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(54) Titre : ANTAGONISTES/AGONISTES INVERSES DE GLUCAGON

(54) Title: GLUCAGON ANTAGONISTS/INVERSE AGONISTS

(57) **Abrégé/Abstract:**

A novel class of compounds, which act to antagonize the action of the glucagon hormone on the glucagon receptor. Owing to their antagonizing effect of the glucagon receptor the compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases such as hyperglycemia, Type 1 diabetes, Type 2 diabetes and obesity.



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(21) International Application Number: PCT/DK00/00264 (22) International Filing Date: 16 May 2000 (16.05.00) (30) Priority Data: PA 1999 00684 17 May 1999 (17.05.99) DK PA 2000 00478 21 March 2000 (21.03.00) DK (71) Applicants: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK). AGOURON PHARMACEUTI- CALS, INC. [US/US]; 10350 North Torrey Pines Road, La Jolla, CA 92037 (US).		(72) Inventors: LING, Anthony; 10933 Caminito Cuesta, San Diego, CA 92131 (US). PLEWE, Michael, Bruno; Caminito Eva 4711, San Diego, CA 92130 (US). TRUESDALE, Larry, Kenneth; 10382 Rue Chamberry, San Diego, CA 92131 (US). LAU, Jesper; Rosenvænget 3, DK-3520 Farum (DK). MADSEN, Peter; Ulvejbjerg 7, DK-2880 Bagsværd (DK). SAMS, Christian; Jakob Dannefærds Vej 4a 1., DK-1973 Frederiksberg C (DK). BEHRENS, Carsten; Lundtoftegade 107, 1.th., DK-2200 Copenhagen N (DK). VAGNER, Josef; 12381 N. Granville Canyon Way, Oro Valley, AZ 85737 (US). CHRISTENSEN, Inge, Thøger; Kulsviertofte 52, DK-2800 Lyngby (DK). LUNDT, Behrend, Frederik; Rosenhaven 118, DK-2980 Kokkedal (DK). SIDELMANN, Ulla, Grove; Dronningeen- gen 10A, DK-2950 Vedbæk (DK). THØGERSEN, Hen- ning; Gregersmindevej 8, DK-3520 Farum (DK). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: GLUCAGON ANTAGONISTS/INVERSE AGONISTS (57) Abstract A novel class of compounds, which act to antagonize the action of the glucagon hormone on the glucagon receptor. Owing to their antagonizing effect of the glucagon receptor the compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases such as hyperglycemia, Type 1 diabetes, Type 2 diabetes and obesity.		

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JUMBO APPLICATIONS / PATENTS

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

THIS IS VOLUME __1__ OF __2__

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GLUCAGON ANTAGONISTS/INVERSE AGONISTS**FIELD OF THE INVENTION**

- 5 The present invention relates to agents that act to antagonize the action of the glucagon peptide hormone. More particularly, it relates to glucagon antagonists or inverse agonists.

BACKGROUND OF THE INVENTION

- 10 Glucagon is a key hormonal agent that, in co-operation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (mostly liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposite to that of insulin, which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones.

15

- Glucagon is produced in the alpha islet cells of the pancreas and insulin in the beta islet cells. Diabetes mellitus is a common disorder of glucose metabolism. The disease is characterized by hyperglycemia and may be classified as Type 1 diabetes, the insulin-dependent form, or Type 2 diabetes, which is non-insulin-dependent in character. Subjects with Type 1 diabetes are hyperglycemic and hypoinsulinemic, and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with Type 1 or Type 2 diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy control animals as well as in animal models of Type 1 and Type 2 diabetes, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level (Brand et al., Diabetologia 37, 985 (1994); Diabetes 43, [suppl 1], 172A (1994); Am. J. Physiol. 269, E469-E477 (1995); Diabetes 44 [suppl 1], 134A (1995); Diabetes 45, 1076 (1996)). These studies suggest that glucagon suppression or an action that antagonizes glucagon could be a useful adjunct to conventional antihyperglycemia treatment of diabetes. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, ie substances that inhibit or prevent glucagon induced responses. The antagonist can be peptidic or non-peptidic in nature. Native glucagon is a 29 amino acid peptide having the sequence:
- 20
25
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His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-NH₂.

35

Glucagon exerts its action by binding to and activating its receptor, which is part of the Glucagon-Secretin branch of the 7-transmembrane G-protein coupled receptor family (Jelinek et

al., Science 259, 1614, (1993)). The receptor functions by an activation of the adenylyl cyclase second messenger system and the result is an increase in cAMP levels.

Several publications disclose peptides that are stated to act as glucagon antagonists. Probably, the most thoroughly characterized antagonist is DesHis¹[Glu⁹]-glucagon amide (Unson et al., Peptides 10, 1171 (1989); Post et al., Proc. Natl. Acad. Sci. USA 90, 1662 (1993)). Other antagonists are eg DesHis¹,Phe⁶[Glu⁹]-glucagon amide (Azizh et al., Bioorganic & Medicinal Chem. Lett. 16, 1849 (1995)) or NLeu⁹,Ala^{11,16}-glucagon amide (Unson et al., J. Biol. Chem. 269(17), 12548 (1994)).

Peptide antagonists of peptide hormones are often quite potent; however, they are generally known not to be orally available because of degradation by physiological enzymes, and poor distribution in vivo. Therefore, orally available non-peptide antagonists of the peptide hormones are preferred. Among the non-peptide glucagon antagonists, a quinoxaline derivative, (2-styryl-3-[3-(dimethylamino)propylmethylamino]-6,7-dichloroquinoxaline was found to displace glucagon from the rat liver receptor (Collins, J.L. et al., Bioorganic and Medicinal Chemistry Letters 2(9):915-918 (1992)). West, R.R. et al., WO 94/14426 (1994) discloses use of skyrin, a natural product comprising a pair of linked 9,10-anthracenedione groups, and its synthetic analogues, as glucagon antagonists. Anderson, P.L., US patent No. 4,359,474 discloses the glucagon antagonistic properties of 1-phenyl pyrazole derivatives. Barcza, S., U.S. Patent No. 4,374,130, discloses substituted disilacyclohexanes as glucagon antagonists. WO 98/04528 (Bayer Corporation) discloses substituted pyridines and biphenyls as glucagon antagonists. WO 97/16442 and US patent No 5,776,954 (Merck & Co., Inc.) disclose substituted pyridyl pyrroles as glucagon antagonists and WO 98/21957, WO 98/22108, WO 98/22109 and US 5,880,139 (Merck & Co., Inc.) disclose 2,4-diaryl-5-pyridylimidazoles as glucagon antagonists. Furthermore, WO 97/16442, US patent Nos 5,837,719 and 5,776,954 (Merck & Co., Inc.) discloses 2,5-substituted aryl pyrroles as glucagon antagonists. WO 98/24780, WO 98/24782, WO 99/24404 and WO 99/32448 (Amgen Inc.) disclose substituted pyrimidinone and pyridone compounds and substituted pyrimidine compounds, respectively, which are stated to possess glucagon antagonistic activity. Madsen et al (J. Med. Chem. 1998 (41) 5151-7) discloses a series of 2-(benzimidazol-2-ylthio)-1-(3,4-dihydroxyphenyl)-1-ethanones as competitive human glucagon receptor antagonists. WO 99/01423 (Novo Nordisk A/S) discloses a series of acylhydrazones as glucagon antagonists/inverse agonists.

These known glucagon antagonists differ structurally from the present compounds.

DEFINITIONS

The following is a detailed definition of the terms used to describe the compounds of the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

The term "C₁₋₆-alkyl" in the present context designates a branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "C₂₋₆-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "C₂₋₆-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "C₁₋₆-alkoxy" as used herein, alone or in combination, refers to the radical -O-C₁₋₆-alkyl where C₁₋₆-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, sec-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C₁₋₆-alkanoyl" as used herein denotes a group -C(O)H or -C(O)-C₁₋₅-alkyl. Representative examples are formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl and the like.

The term "C₃₋₈-cycloalkyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

5 The term "C₃₋₈-cycloalkenyl" as used herein represents a carbocyclic group having from 3 to 8 carbon atoms containing a least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

10

The term "C₄₋₈-cycloalkenyl" as used herein represents a carbocyclic group having from 4 to 8 carbon atoms containing a least one double bond. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

15

The term "heterocyclyl" as used herein represents a saturated or partially unsaturated 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

20

The term "aryl" as used herein is intended to include carbocyclic aromatic ring systems such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydro-

25 genated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

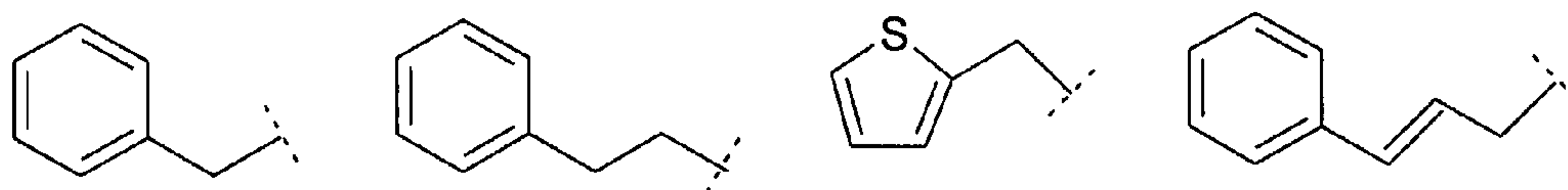
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The term "heteroaryl" as used herein is intended to include heterocyclic aromatic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranlyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-

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thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzothiophenyl (thianaphthenyl), indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazoliny, quinoliziny, quinoliny, isoquinoliny, quinoxaliny, naphthyridiny, pteridiny, carbazolyl, azepiny, diazepiny, acridiny and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrroliny, pyrazoliny, indoliny, oxazolidiny, oxazoliny, oxazepiny and the like.

- 10 "Aryl-C₁₋₆-alkyl", "heteroaryl-C₁₋₆-alkyl", "aryl-C₂₋₆-alkenyl" etc. mean C₁₋₆-alkyl or C₂₋₆-alkenyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:



- 15 The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

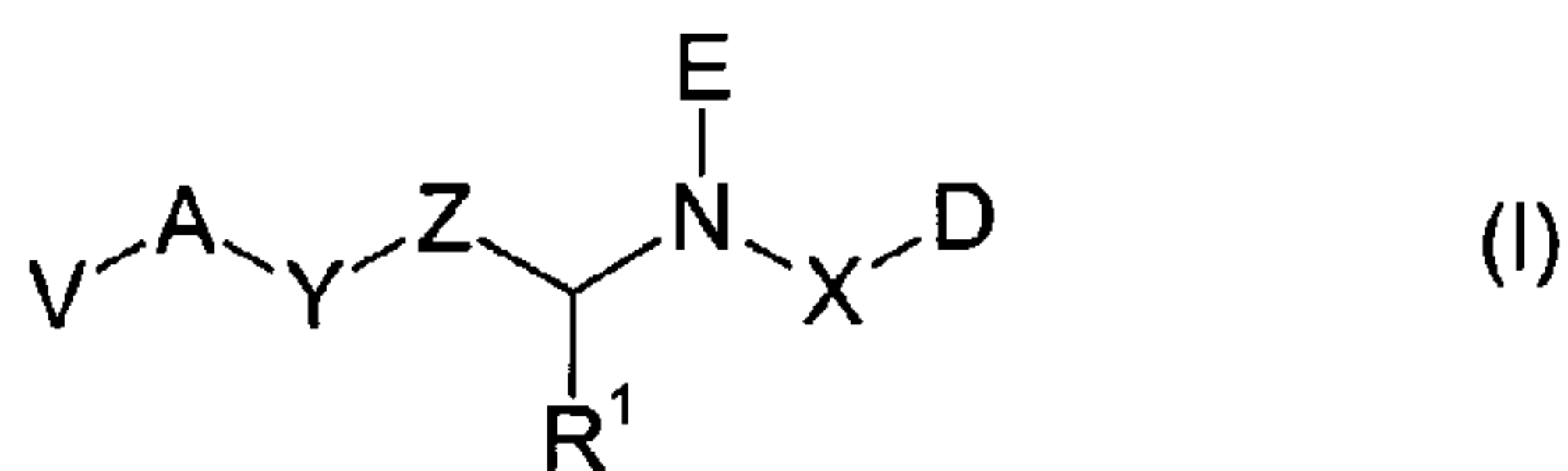
- 20 Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

Furthermore, when using the terms "independently are" and "independently selected from" it should be understood that the groups in question may be the same or different.

- 25 The present invention is based on the unexpected observation that the compounds of the general formula (I) disclosed below antagonize the action of glucagon.

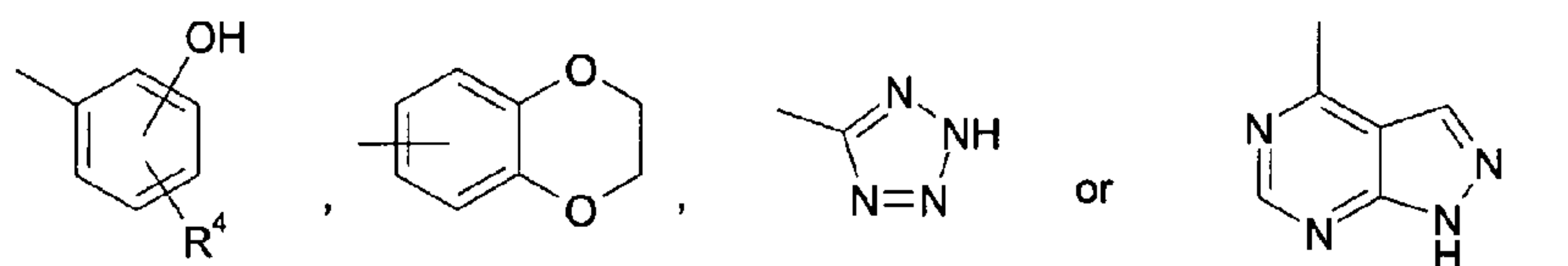
DESCRIPTION OF THE INVENTION

Accordingly, the invention is concerned with compounds of the general formula (I):



wherein

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$, $-\text{S}(\text{O})_2\text{OR}^2$,



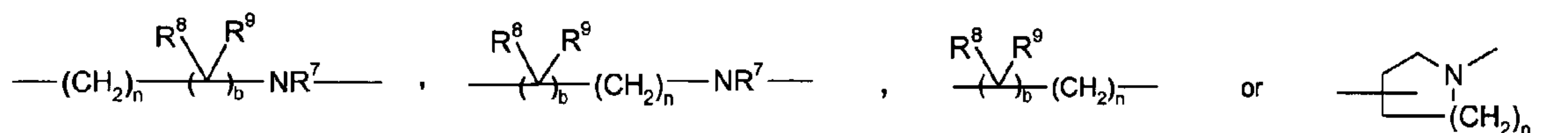
wherein

R^2 and R^3 independently are hydrogen or C_{1-6} -alkyl,

R^4 is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{NR}^5\text{R}^6$ or C_{1-6} -alkyl,

wherein R^5 and R^6 independently are hydrogen or C_{1-6} -alkyl,

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl,

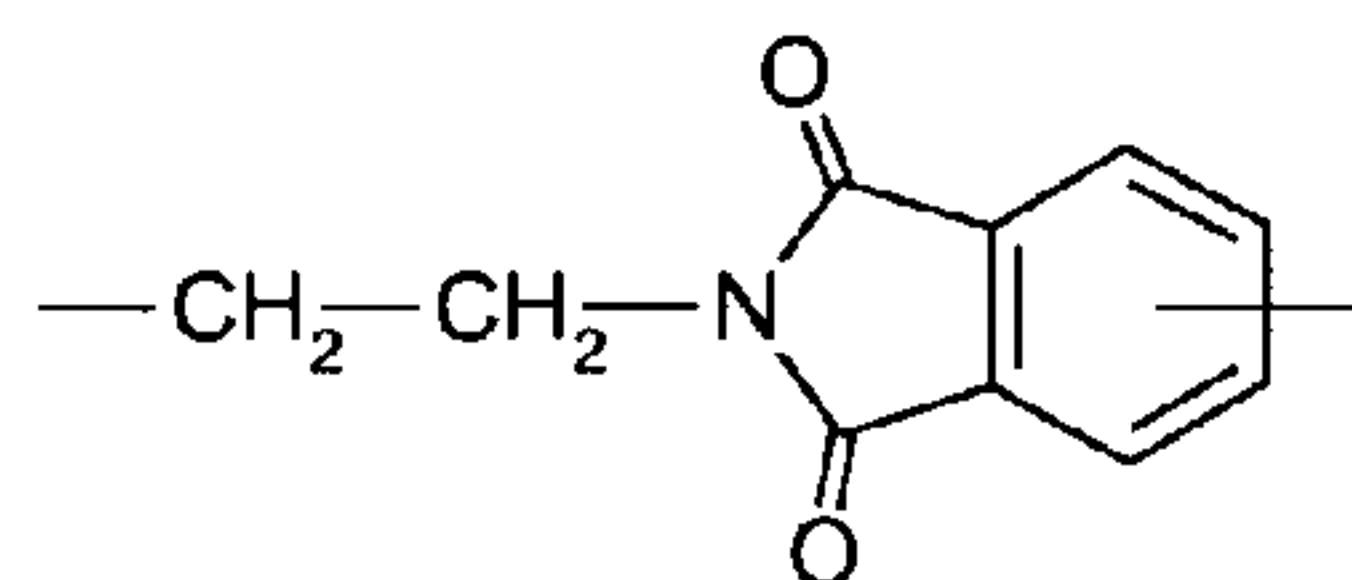
5 Y is $-C(O)-$, $-S(O)_2-$, $-O-$ or a valence bond,

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

10 which may optionally be substituted with one or two groups R^{46} and R^{47} selected from hydrogen, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{10}$, $-NR^{10}R^{11}$ and C_{1-6} -alkyl,

wherein R^{10} and R^{11} independently are hydrogen or C_{1-6} -alkyl,

or $-A-Y-Z-$ together are

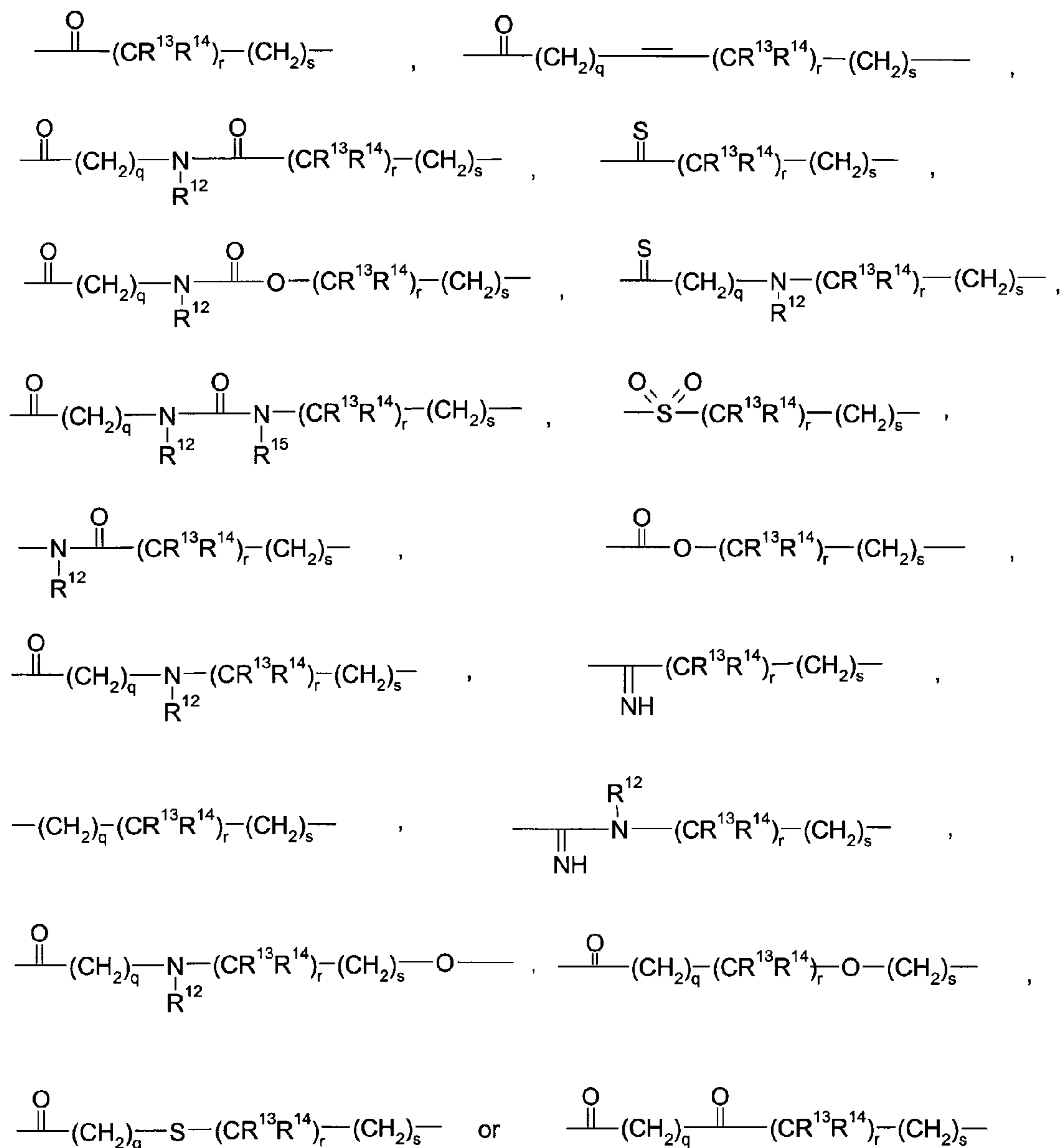


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R^1 is hydrogen or C_{1-6} -alkyl,

8

X is



5 wherein

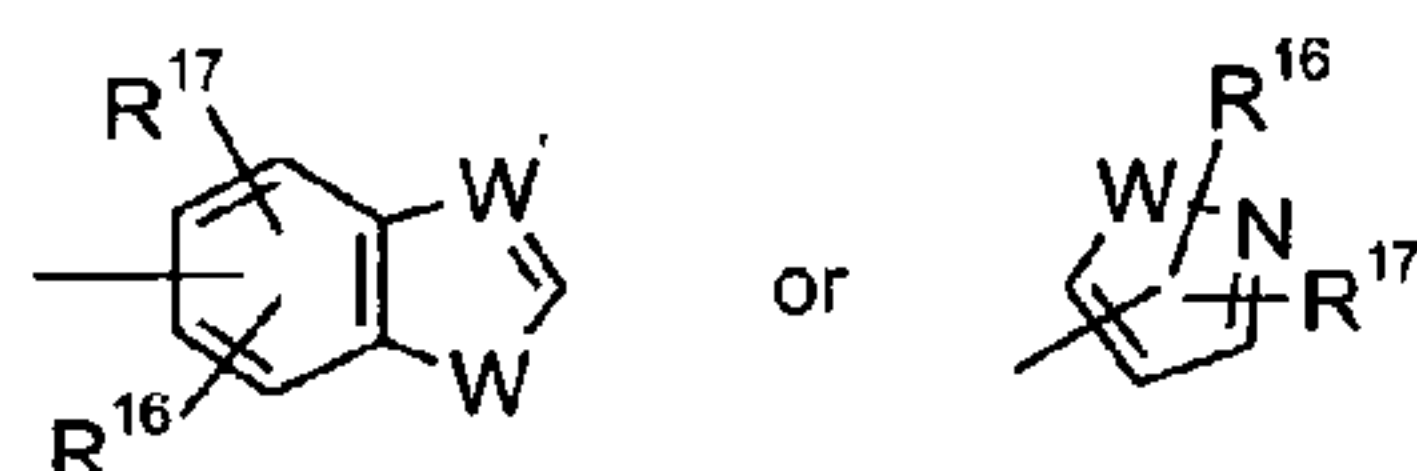
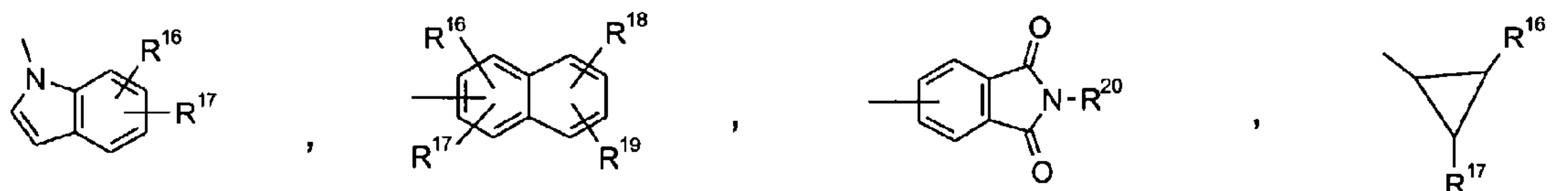
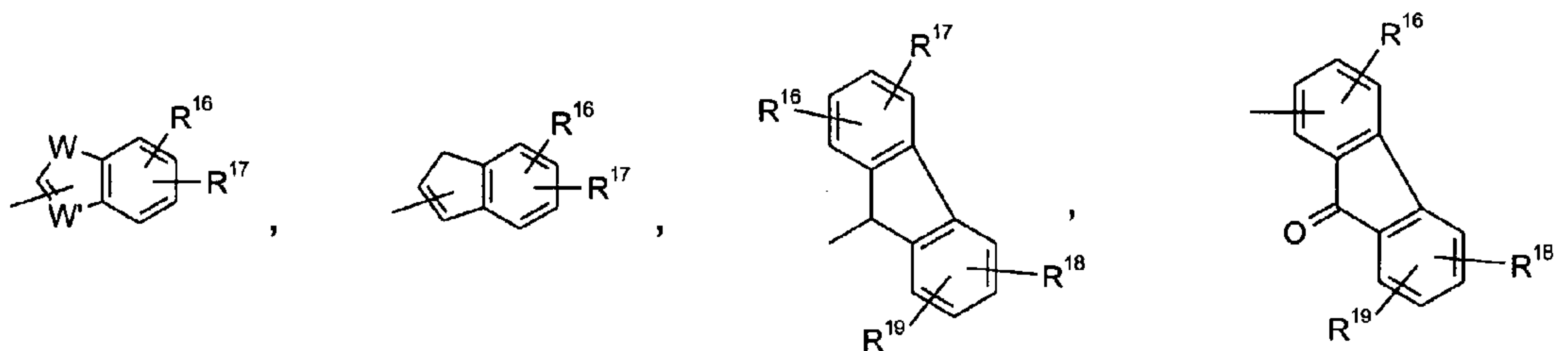
r is 0 or 1,

q and s independently are 0, 1, 2 or 3,









W is -O-, -S-, -S(O)₂- or -NR²⁰-,

W' is $=CR^{20'}$ - or $=N-$,

R^{16} , R^{17} , R^{18} and R^{19} independently are

- 15 • hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cyclo-
 alkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyloxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio, C₃₋₈-cycloalkylthio,
 C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-C₁₋₆-alkyl, C₄₋₈-
 cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocy-
 clyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more sub-
 stituents selected from

-CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
 -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents se-
 lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-
 C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-
 C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one
 or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 -OC(O)R²¹, -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

wherein R²¹ and R²² independently are hydrogen, -CF₃, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl or heteroaryl,

or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
 -(CR^{16'}R^{17'})_a-O-(CR^{18'}R^{19'})_c-O-,

wherein

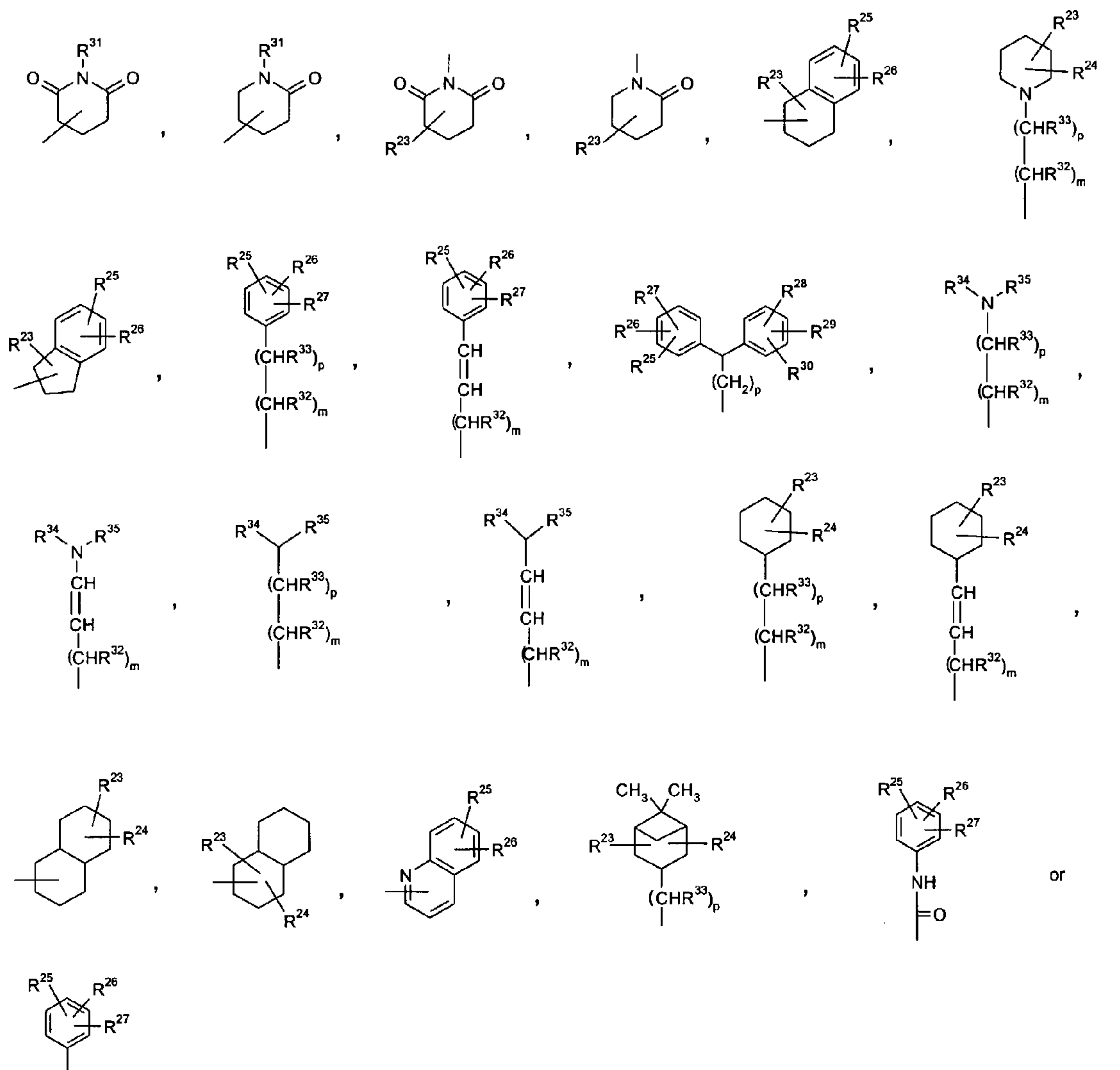
a is 0, 1 or 2,

c is 1 or 2,

R^{16'}, R^{17'}, R^{18'} and R^{19'} independently are hydrogen, C₁₋₆-alkyl or halogen,

R²⁰ and R^{20'} independently are hydrogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or
 5 different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom when present, or



wherein

10

m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R²³ and R²⁴ independently are

- hydrogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 5 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ or -C(O)OR³⁶,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

10 which may optionally be substituted with one or more substituents selected from
 -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

- 15 C₃₋₈-cycloalkyl, C₃₋₈-cycloalkylidene, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-
 C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-
 C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-
 C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

20 of which the cyclic moieties optionally may be substituted with one or more sub-
 stituents selected from

- CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
 -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
 25 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

30 which may optionally be substituted with one or more substituents se-
 lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
 -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
 -C(O)OR³⁶,

- aryl, aryloxy, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -NR³⁶S(O)₂R³⁷, -S(O)₂NR³⁶R³⁷, -S(O)NR³⁶R³⁷, -S(O)R³⁶, -S(O)₂R³⁶, -OS(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂OR³⁶, -CH₂NR³⁶R³⁷, -OC(O)R³⁶, -C(O)R³⁶ and -C(O)OR³⁶,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

wherein R³⁶ and R³⁷ independently are hydrogen, C₁₋₆-alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and C₁₋₆-alkyl,

wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_i-CR⁴⁰R⁴¹-(CH₂)_j-O-, -(CH₂)_i-CR⁴⁰R⁴¹-(CH₂)_j- or

-S-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l-S-,

wherein

5 t and l independently are 0, 1, 2, 3, 4 or 5,

R⁴⁰ and R⁴¹ independently are hydrogen or C₁₋₆-alkyl,

10 R²⁵ to R³⁰ independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl,

wherein R⁴² and R⁴³ independently are hydrogen or C₁₋₆-alkyl, or

15 R⁴² and R⁴³ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

R³¹, R³² and R³³ independently are hydrogen or C₁₋₆-alkyl,

20

R³⁴ and R³⁵ independently are

- hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkanoyl, -C(O)NR⁴⁴R⁴⁵ or -S(O)₂R⁴⁵,
- 25 • aryl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkanoyl or aryl-C₁₋₆-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C₁₋₆-alkyl,

30 wherein R⁴⁴ and R⁴⁵ independently are hydrogen or C₁₋₆-alkyl, or

R³⁴ and R³⁵ when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

35

R^{34} and R^{35} when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

- 5 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

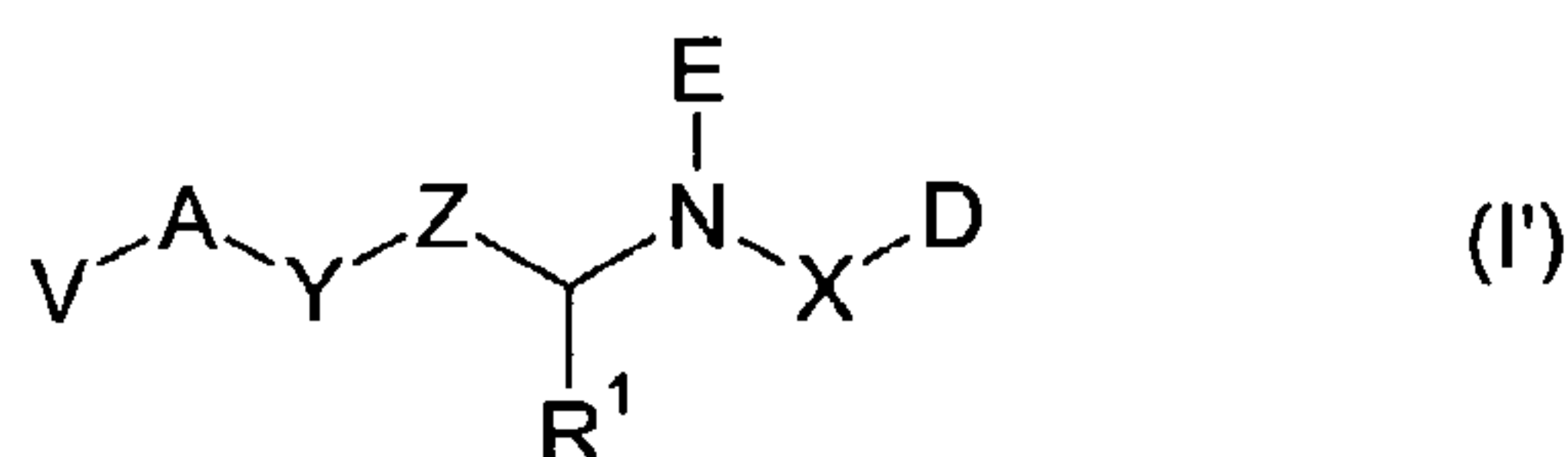
The compounds according to the invention preferably have an IC_{50} value of no greater than 5 μM as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or
10 Glucagon Binding Assay (III) disclosed herein.

More preferably, the compounds according to the invention have a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein corresponding to an IC_{50} value of less than 1 μM ,
15 preferably of less than 500 nM and even more preferred of less than 100 nM.

The compounds according to the invention are useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT (impaired glucose tolerance), Type 2 diabetes, Type 1 diabetes and obesity.

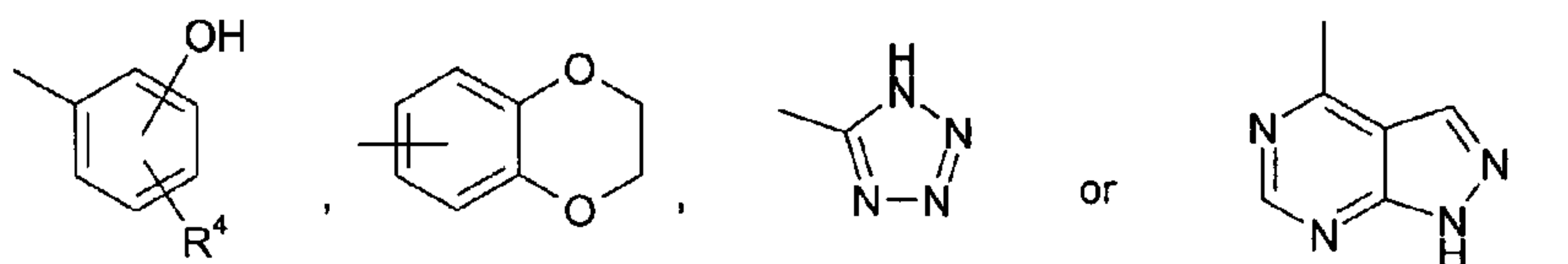
20

In a further aspect the invention relates to compounds of the general formula (I'):



25 wherein

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$,



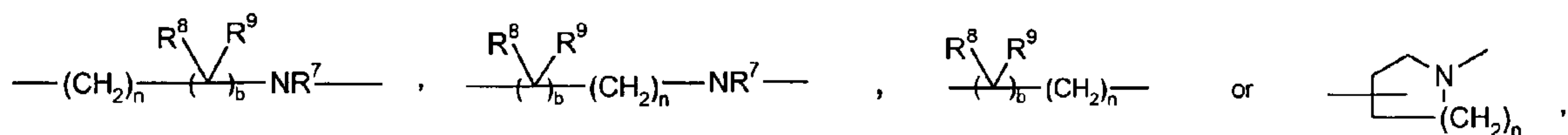
30 wherein

R² and R³ independently are hydrogen or C₁₋₆-alkyl,

R⁴ is hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁵, -NR⁵R⁶ or C₁₋₆-alkyl,

wherein R⁵ and R⁶ independently are hydrogen or C₁₋₆-alkyl;

A is



wherein

b is 0 or 1,

n is 0, 1, 2 or 3,

R⁷ is hydrogen, C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

R⁸ and R⁹ independently are hydrogen or C₁₋₆-alkyl;

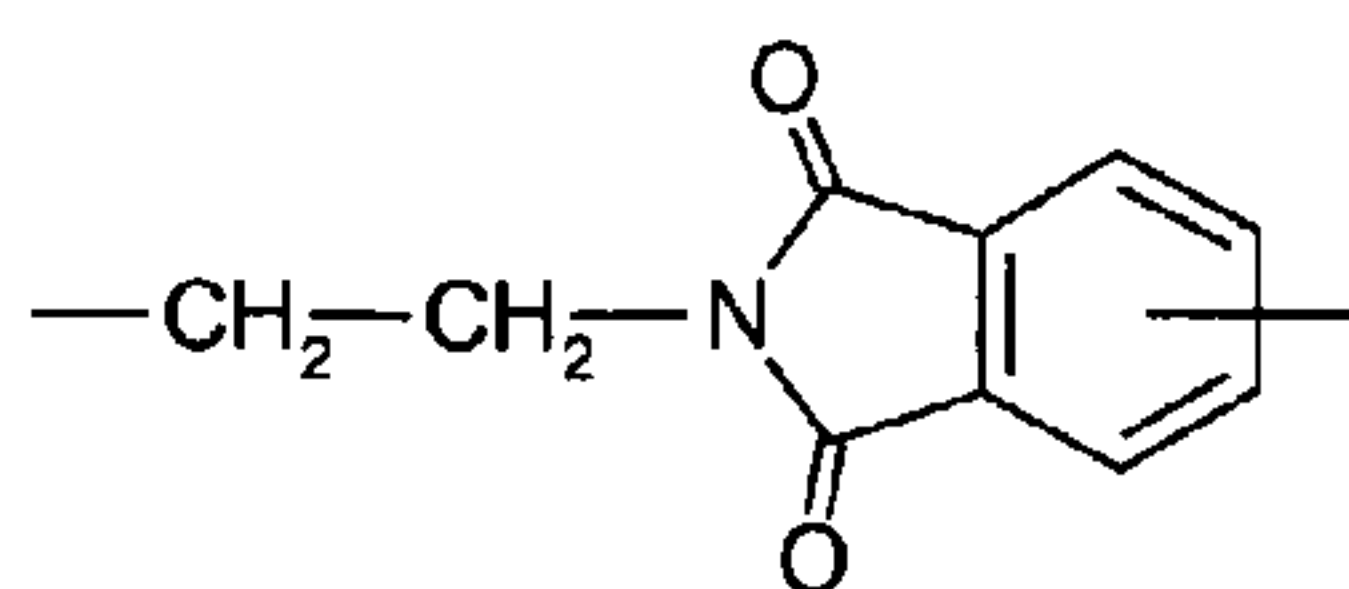
Y is -C(O)-, -S(O)₂- or -O-;

Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR¹⁰, -NR¹⁰R¹¹ and C₁₋₆-alkyl,

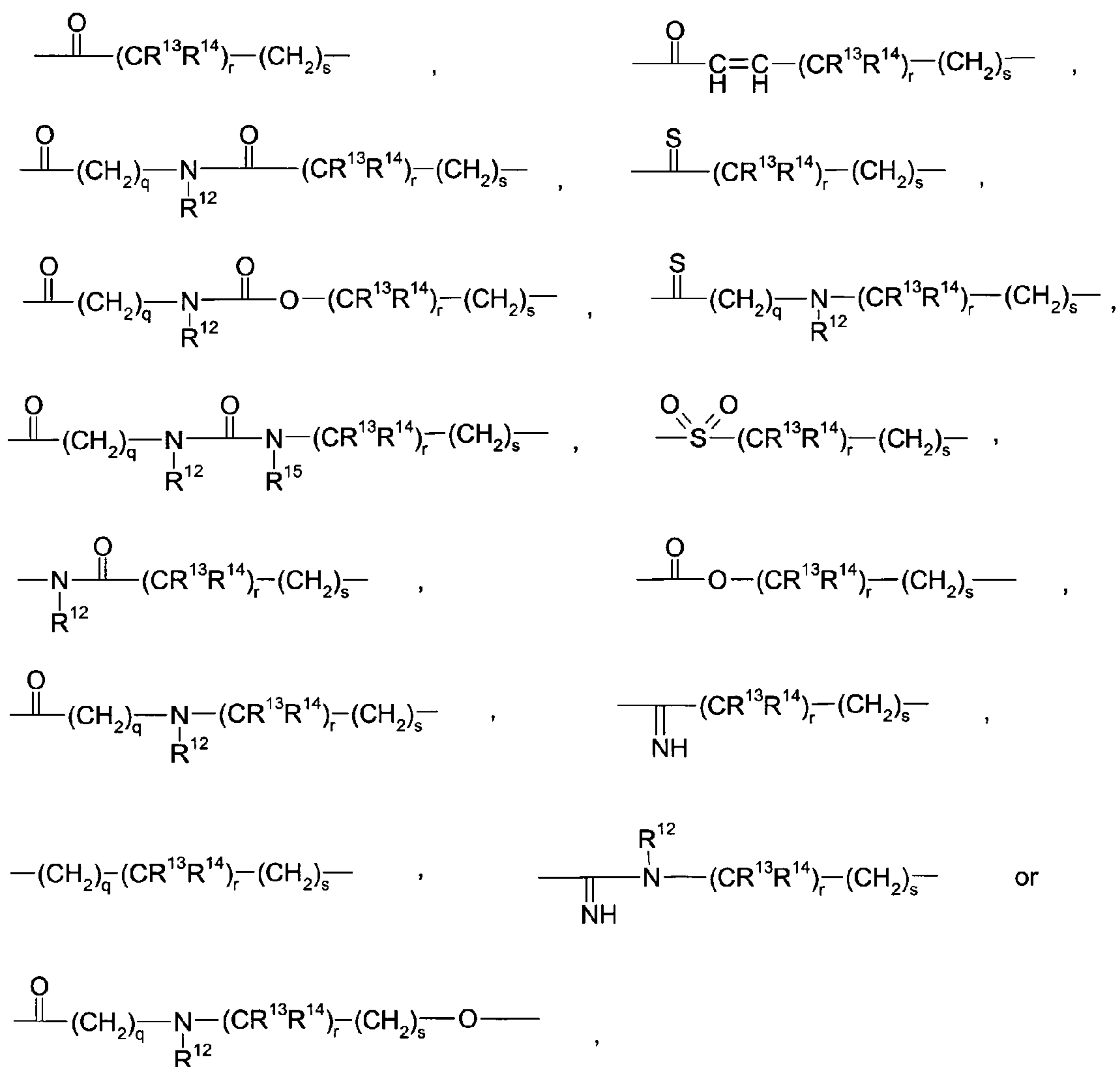
wherein R¹⁰ and R¹¹ independently are hydrogen or C₁₋₆-alkyl;

or -A-Y-Z- together is



R^1 is hydrogen or C_{1-6} -alkyl;

5 X is



wherein

10

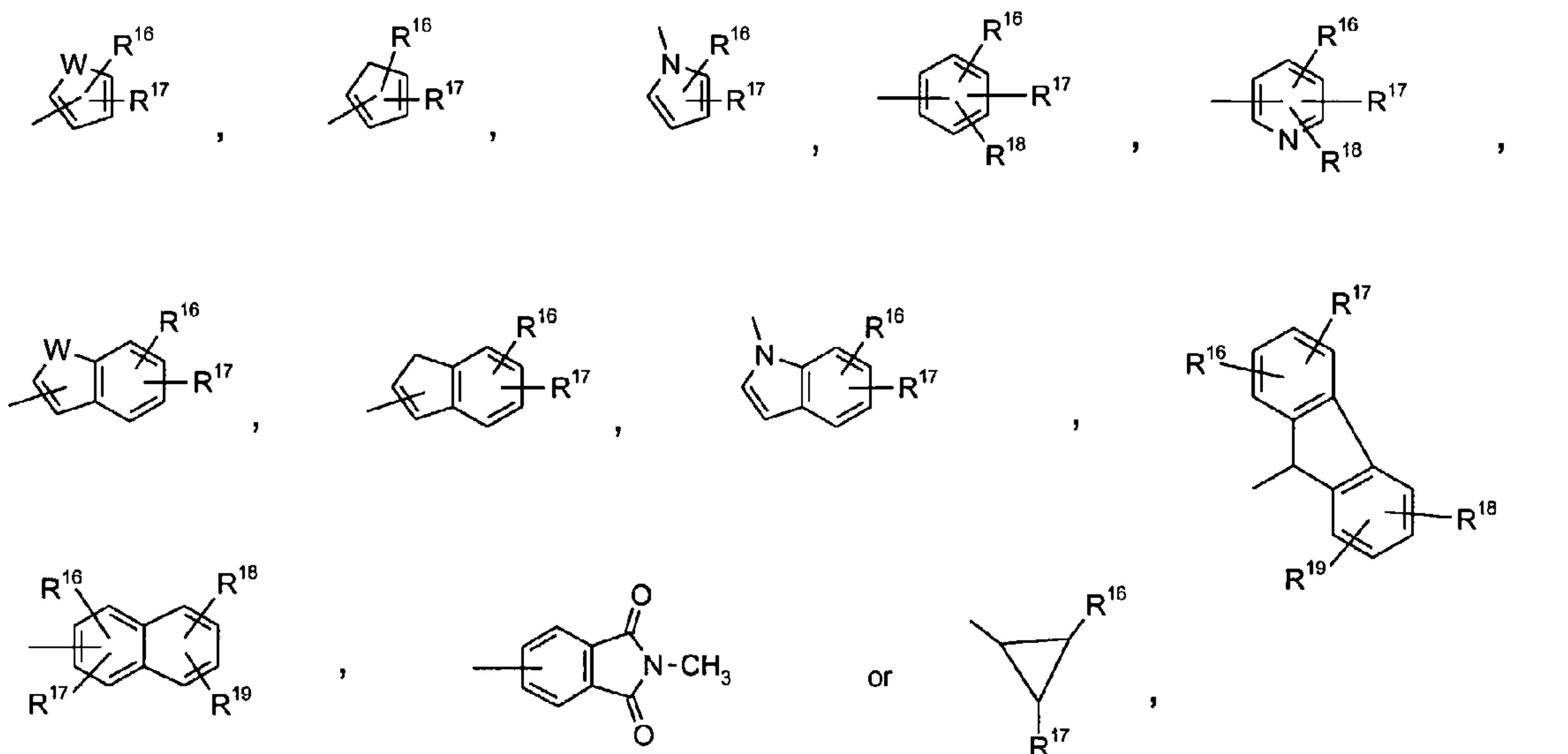
r is 0 or 1,

q and s independently are 0, 1, 2 or 3,

R^{12} , R^{13} , R^{14} and R^{15} independently are hydrogen or C_{1-6} -alkyl;

5

D is



10 wherein

W is -O-, -S- or -NR²⁰-,

wherein R^{20} is hydrogen or C_{1-6} -alkyl,

15

R^{16} , R^{17} , R^{18} and R^{19} independently are

hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 20 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹,
 -C(O)R²¹ or -C(O)OR²¹,

C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF_2 , $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$,
 $-\text{SR}^{21}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$,
 $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$ and $-\text{C}(\text{O})\text{OR}^{21}$,

C_{3-8} -cycloalkyl, C_{3-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl,
 C_{3-8} -cycloalkyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkyl- C_{2-6} -alkynyl, C_{3-8} -cycloalkenyl- C_{1-6} -alkyl,
 C_{3-8} -cycloalkenyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkynyl, heterocyclyl- C_{1-6} -alkyl, heterocy-
 clyl- C_{2-6} -alkenyl or heterocyclyl- C_{2-6} -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more sub-
 stituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$,
 $-\text{SCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$, $-\text{SR}^{21}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$,
 $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$ and $-\text{C}(\text{O})\text{OR}^{21}$,

C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents se-
 lected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$,
 $-\text{SCF}_3$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$, $-\text{SR}^{21}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$,
 $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{C}(\text{O})\text{R}^{21}$ and
 $-\text{C}(\text{O})\text{OR}^{21}$,

aryl, aryloxy, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkyl, aryl- C_{2-6} -alkenyl, aryl- C_{2-6} -alkynyl, het-
 eroaryl, heteroaryl- C_{1-6} -alkyl, heteroaryl- C_{2-6} -alkenyl or heteroaryl- C_{2-6} -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one
 or more substituents selected from halogen, $-\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$,
 $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{OS}(\text{O})_2\text{CF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{21}$, $-\text{NR}^{21}\text{R}^{22}$,
 $-\text{SR}^{21}$, $-\text{NR}^{21}\text{S}(\text{O})_2\text{R}^{22}$, $-\text{S}(\text{O})_2\text{NR}^{21}\text{R}^{22}$, $-\text{S}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{S}(\text{O})\text{R}^{21}$, $-\text{S}(\text{O})_2\text{R}^{21}$,
 $-\text{OS}(\text{O})_2\text{R}^{21}$, $-\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{OC}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{NR}^{21}\text{C}(\text{O})\text{R}^{22}$, $-\text{CH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$,
 $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{21}\text{R}^{22}$, $-\text{CH}_2\text{OR}^{21}$, $-\text{CH}_2\text{NR}^{21}\text{R}^{22}$, $-\text{OC}(\text{O})\text{R}^{21}$, $-\text{C}(\text{O})\text{R}^{21}$ and
 $-\text{C}(\text{O})\text{OR}^{21}$,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

