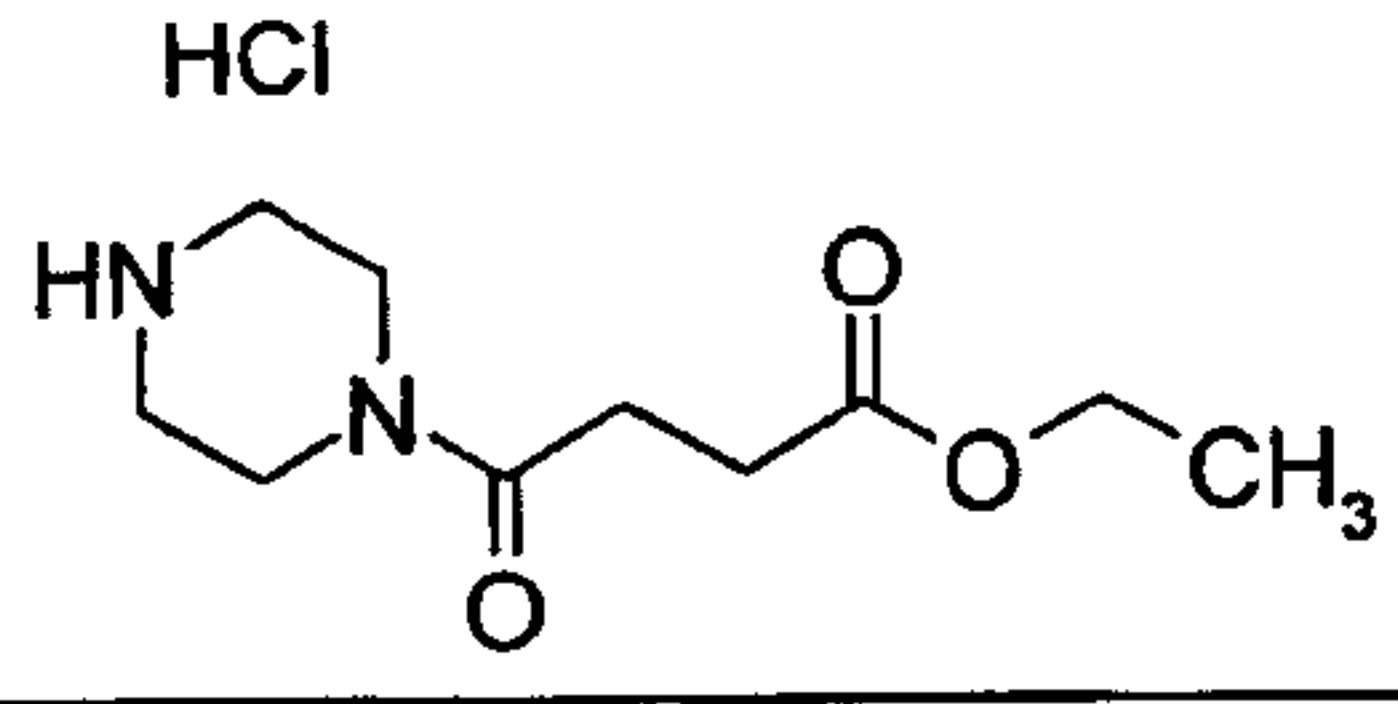
[0154]
[Table 9]

Pr	Str	Pr	Str
46		51	
47		52	
48		53	
49			
50			

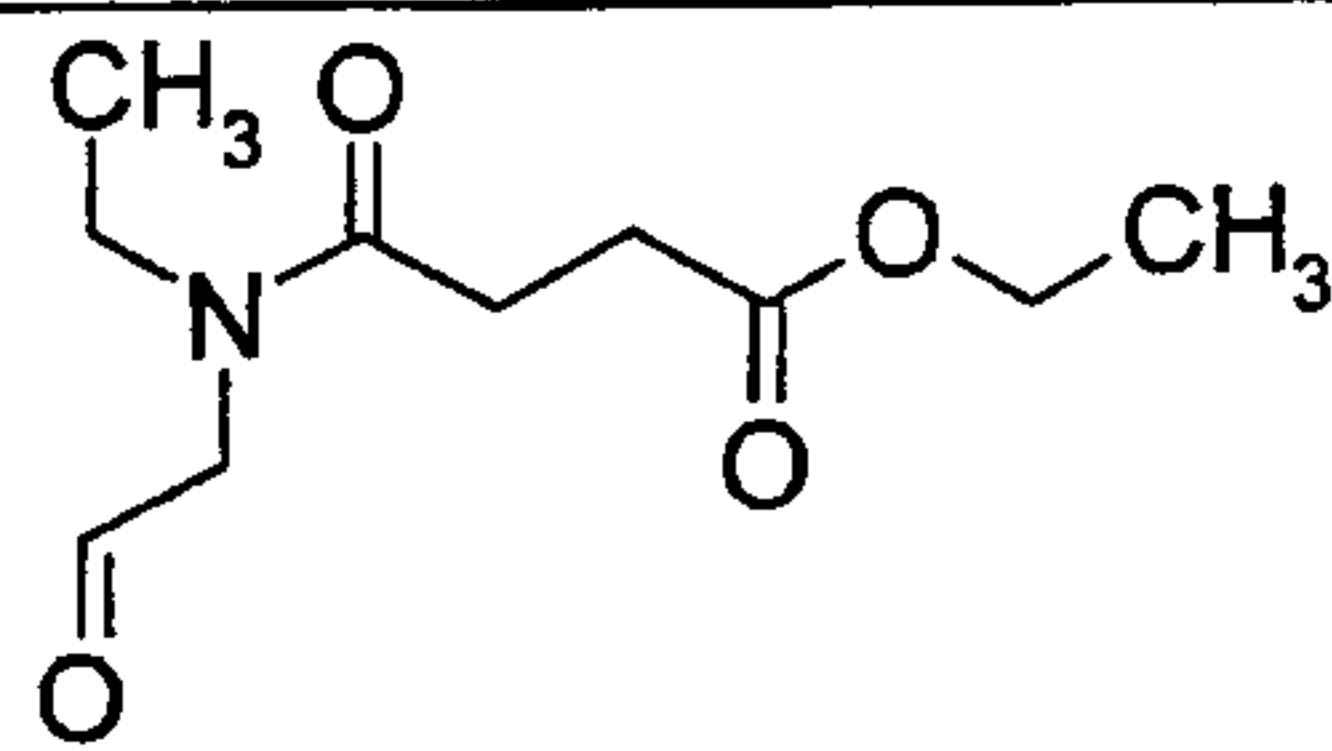
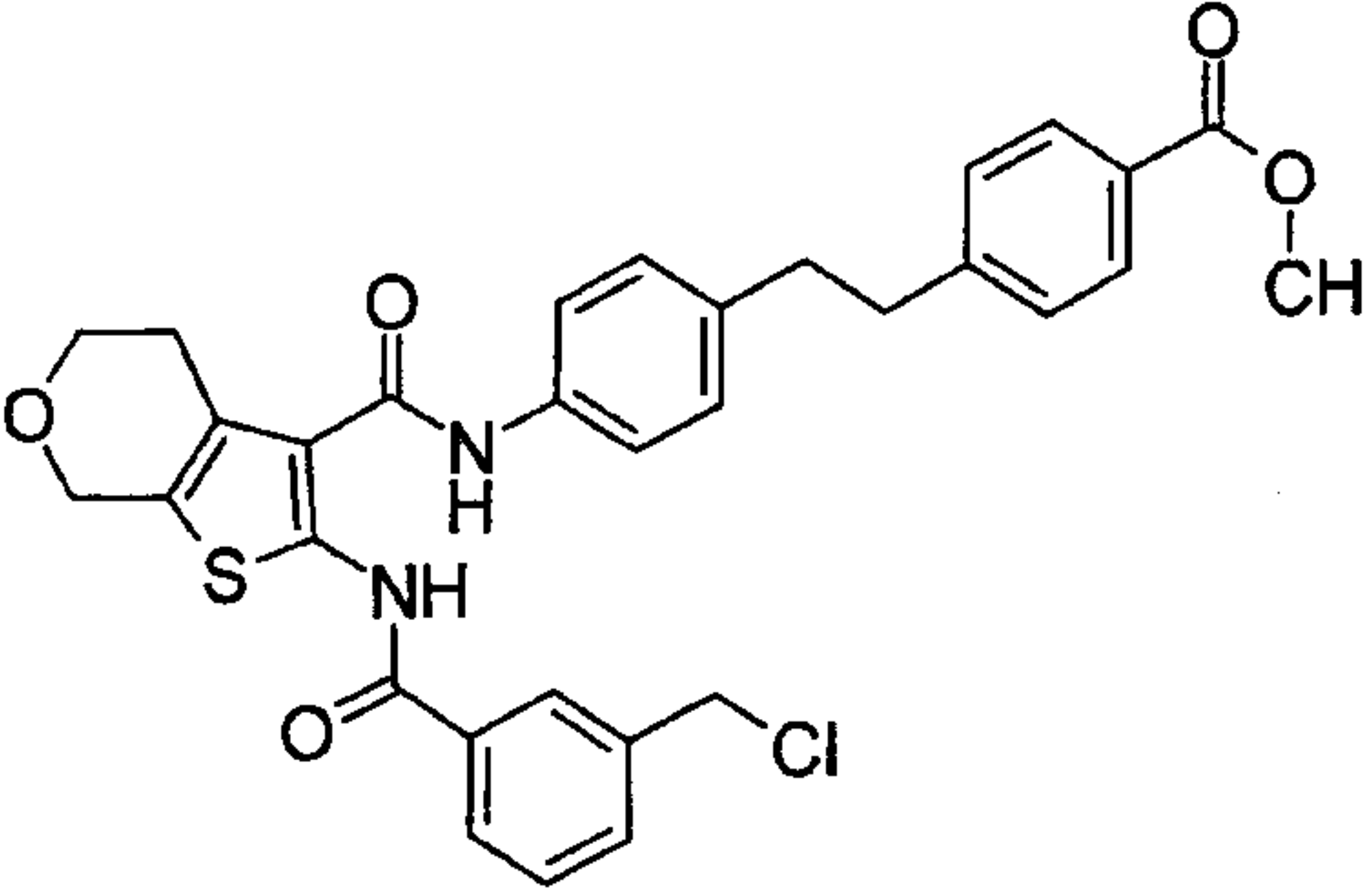
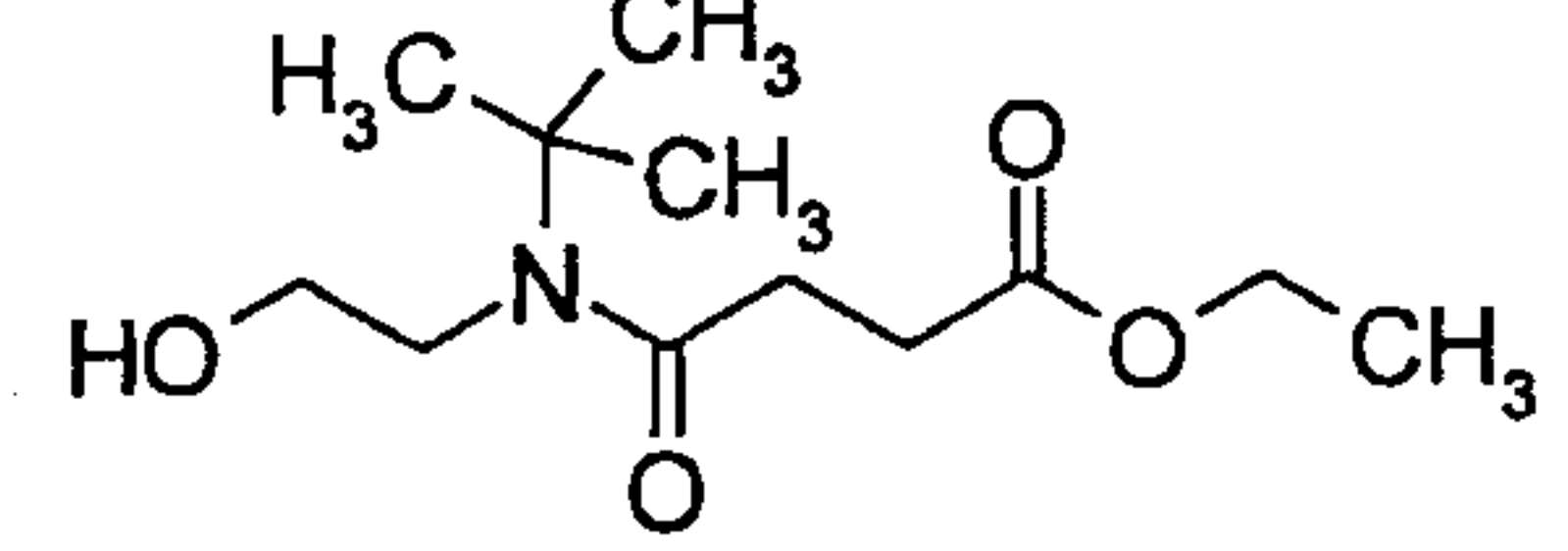
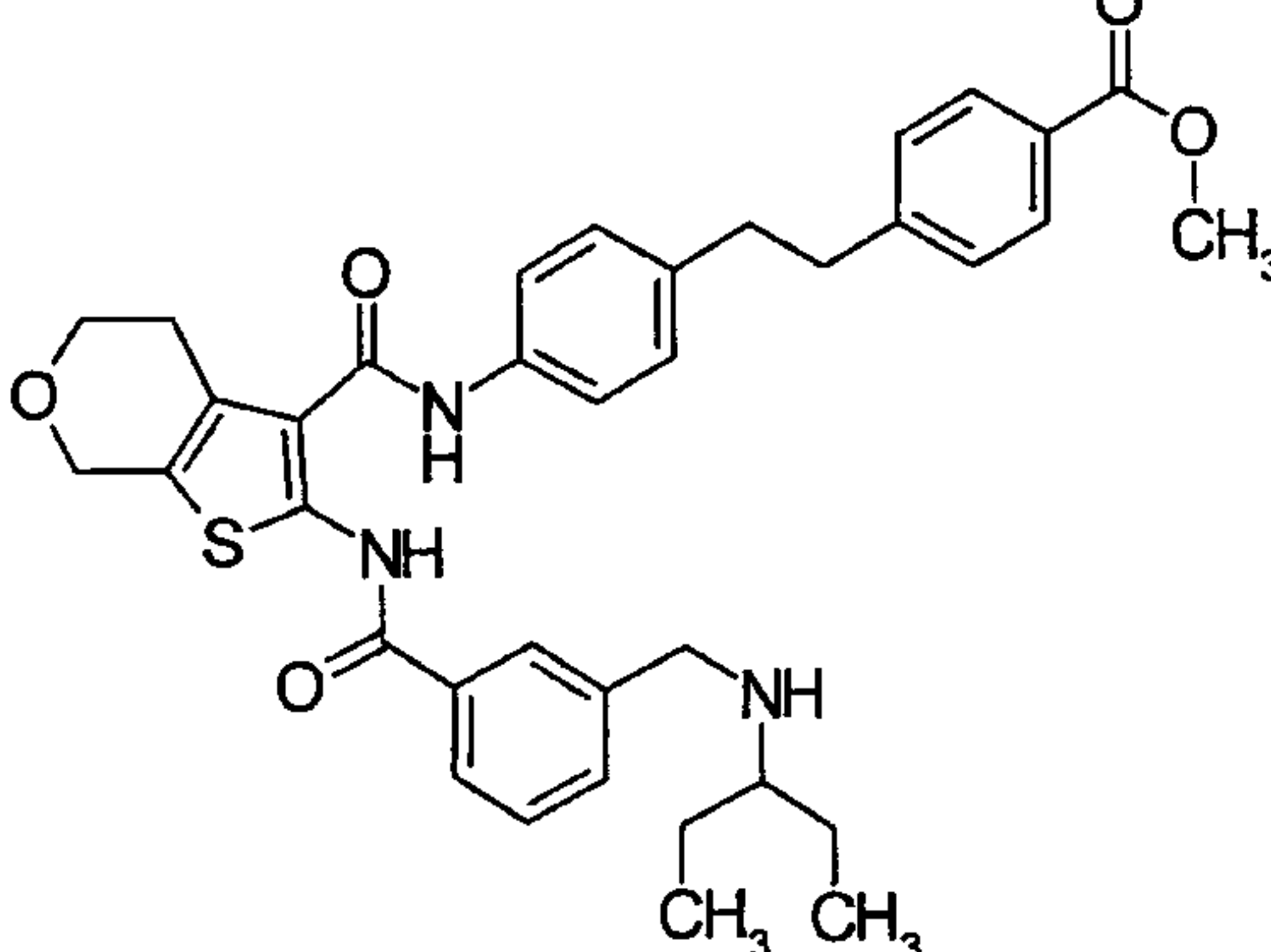
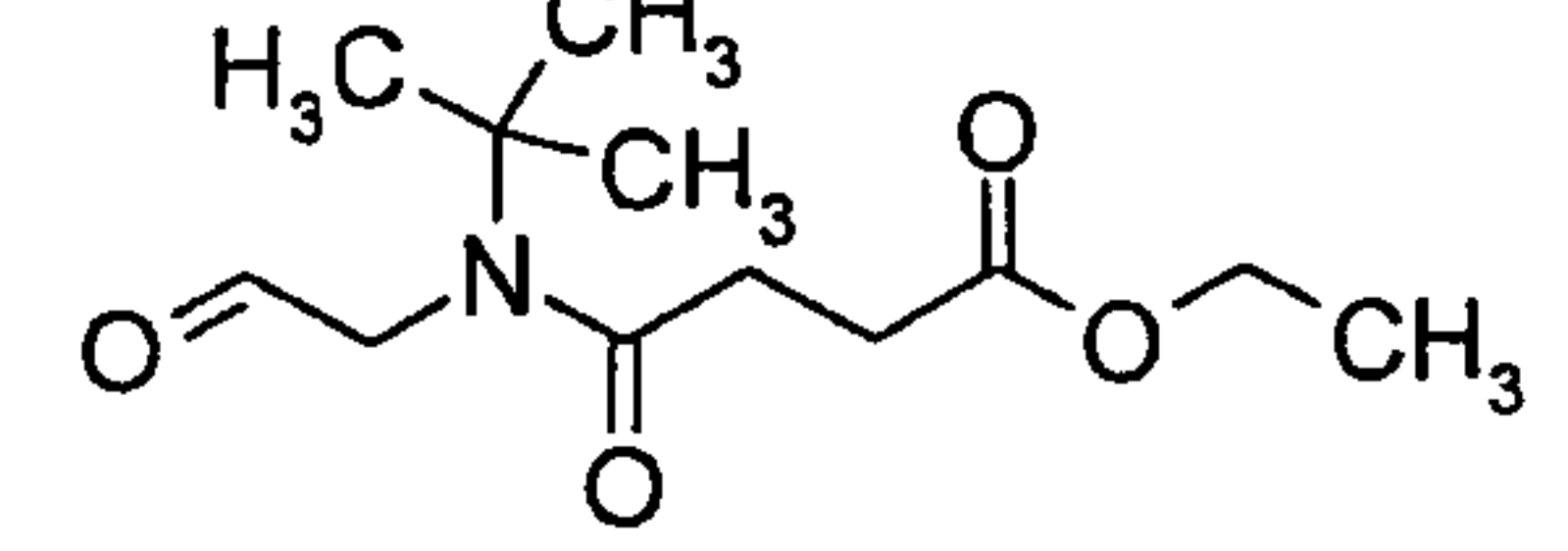
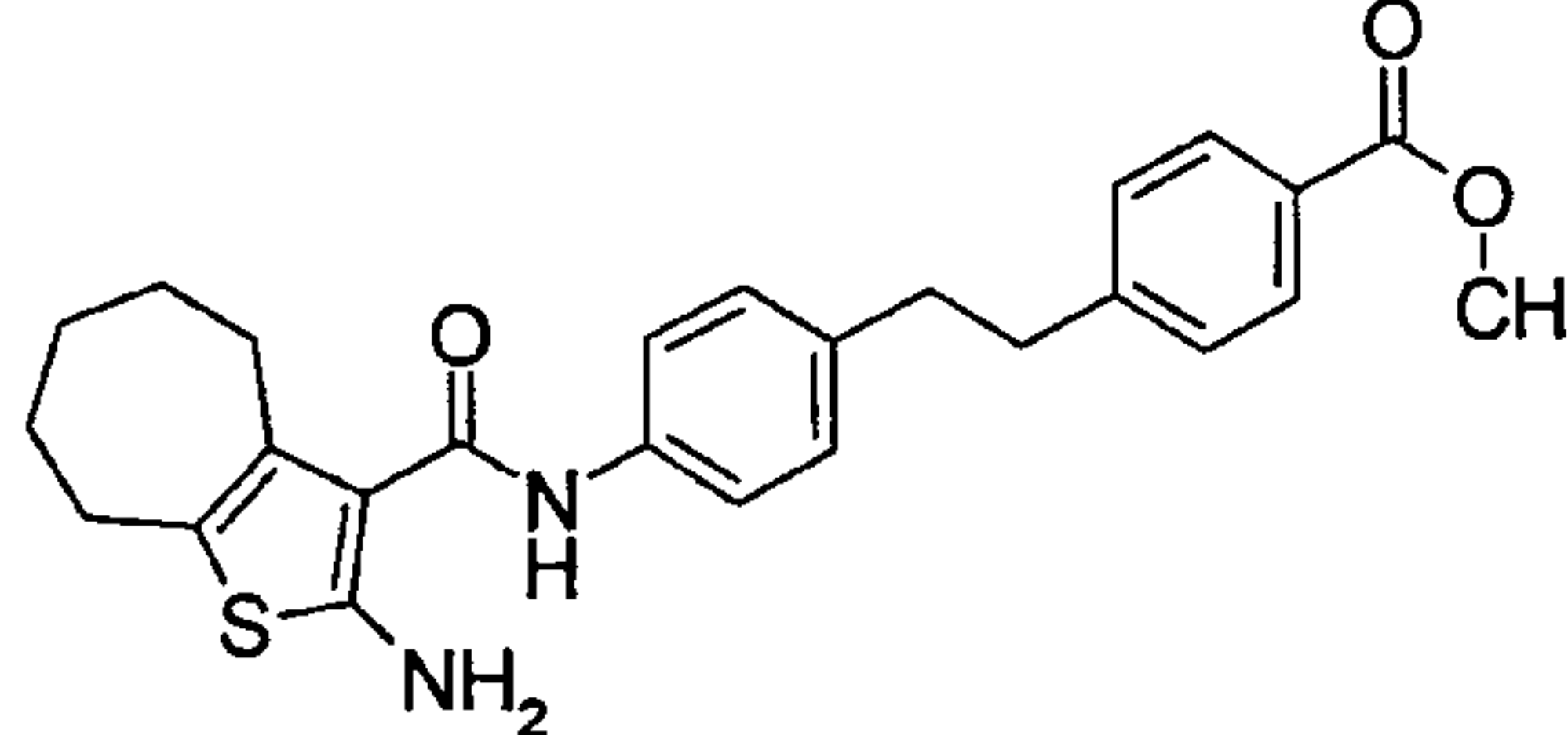
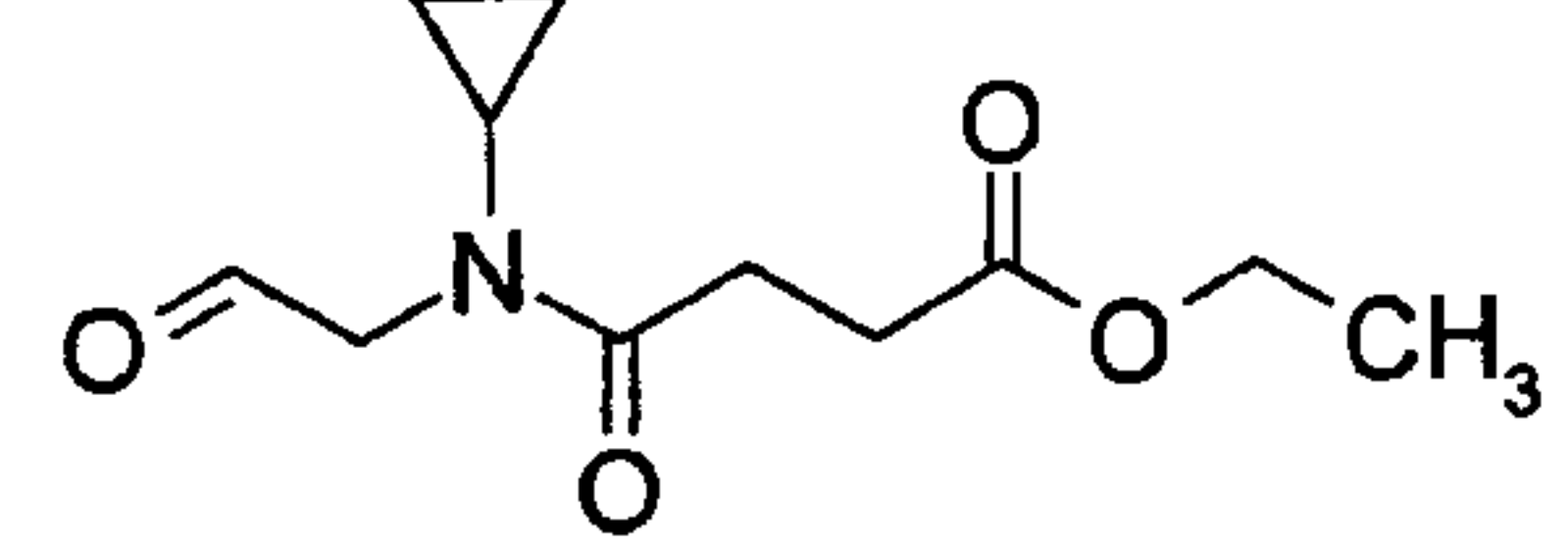
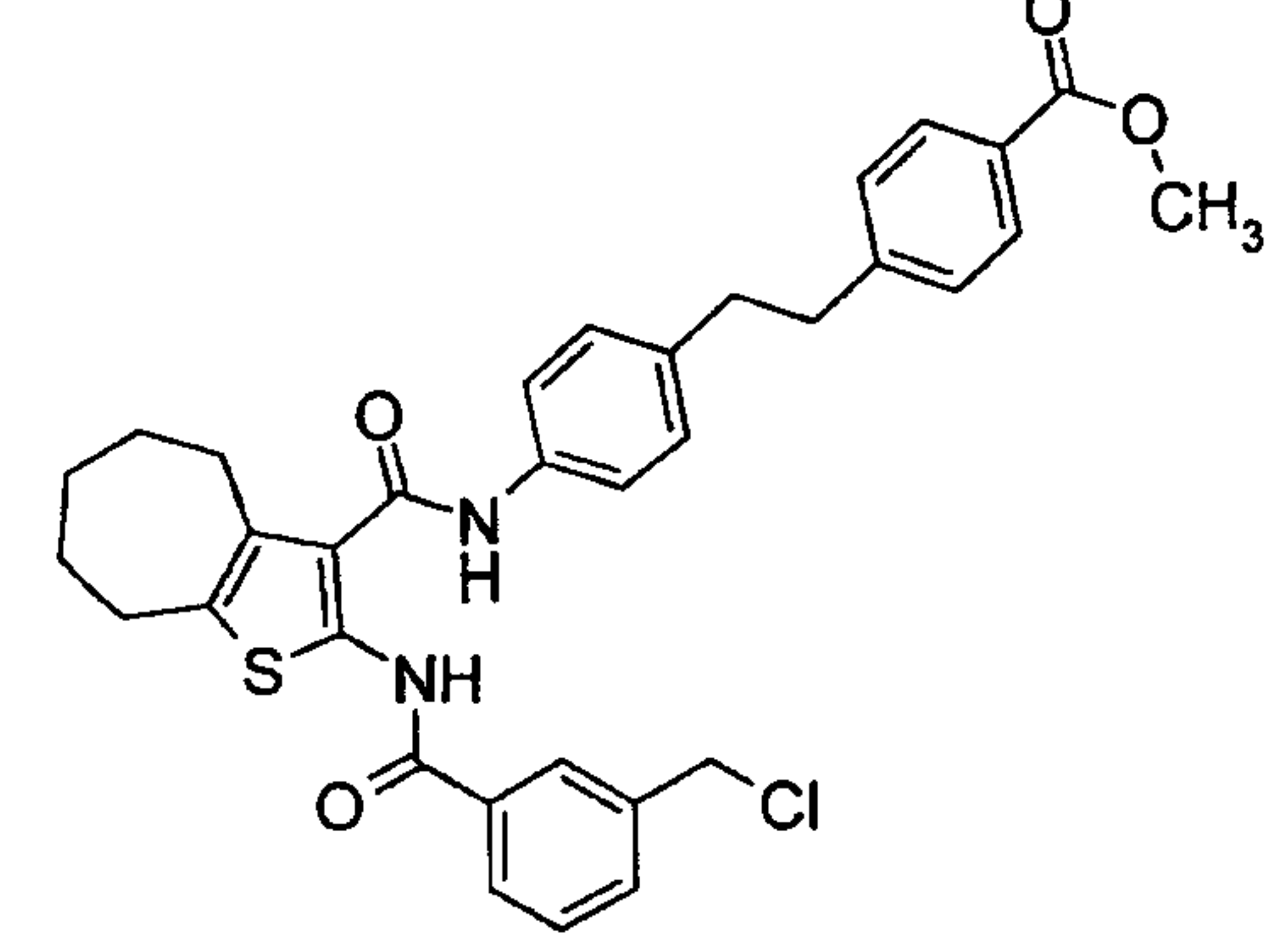
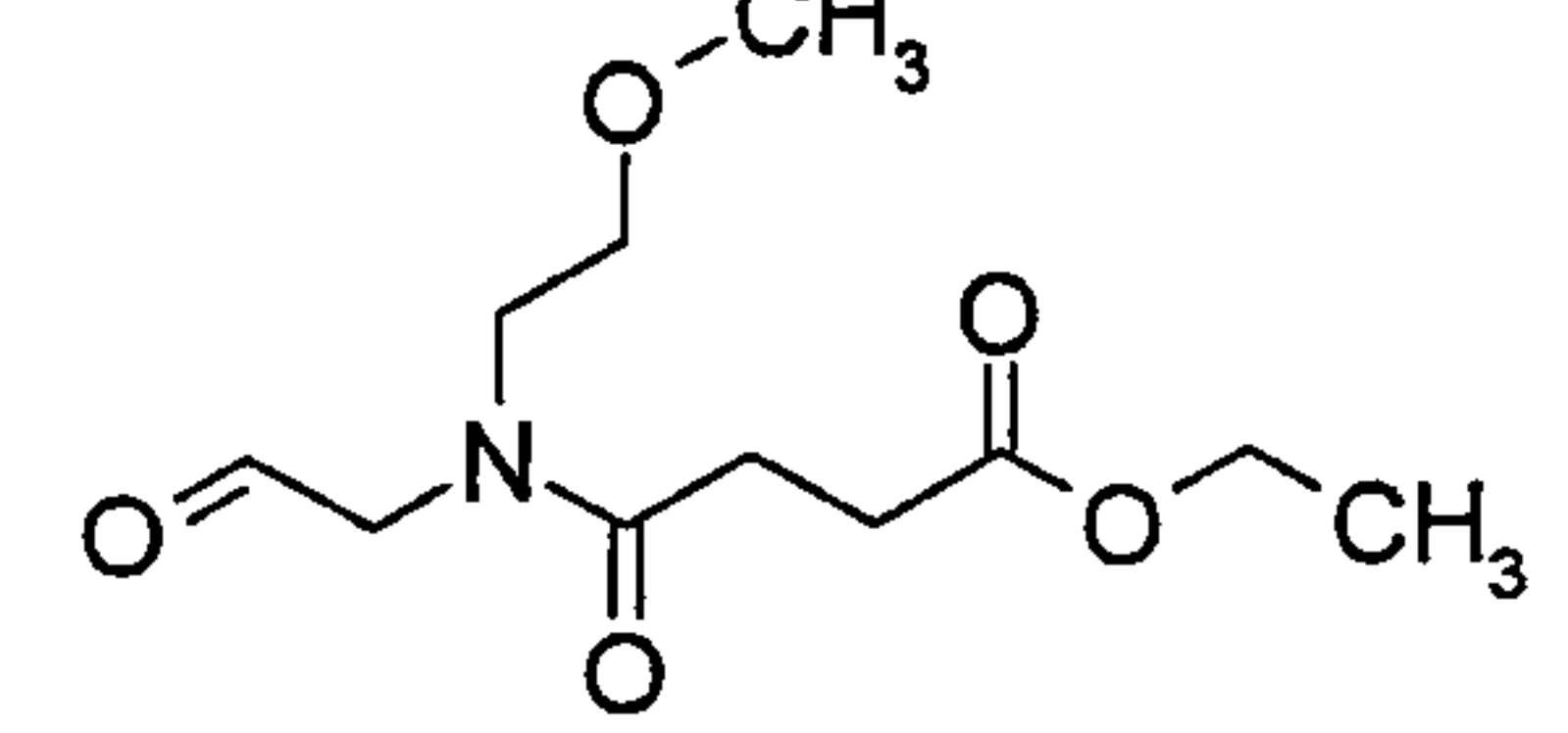
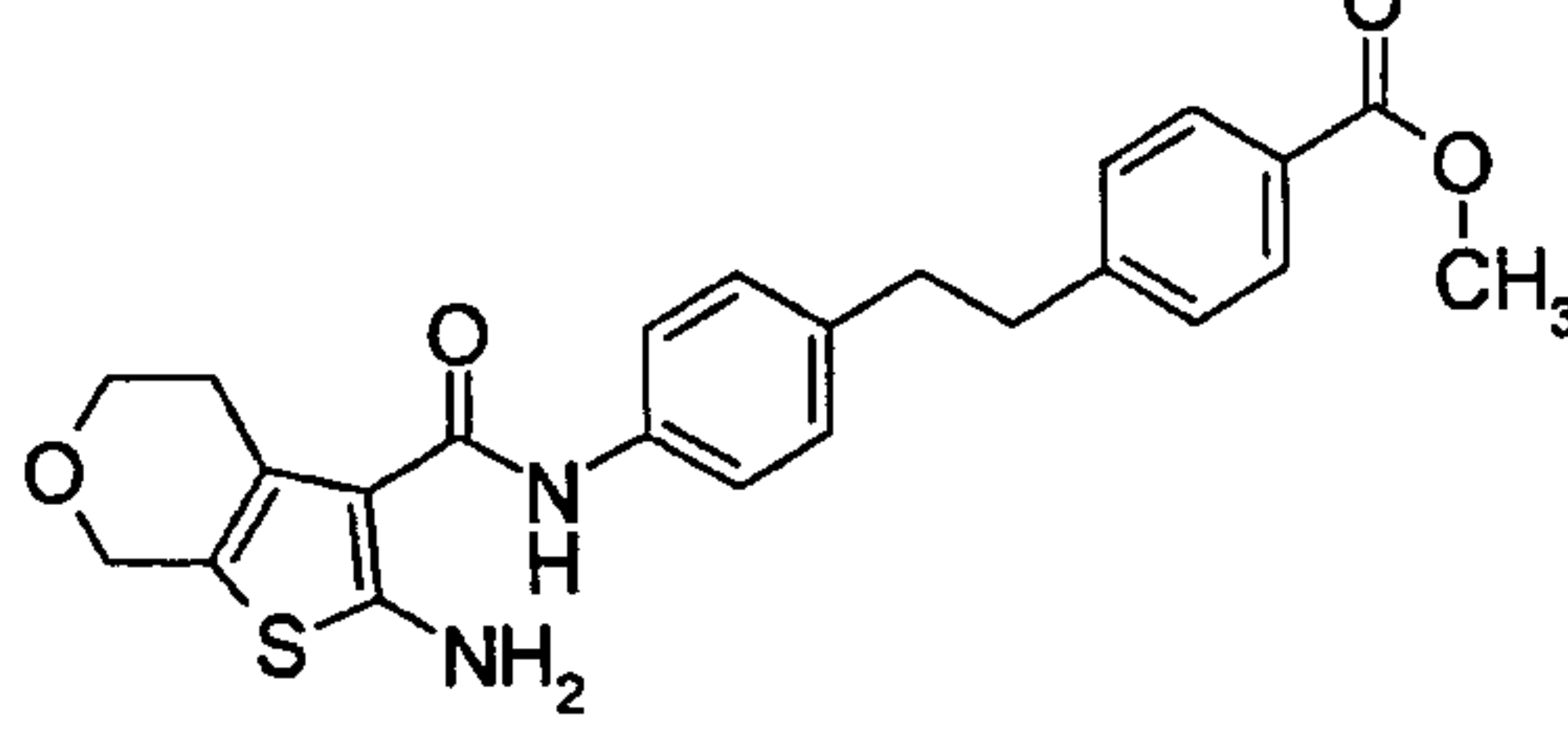
[0155]
[Table 10]

Pr	Str	Pr	Str
54		58	
55		59	
56		60	
57			

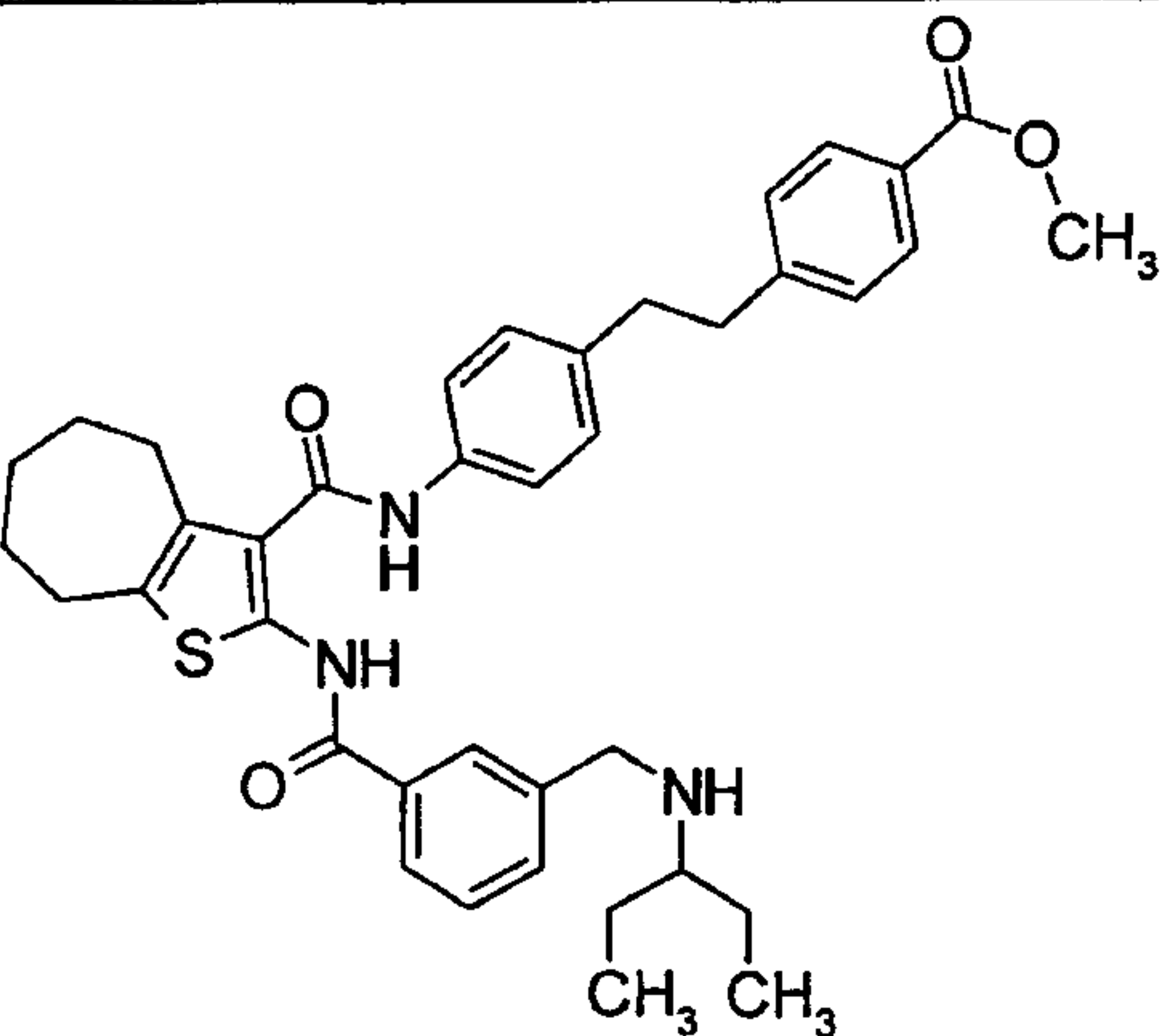
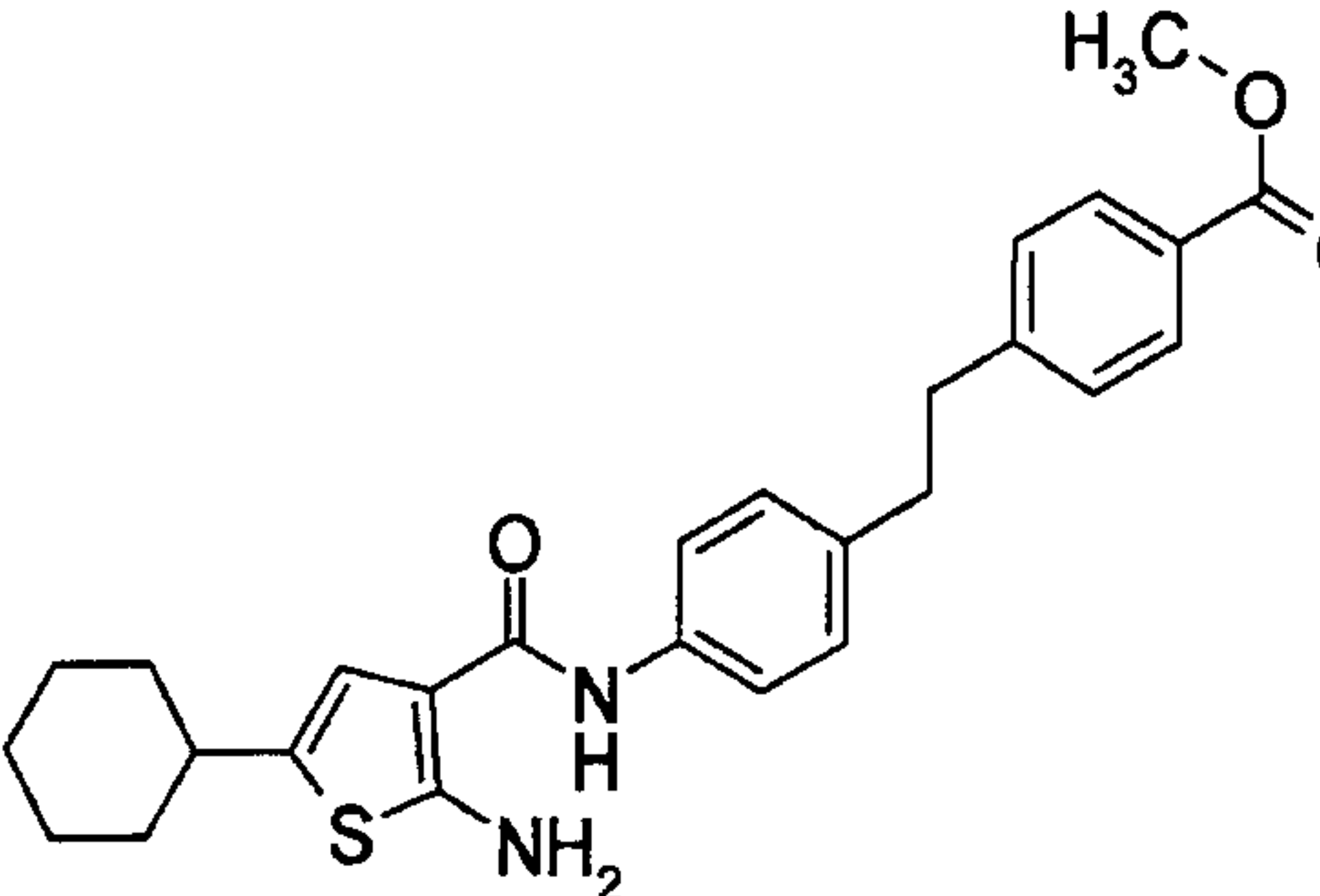
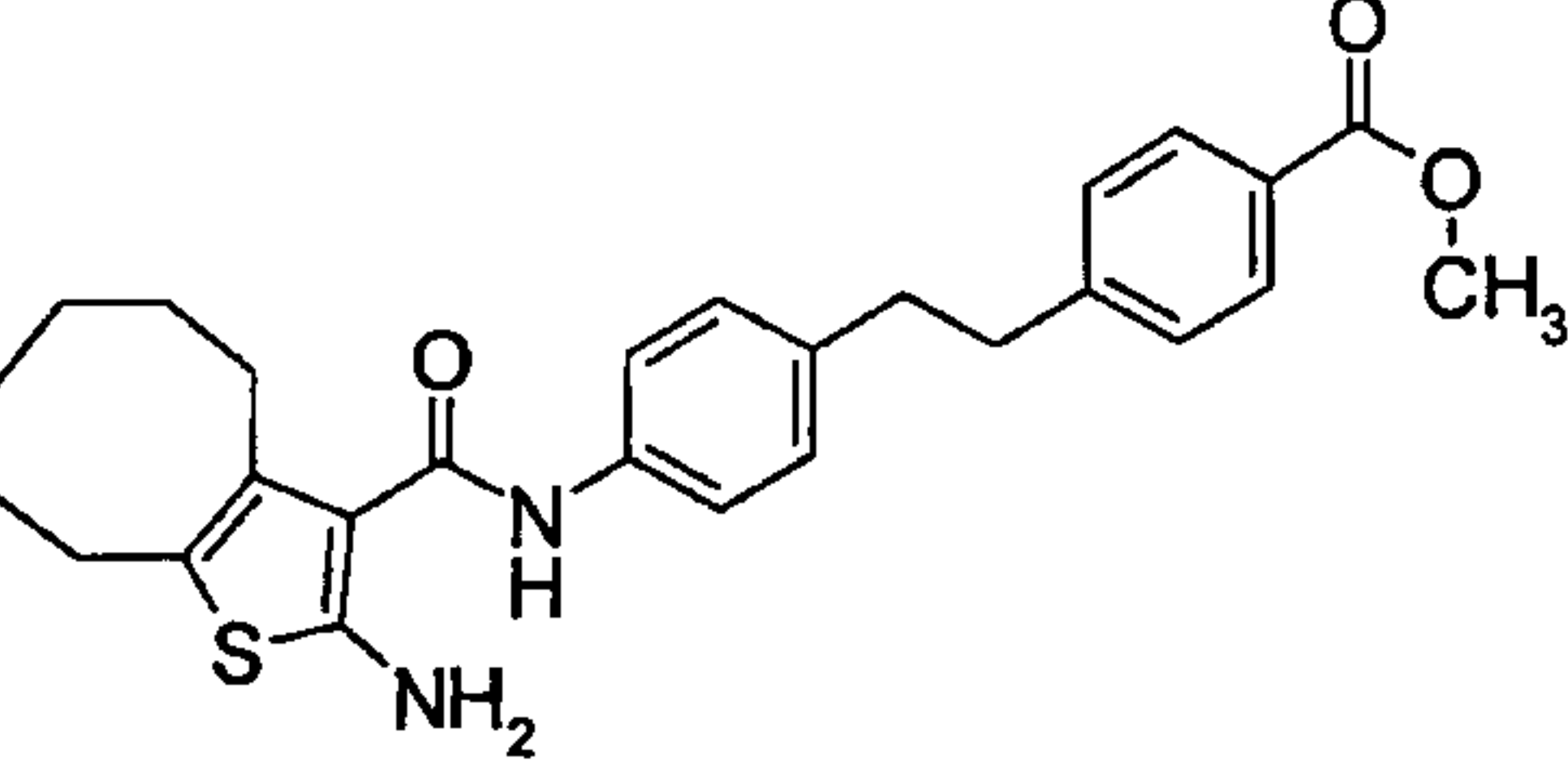
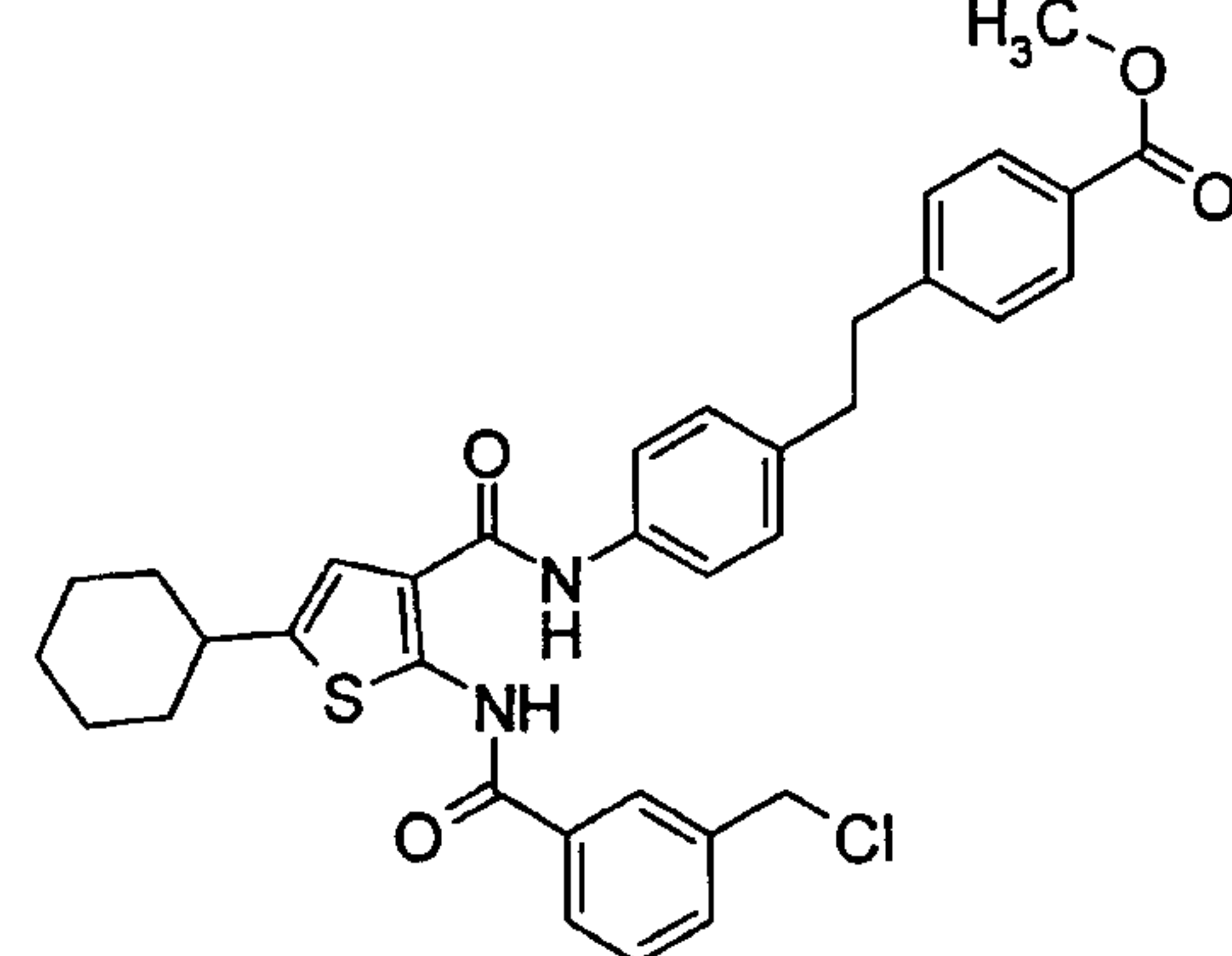
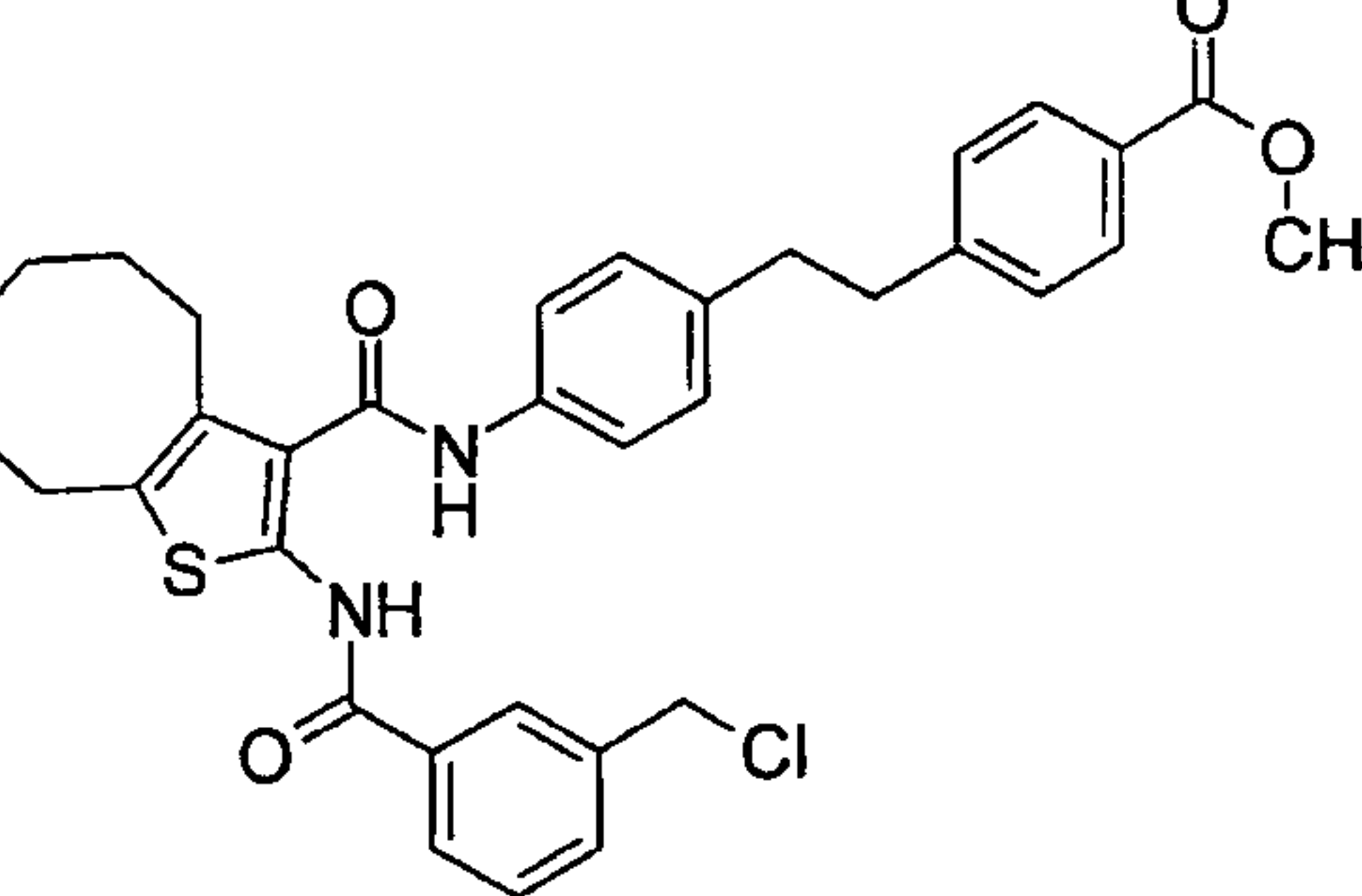
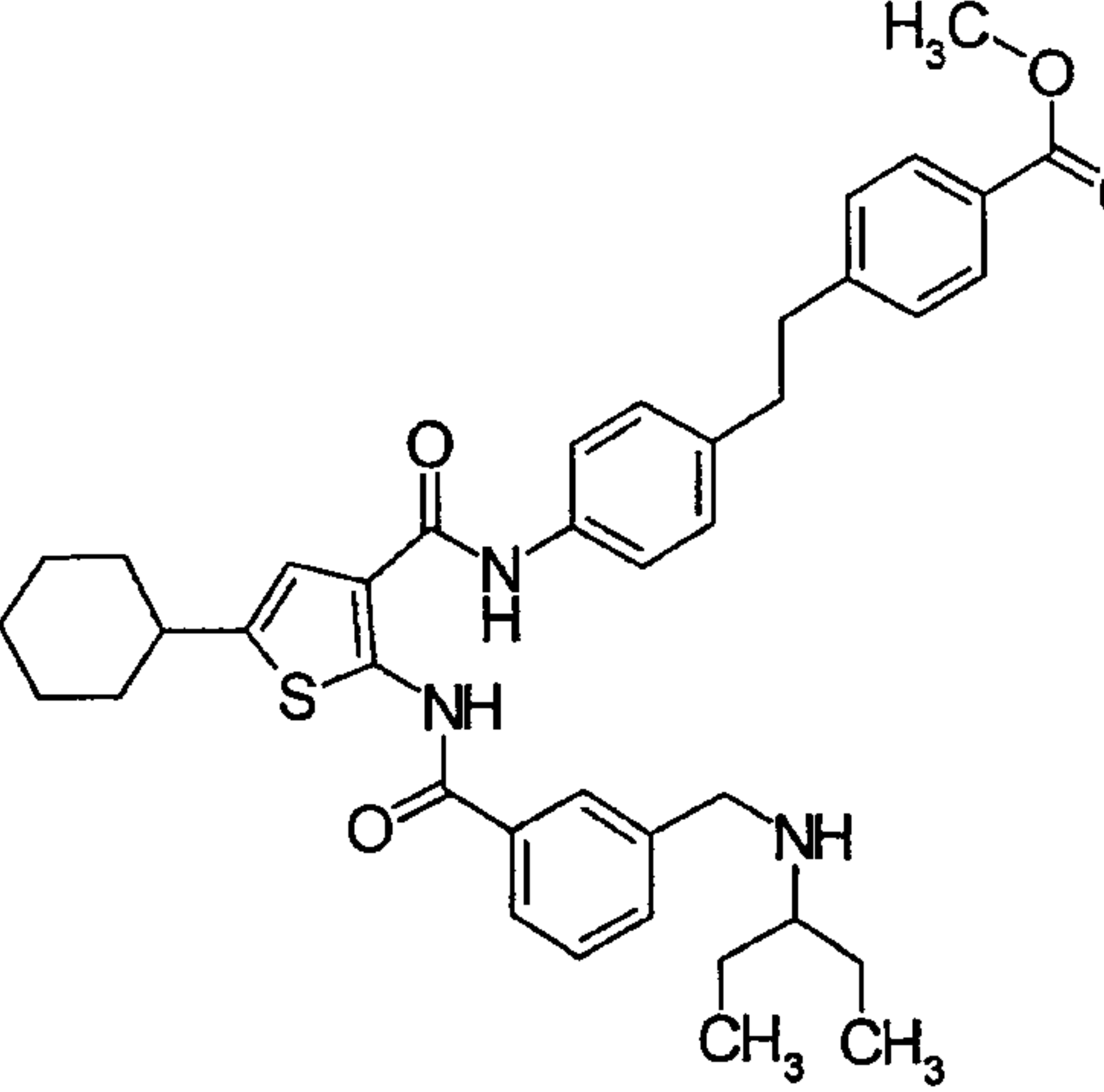
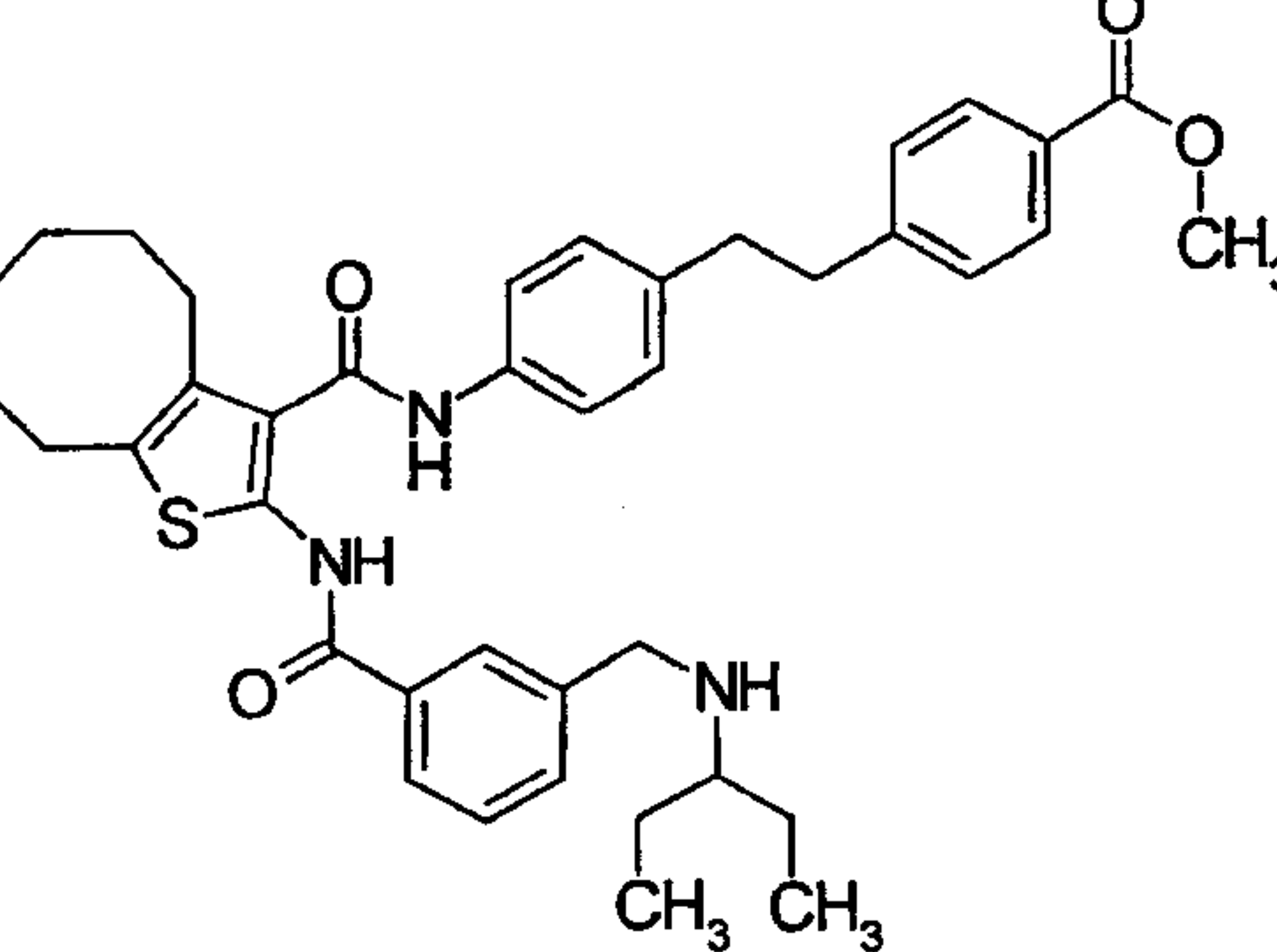
[0156]
[Table 11]

Pr	Str	Pr	Str
61		67	
62			
63		68	
64		69	
65		70	
66			

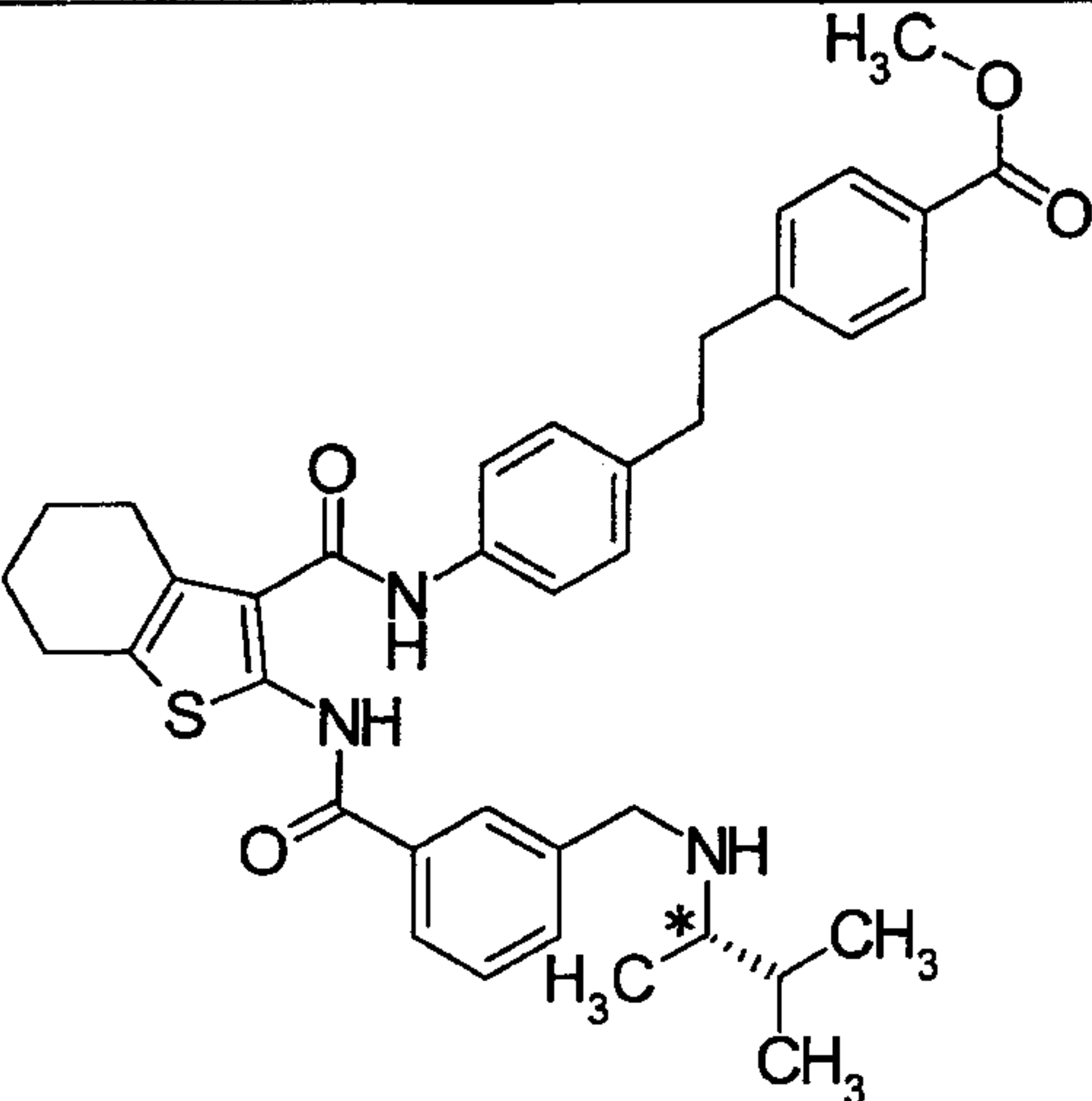
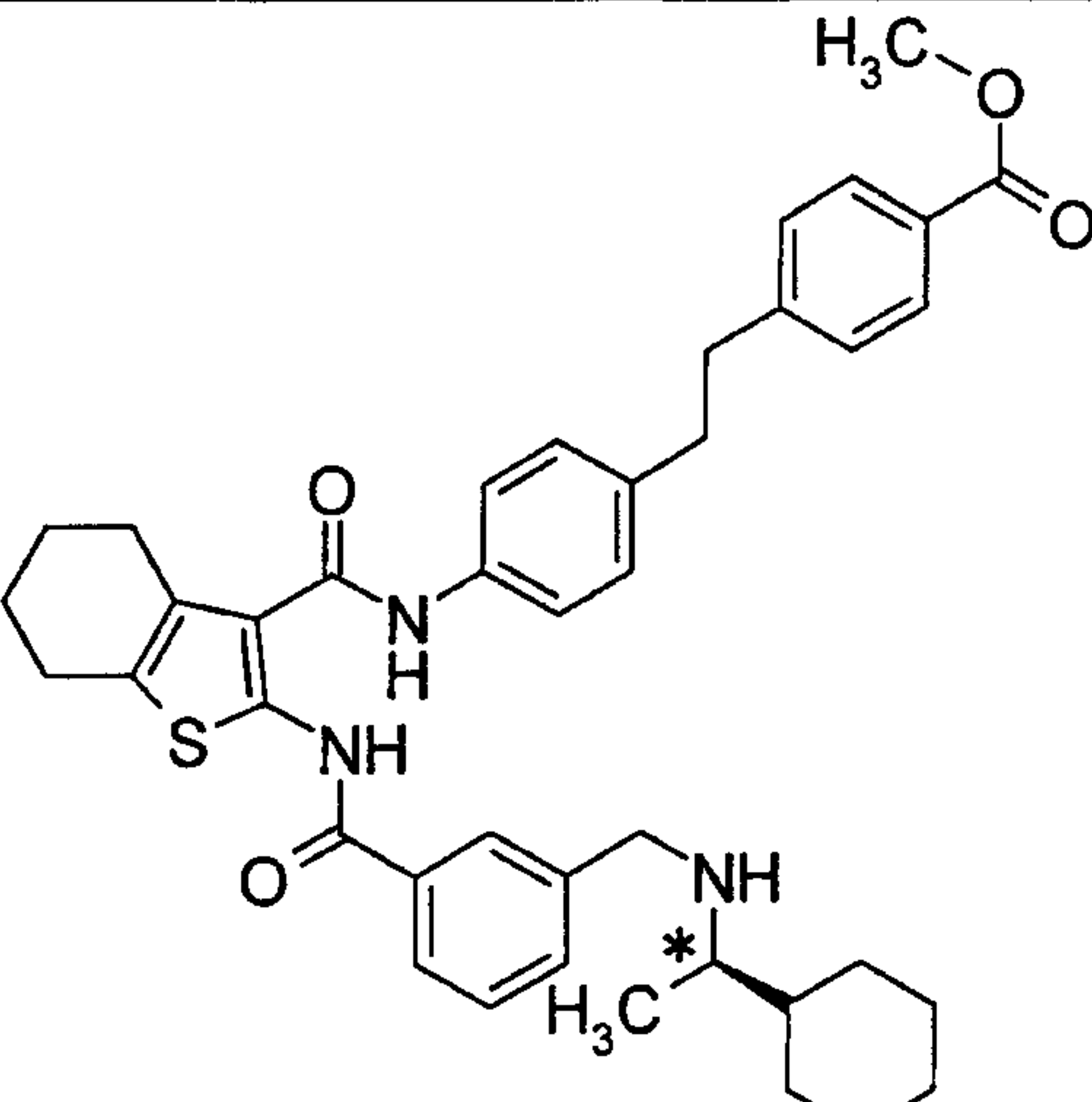
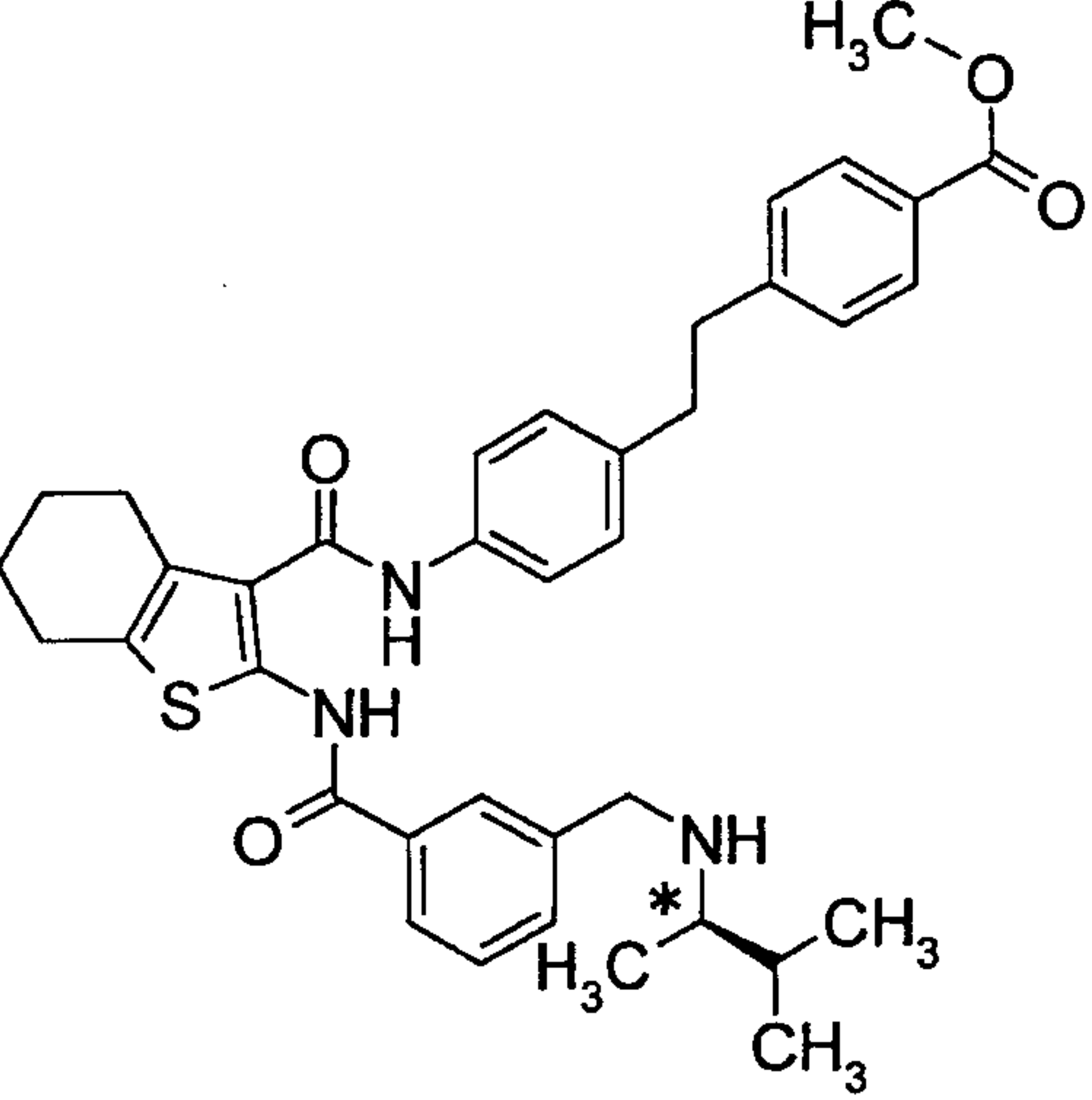
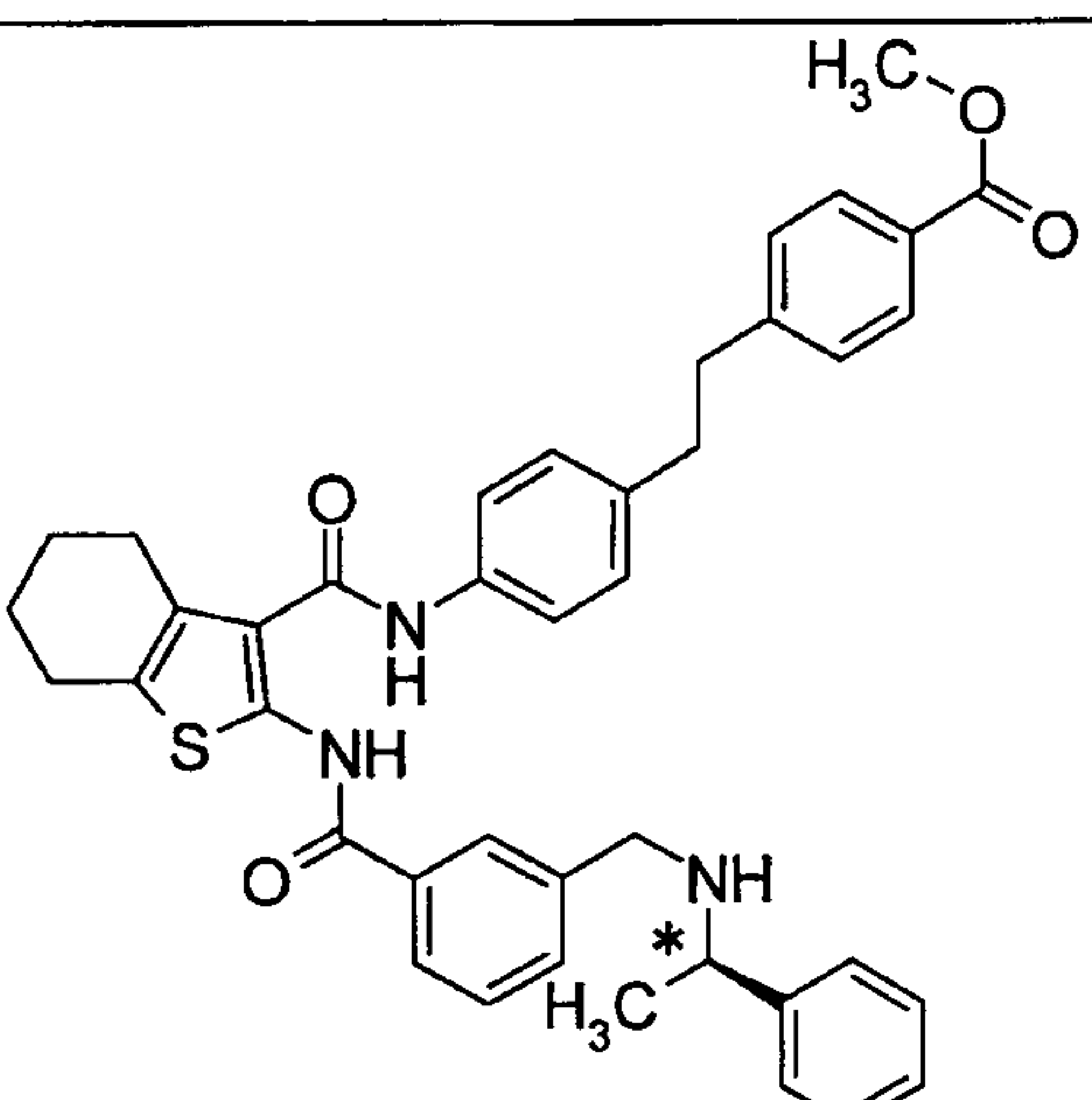
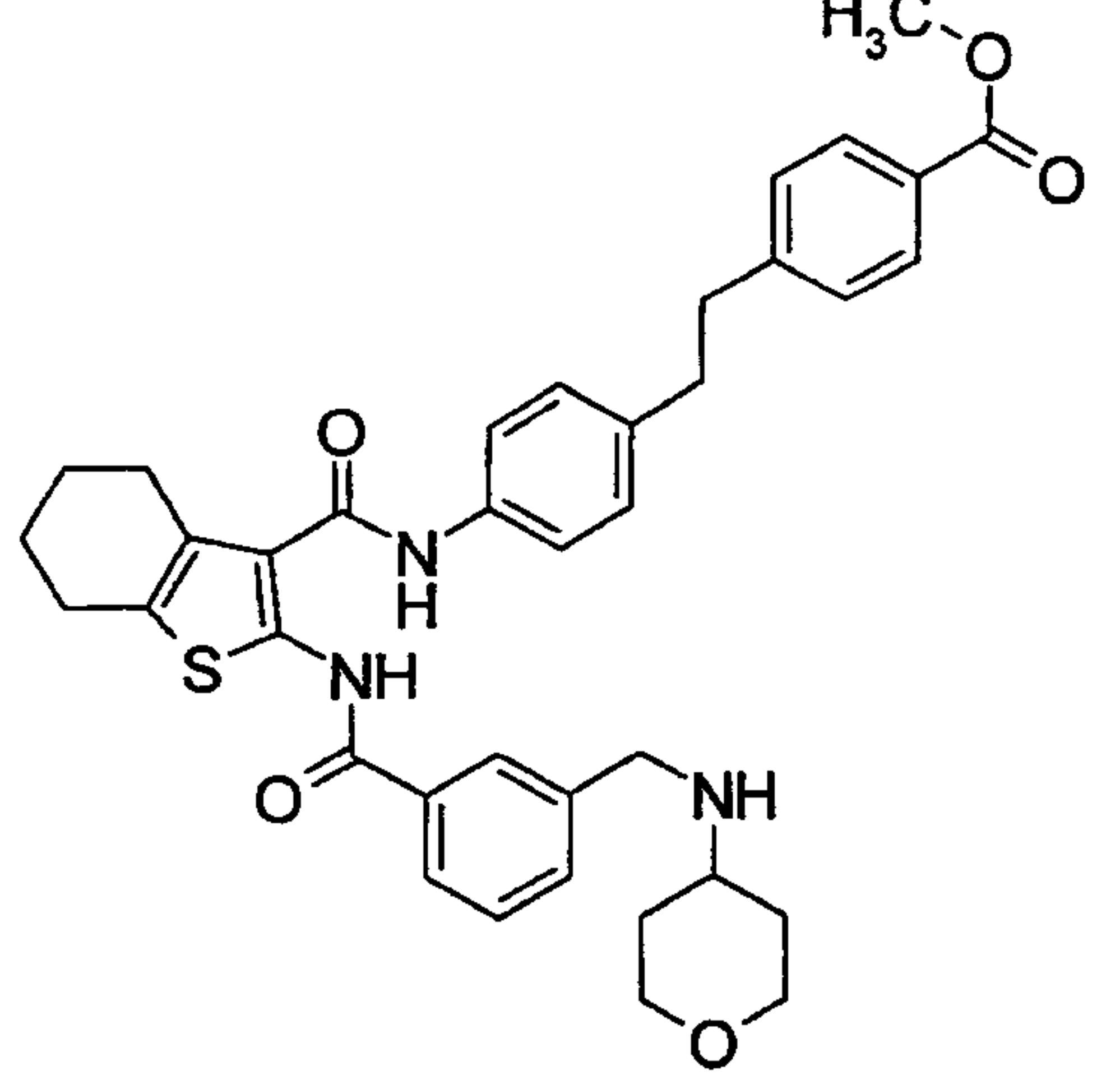
[0157]
[Table 12]

Pr	Str	Pr	Str
71		77	
72		78	
73		79	
74		80	
75			
76			

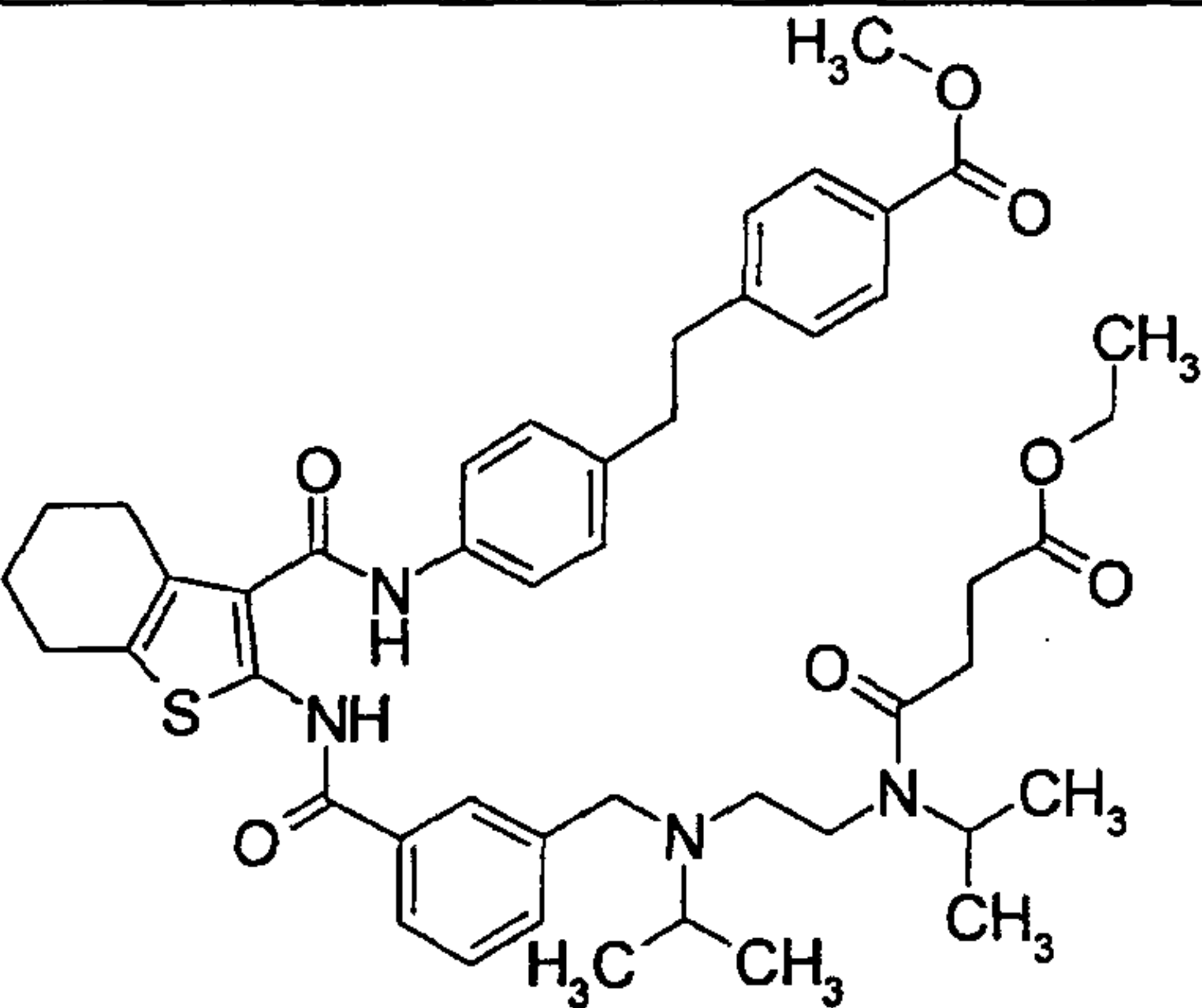
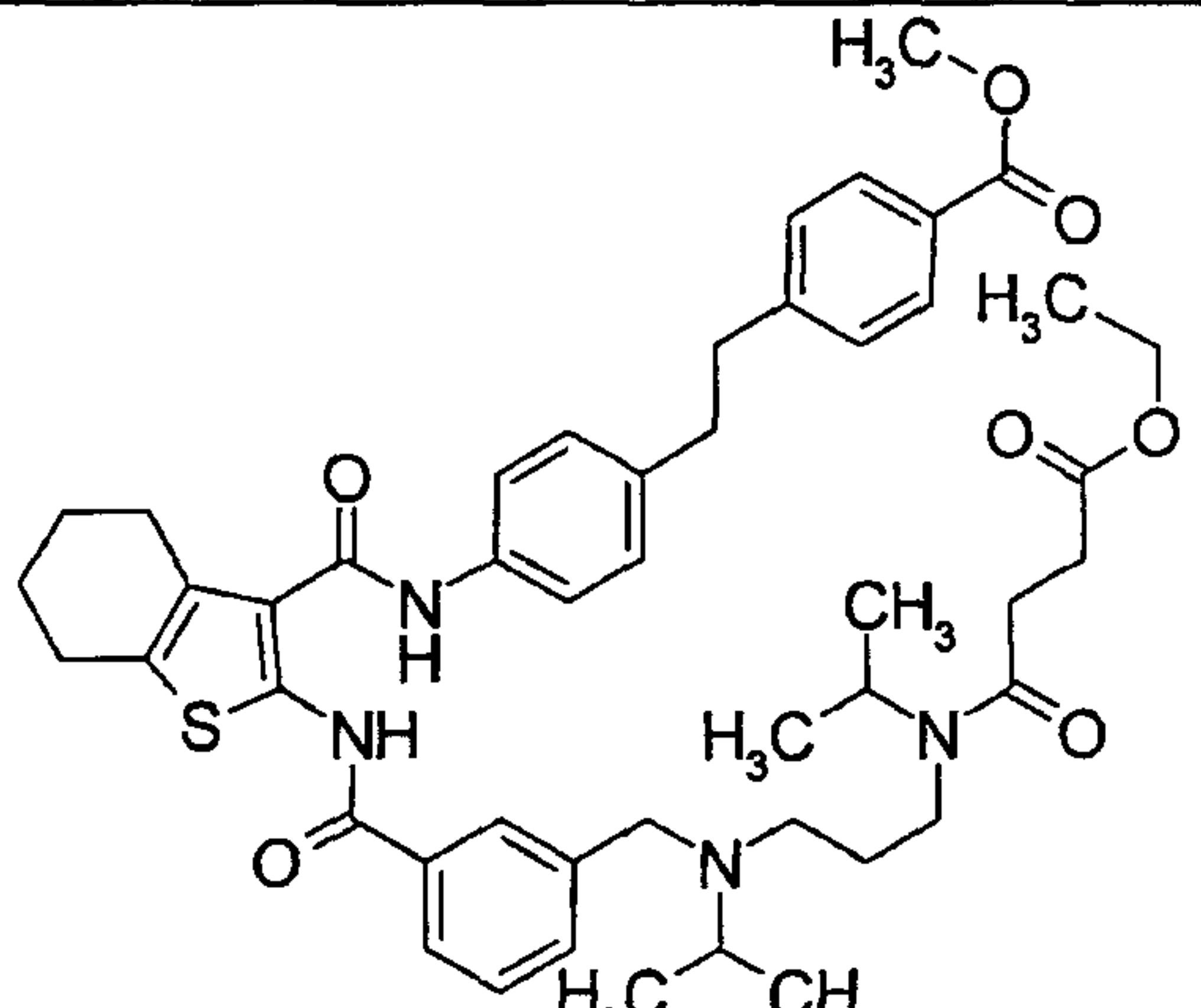
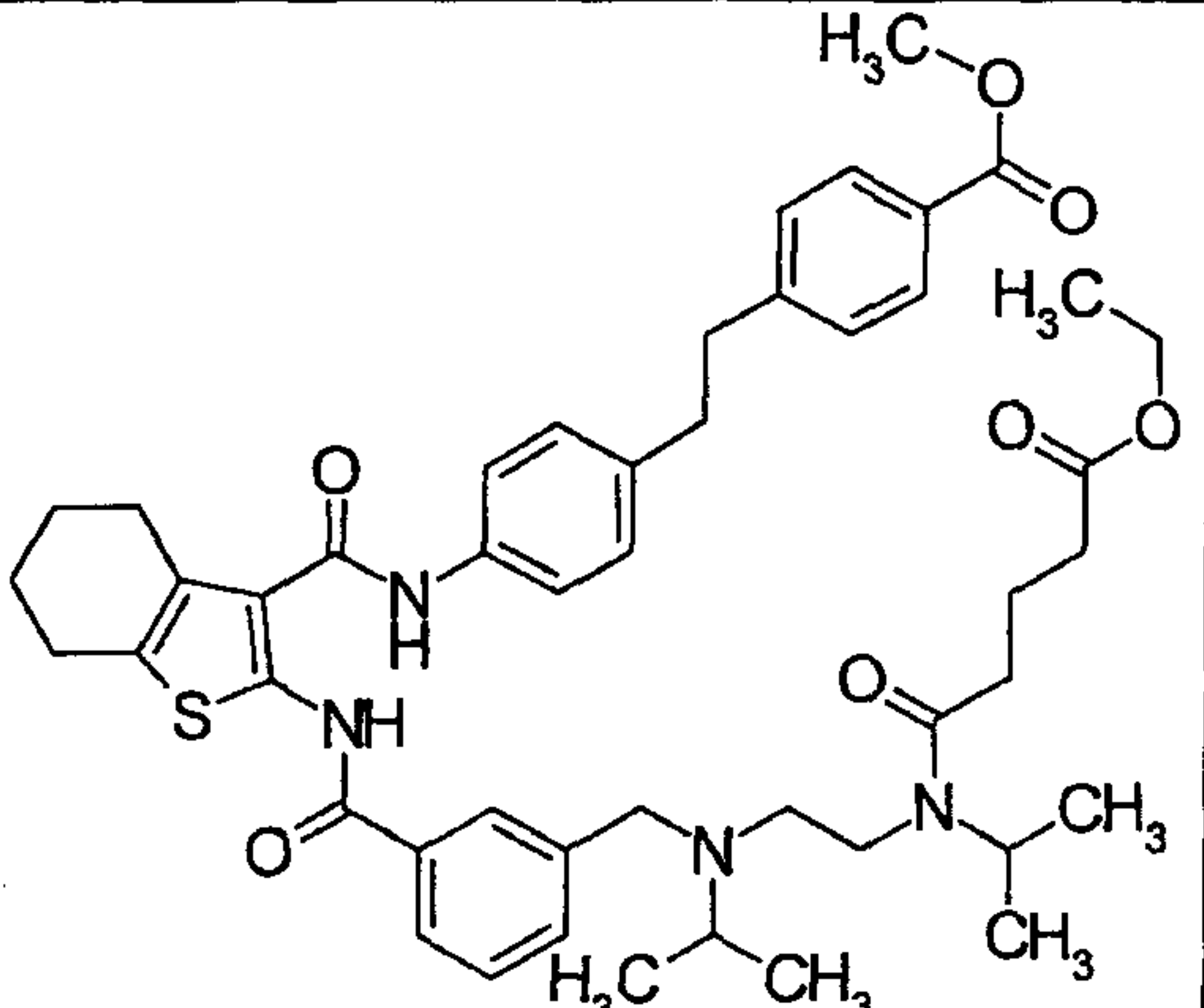
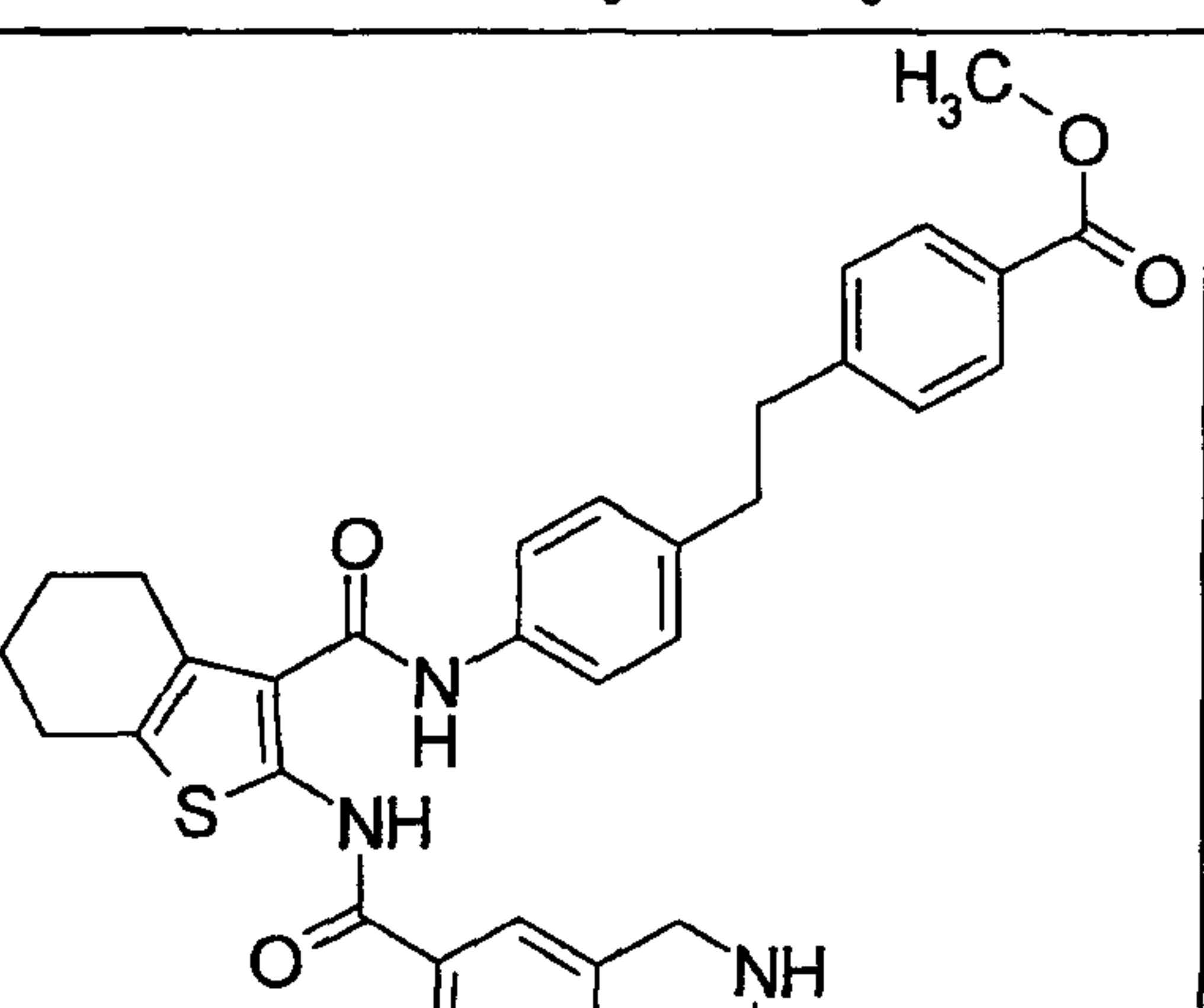
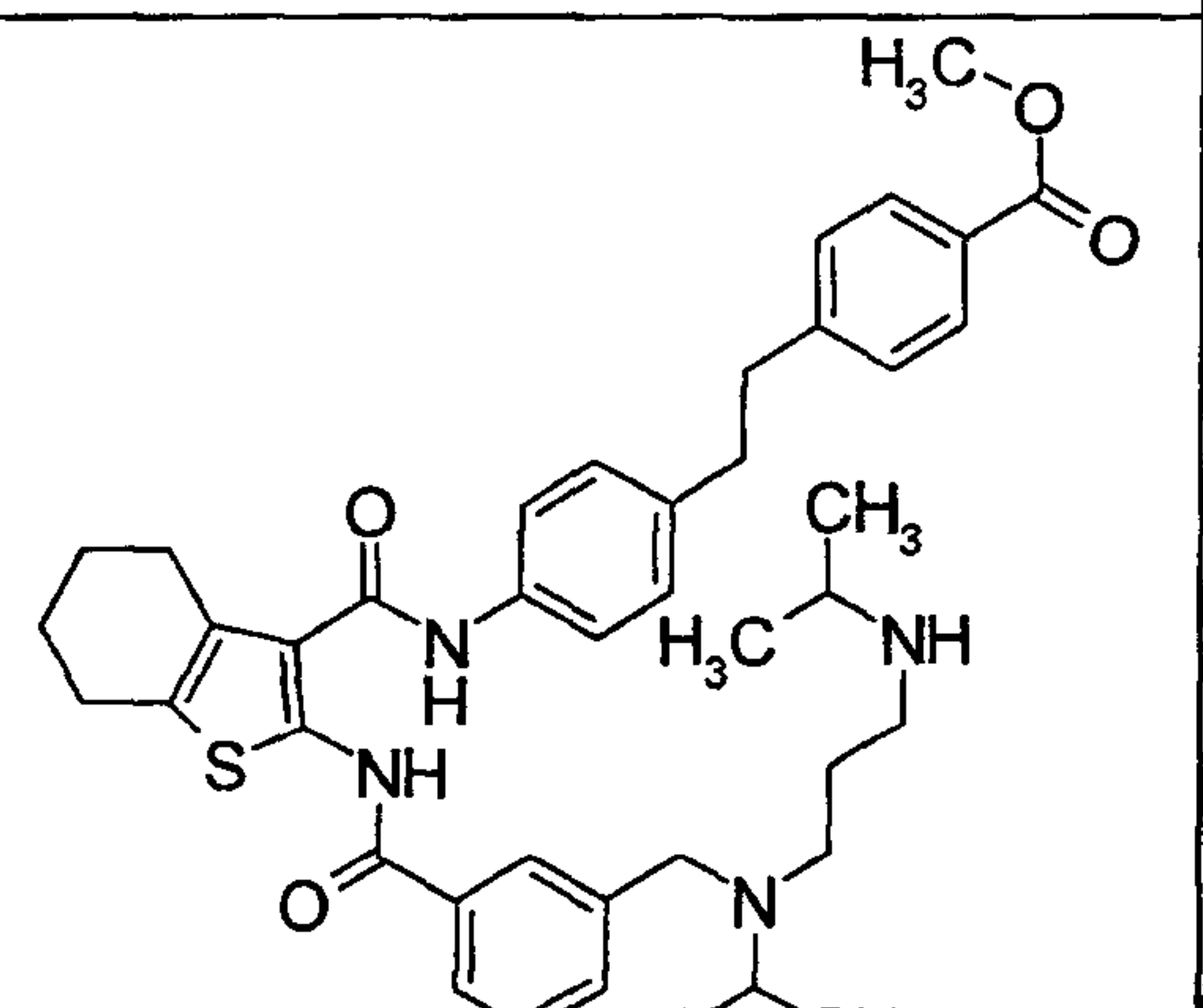
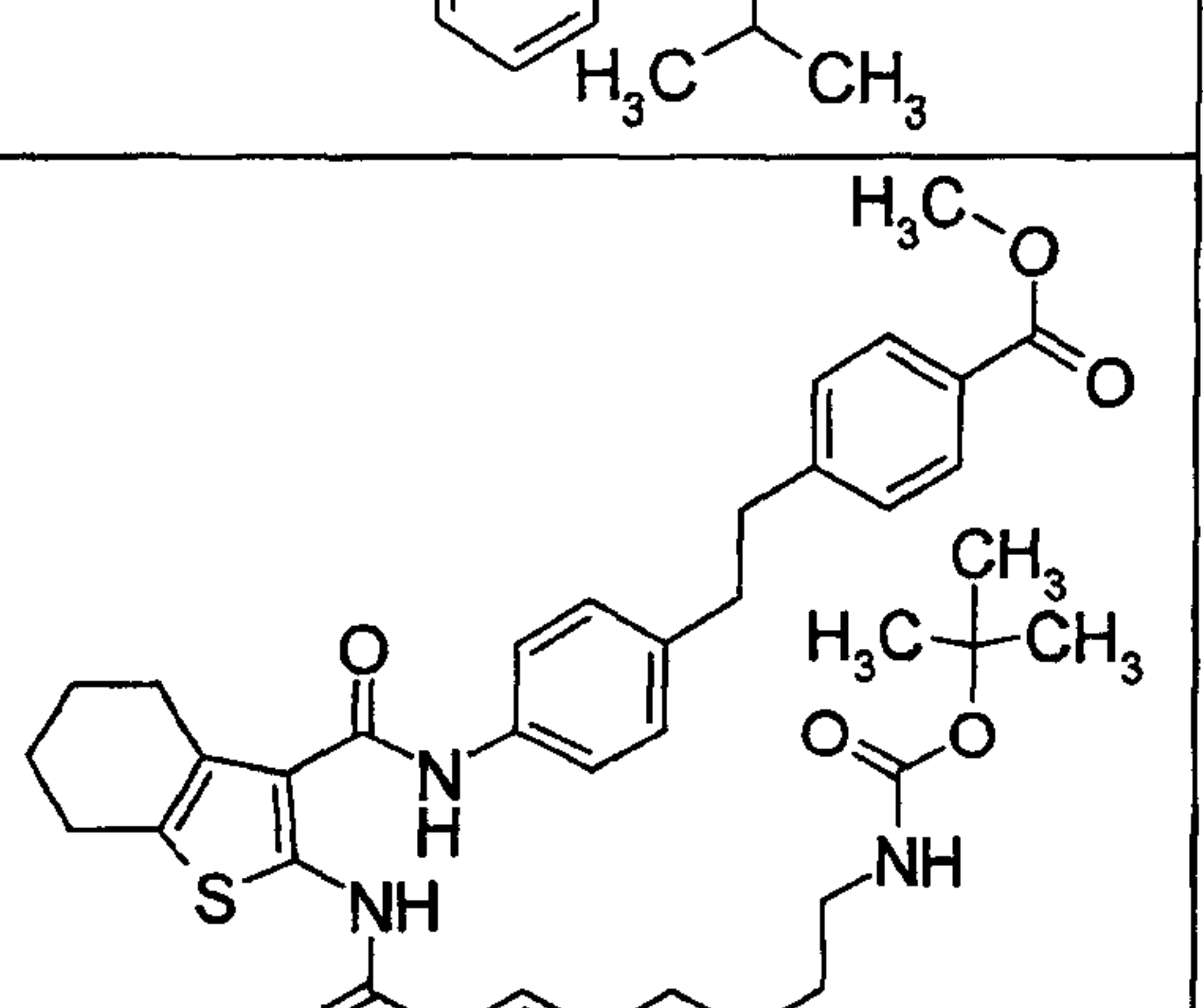
[0158]
[Table 13]

Pr	Str	Pr	Str
81		85	
82		86	
83		87	
84			

[0159]
[Table 14]

Pr	Str	Pr	Str
88		91	
89		92	
90			

[0160]
[Table 15]

Pr	Str	Pr	Str
93		96	
94		97	
95		98	

[0161]
[Table 16]

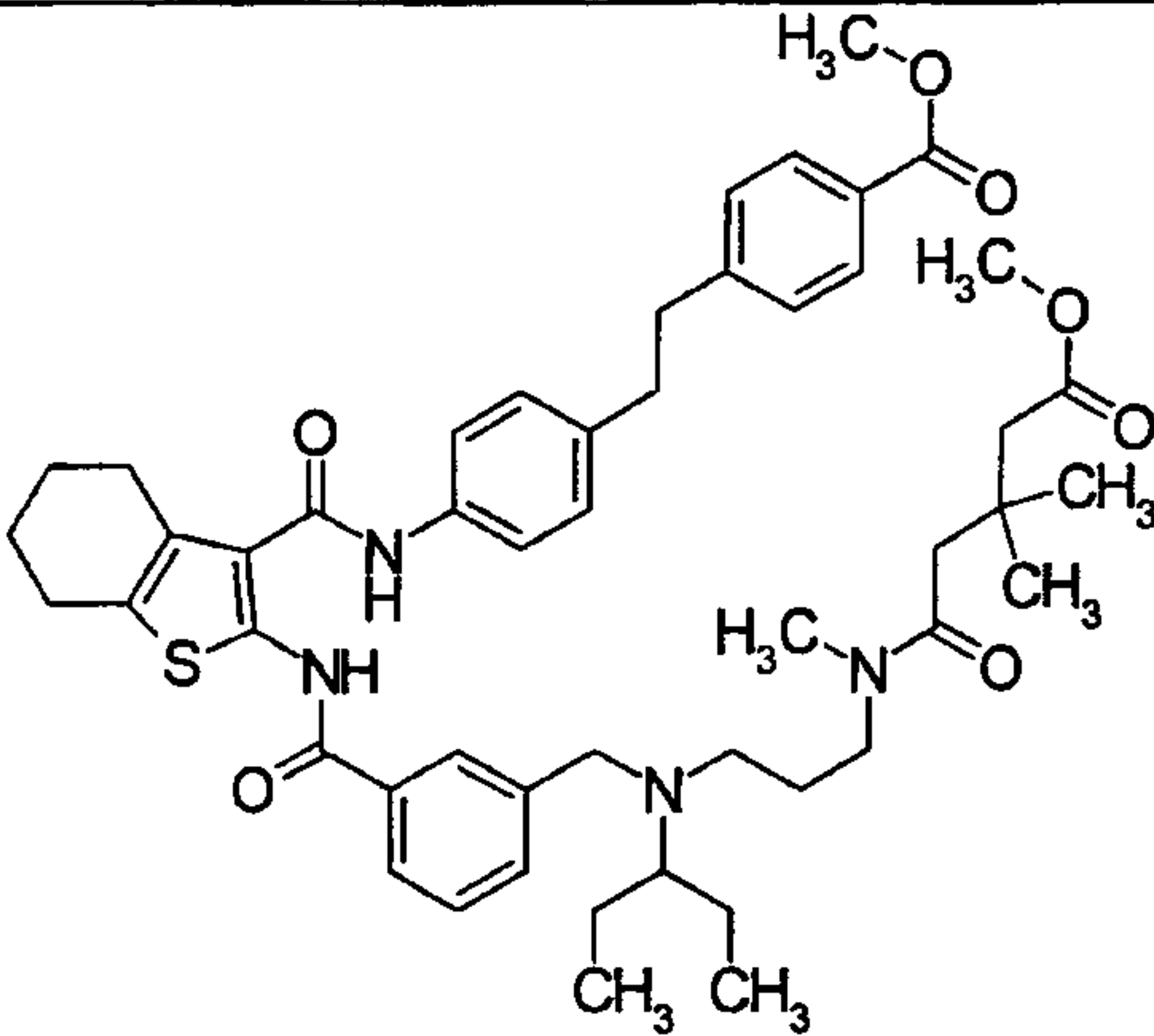
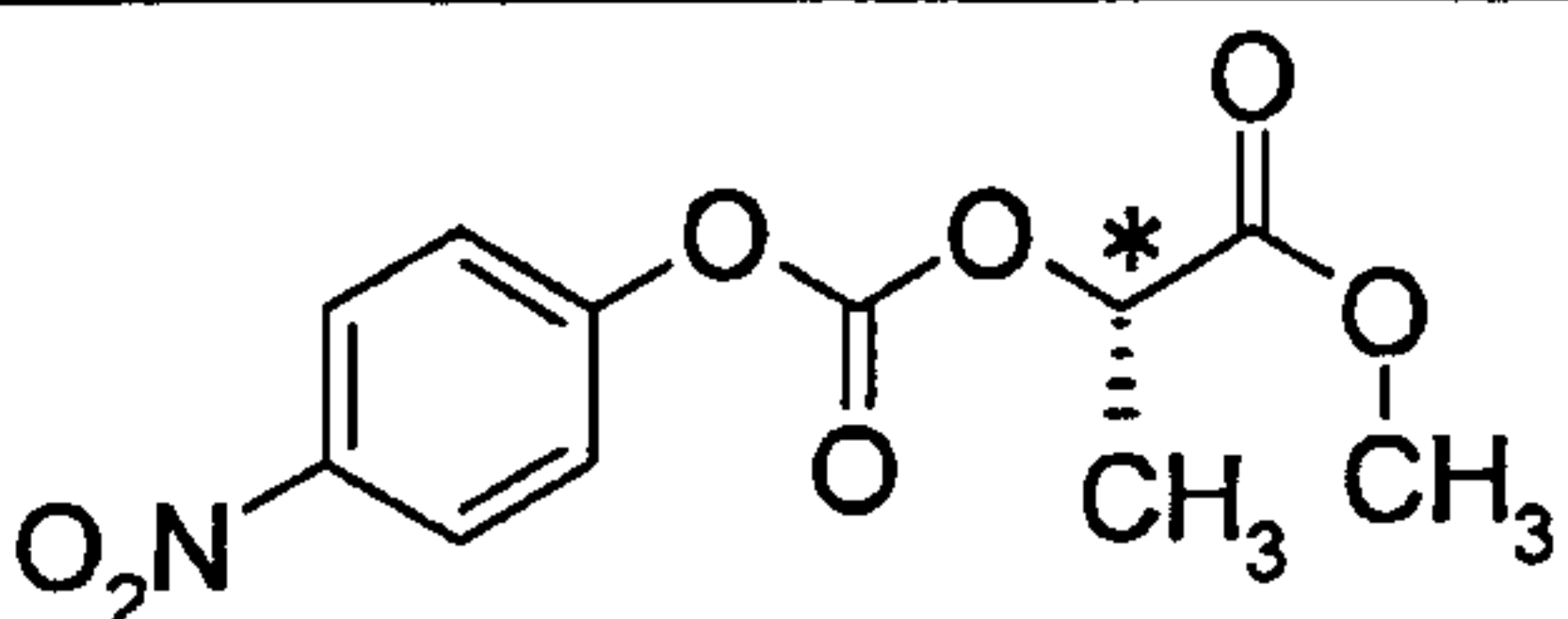
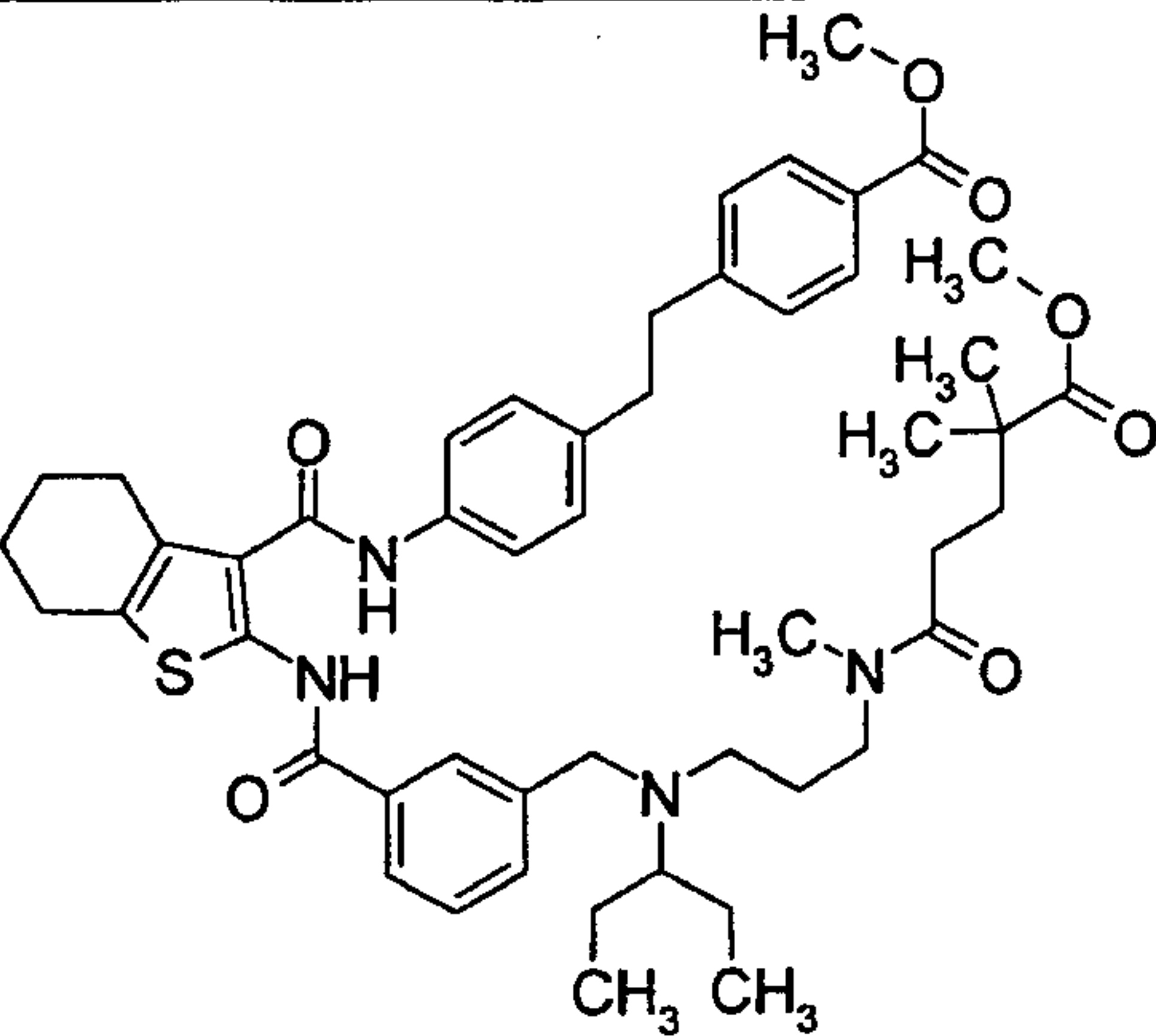
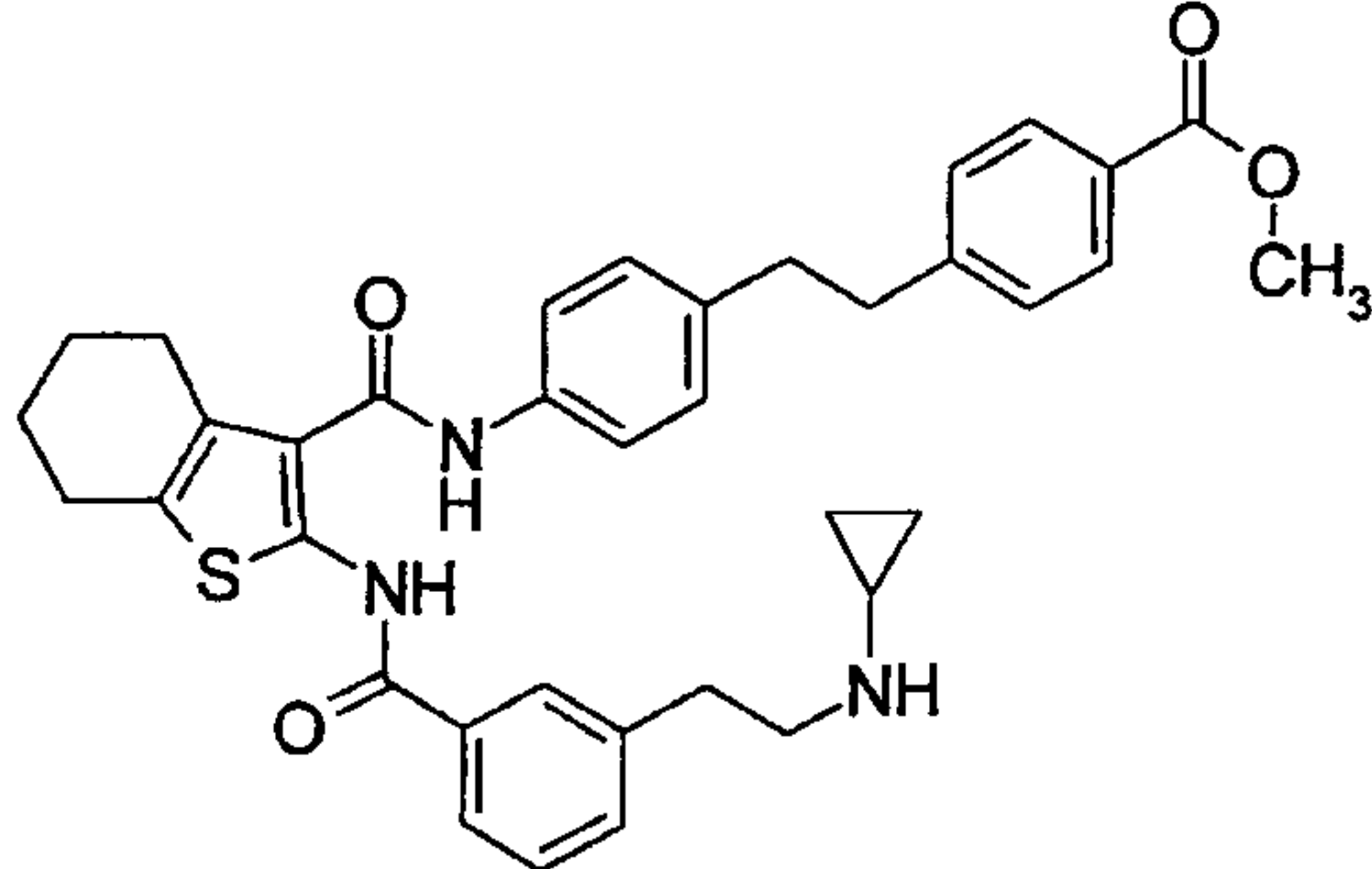
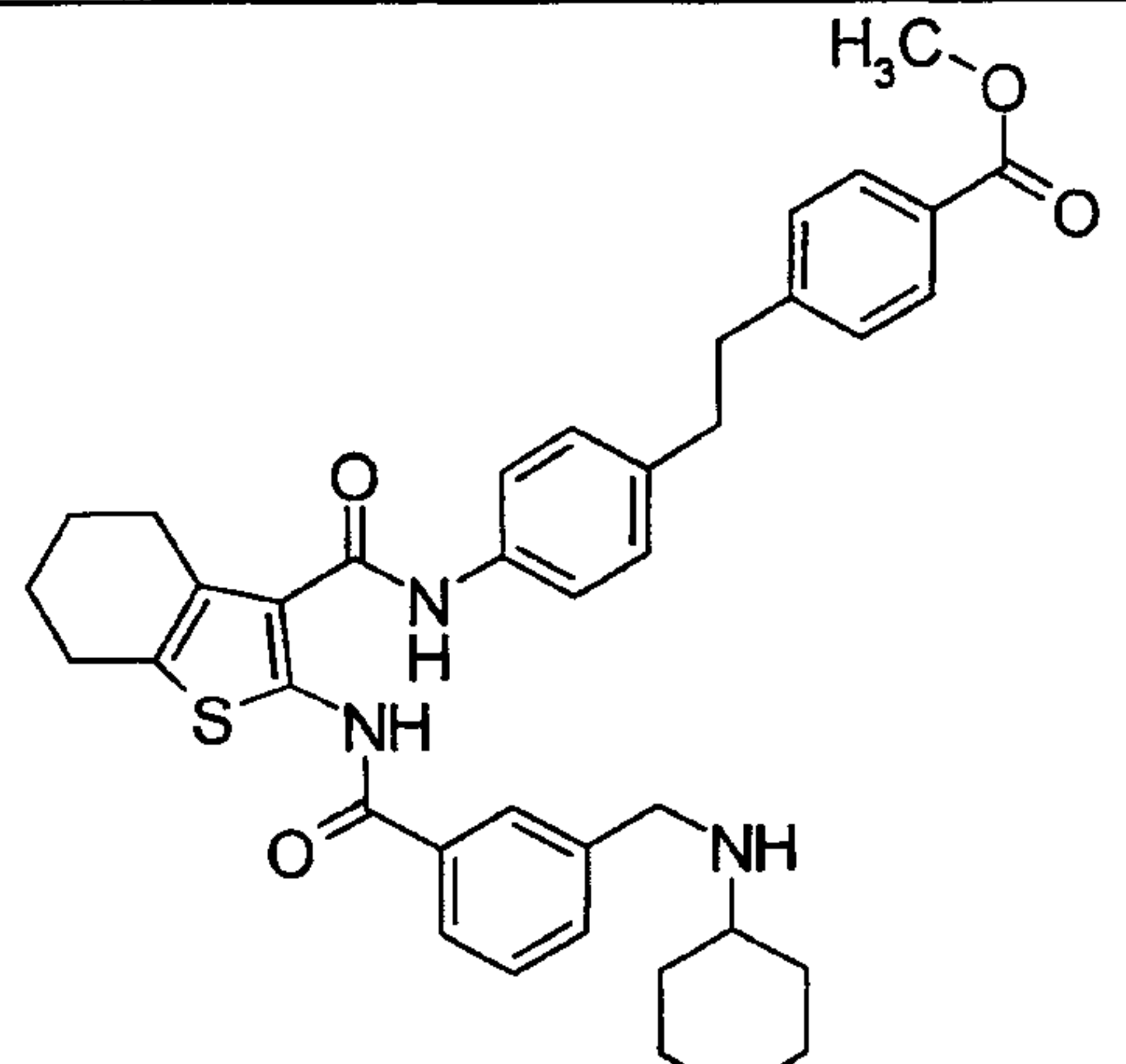
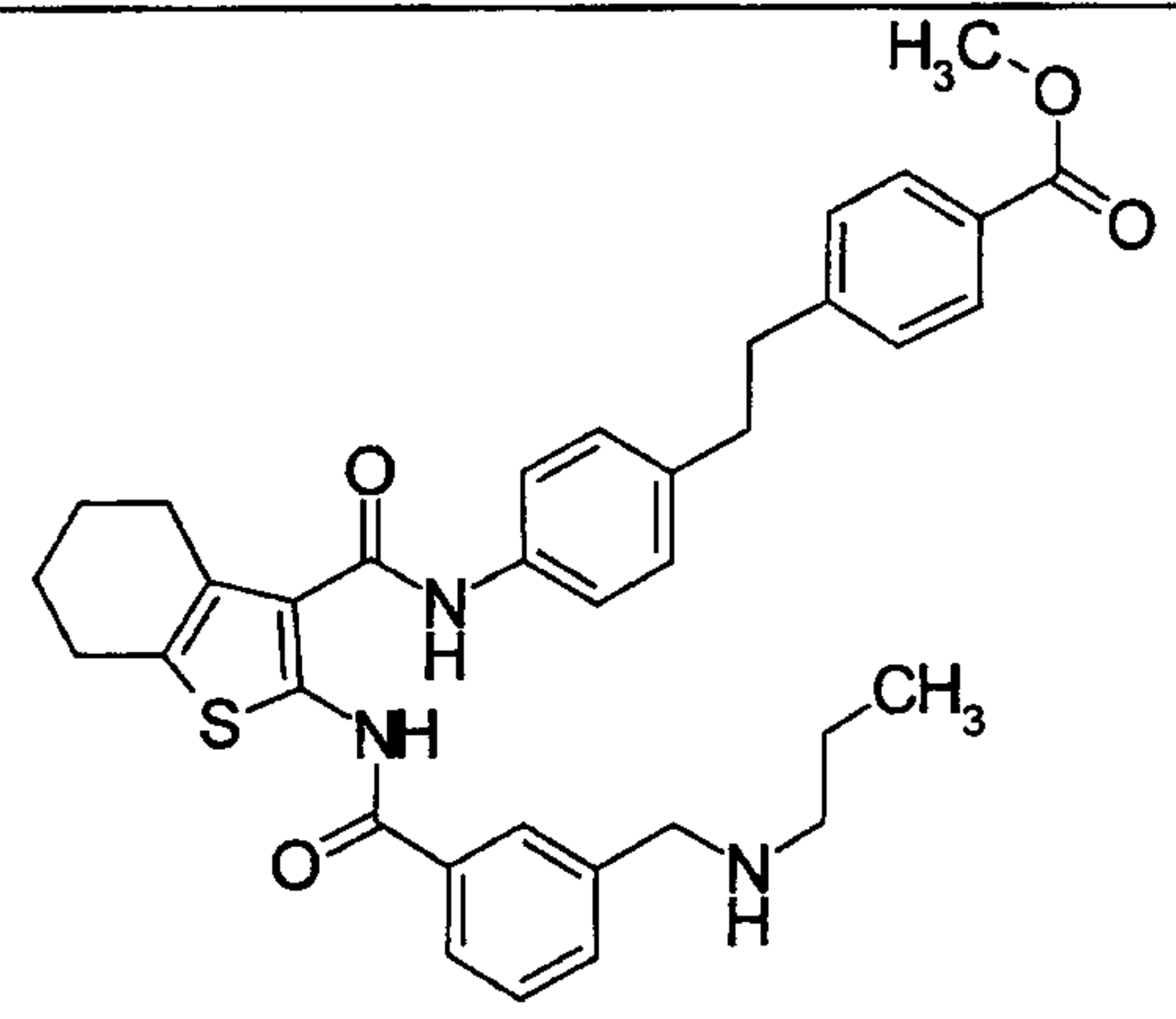
Pr	Str	Pr	Str
99	<chem>COc1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C)CC)C4</chem>	101	<chem>COc1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C)CC)C4</chem>
100	<chem>COc1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C)CC)C4</chem>	102	<chem>COc1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C)CC)C4</chem>
		103	<chem>COc1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C)CC)C4</chem>

[0162]
[Table 17]

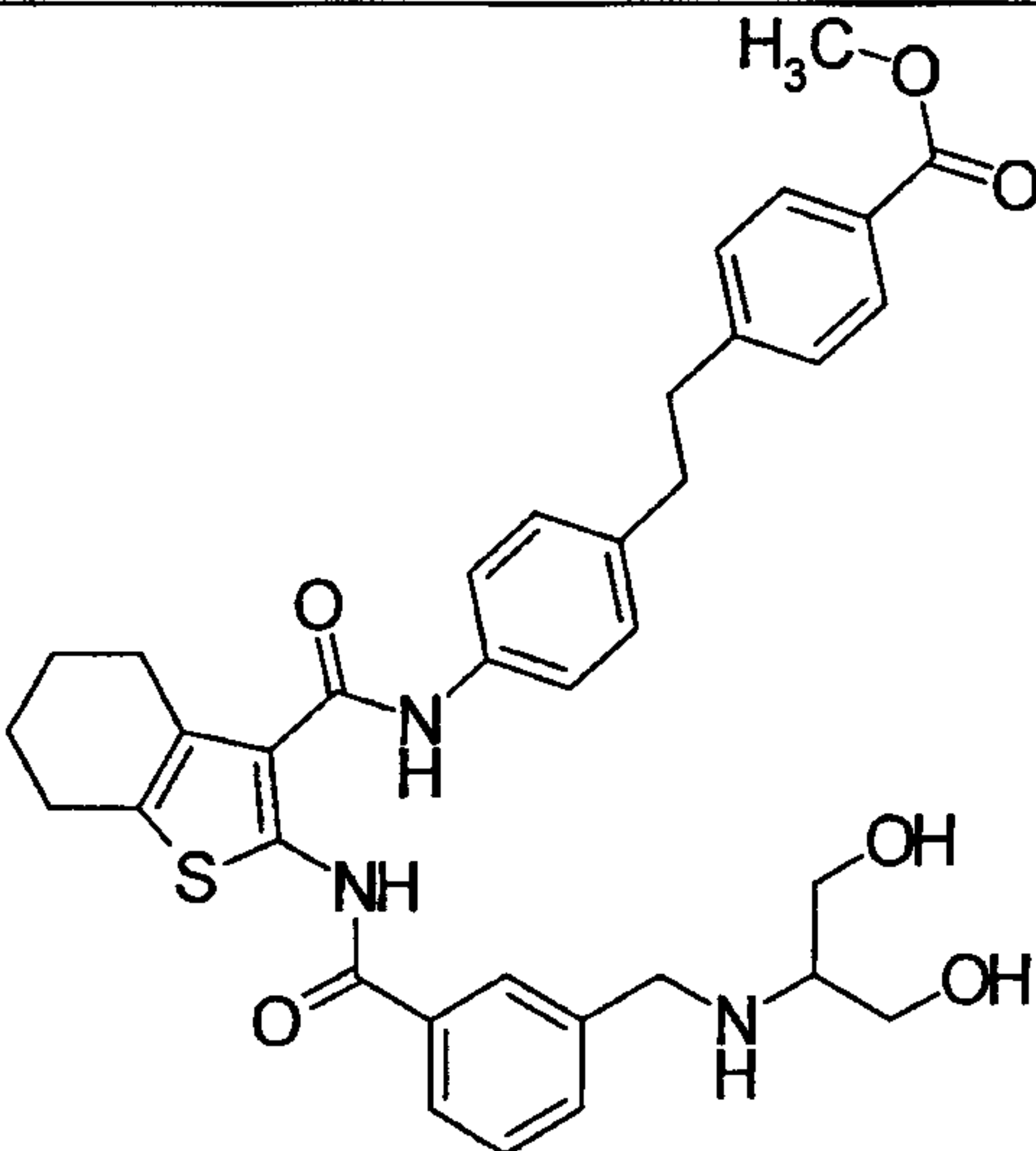
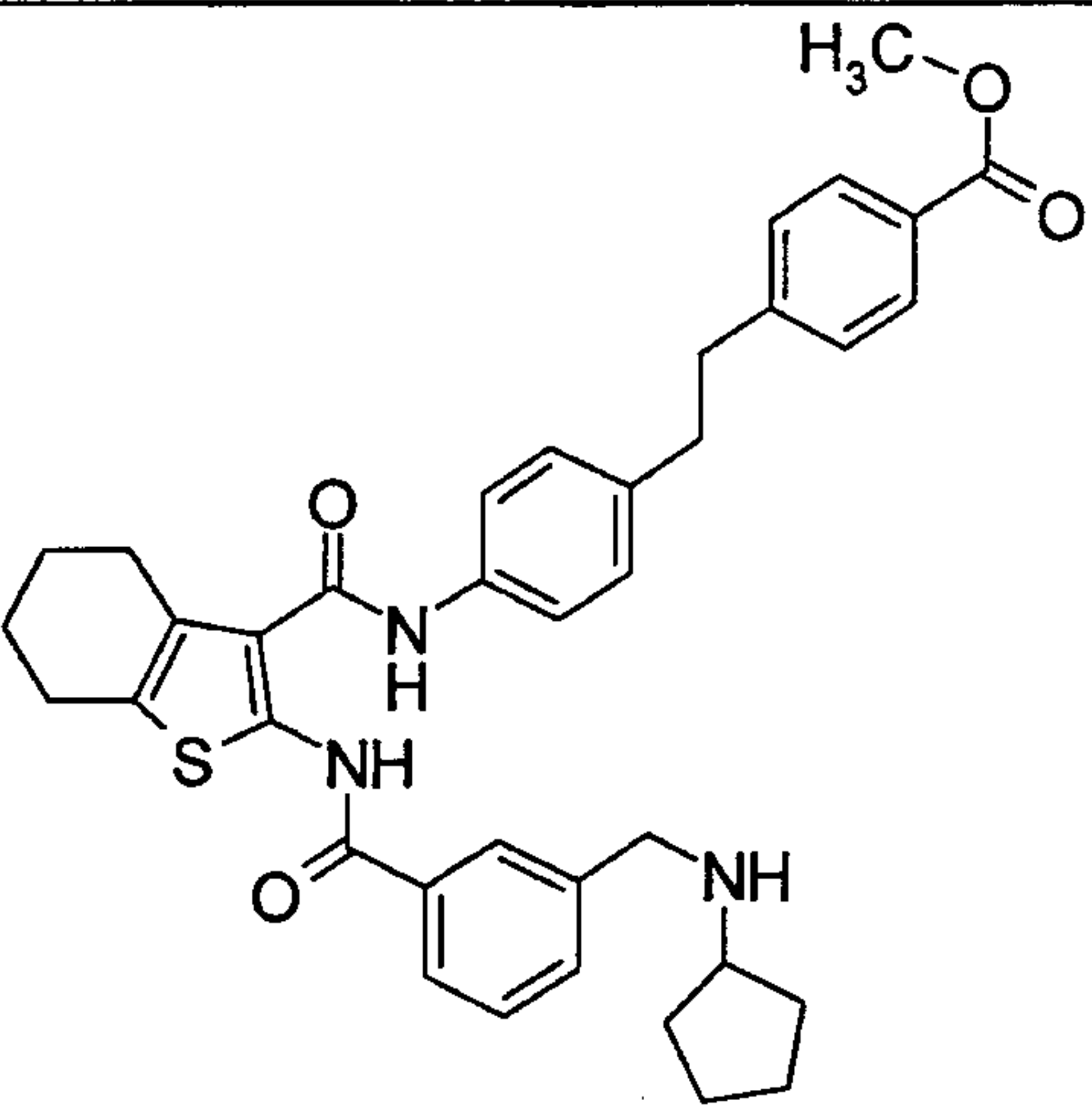
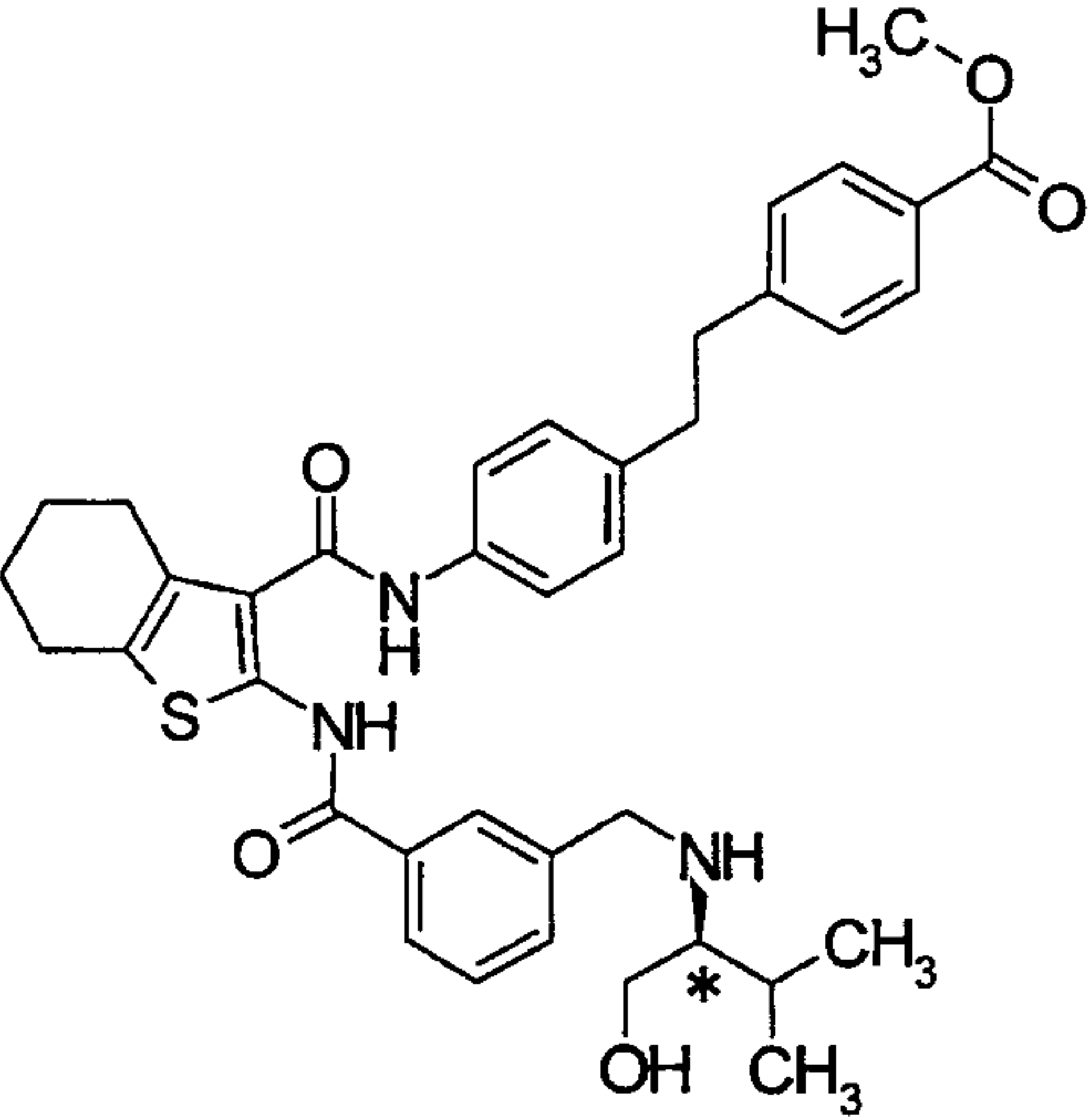
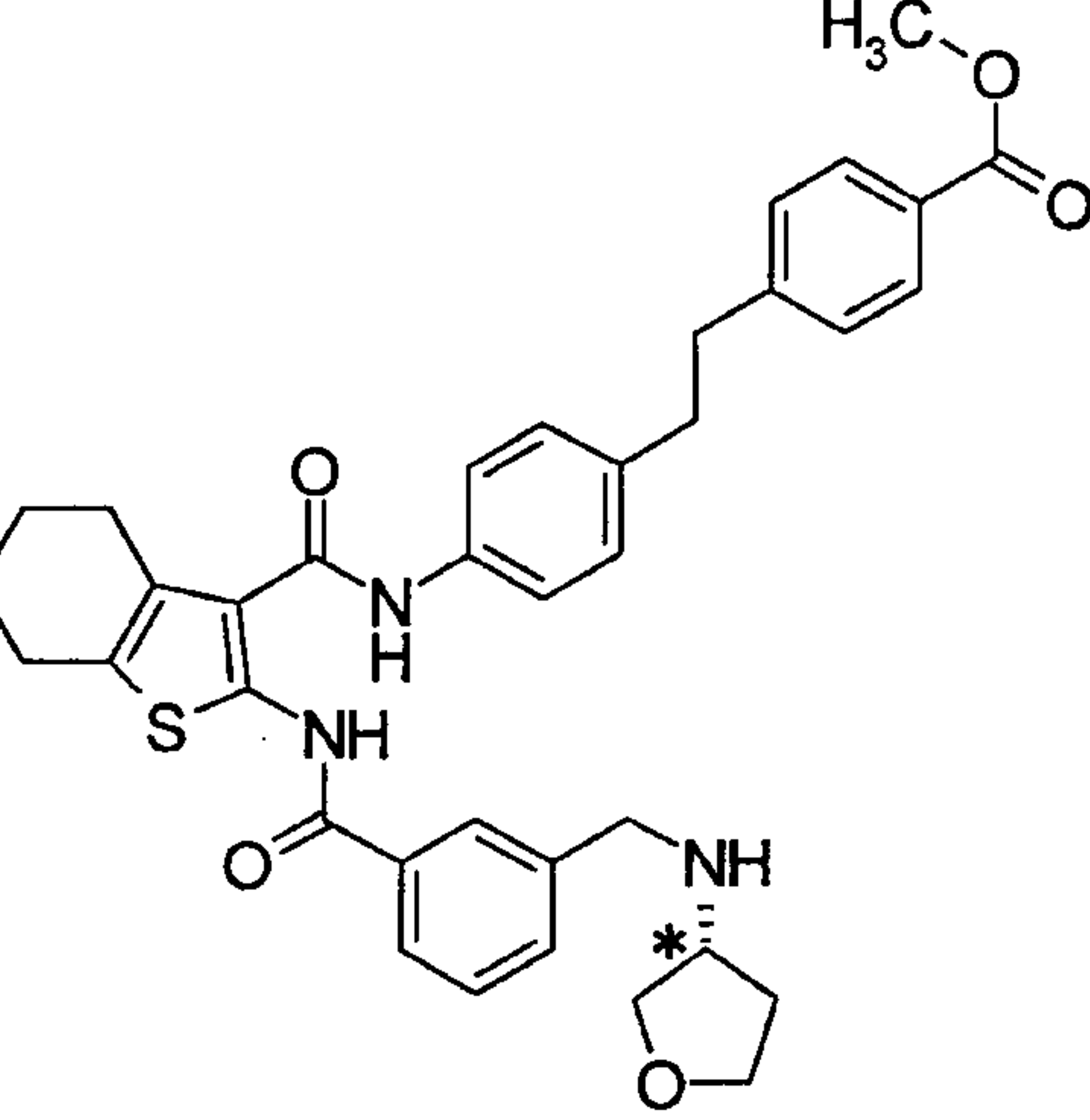
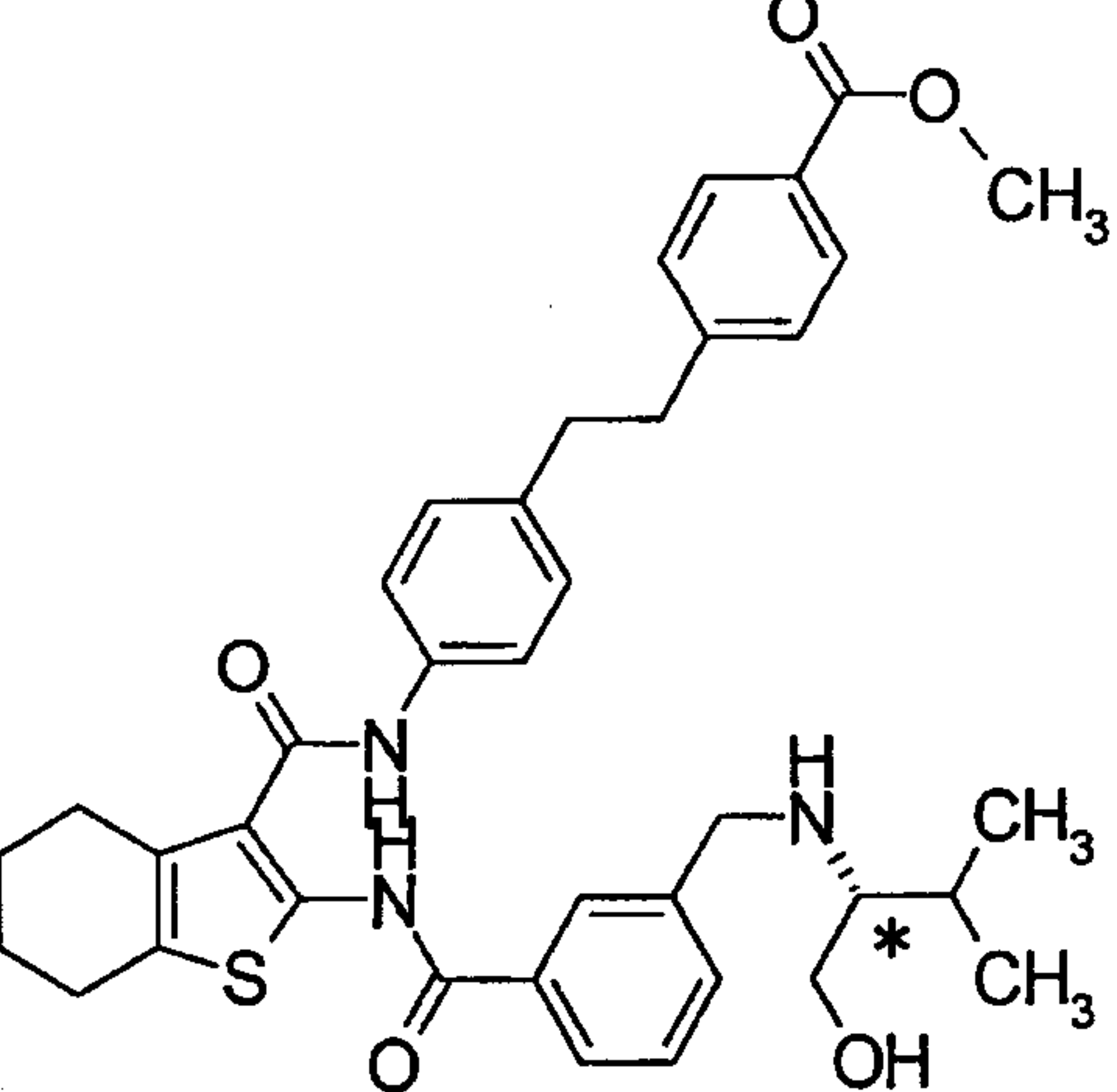
Pr	Str	Pr	Str
104		107	
105		108	
106			

[0163]

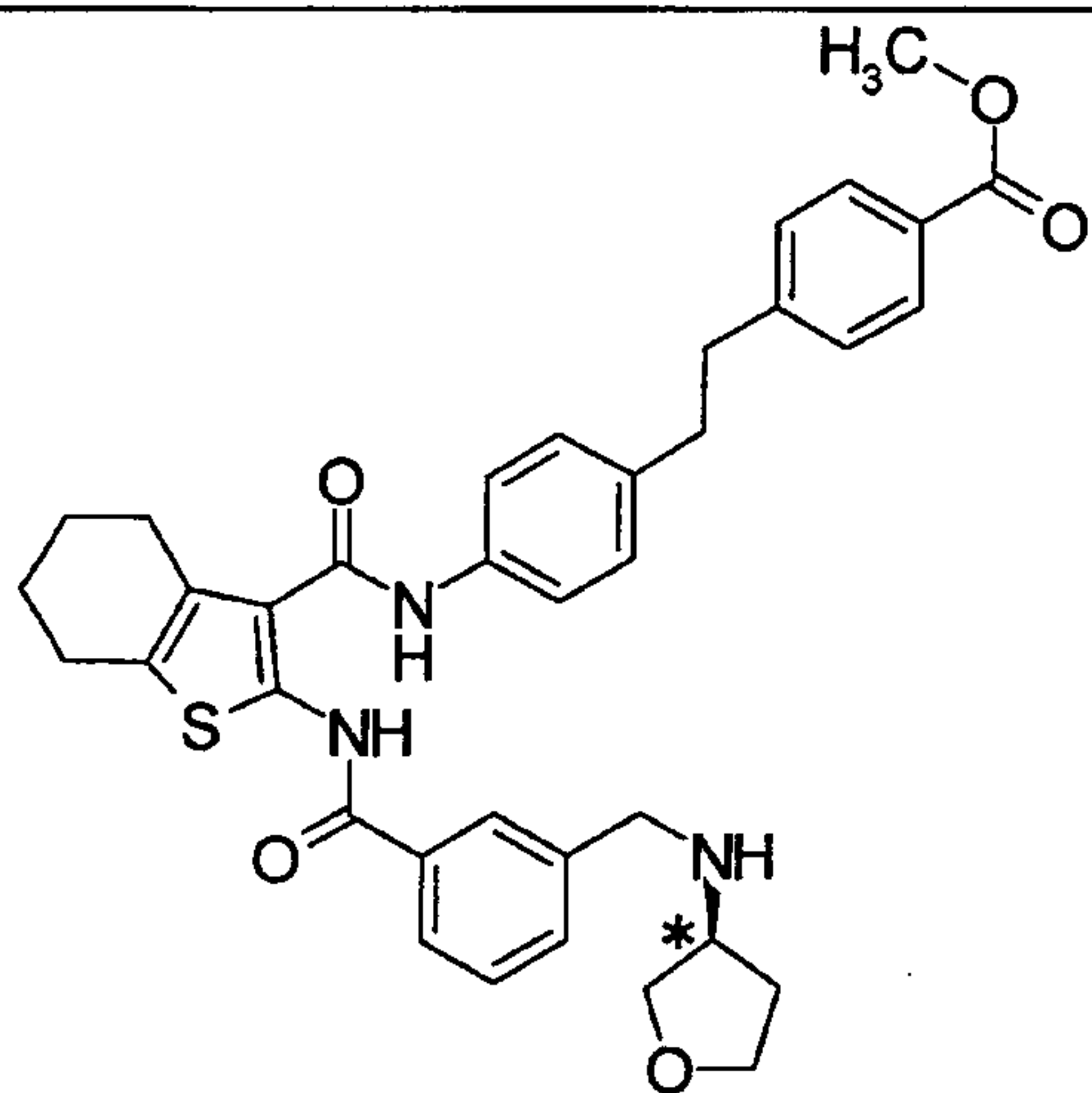
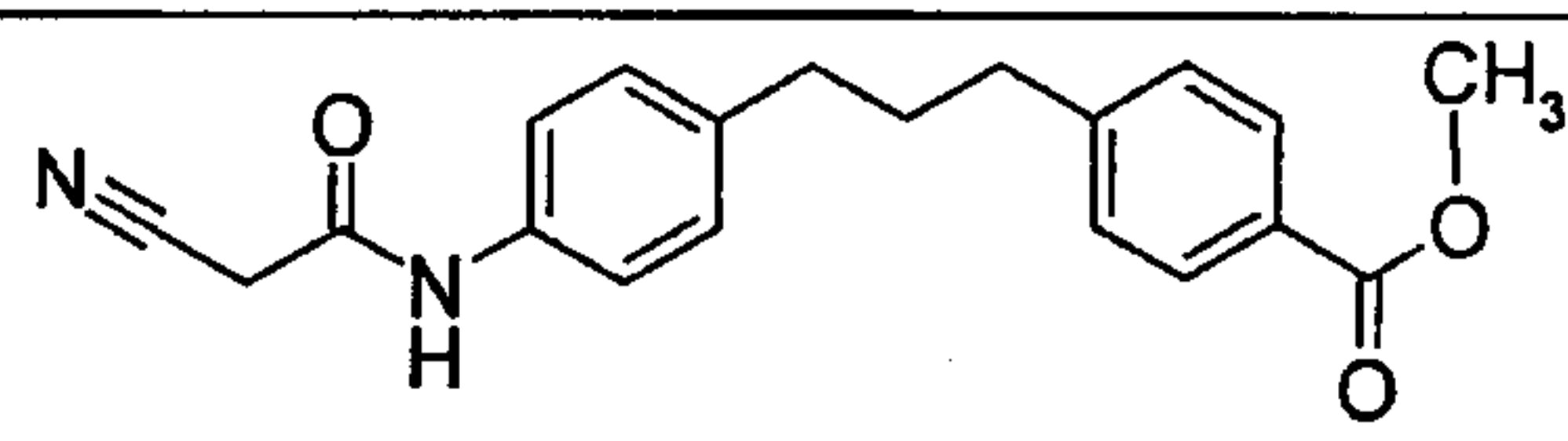
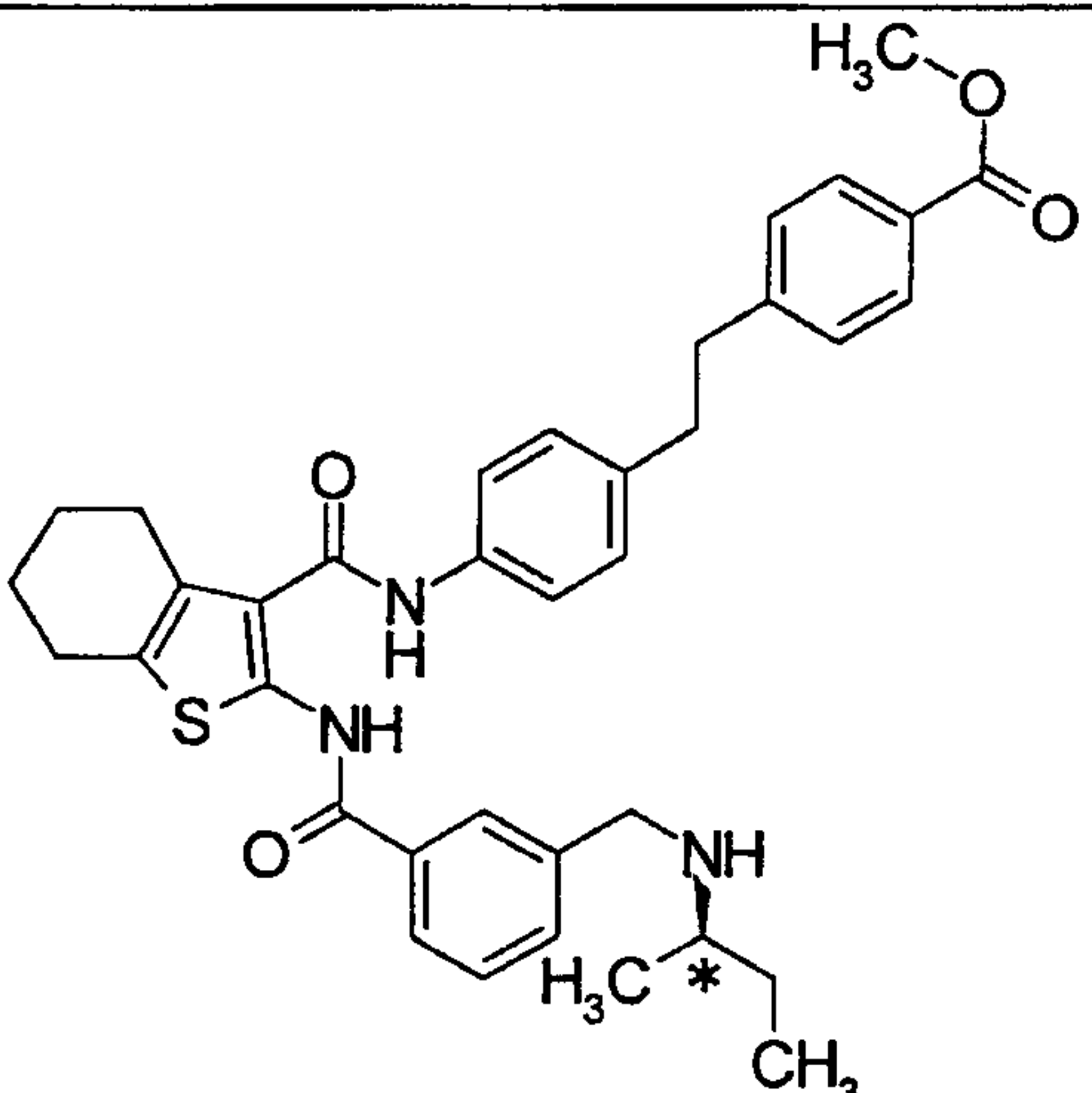
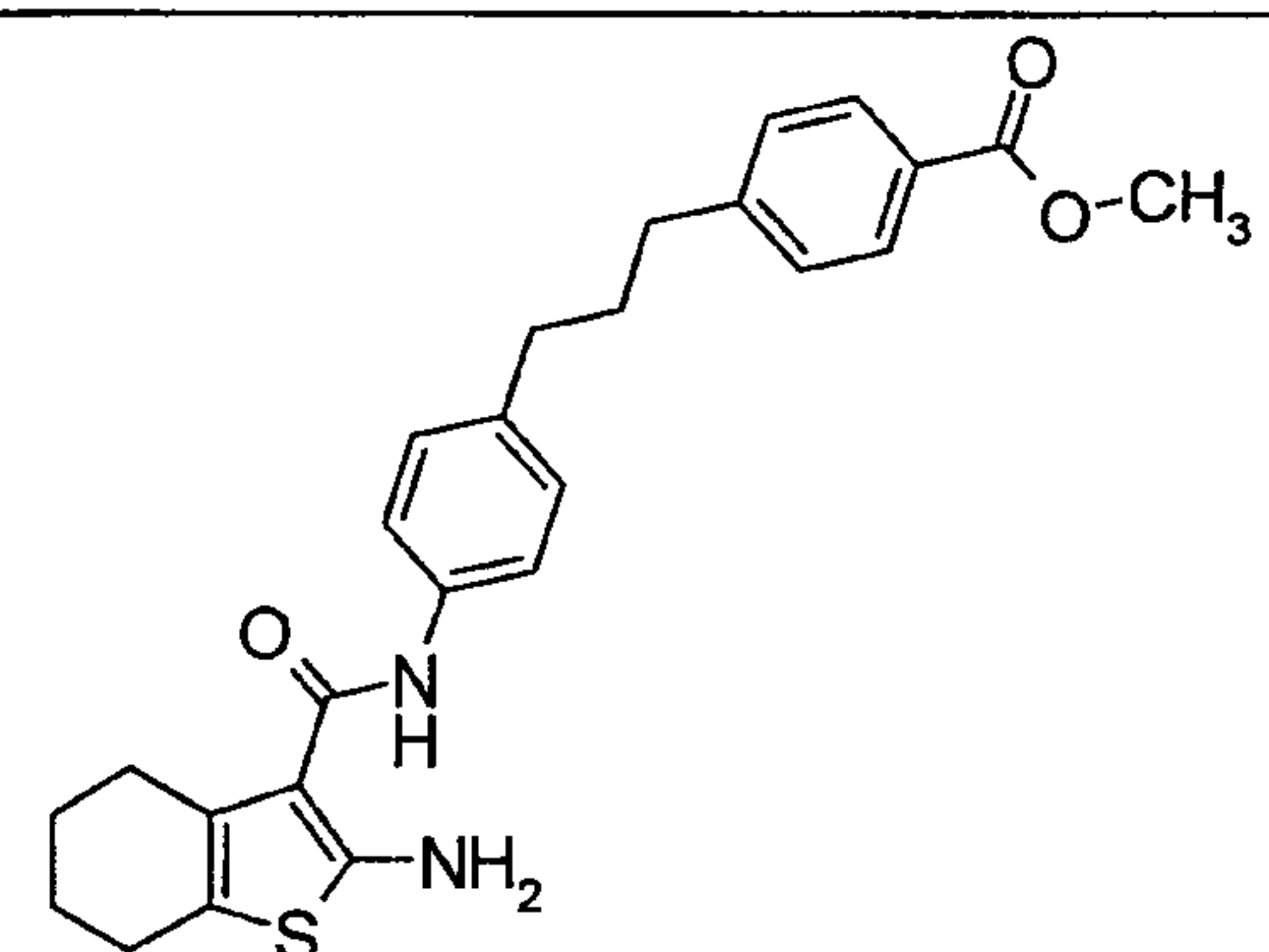
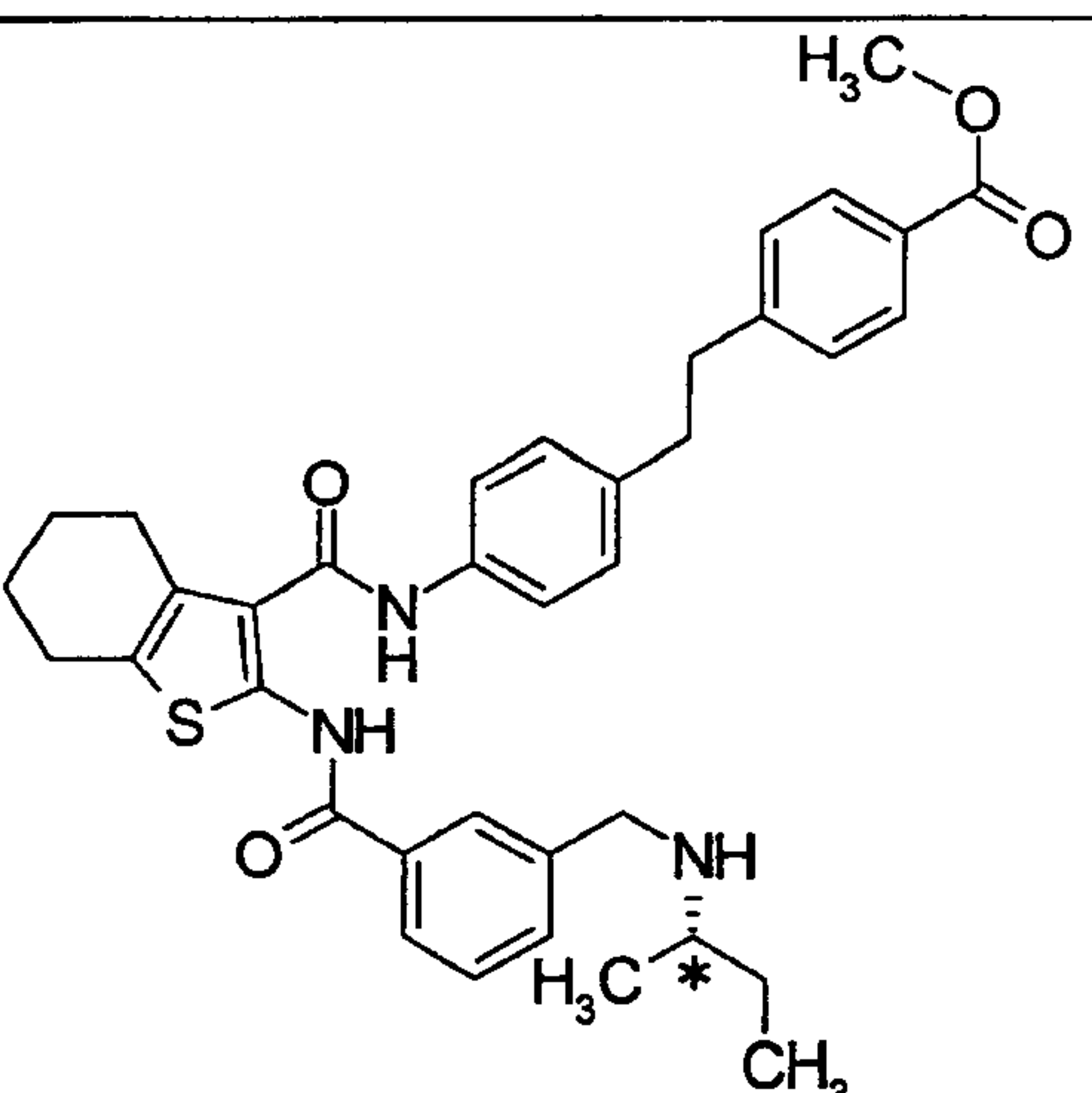
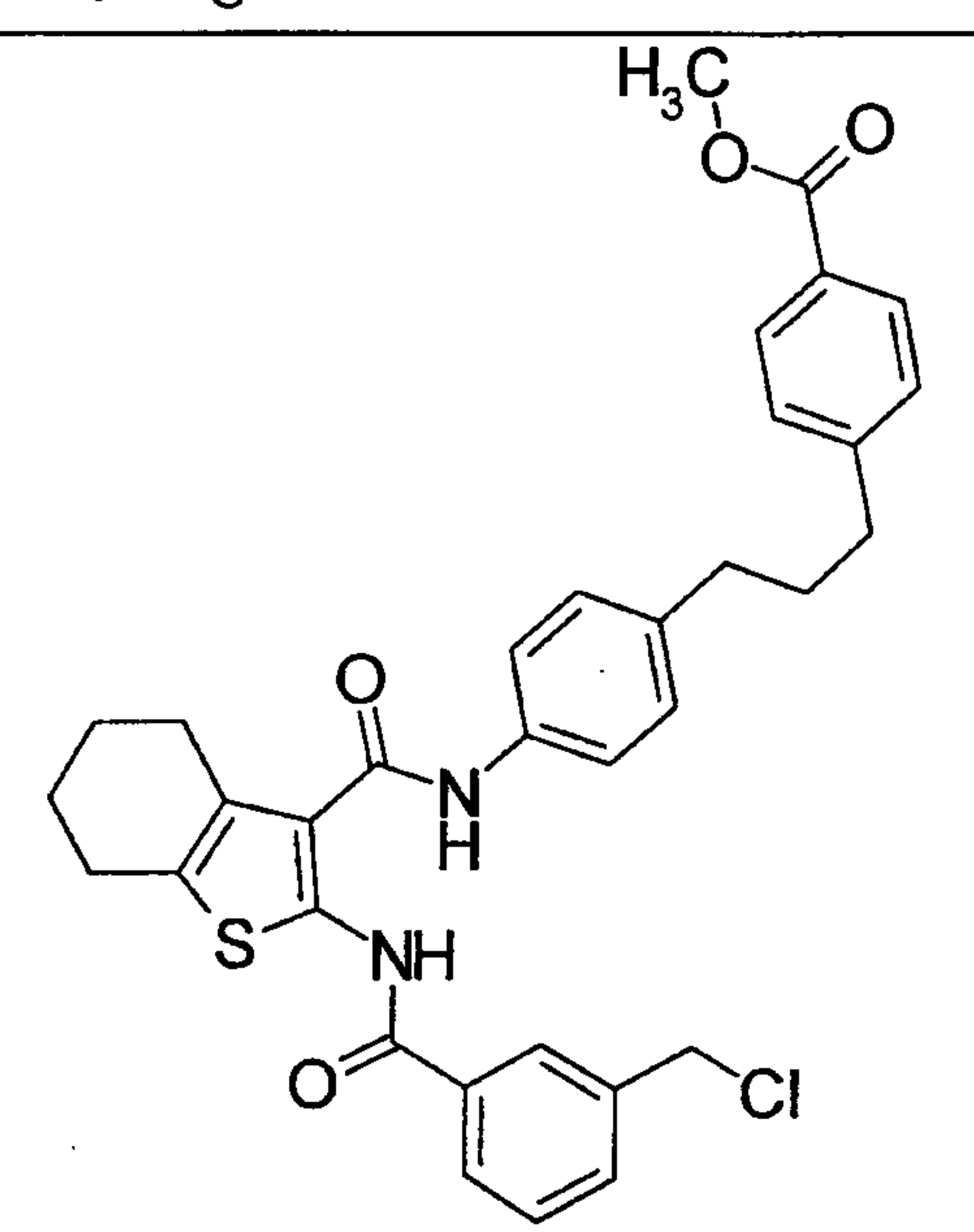
[Table 18]

