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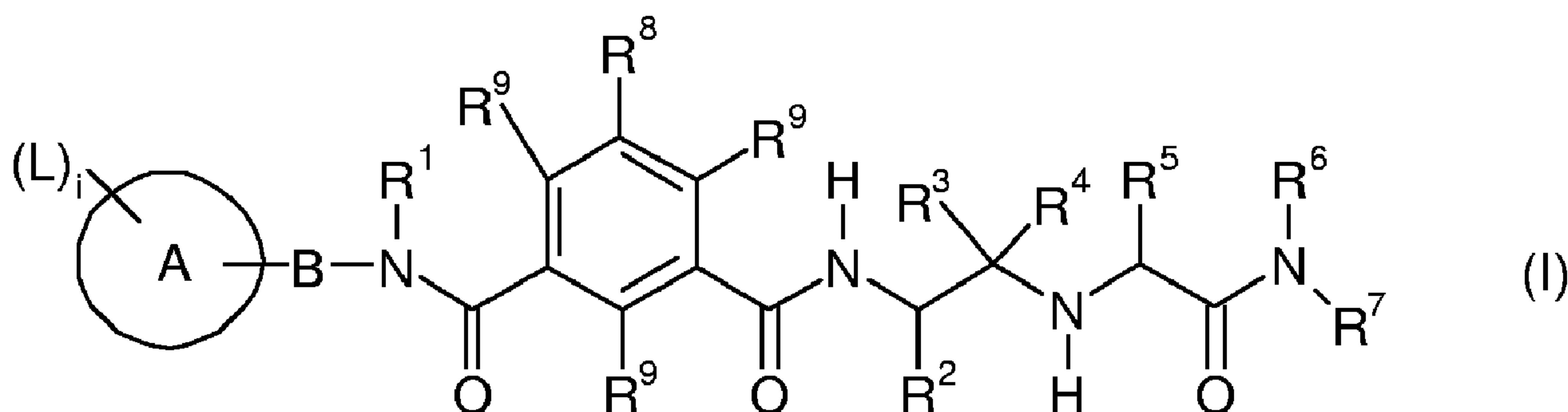
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(71) Demandeur/Applicant:
BOEHRINGER INGELHEIM INTERNATIONAL GMBH,
DE

(72) Inventeurs/Inventors:
FUCHS, KLAUS, DE;
EICKMEIER, CHRISTIAN, DE;
HEINE, NIKLAS, DE;
PETERS, STEFAN, DE;
DORNER-CIOSSEK, CORNELIA, DE; ...

(54) Titre : COMPOSES UTILISES POUR TRAITER LA MALADIE D'ALZHEIMER

(54) Title: COMPOUNDS FOR TREATING ALZHEIMER'S DISEASE



(57) **Abrégé/Abstract:**

The invention relates to substituted 1,2-ethylenediamines of general formula (I), wherein the radicals $R^1 - R^{13}$, A, B, L and i are as defined in the description and the claims. The invention also relates to the use thereof for treating Alzheimer's disease (AD) and similar diseases.



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(13) **A1**

(72) **Inventeurs(suite)/Inventors(continued):** HANDSCHUH, SANDRA, DE; NAR, HERBERT, DE; KLINDER, KLAUS, DE

(74) **Agent:** FETHERSTONHAUGH & CO.

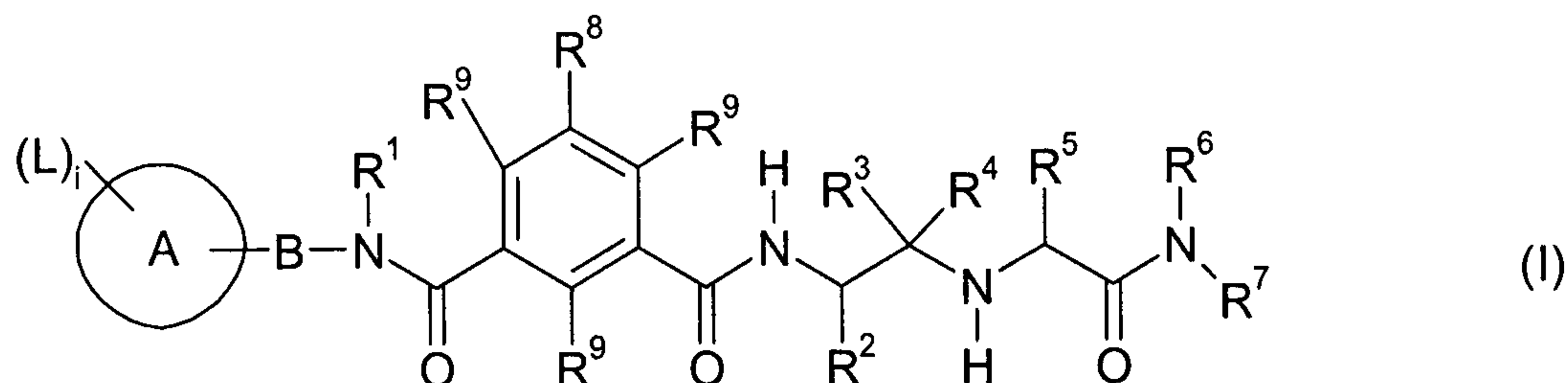
Abstract

The invention relates to substituted 1,2-ethylenediamines of general formula (I), wherein the radicals $R^1 - R^{13}$, A, B, L and i are as defined in the description and the claims. The invention also relates to the use thereof for treating Alzheimer's disease (AD) and similar diseases.

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Compounds for the treatment of Alzheimer's disease

The present invention relates to substituted 1,2-ethylenediamines of general formula (I)



wherein the groups R^1 to R^{13} , A, B, L and i are defined hereinafter, including the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates and solvates thereof. The invention also relates to pharmaceutical compositions containing a compound of formula I according to the invention and the use of a compound according to the invention for preparing a pharmaceutical composition for the treatment and/or prevention of Alzheimer's disease (AD) and other diseases associated with abnormal processing of Amyloid Precursor Protein (APP) or aggregation of Abeta peptide, as well as diseases that can be treated or alleviated by inhibiting β -secretase. Corresponding diseases include MCI ("mild cognitive impairment"), trisomy 21 (Down's syndrome), cerebral amyloidangiopathy, degenerative dementias, hereditary cerebral haemorrhage with amyloidosis - Dutch type (HCHWA-D), Alzheimer's dementia with Lewy bodies, trauma, stroke, pancreatitis, inclusion body myositis (IBM), as well as other peripheral amyloidoses, diabetes and arteriosclerosis.

The compounds according to the invention also inhibit the aspartylprotease cathepsin D and are therefore suitable for suppressing the metastatisation of tumour cells.

This invention also relates to processes for preparing a pharmaceutical composition as well as a compound according to the invention.

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Background to the invention

EP 652 009 A1 describes inhibitors of aspartate protease which inhibit the production of beta-amyloid peptides in cell culture and in vivo.

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WO 00/69262 discloses a beta-secretase and its use in assays for discovering potential active substances for the treatment of AD.

WO 01/00663 discloses memapsin 2 (human beta-secretase) and also a recombinant catalytically active enzyme. In addition, methods of identifying inhibitors of memapsin 2 are described.

WO 01/00665 discloses inhibitors of memapsin 2 for the treatment of AD.

15 WO 03/057721 discloses substituted aminocarboxamides for the treatment of AD.

WO 05/004802 discloses substituted benzyl-substituted N-alkyl-phenylcarboxamides for the treatment of AD.

20 At present there are no effective treatment methods capable of preventing, stopping or reversing AD.

Problem of the invention

25 The problem of the present invention is therefore to provide new substituted 1,2-ethylenediamines which inhibit the cleaving of APP (Amyloid Precursor Protein) mediated by β -secretase.

30 The present invention also sets out to provide physiologically acceptable salts of the compounds according to the invention with inorganic or organic acids.

A further aim of the present invention is to provide pharmaceutical compositions that contain at least one compound according to the invention or a physiologically

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acceptable salt according to the invention, optionally together with one or more inert carriers and/or diluents.

5 The present invention further relates to pharmaceutical compositions containing one or more, preferably one active substance, which is selected from among the compounds according to the invention and/ or the corresponding salts, as well as one or more, preferably one further active substance, optionally in addition to one or more inert carriers and/or diluents.

10 A further aim of this invention relates to the use of at least one of the compounds according to the invention for inhibiting β -secretase.

The invention also sets out to provide new pharmaceutical compositions that are suitable for the treatment or prevention of diseases or conditions that are associated
15 with an abnormal processing of Amyloid Precursor Protein (APP) or aggregation of Abeta peptide.

A further aim of this invention is to provide new pharmaceutical compositions which are suitable for the treatment or prevention of diseases or conditions that can be
20 influenced by inhibiting the β -secretase activity.

The invention also sets out to provide new pharmaceutical compositions which are suitable for the treatment and/or prevention of Alzheimer's disease (AD) as well as other diseases associated with an abnormal processing of APP or aggregation of
25 Abeta peptide, as well as diseases that can be treated or prevented by inhibiting β -secretase, particularly AD.

In a further aspect this invention relates to a method of inhibiting the β -secretase activity.

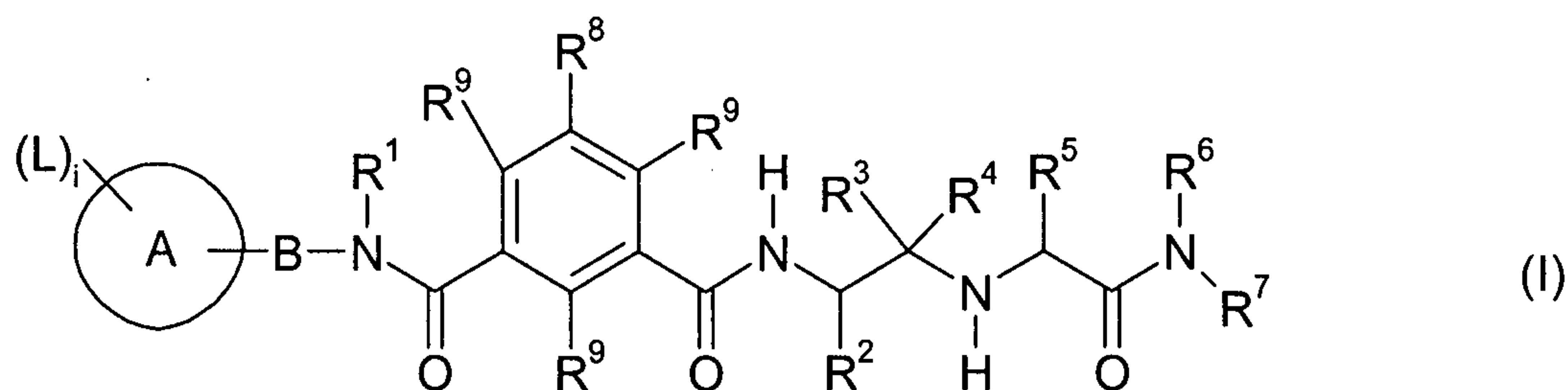
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Further aims of the present invention will become directly apparent to the skilled man from the foregoing remarks and those that follow.

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Subject of the invention

In a first aspect the present invention relates to substituted 1,2-ethylenediamines of general formula (I)



wherein

A denotes aryl or heteroaryl,

wherein the group A, besides the groups L, may optionally be substituted by one or more fluorine atoms,

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, carboxy, formyl, cyano, nitro, F₃C, HF₂C, FH₂C, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkyl-S, C₁₋₆-alkyl-S-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkyl-C₂₋₆-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl, heteroaryl-C₂₋₆-alkynyl, heteroaryl-C₃₋₇-cycloalkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, R¹²-SO₂-(R¹²)N, (R¹²)₂N-SO₂ or C₁₋₆-alkyl-SO₂,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, F₃C, HF₂C, FH₂C, hydroxy-C₁₋₆-alkyl, C₁₋₃-alkyl, C₁₋₆-alkoxy, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO- and HOSO₂-,

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i denotes 0, 1, 2 or 3,

B denotes a C₁₋₄-alkylene bridge,

while the C₁₋₄-alkylene bridge may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, iodine,

hydroxy, oxo, carboxy, cyano, nitro, F₃C, HF₂C, FH₂C, C₁₋₄-alkyl,

C₁₋₆-alkyl-S-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl,

heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, ,

aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, heteroaryl-

C₃₋₇-cycloalkyl, R¹³-O, (R¹²)₂N-SO₂, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-

CO, R¹²-SO₂, R¹²-CO-(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-SO₂, R¹²-CO- and

R¹²-SO-, and

wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the

C₁₋₄-alkylene bridge may be joined together, forming a C₃₋₇-cycloalkyl

group, and

wherein the above mentioned C₁₋₄-alkyl groups and the C₃₋₇-cycloalkyl

group formed from the C₁₋₄-alkyl groups may optionally be substituted

independently of one another by one or more groups selected from

among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,

cyano, nitro, F₃C, C₁₋₃-alkyl, C₁₋₃-alkoxy, R¹³-O-C₁₋₃-alkyl, R¹²-CO(R¹²)N,

R¹²-SO₂(R¹²)N, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, (R¹²)₂N-SO₂- and

HOSO₂-,

R¹ denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl,

C₃₋₇-cycloalkyl-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkyl-C₂₋₆-

alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-

C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-

C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryl-

C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, aryl-C₃₋₇-cycloalkyl,

heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl, heteroaryl-C₂₋₆-

alkynyl or heteroaryl-C₃₋₇-cycloalkyl,

wherein the above mentioned groups may optionally be substituted

independently of one another by one or more groups selected from

among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,

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cyano, nitro, F_3C , C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-6} -alkyl, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $(R^{12})_2N-CO$, $(R^{12})_2N-SO_2$, $R^{12}-CO-(R^{12})N$, $R^{12}-SO_2(R^{12})N$ - and $HOSO_2$ -,

5 R^2 denotes C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -alkoxy- C_{1-3} -alkyl, C_{1-6} -alkyl-S- C_{1-3} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkyl- C_{2-3} -alkenyl, C_{3-7} -cycloalkyl- C_{2-3} -alkynyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl- C_{2-3} -alkenyl, C_{3-7} -cycloalkenyl- C_{2-3} -alkynyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heterocyclyl- C_{2-3} -alkenyl, heterocyclyl- C_{2-3} -alkynyl, aryl, aryl- C_{1-3} -alkyl, aryl- C_{2-3} -alkenyl, aryl- C_{2-3} -alkynyl, aryl- C_{3-7} -cycloalkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, heteroaryl- C_{2-3} -alkenyl, heteroaryl- C_{2-3} -alkynyl or heteroaryl- C_{3-7} -cycloalkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, F_3C , HF_2C , FH_2C - hydroxy, oxo, carboxy, formyl, cyano, nitro, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $HOSO_2$, C_{1-3} -alkyl, C_{1-6} -alkyl-S- C_{1-3} -alkyl, $(R^{12})_2N-SO_2$, $R^{12}-CO-(R^{12})N$, $R^{12}-SO_2(R^{12})N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $(R^{12})_2N-CO$, $R^{13}-O$ - and $R^{13}-O-C_{1-3}$ -alkyl-,

20 R^3 , R^4 in each case independently of one another denote hydrogen, C_{1-6} -alkyl, fluorine, F_3C , HF_2C or FH_2C ,

25 R^5 denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-4} -alkyl, C_{3-7} -cycloalkyl- C_{2-4} -alkenyl, C_{3-7} -cycloalkyl- C_{2-4} -alkynyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-4} -alkyl, C_{3-7} -cycloalkenyl- C_{2-4} -alkenyl, C_{3-7} -cycloalkenyl- C_{2-4} -alkynyl, heterocyclyl, heterocyclyl- C_{1-4} -alkyl, heterocyclyl- C_{2-4} -alkenyl, heterocyclyl- C_{2-4} -alkynyl, aryl, aryl- C_{1-4} -alkyl, aryl- C_{2-4} -alkenyl, aryl- C_{2-4} -alkynyl, aryl- C_{3-7} -cycloalkyl, heteroaryl, heteroaryl- C_{1-4} -alkyl, heteroaryl- C_{2-4} -alkenyl, heteroaryl- C_{2-4} -alkynyl or heteroaryl- C_{3-7} -cycloalkyl,

30 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,

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cyano, nitro, C₁₋₃-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkyl-S, aryl, heteroaryl, heteroaryl-C₁₋₃-alkyl, aryl-C₁₋₆-alkyl, R¹²-CO-(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-SO₂, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO- and HOSO₂-,

5 R⁶ denotes C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₃₋₇-cycloalkyl-C₂₋₄-alkenyl, C₃₋₇-cycloalkyl-C₂₋₄-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, heterocyclyl-C₂₋₄-alkenyl, heterocyclyl-C₂₋₄-alkynyl, aryl-C₂₋₄-alkyl-
10 (R¹²)₂N-aryl, (R¹²)₂N-aryl-C₁₋₃-alkyl, aryl-C₂₋₄-alkenyl, aryl-C₂₋₄-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, heteroaryl-C₂₋₄-alkenyl, heteroaryl-C₂₋₄-alkynyl or heteroaryl-C₃₋₇-cycloalkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from
15 among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C₁₋₃-alkyl, C₃₋₇-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, aryl, heteroaryl, heteroaryl-C₁₋₃-alkyl, aryl-C₁₋₆-alkyl, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-N(R¹²), (R¹²)₂N-SO₂, R¹²-SO₂-(R¹²)N- and HOSO₂-,

20 R⁷ denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from
25 among fluorine, chlorine, bromine, iodine, cyano, hydroxy, C₁₋₃-alkyl, C₁₋₆-alkoxy- and (R¹²)₂N-,

30 R⁸ denotes hydrogen, fluorine, chlorine, bromine, iodine, cyano, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkyl-C₂₋₆-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl,

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aryl-C₂₋₆-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl, heteroaryl-C₂₋₆-alkynyl, heteroaryl-C₃₋₇-cycloalkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, R¹⁰-SO₂-(R¹¹)N or R¹⁰-CO-(R¹¹)N,

wherein the above mentioned groups may optionally be substituted

independently of one another by one or more groups selected from

among C₁₋₆-alkyl, fluorine, chlorine, bromine, hydroxy, oxo, carboxy,

formyl, cyano, nitro, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkyl-S, C₁₋₆-alkyl-S-

C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl,

heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl,

R¹³-O, R¹³-O-CO, R¹³-CO, R¹³-O-CO-(R¹²)N, (R¹²)₂N-CO-O, R¹³-O-C₁₋₃-

alkyl, (R¹²)₂N, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, (R¹²)₂N-

SO₂, (R¹²)₂N-SO₂-(R¹²)N, R¹²-SO₂, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O,

FH₂C-O- and R¹²-SO₂-(R¹²)N-,

R⁹ in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₃-alkyl, R¹³-O or (R¹²)₂N,

while the above mentioned C₁₋₃-alkyl group may optionally be substituted by one or more fluorine atoms,

R¹⁰ denotes C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₄-alkyl, C₃₋₇-cycloalkyl-C₂₋₄-alkenyl, C₃₋₇-cycloalkyl-C₂₋₄-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₄-alkyl, C₃₋₇-cycloalkenyl-C₂₋₄-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₄-alkynyl, heterocyclyl, heterocyclyl-C₁₋₄-alkyl, heterocyclyl-C₂₋₄-alkenyl, heterocyclyl-C₂₋₄-alkynyl, aryl, aryl-C₁₋₄-alkyl, aryl-C₂₋₄-alkenyl, aryl-C₂₋₄-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₄-alkyl, heteroaryl-C₂₋₄-alkenyl, heteroaryl-C₂₋₄-alkynyl, heteroaryl-C₃₋₇-cycloalkyl or (R¹²)₂N,

wherein the above mentioned groups may optionally be substituted

independently of one another by one or more groups selected from

among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, formyl, cyano,

nitro, C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, R¹³-O, R¹³-O-C₁₋₃-

alkyl, R¹²-CO(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-SO₂, R¹²-SO₂, R¹²-SO,

R¹²-S, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl- and (R¹²)₂N-CO-,

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R^{11} denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heterocyclyl- C_{2-3} -alkenyl, heterocyclyl- C_{2-3} -alkynyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, heteroaryl- C_{2-3} -alkenyl or heteroaryl- C_{2-3} -alkynyl,
wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, $(R^{12})_2N-SO_2$, $R^{12}-SO_2$, $R^{12}-SO$, $R^{12}-S$, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl- and $R^{12}CO-$,

or

R^{10} and R^{11} together form a C_{2-6} -alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atom linked to R^{11} and the SO_2- or $CO-$ group linked to R^{10} ,
wherein one or two $-CH_2$ groups of the C_{2-6} -alkylene bridge may be replaced independently of one another by O, S, SO, SO_2 or $-N(R^{12})-$ such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and
wherein the C atoms of the above mentioned C_{2-6} -alkylene bridge may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, formyl, cyano, F_3C , C_{1-6} -alkyl, C_{1-6} -alkoxy, oxo and nitro,

R^{12} in each case independently of one another denote hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy- C_{1-3} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl, wherein
two C_{1-6} -alkyl groups bound to the same nitrogen atom may together form a C_{2-6} -alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atoms linked to the groups R^{12} ,

– 10 –

while a -CH₂ group of the C₂₋₆-alkylene bridge may be replaced by O, S or -N(R¹³)-, and

wherein the above mentioned groups and the heterocyclic ring may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, C₁₋₃-alkoxy, (R¹³)₂N-CO or (R¹³)₂N-, and

R¹³ in each case independently of one another denote hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C₁₋₃-alkyl- and C₁₋₃-alkoxy-,

the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates and solvates thereof.

The compounds according to the invention of general formula (I) and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on β -secretase activity, particularly the β -secretase mediated cleaving of APP.

In view of the inhibitory properties of the compounds according to the invention on the Cathepsin D activity, the compounds are also suitable for suppressing the metastatisation of tumour cells.

The present invention also relates to the physiologically acceptable salts of the compounds according to the invention with inorganic or organic acids.

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Therefore in another aspect the invention also relates to the use of the compounds according to the invention, including the physiologically acceptable salts thereof, as medicaments.

- 5 The invention further relates to pharmaceutical compositions containing at least one compound according to the invention or a physiologically acceptable salt according to the invention, optionally together with one or more inert carriers and/or diluents.

This invention further relates to pharmaceutical compositions, containing one or more,
10 preferably one active substance which is selected from among the compounds according to the invention and/or the corresponding salts, as well as one or more, preferably one active substance, for example selected from among beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors such as e.g. Alzhemed; directly or indirectly acting neuroprotective substances; antioxidants such
15 as e.g. Vitamin E or ginkgolides; anti-inflammatory substances such as e.g. Cox inhibitors, NSAIDs with additionally or only A β lowering properties; HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists such as e.g. memantine; AMPA agonists; substances that modulate the concentration or release of
20 neurotransmitters such as NS-2330; substances that induce the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor antagonists or inverse agonists; antibiotics such as minocycline or rifampicin; PDE-IV and PDE-IX inhibitors, GABA_A inverse agonists, nicotine agonists, histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, α 2-adrenoreceptor antagonists,
25 muscarinic M1 agonists, muscarinic M2 antagonists, metabotropic glutamate-receptor 5 positive modulators, as well as other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced, optionally together with one or more inert carriers and/or diluents.

30

This invention further relates to pharmaceutical compositions, containing one or more, preferably one active substance, which is selected from among the compounds according to the invention and/ or the corresponding salts, as well as one or more, preferably one active substance, selected from among Alzhemed, Vitamin E,

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ginkgolides, donepezil, rivastigmine, tacrine, galantamine, memantine, NS-2330, ibutamoren mesylate, capromorelin, minocycline and/or rifampicin, optionally together with one or more inert carriers and/or diluents.

- 5 This invention further relates to the use of at least one of the compounds according to the invention for inhibiting β -secretase.

This invention also relates to the use of at least one compound according to the invention or a physiologically acceptable salt of such a compound for preparing a
10 pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions that are associated with abnormal processing of Amyloid Precursor Protein (APP) or aggregation of Abeta peptide.

This invention also relates to the use of at least one compound according to the
15 invention or a physiologically acceptable salt of such a compound for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions that can be influenced by inhibiting the β -secretase activity.

This invention further relates to the use of at least one compound according to the
20 invention or a pharmaceutical composition according to the invention for preparing a pharmaceutical composition that is suitable for the treatment and/or prevention of Alzheimer's disease (AD) and other diseases associated with abnormal processing of Amyloid Precursor Protein (APP) or aggregation of Abeta peptide, as well as diseases that can be treated or alleviated by inhibiting β -secretase, particularly AD.

25 Corresponding diseases include MCI ("mild cognitive impairment"), trisomy 21 (Down's syndrome), cerebral amyloidangiopathy, degenerative dementias, hereditary cerebral haemorrhage with amyloidosis - Dutch type (HCHWA-D), Alzheimer's dementia with Lewy bodies, trauma, stroke, pancreatitis, inclusion body myositis (IBM), as well as other peripheral amyloidoses, diabetes and arteriosclerosis.

30

This invention further relates to a method of inhibiting β -secretase activity, characterised in that β -secretase is brought into contact with an inhibitory amount of one of the compounds according to the invention.

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Further subjects of the invention will become apparent to the skilled man in an obvious manner from the foregoing and following description of the invention.

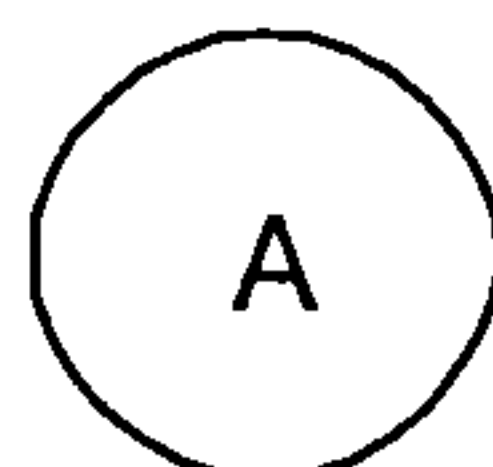
Detailed description of the invention

- 5 Unless otherwise stated, the groups, residues and substituents R^1 to R^{13} , A, B, L and i have the meanings given hereinbefore and hereinafter.

If residues, substituents or groups occur more than once in a compound, they may have the same or different meanings.

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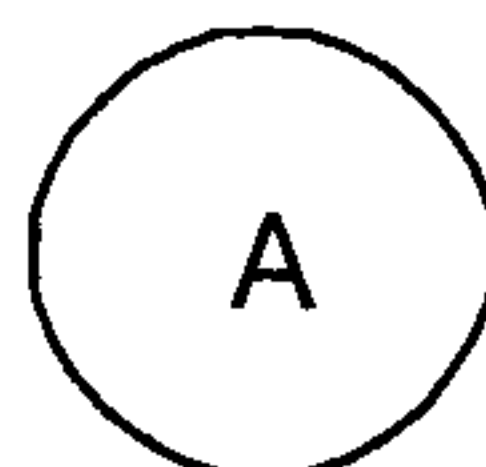
In a preferred embodiment of the compounds of the present invention the group



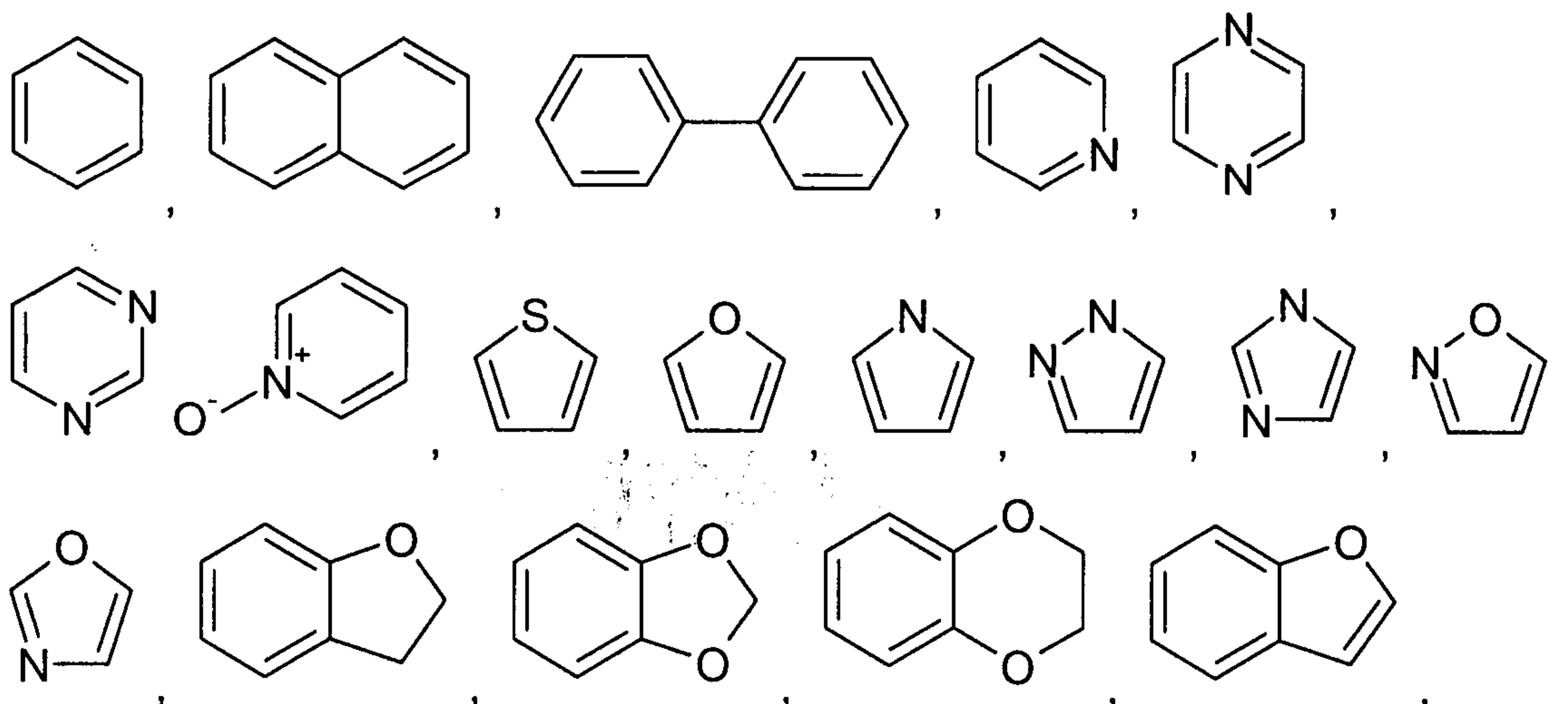
denotes a phenyl ring or a 5- or 6-membered aromatic heteroaryl group which contains 1, 2 or 3 heteroatoms selected from among N, O and S.

15

In another preferred embodiment the group

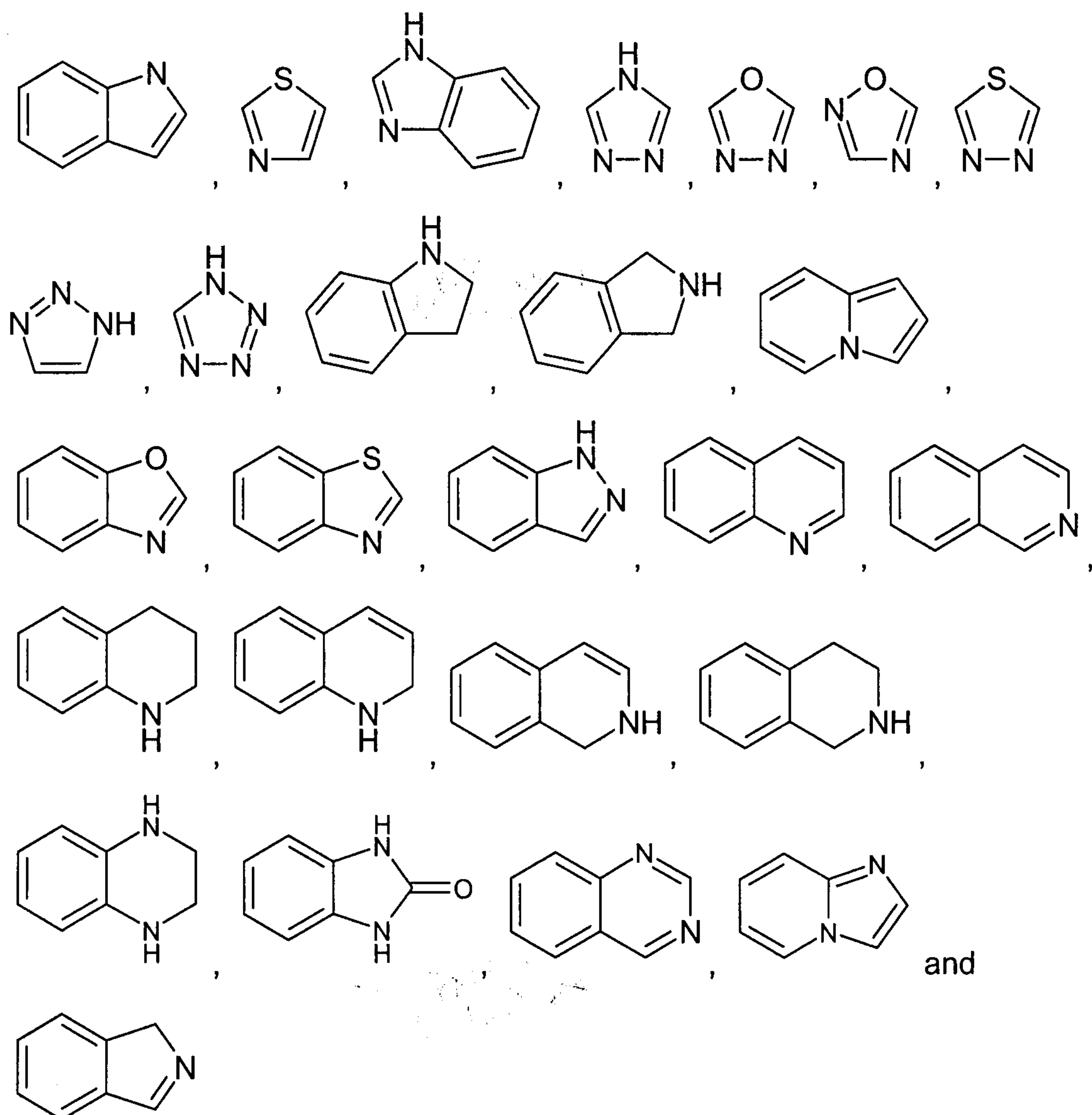


has the following meanings:

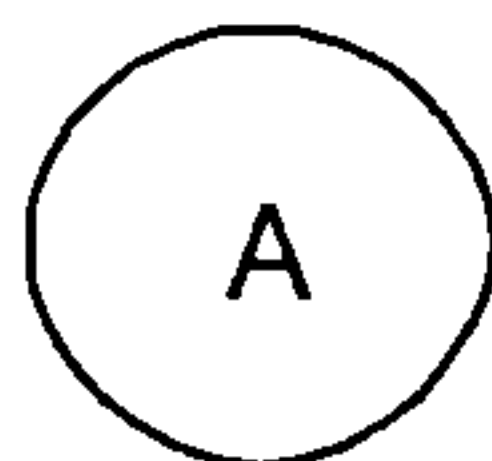


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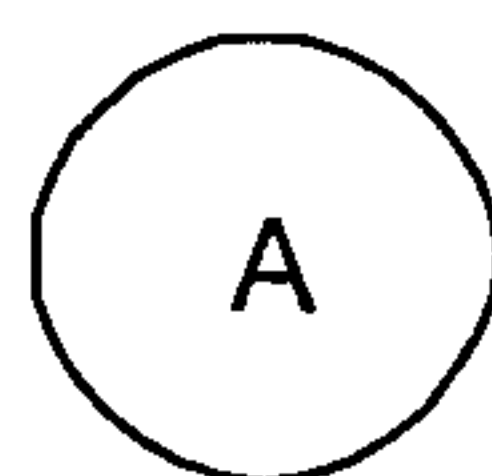
In a more preferred embodiment of the compounds of the present invention the group



denotes a 5- or 6-membered aromatic heteroaryl group which contains 1 or 2 heteroatoms selected from among N, O and S, wherein at most one O or S atom may be present.

In a particularly preferred embodiment of the compounds of the present invention the group

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denotes a phenyl, thienyl, thiazolyl, pyrazolyl or a pyridyl group, while the phenyl, the thienyl, the thiazolyl and the pyridyl group are regarded as being particularly preferred.

- 5 Preferably the substituent L in each case independently denotes hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, F_3C , HF_2C , FH_2C , C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, $(R^{12})_2N$, $(R^{12})_2N-CO$, $R^{12}-CO-(R^{12})N$, $(R^{12})_2N-CO-(R^{12})N$, $(R^{12})_2N-SO_2$, $R^{12}-$
10 $SO_2-(R^{12})N$ or C_{1-3} -alkyl- SO_2 , wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, F_3C , HF_2C , FH_2C , hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl, C_{1-3} -alkoxy, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl- and $(R^{12})_2N-CO$ -.
- 15 Particularly preferably the substituent L in each case independently denotes hydrogen, fluorine, chlorine, bromine, cyano, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, phenyl, $(R^{12})_2N$, $(R^{12})_2N-CO$, $R^{12}-CO-(R^{12})N$, $(R^{12})_2N-CO-(R^{12})N$, $R^{12}-SO_2-(R^{12})N$ or $(R^{12})_2N-SO_2$, wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms.
- 20 Most particularly preferred meanings for the substituent L are in each case independently of one another hydrogen, fluorine, chlorine, bromine, hydroxy, C_{1-4} -alkyl or C_{1-4} -alkoxy, wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms.
- 25 Particularly preferred meanings for the substituent L are in each case independently of one another hydrogen, fluorine, chlorine, trifluoromethyl, trifluoromethoxy, methyl and methoxy.
- 30 Preferably the index i may assume the values 0, 1 or 2. In particularly preferred embodiments the value of the index i is 0 or 1.

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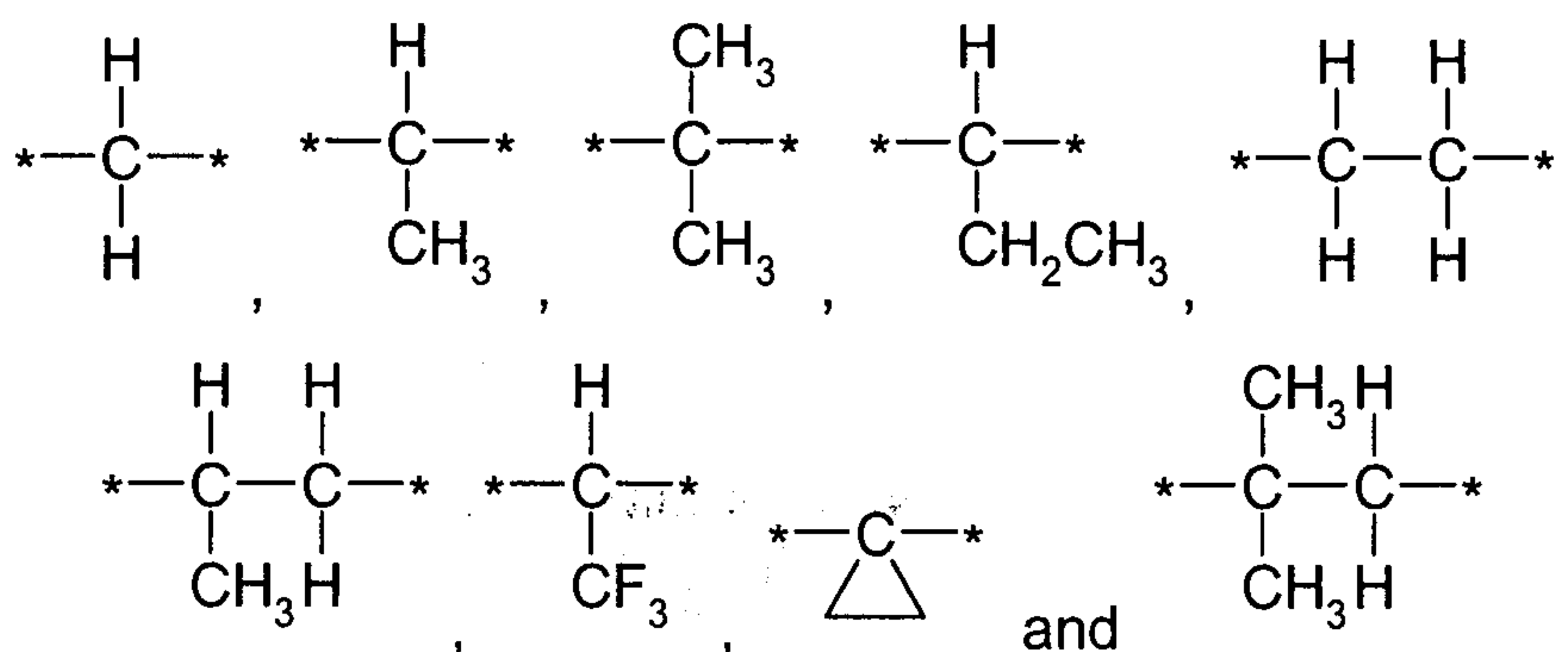
In a preferred embodiment of the compounds according to the invention the group B denotes a C₁₋₄-alkylene bridge, which may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, cyano, nitro, F₃C, HF₂C, FH₂C, C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, R¹³-O, (R¹²)₂N-SO₂- and (R¹²)₂N-, and wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together, forming a C₃₋₇-cycloalkyl group, and wherein the above mentioned groups and the C₃₋₇-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, F₃C, C₁₋₃-alkyl, C₁₋₃-alkoxy and R¹³-O-C₁₋₃-alkyl.

Particularly preferably the group B denotes a C₁₋₄-alkylene bridge, while the C₁₋₄-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, C₁₋₄-alkyl, phenyl or benzyl, and wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together forming a C₃₋₆-cycloalkyl group, and wherein the above mentioned groups and the C₃₋₆-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C₁₋₃-alkoxy.

In a most particularly preferred embodiment B is a C₁₋₂-alkylene bridge, wherein the C₁₋₂-alkylene bridge may optionally be substituted by one or more C₁₋₄-alkyl groups, and wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₂-alkylene bridge may be joined together to form a cyclopropyl group, and wherein one or more hydrogen atoms of the above mentioned C₁₋₂-alkylene bridge and/or the C₁₋₄-alkyl groups and/or the cyclopropyl group formed therefrom may optionally be replaced by one or more fluorine atoms.

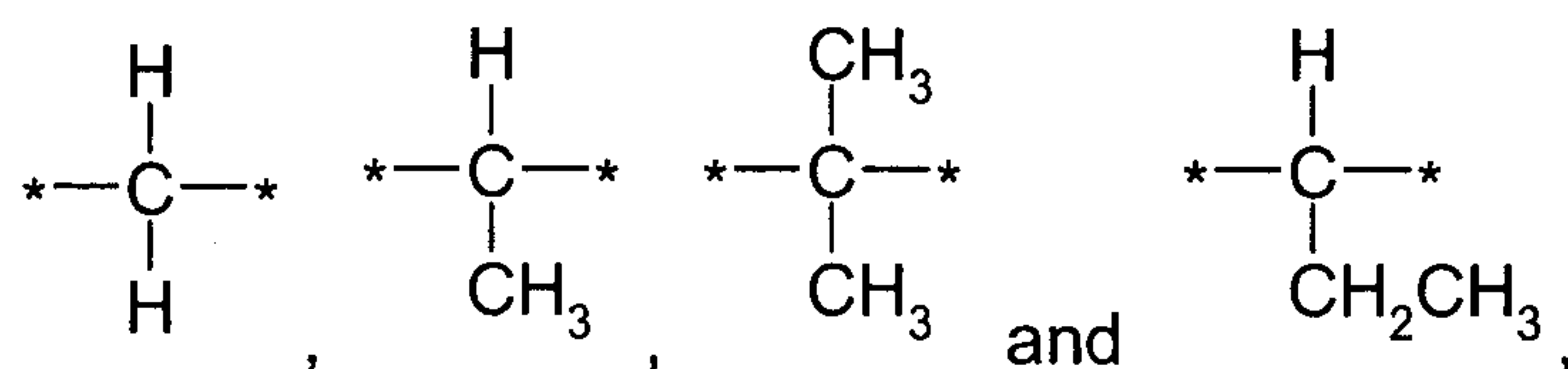
Also most particularly preferred are the compounds according to the invention wherein the group B is selected from among

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wherein one or more hydrogen atoms may optionally be replaced by fluorine.

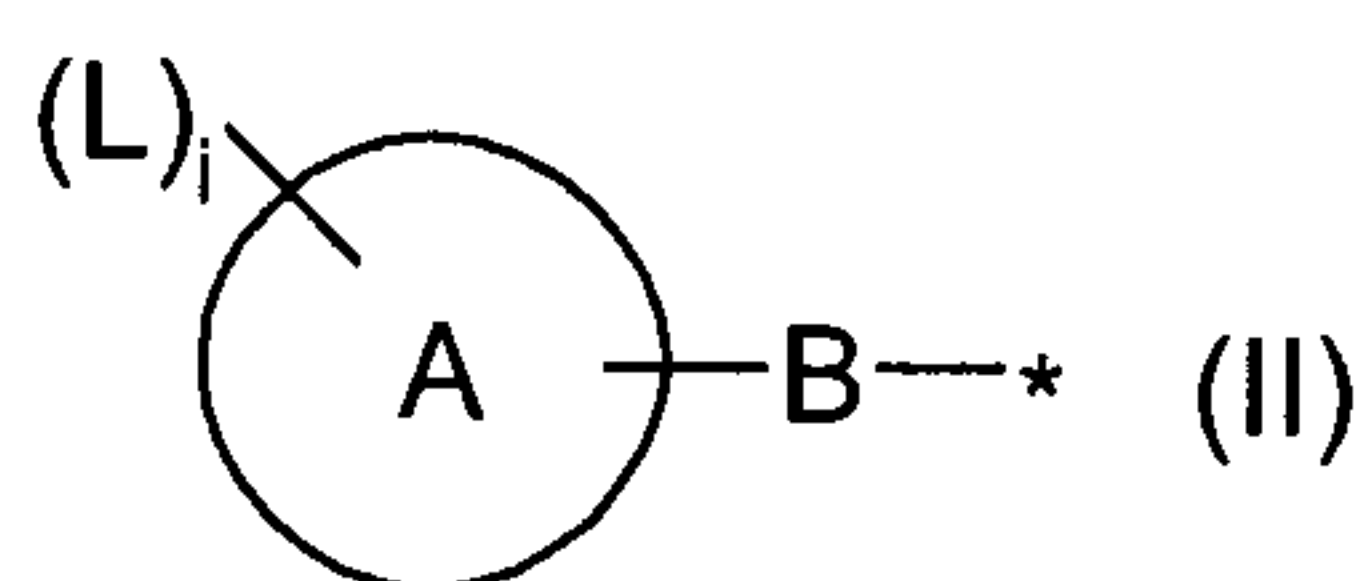
- 5 Particularly preferred are those compounds according to the invention wherein the group B is selected from among



wherein one or more hydrogen atoms may optionally be replaced by fluorine.

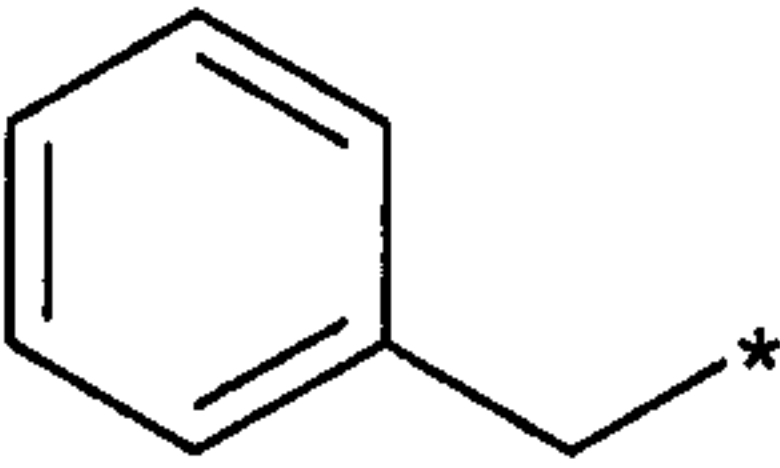
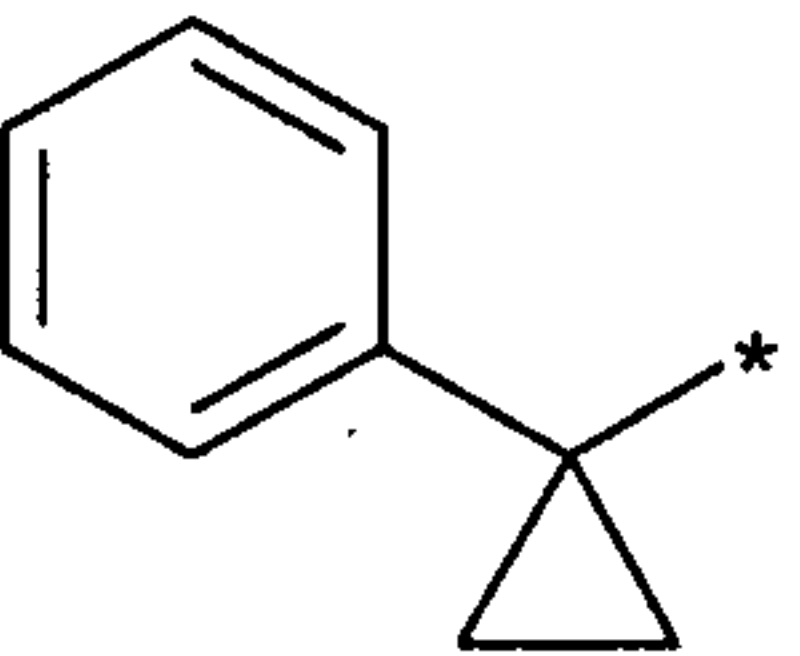
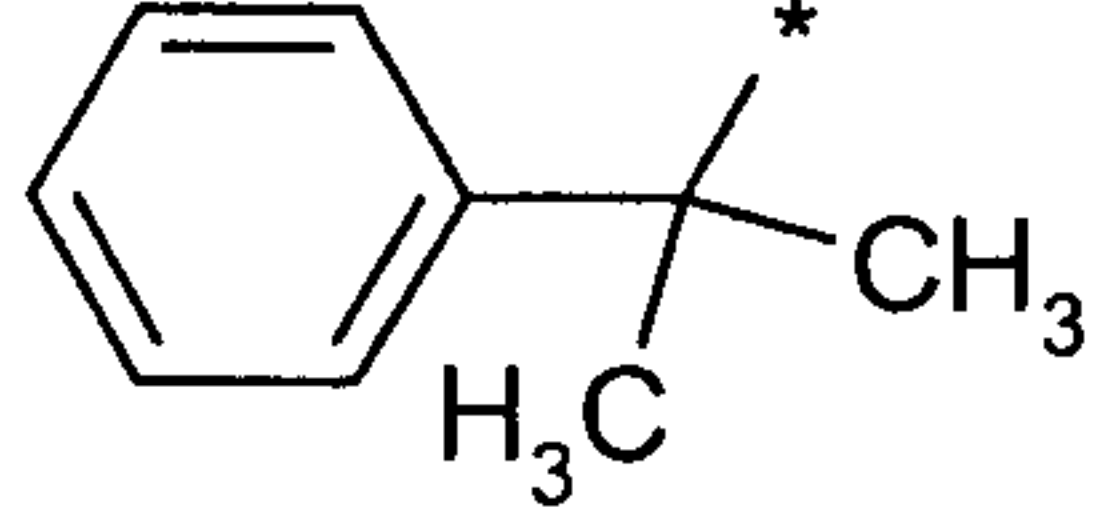
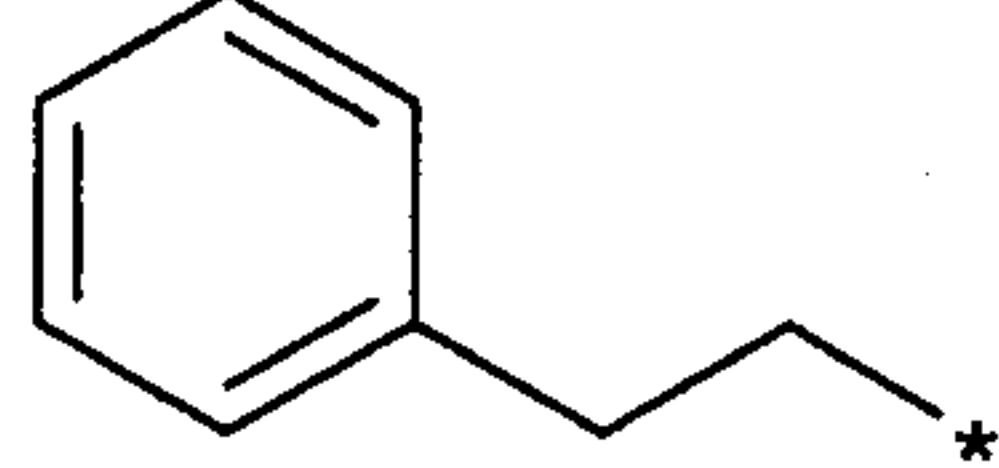
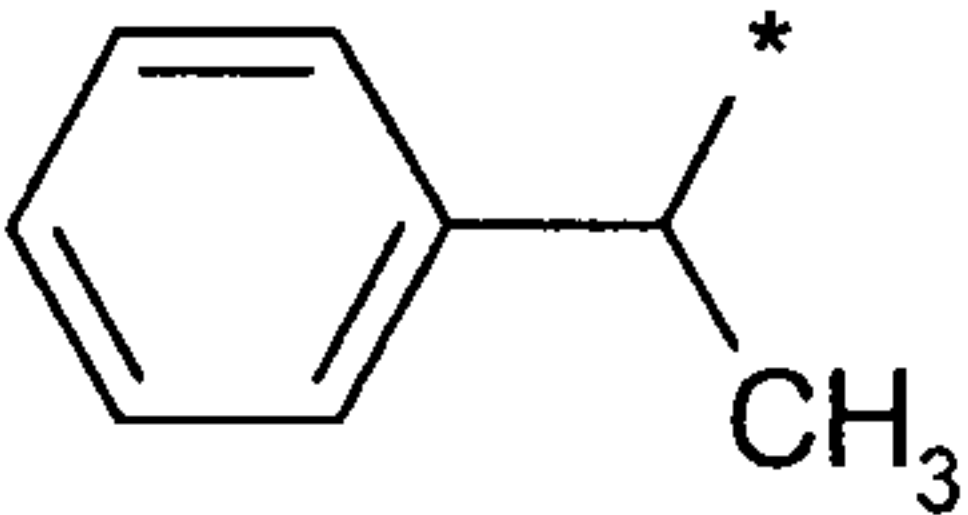
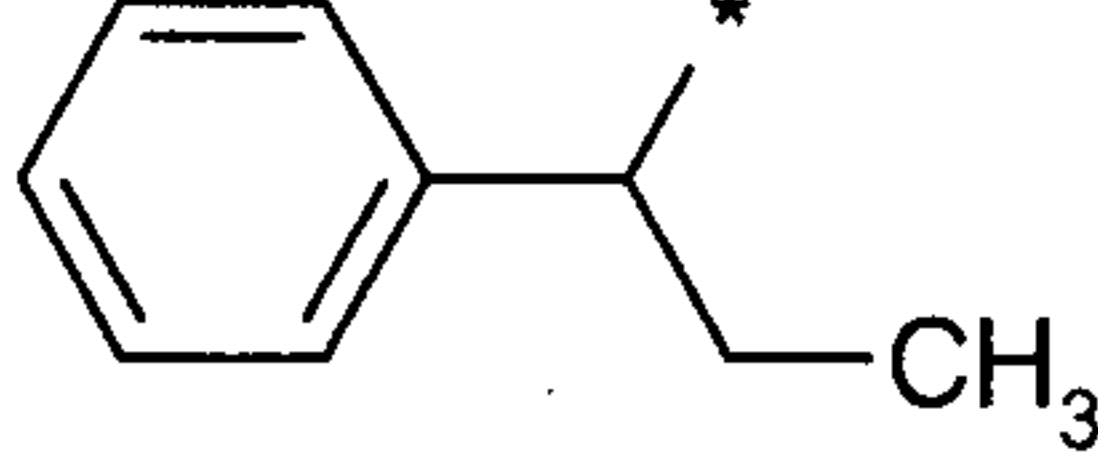
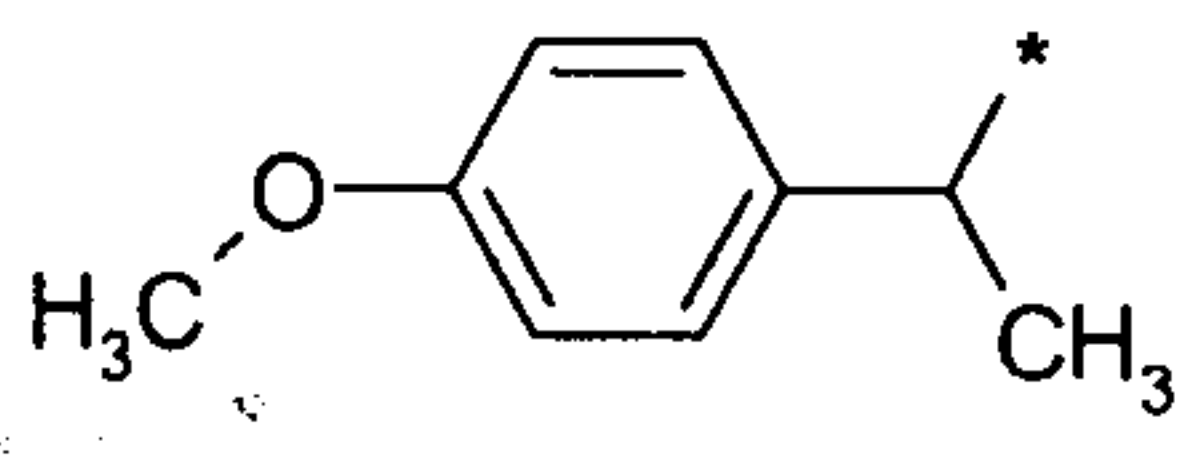
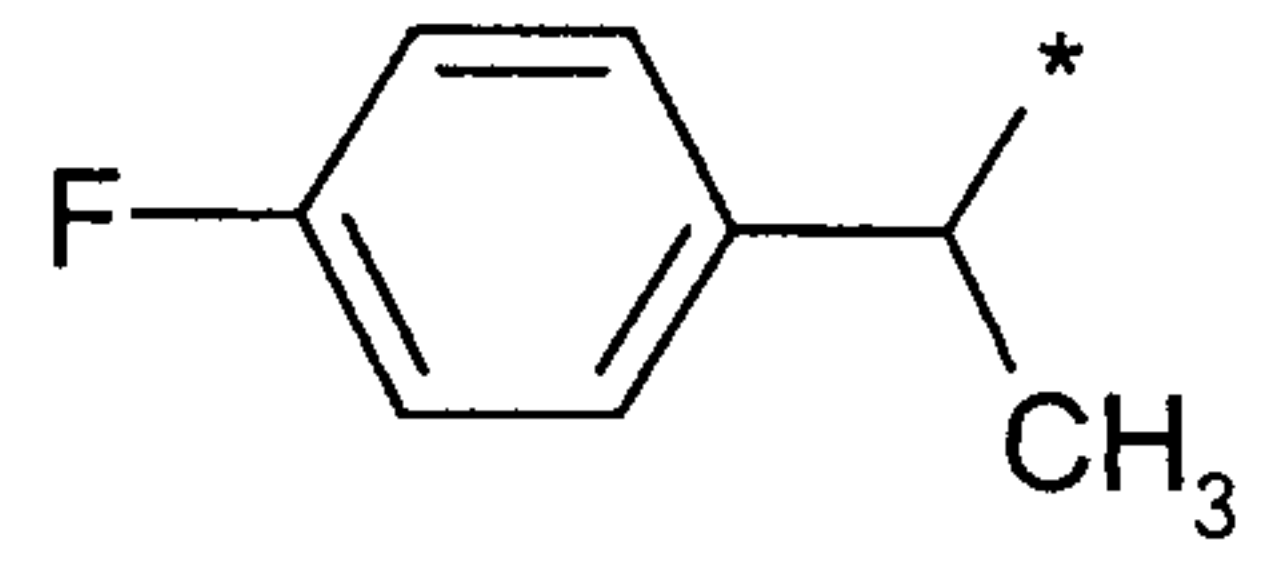
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From another preferred embodiment, the invention encompasses those compounds wherein the partial formula (II)

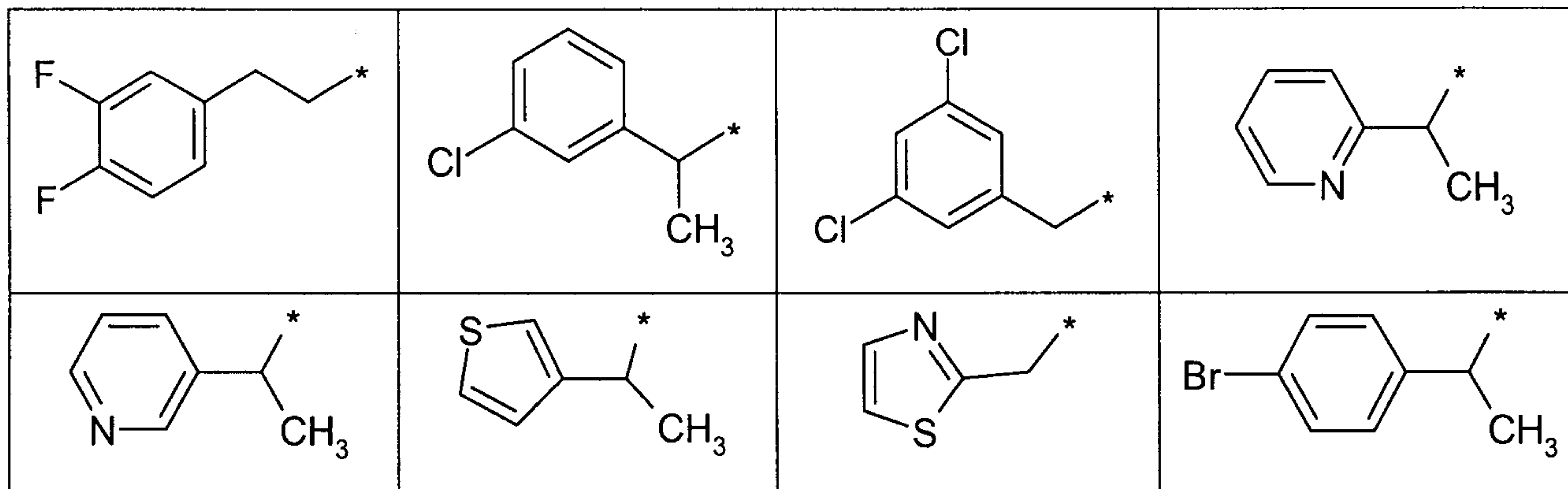


15

is selected from among

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In the compounds of formula (I) according to the invention the group R^1 is preferably selected from among hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, F_3C , C_{1-3} -alkyl, C_{1-3} -alkoxy and hydroxy- C_{1-3} -alkyl.

Particularly preferred are the groups R^1 selected from among hydrogen, C_{1-4} -alkyl, C_{3-4} -alkenyl, C_{3-6} -cycloalkyl- and C_{3-6} -cycloalkyl- C_{1-3} -alkyl wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C_{1-3} -alkoxy.

Most particularly preferred are the groups R^1 selected from among hydrogen and C_{1-4} -alkyl, wherein the C_{1-4} -alkyl group may be substituted by one or more fluorine atoms.

Particularly preferred are those compounds according to the invention wherein R^1 is hydrogen.

In the compounds according to the invention of formula (I) the group R^2 is preferably selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -alkoxy- C_{1-3} -alkyl, C_{1-6} -alkyl-S- C_{1-3} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of

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one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, F_3C , HF_2C , FH_2C , hydroxy, carboxy, cyano, nitro, C_{1-3} -alkyl, $(R^{12})_2N$, $(R^{12})_2N-SO_2$, $R^{12}-CO-(R^{12})N$, $R^{12}-SO_2(R^{12})N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $(R^{12})_2N-CO$, $R^{13}-O-$ and $R^{13}-O-C_{1-3}$ -alkyl.

5

Particularly preferred groups R^2 are groups selected from among C_{1-6} -alkyl, C_{2-6} -alkynyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, C_{1-3} -alkyl, F_3C , HF_2C , FH_2C , H_2N- and C_{1-3} -alkoxy.

15 Most particularly preferred are those groups R^2 which are selected from among n-propyl, n-butyl, 2-propynyl, 2-butyryl, cyclohexylmethyl, cyclopentylmethyl, phenylmethyl, 2-phenylethyl, pyridylmethyl, furanylmethyl, thienylmethyl and thiazolylmethyl, wherein the above mentioned n-propyl, butyl, propynyl, butynyl, cyclohexylmethyl and cyclopentylmethyl groups may optionally be substituted by with one or more fluorine atoms and the phenylmethyl, 2-phenylethyl, pyridylmethyl, furanylmethyl, thienylmethyl or thiazolylmethyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, methyl, F_3C , HF_2C , FH_2C- and H_2N-

25 Particularly preferred are those groups R^2 which are selected from among phenylmethyl, thienylmethyl, pyridylmethyl, particularly 2-pyridylmethyl and thiazolylmethyl.

In the compounds of formula (I) according to the invention the group R^3 is preferably hydrogen, fluorine, methyl, F_3C , HF_2C or FH_2C and particularly preferably R^3 is hydrogen.

The group R^4 is preferably hydrogen or fluorine, particularly preferably hydrogen.

– 20 –

In a particularly preferred embodiment of the compounds according to the invention the group R^3 is selected from among hydrogen, fluorine, methyl, F_3C , HF_2C and FH_2C and the group R^4 is hydrogen or fluorine.

- 5 In a most particularly preferred embodiment of the compounds according to the invention the groups R^3 and R^4 are hydrogen.

In the compounds of formula (I) according to the invention the group R^5 is preferably selected from among hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, 10 C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-3} -alkyl-S, aryl, 15 heteroaryl, heteroaryl- C_{1-3} -alkyl, aryl- C_{1-3} -alkyl, $(R^{12})_2N-SO_2$, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl- and $(R^{12})_2N-CO-$.

Particularly preferred groups R^5 are selected from among C_{1-6} -alkyl, cyclopropyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl and phenyl- C_{1-3} -alkyl, wherein the above mentioned groups may 20 optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, carboxy, C_{1-4} -alkyl, C_{1-4} -alkoxy and $(R^{12})_2N-$.

Most preferably, R^5 is a C_{1-4} -alkyl or a cyclopropyl group, while one or more hydrogen 25 atoms of the above mentioned groups may optionally be replaced by fluorine atoms. Of the particularly preferred C_{1-4} -alkyl groups the n-butyl group in particular is especially preferred.

In the compounds of formula (I) according to the invention the group R^6 is preferably 30 selected from among C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ -aryl, $(R^{12})_2N$ -aryl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy,

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carboxy, cyano, nitro, C₁₋₃-alkyl, C₃₋₇-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-N(R¹²), (R¹²)₂N-SO₂, R¹²-SO₂-(R¹²)N, R¹³-O- and R¹³-O-C₁₋₃-alkyl.

5

Particularly preferred groups R⁶ are groups selected from among C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N-phenyl, (R¹²)₂N-phenyl-C₁₋₃-alkyl, heteroaryl and heteroaryl-C₁₋₃-alkyl, wherein by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S, and wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, carboxy, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, C₃₋₅-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl- (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, (R¹²)₂N-CO-N(R¹²), R¹²-CO-(R¹²)N- and (R¹²)₂N-SO₂-.

15

Most particularly preferred are those groups R⁶ which are selected from among (R¹²)₂N-phenyl-C₁₋₃-alkyl- and C₃₋₆-cycloalkyl-C₁₋₃-alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy-C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO-N(R¹²)- and (R¹²)₂N-SO₂-.

20

Particularly preferred as the group R⁶ is a 4-aminobenzyl, cyclobutylmethyl, 2- or cyclopropylethyl group, while the above-mentioned groups may optionally be substituted by one or more groups selected from among fluorine and C₁₋₃-alkyl, particularly preferably methyl, and the other groups and radicals are defined as above or hereinafter.

25

Also particularly preferred as the group R⁶ is a cyclopropylmethyl group, while the two groups may optionally be substituted independently of one another by one or more groups selected from among fluorine and C₁₋₃-alkyl, particularly preferably by methyl, and the other groups and radicals are defined as above or hereinafter.

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In the compounds of formula (I) according to the invention the group R^7 is preferably selected from among hydrogen and C_{1-4} -alkyl, while one or more hydrogen atoms of the C_{1-4} -alkyl group may be replaced by fluorine.

- 5 In the compounds of formula (I) according to the invention the group R^8 is preferably selected from among hydrogen, fluorine, chlorine, bromine, cyano, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, R^{10} -SO₂-(R^{11})N- and R^{10} -CO-(R^{11})N, wherein the
10 above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among C_{1-6} -alkyl, fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, C_{3-7} -cycloalkyl, heterocyclyl, (R^{12})₂N, (R^{12})₂N-CO, R^{13} -CO, R^{13} -O-CO, R^{12} -CO-(R^{12})N, (R^{12})₂N-CO-(R^{12})N, (R^{12})₂N-SO₂, (R^{12})₂N-SO₂-(R^{12})N, R^{12} -SO₂, R^{13} -O, C_{1-4} -alkyl-S, F_3C , HF_2C , FH_2C , F_3C -O, HF_2C -O, FH_2C -O- and
15 R^{12} -SO₂-(R^{12})N-.

Particularly preferred groups R^8 are groups selected from among hydrogen, fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{1-4} -alkoxy, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl-oxy, C_{3-6} -cycloalkyl- C_{1-3} -alkoxy, phenyl, pyridyl, thienyl, furyl, R^{10} -CO-(R^{11})N- and R^{10} -SO₂-(R^{11})N, wherein the above mentioned groups may optionally be substituted
20 independently of one another by one or more groups selected from among fluorine, chlorine, bromine, carboxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-4} -alkyl-S, R^{13} -CO, R^{13} -O-CO, R^{12} -SO₂, F_3C , HF_2C , FH_2C , F_3C -O, HF_2C -O, FH_2C -O- and (R^{12})₂N-CO-.

- 25 In a most particularly preferred embodiment of the compounds according to the invention the group R^8 has the meaning R^{10} -SO₂-(R^{11})N, R^{10} -CO-(R^{11})N, cyanophenyl, particularly 2-cyanophenyl, or cyanothienyl, wherein the above mentioned cyanophenyl and cyanothienyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine,
30 C_{1-4} -alkyl, C_{1-4} -alkoxy, F_3C , HF_2C , FH_2C , F_3C -O, HF_2C -O- and FH_2C -O-.

Preferred groups R^9 are each independently selected from among hydrogen, fluorine, chlorine, bromine, methyl, F_2HC , FH_2C - and F_3C , wherein the groups hydrogen,

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fluorine, chlorine or bromine are particularly preferred and the group hydrogen is most preferred.

Also preferred are those compounds according to the invention wherein R^8 is selected
5 from among hydrogen, fluorine, chlorine, bromine, cyano, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, R^{10} -SO₂-(R^{11})N- and R^{10} -CO-(R^{11})N, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups
10 selected from among C_{1-6} -alkyl, fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, C_{3-7} -cycloalkyl, heterocyclyl, (R^{12})₂N, (R^{12})₂N-CO, R^{13} -CO, R^{13} -O-CO, R^{12} -CO-(R^{12})N, (R^{12})₂N-CO-(R^{12})N, (R^{12})₂N-SO₂, (R^{12})₂N-SO₂-(R^{12})N, R^{12} -SO₂, R^{13} -O, C_{1-4} -alkyl-S, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O, FH₂C-O- and R^{12} -SO₂-(R^{12})N-, and R^9 in each case independently of one another denotes hydrogen, fluorine, chlorine,
15 bromine, methyl, F₂HC, FH₂C or F₃C-.

Particularly preferred are those compounds according to the invention wherein R^8 is selected from among hydrogen, fluorine, chlorine, bromine, cyano, C_{1-4} -alkyl, C_{1-4} -alkoxy, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl-oxy, C_{3-6} -cycloalkyl- C_{1-3} -alkoxy, phenyl,
20 pyridyl, thienyl, furyl, R^{10} -CO-(R^{11})N- and R^{10} -SO₂-(R^{11})N, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, carboxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-4} -alkyl-S, R^{13} -CO, R^{13} -O-CO, R^{12} -SO₂, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O, FH₂C-O- and (R^{12})₂N-CO-, and R^9 in each case independently of one
25 another denotes hydrogen, fluorine, chlorine or bromine.

Most particularly preferred are those compounds according to the invention wherein the group R^8 denotes a R^{10} -SO₂-(R^{11})N or R^{10} -CO-(R^{11})N, cyanophenyl, particularly 2-cyanophenyl, or cyanothienyl group, wherein the above mentioned cyanophenyl and
30 cyanothienyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, C_{1-4} -alkyl, C_{1-4} -alkoxy, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O- and FH₂C-O-, and R^9 in each case independently of one another denotes hydrogen, fluorine, chlorine or bromine, particularly preferably hydrogen.

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In the compounds of formula (I) according to the invention the group R^{10} is preferably selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl and $(R^{12})_2N$, wherein the above mentioned groups may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, R^{12} -CO(R^{12})N, R^{12} -SO₂(R^{12})N, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl- and $(R^{12})_2N$ -CO-.

Particularly preferred groups R^{10} are groups selected from among C_{1-6} -alkyl, heterocyclyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl and $(R^{12})_2N$, wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl.

Most particularly preferred groups R^{10} are groups selected from among C_{1-4} -alkyl, particularly methyl or ethyl, morpholinyl, piperidinyl, 4-methylpiperidinyl, pyrrolidinyl, phenyl, 4-fluorophenyl, benzyl, pyridyl and $(CH_3)_2N$, wherein the above-mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine and bromine.

In the compounds of formula (I) according to the invention the group R^{11} is preferably selected from among hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl.

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Particularly preferred groups R^{11} are groups selected from among hydrogen, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, while by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl.

Most particularly preferred groups R^{11} are groups selected from among hydrogen, methyl, HF_2C , ethyl, phenyl- and 4-fluorophenyl, wherein the above-mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine and bromine.

Also preferred are compounds according to the invention wherein R^{10} is selected from among C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl- and $(R^{12})_2N$, wherein the above mentioned groups may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, R^{12} -CO(R^{12})N, R^{12} -SO₂(R^{12})N, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl- and $(R^{12})_2N$ -CO-, and R^{11} is selected from among hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl and heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl.

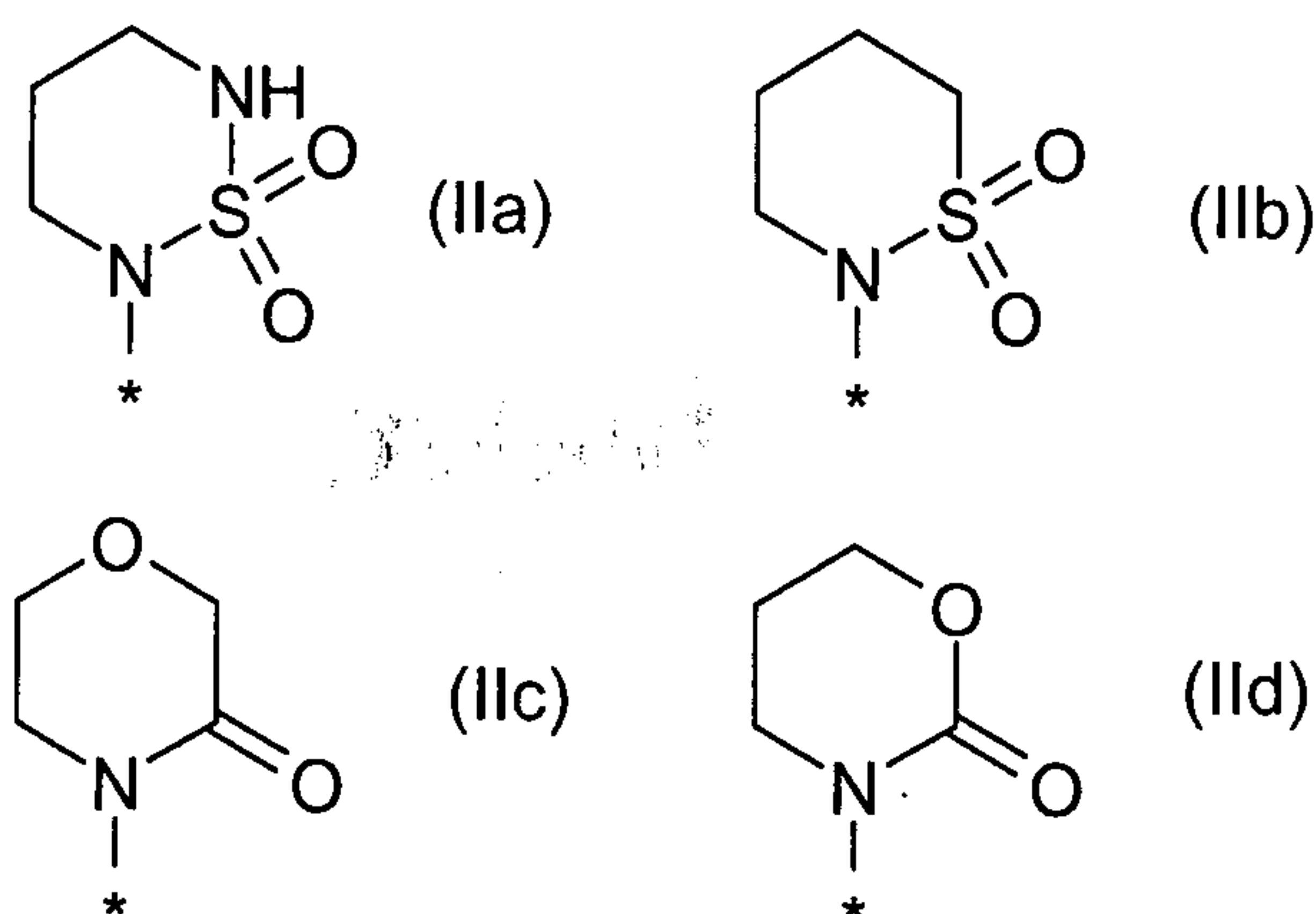
Also particularly preferred are those compounds wherein R^{10} is selected from among C_{1-6} -alkyl, heterocyclyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl and $(R^{12})_2N$, wherein by the above mentioned heteroaryl groups are meant 5- or 6-

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- membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, (R¹²)₂N- and (R¹²)₂N-C₁₋₃-alkyl, and R¹¹ is selected from among hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, phenyl, phenyl-C₁₋₃-alkyl, heteroaryl and heteroaryl-C₁₋₃-alkyl, while by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N- and (R¹²)₂N-C₁₋₃-alkyl.
- Also particularly preferred are compounds wherein R¹⁰ is selected from among C₁₋₄-alkyl, particularly methyl or ethyl, morpholinyl, piperidinyl, 4-methylpiperidinyl, pyrrolidinyl, phenyl, 4-fluorophenyl, benzyl, pyridyl- and (CH₃)₂N, wherein the above-mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine and bromine, and R¹¹ is selected from among hydrogen, methyl, ethyl, HF₂C, phenyl and 4-fluorophenyl, wherein the above-mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine and bromine.
- If R¹⁰ and R¹¹ together form an alkylene bridge, a C₂₋₆-alkylene bridge is preferred, so that a heterocyclic ring is formed with the inclusion of the nitrogen atoms linked to R¹¹ and the SO₂ or CO group linked to R¹⁰, while one or two -CH₂ groups of the C₂₋₆-alkylene bridge may be replaced independently of one another by O, S, SO, SO₂ or -N(R¹²)- such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and wherein the C atoms of the above mentioned C₂₋₆-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, F₃C, C₁₋₃-alkyl- and C₁₋₃-alkoxy.

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Particularly preferred are the heterocyclic rings of formulae (IIa), (IIb), (IIc) or (IId)



5

Particularly preferred are compounds of formula (I) wherein the group R^8 combined with the groups R^{10} and R^{11} forms heterocyclic rings of formulae (IIa), (IIb), (IIc) or (IIId) and the other groups and radicals are defined as above or hereinafter.

- 10 In the compounds of formula (I) according to the invention the group R^{12} is preferably in each case independently selected from among hydrogen and a C_{1-6} -alkyl group, while one or more hydrogen atoms of the C_{1-6} -alkyl group may be replaced by fluorine.

Particularly preferred groups R^{12} are in each case independently of one another
 15 hydrogen or a C_{1-6} -alkyl group.

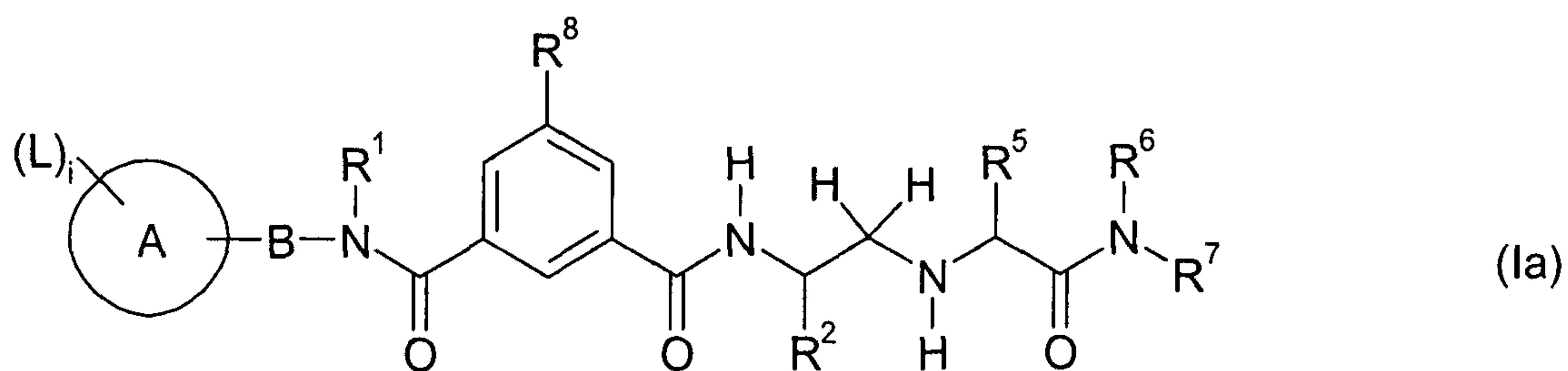
The most preferred groups R^{12} are in each case independently of one another hydrogen or a methyl group.

- 20 In the compounds of formula (I) according to the invention the group R^{13} is preferably each independently selected from among hydrogen and C_{1-3} -alkyl, while one or more hydrogen atoms of the C_{1-3} -alkyl group may be replaced by fluorine.

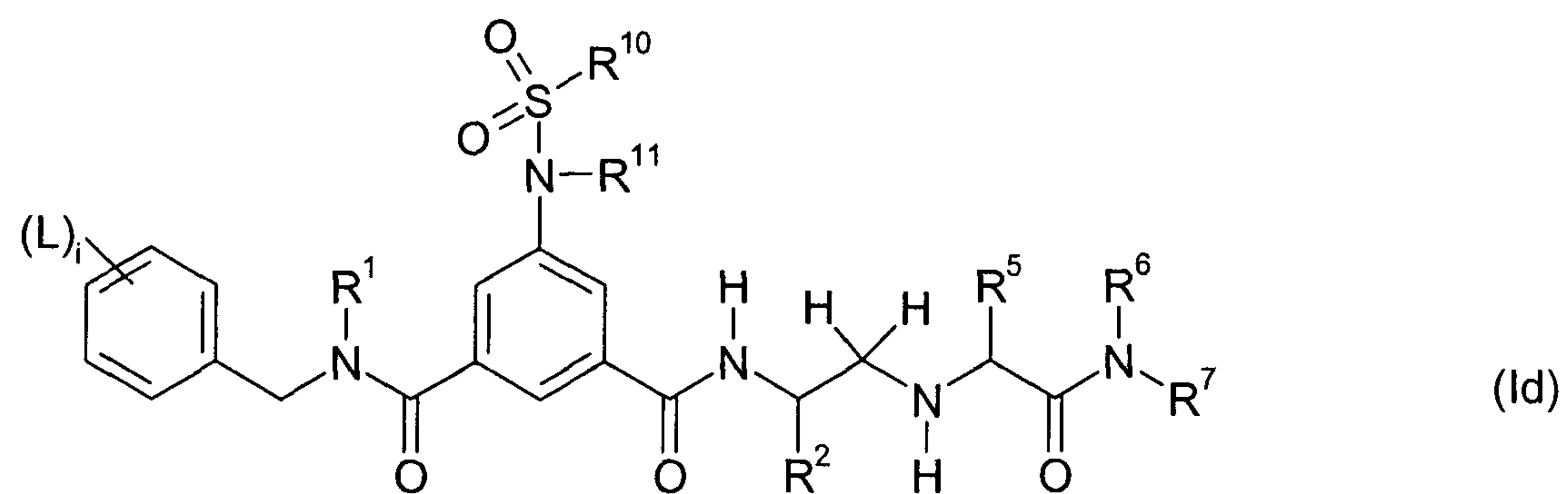
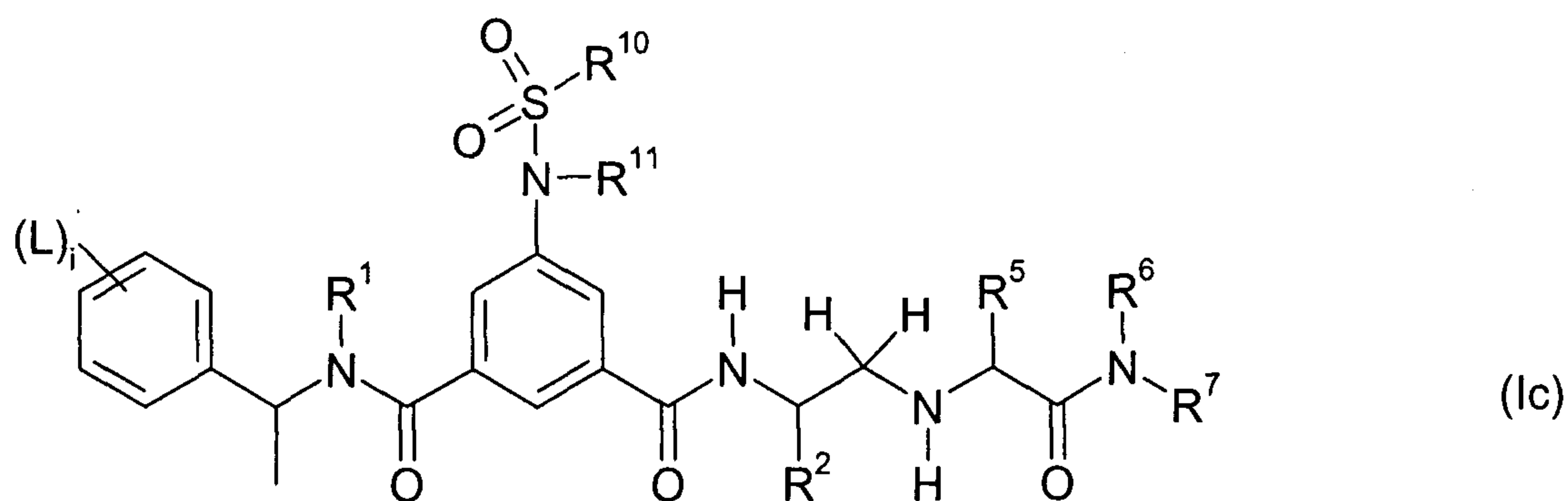
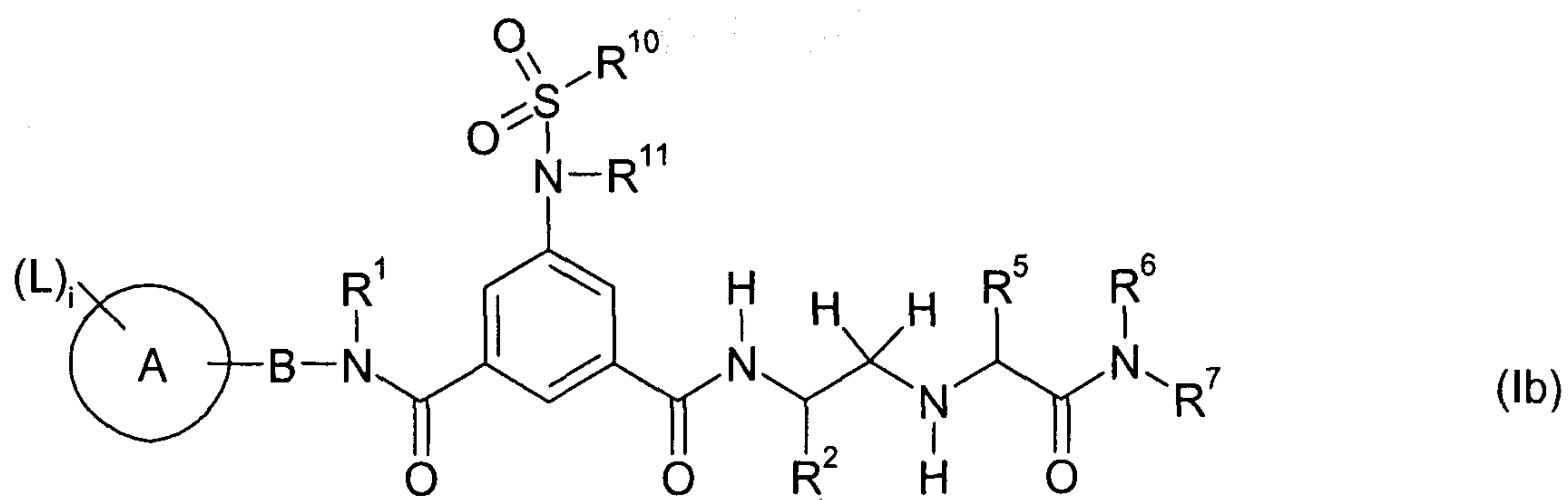
Particularly preferred groups R^{13} are in each case independently of one another
 25 hydrogen or a methyl group.

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Particularly preferred compounds according to the invention are listed in the following group of formulae (Ia), (Ib), (Ic), (Id), (Ie), (If) and (Ig):

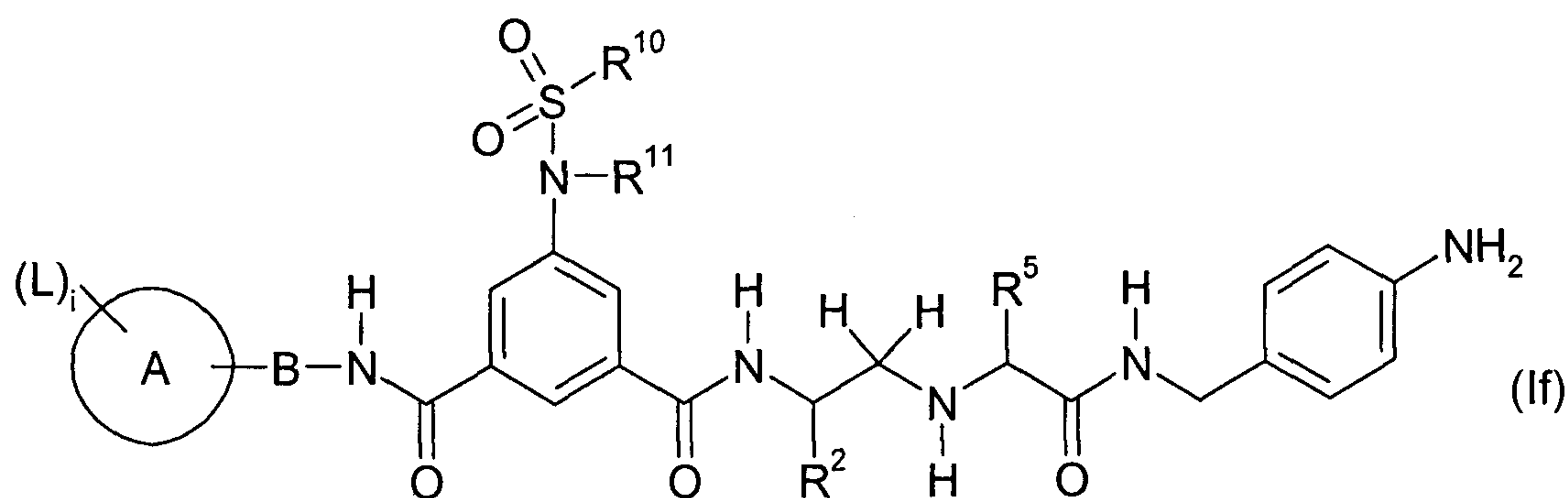
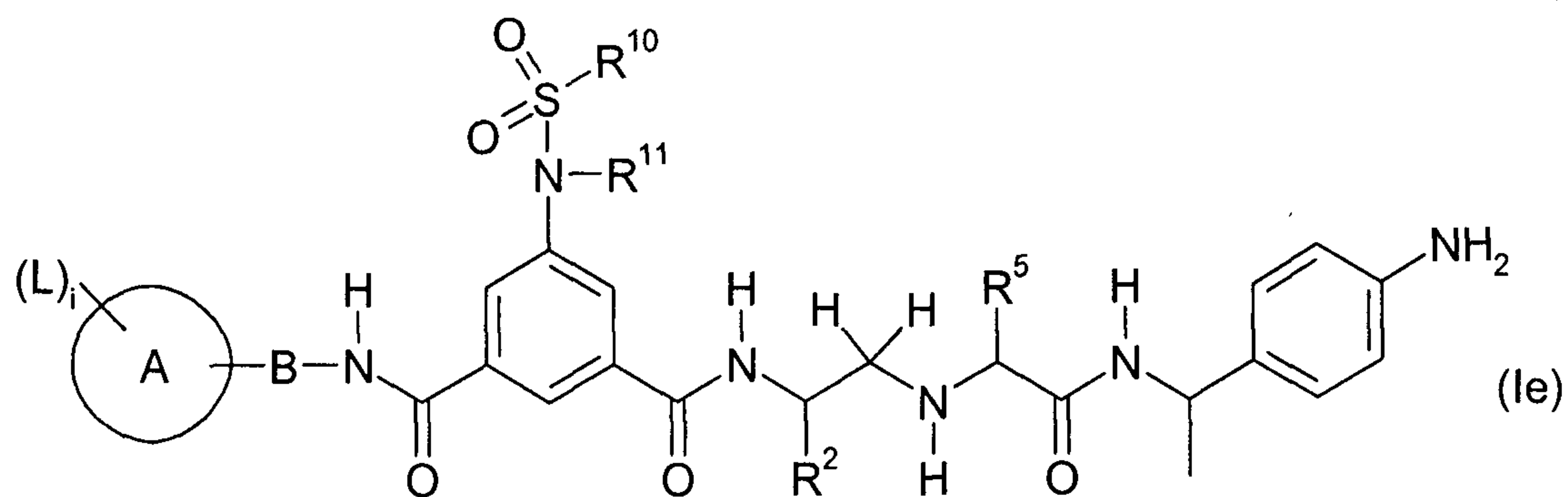


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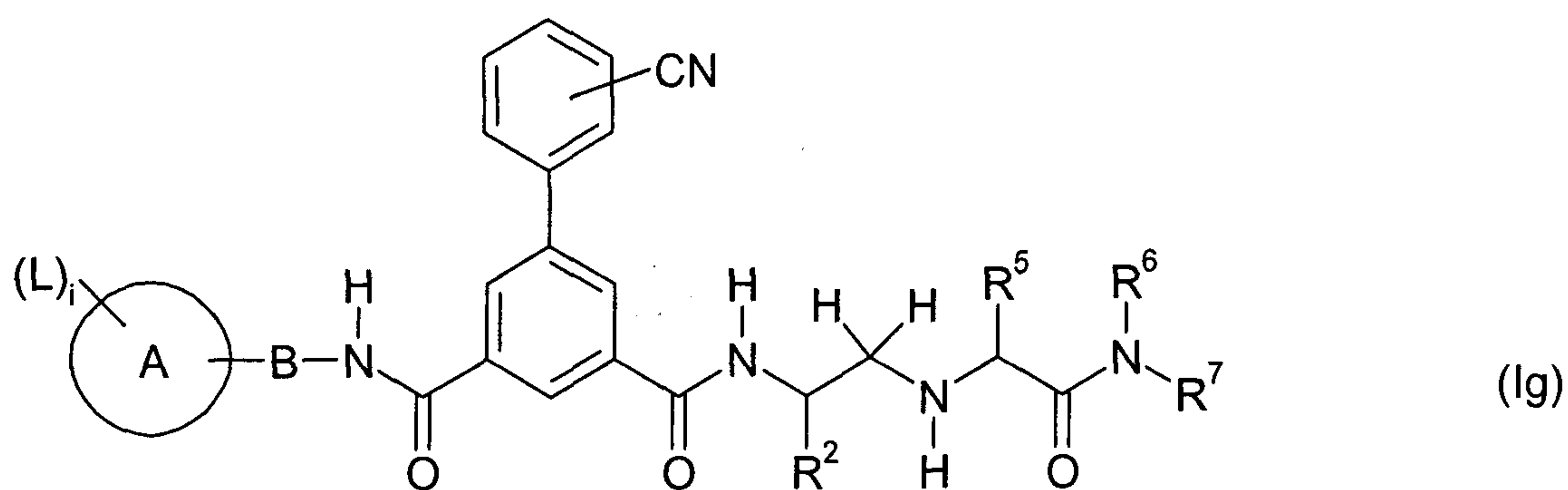


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5



wherein

10 A, B, L, i, R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{13} have the meanings given above.

Particularly preferred are compounds of formula (Ia) according to the invention,

*A(B)N(R1)C(=O)c1ccc(R8)cc1C(=O)NC(R2)C(R5)N(R6)C(=O)N(R7) (Ia)

5 A denotes phenyl or a 5- or 6-membered aromatic heteroaryl group which contains 1, 2 or 3 heteroatoms selected from N, O and S.

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, F_3C , HF_2C , FH_2C , C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, $(R^{12})_2N$, $(R^{12})_2N$ -CO, R^{12} -CO- $(R^{12})N$, $(R^{12})_2N$ -CO- $(R^{12})N$, $(R^{12})_2N$ -SO₂, R^{12} -SO₂- $(R^{12})N$ or C_{1-3} -alkyl-SO₂,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, F₃C, HF₂C, FH₂C, hydroxy-C₁₋₃-alkyl, C₁₋₃-alkyl, C₁₋₃-alkoxy, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl- and (R¹²)₂N-CO-, and

i denotes 0, 1 or 2.

B denotes a C₁₋₄-alkylene bridge, wherein the C₁₋₄-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, cyano, nitro, F₃C, HF₂C, FH₂C, C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, R¹³-O, (R¹²)₂N-SO₂- and (R¹²)₂N-, and

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wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together forming a C₃₋₇-cycloalkyl group, and

wherein the above mentioned groups and the C₃₋₇-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, F₃C, C₁₋₃-alkyl, C₁₋₃-alkoxy- and R¹³-O-C₁₋₃-alkyl,

10 R¹ denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from
15 among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, F₃C, C₁₋₃-alkyl, C₁₋₃-alkoxy- and hydroxy-C₁₋₃-alkyl,

 R² denotes C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkyl-S-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl,
20 heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from
25 among fluorine, chlorine, bromine, iodine, F₃C, HF₂C, FH₂C, hydroxy, carboxy, cyano, nitro, C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-SO₂, R¹²-CO-(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹³-O- and R¹³-O-C₁₋₃-alkyl,

 R⁵ denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₃-alkyl,
30 heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, or heteroaryl-C₁₋₃-alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from

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among fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkyl-S, aryl, heteroaryl, heteroaryl-C₁₋₃-alkyl, aryl-C₁₋₃-alkyl, (R¹²)₂N-SO₂, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl- and (R¹²)₂N-CO-,

5 R⁶ denotes C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N-aryl, (R¹²)₂N-aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl,
 10 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, C₁₋₃-alkyl, C₃₋₇-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-N(R¹²), (R¹²)₂N-SO₂, R¹²-SO₂-(R¹²)N, R¹³-O- and R¹³-O-C₁₋₃-alkyl,

15 R⁷ denotes hydrogen or C₁₋₄-alkyl,
 while one or more hydrogen atoms of the C₁₋₄-alkyl group may be replaced by fluorine,

20 R⁸ denotes hydrogen, fluorine, chlorine, bromine, cyano, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, C₃₋₇-cycloalkenyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, R¹⁰-SO₂-(R¹¹)N or R¹⁰-CO-(R¹¹)N,

25 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among C₁₋₆-alkyl, fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, C₃₋₇-cycloalkyl, heterocyclyl, (R¹²)₂N, (R¹²)₂N-CO, R¹³-CO, R¹³-O-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, (R¹²)₂N-SO₂, (R¹²)₂N-SO₂-(R¹²)N, R¹²-SO₂, R¹³-O, C₁₋₄-alkyl-S, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O, FH₂C-O- and R¹²-SO₂-(R¹²)N-, and
 30

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R^{10} denotes C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl or $(R^{12})_2N$,

5 wherein the above mentioned groups may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, R^{12} -CO(R^{12})N, R^{12} -SO₂(R^{12})N, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl- and $(R^{12})_2N$ -CO-,

10

R^{11} denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl,

15

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl, or

20

R^{10} and R^{11} together form a C_{2-6} -alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atom linked to R^{11} and the SO₂- or CO group linked to R^{10} ,

25

while one or two -CH₂ groups of the C_{2-6} -alkylene bridge may be replaced independently of one another by O, S, SO, SO₂ or

-N(R^{12})- such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and

30

wherein the C atoms of the above mentioned C_{2-6} -alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, F₃C, C_{1-3} -alkyl- and C_{1-3} -alkoxy.

R^{12} in each case independently of one another denote hydrogen or a C_{1-6} -alkyl group

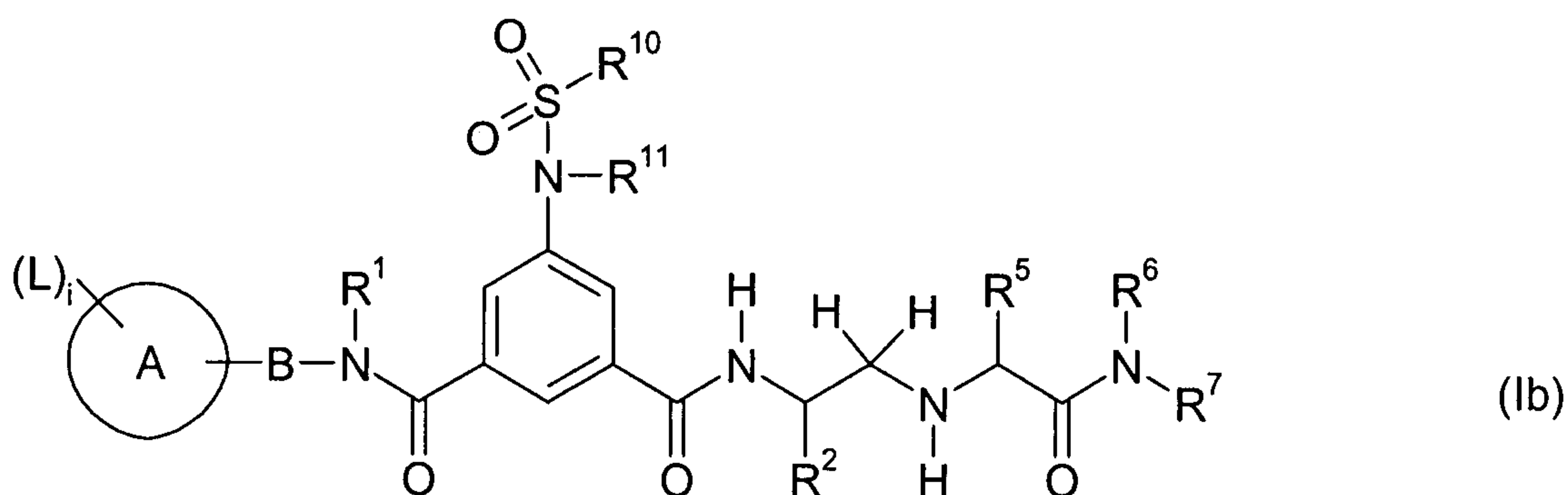
- 34 -

while one or more hydrogen atoms of the C₁₋₆-alkyl group may be replaced by fluorine,

R¹³ in each case independently of one another denote hydrogen or a C₁₋₃-alkyl group

while one or more hydrogen atoms of the C₁₋₃-alkyl group may be replaced by fluorine.

Also particularly preferred are compounds of formula (Ib) according to the invention,



wherein

A denotes phenyl or a 5- or 6-membered aromatic heteroaryl group which contains 1, 2 or 3 heteroatoms selected from N, O and S,

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, cyano, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, phenyl, (R¹²)₂N, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, R¹²-SO₂-(R¹²)N or (R¹²)₂N-SO₂, wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms, and

i denotes 0, 1 or 2,

B denotes a C₁₋₄-alkylene bridge,

– 35 –

wherein the C₁₋₄-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, C₁₋₄-alkyl, phenyl or benzyl, and

wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together, forming a C₃₋₆-cycloalkyl group, and

wherein the above mentioned groups and the C₃₋₆-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C₁₋₃-alkoxy,

R¹ denotes hydrogen, C₁₋₄-alkyl, C₃₋₄-alkenyl, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C₁₋₃-alkoxy,

R² denotes C₁₋₆-alkyl, C₂₋₆-alkynyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, heterocyclyl-C₁₋₃-alkyl, phenyl, phenyl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, C₁₋₃-alkyl-, F₃C, HF₂C, FH₂C, H₂N- and C₁₋₃-alkoxy,

R⁵ denotes C₁₋₆-alkyl, cyclopropyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl or phenyl-C₁₋₃-alkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, carboxy, C₁₋₄-alkyl, C₁₋₄-alkoxy- and (R¹²)₂N-,

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R^6 denotes C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ -phenyl, $(R^{12})_2N$ -phenyl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl,

wherein by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, carboxy, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-3} -alkoxy- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, C_{3-5} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl, $(R^{12})_2N$ -CO, $(R^{12})_2N$ -CO-N(R^{12}), R^{12} -CO-(R^{12})N- and $(R^{12})_2N$ -SO₂-,

R^7 denotes hydrogen or C_{1-4} -alkyl,

while one or more hydrogen atoms of the C_{1-4} -alkyl group may be replaced by fluorine,

R^{10} denotes C_{1-6} -alkyl, heterocyclyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl or $(R^{12})_2N$,

wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl,

R^{11} denotes hydrogen, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl,

while by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

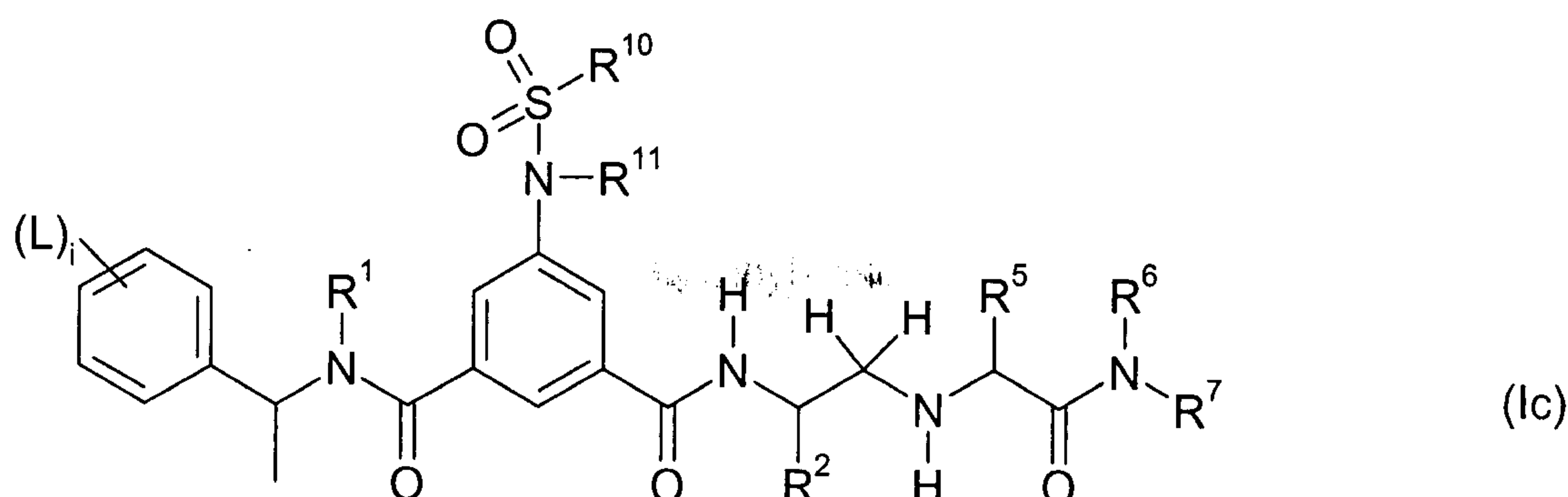
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wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N- and (R¹²)₂N-C₁₋₃-alkyl, or

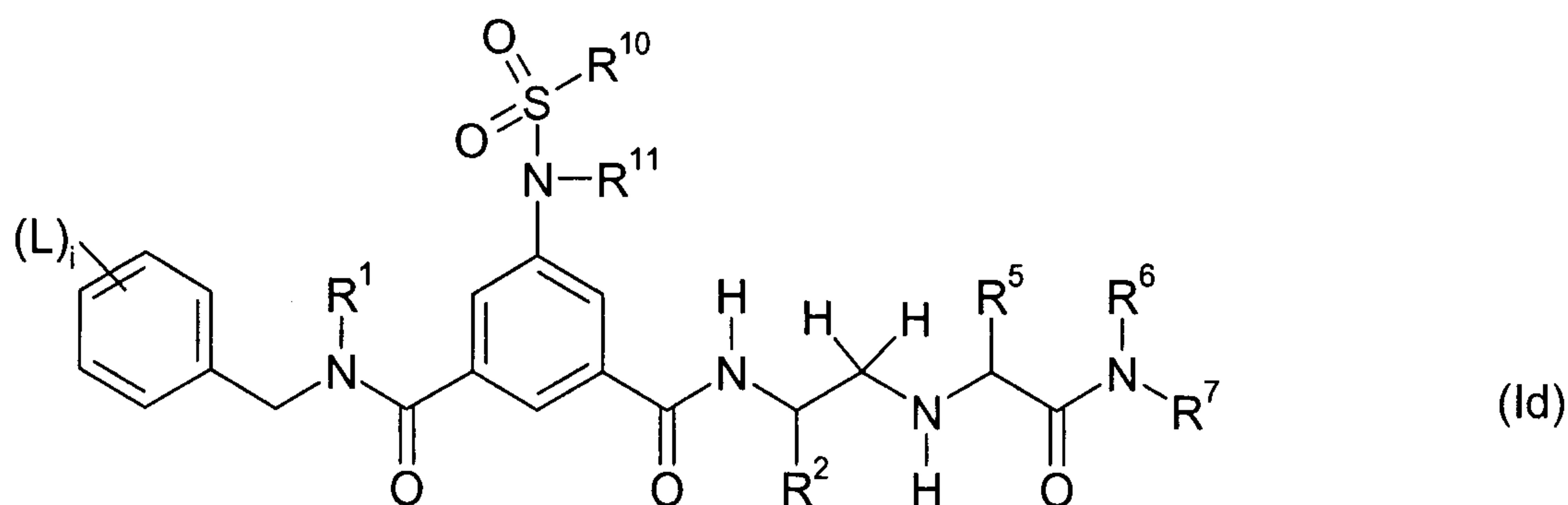
R¹⁰ and R¹¹ together form a C₂₋₆-alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atom linked to R¹¹ and the SO₂- or CO group linked to R¹⁰, while one or two -CH₂ groups of the C₂₋₆-alkylene bridge may be replaced independently of one another by O, S, SO, SO₂ or -N(R¹²)- such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and wherein the C atoms of the above mentioned C₂₋₆-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, F₃C, C₁₋₃-alkyl- and C₁₋₃-alkoxy.

R¹² in each case independently of one another denote hydrogen or a C₁₋₆-alkyl group while one or more hydrogen atoms of the C₁₋₆-alkyl group may be replaced by fluorine.

Also particularly preferred are compounds according to the invention of formulae (Ic) and (1d),



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wherein

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, cyano, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, phenyl, (R¹²)₂N, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, R¹²-SO₂-(R¹²)N or (R¹²)₂N-SO₂,

wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms, and

i denotes 0, 1 or 2,

R¹ denotes hydrogen, C₁₋₄-alkyl, C₃₋₄-alkenyl, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C₁₋₃-alkoxy,

R² denotes C₁₋₆-alkyl, C₂₋₆-alkynyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, heterocyclyl-C₁₋₃-alkyl, phenyl, phenyl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, C₁₋₃-alkyl-, F₃C, HF₂C, FH₂C, H₂N- and C₁₋₃-alkoxy,

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R^5 denotes C_{1-6} -alkyl, cyclopropyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl or phenyl- C_{1-3} -alkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, carboxy, C_{1-4} -alkyl, C_{1-4} -alkoxy- and $(R^{12})_2N$ -,

R^6 denotes C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ -phenyl, $(R^{12})_2N$ -phenyl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl,

wherein by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, carboxy, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-3} -alkoxy- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, C_{3-5} -cycloalkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl, $(R^{12})_2N$ -CO, $(R^{12})_2N$ -CO-N(R^{12}), R^{12} -CO-(R^{12})N- and $(R^{12})_2N$ -SO₂-,

R^7 denotes hydrogen or C_{1-4} -alkyl, while one or more hydrogen atoms of the C_{1-4} -alkyl group may be replaced by fluorine,

R^{10} denotes C_{1-6} -alkyl, heterocyclyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl or $(R^{12})_2N$,

wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, $(R^{12})_2N$ - and $(R^{12})_2N$ - C_{1-3} -alkyl,

- 40 -

R¹¹ denotes hydrogen, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, phenyl, phenyl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl,

5 while by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

10 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N- and (R¹²)₂N-C₁₋₃-alkyl, or

15 R¹⁰ and R¹¹ together form a C₂₋₆-alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atom linked to R¹¹ and the SO₂- or CO group linked to R¹⁰,

20 while one or two -CH₂ groups of the C₂₋₆-alkylene bridge may be replaced independently of one another by O, S, SO, SO₂ or -N(R¹²)- such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and wherein the C atoms of the above mentioned C₂₋₆-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, F₃C, C₁₋₃-alkyl- and C₁₋₃-alkoxy.

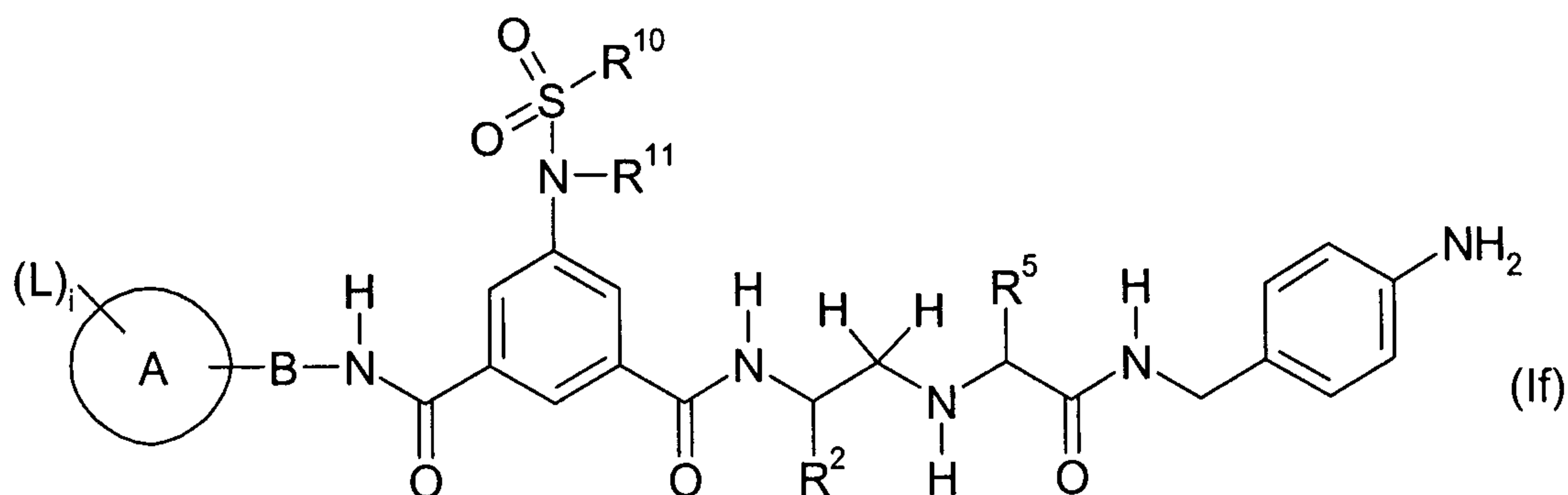
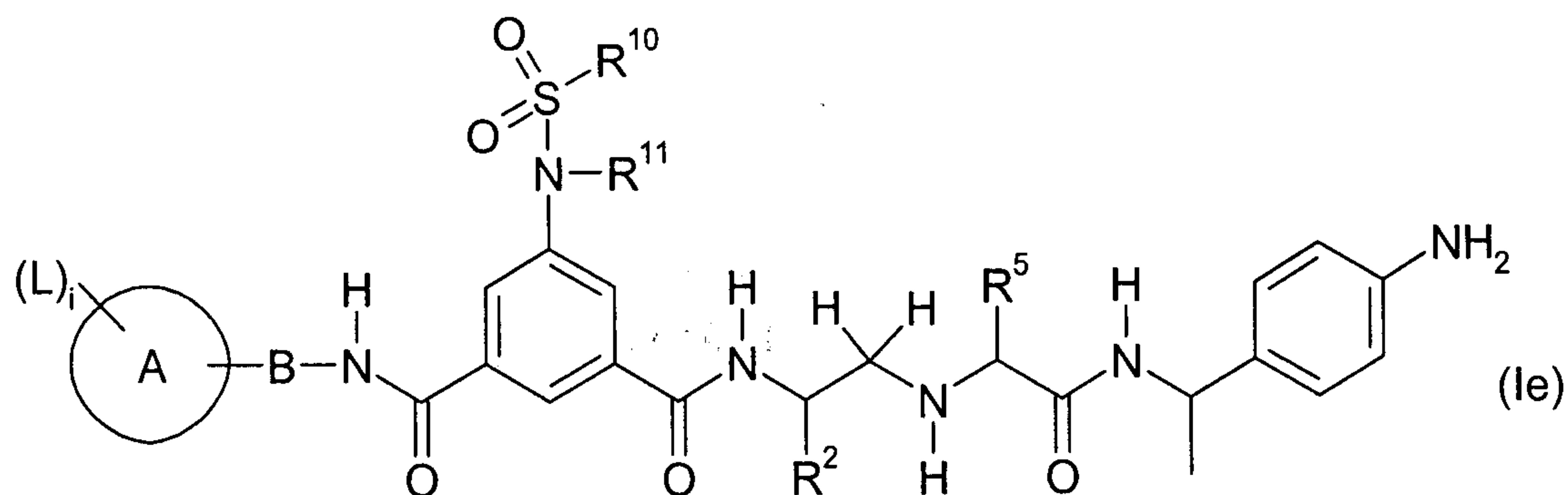
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R¹² in each case independently of one another denote hydrogen or a C₁₋₆-alkyl group while one or more hydrogen atoms of the C₁₋₆-alkyl group may be replaced by fluorine.

30

Also particularly preferred are compounds according to the invention of formula (Ie) and (If),

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5 wherein

A denotes phenyl, thienyl, thiazolyl, pyrazolyl or pyridyl

10 L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy, wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms, and

i denotes 0, 1 or 2, preferably 0 or 1

15

B denotes a C₁₋₂-alkylene bridge, wherein the C₁₋₂-alkylene bridge may optionally be substituted by one or more C₁₋₄-alkyl groups, and wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₂-alkylene bridge may be joined together, forming a cyclopropyl group, and

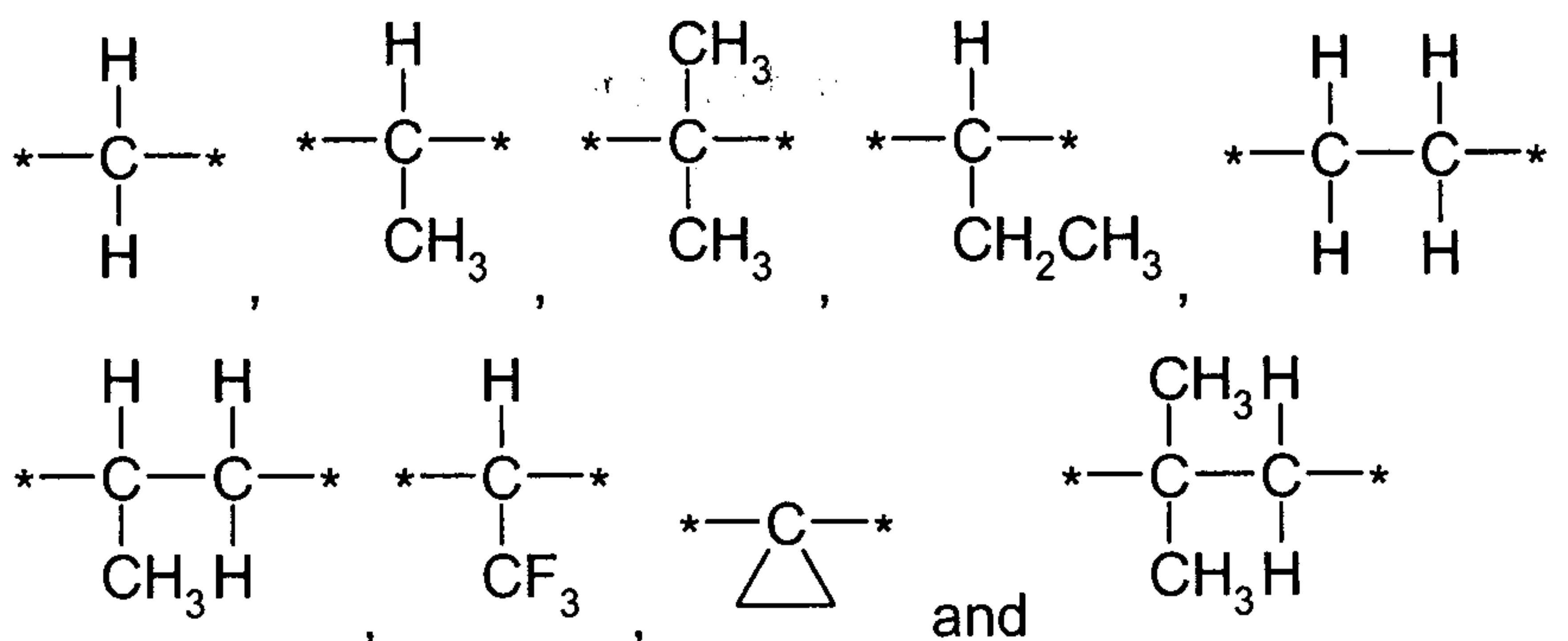
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wherein one or more hydrogen atoms of the above mentioned C₁₋₂-alkylene bridge and/or of the C₁₋₄-alkyl groups and/or of the cyclopropyl group formed therefrom may optionally be replaced by one or more fluorine atoms,

5 or, in a preferred embodiment,

B is selected from among



10 wherein one or more hydrogen atoms may optionally be replaced by fluorine,

R² denotes n-propyl, n-butyl, 2-propynyl, 2-butyryl, cyclohexylmethyl, cyclopentylmethyl, phenylmethyl, 2-phenylethyl, pyridylmethyl, particularly 2-pyridylmethyl, furanylme-
 15 thyl, thienylmethyl or thiazolylmethyl,

wherein the above mentioned propyl, butyl, propynyl, butynyl, cyclohexylmethyl and cyclopentylmethyl groups may optionally be substituted by one or more fluorine atoms and the phenylmethyl, 2-phenylethyl, pyridylmethyl, furanylme-
 20 thyl, thienylmethyl or thiazolylmethyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, methyl, F₃C, HF₂C, FH₂C- and H₂N-,

25 R⁵ denotes C₁₋₄-alkyl or cyclopropyl, while one or more hydrogen atoms of the above mentioned groups may optionally be replaced by fluorine atoms,

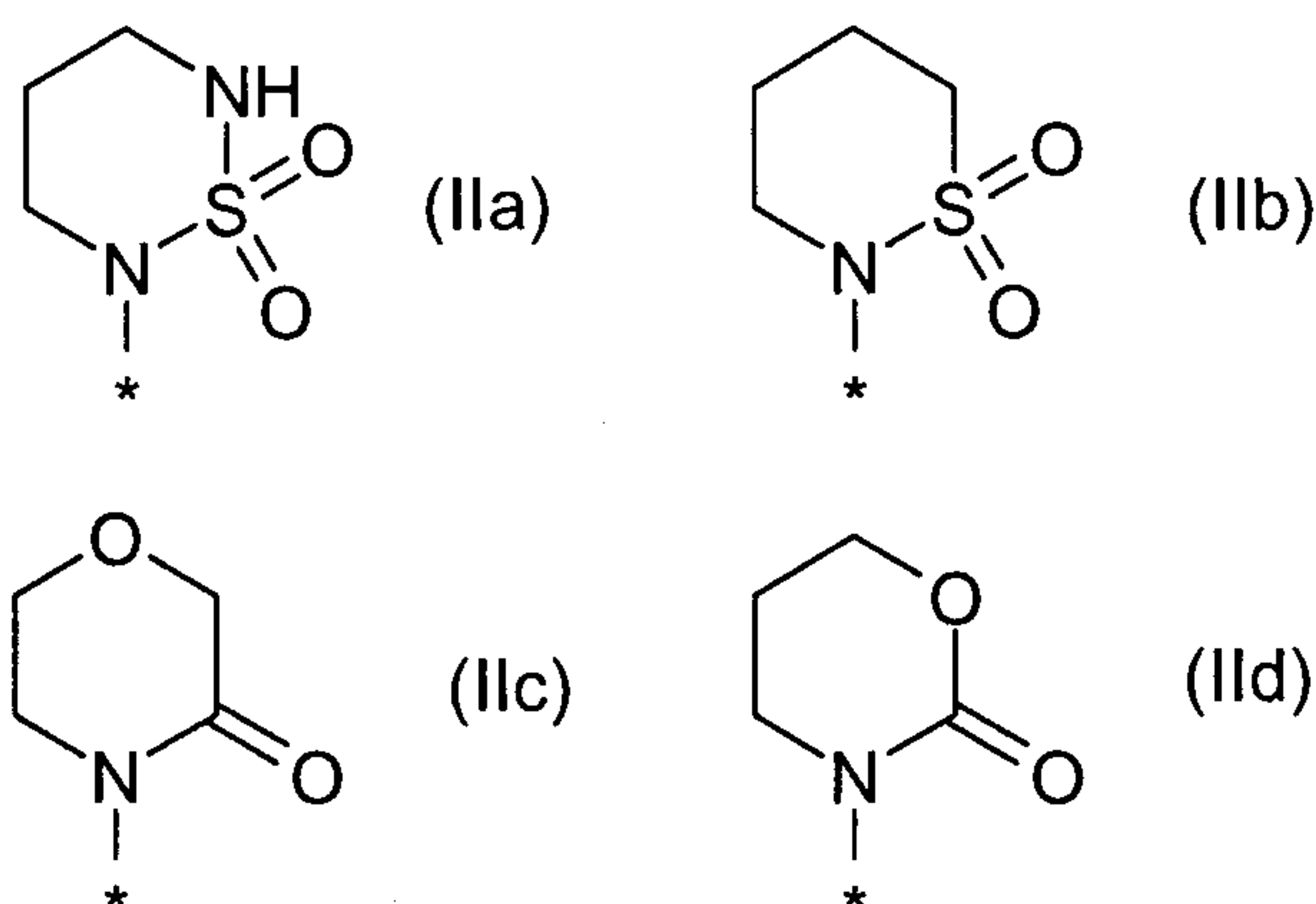
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R^{10} denotes C_{1-4} -alkyl, particularly methyl, or ethyl, morpholinyl, piperidinyl, 4-methylpiperidinyl, pyrrolidinyl, phenyl, 4-fluorophenyl, benzyl, pyridyl or $(CH_3)_2N$,

5 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine and bromine,

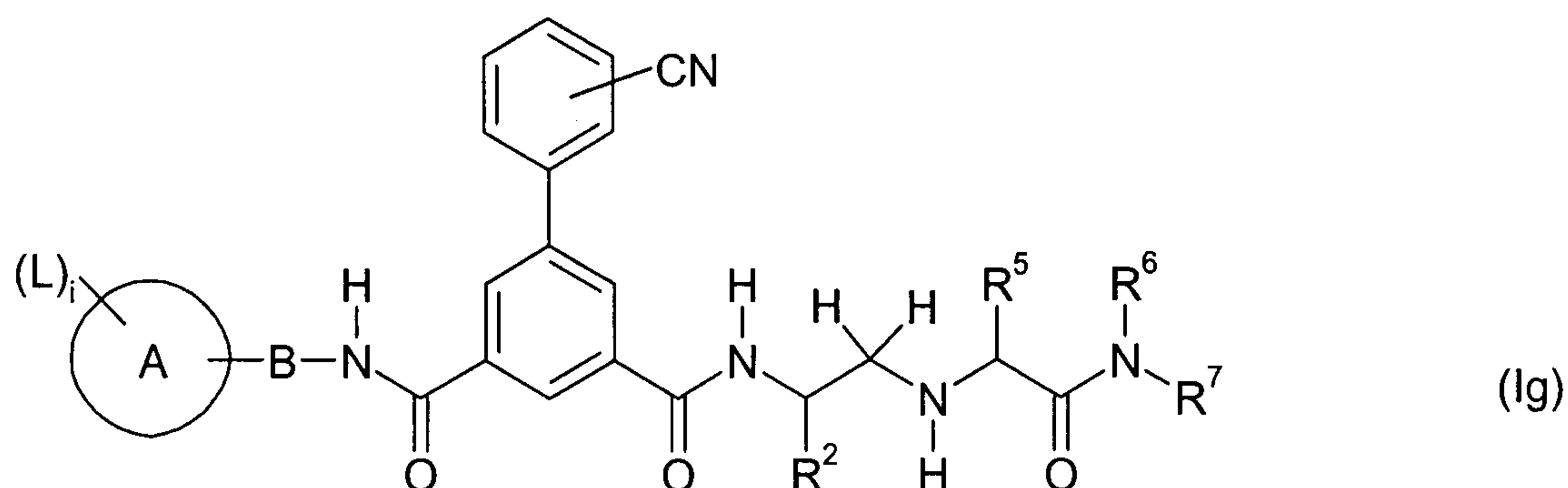
R^{11} denotes hydrogen, methyl, HF_2C , ethyl, phenyl or 4-fluorophenyl, wherein the above mentioned groups may optionally be substituted
10 independently of one another by one or more groups selected from among fluorine, chlorine and bromine, or

R^{10} and R^{11} with the inclusion of the nitrogen atom bound to R^{11} and the SO_2 - or CO group bound to R^{10} , together form a heterocyclic ring of
15 formulae (IIa), (IIb), (IIc) or (IId)



20 Also particularly preferred are compounds of formula (Ig) according to the invention,

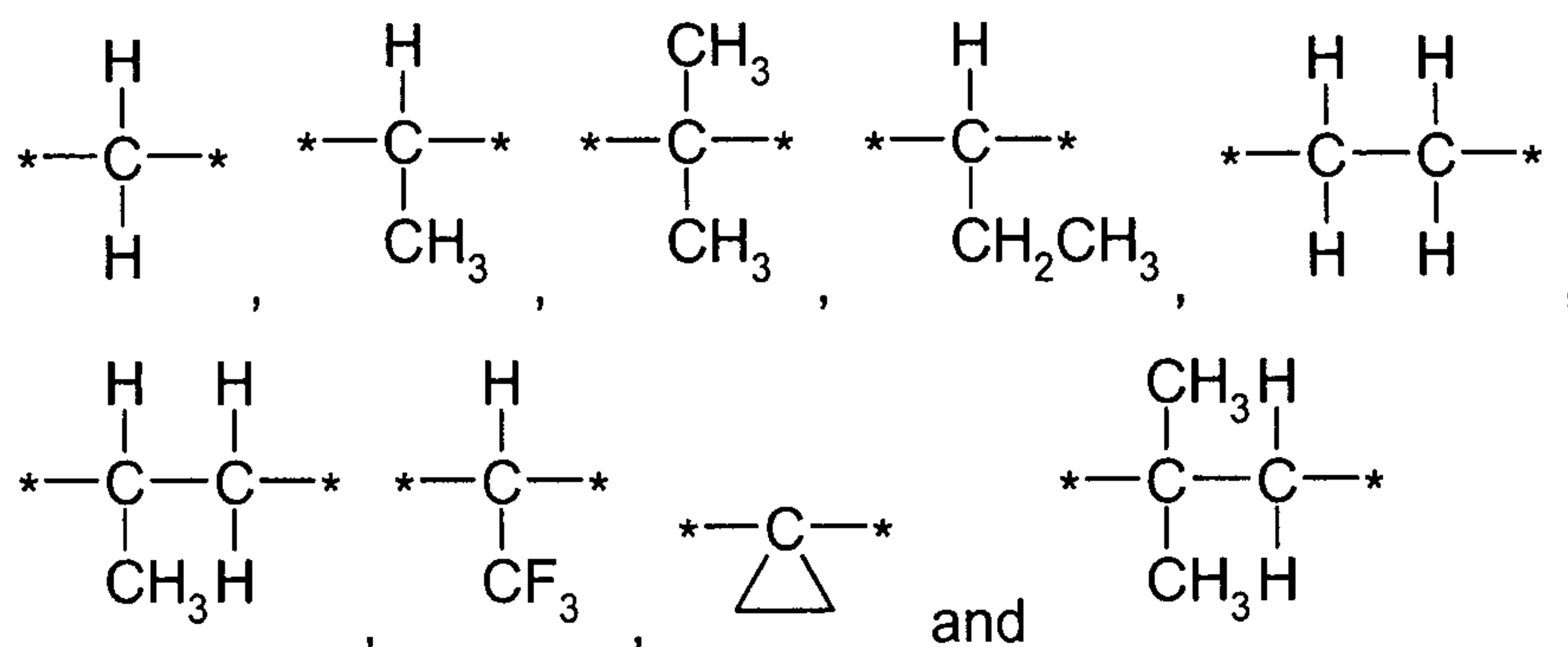
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wherein

- 5 A denotes phenyl, thienyl, thiazolyl, pyrazolyl or pyridyl
- L in each case independently of one another denote hydrogen, fluorine,
 chlorine, bromine, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy,
 wherein the above mentioned groups may optionally be substituted by
10 one or more fluorine atoms, and
- i denotes 0, 1 or 2, preferably 0 or 1
- B denotes a C₁₋₂-alkylene bridge,
15 wherein the C₁₋₂-alkylene bridge may optionally be substituted by one or
 more C₁₋₄-alkyl groups, and
 wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the
 C₁₋₂-alkylene bridge may be joined together, forming a cyclopropyl
 group, and
20 wherein one or more hydrogen atoms of the above mentioned C₁₋₂-
 alkylene bridge and/or of the C₁₋₄-alkyl groups and/or of the cyclopropyl
 group formed therefrom may optionally be replaced by one or more
 fluorine atoms,
- 25 or, in a preferred embodiment,
- B is selected from among

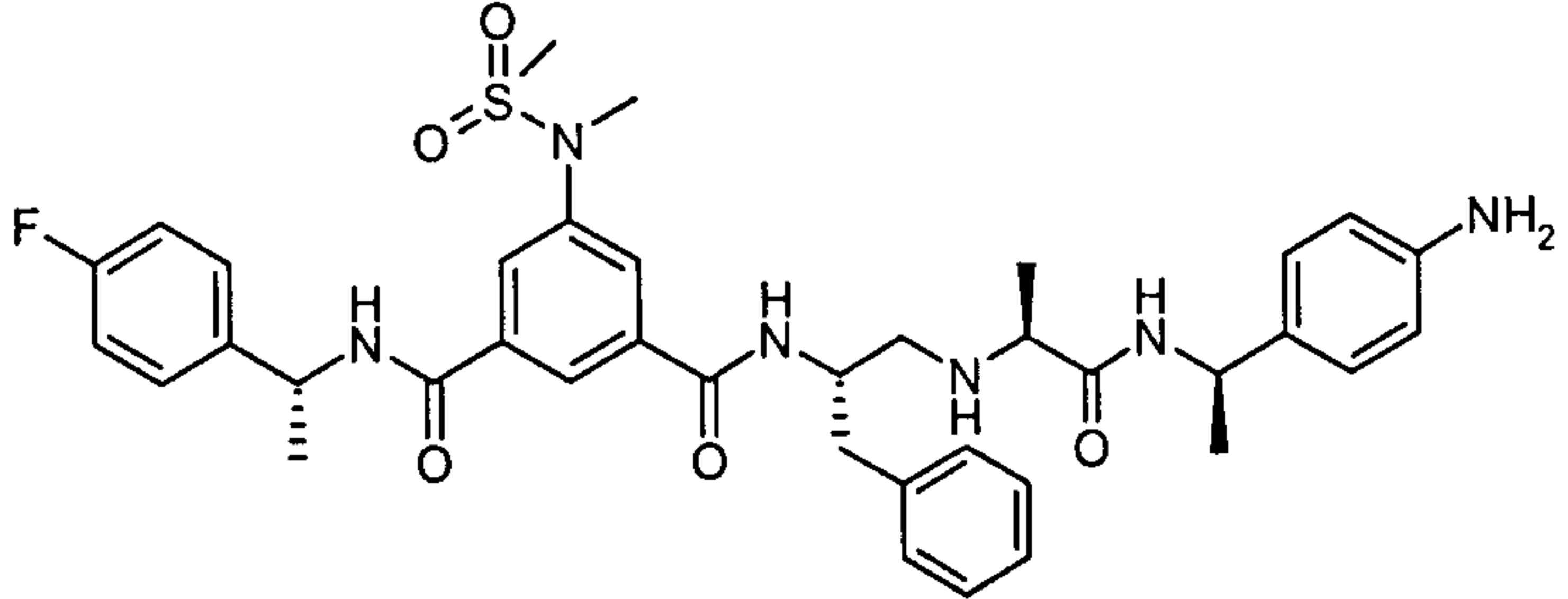
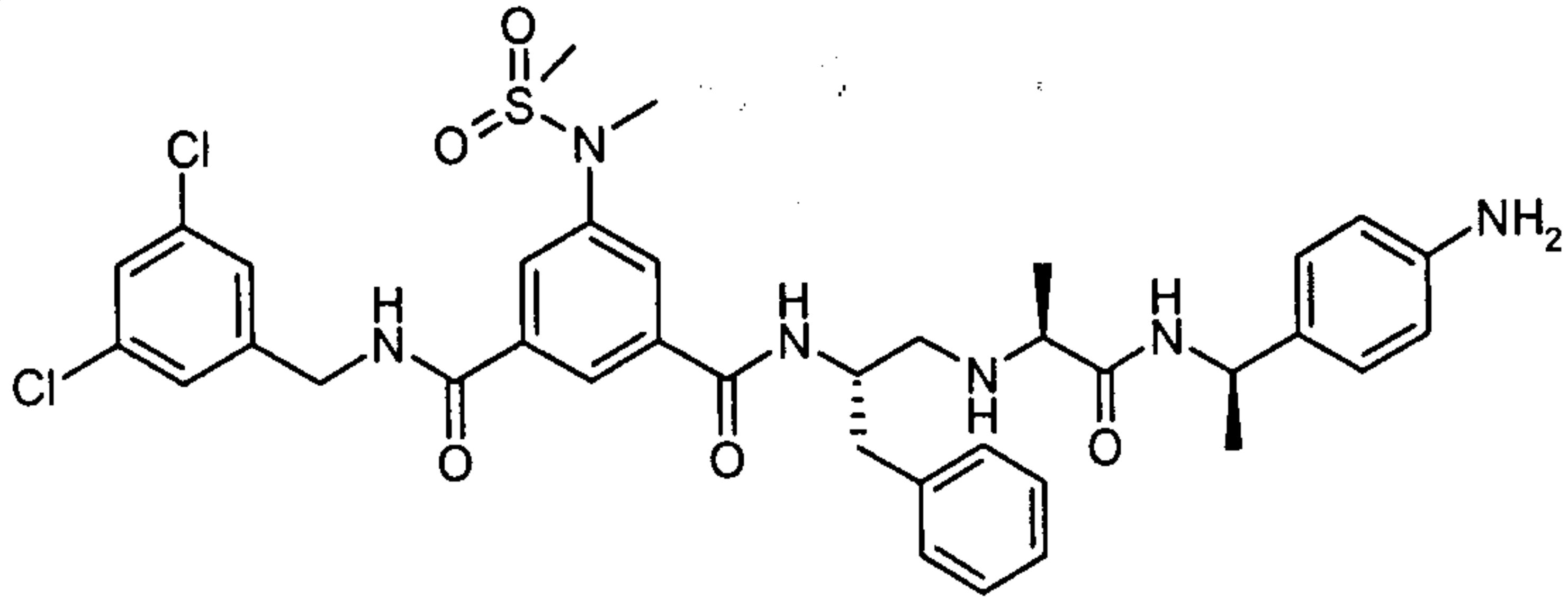
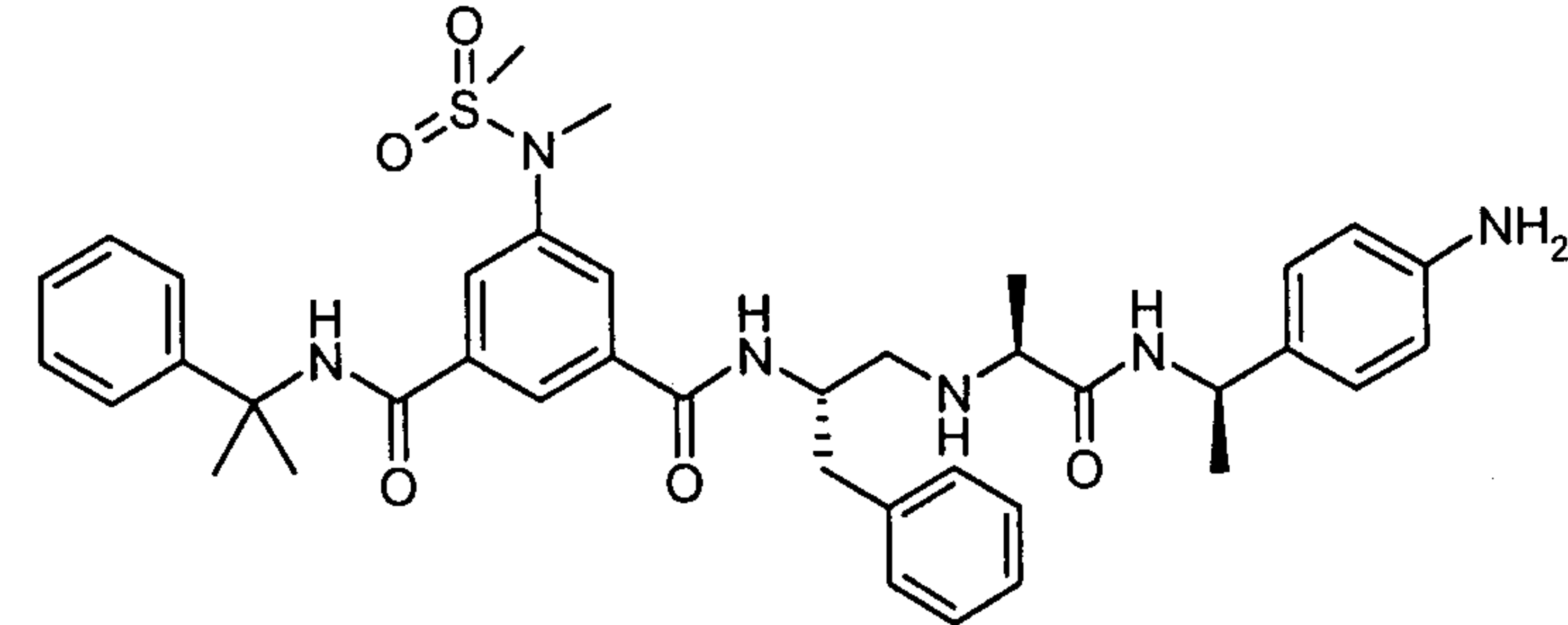
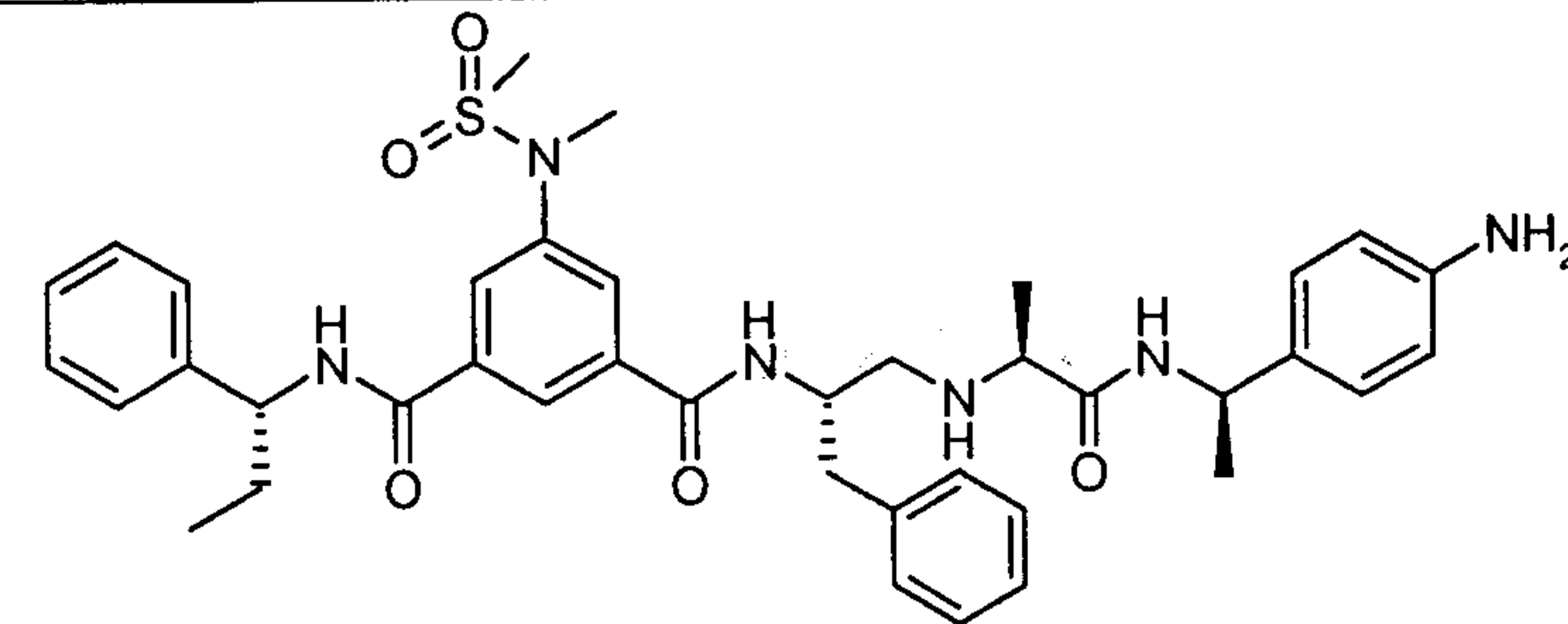
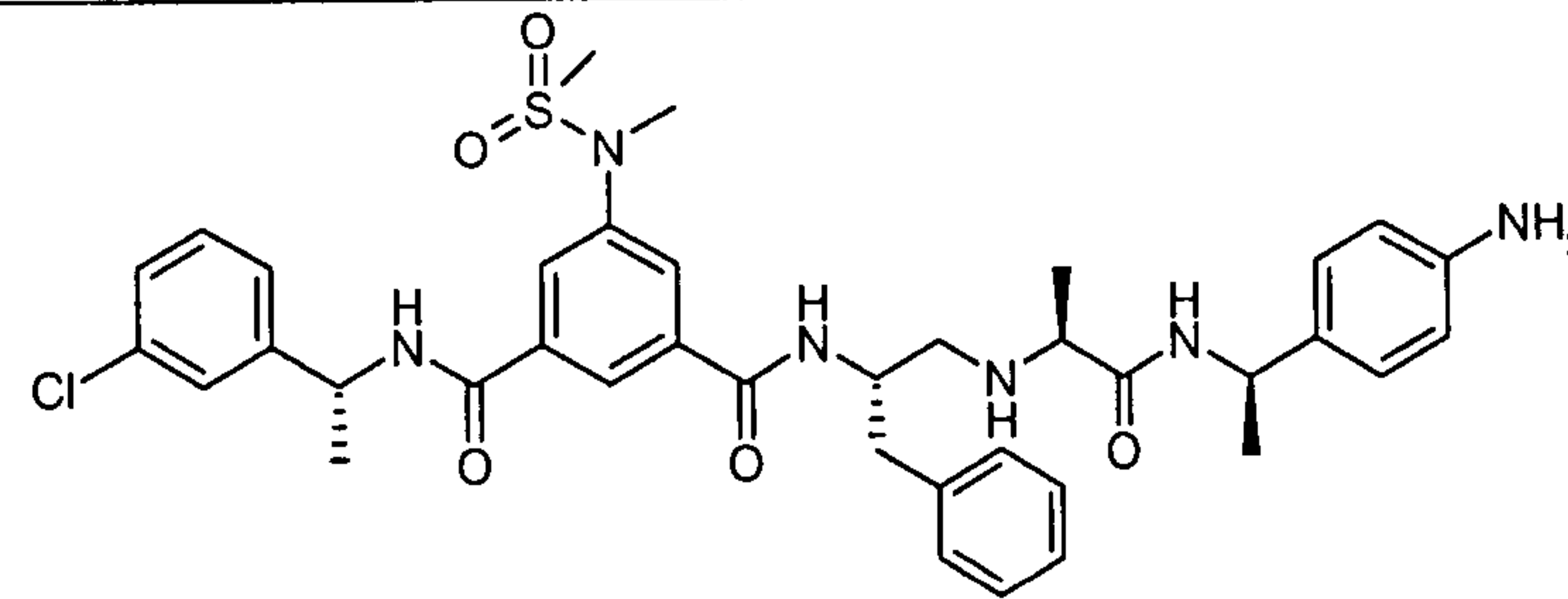
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wherein one or more hydrogen atoms may optionally be replaced by fluorine,

- 5 R^2 denotes n-propyl, n-butyl, 2-propynyl, 2-butyryl, cyclohexylmethyl, cyclopentylmethyl, phenylmethyl, 2-phenylethyl, pyridylmethyl, particularly 2-pyridylmethyl, furanylmehtyl, thienylmethyl or thiazolylmethyl,
- 10 wherein the above mentioned propyl, butyl, propynyl, butynyl, cyclohexylmethyl- and cyclopentylmethyl groups may optionally be substituted by one or more fluorine atoms and the phenylmethyl, 2-phenylethyl, pyridylmethyl, furanylmehtyl, thienylmethyl or thiazolylmethyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine,
- 15 methyl, F_3C , HF_2C , FH_2C - and H_2N -,
- 20 R^5 denotes C_{1-4} -alkyl or cyclopropyl, while one or more hydrogen atoms of the above mentioned groups may optionally be replaced by fluorine atoms,
- 25 R^6 denotes 4-aminobenzyl, cyclobutylmethyl, 2-cyclopropylethyl or cyclopropylmethyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine and C_{1-3} -alkyl, particularly preferably by methyl,
- 30 R^7 denotes hydrogen or C_{1-4} -alkyl, while one or more hydrogen atoms of the C_{1-4} -alkyl group may be replaced by fluorine.

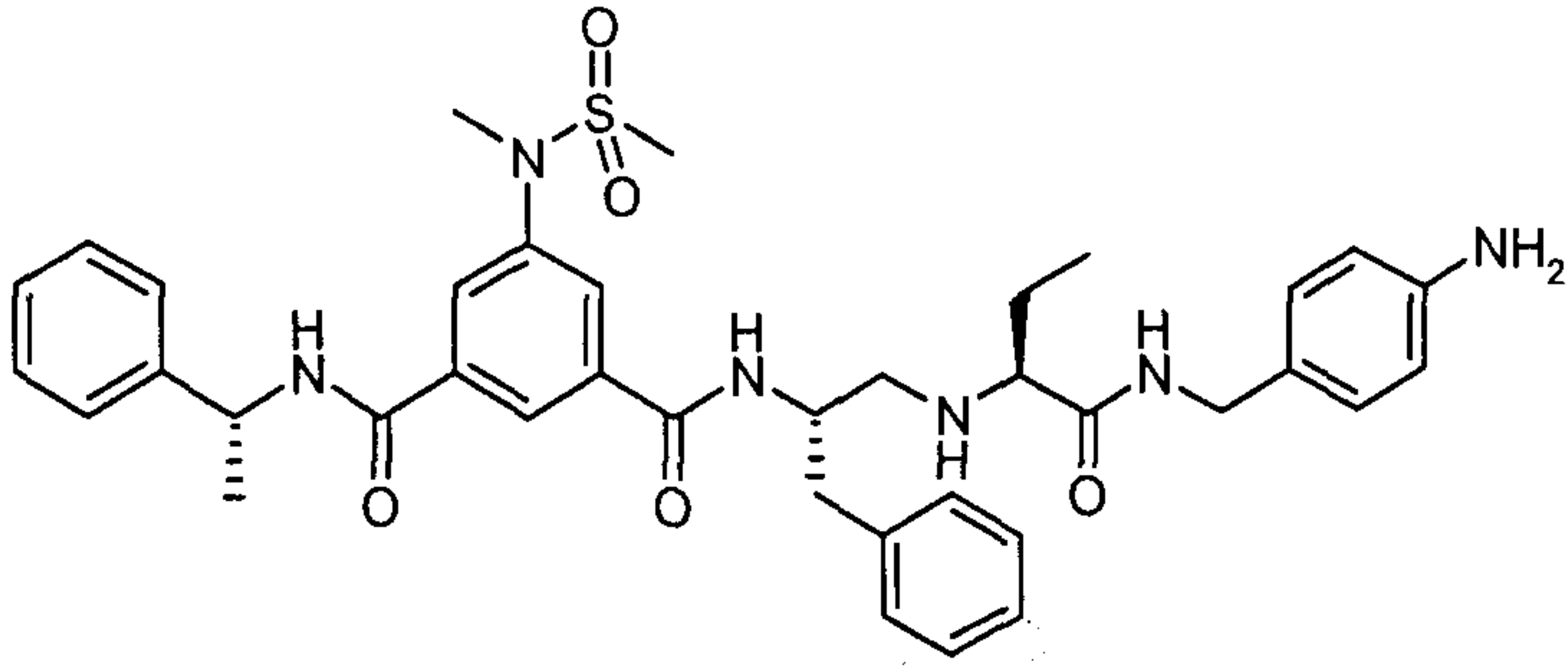
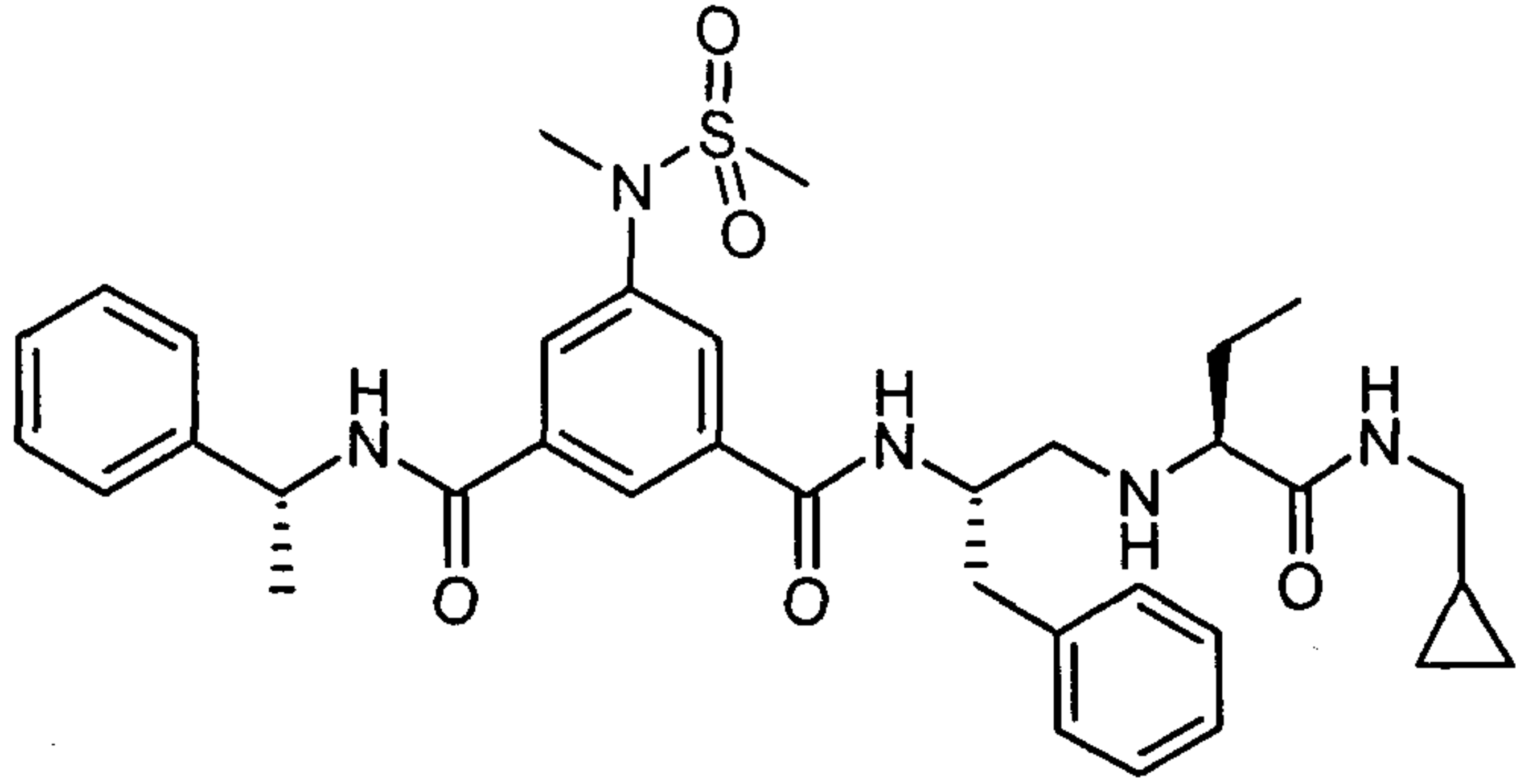
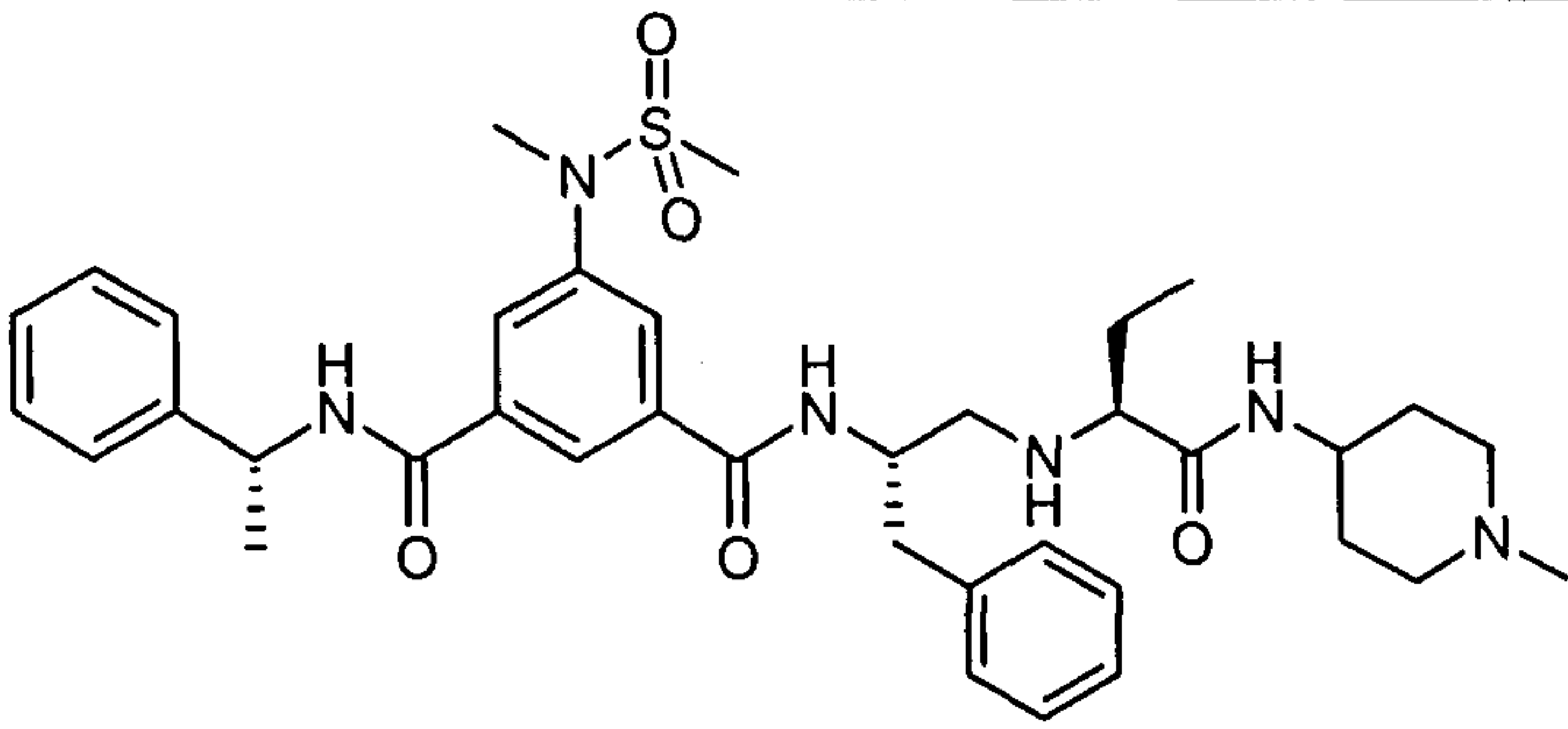
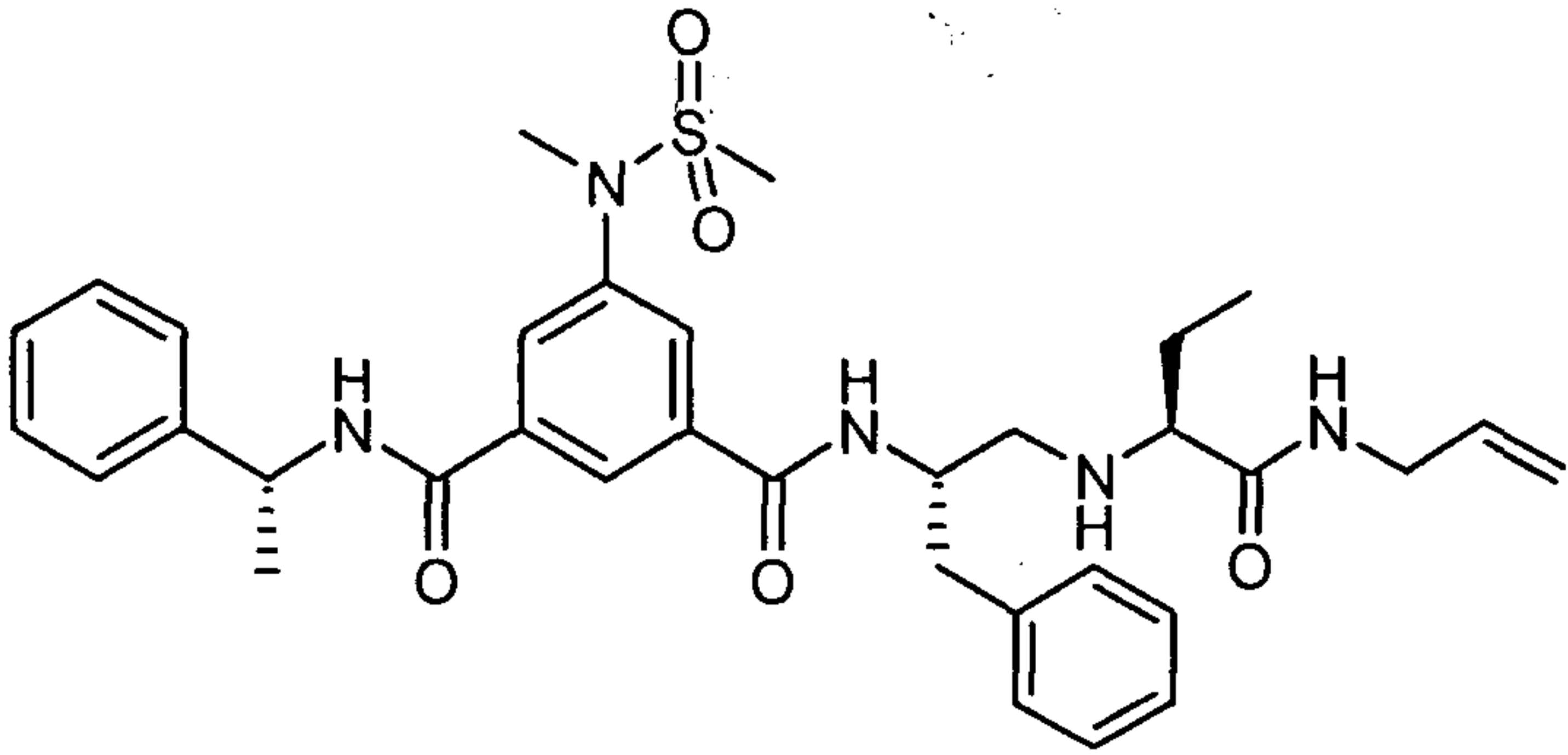
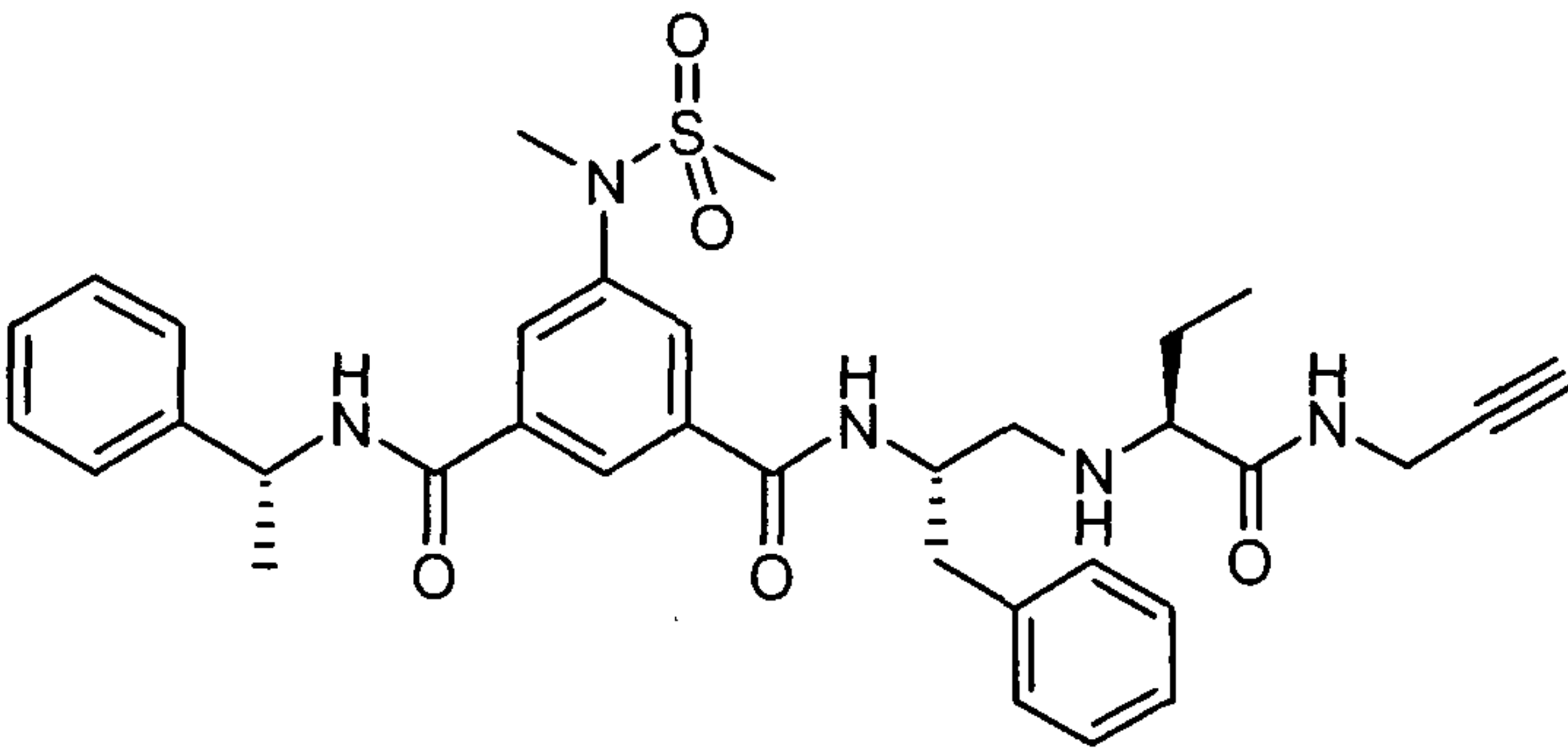
Particularly preferred individual compounds are selected from among

	Compound	Example No.
(1)		1
(2)		1.2
(3)		1.3
(4)		1.4
(5)		1.5

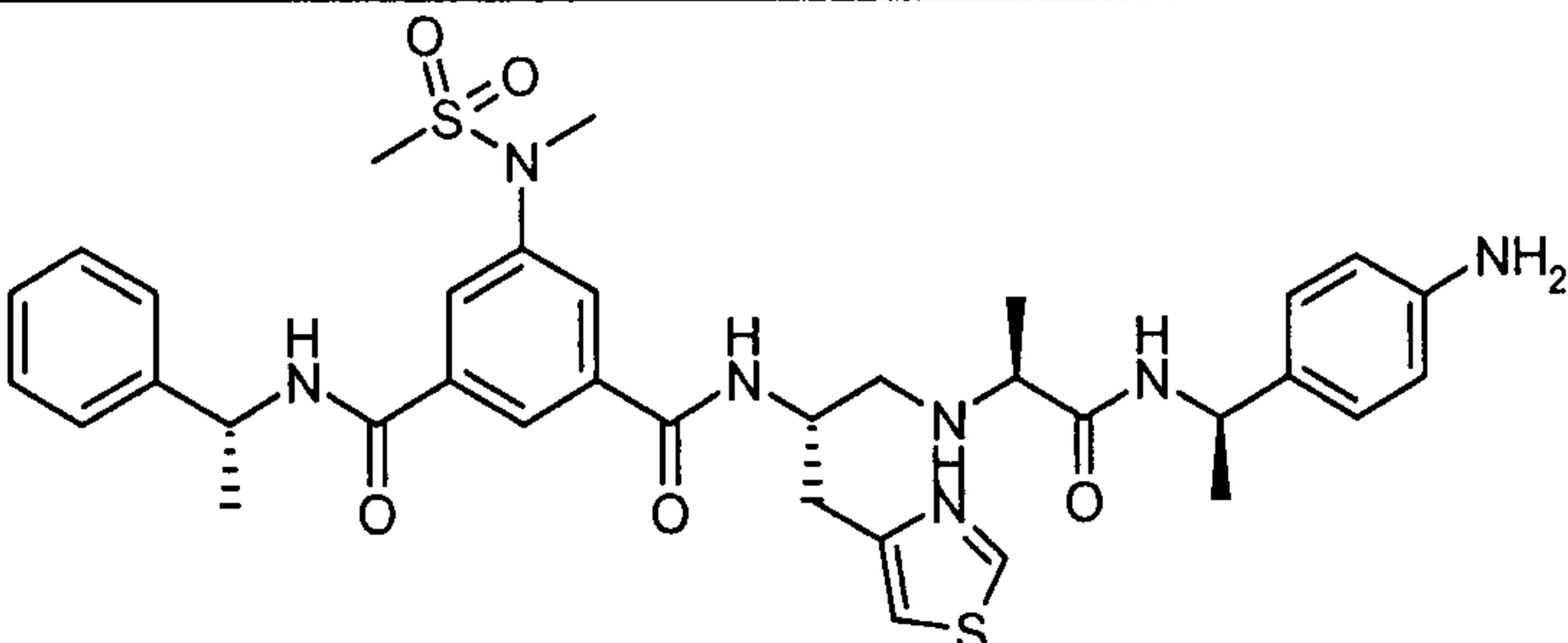
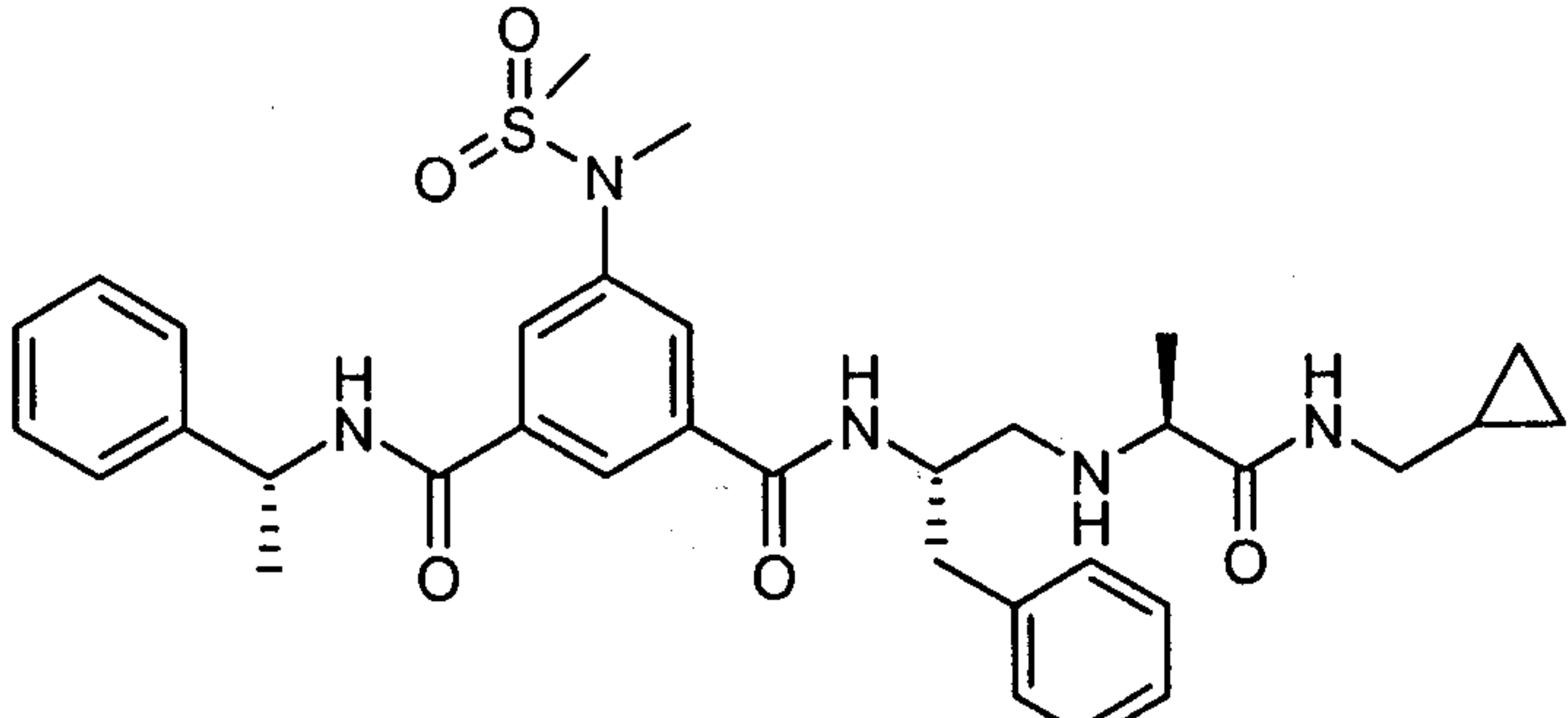
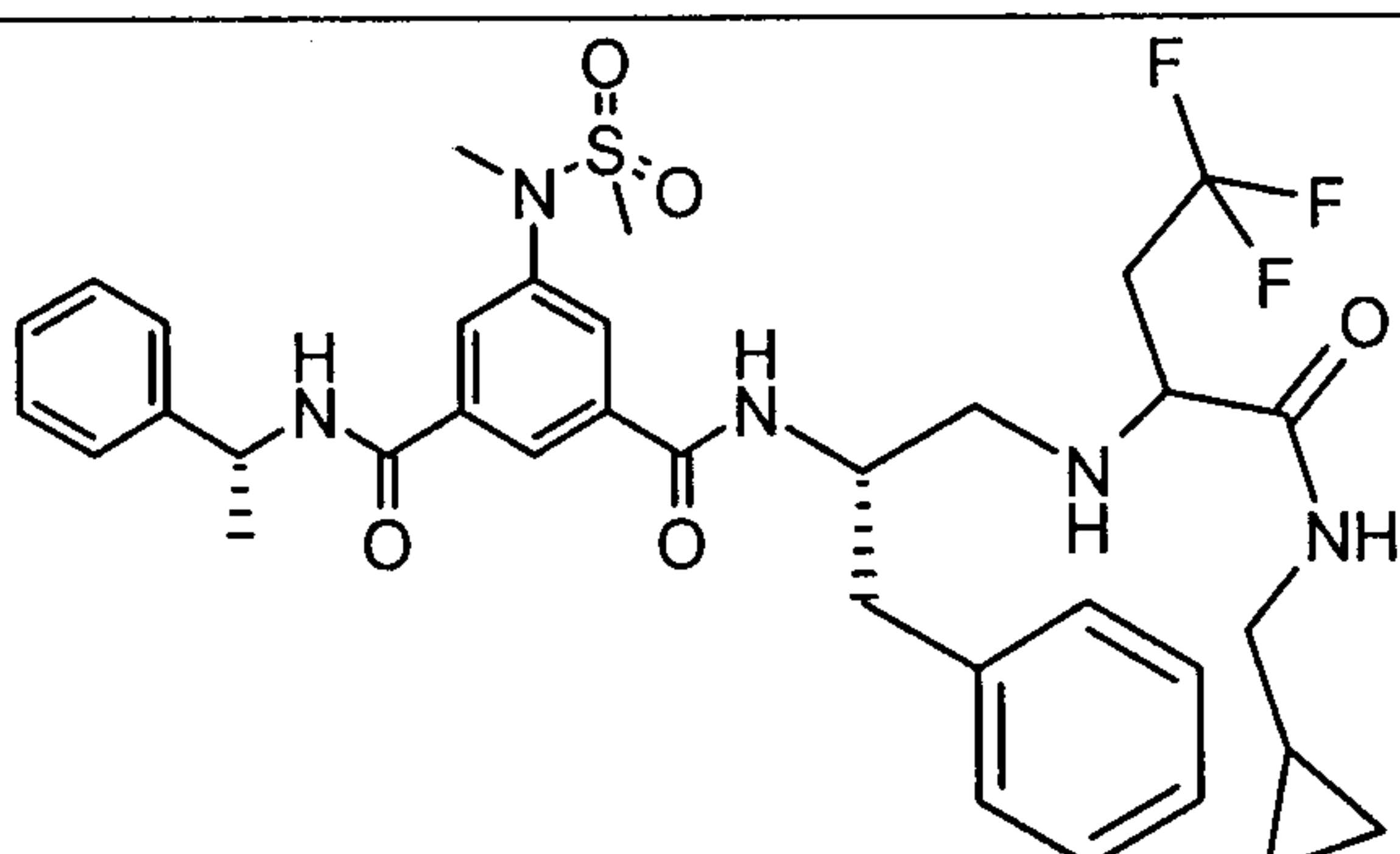
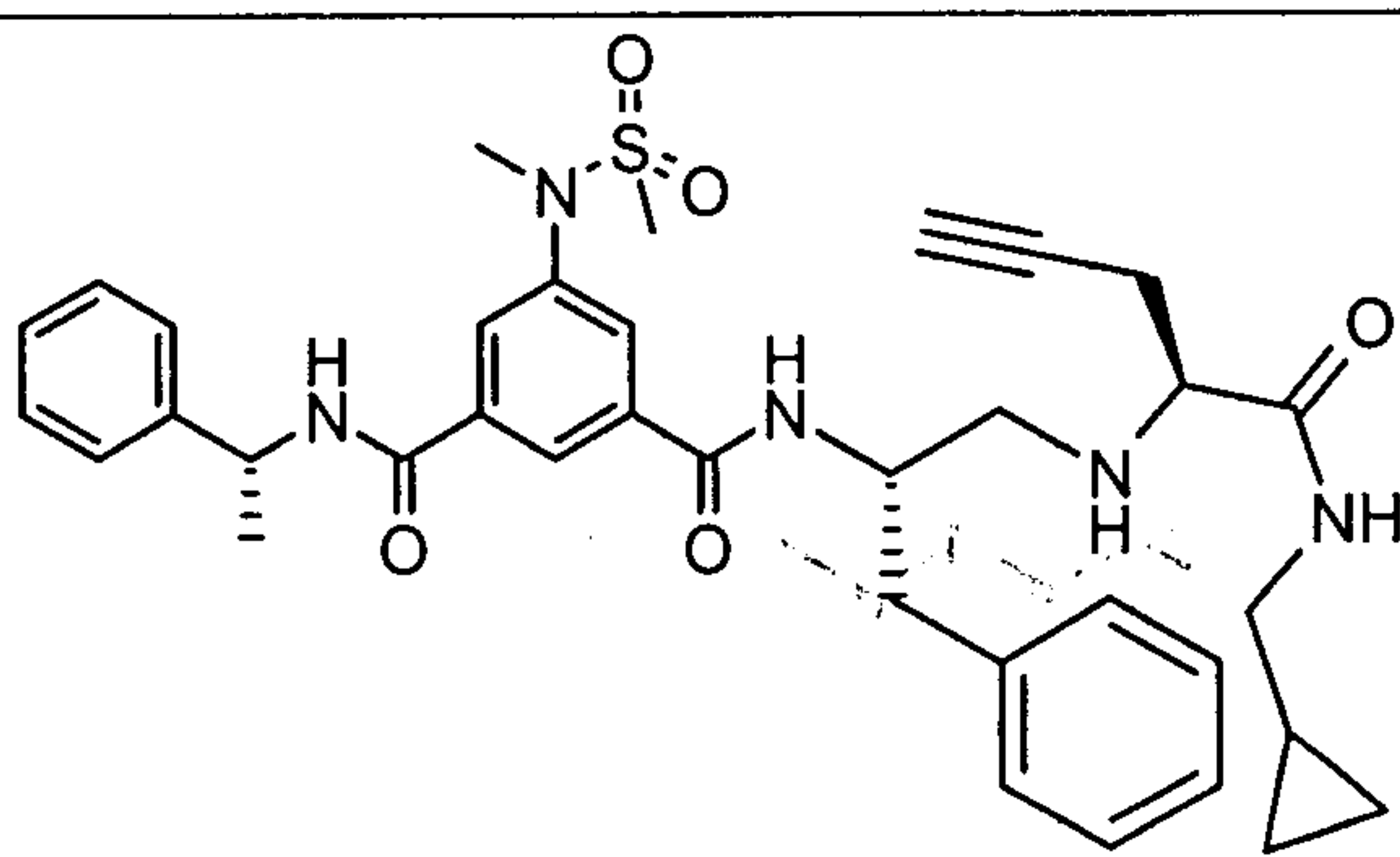
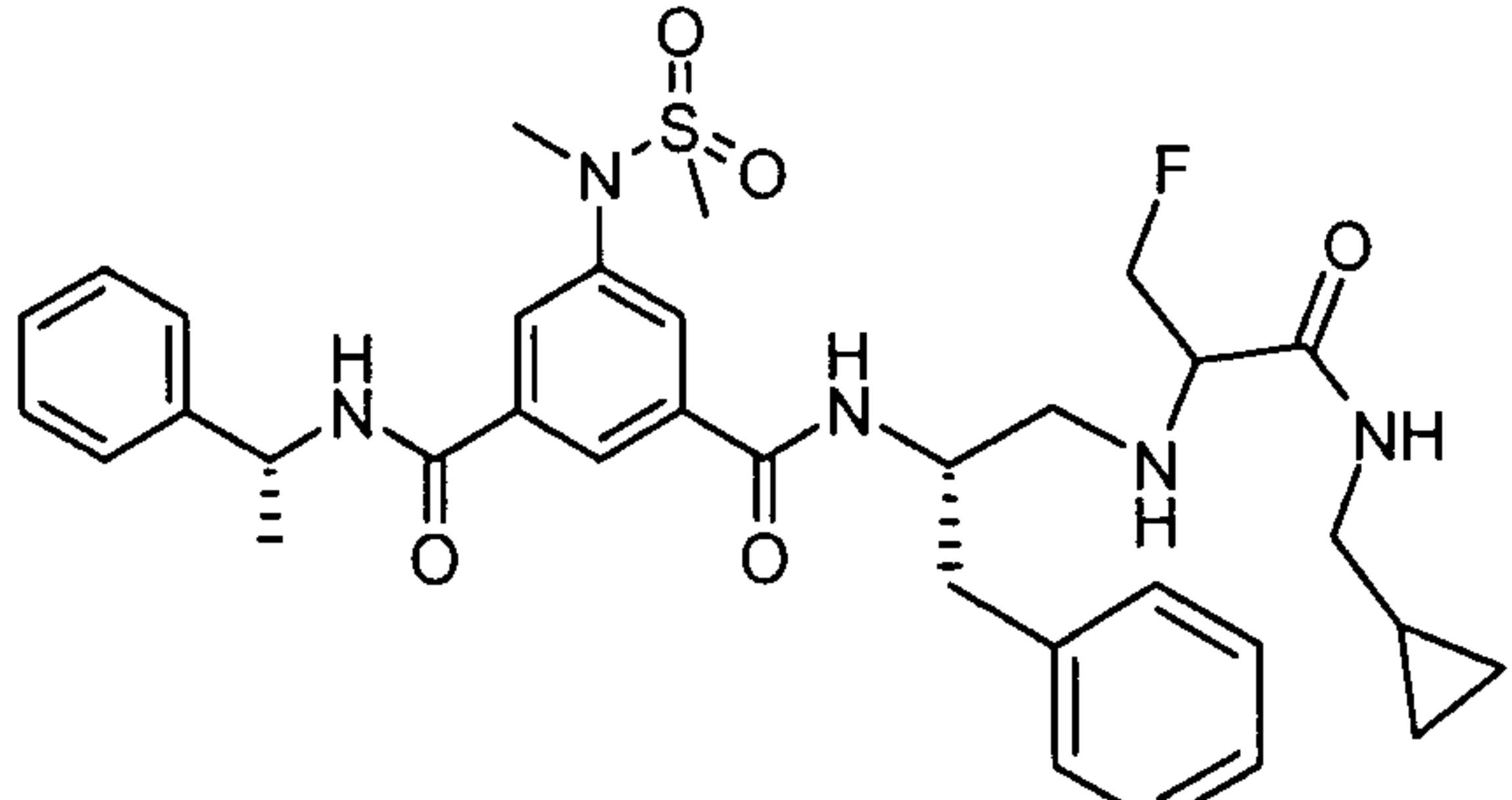
- 47 -

(6)	 <chem>CN(C)S(=O)(=O)c1ccc(cc1C(=O)N[C@@H](Cc2ccc(OC)cc2)C(=O)N[C@@H](Cc3ccccc3)C(=O)N[C@@H](Cc4ccc(N)cc4)C(=O)N)C</chem>	1.6
(7)	 <chem>CN(C)S(=O)(=O)c1ccc(cc1C(=O)N[C@@H](Cc2ccsc2)C(=O)N[C@@H](Cc3ccccc3)C(=O)N[C@@H](Cc4ccc(N)cc4)C(=O)N)C</chem>	1.7
(8)	 <chem>CN(C)S(=O)(=O)c1ccc(cc1C(=O)N[C@@H](Cc2ccccc2)C(=O)N[C@@H](Cc3ccccc3)C(=O)N[C@@H](Cc4ccc(N)cc4)C(=O)N)C</chem>	1.8
(9)	 <chem>CN(C)S(=O)(=O)c1ccc(cc1C(=O)N[C@@H](Cc2ccsc2)C(=O)N[C@@H](Cc3ccccc3)C(=O)N[C@@H](Cc4ccccc4)C(=O)N)C</chem>	1.9
(10)	 <chem>CN(C)S(=O)(=O)c1ccc(cc1C(=O)N[C@@H](Cc2ccsc2)C(=O)N[C@@H](Cc3ccccc3)C(=O)N[C@@H](Cc4cc(C)CC4)C(=O)N)C</chem>	1.10

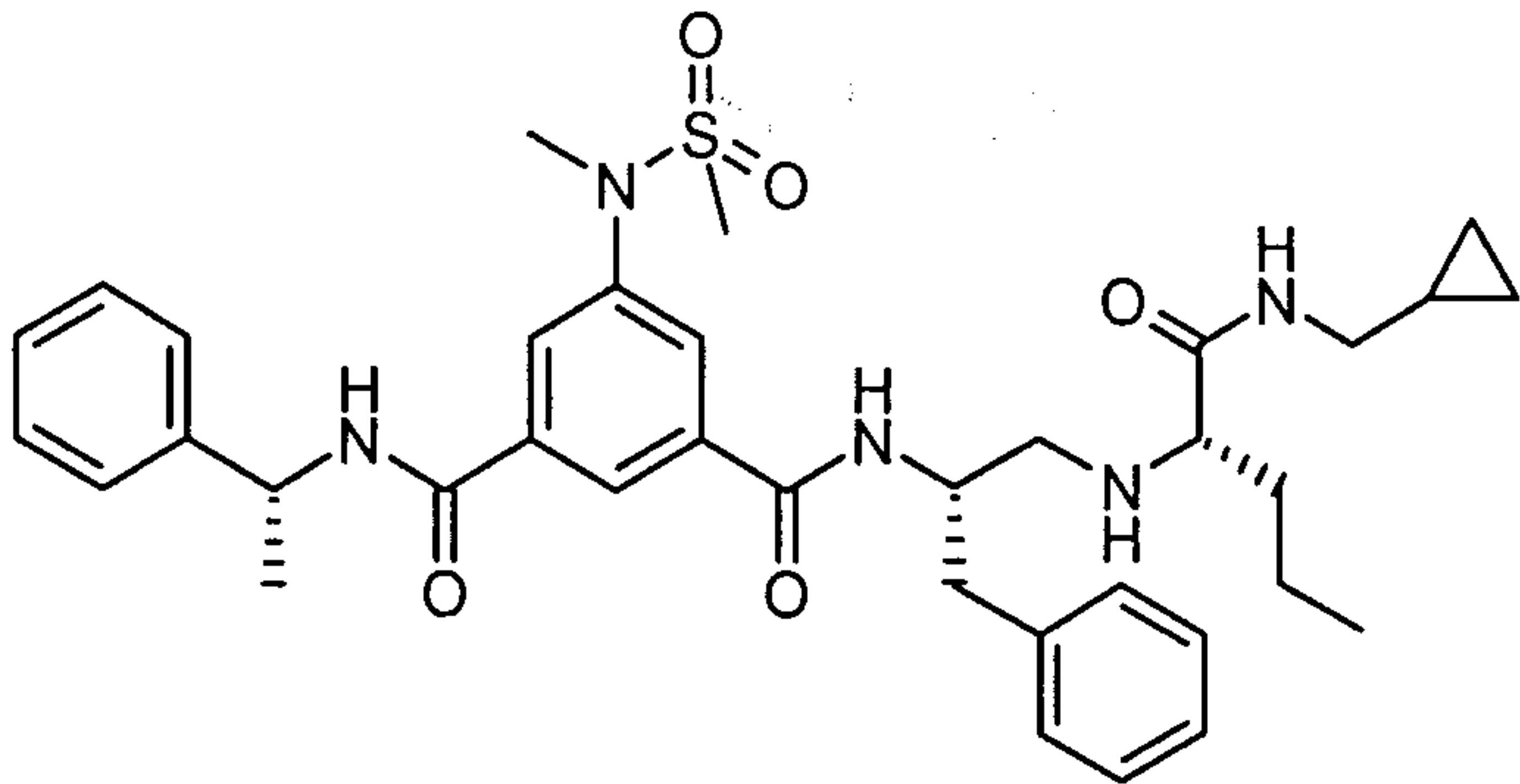
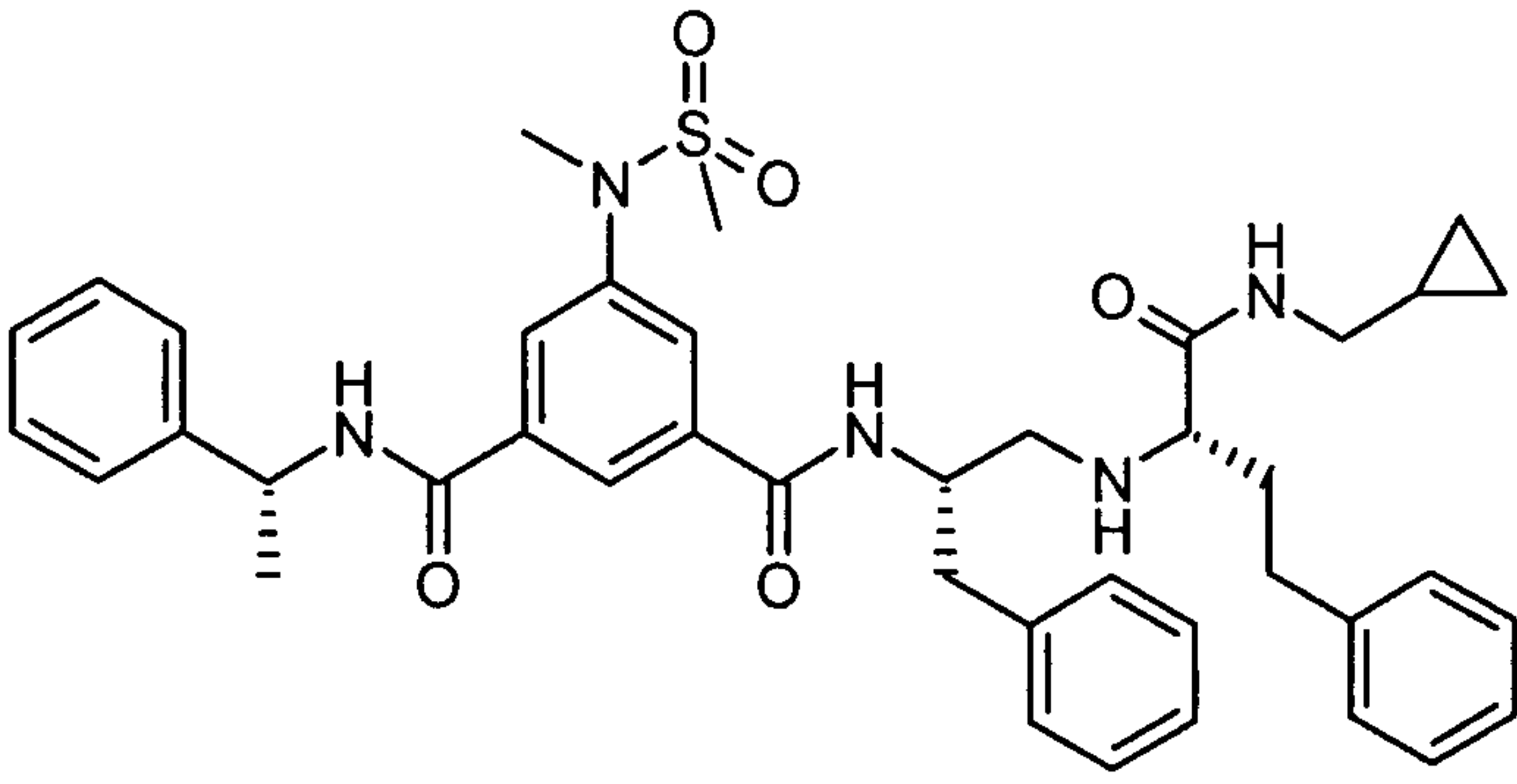
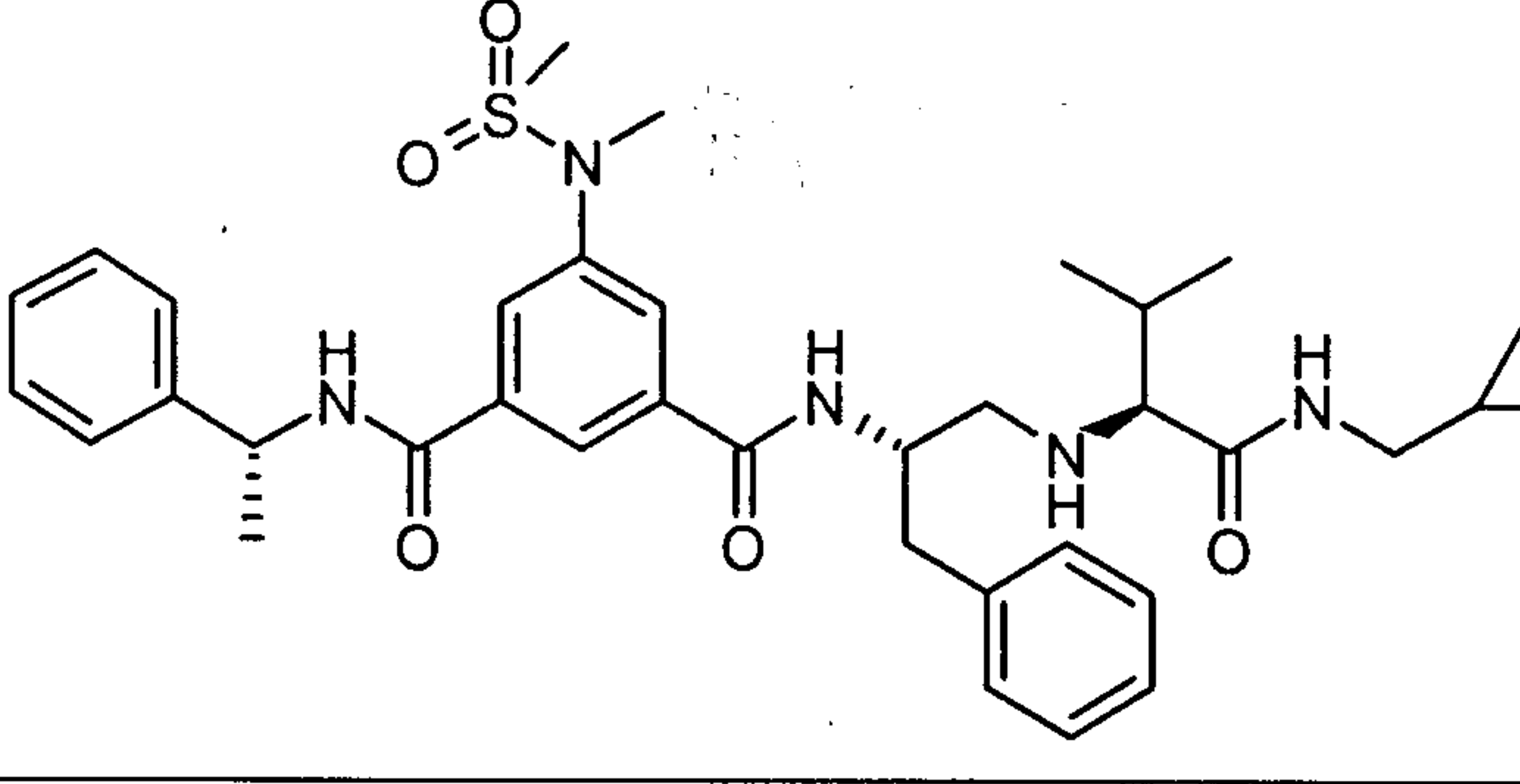
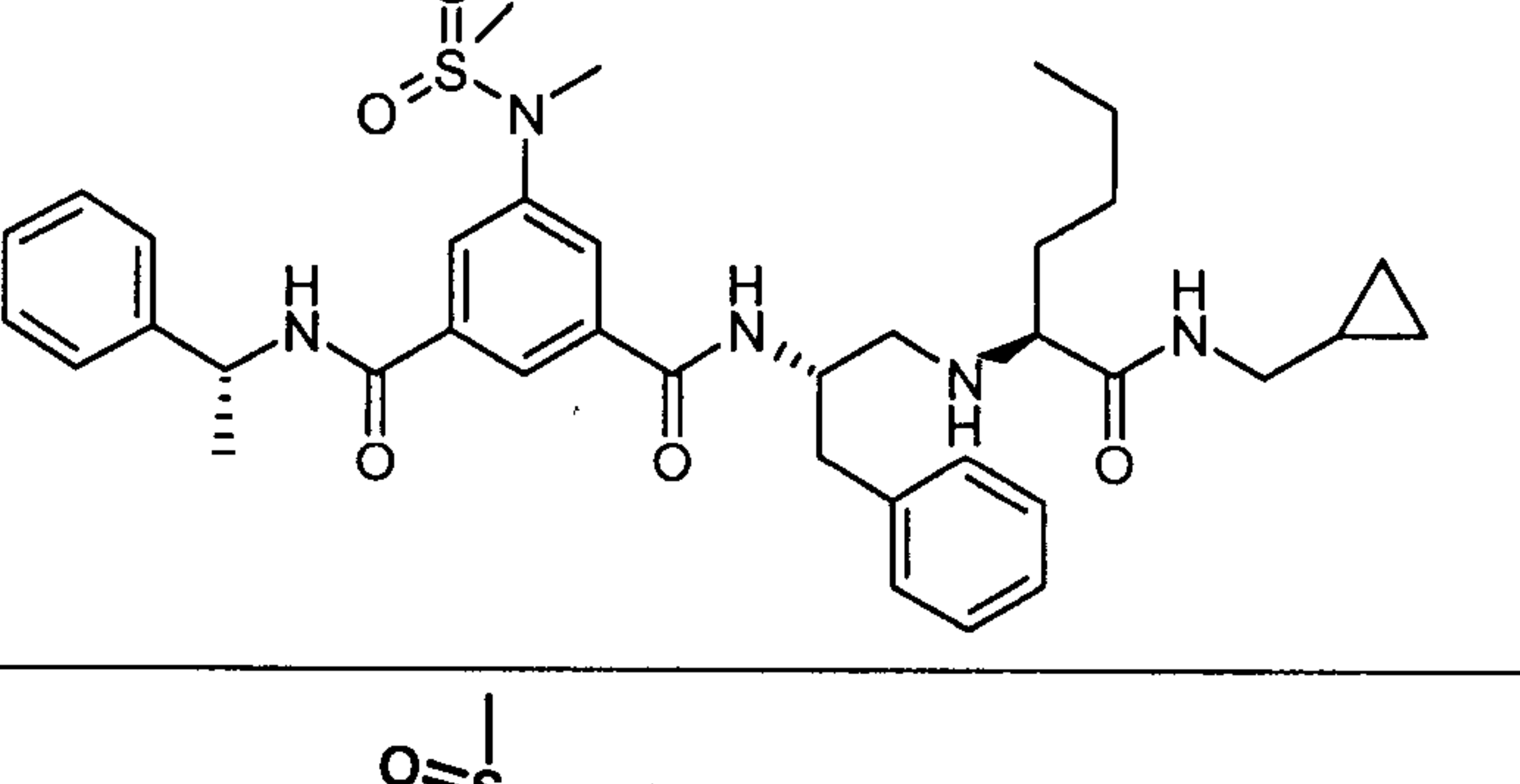
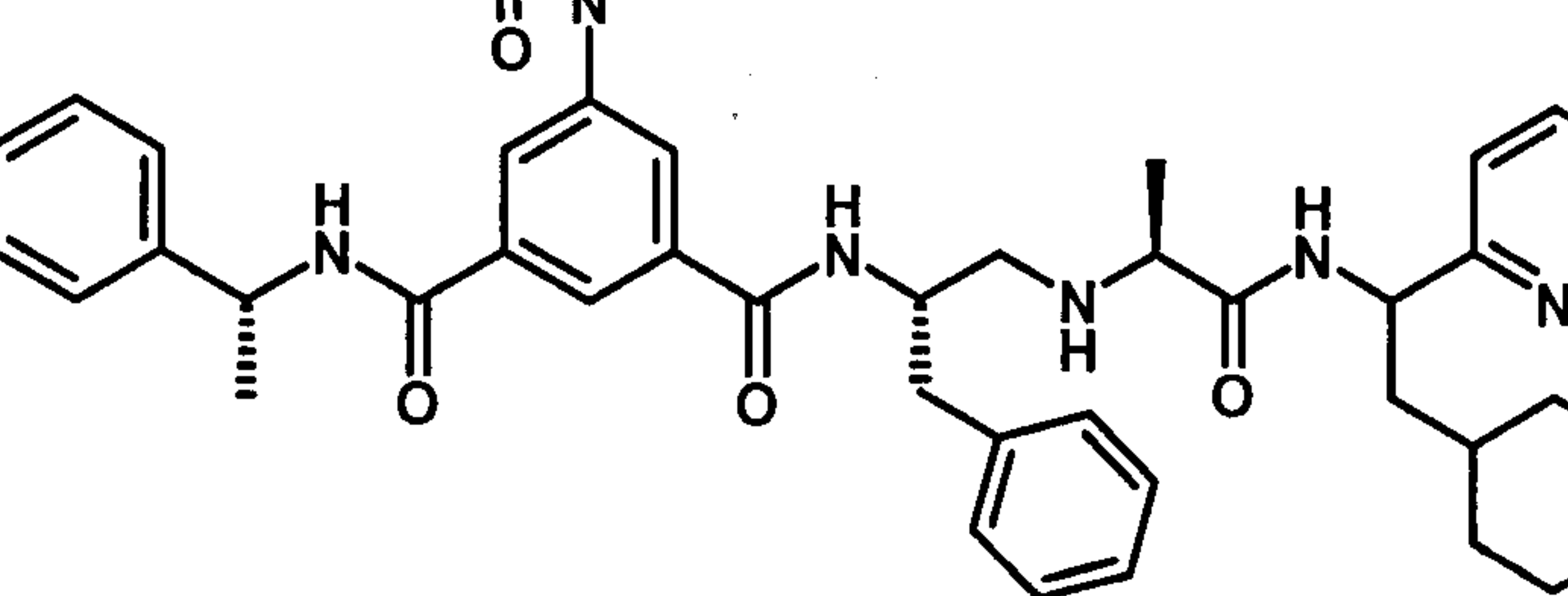
- 48 -