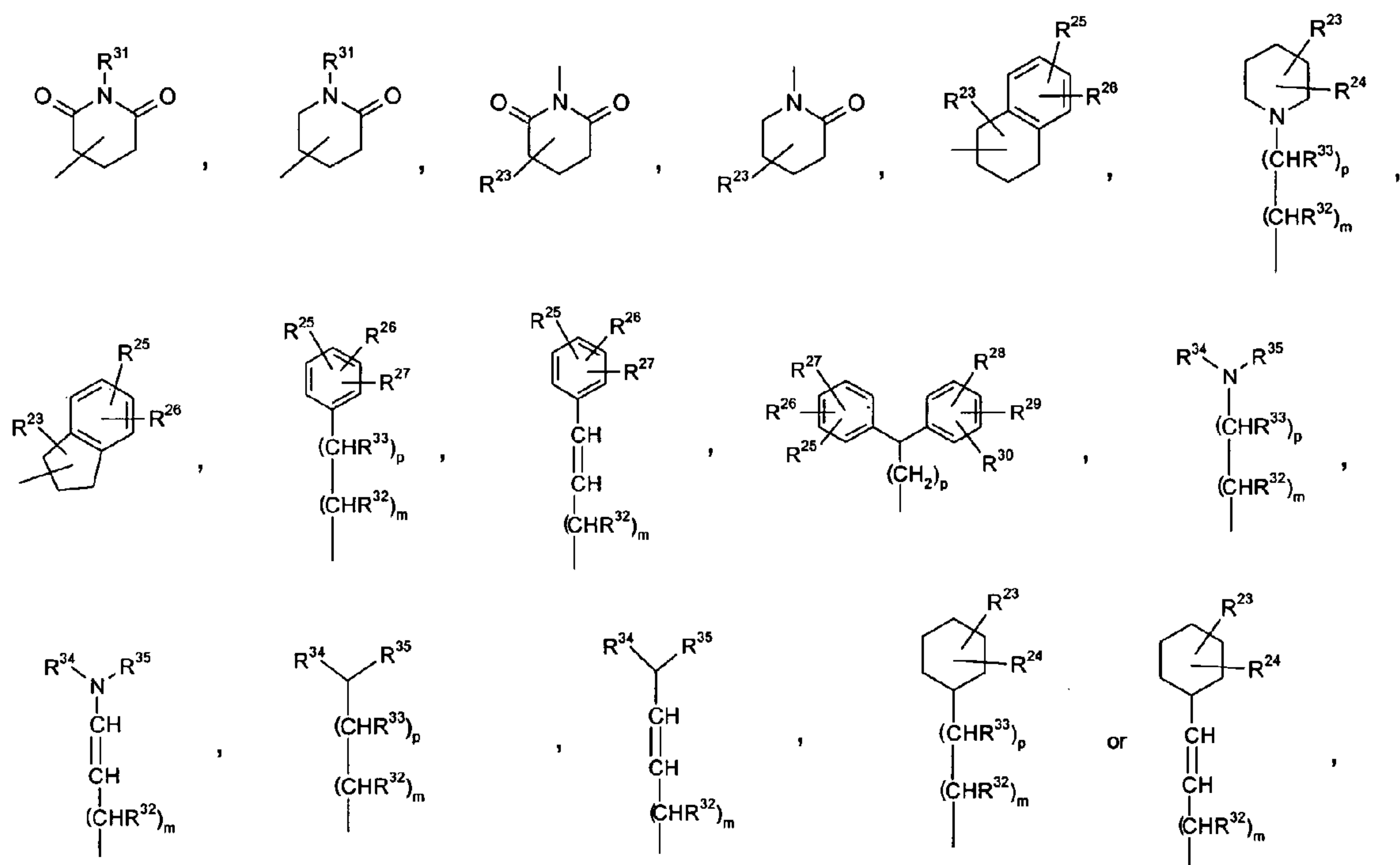
which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
5 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
-OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
-C(O)OR²¹,

wherein R²¹ and R²² independently are hydrogen or C₁₋₆-alkyl, or R²¹ and R²² when attached
10 to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered
heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen,
oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
15 -OCH₂O- or -OCH₂CH₂O-;

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R²³ and R²⁴ may be attached to the same or
20 different ring carbon atoms and wherein a group R³¹ may be attached to a ring nitrogen atom
when present, or

22



wherein

5 m and p independently are 0, 1, 2, 3 or 4,

R^{23} and R^{24} independently are hydrogen, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ or $-\text{C(O)}\text{OR}^{36}$,

10

C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from -
 CHF_2 , $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$,
 15 $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$,
 $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

C_{3-8} -cycloalkyl, C_{3-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

C_{3-8} -cycloalkyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkyl- C_{2-6} -alkynyl, C_{3-8} -cycloalkenyl- C_{1-6} -alkyl,

20 C_{3-8} -cycloalkenyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkynyl, heterocyclyl- C_{1-6} -alkyl, heterocyclyl- C_{2-6} -alkenyl or heterocyclyl- C_{2-6} -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$,
 5 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$,
 10 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

15 aryl, aryloxy, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkyl, aryl- C_{2-6} -alkenyl, aryl- C_{2-6} -alkynyl, heteroaryl, heteroaryl- C_{1-6} -alkyl, heteroaryl- C_{2-6} -alkenyl or heteroaryl- C_{2-6} -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from halogen, $-\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{OS(O)}_2\text{CF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$,
 20 $-\text{SR}^{36}$, $-\text{NR}^{36}\text{S(O)}_2\text{R}^{37}$, $-\text{S(O)}_2\text{NR}^{36}\text{R}^{37}$, $-\text{S(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{OS(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{CH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{CH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{CH}_2\text{OR}^{36}$, $-\text{CH}_2\text{NR}^{36}\text{R}^{37}$, $-\text{OC(O)}\text{R}^{36}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

25 C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S(O)}\text{R}^{36}$, $-\text{S(O)}_2\text{R}^{36}$, $-\text{C(O)}\text{NR}^{36}\text{R}^{37}$,
 30 $-\text{OC(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C(O)}\text{R}^{37}$, $-\text{OCH}_2\text{C(O)}\text{NR}^{36}\text{R}^{37}$, $-\text{C(O)}\text{R}^{36}$ and $-\text{C(O)}\text{OR}^{36}$,

wherein R^{36} and R^{37} independently are hydrogen, C_{1-6} -alkyl or aryl,

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and C₁₋₆-alkyl,

5 wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two
10 double bonds,

or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l-O-, -(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l- or
-S-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l-S-,

15

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

20 R⁴⁰ and R⁴¹ independently are hydrogen or C₁₋₆-alkyl,

R²⁵ to R³⁰ independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C₁₋₆-alkyl or C₃₋₈-cycloalkyl,

25 wherein R⁴² and R⁴³ independently are hydrogen or C₁₋₆-alkyl,

R³¹, R³² and R³³ independently are hydrogen or C₁₋₆-alkyl,

R³⁴ and R³⁵ independently are hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkanoyl, -C(O)NR⁴⁴R⁴⁵
30 or -S(O)₂R⁴⁵,

aryl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkanoyl or aryl-C₁₋₆-alkyl,

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C₁₋₆-alkyl,
35

wherein R^{44} and R^{45} independently are hydrogen or C_{1-6} -alkyl,

or R^{34} and R^{35} when attached to the carbon atom together with the said carbon atom may
 5 form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

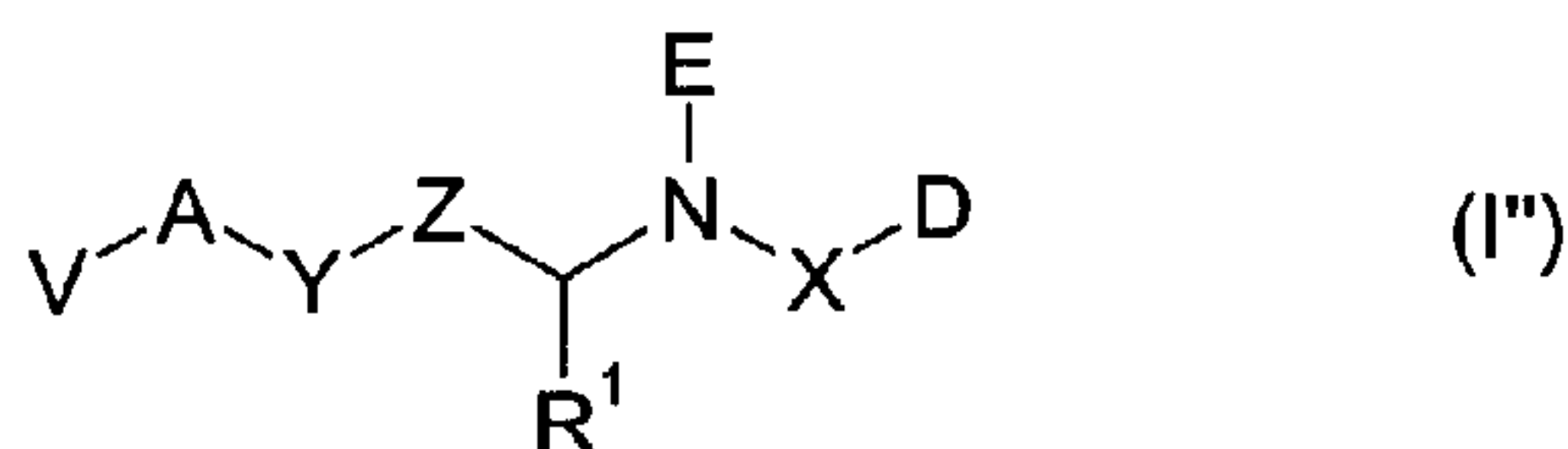
or R^{34} and R^{35} when attached to the nitrogen atom together with the said nitrogen atom may
 10 form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds;

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof;

15 having an IC_{50} value of no greater than $5 \mu M$ as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein.

By a compound of the general formula (I') having an IC_{50} value of no greater than $5 \mu M$ as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) is meant any compound of the defined formula having such activity, without limitation
 20 to any utility or usefulness for treating any specific indication.

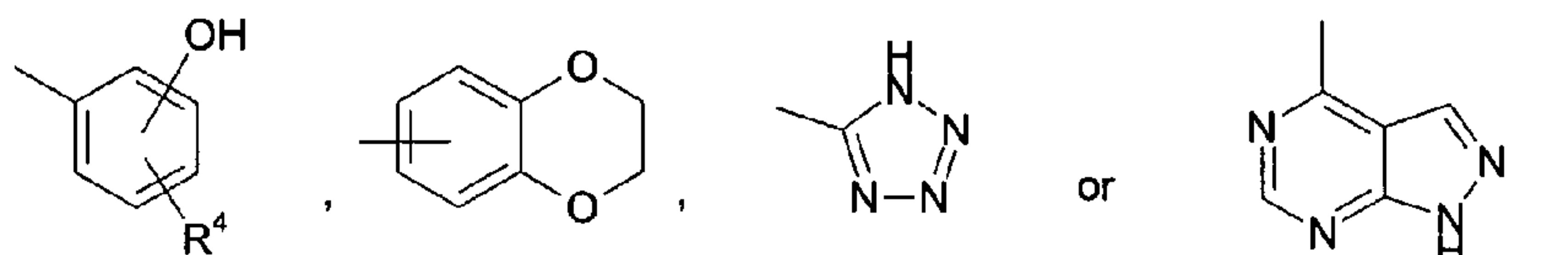
In a further aspect the invention relates to compounds of the general formula (I''):



wherein

26

V is $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-\text{C}(\text{O})\text{NR}^2\text{OR}^3$, $-\text{S}(\text{O})_2\text{OR}^2$,



wherein

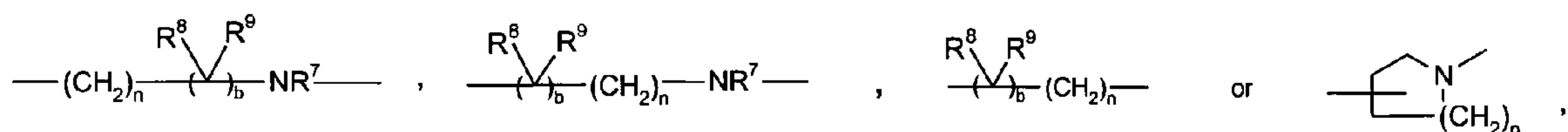
5

R^2 and R^3 independently are hydrogen or C_{1-6} -alkyl,

R^4 is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^5$, $-\text{NR}^5\text{R}^6$ or C_{1-6} -alkyl,

10 wherein R^5 and R^6 independently are hydrogen or C_{1-6} -alkyl,

A is



15

wherein

b is 0 or 1,

20 n is 0, 1, 2 or 3,

R^7 is hydrogen, C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

R^8 and R^9 independently are hydrogen or C_{1-6} -alkyl,

25

Y is $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$ or a valence bond,

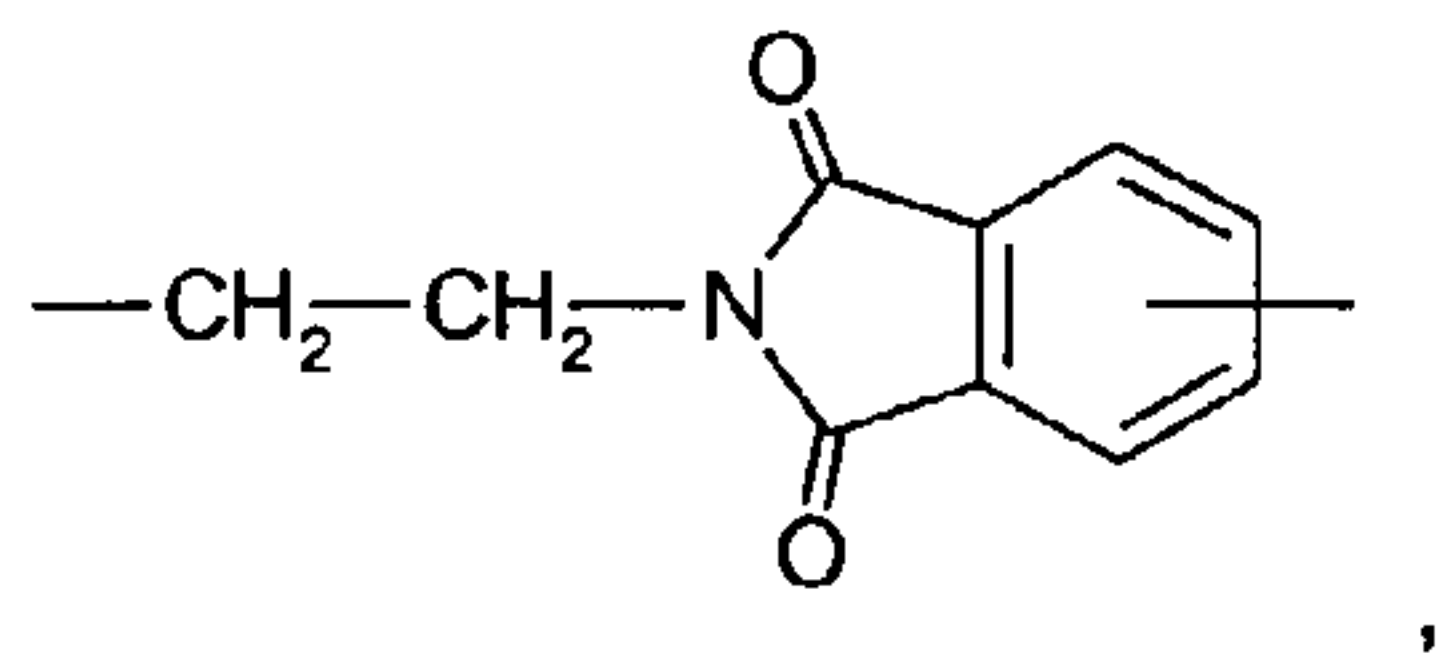
Z is phenylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

30

which may optionally be attached to one or two groups R^{46} and R^{47} selected from hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{NO}_2$, $-\text{OR}^{10}$, $-\text{NR}^{10}\text{R}^{11}$ and C_{1-6} -alkyl,

wherein R^{10} and R^{11} independently are hydrogen or C_{1-6} -alkyl,

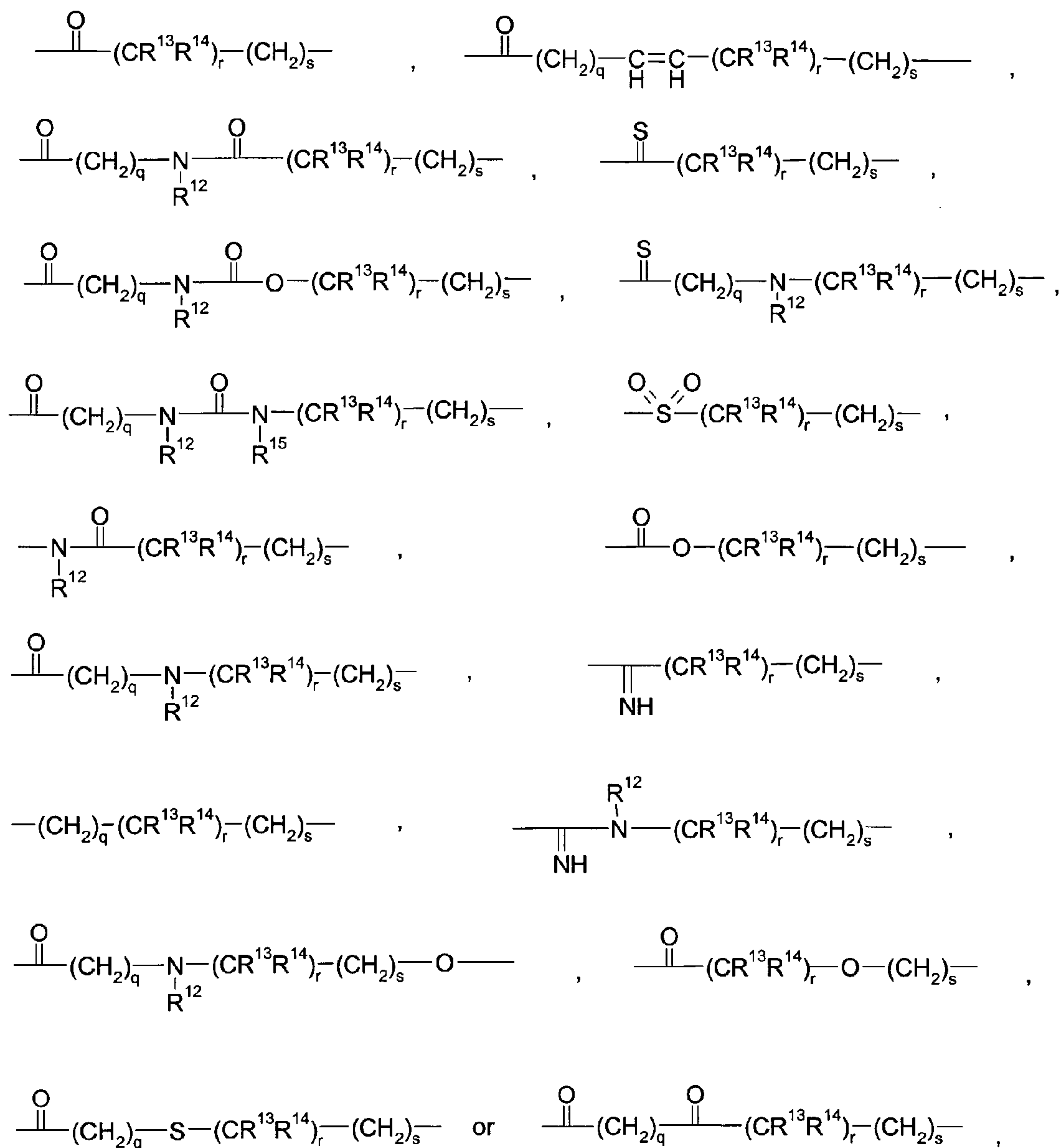
or -A-Y-Z- together are



5

R^1 is hydrogen or C_{1-6} -alkyl,

X is



5 wherein

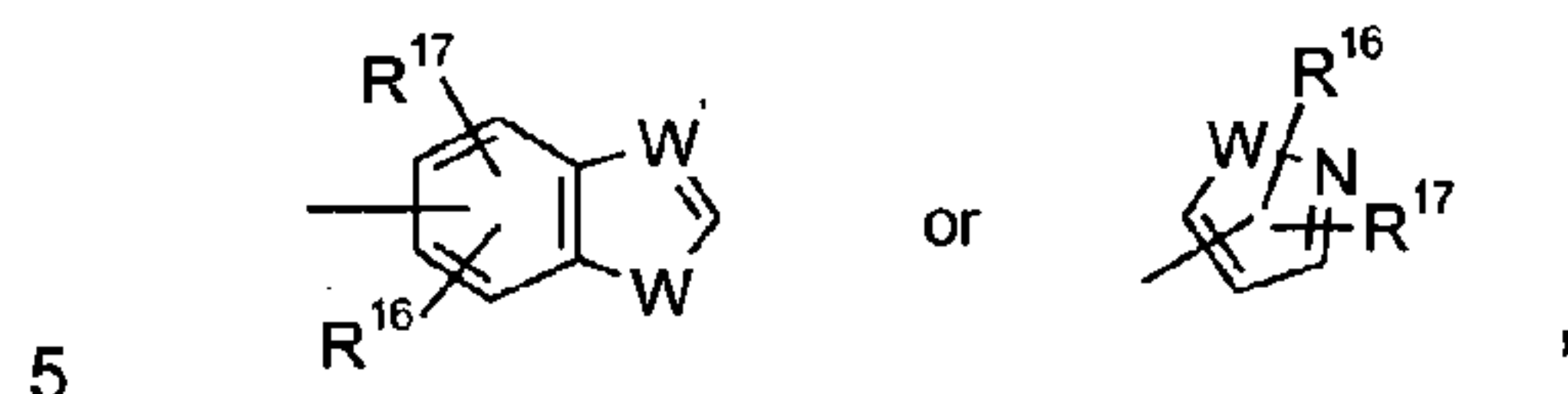
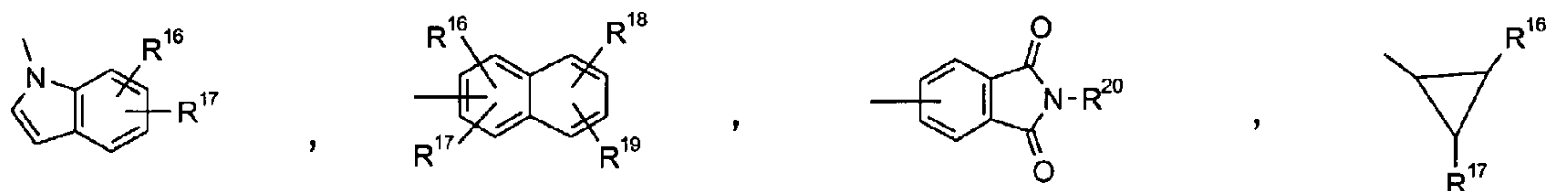
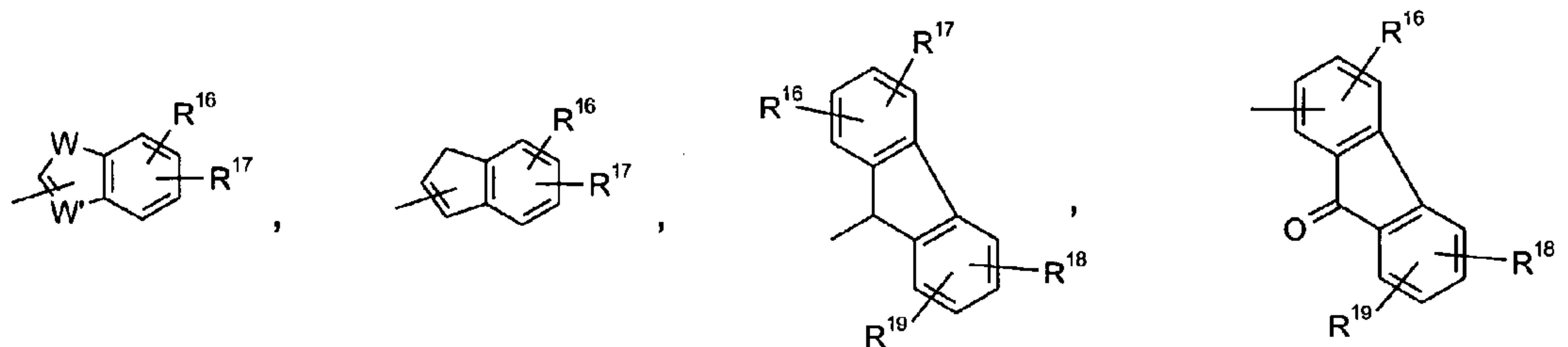
r is 0 or 1,

q and s independently are 0, 1, 2 or 3,









W is -O-, -S-, -S(O)₂- or -NR²⁰-,

W' is $=CR^{20'}$ - or $=N-$,

R²⁰ and R^{20'} are hydrogen, C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

15 R^{16} , R^{17} , R^{18} and R^{19} independently are

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,

-NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
-OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from
-CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
-SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
-OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- C₃₋₈-cycloalkyl, C₃₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cyclo-
alkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyloxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio, C₃₋₈-cycloalkylthio,
C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₃₋₈-cycloalkenyl-C₁₋₆-alkyl,
C₃₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, het-
erocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more sub-
stituents selected from

-CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
-SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
-OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents se-
lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
-SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
-OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
-C(O)OR²¹,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-
C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-
C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 5 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 -OC(O)R²¹, -C(O)R²¹ and -C(O)OR²¹,

10 C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 15 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

wherein R²¹ and R²² independently are hydrogen, -CF₃, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl or heteroaryl, or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8
 20 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
 25 -(CR^{16'}R^{17'})_a-O-(CR^{18'}R^{19'})_c-O-,

wherein

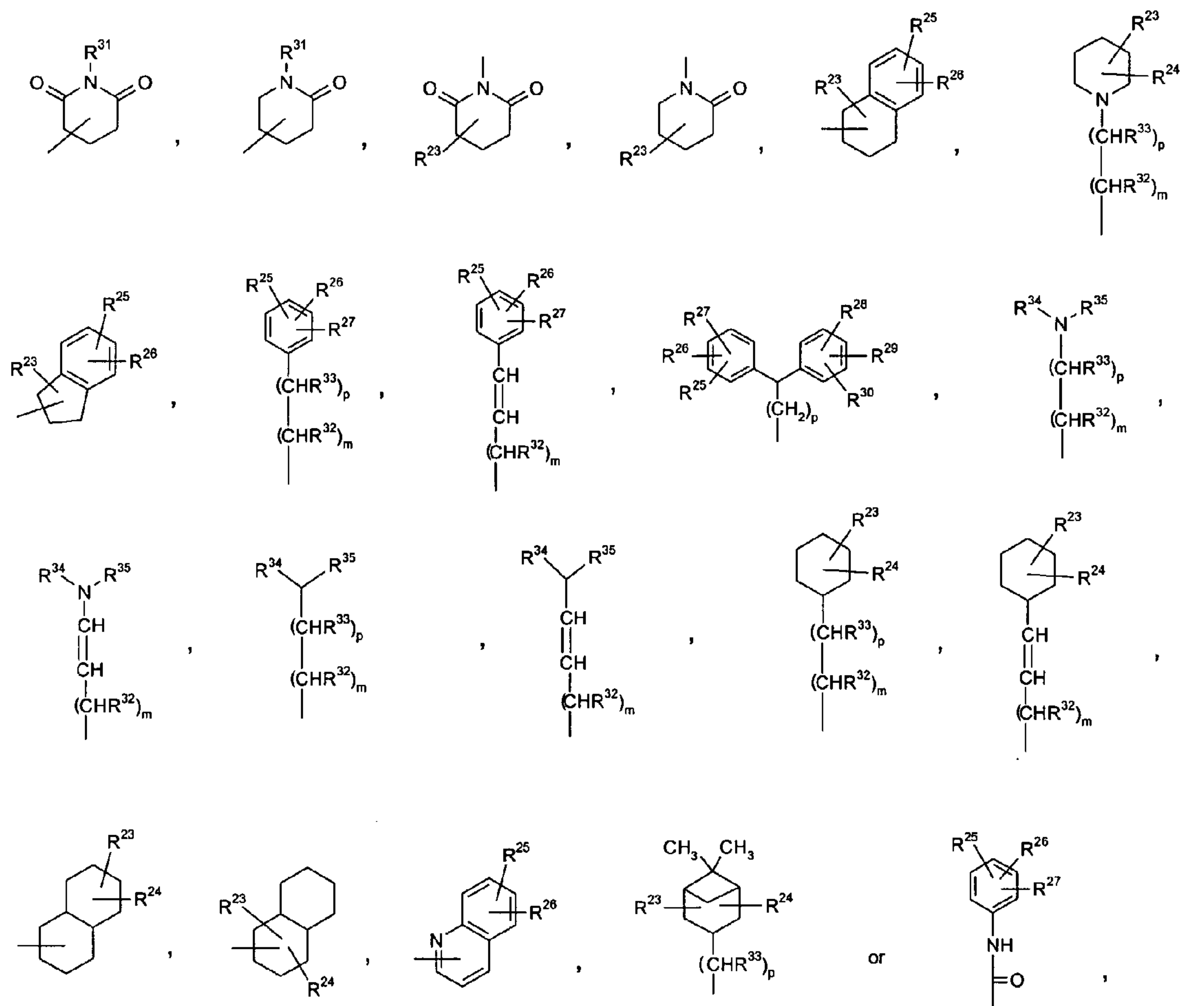
a is 0, 1 or 2,

c is 1 or 2,

R^{16'}, R^{17'}, R^{18'} and R^{19'} independently are hydrogen, C₁₋₆-alkyl or halogen,

E is a 3 to 9 membered mono- or bicyclic ring which may optionally contain one or two double bonds and which may optionally contain one or two heteroatoms selected from nitrogen, oxygen and sulfur, wherein one or two groups R^{23} and R^{24} may be attached to the same or different ring carbon atoms and wherein a group R^{31} may be attached to a ring nitrogen atom

5 when present, or



wherein

- 10 m and p independently are 0, 1, 2, 3 or 4, with the proviso that when both m and p are present in the same formula at least one of m and p is different from 0,

R^{23} and R^{24} independently are

- hydrogen, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S}(\text{O})\text{R}^{36}$, $-\text{S}(\text{O})_2\text{R}^{36}$, $-\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{OC}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C}(\text{O})\text{R}^{37}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{C}(\text{O})\text{R}^{36}$ or $-\text{C}(\text{O})\text{OR}^{36}$,

- 5 • C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from

$-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S}(\text{O})\text{R}^{36}$, $-\text{S}(\text{O})_2\text{R}^{36}$, $-\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{OC}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C}(\text{O})\text{R}^{37}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{C}(\text{O})\text{R}^{36}$ and $-\text{C}(\text{O})\text{OR}^{36}$,

- C_{3-8} -cycloalkyl, C_{3-8} -cycloalkylidene, C_{3-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, C_{3-8} -cycloalkyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkyl- C_{2-6} -alkynyl, C_{3-8} -cycloalkenyl- C_{1-6} -alkyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkenyl, C_{3-8} -cycloalkenyl- C_{2-6} -alkynyl, heterocyclyl- C_{1-6} -alkyl, heterocyclyl- C_{2-6} -alkenyl or heterocyclyl- C_{2-6} -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from

$-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S}(\text{O})\text{R}^{36}$, $-\text{S}(\text{O})_2\text{R}^{36}$, $-\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{OC}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C}(\text{O})\text{R}^{37}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{C}(\text{O})\text{R}^{36}$ and $-\text{C}(\text{O})\text{OR}^{36}$,

C_{1-6} -alkyl, C_{2-6} -alkenyl and C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{SCF}_3$, $-\text{OR}^{36}$, $-\text{NR}^{36}\text{R}^{37}$, $-\text{SR}^{36}$, $-\text{S}(\text{O})\text{R}^{36}$, $-\text{S}(\text{O})_2\text{R}^{36}$, $-\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{OC}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{NR}^{36}\text{C}(\text{O})\text{R}^{37}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{36}\text{R}^{37}$, $-\text{C}(\text{O})\text{R}^{36}$ and $-\text{C}(\text{O})\text{OR}^{36}$,

- aryl, aryloxy, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkyl, aryl- C_{2-6} -alkenyl, aryl- C_{2-6} -alkynyl, heteroaryl, heteroaryl- C_{1-6} -alkyl, heteroaryl- C_{2-6} -alkenyl or heteroaryl- C_{2-6} -alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 5 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -NR³⁶S(O)₂R³⁷, -S(O)₂NR³⁶R³⁷,
 -S(O)NR³⁶R³⁷, -S(O)R³⁶, -S(O)₂R³⁶, -OS(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷,
 -NR³⁶C(O)R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂OR³⁶, -CH₂NR³⁶R³⁷,
 -OC(O)R³⁶, -C(O)R³⁶ and -C(O)OR³⁶,

10 C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
 15 -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
 -C(O)OR³⁶,

wherein R³⁶ and R³⁷ independently are hydrogen, C₁₋₆-alkyl or aryl,

20 of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and
 C₁₋₆-alkyl,

wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

25 or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

30 or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l-O-, -(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l- or
 -S-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_l-S-,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

5 R^{40} and R^{41} independently are hydrogen or C_{1-6} -alkyl,

R^{25} to R^{30} independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{3-8} -cycloalkenyl,

10 wherein R^{42} and R^{43} independently are hydrogen or C_{1-6} -alkyl, or

R^{42} and R^{43} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two
15 double bonds,

R^{31} , R^{32} and R^{33} independently are hydrogen or C_{1-6} -alkyl,

R^{34} and R^{35} independently are

20

- hydrogen, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{1-6} -alkanoyl, -C(O)NR⁴⁴R⁴⁵ or -S(O)₂R⁴⁵,
- aryl, aroyl, aryl- C_{1-6} -alkoxy, aryl- C_{1-6} -alkanoyl or aryl- C_{1-6} -alkyl,

25

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C_{1-6} -alkyl,

wherein R^{44} and R^{45} independently are hydrogen or C_{1-6} -alkyl, or

30

R^{34} and R^{35} when attached to the carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

35

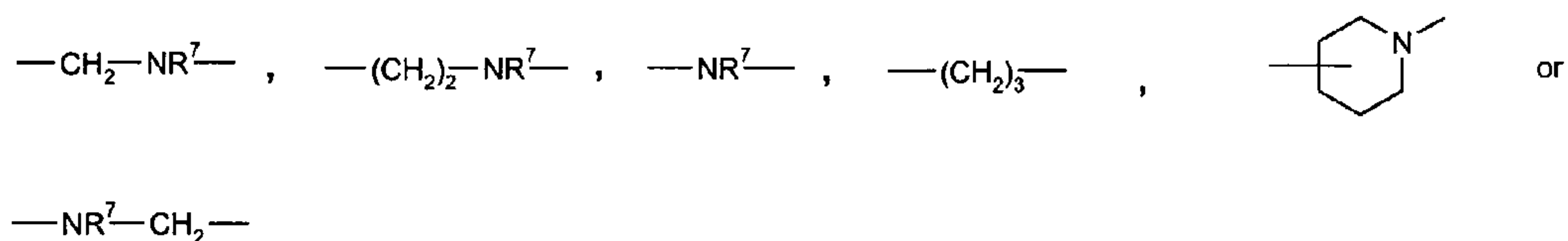
R^{34} and R^{35} when attached to the nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroa-

toms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In a preferred embodiment V is -C(O)OH, -S(O)₂OH, -C(O)NHOH or 5-tetrazolyl, and more preferred -C(O)OH or 5-tetrazolyl.

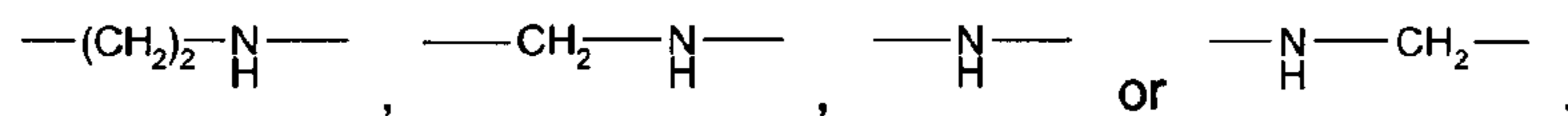
10 In a preferred embodiment A is



wherein R⁷ is as defined for formula (I).

15

More preferred A is

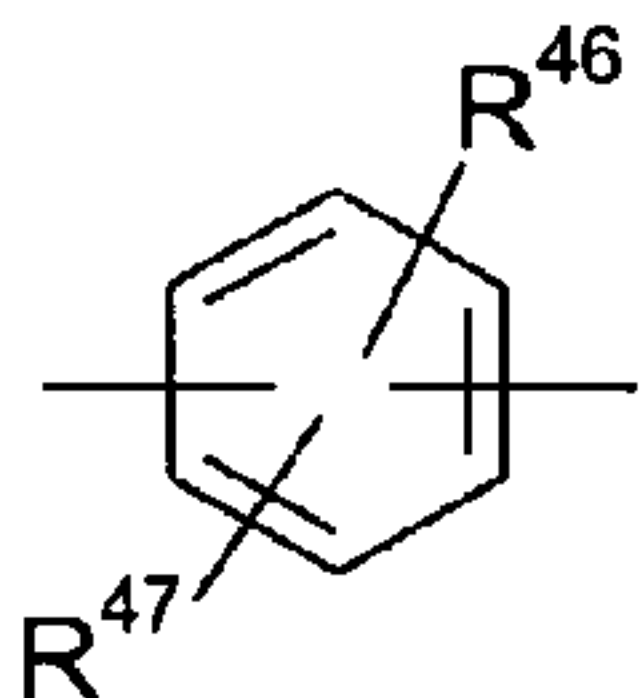


20 In a preferred embodiment Y is -C(O)-.

In another preferred embodiment Y is a valence bond.

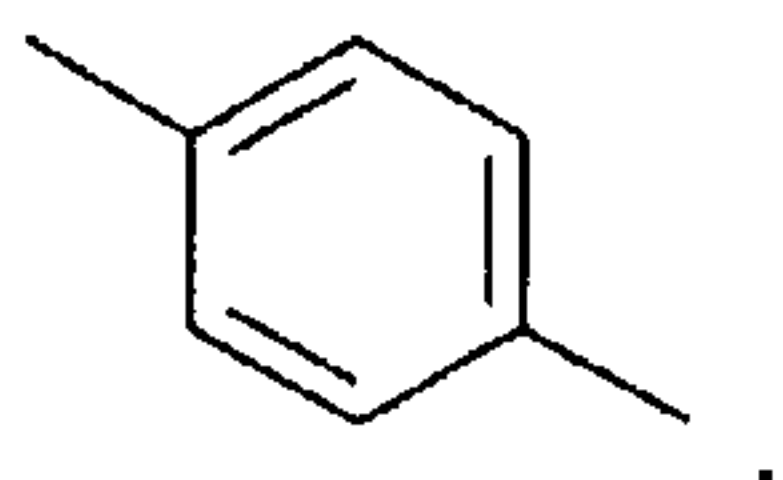
In a preferred embodiment Z is

25



wherein R⁴⁶ and R⁴⁷ are as defined for formula (I).

More preferably, Z is

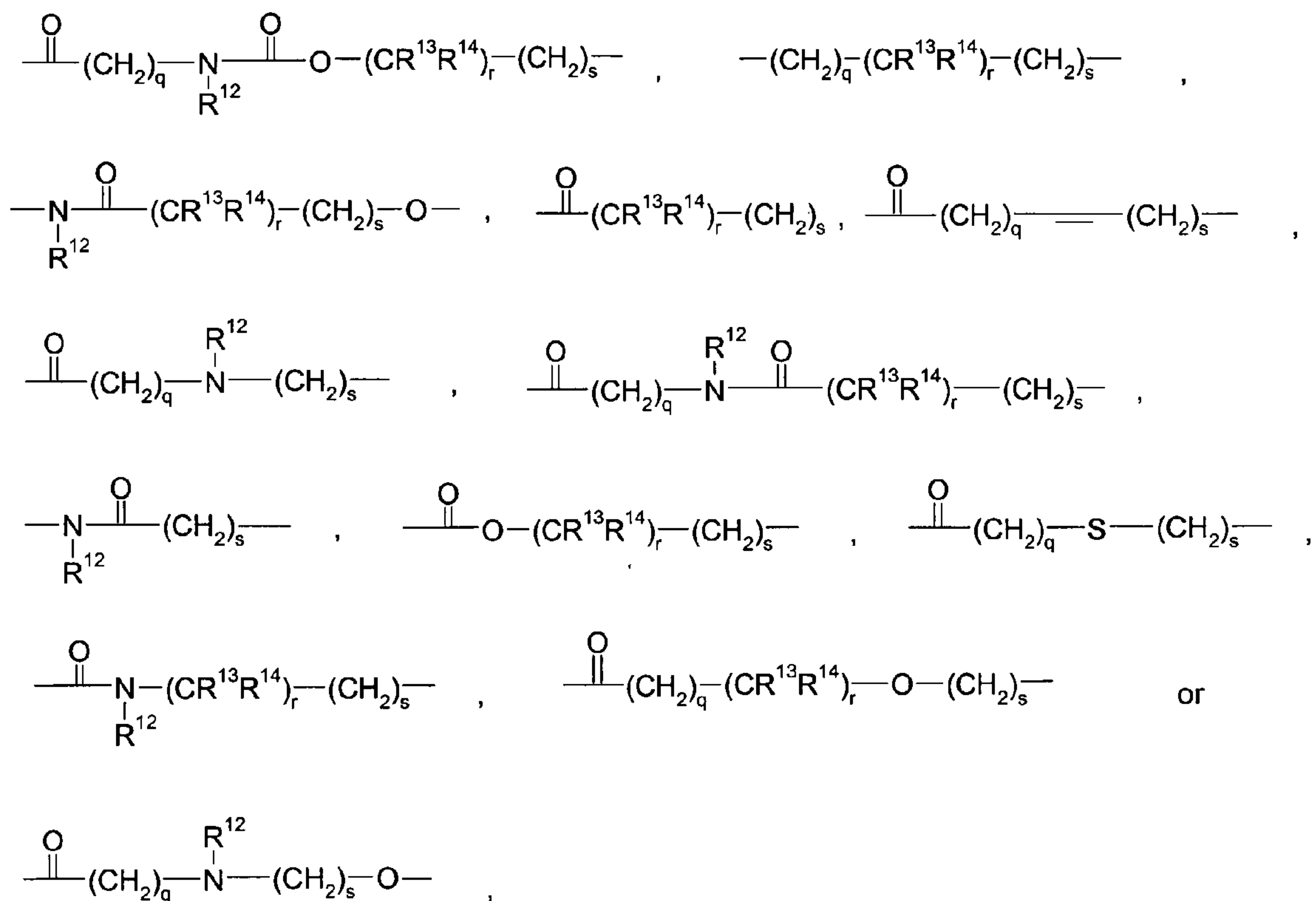


5 In a preferred embodiment R^1 is hydrogen.

In another preferred embodiment R^1 is methyl.

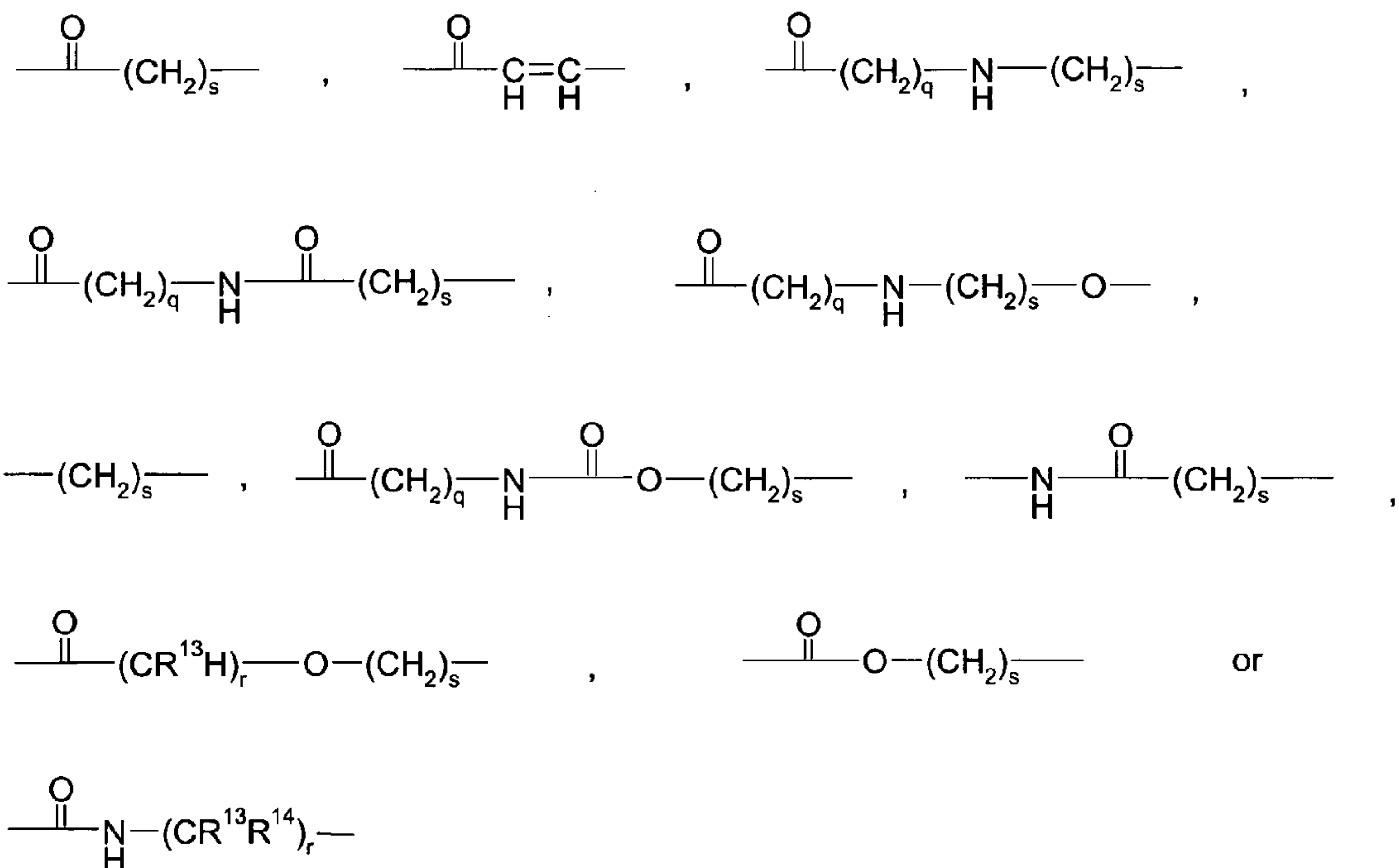
In a preferred embodiment X is

10



wherein q, r, s, R^{12} , R^{13} and R^{14} are as defined for formula (I).

More preferably, X is



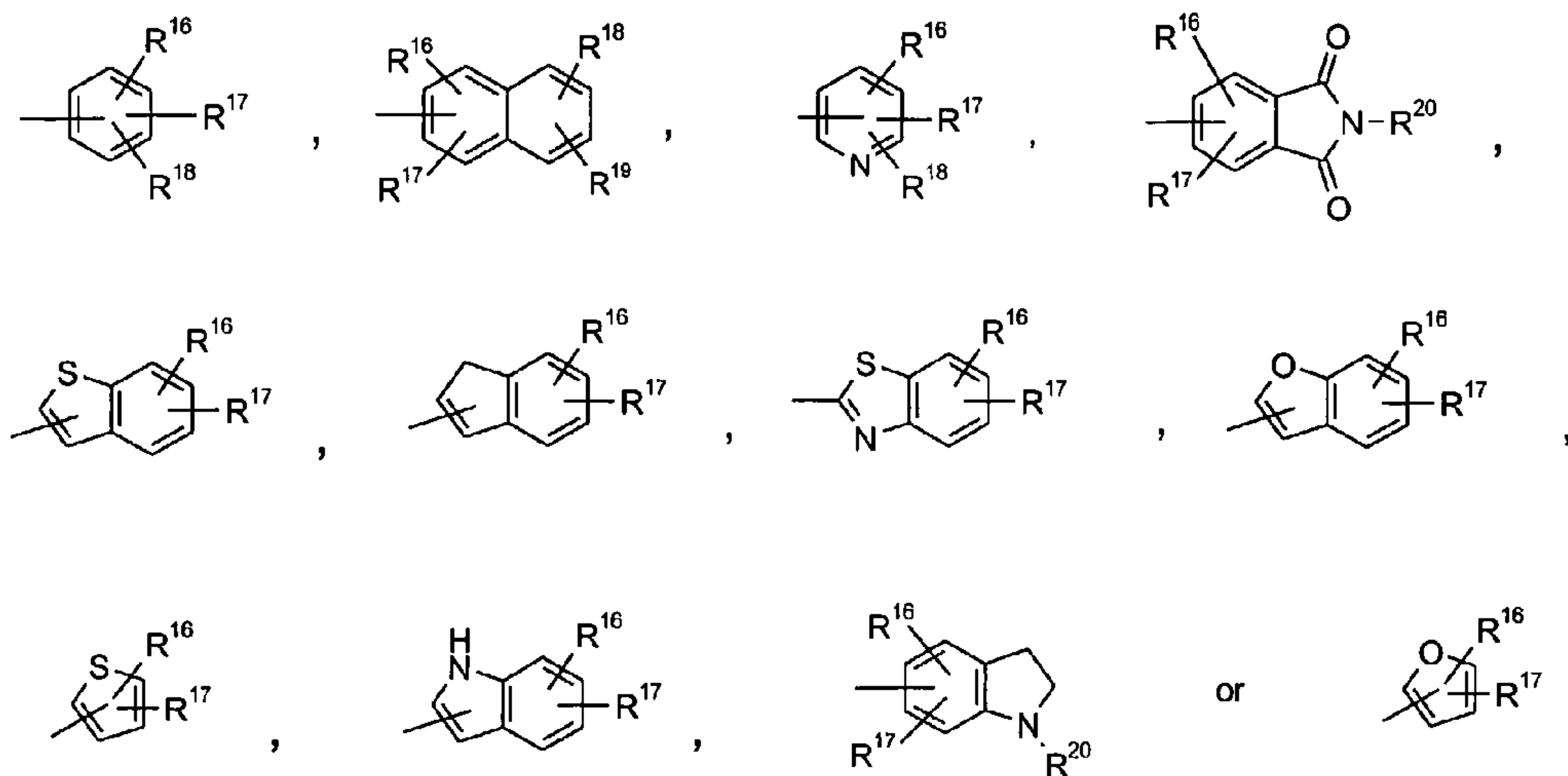
- 5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R¹³ is hydrogen or C₁₋₆-alkyl.

Even more preferably, X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -C(O)CH=CH-, -(CH₂)_s-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

- 10 Still more preferably, X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -(CH₂)-, -C(O)- or -NHC(O)-.