Pr	Str	Pr	Str
109		112	
110		113	
111		114	

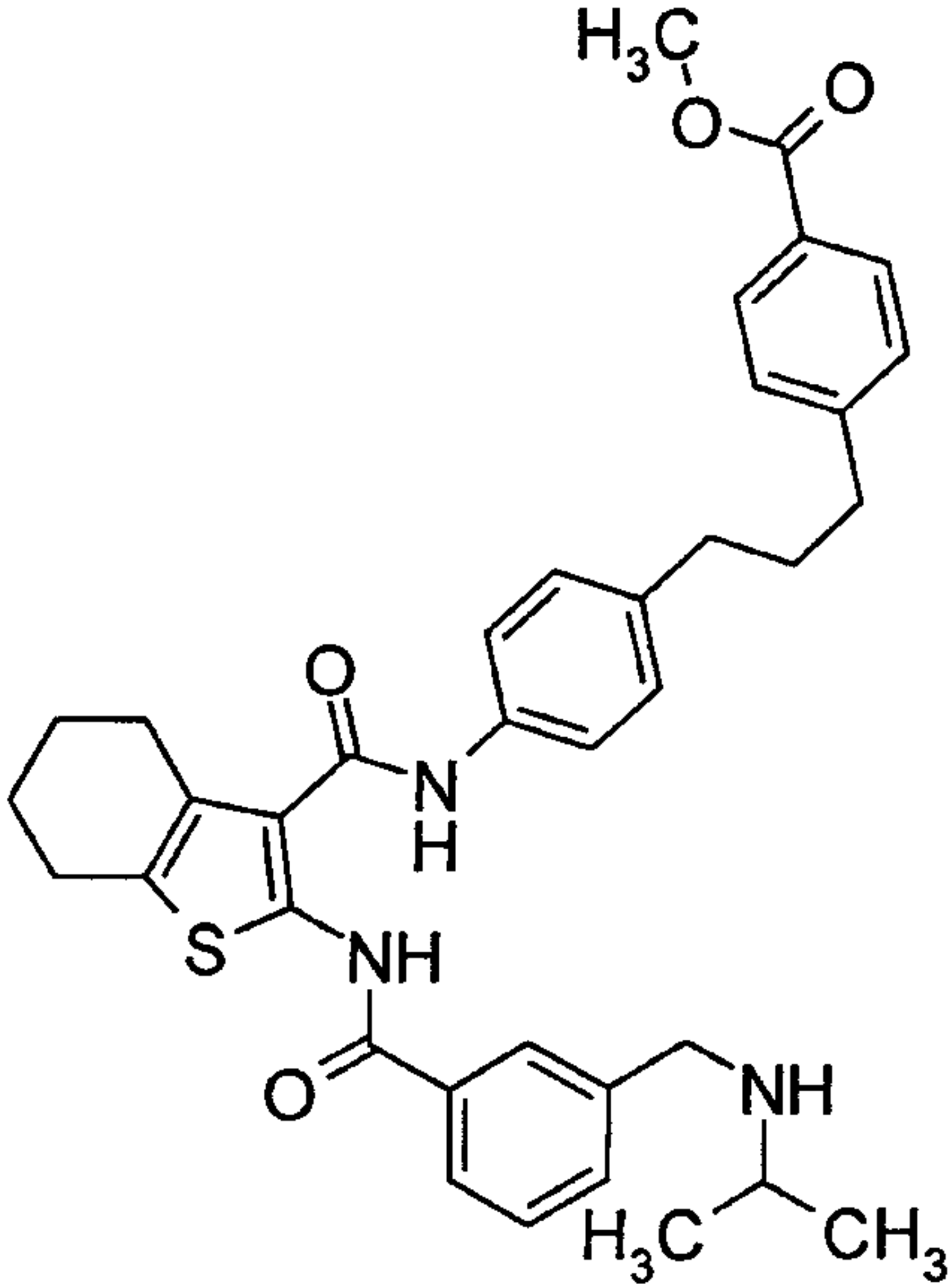
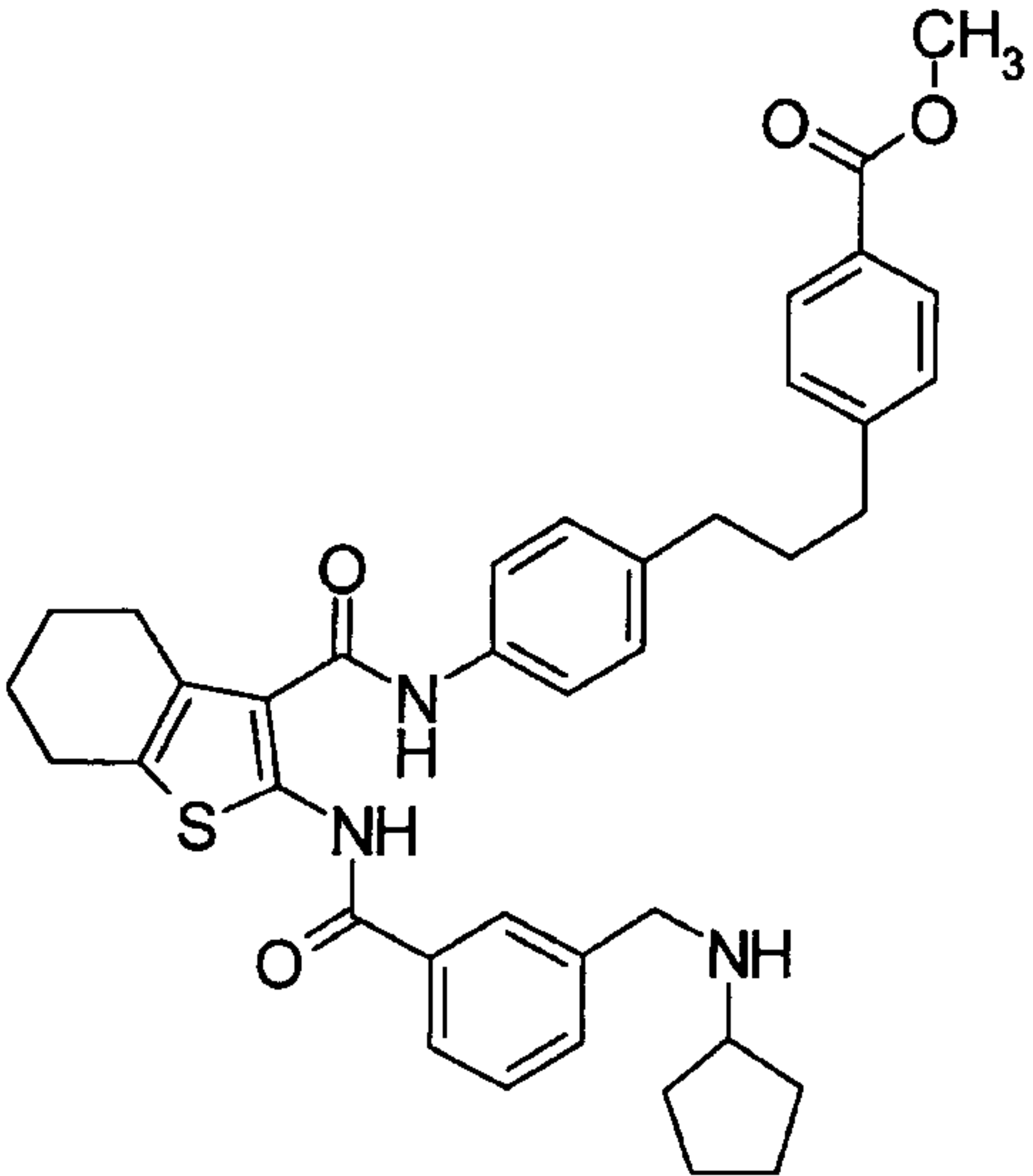
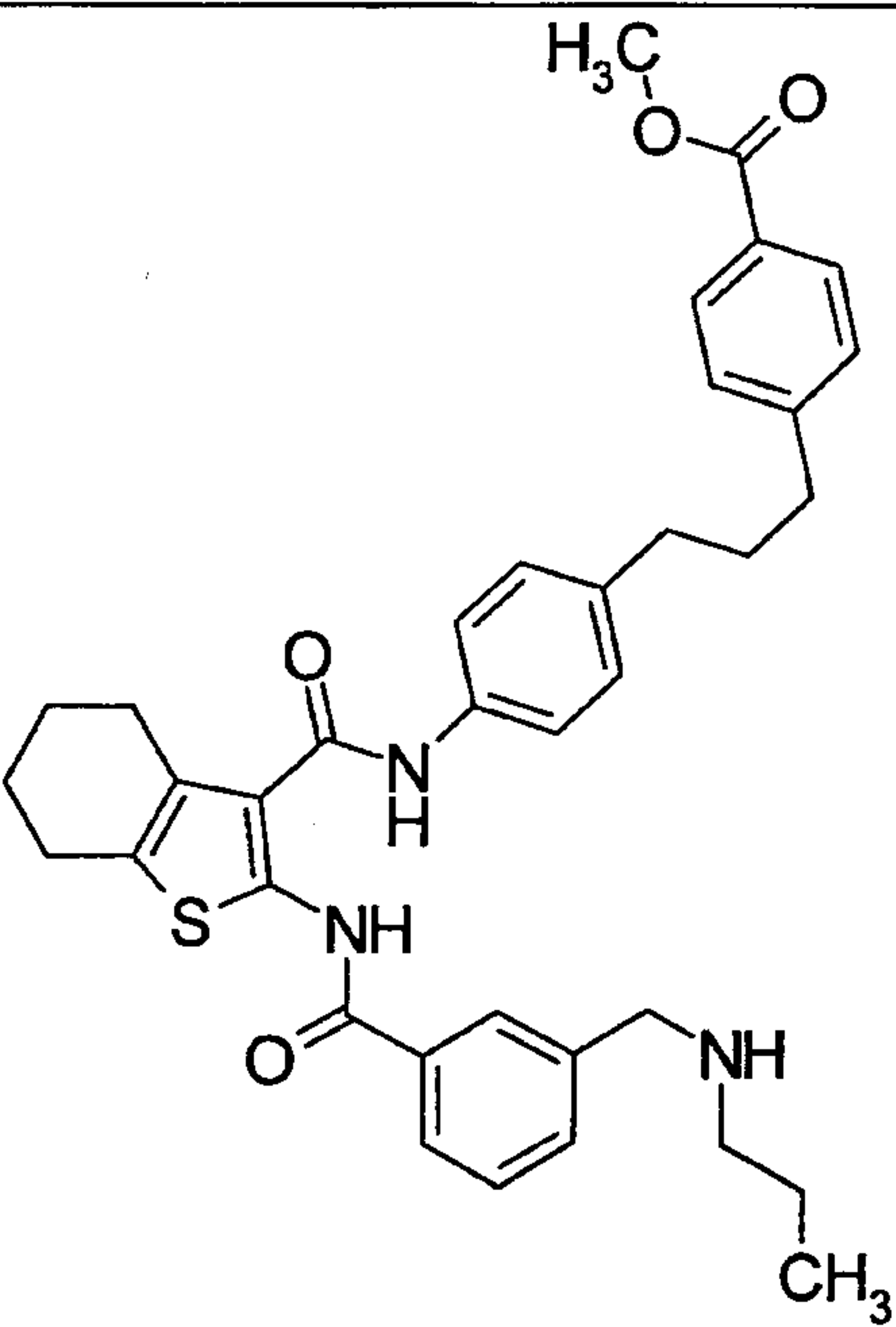
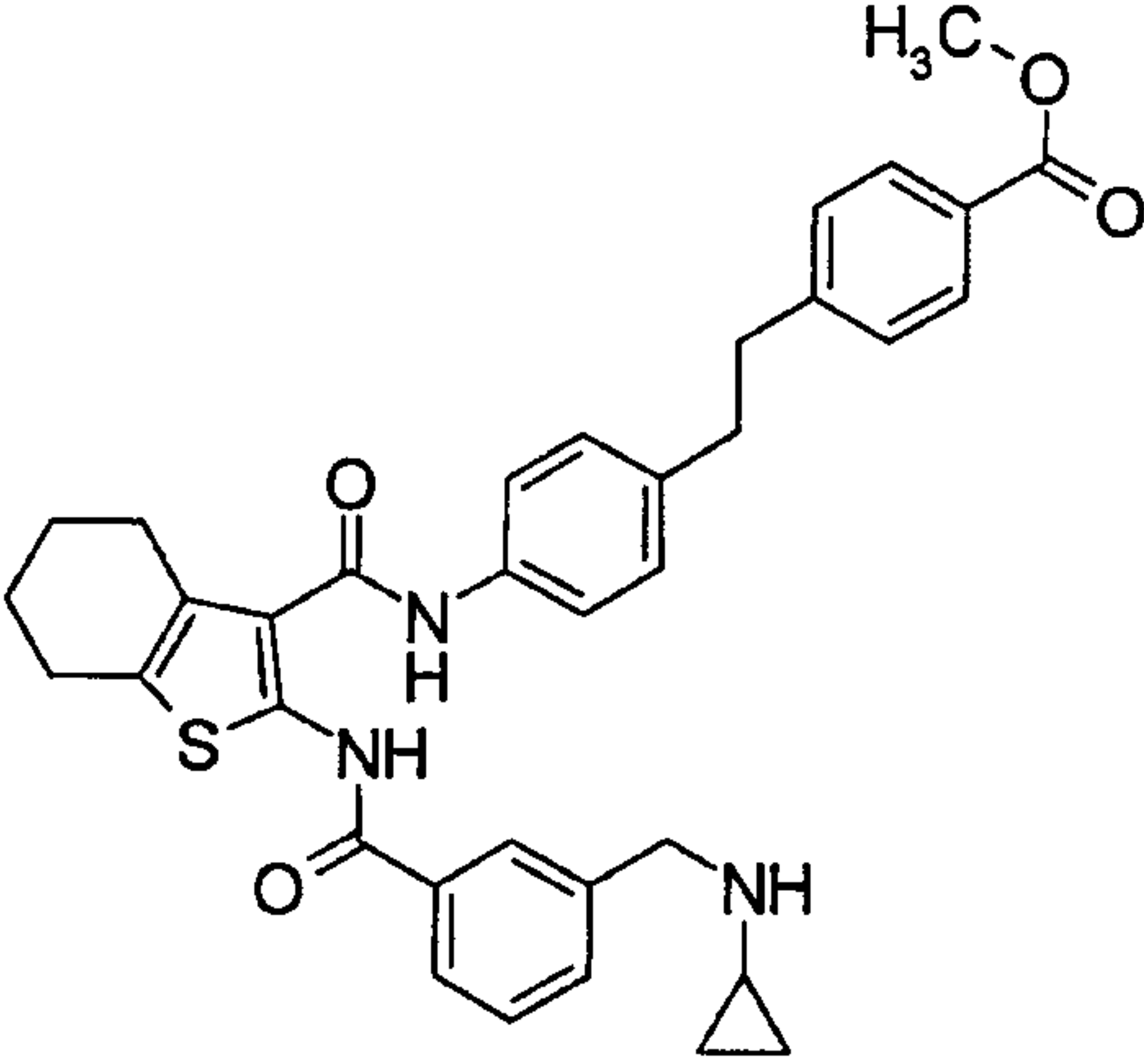
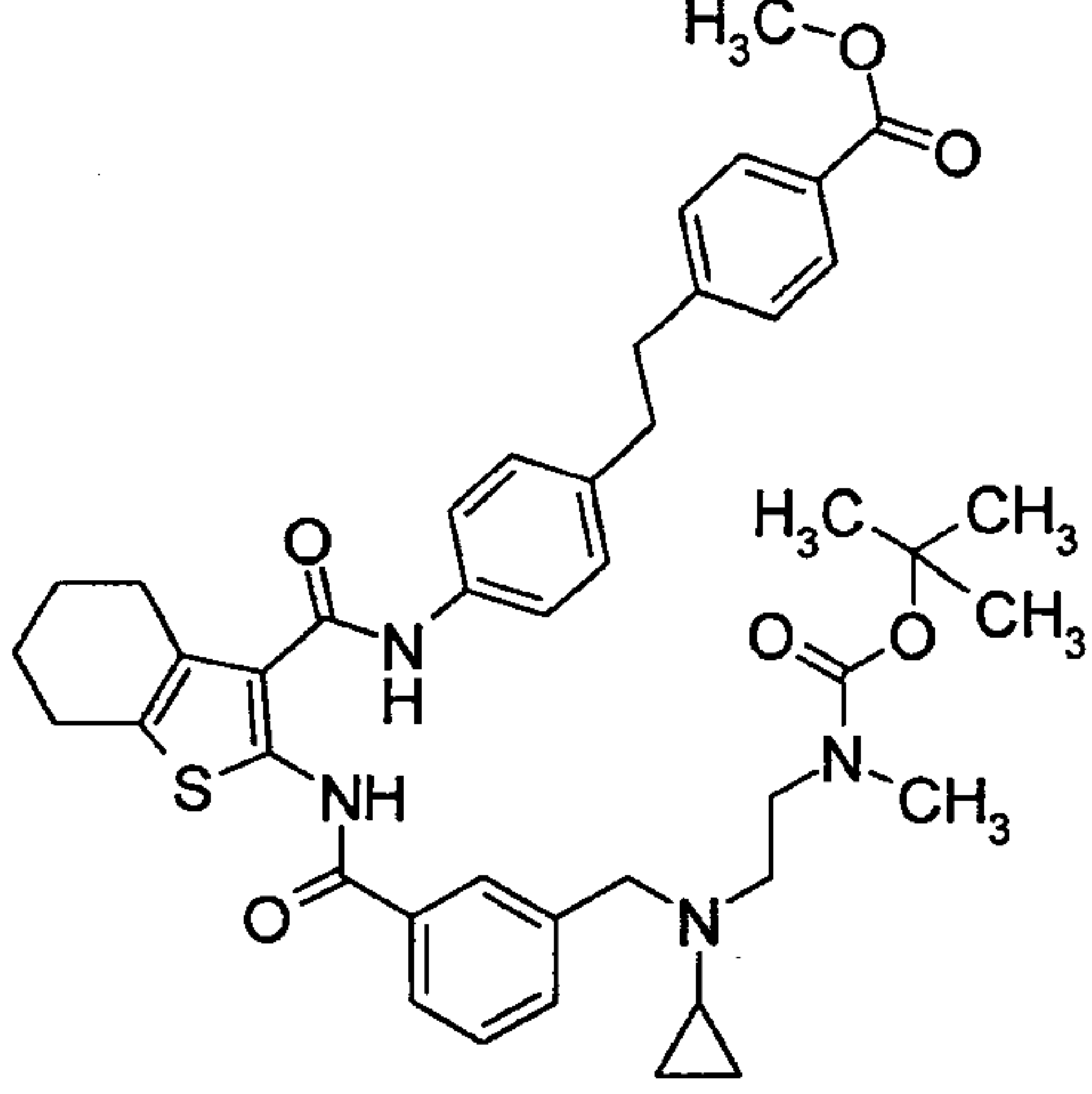
[0164]
[Table 19]

Pr	Str	Pr	Str
115		118	
116		119	
117			

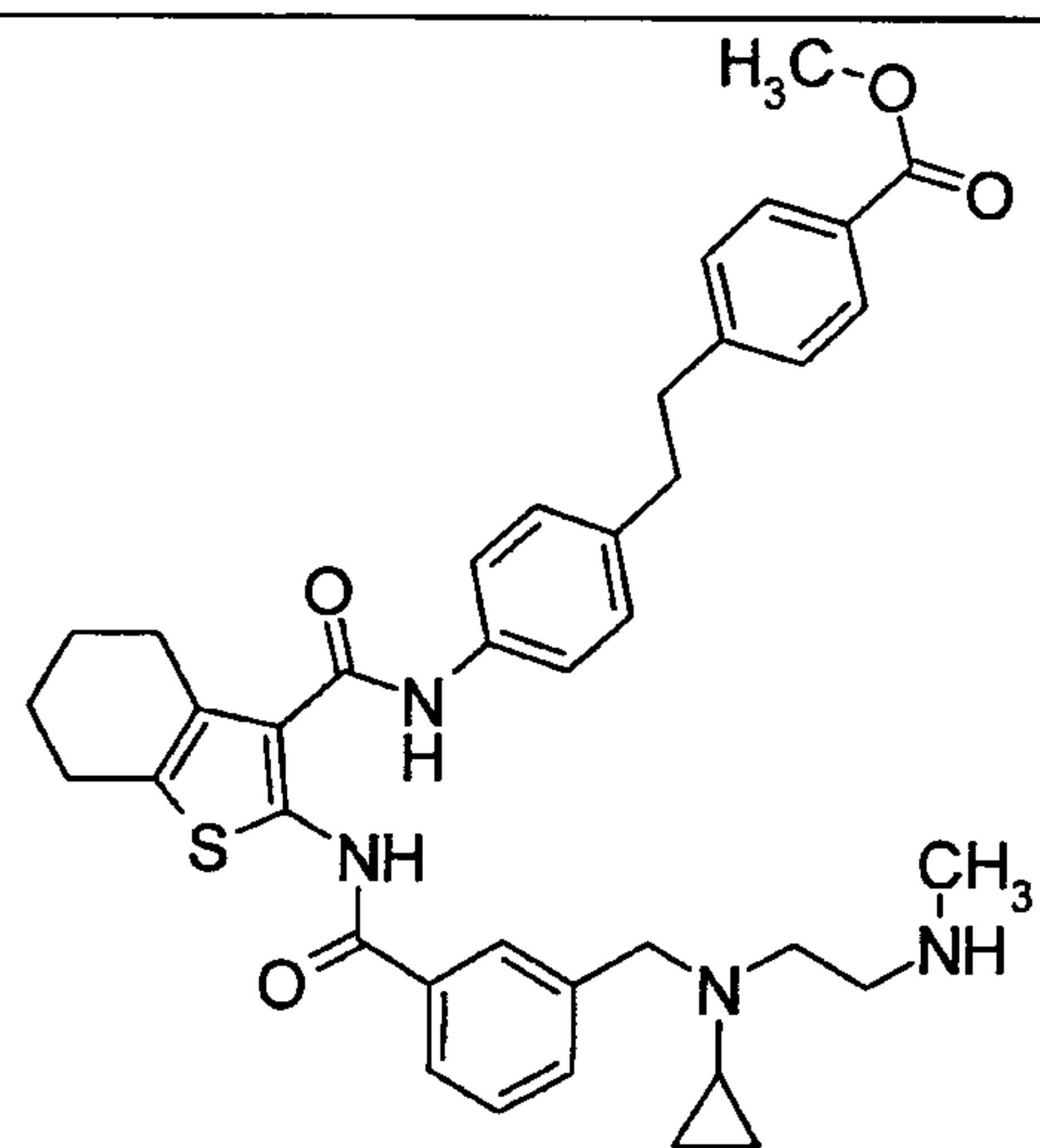
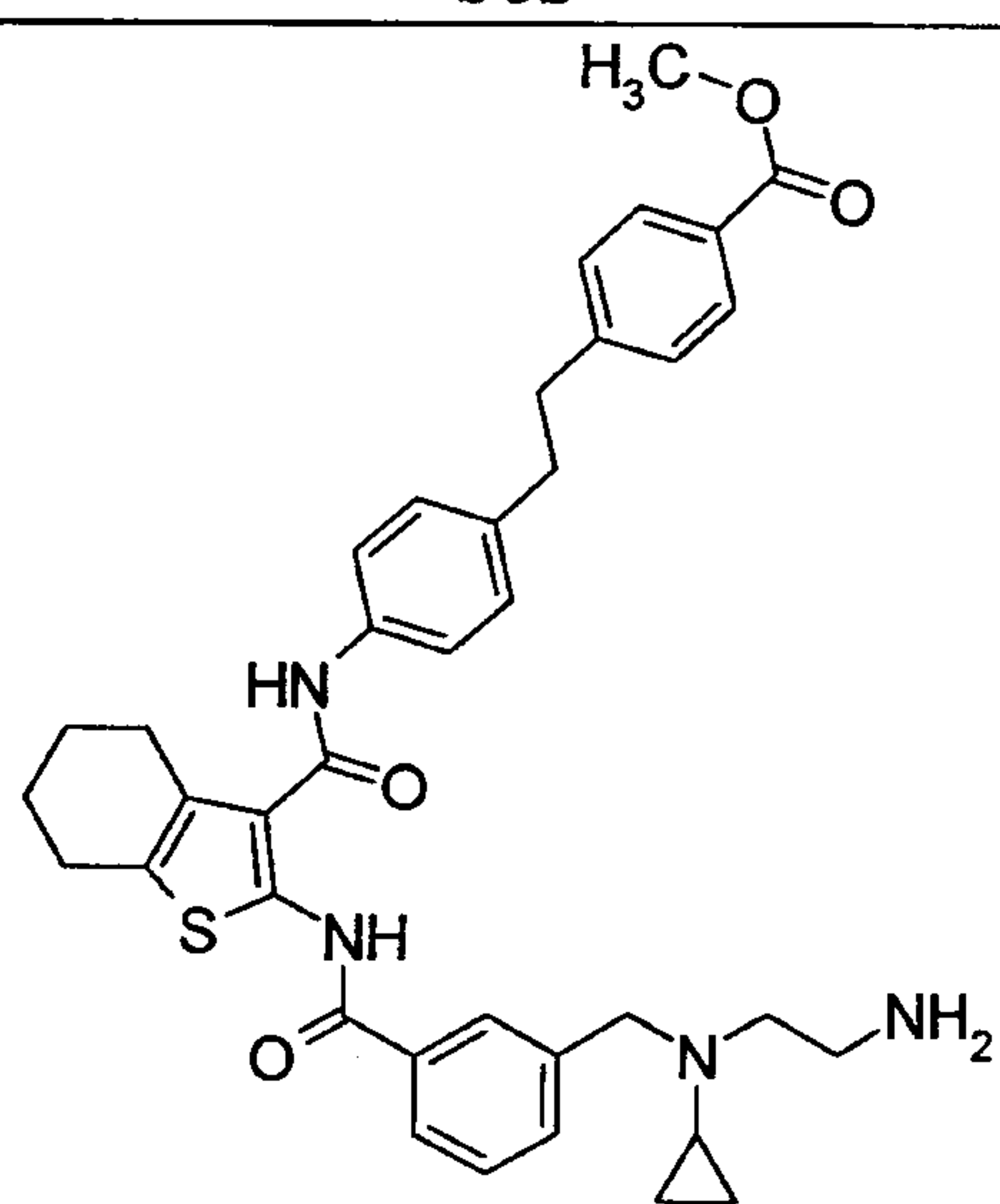
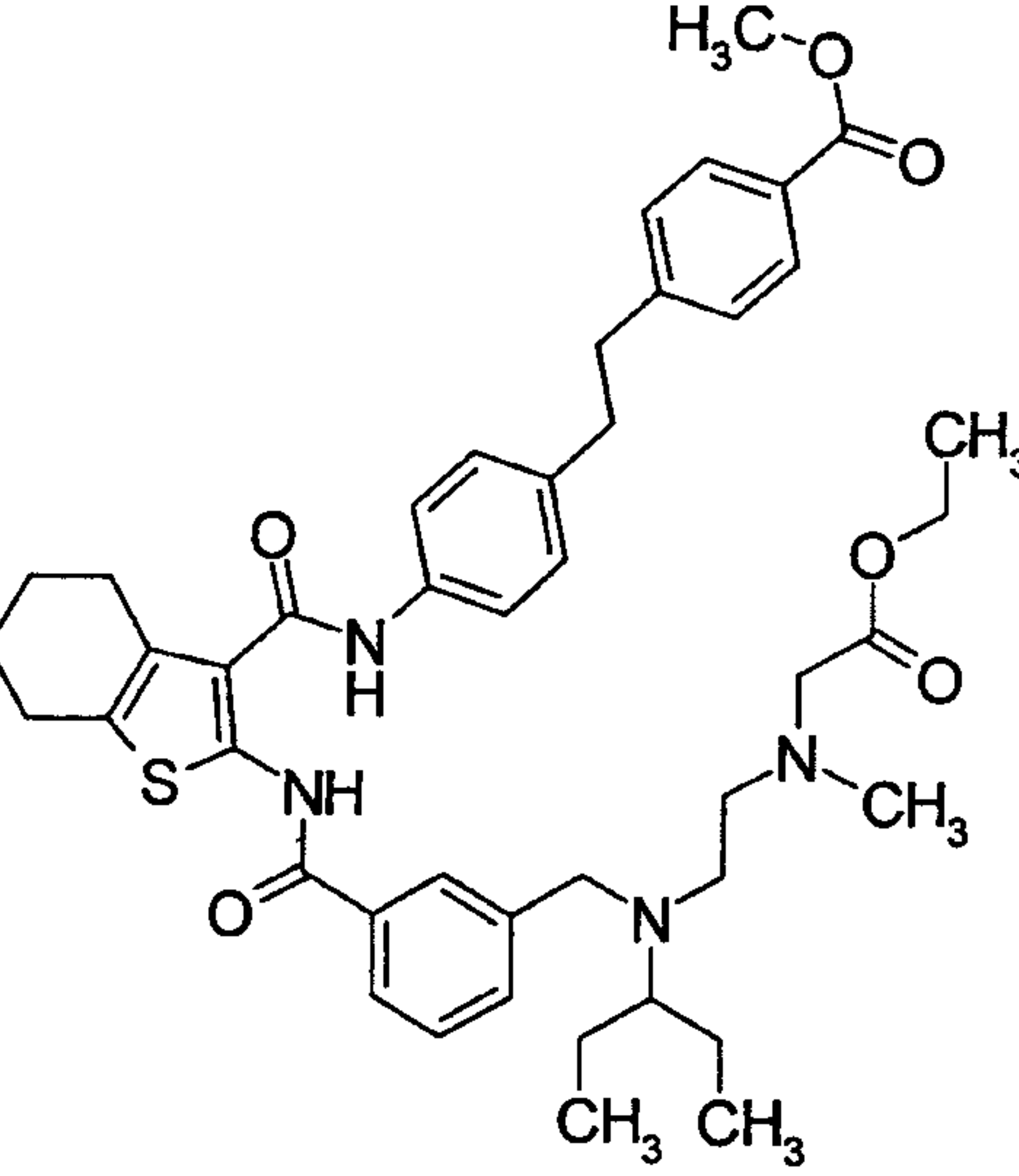
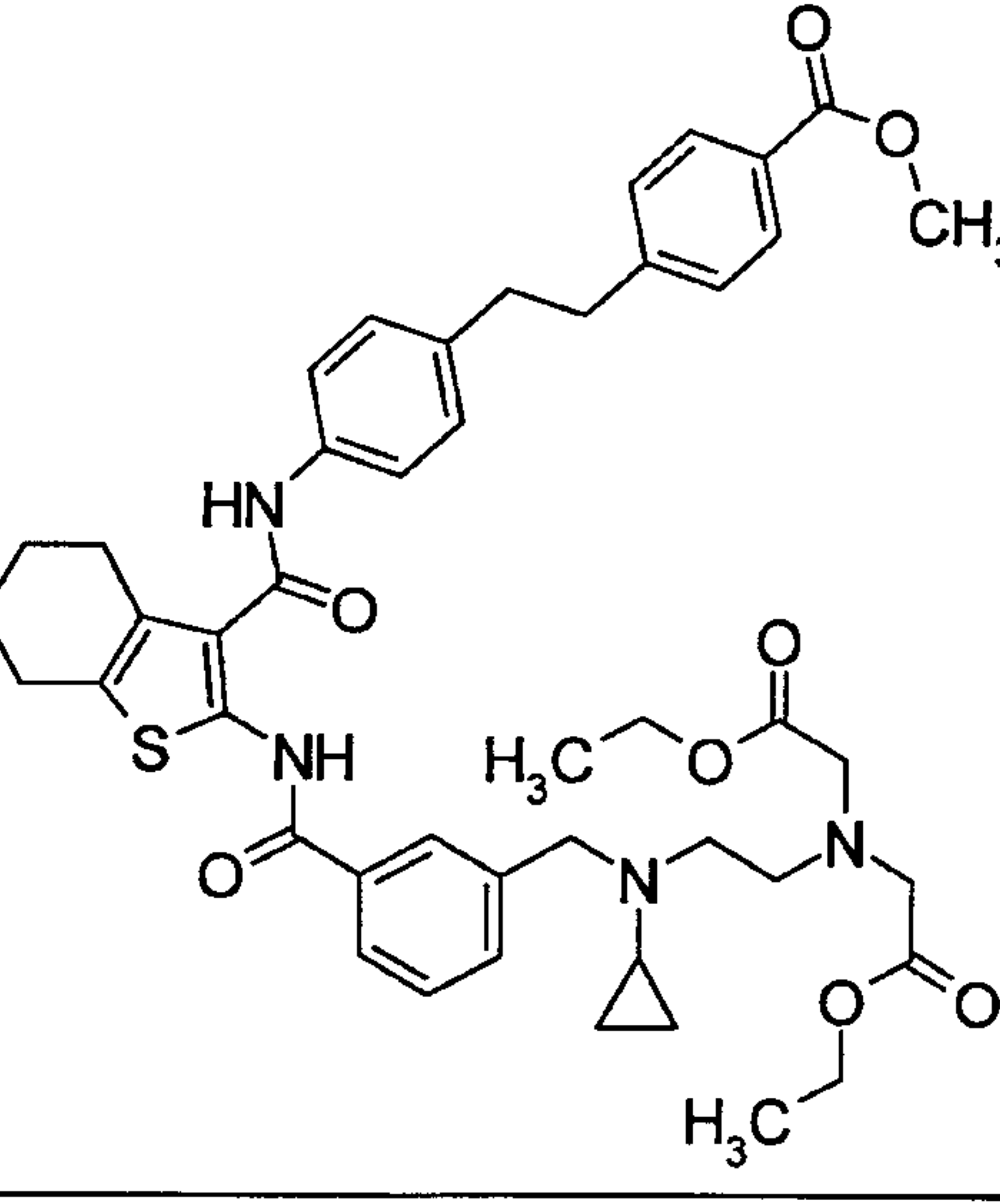
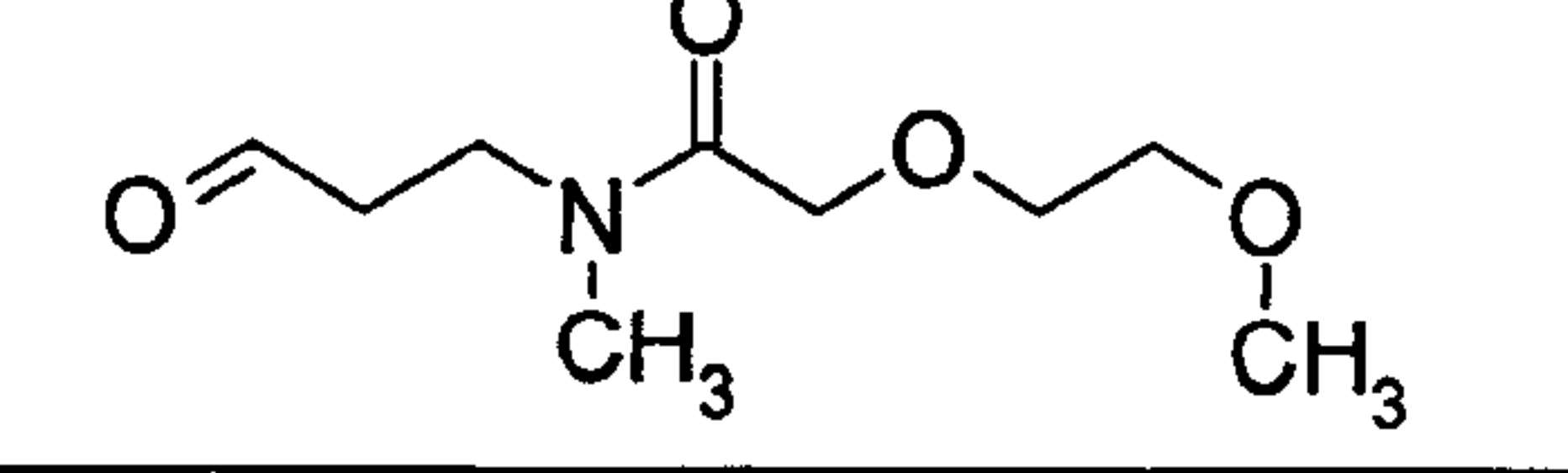
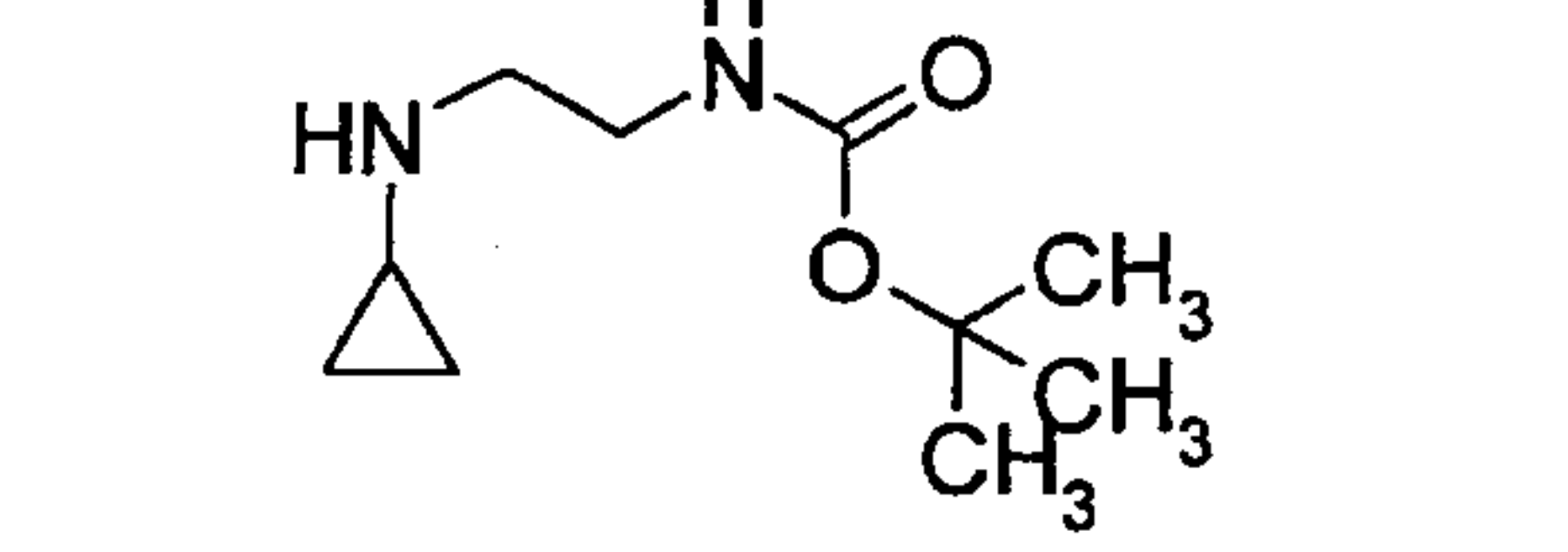
[0165]
[Table 20]

Pr	Str	Pr	Str
120		123	
121		124	
122		125	

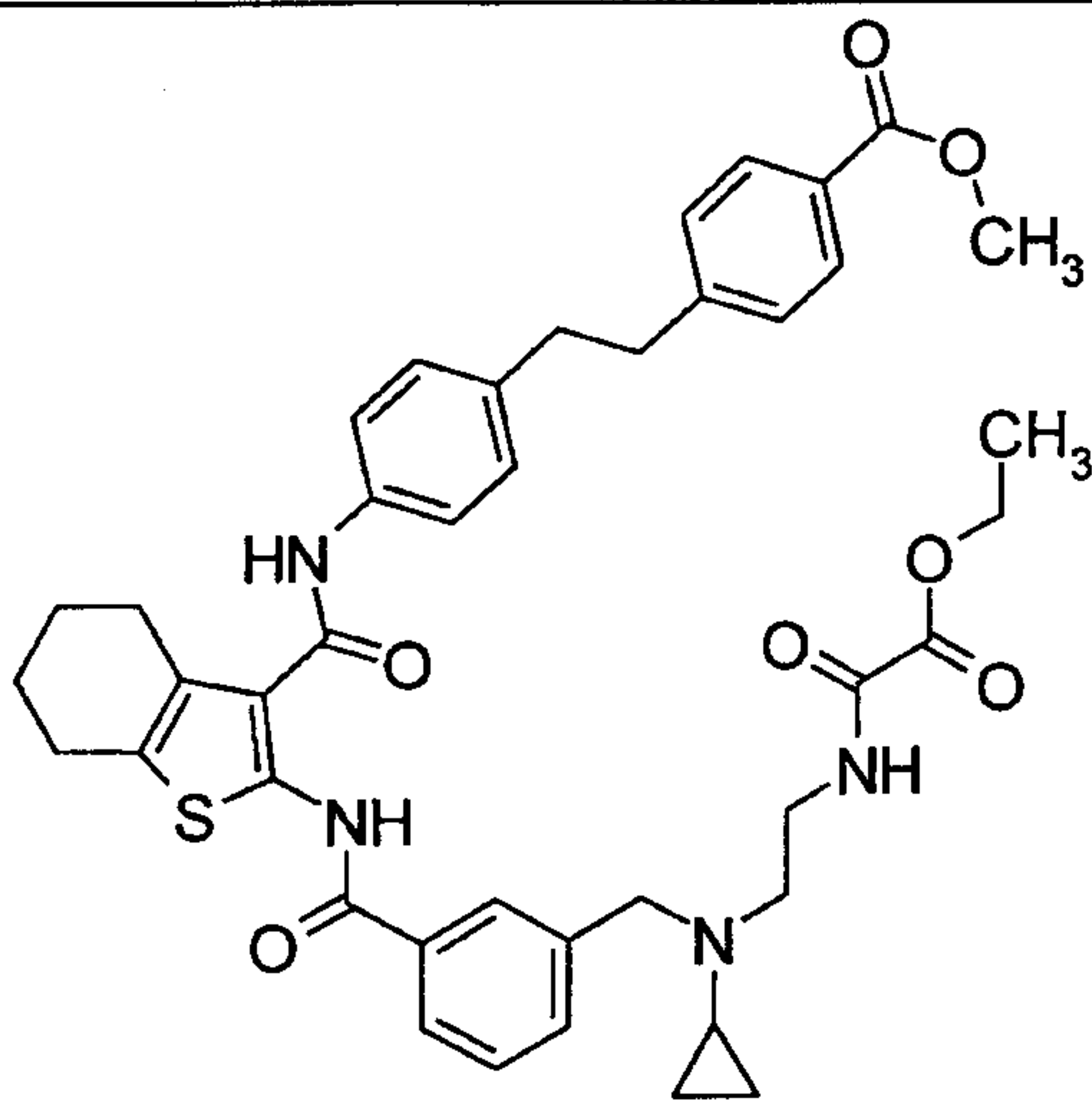
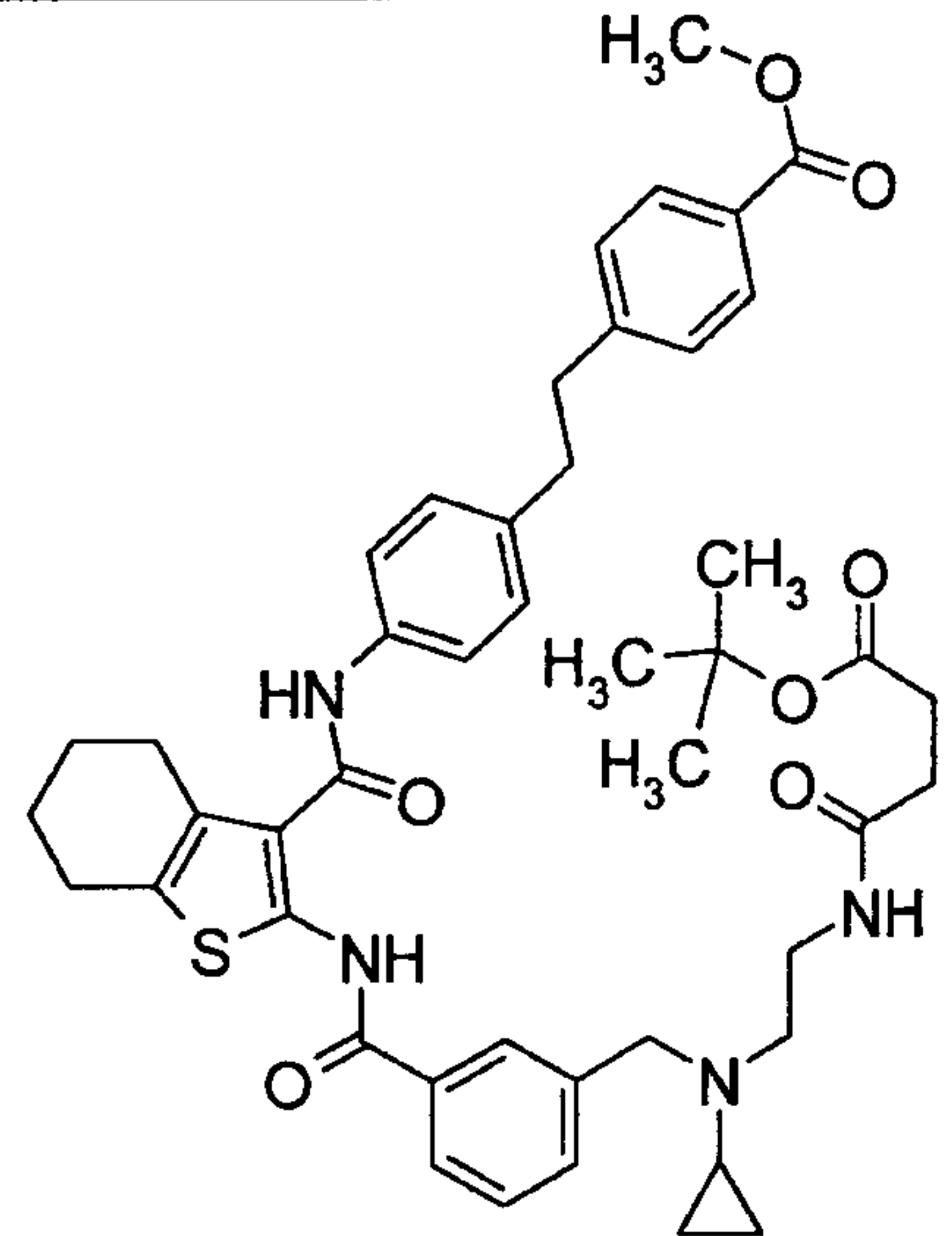
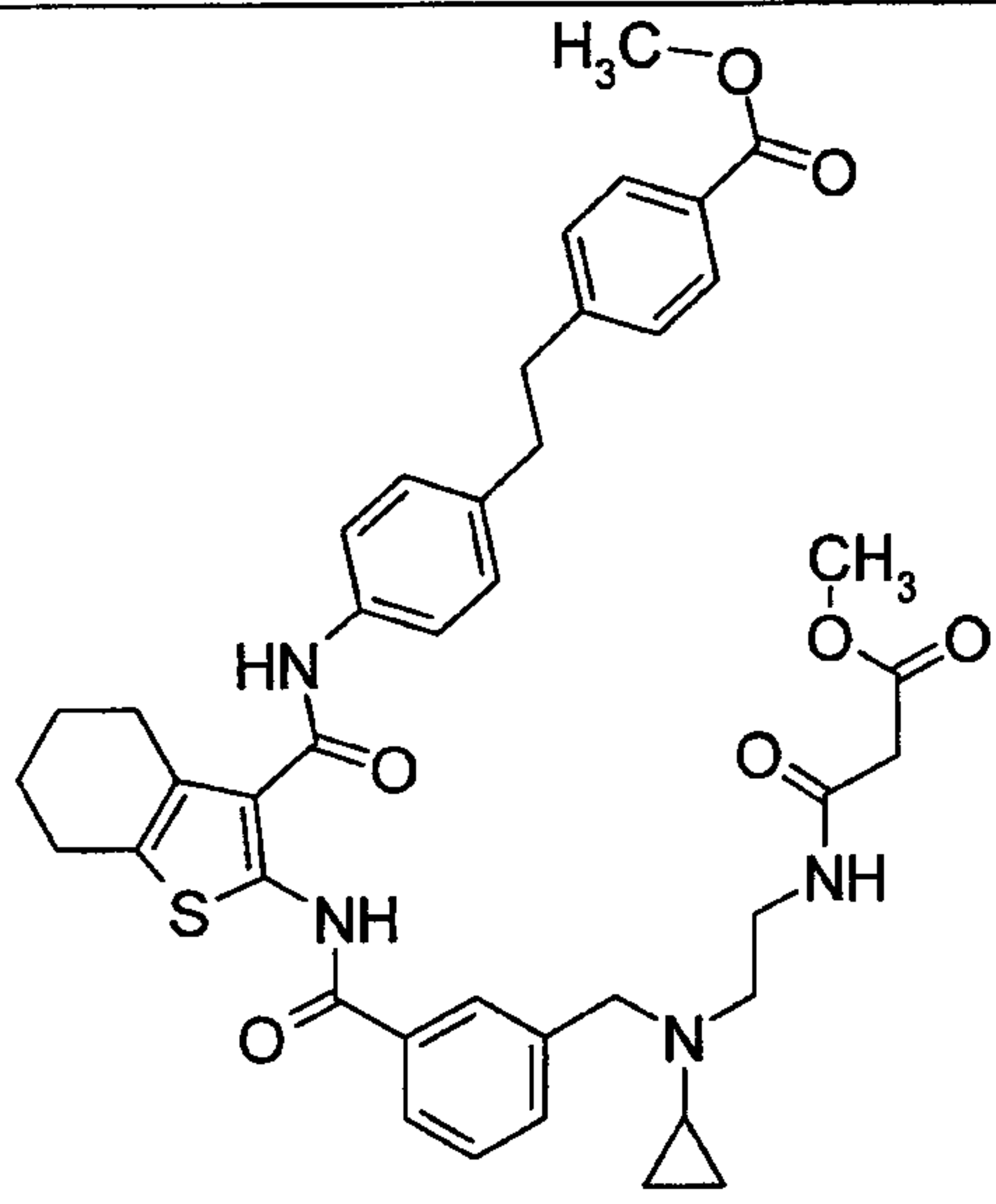
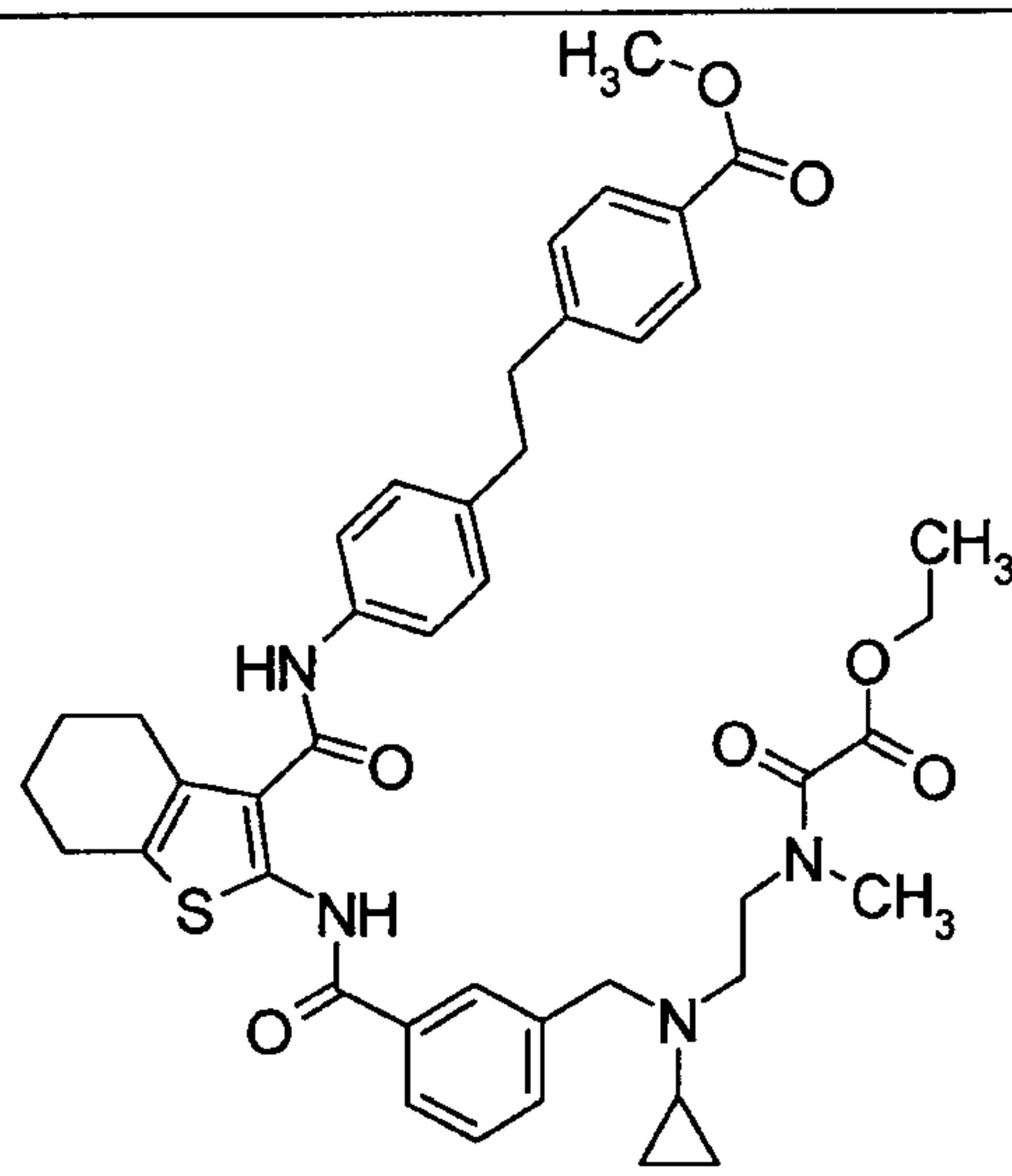
[0166]
[Table 21]

Pr	Str	Pr	Str
126		128	
127		129	
		130	

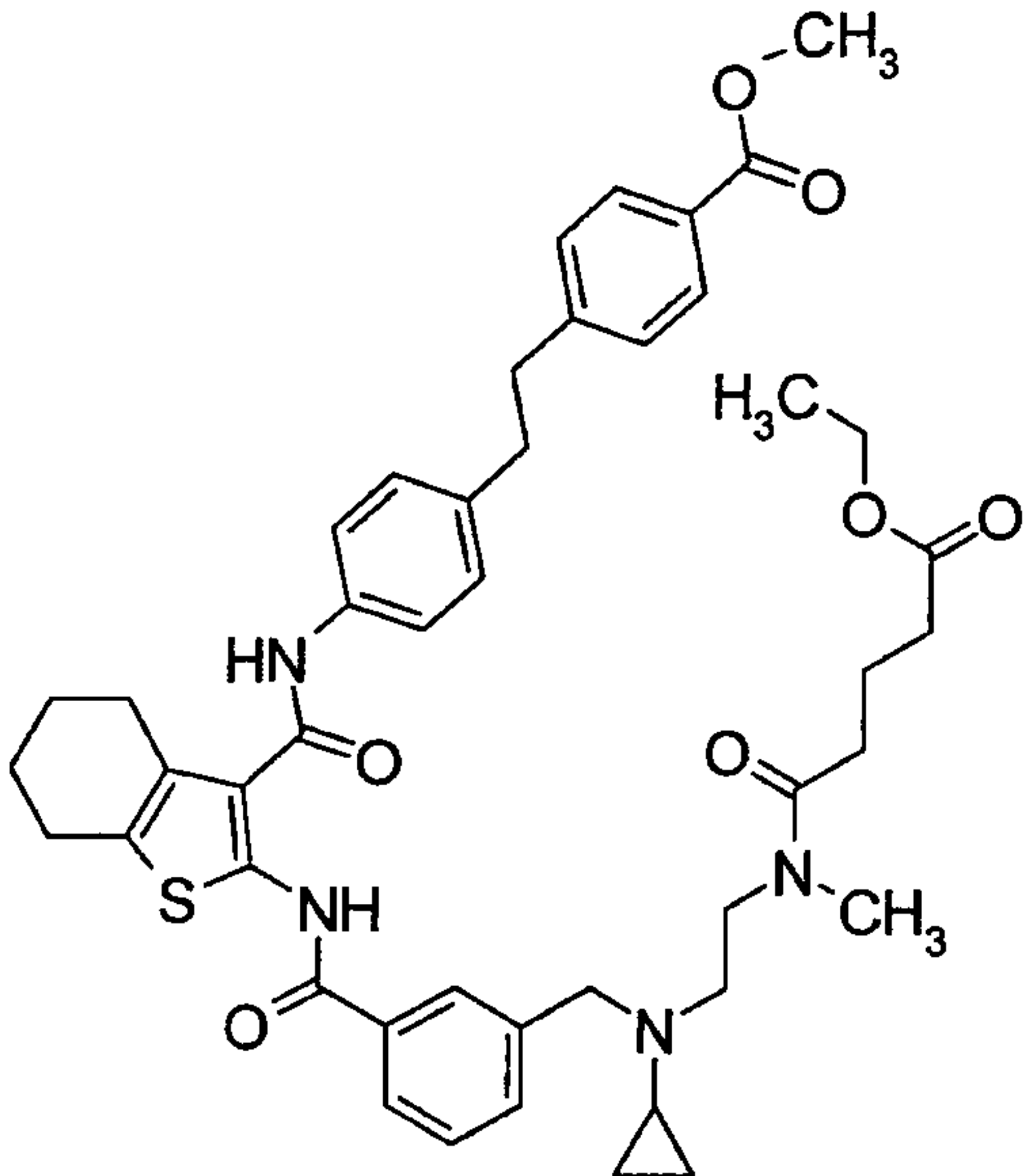
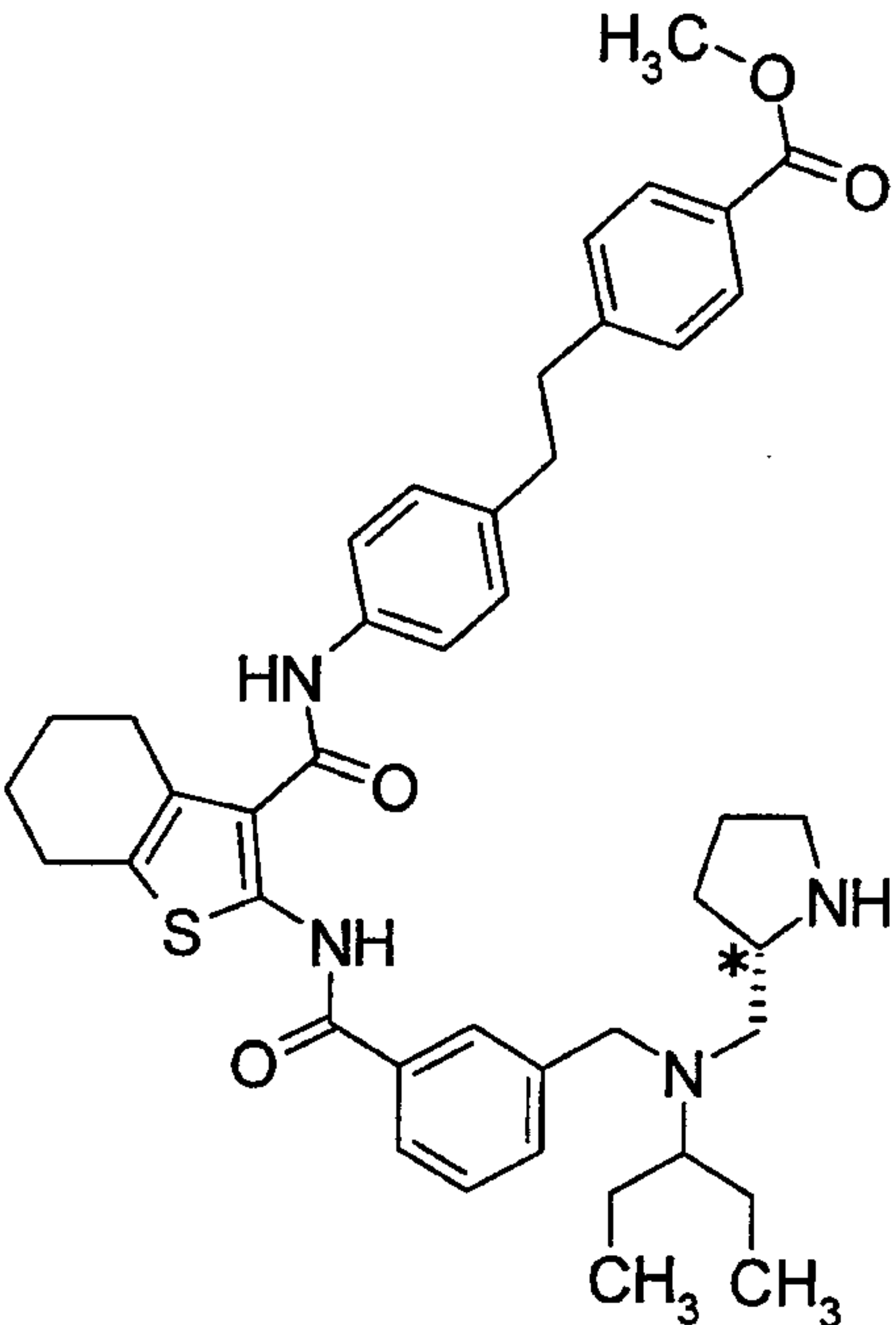
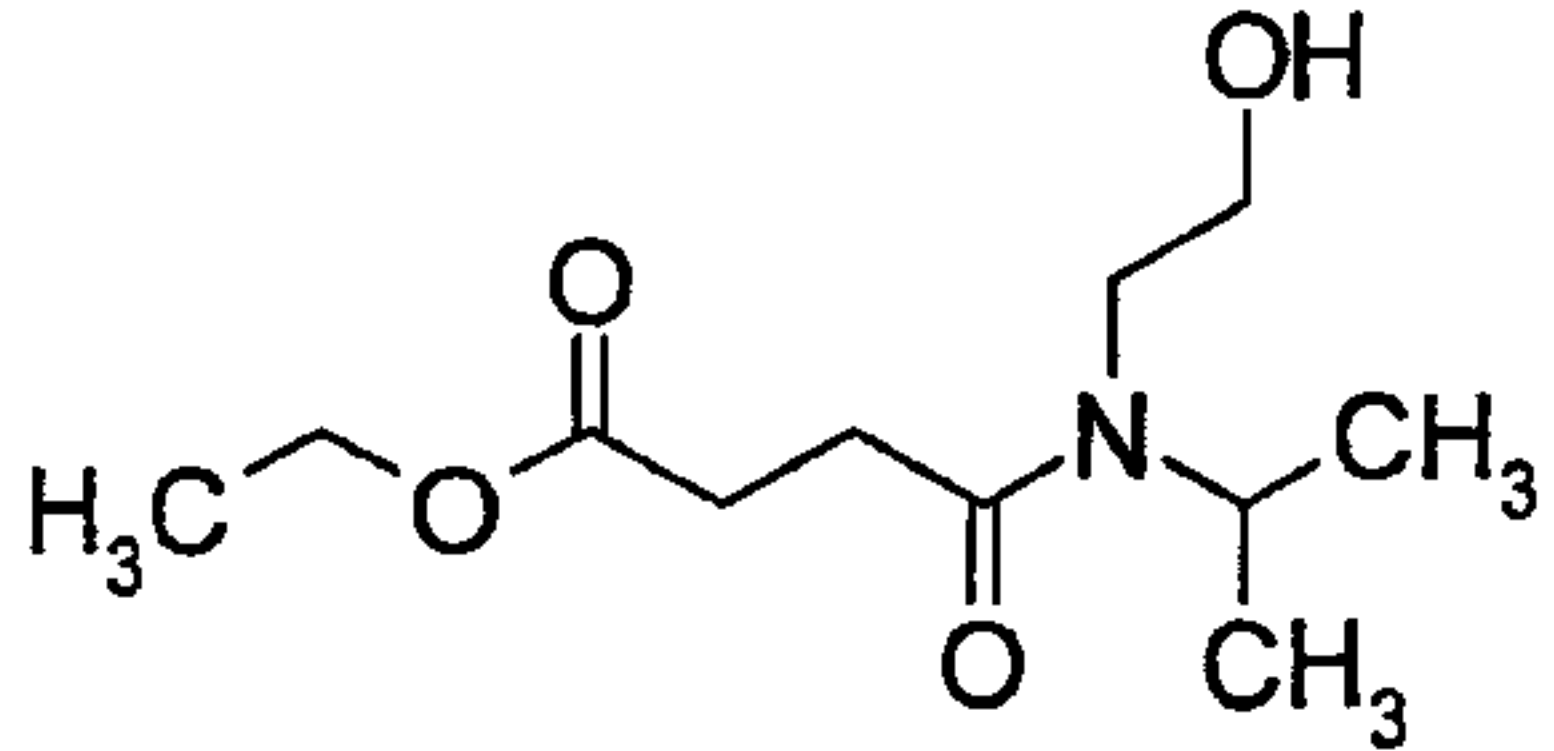
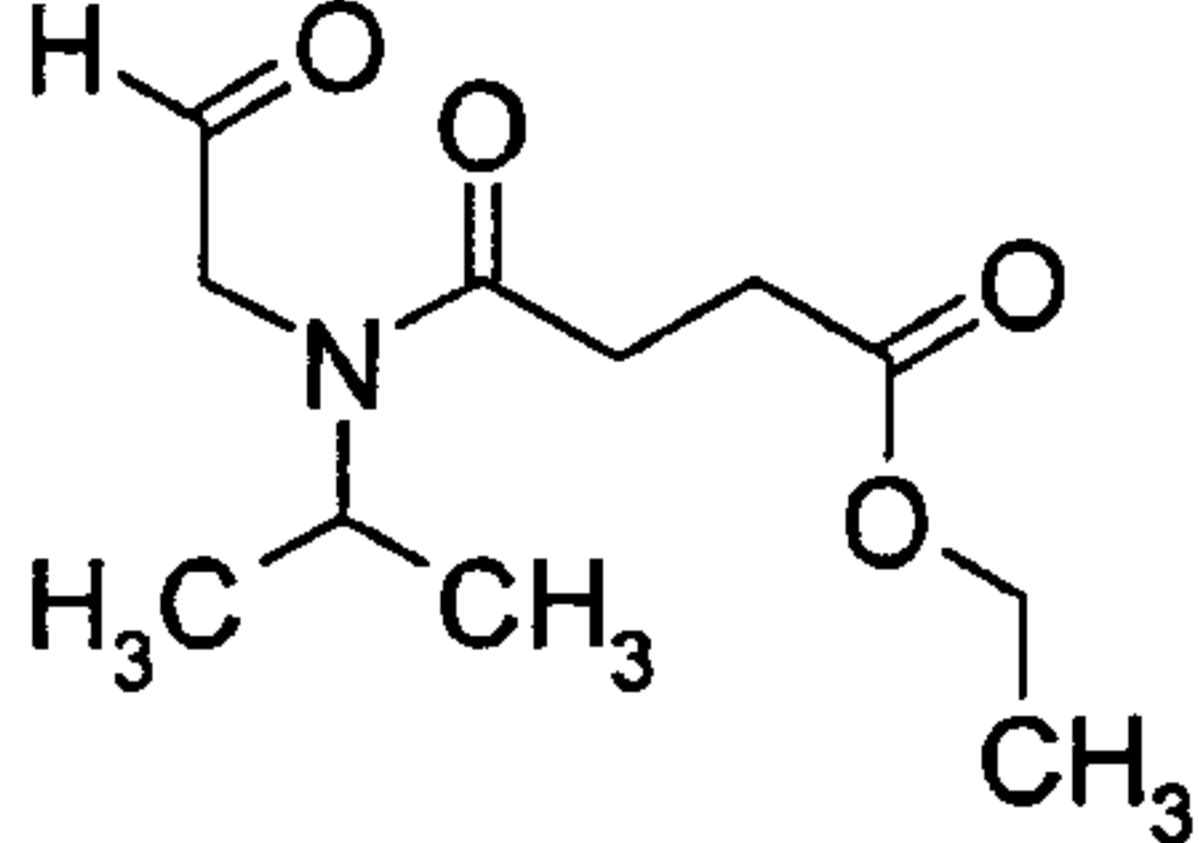
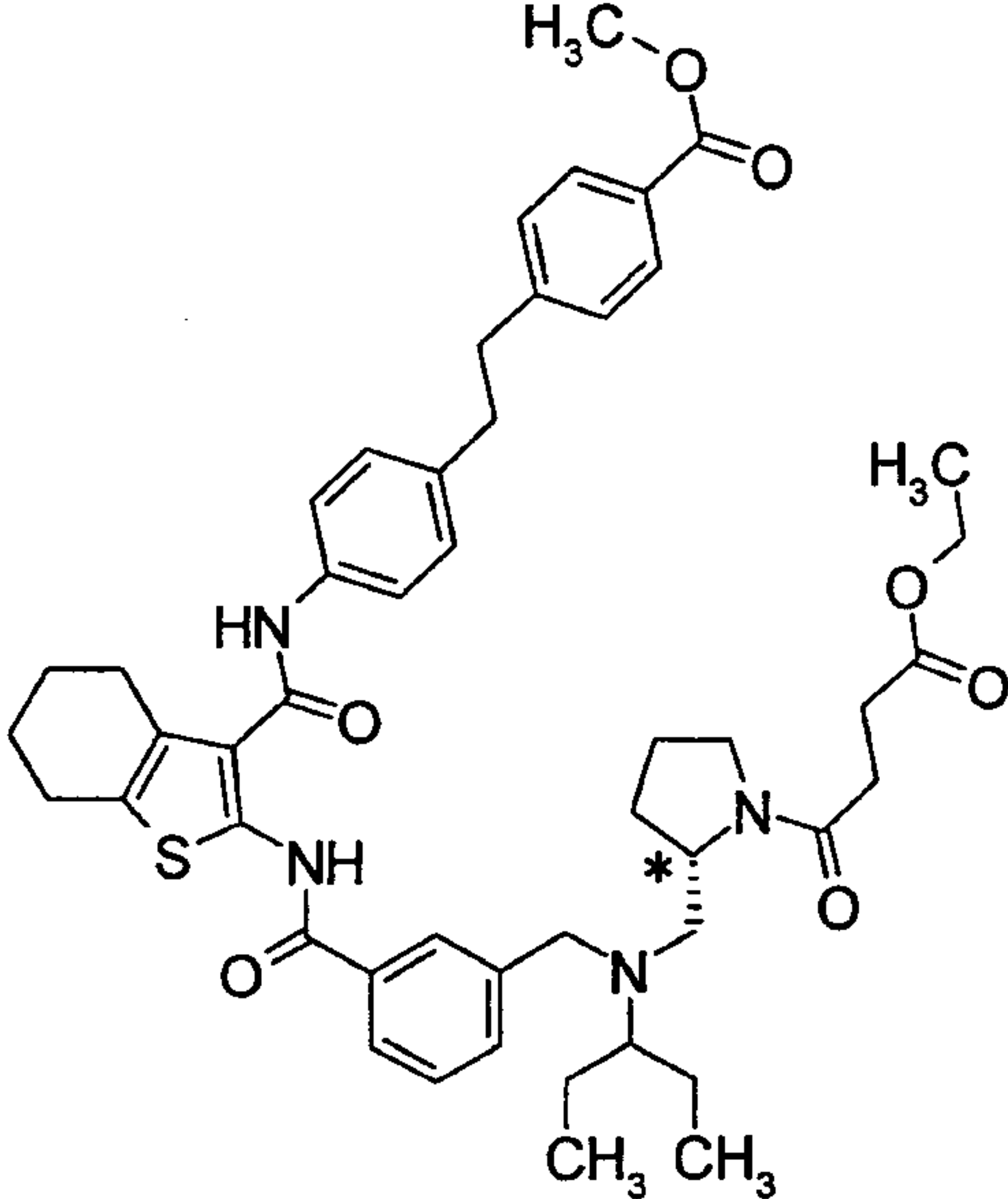
[0167]
[Table 22]

Pr	Str	Pr	Str
131		135	
132		136	
133			
134			

[0168]
[Table 23]

Pr	Str	Pr	Str
137		139	
138		140	

[0169]
[Table 24]

Pr	Str	Pr	Str
141		144	
142			
143		145	

[0170]
[Table 25]

Pr	Str	Pr	Str
146		149	
147		150	
148		151	

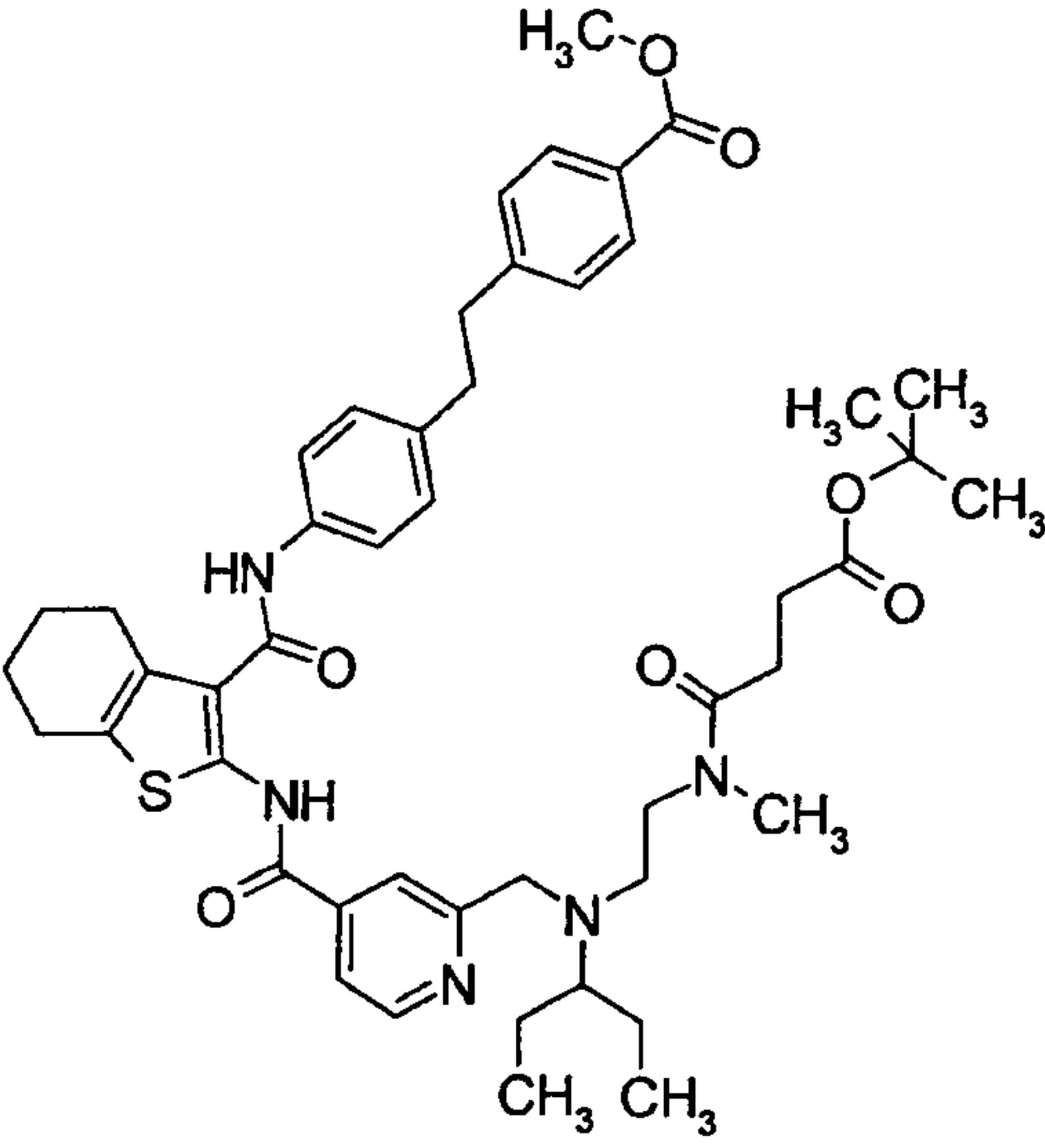
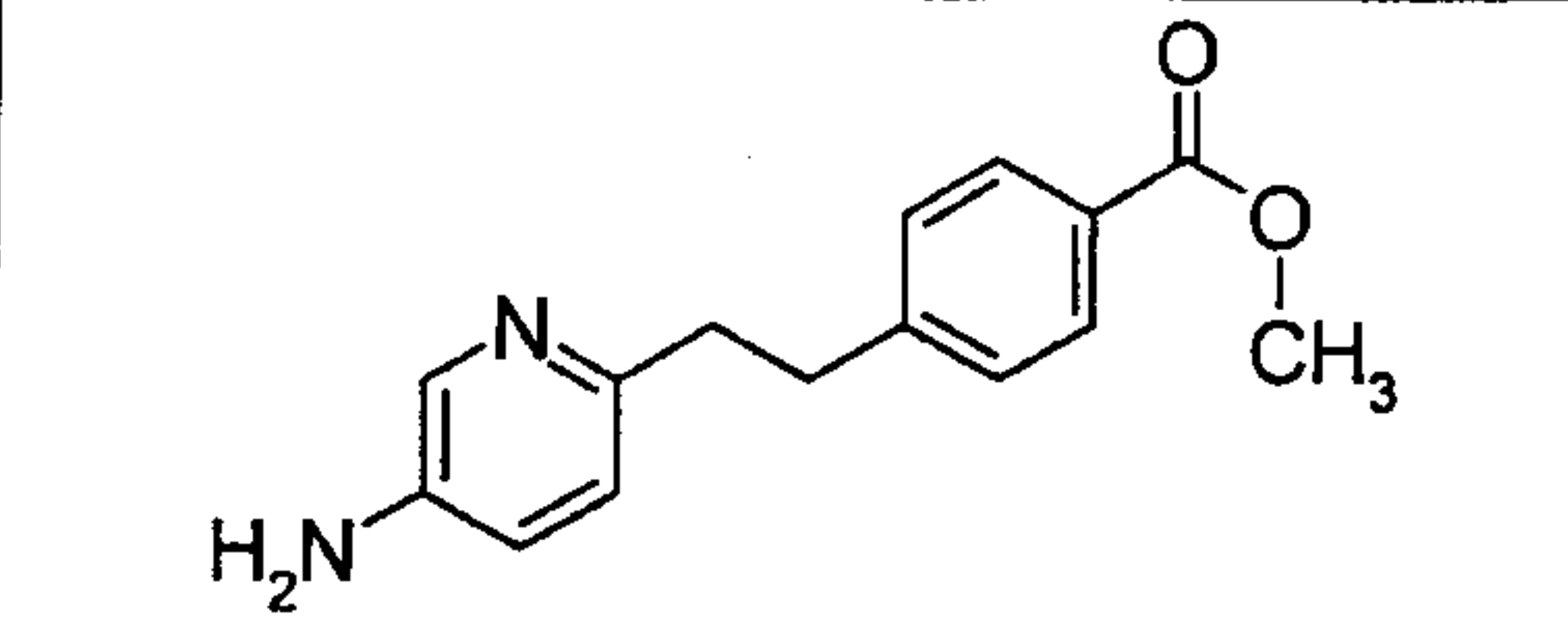
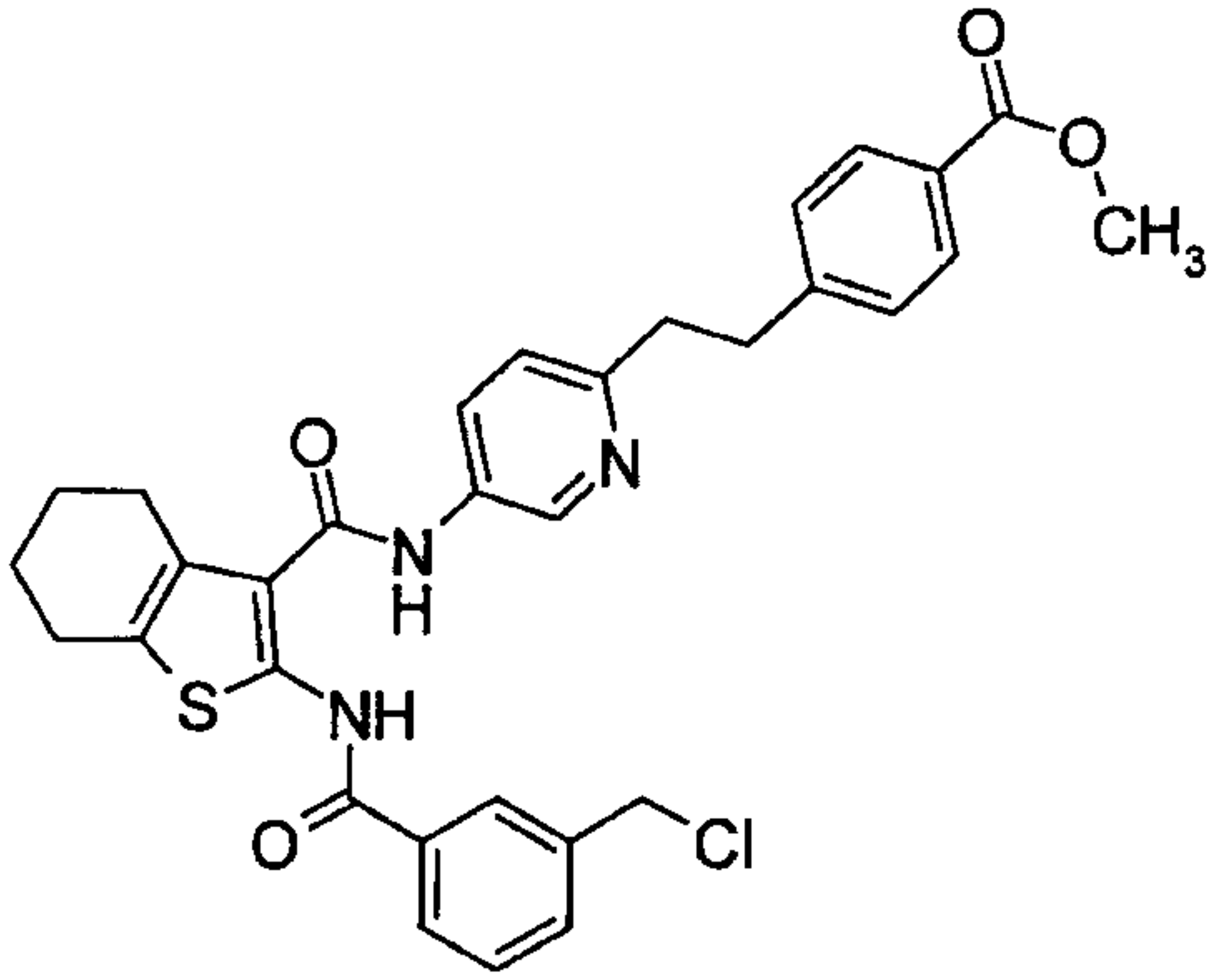
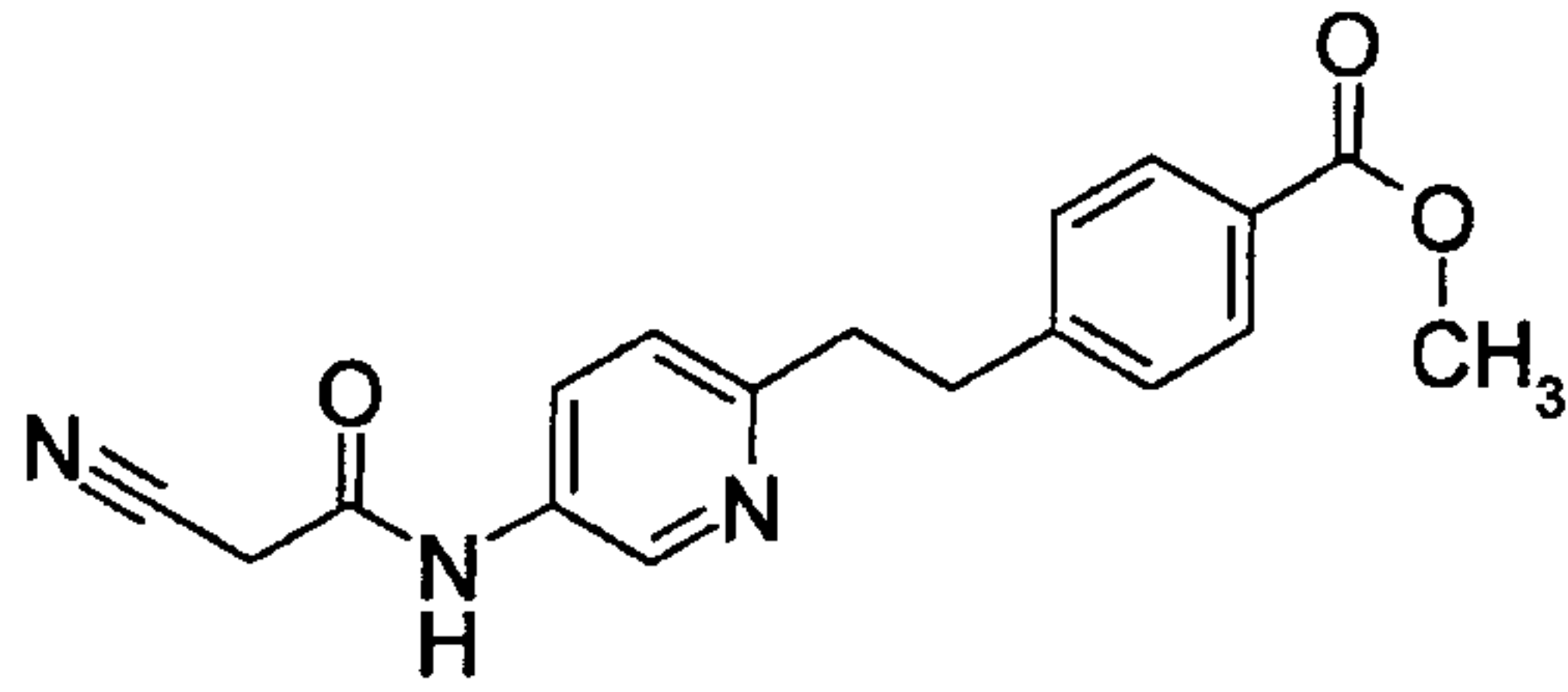
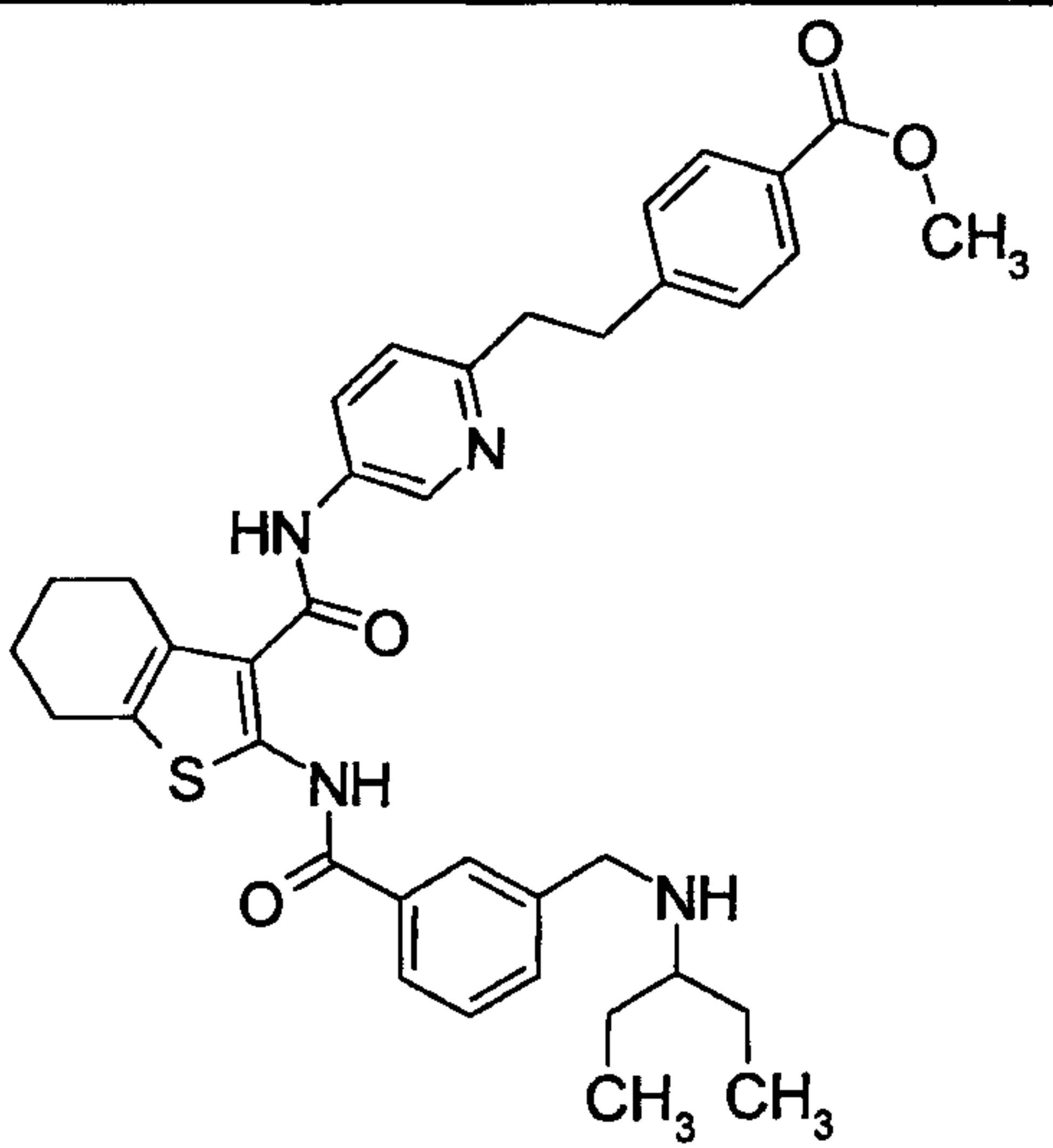
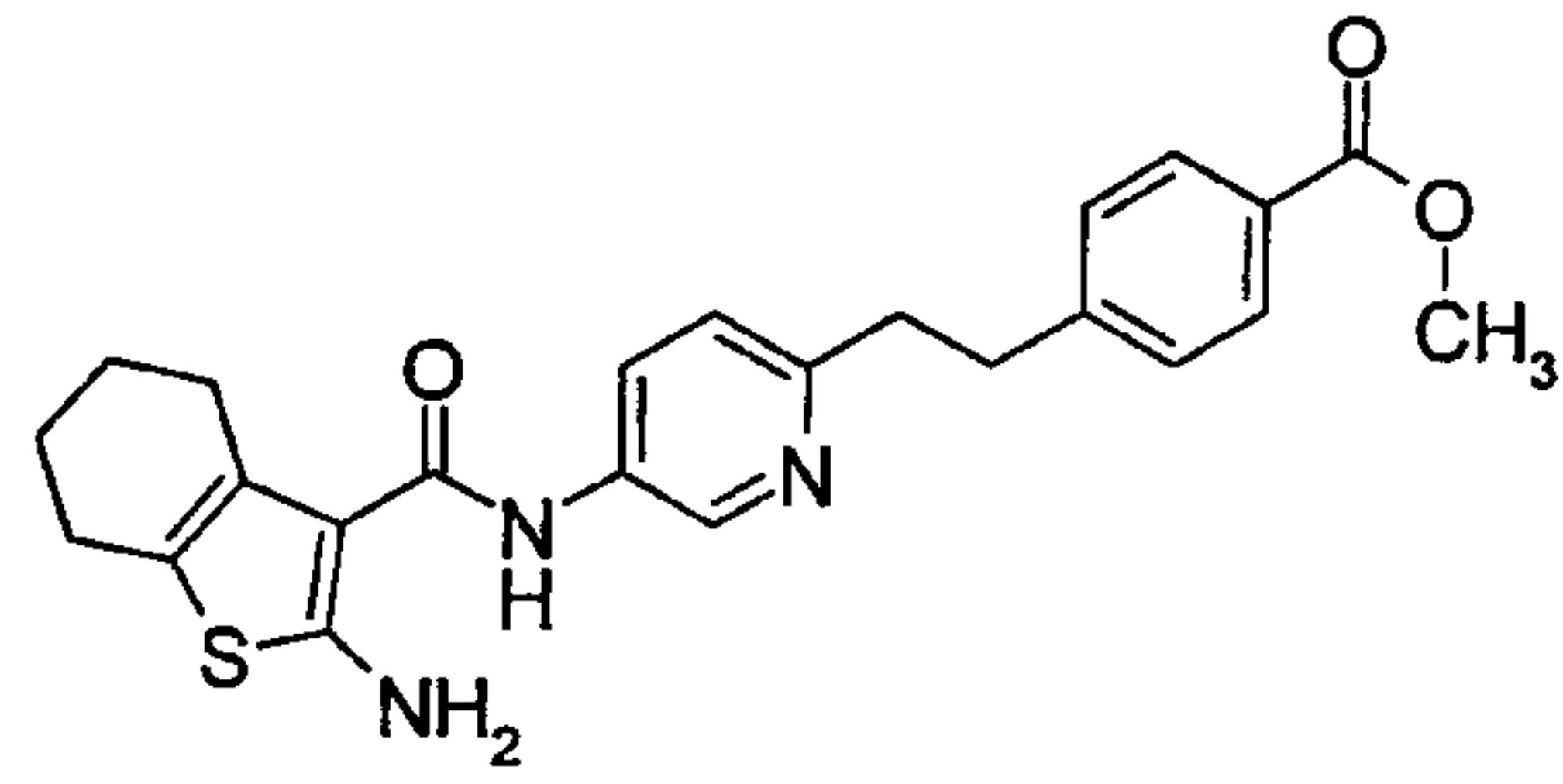
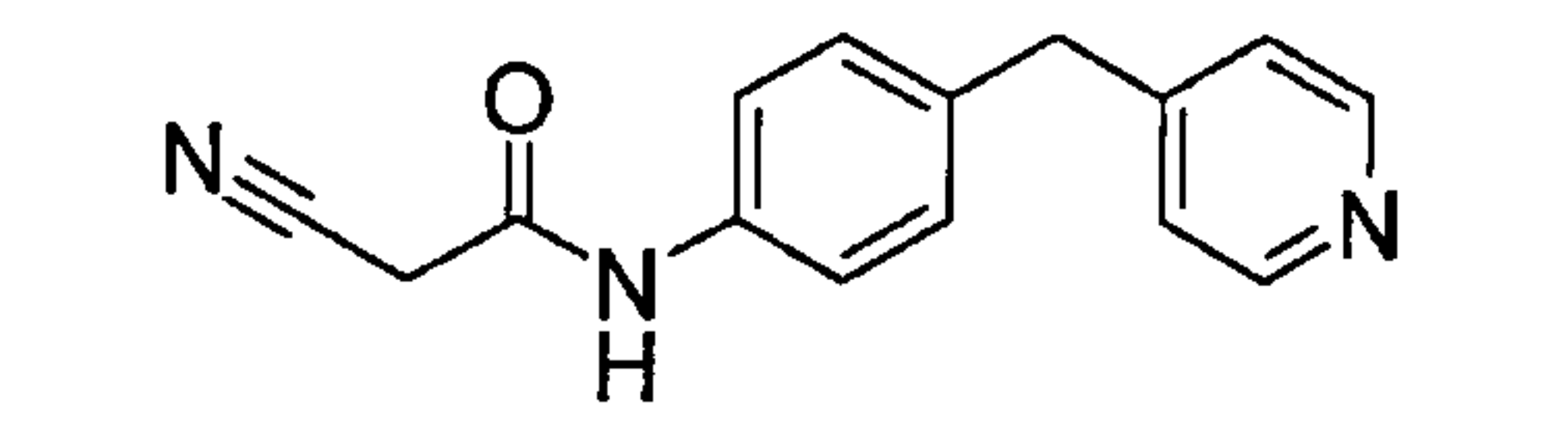
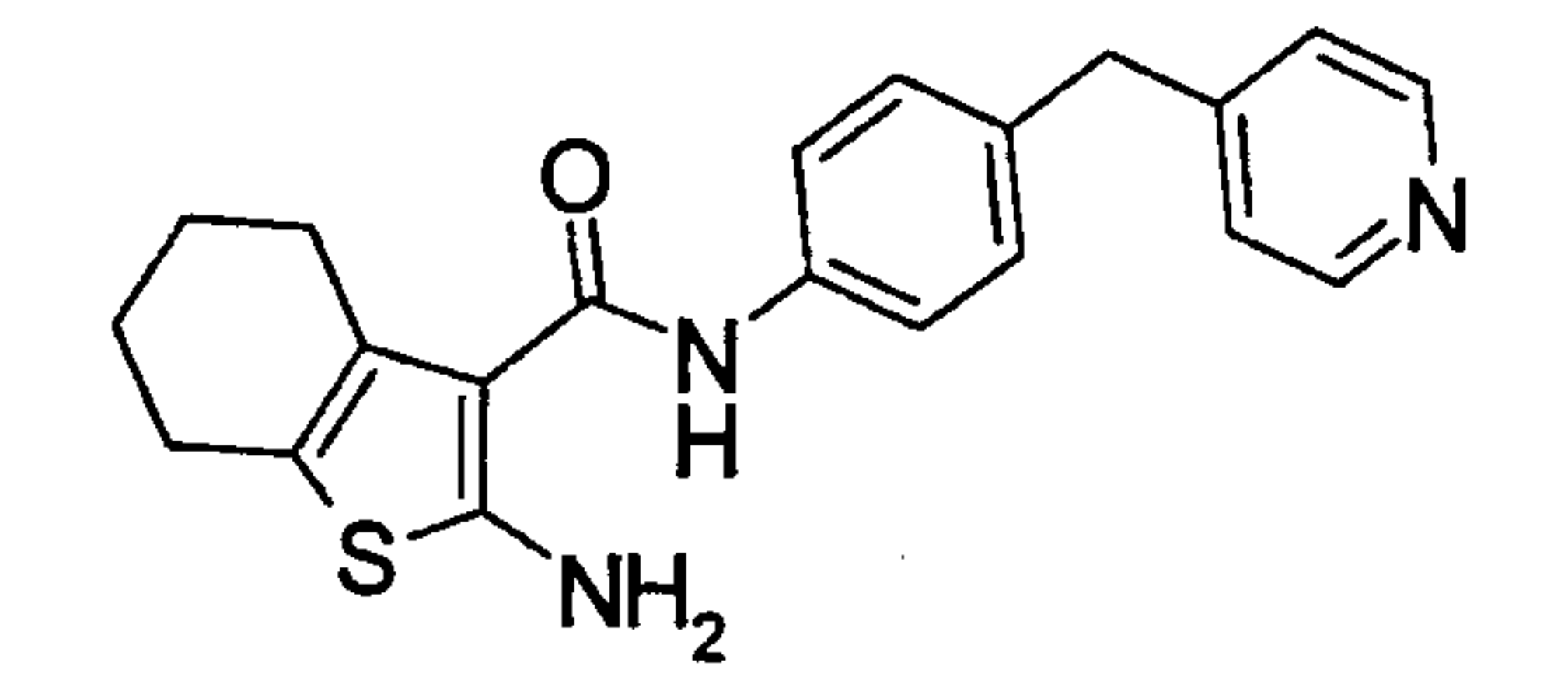
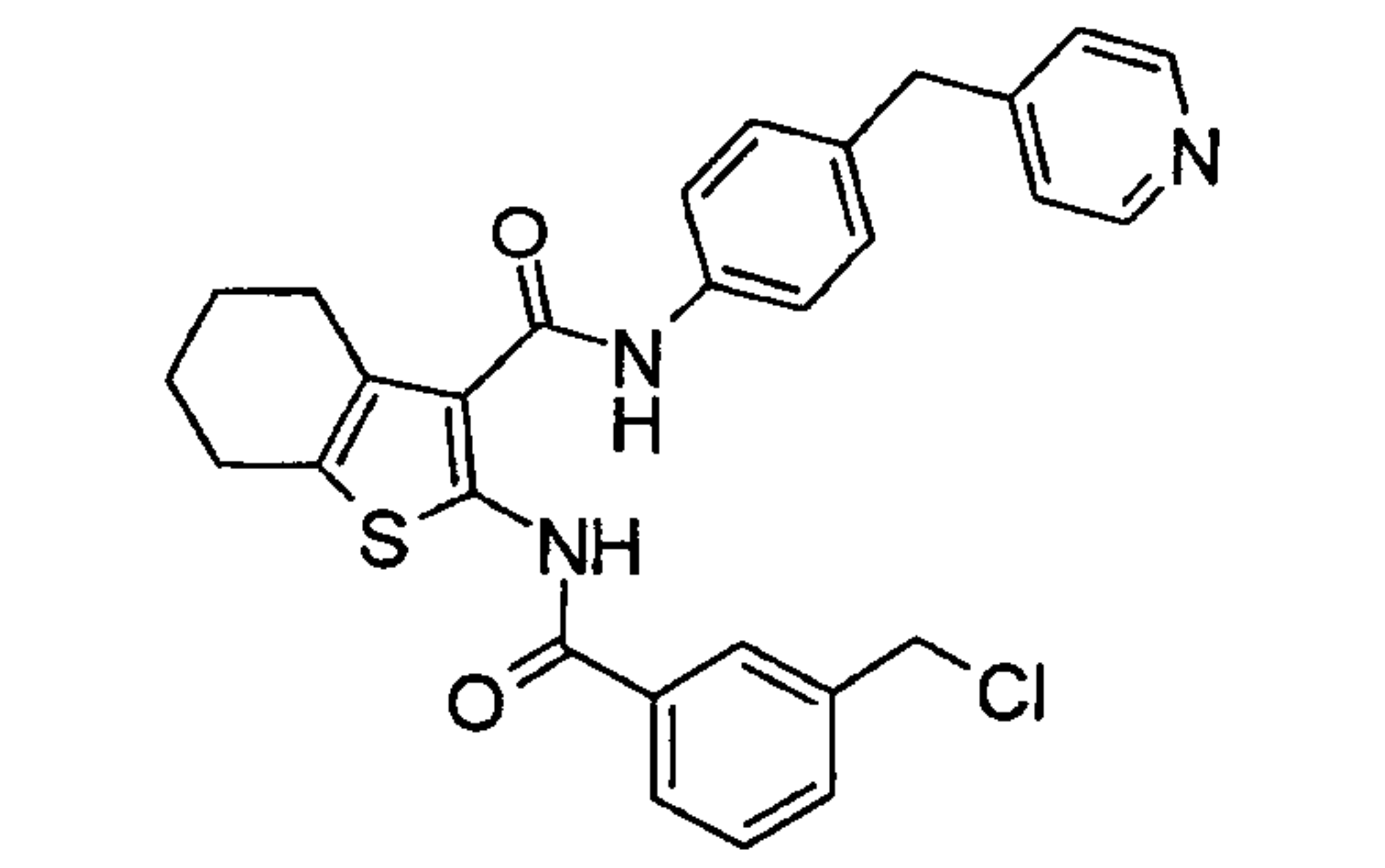
[0171]
[Table 26]

Pr	Str	Pr	Str
152		155	
153		156	
154			

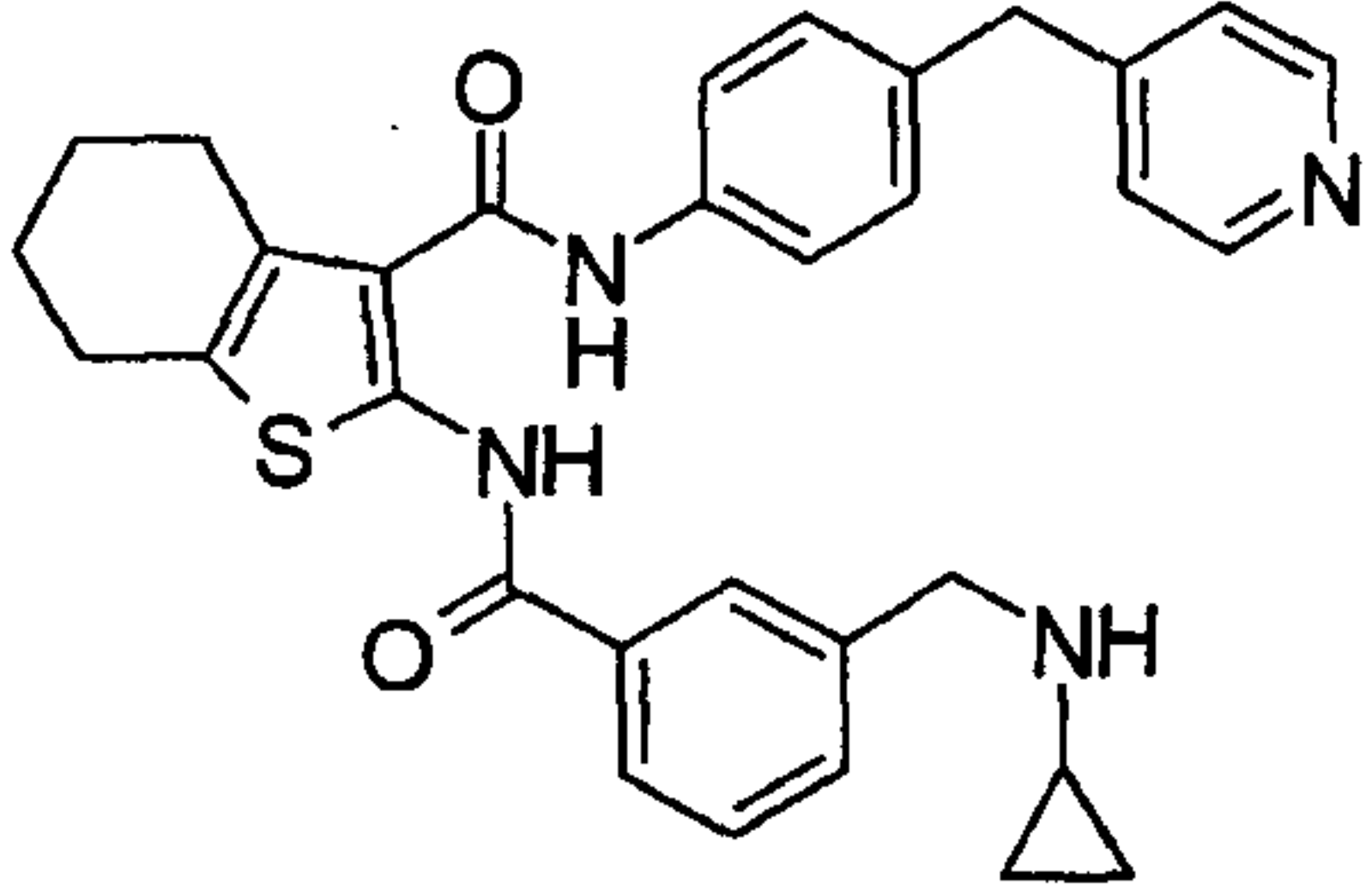
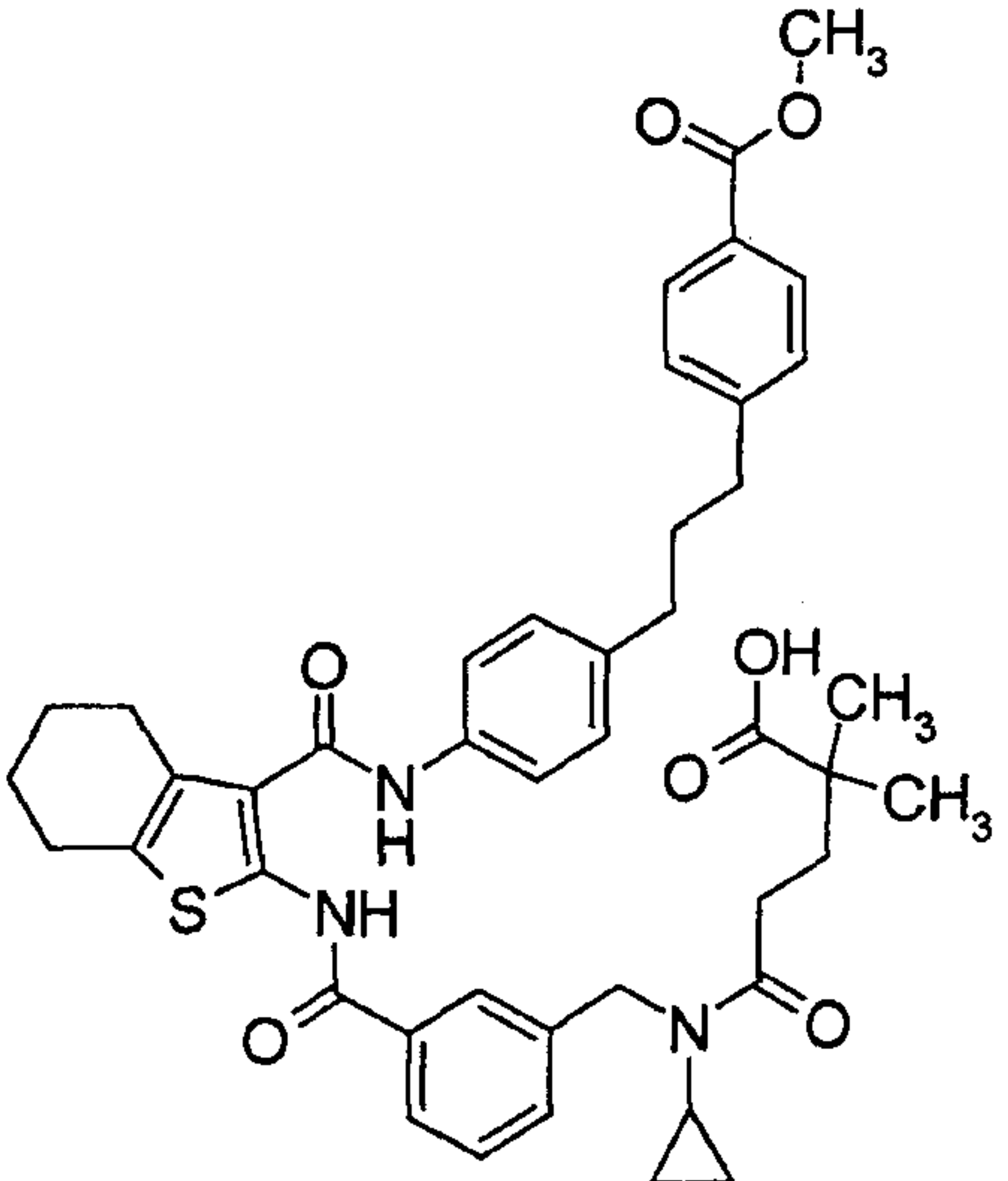
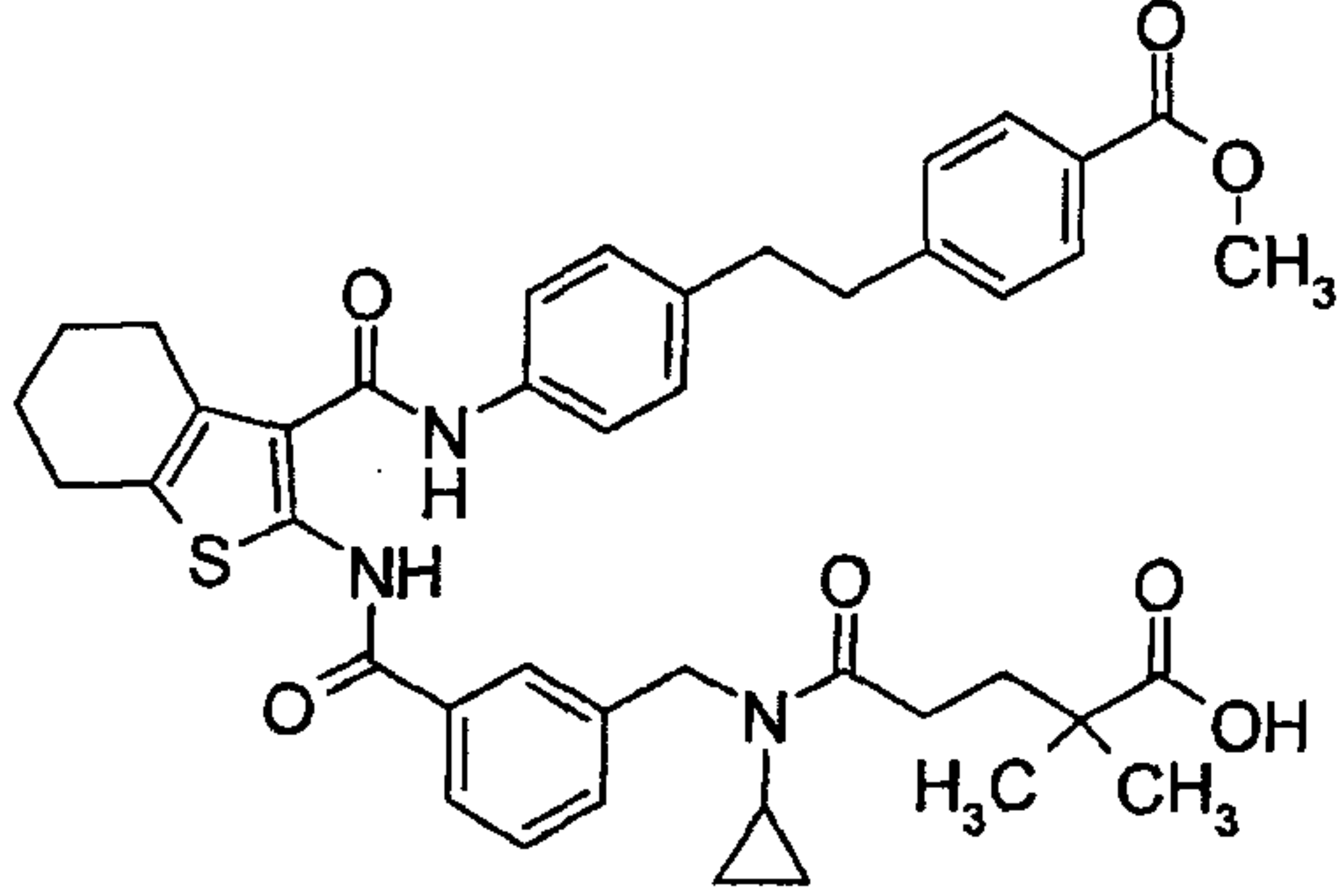
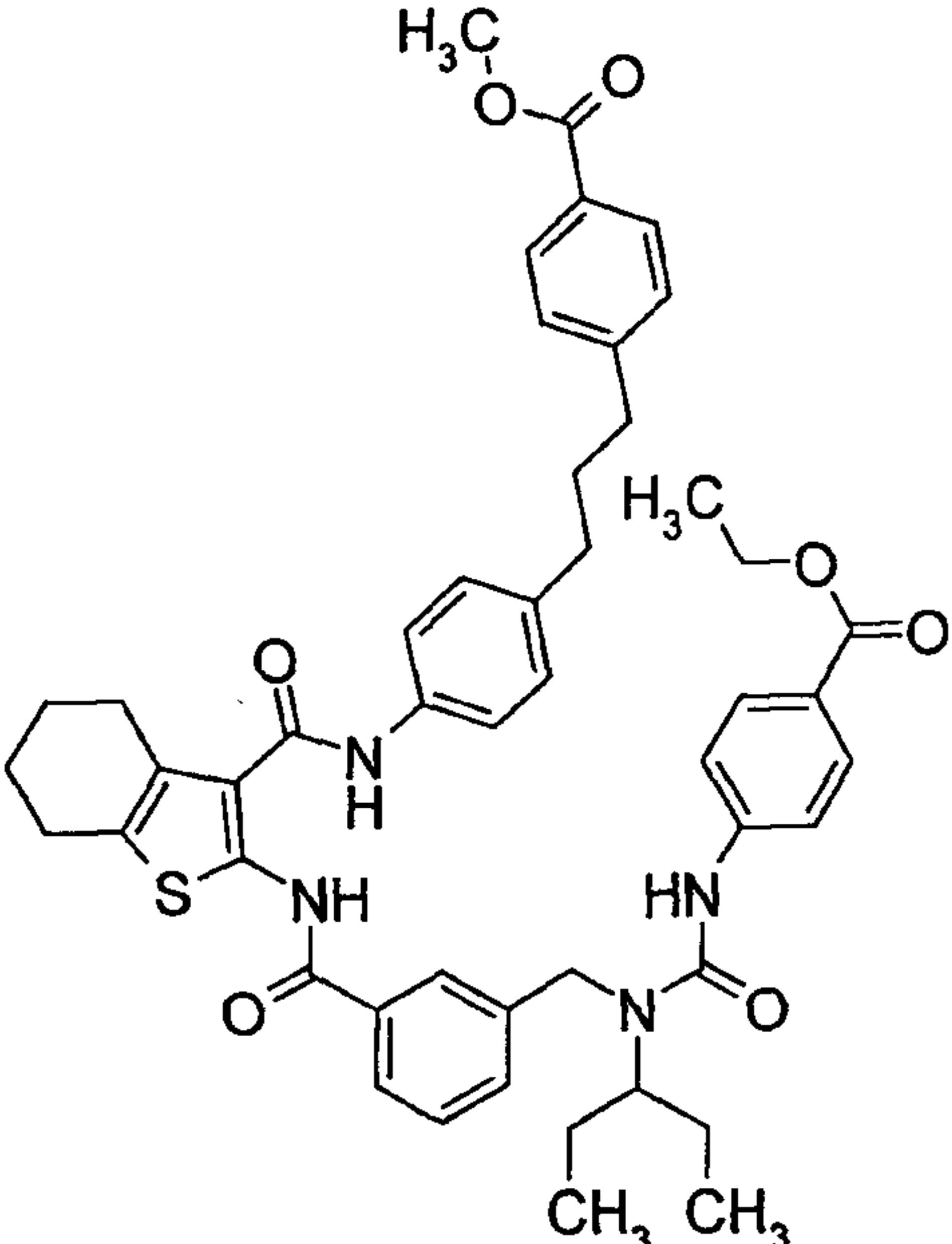
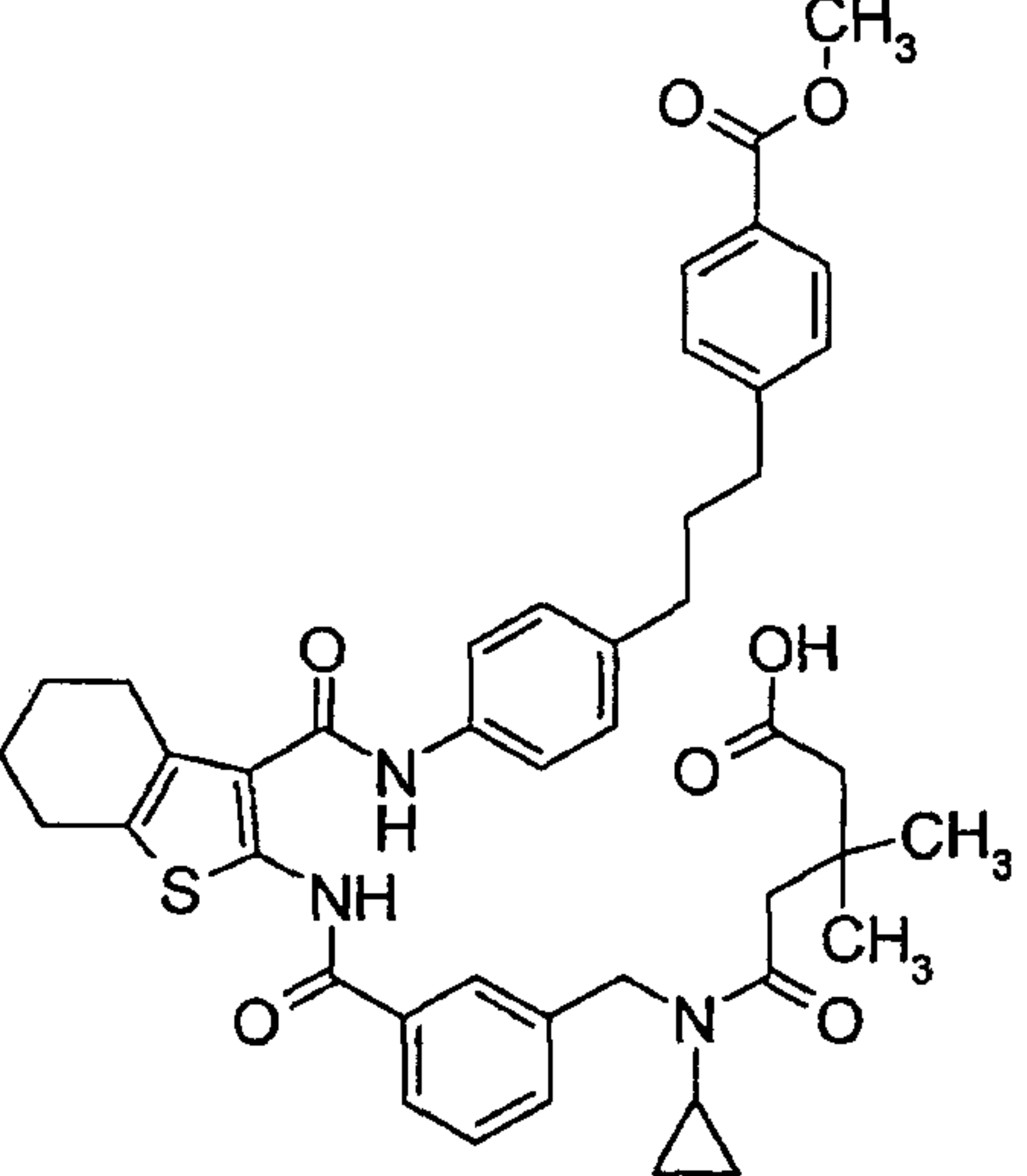
[0172]
[Table 27]

Pr	Str	Pr	Str
157		160	
158		161	
159		162	

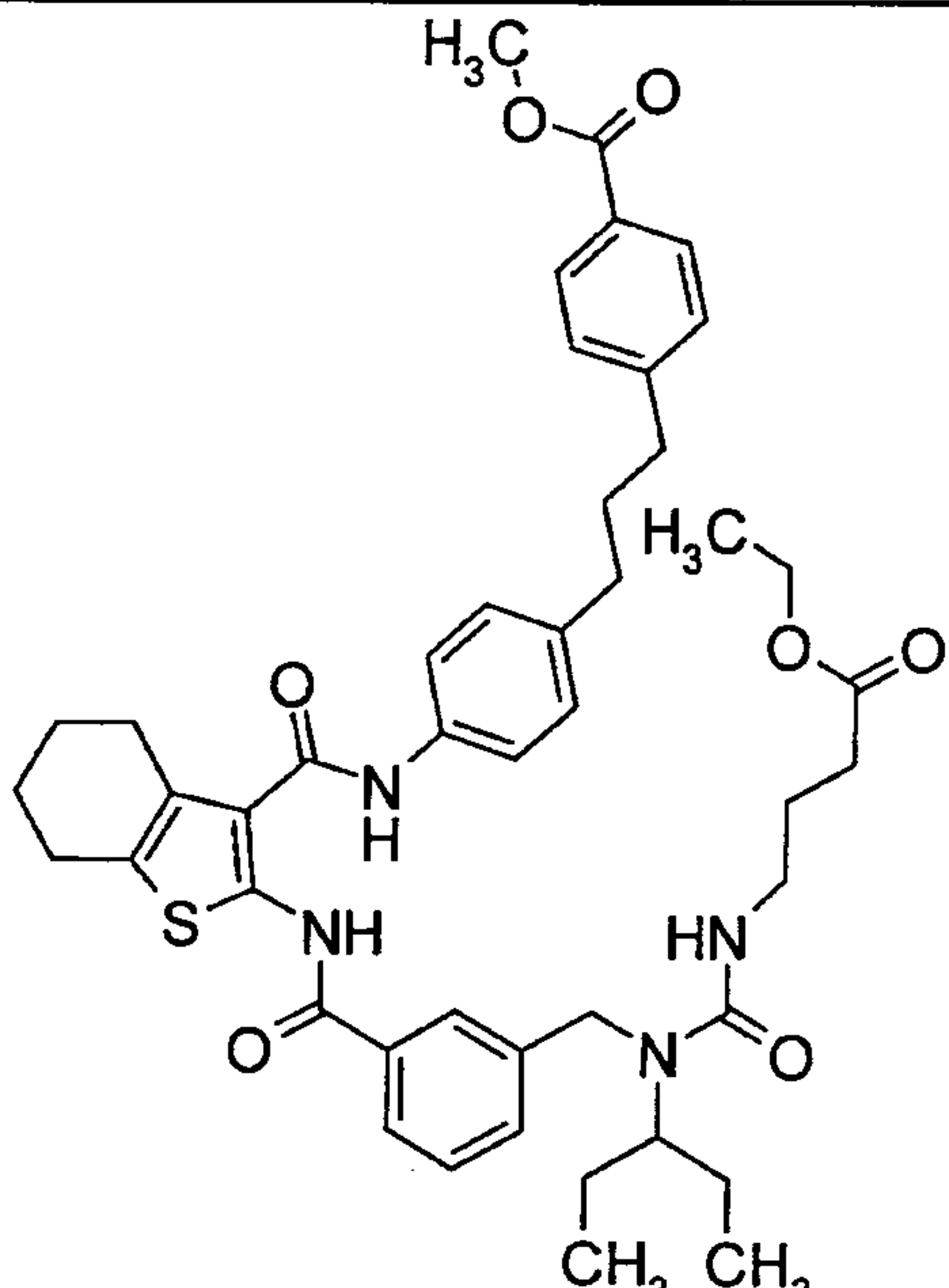
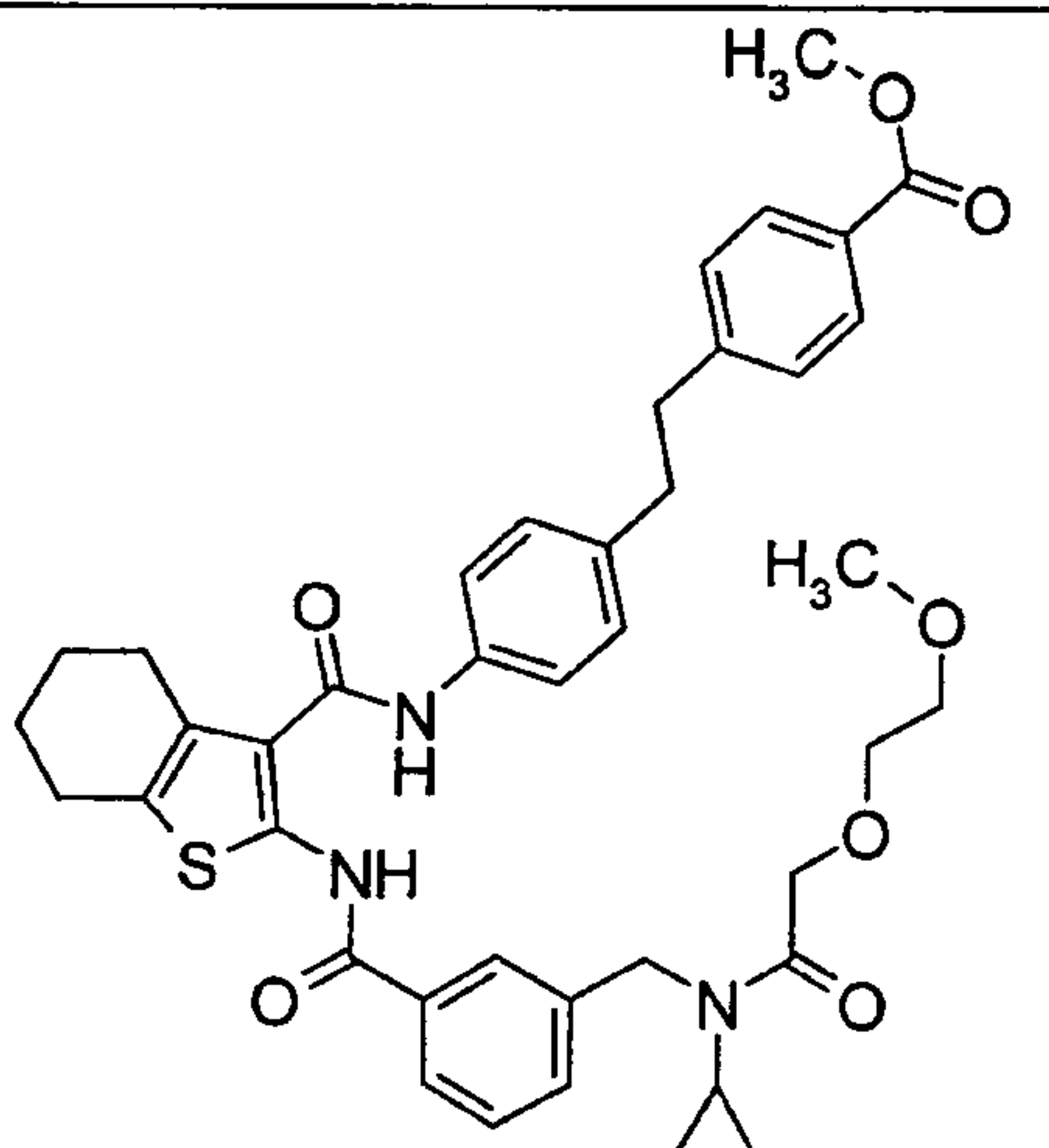
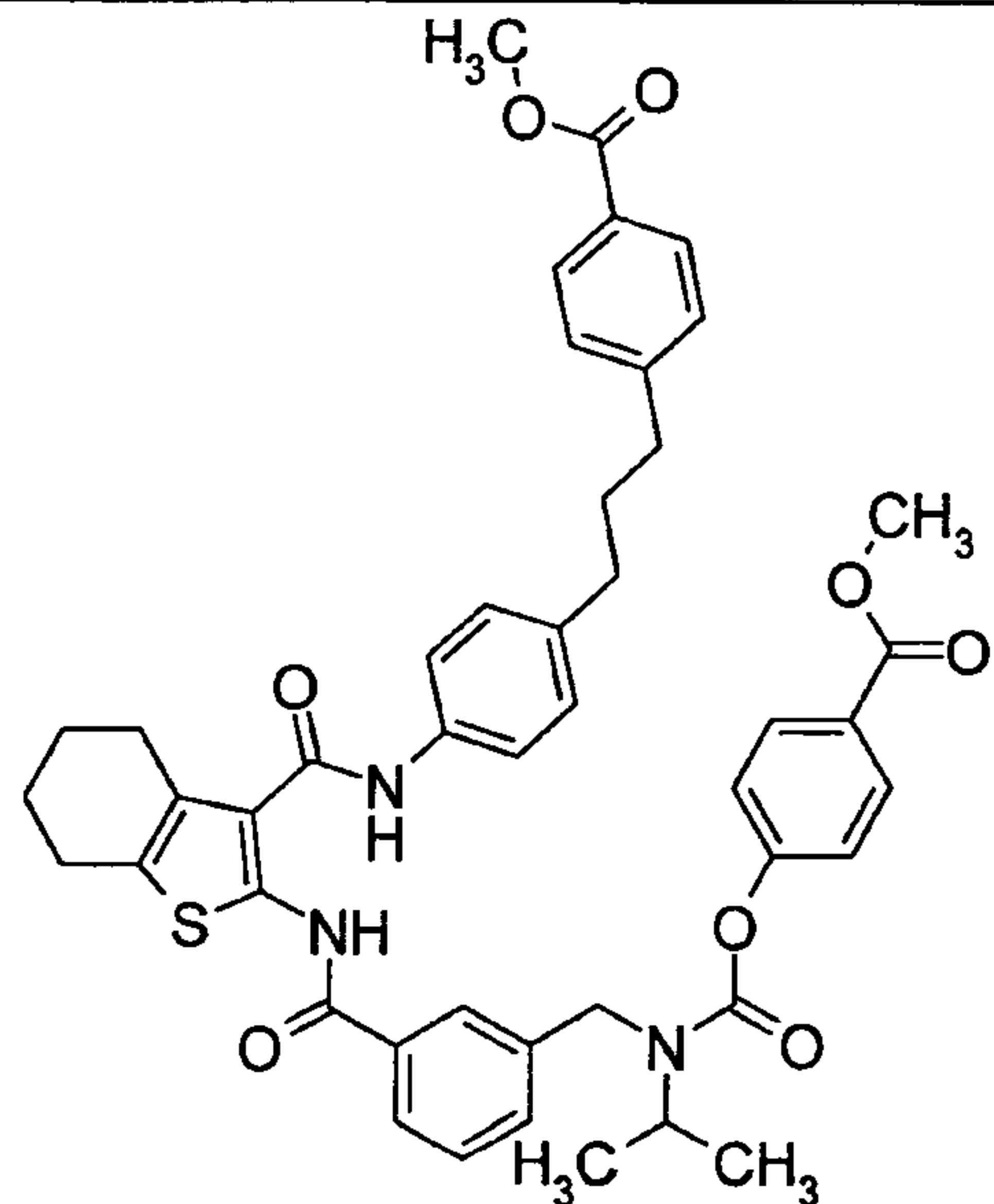
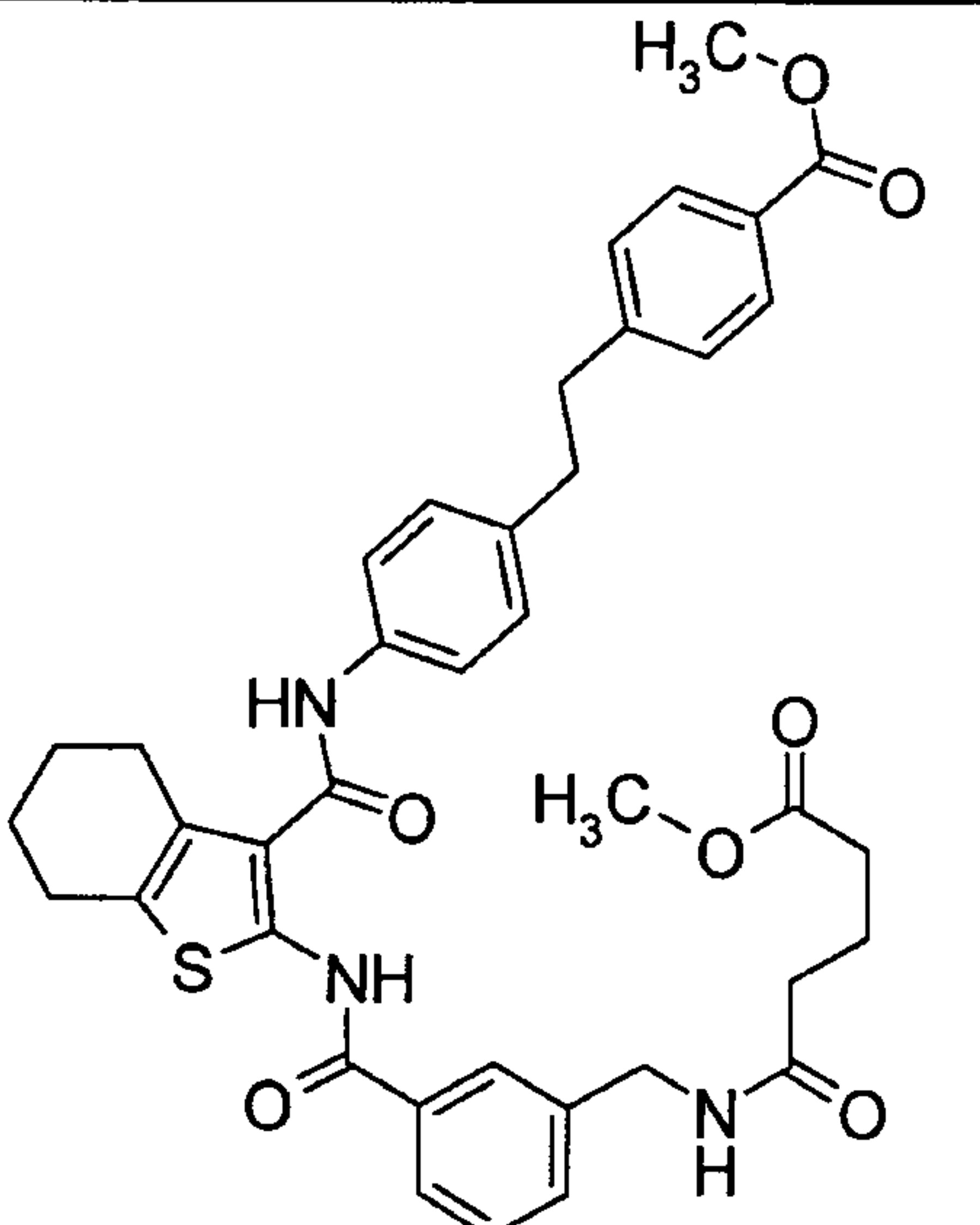
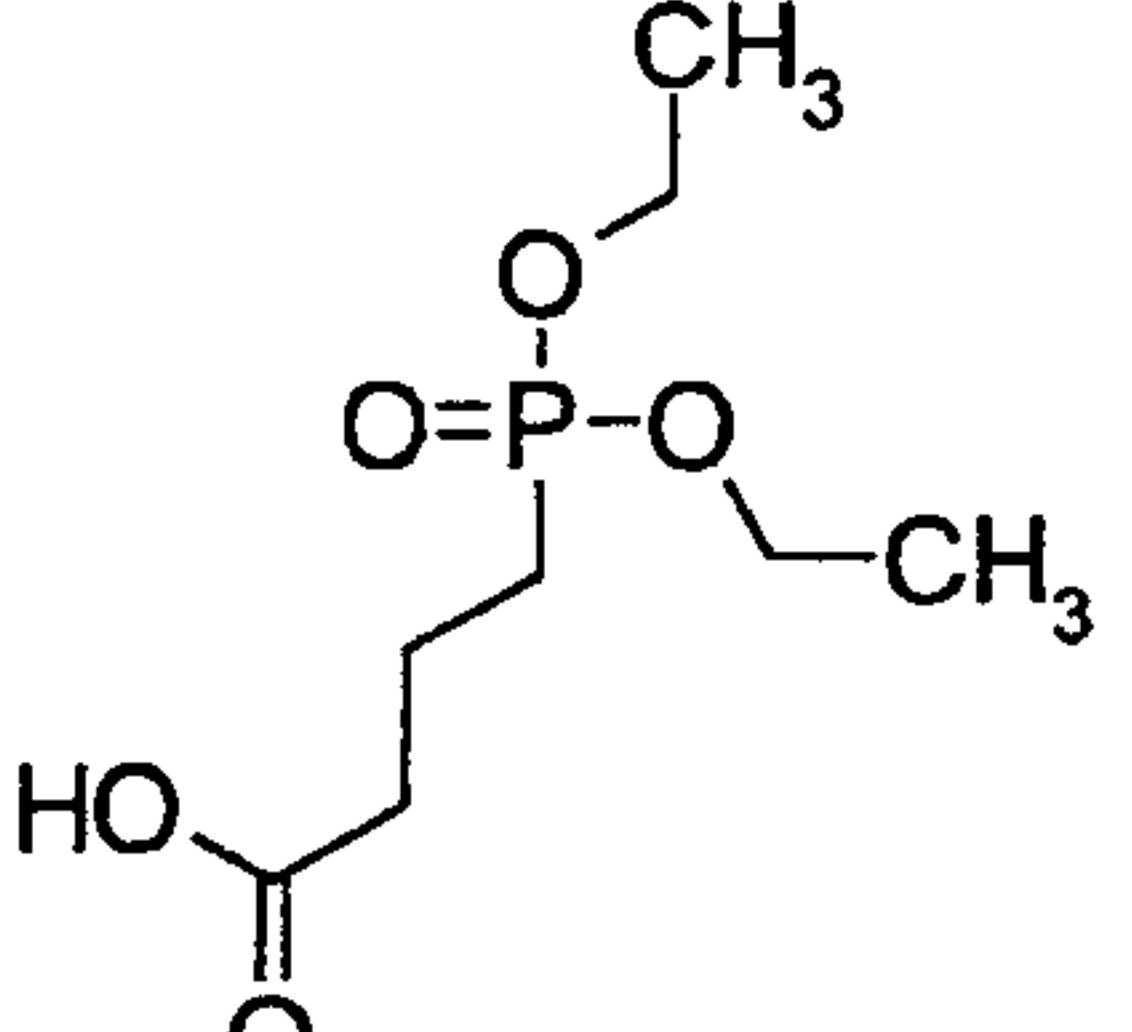
[0173]
[Table 28]