(11)		2
(12)		2.1
(13)		2.2
(14)		2.3
(15)		2.4

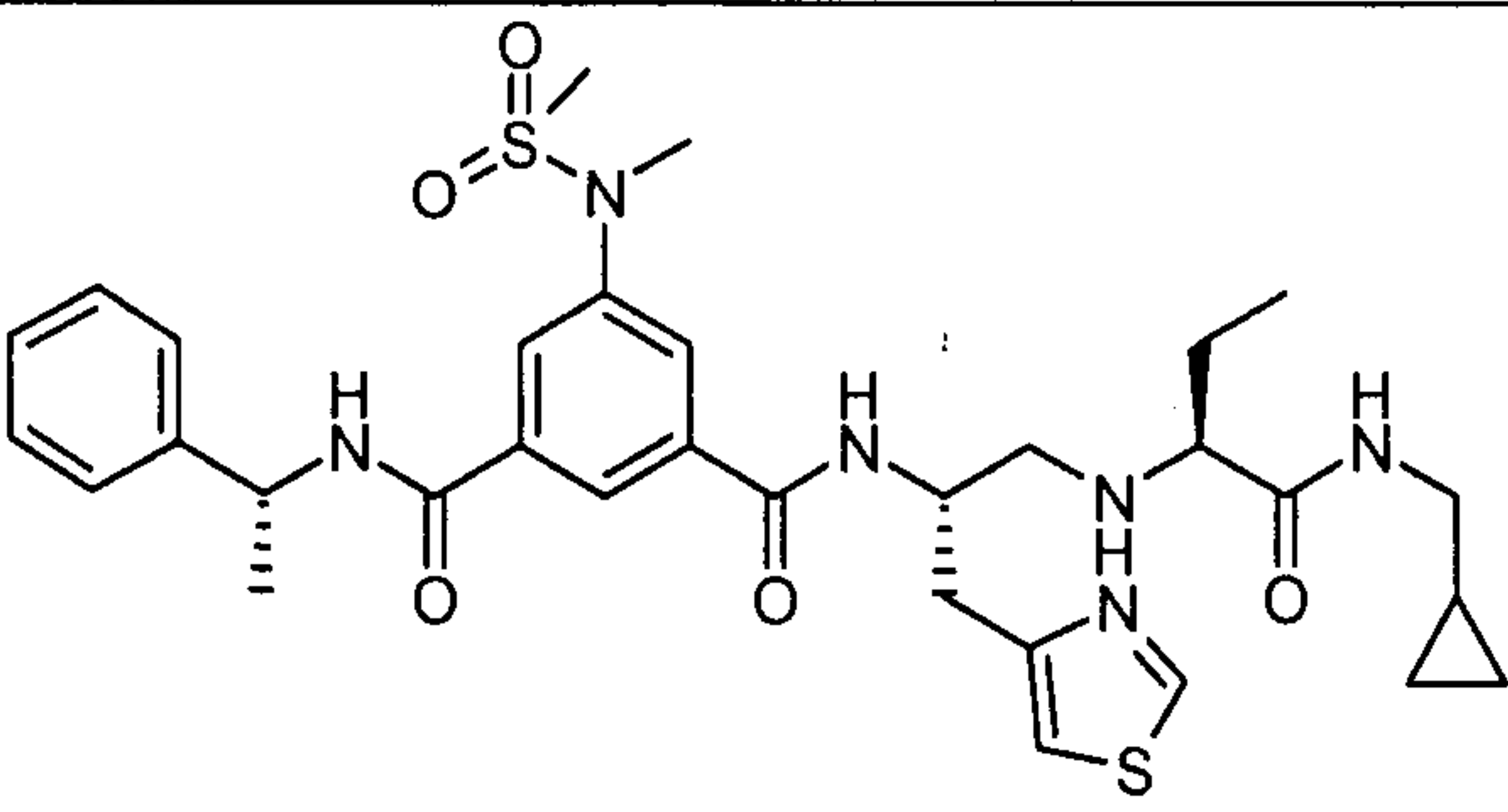
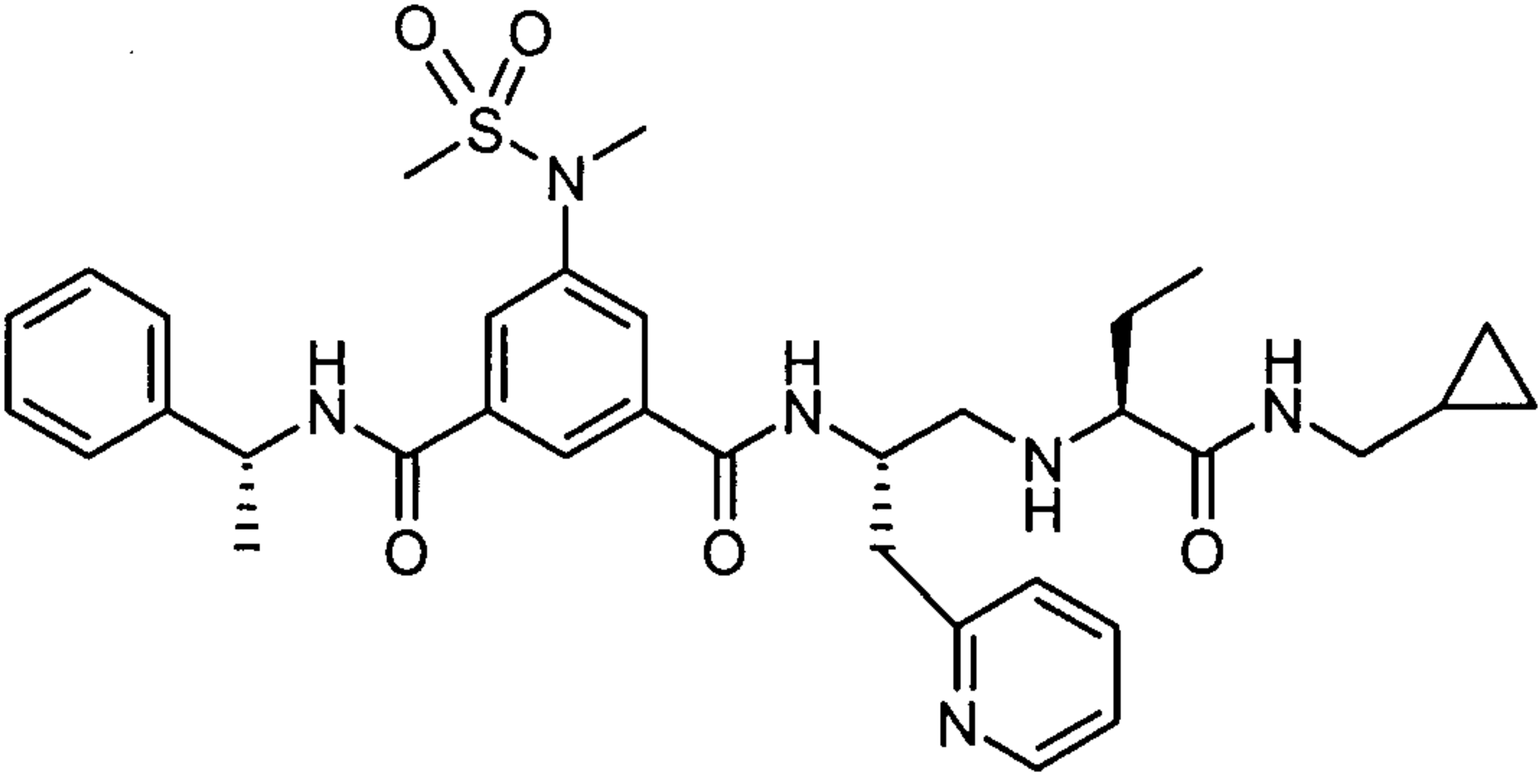
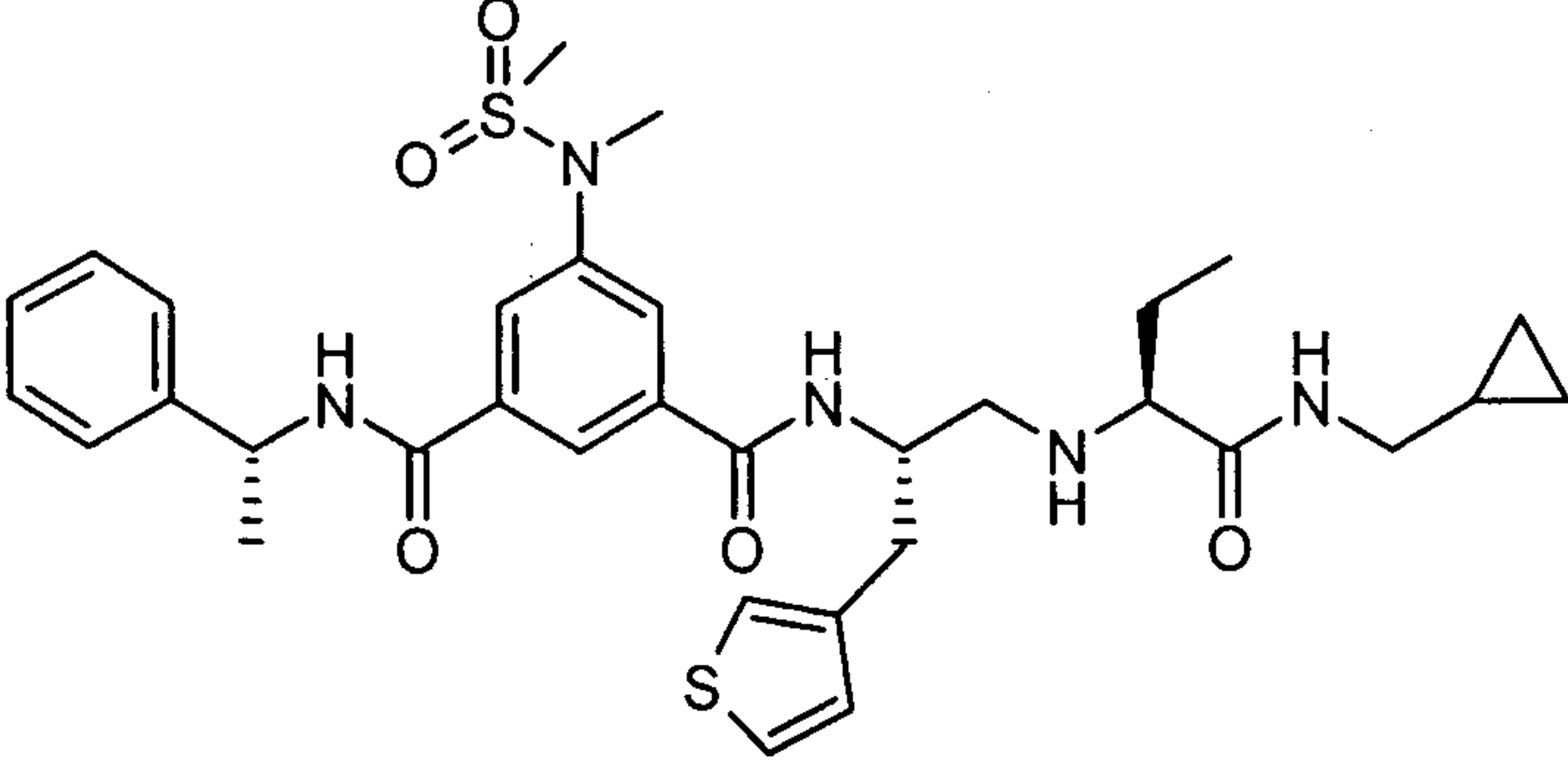
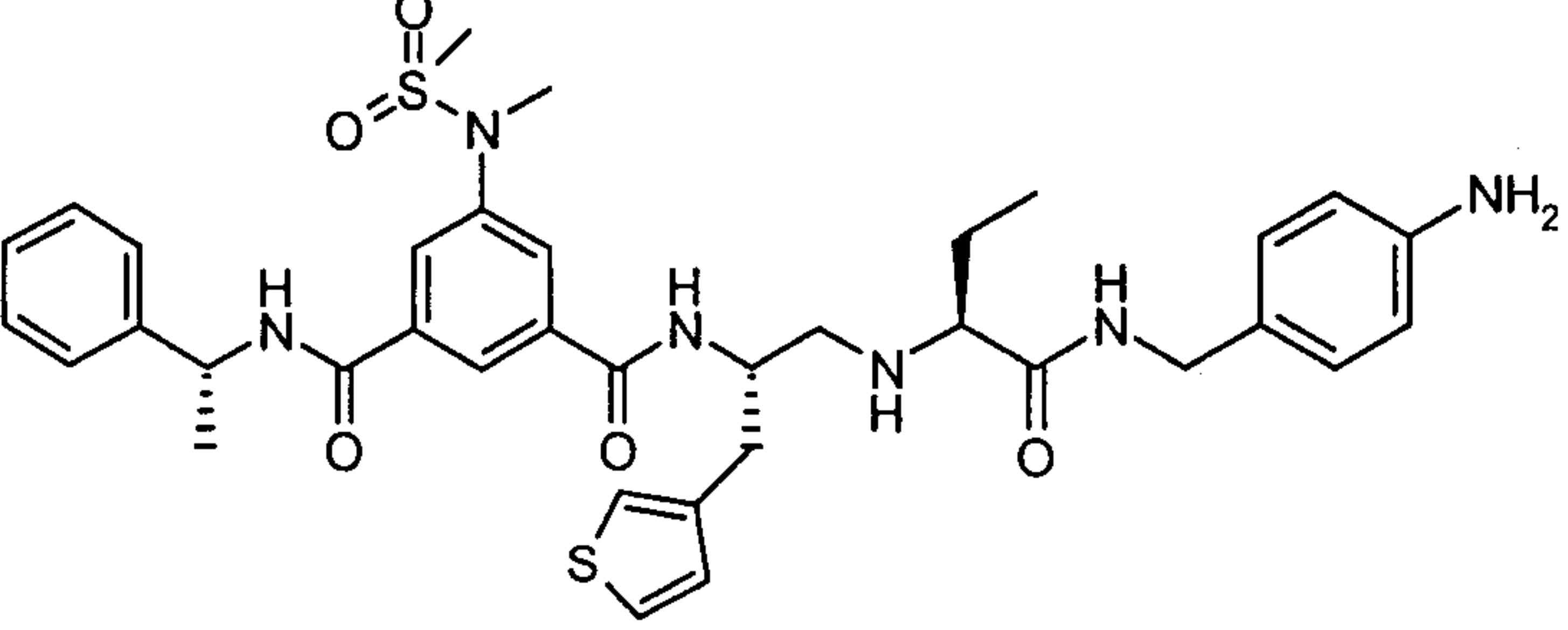
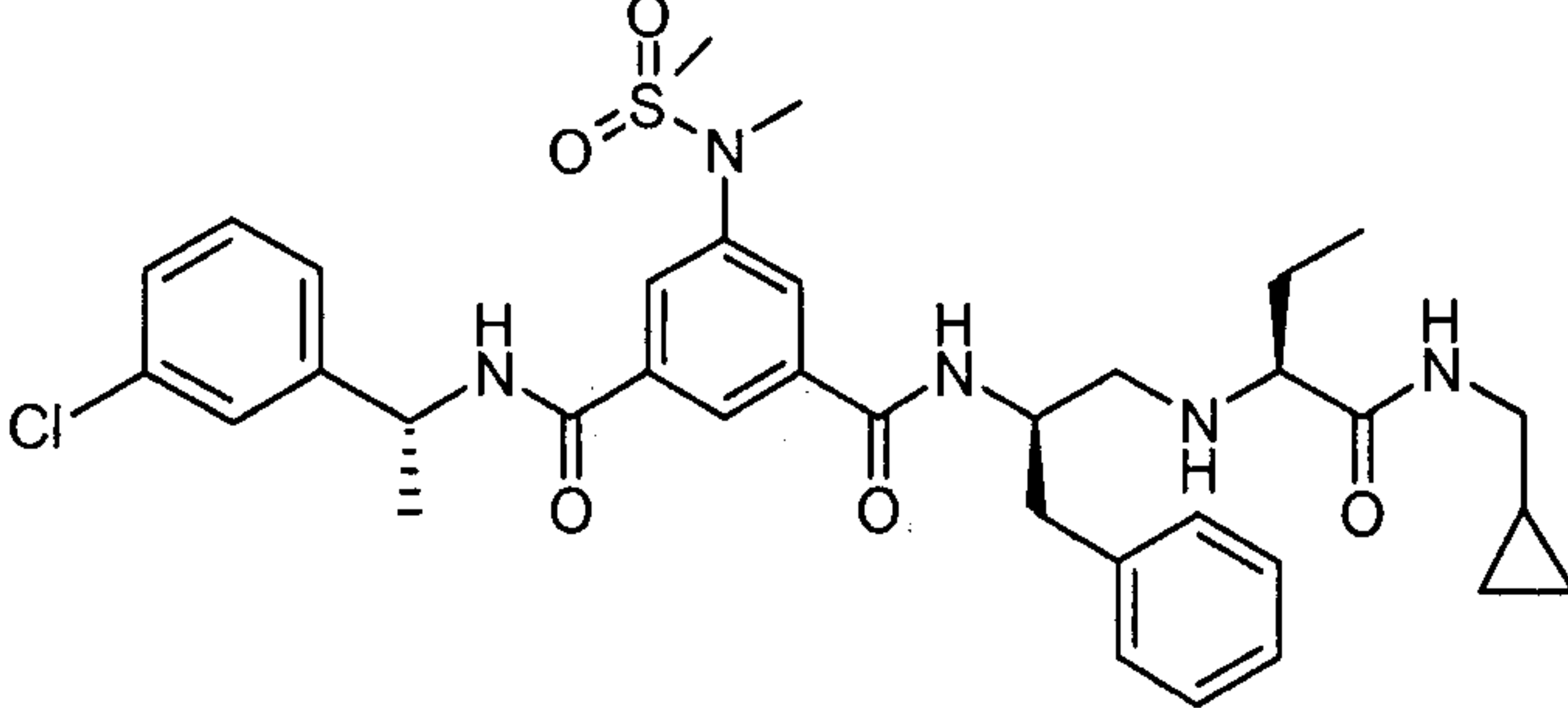
- 49 -

(16)		3
(17)		4
(18)		4.2
(19)		4.3
(20)		4.4

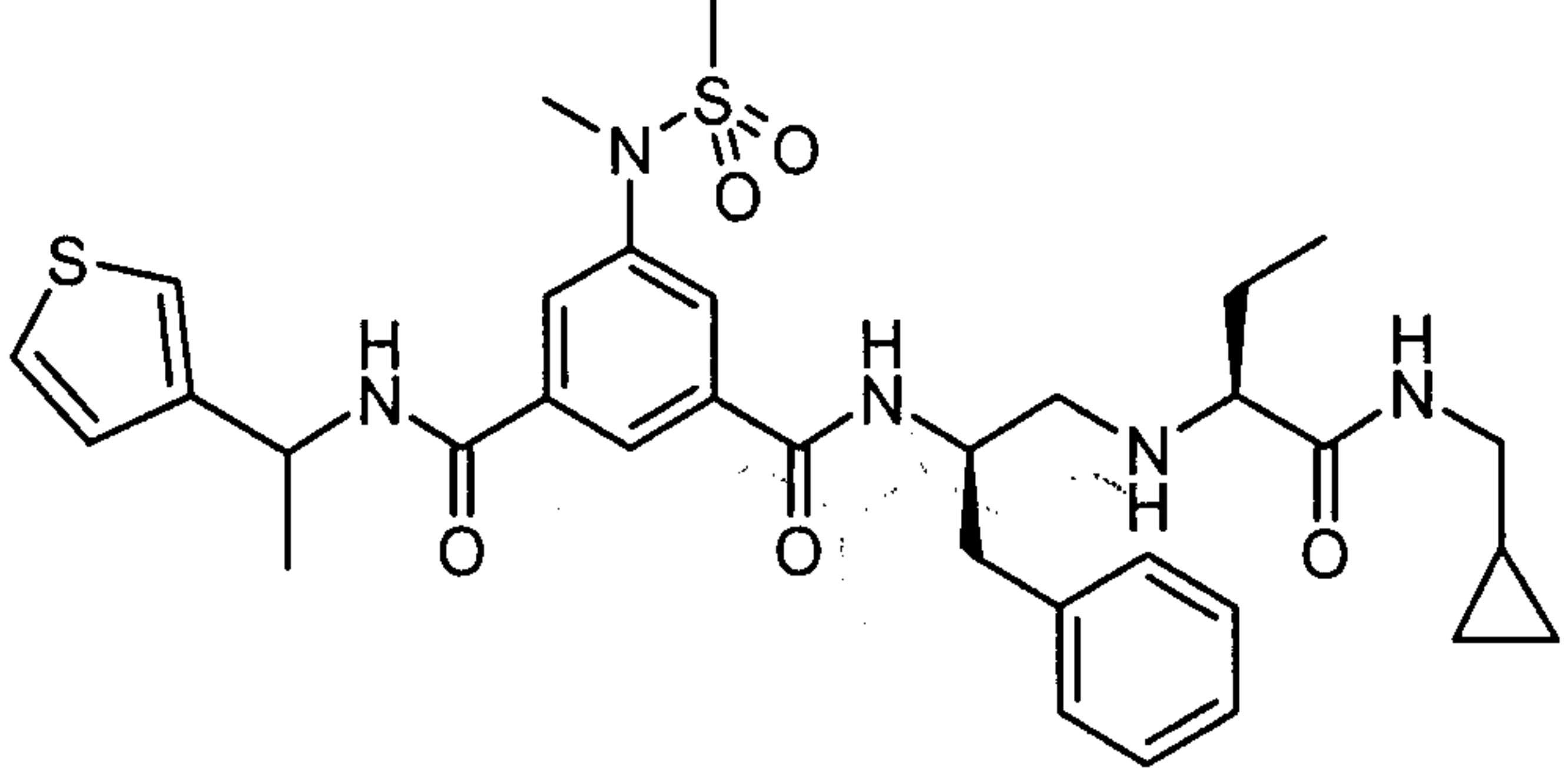
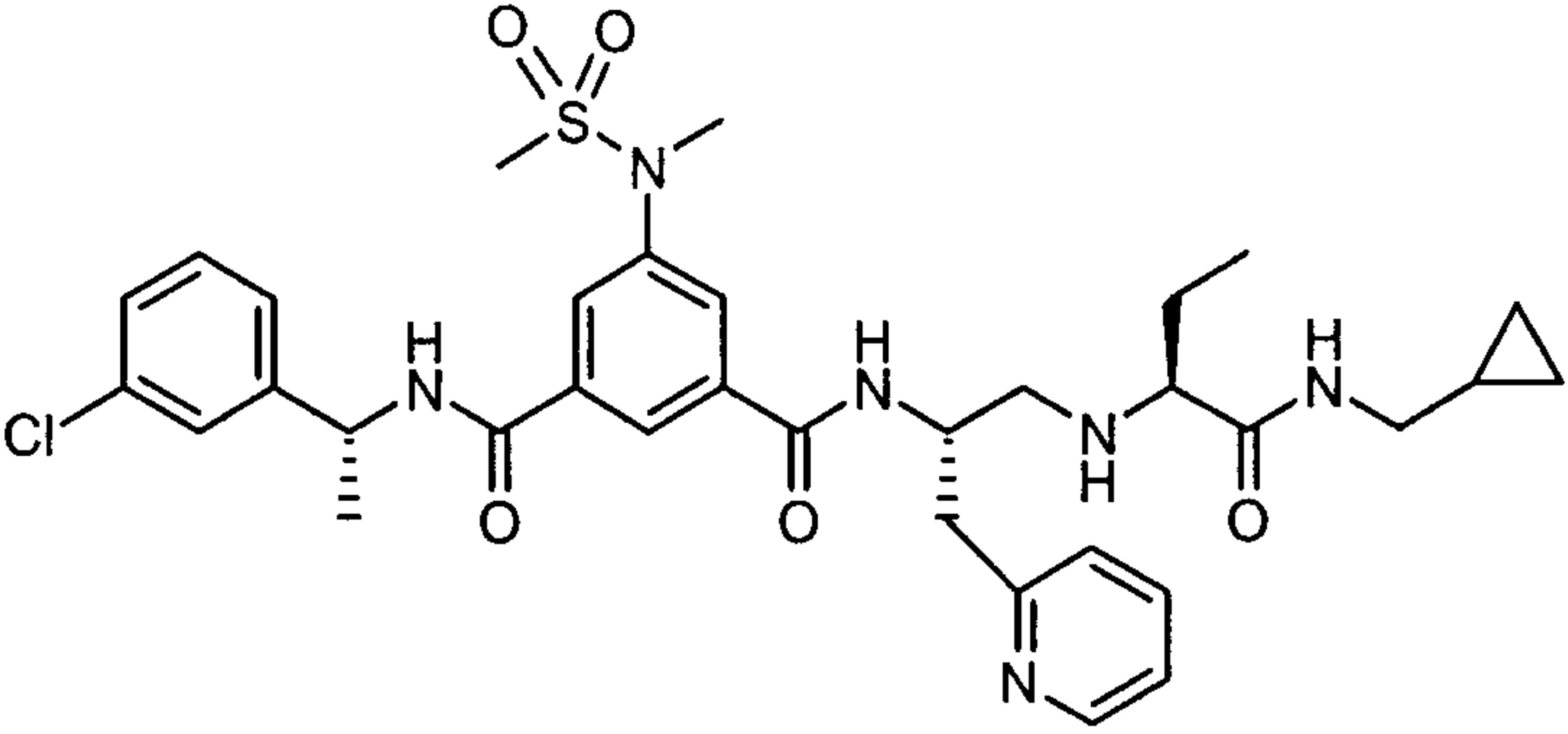
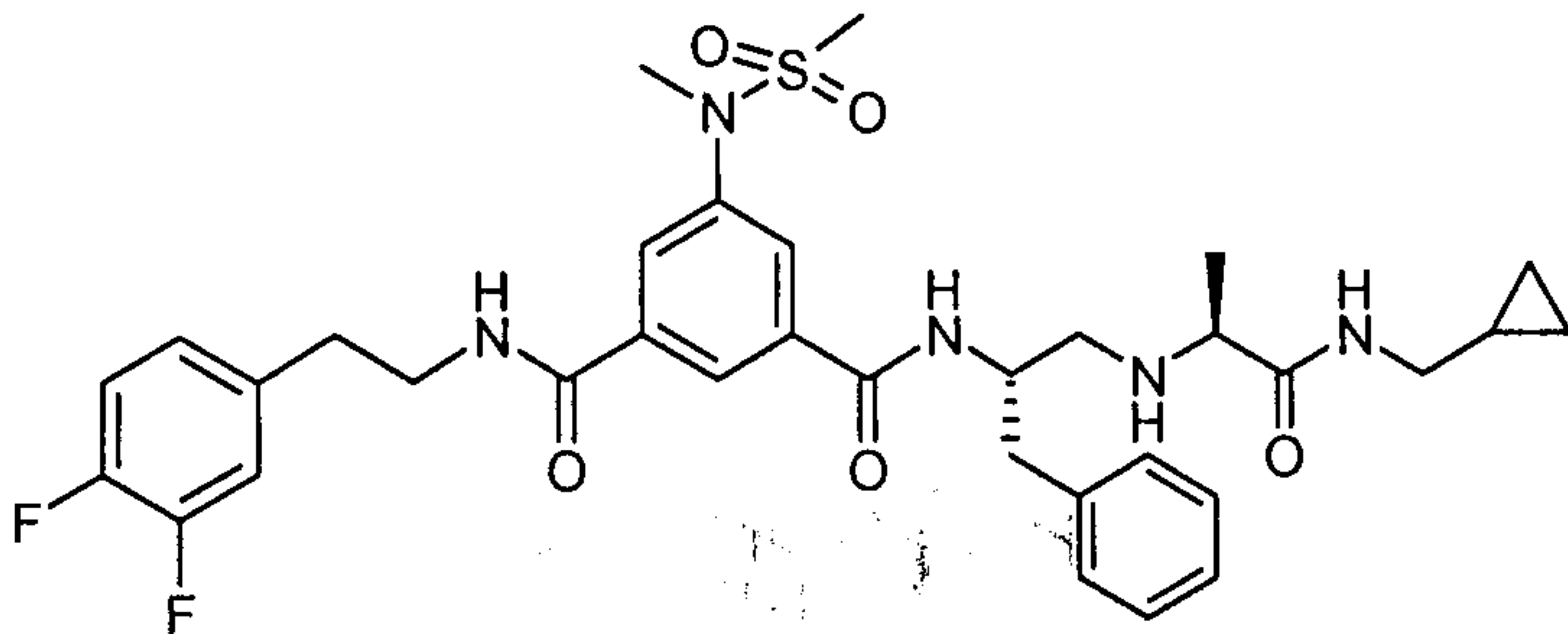
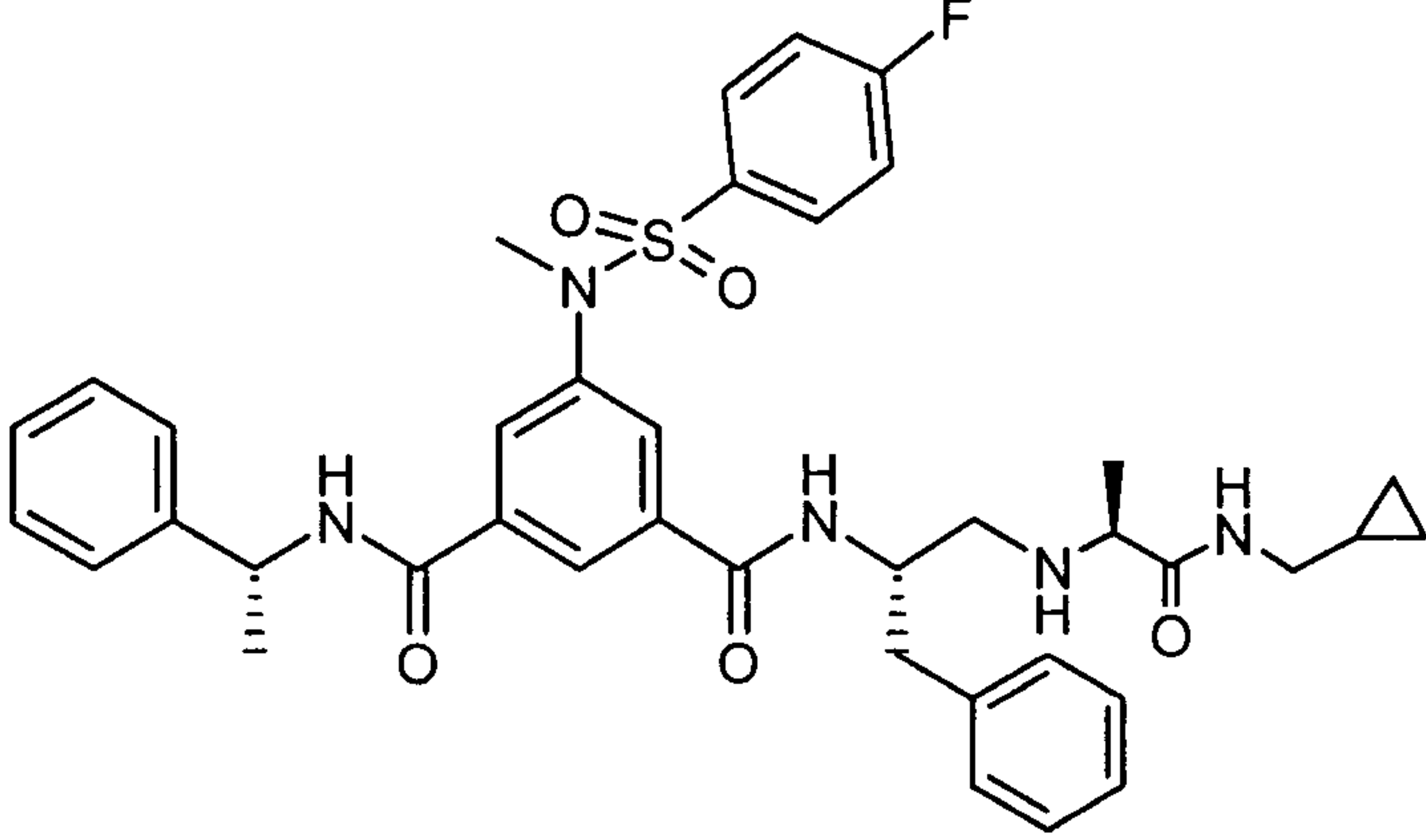
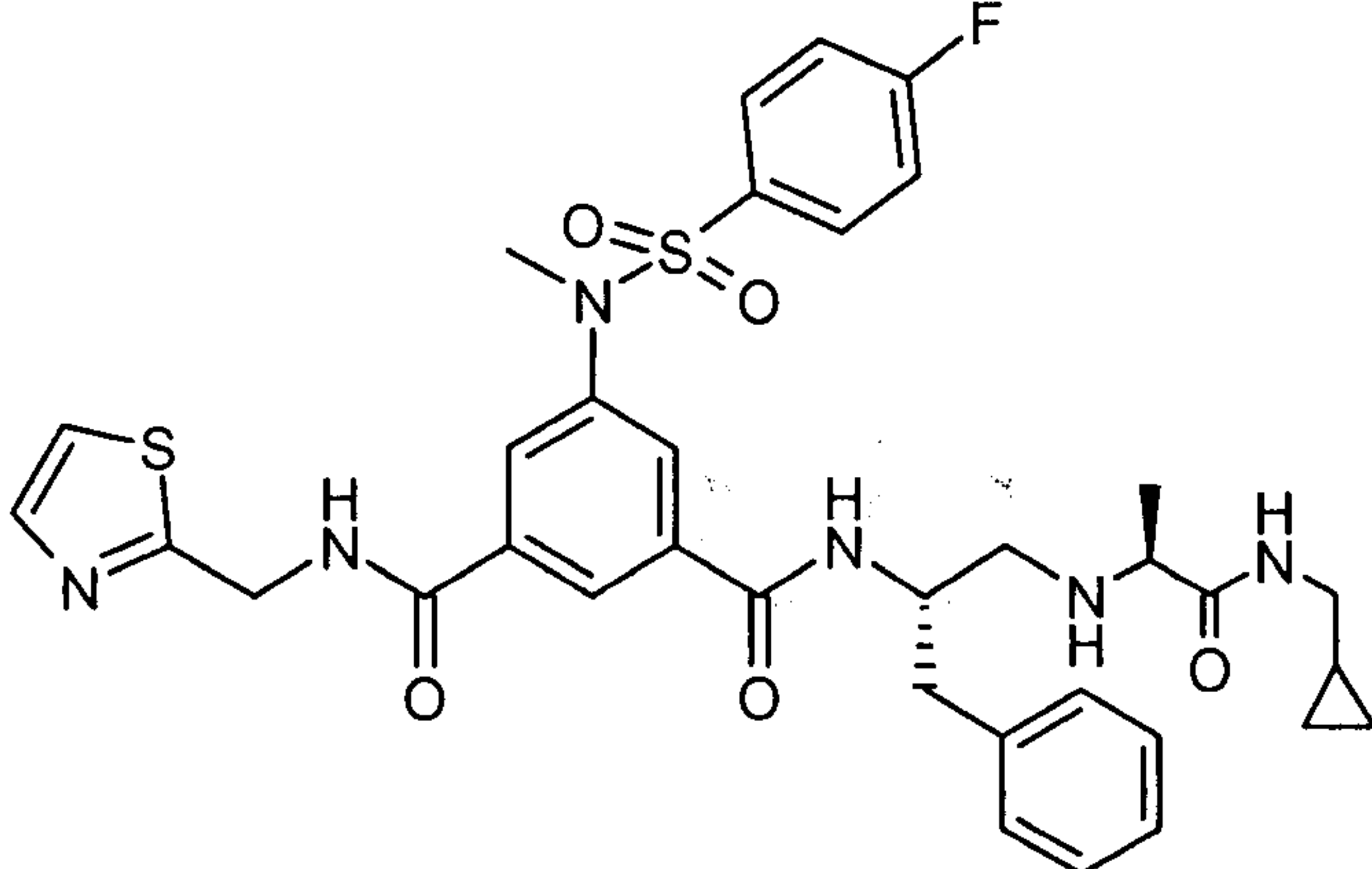
- 50 -

(21)		4.5
(22)		4.6
(23)		4.7
(24)		4.8
(25)		4.9

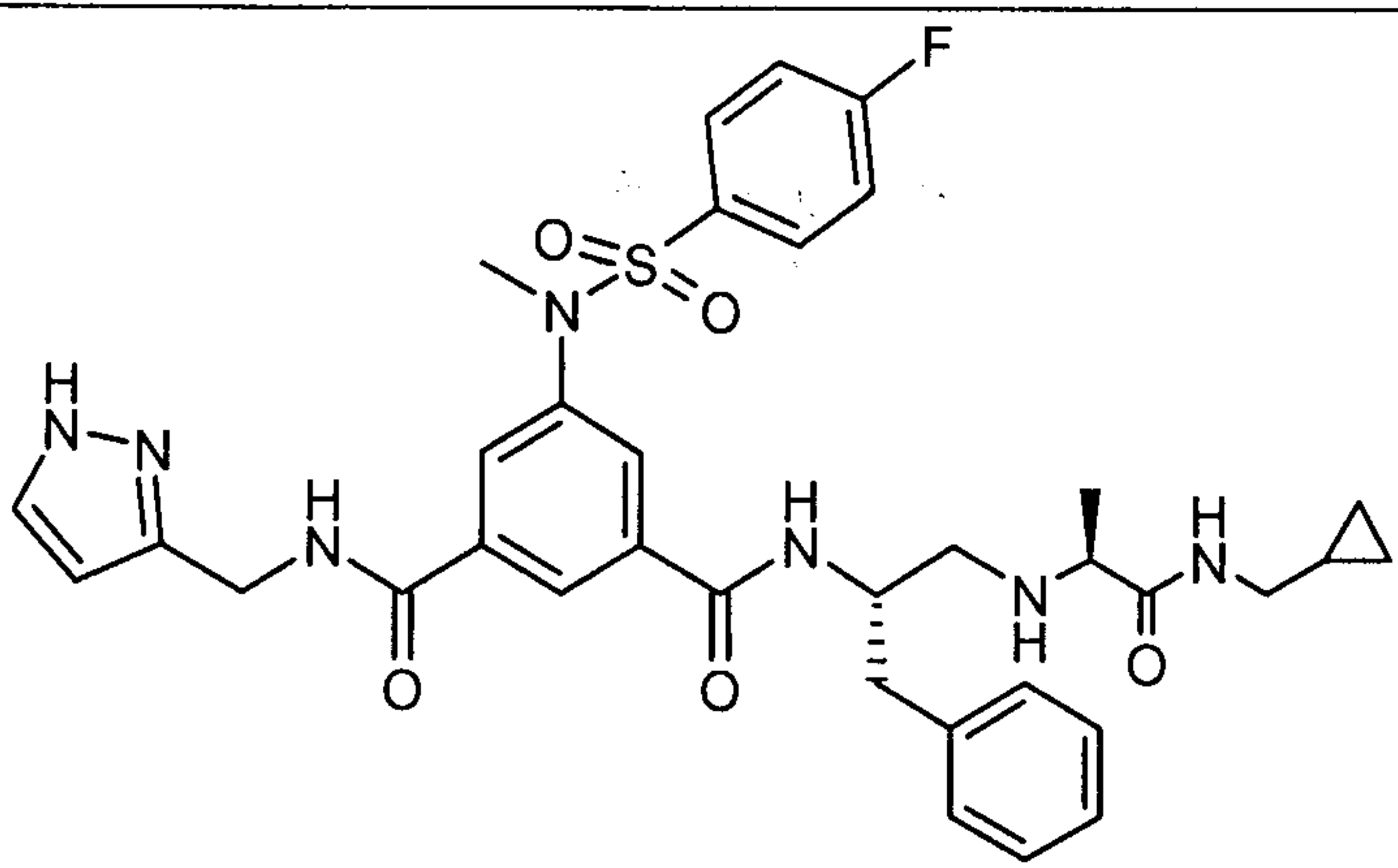
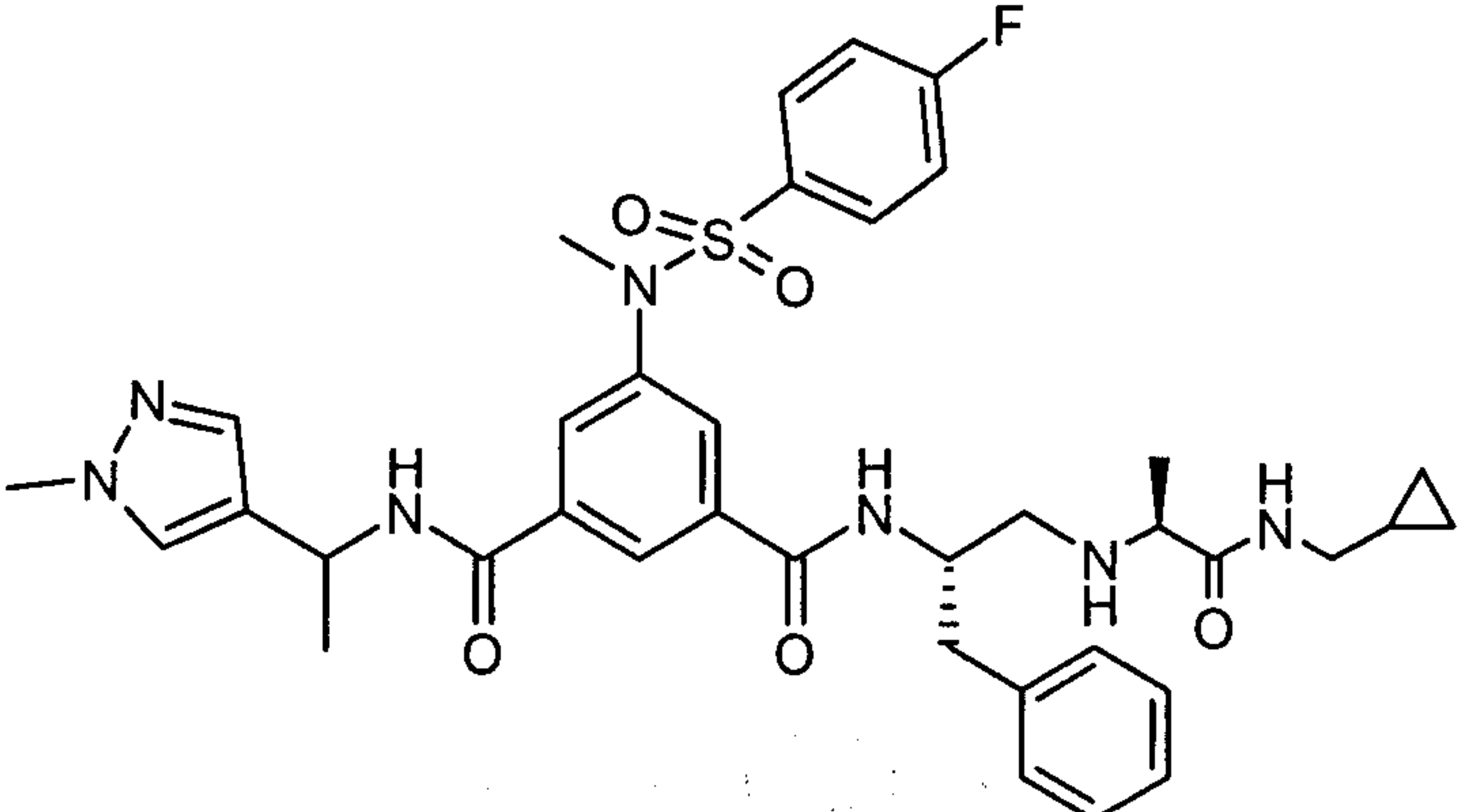
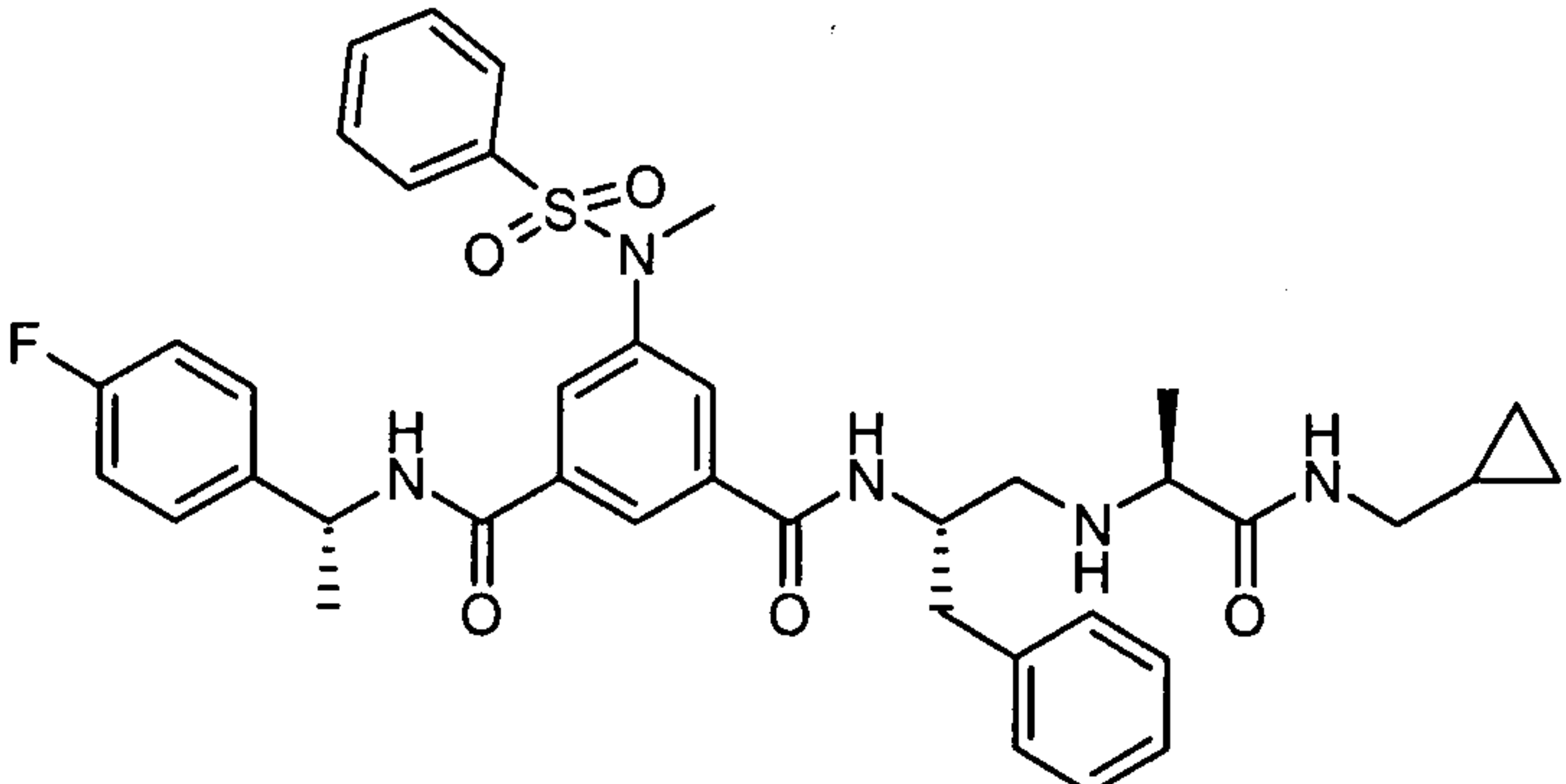
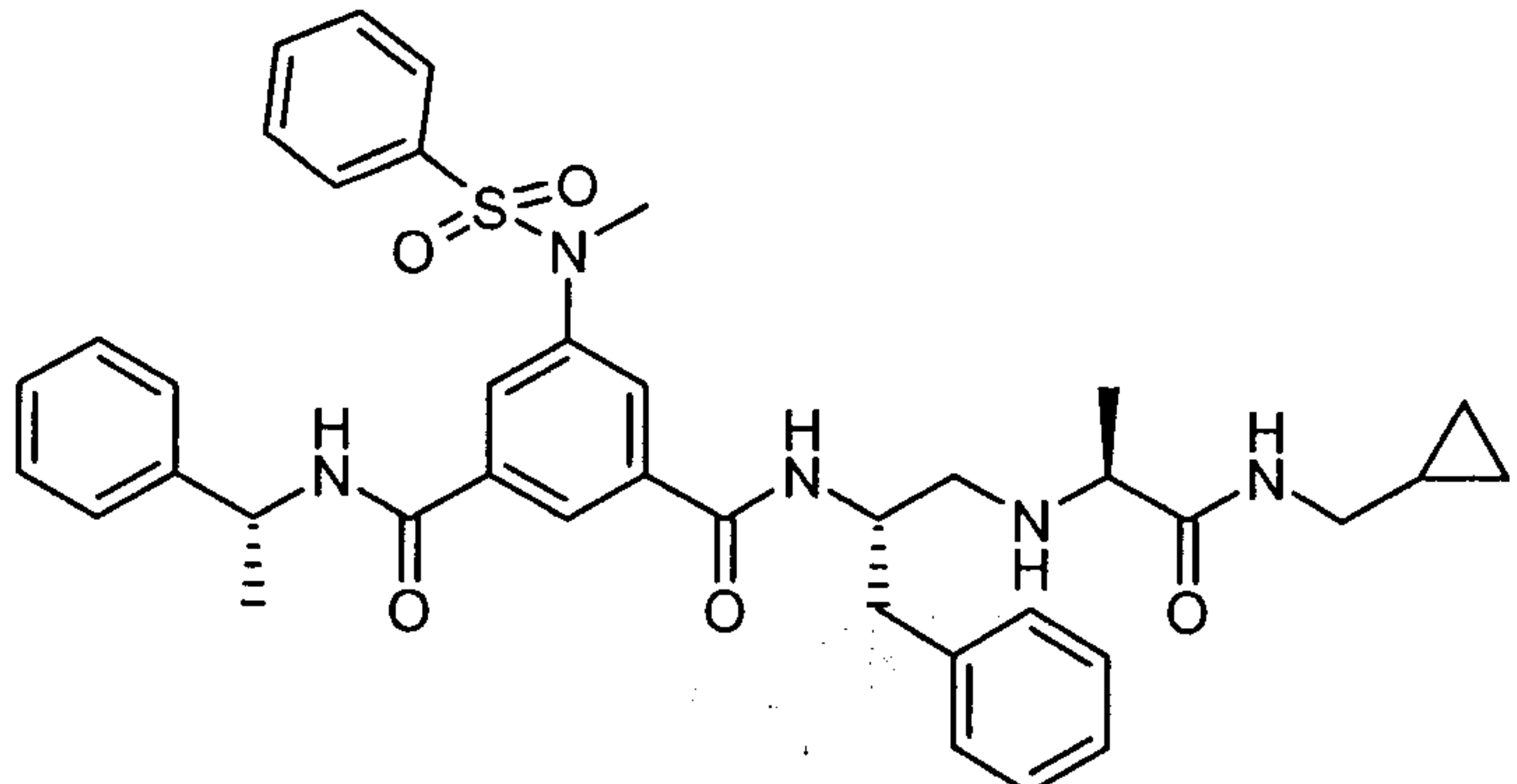
- 51 -

(26)		5
(27)		5.2
(28)		6
(29)		6.2
(30)		6.3

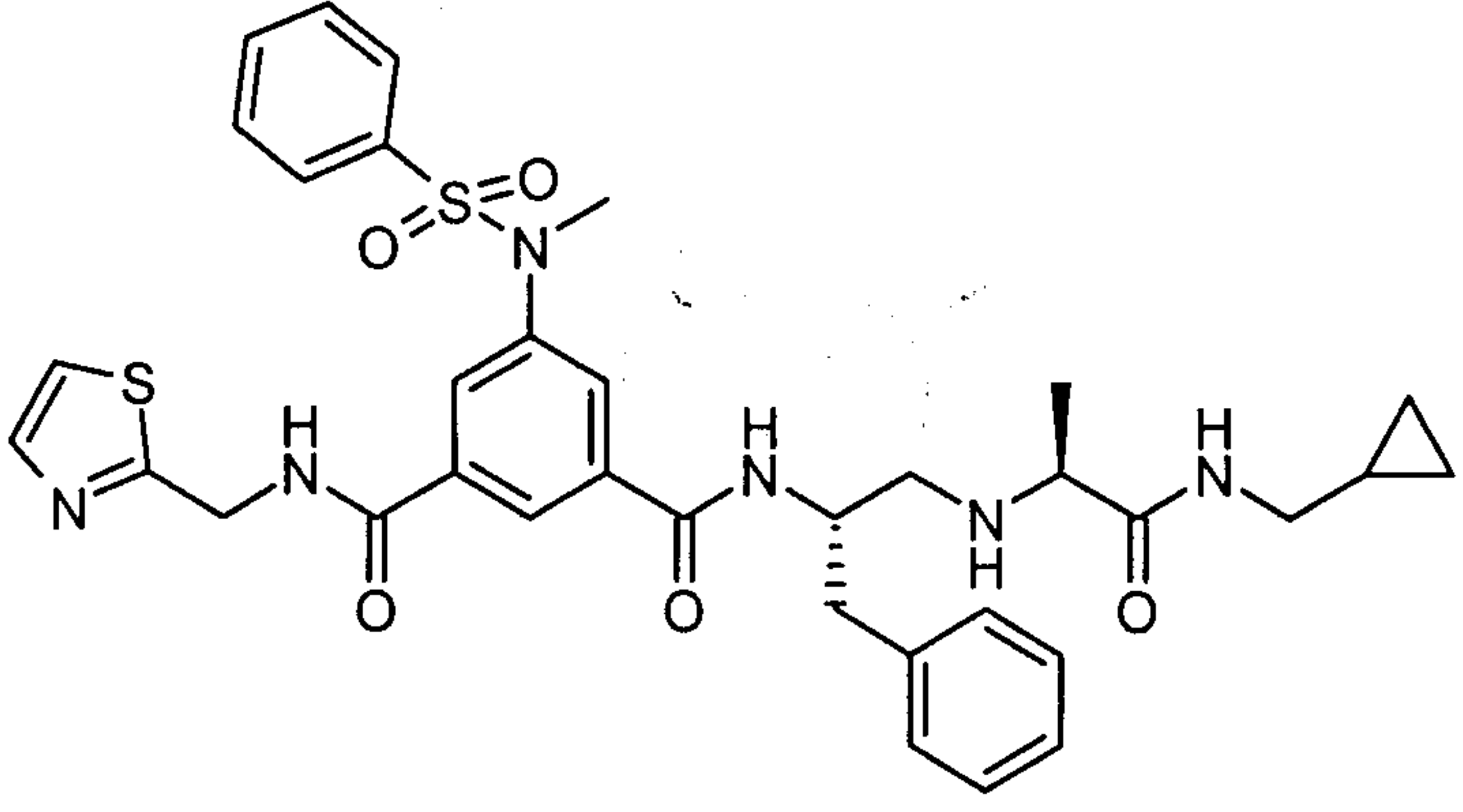
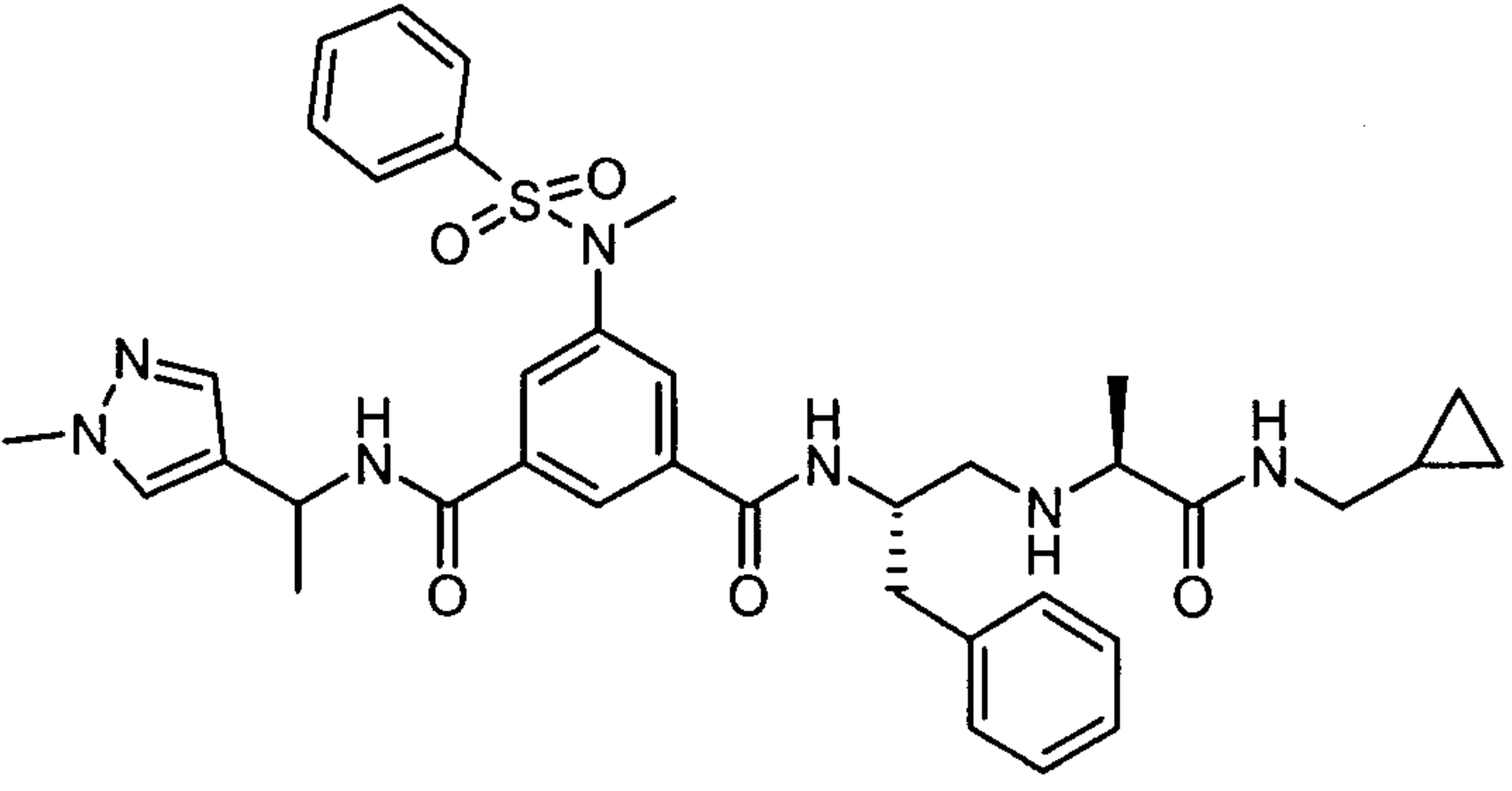
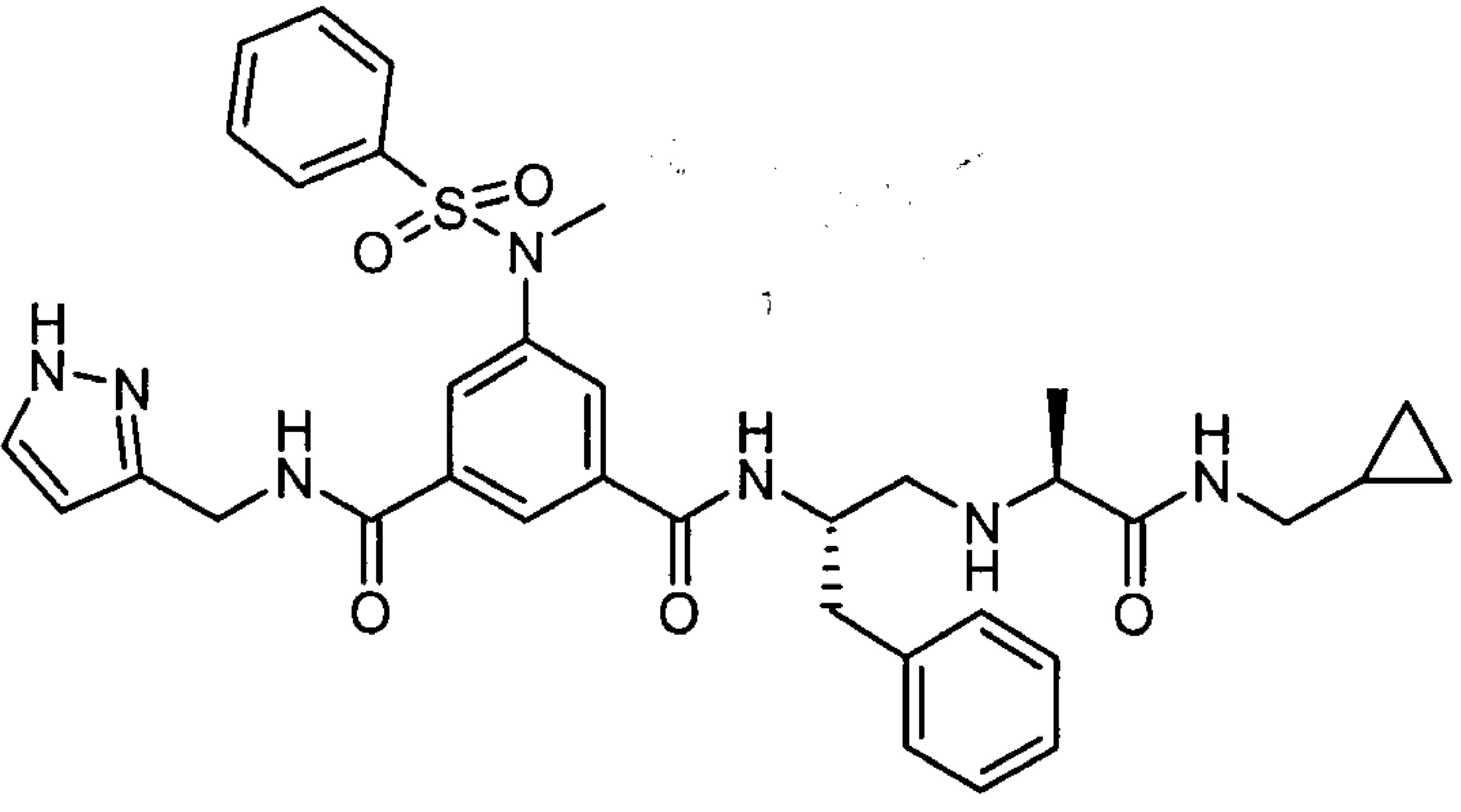
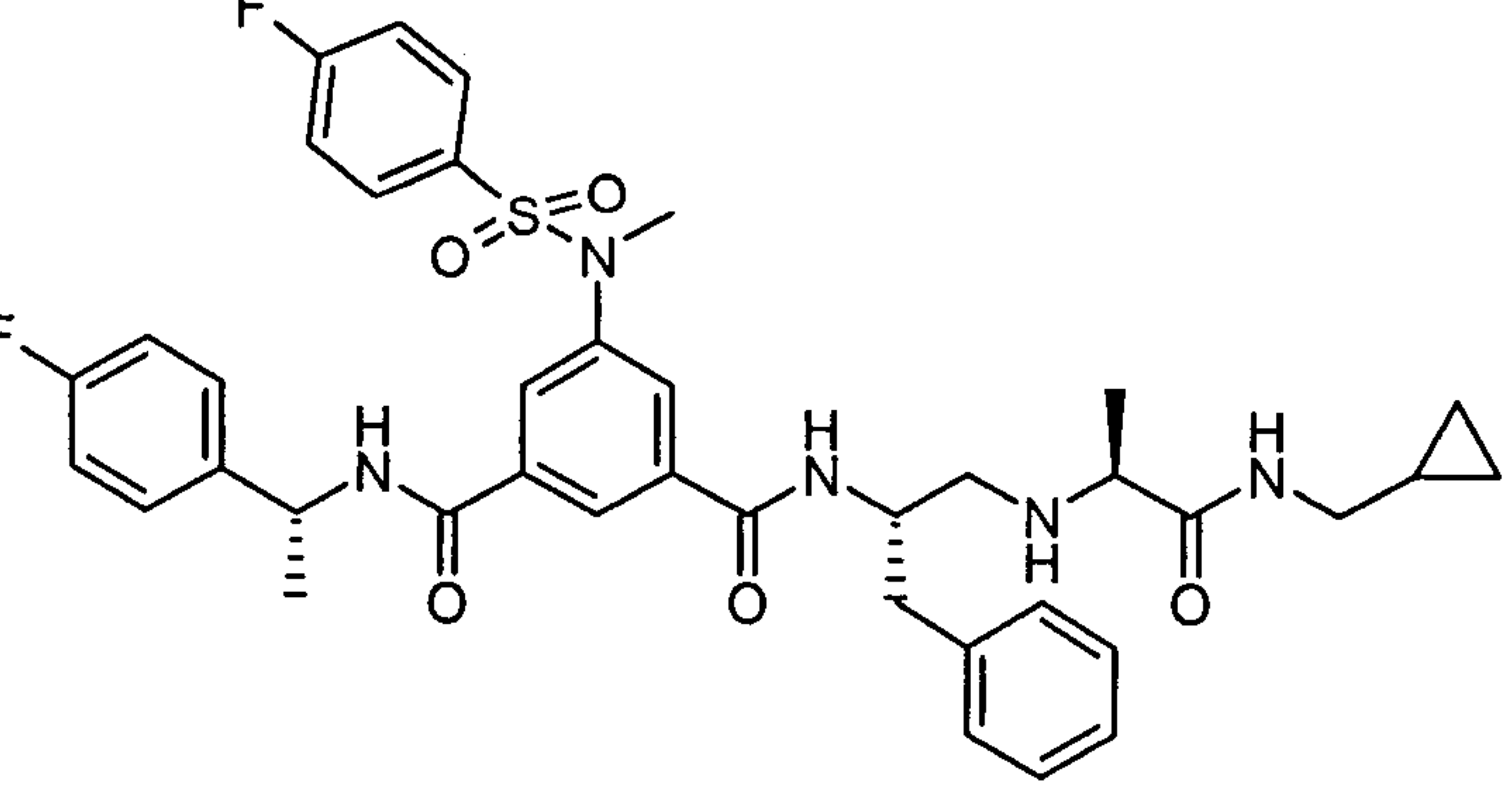
- 52 -

(31)		6.4
(32)		6.5
(33)		6.6
(34)		6.7
(35)		6.8

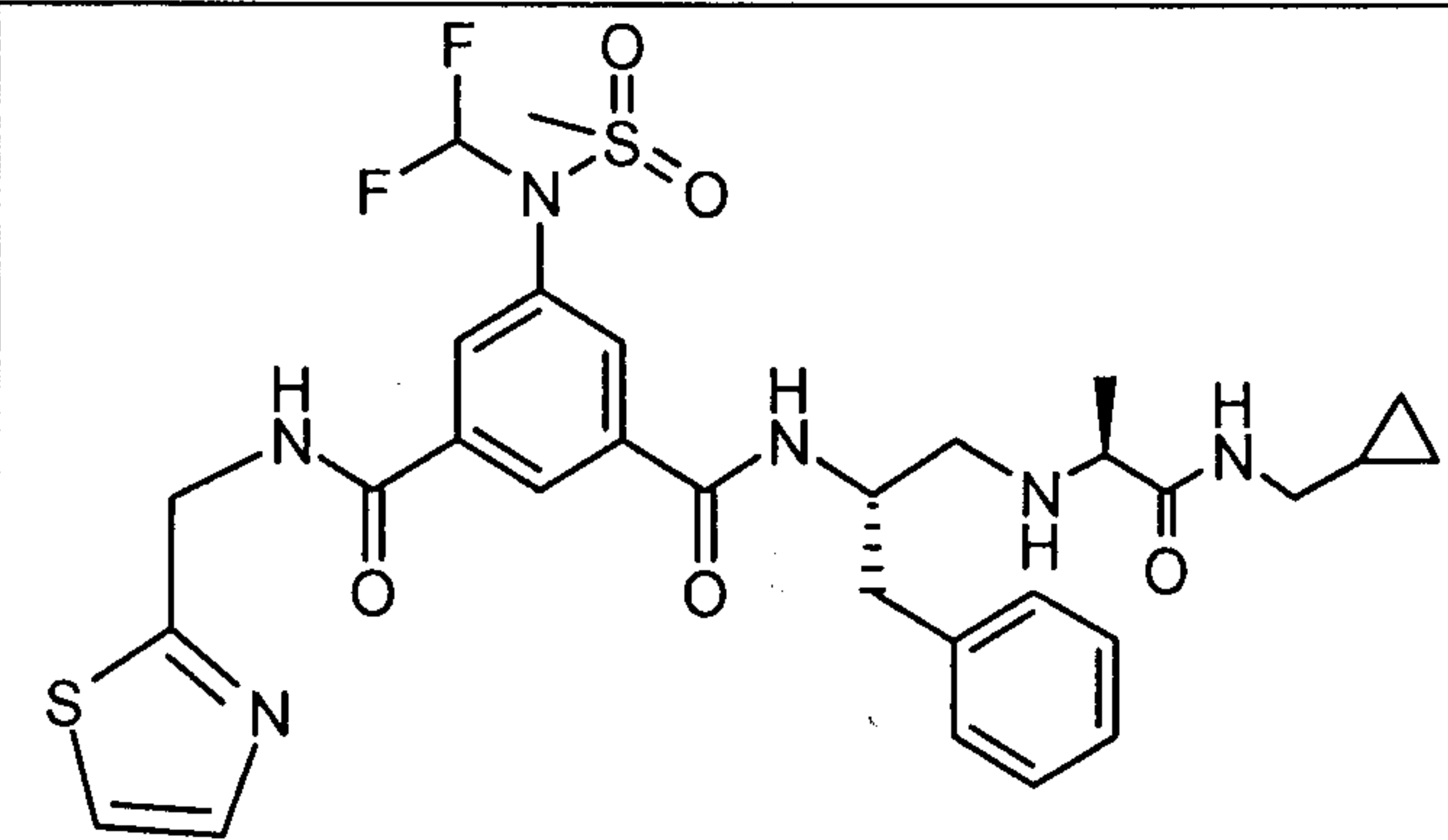
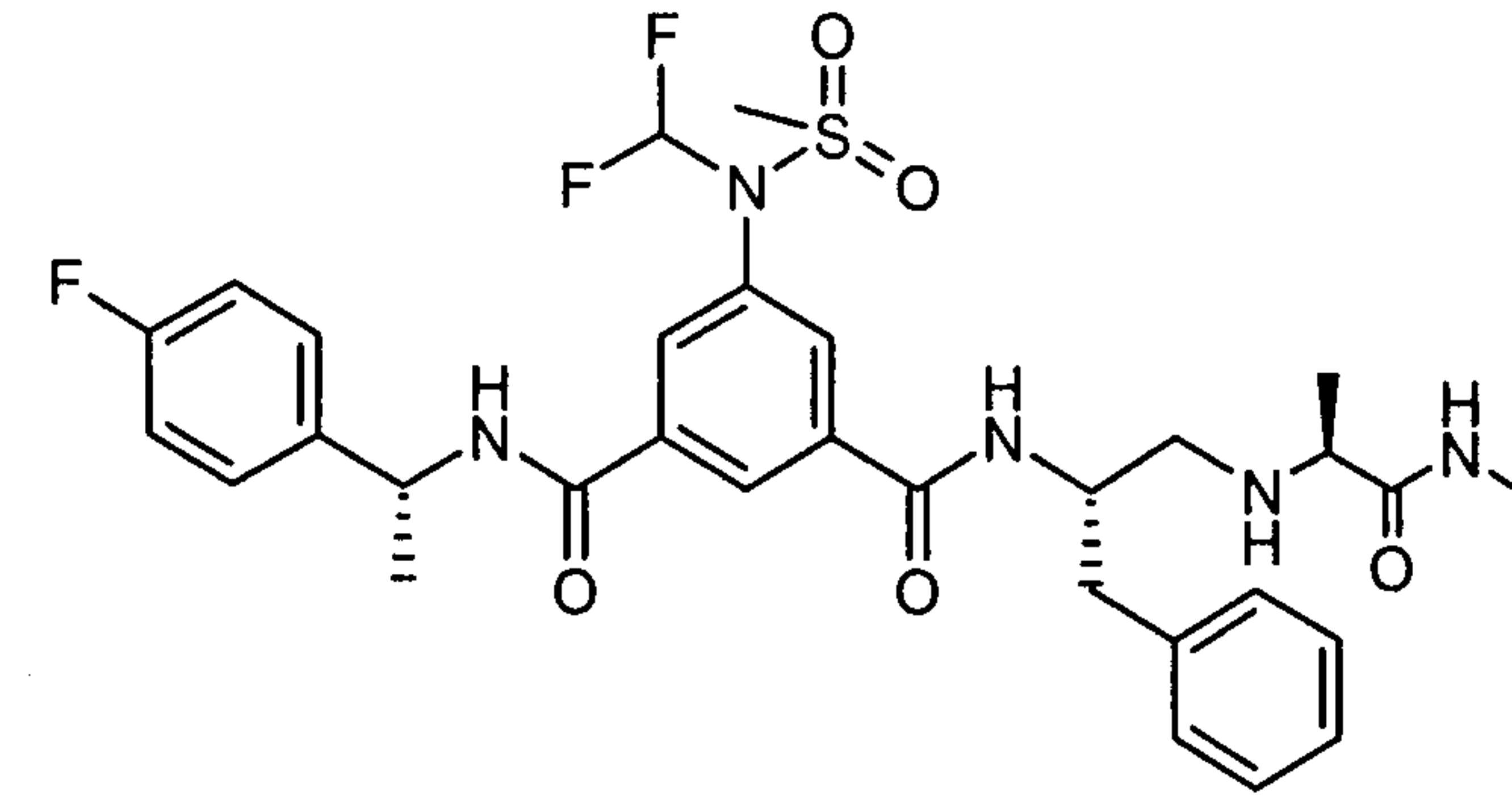
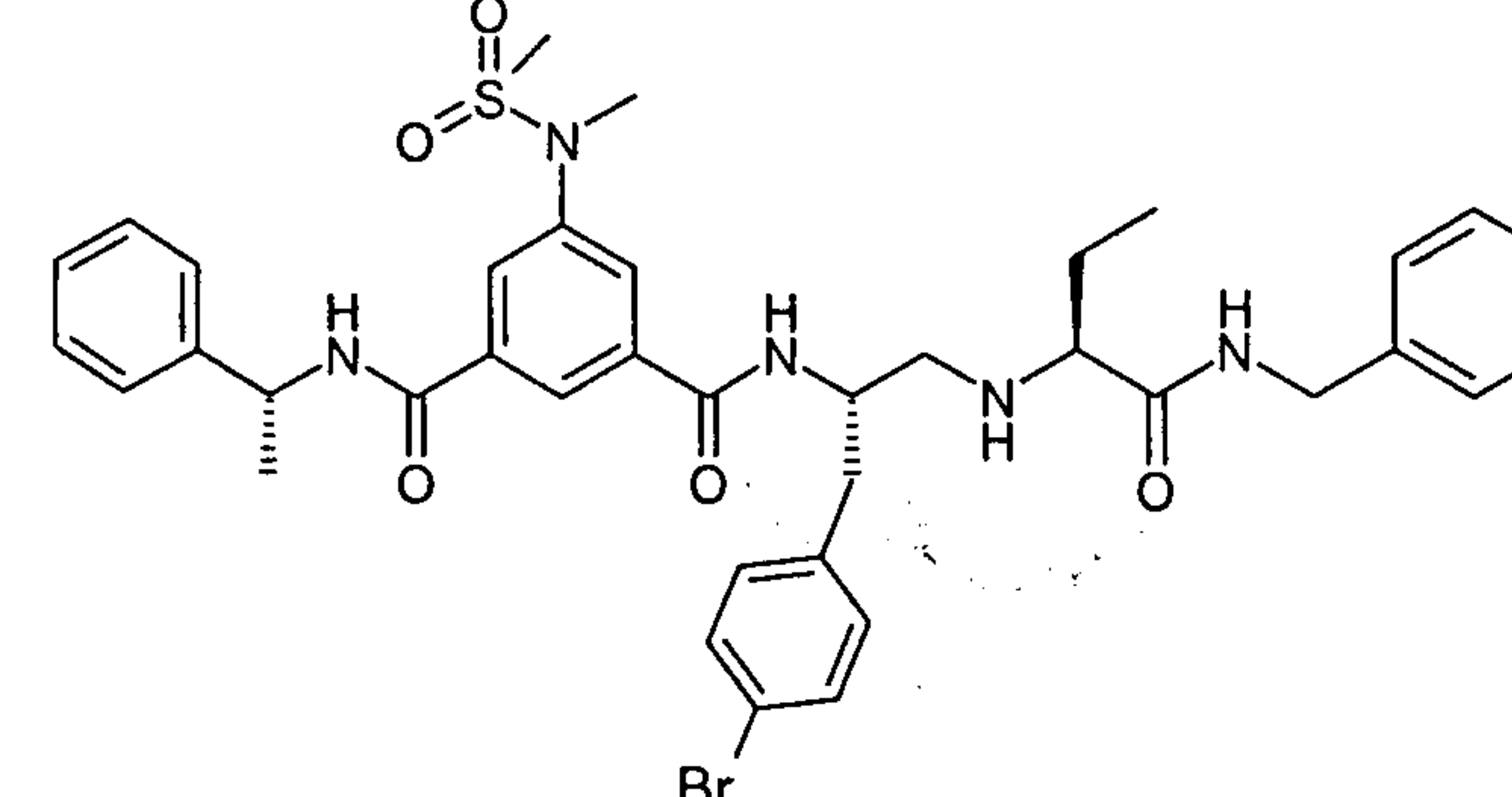
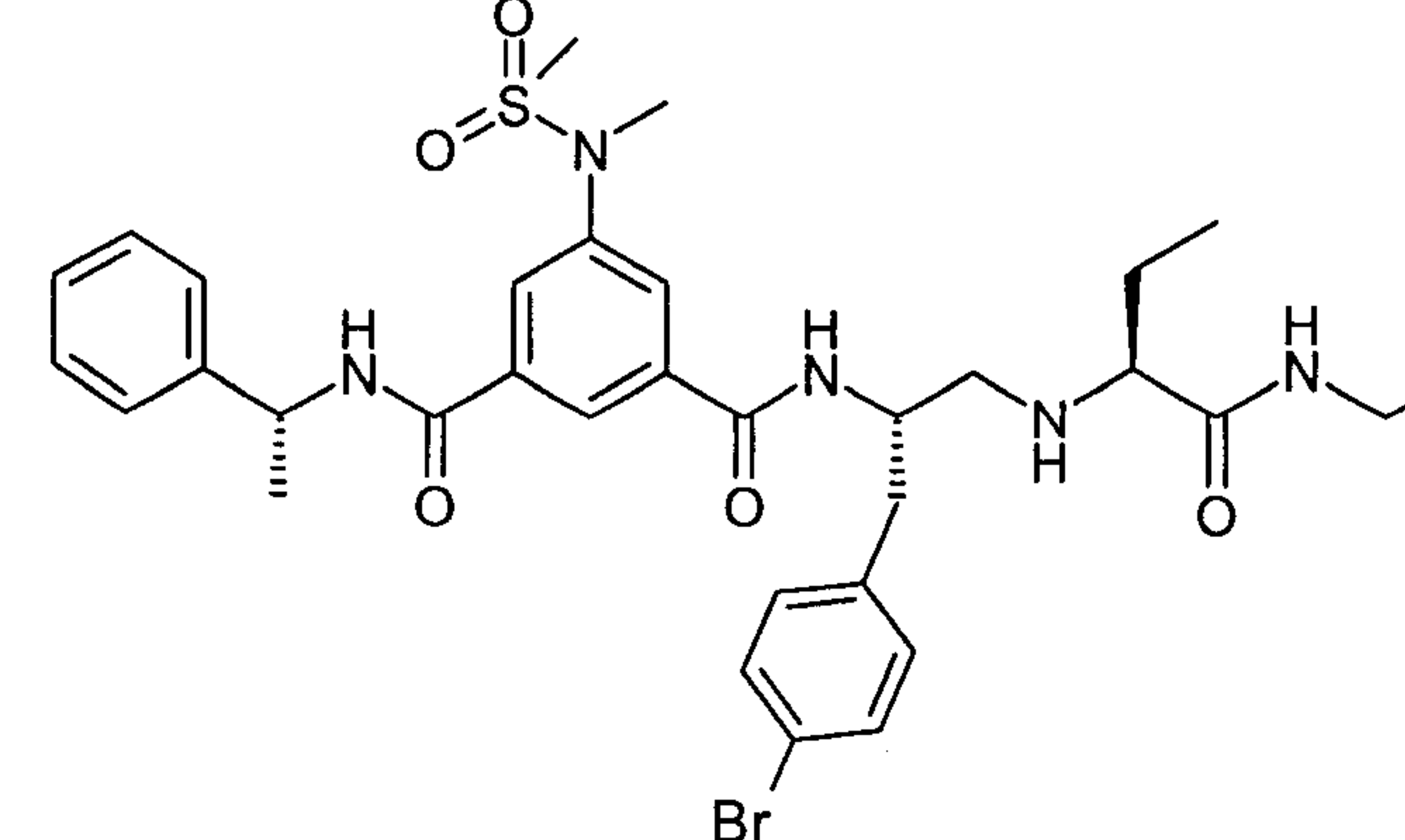
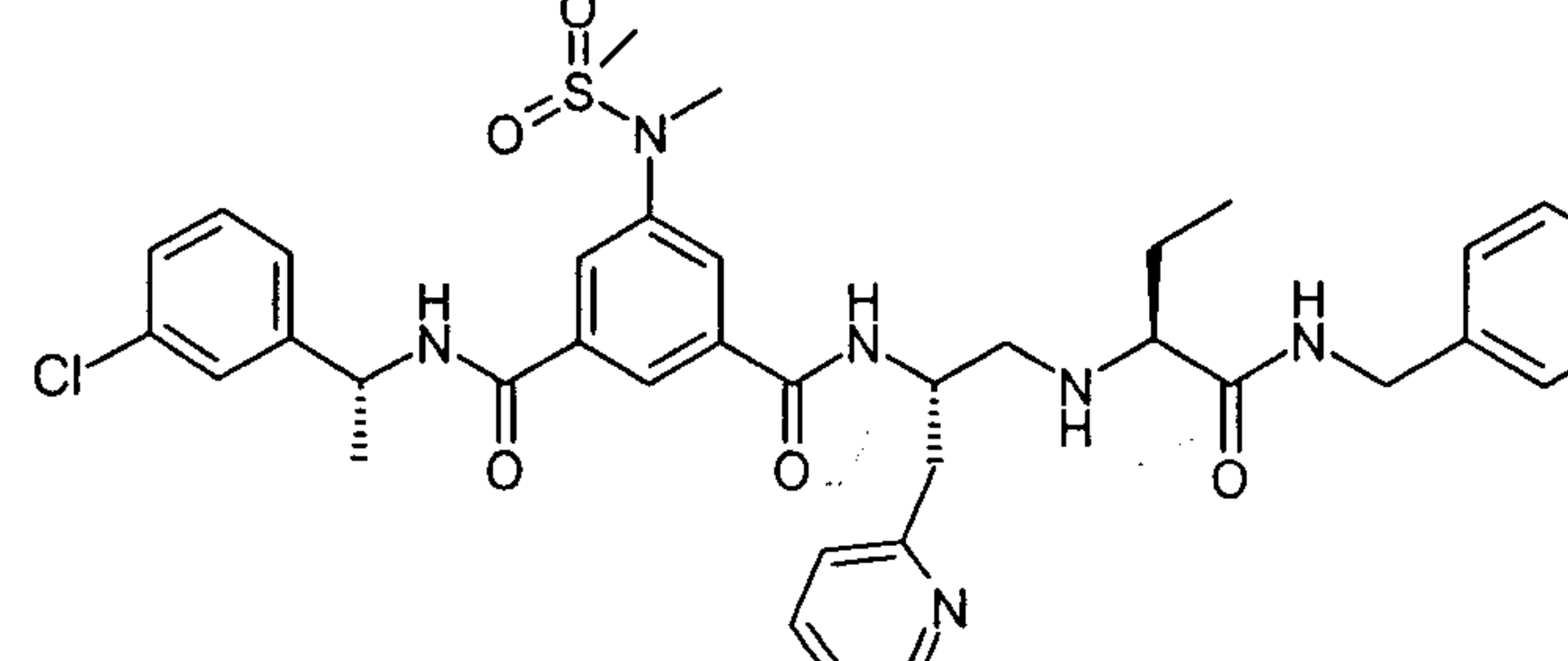
- 53 -

(36)		6.9
(37)		6.10
(38)		6.11
(39)		6.12

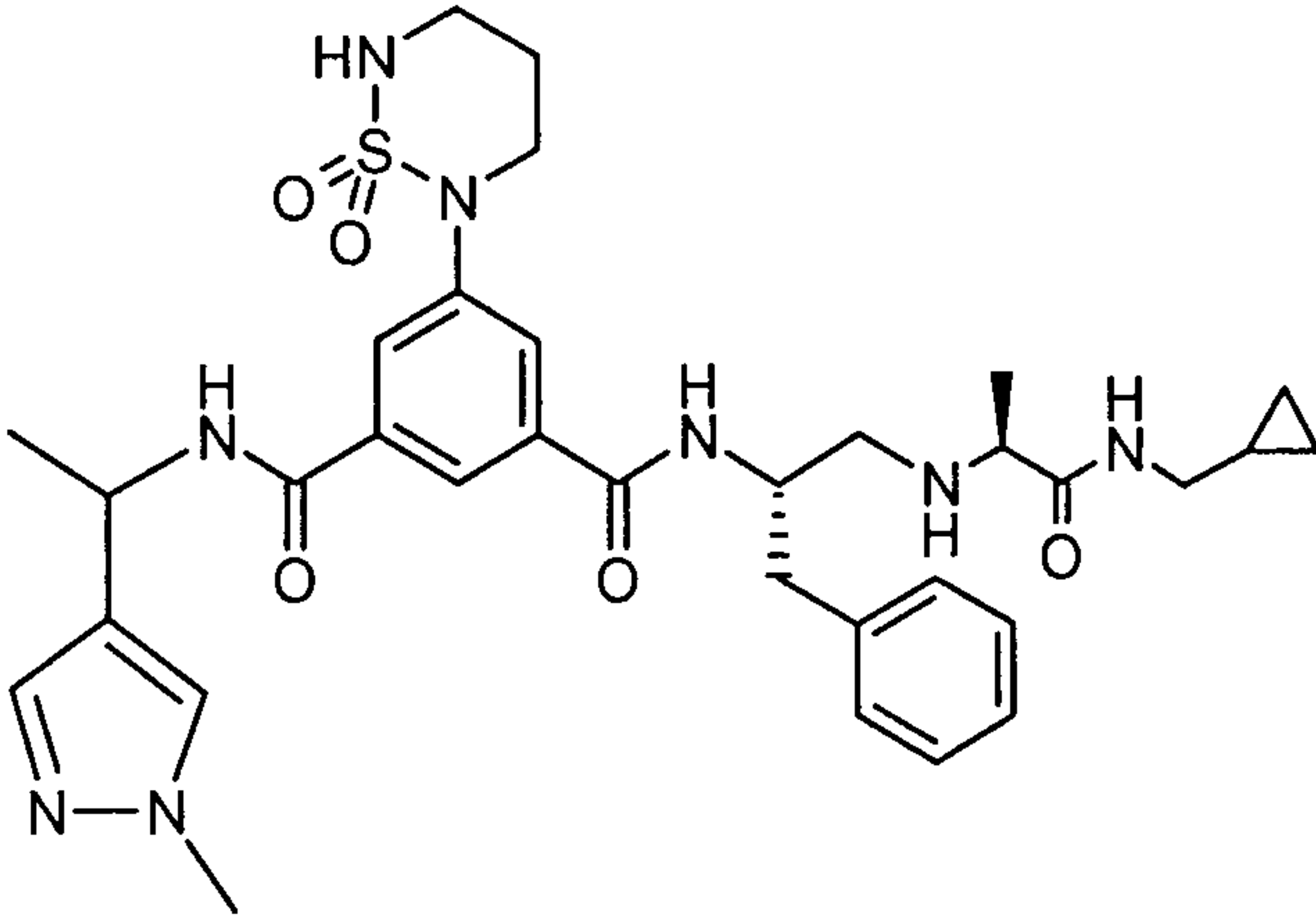
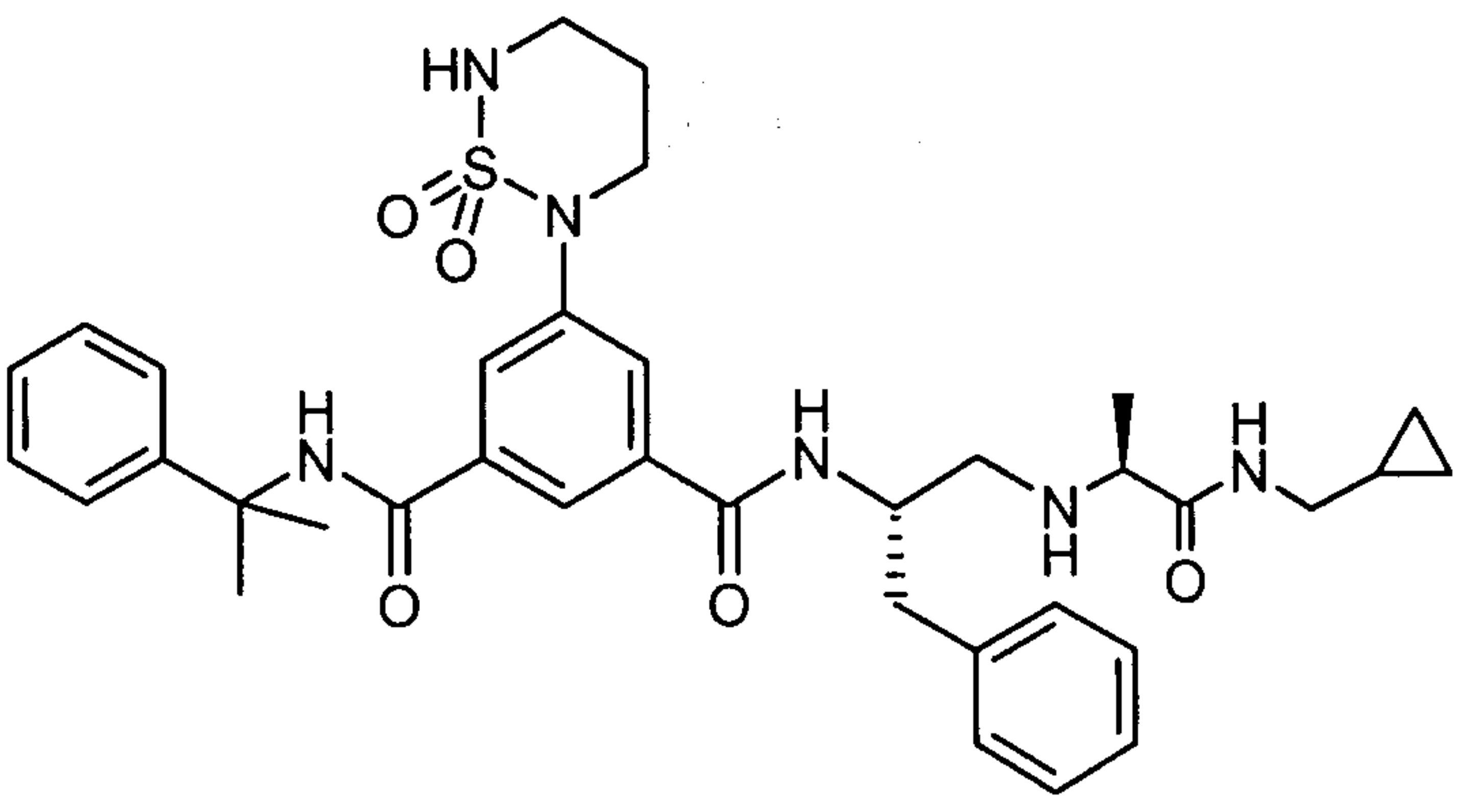
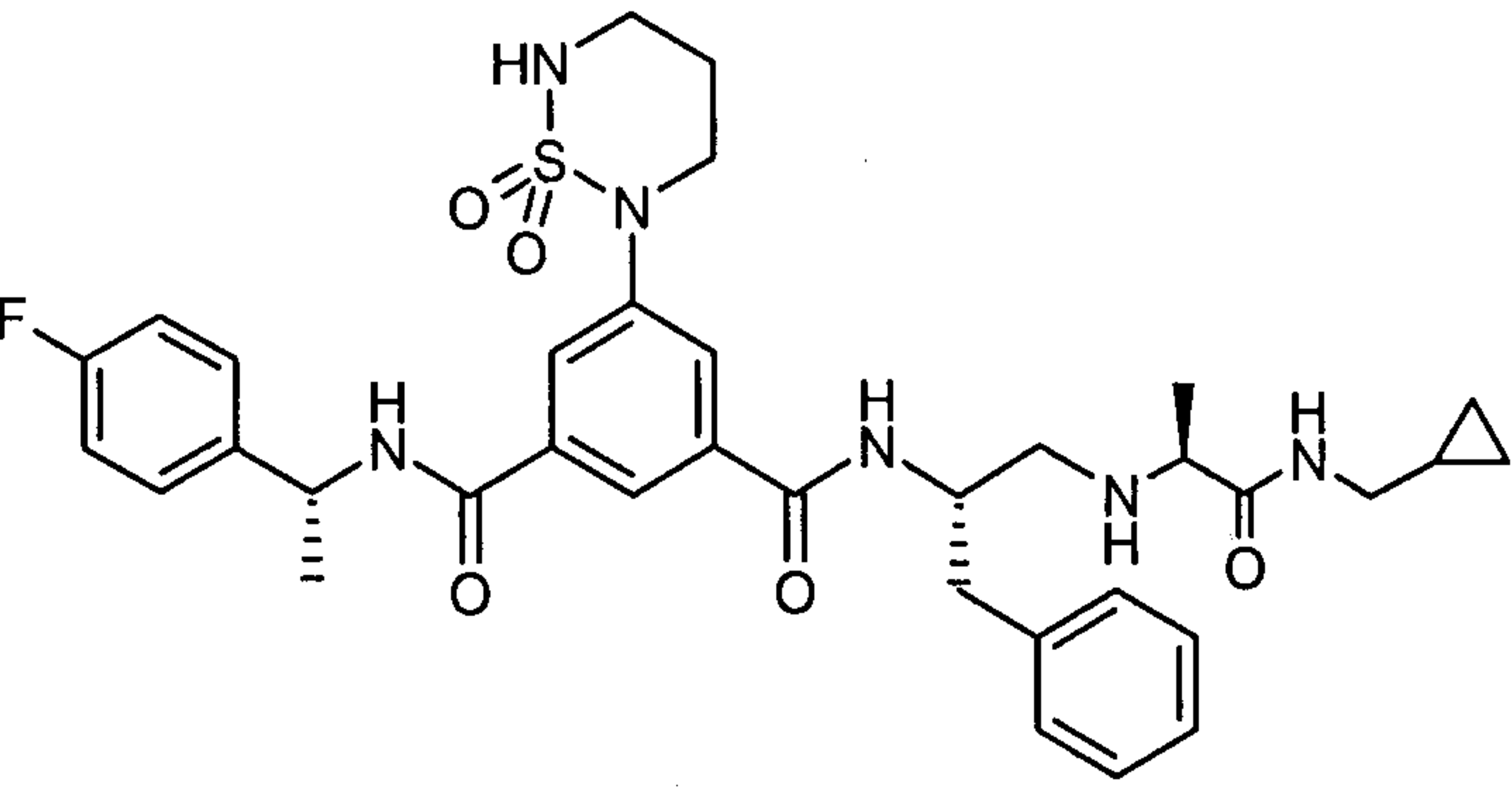
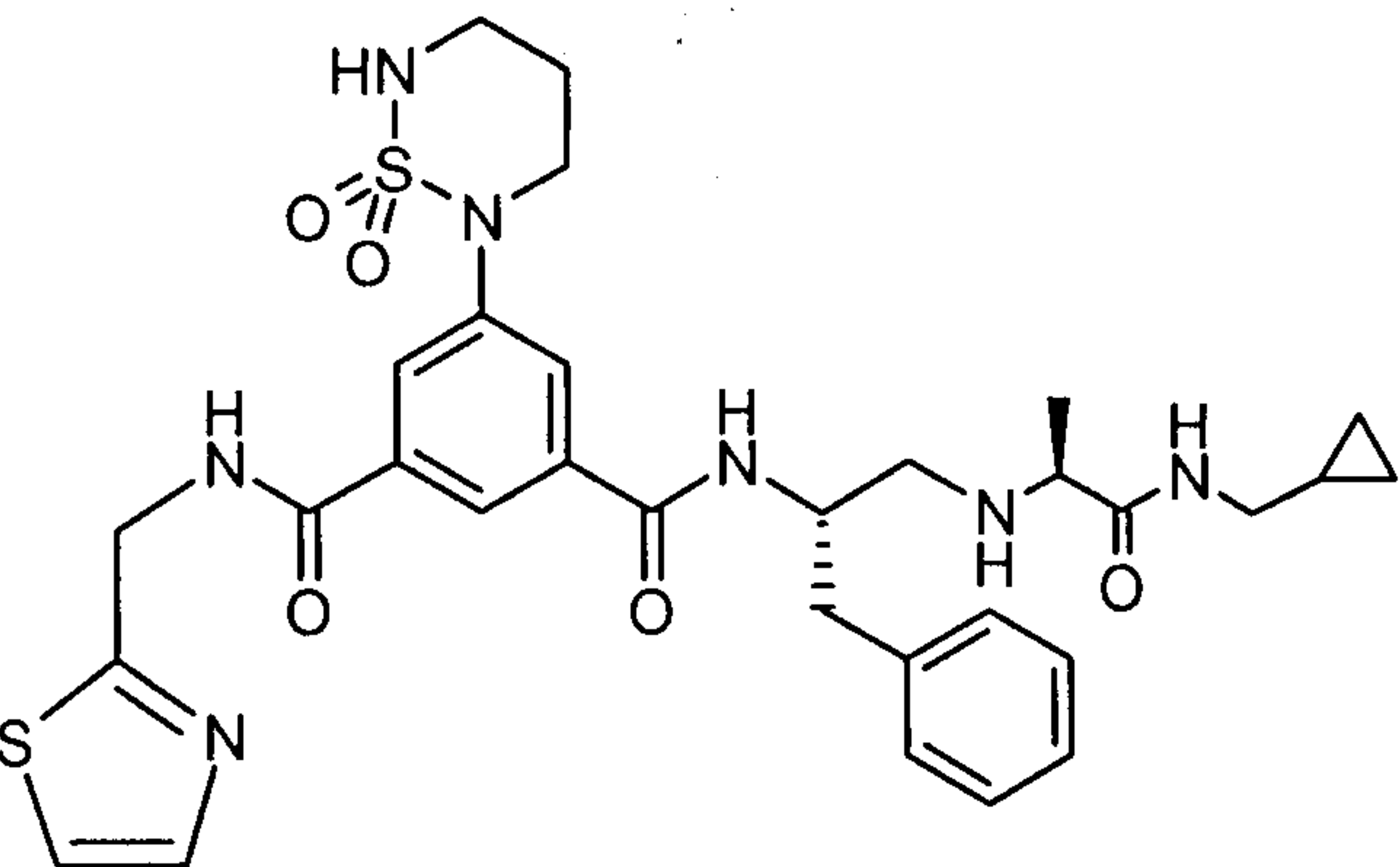
- 54 -

(40)		6.13
(41)		6.14
(42)		6.15
(43)		6.16

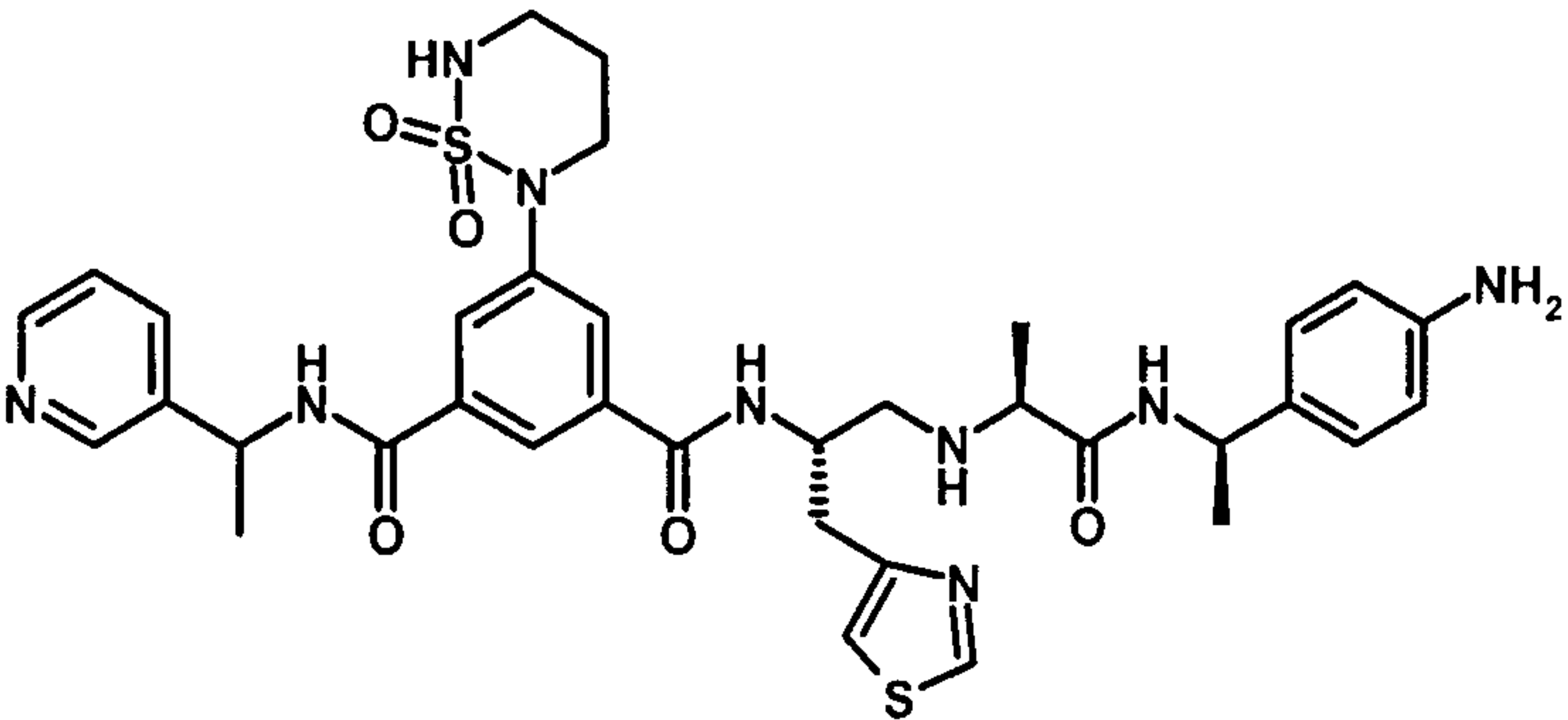
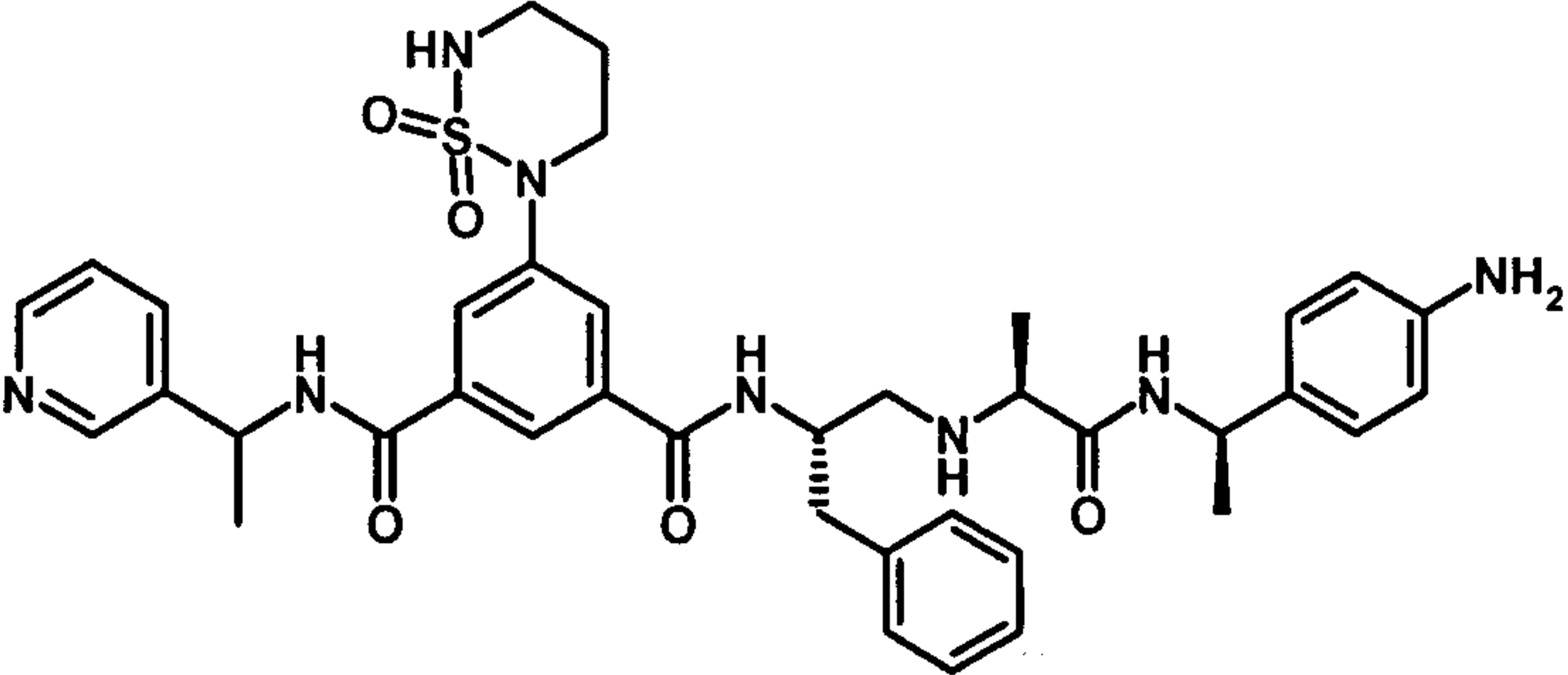
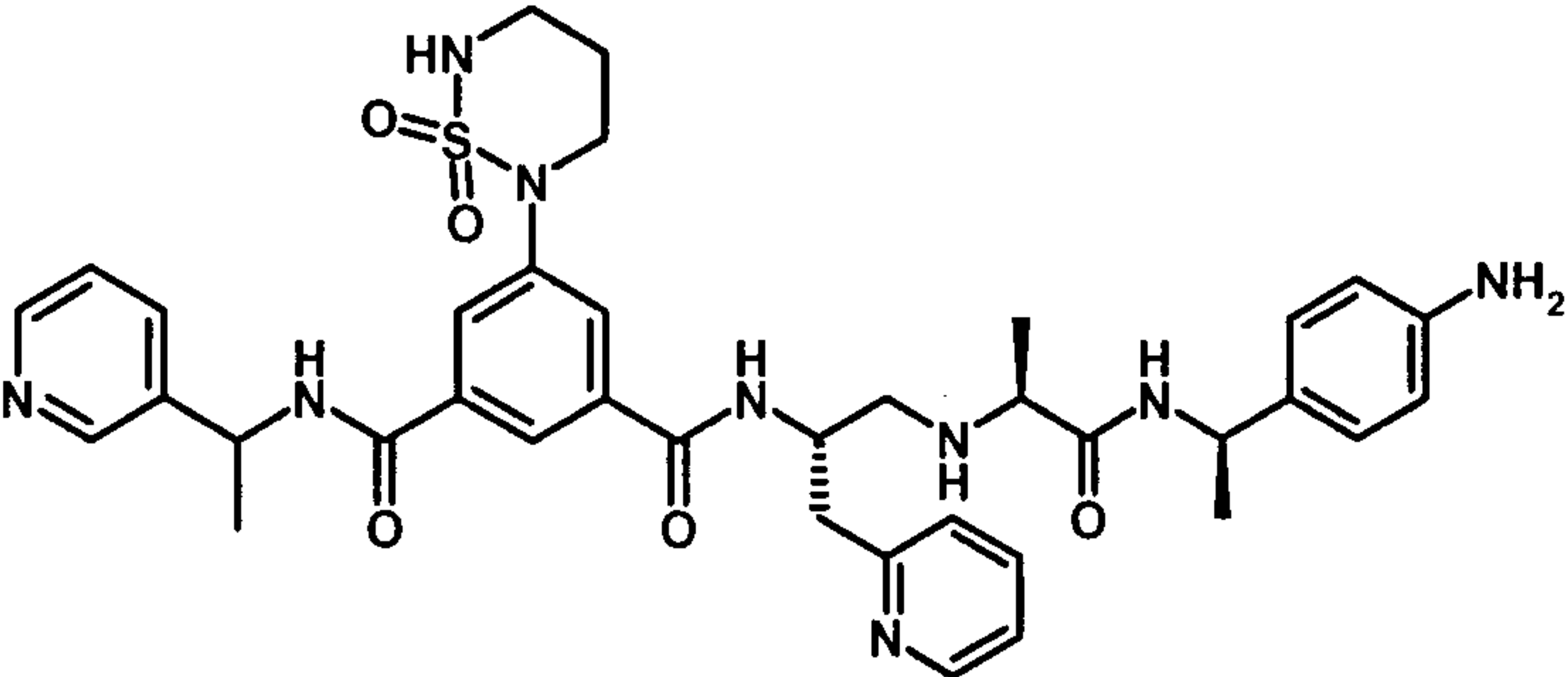
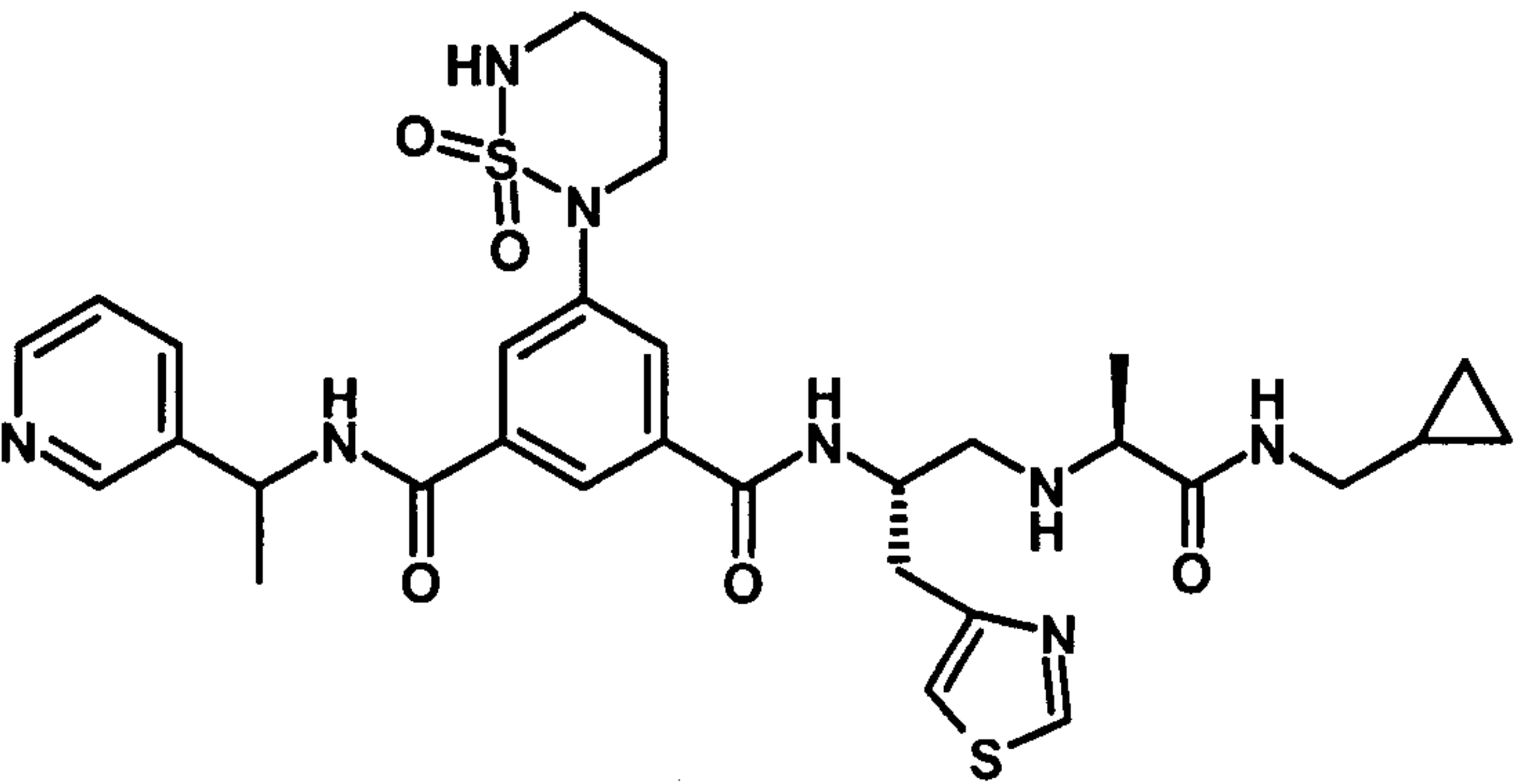
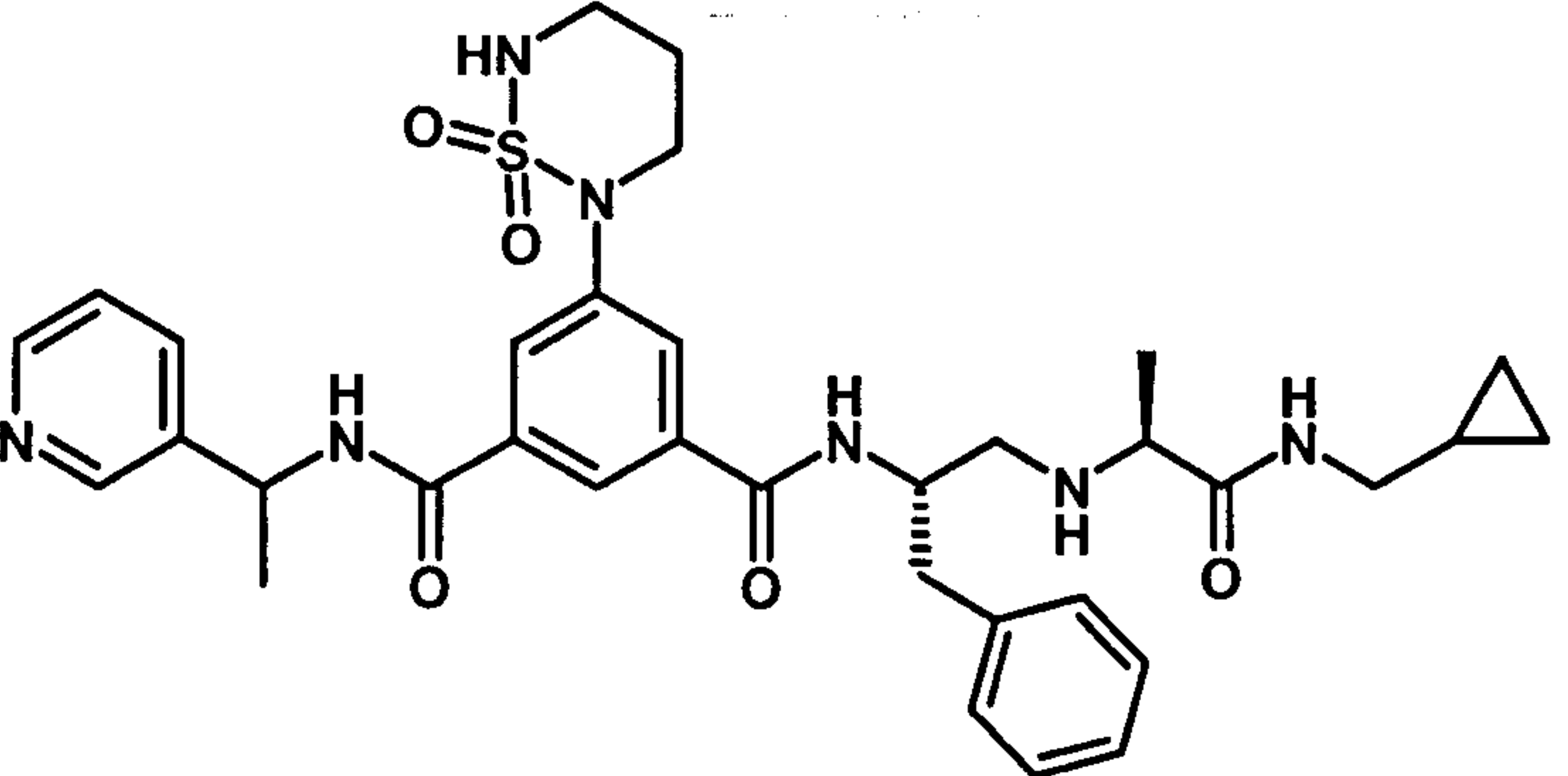
- 55 -

(44)		6.17
(45)		6.18
(46)		6.19
(47)		6.20
(48)		6.21

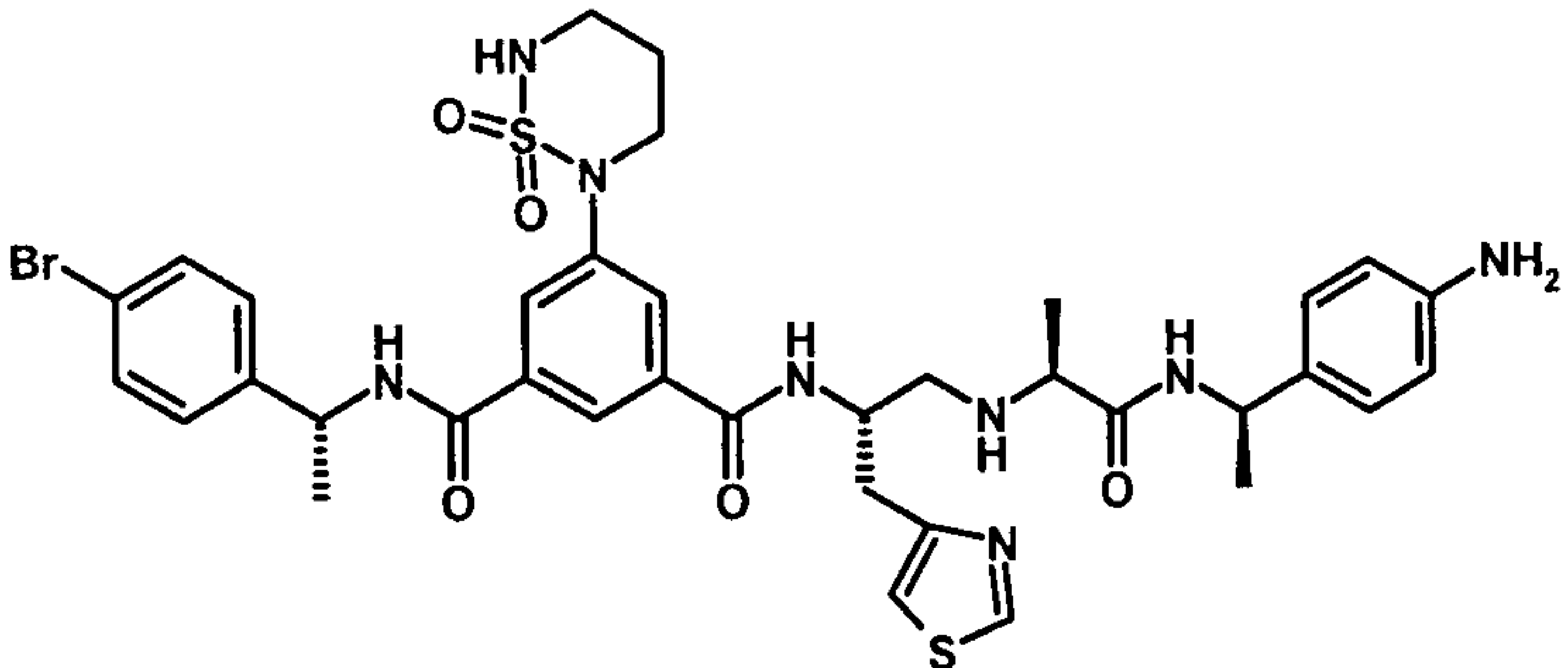
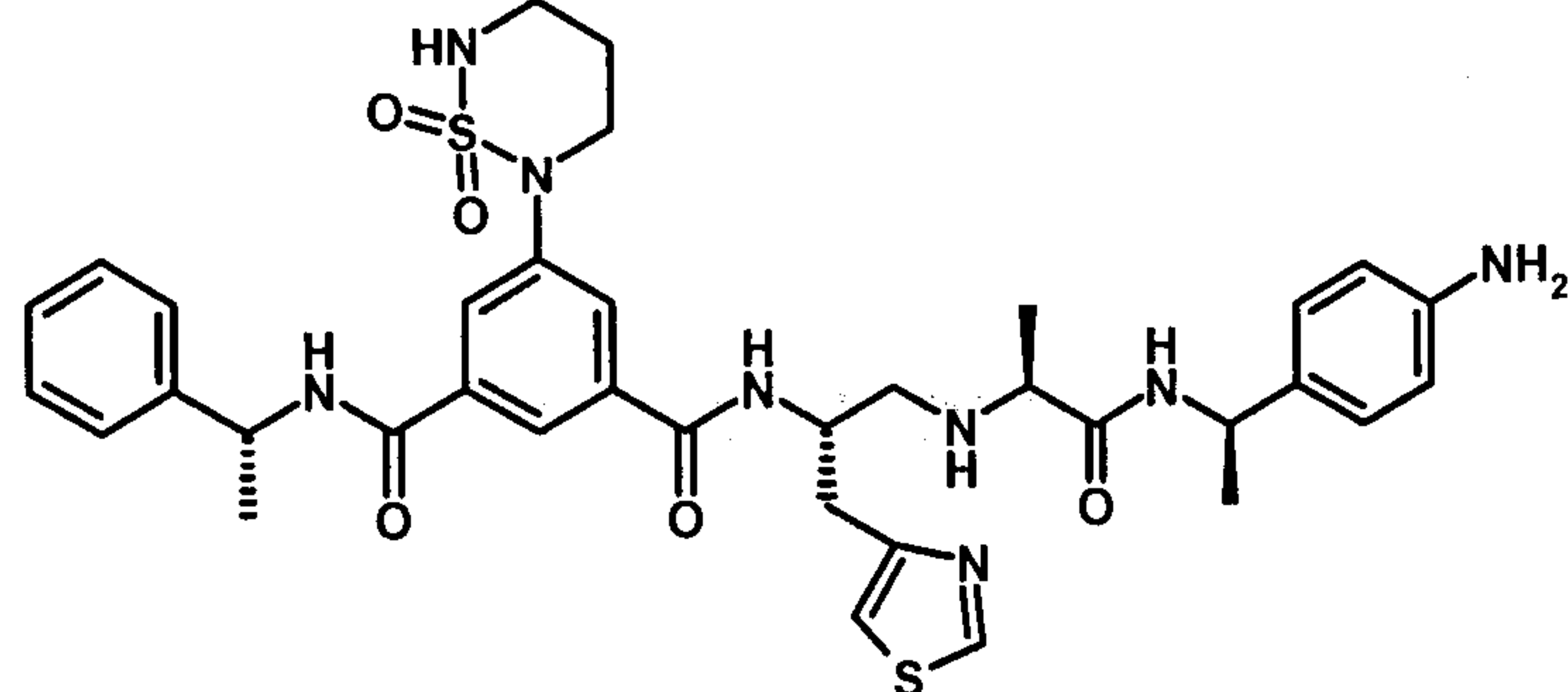
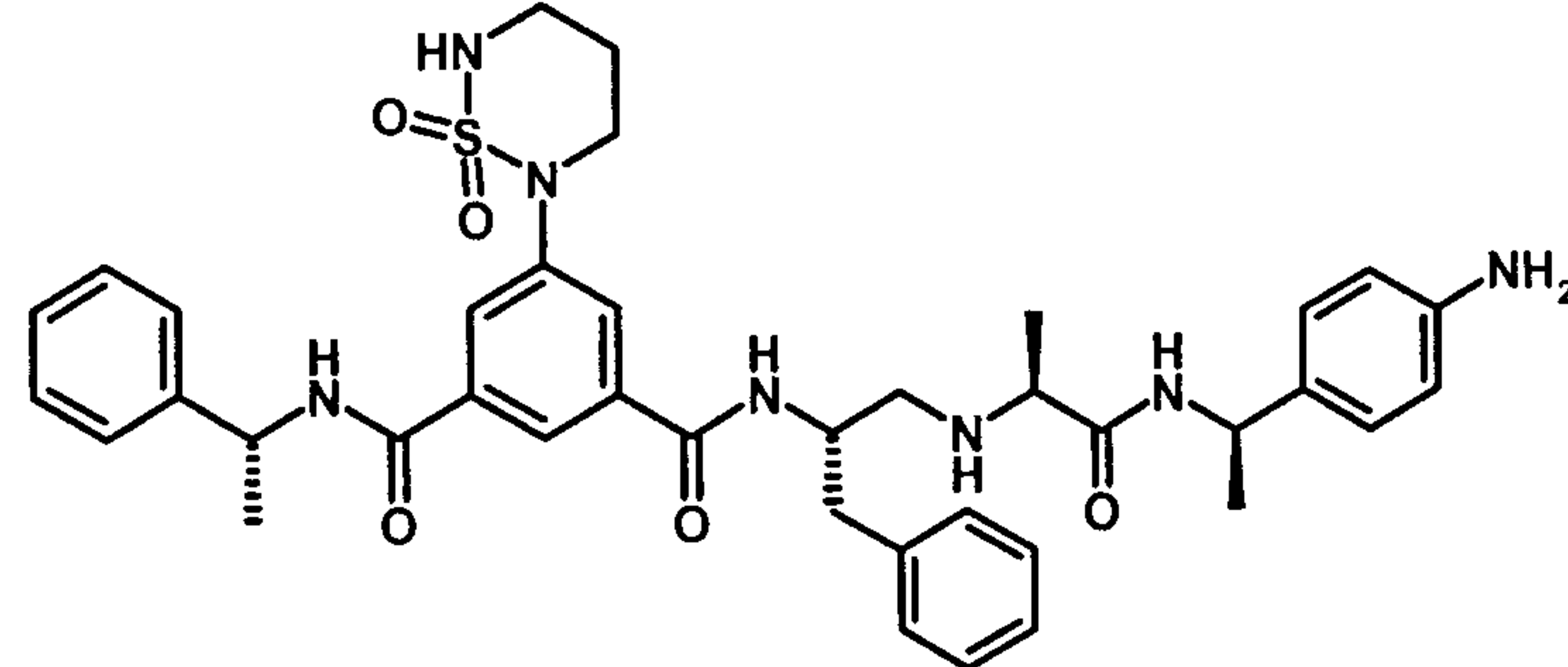
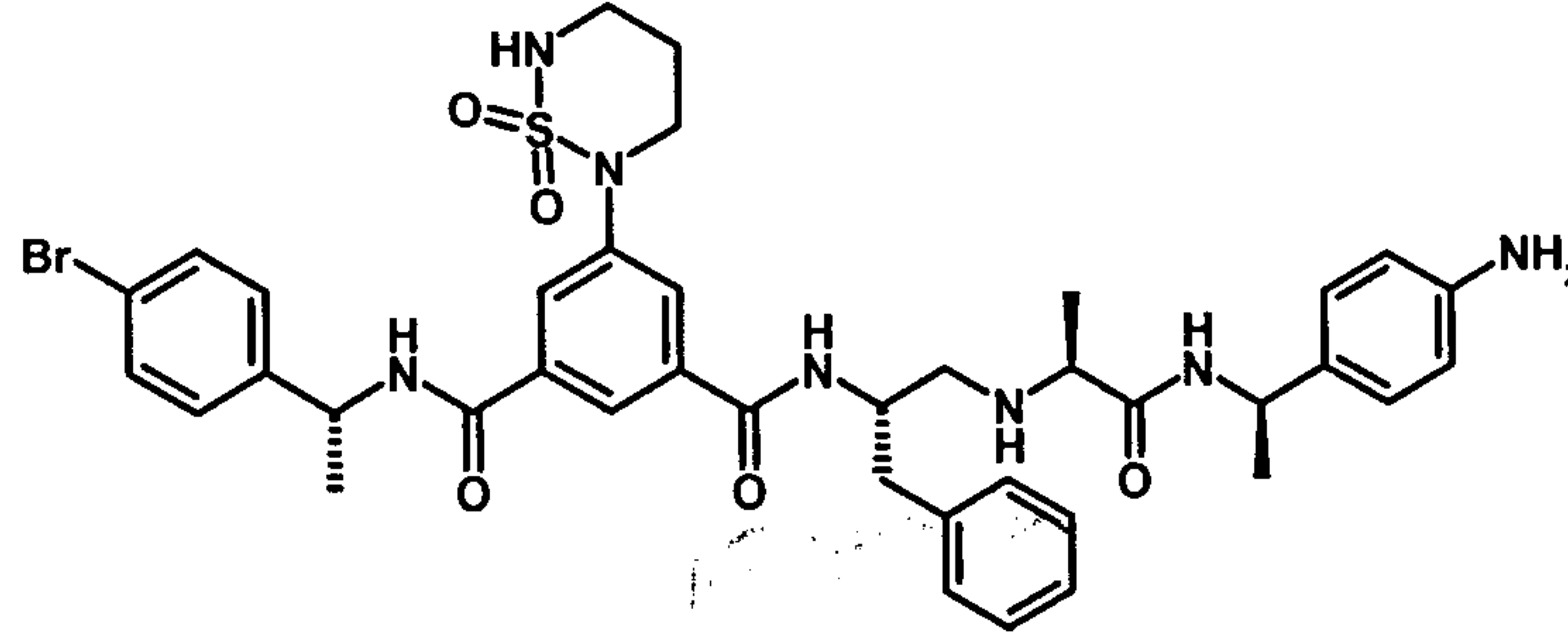
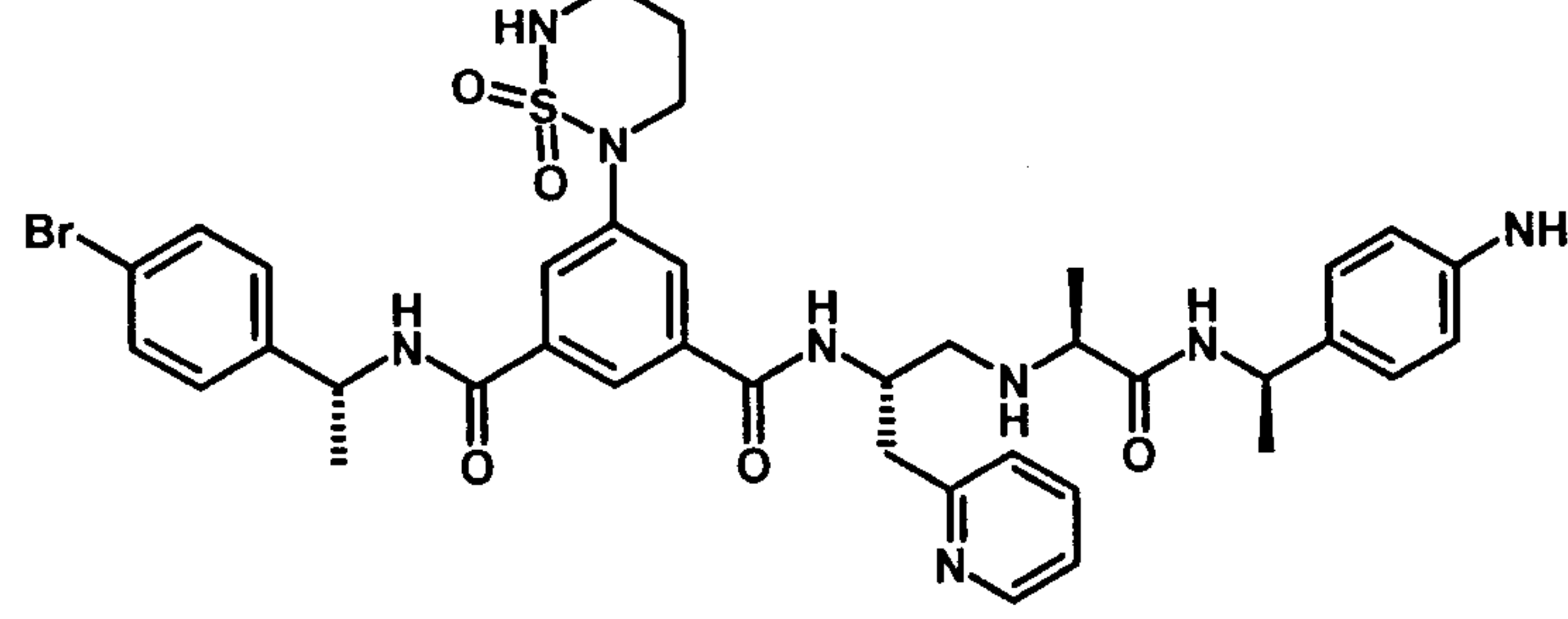
- 56 -

(49)		7
(50)		7.1
(51)		7.2
(52)		7.3

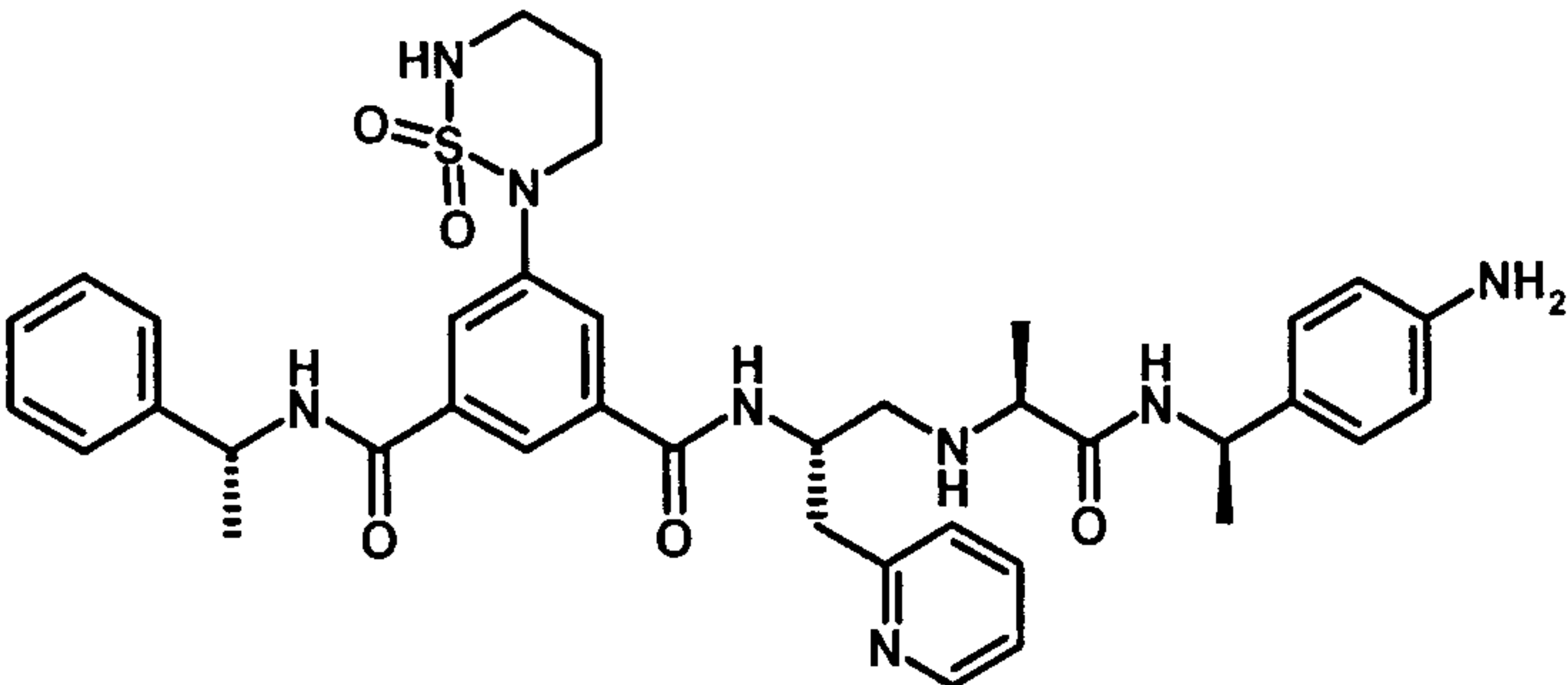
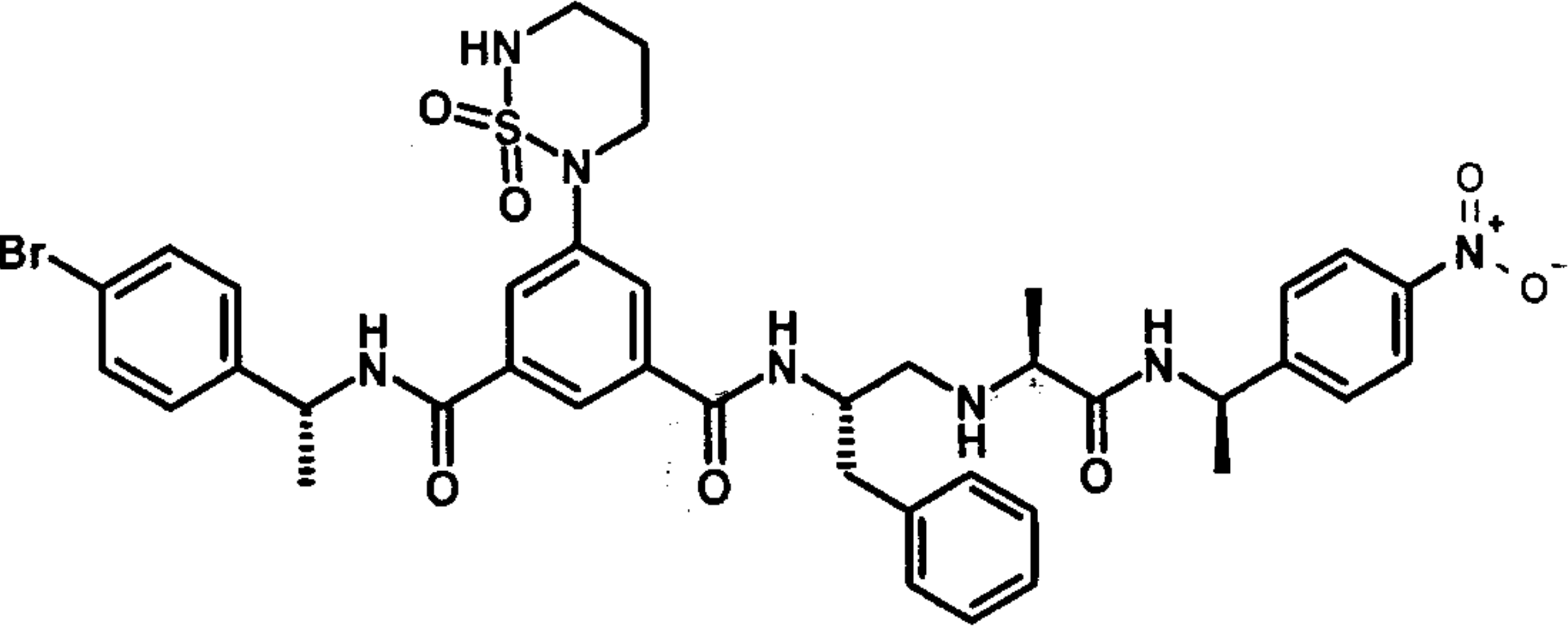
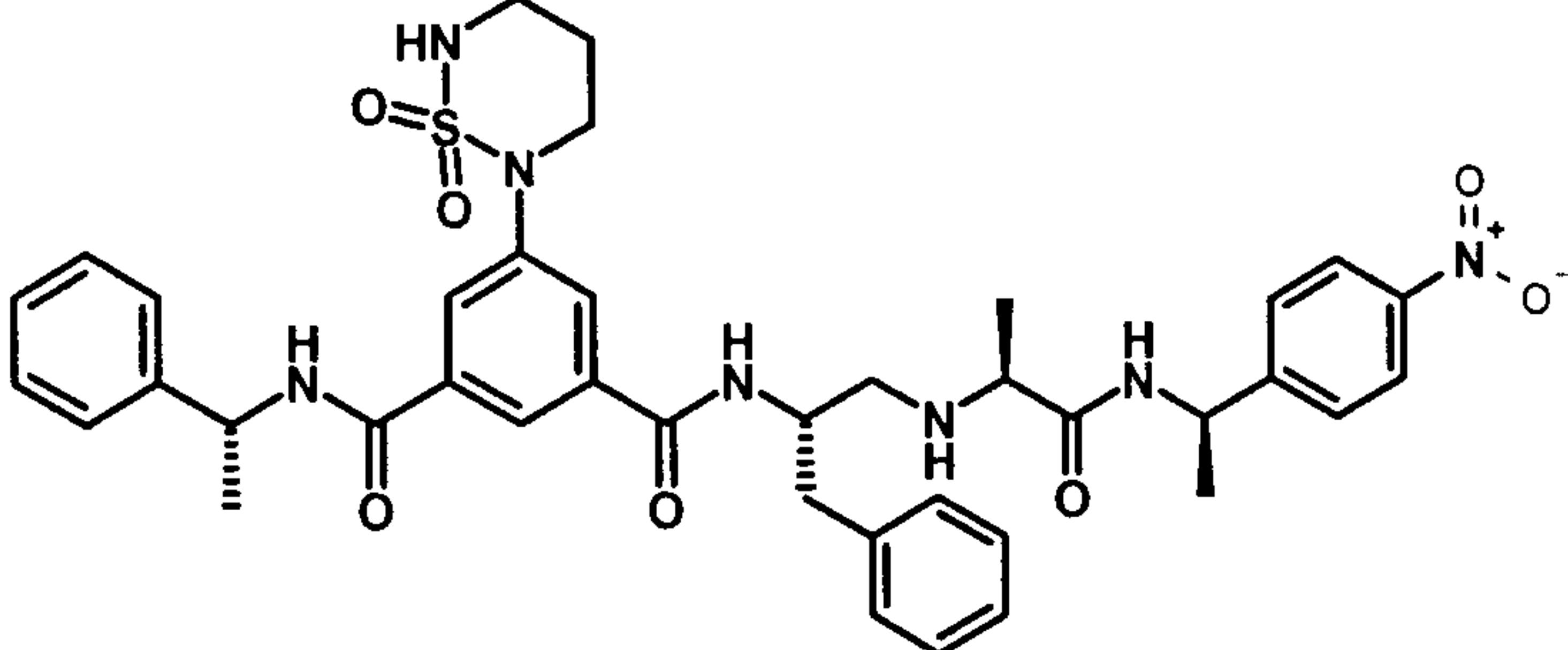
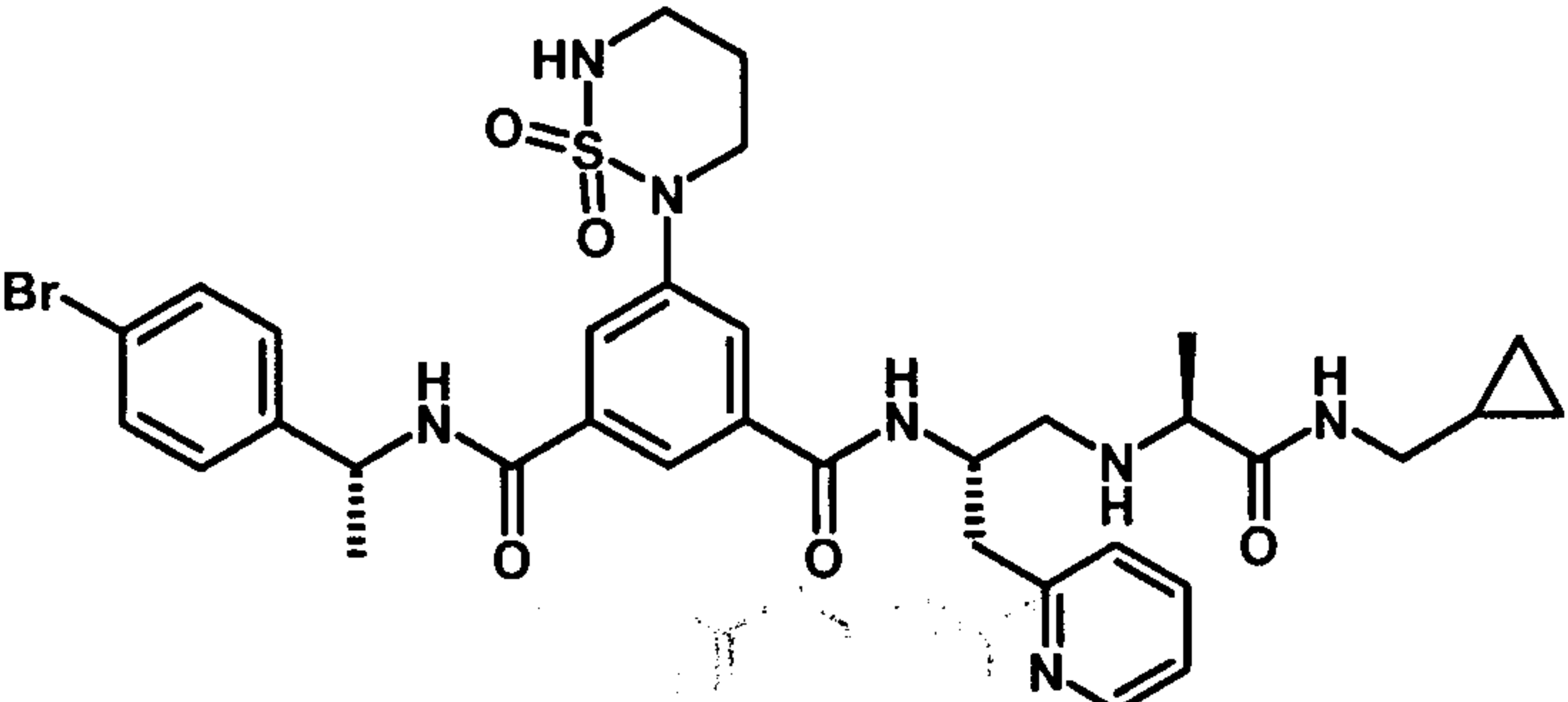
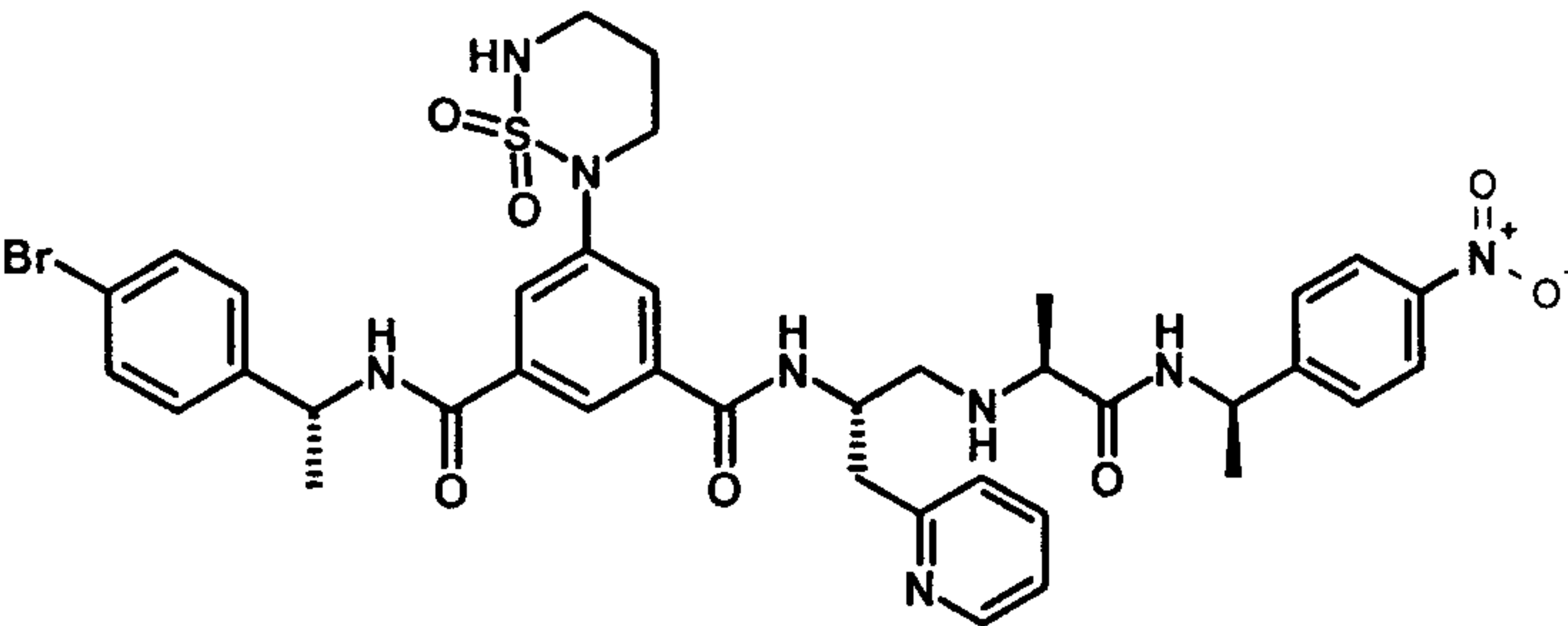
- 57 -

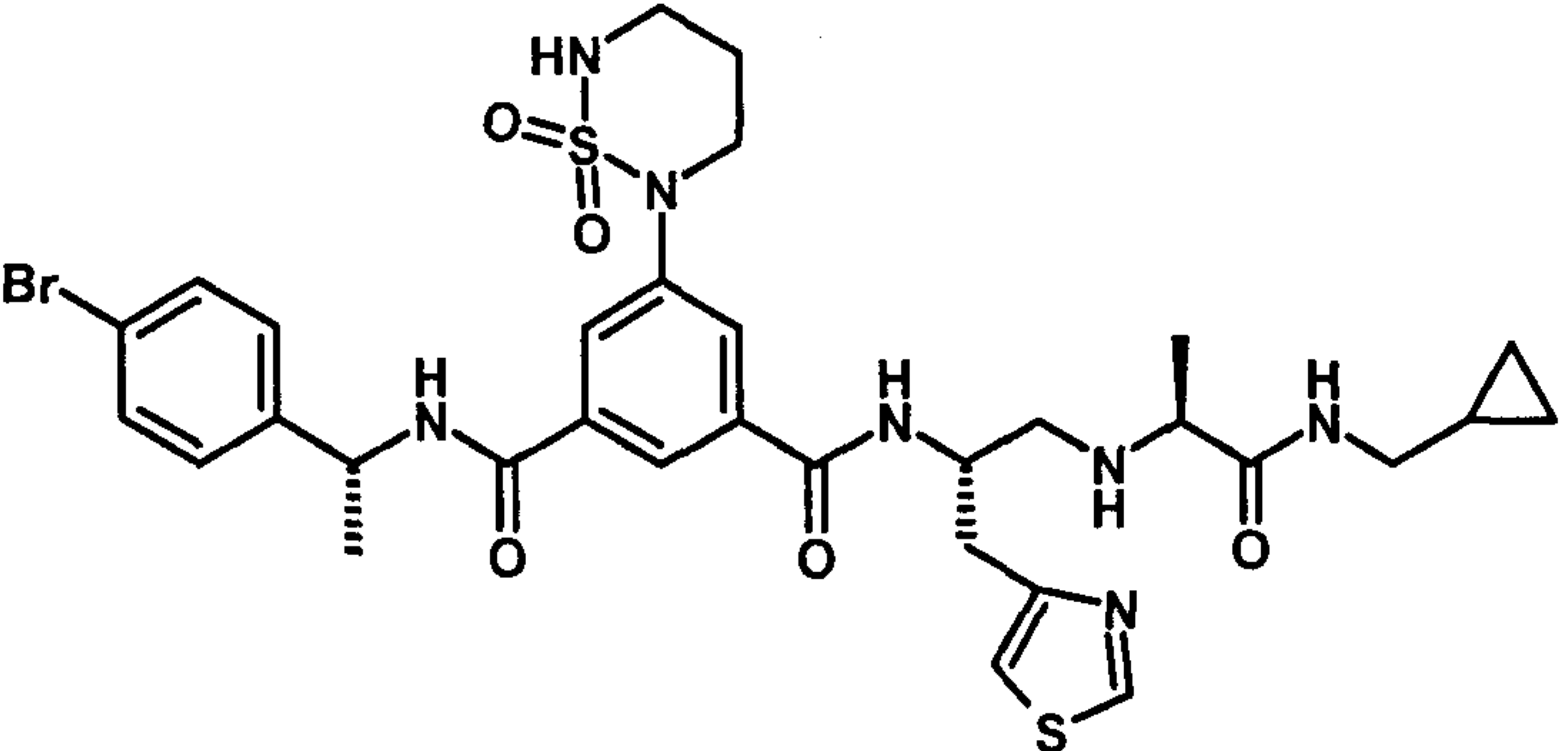
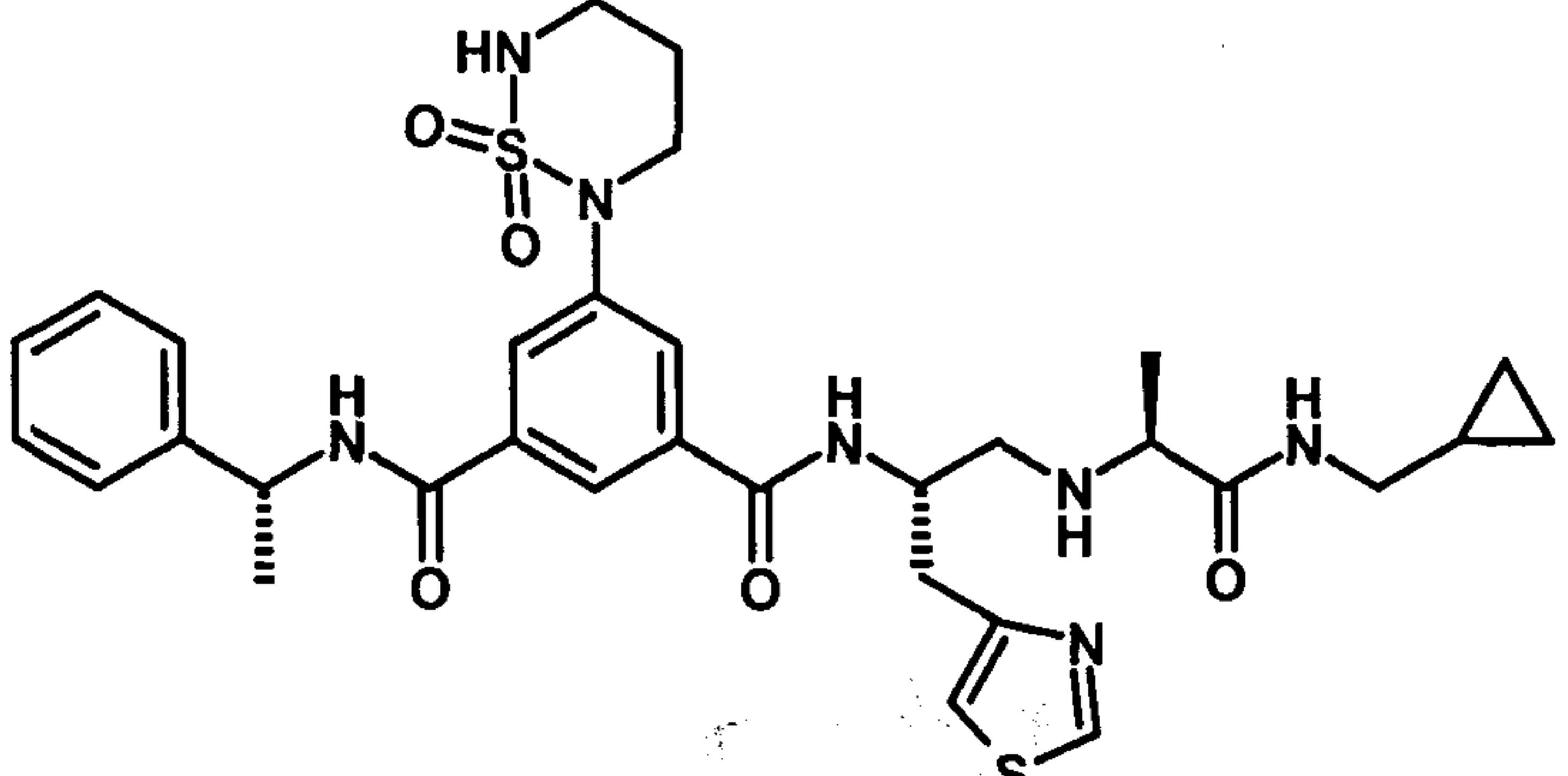
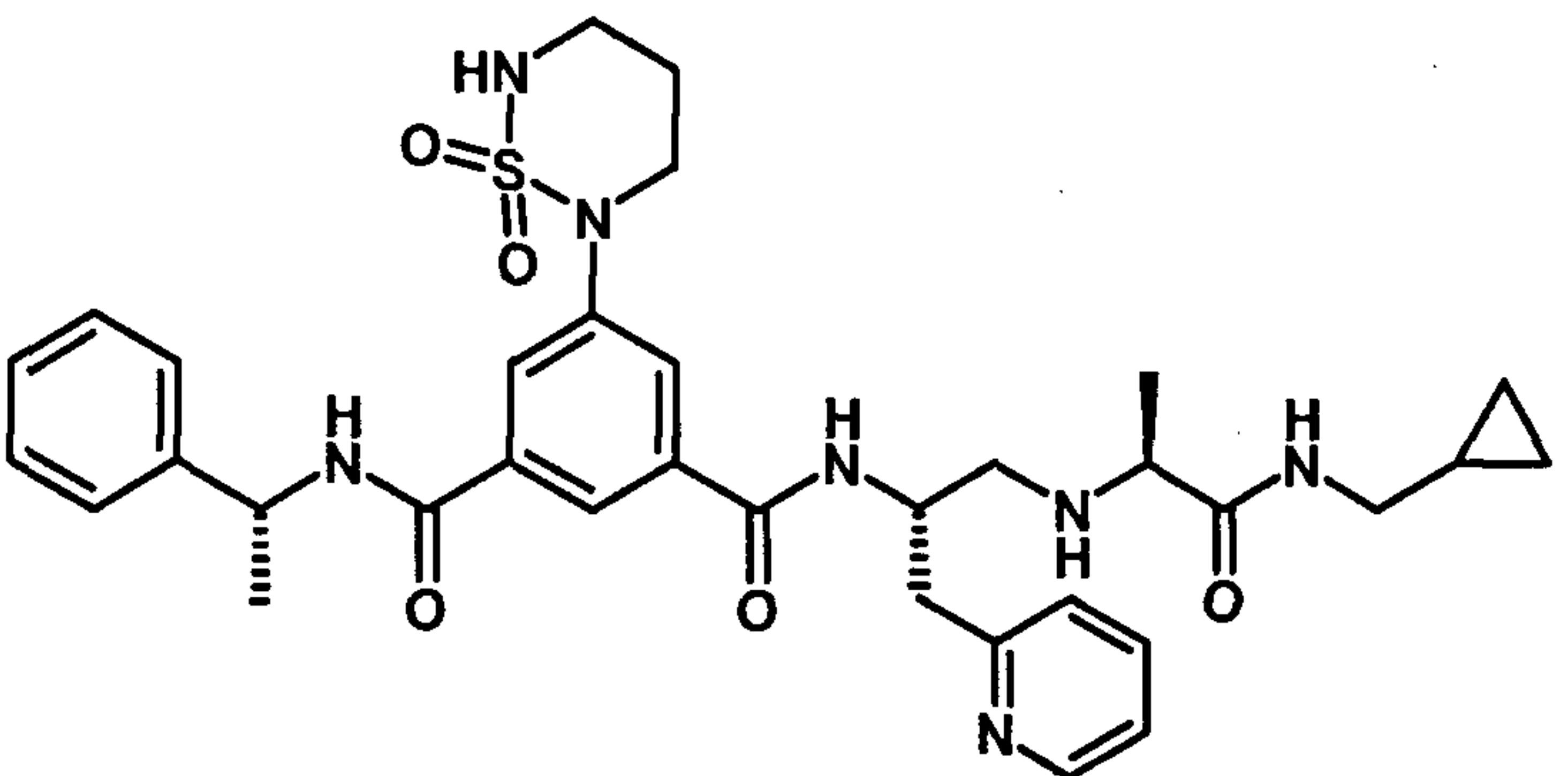
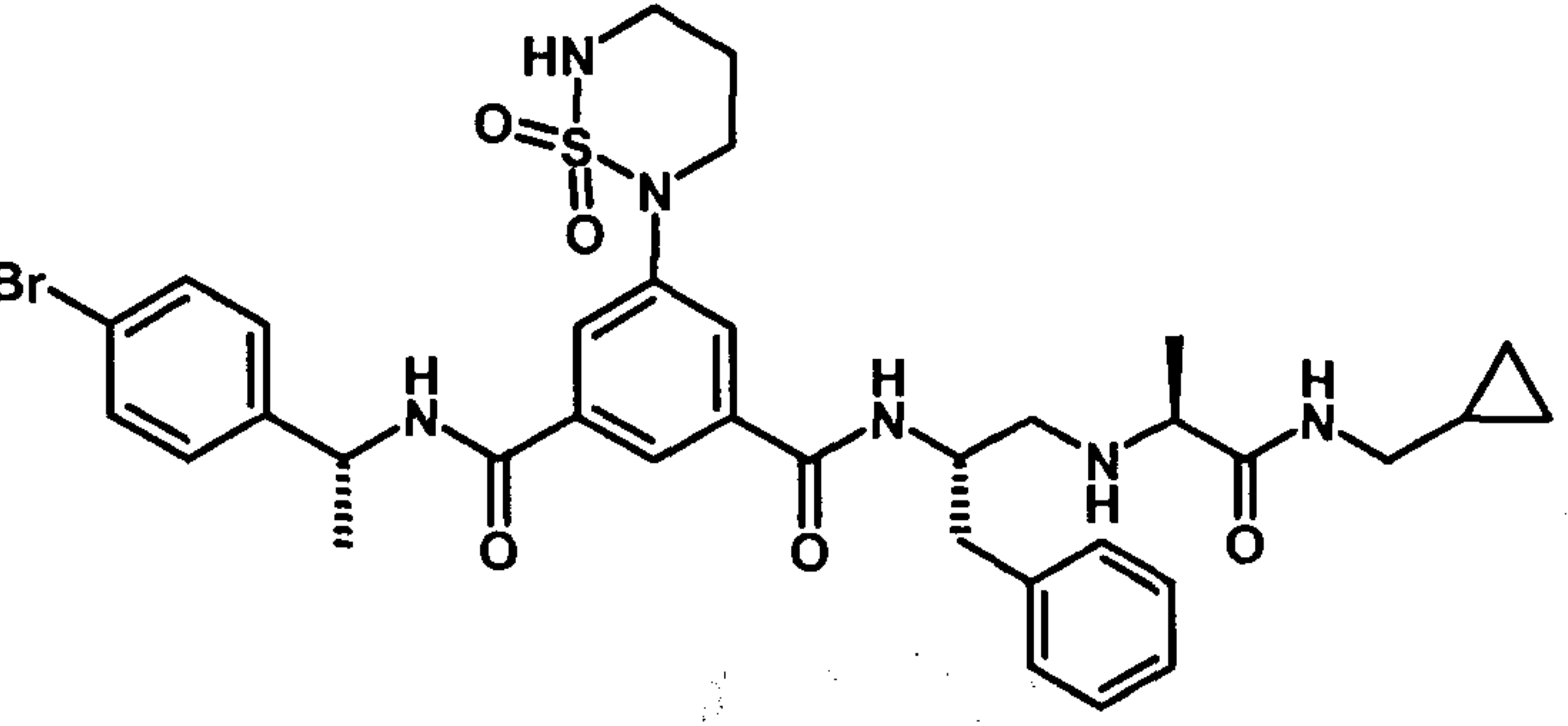
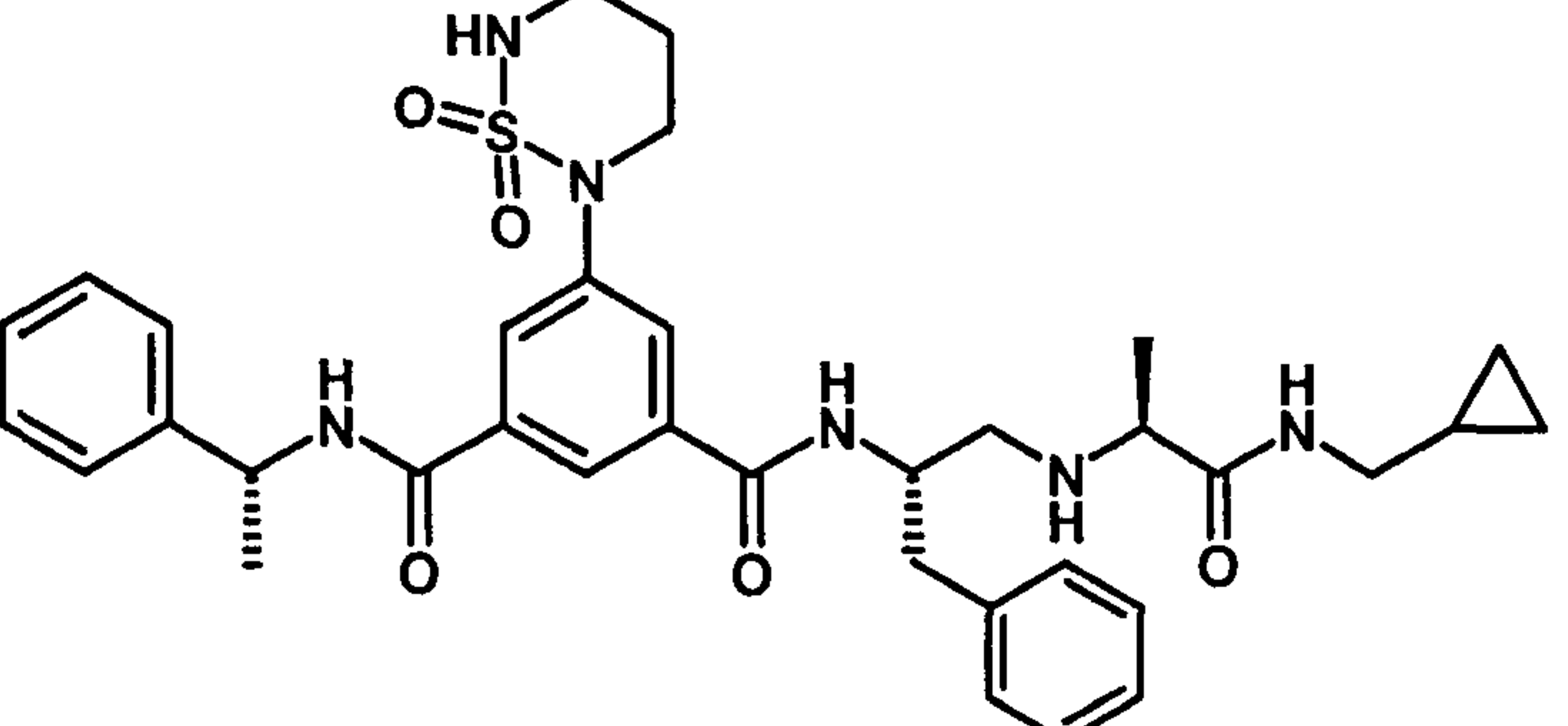
(53)		7.4
(54)		7.5
(55)		7.6
(56)		7.7
(57)		7.8

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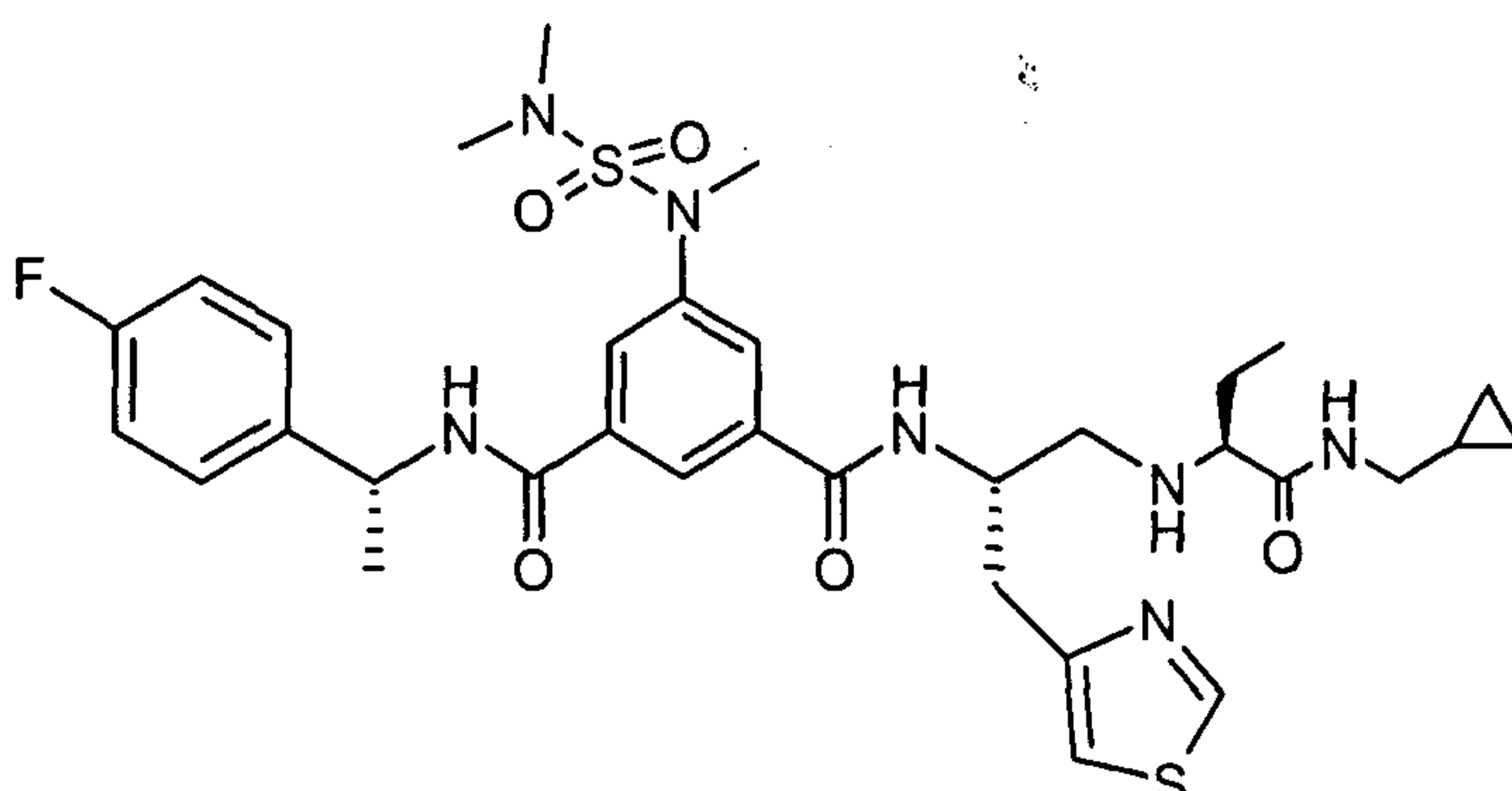
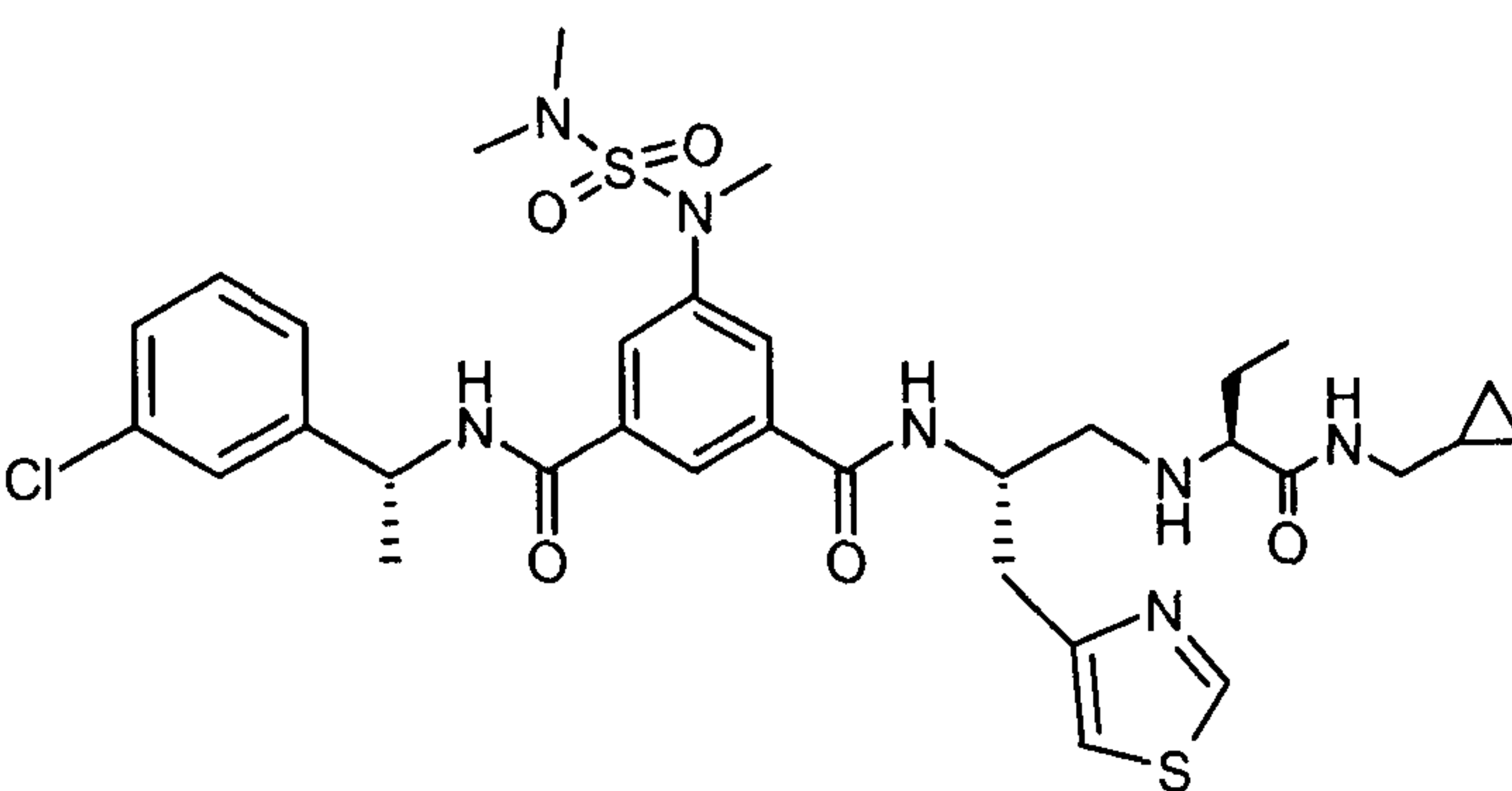
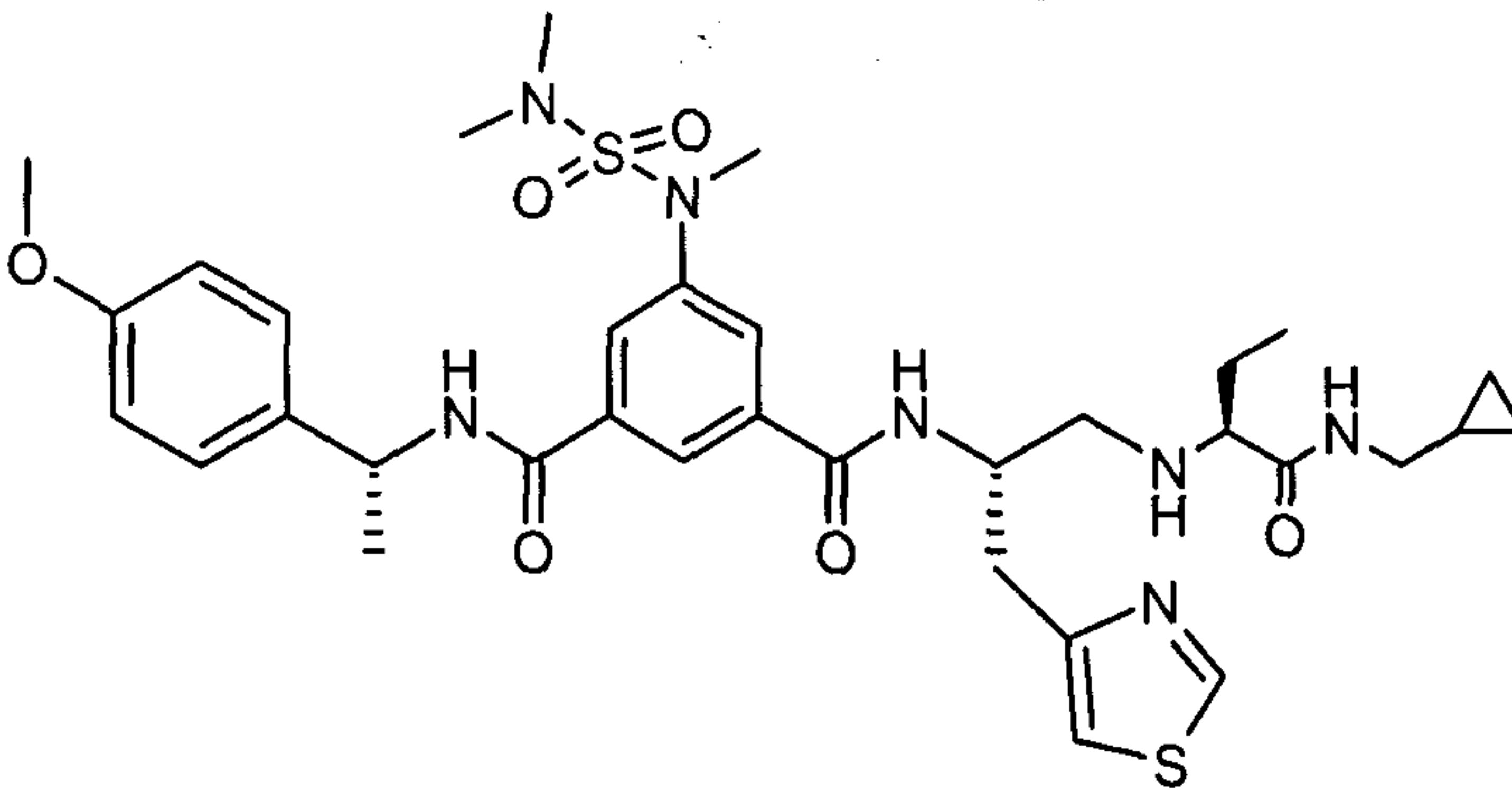
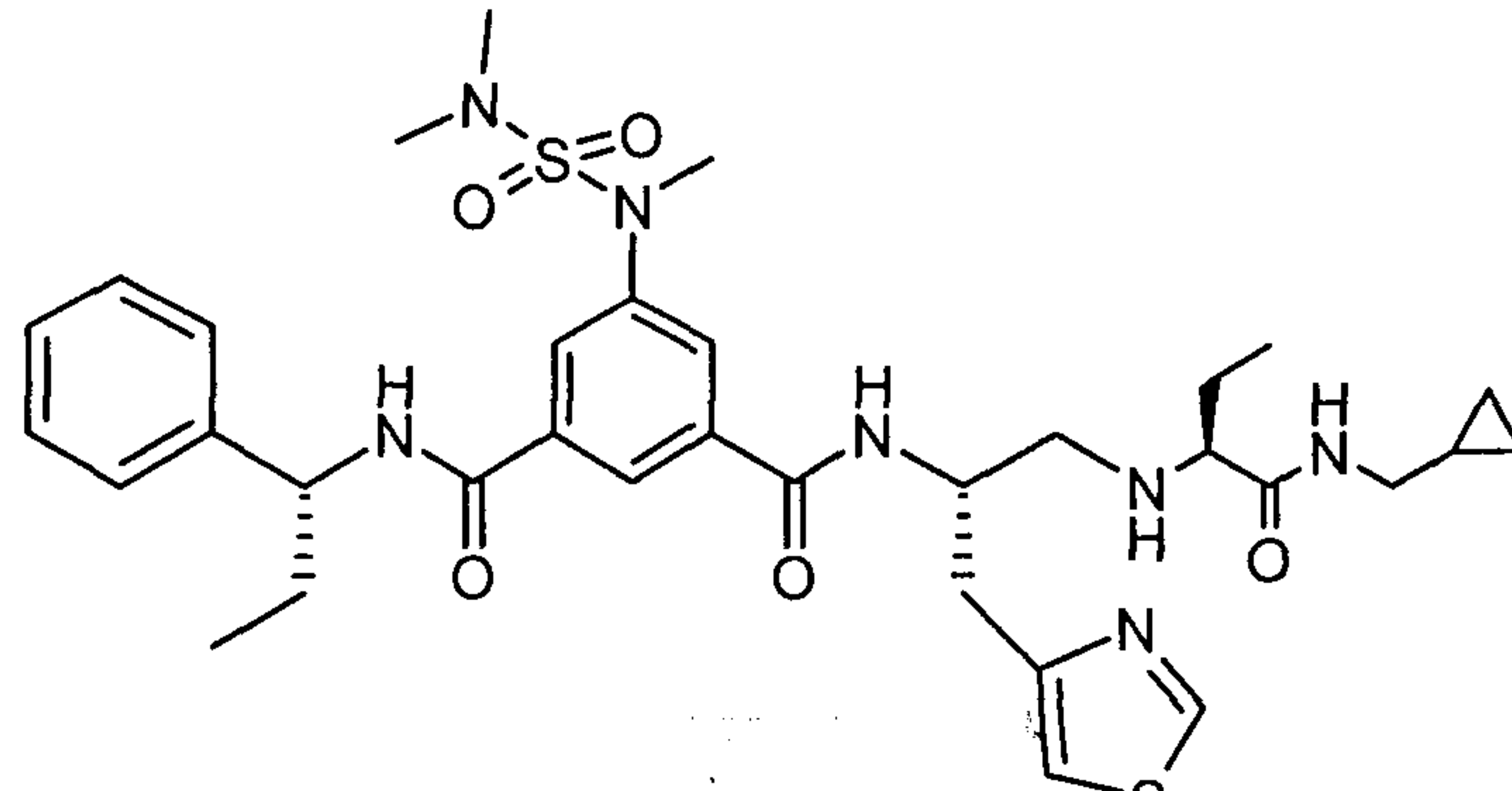
(58)		7.9
(59)		7.10
(60)		7.11
(61)		7.12
(62)		7.13

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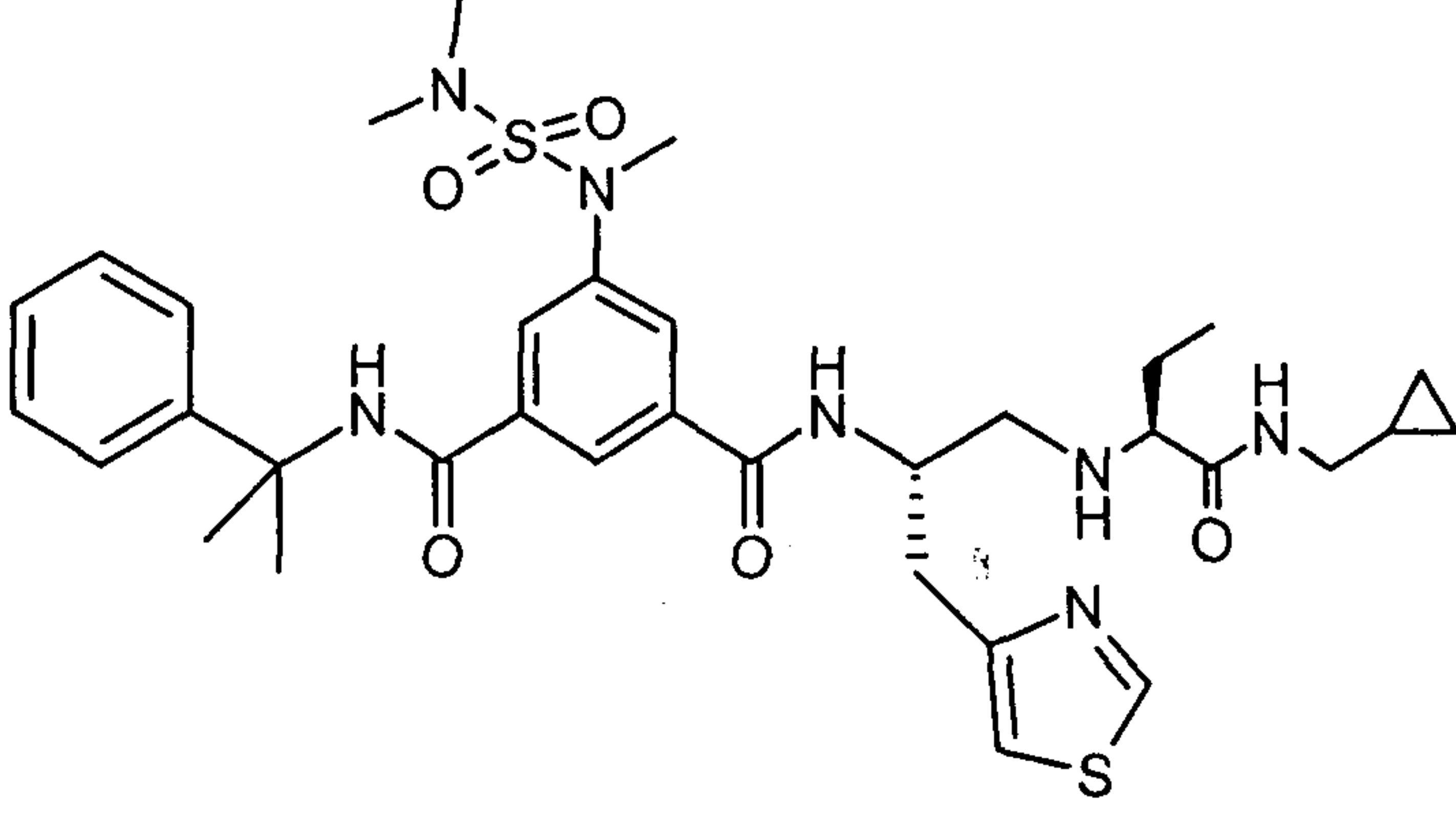
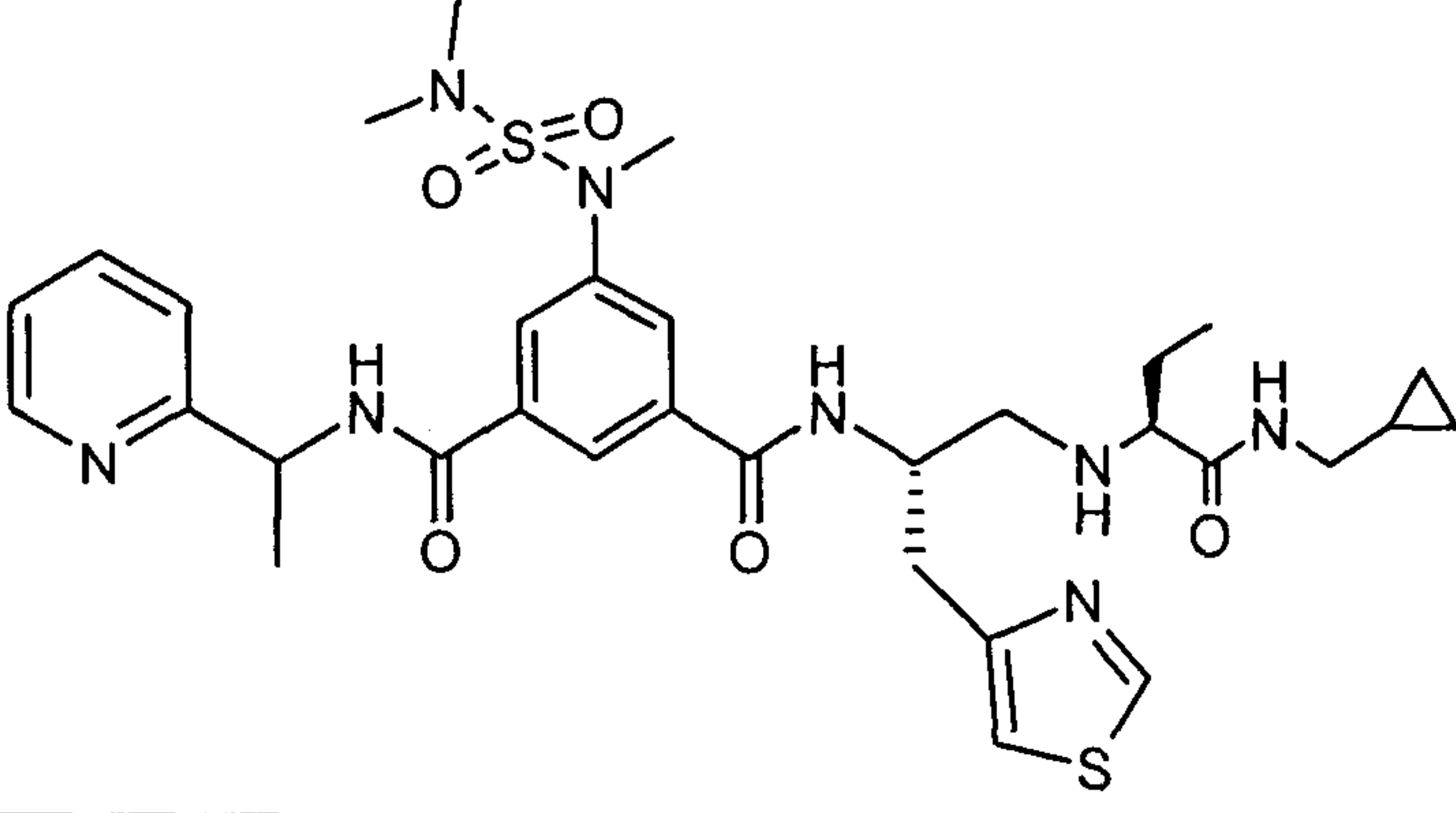
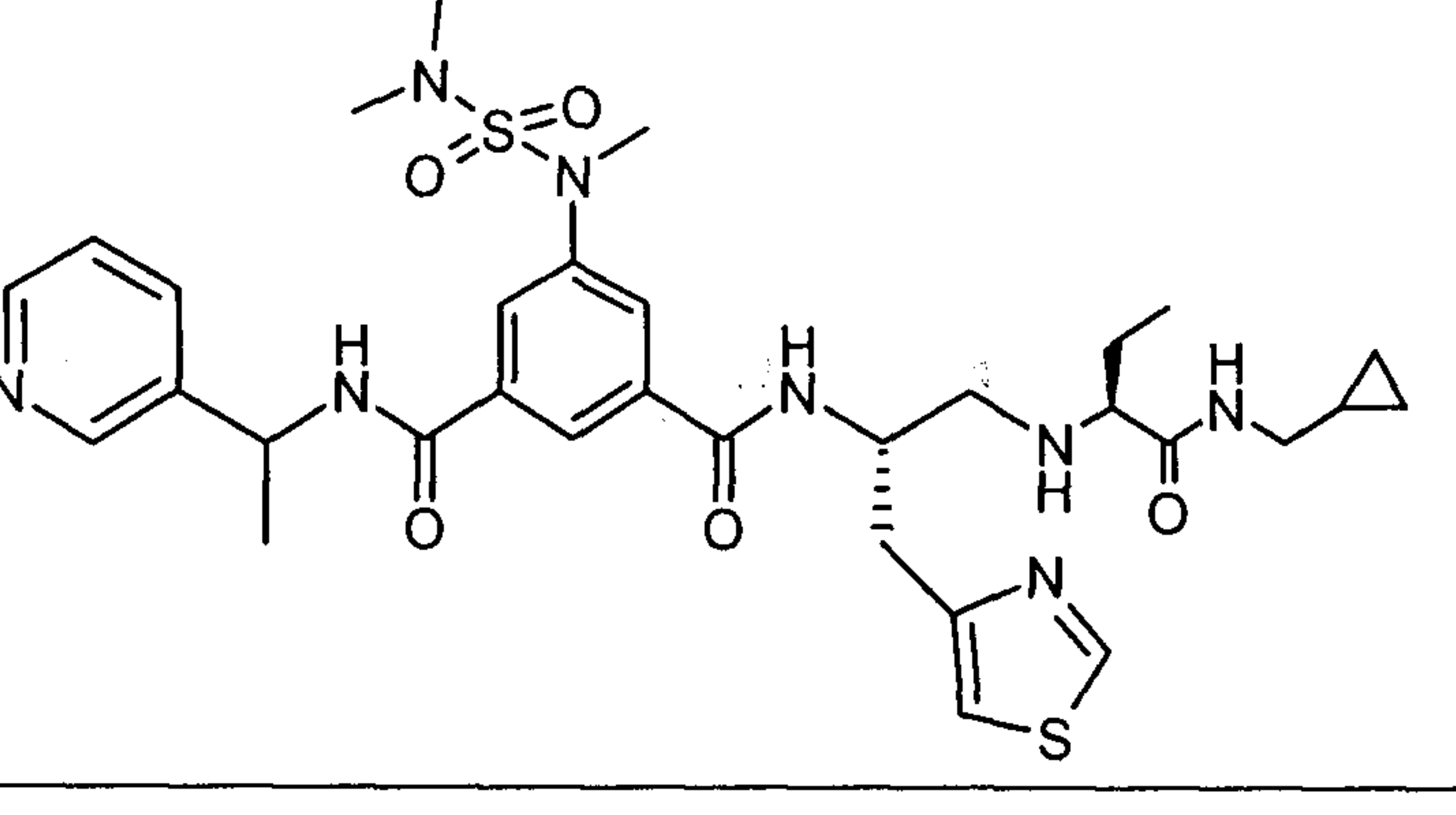
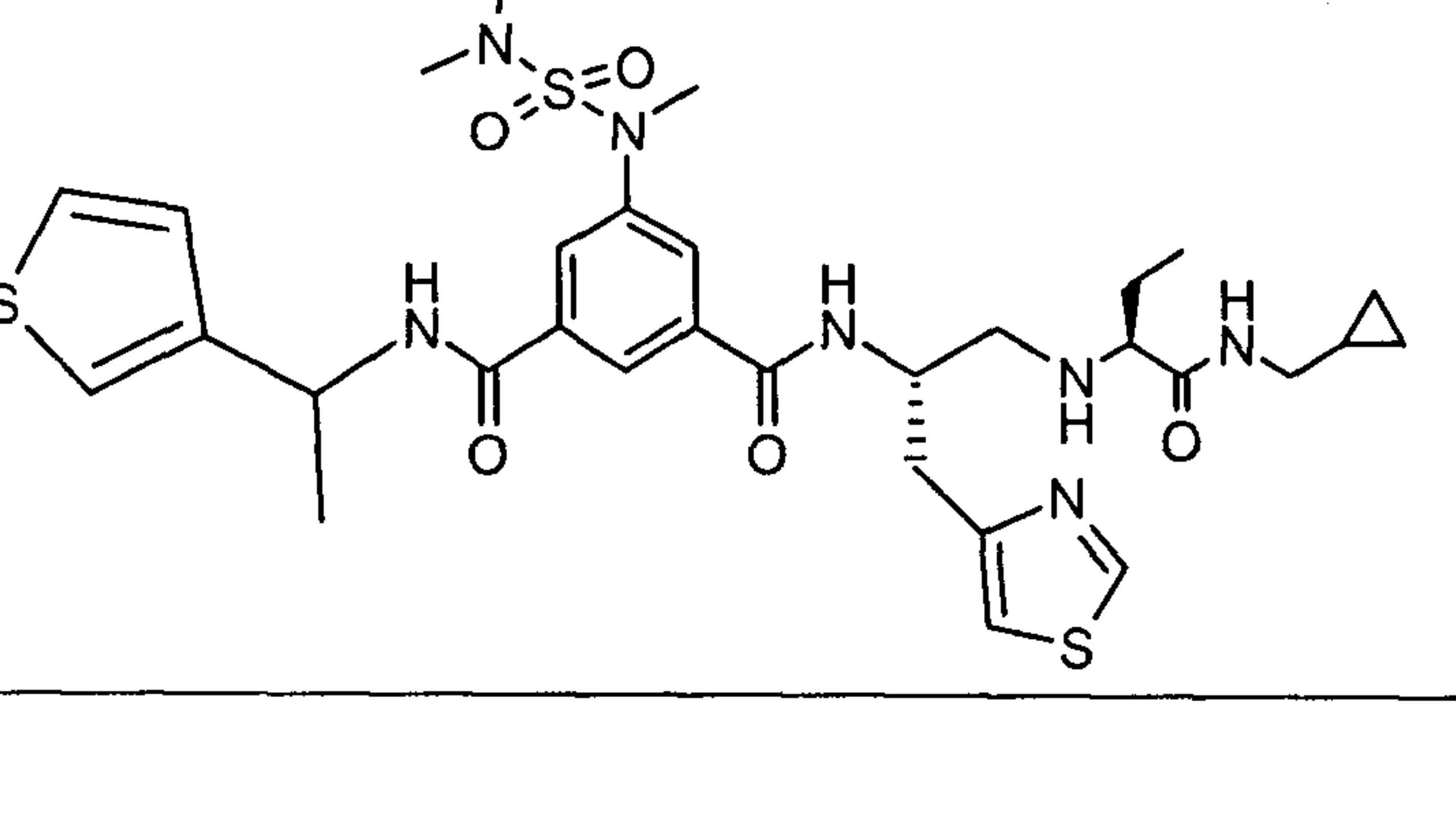
(63)		7.14
(64)		7.15
(65)		7.16
(66)		7.17
(67)		7.18