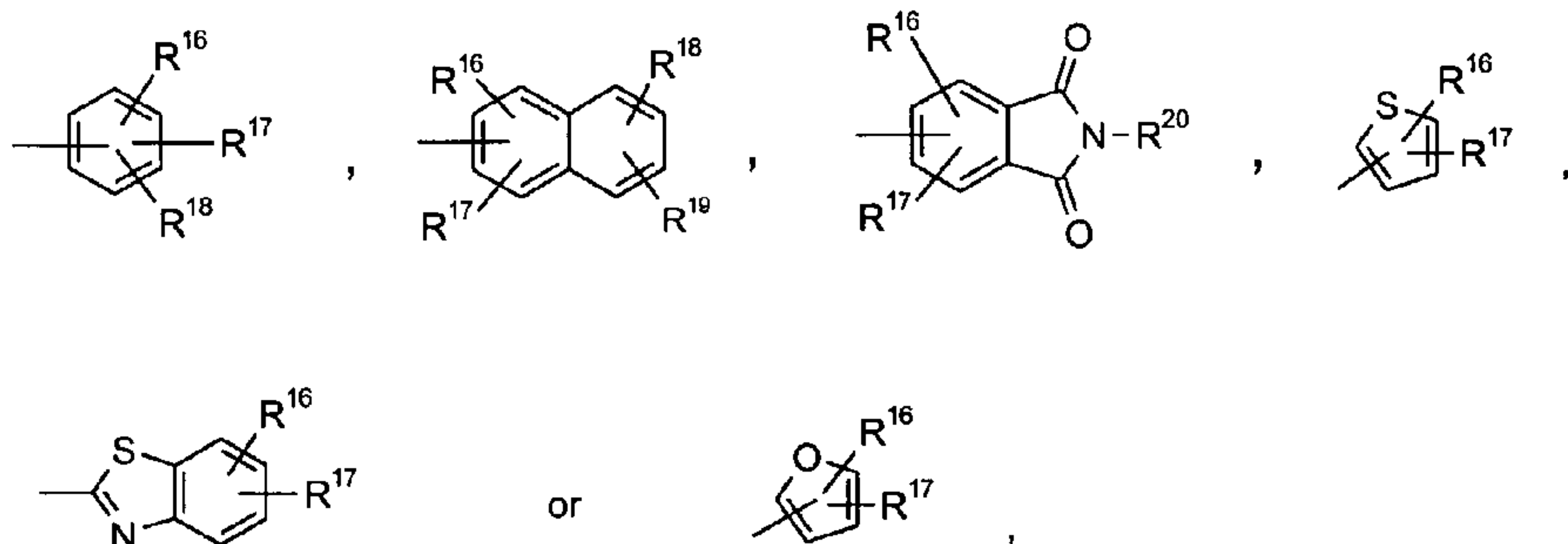
Of these X is preferably -C(O)NH- or -C(O)NHCH(CH₃)-.

In a preferred embodiment D is



5 wherein R^{16} , R^{17} , R^{18} , R^{19} and R^{20} are as defined for formula (I).

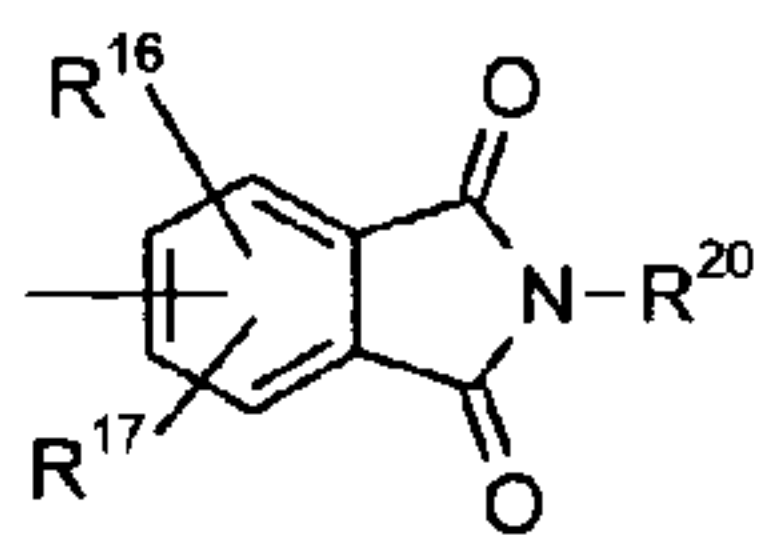
More preferably, D is



10

wherein R^{16} , R^{17} , R^{18} and R^{20} are as defined for formula (I).

In a preferred embodiment D is



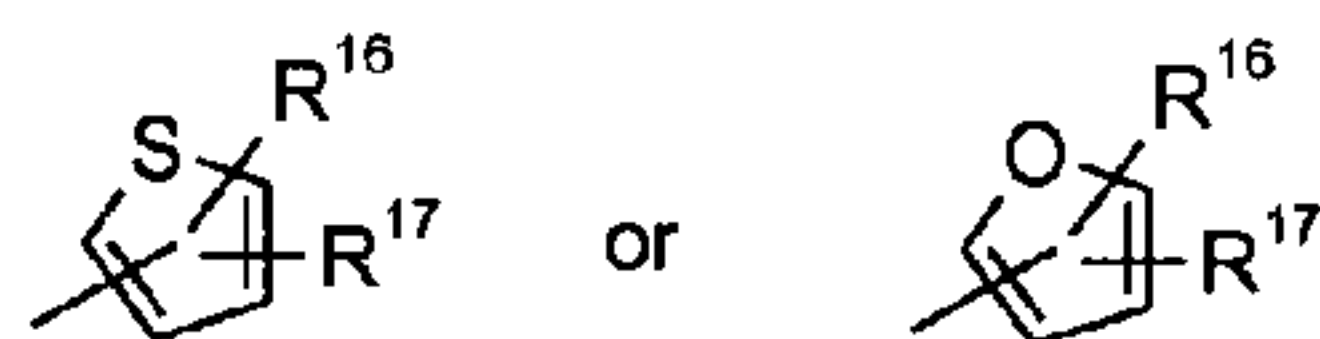
15

wherein R^{16} , R^{17} and R^{20} are as defined for formula (I).

More preferably, R^{16} and R^{17} are both hydrogen and R^{20} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl. Even more preferably, R^{20} is cyclopropylmethyl, butyl or isopropyl, especially preferred isopropyl.

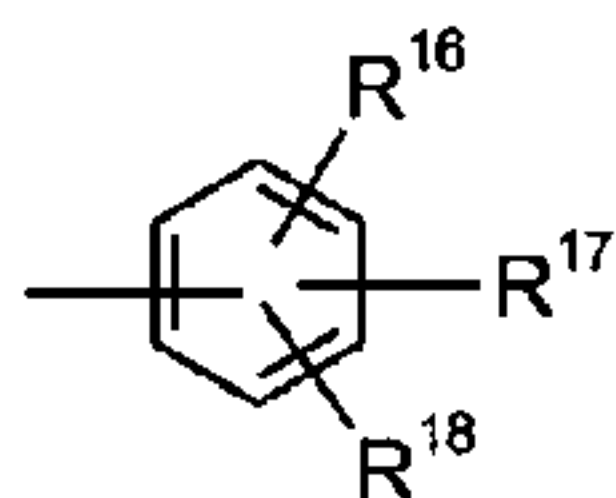
5

In another preferred embodiment D is



10 wherein R^{16} and R^{17} are as defined for formula (I).

In yet another preferred embodiment D is



15

wherein R^{16} , R^{17} and R^{18} are as defined for formula (I).

Preferably, R^{16} , R^{17} and R^{18} are independently

20 hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, hydroxy, -SCF₃, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkyl substituted with -S(O)₂R²¹, C_{1-6} -alkoxy, -S- C_{1-6} -alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio or C_{3-8} -cycloalkylthio,

25 wherein R²¹ and R²² independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, phenyl, phenyl- C_{1-6} -alkyl, 2,3-dihydroindolyl or isoindolyl, or R²¹ and R²² together with the nitrogen atom to which they are attached form a piperidine ring,

phenoxy, phenoxycarbonyl, phenyl, phenyl- C_{1-6} -alkoxy, phenyl- C_{1-6} -alkyl, furanyl, tetrazolyl,

30 benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF₃, -OCF₃, -NO₂, -C(O)OR²¹, -OR²¹, -NR²¹R²² or C_{1-6} -alkyl, wherein R²¹ and R²² independently are hydrogen or C_{1-6} -alkyl, or

wherein R^{16} and R^{17} in adjacent positions form the radical $-O-CH_2-O-$, $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

5 More preferably, R^{16} , R^{17} and R^{18} are independently

hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkyl substituted with $-S(O)_2R^{21}$, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OR^{21}$, $-C(O)R^{21}$, $-CH_2(O)R^{21}$, $-C(O)NR^{21}R^{22}$, $-S(O)R^{21}$, $-S(O)_2R^{21}$, $-S(O)_2CF_3$, $-S(O)_2NR^{21}R^{22}$, C_{3-8} -cyclo-
10 alkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio or C_{3-8} -cycloalkylthio,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, phenyl or 2,3-dihydroindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

15

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, $-C(O)OR^{21}$ or C_{1-6} -alkyl, wherein R^{21} is hydrogen or C_{1-6} -alkyl, or

20

wherein R^{16} and R^{17} in adjacent positions form the radical $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

Even more preferably, R^{16} , R^{17} and R^{18} independently are

25

hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OR^{21}$, $-C(O)R^{21}$, $-CH_2(O)R^{21}$, $-C(O)NR^{21}R^{22}$, $-S(O)_2R^{21}$, $-(O)_2CF_3$ or $-S(O)_2NR^{21}R^{22}$,

wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, phenyl or
30 2,3-dihydroindolyl,

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, $-C(O)OR^{21}$ or C_{1-6} -alkyl, wherein R^{21} is hydrogen or C_{1-6} -alkyl, or

35

wherein R^{16} and R^{17} in adjacent positions form the radical $-CF_2-O-CF_2-O-$ or $-O-CF_2-CF_2-O-$, and R^{18} is hydrogen.

Still more preferably, R^{16} , R^{17} and R^{18} are independently hydrogen, halogen, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, $-SCF_3$, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-S-C_{1-6}$ -alkyl, $-C(O)OC_{1-6}$ -alkyl, $-S(O)_2C_{1-6}$ -alkyl, $-S(O)_2CF_3$, $-C(O)N(C_{1-6}$ -alkyl)(C_{1-6} -alkyl), $-S(O)_2N(phenyl)(C_{1-6}$ -alkyl), $-C(=O)C_{1-6}$ -alkyl, $-CH_2OH$, $-CH_2O(tri-C_{1-6}$ -alkylsilyl), 2,3-dihydroindol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-yl).

In a preferred embodiment one of R^{16} to R^{18} is hydrogen.

In another preferred embodiment two of R^{16} to R^{18} are hydrogen.

In yet another preferred embodiment R^{16} and R^{17} are both hydrogen and R^{18} is $-OCF_3$, $-SCF_3$, $-CF_3$, $-S(O)_2CH_3$, phenyl, halogen, C_{1-6} -alkyl, nitro, $-S-C_{1-6}$ -alkyl or $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.

In still another preferred embodiment R^{16} and R^{17} are both hydrogen and R^{18} is $-OCF_3$ or halogen.

In a further embodiment R^{16} is hydrogen and R^{17} and R^{18} are both halogen or are both $-CF_3$.

In yet a further embodiment R^{16} is hydrogen, R^{17} is $-CF_3$ and R^{18} is halogen, $-CN$, C_{1-6} -alkoxy or $-OCF_3$.

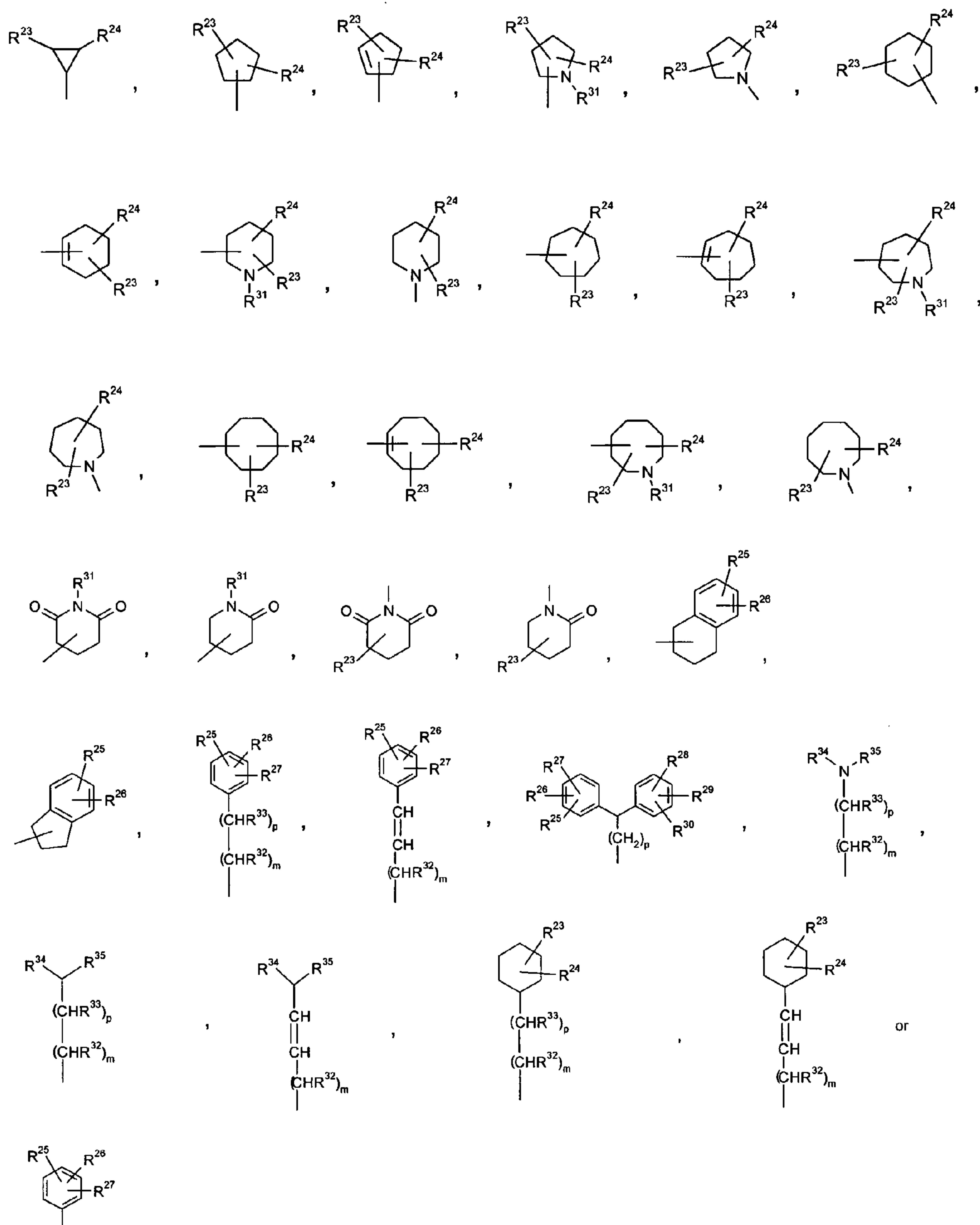
In still a further embodiment R^{16} is hydrogen, R^{17} is $-OCF_3$ and R^{18} is $-S(O)_2CH_3$, $-CH_2O-tri-C_{1-6}$ -alkylsilyl, benzoxazolyl or $-CH_2OH$.

In another embodiment R^{16} is hydrogen, R^{17} is C_{1-6} -alkyl and R^{18} is $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.

In still another embodiment R^{16} , R^{17} and R^{18} are selected from hydrogen, $-OCF_3$, $-CF_3$, $-Br$, $-F$ and $-Cl$.

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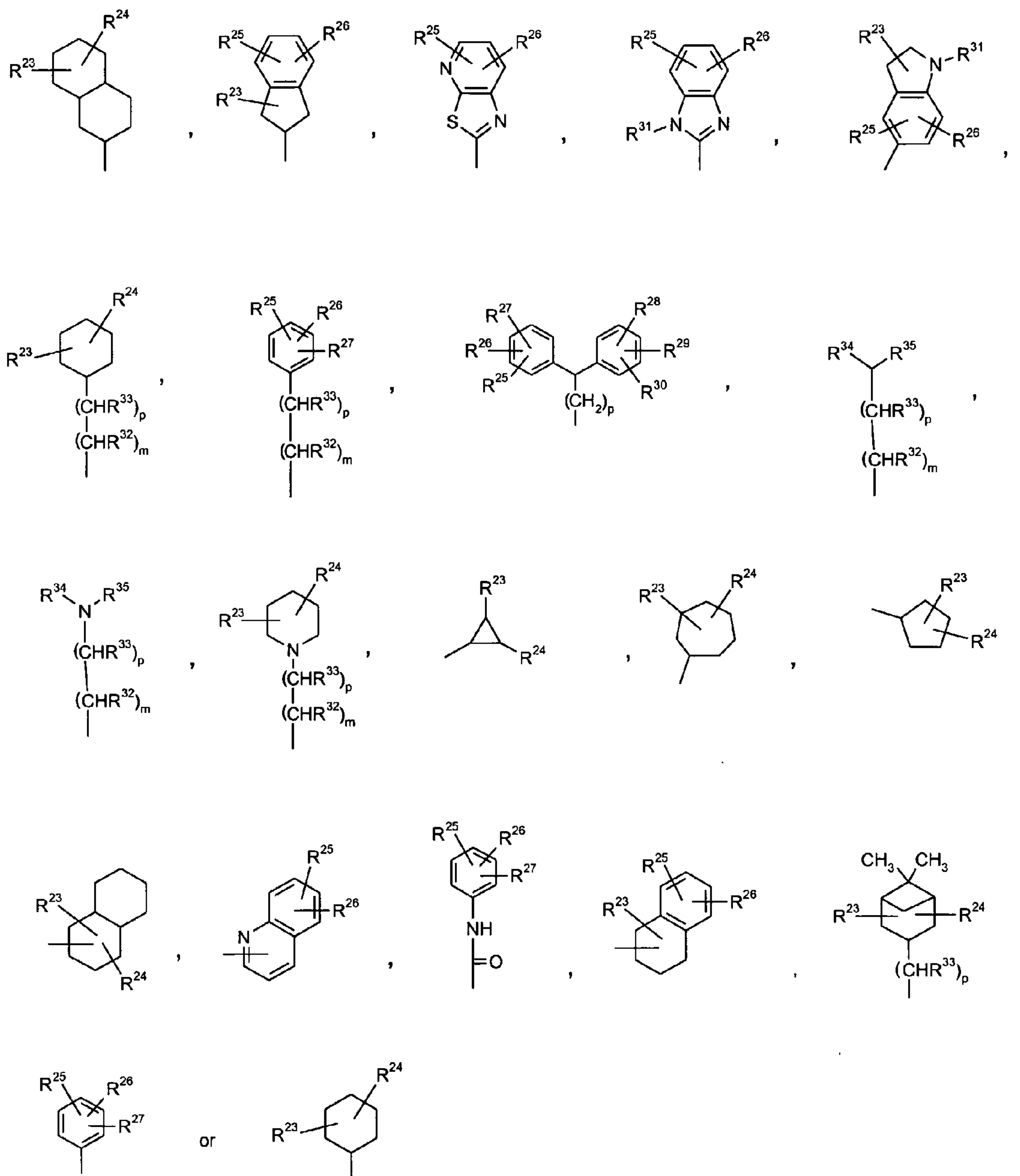
In a preferred embodiment E is



wherein

m, p and R^{23} to R^{35} are as defined for formula (I).

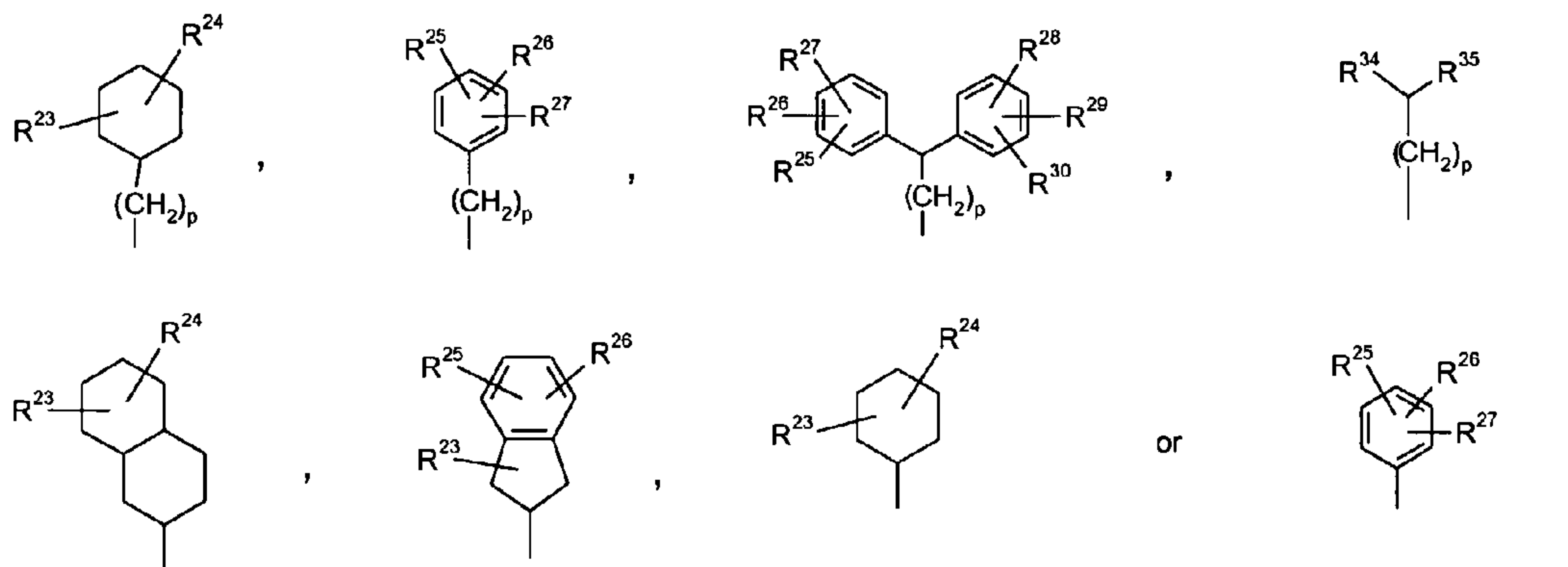
5 Preferably, E is



wherein m, p and R^{23} to R^{35} are as defined for formula (I).

45

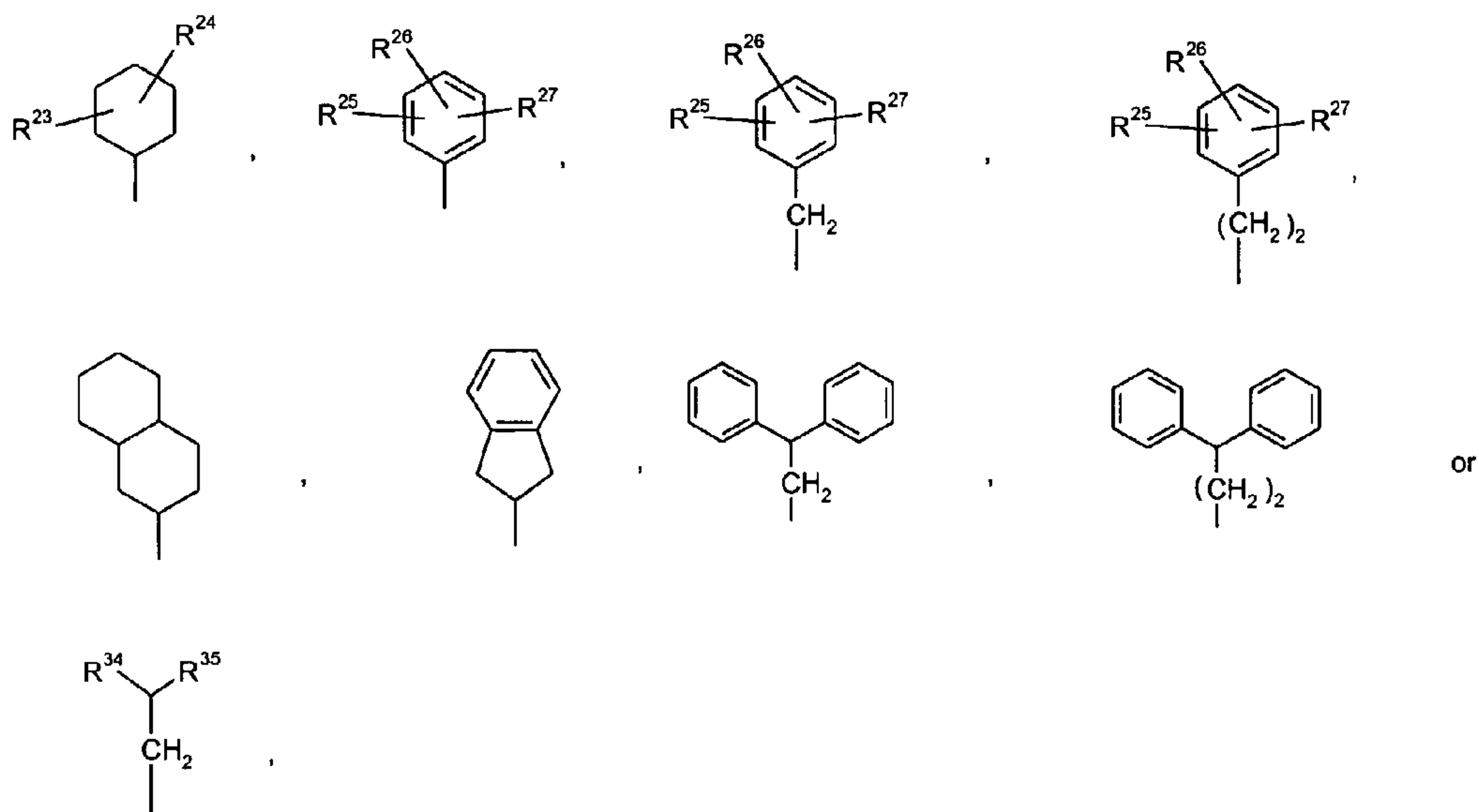
More preferably, E is



5

wherein p , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{34} and R^{35} are as defined for formula (I).

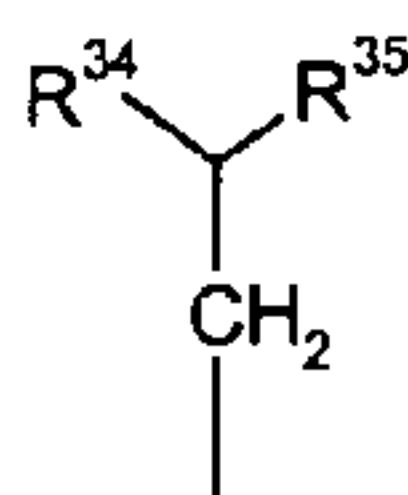
Even more preferably, E is

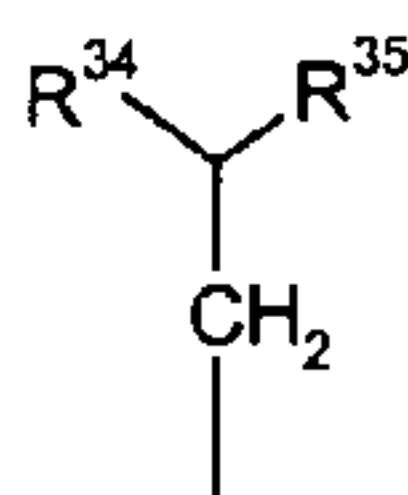


10

wherein R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{34} and R^{35} are as defined for formula (I).

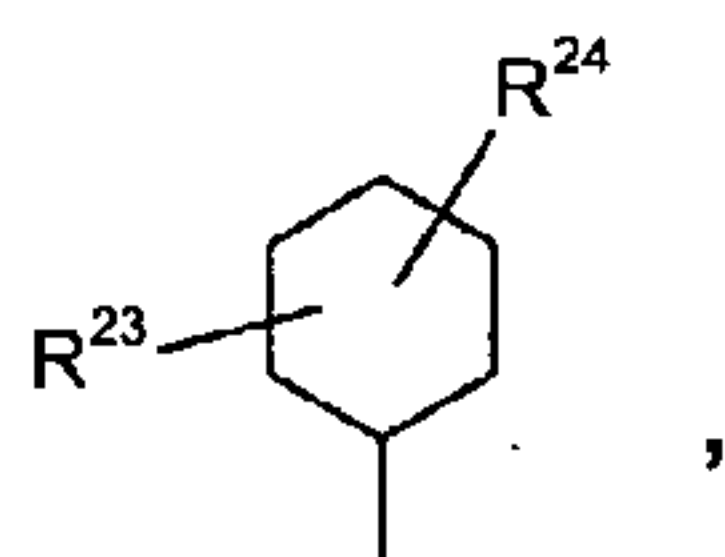
46



When E is , R^{34} and R^{35} are preferably independently C_{1-6} -alkyl, hydrogen or C_{1-6} -alkoxy. More preferably, R^{34} and R^{35} are both C_{1-6} -alkyl.

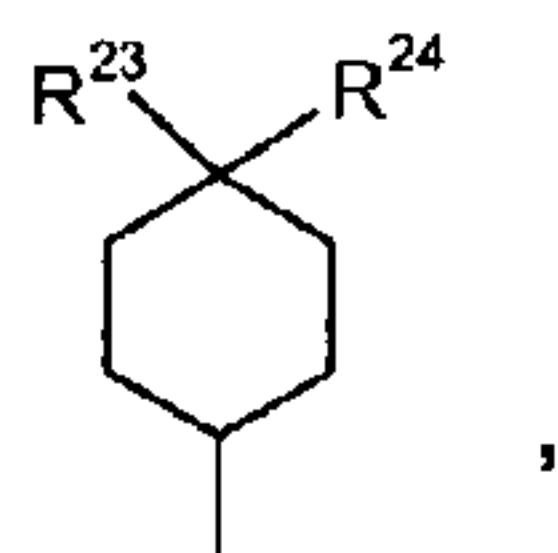
In another preferred embodiment E is

5



wherein R^{23} and R^{24} are as defined for formula (I).

10 Preferably, E is



wherein R^{23} and R^{24} are as defined for formula (I).

15

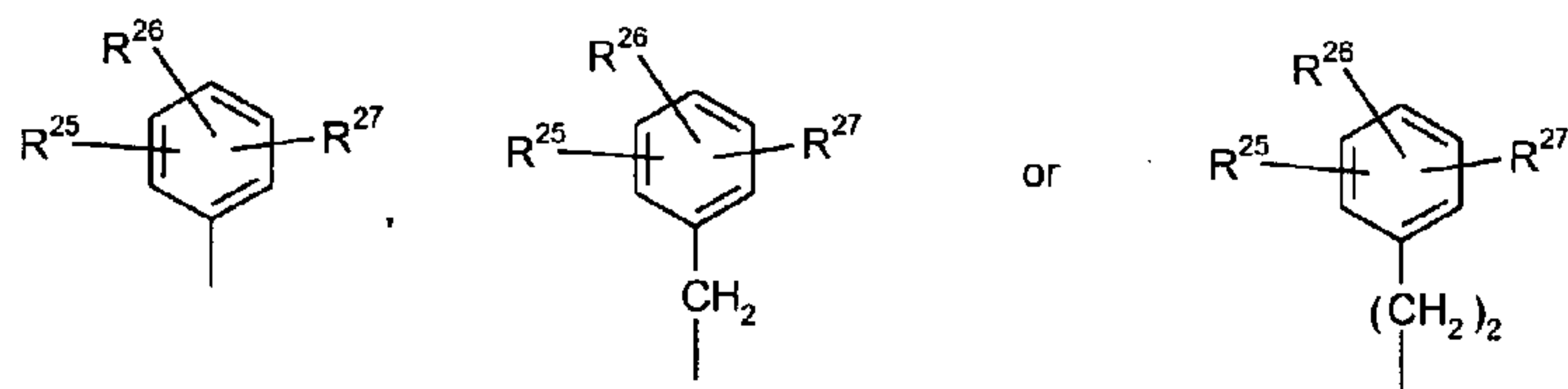
Preferably, R^{23} and R^{24} are independently selected from hydrogen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkylidene, phenoxy, phenyl, $-C(O)NR^{36}R^{37}$ and $-OC(O)NH$ -phenyl, of which the phenyl moiety optionally may be substituted with $-OCF_3$, wherein R^{36} and R^{37} are as defined in claim 1, or R^{23} and R^{24} together form the radical $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-$, $-O-(CH_2)_t-CR^{40}R^{41}-$

20 $(CH_2)_l-O-$, $-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$, wherein t , l , R^{40} and R^{41} are as defined for formula (I).

More preferably, R^{23} is hydrogen and R^{24} is C_{1-6} -alkyl such as *tert*-butyl or C_{3-8} -cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C_{1-6} -alkyl or wherein R^{23} and R^{24} together form the radical $-(CH_2)_5-$.

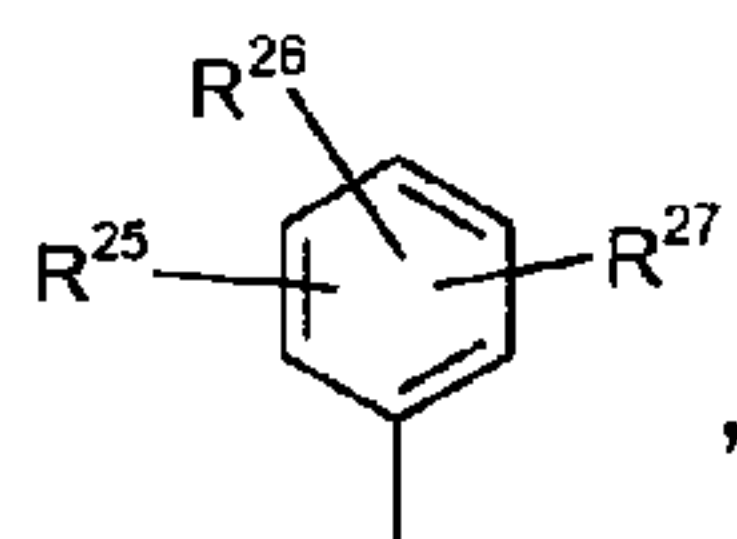
25

In yet another preferred embodiment E is



5 wherein R^{25} , R^{26} and R^{27} are as defined for formula (I).

Preferably, E is



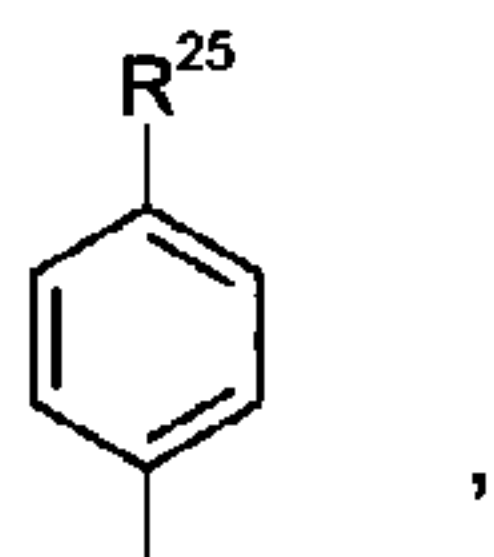
10

wherein R^{25} , R^{26} and R^{27} are as defined for formula (I).

Preferably, R^{25} , R^{26} and R^{27} are independently selected from hydrogen, halogen, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, C_{4-8} -cycloalkenyl, $-CF_3$, $-OCF_3$ or $-NR^{42}R^{43}$, wherein R^{42} and R^{43} are as defined for formula (I).

15

More preferably, E is

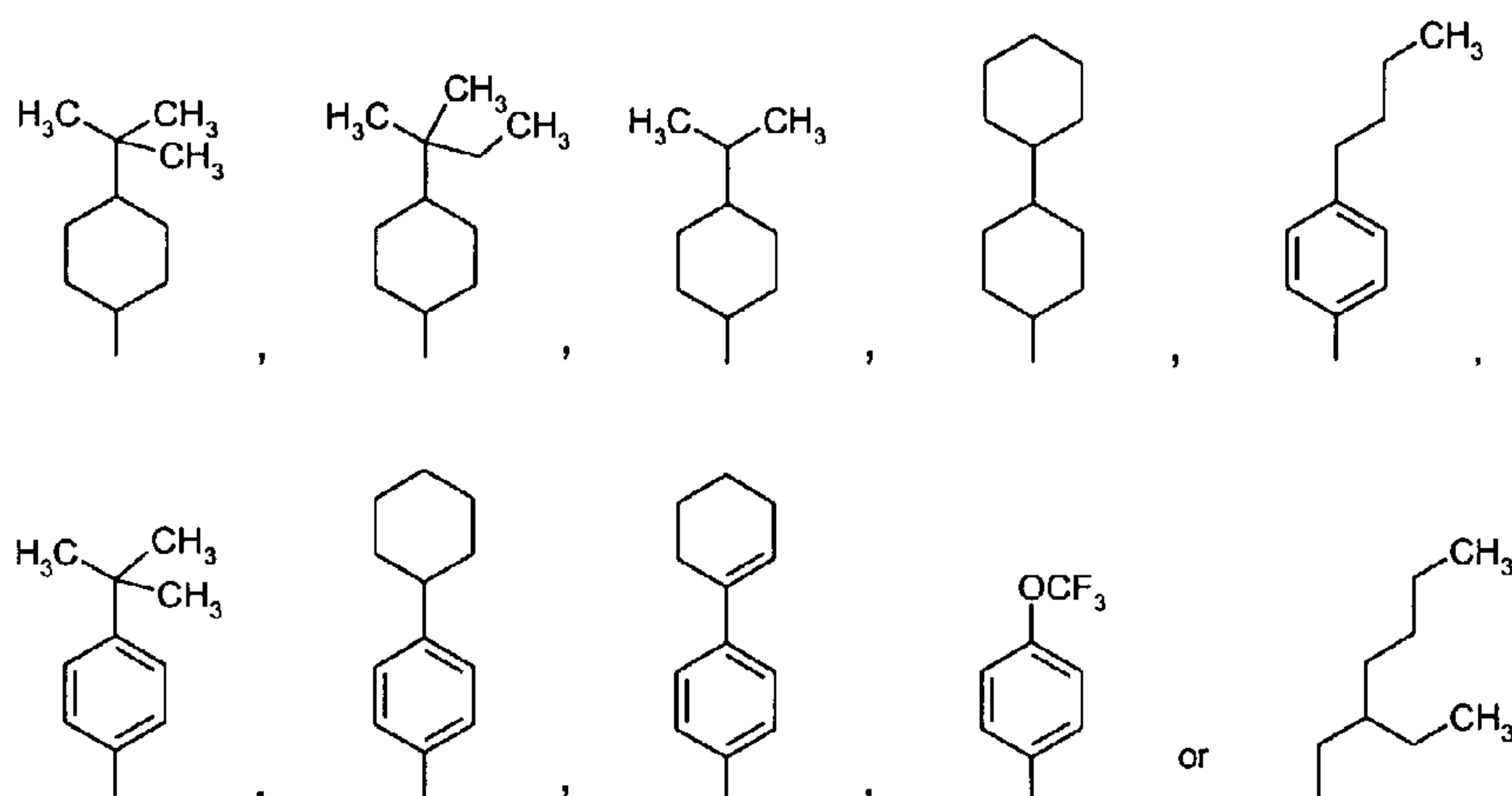


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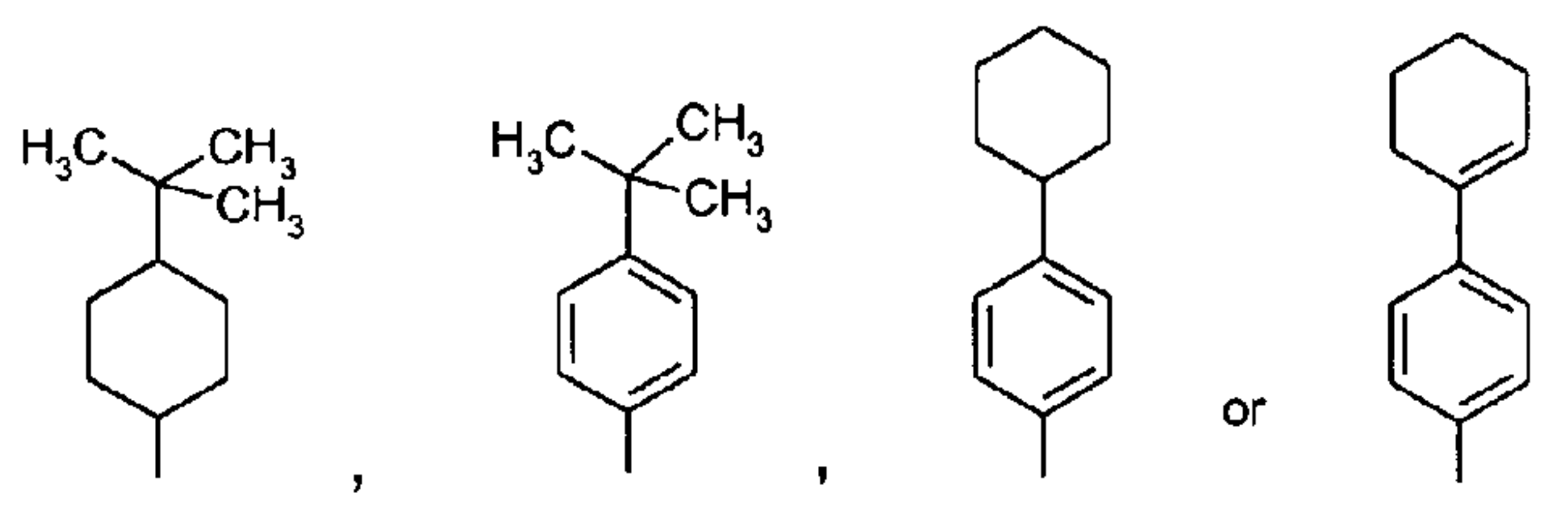
wherein R^{25} is $-OCF_3$, $-CF_3$, C_{1-6} -alkyl such as *tert*-butyl, piperidyl, C_{3-8} -cycloalkyl such as cyclohexyl or C_{4-8} -cycloalkenyl such as cyclohexenyl.

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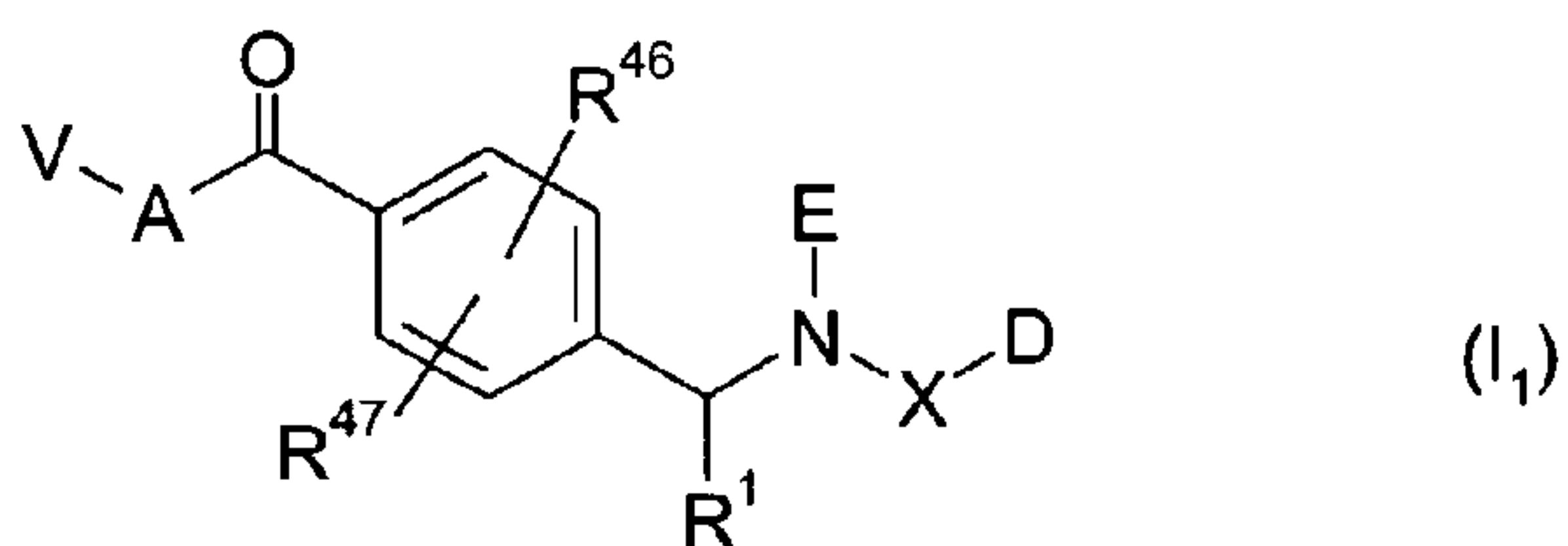
In another preferred embodiment E is



5 Of these E is preferably

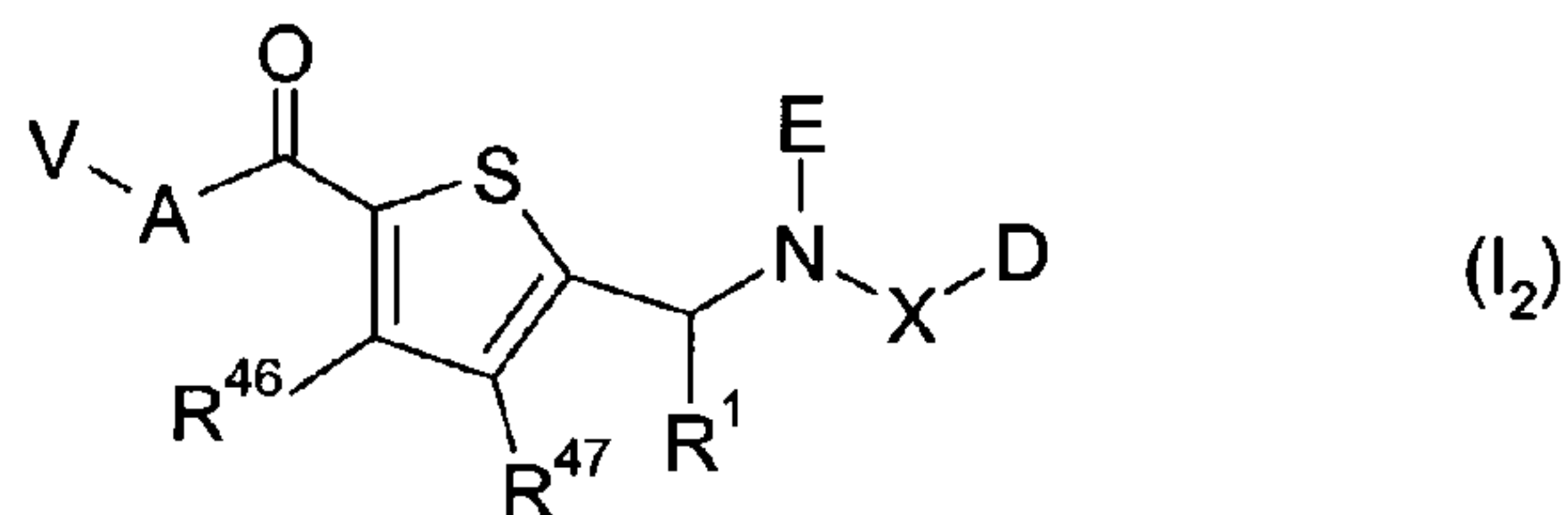


10 In one preferred embodiment the present invention relates to compounds of the general formula (I₁):



15 wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In another preferred embodiment the present invention relates to compounds of the general formula (I₂):

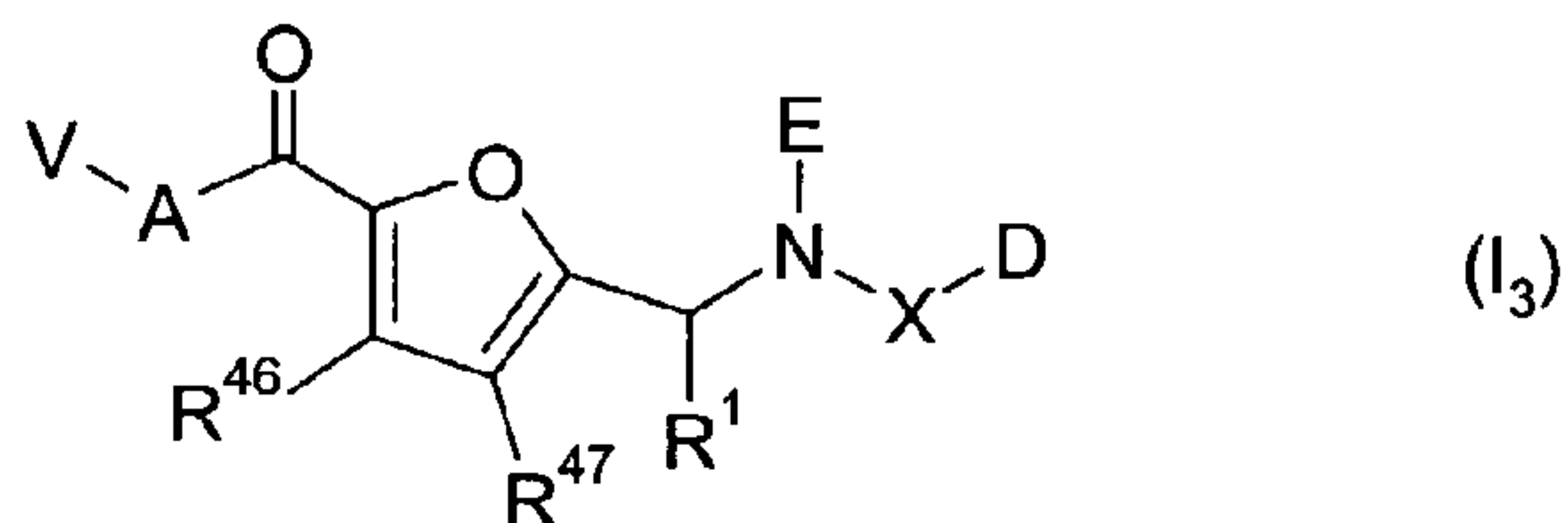


5

wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

10

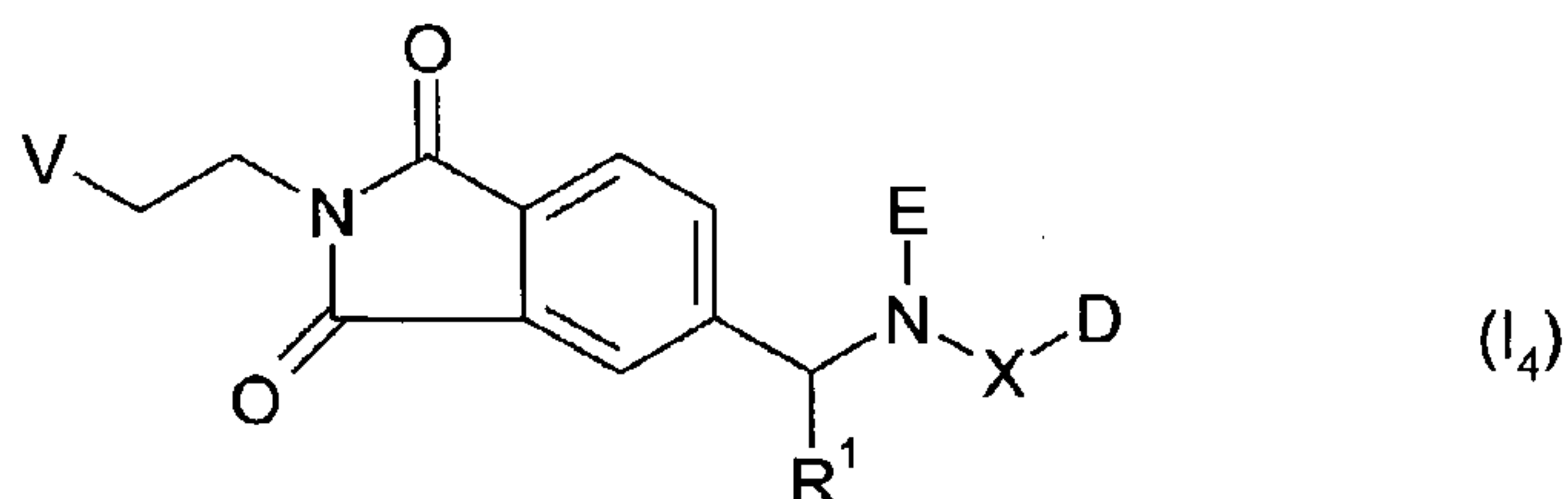
In still another preferred embodiment the present invention relates to compounds of the general formula (I₃):