Pr	Str	Pr	Str
163		166	
164		167	
165		168	
		169	
		170	
		171	

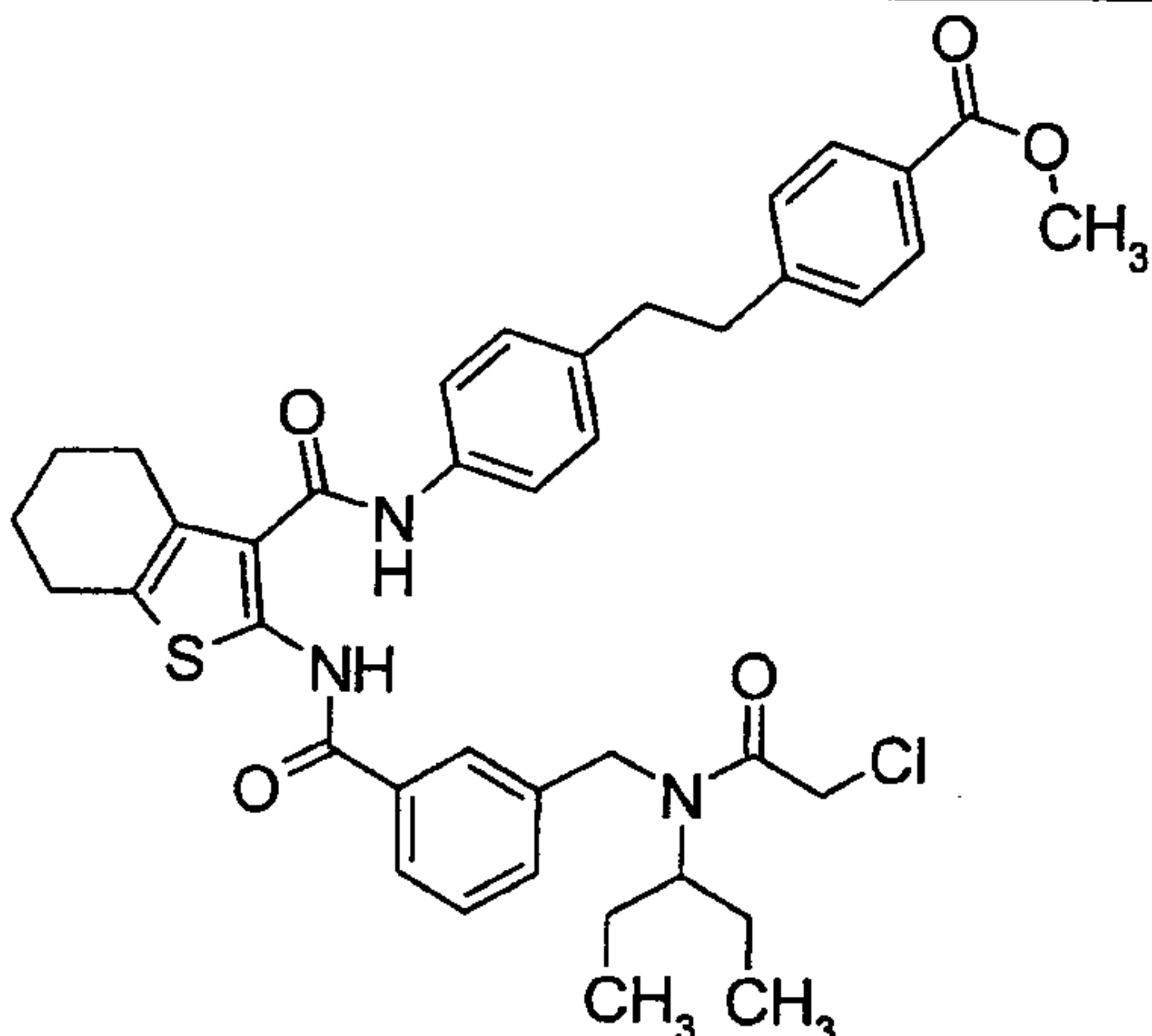
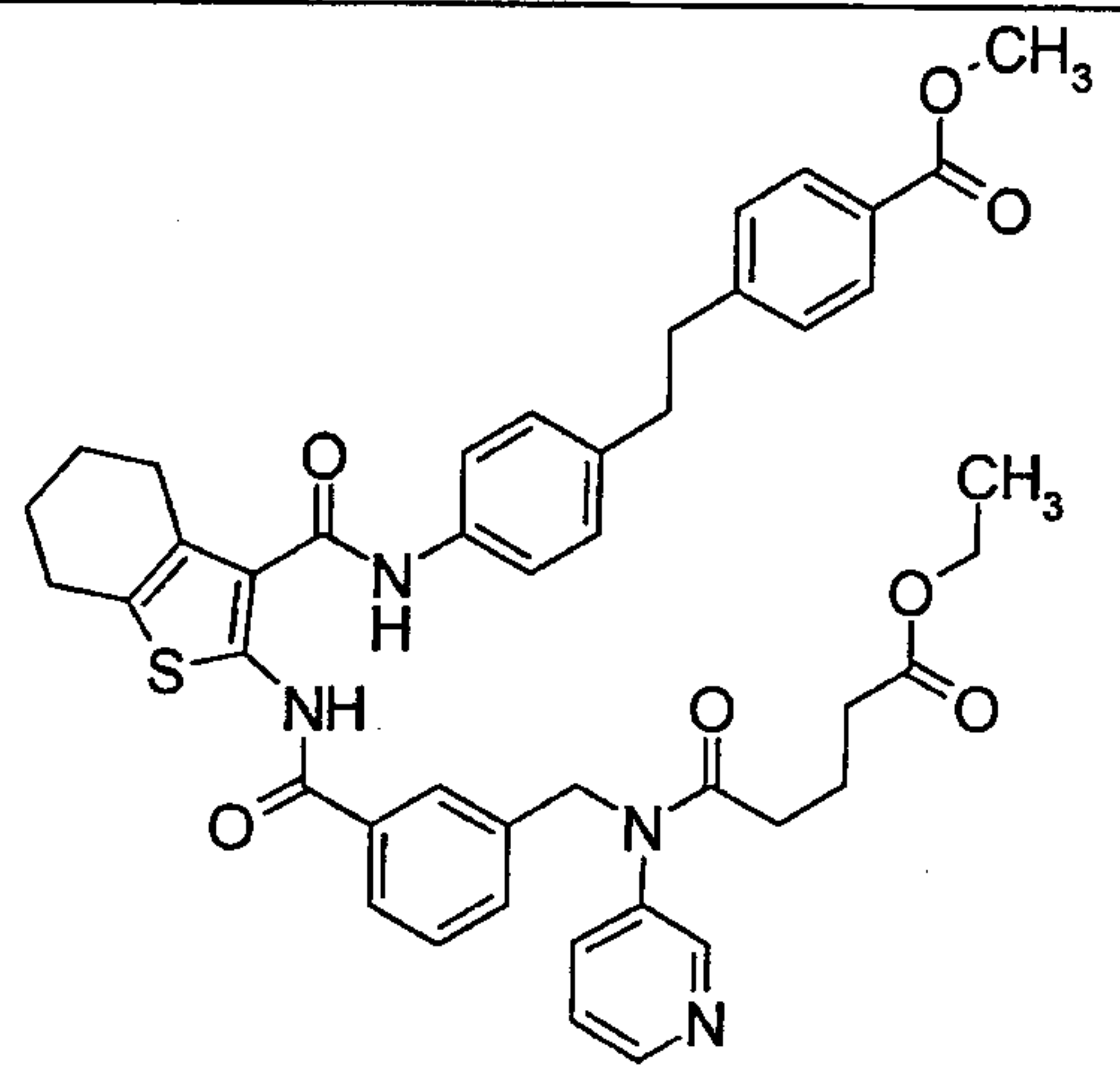
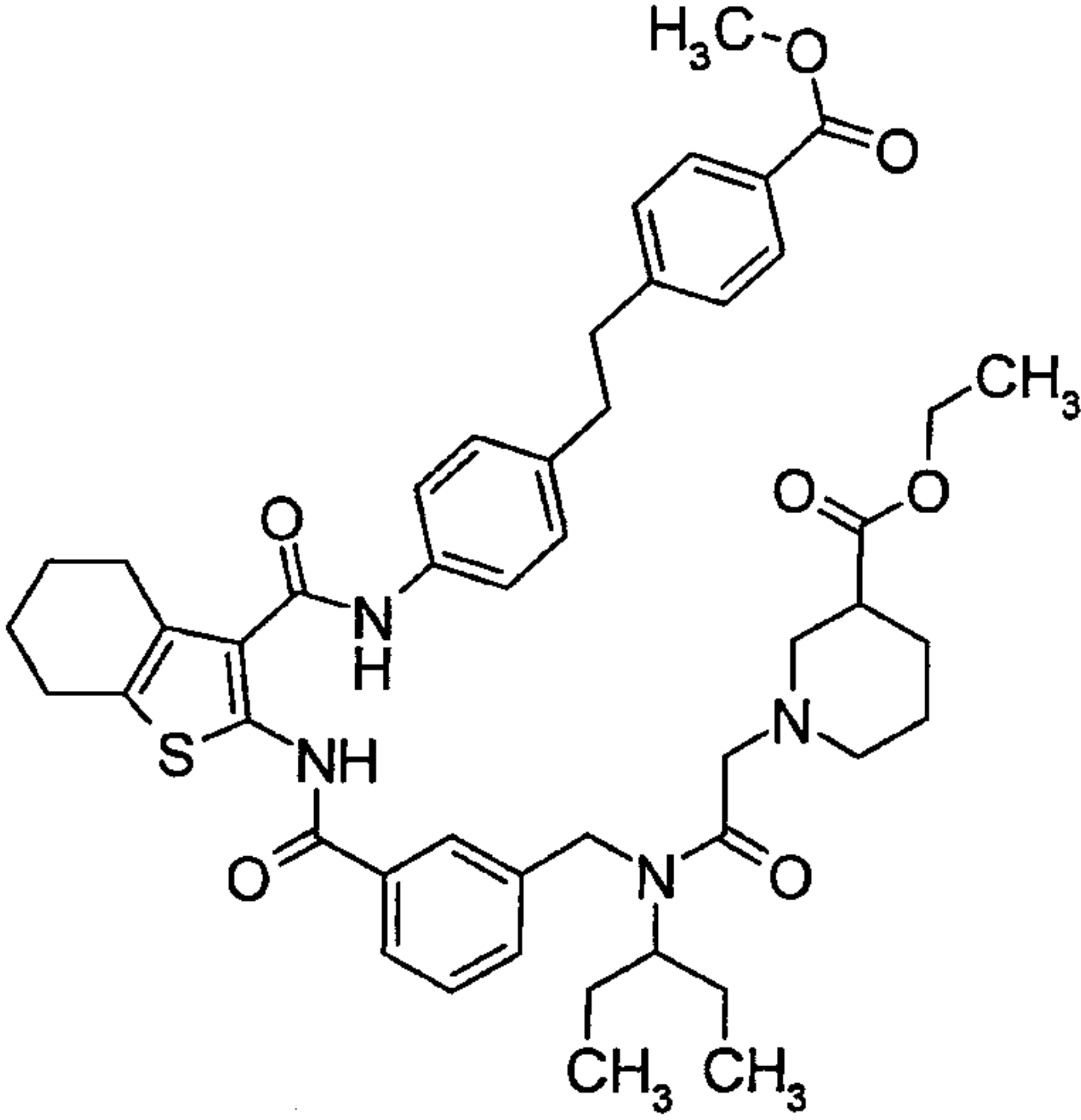
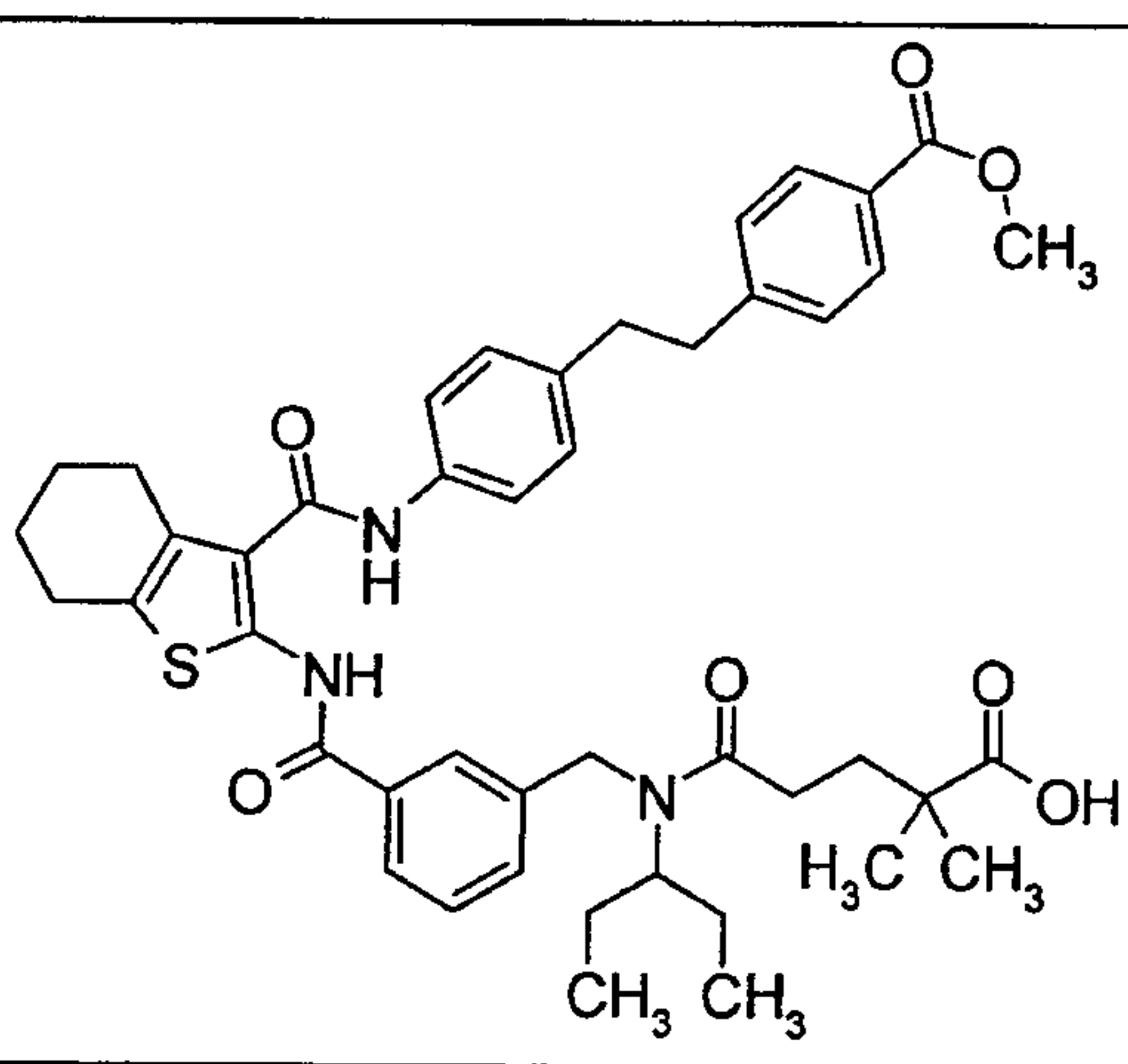
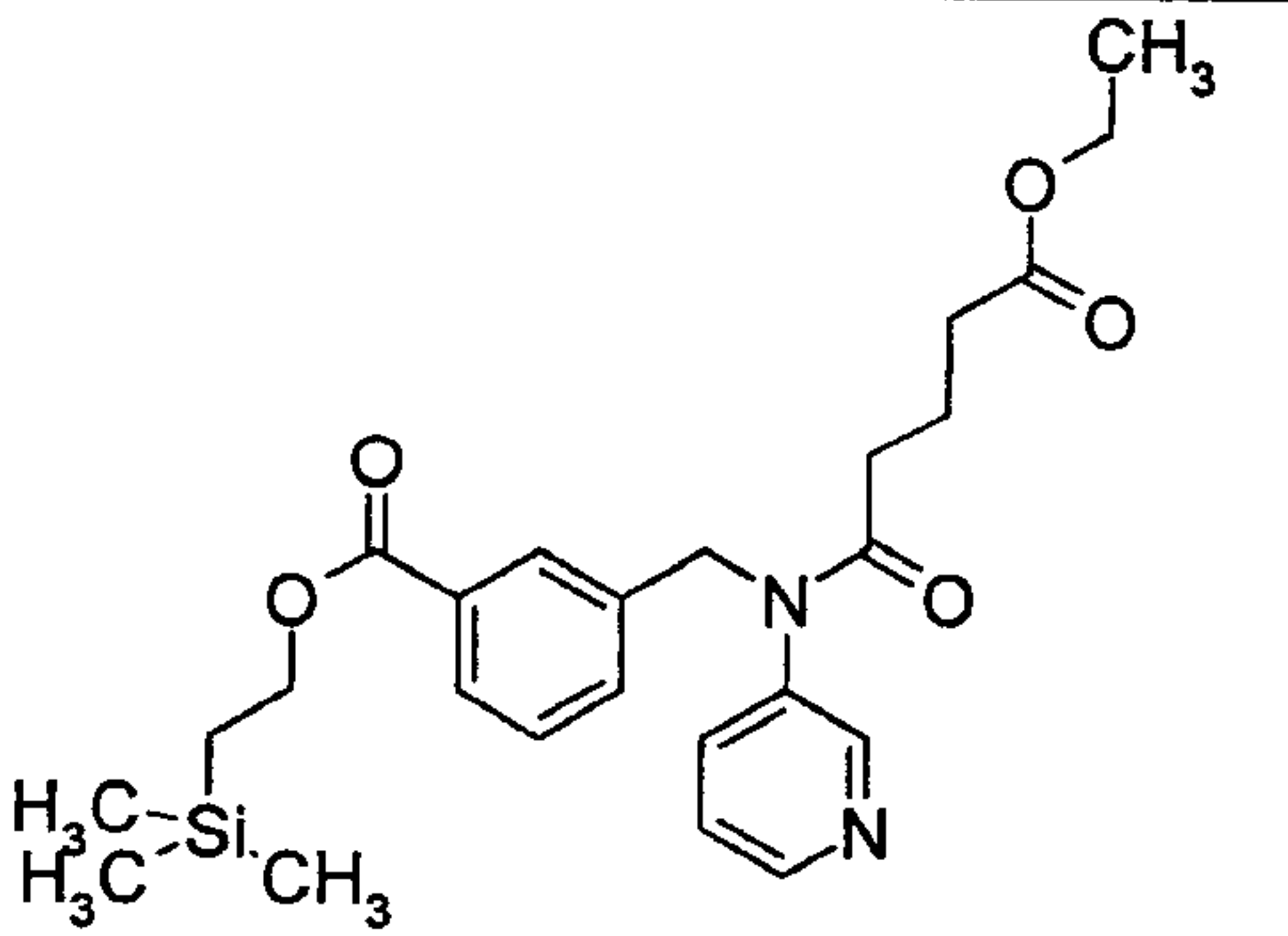
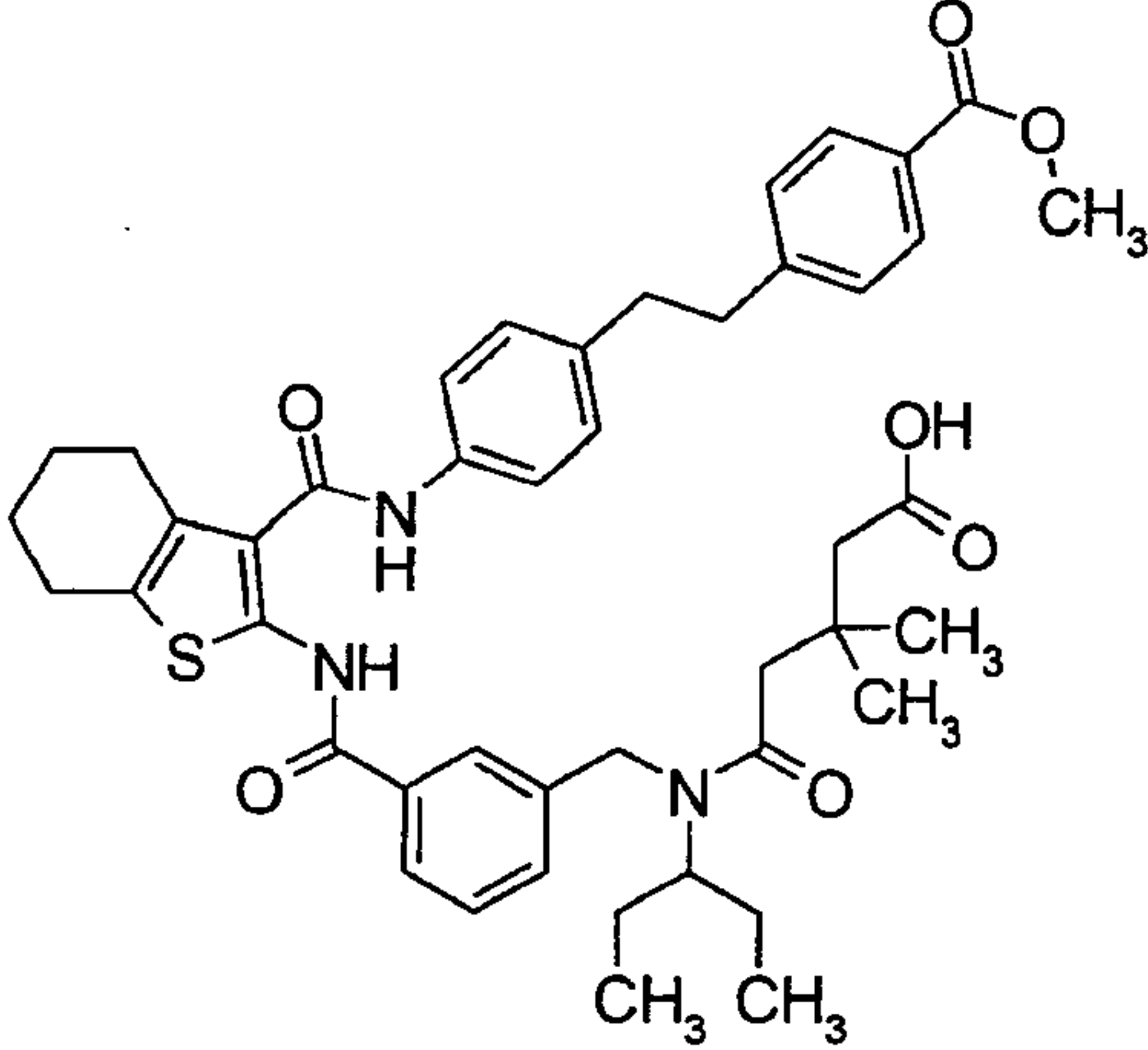
[0174]
[Table 29]

Pr	Str	Pr	Str
172		175	
173		176	
174			

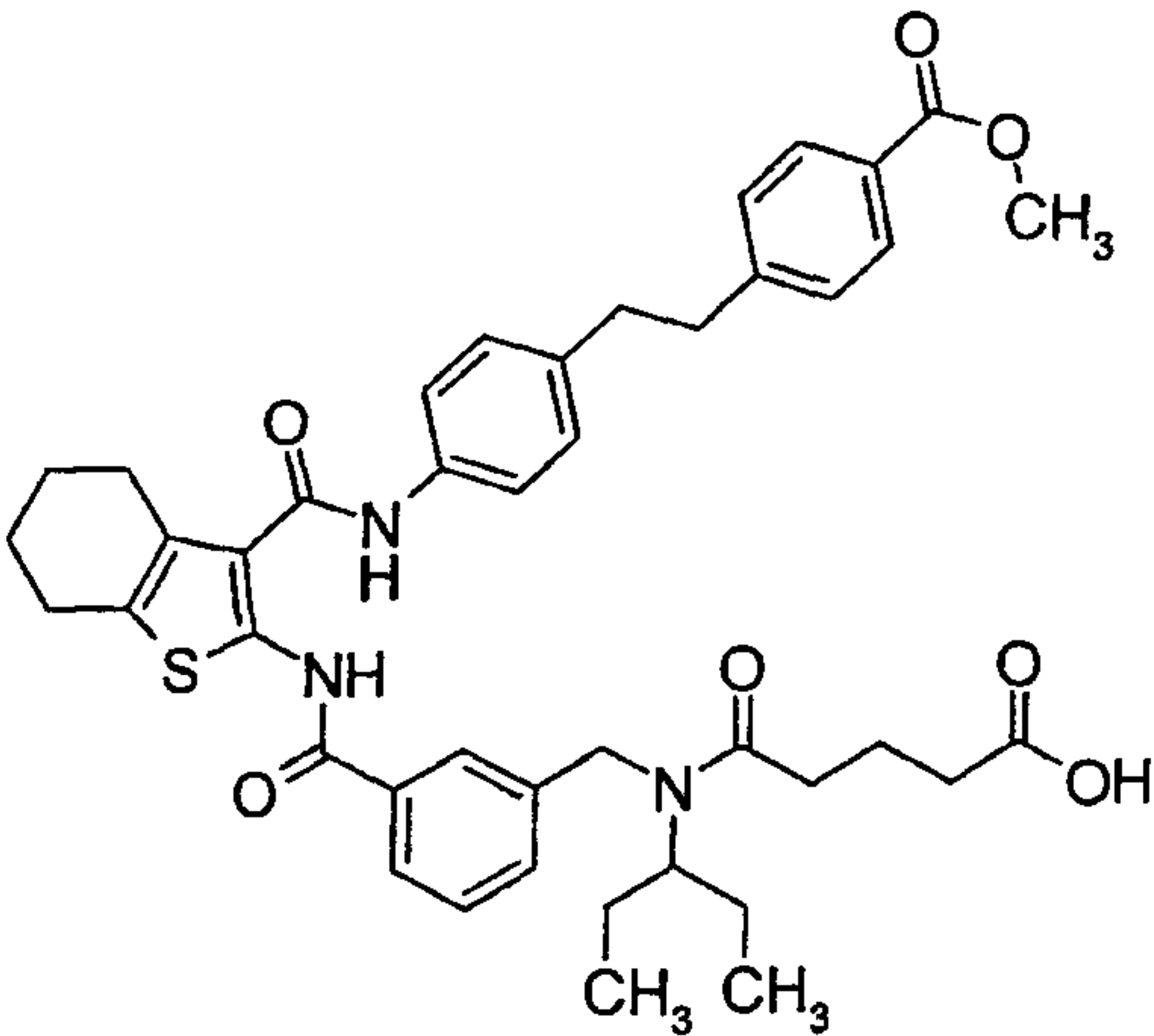
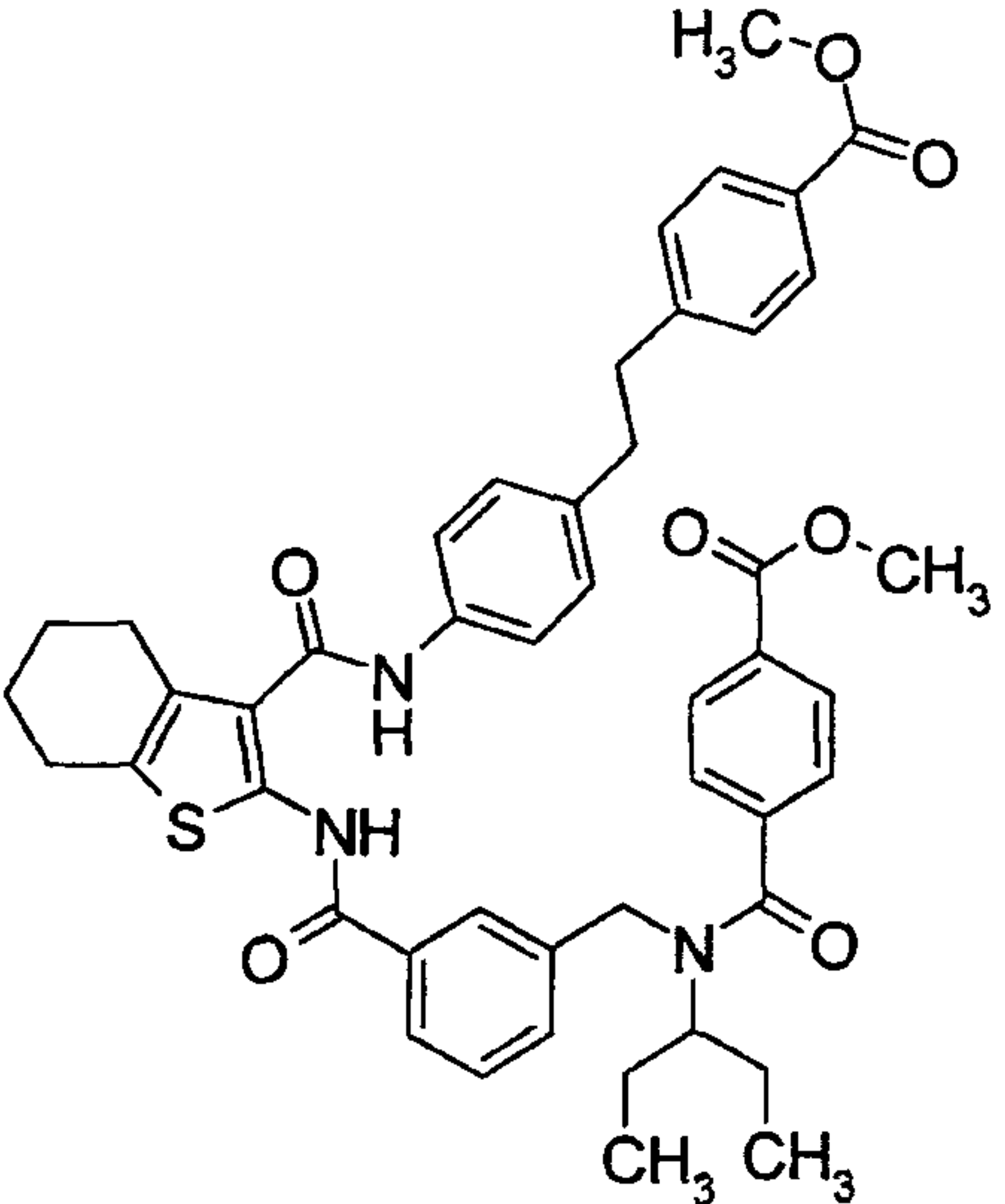
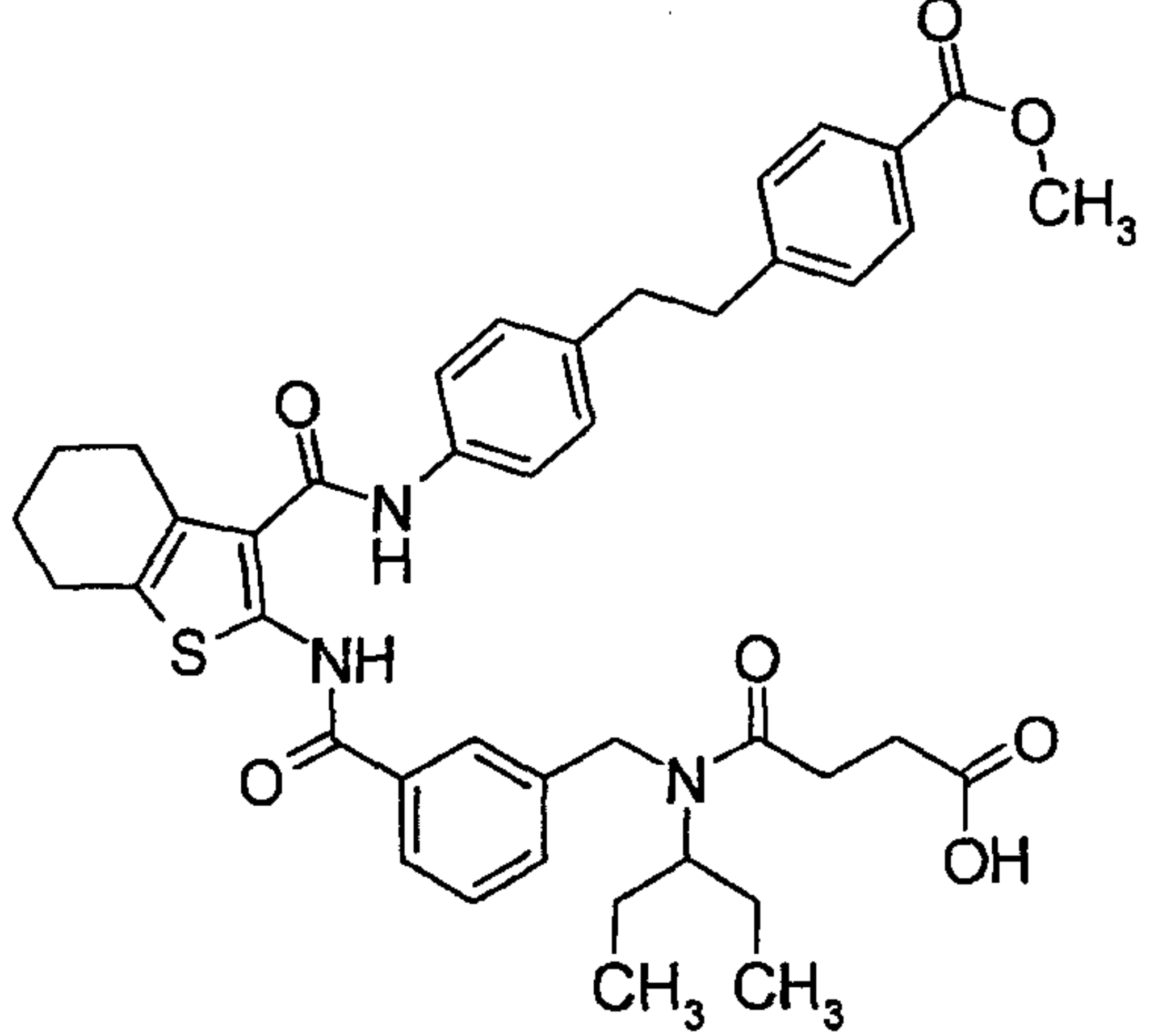
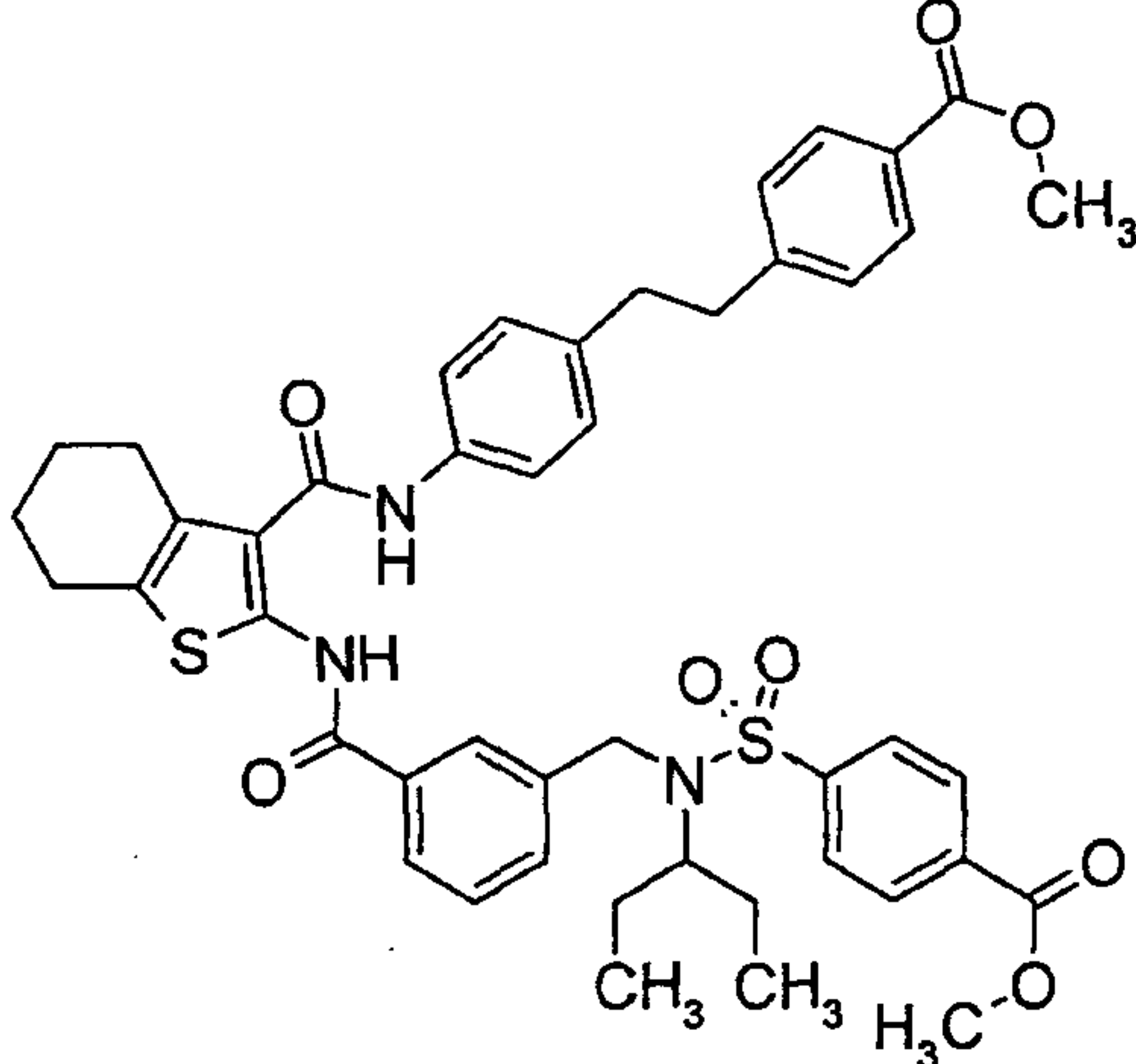
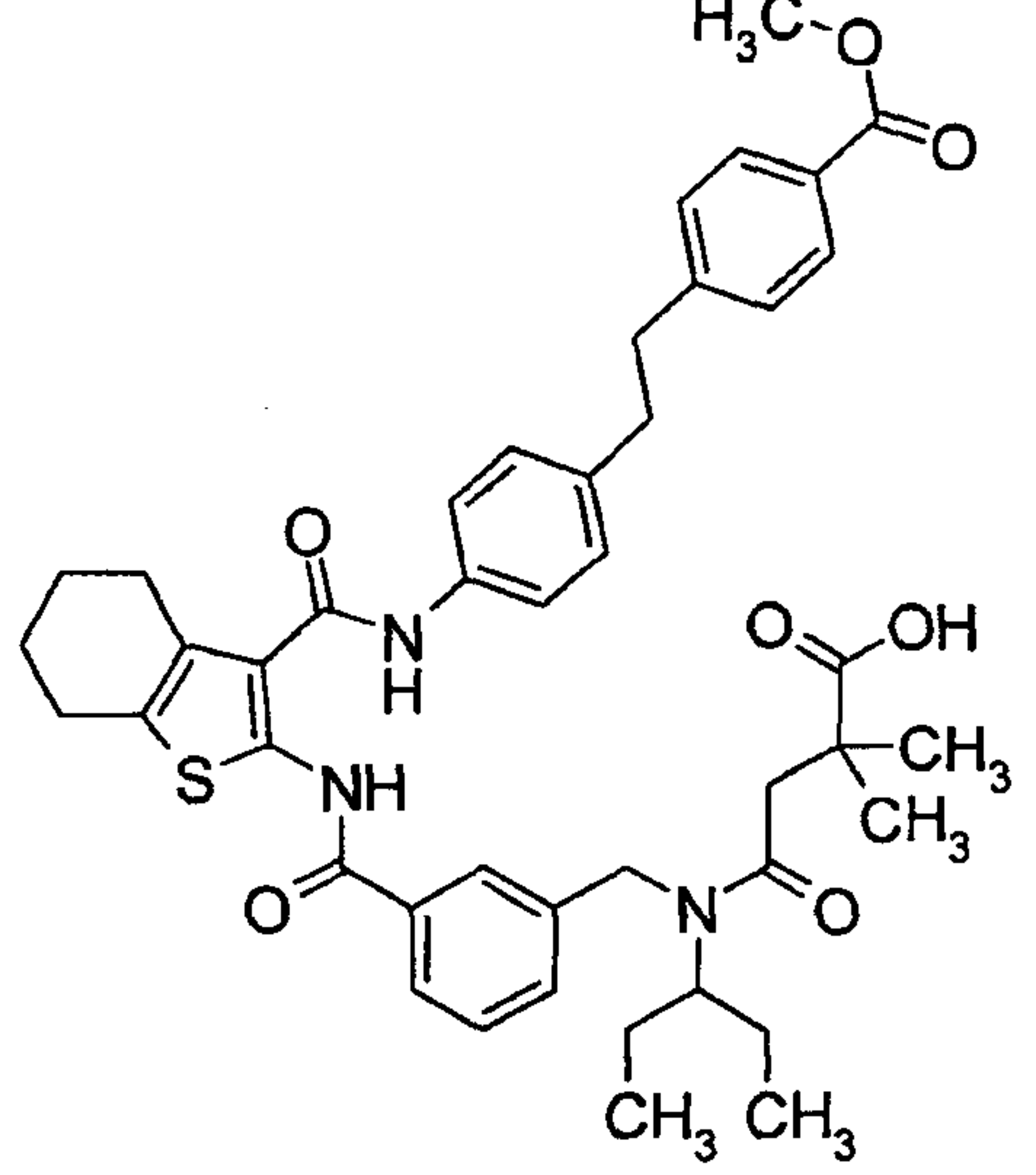
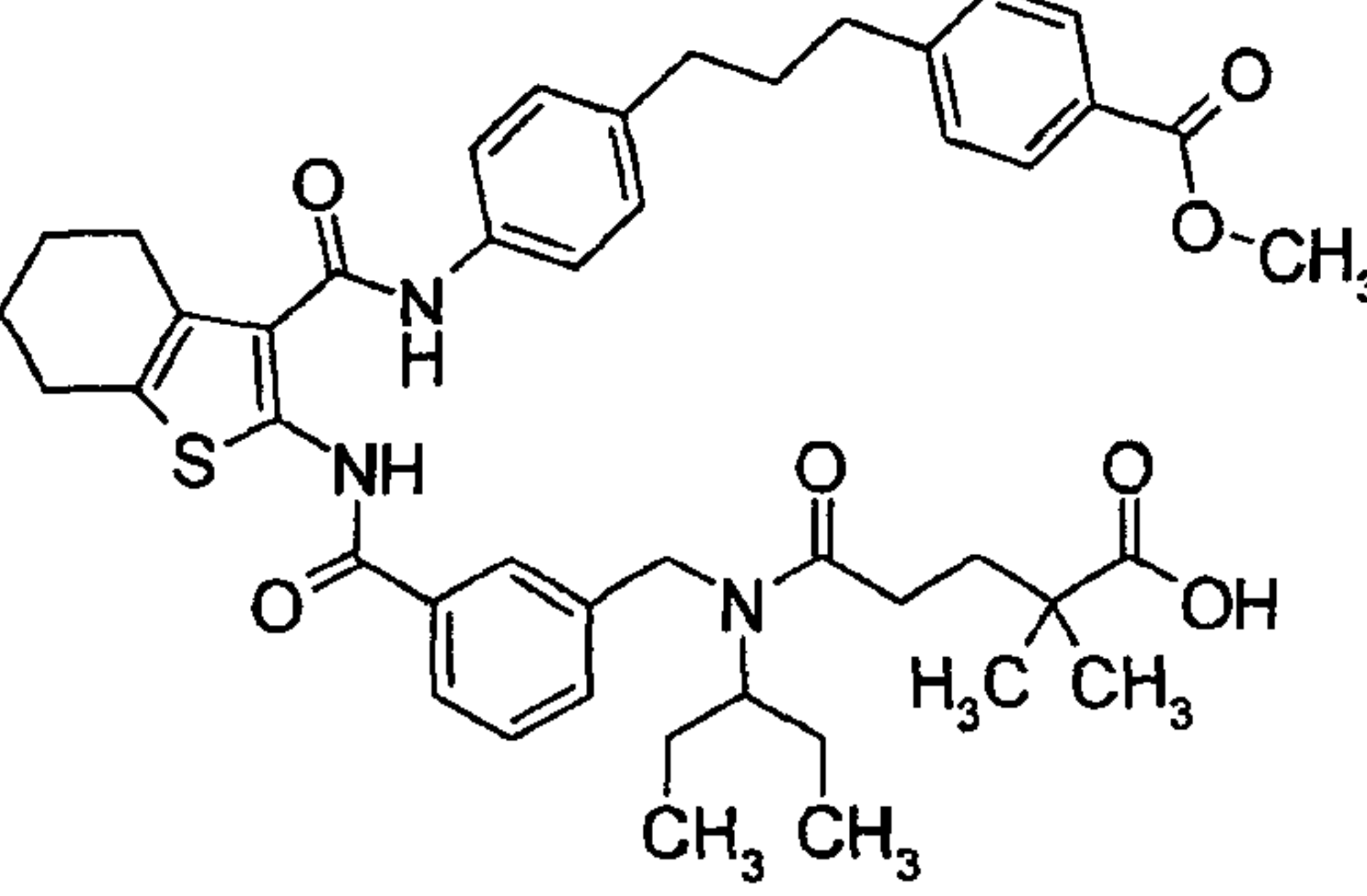
[0175]
[Table 30]

Pr	Str	Pr	Str
177		180	
178		181	
179			

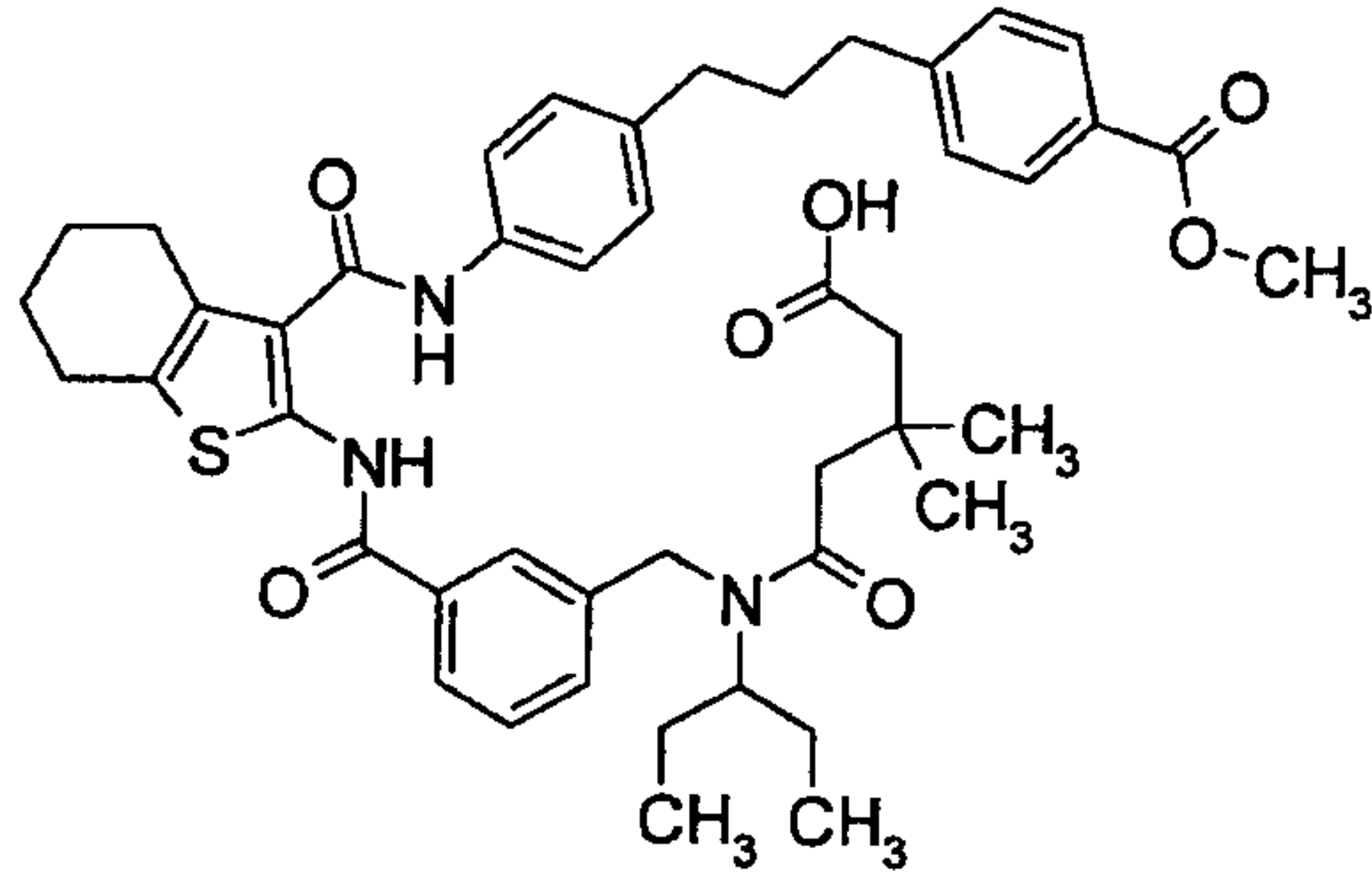
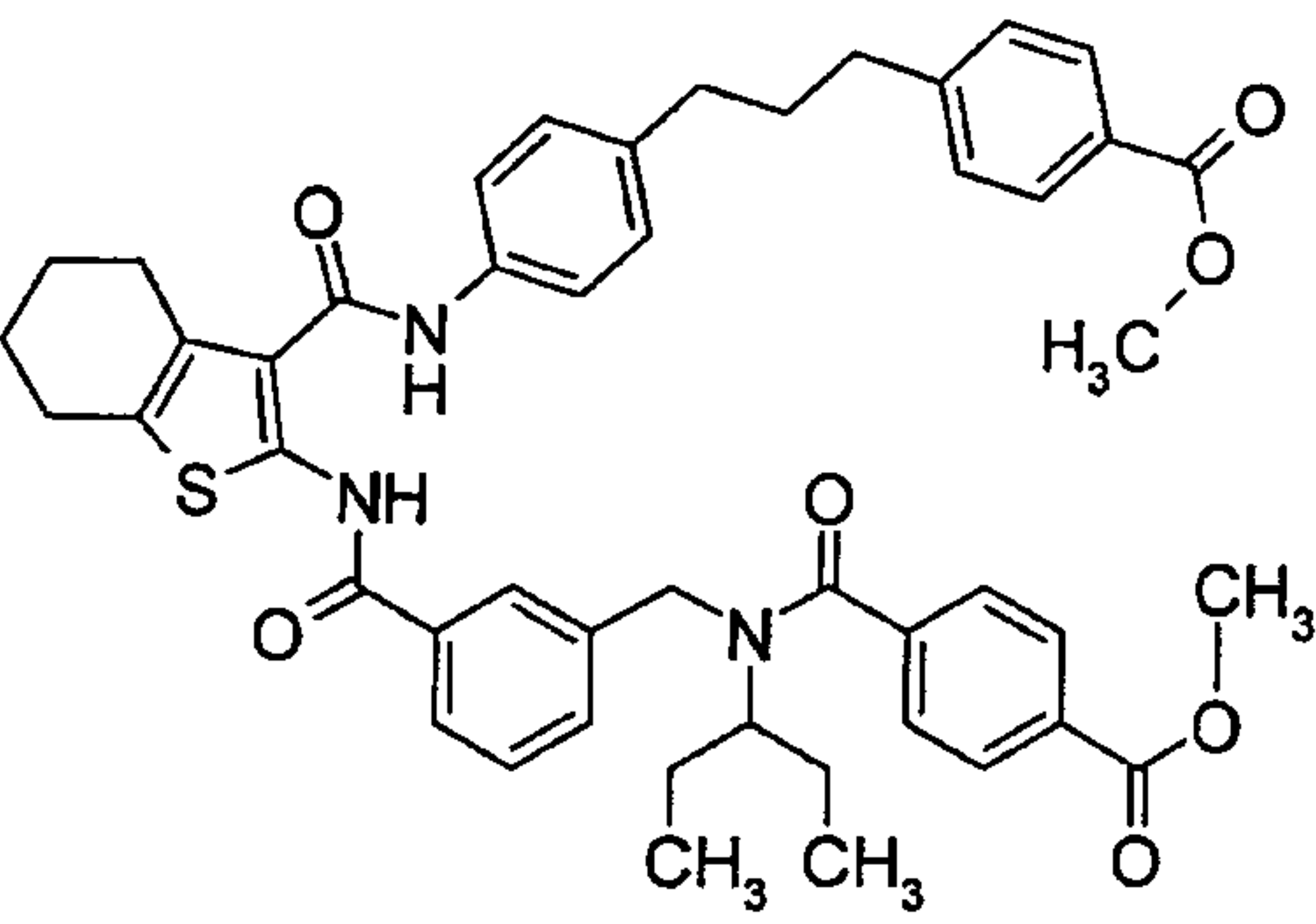
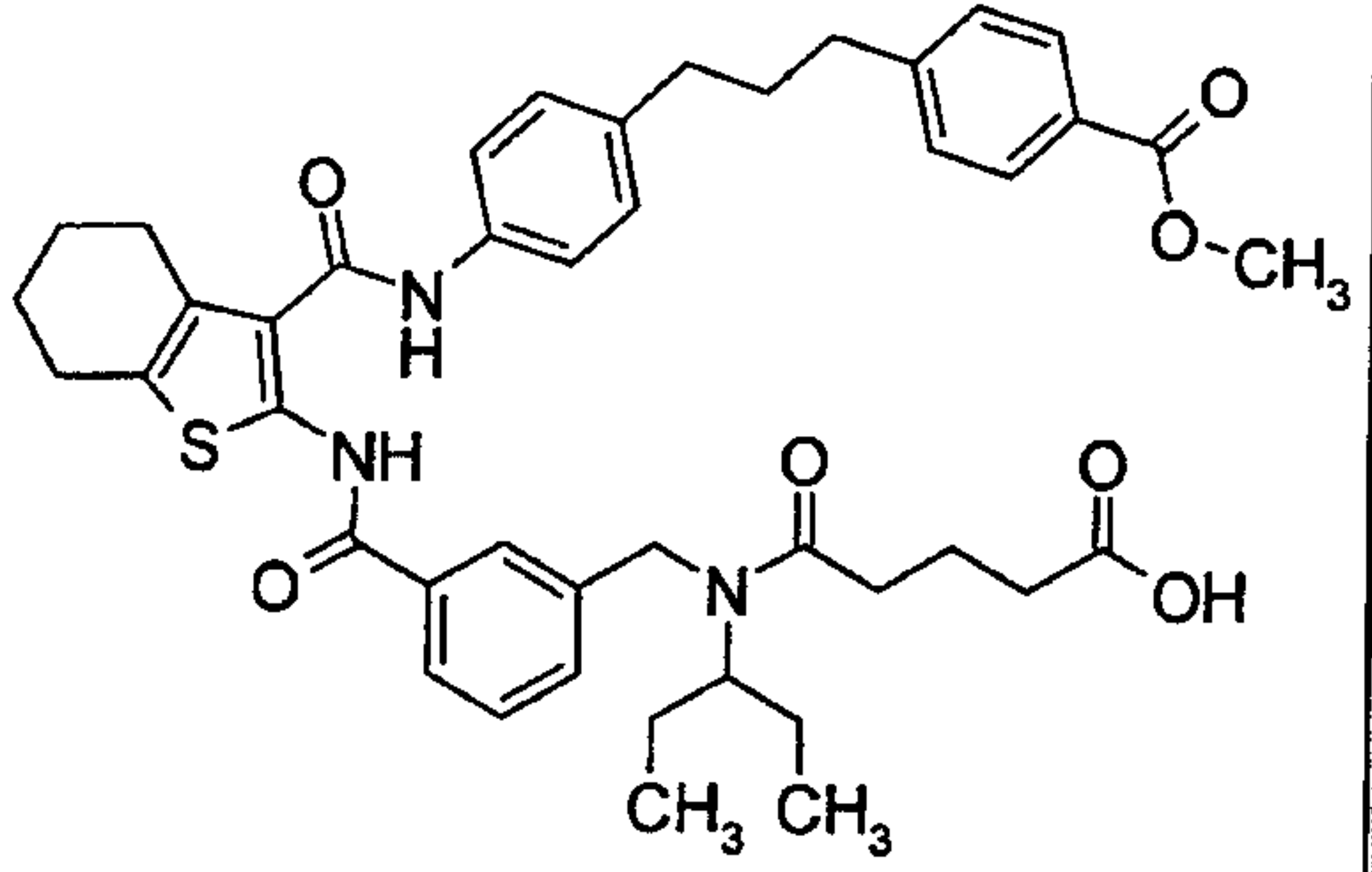
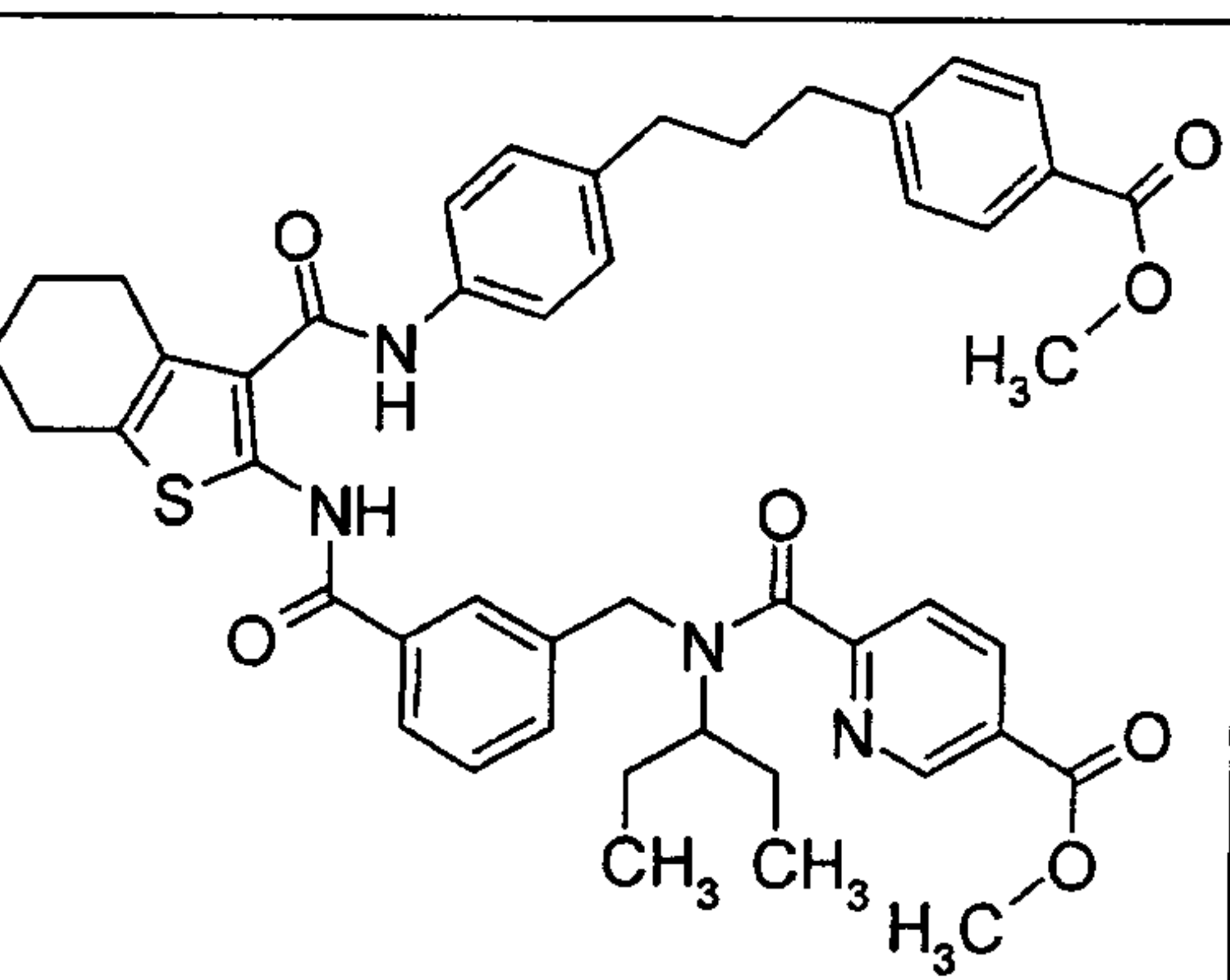
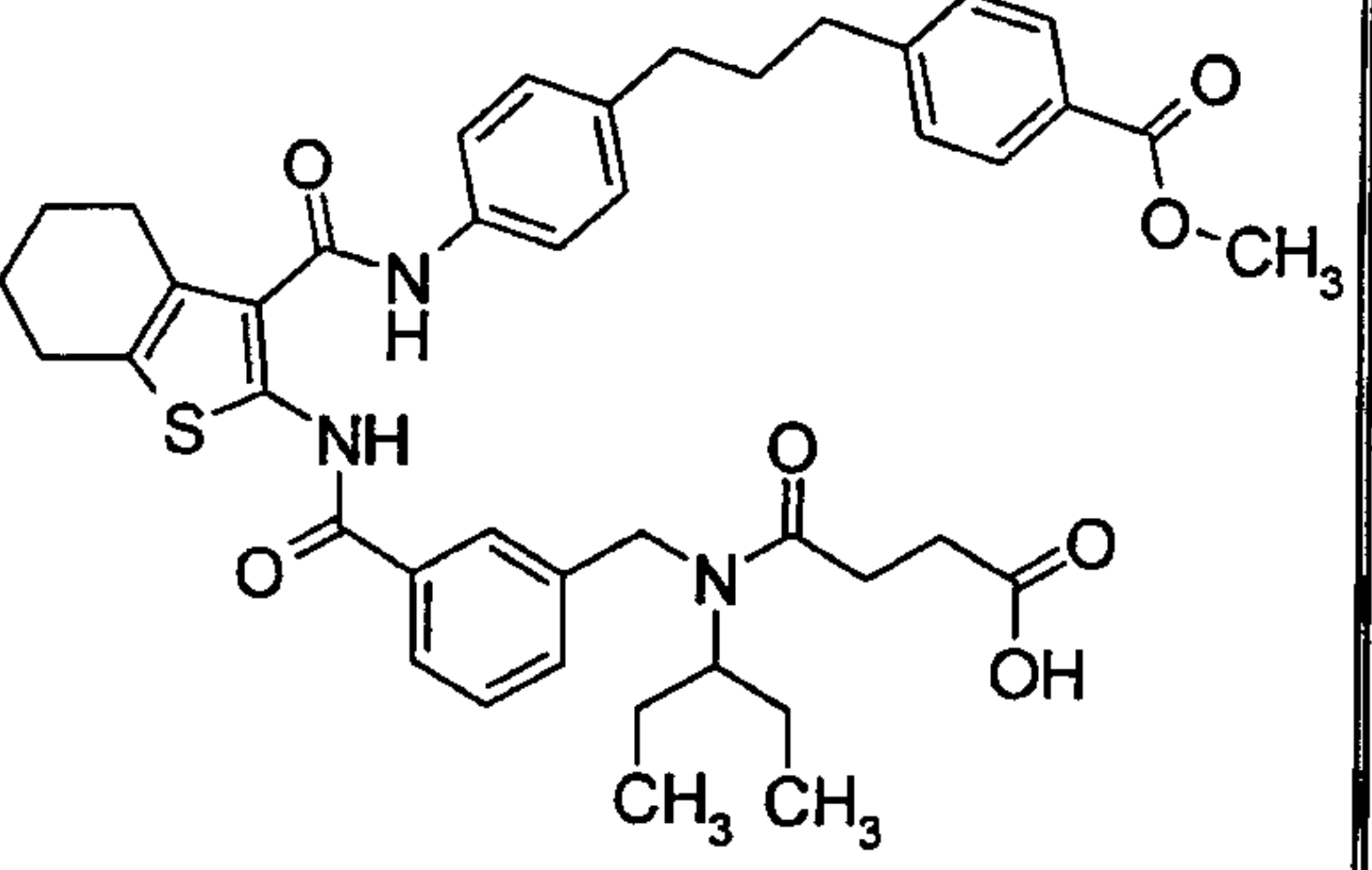
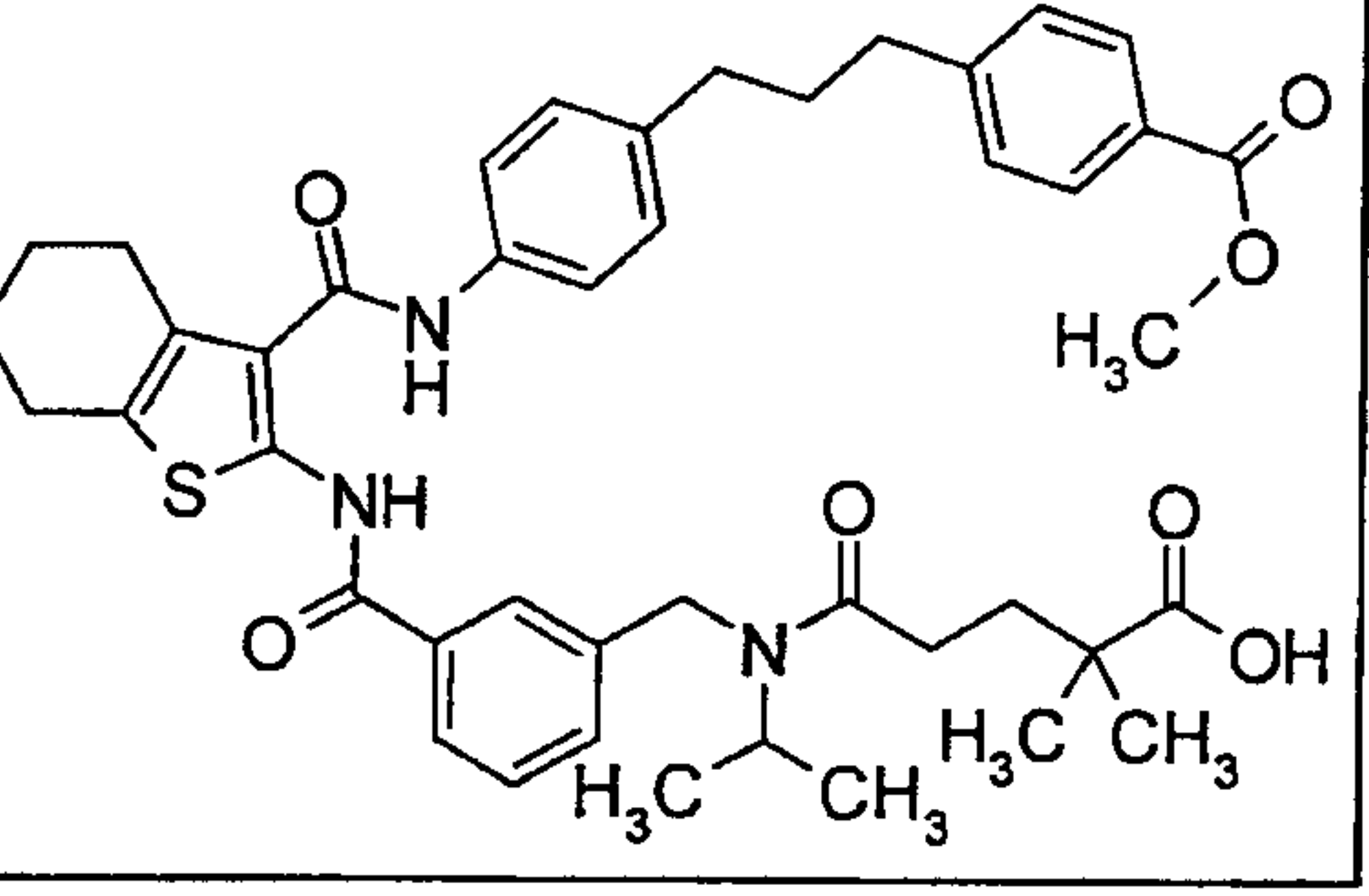
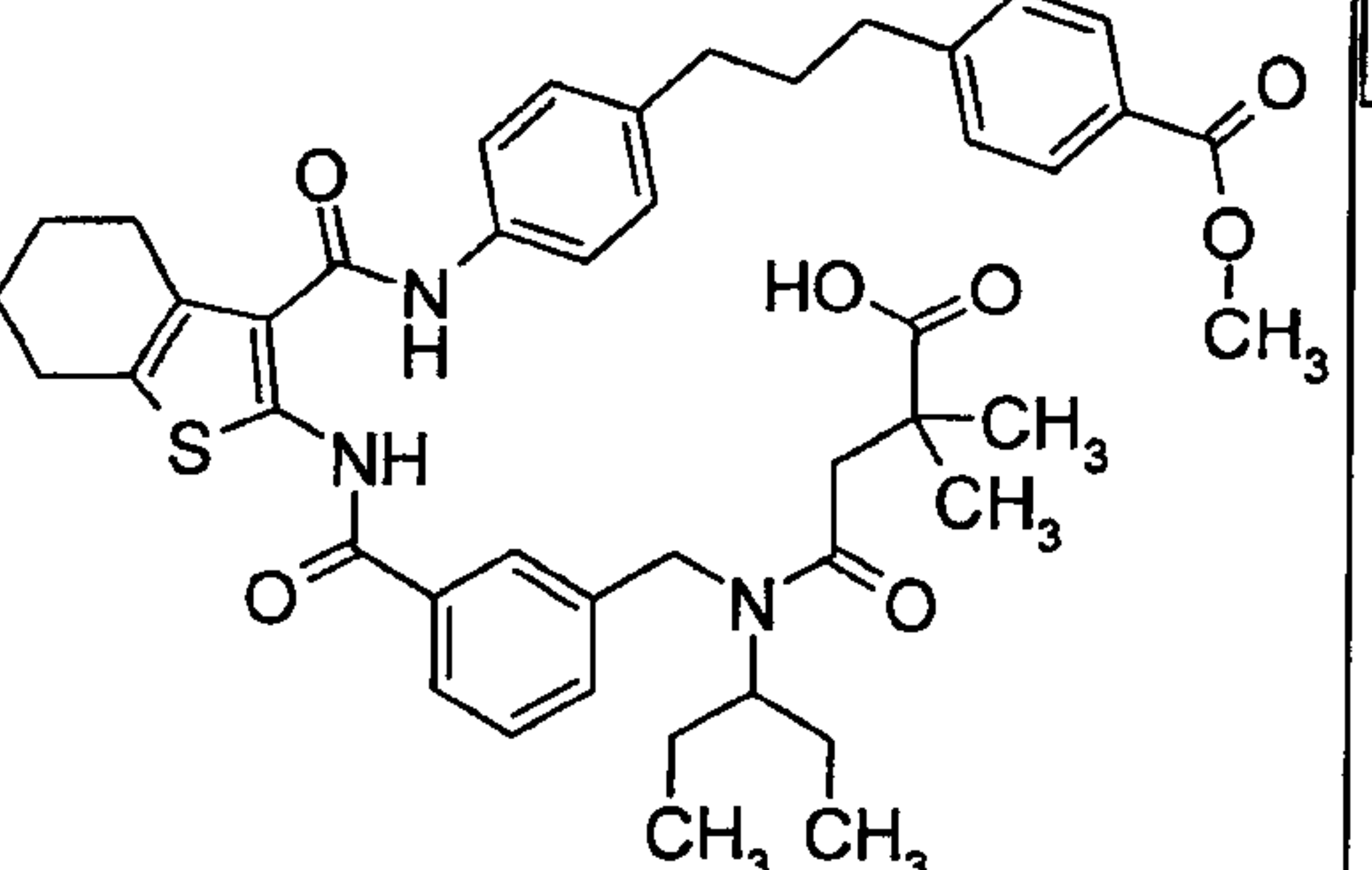
[0176]
[Table 31]

Pr	Str	Pr	Str
182		185	
183		186	
184		187	

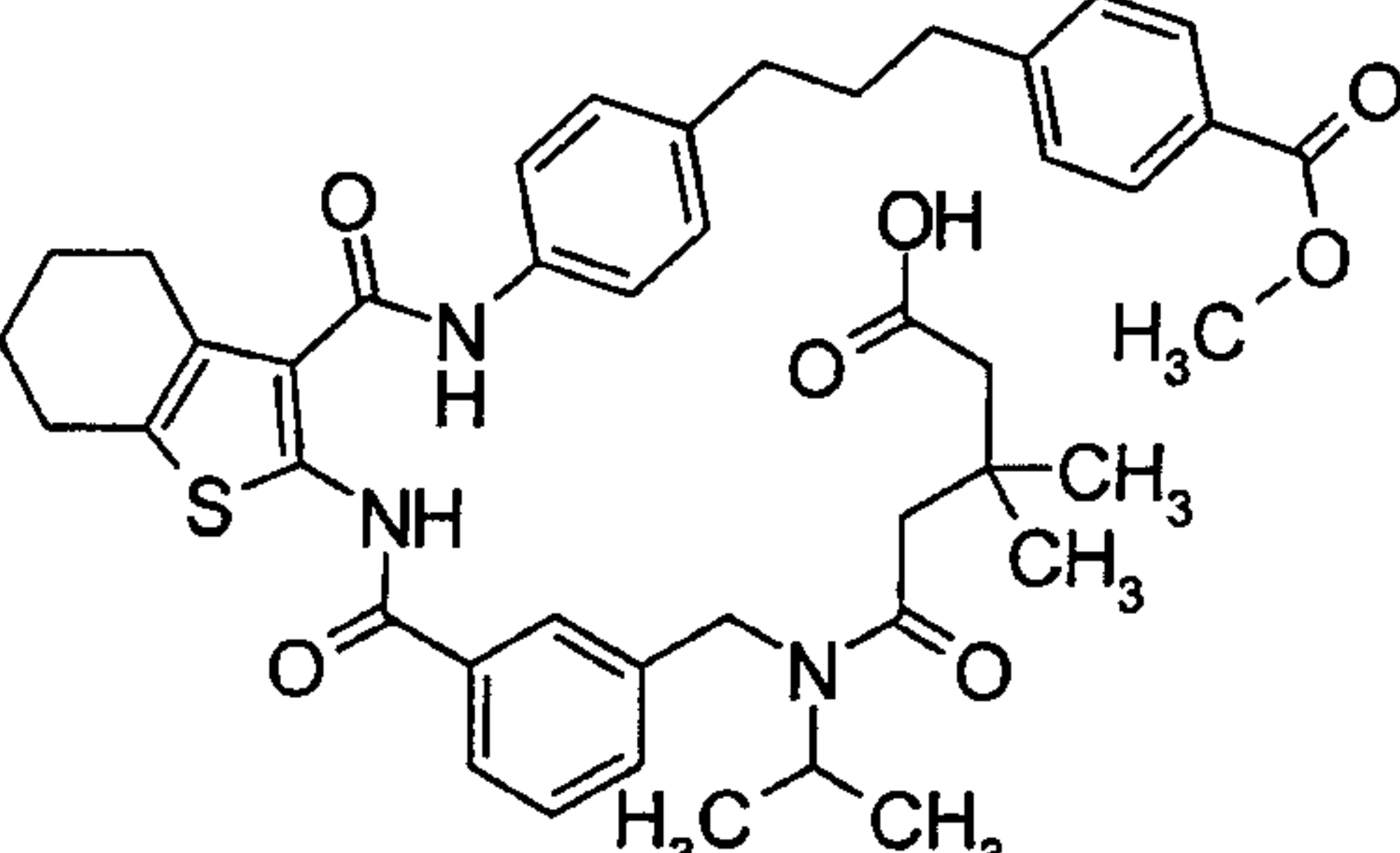
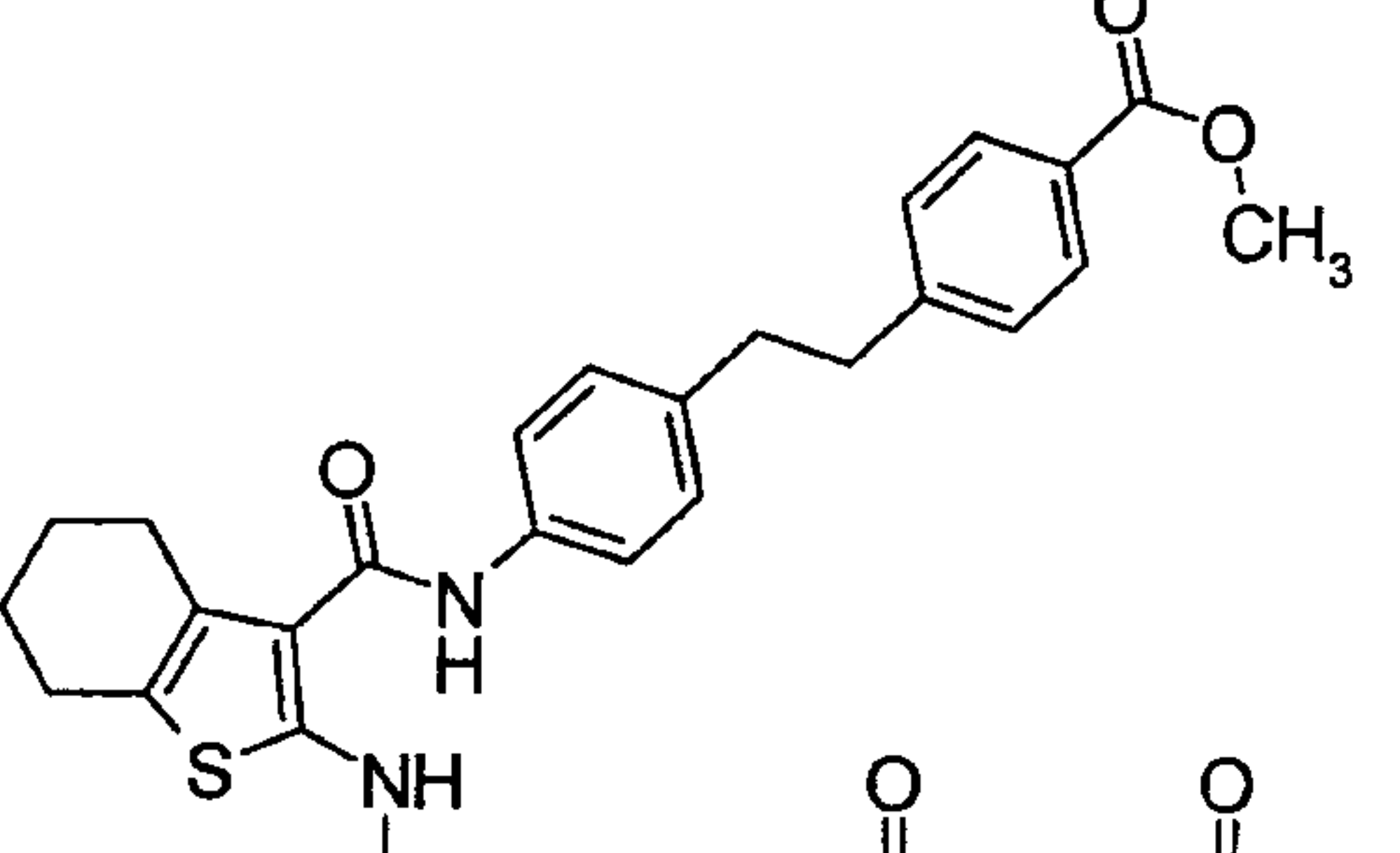
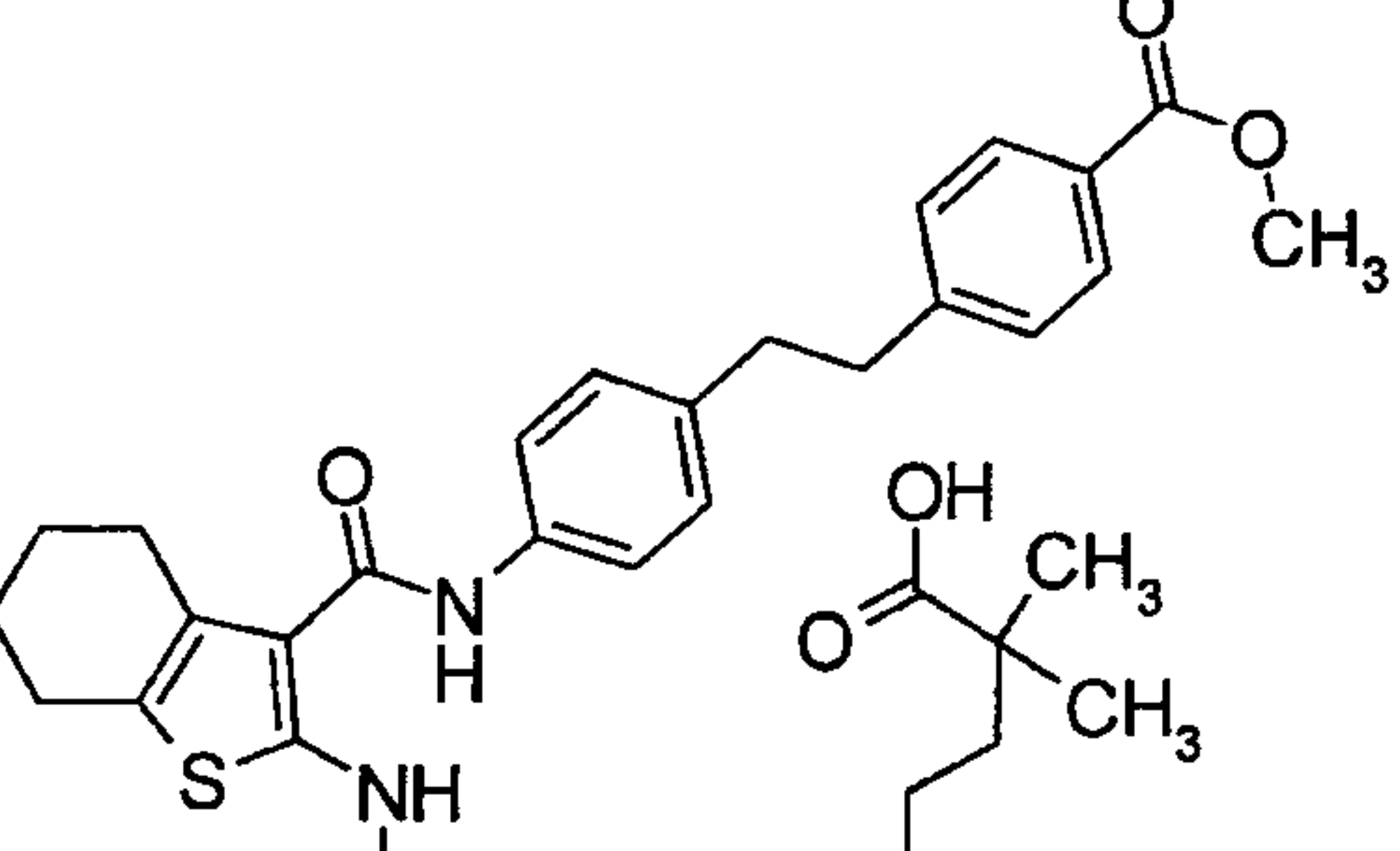
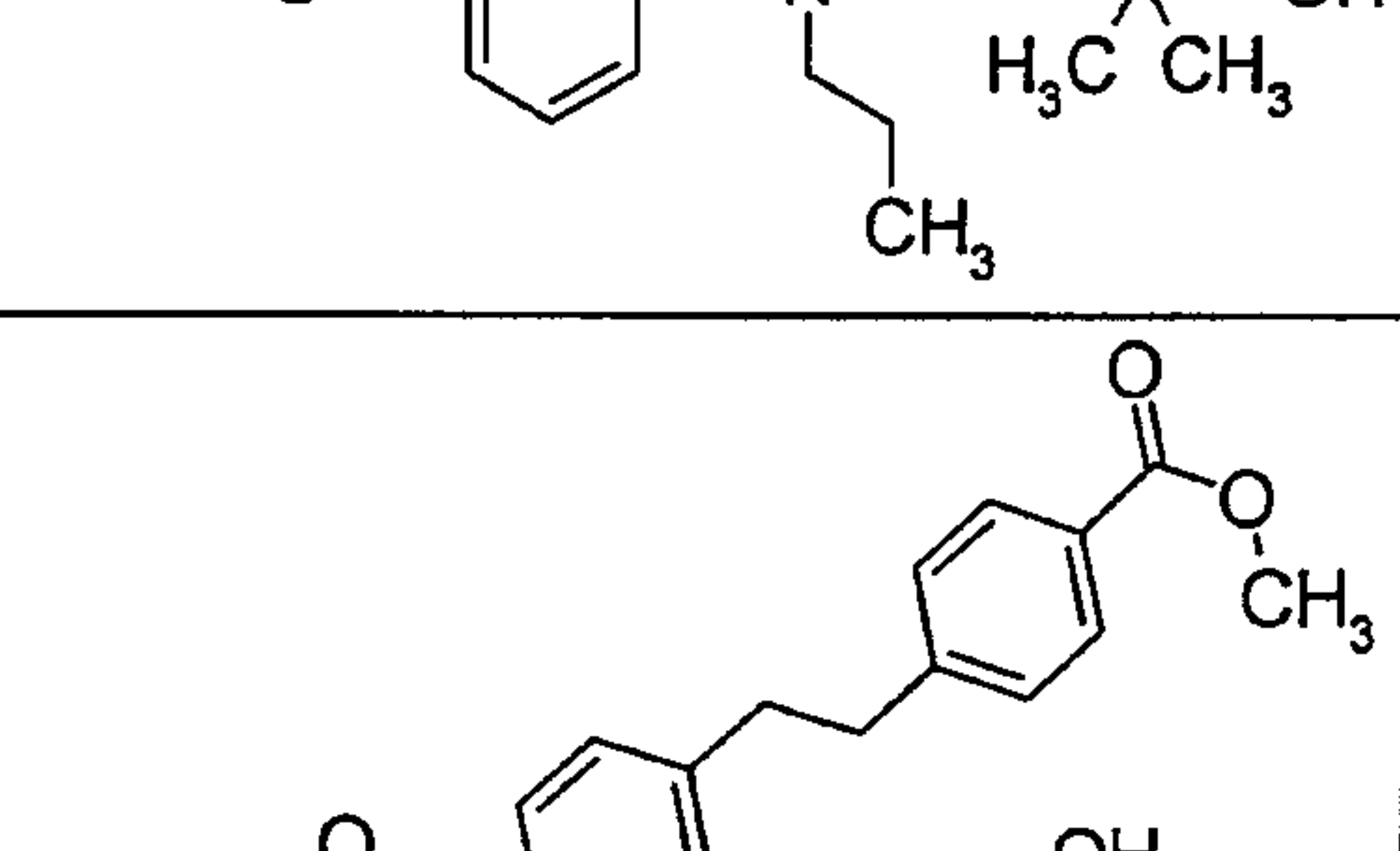
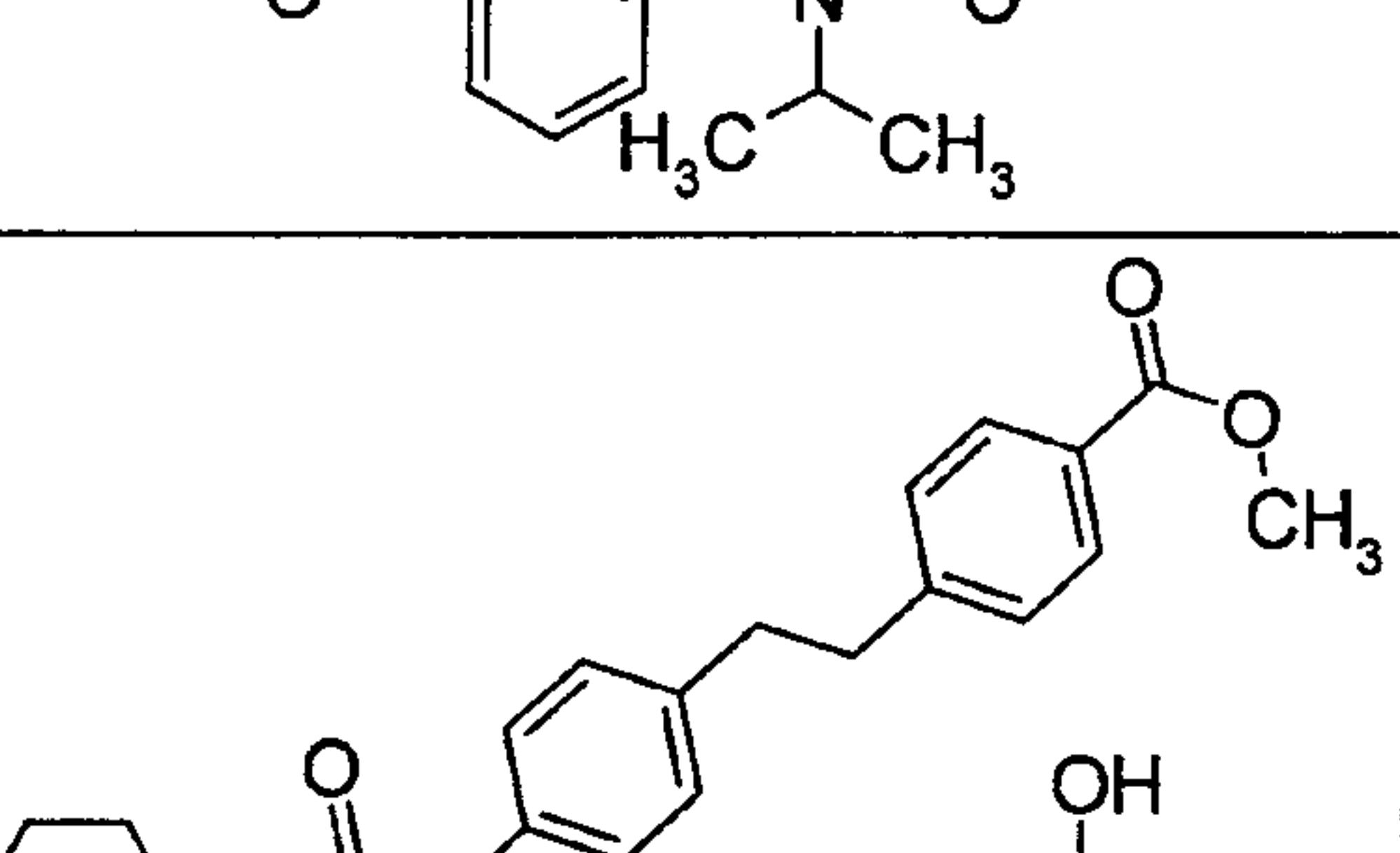
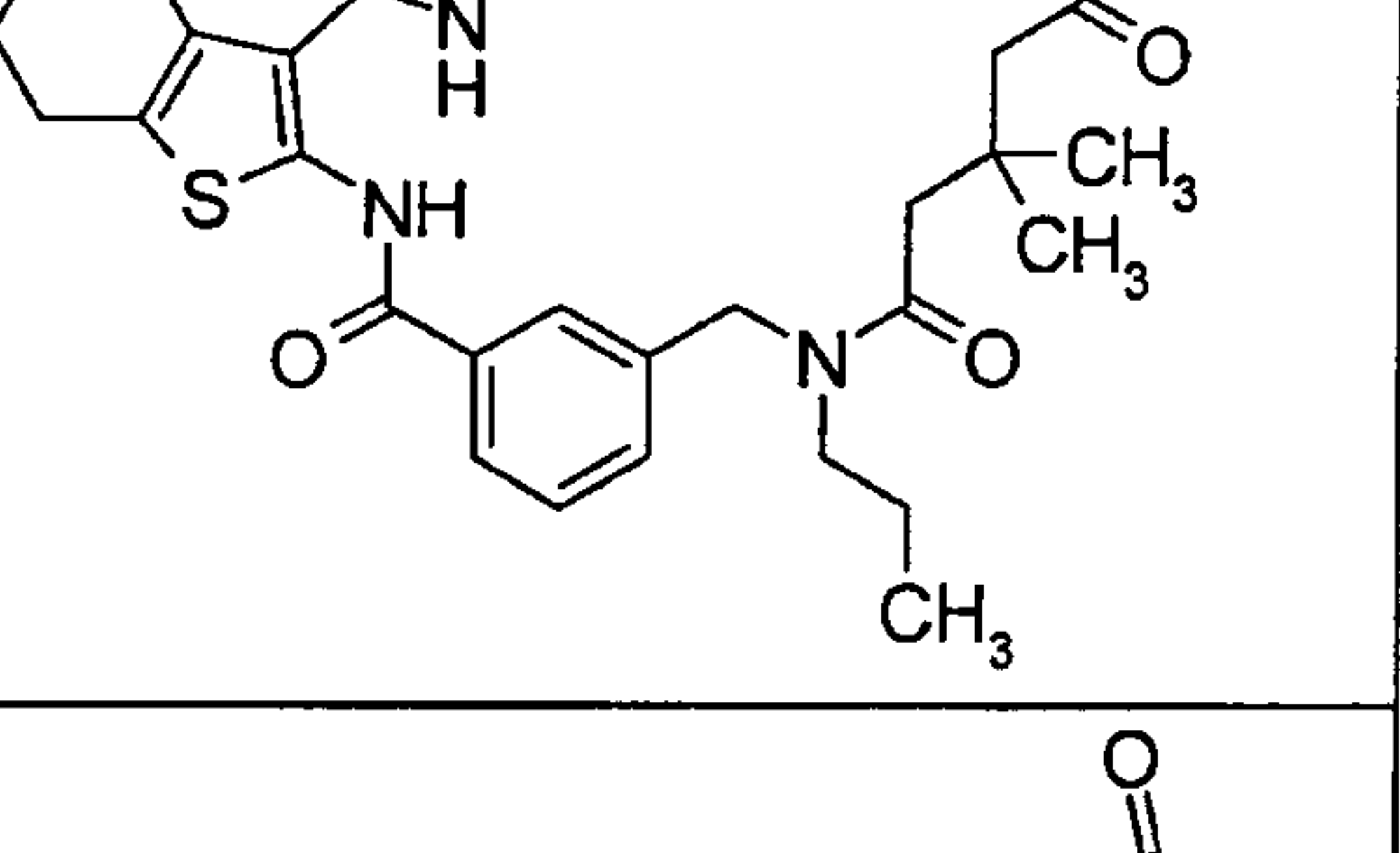
[0177]
[Table 32]

Pr	Str	Pr	Str
188		191	
189		192	
190		193	

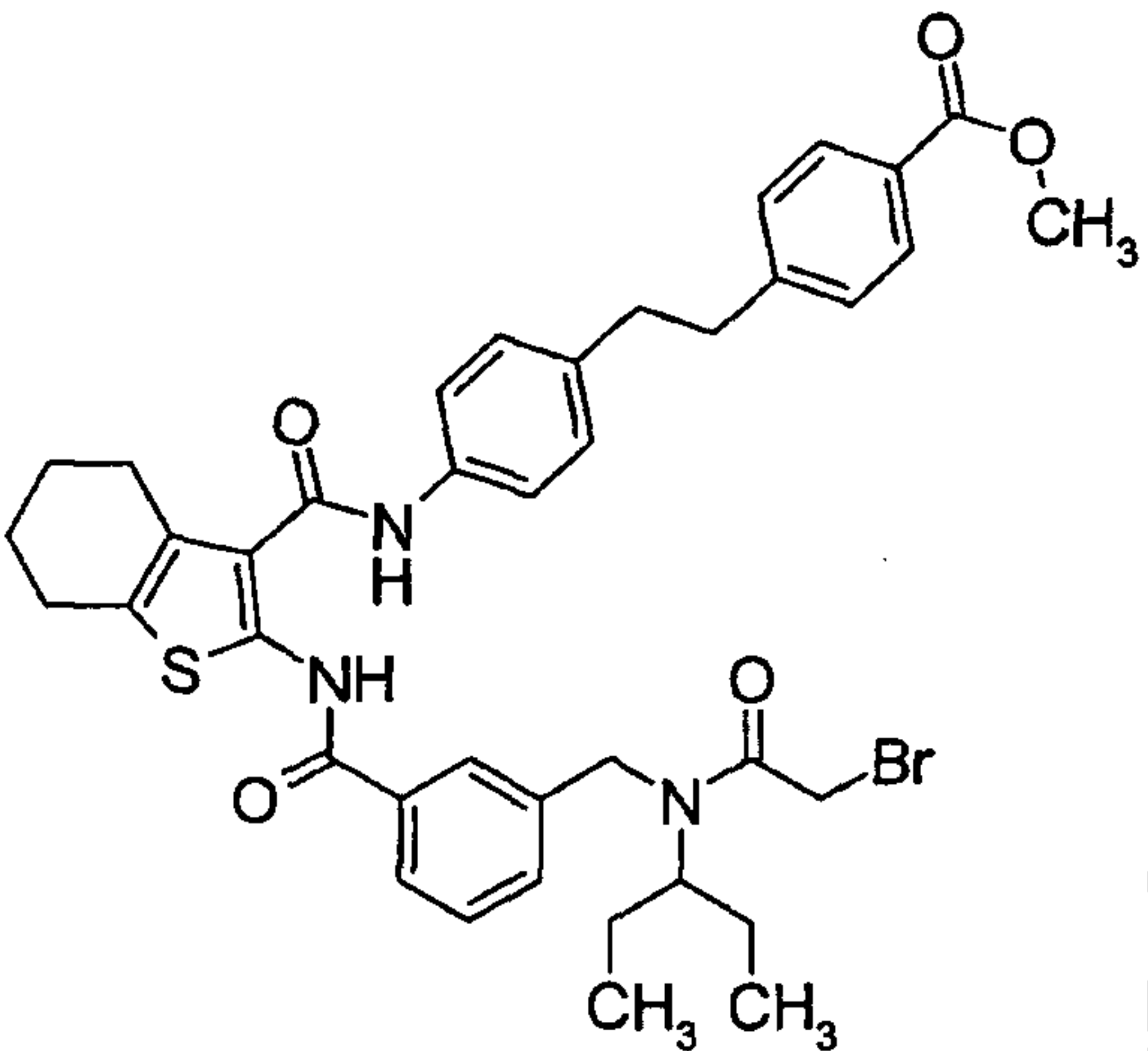
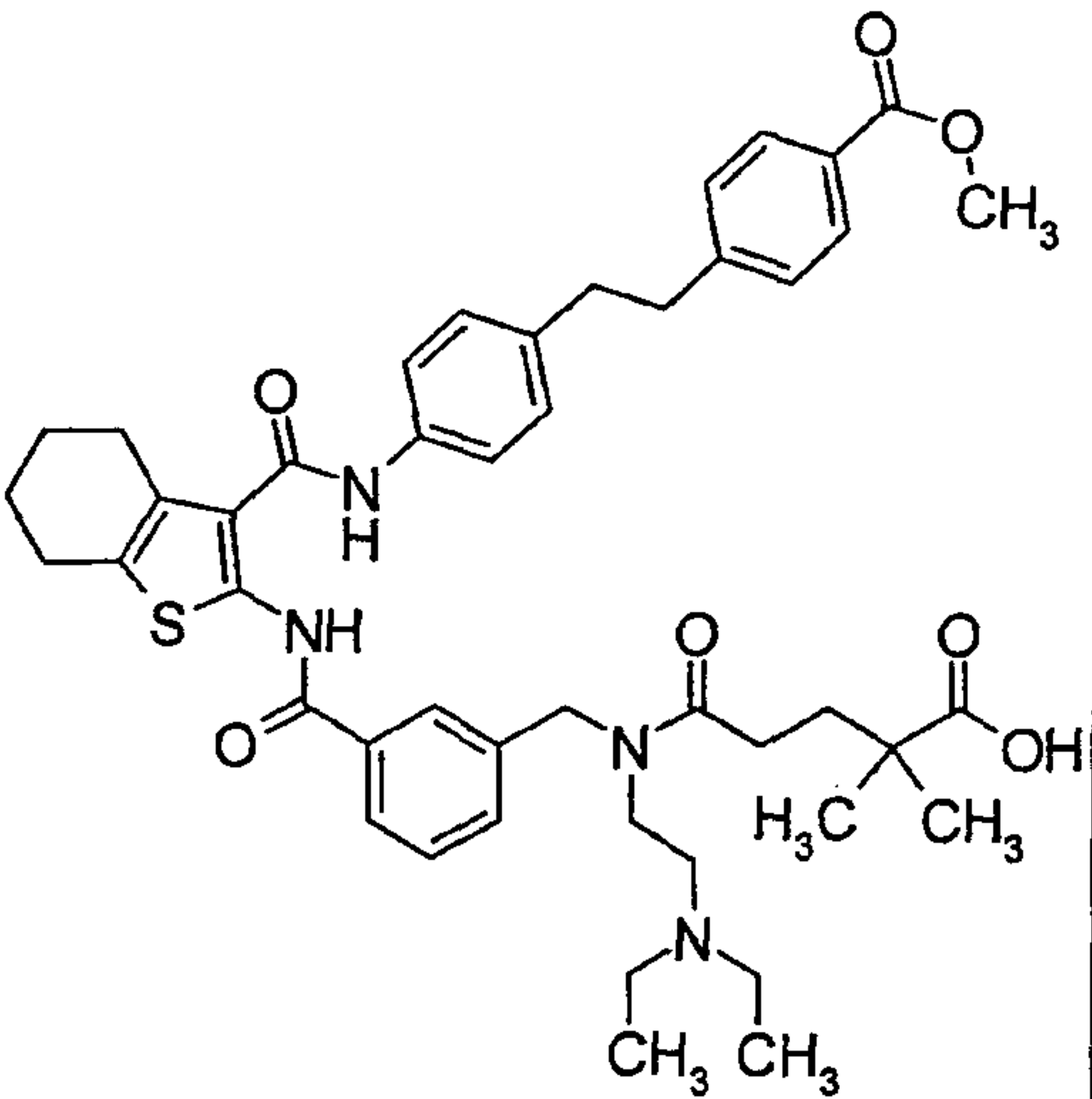
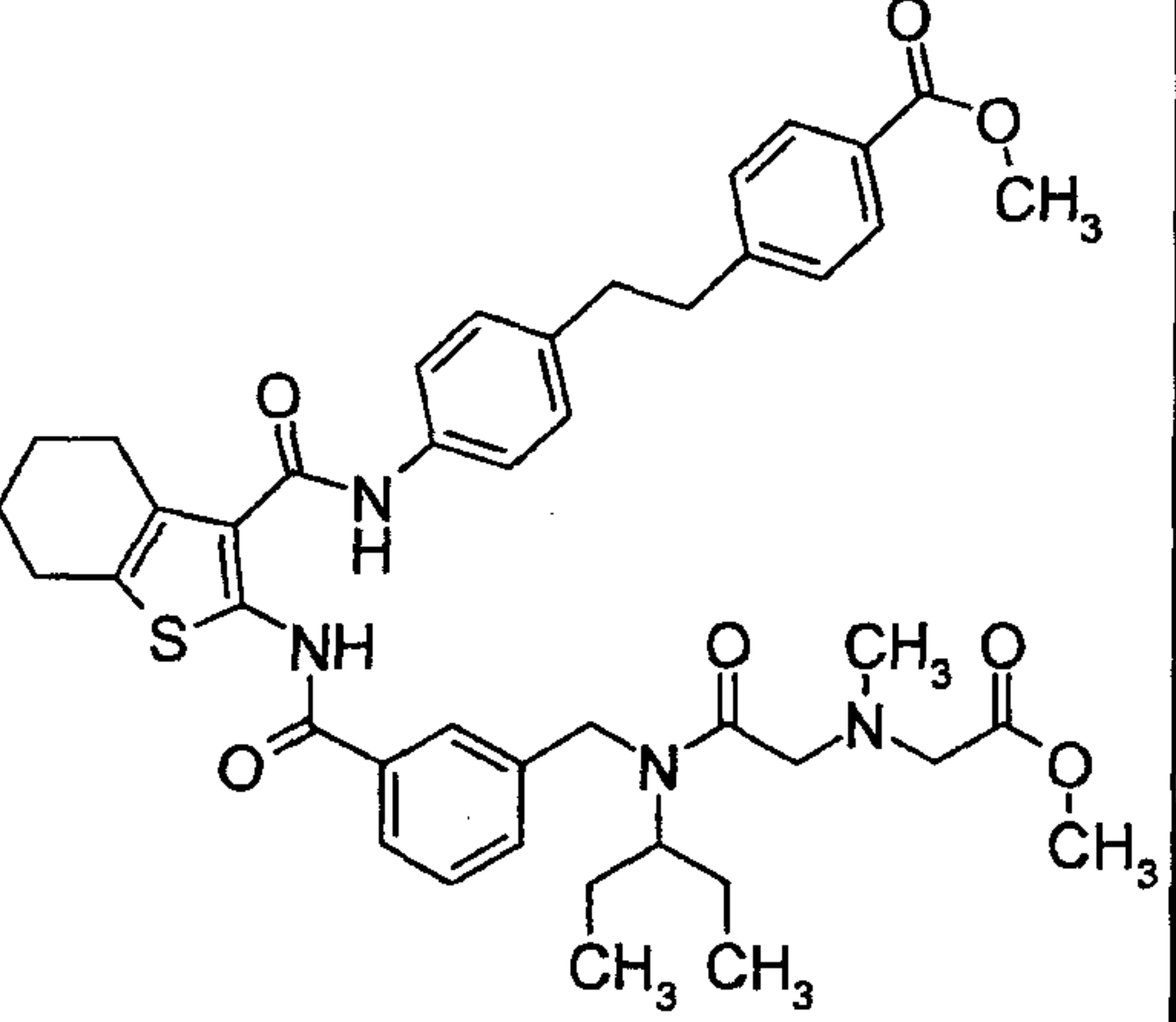
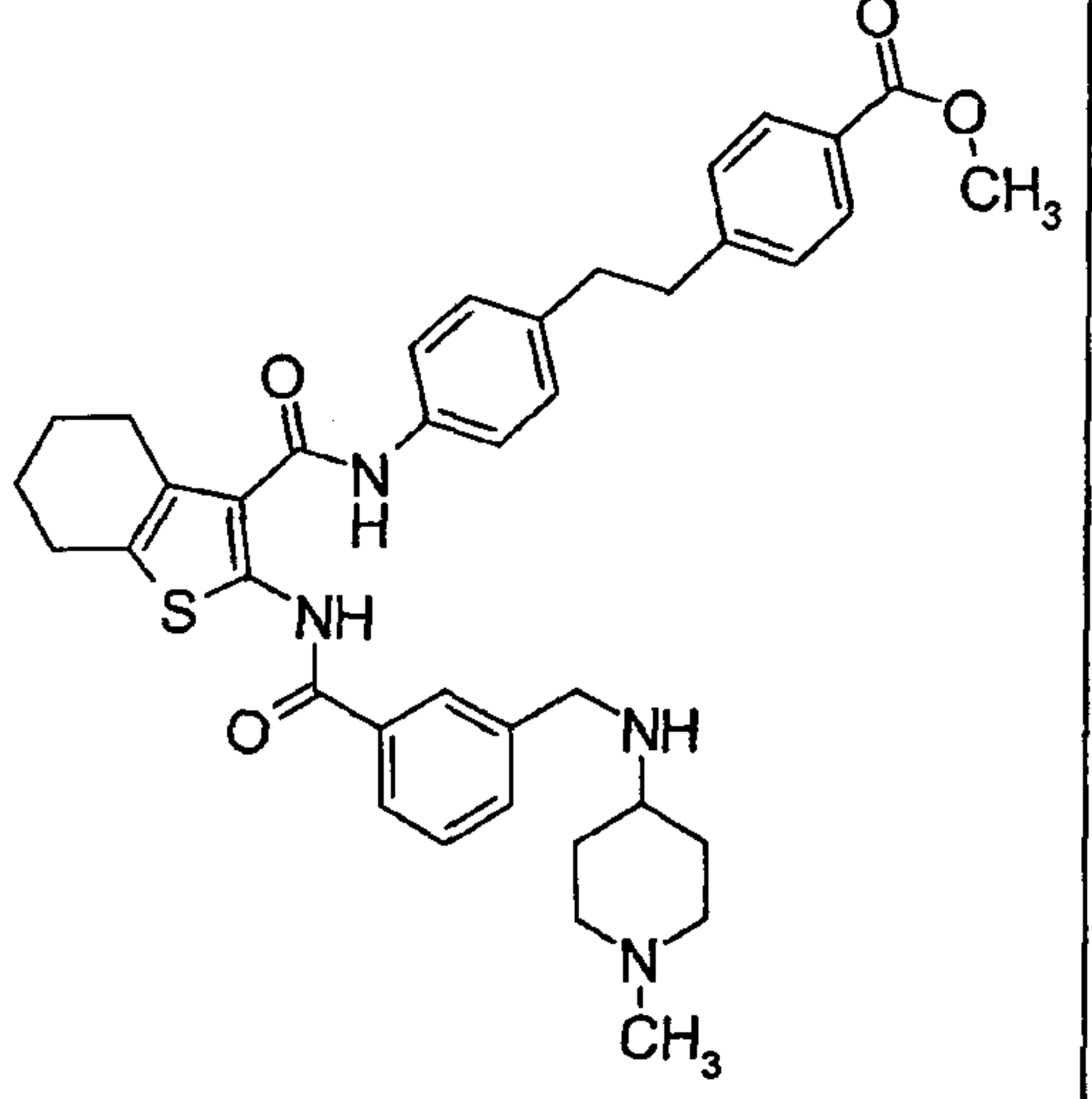
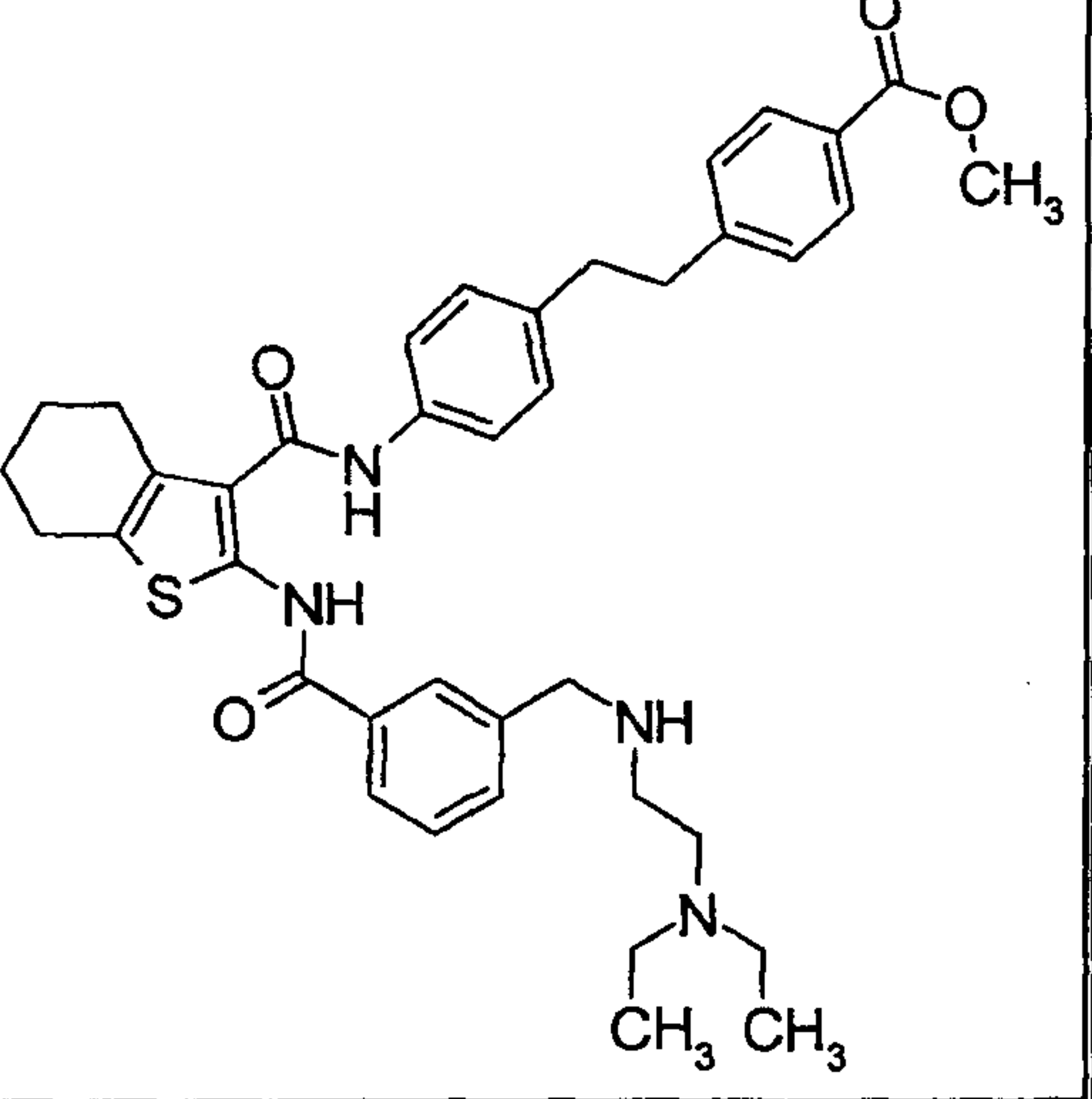
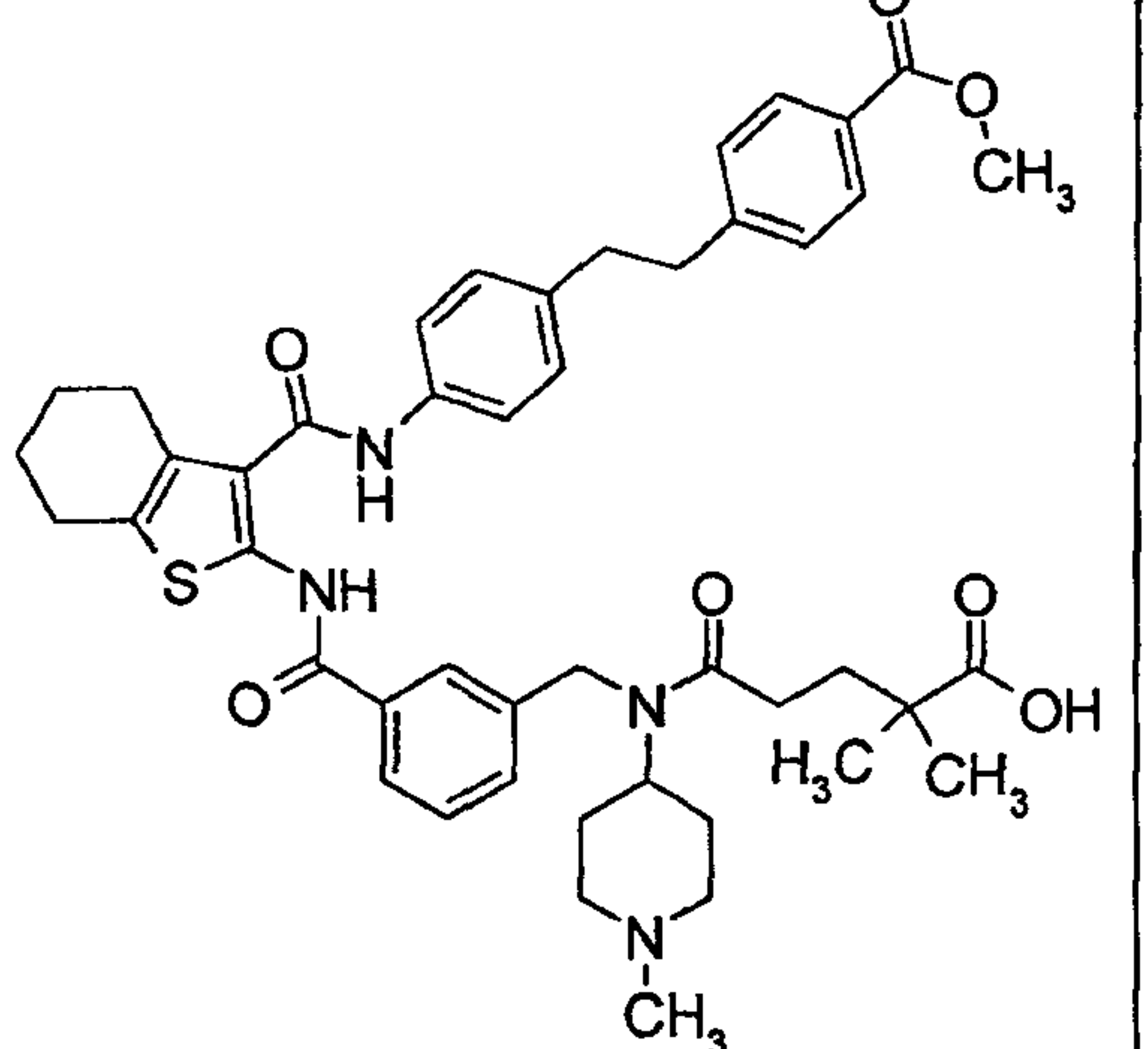
[0178]
[Table 33]

Pr	Str	Pr	Str
194		198	
195		199	
196		200	
197			

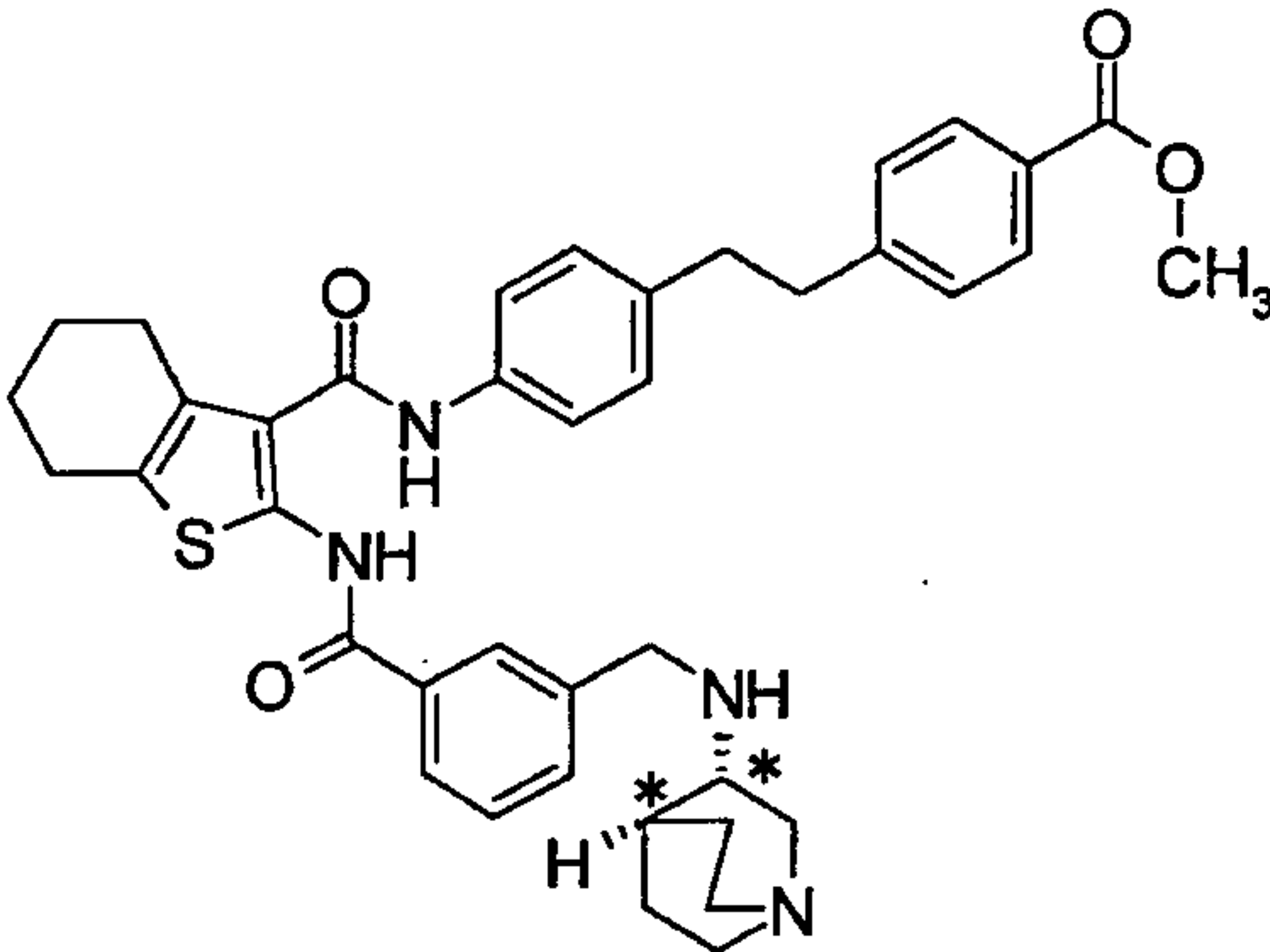
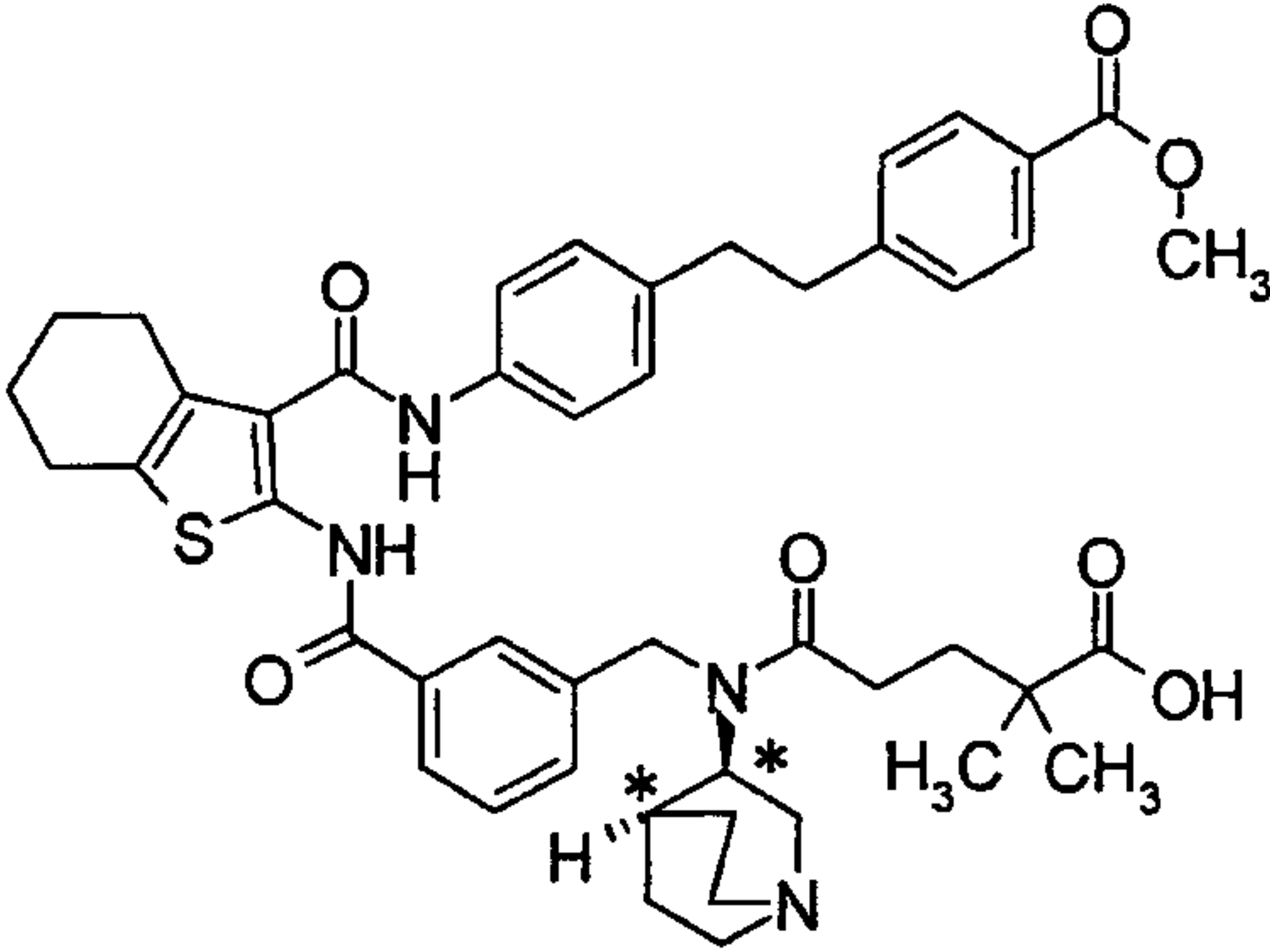
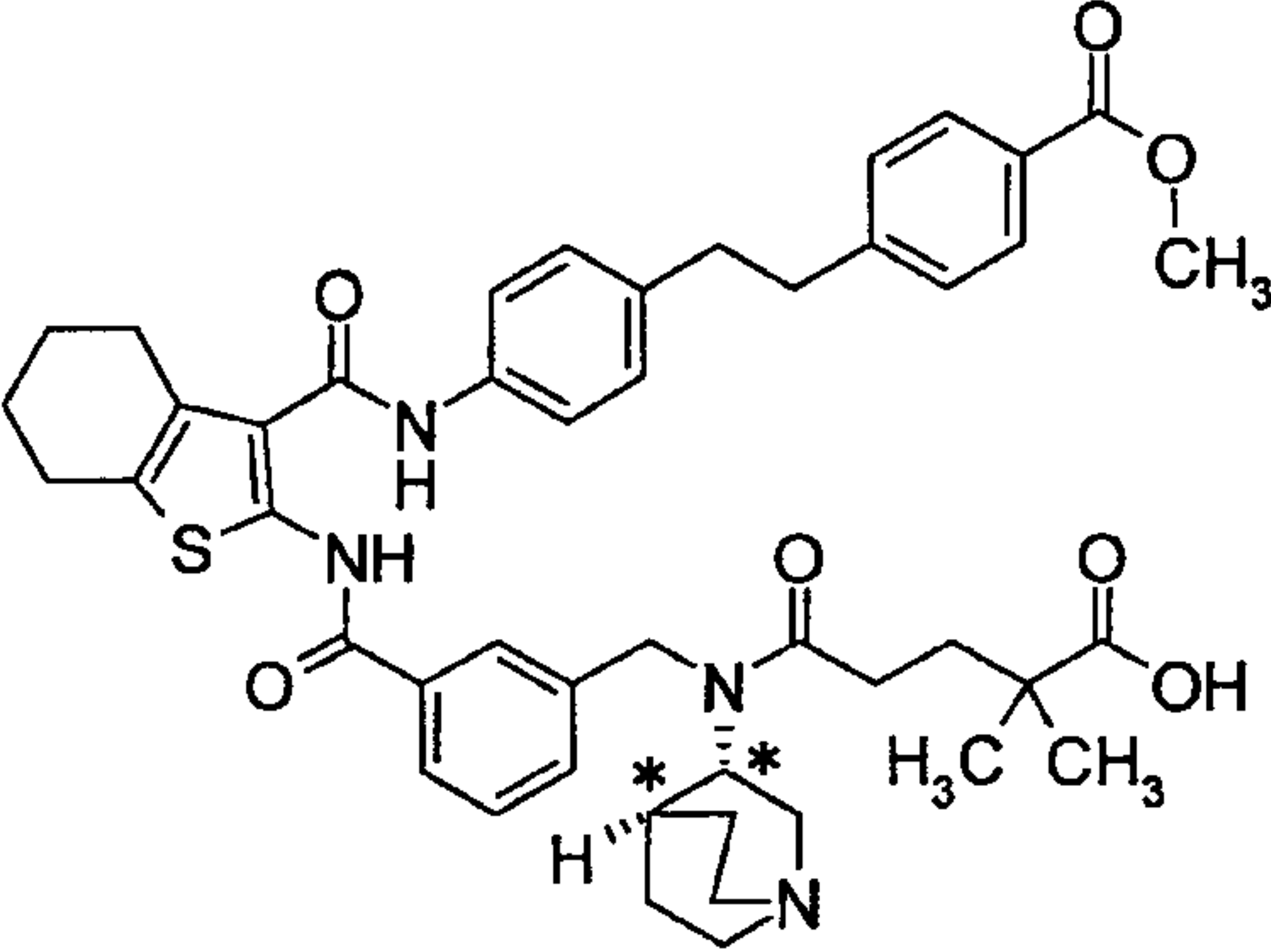
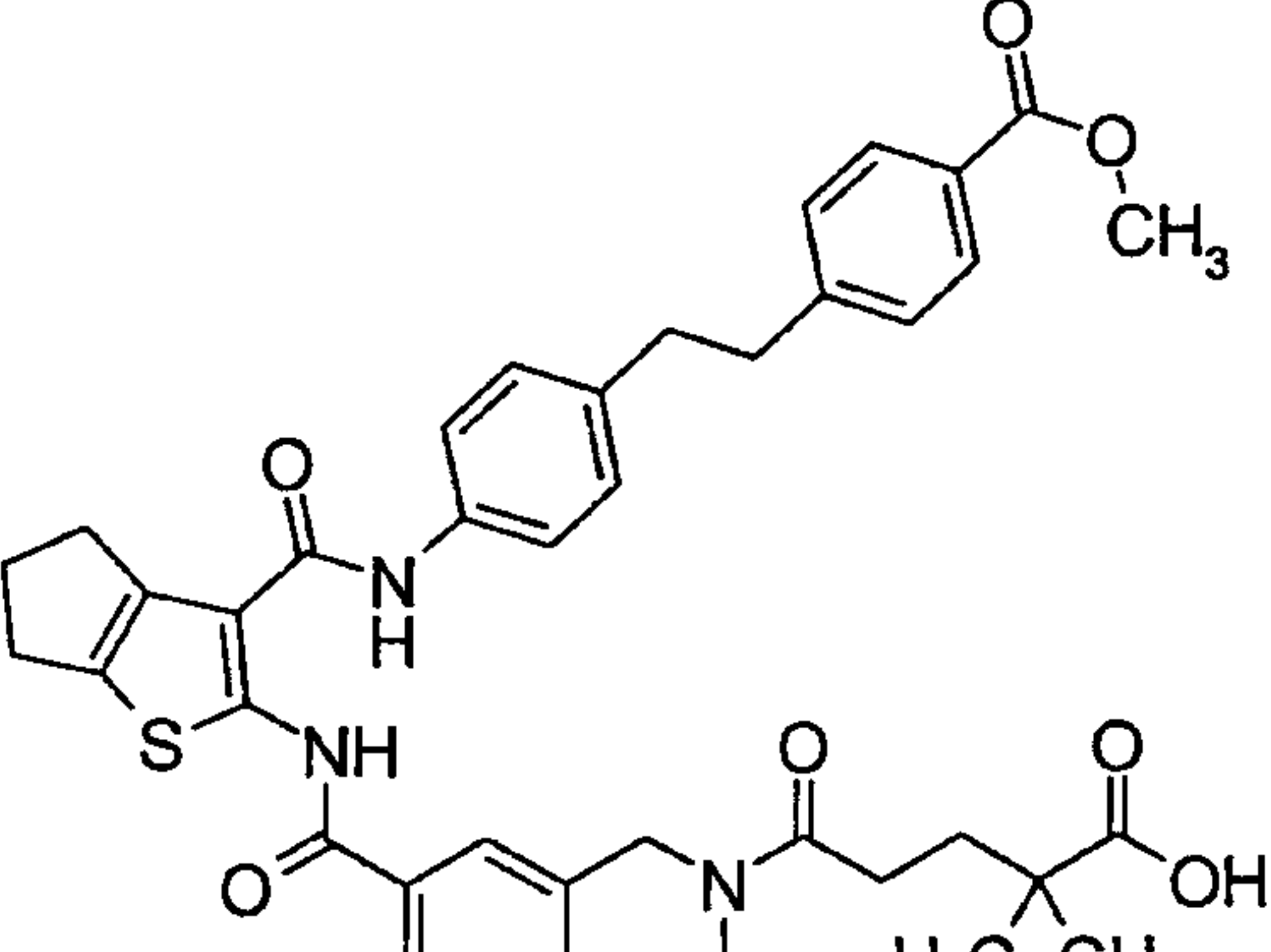
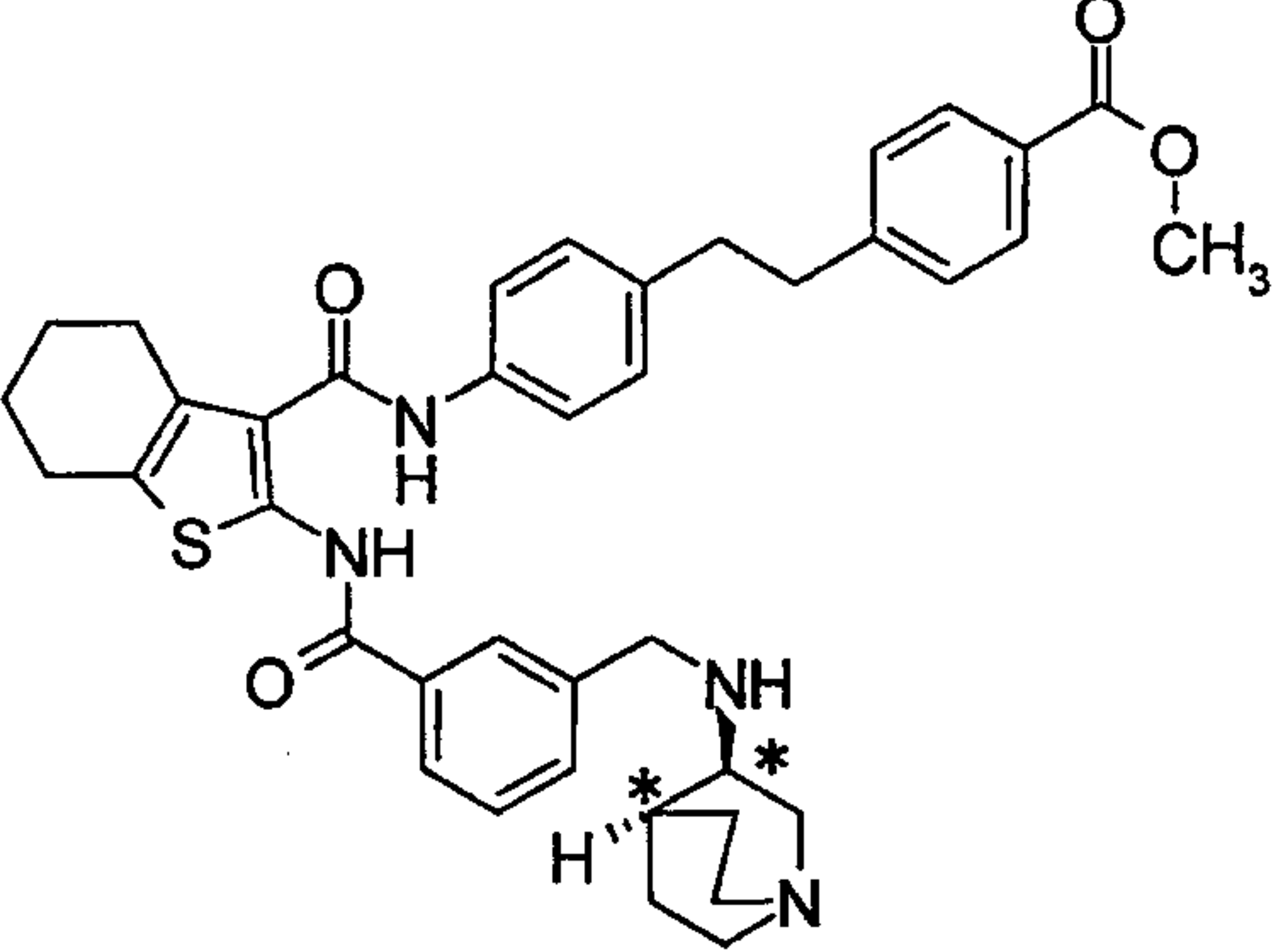
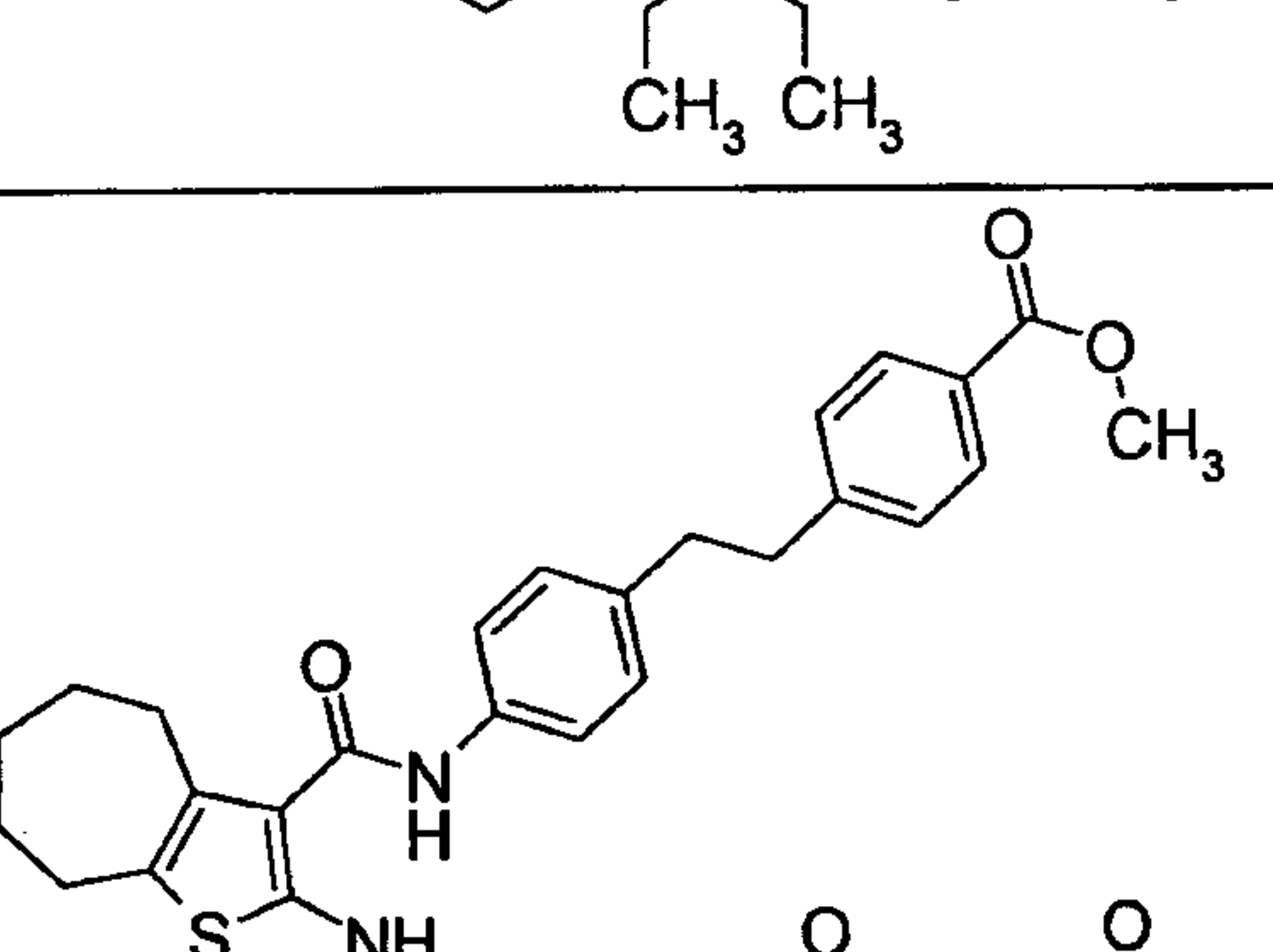
[0179]
[Table 34]

Pr	Str	Pr	Str
201		204	
202		205	
203		206	

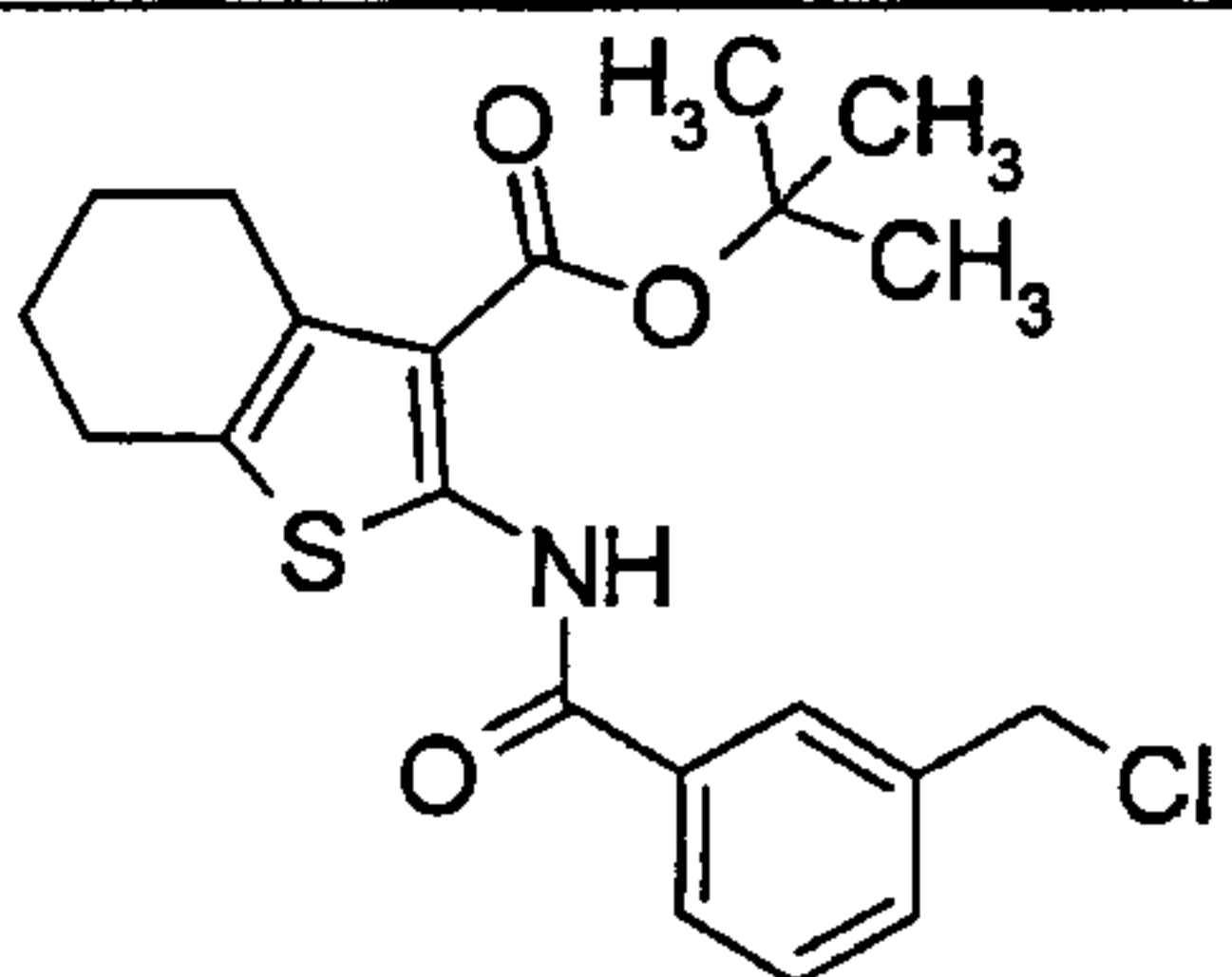
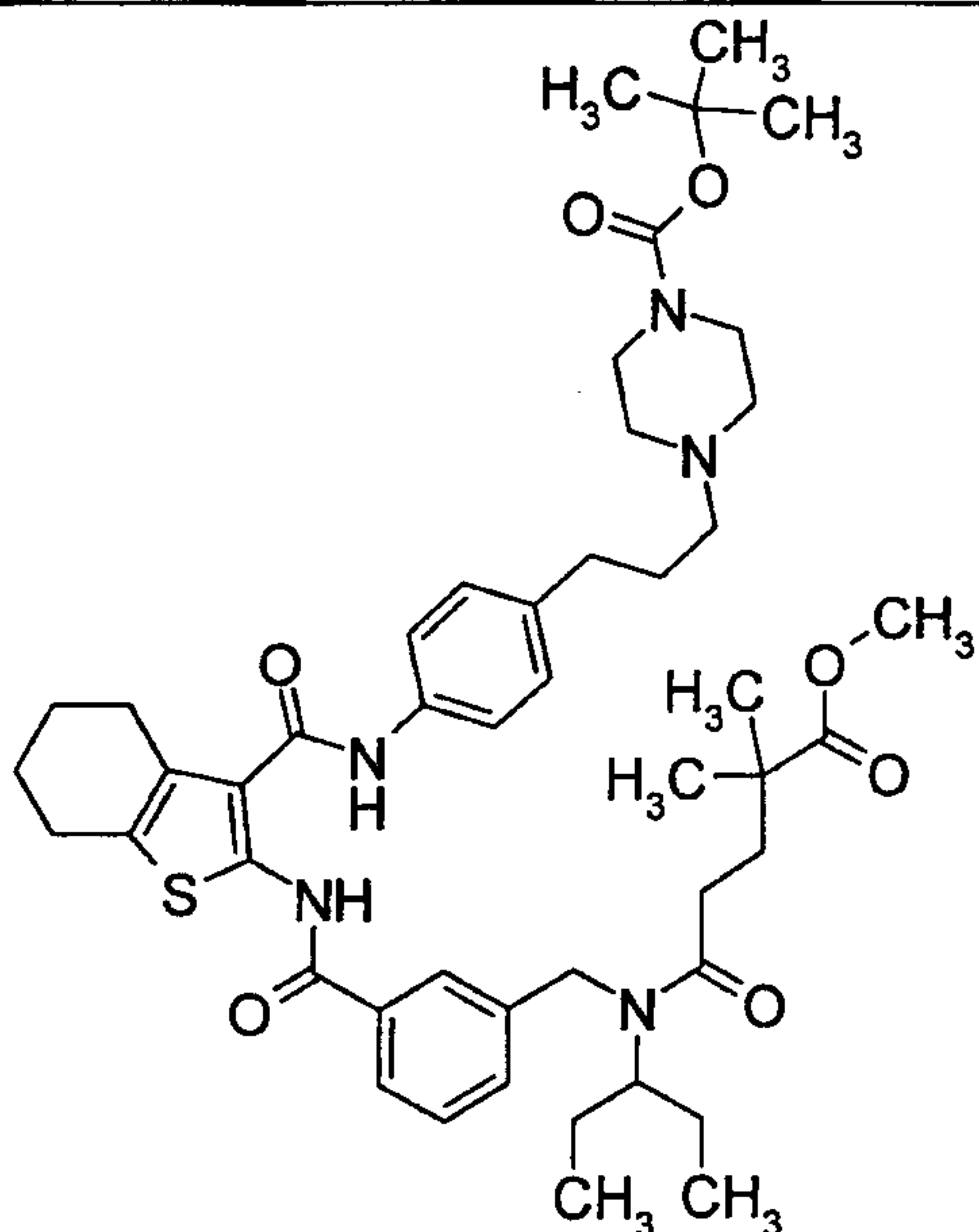
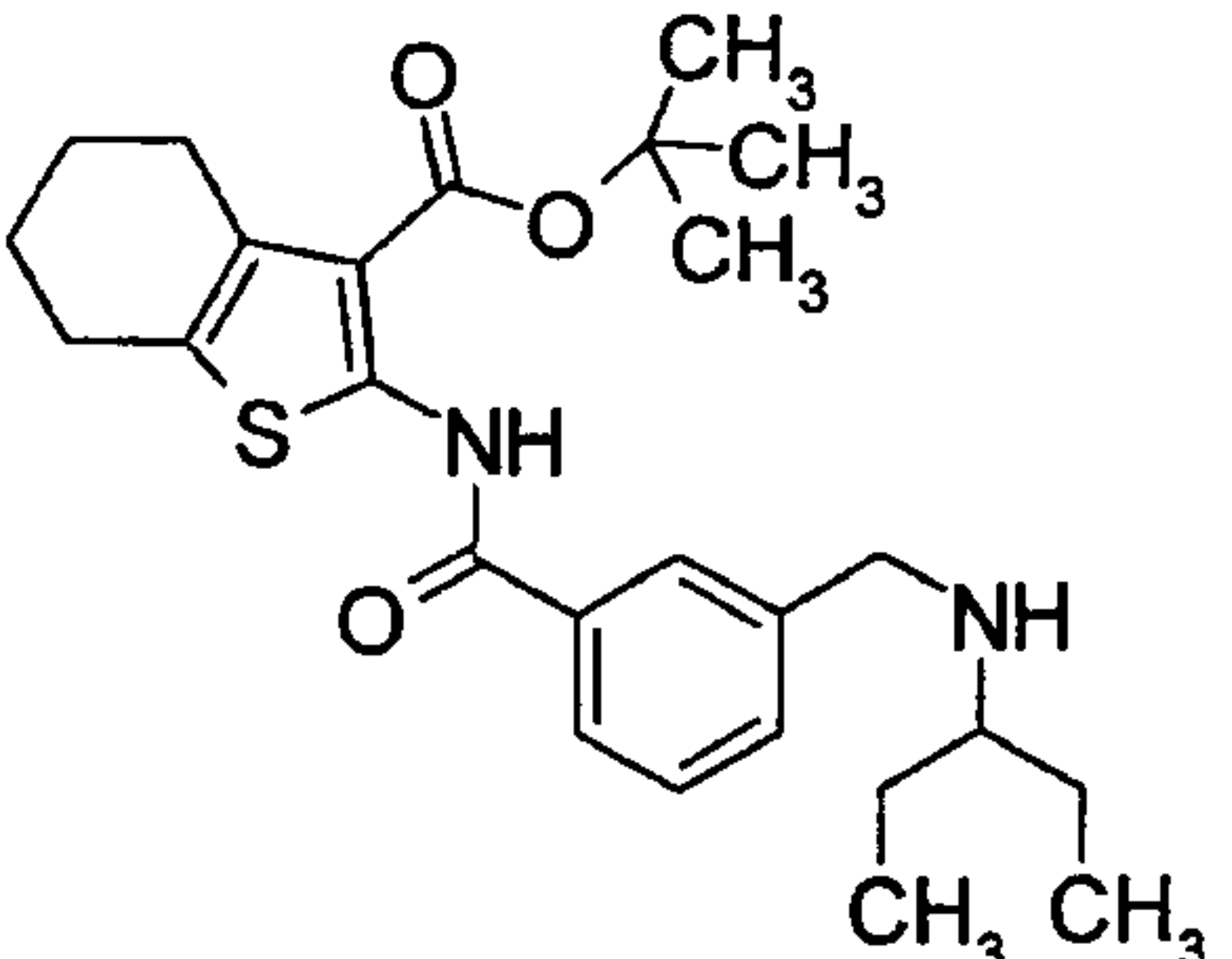
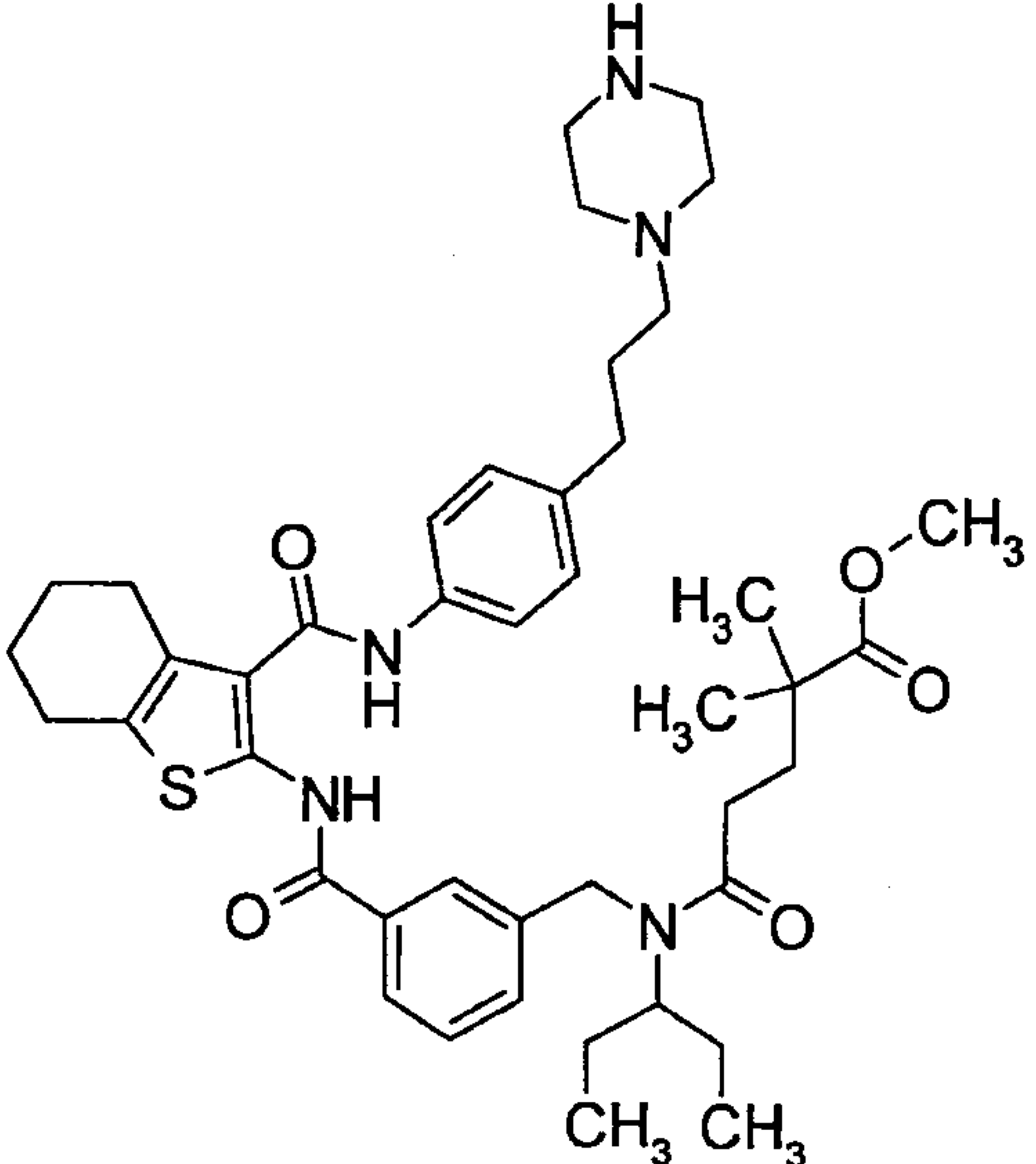
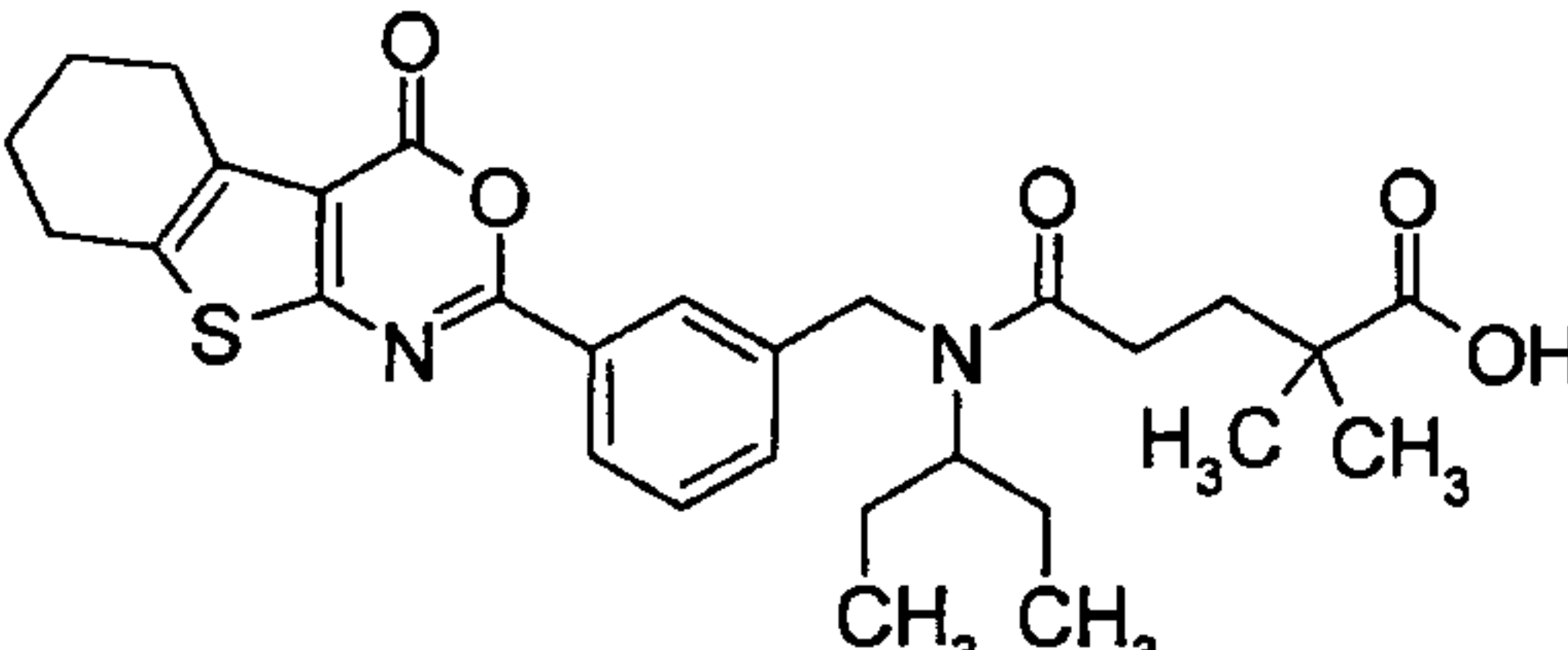
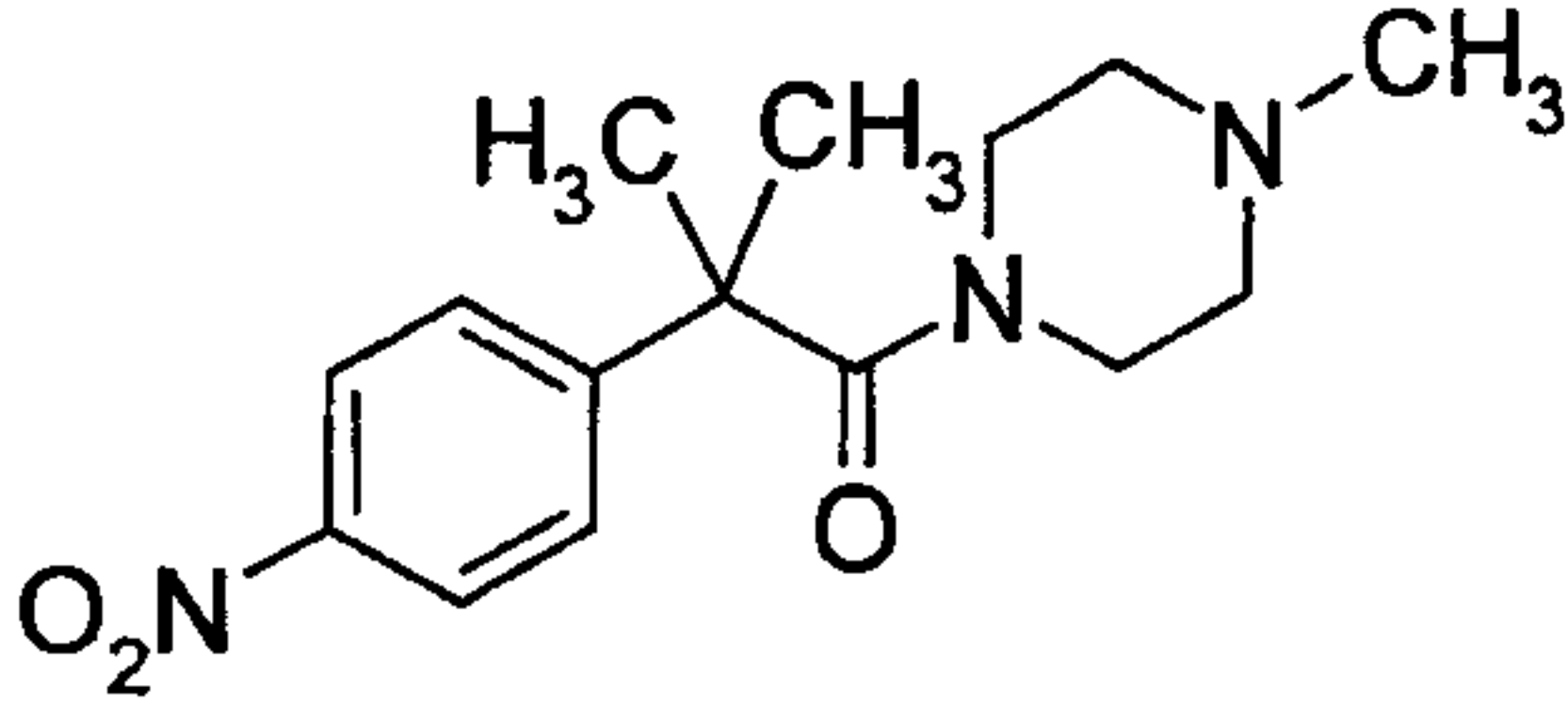
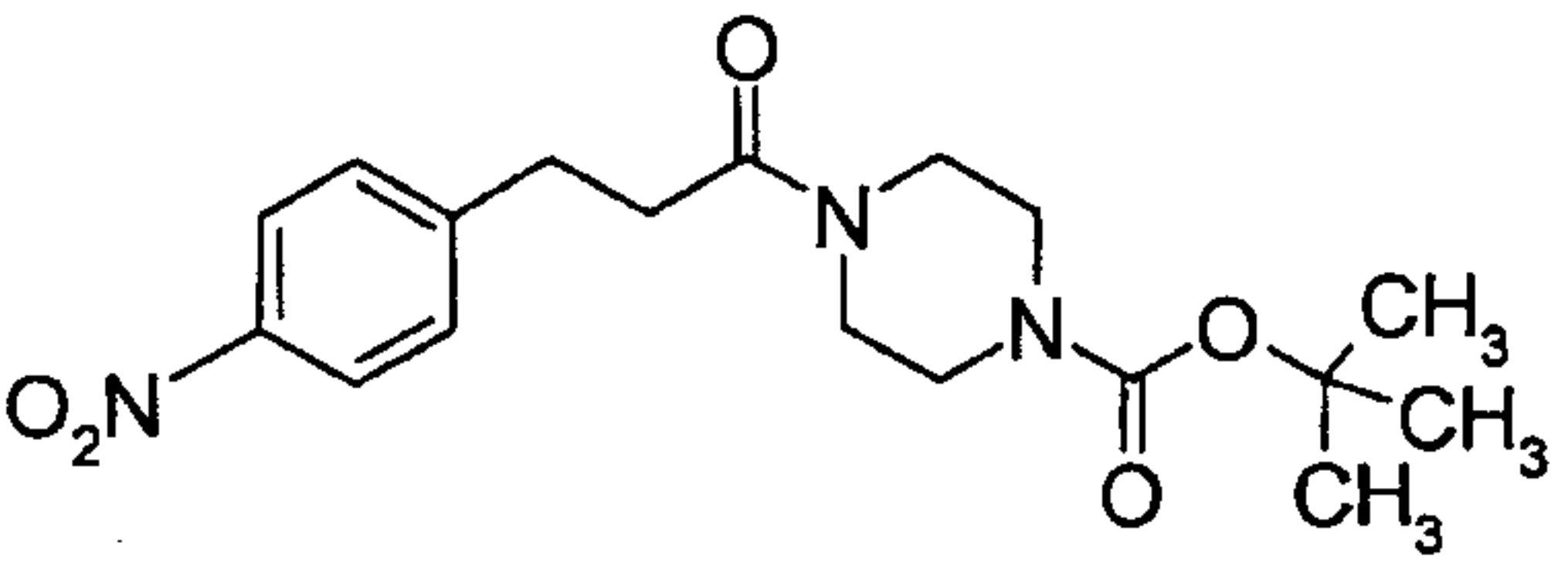
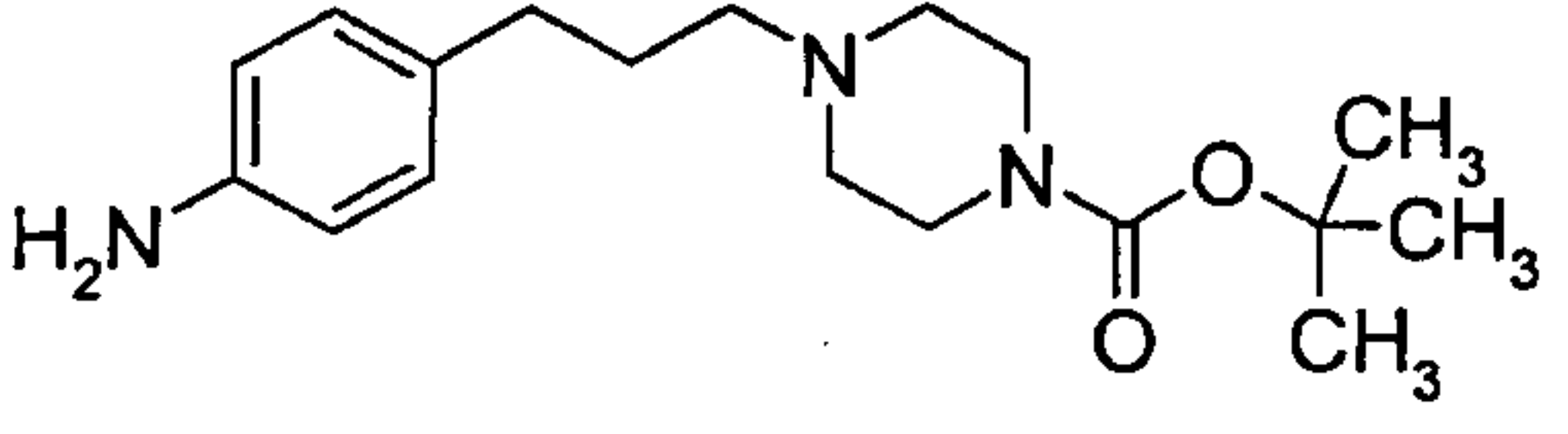
[0180]
[Table 35]