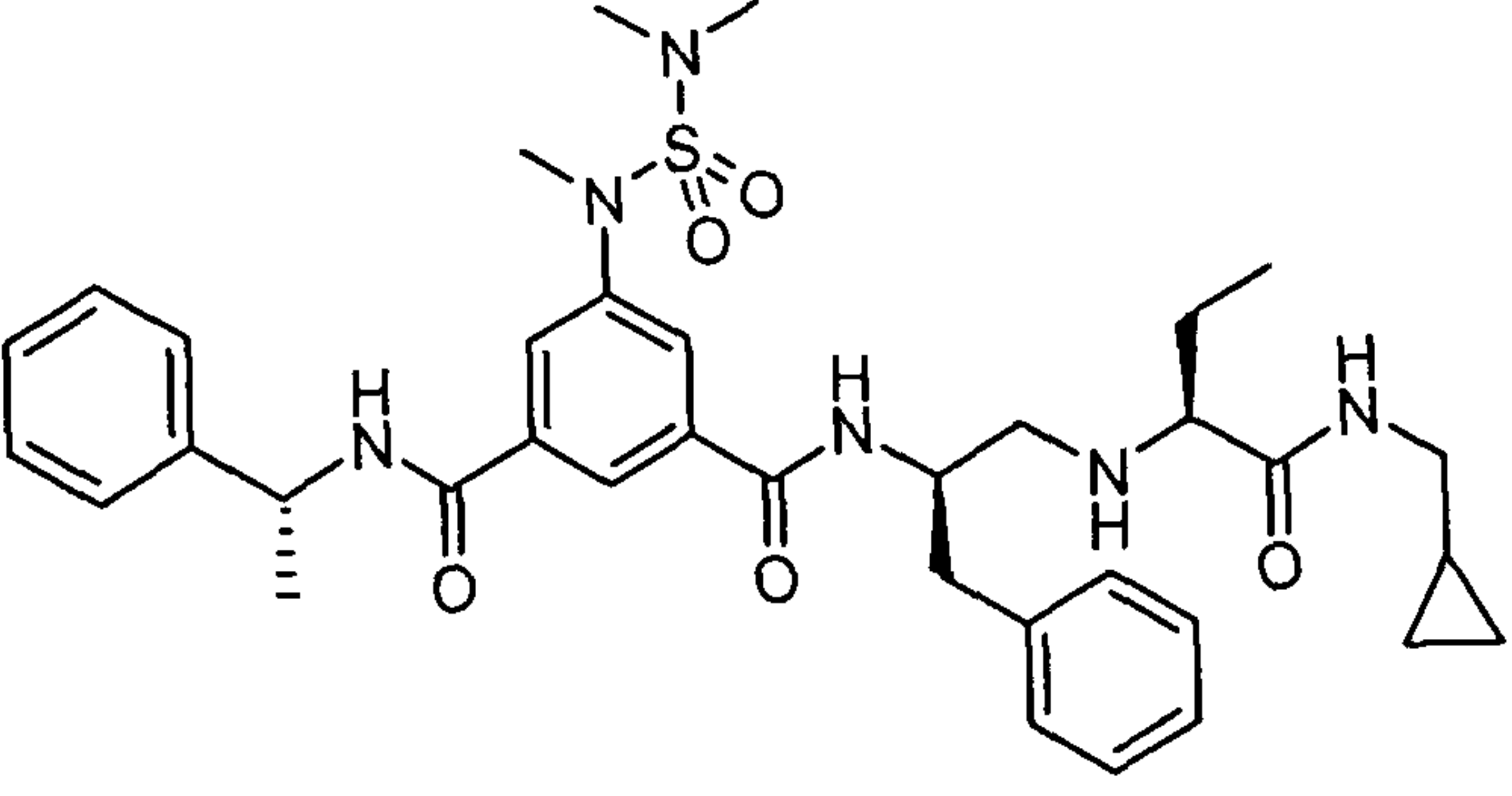
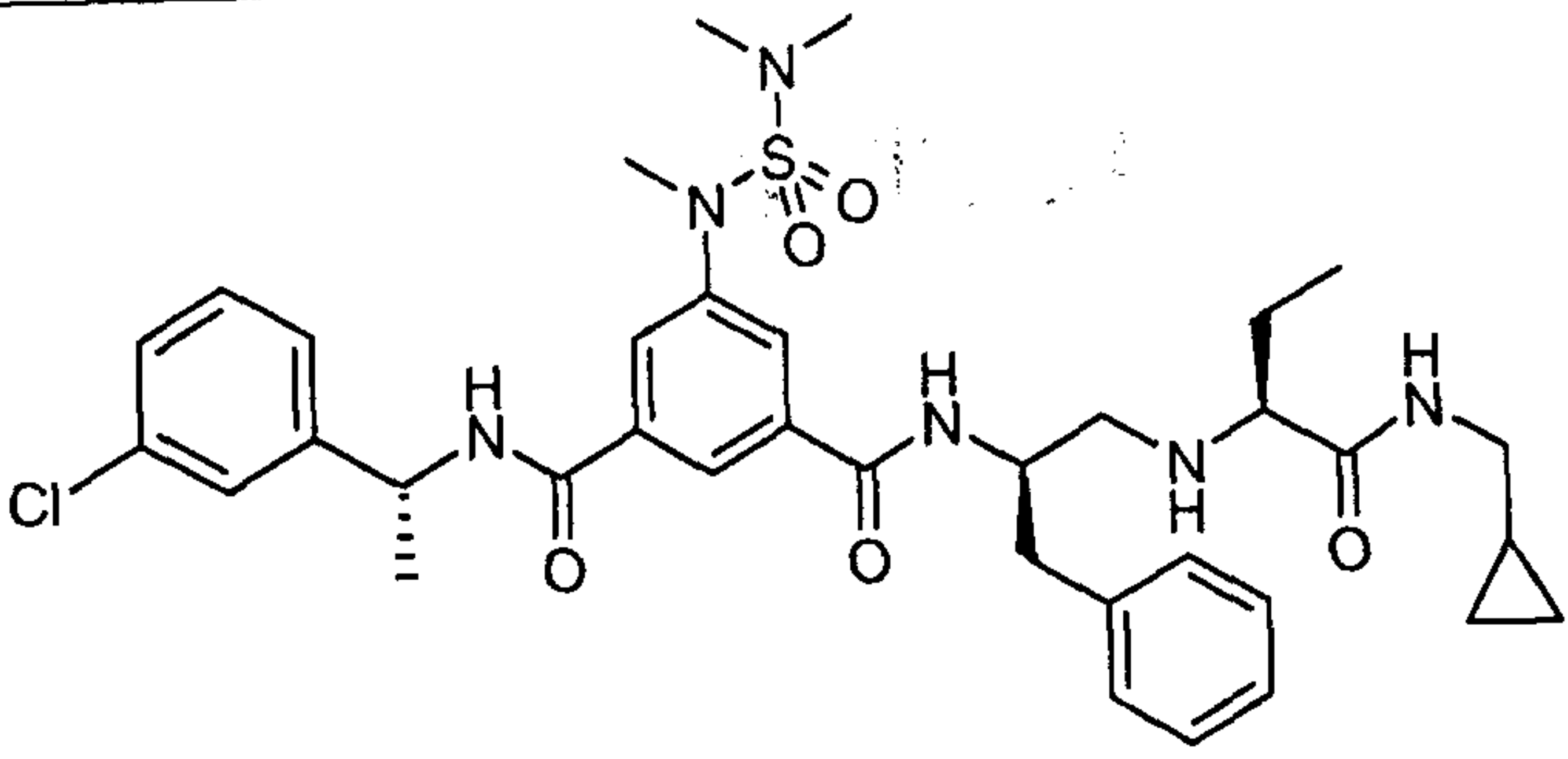
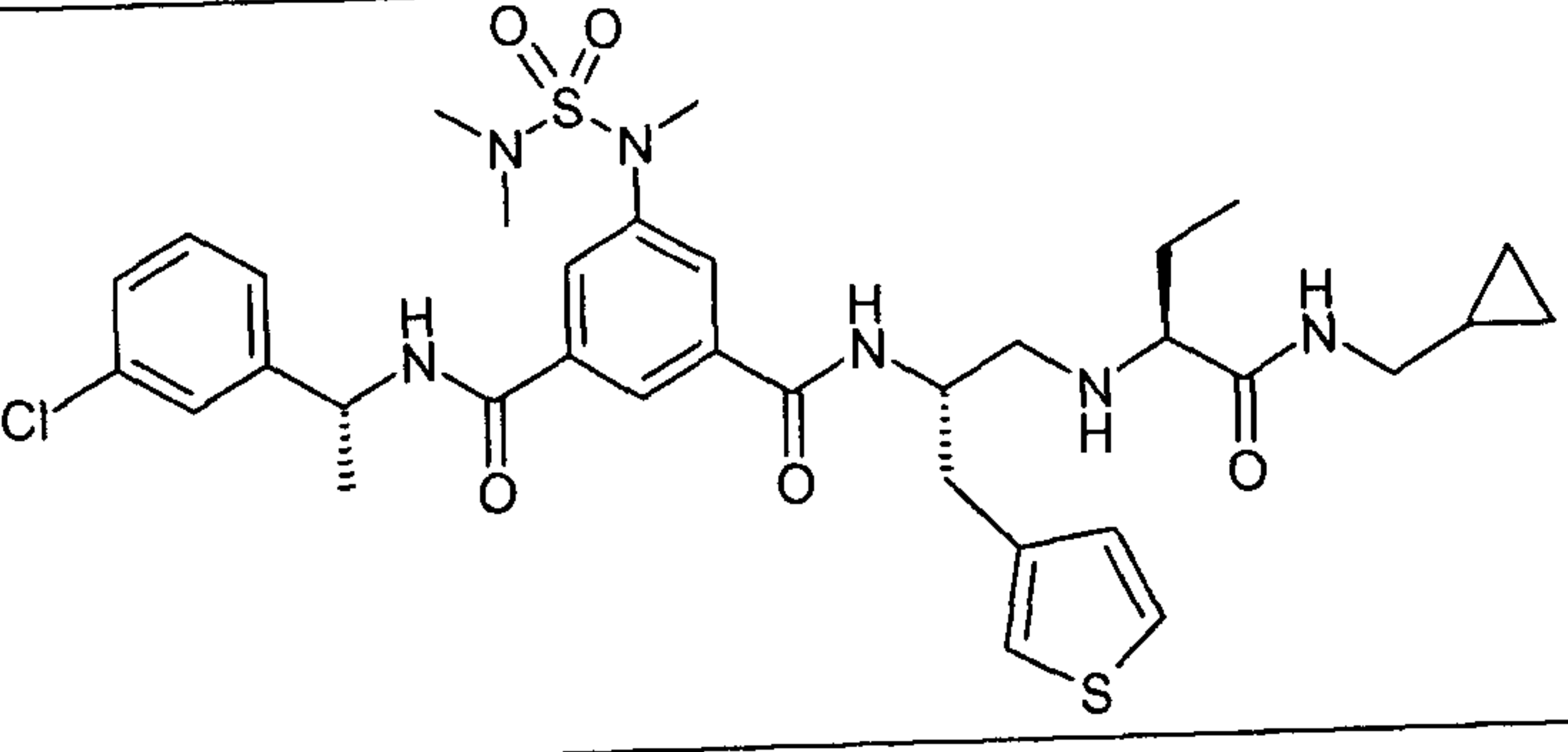
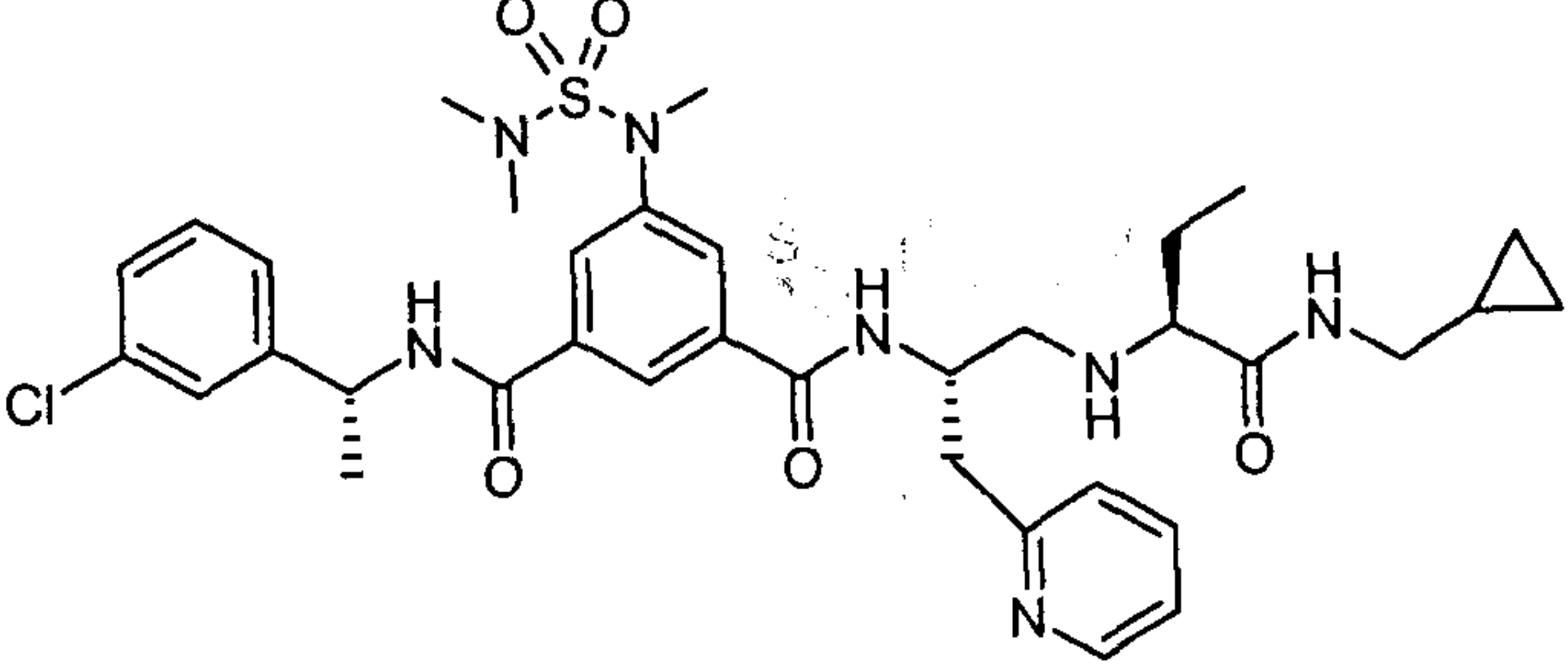
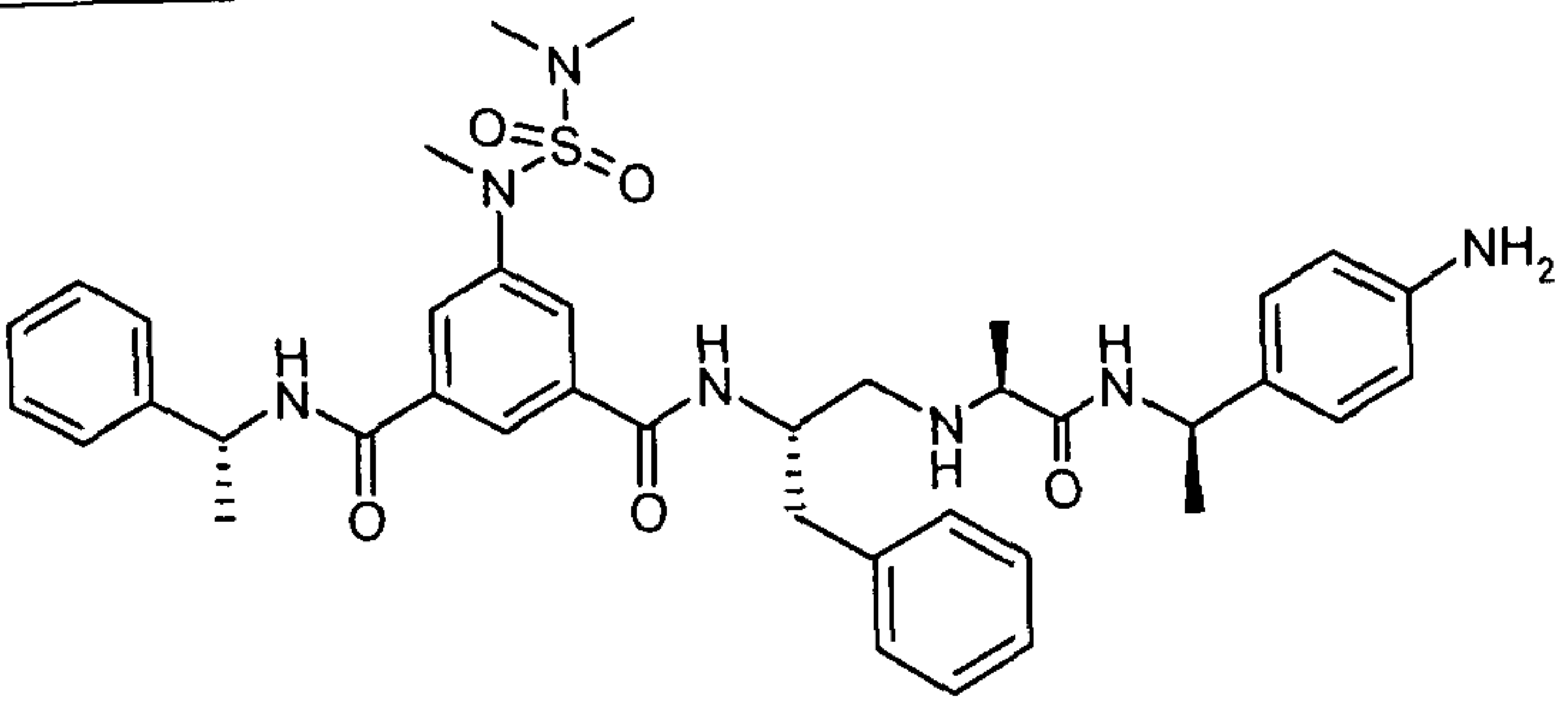
(68)		7.19
(69)		7.20
(70)		7.21
(71)		7.22
(72)		7.23

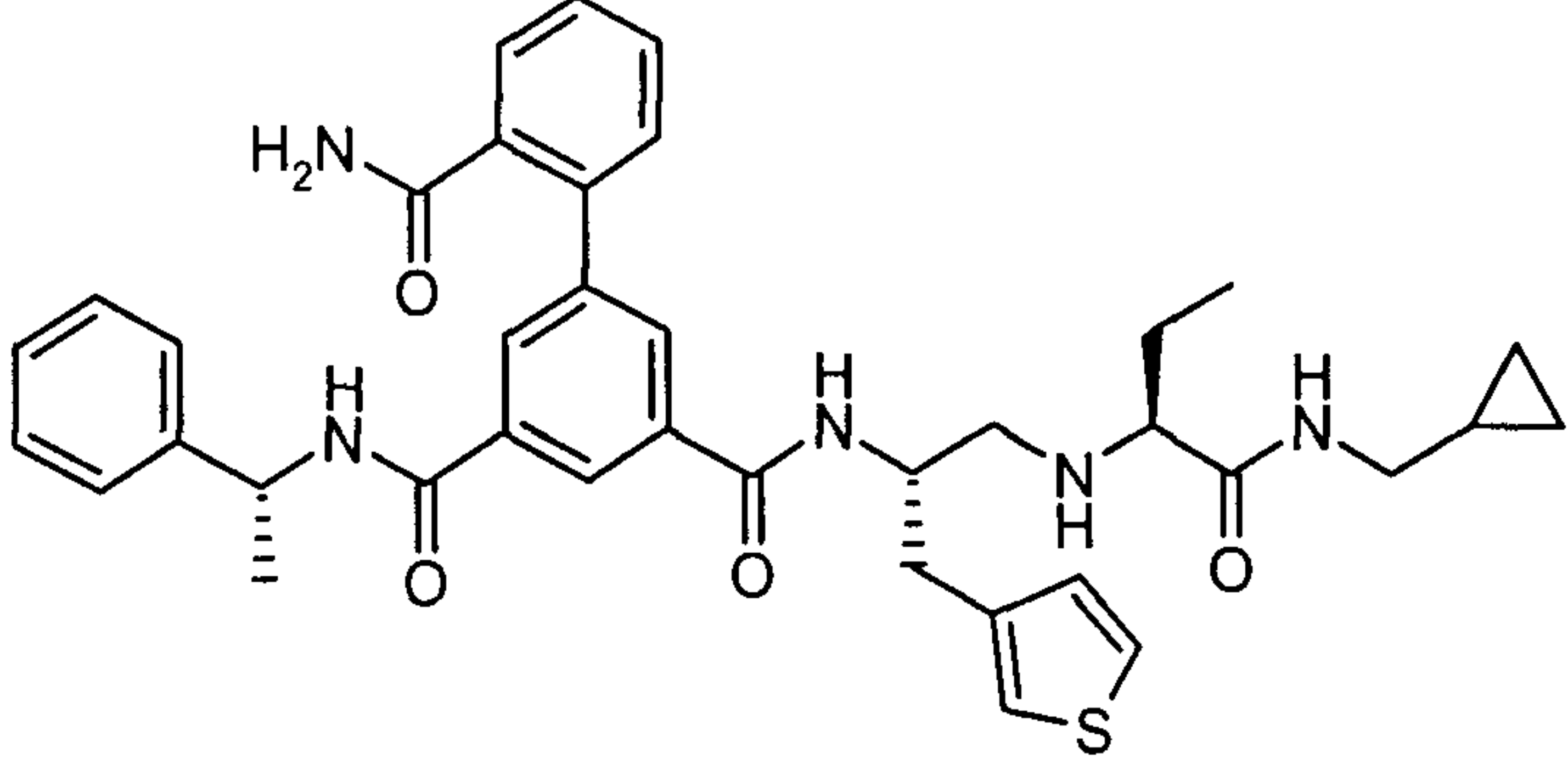
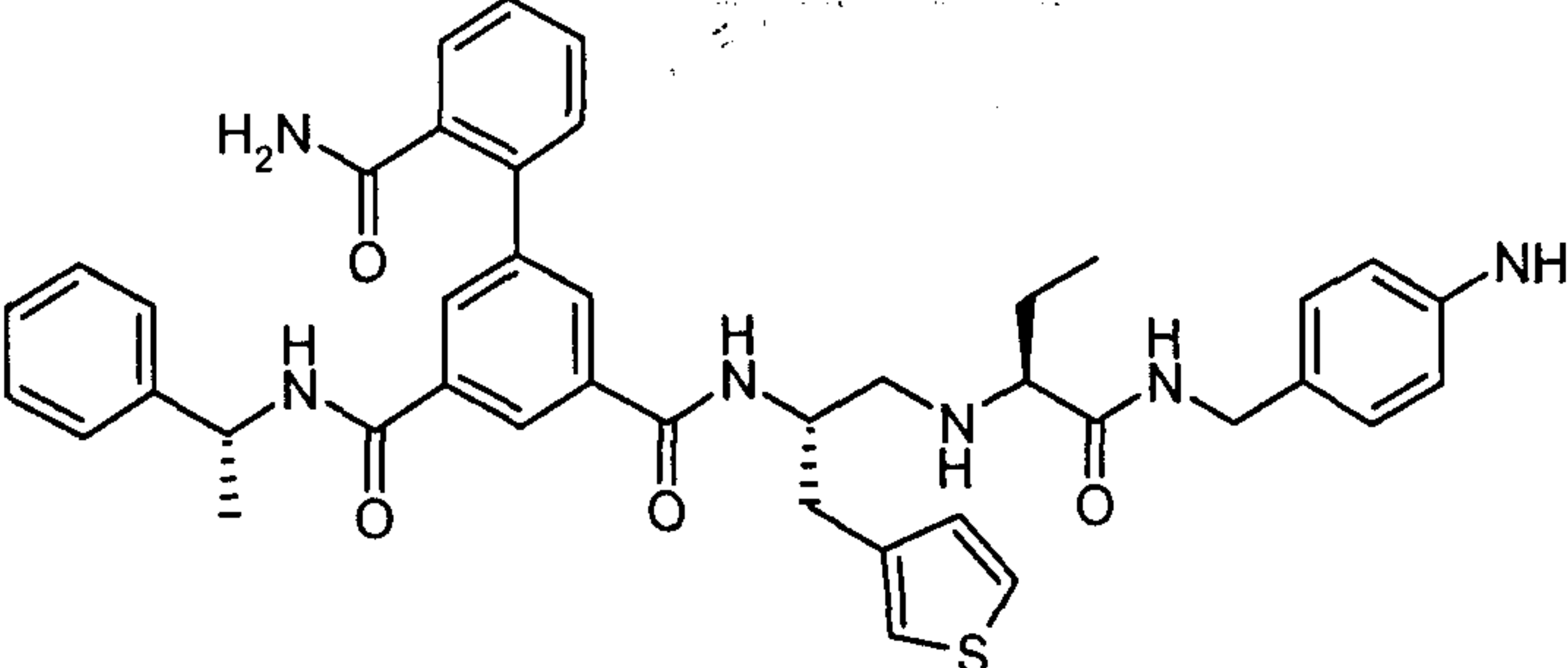
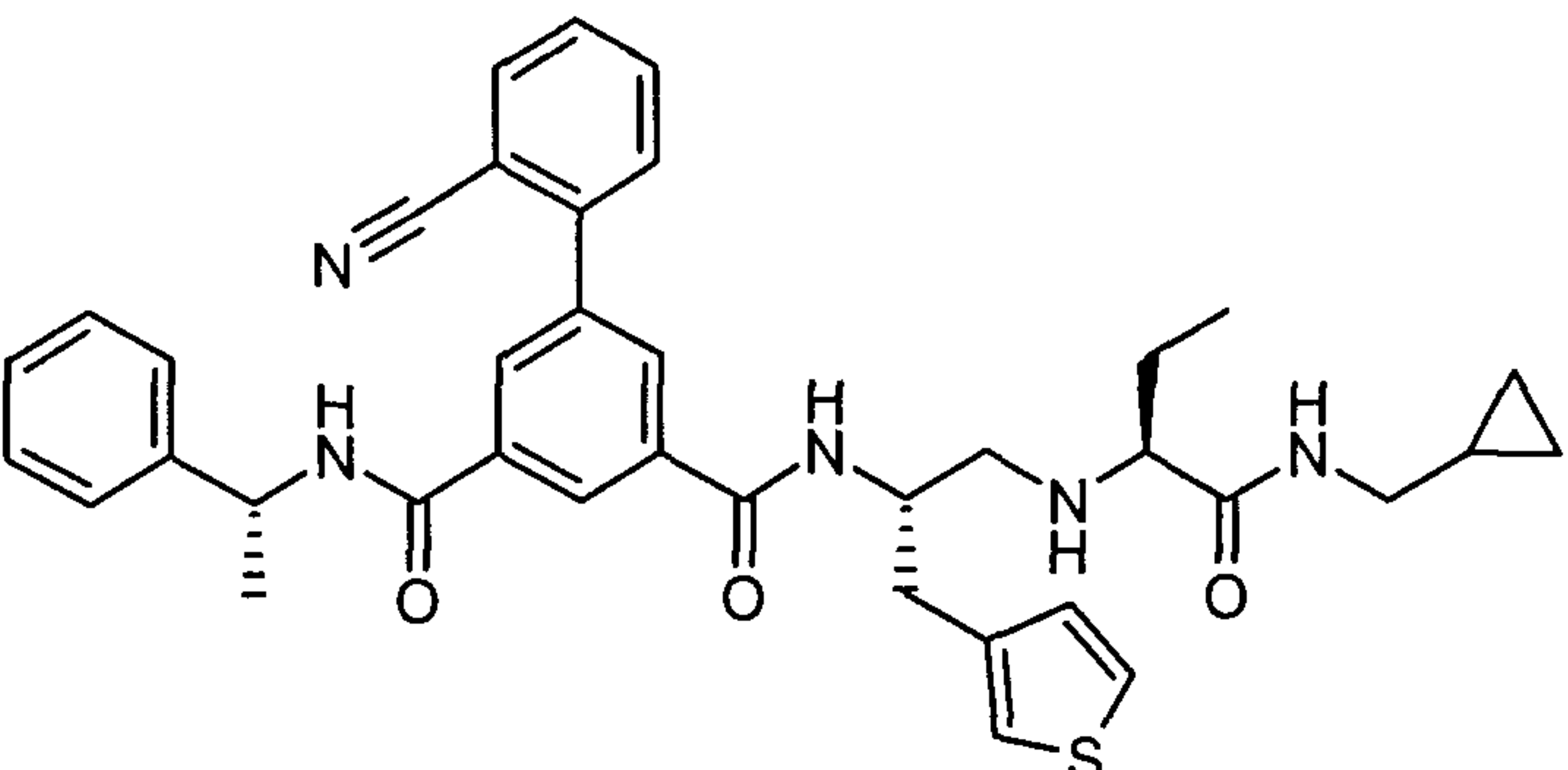
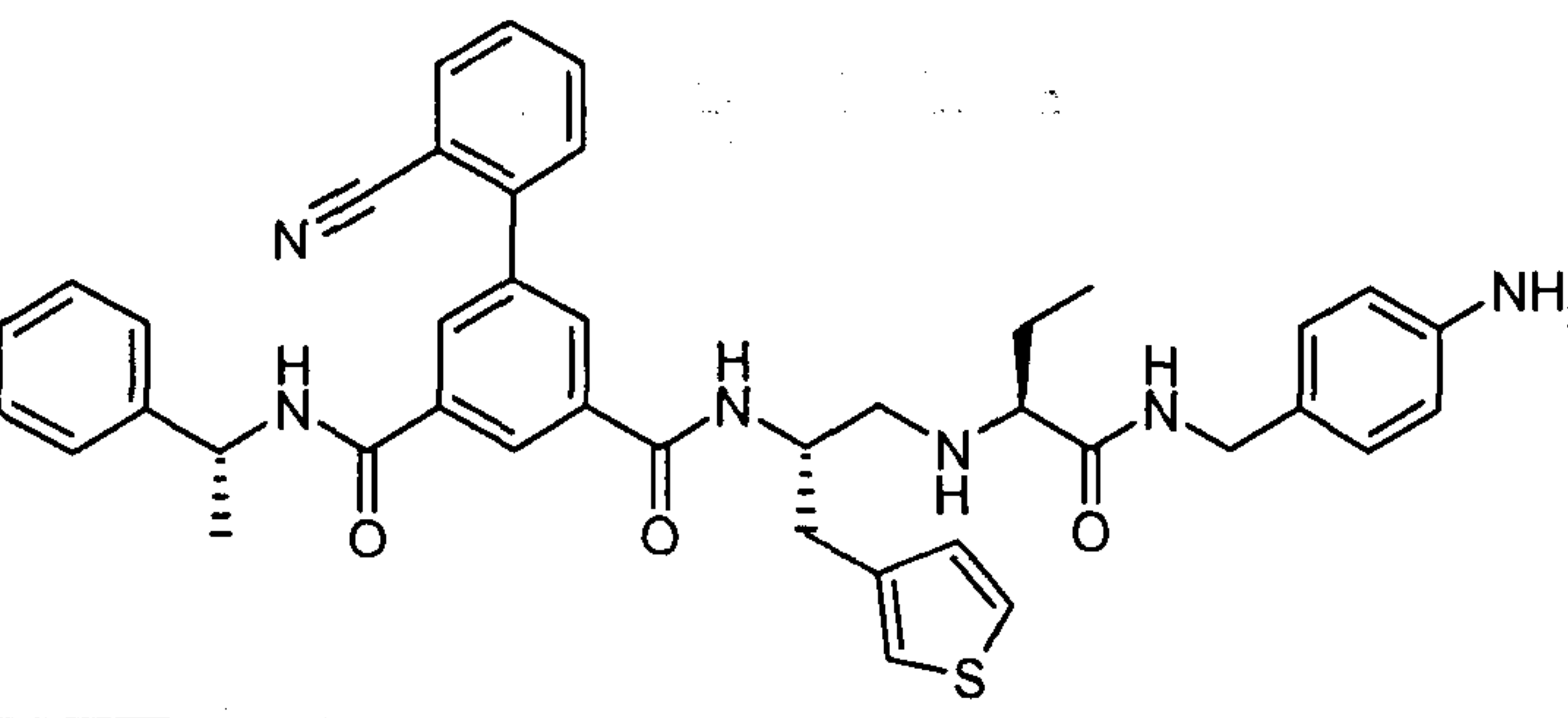
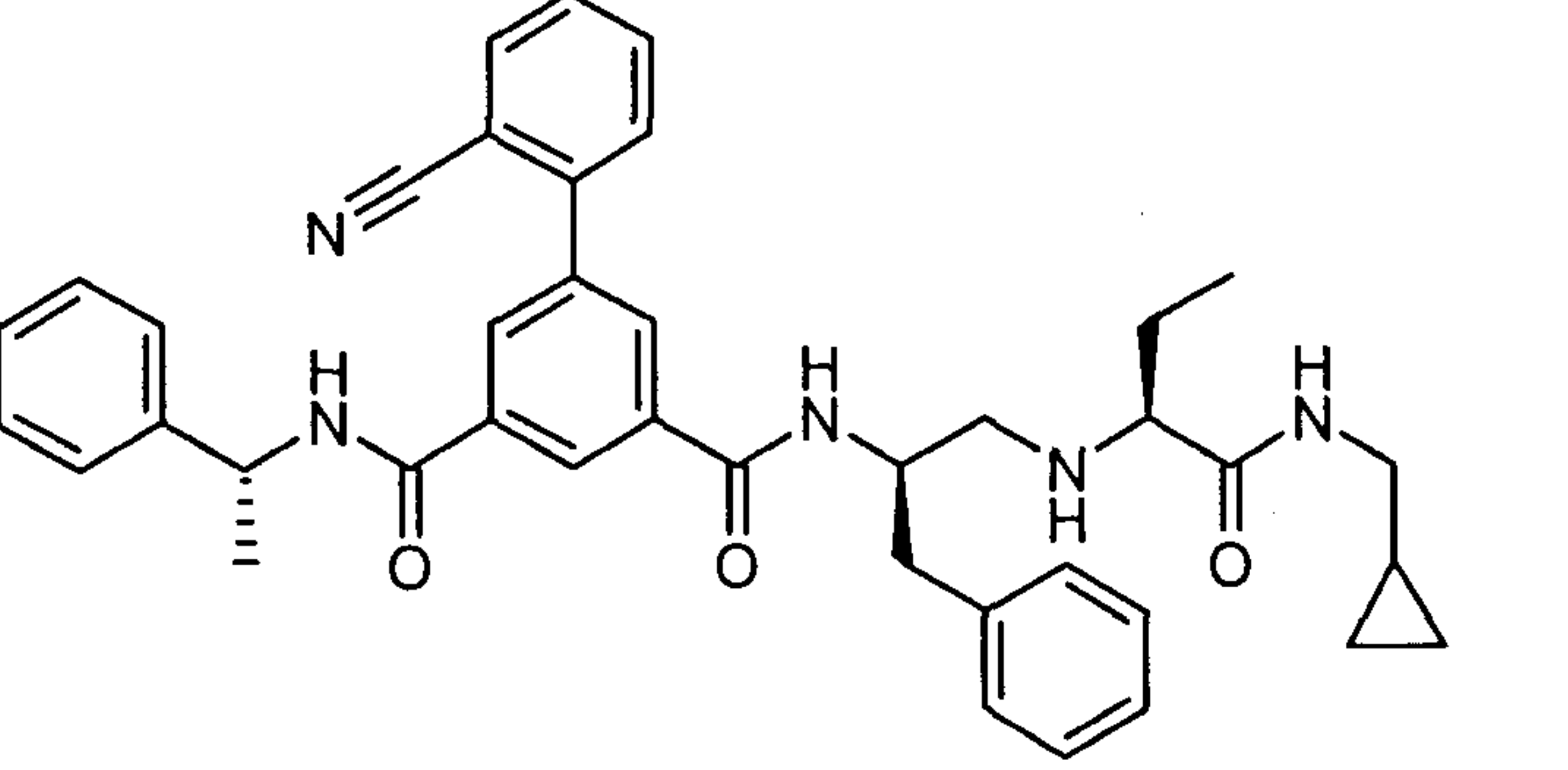
- 61 -

(73)		8
(74)		8.1
(75)		8.2
(76)		8.3

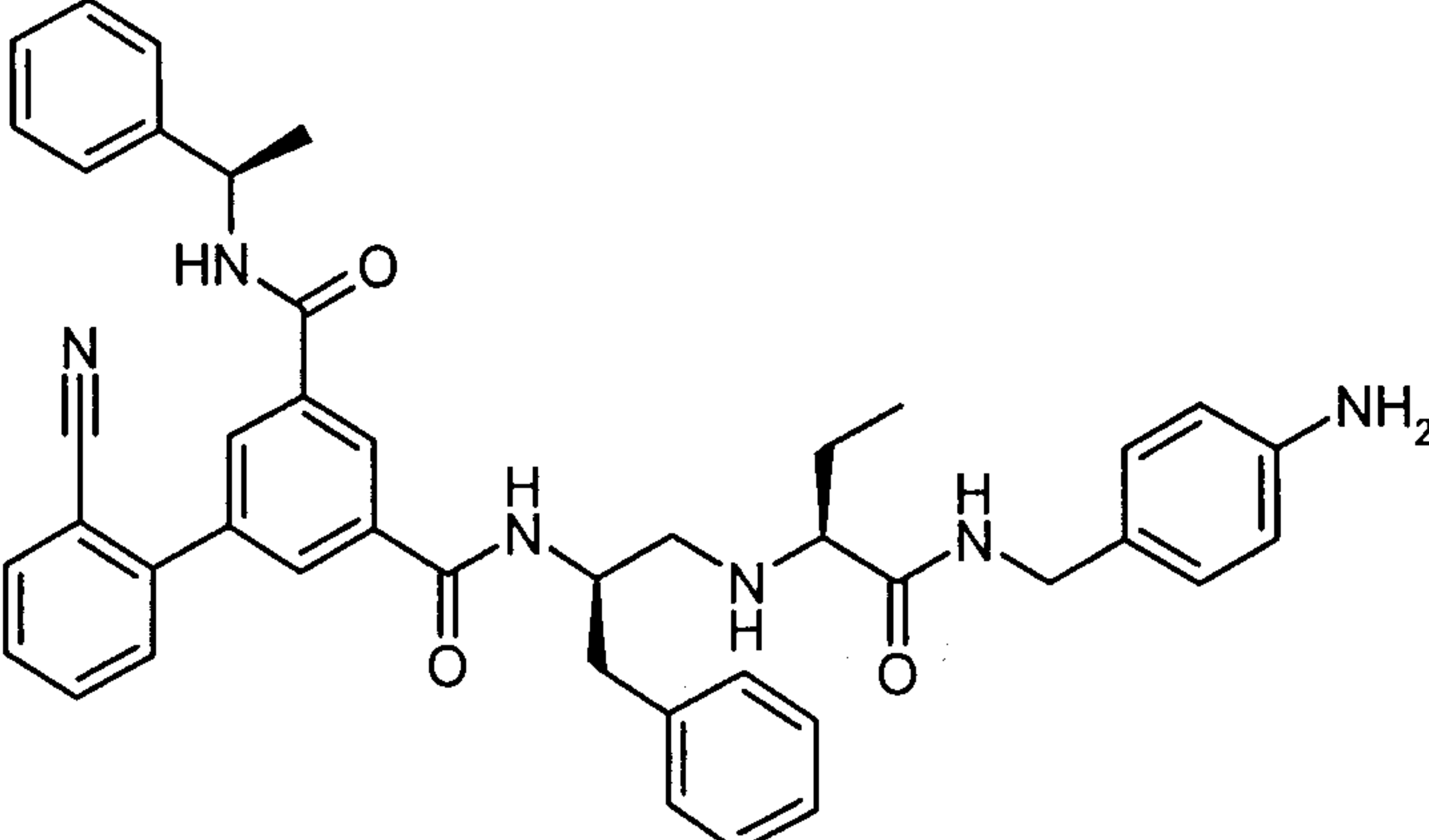
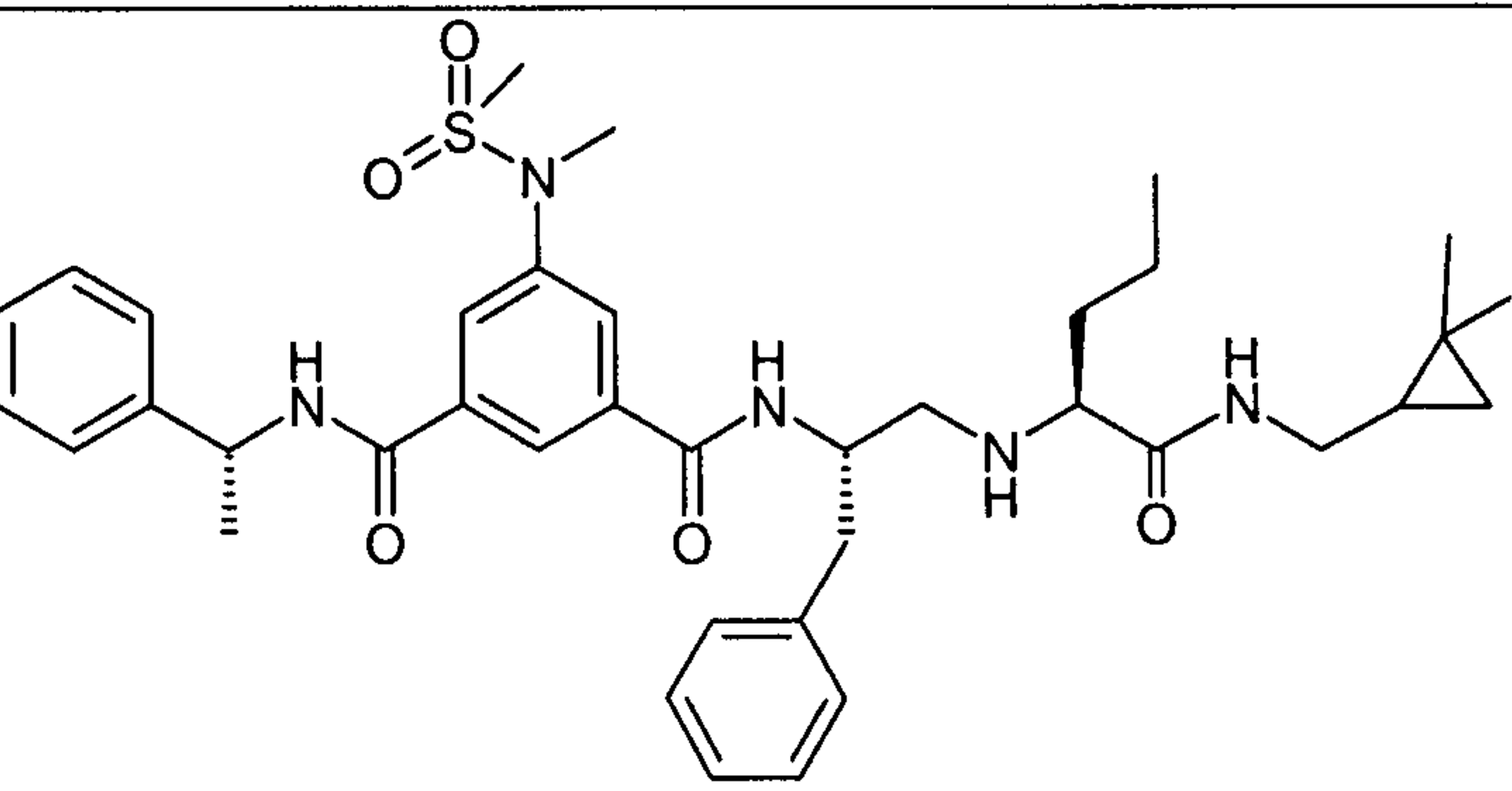
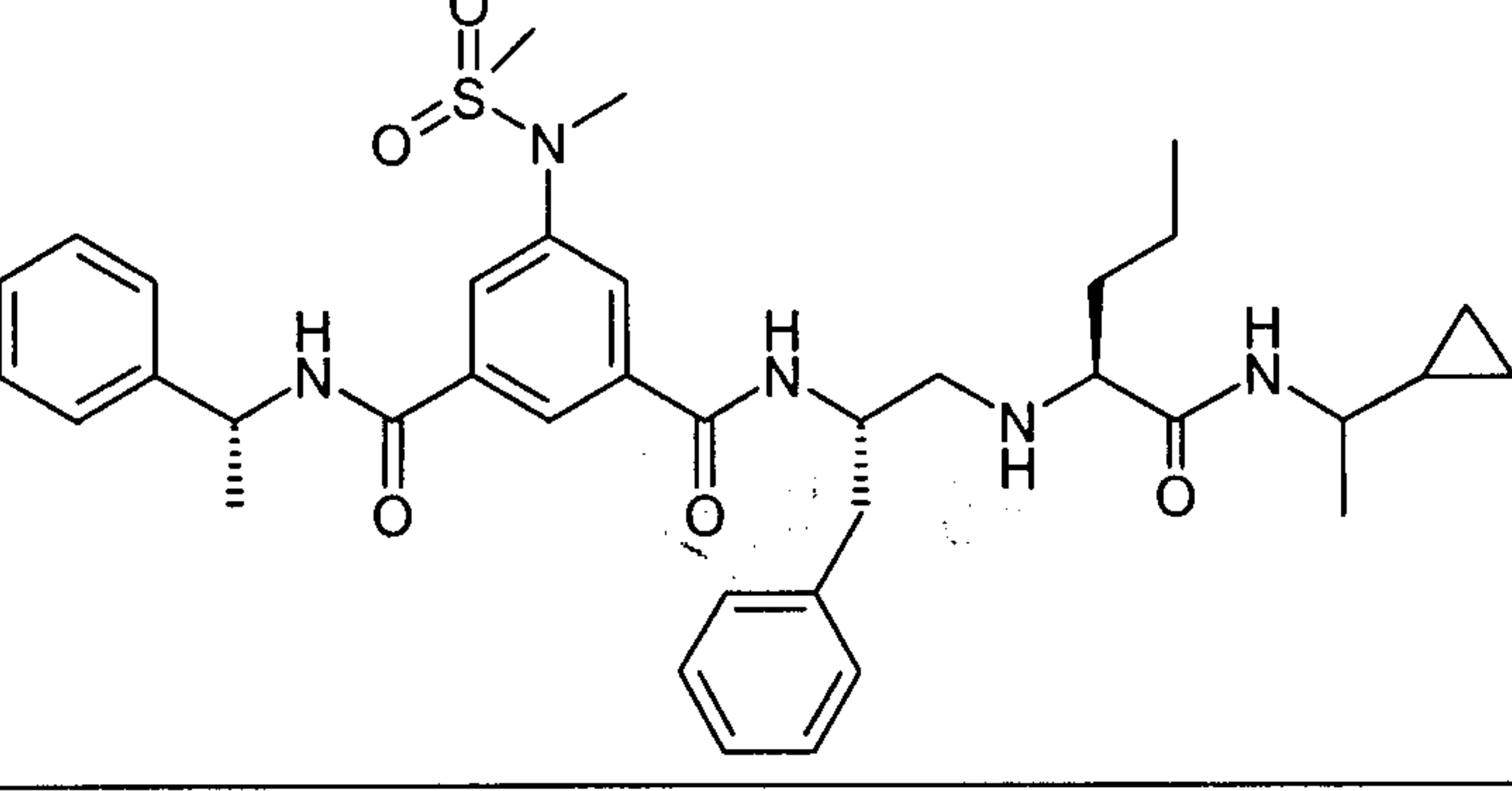
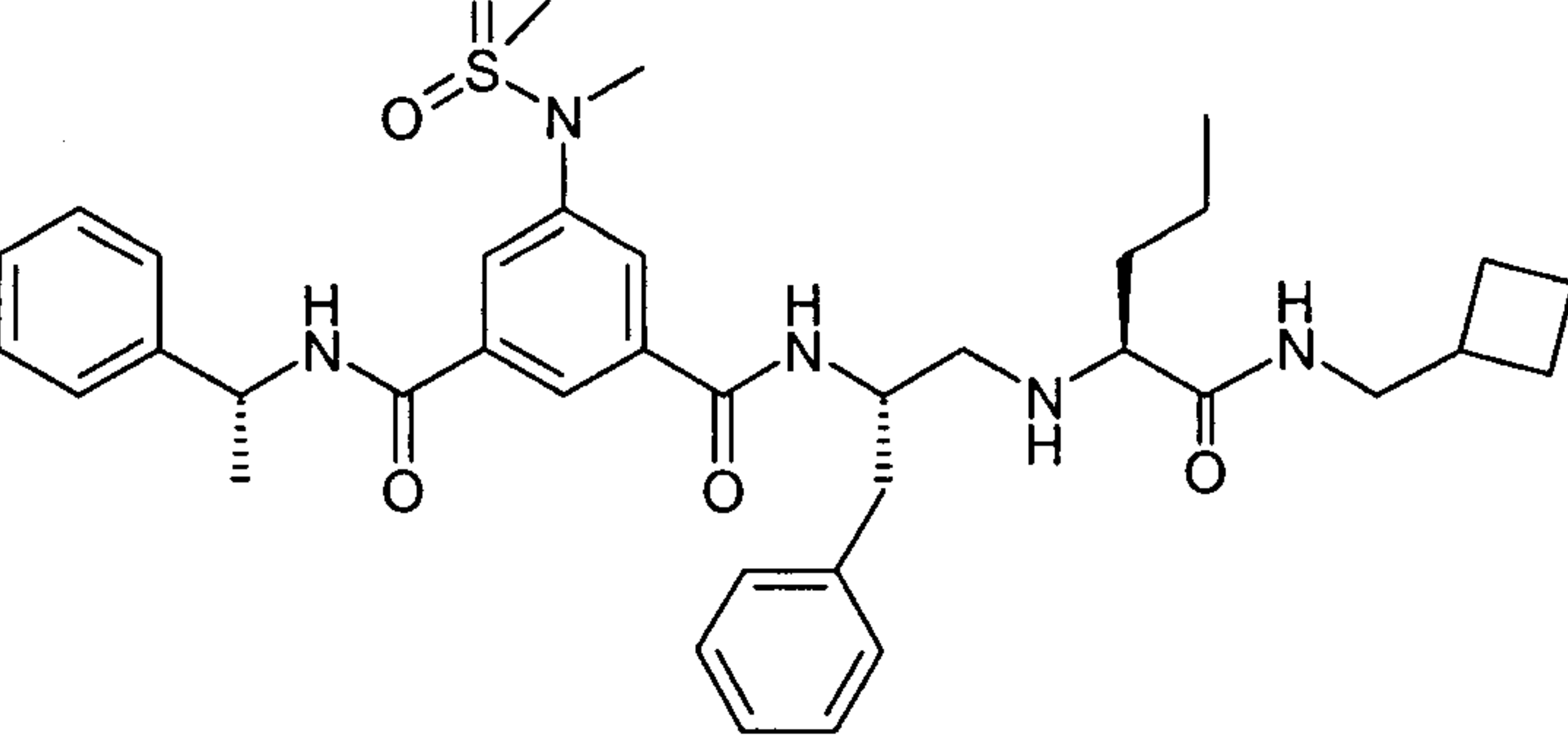
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(77)		8.4
(78)		8.5
(79)		8.6
(80)		8.7

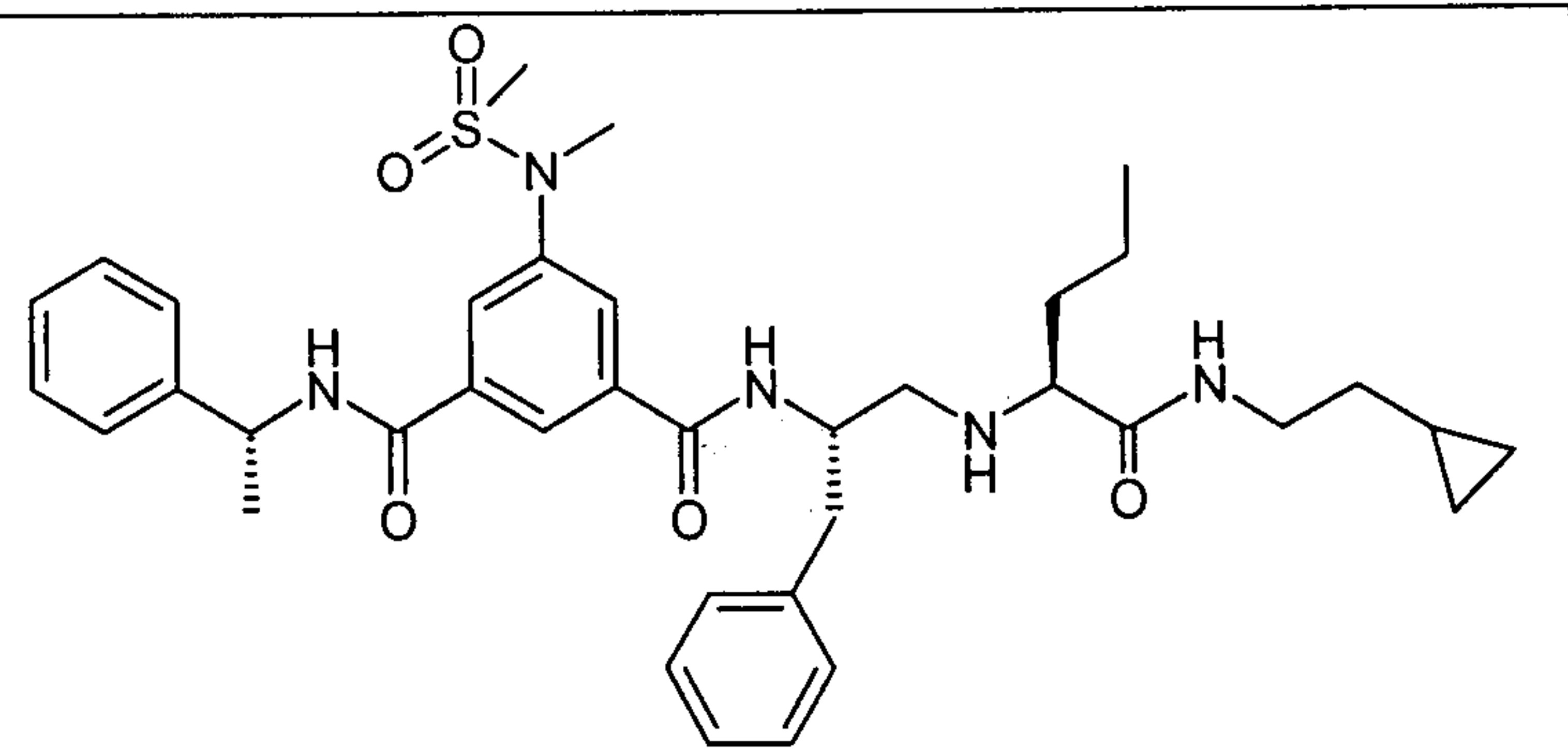
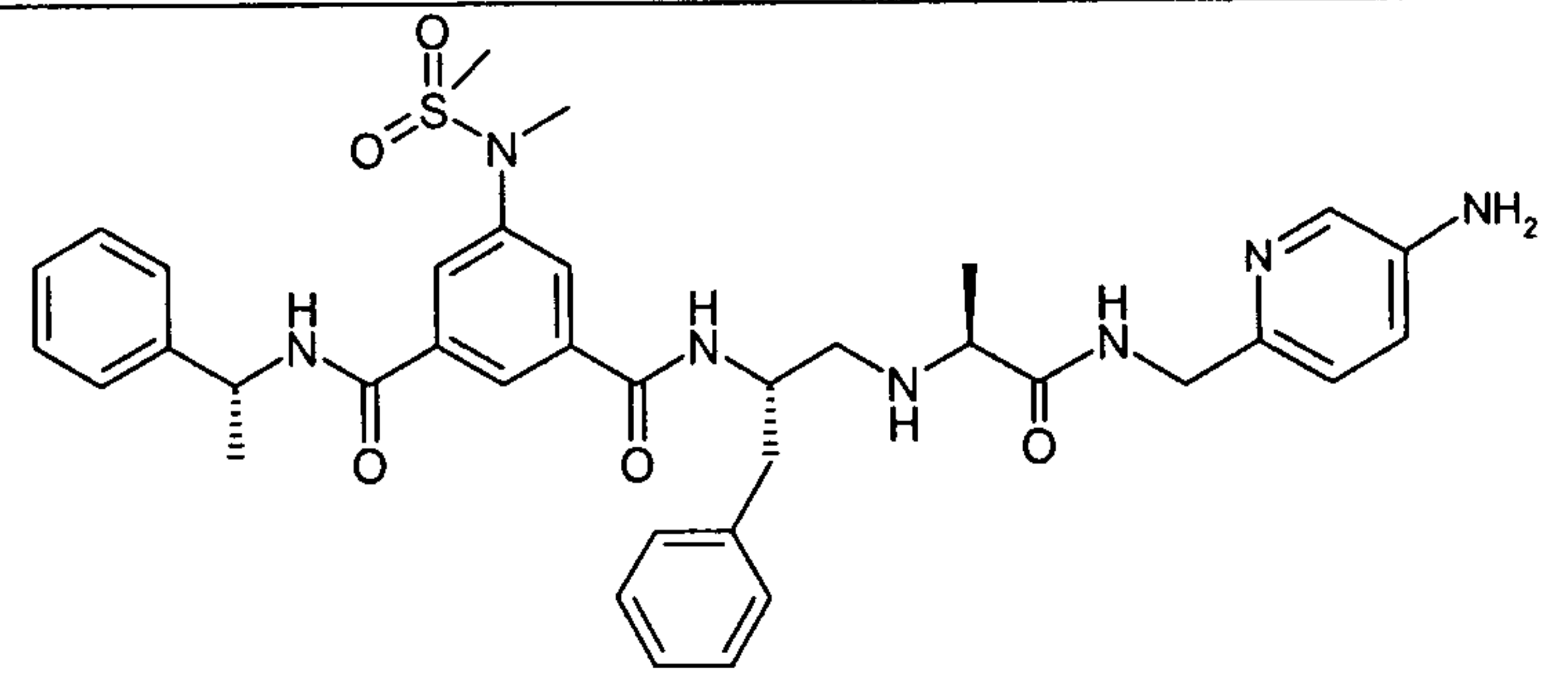
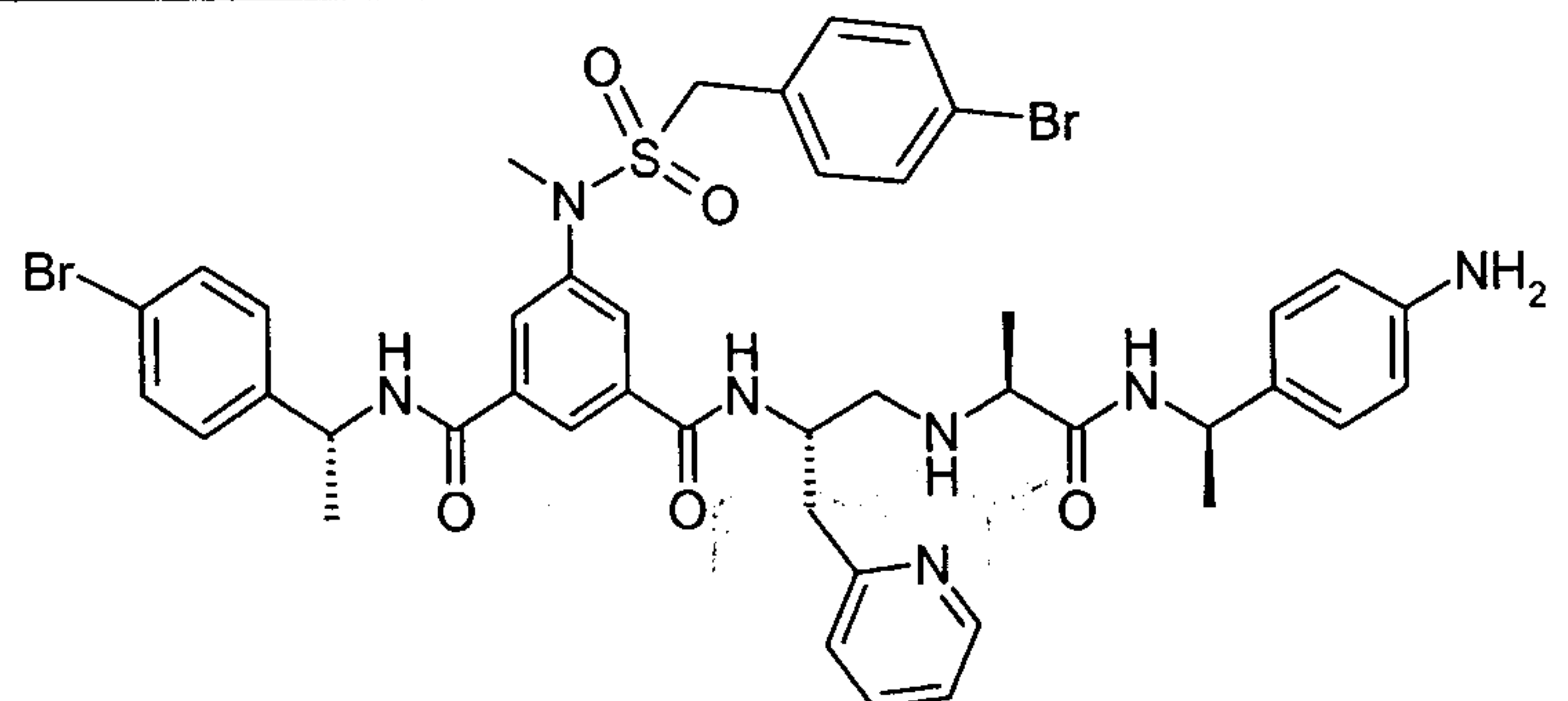
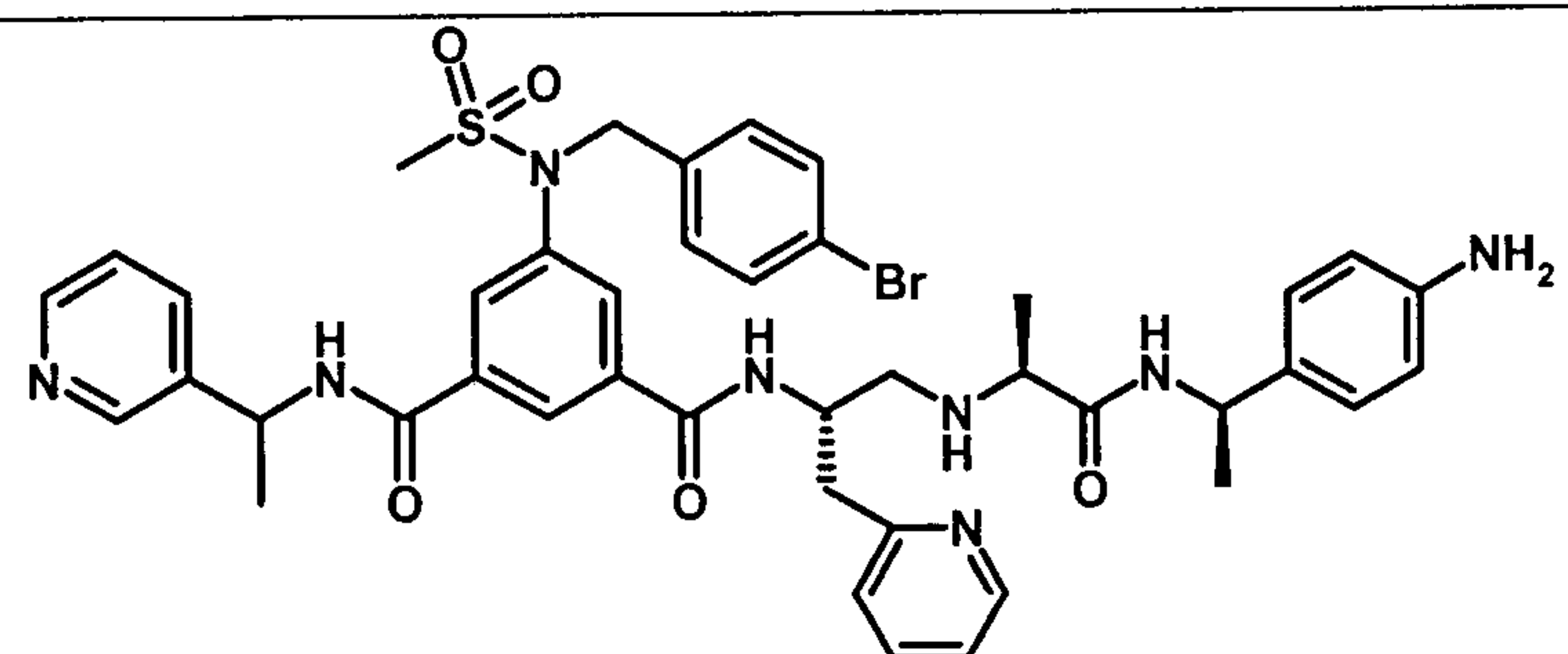
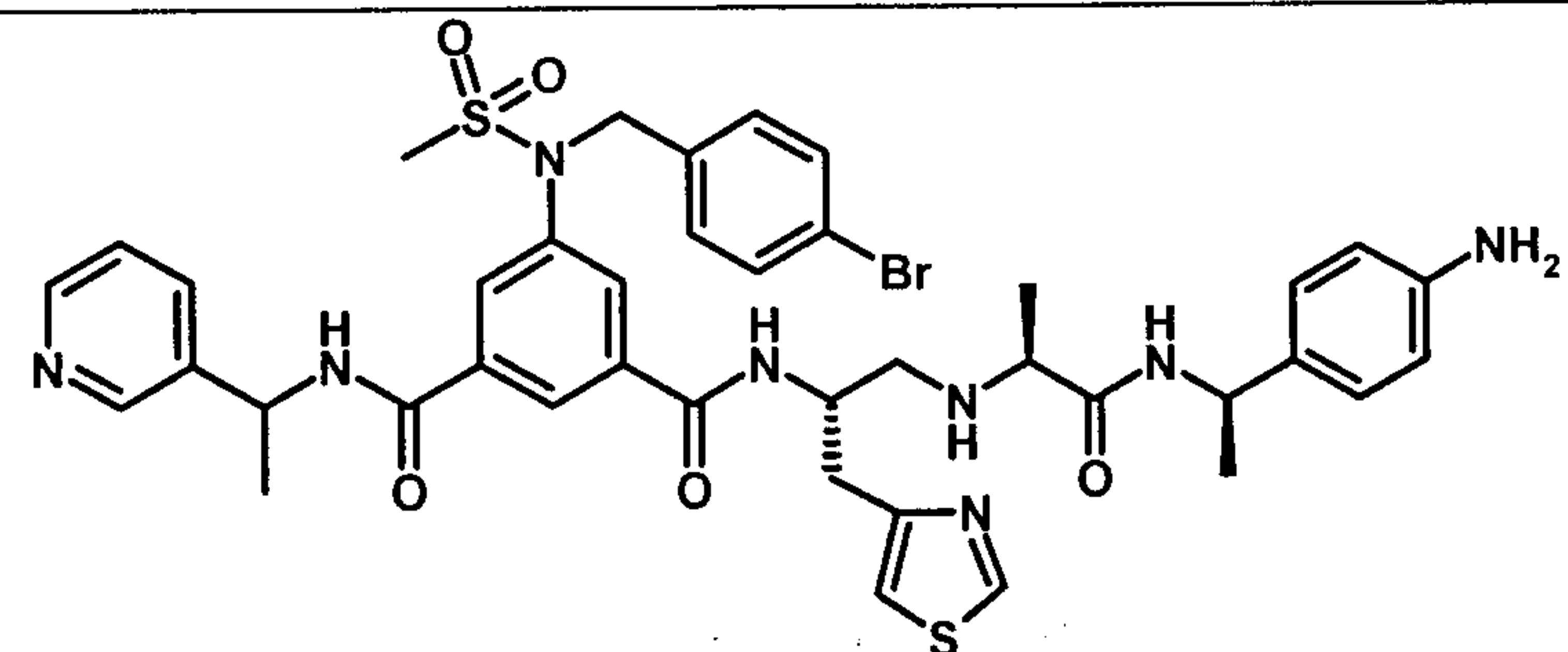
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(83)		8.10
(84)		8.11
(85)		8.12

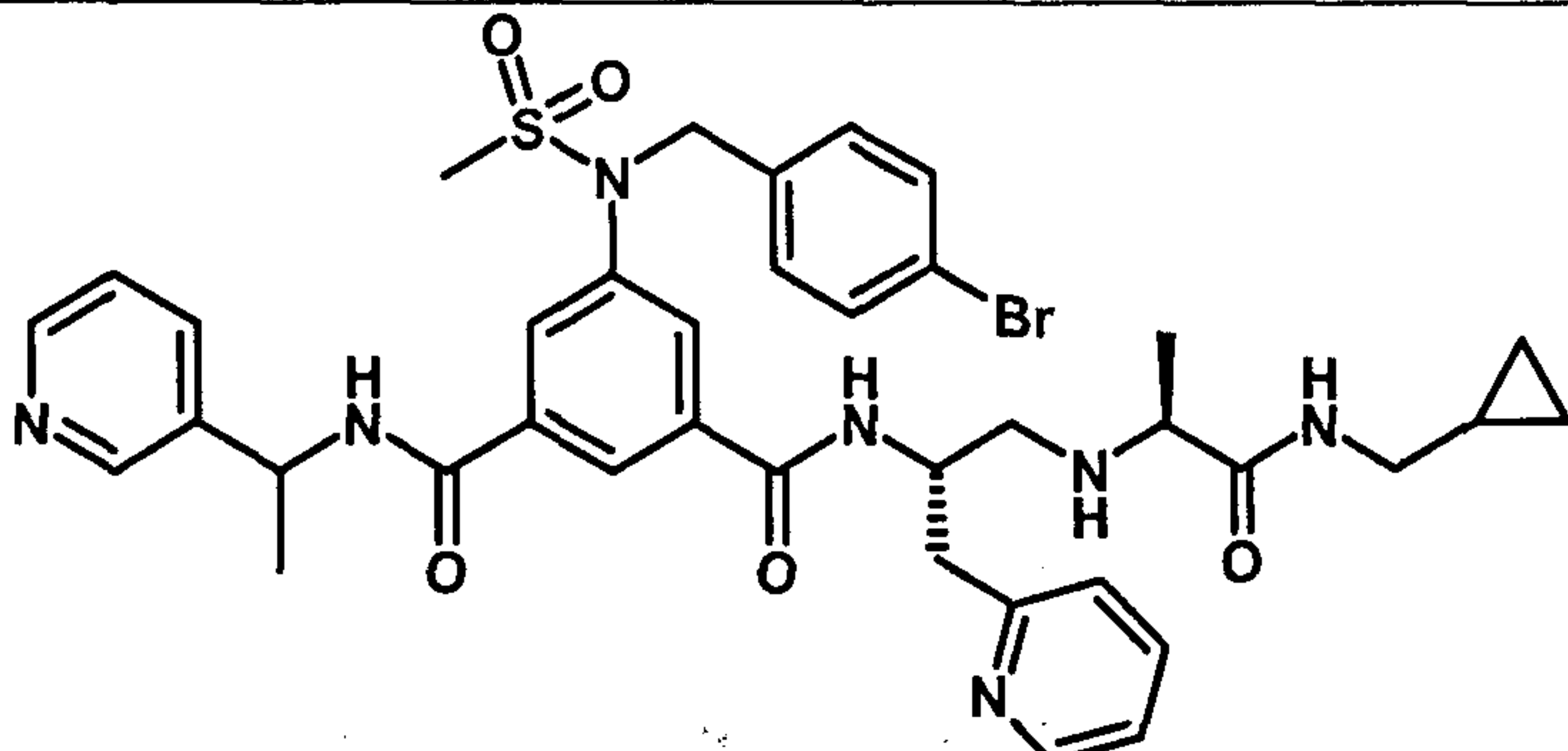
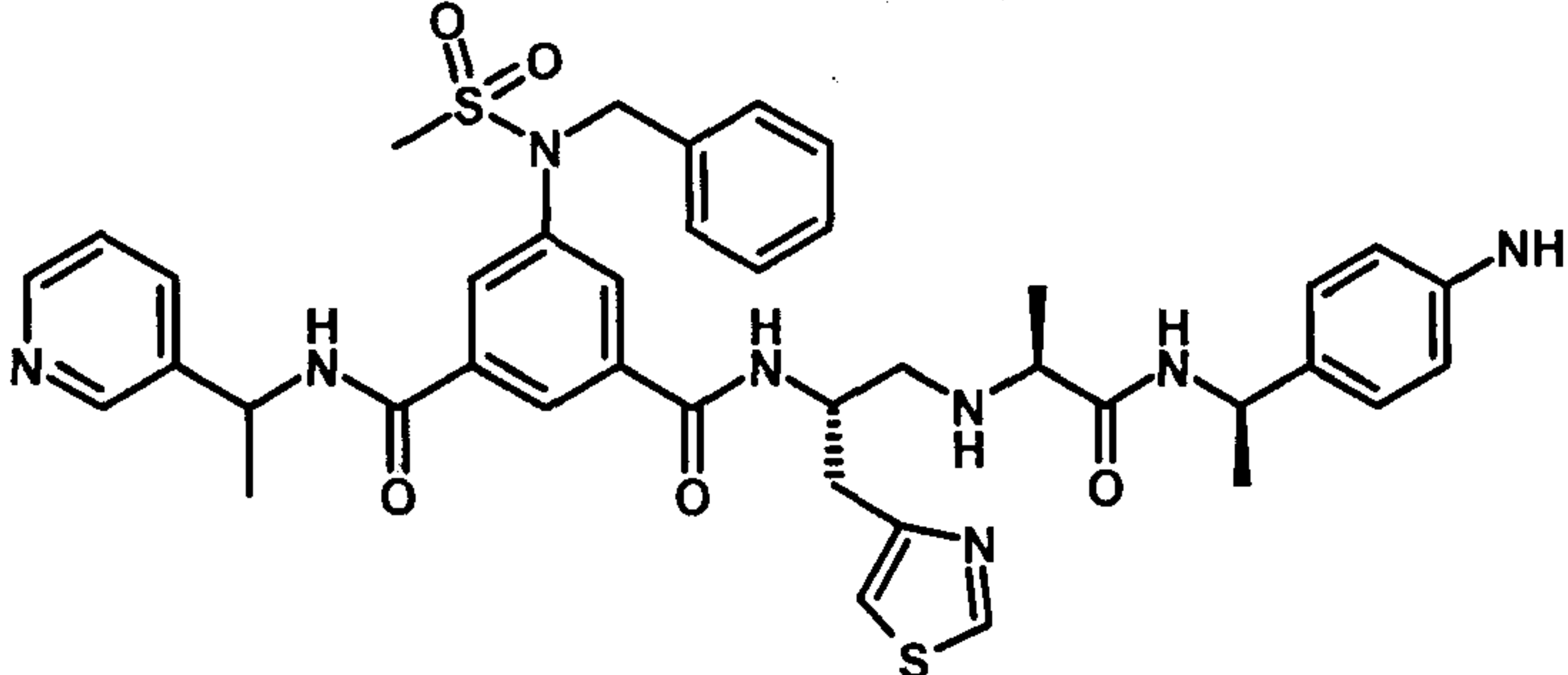
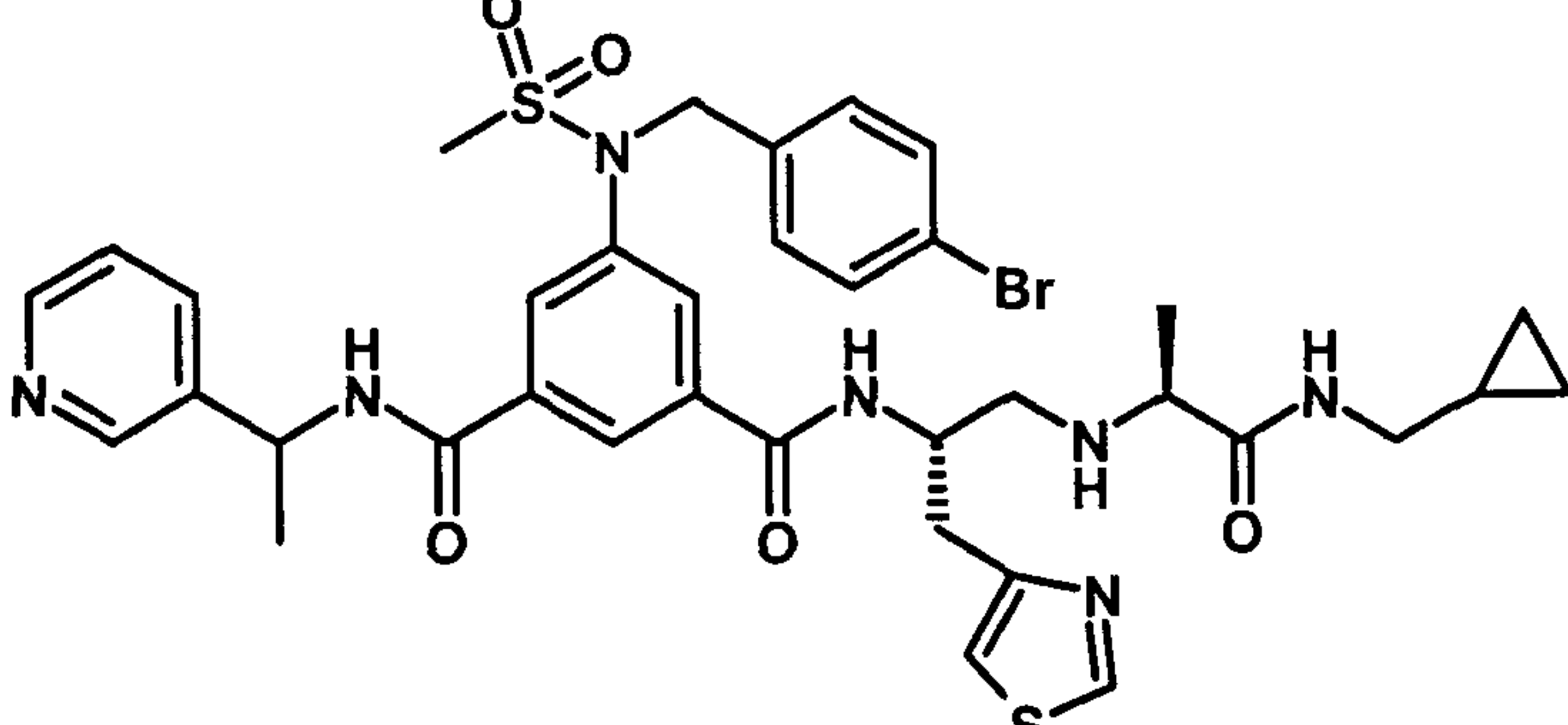
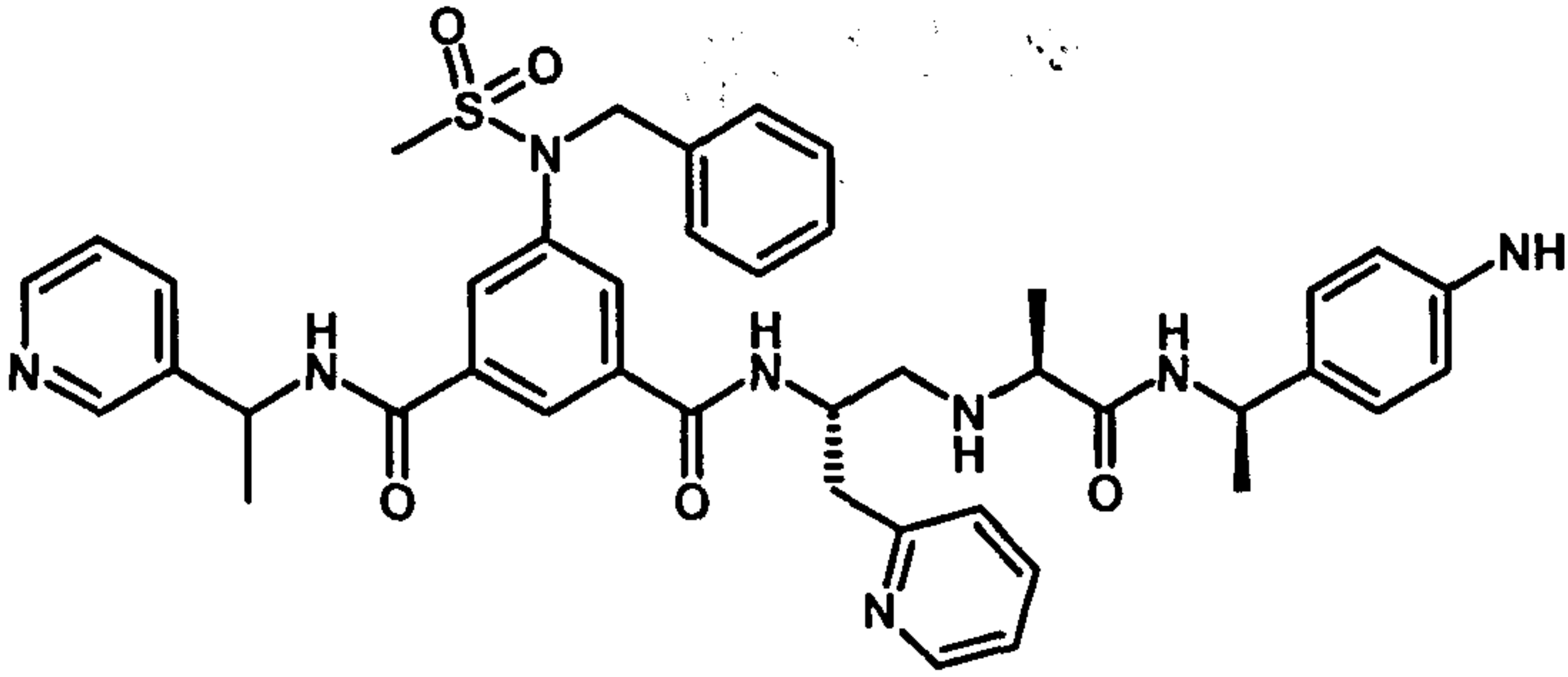
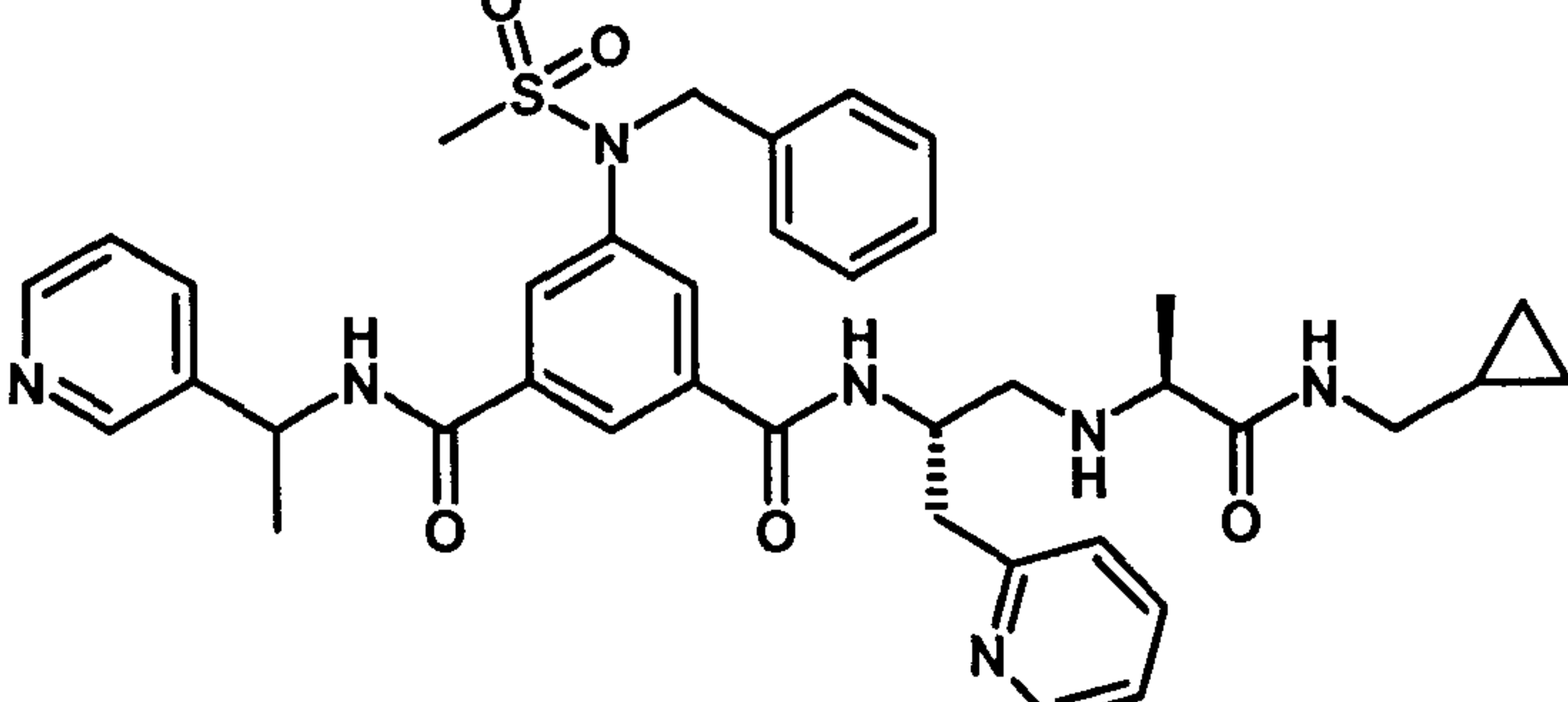
(90)		11
(91)		11.1
(92)		11.2
(93)		11.3
(94)		11.4

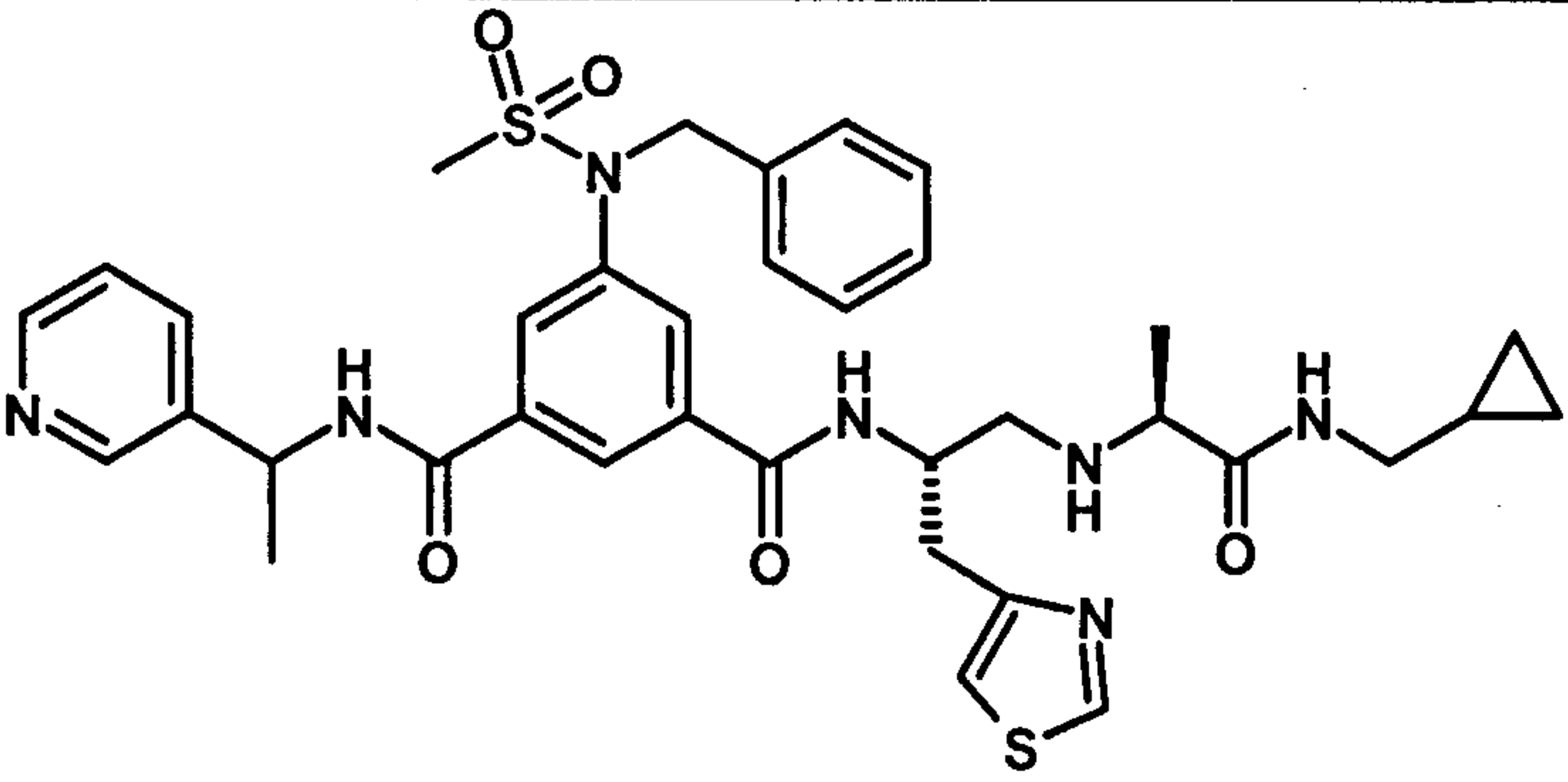
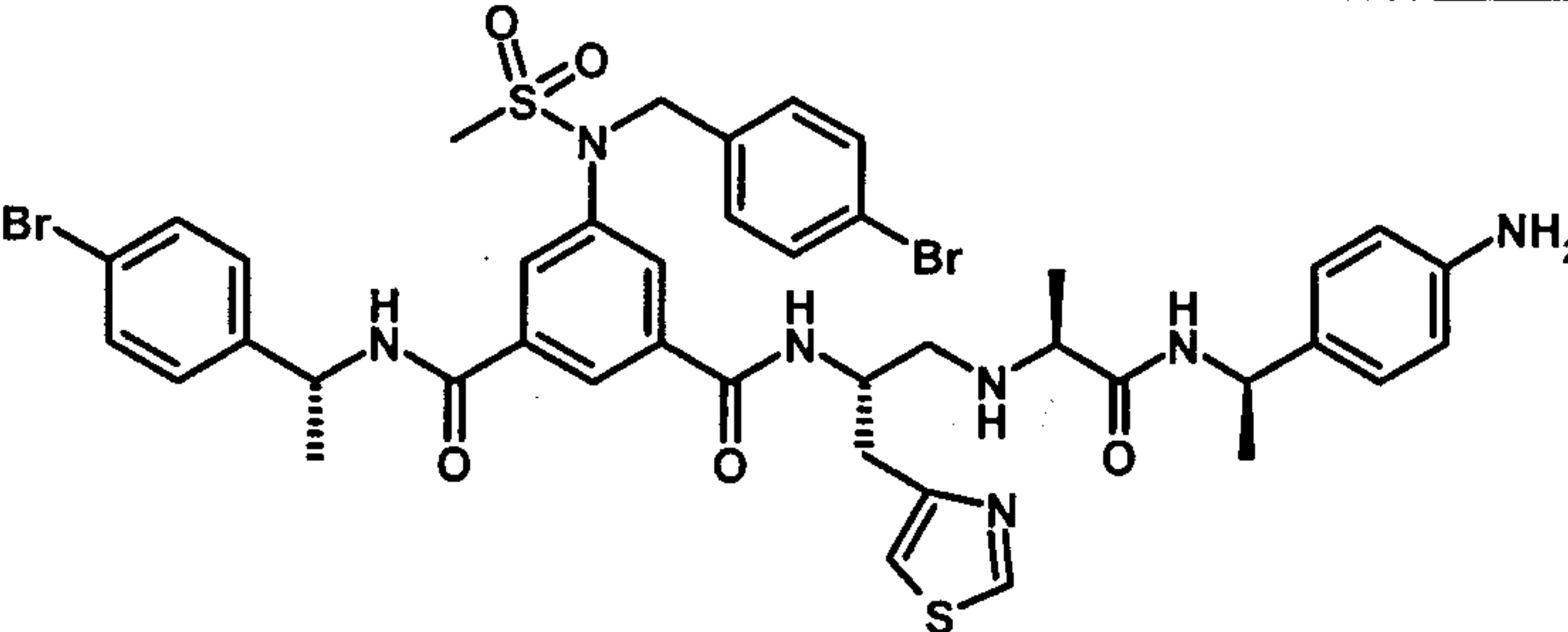
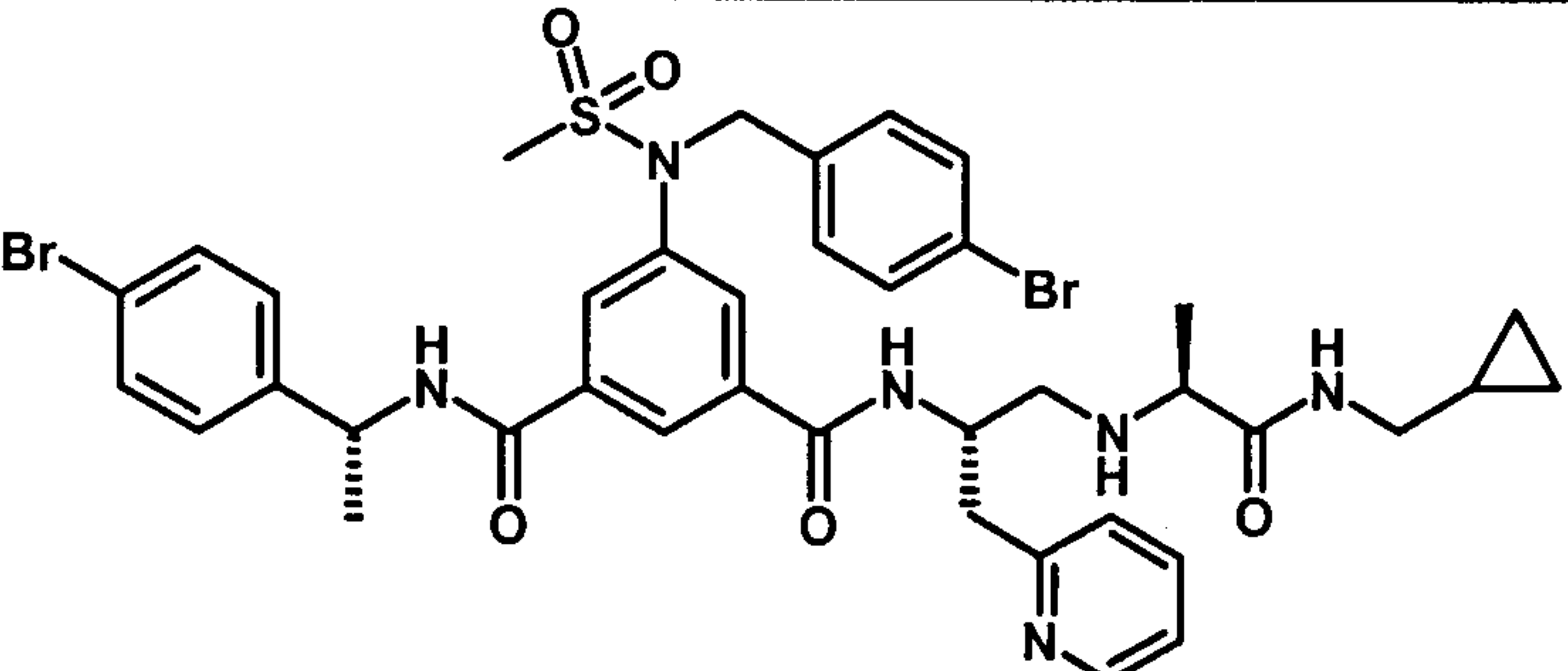
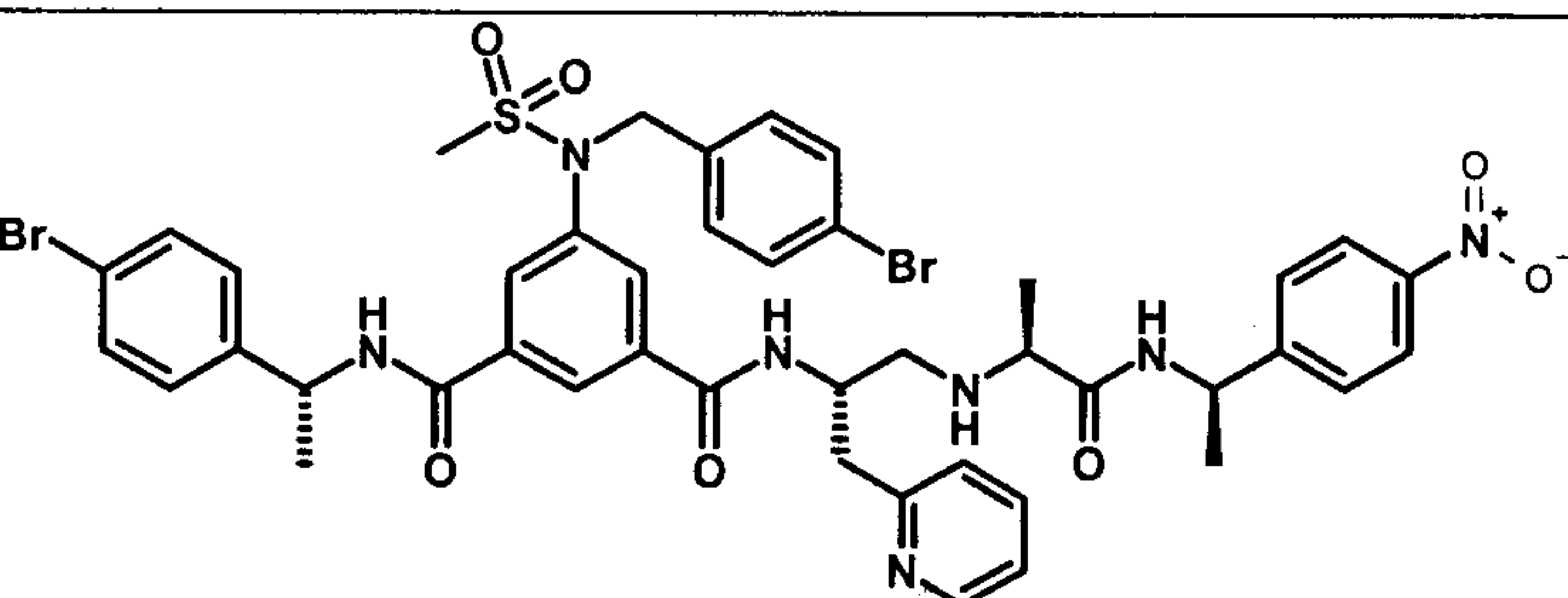
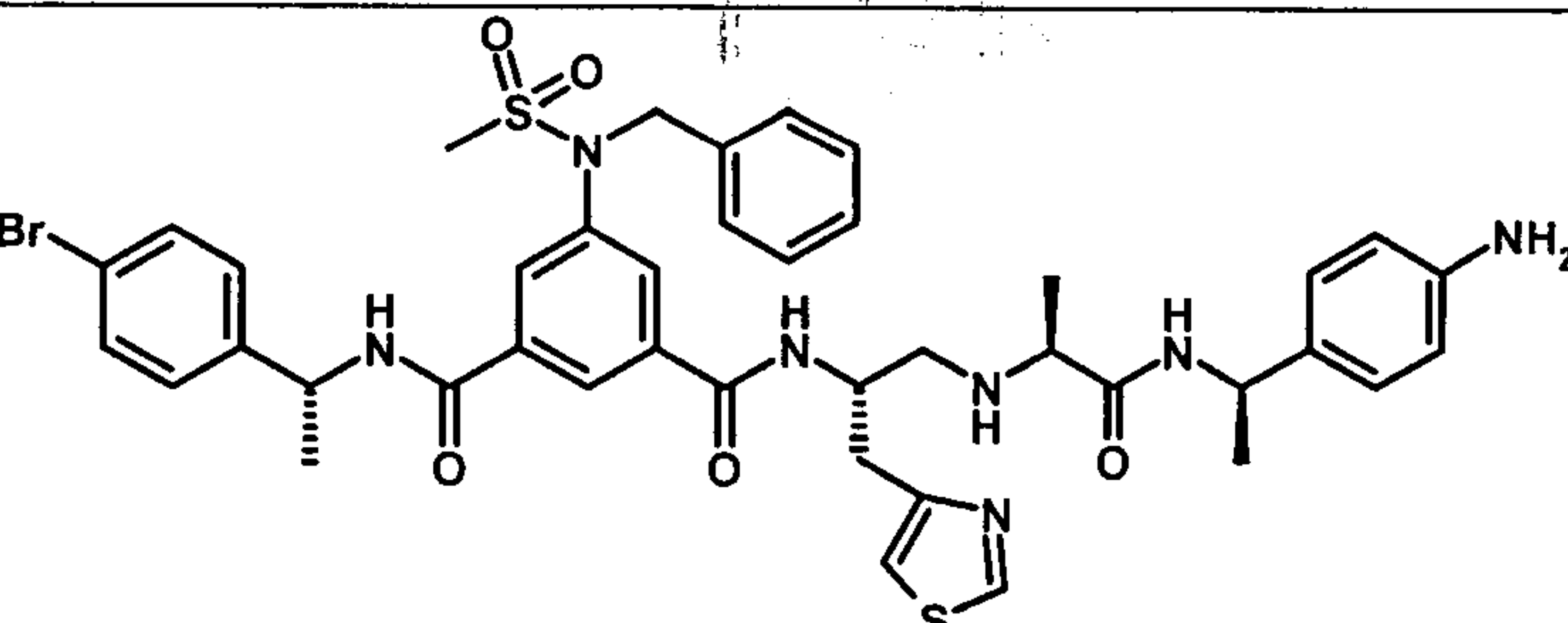
- 66 -

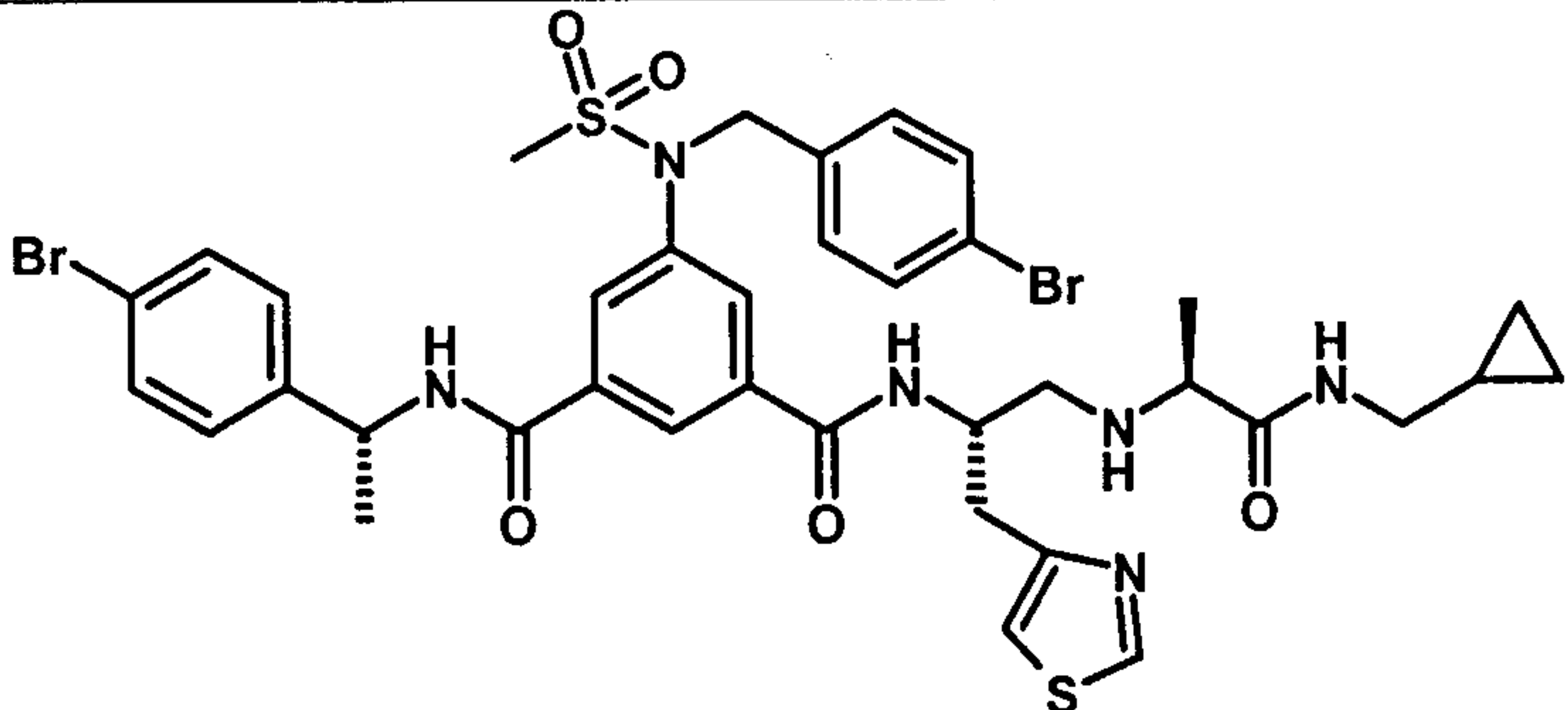
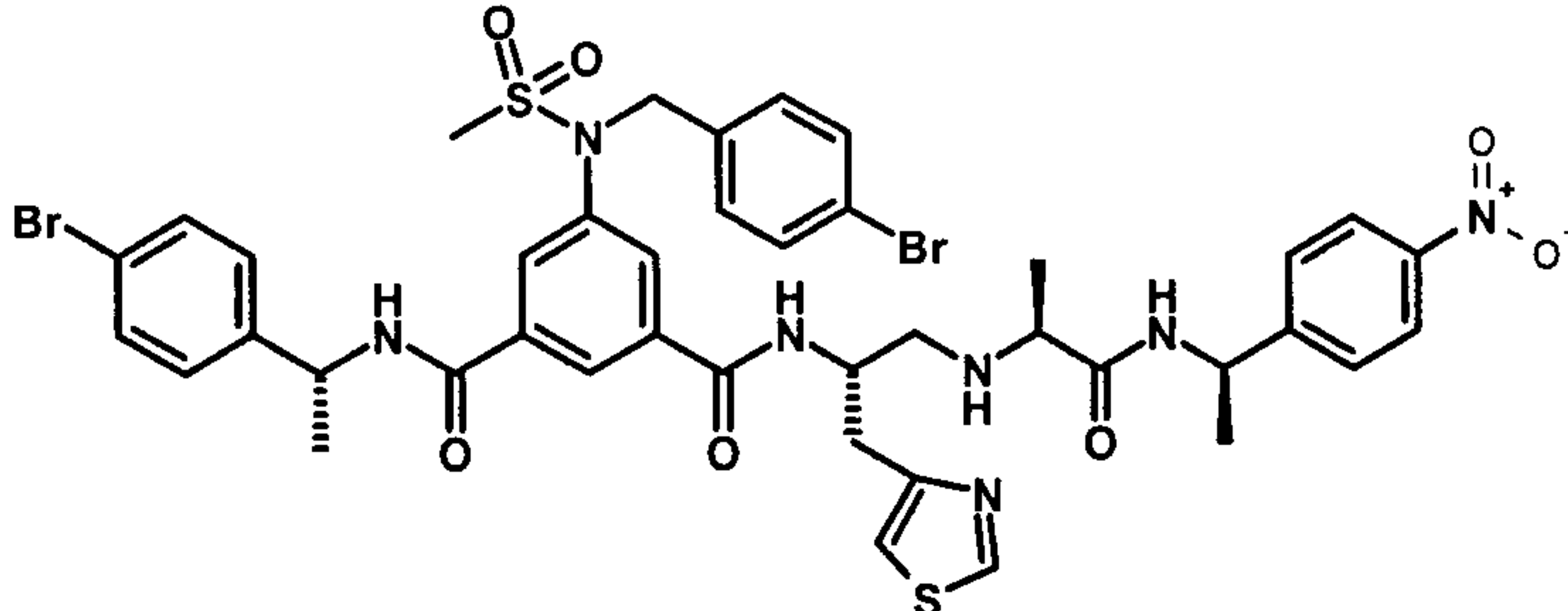
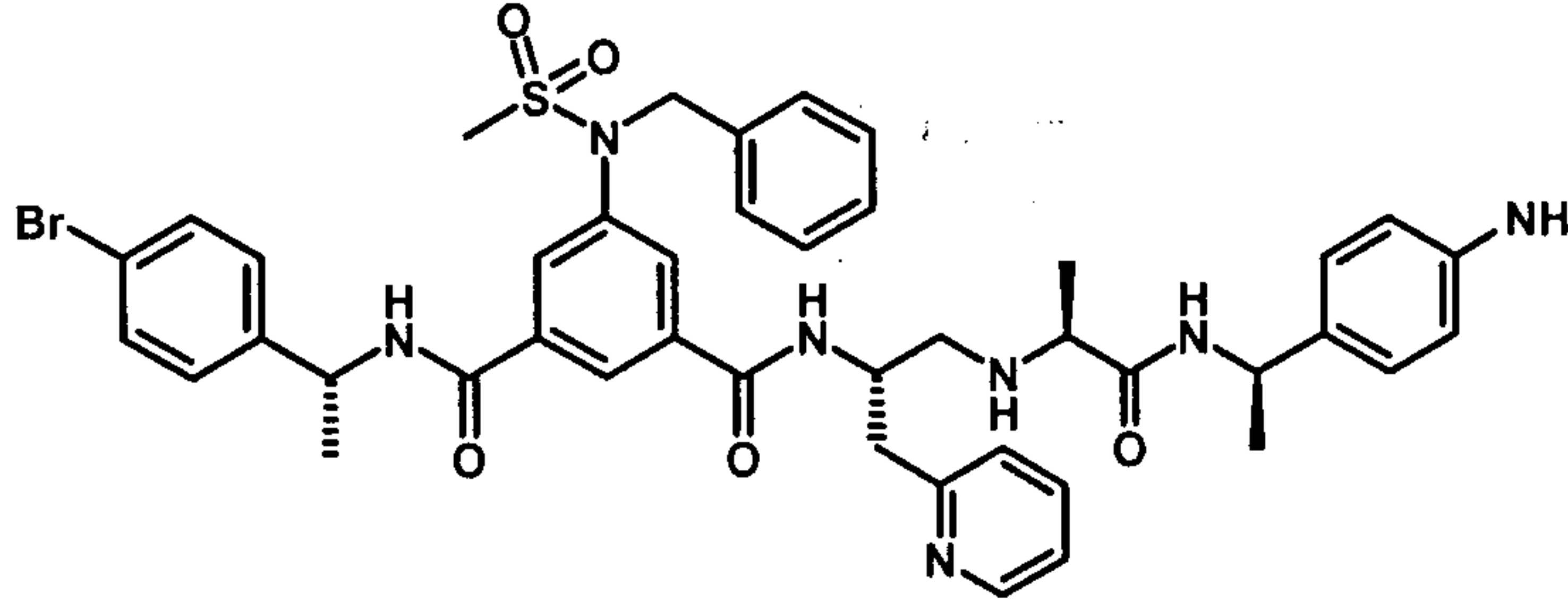
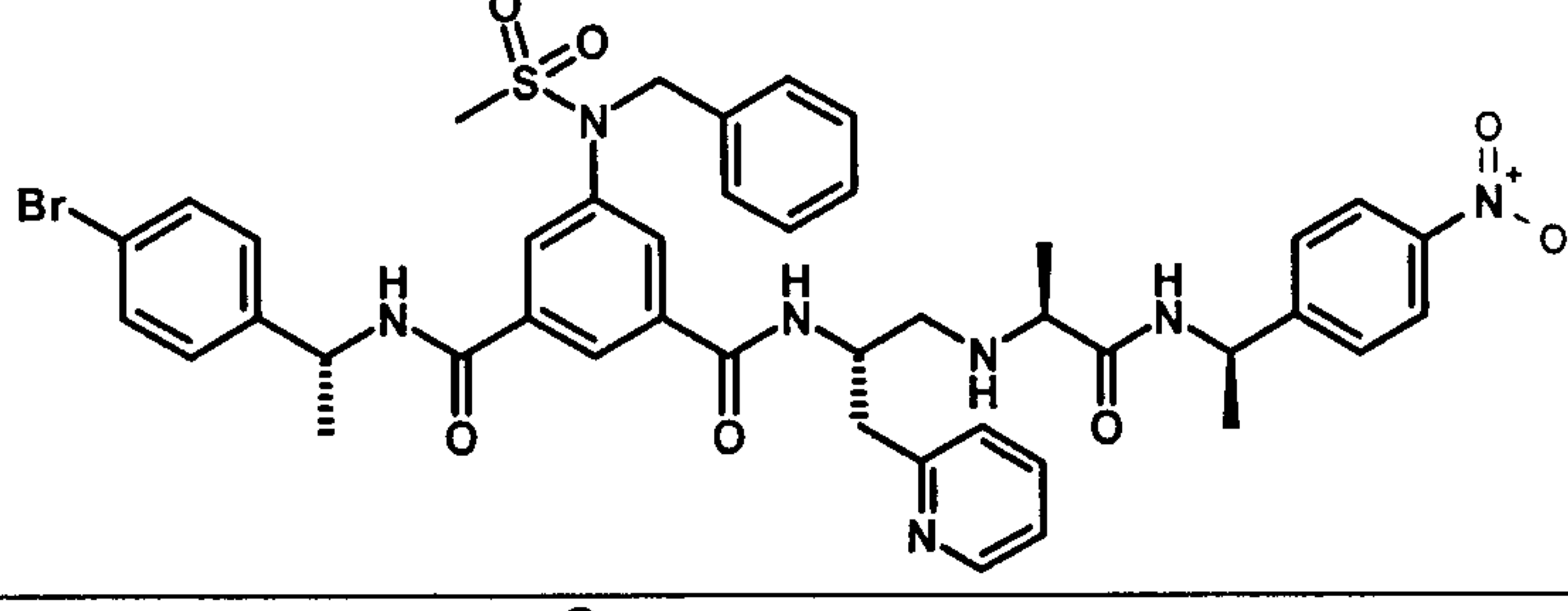
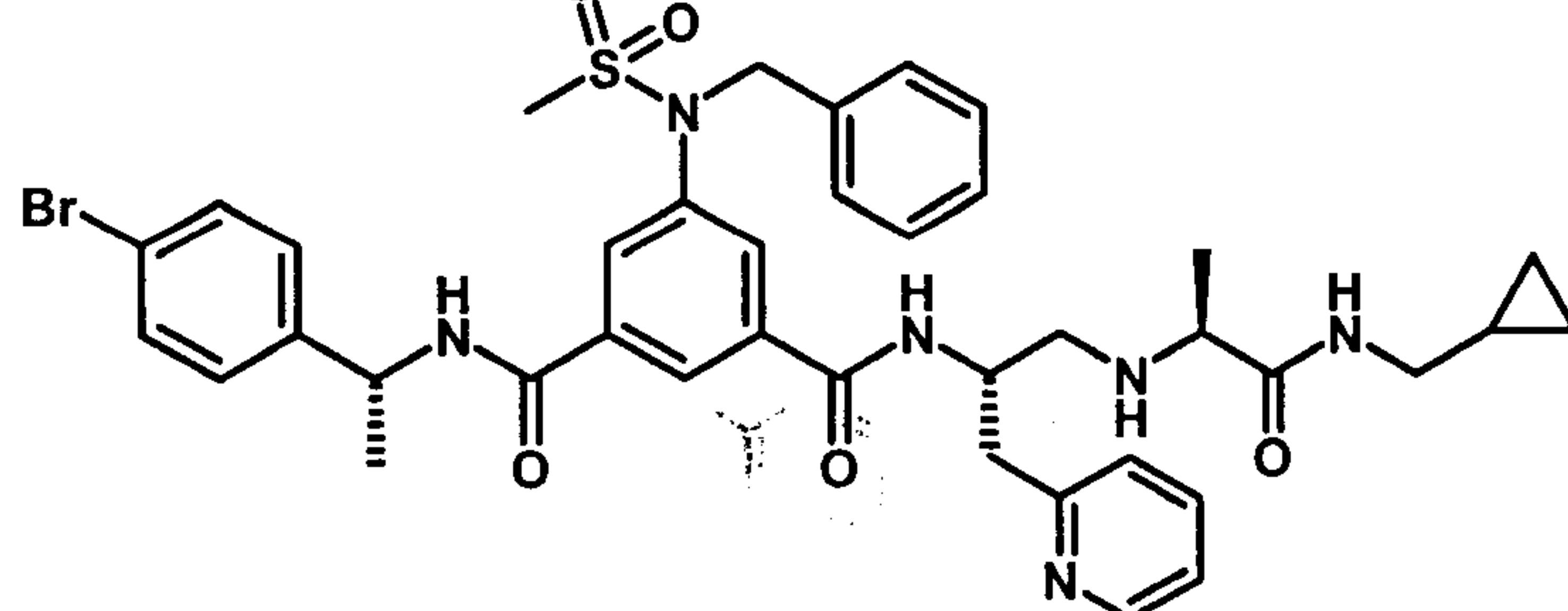
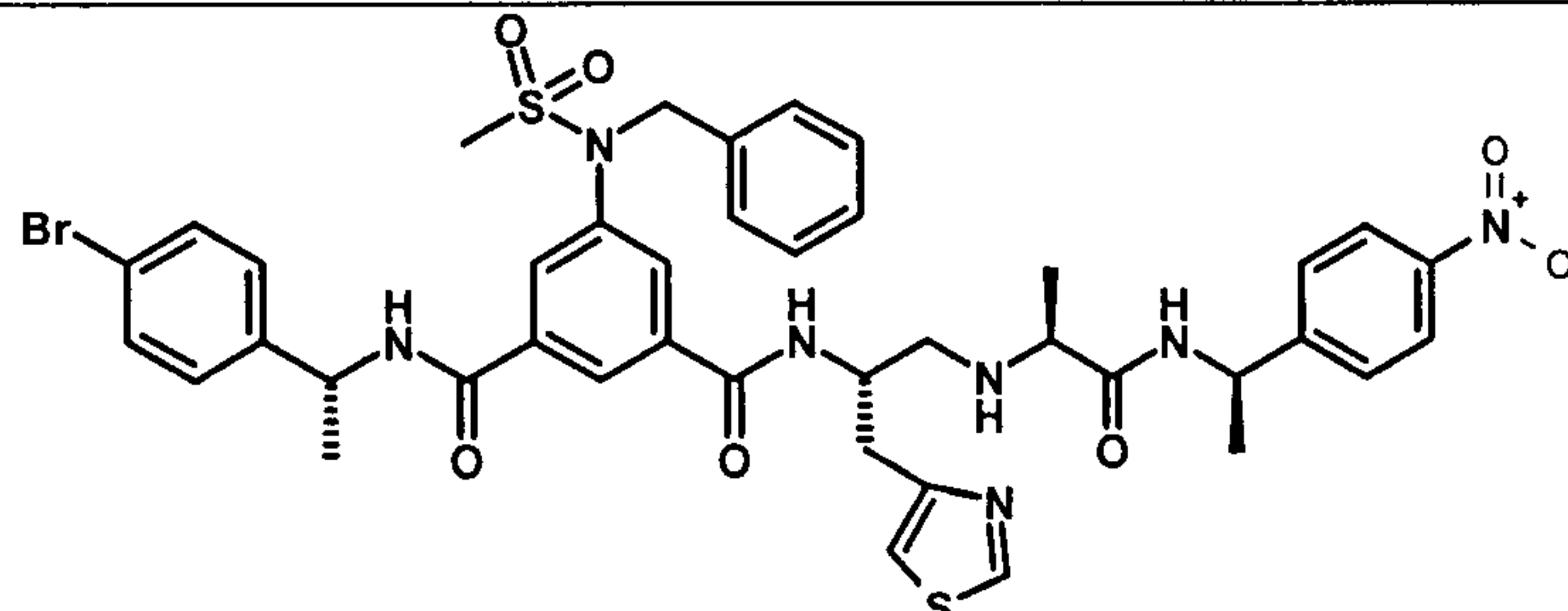
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(96)		12
(97)		12.2
(98)		12.3

- 67 -

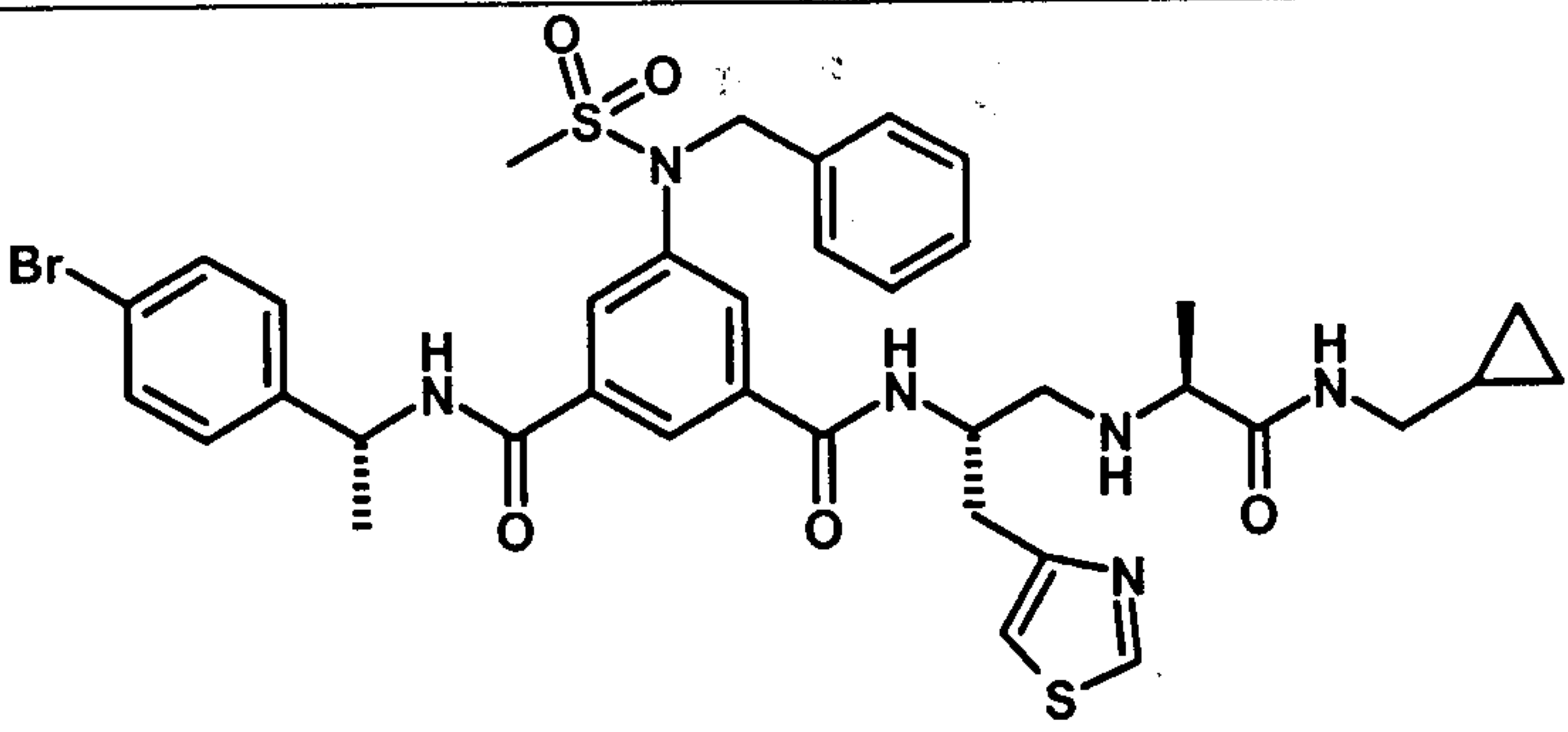
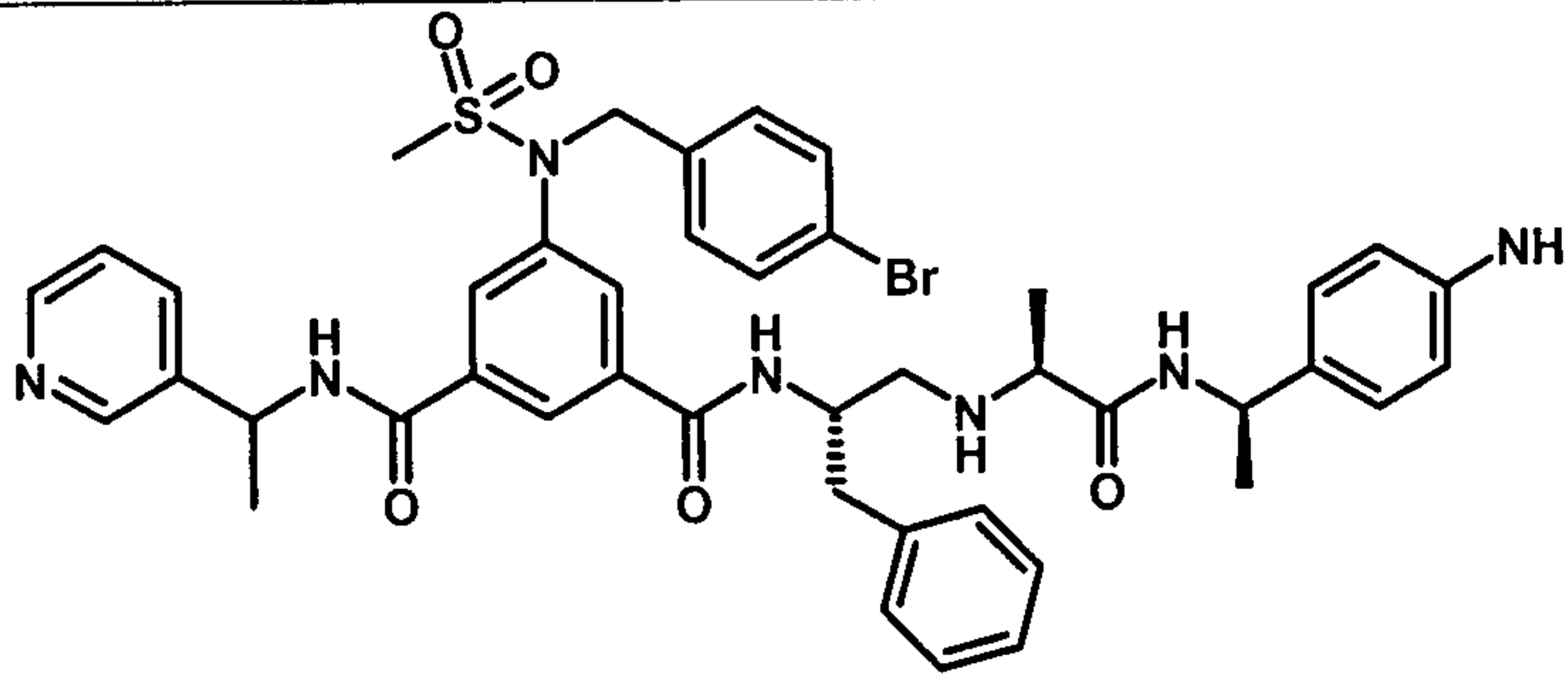
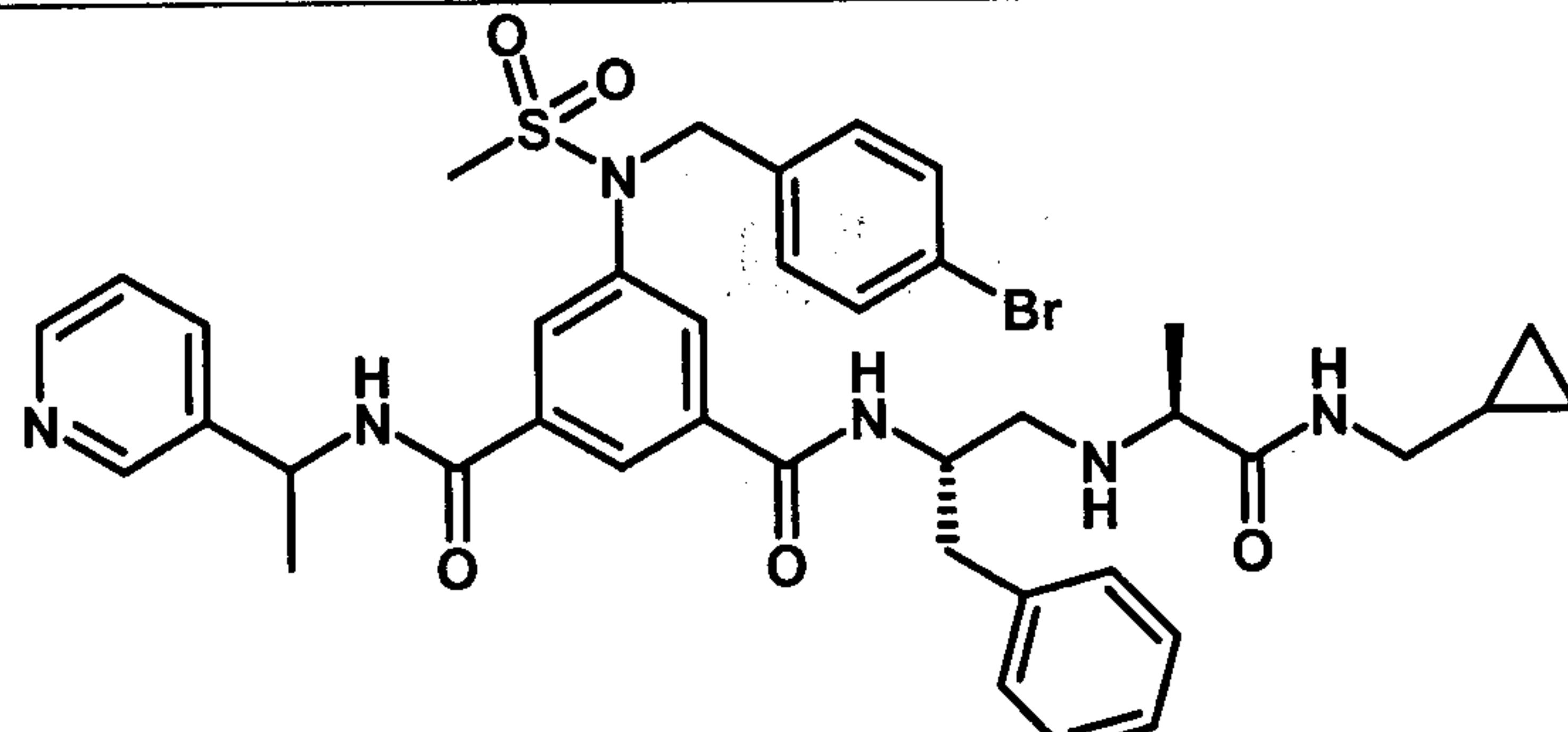
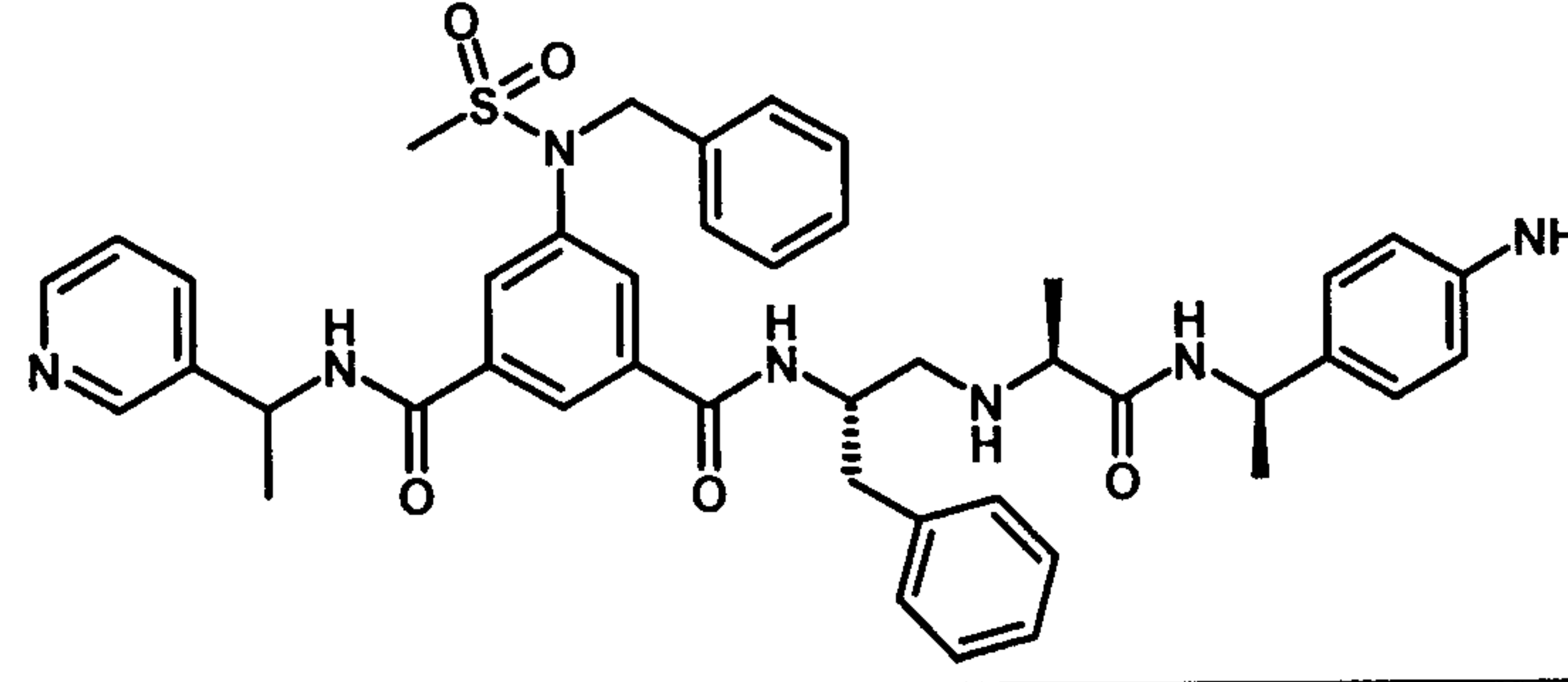
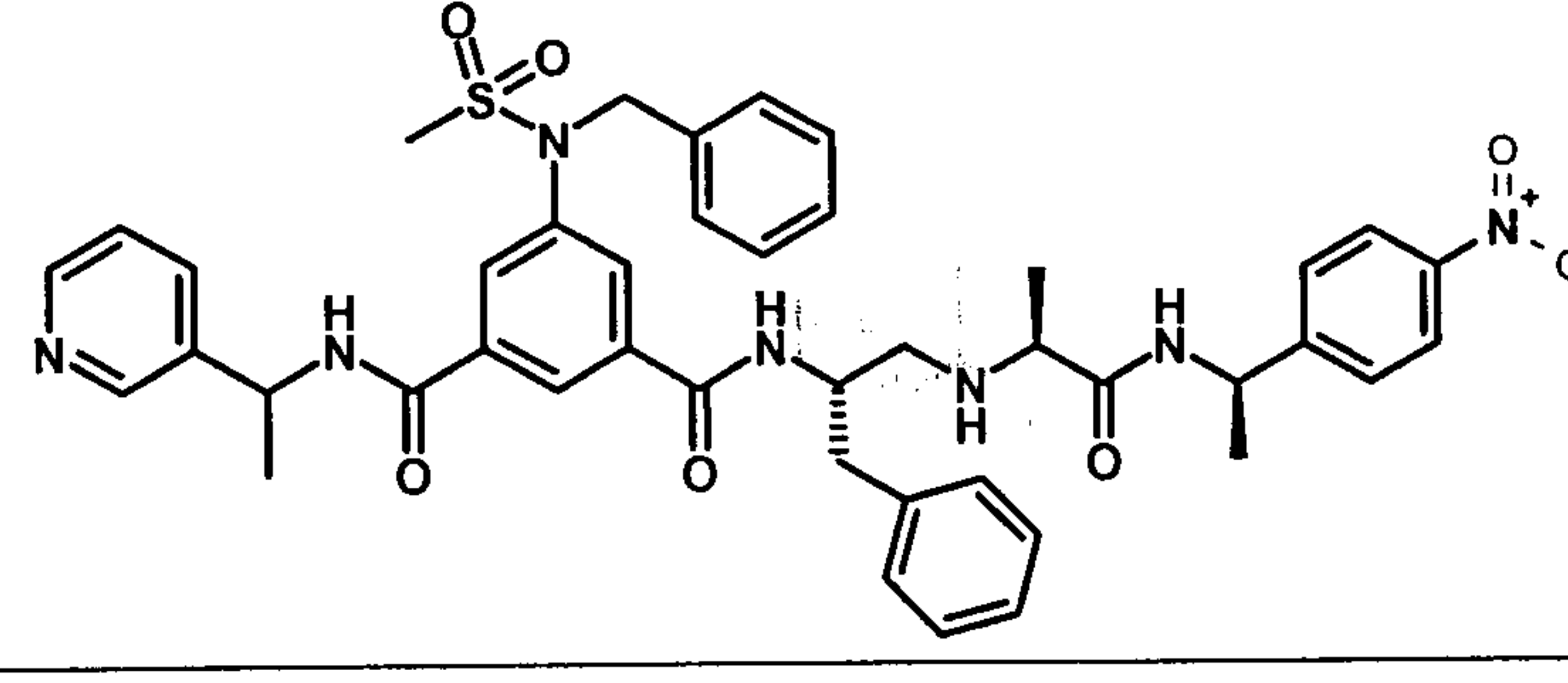
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(100)		13
(101)		14
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(103)		14.2

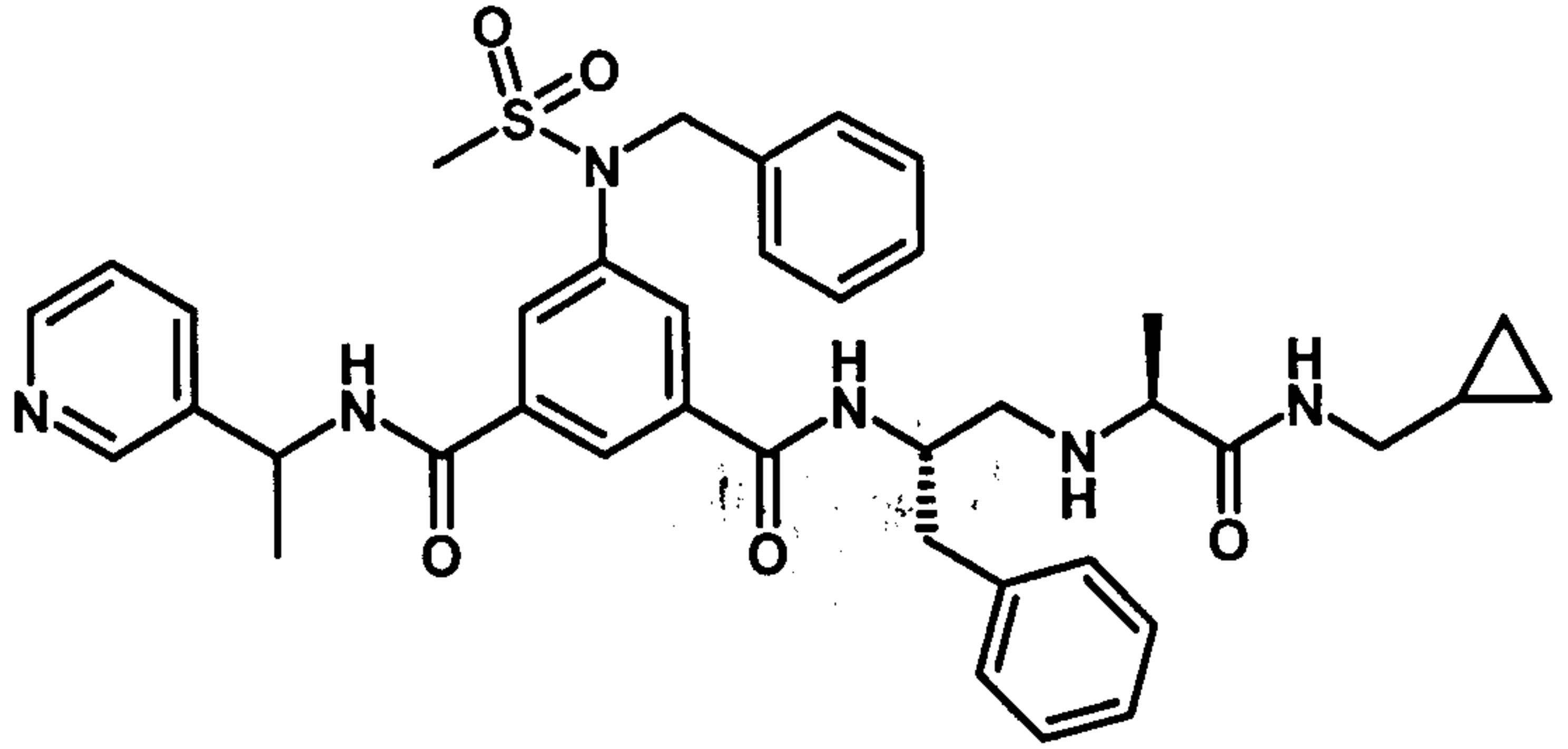
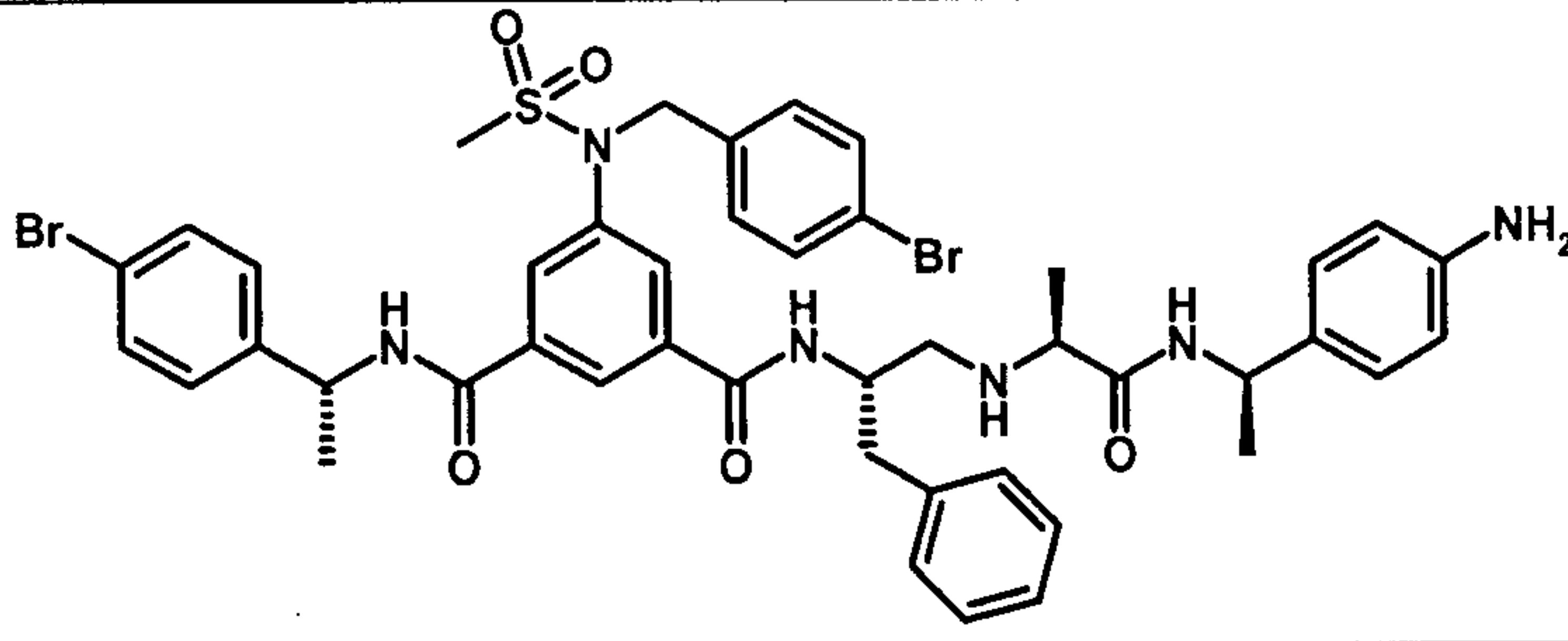
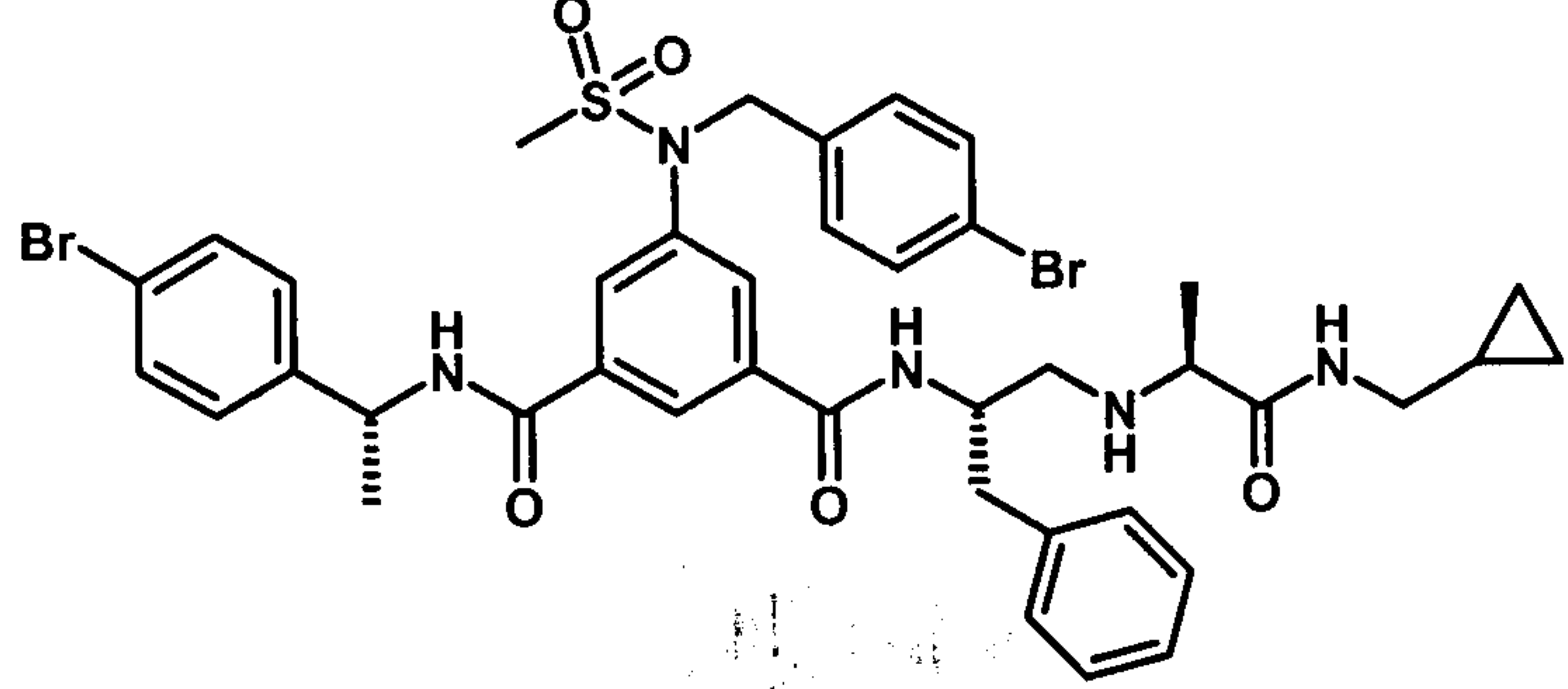
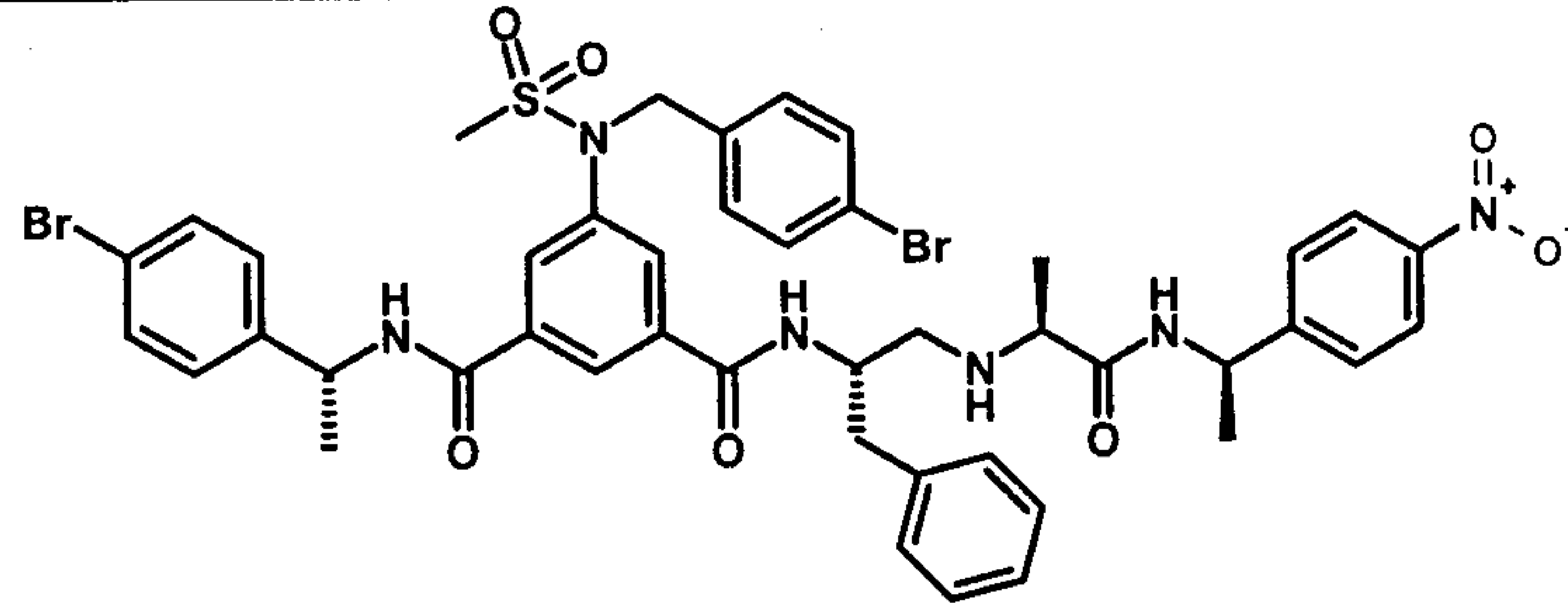
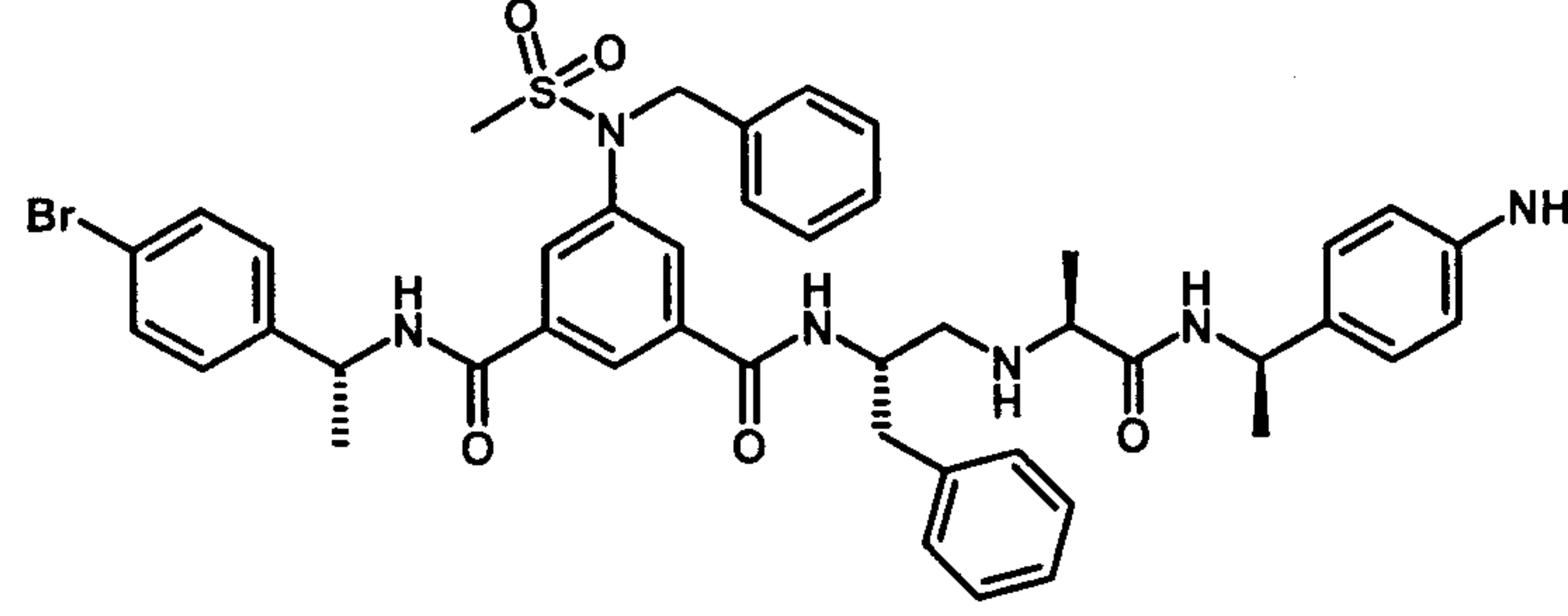
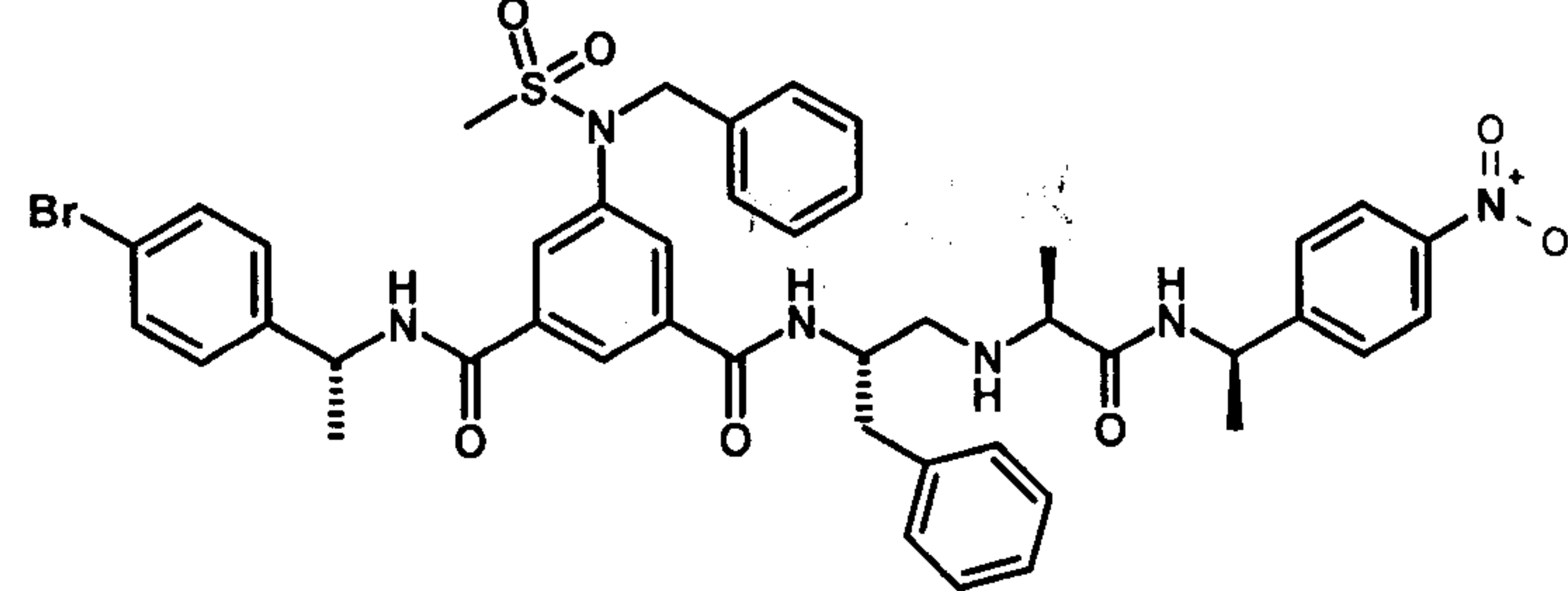
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(105)		14.4
(106)		14.5
(107)		14.6
(108)		14.7

(109)		14.8
(110)		14.9
(111)		14.10
(112)		14.11
(113)		14.12

(114)		14.13
(115)		14.14
(116)		14.15
(117)		14.16
(118)		14.17
(119)		14.18

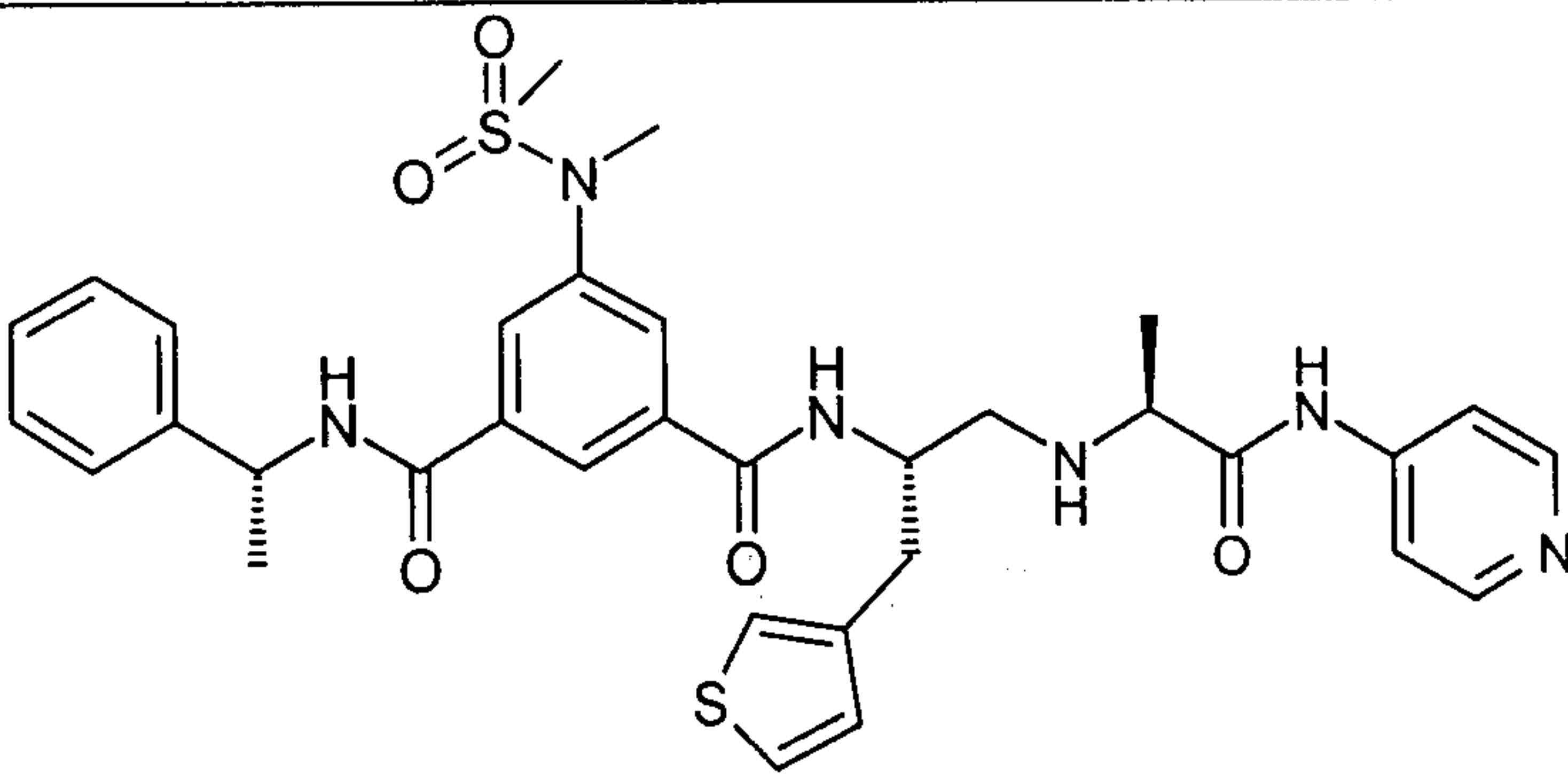
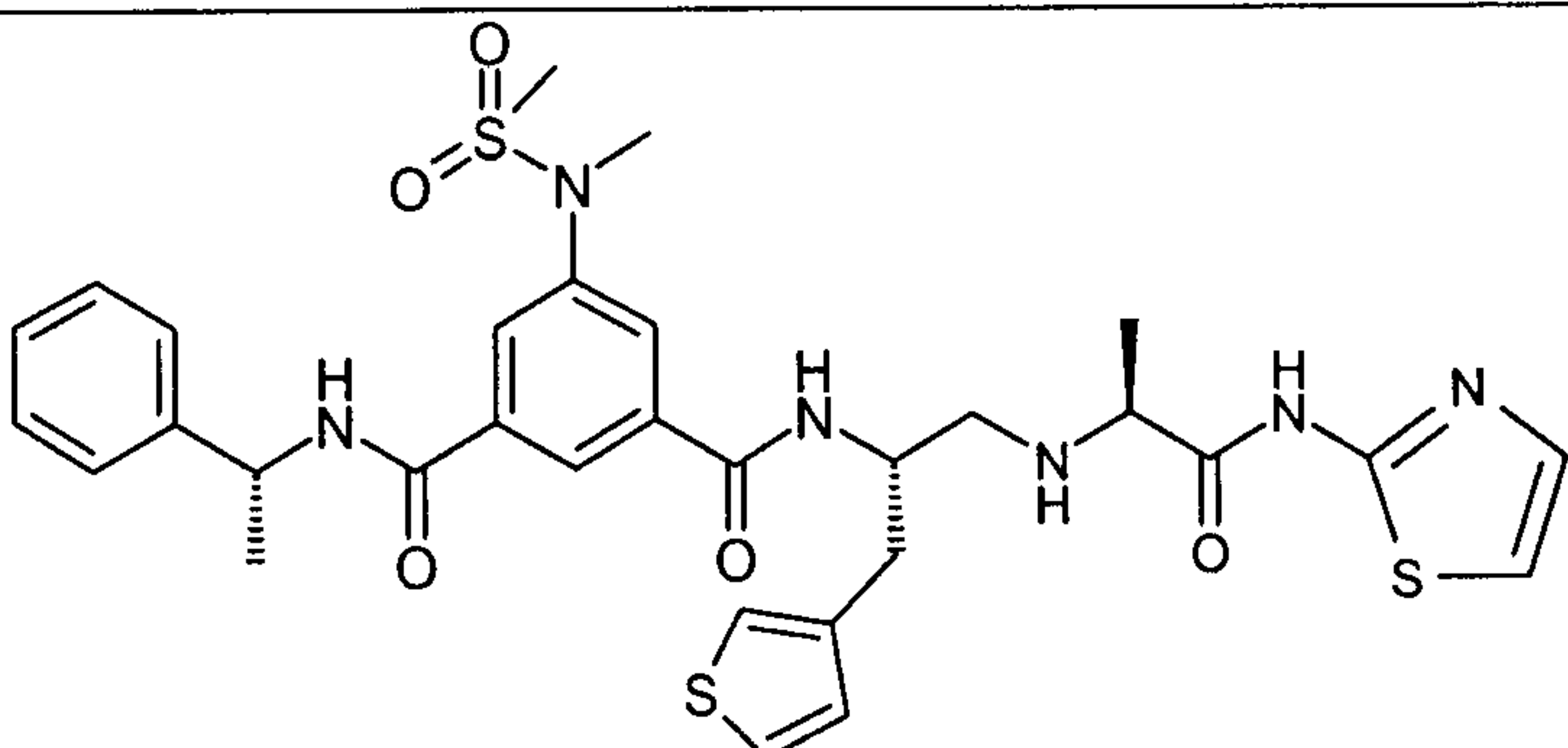
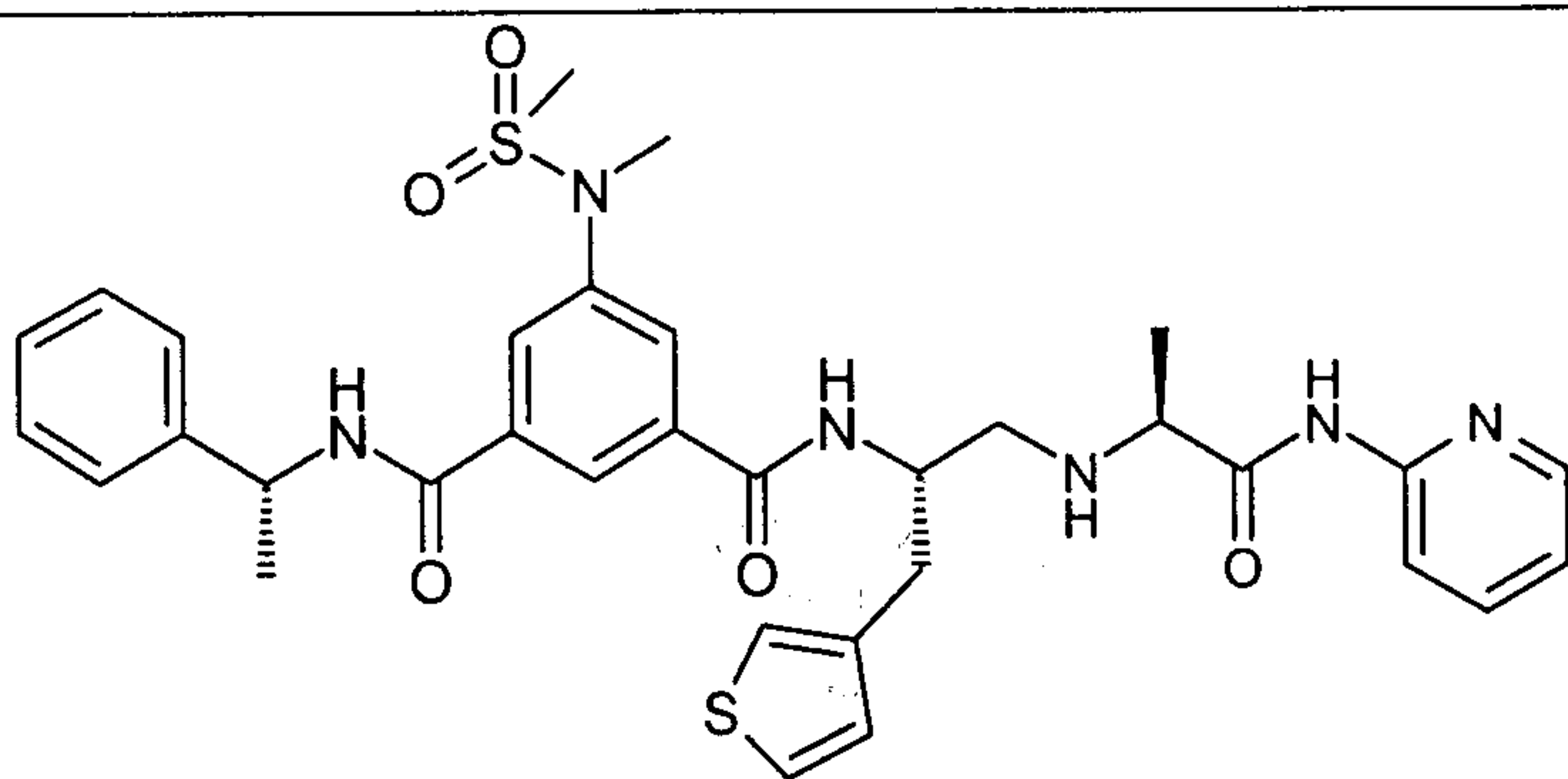
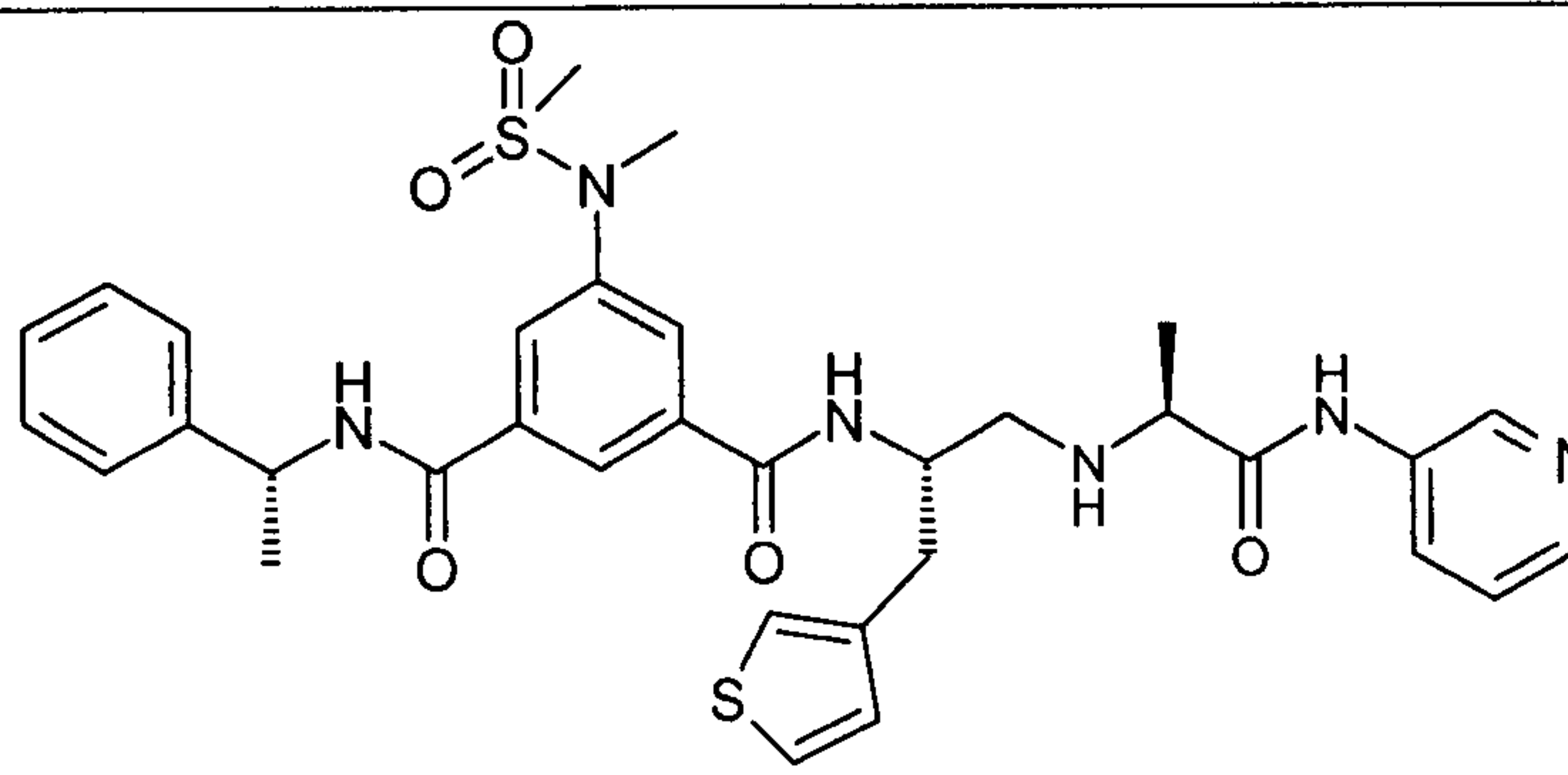
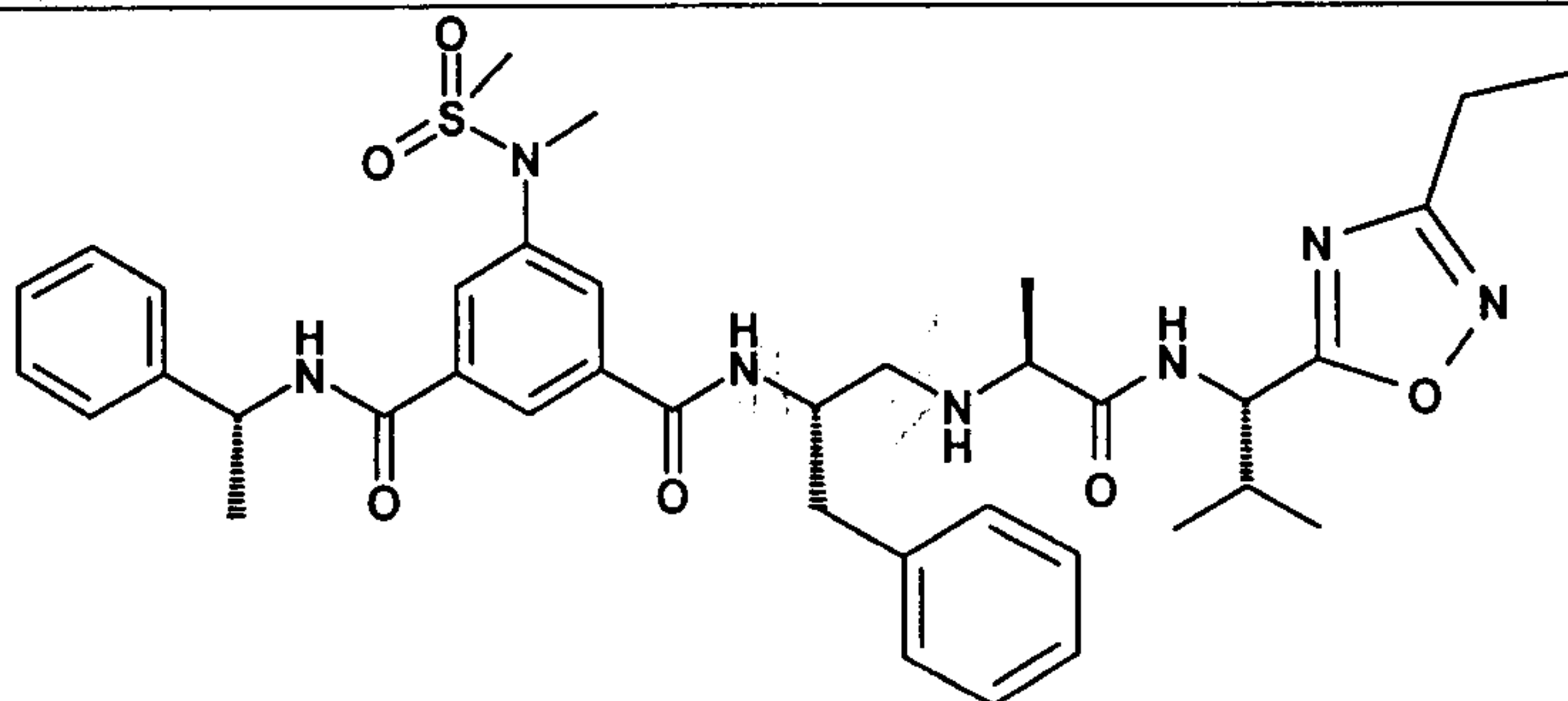
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(120)		14.19
(121)		14.20
(122)		14.21
(123)		14.22
(124)		14.23

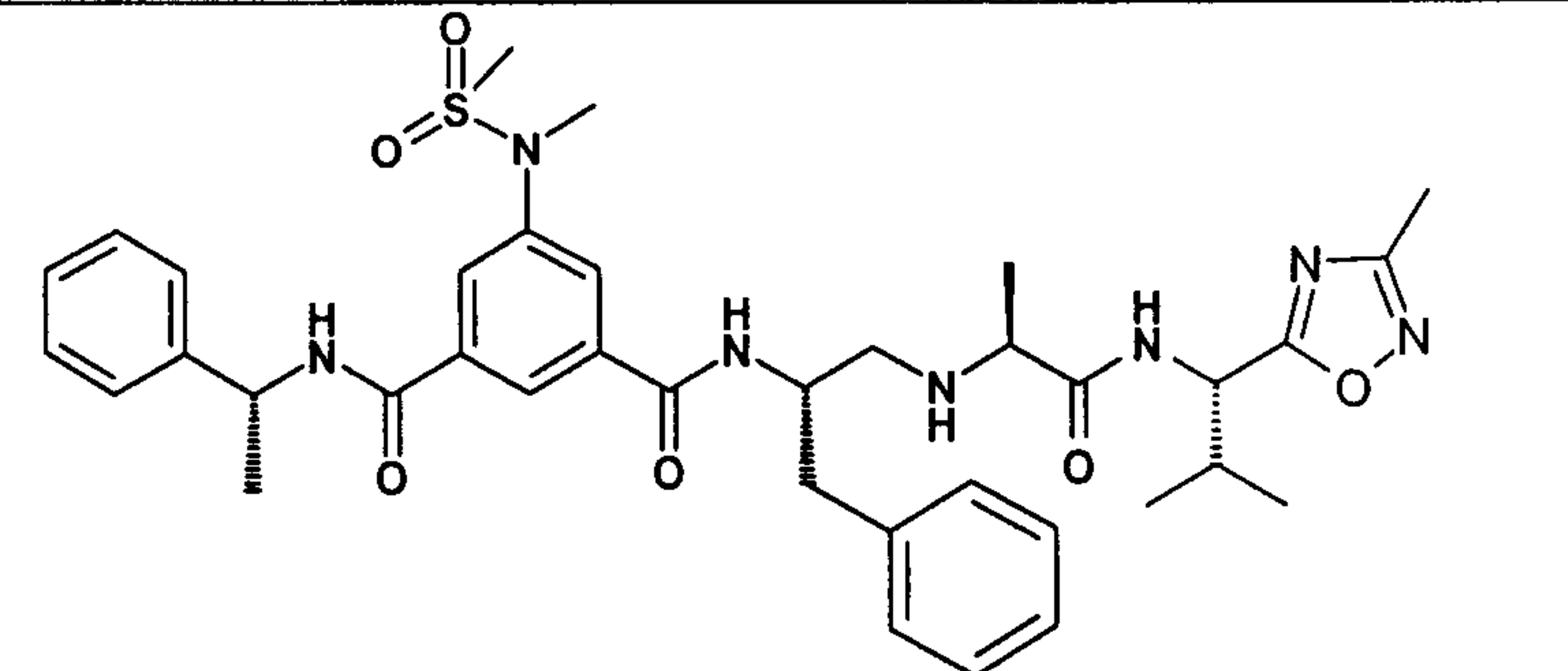
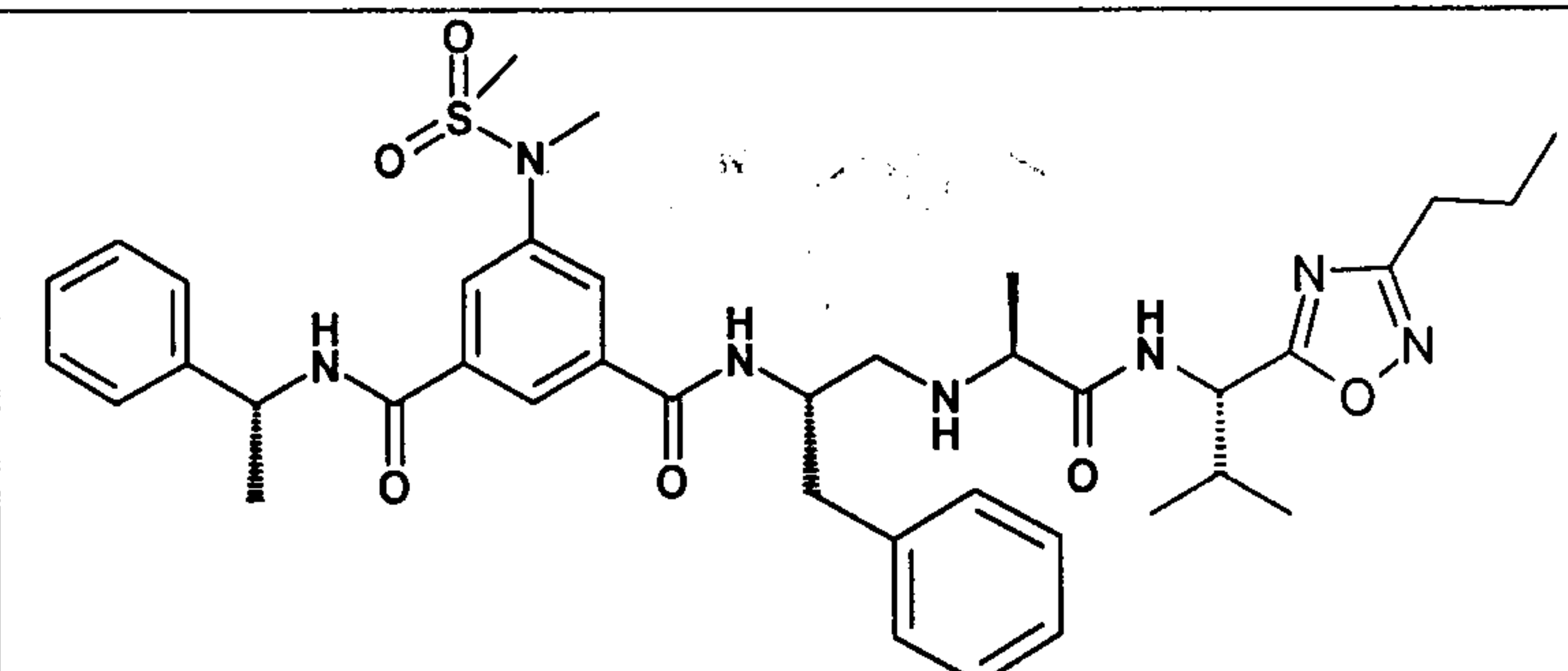
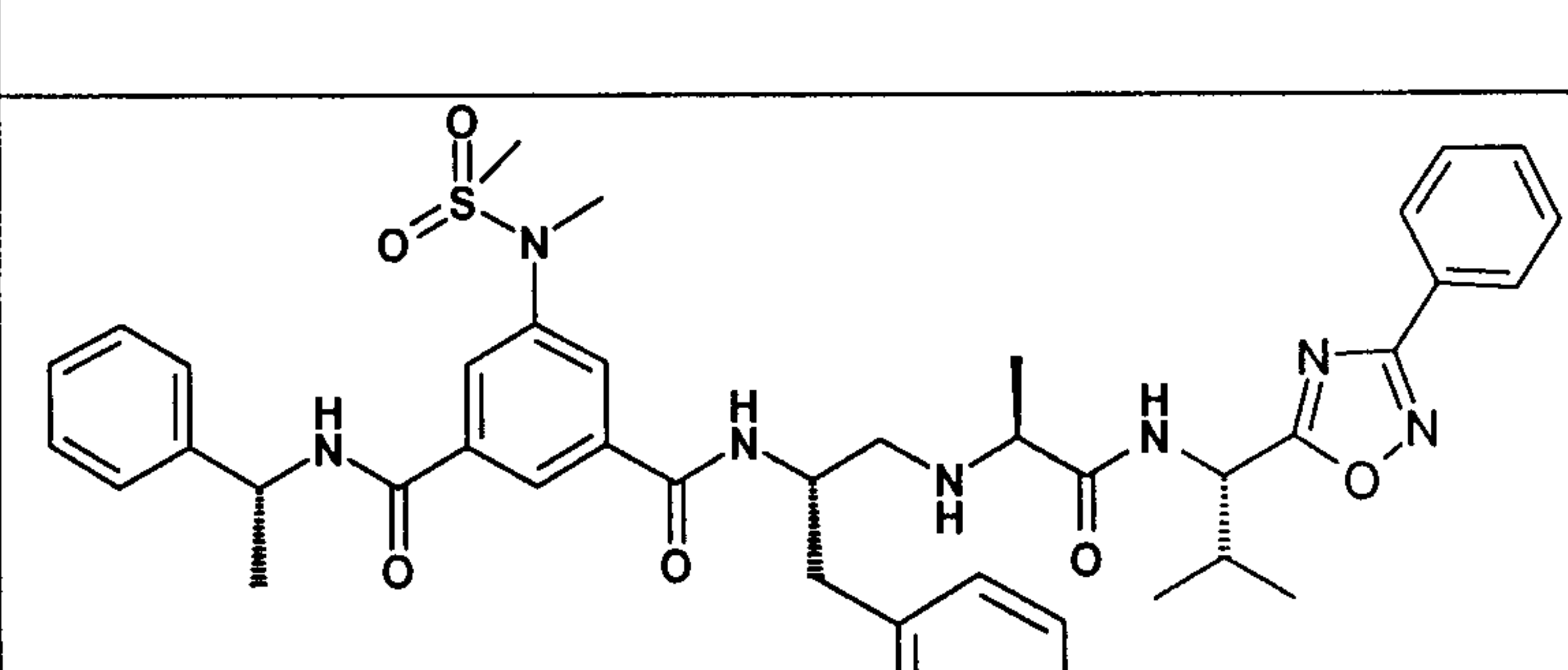
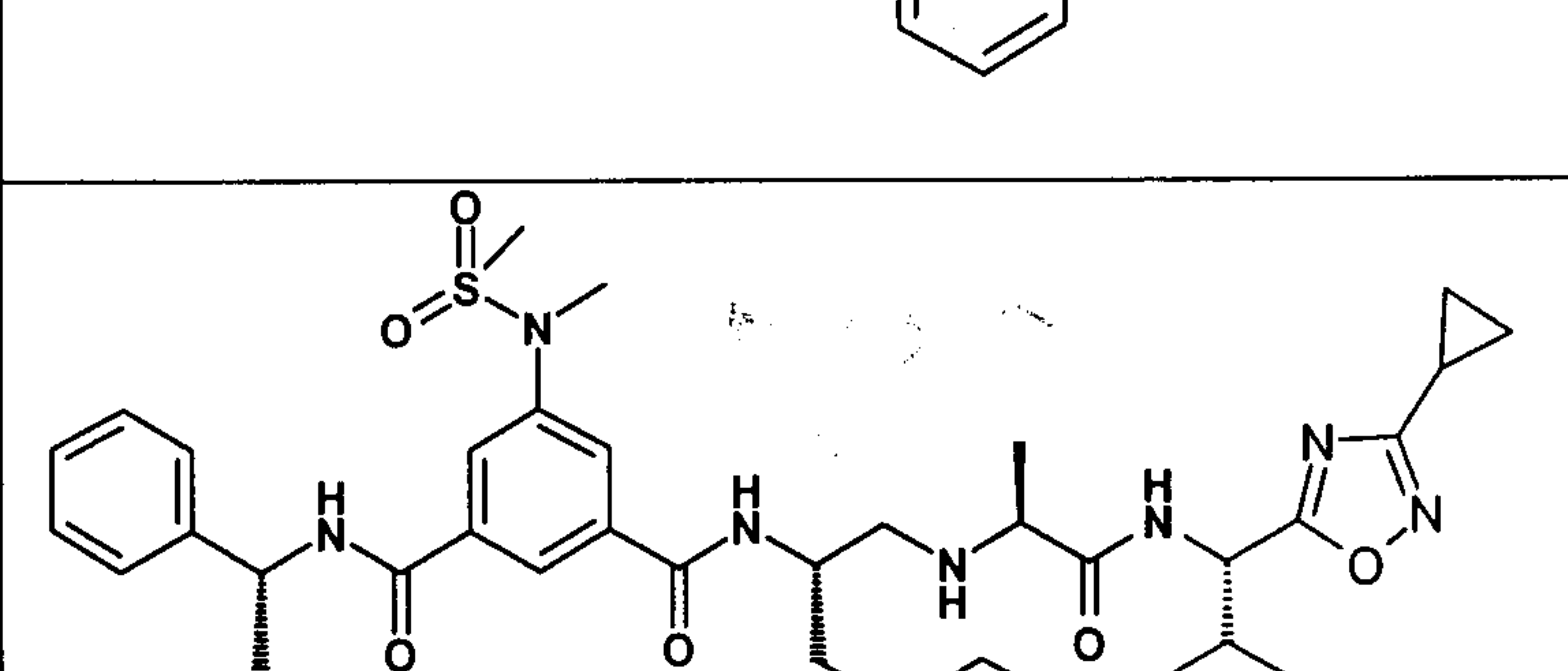
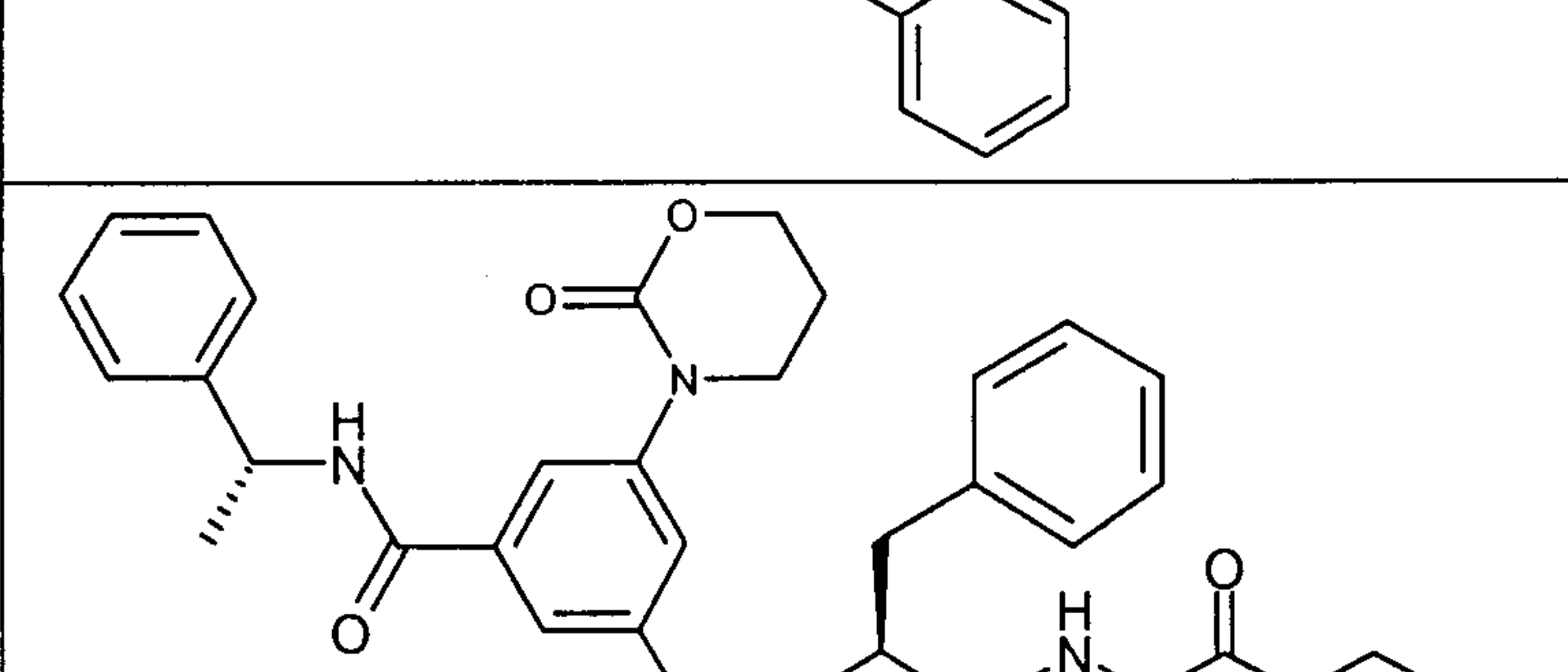
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(126)		14.25
(127)		14.26
(128)		14.27
(129)		14.28
(130)		14.29

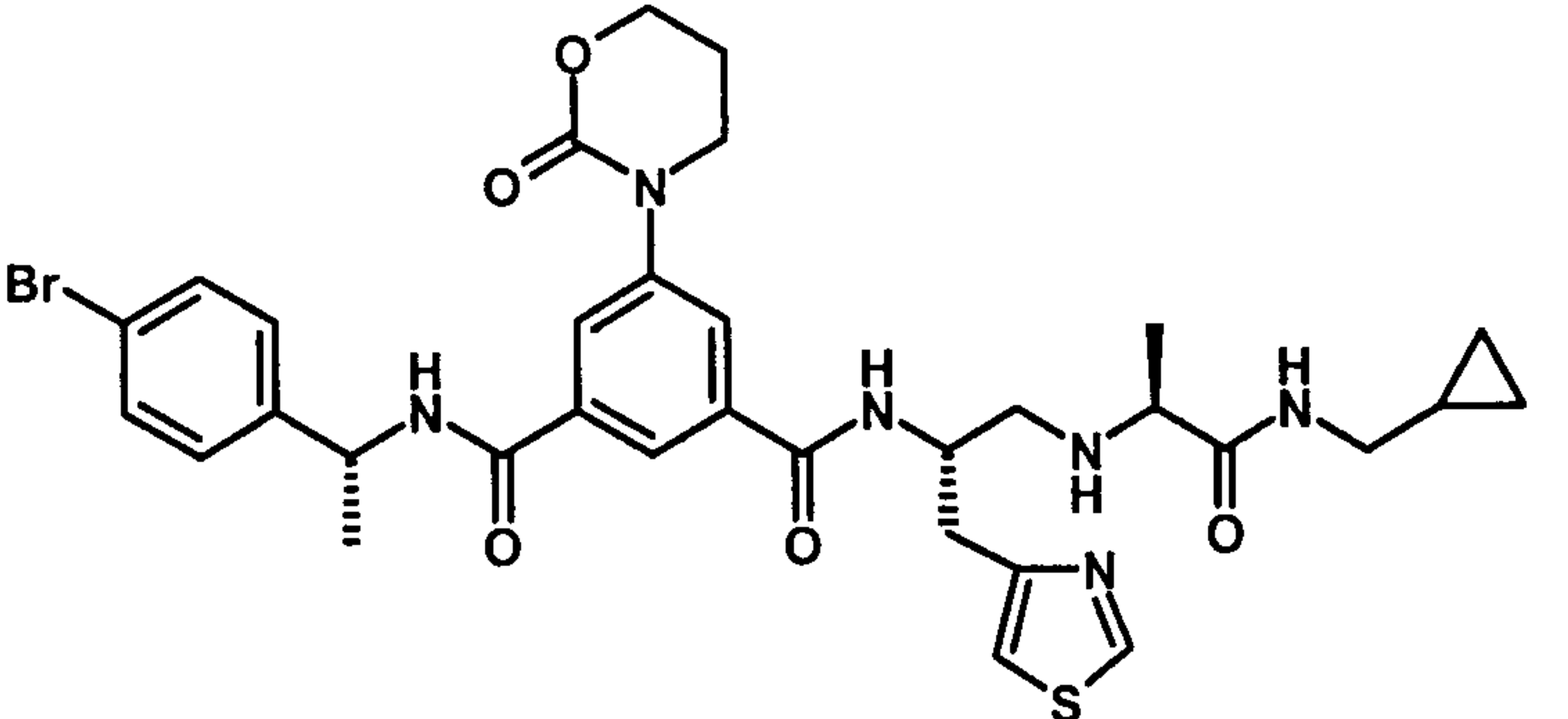
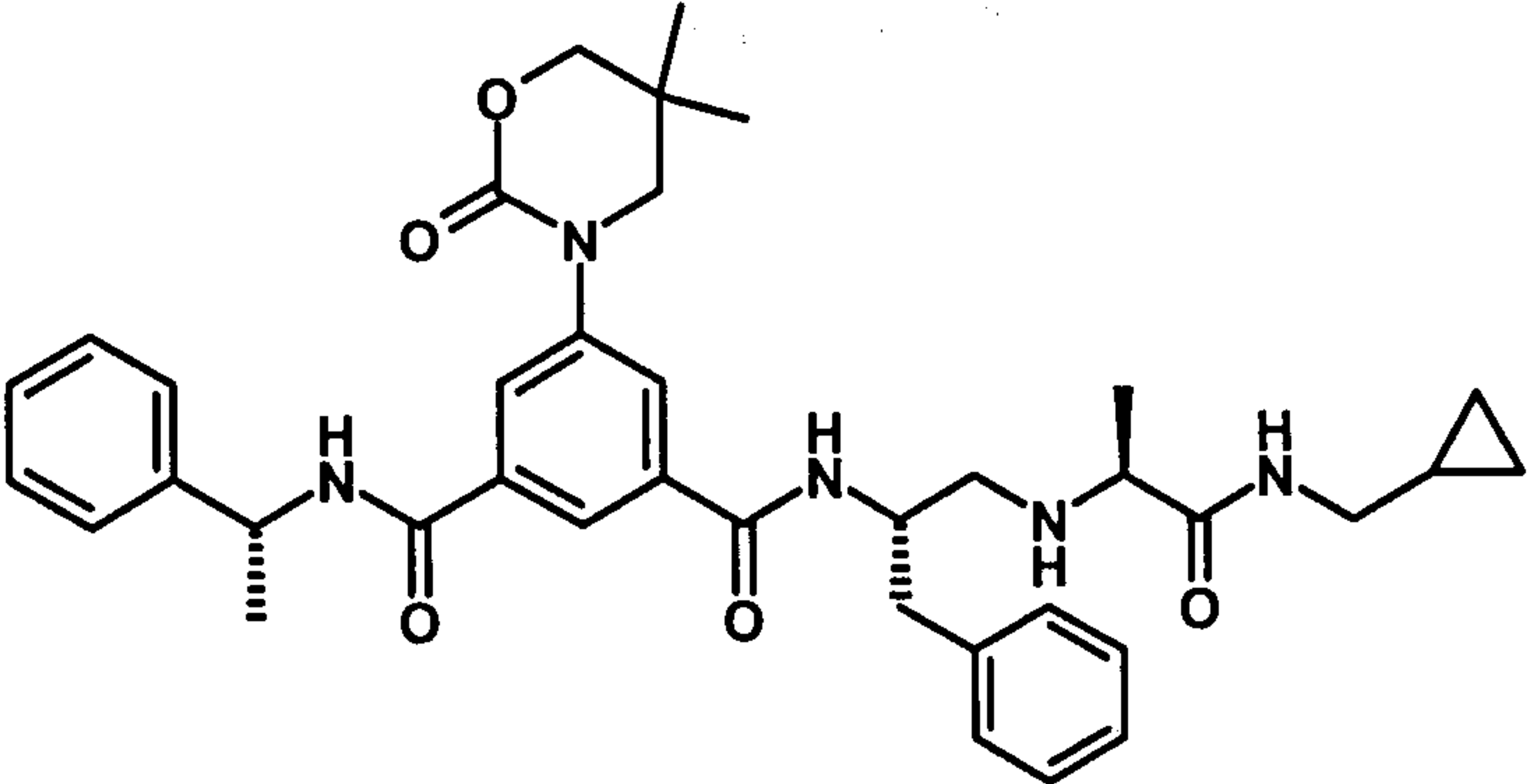
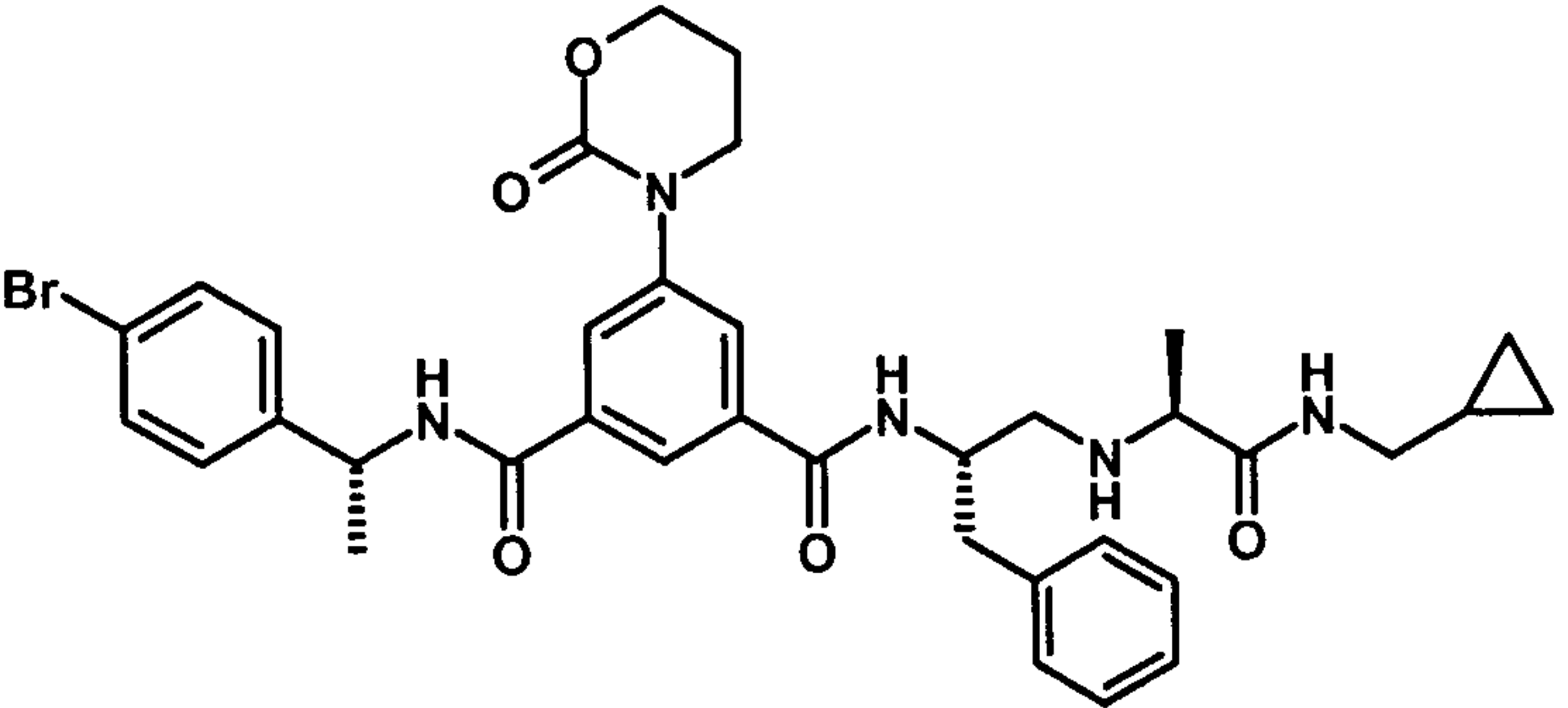
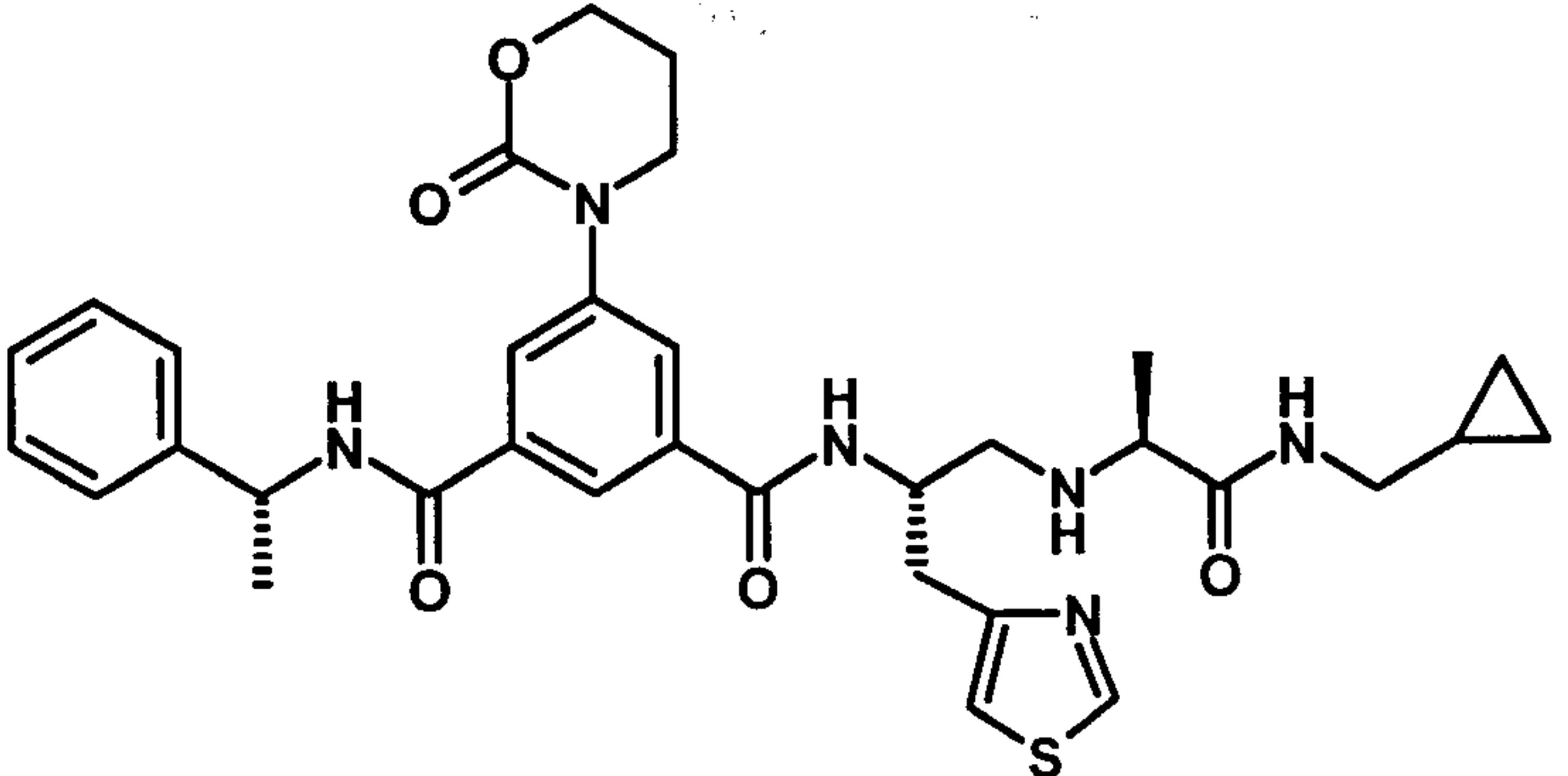
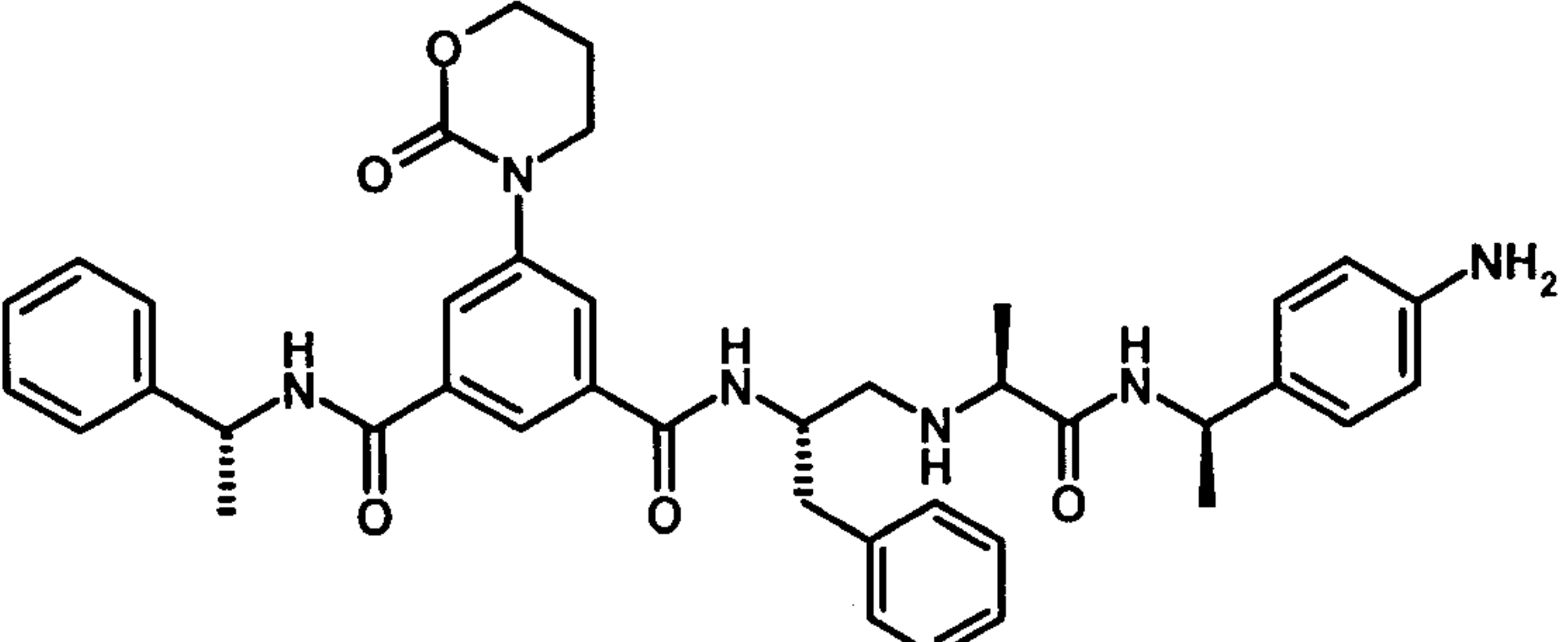
(131)		14.30
(132)		15
(133)		15.1
(134)		15.2
(135)		15.3

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(136)		15.4
(137)		15.5
(138)		15.6
(139)		15.7
(140)		16

- 75 -

(141)		16.1
(142)		16.2
(143)		16.3
(144)		16.4
(145)		17

(146)		17.1
(147)		17.2
(148)		17.3
(149)		17.4
(150)		17.5

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Some terms used hereinbefore and hereinafter to describe the compounds according to the invention are defined below.