15

wherein V, A, R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

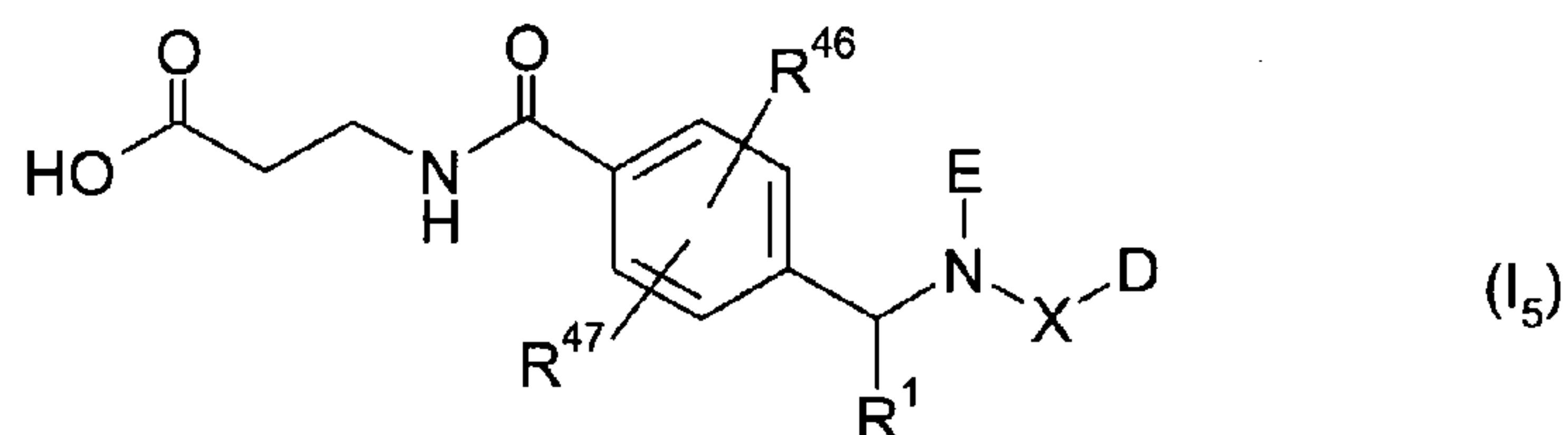
In yet another preferred embodiment the present invention relates to compounds of the general formula (I₄):



20

wherein V is -C(O)OR², -C(O)NR²R³ or -C(O)NR²OR³, and R¹, R², R³, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

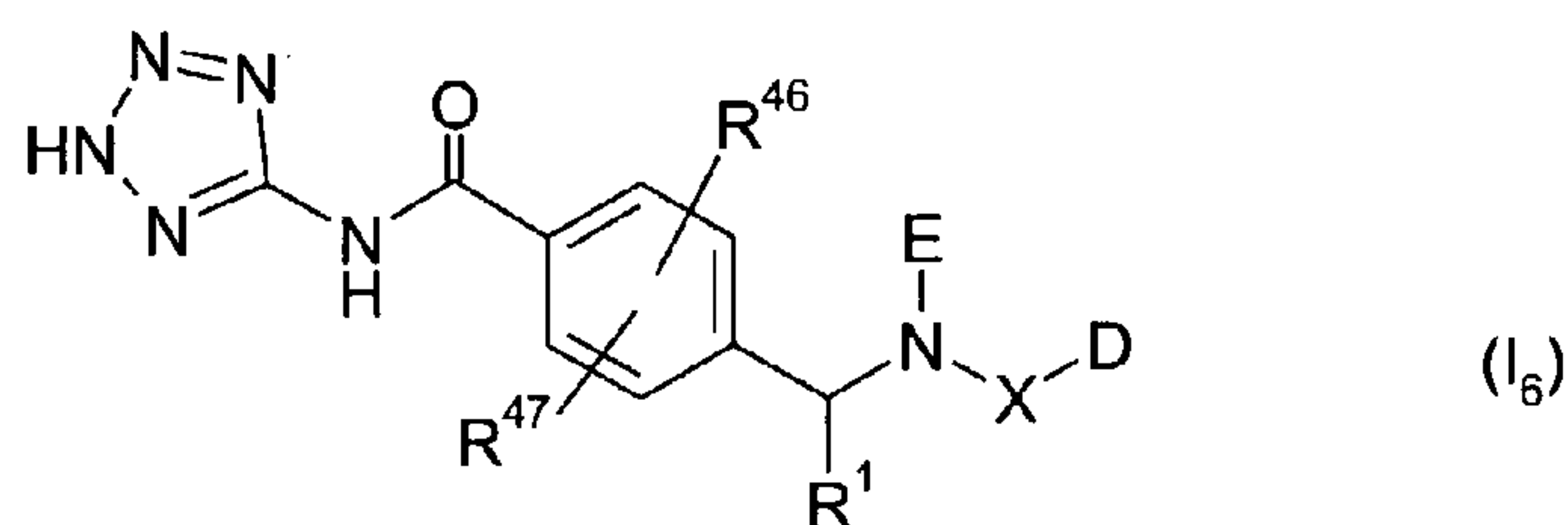
In a further preferred embodiment the present invention relates to compounds of the general formula (I₅):



5

wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

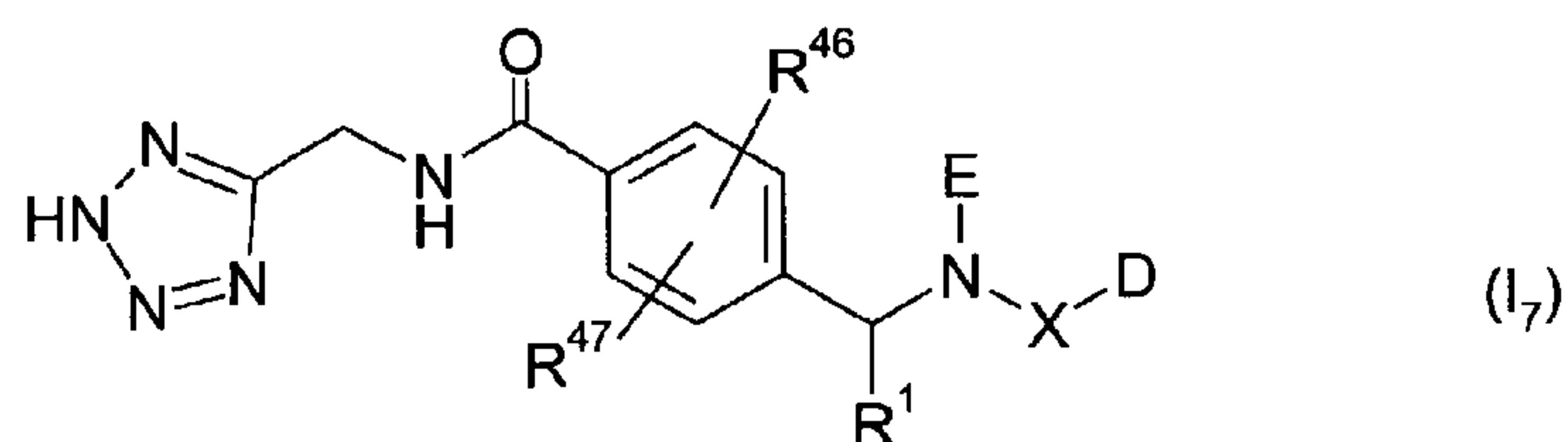
In still a further preferred embodiment the present invention relates to compounds of the general formula (I₆):



15

wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

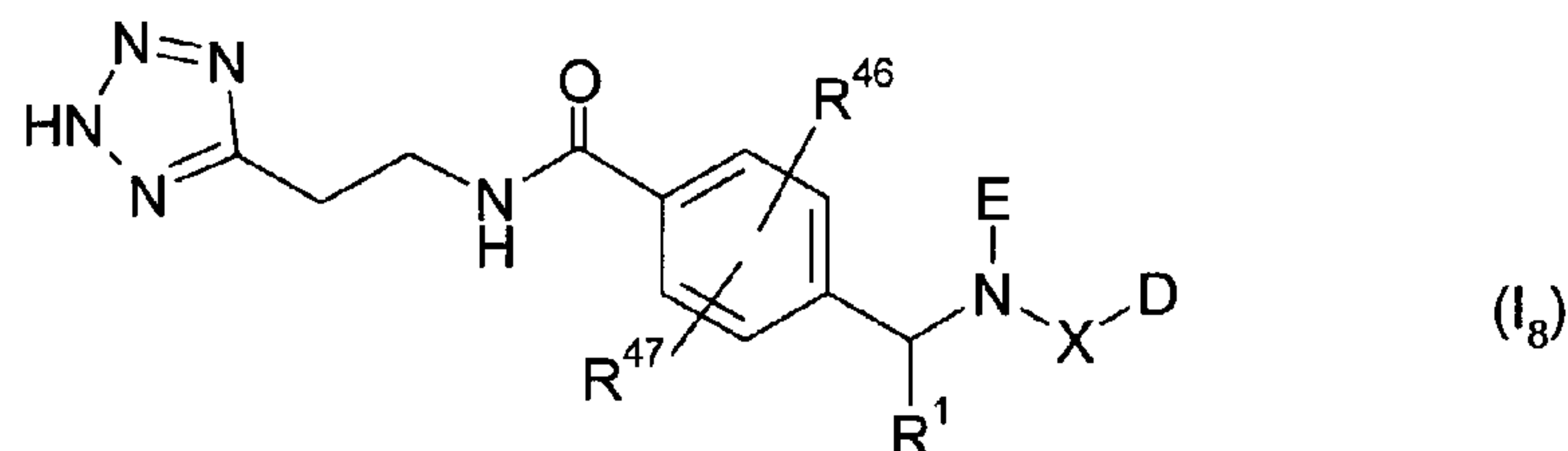
In yet a further preferred embodiment the present invention relates to compounds of the general formula (I₇):



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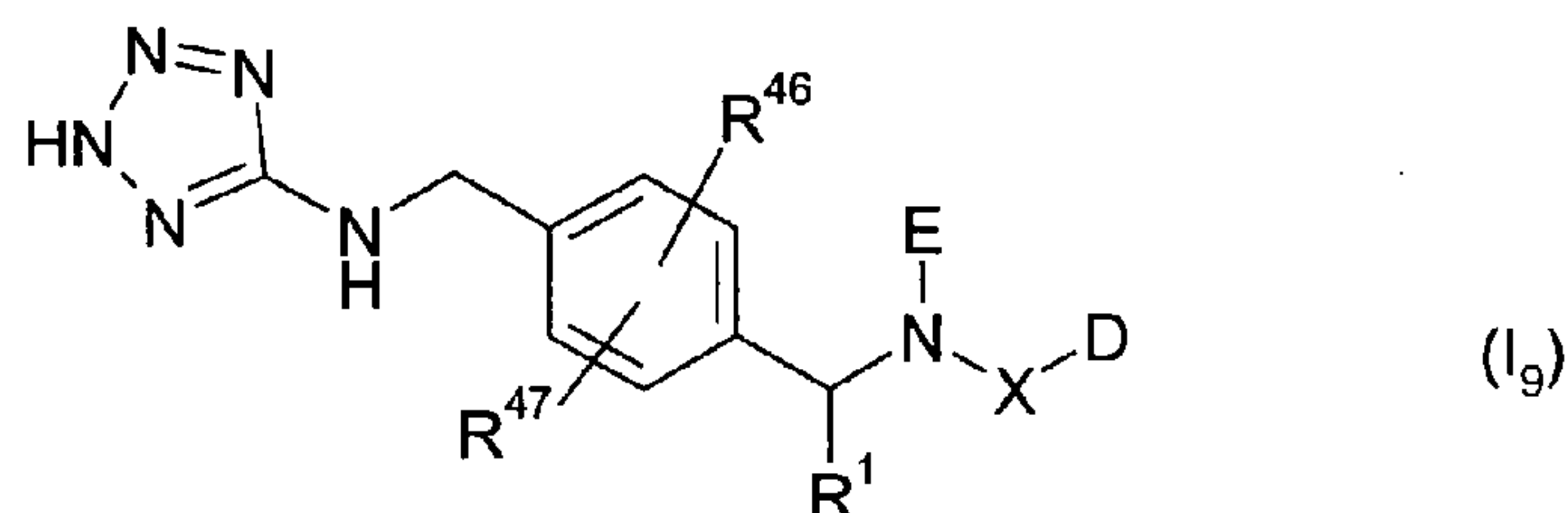
wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In another preferred embodiment the present invention relates to compounds of the general formula (I₈):



wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

10 In still another preferred embodiment the present invention relates to compounds of the general formula (I₉):



15 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined for formula (I) or in any one of the above preferred embodiments.

In the above formulae (I₁) to (I₃) and (I₅) to (I₉), R⁴⁶ and R⁴⁷ are preferably both hydrogen.

20 The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may

form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms which the compounds are able to form are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Furthermore, the pharmaceutically acceptable salts comprise basic amino acid salts such as lysine, arginine and ornithine.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

5

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

10

The invention also encompasses active metabolites of the present compounds.

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The compounds according to the present invention act to antagonize the action of glucagon and are accordingly useful for the treatment and/or prevention of disorders and diseases in which such an antagonism is beneficial.

20

Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a medicament.

The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or excipients.

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The pharmaceutical composition is preferably in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound according to the invention.

30

Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment and/or prevention of a disorder or disease, wherein a glucagon antagonistic action is beneficial.

The invention also relates to a method for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

5

Owing to their antagonizing effect of the glucagon receptor the present compounds may be suitable for the treatment and/or prevention of any glucagon-mediated conditions and diseases.

10

Accordingly, the present compounds may be applicable for the treatment and/or prevention of hyperglycemia, IGT, insulin resistance syndromes, syndrome X, Type 1 diabetes, Type 2 diabetes, hyperlipidemia, dyslipidemia, hypertriglyceridemia, glucagonomas, acute pancreatitis, cardiovascular diseases, hypertension, cardiac hypertrophy, gastrointestinal disorders, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, etc. Furthermore, they may be applicable as diagnostic agents for identifying patients having a defect in the glucagon receptor, as a therapy to increase gastric acid secretions and to reverse intestinal hypomotility due to glucagon administration.

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In a preferred embodiment of the invention the present compounds are used for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

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In yet a preferred embodiment of the invention the present compounds are used for the manufacture of a medicament for lowering blood glucose in a mammal.

25

In another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of IGT.

30

In still another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

- 5 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of Type 1 diabetes. Such treatment and/or prevention is normally accompanied by insulin therapy.

- 10 In a further preferred embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of obesity.

In still a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or prevention of an appetite regulation or energy expenditure disorder.

15

In a further aspect of the invention the present compounds may be administered in combination with one or more pharmacologically active substances eg selected from antidiabetics, antiobesity agents, antihypertensive agents and agents for the treatment and/or prevention of complications resulting from or associated with diabetes.

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Suitable antidiabetics comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference, as well as orally active hypoglycaemic agents.

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The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, insulin sensitizers, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

30

35

In one embodiment of the invention the present compounds are administered in combination with insulin.

5 In a further embodiment the present compounds are administered in combination with a sulphonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg metformin.

10 In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds
15 disclosed in WO 97/41097 to Dr. Reddy's Research Foundation.

Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 to Dr. Reddy's Research Foundation.

20 In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor eg miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells eg tolbutamide, gliben-
25 clamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an
30 antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulphonylurea and

metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the compounds according to the invention may be administered in combination
5 with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, uro-
10 cortin agonists, $\beta 3$ agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing
15 compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA (dopamine) agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR β agonists.

In one embodiment of the invention the antiobesity agent is leptin.

20

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

25 In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

30

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril,
35 quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine,

isradipine, nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- 5 It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more pharmacologically active substances are considered to be within the scope of the present invention.

10 PHARMACEUTICAL COMPOSITIONS

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for in-

5 intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution

10 and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or

15 glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

20 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as

25 an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

30 If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet that may be prepared by conventional tableting techniques may contain:

Core:

	Active compound (as free compound or salt thereof)	5.0 mg
	Lactosum Ph. Eur.	67.8 mg
	Cellulose, microcryst. (Avicel)	31.4 mg
5	Amberlite	1.0 mg
	Magnesii stearas Ph. Eur.	q.s.

Coating:

	HPMC approx.	9 mg
10	Mywacett 9-40 T* approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

15 If desired, the pharmaceutical composition of the invention may comprise the compound of the formula (I) in combination with further pharmacologically active substances such as those described in the foregoing.

EXPERIMENTAL

20 In the following section binding assays as well as functional assays useful for evaluating the efficiency of the compounds of the invention are described.

Binding of compounds to the glucagon receptor was determined in a competition binding assay using the cloned human glucagon receptor.

25

Antagonism was determined as the ability of the compounds to inhibit the amount of cAMP formed in the presence of 5 nM glucagon.

30 For further characterization, antagonism was determined in a functional assay, measured as the ability of the compounds to right-shift the glucagon dose-response curve. Using at least 3 different antagonist concentrations, the K_i was calculated from a Schild plot.

Glucagon Binding Assay (I)

35 Receptor binding was assayed using cloned human receptor (Lok et al., Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SSt1 restriction sites

(Lok et al.) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The K_d was shown to be 0.1 nM.

- 5 Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (10 mM tris/HCl, pH 7.4 containing 30 mM NaCl, 1 mM dithiothreitol, 5 mg/L leupeptin (Sigma), 5 mg/L pepstatin (Sigma), 100 mg/L bacitracin (Sigma) and 15 mg/L recombinant aprotinin (Novo Nordisk A/S)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation upon a
10 layer of 41 w/v % sucrose at 95.000 x g for 75 min. The white band located between the two layers was diluted in buffer and centrifuged at 40.000 x g for 45 min. The precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until use.

- Glucagon was iodinated according to the chloramine T method (Hunter and Greenwood, Nature
15 194, 495 (1962)) and purified using anion exchange chromatography (Jørgensen et al., Hormone and Metab. Res. 4, 223-224 (1972)). The specific activity was 460 $\mu\text{Ci}/\mu\text{g}$ on the day of iodination. Tracer was stored at -18°C in aliquots and were used immediately after thawing.

- Binding assays were carried out in triplicate in filter microtiter plates (MADV N65, Millipore). The
20 buffer used in this assay was 50 mM HEPES, 5 mM EGTA, 5 mM MgCl_2 , 0.005% tween 20, pH 7.4. Glucagon was dissolved in 0.05 M HCl, added an equal amount (w/w) of HSA and freeze-dried. On the day of use, it was dissolved in water and diluted in buffer to the desired concentrations.

- 25 Test compounds were dissolved and diluted in DMSO. 140 μL buffer, 25 μL glucagon or buffer, and 10 μL DMSO or test compound were added to each well. Tracer (50.000 cpm) was diluted in buffer and 25 μL were added to each well. 1-4 μg freshly thawed plasma membrane protein diluted in buffer was then added in aliquots of 25 μL to each well. Plates were incubated at 30°C for 2 hours. Non-specific binding was determined with 10^{-6} M of glucagon. Bound tracer and un-
30 bound tracer were then separated by vacuum filtration (Millipore vacuum manifold). The plates were washed with 2 x 100 μL buffer/ well. The plates were air dried for a couple of hours, whereupon the filters were separated from the plates using a Millipore Puncher. The filters were counted in a gamma counter.

Functional Assay (I)

The functional assay was carried out in 96 well microtiter plates (tissue culture plates, Nunc). The resulting buffer concentrations in the assay were 50 mM tris/HCl, 1 mM EGTA, 1.5 mM MgSO₄, 1.7 mM ATP, 20 μM GTP, 2 mM IBMX (isobutyl-methyl-xanthine), 0.02% tween-20 and 0.1% HSA. pH was 7.4. Glucagon and proposed antagonist were added in aliquots of 35 μL diluted in 50 mM tris/HCl, 1 mM EGTA, 1.85 mM MgSO₄, 0.0222 % tween-20 and 0.111 % HSA, pH 7.4. 20 μL of 50 mM tris/HCl, 1 mM EGTA, 1.5 mM MgSO₄, 11.8 mM ATP, 0.14 mM GTP, 14 mM IBMX and 0.1% HSA, pH 7.4 was added. GTP was dissolved immediately before the assay.

50 μL containing 5 μg of plasma membrane protein was added in a tris/HCl, EGTA, MgSO₄, HSA buffer (the actual concentrations were dependent upon the concentration of protein in the stored plasma membranes).

The total assay volume was 140 μL. The assay was incubated for 2 hours at 37°C with continuous shaking. Reaction was terminated by addition of 25 μL 0.5 N HCl. cAMP was measured by the use of a scintillation proximity kit (Amersham).

Glucagon Binding Assay (II)

Receptor binding was assayed using the cloned human receptor (Lok et al., Gene 140, 203-209 (1994)). The receptor inserted in the pLJ6' expression vector using EcoRI/SstI restriction sites (Lok et al.) was expressed in a baby hamster kidney cell line (A3 BHK 570-25). Clones were selected in the presence of 0.5 mg/mL G-418 and were shown to be stable for more than 40 passages. The K_d was shown to be 0.1 nM.

Plasma membranes were prepared by growing cells to confluence, detaching them from the surface and resuspending the cells in cold buffer (50 mM tris base, pH 7.4 containing 0.32 mM sucrose, 2 mM EGTA, 1 μg/mL leupeptin, 5 μg/mL pepstatin A, 5 μg/mL aprotinin, 1 mM phenylmethylsulfonylfluoride (all from Sigma)), homogenization by two 10-s bursts using a Polytron PT 10-35 homogenizer (Kinematica), and centrifugation. The homogenate was resuspended and centrifuged again. The final precipitate containing the plasma membranes was suspended in buffer and stored at -80°C until use.

Binding assays were carried out in duplicate in polypropylene tubes or microtiter plates. The buffer used in this assay was 50 mM HEPES pH 7.4 containing 5 mM EGTA, 5 mM MgCl₂ and

0.005% Tween 20. Sample (glucagon (Bachem CA) or test compounds) was added to each tube or well. Tracer (~ 25,000 cpm) was diluted in buffer and was added to each tube or well. 0.5 mg freshly thawed plasma membrane protein diluted in buffer was then added in aliquots to each tube or well. Tubes or plates were incubated at 37°C for 1 hour. Non-specific binding was
5 determined with 10^{-7} M of glucagon. Bound tracer and unbound tracer were then separated by vacuum filtration. The tubes or wells were washed twice with 0.01% Triton X-100 buffer. Scintillation fluid was added to the plates and radioactivity was quantified using a scintillation counter.

Functional Assay (II)

10 The functional assay determined the ability of the compounds to antagonize glucagon-stimulated formation of cAMP in a whole-cell assay. The assay was carried out in borosilicate glass 12 x 75 tubes. The buffer concentrations in the assay were 10 mM HEPES, 1 mM EGTA, 1.4 mM MgCl_2 , 0.1 mM IBMX, 30 mM NaCl, 4.7 mM KCl, 2.5 mM NaH_2PO_4 , 3mM glucose and 0.2% BSA. The pH was 7.4. Loose whole cells (0.5 mL, $10^6/\text{mL}$) were pretreated with various
15 concentrations of compounds for 10 min at 37°C, then challenged with glucagon for 20 min. Some aliquots (500 μL) of cells were treated with test compounds (55 μL) alone to test for agonist activity. The reactions were terminated by centrifugation, followed by cell lysis with the addition of 500 μL 0.1% HCl. Cellular debris was pelleted and the supernatant containing cAMP
20 evaporated to dryness. cAMP was measured by the use of an RIA kit (NEN, NEK-033). Some assays were carried out utilizing the adenylate cyclase FlashPlate system from NEN.

Glucagon Binding Assay (III)

BHK (baby hamster kidney cell line) cells were transfected with the human glucagon receptor and a membrane preparation of the cells was prepared. Wheat Germ Agglutinin derivatized
25 SPA beads containing a scintillant (WGA beads) (Amersham) bound the membranes. ^{125}I -glucagon bound to human glucagon receptor in the membranes and excited the scintillant in the WGA beads to light emission. Glucagon or samples binding to the receptor competed with ^{125}I -glucagon.

30 All steps in the membrane preparation were kept on ice or performed at 4°C. BHK cells were harvested and centrifuged. The pellet was resuspended in homogenisation buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl_2 , 1.0 mM MgCl_2 , 250 mg/L bacitracin), homogenised 2 x 10 sec using Polytron 10-35 homogenizer (Kinematica) and added the same amount of homogenisation buffer as used for resuspension. After centrifugation (15 min at 1000 x g) the su-
35 pernatant was transferred to cold centrifuge tubes and centrifuged for 45 min at 40,000 x g.

The pellet was resuspended in homogenisation buffer, homogenised 2 x 10 sec (Polytron) and additional homogenisation buffer was added. The suspension was centrifuged for 45 min at 40.000 x g and the pellet was resuspended in resuspension buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl₂, 1.0 mM MgCl₂) and homogenised 2 x 10 sec. (Polytron). The protein concentration was normally around 1.75 mg/mL. Stabilisation buffer (25 mM HEPES pH = 7.4, 2.5 mM CaCl₂, 1.0 mM MgCl₂, 1% BSA, 500 mg/L bacitracin, 2.5 M sucrose) was added and the membrane preparation was stored at -80°C.

The glucagon binding assay was carried out in opti plates (Polystyrene Microplates, Packard). 50 µL assay buffer (25 mM HEPES pH = 7.5, 2.5 mM CaCl₂, 1.0 mM MgCl₂, 0.003% Tween-20, 0.005% bacitracin, 0.05% sodium azide) and 5 µL glucagon or test compound (in DMSO) were added to each well. 50 µL tracer (¹²⁵I-porcine glucagon, 70.000 cpm) and 50 µL membranes (12.5 µg) containing the human glucagon receptor were then added to the wells. Finally 50 µL WGA beads containing 1 mg beads were transferred to the well. The assay was incubated for 4 hours on a shaker and then settled for 8-48 hours. The opti plates were counted in a Topcounter. Non-specific binding was determined with 500 nM of glucagon.

Synthesis methods

The following synthesis protocols refer to intermediate compounds and final products identified in the specification and in the synthetic schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of the glucagon antagonists of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

Some of the NMR data shown in the following examples are only selected data.

Unless otherwise specified in the examples, the *cis/trans* isomeric compounds were obtained as mixtures of *cis* and *trans* isomers, which may be separated by chromatography. Thus, the present invention comprises the compounds in form of mixtures of *cis* and *trans* isomers as well as the pure isomeric forms.

In the examples the following terms are intended to have the following meanings:

DMF:	<i>N,N</i> -dimethylformamide
DMSO:	dimethyl sulfoxide
Fmoc:	9-fluorenylmethyloxycarbonyl
HBTU:	2-(1 <i>H</i> -Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
M.p.:	melting point
NCS:	<i>N</i> -Chlorosuccinimide
NMP:	<i>N</i> -methylpyrrolidone
-OSu:	2,5-dioxo-pyrrolidin-1-yloxy
TFA:	trifluoroacetic acid
THF:	tetrahydrofuran

The final products obtained were characterized by analytical RP-HPLC (retention time) and/or by HPLC-MS (molecular mass and/or retention time).

The RP-HPLC analyses were performed on a Waters HPLC system consisting of WatersTM 600S Controller, WatersTM 996 Photodiode Array Detector, WatersTM 717 Autosampler, WatersTM 616 Pump, WatersTM 3 mm x 150 mm 3.5 μ C-18 Symmetry column and Millenium QuickSet Control Ver. 2.15 using UV detection at 214 nm. A linear gradient was applied from 5% to 90% acetonitrile/0.1% TFA/water over 15 min at a flow rate of 1 mL/minute.

HPLC-MS (METHOD A):

The following instrumentation was used:

- Sciex API 100 Single quadropole mass spectrometer
- Perkin Elmer Series 200 Quard pump
- Perkin Elmer Series 200 autosampler

- Applied Biosystems 785A UV detector
- Sedex 55 evaporative light scattering detector
- A Valco column switch with a Valco actuator controlled by timed events from the pump.

5 The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to four eluent reservoirs containing:

- A: Acetonitrile
B: Water
C: 0.5 % TFA in water
D: 0.02 M ammonium acetate

10

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

15

The analysis was performed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions were used.

20

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min (1/50) through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

25 The remaining 1.48 mL/min (49/50) was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

30

The LC conditions, detector settings and mass spectrometer settings used for the different

methods are given in the following tables.

Column	Waters Symmetry C ₁₈ 3 mm x 150 mm	
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 15 min at 1 mL/min	
Detection	UV: 214 nm	ELS: 40°C
MS	Experiment: Start: 100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method: Scan 284 times = 9.5 min	

5 HPLC-MS (METHOD B):

This method was identical to METHOD A but using the following conditions and settings:

Column	YMC ODS-A 120Å s - 5μ 3 mm x 50 mm id	
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 mL/min	
Detection	UV: 214 nm	ELS: 40°C
MS	Experiment: Start: 100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method: Scan 284 times = 9.5 min	

10 HPLC-MS (METHOD C):

The following instrumentation was used:

- Hewlett Packard series 1100 MSD G1946A Single quadropole mass spectrometer
- Hewlett Packard series 1100 MSD G1312A Bin pump
- Hewlett Packard series 1100 MSD G1313A ALS autosampler
- 15 • Hewlett Packard series 1100 MSD G1315A DAD diode array detector

The HP LC/MSD ChemStation control software running on a HP Vectra computer was used for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.05% TFA in water
B: Acetonitrile

The analysis was performed at room temperature by injecting 1 μ L of the sample solution on the column which was eluted with a gradient of acetonitrile in 0.05% TFA.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Grom Nucleosil 100 C18, 3 μ m, 2 mm x 60 mm
Gradient	10% - 100% acetonitrile in 0.05% TFA linearly during 5.8 min at 0.6 mL/min
Detection	UV: 210 nm (diode array)
MS	Ionisation mode: API-ES Experiment: Start: 100 amu Stop: 1000 amu Step: 0.1 amu

HPLC-MS (METHOD D):

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Sciex 300 triplequadropole mass spectrometer
- Gilson 215 micro injector
- Sedex 55 evaporative light scattering detector

Pumps and detectors were controlled by MassChrom 1.1.1 software running on a MacIntosh G3 computer. Gilson Unipoint Version 1.90 controls the auto-injector.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water
B: 0.01% TFA in acetonitrile

The analysis was performed at room temperature by injecting an appropriate volume of the sample (preferably 1 μ L) onto the column that was eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are:

5

Column	YMC ODS-A 120Å s 5 μ 3 mm X 50 mm id
Gradient	5% - 90% acetonitrile linearly during 7.5 min at 1.5 ml/min
Detection	210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

HPLC-MS (METHOD E):

The following instrumentation was used:

- 10
- Hewlett Packard series 1100 MSD G1946A Single quadropole mass spectrometer
 - Hewlett Packard series 1100 MSD G1312A Bin pump
 - Hewlett Packard series 1100 MSD G1313A ALS autosampler
 - Hewlett Packard series 1100 MSD G1315A DAD diode array detector
- 15
- The HP LC/MSD ChemStation control software running on a HP Vectra computer was udes for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: Acetonitrile

- 20
- The analysis was performed at room temperature by injecting 1 μ L of the sample solution on the column which was eluted with a gradient of acetonitrile in 0.01% TFA.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra 100A MS C-18 3.5 μ m, 2 mm x 50 mm
Gradient	10% - 100% acetonitrile in 0.05% TFA linearly during 4.5 min at 1.5 mL/min
Detection	UV: 210 nm (diode array)
MS	Ionisation mode: API-ES Experiment: Start: 100 amu Stop: 1000 amu Step: 0.1 amu

5

HPLC-MS (Method F):

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- 10 • Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

15 The HPLC pump was connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis was performed at 40°C by injecting an appropriate volume of the sample (preferably 1 μ L) onto the column, which was eluted with a gradient of acetonitrile.

20 The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile linearly during 7.5 min at 1.0 mL/min
Detection	UV: 210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

The compounds of the present invention may be purified using one of the following HPLC methods:

5 Hit fractionation method I

HPLC purification/fractionation of hits is performed on Nucleosil C-18 7 μ m 8 x 100 mm columns (packed by Grom). A standard gradient with water/acetonitrile added 0.01% TFA is used. Flow rate 9 mL/min starting at 10% organic modifier ending after 18 min on 100% organic modifier. This condition is kept for 1 min. Fractions of 4 mL are collected in a deep well
10 collection plate.

Equipment:

2 Gilson 306 pumps equipped with 25 mL SC pump heads, Gilson 806 manometer and Gilson 811c dynamic mixing chamber. UV detection is performed with Gilson 119 UV/VIS detector. Gilson 215 Nebula is used as combined injector and fraction collector.
15

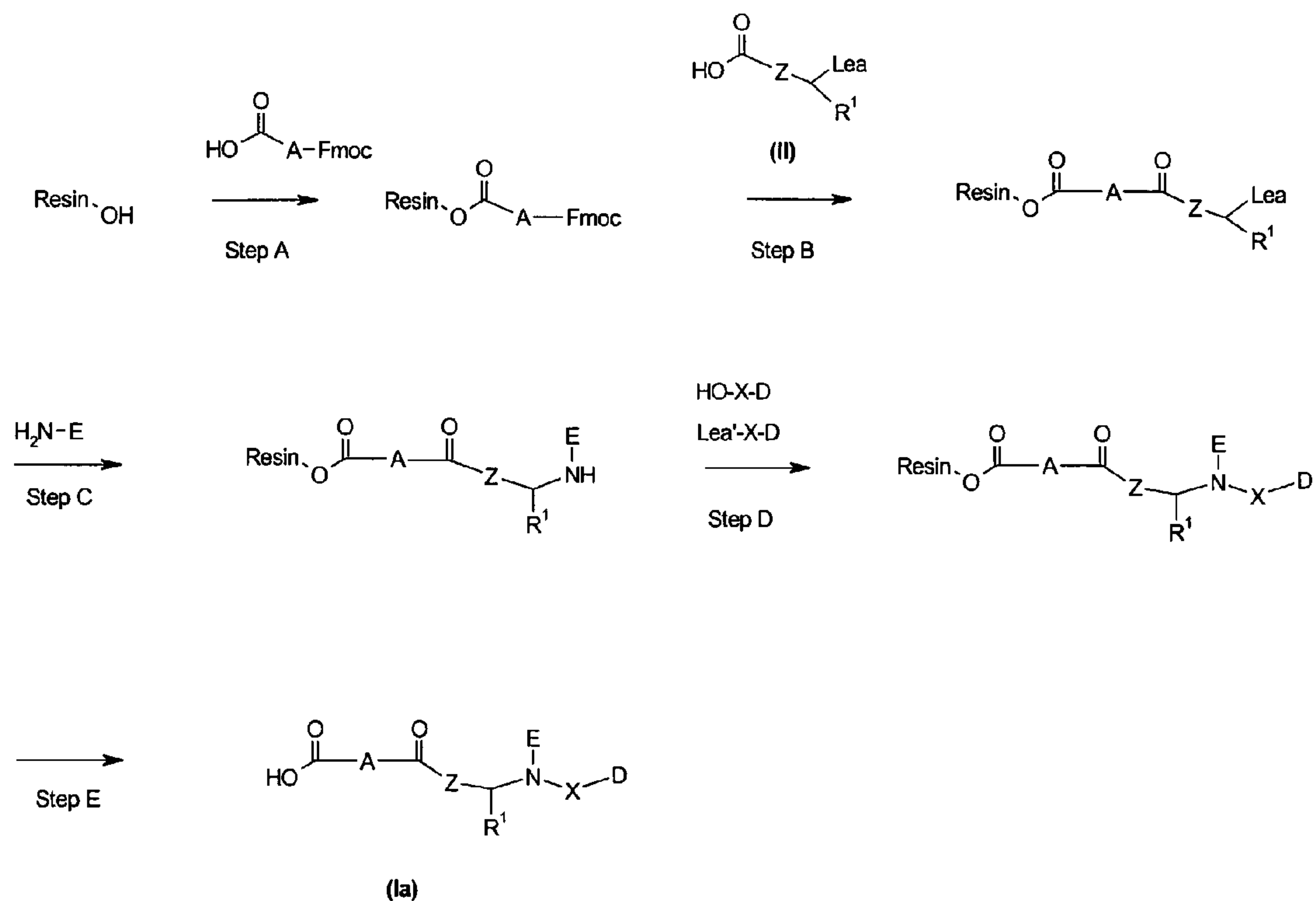
Hit fractionation method II

HPLC purification/fractionation of hits is performed on Waters Xterra columns MS C₁₈ 5 μ m 7.8 x 100 mm columns. A standard gradient with water/acetonitrile added 0.01% TFA is
20 used. Flow rate 15 mL/min starting at 10% organic modifier ending after 11 min on 100% modifier. This condition is kept for 1 min. Fractions of 4 mL are collected in a deep well collection plate.

Equipment:

25 1 Gilson 321 pump equipped with 15 mL H1 pumping heads. UV detection is performed with Gilson 119 UV/VIS detector. Gilson 215 Nebula is used as combined injector and fraction collector.

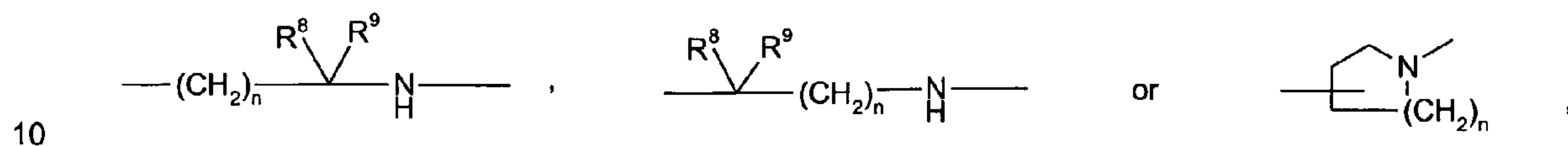
General procedure (A) for the solid phase synthesis of compounds of the general formula (Ia):



5 wherein

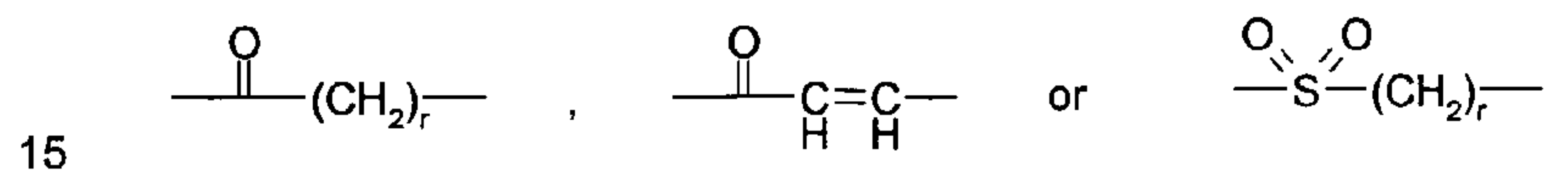
R¹, Z, E and D are as defined for formula (I),

A is



wherein R⁸ and R⁹ are as defined for formula (I),

X is



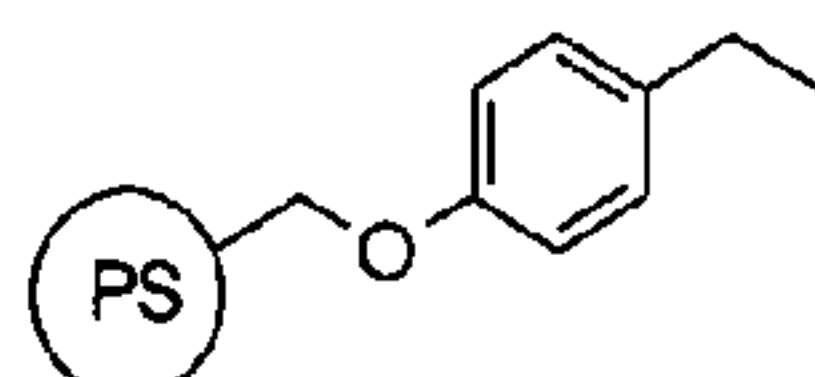
wherein r is as defined for formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

5

Resin denotes a polystyrene resin with a linker such as the Wang linker:



10 wherein PS denotes polystyrene.

Step A:

The reaction is known (Wang S. J., J. Am. Chem. Soc. 95, 1328, 1973) and is generally performed by stirring polystyrene resin loaded with a linker such as the Wang linker with a 4-10 molar excess of Fmoc-protected amino acid activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a catalyst such as *N,N*-4-dimethylaminopyridine. The esterification is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C to 80°C, preferably between 20°C to 40°C. When the esterification is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

15

20

Step B:

N-Fluorenylmethyloxycarbonyl protection group is removed by treating the resin bound derivative with a 20%-50% solution of a secondary amine such as piperidine in a polar solvent such as DMF or NMP (Carpino L., Han G., J. Org. Chem. 37, 3404, 1972). The reaction is performed between 20°C and 180°C, preferably between 20°C and 40°C. The deprotection can be quantitated by the absorbance of piperidine-dibenzofulvene adduct released from the resin (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 219). When the reaction is complete excess of reagents is removed by filtration. The resin is successively washed with solvent used in the reaction. The resulting resin bound intermediate is acylated with acid (II). The acylation is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 78) and is generally performed by stirring resin bound intermediate with a 2-5 molar excess of acid (II)

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activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a side reaction inhibitor such as *N*-hydroxybenzotriazole. The acylation is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C and 80°C, preferably between 20°C and 40°C. When the acylation is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

Step C:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 112) and is generally performed by stirring the resin bound intermediate obtained in step B with a 10-20 molar excess of amine. The nucleophilic displacement is carried out in a solvent such as DMSO, DMF, NMP or a mixture of two or more of these. The reaction is performed between 20°C and 120°C, preferably between 60°C and 80°C. When the reaction is complete excess of reagents is removed by filtration. The resin is successively washed with the solvent used in the reaction, followed by washings with methanol. The resin bound product can be further dried and analyzed.

Step D:

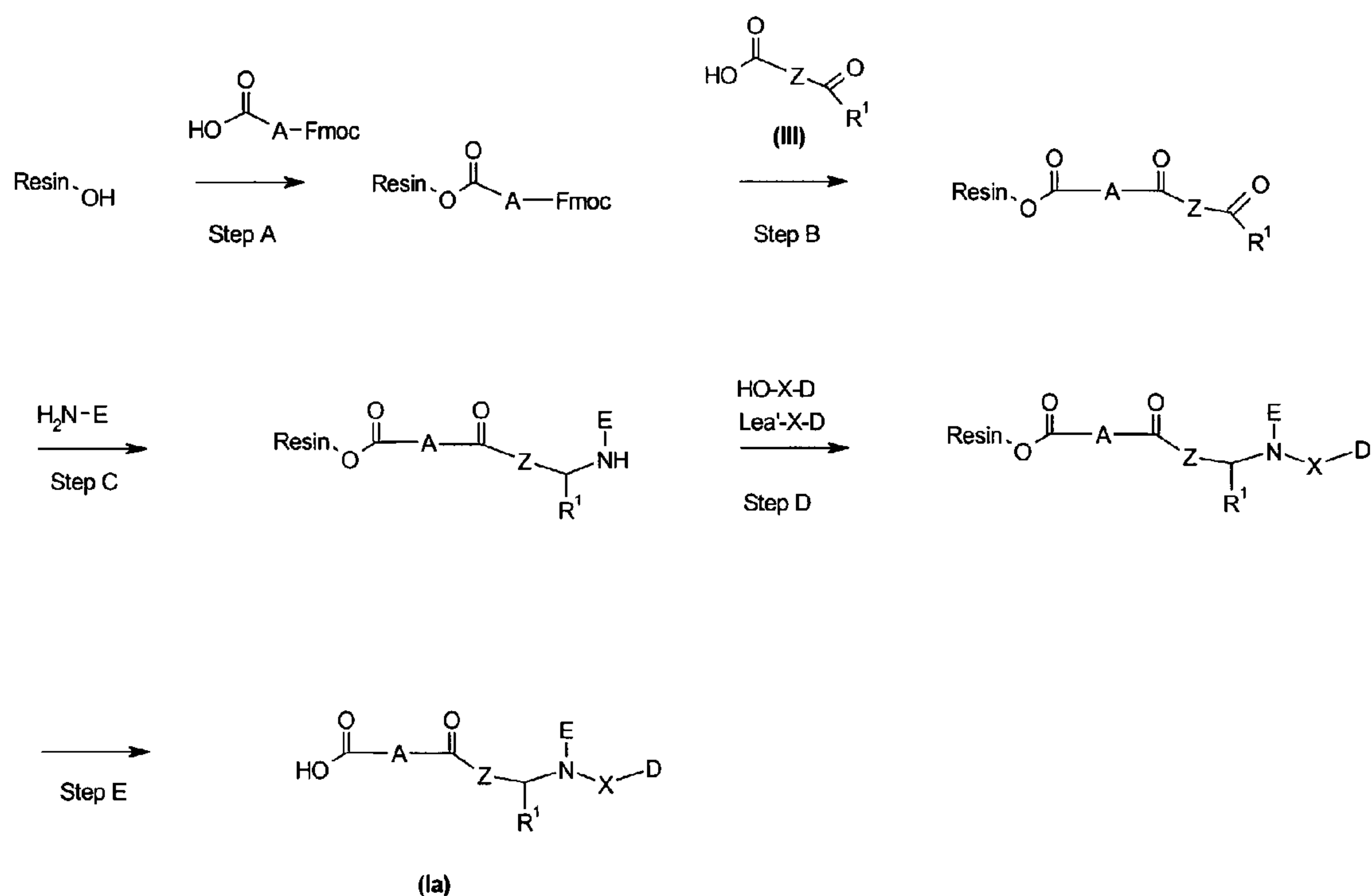
The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 78) and is generally performed by stirring the resin bound intermediate obtained in step C with a 4-10 molar excess of acid HO-X-D activated with a 2-5 molar excess of diisopropylcarbodiimide or dicyclohexylcarbodiimide in the presence of a catalyst such as pyridine and/or 4-dimethylaminopyridine. The reaction is carried out in a solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reactions are performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete excess of reagents is removed by filtration. Alternatively, a solution of Lea'-X-D in an appropriate solvent such as acetonitrile, toluene, DMF, NMP, THF, dichloromethane, 1,2-dichloroethane or DMSO or a mixture of two or more of these, is added and the mixture is vortexed in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate under heating, if necessary. The resin is successively washed with solvent used in the reaction, followed by washings with dichloromethane.

Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring resin bound intermediate obtained in step D with a 50-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or more of these. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with dichloromethane. The product and washings are collected. The solvent is removed and the product is dried in vacuo. The residue is dissolved in a 1:1 mixture of methanol and dichloromethane (1 mL) and concentrated in vacuo. The product (Ia) is dried in vacuo overnight.

General procedure (B) for the solid phase synthesis of compounds of the general formula (Ia):

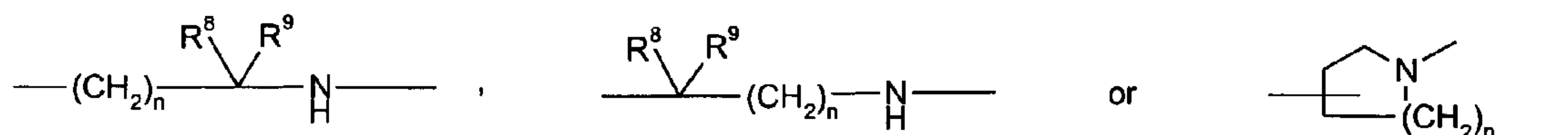
Alternatively, steps B and C of procedure (A) can be modified so that step C is a reductive amination of a resin bound aldehyde or ketone:



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R¹, Z, E and D are as defined for formula (I),

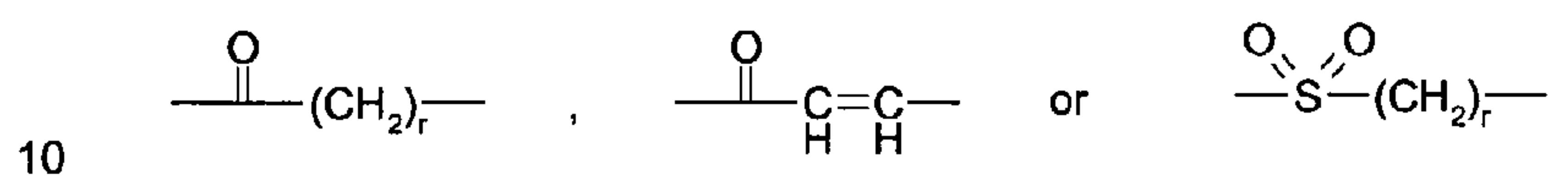
A is



5

wherein R⁸ and R⁹ are as defined for formula (I),

X is



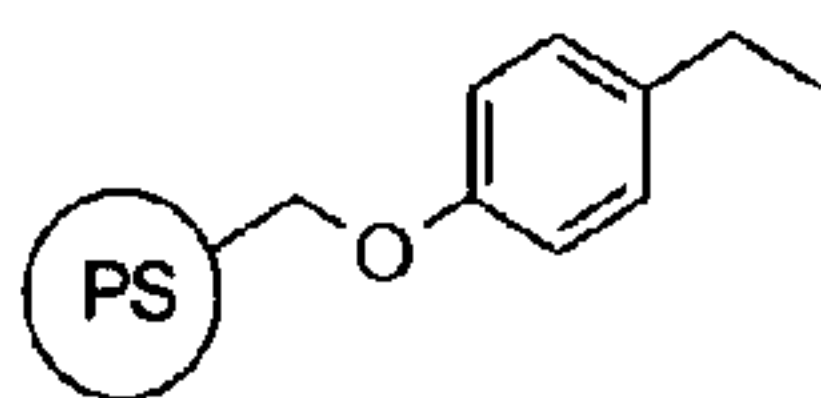
10

wherein r is as defined for formula (I),

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy, and

15

Resin denotes a polystyrene resin with a linker such as the Wang linker:



20 wherein PS denotes polystyrene.