Pr	Str	Pr	Str
207		210	
208		211	
209		212	

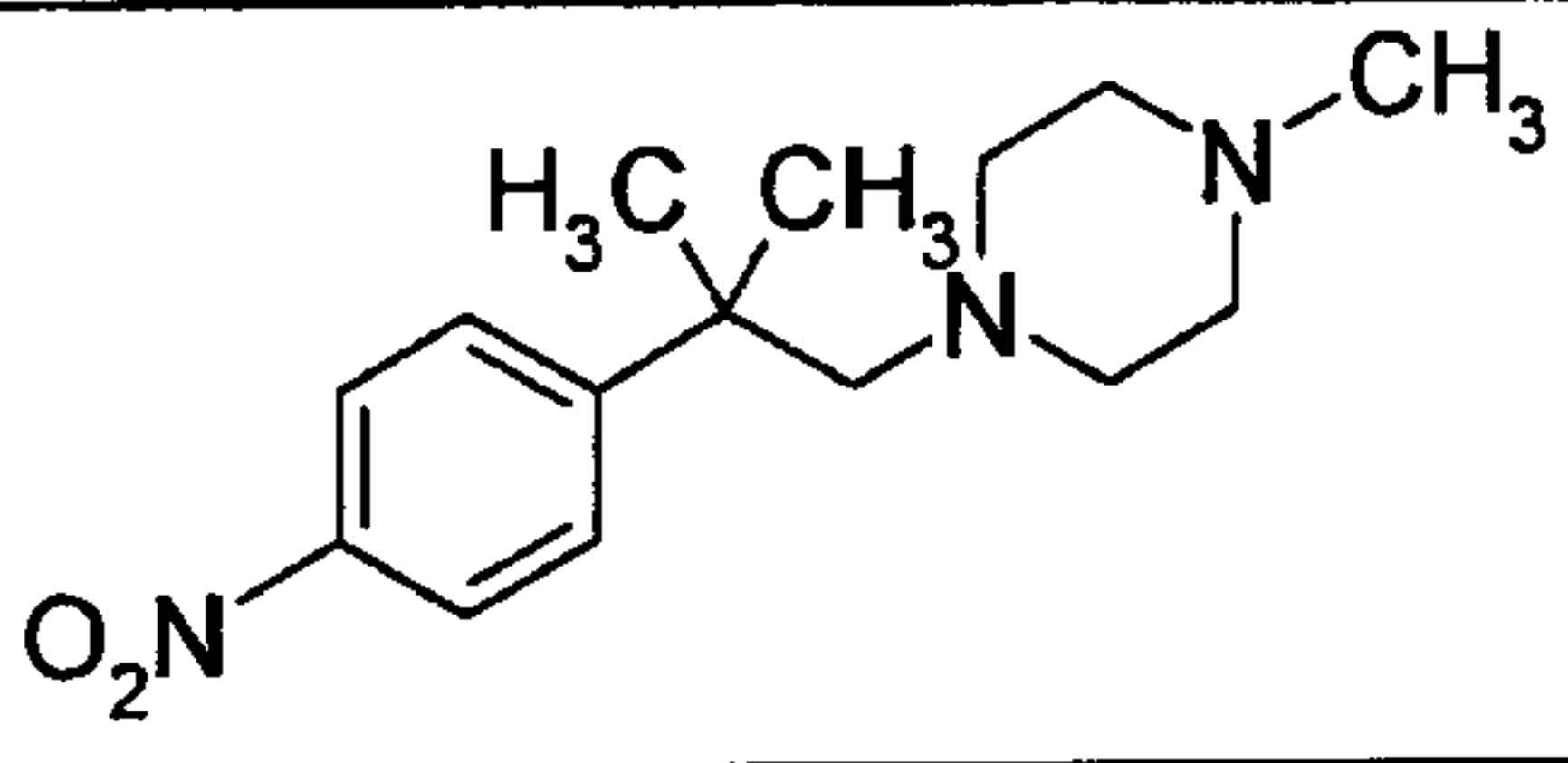
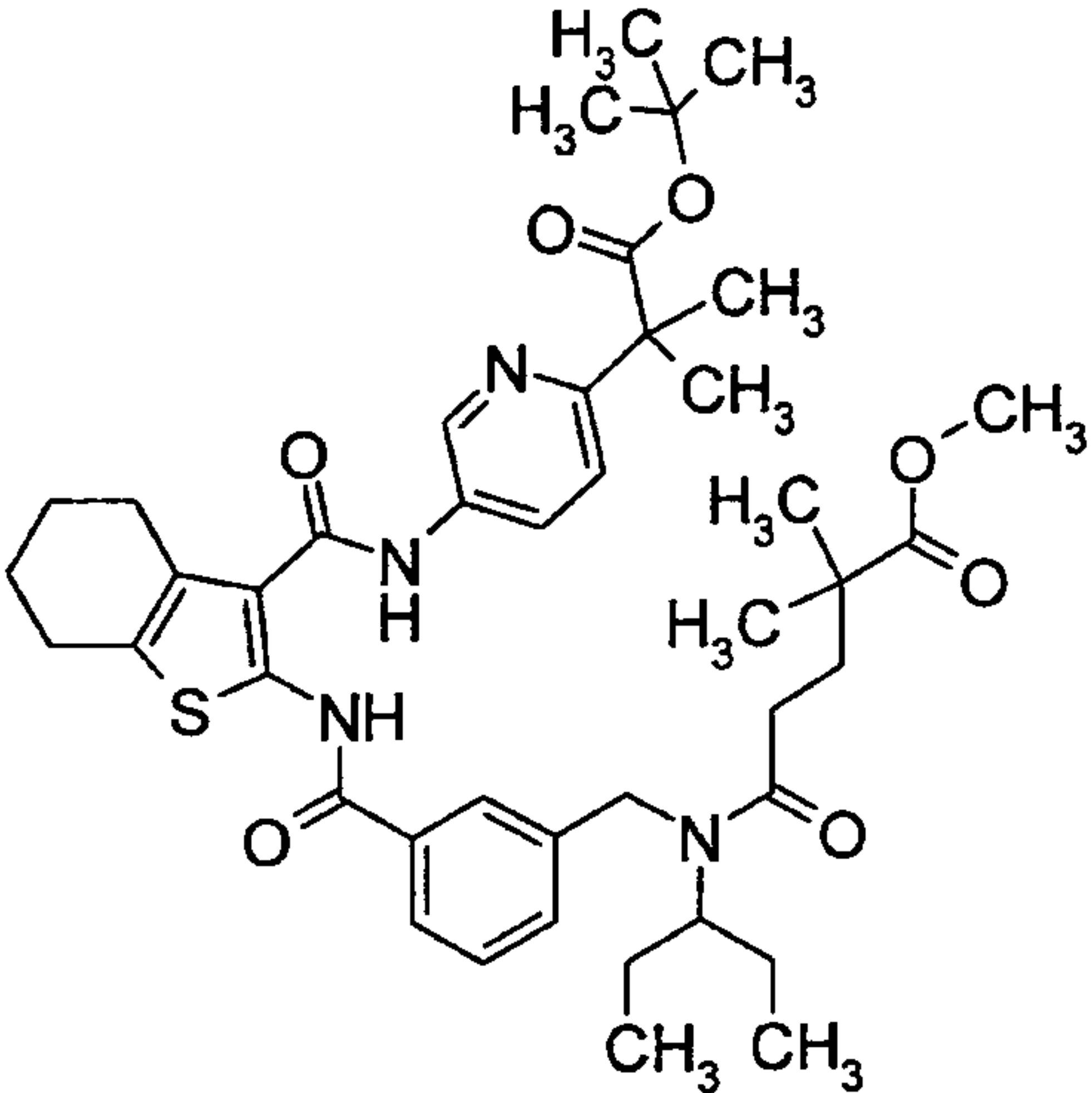
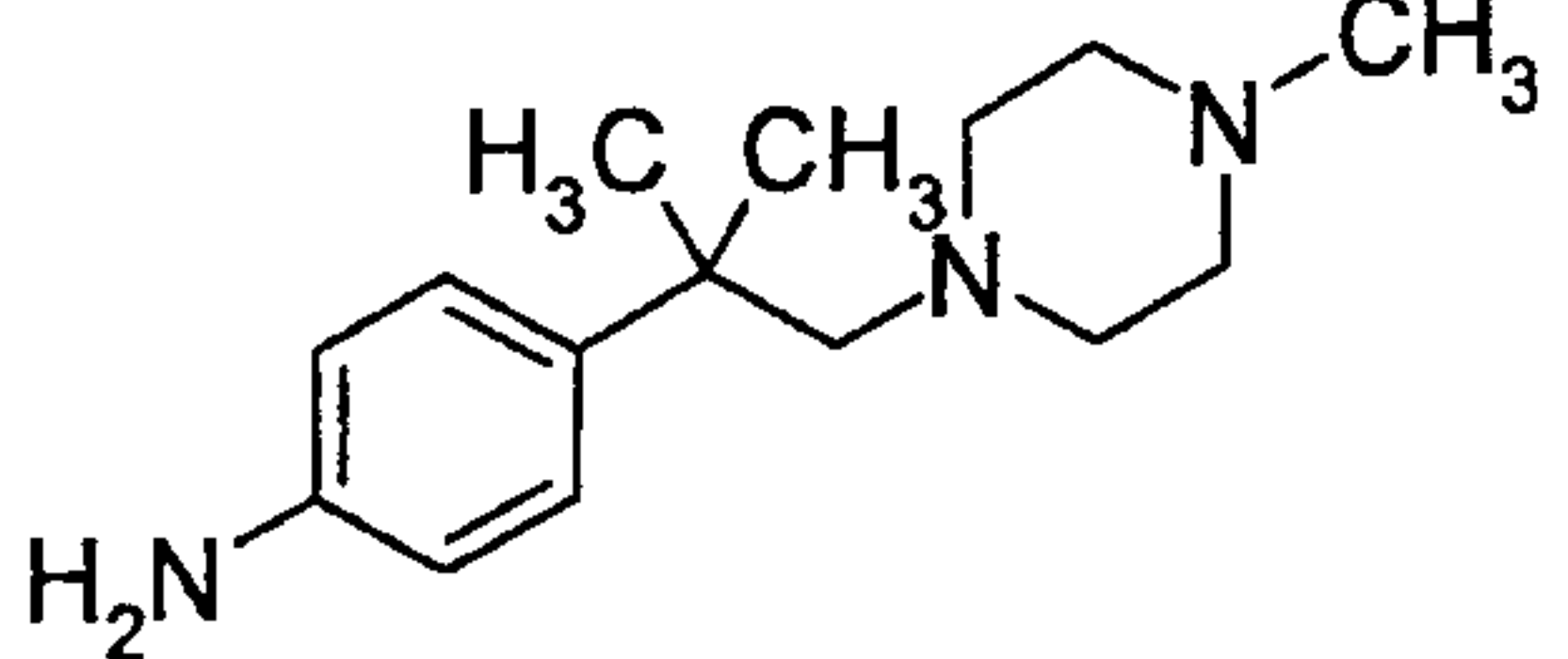
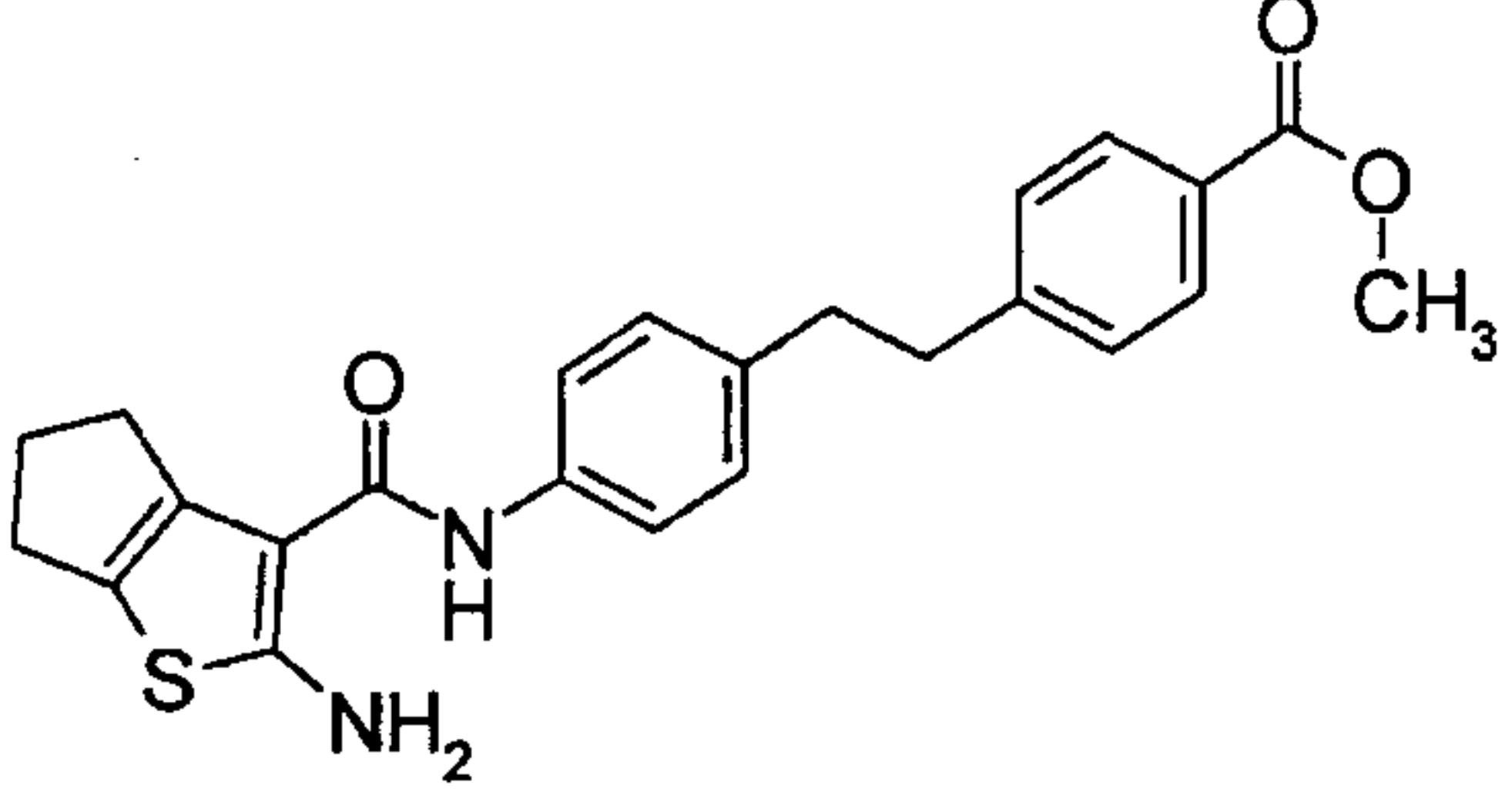
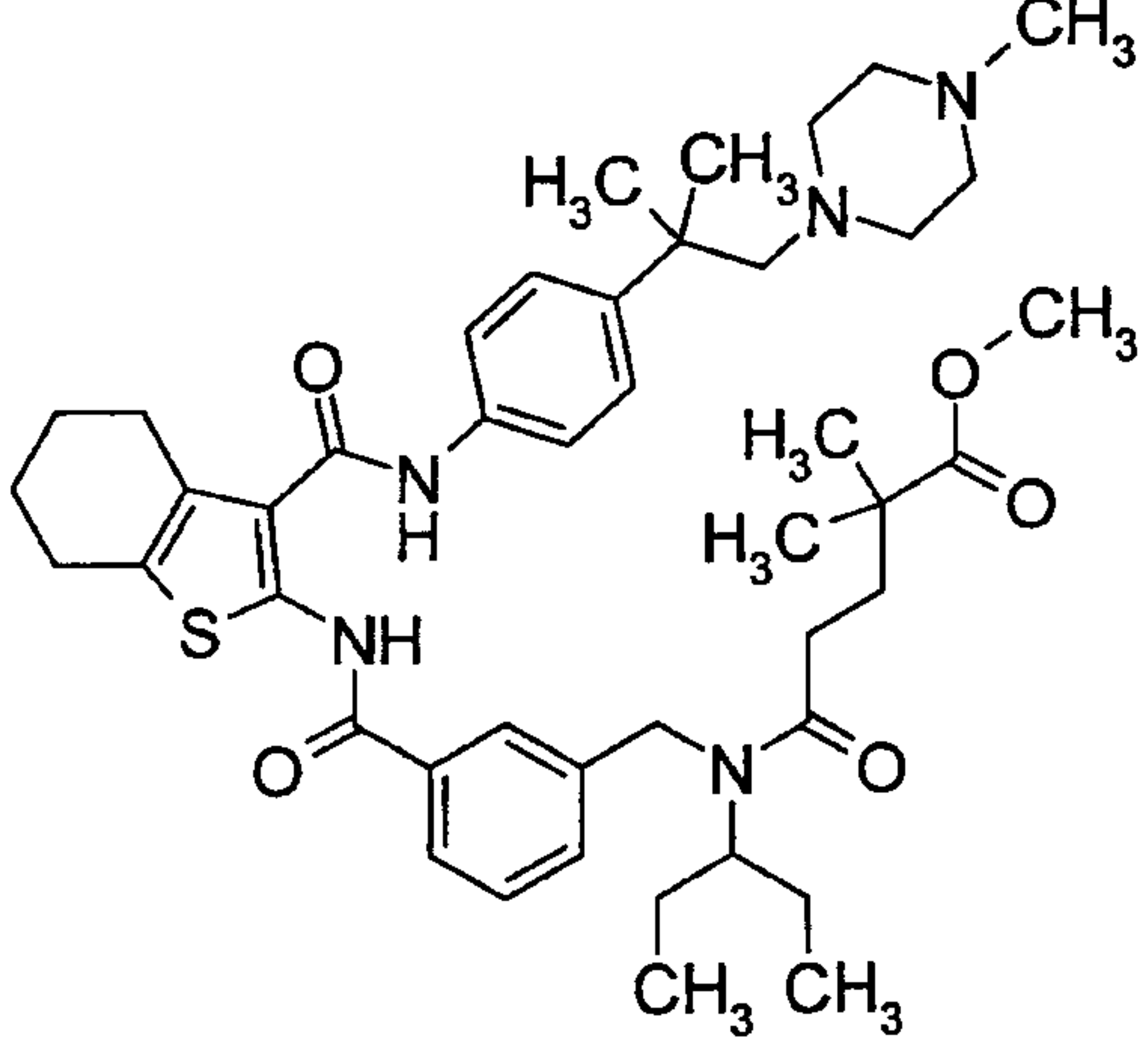
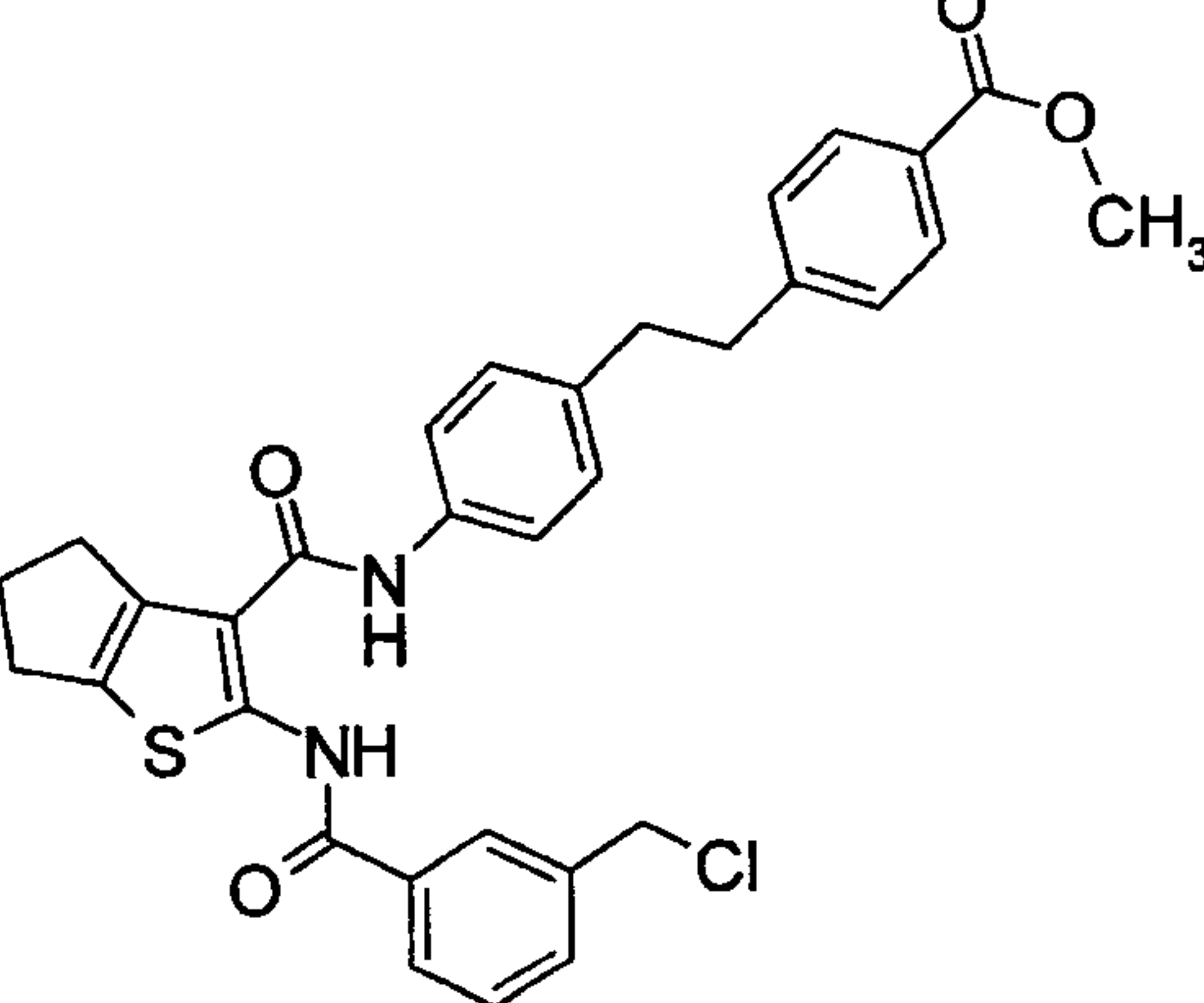
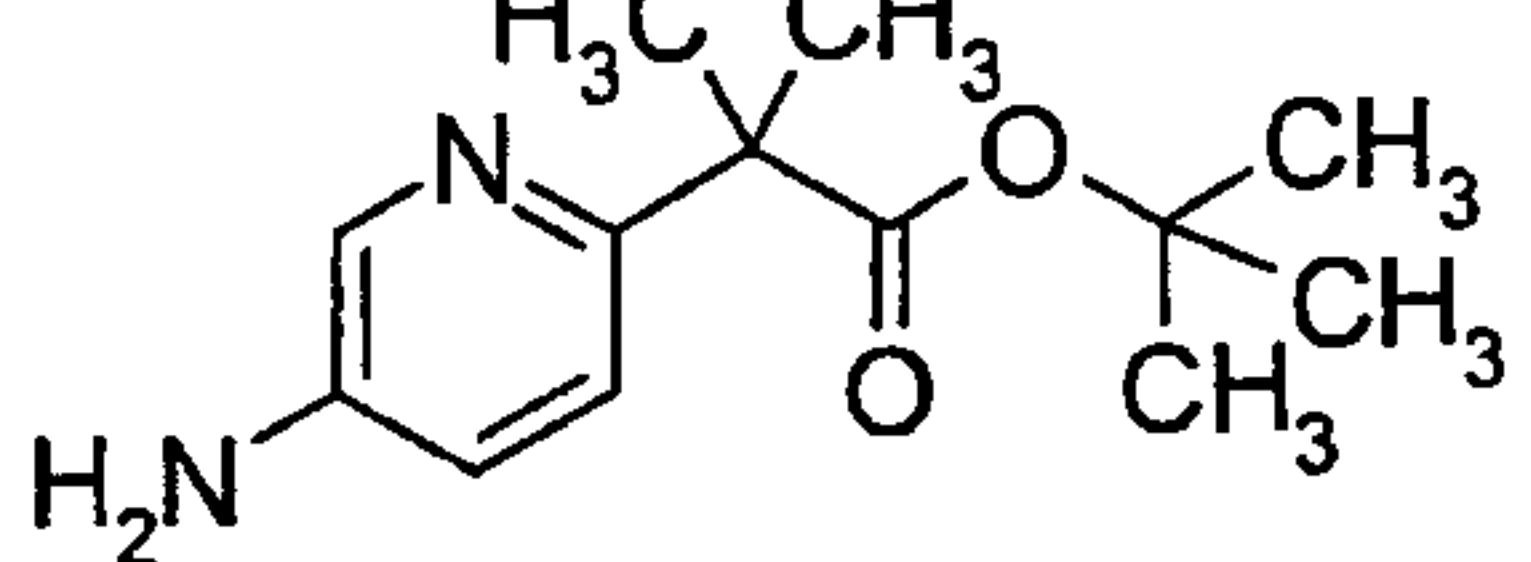
[0181]
[Table 36]

Pr	Str	Pr	Str
213		216	
214		217	
215		218	

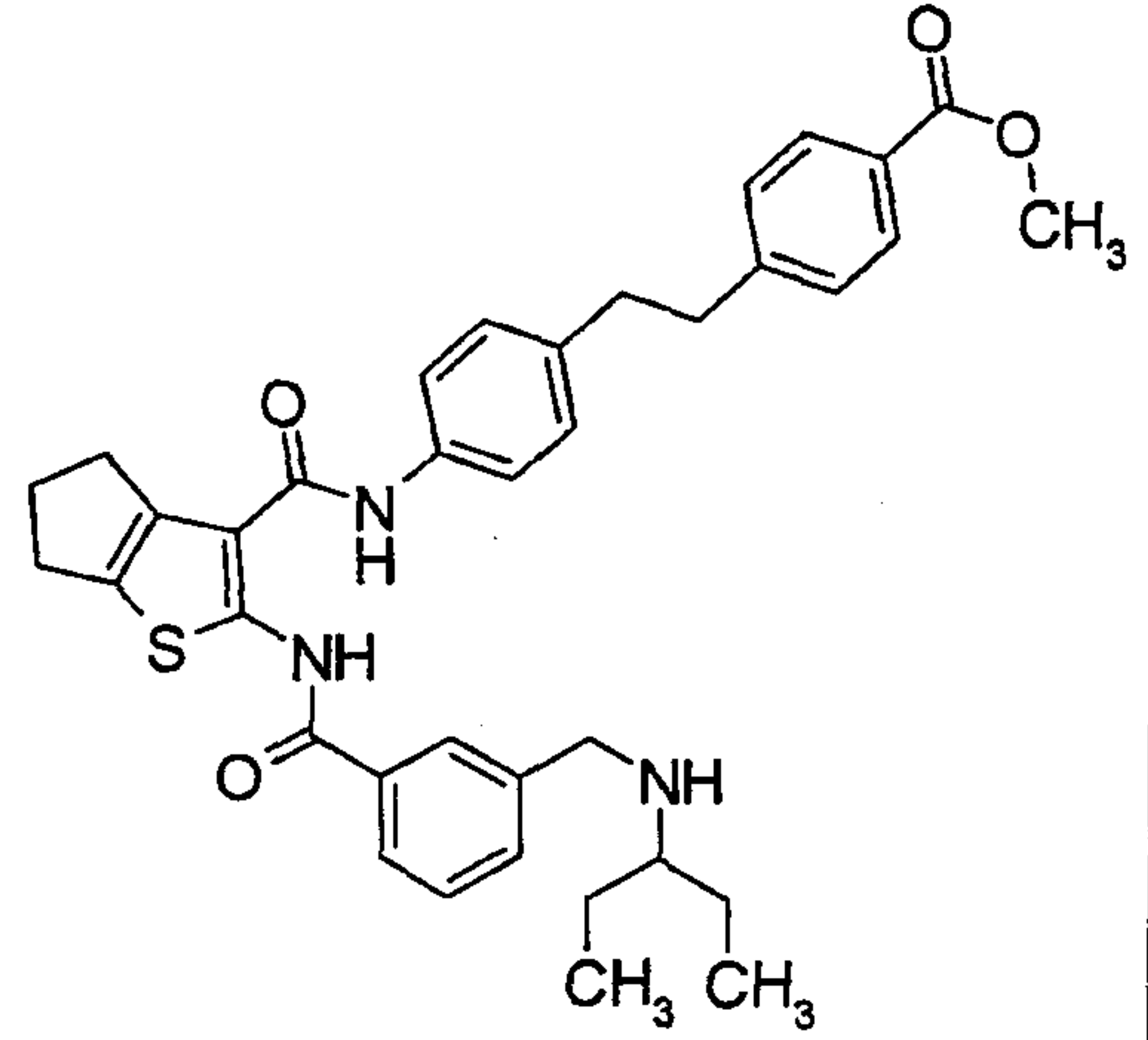
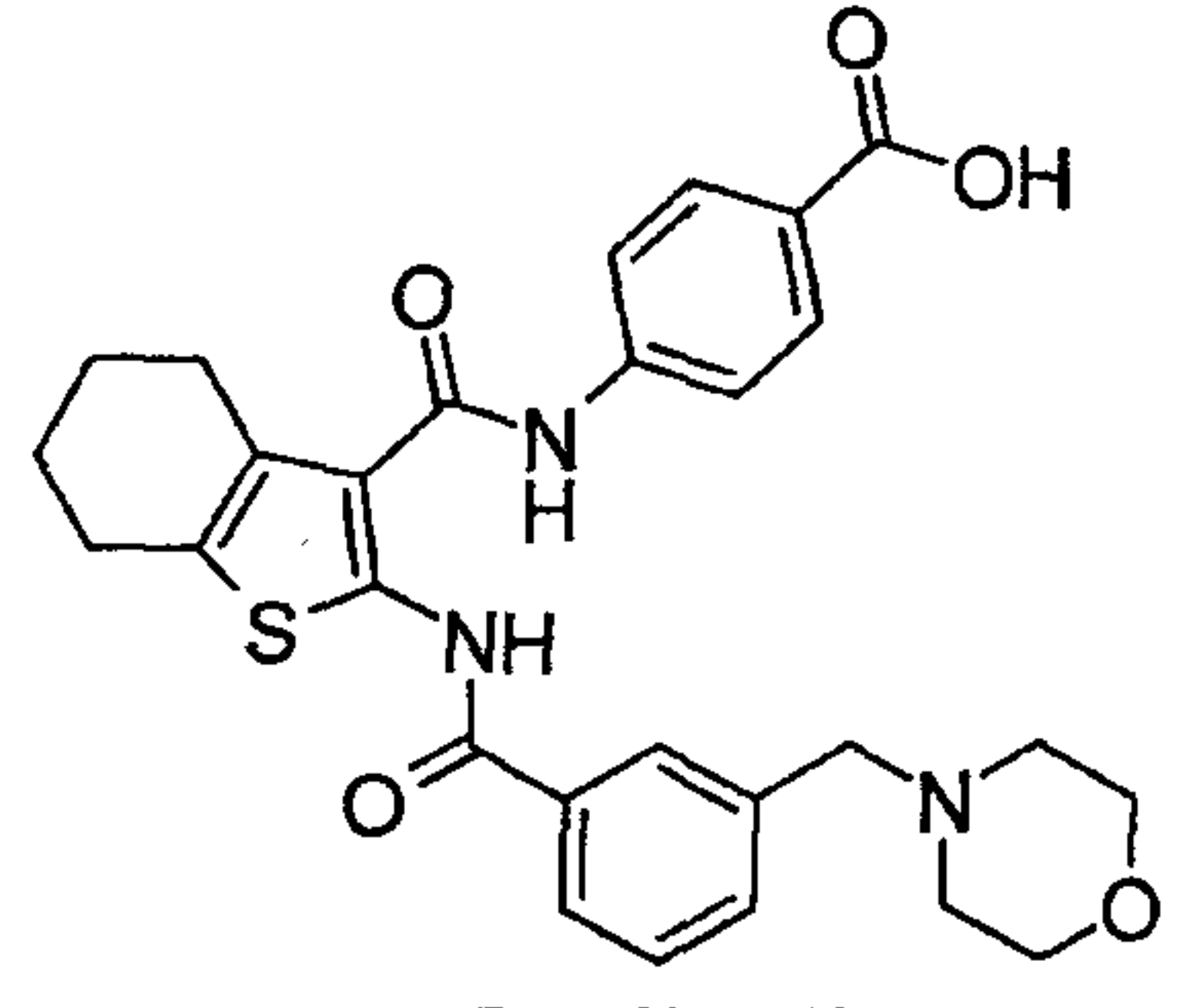
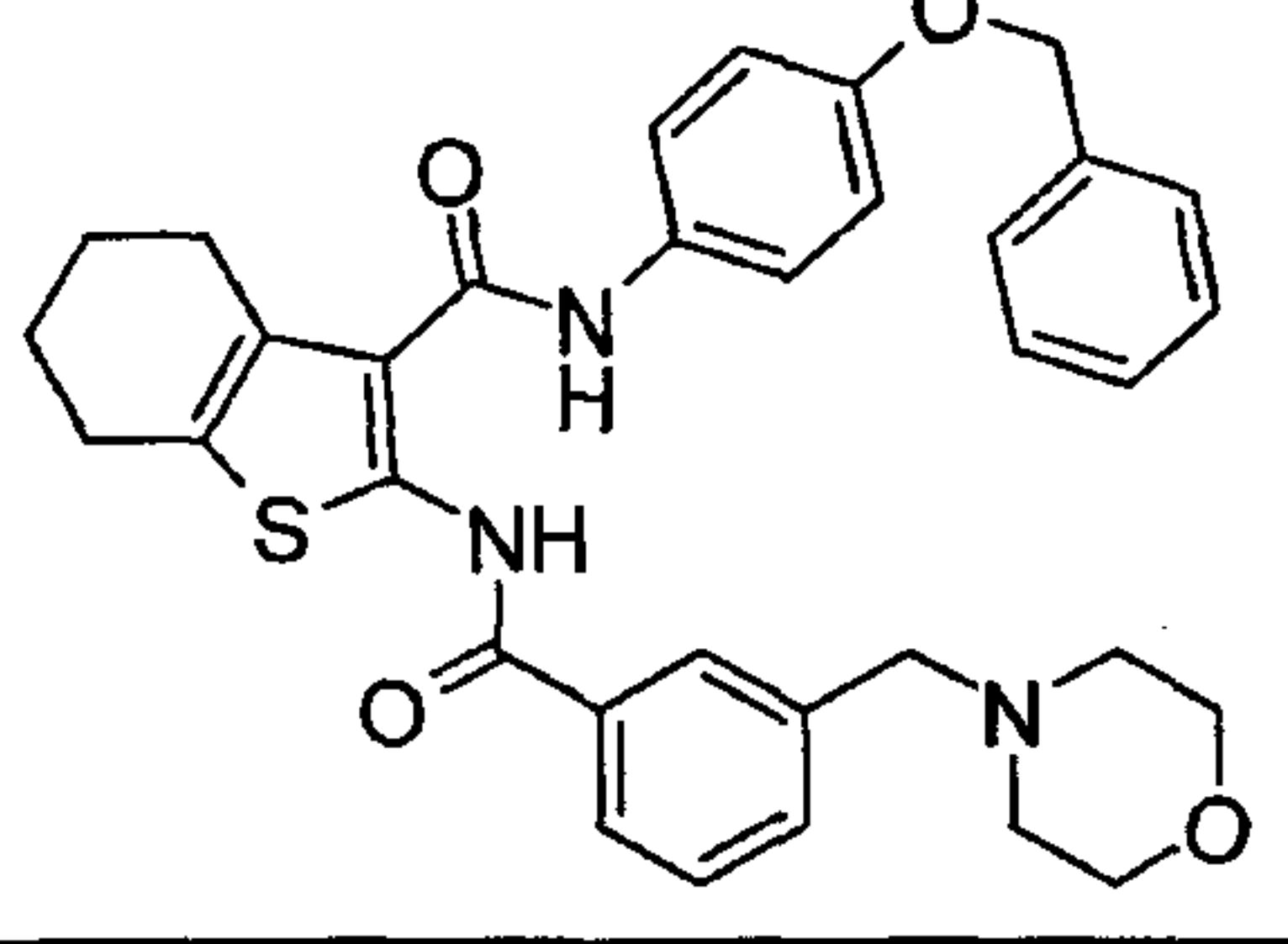
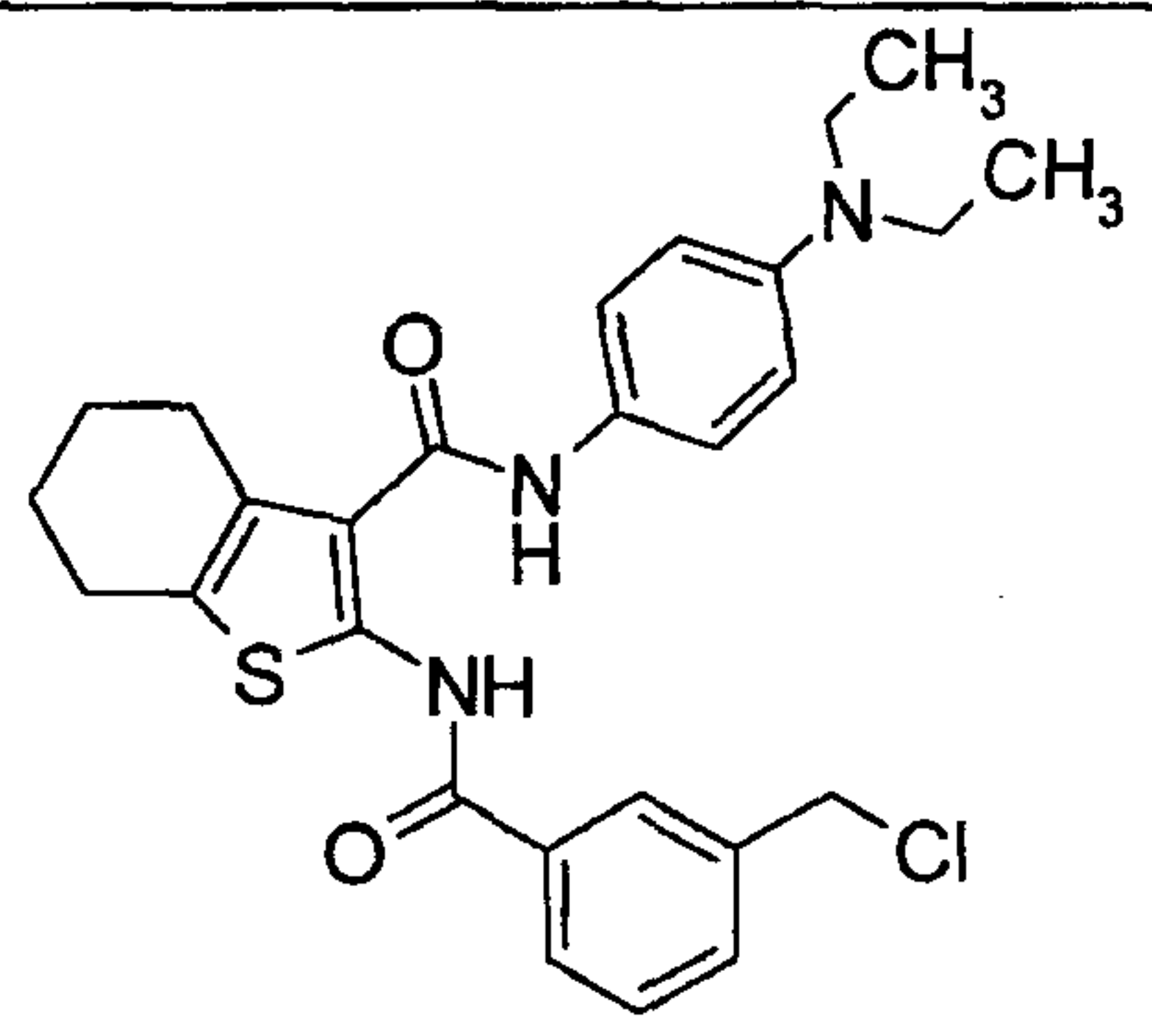
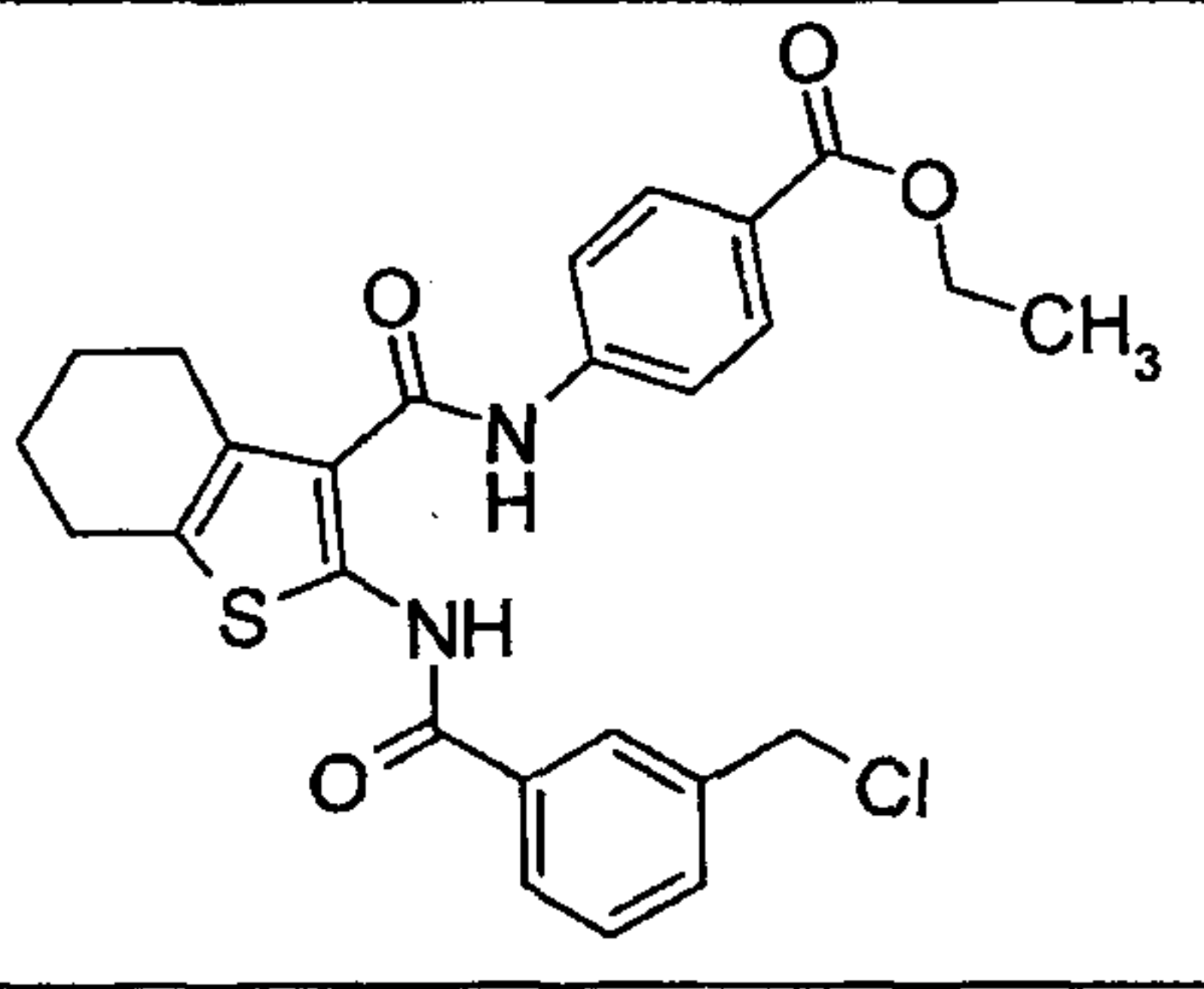
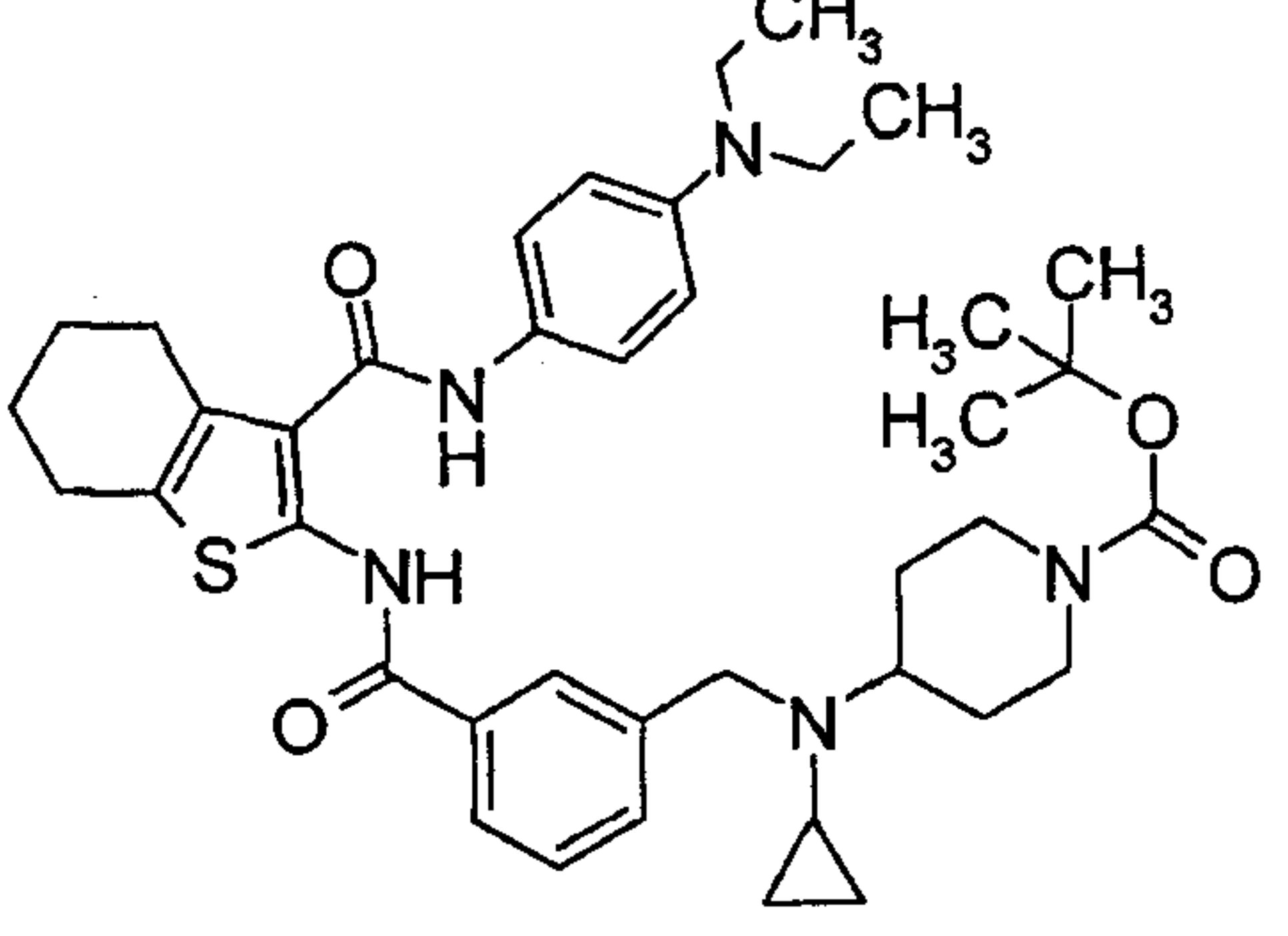
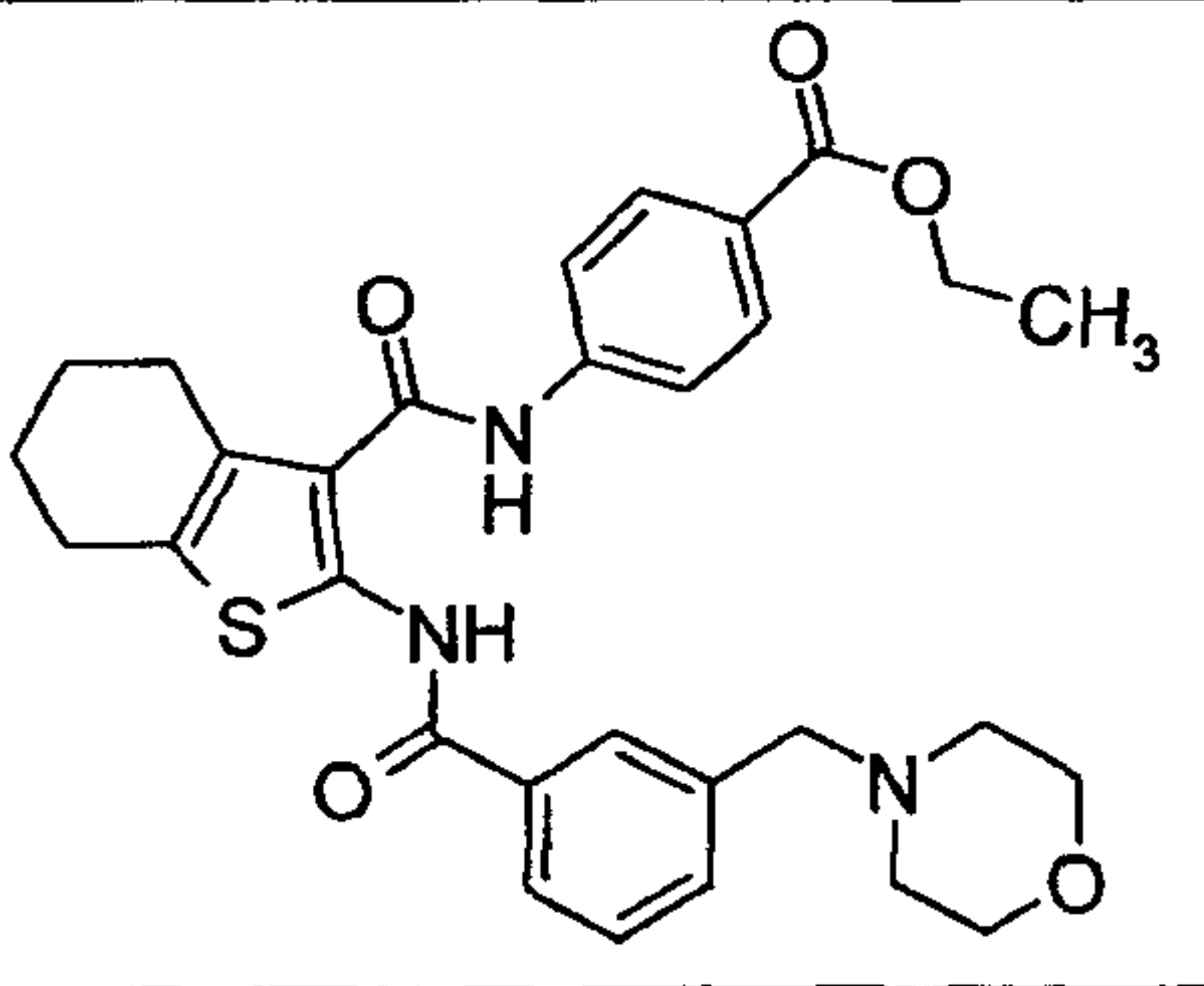
[0182]
[Table 37]

Pr	Str	Pr	Str
219		224	
220		225	
221		226	
222			
223			

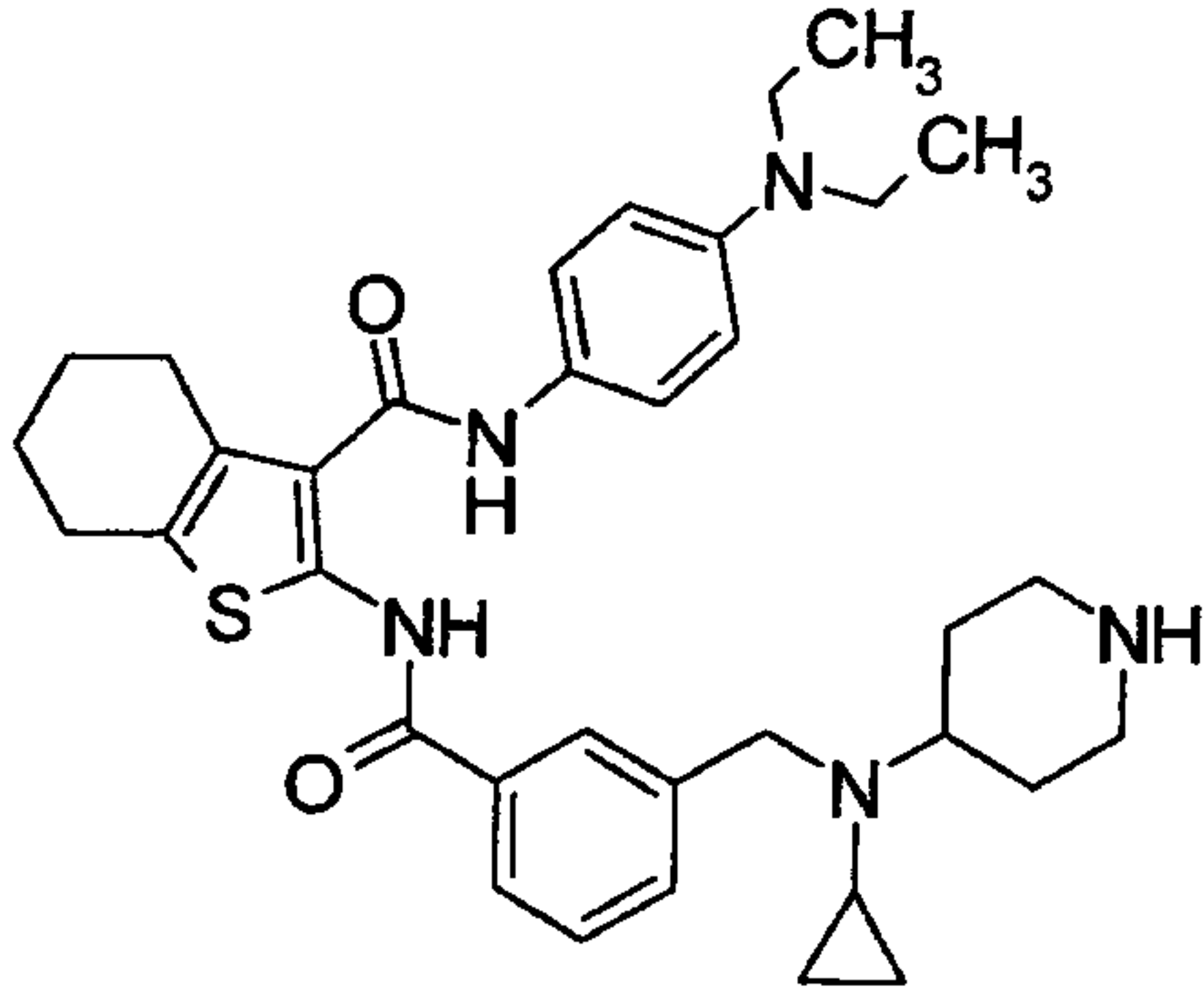
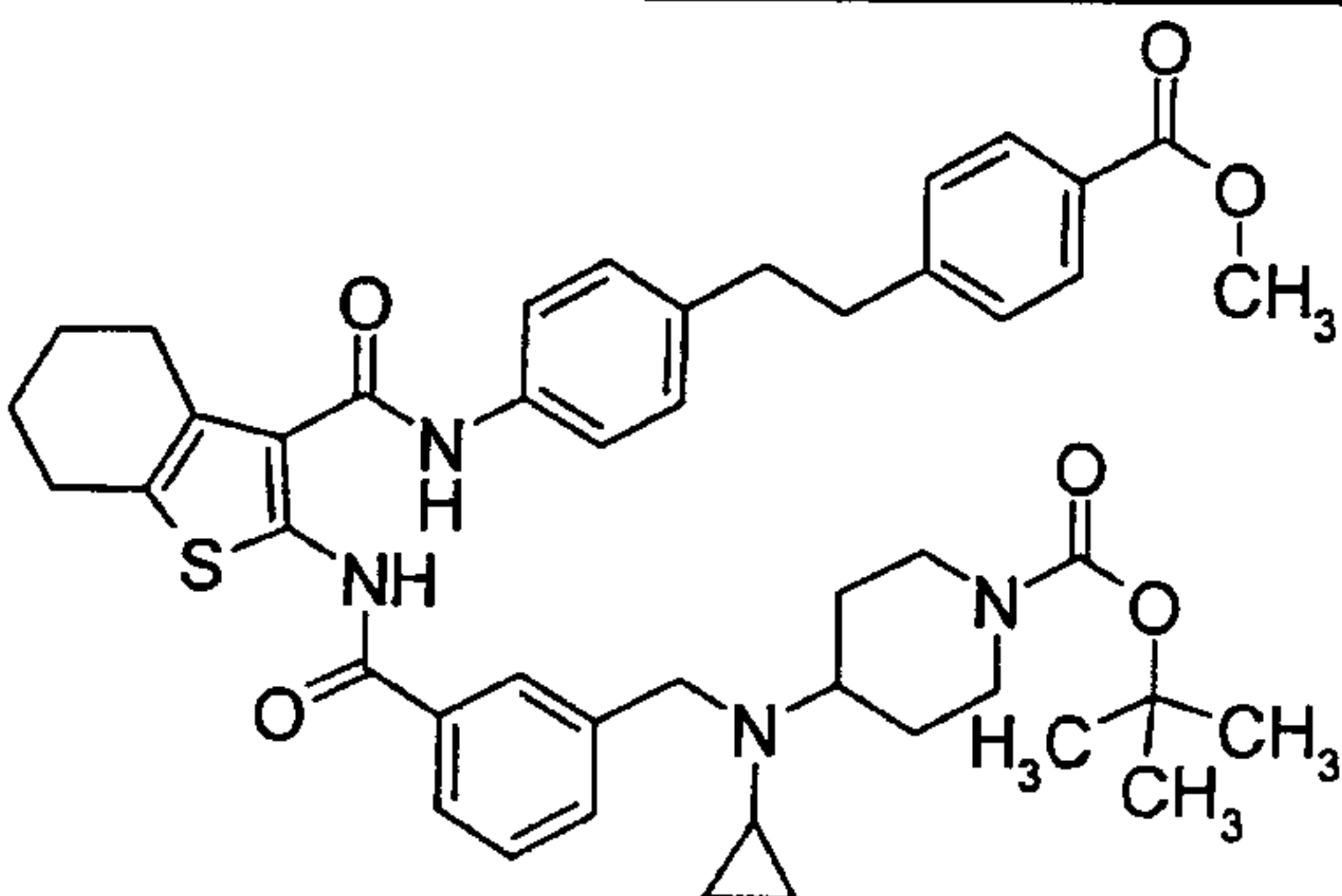
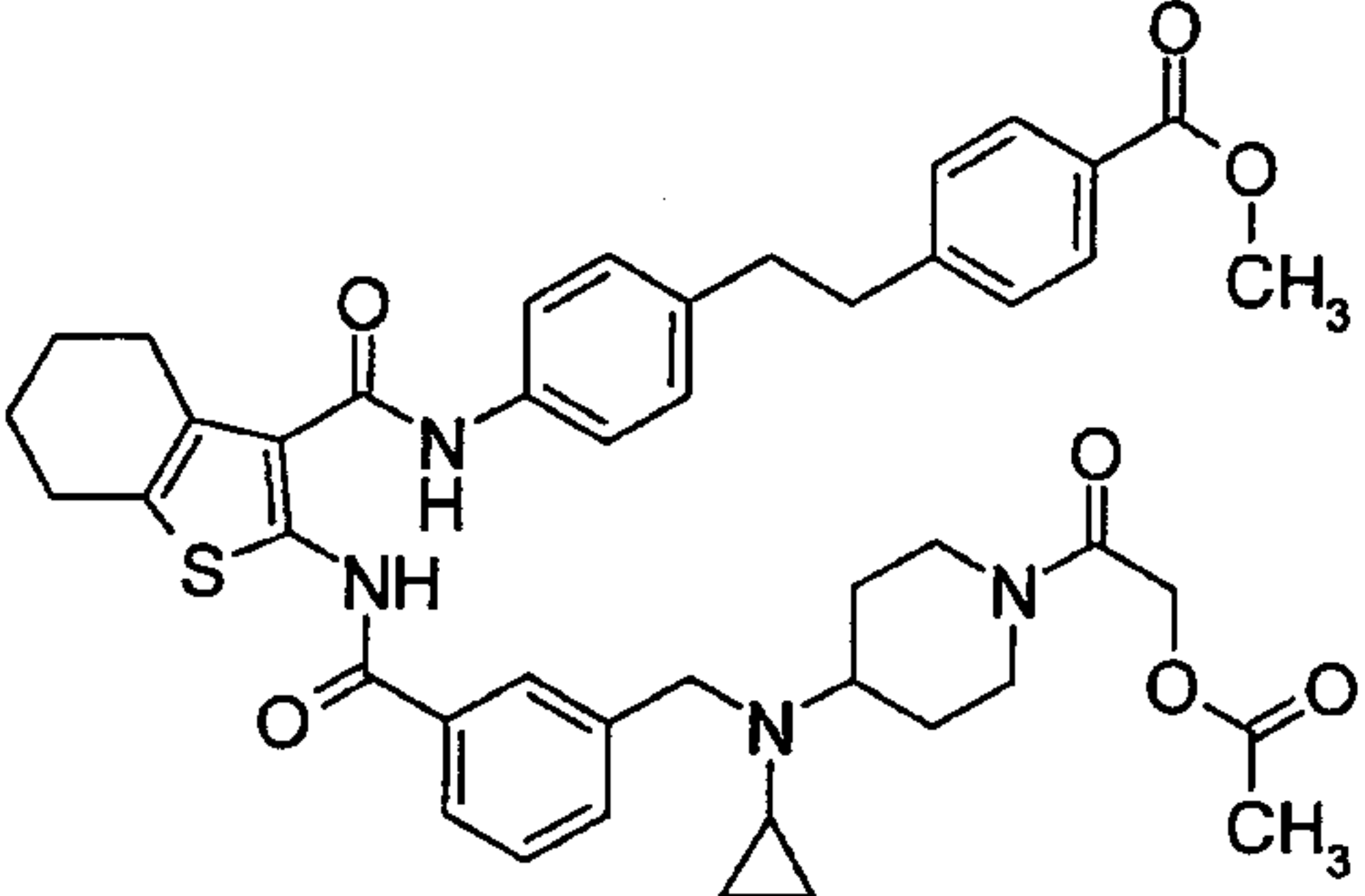
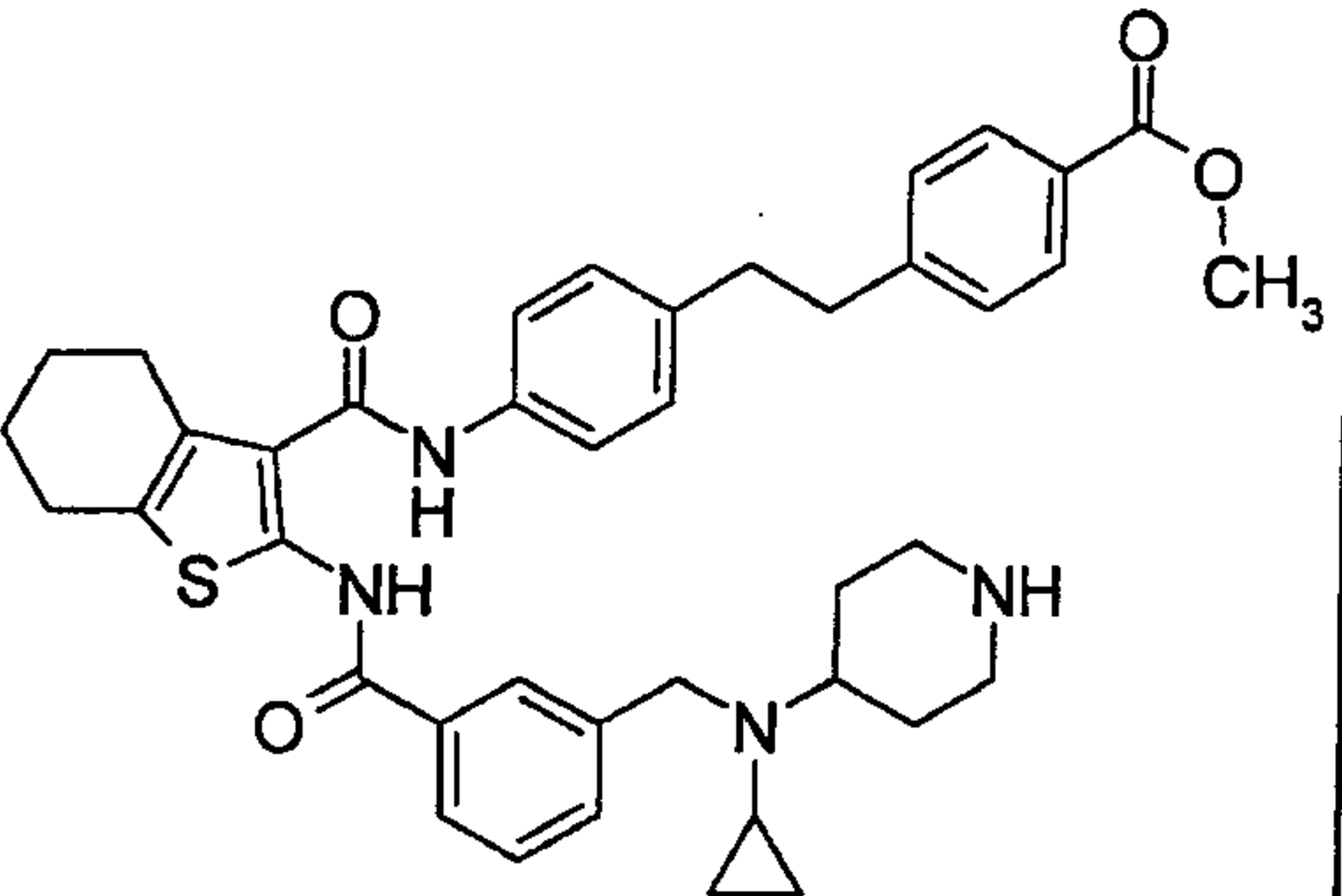
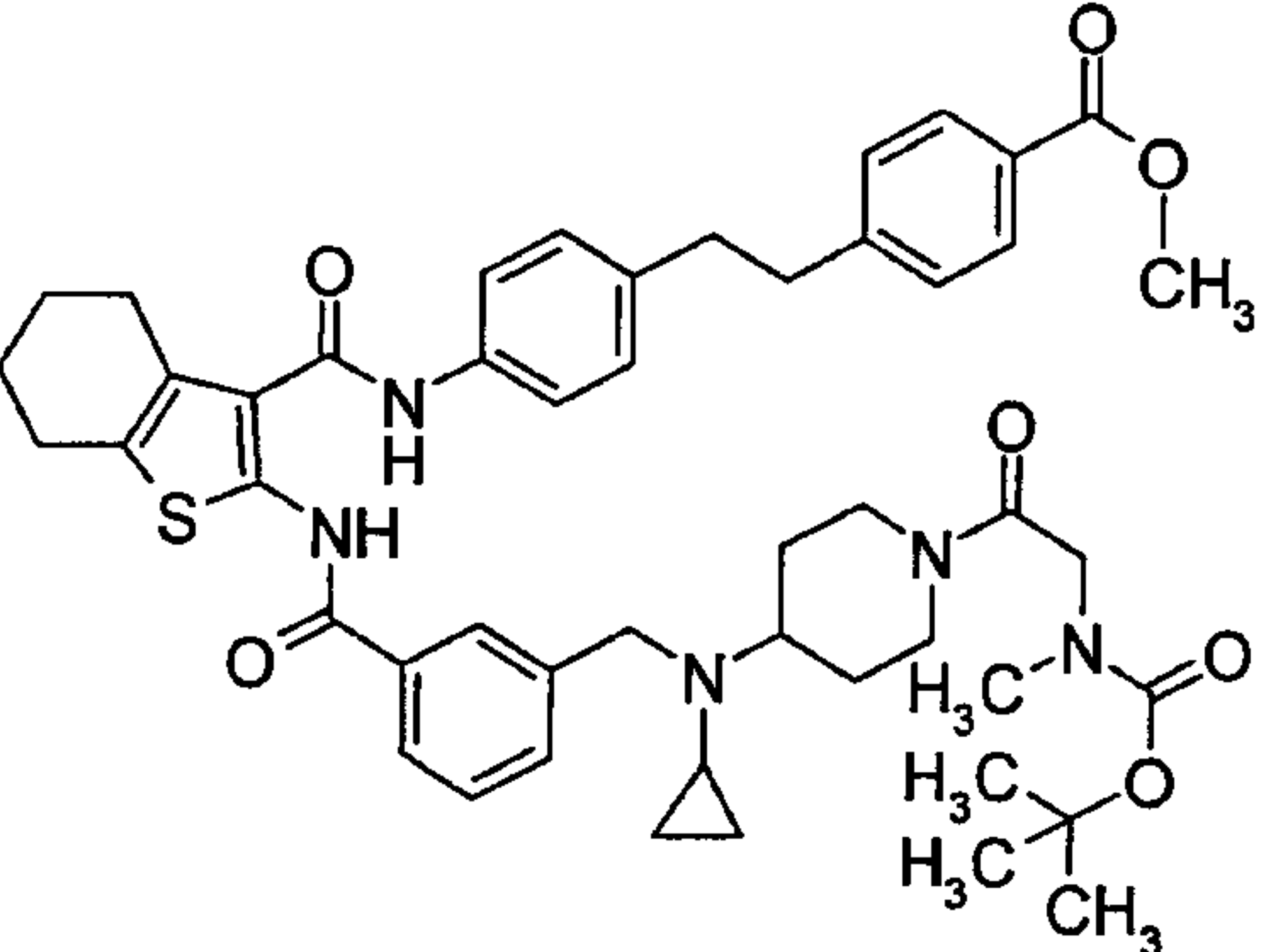
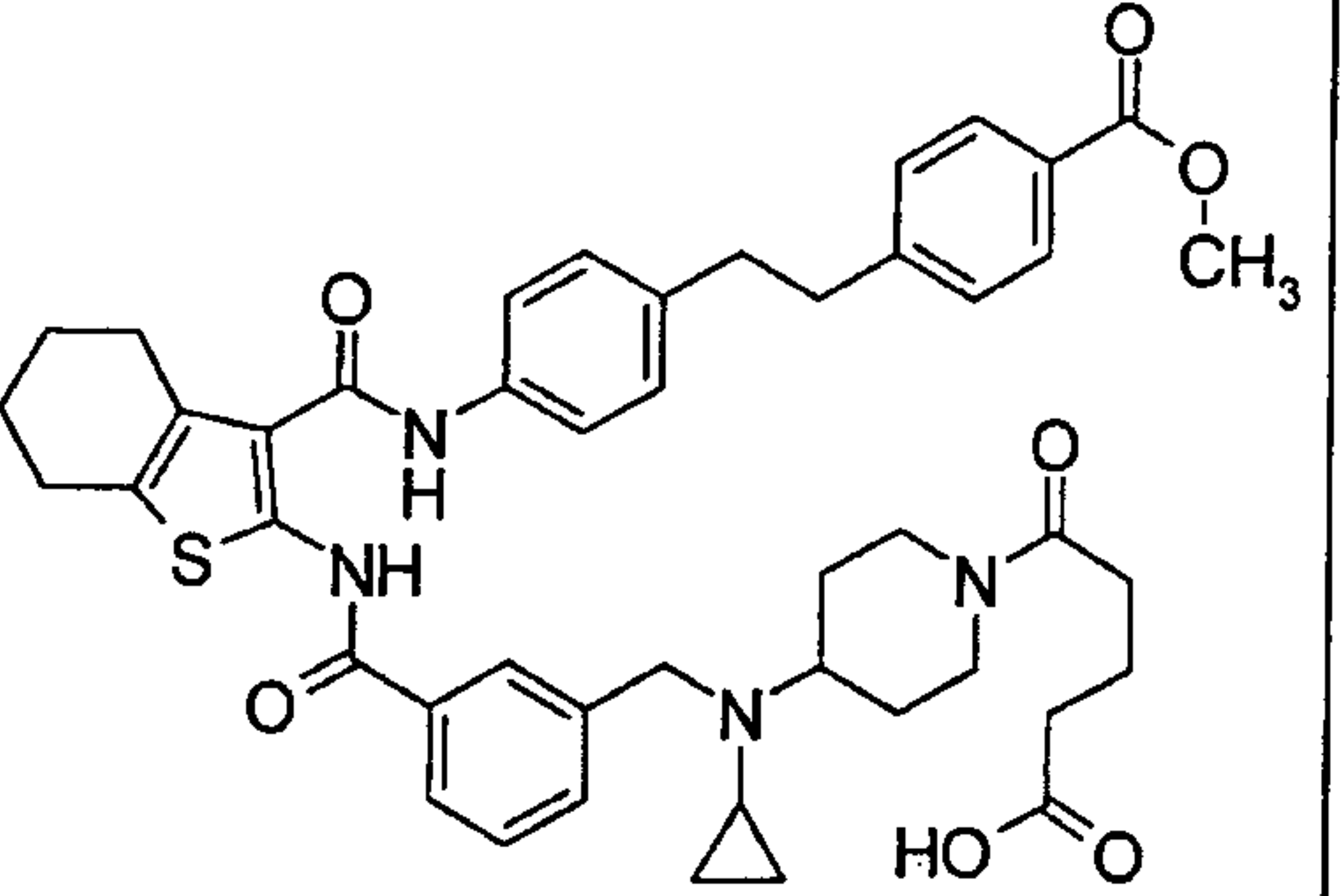
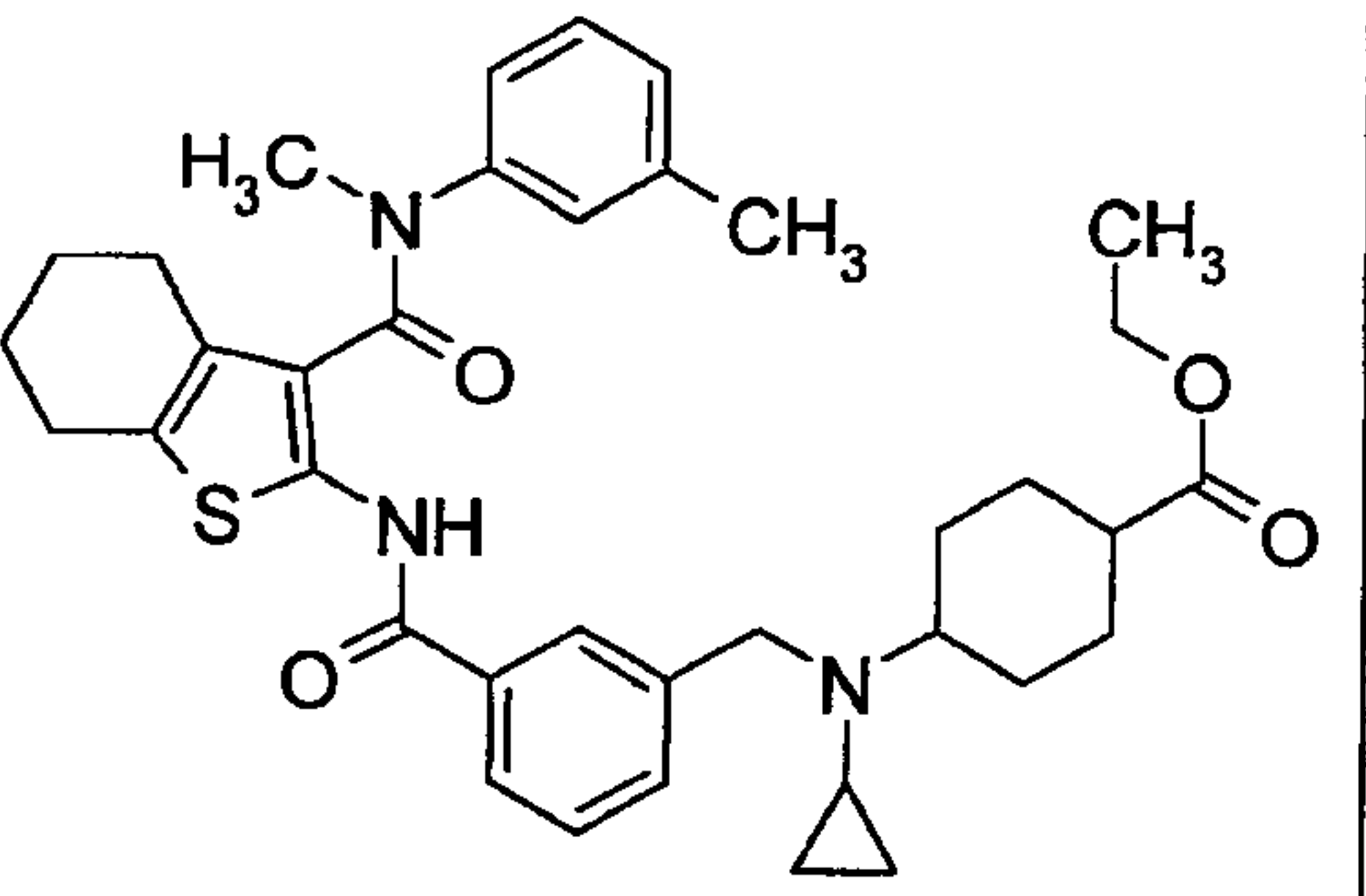
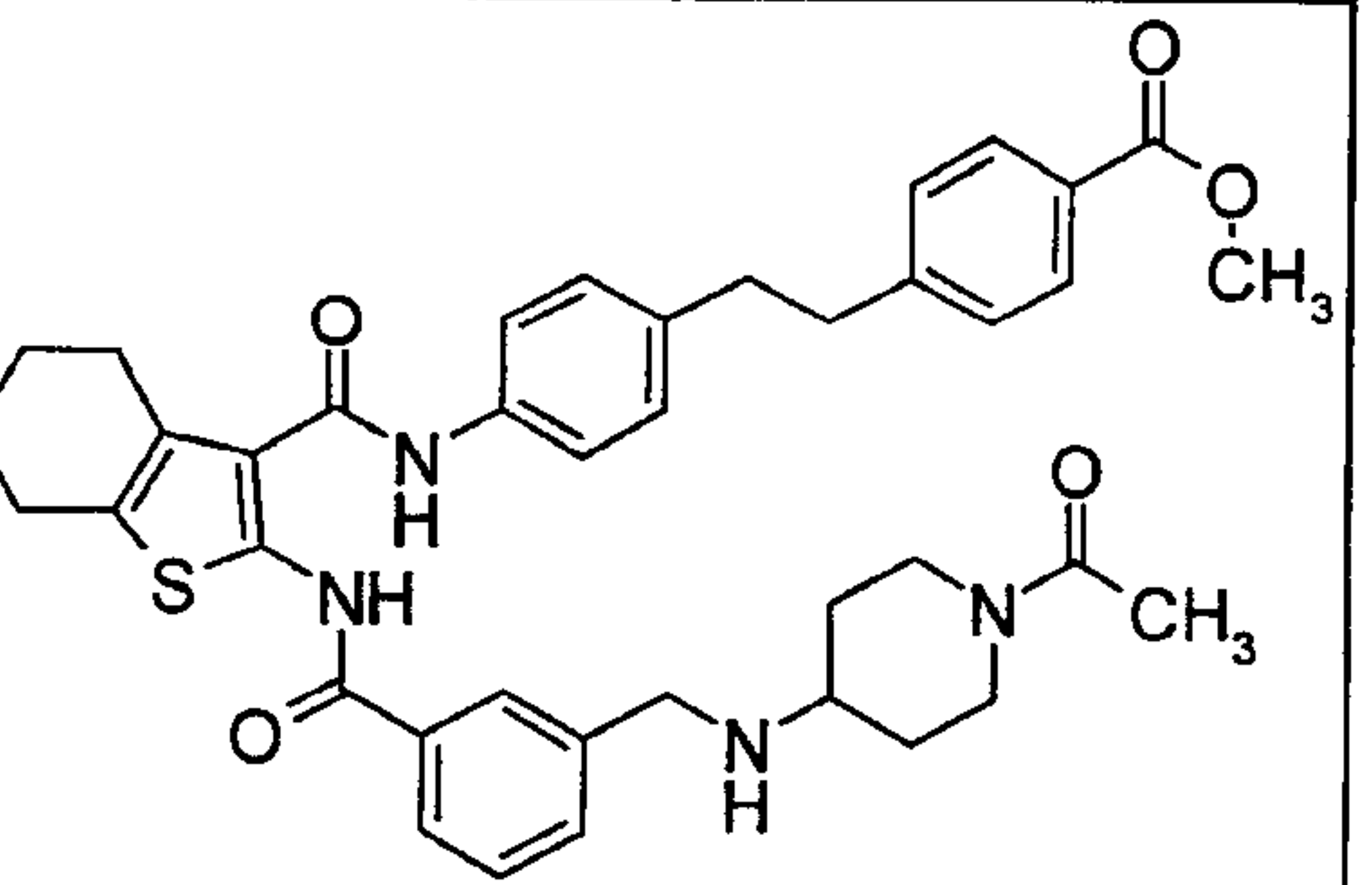
[0183]
[Table 38]

Pr	Str	Pr	Str
227		231	
228		232	
229		233	
230			

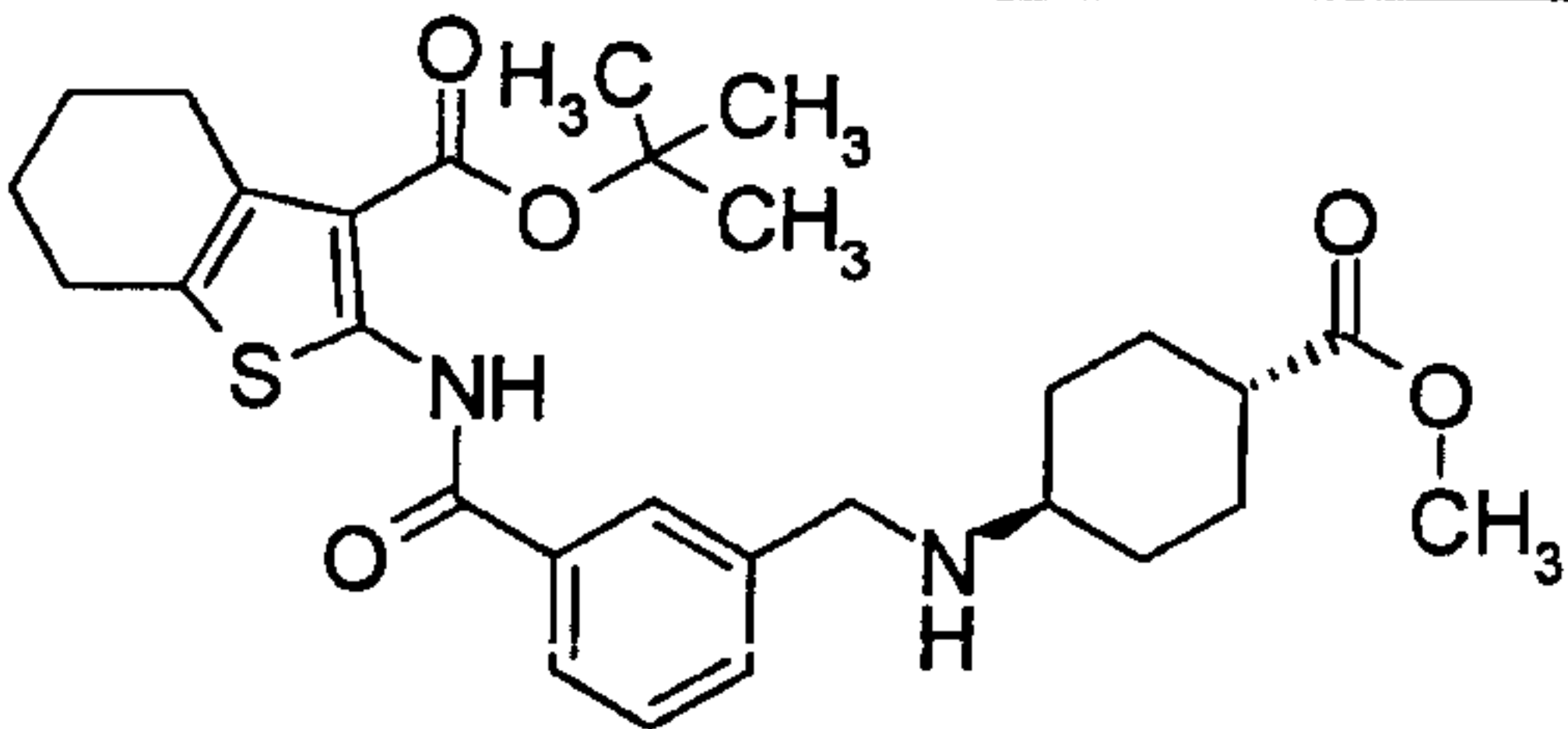
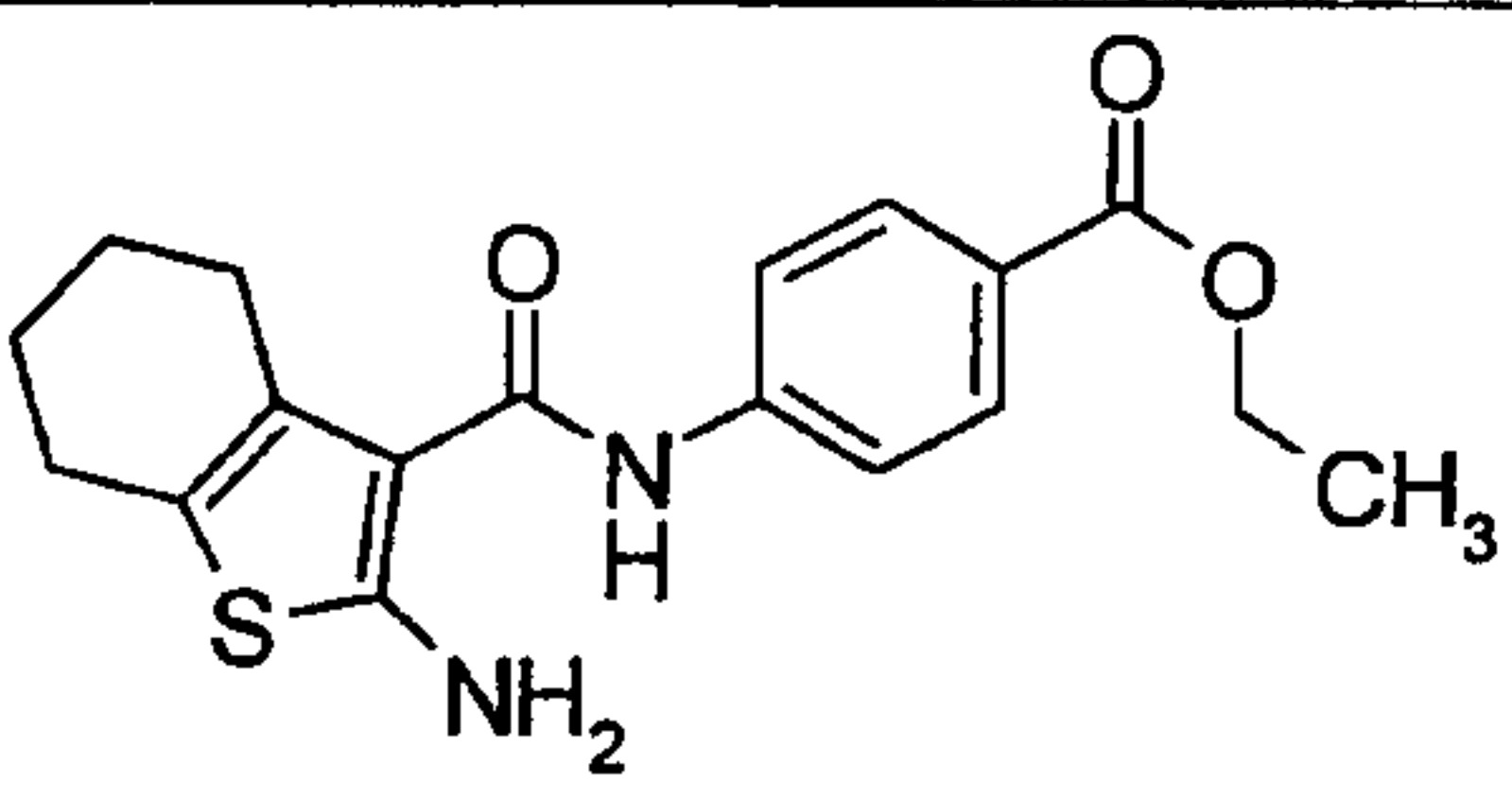
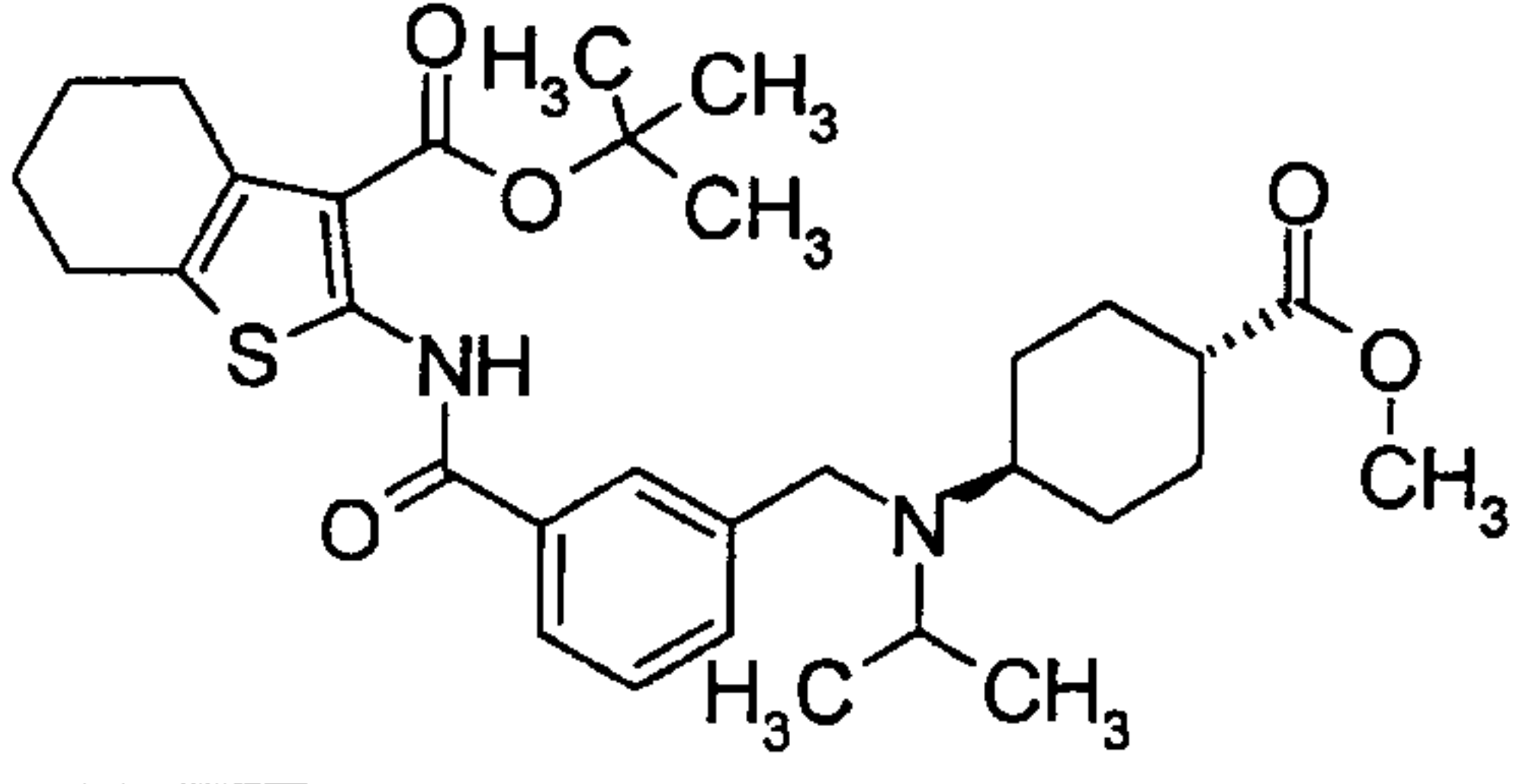
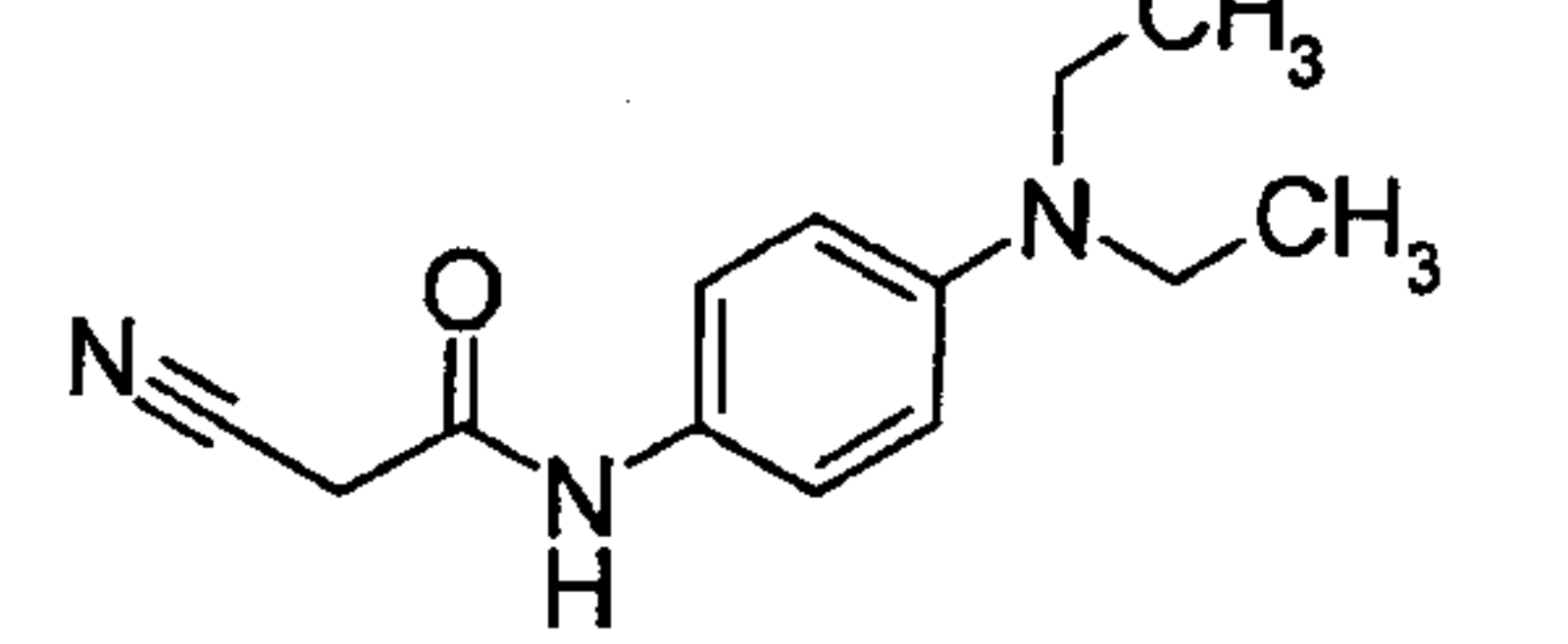
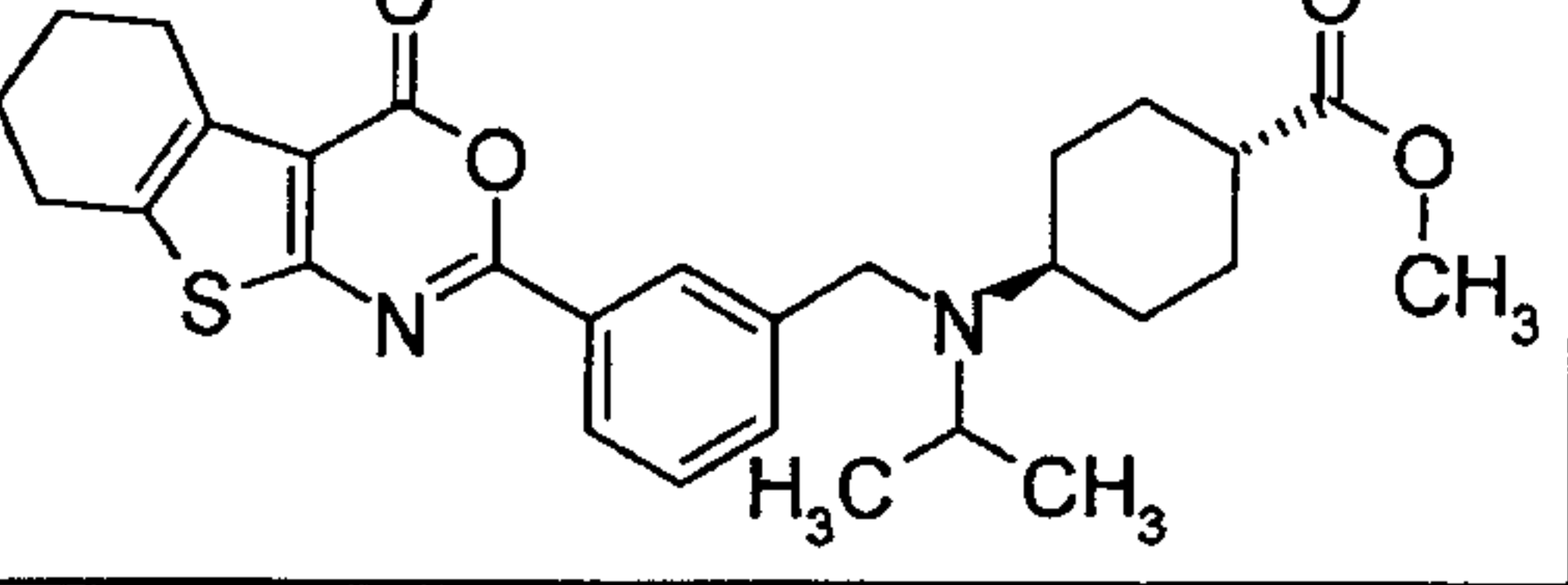
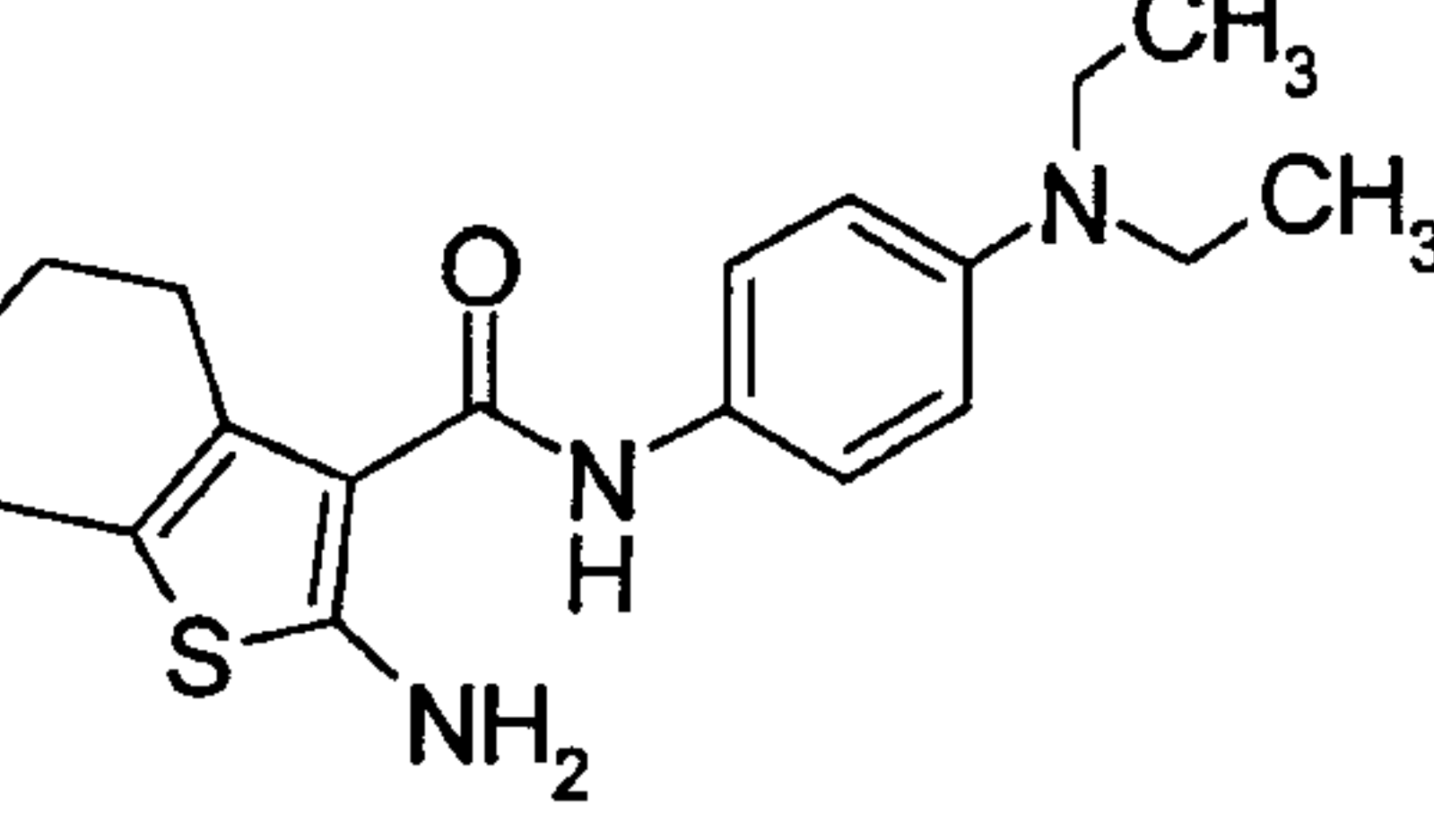
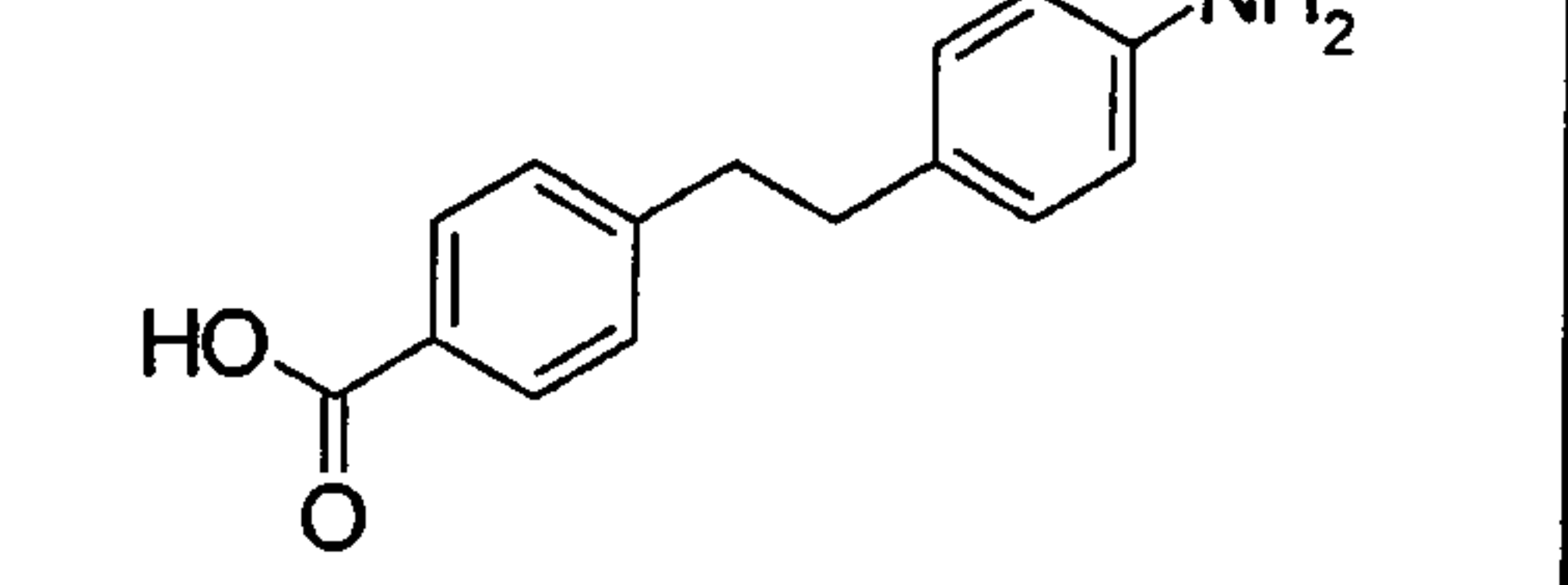
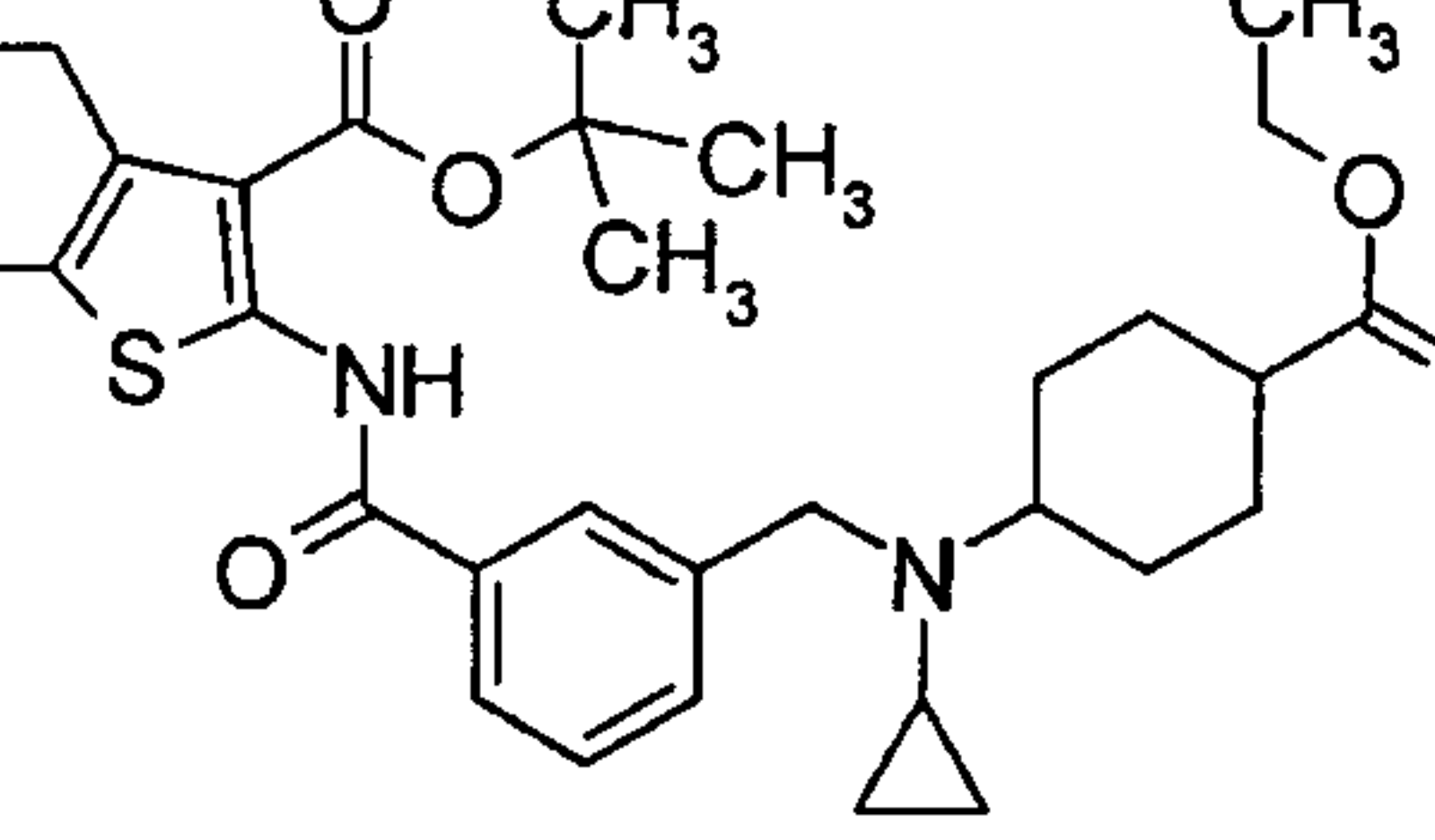
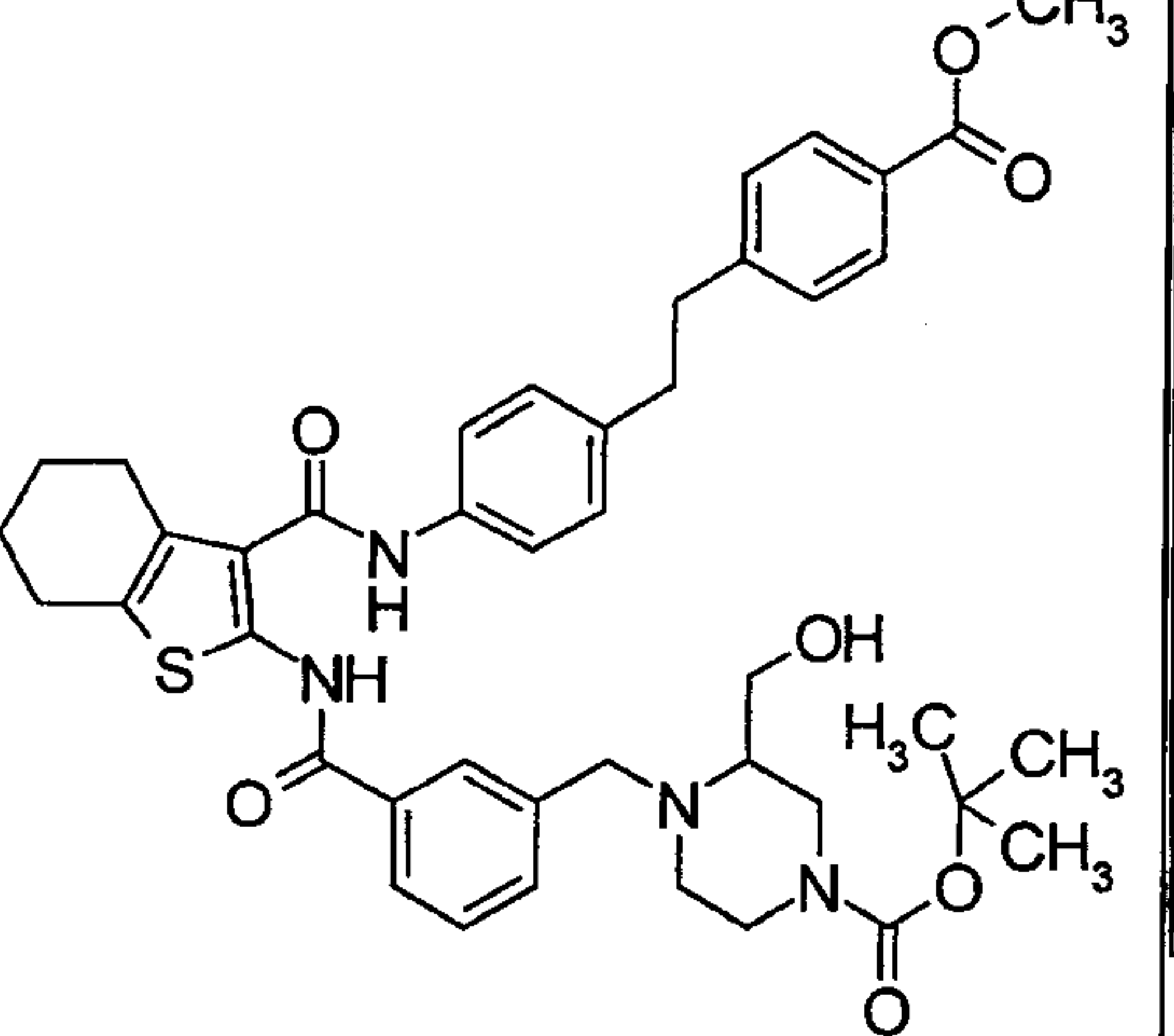
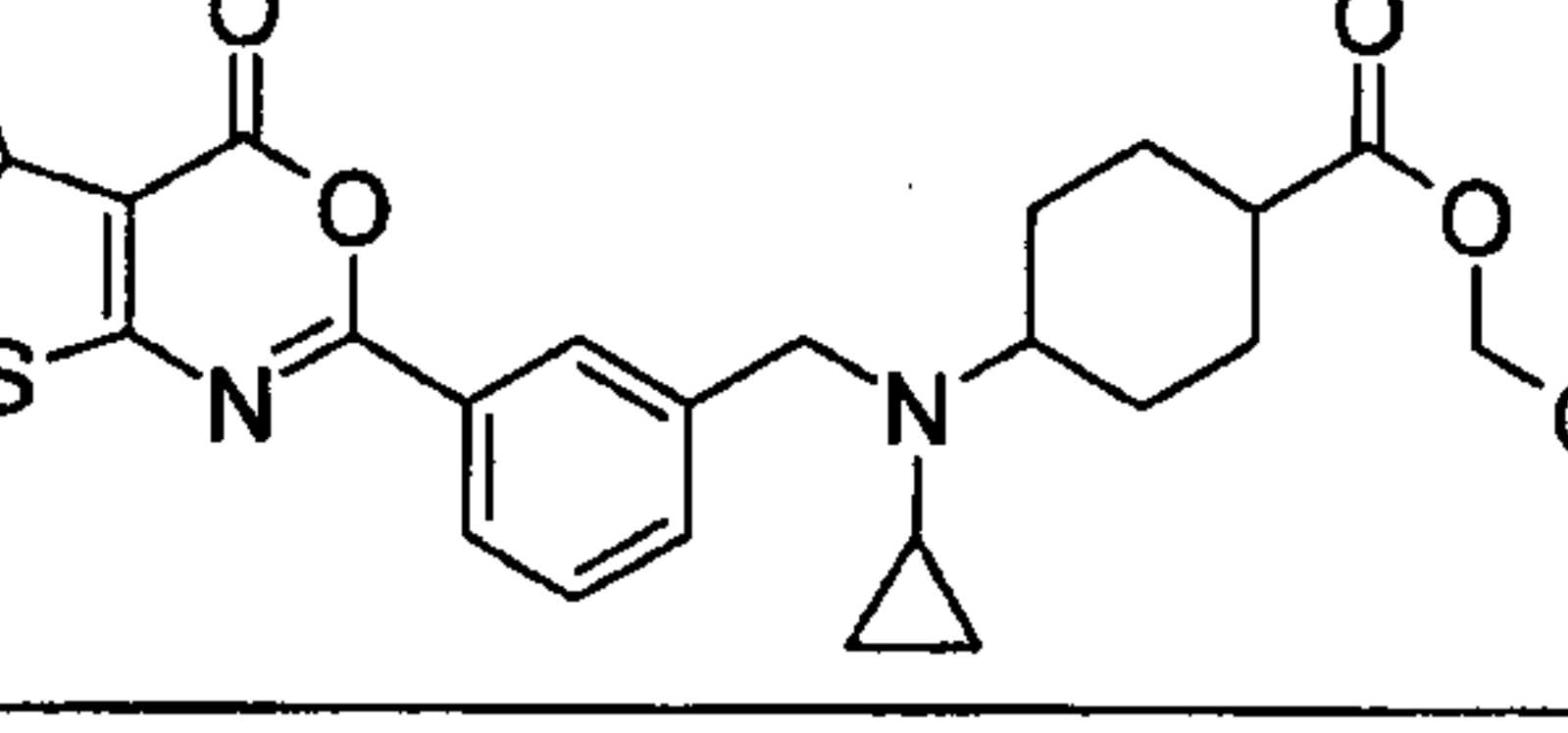
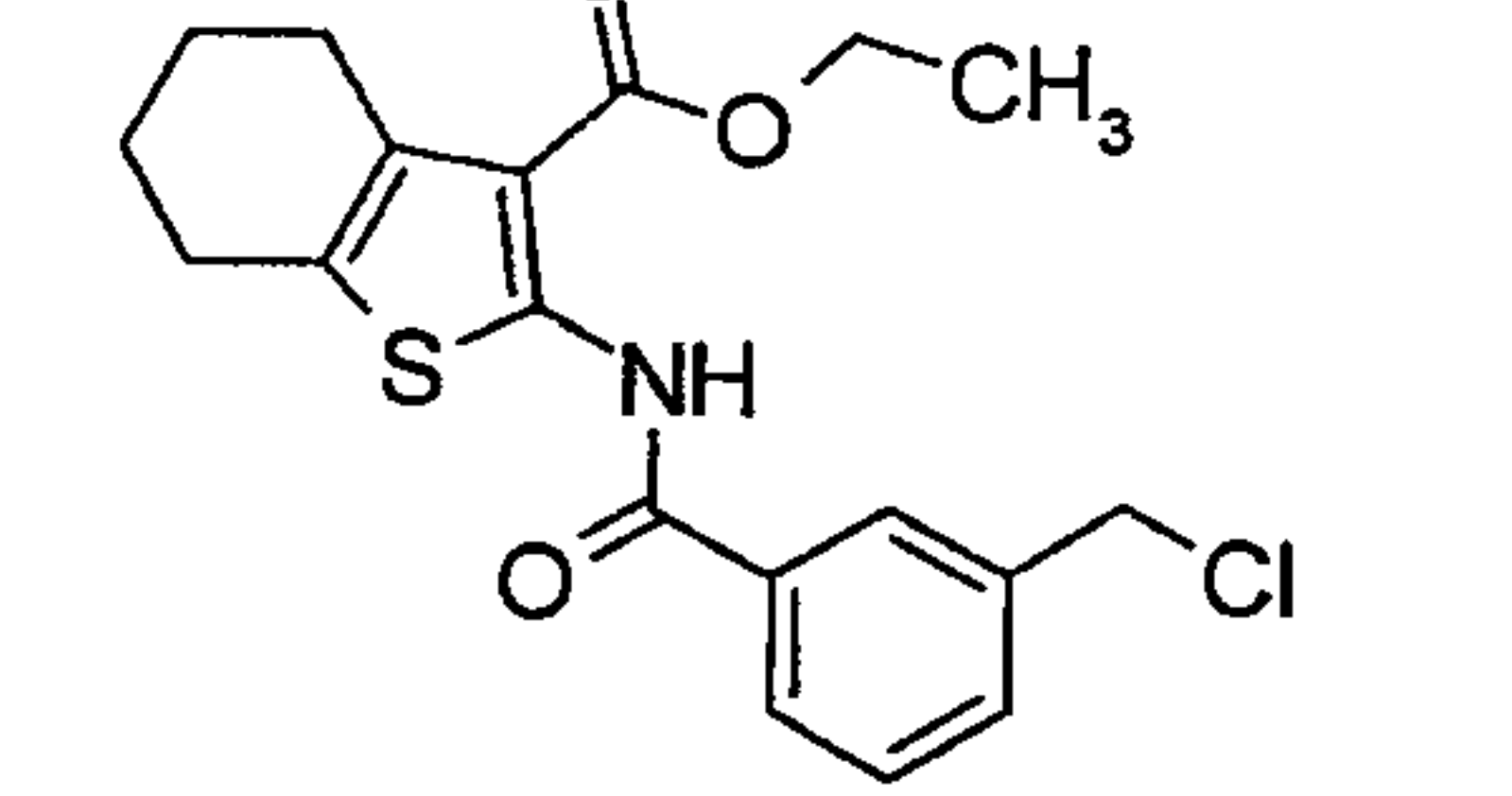
[0184]
[Table 39]

Pr	Str	Pr	Str
234		238	
235		239	
236		240	
237			

[0185]
[Table 40]

Pr	Str	Pr	Str
241		245	
242		246	
243		247	
244		248	

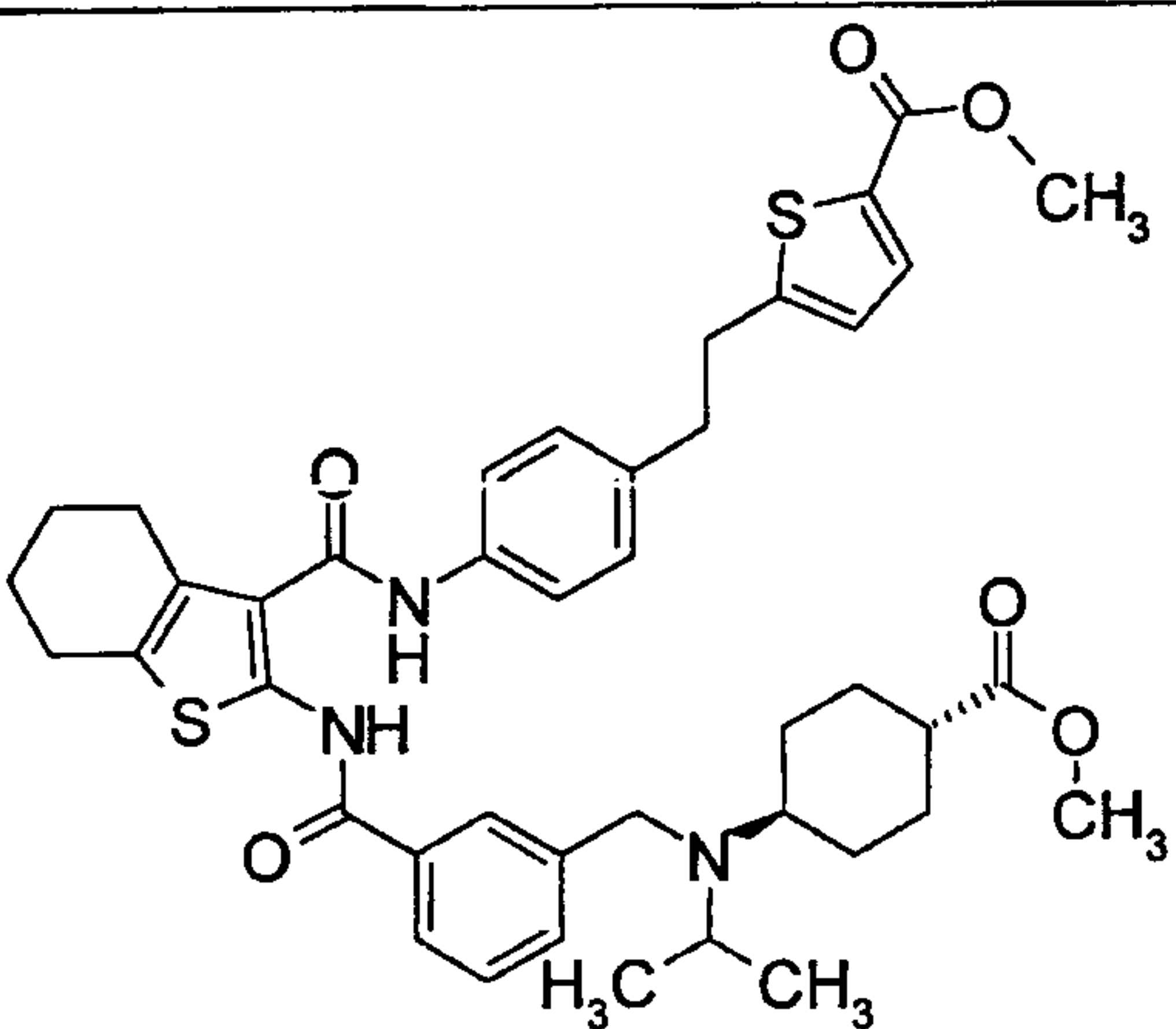
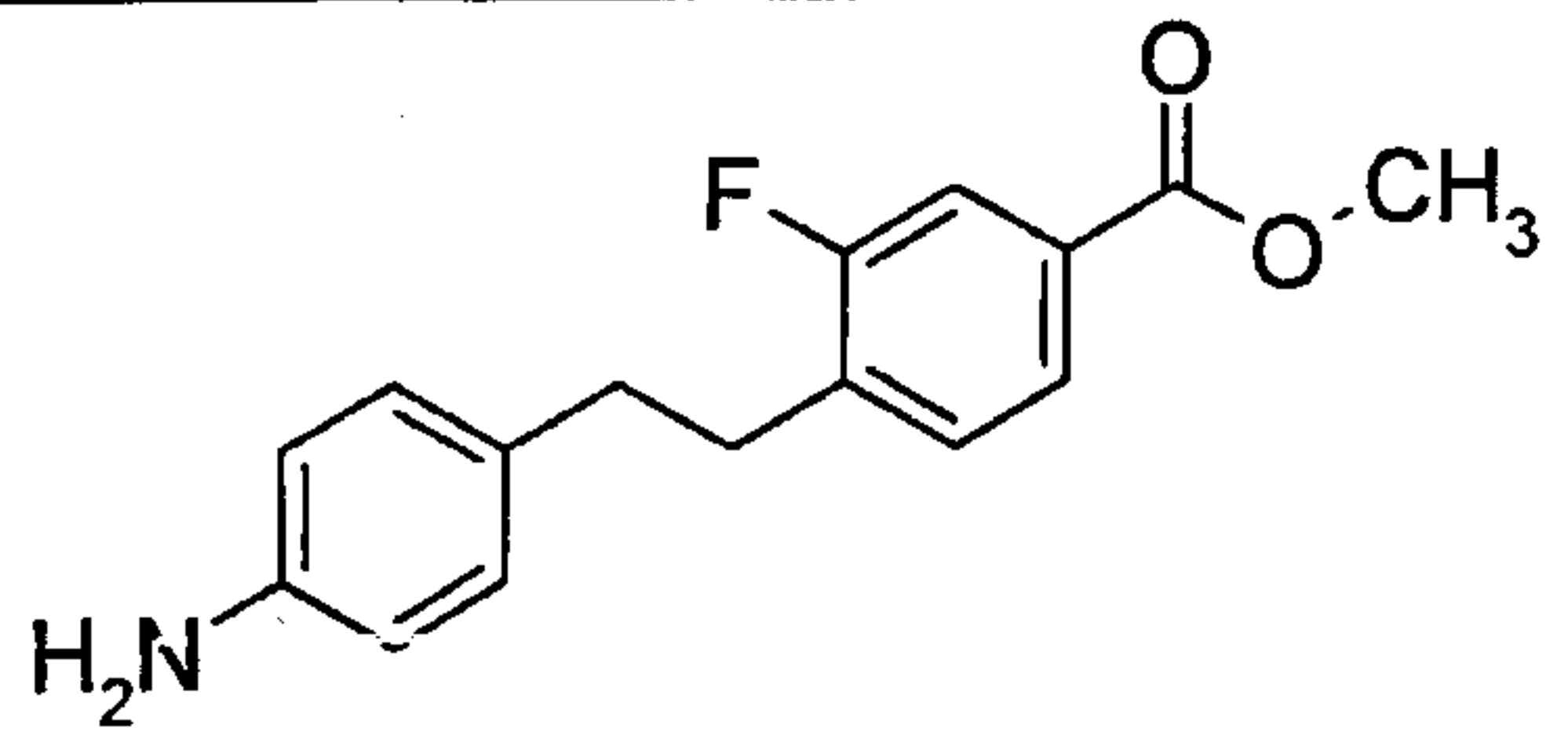
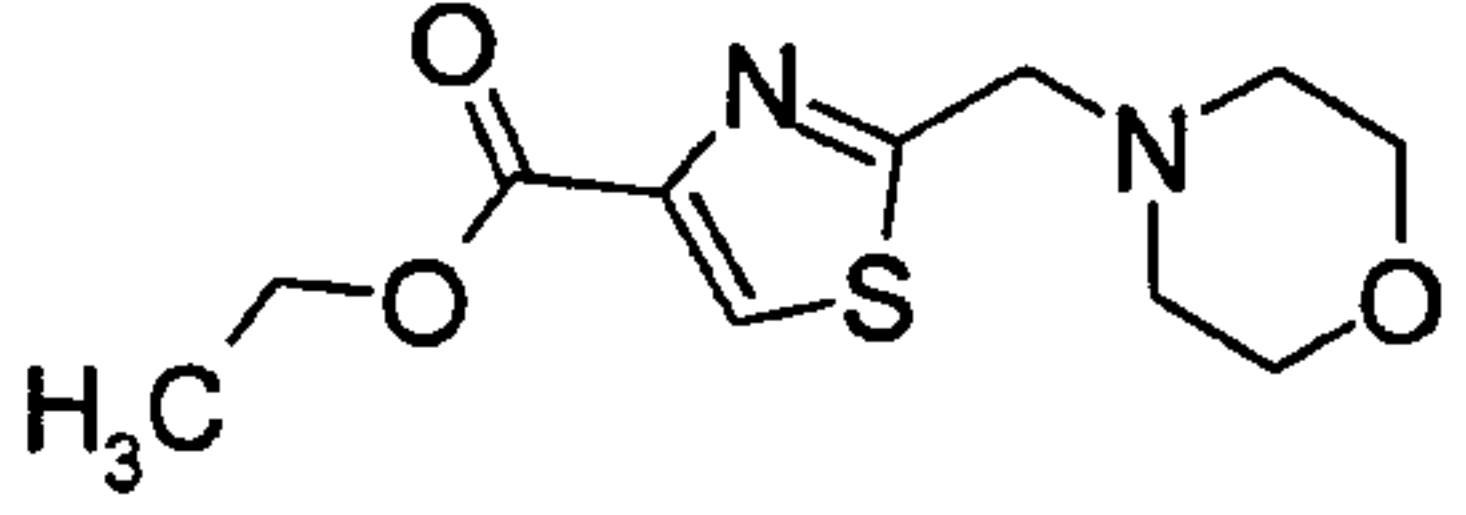
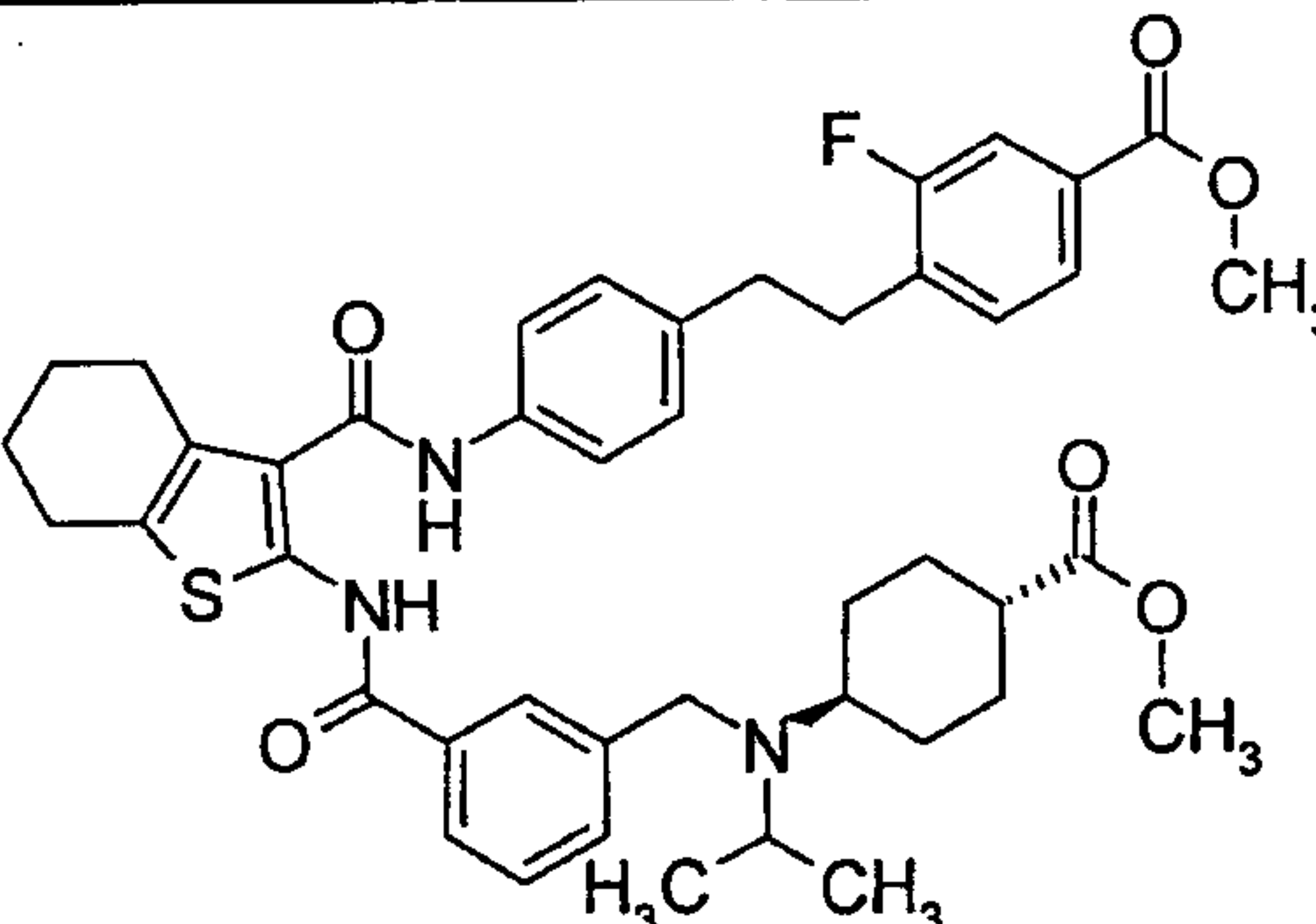
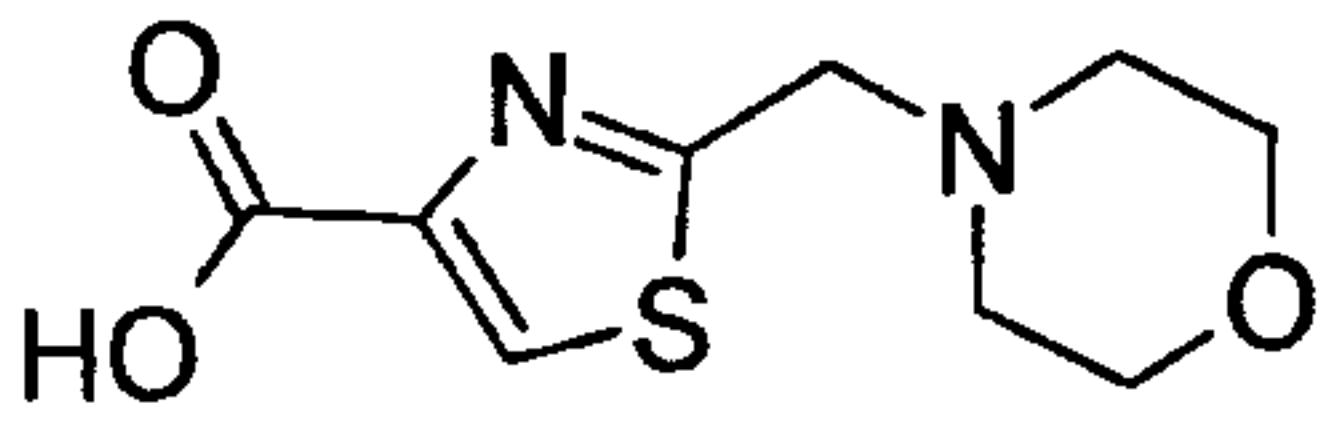
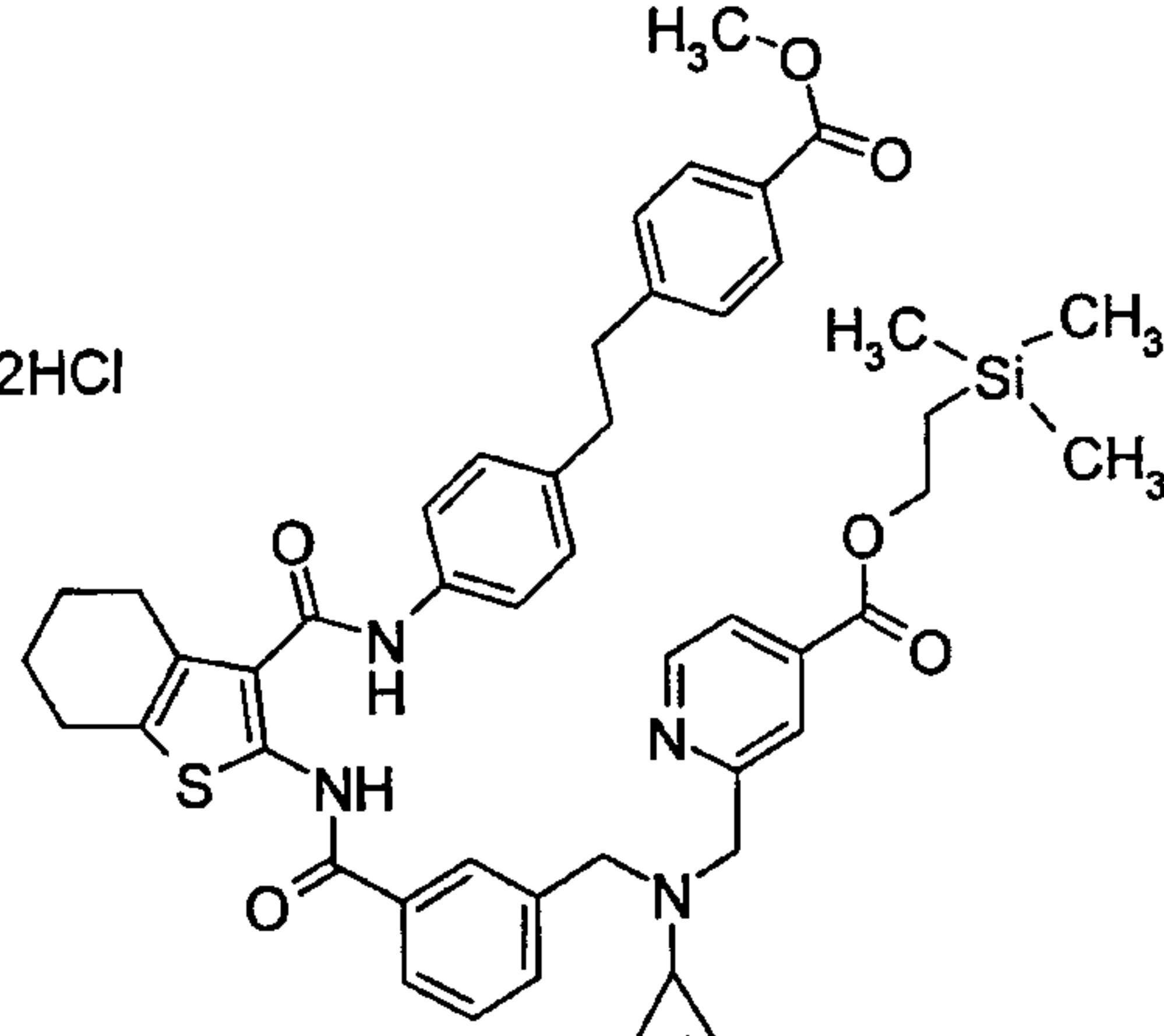
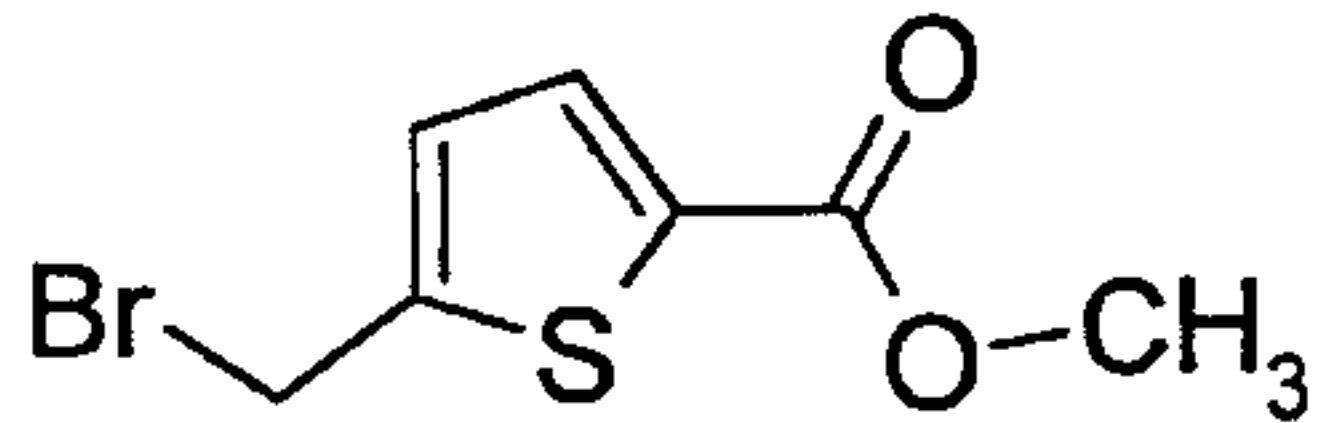
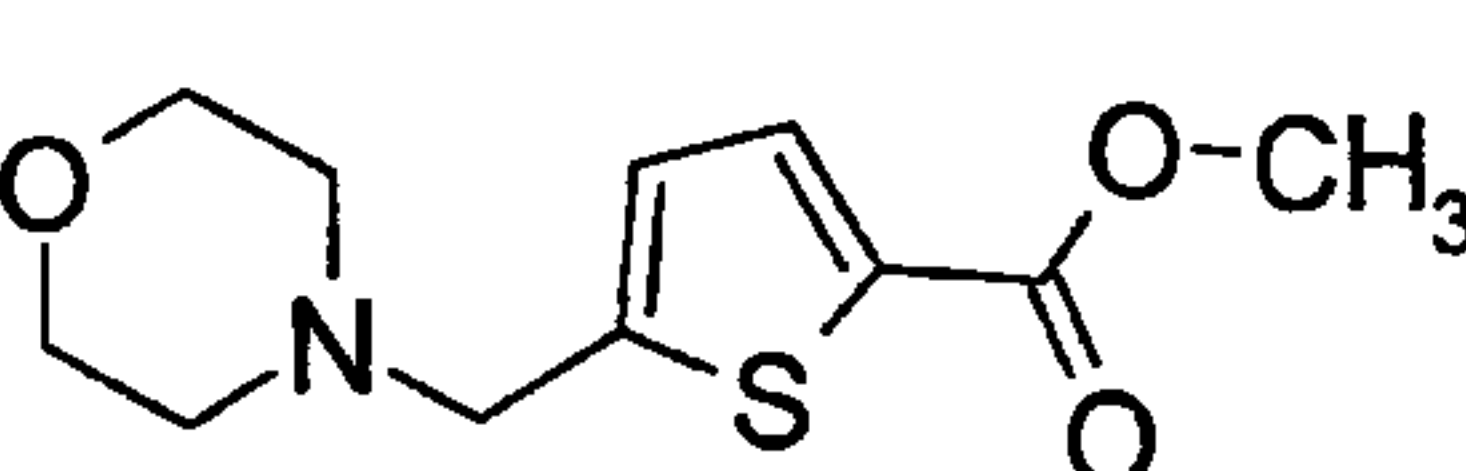
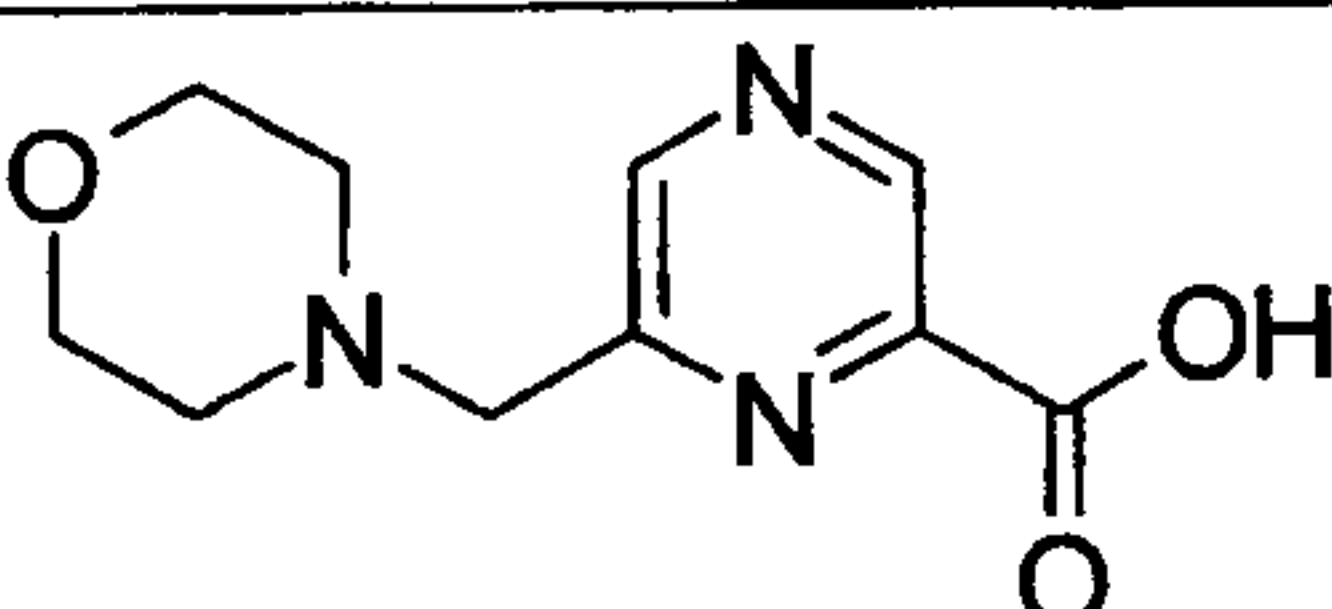
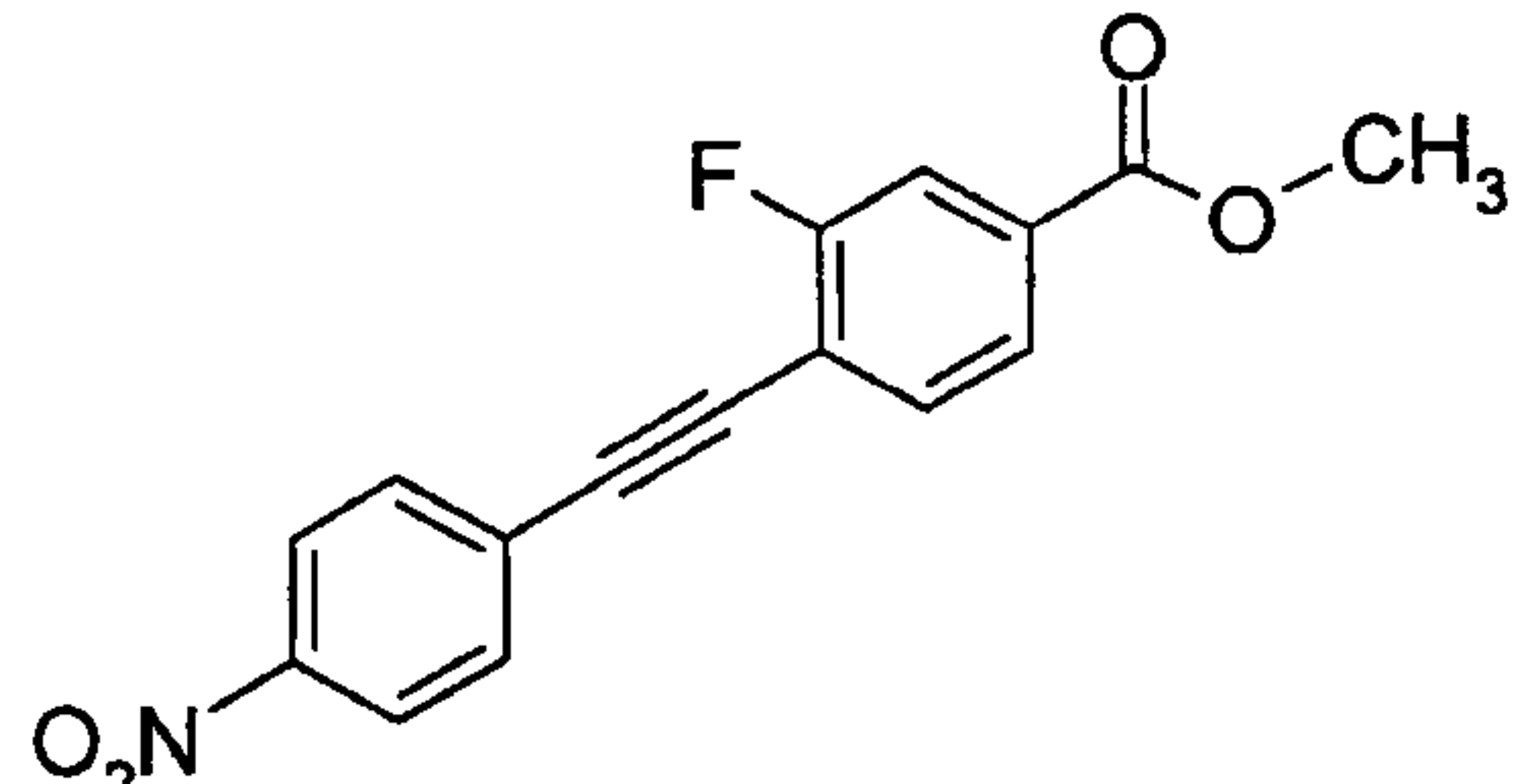
[0186]
[Table 41]

Pr	Str	Pr	Str
249		254	
250		255	
251		256	
252		257	
253		258	
		259	

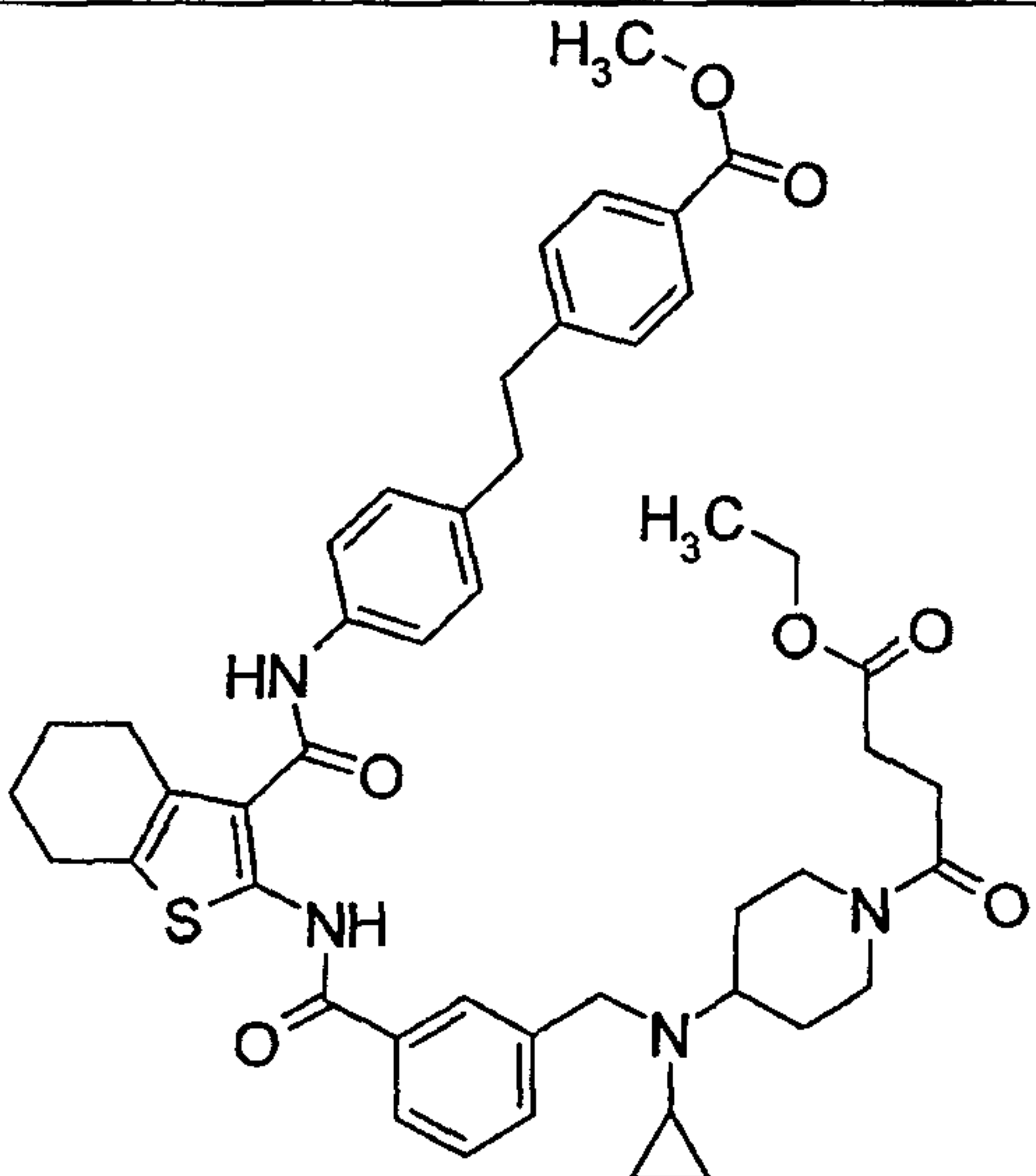
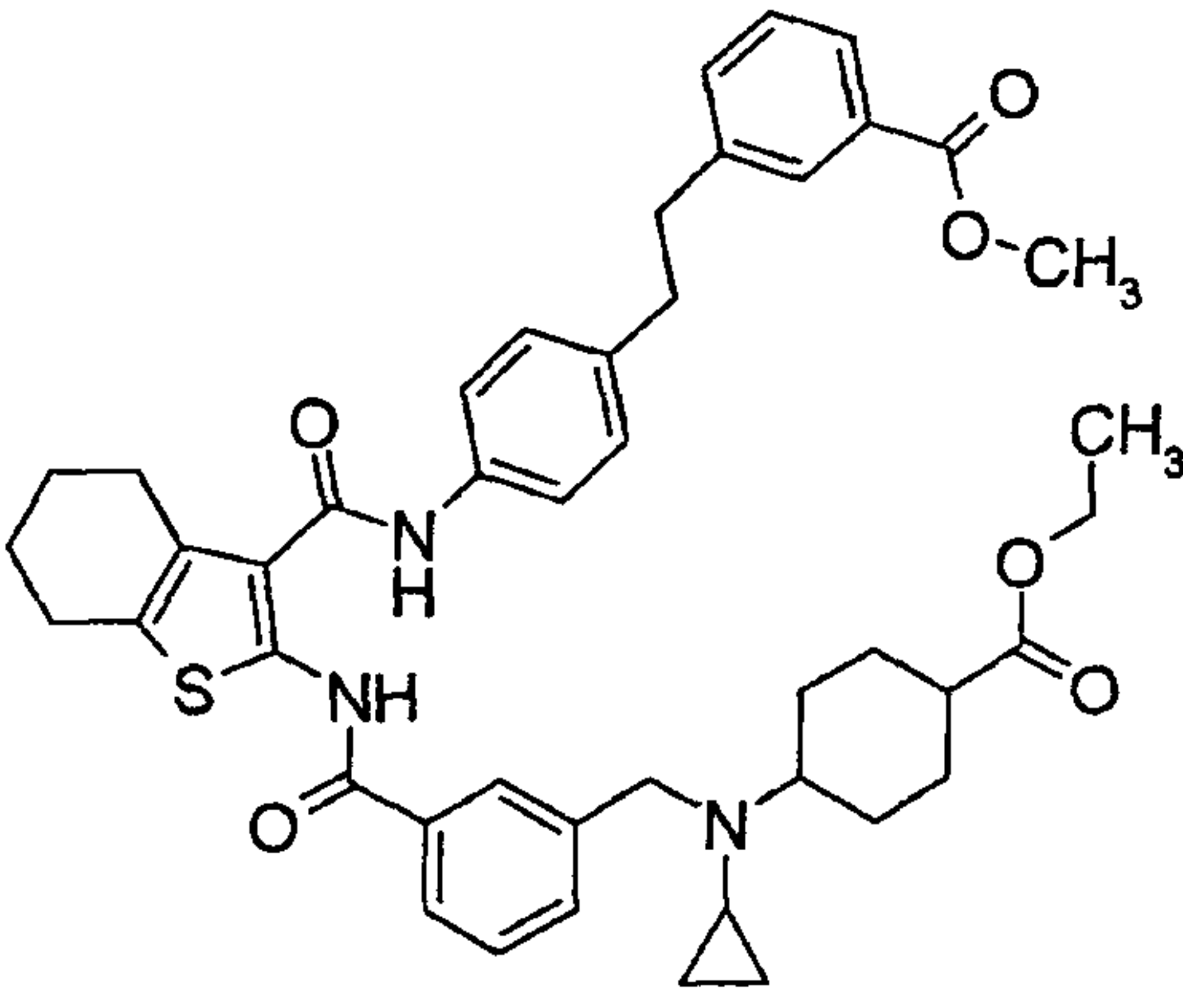
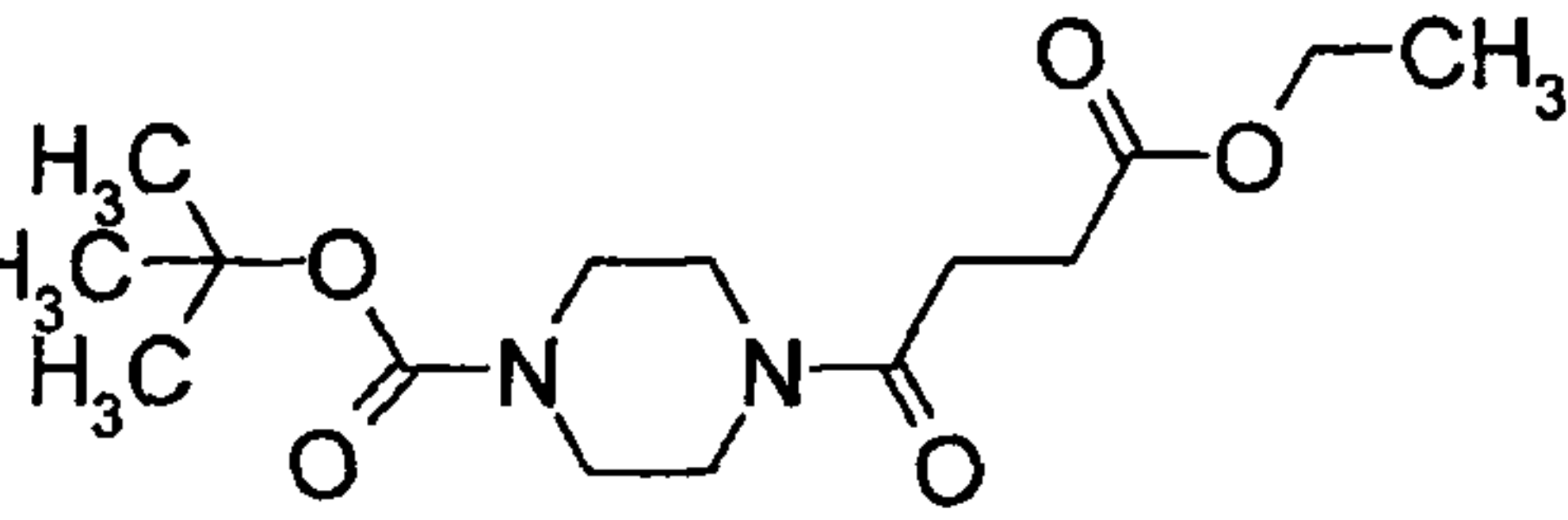
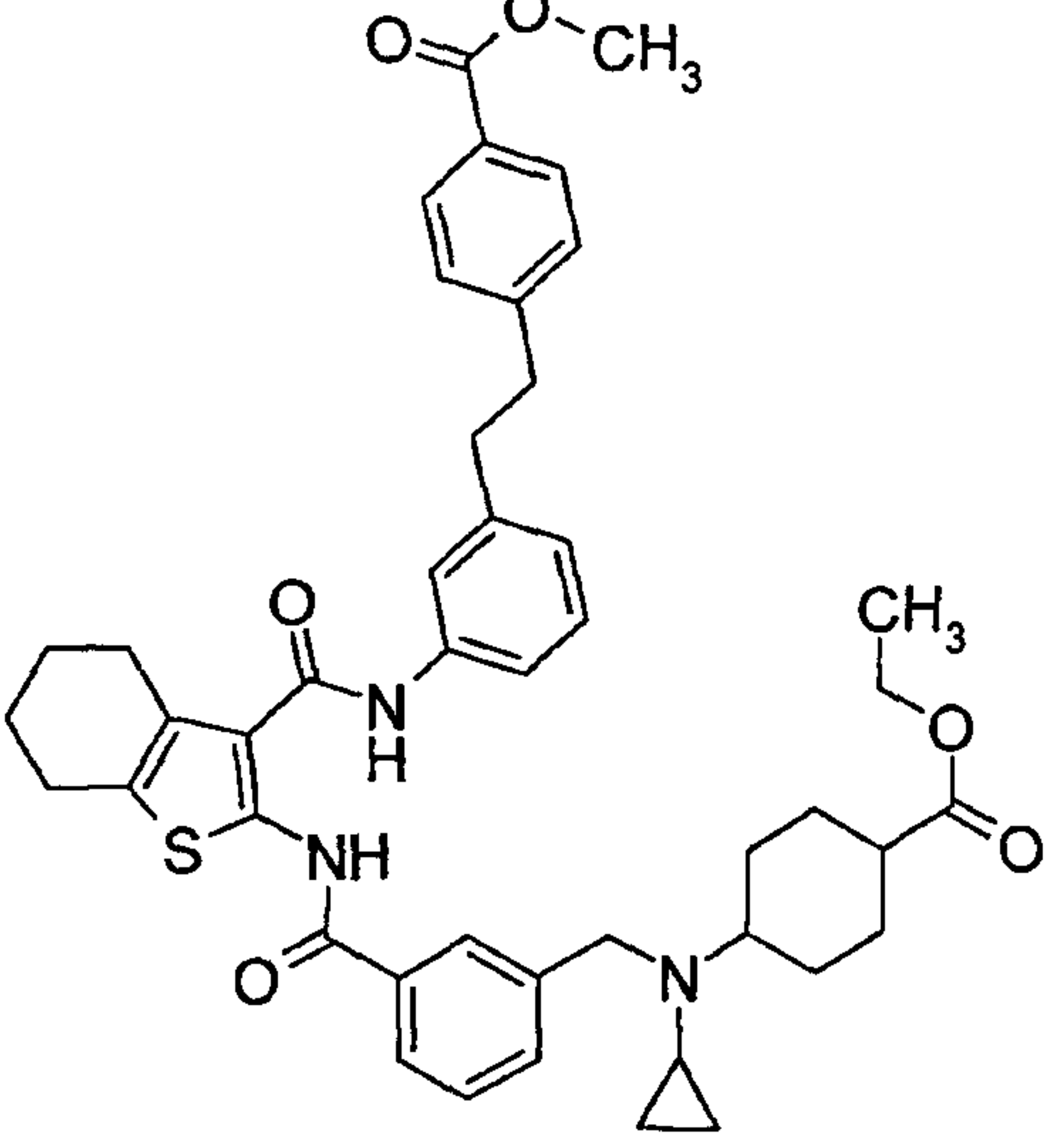
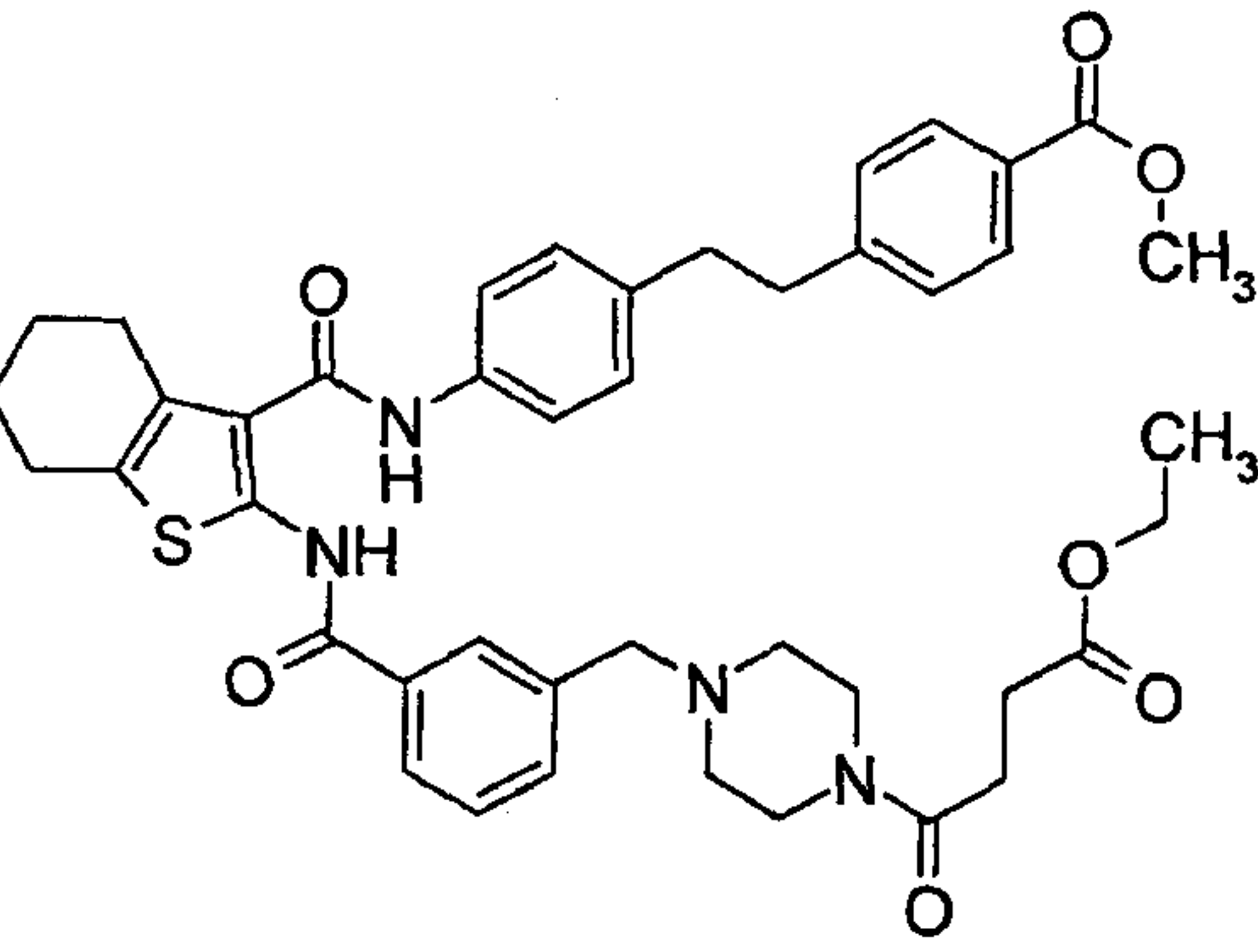
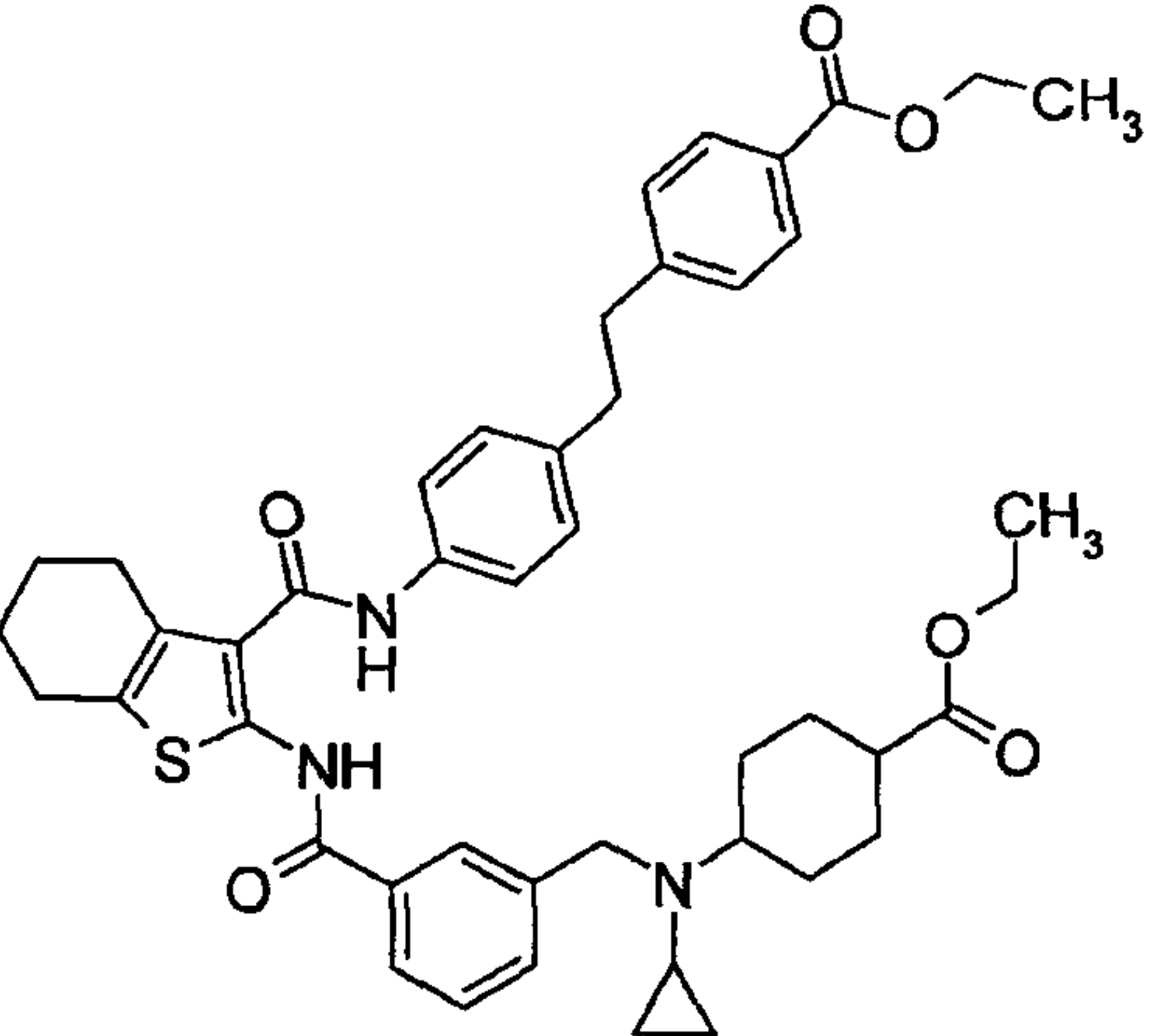
[0187]
[Table 42]