- 5 The term halogen denotes an atom selected from among F, Cl, Br and I.

The term C_{1-n}-alkyl, wherein n may have a value of from 1 to 10, unless otherwise stated, denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms. Examples of such groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-
10 butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl etc..

The term C_{1-n}-alkylene, wherein n may have a value of from 1 to 8, unless otherwise stated, denotes a saturated, branched or unbranched hydrocarbon bridge with 1 to n
15 C atoms. Examples of such groups include methylene (-CH₂-), ethylene (-CH₂-CH₂-), 1-methyl-methylene (-CH(CH₃)-), 1-methyl-ethylene (-CH(CH₃)-CH₂-), 1,1-dimethyl-ethylene (-C(CH₃)₂-CH₂-), n-prop-1,3-ylene (-CH₂-CH₂-CH₂-), 1-methylprop-1,3-ylene (-CH(CH₃)-CH₂-CH₂-), 2-methylprop-1,3-ylene (-CH₂-CH(CH₃)-CH₂-), etc., as well as the corresponding mirror-symmetrical forms.

20

The term C_{2-n}-alkenyl, wherein n may have a value of from 2 to 6, unless otherwise stated, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a C=C-double bond. Examples of such groups include ethenyl, 1-propenyl, 2-propenyl, iso-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-
25 pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc..

The term C_{2-n}-alkynyl, wherein n may have a value of from 2 to 6, unless otherwise stated, denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and a C≡C-triple bond. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc..

30

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The term C_{1-n} -alkoxy or C_{1-n} -alkyloxy denotes a C_{1-n} -alkyl-O group, wherein C_{1-n} -alkyl is as hereinbefore defined. Examples of such groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, iso-pentoxy, neo-pentoxy, tert-pentoxy, n-hexoxy, iso-hexoxy etc..

5

The term C_{3-n} -cycloalkyl denotes a saturated monocyclic group with 3 to n C atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

10 The term C_{3-n} -cycloalkyloxy denotes a C_{3-n} -cycloalkyl-O group, wherein C_{3-n} -cycloalkyl is as hereinbefore defined. Examples of such groups include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy etc..

15 The term C_{3-n} -cycloalkyl- C_{1-n} -alkoxy denotes a C_{3-n} -cycloalkyl group, wherein C_{3-n} -cycloalkyl is as hereinbefore defined and which is linked to a C_{1-n} -alkoxy group through a carbon atom of the C_{1-n} -alkoxy group. Examples of such groups include cyclopropylmethyloxy, cyclobutylethyloxy, cyclopentylmethyloxy, cyclohexylmethyloxy, cyclohexylethyloxy etc..

20 The term C_{3-n} -cycloalkenyl denotes a C_{3-n} -cycloalkyl group which is as hereinbefore defined and additionally has at least one C=C-double bond, but is not of an aromatic nature.

25 The term heterocyclyl used in this application denotes a saturated five-, six- or seven-membered ring system or a 5-12 membered bicyclic ring system which includes one, two, three or four heteroatoms, selected from N, O and/or S, such as for example a morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, oxathiolanyl, imidazolidinyl, tetrahydropyranyl, pyrrolinyl, tetrahydrothienyl, oxazolidinyl, homopiperazinyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, azetidyl, 1,3-diazacyclohexanyl or pyrazolidinyl group.

The term aryl used in this application denotes a phenyl, biphenyl, indanyl, indenyl, 6,7,8,9-tetrahydrobenzocycloheptenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl group.

The term heteroaryl used in this application denotes a heterocyclic, mono- or bicyclic aromatic ring system which comprises in addition to at least one C atom one or more heteroatoms selected from N, O and/or S, while the term heteroaryl also includes the partially hydrogenated heterocyclic, aromatic ring systems. Examples of such groups are pyrrolyl, furanyl, thienyl, pyridyl-N-oxide, thiazolyl, imidazolyl, oxazolyl, triazinyl, triazolyl, triazolyl, 1,2,4-oxadiazoyl, 1,3,4-oxadiazoyl, 1,2,5-oxadiazoyl, isothiazolyl, isoxazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, tetrazolyl, pyridyl, indolyl, isoindoyl, indoliziny, imidazopyridinyl, imidazo[1,2-a]pyridinyl, pyrrolopyrimidinyl, purinyl, pyridopyrimidinyl, pteridinyl, pyrimidopyrimidinyl, benzofuranyl, benzothienyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, isobenzofuranyl, isobenzothienyl, thieno[3,2-b]thiophenyl, thieno[3,2-b]pyrrolyl, thieno[2,3-d]imidazolyl, naphthyridinyl, indazolyl, pyrrolopyridinyl, oxazolopyridinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzoxadiazolyl, benzothiadiazolyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydrobenzo[1,4]dioxinyl, 3,4-dihydrobenzo[1,4]oxazinyl, benzo[1,4]-oxazinyl, 2,3-dihydroindolyl, 2,3-dihydroisoindolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 2-oxo-2,3-dihydrobenzoimidazolyl, 2-oxo-2,3-dihydroindolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, chromanyl, chromenyl, chromonyl, isochromenyl, isochromanyl, dihydroquinolin-4-onyl, dihydroquinolin-2-onyl, quinolin-4-onyl, isoquinolin-2-onyl, imidazo[1,2-a]pyrazinyl, 1-oxoindanyl, benzoxazol-2-onyl, imidazo[4,5-d]thiazolyl or 6,7-dihydropyrrolizinyl groups.

Preferred heteroaryl groups are furanyl, thienyl, thiazolyl, imidazolyl, isoxazolyl, pyrazolyl, pyridyl, indolyl, benzofuranyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuranyl and 2,3-dihydrobenzo[1,4]dioxinyl.

The definition pyrazole includes the isomers 1H-, 3H- and 4H-pyrazole. Preferably pyrazolyl denotes 1H-pyrazolyl.

The definition imidazole includes the isomers 1H-, 2H- and 4H-imidazole. A preferred definition of imidazolyl is 1H-imidazolyl.

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The definition triazole includes the isomers 1H-, 3H- and 4H-[1,2,4]-triazole as well as 1H-, 2H- and 4H-[1,2,3]-triazole. The definition triazolyl therefore includes 1H-[1,2,4]-triazol-1, 3- and -5-yl, 3H-[1,2,4]-triazol-3- and -5-yl, 4H-[1,2,4]-triazol-3, 4- and -5-yl, 1H-[1,2,3]-triazol-1, 4- and -5-yl, 2H-[1,2,3]-triazol-2, 4- and -5-yl as well as 4H-[1,2,3]-triazol-4- and -5-yl.

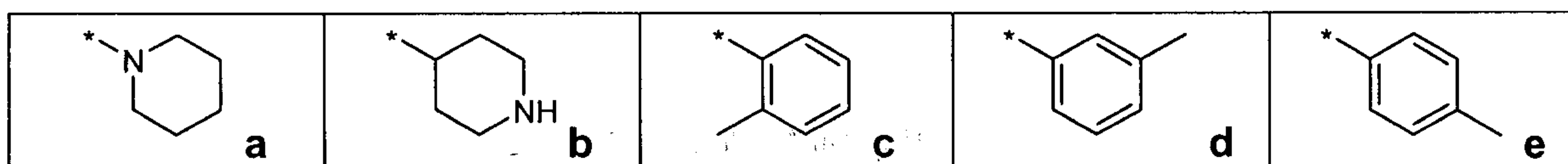
The term tetrazole includes the isomers 1H-, 2H- and 5H-tetrazole. The definition tetrazolyl therefore includes 1H-tetrazol-1- and -5-yl, 2H-tetrazol-2- and -5-yl as well as 5H-tetrazol-5-yl.

The definition indole includes the isomers 1H- and 3H-indole. The term indolyl preferably denotes 1H-indol-1-yl.

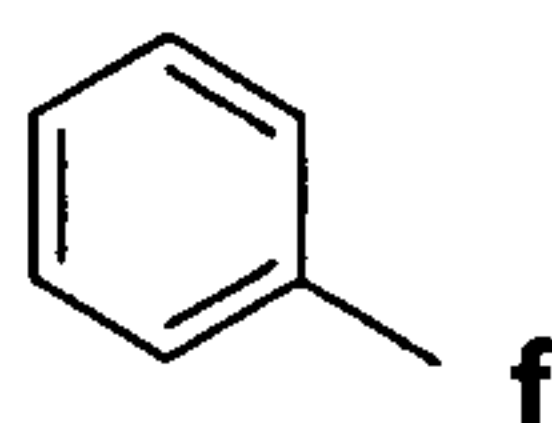
The definition isoindole includes the isomers 1H- and 2H-isoindole.

Generally, the bonding to one of the above-mentioned heterocyclic or heteroaromatic groups may take place via a C atom or optionally an N atom.

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent indicates the point of connection to the remainder of the molecule. Thus, for example, the groups N-piperidiny (a), 4-piperidiny (b), 2-tolyl (c), 3-tolyl (d) and 4-tolyl (e) are shown as follows:



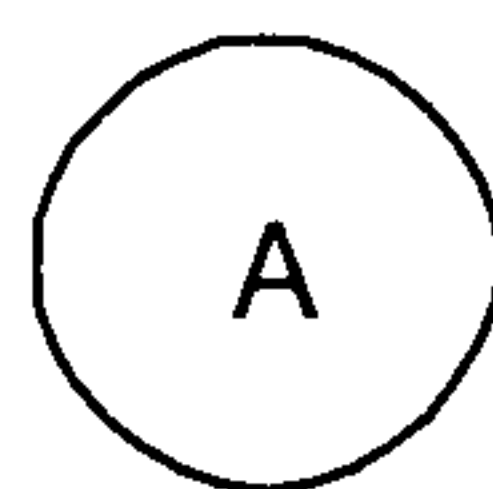
If there is no asterisk (*) in the structural formula of the substituent, every hydrogen atom may be removed from the substituent and the valency thus freed may be used as a binding site to the remainder of a molecule. Thus, for example, (f)



may have the meaning of 2-tolyl, 3-tolyl, 4-tolyl and benzyl.

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The style used, in which in group



5 a bond of a substituent is shown towards the centre of the group A, denotes, unless otherwise stated, that this substituent may be bound to any free position of the group A carrying a H atom.

The term "optionally substituted" used in this application denotes that the group thus designated is either unsubstituted or mono- or polysubstituted by the substituents
10 specified. If the group in question is polysubstituted, the substituents may be identical or different.

The groups and substituents described hereinbefore may, unless stated otherwise, be mono- or polysubstituted by fluorine. Preferred fluorinated alkyl groups are
15 fluoromethyl, difluoromethyl and trifluoromethyl. Preferred fluorinated alkoxy groups are fluoromethoxy, difluoromethoxy and trifluoromethoxy. Preferred fluorinated alkylsulphanyl and alkylsulphonyl groups are trifluoromethylsulphanyl and trifluoromethylsulphonyl.

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

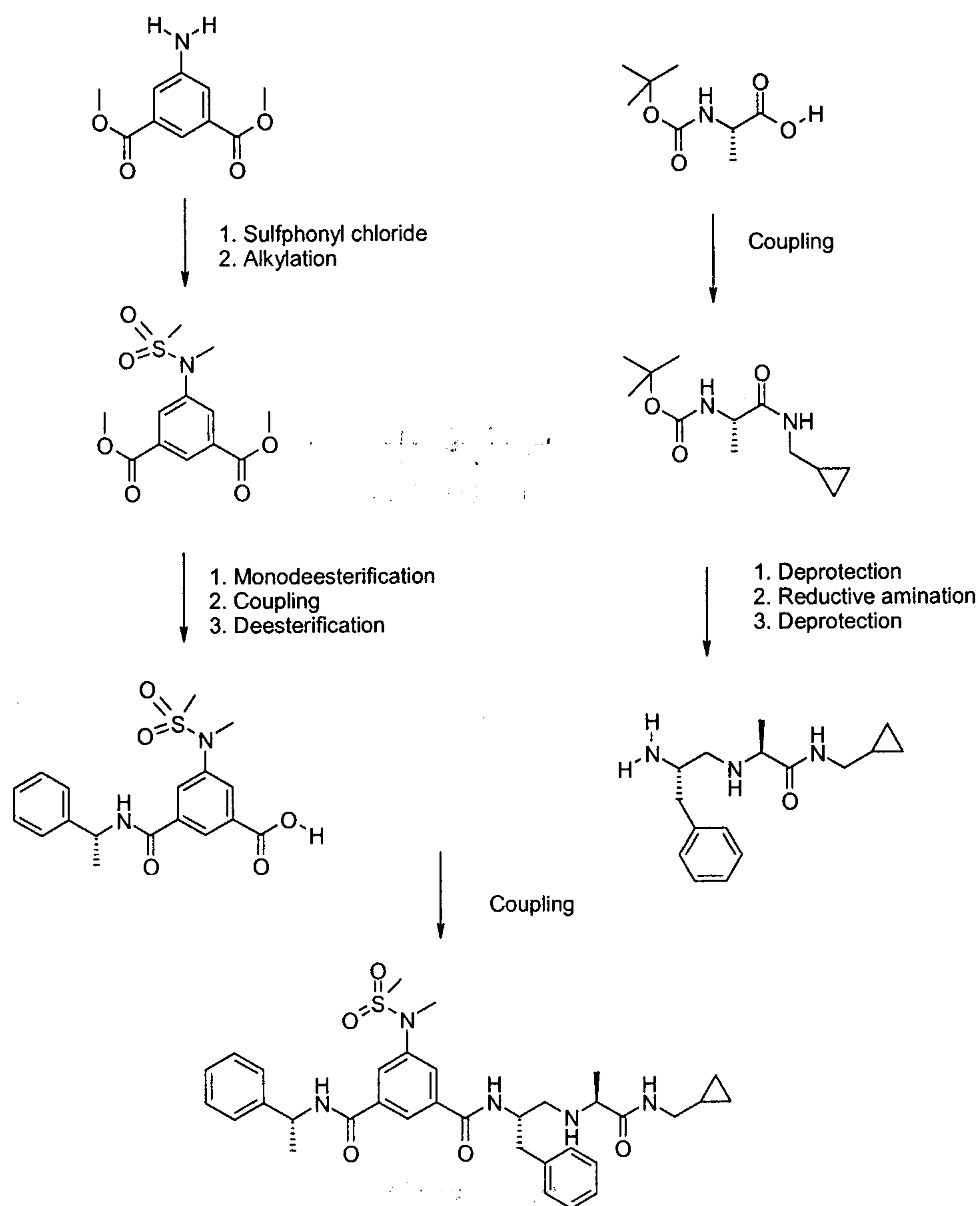
30 The compounds according to the invention may be obtained using methods of synthesis which are known in principle, from starting compounds familiar to those skilled in the art (cf. for example: Houben Weyl - Methods of Organic Chemistry, Vol.

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E22, Synthesis of Peptides and Peptidomimetics, M. Goodman, A. Felix, L. Moroder, C. Toniolo Eds., Georg Thieme Verlag Stuttgart, New York). Provided that he knows their structure the skilled man will be able to synthesise the compounds according to the invention starting from known starting materials without any further instructions.

- 5 Thus, the compounds may be obtained according to the preparation processes described in more detail hereinafter.

Scheme A:



10

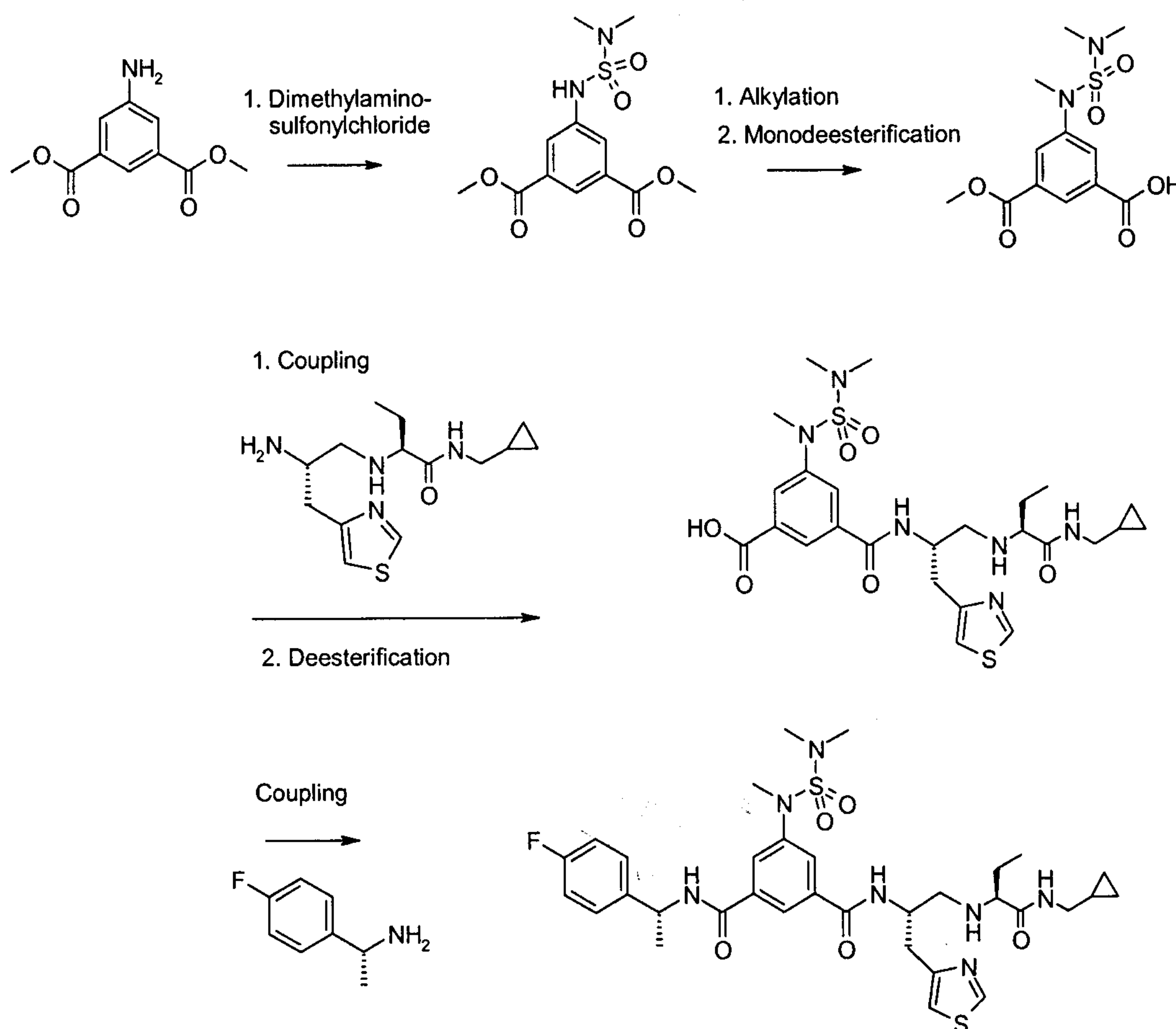
Diagram A illustrates by way of example the synthesis of the compounds according to the invention. Starting from a Boc-protected amino acid an amide is prepared by

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standard coupling methods. The amine obtained after deprotection has been carried out again is reductively aminated with a Boc-protected aminoaldehyde. The amine obtained after deprotection has been carried out again is coupled with an isophthalic acid monoamide component to obtain the end product.

5

In an alternative method of synthesis the compounds according to the invention may be prepared according to Scheme B:



For this, aminoisophthalic acid diester is reacted with a corresponding sulphonic acid chloride, the sulphonamide nitrogen is alkylated and one of the two ester groups is cleaved. Then the compound is coupled to a dipeptide component which is prepared according to Scheme A by reductive amination, the ester function is saponified and the acid is coupled with a corresponding amine to produce the end product.

15

As stated previously, the compounds of formula (I) may be converted into the salts thereof, and particularly, for pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may be present on the one hand as physiologically and pharmacologically acceptable acid addition salts of the

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compounds of formula (I) with inorganic or organic acids. On the other hand, in the case of acidically bound hydrogen, the compound of formula (I) may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter-ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, trifluoroacetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. Moreover mixtures of the above-mentioned acids may be used. For preparing the alkali and alkaline earth metal salts of the compound of formula (I) with acidically bound hydrogen it is preferable to use the alkali and alkaline earth metal hydroxides and hydrides, while the hydroxides and hydrides of the alkali metals, particularly of sodium and potassium, preferably sodium and potassium hydroxide, are particularly preferred.

The compounds of general formula (I) according to the invention and the corresponding pharmaceutically acceptable salts thereof are theoretically suitable for treating and/or preventatively treating all those conditions or diseases that are characterised by a pathological form of β -amyloid-peptide, such as for example β -amyloid-plaques, or that can be influenced by inhibiting β -secretase. For example the compounds according to the invention are particularly suitable for the prevention, treatment or for slowing down the progress of diseases such as Alzheimer's disease (AD) and other diseases associated with, die with abnormal processing of the Amyloid Precursor Protein (APP) or aggregation of Abeta peptide, as well as diseases that can be treated or prevented by inhibiting β -secretase or cathepsin D.

Corresponding diseases include MCI ("mild cognitive impairment"), trisomy 21 (Down's syndrome), cerebral amyloidangiopathy, degenerative dementias, hereditary cerebral haemorrhage with amyloidosis - Dutch type (HCHWA-D), Alzheimer's dementia with Lewy bodies, trauma, stroke, pancreatitis, inclusion body myositis (IBM), as well as other peripheral amyloidoses, diabetes and arteriosclerosis.

The compounds are preferably suitable for the prevention and treatment of Alzheimer's disease. The compounds according to the invention may be used as a monotherapy and also in combination with other compounds that can be administered for the treatment of the above mentioned diseases.

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The compounds according to the invention are particularly suitable for use in mammals, preferably primates, particularly preferably humans, for the treatment and/or prevention of the above mentioned conditions and diseases.

5

The compounds according to the invention may be administered orally, parenterally (by intravenous, intramuscular route, etc.), by intranasal, sublingual, inhalative, intrathecal, topical or rectal route.

10

In the case of the preferred oral administration, the compounds according to the invention may be formulated such that the compounds according to the invention do not come into contact with the acidic gastric juices. Suitable oral formulations may for example have gastric juice-resistant coatings which only release the active substances in the small bowel. Such tablet coatings are known to the skilled man.

15

Suitable pharmaceutical formulations for administering the compounds according to the invention are for example tablets, pellets, coated tablets, capsules, powders, suppositories, solutions, elixirs, active substance plasters, aerosols and suspensions.

20

About 0.1 to 1000 mg of one of the compounds according to the invention or of a mixture of several of these compounds are formulated on their own or together with pharmaceutically conventional excipients such as carriers, diluents, binders, stabilisers, preservatives, dispersants etc. To form a dosage unit in a manner known to those skilled in the art.

25

A dosage unit (e.g. tablet) preferably contains between 2 and 250 mg, particularly preferably between 10 and 100 mg of the compounds according to the invention.

30

Preferably the pharmaceutical formulations are administered 1, 2, 3 or 4 times, particularly preferably once or twice, most preferably once a day.

The dosage required to achieve the corresponding activity for treatment or prevention usually depends on the compound which is to be administered, the patient, the nature

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and gravity of the illness or condition and the method and frequency of administration and is for the patient's doctor to decide.

Expediently, the amount of the compounds according to the invention administered is
5 in the range from 0.1 to 1000 mg/day, preferably 2 to 250 mg/day, particularly preferably 5 to 100 mg/day when administered orally. For this purpose, the compounds of formula (I) prepared according to the invention may be formulated, optionally with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline
10 cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as tablets, pellets, coated tablets, capsules, powders, suppositories, solutions, elixirs,
15 active substance plasters, aerosols and suspensions.

The compounds according to the invention may also be used in conjunction with other active substances, particularly for the treatment and/or prevention of the diseases and conditions mentioned above. Other active substances which are suitable for such
20 combinations include, in particular, those which potentiate the therapeutic effect of a compound according to the invention with respect to one of the indications mentioned and/or which allow the dosage of a compound according to the invention to be reduced. Therapeutic agents which are suitable for such a combination include, for example, beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation
25 inhibitors such as e.g. Alzhemed; directly or indirectly acting neuroprotective substances; antioxidants such as e.g. Vitamin E or ginkgolides; anti-inflammatory substances such as e.g. Cox inhibitors, NSAIDs with additionally or solely A β lowering properties; HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists
30 such as e.g. memantine; AMPA agonists; substances that modulate the concentration or release of neurotransmitters such as NS-2330; substances that induce the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor antagonists or inverse agonists; antibiotics such as minocycline or rifampicin; PDE-IV and PDE-IX inhibitors, GABA_A inverse agonists, nicotine agonists, histamine

H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, α 2-adrenoreceptor antagonists, muscarinic M1 agonists, muscarinic M2 antagonists, metabotropic glutamate-receptor 5 positive modulators, as well as other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety
5 of the compounds according to the invention is increased and/or unwanted side effects are reduced.

Preferred combinations are those comprising one or more of the compounds according to the invention with one or more of the following substances selected from
10 among Alzhemed, Vitamin E, ginkgolides, donepezil, rivastigmine, tacrine, galantamine, memantine, NS-2330, ibutamoren mesylate, capromorelin, minocycline and/or rifampicin.

The compounds according to the invention, or the physiologically acceptable salts thereof, and the other active substances to be combined therewith, may be present
15 together in one dosage unit, for example a tablet or capsule, or separately in two identical or different dosage units, for example as a so-called kit-of-parts.

The compounds according to the invention may also be used in conjunction with
20 immunotherapies such as e.g. active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies for the treatment of the above mentioned diseases and conditions.

The dosage for the combination partners mentioned above is usefully 1/5 of the lowest
25 dose normally recommended up to 1/1 of the normally recommended dose.

Therefore, in another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt of such a compound combined with at least one of the active substances described above as a
30 combination partner, for preparing a pharmaceutical composition which is suitable for the treatment or prevention of diseases or conditions which can be affected by inhibiting β -secretase.

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The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; while if they are used at staggered times the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a pharmaceutical composition which comprises a compound according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

Thus, for example, a pharmaceutical composition according to the invention comprises a combination of a compound of formula (I) according to the invention or a physiologically acceptable salt of such a compound and at least one other of the above-mentioned active substances, optionally together with one or more inert carriers and/or diluents.

20

The compounds according to the invention inhibit the proteolysis of the APP protein between the amino acids Met595 and Asp596 (the numbering relates to the APP695 isoform) or the proteolysis of other APP isoforms such as APP751 and APP770 or mutated APP at the corresponding site, which is also referred to as the β -secretase cutting site. The inhibition of β -secretase should therefore lead to a decreased production of the β -amyloid peptide ($A\beta$).

25

The activity of β -secretase may be investigated in assays based on different detection technologies. In the test set-up a catalytically active form of β -secretase is incubated with a potential substrate in a suitable buffer. The reduction in the substrate concentration or the increase in product concentration may be achieved using various technologies depending on the substrate used: HPLS-MS analysis, fluorescence assays, fluorescence-quenching assays, luminescence assays are a non-representative selection of the different possibilities. Assay systems in which the

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effectiveness of a compound can be demonstrated are described e.g. In U.S. Patents US 5.942.400 and US 5.744.346 and hereinafter. An alternative assay format comprises displacing a known β -secretase ligand with a test substance (US 2003/0125257).

5

The substrate used may be either the APP protein or parts thereof or any amino acid sequence that can be hydrolysed by the β -secretase. A selection of these sequences can be found e.g. in Tomasselli et al. 2003 in J. Neurochem 84: 1006. A peptide sequence of this kind may be coupled to suitable dyes that provide indirect evidence of proteolysis.

10

The enzyme source used may be the complete β -secretase enzyme or mutants with a catalytic activity or only parts of the β -secretase which still contain the catalytically active domain. Various forms of β -secretase are known and available and may serve as an enzyme source in a corresponding test set-up. This includes the native enzyme and also the recombinant or synthetic enzyme. Human β -secretase is known by the name Beta Site APP Cleaving Enzyme (BACE), Asp2 and memapsin 2 and is described e.g. In U.S. Patent US 5.744.346 and in the patent applications W0 98/22597, W0 00/03819, W0 01/23533, and W0 00/17369, as well as in the scientific literature (Hussain et al., 1999, Mol. Cell. Neurosci. 14: 419-427; Vassar et. Al., 1999, Science 286 : 735-741; Yan et al., 1999, Nature 402: 533-537; Sinha et. Al., 1999, Nature 40: 537-540; and Lin et. Al., 2000, PNAS USA 97 : 1456-1460). Synthetic forms of the enzyme have also been described (W0 98/22597 and W0 00/17369). β -Secretase may be extracted and purified from human brain tissue, for example, or produced recombinantly in mammalian cell cultures, insect cell cultures, yeasts or bacteria.

15

20

25

To calculate the IC₅₀ value of a substance, different amounts of substance are incubated with the β -secretase in an assay. The IC₅₀ value of a compound is defined as the substance concentration at which a 50% reduction in the detected signal is measured by comparison with the mixture without any test compound. Substances are evaluated as having an inhibiting effect on β -secretase if under these conditions their IC₅₀ value is less than 50 μ M, preferably less than 10 μ M, particularly preferably less than 1 μ M and most particularly preferably less than 100 nM.

30

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An assay for detecting β -secretase activity may have the following appearance, in detail:

The ectodomain of BACE (amino acids 1-454) fused to the recognition sequence for an anti-Myc antibody and a poly-histidine is secreted overnight by
5 HEK293/APP/BACE_{ect.} cells in OptiMEM[®] (Invitrogen). A 10 μ l aliquot of this cell culture supernatant serves as an enzyme source. The enzyme is stable over more than 3 months when stored at 4°C or -20°C in OptiMEM[®]. The substrate used is a peptide with the amino acid sequence SEVNLDAEFK to which the Cy3 fluorophore
10 (Amersham) is coupled N-terminally and the Cy5Q fluorophore (Amersham) is coupled C-terminally. The substrate is dissolved in DMSO in a concentration of 1 mg/ml and used in the test in a concentration of 1 μ M. In addition the test mixture contains 20 mM NaOAc, pH 4.4, and at most 1% DMSO. The test is carried out in a 96-well dish in an overall volume of 200 μ l over 30 minutes at 30°C. The cleaving of the substrate
15 is recorded kinetically in a fluorimeter (ex: 530 nm, em: 590 nm). The assay is started by the addition of the substrate.

As controls, mixtures with no enzyme or with no inhibitor are included on each dish. The IC₅₀ value for the test compound is calculated using standard software (e.g. GraphPad Prism[®]) from the percentage inhibition of the substance at different test
20 concentrations. The relative inhibition is calculated from the reduction in the signal intensity in the presence of the substance based on the signal intensity without the substance.

The compounds (1) - (150) mentioned in the Table hereinbefore have IC₅₀ values of less than 30 μ M, measured using the test described above.

25

The activity of the β -secretase may also be investigated in cellular systems. As APP is a substrate for β -secretase and A β is secreted by the cells after the processing of APP by β -secretase, cellular test systems for detecting β -secretase activity are based on detecting the amount of A β formed over a defined period of time.

30 The selection of suitable cells comprises, but is not restricted to, human embryonic kidney fibroblasts 293 (HEK293), Chinese Hamster Ovary cells (CHO), human H4 neuroglioma cells, human U373 MG astrocytoma glioblastoma cells, neuroblastoma N2a cells in the mouse, which stably or transiently express APP or mutated forms of APP, such as e.g. The Swedish or London or Indiana Mutation. The transfection of

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the cells is carried out for example by cloning the cDNA of human APP into an expression vector such as e.g. PcDNA3 (Invitrogen) and adding it to the cells with a transfection reagent such as e.g. Lipofectamine (Invitrogen) according to the manufacturer's instructions.

5 The secretion of A β may also be measured from cells without genetic modification using a suitably sensitive A β detection assay such as e.g. ELISA or HTRF. Cells that may be used for this are, besides other cells, human IMR32 neuroblastoma cells, for example.

10 The secretion of A β may also be investigated in cells obtained from the brains of embryos or the young of APP transgenic mice, such as e.g. In those obtained by Hsiao et al 1996 Science 274: 99-102, or from other organisms such as e.g. guinea pigs or rats.

Substances are evaluated as having an inhibiting effect on β -secretase if under these
15 conditions their IC50 value is less than 50 μ M, preferably less than 10 μ M, particularly preferably less than 1 μ M and most particularly preferably less than 100 nM.

An example of the procedure for carrying out a cell assay is described below: U373-MG cells which stably express APP (isoform 751) are cultivated in a culture medium
20 such as DMEM+glucose, sodium pyruvate, glutamine and 10% FCS at 37°C in a steam-saturated atmosphere containing 5% CO₂. In order to investigate the β -secretase inhibiting activity of substances, the cells are incubated with different concentrations of the compound between 50 μ M and 50 pM for 12-24 h. The substance is dissolved in DMSO and is diluted for the assay in culture medium so that
25 the DMSO concentration does not exceed 0.5%. The production of A β during this period is detected using an ELISA, which uses the antibodies 6E10 (Senentek) and SGY3160 (C. Eckman, Mayo Clinic, Jacksonville, Florida, USA) as capturing antibodies that are bound to the microtitre plate and A β 40- and A β 42-specific
30 antibodies (Nanotools, Germany), coupled to alkaline phosphatase, as detecting antibodies. Non-specific binding of proteins to the microtitre plate is prevented by blocking with Block Ace (Serotec) before the addition of the A β -containing culture supernatant. The quantifying of the amounts of A β contained in the cell supernatant is carried out by adding the substrate for alkaline phosphatase CSPD/Sapphire II

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(Applied Biosystems) according to the manufacturer's instructions. Possible non-specific effects of the test compound on the vitality of the cells are excluded by determining precisely these effects by AlamarBlue (resazurin) reduction over a period of 60 minutes.

- 5 The potency of non-toxic substances is determined by calculating the concentration that brings about a 50% reduction in the amount of A β secreted compared with untreated cells.

Moreover, different animal models may be used to investigate the β -secretase activity
10 and/or the APP processing and the release of A β . Thus, for example, transgenic animals that express APP and/or β -secretase may be used to test the inhibitory activity of compounds of this invention. Corresponding transgenic animals are described for example in US Patents US 5,877,399, US 5,612,486, US 5,387,742, US 5,720,936, US 5,850,003, US 5,877,015 and US 5,811,633, and in Games et al.,
15 1995, Nature 373: 523. Preferably, animal models are used that display some of the characteristics of AD pathology. The administering of β -secretase inhibitors according to this invention and the subsequent investigation of the pathology of the animals constitutes a further alternative method of demonstrating β -secretase inhibition using the compounds. The compounds are administered in such a way that
20 they can reach their intended site of activity in a pharmaceutically effective form and quantity.

The test for detecting cathepsin D (EC: 3.4.23.5) inhibition was carried out as follows: 20 mU of recombinant cathepsin D (Calbiochem, Cat.No. 219401) in 20 mM sodium
25 acetate puffer pH 4.5 with 5 μ M substrate peptide and different concentrations of the test substance are incubated at 37°C in a 96-well dish and the conversion is recorded for 60 minutes in a fluorimeter (emission: 535 nm, extinction: 340 nm). The peptide substrate used has the following sequence: NH₂-Arg-Glu(Edans)-Glu-Val-Asn-Leu-Asp-Ala-Glu-phe-Lys(DabcyI)-Arg-COOH (Bachem). However, a peptide or protein
30 substrate with a sequence that can be cleaved proteolytically from Cathepsin D may also be used. The test substances are dissolved in DMSO and are used in the assay after dilution to a maximum of 1% DMSO.

The assay is started by the addition of the substrate.

As controls, mixtures with no enzyme or with no inhibitor are included on each dish.

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The IC₅₀ value for the test compound is calculated using standard software (e.g. GraphPad Prism[®]) from the percentage inhibition of the substance at different test concentrations. The relative inhibition is calculated from the reduction in the signal intensity in the presence of the substance based on the signal intensity without the substance.

The compounds (1) - (150) mentioned in the Table hereinbefore exhibited an inhibitory effect on cathepsin D in the test described here.

The following Examples are intended to illustrate the invention, without restricting it.

Examples

The following abbreviations are used in the descriptions of the tests:

15	BOC	<i>tert.</i> -butoxycarbonyl
	TLC	thin layer chromatography
	DIPEA	<i>N</i> -ethyl-diisopropylamine
	DMF	dimethylformamide
	HPLC	high pressure liquid chromatography
20	HPLC-MS	high pressure liquid chromatography with mass detection
	sat.	saturated
	HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
	HOBt	1-hydroxy-benzotriazole-hydrate
25	conc.	concentrated
	RF	retention factor
	RT	retention time
	TBTU	O-(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
	TEA	triethylamine
30	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	-*	indicates the binding site of a group

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The HPLC 1 data were generated under the following conditions:

Alliance 2695 HPLC, Waters 2700 Autosampler, Waters 2996 Diode array detector

The eluant used was as follows:

A: water with 0.13% TFA

5 B: acetonitrile with 0.10% TFA

	time in min.	%A	%B	flow rate in ml/min.
	0.00	95	5	1.00
	0.75	95	5	1.00
	5.25	2	98	1.00
10	5.75	2	98	1.00
	6.05	95	5	1.00
	6.55	95	5	1.00

The stationary phase used was a Varian column, Microsorb 100 C₁₈ 3 µm, 4.6 mm x 50 mm, batch no. 2231108 (column temperature: constant at 25°C).

15 The diode array detection took place in the wavelength range from 210-300 nm.

The HPLC 2 data were generated under the following conditions:

Abimed Gilson, Autoinjector 231 XL, Fraction collector 202 C, Detector 118 UV/Vis,

The eluant used was as follows:

20 A: water with 0.10% TFA

B: acetonitrile with 0.10% TFA

	time in min	%A	%B	flow rate in ml/min
	0	90	10	20.00
	5	90	10	20.00
25	16	50	50	20.00
	25	50	50	20.00
	31	0	100	20.00
	32	90	10	20.00
	37	90	10	20.00

30 The stationary phase used was a Varian column, Microsorb C₁₈ 8 µm, 21.2 mm x 250 mm; the diode array detection took place in the wavelength range from 210-300 nm.

The same method (HPLC 2) was used for preparative HPLC.

The HPLC 3 data were generated under the following conditions:

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Waters ZQ2000, HP1100LC, Gilson Autosampler 215,

HP1100PDA Diode array detector

A: water with 0.1% TFA

B: acetonitrile with 0.1% TFA

5	time in min.	%A	%B	flow rate in ml/min
	0.00	95	5	1.00
	0.50	95	5	1.00
	4.00	2	98	1.00
	4.35	2	98	1.00
10	4.50	95	5	1.00

The stationary phase used was a Waters column, Xterra MS C₁₈ 2.5 µm, 4.6mm.

The HPLC 4 data were generated under the following conditions:

15 Waters ZQ2000, Alliance 2795, Waters 996 PDA Diode array detector

A: water with 0.1% TFA

B: acetonitrile with 0.1% TFA

	time in min.	%A	%B	flow rate in ml/min
	0.00	95	5	1.00
20	0.10	95	5	1.00
	5.10	2	98	1.00
	6.50	2	98	1.00
	7.00	95	5	1.00

25 The stationary phase used was a Waters column, Xterra MS C₁₈ 2.5 µm, 4.6mm.

The HPLC-MS data were generated under the following conditions:

Waters ZMD, Waters Alliance 2690 HPLC, Waters 2700 Autosampler, Waters 996 diode array detector

30 The eluant used was as follows:

A: water with 0.13% TFA

B: acetonitrile with 0.10% TFA

	time in min.	%A	%B	flow rate in ml/min.
	0.0	95	5	1.00

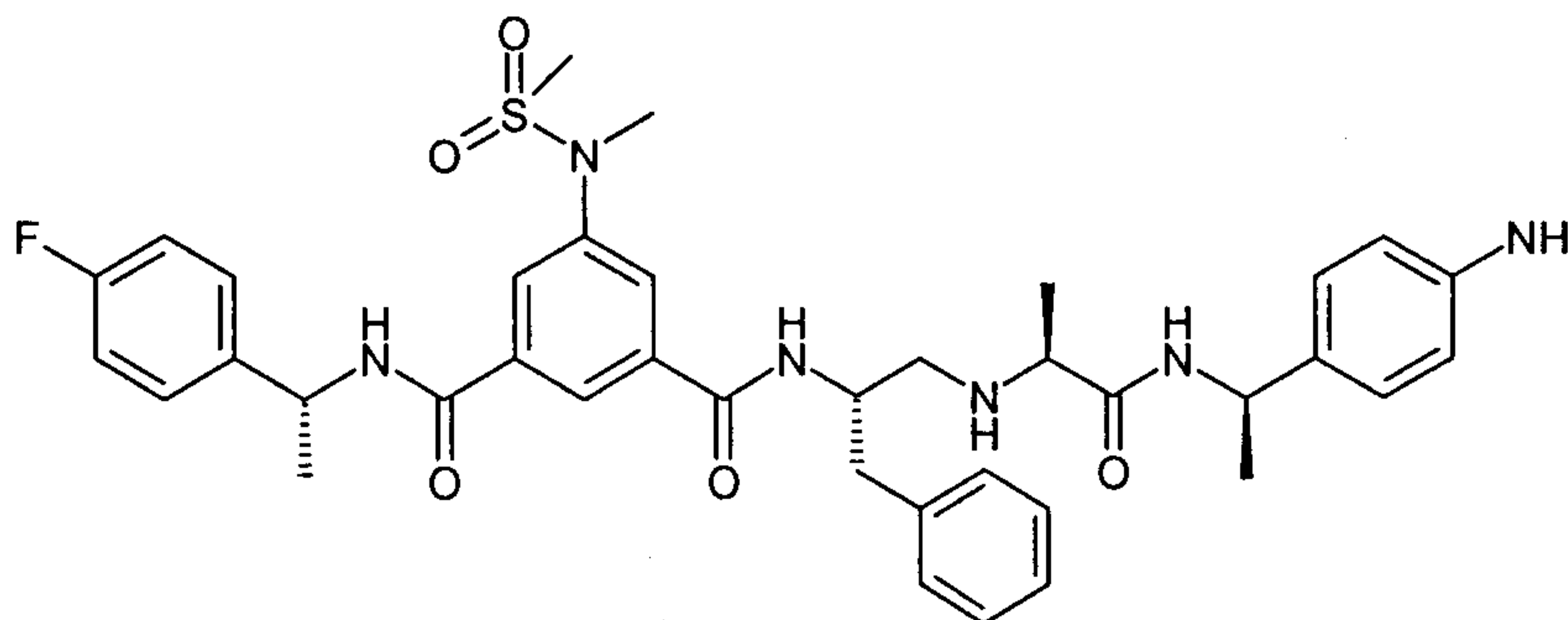
- 96 -

0.1	95	5	1.00
3.1	2	98	1.00
4.5	2	98	1.00
5.0	95	5	1.00

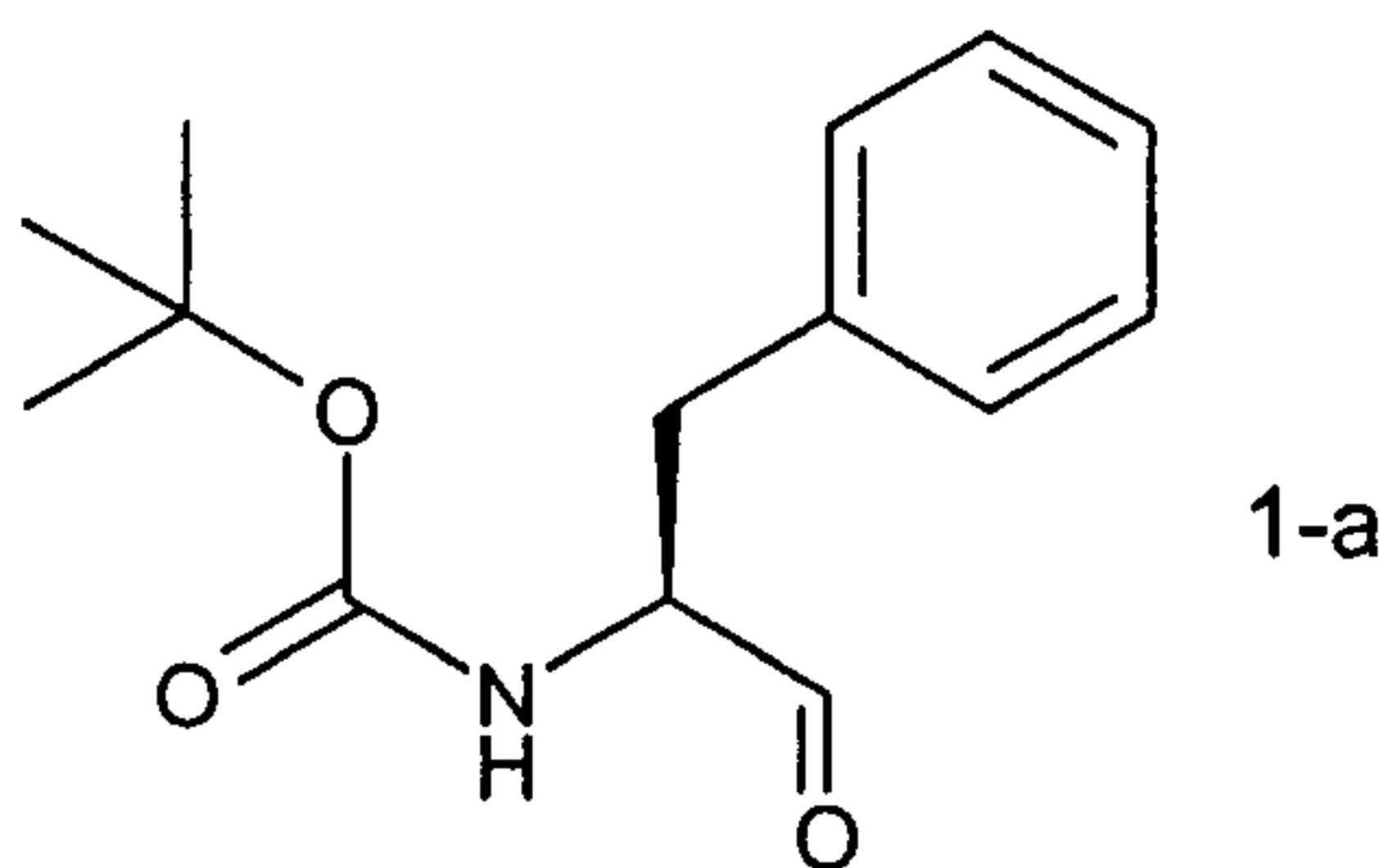
- 5 The stationary phase used was a Waters column, Xterra MS C₁₈ 2.5 µm, 4.6 mm x 30 mm (column temperature: constant at 25°C).

The diode array detection took place in the wavelength range from 210-500 nm.

10 **Example 1:**



15 **Preparation of 1-a:**



- 11.4 g (26.9 mmol) of Dess-Martin periodinane were suspended in 75 ml dichloromethane and a solution of 6.08 g (24.2 mmol) (S)-(-)-2-(*tert*-butoxycarbonylamino)-3-phenyl-1-propanol and 25 ml dichloromethane was added dropwise to the existing suspension within 15 min at ambient temperature and then stirred for 14 h at ambient temperature. Then Na₂S₂O₃ solution (10 %) and saturated NaHCO₃ were added dropwise and the mixture was stirred for 30 min at ambient temperature. The phases were separated, the inorganic phase was extracted with dichloromethane, the combined organic phases were washed with saturated NaHCO₃

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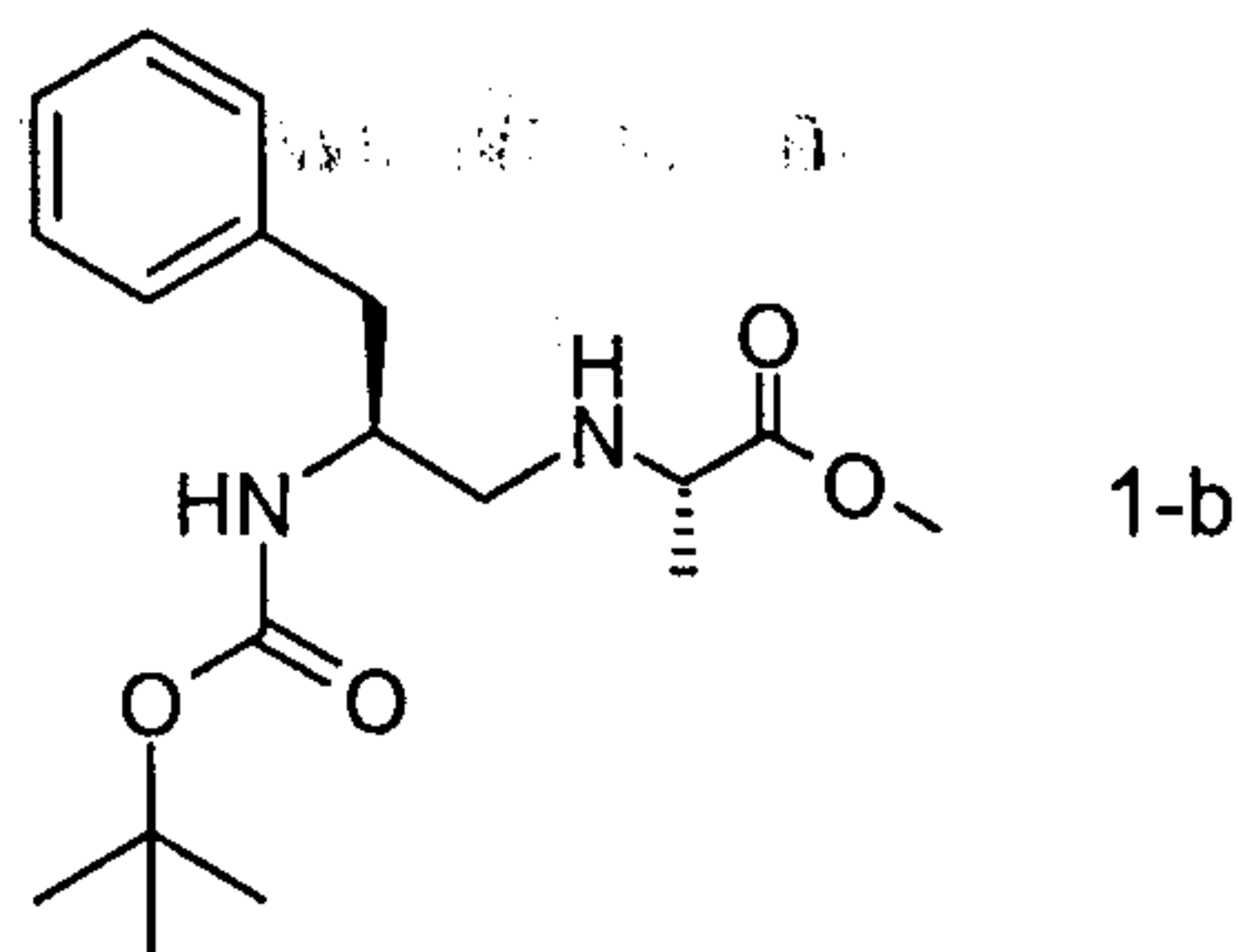
solution, dried and evaporated down in vacuo. The crude product was used in the next test without any further purification.

Yield: 6.0 g (20.5 mmol) (85 %) 1-a.

ES-MS (M^+) = 249

5

Preparation of 1-b:



A solution of 5.0 g (20.1 mmol) **1-a**, 2.8 g (20.1 mmol) L-alanine methyl ester hydrochloride, 3.43 ml (20.1 mmol) N,N-diisopropylethylamine in 150 ml dichloromethane was stirred for 1 h at ambient temperature, then 6.3 g (28.1 mmol) sodium triacetoxyborohydride and 1.2 ml (20.1 mmol) acetic acid were added and the mixture was stirred overnight at ambient temperature. The suspension was combined with saturated NaHCO₃ solution, stirred for 20 min, extracted with dichloromethane, dried and evaporated down in vacuo. The crude yield was purified using the Flashmaster (50 g silica gel with the eluting gradient (dichloromethane/ ethanol, 100 % → 95 % / 5 %)).

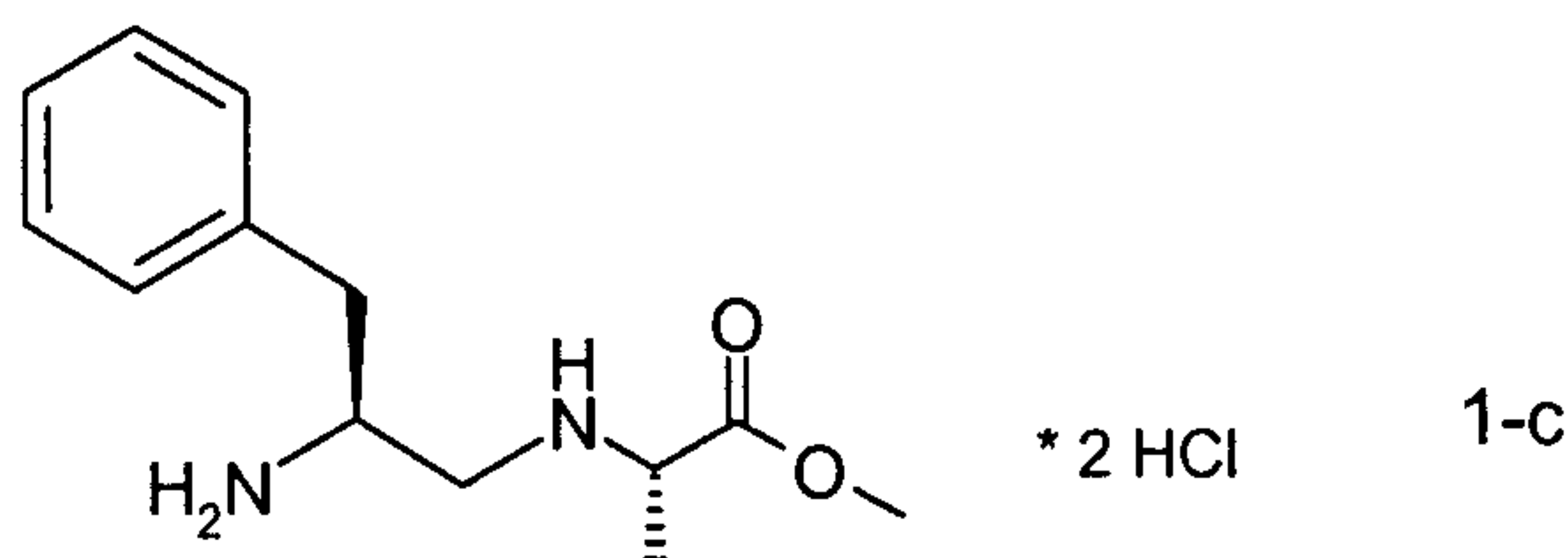
Yield: 3.9 g (58 %) **1-b**.

ES-MS (M+H)⁺ = 337

20 RT(HPLC-MS) = 2.51 min

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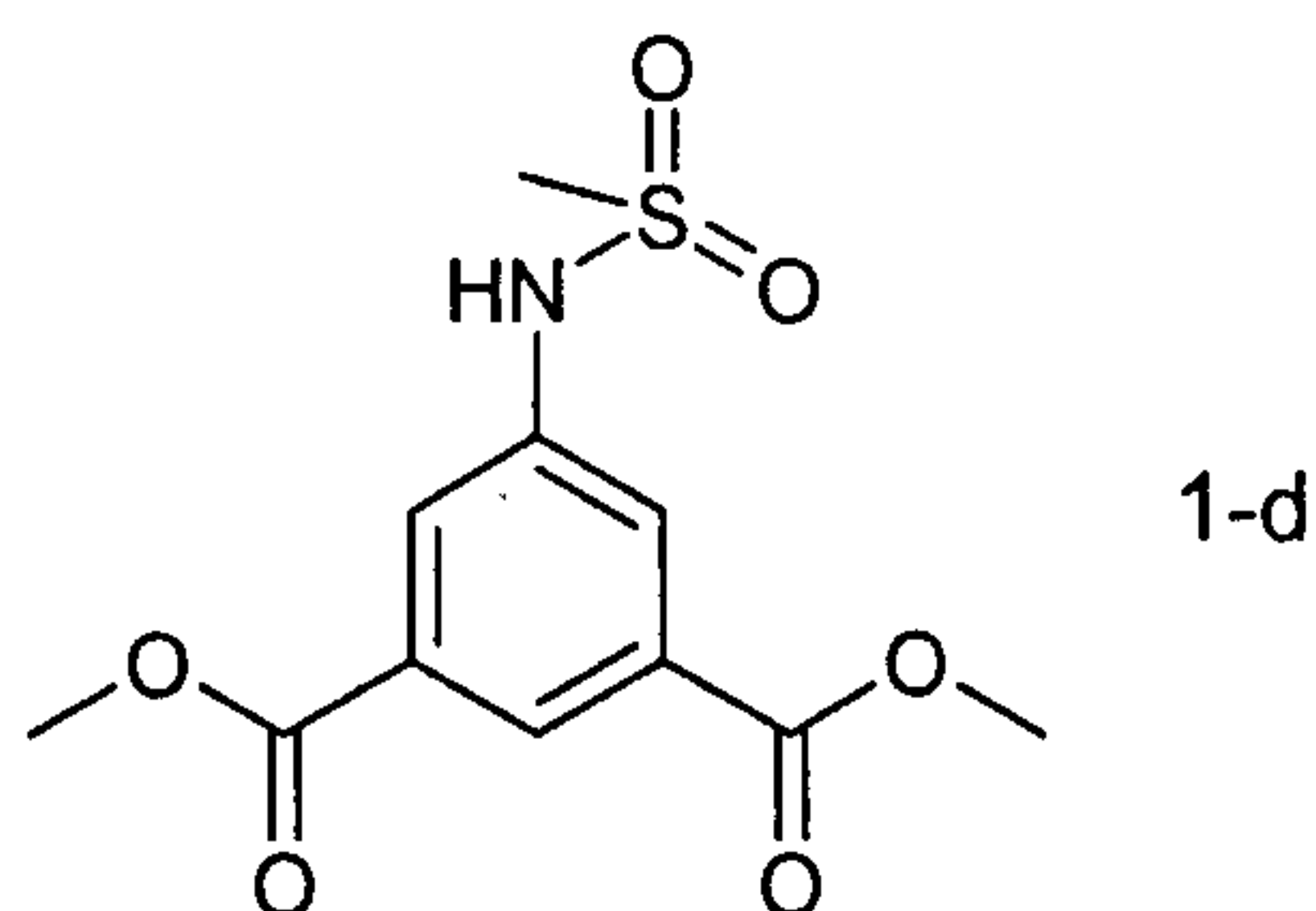
- 98 -

Preparation of **1-c**:

5 ml (20 mmol) HCl in dioxane was added to a solution of 3.9 g (11.6 mmol) **1-b** in ethyl acetate and the mixture was stirred for 14 h at ambient temperature. Then the solid was suction filtered.

Yield: 3.1 g (84 %) **1-c**.ES-MS (M+H)⁺ = 237

RT(HPLC-MS) = 2.88 min

Preparation of **1-d**:

1.5 ml (19.1 mmol) pyridine were added to a solution of 2.0 g (9.56 mmol) dimethyl-5-aminoisophthalate in 19 ml dichloromethane. Then the mixture was cooled to 0°C and slowly 0.82 ml (10.5 mmol) methanesulphonyl chloride were added and the mixture was stirred for 2 h at ambient temperature. It was extracted with 1N hydrochloric acid, the crystals formed in the organic phase were suction filtered and washed with dichloromethane. The crystals were dried for 14 h at 50°C.

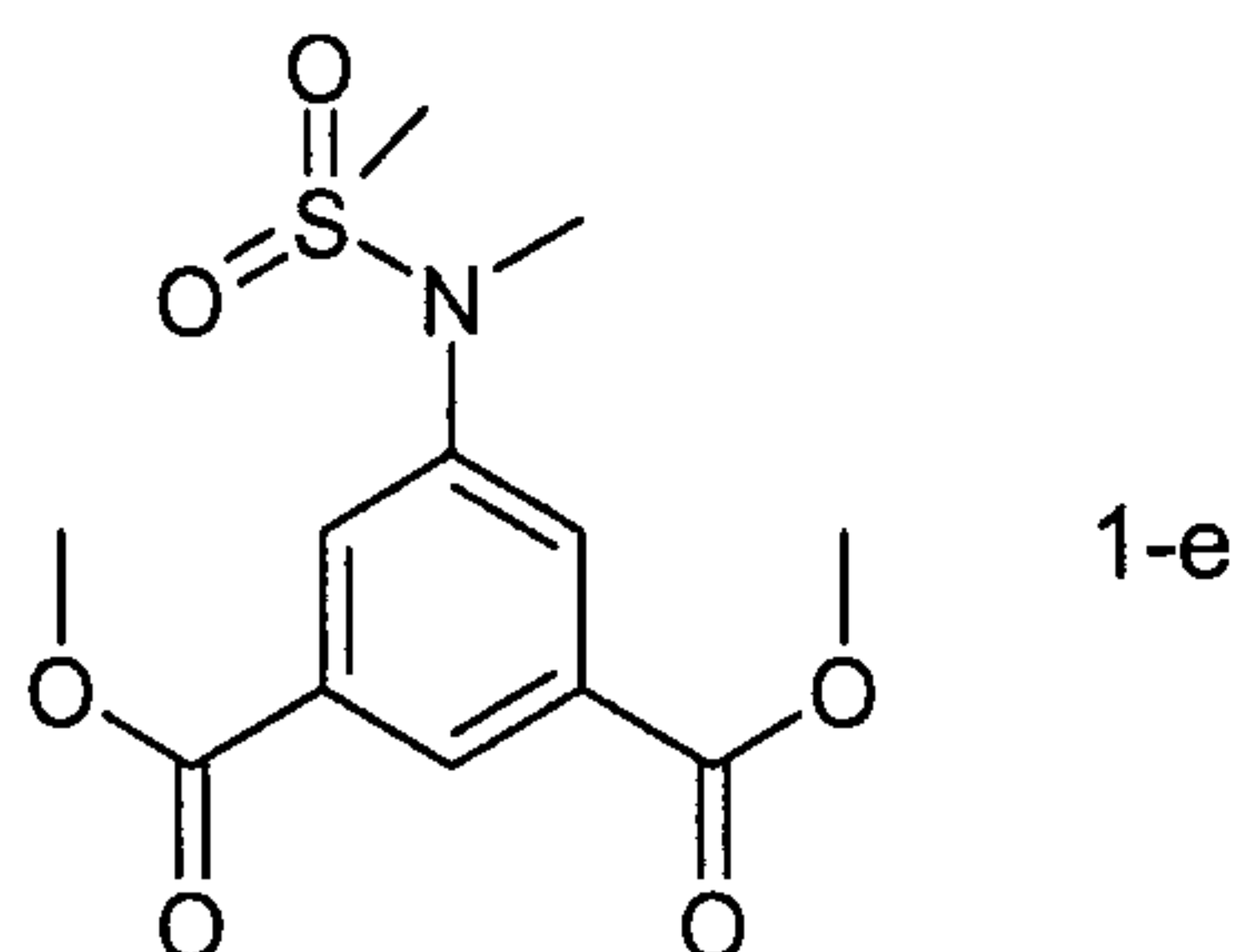
Yield: 2.7 g (96 %) **1-d**.

Uniform substance according to TLC in dichloromethane/methanol (95/5)

ES-MS (M-H)⁺ = 286

RT(HPLC-MS) = 2.65 min

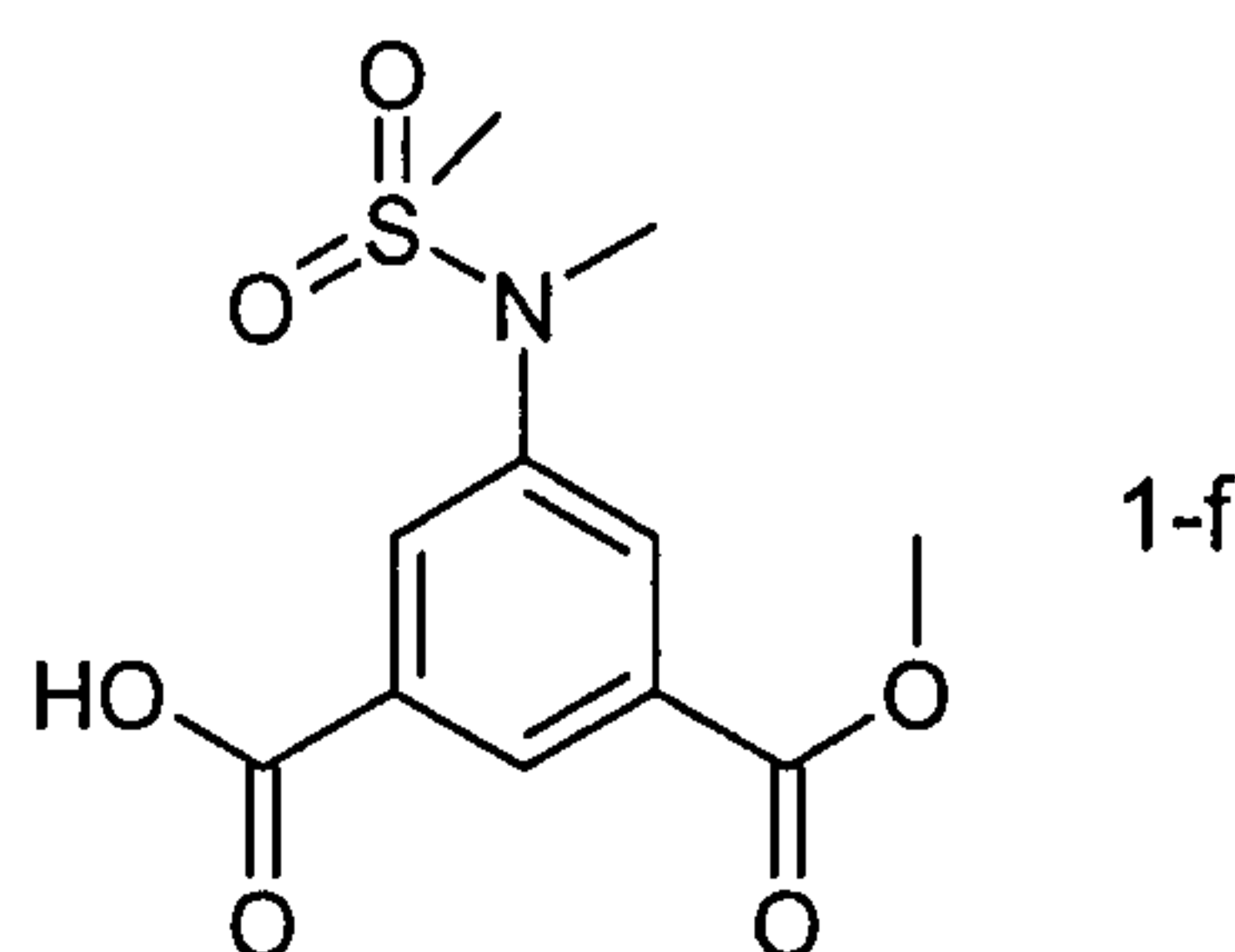
- 99 -

Preparation of **1-e**:

2.65 g (9.22 mmol) **1-d** was added to a suspension of 0.74 g (18.5 mmol) sodium hydride (60% in mineral oil) and 10 ml N,N-dimethylformamide and then combined with 1.38 ml (18.4 mmol) methyl iodide. The solution was stirred for 1 h at ambient temperature, then 100 ml of water were added and the solution was extracted with ethyl acetate. The combined organic phases were dried and evaporated down in vacuo.

Yield: 2.7 g (97 %) **1-e**.

ES-MS ($M+NH_4^+$) = 319
RT(HPLC-MS) = 2.72 min

Preparation of **1-f**:

2.7 g (8.96 mmol) **1-e** were dissolved in a mixture of 20 ml of methanol and 20 ml of tetrahydrofuran and cooled to 0°C. Then 8.9 ml (8.96 mmol) 1 N sodium hydroxide solution were added and the mixture was stirred for 4 h at ambient temperature. Then the reaction mixture was evaporated down, acidified with 30 ml 1 N hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with saturated NaCl solution, dried and evaporated down in vacuo. The crude yield was purified through a flash column (500 ml volume) with the eluant mixture dichloromethane/methanol 95/5.

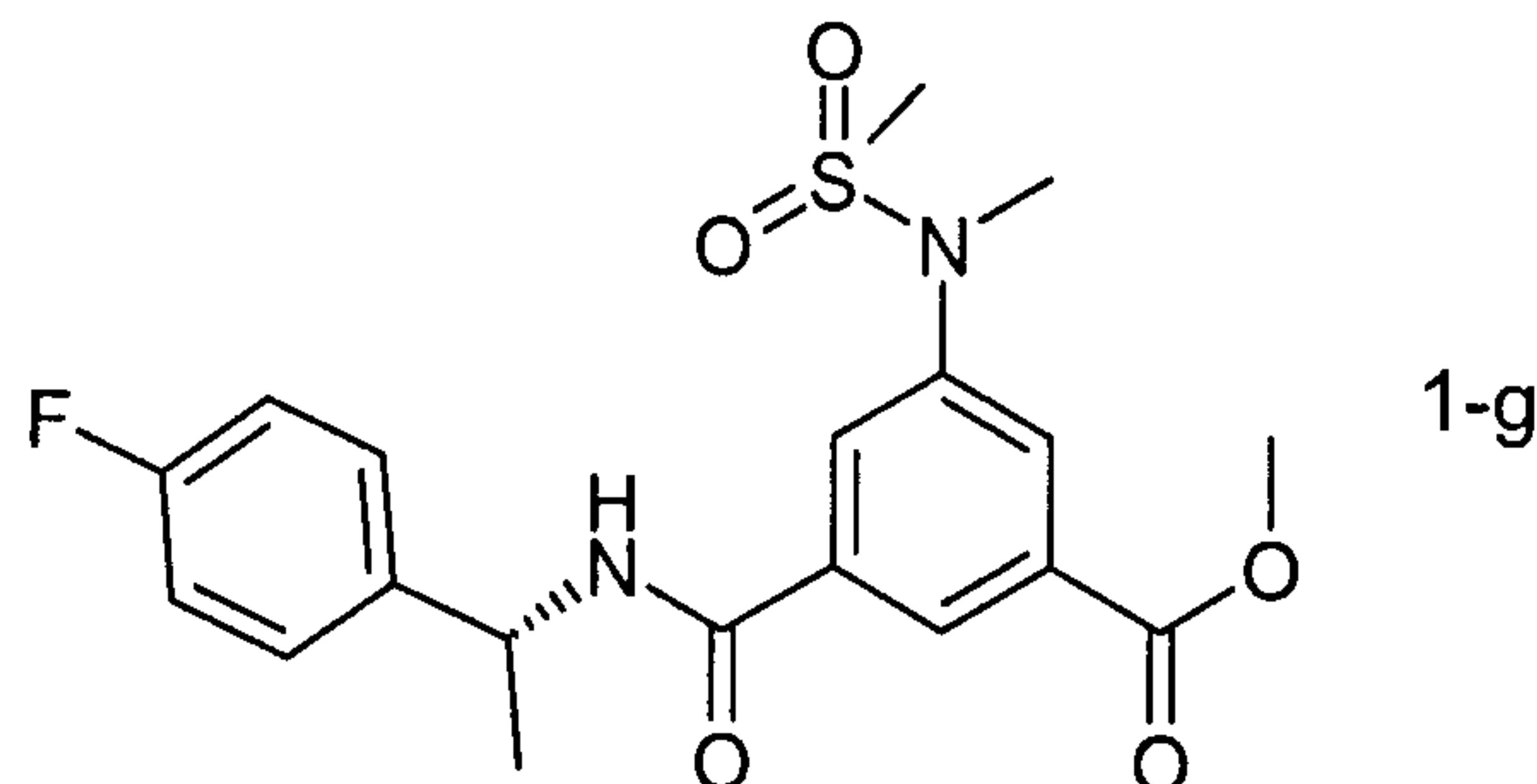
Yield: 1.2 g (47 %) **1-f**.

ES-MS ($M+H^+$) = 288

RT(HPLC-MS) = 3.36 min

– 100 –

RT (HPLC 1) = 3.86 min

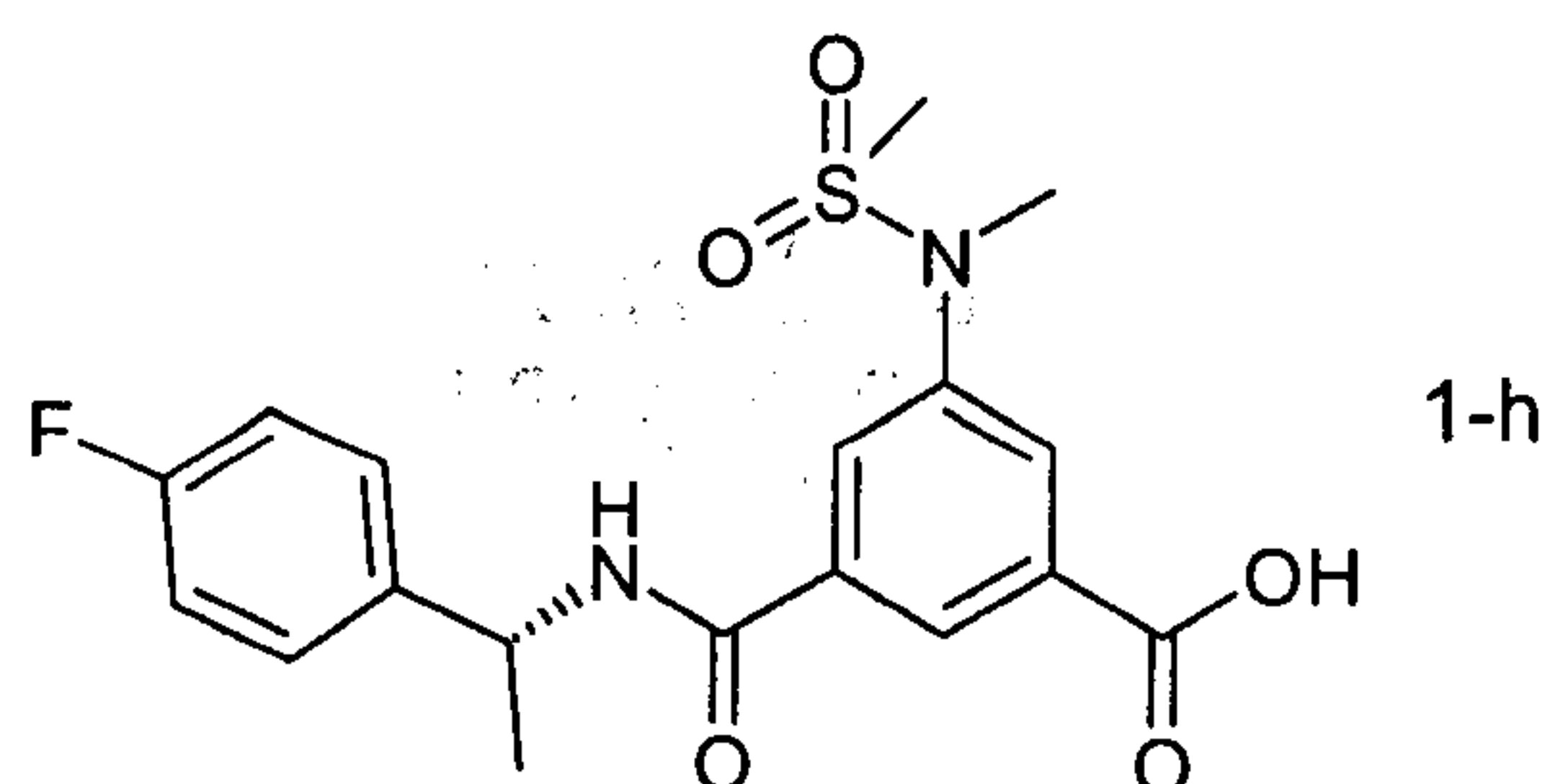
Preparation of **1-g**:

- 5 0.20 g (0.70 mmol) **1-f** were dissolved in 10 ml dichloromethane, then 0.47 ml (2.79 mmol) N,N-diisopropylethylamine, 0.25 g (0.77 mmol) TBTU, 0.10 g (0.70 mmol) R-1-(4-fluorophenyl)ethylamine were added and the mixture was stirred for 1 h. The reaction mixture was washed first of all with KHCO₃ solution, then with water. The organic phase was separated off through a phase separation cartridge and
- 10 evaporated down in vacuo. The crude yield was purified through a flash column (250 ml volume) with a gradient of dichloromethane/methanol 100% → 99% / 1%.

Yield 0.28 g (98 %) **1-g**.ES-MS (M+H)⁺ = 409

RT (HPLC-MS) = 3.00 min

15

Preparation of **1-h**:

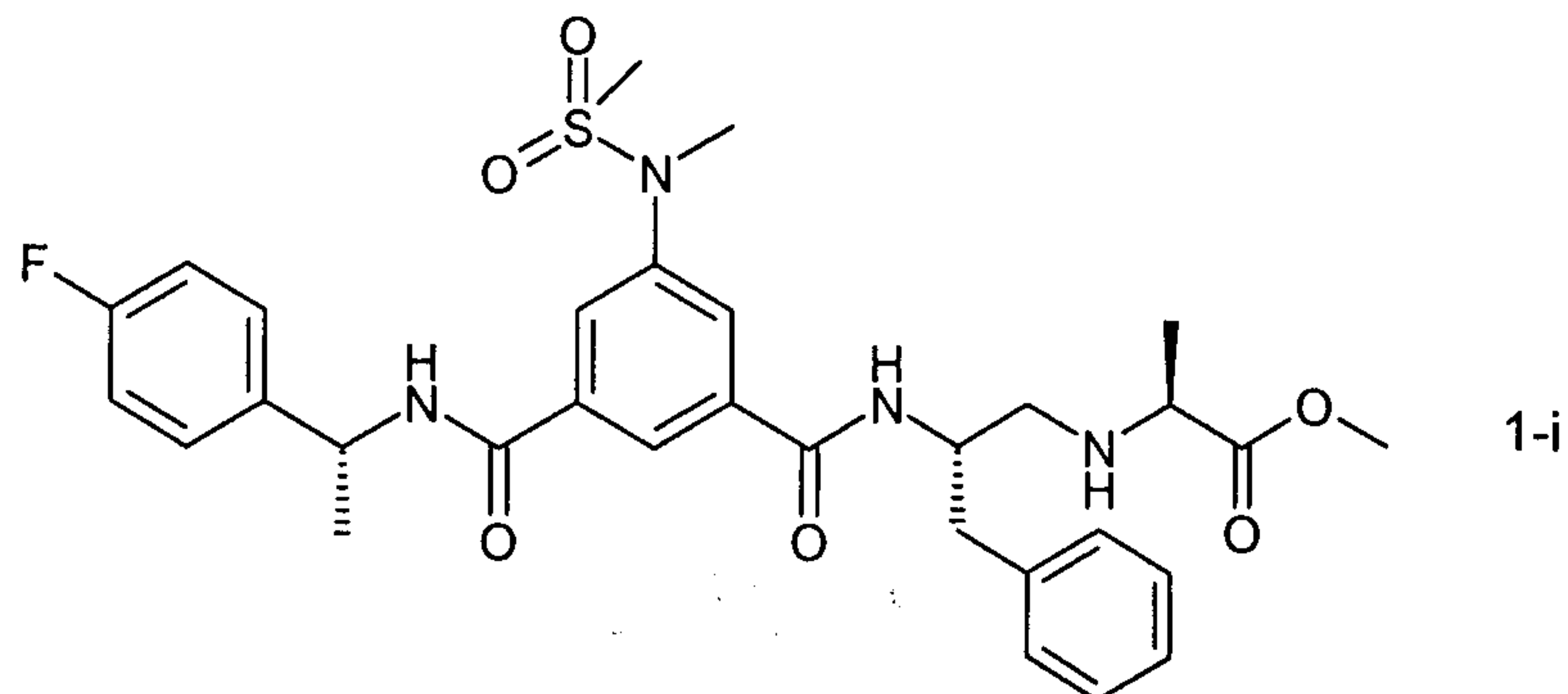
- 20 0.26 g (0.64 mmol) **1-g** were dissolved in 10 ml of methanol, 3.18 ml (6.37 mmol) 1N sodium hydroxide solution were added and the mixture was stirred for 2 h at ambient temperature. Then the solvent was eliminated in vacuo, the residue was acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The combined organic phases were dried and evaporated down in vacuo.

Yield: 200 mg (80 %) **1-h**.

- 25 ES-MS (M-H)⁻ = 393

- 101 -

RT (HPLC-MS) = 2.75 min

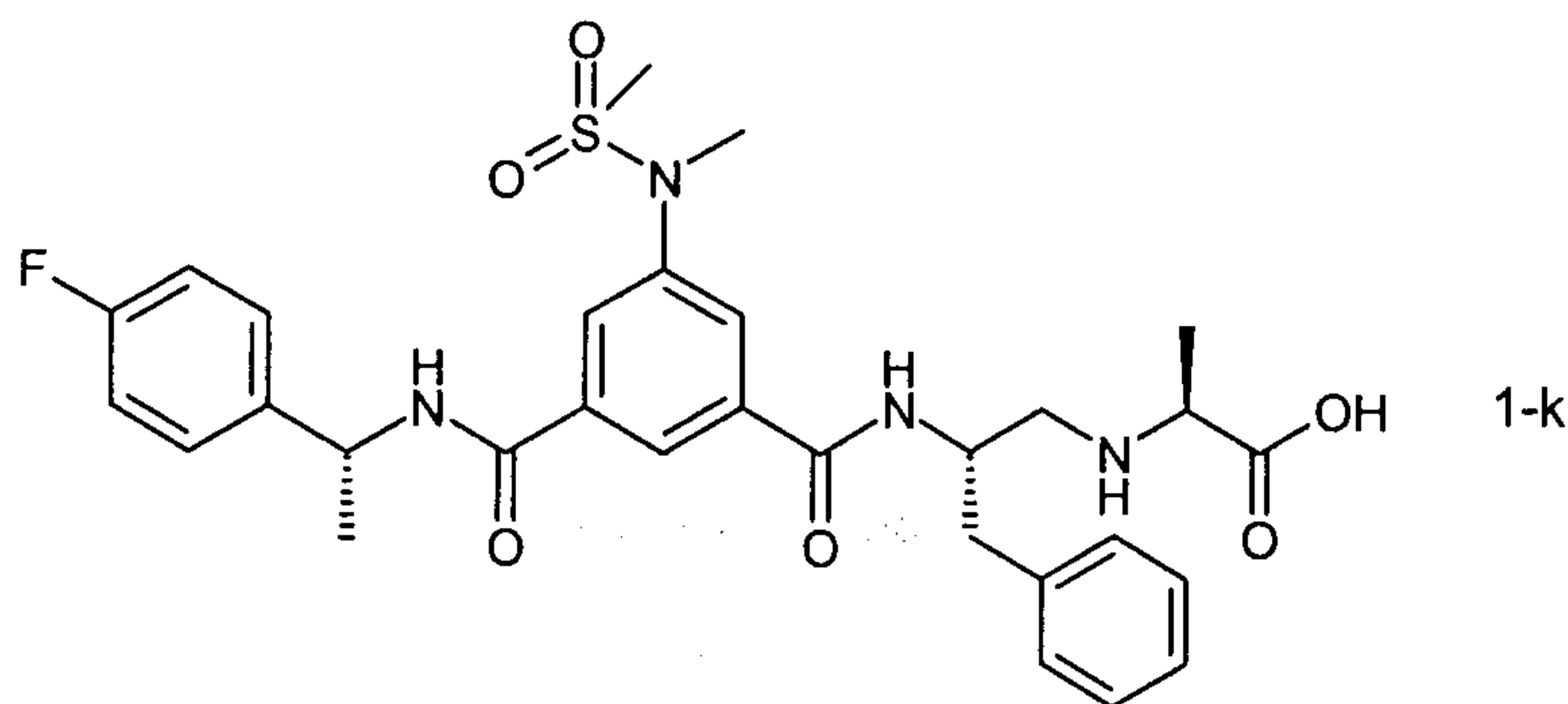
Preparation of **1-i**:

- 5 **1-i** was prepared analogously to **1-g** from 63.8 mg (0.16 mmol) **1-h** and 50.0 mg (0.16 mmol) **1-c** in 5 ml of tetrahydrofuran.

Yield 100 mg (74 %) **1-i**.HPLC-MS (M+H)⁺ = 613

RT (HPLC 1) = 4.58 min

10

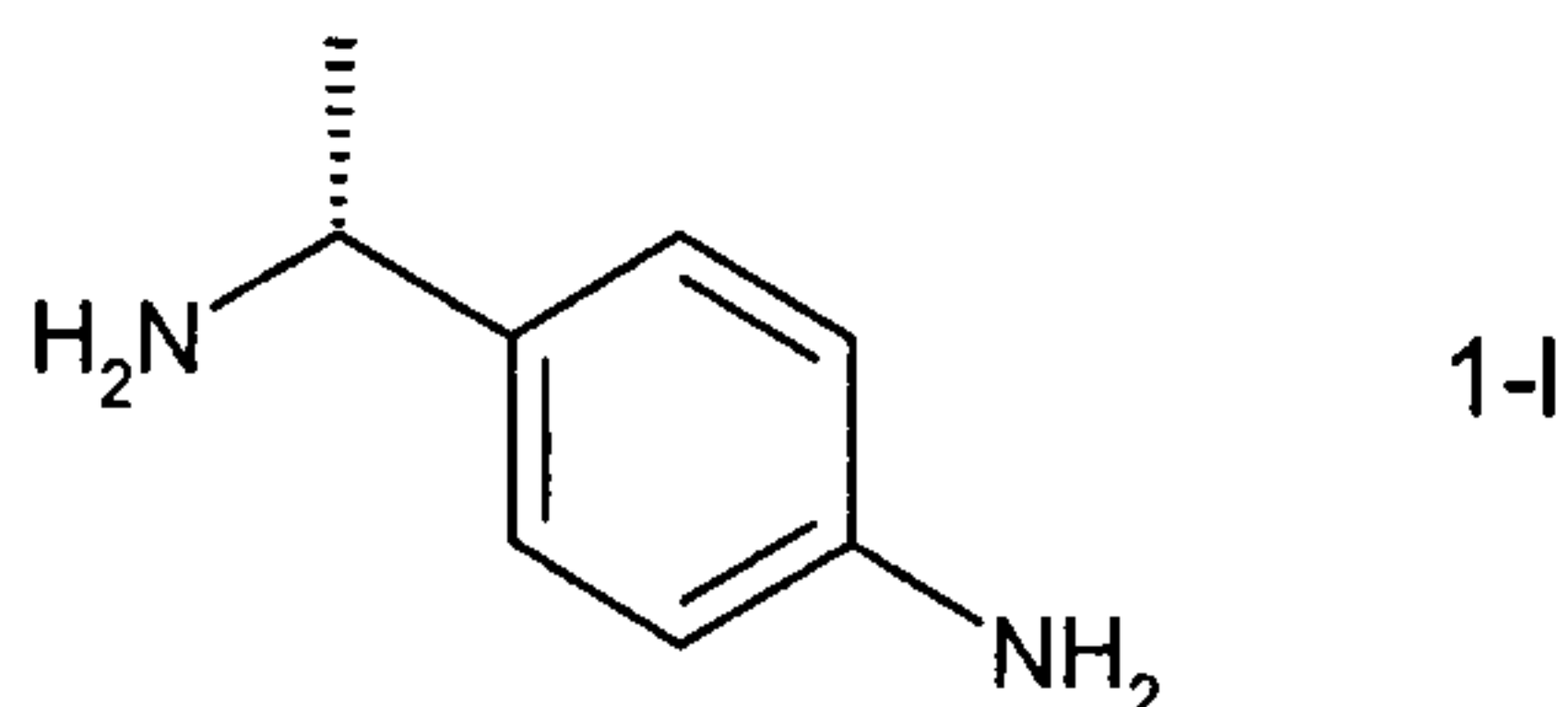
Preparation of **1-k**:

- 15 **1-i** was dissolved in 2 ml of methanol, then combined with 0.3 ml (1.00 mmol) lithium hydroxide solution (8 percent) and stirred for 2 h at ambient temperature. Then the mixture was acidified with 2 N hydrochloric acid, extracted with ethyl acetate, the organic phase was evaporated down in vacuo. The crude product was used in the next step.

Yield: 100 mg (102%) **1-k**.HPLC-MS (M+H)⁺ = 599

20

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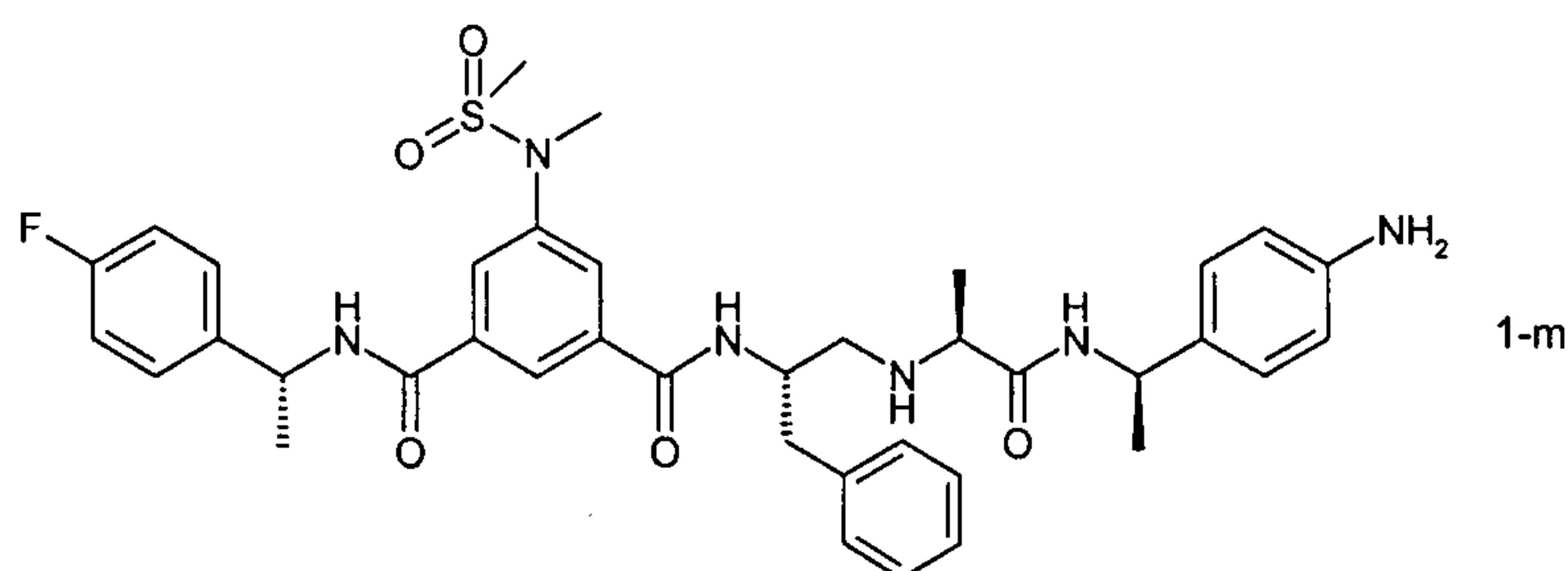
Preparation of **1-l**:

1.9 g (9.38 mmol) R-alpha-methyl-4-nitrobenzylamine were dissolved in 50 ml of ethyl acetate, then 7.4 g (32.8 mmol) tin-(II)-chloride dihydrate were added and the mixture was stirred overnight at ambient temperature. Then it was made alkaline with concentrated ammonia, the precipitated solid was suction filtered, the filtrate was washed with water, dried and evaporated down in vacuo.

Yield: 794 mg (62%) **1-l**.

ES-MS (M+H)⁺ = 137

RT (HPLC-MS) = 1.71 min

Preparation of **1-m**:

1-m was prepared analogously to **1-i** from 50 mg (0.084 mmol) **1-k** and 11.4 mg (0.084 mmol) **1-l** in 5 ml of tetrahydrofuran .

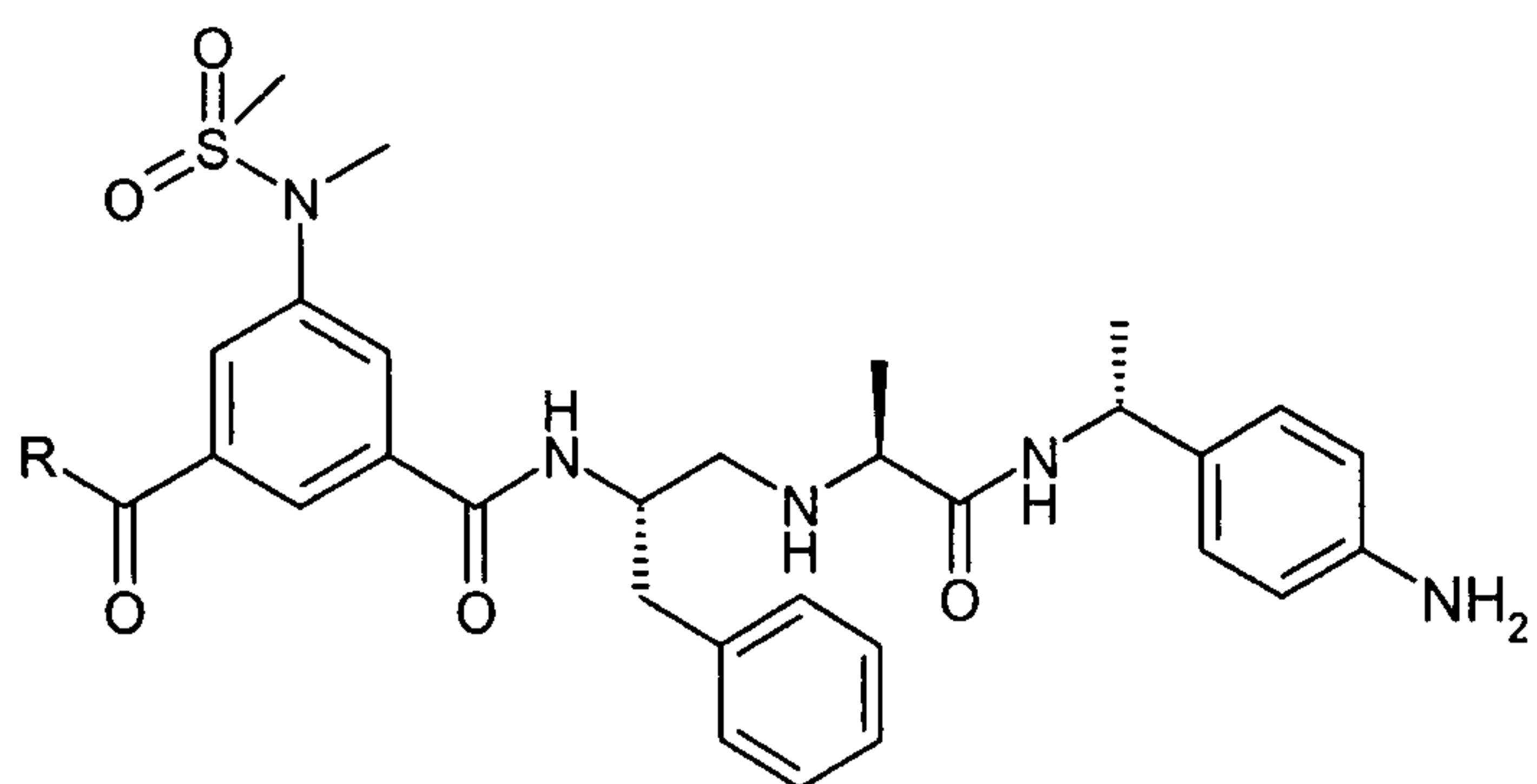
Yield 29 mg (48 %) **1-m**.

ES-MS (M+H)⁺ = 717

RT (HPLC-MS) = 2.5 min

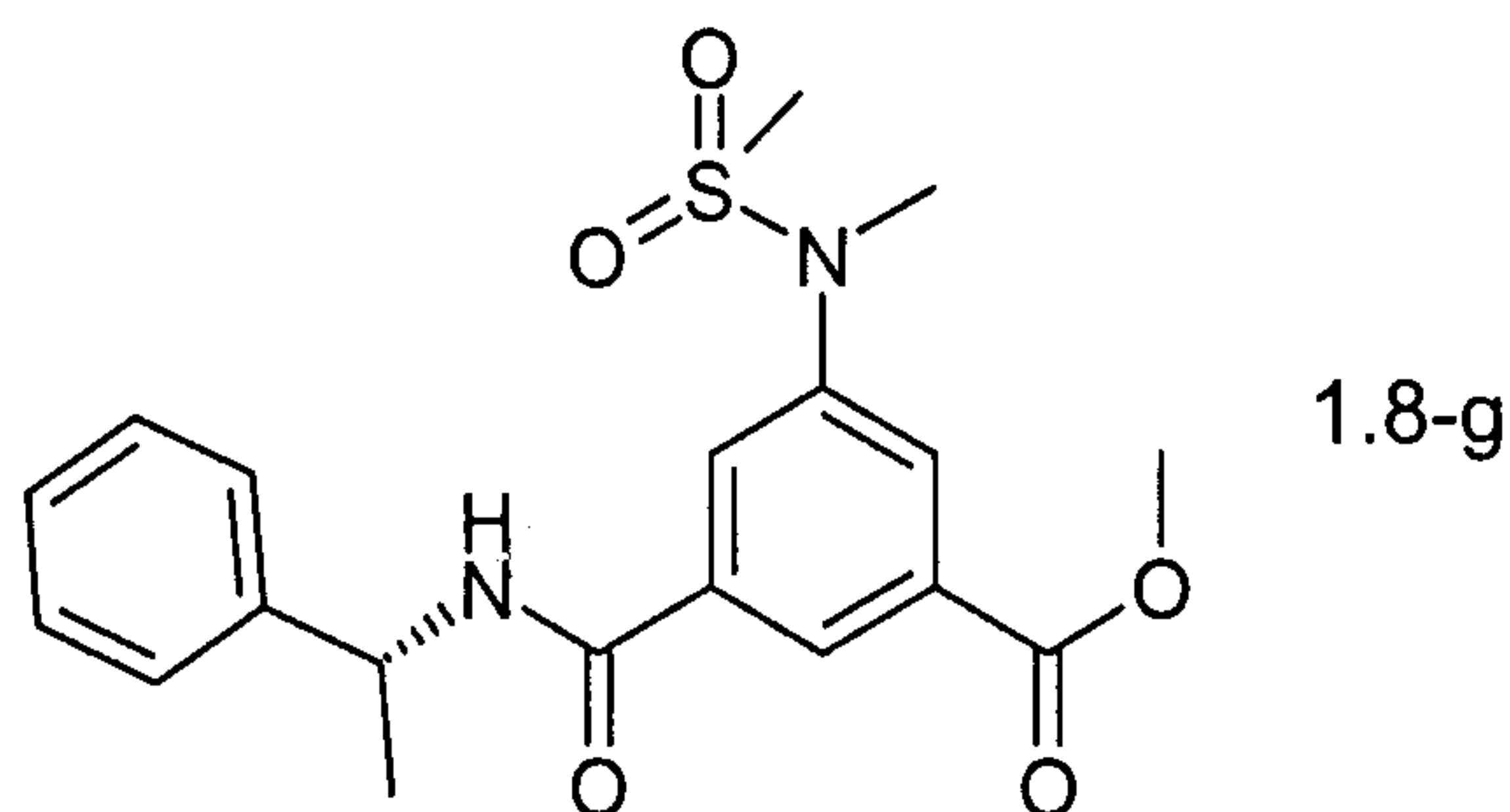
The following Examples were prepared analogously to the series **1-d** to **1-m**:

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Example	R	MS	RT HPLC- MS
1.2	Chemical structure of R for Example 1.2: 3,5-dichlorobenzylamine derivative.	753/755/757 (M+H) ⁺	2.81 min
1.3	Chemical structure of R for Example 1.3: 1-phenylpropan-2-amine derivative.	713 (M+H) ⁺	2.56 min
1.4	Chemical structure of R for Example 1.4: 1-phenylethylamine derivative.	713 (M+H) ⁺	2.54 min
1.5	Chemical structure of R for Example 1.5: 1-(3-chlorophenyl)ethylamine derivative.	733/735 (M+H) ⁺	2.63 min
1.6	Chemical structure of R for Example 1.6: 1-(4-methoxyphenyl)ethylamine derivative.	729 (M+H) ⁺	2.47 min
1.7	Chemical structure of R for Example 1.7: 1-(thiophen-2-yl)ethylamine derivative.	705 (M+H) ⁺	2.47 min
1.8	Chemical structure of R for Example 1.8: 1-phenylethylamine derivative.	699 (M+H) ⁺	2.51 min

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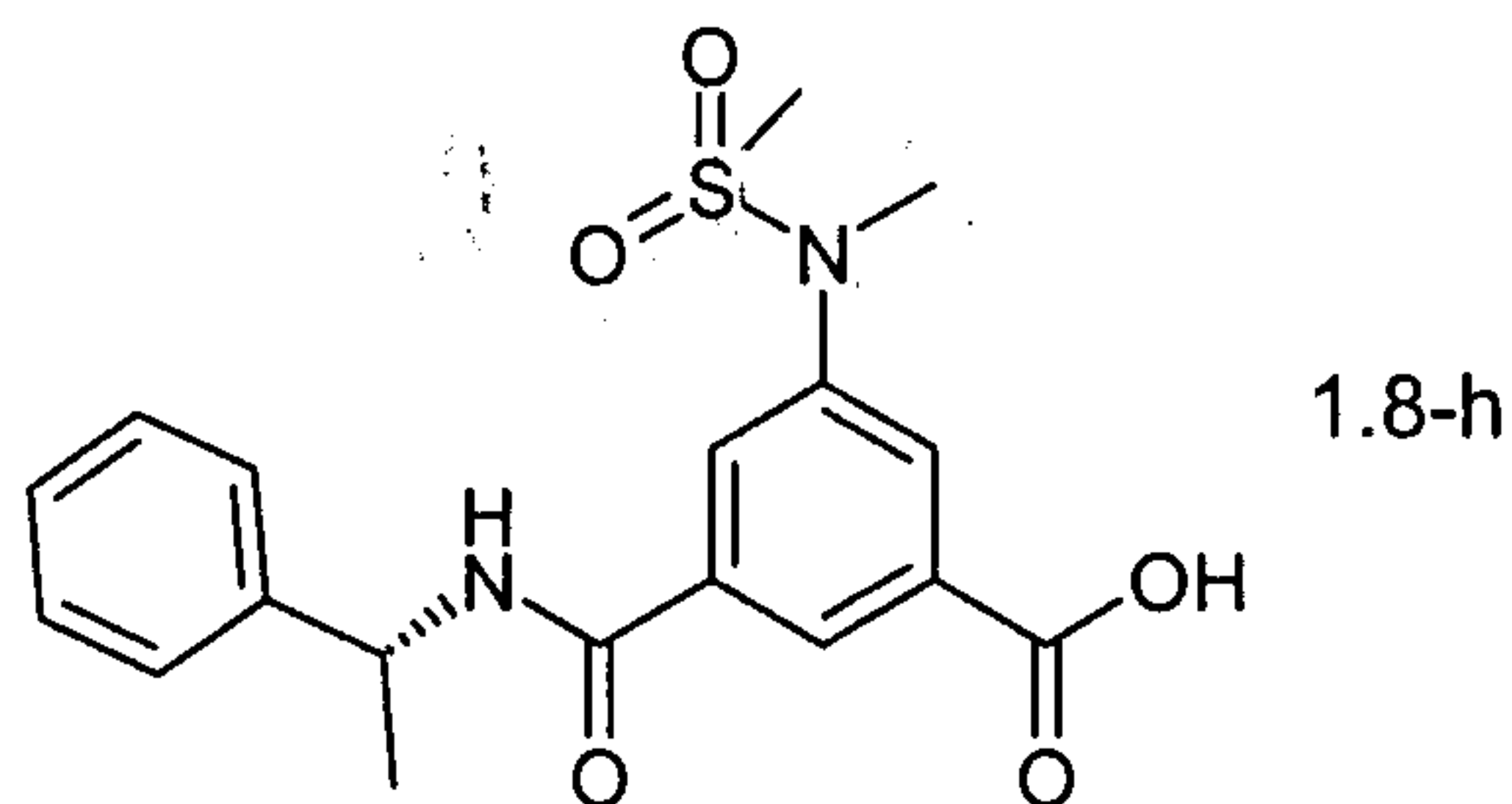
Preparation of **1.8-g**:

0.50 g (1.74 mmol) **1-f** were dissolved in 10 ml dichloromethane, then 1.18 ml (6.92 mmol) DIPEA, 0.62 g (1.91 mmol) TBTU and 0.23 ml (1.74 mmol) (R)-1-phenyl-ethylamine were added. After 1 h the solution was extracted with sat. aqueous KHCO₃ solution and water. The organic phase was evaporated down in vacuo. The crude product was chromatographed on 250 g silica gel (hexane/ethyl acetate).

Yield: 0.58 g (85 %) **1.8-g**

10 RT (HPLC-MS) = 2.99 min.

ES-MS (M+H)⁺ = 391

Preparation of **1.8-h**:

15

0.17 g (0.44 mmol) **1.8-g** were dissolved in 5 ml THF/methanol (1:1), 0.44 ml (1.76 mmol) 4M sodium hydroxide solution were added and the mixture was stirred for 5 h at ambient temperature. The solution was adjusted to pH 3 using 2 M hydrochloric acid and evaporated down in vacuo. The precipitate formed was filtered off, washed with water and dried in vacuo.

20

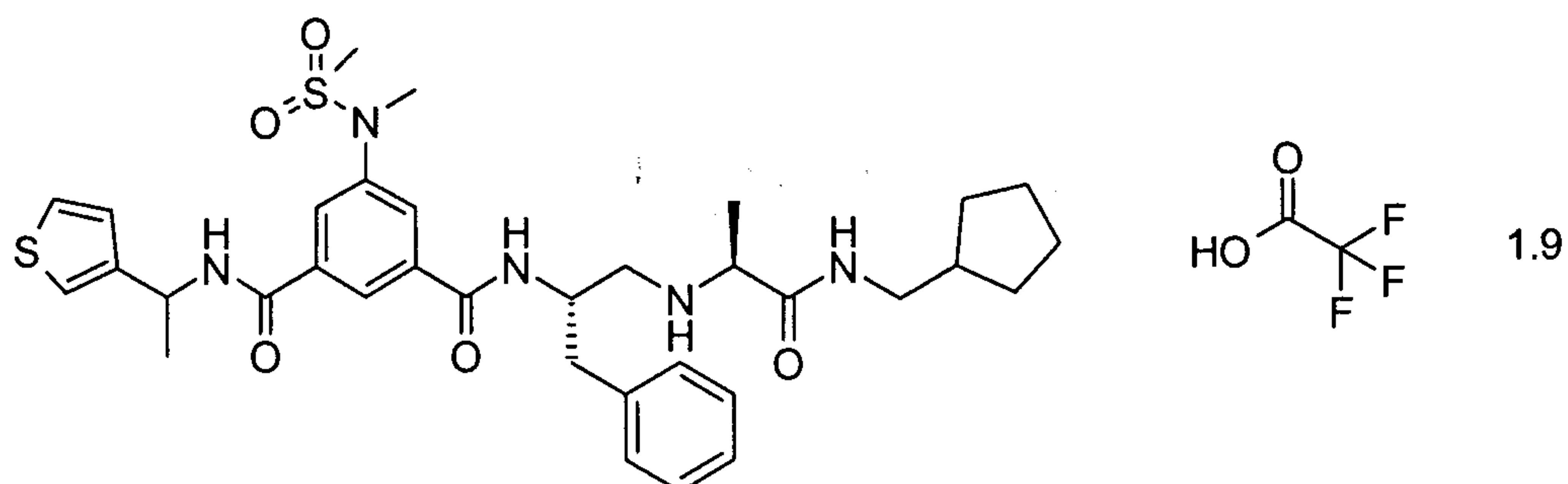
Yield: 0.13 g (79 %) **1.8-g**

ES-MS (M-H)⁺ = 375

RT (HPLC-MS) = 2.71 min

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Example 1.9



Example 1.9 was prepared analogously to Example 1. The crude product was purified by HPLC-2.

5 Yield: 33 mg (58 %)

ES-MS (M-H)⁺ = 688

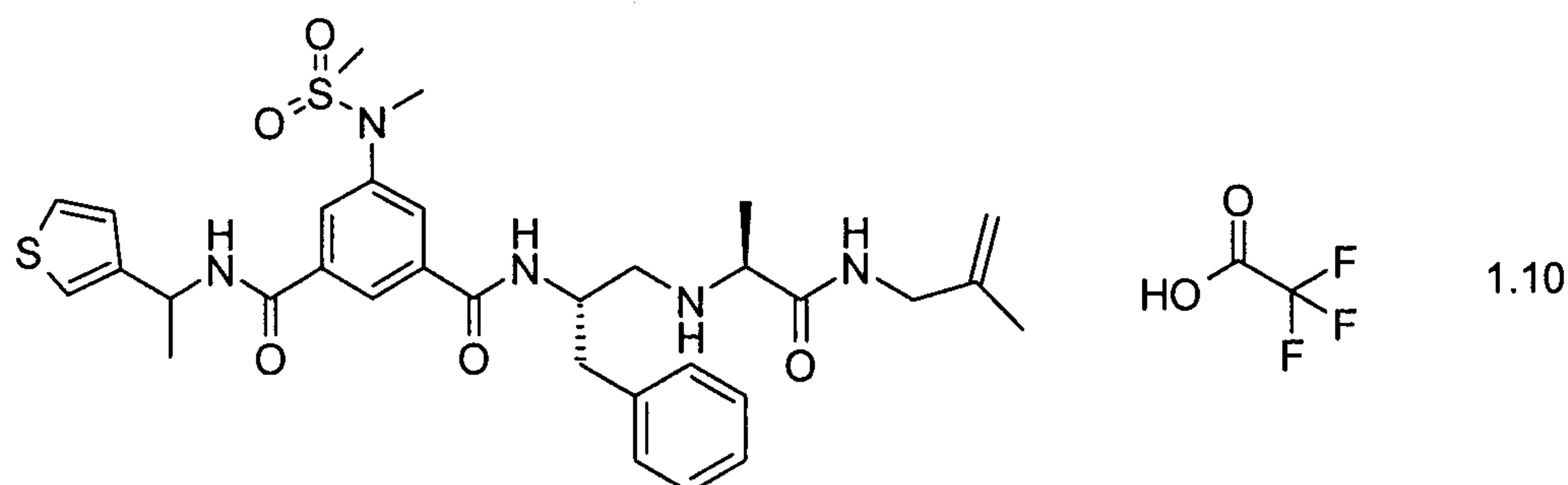
RT (HPLC-MS) = 2.87 min

RT (HPLC-1) = 4.85 min

RT (HPLC-2) = 20.1 min

10

Example 1.10



Example 1.10 was prepared analogously to Example 1. The crude product was purified by HPLC-2.

15 Yield: 26 mg (60 %)

ES-MS (M-H)⁺ = 640

RT (HPLC-MS) = 2.76 min

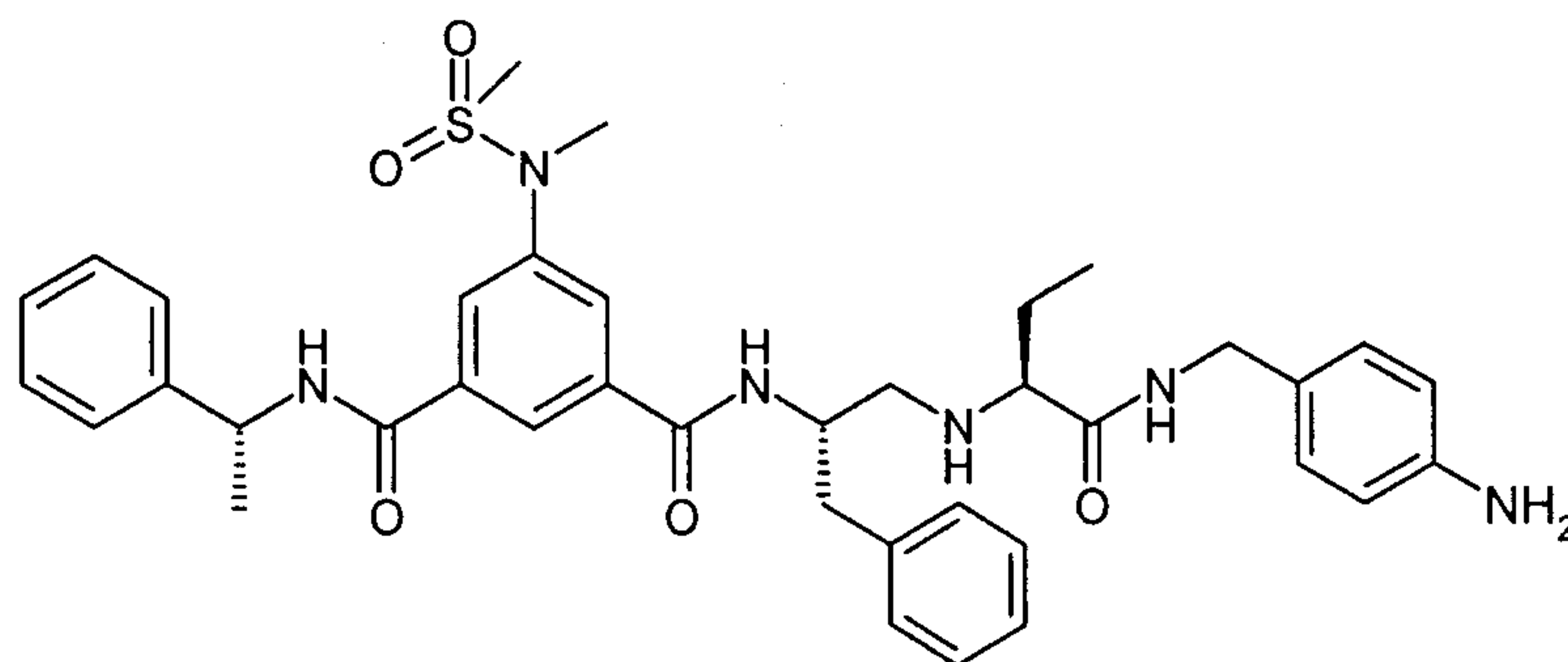
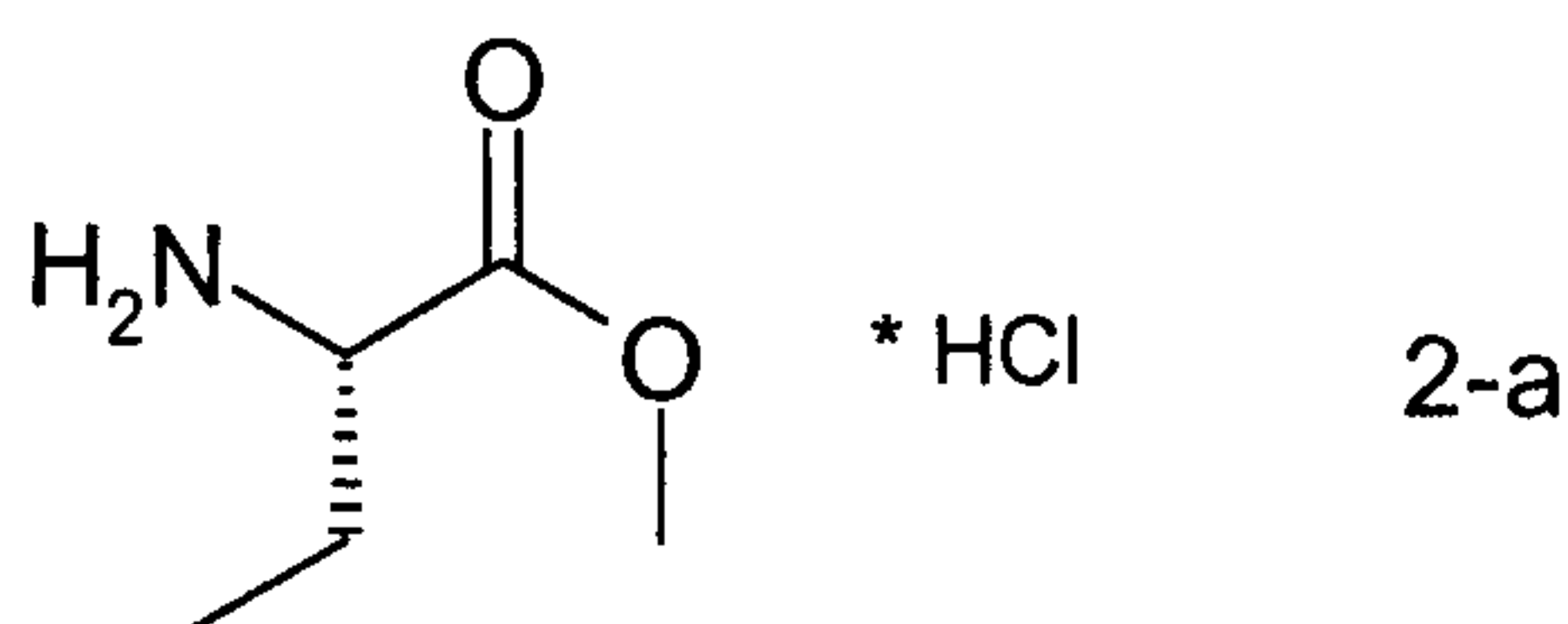
RT (HPLC-1) = 4.63 min

RT (HPLC-2) = 19.2 min

20

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Example 2:

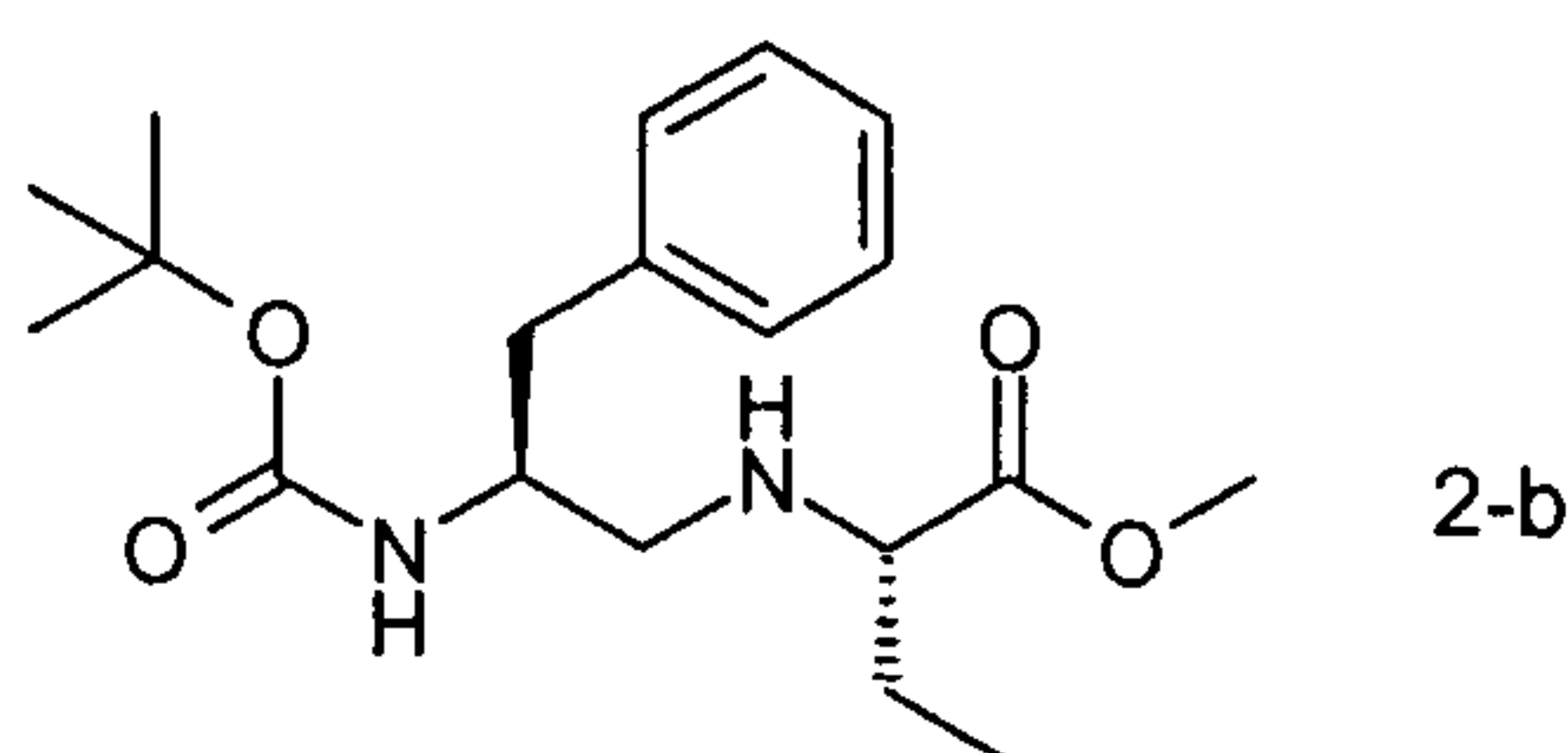
Preparation of **2-a**:

5

10.0 g (49.2 mmol) BOC-L-2-aminobutyric acid was dissolved in 100 ml of methanol and 6 ml (82.2 mmol) thionyl chloride were added dropwise at 0°C. The solution was stirred for 14 h at ambient temperature and then evaporated down in vacuo.

Yield: 7.6 g (101%) **2-a**.

10 ES-MS (M+H)⁺ = 118

Preparation of **2-b**:

2-b

The preparation of **2-b** proceeded analogously to **1-b** starting from 3.3 g (21.5 mmol) **2-a** and 5.3 g (21.3 mmol) BOC-L-phenylalaninal.

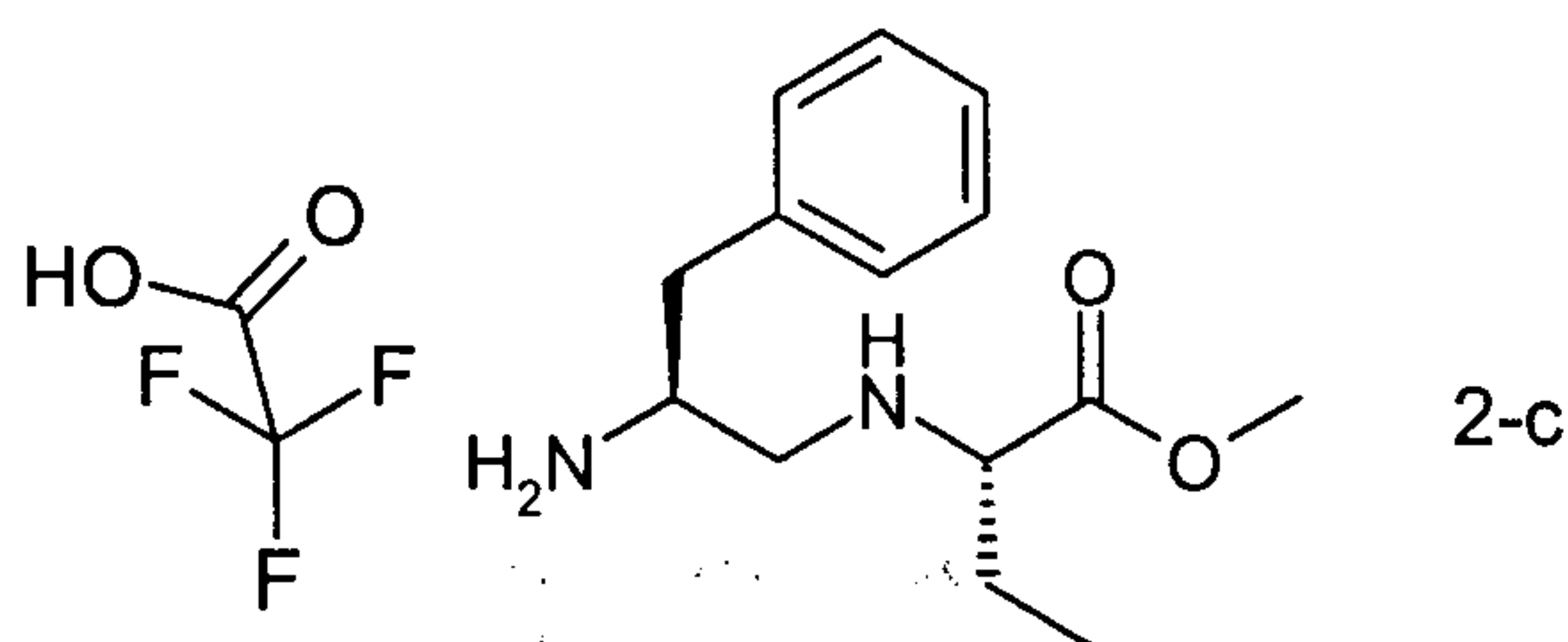
15 Yield 7.46 g (99 %) **2-b**.

Yield 7.46 g (99 %) **2-b**.

RT (HPLC-MS) = 2.51 min

Preparation of **2-c**:

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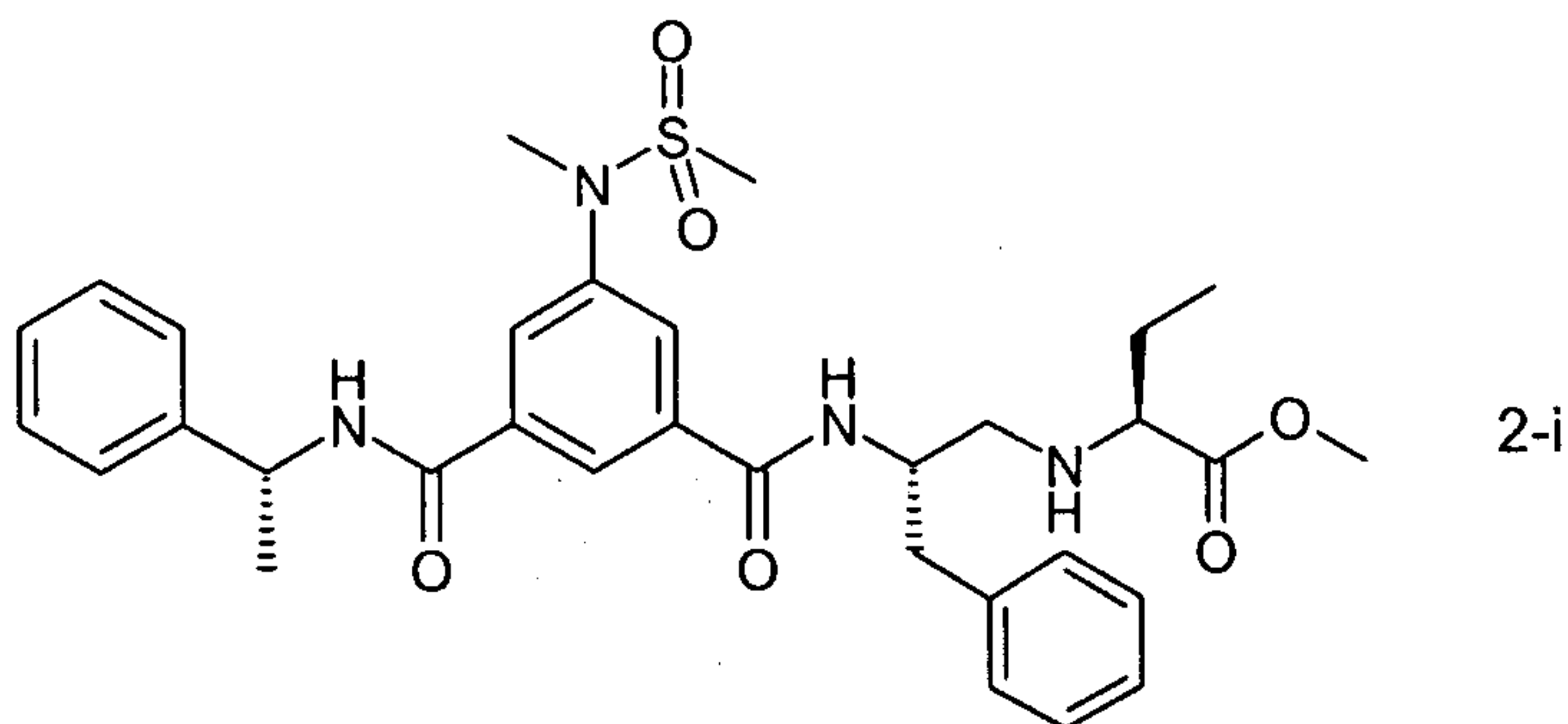
8 ml trifluoroacetic acid were added to 7.46 g (21.3 mmol) **2-b** dissolved in 200 ml dichloromethane and the mixture was stirred for 14 h at ambient temperature. Then the solution was again refluxed for 2 h, cooled and evaporated down in vacuo.

5 Yield in crude form 12.7 g (164 %) **2-c**.

ES-MS (M+H)⁺ = 251

RT (HPLC-MS) = 1.87 min

Preparation of **2-i**:



10

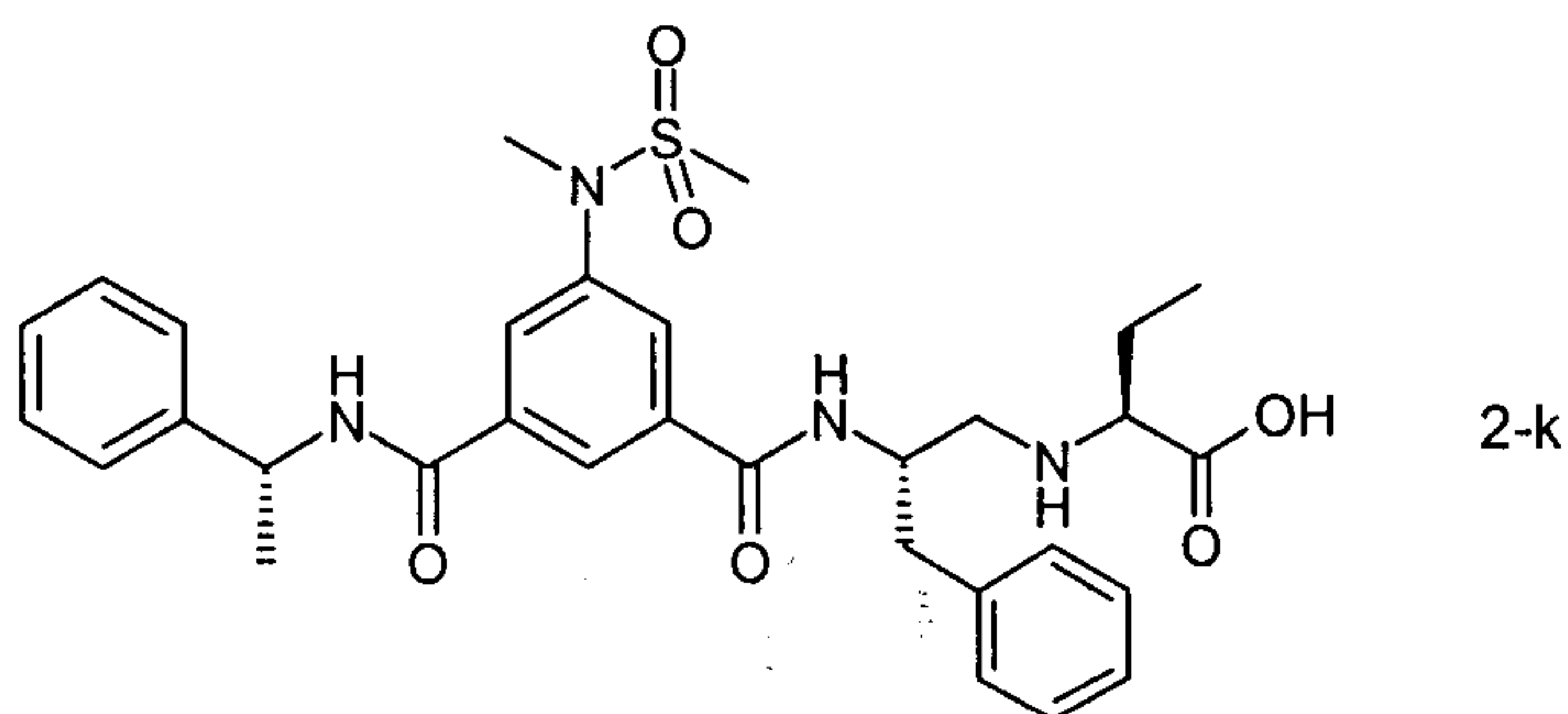
2-i was prepared analogously to **1-i** starting from 1.2 g (3.1 mmol) **1.8-h** and 1.16 g (3.19 mmol) **2-c** in 40 ml of tetrahydrofuran.

Yield: 1.03 g (53 %) **2-i**.

ES-MS (M+H)⁺ = 609

15

Preparation of **2-k**:

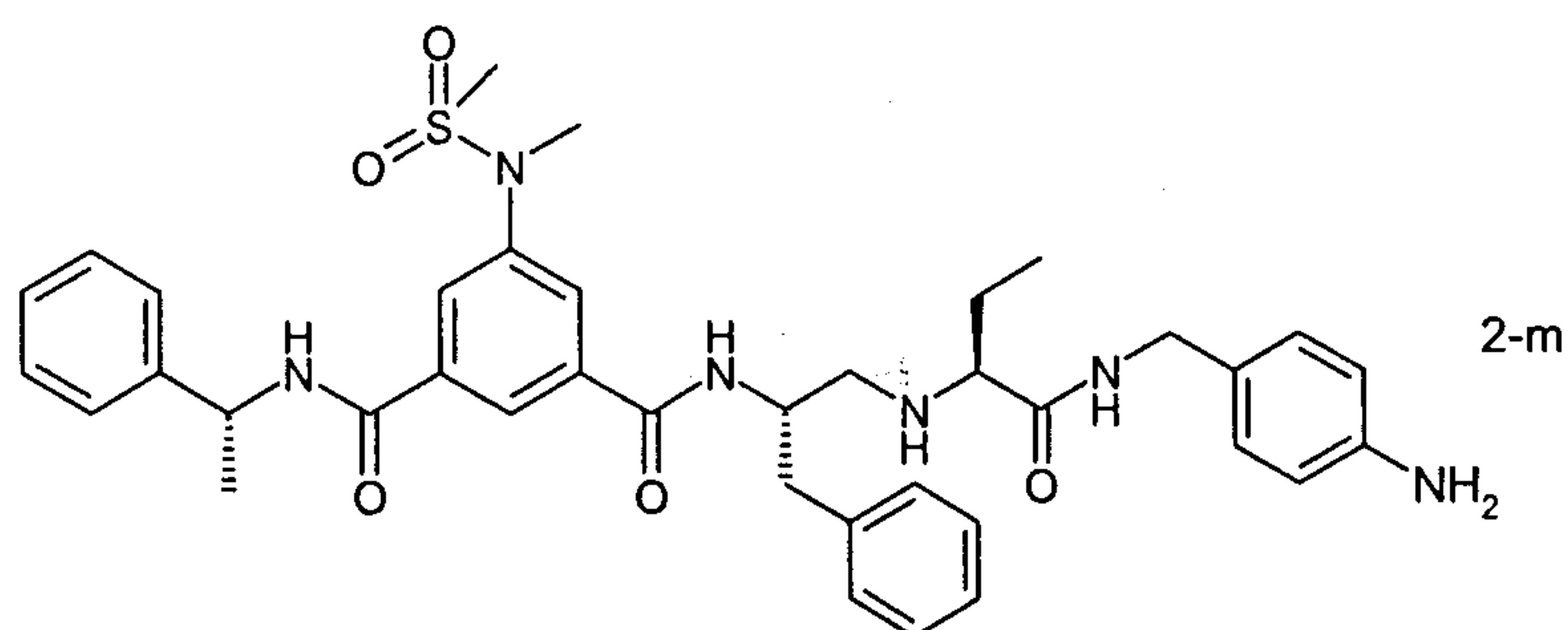


The preparation of **2-k** was carried out analogously to **1-k** starting from 630 mg (1.04 mmol) **2-i**,

- 108 -

Yield 339 mg (55 %) **2-k**ES-MS (M+H)⁺ = 595

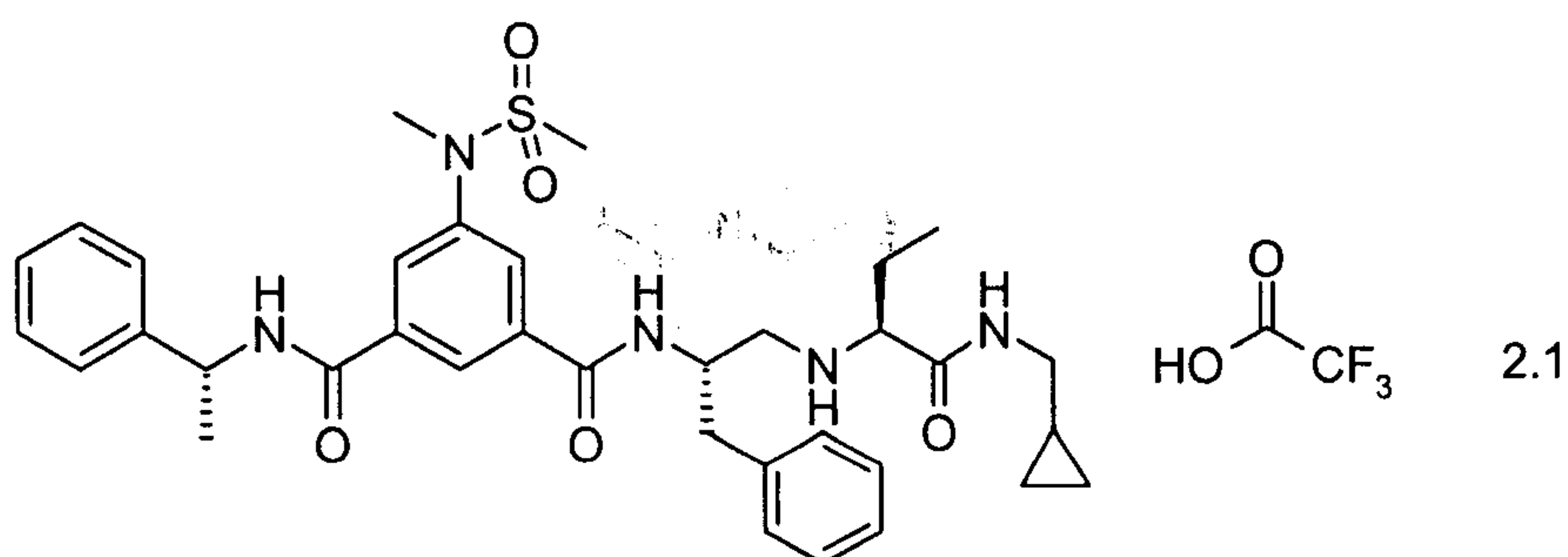
RT (HPLC 1) = 4.4 min

5 Preparation of **2-m**:

The preparation of **2-m** was carried out analogously to **1-m** starting from 20 mg (0.034 mmol) **2-k** and 4.2 mg (0.034 mmol) 4-aminobenzylamine.

Yield 9.0 mg (33 %) **2-m**10 ES-MS (M+H)⁺ = 699

RT (HPLC 2) = 18 min

Preparation of **2.1**

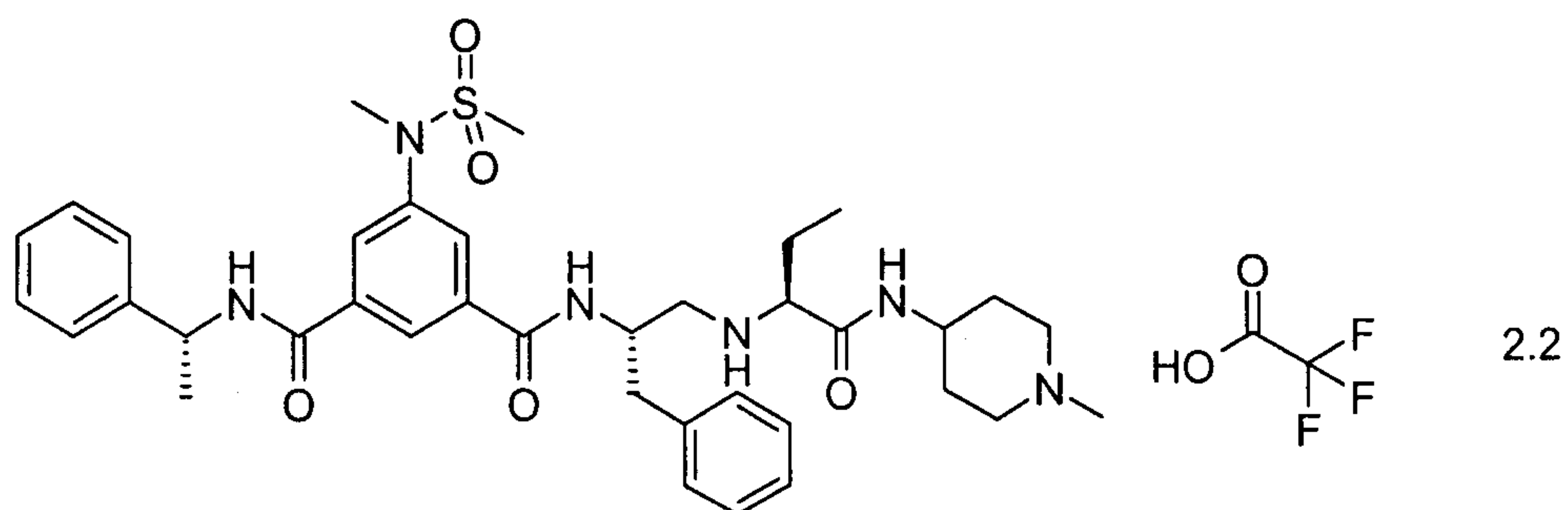
15

2.1 was prepared analogously to **2-m** starting from 20.2 mg (0.034 mmol) **2-k** and 2.42 mg (0.034 mmol) cyclopropylmethylamine. The crude product was purified by HPLC-2.

20 Yield 12.0 mg (55 %) **2.1**ES-MS (M+H)⁺ = 648

RT (HPLC 2) = 20.4 min

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Preparation of **2.2**

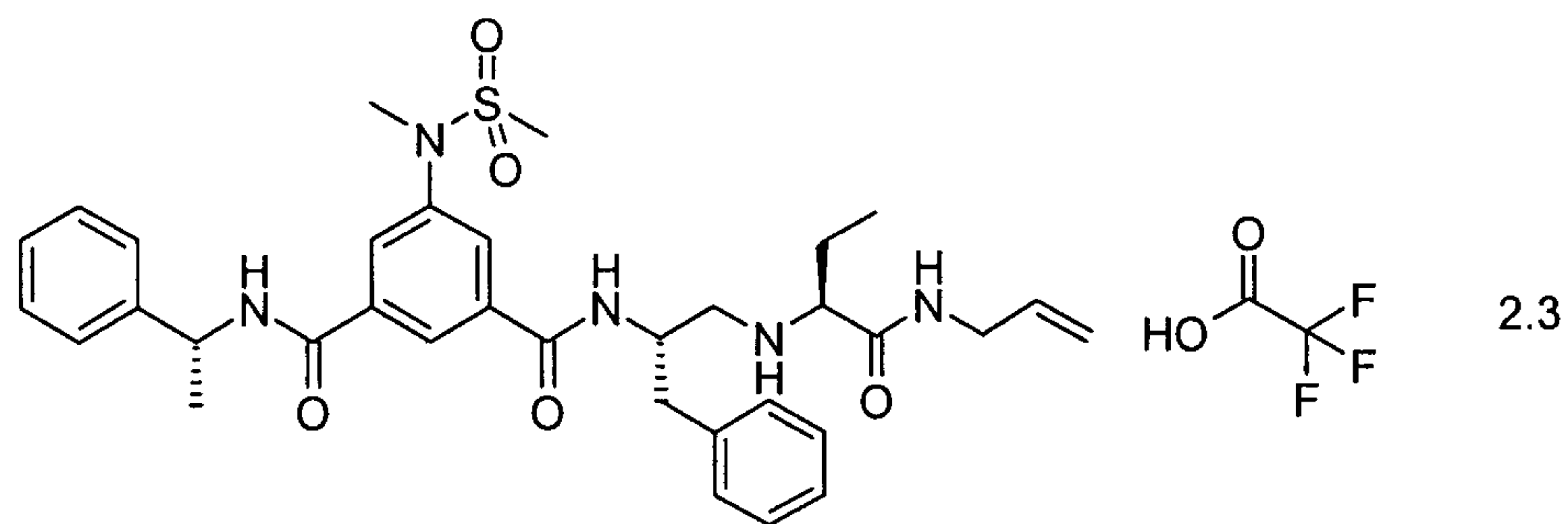
2.2 was prepared analogously to **2-m** starting from 20.2 mg (0.034 mmol) **2-k** and
5 3.88 mg (0.034 mmol) 4-amino-1-methylpiperidine. The crude product was purified by HPLC-2.

Yield 8 mg (29 %) **2.2**

ES-MS (M+H)⁺ = 691

RT (HPLC 2) = 17.6 min

10

Preparation of **2.3**

15 **2.3** was prepared analogously to **2-m** starting from 19.4 mg (0.031 mmol) **2-k** and 20 mg (0.35 mmol) allylamine. The crude product was purified by HPLC-2.

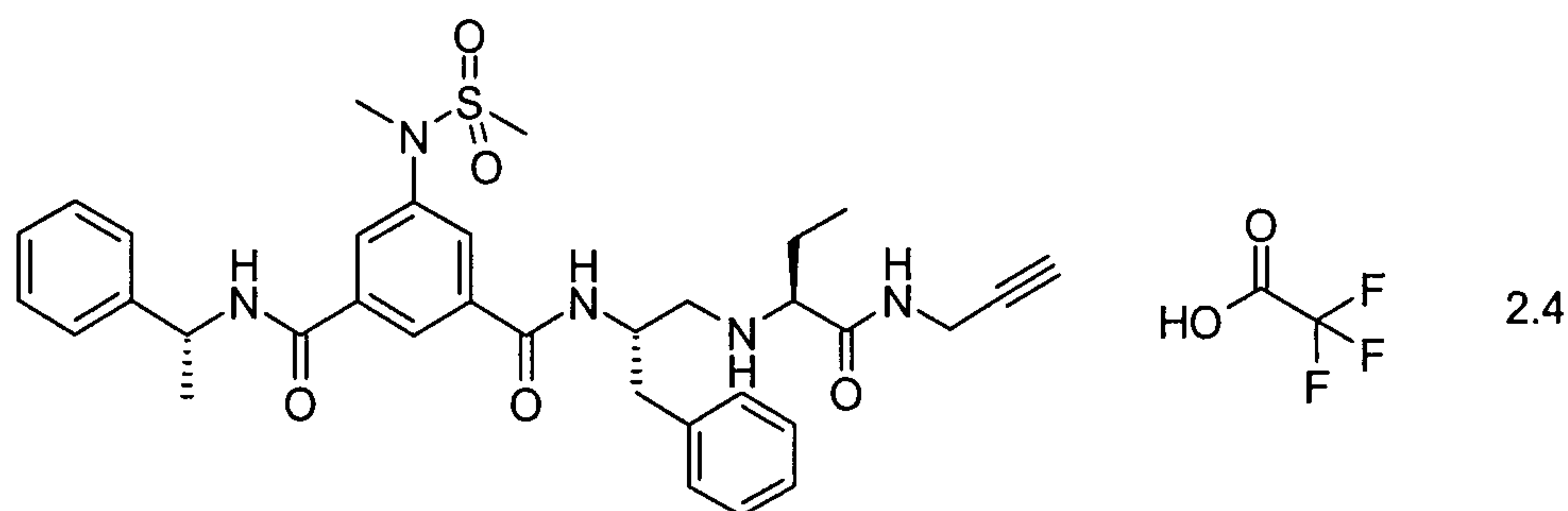
Yield 8 mg (35 %) **2.3**

ES-MS (M+H)⁺ = 634

RT (HPLC 1) = 2.7 min

20 RT (HPLC 2) = 19.1 min

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Preparation of **2.4**

2.4 was prepared analogously to **2-m** starting from 19.9 mg (0.033 mmol) **2-k** and 20 mg (0.36 mmol) 2-propynylamine. The crude product was purified by HPLC-2.

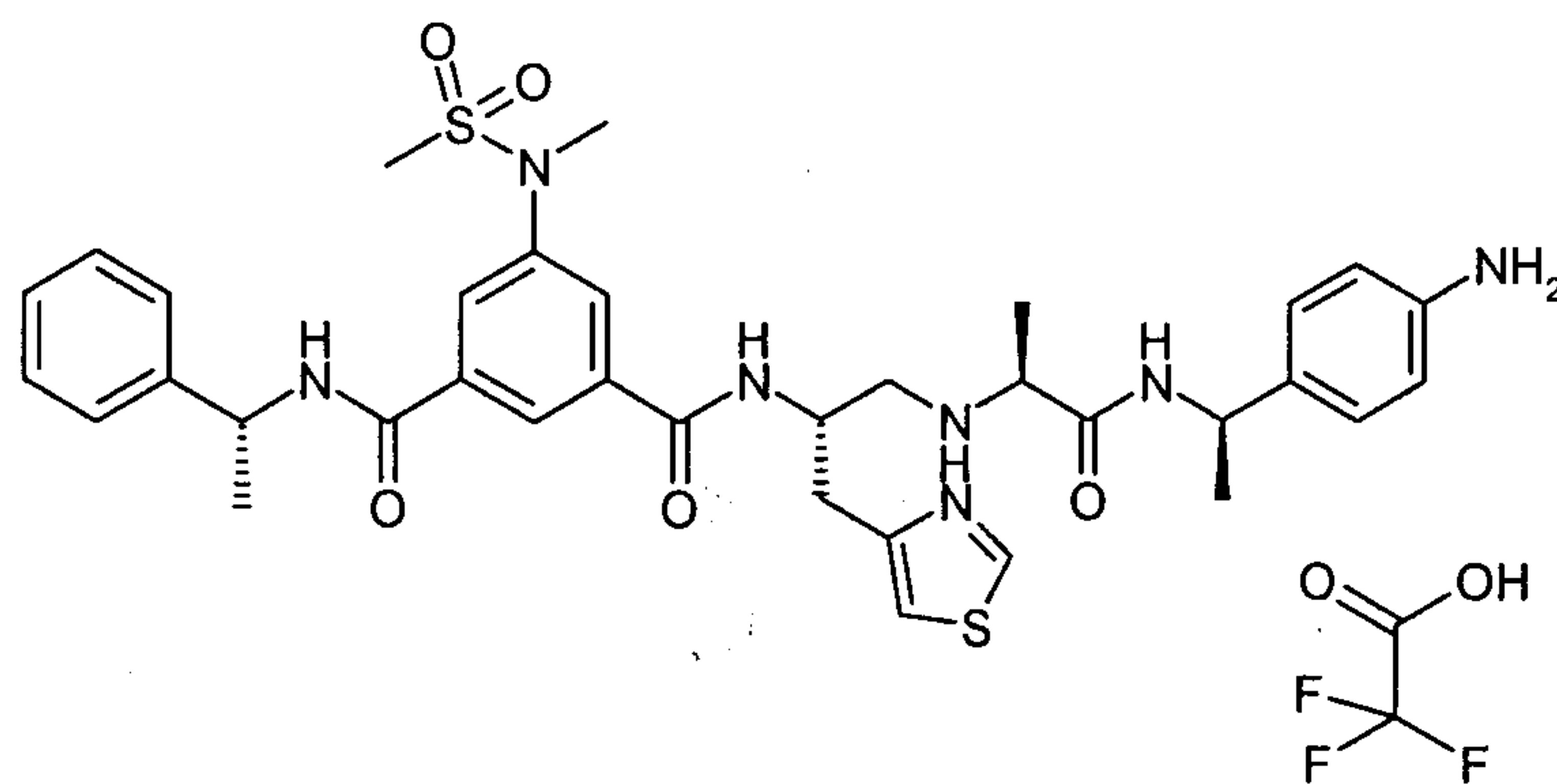
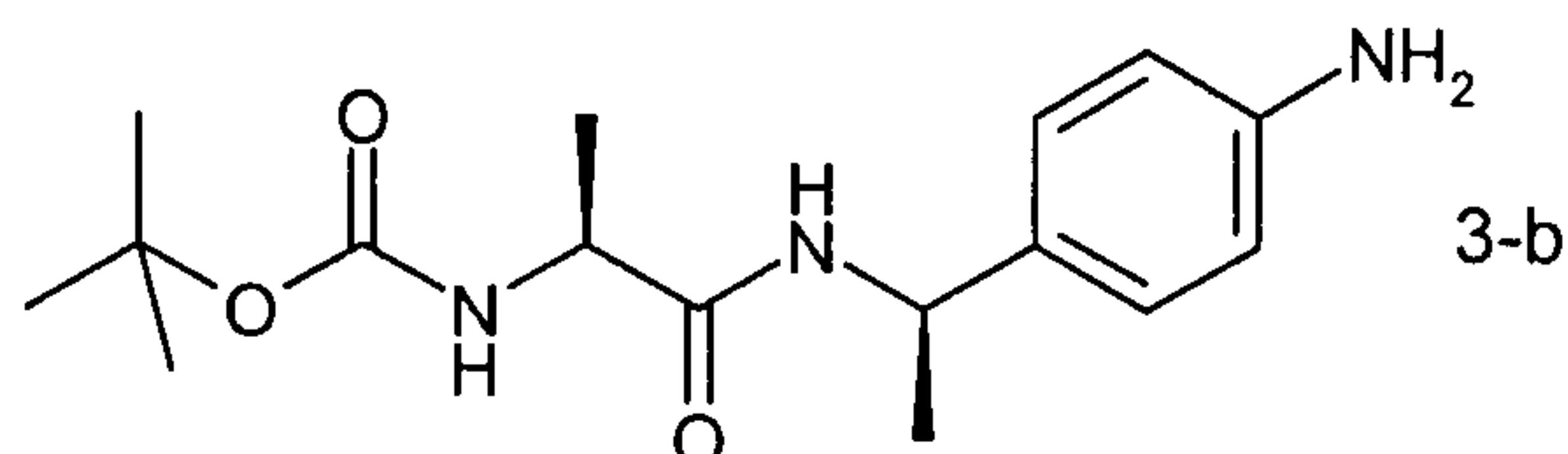
Yield 9 mg (36 %) **2.4**

ES-MS (M+H)⁺ = 632

RT (HPLC-MS) = 2.75 min

RT (HPLC 2) = 19.2 min

Example 3:

Preparation of **3-b**:

700 mg (3.70 mmol) BOC-L-alanine was placed in 30 ml acetonitrile, 500 mg (3.70 mmol) HOBT and 1.4 ml diisopropylethylamine were added, the mixture was cooled to 0°C and 1.0 ml 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide were added. After 15 min **1-I** was added and the mixture was stirred for 6 h at ambient temperature. The

- 111 -

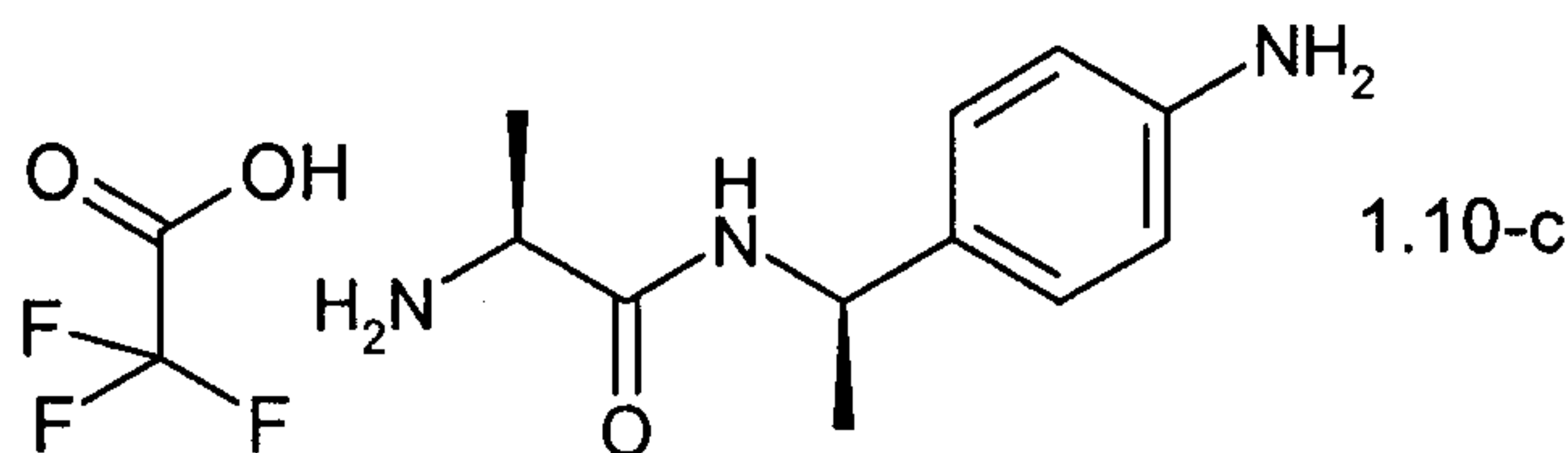
solvent was distilled off in vacuo, the residue was taken up in acetonitrile/water 1:1 and combined with 1% trifluoroacetic acid and purified by HPLC 1.

Yield 850 mg (75 %) **3-b**.

RT (HPLC-MS) = 2.06 min

5 ES-MS (M+H)⁺ = 308

Preparation of **3-c**:



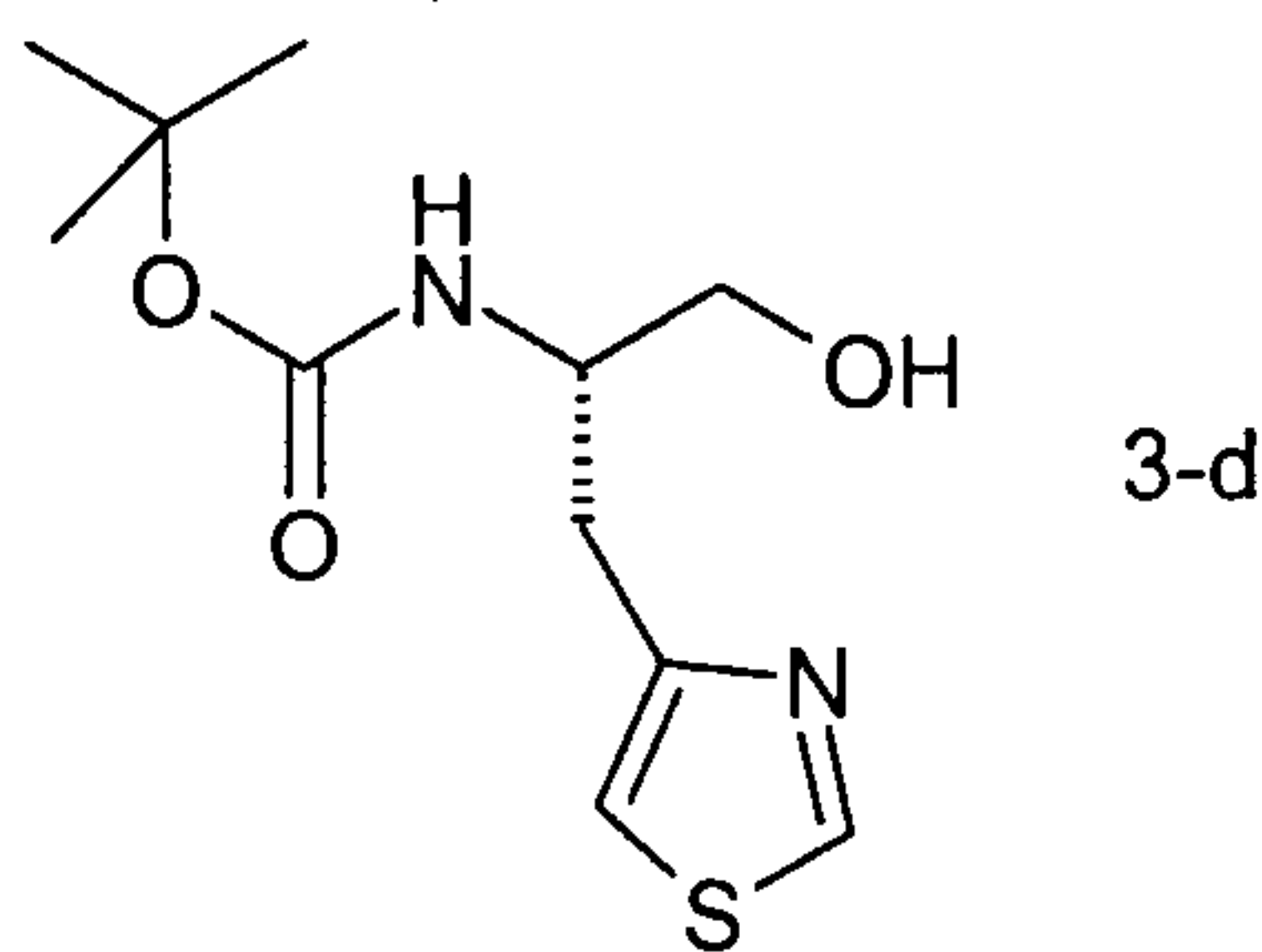
10

850 mg (2.77 mmol) **3-b** was dissolved in 5 ml dichloromethane, then 5 ml trifluoroacetic acid were added and the mixture was stirred for 3 h at ambient temperature. Then the solvent was dissolved off in vacuo, the crude product was triturated with diethyl ether, the solid was suction filtered and dried in vacuo.

15 Yield 900 mg (101 %) **3-c**.

ES-MS (M+H)⁺ = 208

Preparation of **3-d**:



20 1.0 g (3.67 mmol) BOC-L-4-thiazolylalanine was dissolved in 10 ml dimethoxyethane, cooled to -22°C and combined with 0.4 ml (3.64 mmol) N-methylmorpholine. Then 0.48 ml (369 mmol) isobutylchloroformate were dissolved in 2 ml dimethoxyethane and added dropwise at -22°C. After all this had been added, the solution was heated to ambient temperature and stirred for 1 h.

25 The precipitate formed was suction filtered, the filtrate was cooled to -15°C again and combined with 0.22g (5.81 mmol) sodium borohydride and a few drops of water. The

- 112 -

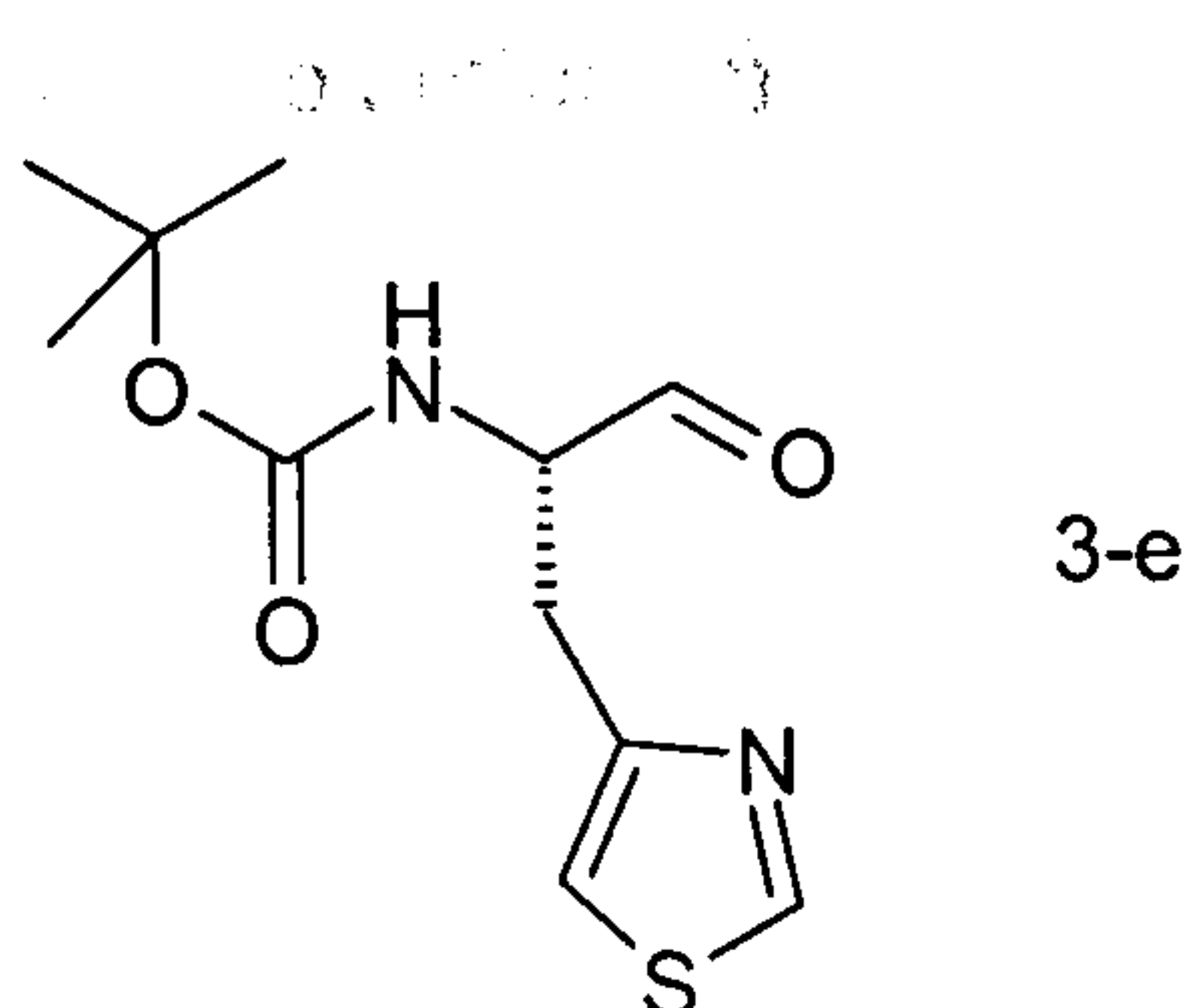
mixture was allowed to come slowly up to ambient temperature and then stirred for another 30 min. After the further addition of water the organic solvent was distilled off in vacuo and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried and evaporated down in vacuo.

5 Yield 0.9 g (76 %) **3-d**.

RT (HPLC-MS) = 2.03 min

RT (HPLC 1) = 3.22 min

Preparation of **3-e**:

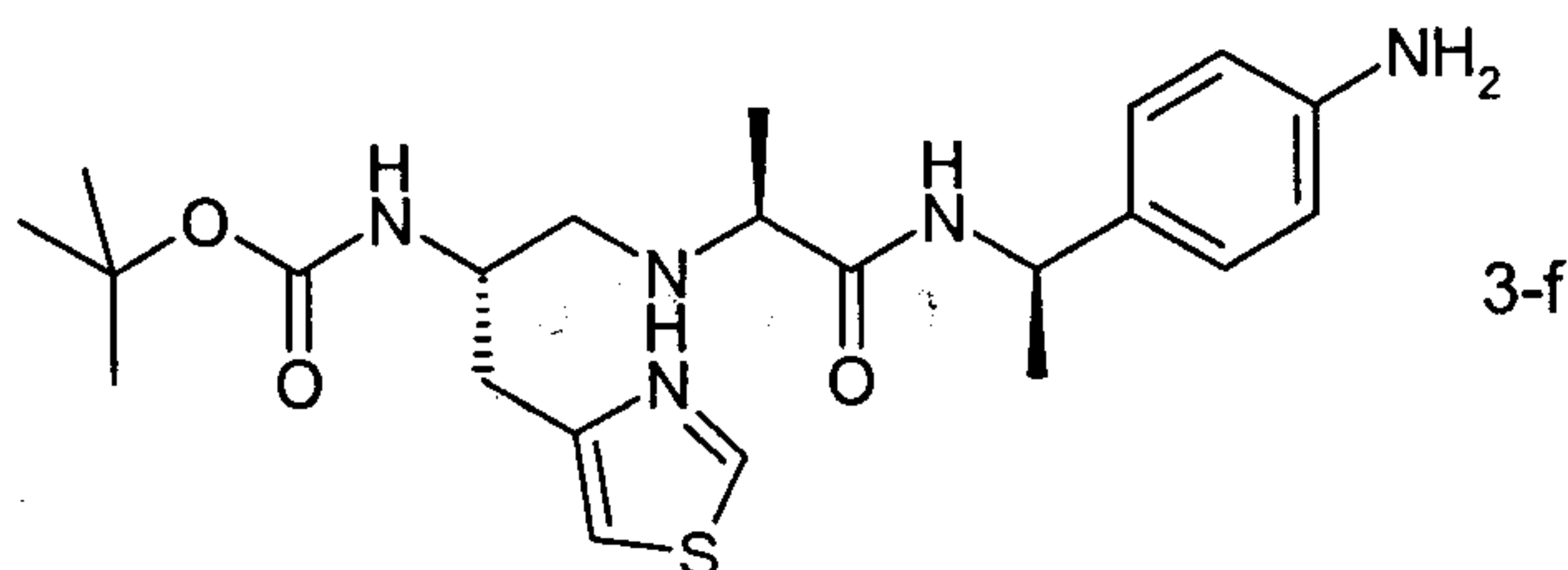


10

The preparation of **3-e** was carried out analogously to **1-a**. 0.20 g (0.77 mmol) **3-d** and the corresponding amount of Dess-Martin periodinane were used.

Yield: 0.18 g (91 %) **3-e**.

15 Preparation of **3-f**:



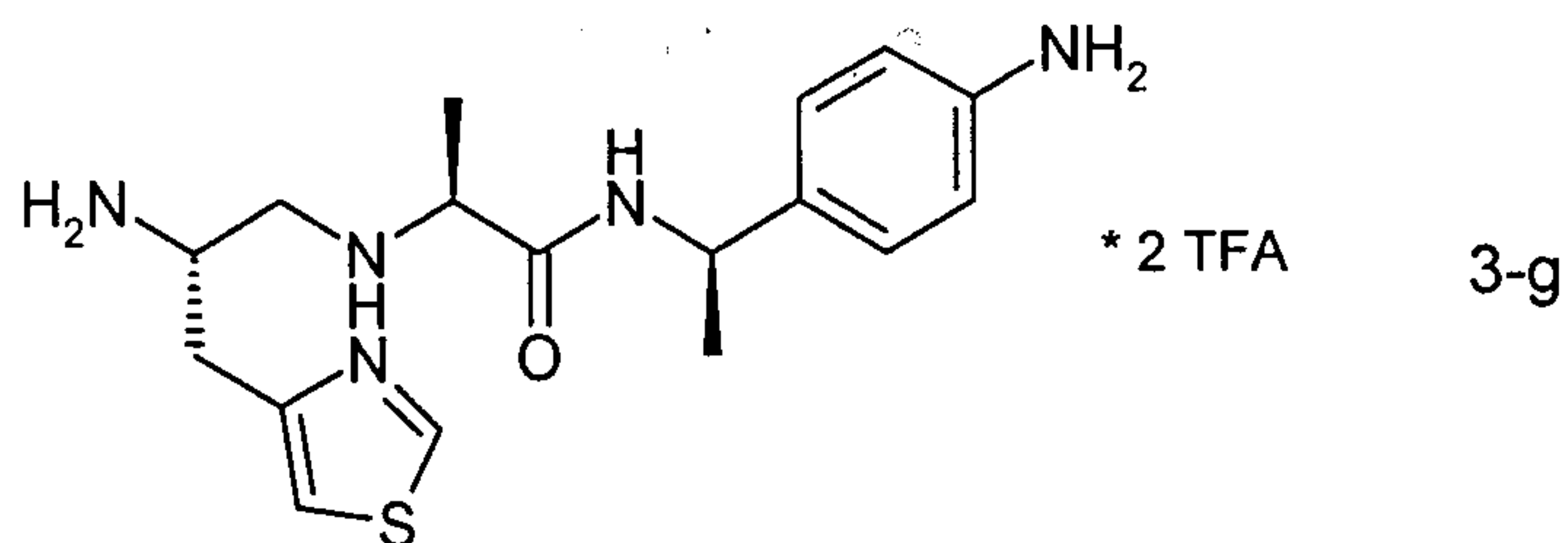
The preparation of **3-f** was carried out analogously to **1-b** starting from 200 mg (0.62 mmol) **3-c** and 150 mg (0.59 mmol) **3-e**.

Yield: 25 mg (9 %) **3-f**

20 RT (HPLC-MS) = 2.00 min

ES-MS (M+H)+ = 448

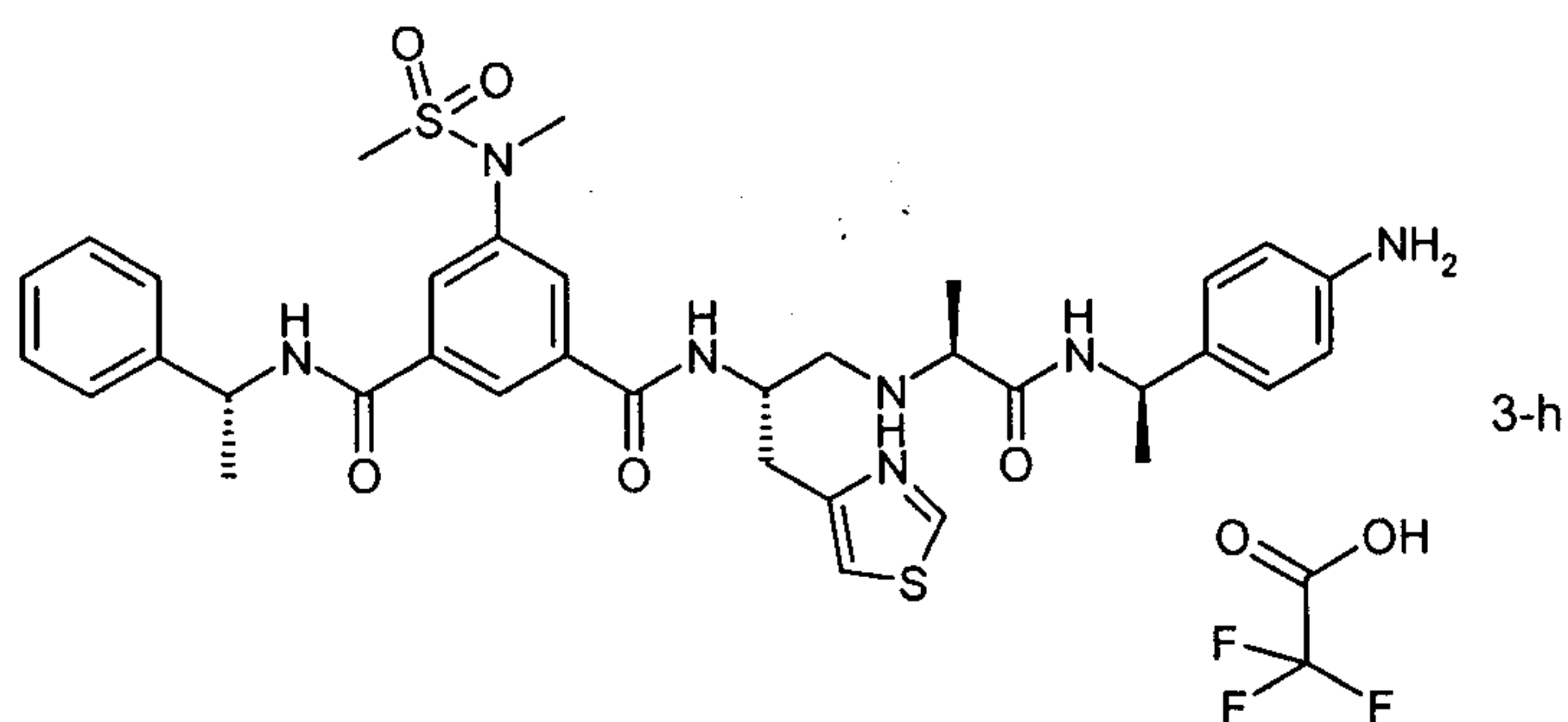
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Preparation of **3-g**:

The preparation of **3-g** was carried out analogously to **3-c** starting from 25 mg (0.056 mmol) **3-f**.

5 Yield: 25 mg (97 %) **3-g**.

ES-MS (M+H)⁺ = 348

Preparation of **3-h**:

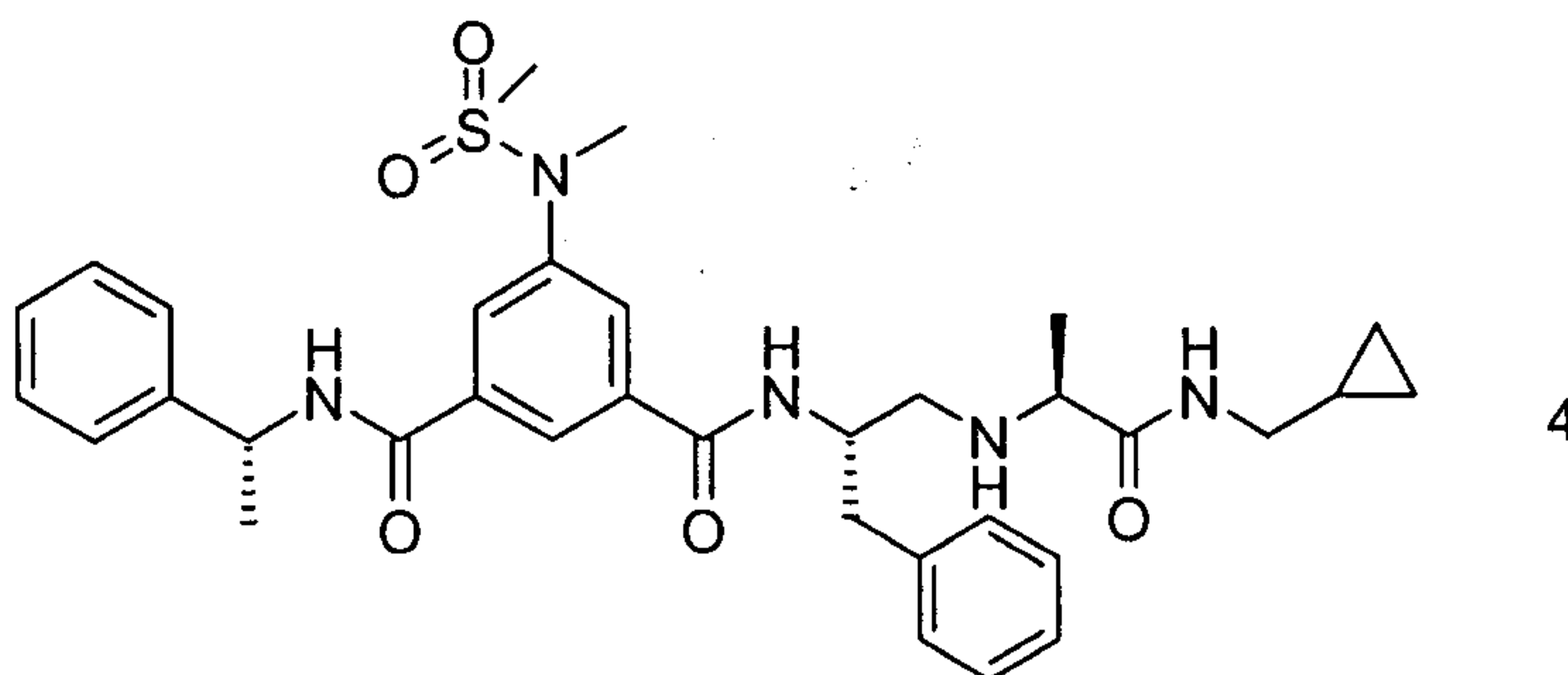
10

3-h was prepared analogously to **1-g** from 22 mg (0.058 mmol) **1.8-h** and 25 mg (0.054 mmol) **3-g** in 5 ml of tetrahydrofuran.

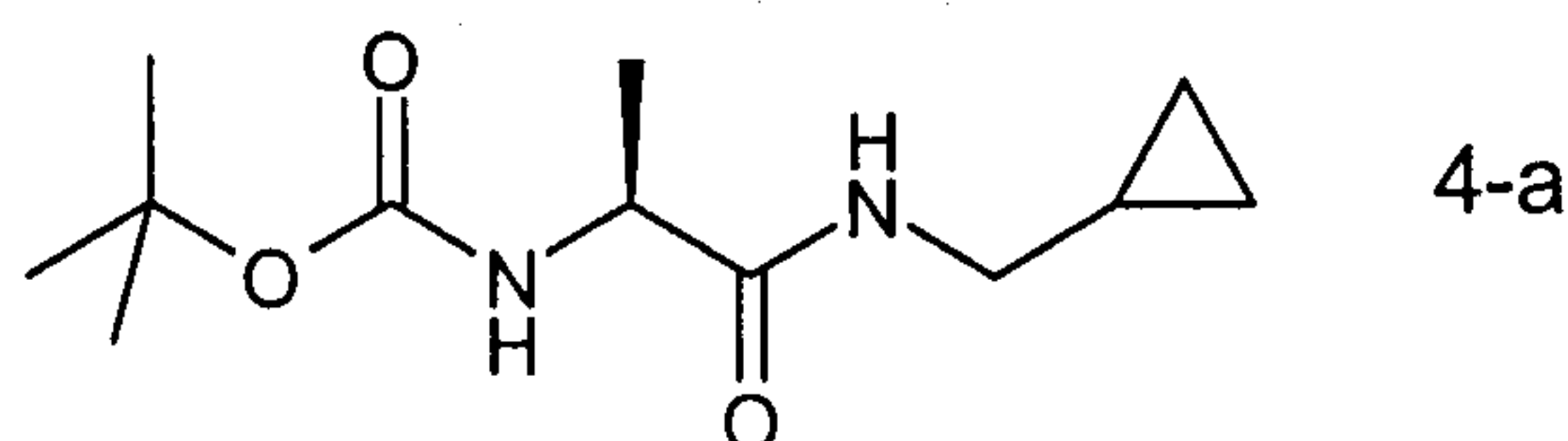
Yield 8 mg (17 %) **3-h**.

ES-MS (M+H)⁺ = 707

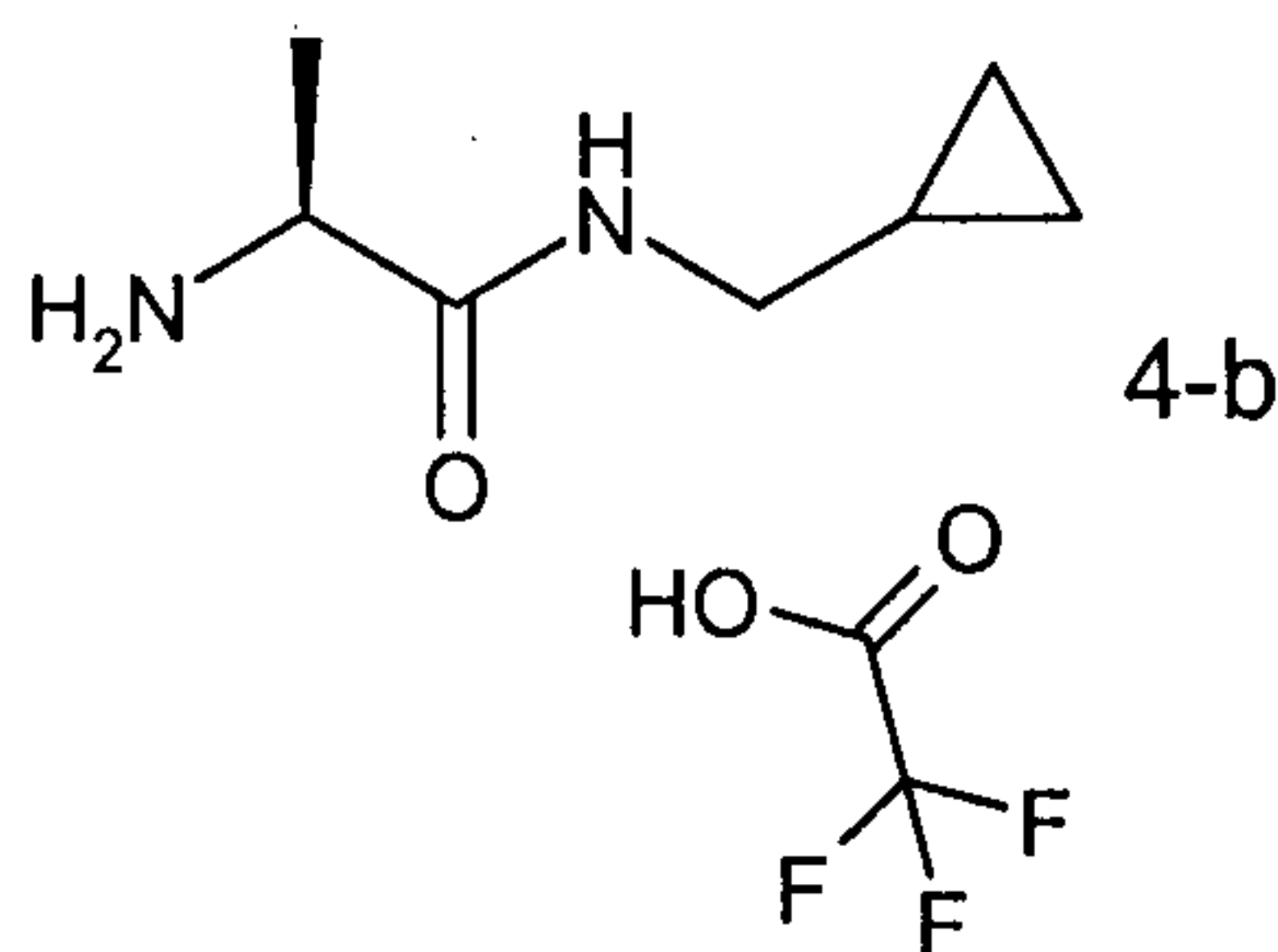
15

Preparation of **4**

- 114 -

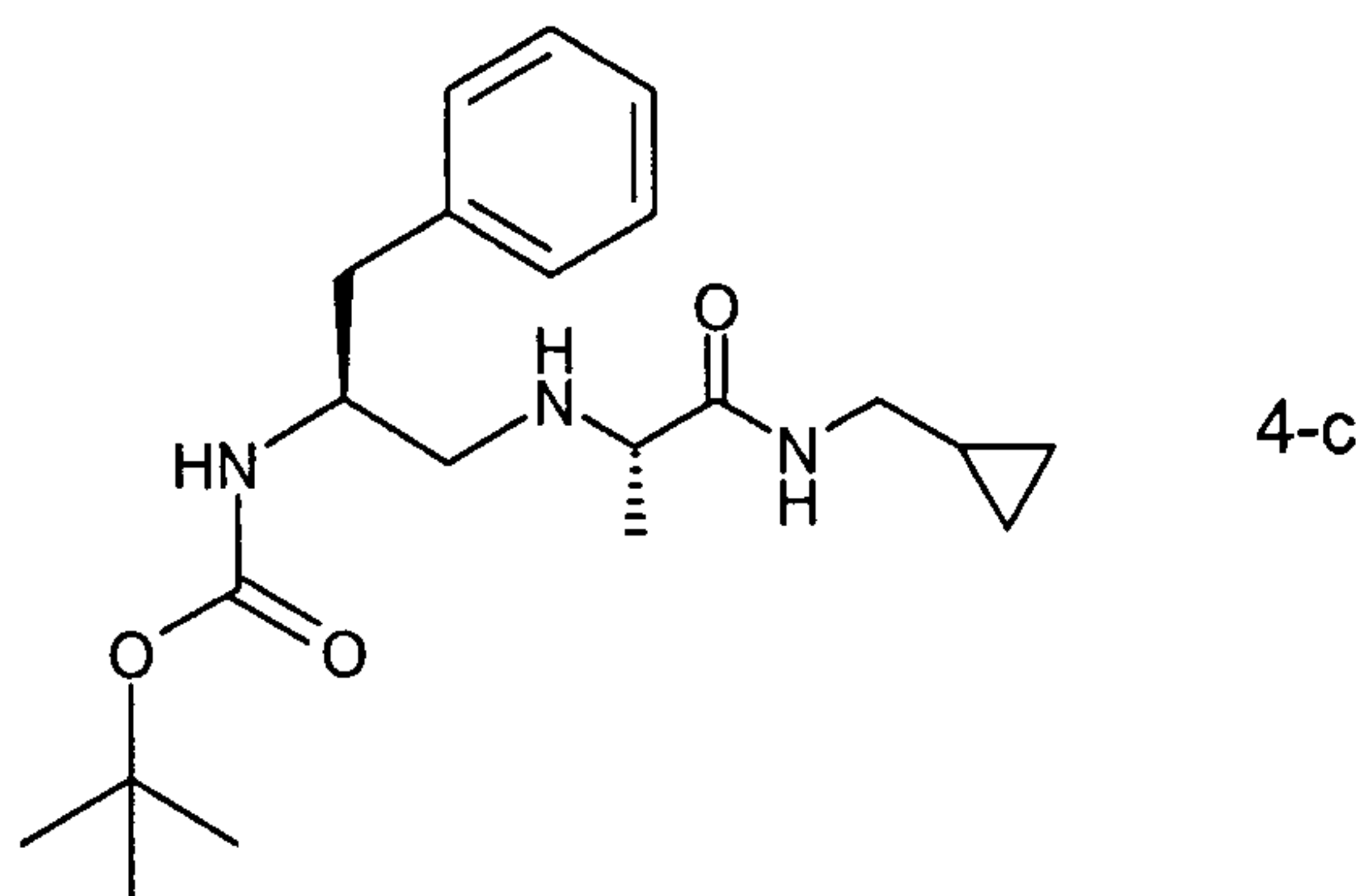
Preparation of **4-a**:

- 5 9.46 g (50.0 mmol) BOC-L-alanine were combined in 120 ml dichloromethane with 16.1 g (50.0 mmol) TBTU and 25.5 ml (15.0 mmol) DIPEA while cooling with an ice bath, then 5.38 g (50.0 mmol) cyclopropylmethylamine-hydrochloride were added. The reaction solution was stirred for 5 hours at ambient temperature and then extracted with 20% KHCO₃ solution and water. The organic phases were separated
10 off through a phase separation cartridge and evaporated to dryness in vacuo. Yield: 12.8 g (95%) of a colourless oil **4-a**. RT (HPLC-MS) = 2.48 min

Preparation of **4-b**:

- 15 29.0 g (0.1 mol) **4-a** was dissolved in 130 ml dichloromethane and combined with 100 ml (1.3 mol) trifluoroacetic acid. The reaction solution was stirred for 1 h at ambient temperature, then evaporated to dryness using the rotary evaporator. Yield: quantitative **4-b** as a yellow oil.

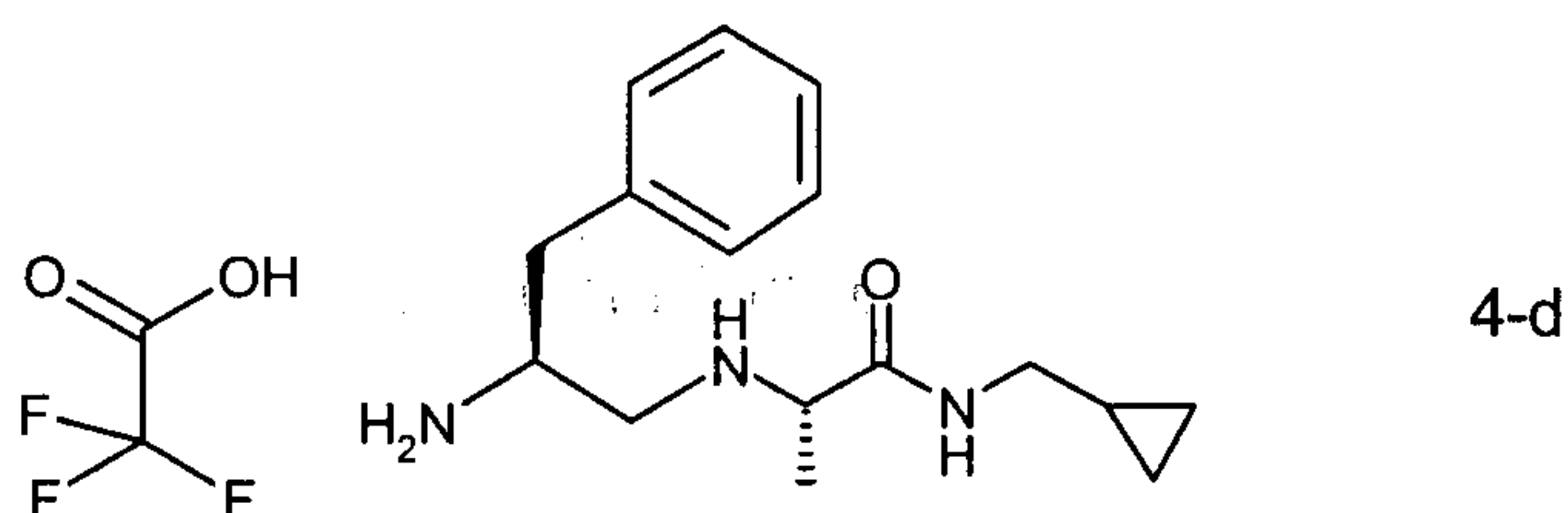
- 115 -

Preparation of **4-c**:

15.4 g (61.2 mmol) **4-b** were dissolved in 200 ml acetonitrile and combined with 10.5
5 ml (61.2 mmol) DIPEA. The mixture was stirred for 10 min at ambient temperature,
15.3 g (61.2 mmol) **1-a** were added and the mixture was cooled to 0°C. Then the
reaction solution was combined with 7.0 ml (122 mmol) acetic acid and 20.5 g (91.8
mmol) sodium triacetoxyborohydride and left overnight at ambient temperature with
stirring. The reaction solution was evaporated to dryness using the rotary evaporator
10 and the residue was combined with dichloromethane and 1N NaHCO₃ solution. The
phases were separated, the organic phase was dried and evaporated to dryness i.
vac.. The residue was purified by chromatography on silica gel with the eluant (ethyl
acetate/heptane 7:3 to ethyl acetate/heptane 1:0).

Yield 13.1 g (43%) light yellow crystals **4-c**.

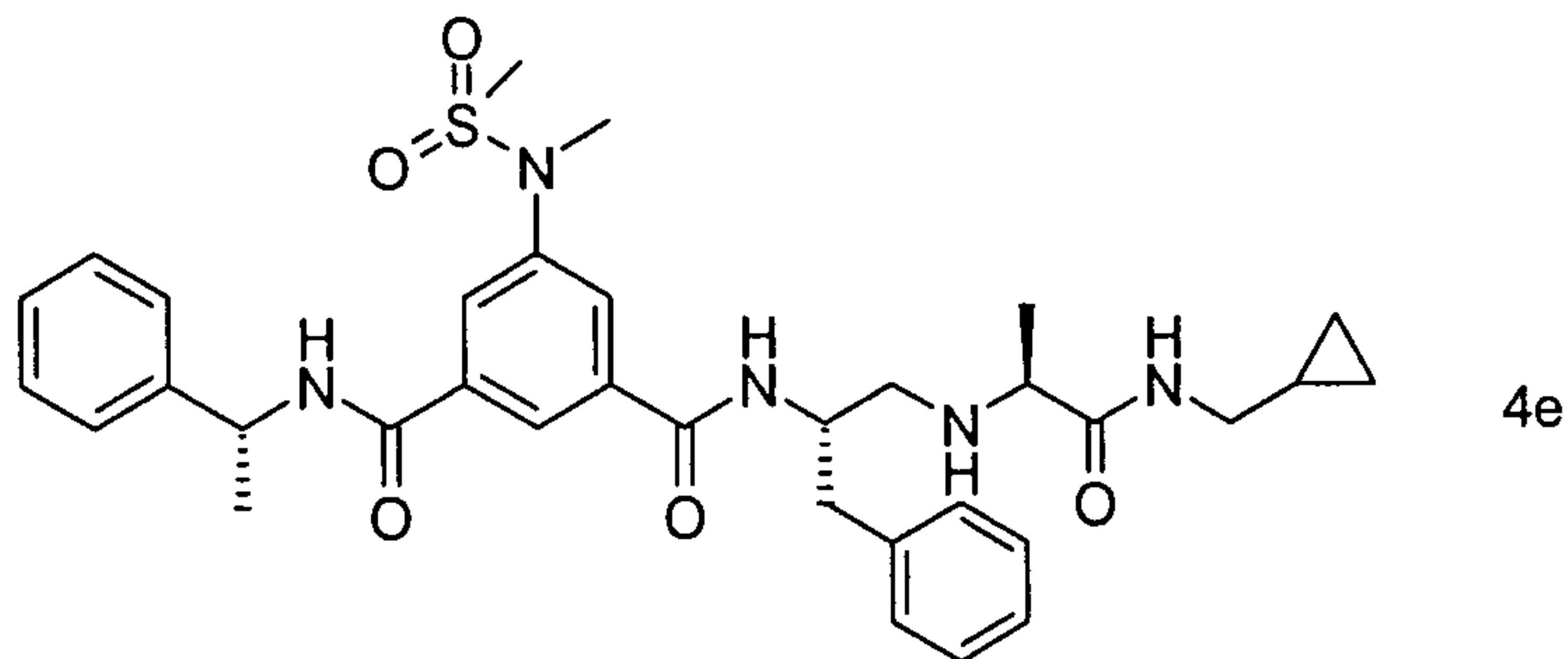
RT (HPLC 1) = 4.36 min

ES-MS (M+H)⁺ = 376Preparation of **4-d**:

2.59 g (6.90 mmol) **4-c** was dissolved in 37 ml dichloromethane and combined with
7.4 ml (96.6 mmol) trifluoroacetic acid. Then the reaction solution was stirred for 3 h
at ambient temperature, and then evaporated to dryness using the rotary evaporator.
Yield: quantitative **1-d** as a colourless oil.