Step B:

This step is identical to step B of general procedure (A) with the modification that acid (III) is used instead of acid (II).

25

Step C:

The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring resin bound aldehyde or ketone with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. A

30

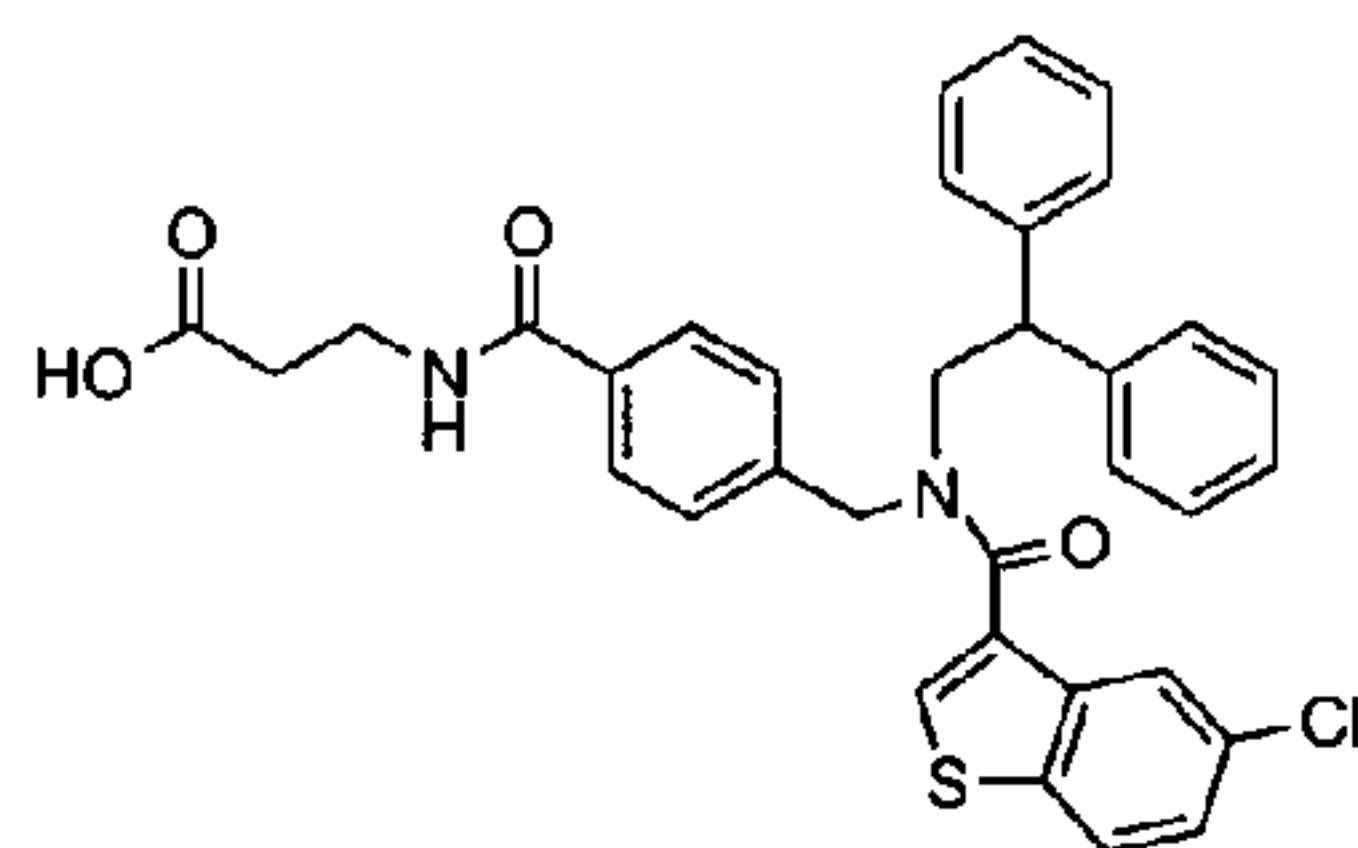
reducing agent such as sodium cyanoborohydride may be used. The reaction is performed between 20°C and 120°C, preferably at 25°C.

The following examples 1 to 9 were prepared according to general procedure (A).

5

EXAMPLE 1 (general procedure (A))

3-(4-{{N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino}methyl}benzoyl-amino)propionic acid



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Step A: Resin bound Fmoc-3-aminopropionic acid

Polystyrene resin loaded with the Wang linker (1.07 mmol/g, 25.0 g, 26.75 mmol) was treated overnight at 25°C with a solution of *N*-Fmoc-3-aminopropionic acid (33.3 g, 107 mmol) in 100 mL THF activated with diisopropylcarbodiimide (8.5 mL, 54 mmol) in the presence of 4-dimethylaminopyridine (0.2 g). Excess of reagents was removed by filtration. The resin bound intermediate was successively washed with 3 x 100 mL THF, 3 x 100 mL DMF and 3 x 100 mL methanol. The resin was dried overnight in vacuo at 50°C for 16 hours to afford 31.54 g resin bound Fmoc-3-aminopropionic acid.

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20

A small sample of resin bound intermediate (25 mg) was withdrawn and treated with 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was diluted with 10 mL acetonitrile and analyzed by HPLC. The yield was calculated from HPLC trace at 214 nm compared to the solution of a standard.

25

Step B: Resin bound 3-[4-(bromomethyl)benzoyl]aminopropionic acid

The above resin bound Fmoc-3-aminopropionic acid (3.95 g, 2.4 mmol) was treated with 40 mL 50% piperidine in DMF for 15 min. The reagent was removed by filtration. The resin was successively washed with 3 x 20 mL DMF and 20 mL of a 1M solution of *N*-hydroxybenzotriazole in DMF. The resulting resin bound intermediate was treated with a solution of 4-bromomethylbenzoic acid (2.15 g, 10 mmol) and *N*-hydroxybenzotriazole (1.52 g, 10 mmol) in 25 mL THF

30

activated by diisopropylcarbodiimide (1.57 mL, 10 mmol). The reaction was performed at 25°C for 12 hours. Excess of reagents was removed by filtration. The resin bound intermediate was successively washed with 3 x 20 mL THF, 3 x 20 mL DMF and 3 x 20 mL methanol. The resin was dried in vacuo at 50°C for 16 hours to afford 3.77 g resin bound 3-[4-(bromo-methyl)benzoyl]aminopropionic acid.

An analytical sample of resin bound intermediate (0.05 g) was withdrawn and treated with 1 mL 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was diluted with 20 mL of acetonitrile and characterized by analytical RP-HPLC (R_t = 8.25 min) and by HPLC-MS (Method A) (m/z = 287 ($M + 1$)).

Step C: Resin bound 3-(4-[(N-2,2-diphenylethyl)methyl]benzoyl)amino)propionic acid

The above resin bound 3-[4-(bromomethyl)benzoyl]aminopropionic acid (1.0 g, 0.64 mmol) was treated with 2,2-diphenylethylamine (1.26 g, 6.4 mmol) in 4 mL DMSO. The reaction was stirred at 80°C for 12 hours. Excess of reagents was removed by filtration. The resin was successively washed with 3 x 10 mL DMSO and 3 x 10 mL methanol and dried in vacuo at 50°C for 16 hours to afford 1.07 g resin bound 3-(4-[(N-2,2-diphenylethyl)methyl]benzoyl)amino)propionic acid.

An analytical sample of resin bound intermediate (0.05 g) was withdrawn and treated with 1 mL 50% TFA in dichloromethane for 30 min. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was dissolved in 20 mL of acetonitrile and characterized by analytical RP-HPLC (R_t = 8.70 min) and by HPLC-MS (Method A) (m/z = 417 ($M + 1$)).

Step D: Resin bound 3-(4-[(N-(5-chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino)methyl]benzoylamino)propionic acid

The above resin bound 3-(4-[(N-2,2-diphenylethyl)methyl]benzoyl)amino)propionic acid (1.02 g, 0.61 mmol) was suspended in THF and successively washed with 2 x 10 mL THF, 2 x 10 mL 5% diisopropylethylamine in THF and 5 x 10 mL THF. The resin slurry was then treated with 5-chlorobenzo[b]thiophen-3-carboxylic acid (0.51 g, 2.4 mmol) in 4 mL THF, 4 mL pyridine, diisopropylcarbodiimide (0.19 mL, 1.2 mmol) and 4-dimethylaminopyridine (24 mg, 0.12 mmol). The reaction mixture was stirred at 25°C for 12 hours. The resin was drained and

successively washed with 3 x 10 mL THF, 3 x 10 mL DMF and 5 x 10 mL dichloromethane and used in next step without any characterization.

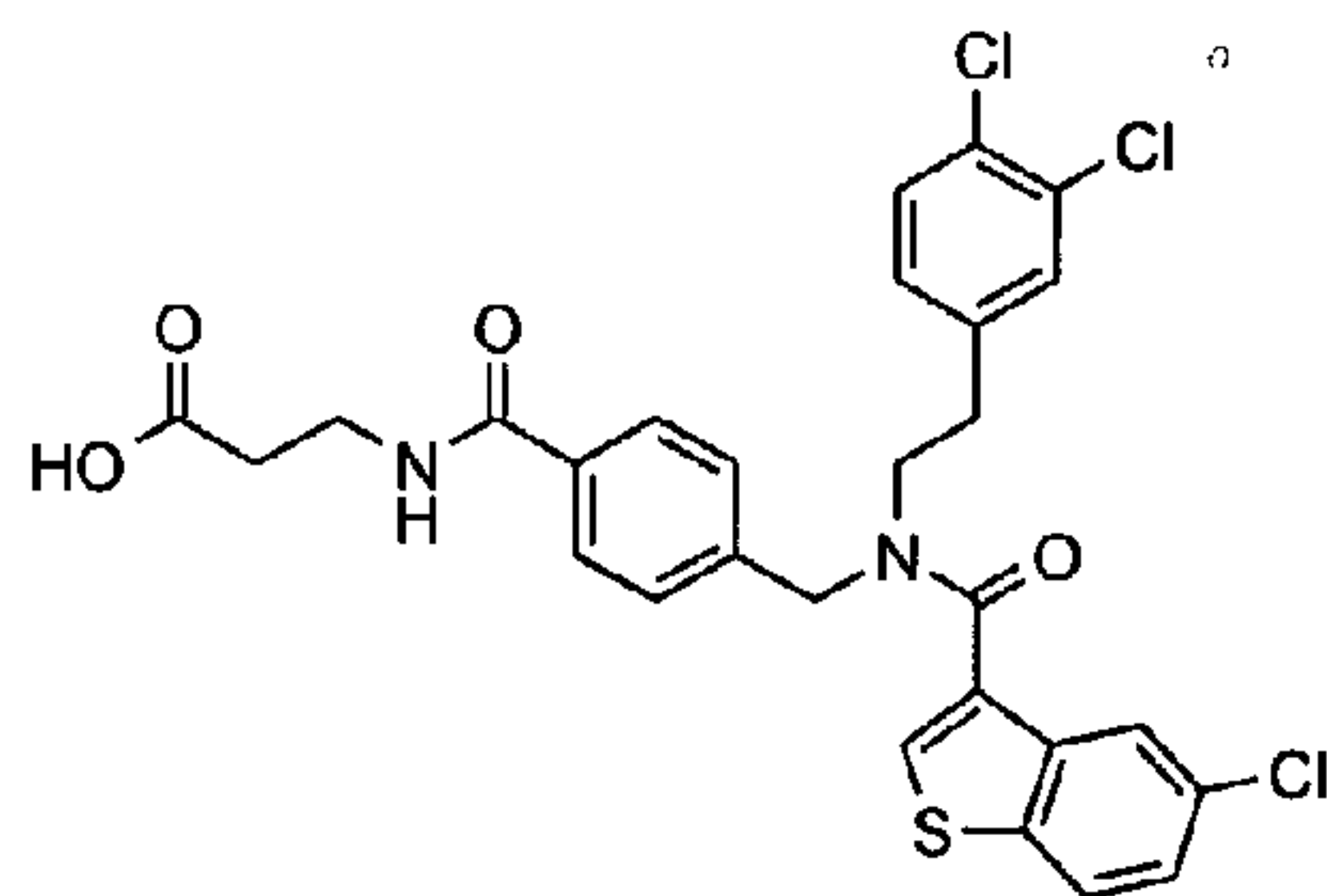
Step E: 3-(4-{[N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl}-benzoylamino)propionic acid

The resin bound 3-(4-{[N-(5-chlorobenzo[b]thiophen-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl}benzoylamino)propionic acid was treated with a 50% solution of TFA in dichloromethane (10 mL). The cleavage mixture was stirred for 45 min at 25°C. The resin was drained and washed with dichloromethane several times. The combined filtrates were concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol and dichloromethane (1 mL) and concentrated in vacuo to afford 0.359 g of the title compound. The product was characterized by analytical RP-HPLC ($R_t = 14.2$ min) and by HPLC-MS (Method A) ($m/z = 597$ ($M + 1$)).

The crude product (50 mg) was purified by column chromatography on RP-C18 silica gel (Sep-Pak, Waters) eluting with a mixture of acetonitrile and water. Pure fractions were pooled and evaporated in vacuo to afford 16.7 mg of pure title compound.

EXAMPLE 2 (general procedure (A))

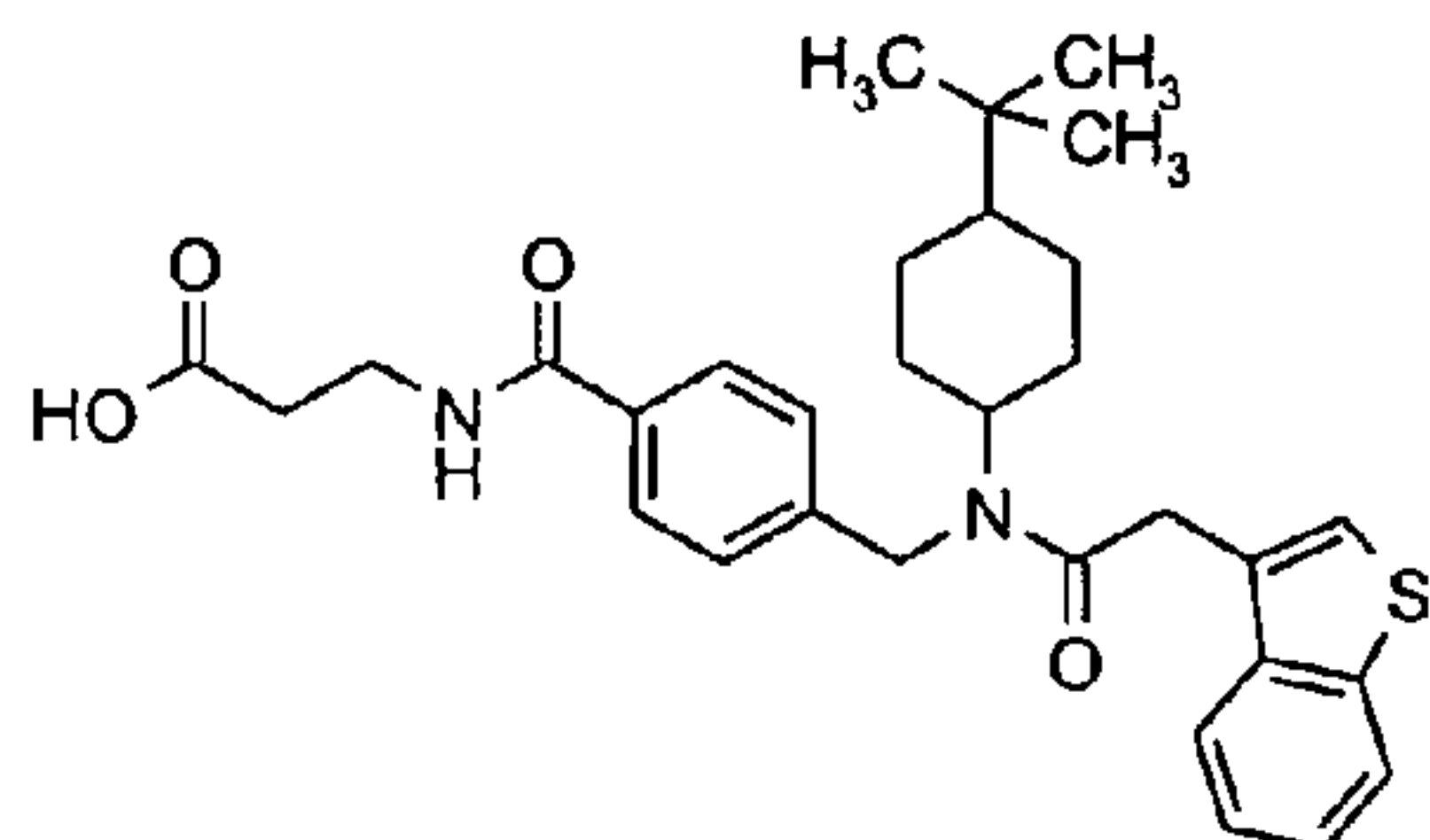
3-(4-{[N-(5-Chlorobenzo[b]thiophen-3-carbonyl)-N-(3,4-dichlorophenylethyl)amino]methyl}-benzoylamino)propionic acid



The product was characterized by analytical RP-HPLC ($R_t = 14.12$ min) and by HPLC-MS (Method A) ($m/z = 589$ ($M + 1$)).

EXAMPLE 3 (general procedure (A))

3-(4-([N-(2-Benzo[b]thiophen-3-yl-acetyl)-N-(4-*tert*-butylcyclohexyl)amino]methyl}benzoyl-amino)propionic acid

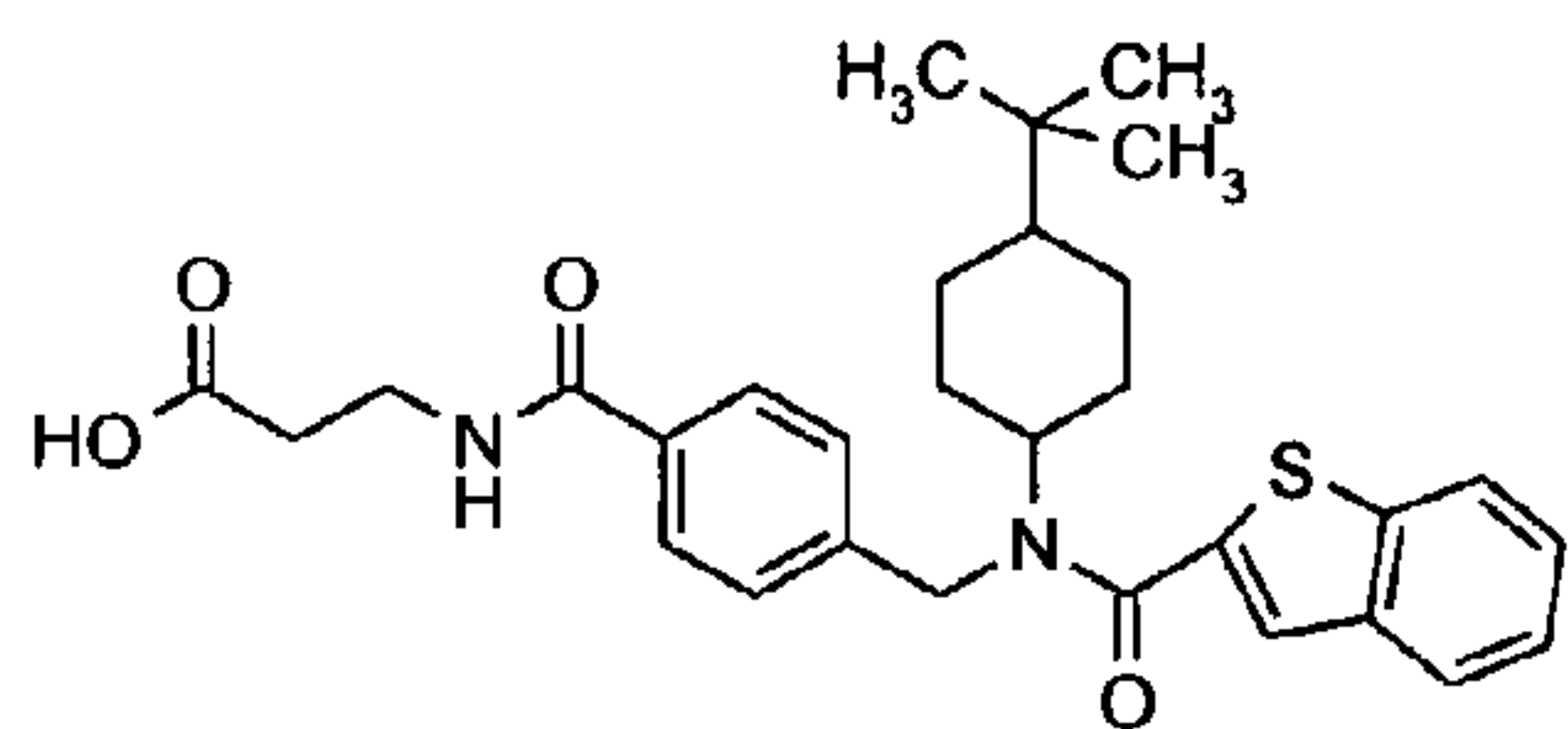


5

The product was characterized by analytical RP-HPLC ($R_t = 14.96$ min) and by HPLC-MS (Method A) ($m/z = 535$ ($M + 1$)).

EXAMPLE 4 (general procedure (A))

10 3-(4-([N-(Benzo[b]thiophen-2-carbonyl)-N-(4-*tert*-butylcyclohexyl)amino]methyl}benzoyl-amino)propionic acid

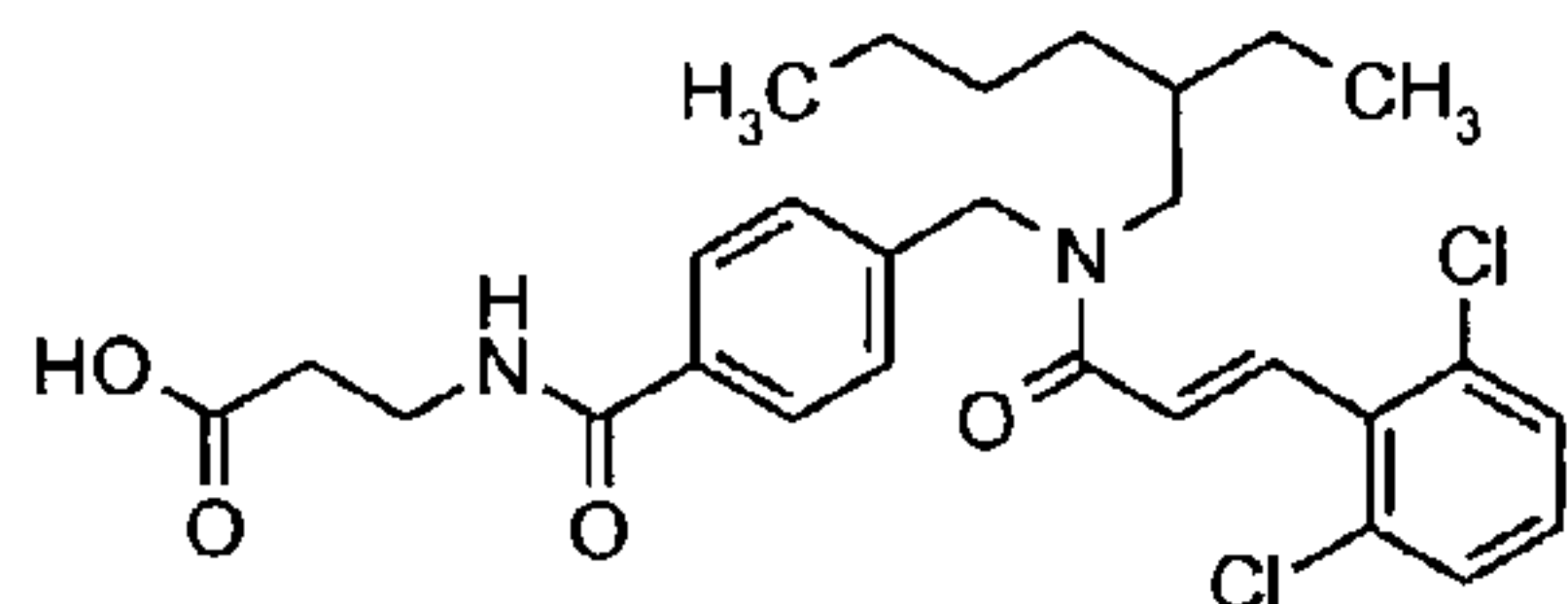


15

The product was characterized by analytical RP-HPLC ($R_t = 15.17$ min) and by HPLC-MS (Method A) ($m/z = 521$ ($M + 1$)).

EXAMPLE 5 (general procedure (A))

3-(4-([N-[3-(2,6-Dichlorophenyl)acryloyl]-N-(2-ethylhexyl)amino]methyl}benzoylamino)-propionic acid

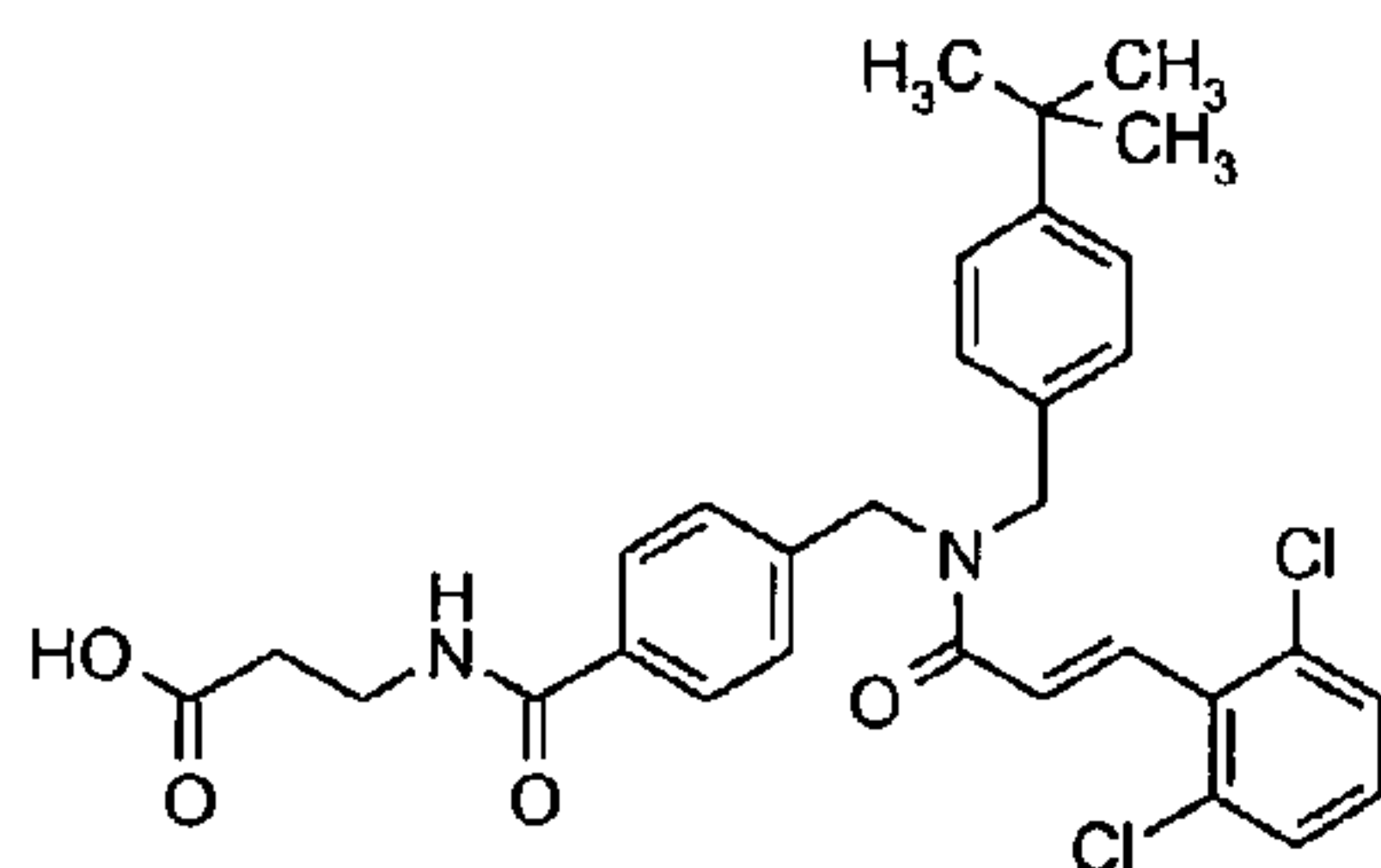


20

The product was characterized by analytical RP-HPLC ($R_t = 15.26$ min) and by HPLC-MS (Method A) ($m/z = 533$ ($M + 1$)).

EXAMPLE 6 (general procedure (A))

3-(4-([N-[3-(2,6-Dichlorophenyl)acryloyl]-N-(4-*tert*-butylbenzyl)amino]methyl)benzoylamino)-propionic acid

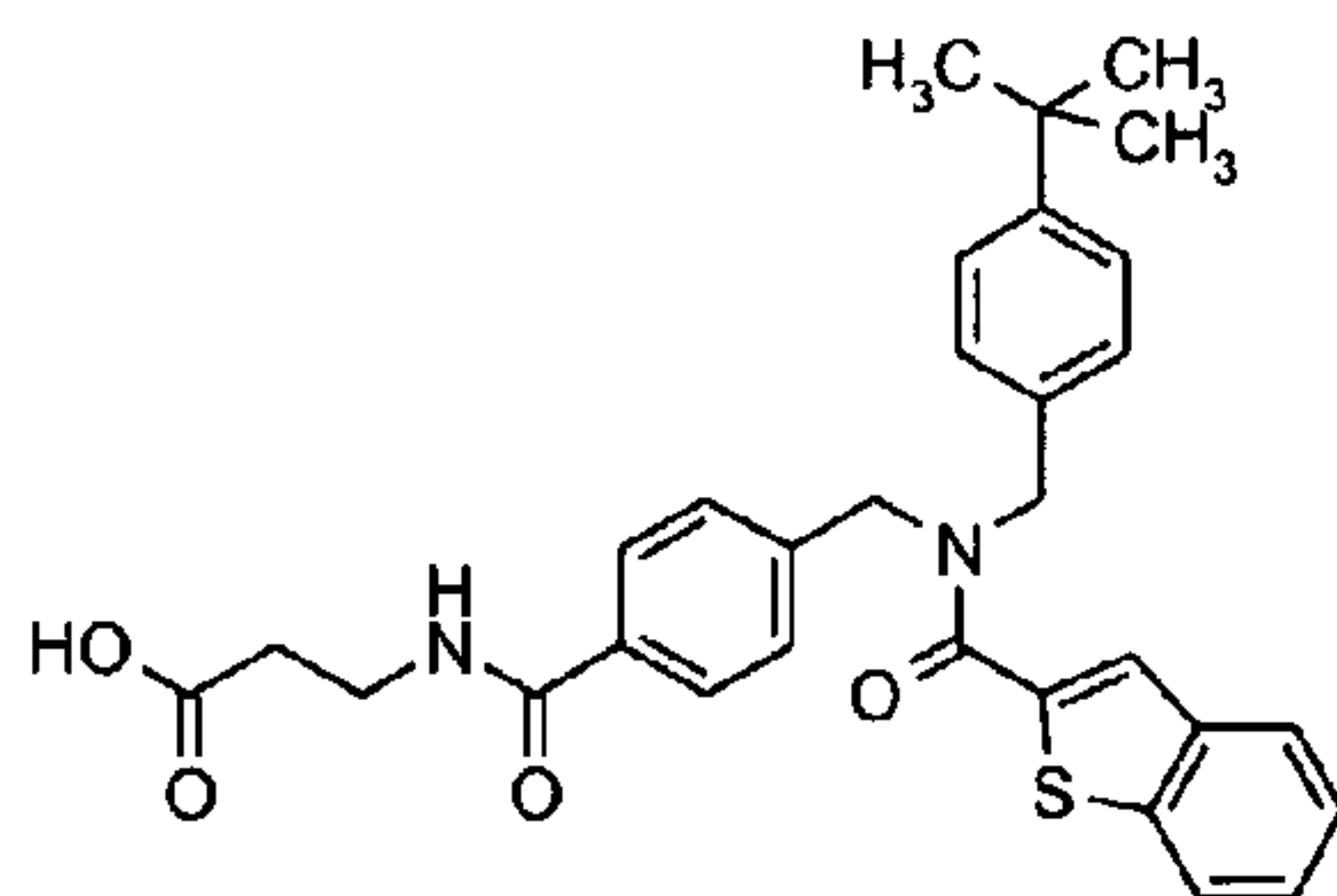


5

The product was characterized by analytical RP-HPLC ($R_t = 15.08$ min) and by HPLC-MS (Method A) ($m/z = 567$ ($M + 1$)).

EXAMPLE 7 (general procedure (A))

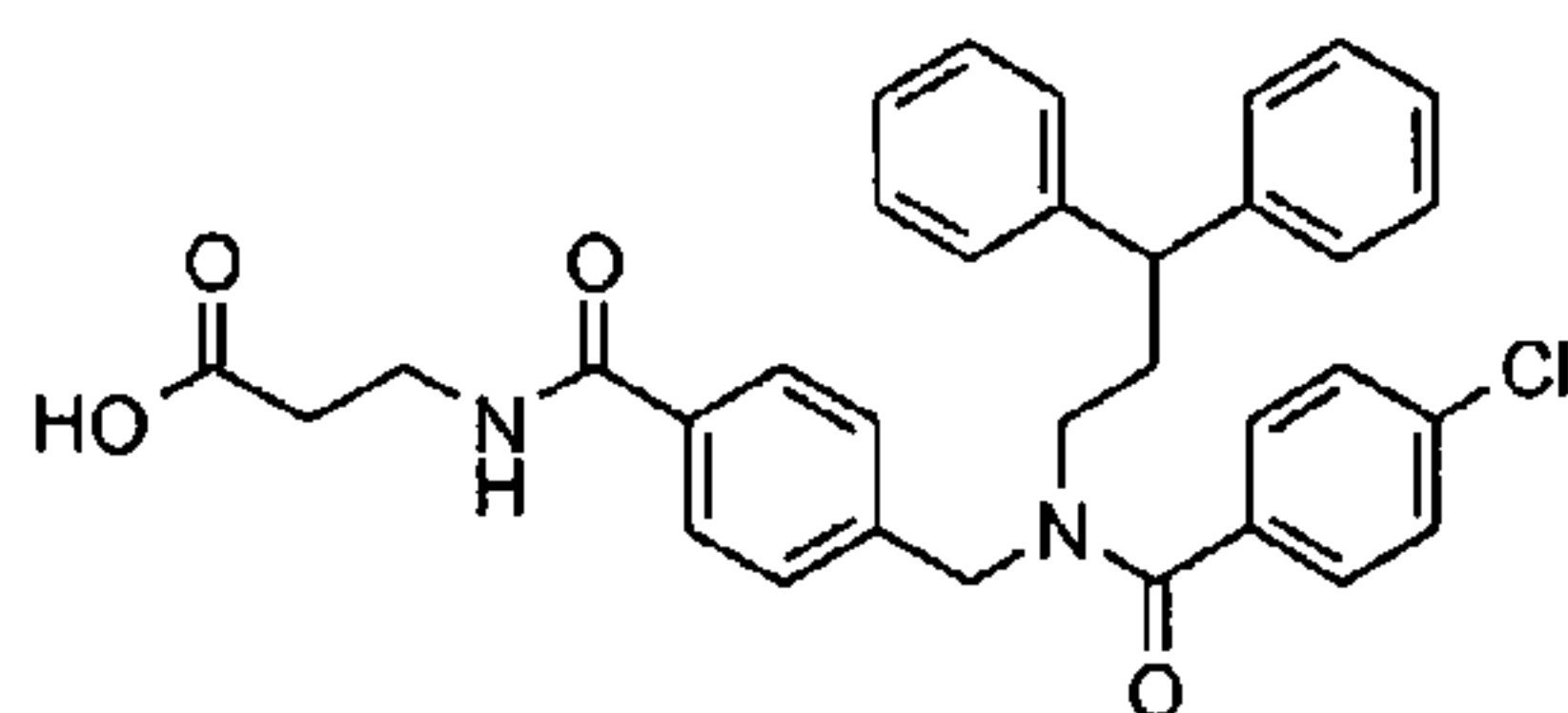
10 3-(4-([N-(Benzo[b]thiophen-2-carbonyl)-N-(4-*tert*-butylbenzyl)amino]methyl)benzoylamino)-propionic acid



15 The product was characterized by analytical RP-HPLC ($R_t = 14.70$ min) and by HPLC-MS (Method A) ($m/z = 529$ ($M + 1$)).

EXAMPLE 8 (general procedure (A))

3-(4-([N-(4-Chlorobenzoyl)-N-(3,3-diphenylpropyl)amino]methyl)benzoylamino)propionic acid

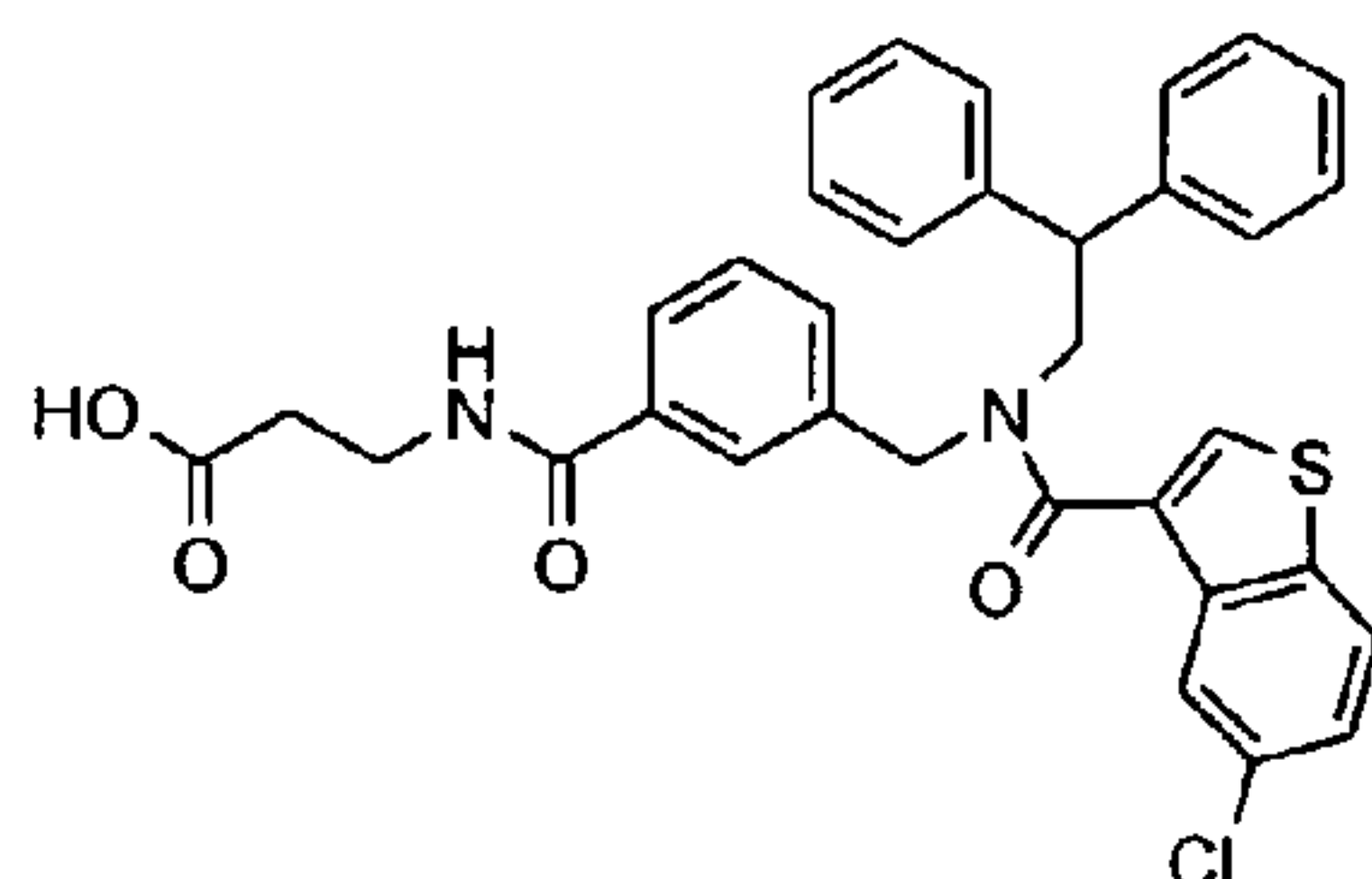


20

The product was characterized by analytical RP-HPLC ($R_t = 13.6$ min) and by HPLC-MS (Method A) ($m/z = 555$ ($M + 1$)).

EXAMPLE 9 (general procedure (A))

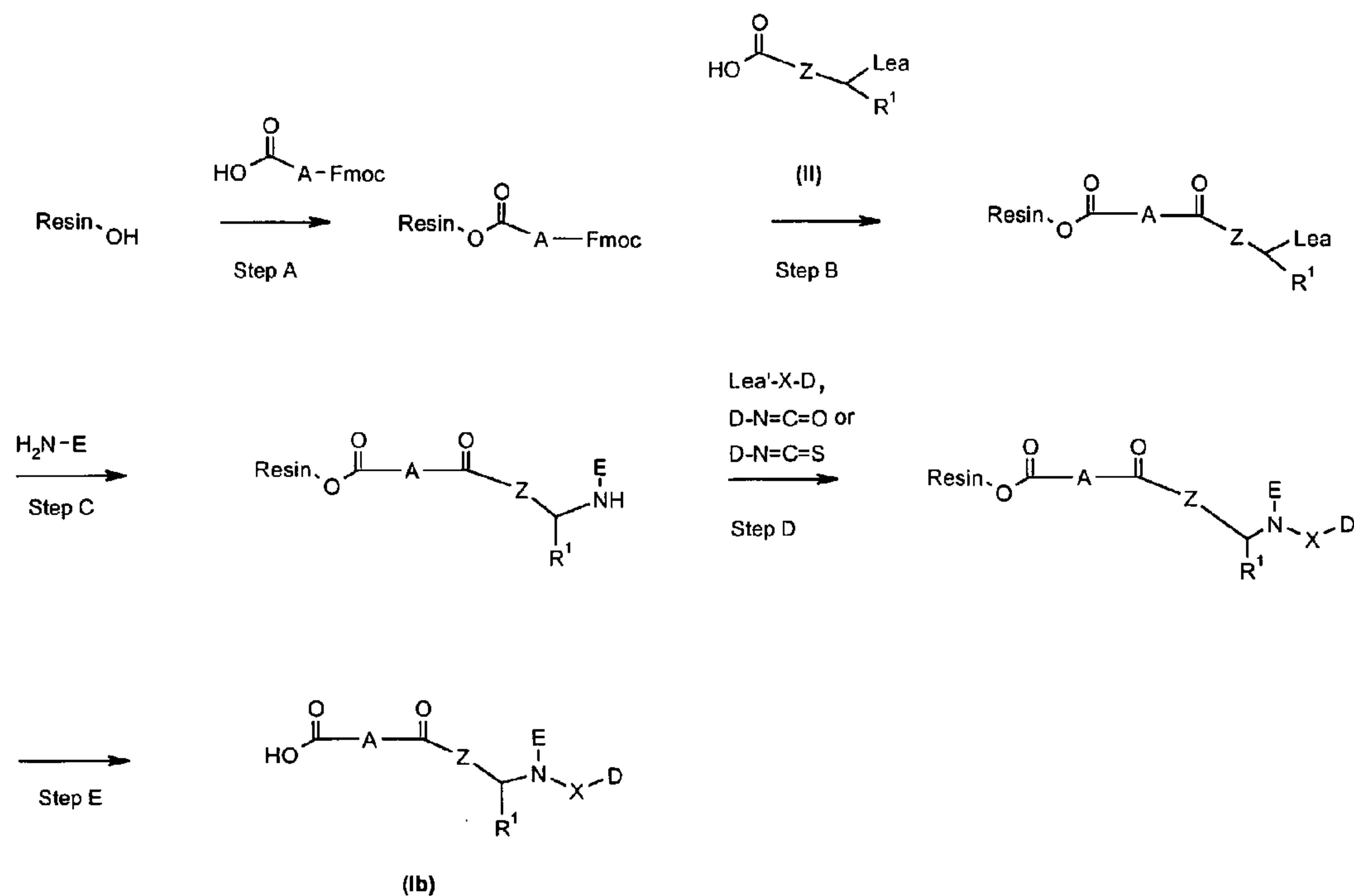
3-(3-([N-(5-Chlorobenzo[b]thiophene-3-carbonyl)-N-(2,2-diphenylethyl)amino]methyl)-benzoylamino)propionic acid



5

The product was characterized by analytical RP-HPLC ($R_t = 14.5$ min) and by HPLC-MS (Method A) ($m/z = 597$ ($M + 1$)).

10 General procedure (C) for the solid phase synthesis of compounds of the general formula (Ib):



wherein

15

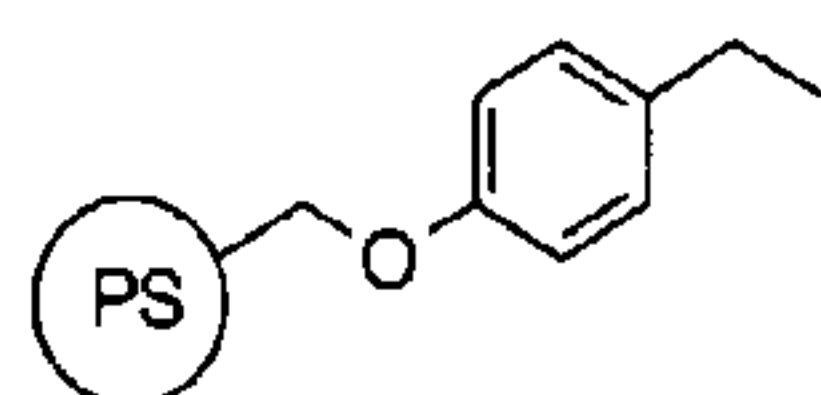
A, Z, R^1 , E and D are as defined for formula (I),

X is $-\text{S}(\text{O})_2-(\text{CH}_2)_r-$, $-\text{C}(\text{O})\text{NH}-$ or $-\text{C}(\text{S})\text{NH}-$, wherein r is as defined for formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl,

Lea' is a leaving group such as $-\text{OSu}$, chloro, phenoxy or 4-nitrophenoxy, and

Resin denotes a polystyrene resin with a linker such as the Wang linker:



wherein PS denotes polystyrene.

Step A:

Wang resin (10.0 g, Bachem 1250, 0.96 mmol/g) is suspended in NMP (100 mL) and drained, resuspended in THF (100 mL) and drained again. A solution of a Fmoc-protected amino acid (eg Fmoc- β -alanine) (58 mmol), diisopropylcarbodiimide (4.2 g, 34 mmol) and 4-dimethylaminopyridine (0.07 g, 0.6 mmol) in THF (80 mL) is added to the resin and vortexed for 16 hours. The resin is drained and washed with THF (3 x 100 mL) and NMP (3 x 100 mL).

Step B:

All the resin synthesised in step A is used in this step. A solution of 20% piperidine in NMP (100 mL) is added to the resin and the mixture vortexed for 1 hour. After draining the resin is washed in NMP (3 x 100 mL) and THF (5 x 100 mL). A solution of intermediate (II), eg 4-(bromomethyl)benzoic acid (or a substituted analogue thereof) (29 mmol), hydroxybenzotriazole (4.4 g, 29 mmol) and diisopropylcarbodiimide (3.6 g, 29 mmol) in THF (70 mL) is added and the mixture is vortexed for 16 hours. The resin is drained and washed with THF (2 x 100 mL), NMP (2 x 100 mL), dichloromethane (2 x 100 mL) and methanol (5 x 100 mL), and dried in vacuo.

Step C:

6 g of the resin synthesised in step B is used in this step. A solution of a primary amine (eg 2-phenethylamine or 4-*tert*-butylcyclohexylamine) (48 mmol) in DMSO is added to the resin

and vortexed at 80°C for 16 hours. The resin is drained and washed with NMP (3 x 100 mL), dichloromethane (3 x 100 mL) and methanol (4 x 100 mL), and dried in vacuo.

Step D:

5 50 mg of the resin produced in step C is used in this step. The resin is suspended in NMP (1.5 mL) and drained. A solution of an isothiocyanate or an isocyanate (eg phenylisocyanate or 4-trifluoromethoxyphenylisocyanate) (0.24 mmol) in NMP (1 mL) is added and the mixture is vortexed for 16 hours. Alternatively, a solution of Lea'-X-D in an appropriate solvent such as acetonitrile, toluene, DMF, NMP, THF, dichloromethane, 1,2-dichloroethane or DMSO or
10 a mixture of two or more of these, is added and the mixture is vortexed in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate under heating, if necessary. The resin is drained and washed with DMF (3 x 1 mL), methanol (3 x 1 mL), 2-propanol (3 x 1 mL), *tert*-butyl-methylether (3 x 1 mL) and dichloromethane (3 x 1 mL).

15

Step E:

All the resin synthesised in step D is used. A solution of TFA and dichloromethane (1:1, 2 mL) is added to the resin and vortexed for 45 min. The resin is drained and the eluent evaporated in vacuo to give a compound of general formula (Ib).

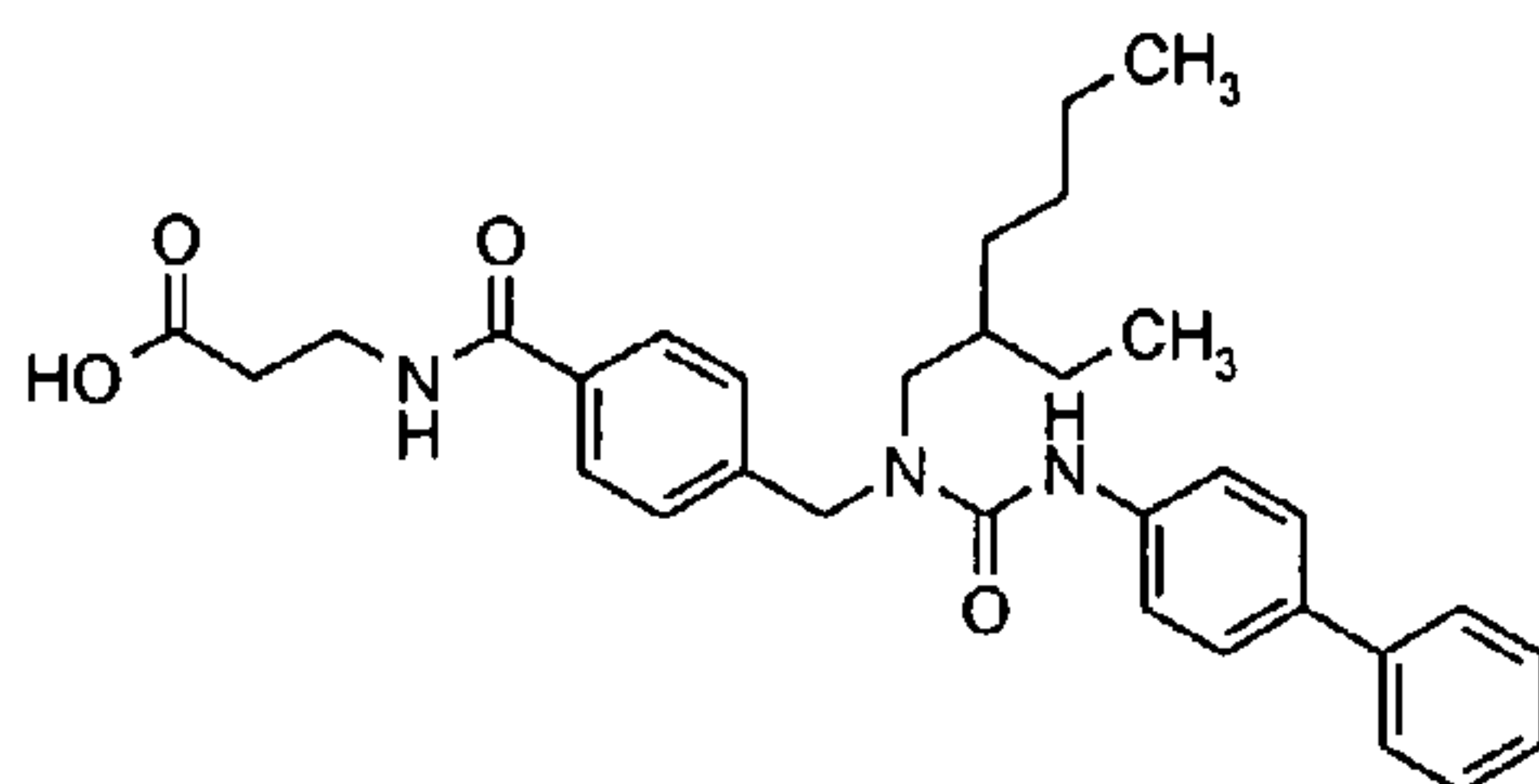
20

Optionally, the compound can be purified by chromatography eg HPLC.