Pr	Str	Pr	Str
260		265	
261		266	
262		267	
263			
264			

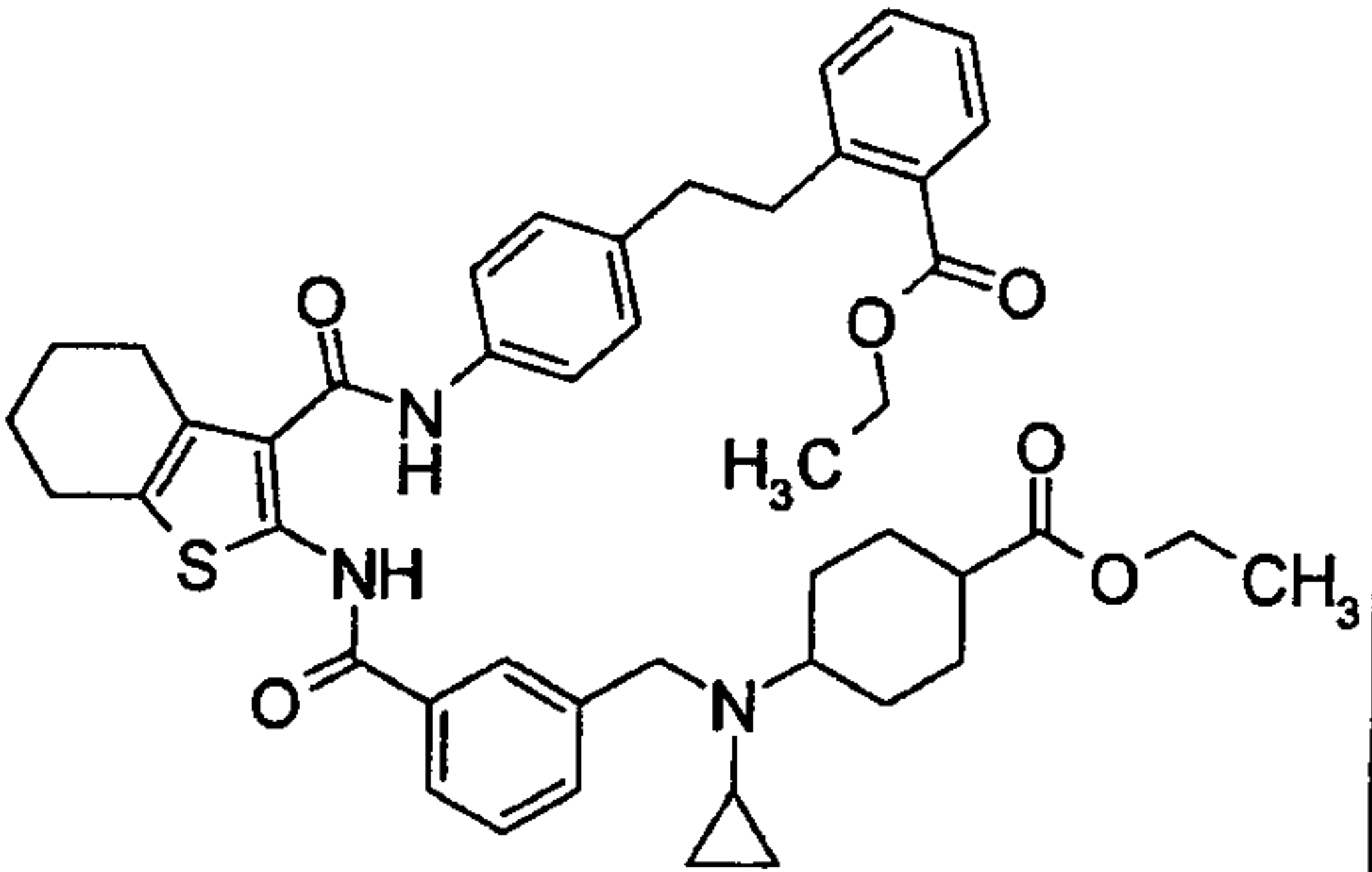
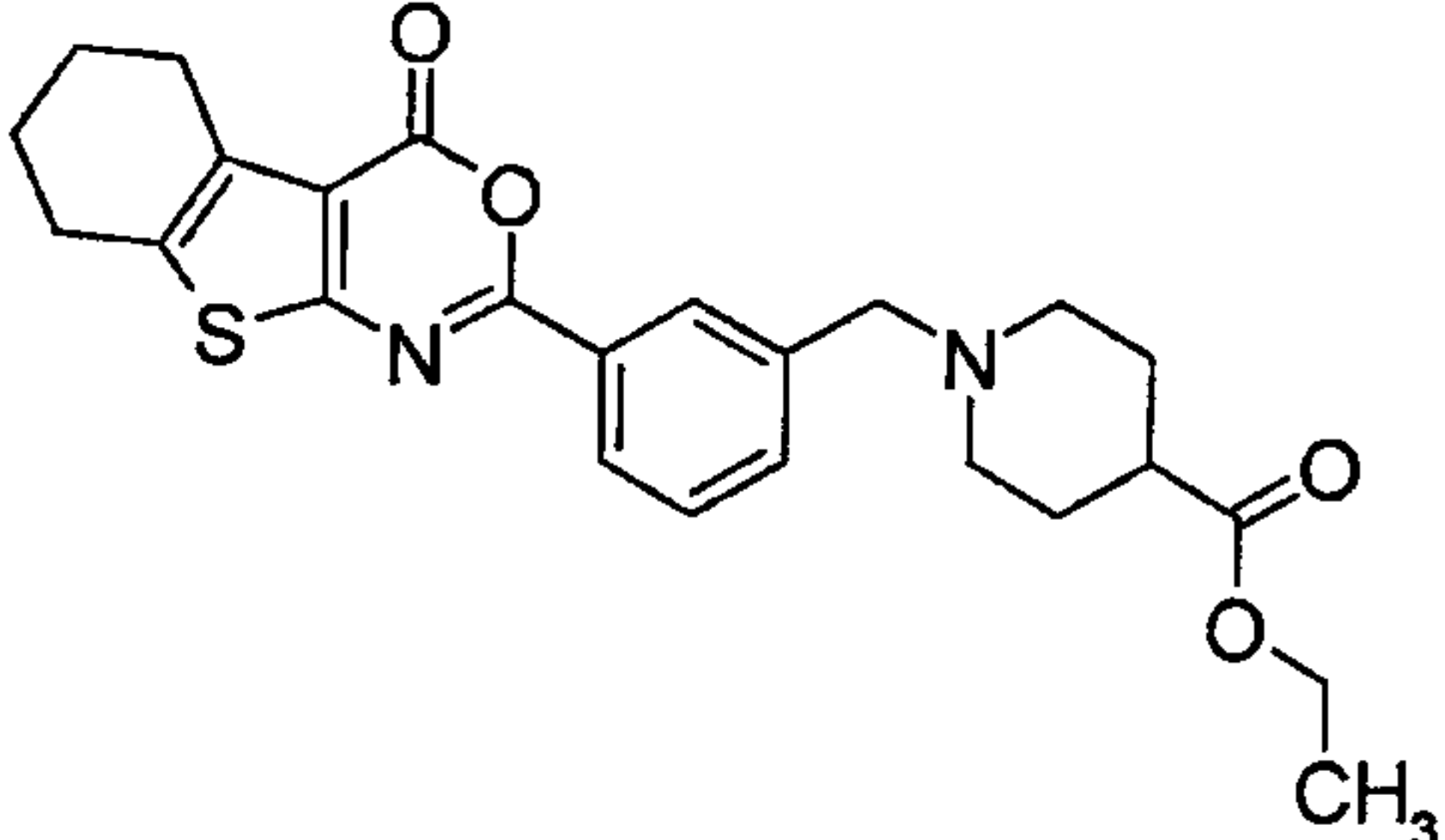
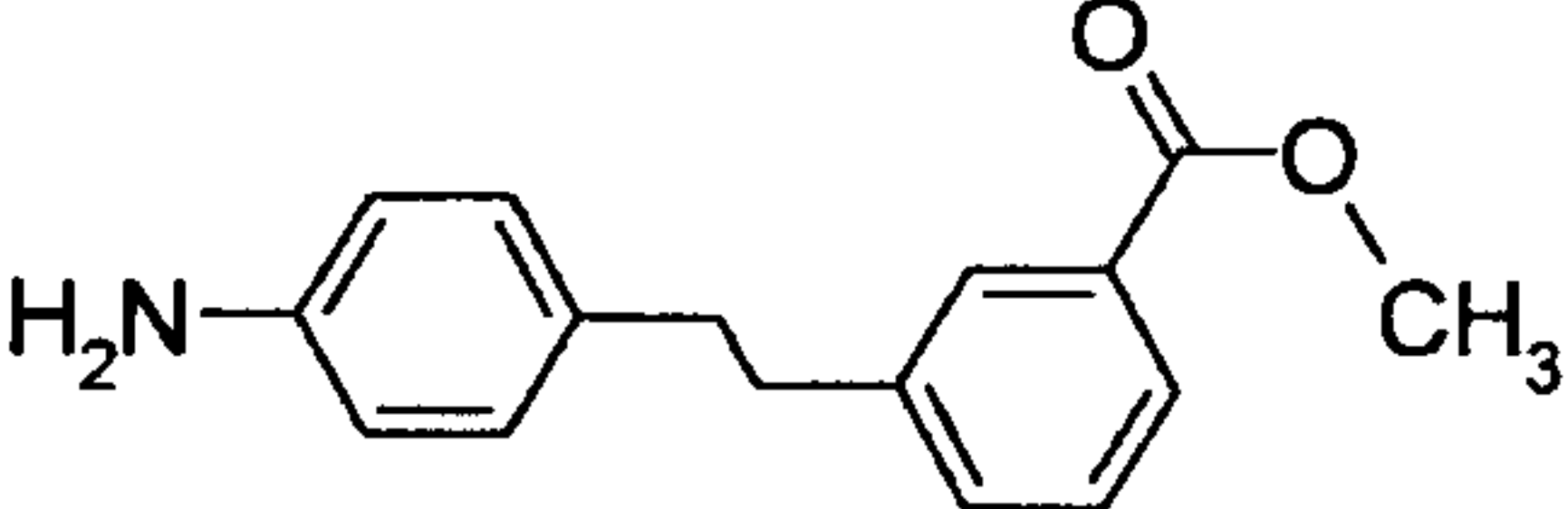
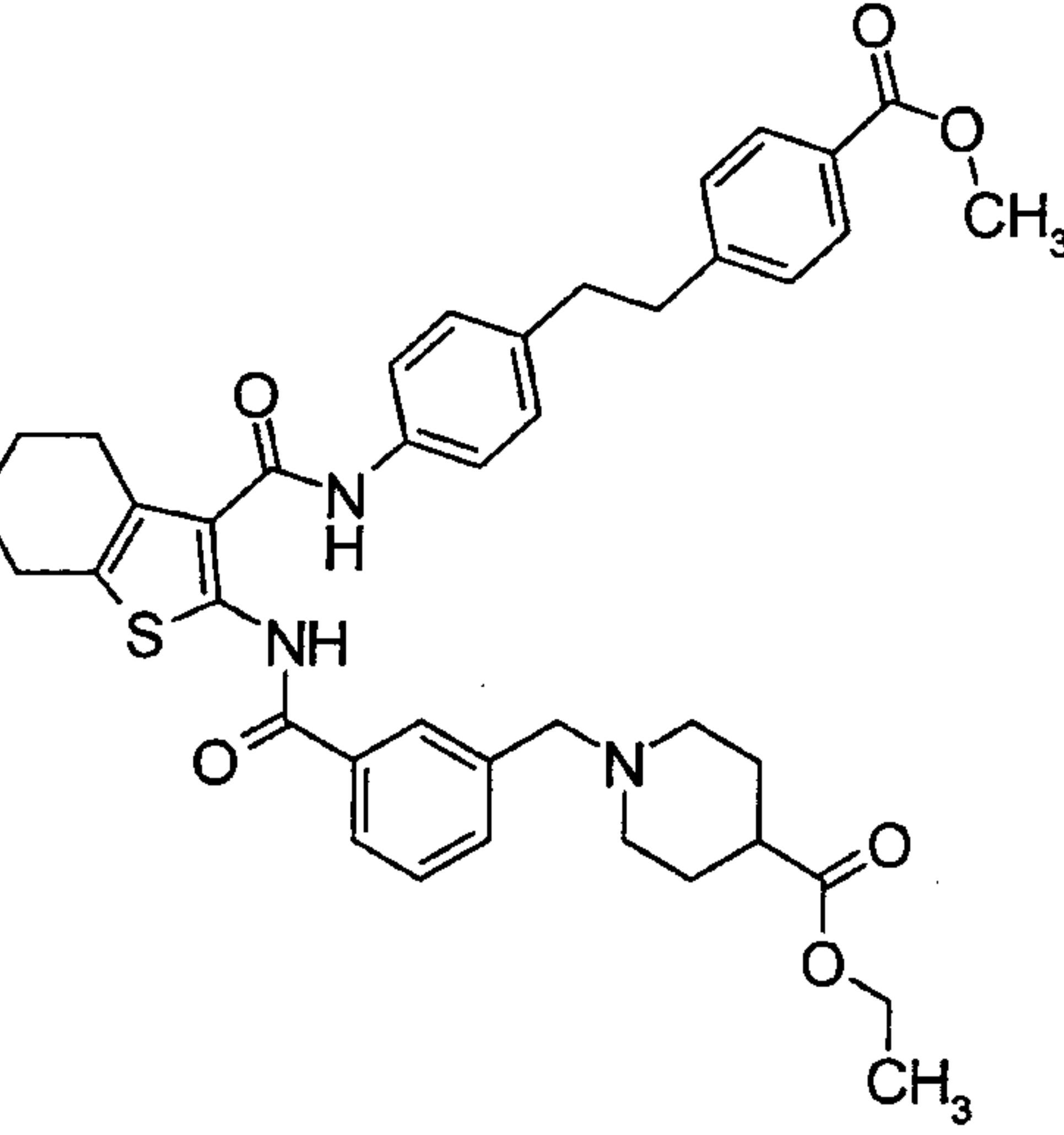
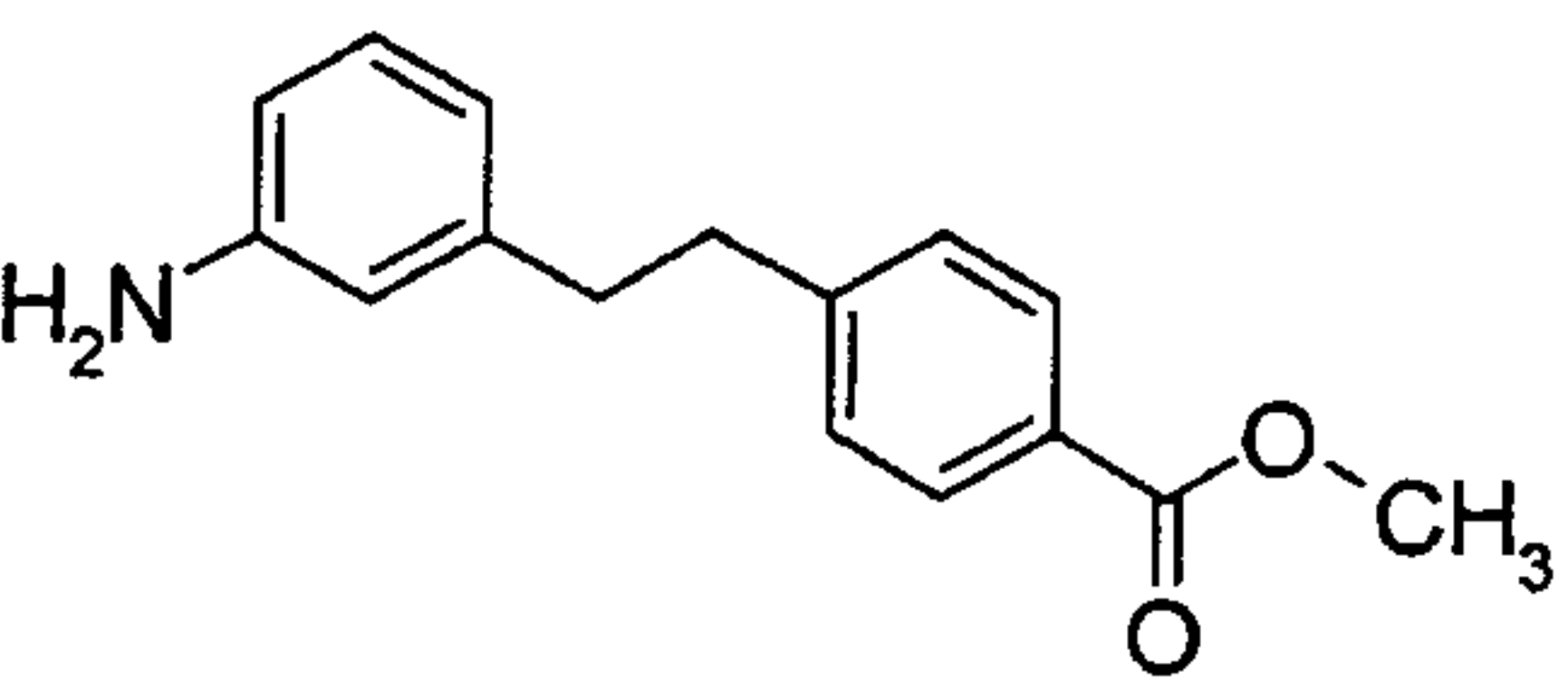
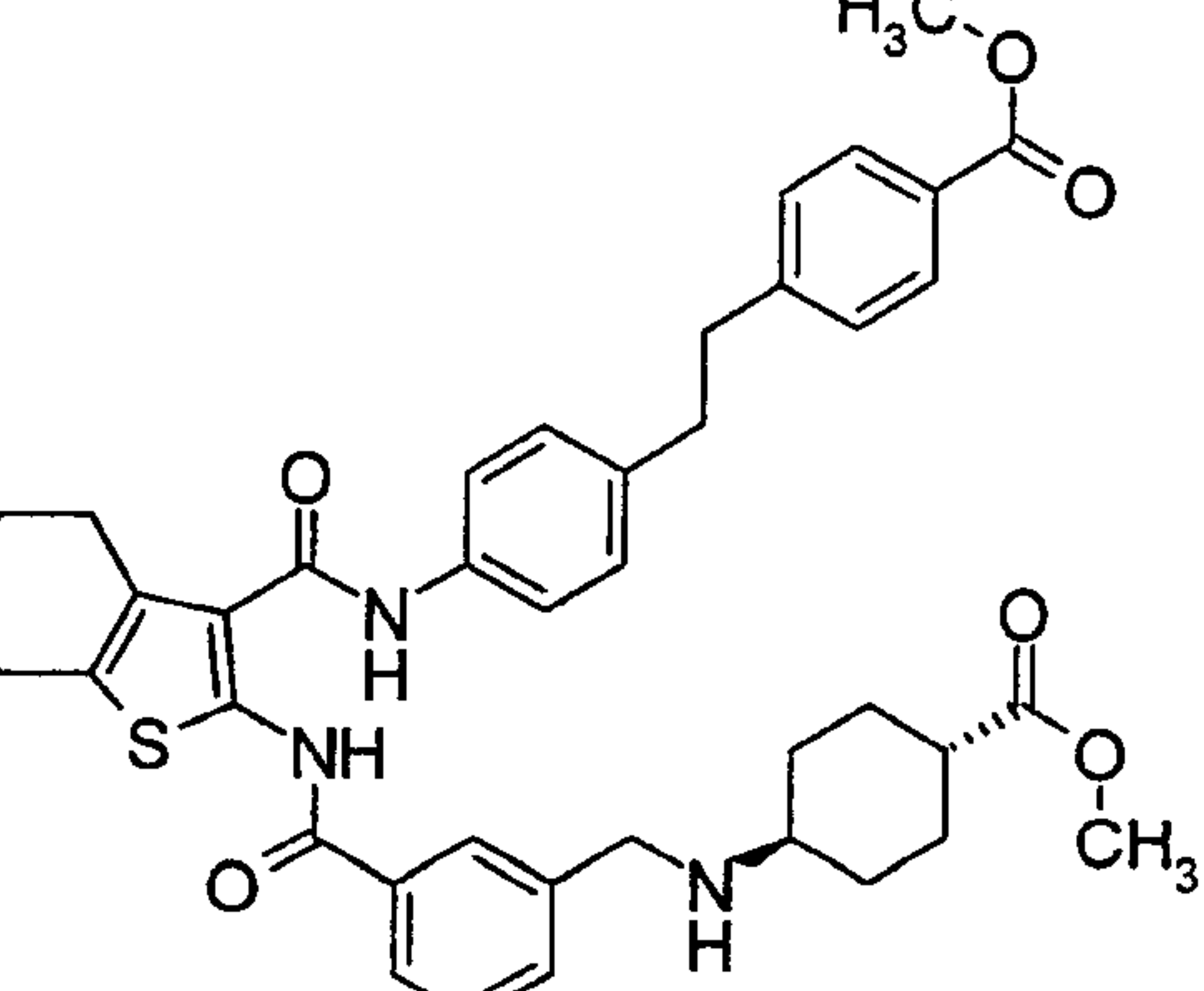
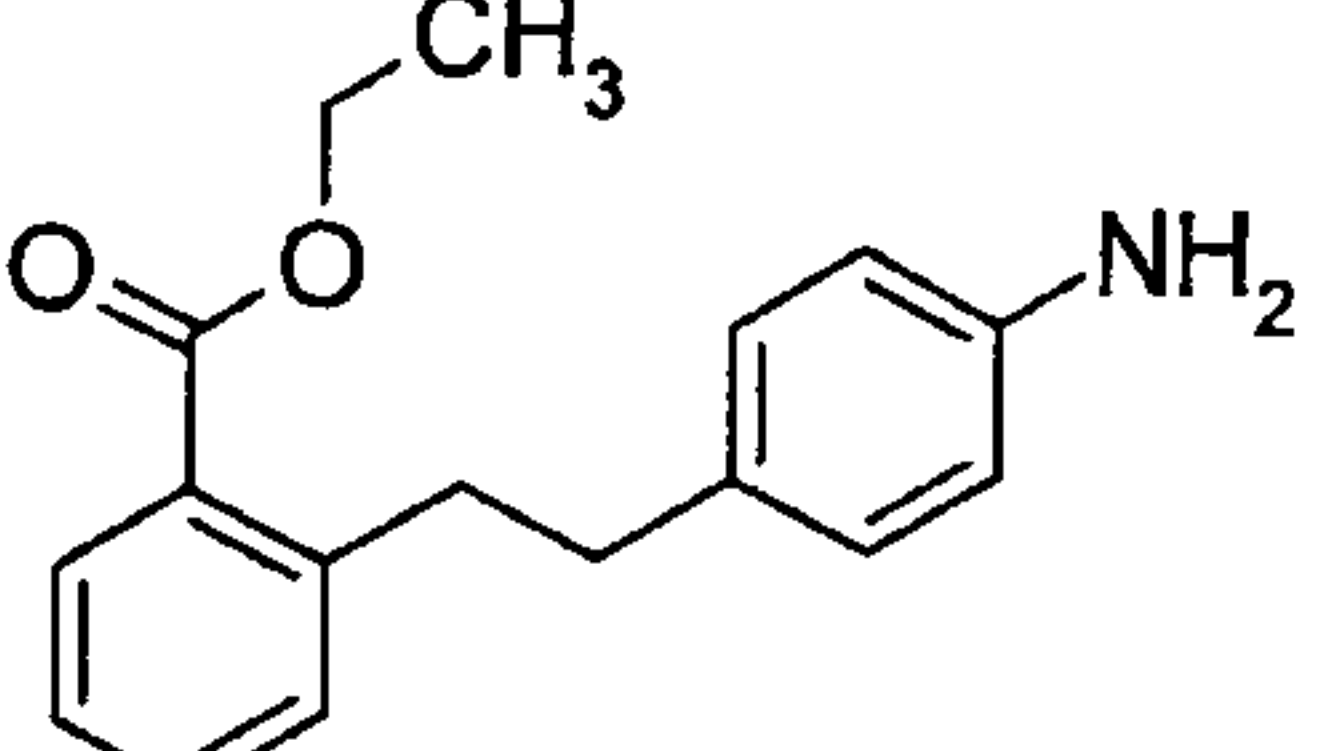
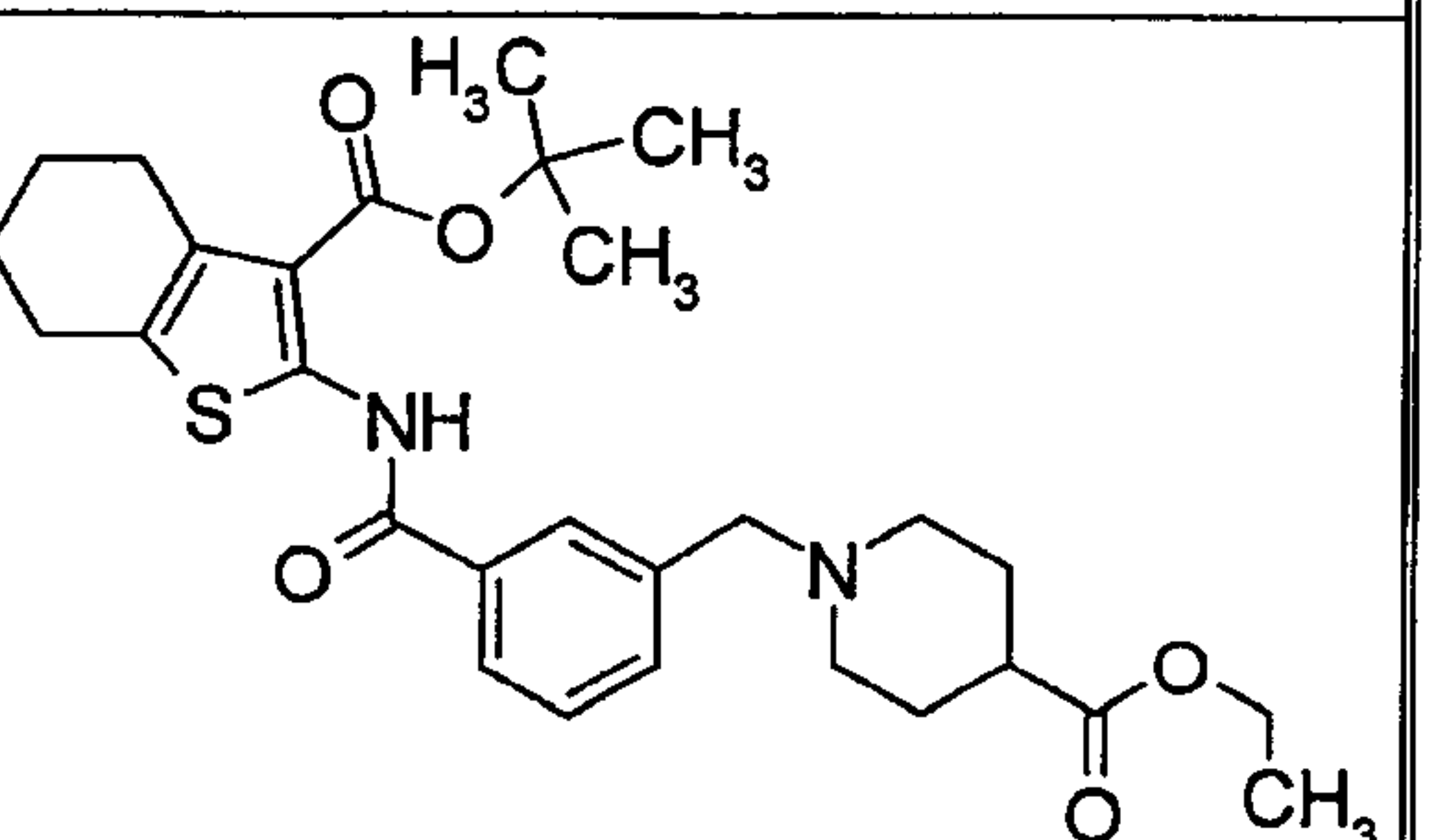
[0188]
[Table 43]

Pr	Str	Pr	Str
268		275	
269		276	
270		277	
271			
272			
273			
274			

[0189]
[Table 44]

Pr	Str	Pr	Str
278		282	
279		283	
280			
281			

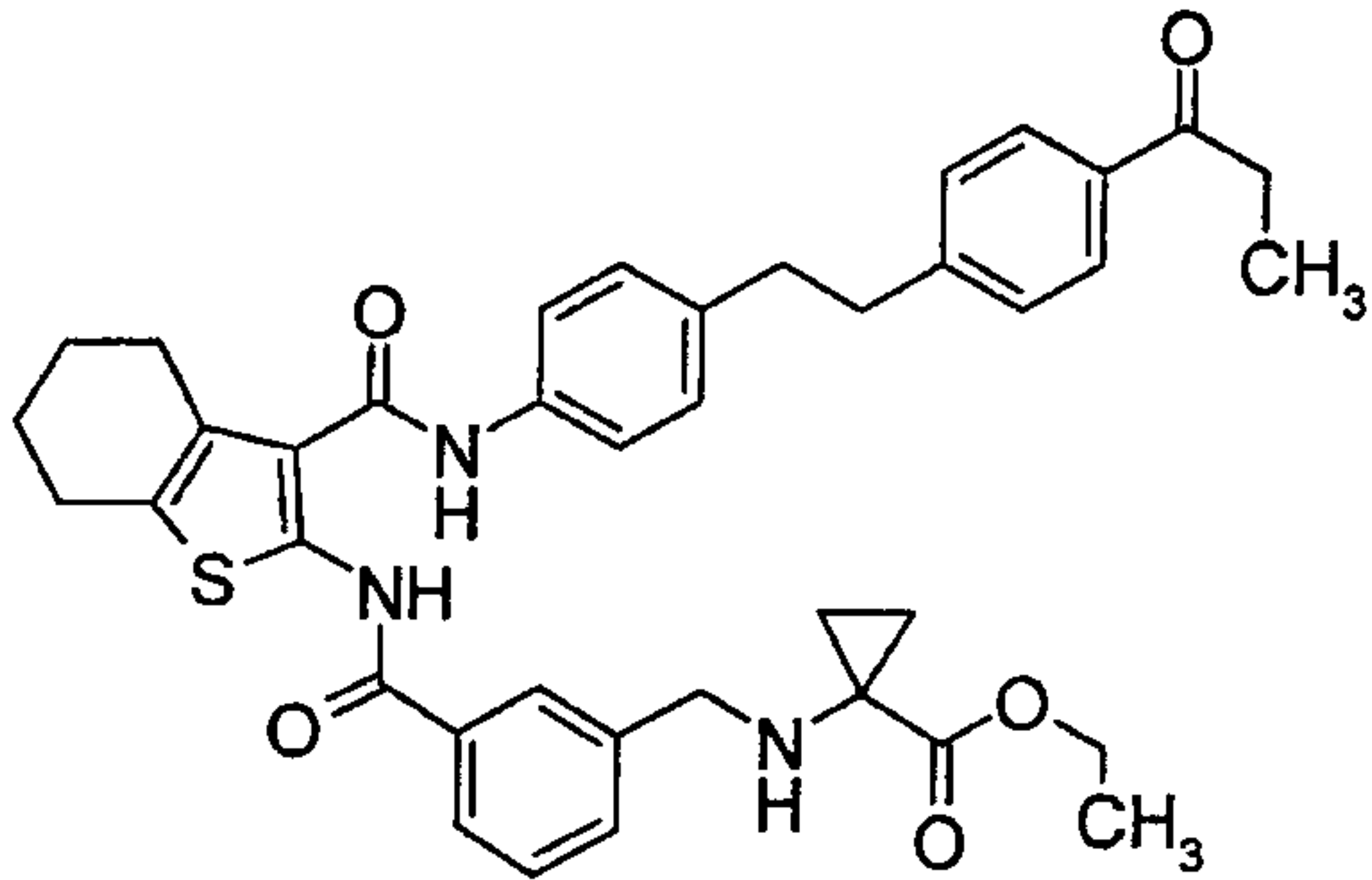
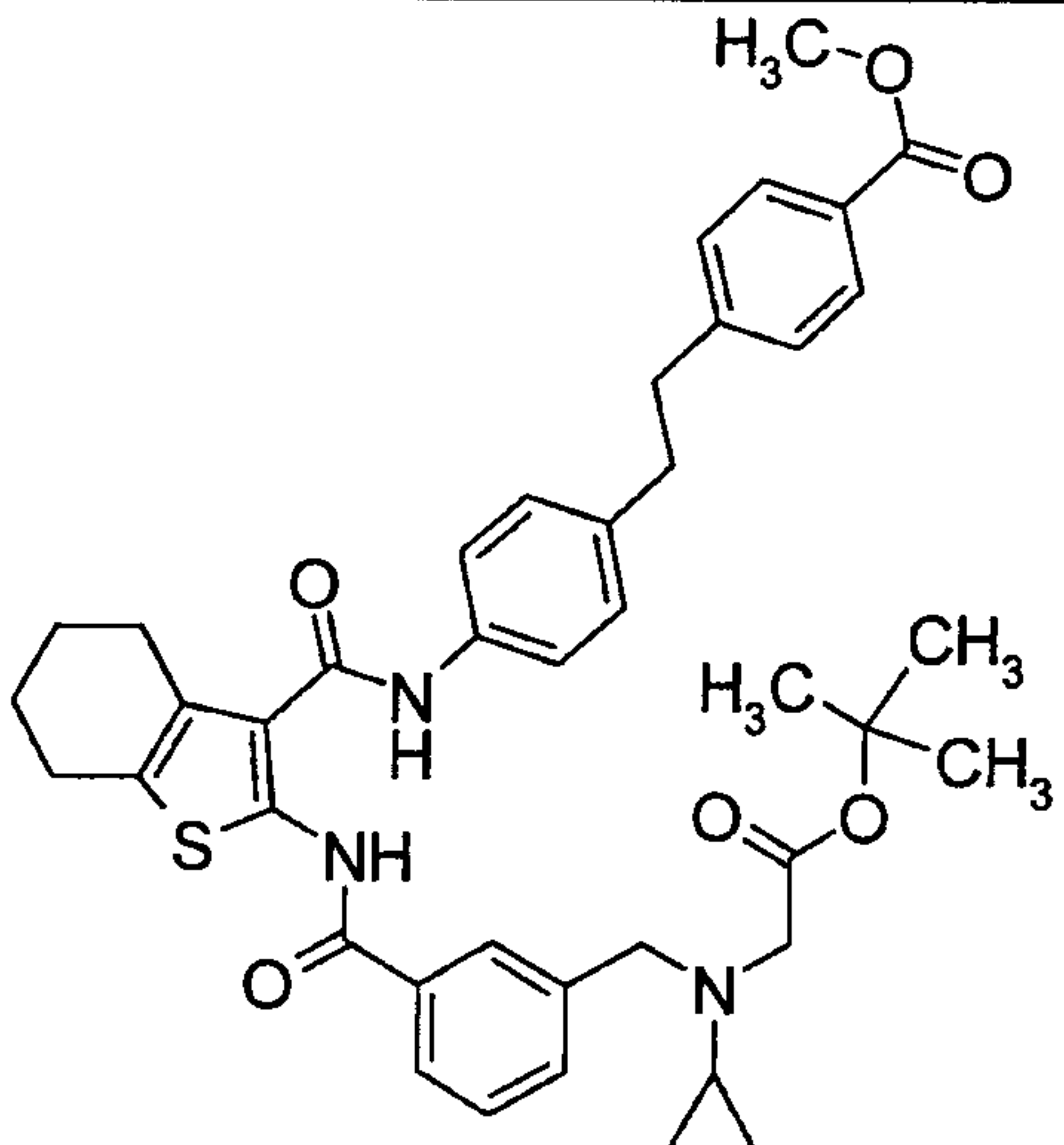
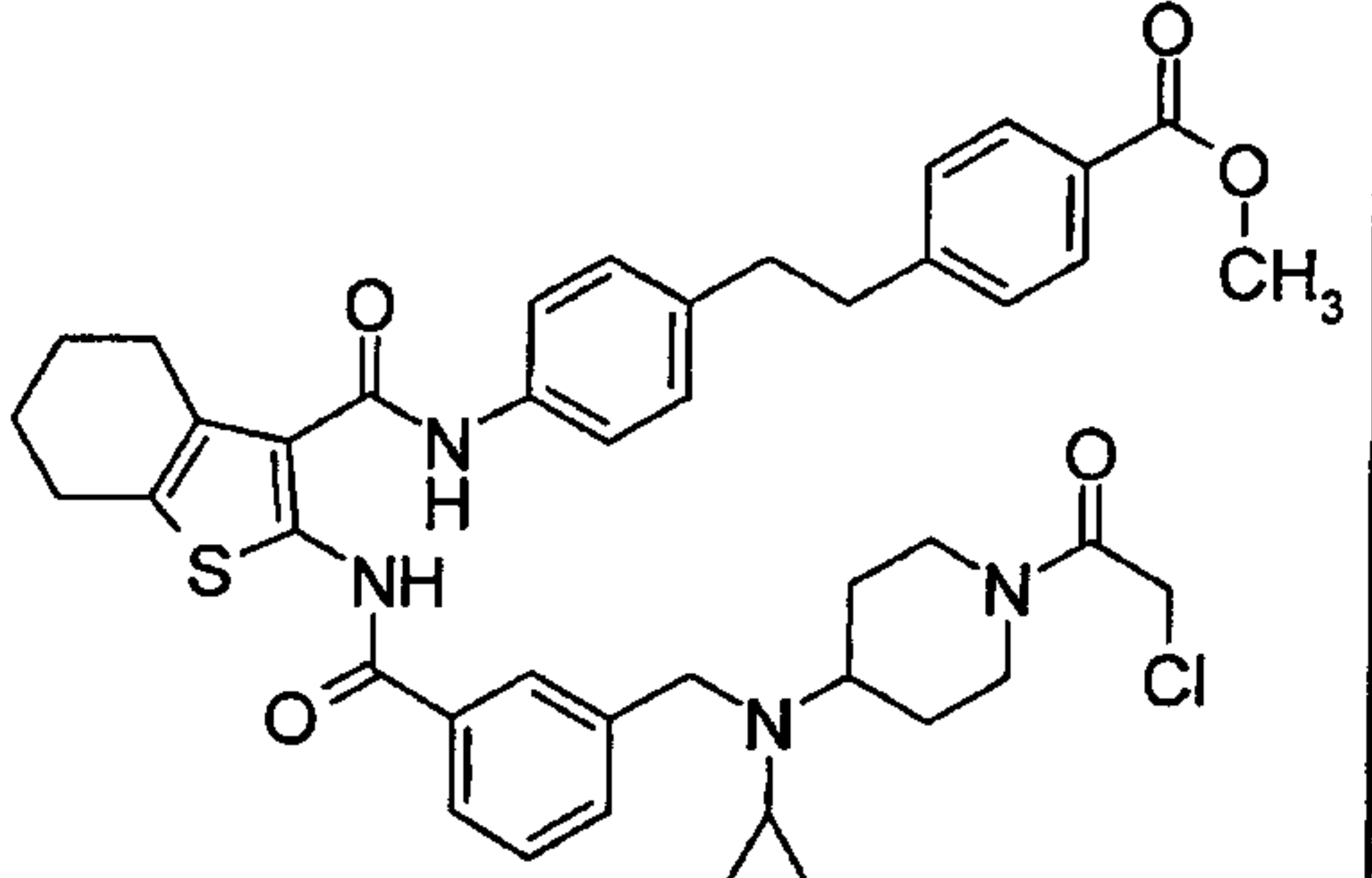
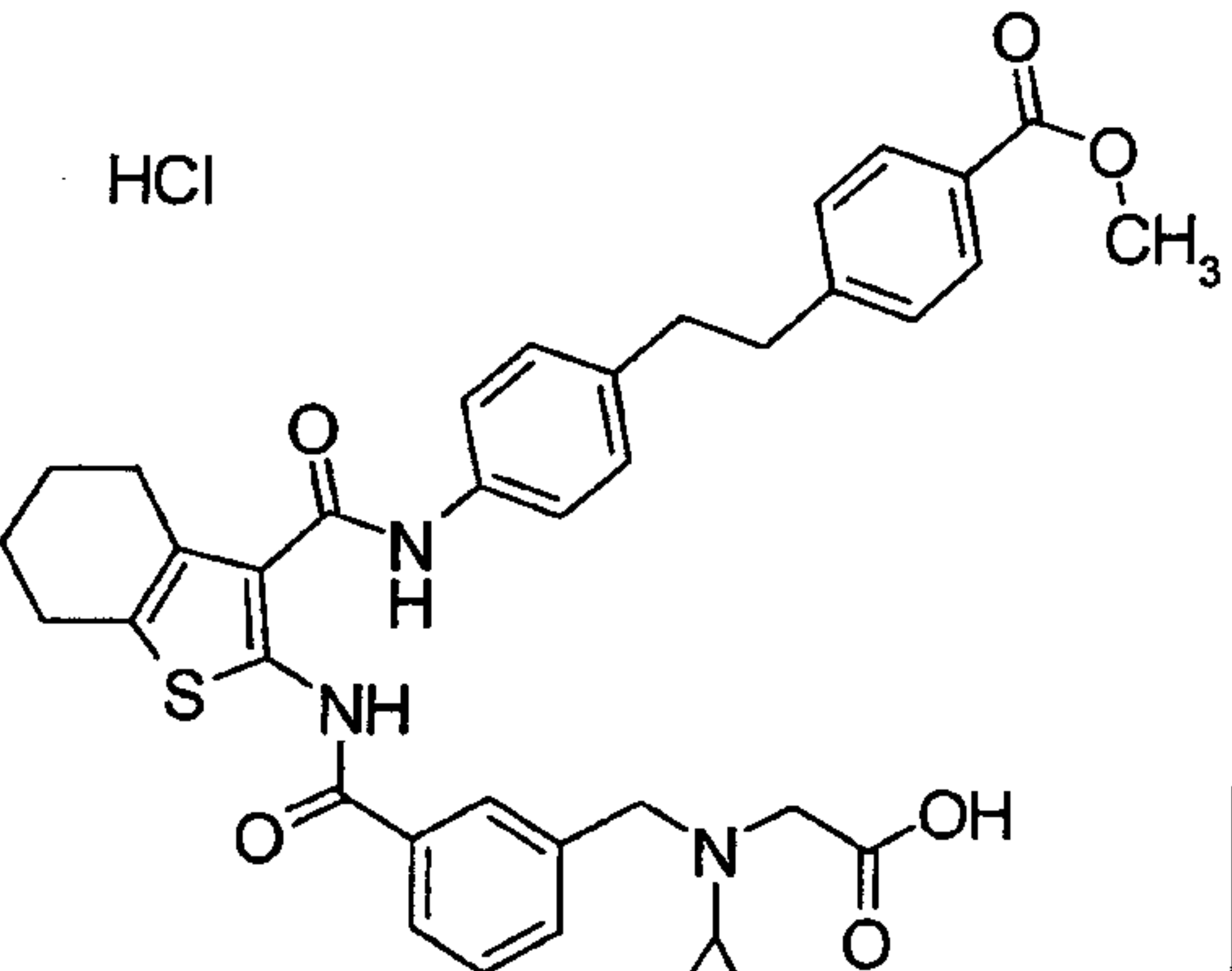
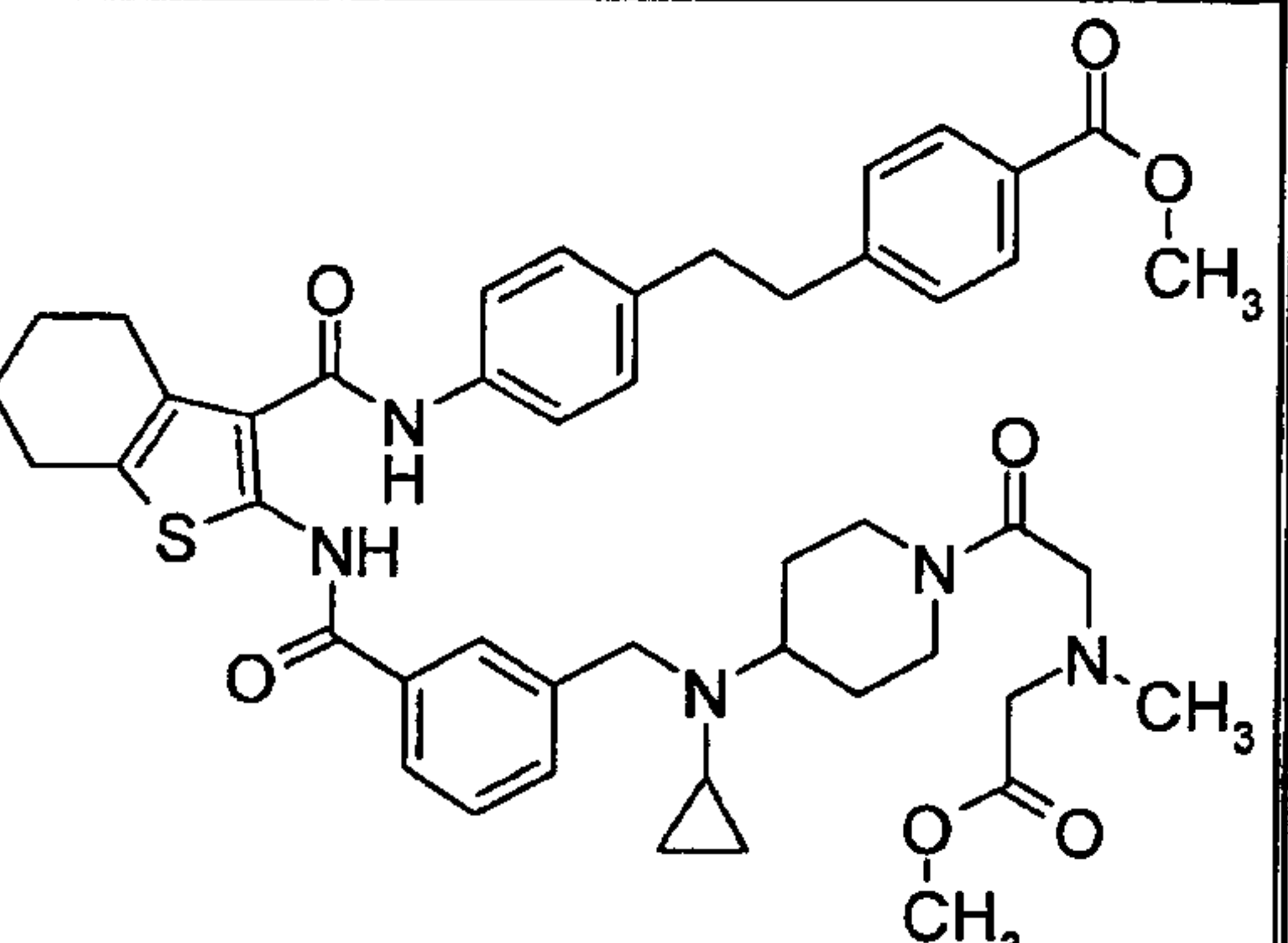
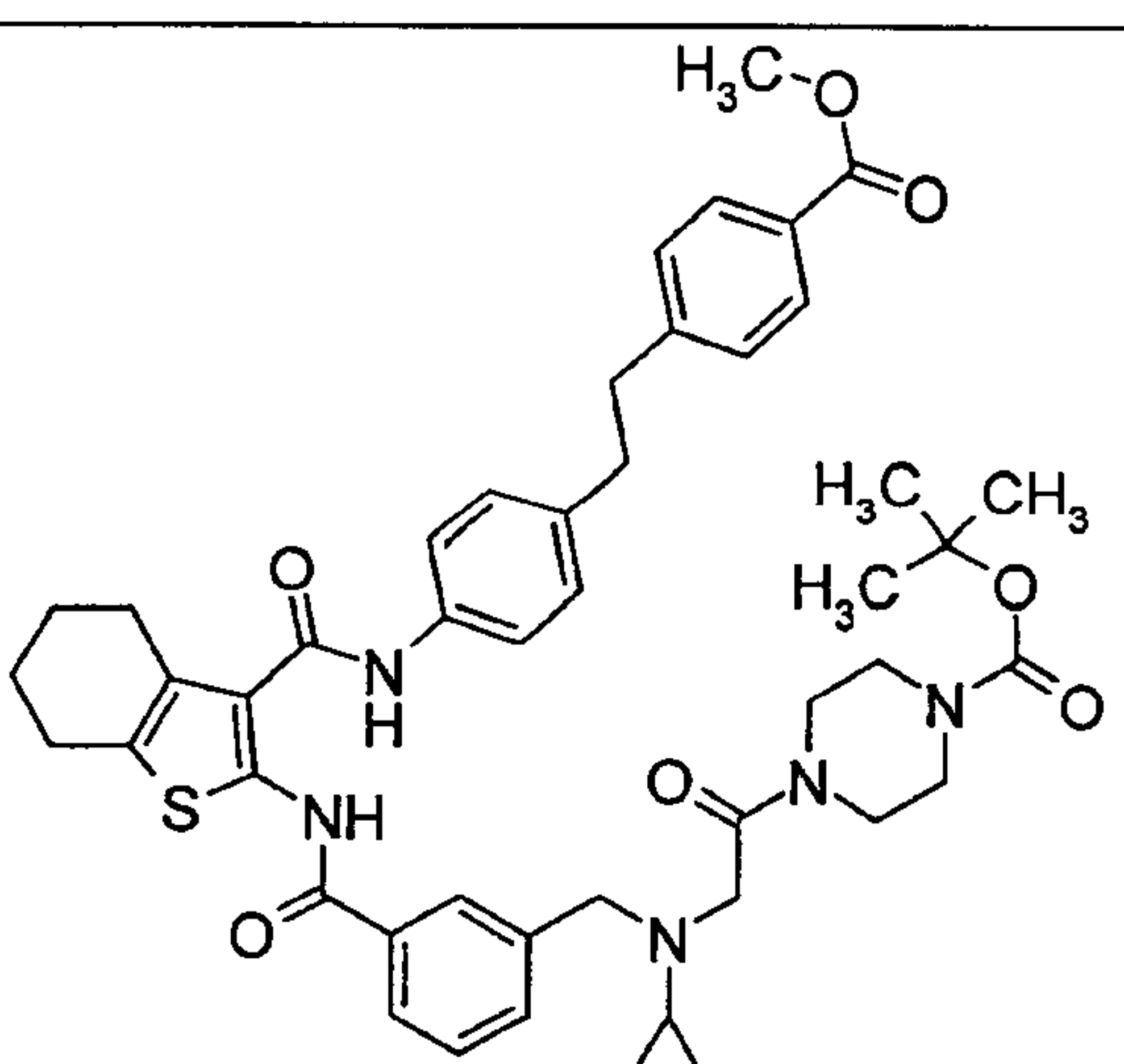
[0190]
[Table 45]

Pr	Str	Pr	Str
284		289	
285		290	
286		291	
287			
288			

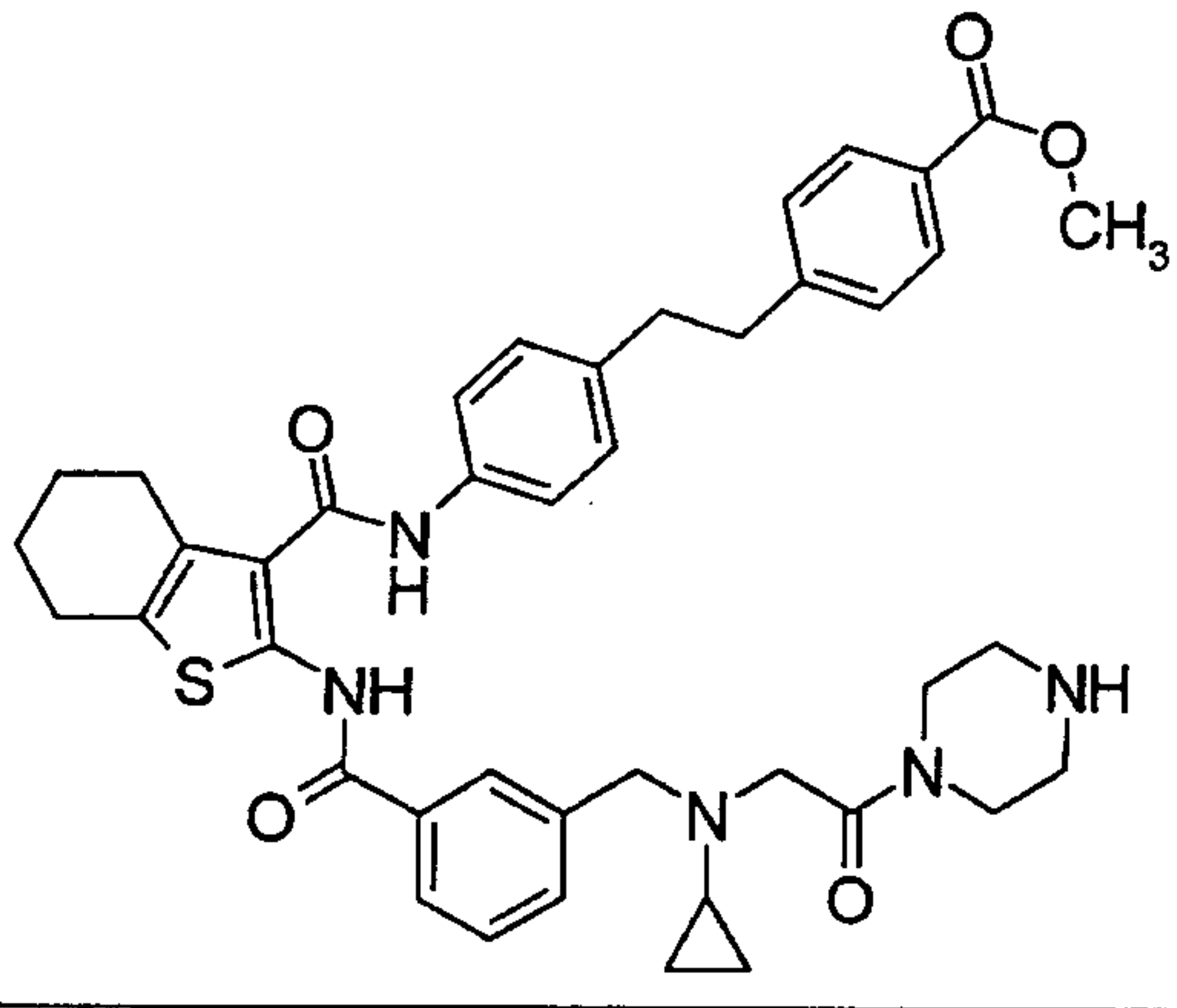
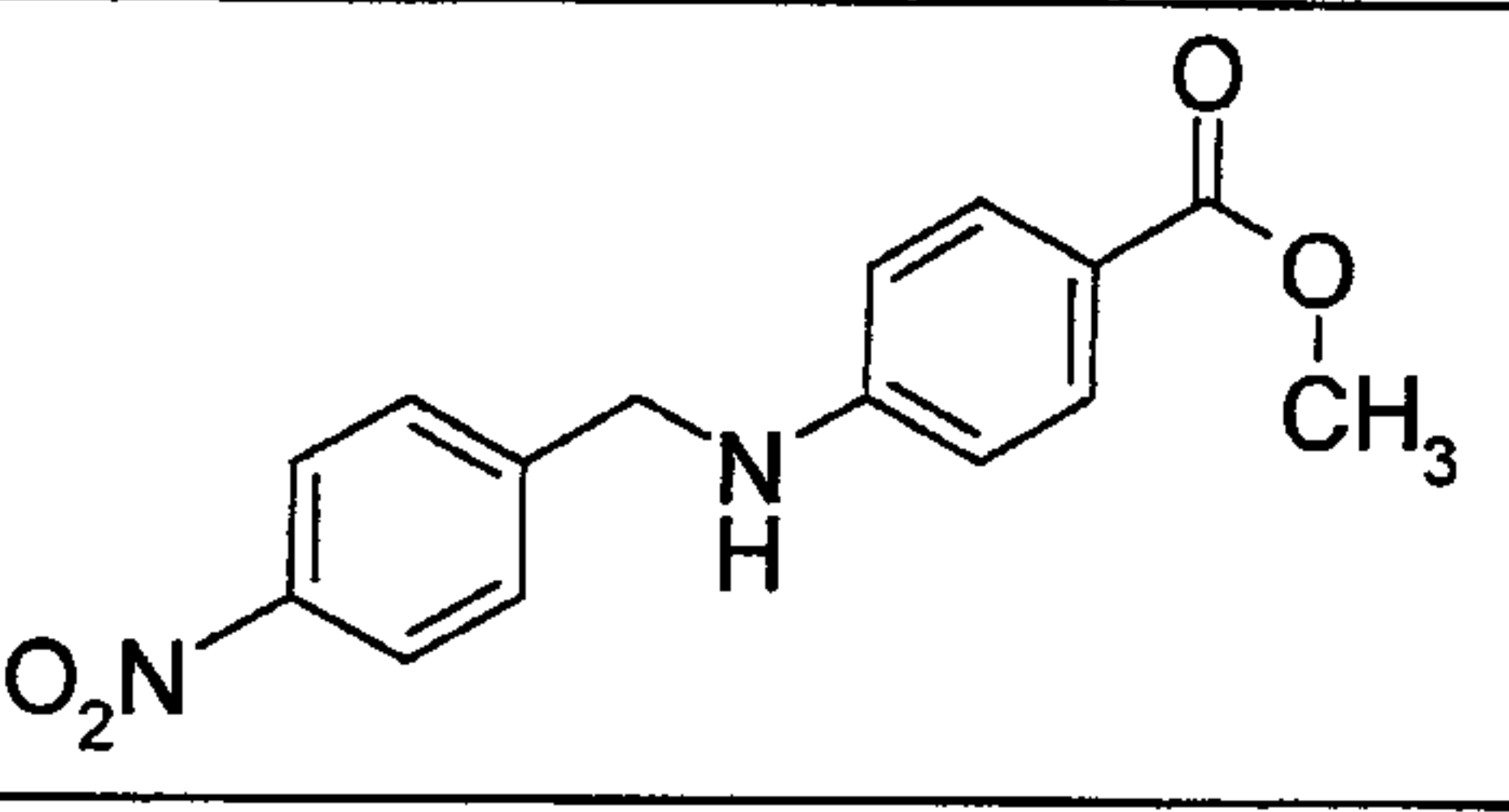
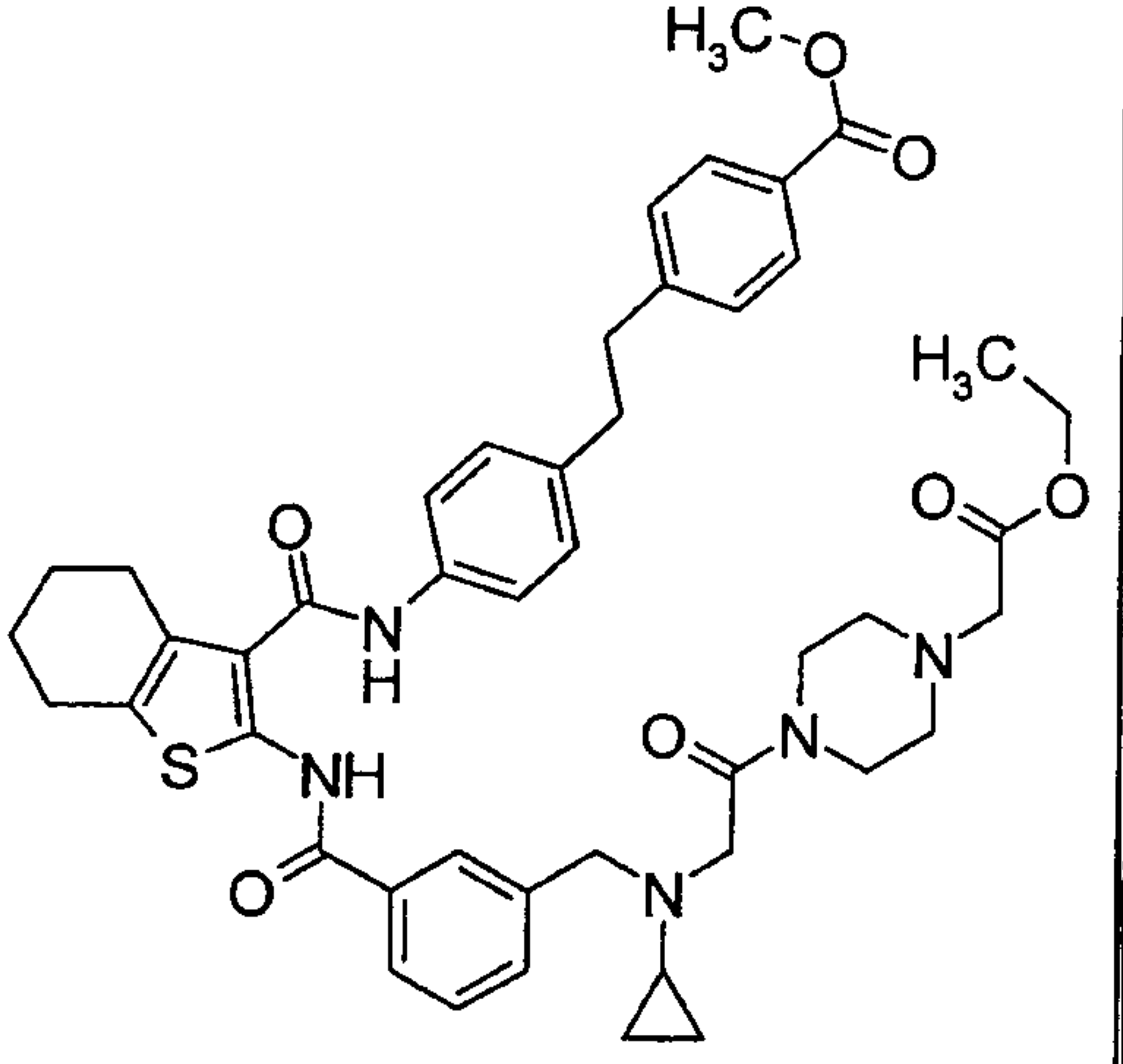
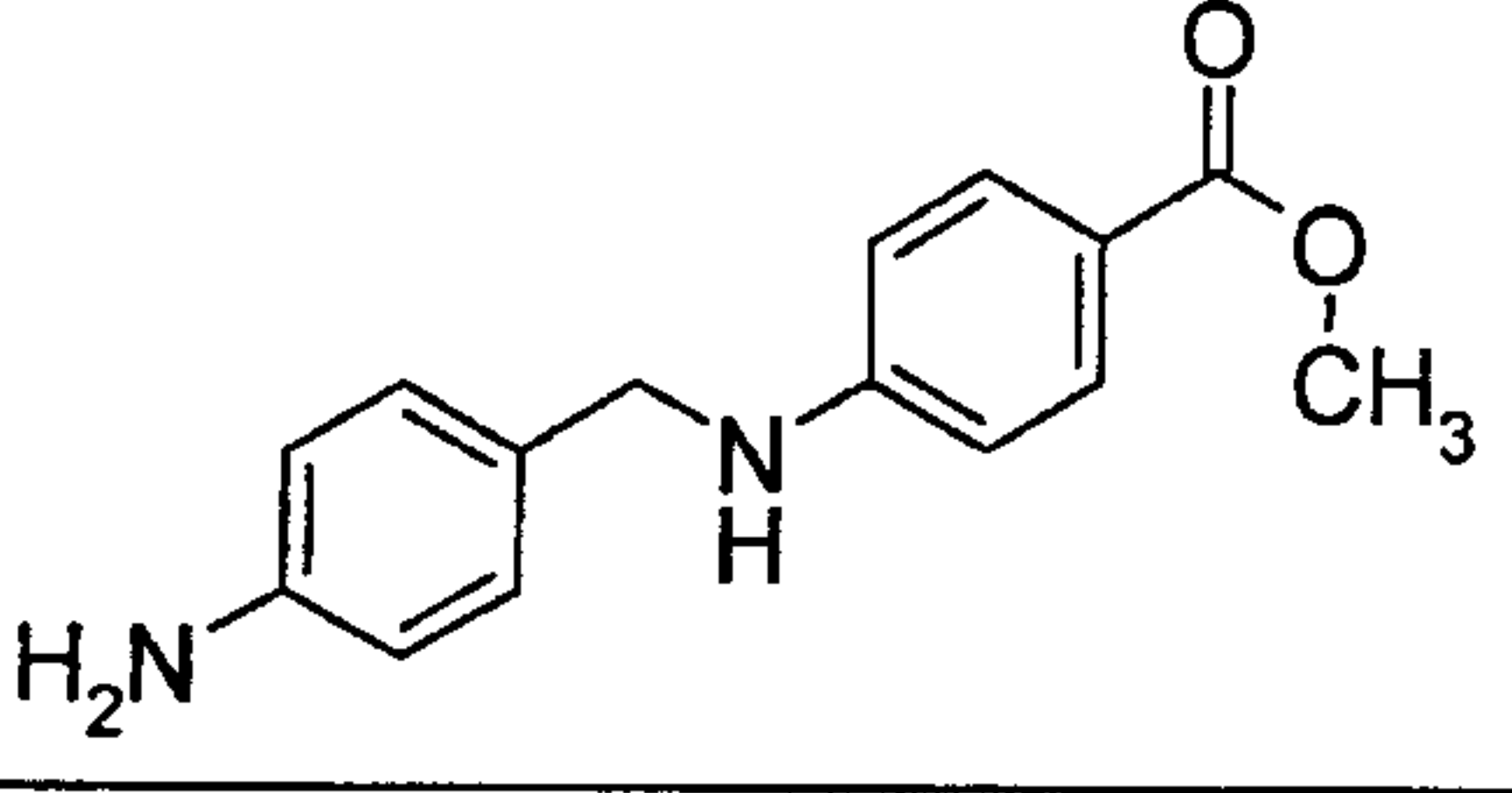
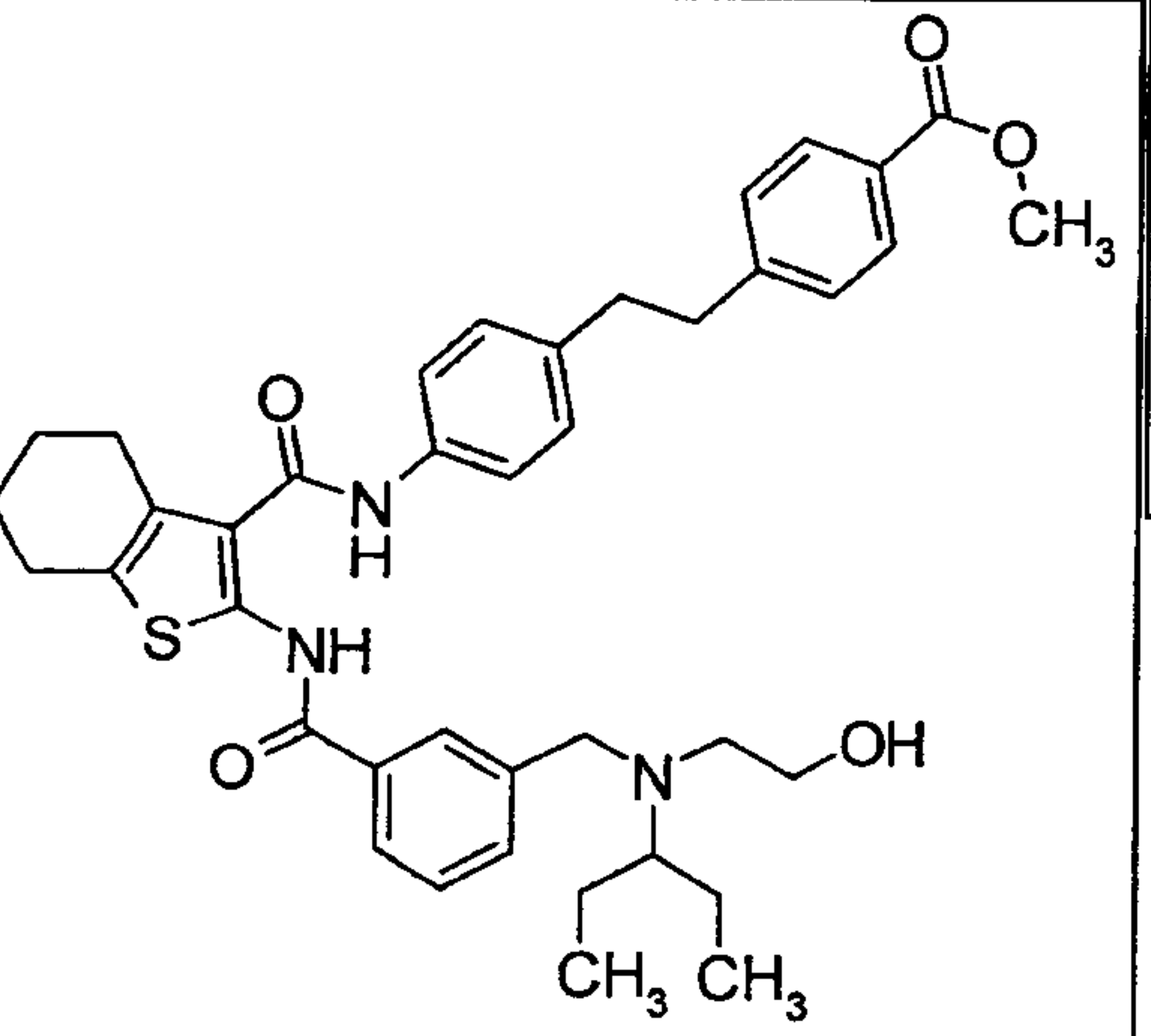
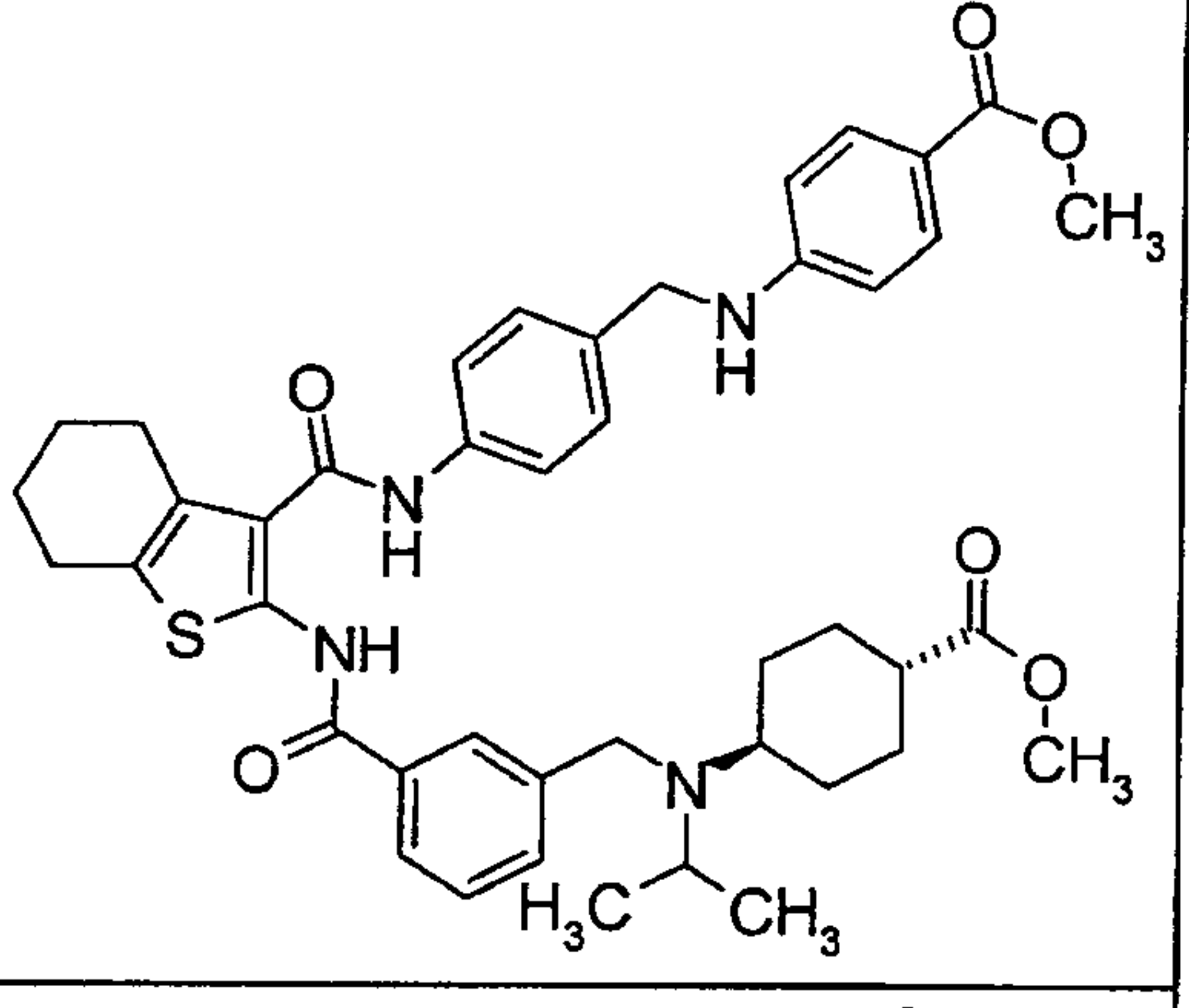
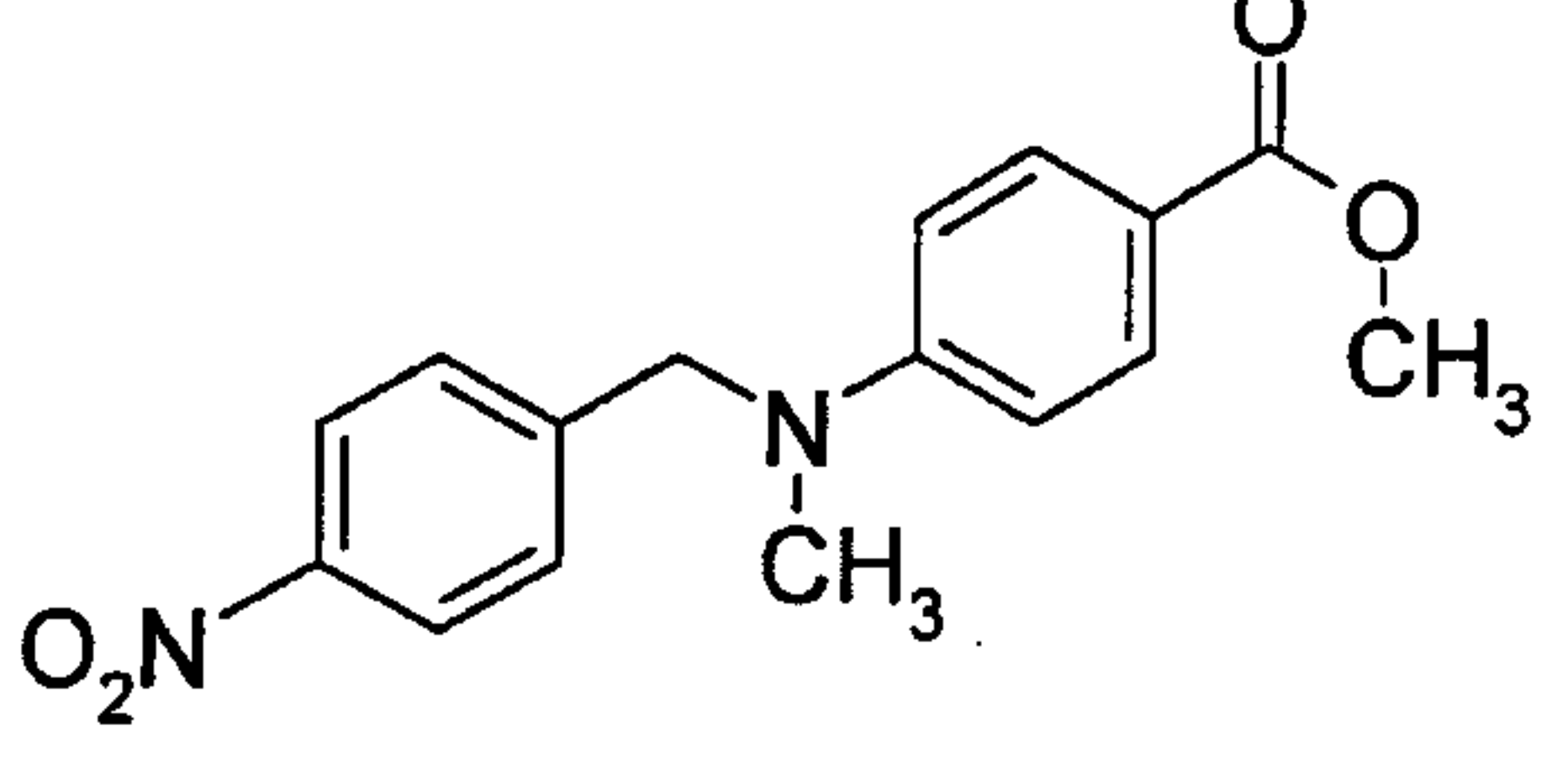
[0191]
[Table 46]

Pr	Str	Pr	Str
292		295	
293		296	
294		297	

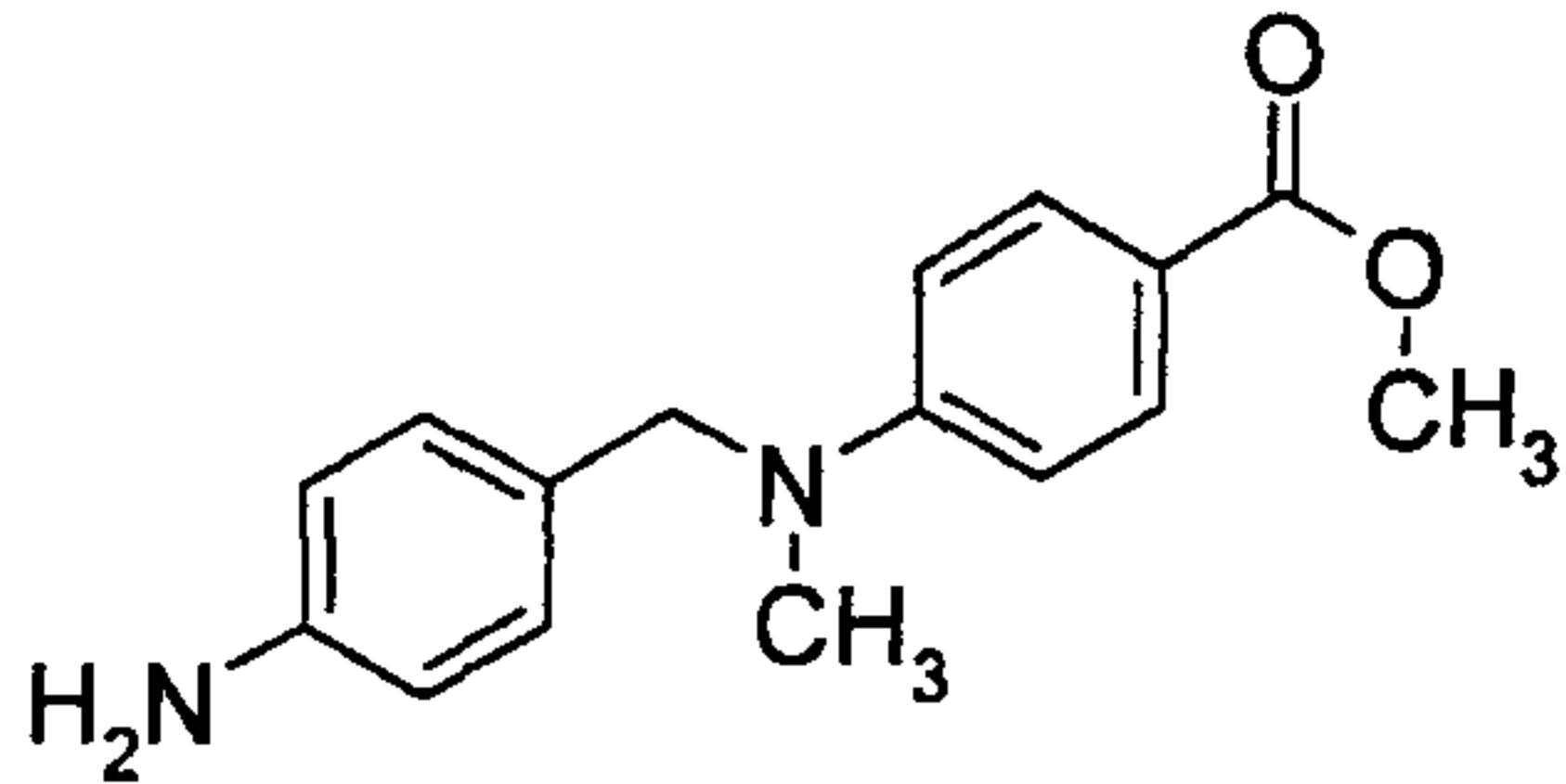
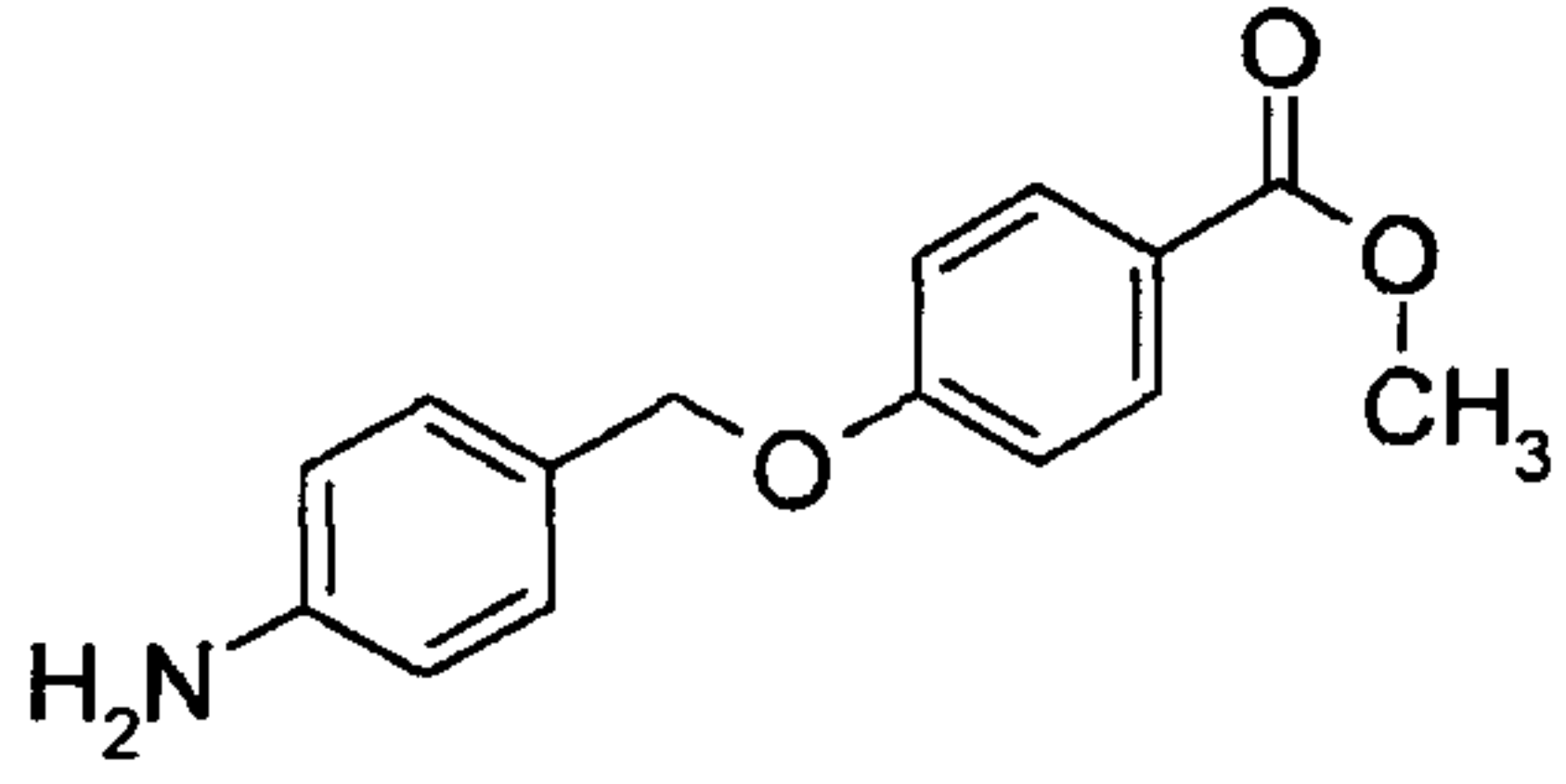
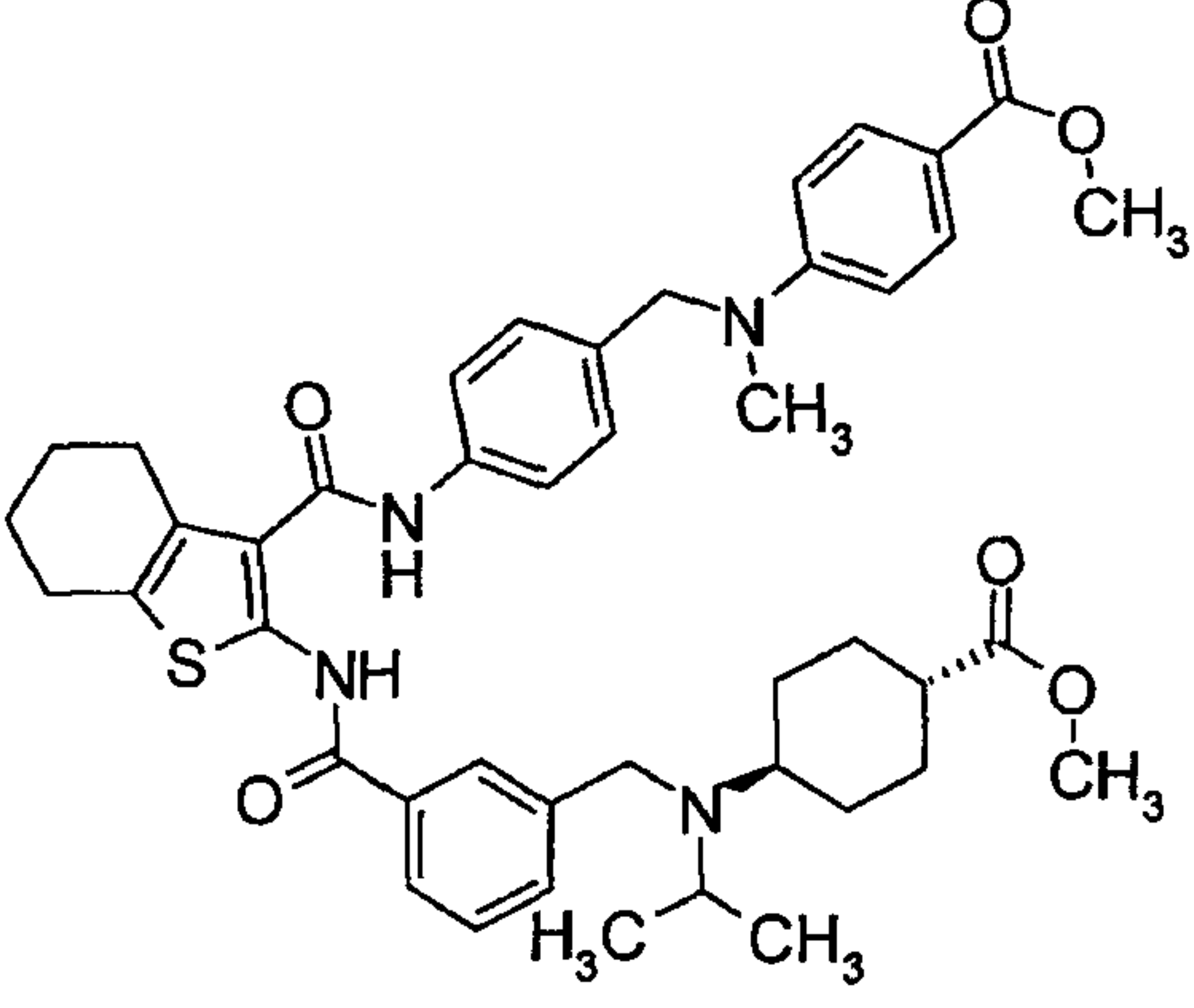
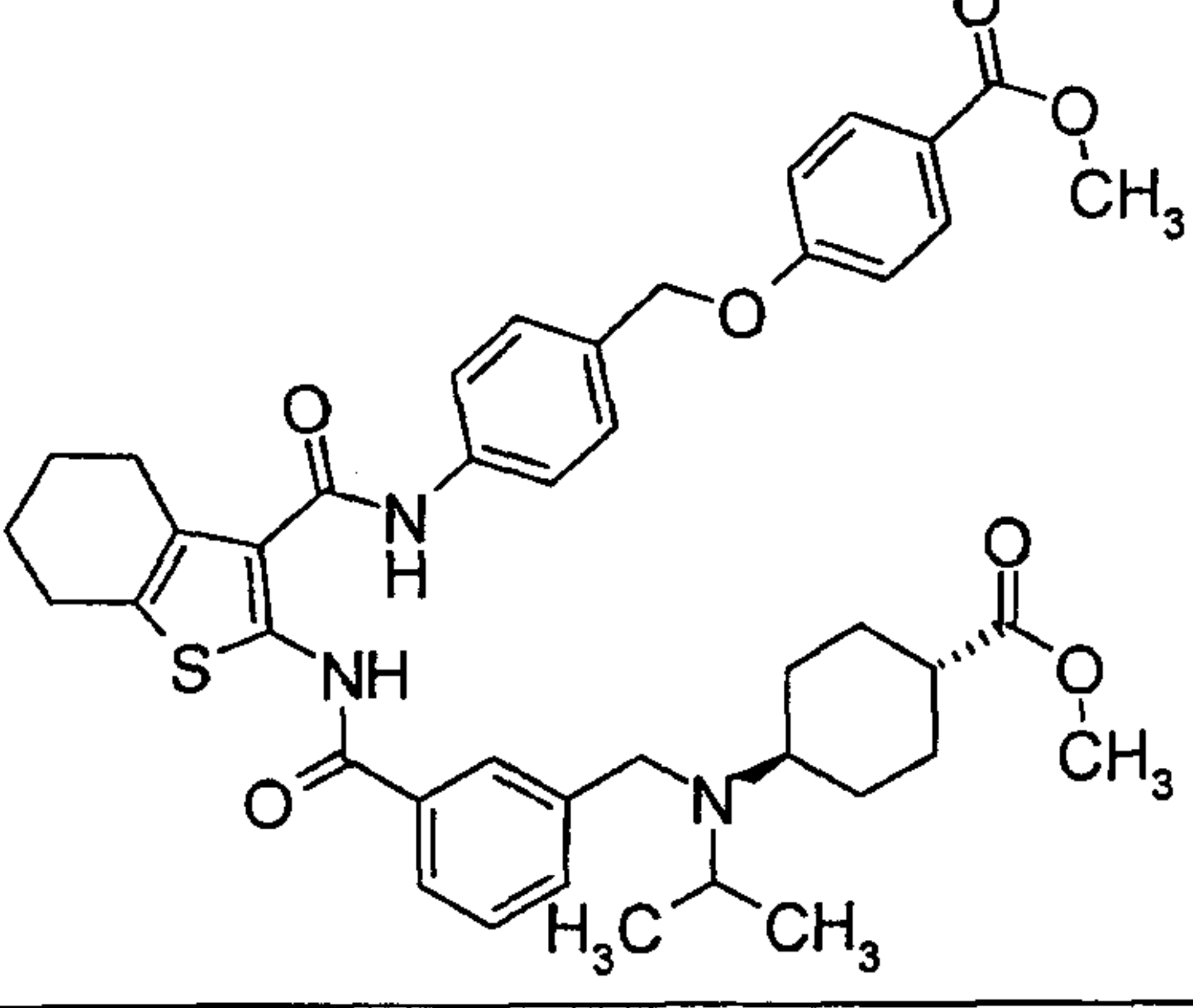
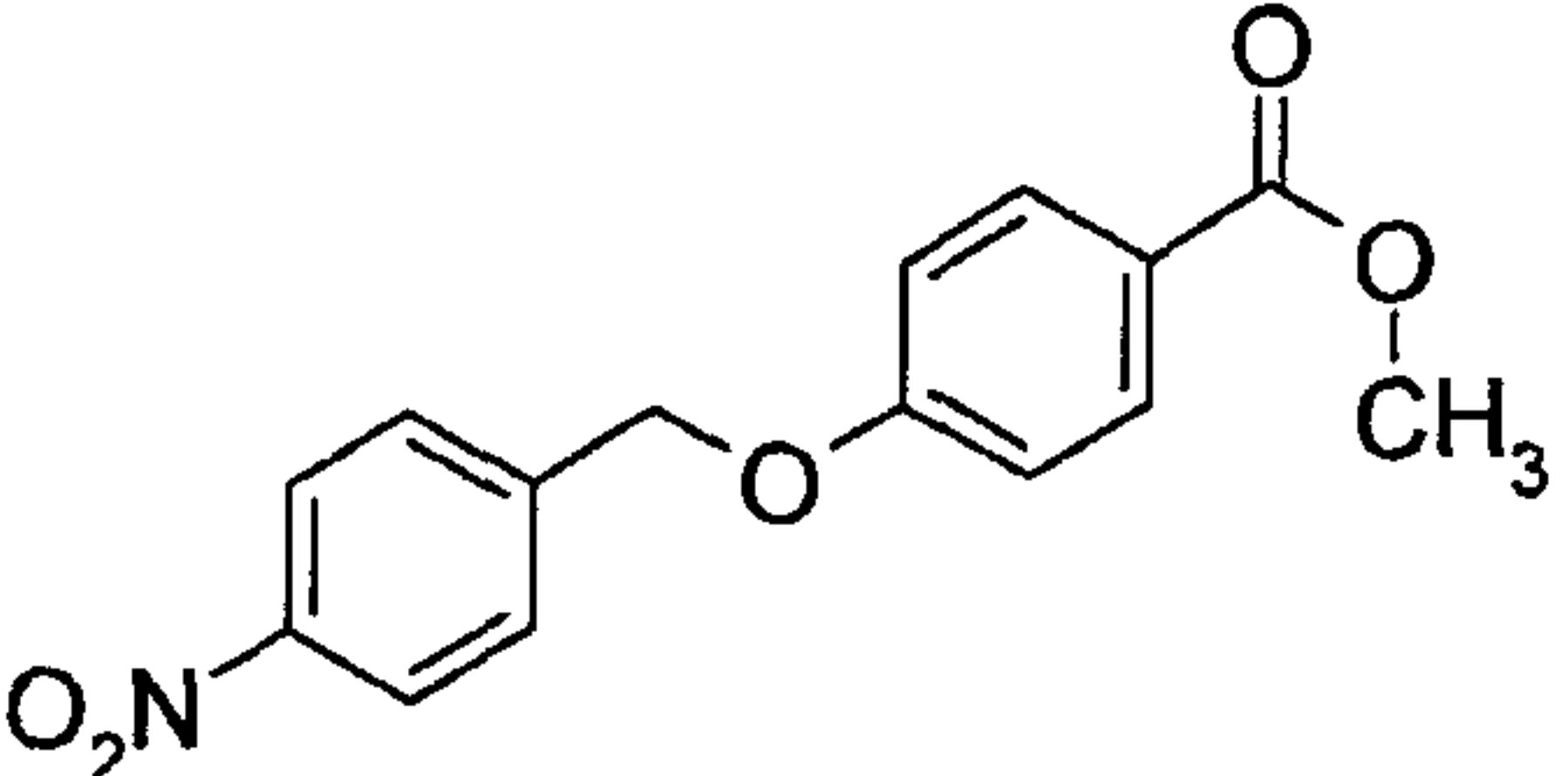
[0192]
[Table 47]

Pr	Str	Pr	Str
298		301	
299		302	
300		303	

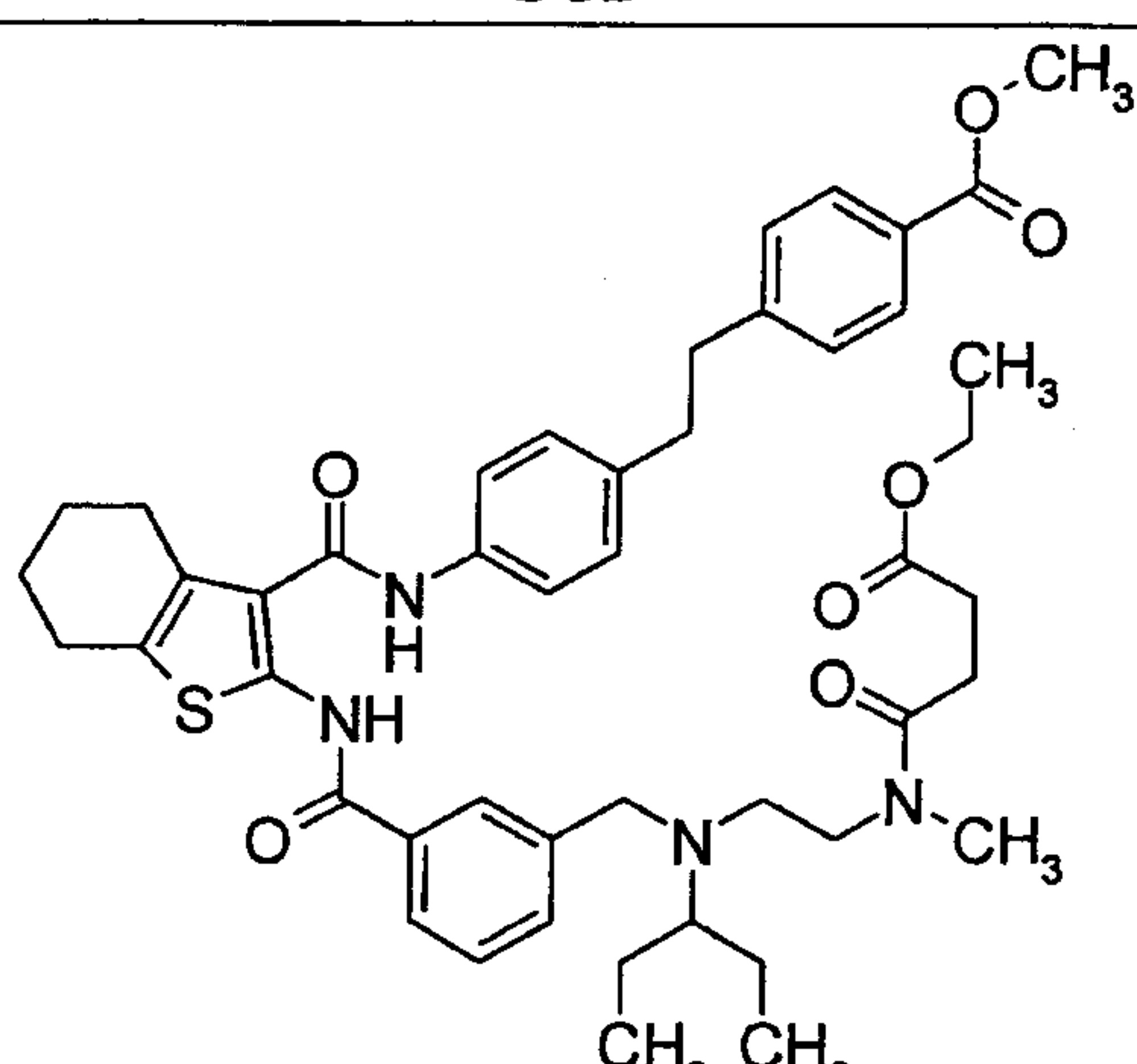
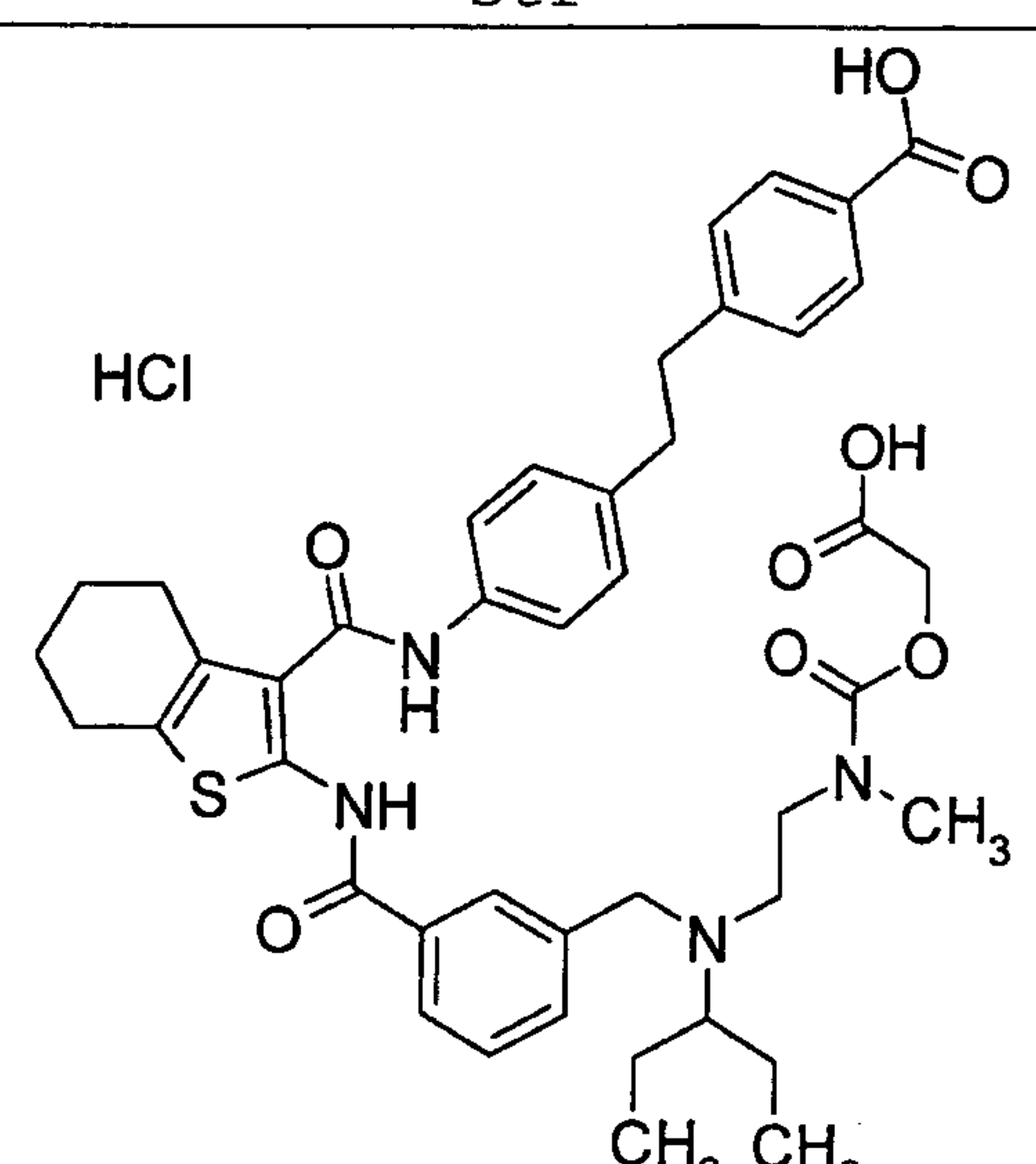
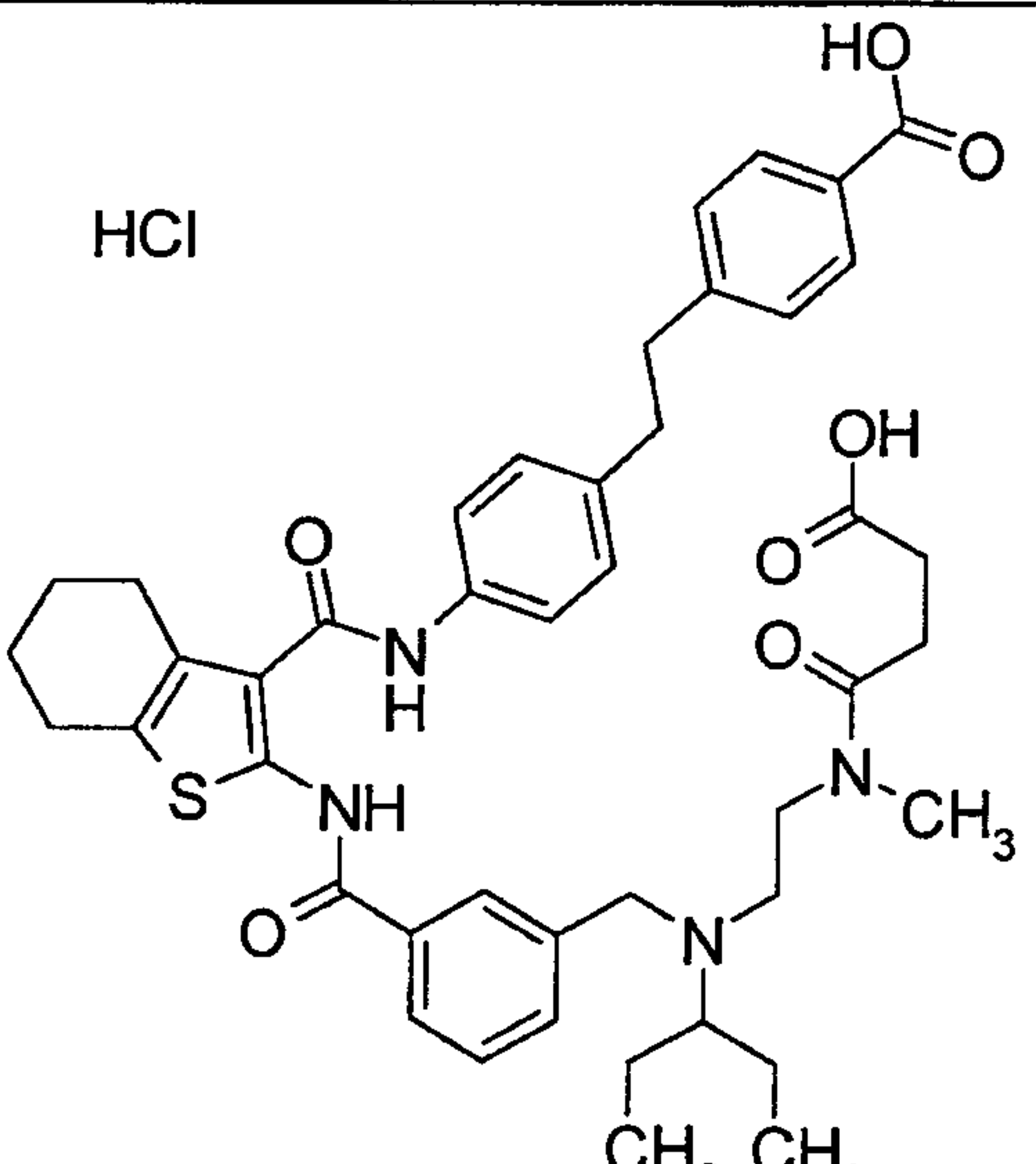
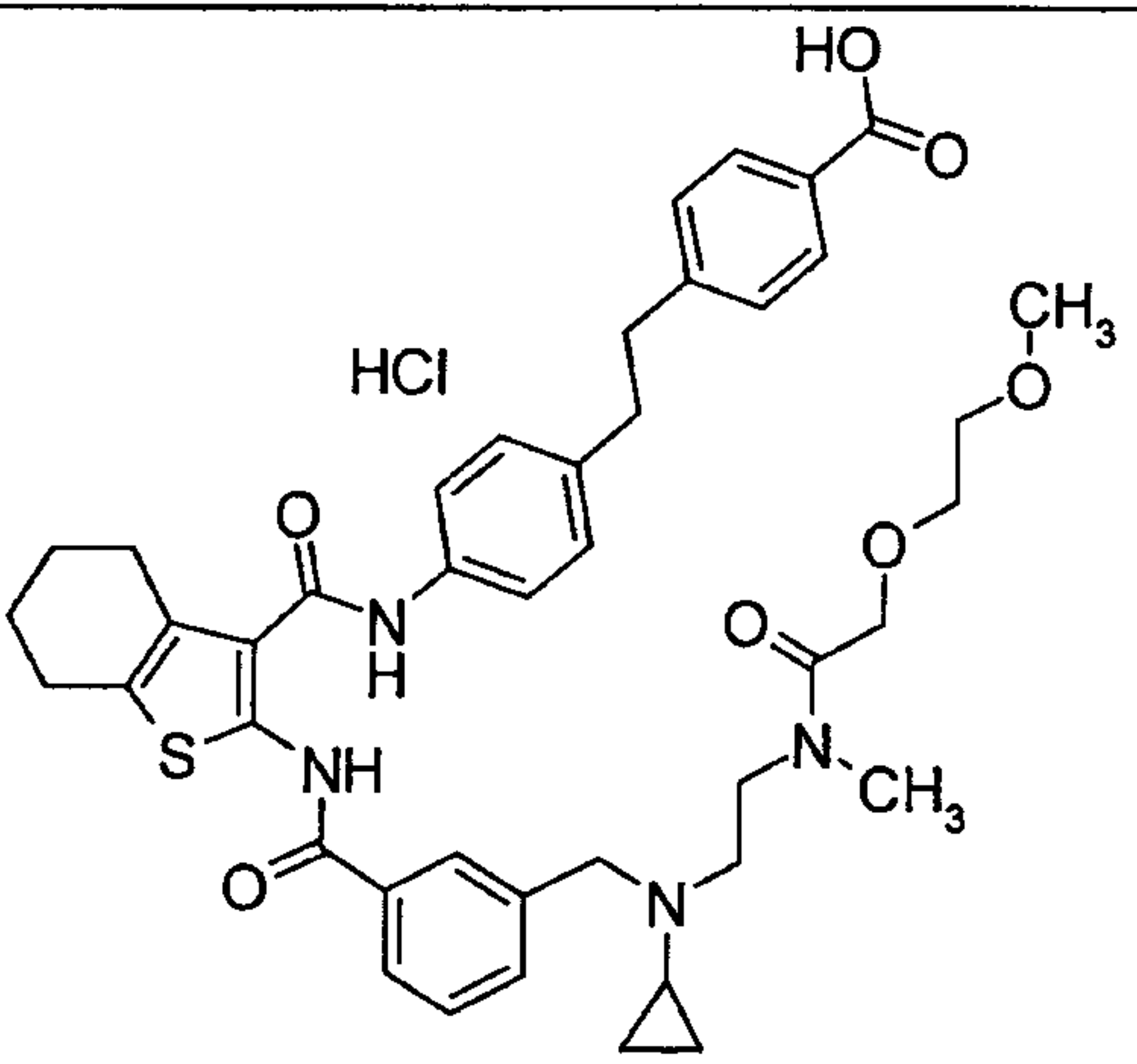
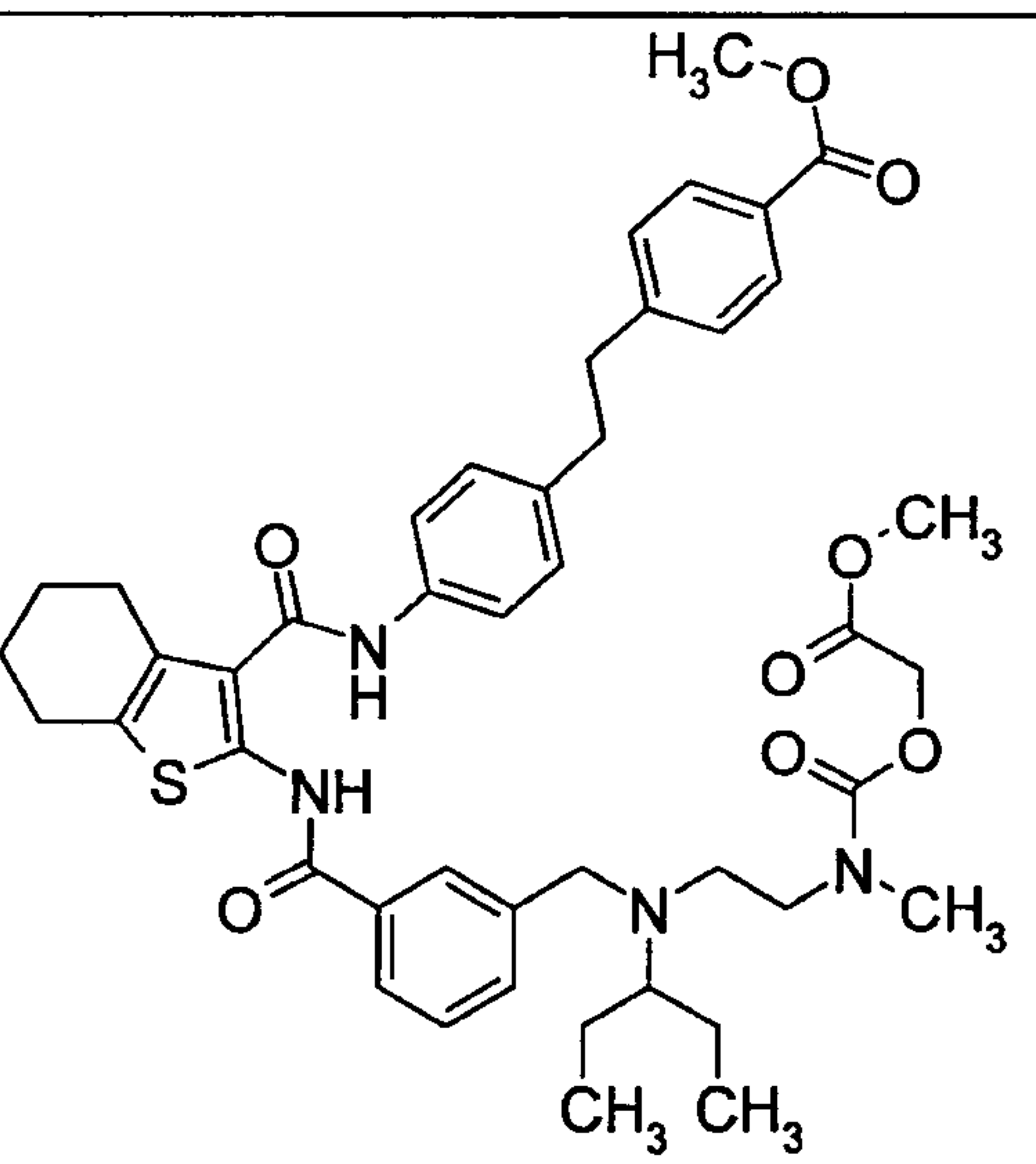
[0193]
[Table 48]

Pr	Str	Pr	Str
304		307	
305		308	
306		309	
310		310	

[0194]
[Table 49]

Pr	Str	Pr	Str
311		314	
312		315	
313			

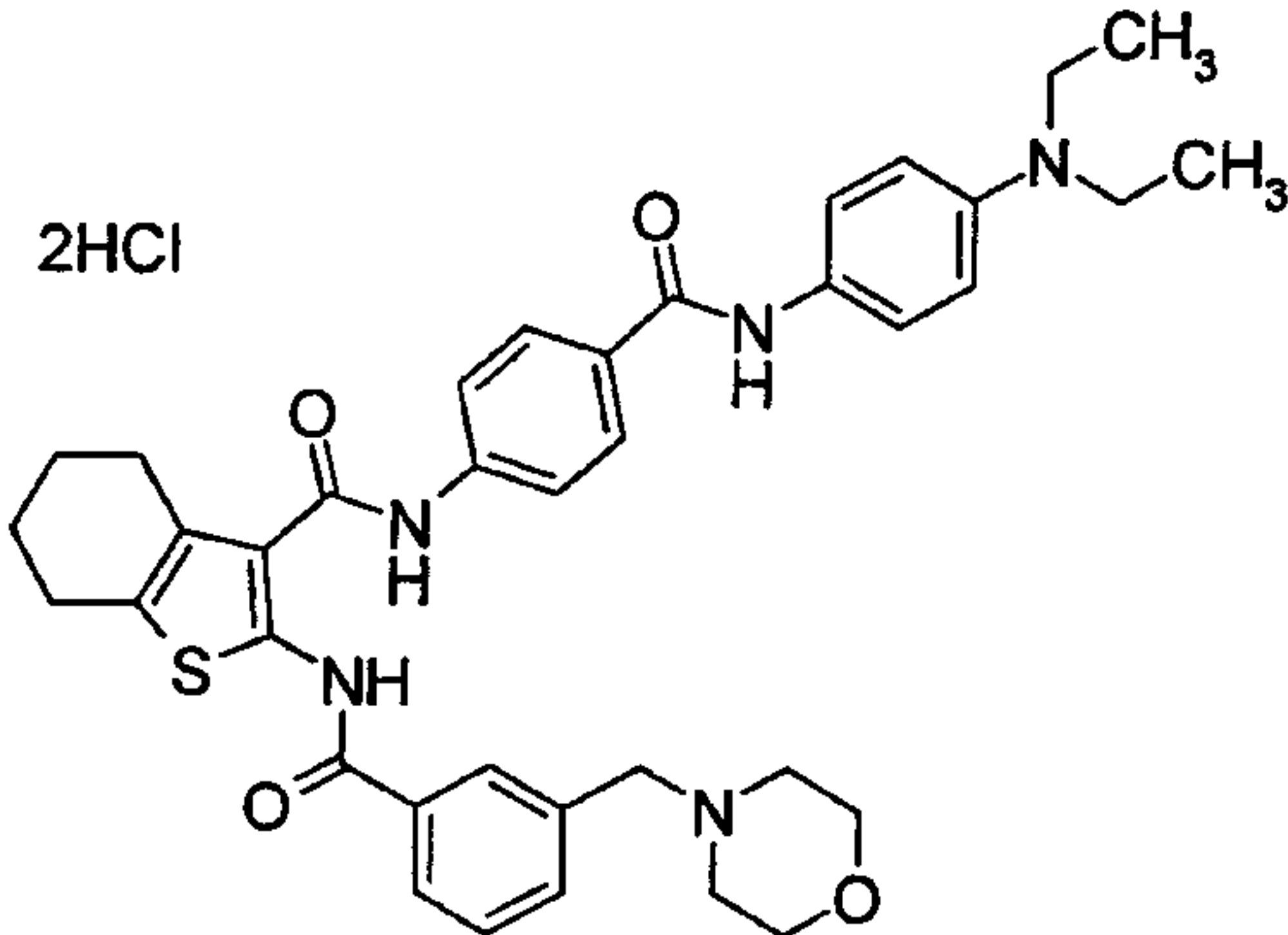
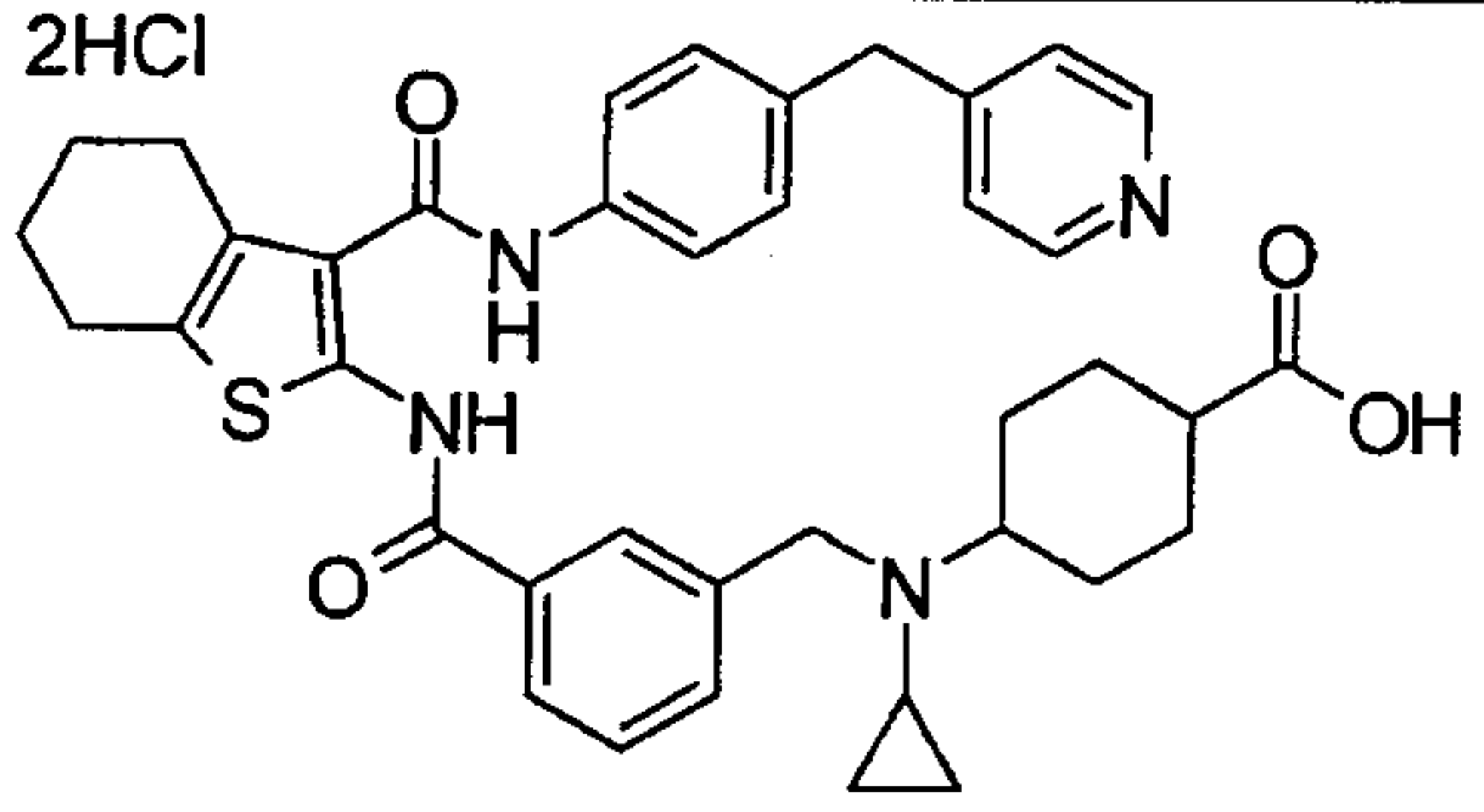
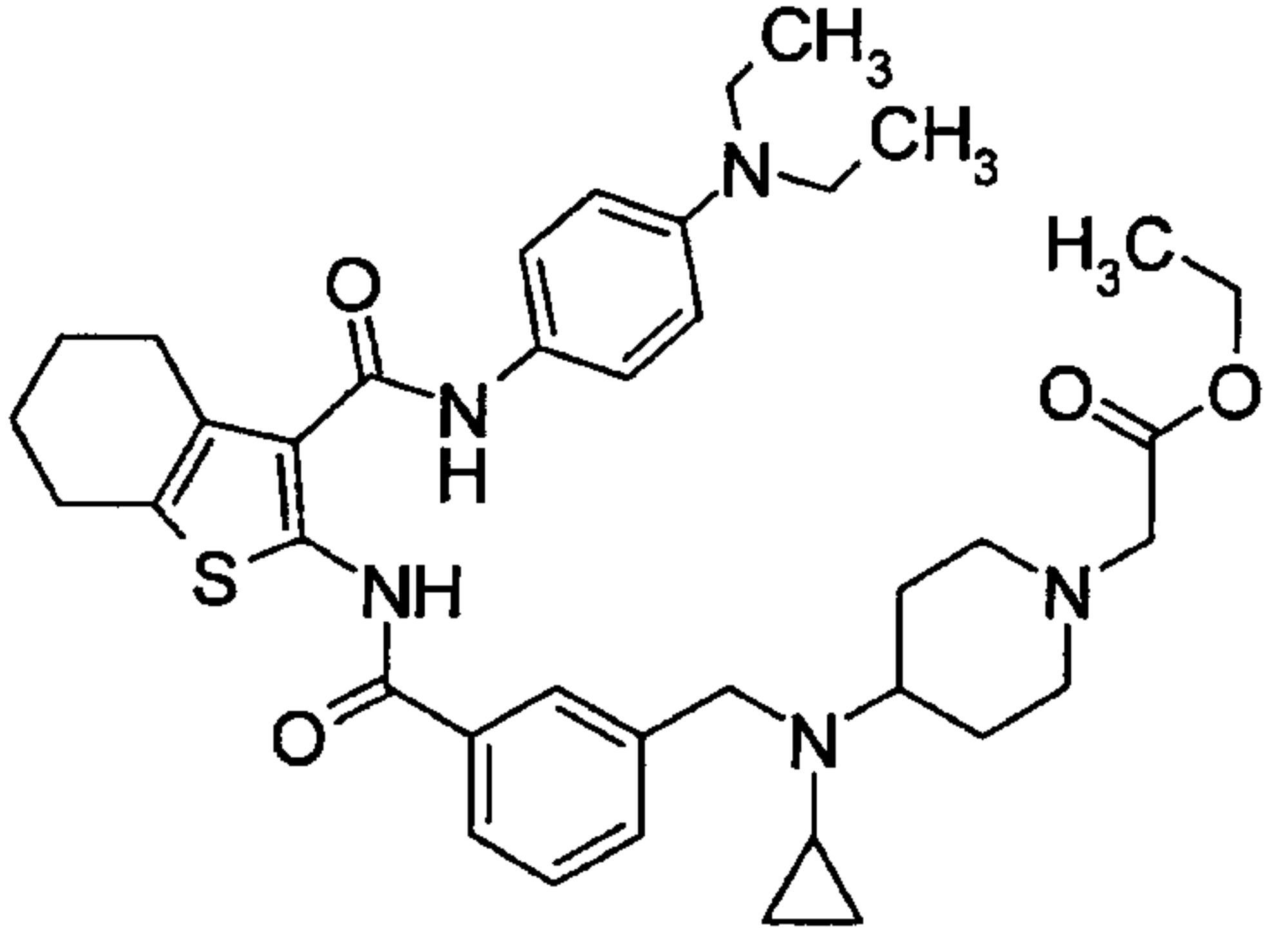
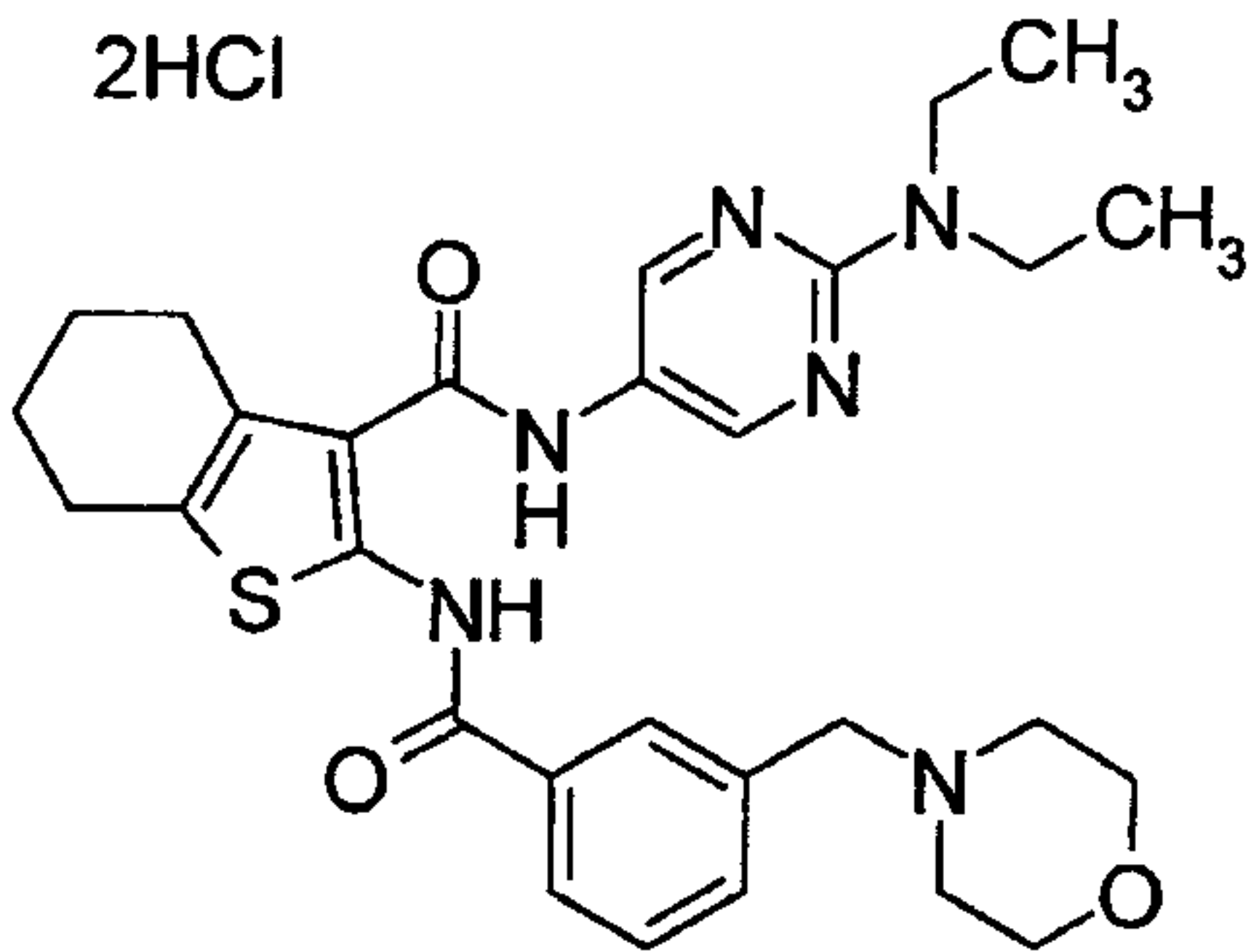
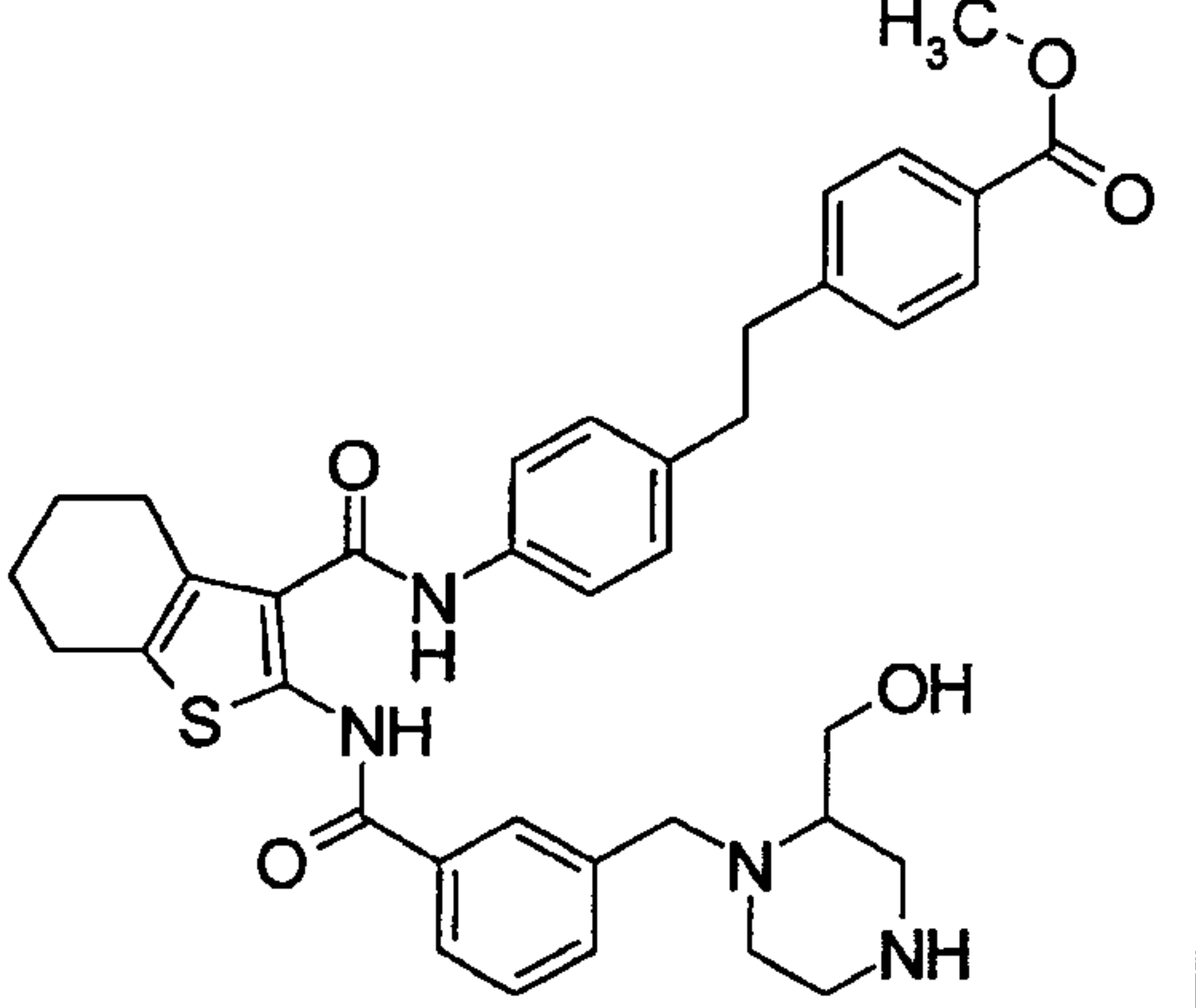
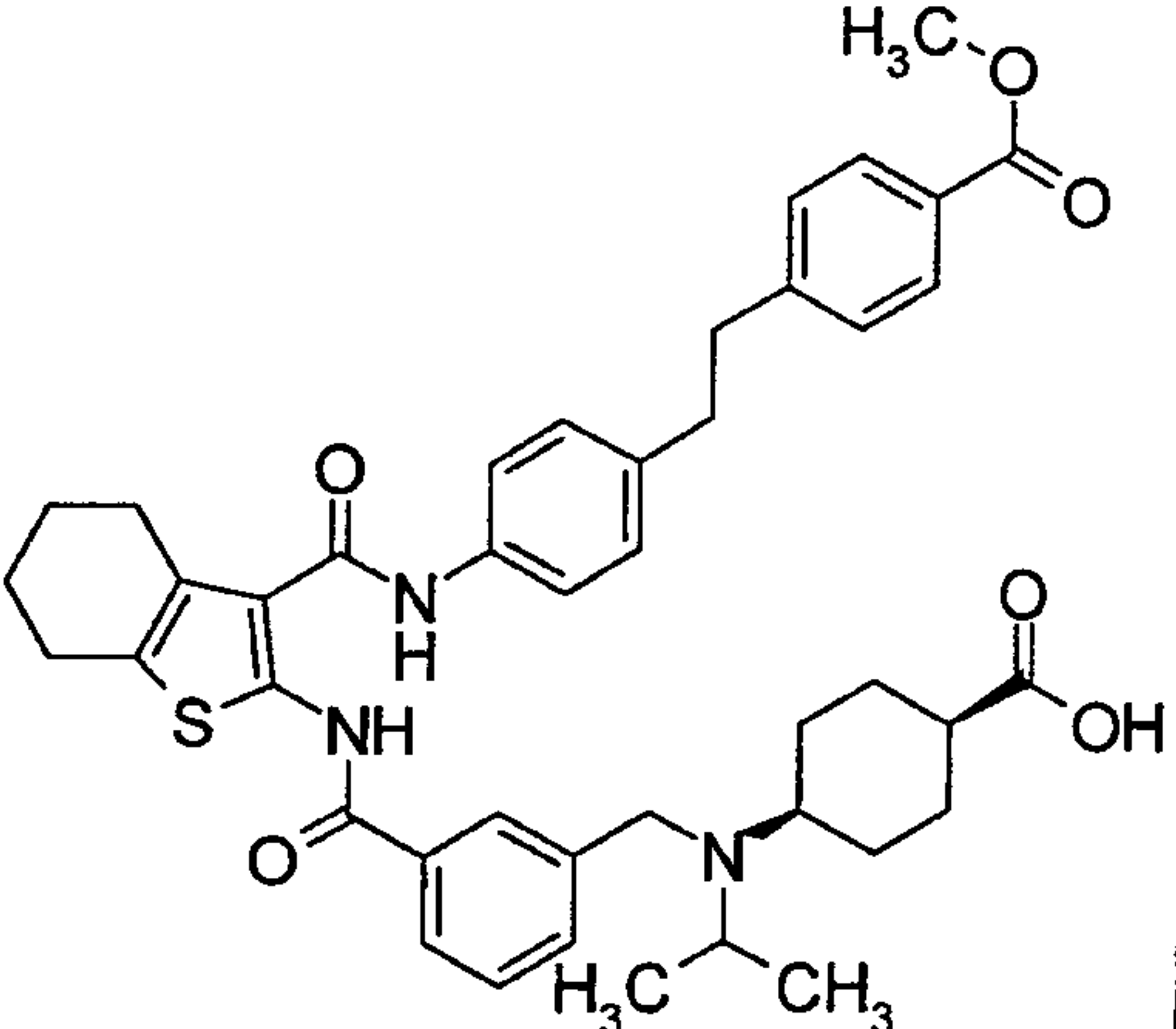
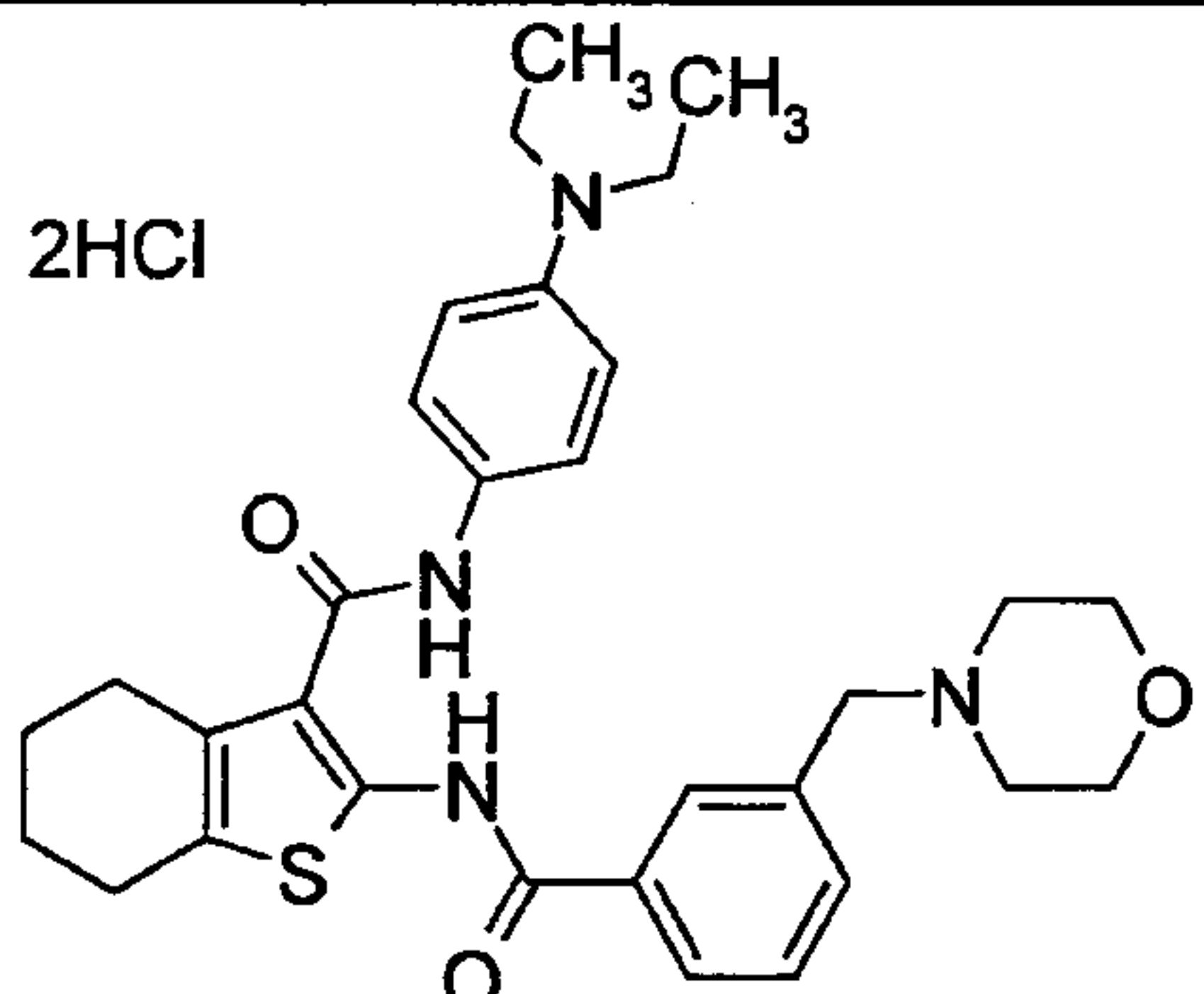
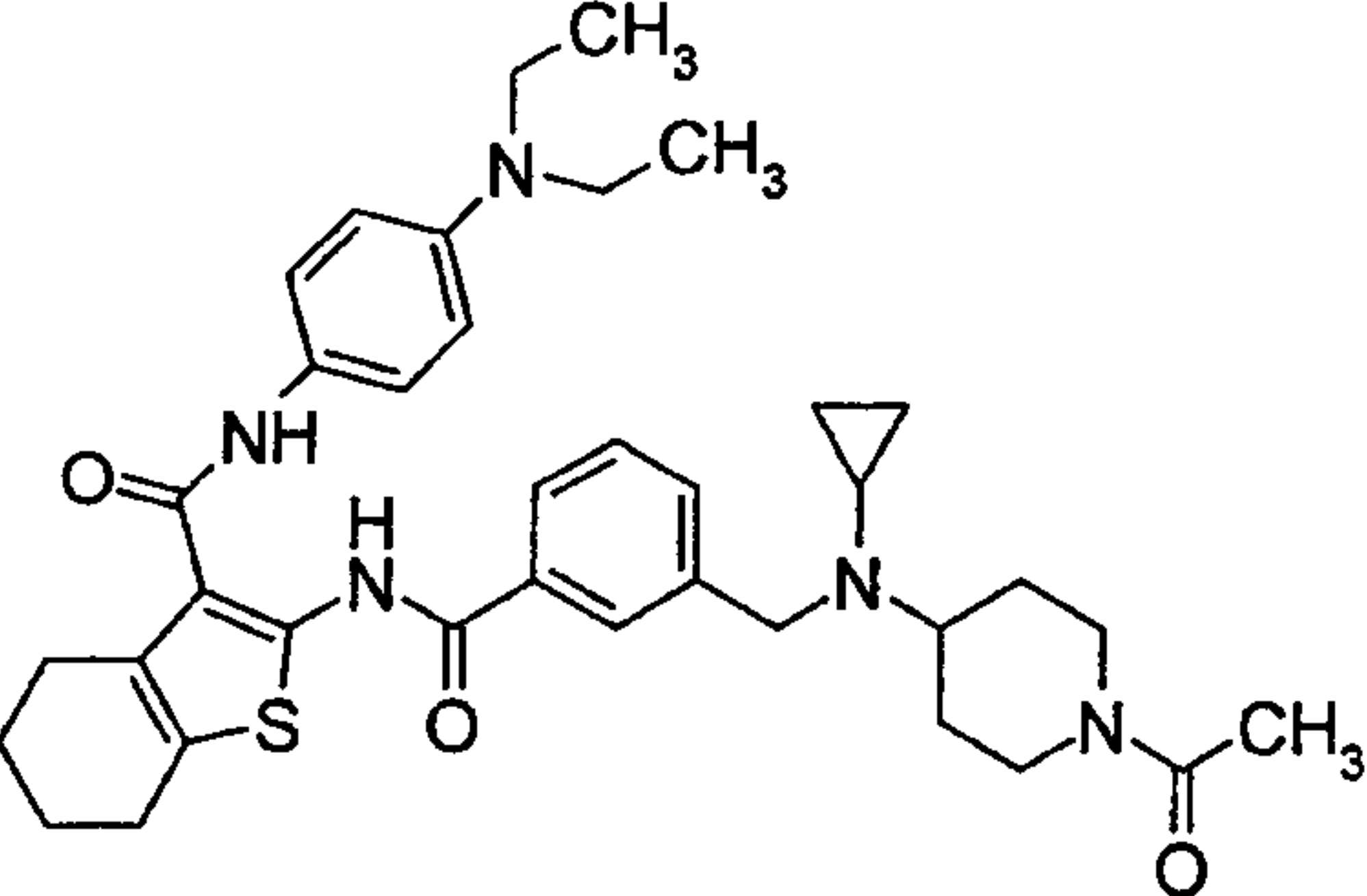
[0195]
[Table 50]