RT (HPLC 1) = 3.37 min

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Preparation of **4-e**:

4-e was prepared analogously to **1-g** starting from 82.0 mg (0.218 mmol) **1.8-h** and 84.8 mg (0.218 mmol) **4-d**. The crude product was purified using Flashmaster (20-g-column) with DCM : MeOH 100% to 95/5 (run time 35 min).

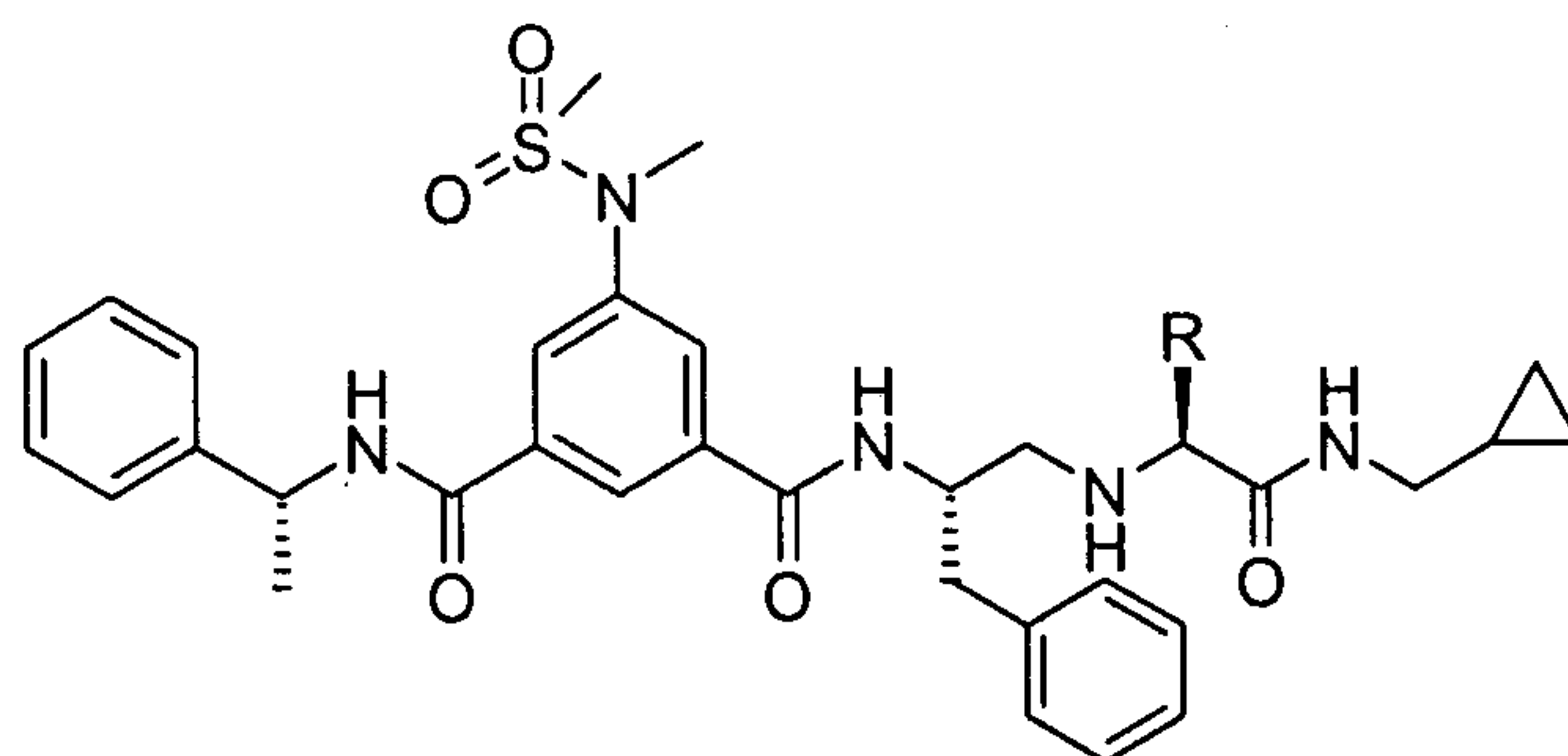
Yield 53 mg (38 %) **4-e**.

RT (HPLC-MS) = 2.83 min

ES-MS (M+H)⁺ = 634

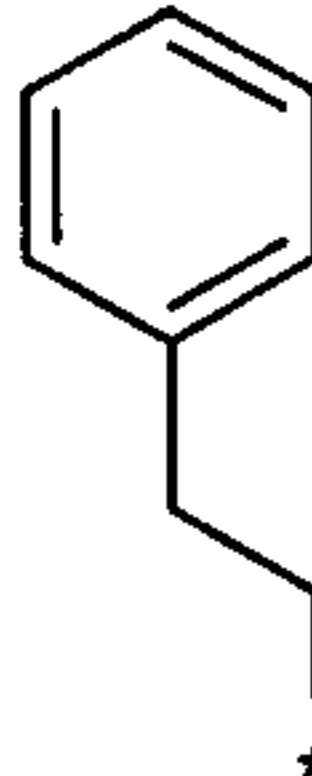
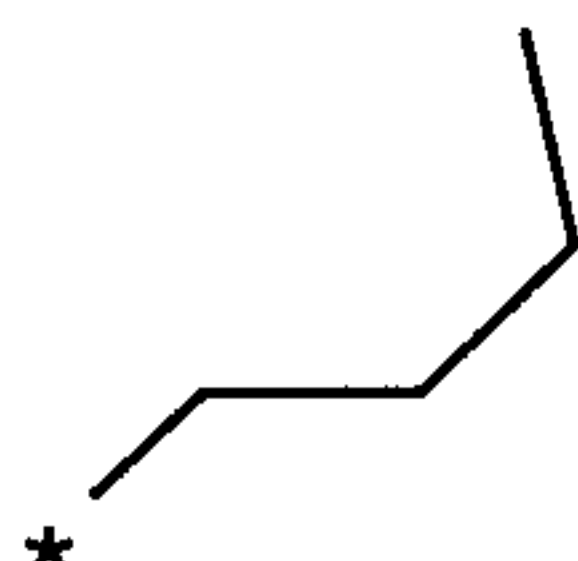
10

The following Examples were prepared analogously to **4**:



Example	R	MS	RT HPLC-MS
4.2		703 (M+H) ⁺	
4.3		658 (M+H) ⁺	
4.4		653 (M+H) ⁺	

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4.5		663 (M+H) ⁺	2.98 min
4.6		724 (M+H) ⁺	3.17 min
4.7		662 (M+H) ⁺	2.95 min
4.8		676 (M+H) ⁺	1.51 min

To this end, for **4.2**, 230 mg (0.895 mmol) of L-2-tert-butoxycarbonylamino-4,4,4-trifluorobutyric acid and 69 mg (0.976 mmol) cyclopropylmethylamine were used analogously to **4-a**.

5

For **4.3** 200 mg (0.938 mmol) BOC-L-propargylglycine and 73 mg (1.03 mmol) cyclopropylmethylamine were used analogously to **4-a**.

For **4.4** 240 mg (1.16 mmol) L-2-tert-butoxycarbonylamino-3-fluoropropionic acid and
10 90 mg (1.26 mmol) cyclopropylmethylamine were used analogously to **4-a**.

For **4.5** 400 mg (1.84 mmol) BOC- L-norvaline and 131 mg (1.84 mmol) cyclopropylmethylamine were used analogously to **4-a**.

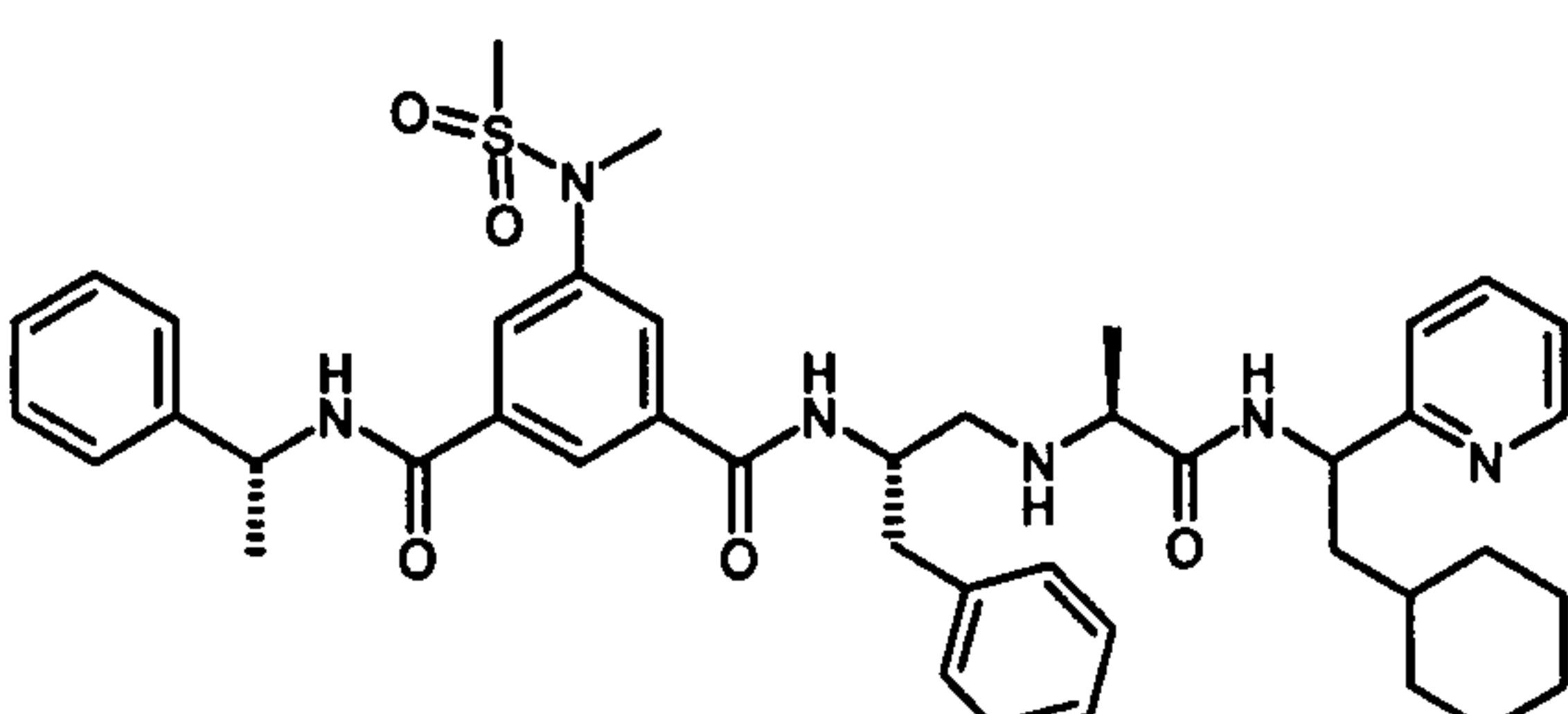
15 For **4.6** 400 mg (1.43 mmol) BOC- L-phenylalanine and 102 mg (1.43 mmol) cyclopropylmethylamine were used analogously to **4-a**.

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The synthesis of **4.7** was carried out analogously to **4** starting from 300 mg (0.856 mmol) 2-(S,S)-(2-tert-butoxycarbonylamino-3-phenylpropylamino)-3-methylbutyric acid and 73.4 μ L (0.856 mmol) cyclopropylmethylamine.

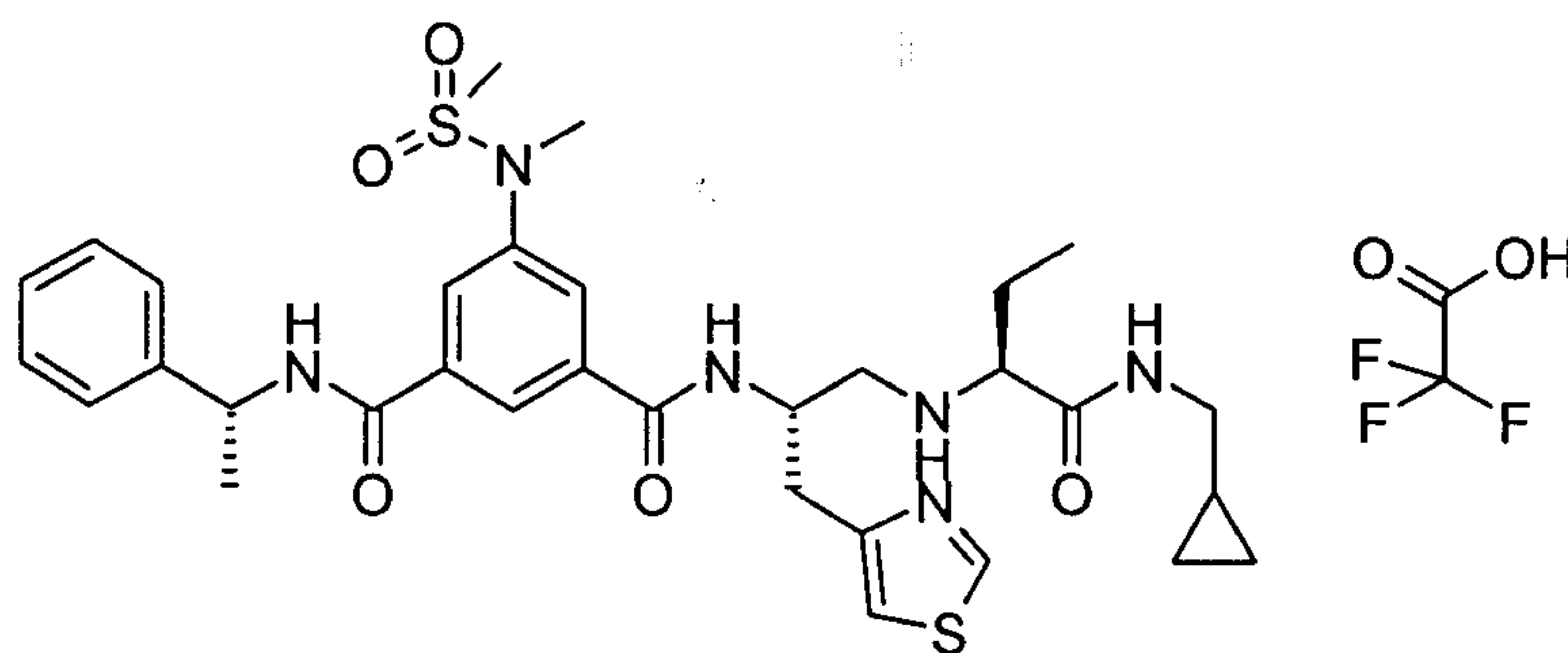
- 5 For **4.8** BOC- L-norleucine and cyclopropylmethylamine were used analogously to **4-a**.

Analogously to **Example 4** the following compounds were prepared by using the corresponding educts:

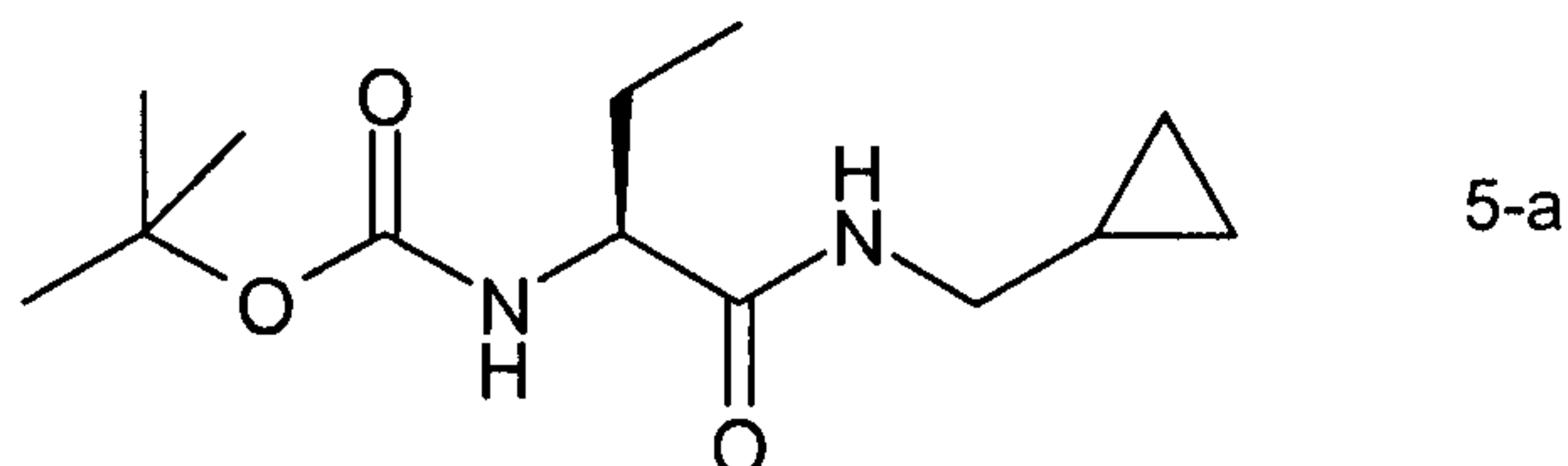
Example		
4.9		RT (HPLC1) = 4.70 min. ES-MS (M+H) ⁺ = 767

10

Example 5:



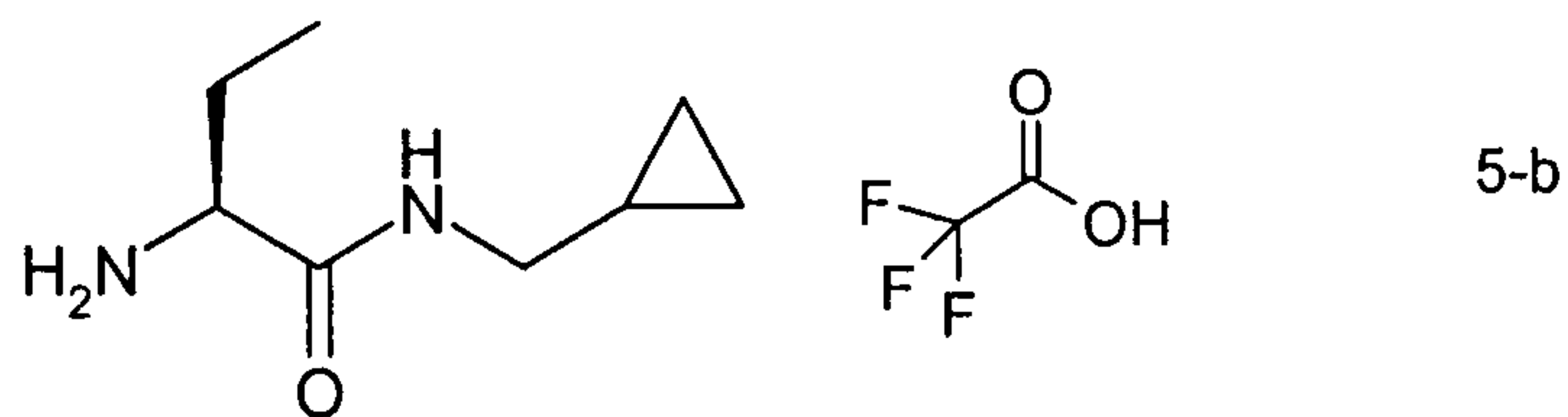
- 15 Preparation of **5-a**:



The synthesis of **5-a** was carried out analogously to **4-a** using 13.3 g (60.5 mmol) BOC-L-2-aminobutyric acid and 5.40 ml (60.5 mmol) cyclopropylmethylamine. The crude product was used directly in the next step.

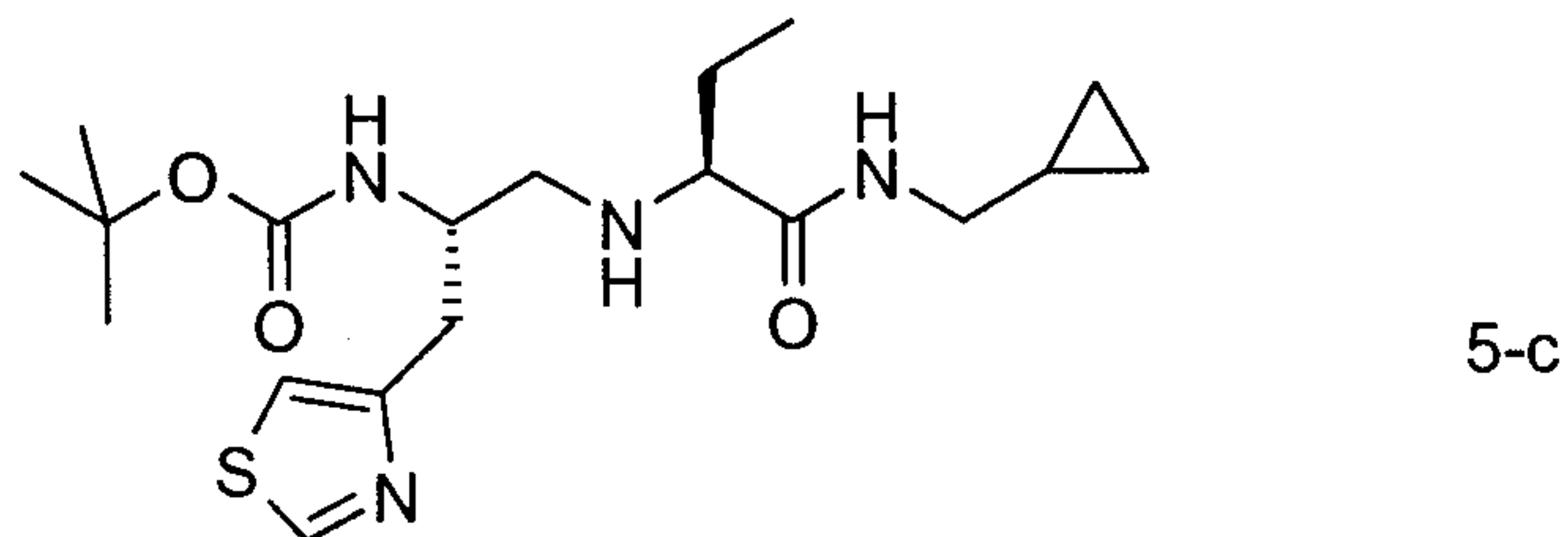
- 20 Yield 15.5 g (content 80 %) **5-a** as a reddish-brown oil

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Preparation of **5-b**:

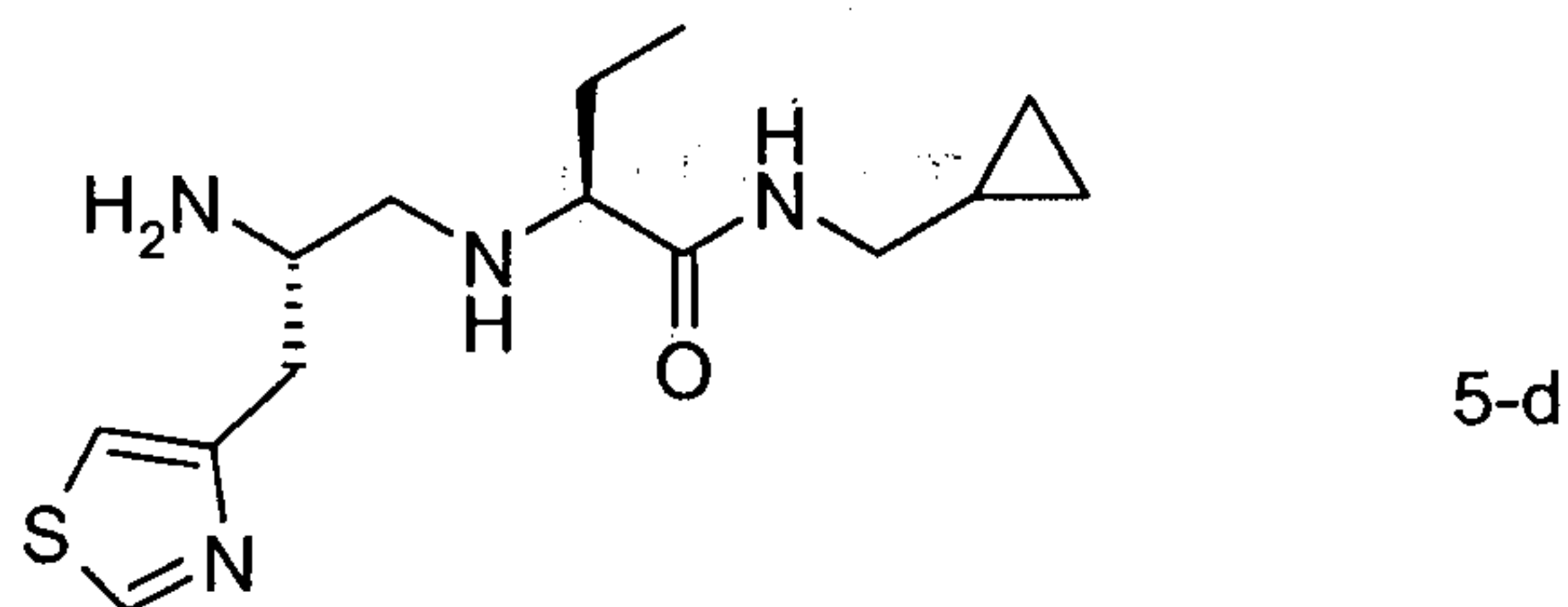
The synthesis of **5-b** was carried out analogously to **4-b** starting from 18.2 g (56.8 mmol) **5-a**. The crude product was used directly in the next step.

Yield: quantitative **5-b** as a reddish-brown oil

Preparation of **5-c**

5-c was synthesised analogously to **4-c** starting from 1.40 g (5.46 mmol) **3-e** and 1.50 g (5.55 mmol) **5-b**.

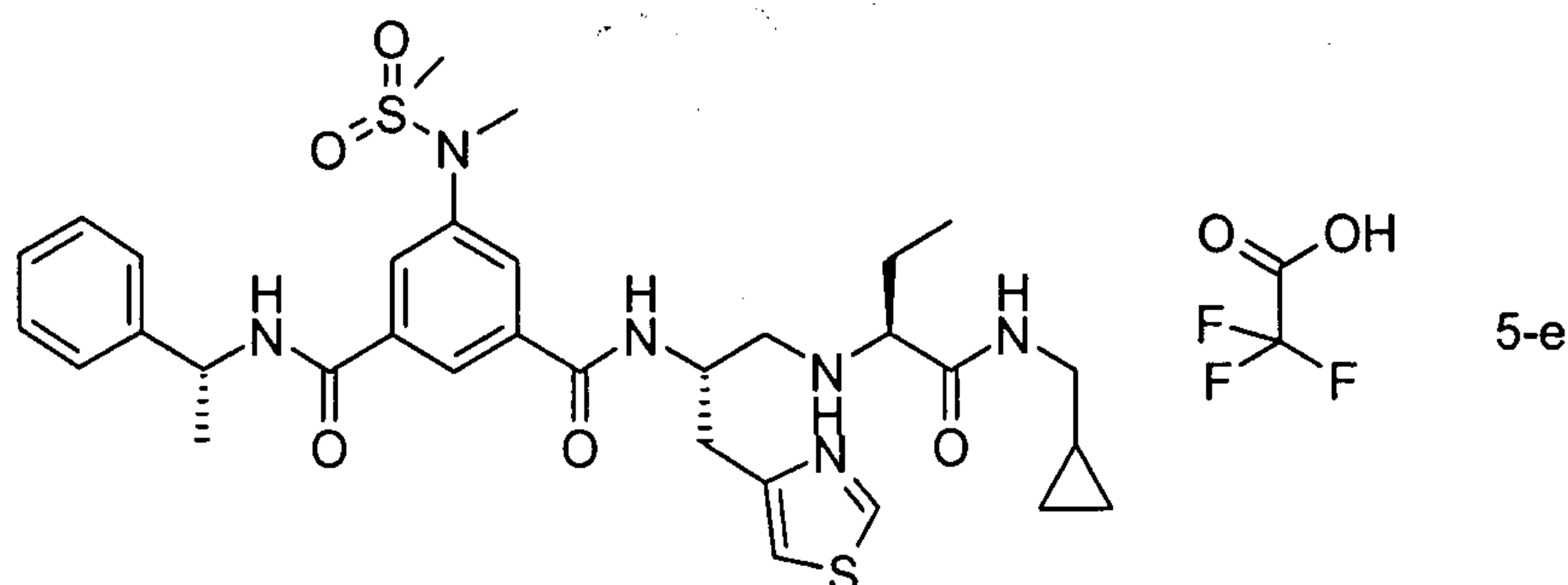
Yield: 800 mg (80 %) **5-c** as brown crystals

Preparation of **5-d**

5-d was prepared analogously to **4-d** starting from 46 mg (0.116 mmol) **5-c**.

Yield: 44 mg (100 %)

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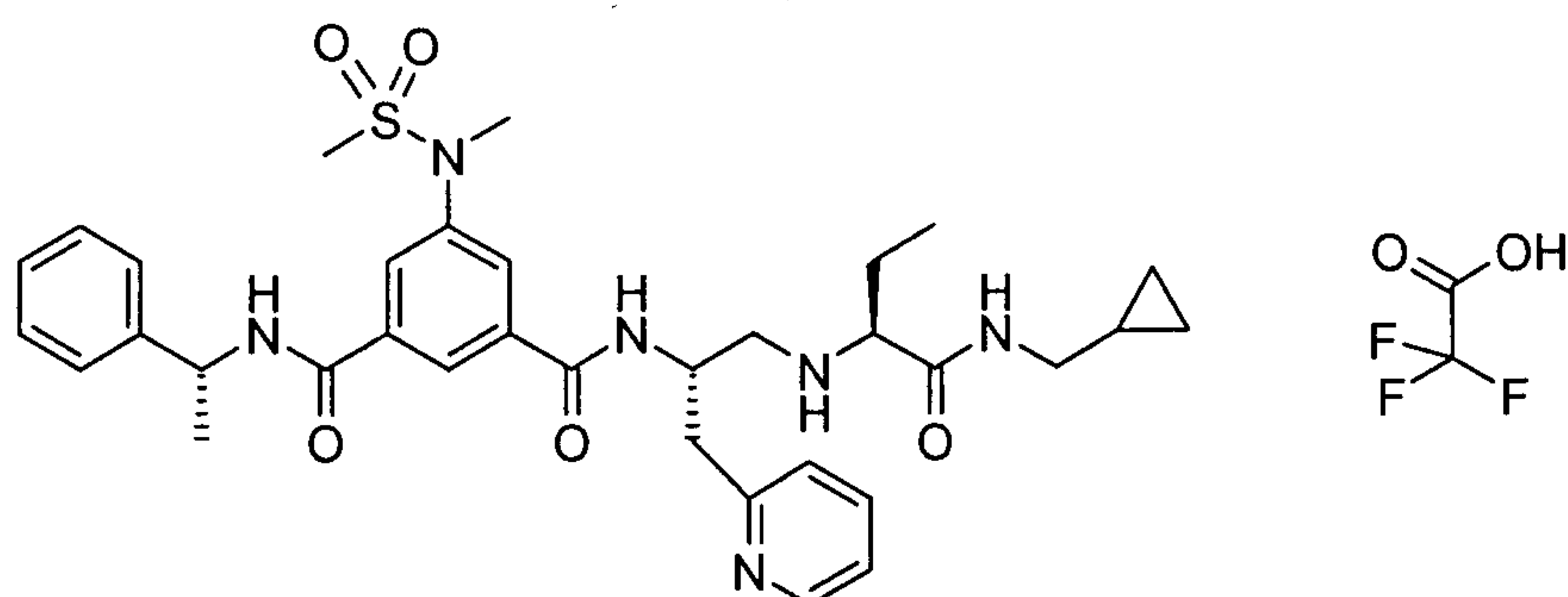
Preparation of **5-e**

5-e was prepared analogously to **1-g** starting from 56 mg (0.149 mmol) **1.8-h** and 44 mg (0.148 mmol) **5-d**.

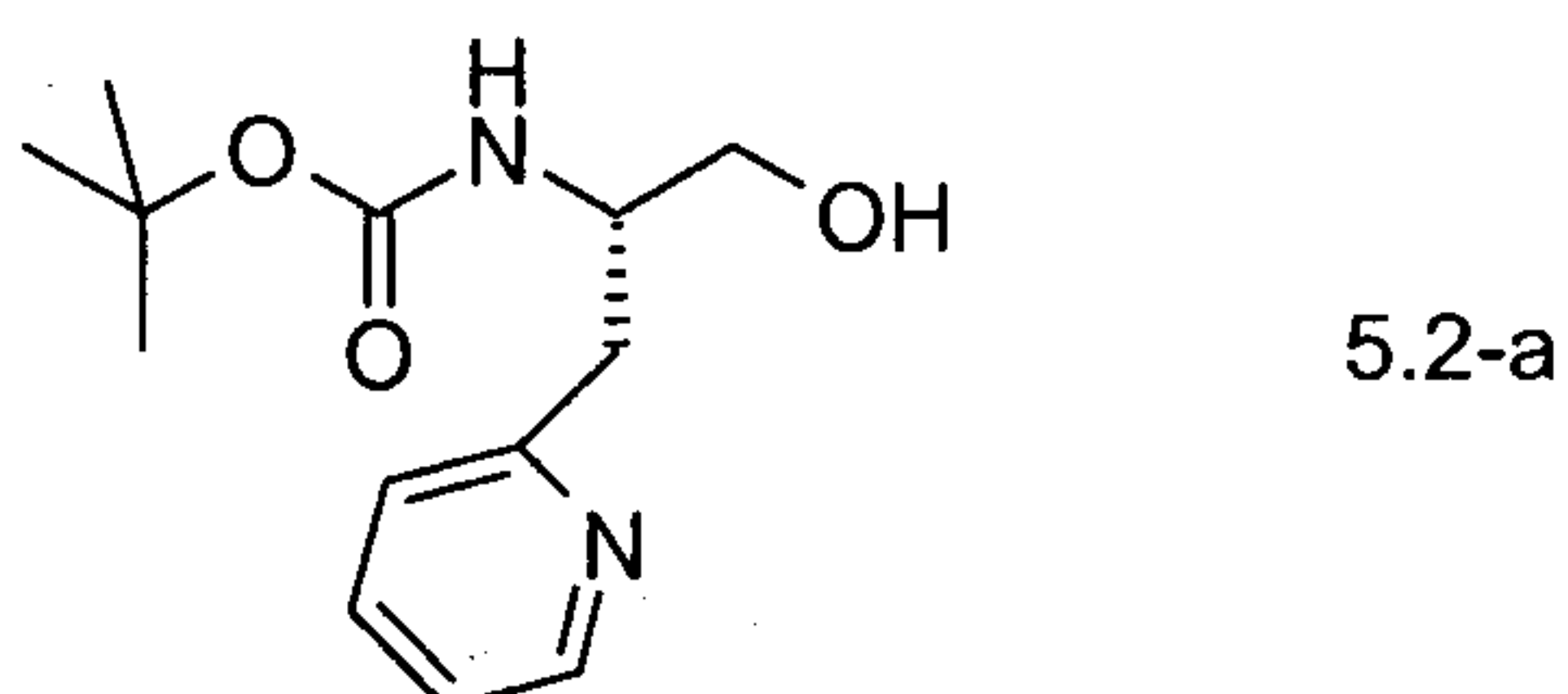
5 Yield: 23 mg (20 %) white solid

RT (HPLC-MS) = 2.59 min

ES-MS (M+H)⁺ = 655

Example **5.2**:

10

Preparation of **5.2-a**

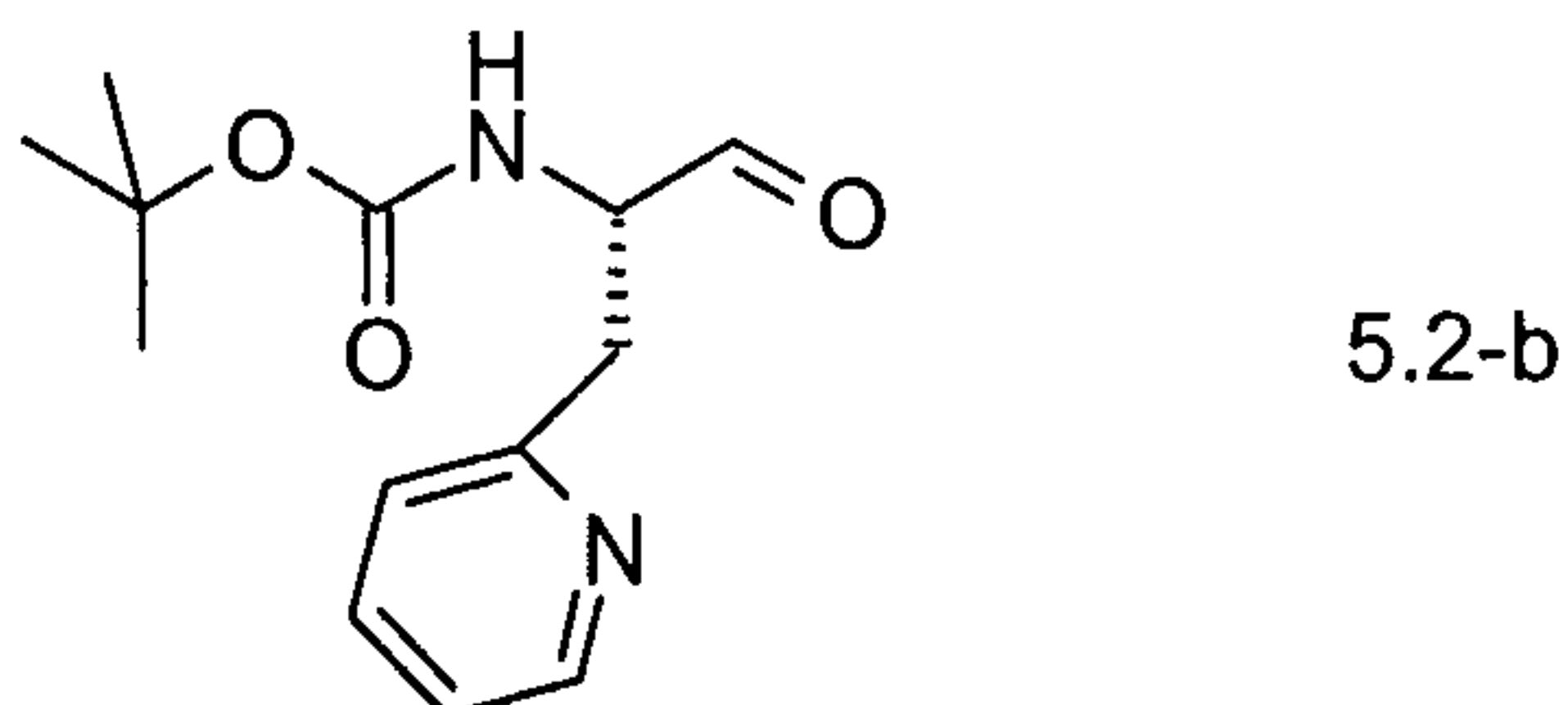
- 15 A solution of 500 mg (1.88 mmol) BOC-L-2-pyridylalanine in 20 ml THF was added dropwise at 0°C to 4 ml (4 mmol) of a 1 M solution of LiAlH₄ in THF. The mixture was allowed to warm up to ambient temperature and hydrolysed after 1 h by the addition of 0.15 ml of water, 0.19 ml NaOH solution and another 0.66 ml of water. The precipitate

– 121 –

formed was washed with water. The filtrate is freed from THF in vacuo, the residue is extracted with dichloromethane and evaporated down in vacuo.

Yield: 410 mg (87 %) **5.2-a**

5 Preparation of **5.2-b**

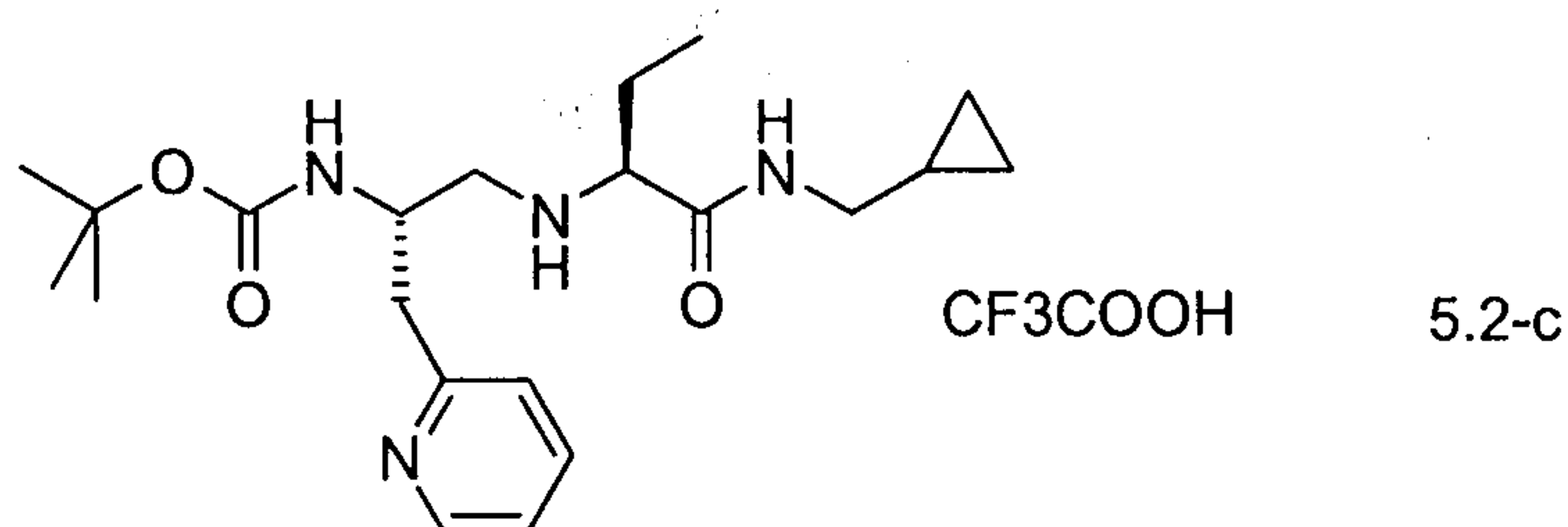


5.2-b was synthesised analogously to **1-a** starting from and 1.00 g (3.96 mmol) **5.2-a** and 2.69 g (6.34 mmol) Dess-Martin periodinane.

Yield: 1.0 g (content: 90 %) **5.2-b**

10

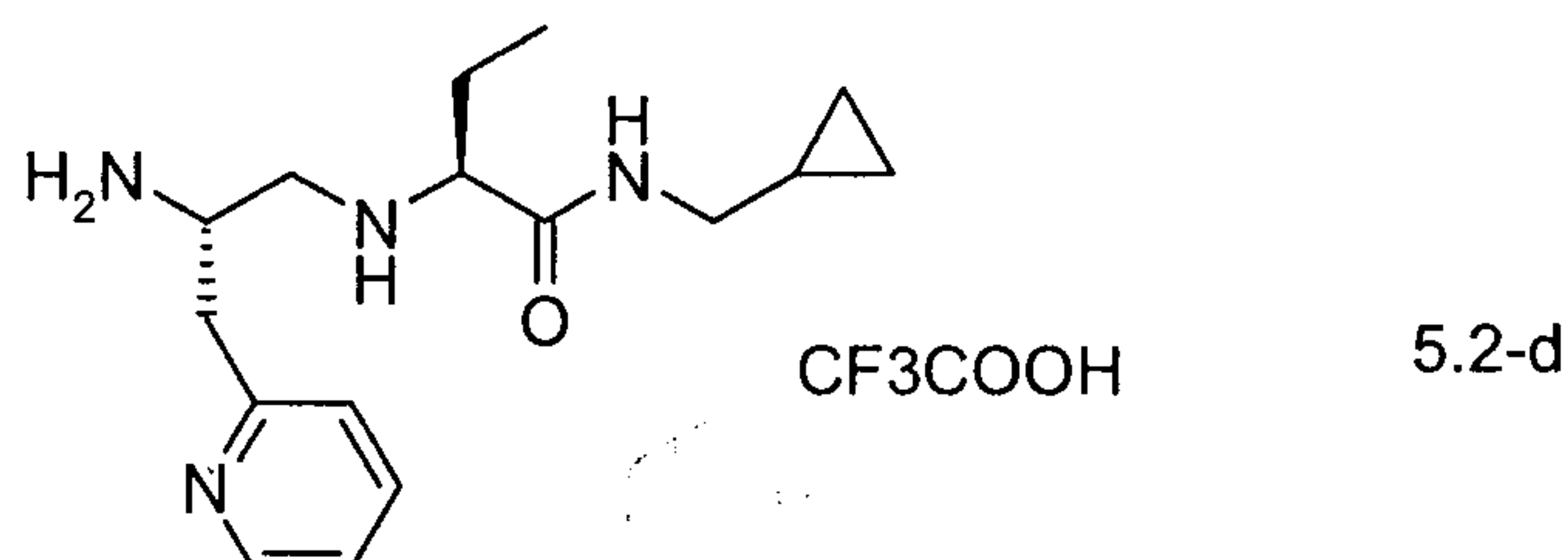
Preparation of **5.2-c**



5.2-c was synthesised analogously to **4-c** starting from 1.00 g (90 percent, 3.60 mmol) **5.2-b** and 972 mg (3.60 mmol) **5-b**. The crude product is purified by HPLC-2.

15 Yield: 730 mg (40 %) **5.2-c**

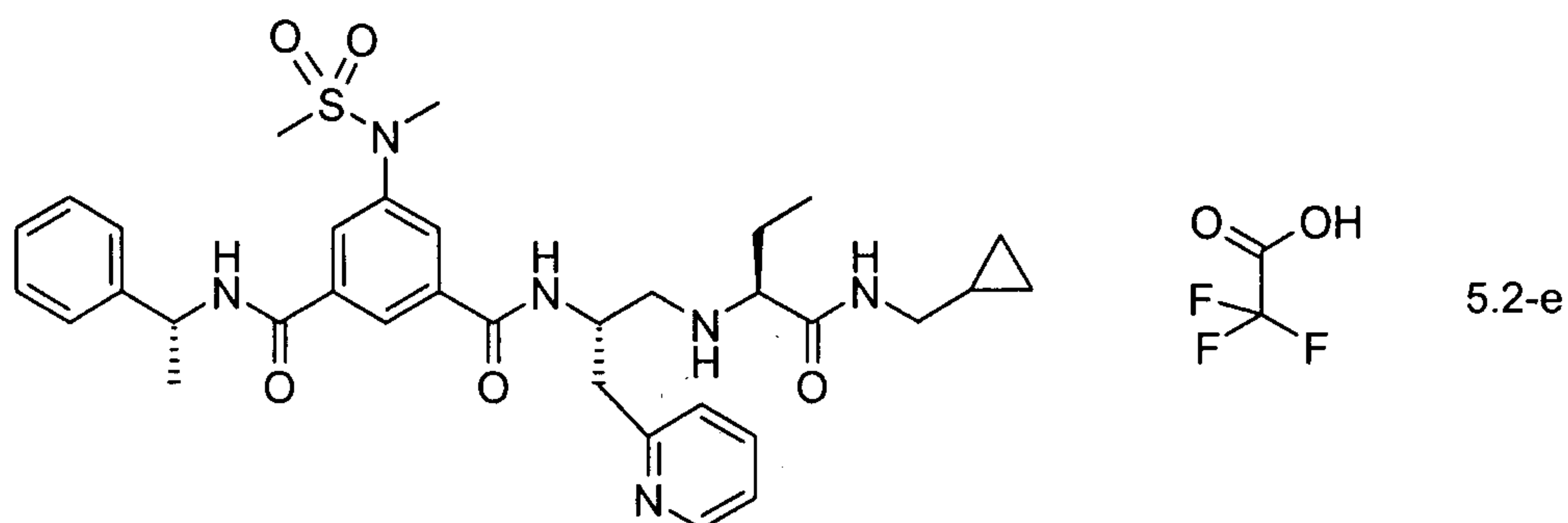
Preparation of **5.2-d**



5.2-d was prepared analogously to **4-d** starting from 730 mg (1,45 mmol) **5.2-c**.

20 Yield: 585 mg (100 %)

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Preparation of **5.2-e**

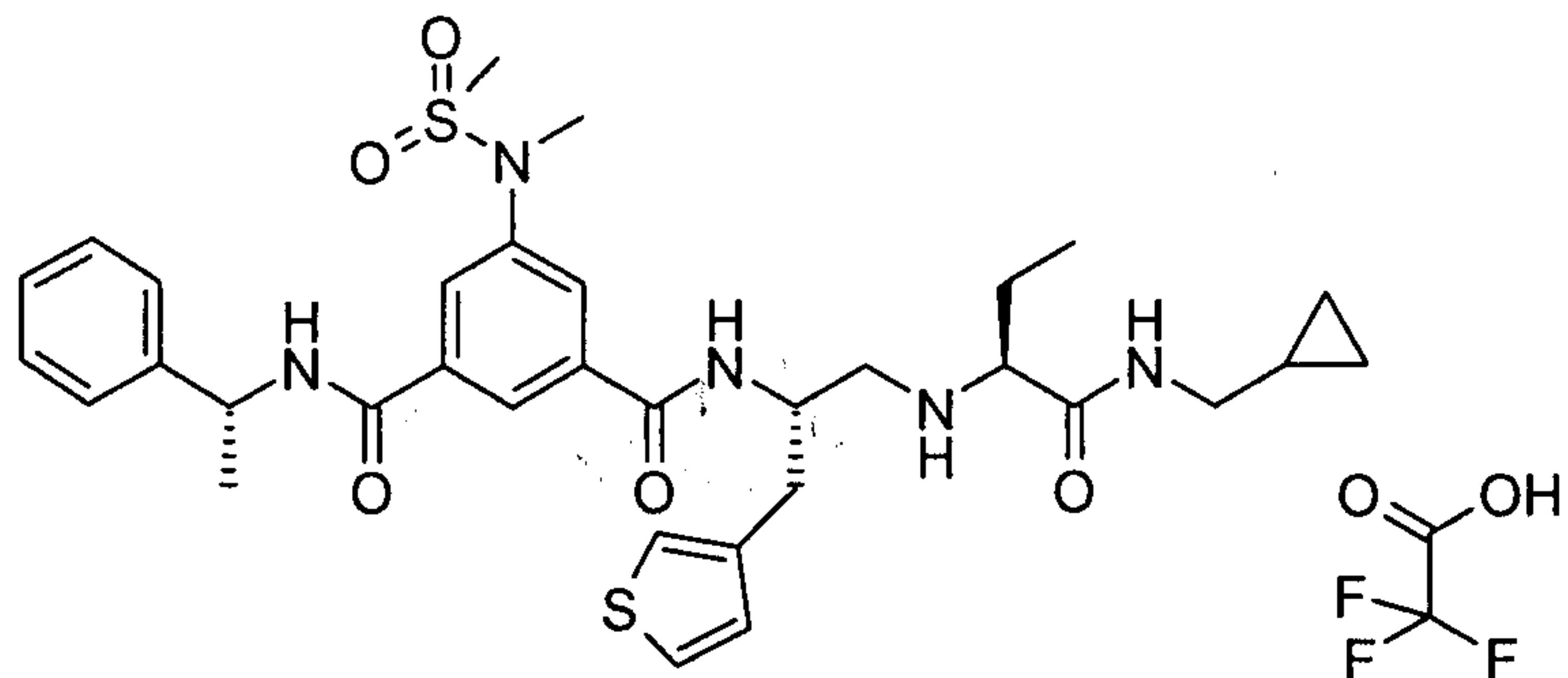
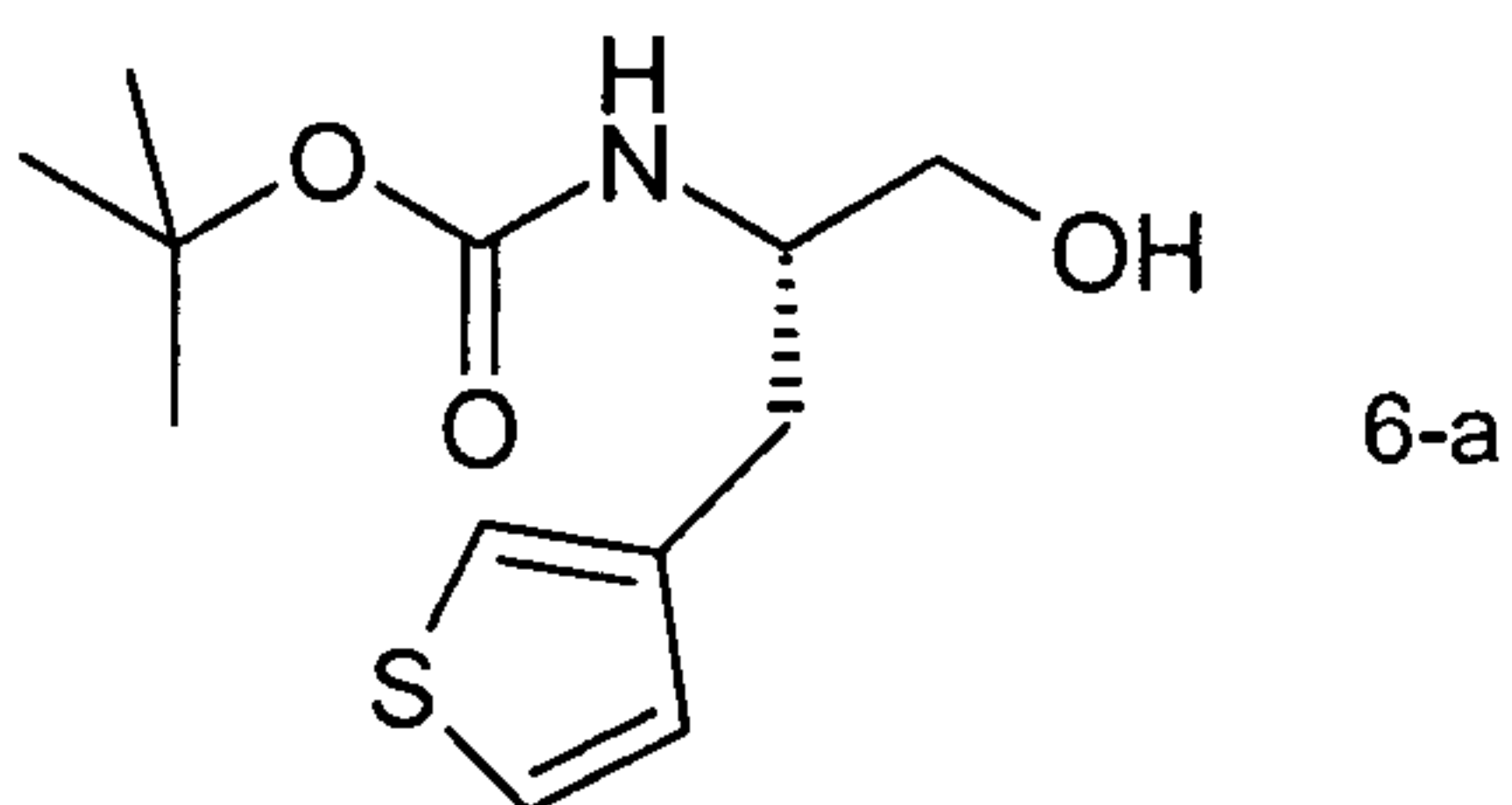
5.2-e was prepared analogously to **1-g** starting from 61.1 mg (0.148 mmol) **1.8-h** and
5 60 mg (0.148 mmol) **5.2-d**.

Yield: 37 mg (33 %) white solid

RT (HPLC-MS) = 2.44 min

ES-MS (M+H)⁺ = 649

10 Example 6:

Preparation of **6-a**

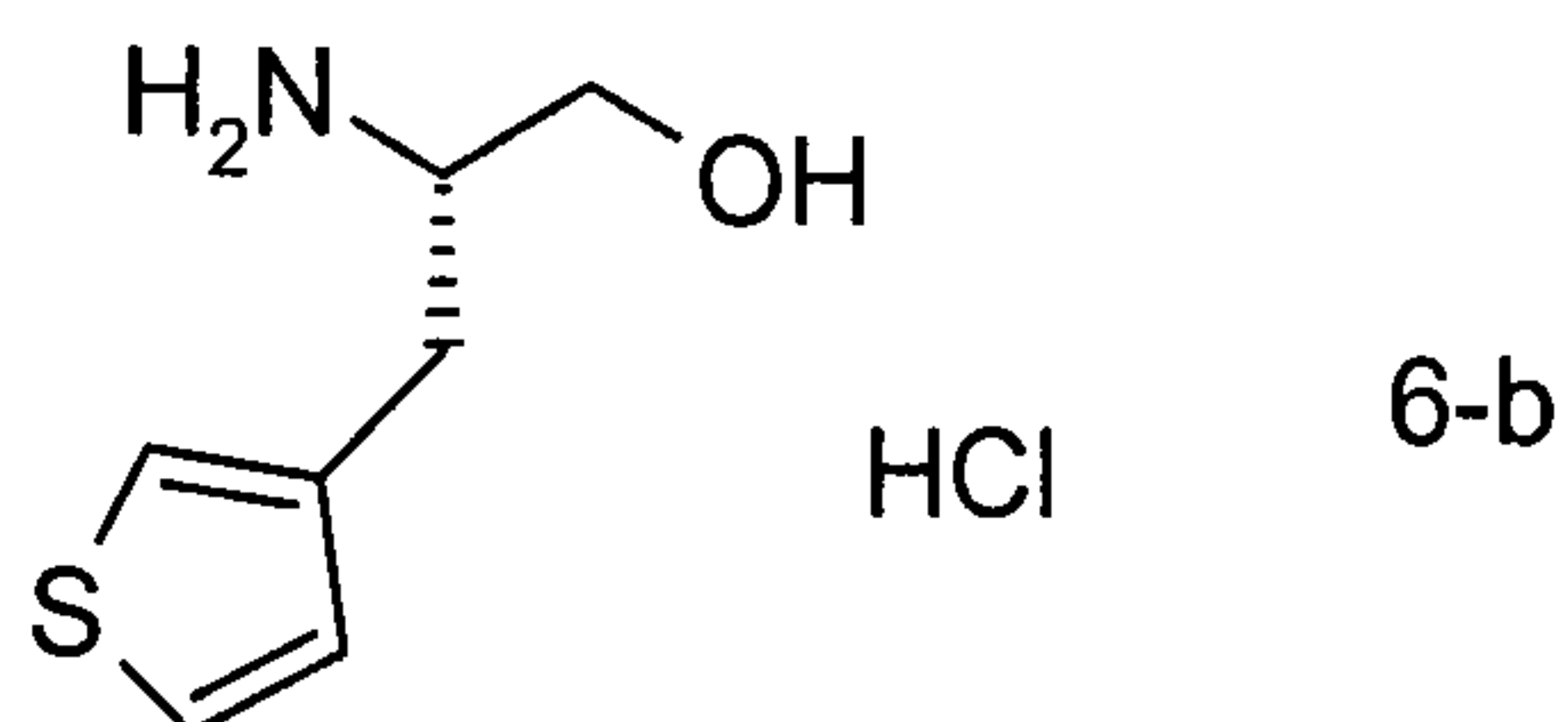
15 **6-a** was prepared analogously to **3-d** starting from 1.00 g (3.69 mmol) BOC-L-3-thienylalanine and 84.8 mg (0.218 mmol) **4-d**.

Yield 900 mg (96 %) **6-a** as an oil.

RT (HPLC-1) = 2.75 min

ES-MS (M+H)⁺ = 258

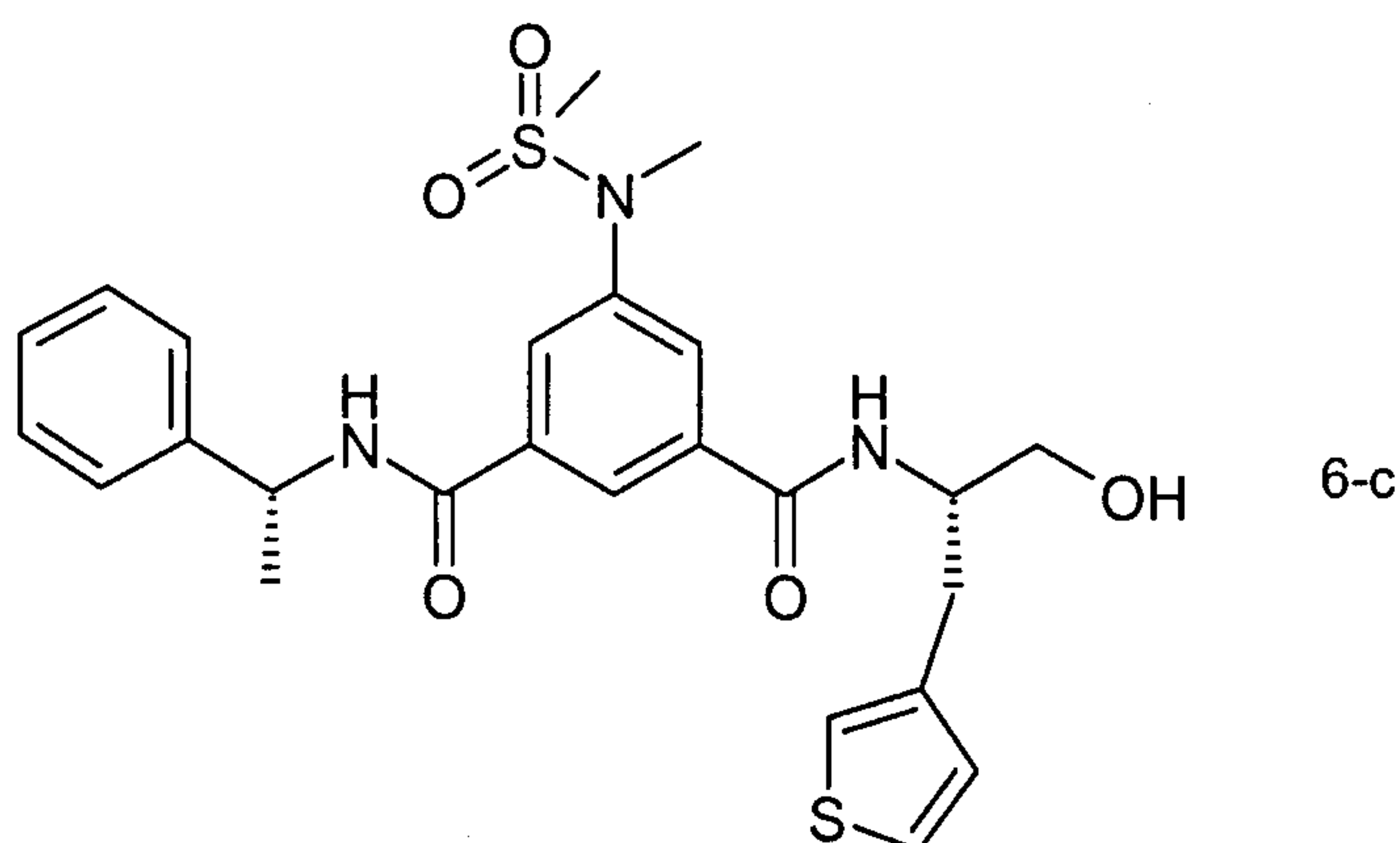
- 123 -

Preparation of **6-b**

6-b was prepared analogously to **1-c** starting from 300 mg (1.17 mmol) **6-a**. The reaction mixture was evaporated down, triturated with ether and the resinous product was separated off.

Yield 180 mg (80 %) **6-b**

RT (HPLC-1) = 1.44 min

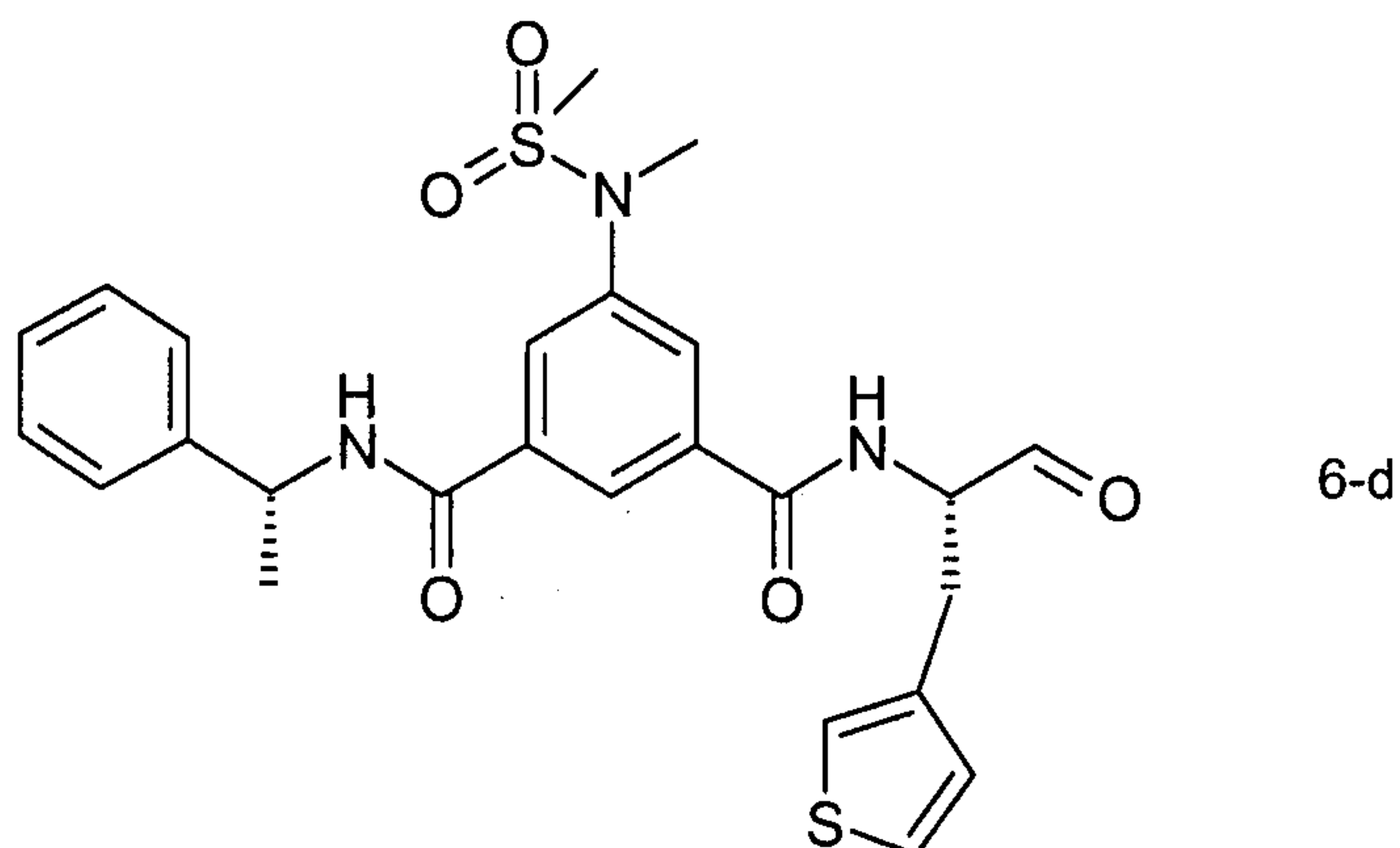
10 Preparation of **6-c**

6-c was prepared analogously to **1-g** starting from 320 mg (0.850 mmol) **1.8-h** and 180 mg (0.929 mmol) **6-b**.

Yield: 400 mg (91 %) **6-c**

15 RT (HPLC-1) = 2.88 min

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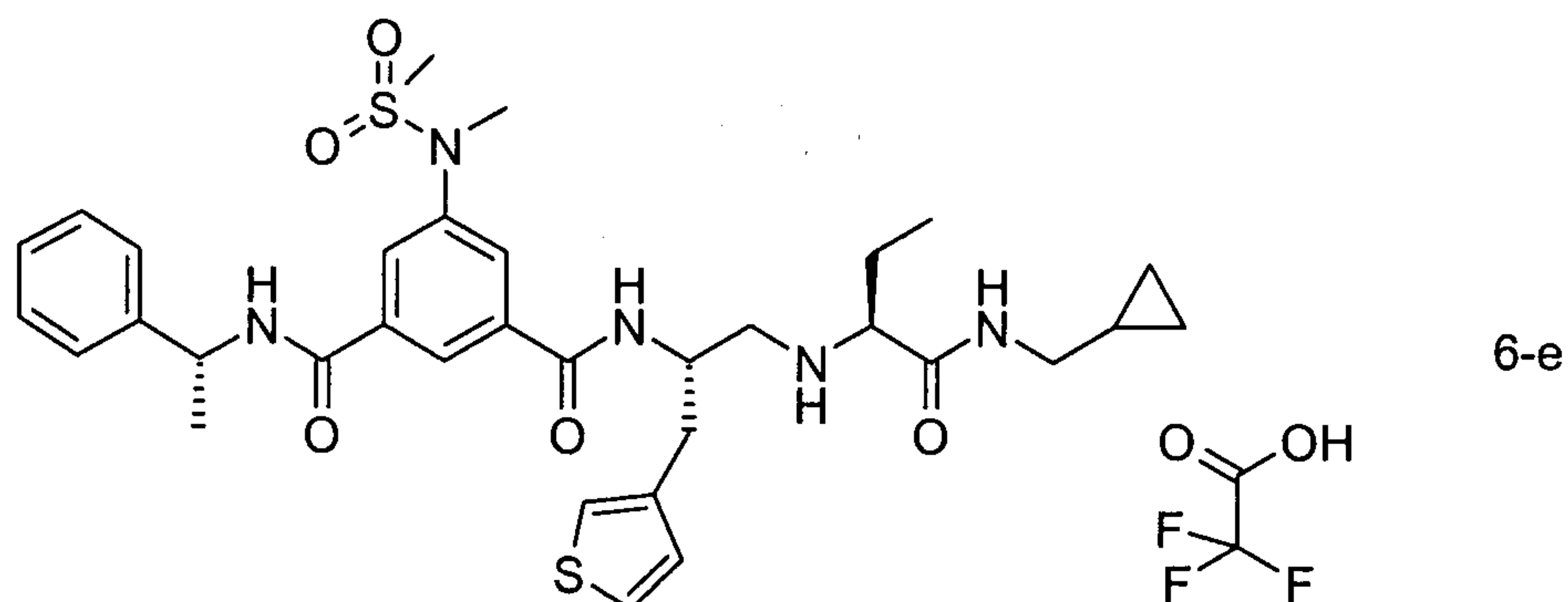
Preparation of **6-d**

6-d was prepared analogously to **1-a** starting from 400 mg (0.776 mmol) **6-c** and 526 mg (1.24 mmol) Dess-Martin periodinane. The product was used directly in the next step.

Yield: 398 mg (content 90 %) **6-d**

RT (HPLC-1) = 2.88 min

ES-MS (M+H)⁺ = 516

10 Preparation of **6-e**

6-e was prepared analogously to **1-b** starting from 150 mg (0.292 mmol) **6-d** and 79.0 mg (0.292 mmol) **5-b**. The crude product was purified by HPLC-2.

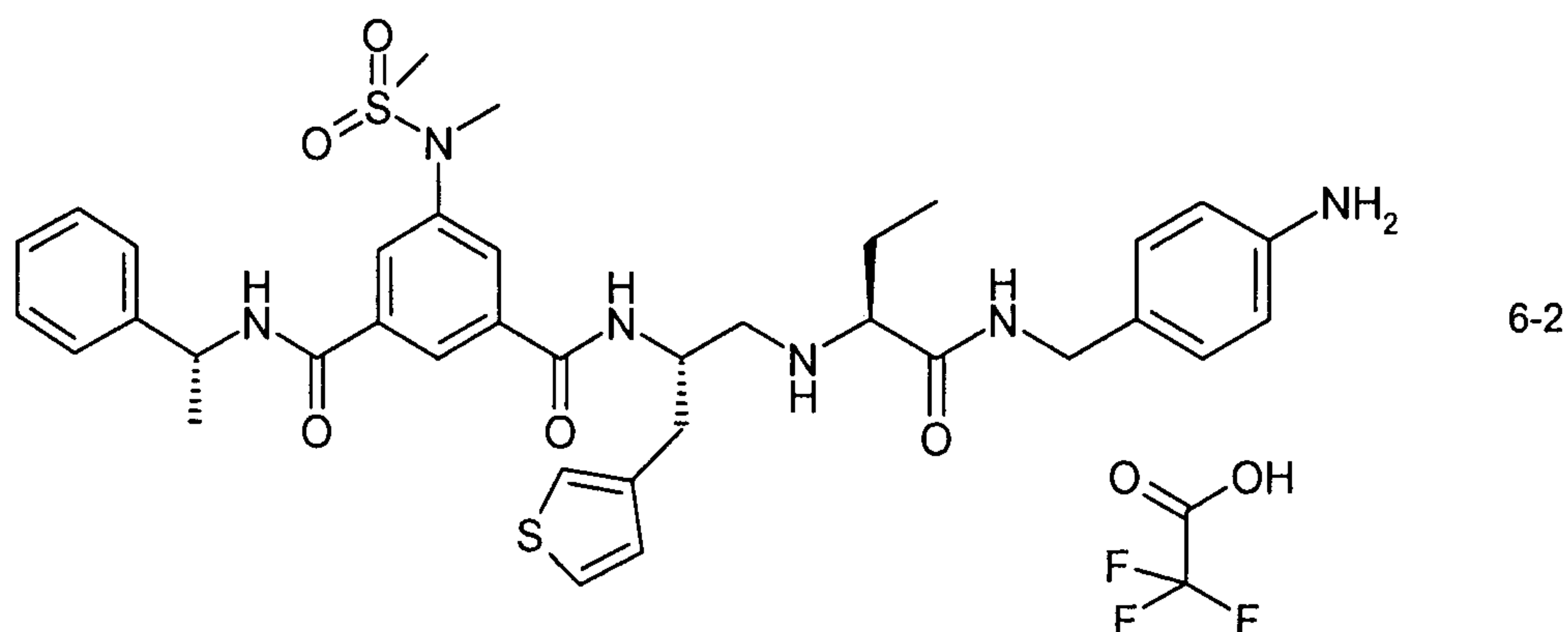
Yield: 26.9 mg (12 %) **6-e**

15 RT (HPLC-MS) = 2.77 min

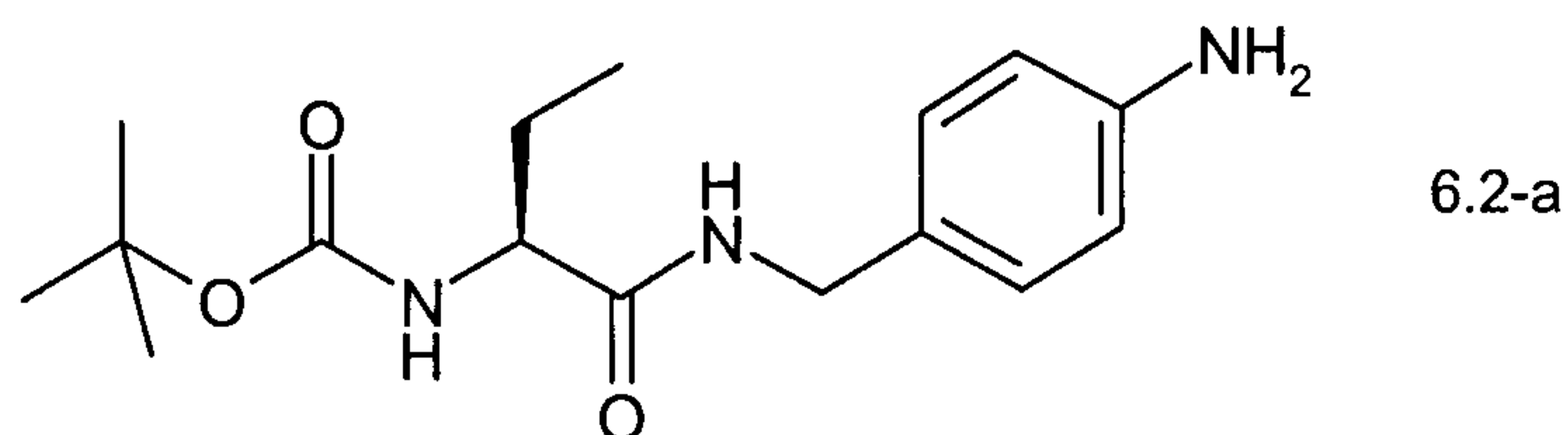
ES-MS (M+H)⁺ = 654

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Example 6.2



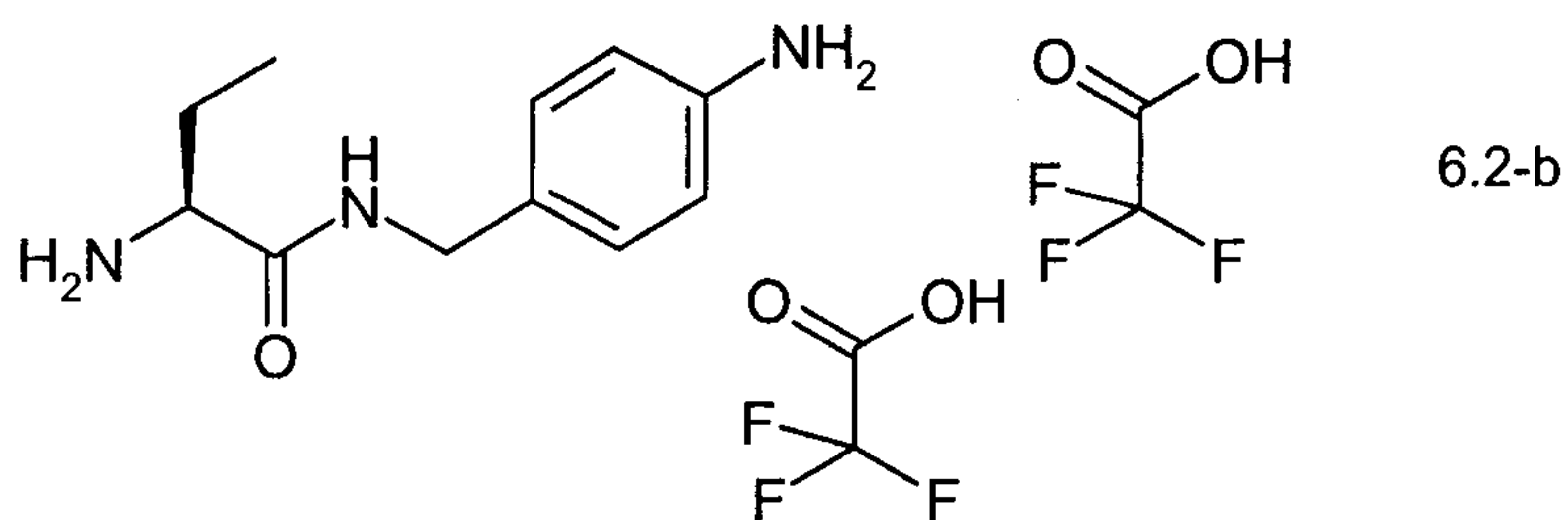
Preparation of 6.2-a



The synthesis of **6.2-a** was carried out analogously to **3-b** starting from 5.00 g (24.6 mmol) BOC-L-2-aminobutyric acid and 2.90 g (23.7 mmol) 4-aminomethylphenylamine. The crude product was purified by HPLC-2.

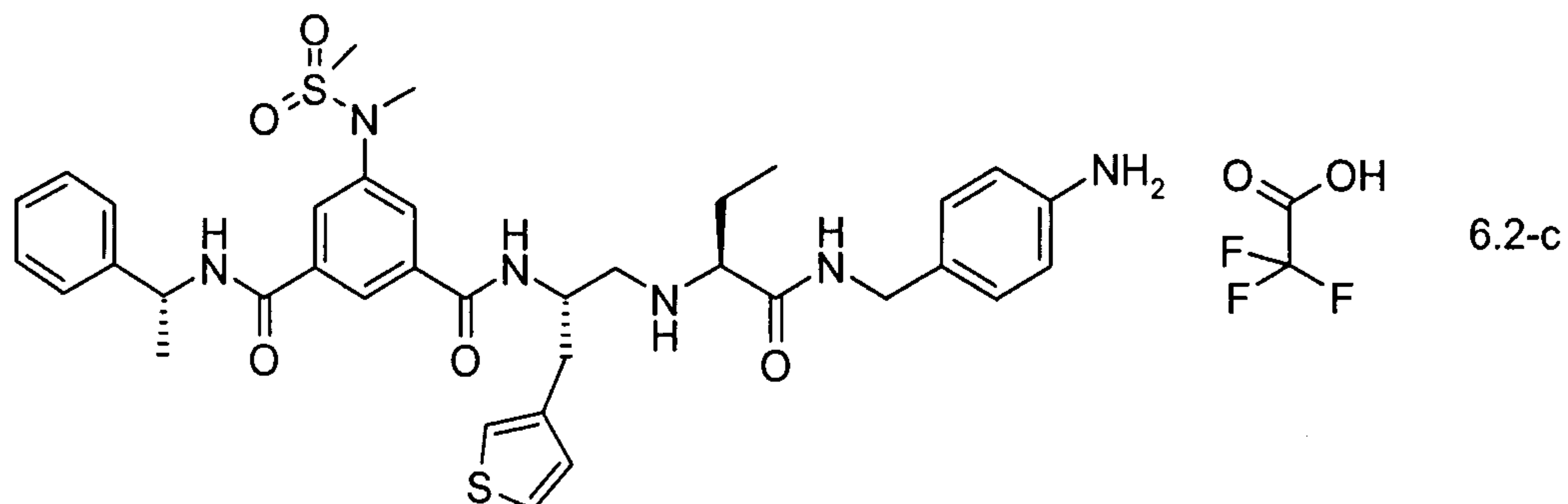
Yield: 3.82 g (51 %) **6.2-a**

Preparation of 6.2-b



The synthesis of **6.2-b** was carried out analogously to **3-c** starting from 3.82 g (12.4 mmol) **6.2-a**. Yield: 3.79 g (70 %)

Preparation of 6.2-c



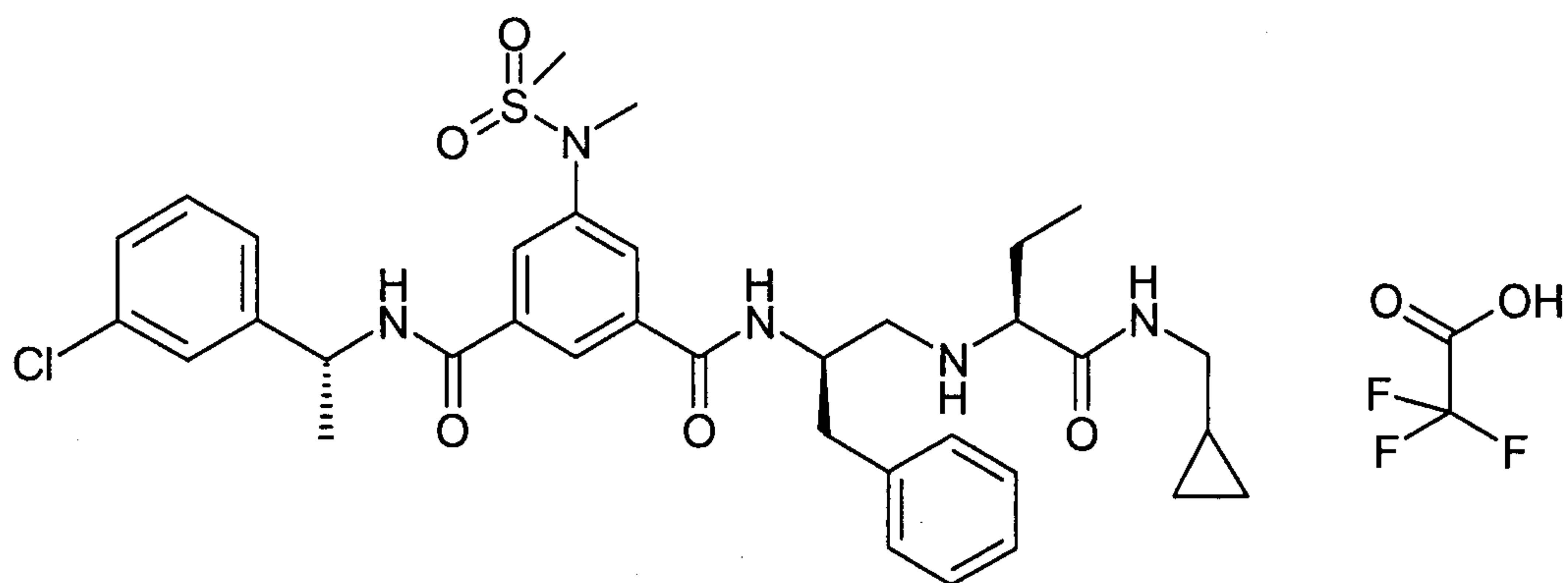
6.2-c was prepared analogously to **1-b** starting from 250 mg (0.487 mmol) **6-d** and 212 mg (0.487 mmol) **6.2-b**. The crude product was purified by HPLC-2.

5 Yield: 18 mg (5 %) **6.2-c**

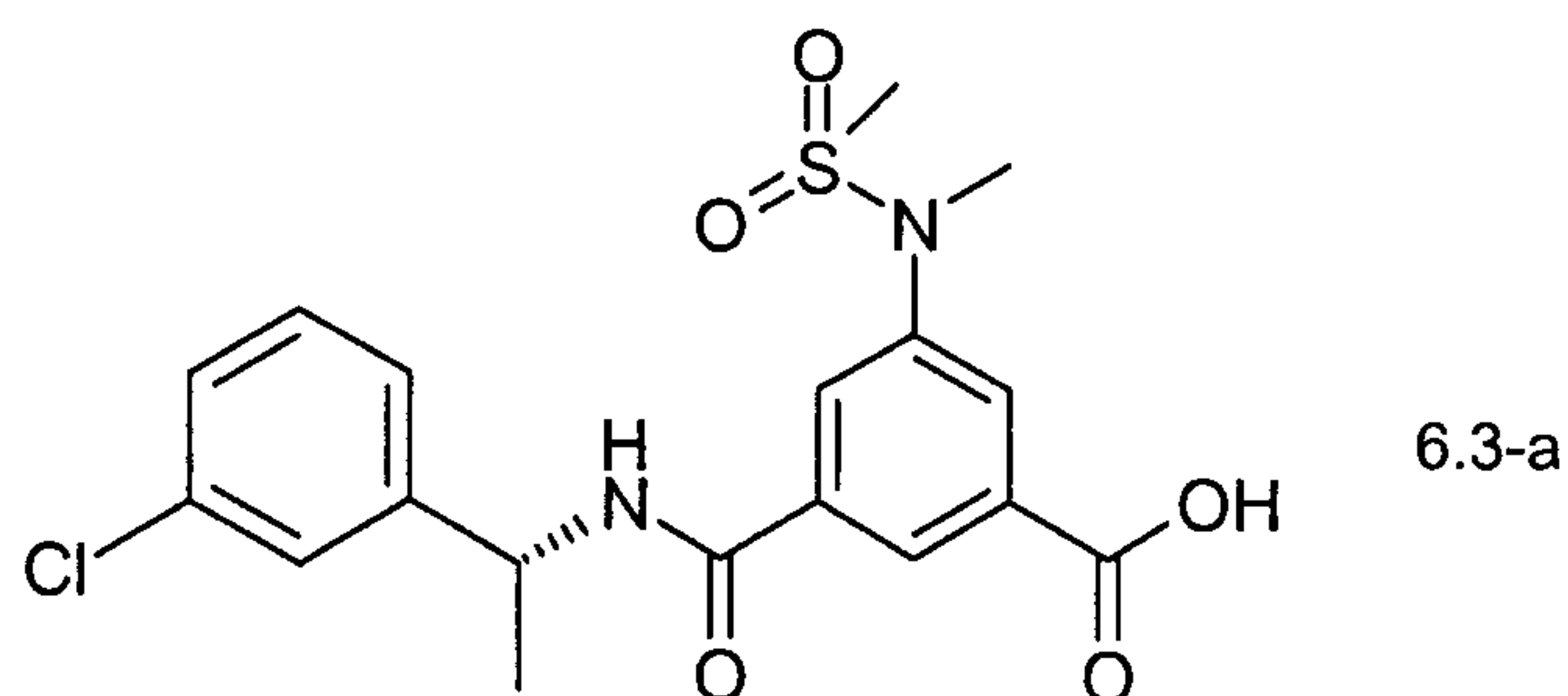
RT (HPLC-MS) = 2.44 min

ES-MS (M+H)⁺ = 705

Example 6.3:



Preparation of 6.3-a:

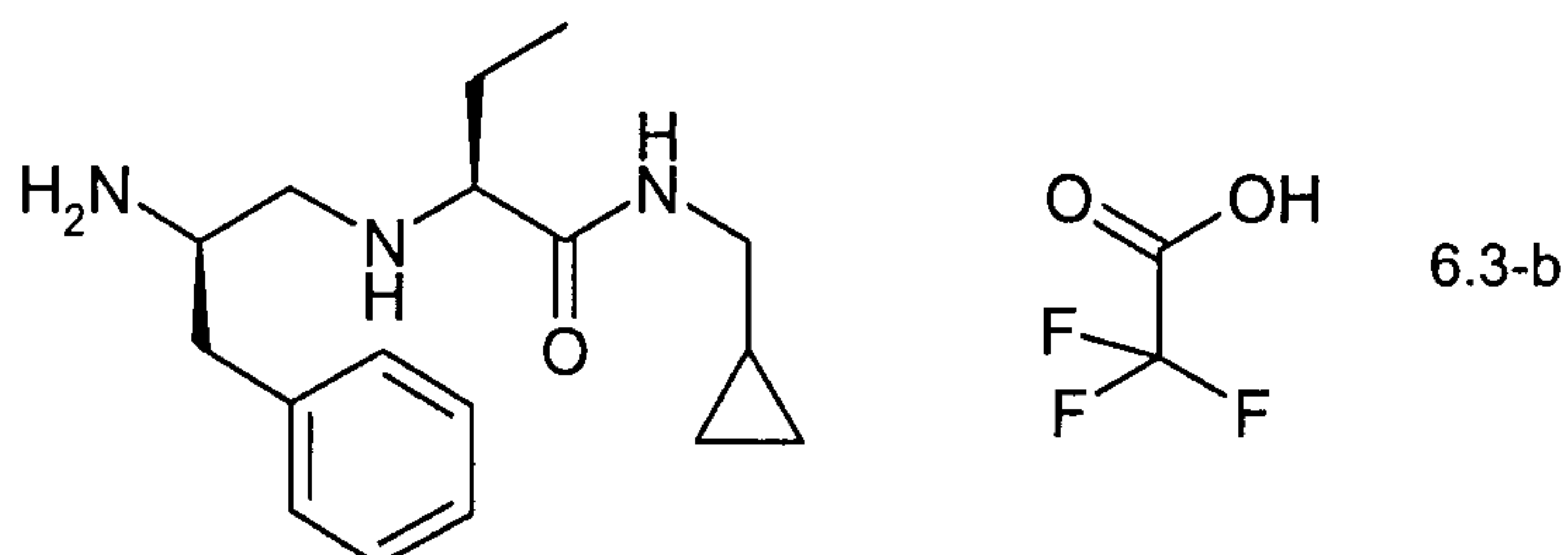


15 The preparation of **6.3-a** was carried out analogously to **1-h** using R-1-(3-chlorophenyl)ethylamine instead of R-1-(4-fluorophenyl)ethylamine.

Yield in the last step: 880 mg **6.3-a**

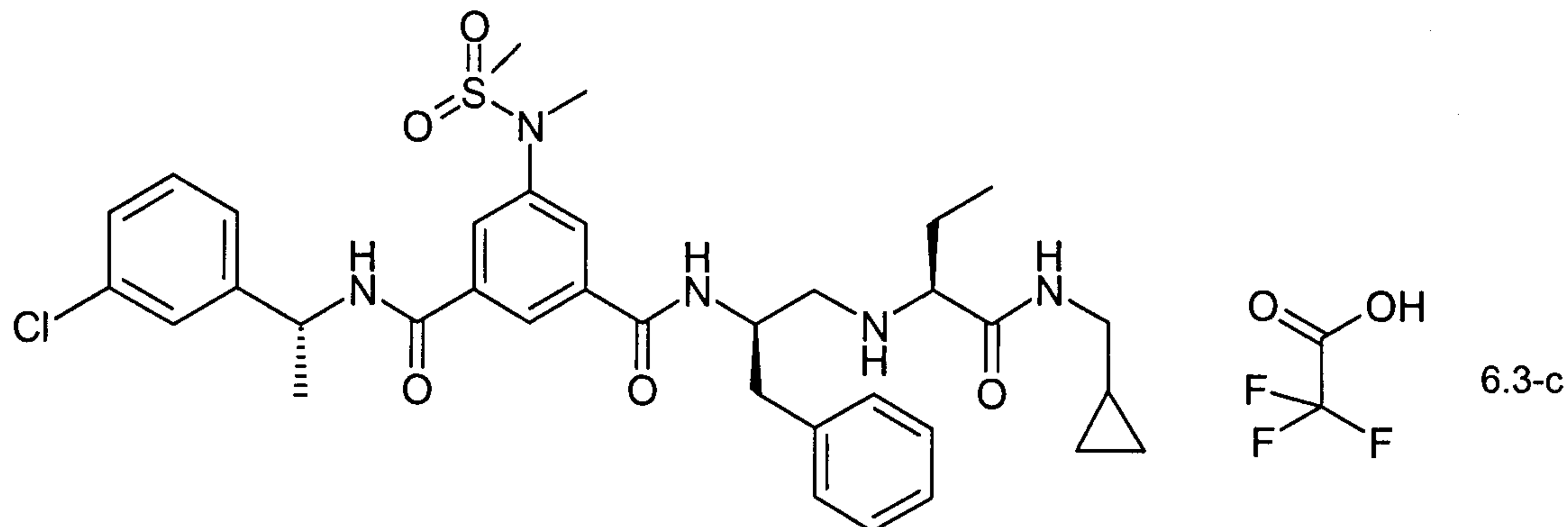
- 127 -

RT (HPLC-1) = 2.91 min

ES-MS (M+H)⁺ = 411/413 (Cl)Preparation of **6.3-b**

5

6.3-b was prepared analogously to **4-d**, using BOC-D-2-aminobutyric acid instead of BOC-L-alanine in step **4-a** and BOC-D-phenylalaninal instead of BOC-L-phenylalaninal in step **4-c**

10 Preparation of **6.3-c**

6.3-c was prepared analogously to **4-e** starting from 50 mg (0.173 mmol) **6.3-b** and 71.1 mg (0.173 mmol) **6.3-a**. The crude product was purified by HPLC-2.

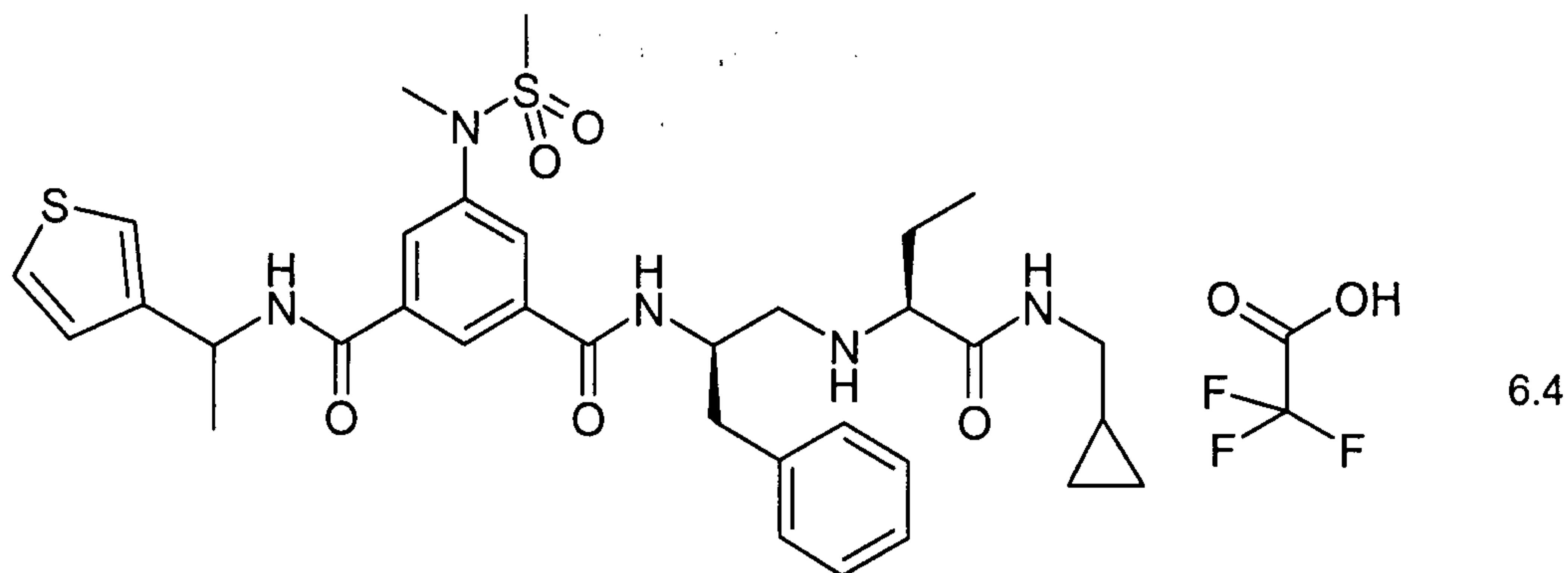
15 Yield: 6 mg (4 %) **6.3-c** as a white solid.

RT (HPLC-MS) = 2.85 min

ES-MS (M+H)⁺ = 682/684

- 128 -

Example 6.4:



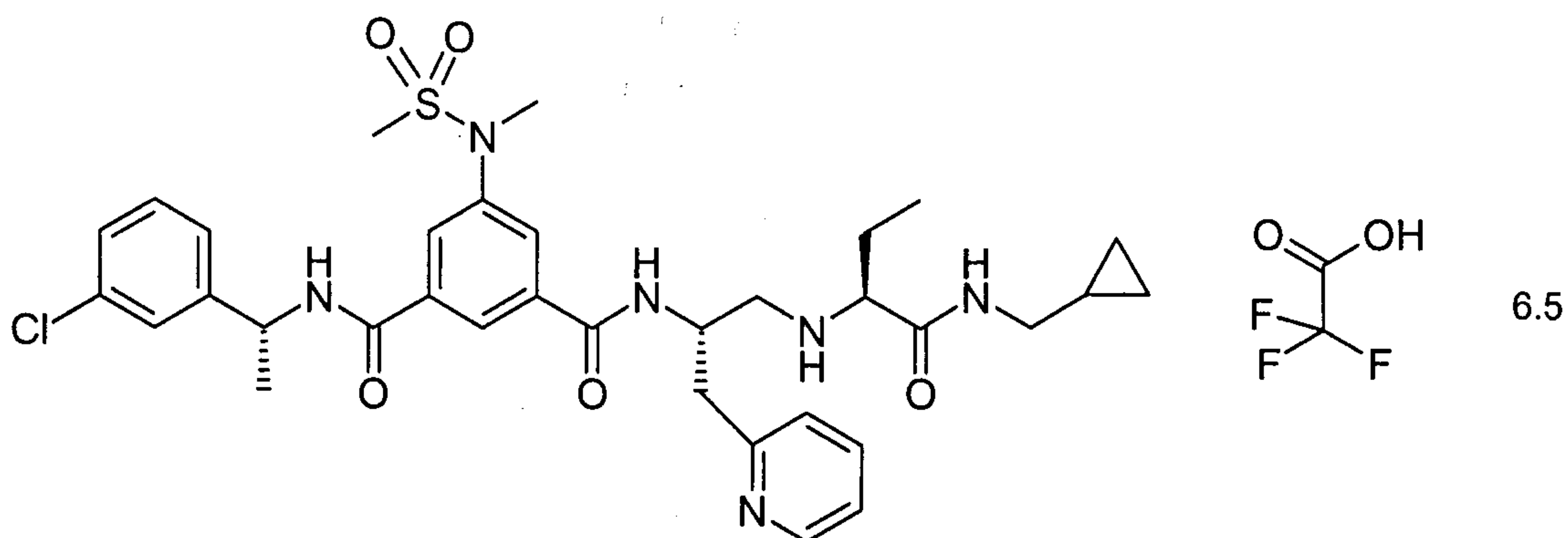
6.4 was prepared analogously to 4-e. The end product was purified by HPLC-2.

Yield: 5.8 mg (4 %) 6.4 as white solid.

5 RT (HPLC-MS) = 2.71

ES-MS (M+H)⁺ = 654

Example 6.5:



10 6.5 was prepared analogously to 4-e. The end product was purified by HPLC-2.

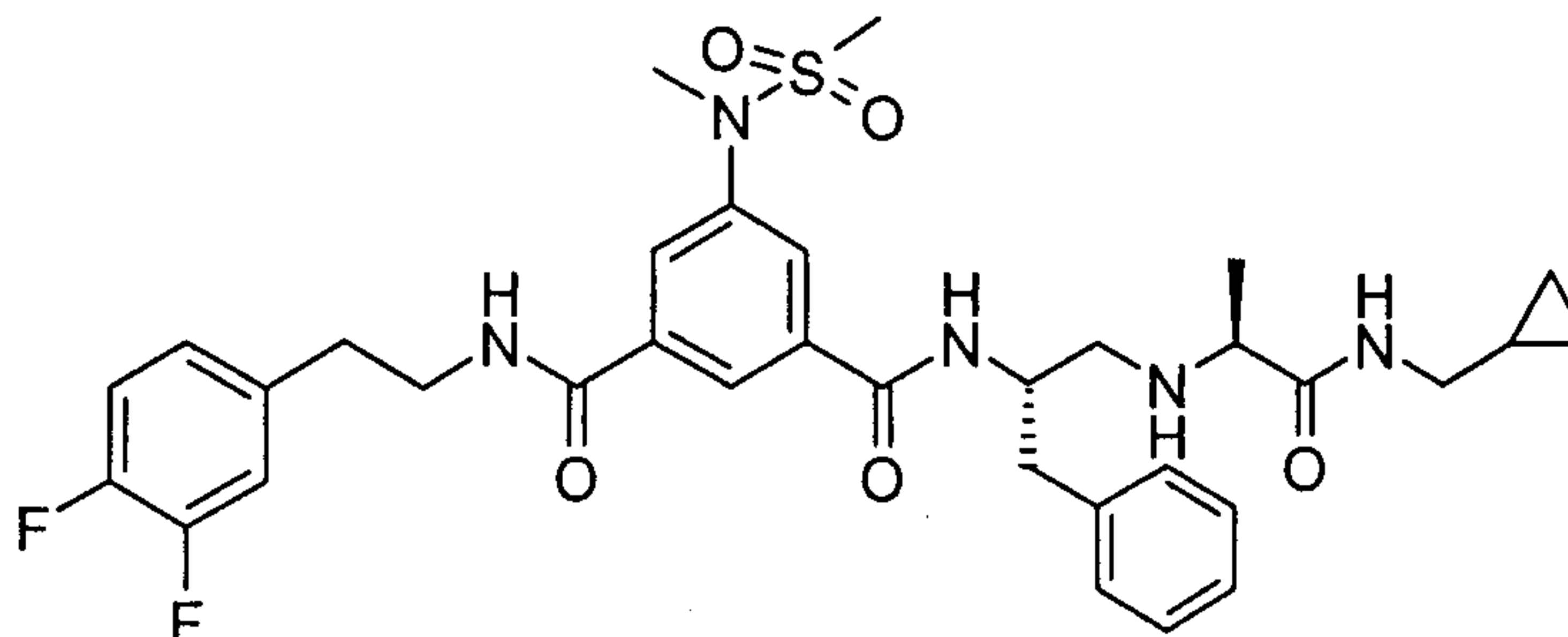
Yield: 25 mg (21 %) 6.5 as a white solid.

RT (HPLC-MS) = 2.62

ES-MS (M+H)⁺ = 683/685 (Cl)

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Example 6.6

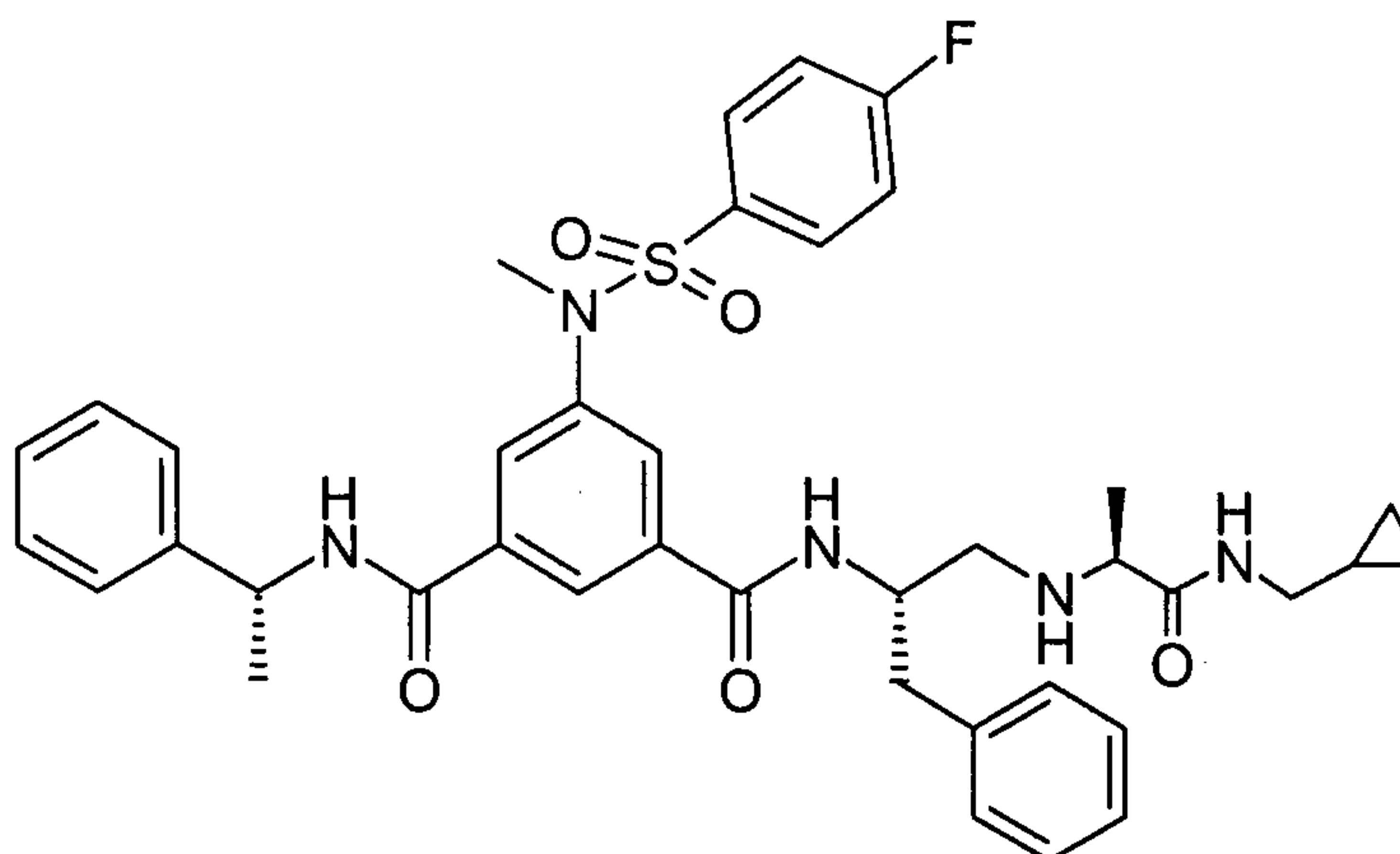


6.6 was prepared analogously to **4-e**. The end product was purified by MPLC.

Yield: 99 mg (78 %) **6.6** as a colourless oil

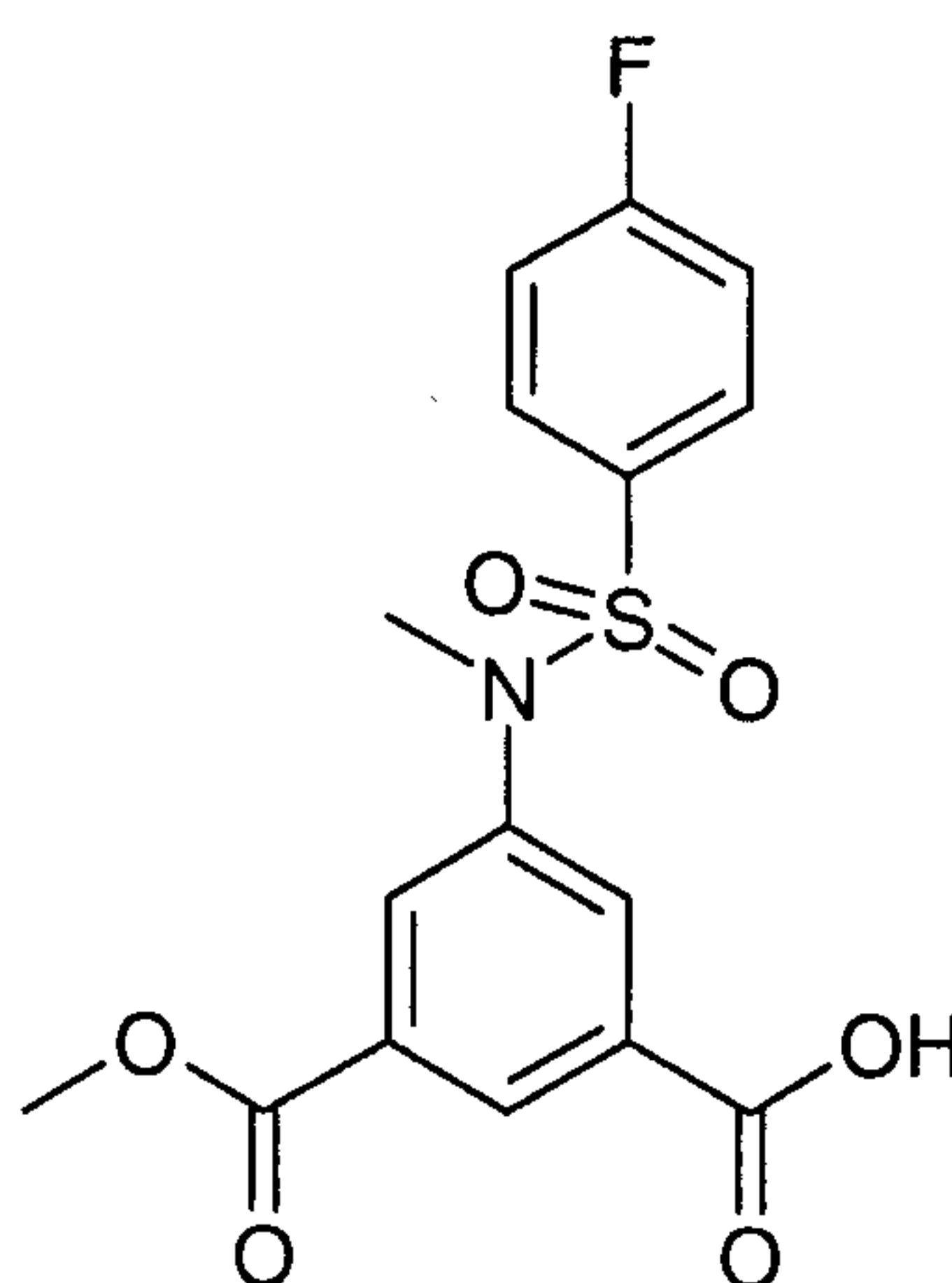
- 5 RT (HPLC-1) = 2.84 min
RT (HPLC-MS) = 4.67 min
ES-MS (M+H)⁺ = 670

Example 6.7



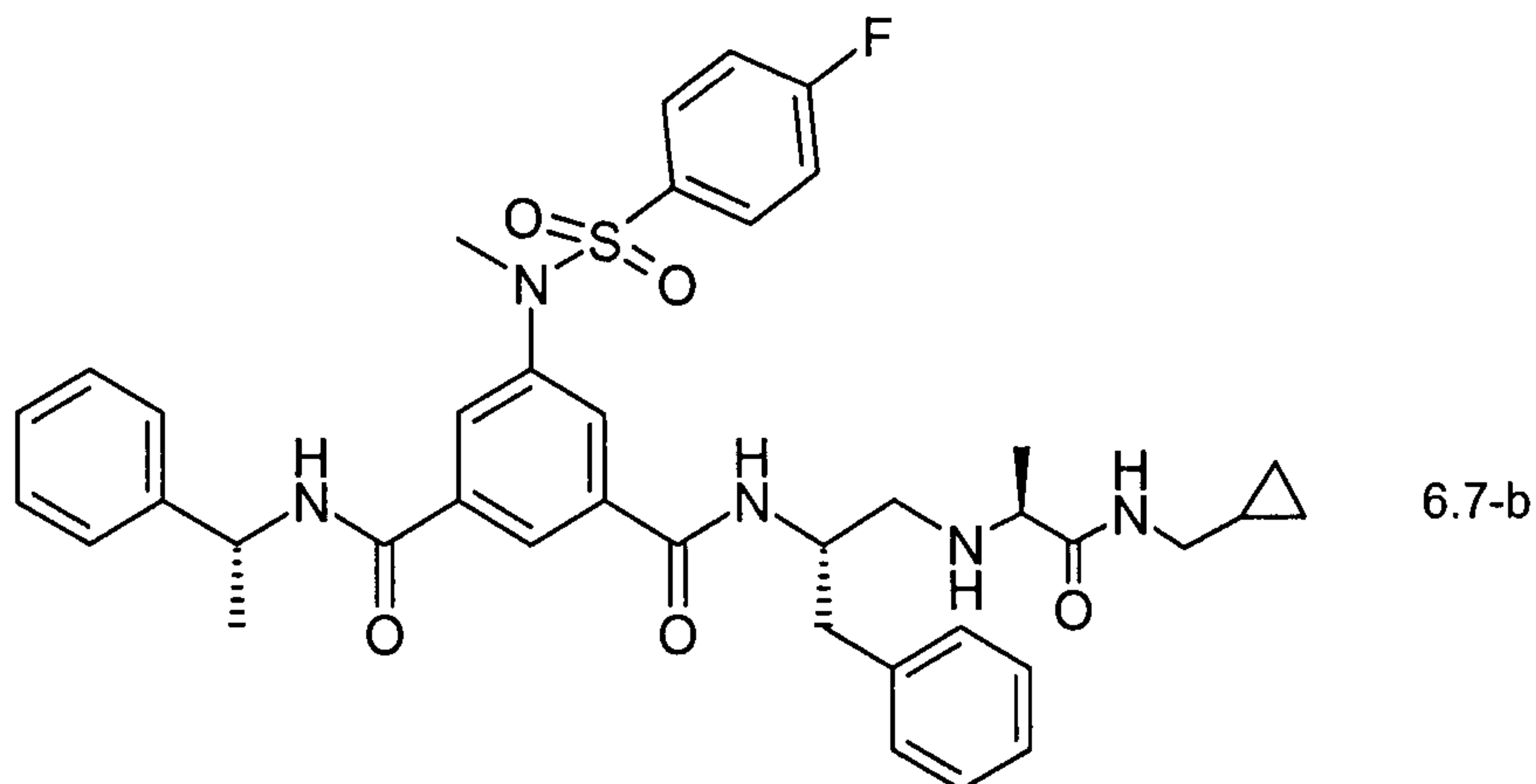
10

Preparation of 6.7-a



6.7-a was prepared analogously to **1-f**, but using 4-fluorobenzenesulphonic acid chloride instead of methanesulphonic acid chloride in step **1.d**.

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Preparation of **6.7 b**

6.7-b was prepared analogously to **4-e** using **6.7-a**. The end product was purified by MPLC.

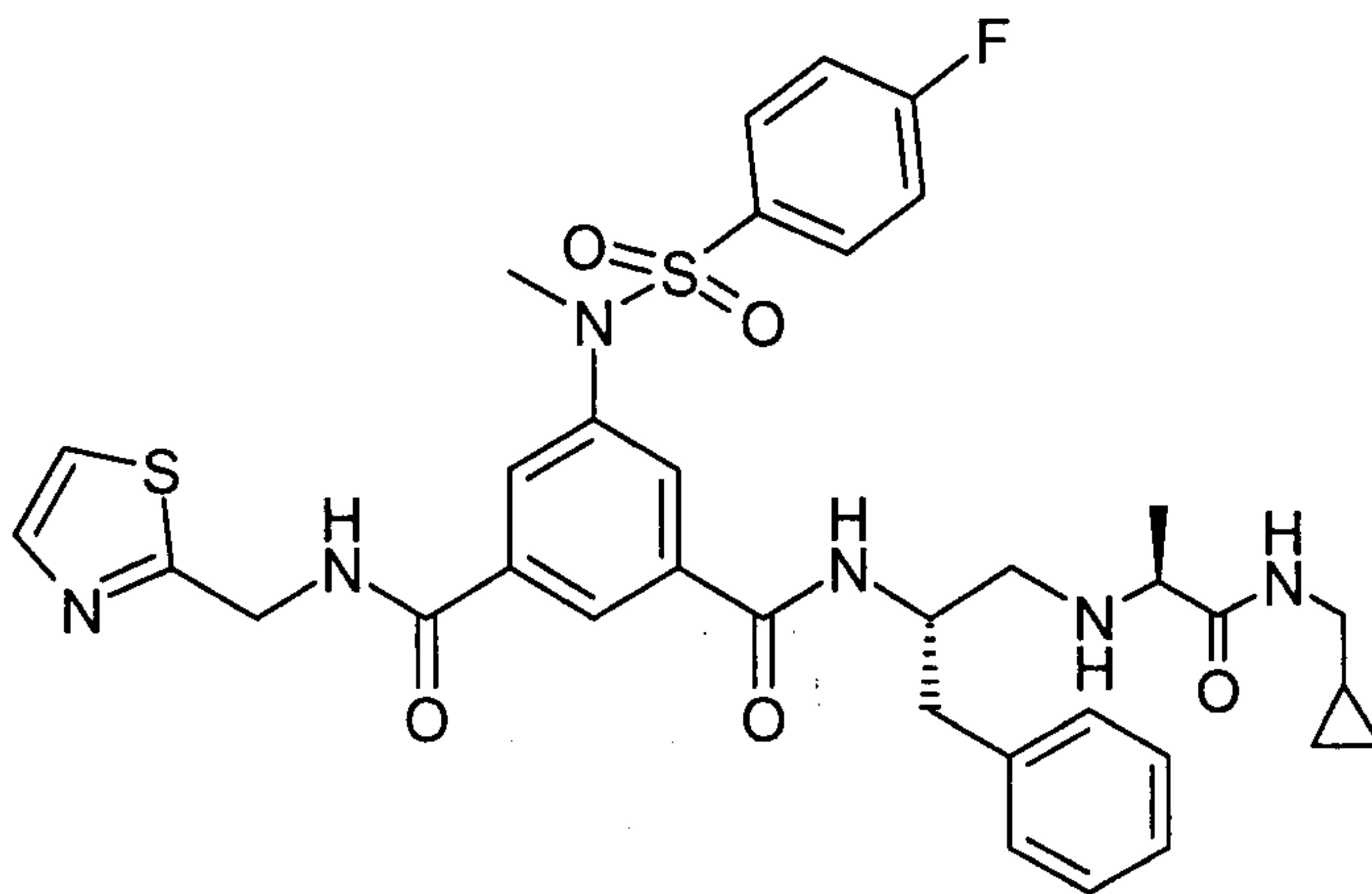
5 Yield: 70 mg (53 %) **6.7-b** as a colourless oil

RT (HPLC-1) = 2.84 min

RT (HPLC-MS) = 3.02 min

ES-MS (M+H)⁺ = 714/715/717

10 Example **6.8**:



6.8 was prepared analogously to **6.7**. The end product was purified by MPLC.

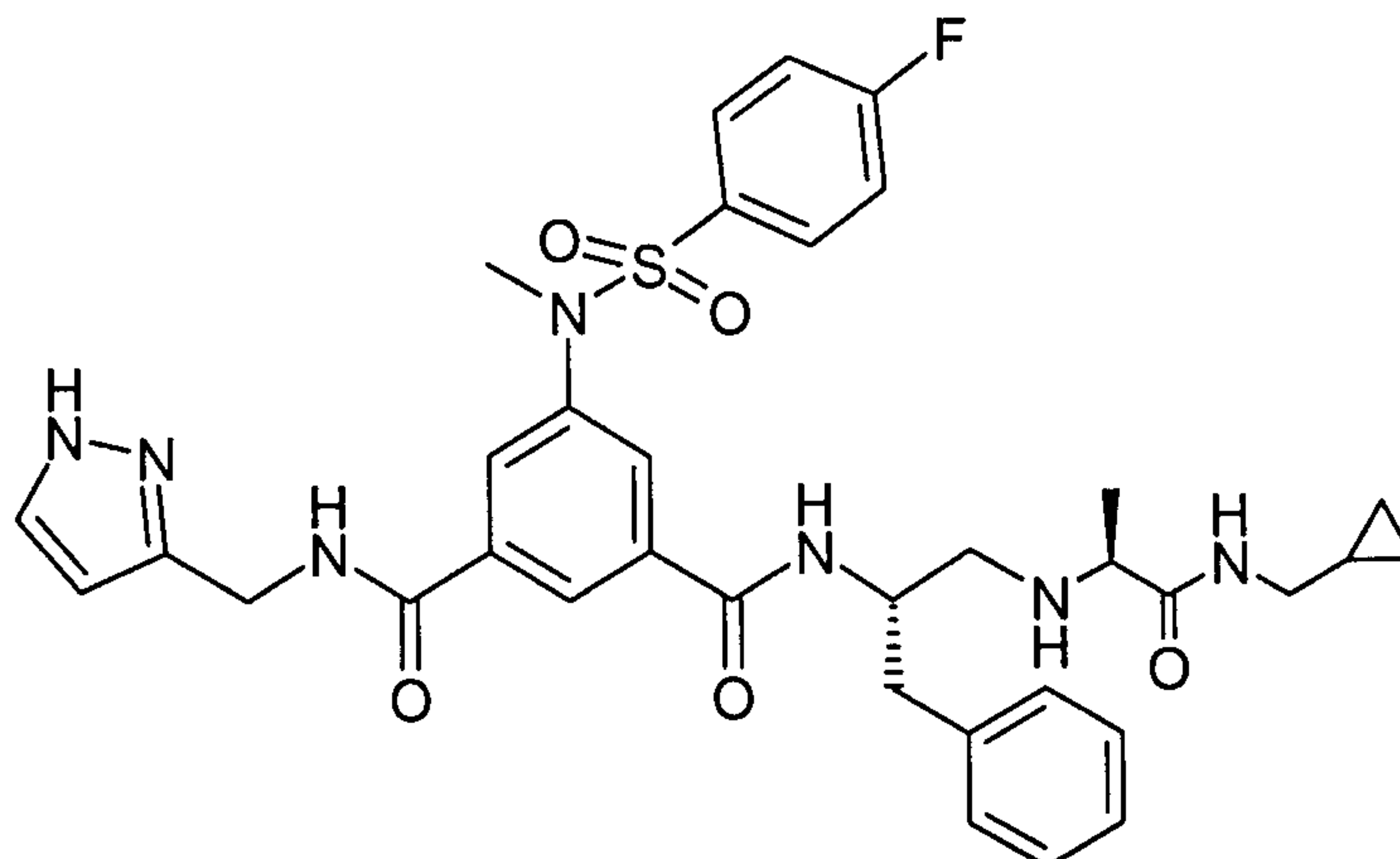
Yield: 20 mg (15 %) **6.8** as yellow crystals

RT (HPLC-MS) = 2.77 min

15 ES-MS (M+H)⁺ = 707/708

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Example 6.9:



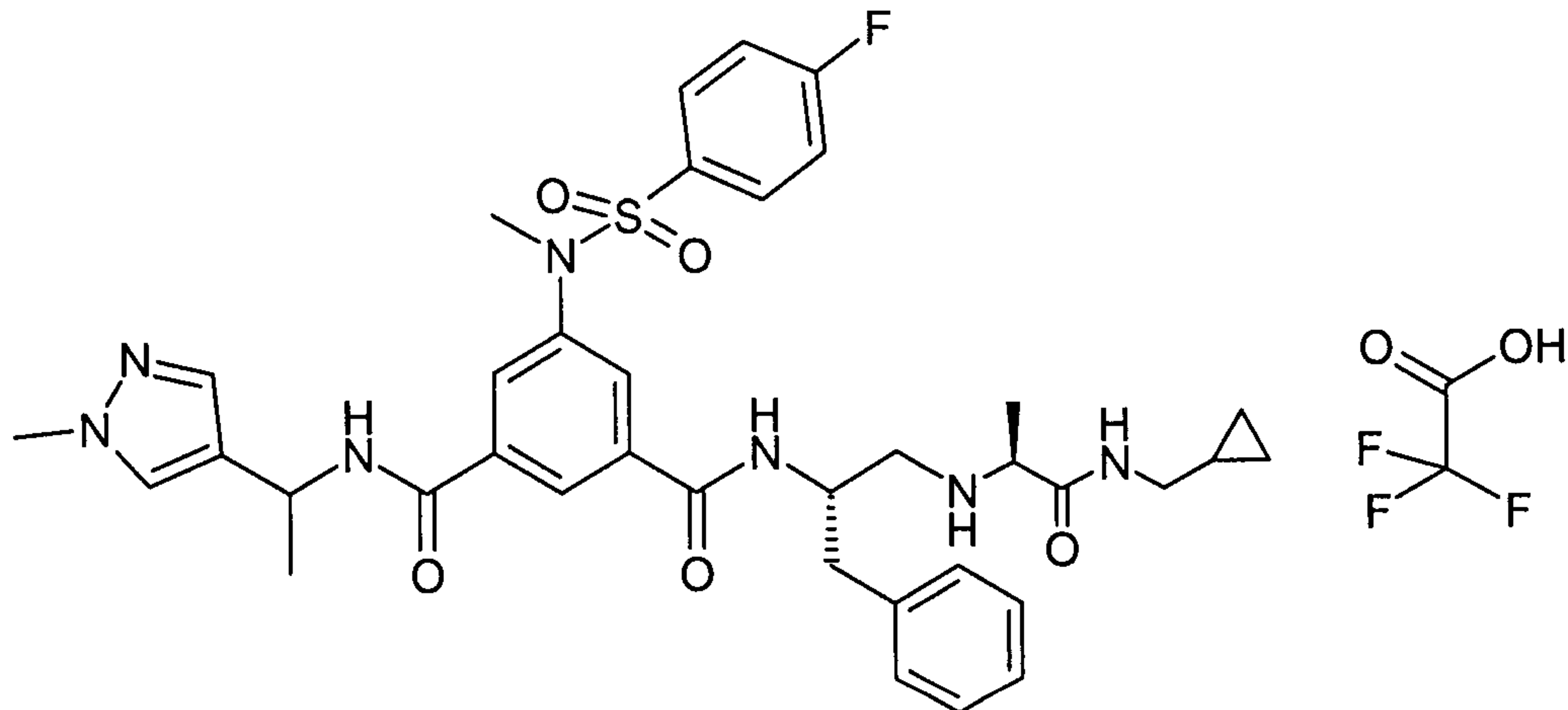
6.9 was prepared analogously to **6.7**. The end product was purified by MPLC.

Yield: 30 mg (23 %) **6.9** as yellow crystals

5 RT (HPLC-MS) = 2.63 min

ES-MS (M+H)⁺ = 690

Example 6.10:



10 **6.10** was prepared analogously to **6.7**. The end product was purified by HPLC-2.

Yield: 30 mg (34 %) **6.10** as a white solid

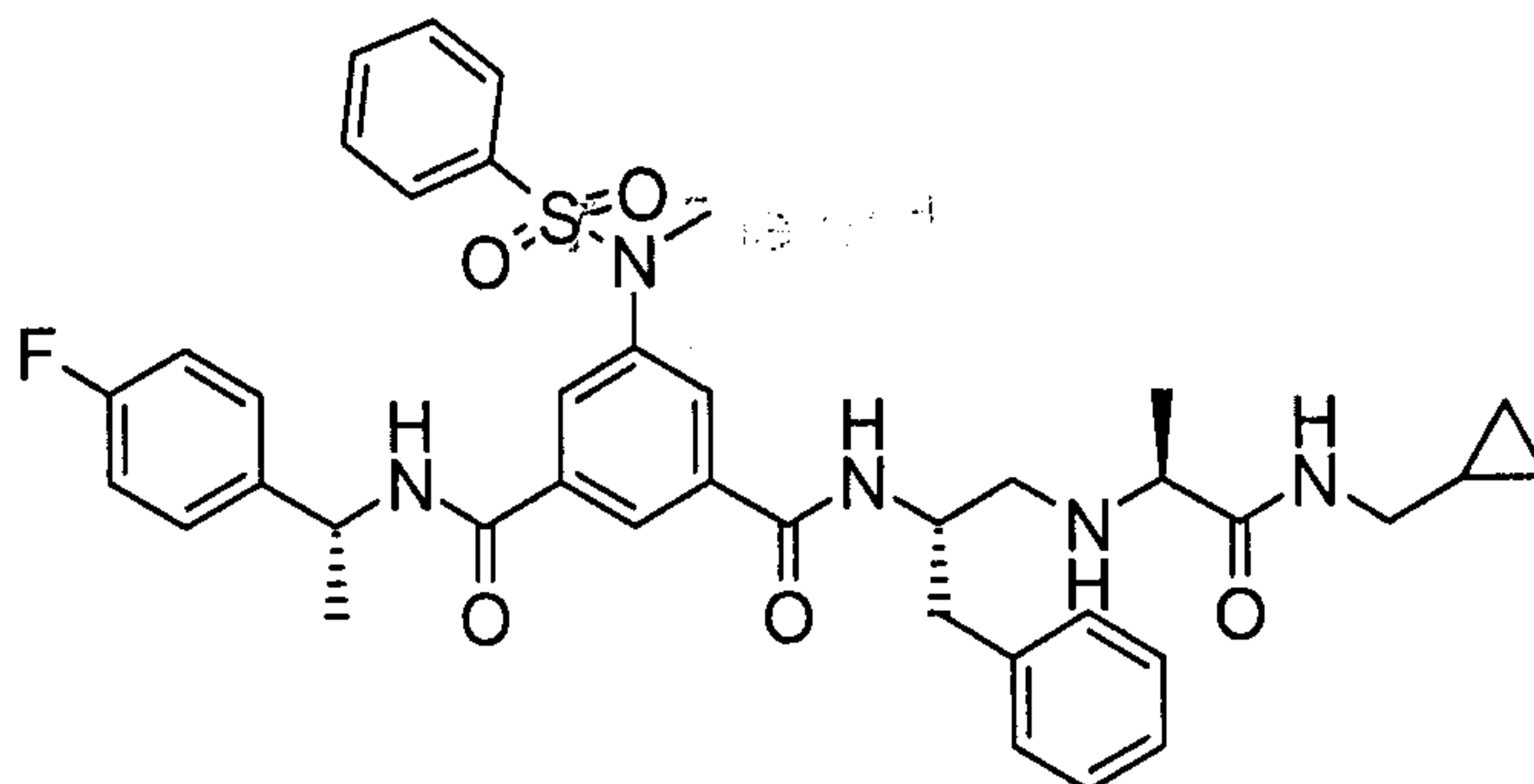
RT (HPLC-1) = 4.61 min

RT (HPLC-MS) = 2.72 min

ES-MS (M+H)⁺ = 718

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Example 6.11:



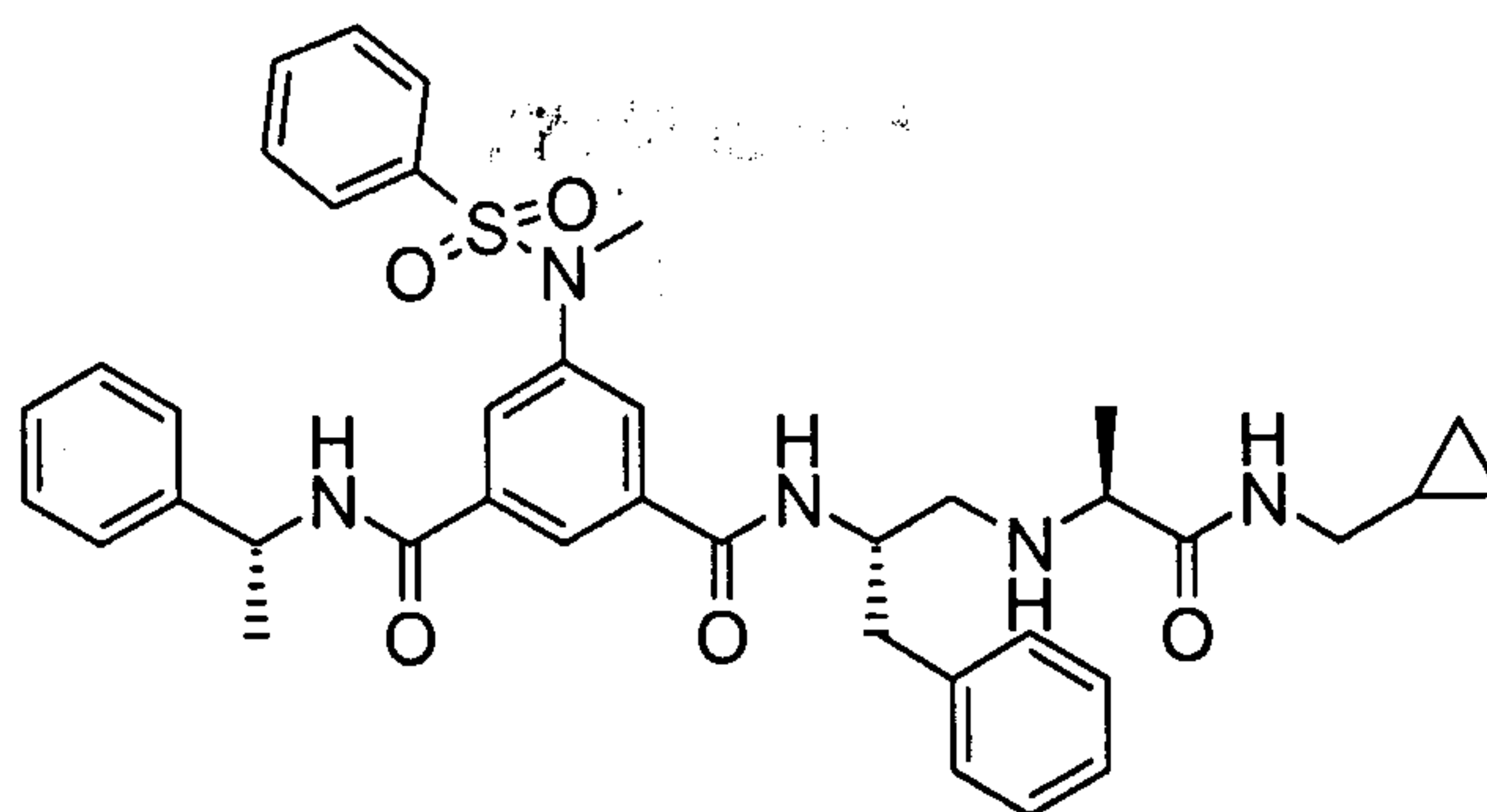
6.11 was prepared analogously to **6.7**. The end product was flash-purified by chromatography (eluant CH₂Cl₂/MeOH 100% --> 95/5).

5 Yield: 30 mg (19 %) **6.11** as a yellow solid

RT (HPLC-MS) = 3.07 min

ES-MS (M+H)⁺ = 714/715/717

Example 6.12:



10

6.12 was prepared analogously to **6.7**. The end product was flash-purified by chromatography (eluant CH₂Cl₂/MeOH 100% --> 97/3).

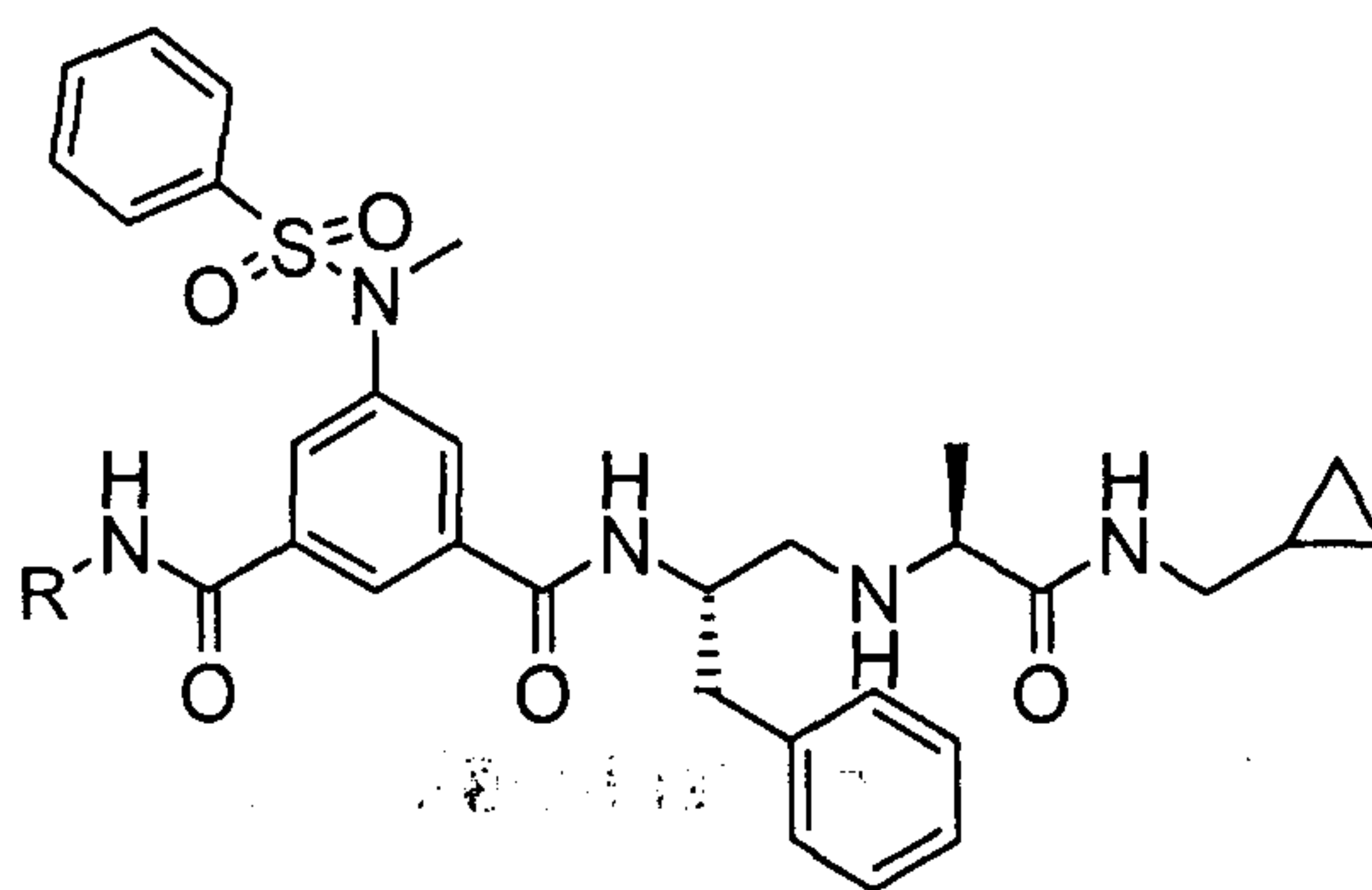
Yield: 185 mg (40 %) **6.12** as a white solid

15 RT (HPLC-MS) = 3.01 min

ES-MS (M+H)⁺ = 696

The following Examples were prepared analogously to **6.7**:

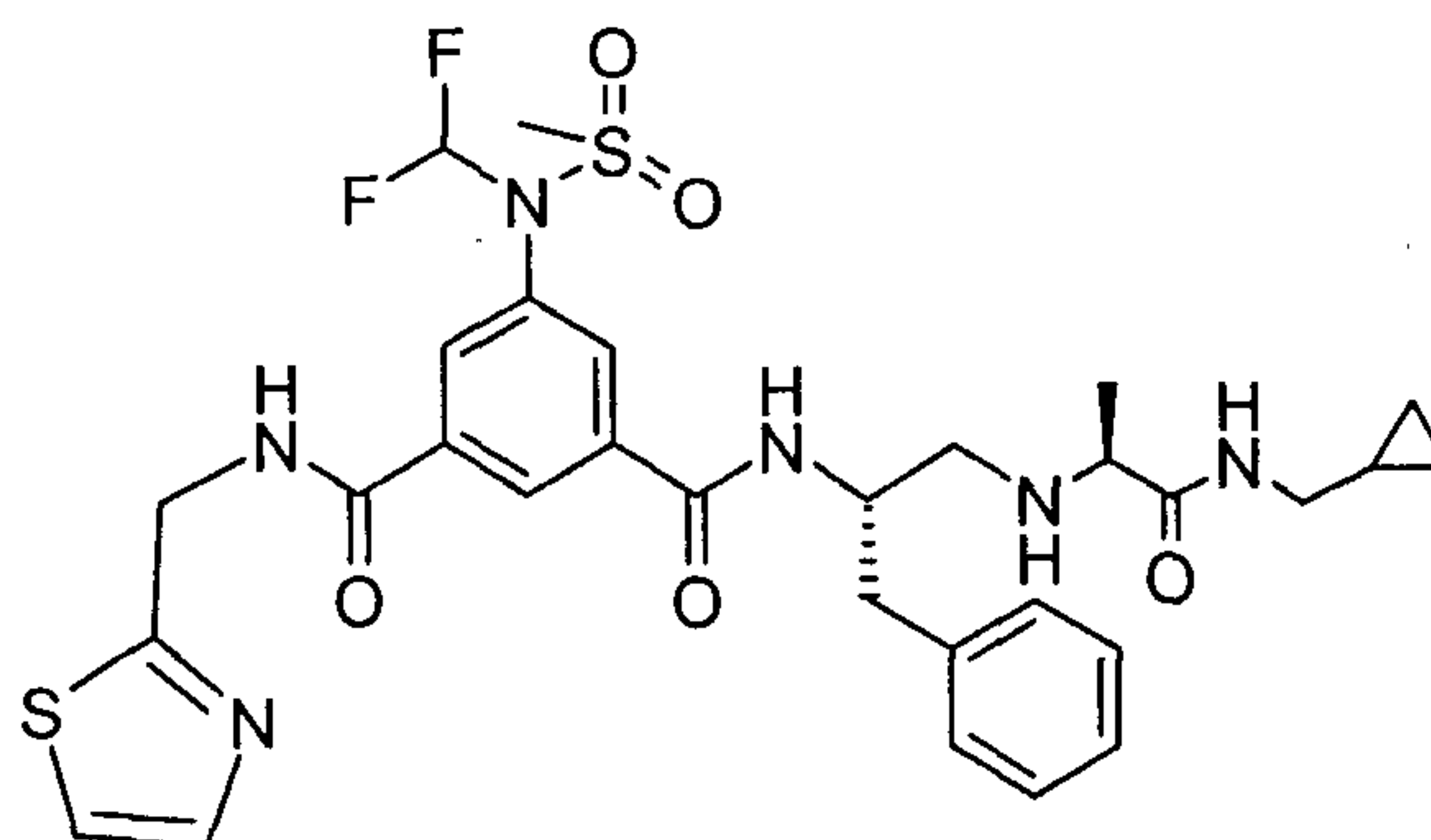
- 133 -



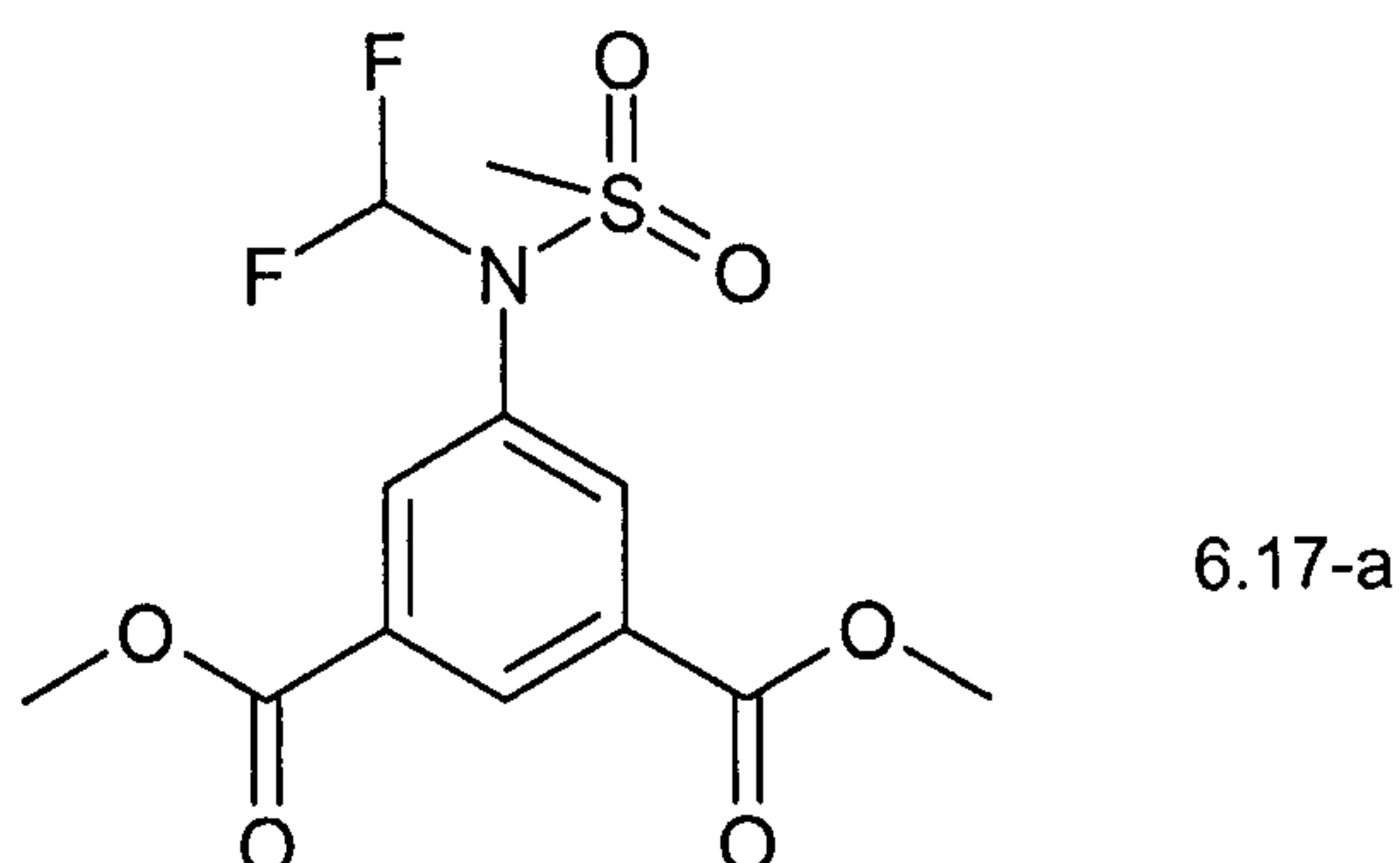
Example	R	MS	RT HPLC-MS
6.13		689 (M+H) ⁺	
6.14		700 (M+H) ⁺	
6.15		672 (M+H) ⁺	
6.16		732 (M+H) ⁺	

5

Example 6.17



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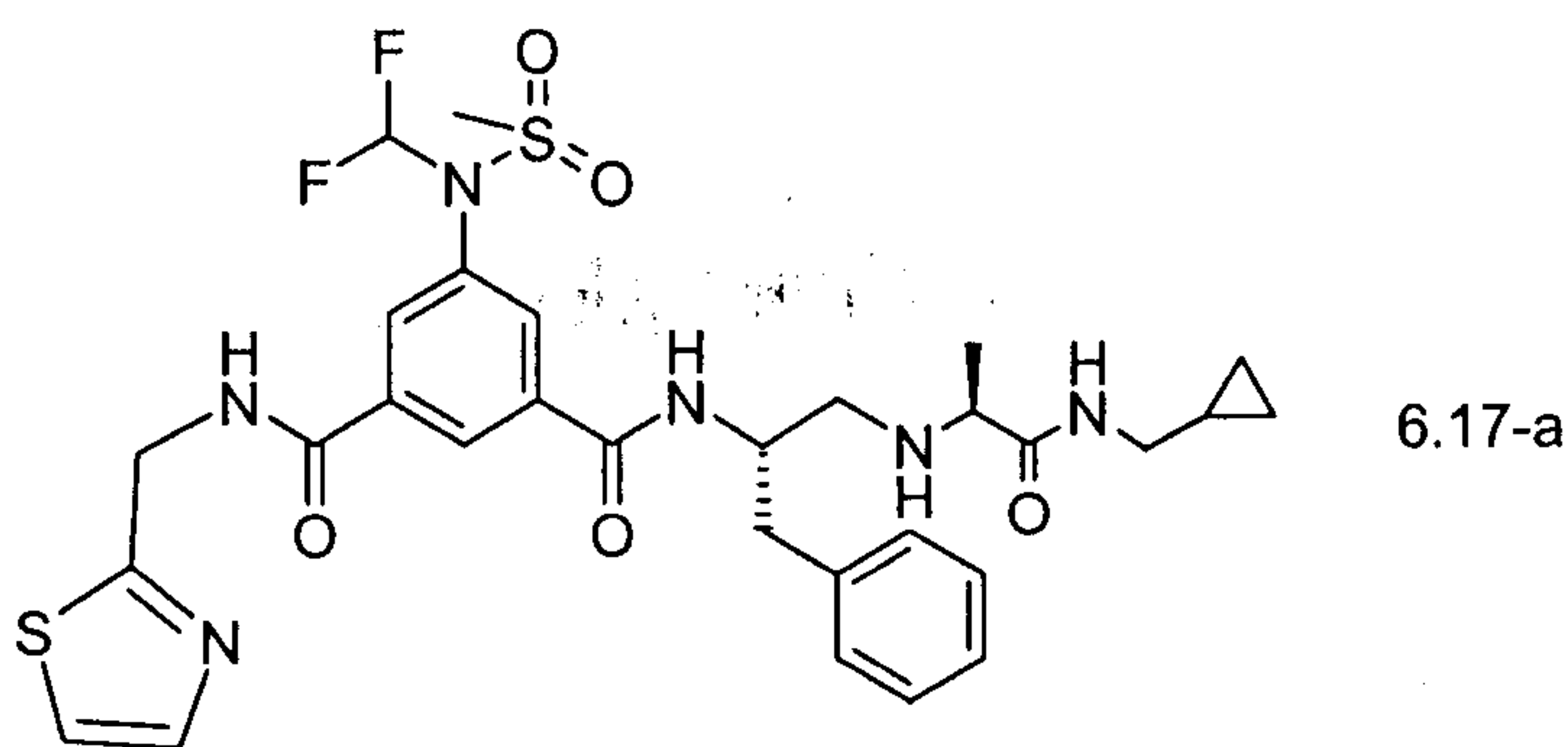
Preparation of **6.17-a**

2.00 g (6.96 mmol) **1-d** were placed in the autoclave in 50 ml DMF and 1.2 g of KOH powder were added. Then 5 bar of chlorodifluoromethane were compressed in. The reaction mixture was heated to 80°C and stirred for 14 h. Another 1.0 g of KOH powder was added, chlorodifluoromethane was compressed in and stirred for 14 h at 80°C. The solution was cooled, water was slowly added (vigorous foaming) and the mixture was extracted with ethyl acetate. After evaporation, brown crystals were obtained which were extracted with MeOH and suction filtered.

Yield: 400 mg (17 %) **6.17-a** as brown crystals

RT (HPLC-MS) = 3.04 min

ES-MS (M)⁺ = 337

Preparation of **6.17-b**

6.17-b was prepared analogously to **6.7** using **6.17-a**. The end product was purified by MPLC.

Yield: 42 mg (51 %) **6.17-b** as a colourless oil

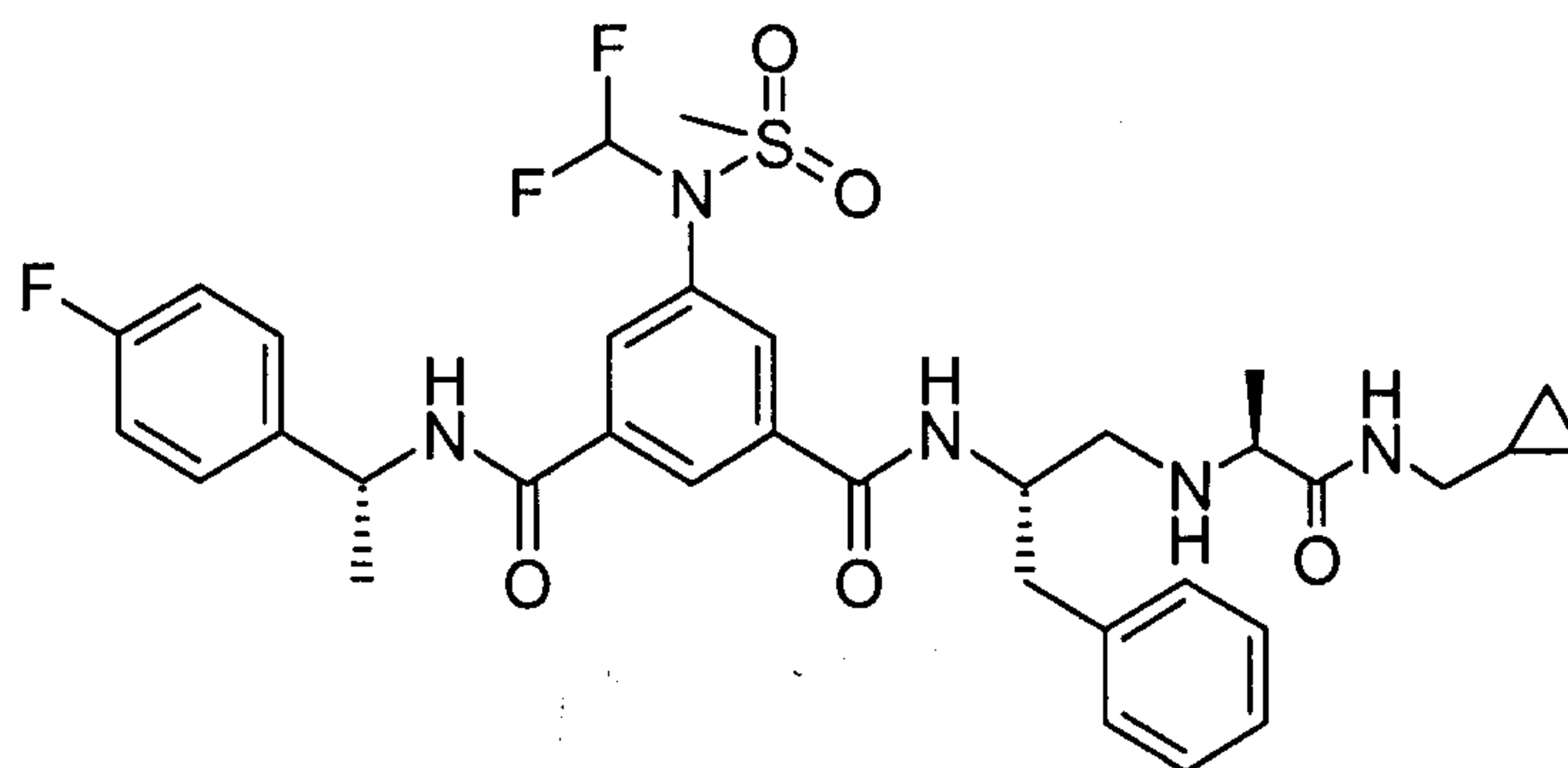
RT (HPLC-1) = 4.35 min

RT (HPLC-MS) = 2.61 min

ES-MS (M+H)⁺ = 663

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Example 6.18

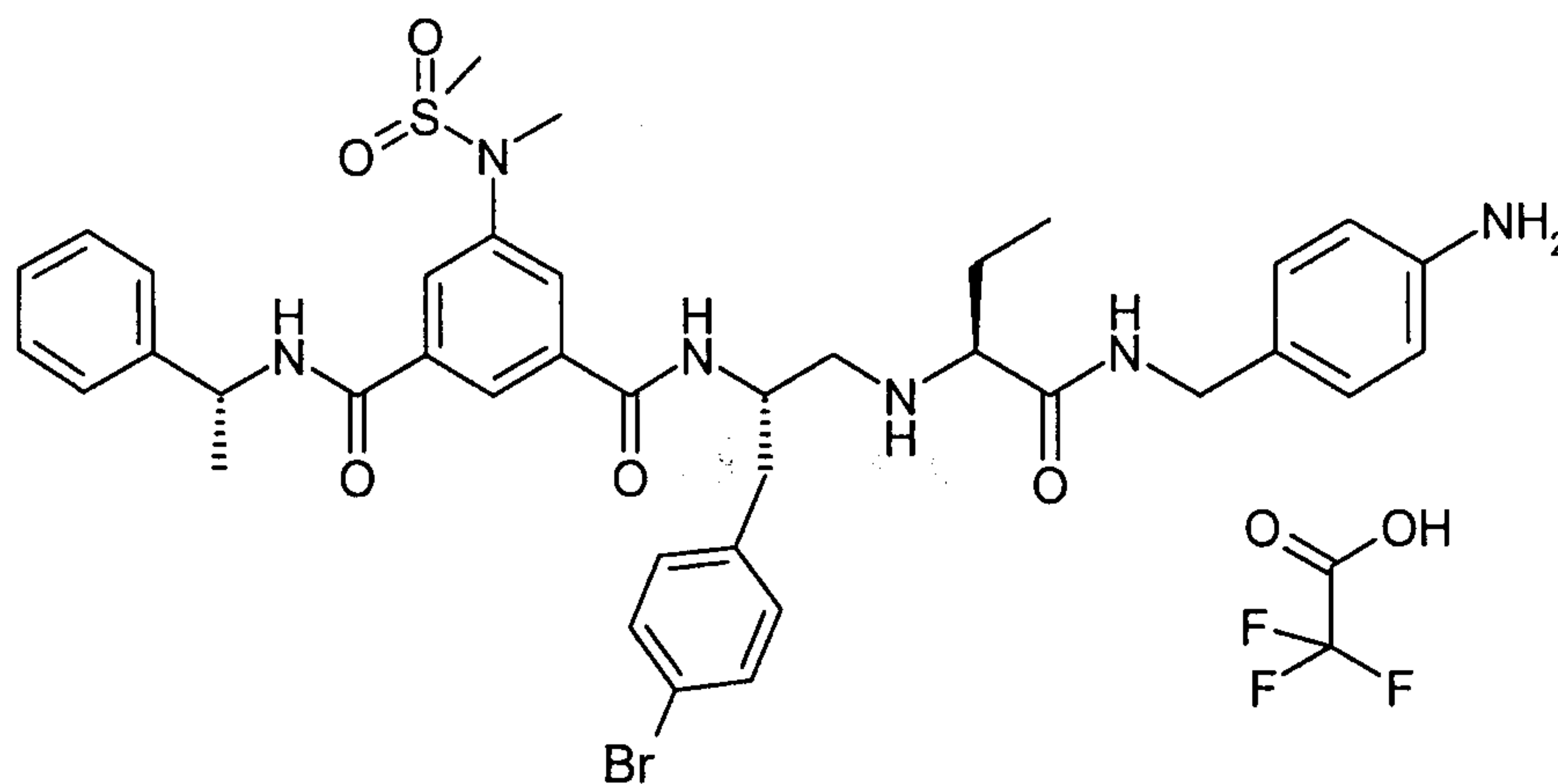


6.18 was prepared analogously to **6.17**. The end product was purified by MPLC.

Yield: 42 mg (61 %) **6.18** as a colourless oil

- 5 RT (HPLC-1) = 4.81 min
 RT (HPLC-MS) = 2.90 min
 ES-MS (M+H)⁺ = 688

Example 6.19



6-19

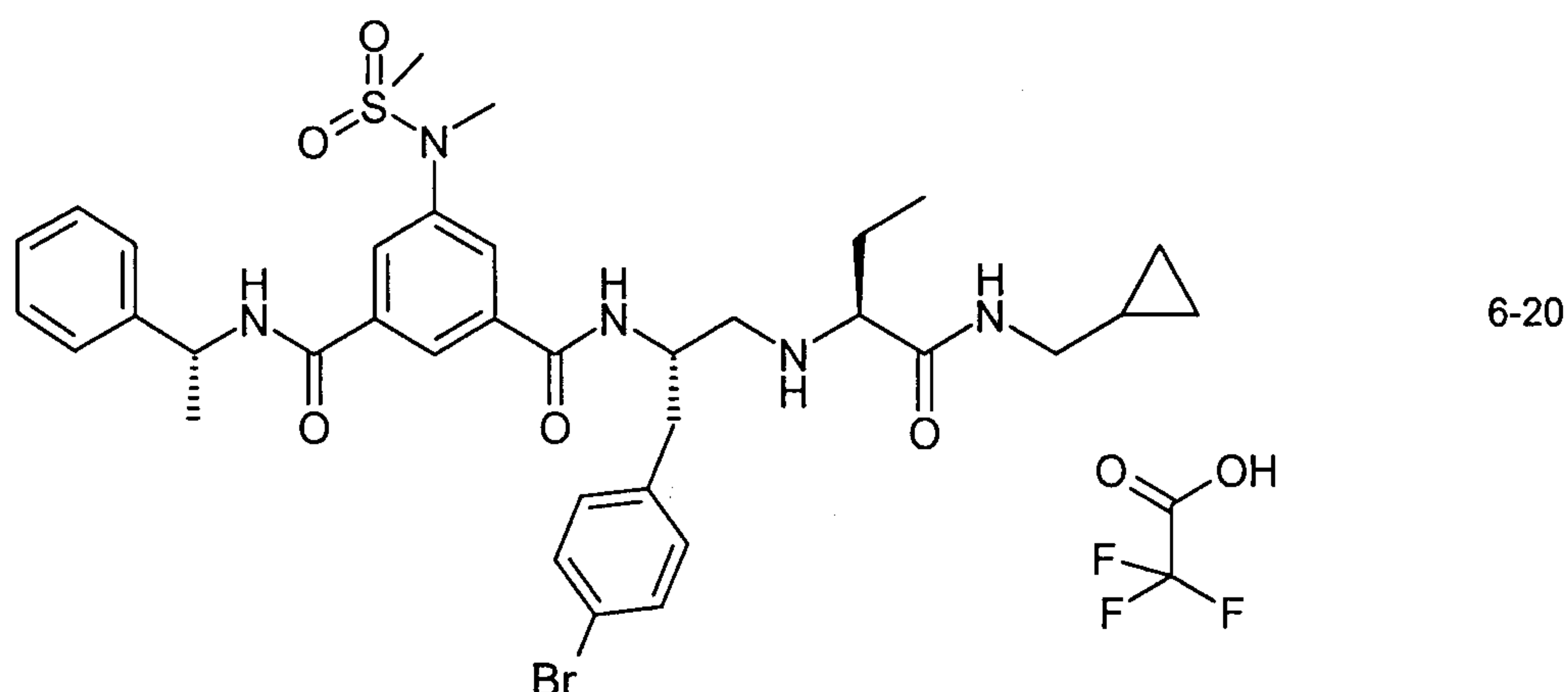
6.19 was prepared analogously to **1-b** starting from **6.2-b** and the aldehyde analogous to **6-d**, which was obtained by replacing BOC-L-3-thienylalanine by BOC-4-bromo-L-phenylalanine (step **6-a**). The crude product was purified by preparative HPLC.

RT (HPLC-MS) = 2.63 min

- 15 ES-MS (M+H)⁺ = 777/779 (Br)

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Example 6.20

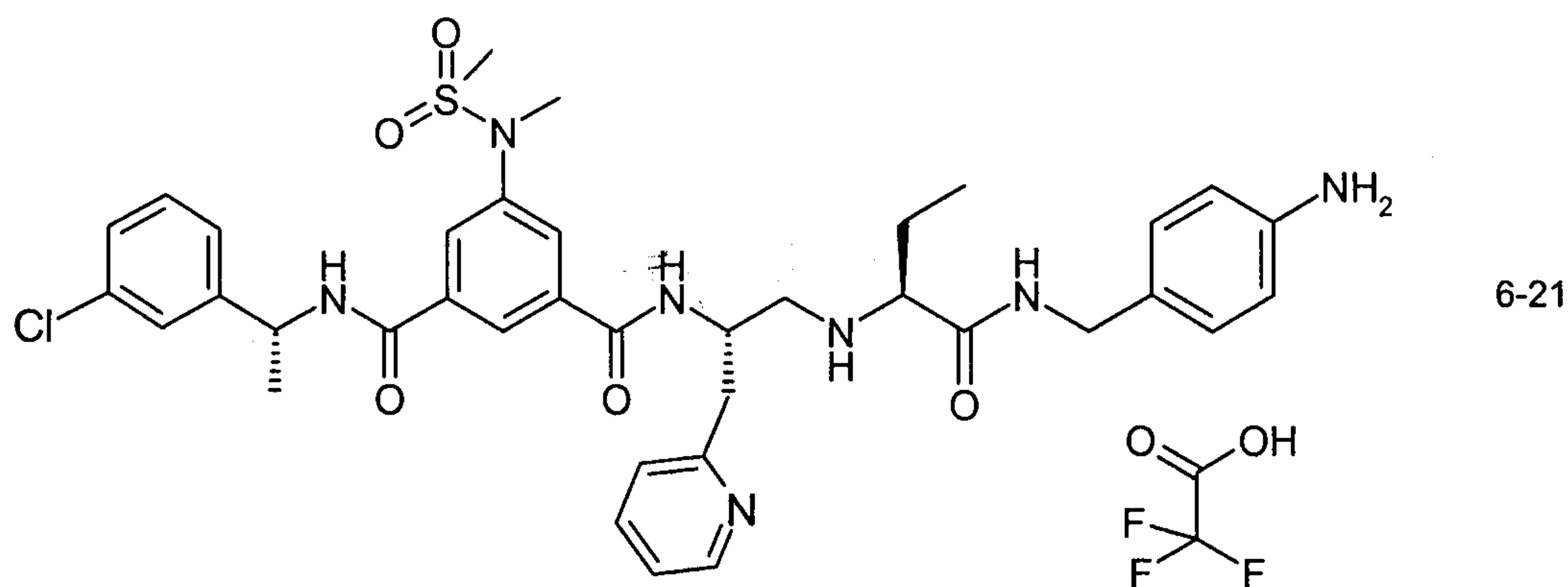


6.20 was prepared analogously to 1-b starting from 5-b and the aldehyde analogous to 6-d, which was obtained by replacing BOC-L-3-thienylalanine by BOC-4-bromo-L-phenylalanine (step 6-a). The crude product was purified by preparative HPLC.

RT (HPLC-MS) = 2.98 min

ES-MS (M+H)⁺ = 726/728 (Br)

Example 6.21



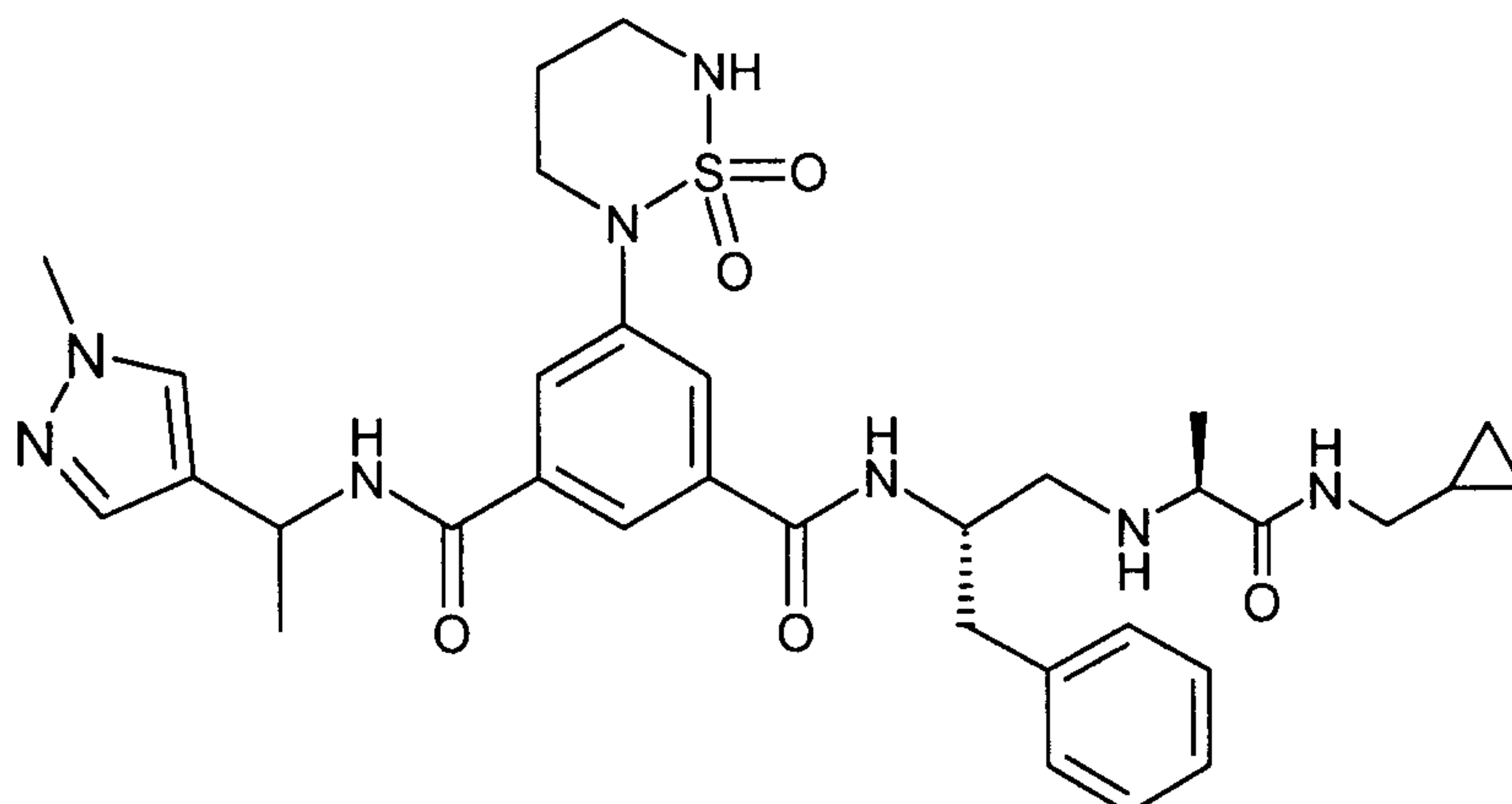
6.21 was prepared analogously to 1-b starting from 6.2-b and the aldehyde analogous to 6-d, which was obtained by replacing BOC-L-3-thienylalanine by BOC-L-2-pyridyl-alanine (step 6-a) and replacing 1.8-h by 6.3-a (step 6-c). The crude product was purified by preparative HPLC.

RT (HPLC-MS) = 2.39 min

ES-MS (M+H)⁺ = 734

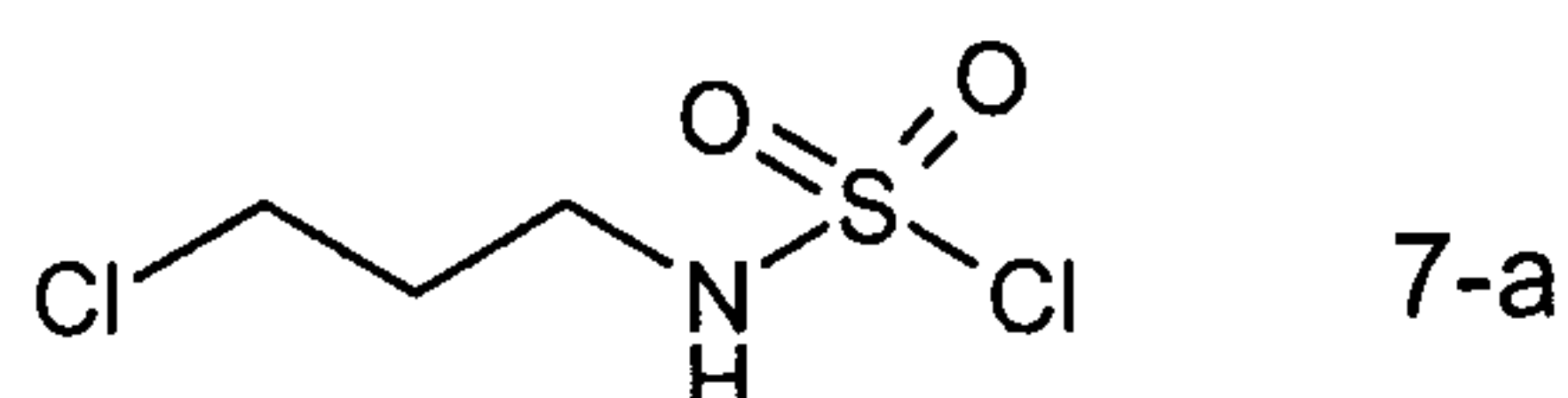
- 137 -

Example 7:



a) Preparation of 7-a:

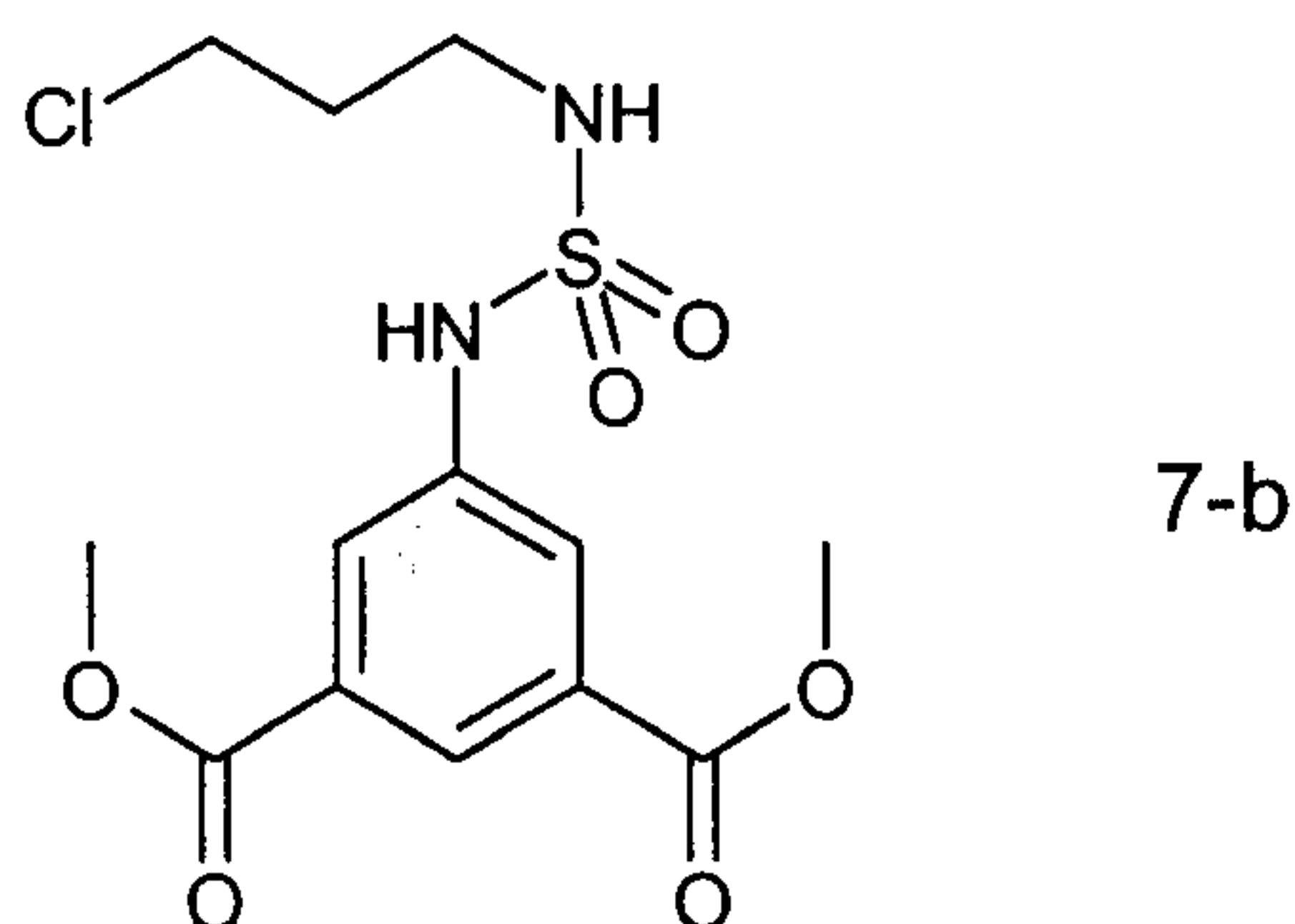
5



7-a

1.3 ml (15.4 mmol) sulphonyl chloride were metered into a solution of 1.0 g (7.7 mmol) 3-chloro-propylamine-hydrochloride in 10 ml acetonitrile while cooling with an ice bath and stirred overnight at 85°C. Then the reaction solution was evaporated down i. vac. **7-a** was obtained in a quantitative yield.

b) Preparation of 7-b:



7-b

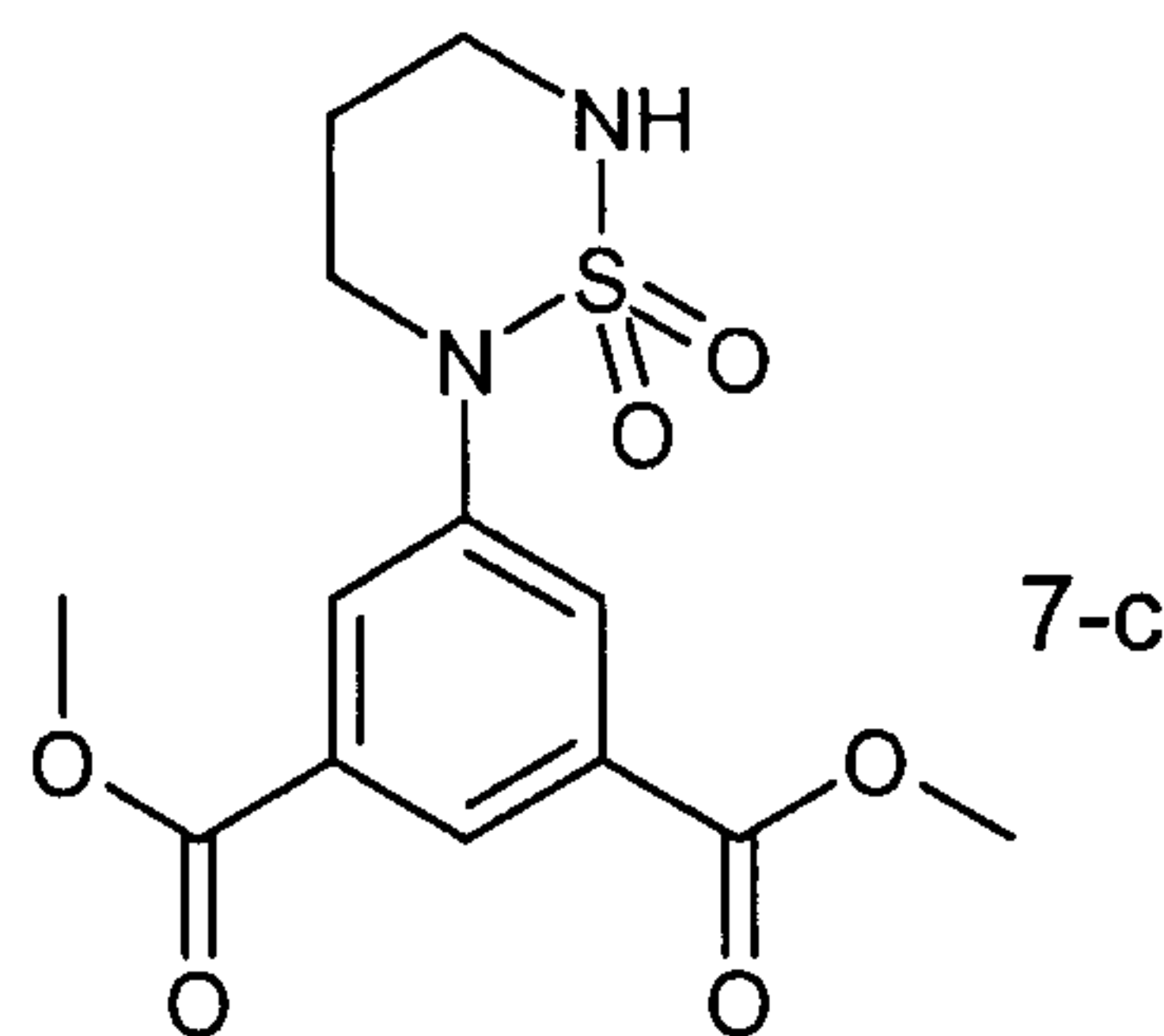
15

1.0 g (4.8 mmol) dimethyl 5-amino-isophthalate were suspended in 10 ml of pyridine and slowly combined with 1.5 g (7.8 mmol) **7-a** and stirred overnight at ambient temperature. Then the reaction solution was combined with dichloromethane and washed with 1N HCl and water, the organic phase was separated off through a phase separation cartridge and evaporated down i. vac.. This yielded 1.1 g (41%) brown crystals **7-b**.

20

RT (HPLC 1) = 4.51 min

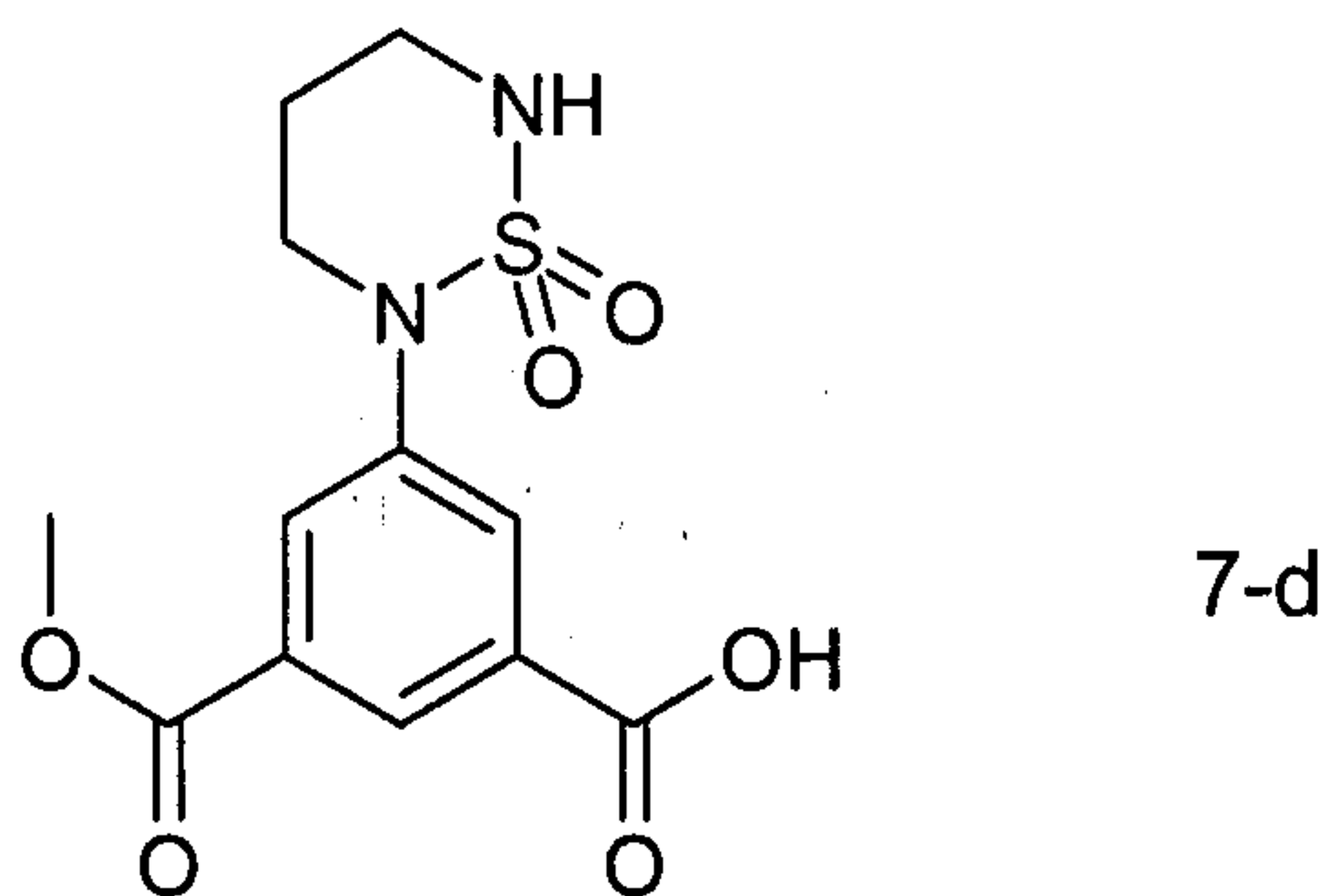
- 138 -

c) Preparation of **7-c**:

10.86 g (29.8 mmol) **7-b** were dissolved in 100 ml DMF, combined with 6.85 g (61.0
5 mmol) potassium-*tert*-butoxide and stirred overnight at 60°C. Then the reaction
solution was combined with water and extracted with dichloromethane. The combined
organic phases were dried on MgSO₄, filtered and the filtrate was evaporated to
dryness i. vac. The residue was purified by MPLC with the eluant (ethyl acetate/
heptane 7:3 to pure methanol). This yielded 2.65 g (27 %) **7-c** as yellowish crystals.

ES-MS (M+H)⁺ = 329

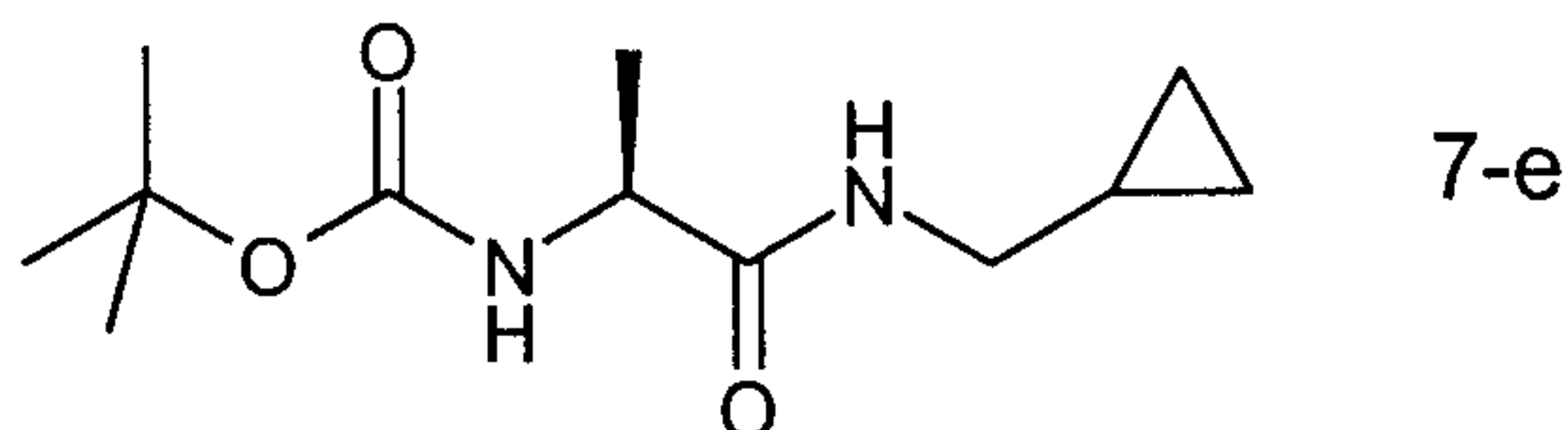
RT (HPLC 1) = 4.29 min

d) Preparation of **7-d**:

2.65 g (8.1 mmol) **7-c** were dissolved in 50 ml of methanol and 50 ml THF, 8.0 ml (8.0
mmol) 1N NaOH were added at 0°C and the reaction solution was stirred for 7 hours
at ambient temperature. Then the solvent was eliminated using the rotary evaporator,
20 the residue was dissolved in 30 ml 1N HCl and extracted with ethyl acetate. The
combined organic phases were dried and purified by chromatography on silica gel with
the eluant (dichloromethane/methanol 80:20). This yielded 1.3 g (51 %) of white
crystals **7-d**.

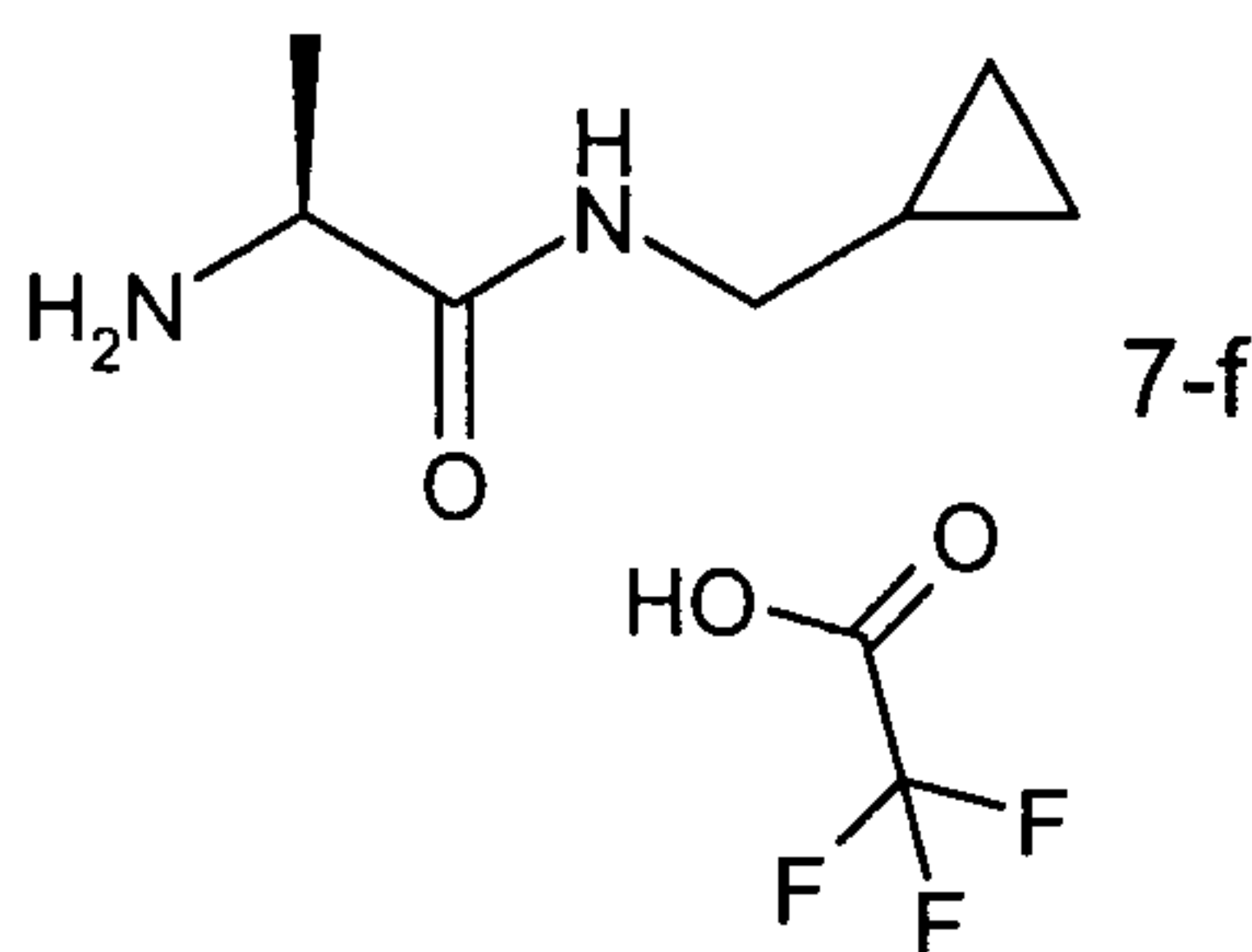
RT (HPLC 1) = 3.79 min

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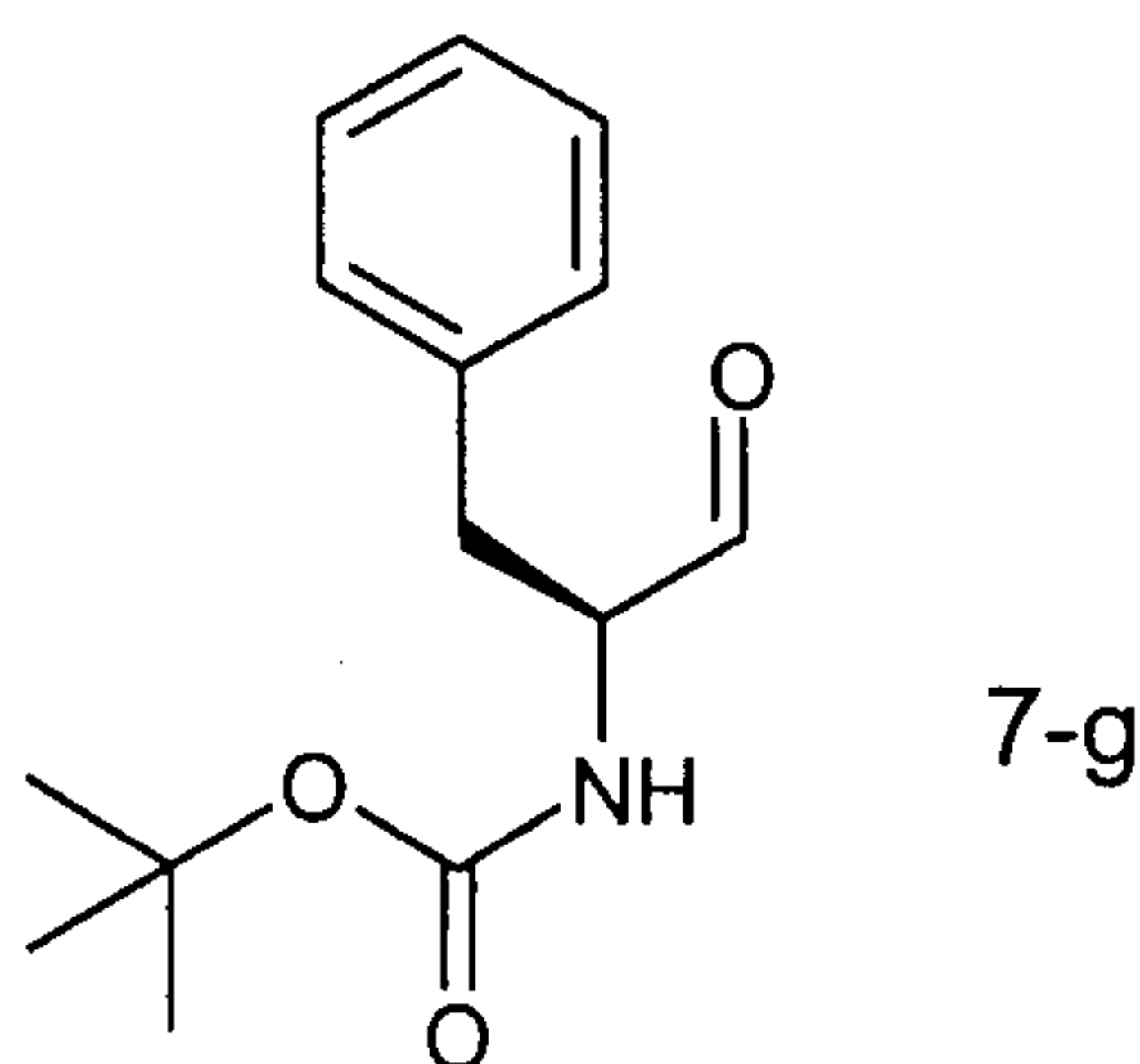
e) Preparation of **7-e**:

9.46 g (50.0 mmol) Boc-L-alanine in 120 ml dichloromethane were combined with 16.1 g (50.0 mmol) TBTU and 25.5 ml (15.0 mmol) DIPEA while cooling with an ice bath, then 5.38 g (50.0 mmol) cyclopropylmethylamine-hydrochloride were added. The reaction solution was stirred for 5 hours at ambient temperature and then extracted with 20% KHCO_3 solution and water. The organic phases were separated using a phase separation cartridge and evaporated to dryness i. vac.. This yielded 12.8 g (95%) of a colourless oil **7-e**.

RT (HPLC-MS) = 2.48 min

f) Preparation of **7-f**:

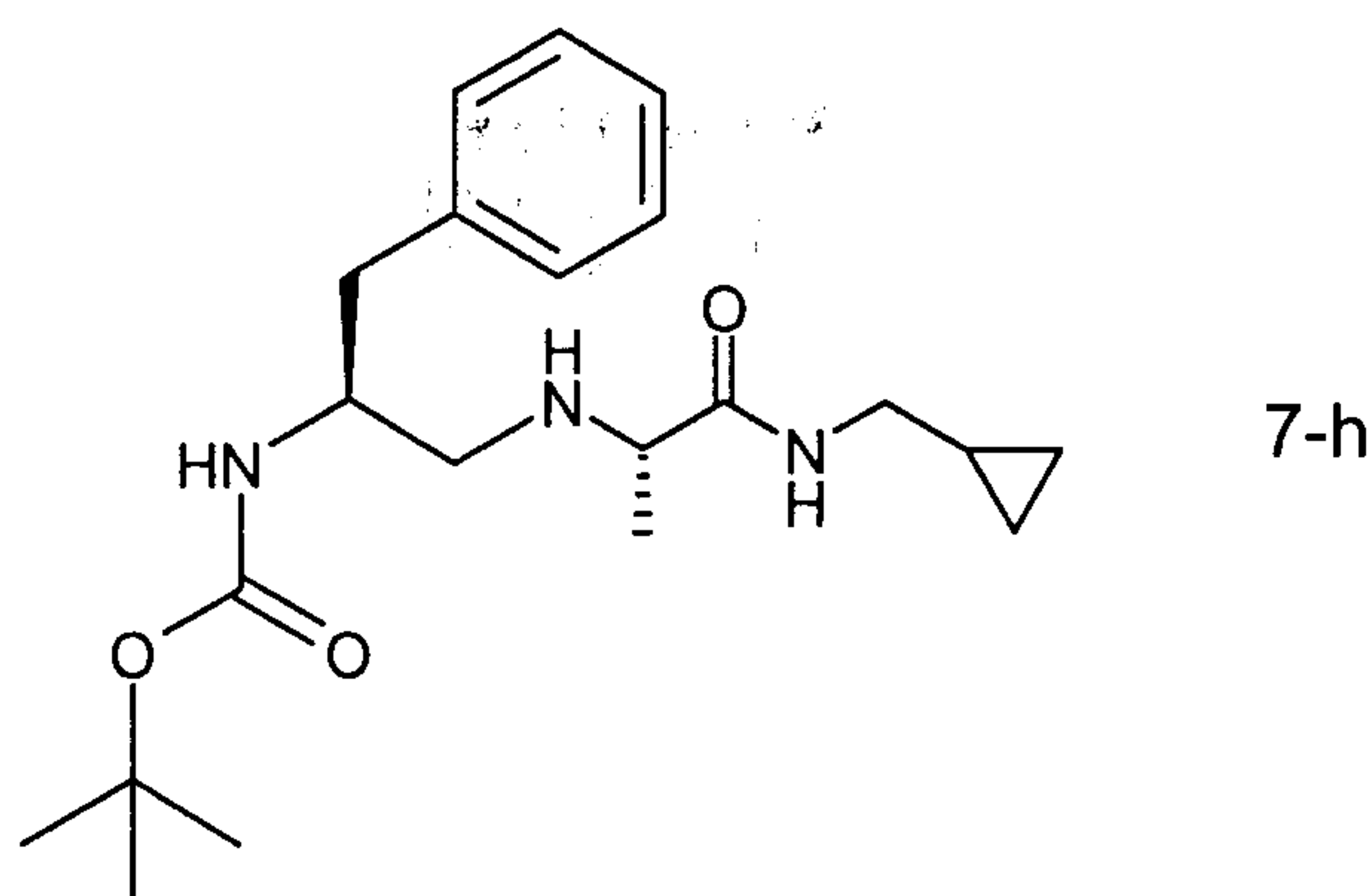
29.0 g (0.1 mol) **7-e** was dissolved in 130 ml dichloromethane and combined with 100 ml (1.3 mol) trifluoroacetic acid. The reaction solution was stirred for 1 h at ambient temperature, then evaporated to dryness using the rotary evaporator. This gave a quantitative yield of **7-f** as a yellow oil.

g) Preparation of **7-g**:

29.7 g (70.0 mmol) Dess-Martin-periodinane were suspended in 150 ml dichloromethane, then within 40 minutes a solution of 16.0 g (63.7 mmol) Boc-

- 140 -

phenylalaninol in 150 ml dichloromethane was metered in. The reaction solution was stirred for 2 hours at ambient temperature, then combined with 200 ml 20% KHCO_3 solution and 200 ml 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was stirred for 20 min at ambient temperature, the phases were separated and the organic phase was washed with 20% KHCO_3 solution and water. The organic phase was dried and evaporated to dryness using the rotary evaporator. This gave a quantitative yield of **7-g** as white crystals.

h) Preparation of **7-h**:

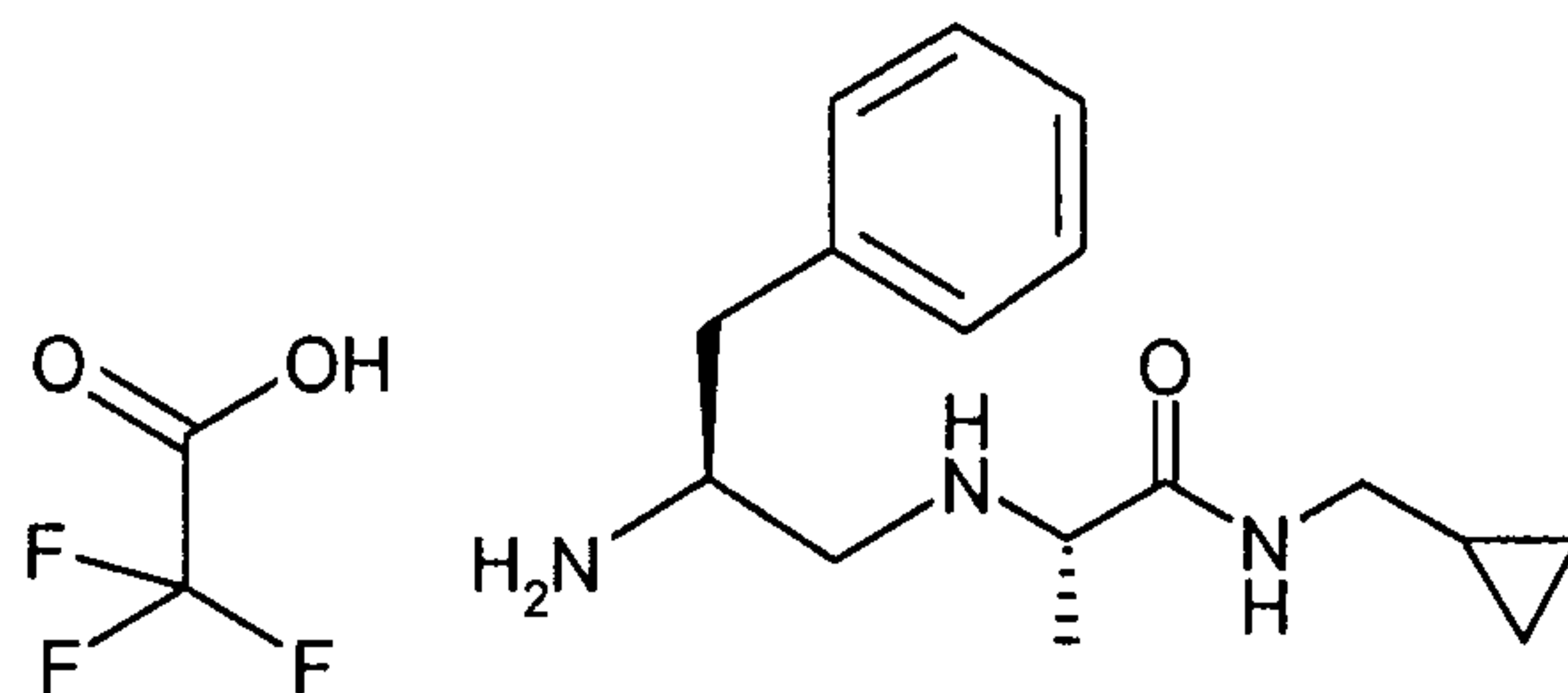
15.4 g (61.2 mmol) **7-f** were dissolved in 200 ml acetonitrile and combined with 10.5 ml (61.2 mmol) DIPEA. The mixture was stirred for 10 min at ambient temperature, 15.3 g (61.2 mmol) **7-g** were added and the mixture was cooled to 0°C. Then the reaction solution was combined with 7.0 ml (122 mmol) acetic acid and 20.5 g (91.8 mmol) sodium triacetoxyborohydride and stirred overnight at ambient temperature. The reaction solution was evaporated to dryness using the rotary evaporator and the residue was combined with dichloromethane and 1N NaHCO_3 solution. The phases were separated, the organic phase was dried and evaporated to dryness i. vac.. The residue was purified by chromatography on silica gel with the eluant (ethyl acetate/heptane 7:3 to ethyl acetate/heptane 1:0). This yielded 13.1 g (43%) of light yellow crystals **7-h**.