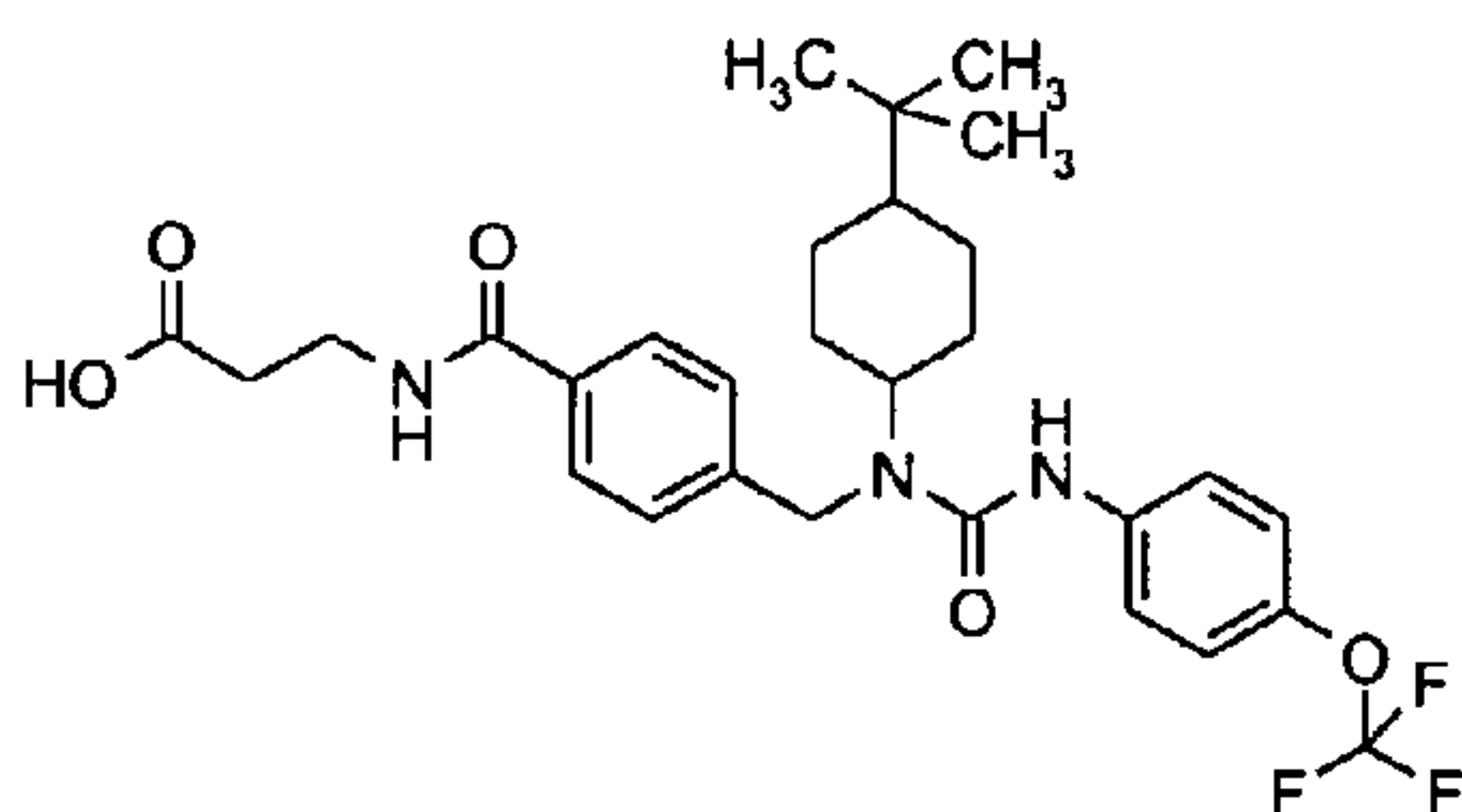
The compounds of general formula (Ib) can be prepared either as single compounds or by parallel synthesis using the protocol mentioned above in a combinatorial approach. Thousands of
25 compounds of formula (Ib) can thus be prepared by this combinatorial approach which can be semi-automated or fully automated. The automation of this protocol can be performed eg using a 96 well setup using an automated synthesizer device.

The following examples were prepared according to general procedure (C).

30

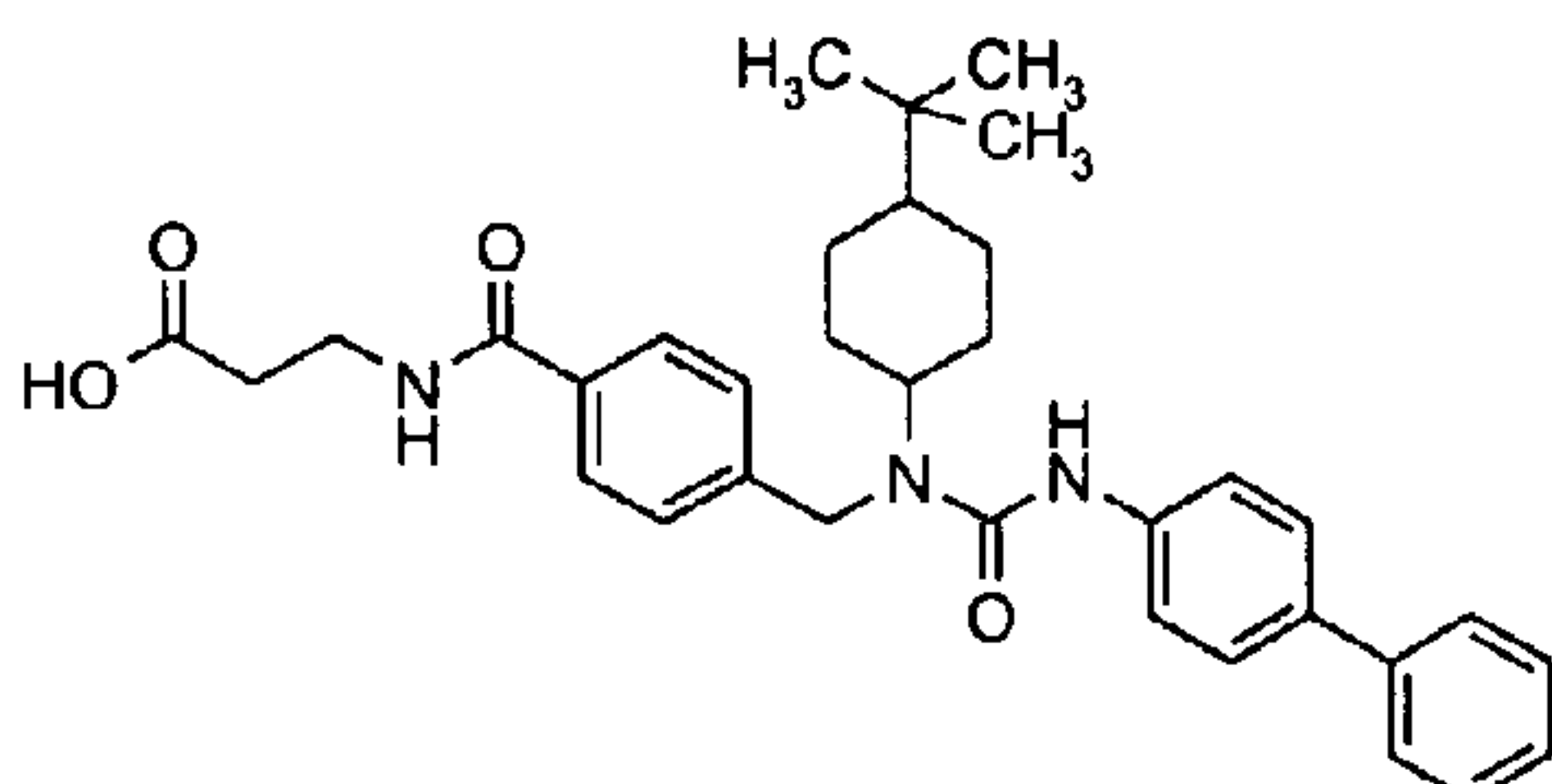
EXAMPLE 10 (general procedure (C))3-{4-[3-Biphenyl-4-yl-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method C): $R_t = 4.30$ min, $m/z = 530$ ($M + 1$).

EXAMPLE 11 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

10

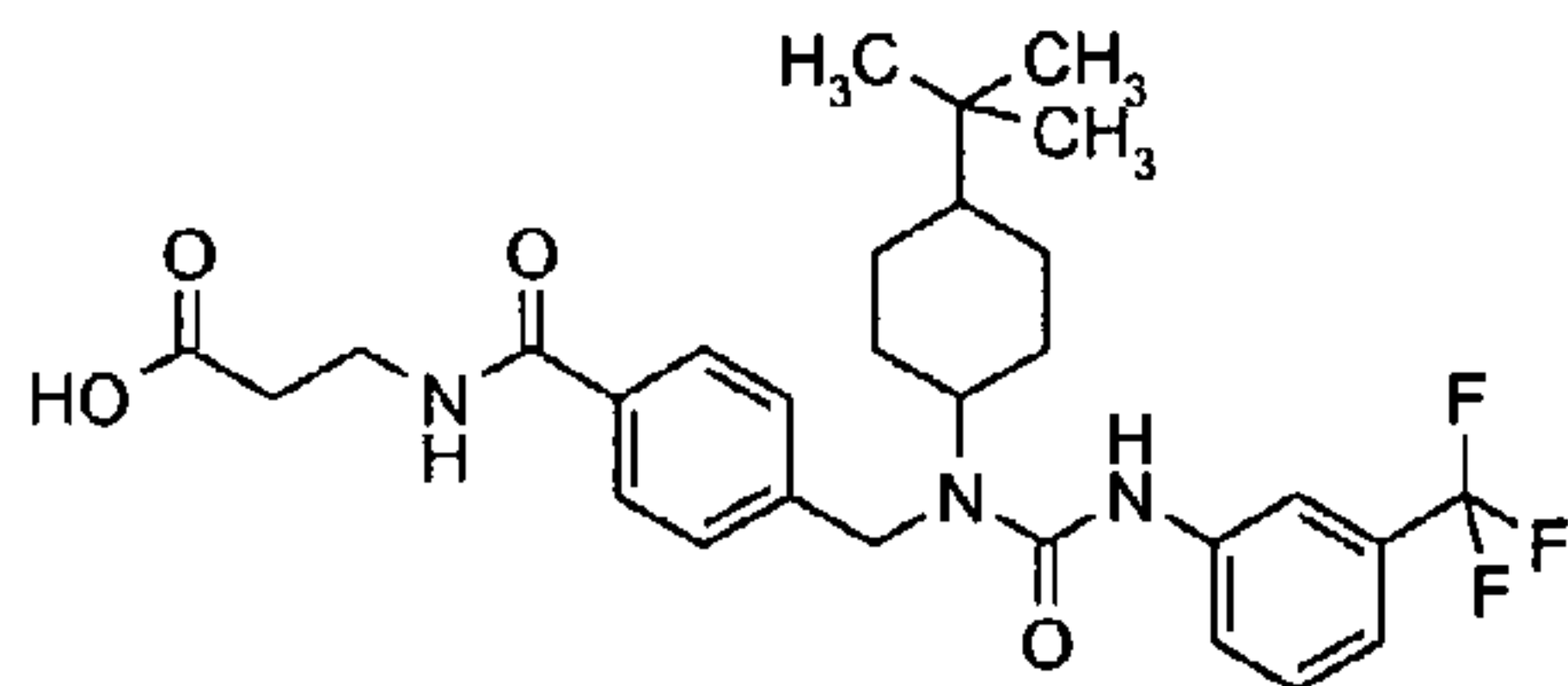
The product was characterized by HPLC-MS (Method C): $R_t = 4.33$ min, $m/z = 564$ ($M + 1$).

EXAMPLE 12 (general procedure (C))15 3-{4-[3-Biphenyl-4-yl-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

The product was characterized by HPLC-MS (Method C): $R_t = 4.40$ min, $m/z = 556$ ($M + 1$).

EXAMPLE 13 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

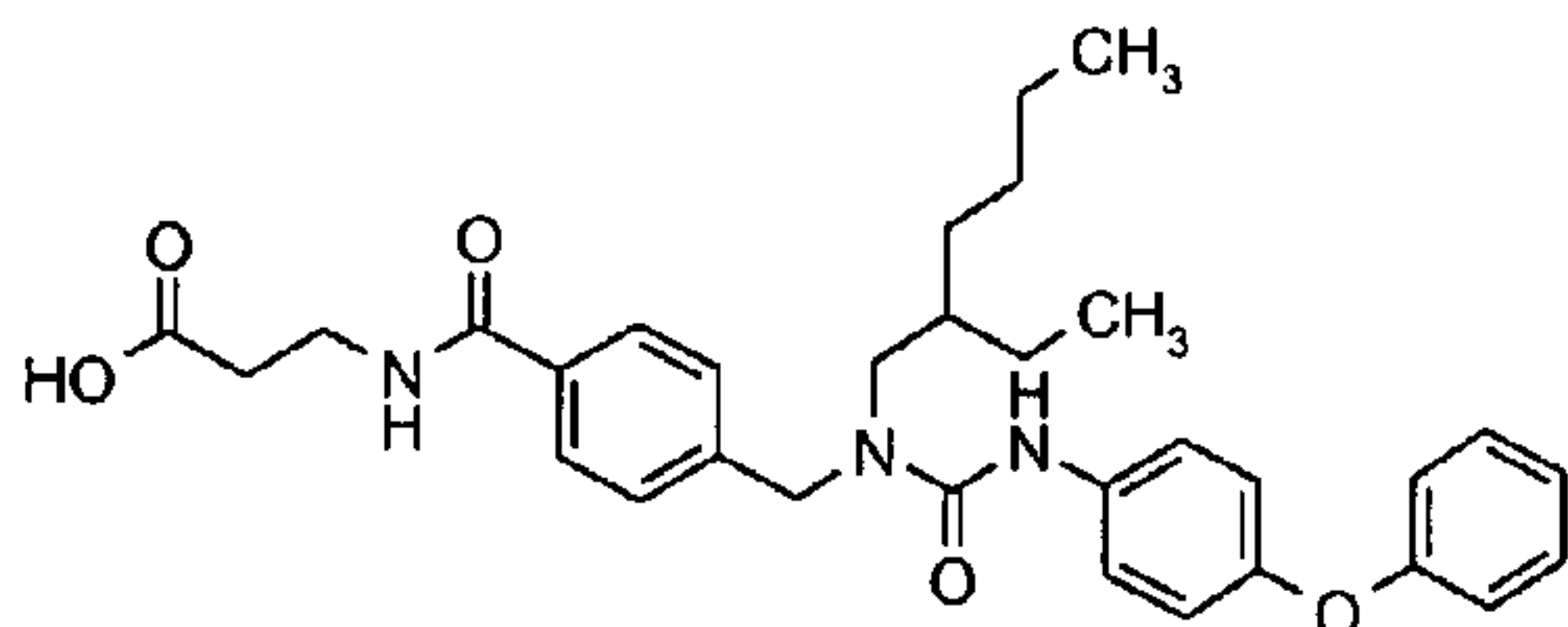


5

The product was characterized by HPLC-MS (Method C): $R_t = 4.31$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 14 (general procedure (C))

3-{4-[1-(2-Ethylhexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

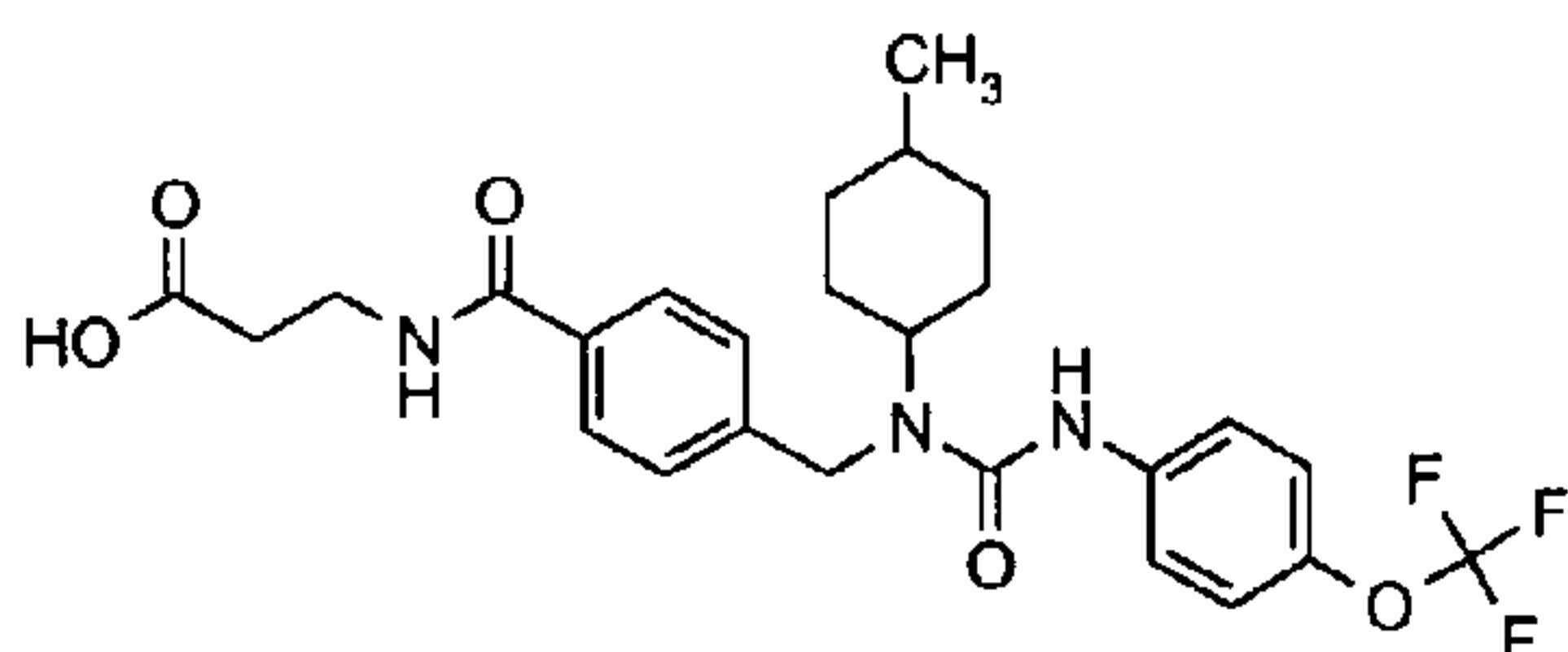


10

The product was characterized by HPLC-MS (Method C): $R_t = 4.30$ min, $m/z = 546$ ($M + 1$).

EXAMPLE 15 (general procedure (C))

15 3-{4-[1-(4-Methylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

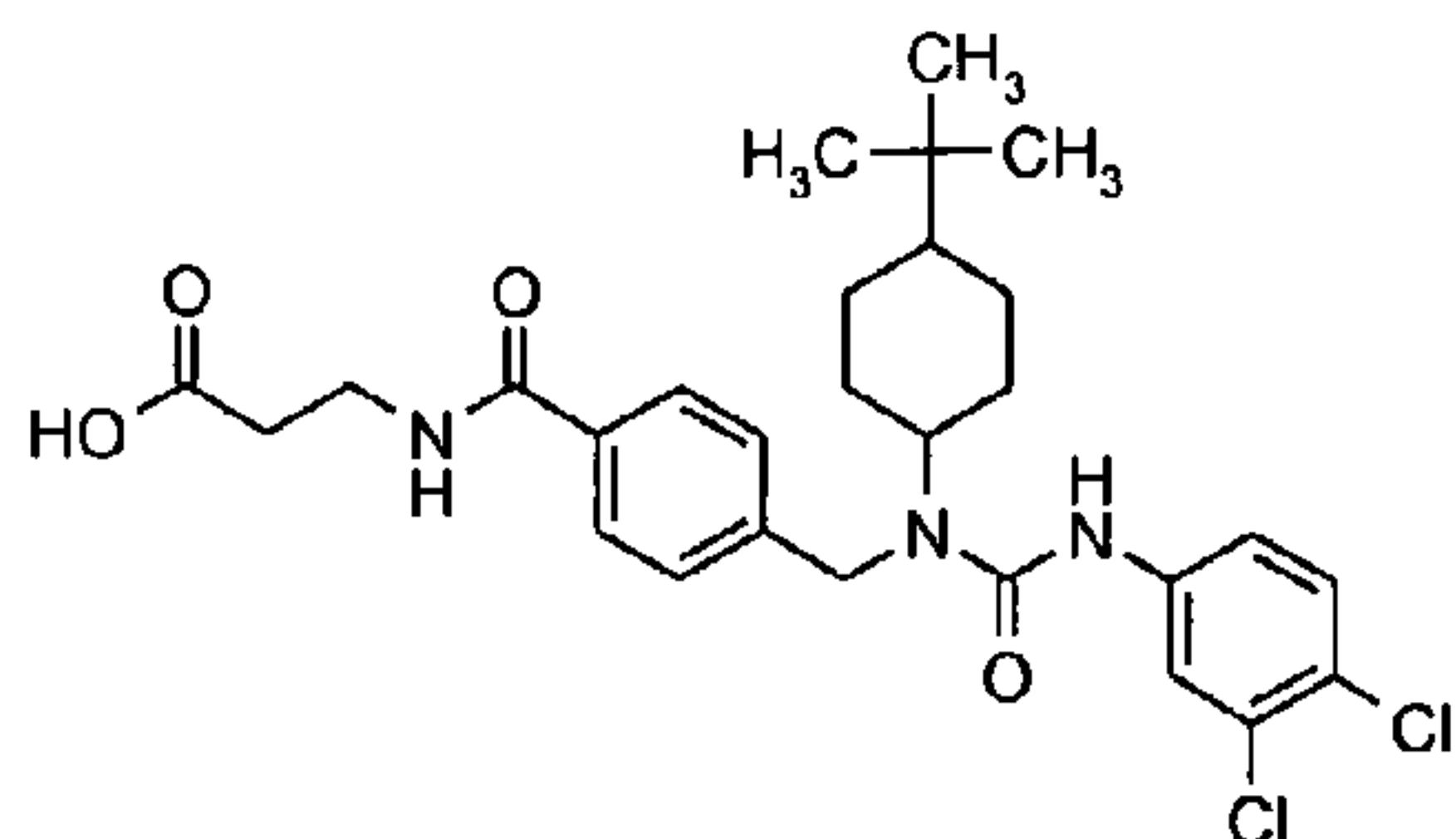


The product was characterized by HPLC-MS (Method C): $R_t = 3.78$ min, $m/z = 522$ ($M + 1$).

20

EXAMPLE 16 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



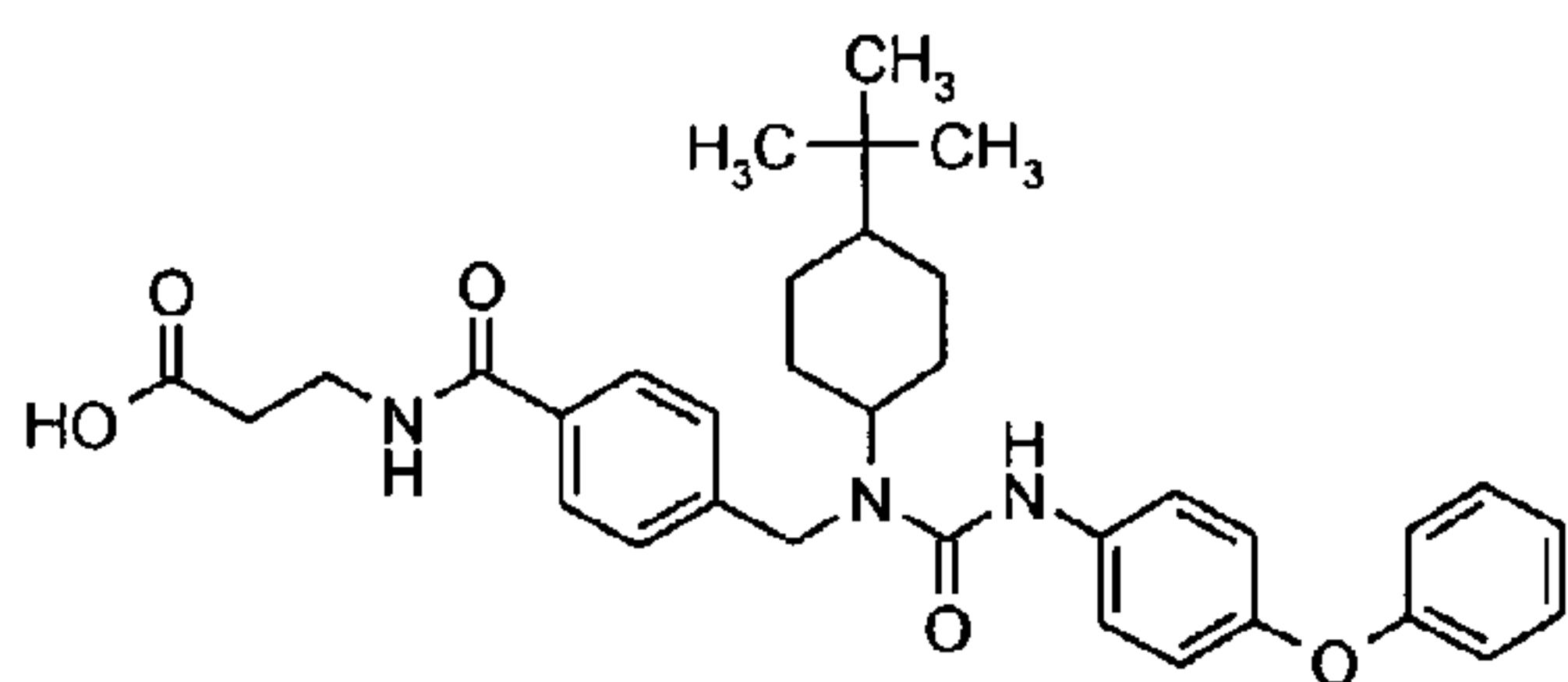
5

The product was characterized by HPLC-MS (Method C): $R_t = 4.62$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 17 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

10

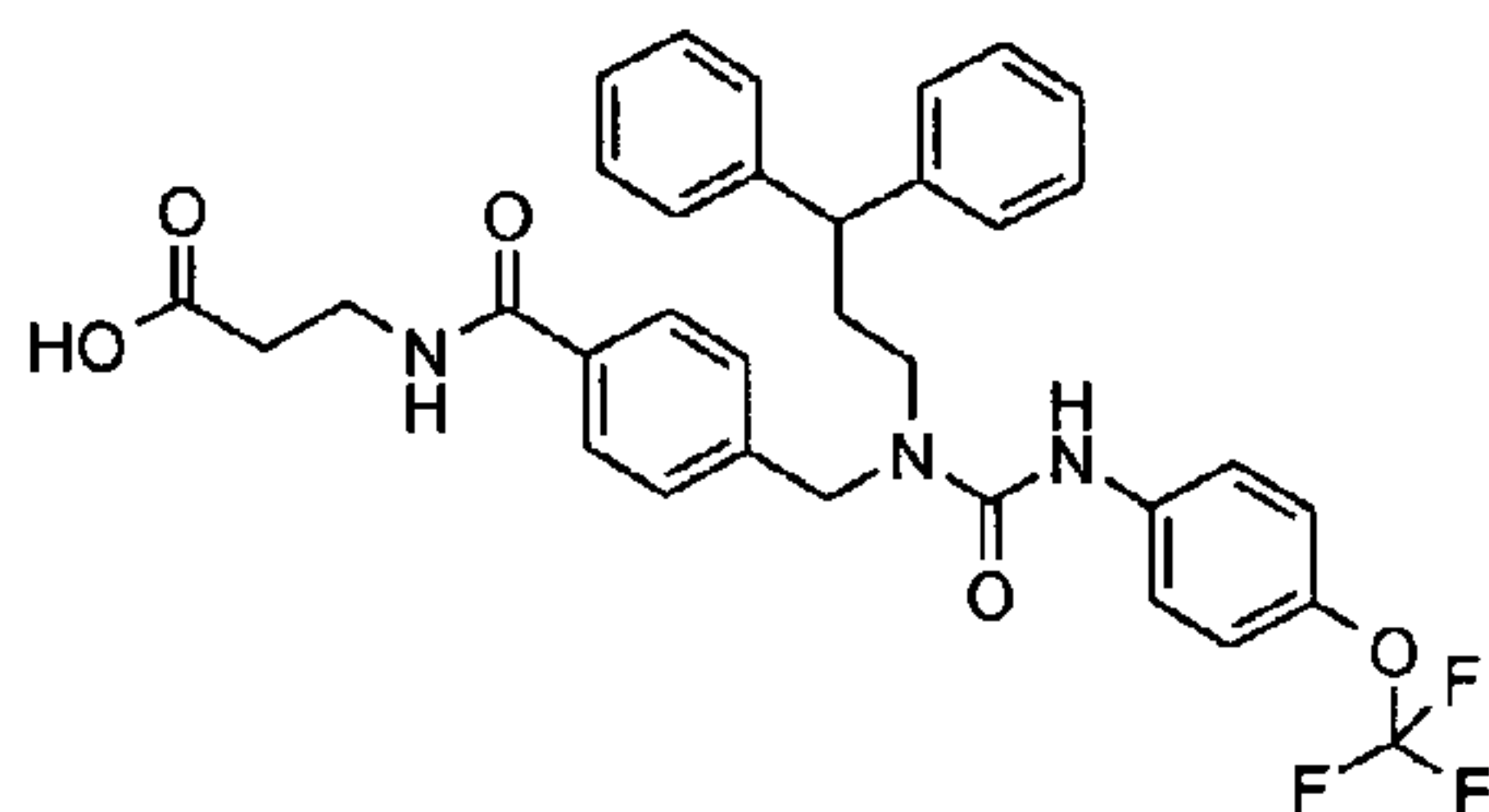


The product was characterized by HPLC-MS (Method C): $R_t = 4.30$ min, $m/z = 572$ ($M + 1$).

EXAMPLE 18 (general procedure (C))

3-{4-[1-(3,3-Diphenylpropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

15

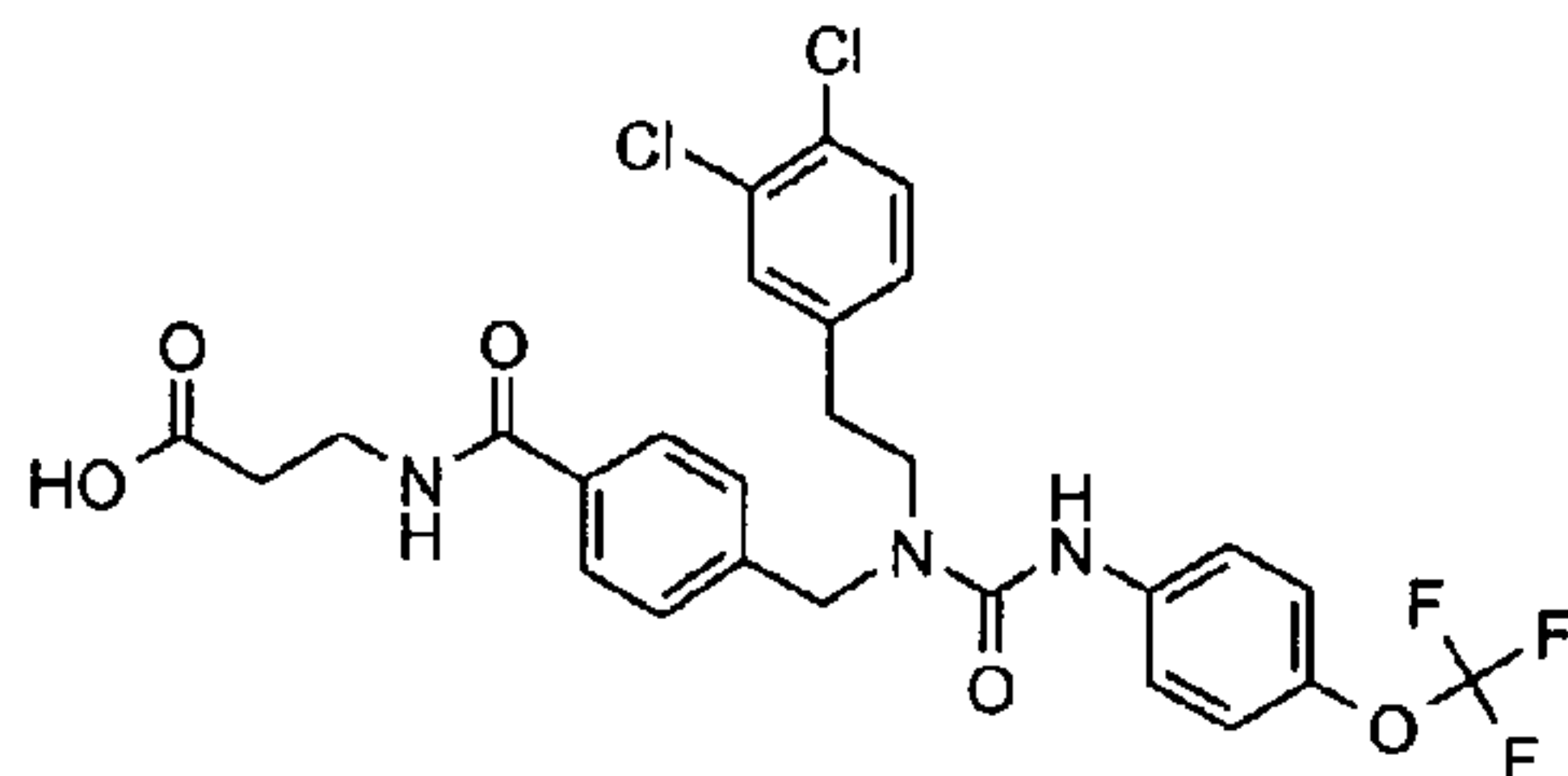


20

The product was characterized by HPLC-MS (Method C): $R_t = 4.13$ min, $m/z = 620$ ($M + 1$).

EXAMPLE 19 (general procedure (C))

3-{4-[1-[2-(3,4-Dichlorophenyl)ethyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid

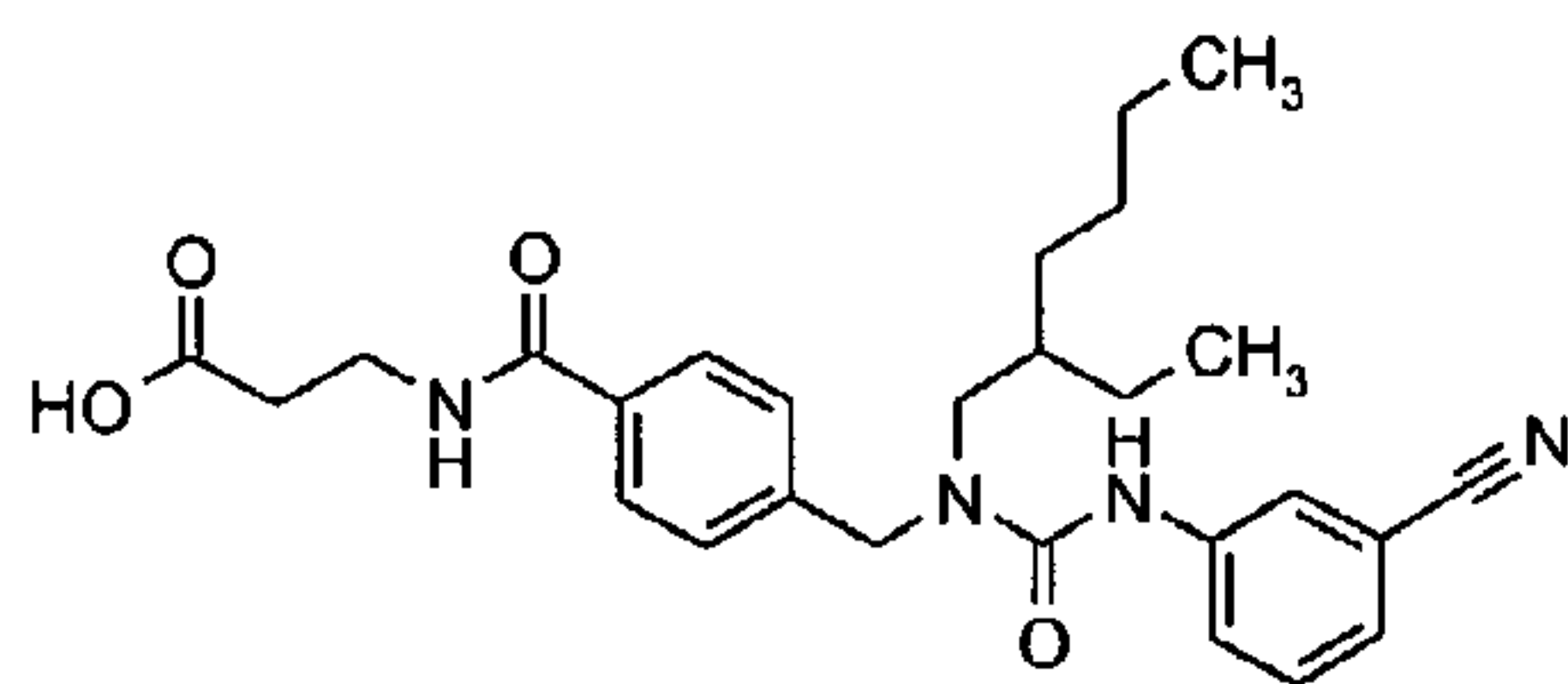


5

The product was characterized by HPLC-MS (Method C): $R_t = 4.00$ min, $m/z = 598$ ($M + 1$).

EXAMPLE 20 (general procedure (C))

3-{4-[3-(3-Cyanophenyl)-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid

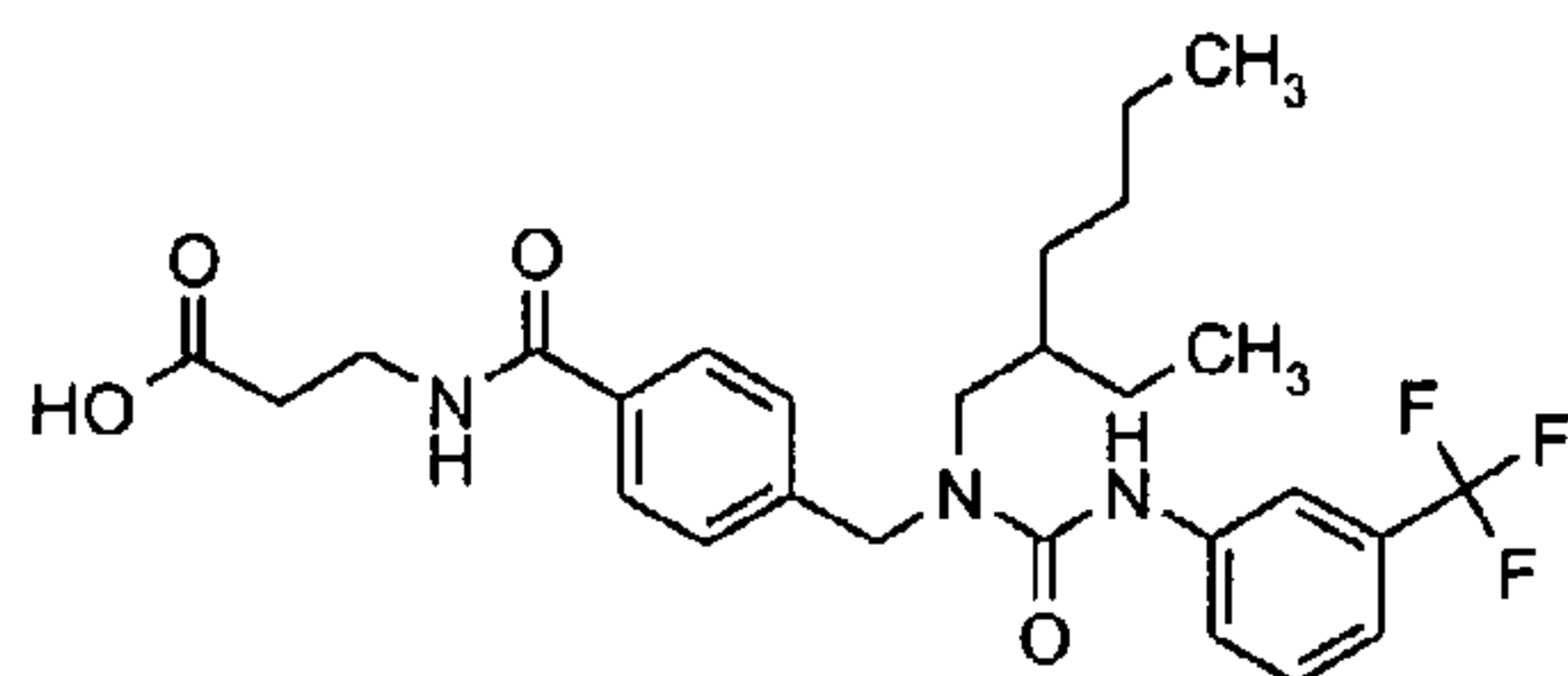


10

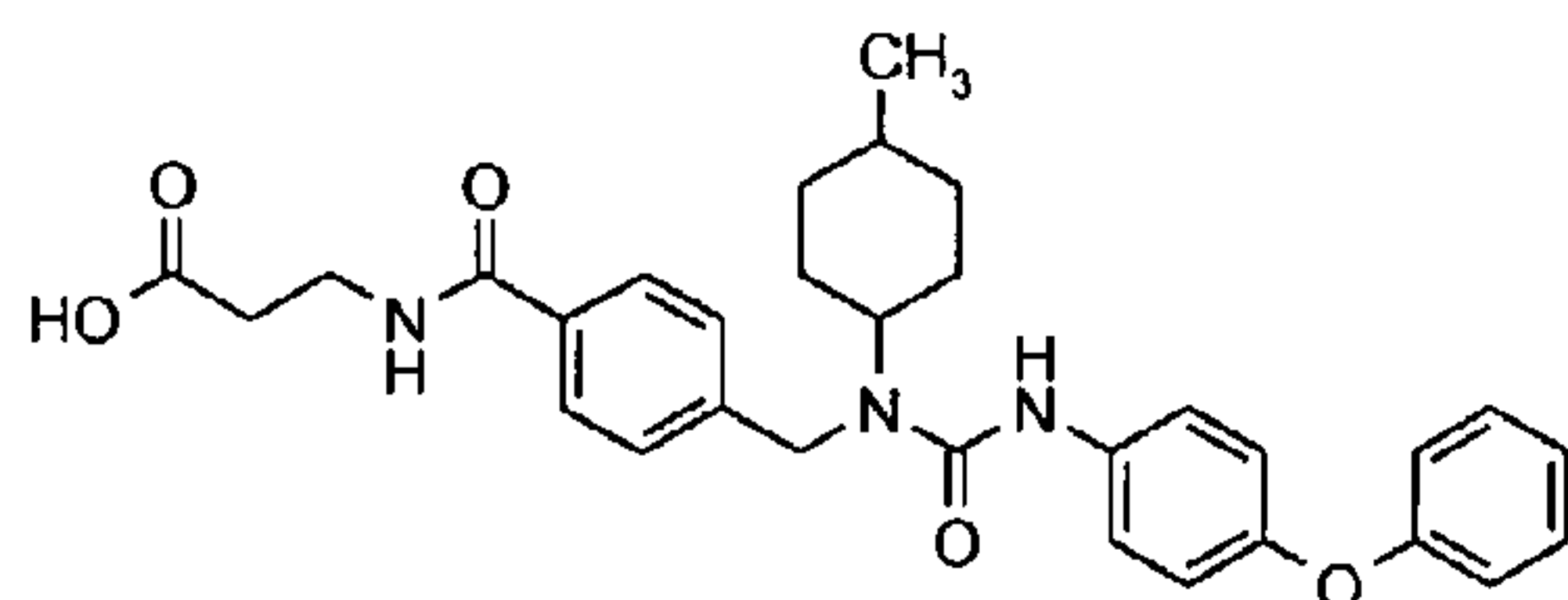
The product was characterized by HPLC-MS (Method B): $R_t = 5.50$ min, $m/z = 479$ ($M + 1$).

EXAMPLE 21 (general procedure (C))

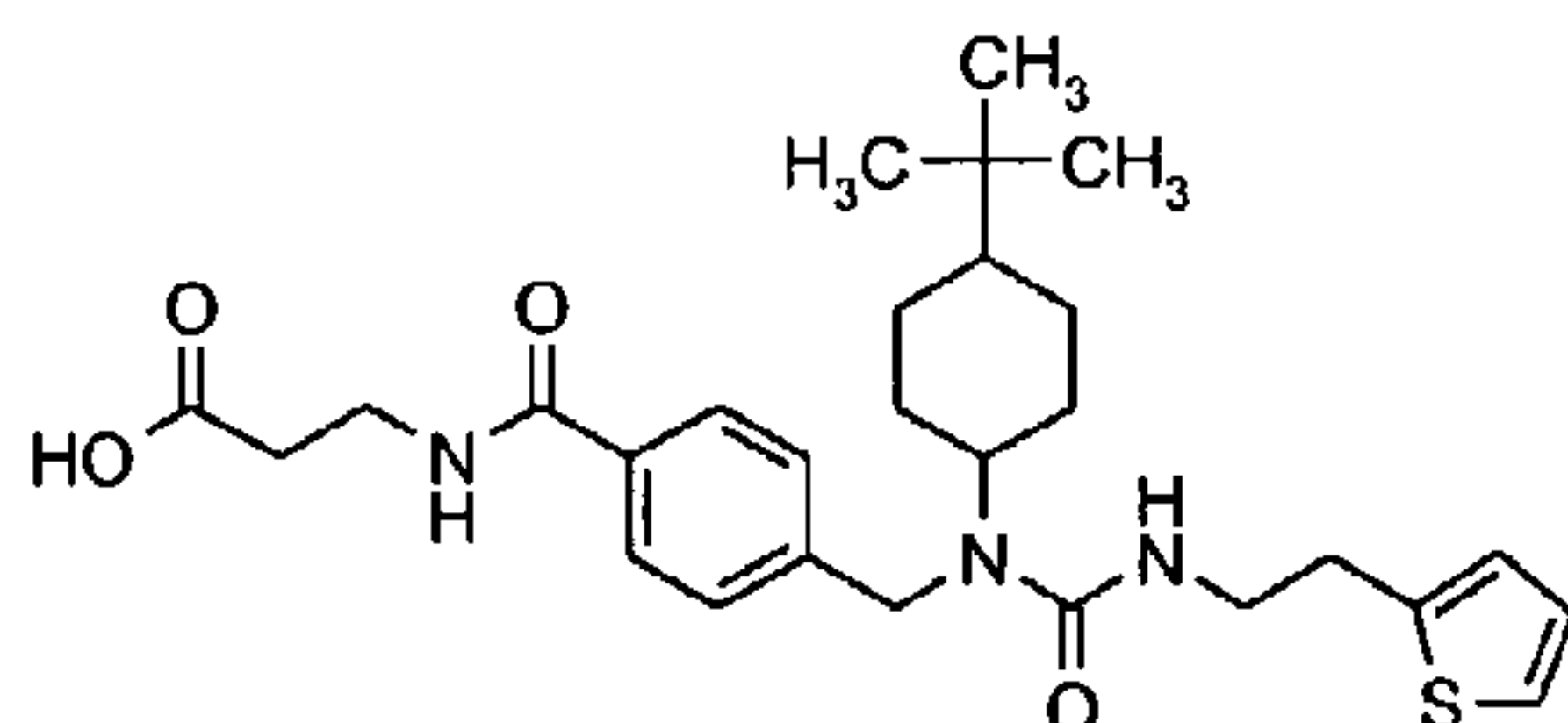
15 3-{4-[1-(2-Ethylhexyl)-3-(3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid



The product was characterized by HPLC-MS (Method B): $R_t = 6.17$ min, $m/z = 552$ ($M + 1$).

EXAMPLE 22 (general procedure (C))3-{4-[1-(4-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method B): $R_t = 5.73$ min, $m/z = 530$ ($M + 1$).