Ex	Str	Ex	Str
1		4	
2		5	
3			

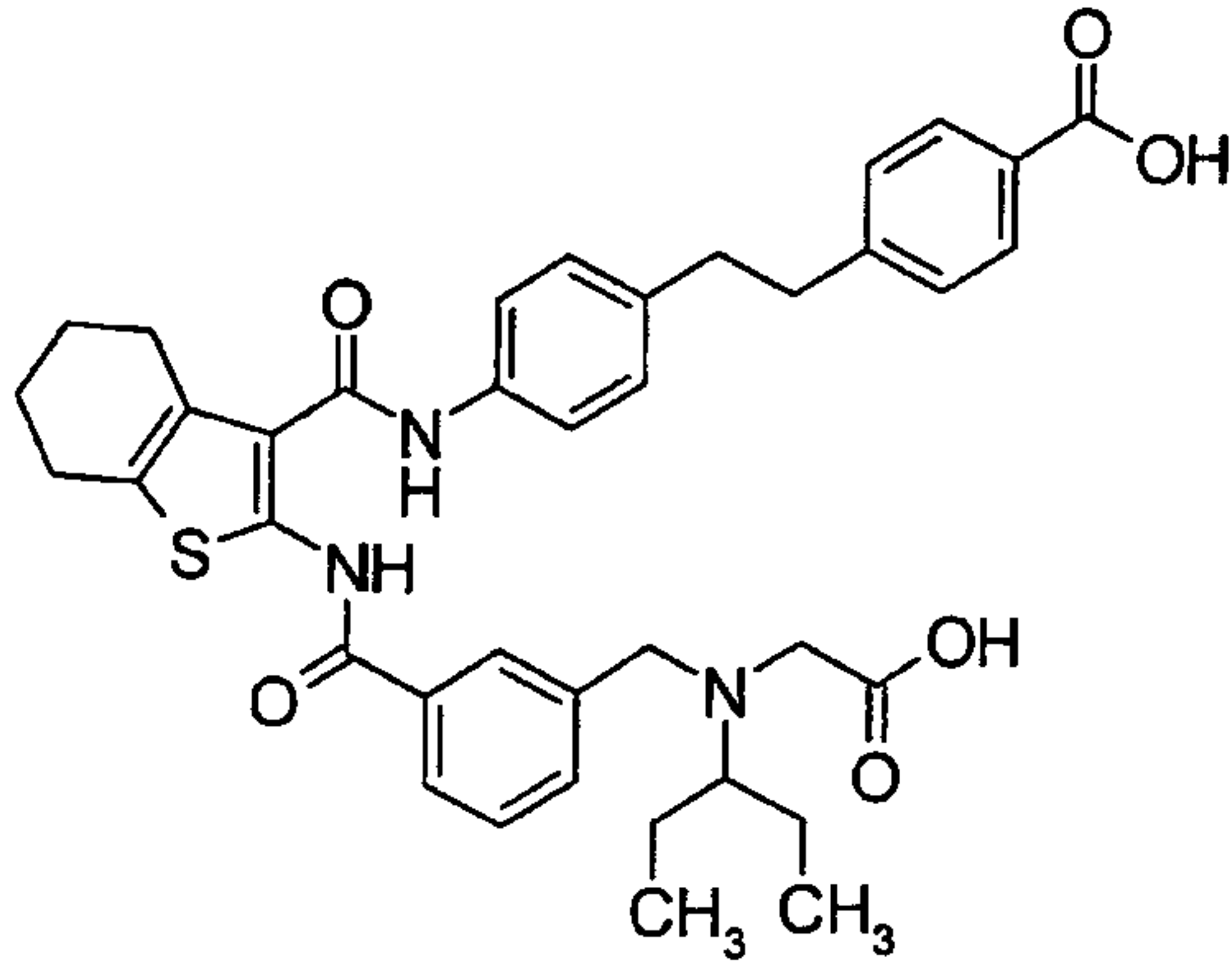
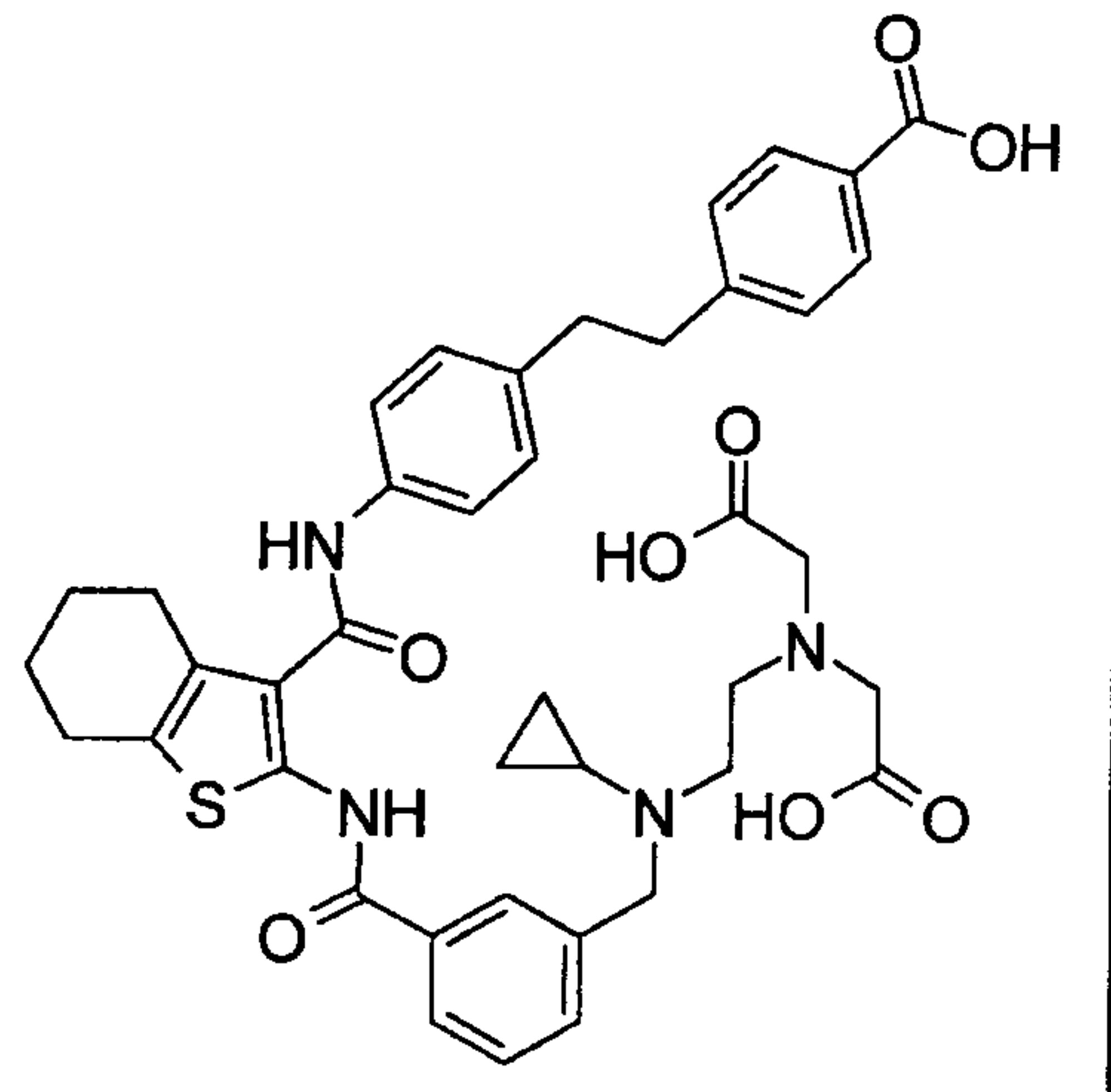
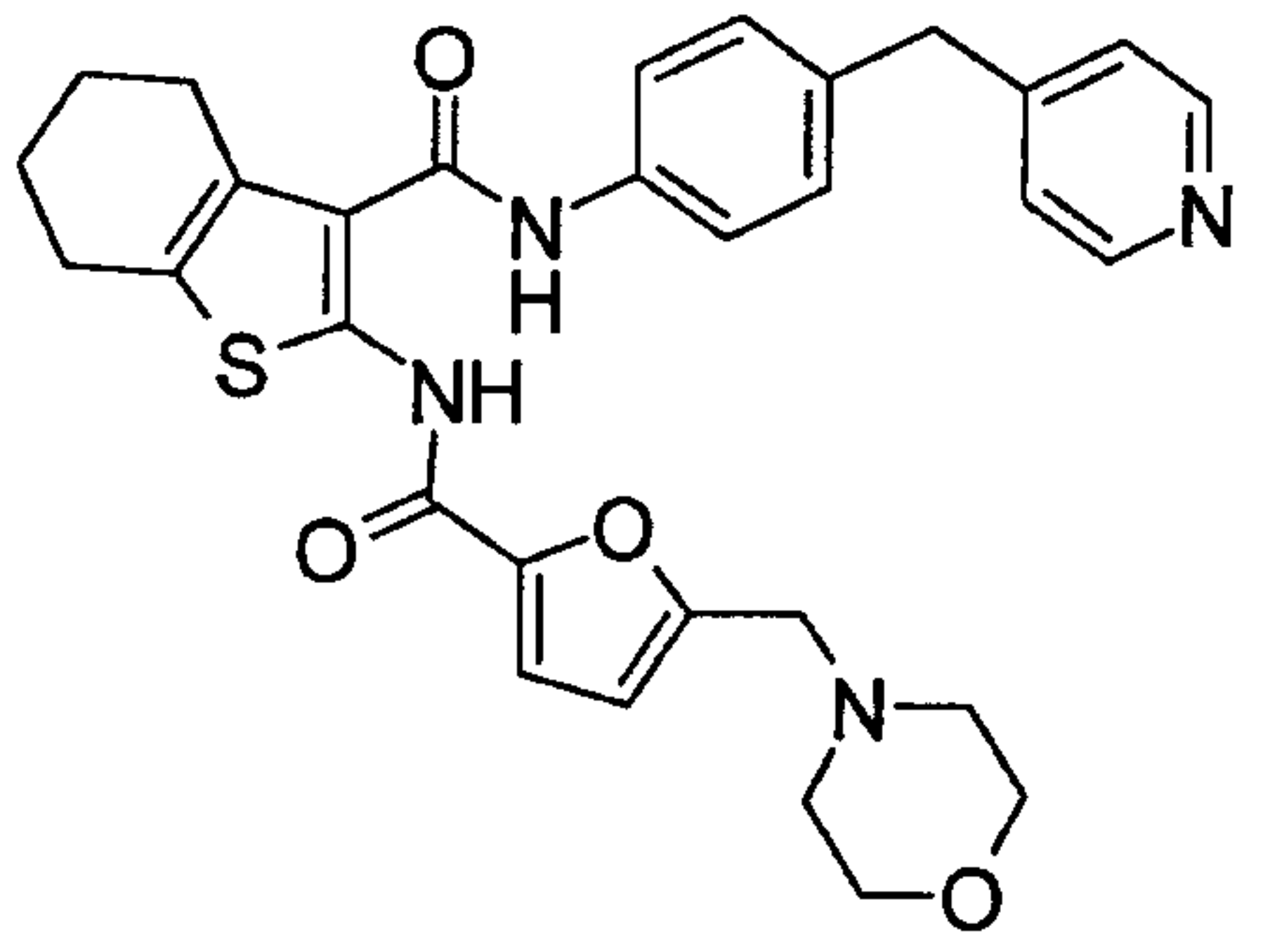
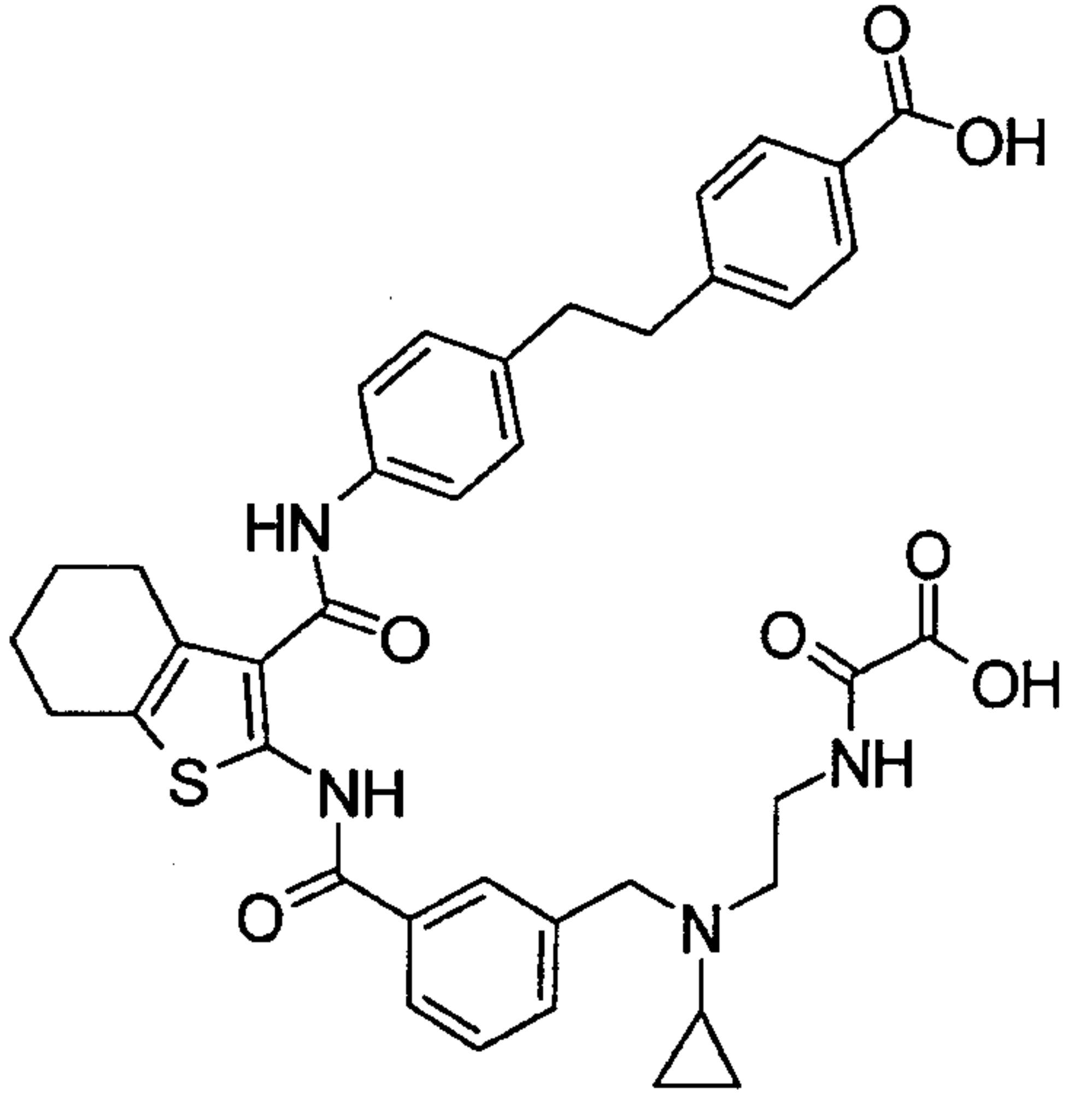
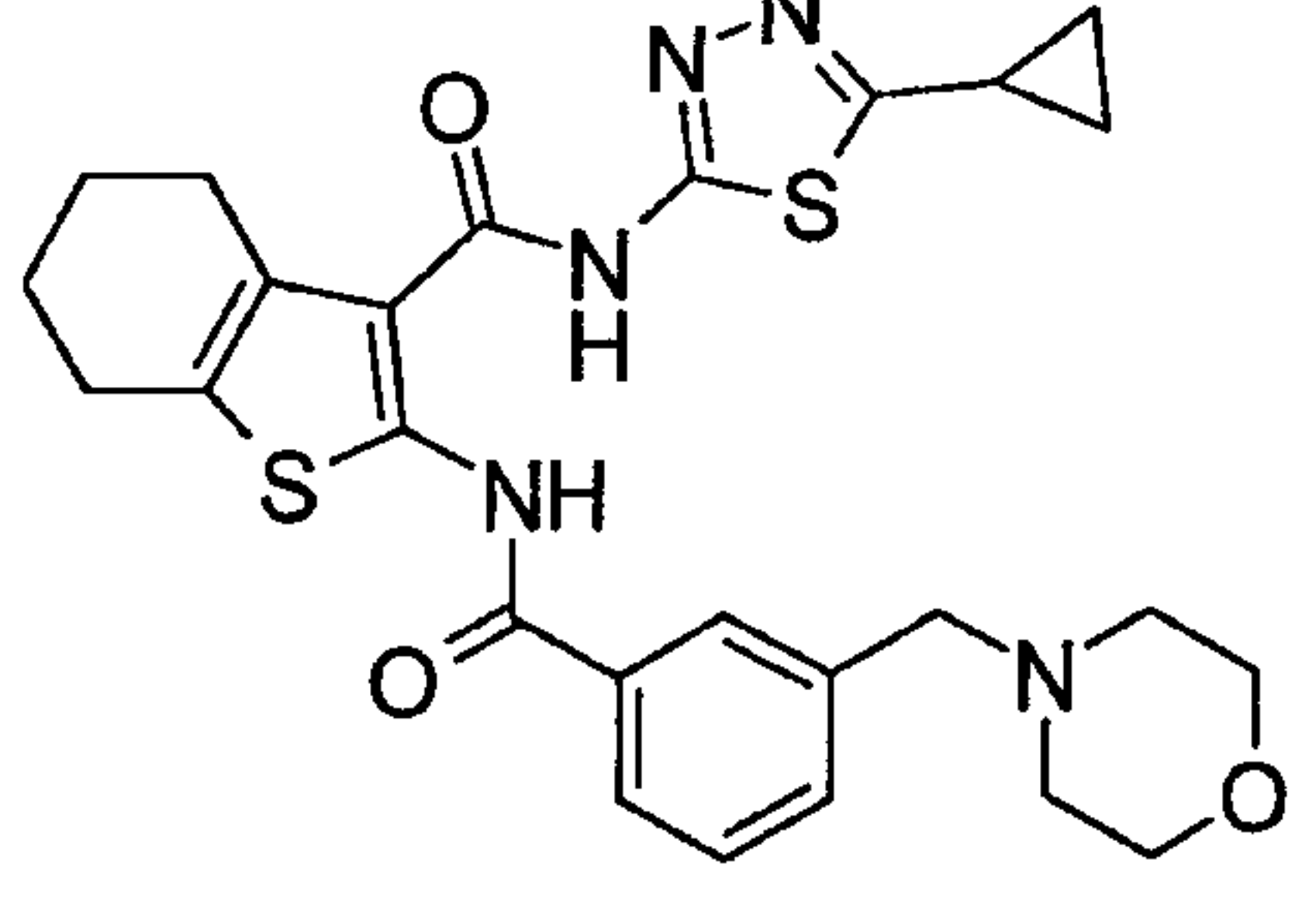
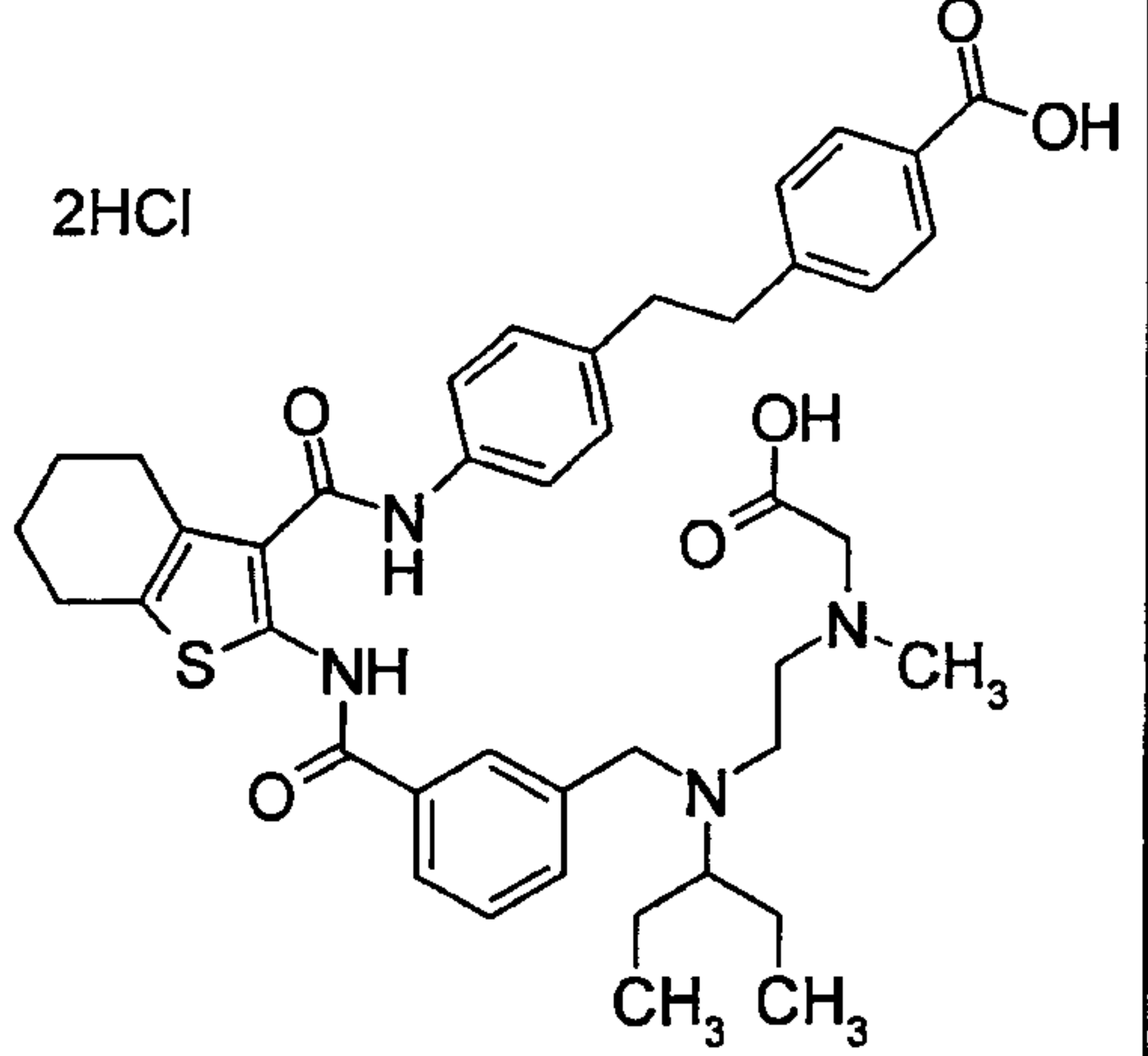
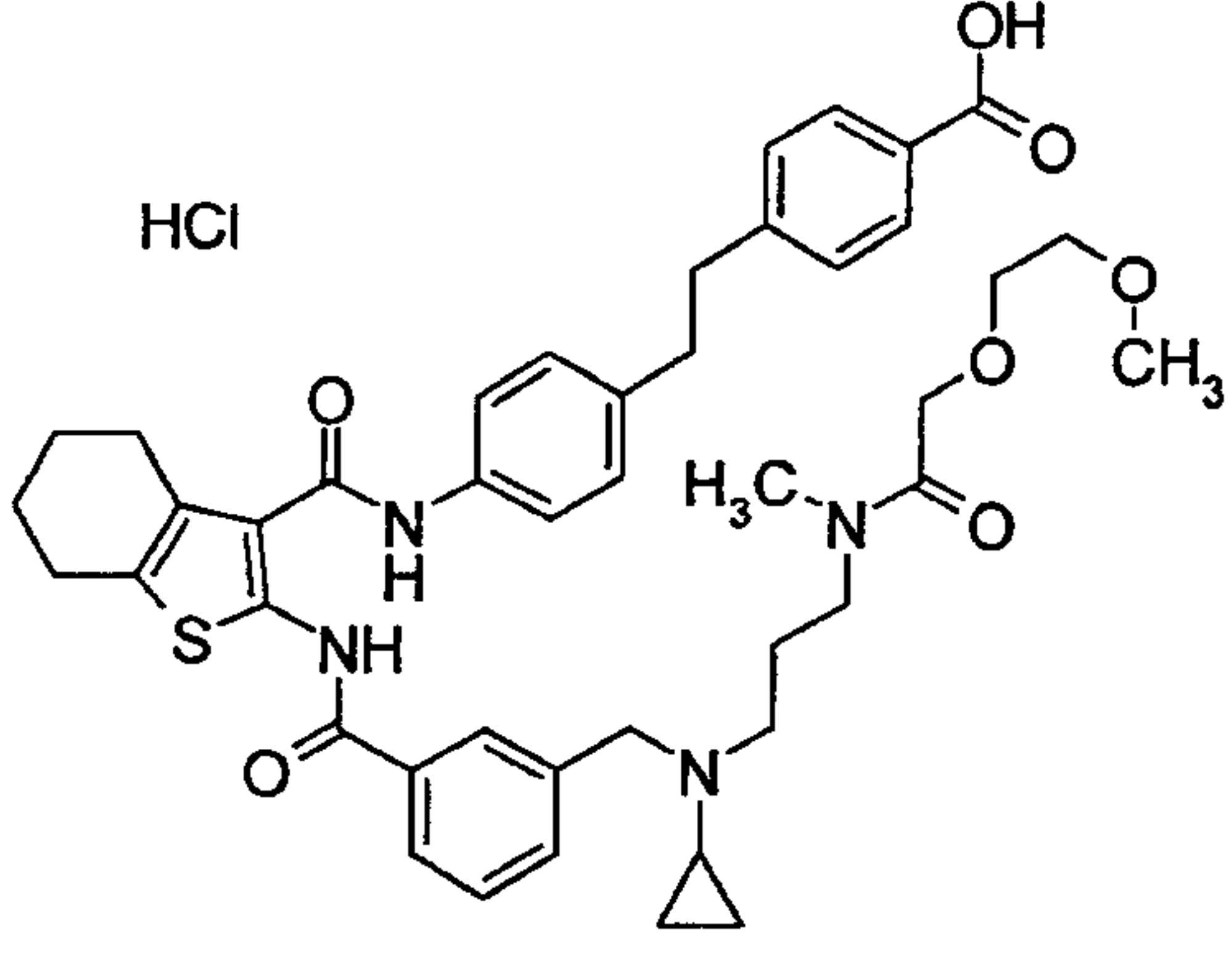
[0196]
[Table 51]

Ex	Str	Ex	Str
6		9	
7		10	
8		11	

[0197]
[Table 52]

Ex	Str	Ex	Str
12	2HCl 	16	2HCl 
13		17	2HCl 
14		18	
15	2HCl 	19	

[0198]
[Table 53]

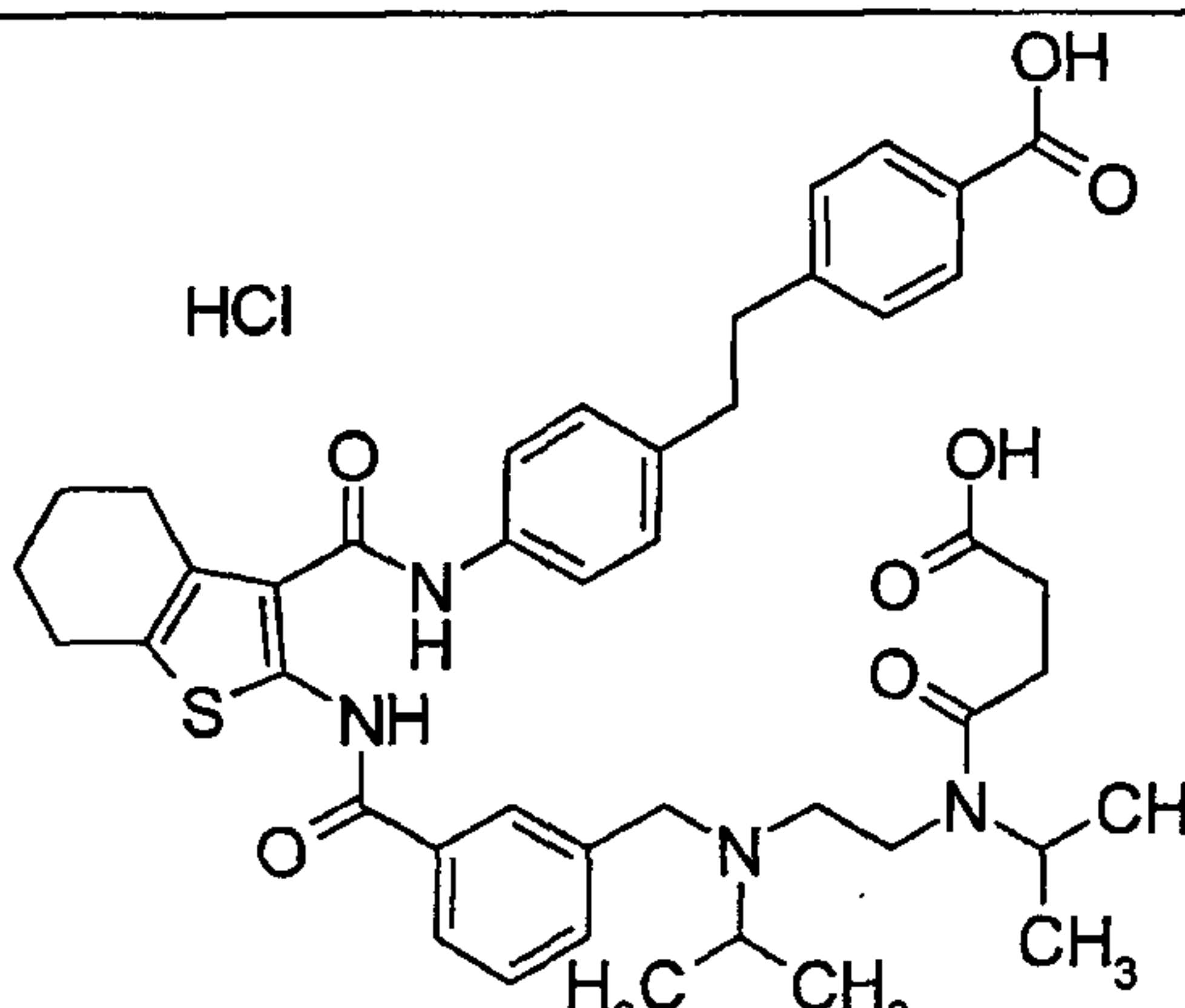
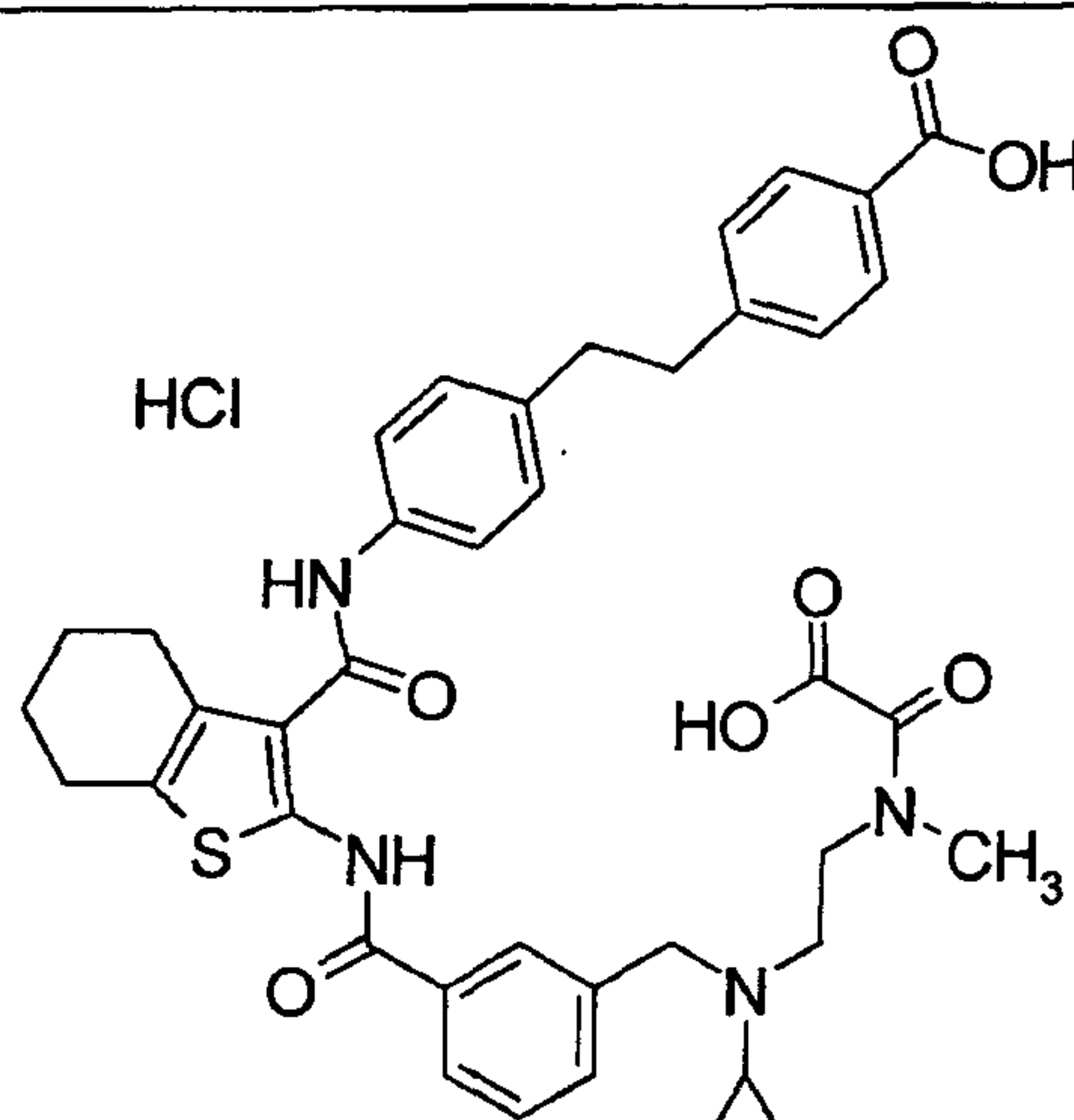
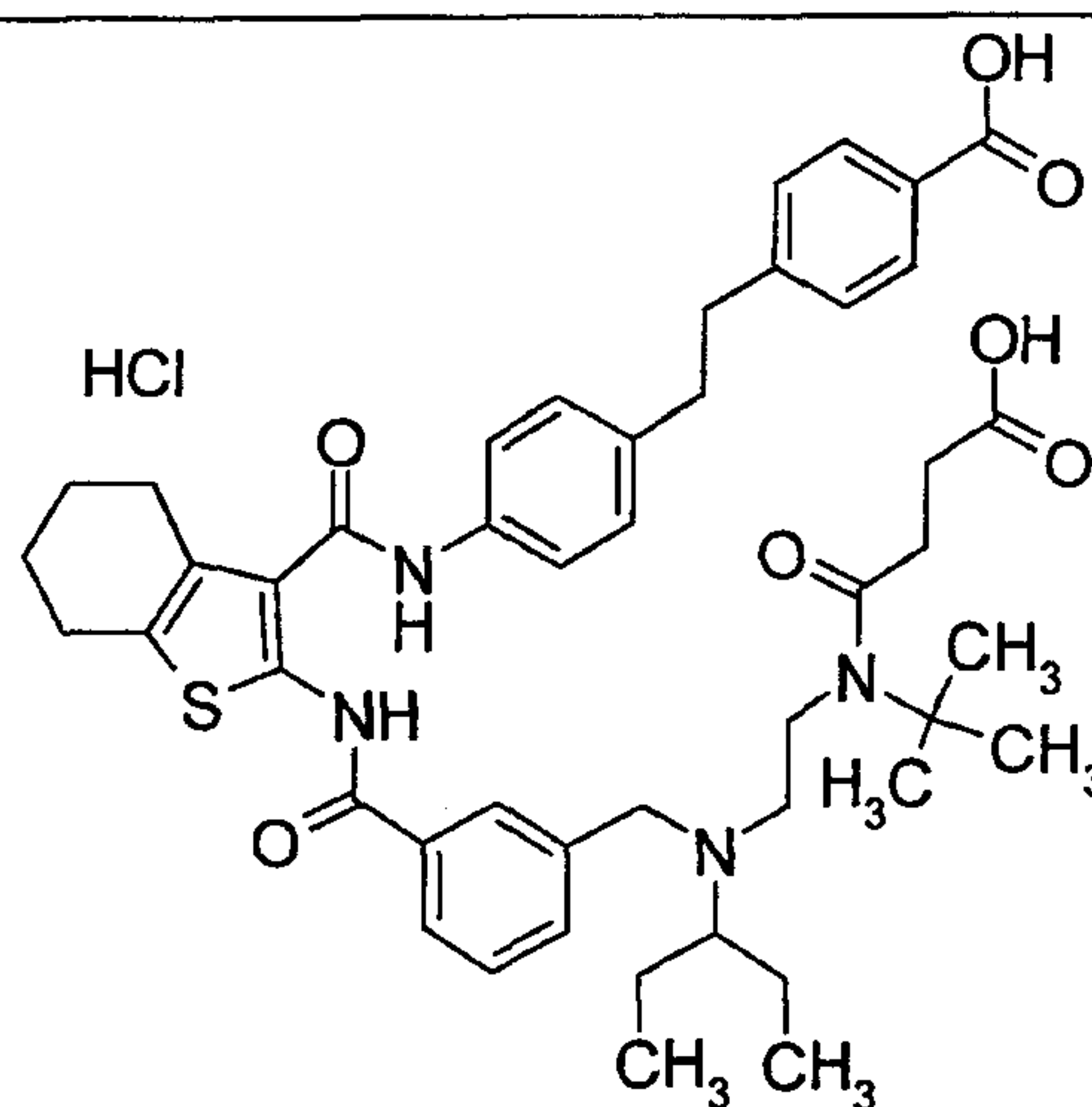
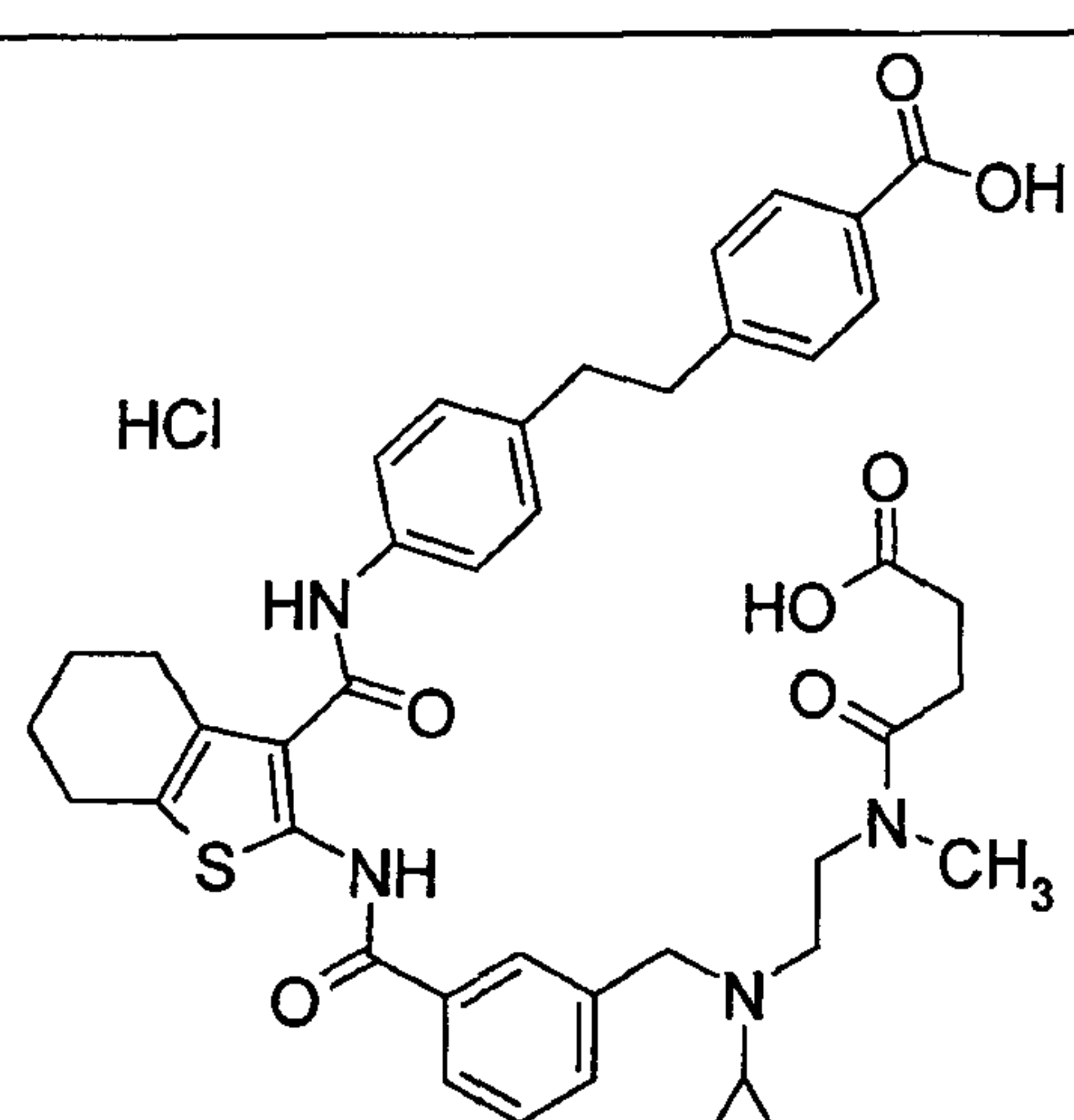
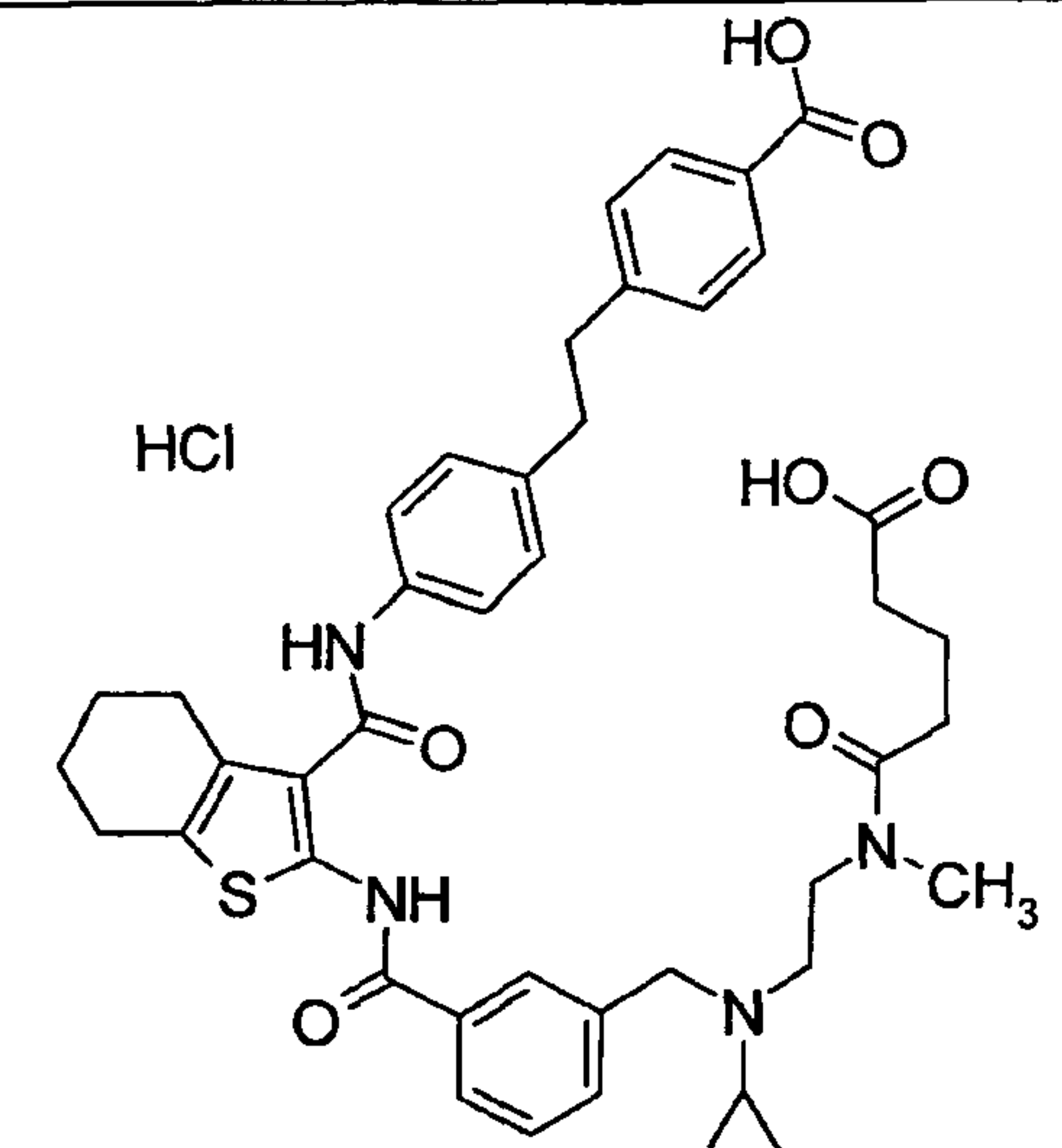
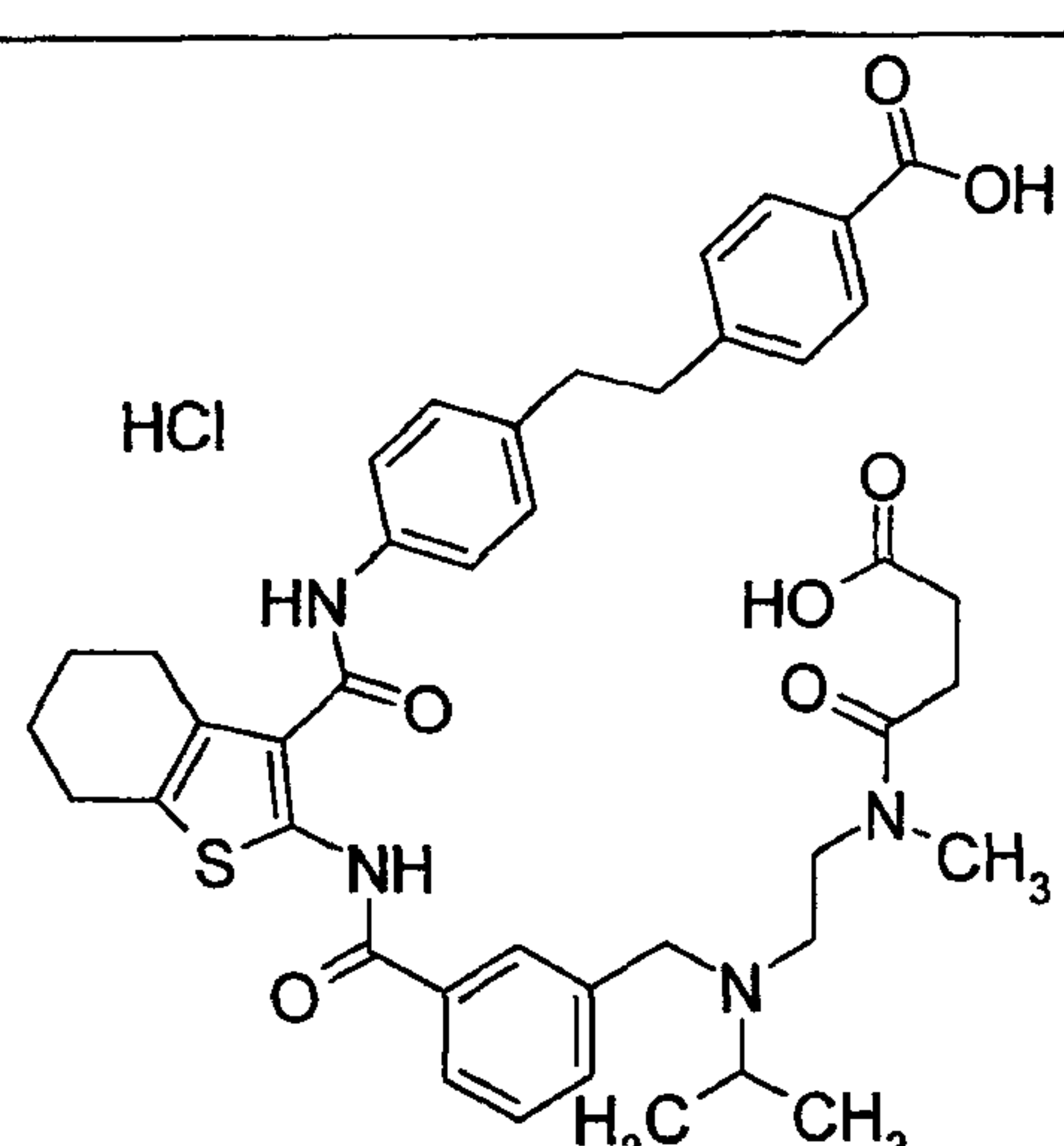
Ex	Str	Ex	Str
20		24	
21	2HCl 	25	
22		26	2HCl 
23	HCl 		

[0199]
[Table 54]

Ex	Str	Ex	Str
27		30	
28		31	
29		32	

[0200]

[Table 55]

Ex	Str	Ex	Str
33		36	
34		37	
35		38	

[0201]
[Table 56]

Ex	Str	Ex	Str
39		42	
40		43	
41		44	

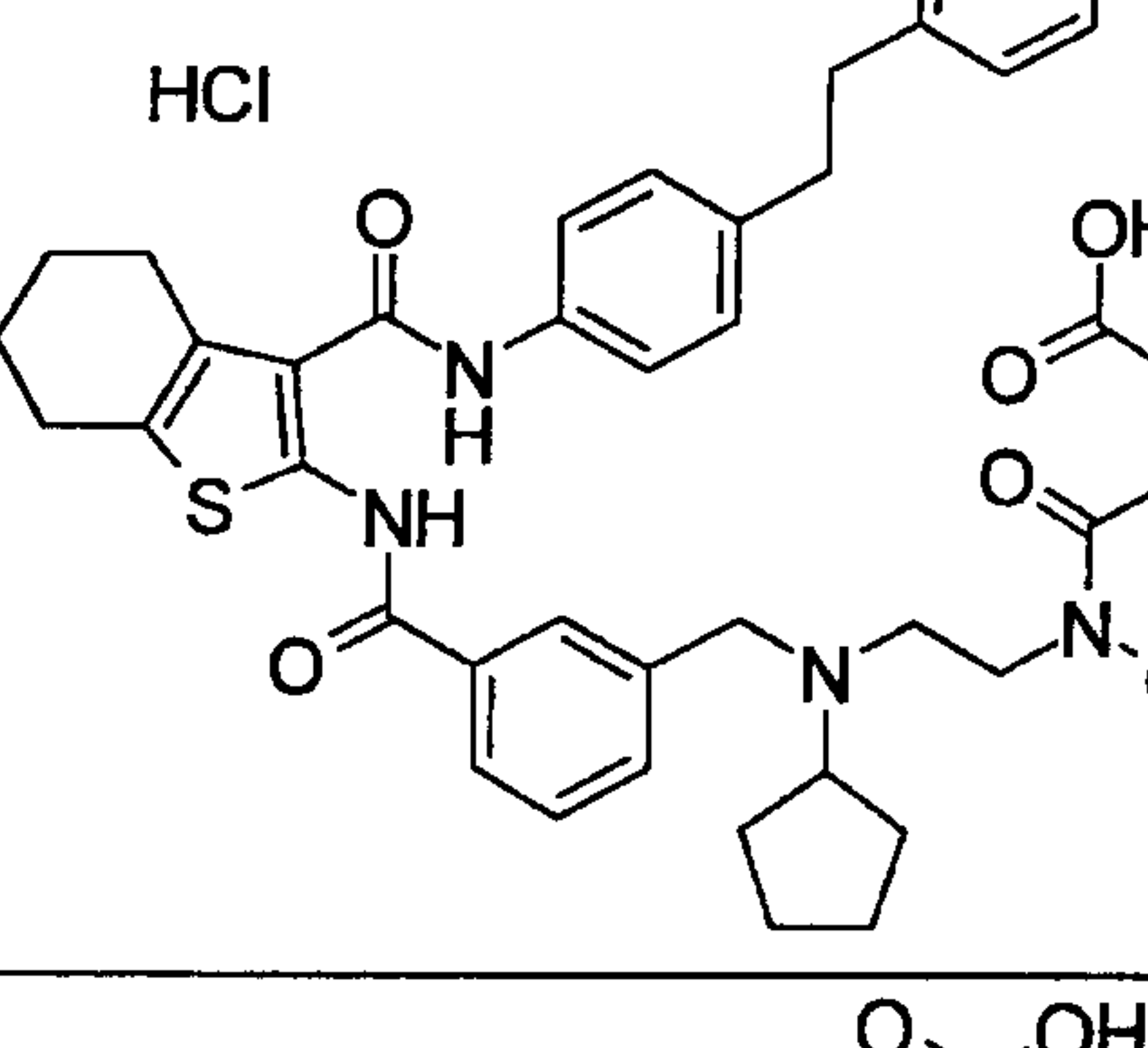
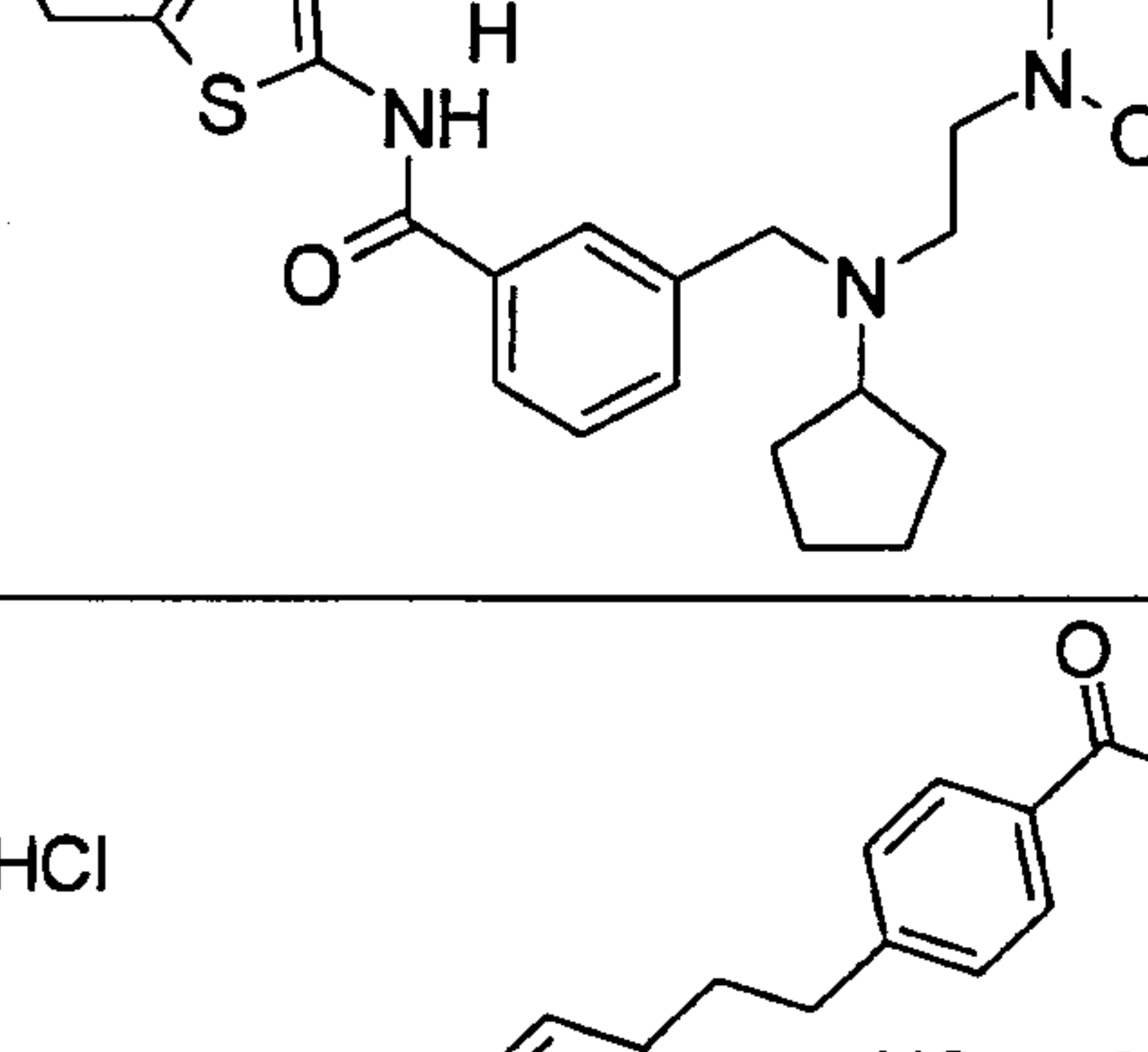
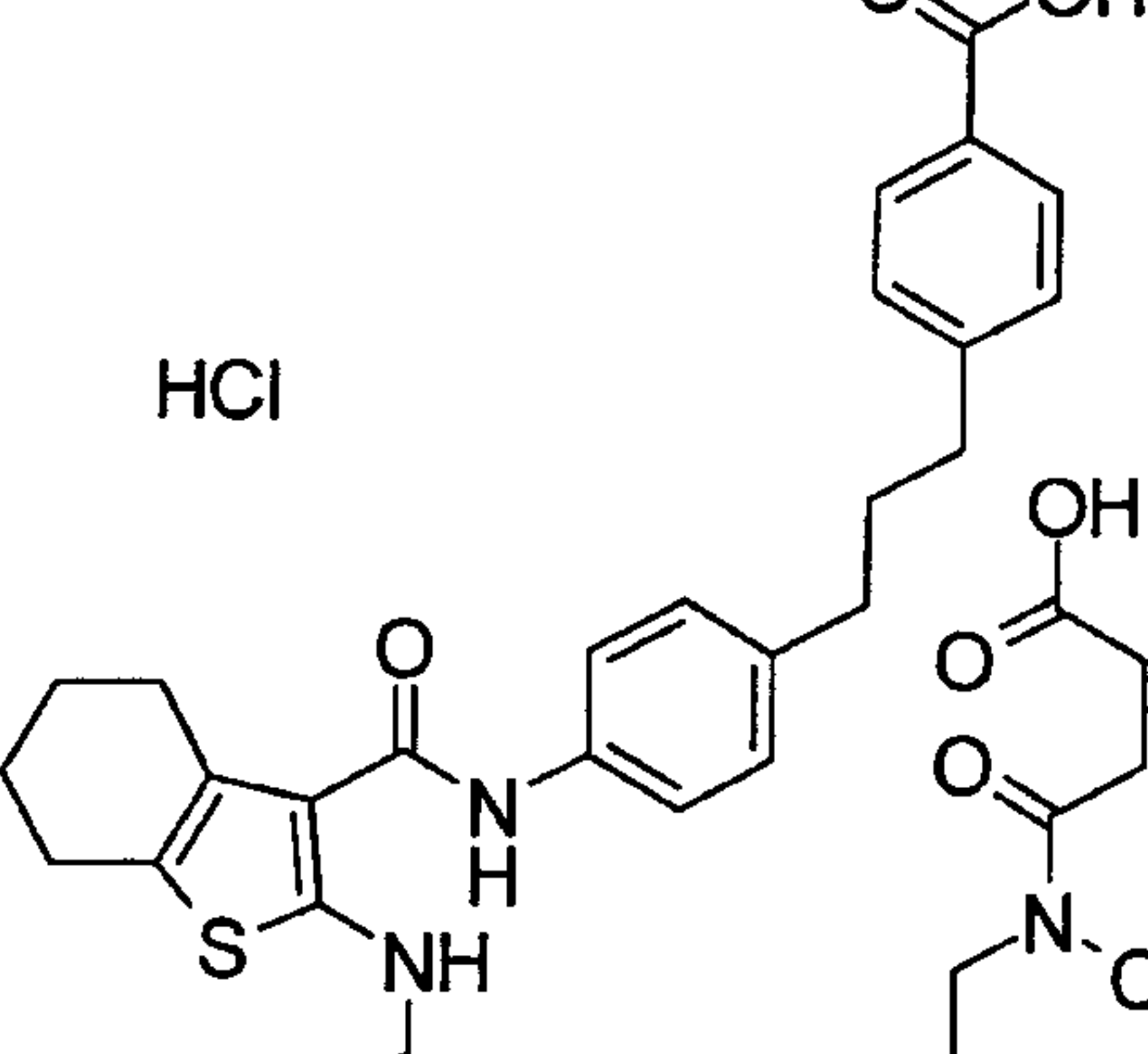
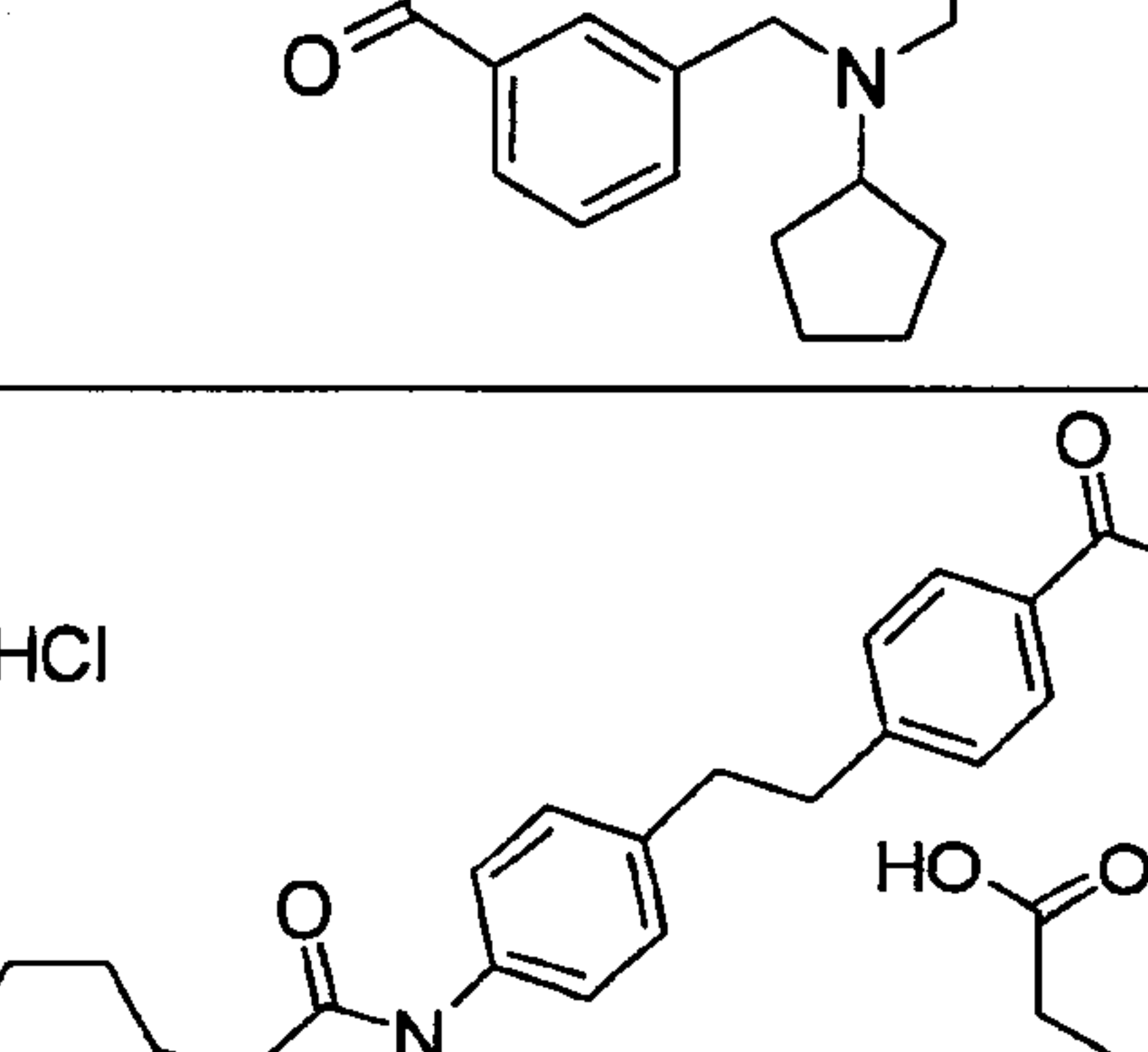
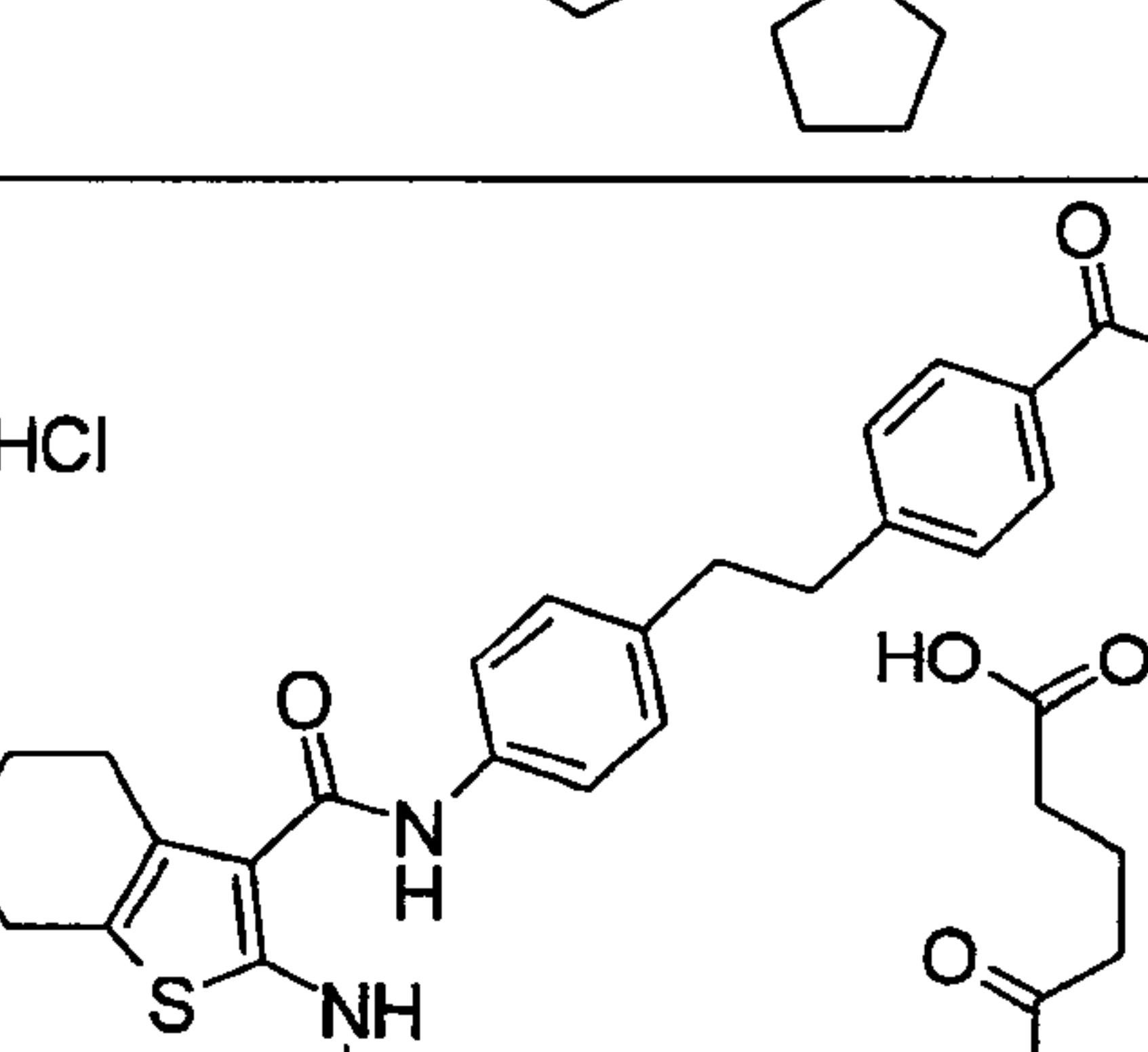
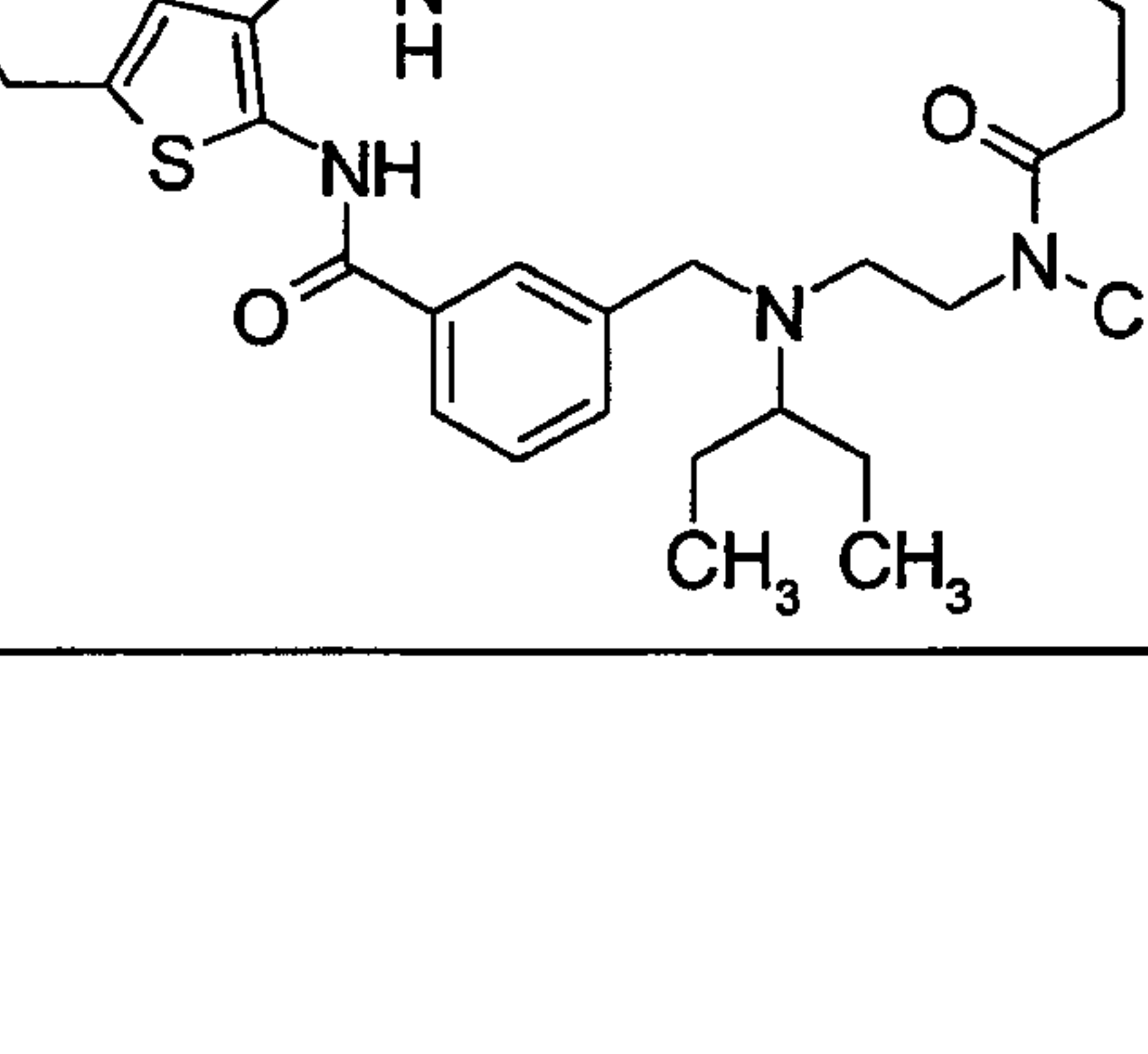
[0202]
[Table 57]

Ex	Str	Ex	Str
45	HCl	48	HCl
46	HCl	49	HCl
47	HCl	50	HCl

[0203]
[Table 58]

Ex	Str	Ex	Str
51		54	
52		55	
53		56	

[0204]
[Table 59]

Ex	Str	Ex	Str
57		60	
58		61	
59		62	

[0205]
[Table 60]

Ex	Str	Ex	Str
63	HCl	66	HCl
64	HCl	67	HCl
65	2HCl	68	HCl

[0206]

[Table 61]

Ex	Str	Ex	Str
69		72	
70		73	
71			

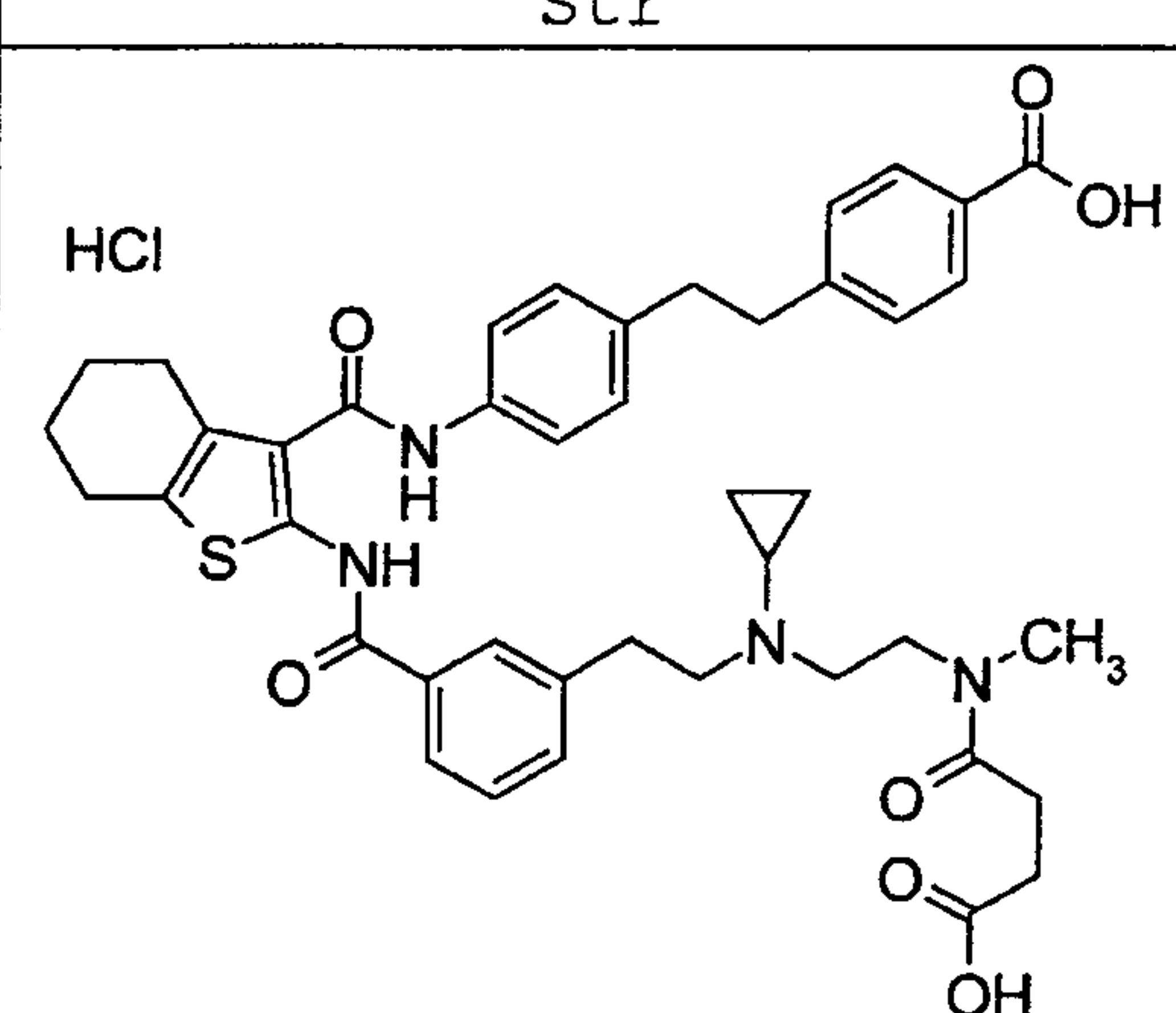
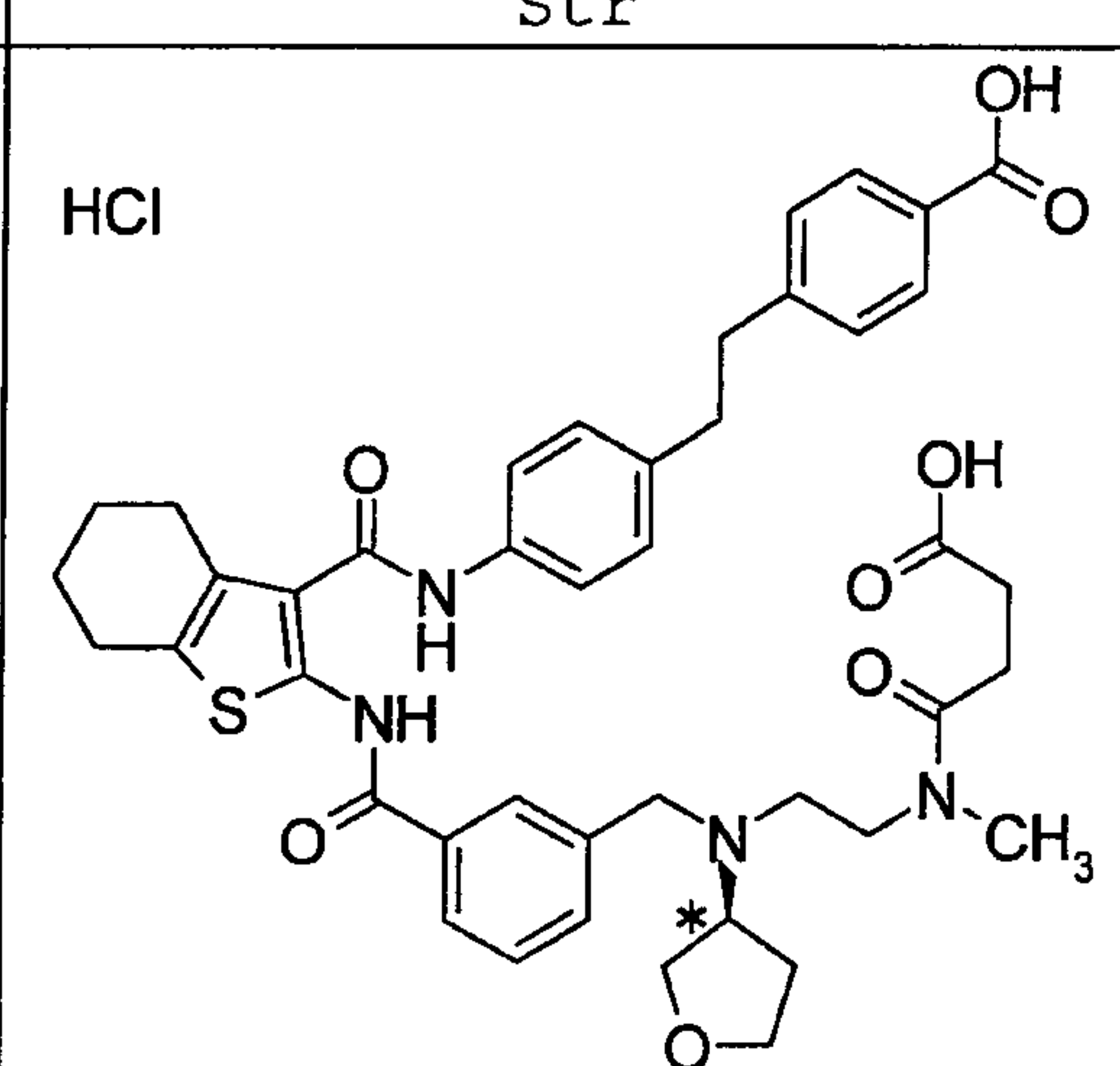
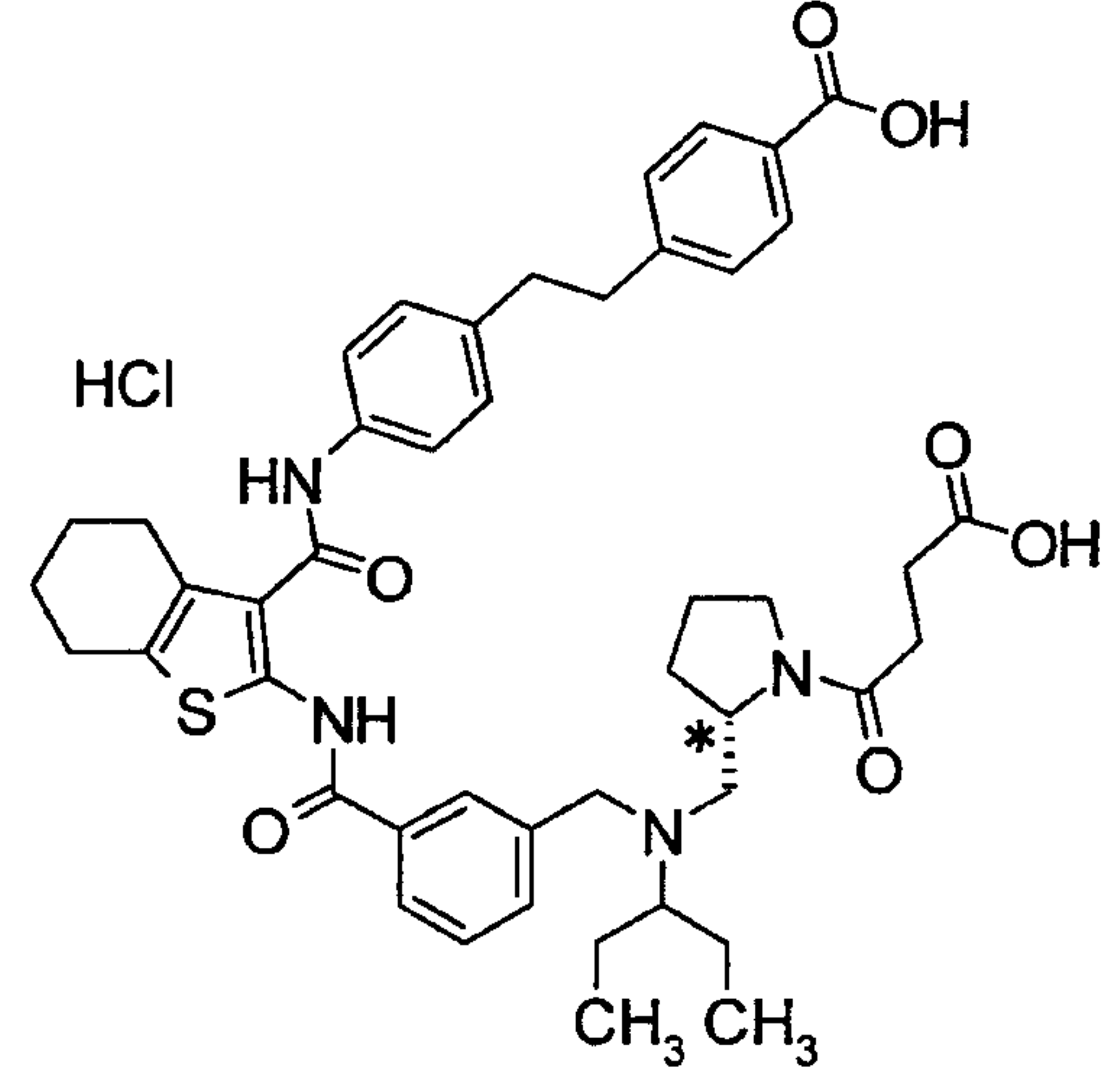
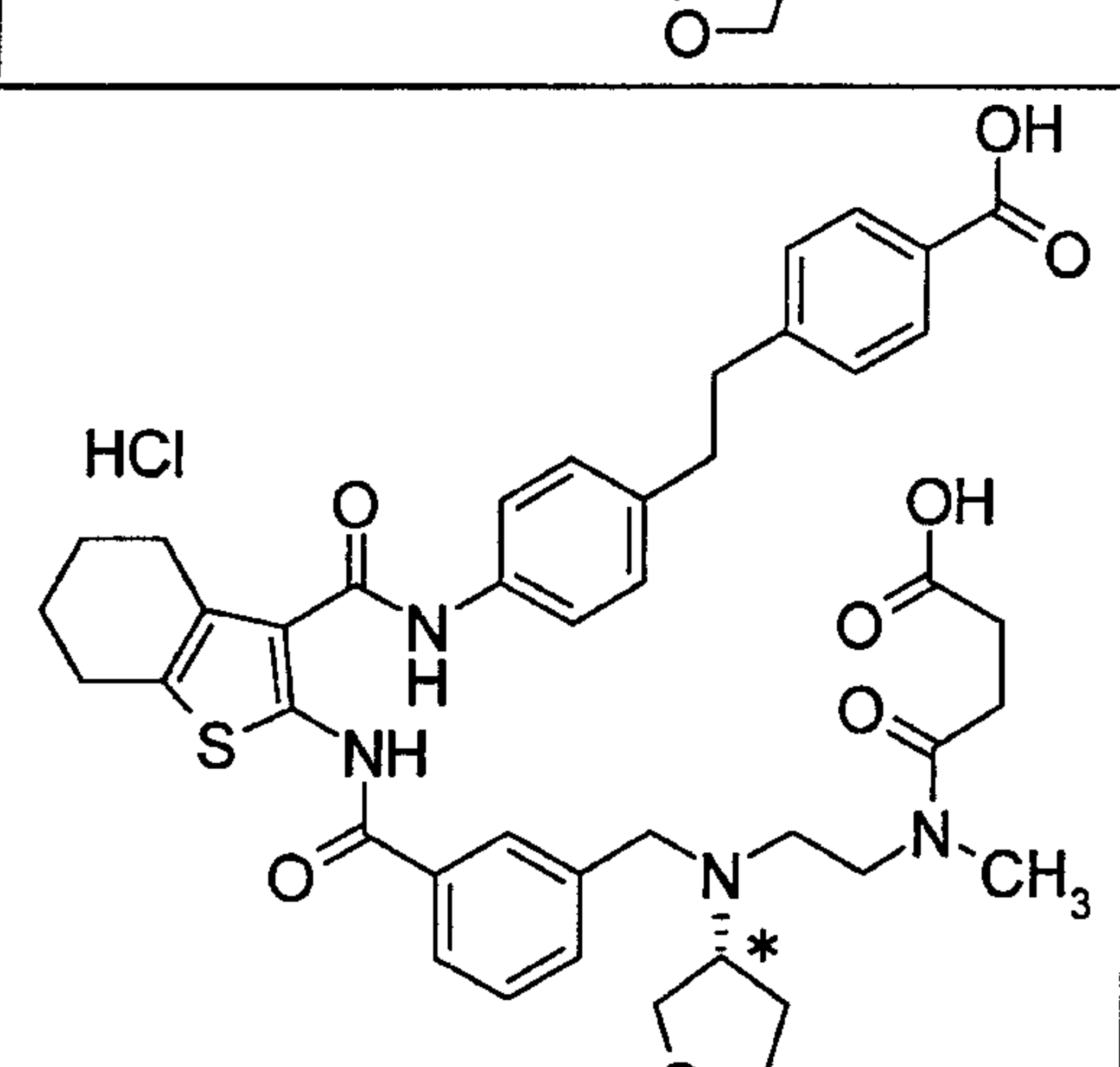
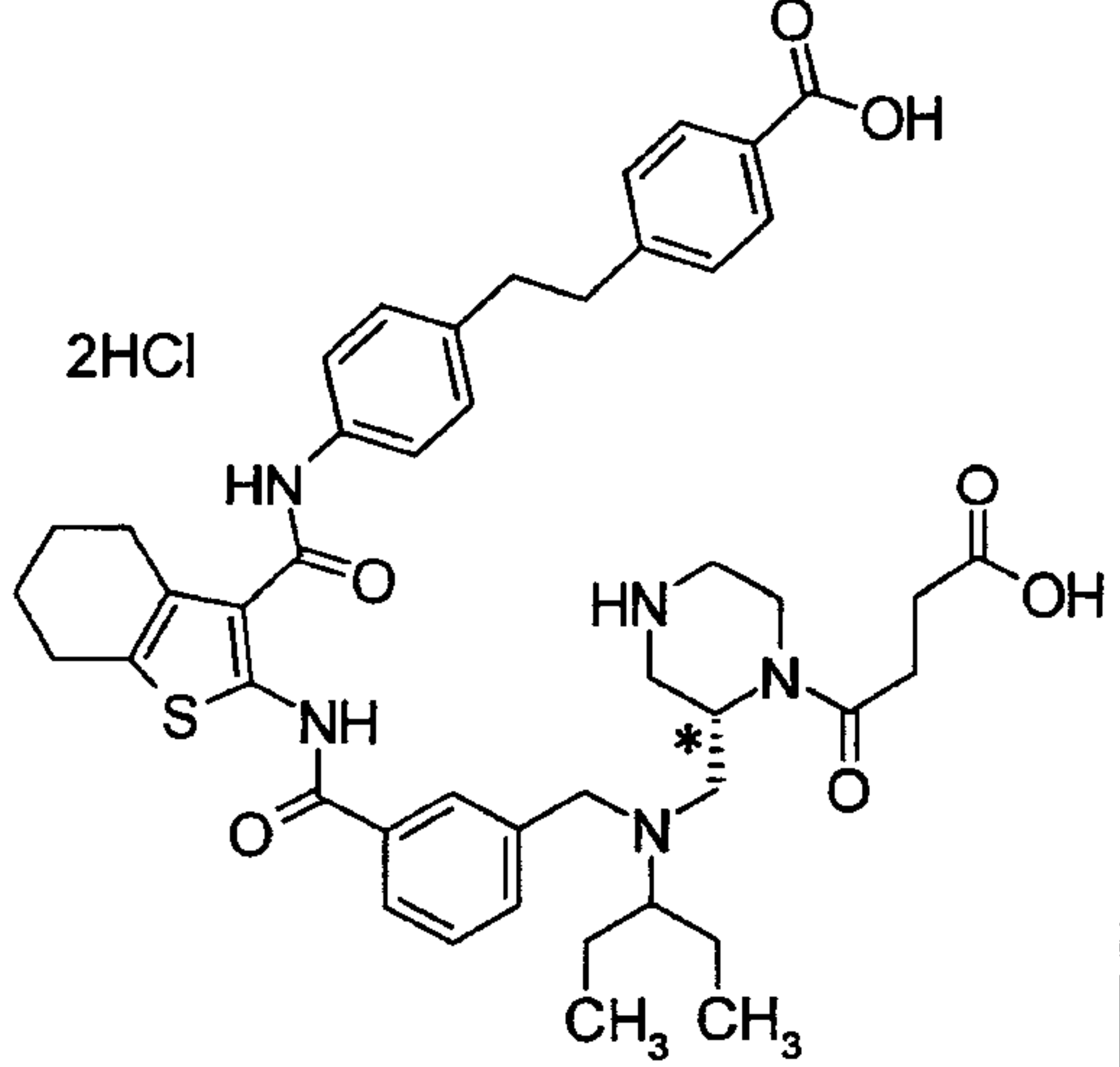
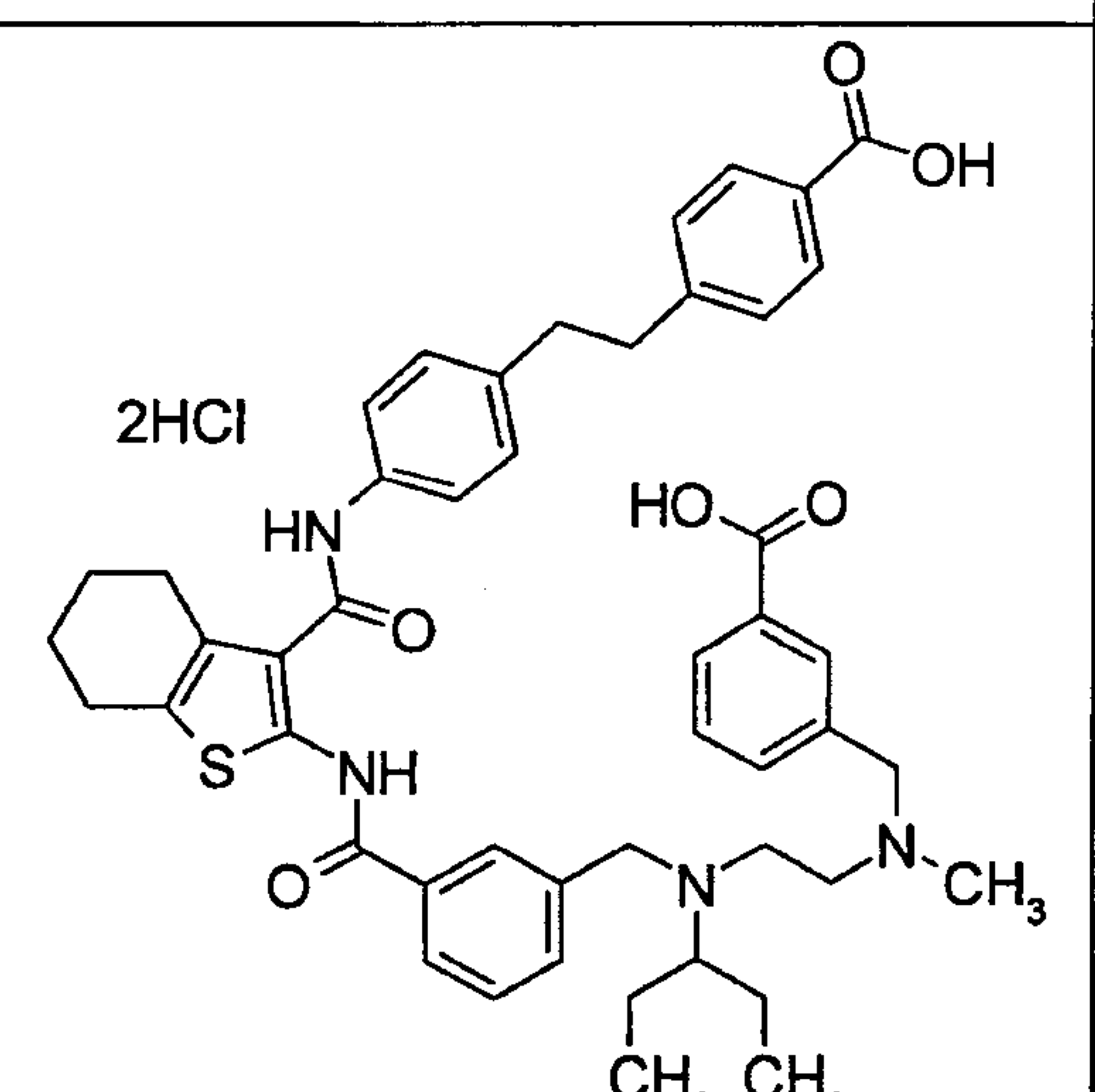
[0207]
[Table 62]

Ex	Str	Ex	Str
74	3HCl	77	HCl
75	HCl	78	HCl
76	2HCl	79	HCl

[0208]
[Table 63]

Ex	Str	Ex	Str
80	 Chemical structure 80 shows a thienothiopyran core. It has a carboxylic acid group (-COOH) at the 4-position of the thiopyran ring. A side chain at the 2-position includes a chiral center marked with an asterisk (*), a hydroxyl group (-OH), and a methyl group (-CH ₃). The side chain also features a dimethylamino group (-N(CH ₃) ₂) and a phenyl ring.	83	 Chemical structure 83 shows a thienothiopyran core. It has a carboxylic acid group (-COOH) at the 4-position of the thiopyran ring. A side chain at the 2-position includes a dimethylamino group (-N(CH ₃) ₂) and a phenyl ring.
81	 Chemical structure 81 shows a thienothiopyran core. It has a carboxylic acid group (-COOH) at the 4-position of the thiopyran ring. A side chain at the 2-position includes a dimethylamino group (-N(CH ₃) ₂) and a phenyl ring.	84	 Chemical structure 84 shows a thienothiopyran core. It has a carboxylic acid group (-COOH) at the 4-position of the thiopyran ring. A side chain at the 2-position includes a dimethylamino group (-N(CH ₃) ₂) and a phenyl ring.
82	 Chemical structure 82 shows a thienothiopyran core. It has a carboxylic acid group (-COOH) at the 4-position of the thiopyran ring. A side chain at the 2-position includes a dimethylamino group (-N(CH ₃) ₂) and a phenyl ring.	85	 Chemical structure 85 shows a thienothiopyran core. It has a carboxylic acid group (-COOH) at the 4-position of the thiopyran ring. A side chain at the 2-position includes a dimethylamino group (-N(CH ₃) ₂) and a phenyl ring.

[0209]
[Table 64]

Ex	Str	Ex	Str
86		89	
87		90	
88		91	

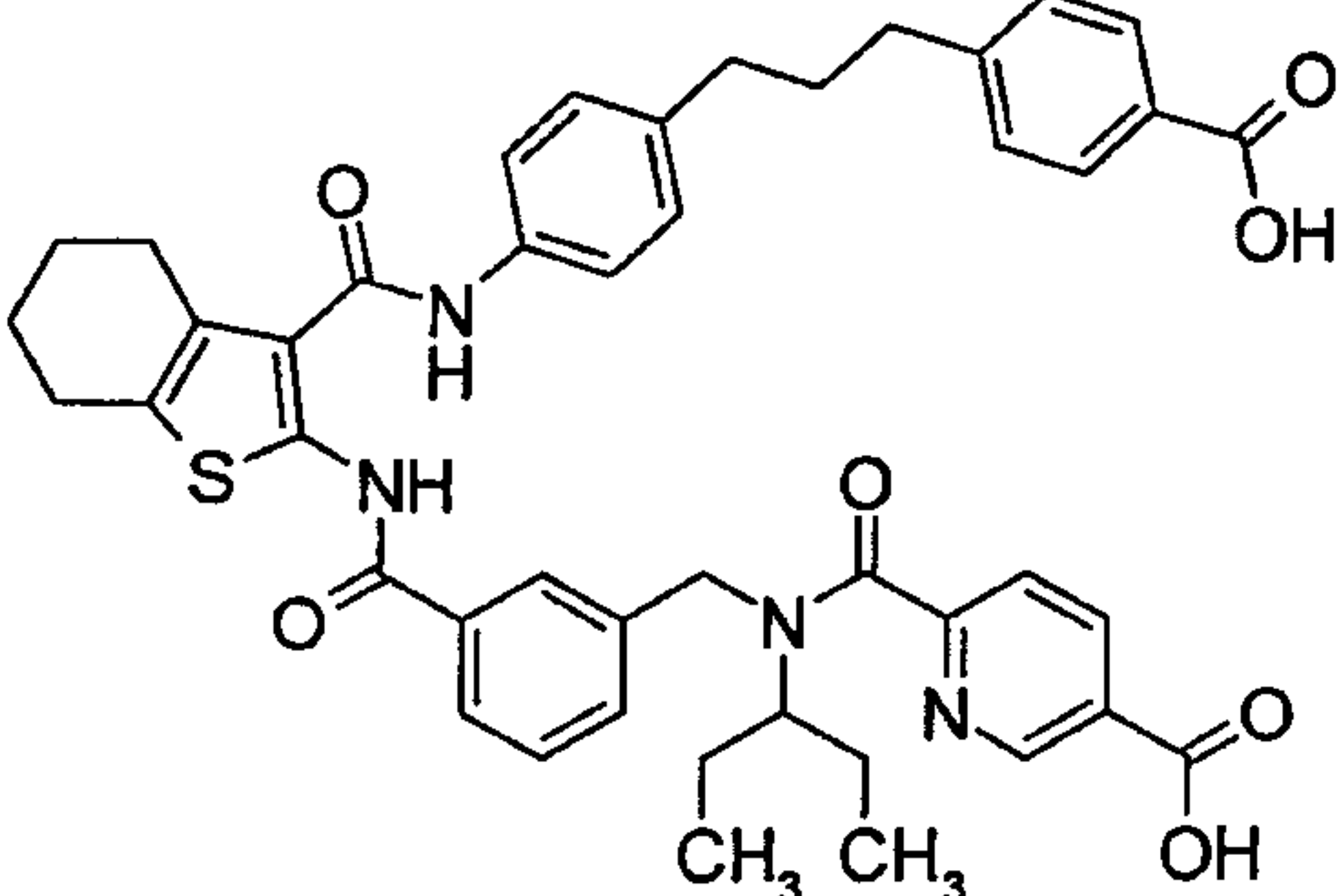
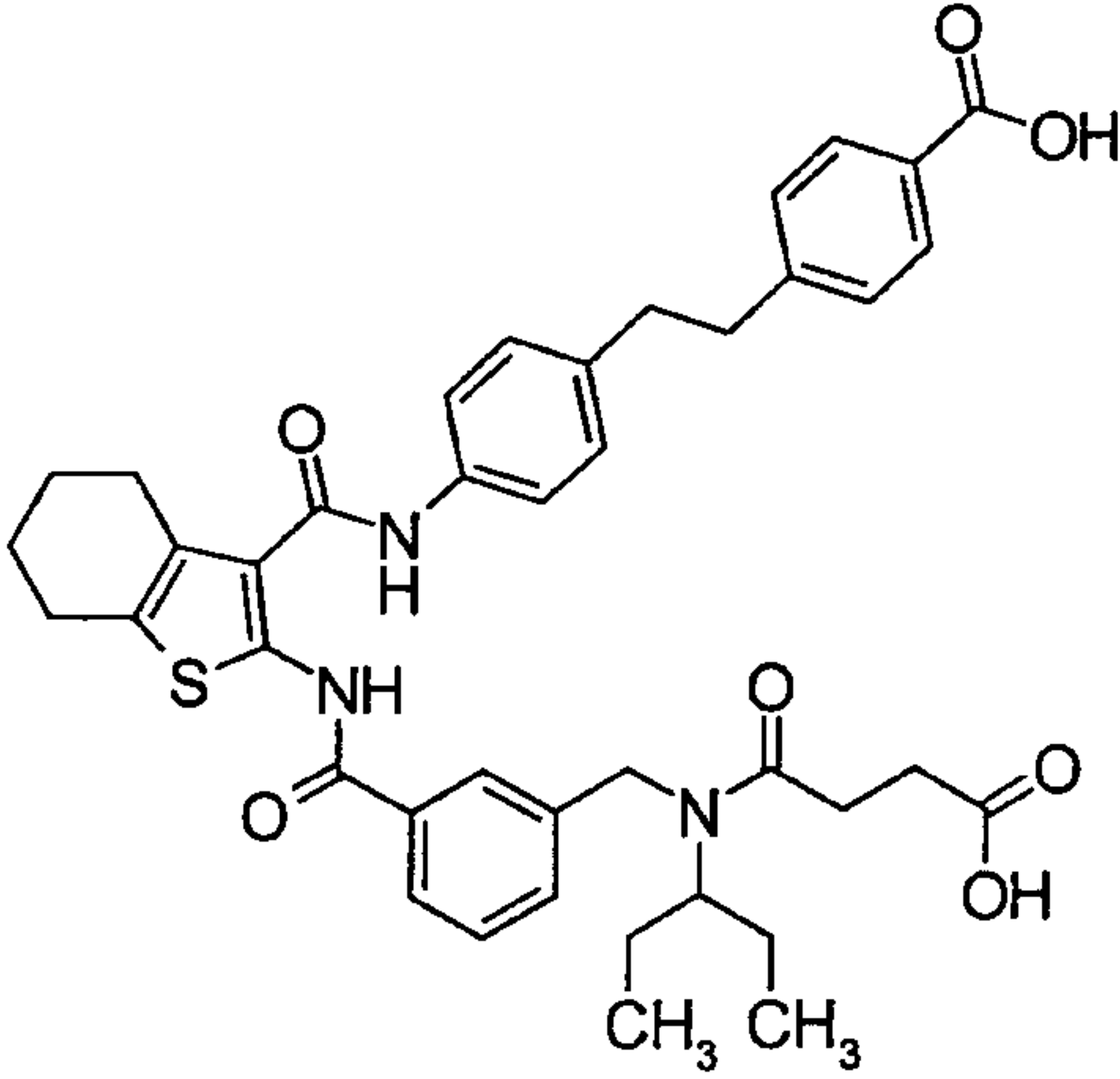
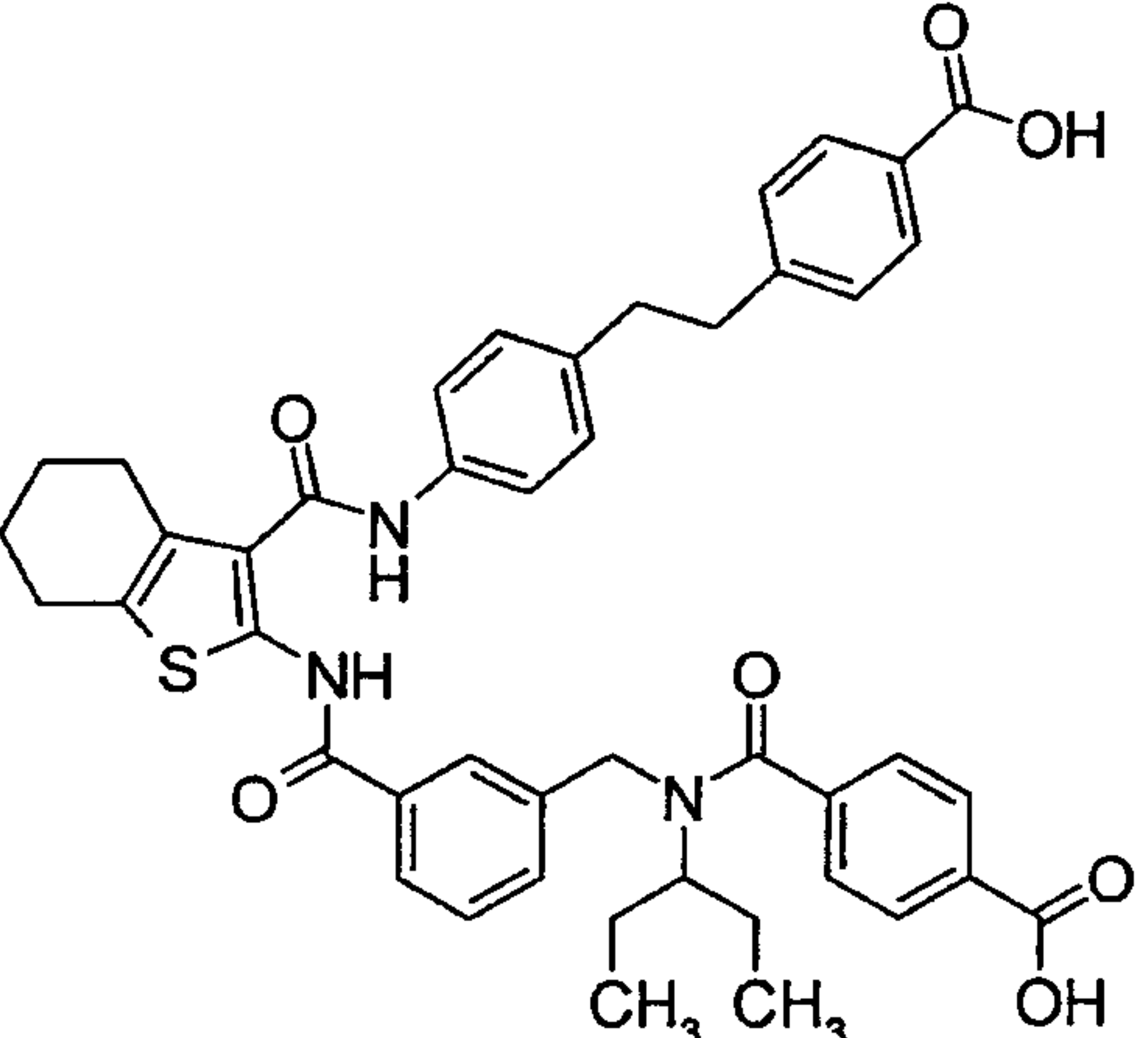
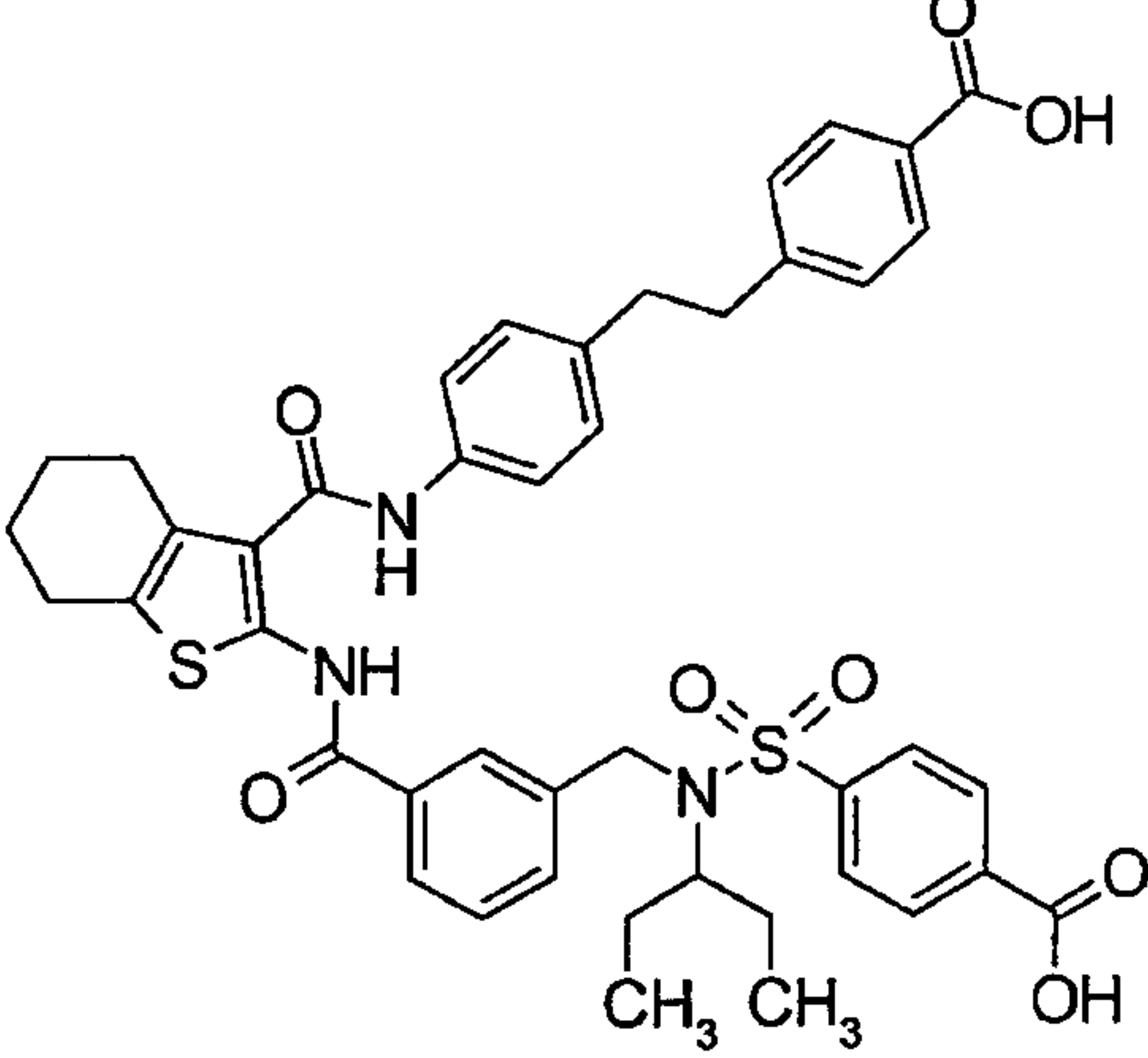
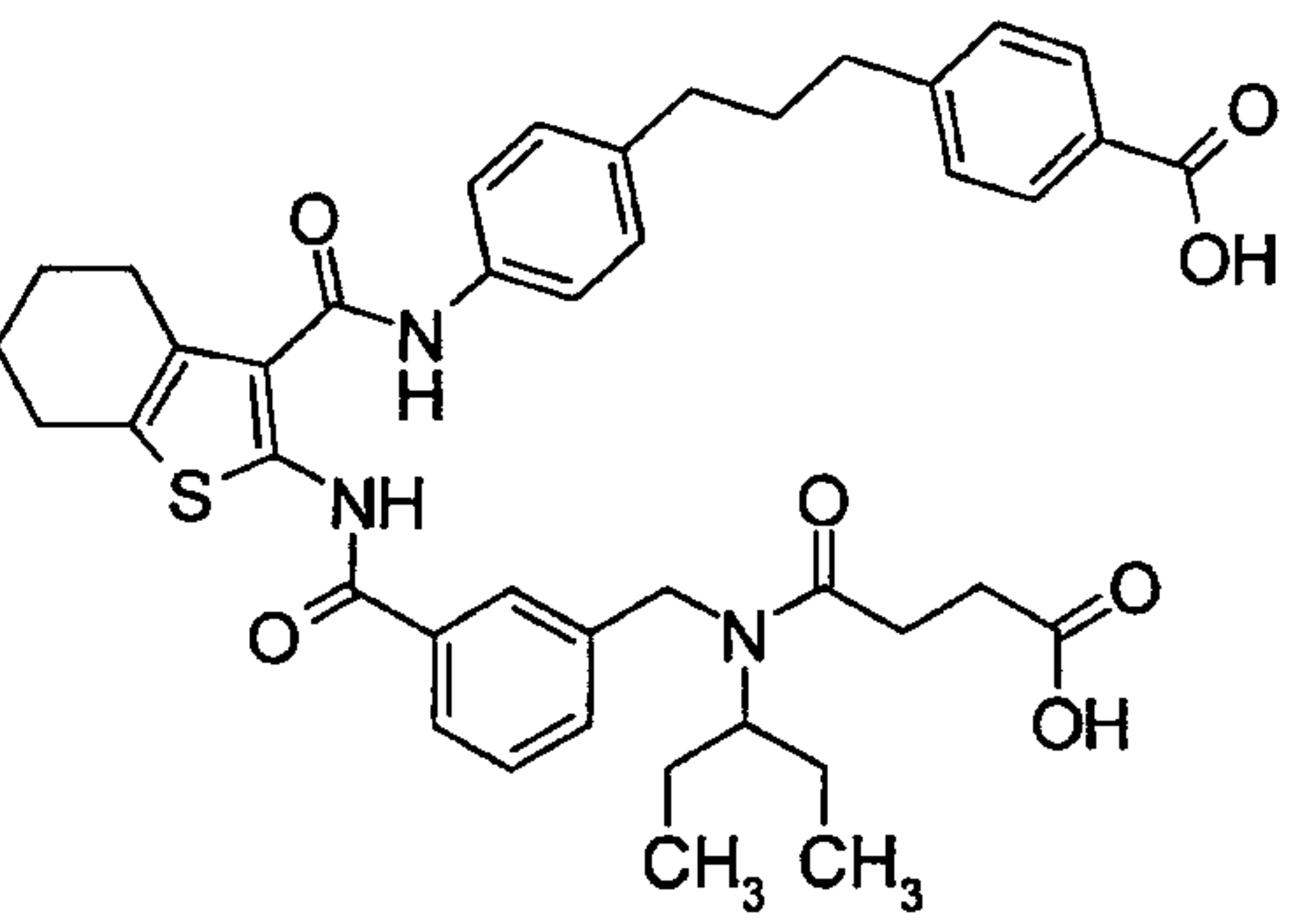
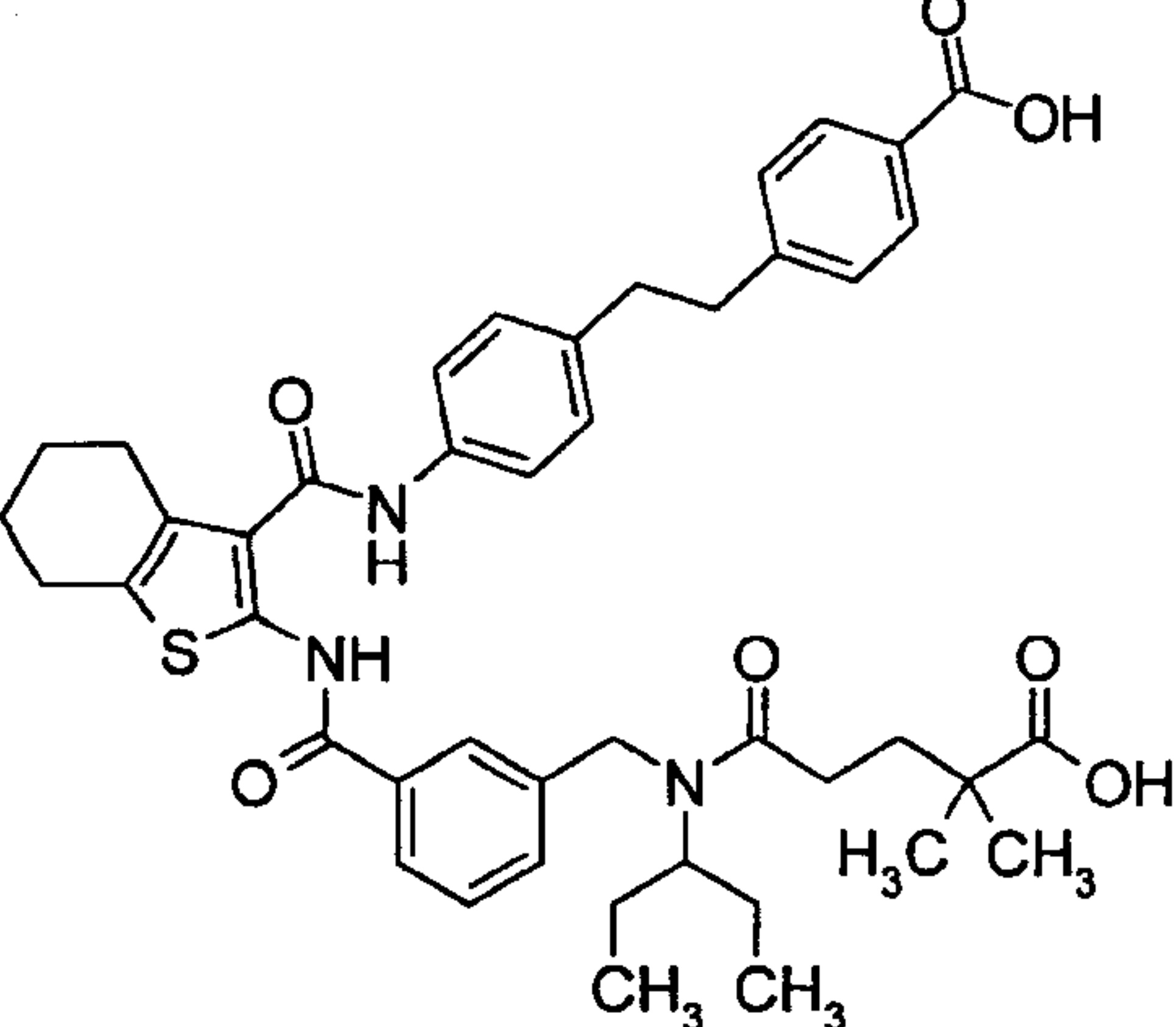
[0210]
[Table 65]

Ex	Str	Ex	Str
92	2HCl	95	HCl
93	2HCl	96	2HCl
94	HCl	97	HCl

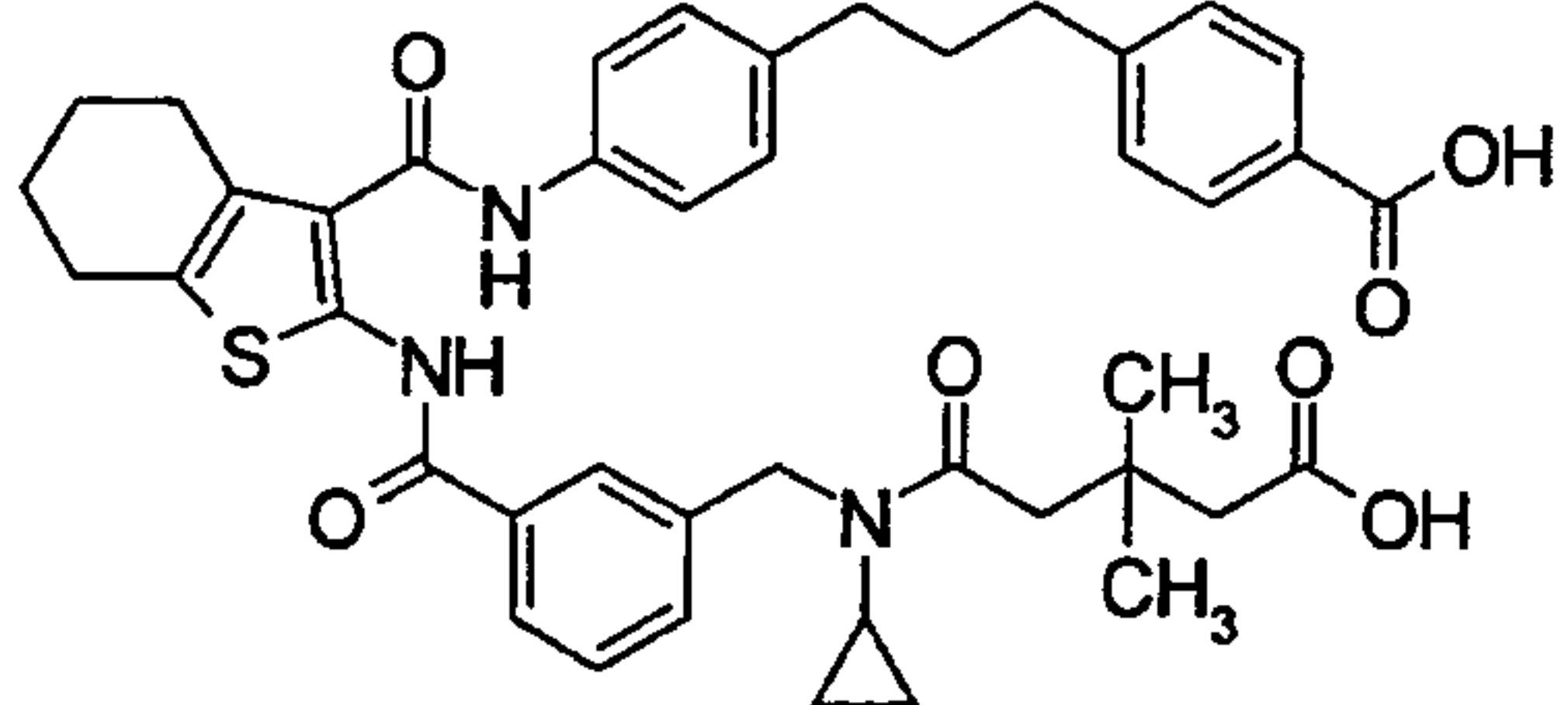
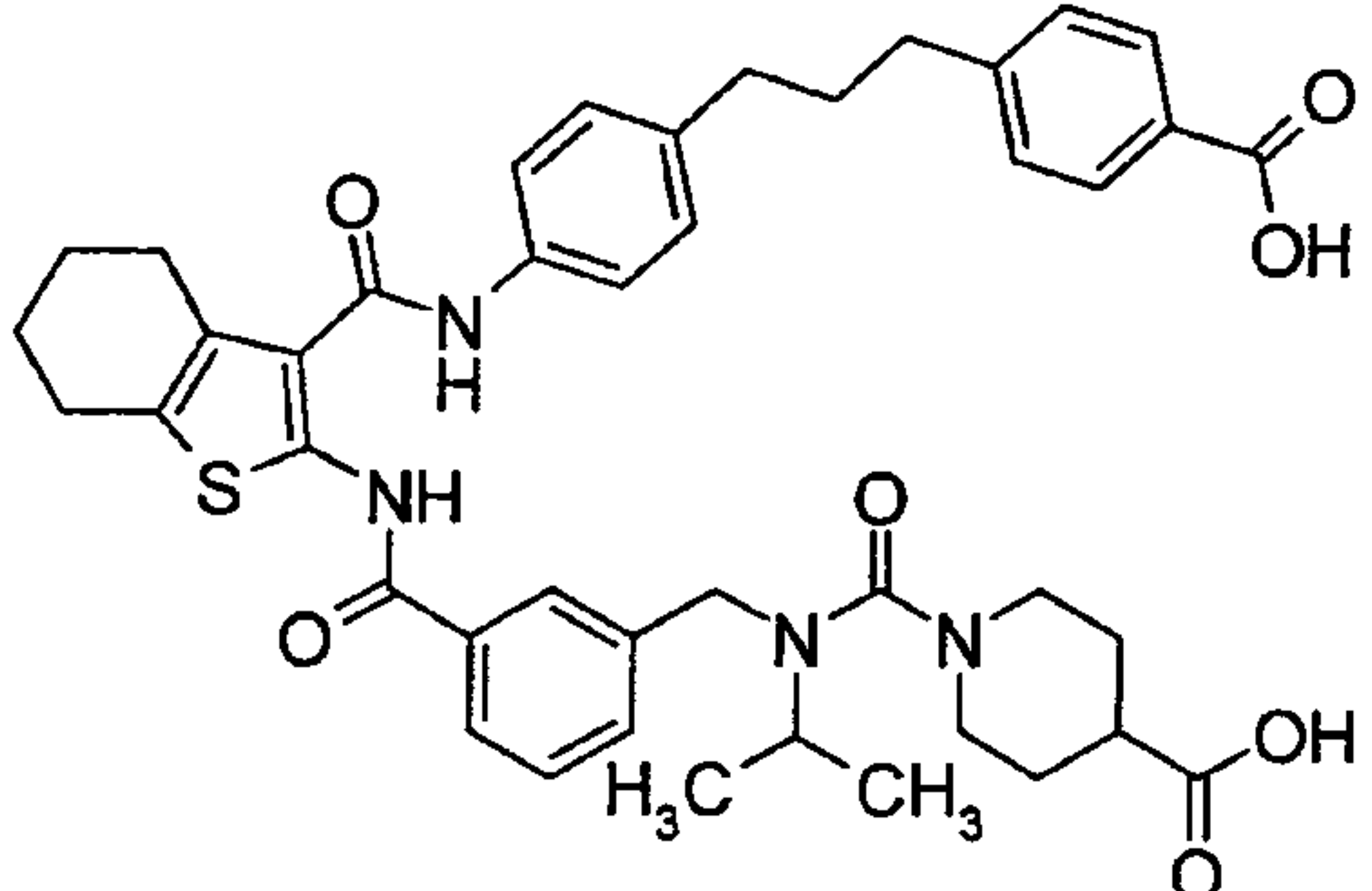
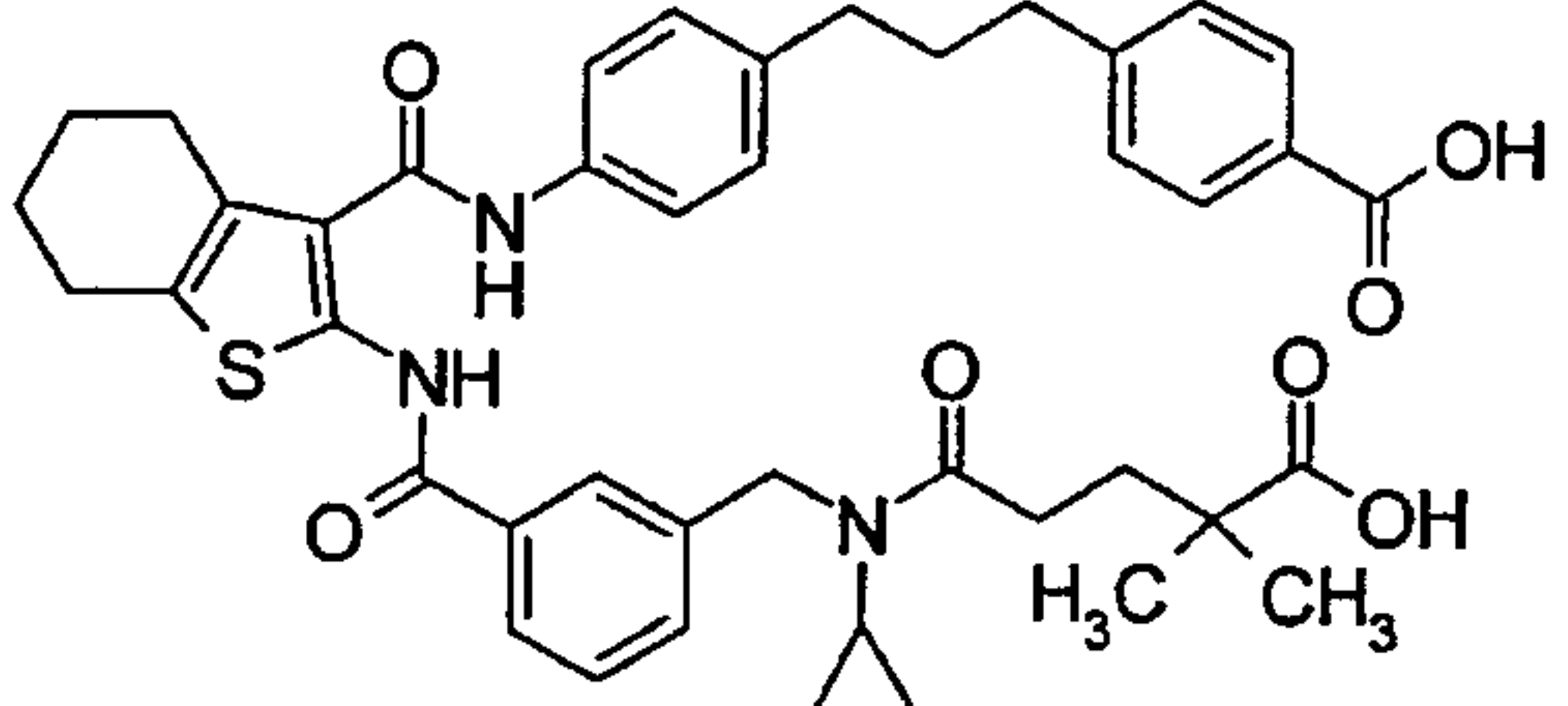
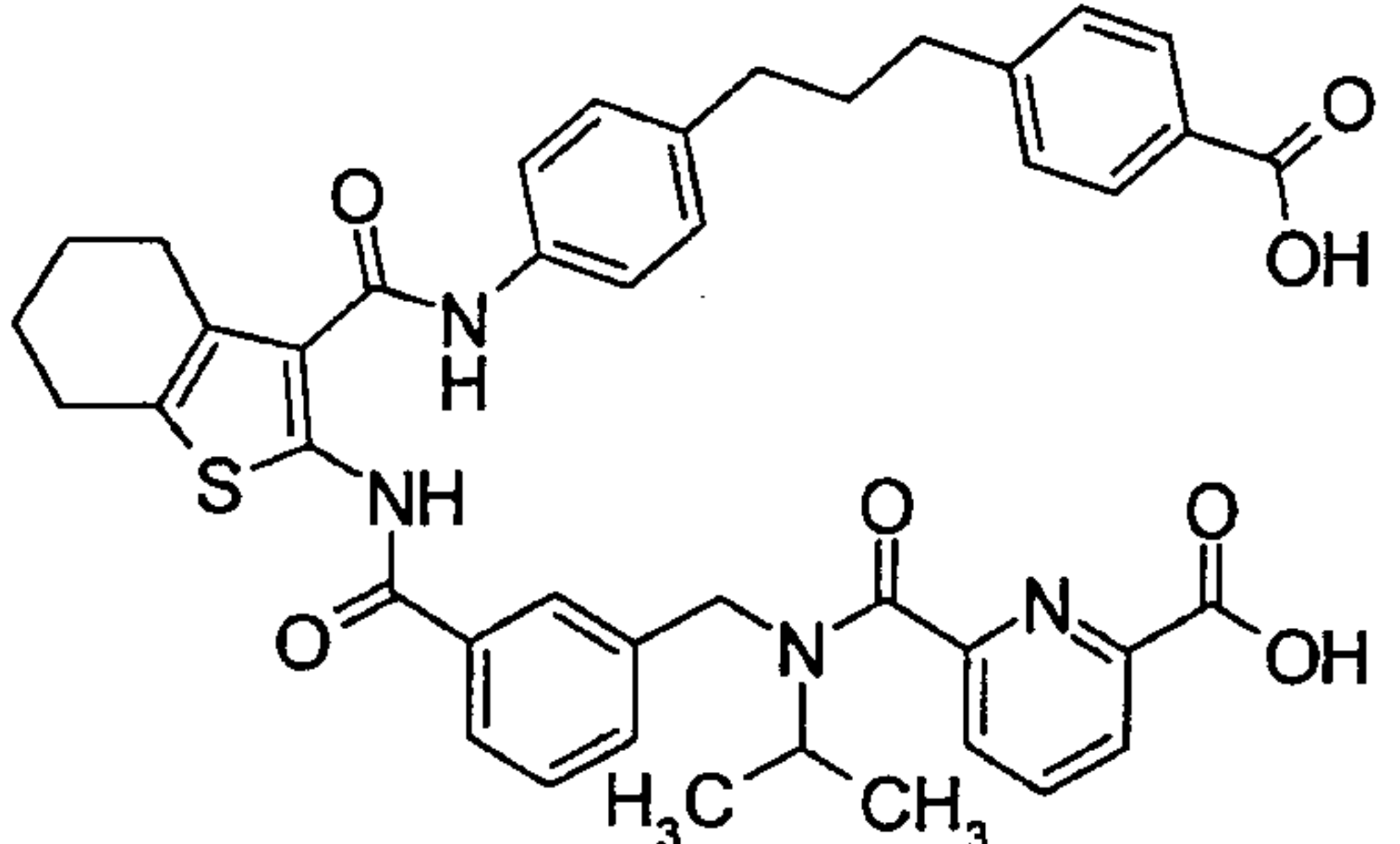
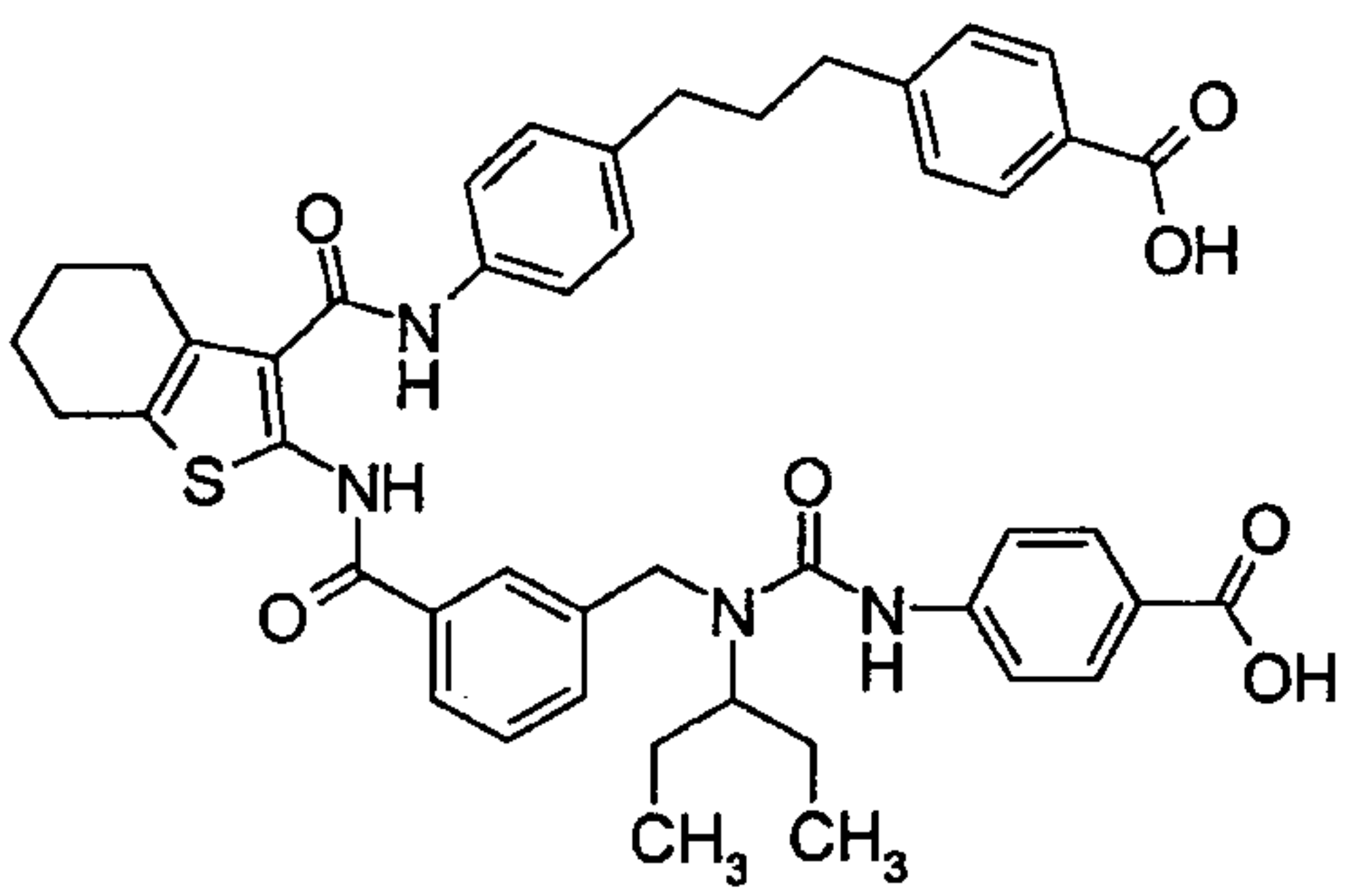
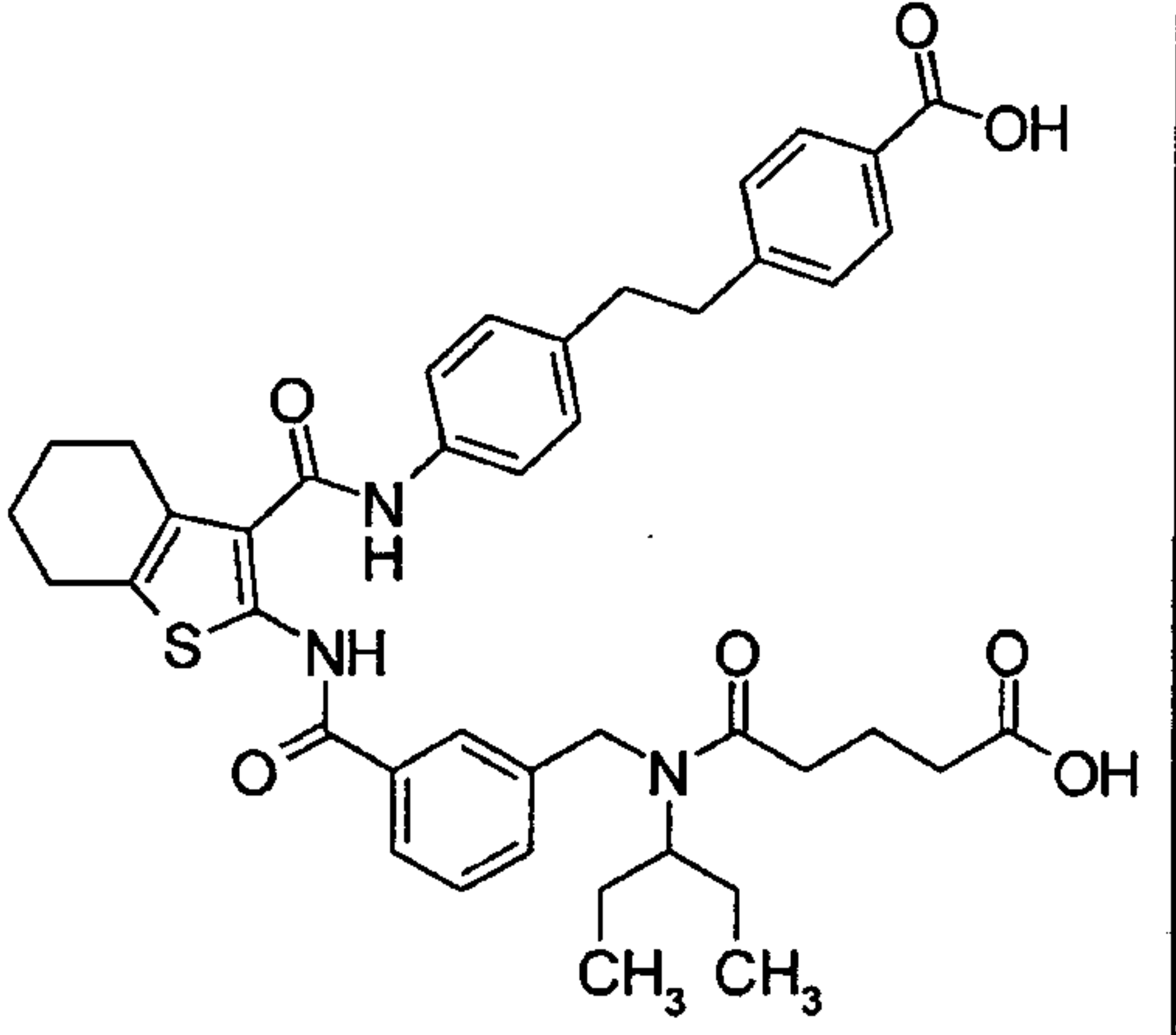
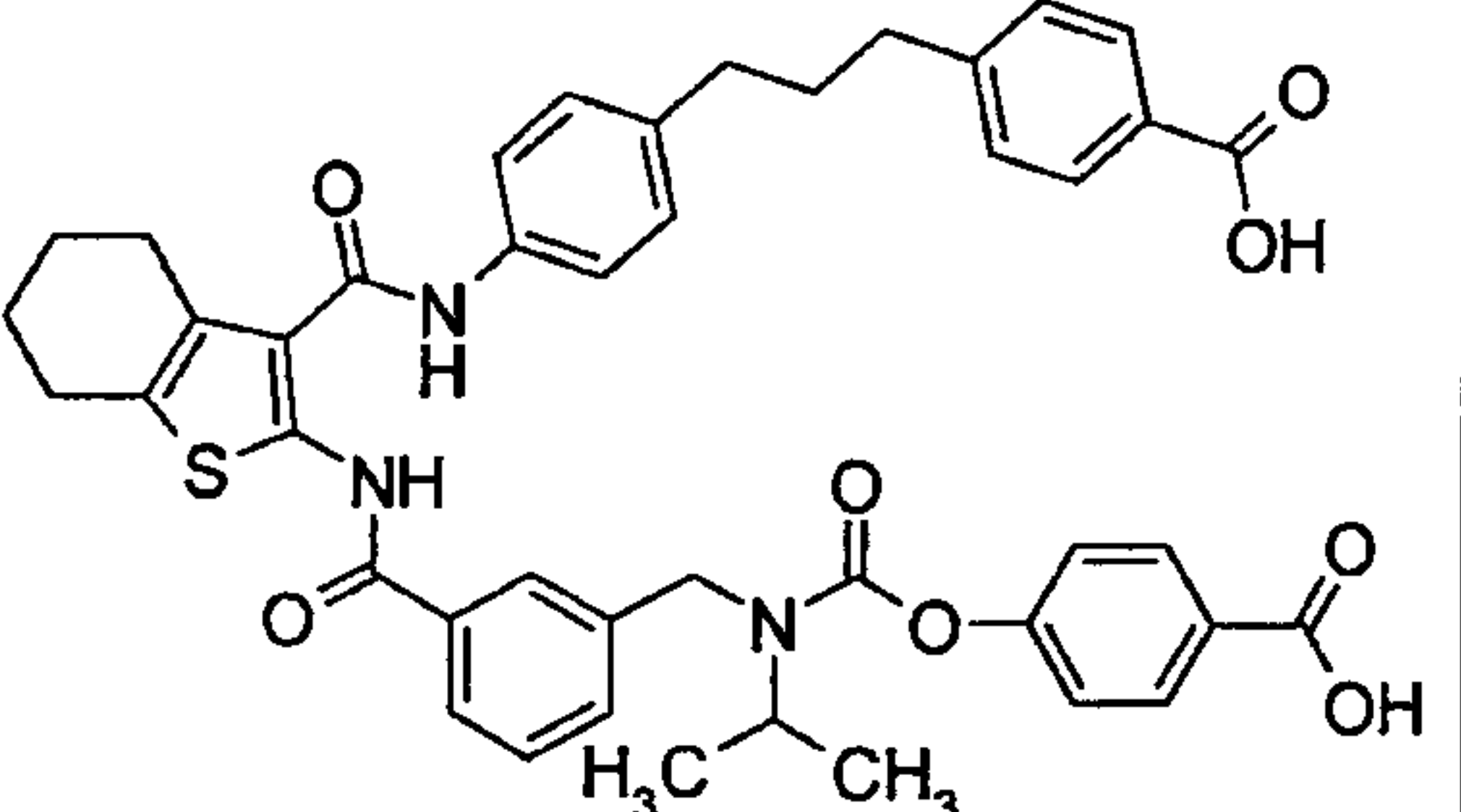
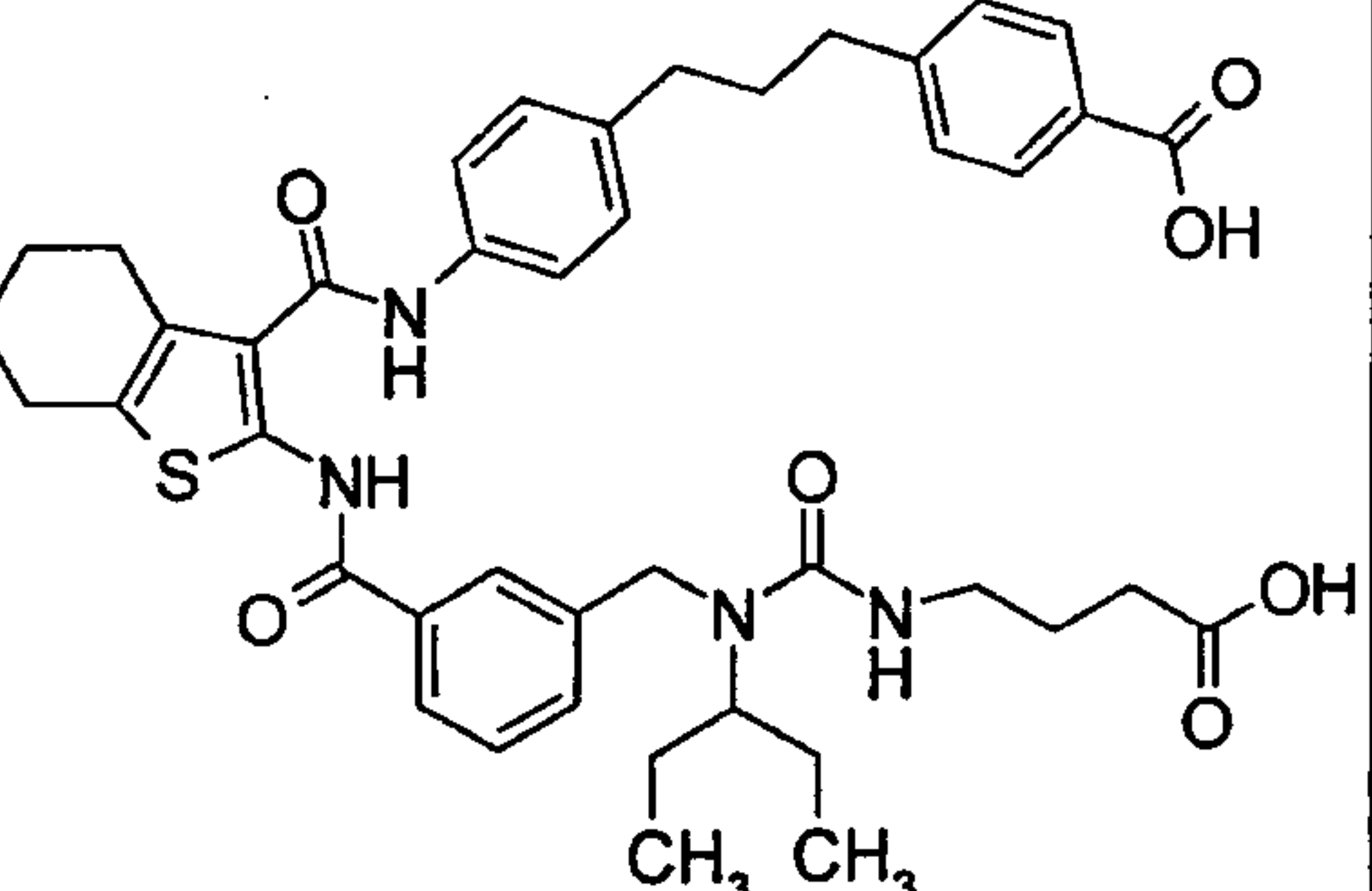
[0211]
[Table 66]

Ex	Str	Ex	Str
98	HCl	101	
99	2HCl	102	
100		103	

[0212]
[Table 67]

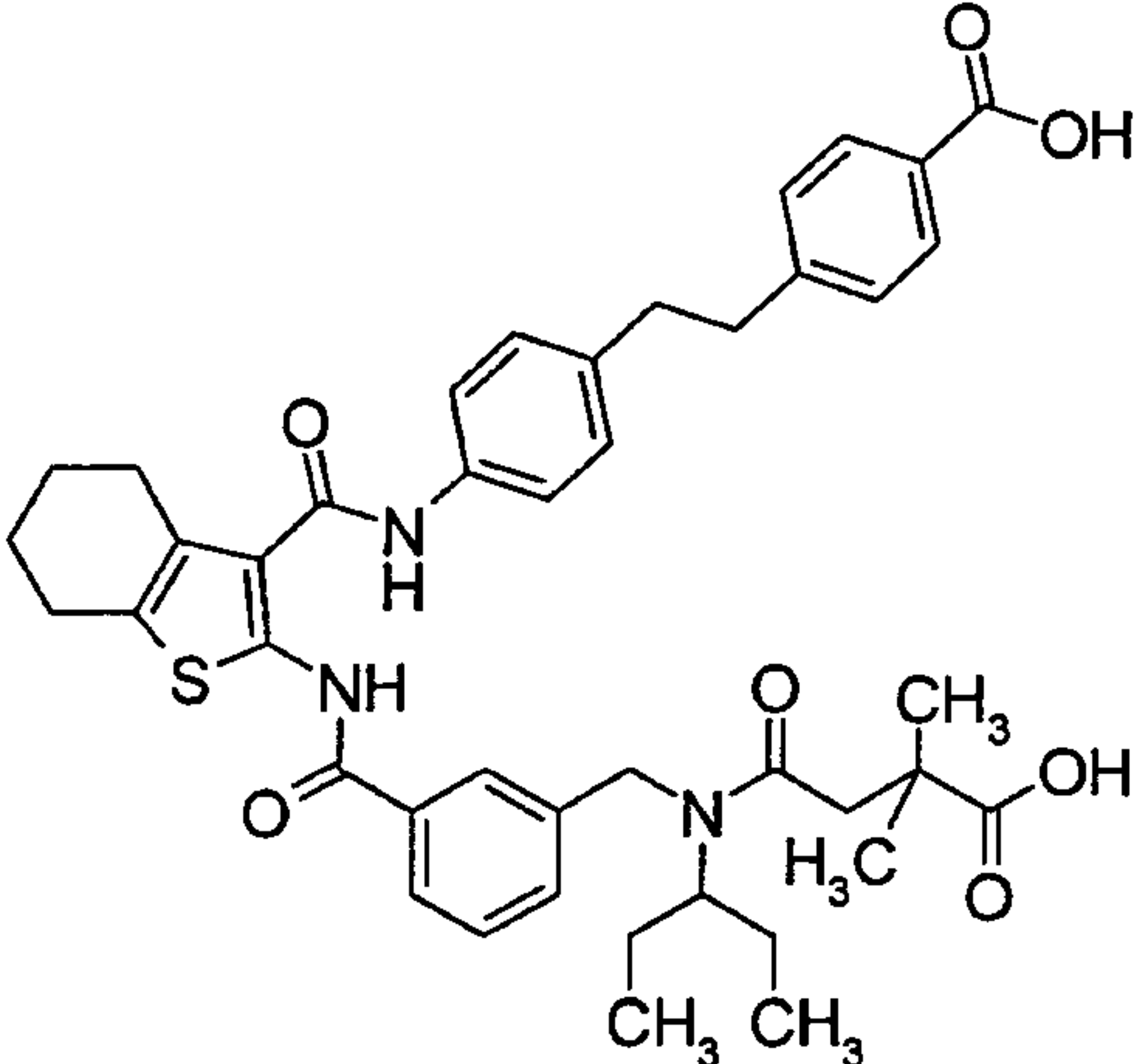
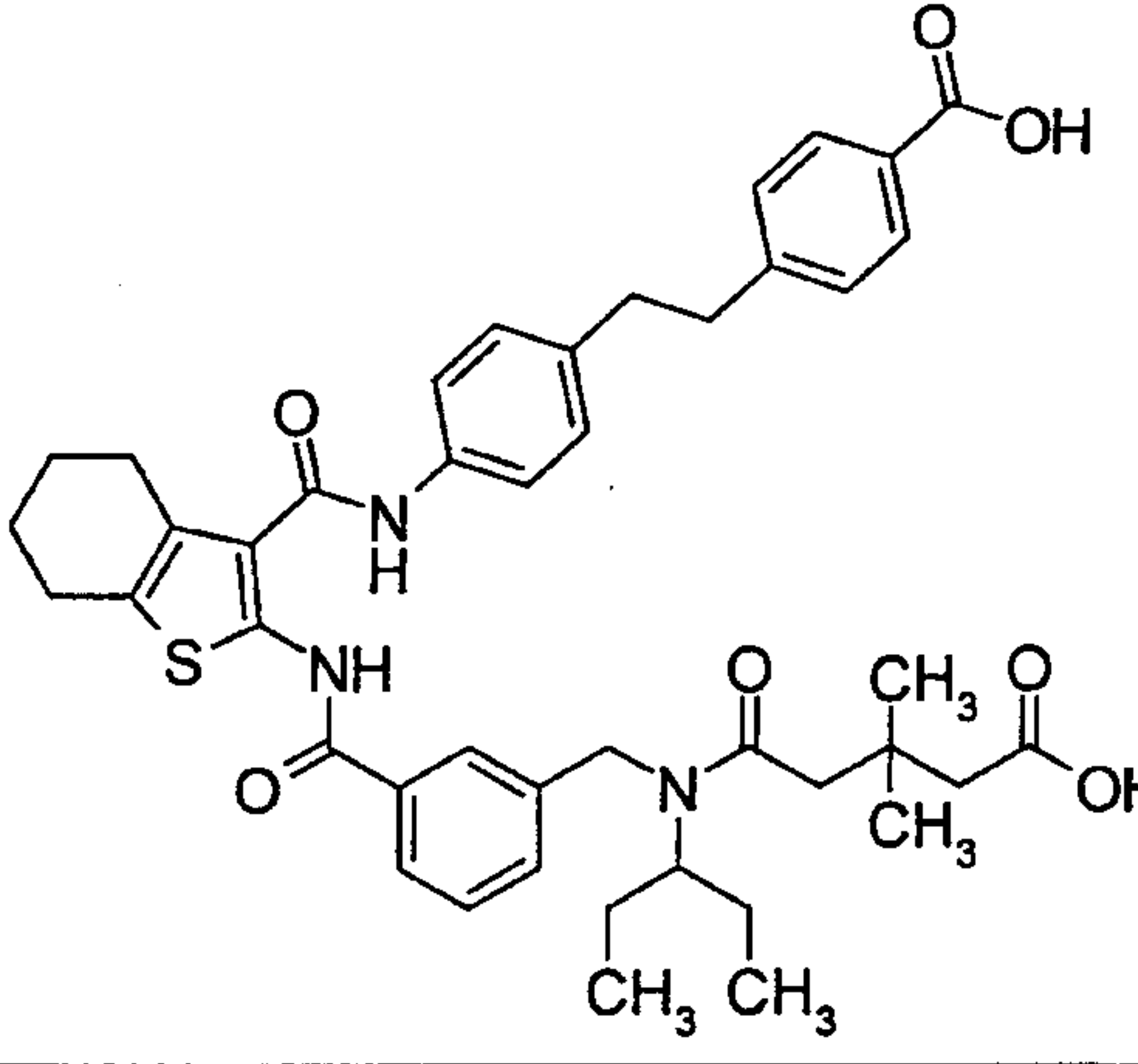
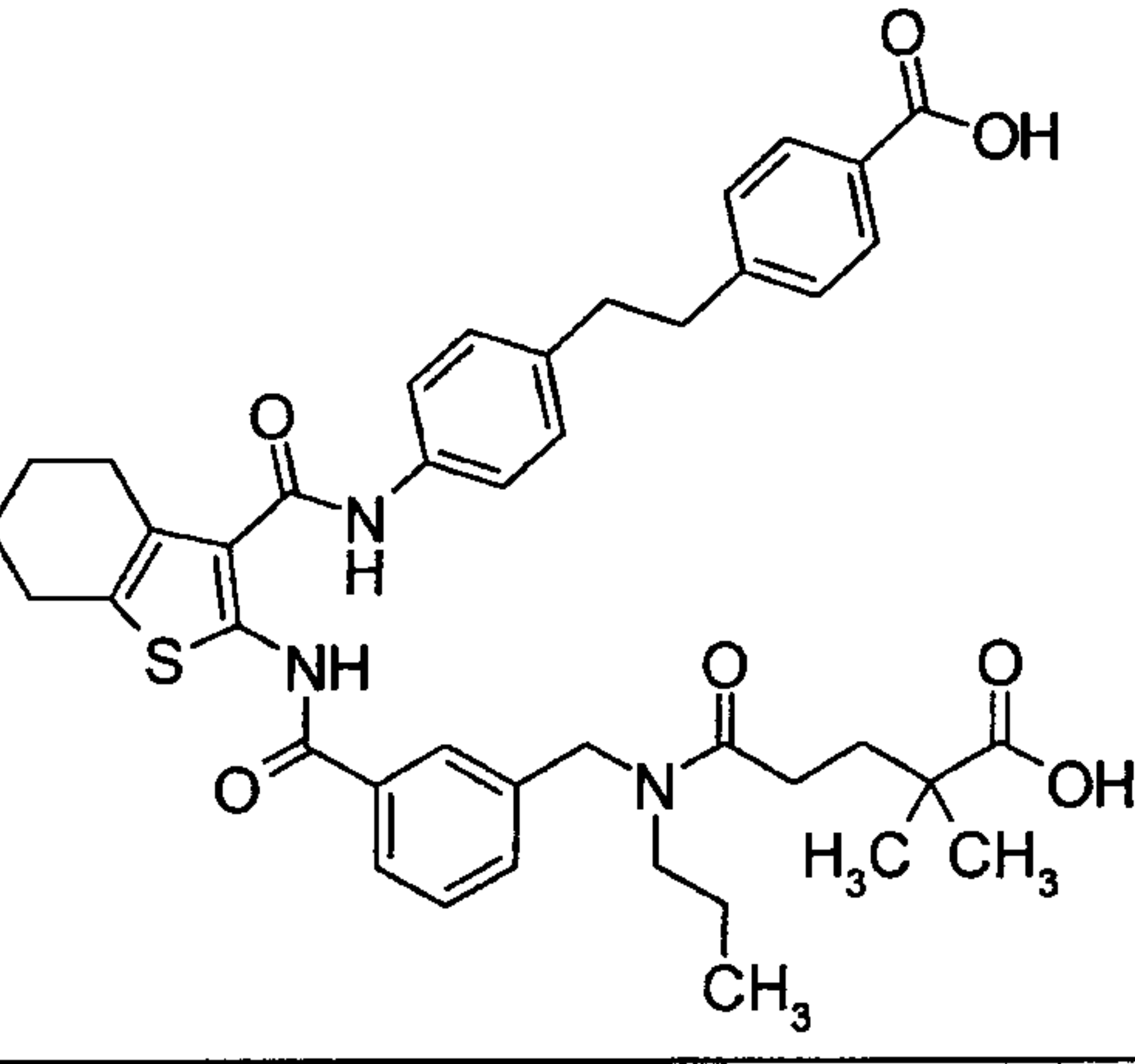
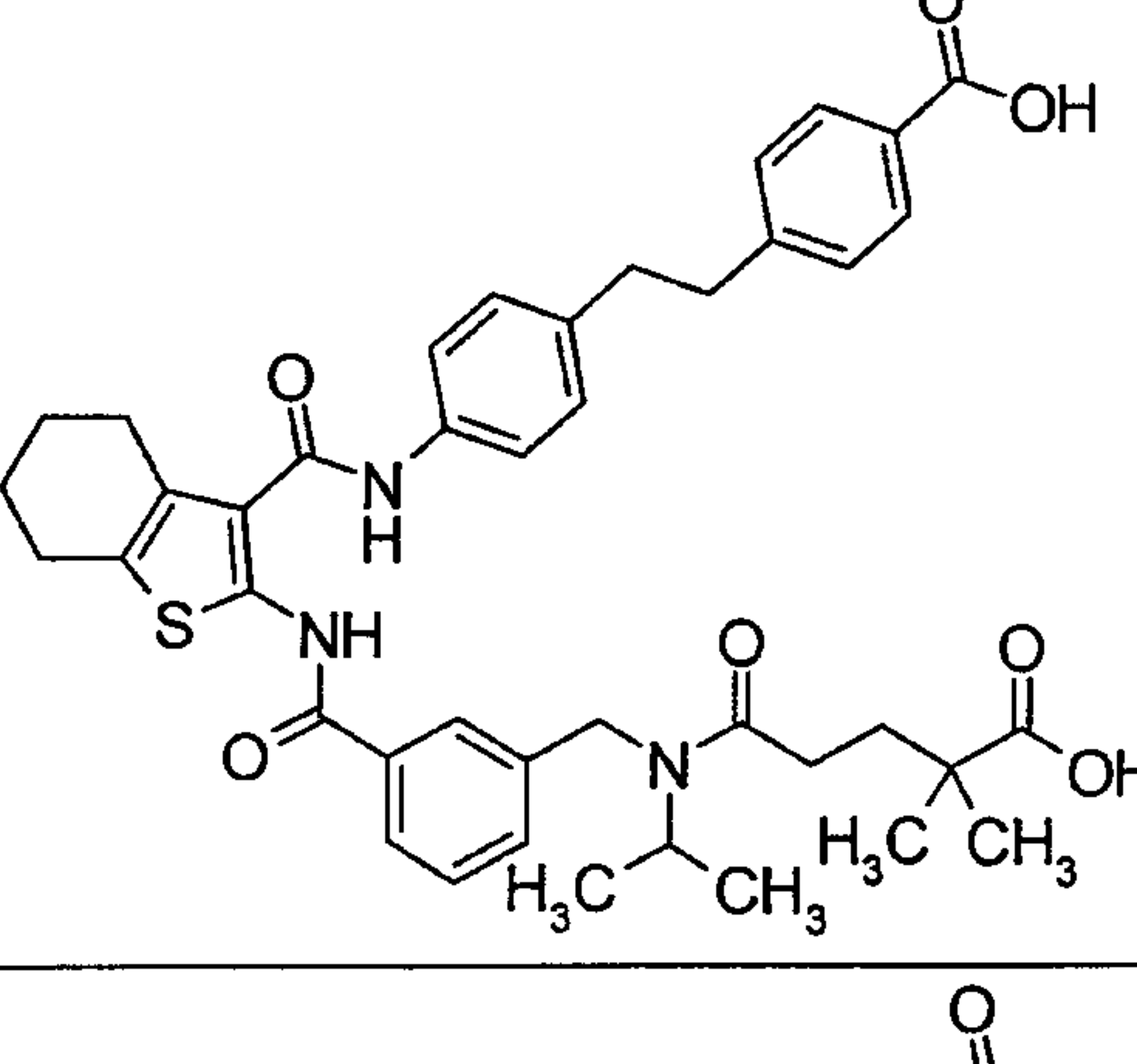
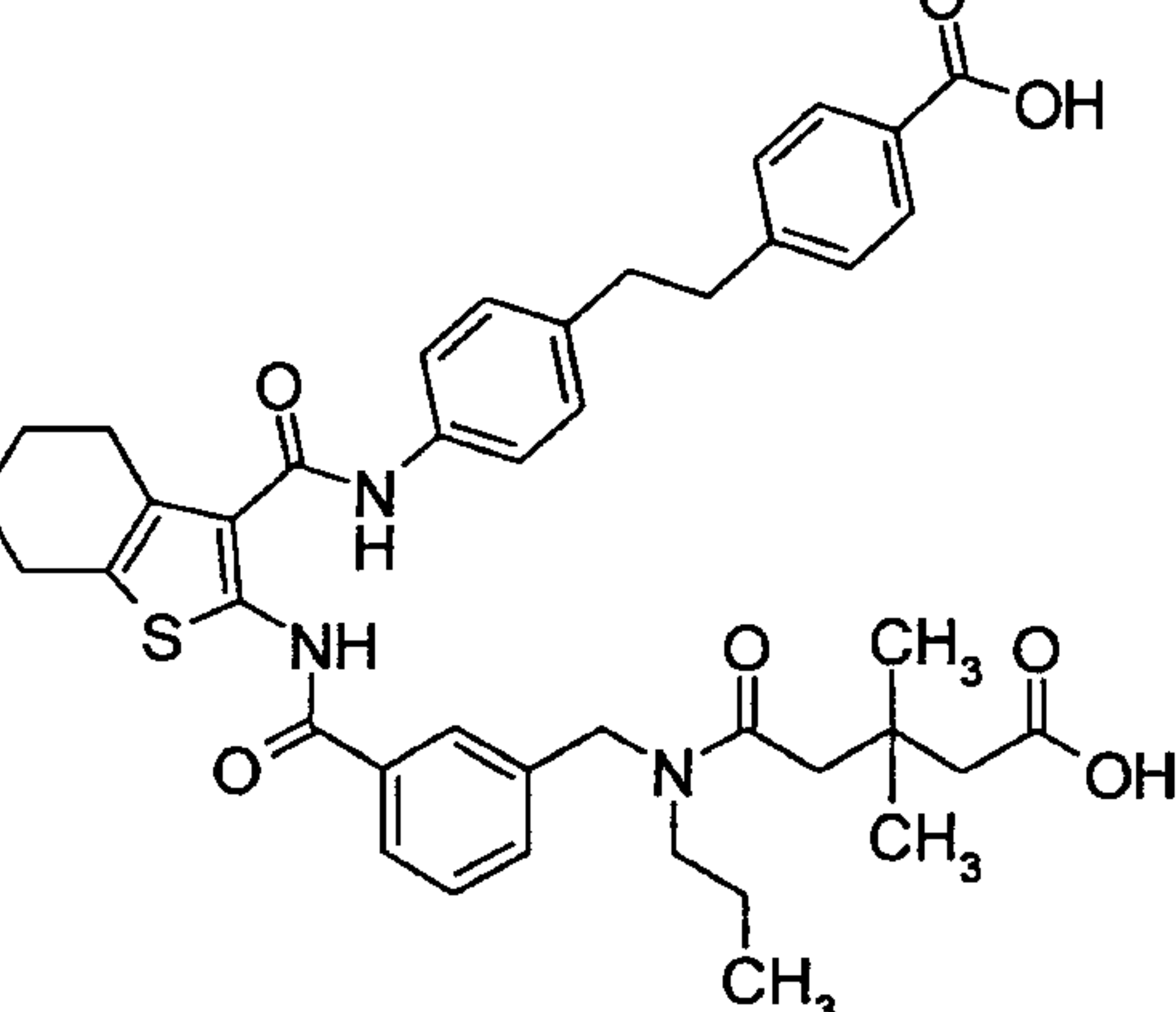
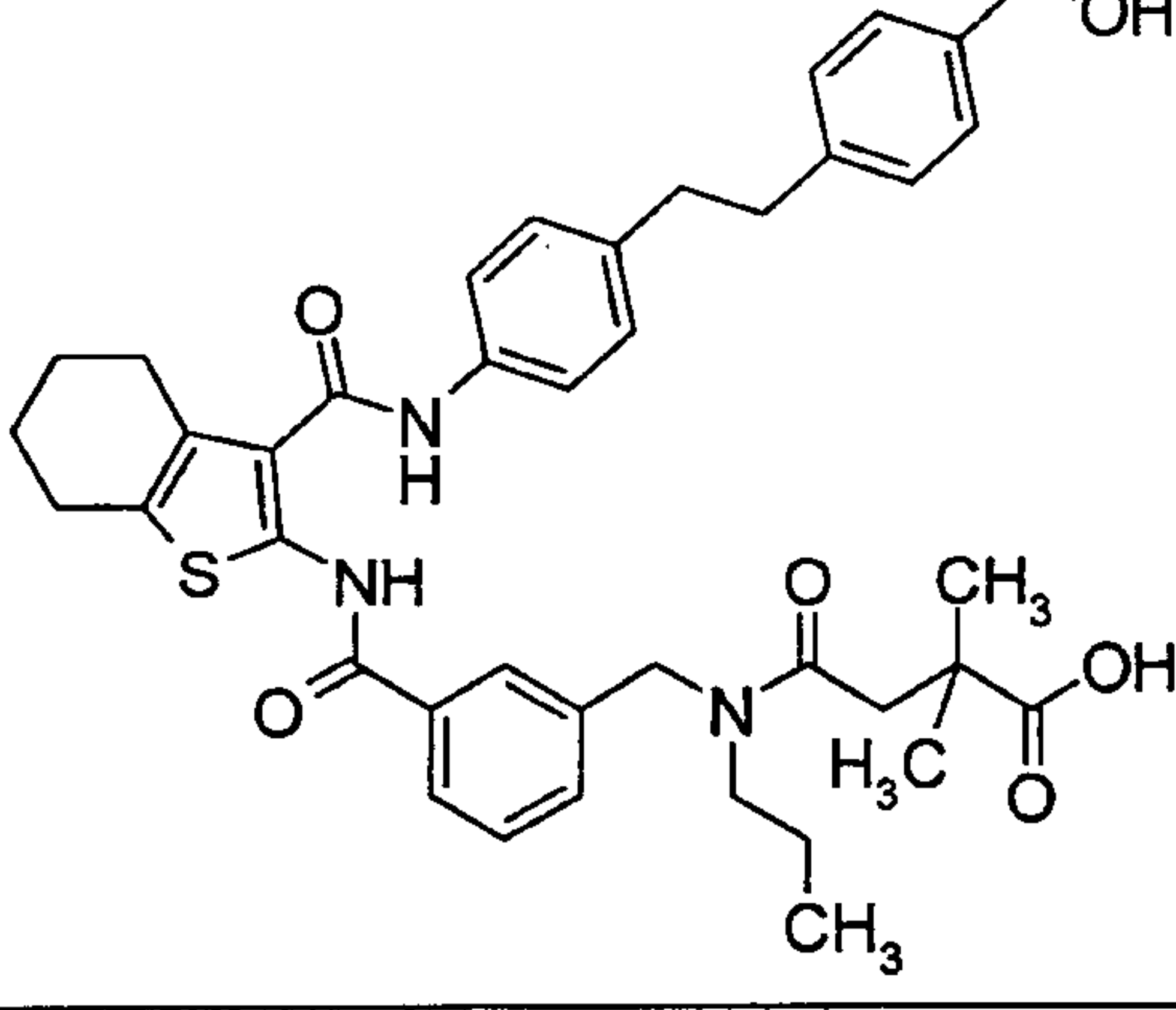
Ex	Str	Ex	Str
104		107	
105		108	
106		109	