RT (HPLC 1) = 4.36 min

ES-MS $(\text{M}+\text{H})^+ = 376$

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i) Preparation of 7-i:

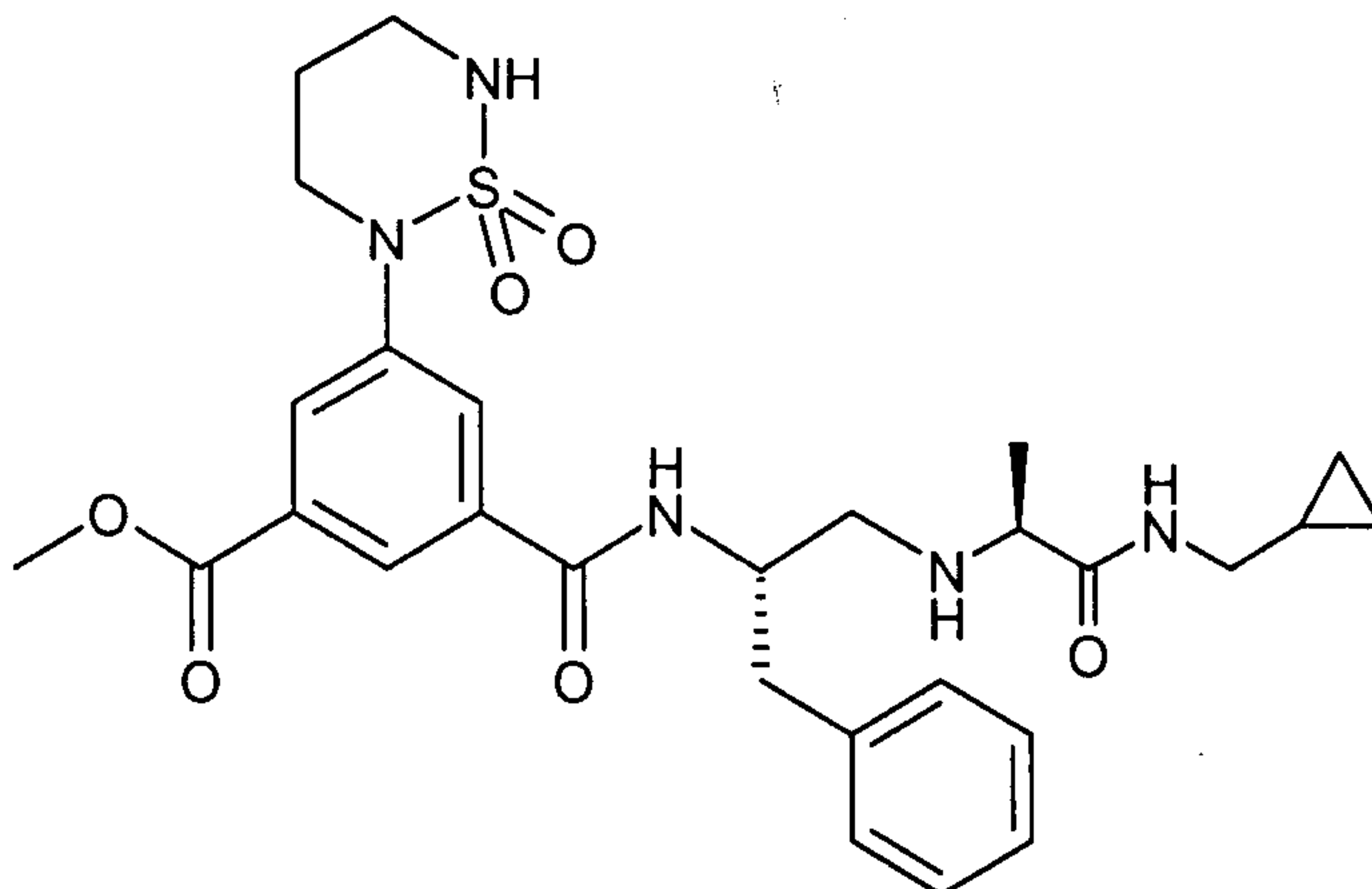


7-i

7-i was prepared analogously to Example 7-f from 7-h.

5 RT (HPLC 1) = 3.37 min

j) Preparation of 7-j:



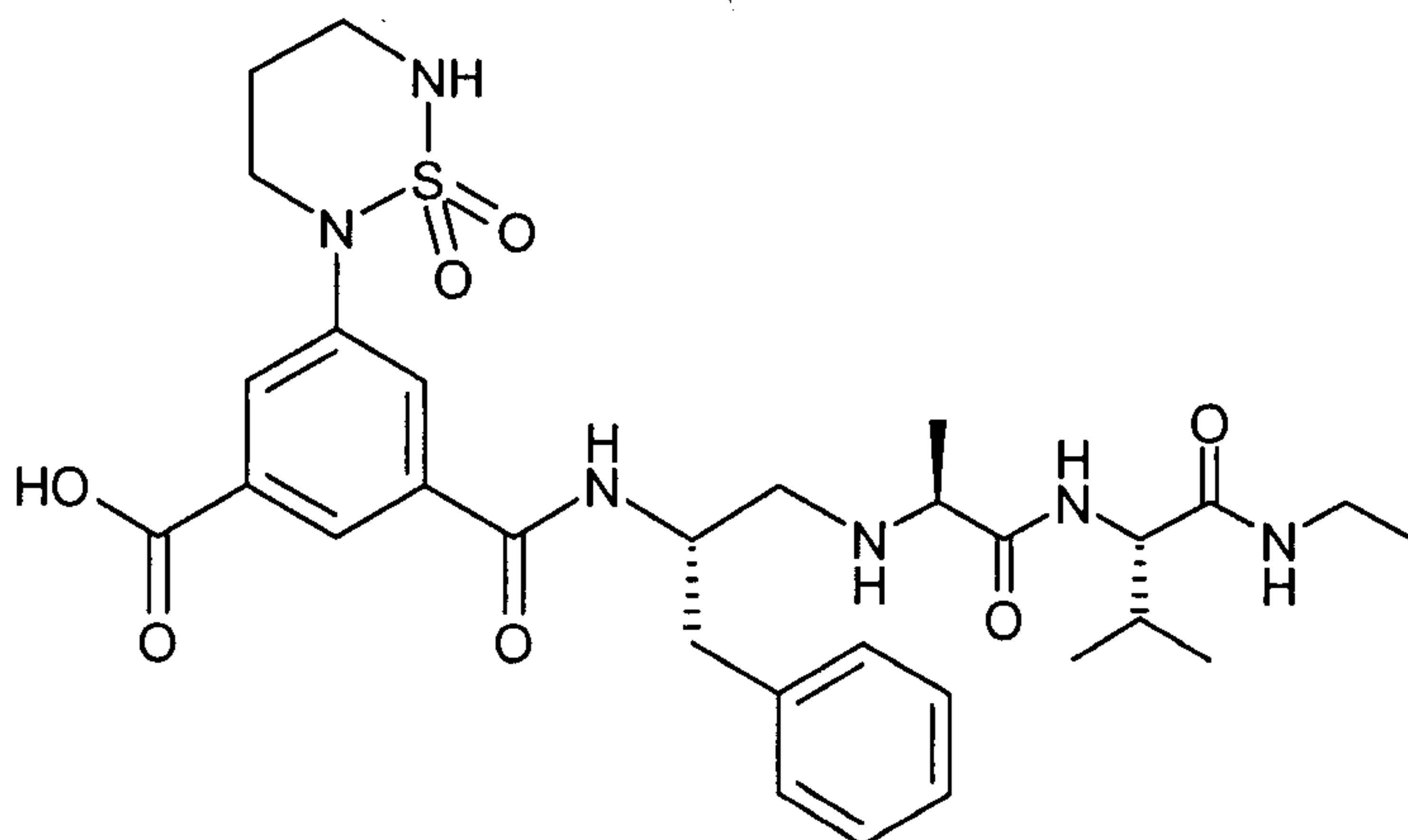
7-j

10 7-j was prepared analogously to 7-e from 7-d and 7-i.

RT (HPLC-MS) = 2.55 min

(M+H)⁺ (HPLC-MS) = 573

k) Preparation of 7-k:



7-k

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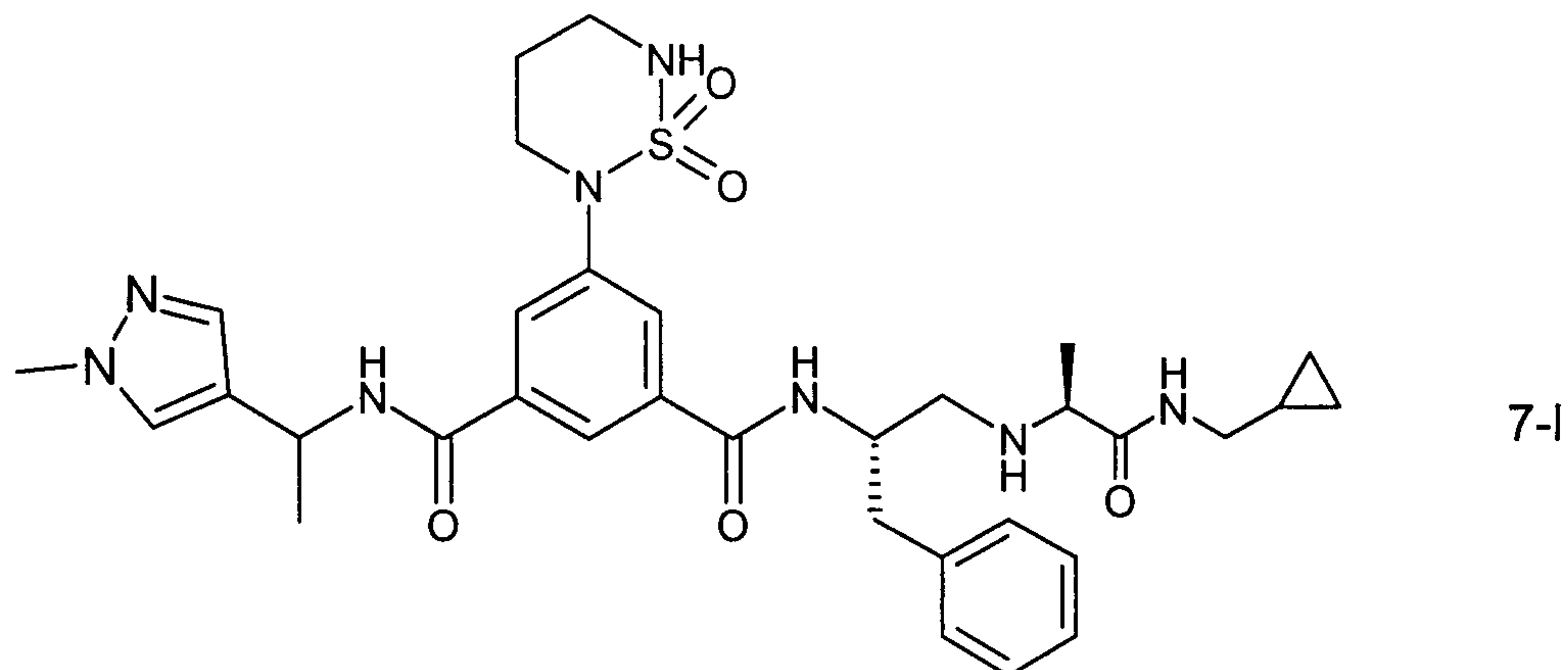
7-k was prepared analogously to **7-d** from **7-j**.

RT (HPLC 1) = 4.03 min

ES-MS (M+H)⁺ = 556

5

I) Preparation of **7-l**:

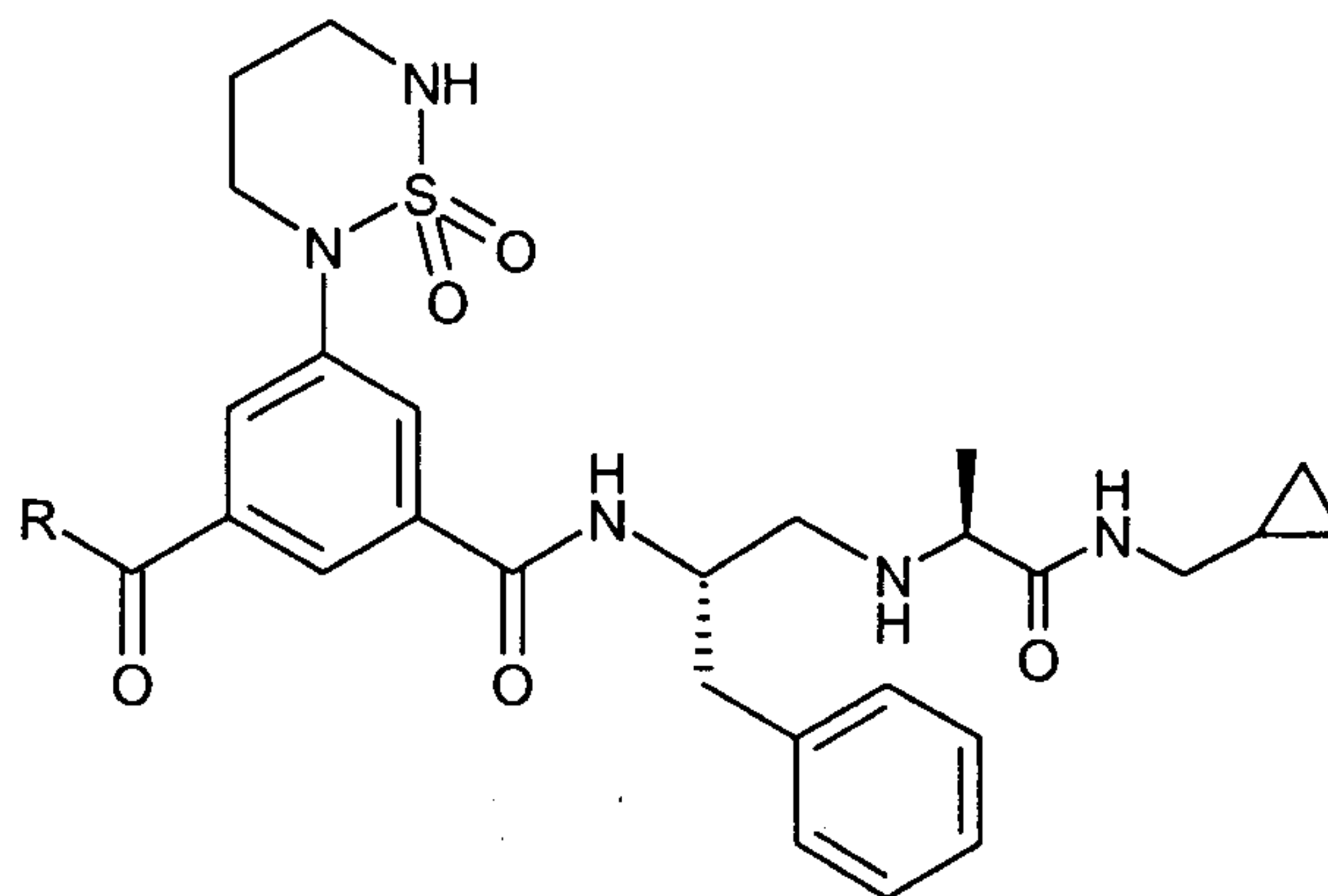


7-l was prepared analogously to **7-e** from **7-k** and 1-(1-methyl-1*H*-pyrazol-4-yl)-ethylamine.

10 RT (HPLC 1) = 4.08 min

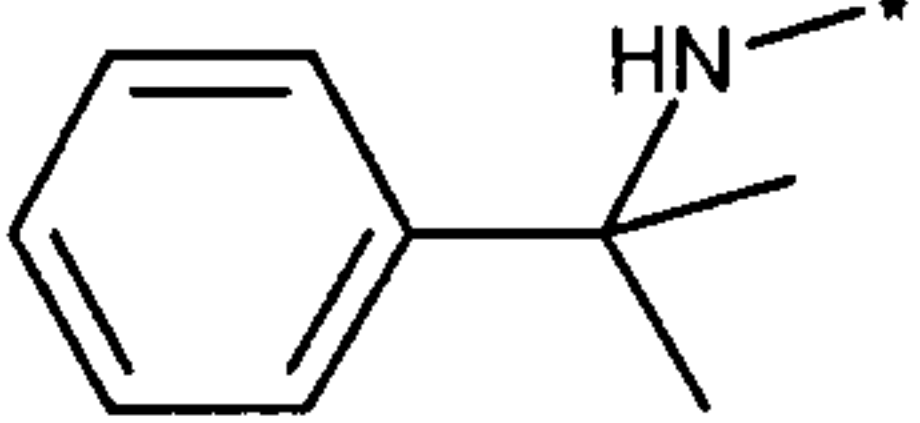
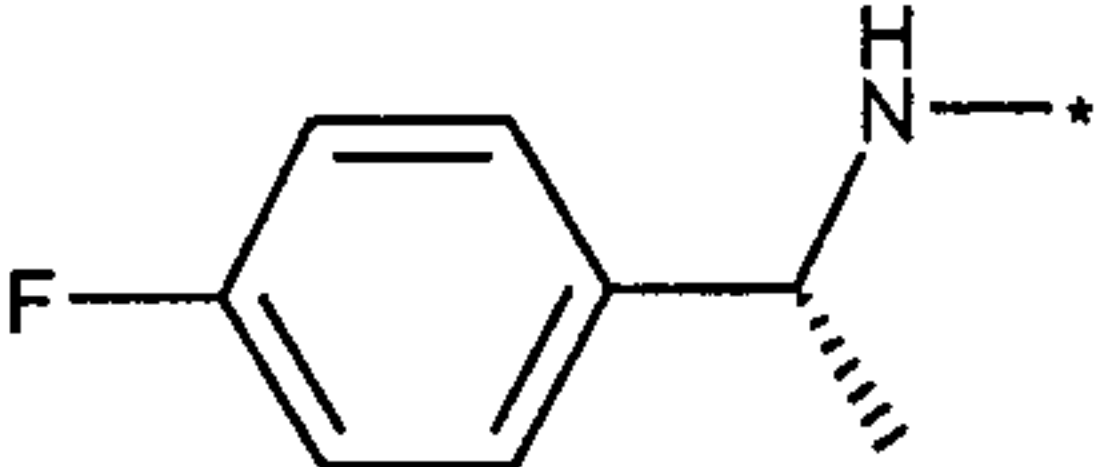
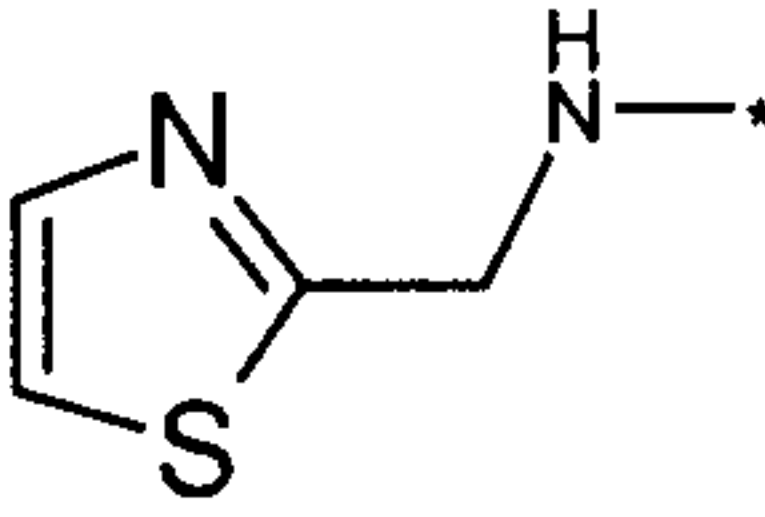
ES-MS (M+H)⁺ = 665

The following compounds were prepared analogously to **7-l** from **7-k** and the corresponding amount of amine:



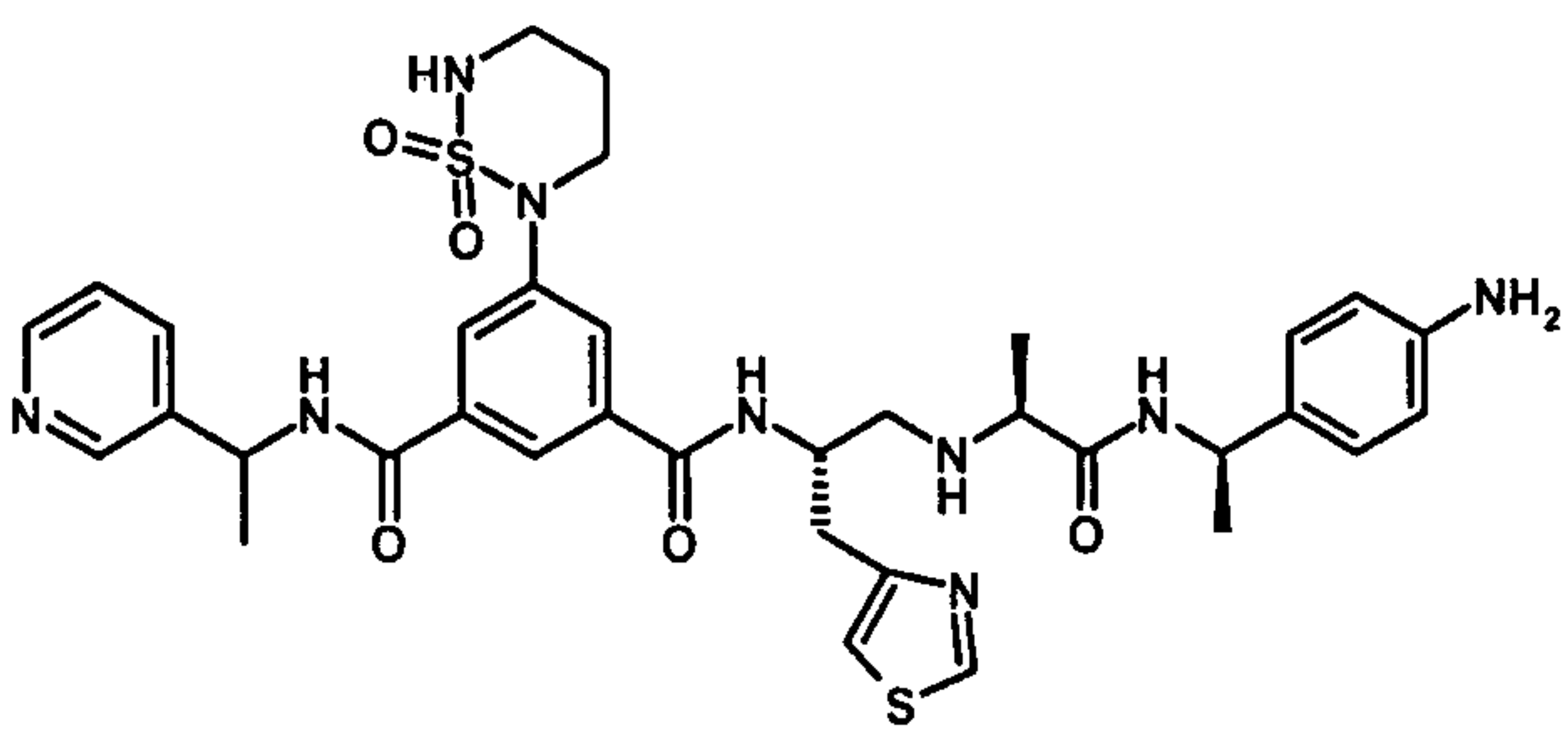
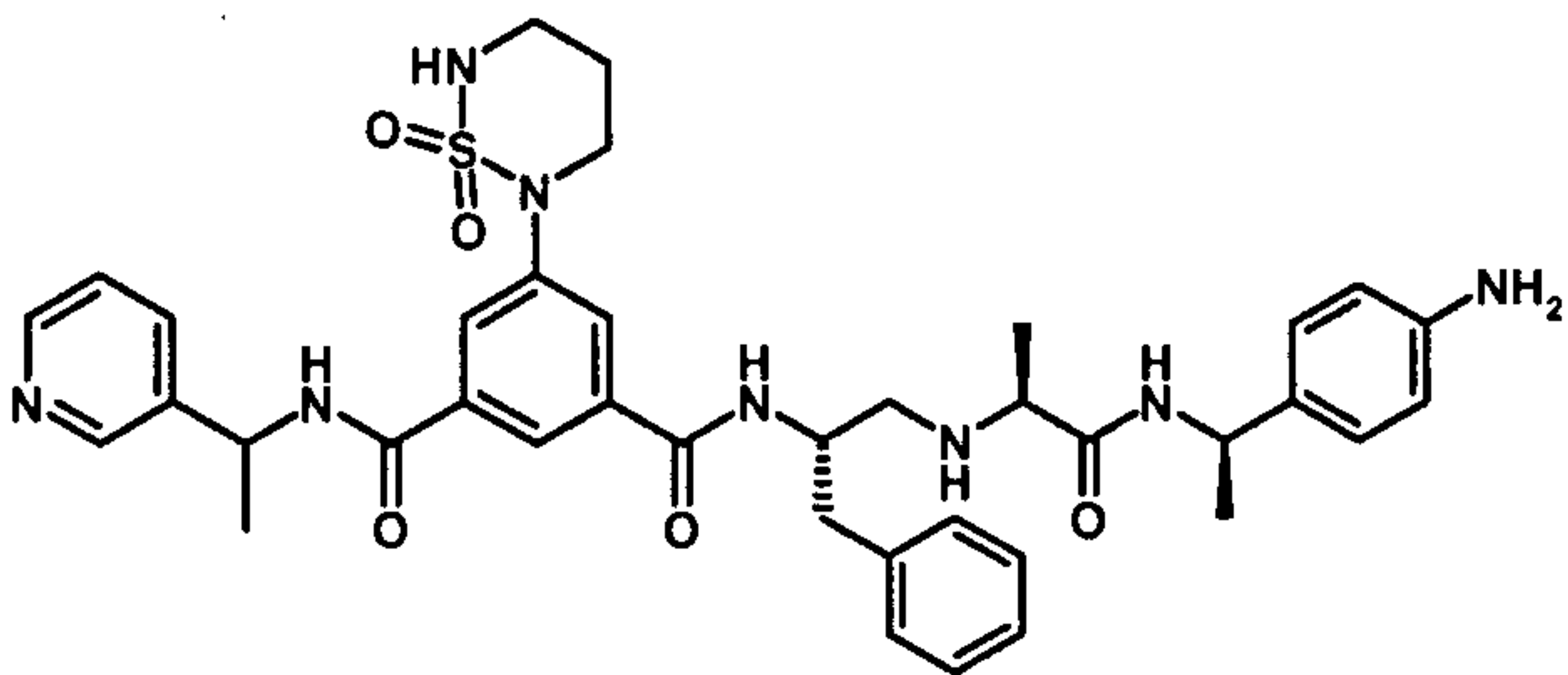
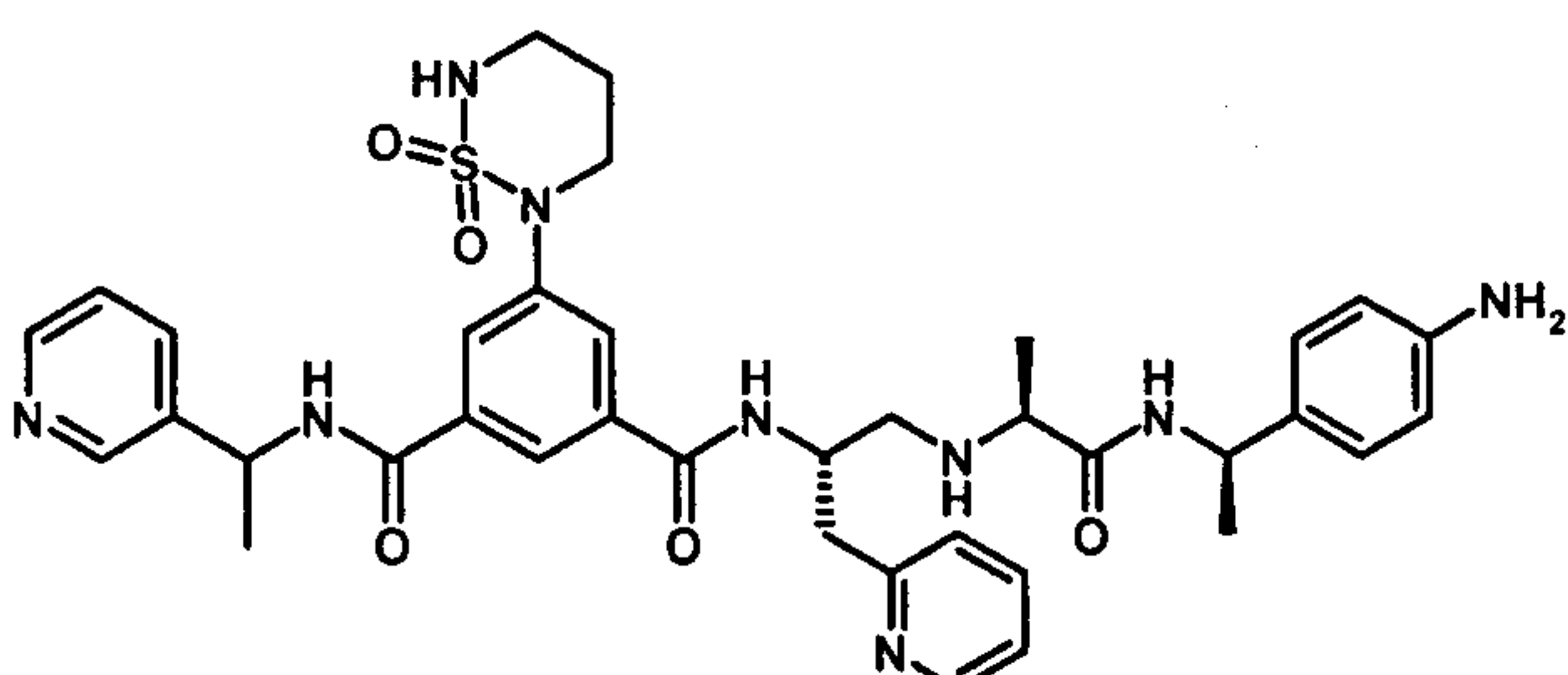
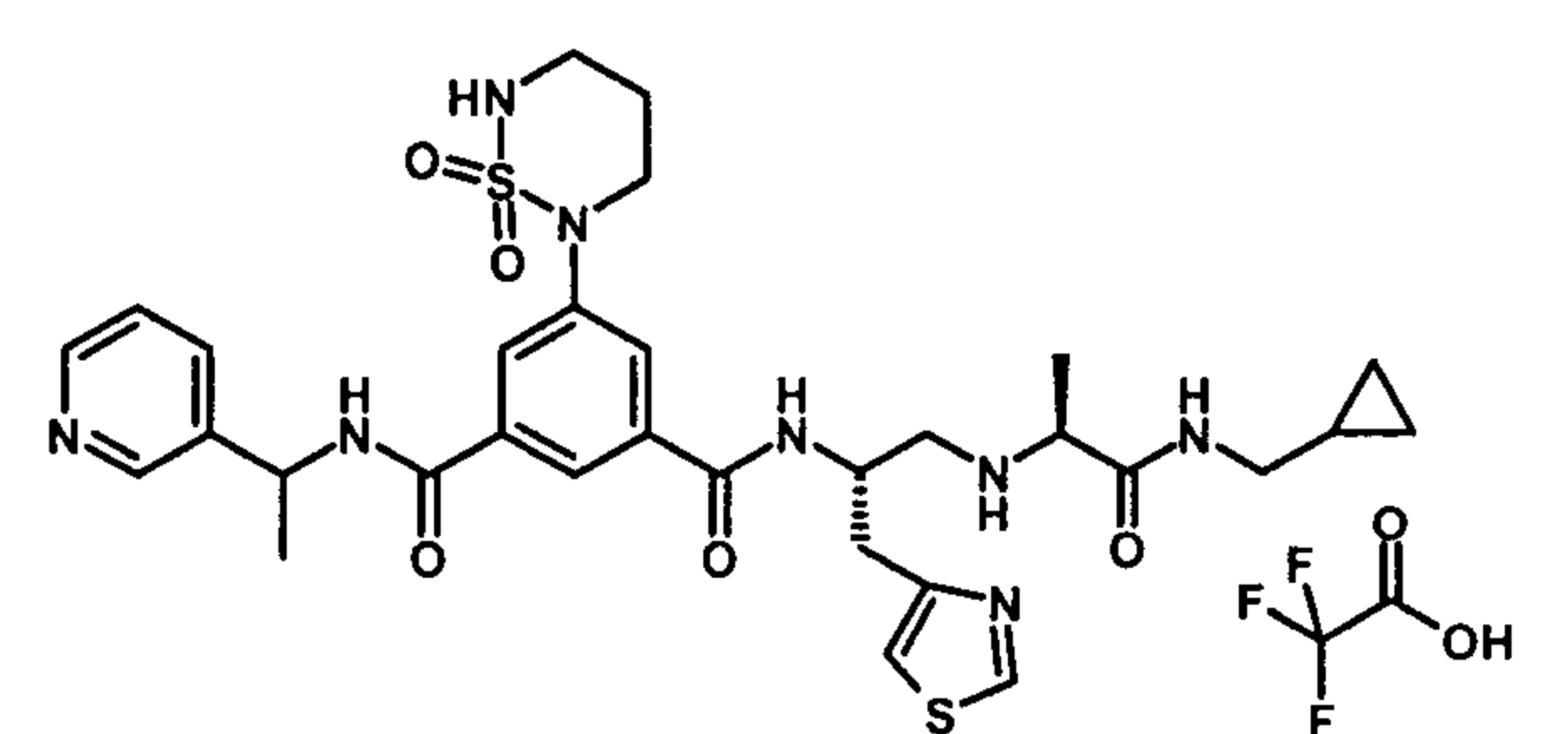
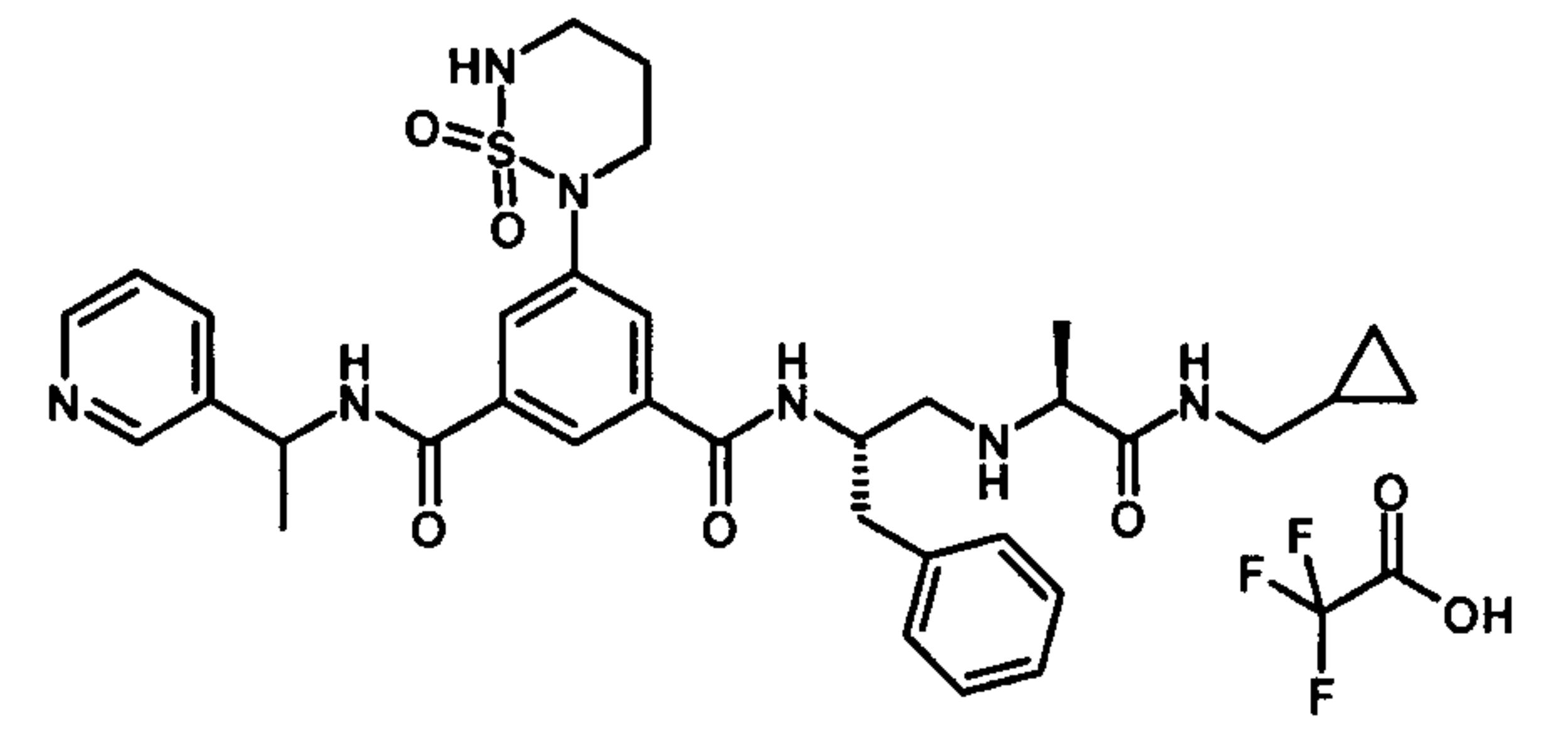
15

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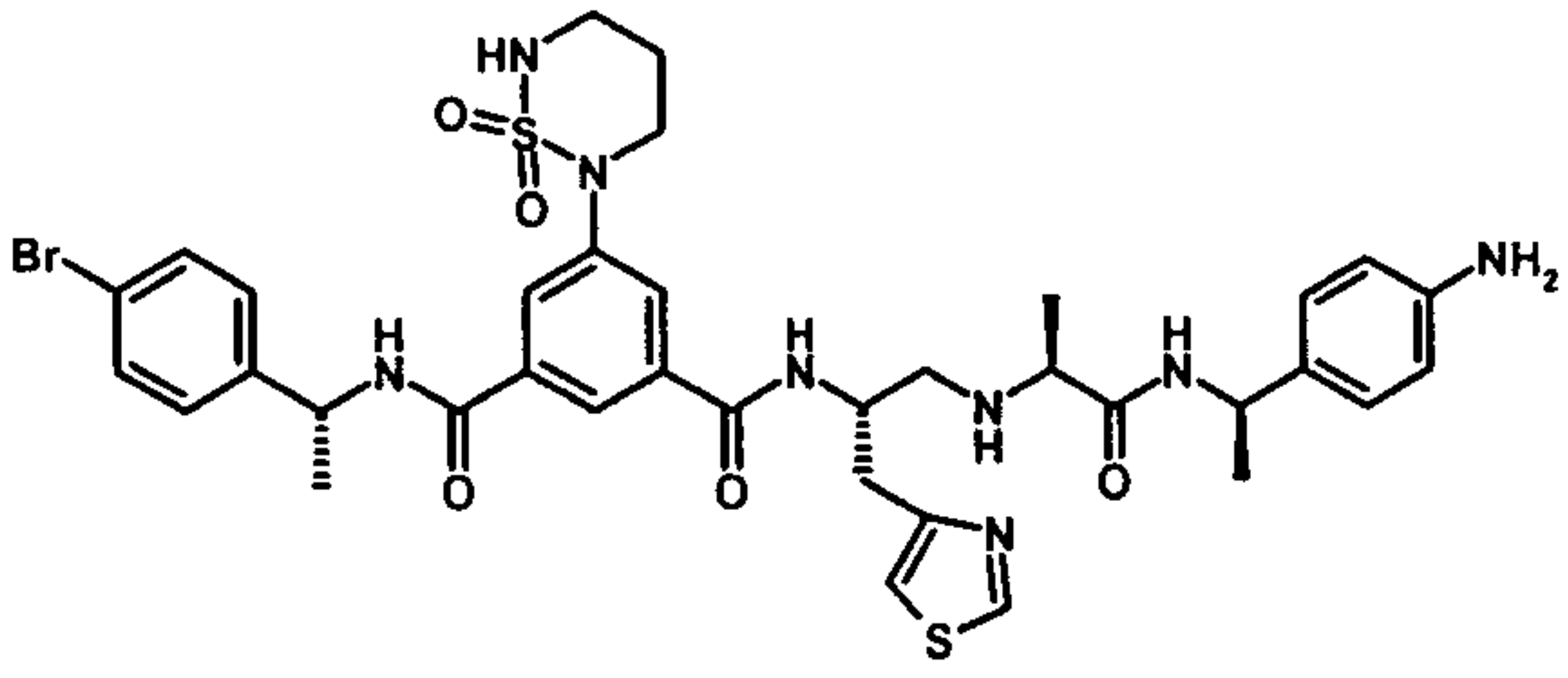
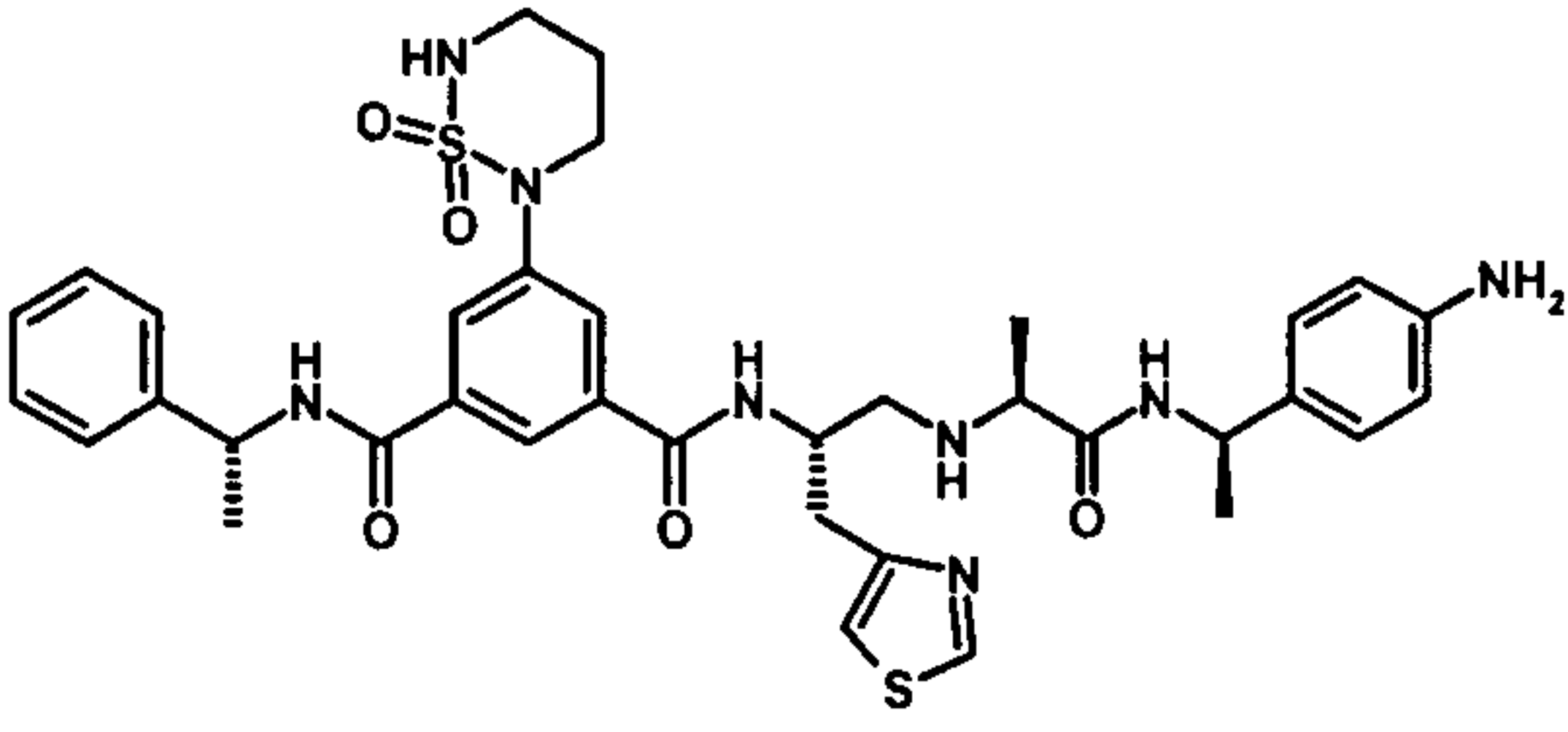
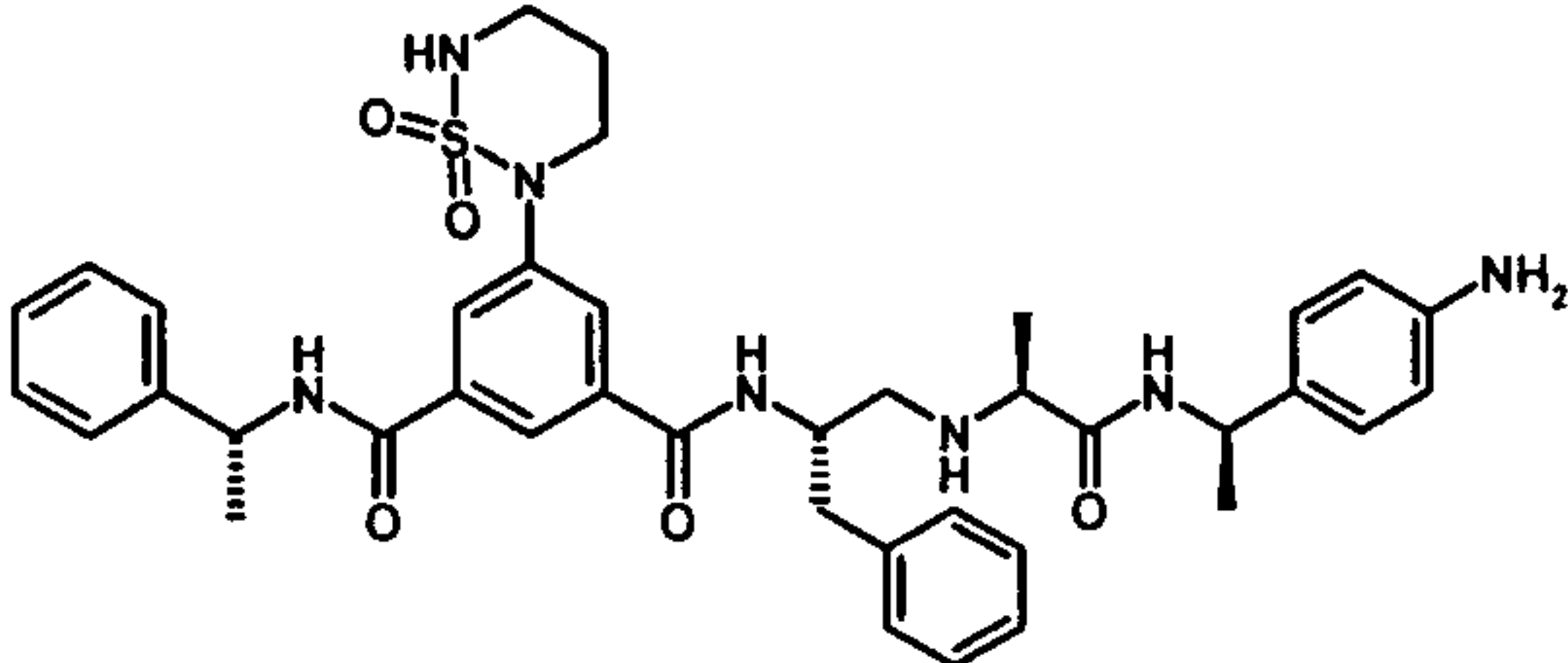
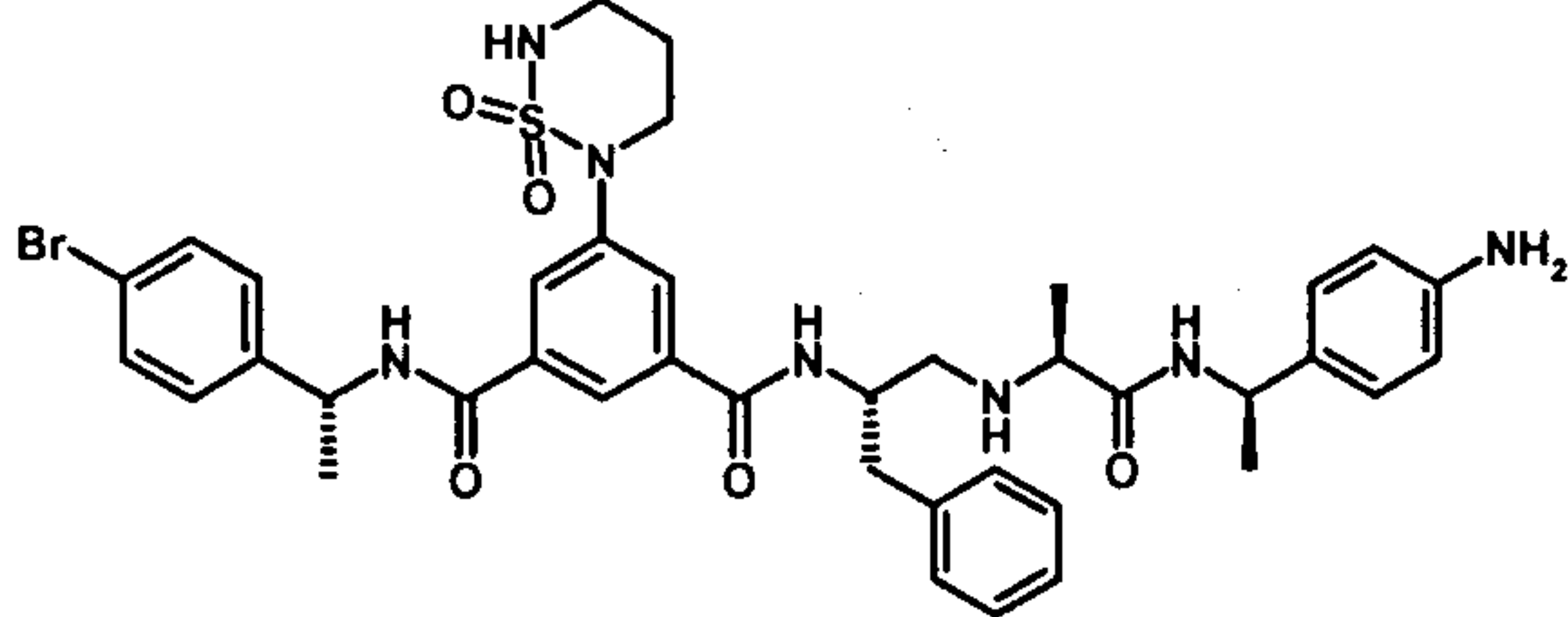
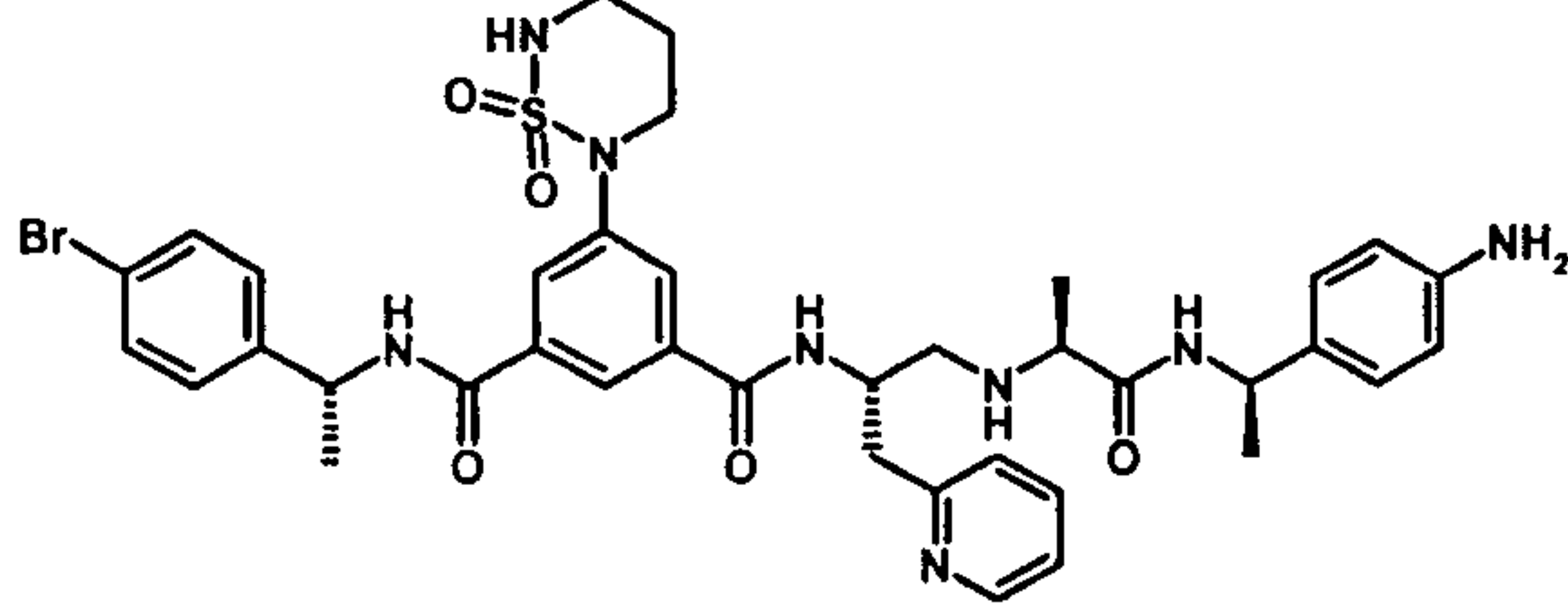
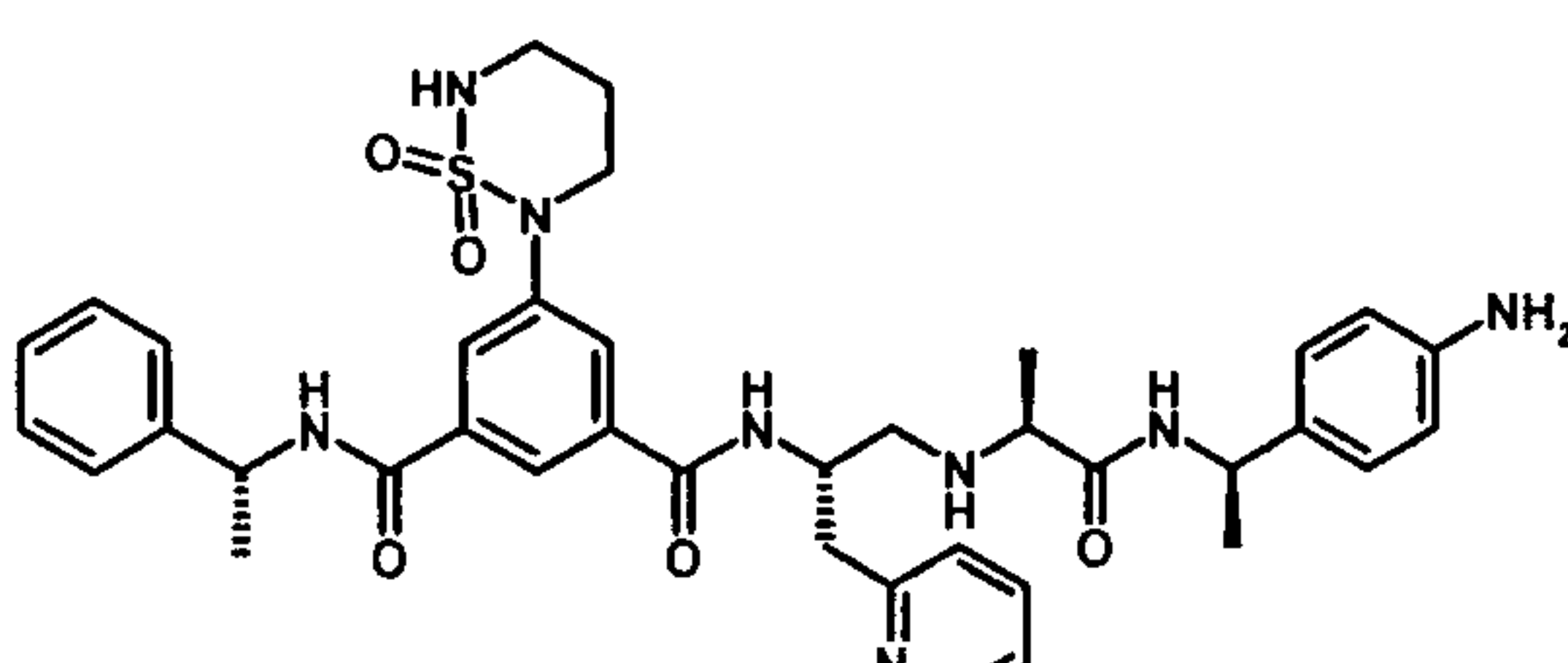
Example	R	
7.1		RT (HPLC 1) = 4.72 min ES-MS (M-H) ⁺ = 673
7.2		RT (HPLC 1) = 4.62 min ES-MS (M+H) ⁺ = 679
7.3		RT (HPLC 1) = 4.09 min ES-MS (M+H) ⁺ = 654

The following compounds were prepared analogously to **Example 7** by using the
5 corresponding educts:

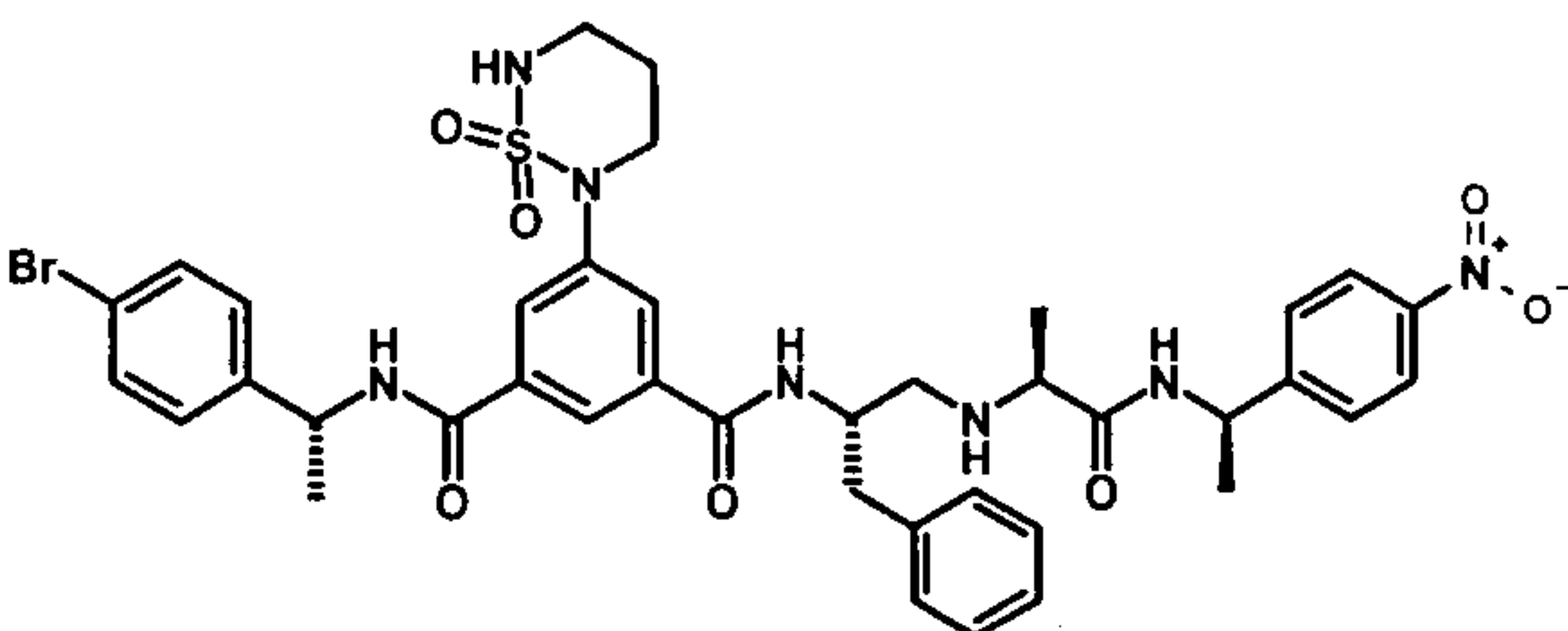
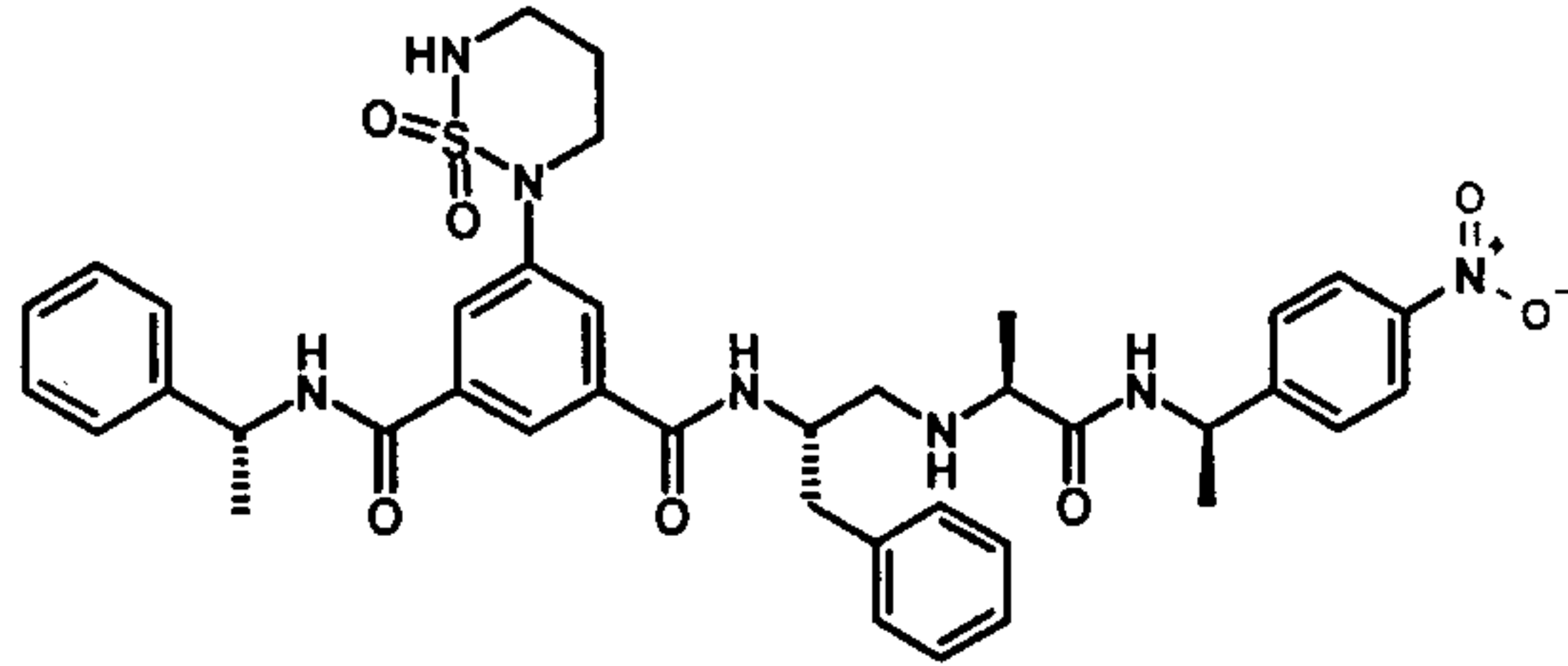
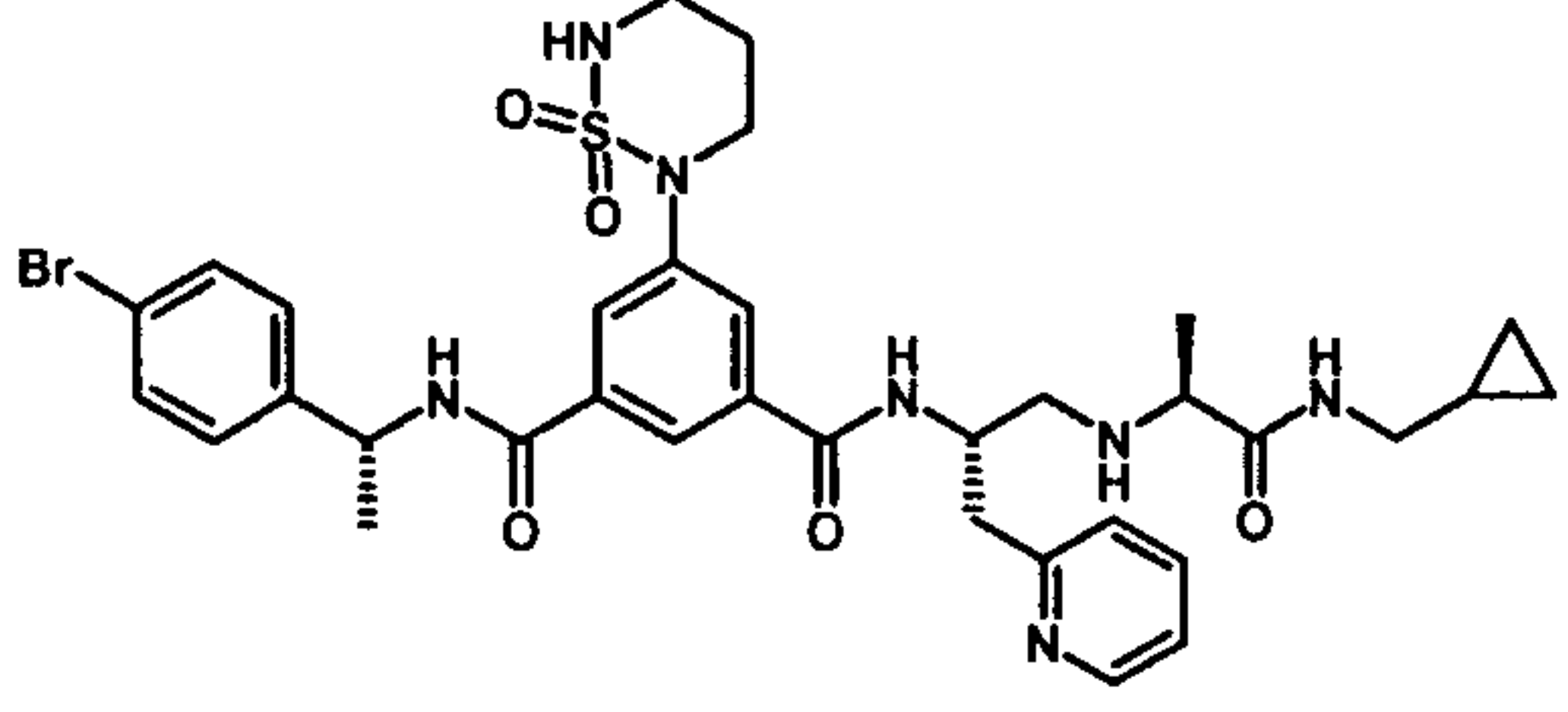
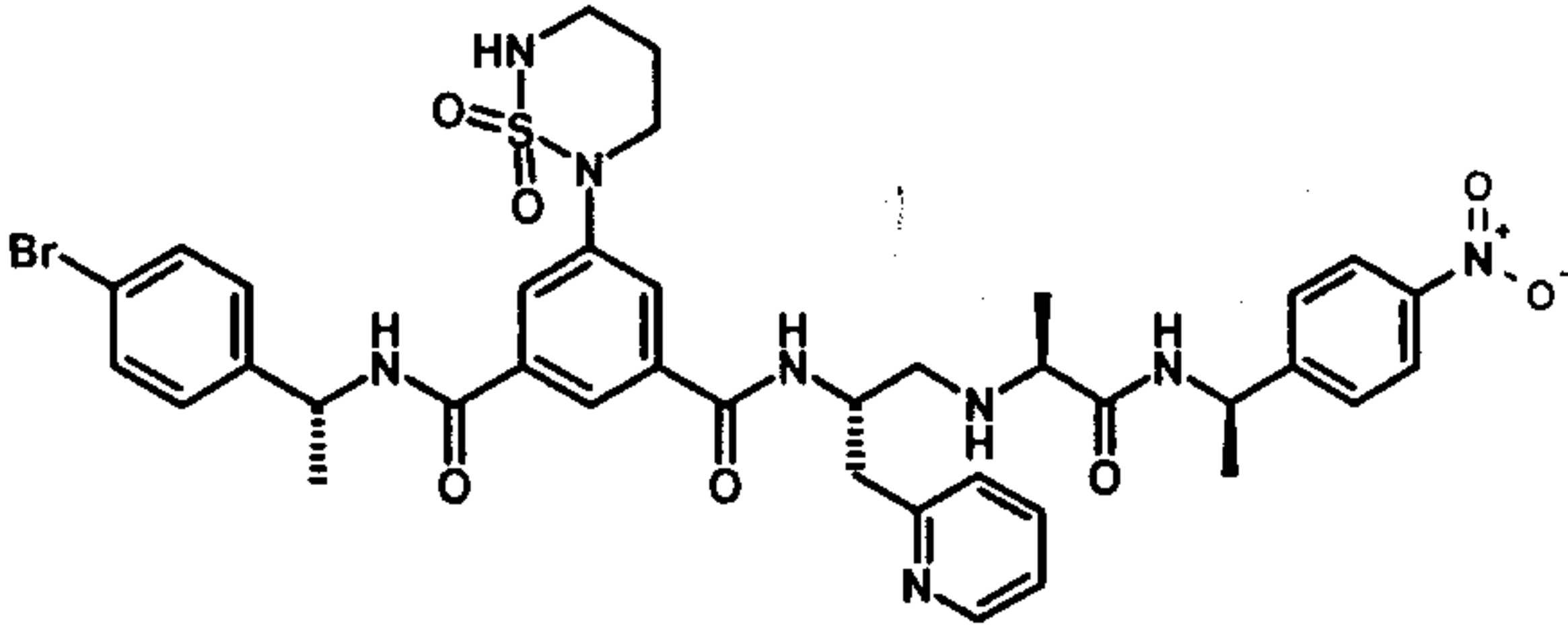
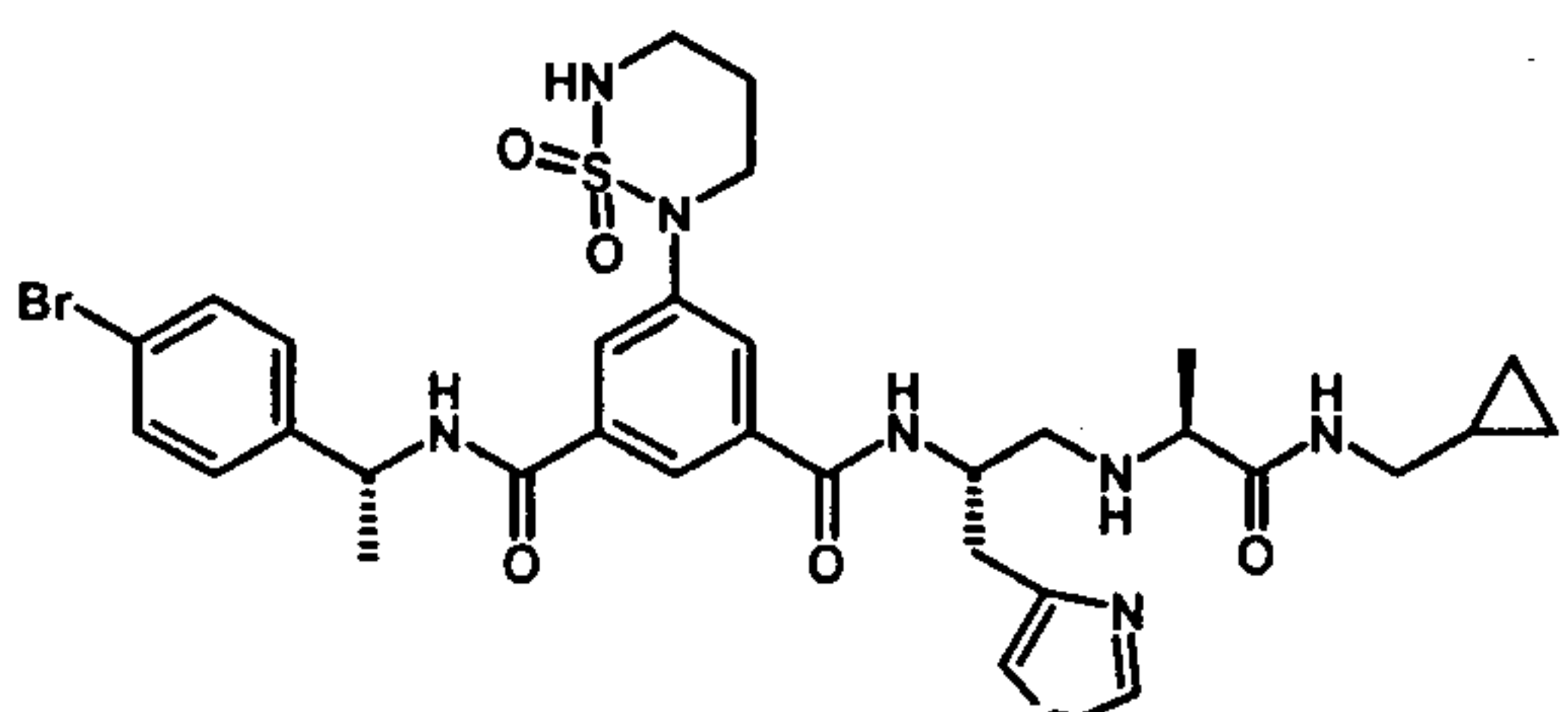
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Example		
7.4		RT (HPLC-MS) = 1.91 min. ES-MS (M+H) ⁺ = 734
7.5		RT (HPLC-MS) = 2.01 min. ES-MS (M+H) ⁺ = 727
7.6		RT (HPLC-MS) = 1.77 min. ES-MS (M+H) ⁺ = 728
7.7		RT (HPLC-1) = 3.56 min. ES-MS (M+H) ⁺ = 669
7.8		RT (HPLC-1) = 3.80 min. ES-MS (M+H) ⁺ = 662

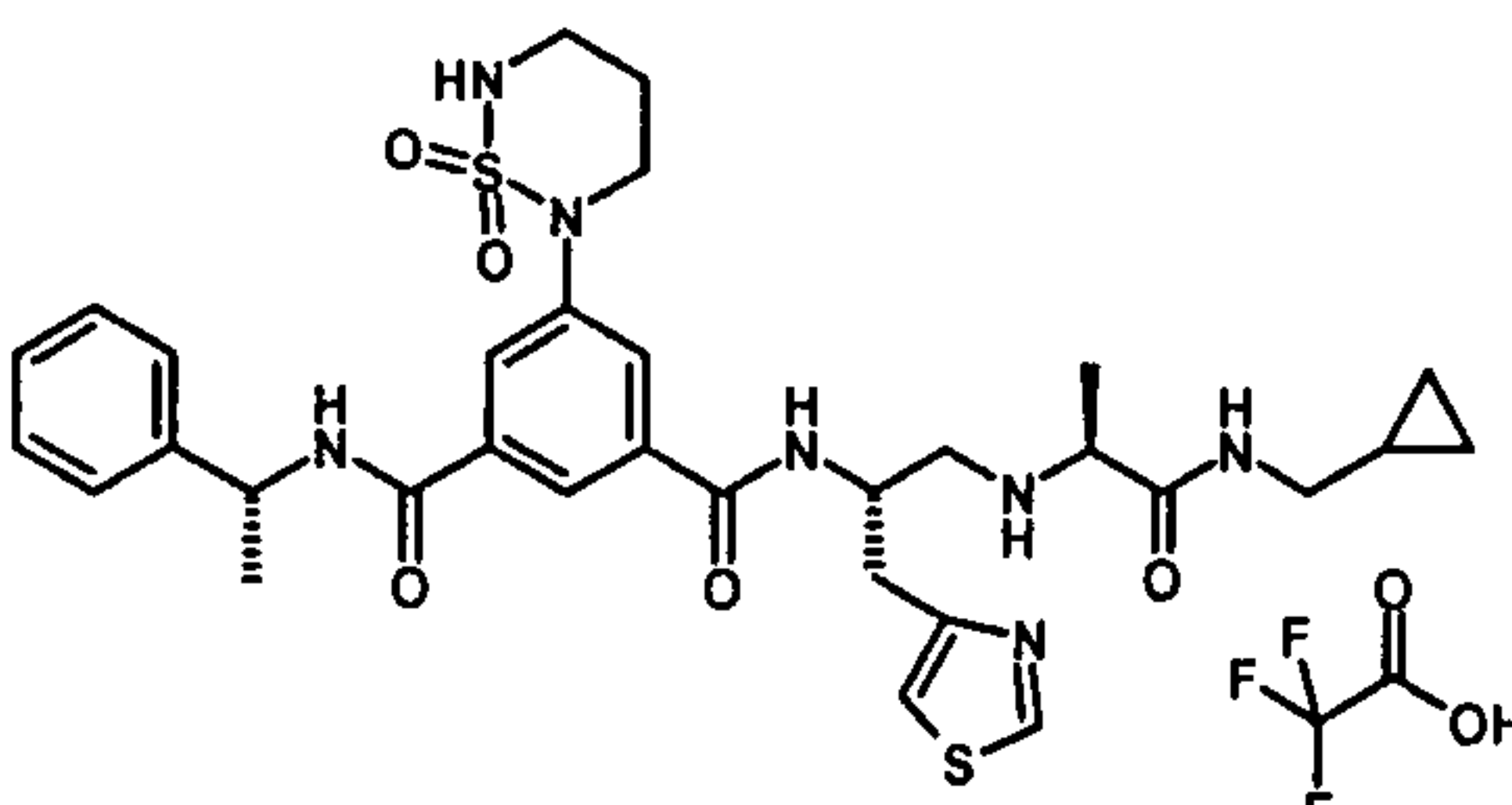
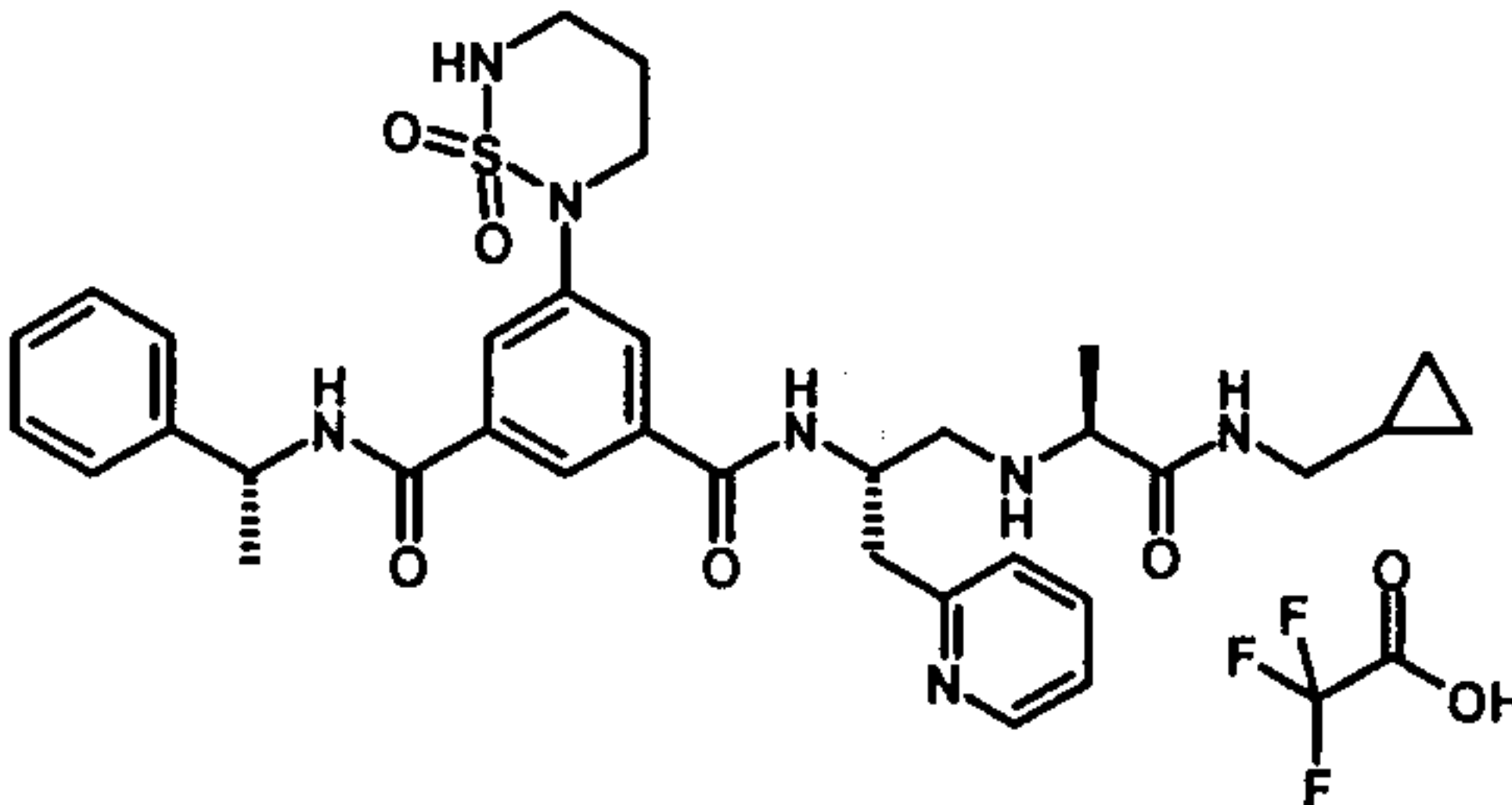
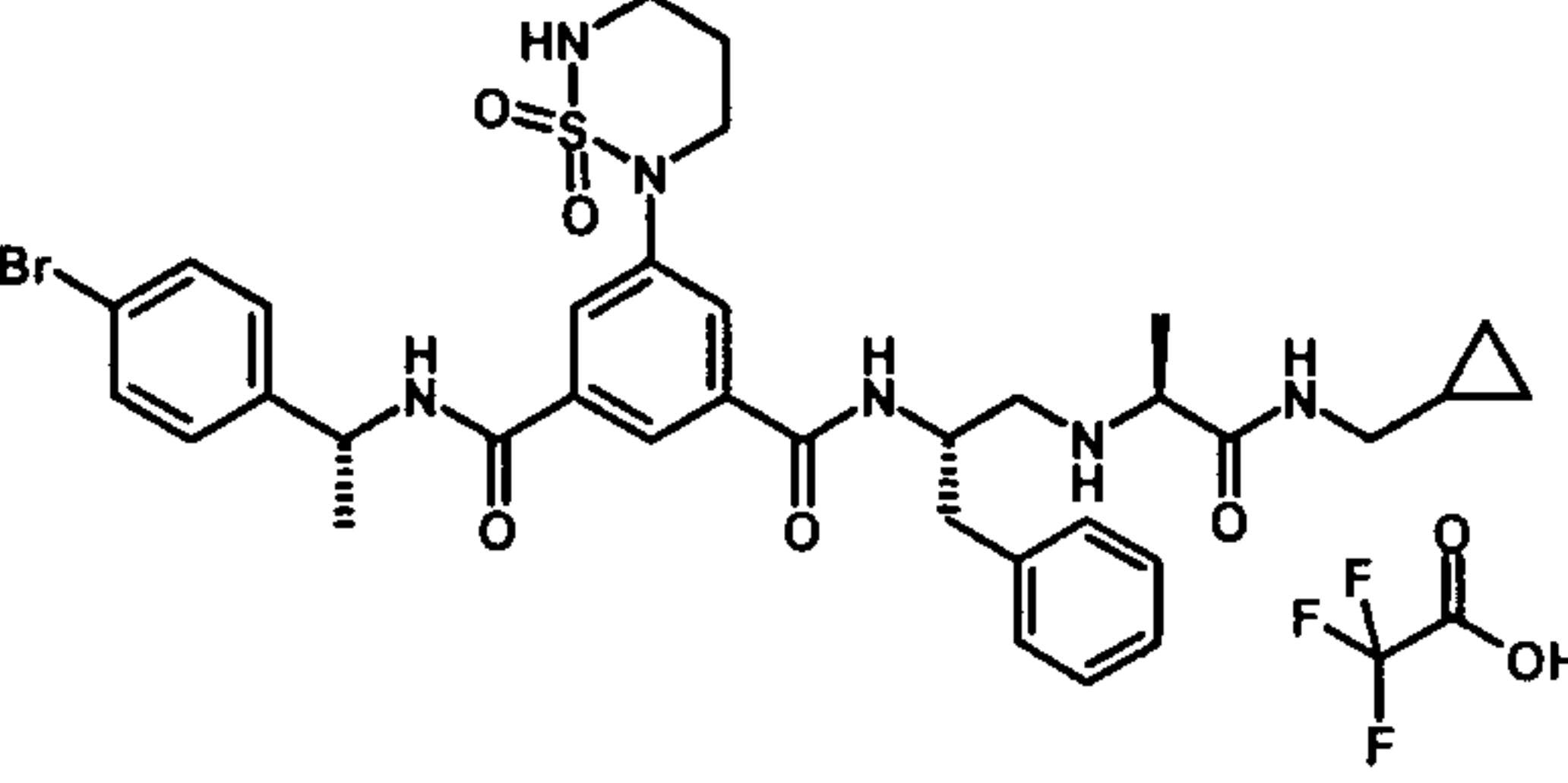
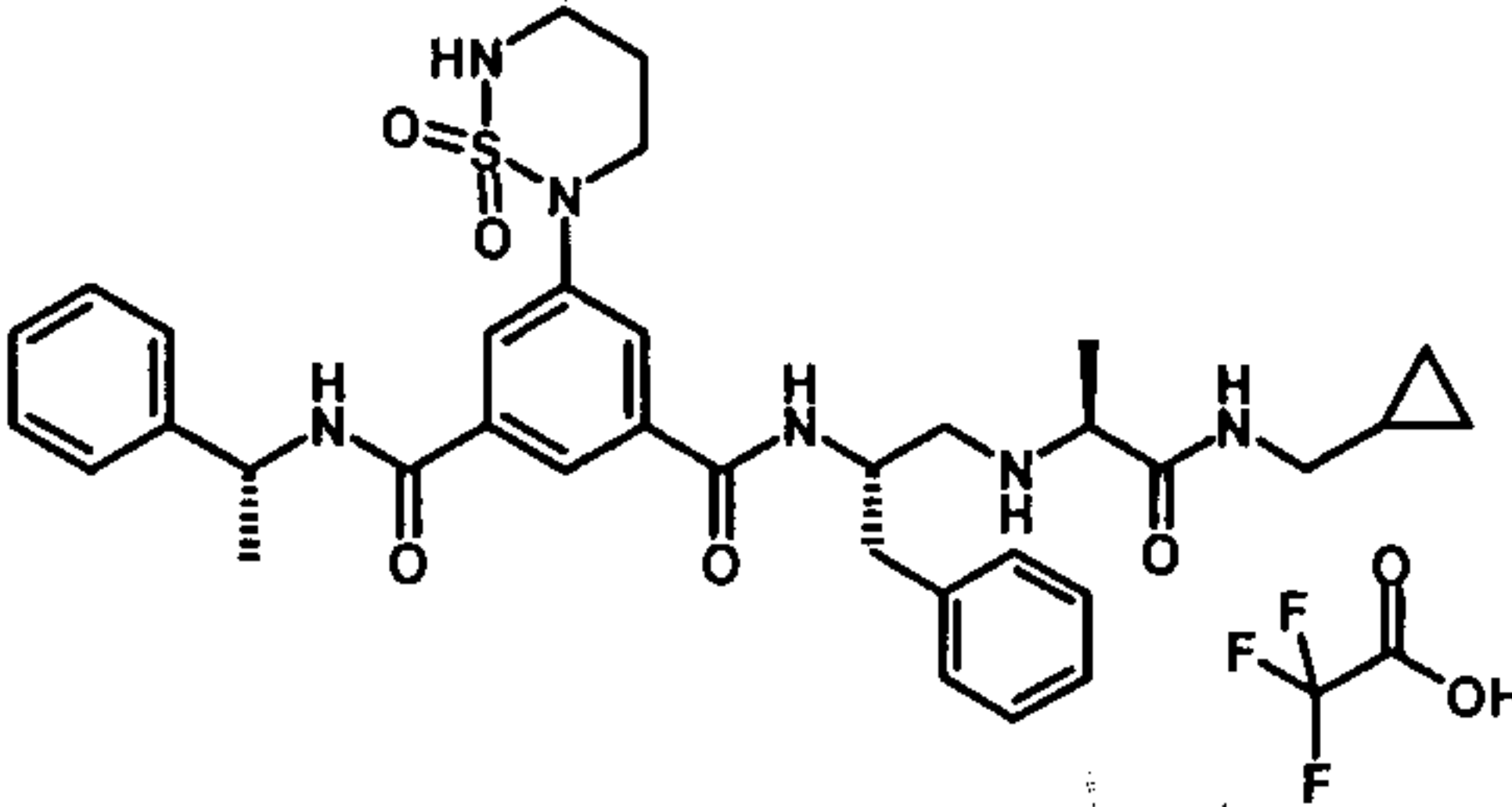
- 145 -

7.9		RT (HPLC-MS) = 2.49 min. ES-MS (M+H) ⁺ = 811/813 (Br)
7.10		RT (HPLC-MS) = 2,37 min. ES-MS (M+H) ⁺ = 733
7.11		RT (HPLC-MS) = 2.49 min. ES-MS (M+H) ⁺ = 726
7.12		RT (HPLC-MS) = 2.59 min. ES-MS (M+H) ⁺ = 804/806 (Br)
7.13		RT (HPLC-MS) = 2,36 min. ES-MS (M+H) ⁺ = 805/807 (Br)
7.14		RT (HPLC-1) = 3.80 min. ES-MS (M+H) ⁺ = 727

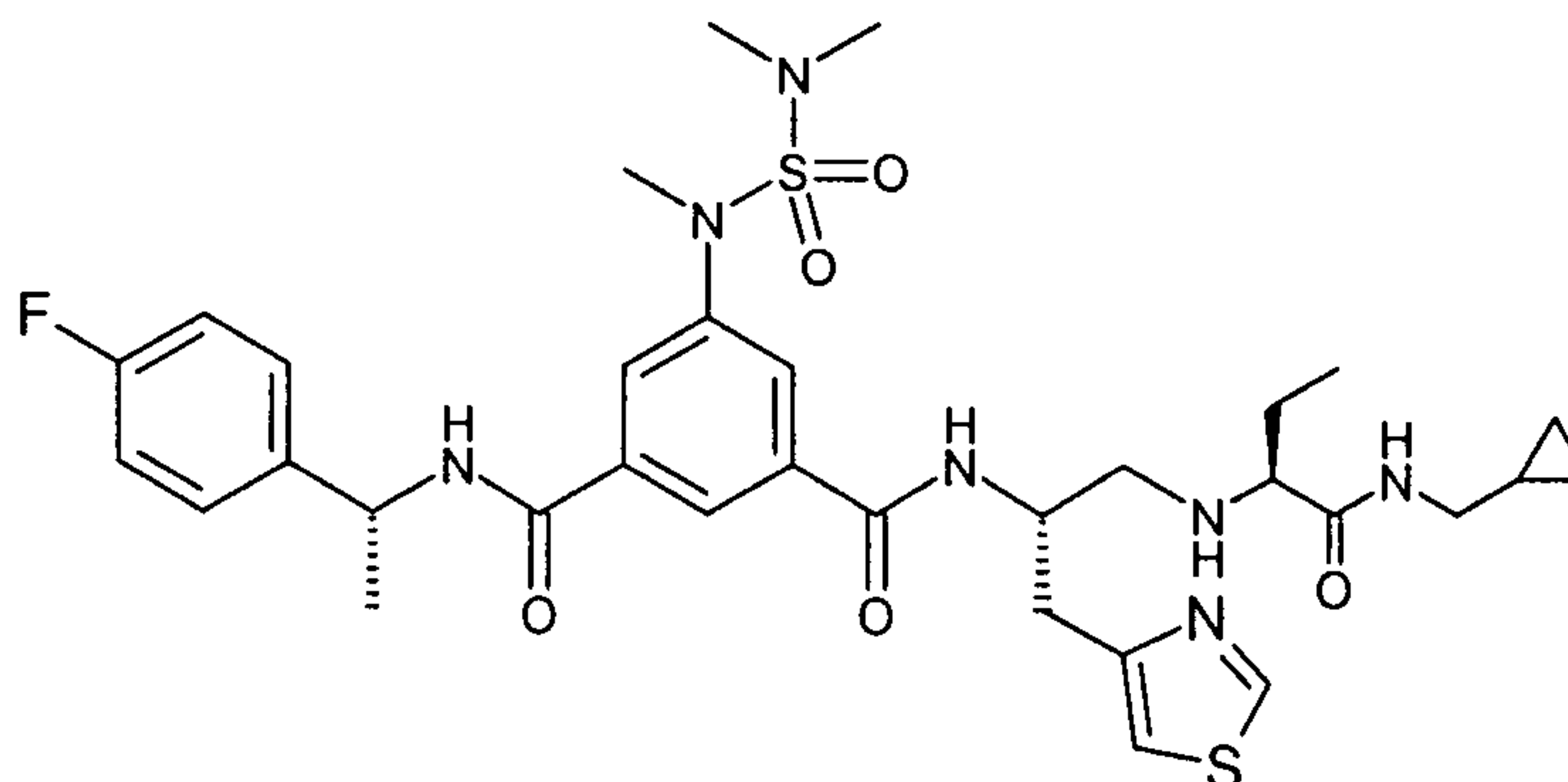
- 146 -

7.15		RT (HPLC-1) = 4.98 min. ES-MS (M+H) ⁺ = 834/836 (Br)
7.16		RT (HPLC-1) = 4.82 min. ES-MS (M+H) ⁺ = 756
7.17		RT (HPLC-1) = 4.30 min. ES-MS (M+H) ⁺ = 740/742 (Br)
7.18		RT (HPLC-1) = 4.51 min. ES-MS (M+H) ⁺ = 835/837 (Br)
7.19		RT (HPLC-1) = 4.55 min. ES-MS (M+H) ⁺ = 746/748 (Br)

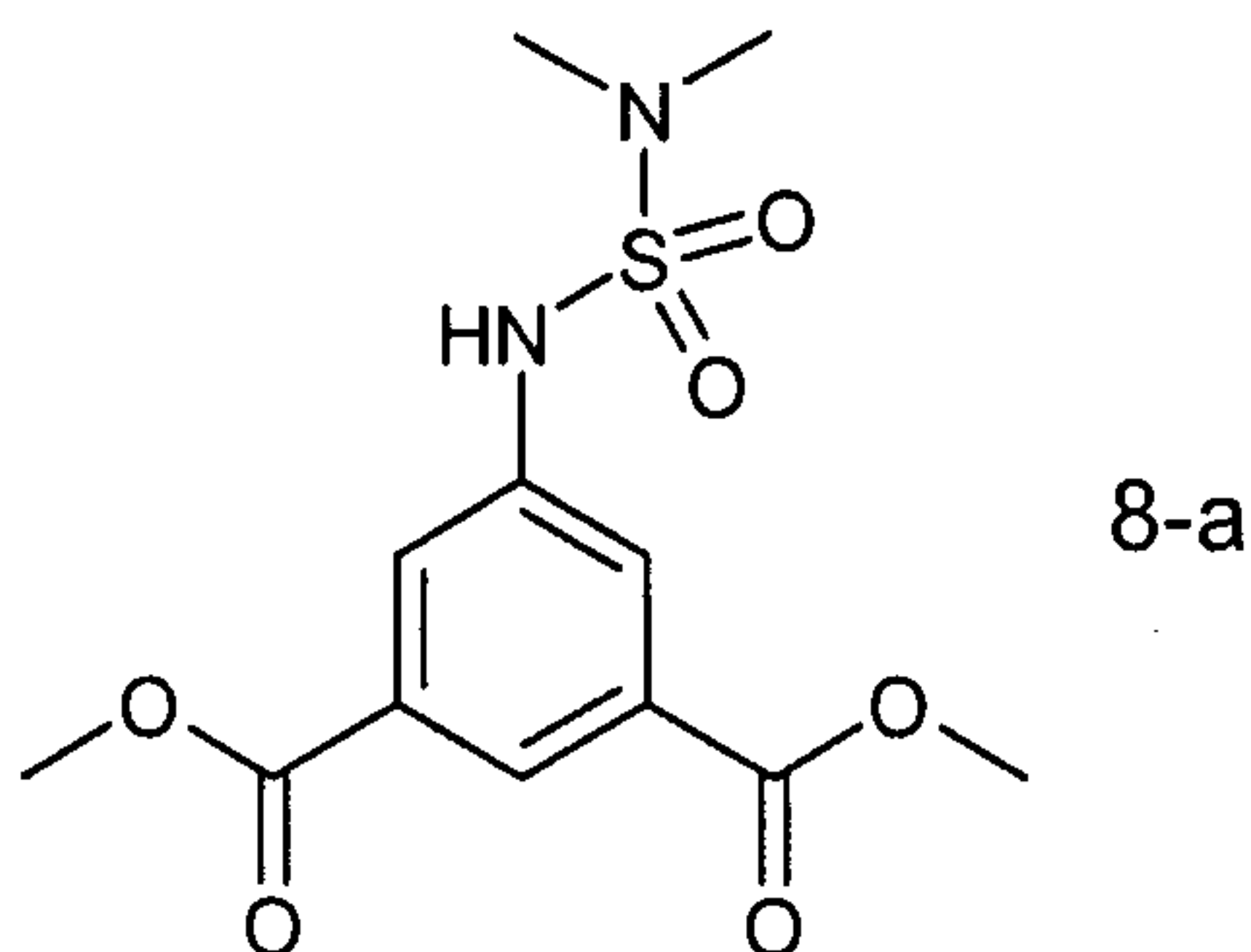
- 147 -

7.20		RT (HPLC-1) = 4.34 min. ES-MS (M+H) ⁺ = 668
7.21		RT (HPLC-1) = 3.98 min. ES-MS (M+H) ⁺ = 662
7.22		RT (HPLC-1) = 4.79 min. ES-MS (M+H) ⁺ = 739/741 (Br)
7.23		RT (HPLC-1) = 4.63 min. ES-MS (M+H) ⁺ = 661

Example 8:



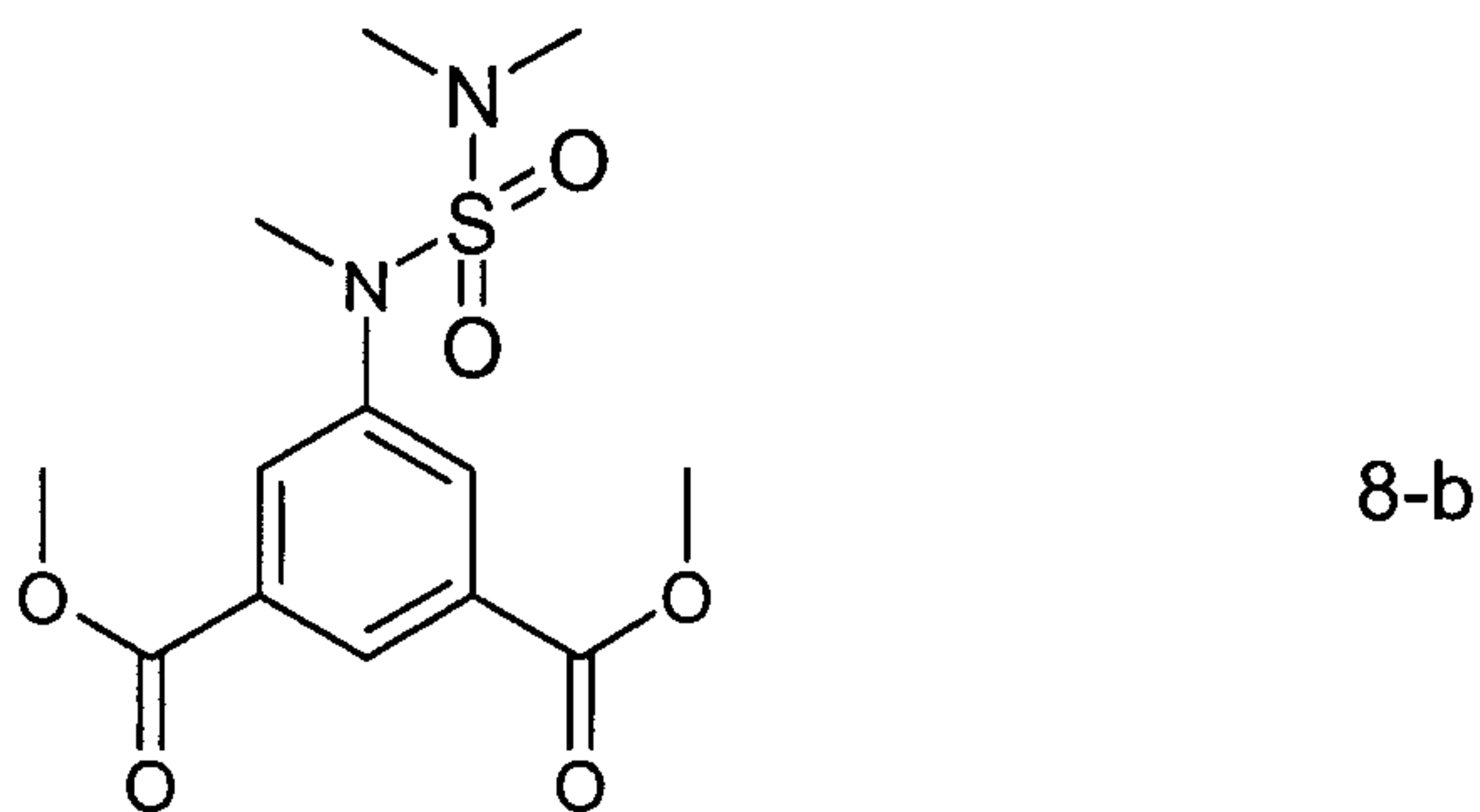
- 148 -

a) Preparation of **8-a**:

15 g (70.3 mmol) dimethyl 5-amino-isophthalate were dissolved in 150 ml of pyridine.

- 5 The reaction solution was cooled to 0°C, at this temperature 12.0 ml (111.7 mmol) dimethylaminosulphonyl chloride were metered in, the mixture was heated to 90°C and stirred for 12 h. Then it was poured onto 200 ml 4N HCl and the crystals precipitated were suction filtered. After extracting with diethyl ether and suction filtering again, the residue was dried in the drying cupboard at 40°C and 17.9 g (64%) of whitish crystals **8-a** were obtained.

RT (HPLC 1) = 4.14 min

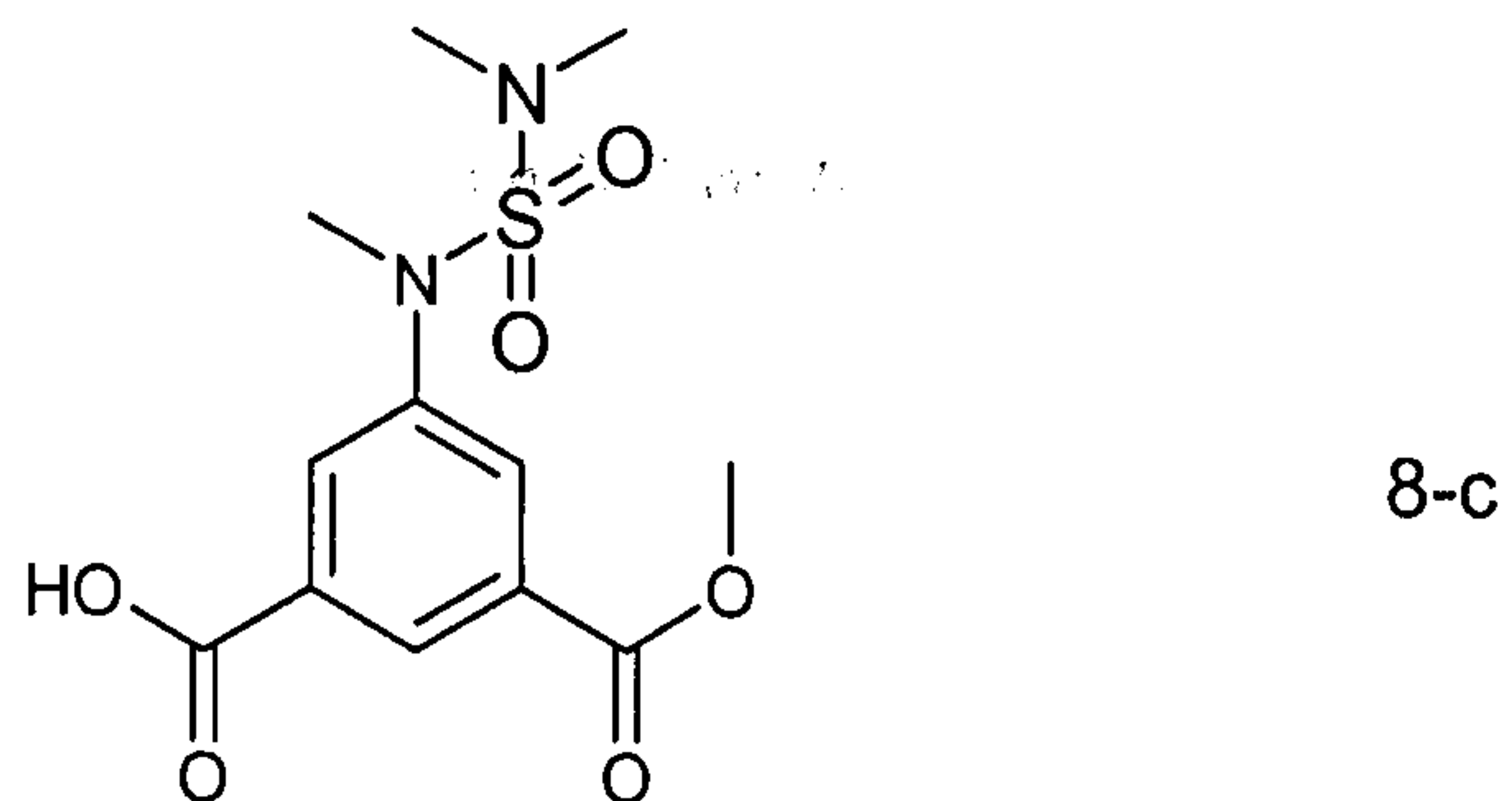
b) Preparation of **8-b**:

First 17.9 g (56.6 mmol) **8-a** and then 9.3 ml (124.5 mmol) methyl iodide were added to a solution of 5.0 g (125 mmol) sodium hydride (60% in mineral oil) in 500 ml DMF.

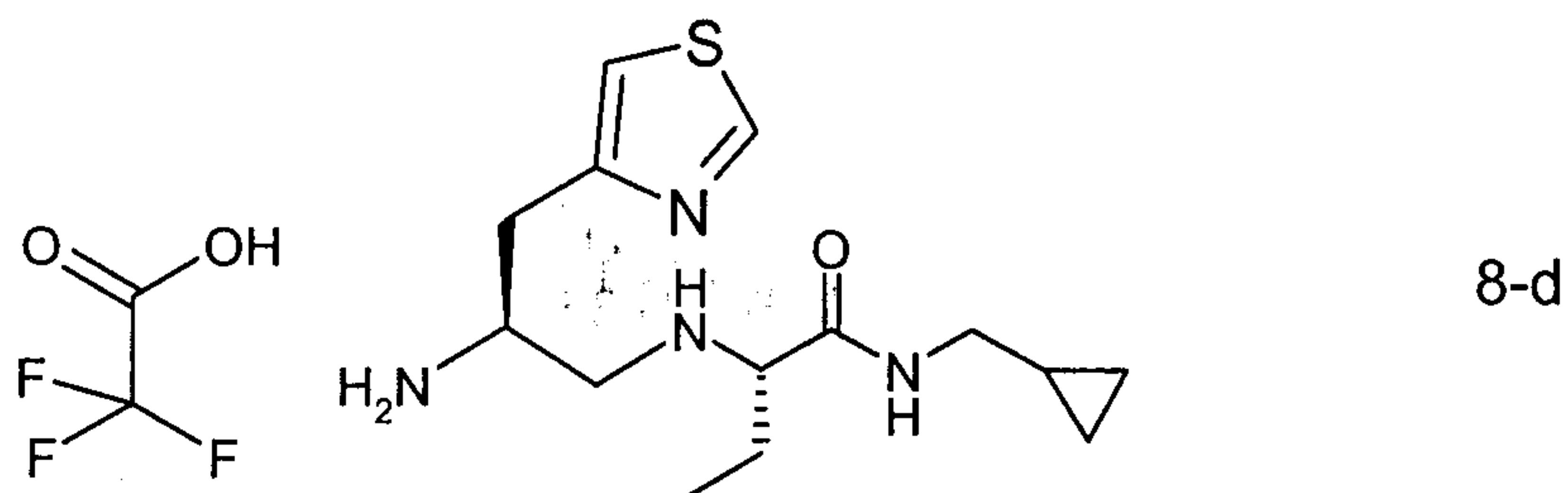
- 20 The reaction solution was stirred for 1 h at ambient temperature, combined with 500 ml of water and extracted with ethyl acetate. The combined organic phases were dried and evaporated to dryness using the rotary evaporator. This yielded 12.5 g (57%) **8-b** as brown crystals.

RT (HPLC 1) = 4.67 min

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c) Preparation of **8-c**:**8-c** was obtained analogously to **7-d** from **8-b**.

5 RT (HPLC-MS) = 2.58 min

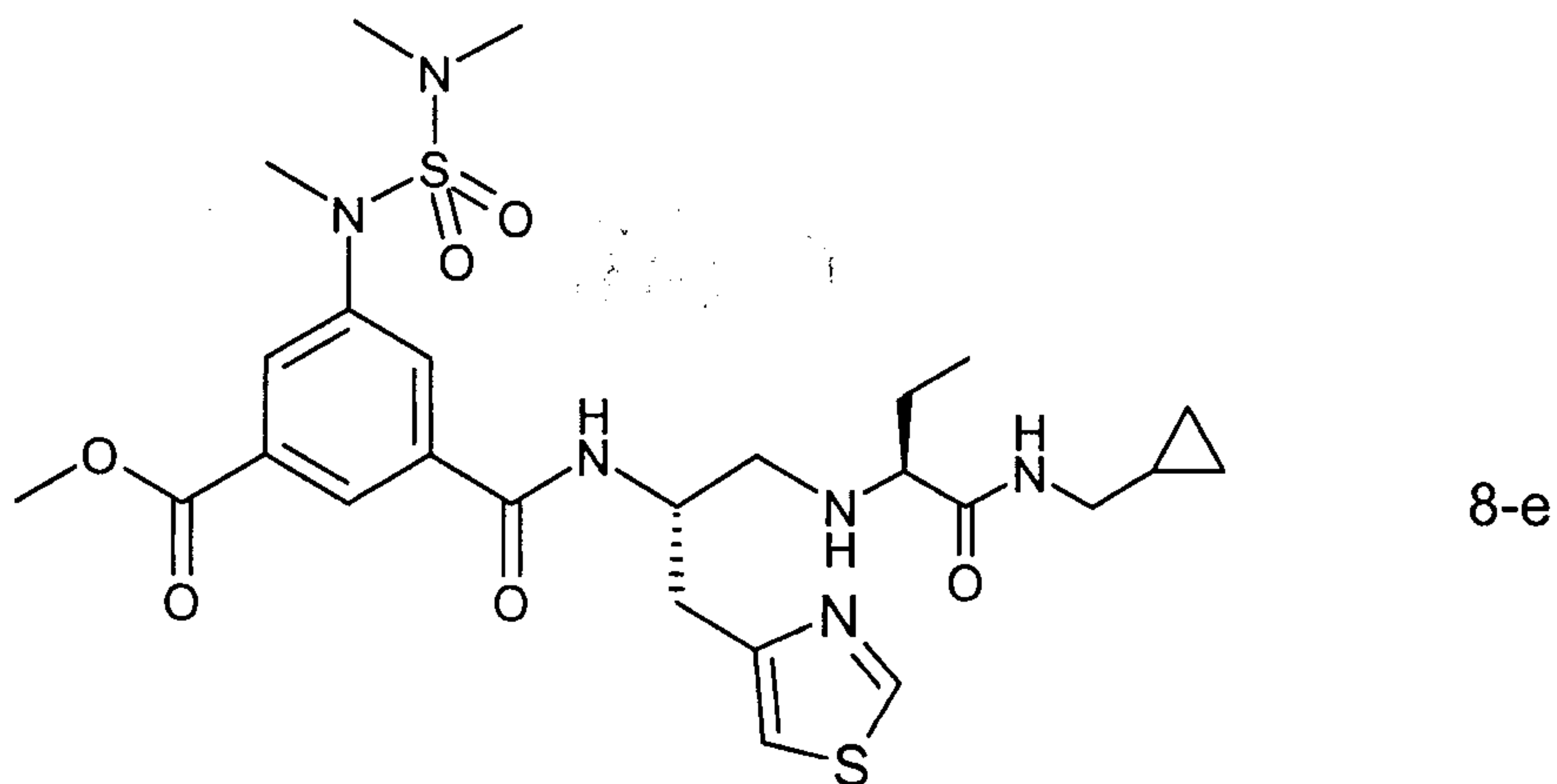
(M+H)⁺ (HPLC-MS) = 318d) Preparation of **8-d**

10 **8-d** was prepared analogously to **7-i**, by substituting Boc-L-alanine with Boc-L-aminobutyric acid (step 1e) and Boc-phenyl-alaninol with Boc-L-thiazol-4-yl-alaninol (step 1g).

RT (HPLC-MS) = 1.85 min

(M+H)⁺ (HPLC-MS) = 298

15

e) Preparation of **8-e**:

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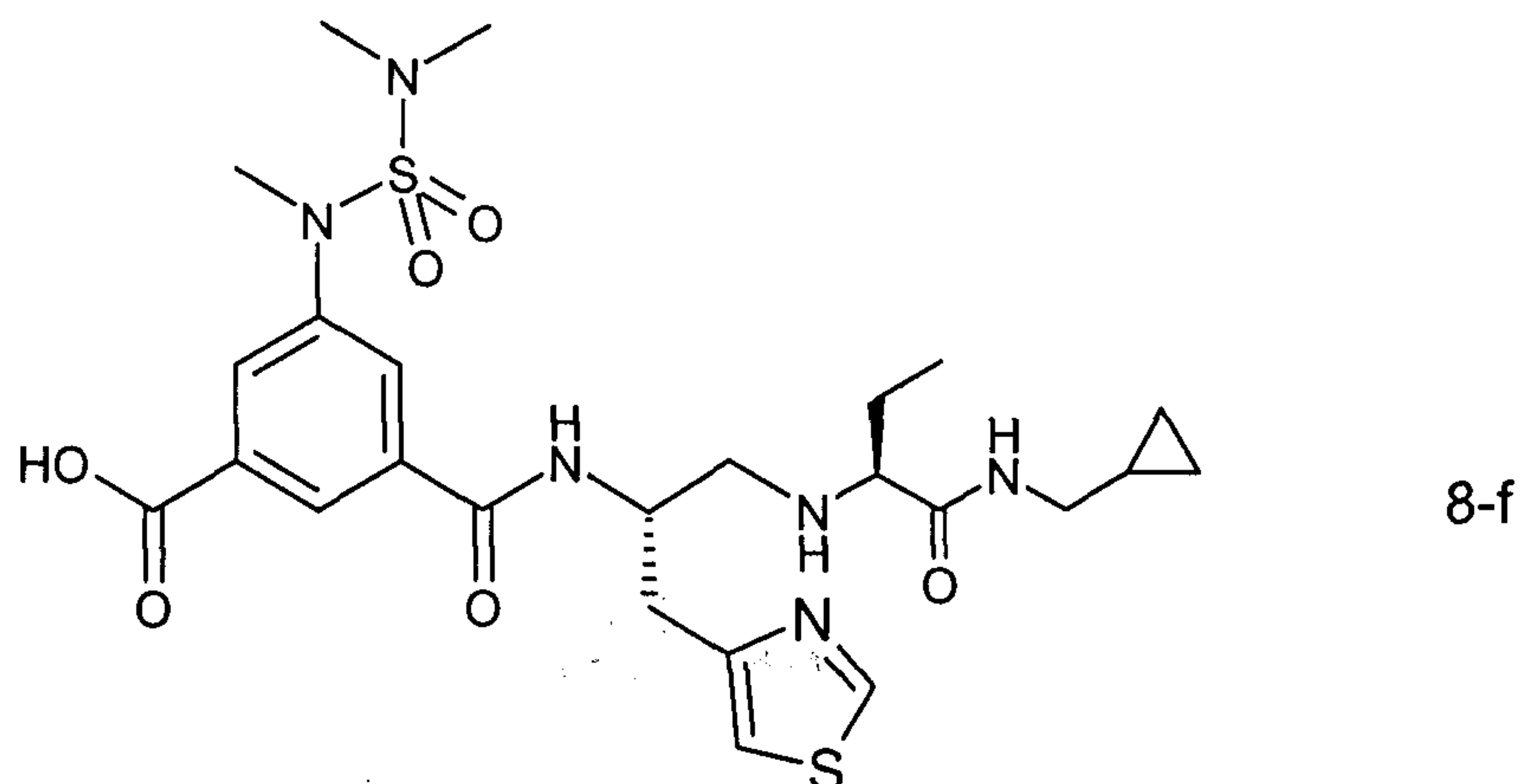
8-e was prepared analogously to **7-j** from **8-c** and **8-d**.

RT (HPLC-MS) = 2.54 min

(M+H)⁺ (HPLC-MS) = 596

5

f) Preparation of **8-f**:

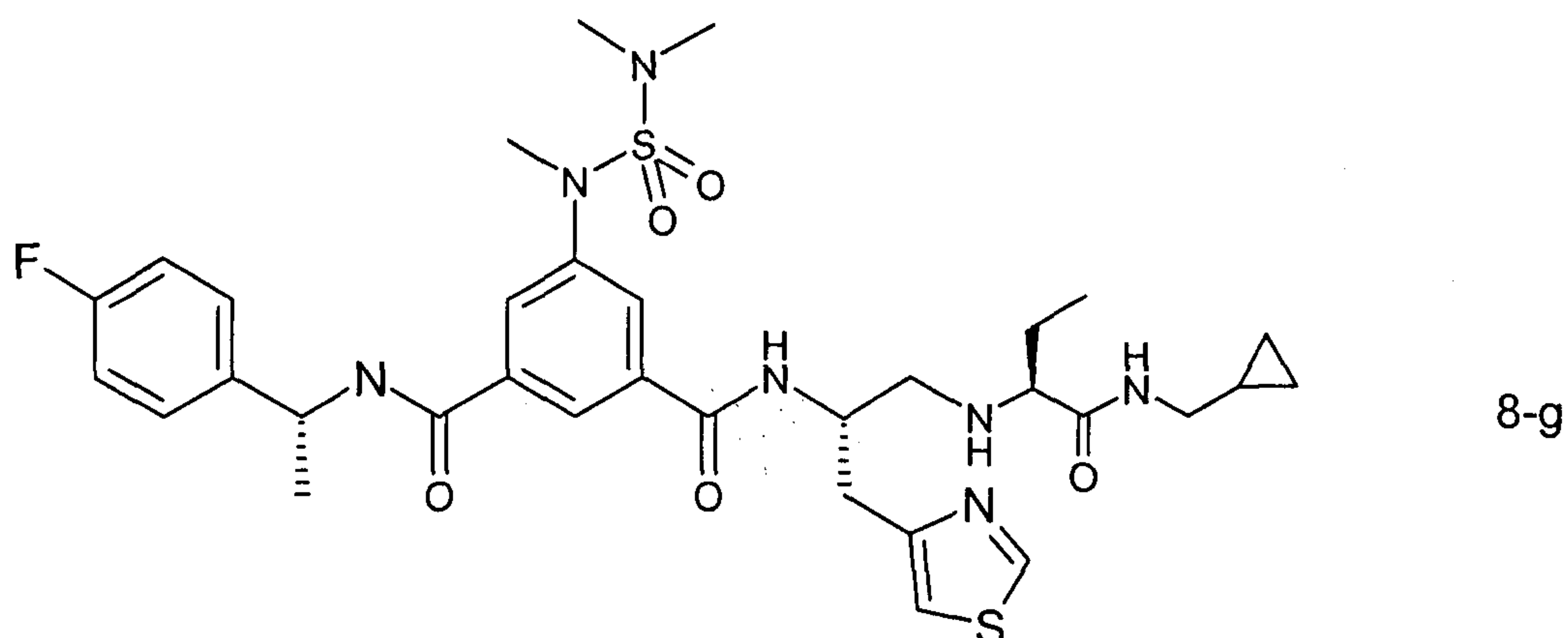


8-f was prepared analogously to **7-k** from **8-e**.

10 RT (HPLC 1) = 3.95 min

ES-MS (M-H)⁺ = 579

g) Preparation of **8-g**:



15

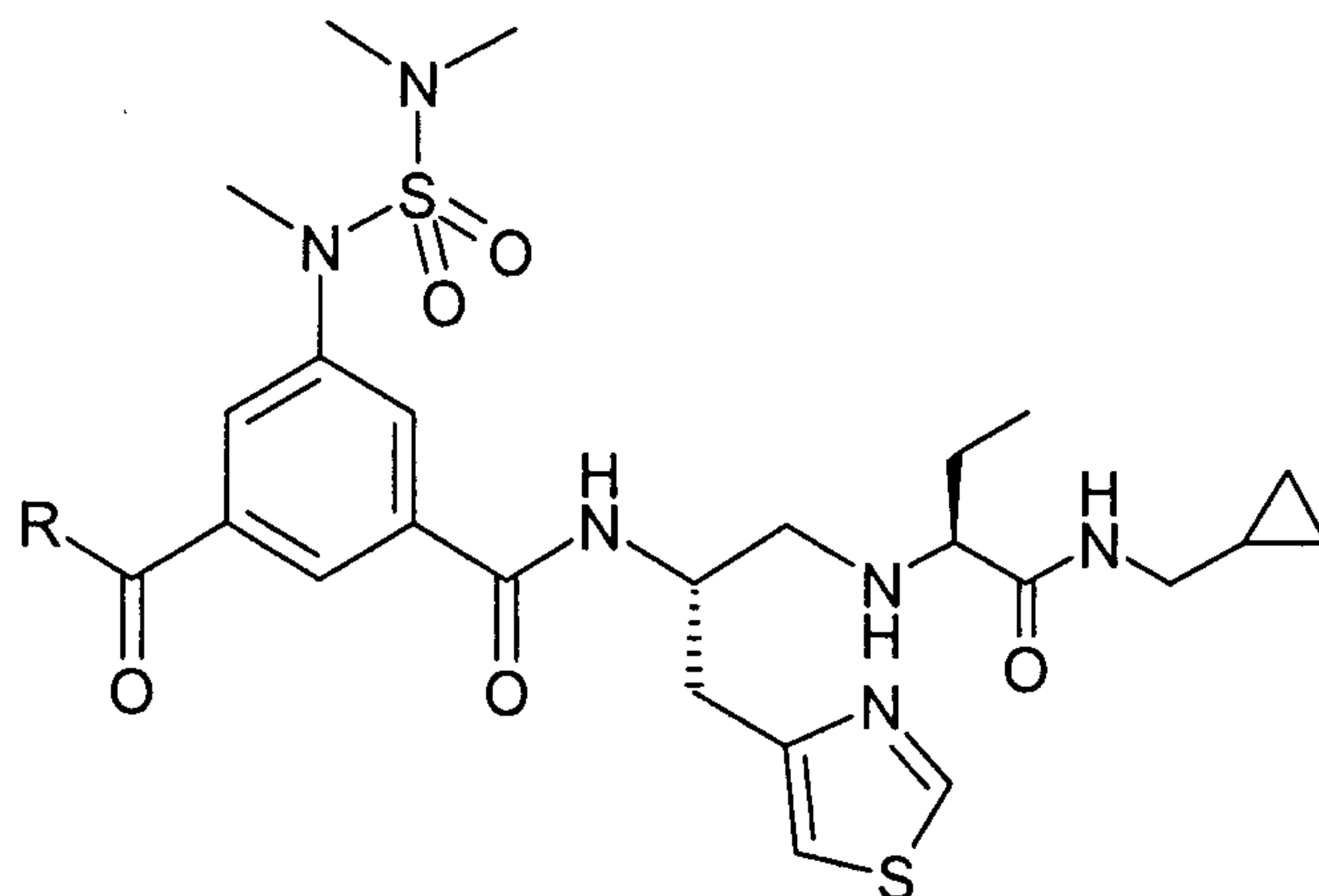
8-g was prepared analogously to **7-l** from **8-f** and (R)-1-(4-fluoro-phenyl)-ethylamine.

RT (HPLC 1) = 4.62 min

ES-MS (M+H)⁺ = 702

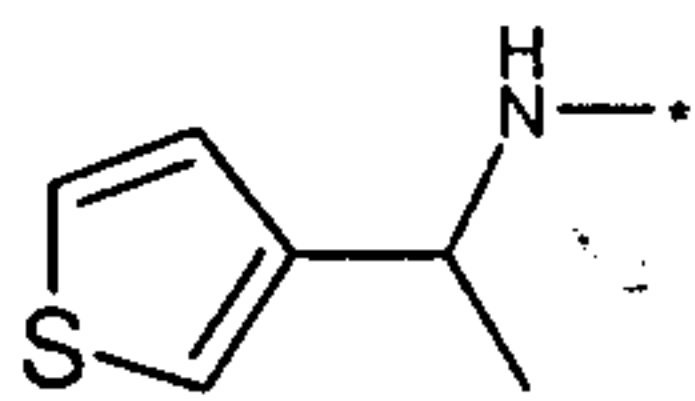
20

The following compounds were prepared analogously to **8-g** from **8-f** and the corresponding amount of amine:



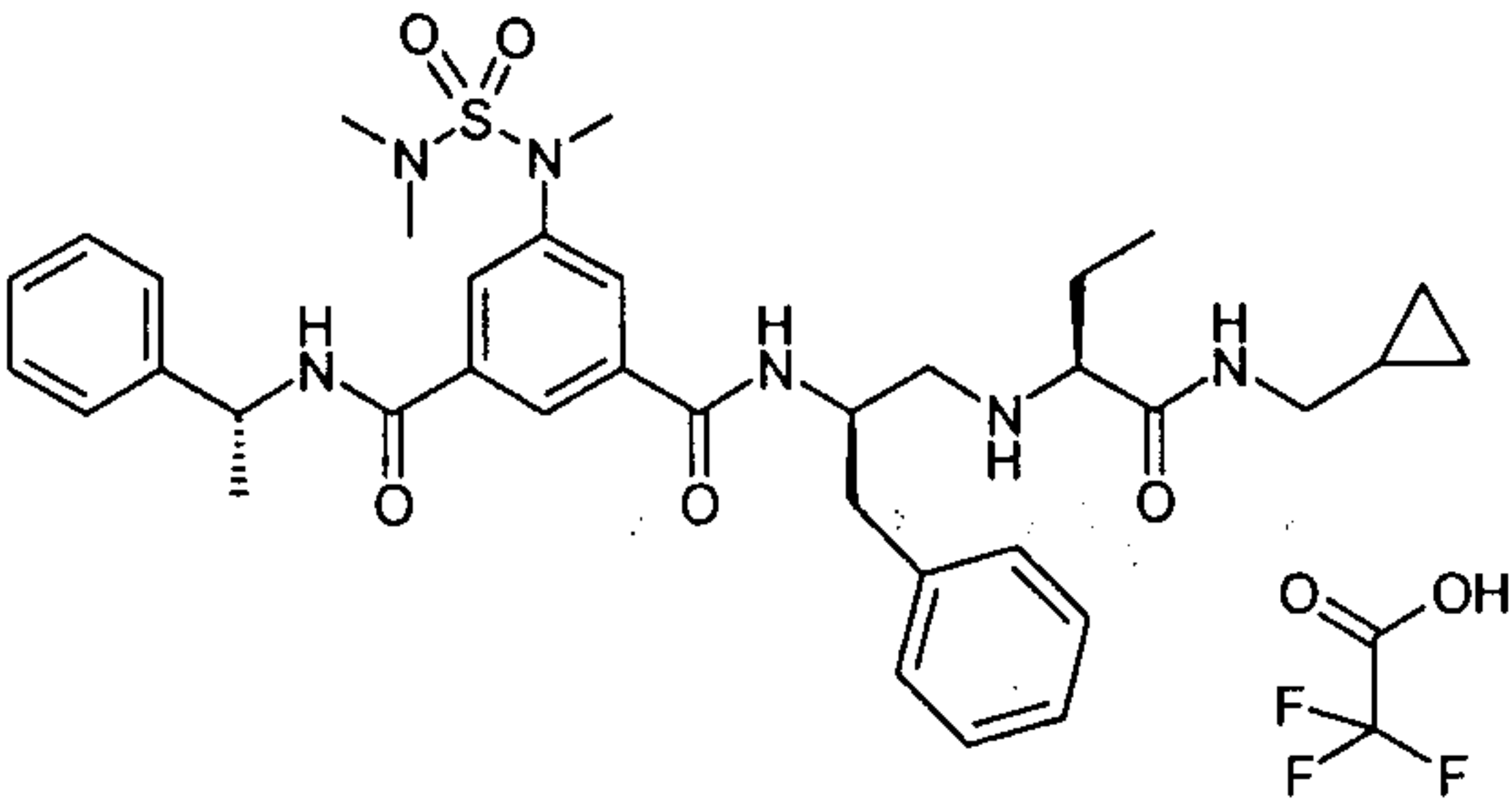
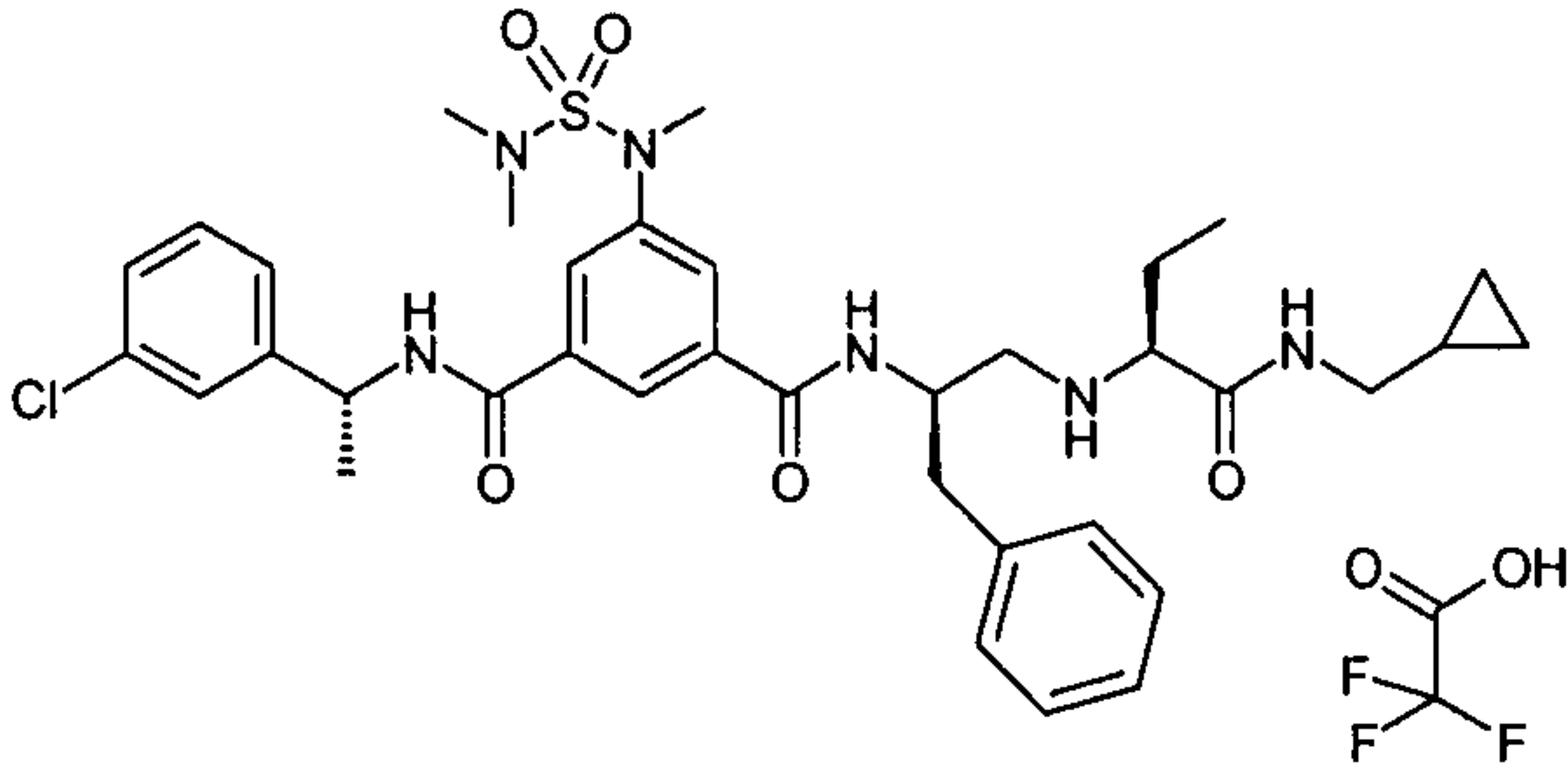
Example	R	
8.1		RT (HPLC 1) = 4.82 min ES-MS (M+H) ⁺ = 718/720 (CI)
8.2		RT (HPLC 1) = 4.57 min ES-MS (M+H) ⁺ = 714
8.3		RT (HPLC 1) = 4.74 min ES-MS (M+H) ⁺ = 698
8.4		RT (HPLC 1) = 4.68 min ES-MS (M+H) ⁺ = 698
8.5		RT (HPLC 1) = 3.83 min ES-MS (M+H) ⁺ = 685
8.6		RT (HPLC 1) = 3.78 min ES-MS (M+H) ⁺ = 685

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8.7		RT (HPLC 1) = 4.55 min ES-MS (M+H) ⁺ = 690
-----	---	--

The following compounds were obtained analogously to **8-g** from an amine analogous to **8-d**, which was prepared by substitution of Boc-L-alanine by Boc-L-aminobutyric acid (step 1e) and Boc-phenyl-alaninol by Boc-D-phenyl-alaninol (step 1g). The

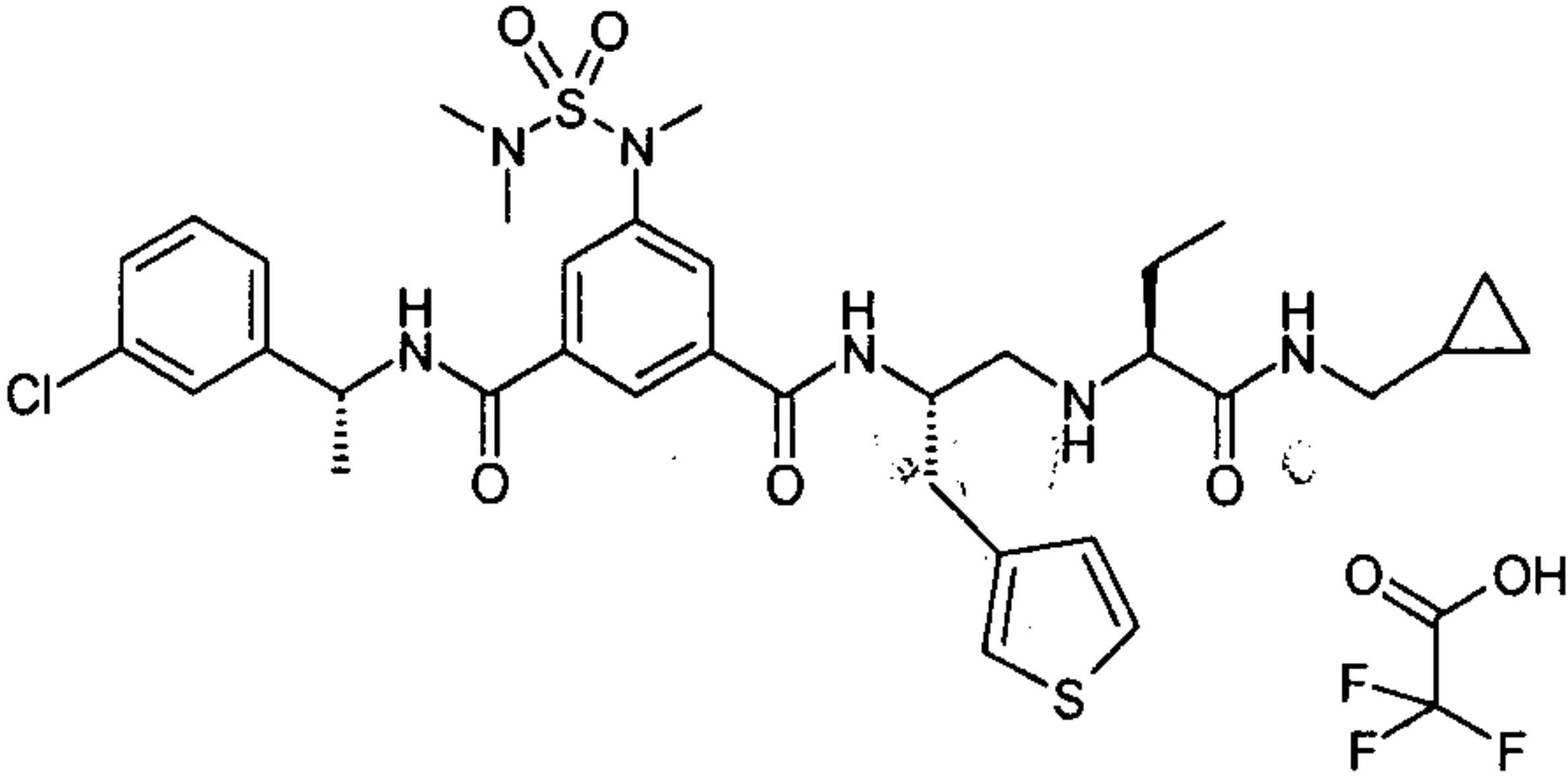
5 amine components used for the last step were (R)-1-phenyl-ethylamine or (R)-1-(3-chloro-phenyl)-ethylamine:

Example		
8.8		RT (HPLC-MS) = 2.83 min. ES-MS (M+H) ⁺ = 677
8.9		RT (HPLC-MS) = 2.93 min. ES-MS (M+H) ⁺ = 711/713 (Cl)

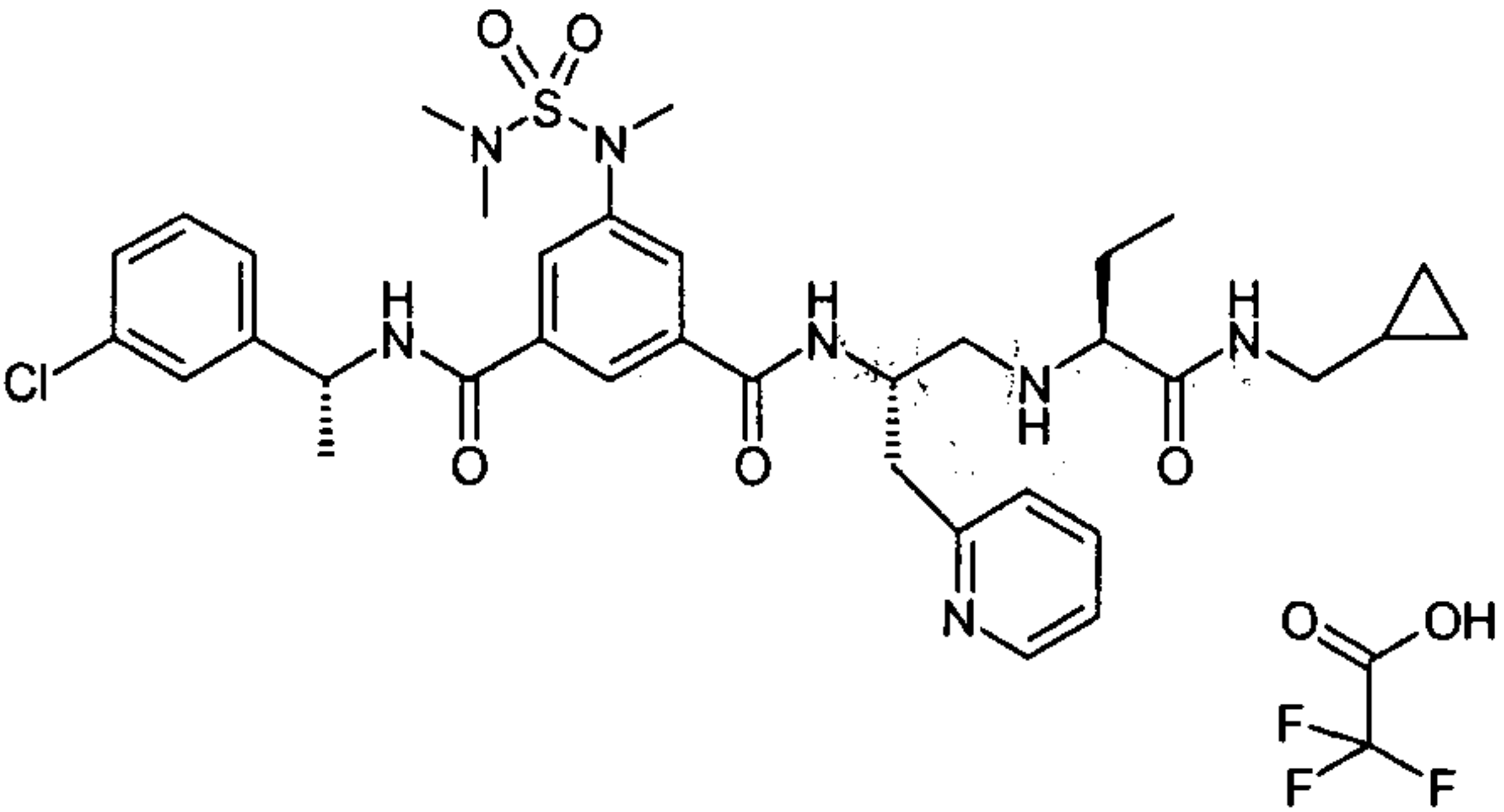
The following compound was obtained analogously to **8-g** from an amine analogous to **8-d**, which was prepared by substituting Boc-L-alanine by Boc-L-aminobutyric acid

10 (step 1e) and Boc-phenyl-alaninol by BOC-L-3-thienylalaninol (step 1g). The amine component used for the last step was (R)-1-(3-chloro-phenyl)-ethylamine:

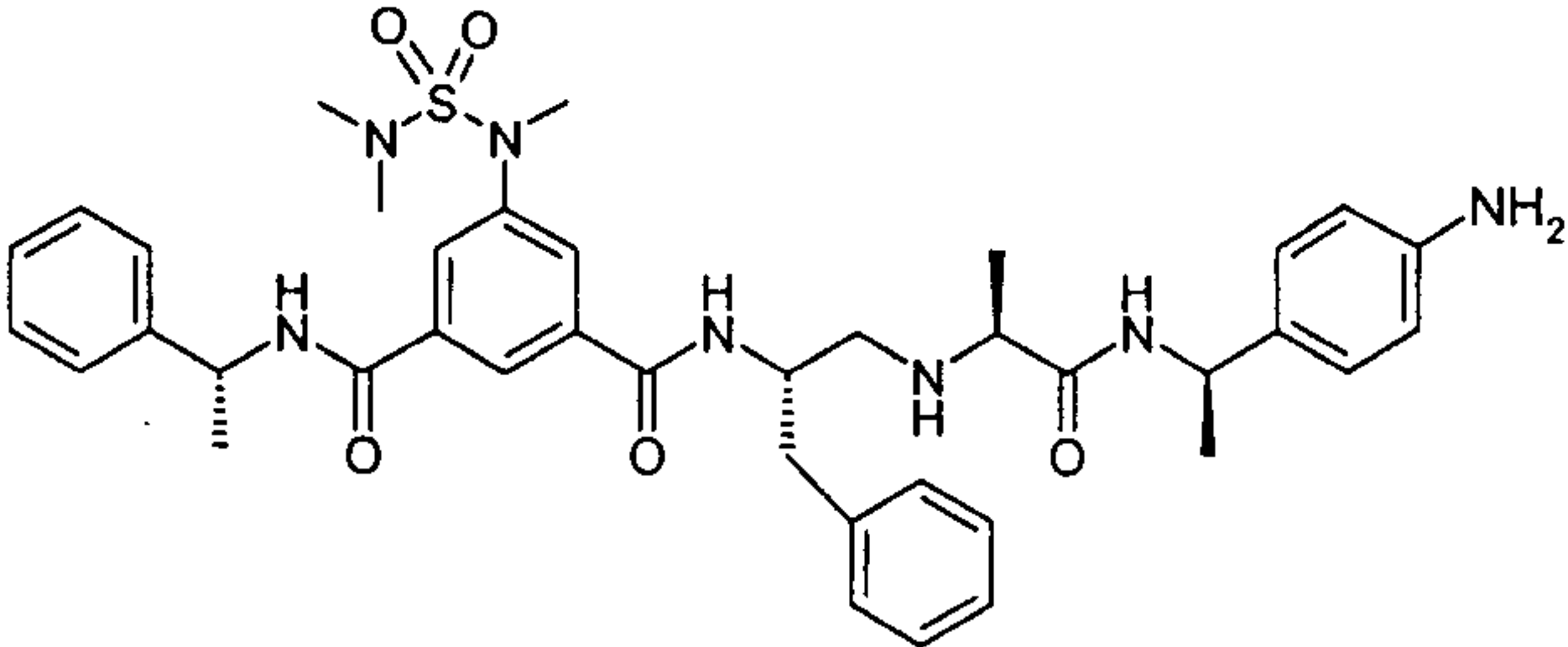
- 153 -

Example		
8.10		RT (HPLC-MS) = 3.01 min. ES-MS (M+H) ⁺ = 717/719 (Cl)

The following compound was obtained analogously to **8-g** from an amine analogous to **8-d**, which was prepared by substituting Boc-L-alanine by Boc-L-aminobutyric acid (step 1e) and Boc-phenyl-alaninol by BOC-L-2-pyridylalaninol (step 1g). The amine component used for the last step was (R)-1-(3-chloro-phenyl)-ethylamine:

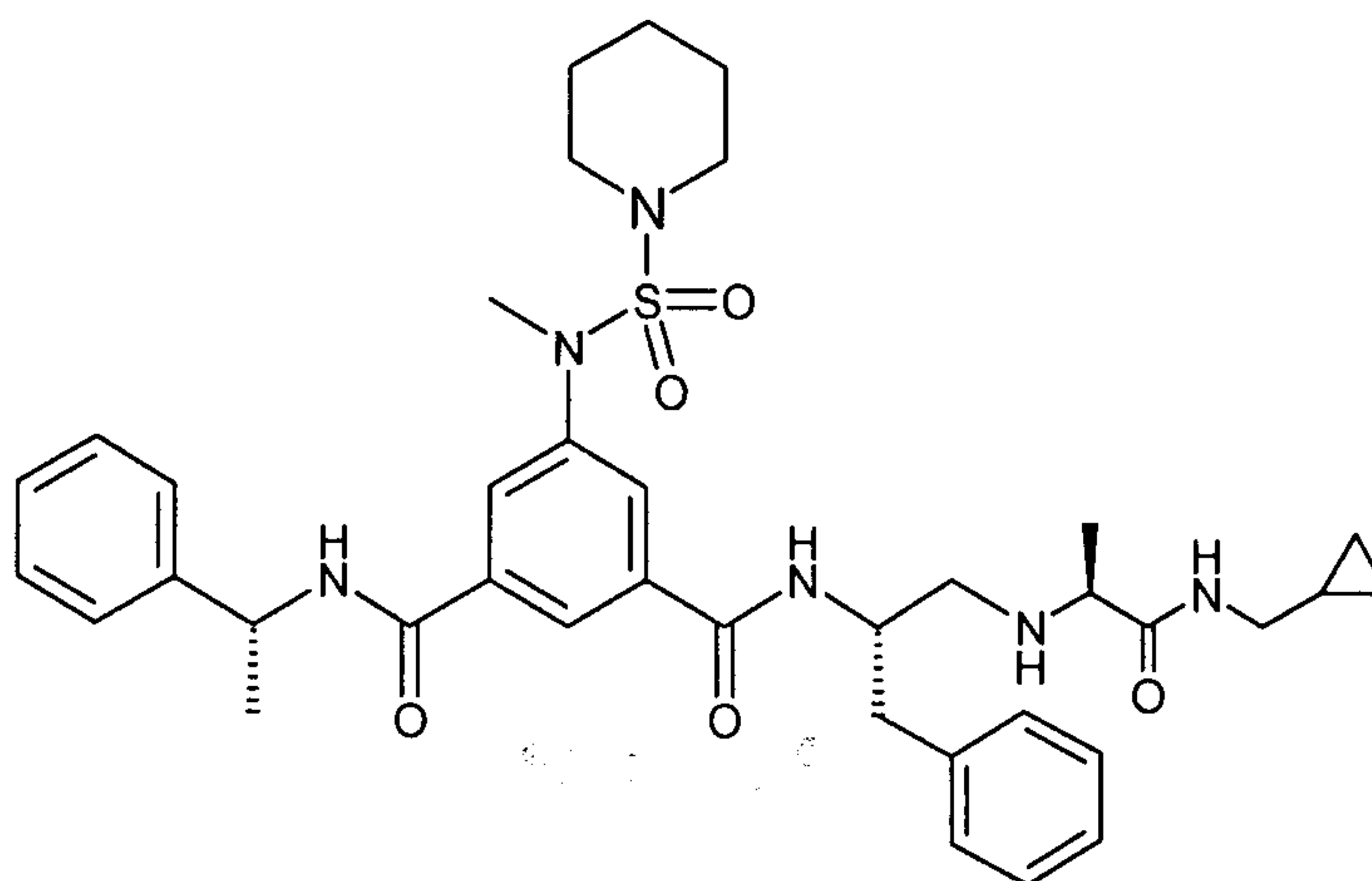
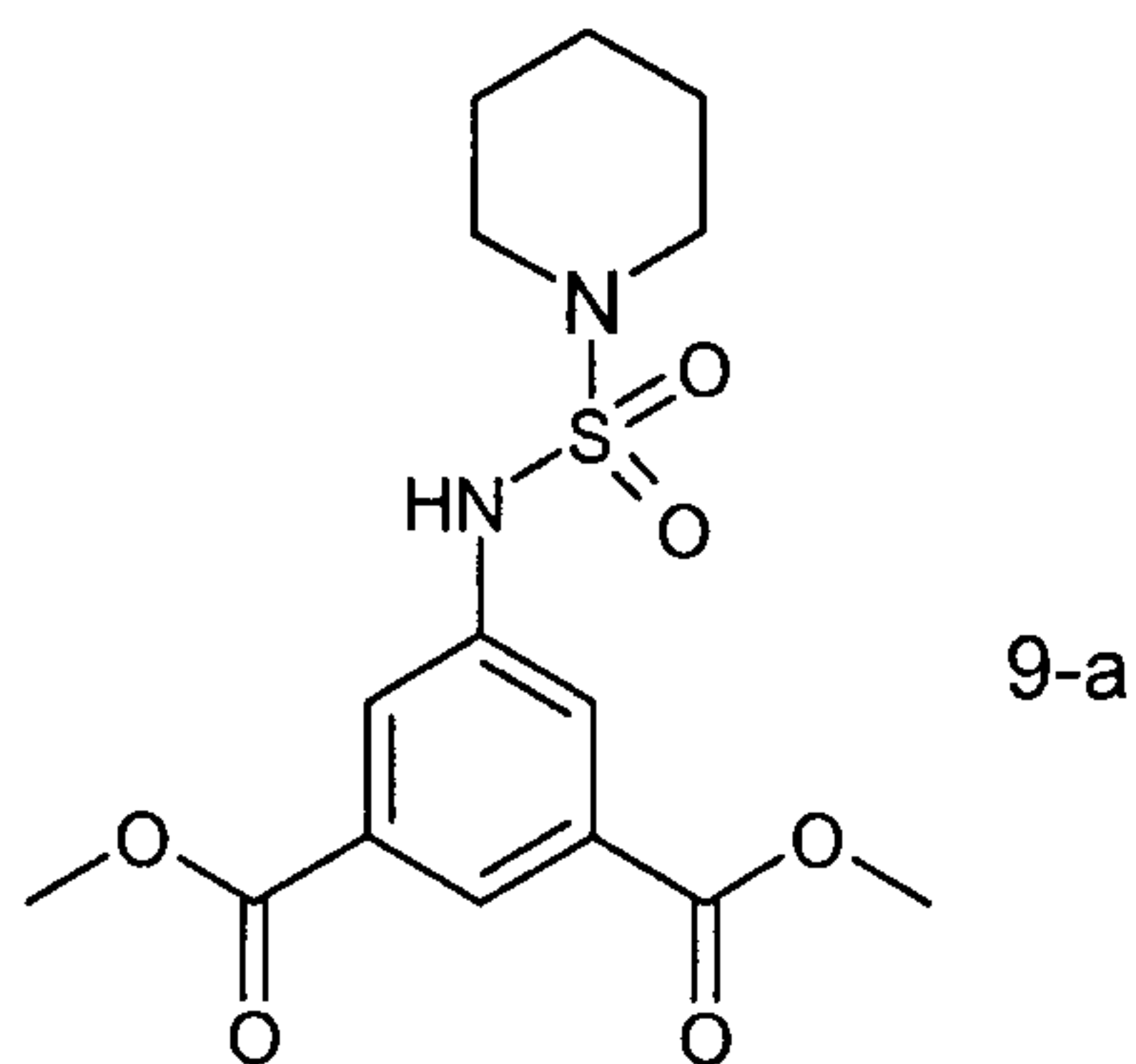
Example		
8.11		RT (HPLC-MS) = 2.69 min. ES-MS (M+H) ⁺ = 712/714 (Cl)

Example 8.12 was prepared analogously to 8.8:

Example		
8.12		RT (HPLC-MS) = 2.49 min. ES-MS (M+H) ⁺ = 728

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Example 9:

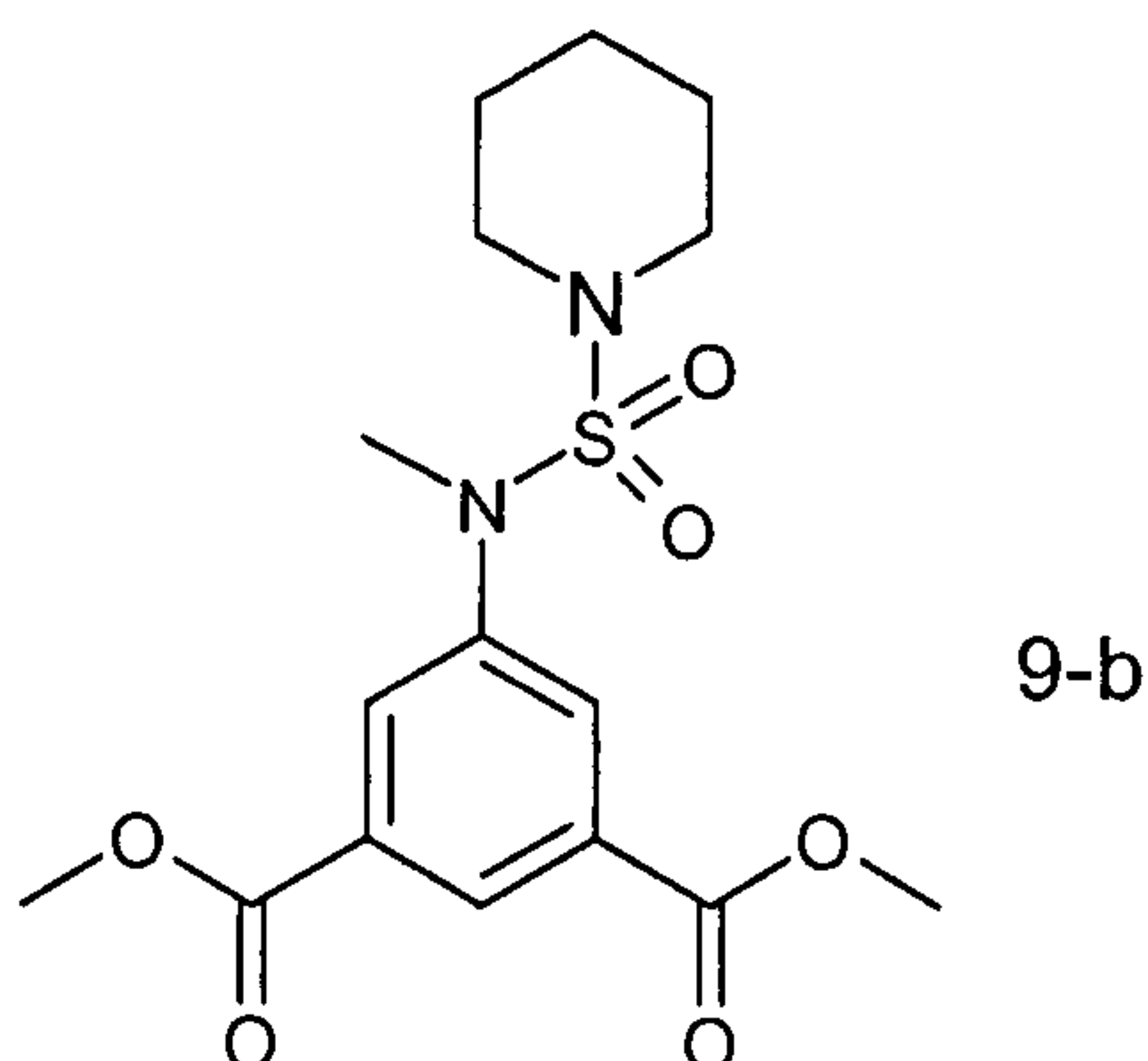
a) Preparation of **9-a**:

5

9-a was obtained analogously to **8-a** by using piperidylsulphonyl chloride instead of dimethylaminosulphonyl chloride.

RT (HPLC-MS) = 3.13 min

10 (M+H)⁺ (HPLC-MS) = 356

b) Preparation of **9-b**:

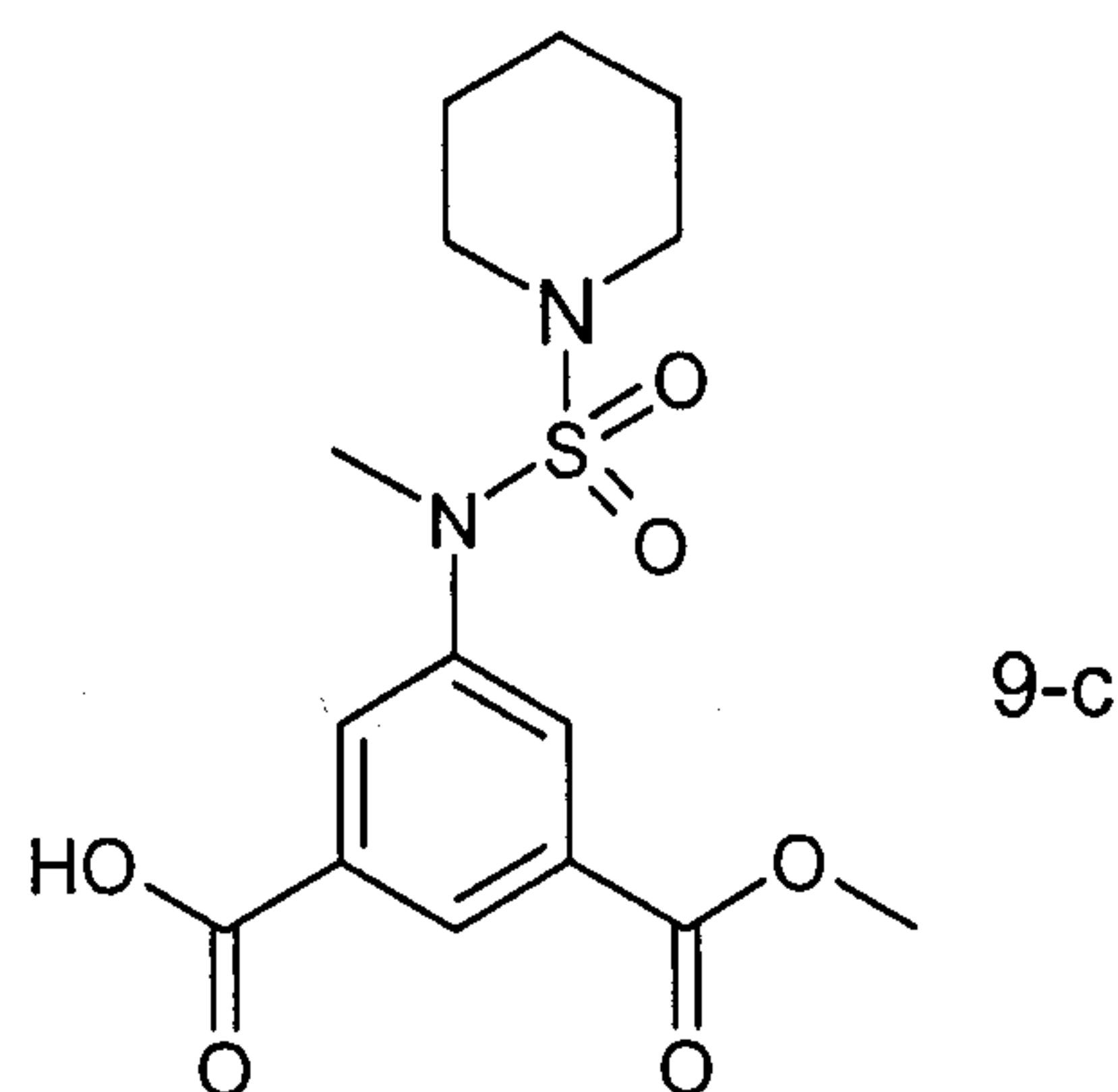
15

9-b was obtained analogously to **8-b** from **9-a**.

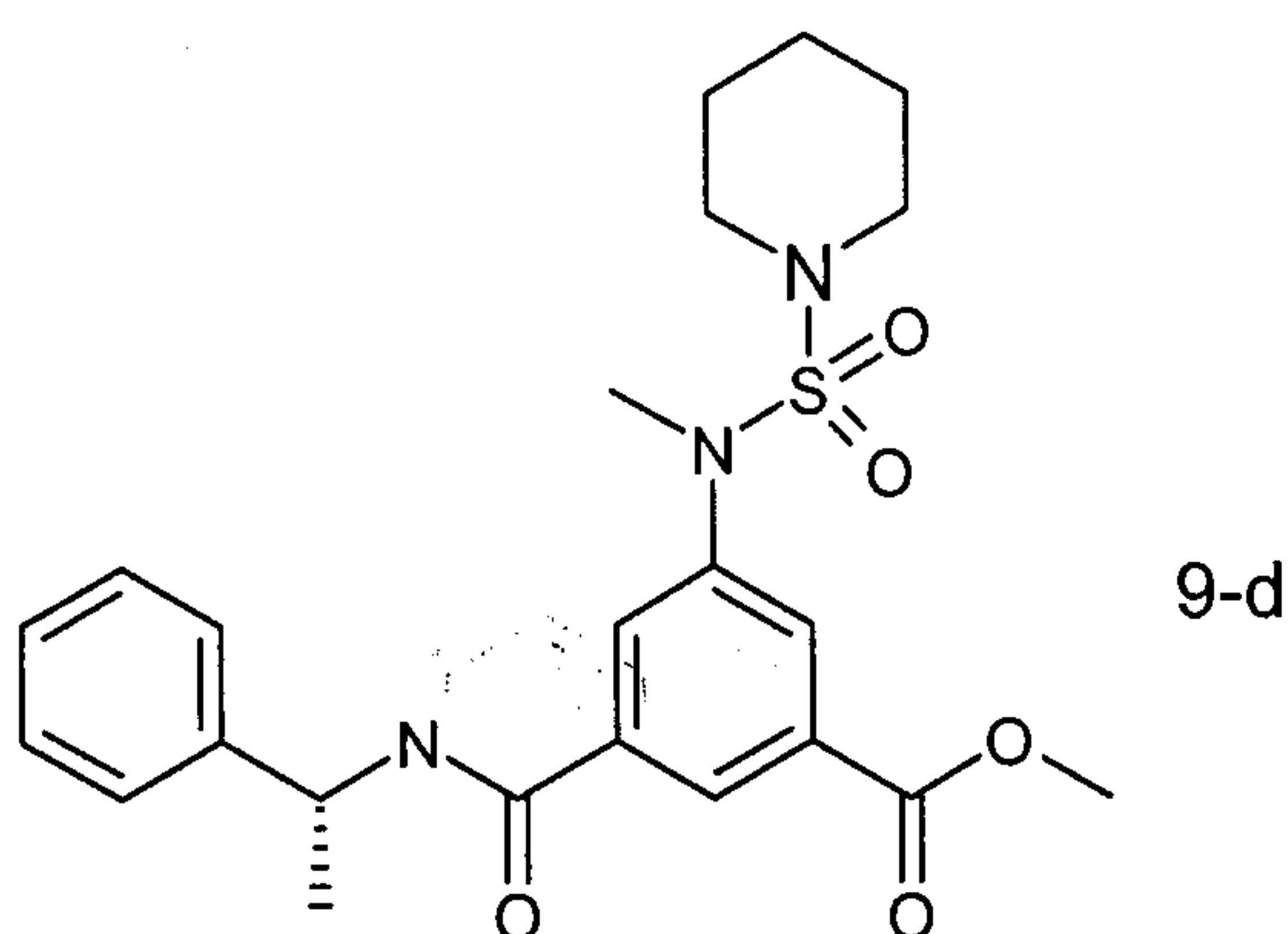
RT (HPLC-MS) = 3.34 min

(M+H)⁺ (HPLC-MS) = 370

- 155 -

c) Preparation of **9-c**:**9-c** was obtained analogously to **8-c** from **9-b**.

5 RT (HPLC-MS) = 2.91 min
(M+H)⁺ (HPLC-MS) = 356

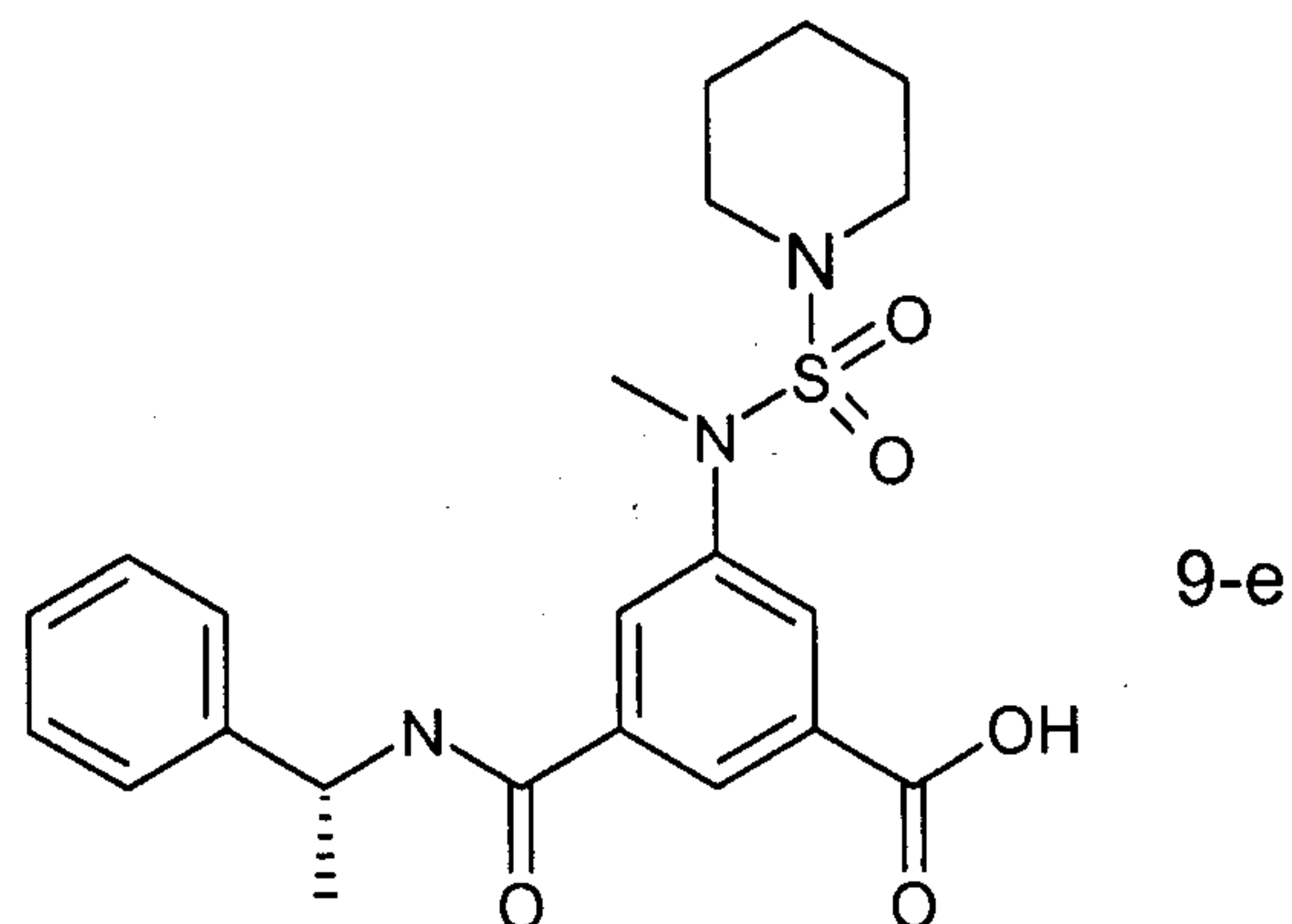
d) Preparation of **9-d**:

10

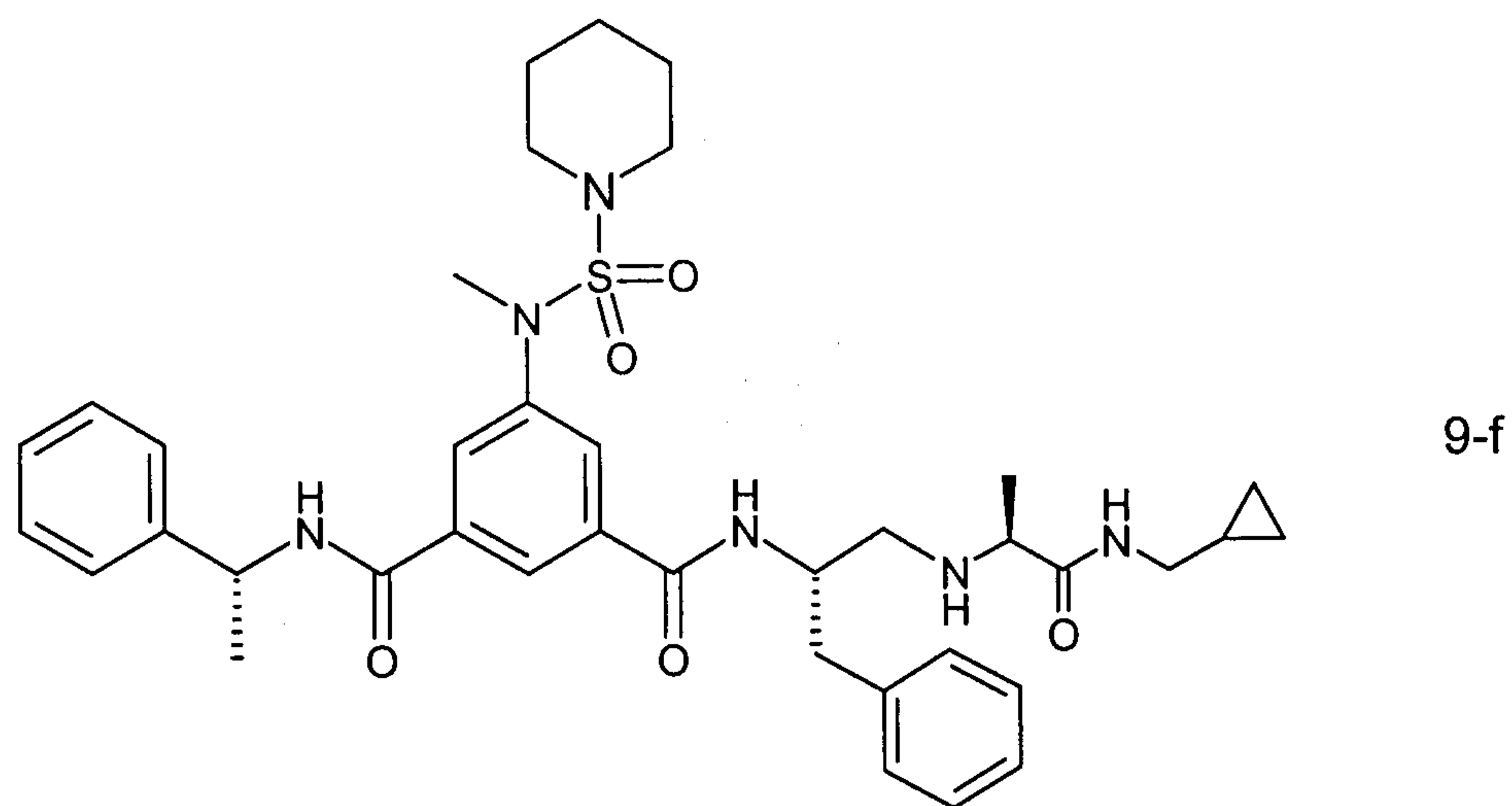
1,45 g (3.25 mmol) **9-c** in 30 ml dichloromethane were combined with 1.04 g (3.25 mmol) TBTU and 1.67 ml (9.75 mmol) DIPEA, then 0.42 ml (3.25 mmol) (R)-1-phenyl-ethylamine were added and the mixture was stirred for 1 hour at ambient temperature. The reaction solution was extracted with 20% KHCO₃ solution and water. The organic phases were separated through a phase separation cartridge and evaporated to dryness i. vac.. The residue was purified by chromatography on silica gel with the eluant (ethyl acetate/heptane 9:1). This yielded 2.24 g (90 %) of beige crystals **9-d**.

15

- 156 -

e) Preparation of **9-e**:**9-e** was obtained analogously to **8-d** from **9-d**.

5 RT (HPLC-MS) = 3.05 min
(M+H)⁺ (HPLC-MS) = 445

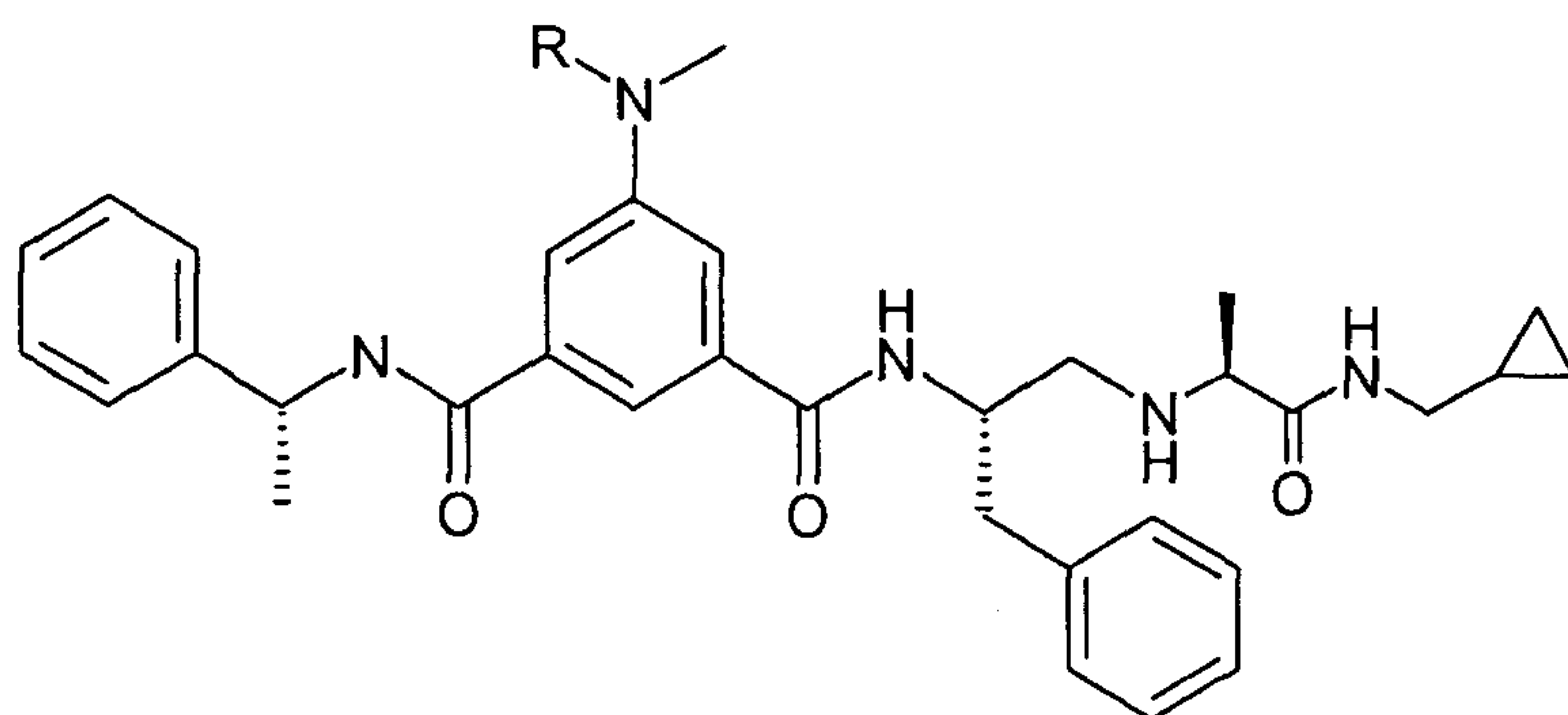
f) Preparation of **9-f**:

10 **9-f** was obtained analogously to **7-j** from **9-e** and **7-i**.

RT (HPLC-MS) = 3.02 min
(M+H)⁺ (HPLC-MS) = 703

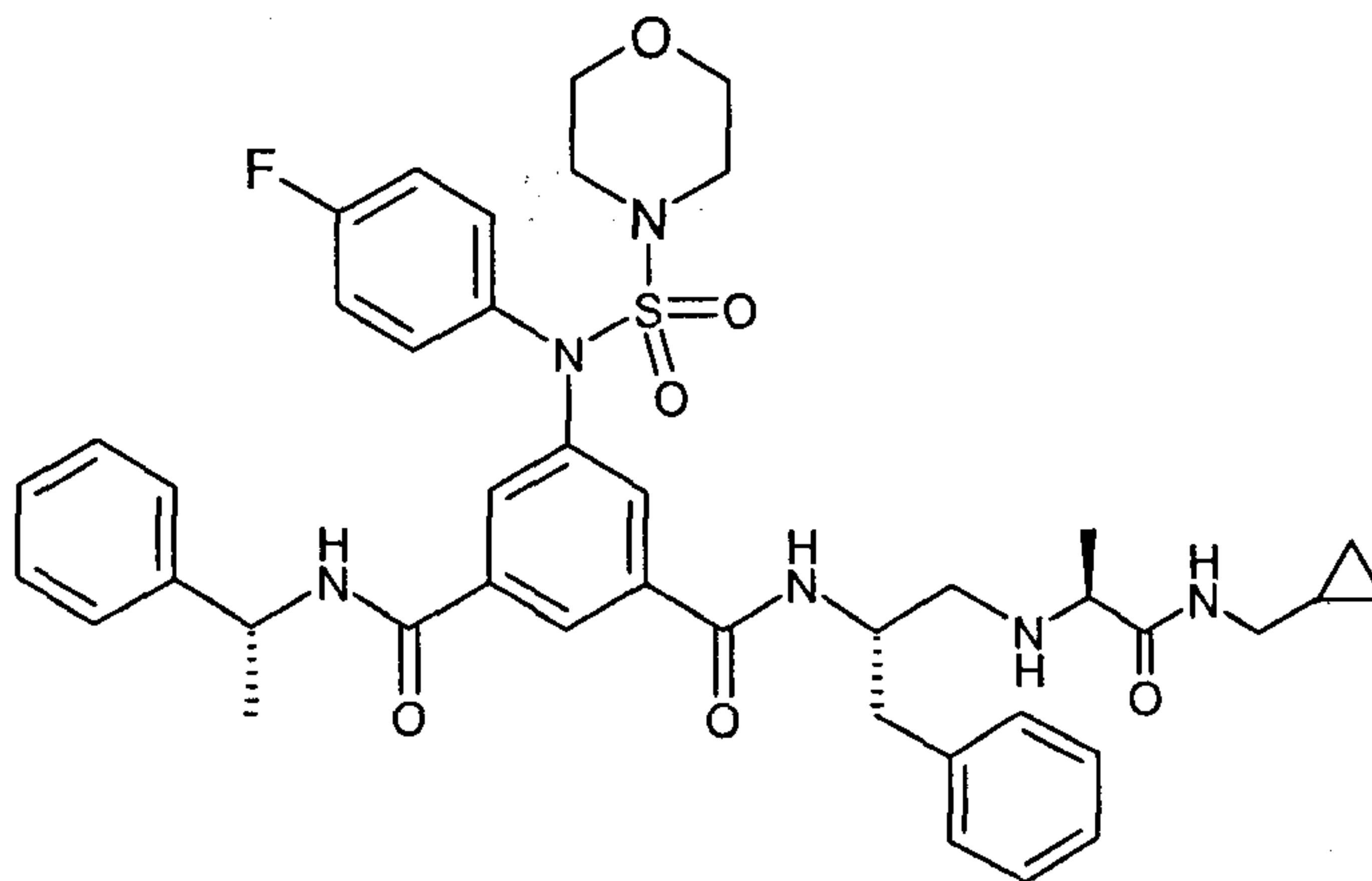
15 The following compounds were obtained analogously to Example 9 by using the corresponding sulphonyl chlorides:

- 157 -

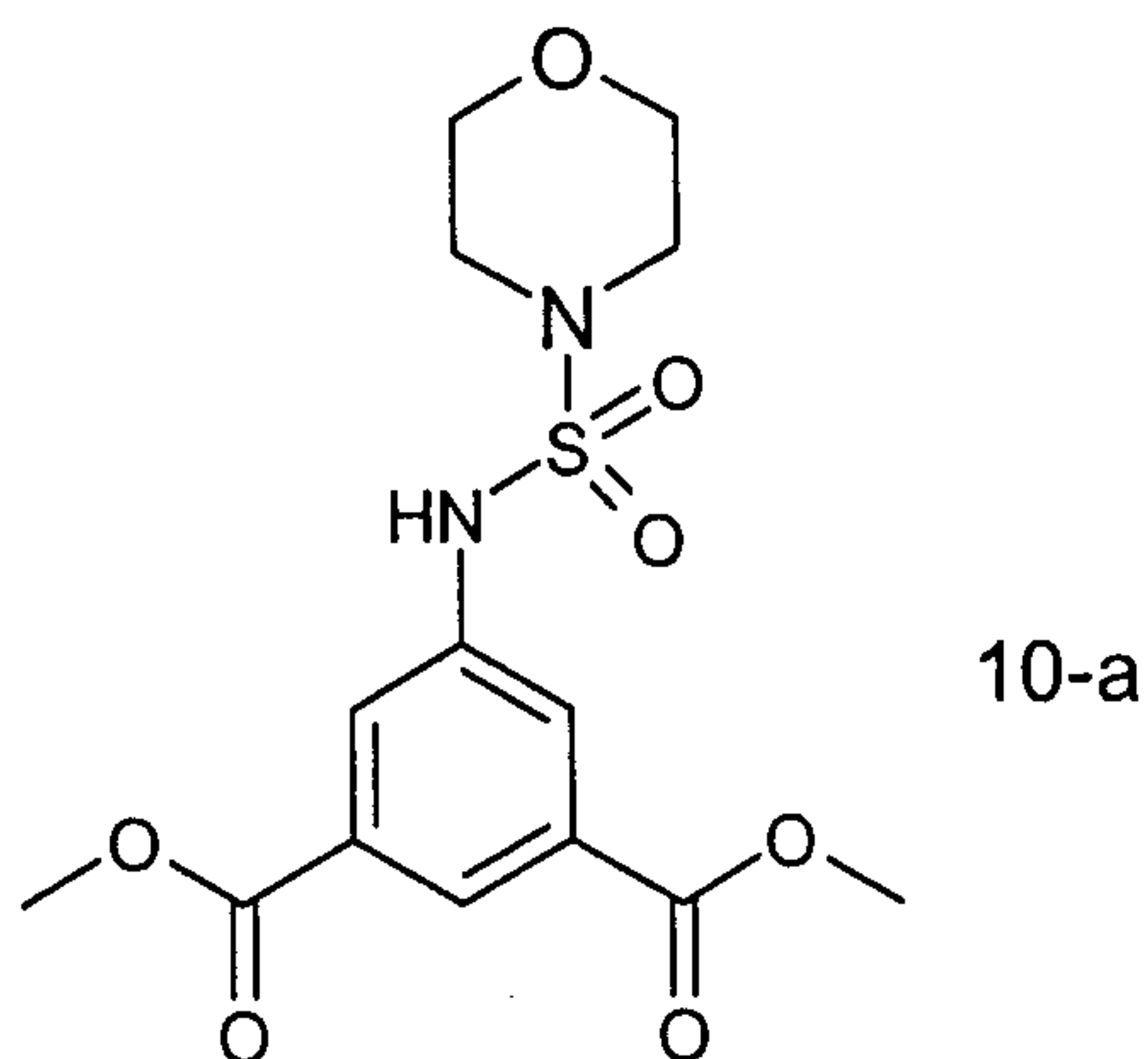


Example	R	
9.1		RT (HPLC-MS) = 3.08 min ES-MS (M+H) ⁺ = 717
9.2		RT (HPLC-MS) = 2.94 min ES-MS (M+H) ⁺ = 689

5 Example 10:



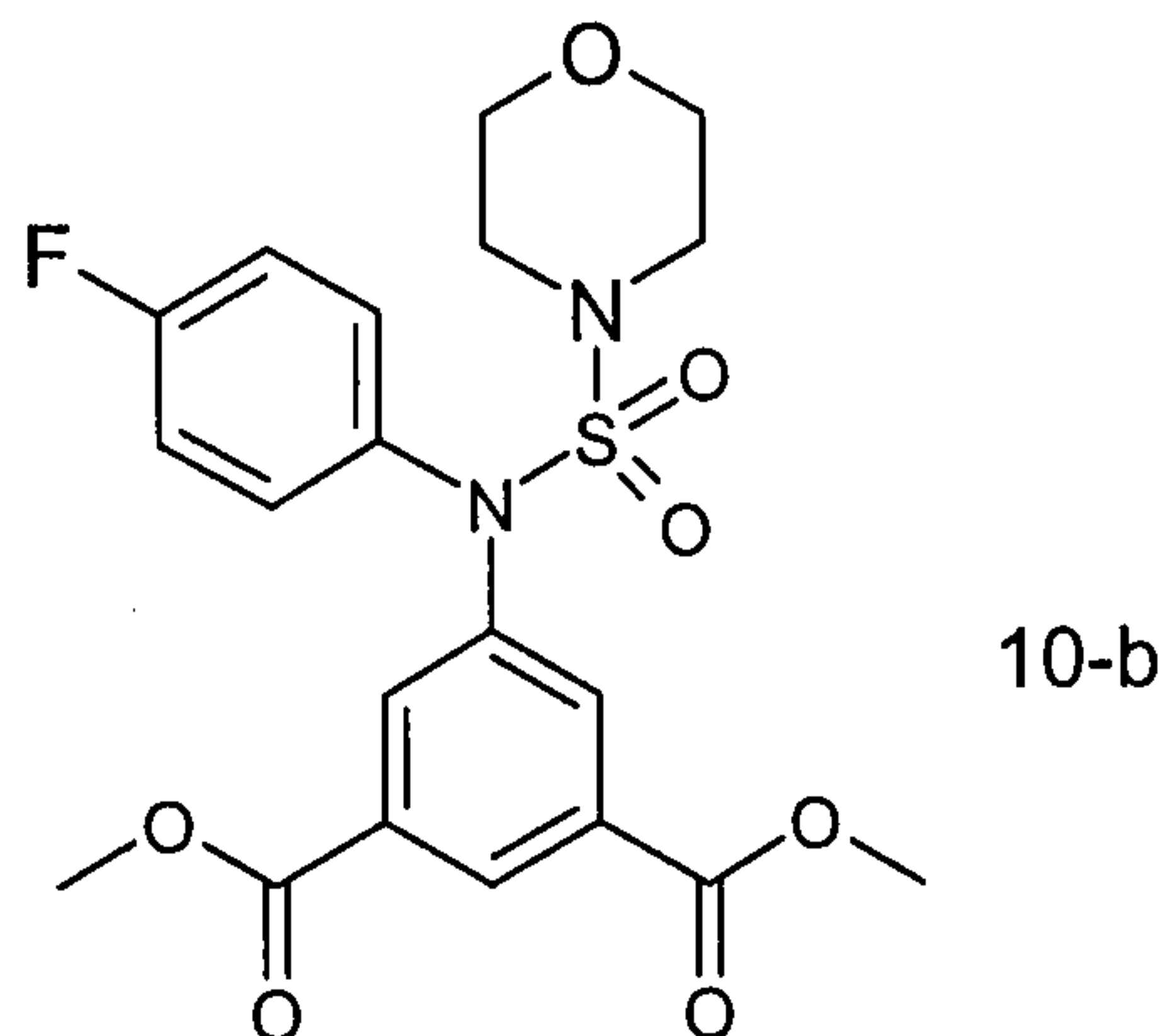
- 158 -

a) Preparation of **10-a**:

10-a was obtained analogously to **8-a**, by using morpholinylsulphonyl chloride instead of dimethylaminosulphonyl chloride.

RT (HPLC-MS) = 3.58 min

(M+H)⁺ (HPLC-MS) = 359

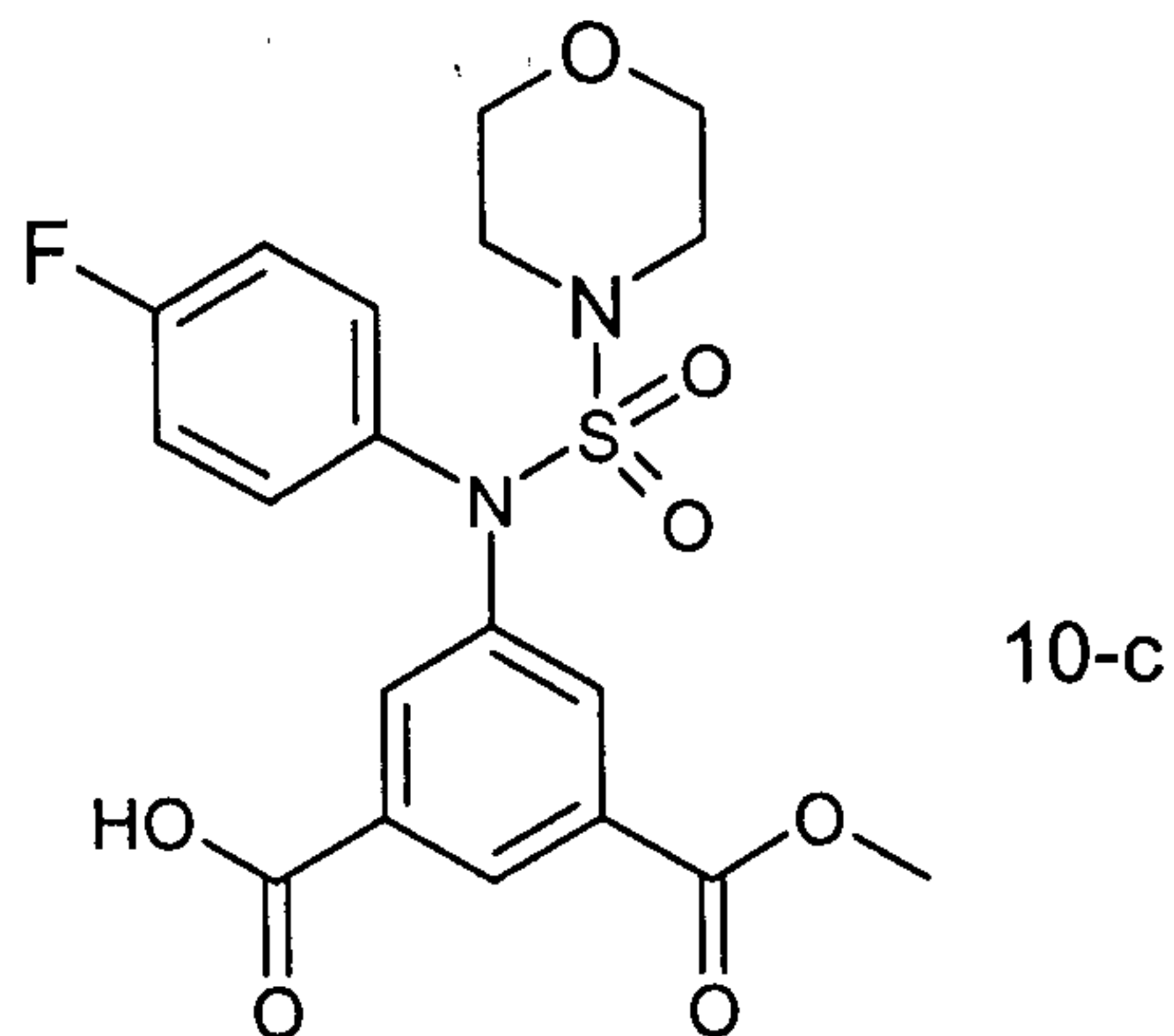
b) Preparation of **10-b**:

1 g (2.79 mmol) **10-a** and 780 mg (5.56 mmol) 4-fluorophenylboric acid were combined in 20 ml dichloromethane with 590 mg (3.25 mmol) copper-(II)-acetate, 800 μ l (5.77 mmol) triethylamine and 500 mg molecular sieve 4Å. The reaction solution was stirred overnight at ambient temperature and filtered off through silica gel. The filtrate was washed first with 2N HCl and then with sat. NaHCO₃ solution. The organic phases were separated using phase separation cartridges and evaporated to dryness. The residue was purified by HPLC. This yielded 200 mg (16%) **10-b**.

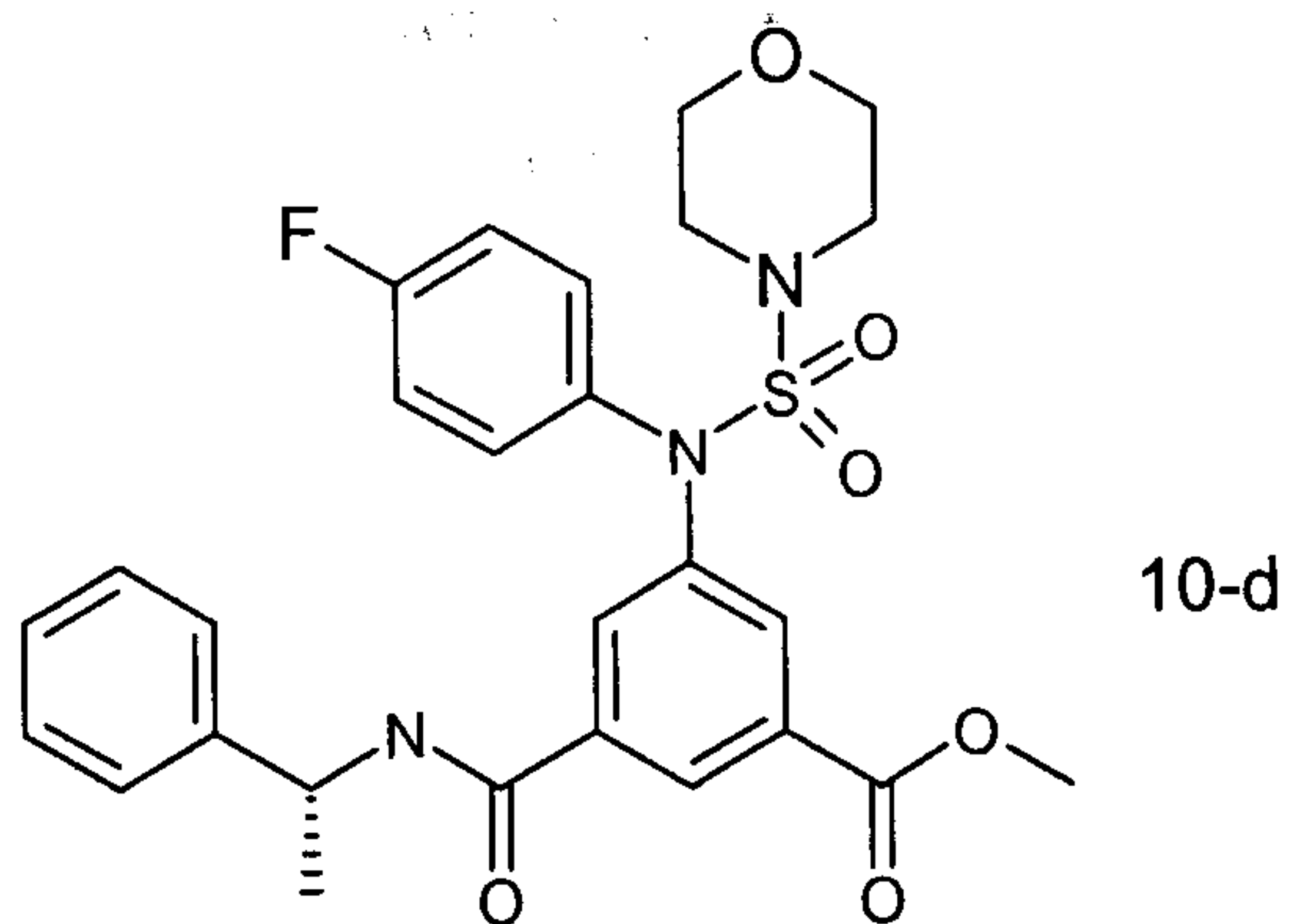
RT (HPLC-MS) = 2.75 min

(M+H)⁺ (HPLC-MS) = 453

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c) Preparation of **10-c**:**10-c** was obtained analogously to **8-c** from **10-b**.

5 RT (HPLC-MS) = 2.98 min
(M+H)⁺ (HPLC-MS) = 439

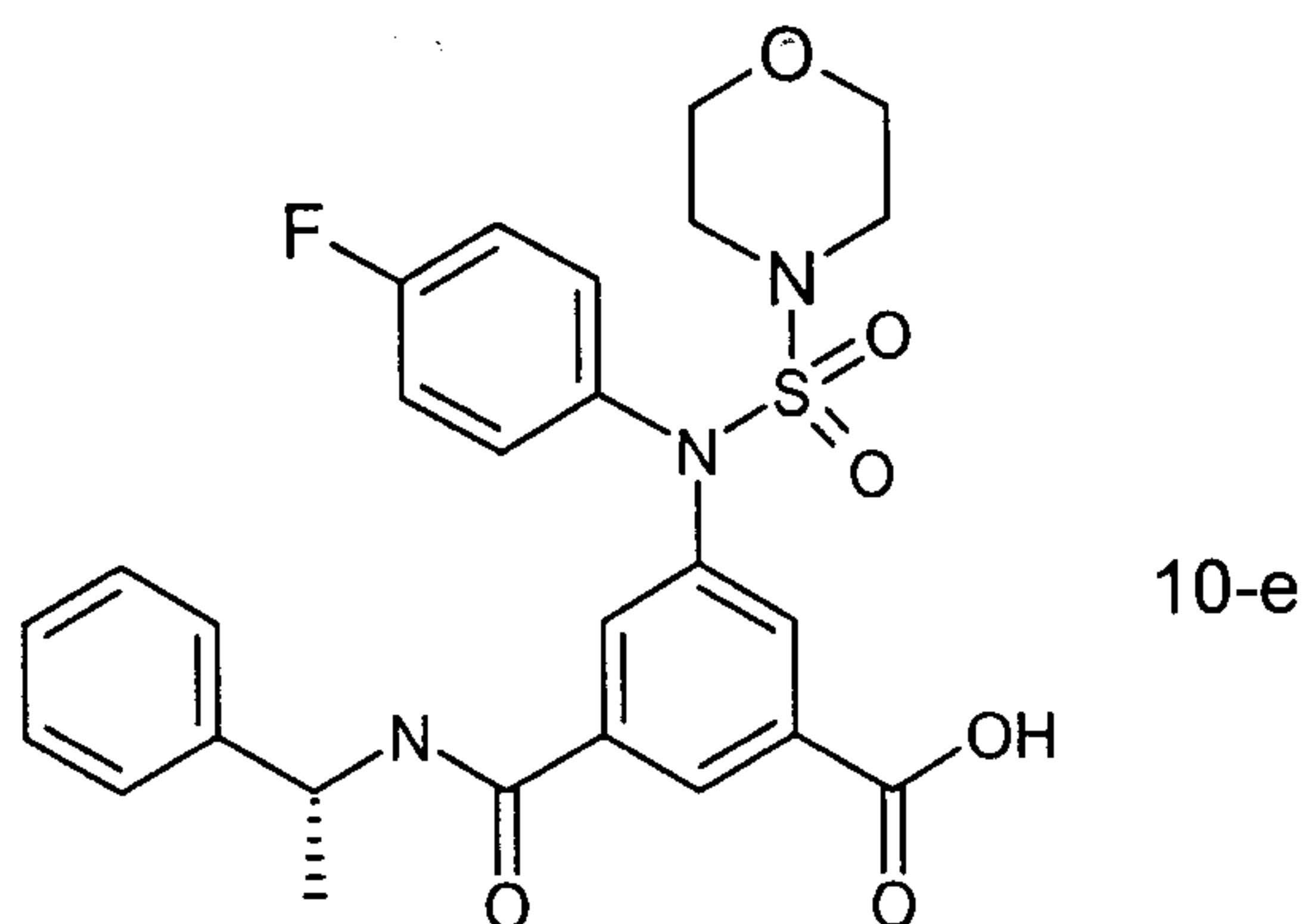
d) Preparation of **10-d**:

10

10-d was obtained analogously to **9-d** from **10-c**.