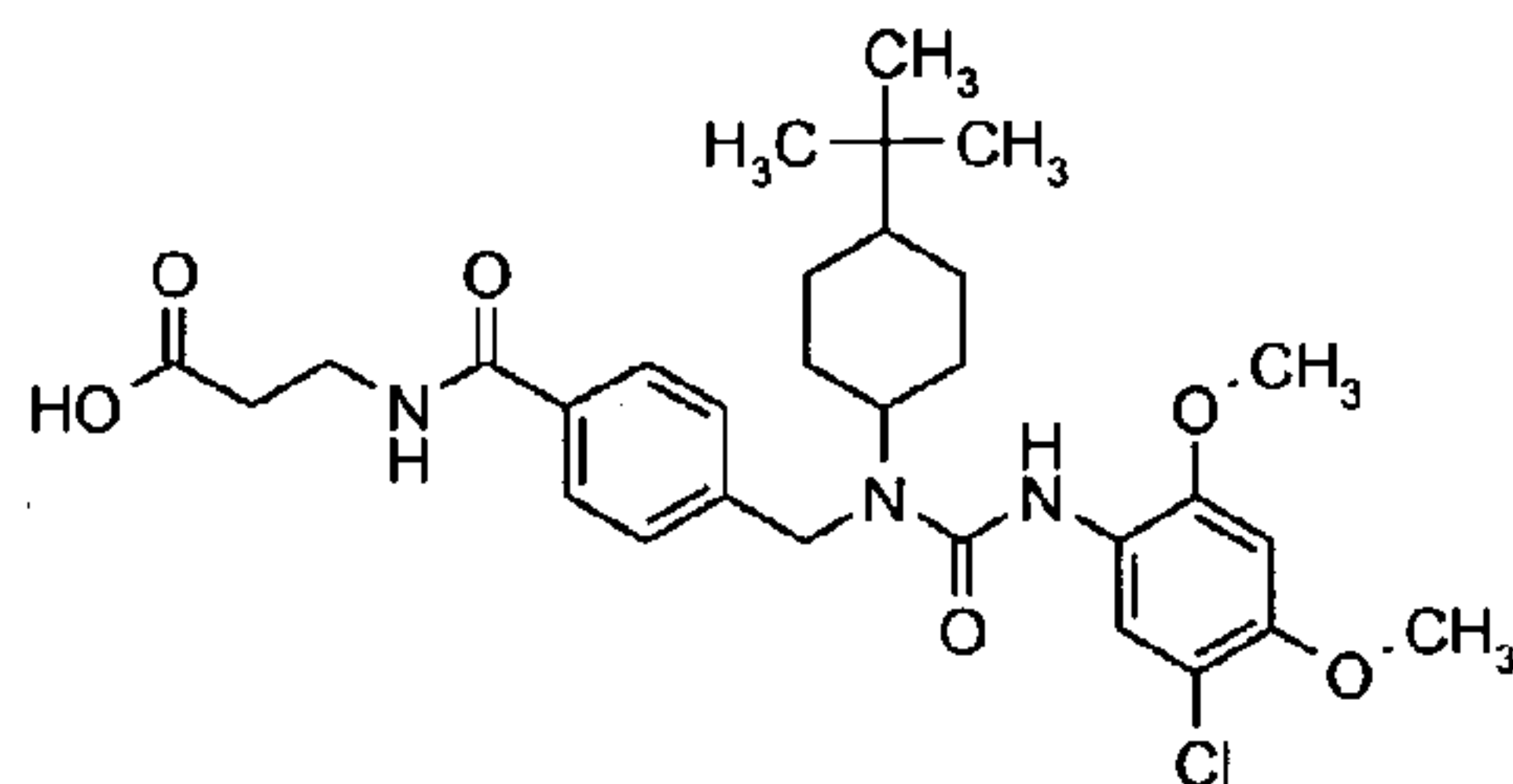
EXAMPLE 23 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-thiophen-2-ylethyl)ureidomethyl]benzoylamino}propionic acid

10

The product was characterized by HPLC-MS (Method B): $R_t = 5.60$ min, $m/z = 514$ ($M + 1$).

EXAMPLE 24 (general procedure (C))

- 15 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(5-chloro-2,4-dimethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

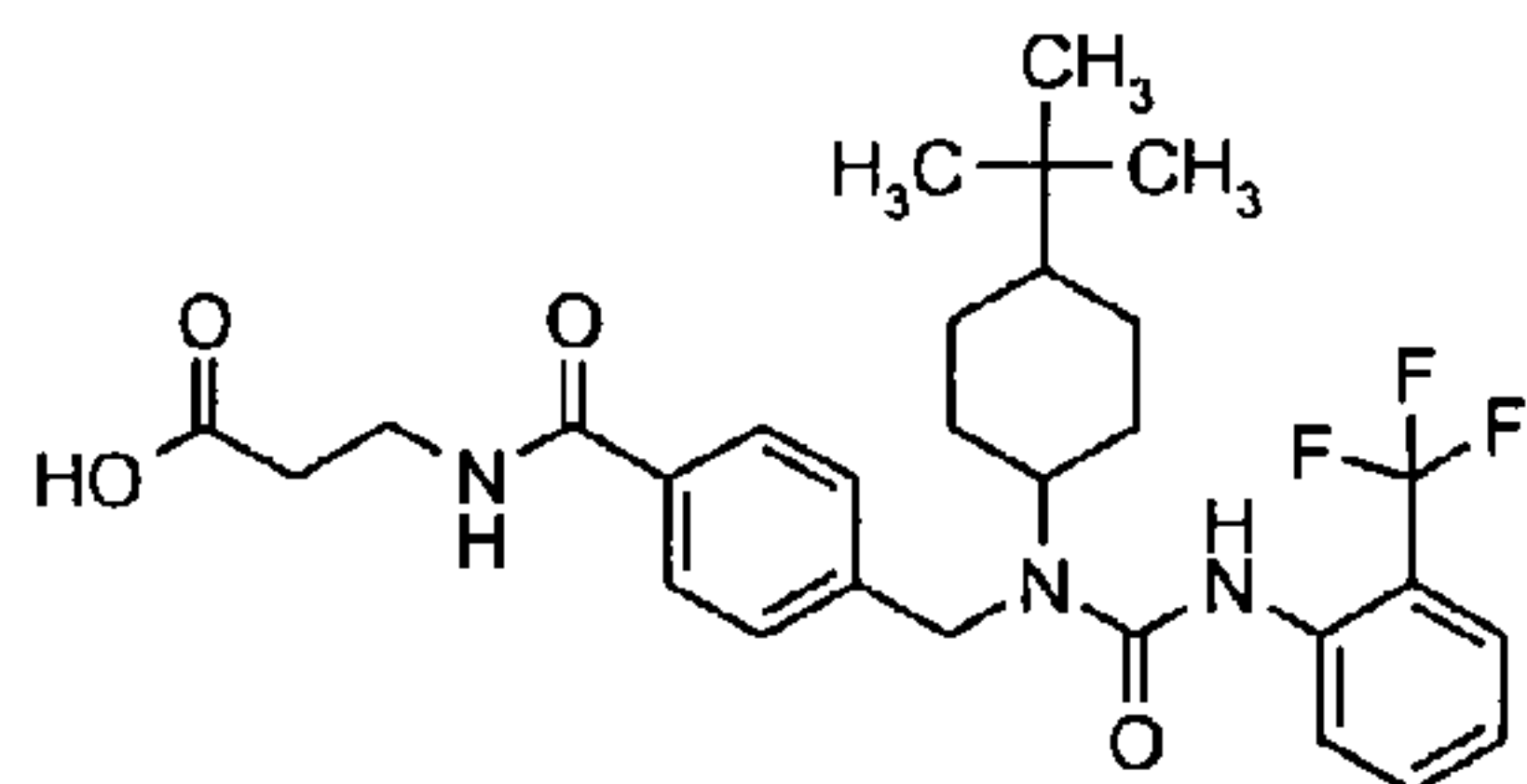


The product was characterized by HPLC-MS (Method B): $R_t = 6.30$ min, $m/z = 574$ ($M + 1$).

20

EXAMPLE 25 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



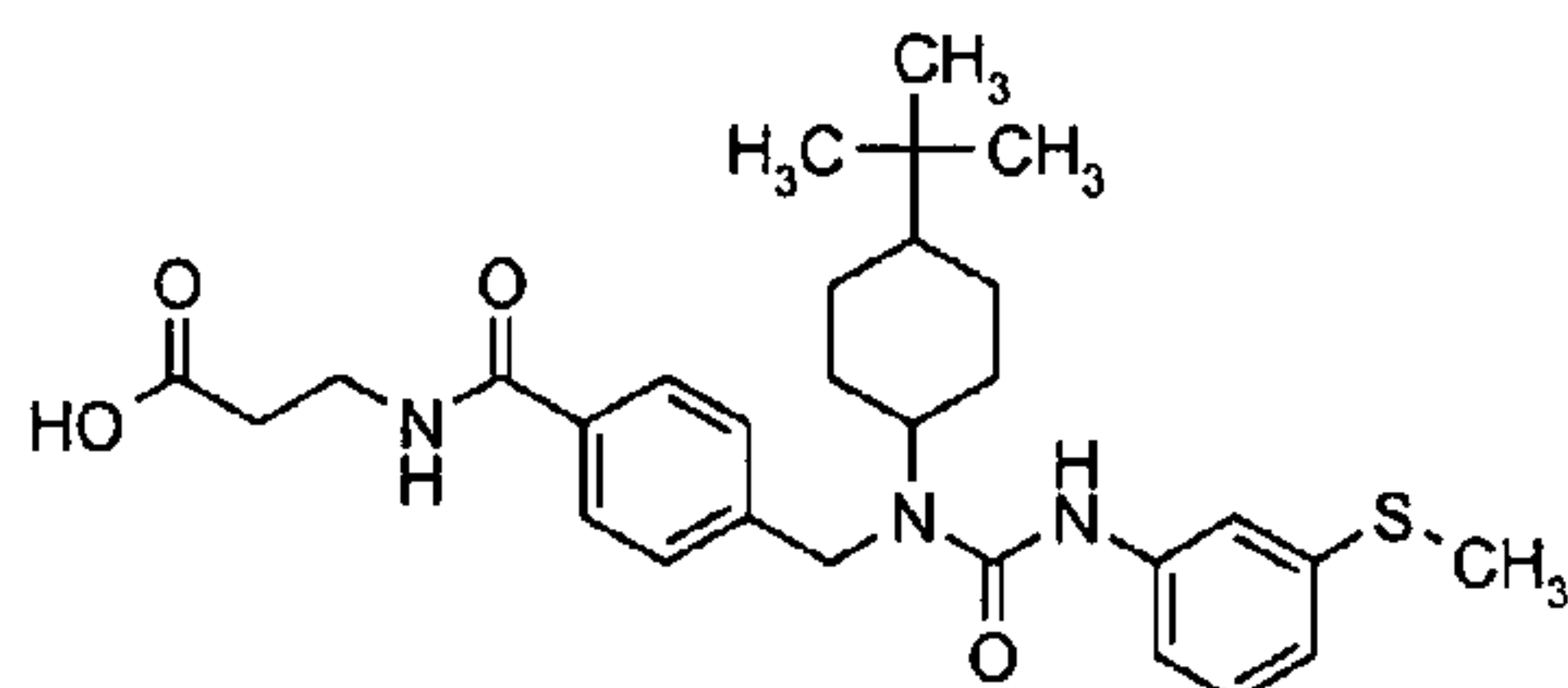
5

The product was characterized by HPLC-MS (Method B): $R_t = 6.10$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 26 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfanylphenyl)ureidomethyl]benzoylamino}-propionic acid

10

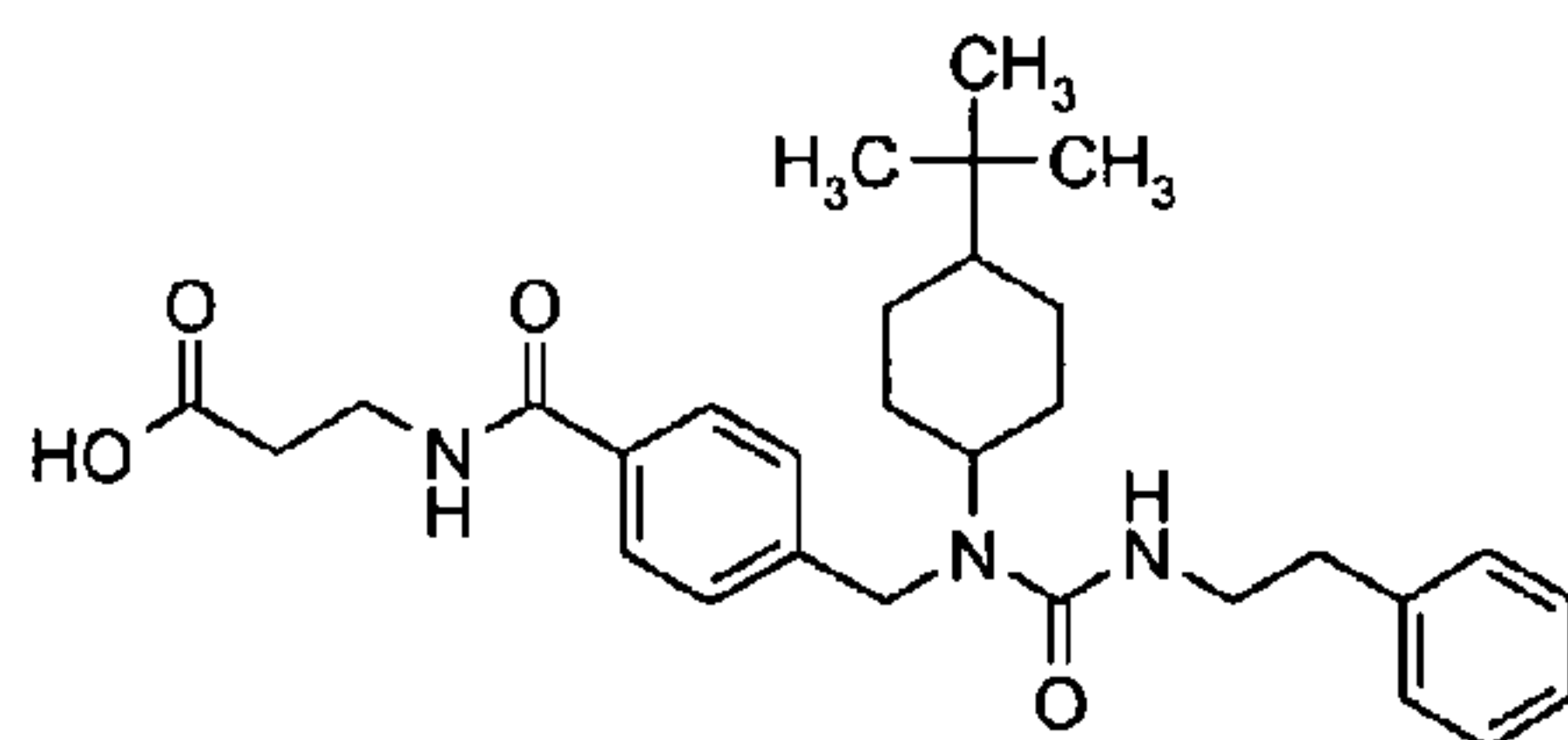


The product was characterized by HPLC-MS (Method B): $R_t = 6.03$ min, $m/z = 526$ ($M + 1$).

EXAMPLE 27 (general procedure (C))

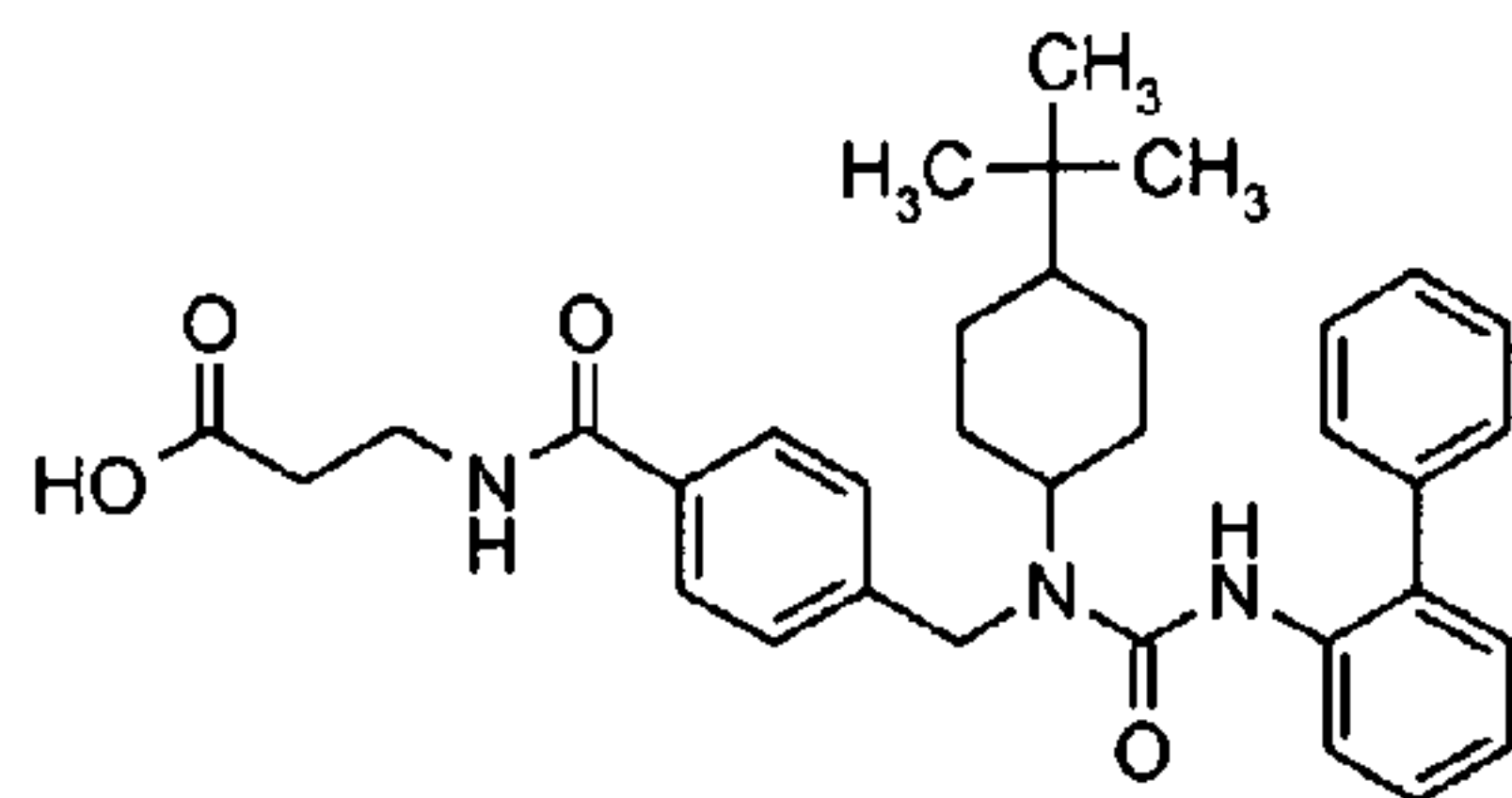
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-phenethylureidomethyl]benzoylamino}propionic acid

15

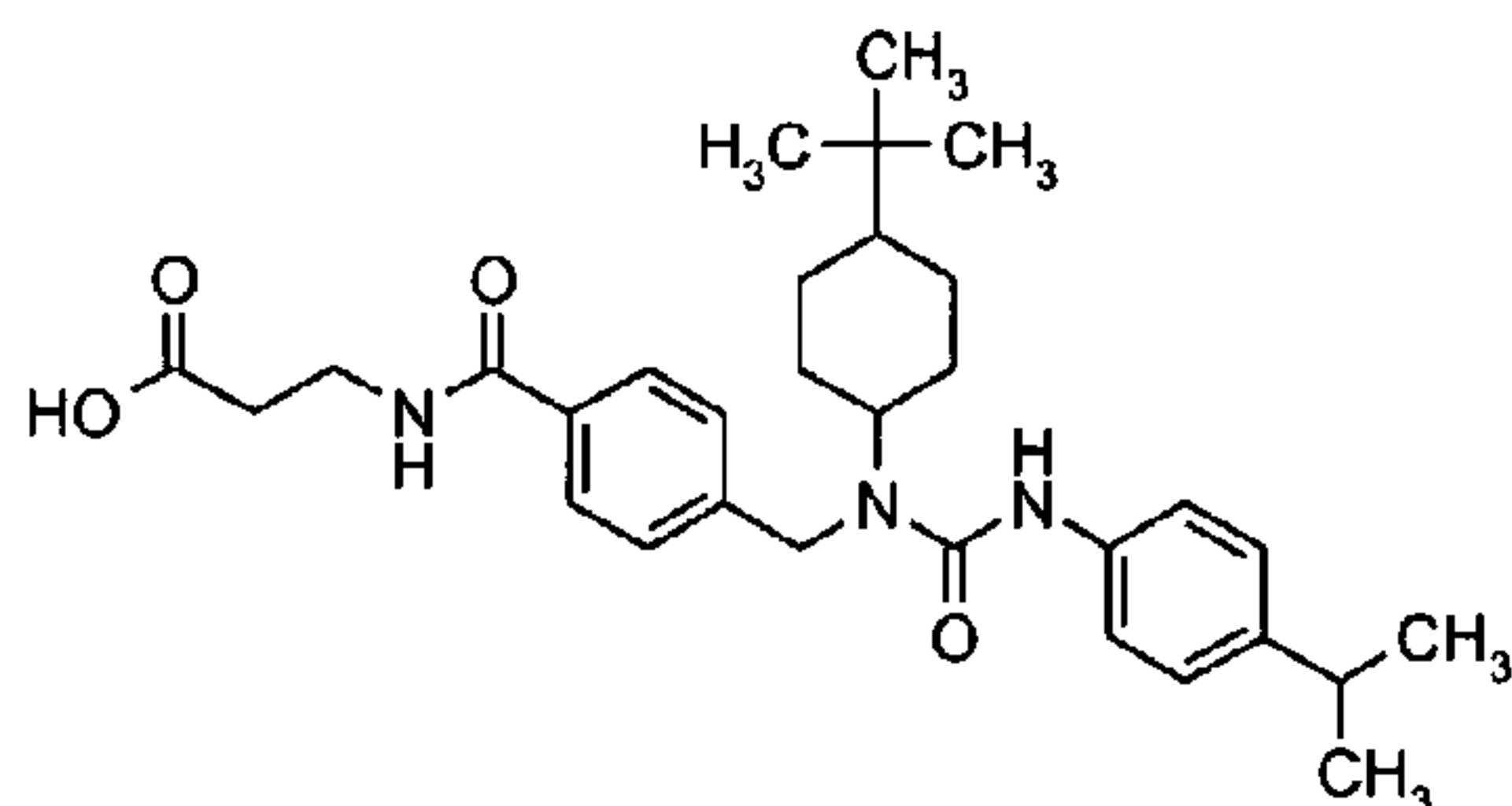


The product was characterized by HPLC-MS (Method B): $R_t = 5.53$ min, $m/z = 508$ ($M + 1$).

20

EXAMPLE 28 (general procedure (C))3-{4-[3-Biphenyl-2-yl-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

- 5 The product was characterized by HPLC-MS (Method B): $R_t = 6.14$ min, $m/z = 556$ ($M + 1$).

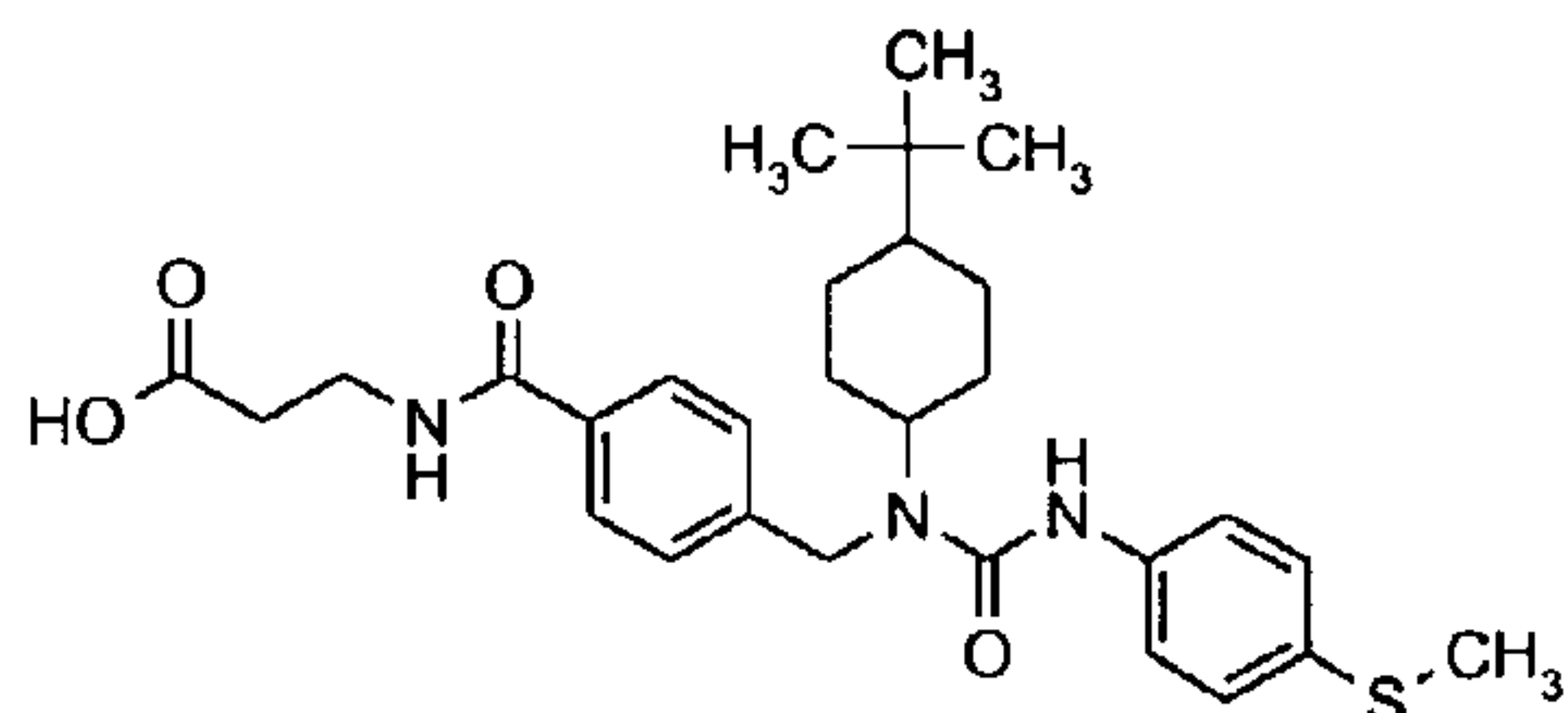
EXAMPLE 29 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoyl}aminopropionic acid

10

The product was characterized by HPLC-MS (Method B): $R_t = 7.98$ min, $m/z = 522$ ($M+1$).

EXAMPLE 30 (general procedure (C))

- 15 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methylsulfanylphenyl)ureidomethyl]benzoyl}amino-propionic acid

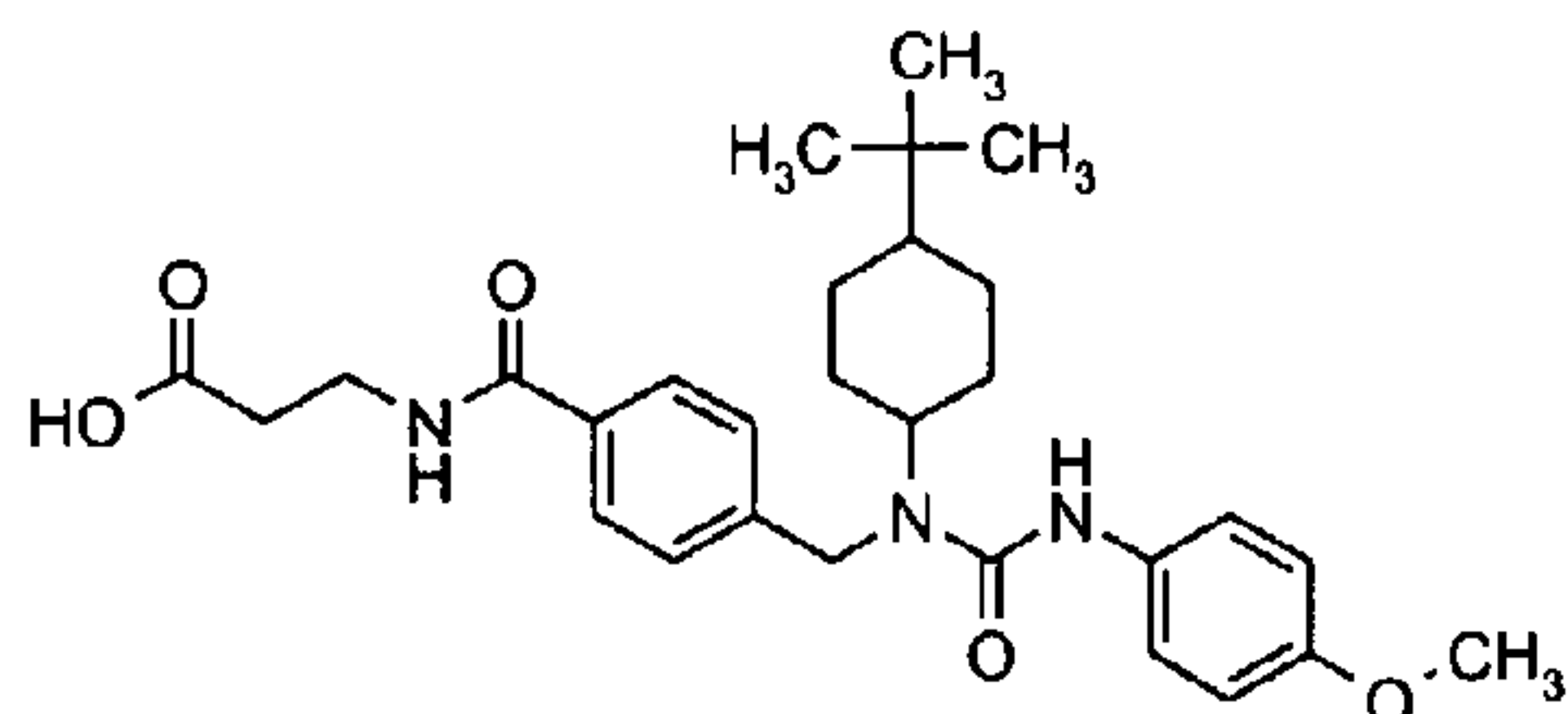


The product was characterized by HPLC-MS (Method B): $R_t = 7.58$ min, $m/z = 526$ ($M+1$).

20

EXAMPLE 31 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methoxyphenyl)ureidomethyl]benzoyl}aminopropionic acid

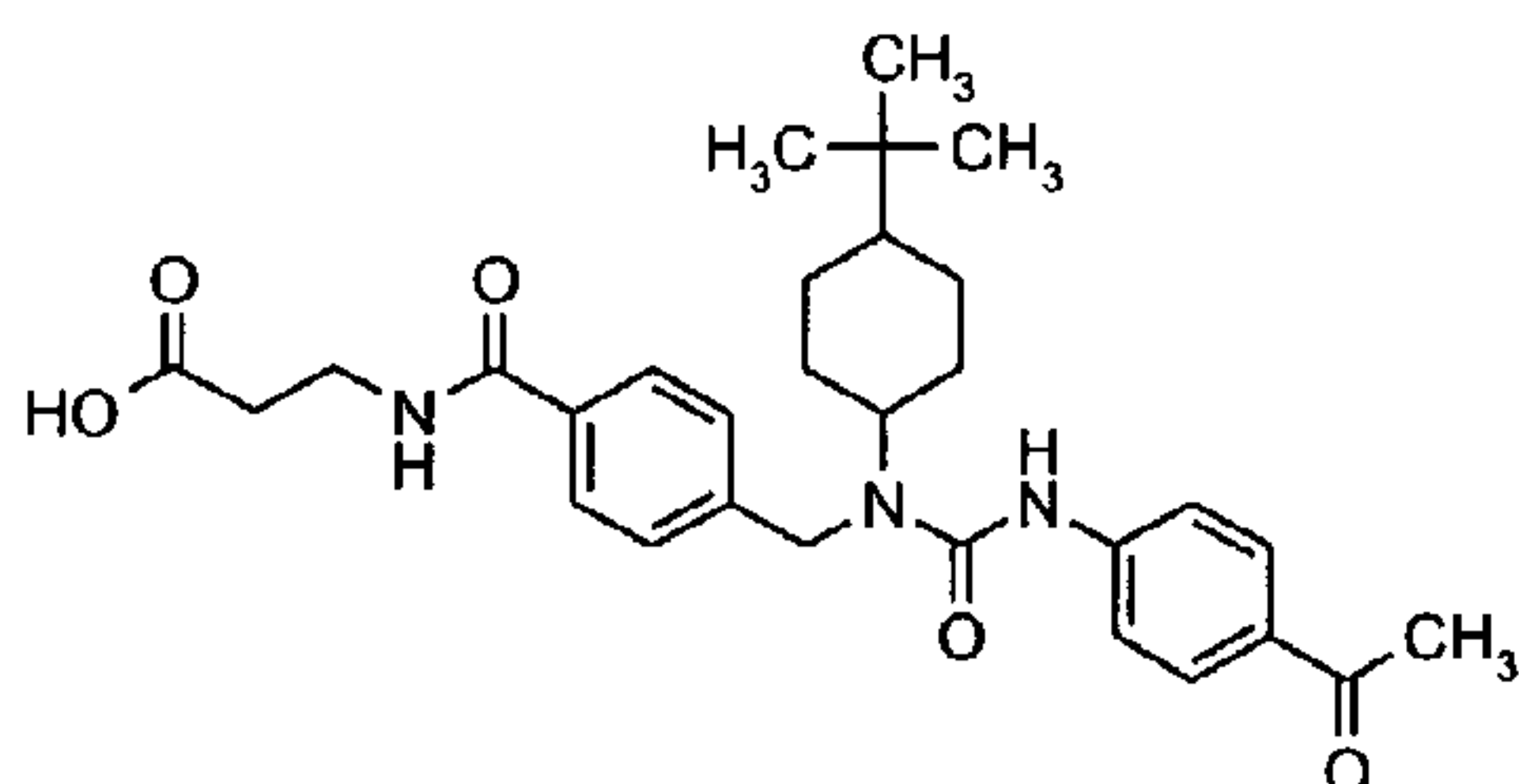


5

The product was characterized by HPLC-MS (Method B): $R_t = 6.93$ min, $m/z = 510$ ($M+1$).

EXAMPLE 32 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-acetylphenyl)ureidomethyl]benzoyl}aminopropionic acid

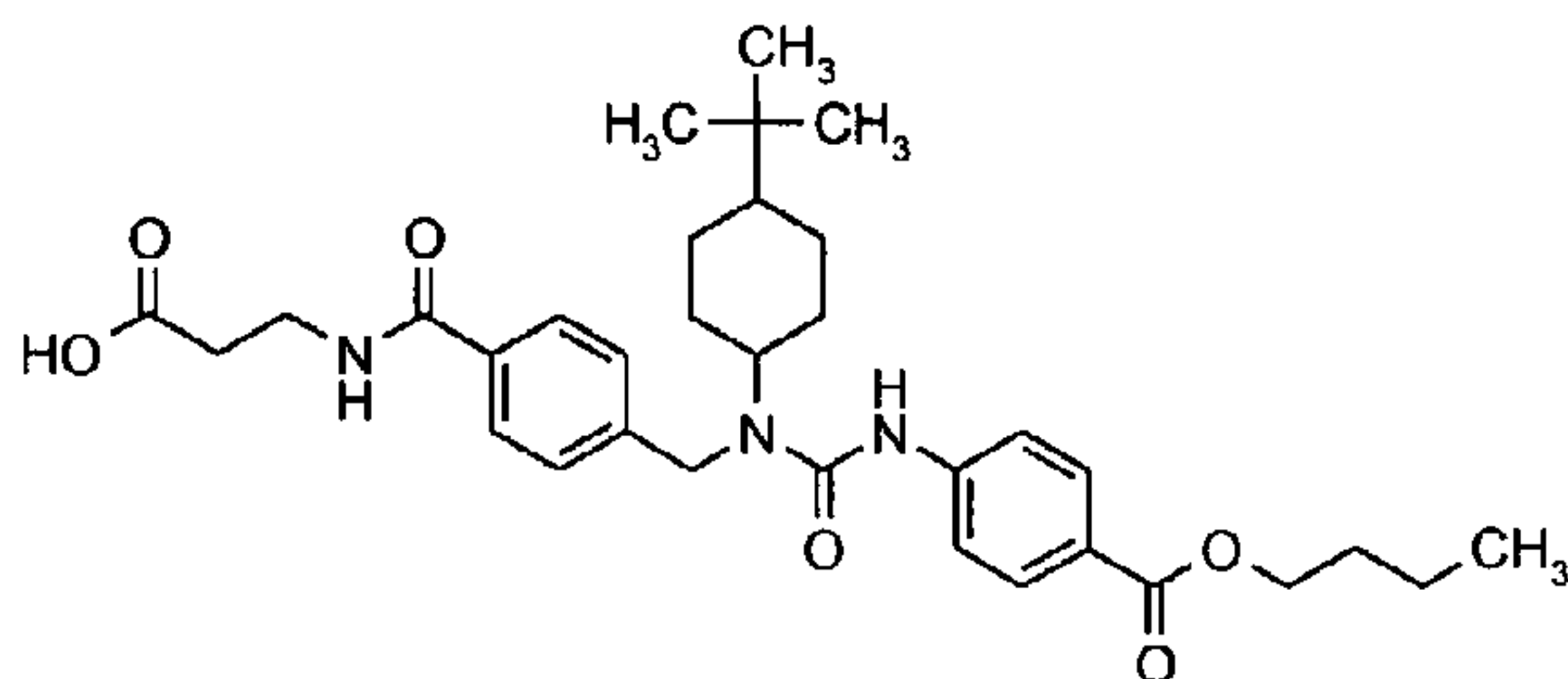


10

The product was characterized by HPLC-MS (Method B): $R_t = 7.03$ min, $m/z = 522$ ($M+1$).

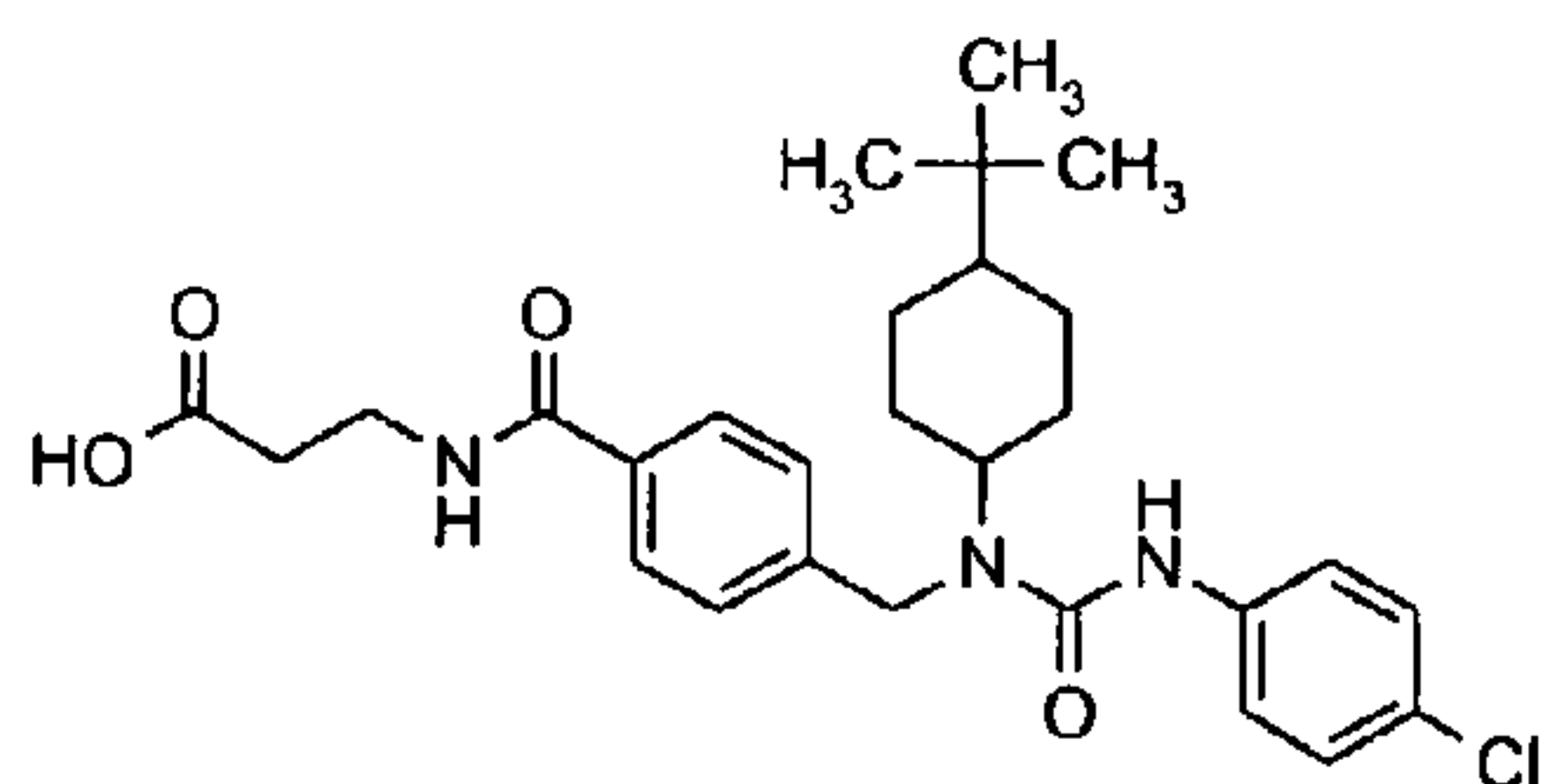
EXAMPLE 33 (general procedure (C))

15 4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid butyl ester

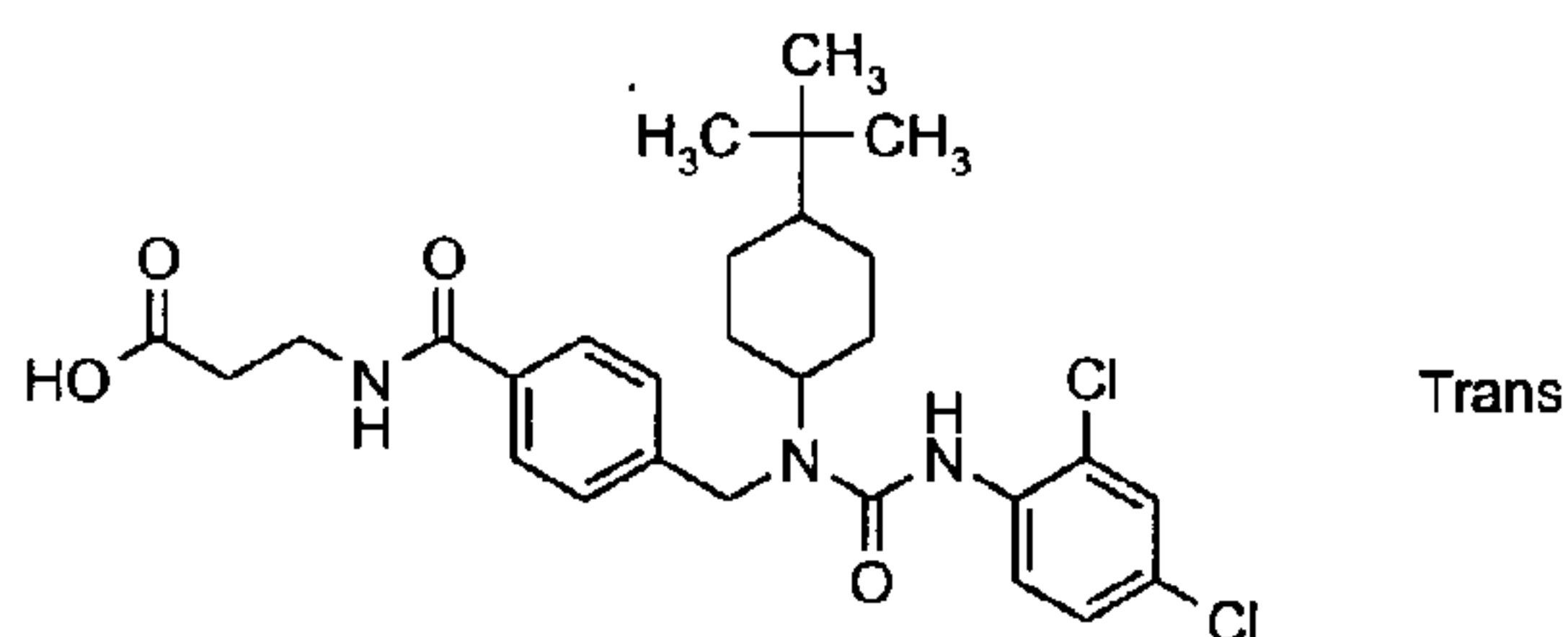


The product was characterized by HPLC-MS (Method B): $R_t = 8.33$ min.

20

EXAMPLE 34 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoyl}aminopropionic acid

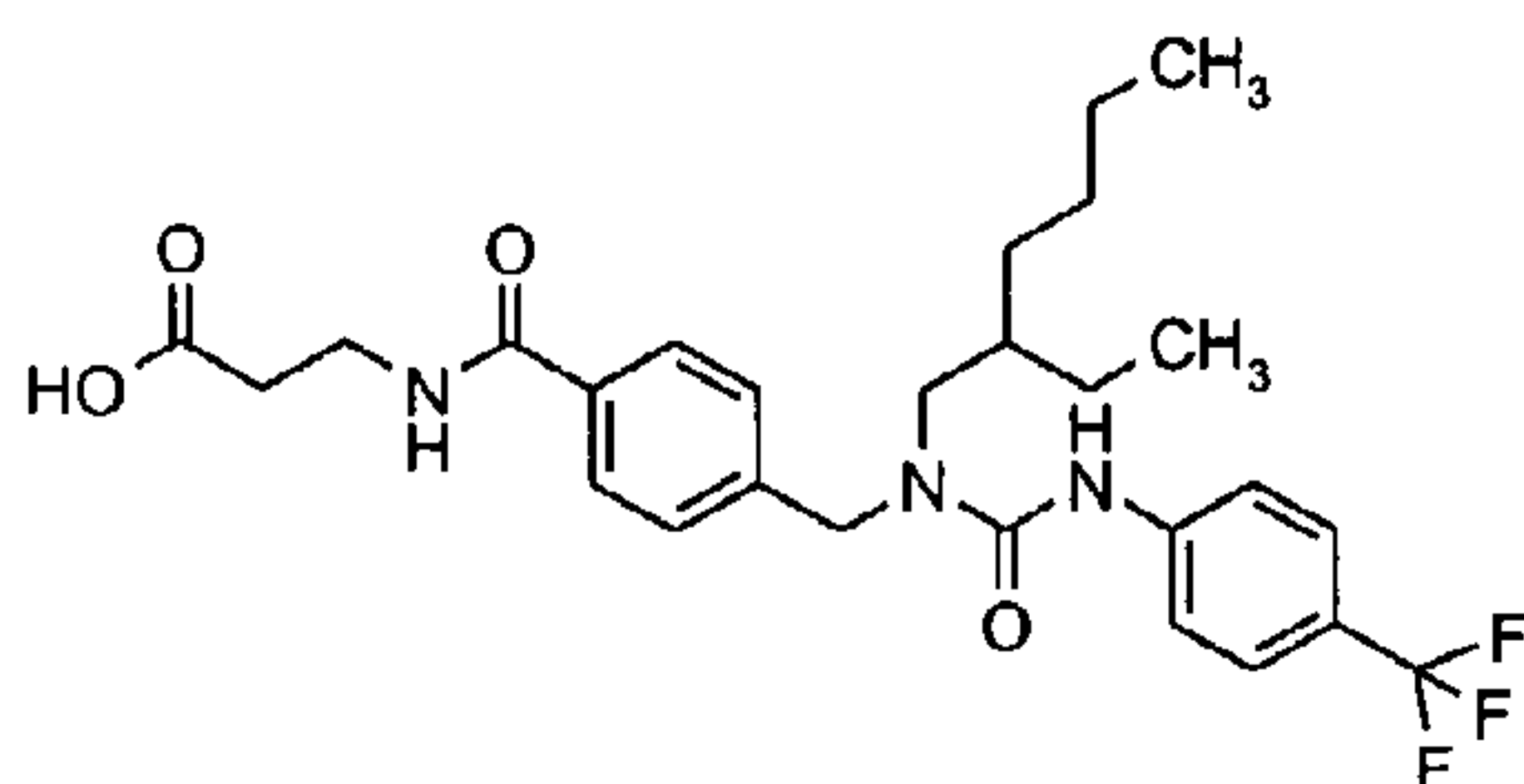
- 5 The product was characterized by HPLC-MS (Method B): $R_t = 7.68$ min, $m/z = 514$ ($M+1$).

EXAMPLE 35 (general procedure (C))3-{4-[1-(4-*trans-tert*-Butylcyclohexyl)-3-(2,4-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid

10

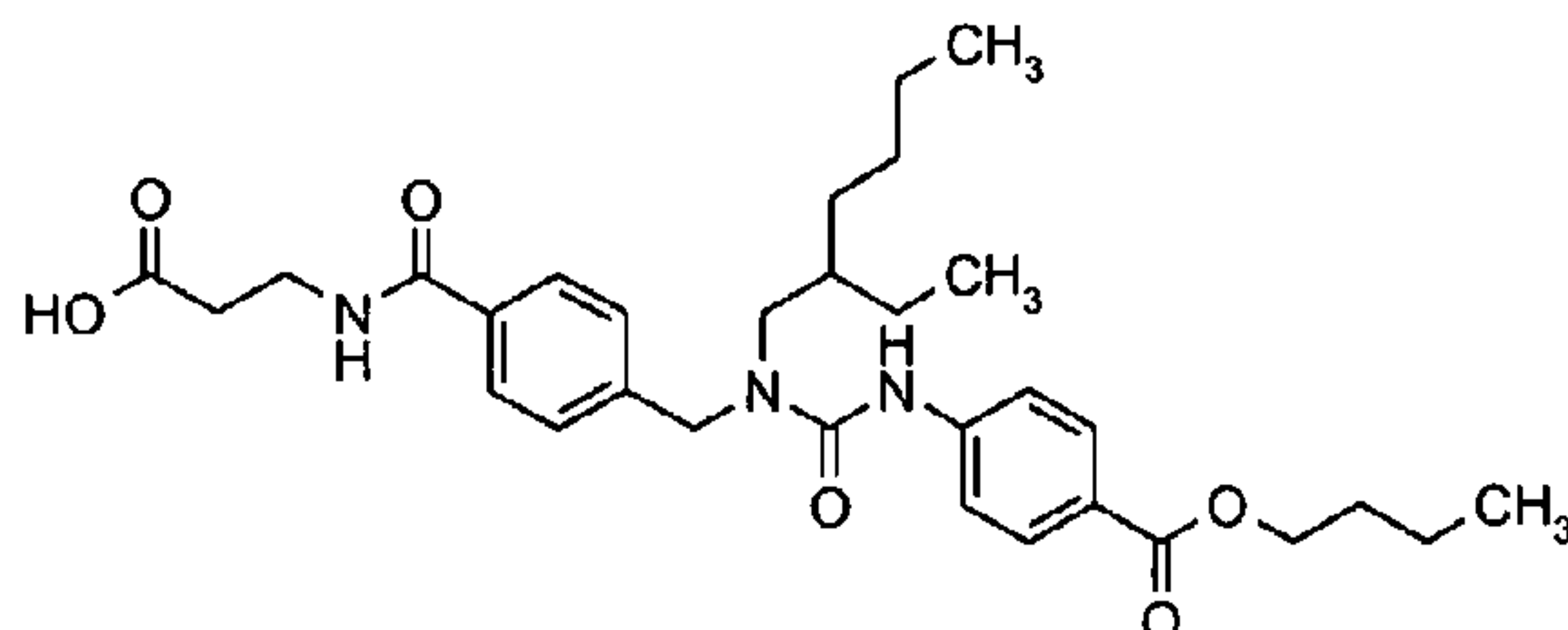
^1H NMR ($\text{DMSO}-d_6$): δ 0.82 (9H, s), 0.9-1.7 (9H, m), 4.04 (1H, t), 4.60 (2H, s), 7.38 (4H, m), 7.60 (2H, m), 7.78 (2H, d), 8.48 (1H, t).

- 15 HPLC-MS (Method B): $R_t = 8.25$ min, $m/z = 548$ ($M + 1$).