[0213]
[Table 68]

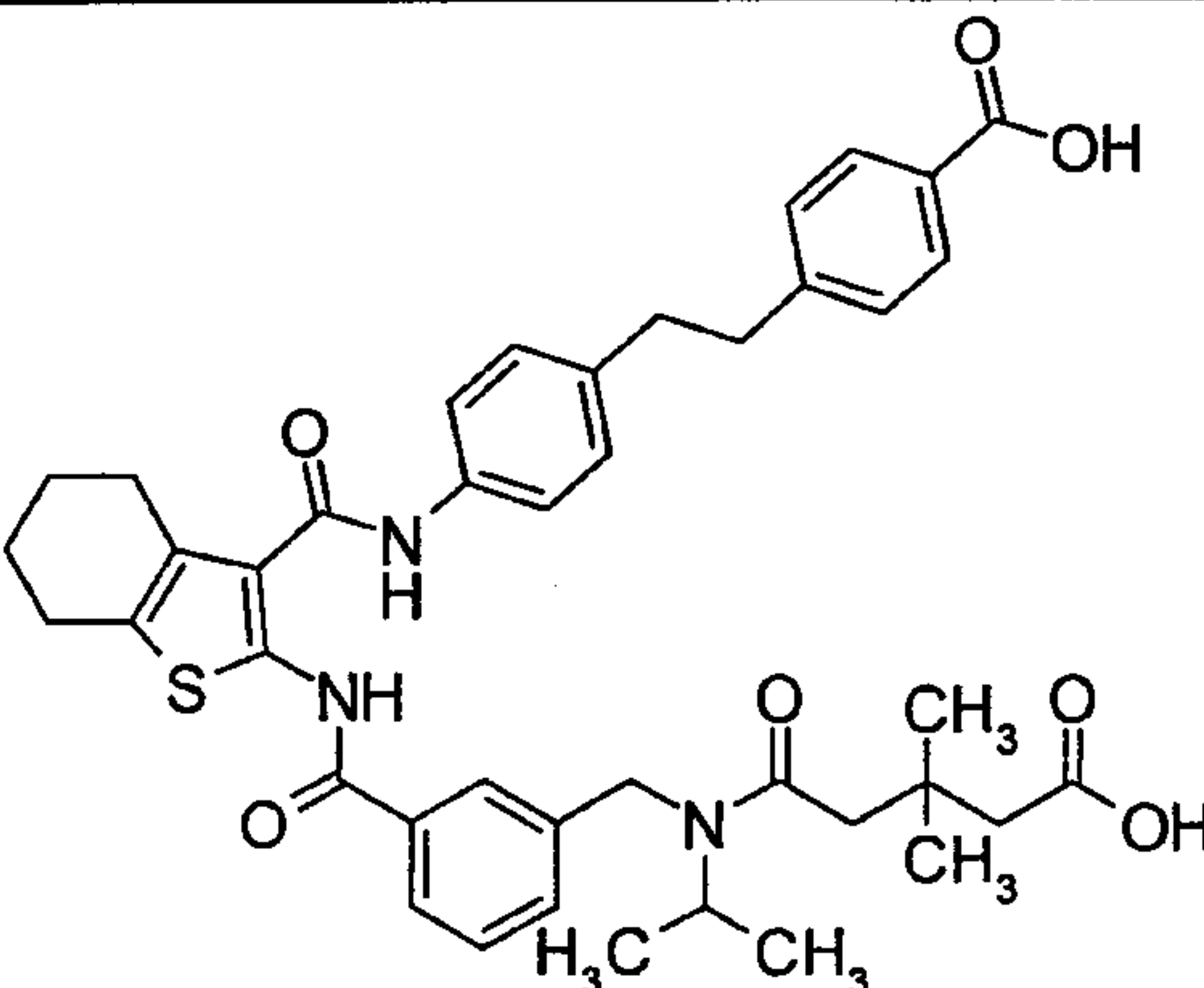
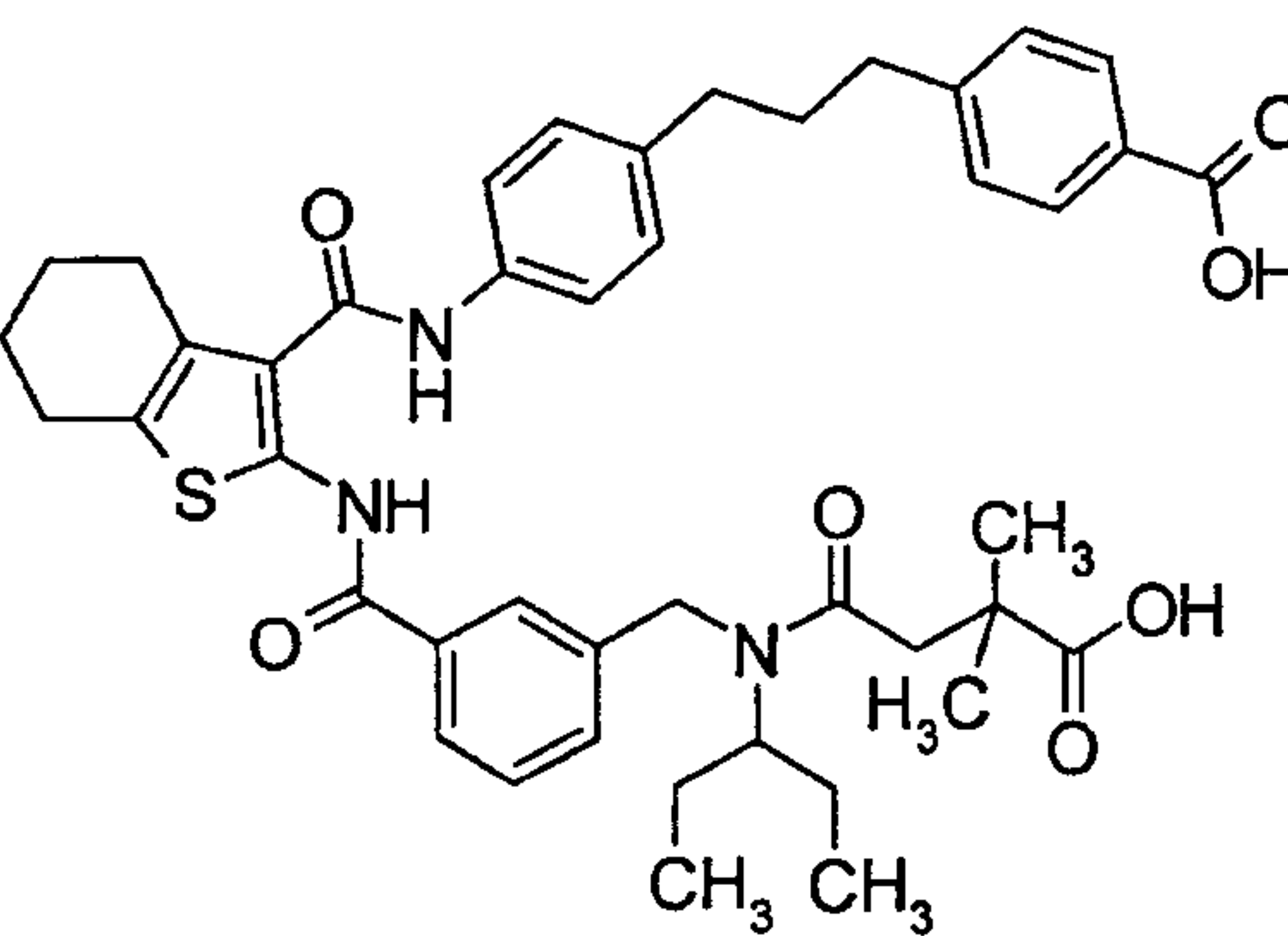
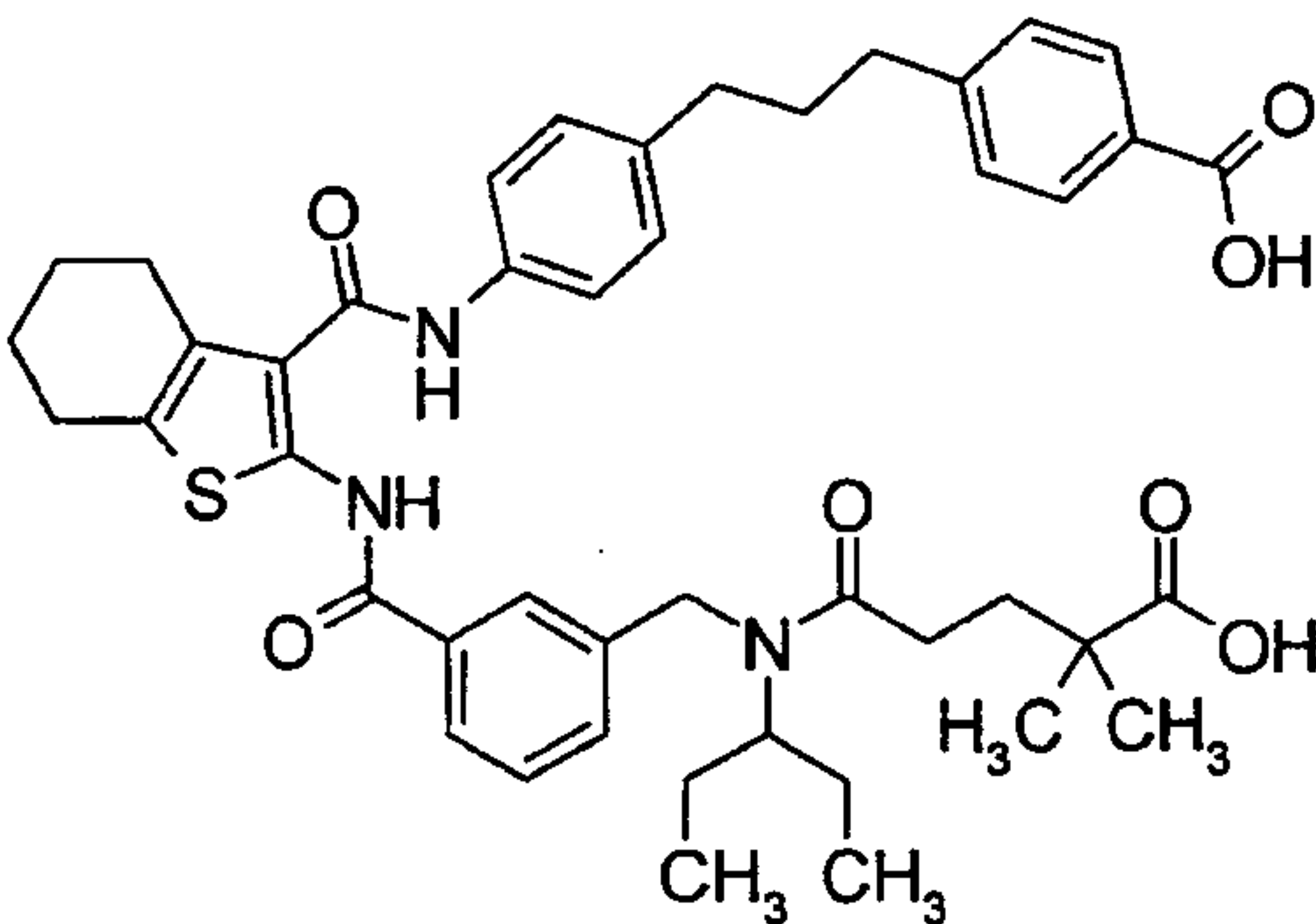
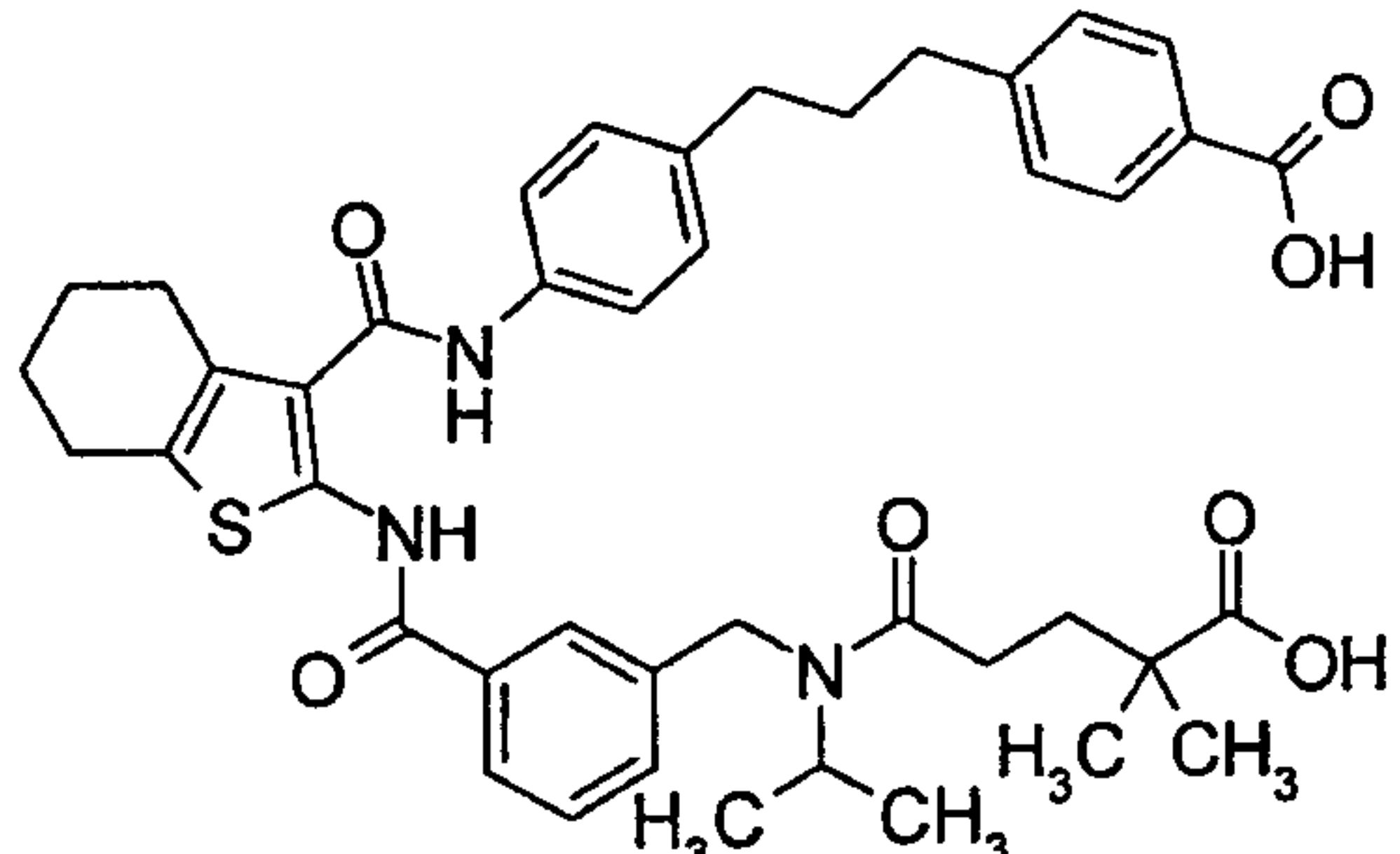
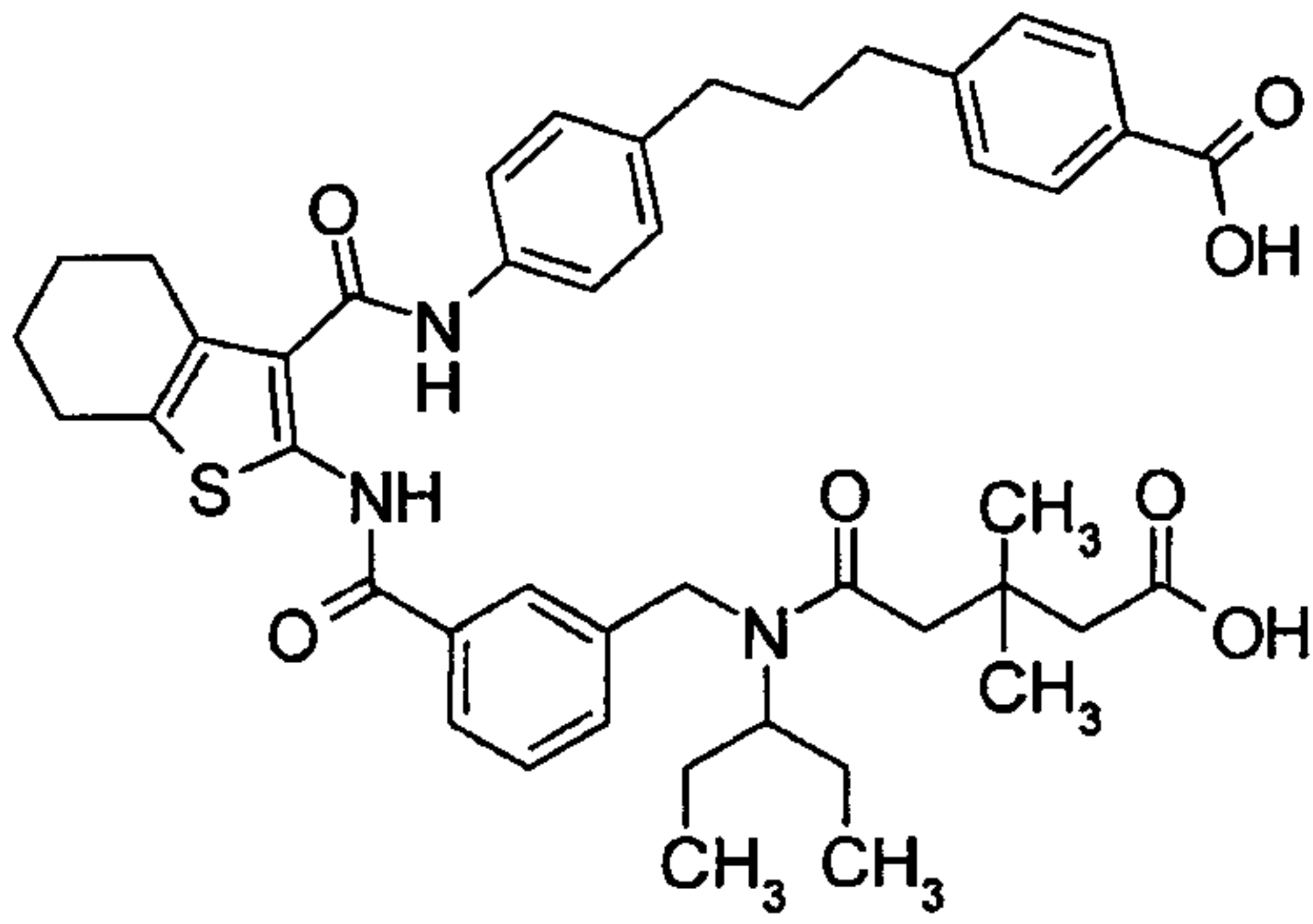
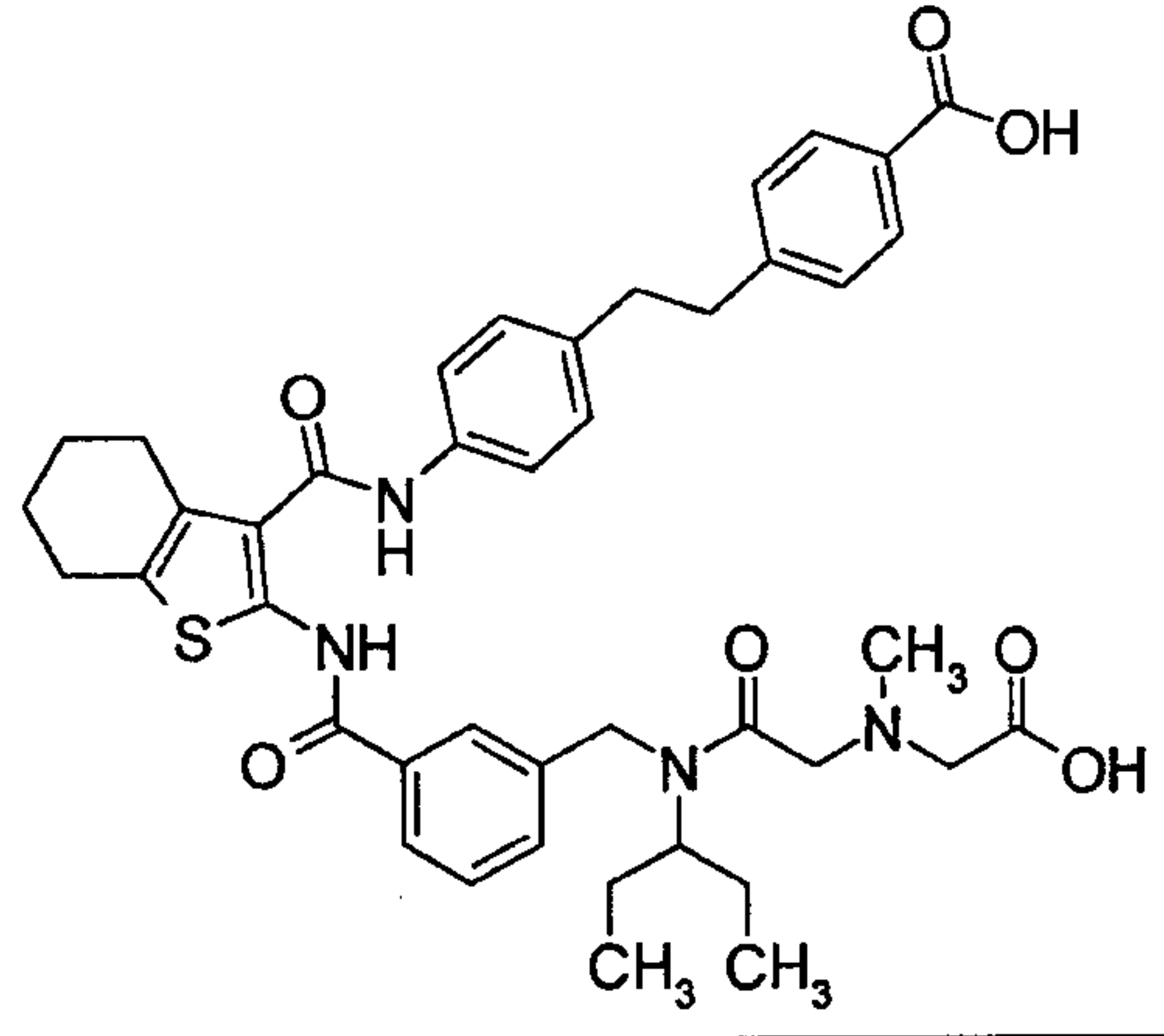
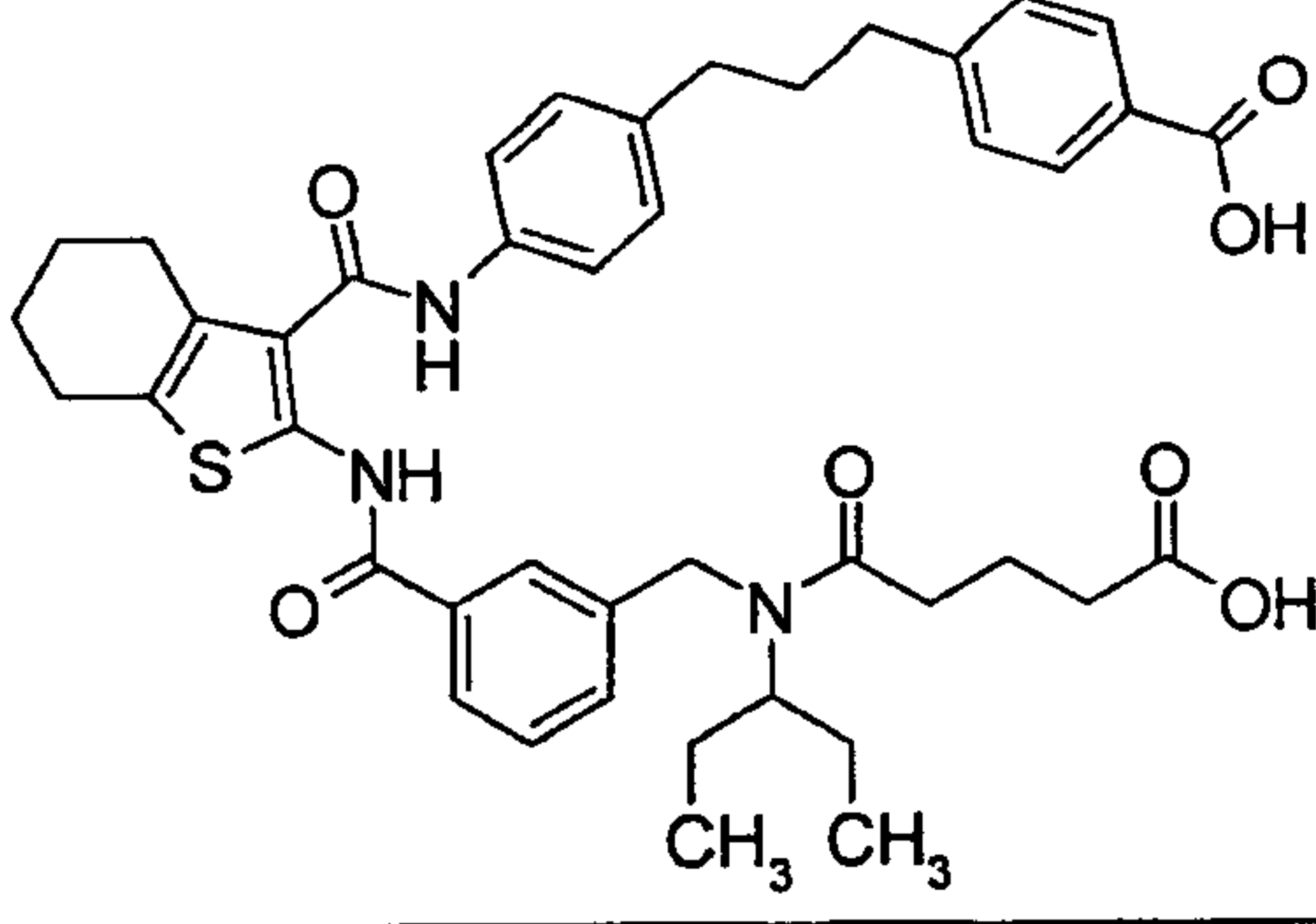
Ex	Str	Ex	Str
110		115	
111		116	
112		117	
113			
114			

[0214]

[Table 69]

Ex	Str	Ex	Str
118		121	
119		122	
120		123	

[0215]
[Table 70]

Ex	Str	Ex	Str
124		128	
125		129	
126		130	
127			

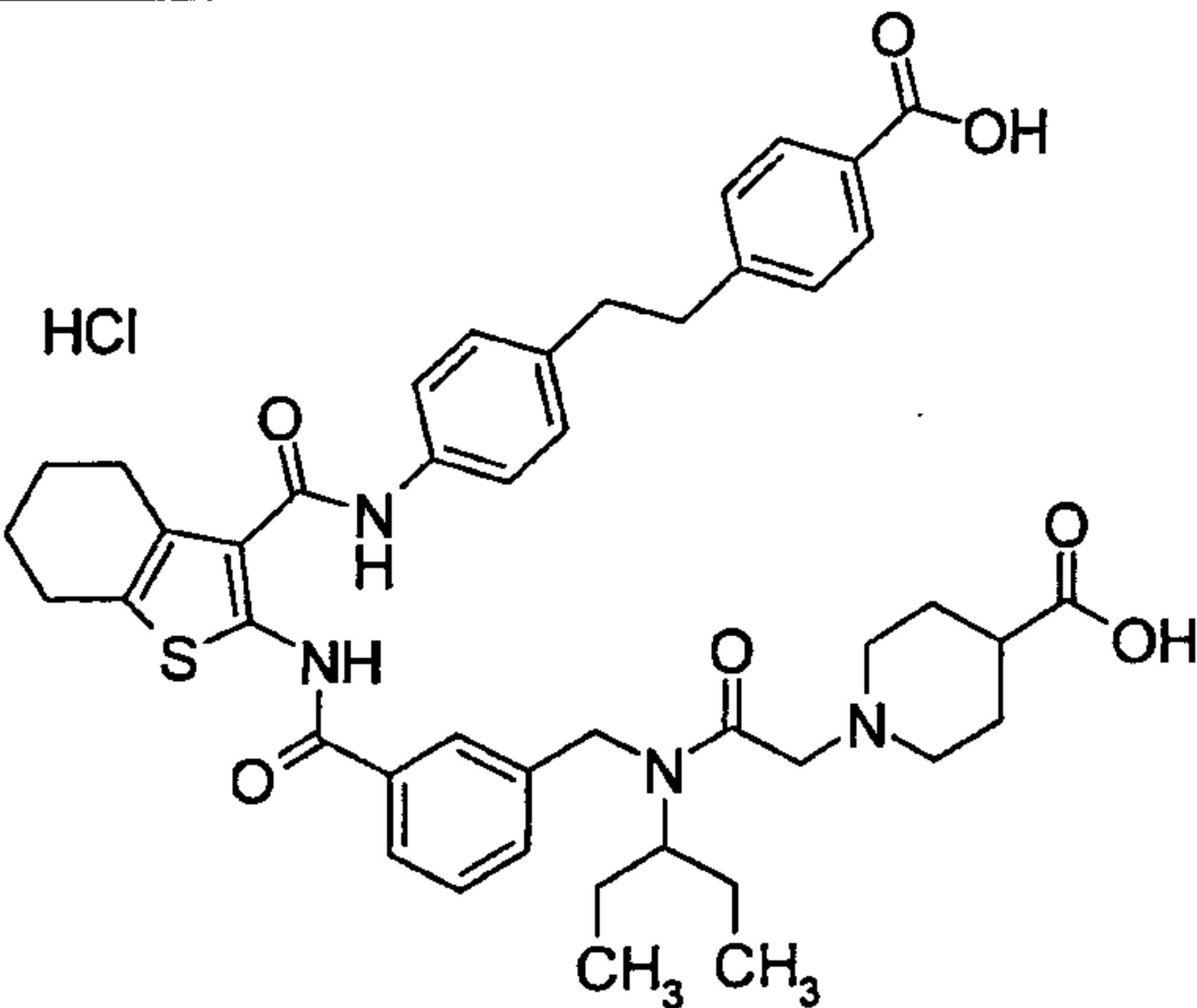
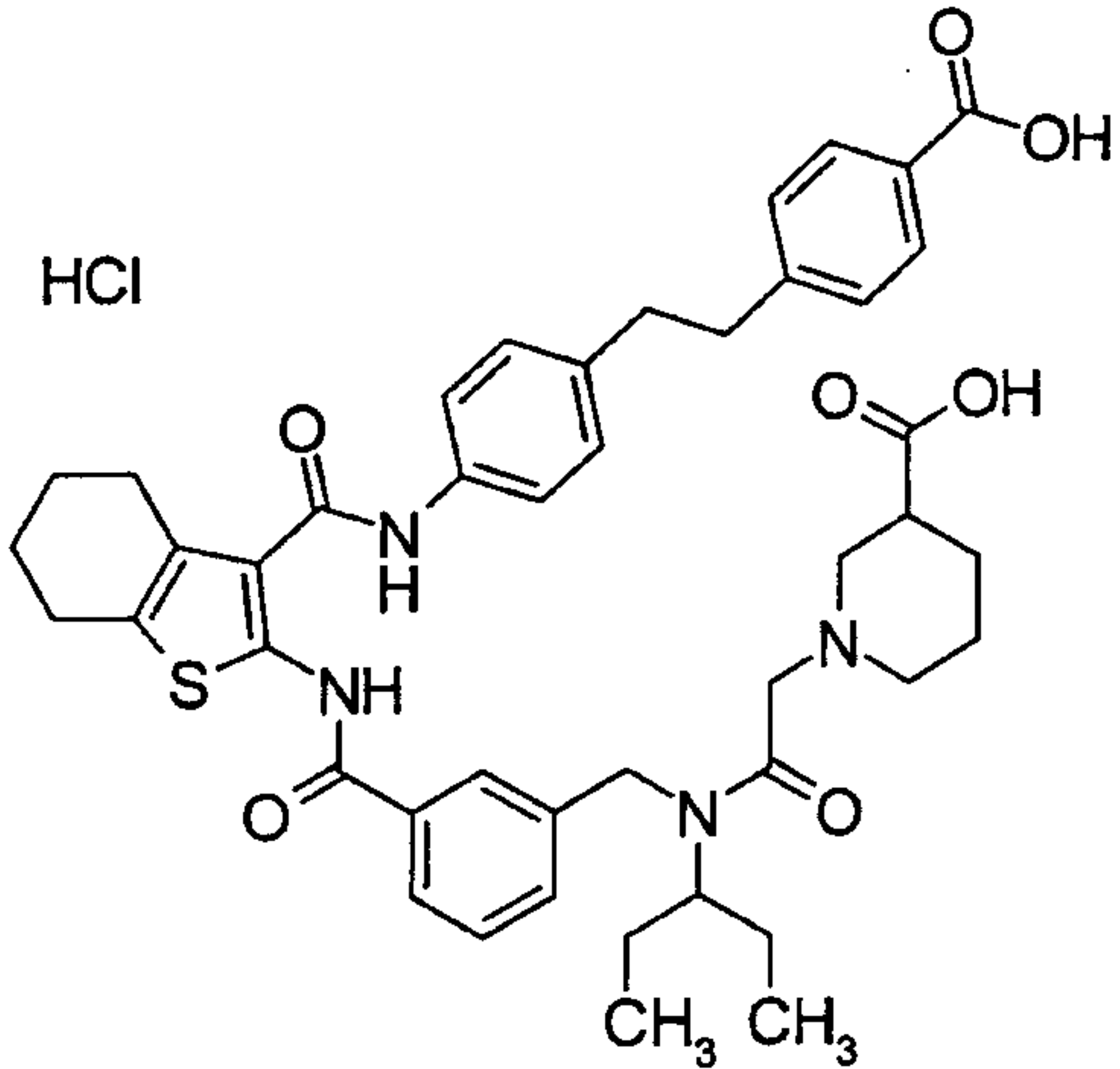
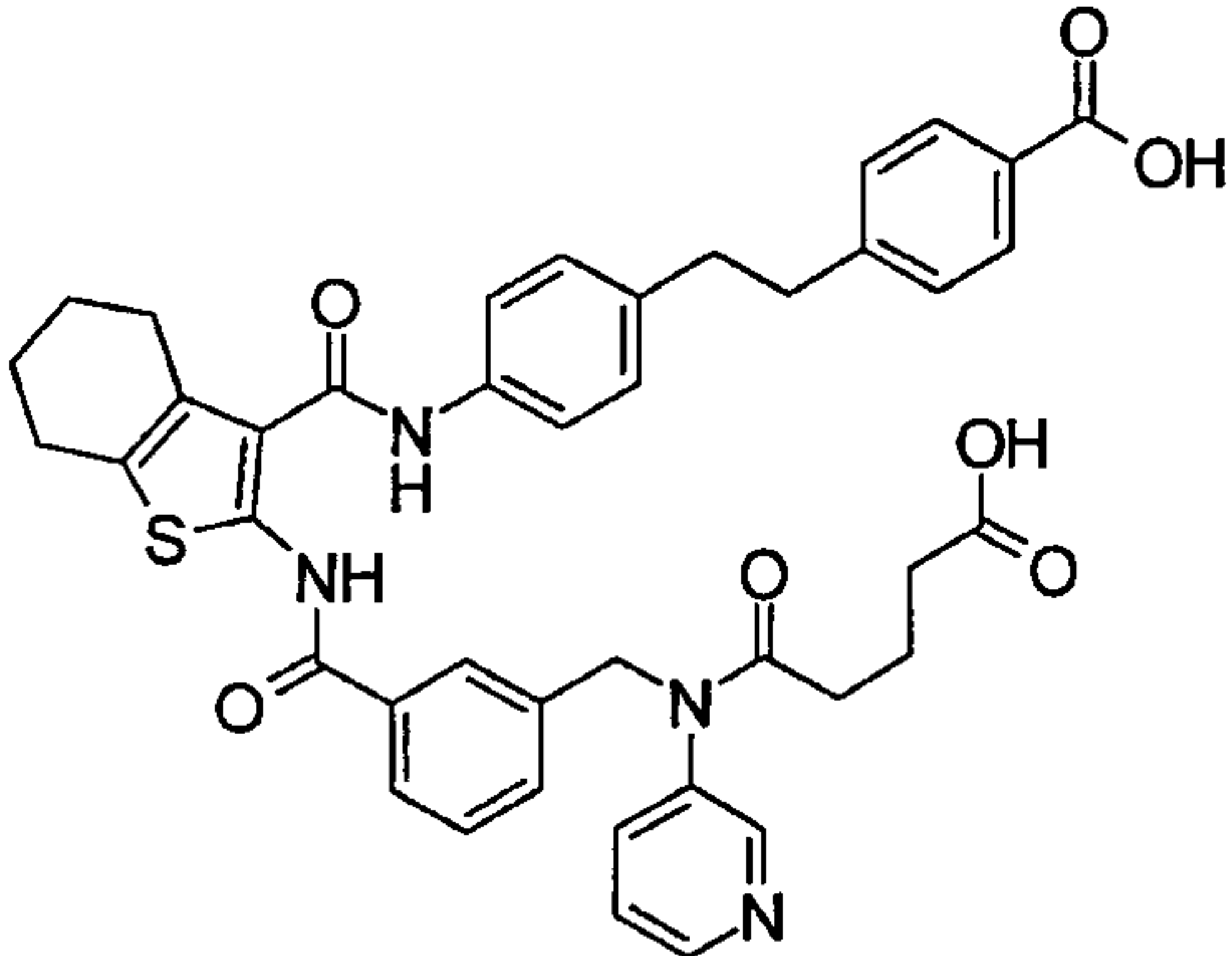
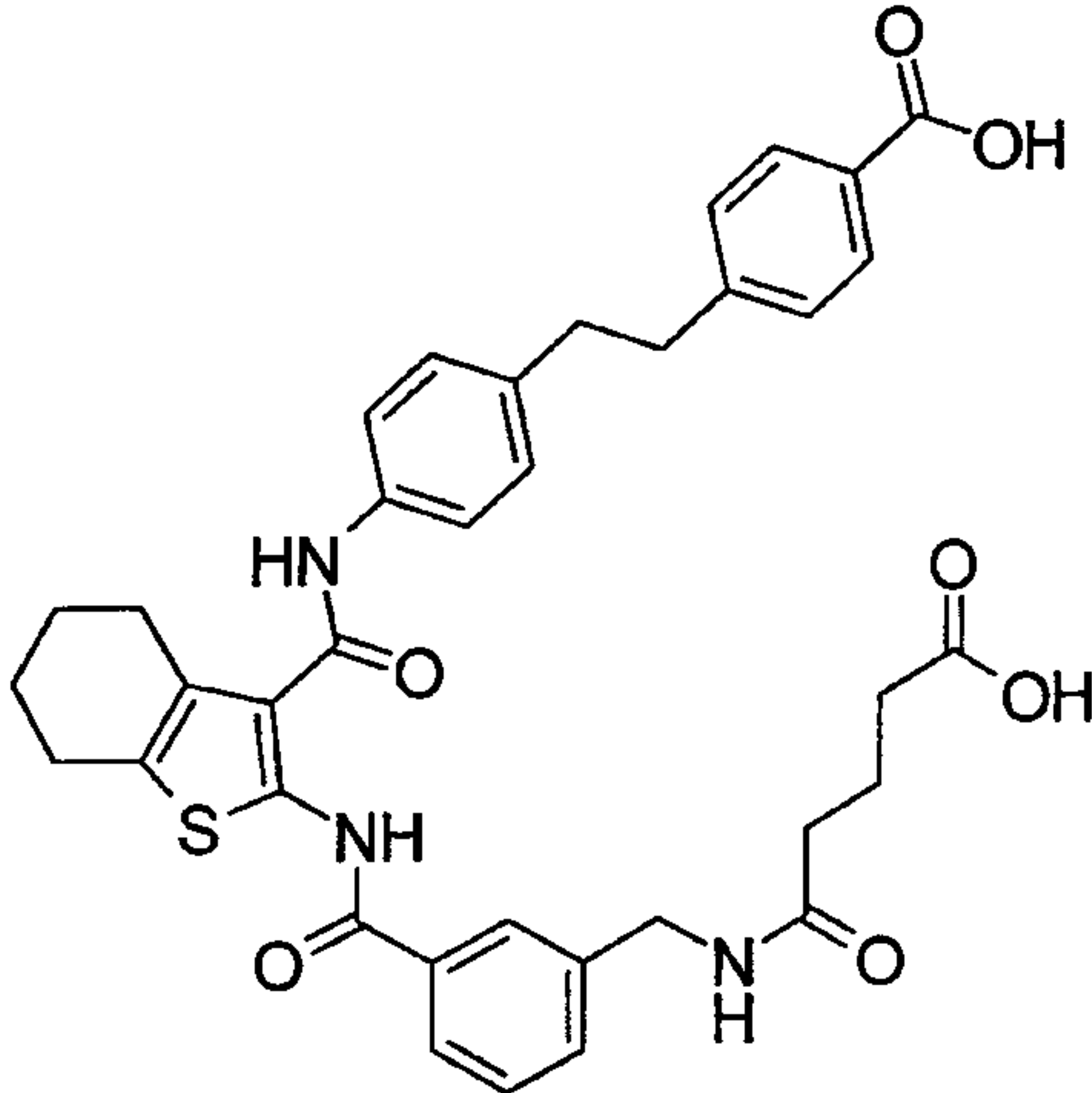
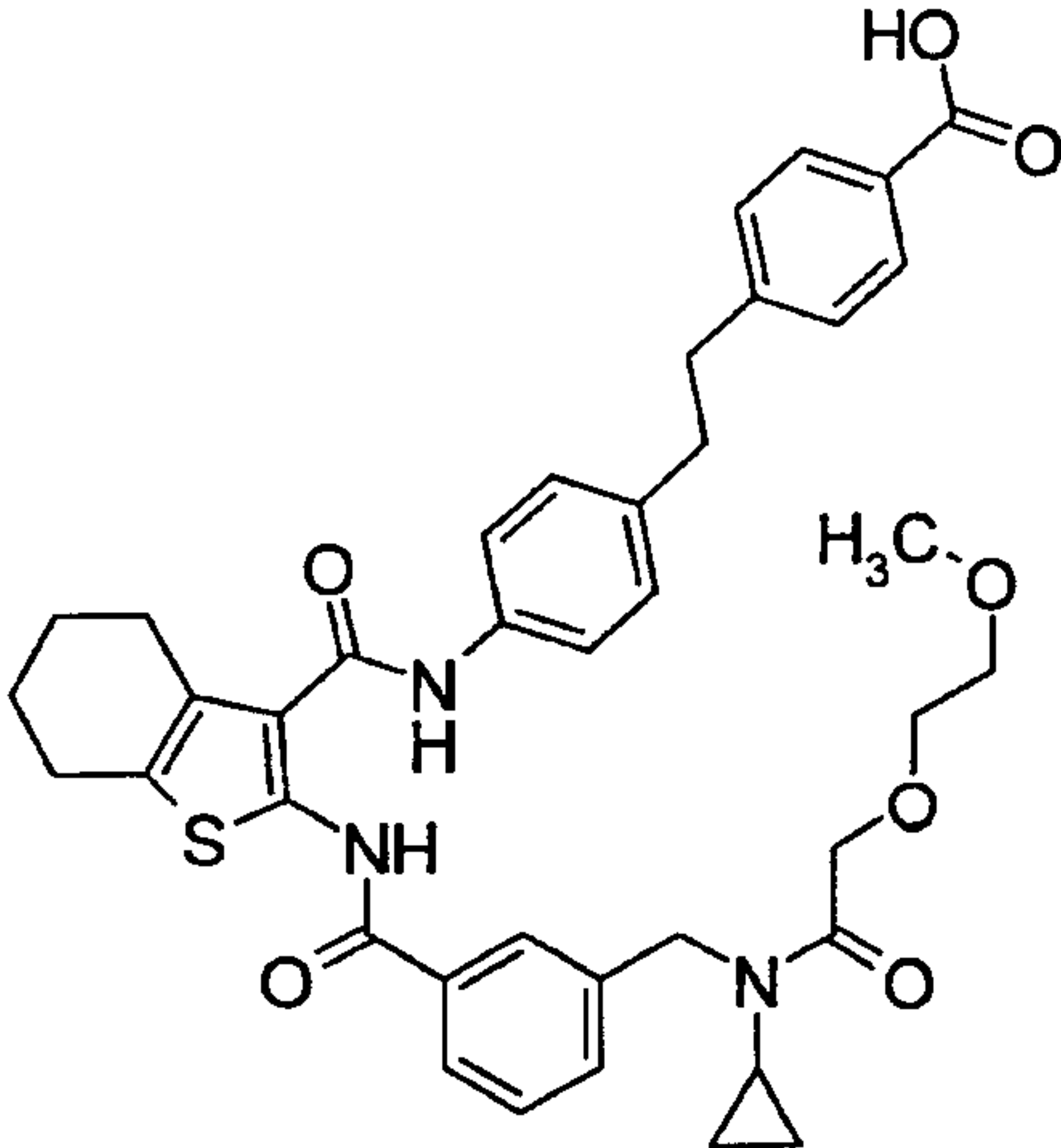
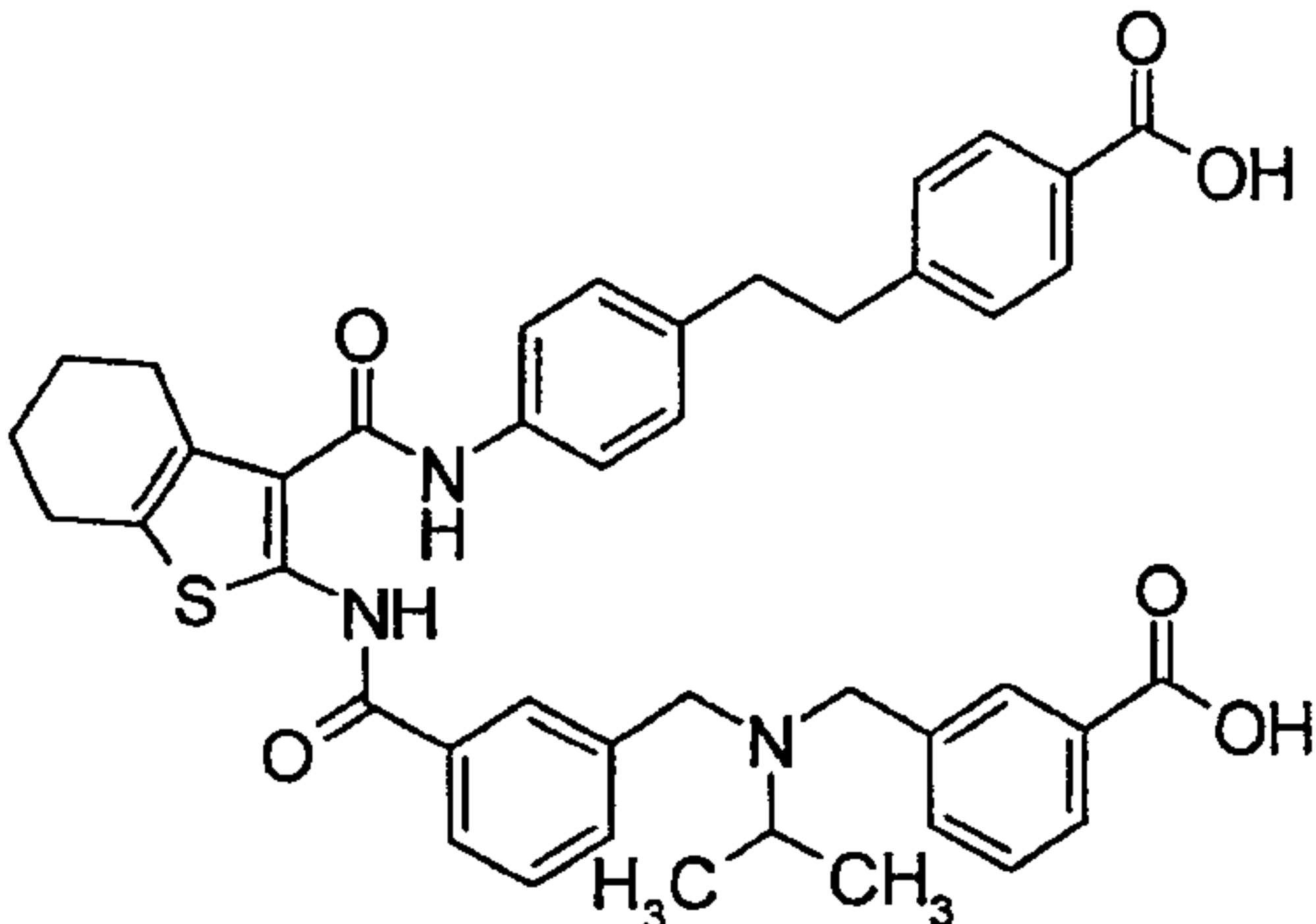
[0216]
[Table 71]

Ex	Str	Ex	Str
131	 <chem>Cc1ccc(cc1)C(=O)Nc2sc3ccccc3c2C(=O)NC(=O)c4ccc(cc4)CN(C)C(=O)CC(C)C(=O)O</chem>	134	 <chem>Cc1ccc(cc1)C(=O)Nc2sc3ccccc3c2C(=O)NC(=O)c4ccc(cc4)CN(C)C(=O)CC(C)C(=O)O</chem>
132	 <chem>Cc1ccc(cc1)C(=O)Nc2sc3ccccc3c2C(=O)NC(=O)c4ccc(cc4)CN(CC)C(=O)CC(C)C(=O)O</chem>	135	 <chem>Cc1ccc(cc1)C(=O)Nc2sc3cccccc3c2C(=O)NC(=O)c4ccc(cc4)CN(C)C(=O)CC(C)C(=O)O</chem>
133	 <chem>Cc1ccc(cc1)C(=O)Nc2sc3ccccc3c2C(=O)NC(=O)c4ccc(cc4)CN(C1CCCCC1)C(=O)CC(C)C(=O)O</chem>	136	 <chem>Cc1ccc(cc1)C(=O)Nc2sc3ccccc3c2C(=O)NC(=O)c4ccc(cc4)CN(C1COCCO1)C(=O)CC(C)C(=O)O.Cl</chem>

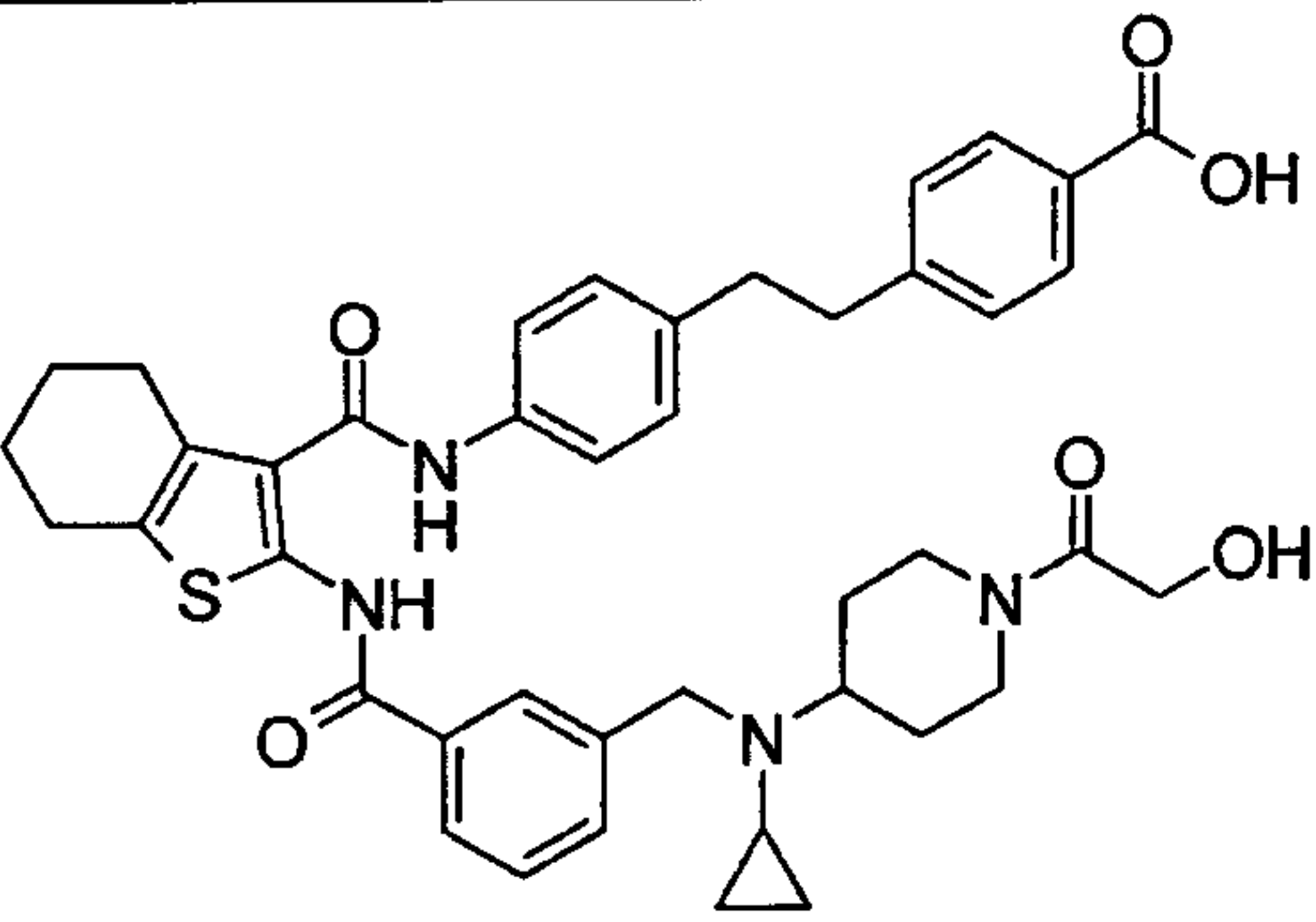
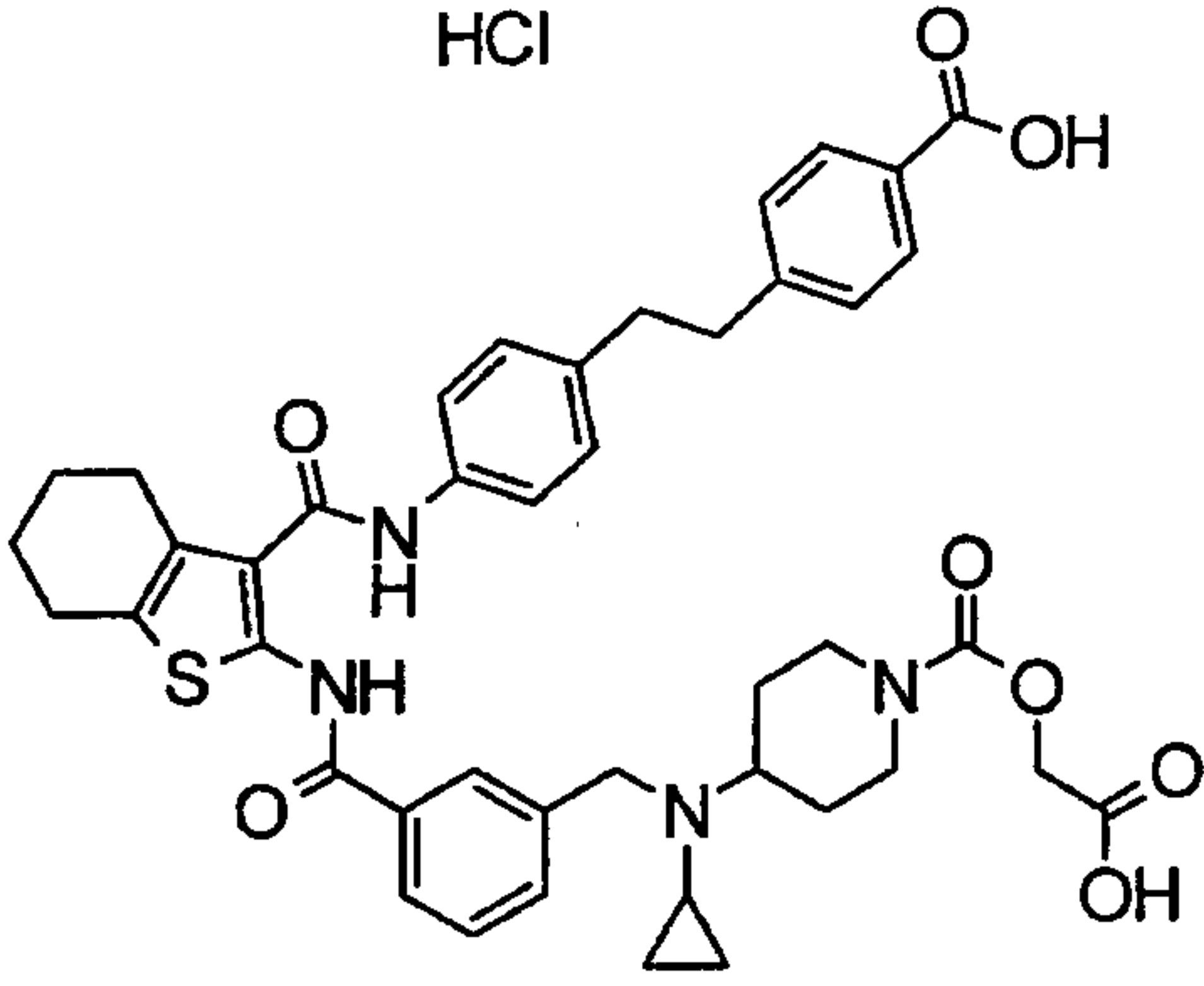
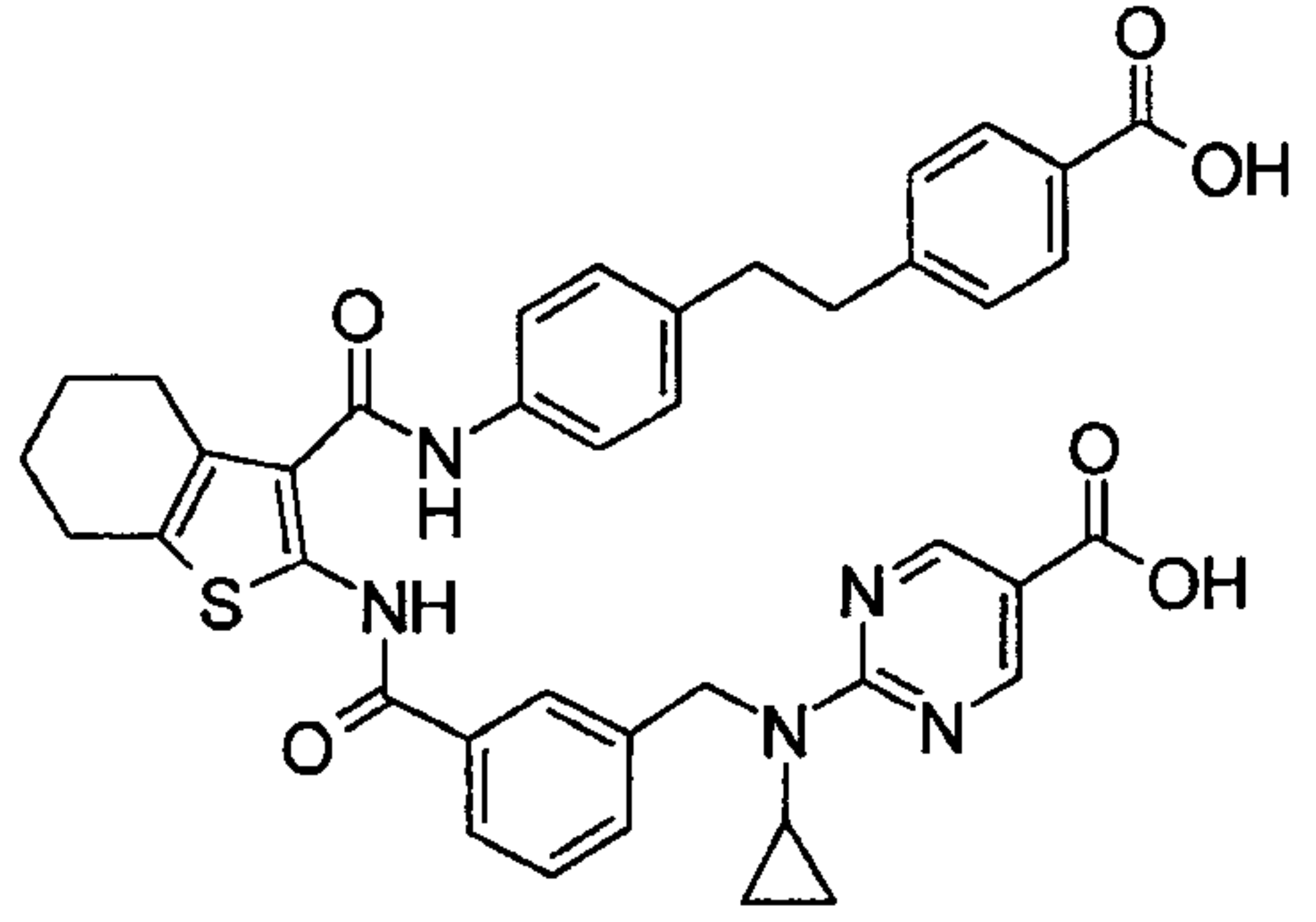
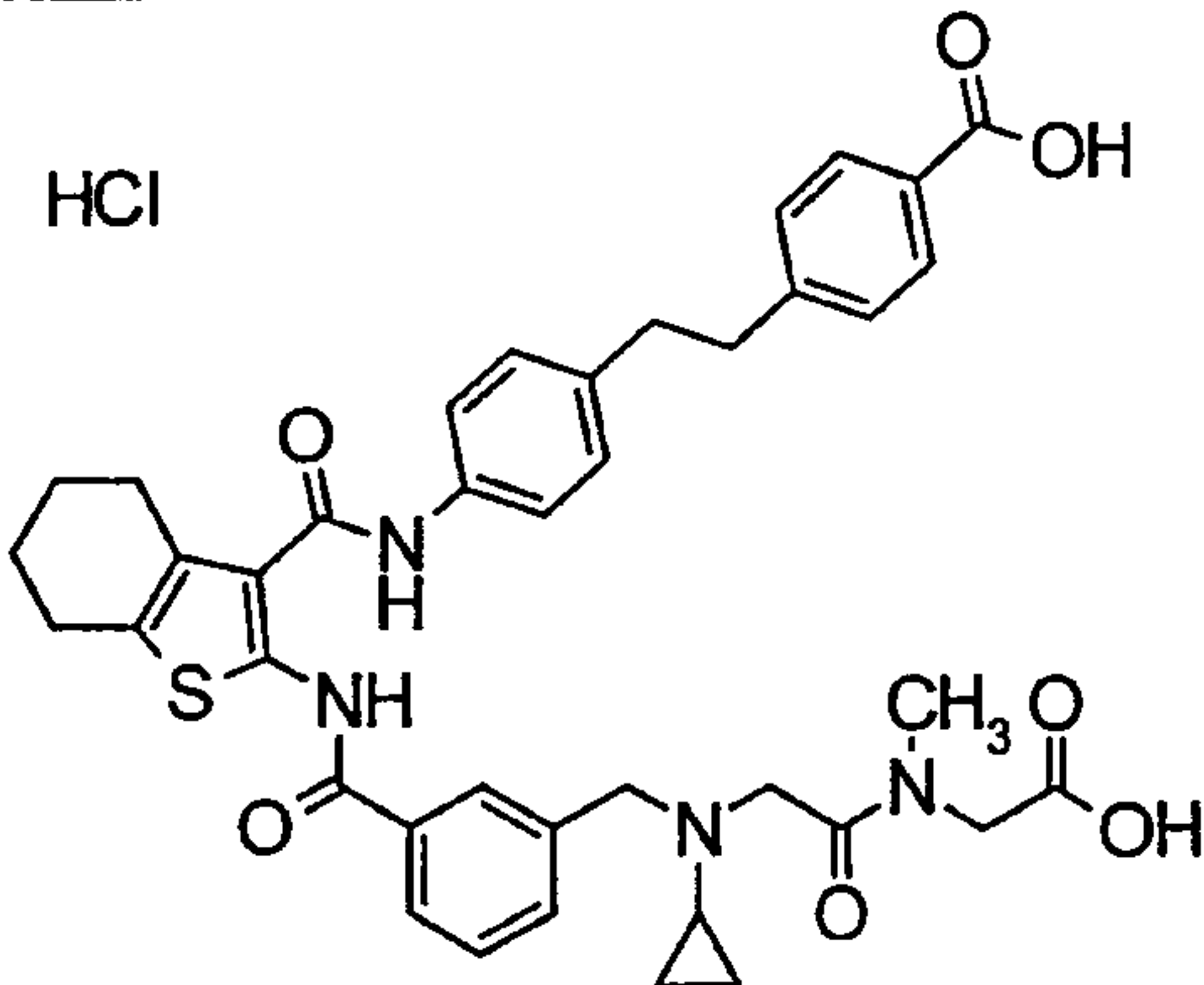
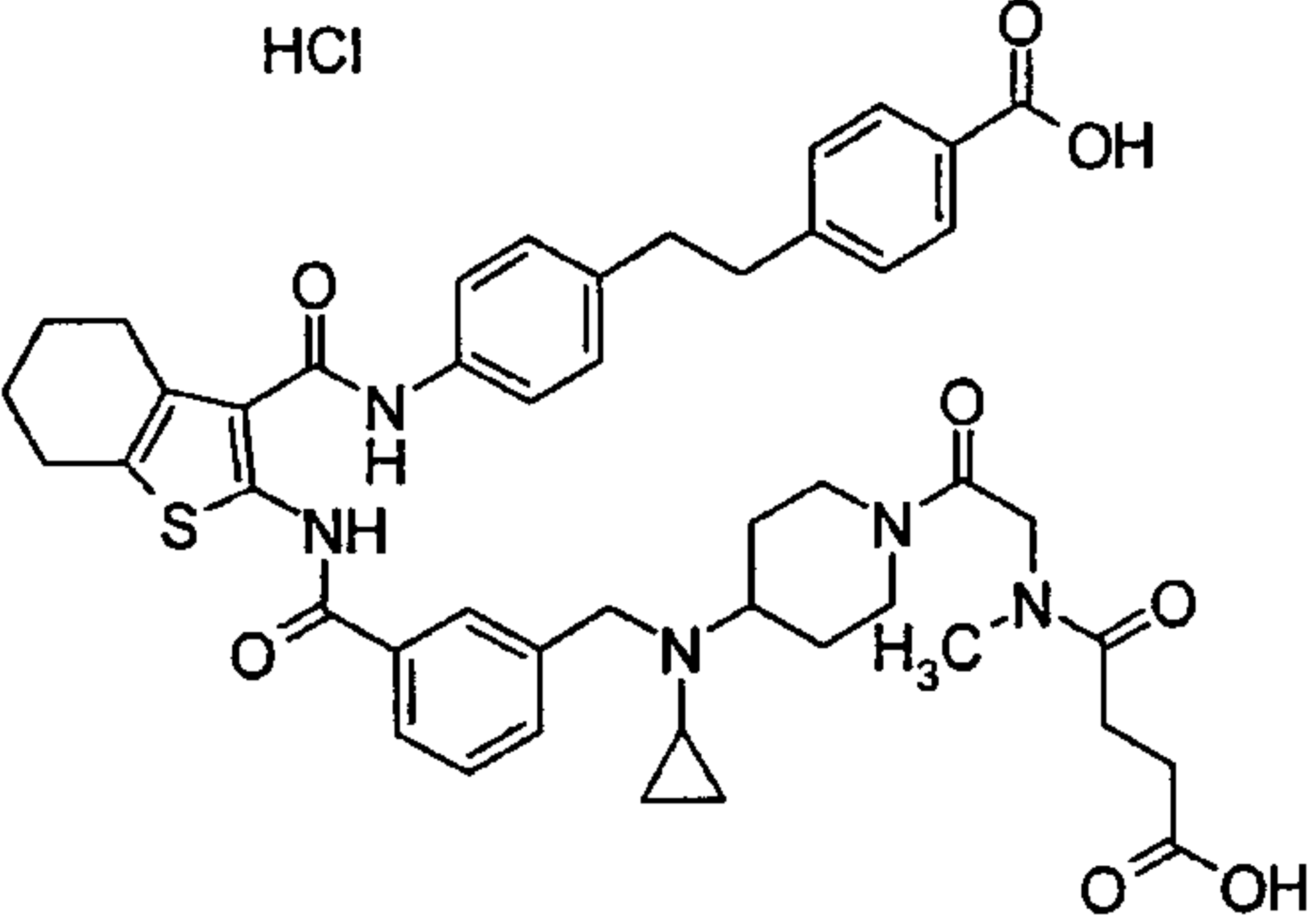
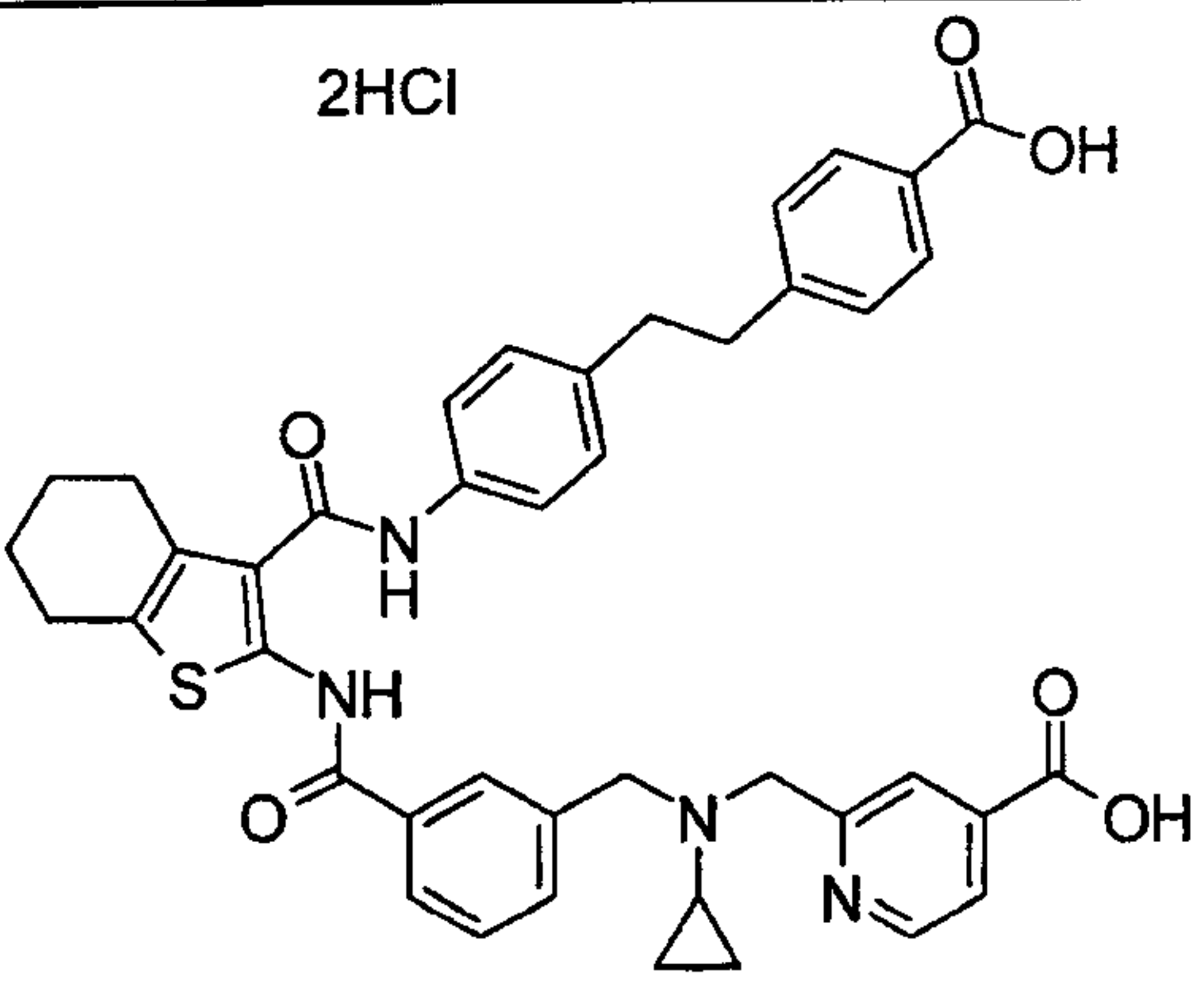
[0217]
[Table 72]

Ex	Str	Ex	Str
137	2HCl	140	
138	2HCl	141	HCl
139	HCl	142	HCl

[0218]
[Table 73]

Ex	Str	Ex	Str
143		146	
144		147	
145		148	

[0219]
[Table 74]

Ex	Str	Ex	Str
149		152	
150		153	
151		154	

[0220]

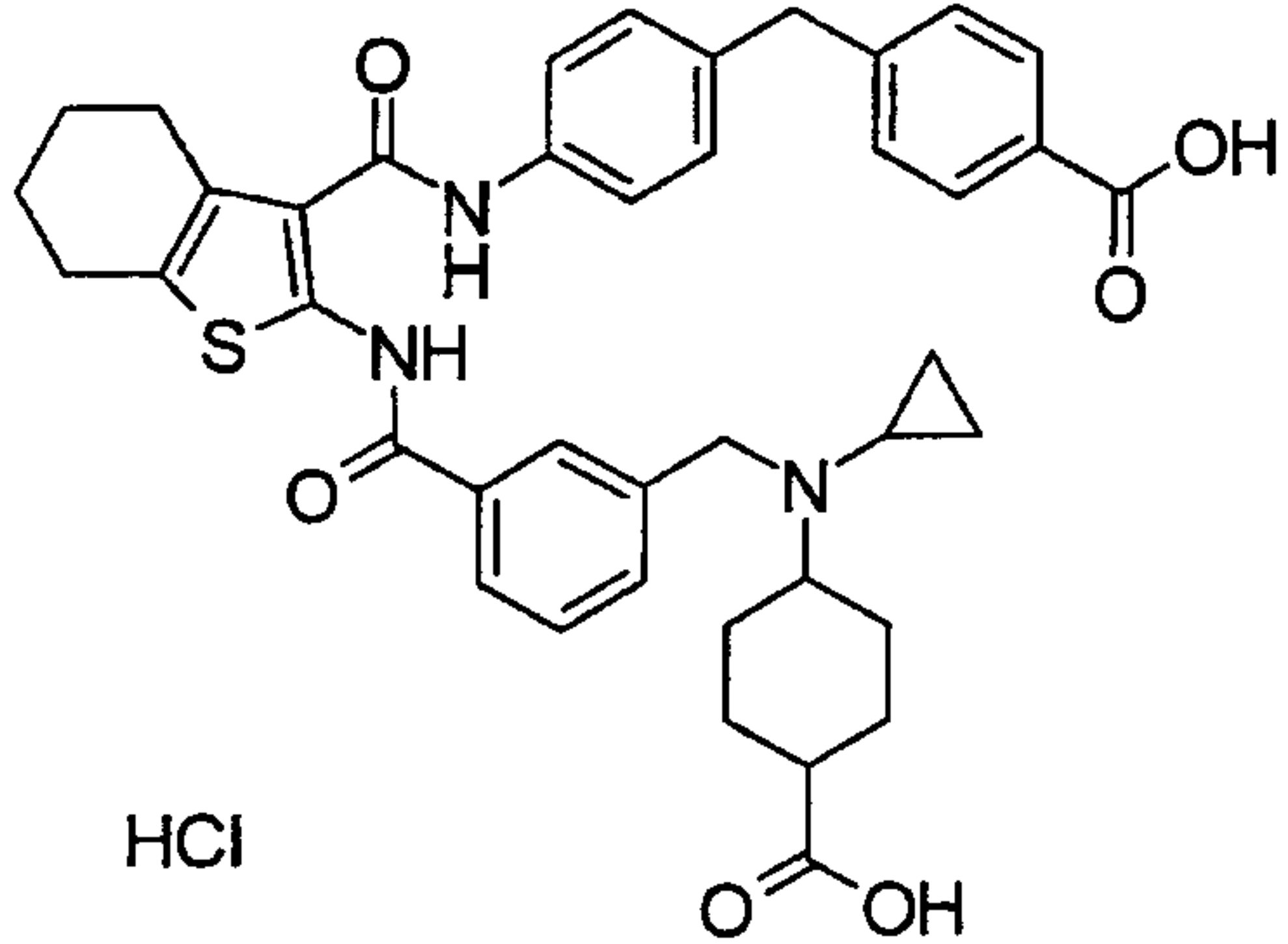
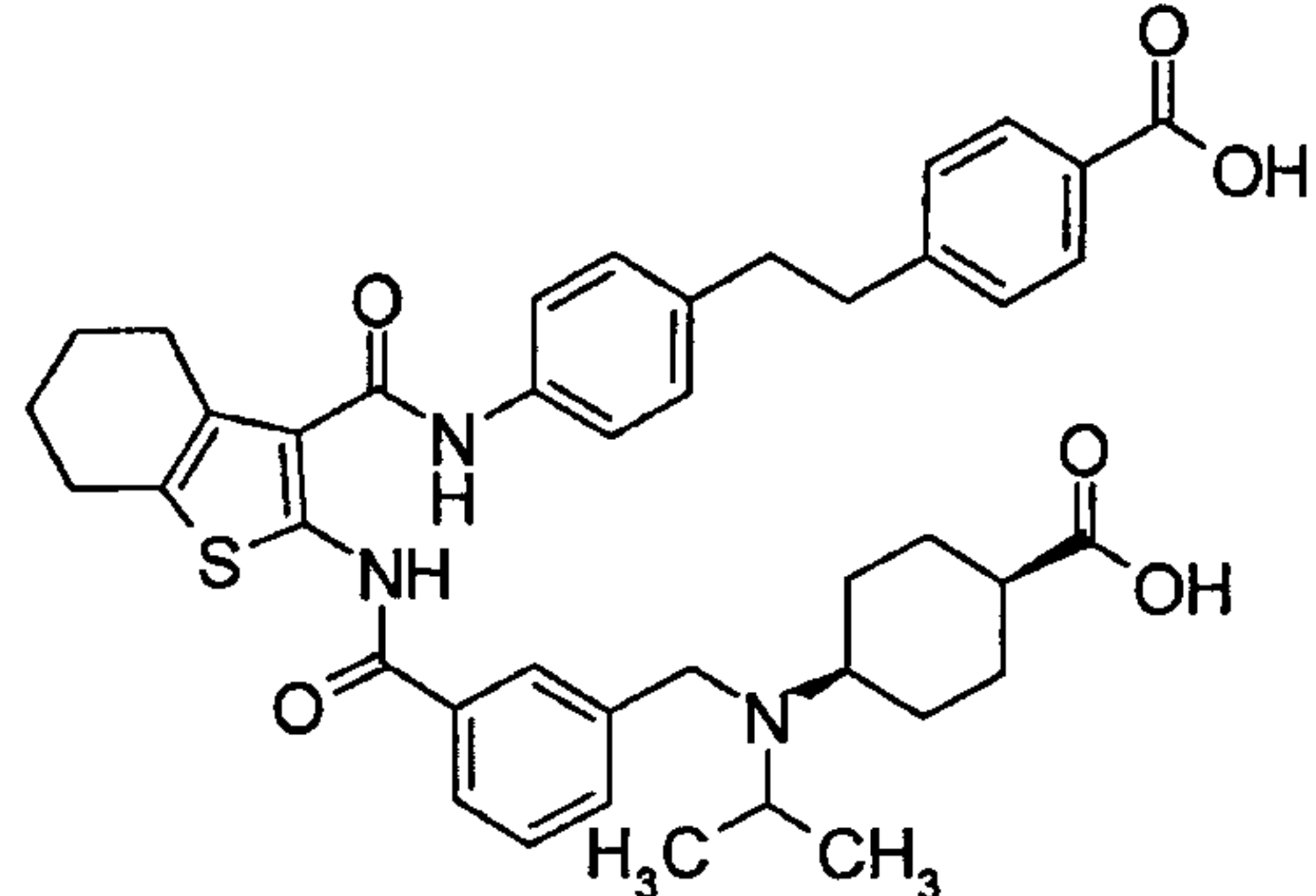
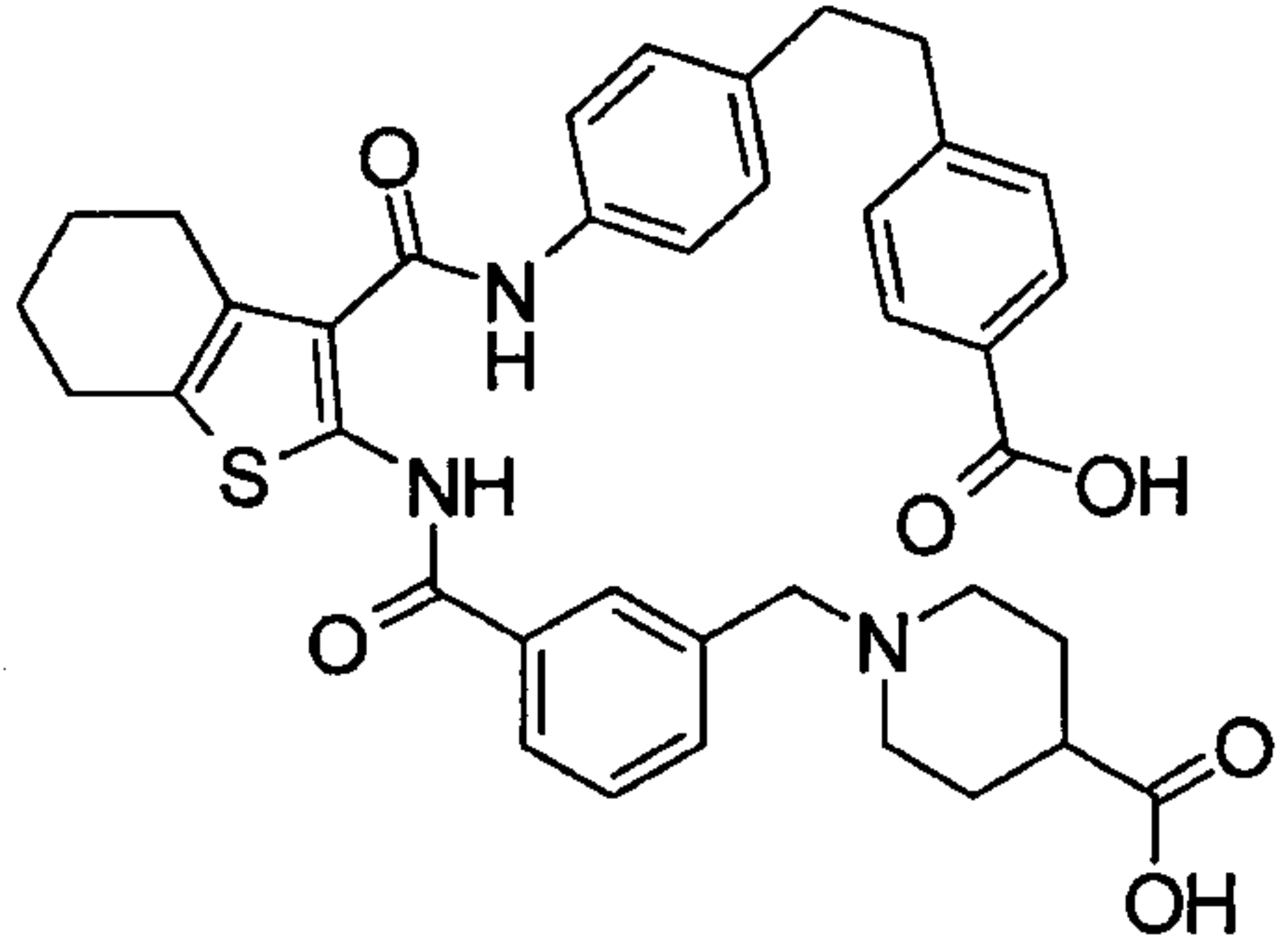
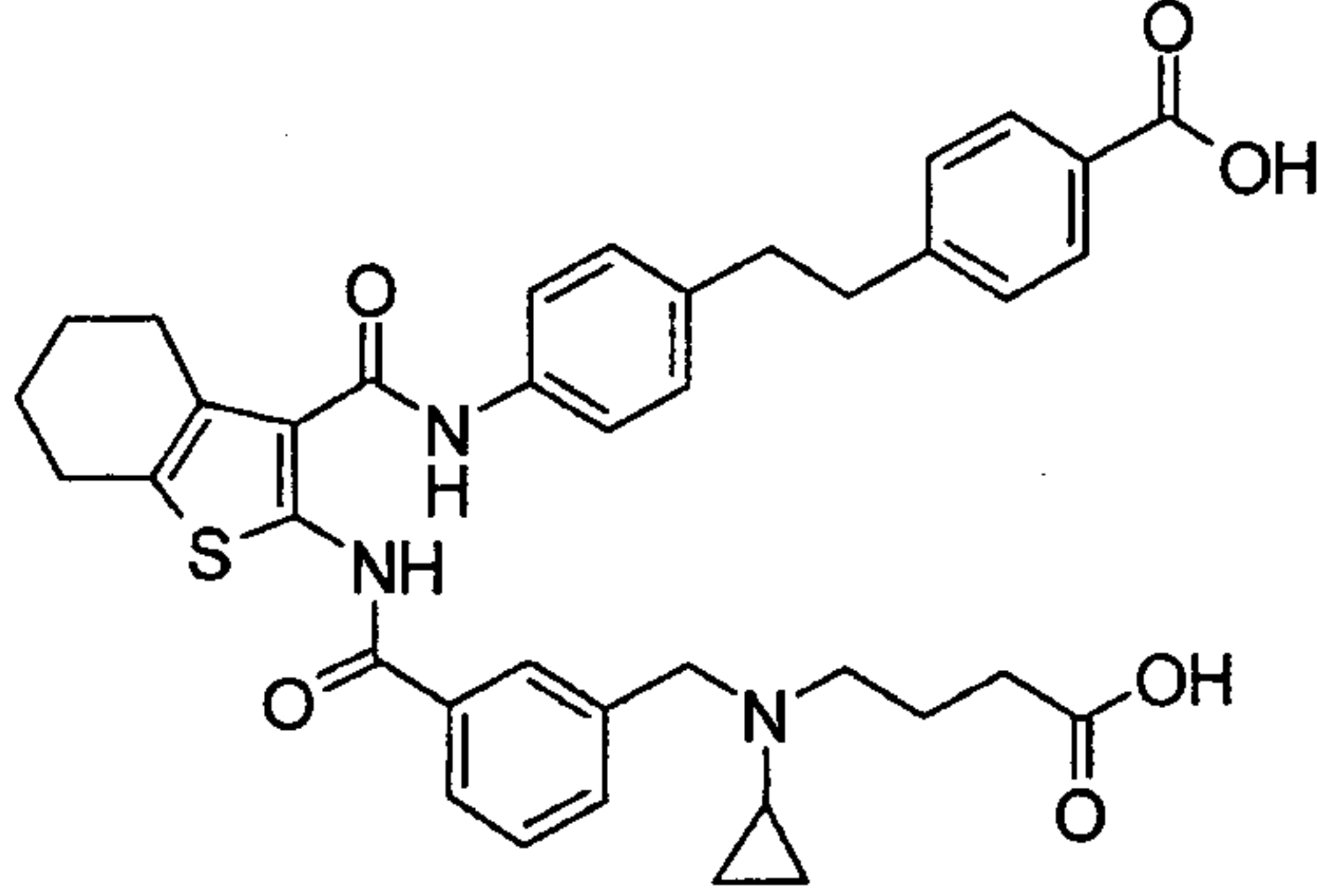
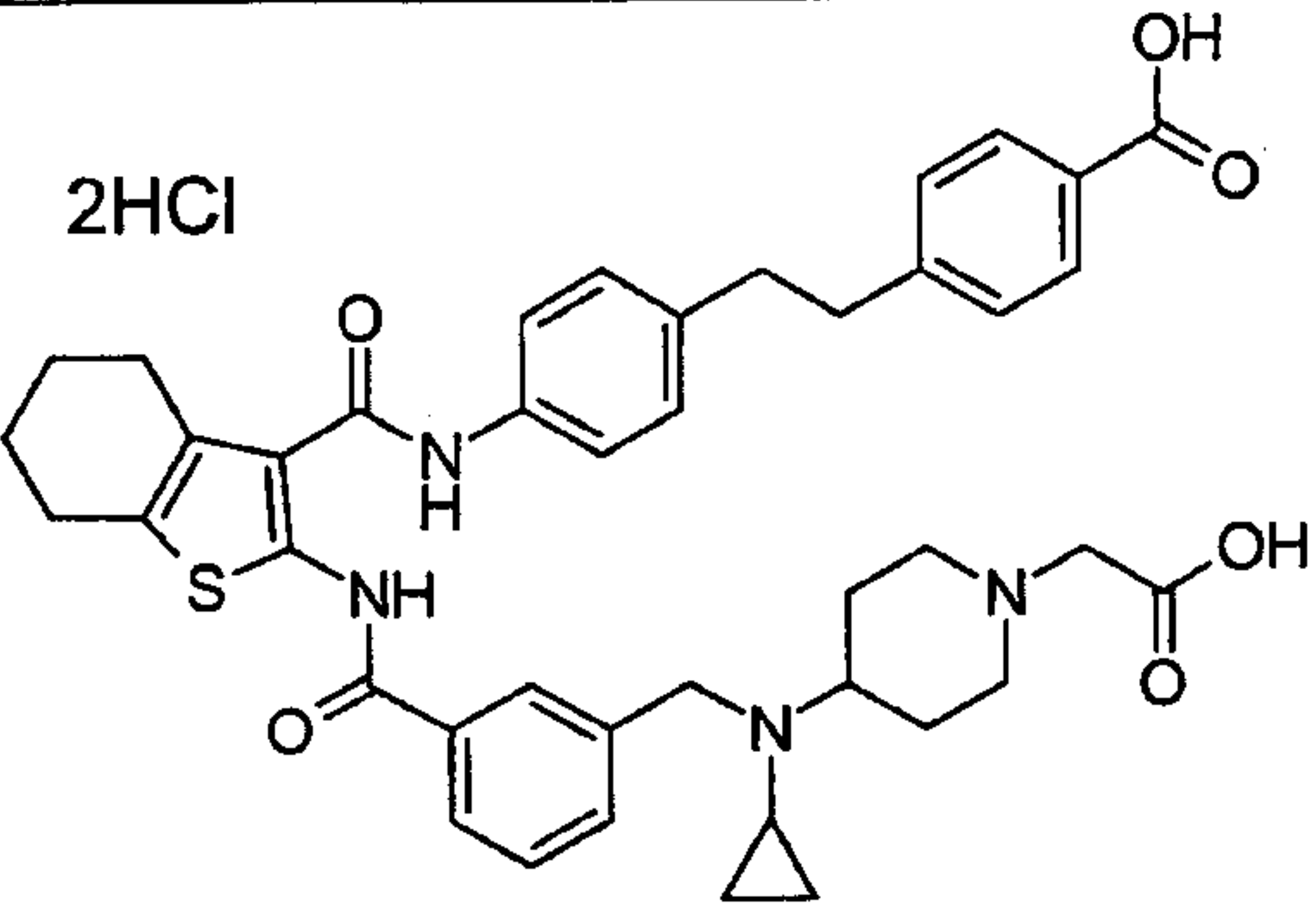
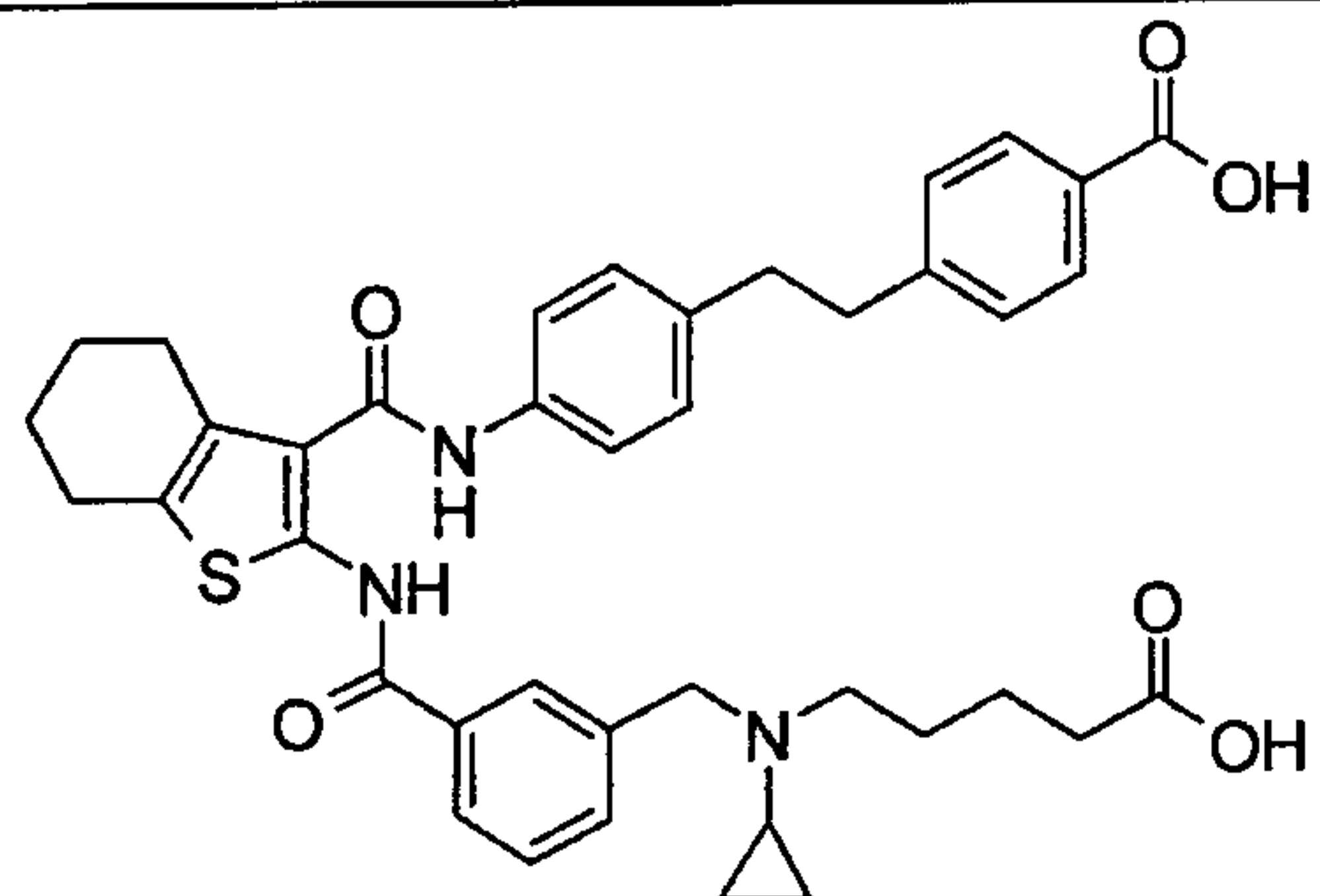
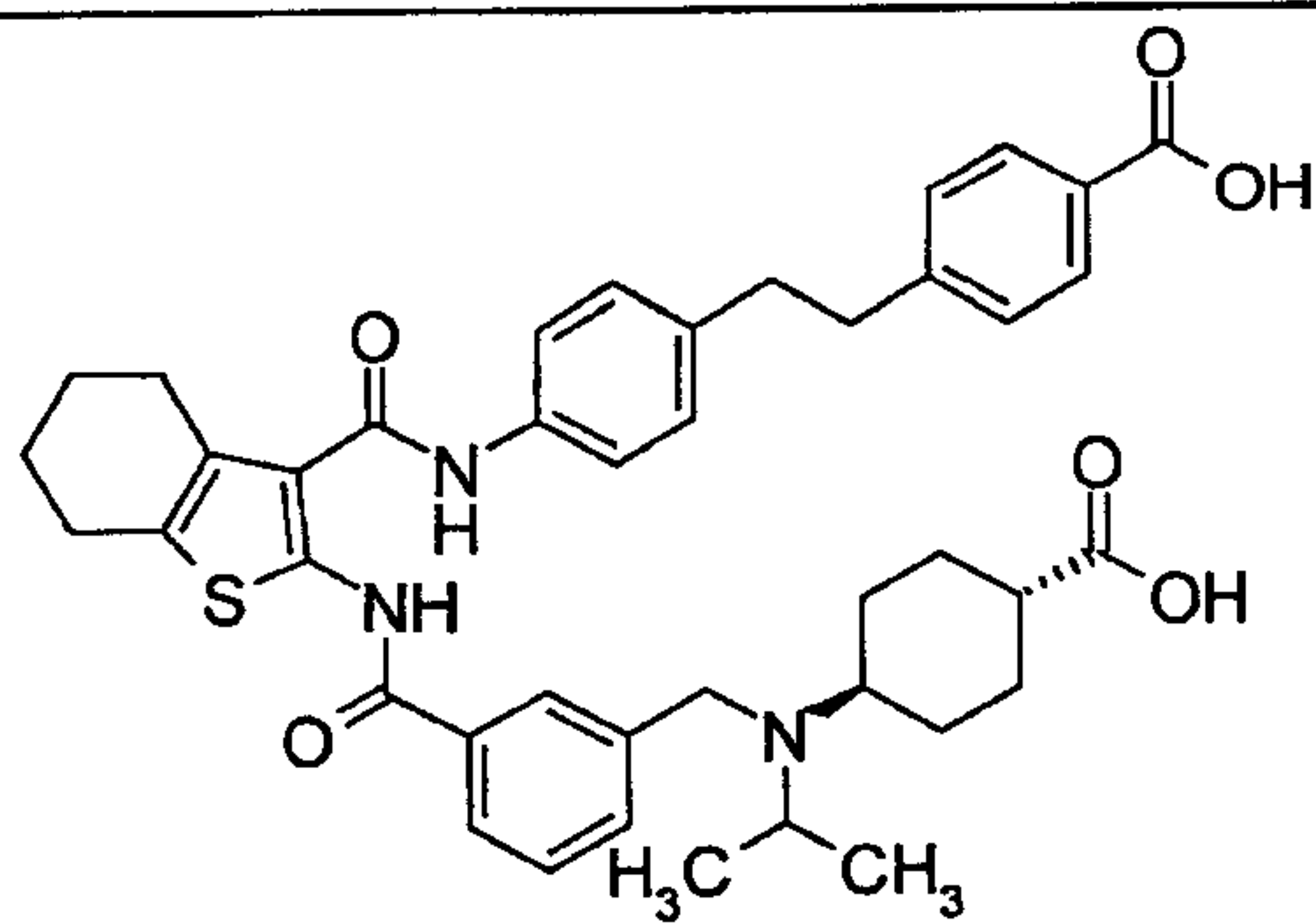
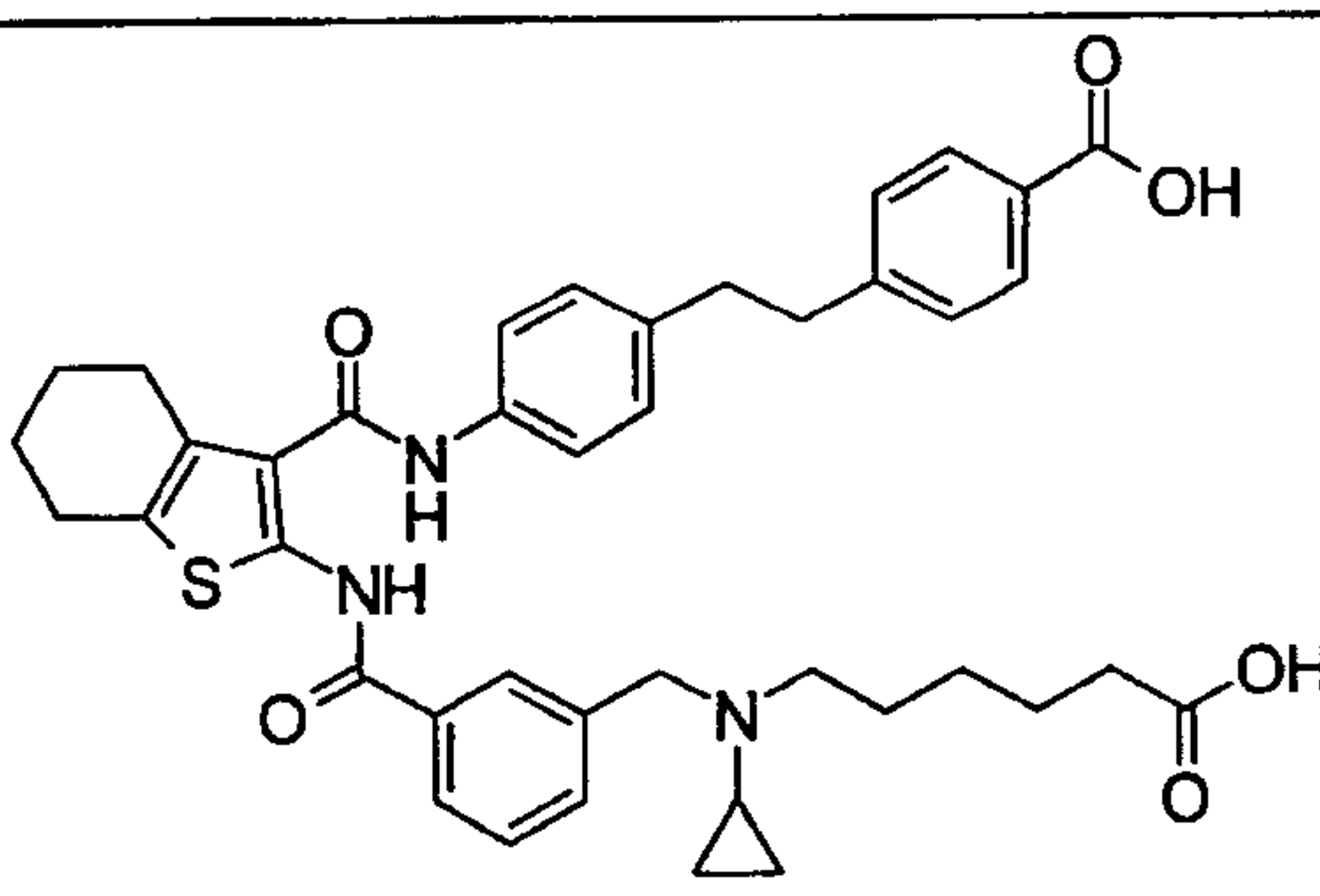
[Table 75]

Ex	Str	Ex	Str
155	2HCl	158	HCl
156	2HCl	159	HCl
157	2HCl	160	3HCl

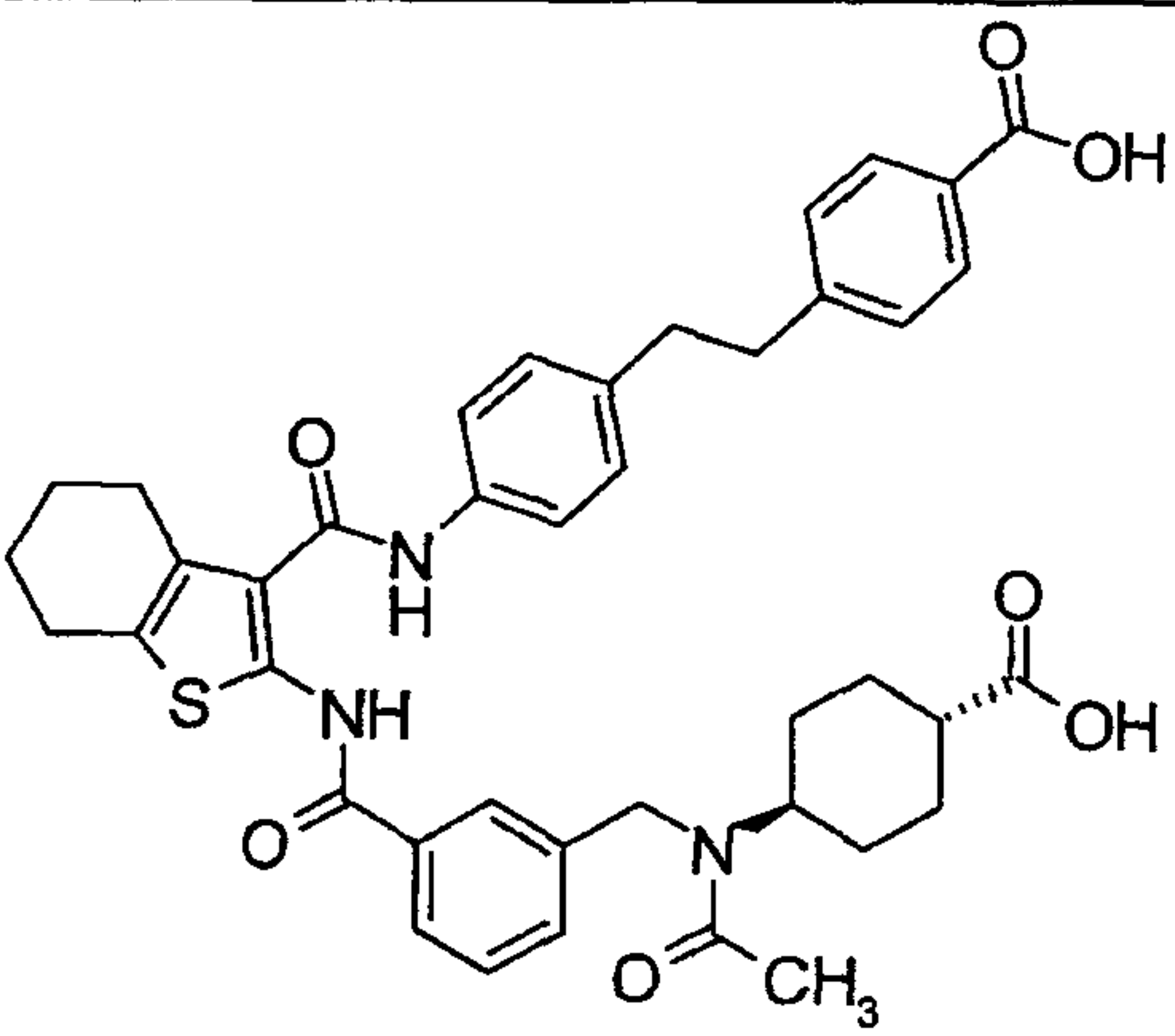
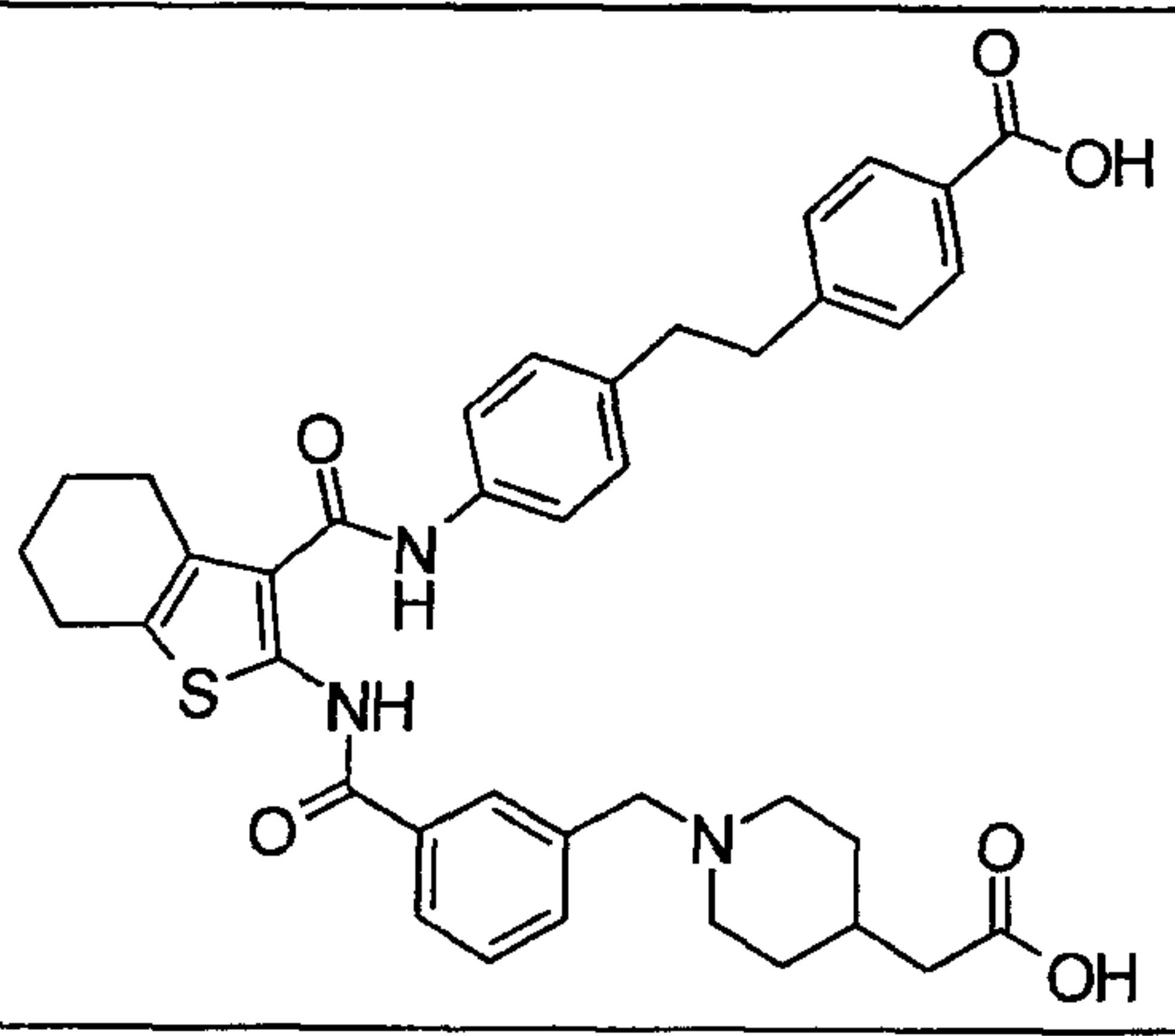
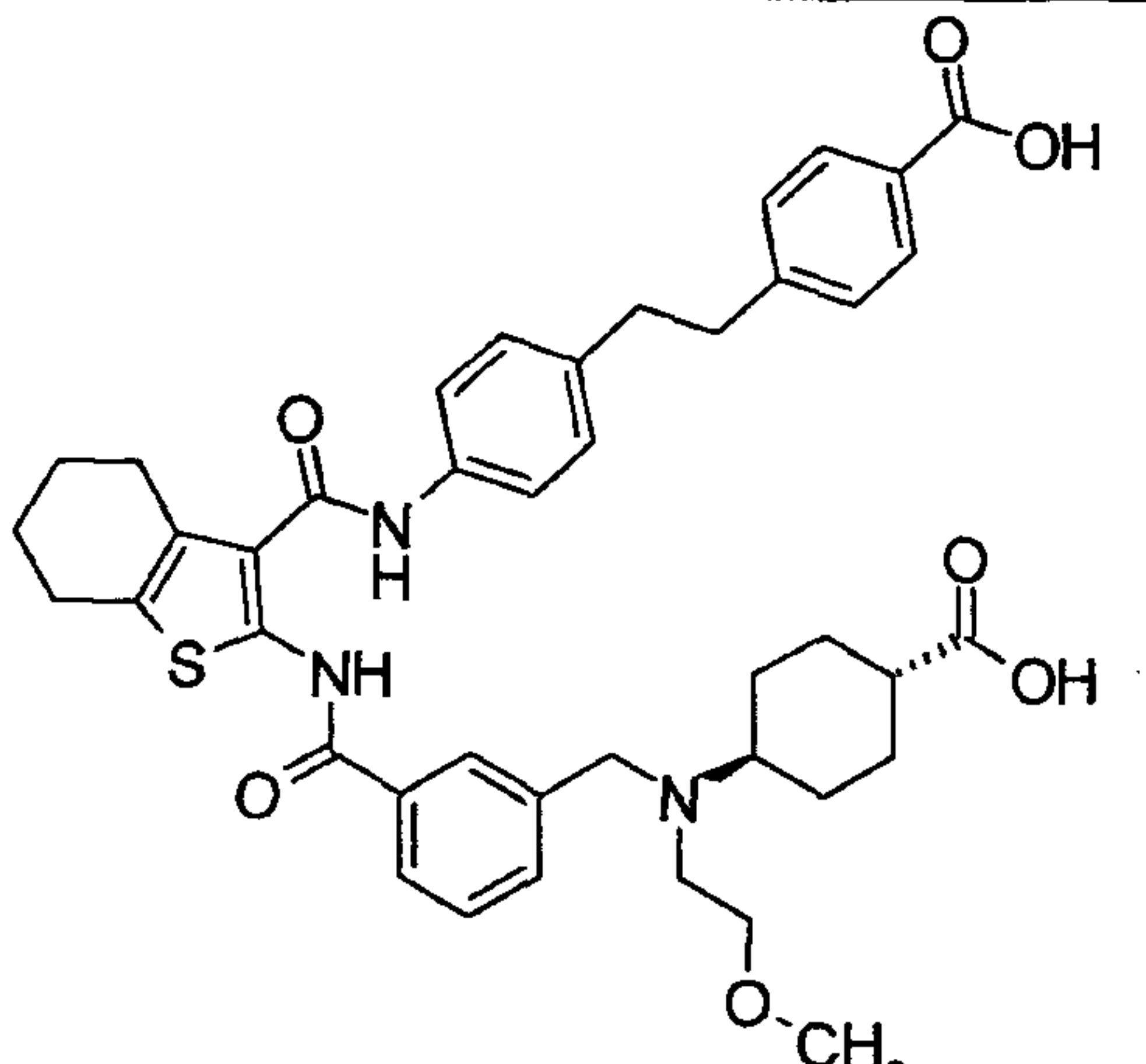
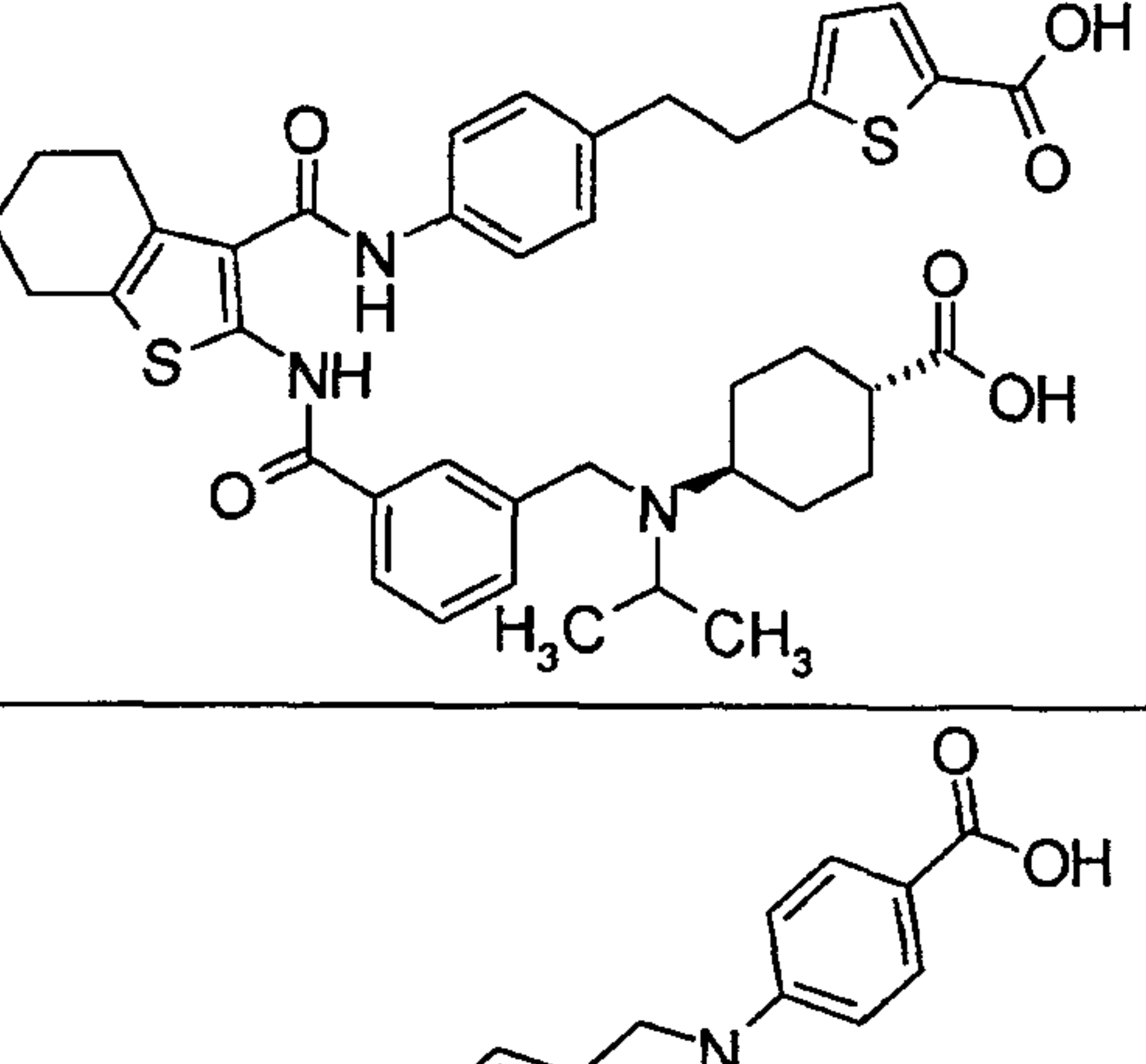
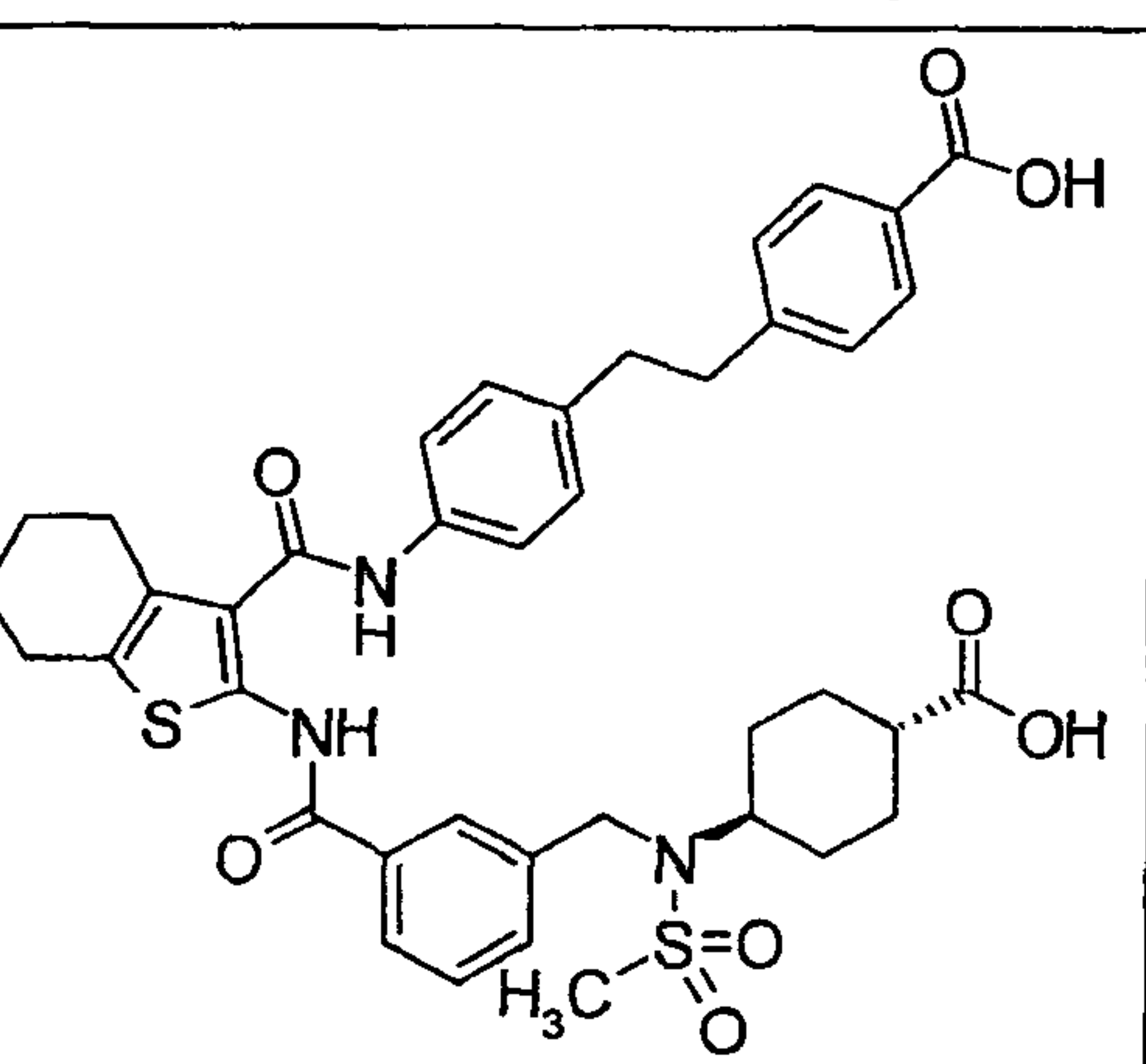
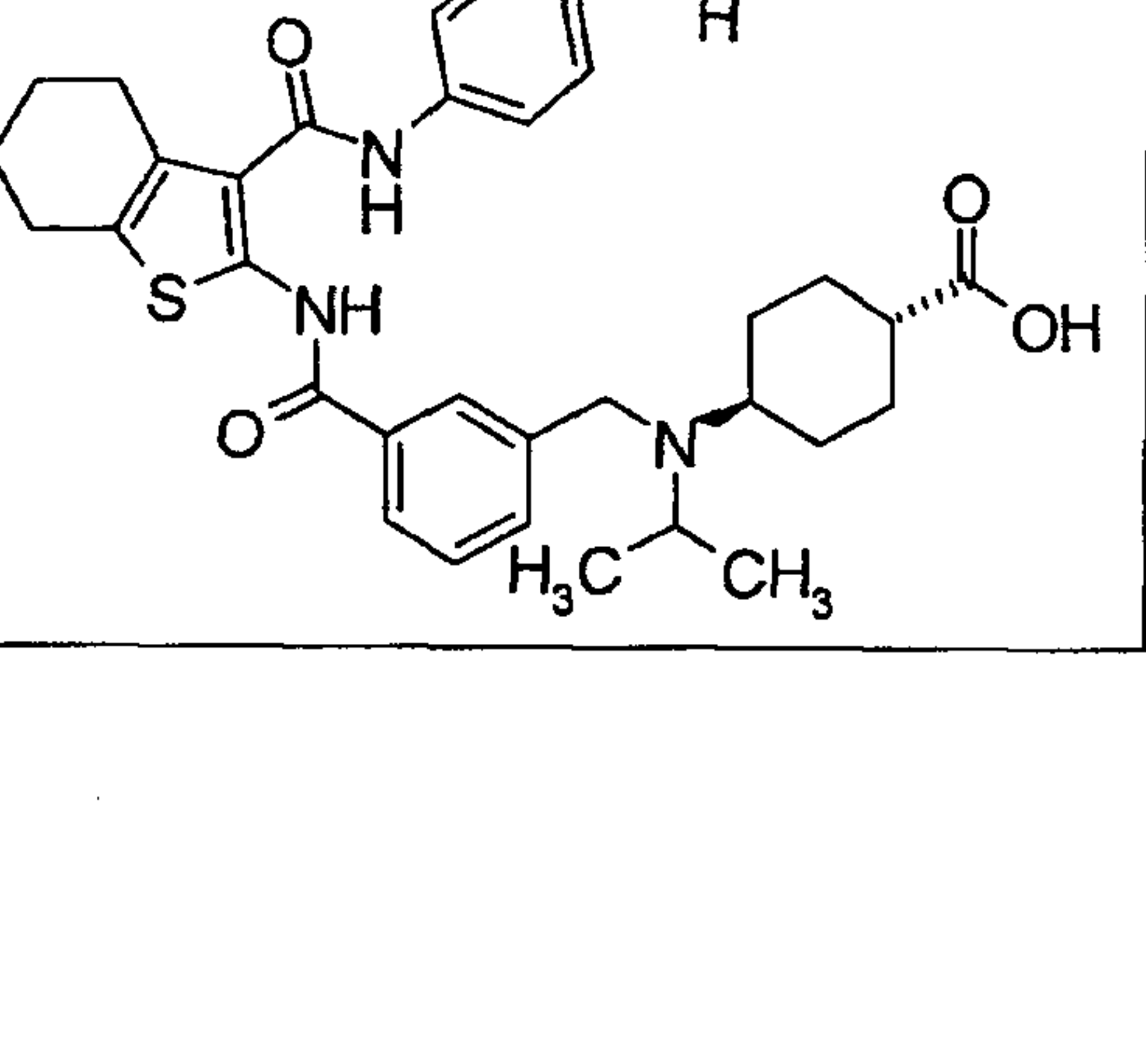
[0221]
[Table 76]

Ex	Str	Ex	Str
161	2HCl	165	
162		166	
163		167	
164		168	

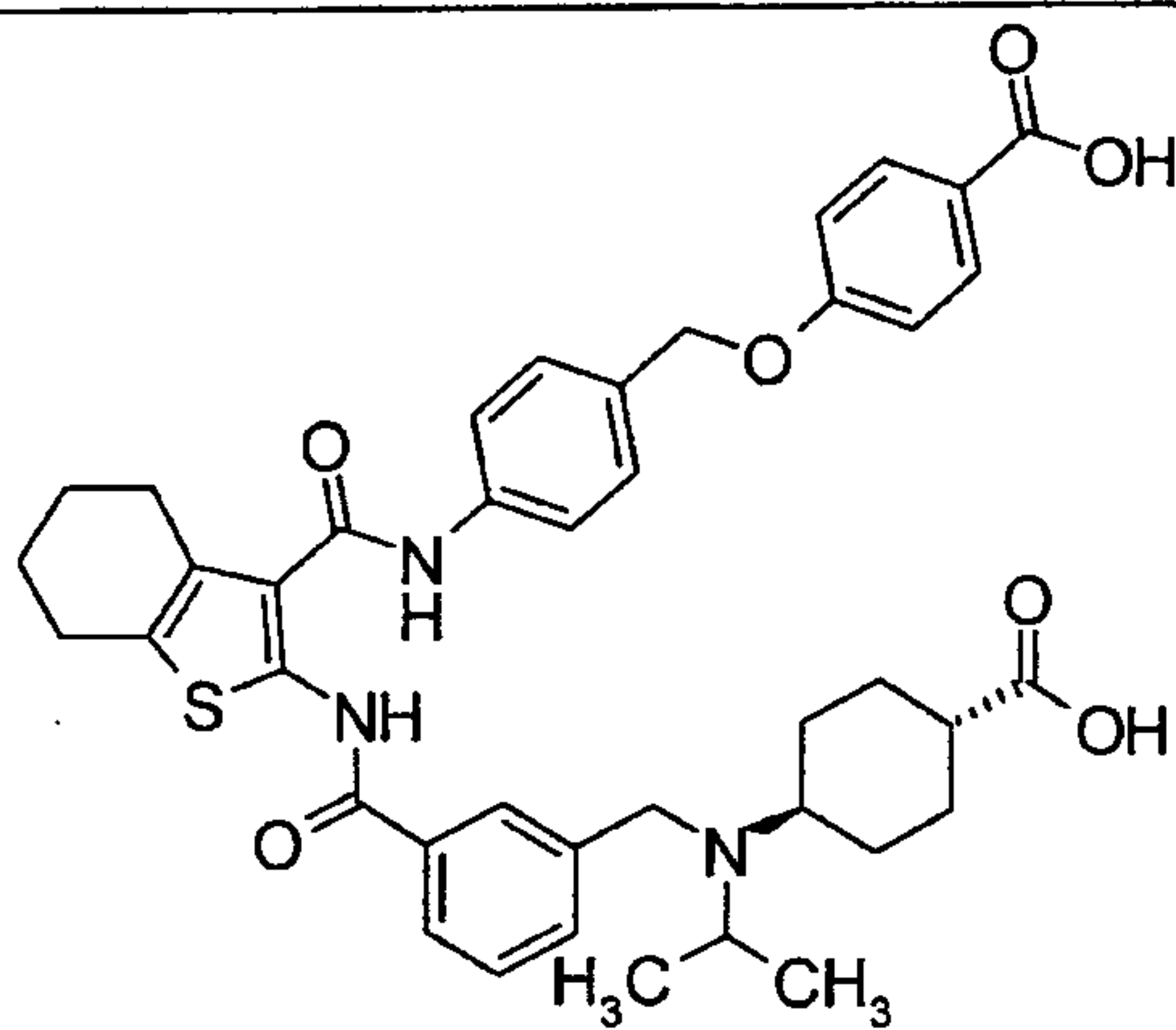
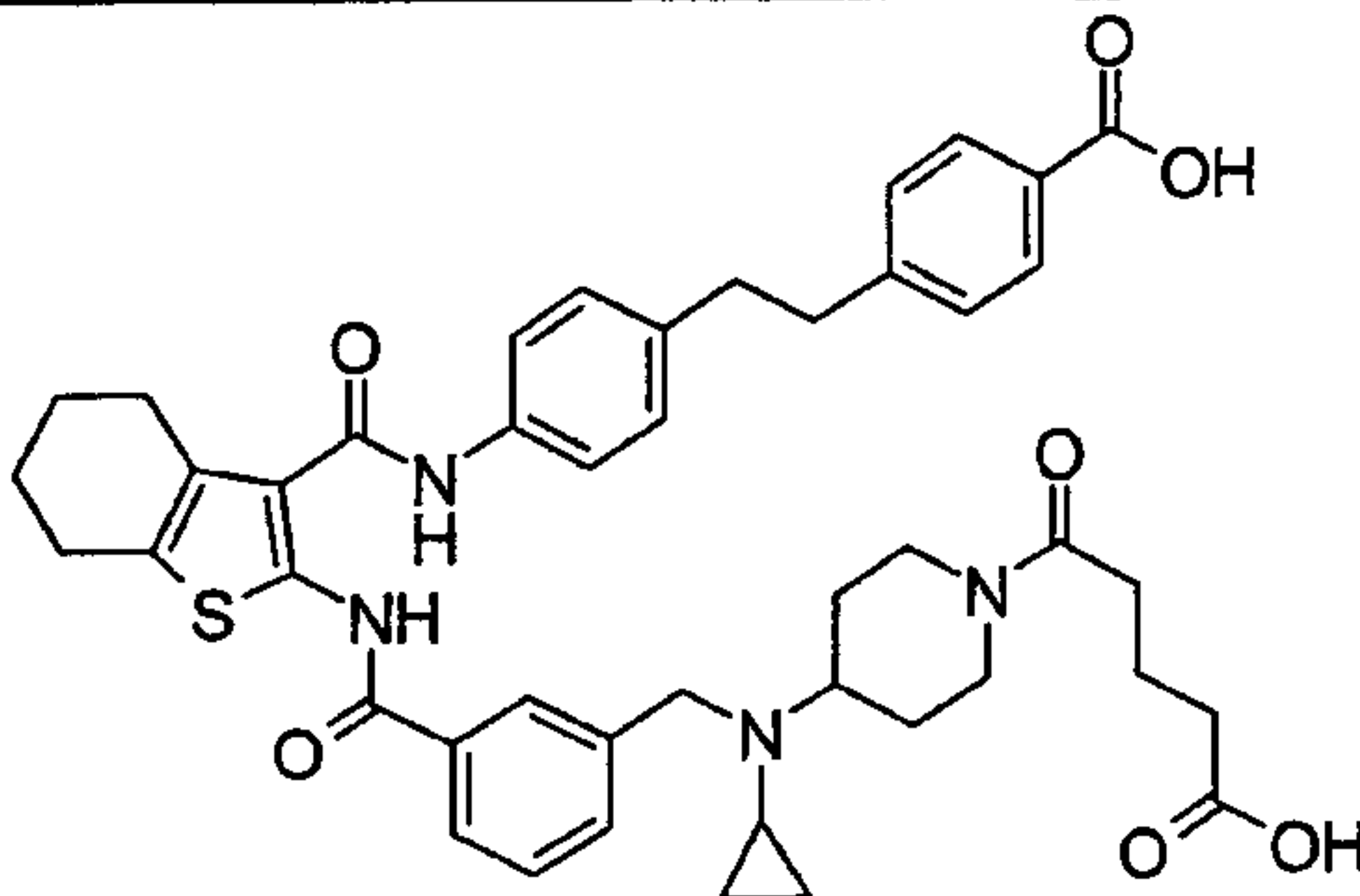
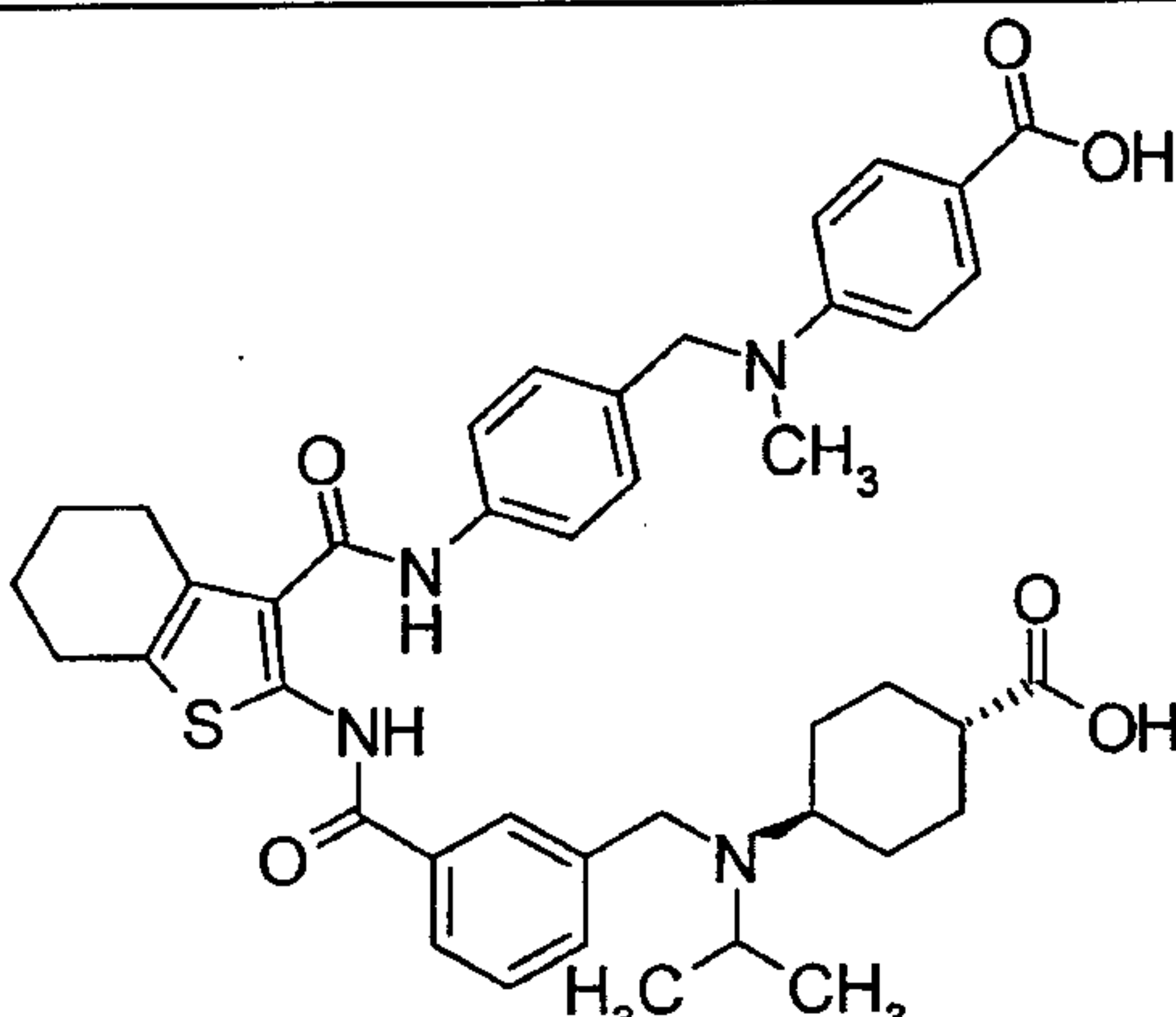
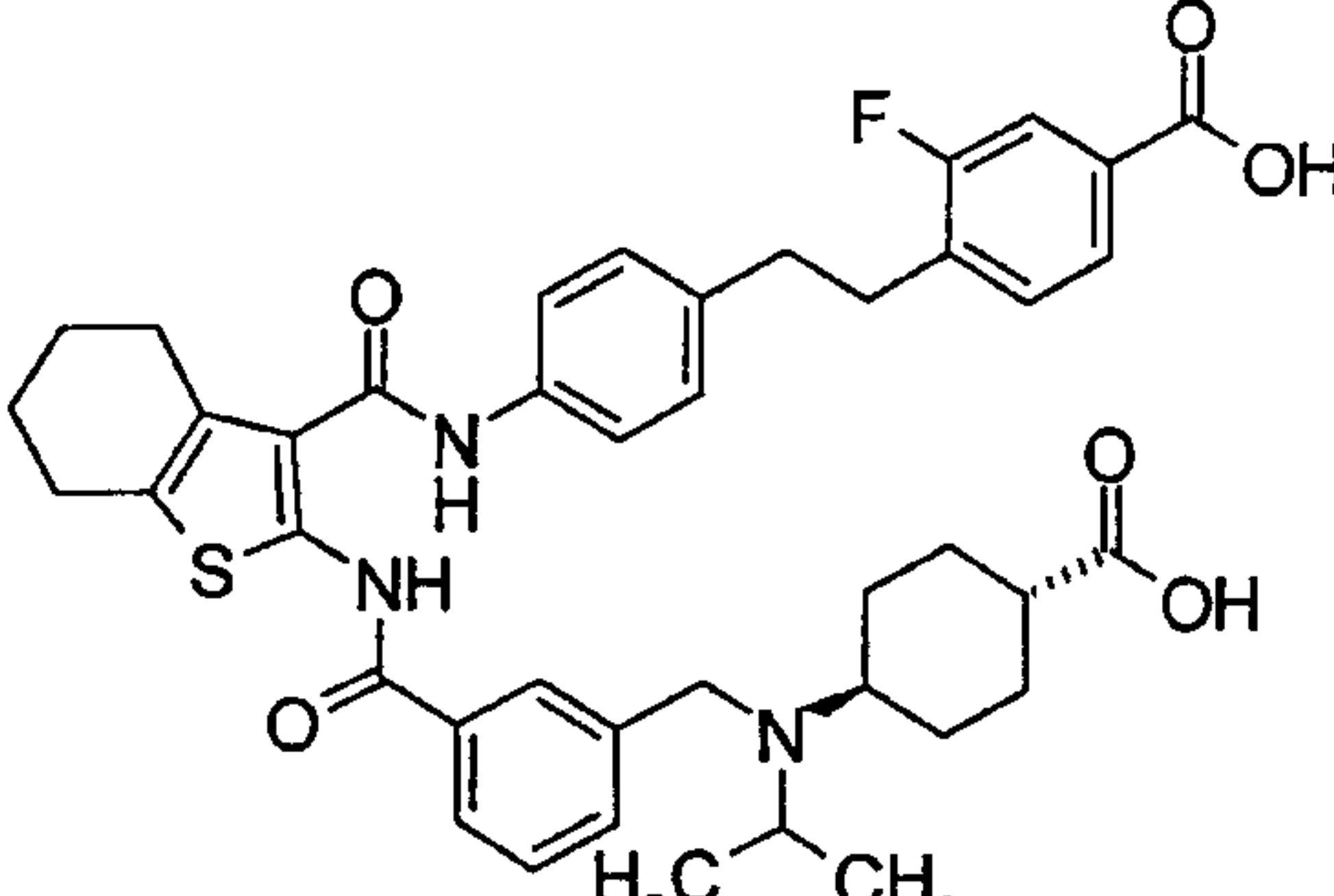
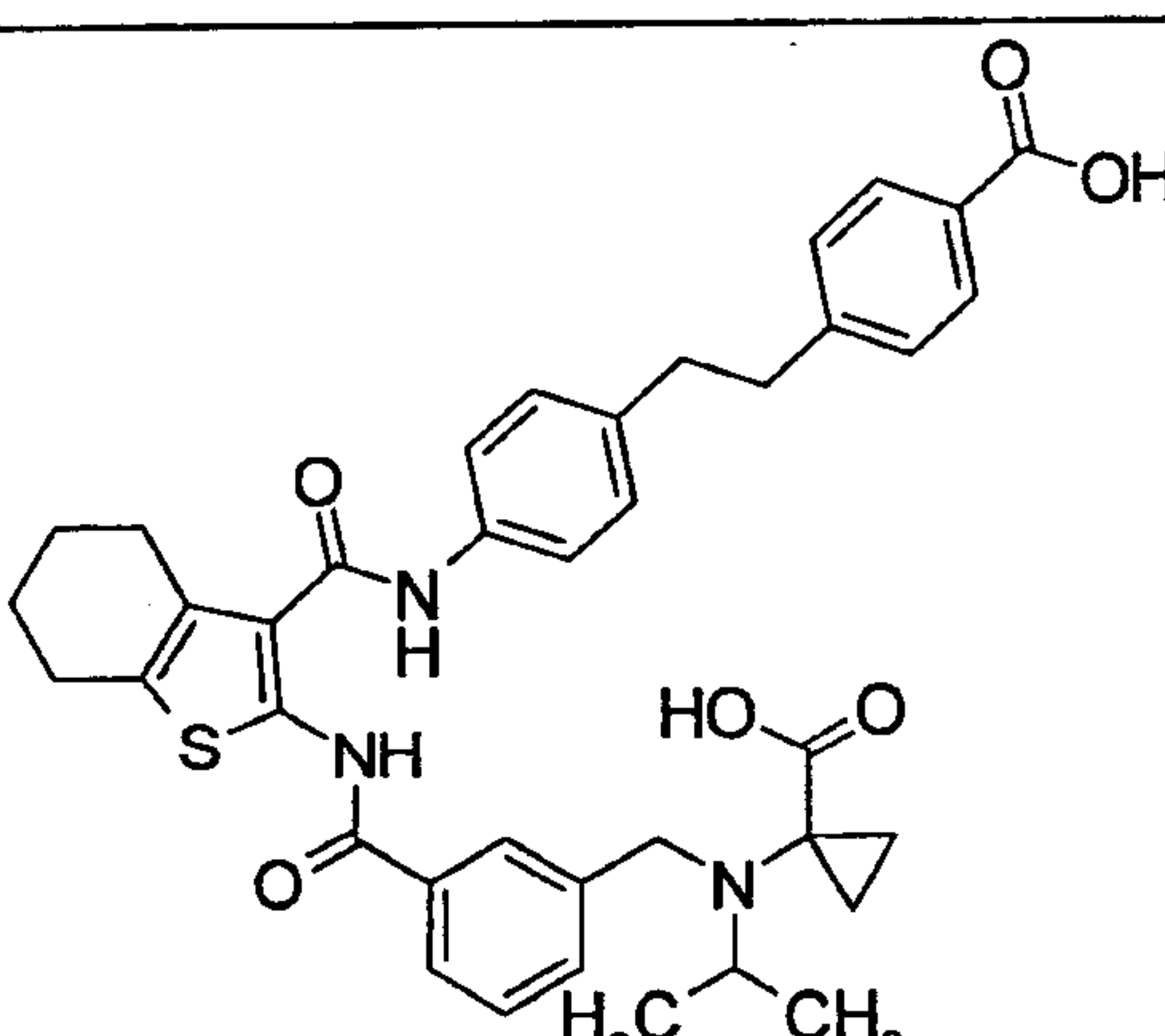
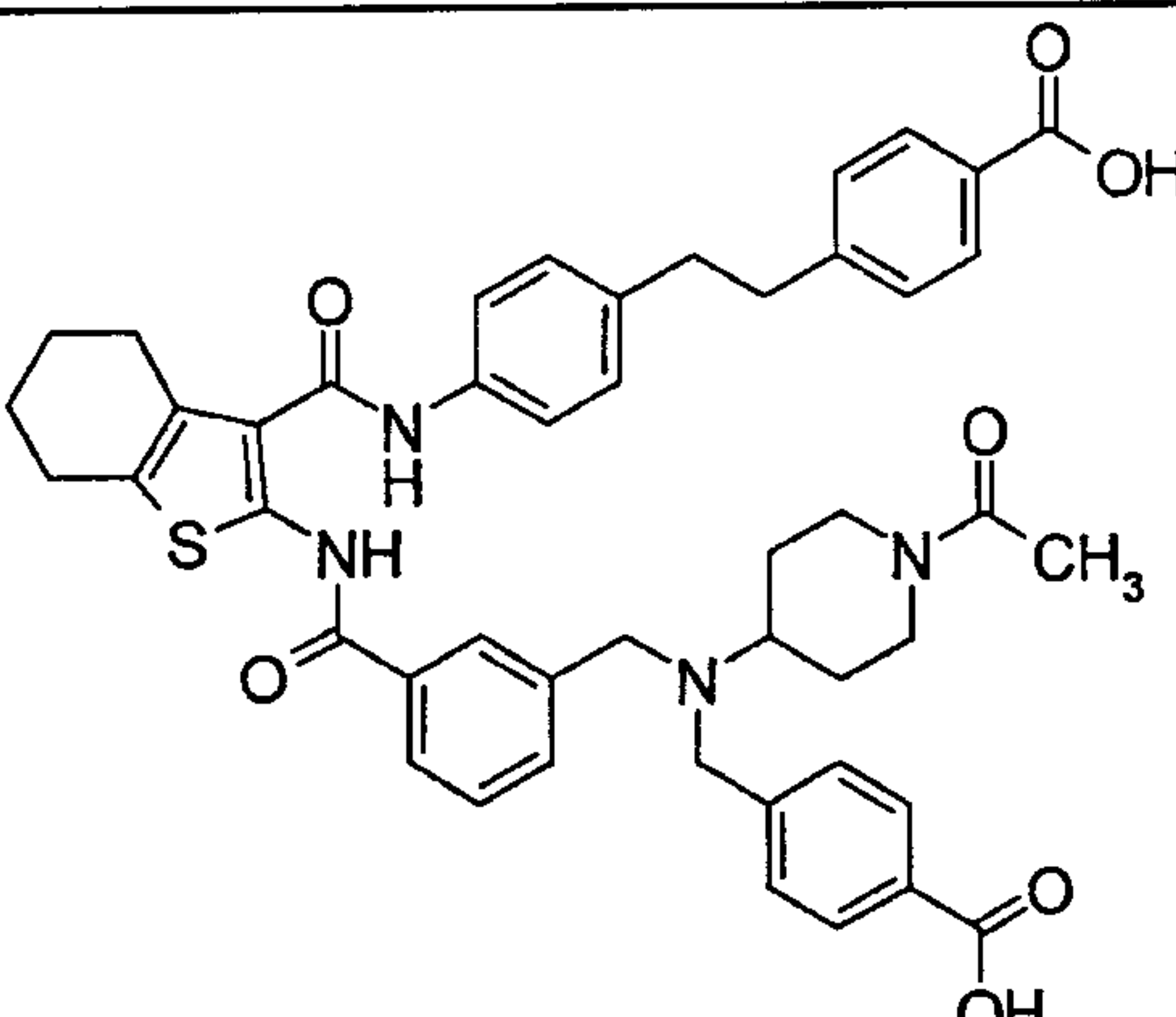
[0222]
[Table 77]