RT (HPLC-MS) = 3.30 min
(M+H)⁺ (HPLC-MS) = 543

15

e) Preparation of **10-e**:

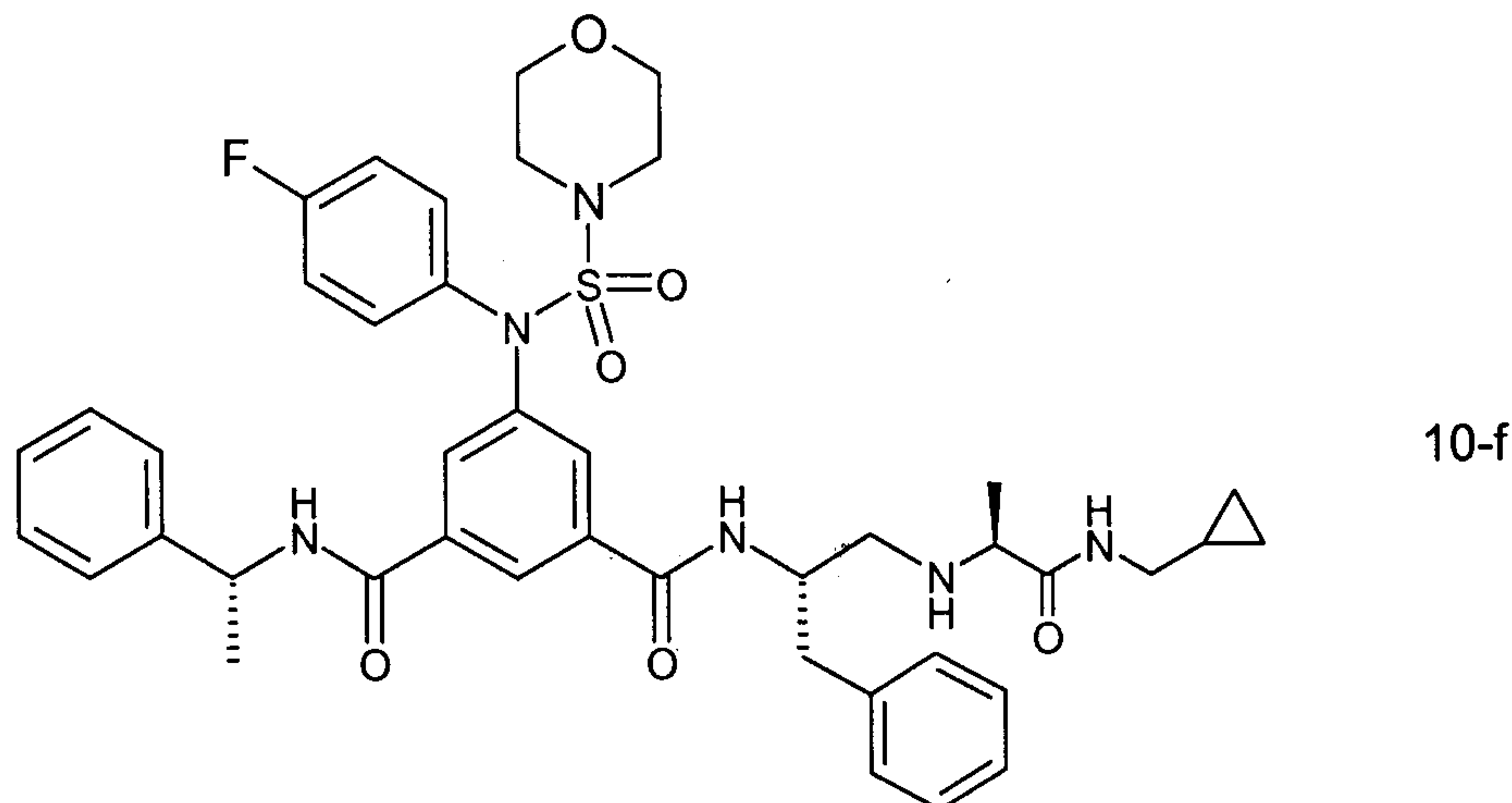
- 160 -

10-e was obtained analogously to **7-d** from **10-d**.

RT (HPLC-MS) = 3.11 min

(M+H)⁺ (HPLC-MS) = 528

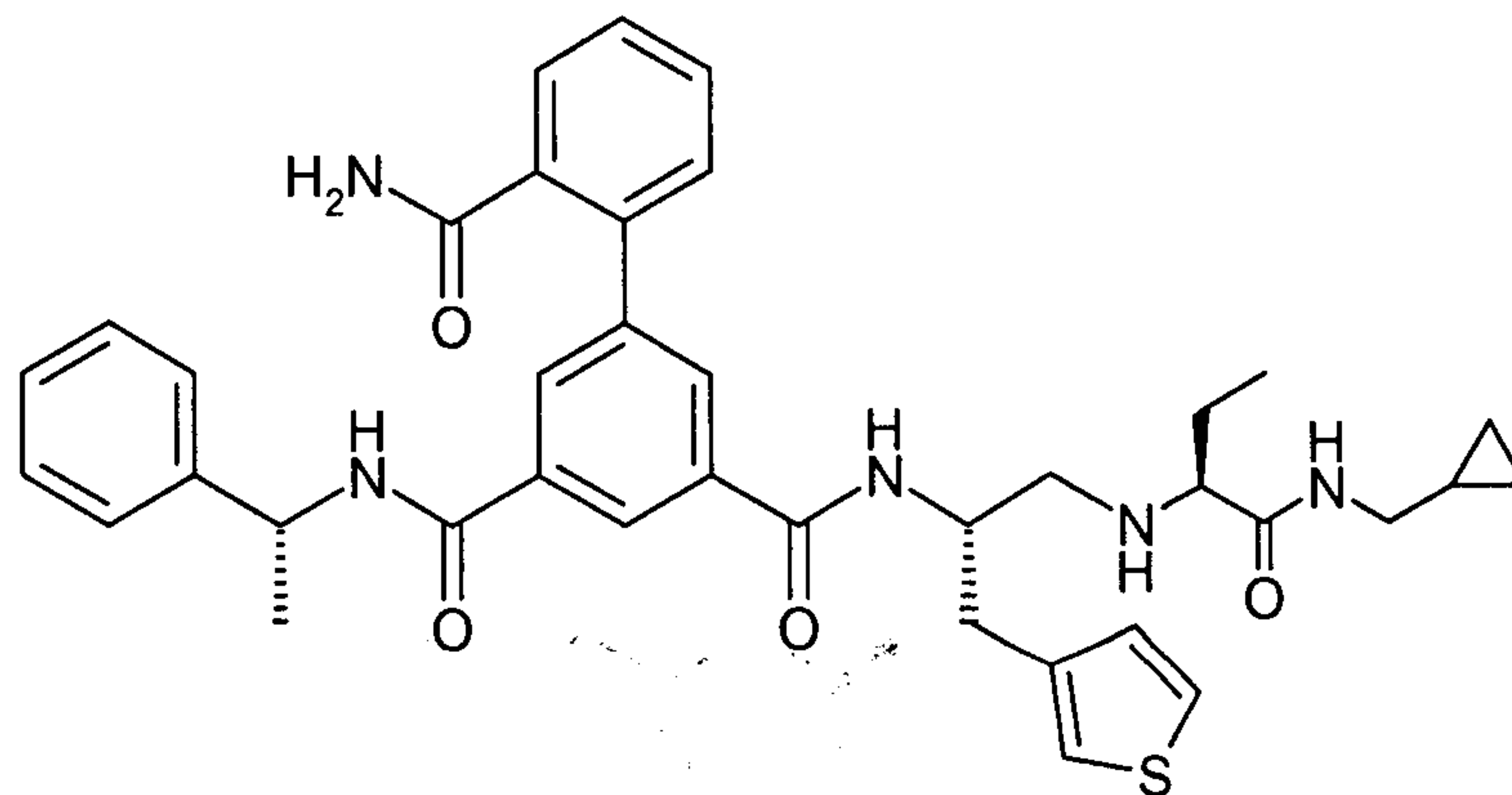
5 f) Preparation of **10-f**:



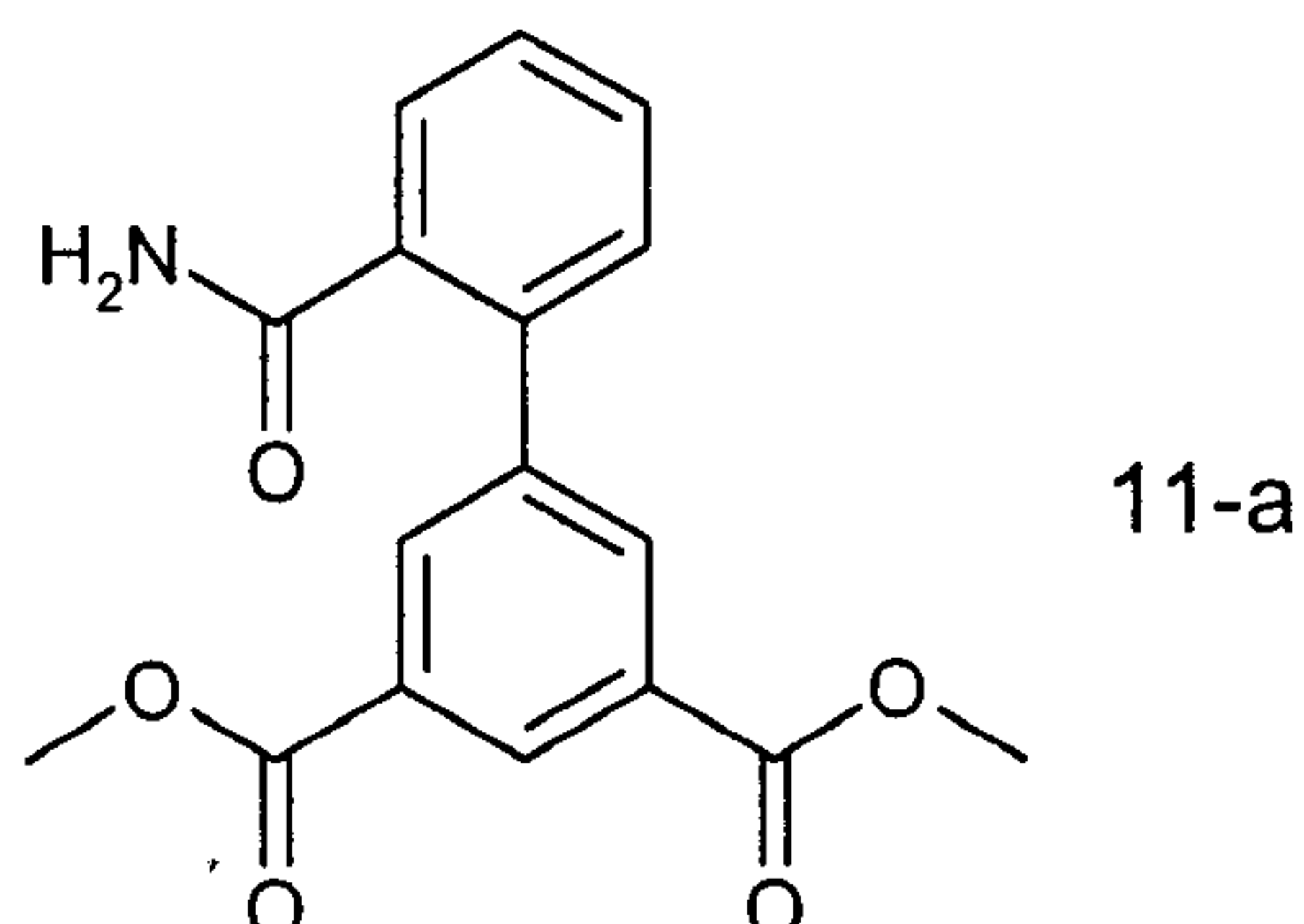
10-f was obtained analogously to **7-j** from **10-e** and **7-i**.

ES-MS (M+H)⁺ = 785

10 Example **11**:



a) Preparation of **11-a**:



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4.10 g (12.8 mmol) dimethyl 5-iodo-isophthalate were dissolved in 80 ml DMF. 3.32 g (20.1 mmol) 2-carbamoyl-phenylboric acid, 3.00 ml (21.6 mmol) TEA, 3.00 ml (167 mmol) water, 75 mg (0.33 mmol) palladium(II)-acetate as well as 102 mg (0.34 mmol) tri-ortho-tolylphosphine were added and the solution was heated to 100°C for 2.5 h.

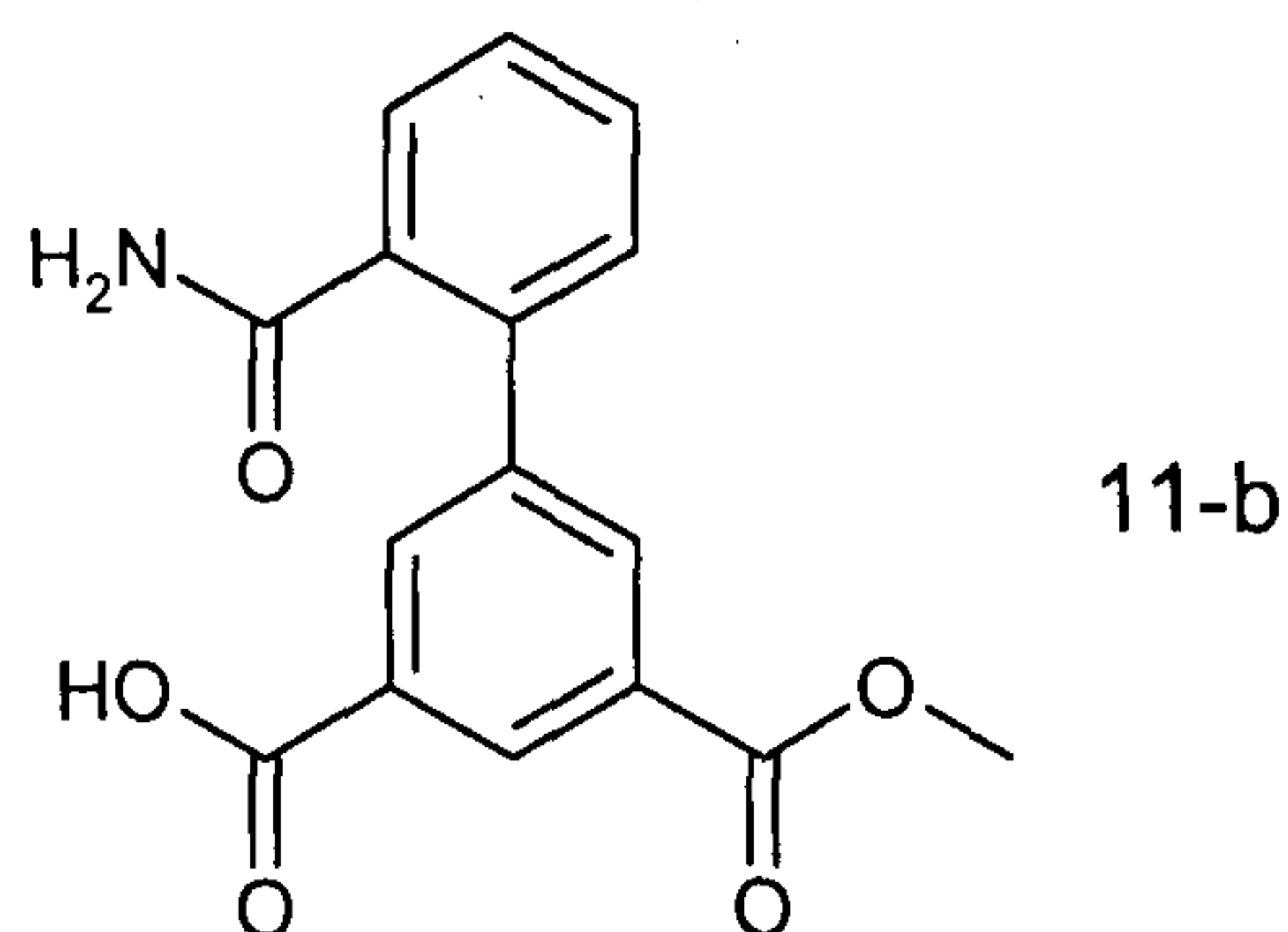
- 5 The reaction solution was cooled and the solvent was distilled off i. vac.. The residue was chromatographed on silica gel (gradient: DCM auf DCM/MeOH 7:3). 2.53 g (63%) of **11-a** were obtained.

RT (HPLC-MS) = 2.68 min.

ES-MS (M+H)⁺ = 314

10

b) Preparation of **11-b**:

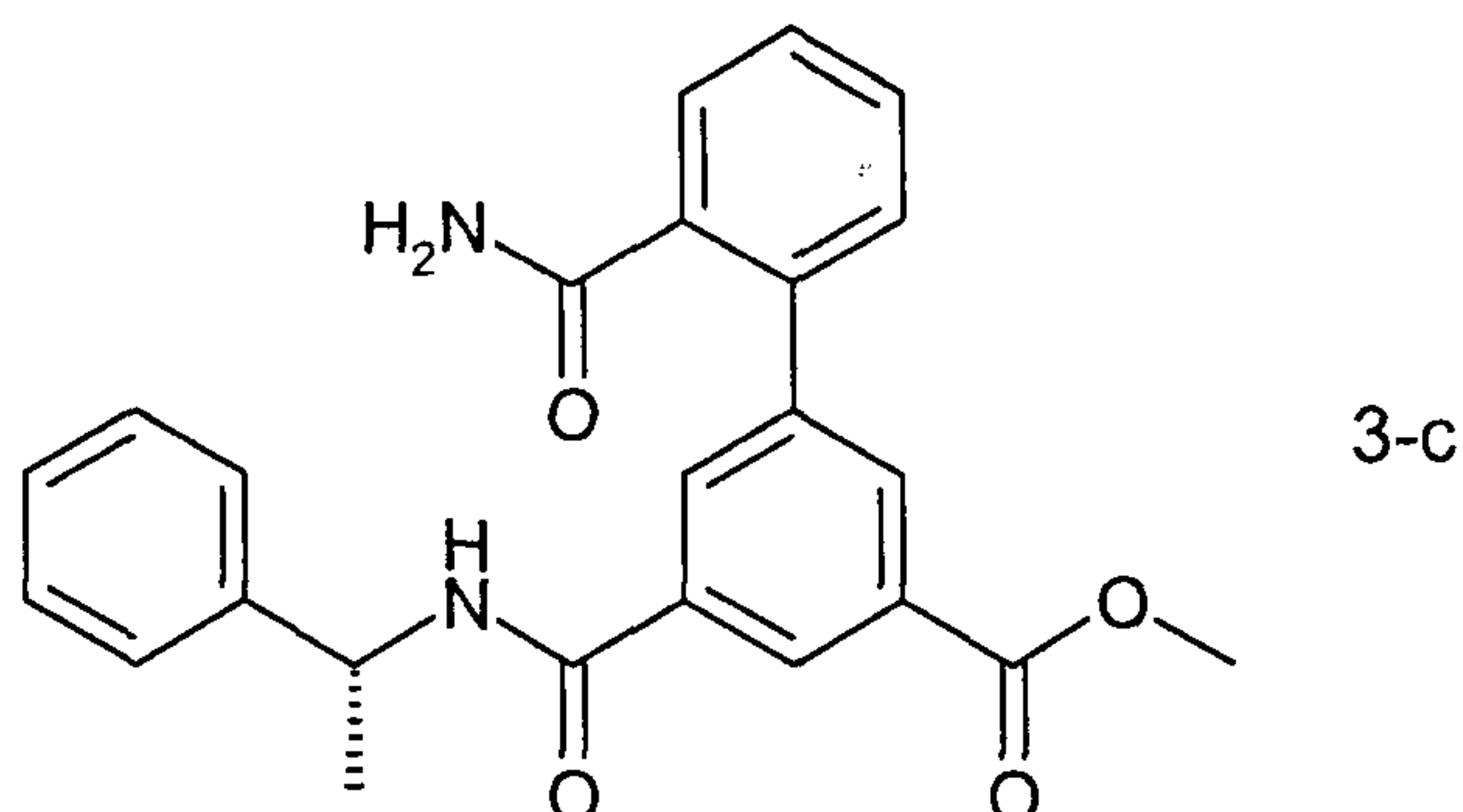


11-b was obtained analogously to **1-f** from **11-a**.

- 15 RT (HPLC-MS) = 2.40 min.

ES-MS (M+H)⁺ = 300

d) Preparation of **11-c**

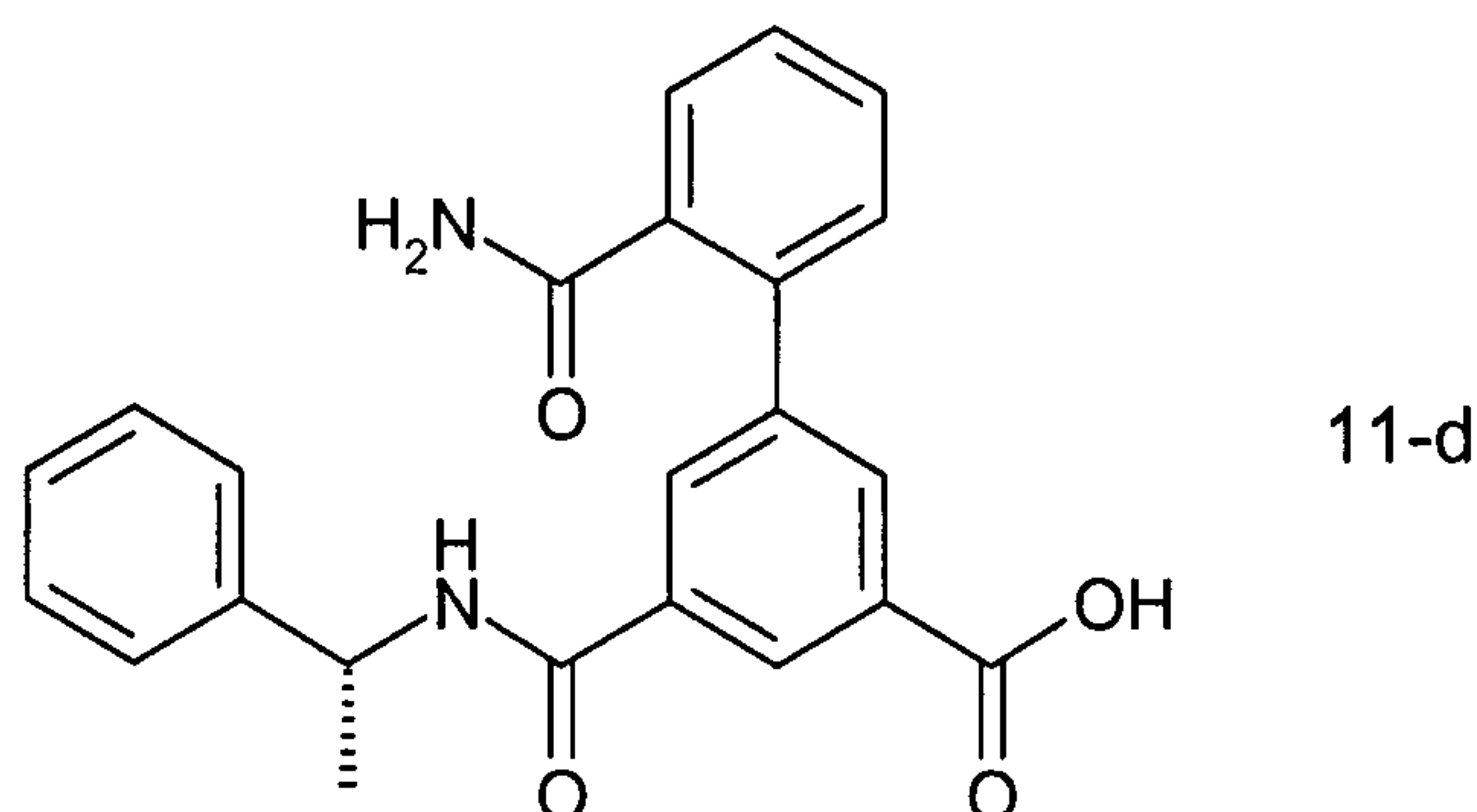


- 20 **11-c** was prepared analogously to **1-g** from **11-b**.

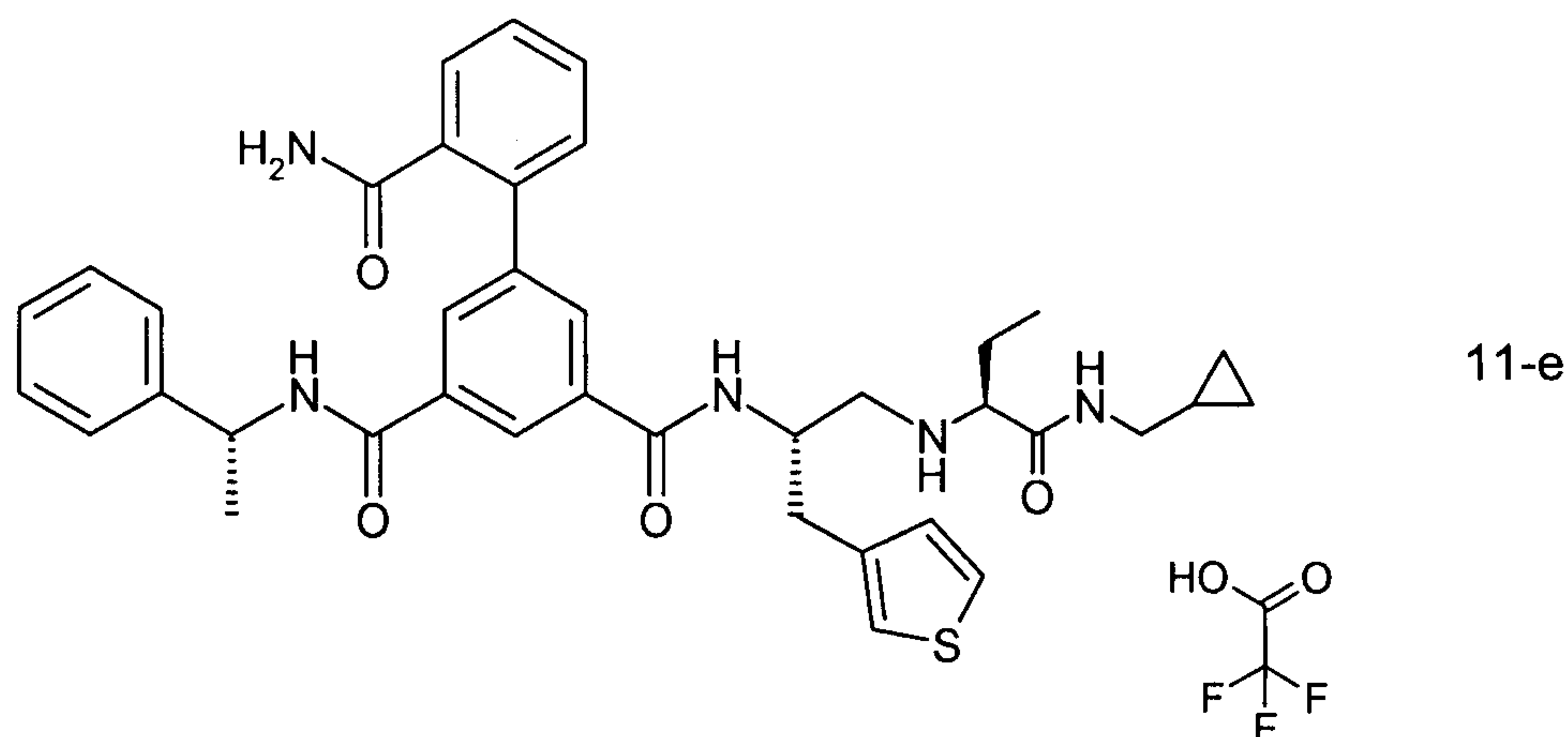
RT (HPLC-MS) = 2.87 min.

ES-MS (M+H)⁺ = 403

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e) Preparation of **11-d**:**11-d** was prepared analogously to **1-h** from **11-c**.

5 RT (HPLC-MS) = 2.89 min.

ES-MS (M+H)⁺ = 389f) Preparation of **11-e**:

10

11-e was prepared analogously to **1-g** from **11-d** and the amine analogous to **3-g**, which was obtained by substituting BOC-L-alanine by BOC-L-aminobutyric acid and **1-l** by cyclopropylmethylamine (step 3b) and also BOC-L-4-thiazolylalanine by BOC-L-3-thienylalanine (step 3d). The product was purified by preparative HPLC.

15 RT (HPLC-MS) = 2.79 min.

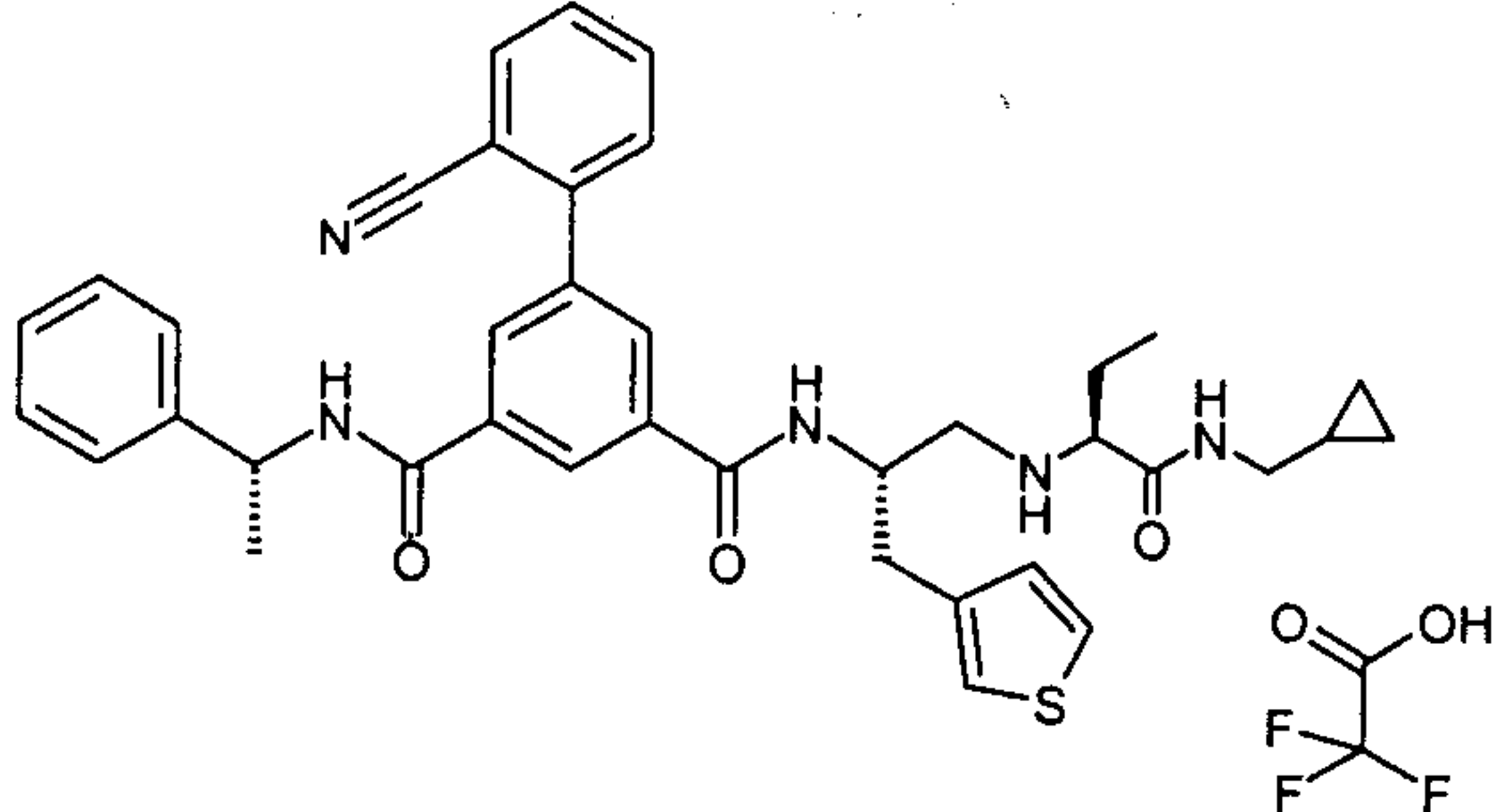
ES-MS (M+H)⁺ = 666

Analogously to **11-e** the following compound was prepared from **11-d** and the amine analogous to **3-g**, which was obtained by substituting BOC-L-alanine by BOC-L-aminobutyric acid and **1-l** by 4-aminobenzylamine (step 3b) and also BOC-L-4-thiazolylalanine by BOC-L-3-thienylalanine (step 3d):

20

Example		
11.1		RT (HPLC-MS) = 2.42 min. ES-MS (M+H)⁺ = 717

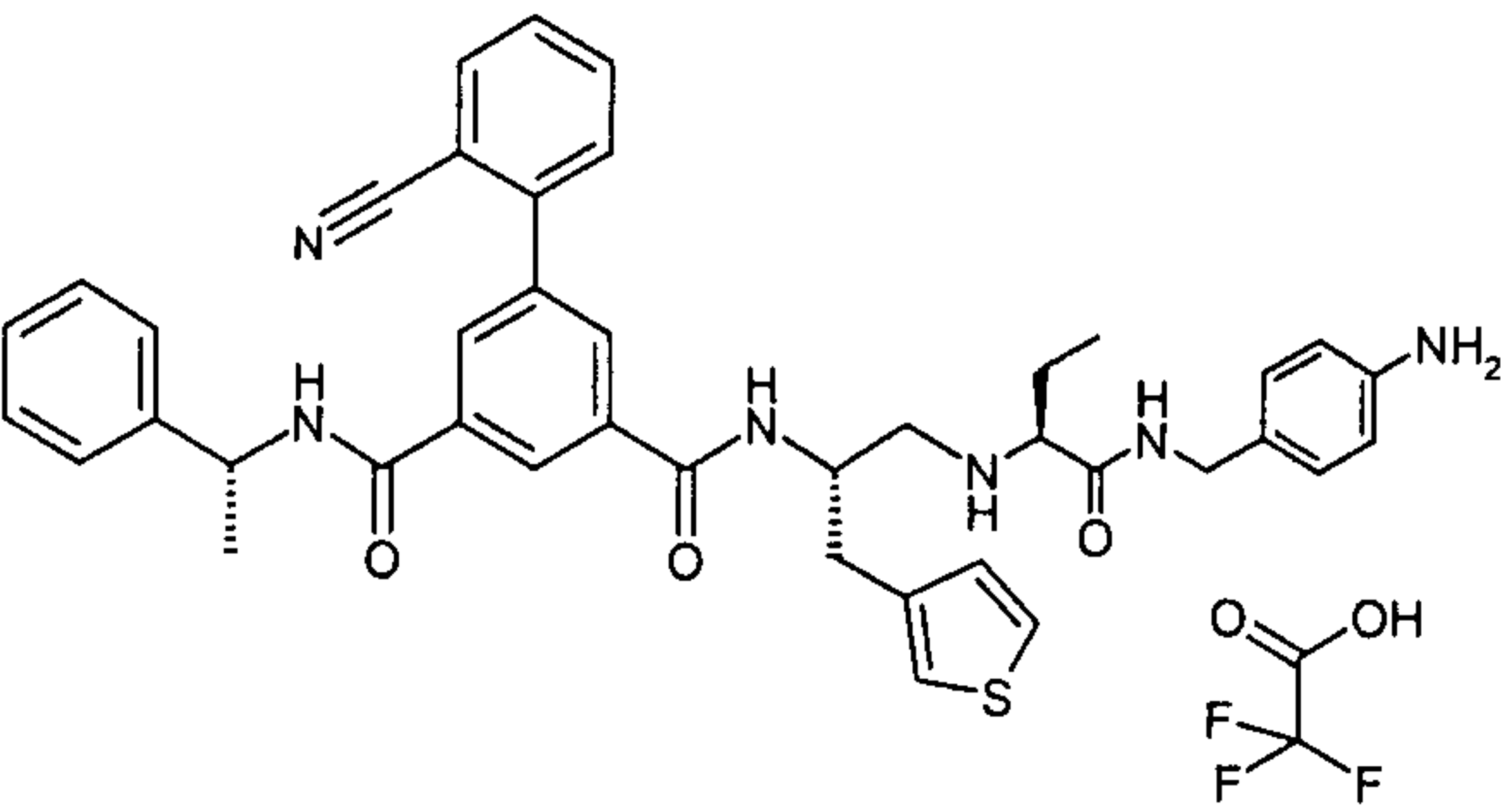
The following compound was obtained analogously to **11-e** from the acid analogous to **11-d**, which was prepared by substituting 2-carbamoyl-phenylboric acid by 2-cyano-phenylboric acid (step 11a), and the amine analogous to **3-g**, which was obtained by substituting BOC-L-alanine by BOC-L-aminobutyric acid and **1-I** by cyclopropylmethylamine (step 3b) and BOC-L-4-thiazolylalanine by BOC-L-3-thienylalanine (step 3d):

Example		
11.2		RT (HPLC-MS) = 3.01 min. ES-MS (M+H) ⁺ = 648

10

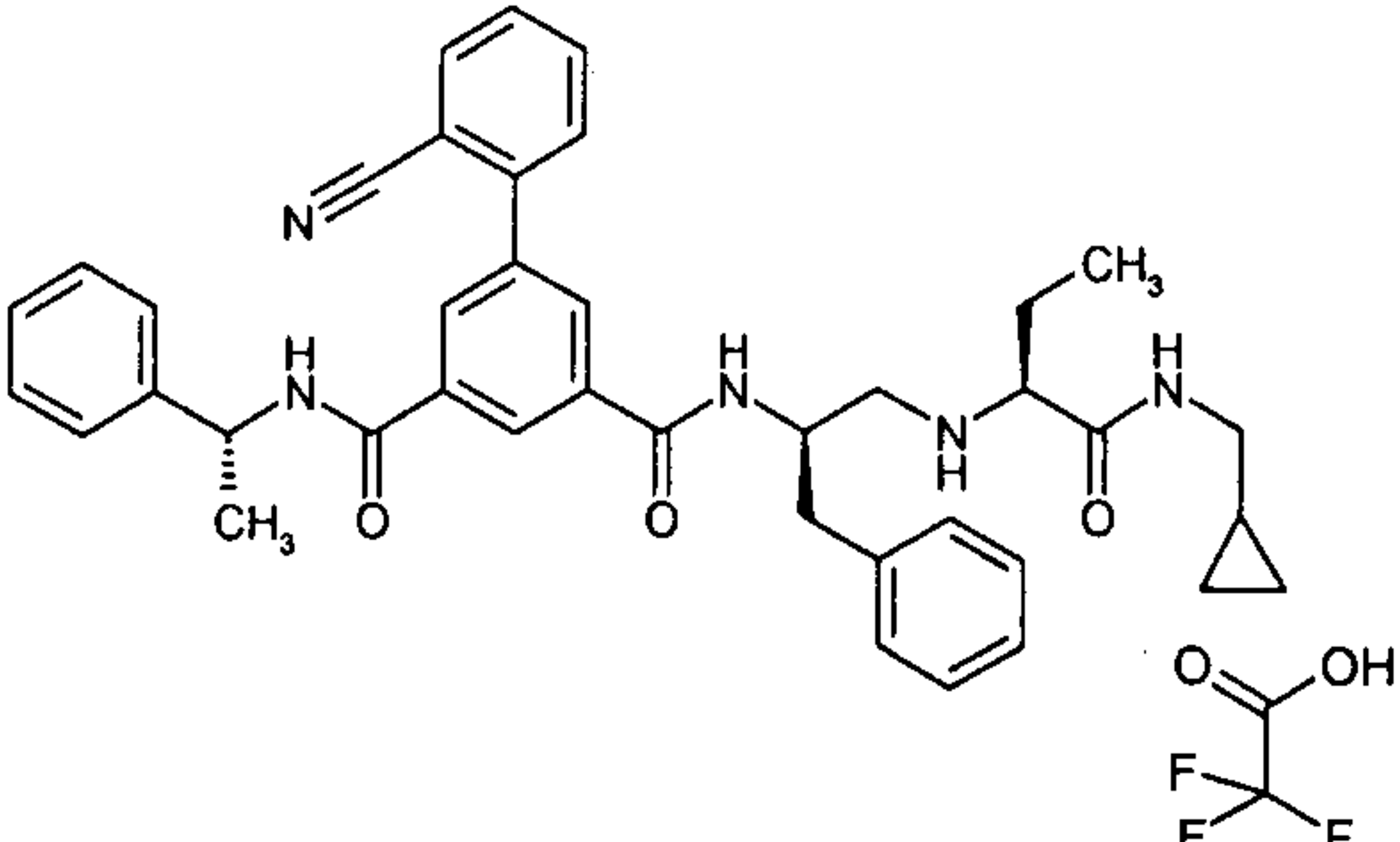
The following compound was prepared analogously to **11-e** from the acid analogous to **11-d**, which was obtained by substituting 2-carbamoyl-phenylboric acid by 2-cyano-phenylboric acid (step 11a), and the amine analogous to **3-g**, which was obtained by substituting BOC-L-alanine by BOC-L-aminobutyric acid and **1-l** by 4-aminobenzylamine (step 3b) and also BOC-L-4-thiazolylalanine by BOC-L-3-thienylalanine (step 3d):

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Example		
11.3		RT (HPLC-MS) = 2.59 min. ES-MS (M+H) ⁺ = 699

The following compound was prepared analogously to **11-e** from the acid analogous to **11-d**, which was obtained by substituting 2-carbamoyl-phenylboric acid by 2-cyano-phenylboric acid (step 11a), and **6-3-b**:

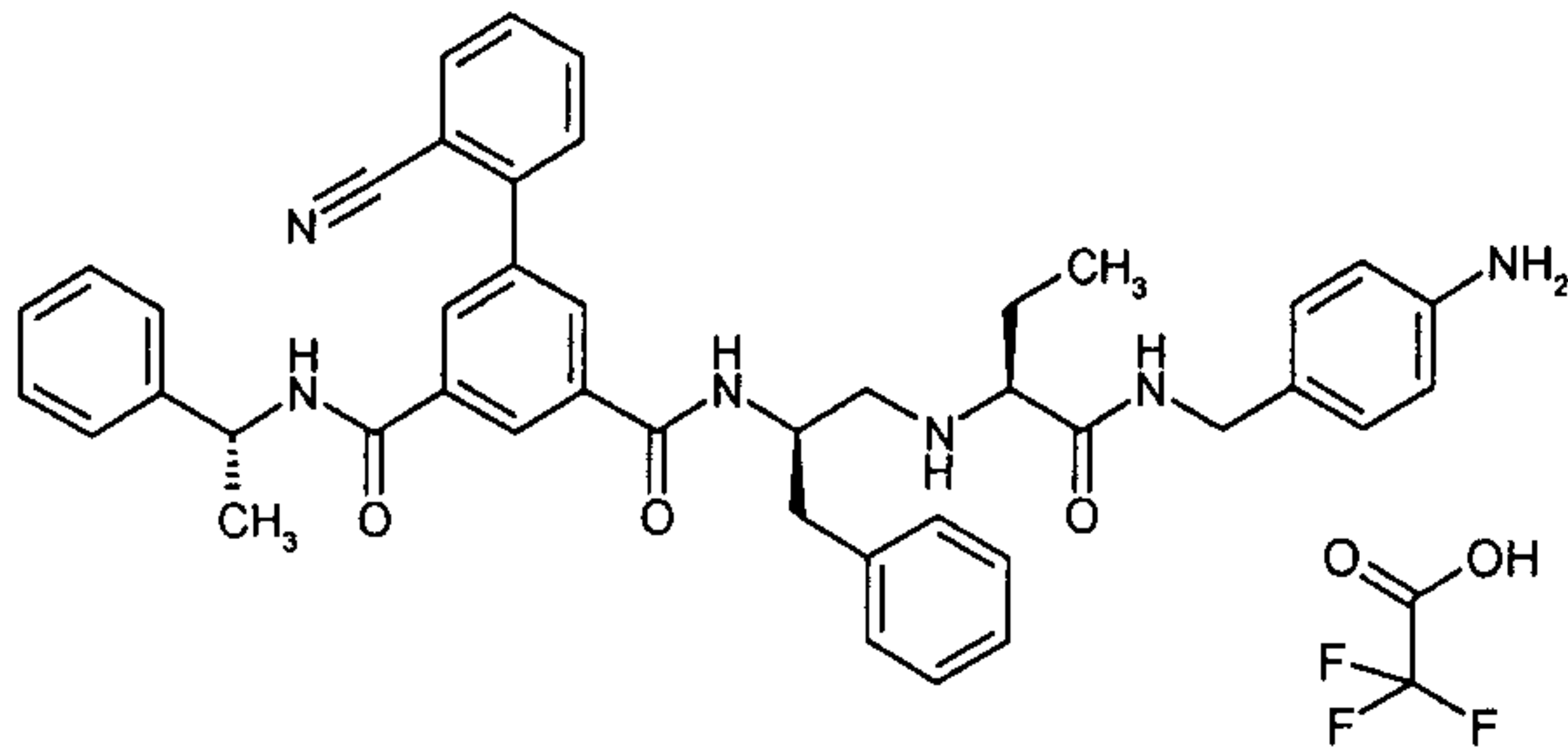
5

Example		
11.4		RT (HPLC-MS) = 2.93 min. ES-MS (M+H) ⁺ = 642

The following compound was prepared analogously to **11-e** from the acid analogous to **11-d**, which was obtained by substituting 2-carbamoyl-phenylboric acid by 2-cyano-phenylboric acid (step 11a), and the amine analogous to **3-g**, which was obtained by substituting BOC-L-alanine by BOC-L-aminobutyric acid and **1-I** by 4-aminobenzylamine (step 3b) and BOC-L-4-thiazolylalanine by BOC-D-phenylalanine (step 3d):

10

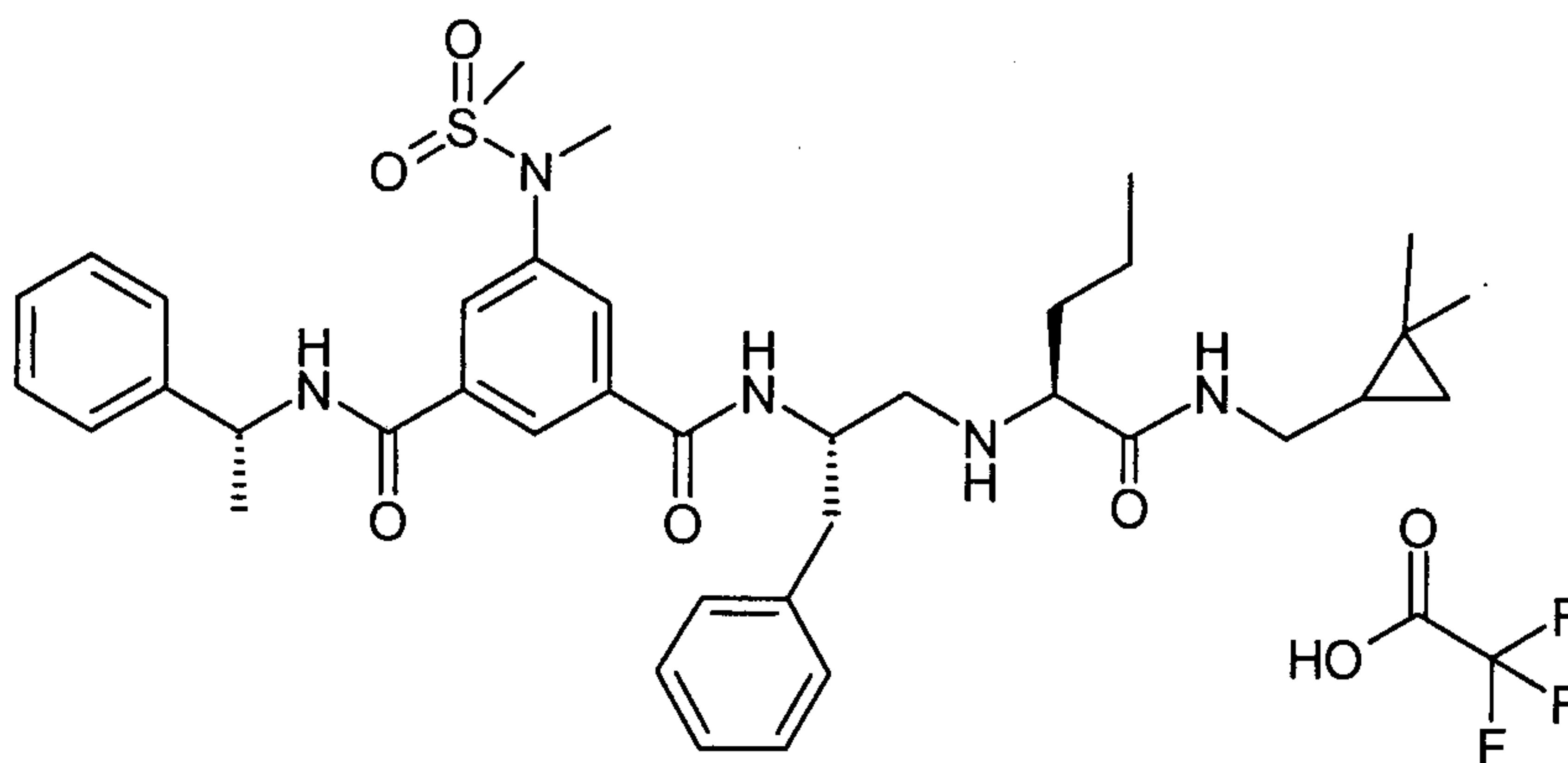
- 165 -

Example		
11.5		RT (HPLC-MS) = 2.83 min. ES-MS (M+H) ⁺ = 693

The following are examples of preparation forms in which the term "active substance" denotes one or more compounds according to the invention including the salts thereof.

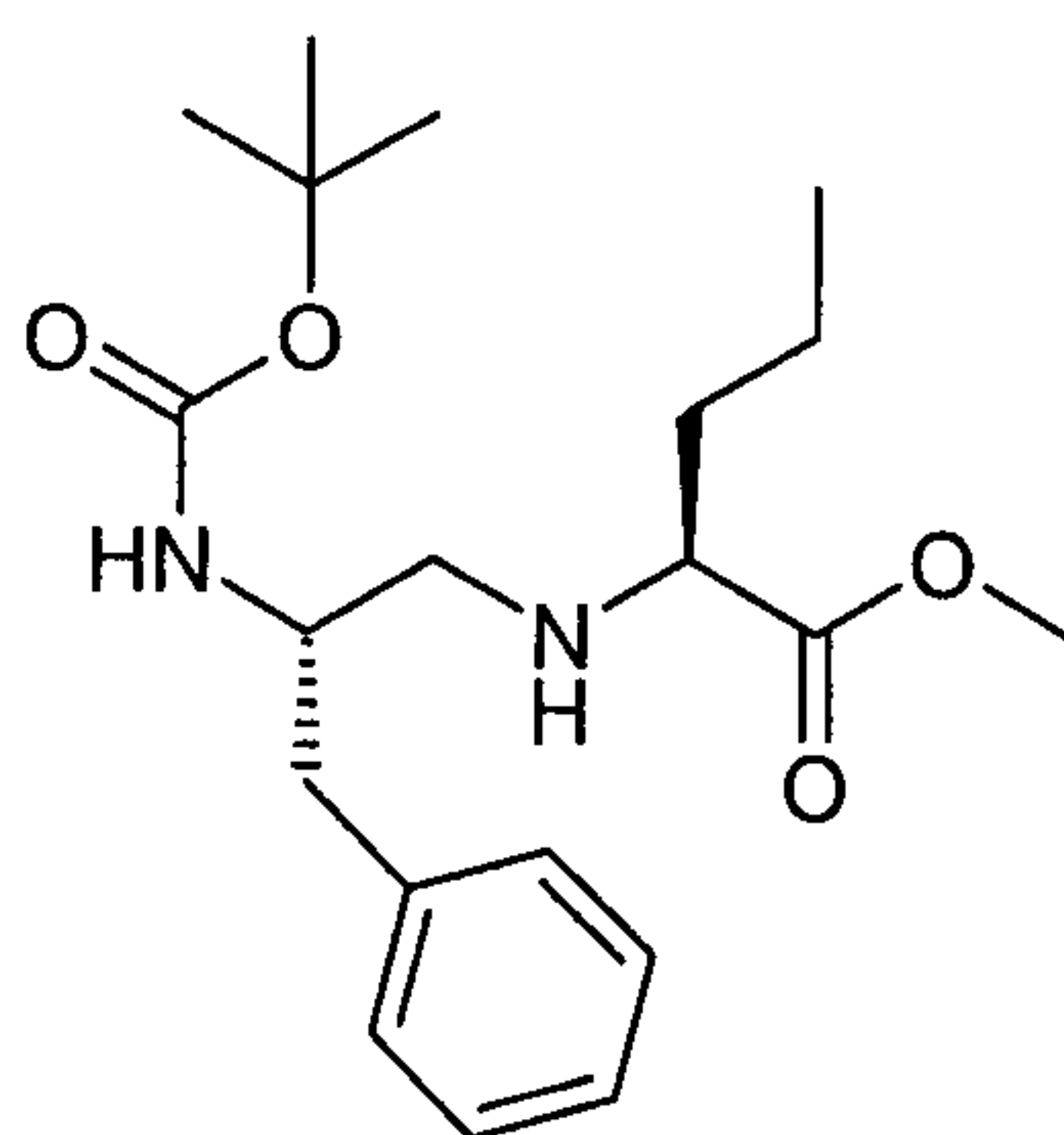
- 5 In the case of one of the combinations with one or more additional active substances the term "active substance" also includes the additional active substances.

Example 12:



10

Preparation of 12-a:



12-a

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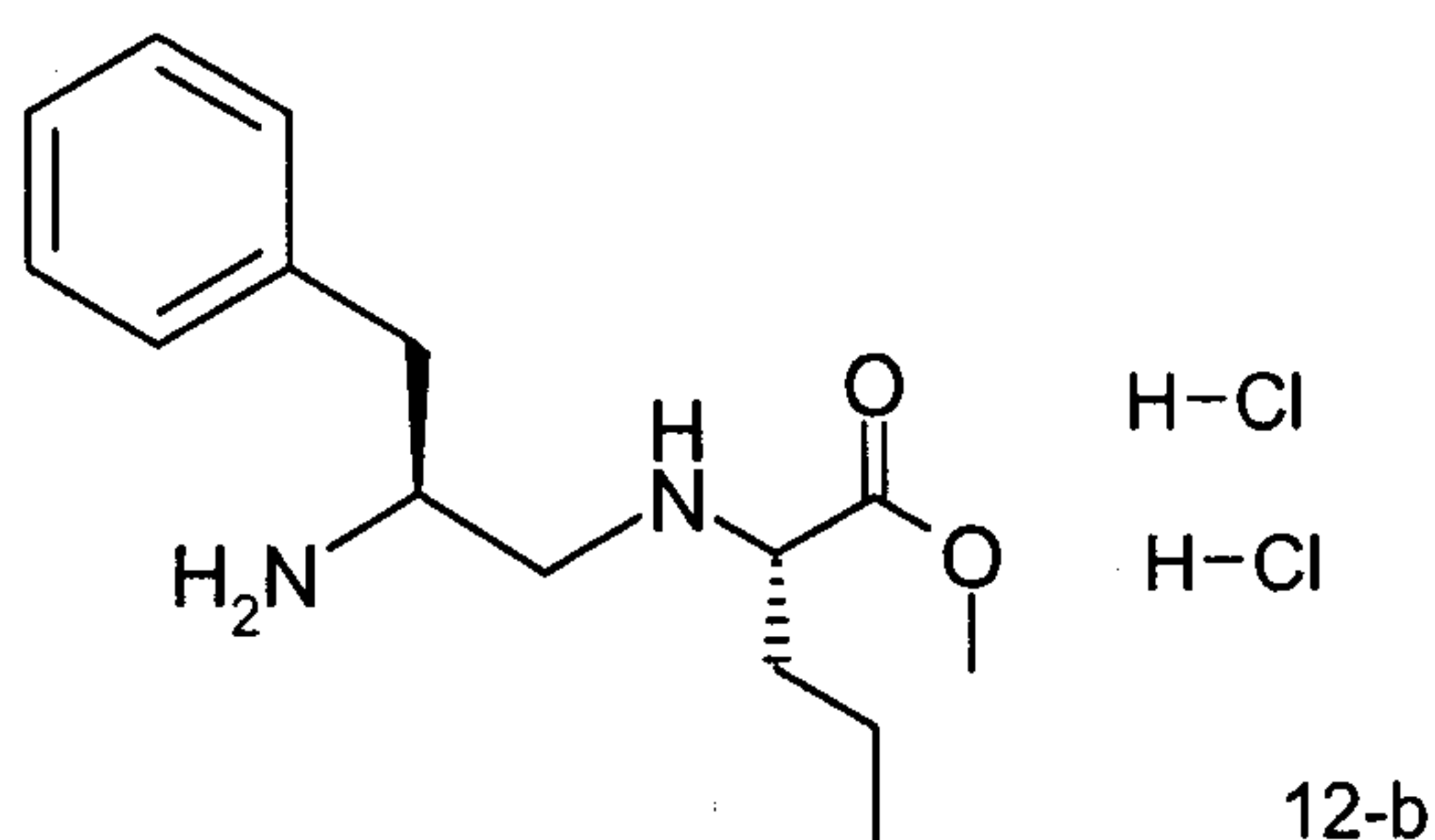
12-a was prepared by reacting 10 g (40.1 mmol) **1-a** with 9.0 g (40.2 mmol) Boc-L-norvaline methylester hydrochloride analogously to **1-b**.

Yield: 4.1 g (28 %).

ES-MS (M+H)⁺ = 365

5 RT (HPLC-MS) = 1.90 min

Preparation of **12-b**:



1.2 ml (16.5 mmol) thionyl chloride were added dropwise to a solution of 6.8 g (18.7 mmol) **12-a** in 300 ml of methanol. The mixture was stirred for 14 h, the reaction mixture was evaporated down, and the desired product was thus obtained.

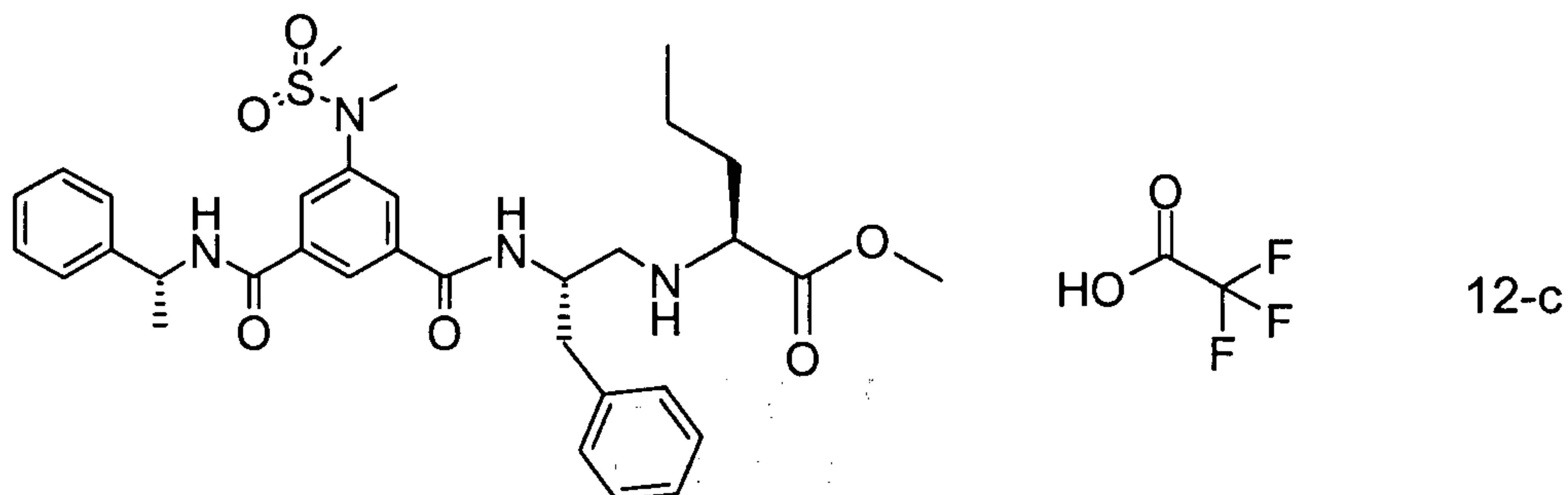
Yield: 5.3 g (85 %).

ES-MS (M+H)⁺ = 265

RT (HPLC-MS) = 1,41 min

15

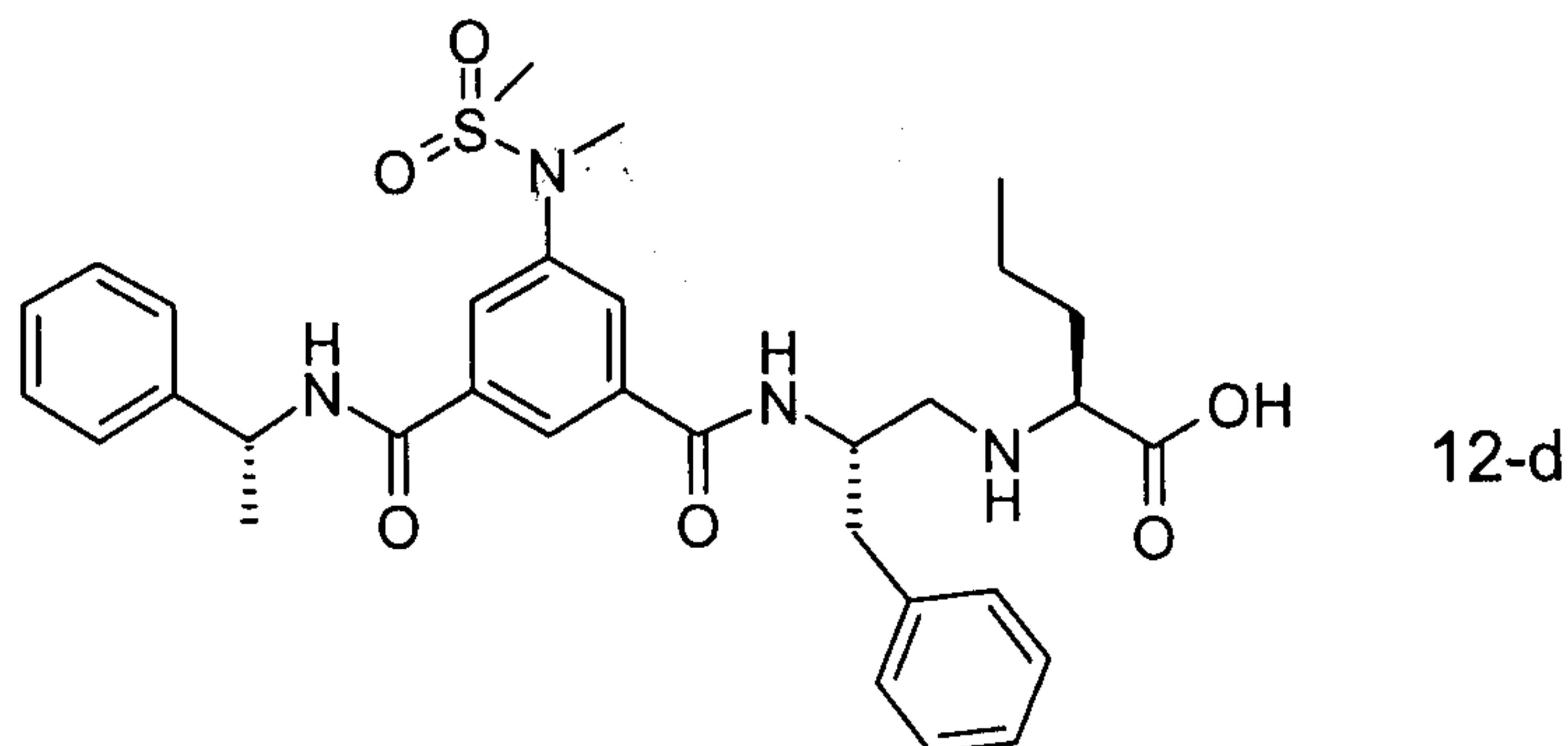
Preparation of **12-c**:



12-c was prepared analogously to **2-i** starting from 1.88 g (5.00 mmol) **1.8-h** and 1.67 g (5.00 mmol) **12-b**.

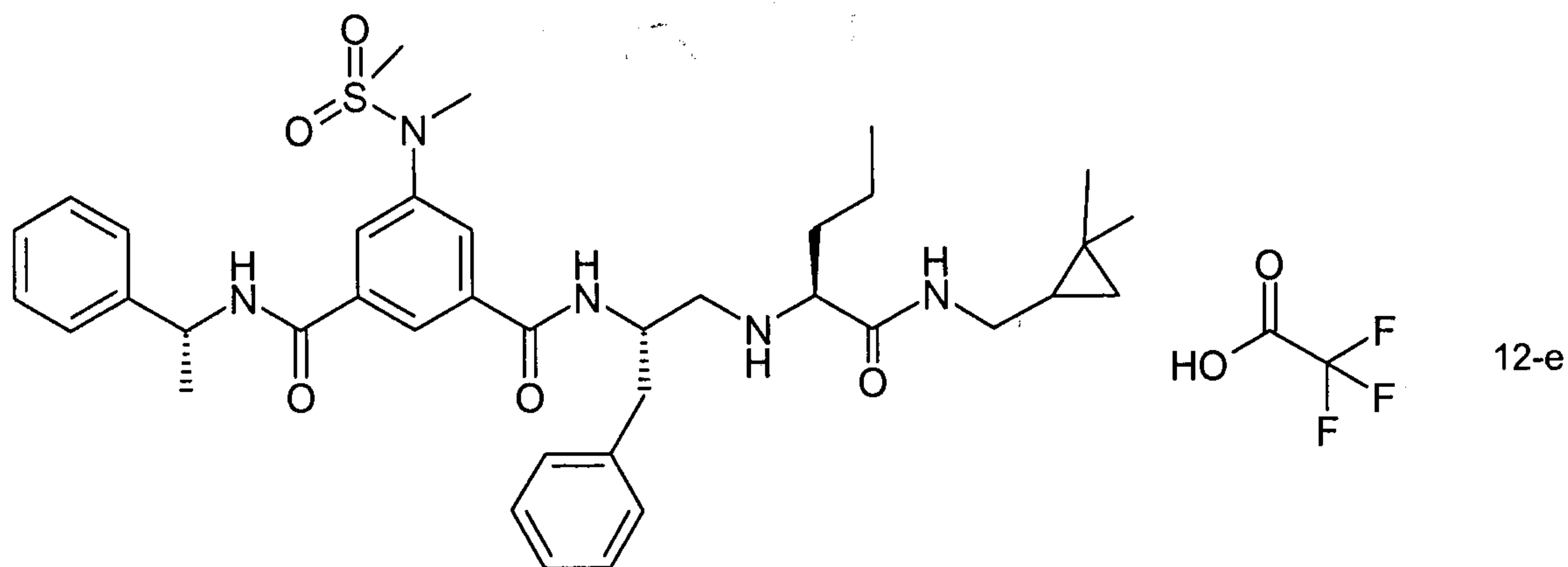
20 RT (HPLC-MS) = 1.96 min

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Preparation of **12-d**:

The preparation of **12-d** was carried out analogously to **2-k** starting from 1.70 g (2.31 mmol) **12-c**.

- 5 Yield: 1.25 g (89 %).
ES-MS (M+H)⁺ = 609
RT (HPLC-MS) = 1.89 min

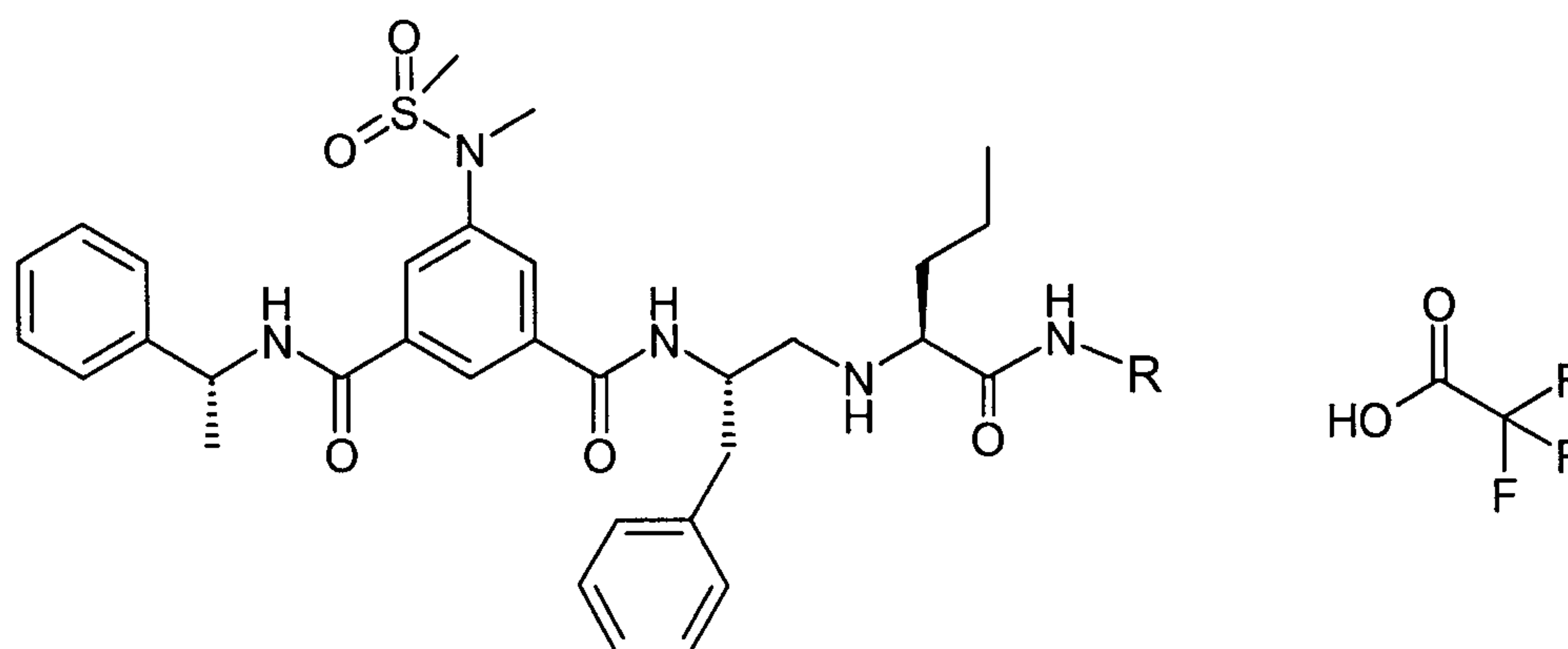
Preparation of **12-e**:

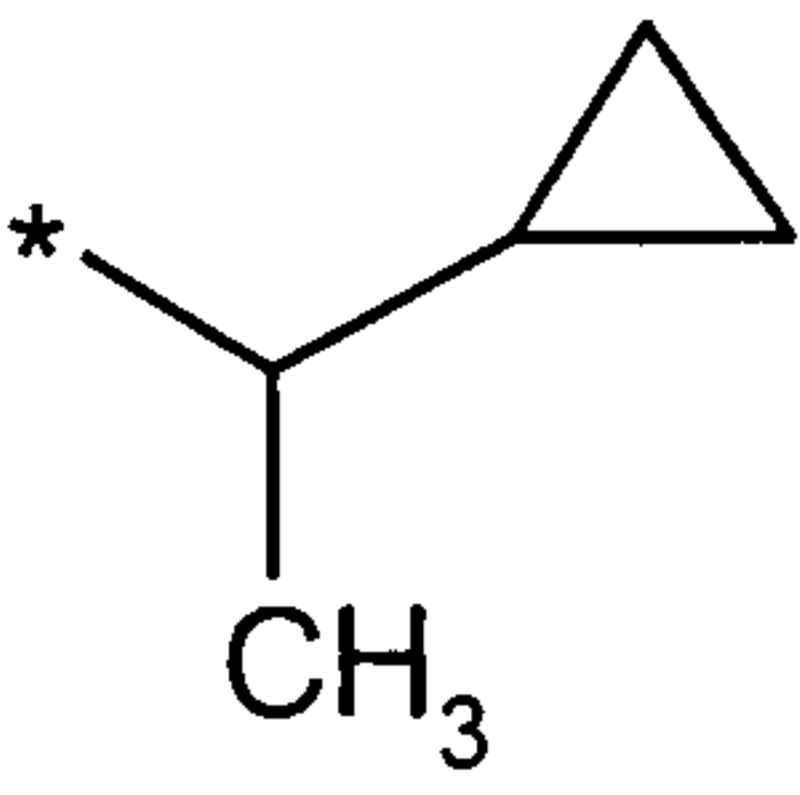
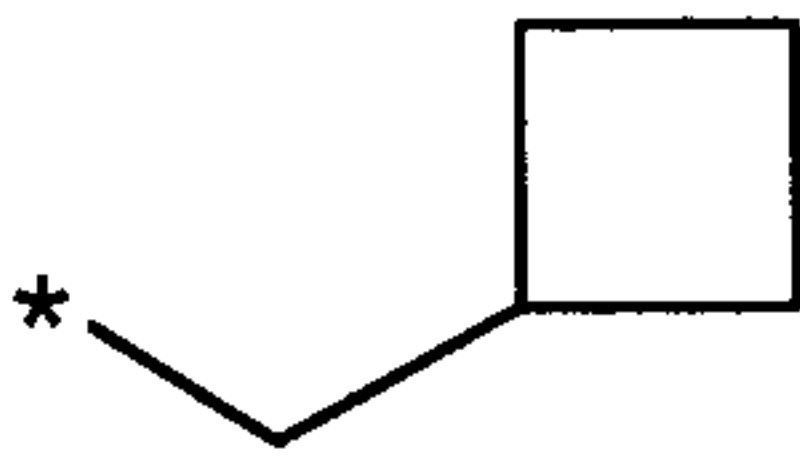
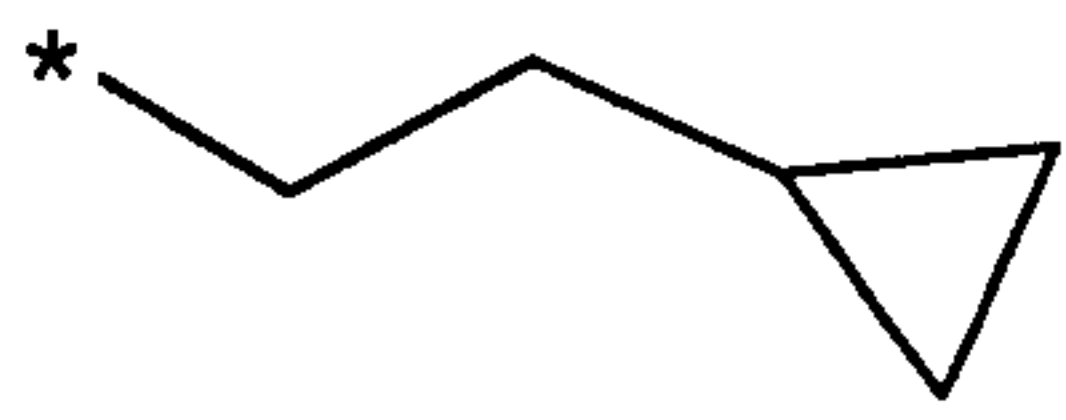
10 **12-e** was prepared starting from 100 mg (0.164 mmol) **12-d** and 25.5 mg (0.18 mmol) (2,2-dimethylcyclopropyl)-methylamine hydrochloride (Catalogue number: AL BW 0960, Rare Chemicals GmbH, Schulstrasse 6, D-24214 Gettorf, GERMANY) analogously to **2-m**. The crude product was purified by preparative HPLC and thus
15 obtained as the trifluoroacetate.

Yield: 7.6 mg (6 %).
ES-MS (M+H)⁺ = 690
RT (HPLC-MS) = 1.57 min

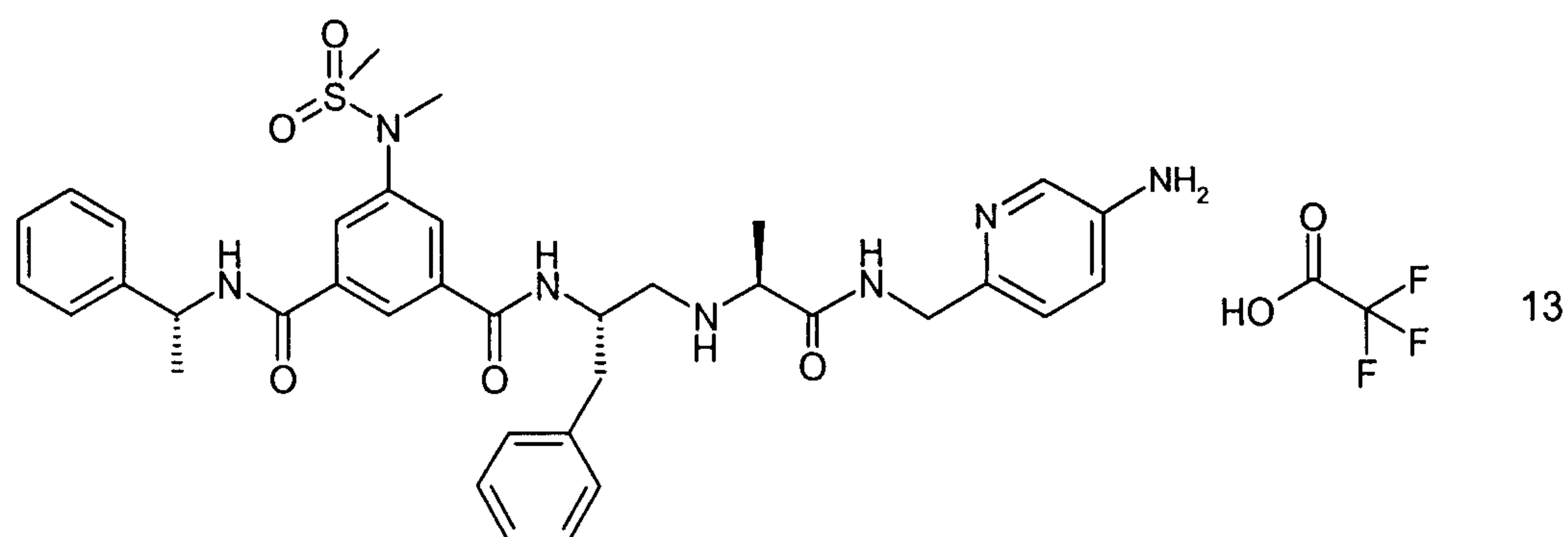
20 The following Examples were prepared analogously to Example **12-e**:

- 168 -

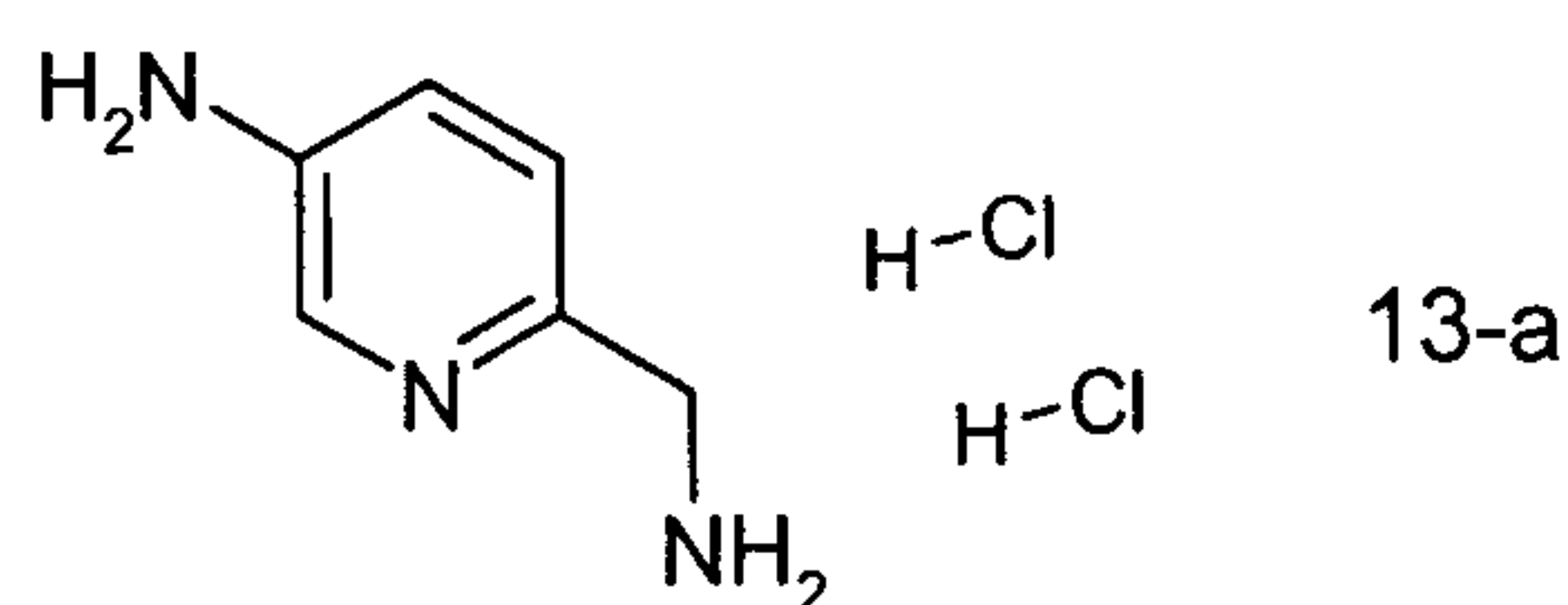


Examples	R	MS	RT HPLC-MS
12.2		676 (M+H) ⁺	1.51 min
12.3		676 (M+H) ⁺	2.09 min
12.4		676 (M+H) ⁺	1.50 min

Preparation of 13:



Preparation of 13-a:



5

1.24 g (96 percent, 10.0 mmol) 5-amino-2-cyanopyridine in methanolic ammonia solution were hydrogenated at 5 bar hydrogen pressure and ambient temperature for 24 h through Raney nickel. Then the catalyst was separated off, and the mixture was filtered through silica gel. 500 mg of the residue remaining after evaporation were stirred with dichloromethane. Then 4-molar hydrogen chloride/dioxane mixture was added and stirred for 14 h. The resulting solid was suction filtered and dried.

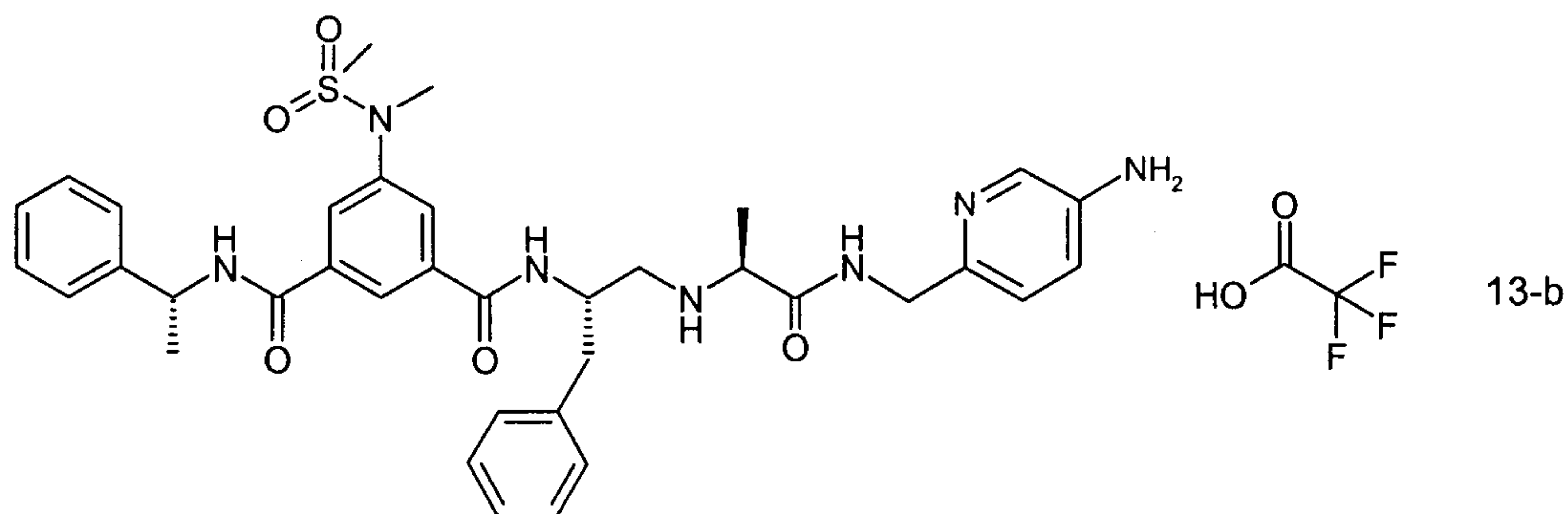
Yield: 750 mg (57 %).

ES-MS $(M+H)^+ = 124$

RT (HPLC-MS) = 0.73 min

15

Preparation of 13-b:



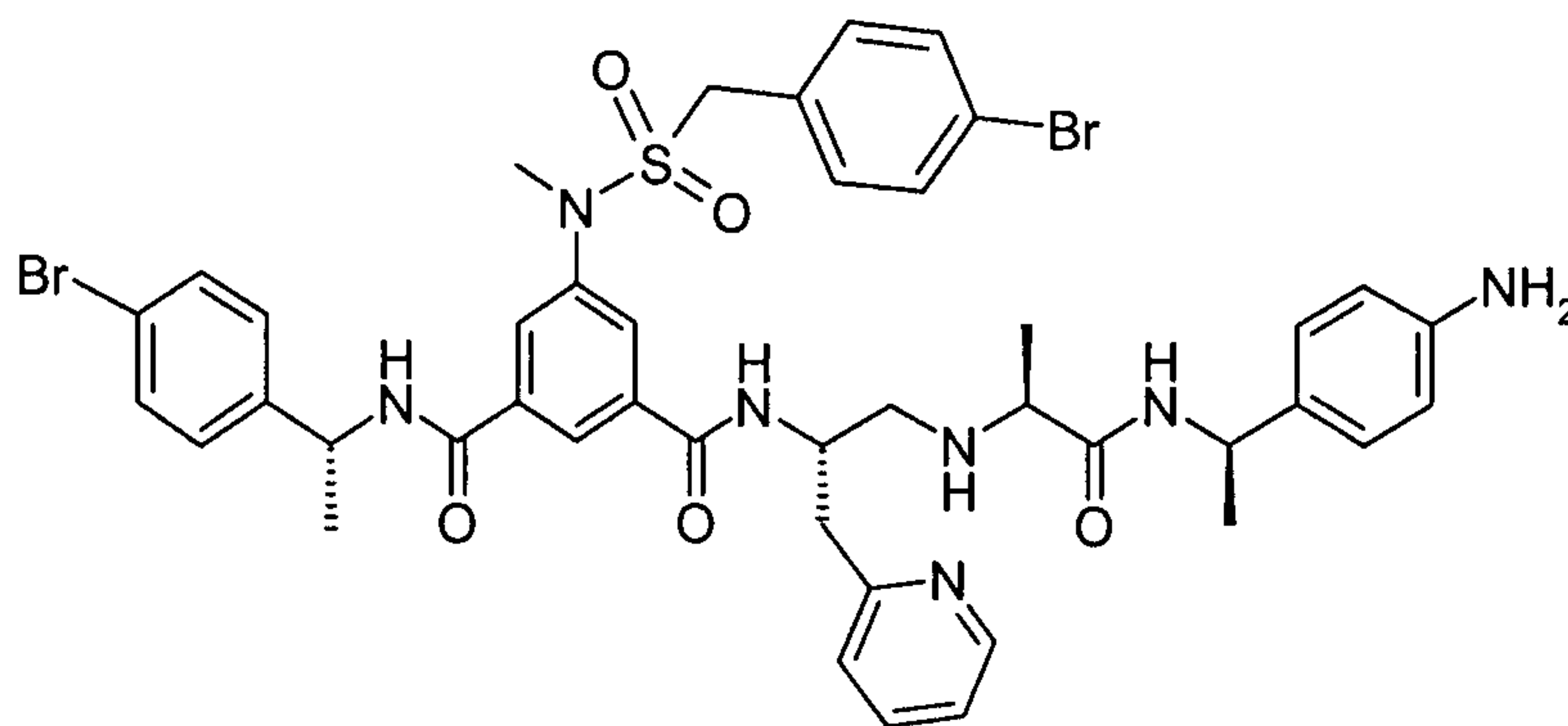
- 170 -

13-b was prepared analogously to **4-e**, by reacting Boc-L-alanine with the amine component **13-a** in the step "Preparation of **4-a**". The crude product was purified by HPLC and in this way the product was obtained as the trifluoroacetate.

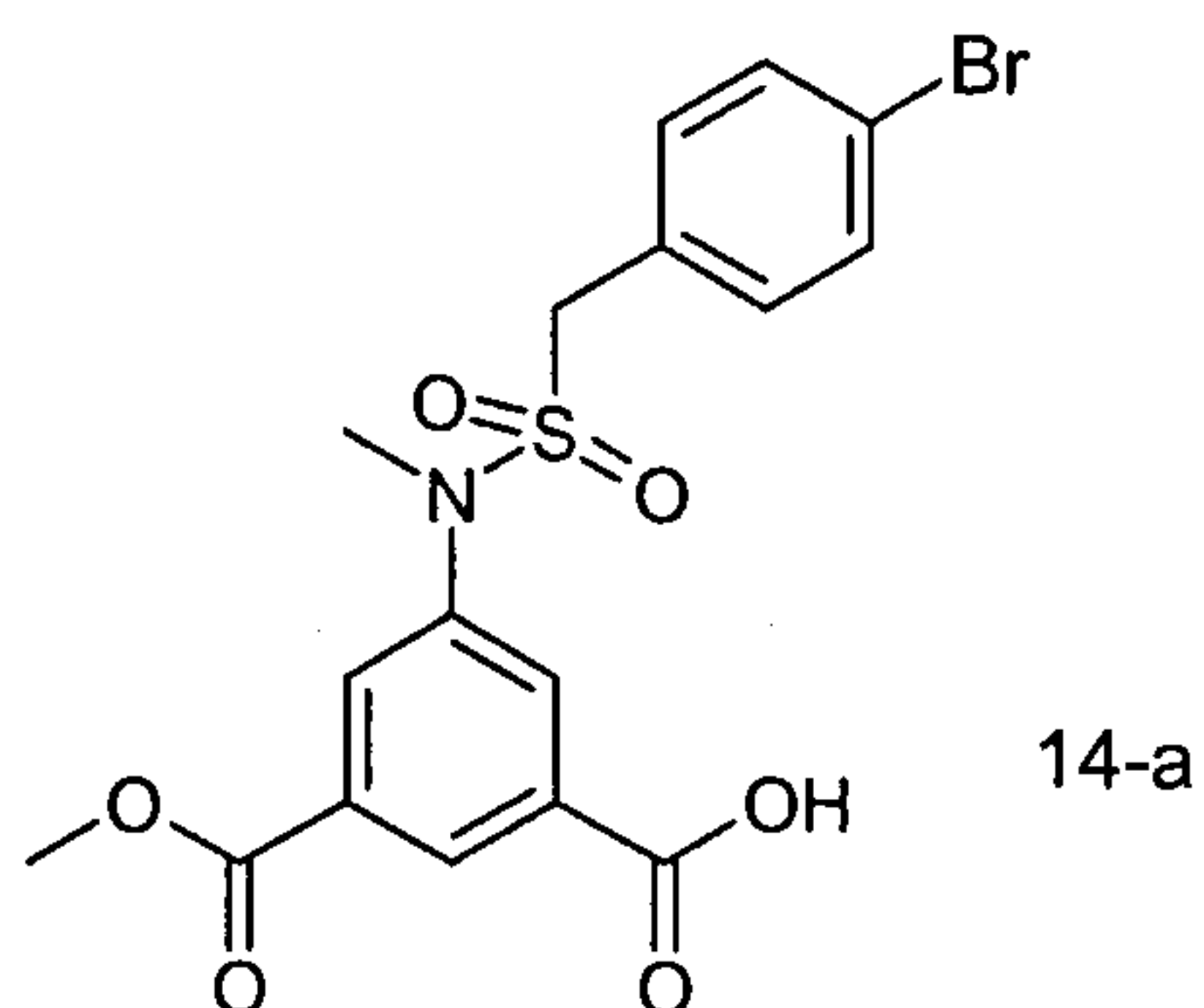
Yield: 7.9 mg (6 %).

- 5 ES-MS (M+H)⁺ = 686
RT (HPLC-MS) = 1.71 min

Example 14:



- 10 Preparation of **14-a**:

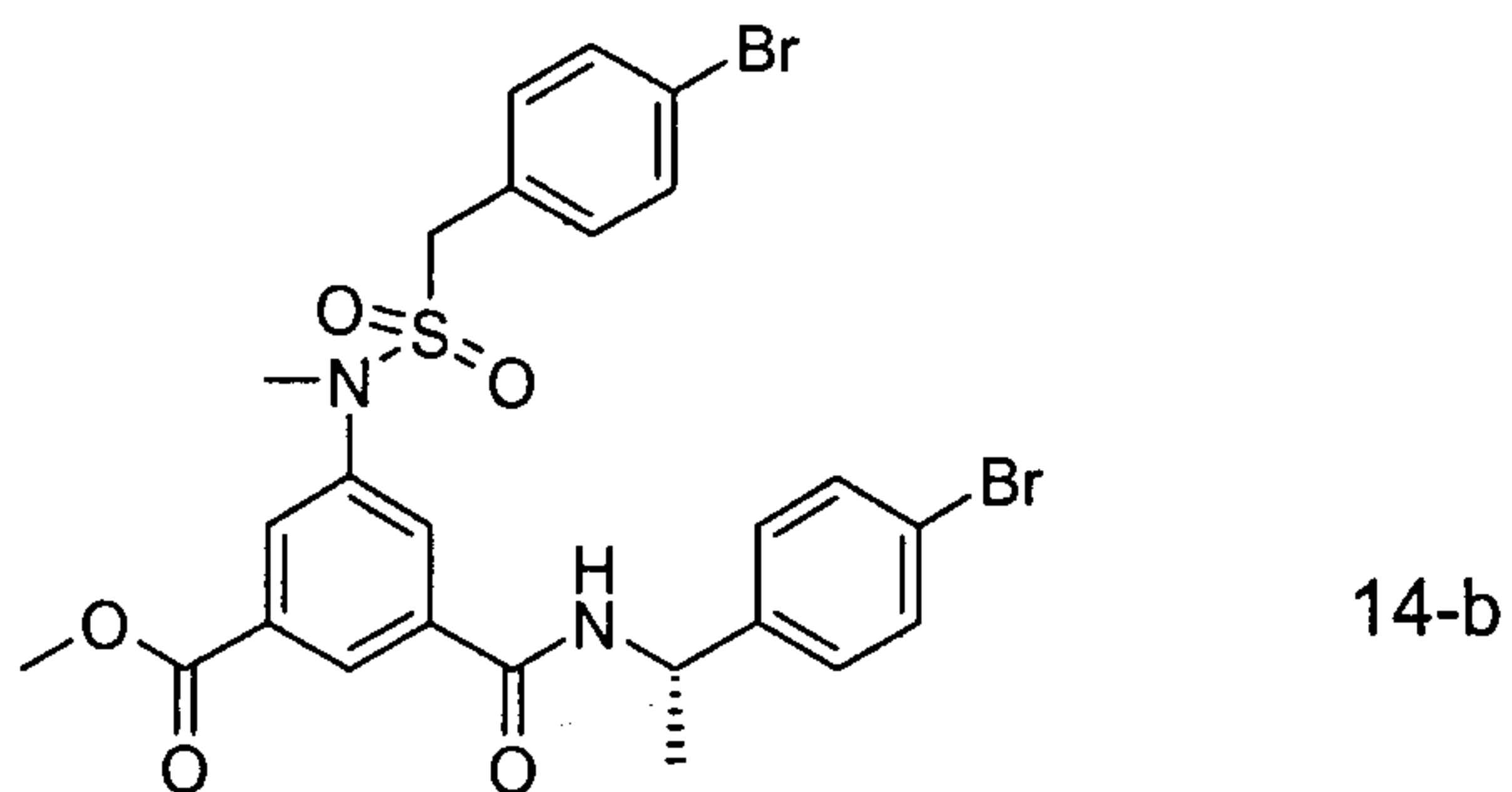


14-a was prepared analogously to **1-f**, but (4-bromophenyl)-methanesulphonic acid chloride was used instead of methanesulphonic acid chloride in step **1-d**.

Yield: 3.6 g (63 %).

- 15 ES-MS (M-H)⁻ = 440, 442 (Br)
RT (HPLC-MS) = 2.98 min

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Preparation of **14-b**:

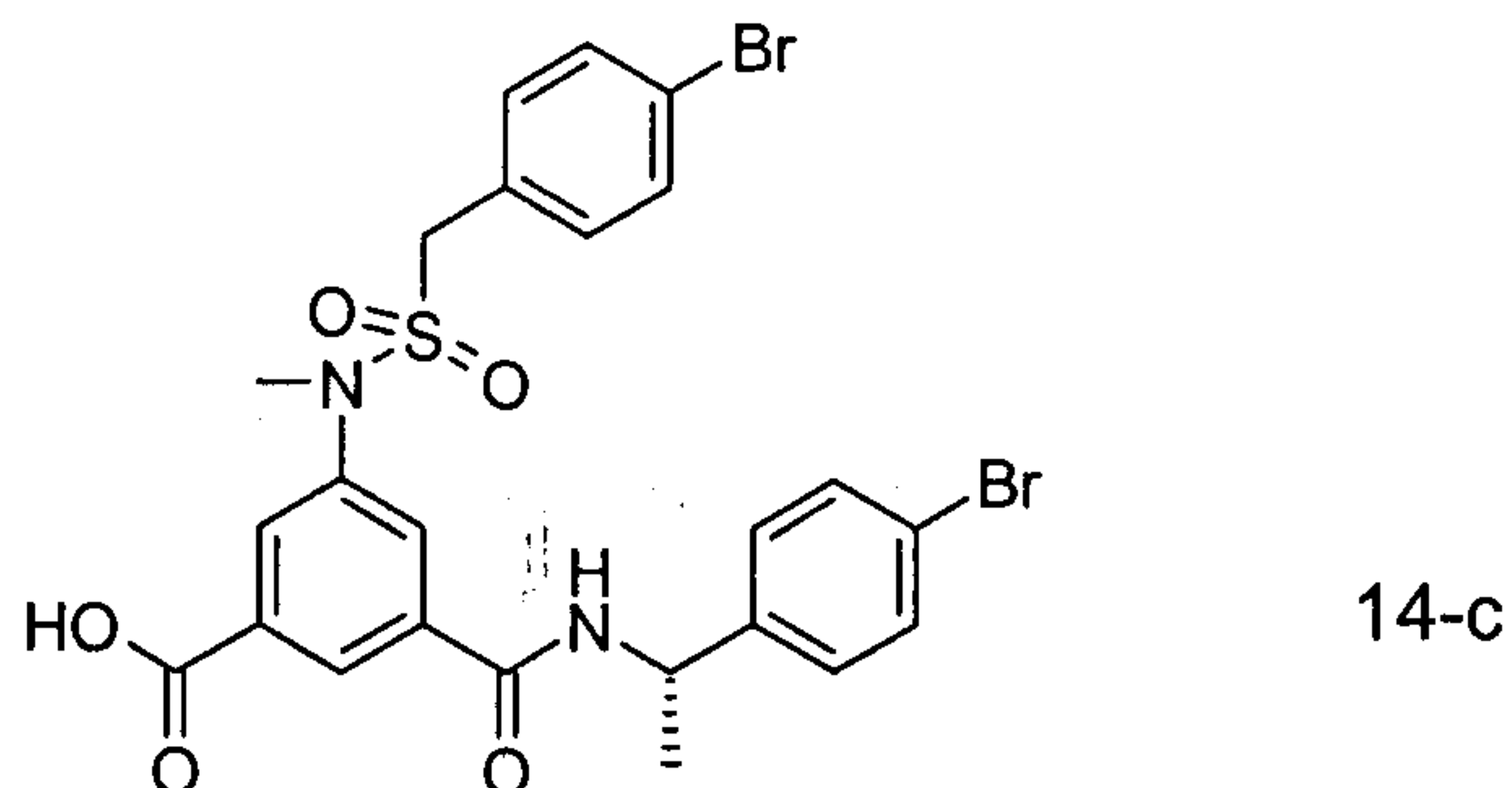
14-b was prepared analogously to **1-g**, but R-1-(4-bromophenyl)ethylamine was used instead of R-1-(4-fluorophenyl)ethylamine in step **1-g**.

Yield: 1.2 g (77 %).

ES-MS ($M+COO^-$) = 667, 669, 671 (2 Br)

RT (HPLC-1) = 5.54 min

10 Preparation of **14-c**:

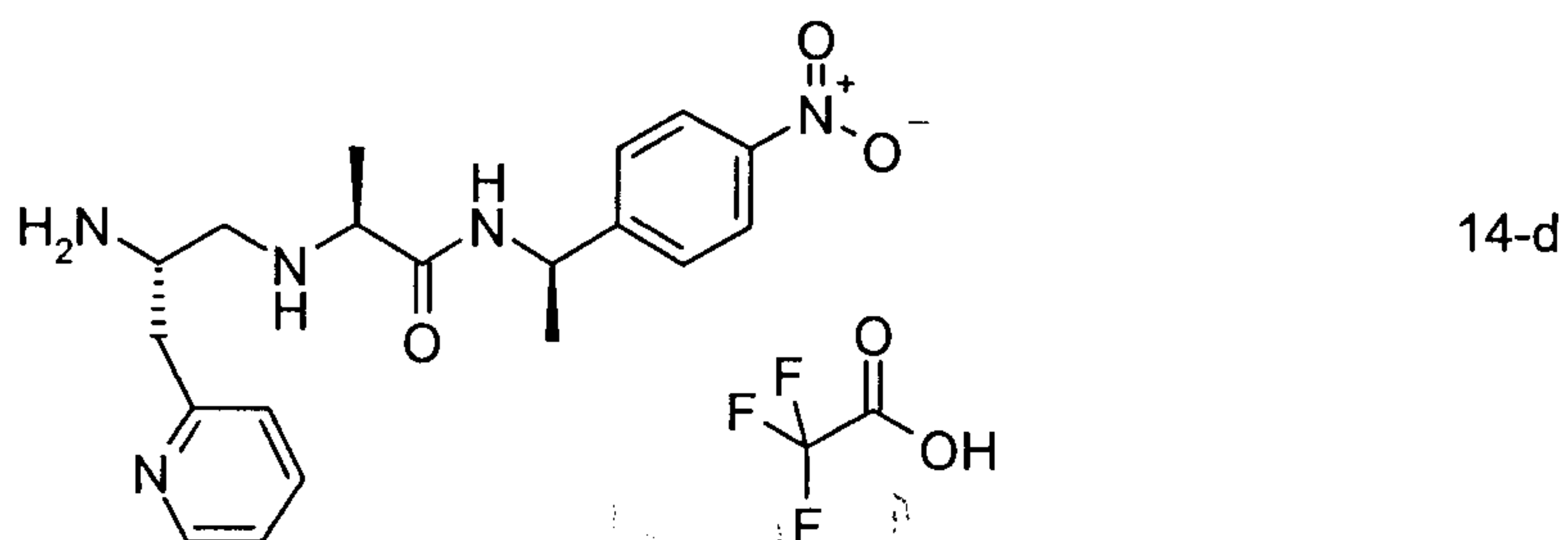


14-c was prepared analogously to **1-h**.

Yield: 950 mg (81 %).

ES-MS ($M+H^+$) = 609, 611, 613 (2 Br)

15 RT (HPLC-1) = 5.25 min

Preparation of **14-d**:

- 172 -

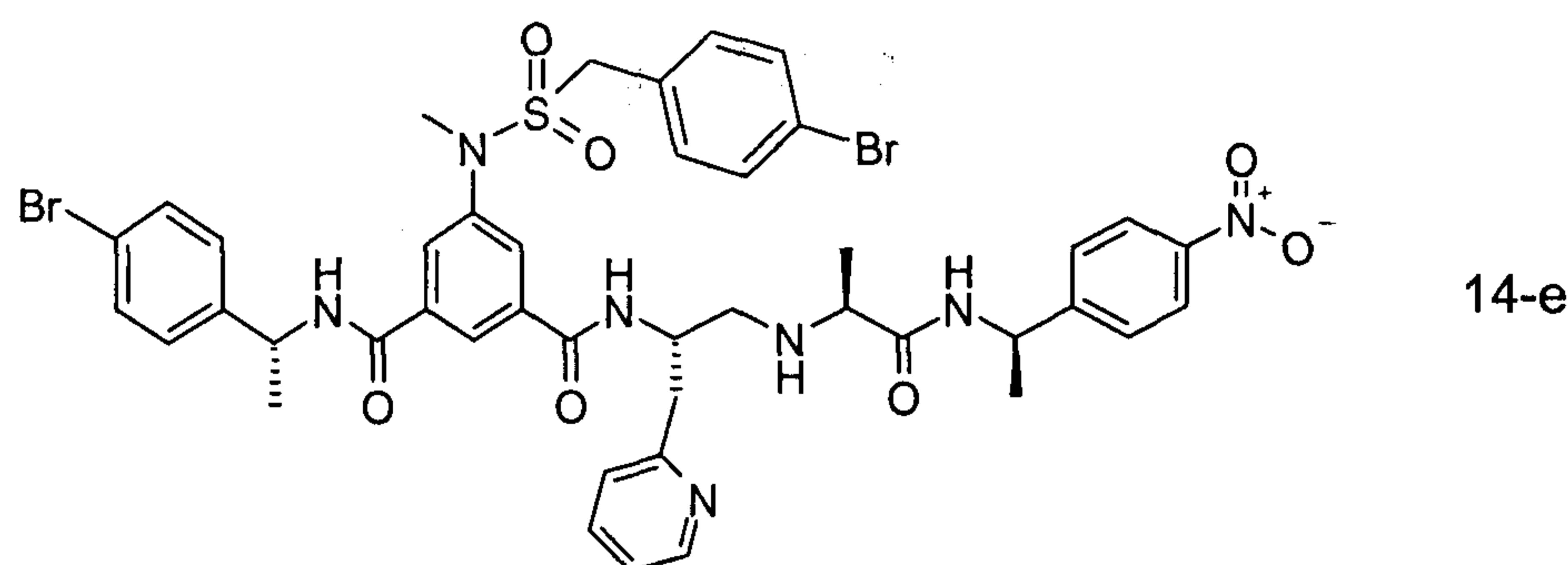
14-d was prepared analogously to **3-g**, using R-1-(4-nitrophenyl)ethylamine in step **3-b** instead of **1-l**, and **5.2-b** in the step **3-f** instead of **3-e**.

Yield: 1.80 g (96 %).

ES-MS (M+H)⁺ = 372

5 RT (HPLC-MS) = 2.06 min

Preparation of **14-e**:



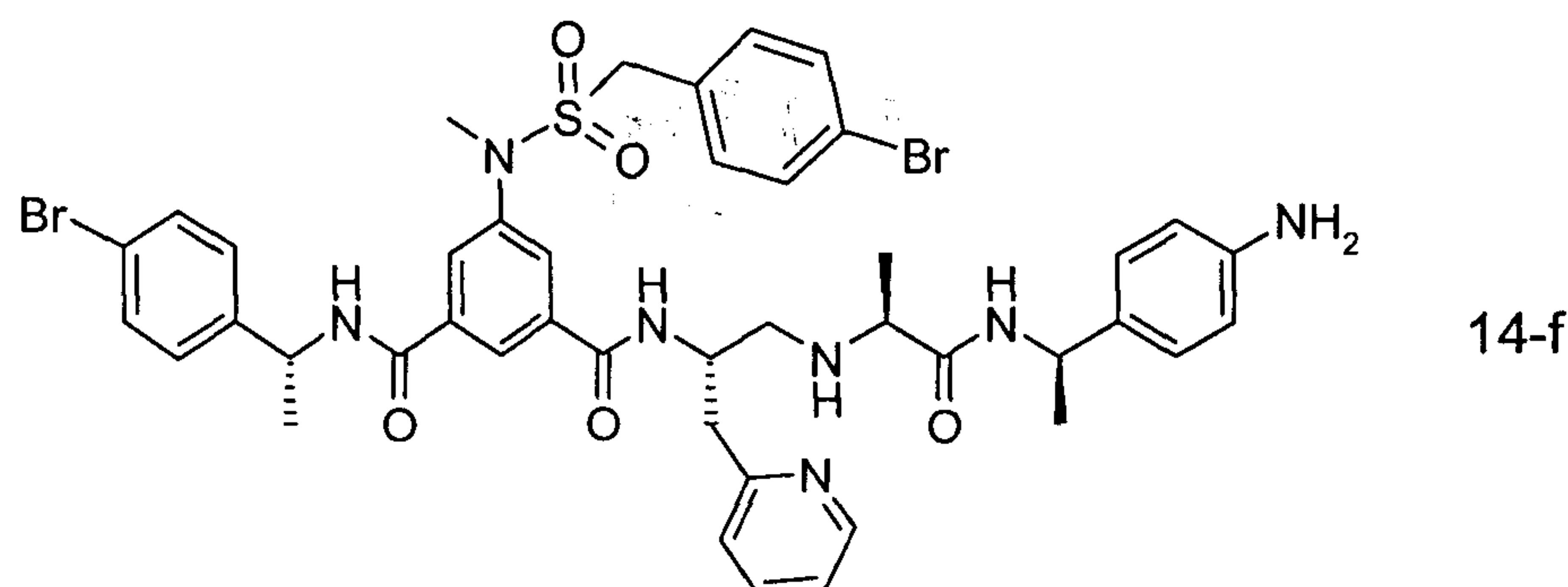
14-e was prepared by reacting **14-c** with **14-d** analogously to **3-h**.

10 Yield: 100 mg (78 %).

ES-MS (M+H)⁺ = 962, 964, 966 (2 Br)

RT (HPLC-1) = 5.03 min

Preparation of **14-f**:



15

100 mg (0.104 mmol) **14-e** were dissolved in ethyl acetate and combined with a solution of 234 mg (1.04 mmol) SnCl₂ dihydrochloride in 300 ml DMF. The mixture was stirred for 14 h, evaporated down and the residue was purified by column chromatography.

20 Yield: 90 mg (89 %).

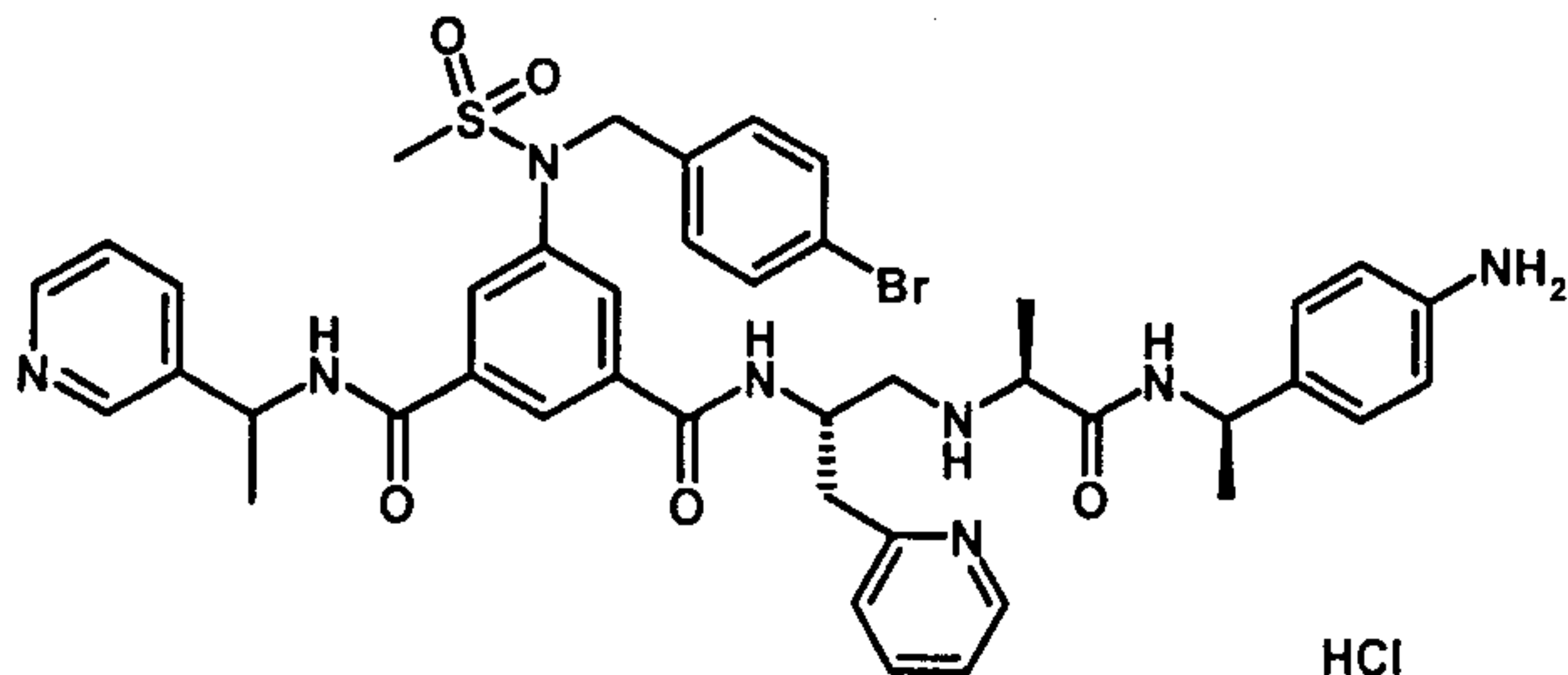
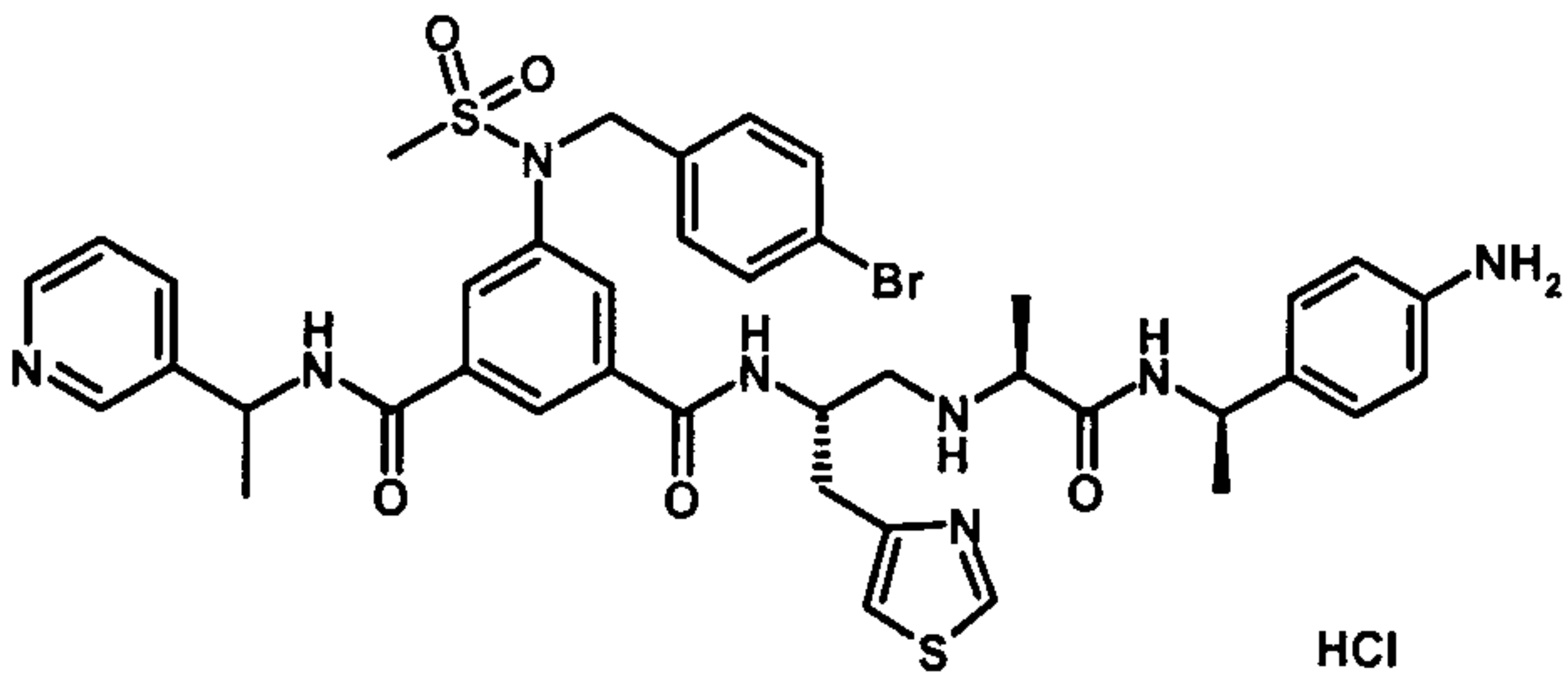
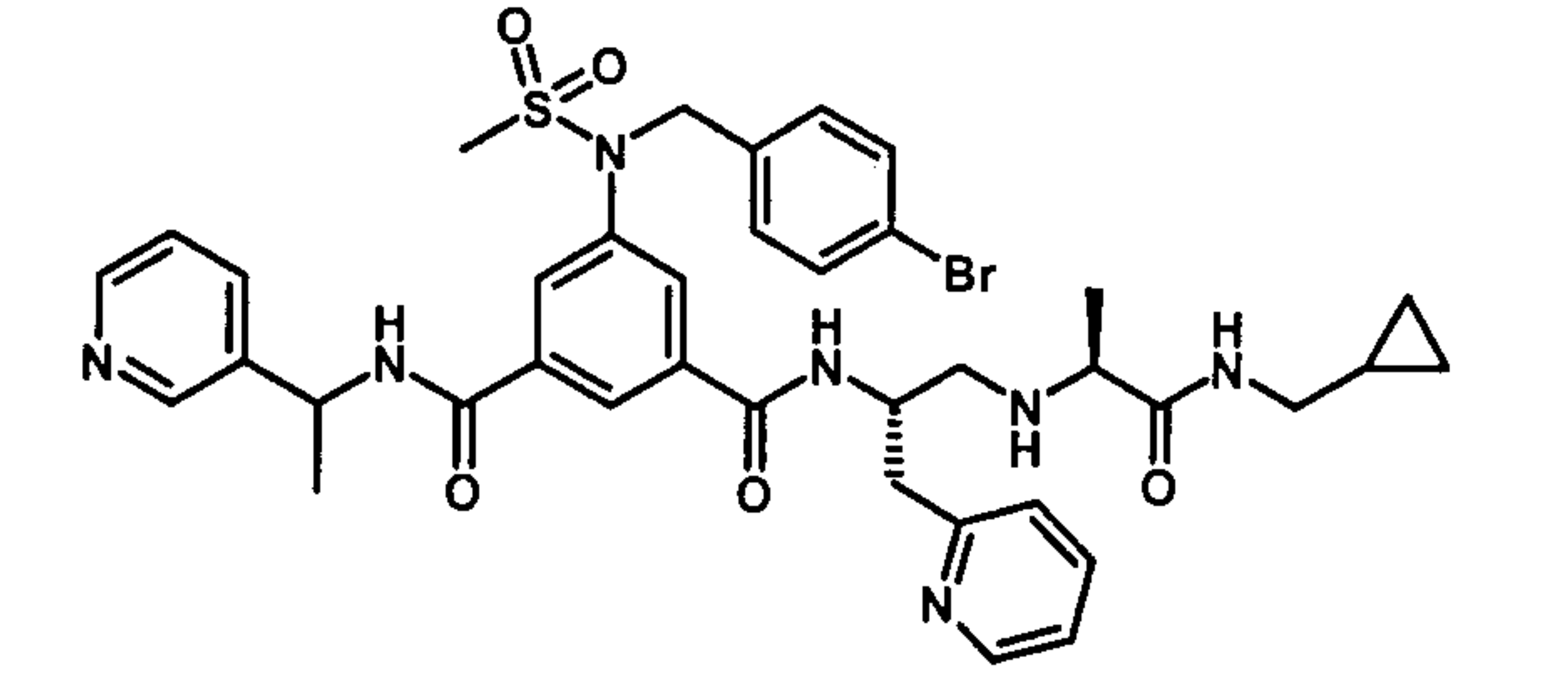
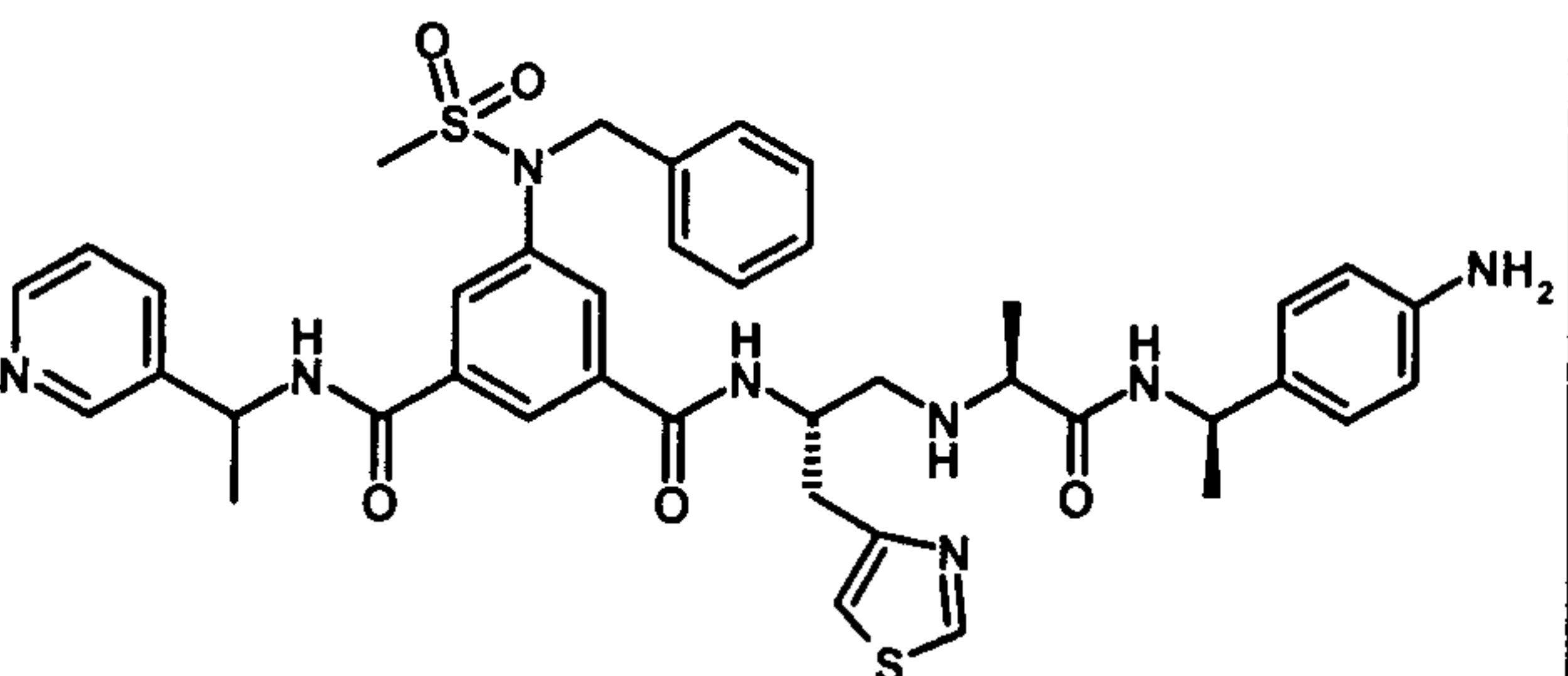
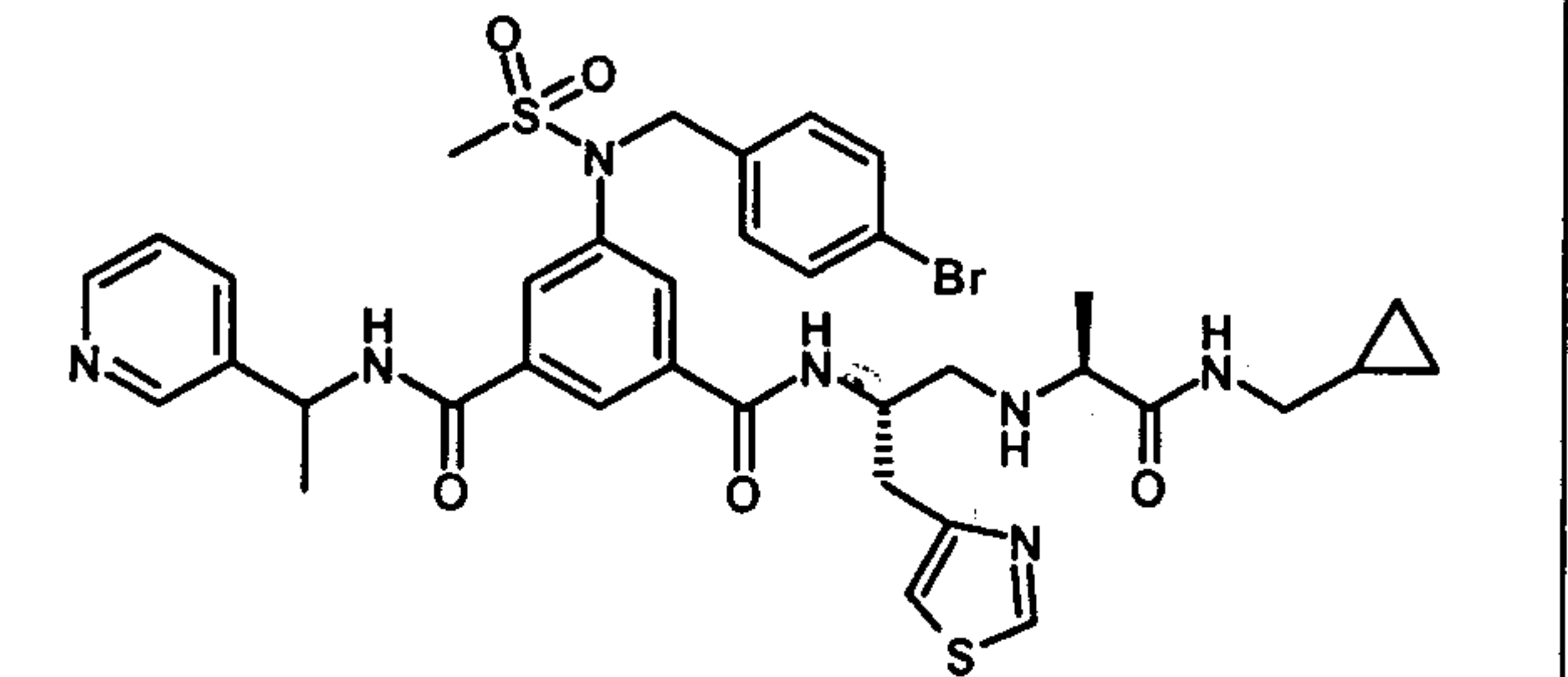
ES-MS (M+H)⁺ = 932, 934, 936 (2 Br)

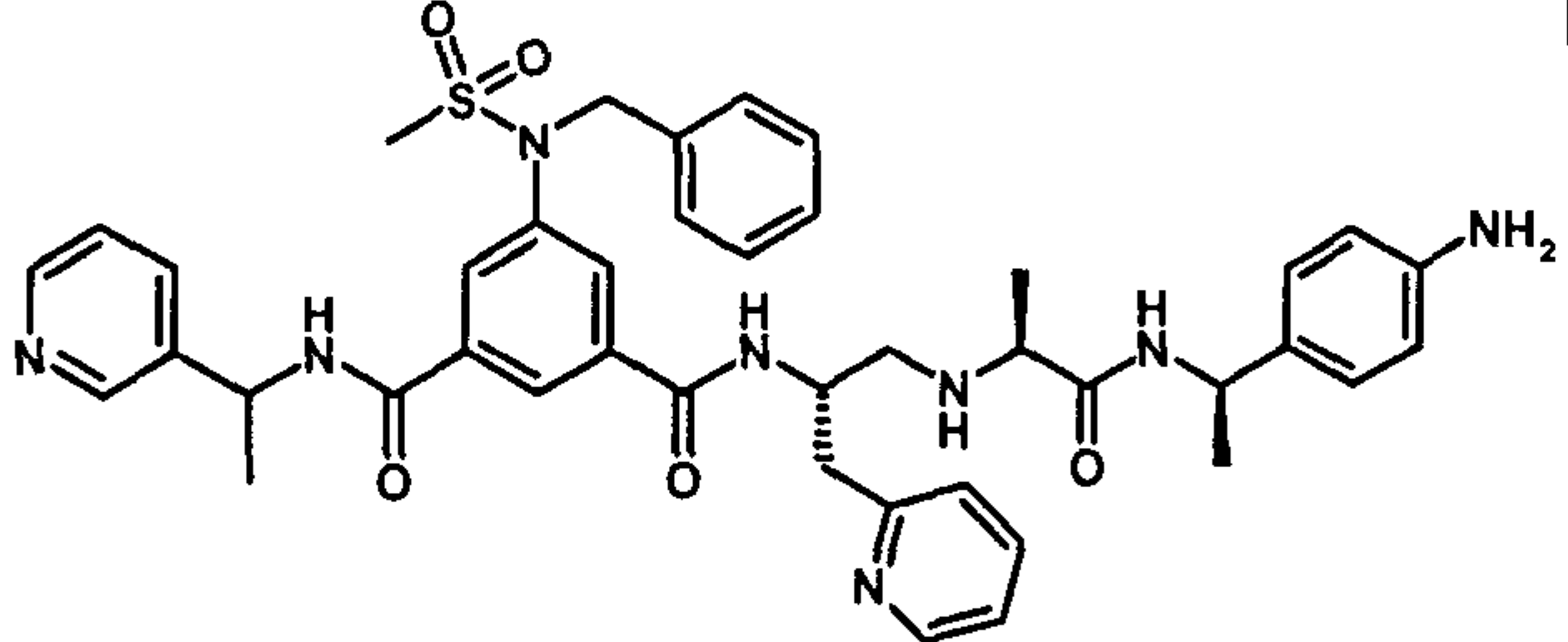
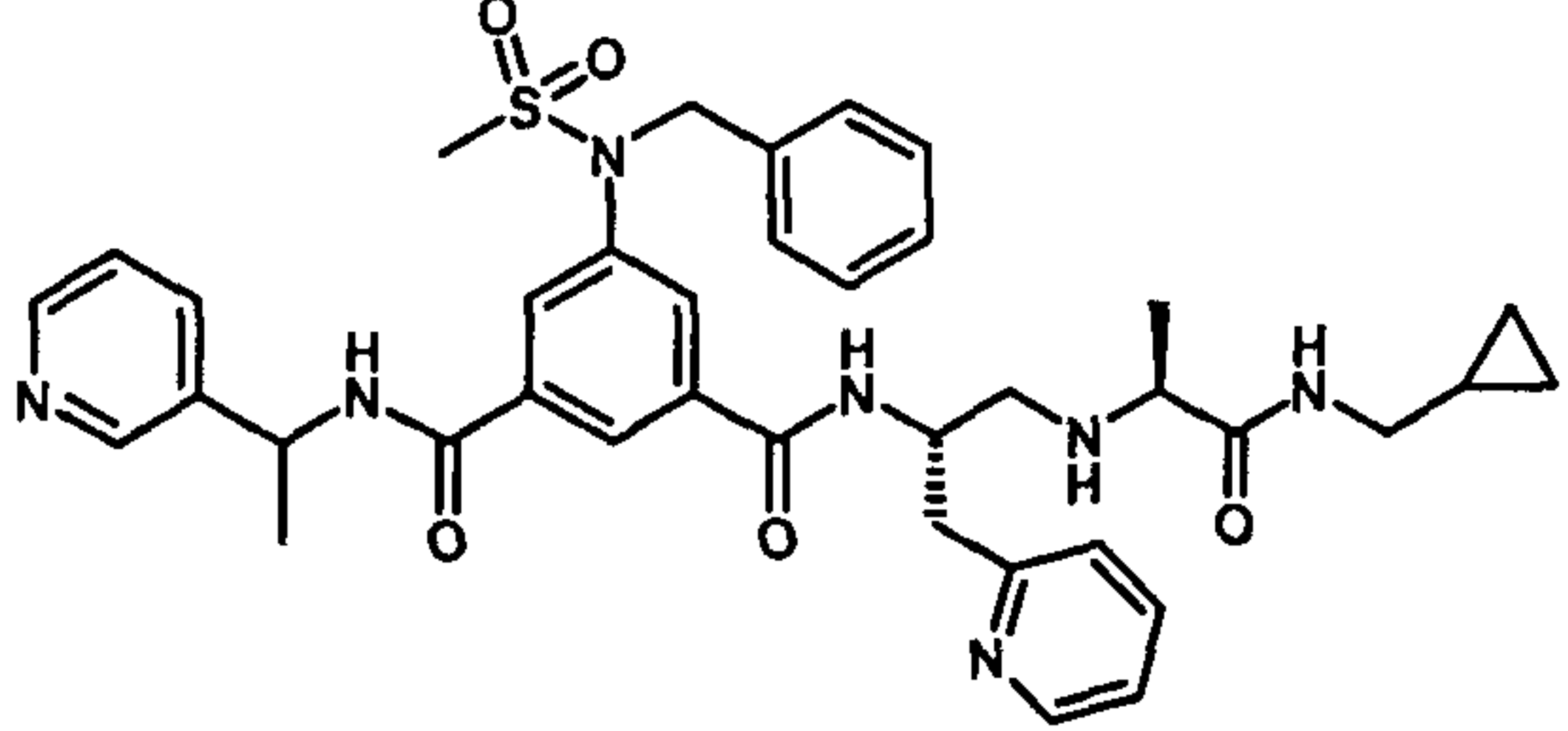
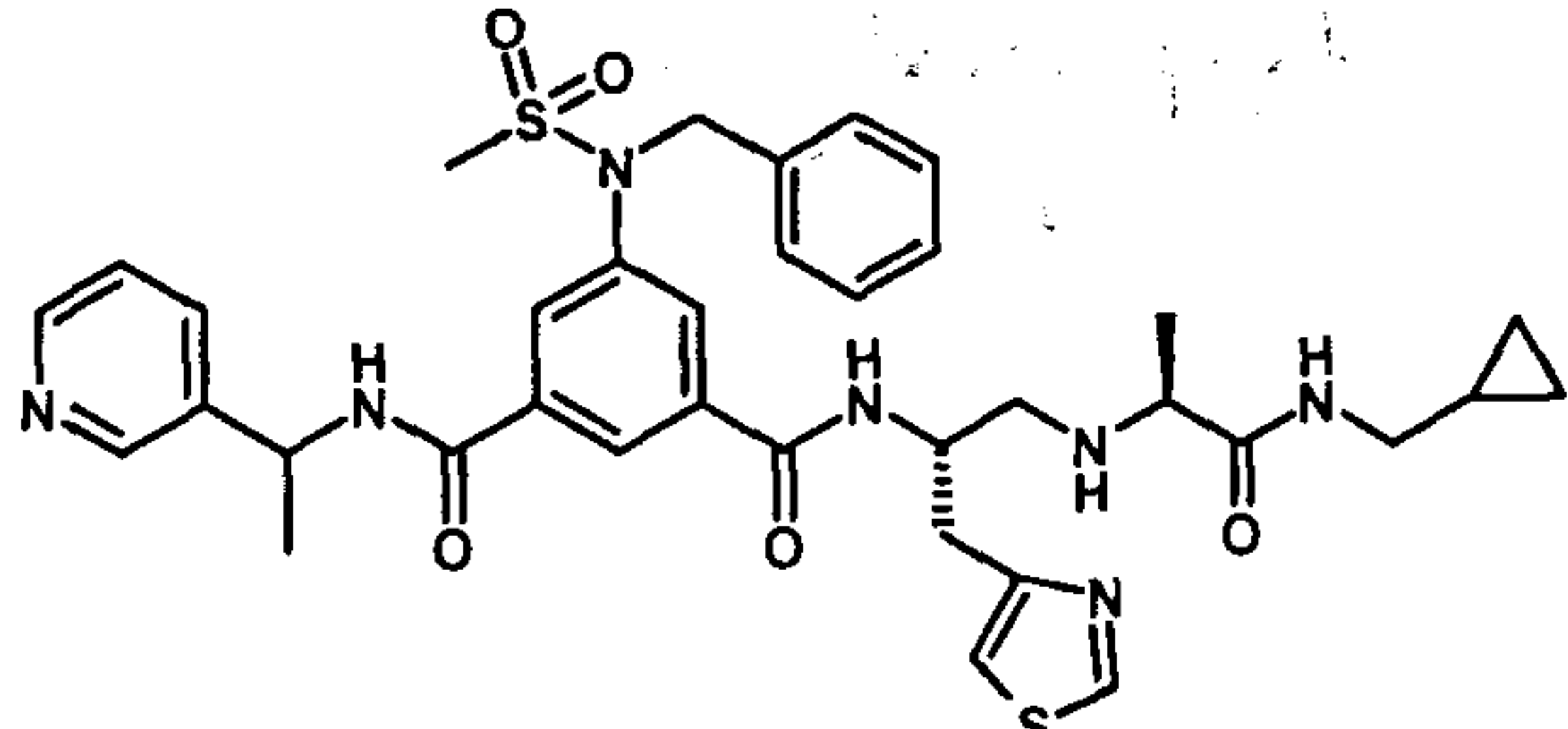
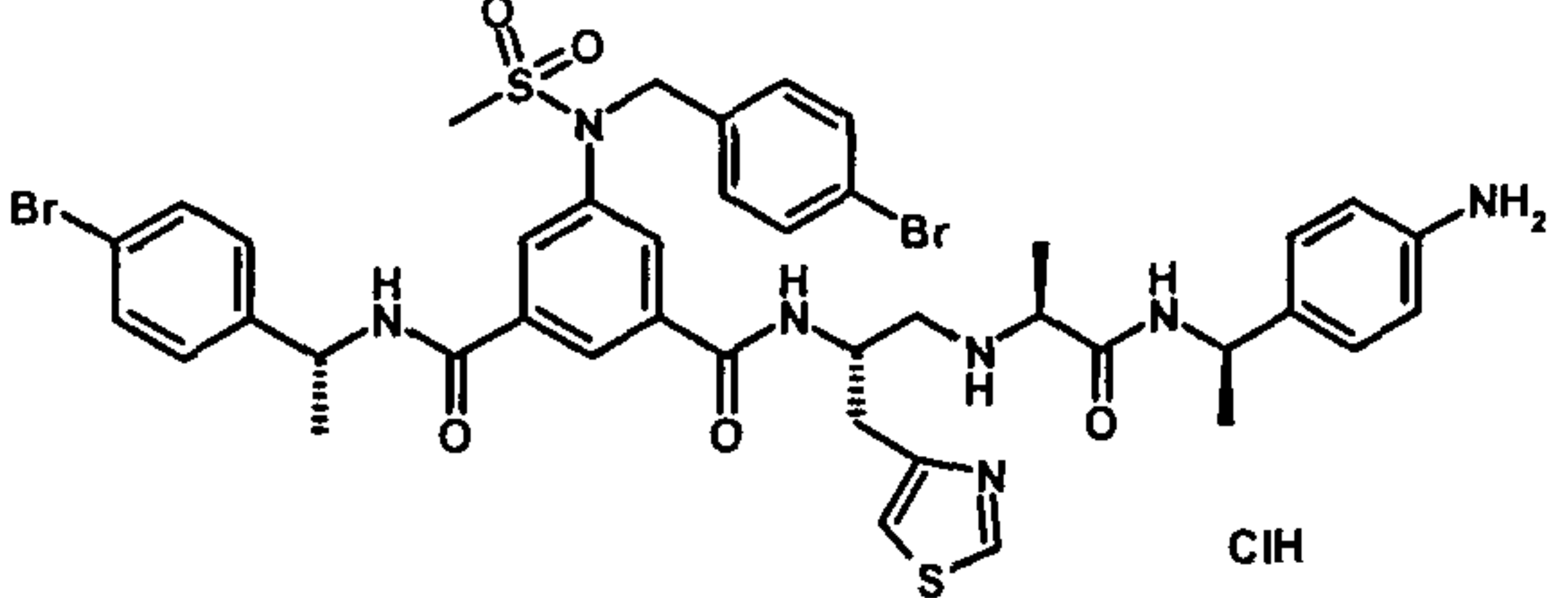
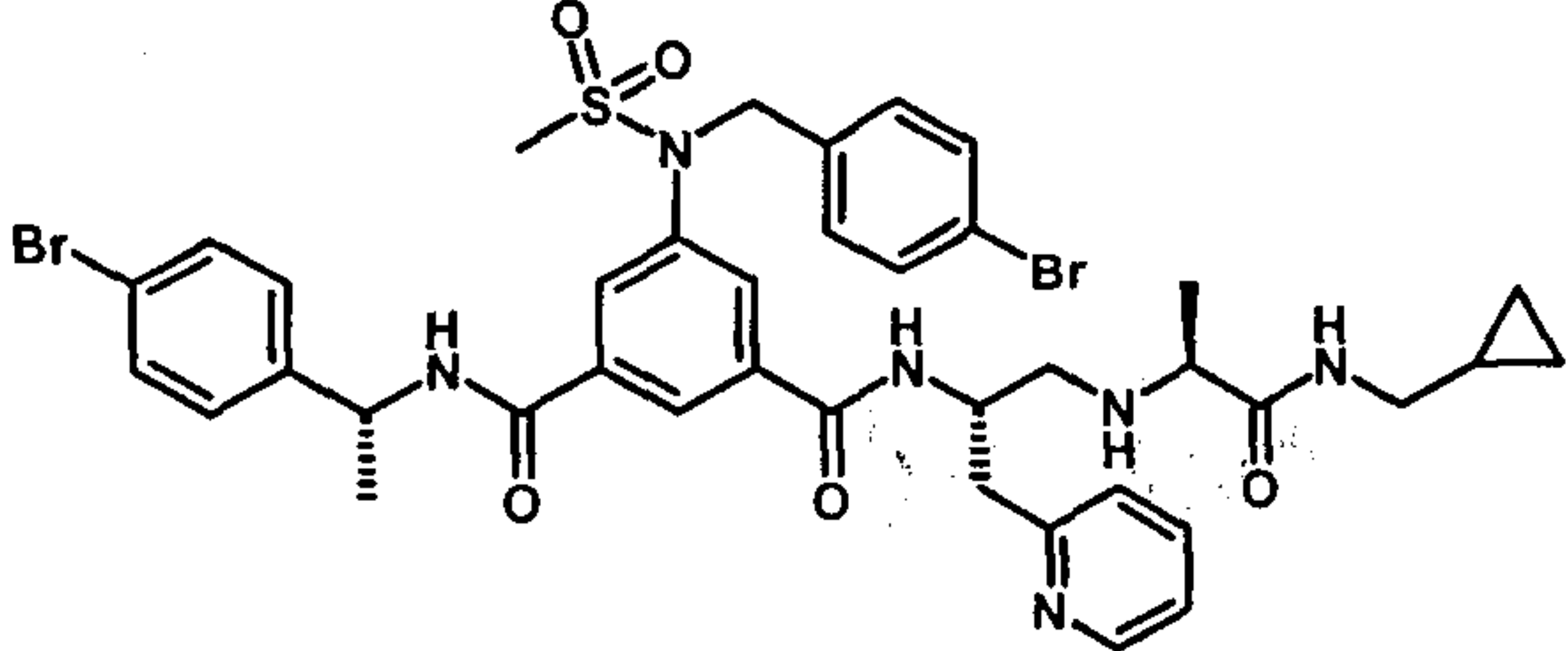
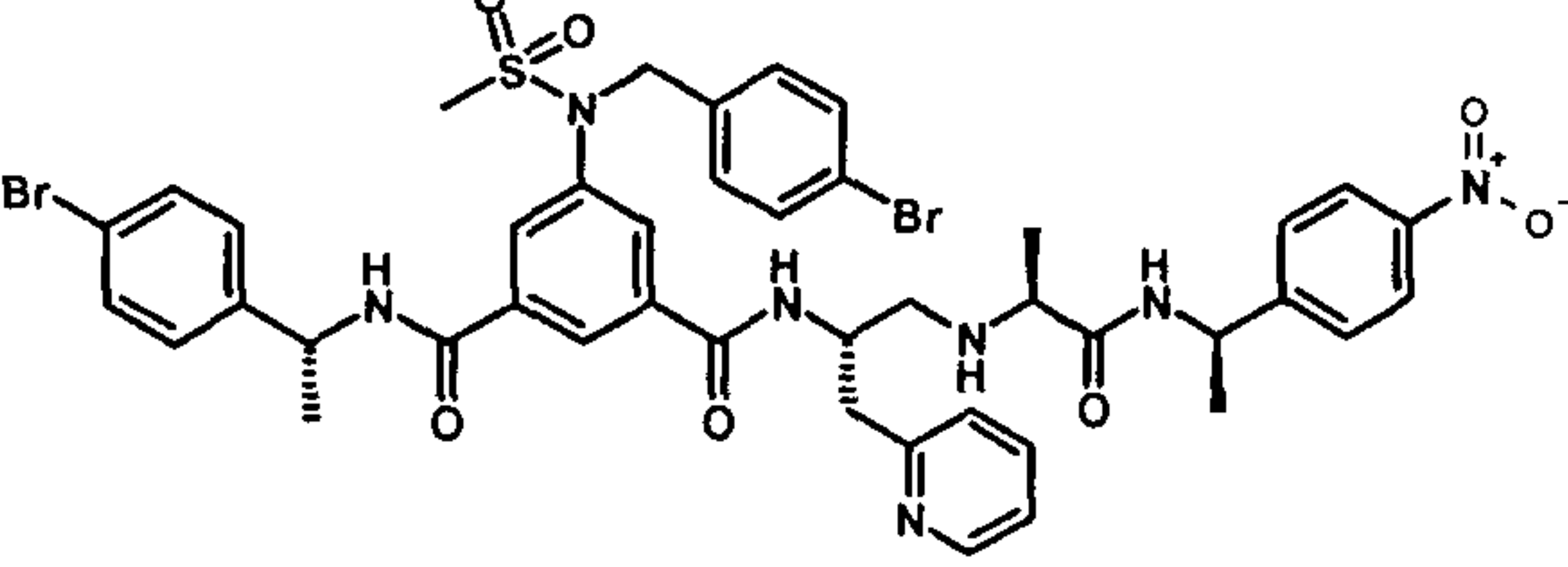
RT (HPLC-1) = 4.48 min

– 173 –

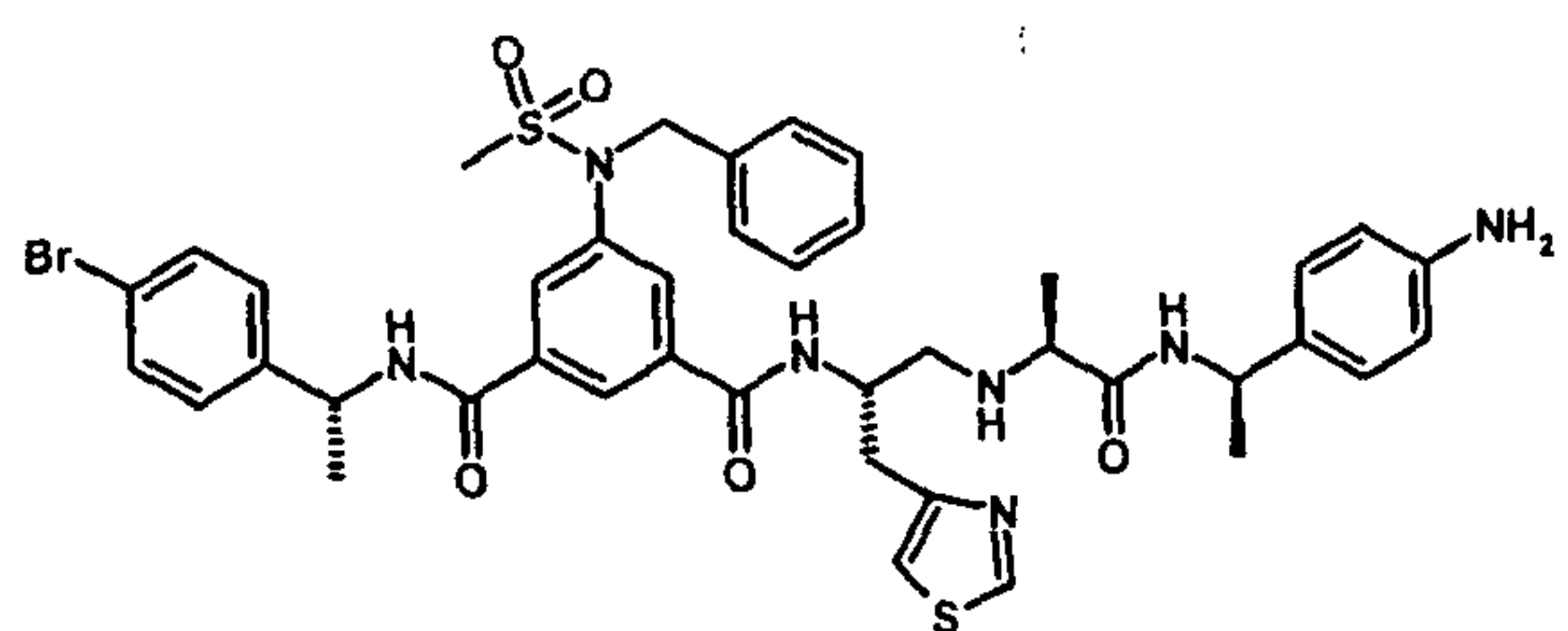
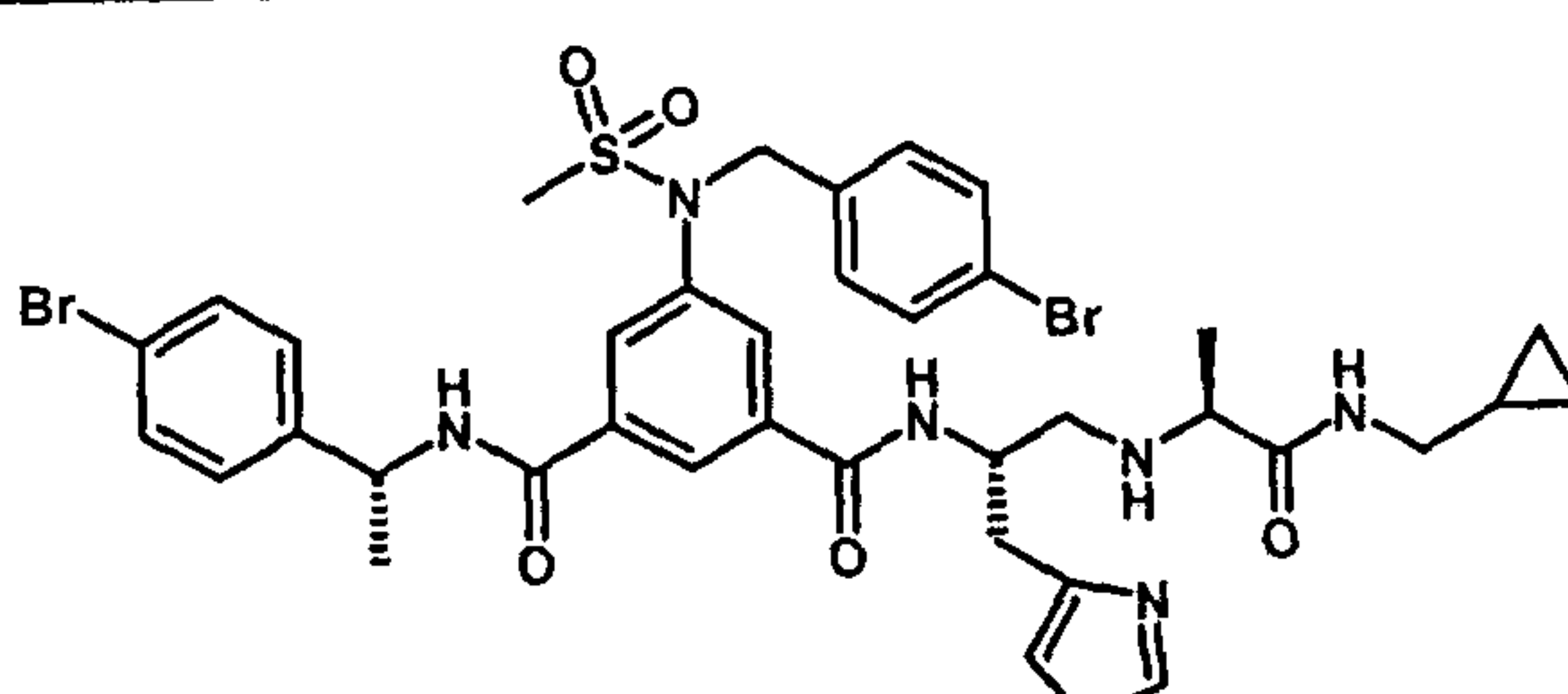
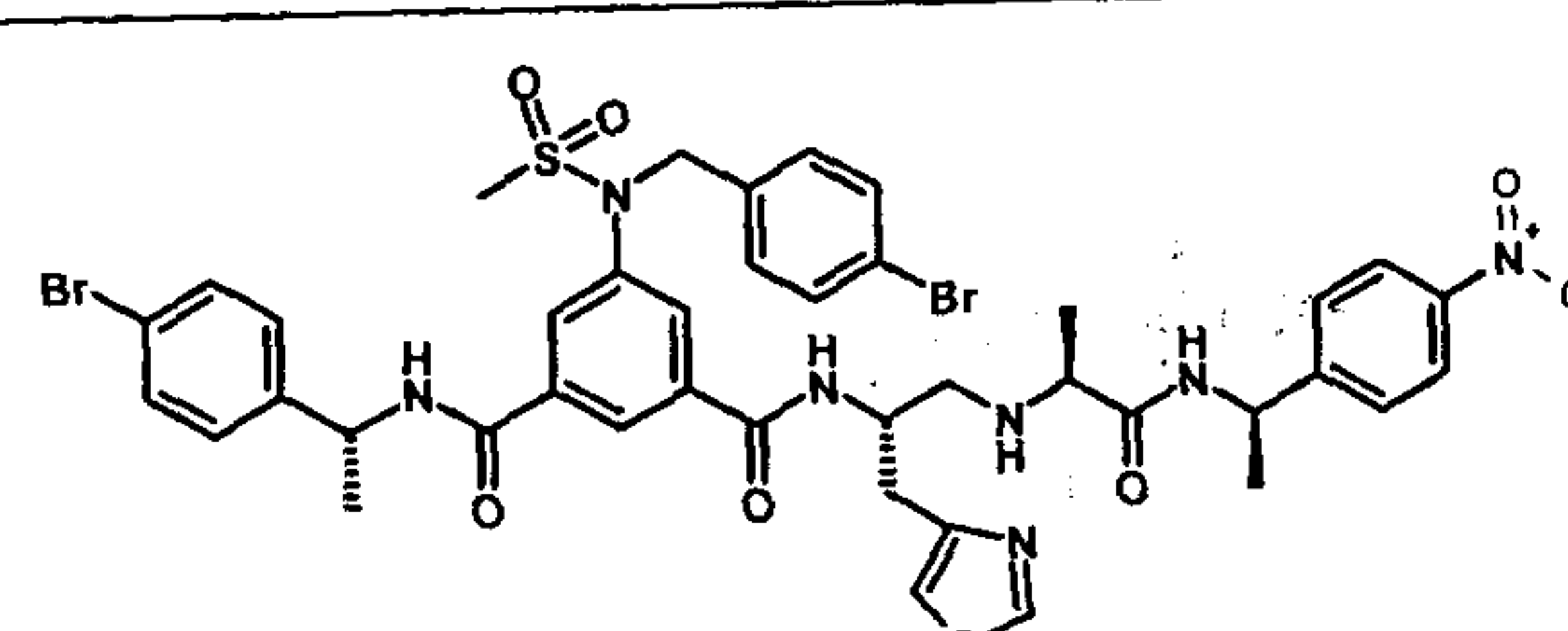
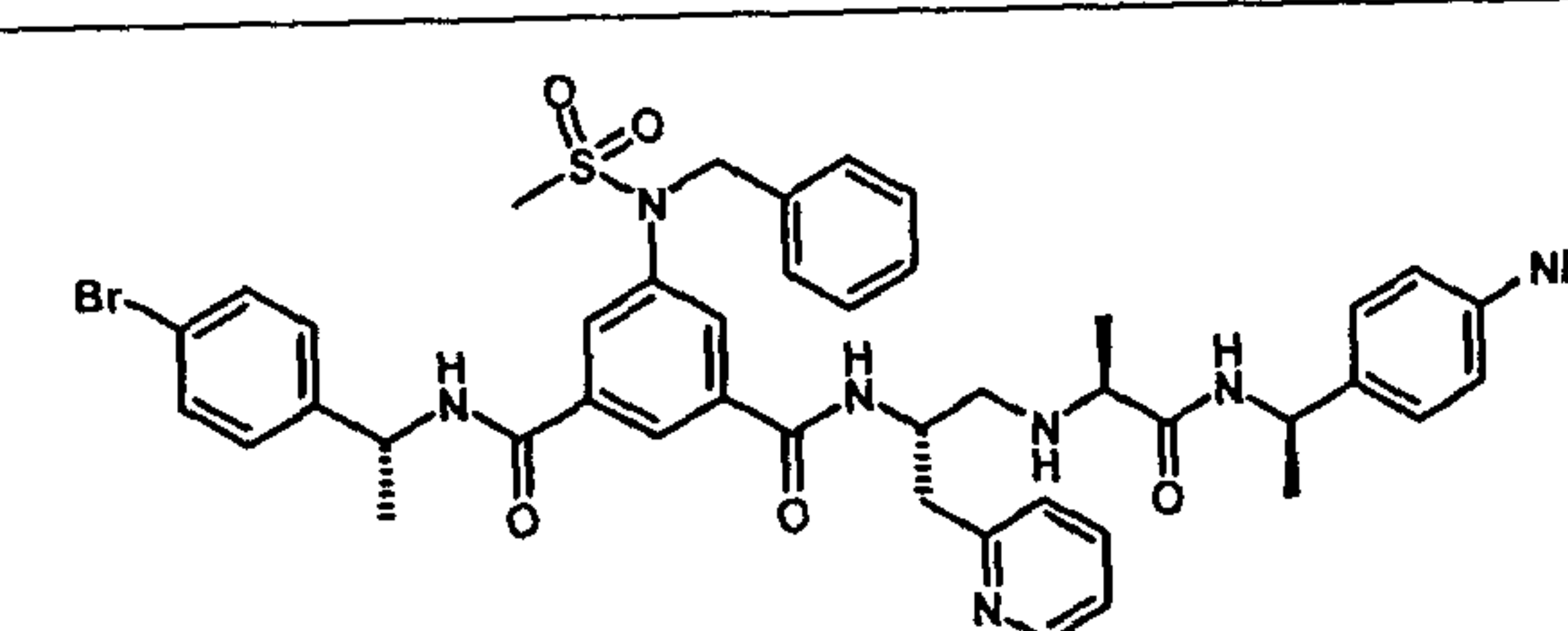
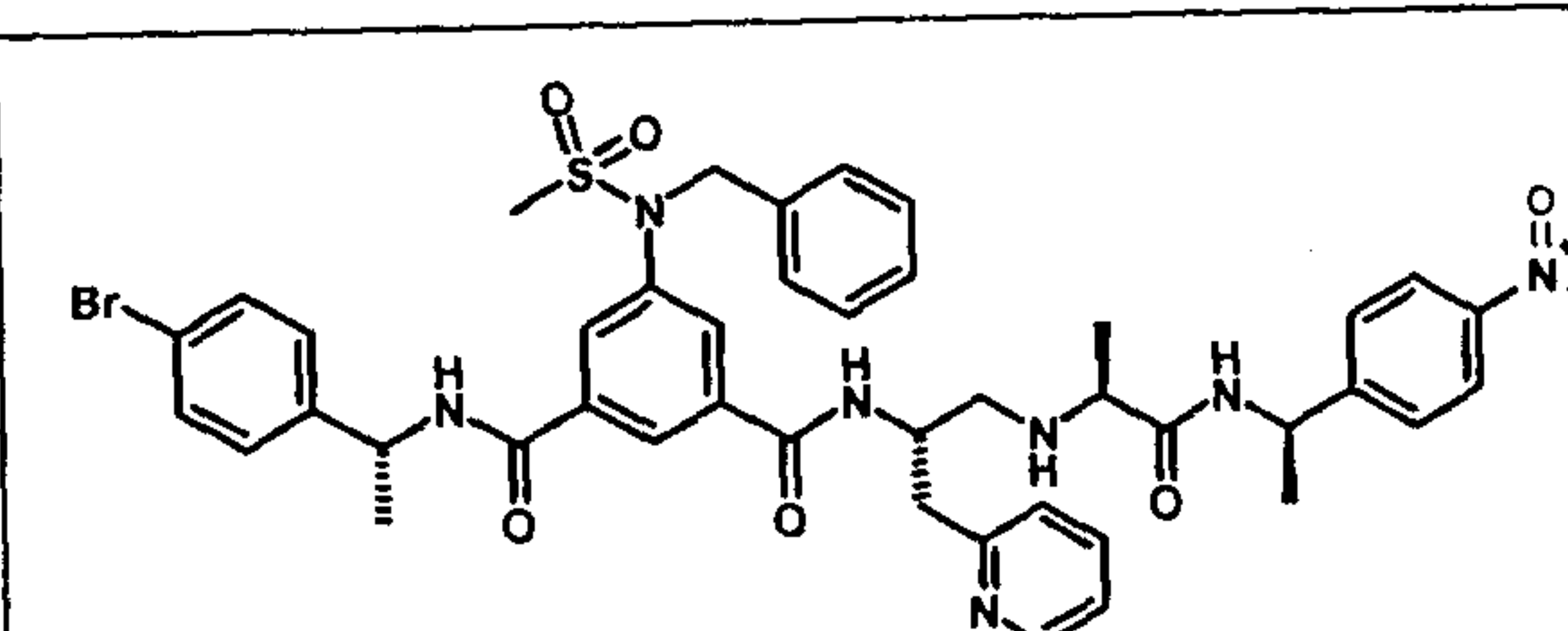
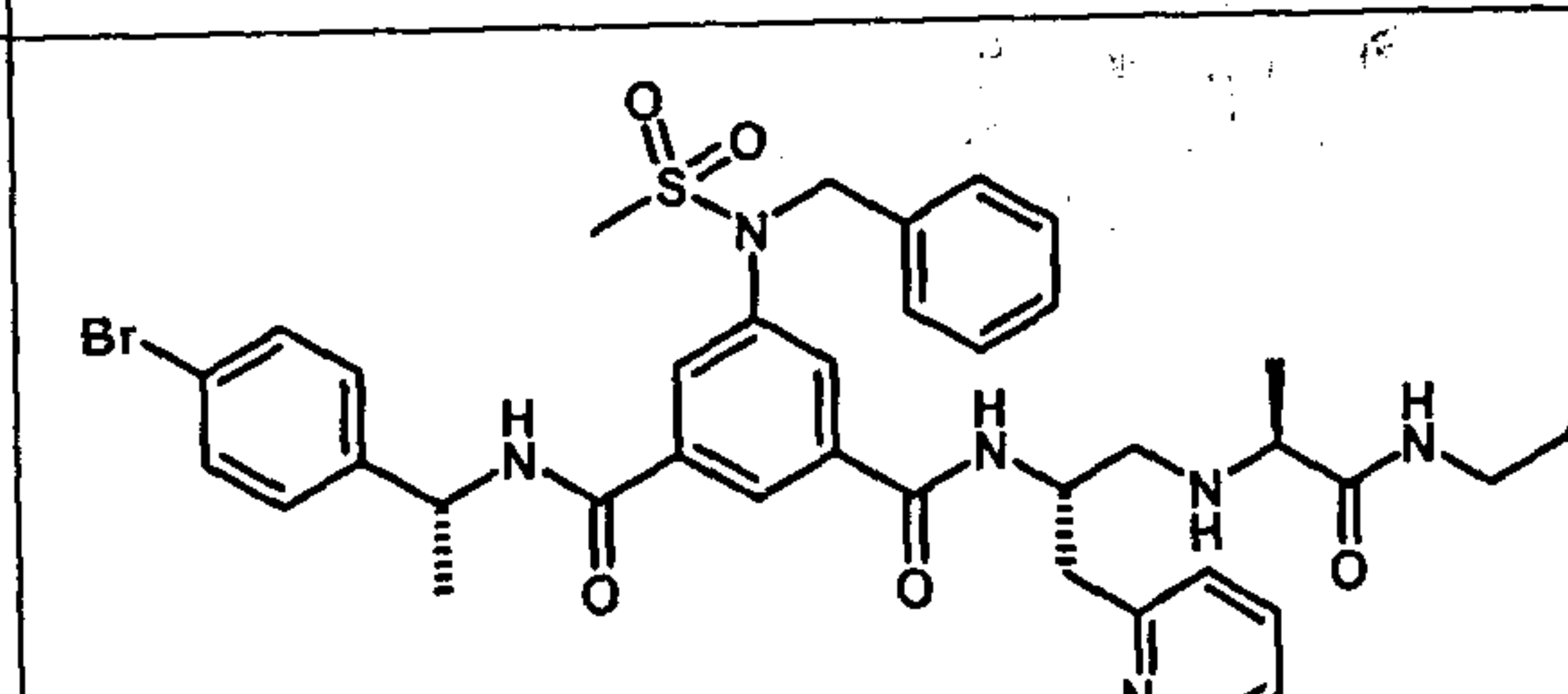
The following compounds were prepared analogously to **Example 14** by using the corresponding educts:

- 174 -

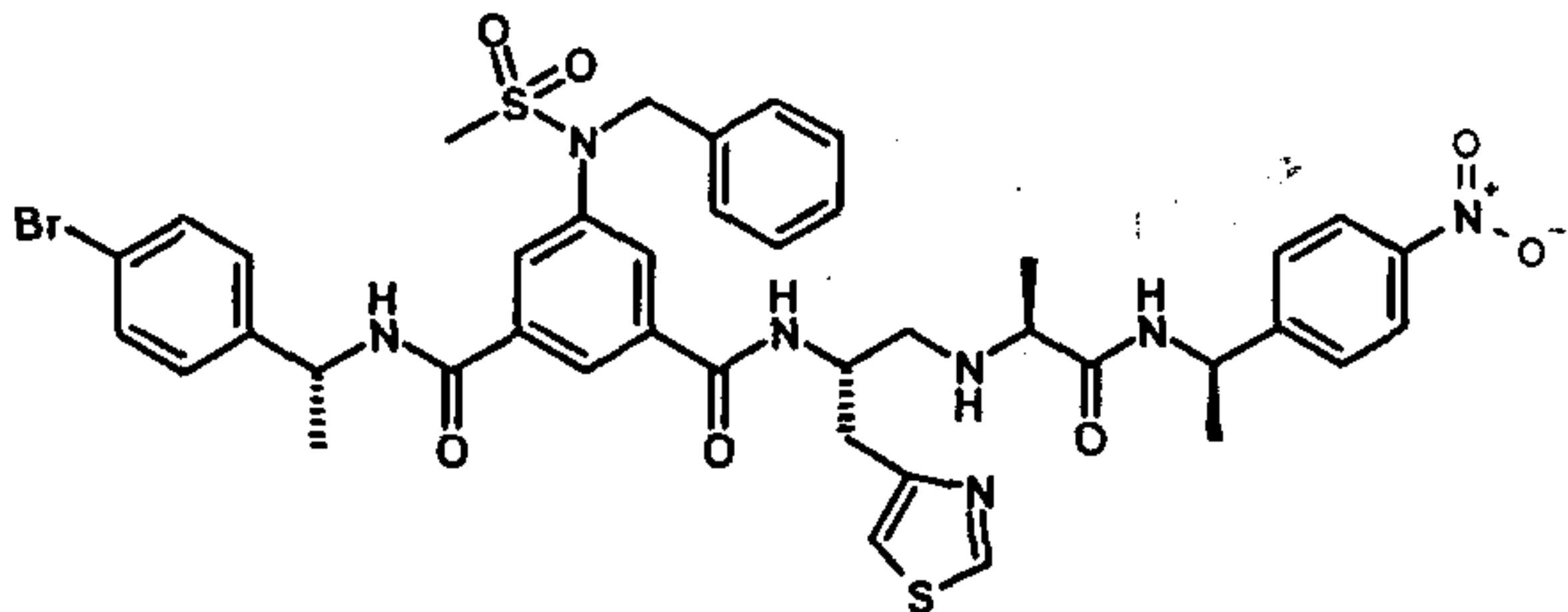
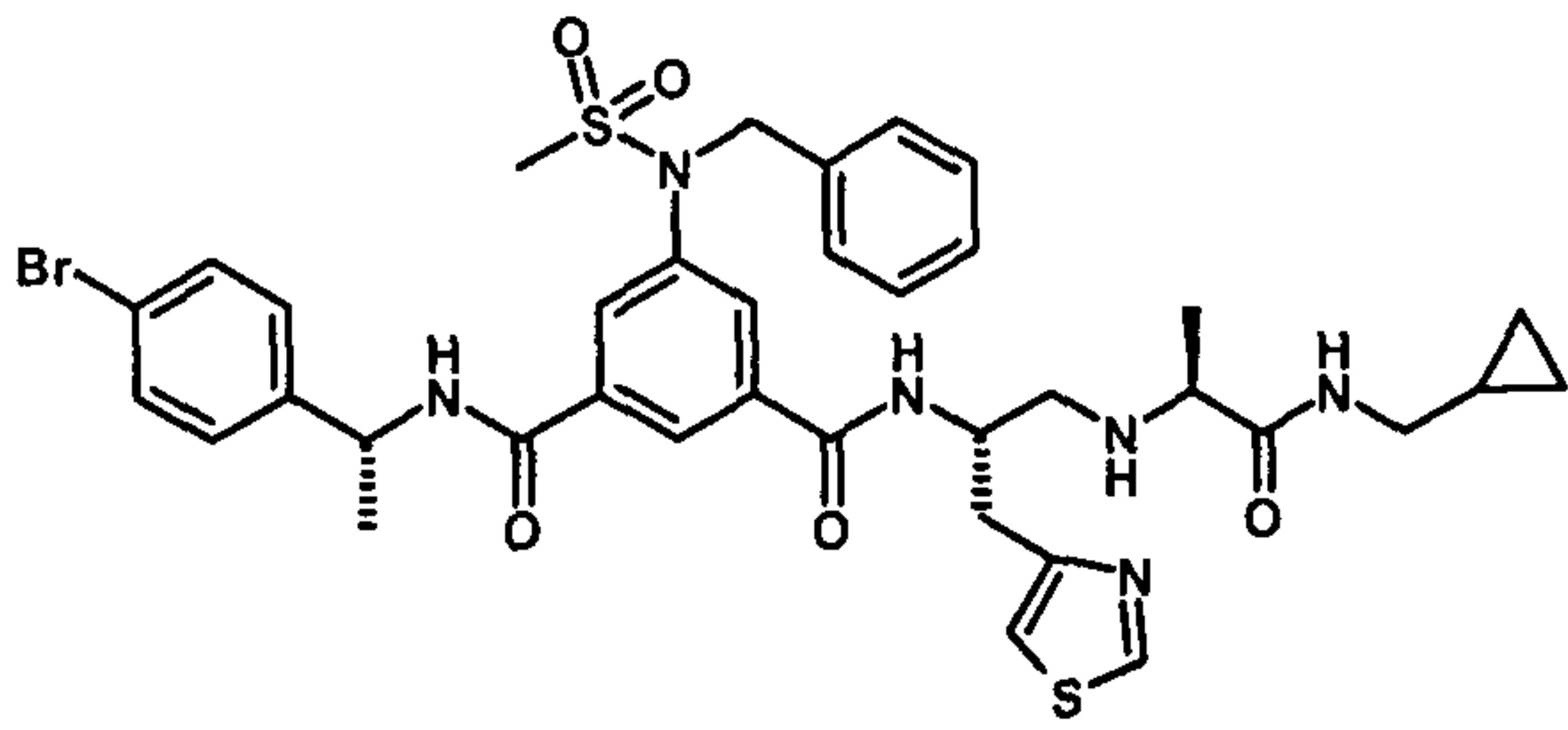
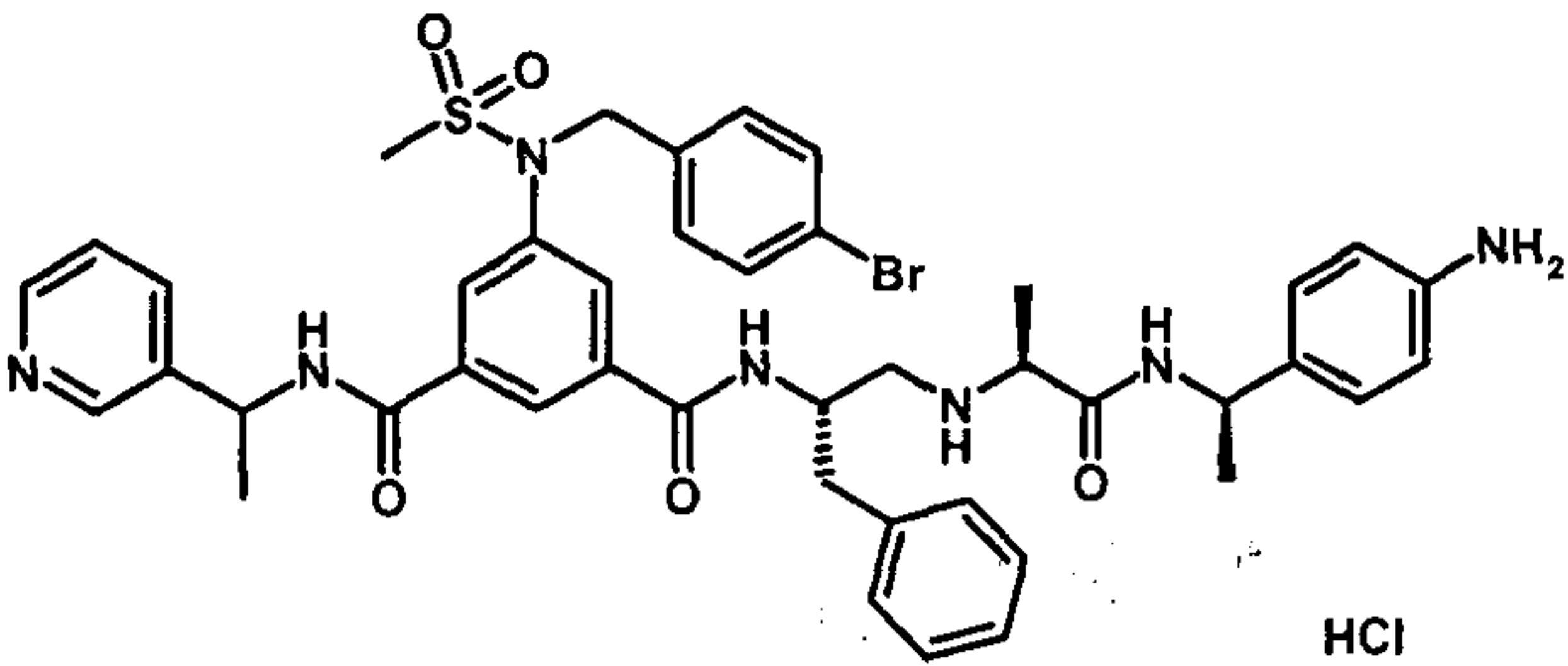
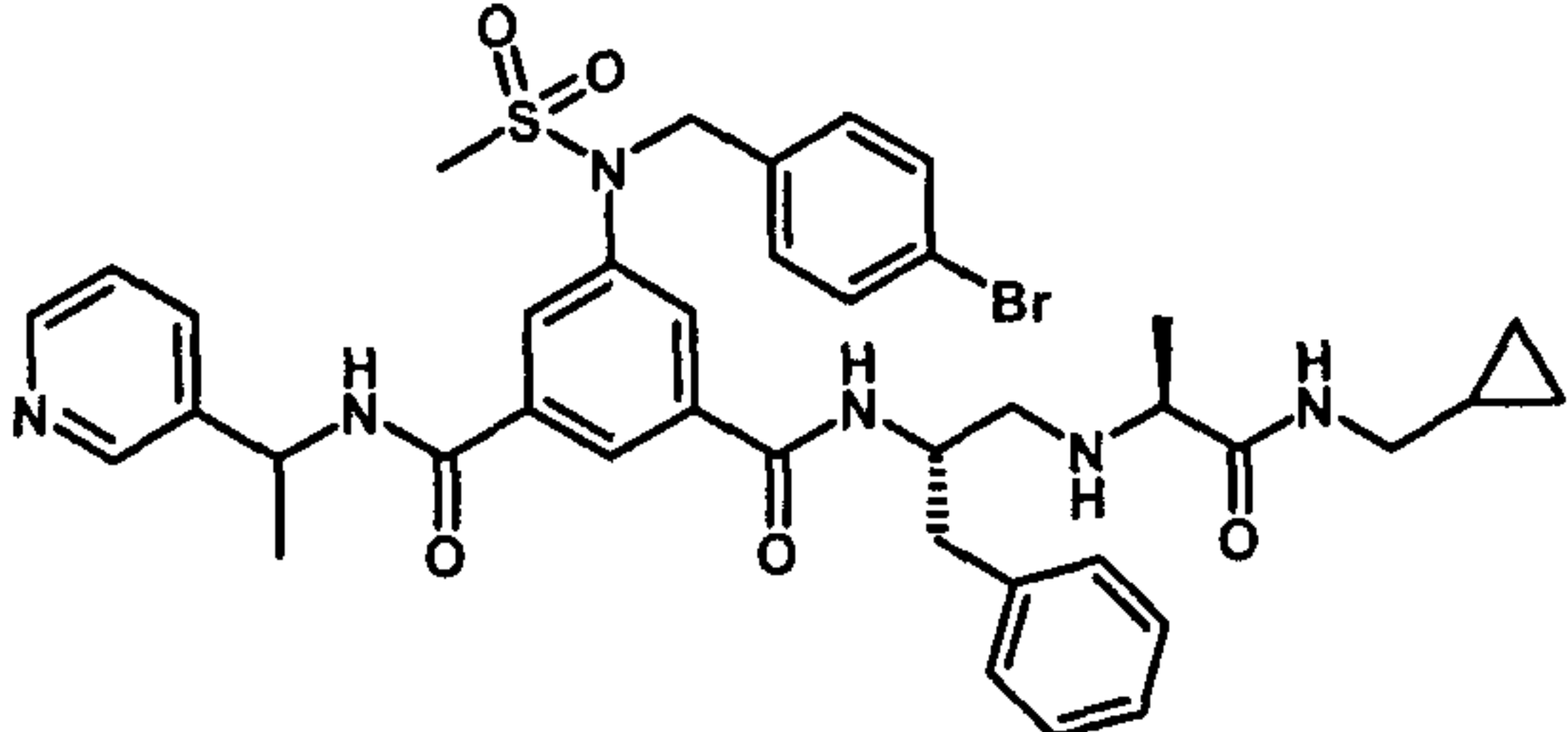
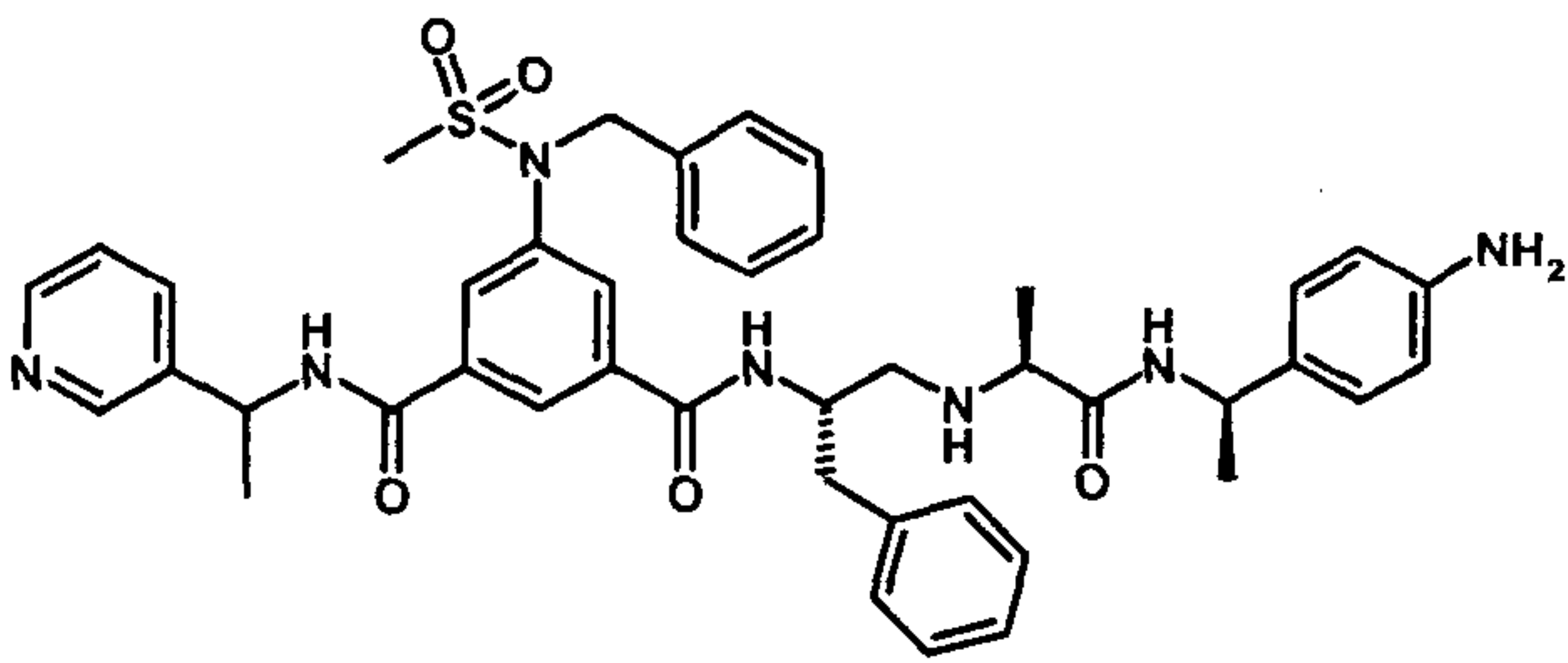
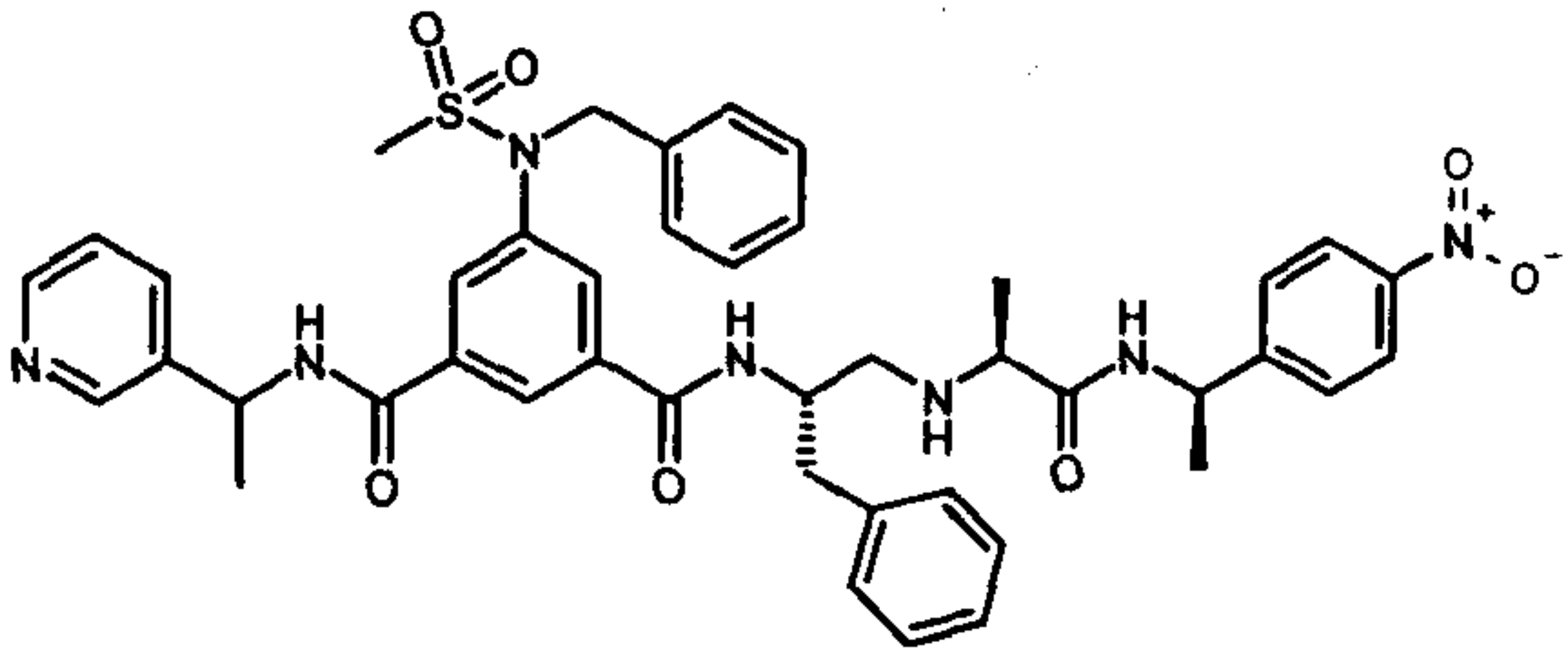
Example		
14.1	 HCl	RT (HPLC-1) = 3.66 min. ES-MS (M+H) ⁺ = 855/857 (Br)
14.2	 HCl	RT (HPLC-1) = 3.83 min. ES-MS (M+H) ⁺ = 861/863 (Br)
14.3	 HCl	RT (HPLC-1) = 3.89 min. ES-MS (M+H) ⁺ = 790/792 (Br)
14.4	 HCl	RT (HPLC-1) = 3.71 min. ES-MS (M+H) ⁺ = 783
14.5	 HCl	RT (HPLC-1) = 4.13 min. ES-MS (M+H) ⁺ = 796/798 (Br)

14.6		RT (HPLC-MS) = 2.09 min. ES-MS (M+H) ⁺ = 777
14.7		RT (HPLC-1) = 2.16 min. ES-MS (M+H) ⁺ = 712
14.8		RT (HPLC-MS) = 2,33 min. ES-MS (M+H) ⁺ = 718
14.9		RT (HPLC-1) = 4.75 min. ES-MS (M+H) ⁺ = 938/940/942 (2Br)
14.10		RT (HPLC-1) = 4.76 min. ES-MS (M+H) ⁺ = 867/869/871 (2Br)
14.11		RT (HPLC-1) = 5.03 min. ES-MS (M+H) ⁺ = 962/964/966 (2Br)

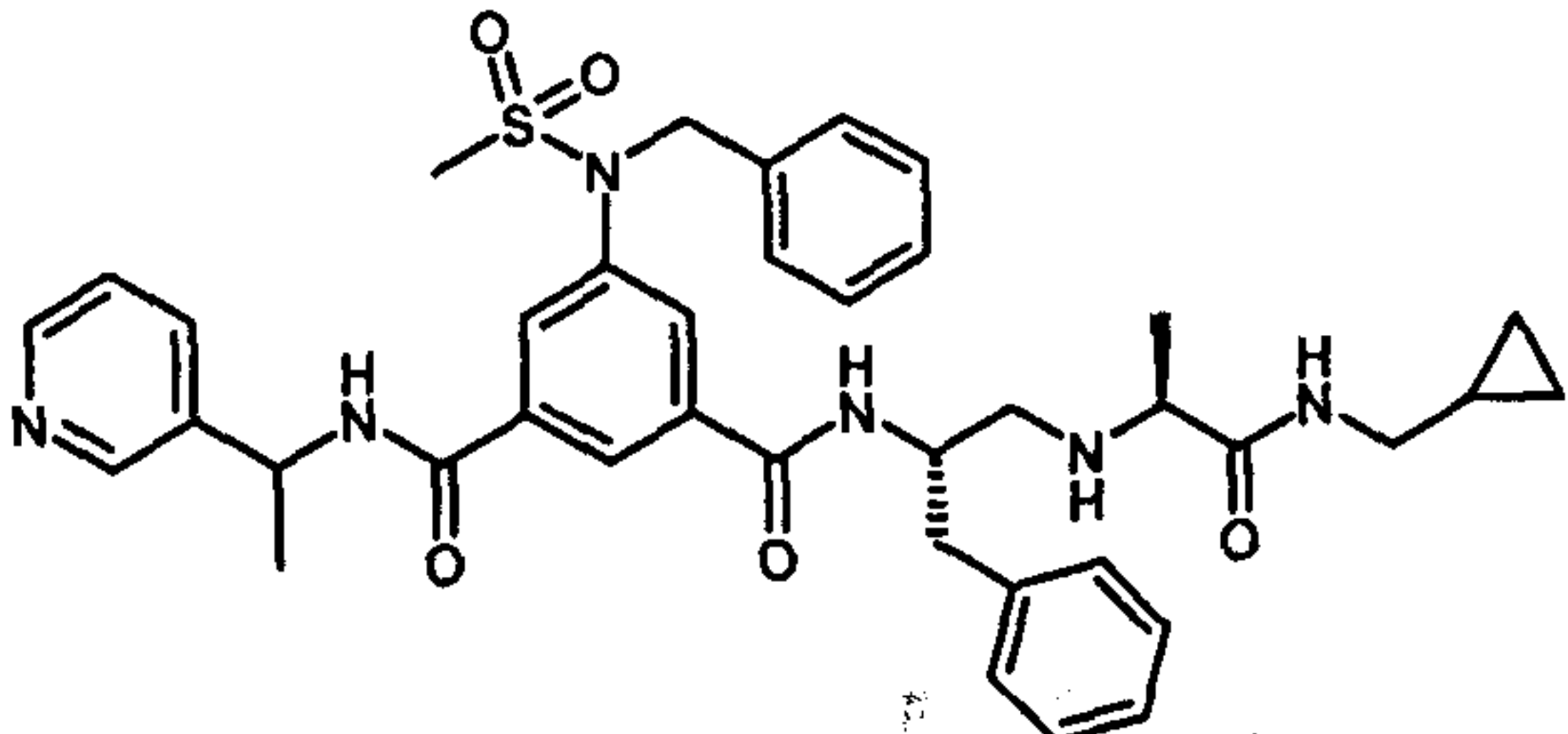
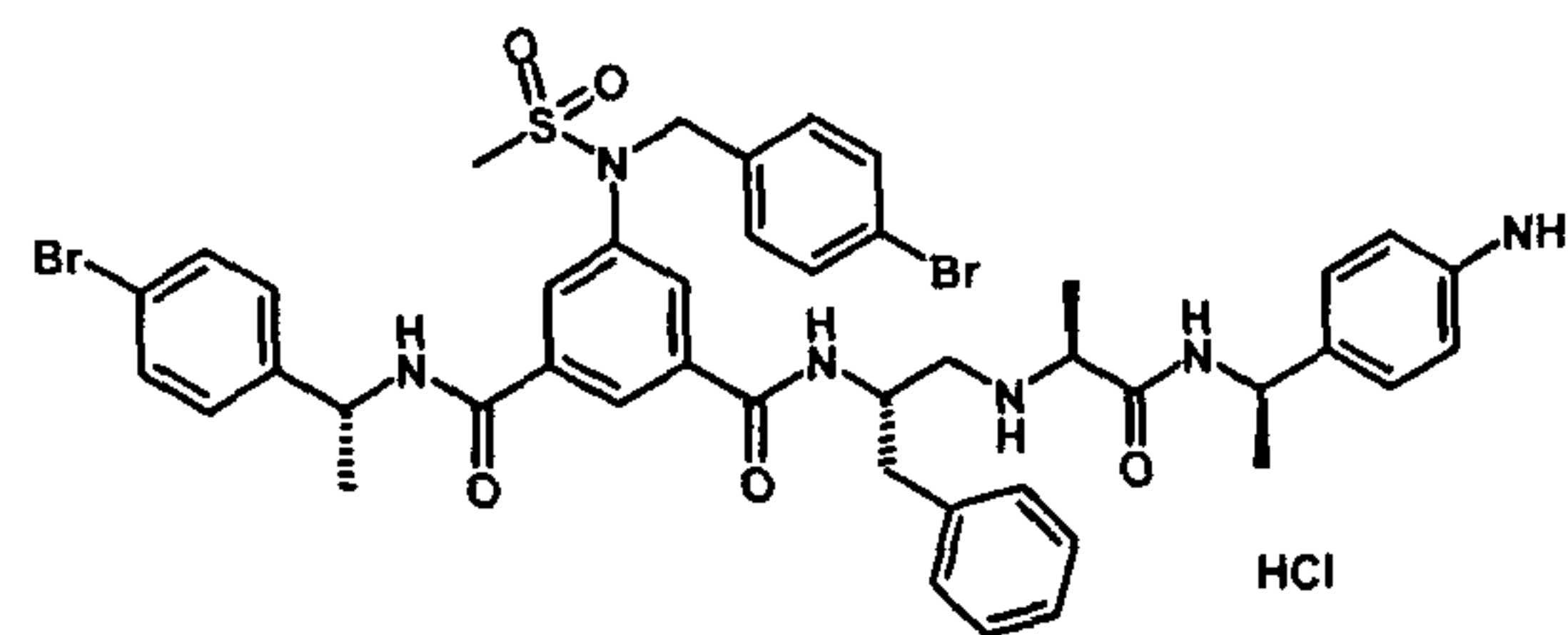
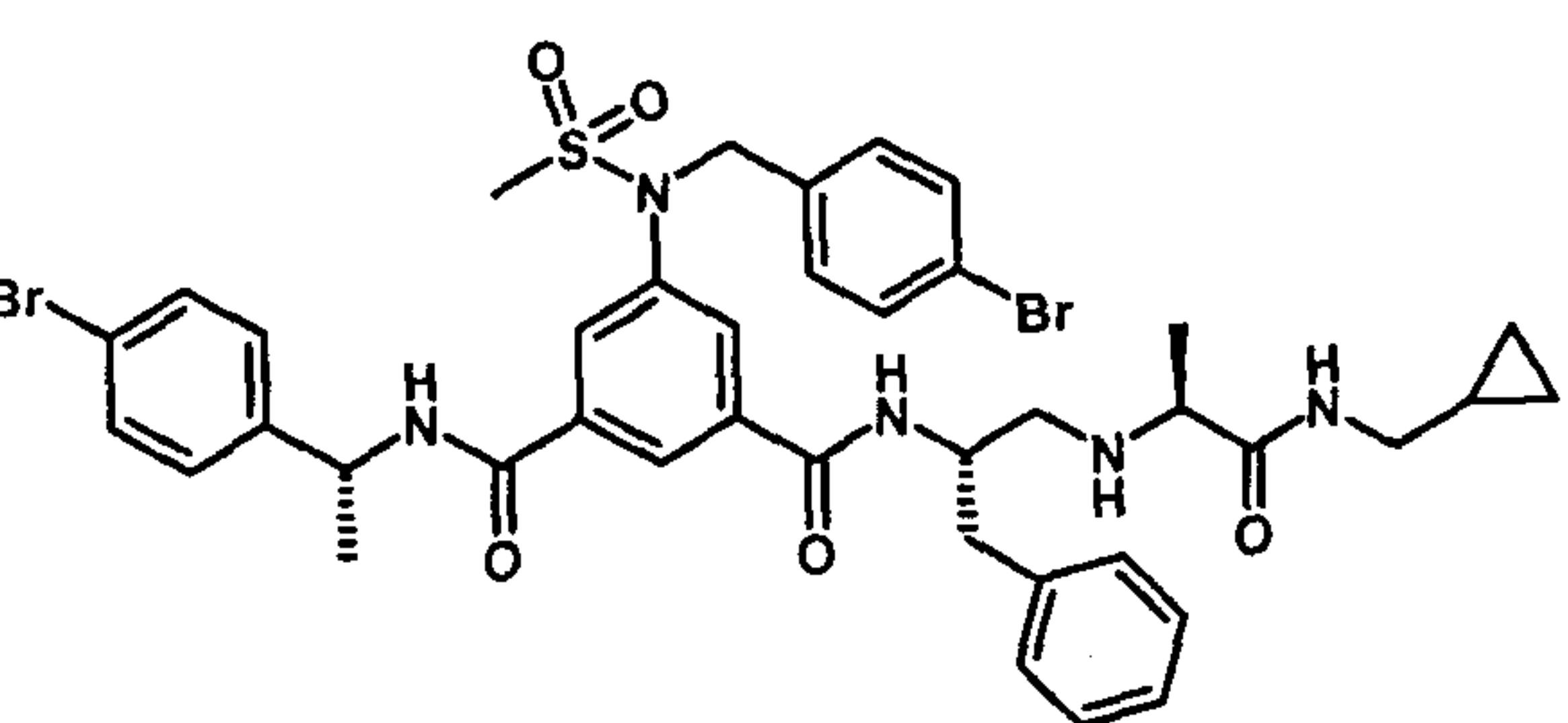
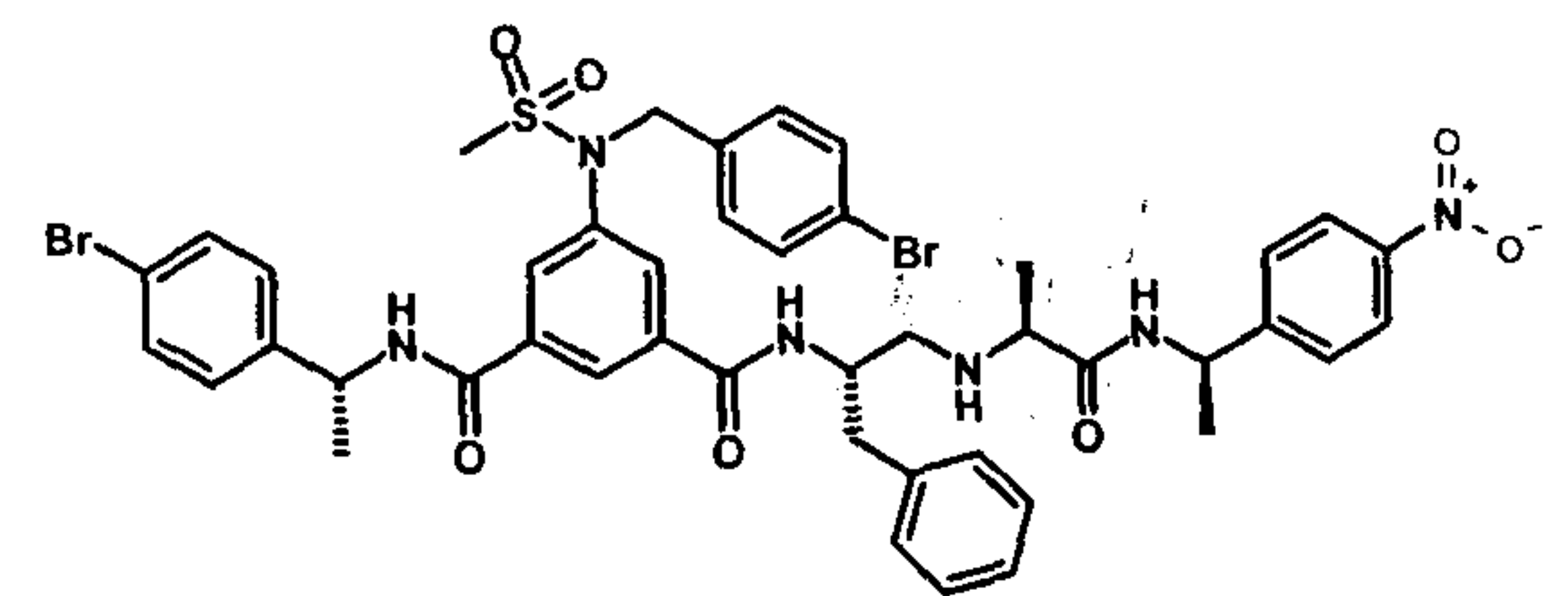
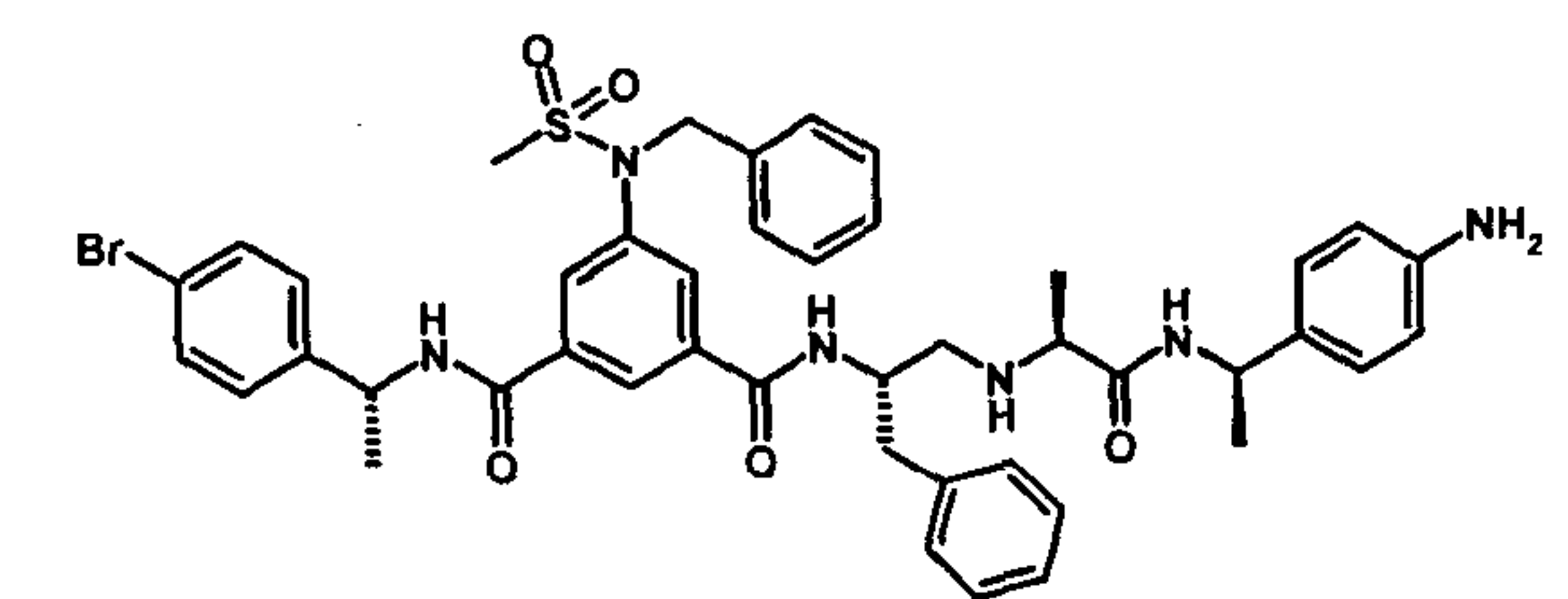
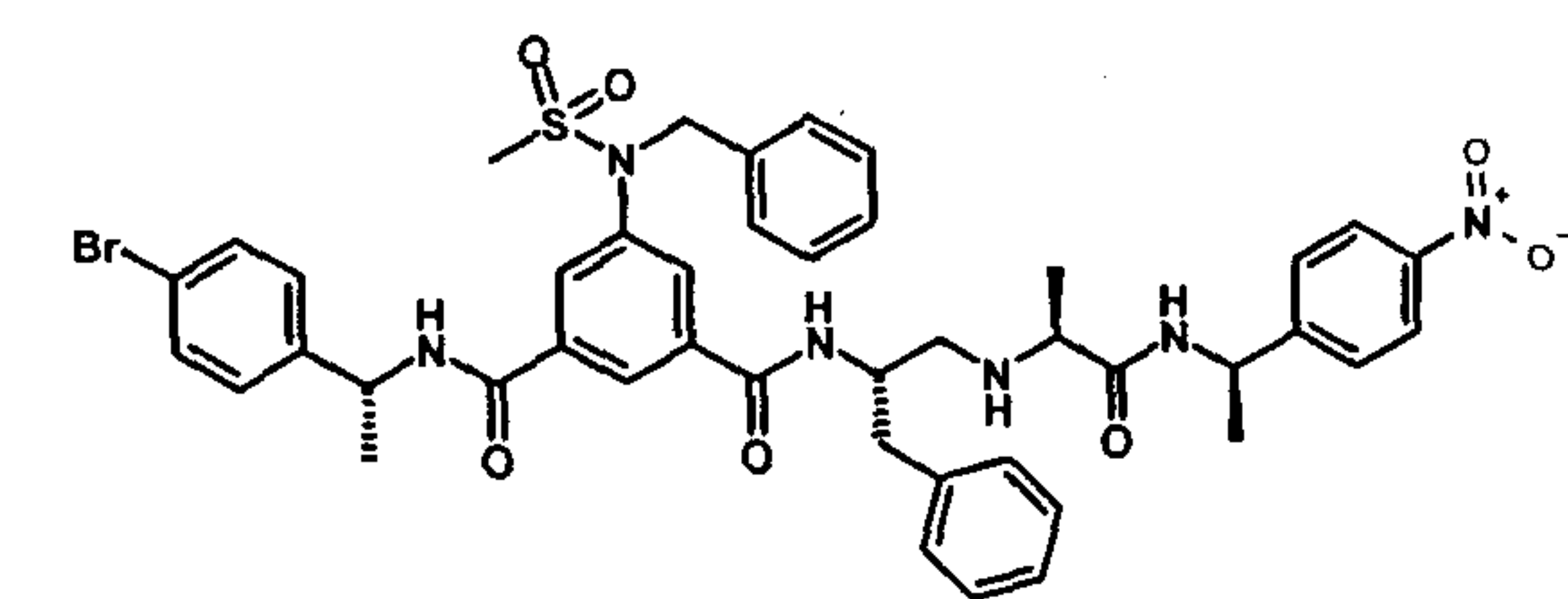
- 176 -

14.12		RT (HPLC-1) = 4.48 min. ES-MS (M+H) ⁺ = 860/862 (Br)
14.13		RT (HPLC-1) = 5.15 min. ES-MS (M+H) ⁺ = 873/875/877 (2Br)
14.14		RT (HPLC-1) = 5.27 min. ES-MS (M+H) ⁺ = 968/970/972 (2Br)
14.15		RT (HPLC-MS) = 2.67 min. ES-MS (M+H) ⁺ = 854/856 (Br)
14.16		RT (HPLC-MS) = 2.86 min. ES-MS (M+H) ⁺ = 884/886 (Br)
14.17		RT (HPLC-MS) = 2.75 min. ES-MS (M+H) ⁺ = 789/791 (Br)

- 177 -

14.18		RT (HPLC-MS) = 3.08 min. ES-MS (M+H) ⁺ = 890/892 (Br)
14.19		RT (HPLC-MS) = 2.99 min. ES-MS (M+H) ⁺ = 795/797 (Br)
14.20		RT (HPLC-1) = 4.05 min. ES-MS (M+H) ⁺ = 854/856 (Br)
14.21		RT (HPLC-1) = 4.39 min. ES-MS (M+H) ⁺ = 789/791 (Br)
14.22		RT (HPLC-1) = 3.83 min. ES-MS (M+H) ⁺ = 776
14.23		RT (HPLC-1) = 4.40 min. ES-MS (M+H) ⁺ = 806

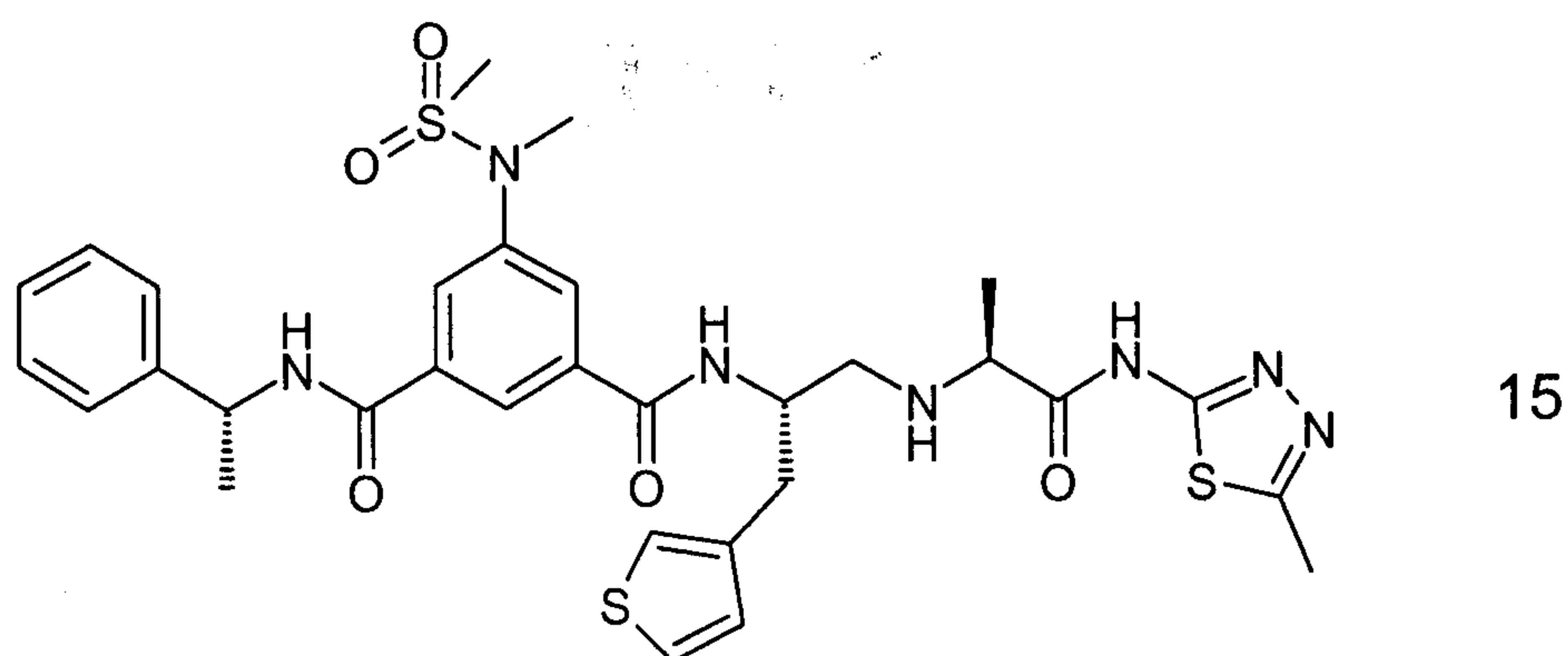
- 178 -

14.24		RT (HPLC-1) = 4.24 min. ES-MS (M+H) ⁺ = 711
14.25		RT (HPLC-1) = 4.88 min. ES-MS (M+H) ⁺ = 931/933/935 (2 Br)
14.26		RT (HPLC-1) = 5.39 min. ES-MS (M+H) ⁺ = 866/868/870 (2 Br)
14.27		RT (HPLC-1) = 5.51 min. ES-MS (M+H) ⁺ = 961/963/965 (2 Br)
14.28		RT (HPLC-1) = 4.66 min. ES-MS (M+H) ⁺ = 854/856 (Br)
14.29		RT (HPLC-1) = 5.29 min. ES-MS (M+H) ⁺ = 883/885 (Br)

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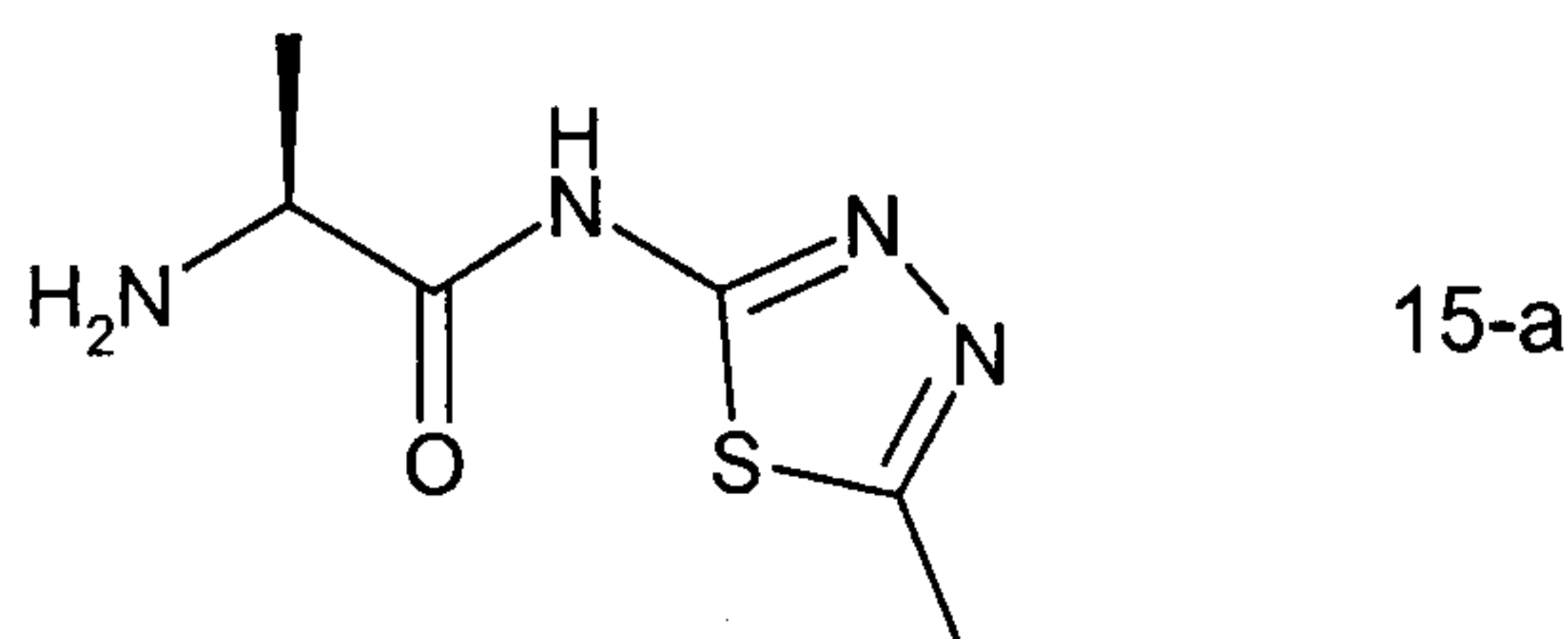
14.30		RT (HPLC-1) = 5.15 min. ES-MS (M+H)⁺ = 788/790 (Br)
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Example 15:



5

a) Preparation of **15-a**:



10

A solution of 378 mg (2 mmol) Boc-L-alanine, 776 mg DiPea (6 mmol) and 761 mg (2 mmol) HATU in 5 ml DMSO was added to 230.3 mg (2 mmol) 2-amino-5-methyl-1,3,4-thiadiazole and stirred overnight at ambient temperature. The solvent was distilled off and the residue was purified by preparative reversed phase HPLC. The product was dissolved in ether in order to cleave the Boc protective group and combined with 5 ml ethereal HCl (5 mol/l) and stirred overnight at ambient temperature. Then the solvent was distilled off i. vac.. The product was reacted without further purification.