Ex	Str	Ex	Str
169	 HCl	173	
170		174	
171	 2HCl	175	
172		176	

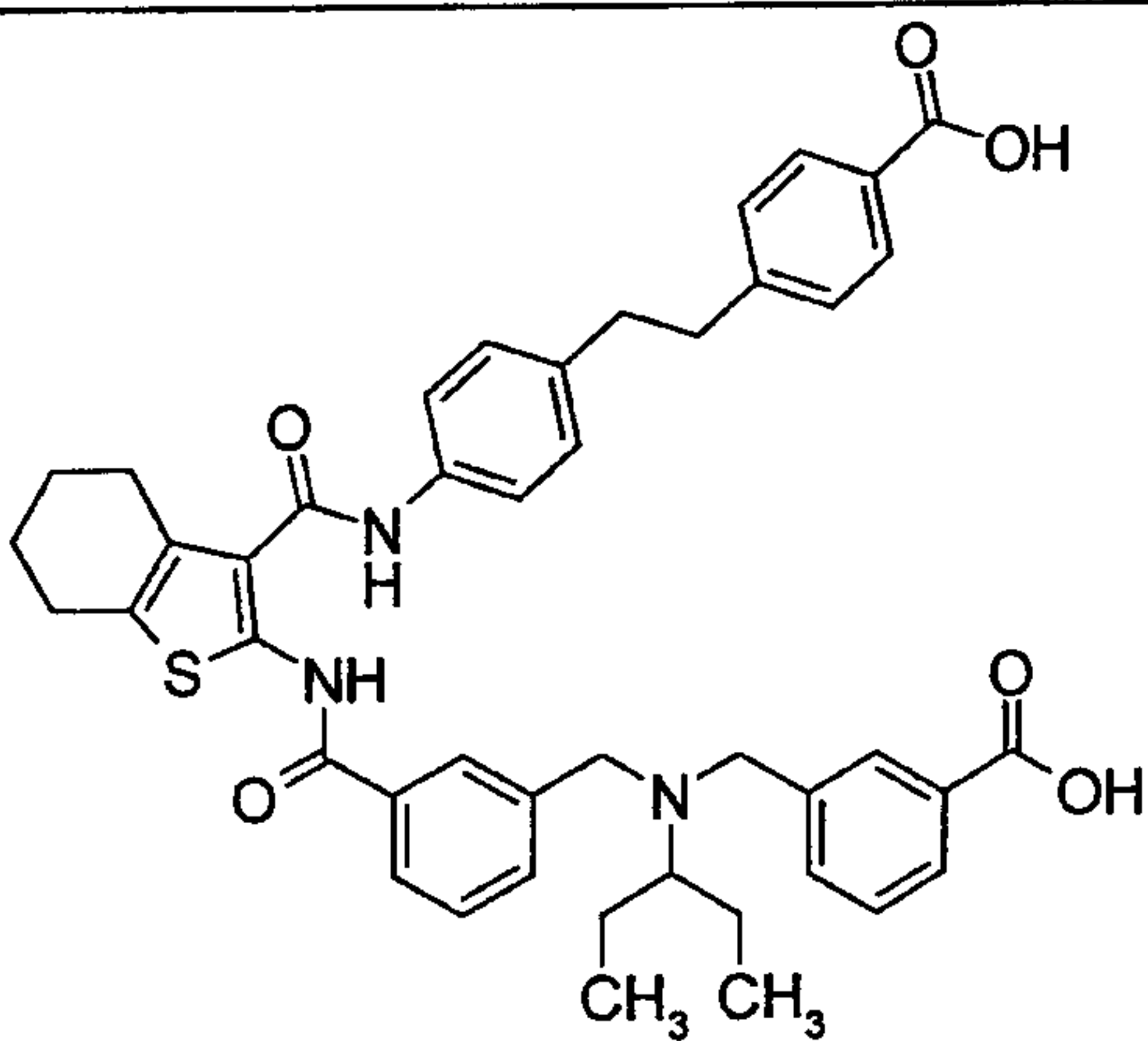
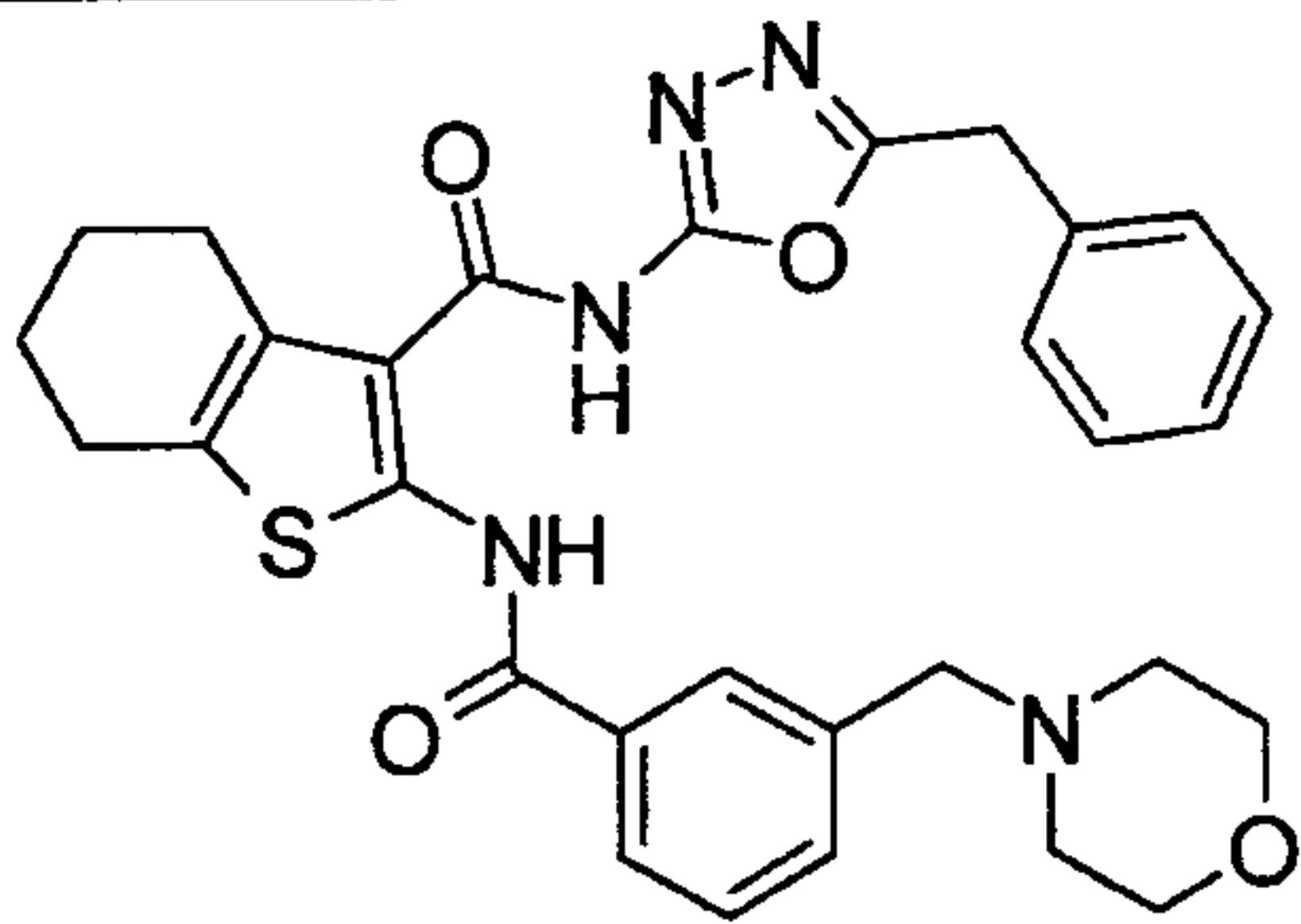
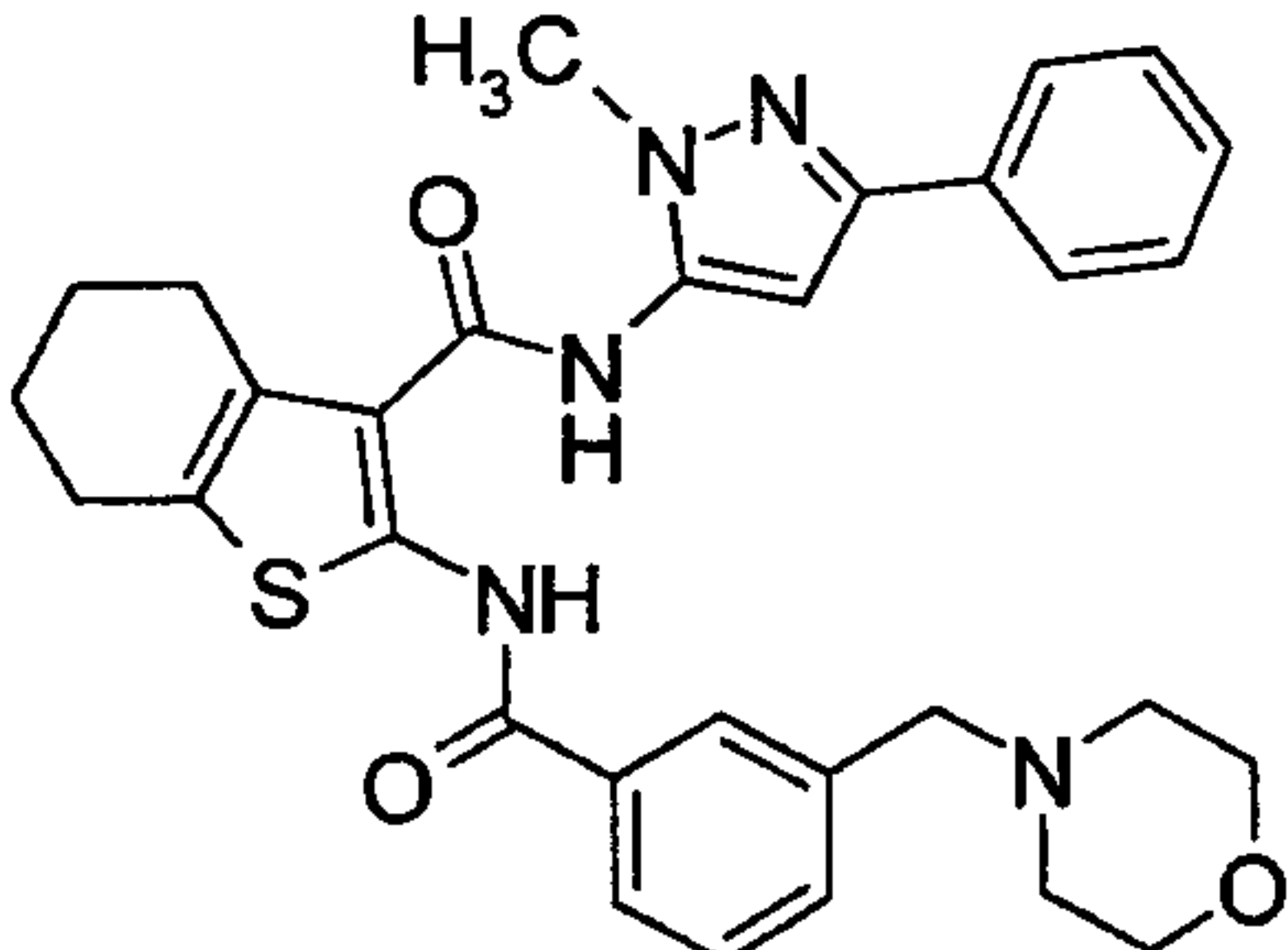
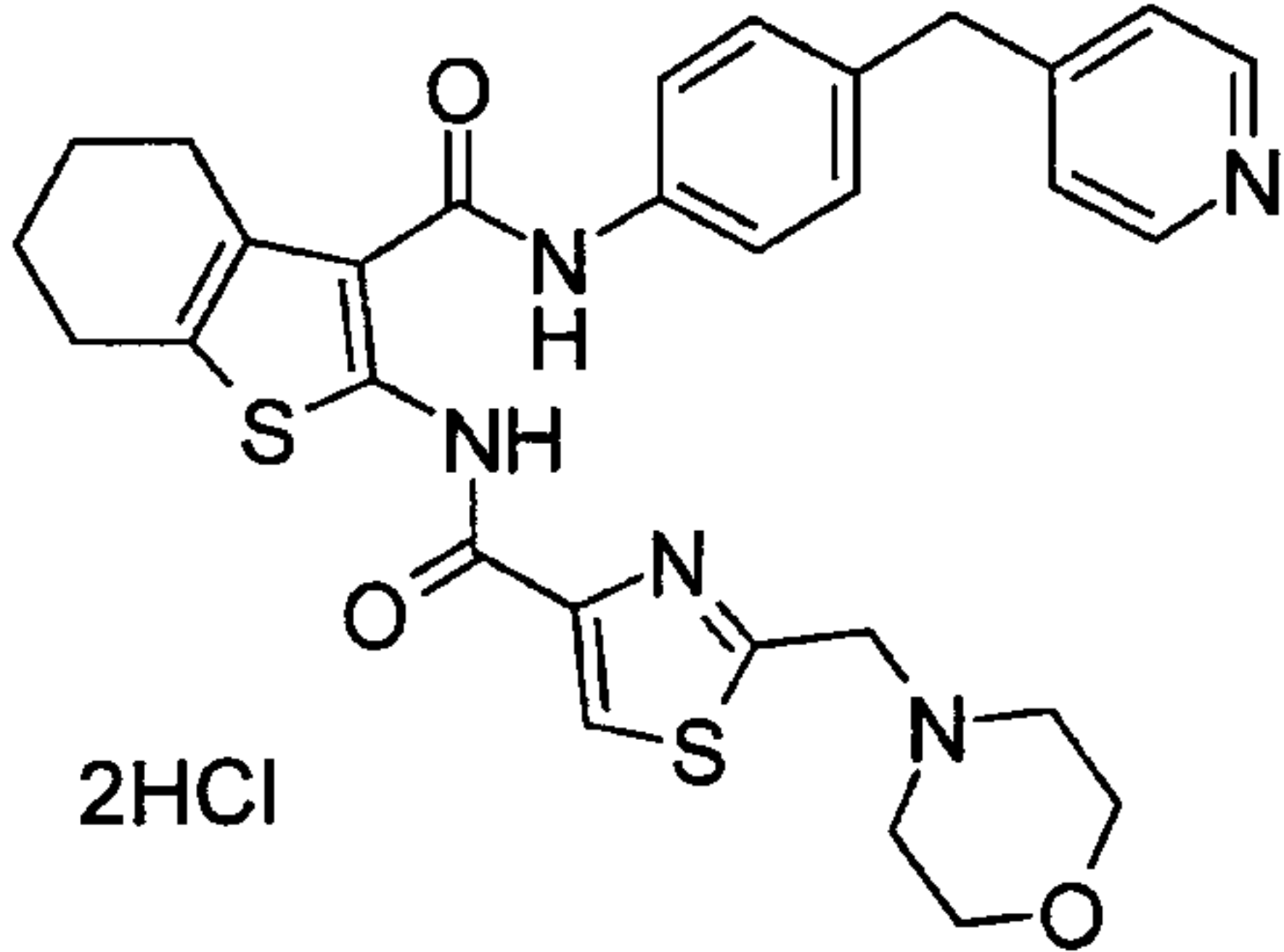
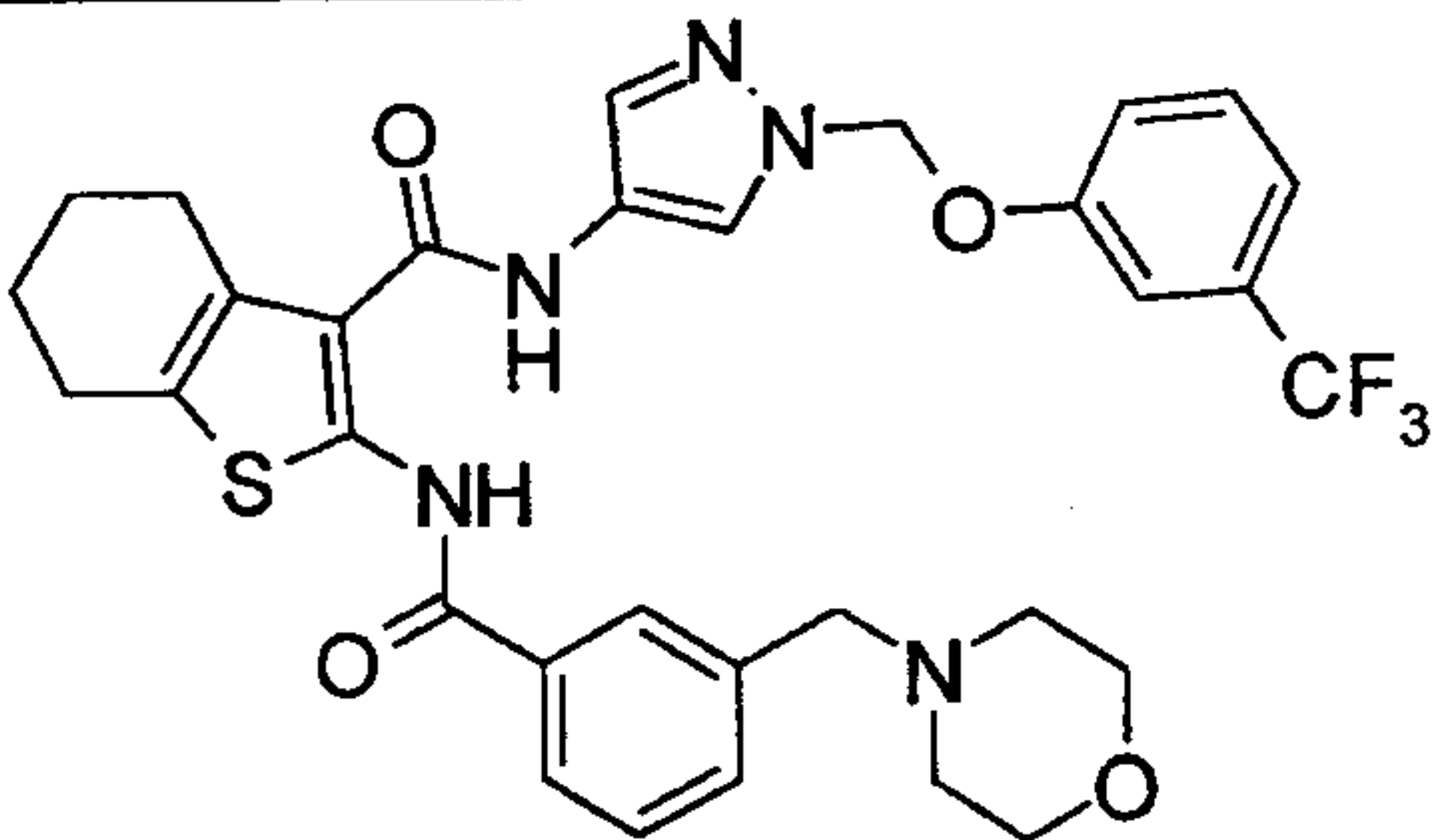
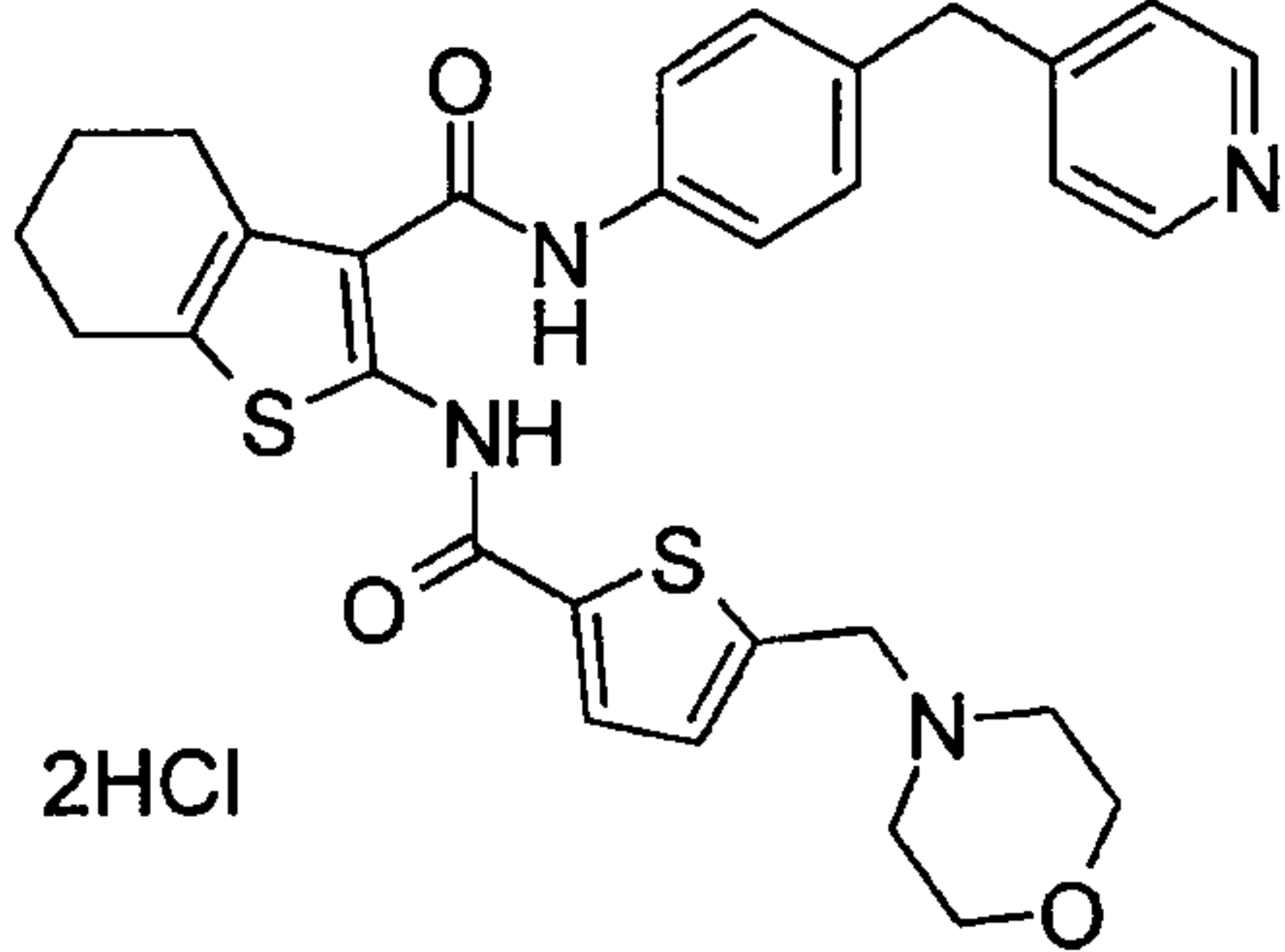
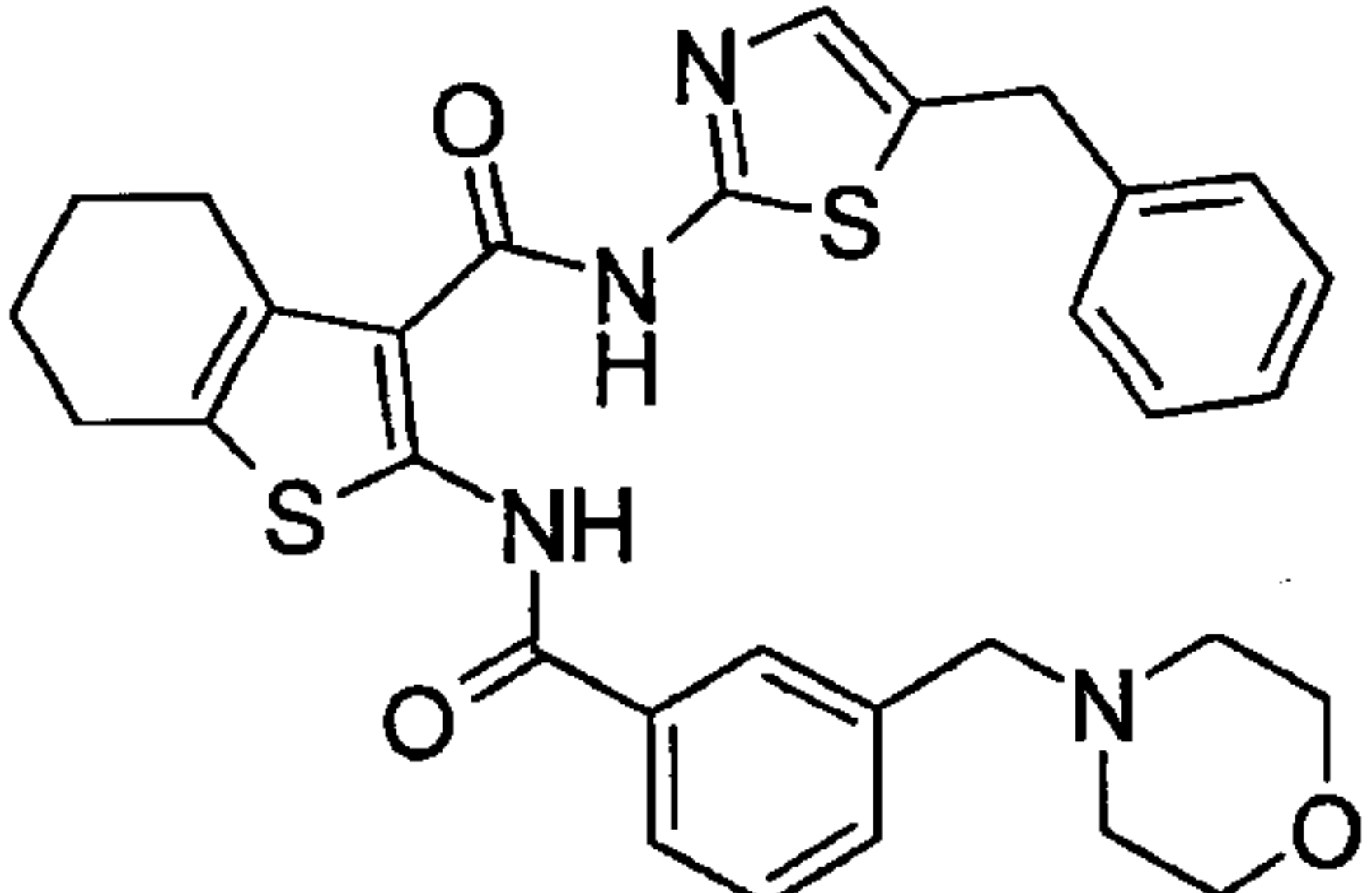
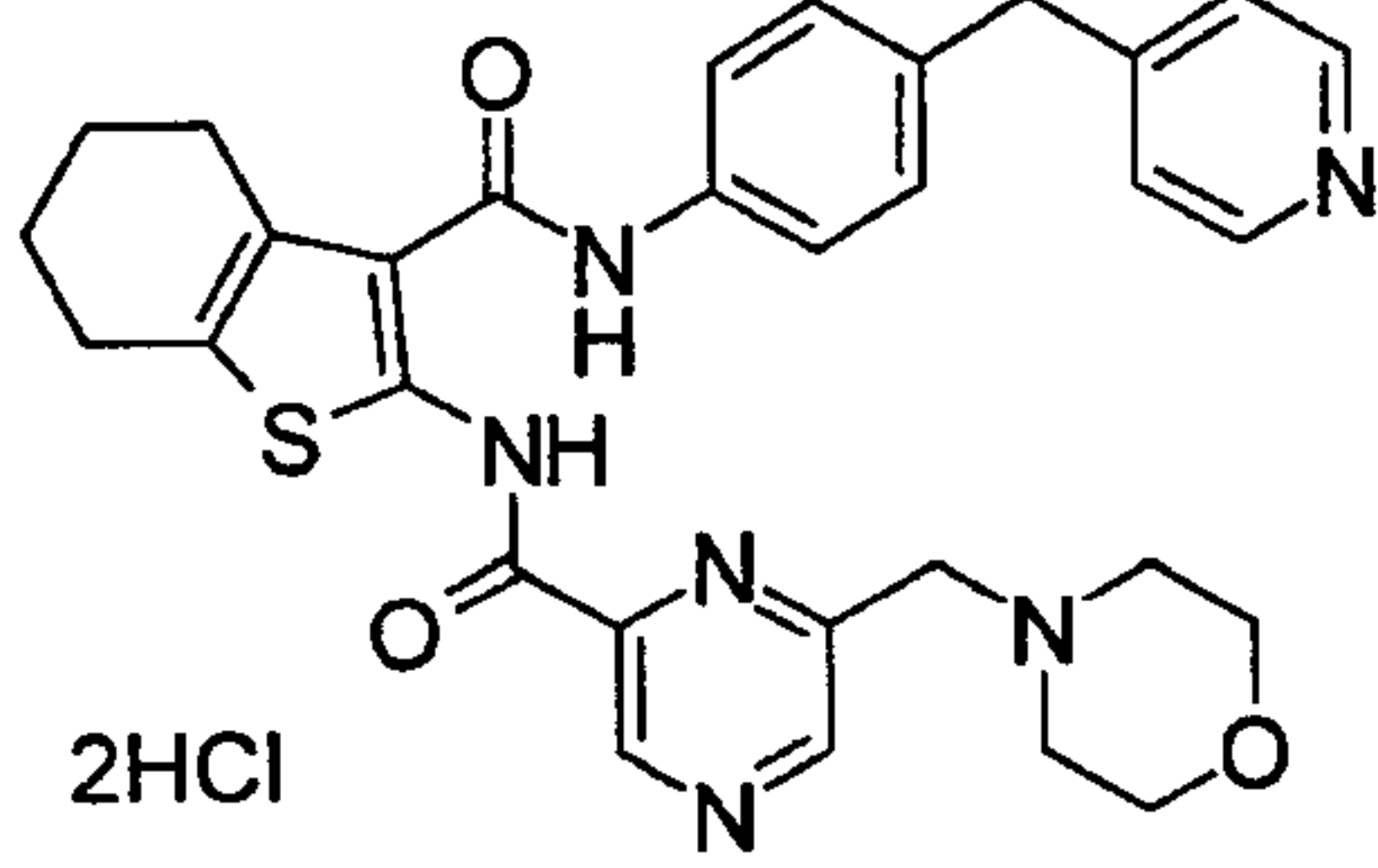
[0223]
[Table 78]

Ex	Str	Ex	Str
177		180	
178		181	
179		182	

[0224]
[Table 79]

Ex	Str	Ex	Str
183		186	
184		187	
185		188	

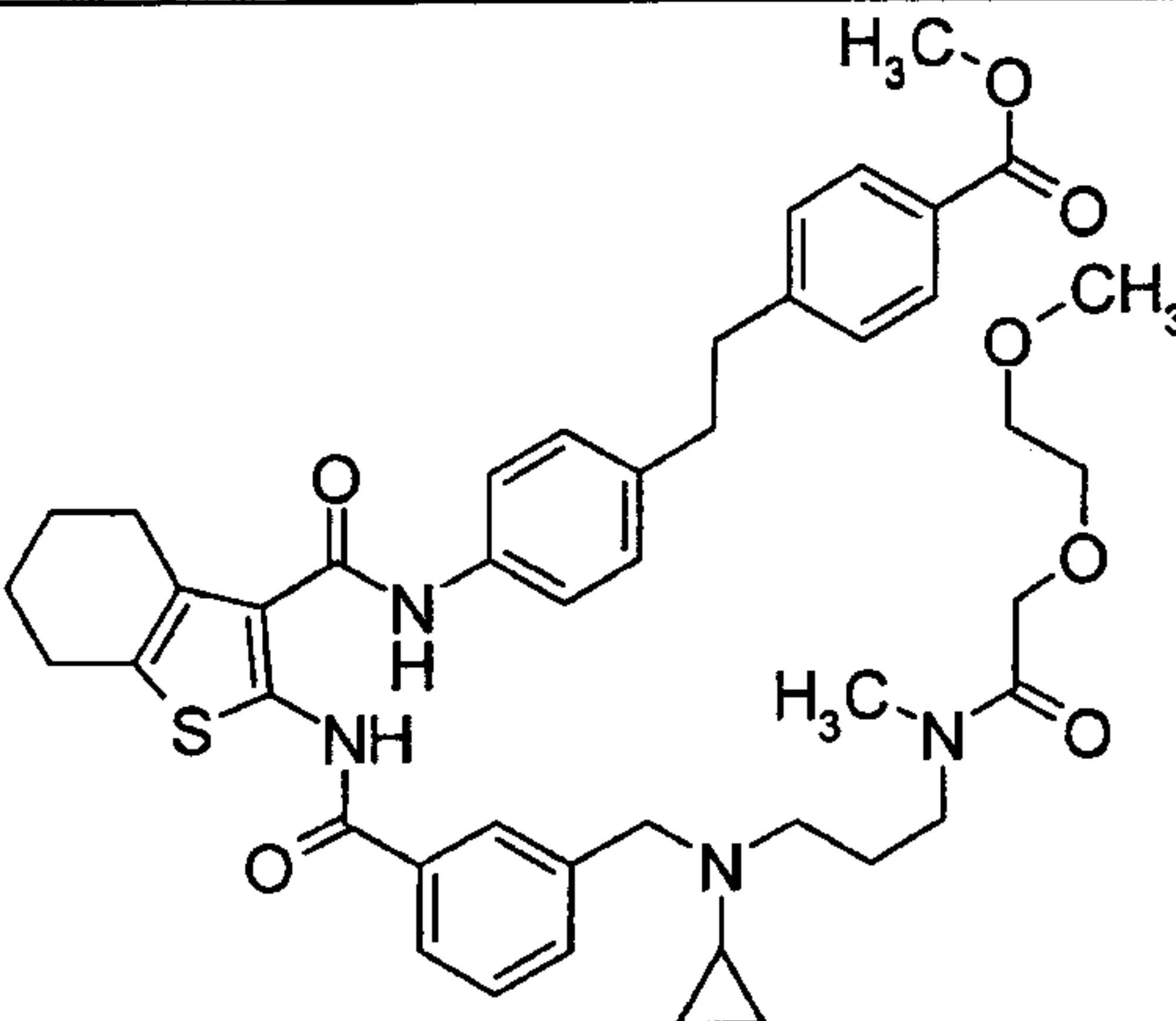
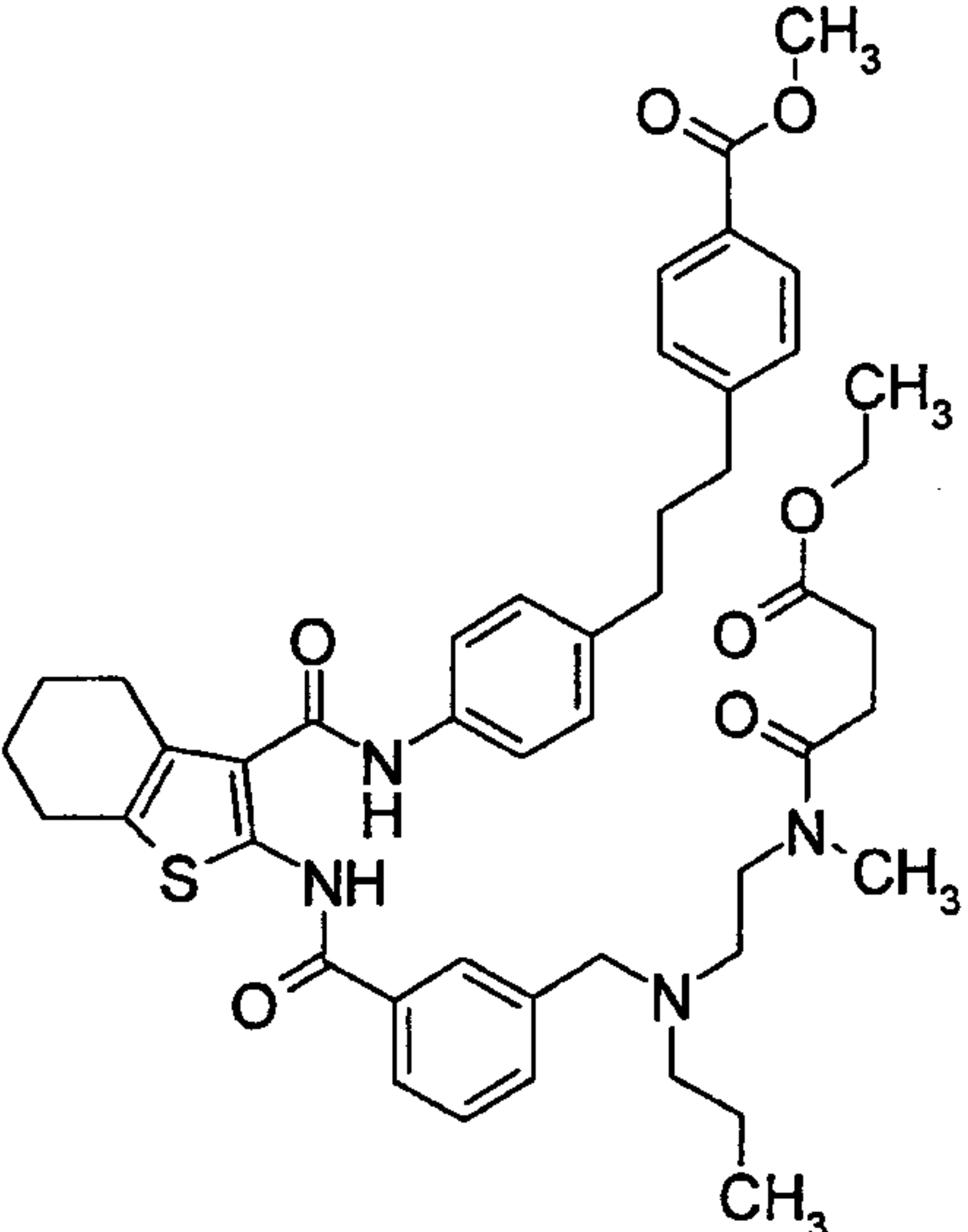
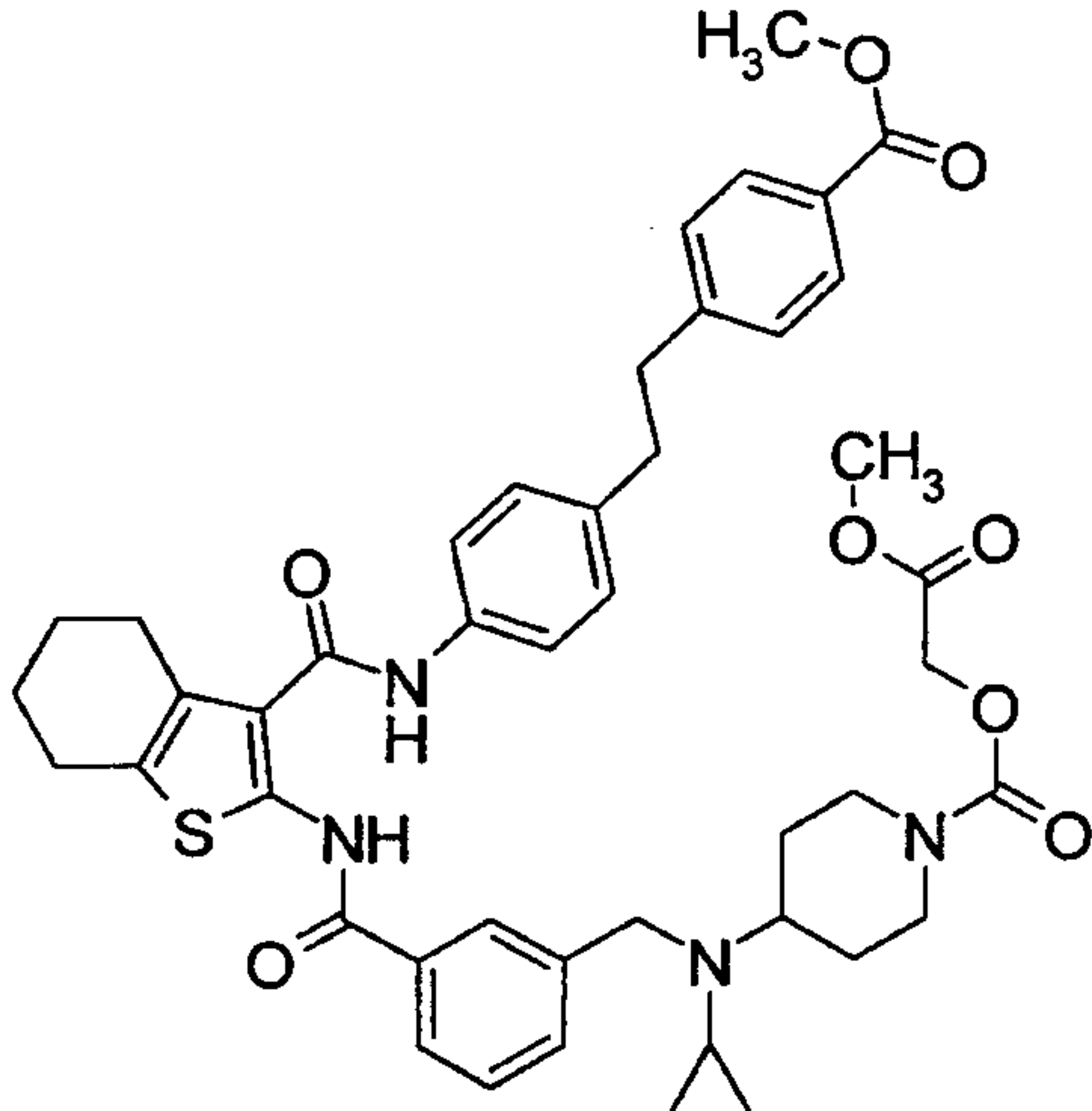
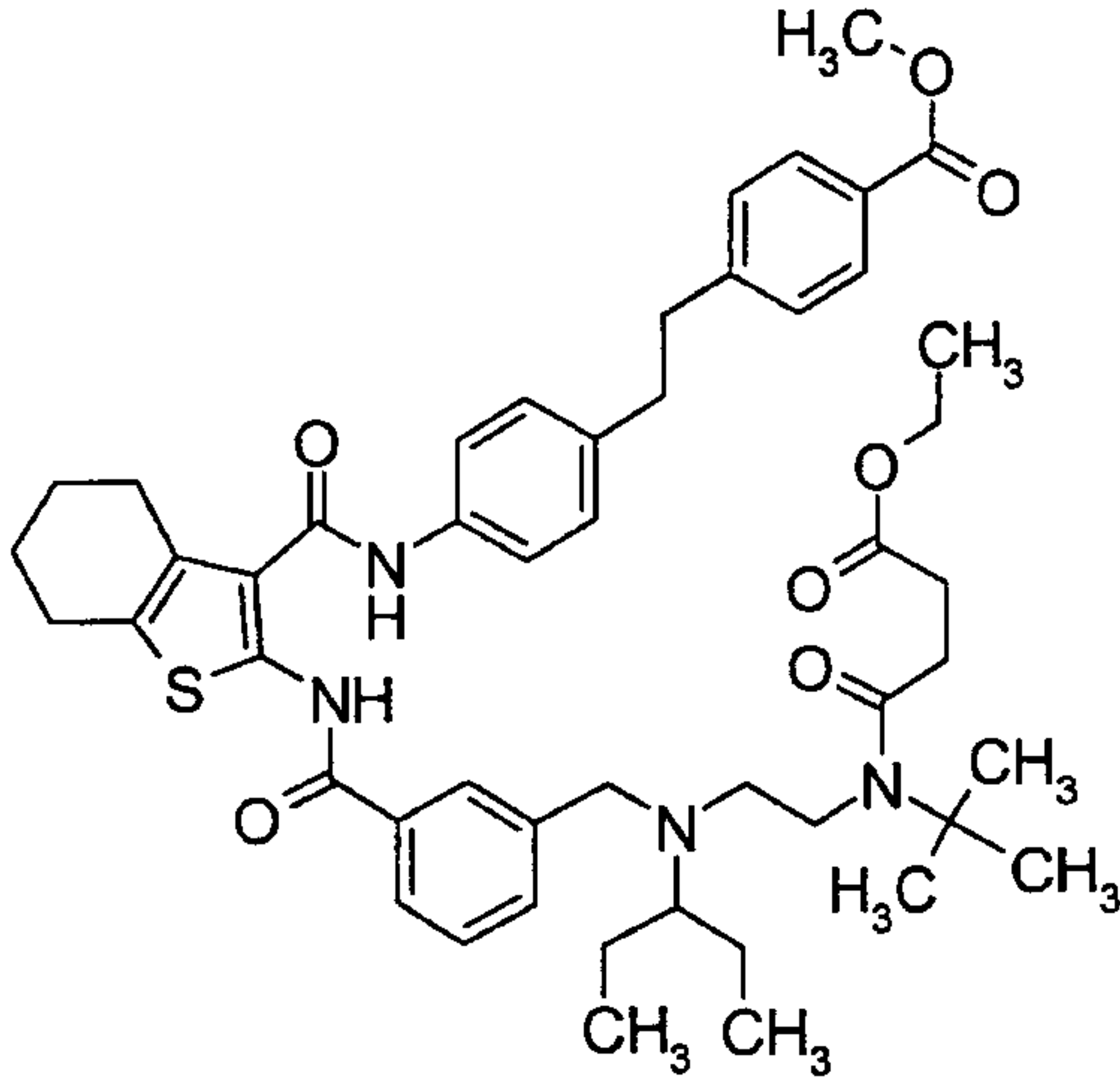
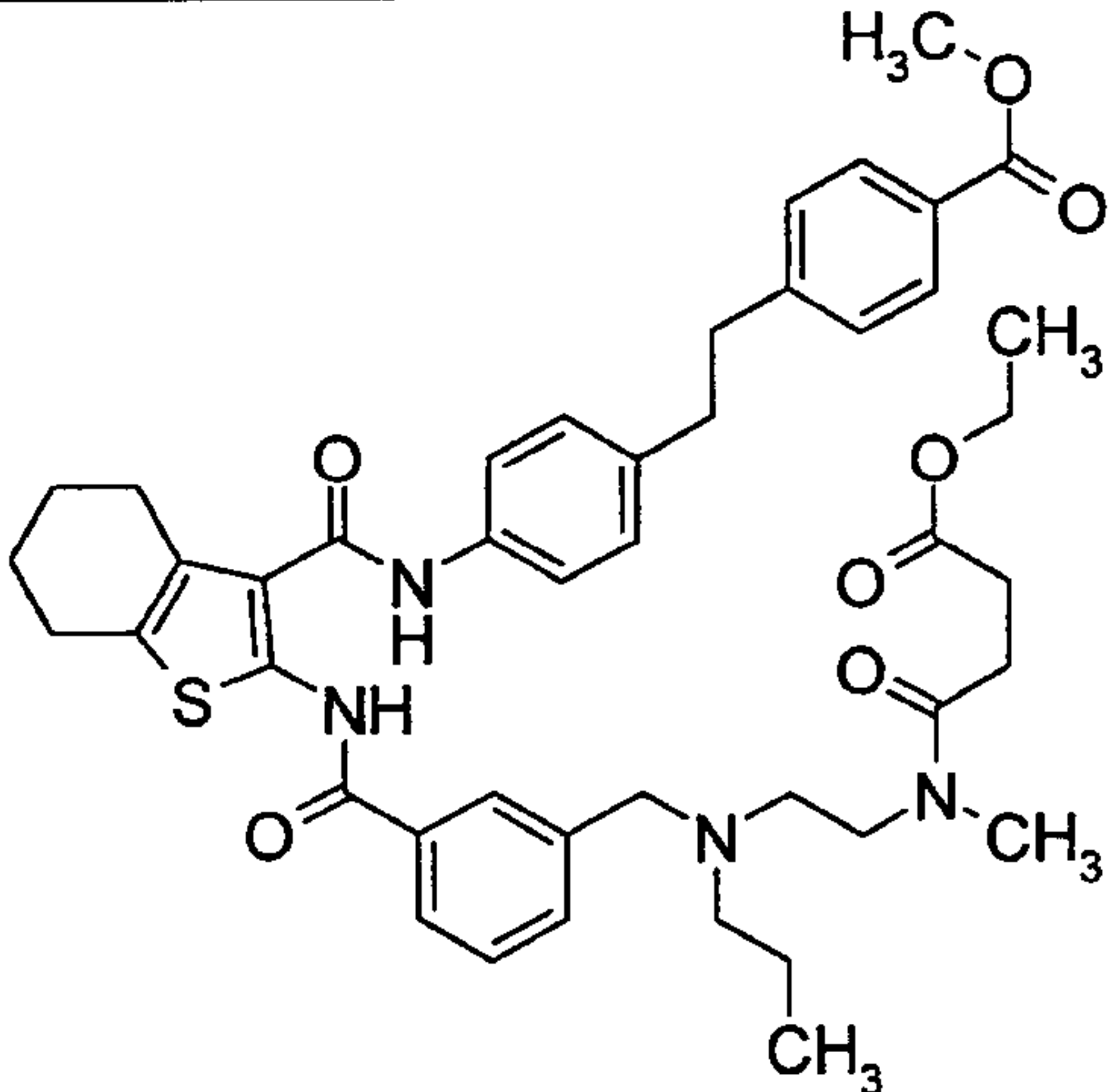
[0225]
[Table 80]

Ex	Str	Ex	Str
189		193	
190		194	 2HCl
191		195	 2HCl
192		196	 2HCl

[0226]
[Table 81]

Ex	Str	Ex	Str
197		199	
198		200	
		201	

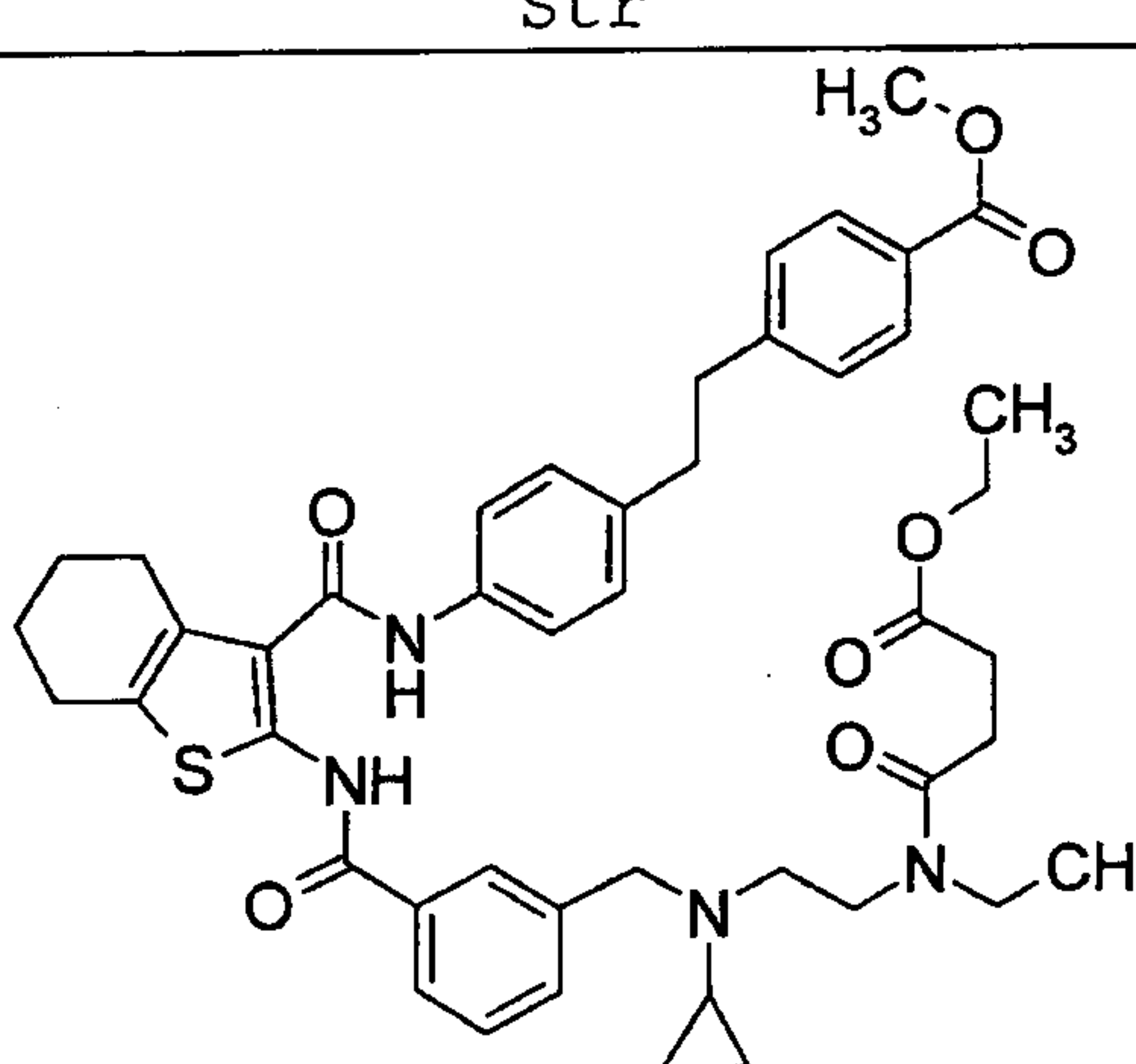
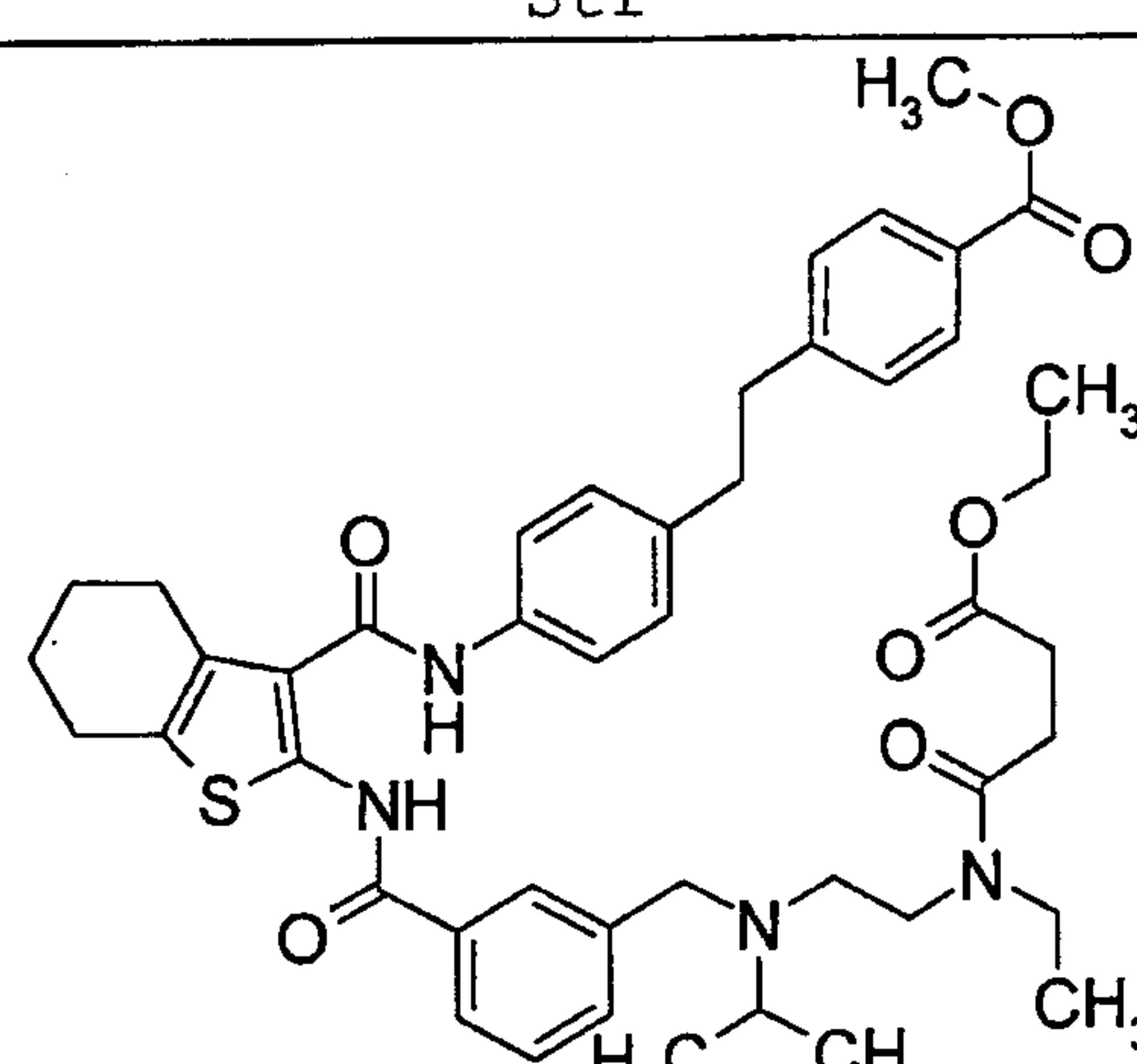
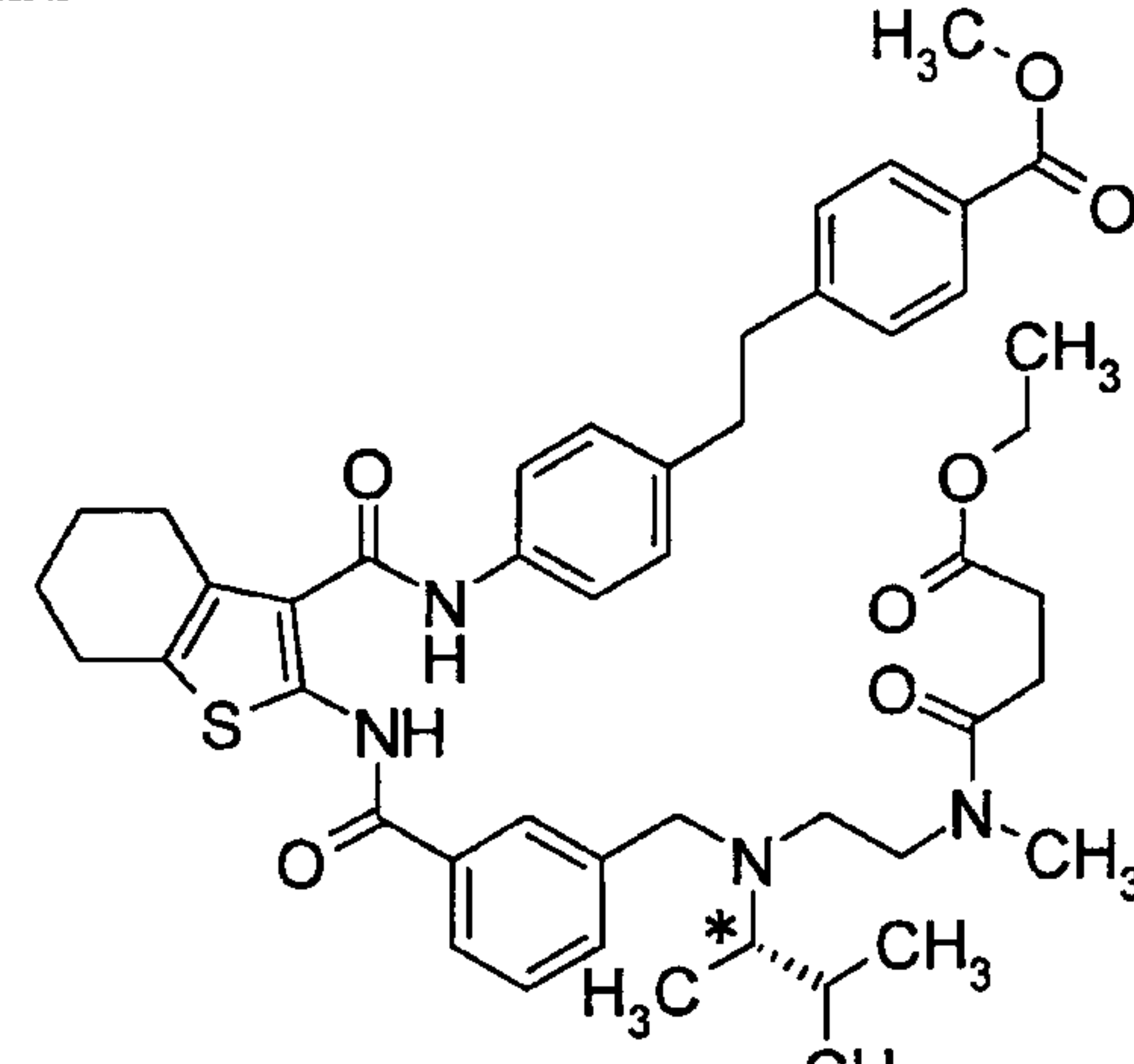
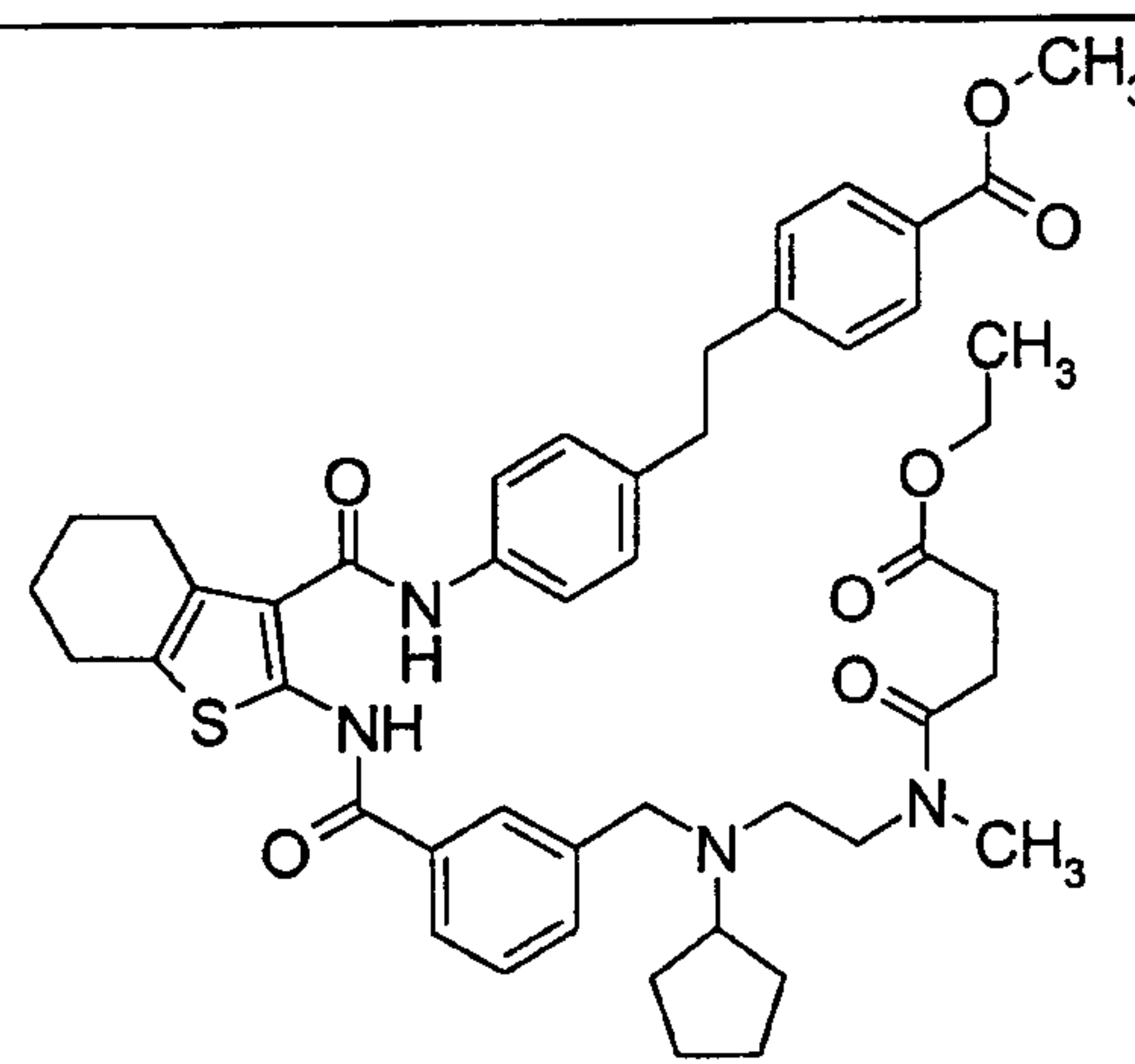
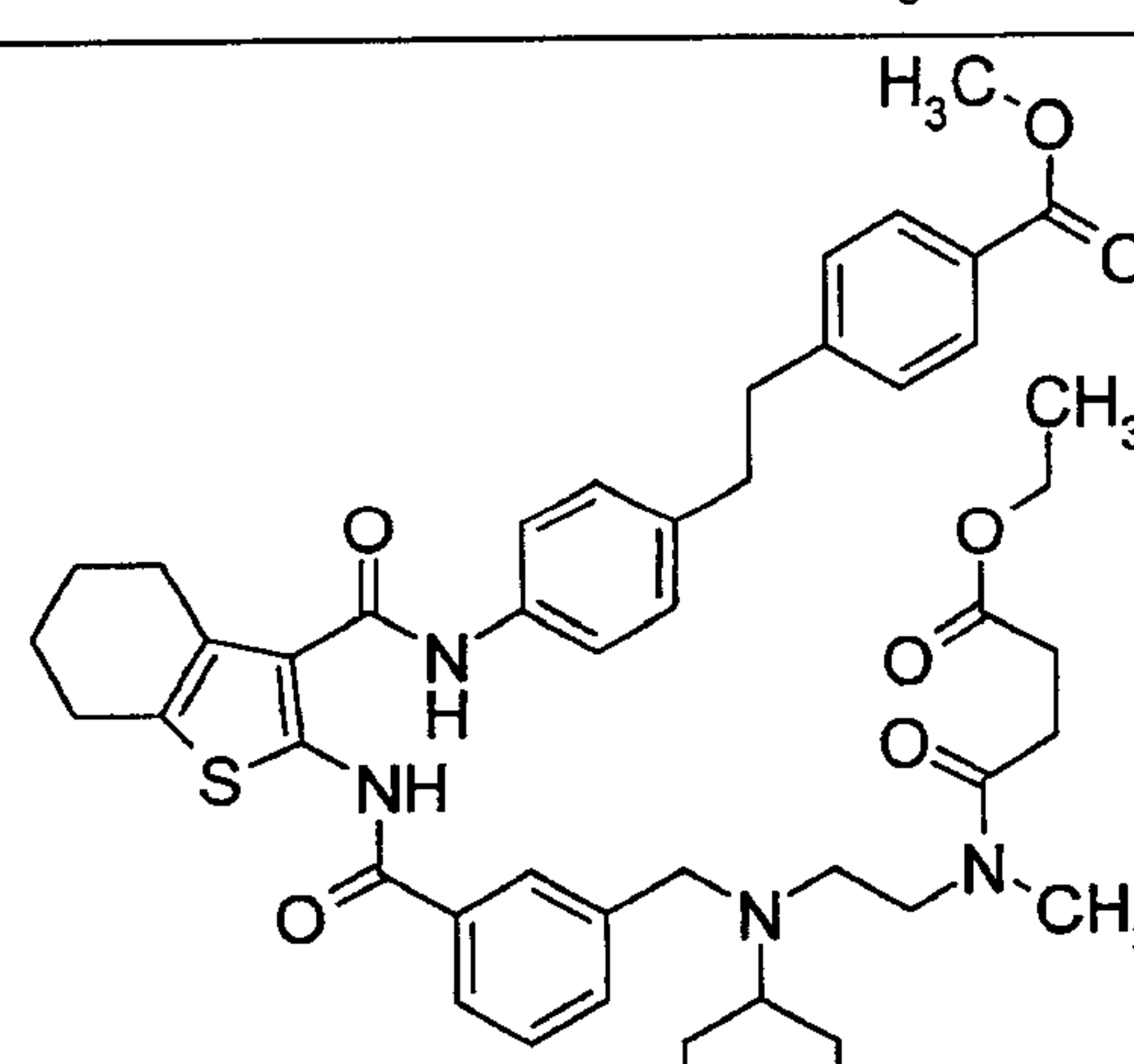
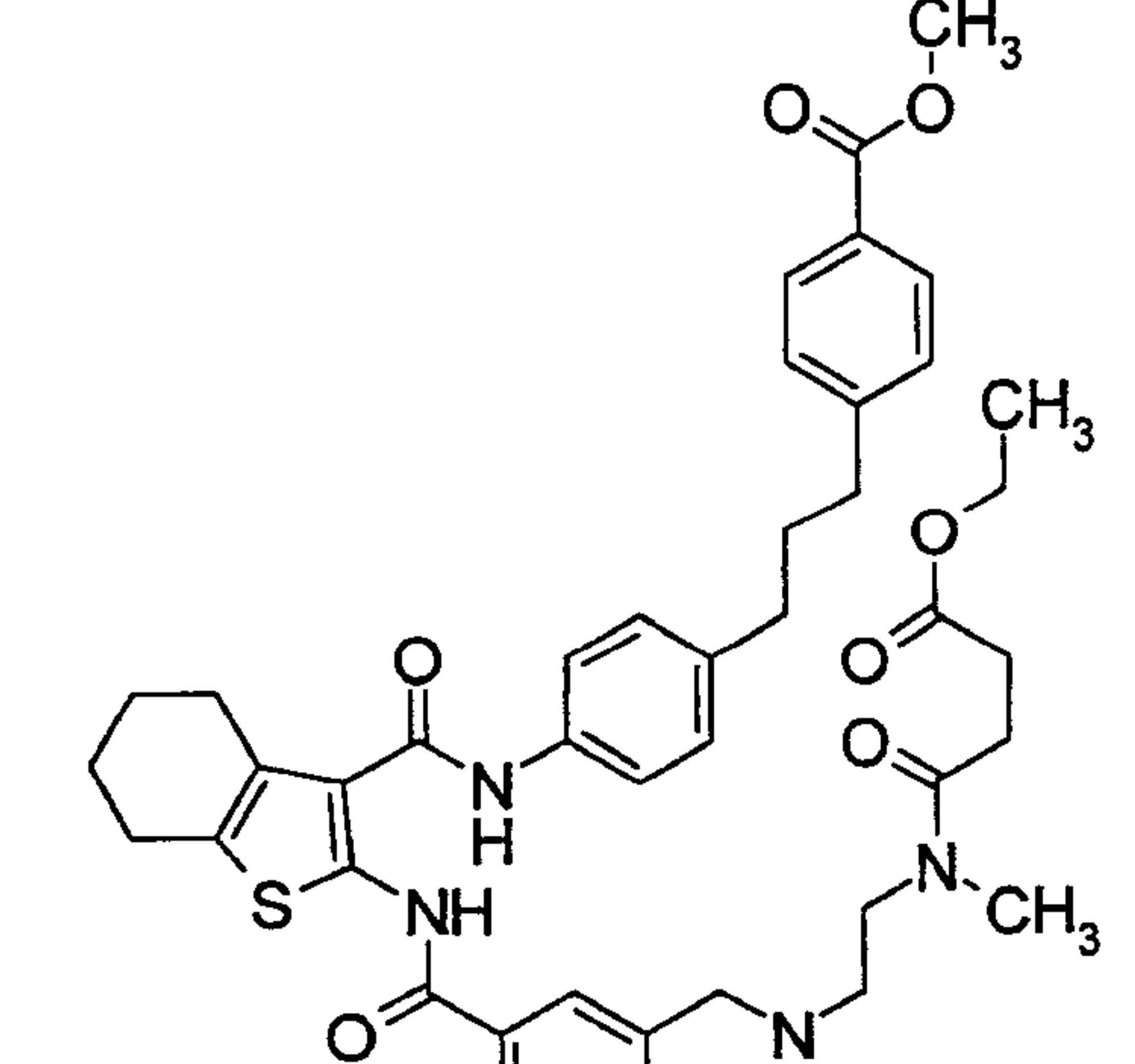
[0227]
[Table 82]

Ex	Str	Ex	Str
202		205	
203		206	
204			

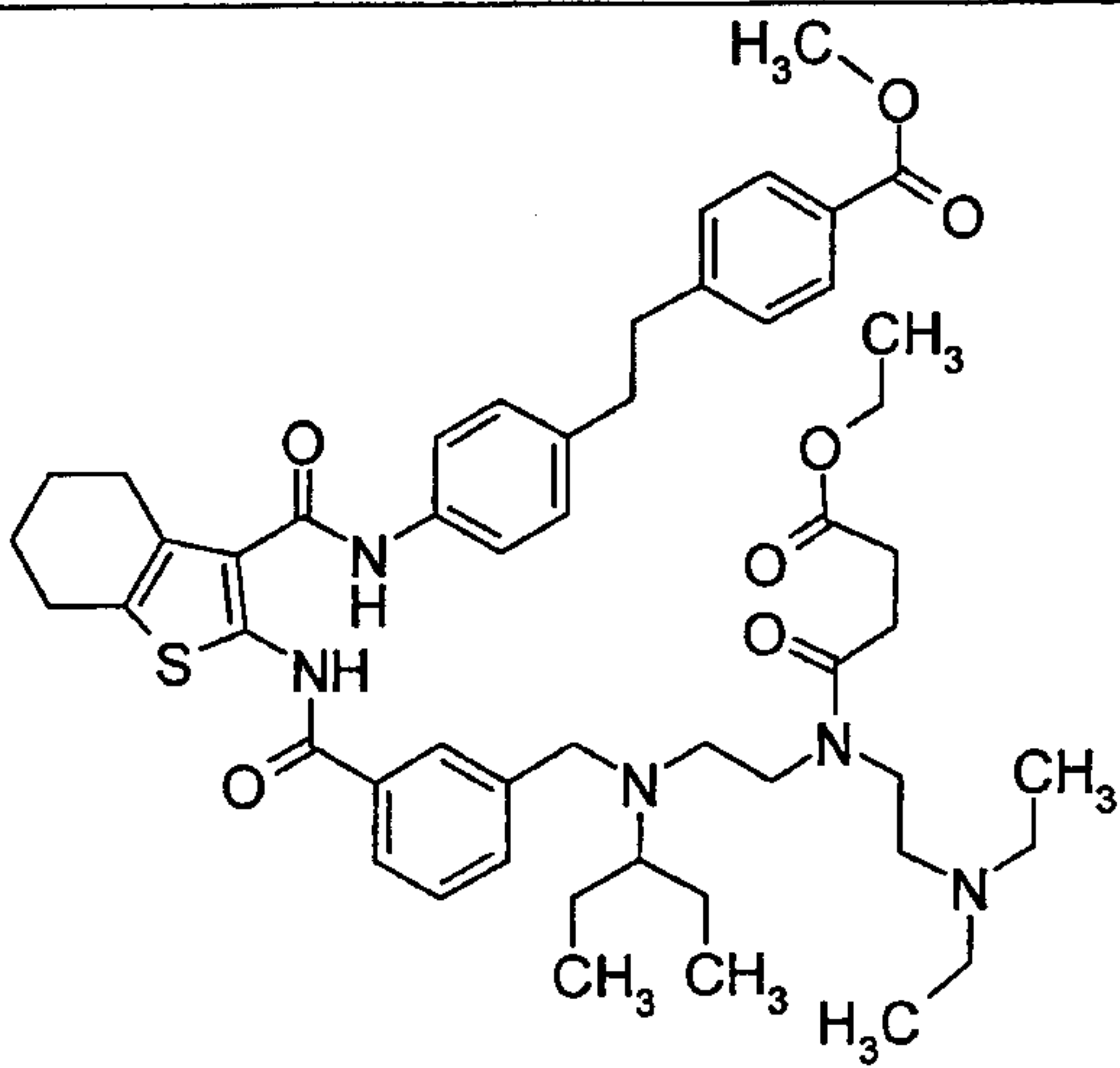
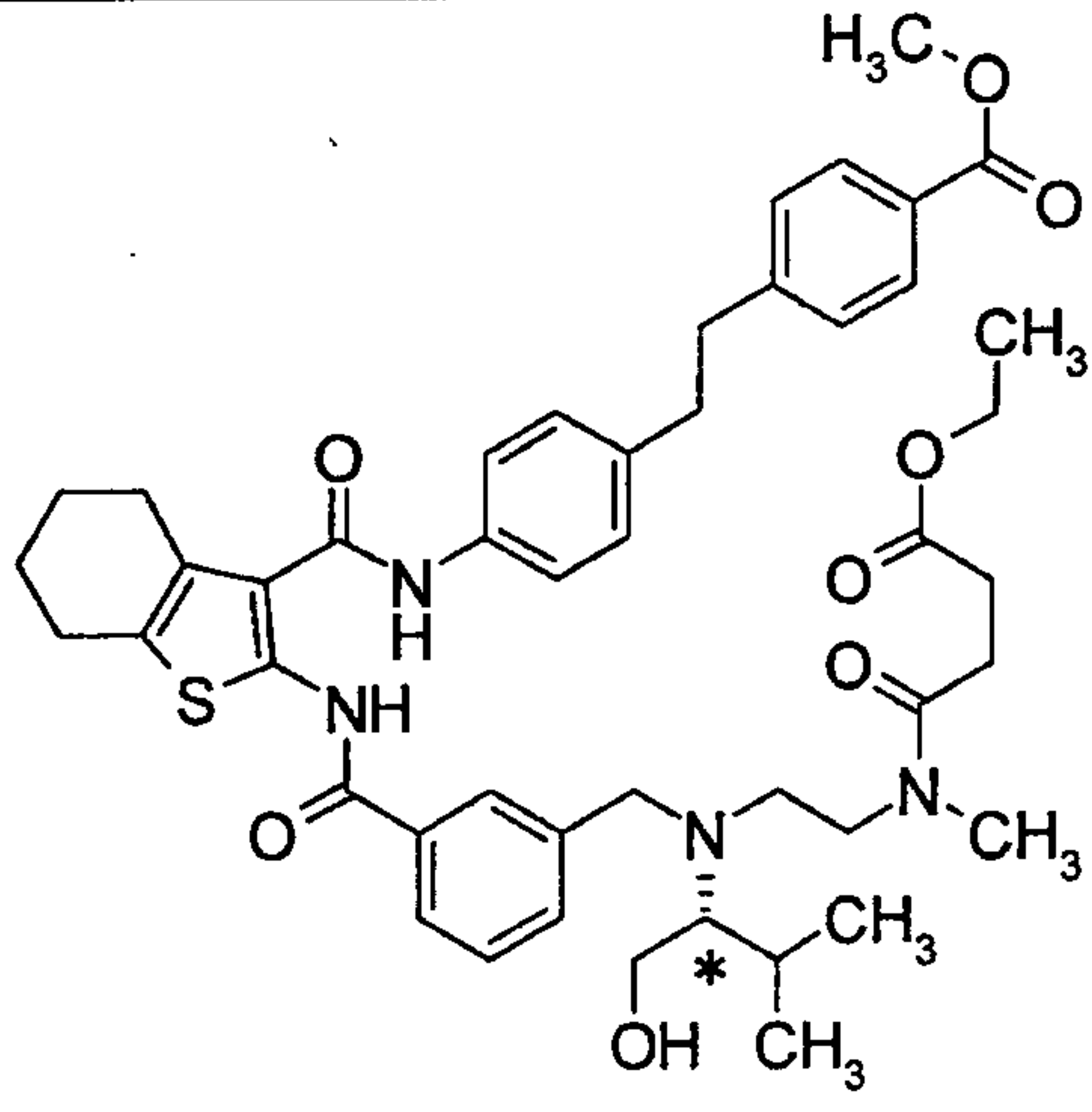
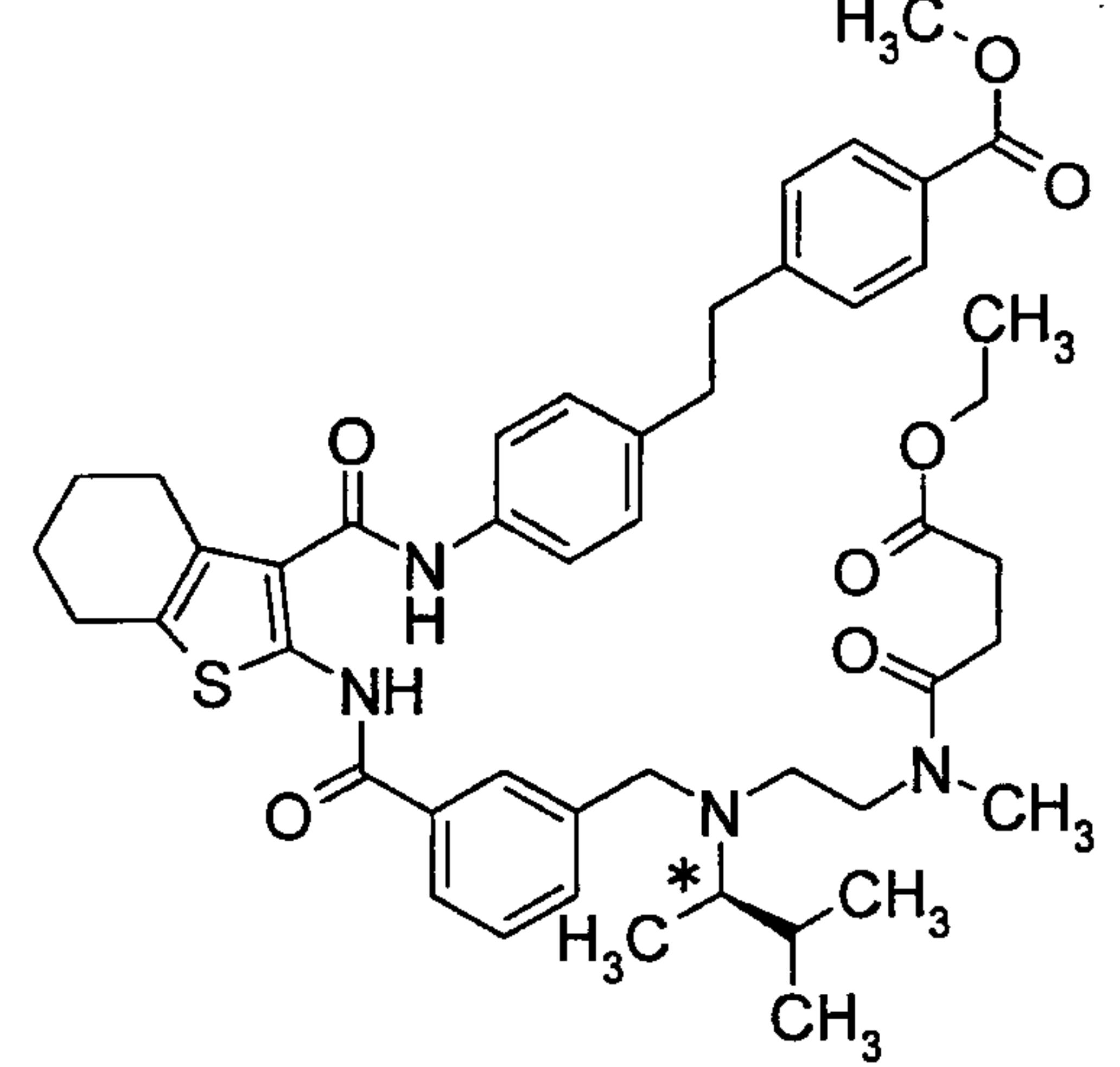
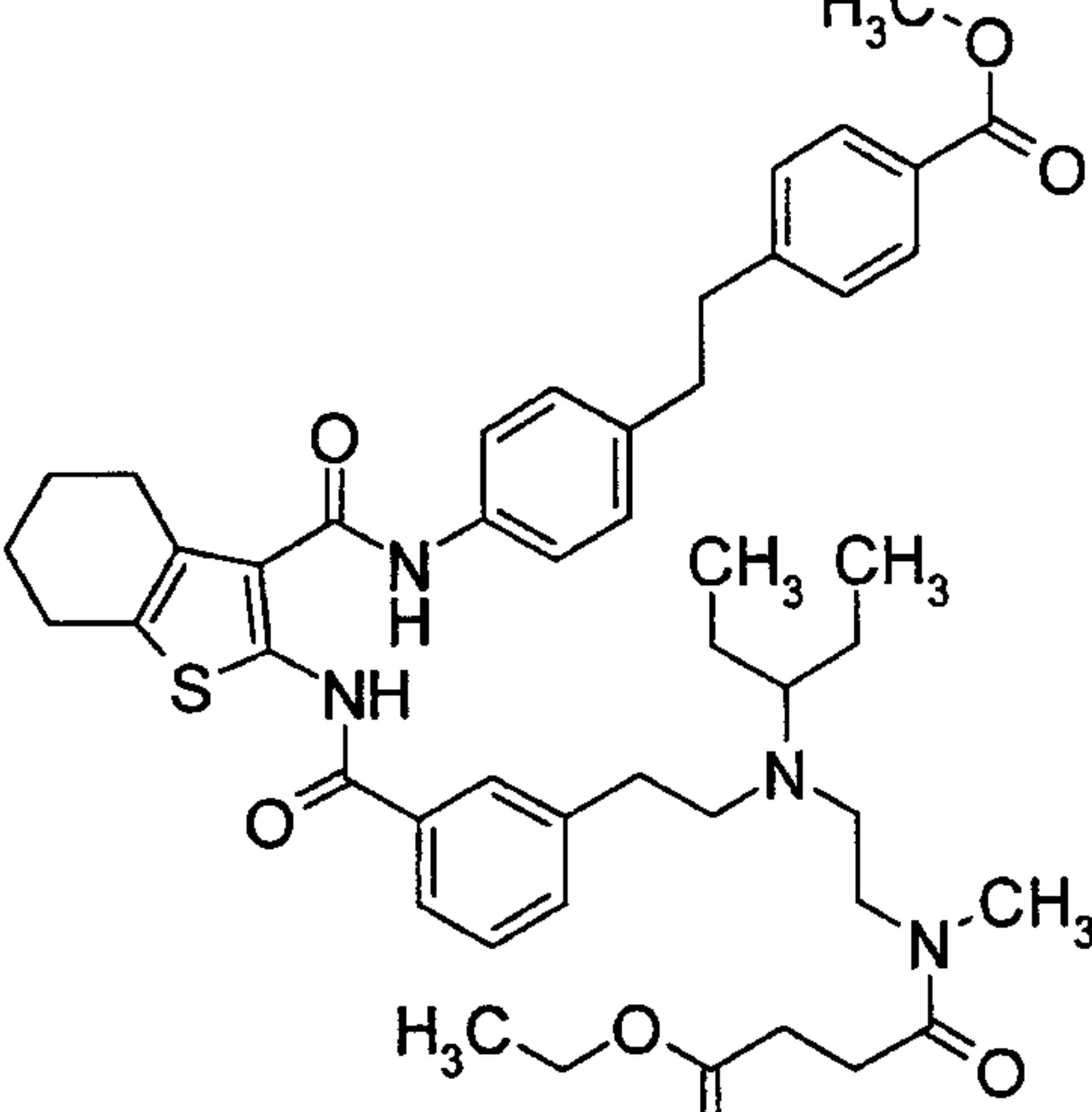
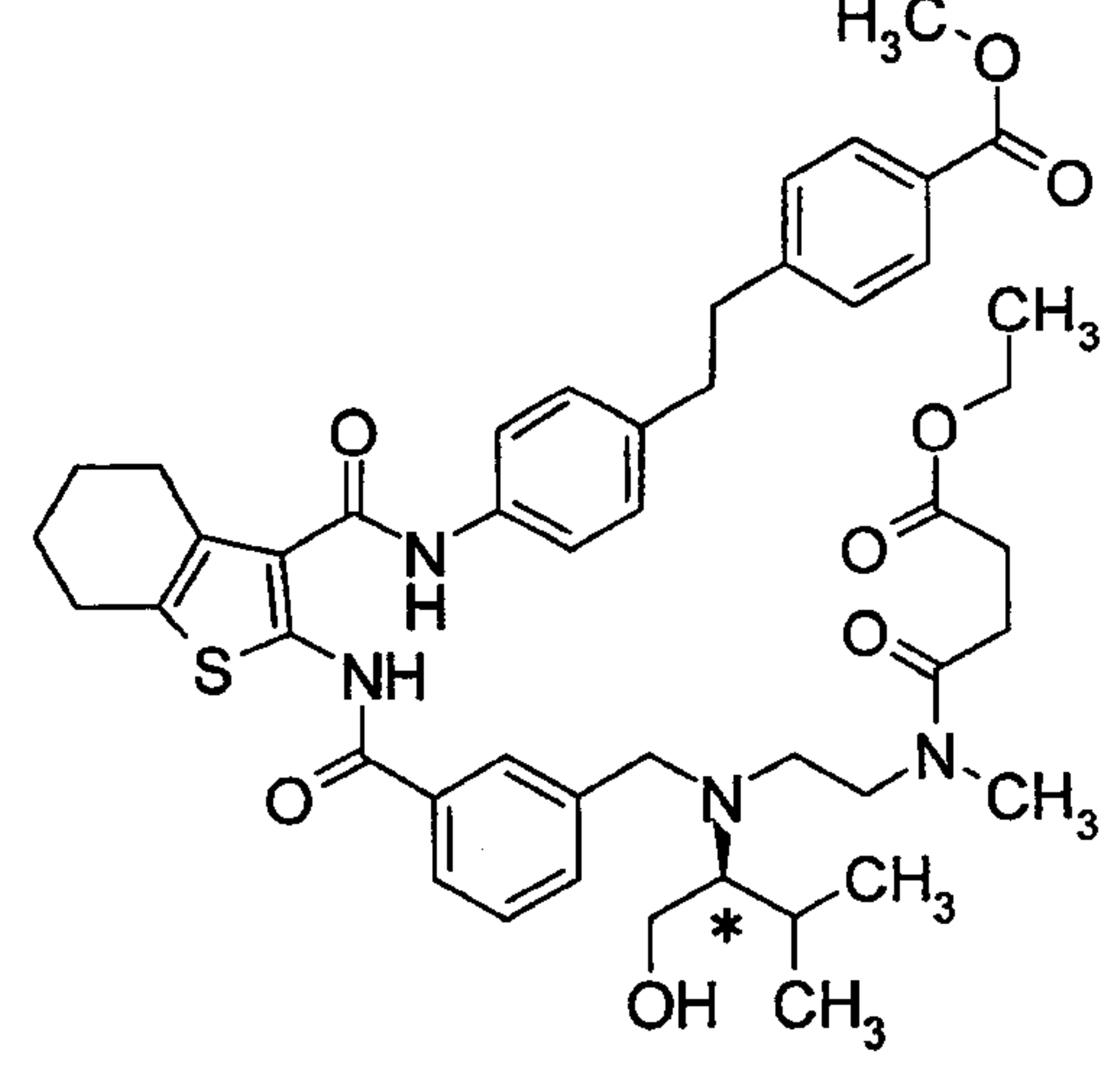
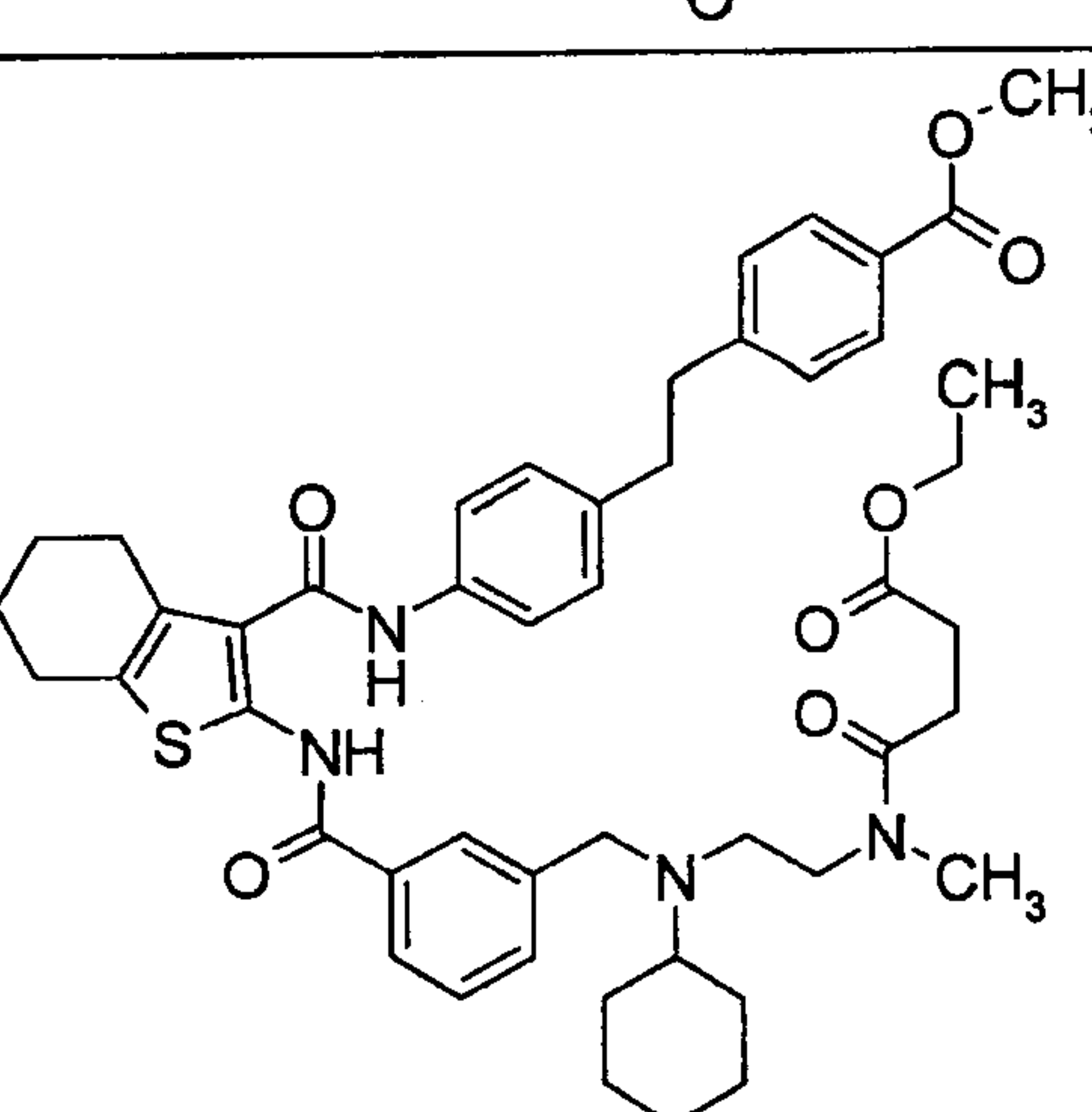
[0228]
[Table 83]

Ex	Str	Ex	Str
207		210	
208		211	
209		212	

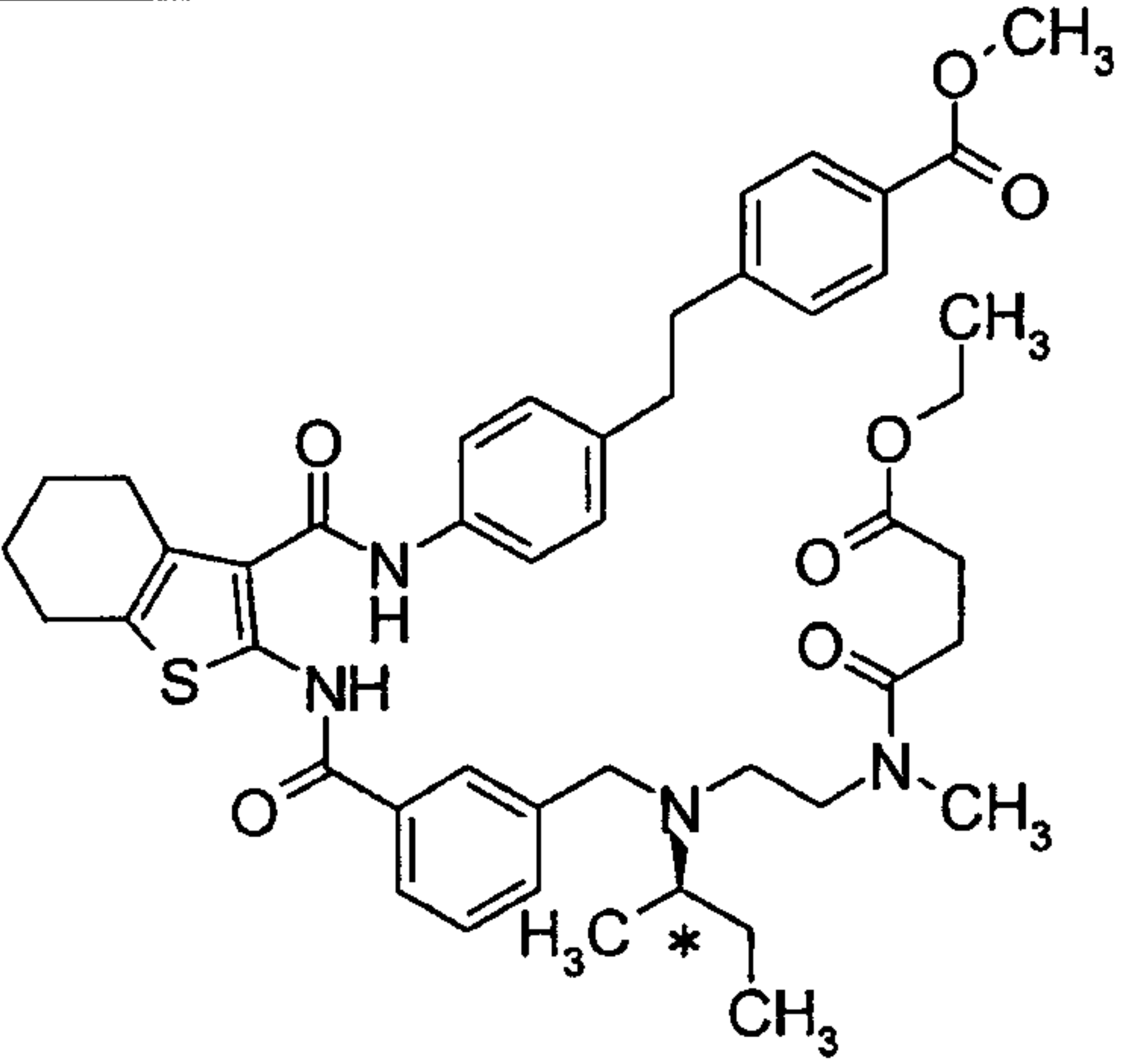
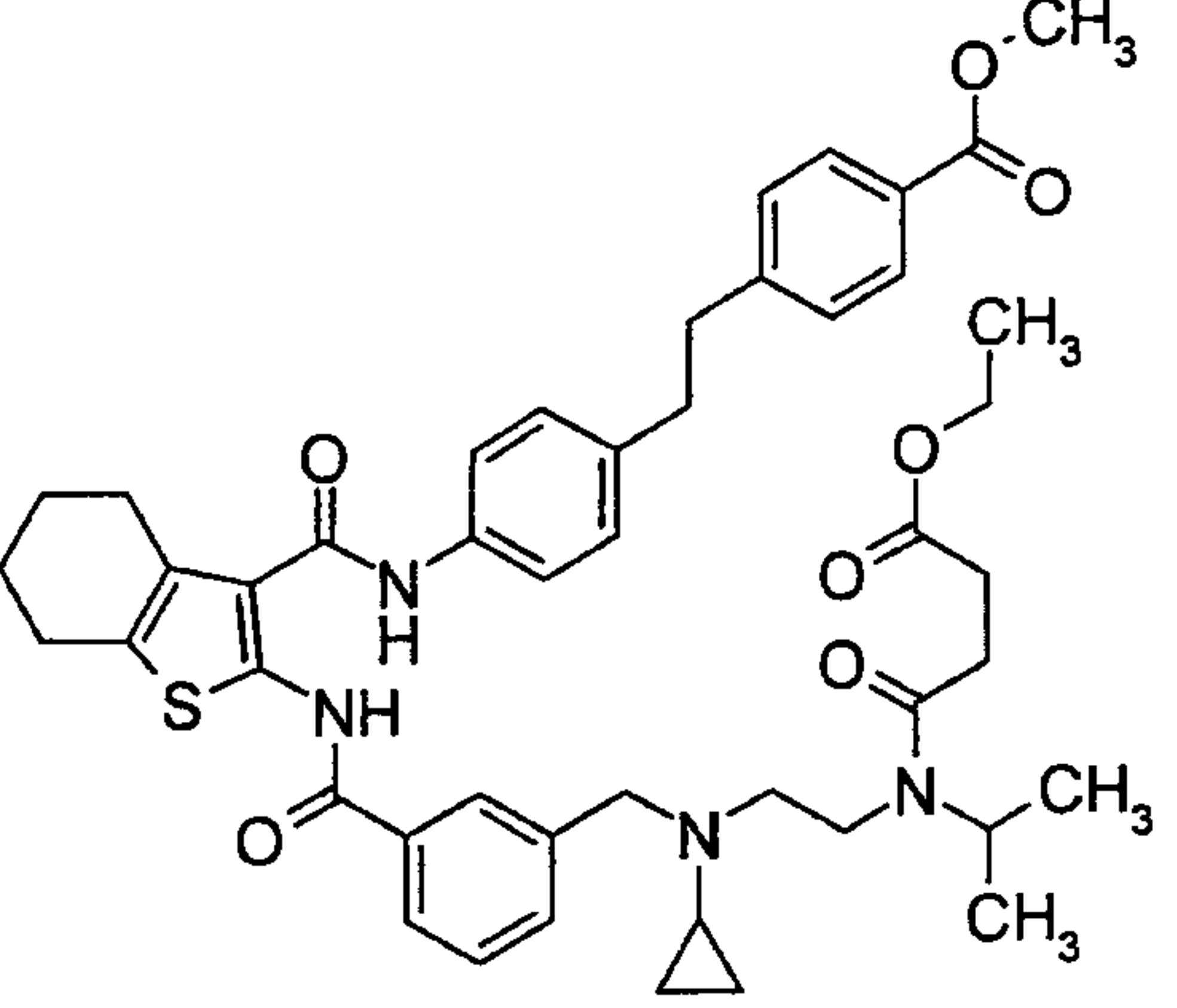
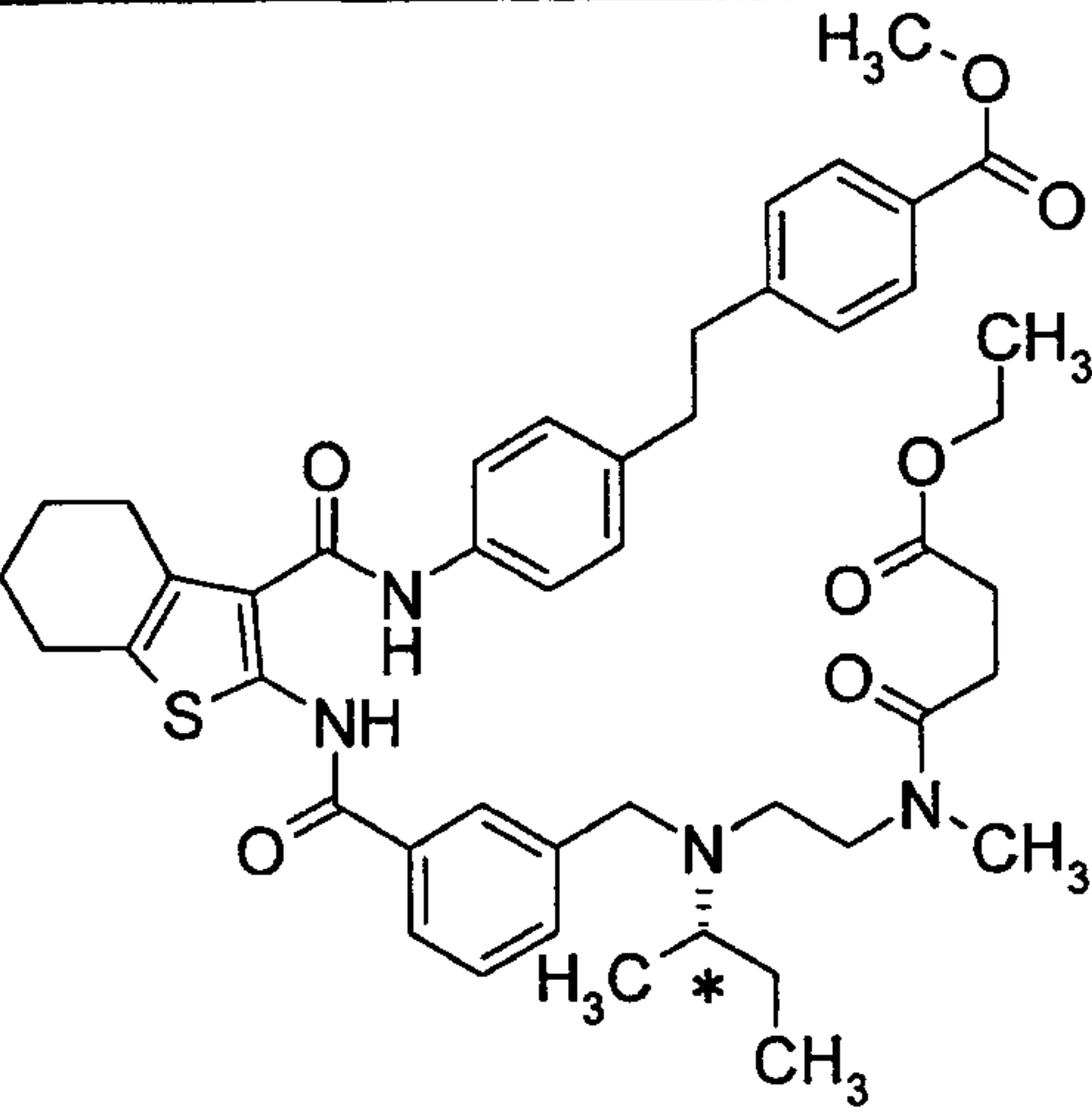
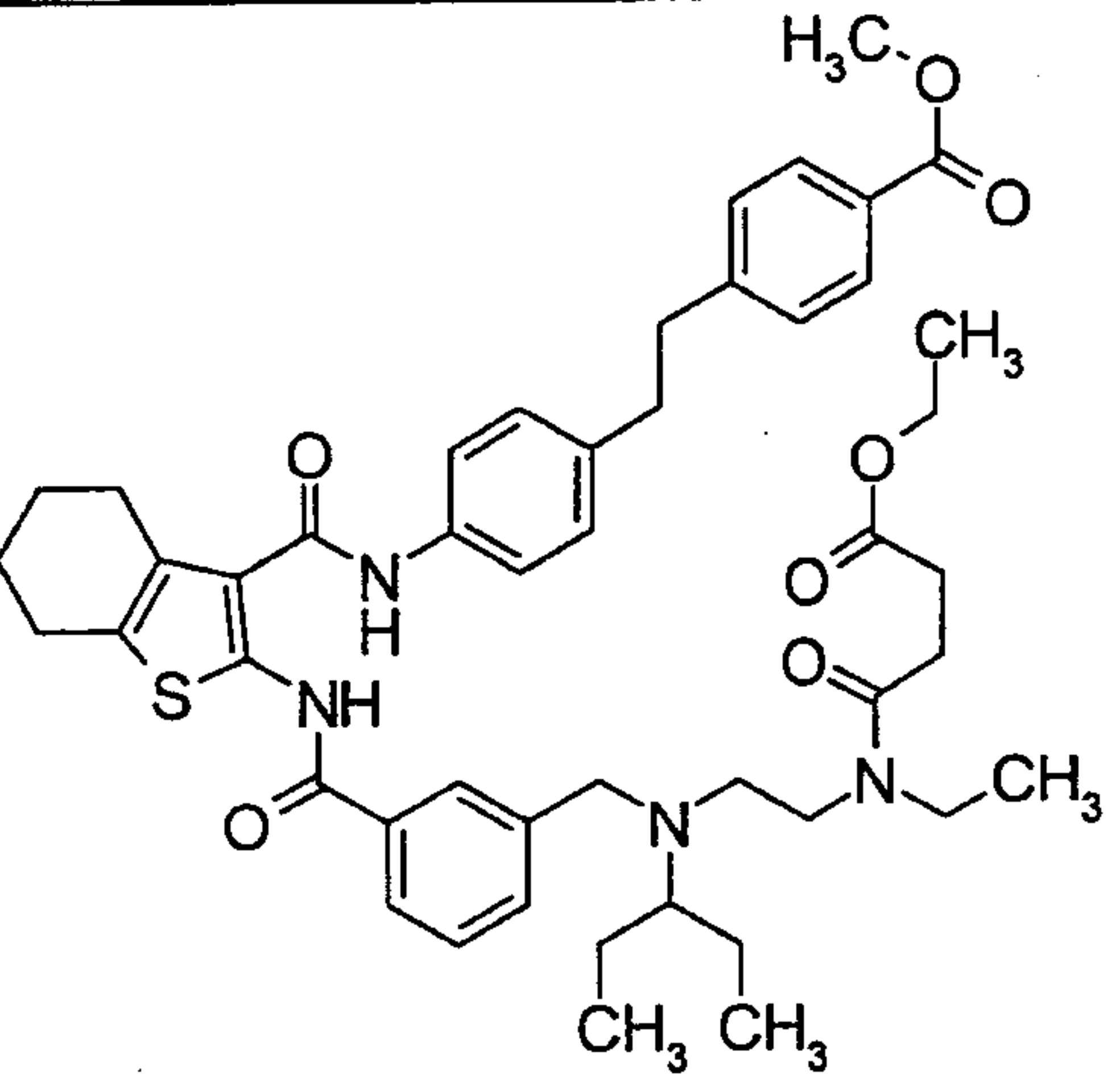
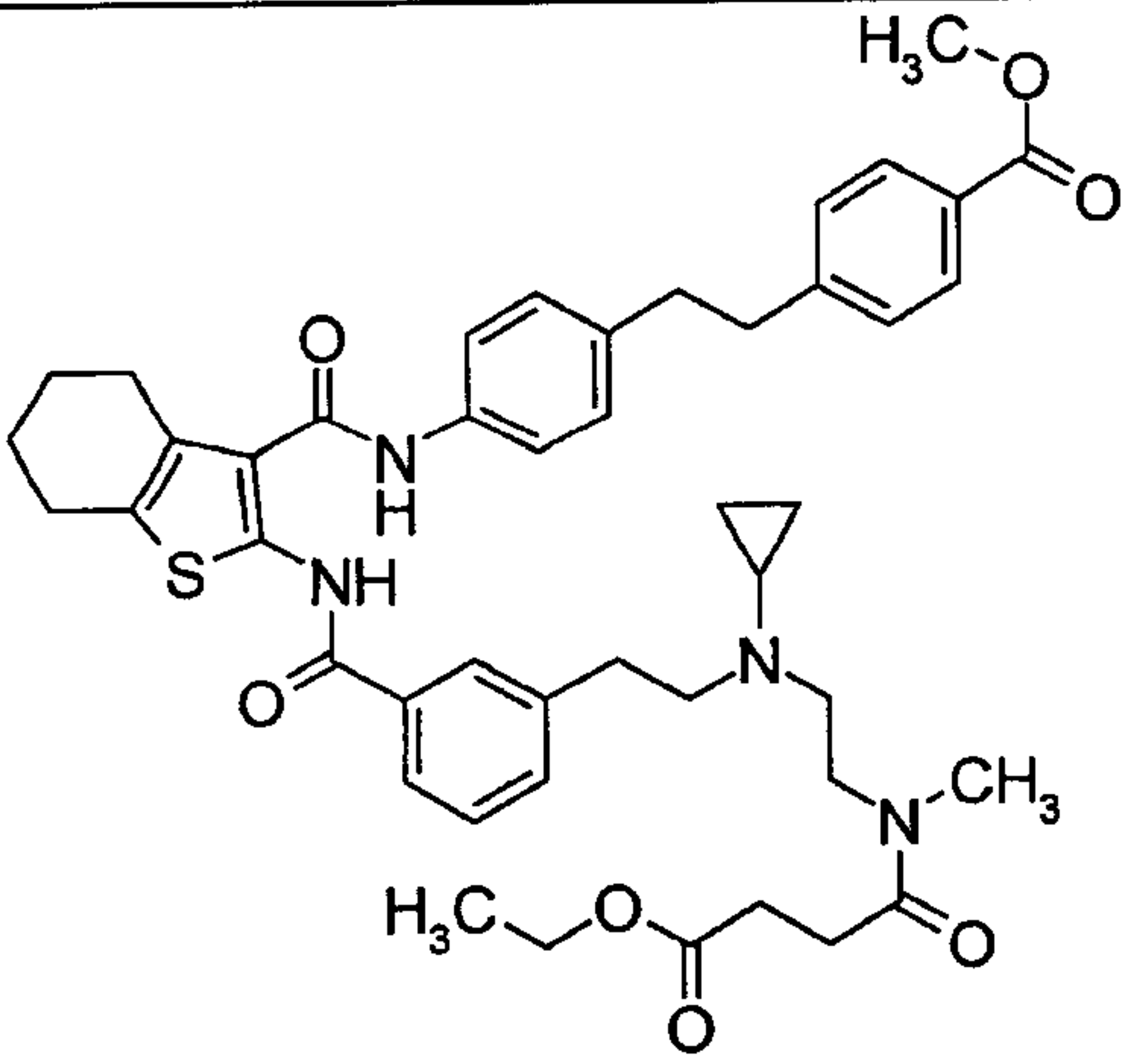
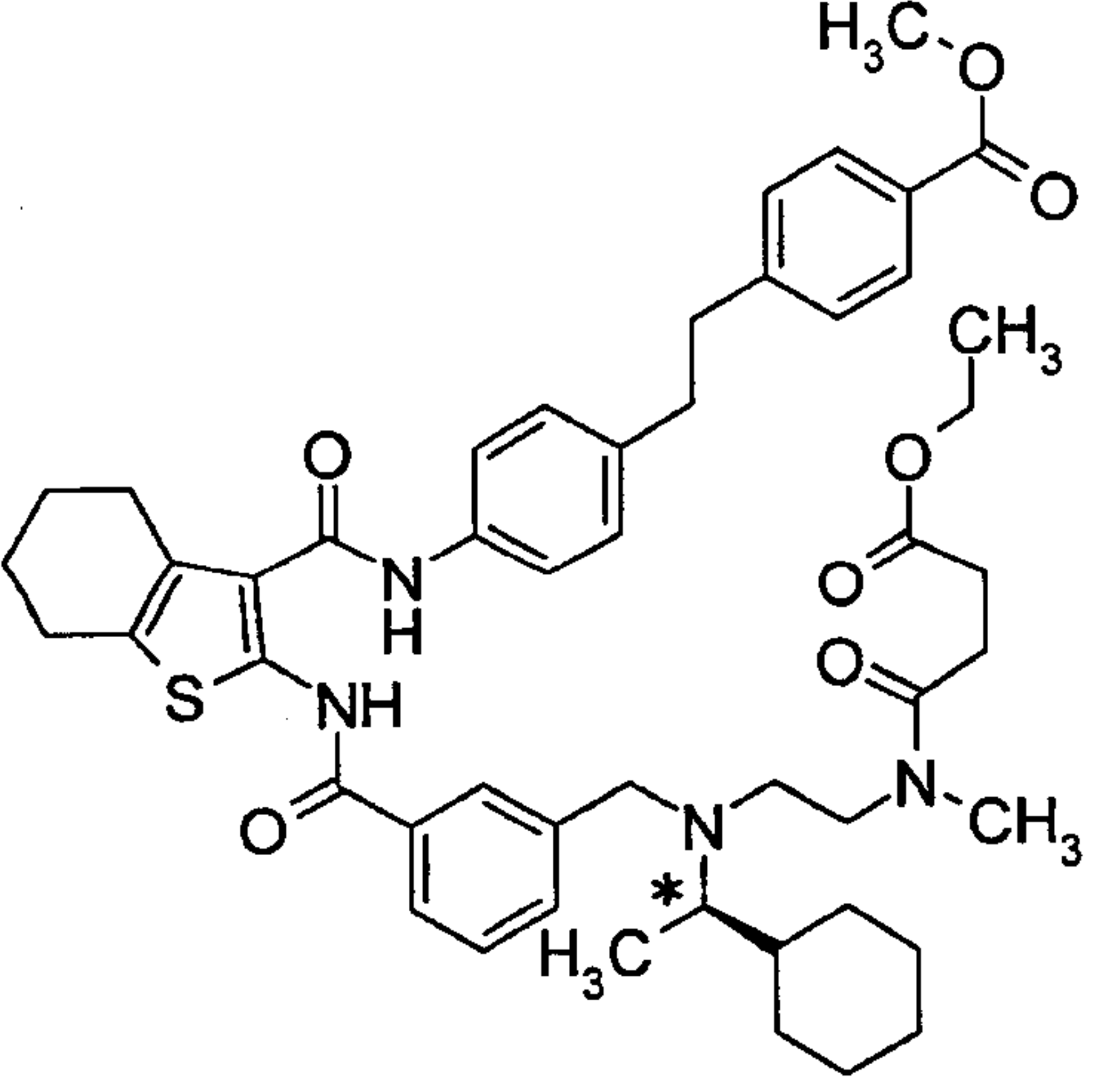
[0229]
[Table 84]

Ex	Str	Ex	Str
213		216	
214		217	
215		218	

[0230]
[Table 85]

Ex	Str	Ex	Str
219		222	
220		223	
221		224	

[0231]
[Table 86]

Ex	Str	Ex	Str
225		228	
226		229	
227		230	

[0232]
[Table 87]

Ex	Str	Ex	Str
231		234	
232		235	
233			

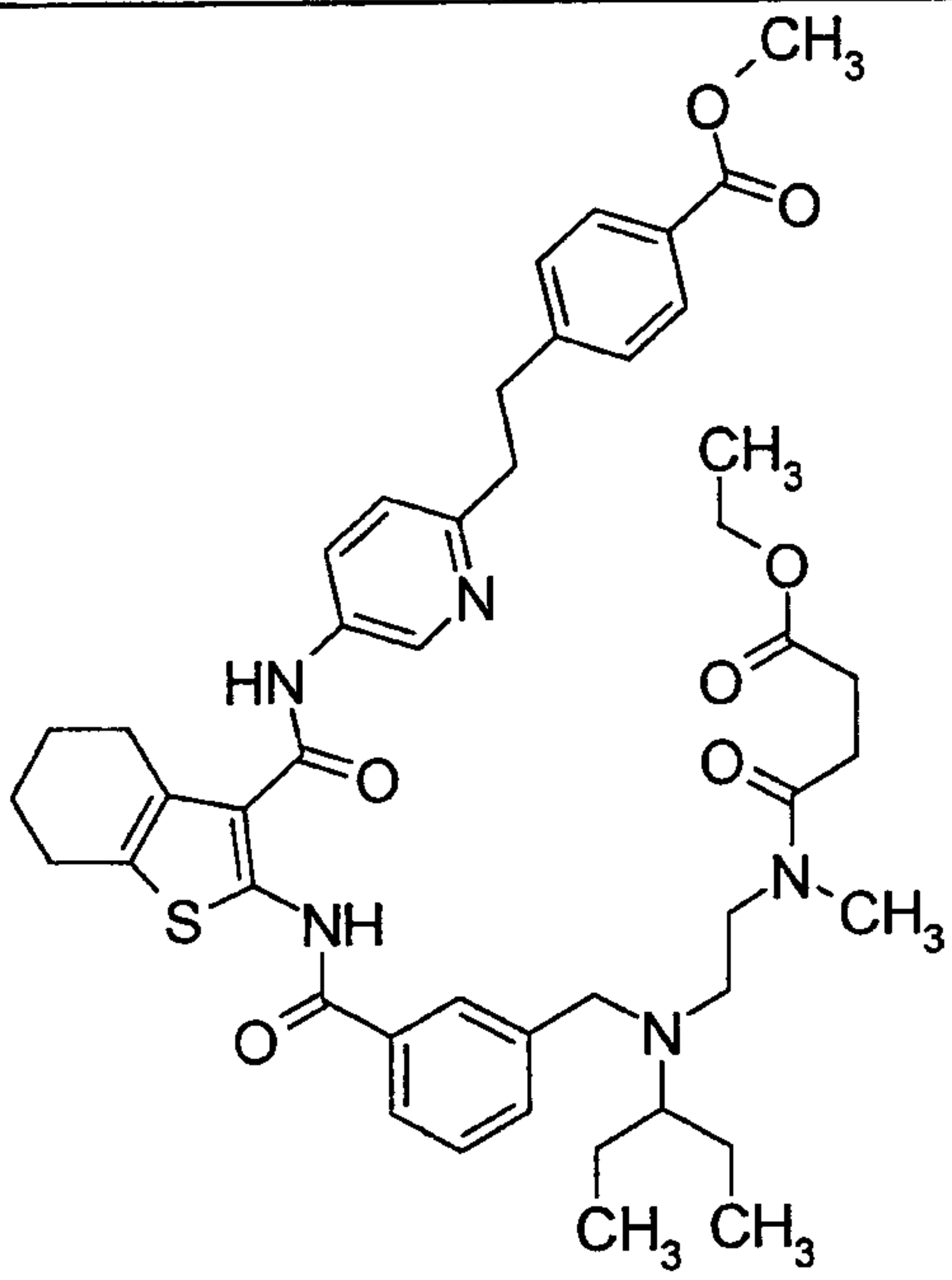
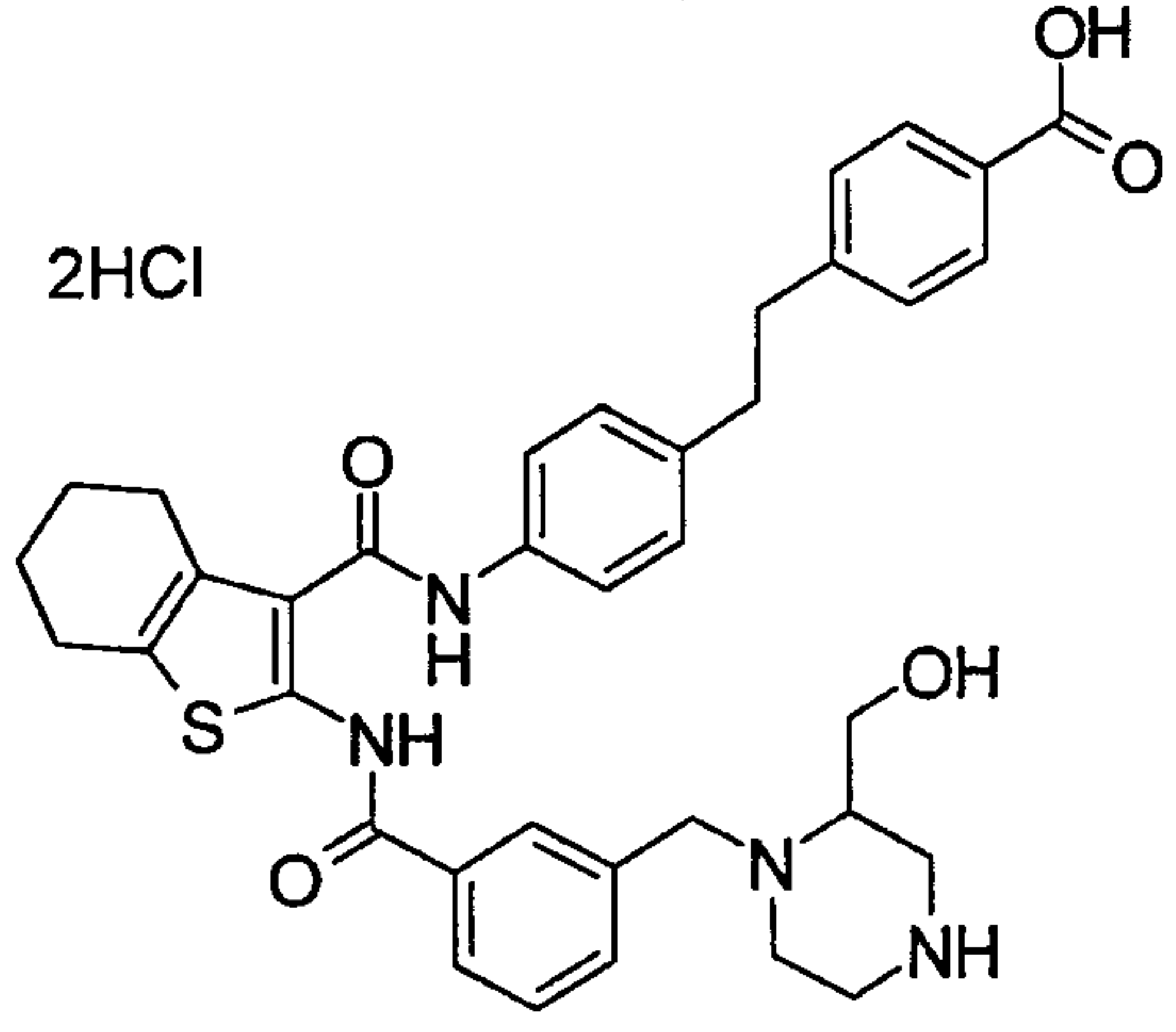
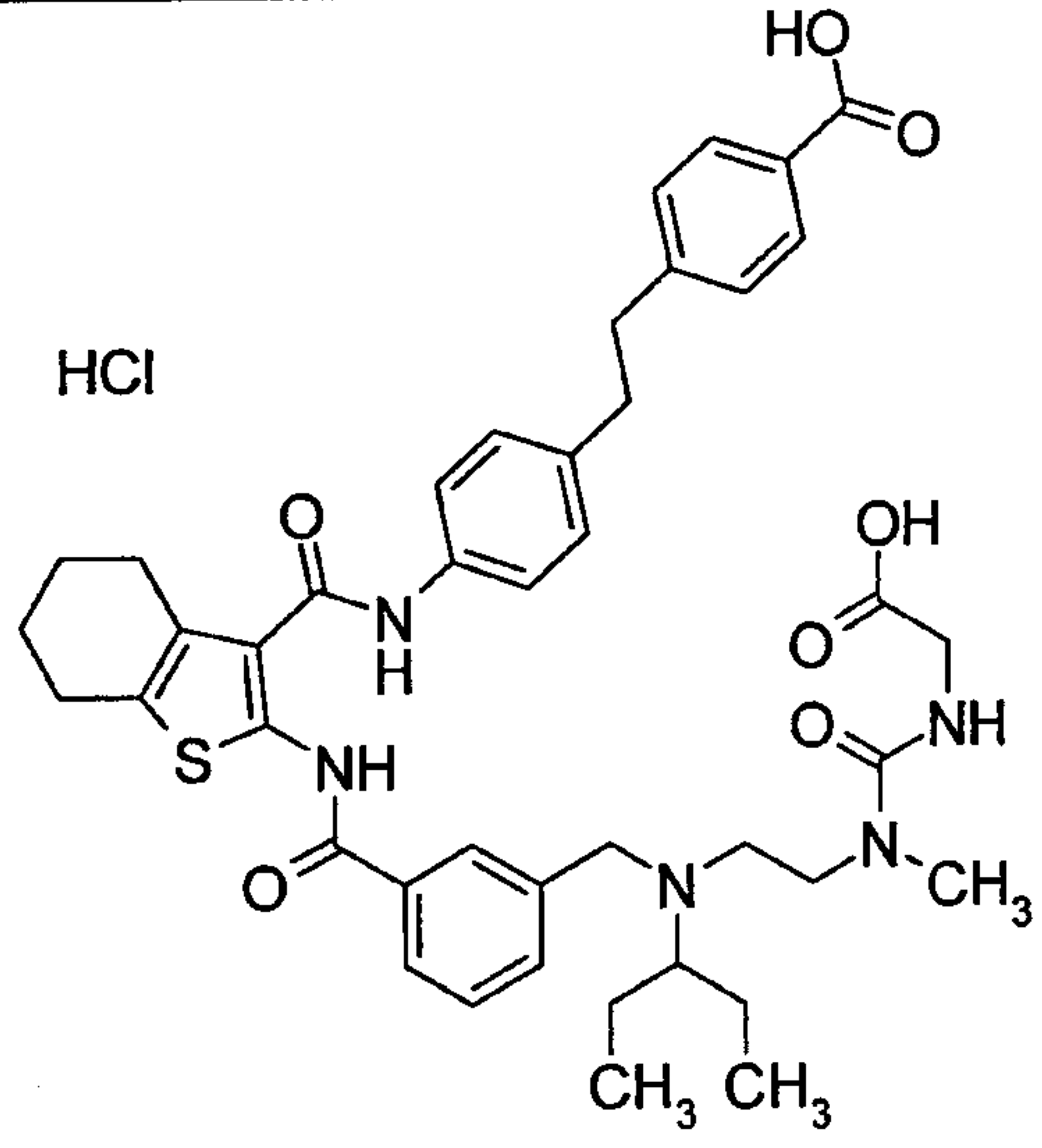
[0233]
[Table 88]

Ex	Str	Ex	Str
236		238	
237		239	

[0234]
[Table 89]

Ex	Str	Ex	Str
240	<chem>COC(=O)c1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C(C)C)CCN(C(C)C)CCOC(=O)C)C6CCCCC6</chem>	242	<chem>COC(=O)c1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C(C)C)CCN(C(C)C)CCOC(=O)C)C6CCCCC6</chem>
241	<chem>COC(=O)c1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C(C)C)CCN(C(C)C)CCOC(=O)C)C6CCCCC6</chem>	243	<chem>COC(=O)c1ccc(cc1)CCc2ccc(cc2)NC(=O)c3c4c(s3)C(=O)N(C(=O)c5ccc(cc5)CN(C(C)C)CCN(C(C)C)CCOC(=O)C)C6CCCCC6</chem>

[0235]
[Table 90]

Ex	Str	Ex	Str
244		245	
		246	

[0236]
[Table 91]

Pr	PSy	Dat	Pr	PSy	Dat
1	1	ESI+: 204	44	44	ESI+: 816
2	2	CI+: 202	45	45	ESI+: 568
3	3	ESI+: 230	46	46	ESI+: 835
4	4	CI+: 287	47	47	CI+: 251
5	5	ESI+: 256	48	48	ESI+: 329
6	6	ESI+: 323	49	49	ESI+: 371
7	7	ESI+: 435	50	50	ESI+: 383
8	8	ESI+: 587	51	51	ESI+: 539
9	9	ESI+: 638	52	52	ESI+: 745
10	10	ESI+: 695	53	53	ESI+: 350
11	11	ESI+: 231	54	54	ESI+: 772
12	12	ESI+: 681	55	55	ESI+: 267
13	13	ESI+: 809	56	56	ESI+: 492
14	14	ESI+: 795	57	57	ESI+: 640
15	15	ESI+: 824	58	58	ESI+: 862
16	16	ESI+: 823	59	59	ESI+: 758
17	17	ESI+: 851	60	60	ESI+: 383
18	18	ESI+: 190	61	61	ESI+: 722
19	19	ESI+: 439	62	62	EI: 309
20	20	ESI-: 403	63	63	APCI/ESI+: 494
21	21	ESI+: 821	64	64	ESI+: 228
22	22	ESI+: 583	65	65	ESI+: 238
23	23	ESI+: 652	66	66	APCI/ESI+: 215
24	24	CI+: 256	67	67	ESI+: 751
25	25	ESI+: 312	68	68	APCI/ESI+: 821
26	26	ESI+: 270	69	69	APCI/ESI+: 262
27	27	ESI+: 781	70	1	ESI+: 218
28	28	ESI+: 206	71	2	ESI+: 216
29	29	APCI/ESI+: 751	72	1	ESI+: 246
30	30	APCI/ESI+: 737	73	2	ESI+: 244
31	31	APCI/ESI+: 821	74	2	ESI+: 228
32	32	APCI/ESI+: 823	75	4	ESI+: 246
33	33	APCI/ESI+: 851	76	7	APCI/ESI+: 437
34	34	APCI/ESI+: 852	77	8	APCI/ESI+: 589
35	35	APCI/ESI+: 231	78	9	ESI+: 640
36	36	APCI/ESI+: 843	79	7	APCI/ESI+: 449
37	37	APCI/ESI+: 251	80	8	ESI+: 601
38	38	APCI/ESI+: 436	81	9	ESI+: 652
39	39	APCI/ESI+: 283	82	7	ESI+: 463
40	40	ESI+: 679	83	8	ESI+: 615
41	41	ESI+: 750	84	9	ESI+: 666
42	42	ESI+: 807	85	7	APCI/ESI+: 463
43	43	ESI+: 787	86	8	APCI/ESI+: 615

[0237]
[Table 92]

Pr	PSy	Dat	Pr	PSy	Dat
87	9	ESI+: 666	130	14	ESI+: 765
88	9	ESI+: 638	131	12	ESI+: 665
89	9	ESI+: 638	132	30	ESI+: 781
90	9	ESI+: 652	133	2	CI+: 204
91	9	ESI+: 678	134	11	APCI/ESI+: 201
92	9	ESI+: 672	135	12	APCI/ESI+: 651
93	13	ESI+: 823	136	30	APCI/ESI+: 823
94	13	ESI+: 837	137	13	APCI/ESI+: 751
95	10	ESI+: 709	138	13	APCI/ESI+: 751
96	13	ESI+: 837	139	27	APCI/ESI+: 807
97	10	FAB+: 610	140	13	ESI+: 765
98	9	ESI+: 781	141	13	ESI+: 807
99	12	ESI+: 695	142	1	APCI/ESI+: 232
100	13	ESI+: 837	143	2	APCI/ESI+: 230
101	15	ESI+: 824	144	12	APCI/ESI+: 721
102	17	ESI+: 851	145	13	APCI/ESI+: 849
103	2	CI+: 188	146	3	APCI/ESI+: 345
104	14	ESI+: 809	147	31	APCI/ESI+: 964
105	12	ESI+: 709	148	12	APCI/ESI+: 864
106	13	ESI+: 837	149	10	ESI-: 620
107	13	ESI+: 851	150	10	APCI/ESI+: 652
108	16	ESI+: 837	151	33	APCI/ESI+: 811
109	17	ESI+: 865	152	13	APCI/ESI+: 845
110	17	ESI+: 865	153	13	APCI/ESI+: 771
111	10	ESI+: 650	154	30	APCI/ESI+: 287
112	24	ESI+: 270	155	33	APCI/ESI+: 907
113	23	ESI+: 622	156	36	APCI/ESI+: 857
114	10	ESI+: 610	157	36	APCI/ESI+: 843
115	10	ESI+: 642	158	36	ESI+: 779
116	9	ESI+: 654	159	14	APCI/ESI+: 408
117	9	ESI+: 654	160	12	APCI/ESI+: 308
118	10	ESI+: 636	161	33	ESI+: 464
119	9	ESI+: 638	162	21	APCI/ESI+: 853
120	9	ESI+: 638	163	21	APCI/ESI+: 852
121	9	ESI+: 624	164	8	APCI/ESI+: 588
122	9	ESI+: 624	165	10	APCI/ESI+: 639
123	6	ESI+: 337	166	5	APCI/ESI+: 257
124	7	ESI+: 449	167	6	APCI/ESI+: 324
125	8	ESI+: 601	168	7	APCI/ESI+: 436
126	10	ESI+: 624	169	6	ESI+: 252
127	10	ESI+: 624	170	7	ESI+: 364
128	10	ESI+: 650	171	8	ESI+: 516
129	10	ESI+: 608			

[0238]
[Table 93]

Pr	PSy	Dat	Pr	PSy	Dat
172	10	ESI+: 537	215	9	ESI+: 677
173	41	ESI+: 750	216	41	ESI+: 819
174	41	ESI+: 764	217	41	ESI+: 766
175	41	ESI+: 764	218	41	ESI+: 794
176	15	ESI+: 843	219	8	ESI+: 406
177	15	ESI+: 809	220	10	ESI+: 457
178	13	ESI+: 802	221	41	ESI+: 525
179	38	ESI+: 225	222	27	ESI+: 364
180	44	APCI/ESI-: 722	223	5	ESI+: 320
181	44	APCI/ESI+: 696	224	52	ESI+: 858
182	40	ESI+: 714	225	12	ESI+: 758
183	46	ESI+: 835	226	27	ESI+: 292
184	40	ESI+: 471	227	53	ESI+: 278
185	21	ESI+: 787	228	5	ESI+: 248
186	41	ESI+: 780	229	52	ESI+: 786
187	41	ESI+: 780	230	5	ESI+: 237
188	41	ESI+: 752	231	52	ESI+: 775
189	41	ESI+: 738	232	7	ESI+: 421
190	41	ESI+: 766	233	8	FAB-: 571
191	44	ESI+: 800	234	10	ESI+: 624
192	40	ESI+: 836	235	52	ESI+: 582
193	41	ESI+: 794	236	8	ESI+: 497
194	41	ESI+: 794	237	10	ESI+: 548
195	41	ESI+: 766	238	38	ESI+: 520
196	41	ESI+: 752	239	8	ESI-: 494
197	41	ESI+: 780	240	29	ESI+: 700
198	44	ESI+: 814	241	12	
199	44	ESI+: 815	242	13	ESI+: 791
200	41	ESI+: 766	243	33	ESI+: 862
201	41	ESI+: 766	244	52	ESI+: 628
202	41	ESI+: 752	245	29	ESI+: 791
203	41	ESI+: 752	246	12	ESI+: 691
204	41	ESI+: 752	247	32	ESI+: 805
205	41	ESI+: 752	248	29	ESI+: 693
206	41	FAB+: 738	249	29	ESI+: 527
207	40	ESI+: 758	250	14	ESI+: 569
208	46	ESI+: 781	251	50	ESI+: 495
209	10	ESI+: 667	252	38	FAB-: 240
210	41	ESI+: 809	253	29	ESI+: 767
211	10	ESI+: 665	254	6,7	ESI+: 345
212	41	ESI+: 807	255	16	ESI+: 232
213	9	ESI+: 677	256	7	ESI+: 344
214	41	ESI+: 819	257	29	ESI+: 581

[0239]
[Table 94]

Pr	PSy	Dat	Pr	PSy	Dat
258	50	ESI+: 507	281	52	ESI+: 776
259	8	ESI+: 378	282	52	ESI+: 762
260	10	ESI+: 429	283	52	ESI+: 762
261	38	ESI+: 401	284	52	ESI+: 776
262	10	APCI/ESI+: 552	285	69	ESI+: 256
263	50	ESI+: 478	286	69	ESI+: 256
264	52	ESI+: 748	287	63,69	ESI+: 270
265	29	ESI+: 777	288	10	ESI+: 527
266	61	ESI+: 736	289	50	ESI+: 453
267	61	ESI+: 750	290	52	ESI+: 708
268	52	APCI/ESI+: 756	291	29	ESI+: 708
269	10	FAB+: 257	292	29	ESI+: 784
270	38	FAB+: 229	293	40	ESI+: 750
271	62	EI: 235	294	11	ESI+: 216
272	10	ESI+: 242	295	29	ESI+: 766
273	38	ESI+: 224	296	40	ESI+: 786
274	39	EI: 299	297	29	ESI+: 722
275	5	ESI+: 274	298	29	ESI+: 680
276	52	ESI+: 768	299	13	ESI+: 767
277	61	NMR:0.04 (9H, s), 0.48-0.77 (4H, m), 1.05-1.12 (2H, m), 1.67-1.88 (4H, m), 2.62-3.04 (12H, m), 3.83 (3H, s), 4.37-4.44 (2H, m), 4.48-4.57 (2H, m), 7.15 (2H, d, J = 8.4 Hz), 7.37 (2H, d, J = 8.4 Hz), 7.53-7.64 (3H, m), 7.77-8.12 (6H, m), 8.82-8.88 (1H, m), 9.57 (1H, s), 11.70 (1H, s)	300	34	ESI+: 834
			301	61	ESI+: 722
			302	35	ESI+: 666
			303	61	ESI+: 834
			304	12	ESI+: 734
			305	36	ESI+: 820
			306	14	ESI+: 682
			307	54	ESI+: 287
			308	5	ESI+: 257
			309	52	ESI+: 751
278	13	NMR:0.36-0.54 (4H, m), 1.25 (3H, t, J = 7.2 Hz), 1.83-2.08 (8H, m), 2.43 (1H, t, J = 14.4 Hz), 2.62 (4H, t, J = 4.4 Hz), 2.68-2.81 (3H, m), 2.84-3.03 (8H, m), 4.13 (2H, q, J = 7.6 Hz), 4.61-4.69 (1H, m), 7.16 (2H, d, J = 8.4 Hz), 7.39-7.53 (4H, m), 7.65 (1H, s), 7.86-8.01 (4H, m), 13.03 (1H, s)	310	54	ESI+: 301
			311	5	FAB+: 271
			312	52	ESI+: 765
			313	57	EI: 287
			314	5	NMR:3.88 (3H, s), 4.98 (2H, s), 6.69 (2H, d, J = 8.4 Hz), 6.97 (2H, d, J = 8.9 Hz), 7.21 (2H, d, J = 8.4 Hz), 7.98 (2H, d, J = 8.9 Hz)
279	13	APCI/ESI+: 315	315	52	ESI+: 752
280	29	ESI+: 765			

[0240]
[Table 95]

Ex	Syn	Dat	Ex	Syn	Dat
1	1	ESI+: 823	13	13	ESI+:686
2	2	ESI+: 781 NMR: 0.80-1.00 (6H, m), 1.59-2.04 (7H, m), 2.30-2.47 (2H, m), 2.65-2.81 (4H, m), 2.81-3.05 (7H, m), 3.11-3.22 (1H, m), 3.60-3.80 (1H, m), 4.44-4.56 (2H, m), 7.18 (2H, d, J = 8.5 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.65-7.71 (1H, m), 7.81- 8.00 (4H, m), 8.11-8.19 (1H, m), 9.38 (1H, s), 9.60 (1H, s), 11.67 (1H, s), 12.00-12.80 (2H, m)	14	14	ESI+: 667
			15	15	ESI+:547
			16	16	ESI+: 663
			17	17	FAB+: 549
			18	18	ESI+: 736
			19	19	ESI+: 642
			20	20	ESI+: 682
			21	21	ESI+: 557
			22	22	ESI+: 524
			23	5	ESI+: 781
			24	6	APCI/ESI+: 753
			25	6	APCI/ESI+: 709
			26	5	ESI+: 739
			27	5	APCI/ESI+: 723
			28	6	APCI/ESI+: 737
			29	4	ESI+: 753
3	3	ESI+: 783 NMR: 0.76-1.01 (6H, m), 1.59-2.04 (8H, m), 2.65-3.06 (12H, m), 3.06-3.30 (1H, m), 3.64-3.80 (1H, m), 4.38-4.60 (4H, m), 7.18 (2H, d, J = 8.5 Hz), 7.35 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.5 Hz), 7.63- 7.70 (1H, m), 7.85 (2H, d, J = 8.3 Hz), 7.88-8.00 (2H, m), 8.13-8.22 (1H, m), 9.50-9.90 (2H, m), 11.67 (1H, s), 12.43- 13.27 (2H, m)	30	4	ESI+: 767
			31	2	ESI+: 765
			32	2	ESI+: 779
			33	2	ESI+: 781
			34	2	ESI+: 823
			35	2	ESI+: 765
			36	2	ESI+: 723
			37	2	ESI+: 751
			38	2	ESI+: 753
			39	2	ESI+: 765
			40	2	ESI+: 783
			41	2	ESI+: 809
			42	2	ESI+: 795
			43	2	ESI+: 809
			44	4	ESI+: 785
			45	2	ESI+: 795
			46	2	ESI+: 795
5	5	ESI+: 767			
6	6	APCI/ESI+: 695			
7	7	APCI/ESI+: 785			
8	8	ESI+: 783			
9	9	APCI/ESI+: 774			
10	10	ESI+: 719			
11	11	ESI+: 705			
12	12	ESI+:666			

[0241]
[Table 96]

Ex	Syn	Dat	Ex	Syn	Dat
47	2	ESI+: 767	67	2	ESI+: 823
48	4	ESI+: 767			NMR:0.88-1.00 (6H, m), 1.07
49	2	ESI+: 809			(6H, s), 1.57-1.88 (9H, m),
50	2	ESI+: 779			1.89-2.03 (1H, m), 2.07-2.25
51	2	ESI+: 807			(2H, m), 2.66-2.81 (4H, m),
52	2	ESI+: 795			2.85-3.08 (8H, m), 3.11-3.23
53	2	ESI+: 795			(1H, m), 3.63-3.76 (1H, m),
54	2	ESI+: 737			4.41-4.57 (2H, m), 7.19 (2H,
55	2	ESI+: 809			d, J = 8.5 Hz), 7.35 (2H, d, J
56	2	ESI+: 767			= 8.3 Hz), 7.61 (2H, d, J = 8.5
57	4	ESI+: 779			Hz), 7.64-7.71 (1H, m), 7.81-
58	4	ESI+: 793			7.98 (4H, m), 8.13-8.20 (1H,
59	2	ESI+: 795			m), 9.63 (1H, s), 9.72 (1H, s),
60	2	ESI+: 825	68	4	11.68 (1H, s), 12.20-12.80
		NMR:0.84-1.09 (6H, m),			(2H, m)
		1.26-2.03 (8H, m), 2.66-2.85			ESI+: 797
		(3H, m), 3.66-3.82 (1H, m),			ESI+: 797
		4.42-4.60 (1H, m), 7.16 (2H,			ESI+: 781
		d, J = 8.4 Hz), 7.32 (2H, d, J			ESI+: 809
		= 8.0 Hz), 7.43-7.54 (1H, m),			ESI+: 803
		7.57 (2H, d, J = 8.0 Hz), 7.84			APCI/ESI+: 681
		(2H, d, J = 8.4 Hz), 7.87-8.22			ESI+: 865
		(1H, m), 9.15-9.37 (1H, m),			ESI+: 809
		11.68 (1H, s)			ESI+: 810
					ESI+: 809
61	2	ESI+: 781	69	4	ESI+: 809
62	2	ESI+: 795	70	2	ESI+: 795
63	2	ESI+: 795	71	2	ESI+: 797
64	2	ESI+: 823	72	2	ESI+: 837
65	2	ESI+: 866	73	2	ESI+: 767
66	2	ESI+: 795	74	2	ESI+: 767
		NMR:0.91-1.00 (6H, m),	75	2	ESI+: 837
		1.58-2.10 (10H, m), 2.36-2.48	76	2	ESI+: 793
		(4H, m), 2.67-2.81 (4H, m),	77	2	ESI+: 765
		2.86-3.14 (8H, m), 3.20-3.30	78	2	ESI+: 807
		(1H, m), 4.32-4.53 (2H, m),	79	2	ESI+: 822
		7.19 (2H, d, J = 8.5 Hz), 7.35	80	4	ESI+: 781
		(2H, d, J = 8.3 Hz), 7.60 (2H,	81	4	ESI+: 781
		d, J = 8.5 Hz), 7.63-7.69 (1H,	82	2	ESI+: 815
		m), 7.83-7.96 (4H, m), 8.12-	83	2	ESI+: 815
		8.19 (1H, m), 9.52 (1H, s),	84	2	APCI/ESI+: 815
		9.61 (1H, s), 11.67 (1H, s),	93	2	
		12.16-12.66 (2H, m)			

[0242]
[Table 97]

Ex	Syn	Dat	Ex	Syn	Dat
94	2	ESI+: 821	121	6	ESI+: 766
95	2	ESI+: 815			NMR:0.68-0.81 (6H, m),
96	2	ESI+: 782			0.97-1.11 (6H, m), 1.32-1.53
97	2	ESI+: 797			(4H, m), 1.68-1.87 (4H, m),
98	2	ESI+: 796			2.33-2.61 (4H, m), 2.66-2.82
99	8	ESI+: 782			(4H, m), 2.85-3.00 (4H, m),
100	6	ESI+: 651			3.73-4.37 (1H, m), 4.40-4.62
101	6	ESI+: 786			(2H, m), 7.19 (2H, d, J = 8.4
102	6	ESI+: 736			Hz), 7.35 (2H, d, J = 8.2 Hz),
103	6	ESI+: 736			7.42-7.81 (6H, m), 7.85 (2H,
104	6	ESI+: 787			d, J = 8.2 Hz), 9.46-9.57 (1H,
105	6	ESI+: 772			m), 11.68 (1H, s), 12.12-
106	6	ESI+: 738			12.55 (2H, m)
107	6	ESI+: 724	122	6	ESI+: 738
108	6	ESI+: 808	123	6	ESI+: 724
109	6	ESI+: 766	124	6	ESI+: 738
		NMR:0.69-0.80 (6H, m),	125	6	ESI+: 780
		0.93-1.15 (6H, m), 1.34-1.53	126	6	ESI+: 780
		(4H, m), 1.67-1.85 (6H, m),	127	6	ESI+: 752
		2.13-2.43 (2H, m), 2.65-2.82	128	6	ESI+: 766
		(4H, m), 2.85-3.00 (4H, m),	129	6	ESI+: 752
		3.64-4.36 (1H, m), 4.39-4.58	130	6	ESI+: 753
		(2H, m), 7.19 (2H, d, J = 8.4	131	6	ESI+: 752
		Hz), 7.35 (2H, d, J = 8.2 Hz),	132	6	ESI+: 795
		7.42-7.90 (8H, m), 9.52 (1H,	133	6	ESI+: 793
		s), 11.56-11.77 (1H, m),	134	6	ESI+: 752
		12.26-12.62 (2H, m)	135	6	ESI+: 780
110	6	ESI+: 750	136	5	ESI+: 731
111	6	ESI+: 750	137	5	ESI+: 772
112	6	ESI+: 823 [M+Na]+	138	5	ESI+: 758
113	6	ESI+: 774	139	5	ESI+: 691
114	6	ESI+: 767	140	6	APCI/ESI+: 802
115	6	ESI+: 765	141	5	ESI+: 805
116	6	ESI+: 759	142	5	ESI+: 805
117	6	ESI+: 738	143	5	ESI+: 793
118	6	ESI+: 752	144	6	ESI+: 745
119	6	ESI+: 738	145	6	APCI/ESI-: 708
120	6	ESI+: 738	146	5	ESI+: 793
			147	6	APCI/ESI+: 668
			148	148	ESI+: 730
			149	6	ESI+: 735
			150	6	APCI/ESI+: 716

[0243]
[Table 98]

Ex	Syn	Dat	Ex	Syn	Dat
151	5	ESI+: 848	193	22	ESI+: 558
152	5	ESI+: 779	194	21	ESI+: 574
153	5	ESI+: 723	195	21	ESI+: 573
154	5	APCI/ESI+: 729	196	21	ESI+: 569
155	5	ESI+: 806	197	1	ESI+: 750
156	5	ESI+: 778	198	1	ESI+: 826
157	5	ESI+: 779	199	1	ESI+: 722
158	6	ESI+: 777	200	1	ESI+: 841
159	2	ESI+: 723	201	1	ESI+: 786
160	5	ESI+: 658	202	1	ESI+: 795
161	17	ESI+: 676	203	3	ESI+: 807
162	6	ESI+: 600	204	1	ESI+: 795
163	22	FAB+: 719	205	1	ESI+: 809
164	6	ESI+: 720	206	1	ESI+: 865
165	6	ESI+: 720	207	1	ESI+: 851
166	6	ESI+: 720	208	1	ESI+: 837
167	6	ESI+: 626	209	1	ESI+: 851
168	6	ESI+: 720	210	1	ESI+: 825
169	5	ESI+: 706	211	1	ESI+: 827
170	6	ESI+: 666	212	1	ESI+: 809
171	5	ESI+: 735	213	1	APCI/ESI+: 807
172	6	ESI+: 722	214	1	ESI+: 823
173	6	ESI+: 722	215	1	ESI+: 837
174	6	ESI+: 680	216	1	ESI+: 809
175	6	ESI+: 694	217	1	ESI+: 821
176	6	ESI+: 708	218	1	ESI+: 835
177	6	ESI+: 722	219	1	ESI+: 908
178	6	ESI+: 738	220	1	ESI+: 823
179	6	FAB+: 758	221	1	ESI+: 839
180	6	ESI+: 680	222	1	ESI+: 839
181	6	ESI+: 728	223	1	ESI+: 837
182	6	ESI+: 723	224	1	ESI+: 835
183	6	ESI+: 724	225	1	ESI+: 809
184	6	ESI+: 737	226	1	ESI+: 809
185	6	ESI+: 680	227	1	ESI+: 807
186	6	ESI+: 791	228	1	APCI/ESI+: 821
187	6	ESI+: 740	229	1	ESI+: 837
188	6	FAB+: 813	230	1	ESI+: 863
189	6	ESI+: 758	231	1	ESI+: 857
190	22	ESI+: 556	232	1	ESI+: 823
191	22	ESI+: 640	233	1	ESI+: 823
192	22	ESI+: 573	234	3	ESI+: 825

[0244]
[Table 99]

Ex	Syn	Dat	Ex	Syn	Dat
235	1	APCI/ESI+: 837	241	1	APCI/ESI+: 851
236	1	APCI/ESI+: 807	242	1	APCI/ESI+: 821
237	1	APCI/ESI+: 795	243	1	ESI+: 867
238	1		244	1	APCI/ESI+: 824
239	1	APCI/ESI+: 851	245	5	ESI+: 653
240	1	APCI/ESI+: 849	246	2	ESI+: 782

5

Industrial Applicability

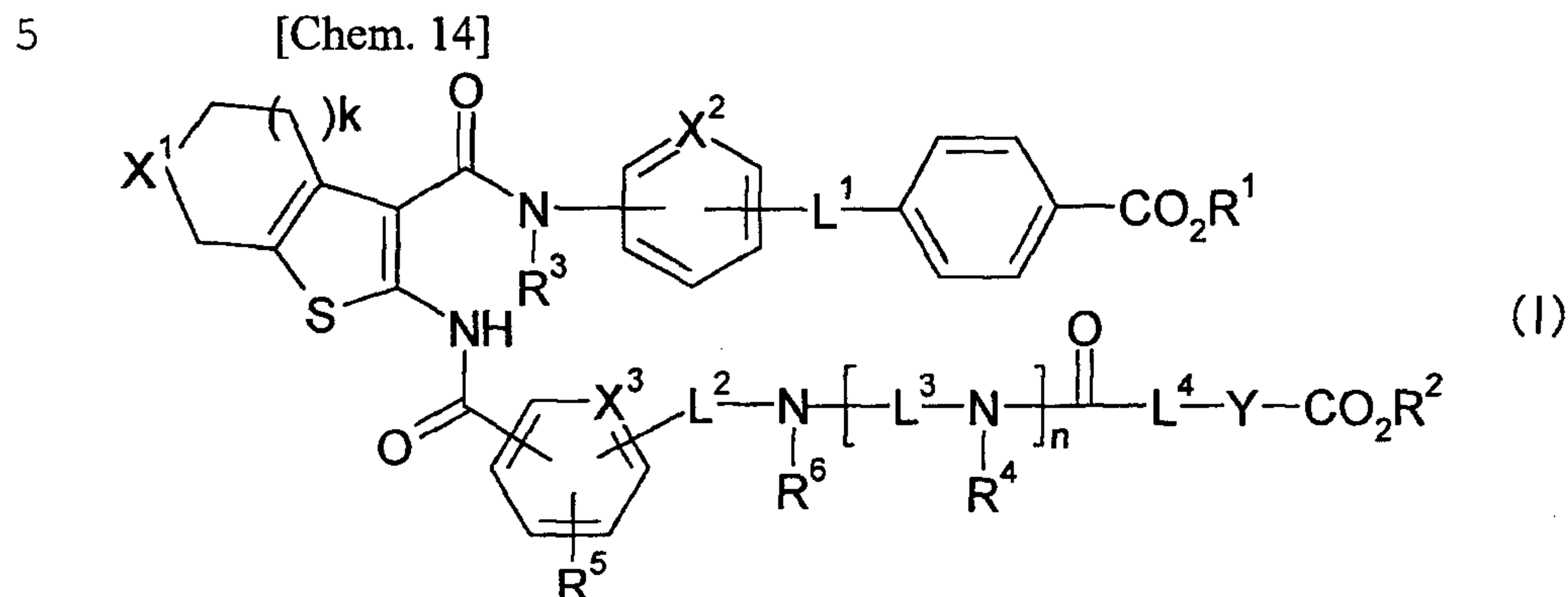
[0245]

The compound of Formula (I) and a salt thereof has an NPT-IIb inhibitory action, and can be used as an agent for preventing and/or treating hyperphosphatemia, renal insufficiency, or abnormality in bone metabolism caused by renal insufficiency.

10

Claims

[Claim 1] A compound of Formula (I) or a salt thereof,



(wherein,

X^1 represents CH_2 or O ,

k represents 1, 2, or 3,

10 R^3 represents H or lower alkyl,

X^2 represents CH or N,

L^1 represents lower alkylene,

R^1 represents H or lower alkyl,

X^3 represents CH or N,

15 L^2 represents lower alkylene,

R^5 represents H or lower alkyl,

R^6 represents H, lower alkyl, lower alkyl substituted with one to two of $-\text{OR}^0$, $-\text{C}(\text{O})$ -lower alkyl, $-\text{S}(\text{O})_m$ -lower alkyl, $-\text{lower alkylene-N}(\text{lower alkyl})_2$, $-\text{R}^{00}$ -heterocycle, $-\text{R}^{00}$ -phenyl, or $-\text{R}^{00}$ -cycloalkyl, wherein the heterocycle, phenyl and cycloalkyl may be substituted with

20 one to two lower alkyl or $\text{C}(\text{O})$ -lower alkyl, and $-\text{R}^{00}$ may be substituted with one $-\text{OR}^0$,

R^{00} represents a bond or lower alkylene,

R^0 represents H or lower alkyl,

m represents 0, 1, or 2,

L^3 represents lower alkylene,

25 n represents 0 or 1,

R^4 represents H, lower alkyl, $-\text{lower alkylene-COO-R}^0$, $-\text{lower alkylene-OR}^0$, $-\text{lower alkylene-NHR}^0$, $-\text{lower alkylene-N}(\text{lower alkyl})_2$, or cycloalkyl,

L^4 represents a bond, O, or $-\text{NR}^0$,

Y represents $-\text{R}^{00}$ -monocyclic heterocycle- R^{00} -, $-\text{R}^{00}$ -phenyl- R^{00} -, $-\text{lower alkylene-NR}^0$ -

30 lower alkylene-, lower alkylene-O-lower alkylene-, or lower alkylene which may be substituted with a hydroxyl group, and,

R^2 represents H or lower alkyl).

[Claim 2] The compound or a salt thereof according to Claim 1,
wherein in Formula (I), R⁶ represents lower alkyl or cycloalkyl.

[Claim 3] The compound or a salt thereof according to Claim 2,
wherein in Formula (I), n represents 1, and R⁴ represents H, lower alkyl, or lower
5 alkylene-OR⁰.

[Claim 4] The compound or a salt thereof according to Claim 3,
wherein in Formula (I), Y represents lower alkylene which may be substituted with
a hydroxyl group.

[Claim 5] The compound or a salt thereof according to Claim 4,
10 wherein in Formula (I), X¹ represents CH₂, and k represents 1.

[Claim 6] The compound or a salt thereof according to Claim 5,
wherein in Formula (I), both the X² and X³ represent CH.

[Claim 7] The compound of Claim 1, wherein said compound is selected from the
group consisting of

15 4-(2-{4-[(2-{(3-{(2-{(3-carboxypropanoyl)(methyl)amino}ethyl)(pentan-3-
yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-
yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-{(3-{(2-{[(carboxymethoxy)carbonyl](methyl)amino}ethyl)
(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-
20 yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-{(3-{(2-{(4-carboxy-4-
methylpentanoyl)(methyl)amino}ethyl)(pentan-3-yl)amino)methyl}benzoyl)amino]-
4,5,6,7-tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-{(3-{(3-{(3-carboxypropanoyl)(methyl)amino}propyl)(pentan-3-
25 yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-
yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

4-(2-{4-[(2-{(3-{(2-{(3-carboxypropanoyl)(2-
methoxyethyl)amino}ethyl)(pentan-3-yl)amino)methyl}benzoyl)amino]-4,5,6,7-
tetrahydro-1-benzothiophen-3-yl}carbonyl)amino]phenyl}ethyl)benzoic acid,

30 4-(2-{4-[(2-{(3-{(4-carboxy-4-methylpentanoyl)(pentan-3-
yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-
yl}carbonyl)amino]phenyl}ethyl)benzoic acid, and

4-(2-{4-[(2-{(3-{(4-carboxy-3,3-dimethylbutanoyl)(pentan-3-
yl)amino)methyl}benzoyl)amino]-4,5,6,7-tetrahydro-1-benzothiophen-3-
35 yl}carbonyl)amino]phenyl}ethyl)benzoic acid, or a salt thereof.

[Claim 8] A pharmaceutical composition comprising:
the compound or a salt thereof according to Claim 1; and
a pharmaceutically acceptable excipient.

[Claim 9] The pharmaceutical composition according to Claim 8, which is for treating or preventing hyperphosphatemia.

[Claim 10] Use of the compound or a salt thereof according to Claim 1 for the manufacture of a pharmaceutical composition for treating or preventing
5 hyperphosphatemia.

[Claim 11]

The compound or a salt thereof according to Claim 1 for preventing or treating hyperphosphatemia.

[Claim 12] A method of preventing or treating hyperphosphatemia, comprising
10 administering an effective amount of the compound or a salt thereof according to Claim 1 to a subject.