Preparation of compound 15:

20

(0.14 mmol) of the crude product **15-a** and 71.8 mg (0.14 mmol) of compound **6-d** were dissolved in 2 ml DMF/glacial acetic acid 97:3 and stirred for 10 min at ambient

- 180 -

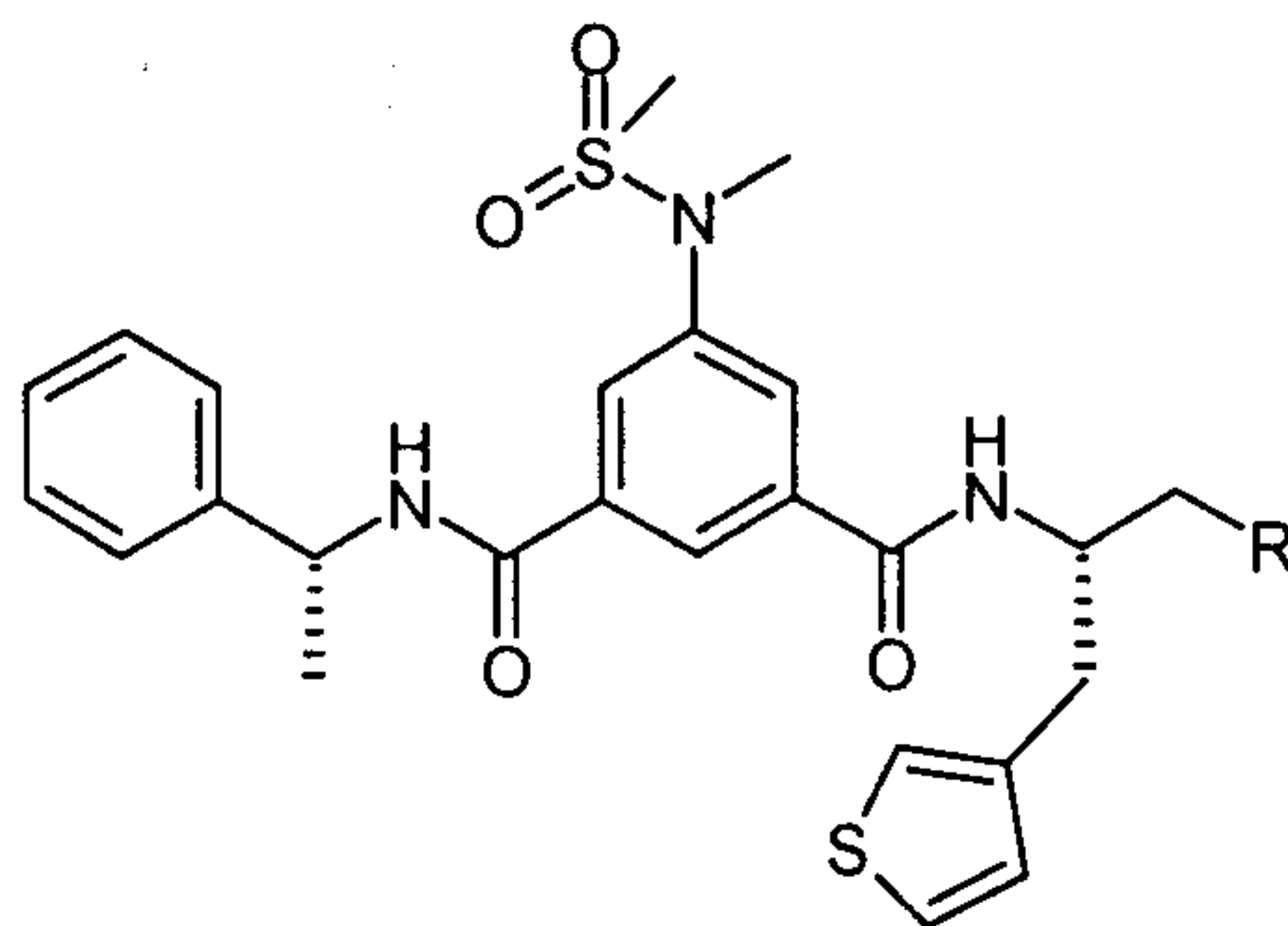
temperature. Then 173.8 mg (0.82 mmol) sodium triacetoxymethylborohydride were added and the mixture was stirred at ambient temperature for 3 days. 200 μ l water were added and the mixture was evaporated down i. vac.. Purification was carried out by preparative reversed phase HPLC.

5

RT (HPLC3) = 3.49 min

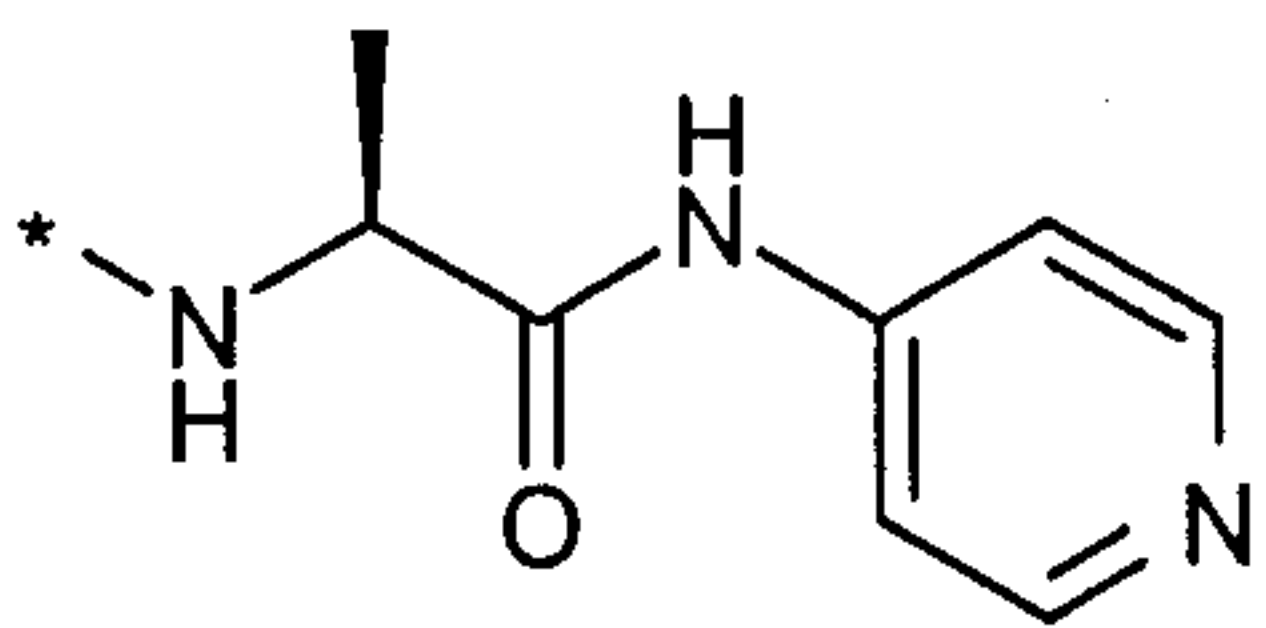
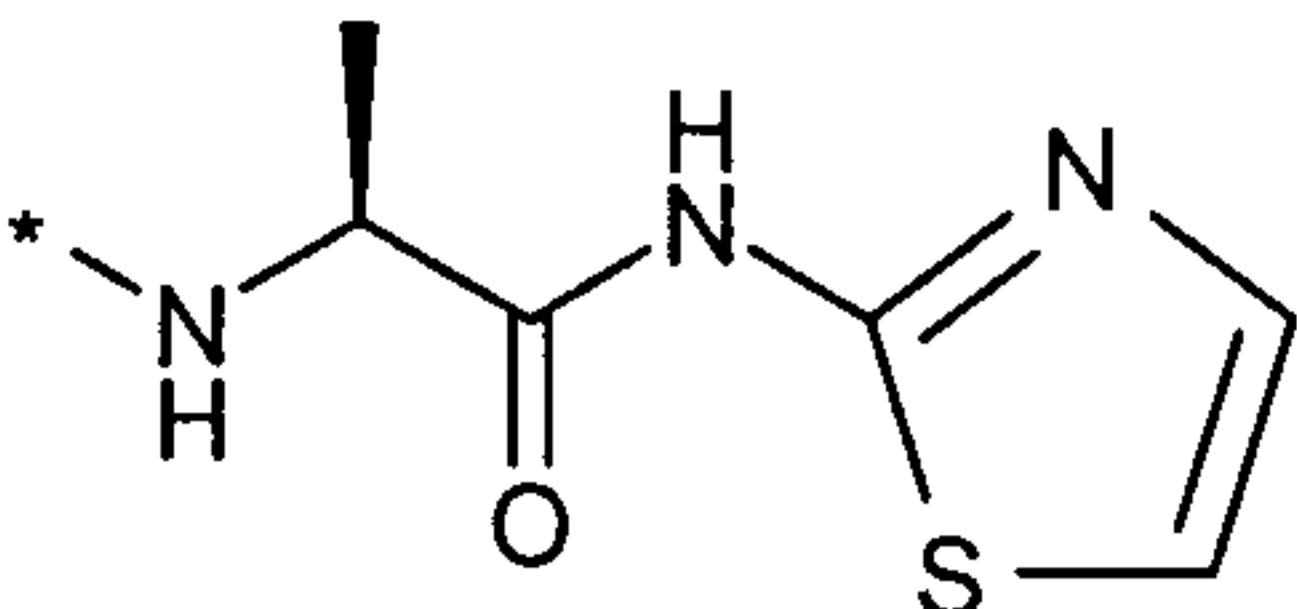
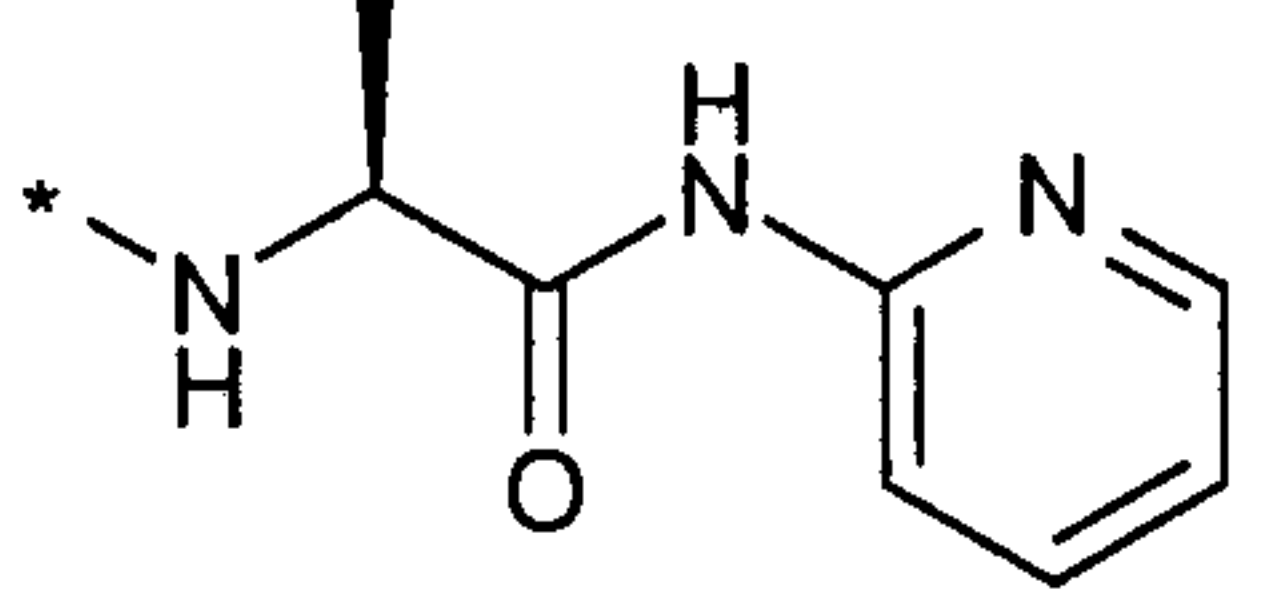
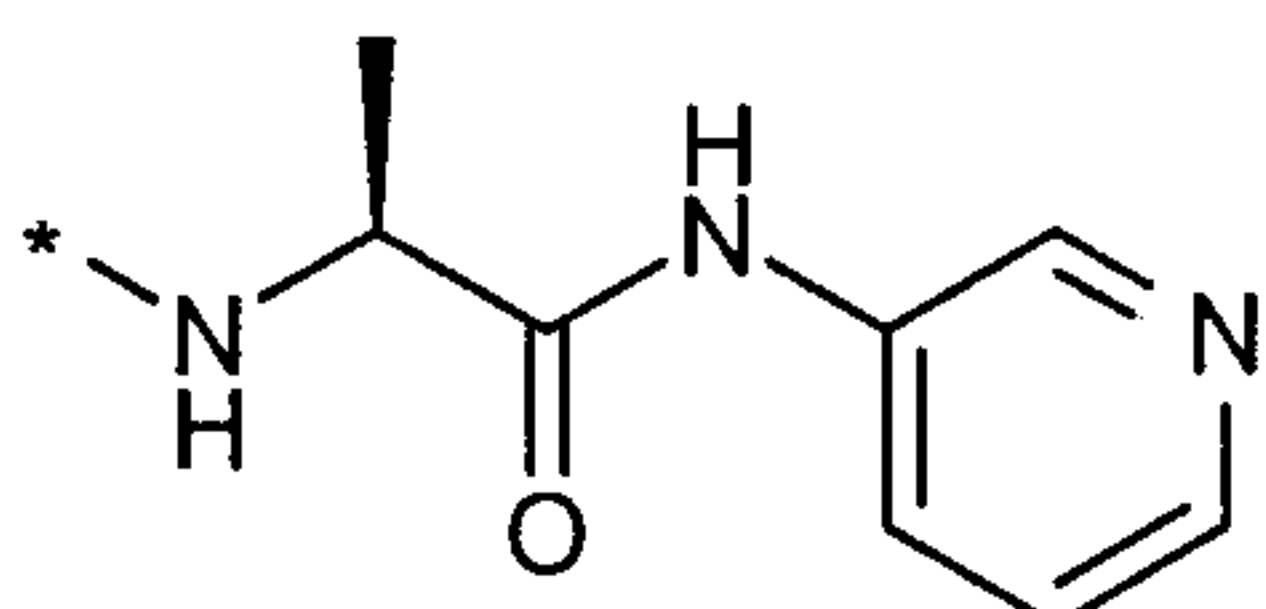
ES-MS (M+H)⁺ = 684

The following compounds were prepared analogously to **15** from **6-d** and the
10 corresponding alanineamide (analogously to **15-a**):

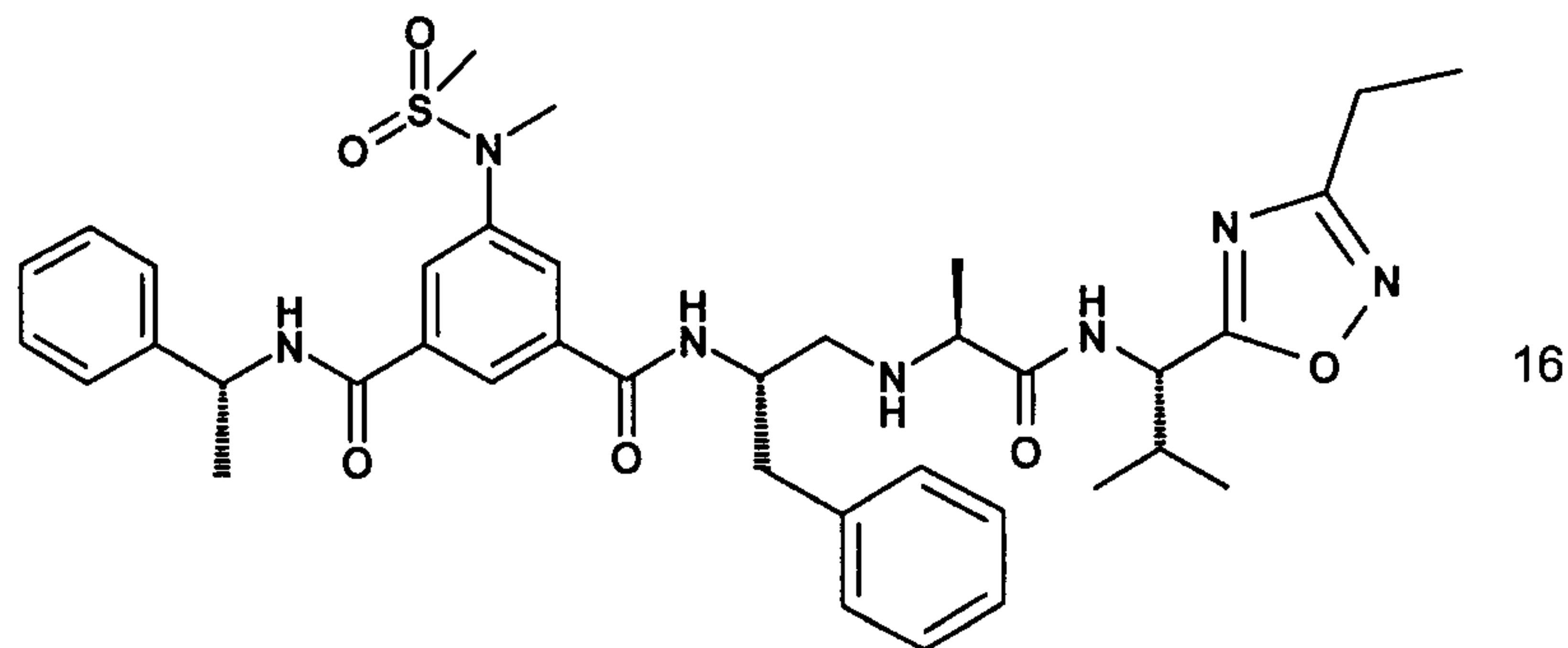


EXAMPLE	R	
15.1		RT (HPLC3) = 3.52 min ES-MS (M+H) ⁺ = 664
15.2		RT (HPLC3) = 3.48 min ES-MS (M+H) ⁺ = 680
15.3		RT (HPLC3) = 3.45 min ES-MS (M+H) ⁺ = 681

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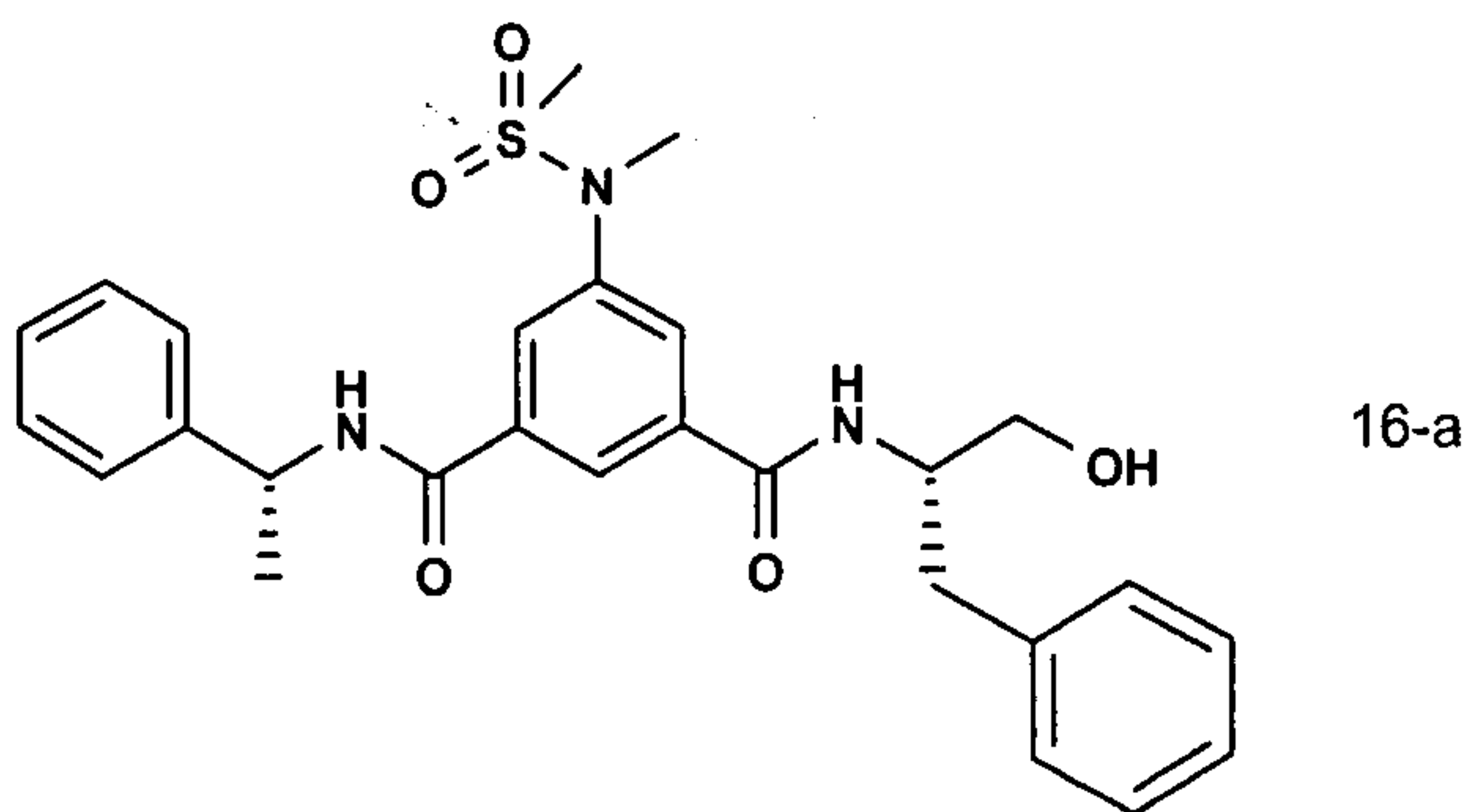
15.4		RT (HPLC3) = 3.29 min ES-MS (M+H) ⁺ = 663
15.5		RT (HPLC3) = 3.60 min ES-MS (M+H) ⁺ = 669
15.6		RT (HPLC3) = 3.51 min ES-MS (M+H) ⁺ = 663
15.7		RT (HPLC3) = 3.32 min ES-MS (M+H) ⁺ = 663

Example 16:



5

a) Preparation of 16-a:



10

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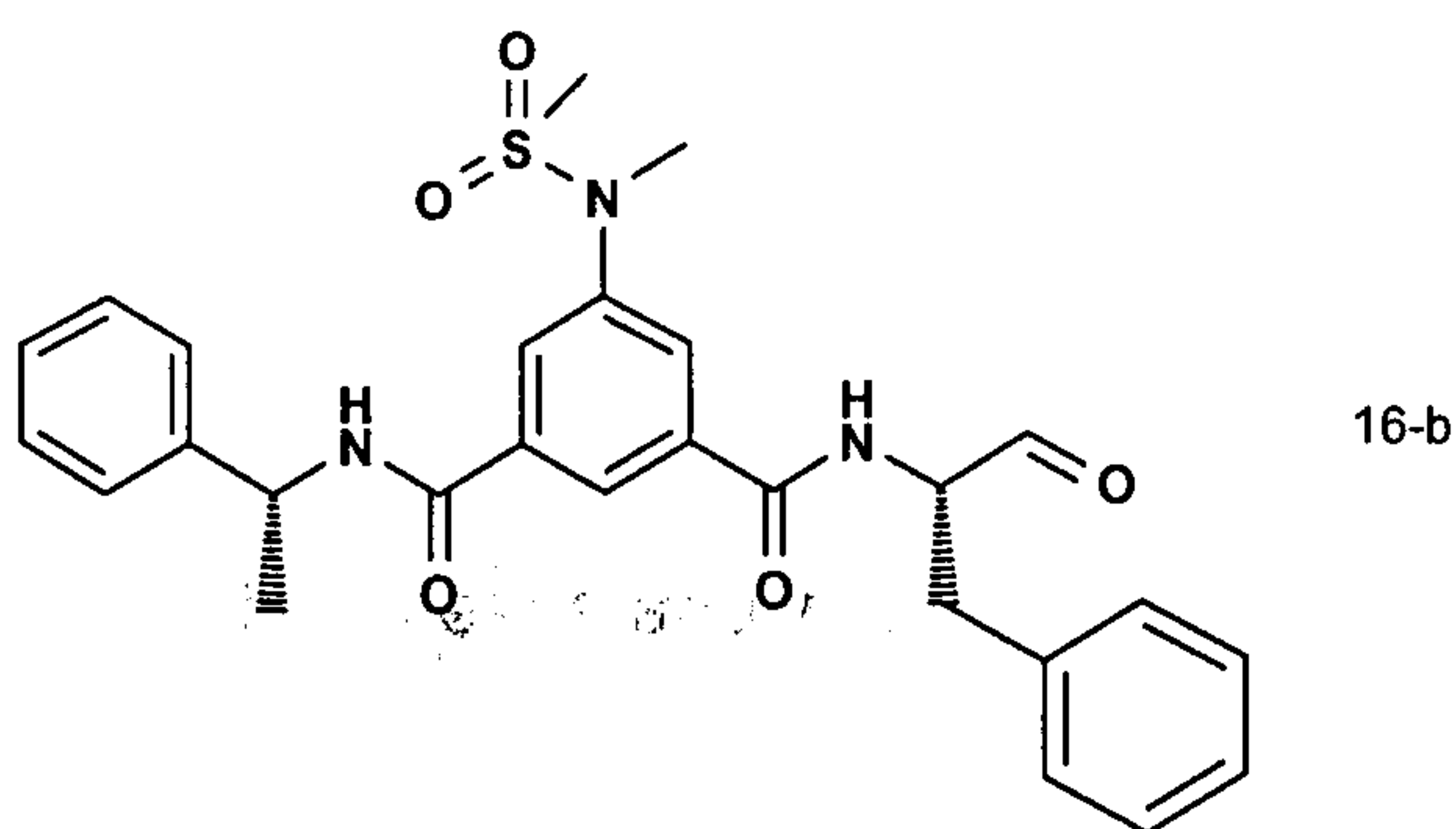
4.7 g (12.5 mmol) **1.8-h** were suspended in 200 ml acetonitrile and combined successively with 4.0 g TBTU (12.49 mmol) and 4.35 ml diisopropylethylamine (24.97 mmol) and stirred for 10 min at ambient temperature. Then 2.0 g (13.23 mmol) (S)-(-)-2-amino-3-phenylpropanol was added and the mixture was stirred overnight at ambient temperature. The acetonitrile was distilled off i. vac., the residue was dissolved in ethyl acetate and washed twice with 5% sodium hydrogen carbonate solution and once with saturated saline solution. The organic phase was dried on magnesium sulphate, filtered and the solvent was distilled off i. vac.. The residue was purified by chromatography on silica gel.

Yield: 4.4 g (69%)

RT (HPLC 4) = 3.94 min

(M+H)⁺ (HPLC-MS) 510.6

b) Preparation of **16-b**:

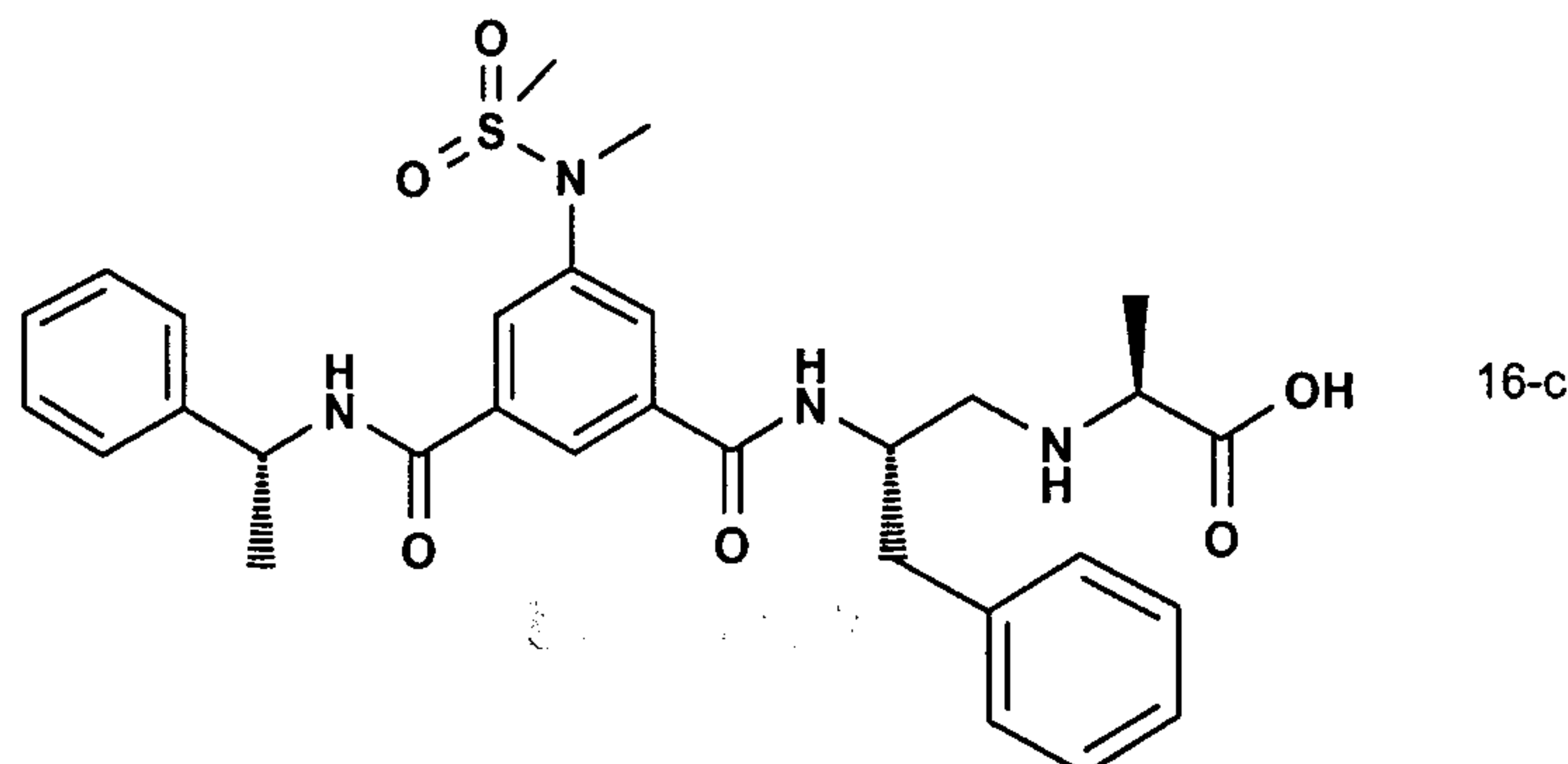


2.2 g (4.32 mmol) **16-a** were dissolved in 200 ml dichloromethane and combined with 3.85 g (9.07 mmol) Dess-Martin-periodinane with stirring. After 30 min 0.16 ml (9.07 mmol) water were added and the mixture was vigorously stirred for a further 2 h. Then a solution of 5.36 g sodium thiosulphate-5-hydrate and 4.42 g sodium hydrogen carbonate in 280 ml of water was added and the mixture was vigorously stirred for 1 h. The organic phase was separated off and the aqueous phase was extracted twice with dichloromethane. The combined organic phases were extracted once with 200 ml saturated sodium hydrogen carbonate solution and twice with 200 ml of water, dried on magnesium sulphate, filtered off and evaporated down i. vac.. The residue was dissolved in acetonitrile/tert. butanol and freeze-dried.

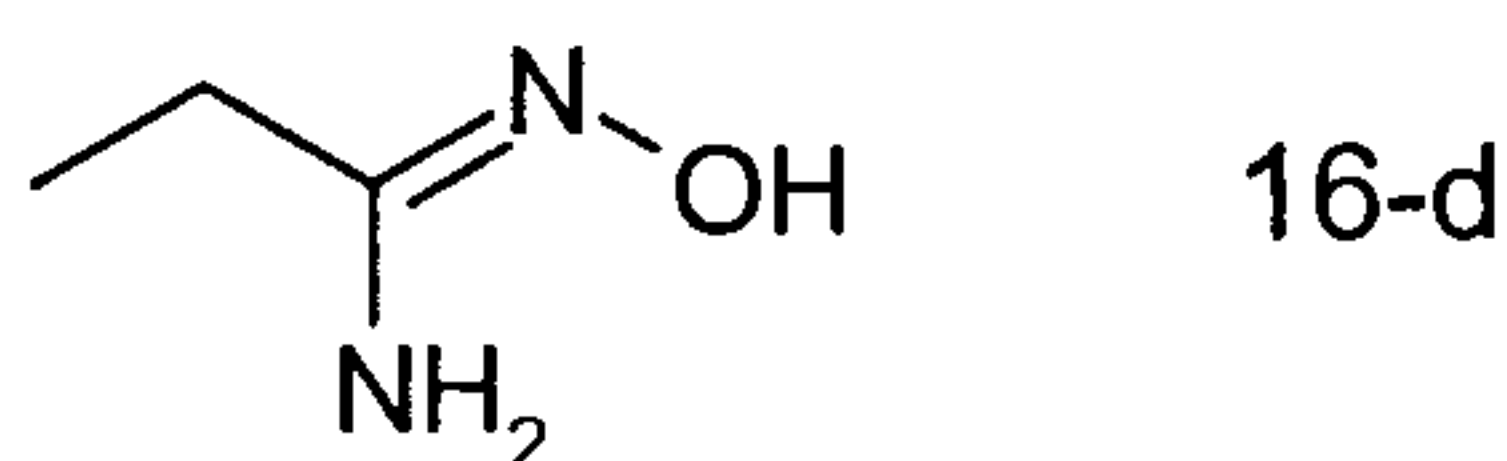
Yield: 2.1 g (96%)

RT (HPLC 4) = 4.03 min

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 $(M+H)^+$ (HPLC-MS) 508.6c) Preparation of **16-c**:

0.83 g (1.66 mmol) **16-b** were dissolved in 5 ml dimethylacetamide and combined with 0.23 g (1.28 mmol) L-alanine-t-butylester hydrochloride and 0.1 ml (1.66 mmol) glacial acetic acid. The mixture was stirred for 10 min at ambient temperature and then 1.63 g (7.68 mmol) sodium triacetoxyborohydride was added. The mixture was stirred for 2 h at ambient temperature, filtered through Alox B, washed with dimethylformamide and evaporated down i. vac.. The residue was dissolved in dichloromethane and extracted 3 times with water. The organic phase was dried on magnesium sulphate, filtered off and evaporated down. The residue was combined with 50 ml trifluoroacetic acid/dichloromethane 1:1 and stirred for one hour at ambient temperature. The solution was evaporated down i. vac., the residue was taken up in acetonitrile and finally freeze-dried. The product was reacted without any further purification.

Preparation of **16-d**:

20

25

17.37g (0.25 mol) hydroxylamine hydrochloride were dissolved in 400 ml of ethanol and 50 ml of water and combined with a solution of 10.31 g (0.25 mol) sodium hydroxide in 100 ml of ethanol and 50 ml of water. Then the mixture was heated to 50°C and 27.54 g (0.5 mol) propionitrile were added within 2 min. The mixture was stirred overnight at 50°C. After cooling, the sodium chloride precipitated was suction filtered and the solvent was distilled off i. vac.. The mixture was combined

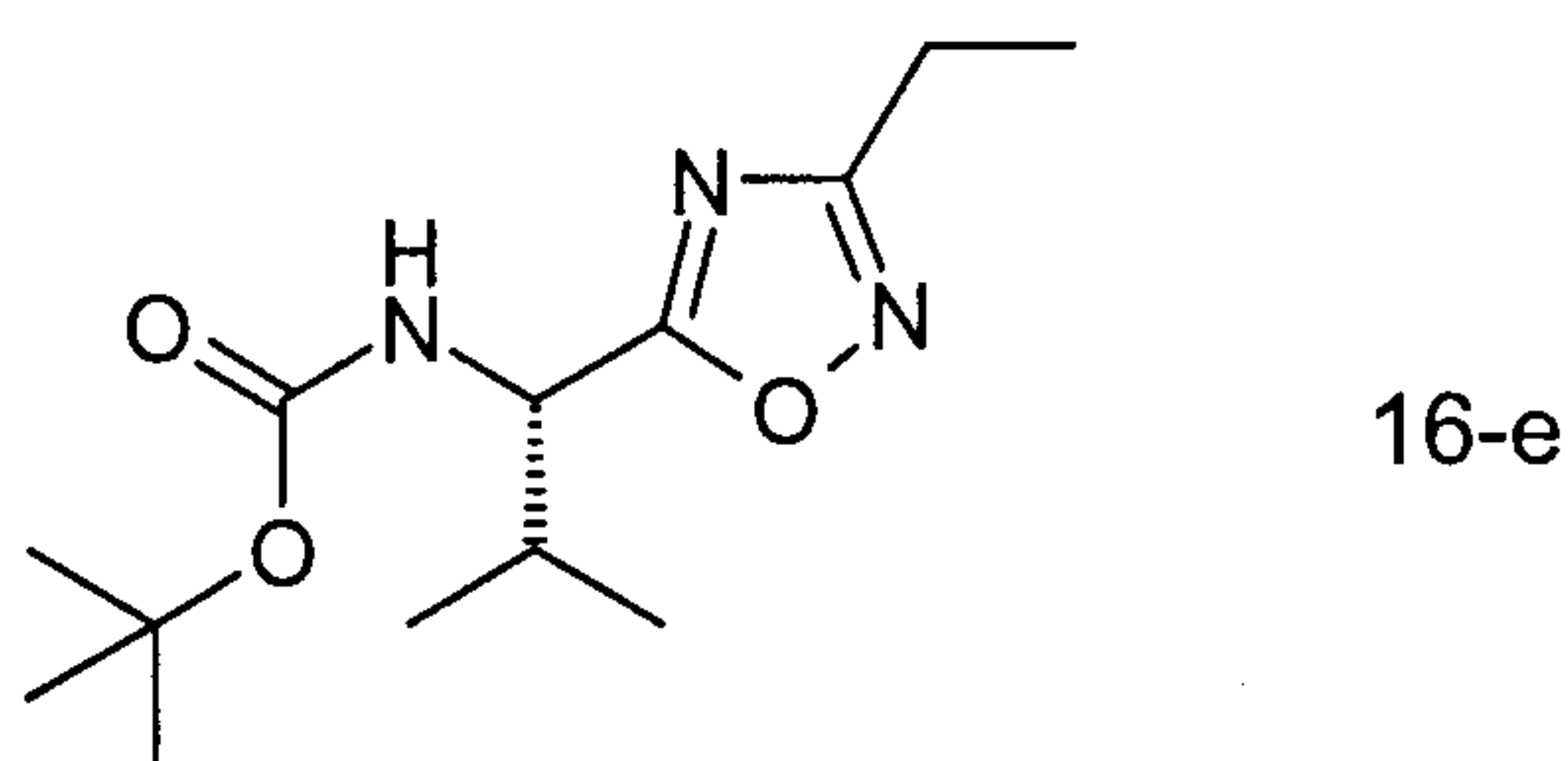
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several times with toluene and evaporated down i. vac., then suspended hot in 200 ml chloroform and filtered to remove the precipitated salt. The mother liquor is finally evaporated down i. vac..

Yield: 14.5g (58%)

5

Preparation of **16-e**:



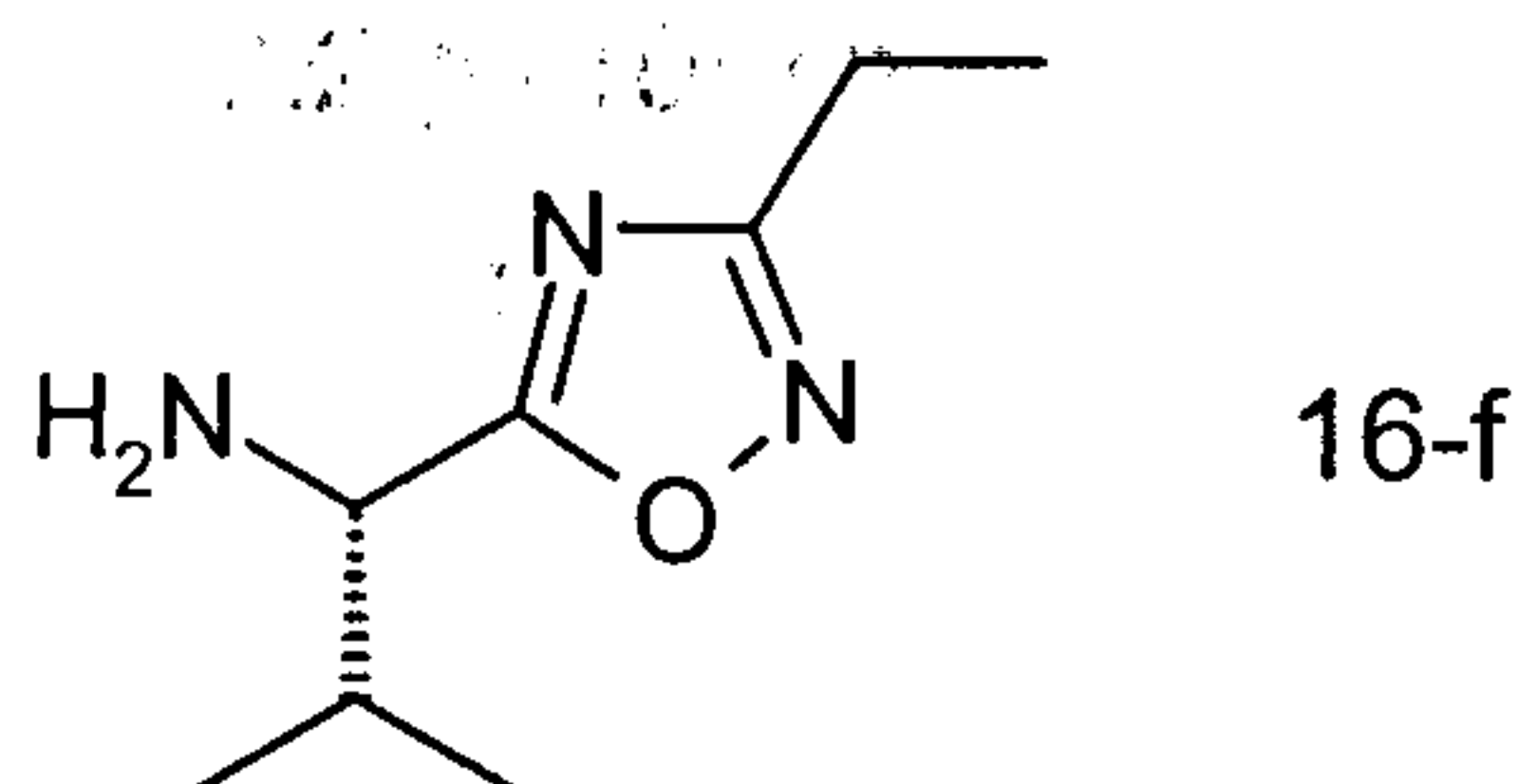
2.17 g (10 mmol) Boc-L-valine, 3.2 g (10 mmol) TBTU, 0.31 g (2 mmol) HOBt and 8.29 ml diisopropylethylamine were dissolved in 50 ml dimethylformamide and stirred for 10 min at ambient temperature. Then a solution of 1 g **16-d** in 5 ml dimethylformamide was added. The mixture was stirred for a further hour at ambient temperature, then stirred overnight at 110°C. 0.9 ml of water were added to the cooled reaction mixture, which was filtered through approx. 70 ml basic Alox and washed with DMF/MeOH 9/1. The filtrate was evaporated down, dissolved in acetonitrile and purified by reversed phase HPLC.

Yield: 1.4 g (52%)

RT (HPLC 4) = 4.32 min

(M+H)⁺ (HPLC-MS) 270

Preparation of **16-f**:



1.4g (5.2 mmol) **16-e** were stirred in 10 ml 50% trifluoroacetic acid in dichloromethane for 30 min at ambient temperature. The solution was evaporated down i. vac. And the product was reacted directly without any further purification.

25

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Preparation of **16**:

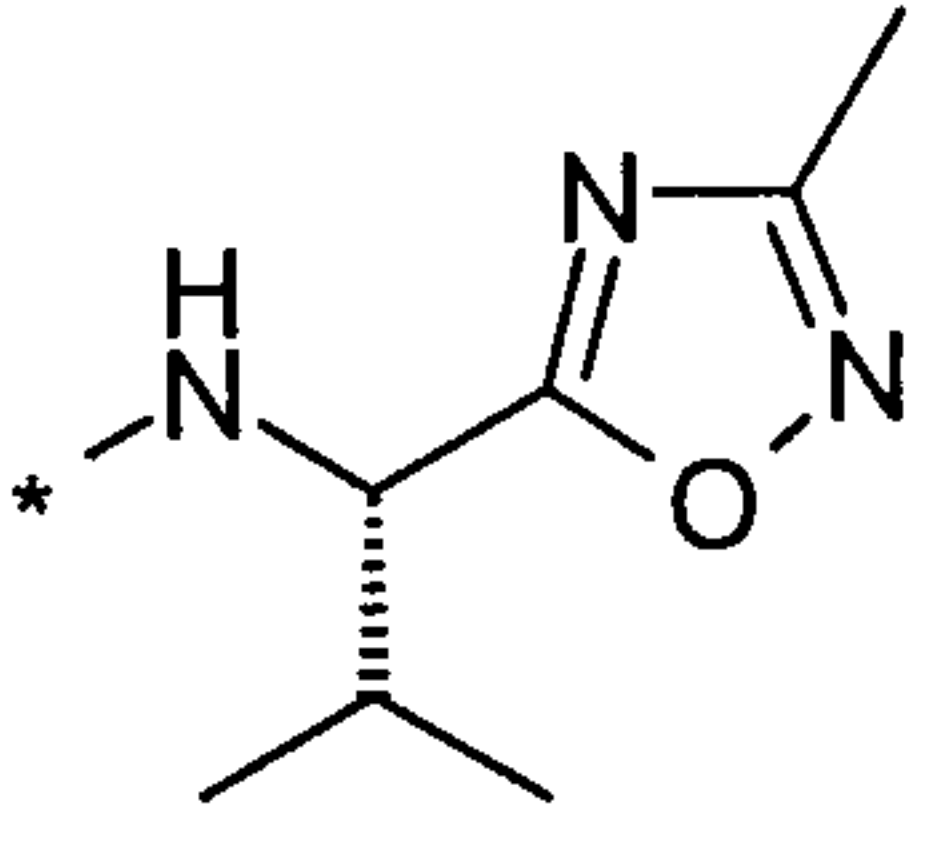
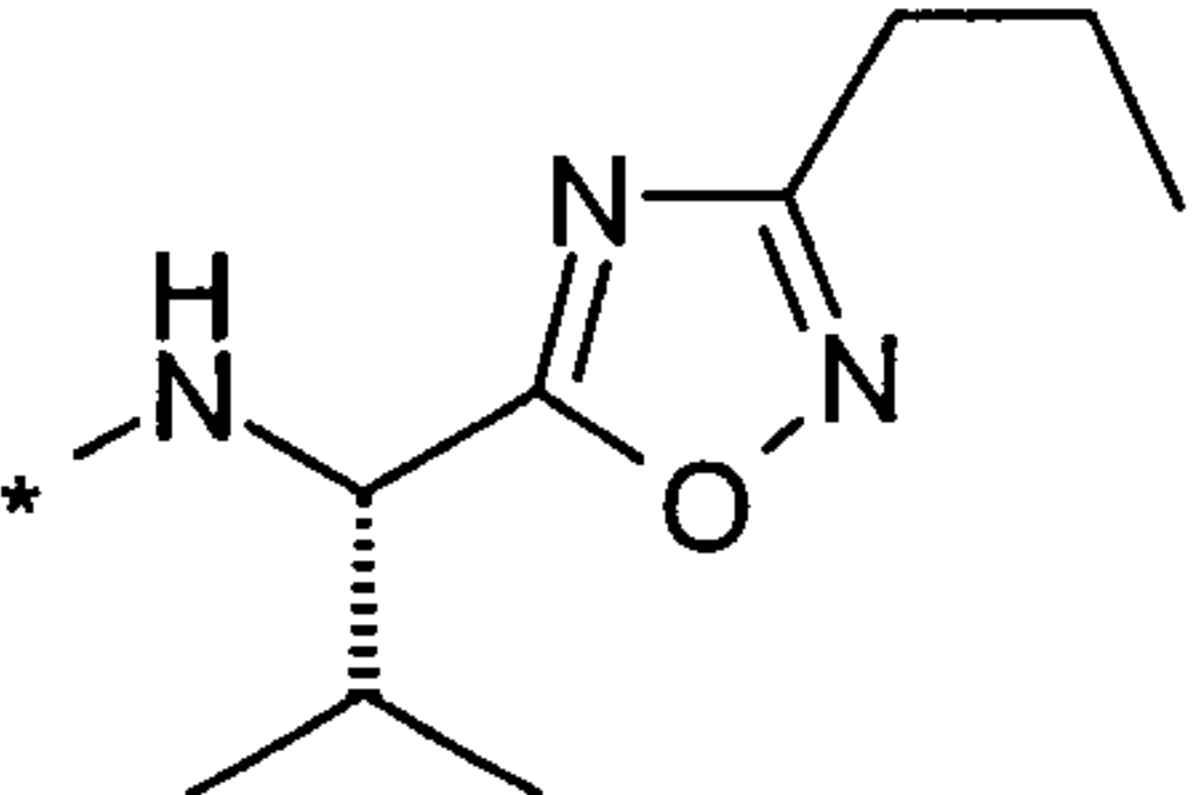
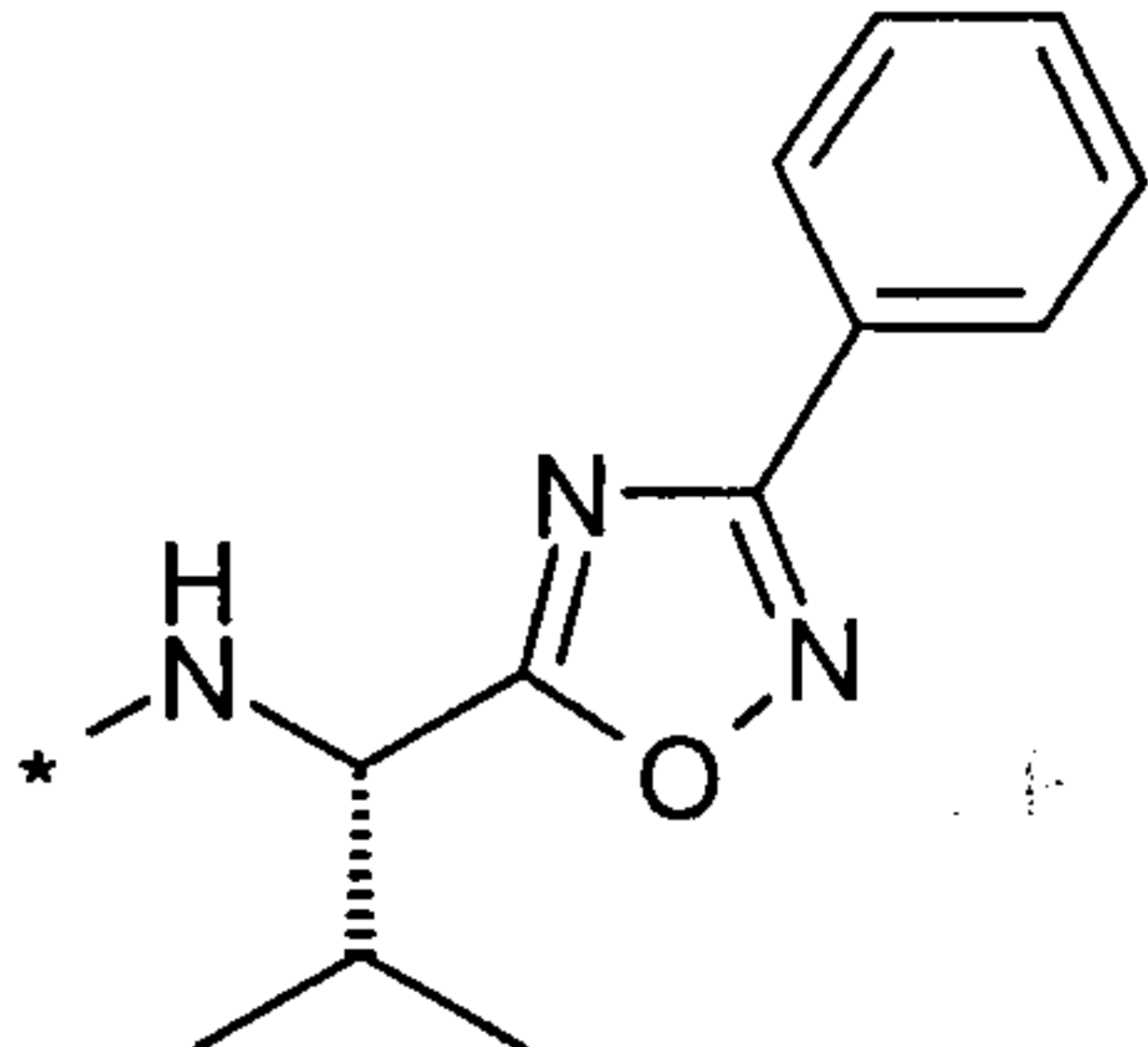
69.4 mg (0.1 mmol) **16-c** were dissolved in 2 ml dimethylformamide and combined successively with 32.1 mg (0.1 mmol) TBTU, 15.3 mg HOBt and 0.85 ml diisopropylethylamine (0.5 mmol). After 10 min stirring at ambient temperature 31.1 mg (0.11 mmol) **16-f** were added and the mixture was stirred overnight at ambient temperature. Purification was carried out by preparative reversed phase HPLC and freeze-drying.

Yield: 2.4 mg

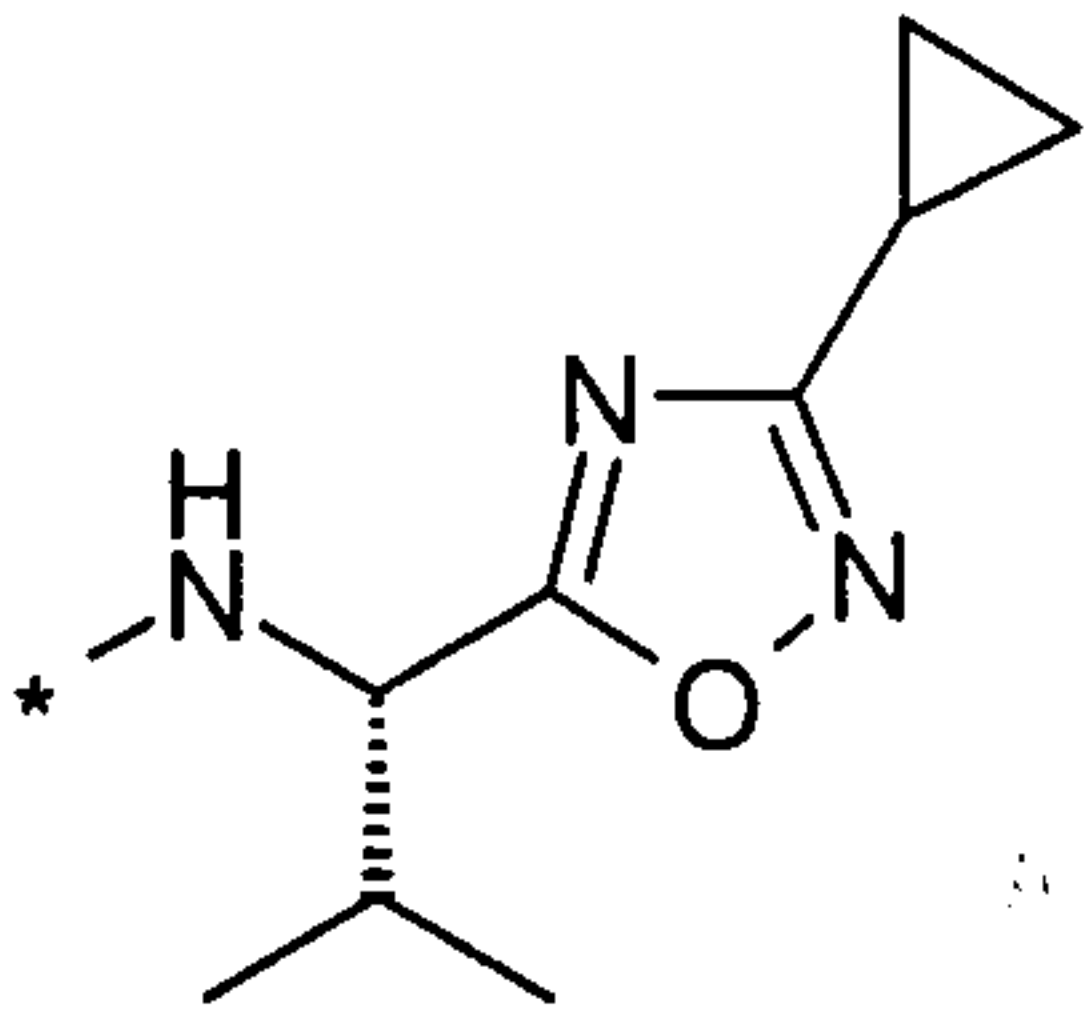
RT (HPLC4) = 4.11 min

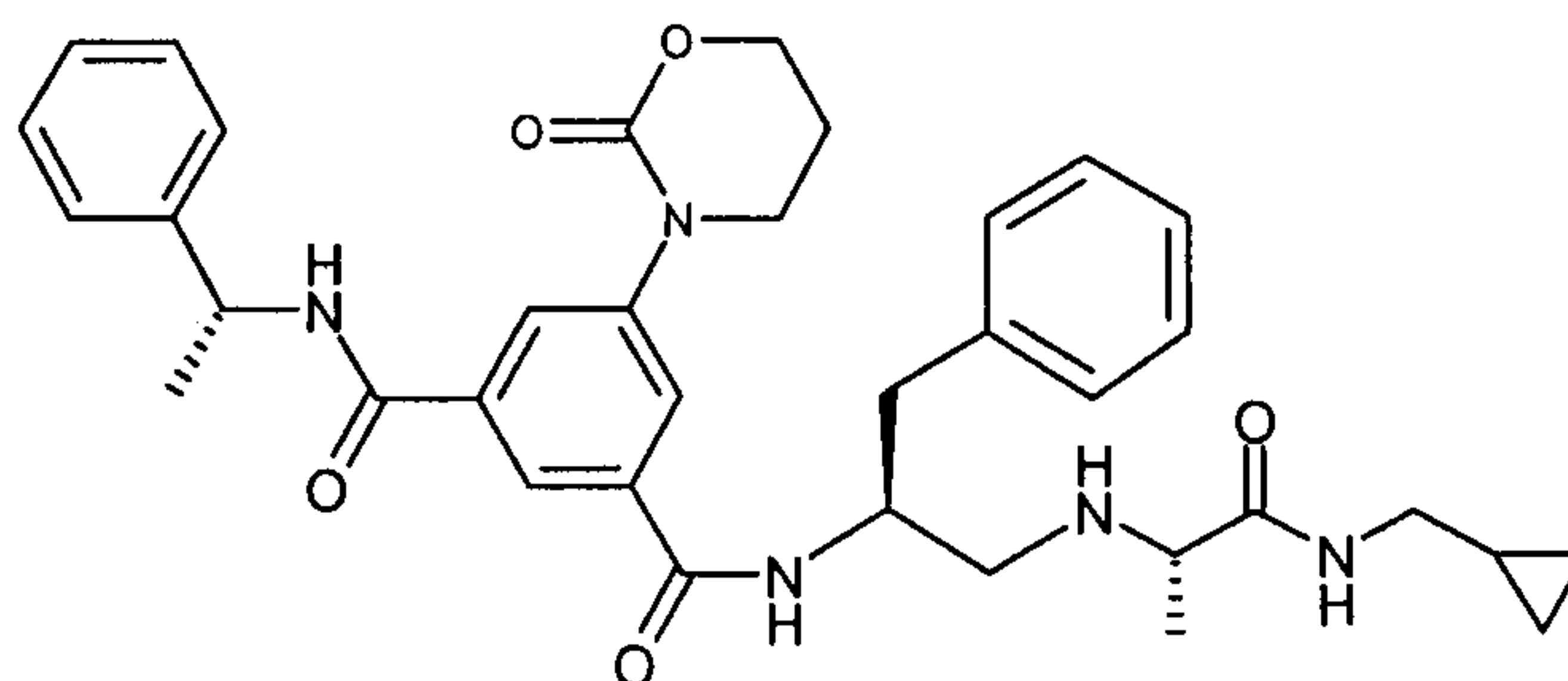
10 ES-MS (M+H)⁺ = 746.8

The following compounds were prepared analogously to **16** from **16-c** and the corresponding oxadiazoles (analogously to **16-f**):

Example	R	
16.1		RT (HPLC4) = 3.86 min ES-MS (M+H) ⁺ = 718
16.2		RT (HPLC4) = 4.11 min ES-MS (M+H) ⁺ = 746
16.3		RT (HPLC4) = 4.32 min ES-MS (M+H) ⁺ = 780

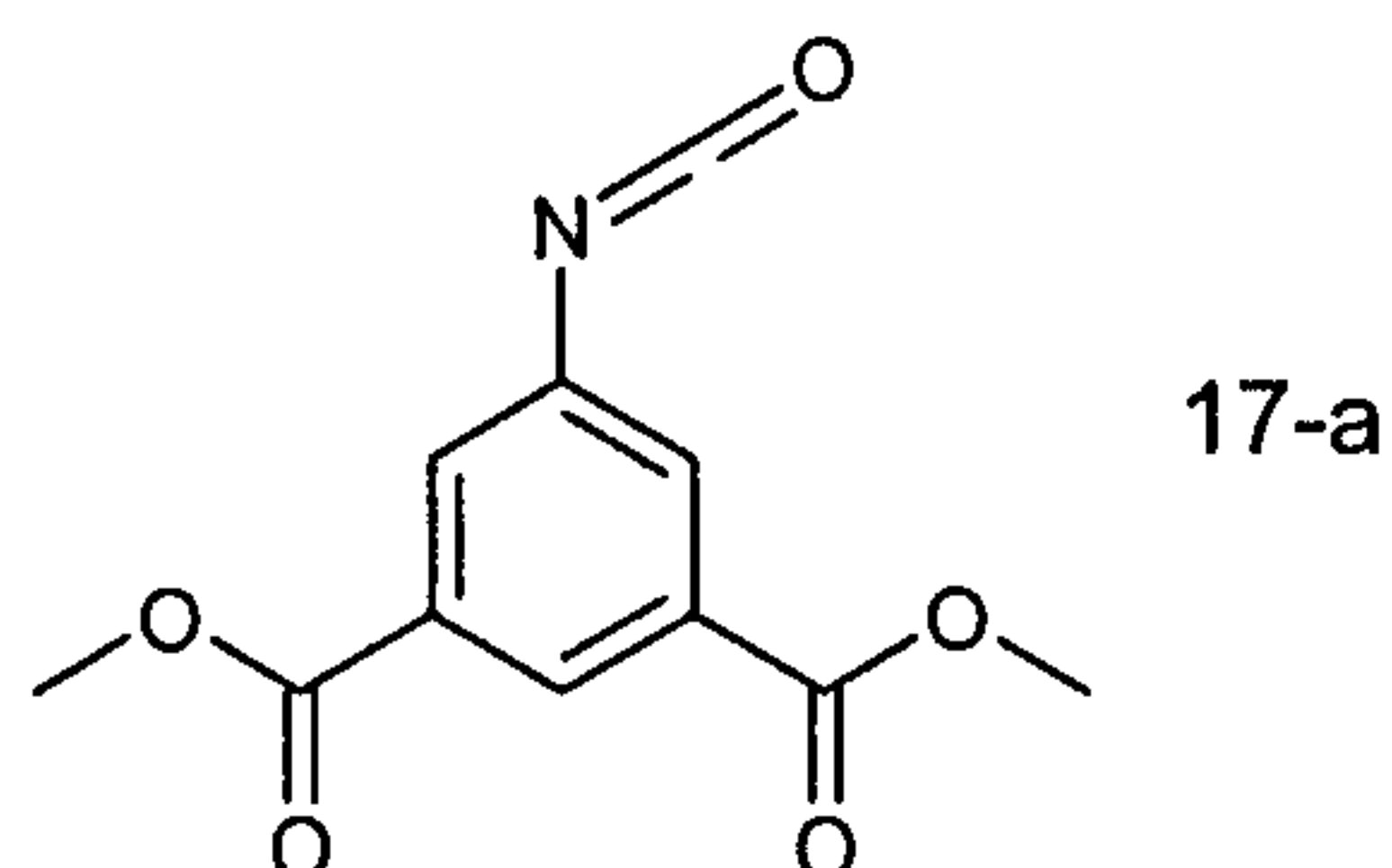
- 186 -

16.4		RT (HPLC4) = 4.04 min ES-MS (M+H) ⁺ = 744
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Example 17:

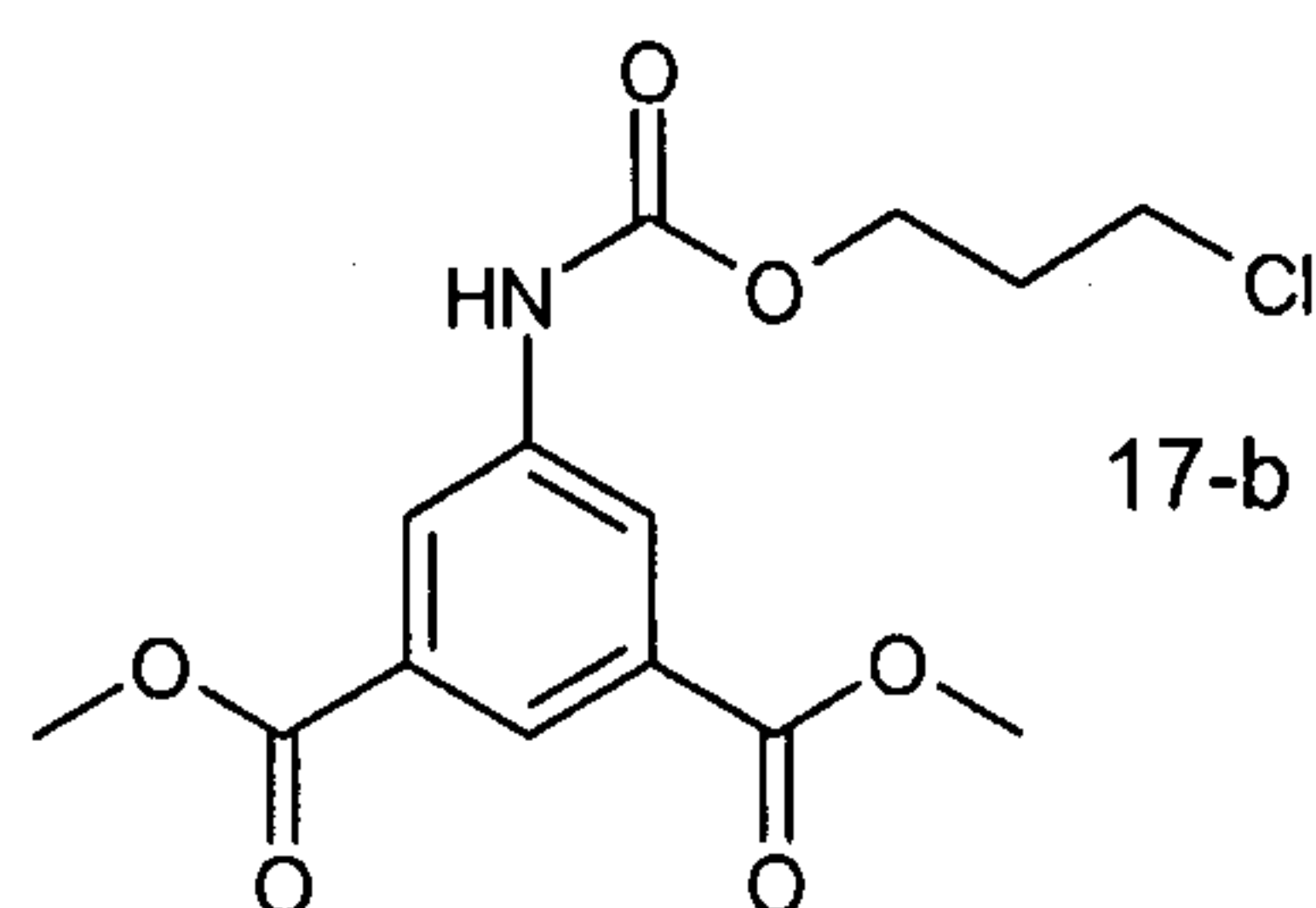
Example 17 was prepared analogously to Example 4 from **17-c** and the corresponding precursors.

ES-MS (M+H)⁺ = 626
RT (HPLC-MS): 2.66 min

a) Preparation of 17-a:

10.46 g (50 mmol) dimethyl 5-amino-isophthalate were dissolved in 200 ml of toluene and combined with 7.3 ml (60 mmol) diphosgene. The reaction solution was heated for 1 h at reflux temperature. Then the reaction solution was evaporated down i. vac., mixed twice with toluene and distilled off again. The residue (10.6 g) was used in **17-b** without being purified.

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b) Preparation of **17-b**:

5

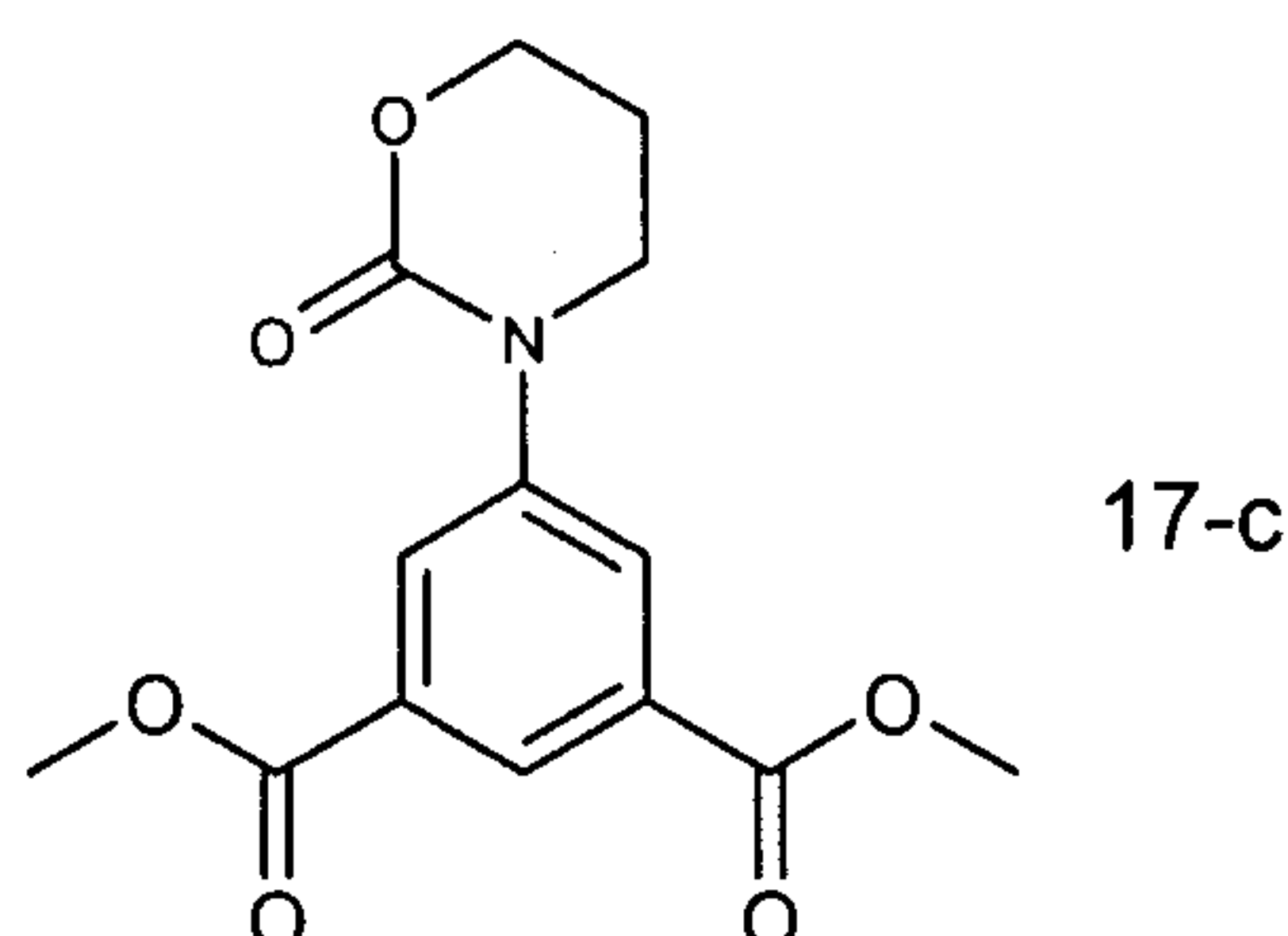
10.6 g (45 mmol) **17-a** were dissolved in 450 ml of toluene and combined with 3.88 ml (45 mmol) 3-chloro-1-propanol. The reaction solution was heated to 75°C for 1 h.

Then the reaction solution was evaporated down i. vac.. The residue was purified by chromatography on silica gel with the eluant (ethyl acetate/heptane 7:3). This yielded

10

8.5 g **17-b** (57%)

ES-MS (M+H)⁺ = 330

c) Preparation of **17-c**:

15

8.49 g (25.8 mmol) **17-b** were dissolved in 140 ml acetonitrile, combined with 4.27 g (30.9 mmol) potassium carbonate and refluxed for 2 h. Then the mixture was filtered to remove any insoluble ingredients, the reaction solution was evaporated down i. vac. And stirred with ether. The crystals formed were filtered off and washed with ether.

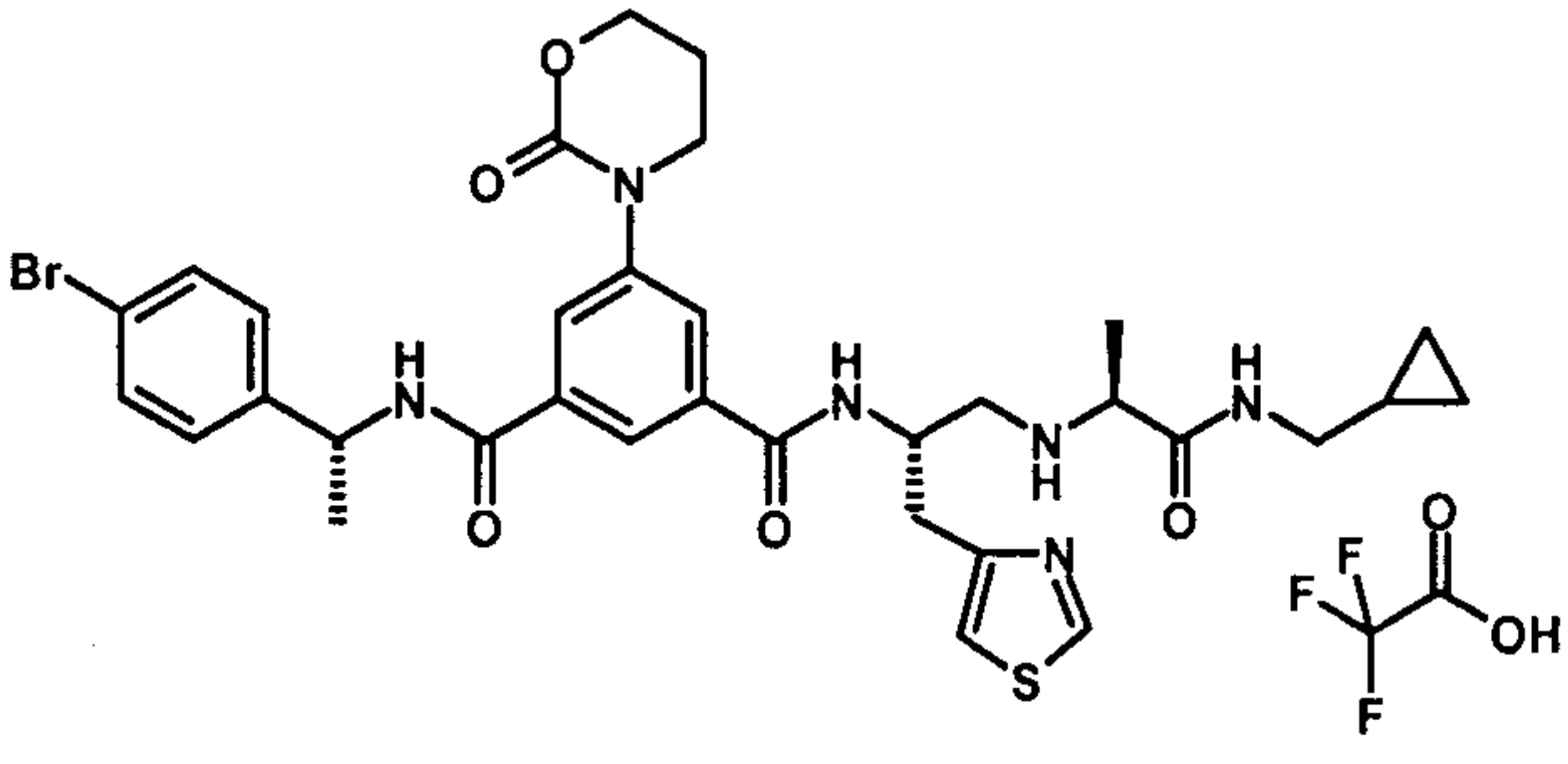
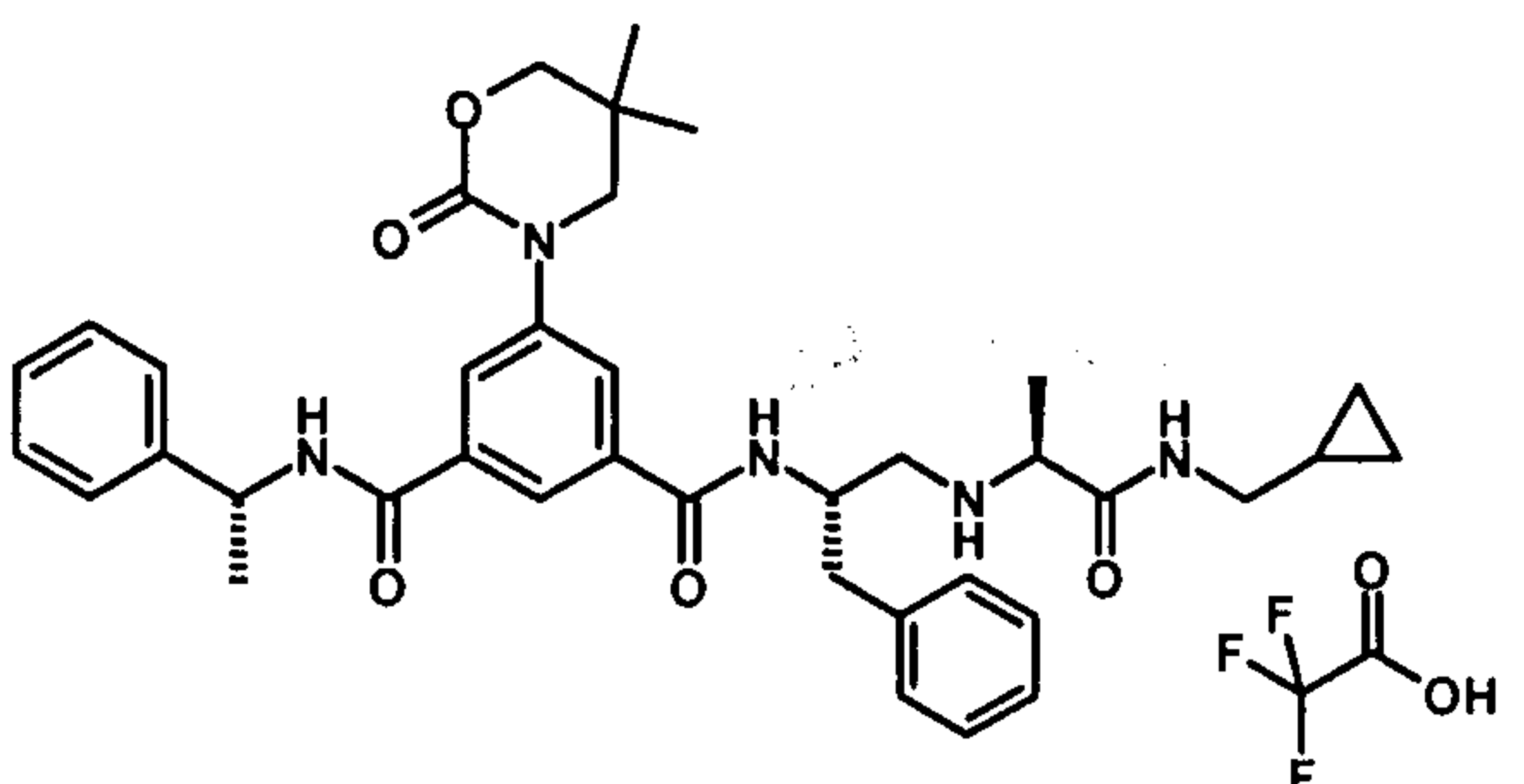
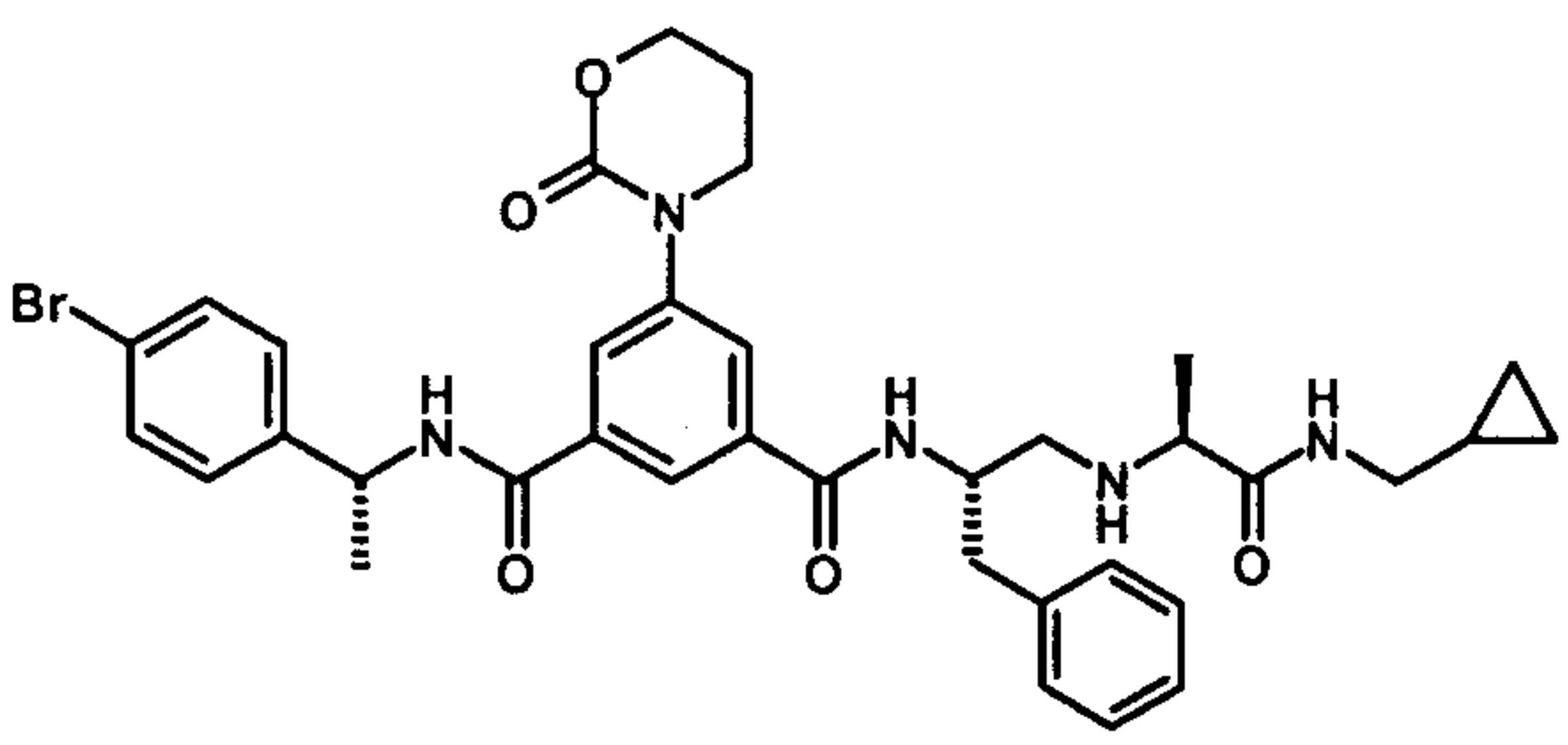
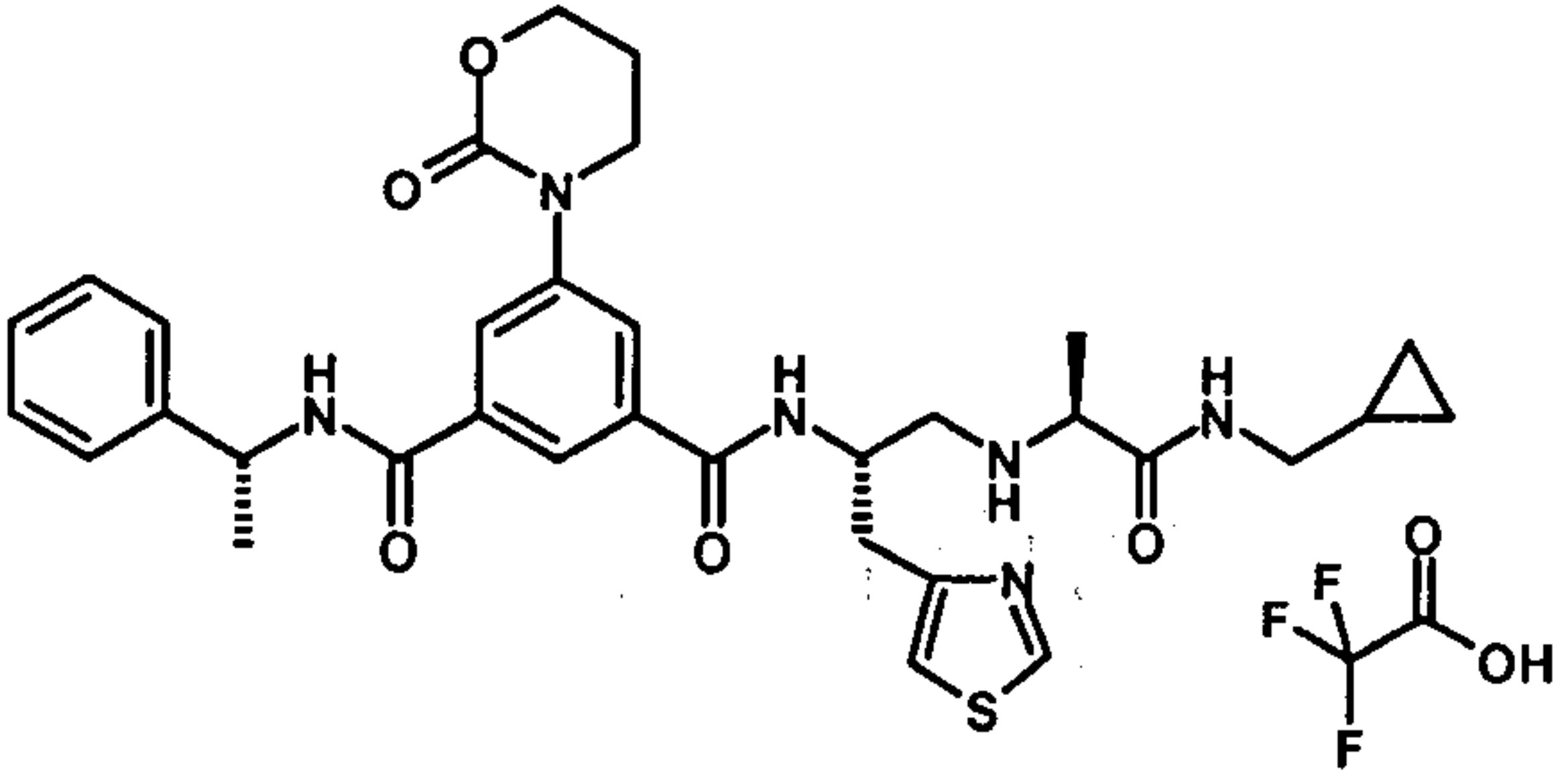
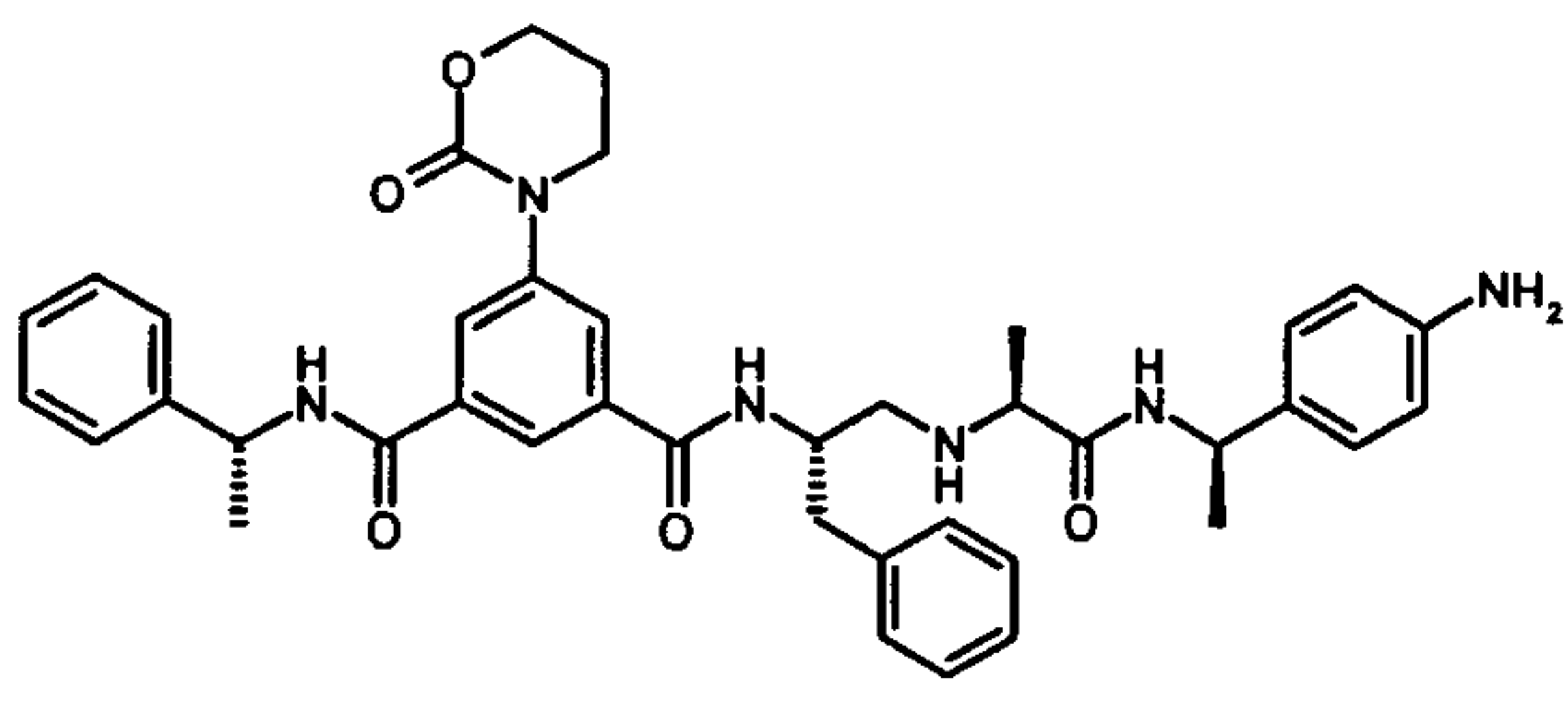
20

This yielded 6.5 g **17-c** (77%)

ES-MS (M+H)⁺ = 294

The following compounds were prepared analogously to **Example 17** by using the corresponding educts:

25

Example		
17.1		RT (HPLC-MS) = 2.62 min. ES-MS (M+H) ⁺ = 711/713 (Br)
17.2		RT (HPLC-MS) = 2.79 min. ES-MS (M+H) ⁺ = 654
17.3		RT (HPLC-MS) = 2.79 min. ES-MS (M+H) ⁺ = 704/706 (Br)
17.4		RT (HPLC-MS) = 2.40 min. ES-MS (M+H) ⁺ = 633
17.5		RT (HPLC-MS) = 2,38 min. ES-MS (M+H) ⁺ = 691

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Example A

Tablets containing 100 mg of active substance

5 Composition

1 tablet contains:

	active substance	100.0 mg
	lactose	80.0 mg
	corn starch	34.0 mg
10	polyvinylpyrrolidone	4.0 mg
	magnesium stearate	<u>2.0 mg</u>
		220.0 mg

Method of Preparation:

15 The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

20 Diameter: 10 mm, biplanar, faceted on both sides and notched on one side.

Example B

Tablets containing 150 mg of active substance

25

Composition

1 tablet contains:

	active substance	150.0 mg
	powdered lactose	89.0 mg
30	corn starch	40.0 mg
	colloidal silica	10.0 mg
	polyvinylpyrrolidone	10.0 mg
	magnesium stearate	<u>1.0 mg</u>
		300.0 mg

35

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Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example C

Hard gelatine capsules containing 150 mg of active substance

Composition

15	1 capsule contains:		
	active substance		150.0 mg
	corn starch (dried	approx.	180.0 mg
	lactose (powdered)	approx.	87.0 mg
	magnesium stearate		<u>3.0 mg</u>
20		approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

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Example D

Suppositories containing 150 mg of active substance

5 Composition

1 suppository contains:

active substance 150.0 mg

polyethyleneglycol 1500 550.0 mg

polyethyleneglycol 6000 460.0 mg

10 polyoxyethylene sorbitan monostearate 840.0 mg

2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously
15 distributed therein and the melt is poured into chilled moulds.

Example E

Ampoules containing 10 mg active substance

20

Composition

active substance 10.0 mg

0.01 N hydrochloric acid q.s.

25 double-distilled water ad 2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made
30 isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

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Example F

Ampoules containing 10 mg active substance

5 Composition

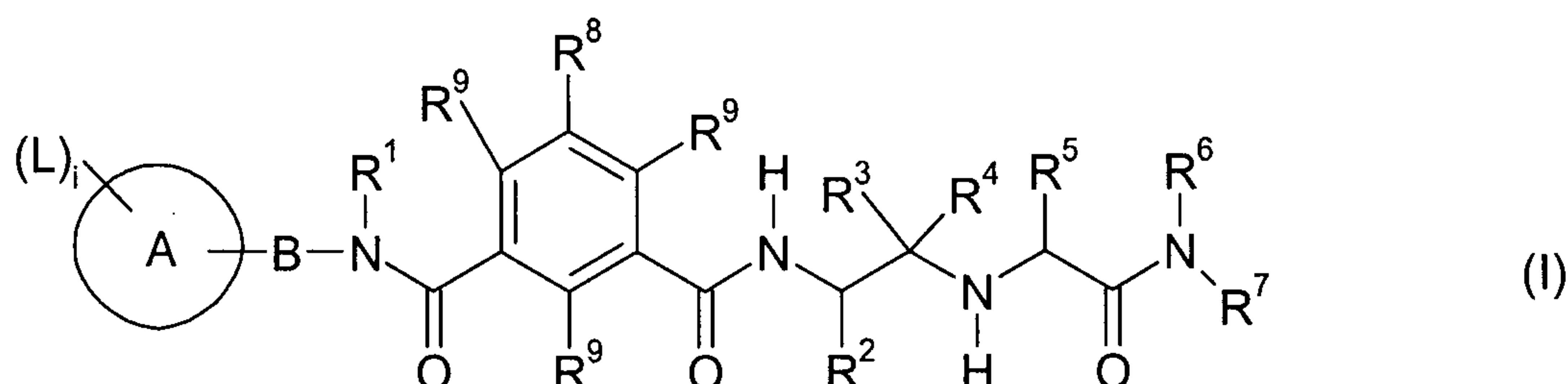
active substance		50.0 mg
0.01 N hydrochloric acid	q.s.	
double-distilled water	ad	10.0 ml

10 Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Claims

1. Compounds of general formula (I)



wherein

A denotes aryl or heteroaryl,
wherein the group A, besides the groups L, may optionally be substituted
by one or more fluorine atoms,

L in each case independently of one another denote hydrogen, fluorine,
chlorine, bromine, iodine, hydroxy, carboxy, formyl, cyano, nitro, F₃C,
HF₂C, FH₂C, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkyl-S, C₁₋₆-alkyl-
S-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₂₋₆-
alkenyl, C₃₋₇-cycloalkyl-C₂₋₆-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-
C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkynyl,
heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl,
heterocyclyl-C₂₋₆-alkynyl, aryl, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-
alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-
C₂₋₆-alkenyl, heteroaryl-C₂₋₆-alkynyl, heteroaryl-C₃₋₇-cycloalkyl, R¹³-O,
R¹³-O-C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-
(R¹²)N, R¹²-SO₂-(R¹²)N, (R¹²)₂N-SO₂ or C₁₋₆-alkyl-SO₂,
wherein the above mentioned groups may optionally be substituted
independently of one another by one or more groups selected from
among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,
cyano, nitro, F₃C, HF₂C, FH₂C, hydroxy-C₁₋₆-alkyl, C₁₋₃-alkyl, C₁₋₆-alkoxy,
(R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO- and HOSO₂-,

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i denotes 0, 1, 2 or 3,

B denotes a C₁₋₄-alkylene bridge,

while the C₁₋₄-alkylene bridge may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, cyano, nitro, F₃C, HF₂C, FH₂C, C₁₋₄-alkyl, C₁₋₆-alkyl-S-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, ,

aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, heteroaryl-

C₃₋₇-cycloalkyl, R¹³-O, (R¹²)₂N-SO₂, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹²-SO₂, R¹²-CO-(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-SO₂, R¹²-CO- and R¹²-SO-, and

wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together, forming a C₃₋₇-cycloalkyl group, and

wherein the above mentioned C₁₋₄-alkyl groups and the C₃₋₇-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, F₃C, C₁₋₃-alkyl, C₁₋₃-alkoxy, R¹³-O-C₁₋₃-alkyl, R¹²-CO(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, (R¹²)₂N-SO₂- and HOSO₂-,

R¹ denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkyl-C₂₋₆-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl, heteroaryl-C₂₋₆-alkynyl or heteroaryl-C₃₋₇-cycloalkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,

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cyano, nitro, F_3C , C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-6} -alkyl, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $(R^{12})_2N-CO$, $(R^{12})_2N-SO_2$, $R^{12}-CO-(R^{12})N$, $R^{12}-SO_2(R^{12})N$ - and $HOSO_2$ -,

5 R^2 denotes C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{1-6} -alkoxy- C_{1-3} -alkyl, C_{1-6} -alkyl-S- C_{1-3} -alkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkyl- C_{2-3} -alkenyl, C_{3-7} -cycloalkyl- C_{2-3} -alkynyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl- C_{2-3} -alkenyl, C_{3-7} -cycloalkenyl- C_{2-3} -alkynyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heterocyclyl- C_{2-3} -alkenyl, heterocyclyl- C_{2-3} -alkynyl, aryl, aryl- C_{1-3} -alkyl, aryl- C_{2-3} -alkenyl, aryl- C_{2-3} -alkynyl, aryl- C_{3-7} -cycloalkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, heteroaryl- C_{2-3} -alkenyl, heteroaryl- C_{2-3} -alkynyl or heteroaryl- C_{3-7} -cycloalkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, F_3C , HF_2C , FH_2C - hydroxy, oxo, carboxy, formyl, cyano, nitro, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $HOSO_2$, C_{1-3} -alkyl, C_{1-6} -alkyl-S- C_{1-3} -alkyl, $(R^{12})_2N-SO_2$, $R^{12}-CO-(R^{12})N$, $R^{12}-SO_2(R^{12})N$, $(R^{12})_2N-C_{1-3}$ -alkyl, $(R^{12})_2N-CO$, $R^{13}-O$ - and $R^{13}-O-C_{1-3}$ -alkyl-,

20 R^3 , R^4 in each case independently of one another denote hydrogen, C_{1-6} -alkyl, fluorine, F_3C , HF_2C or FH_2C ,

25 R^5 denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-4} -alkyl, C_{3-7} -cycloalkyl- C_{2-4} -alkenyl, C_{3-7} -cycloalkyl- C_{2-4} -alkynyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-4} -alkyl, C_{3-7} -cycloalkenyl- C_{2-4} -alkenyl, C_{3-7} -cycloalkenyl- C_{2-4} -alkynyl, heterocyclyl, heterocyclyl- C_{1-4} -alkyl, heterocyclyl- C_{2-4} -alkenyl, heterocyclyl- C_{2-4} -alkynyl, aryl, aryl- C_{1-4} -alkyl, aryl- C_{2-4} -alkenyl, aryl- C_{2-4} -alkynyl, aryl- C_{3-7} -cycloalkyl, heteroaryl, heteroaryl- C_{1-4} -alkyl, heteroaryl- C_{2-4} -alkenyl, heteroaryl- C_{2-4} -alkynyl or heteroaryl- C_{3-7} -cycloalkyl,

30 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,

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cyano, nitro, C₁₋₃-alkyl, C₁₋₆-alkoxy, C₁₋₃-alkyl-S, aryl, heteroaryl, heteroaryl-C₁₋₃-alkyl, aryl-C₁₋₆-alkyl, R¹²-CO-(R¹²)N, R¹²-SO₂(R¹²)N- (R¹²)₂N-SO₂, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO- and HOSO₂-,

5 R⁶ denotes C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₃₋₇-
cycloalkyl-C₂₋₄-alkenyl, C₃₋₇-cycloalkyl-C₂₋₄-alkynyl, C₃₋₇-cycloalkenyl,
C₃₋₇-cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-
cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl,
heterocyclyl-C₂₋₄-alkenyl, heterocyclyl-C₂₋₄-alkynyl, aryl-C₂₋₄-alkyl-
10 (R¹²)₂N-aryl, (R¹²)₂N-aryl-C₁₋₃-alkyl, aryl-C₂₋₄-alkenyl, aryl-C₂₋₄-alkynyl,
aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, heteroaryl-C₂₋₄-
alkenyl, heteroaryl-C₂₋₄-alkynyl or heteroaryl-C₃₋₇-cycloalkyl,
wherein the above mentioned groups may optionally be substituted
independently of one another by one or more groups selected from
15 among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl,
cyano, nitro, C₁₋₃-alkyl, C₃₋₇-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-
alkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, aryl, heteroaryl, heteroaryl-C₁₋₃-alkyl, aryl-
C₁₋₆-alkyl, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹²-CO-(R¹²)N,
(R¹²)₂N-CO-N(R¹²), (R¹²)₂N-SO₂, R¹²-SO₂-(R¹²)N- and HOSO₂-,

20 R⁷ denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy-C₁₋₃-
alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl-C₁₋₃-alkyl,
aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl,
wherein the above mentioned groups may optionally be substituted
independently of one another by one or more groups selected from
25 among fluorine, chlorine, bromine, iodine, cyano, hydroxy, C₁₋₃-alkyl,
C₁₋₆-alkoxy- and (R¹²)₂N-,

30 R⁸ denotes hydrogen, fluorine, chlorine, bromine, iodine, cyano, C₁₋₆-alkyl,
C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, C₃₋₇-
cycloalkyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkyl-C₂₋₆-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-
cycloalkenyl-C₁₋₆-alkyl, C₃₋₇-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₇-cycloalkenyl-
C₂₋₆-alkynyl, heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heterocyclyl-C₂₋₆-
alkenyl, heterocyclyl-C₂₋₆-alkynyl, aryl, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl,

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aryl-C₂₋₆-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl, heteroaryl-C₂₋₆-alkynyl, heteroaryl-C₃₋₇-cycloalkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, R¹⁰-SO₂-(R¹¹)N or R¹⁰-CO-(R¹¹)N,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from

among C₁₋₆-alkyl, fluorine, chlorine, bromine, hydroxy, oxo, carboxy,

formyl, cyano, nitro, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkyl-S, C₁₋₆-alkyl-S-

C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl,

heterocyclyl, heterocyclyl-C₁₋₆-alkyl, heteroaryl, heteroaryl-C₁₋₆-alkyl,

R¹³-O, R¹³-O-CO, R¹³-CO, R¹³-O-CO-(R¹²)N, (R¹²)₂N-CO-O, R¹³-O-C₁₋₃-

alkyl, (R¹²)₂N, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, (R¹²)₂N-

SO₂, (R¹²)₂N-SO₂-(R¹²)N, R¹²-SO₂, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O,

FH₂C-O- and R¹²-SO₂-(R¹²)N-,

R⁹ in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₃-alkyl, R¹³-O or (R¹²)₂N,

while the above mentioned C₁₋₃-alkyl group may optionally be substituted by one or more fluorine atoms,

R¹⁰ denotes C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₄-alkyl, C₃₋₇-cycloalkyl-C₂₋₄-alkenyl, C₃₋₇-cycloalkyl-C₂₋₄-alkynyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₄-alkyl, C₃₋₇-cycloalkenyl-C₂₋₄-alkenyl, C₃₋₇-cycloalkenyl-C₂₋₄-alkynyl, heterocyclyl, heterocyclyl-C₁₋₄-alkyl, heterocyclyl-C₂₋₄-alkenyl, heterocyclyl-C₂₋₄-alkynyl, aryl, aryl-C₁₋₄-alkyl, aryl-C₂₋₄-alkenyl, aryl-C₂₋₄-alkynyl, aryl-C₃₋₇-cycloalkyl, heteroaryl, heteroaryl-C₁₋₄-alkyl, heteroaryl-C₂₋₄-alkenyl, heteroaryl-C₂₋₄-alkynyl, heteroaryl-C₃₋₇-cycloalkyl or (R¹²)₂N,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from

among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, formyl, cyano,

nitro, C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, R¹³-O, R¹³-O-C₁₋₃-

alkyl, R¹²-CO(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-SO₂, R¹²-SO₂, R¹²-SO,

R¹²-S, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl- and (R¹²)₂N-CO-,

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R^{11} denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heterocyclyl- C_{2-3} -alkenyl, heterocyclyl- C_{2-3} -alkynyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, heteroaryl- C_{2-3} -alkenyl or heteroaryl- C_{2-3} -alkynyl,
wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, $(R^{12})_2N-SO_2$, $R^{12}-SO_2$, $R^{12}-SO$, $R^{12}-S$, $(R^{12})_2N$, $(R^{12})_2N-C_{1-3}$ -alkyl- and $R^{12}CO-$,

or

R^{10} and R^{11} together form a C_{2-6} -alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atom linked to R^{11} and the SO_2- or $CO-$ group linked to R^{10} ,
wherein one or two $-CH_2$ groups of the C_{2-6} -alkylene bridge may be replaced independently of one another by Q, S, SO, SO_2 or $-N(R^{12})-$ such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and
wherein the C atoms of the above mentioned C_{2-6} -alkylene bridge may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, formyl, cyano, F_3C , C_{1-6} -alkyl, C_{1-6} -alkoxy, oxo and nitro,

R^{12} in each case independently of one another denote hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy- C_{1-3} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl, wherein
two C_{1-6} -alkyl groups bound to the same nitrogen atom may together form a C_{2-6} -alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atoms linked to the groups R^{12} ,

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while a $-\text{CH}_2$ group of the C_{2-6} -alkylene bridge may be replaced by O, S or $-\text{N}(\text{R}^{13})-$, and

wherein the above mentioned groups and the heterocyclic ring may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, C_{1-3} -alkoxy, $(\text{R}^{13})_2\text{N}-\text{CO}$ or $(\text{R}^{13})_2\text{N}-$, and

R^{13} in each case independently of one another denote hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl,

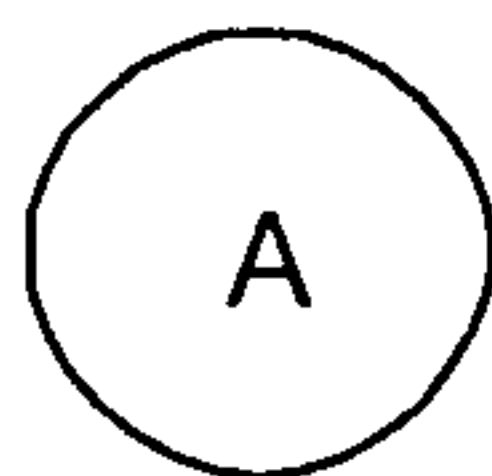
wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, oxo, carboxy, formyl, cyano, nitro, C_{1-3} -alkyl- and C_{1-3} -alkoxy-,

the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates and solvates thereof.

2. Compounds according to claim 1, characterised in that

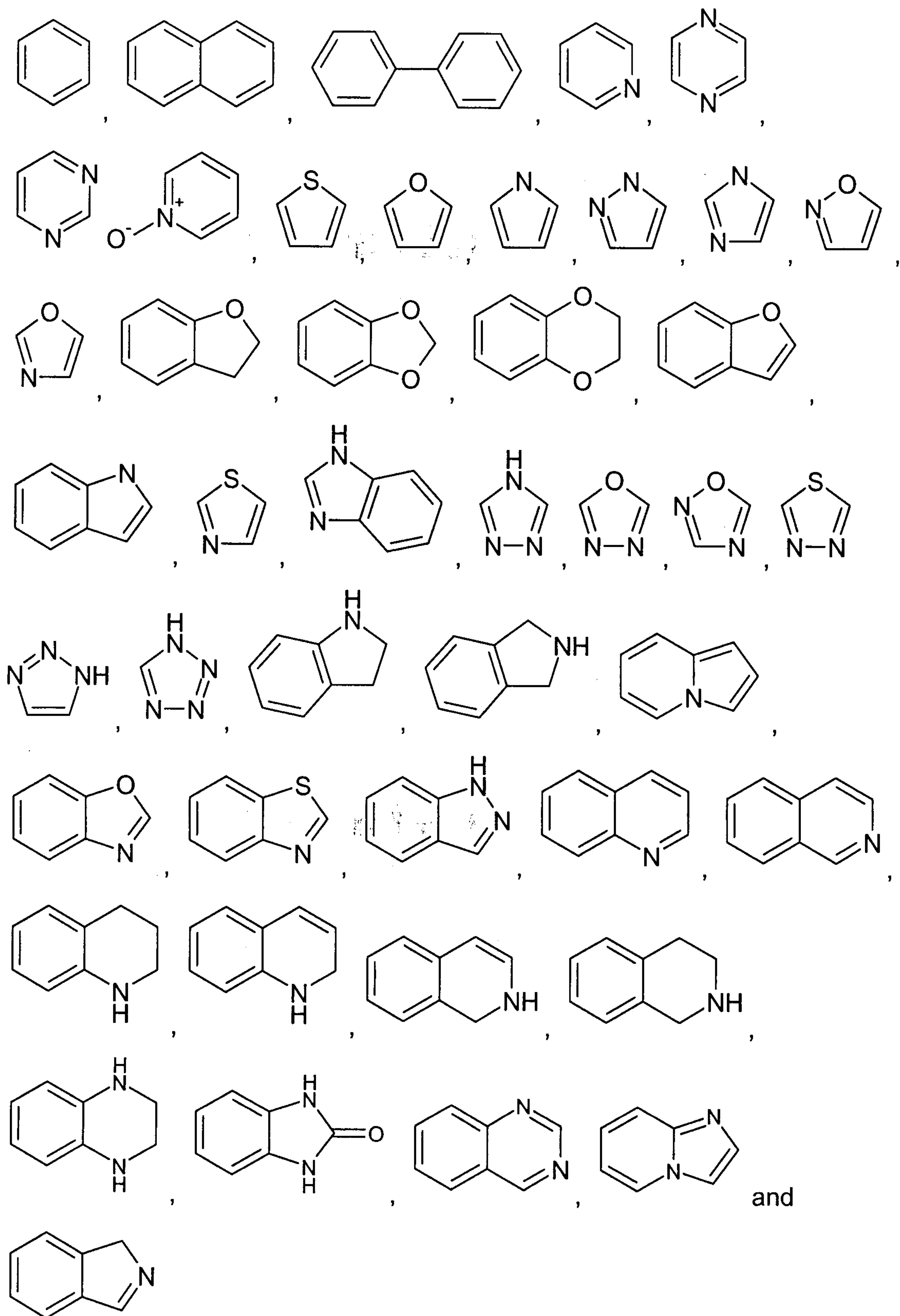
A denotes phenyl or a 5- or 6-membered aromatic heteroaryl group which contains 1, 2 or 3 heteroatoms selected from N, O and S.

3. Compounds according to claim 1, characterised in that the group



is selected from among

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4. Compounds according to claim 1, characterised in that

A denotes phenyl, thienyl, thiazolyl, pyrazolyl or pyridyl.

5. Compounds according to one or more of claims 1 to 4, characterised in that

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, F_3C , HF_2C , FH_2C , C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl, R^{13} -O, R^{13} -O- C_{1-3} -alkyl, $(R^{12})_2N$, $(R^{12})_2N$ -CO, R^{12} -CO- $(R^{12})N$, $(R^{12})_2N$ -CO- $(R^{12})N$, $(R^{12})_2N$ -SO₂, R^{12} -SO₂- $(R^{12})N$ or C_{1-3} -alkyl-SO₂,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, F_3C , HF_2C , FH_2C , hydroxy- C_{1-3} -alkyl, C_{1-3} -alkyl, C_{1-3} -alkoxy, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl- and $(R^{12})_2N$ -CO-, and

i denotes 0, 1 or 2.

6. Compounds according to one or more of claims 1 to 4, characterised in that

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, cyano, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, phenyl, $(R^{12})_2N$, $(R^{12})_2N$ -CO, R^{12} -CO- $(R^{12})N$, $(R^{12})_2N$ -CO- $(R^{12})N$, R^{12} -SO₂- $(R^{12})N$ or $(R^{12})_2N$ -SO₂,

wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms, and

i denotes 0, 1 or 2.

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7. Compounds according to one or more of claims 1 to 4, characterised in that

L in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, hydroxy, C₁₋₄-alkyl or C₁₋₄-alkoxy, wherein the above mentioned groups may optionally be substituted by one or more fluorine atoms, and

i denotes 0, 1 or 2.

8. Compounds according to one or more of claims 1 to 7, characterised in that

B denotes a C₁₋₄-alkylene bridge, wherein the C₁₋₄-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, cyano, nitro, F₃C, HF₂C, FH₂C, C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, R¹³-O, (R¹²)₂N-SO₂- and (R¹²)₂N- may be substituted, and wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together, forming a C₃₋₇-cycloalkyl group, and wherein the above mentioned groups and the C₃₋₇-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, F₃C, C₁₋₃-alkyl, C₁₋₃-alkoxy and R¹³-O-C₁₋₃-alkyl.

9. Compounds according to one or more of claims 1 to 7, characterised in that

B denotes a C₁₋₄-alkylene bridge, wherein the C₁₋₄-alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, C₁₋₄-alkyl, phenyl or benzyl, and

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wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₄-alkylene bridge may be joined together, forming a C₃₋₆-cycloalkyl group, and

wherein the above mentioned groups and the C₃₋₆-cycloalkyl group formed from the C₁₋₄-alkyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C₁₋₃-alkoxy.

10. Compounds according to one or more of claims 1 to 7, characterised in that

B denotes a C₁₋₂-alkylene bridge,

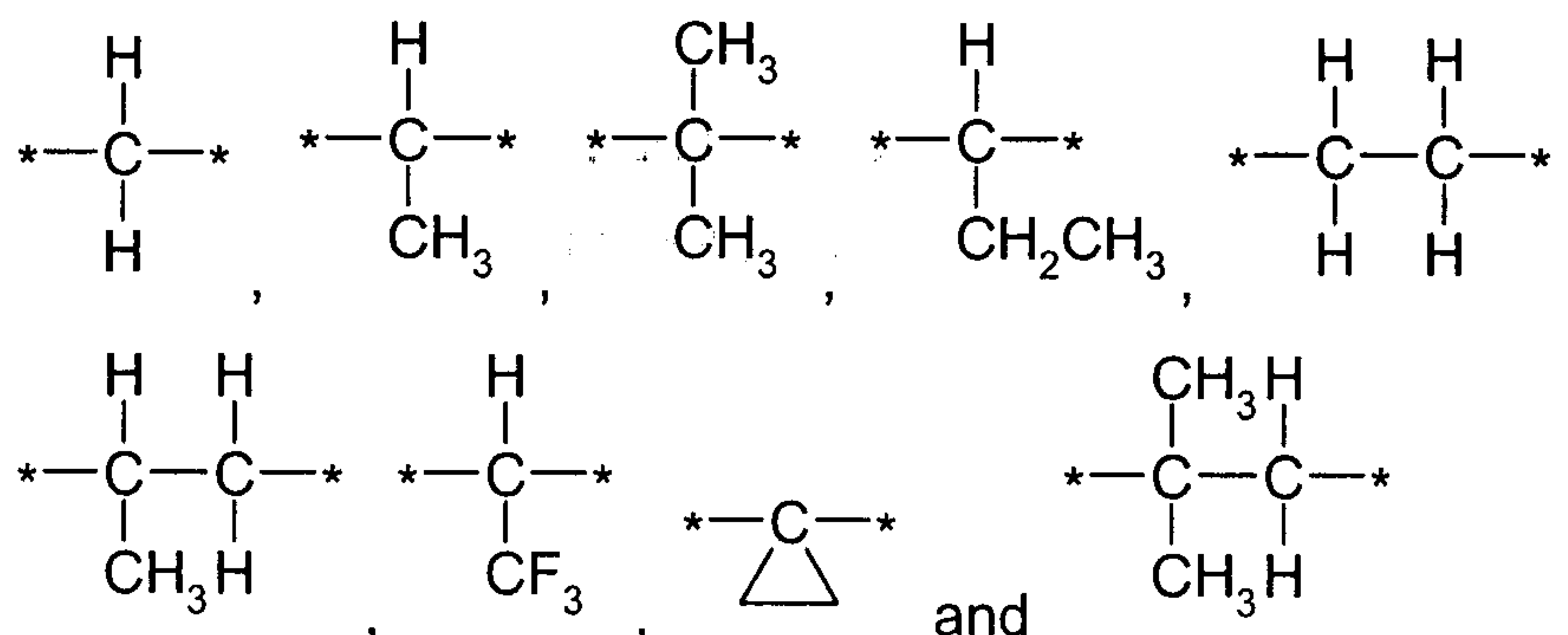
wherein the C₁₋₂-alkylene bridge may optionally be substituted by one or more C₁₋₄-alkyl groups, and

wherein two C₁₋₄-alkyl groups bound to the same carbon atom of the C₁₋₂-alkylene bridge may be joined together forming a cyclopropyl group, and

wherein one or more hydrogen atoms of the above mentioned C₁₋₂-alkylene bridge and/or of the C₁₋₄-alkyl groups and/or the cyclopropyl group formed therefrom may optionally be replaced by one or more fluorine atoms.

11. Compounds according to one or more of claims 1 to 7, characterised in that

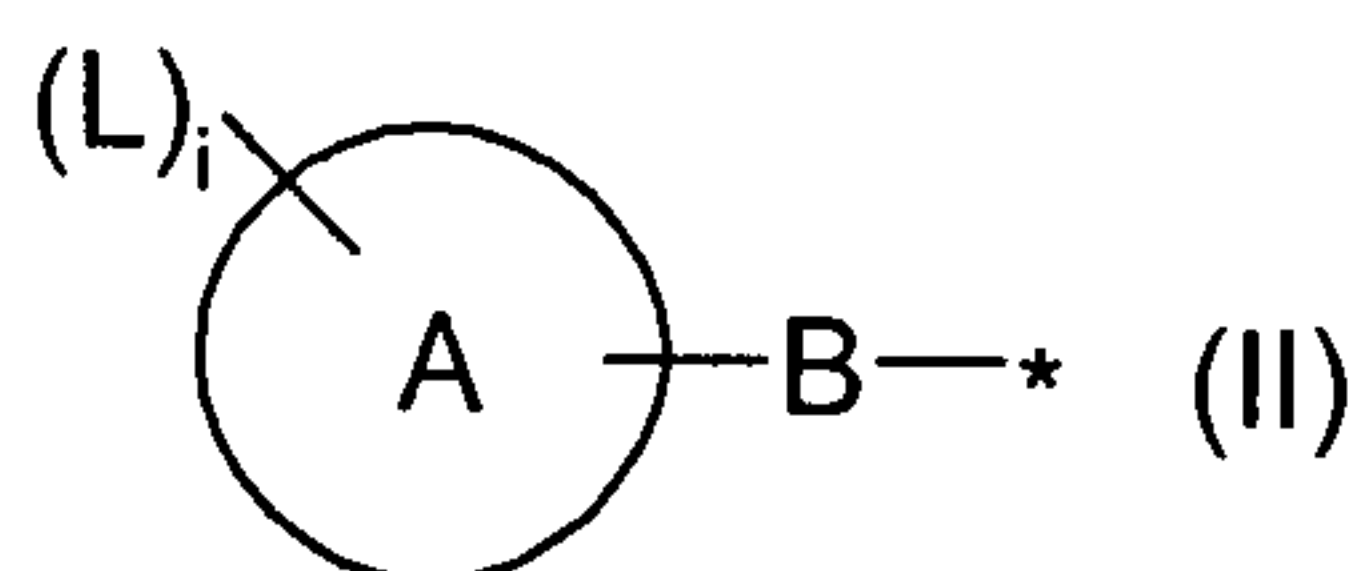
B is selected from among



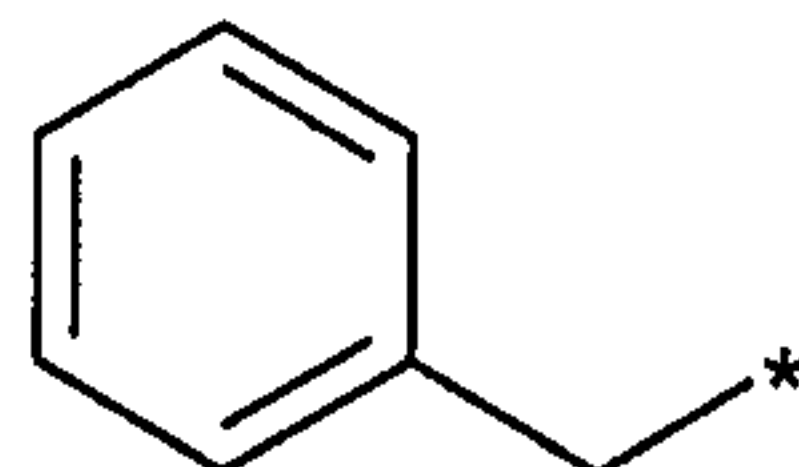
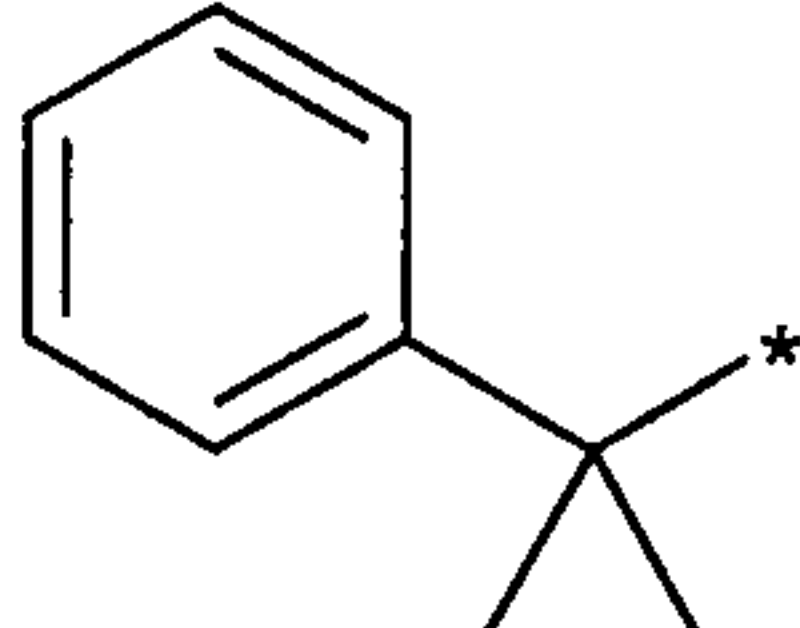
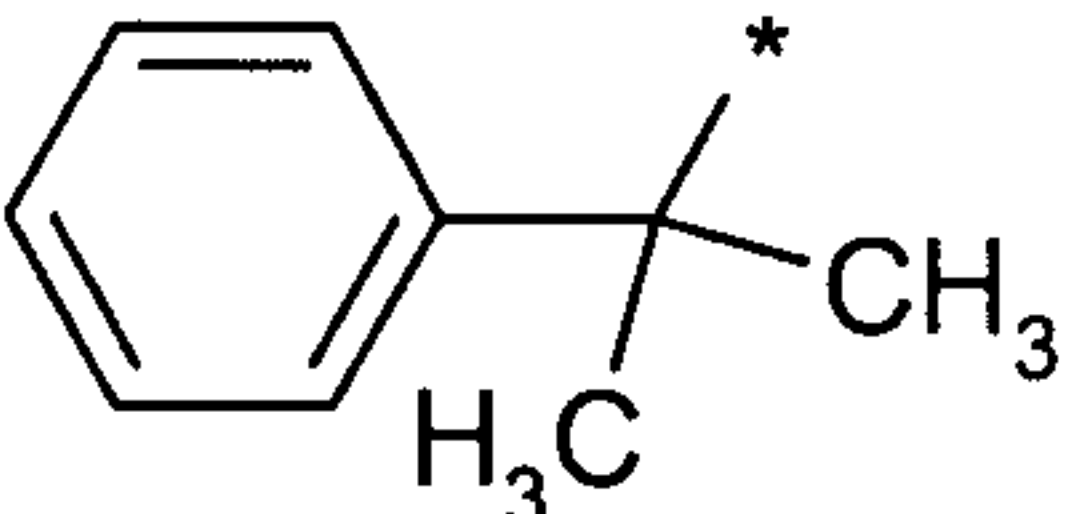
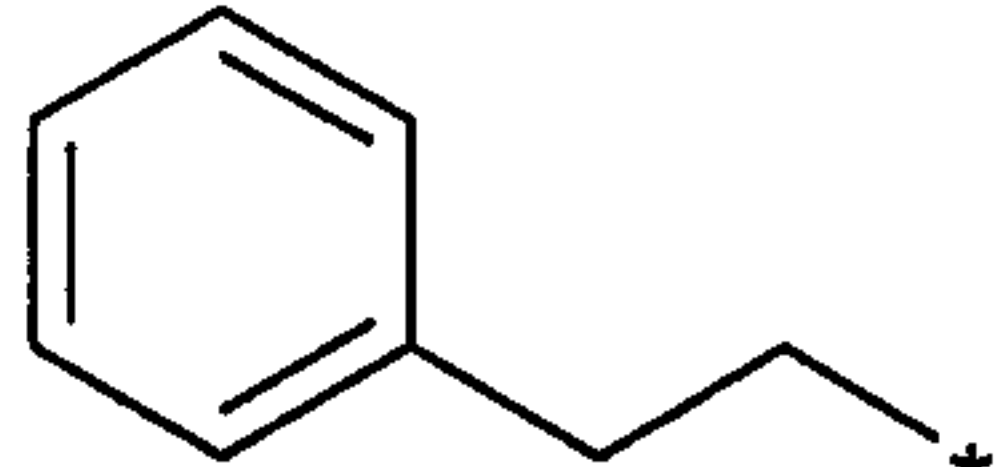
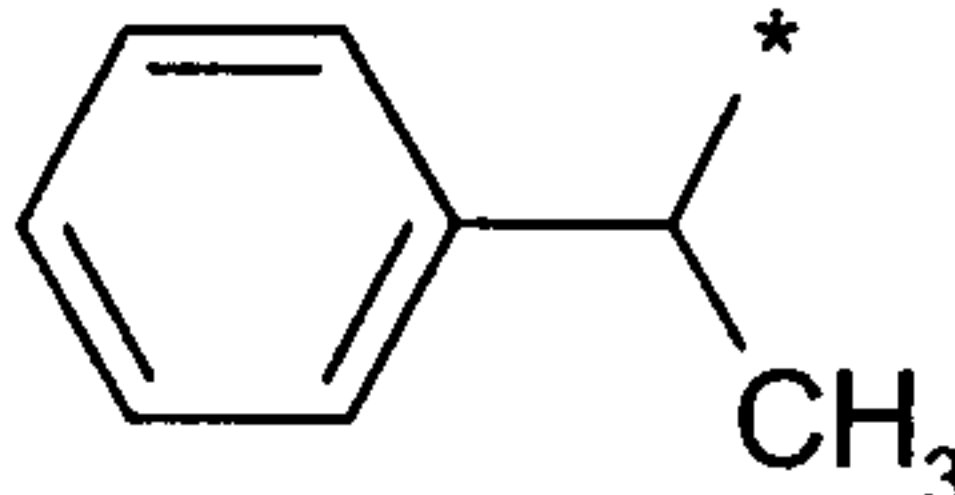
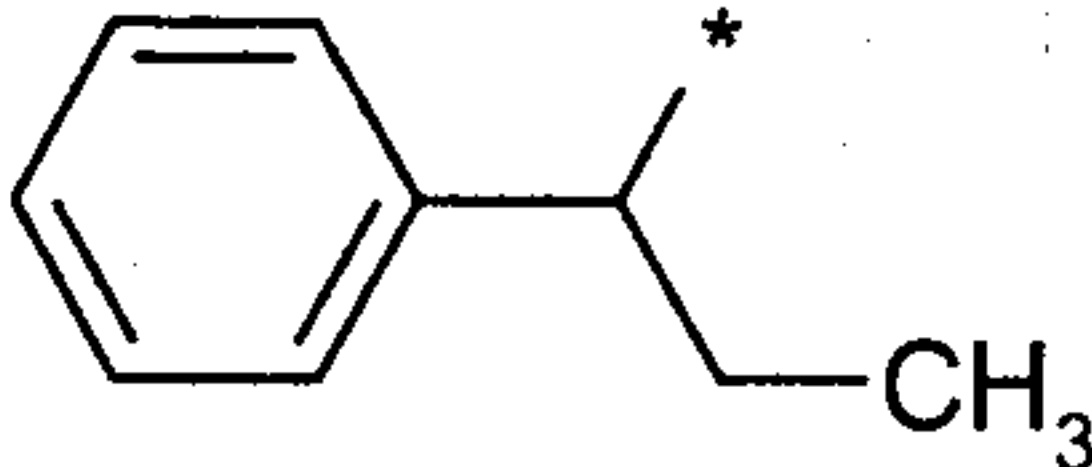
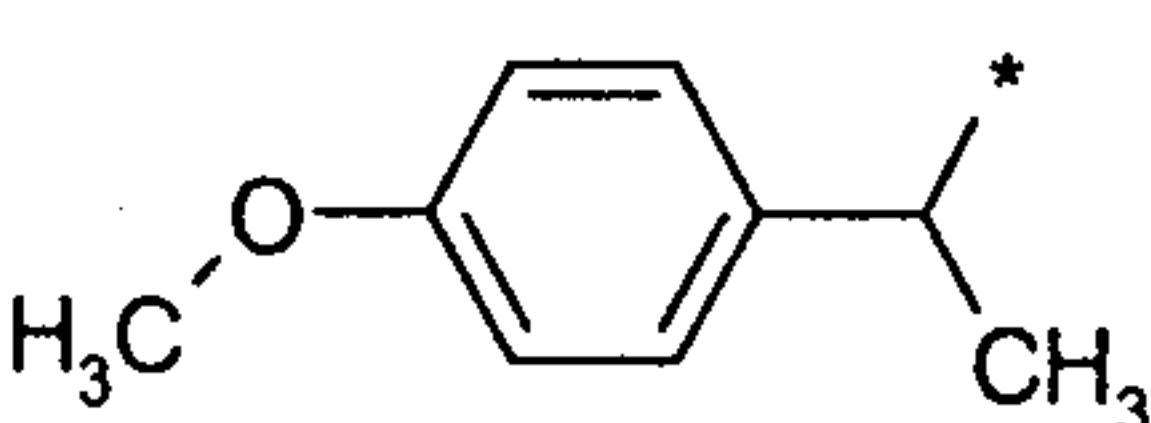
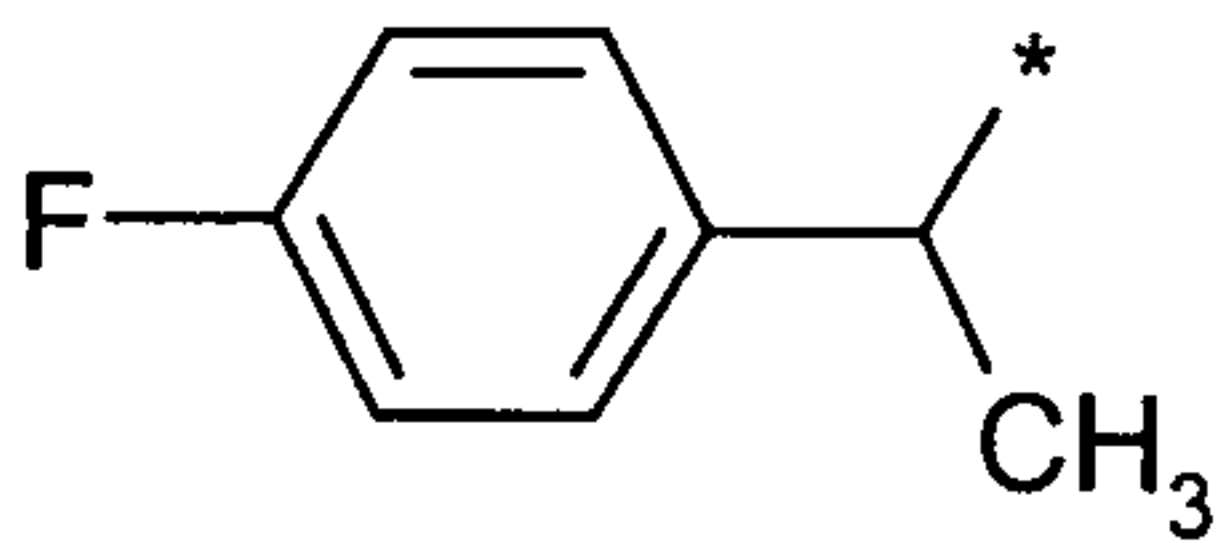
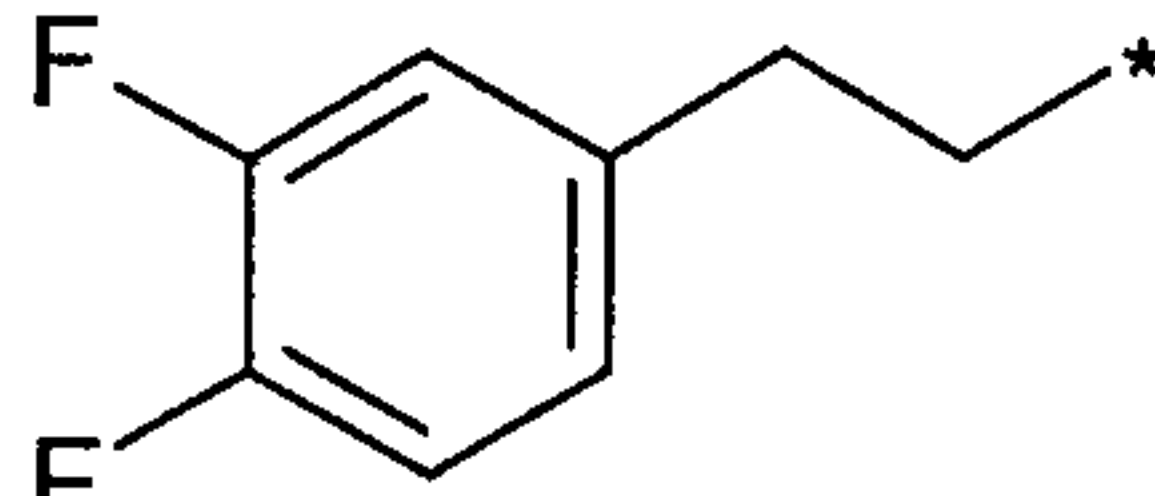
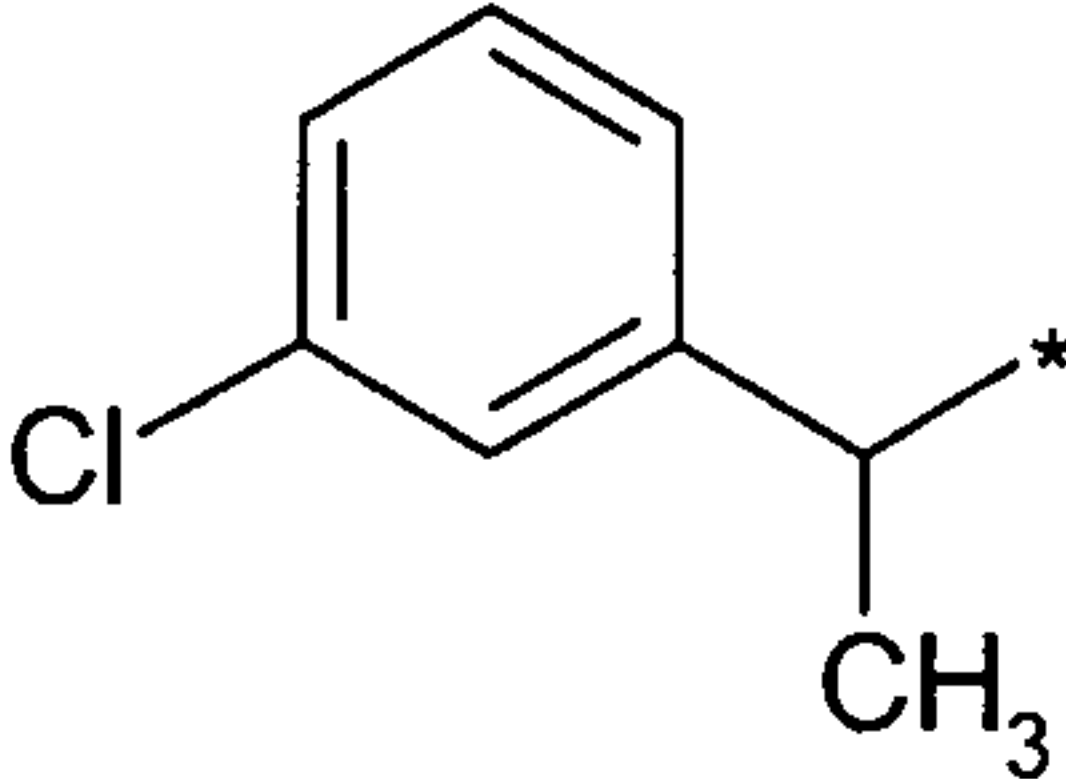
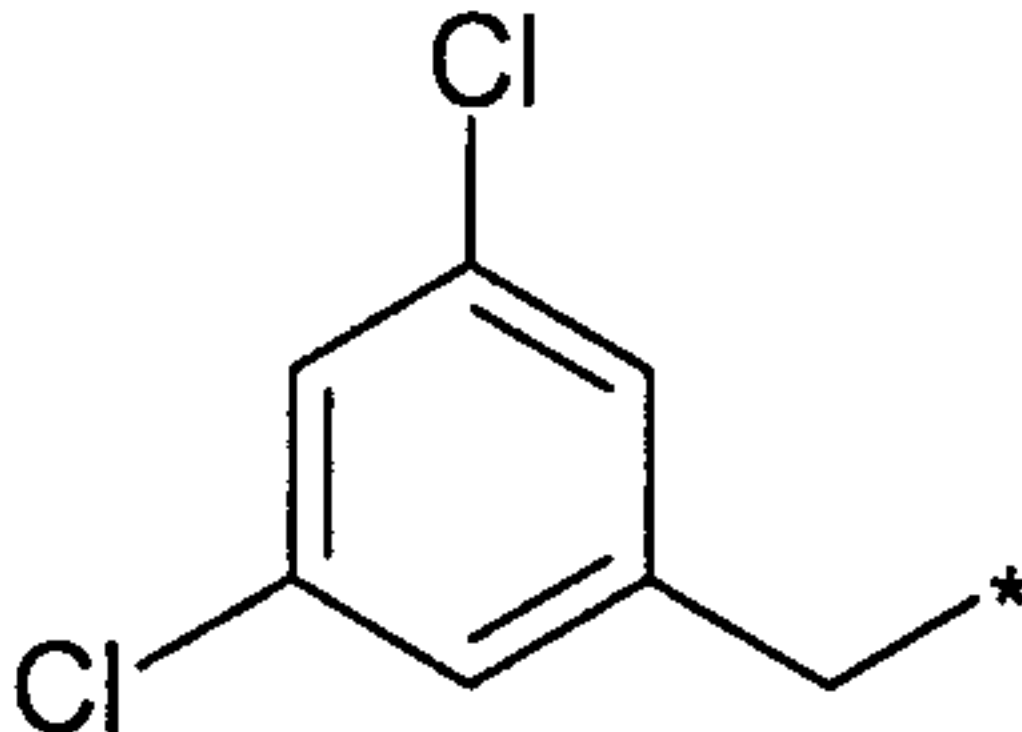
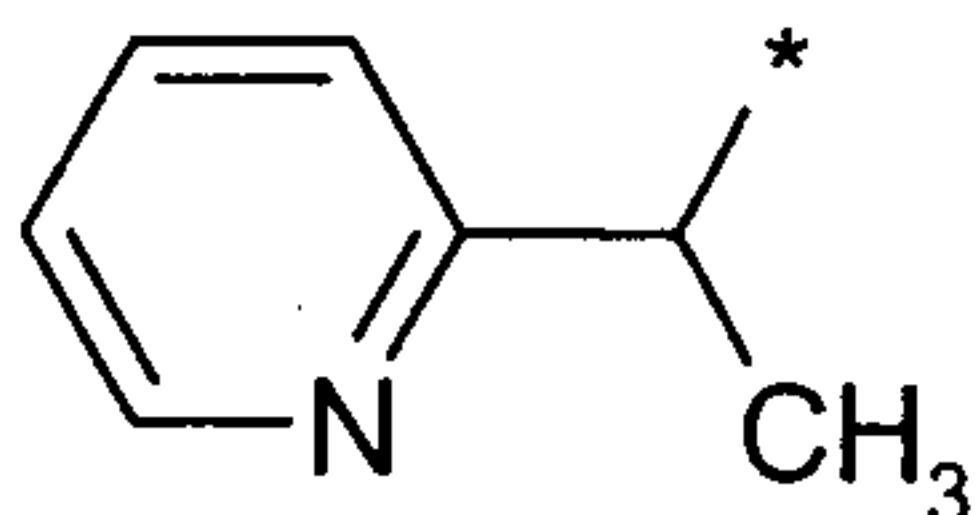
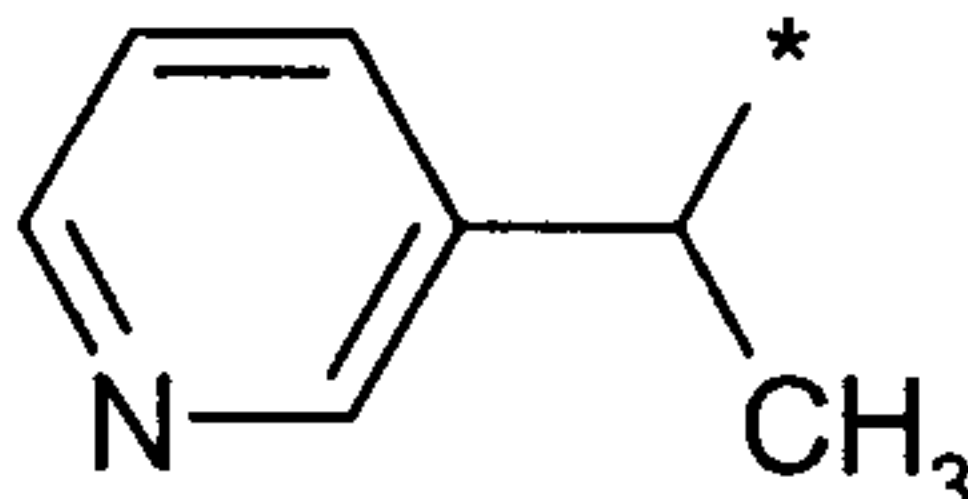
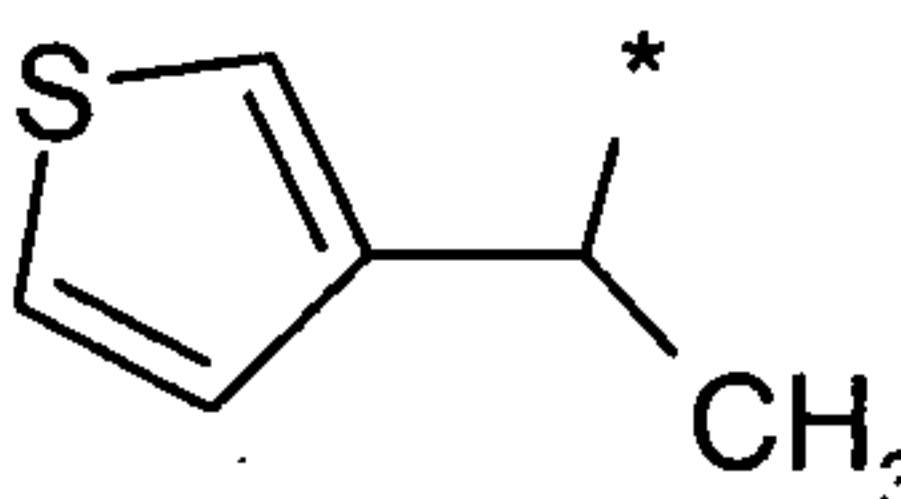
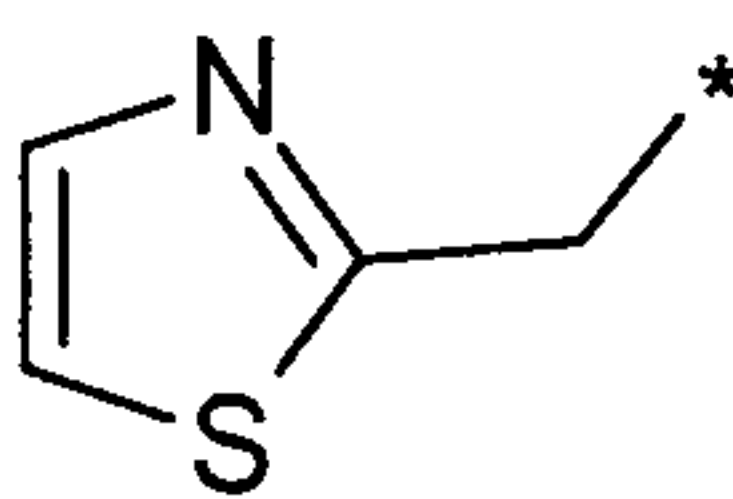
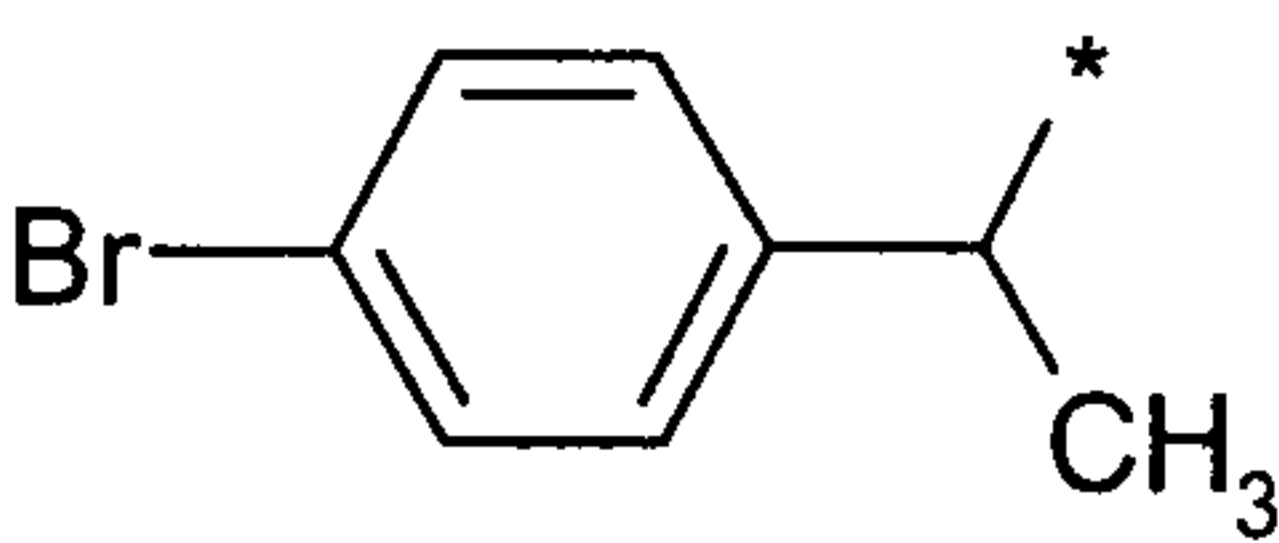
wherein one or more hydrogen atoms may optionally be replaced by fluorine.

12. Compounds according to claim 1, characterised in that the partial formula (II)

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is selected from among

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13. Compounds according to one or more of claims 1 to 12, characterised in that

R^1 denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, F_3C , C_{1-3} -alkyl, C_{1-3} -alkoxy- and hydroxy- C_{1-3} -alkyl.

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14. Compounds according to one or more of claims 1 to 12, characterised in that

R¹ denotes hydrogen, C₁₋₄-alkyl, C₃₋₄-alkenyl, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl,

5 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy and C₁₋₃-alkoxy.

15. Compounds according to one or more of claims 1 to 14, characterised in that

10 R² denotes C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₁₋₆-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkyl-S-C₁₋₃-alkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl,

15 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, F₃C, HF₂C, FH₂C, hydroxy, carboxy, cyano, nitro, C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-SO₂, R¹²-CO-(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹³-O- and R¹³-O-C₁₋₃-alkyl.

16. Compounds according to one or more of claims 1 to 14, characterised in that

25 R² denotes C₁₋₆-alkyl, C₂₋₆-alkynyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl, heterocyclyl-C₁₋₃-alkyl, phenyl, phenyl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein by the above mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3 heteroatoms selected from among N, O and S and

30 wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, cyano, hydroxy, C₁₋₃-alkyl, F₃C, HF₂C, FH₂C, H₂N- and C₁₋₃-alkoxy.

17. Compounds according to one or more of claims 1 to 14, characterised in that

R^2 denotes n-propyl, n-butyl, 2-propynyl, 2-butylnyl, cyclohexylmethyl, cyclopentylmethyl, phenylmethyl, 2-phenylethyl, pyridylmethyl, furanylmethyl, thienylmethyl or thiazolylmethyl, wherein the above mentioned propyl, butyl, propynyl, butynyl, cyclohexylmethyl and cyclopentylmethyl groups may optionally be substituted by one or more fluorine atoms and the phenylmethyl, 2-phenylethyl, pyridylmethyl, furanylmethyl, thienylmethyl or thiazolylmethyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, methyl, F_3C , HF_2C , FH_2C - and H_2N .

18. Compounds according to one or more of claims 1 to 17, characterised in that

R^3 denotes hydrogen, fluorine, methyl, F_3C , HF_2C or FH_2C - and

R^4 denotes hydrogen or fluorine.

19. Compounds according to one or more of claims 1 to 17, characterised in that

R^3 denotes hydrogen and

R^4 denotes hydrogen.

20. Compounds according to one or more of claims 1 to 19, characterised in that

R^5 denotes hydrogen, C_{1-6} -alkyl, C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-3} -alkyl, C_{3-7} -cycloalkenyl, C_{3-7} -cycloalkenyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, aryl- C_{1-3} -alkyl, heteroaryl, or heteroaryl- C_{1-3} -alkyl, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro,

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C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkyl-S, aryl, heteroaryl, heteroaryl-C₁₋₃-alkyl, aryl-C₁₋₃-alkyl, (R¹²)₂N-SO₂, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl- and (R¹²)₂N-CO.

21. Compounds according to one or more of claims 1 to 19, characterised in that

5

R⁵ denotes C₁₋₆-alkyl, cyclopropyl, C₃₋₆-cycloalkyl-C₁₋₃-alkyl or phenyl-C₁₋₃-alkyl,

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from

10

among fluorine, chlorine, bromine, iodine, cyano, hydroxy, carboxy, C₁₋₄-alkyl, C₁₋₄-alkoxy- and (R¹²)₂N-.

22. Compounds according to one or more of claims 1 to 19, characterised in that

15

R⁵ denotes C₁₋₄-alkyl or cyclopropyl, wherein one or more hydrogen atoms of the above mentioned groups may optionally be replaced by fluorine atoms.

23. Compounds according to one or more of claims 1 to 22, characterised in that

20

R⁶ denotes C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N-aryl, (R¹²)₂N-aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl,

25

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, iodine, hydroxy, carboxy, cyano, nitro, C₁₋₃-alkyl, C₃₋₇-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl, (R¹²)₂N-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-N(R¹²), (R¹²)₂N-SO₂, R¹²-SO₂-(R¹²)N, R¹³-O- and R¹³-O-C₁₋₃-alkyl.

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24. Compounds according to one or more of claims 1 to 22, characterised in that

R^6 denotes C_{2-6} -alkenyl, C_{2-6} -alkynyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ -phenyl, $(R^{12})_2N$ -phenyl- C_{1-3} -alkyl, heteroaryl or heteroaryl- C_{1-3} -alkyl,

wherein by the above-mentioned heteroaryl groups are meant 5- or 6-membered aromatic heteroaryl groups which contain 1, 2 or 3

heteroatoms selected from among N, O and S and

wherein the above mentioned groups may optionally be substituted

independently of one another by one or more groups selected from

among fluorine, chlorine, bromine, carboxy, hydroxy, cyano, C_{1-3} -alkyl,

C_{1-3} -alkoxy, C_{1-3} -alkoxy- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, C_{3-5} -cycloalkyl,

heterocyclyl, heterocyclyl- C_{1-3} -alkyl, aryl, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl,

$(R^{12})_2N$ -CO, $(R^{12})_2N$ -CO-N(R^{12}), R^{12} -CO-(R^{12})N- and $(R^{12})_2N$ -SO₂-.

25. Compounds according to one or more of claims 1 to 22, characterised in that

R^6 denotes $(R^{12})_2N$ -phenyl- C_{1-3} -alkyl or C_{3-6} -cycloalkyl- C_{1-3} -alkyl,

wherein the above mentioned groups may optionally be substituted

independently of one another by one or more groups selected from

among fluorine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -alkoxy, hydroxy- C_{1-3} -

alkyl, $(R^{12})_2N$, $(R^{12})_2N$ - C_{1-3} -alkyl, $(R^{12})_2N$ -CO-N(R^{12})- and $(R^{12})_2N$ -SO₂-.

26. Compounds according to one or more of claims 1 to 22, characterised in that

R^6 denotes 4-aminobenzyl, cyclobutylmethyl, 2-cyclopropylethyl or cyclopropylmethyl,

wherein the above mentioned groups may optionally be substituted

independently of one another by one or more groups selected from

among fluorine and C_{1-3} -alkyl, particularly preferably by methyl.

27. Compounds according to one or more of claims 1 to 26, characterised in that

R^7 denotes hydrogen or C_{1-4} -alkyl,

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while one or more hydrogen atoms of the C₁₋₄-alkyl group may be replaced by fluorine.

28. Compounds according to one or more of claims 1 to 27, characterised in that

5

R⁸ denotes hydrogen, fluorine, chlorine, bromine, cyano, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, C₃₋₇-cycloalkenyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl, R¹³-O, R¹³-O-C₁₋₃-alkyl, R¹⁰-SO₂-(R¹¹)N or R¹⁰-CO-(R¹¹)N,

10

wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among C₁₋₆-alkyl, fluorine, chlorine, bromine, hydroxy, oxo, carboxy, cyano, nitro, C₃₋₇-cycloalkyl, heterocyclyl, (R¹²)₂N, (R¹²)₂N-CO, R¹³-CO, R¹³-O-CO, R¹²-CO-(R¹²)N, (R¹²)₂N-CO-(R¹²)N, (R¹²)₂N-SO₂, (R¹²)₂N-SO₂-(R¹²)N, R¹²-SO₂, R¹³-O, C₁₋₄-alkyl-S, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O, FH₂C-O- and R¹²-SO₂-(R¹²)N-, and

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R⁹ in each case independently of one another denote hydrogen, fluorine, chlorine, bromine, methyl, F₂HC, FH₂C or F₃C.

20

29. Compounds according to one or more of claims 1 to 27, characterised in that

R⁸ denotes hydrogen, fluorine, chlorine, bromine, cyano, C₁₋₄-alkyl, C₁₋₄-alkoxy, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-oxy, C₃₋₆-cycloalkyl-C₁₋₃-alkoxy, phenyl, pyridyl, thienyl, furyl, R¹⁰-CO-(R¹¹)N or R¹⁰-SO₂-(R¹¹)N, wherein the above mentioned groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, carboxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₄-alkyl-S, R¹³-CO, R¹³-O-CO, R¹²-SO₂, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O, FH₂C-O- and (R¹²)₂N-CO-, and

25

30

R⁹ in each case independently of one another denote hydrogen, fluorine, chlorine or bromine.

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30. Compounds according to one or more of claims 1 to 27, characterised in that

5 R^8 denotes R^{10} -SO₂-(R¹¹)N, R^{10} -CO-(R¹¹)N, cyanophenyl or cyanothienyl, wherein the above mentioned cyanophenyl- and cyanothienyl groups may optionally be substituted independently of one another by one or more groups selected from among fluorine, chlorine, bromine, C₁₋₄-alkyl, C₁₋₄-alkoxy, F₃C, HF₂C, FH₂C, F₃C-O, HF₂C-O- and FH₂C-O-, and

10 R^9 in each case independently of one another denote hydrogen, fluorine, chlorine or bromine.

31. Compounds according to one or more of claims 1 to 30, characterised in that

15 R^{10} denotes C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, C₃₋₇-cycloalkenyl, C₃₋₇-cycloalkenyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl, heteroaryl-C₁₋₃-alkyl or (R¹²)₂N, wherein the above mentioned groups may optionally be substituted by
20 one or more groups selected from among fluorine, chlorine, bromine, hydroxy, carboxy, cyano, nitro, C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy-C₁₋₃-alkyl, R¹²-CO(R¹²)N, R¹²-SO₂(R¹²)N, (R¹²)₂N, (R¹²)₂N-C₁₋₃-alkyl- and (R¹²)₂N-CO-, and

25 R^{11} denotes hydrogen, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₂₋₆-alkynyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, aryl, aryl-C₁₋₃-alkyl, heteroaryl or heteroaryl-C₁₋₃-alkyl, wherein the above mentioned groups may optionally be substituted
30 independently of one another by one or more groups selected from among fluorine, chlorine, bromine, hydroxy, cyano, C₁₋₃-alkyl, C₁₋₃-alkoxy, hydroxy-C₁₋₃-alkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl, (R¹²)₂N- and (R¹²)₂N-C₁₋₃-alkyl.

continued

32. Compounds according to one or more of claims 1 to 30, characterised in that

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R^{10} denotes C_{1-6} -alkyl, heterocyclyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl, heteroaryl- C_{1-3} -alkyl or $(R^{12})_2N$,
wherein by the above mentioned heteroaryl groups are meant 5- or 6-
5 membered aromatic heteroaryl groups which contain 1, 2 or 3
heteroatoms selected from among N, O and S and
wherein the above mentioned groups may optionally be substituted
independently of one another by one or more groups selected from
among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -
10 alkoxy, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, hydroxy- C_{1-3} -alkyl, $(R^{12})_2N$ -
and $(R^{12})_2N$ - C_{1-3} -alkyl, and

R^{11} denotes hydrogen, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, C_{3-6} -cycloalkyl- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, phenyl, phenyl- C_{1-3} -alkyl, heteroaryl
15 or heteroaryl- C_{1-3} -alkyl,
wherein by the above-mentioned heteroaryl groups are meant 5- or 6-
membered aromatic heteroaryl groups which contain 1, 2 or 3
heteroatoms selected from among N, O and S, and
wherein the above mentioned groups may optionally be substituted
independently of one another by one or more groups selected from
20 among fluorine, chlorine, bromine, hydroxy, cyano, C_{1-3} -alkyl, C_{1-3} -
alkoxy, hydroxy- C_{1-3} -alkyl, heterocyclyl, heterocyclyl- C_{1-3} -alkyl, $(R^{12})_2N$ -
and $(R^{12})_2N$ - C_{1-3} -alkyl.

25 33. Compounds according to one or more of claims 1 to 30, characterised in that

R^{10} denotes C_{1-4} -alkyl, morpholinyl, piperidinyl, 4-methylpiperidinyl, pyrrolidinyl, phenyl, 4-fluorophenyl, benzyl, pyridyl or $(CH_3)_2N$,
wherein the above mentioned groups may optionally be substituted
independently of one another by one or more groups selected from
30 among fluorine, chlorine and bromine,

R^{11} denotes hydrogen, methyl, HF_2C , ethyl, phenyl or 4-fluorophenyl,
wherein the above mentioned groups may optionally be substituted

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independently of one another by one or more groups selected from among fluorine, chlorine and bromine.

34. Compounds according to one or more of claims 1 to 30, characterised in that

5

R^{10} and R^{11} together form a C_{2-6} -alkylene bridge, so that a heterocyclic ring is formed with the inclusion of the nitrogen atom linked to R^{11} and the SO_2 - or CO - group linked to R^{10} , wherein one or two $-CH_2$ groups of the C_{2-6} -alkylene bridge may be replaced independently of one another by O, S, SO, SO_2 or $-N(R^{12})-$ such that in each case two O or S atoms or an O and an S atom are not directly connected to one another, and wherein the C atoms of the above mentioned C_{2-6} -alkylene bridge may optionally be substituted independently of one another by one or more groups selected from among fluorine, hydroxy, carboxy, F_3C , C_{1-3} -alkyl and C_{1-3} -alkoxy.

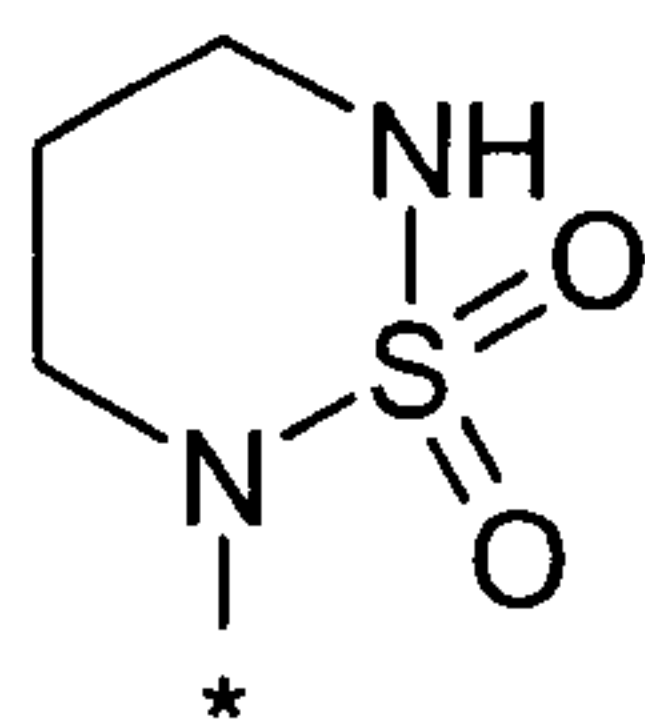
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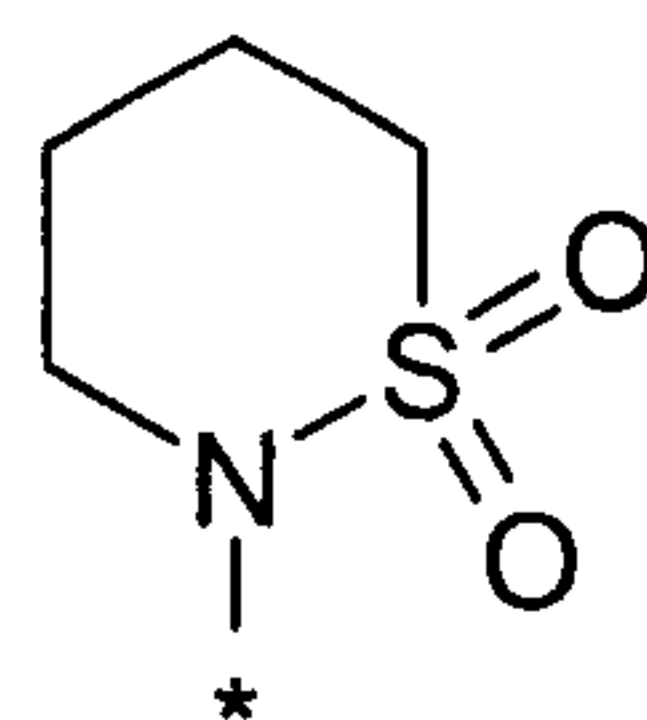
35. Compounds according to one or more of claims 1 to 30, characterised in that

20

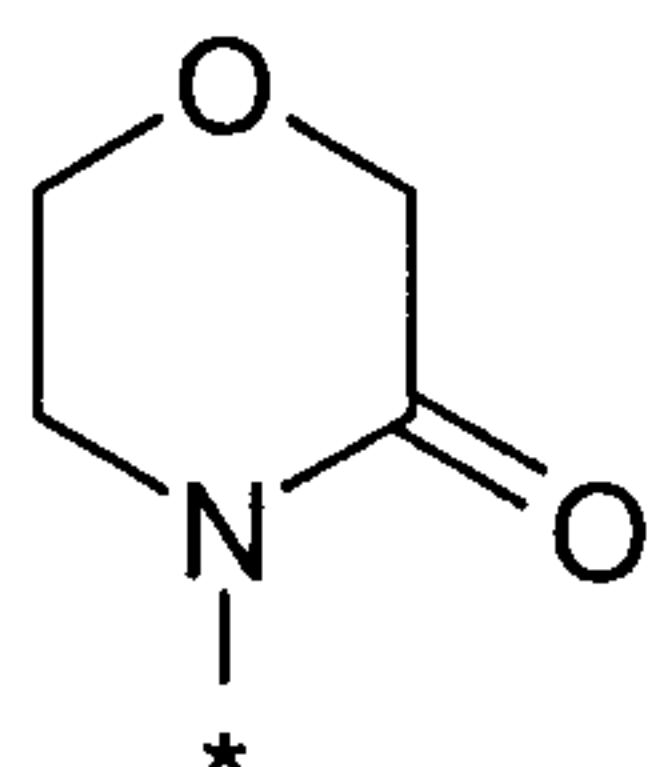
R^{10} and R^{11} with the inclusion of the nitrogen atom bound to R^{11} and the SO_2 - or CO group bound to R^{10} , together form a heterocyclic ring of formulae (IIa), (IIb), (IIc) or (IId)



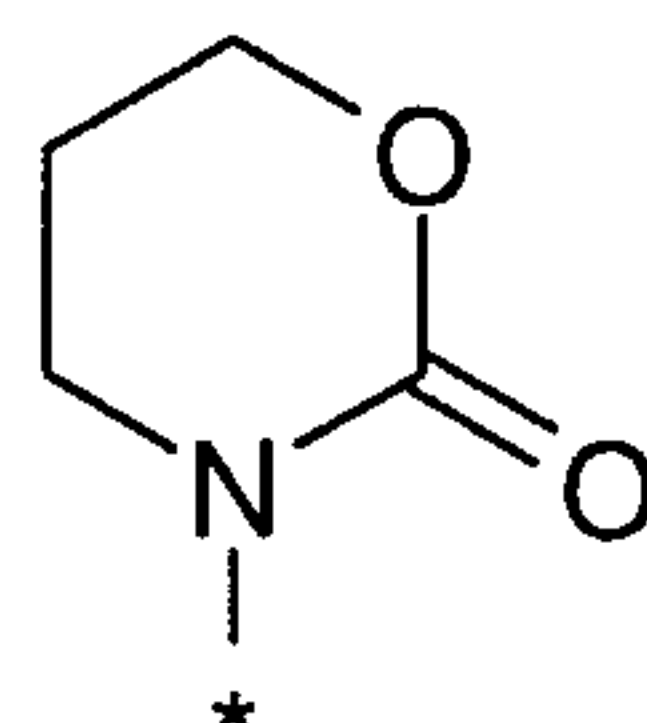
(IIa)



(IIb)



(IIc)



(IId)

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36. Compounds according to one or more of claims 1 to 35, characterised in that

R^{12} in each case independently of one another denotes hydrogen or a C_{1-6} -alkyl group

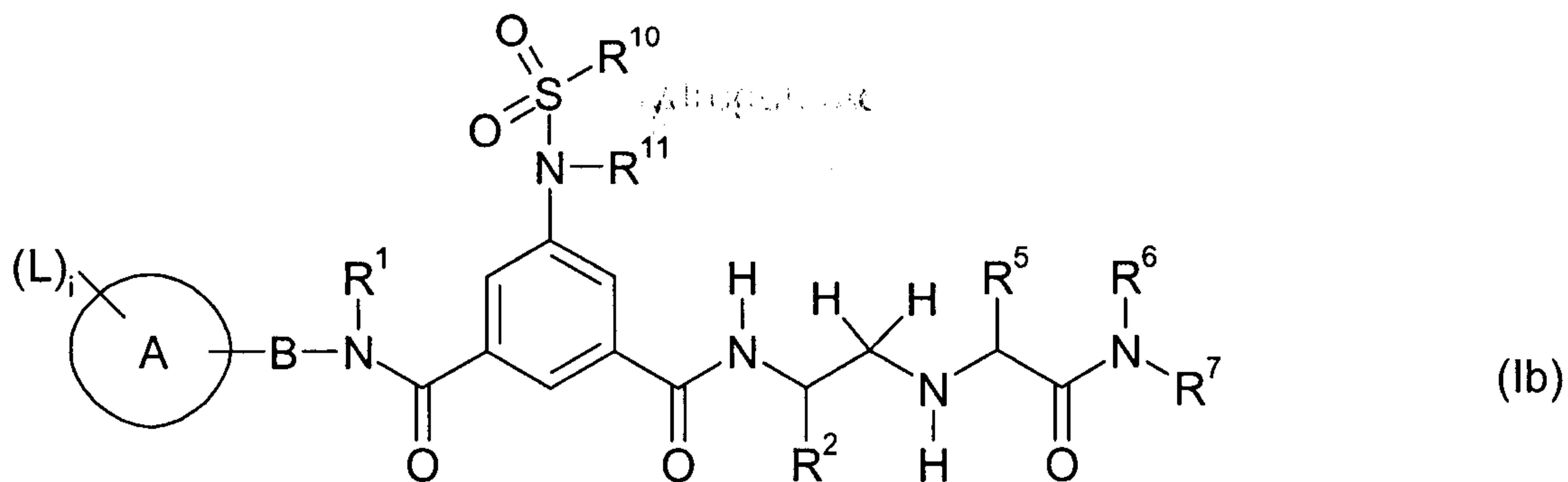
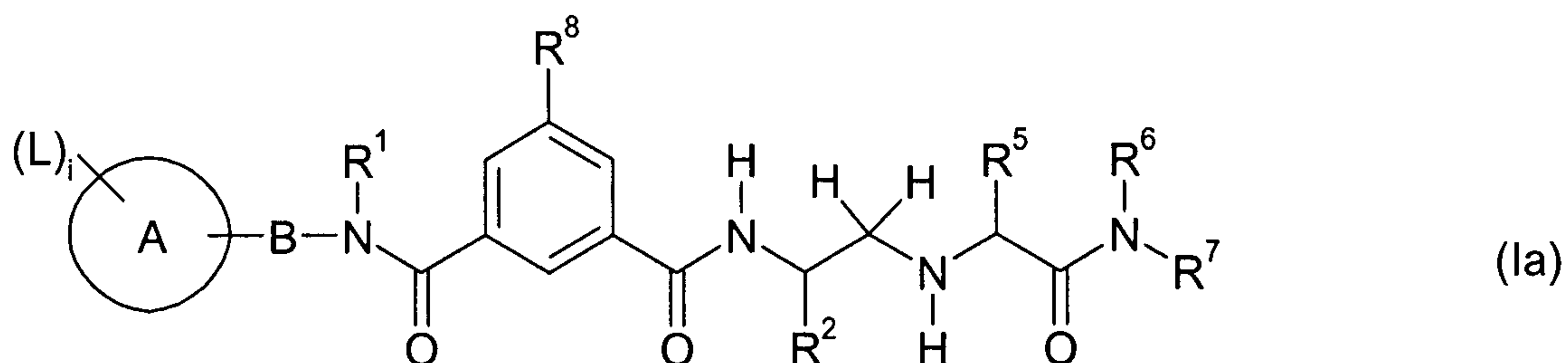
5 wherein one or more hydrogen atoms of the C_{1-6} -alkyl group may be replaced by fluorine.

36. Compounds according to one or more of claims 1 to 35, characterised in that

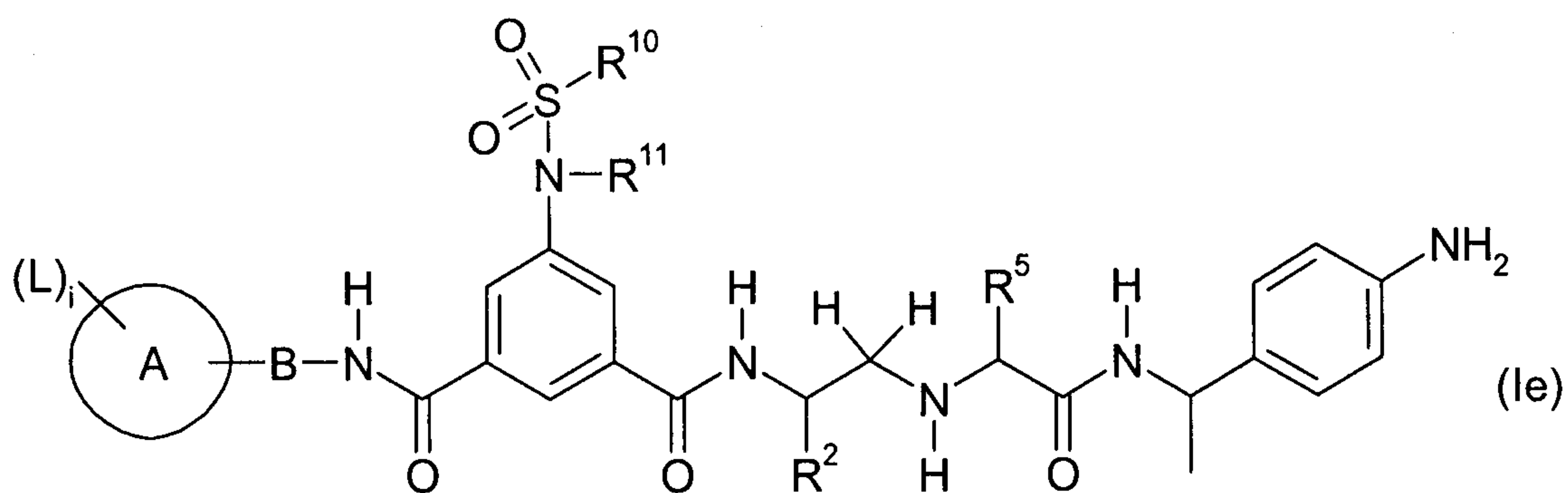
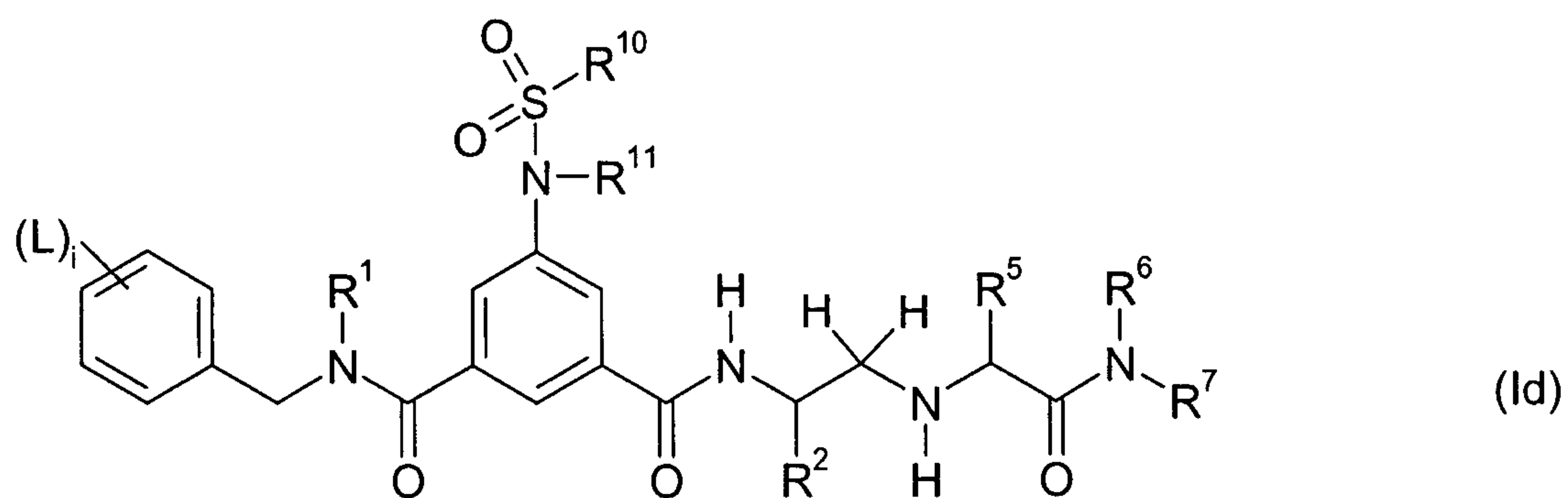
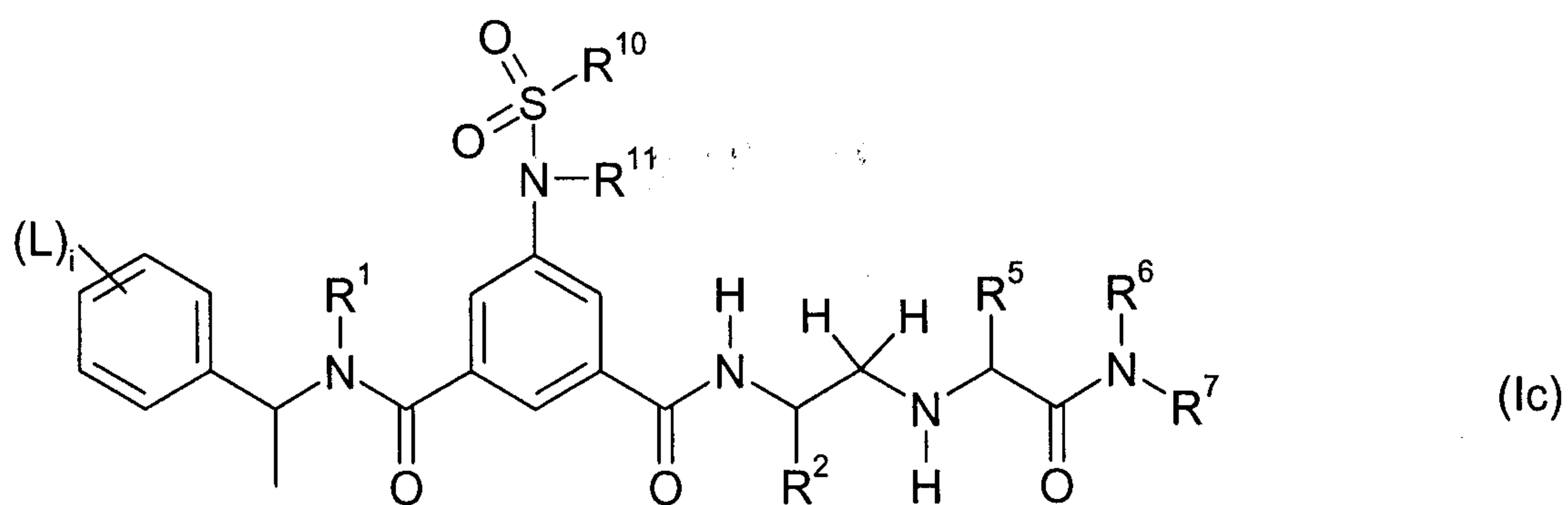
10 R^{13} in each case independently of one another denotes hydrogen or a C_{1-3} -alkyl group,

wherein one or more hydrogen atoms of the C_{1-3} -alkyl group may be replaced by fluorine.

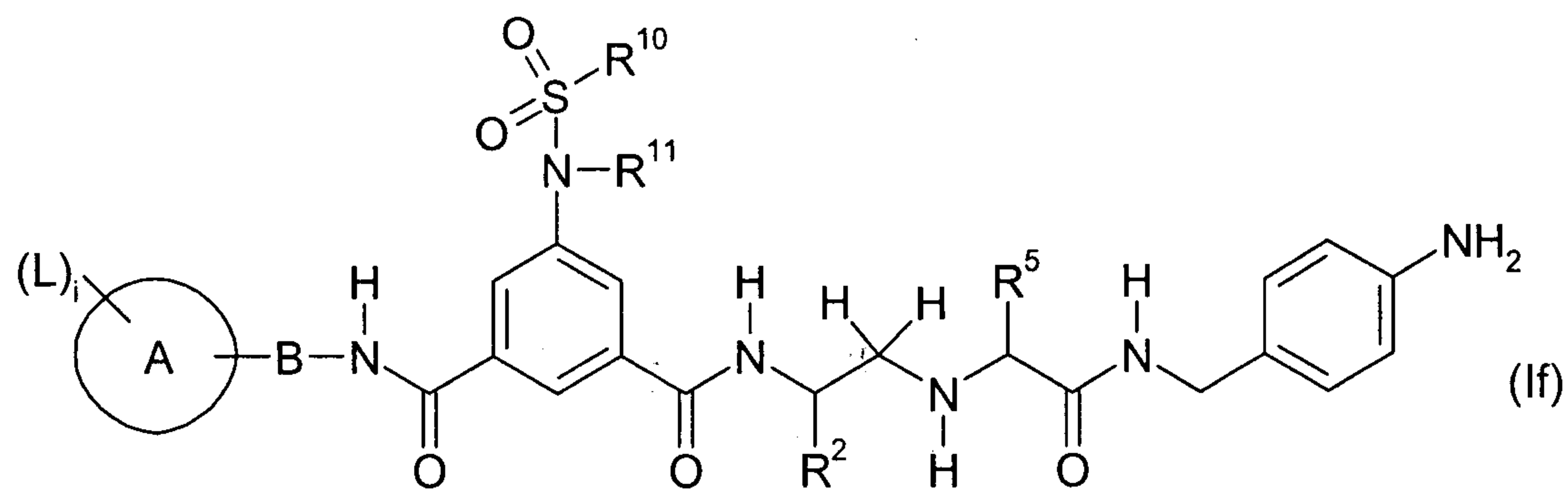
15 38. Compounds according to one or more of claims 1-37 selected from among the formulae (Ia), (Ib), (Ic), (Id), (Ie), (If) or (Ig)



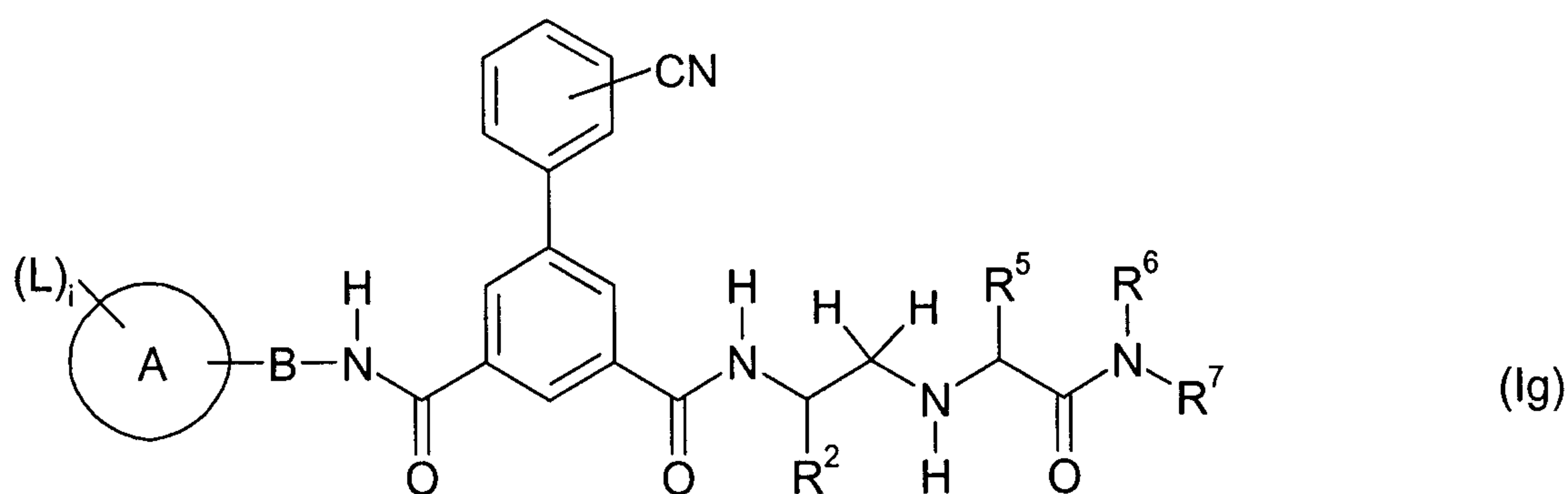
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wherein

- 5 A, B, L, i, R¹, R², R³, R⁴, R⁵, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹² and R¹³ have the meanings given in the preceding claims.
38. Physiologically acceptable salts of the compounds according to one or more of claims 1 to 37.
- 10 39. Use of a compound according to one or more of claims 1 to 38 as a medicament.
- 15 40. Pharmaceutical composition containing a compound according to one or more of claims 1 to 38 optionally together with one or more inert carriers and/or diluents.
- 20 41. Pharmaceutical composition according to claim 40, containing one or more medicinally effective active substances selected from among beta-secretase inhibitors, gamma-secretase inhibitors, amyloid aggregation inhibitors, directly or indirectly acting neuroprotective substances, antioxidants, Cox inhibitors, NSAIDs with additionally or only Aβ lowering properties; HMG-CoA reductase inhibitors, AMPA agonists; substances that modulate the concentration or release of neurotransmitters, substances that induce the secretion of growth hormone, CB-1 receptor antagonists or inverse agonists, antibiotics, PDE-IV inhibitors, PDE-IX inhibitors, GABA_A inverse agonists, nicotine agonists, histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, α2-adrenoreceptor antagonists, muscarinic M1 agonists,
- 25

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muscarinic M2 antagonists, metabotropic glutamate-receptor 5 positive modulators.

- 5 42. Pharmaceutical composition according to claim 40 or 41, containing one or more medicinally effective active substances selected from among Alzhemed, Vitamin E, ginkgolides, donepezil, rivastigmine, tacrine, galantamine, memantine, NS-2330, ibutamoren mesylate, capromorelin, minocycline and rifampicin.
- 10 43. Use of at least one compound according to one or more of claims 1 to 38 as a β -secretase inhibitor.
- 15 44. Use of at least one compound according to one or more of claims 1 to 38 or a pharmaceutical composition according to one or more of claims 40 to 42 for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions that are associated with abnormal processing of Amyloid Precursor Protein (APP) or aggregation of Abeta peptide.
- 20 45. Use of at least one compound according to one or more of claims 1 to 38 or a pharmaceutical composition according to one or more of claims 40 to 42 for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions that can be influenced by inhibiting the β -secretase activity.
- 25 46. Use of at least one compound according to one or more of claims 1 to 38 or a pharmaceutical composition according to one or more of claims 40 to 42 for preparing a medicament for the treatment or prevention of Alzheimer's disease (AD), MCI ("mild cognitive impairment"), trisomy 21 (Down's syndrome), cerebral amyloidangiopathy, degenerative dementias, hereditary cerebral haemorrhage with amyloidosis - Dutch type (HCHWA-D), Alzheimer's dementia with Lewy bodies, trauma, stroke, pancreatitis, inclusion body myositis (IBM), as well as peripheral amyloidoses, diabetes or arteriosclerosis.
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47. Use of at least one compound according to one or more of claims 1 to 38 or a pharmaceutical composition according to one or more of claims 40 to 42 for preparing a medicament for the treatment or prevention of Alzheimer's disease (AD).

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48. Method of inhibiting β -secretase activity, characterised in that β -secretase is brought into contact with an inhibitory amount of a compound according to one or more of claims 1 to 38.

Fetherstonhaugh
Ottawa, Canada
Patent Agents