EXAMPLE 36 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid

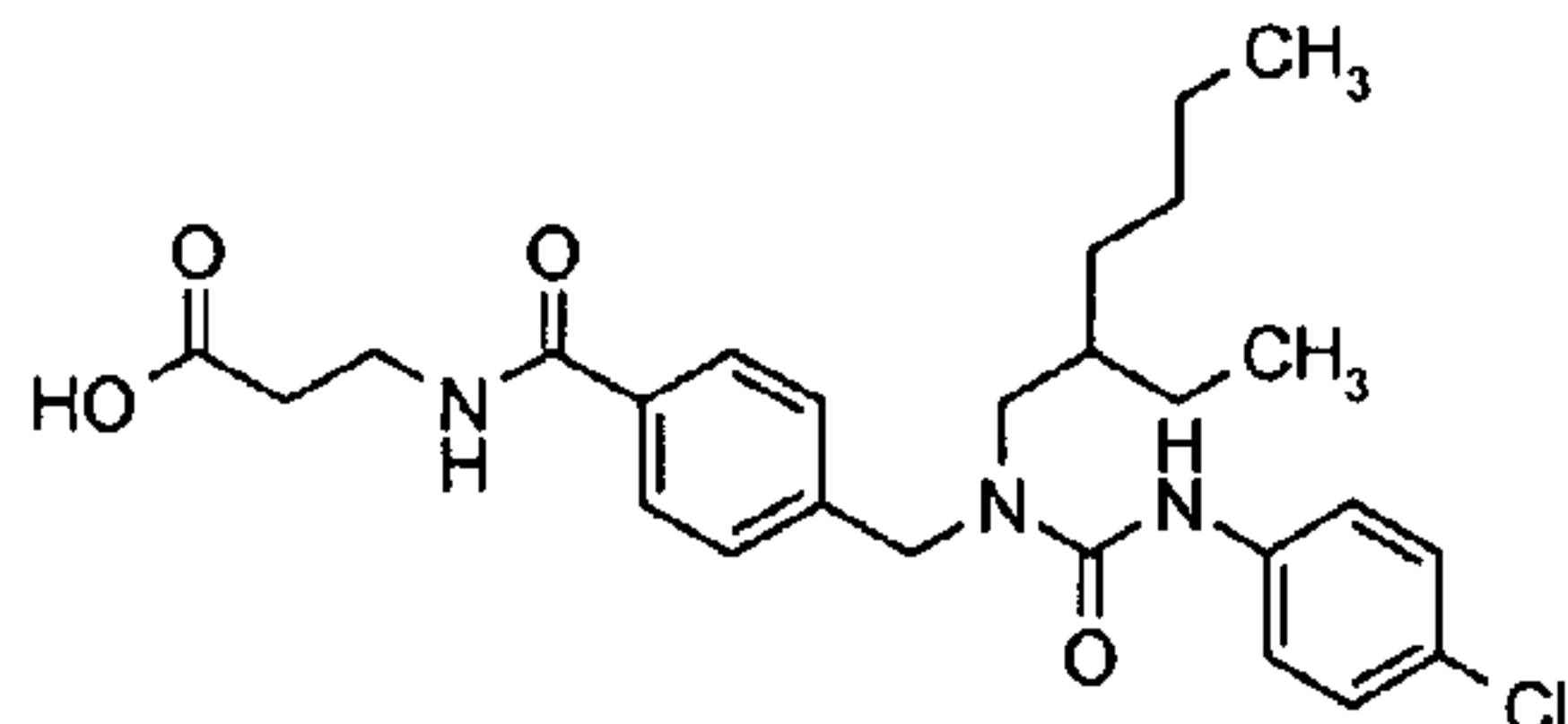
20

^1H NMR ($\text{DMSO}-d_6$): δ 7.33 (2H, d), 7.59 (2H, d), 7.68 (2H, d), 7.81 (2H, d), 8.50 (1H, t), 8.81 (1H, s).

EXAMPLE 37 (general procedure (C))**4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-ethylhexyl)ureido]benzoic acid butyl ester**

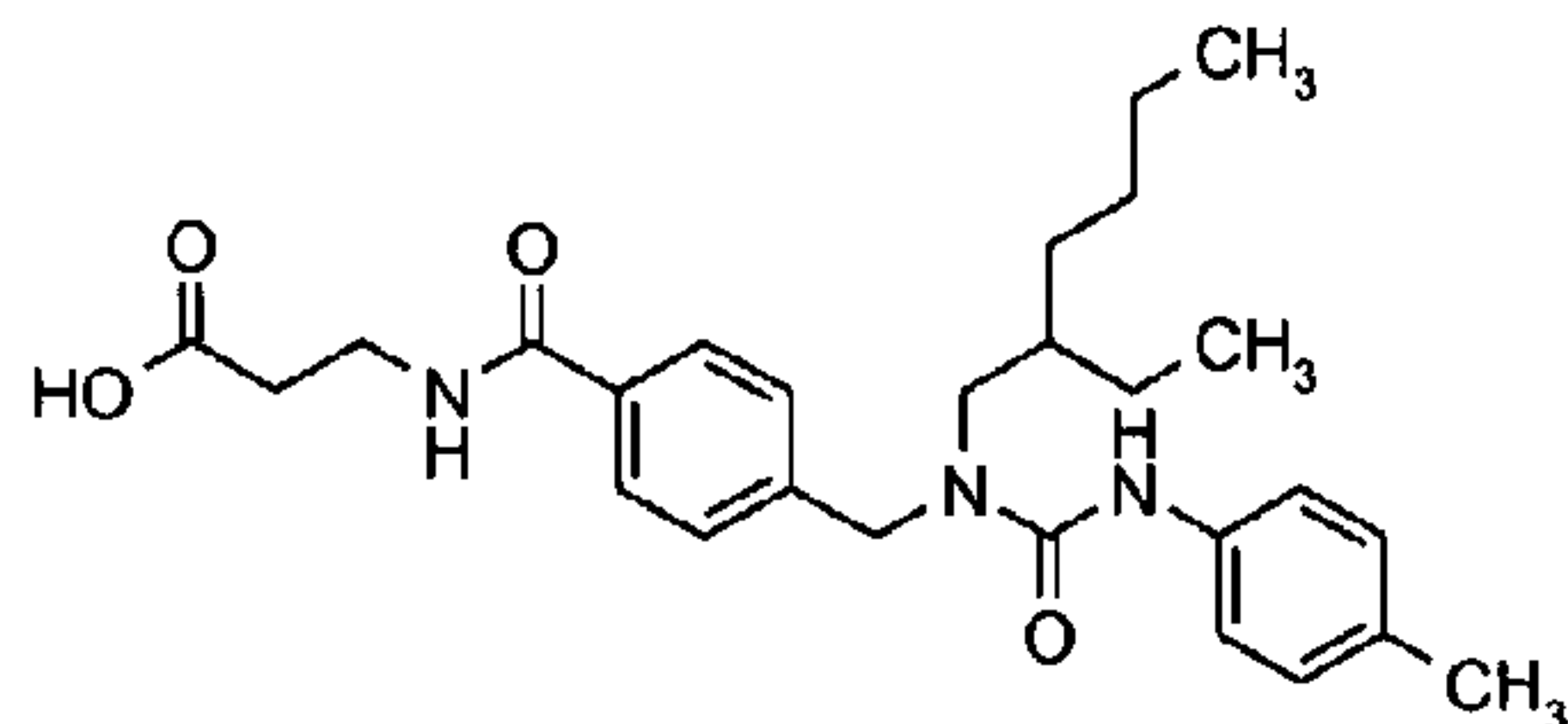
5

^1H NMR (DMSO- d_6): δ 4.23 (2H, t), 4.69 (2H, s), 7.33 (2H, d), 7.60 (2H, d), 7.80 (2H, d), 7.84 (2H, d), 8.49 (1H, bt), 8.81 (1H, s).

EXAMPLE 38 (general procedure (C))**3-{4-[3-(4-Chlorophenyl)-1-(2-ethylhexyl)ureidomethyl]benzoylamino}propionic acid**

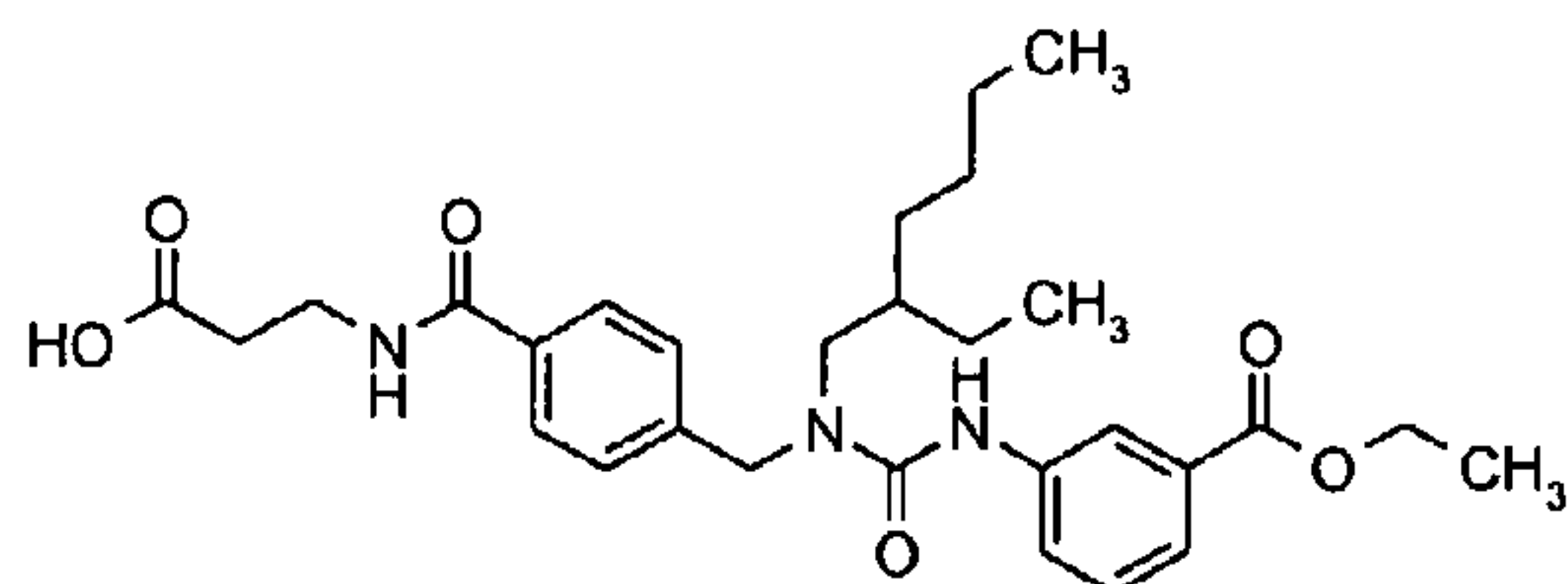
^1H NMR (DMSO- d_6): δ 4.64 (2H, s), 7.04 (2H, d), 7.3-7.35 (4H, m), 7.81 (2H, d), 8.28 (1H, s), 8.48 (1H, bt).

15

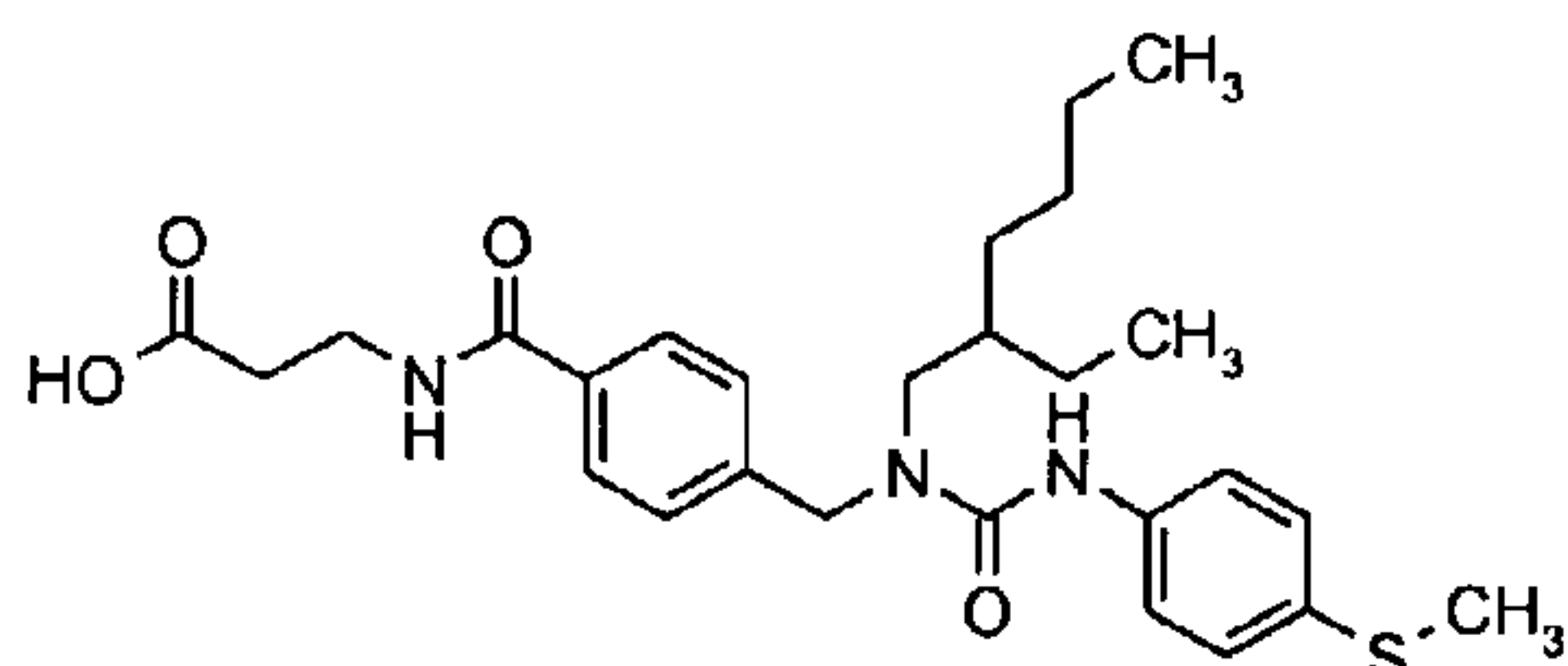
EXAMPLE 39 (general procedure (C))**3-{4-[1-(2-Ethylhexyl)-3-p-tolylureidomethyl]benzoylamino}propionic acid**

^1H NMR (DMSO- d_6): δ 4.65 (2H, s), 7.06 (2H, d), 7.31-7.33 (4H, m), 7.81 (2H, d), 8.29 (1H, s), 8.49 (1H, bt).

20

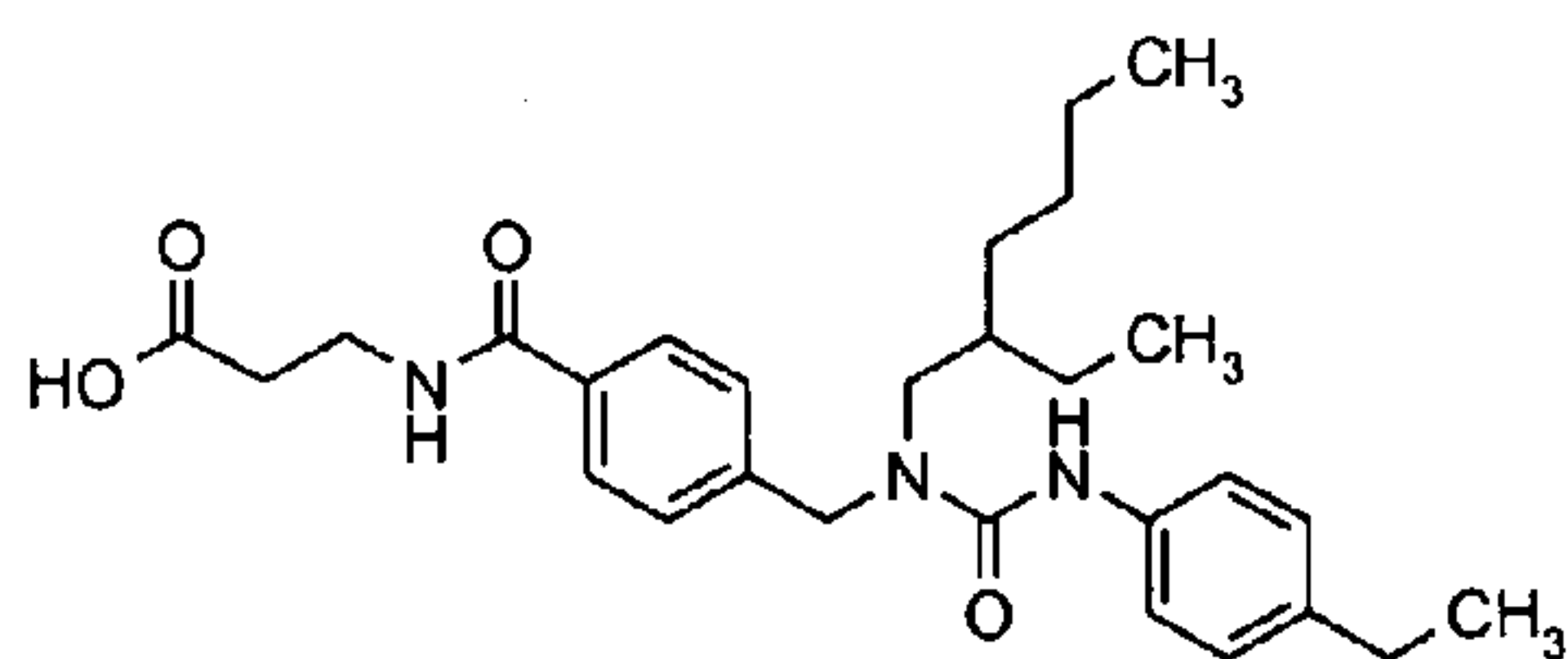
EXAMPLE 40 (general procedure (C))3-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-ethylhexyl)ureido]benzoic acid ethyl ester

- 5 ^1H NMR (DMSO- d_6): δ 4.30 (2H, q), 4.67 (2H, s), 7.33 (2H, d), 7.36 (1H, t), 7.53 (1H, t), 7.74 (1H, bd), 7.80 (2H, d), 8.07 (1H, s), 8.48 (1H, bt), 8.65 (1H, s).

EXAMPLE 41 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-methylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid

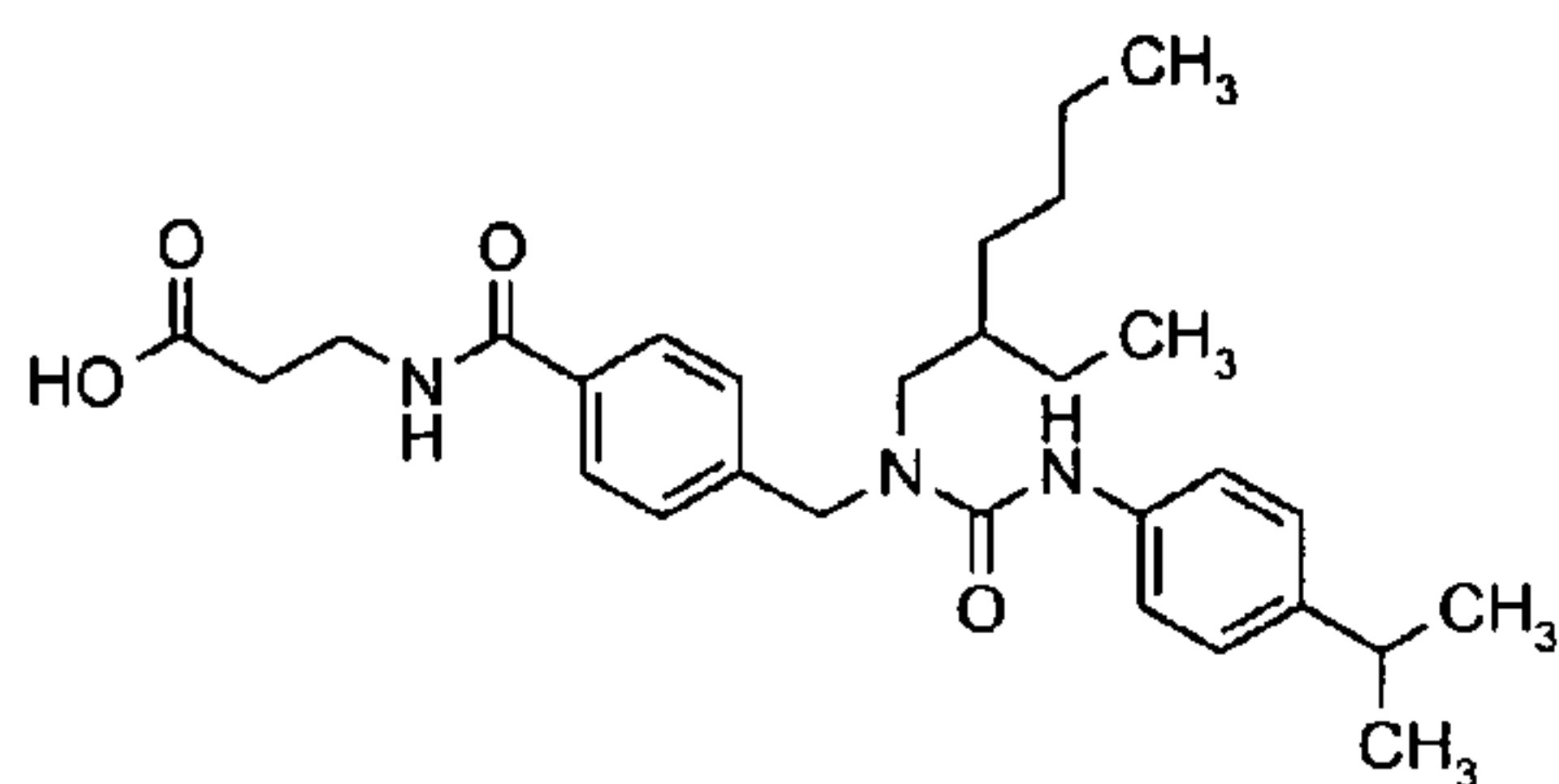
10

- ^1H NMR (DMSO- d_6): δ 4.66 (2H, s), 7.18 (2H, d), 7.31 (2H, d), 7.39 (2H, d), 7.78 (2H, d), 8.40 (1H, s), 8.50 (1H, bt).

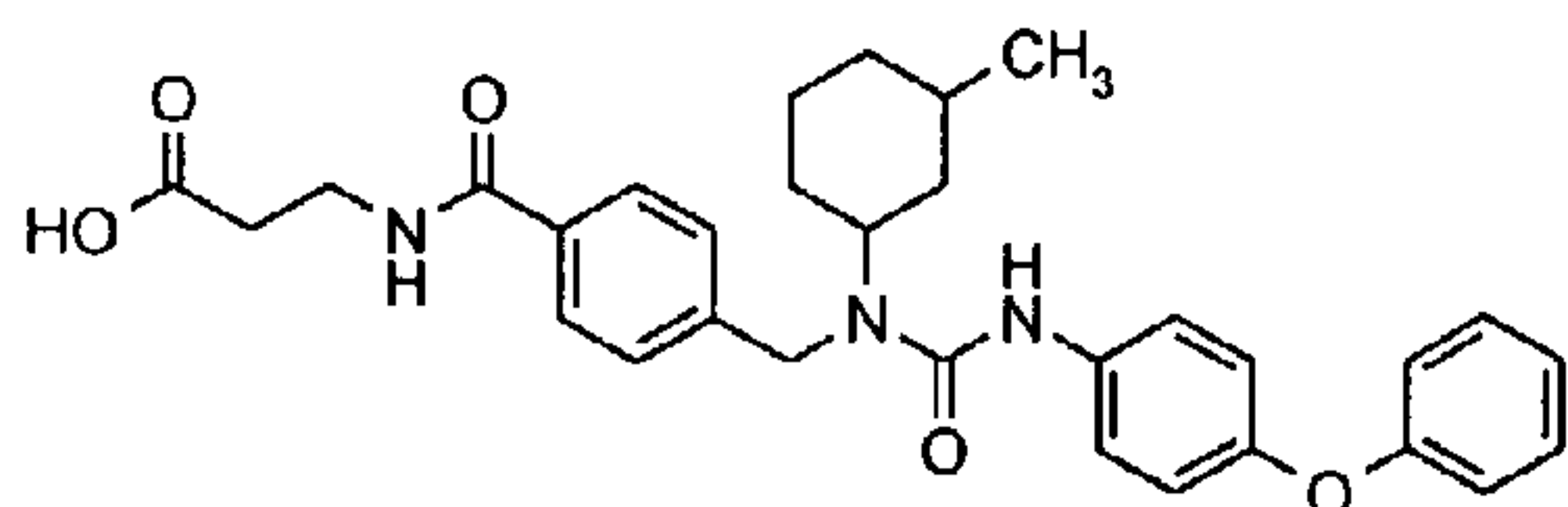
EXAMPLE 42 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-ethylphenyl)ureidomethyl]benzoylamino}propionic acid

- ^1H NMR (DMSO- d_6): δ 4.51 (2H, s), 7.10 (2H, d), 7.32 (4H, m), 7.79 (2H, d), 8.28 (1H, s), 8.48 (1H, t).

20

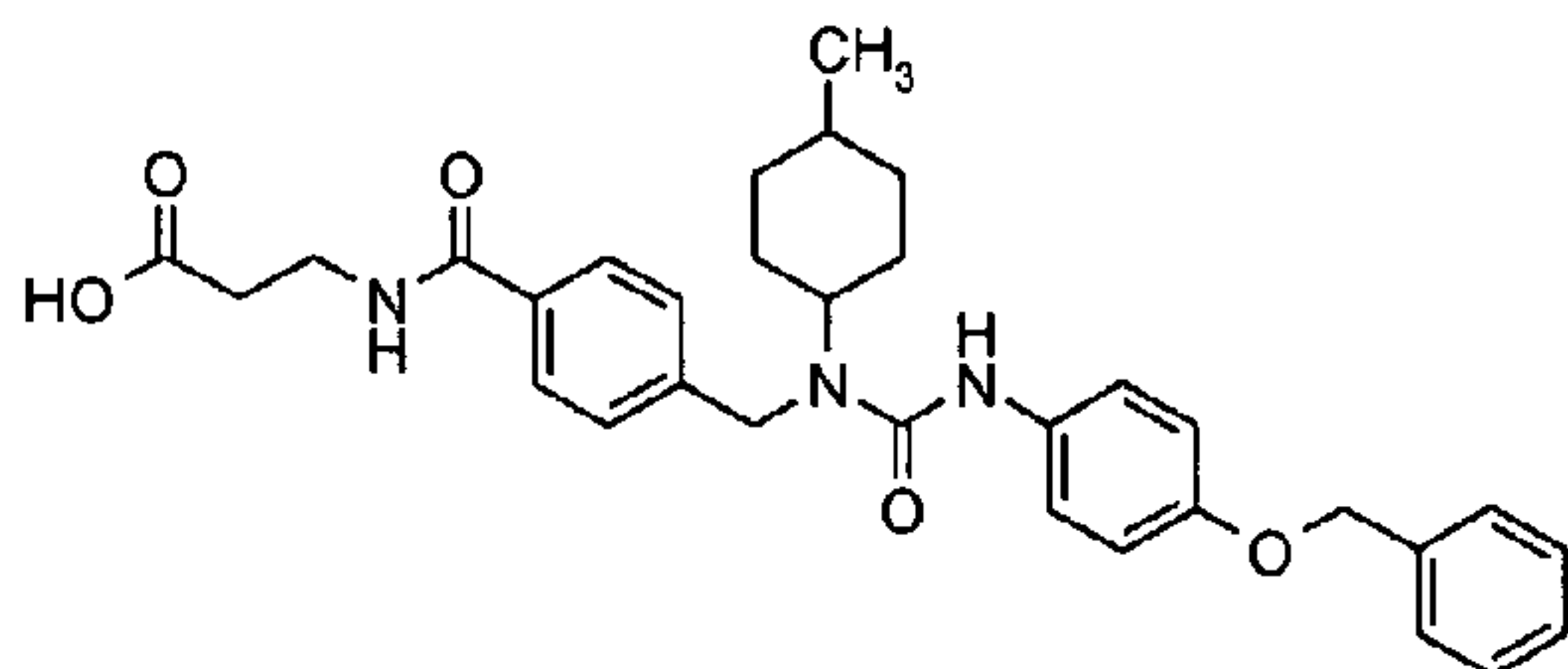
EXAMPLE 43 (general procedure (C))3-{4-[1-(2-Ethylhexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

- 5 ^1H NMR (DMSO- d_6): δ 4.70 (2H, s), 7.33 (2H, d), 7.58 (2H, d), 7.67 (2H, d), 7.78 (2H, d), 8.46 (1H, t), 8.70 (1H, d).

EXAMPLE 44 (general procedure (C))3-{4-[1-(3-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

10

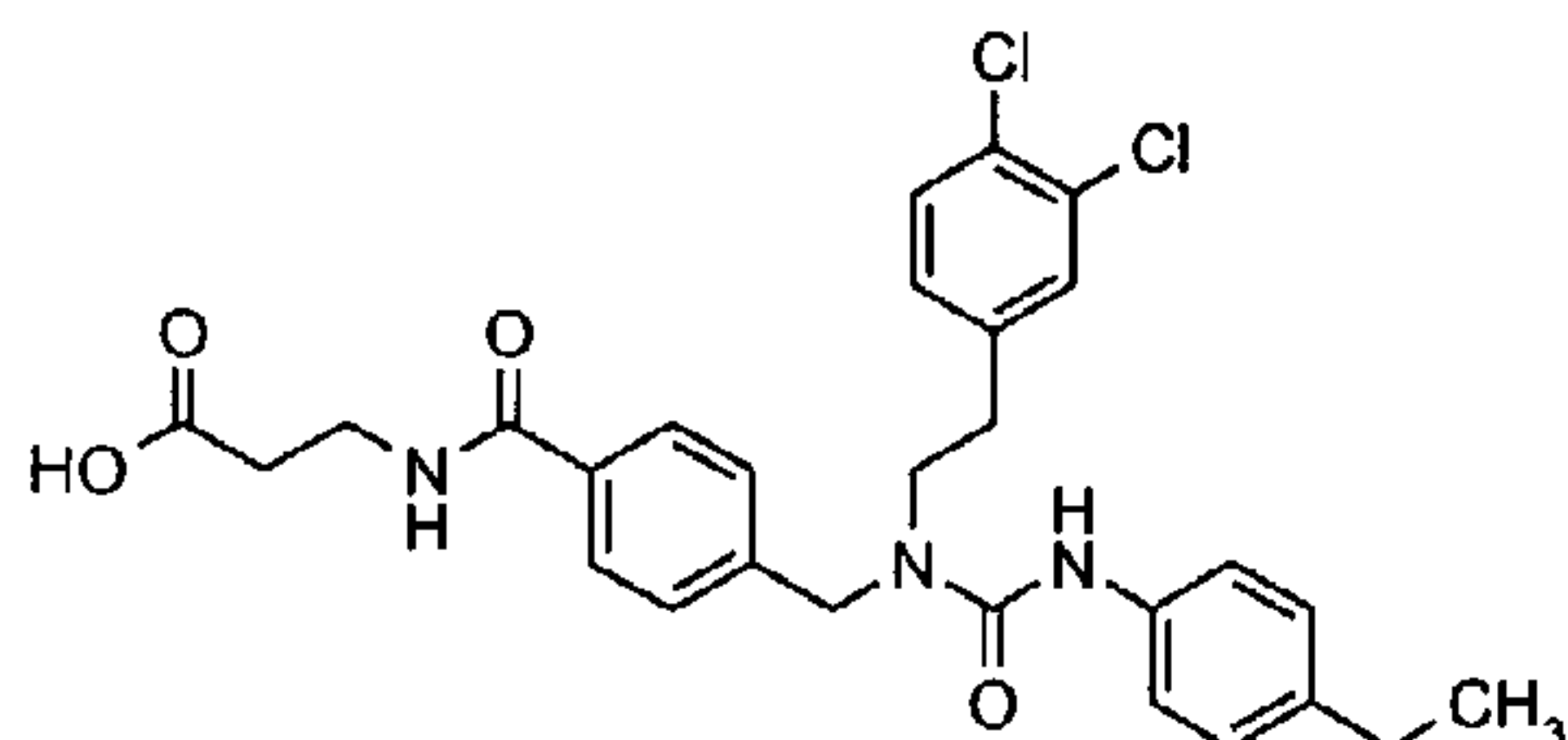
- ^1H NMR (DMSO- d_6): δ 4.61 (2H, s), 6.92 (4H, m), 7.07 (1H, t), 7.33 (4H, m), 7.41 (2H, m), 7.76 (2H, d), 8.29 (1H, d), 8.45 (1H, t).

15 EXAMPLE 45 (general procedure (C))3-{4-[3-(4-Benzyloxyphenyl)-1-(4-methylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

- 20 ^1H NMR (DMSO- d_6): δ 5.01 (2H, s), 6.90 (2H, d), 7.1-7.3 (10H, m), 7.77 (2H, d), 8.15 (1H, s), 8.44 (1H, bt).

EXAMPLE 46 (general procedure (C))

3-{4-[1-[2-(3,4-Dichlorophenyl)ethyl]-3-(4-ethylphenyl)ureidomethyl]benzoylamino}propionic acid

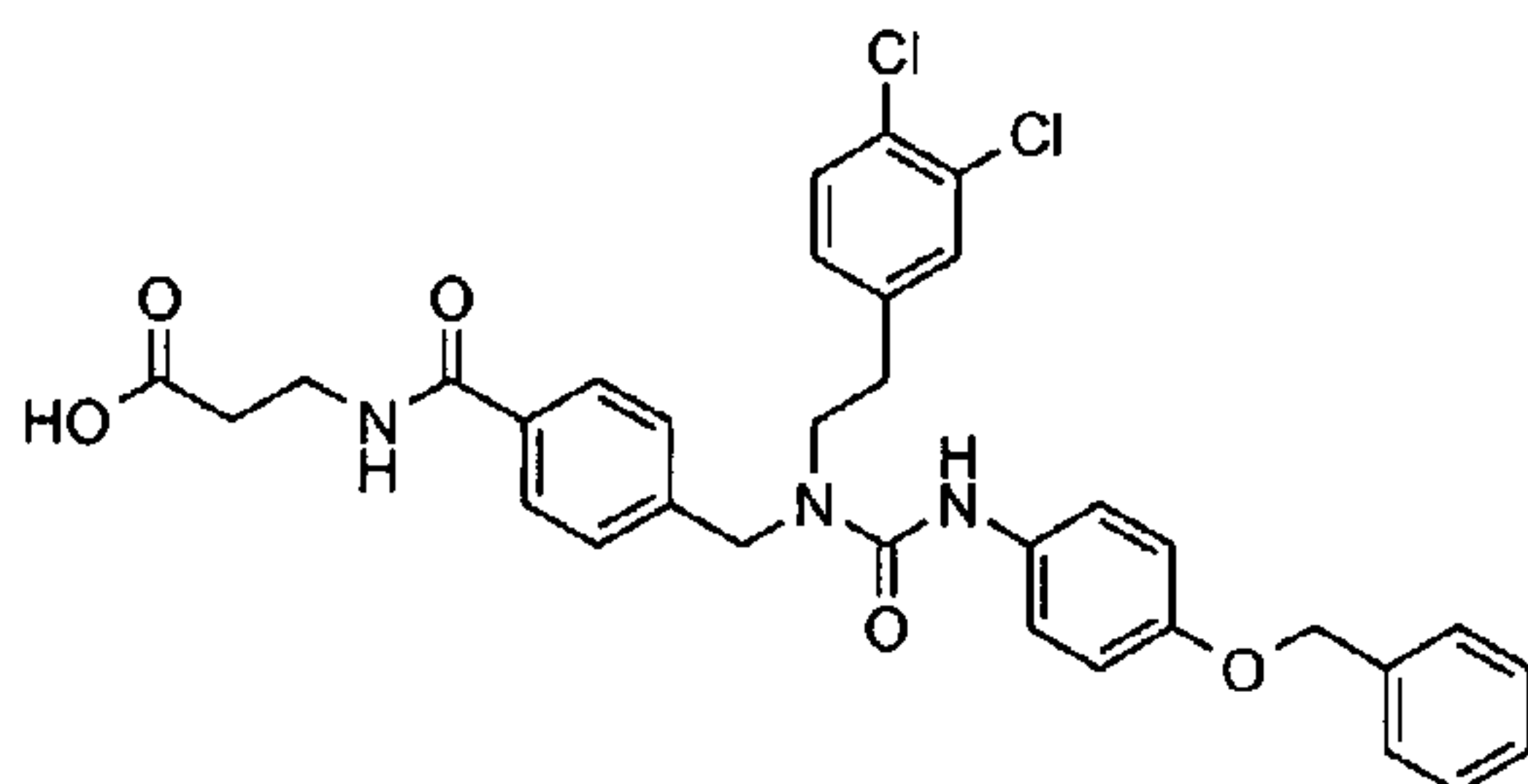


5

^1H NMR (DMSO- d_6): δ 4.67 (2H, s), 7.08 (2H, d), 7.25 (1H, d), 7.35 (4H, m), 7.53 (2H, m), 7.81 (2H, d), 8.31 (1H, s), 8.48 (1H, bt).

EXAMPLE 47 (general procedure (C))

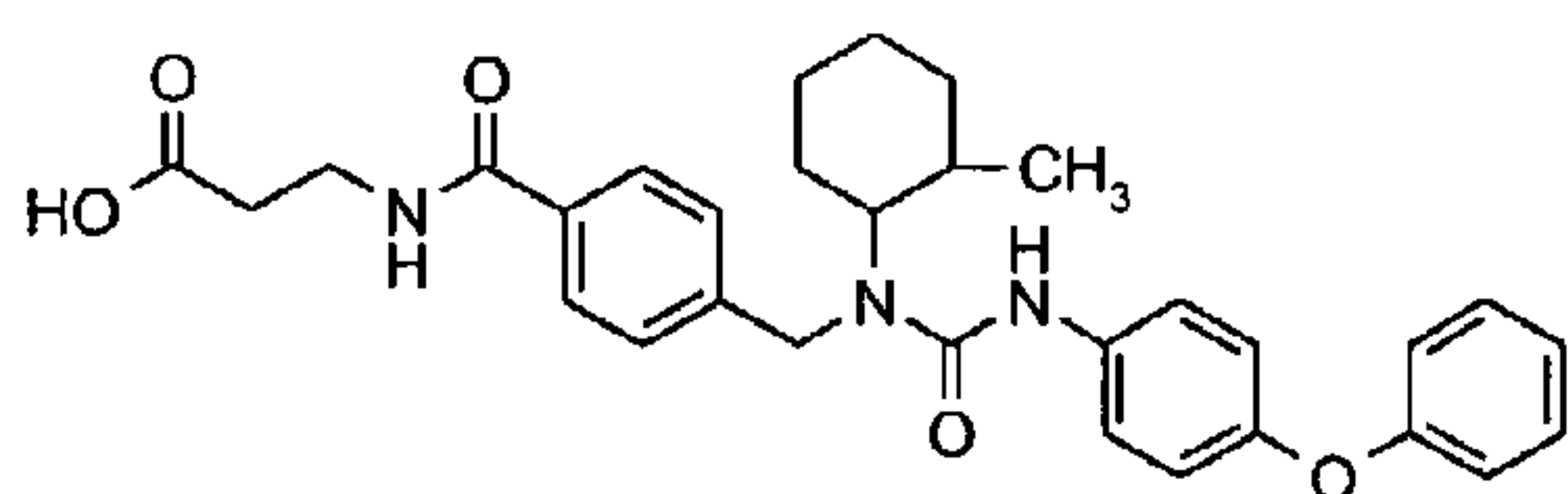
10 3-{4-[3-(4-Benzoyloxyphenyl)-1-[2-(3,4-dichlorophenyl)ethyl]ureidomethyl]benzoylamino}-propionic acid



15 ^1H NMR (DMSO- d_6): δ 4.60 (2H, s), 5.10 (2H, s), 6.92 (2H, d), 7.25-7.47 (10H, m), 7.55 (2H, m), 7.25 (1H, d), 7.81 (2H, d), 8.27 (1H, s), 8.45 (1H, t).

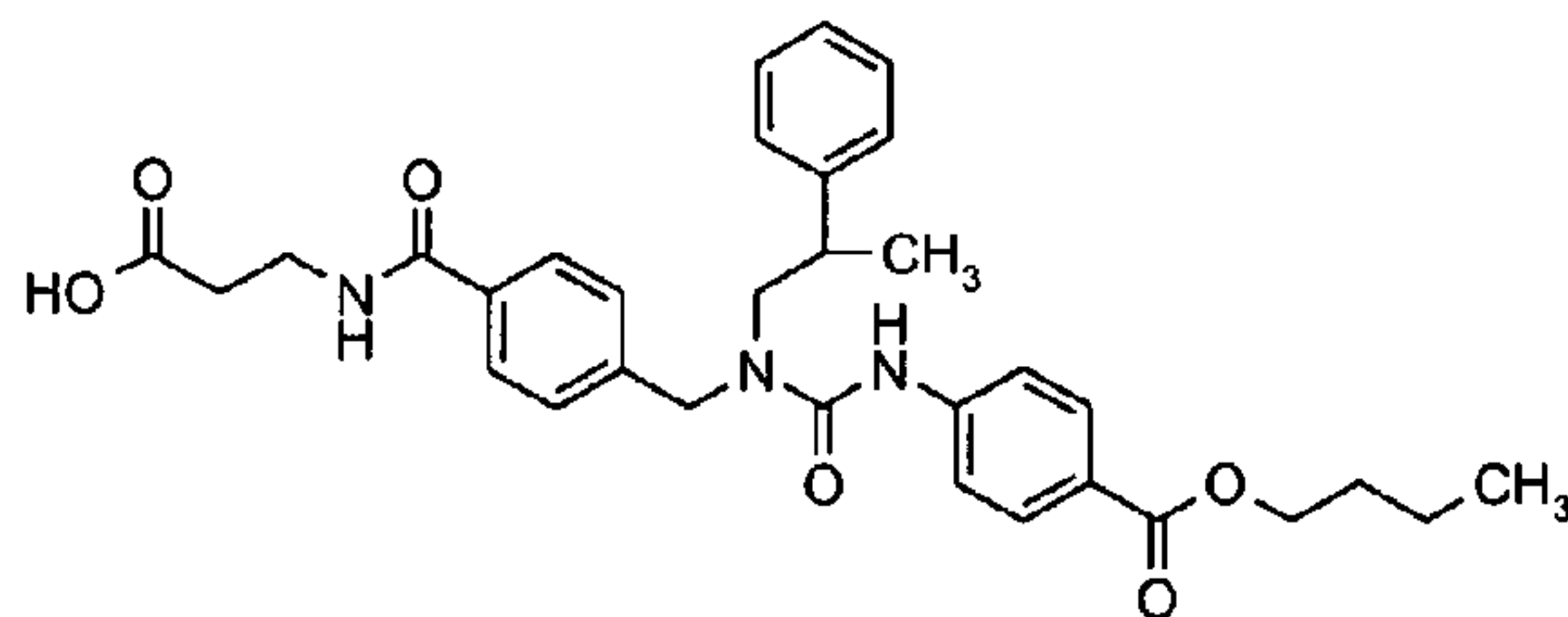
EXAMPLE 48 (general procedure (C))

3-{4-[1-(2-Methylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

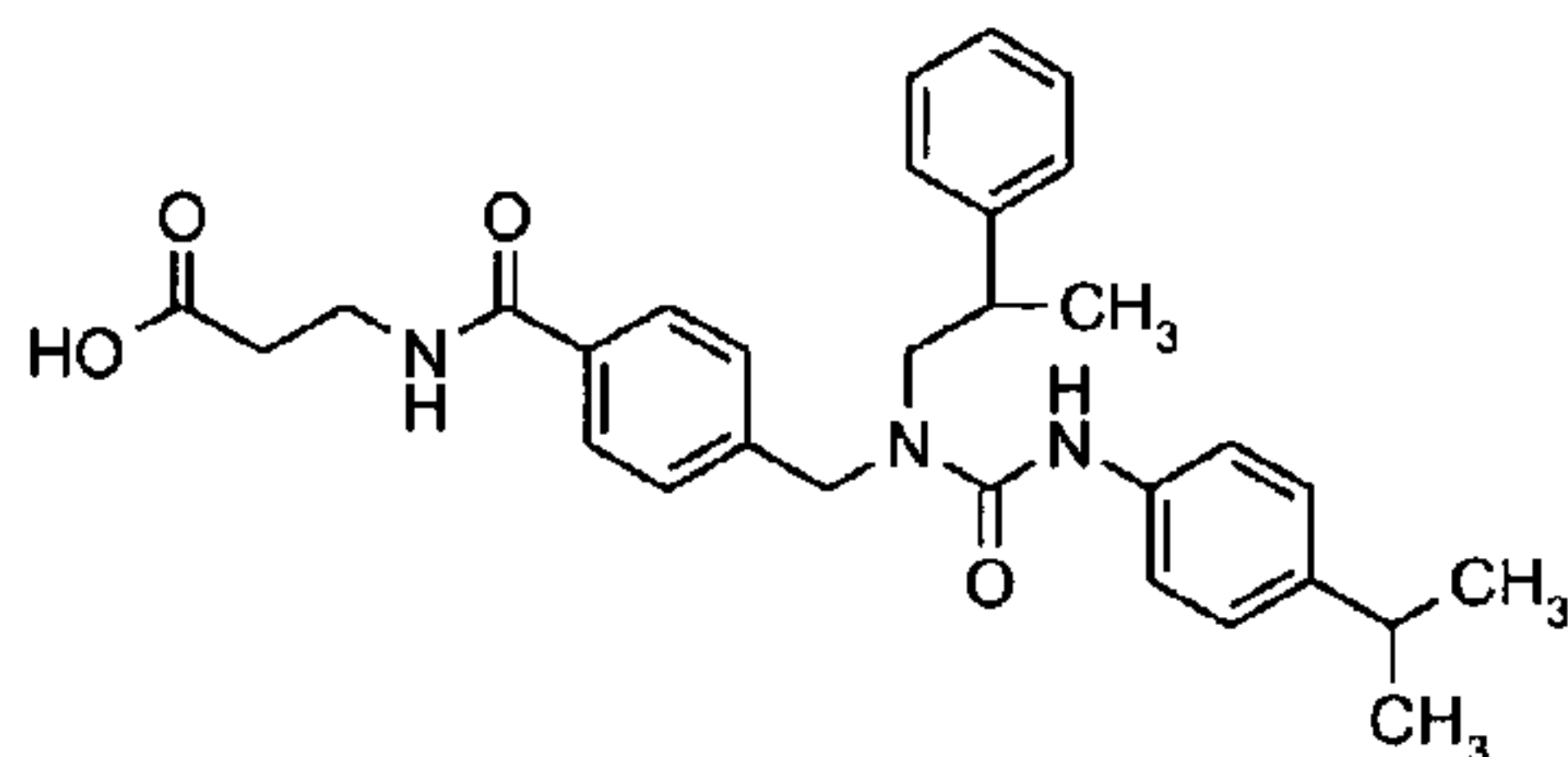


20

HPLC-MS (Method C): m/z : 530, R_t = 6.96 min.

EXAMPLE 49 (general procedure (C))4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2-phenylpropyl)ureido]benzoic acid butyl ester

- 5 ^1H NMR (DMSO- d_6): δ 7.20 (2H, t), 7.3 (6H, m), 7.55 (2H, d), 7.77 (2H, d), 7.83 (2H, d), 8.46 (1H, d), 8.69 (1H, s).

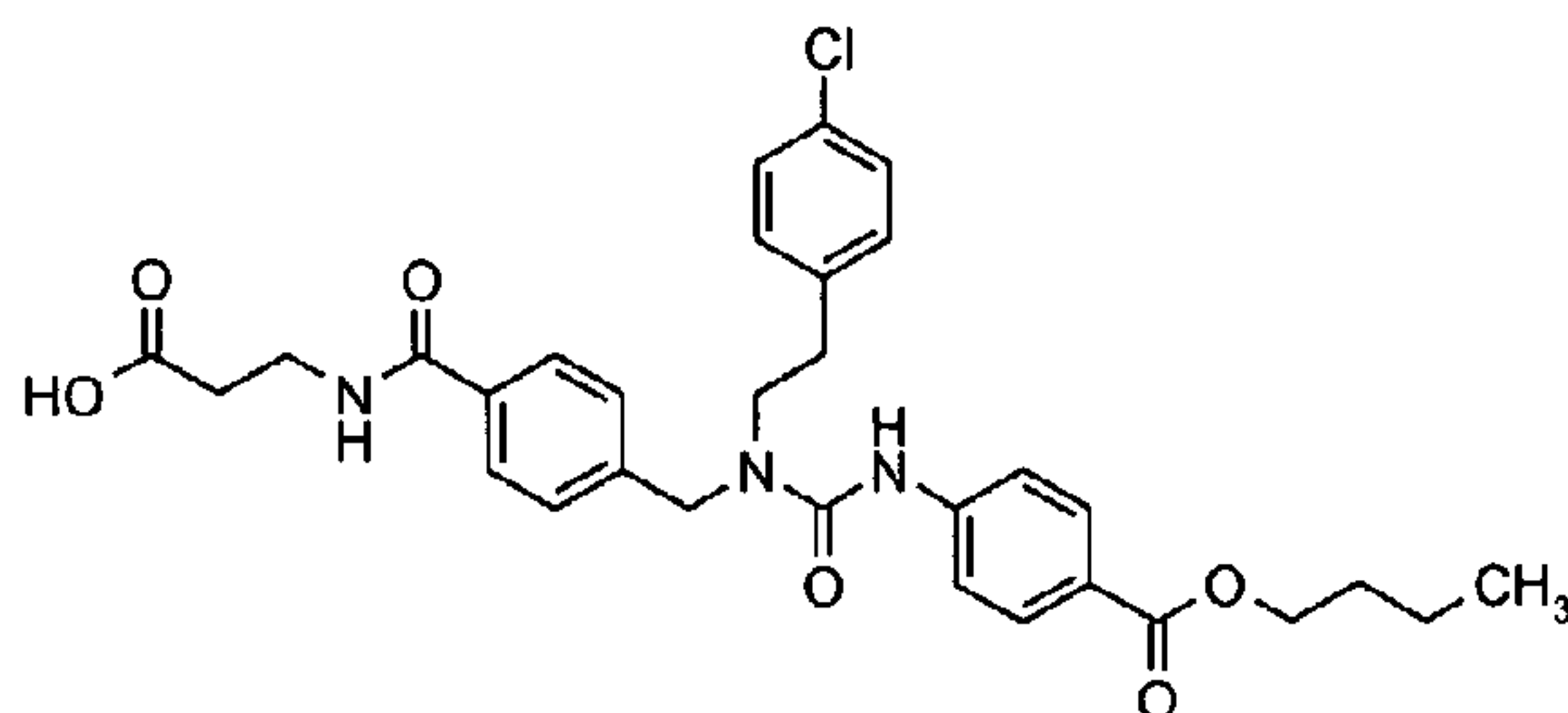
EXAMPLE 50 (general procedure (C))3-{4-[3-(4-Isopropylphenyl)-1-(2-phenylpropyl)ureidomethyl]benzoylamino}propionic acid

10

- ^1H NMR (DMSO- d_6): δ 7.11 (2H, d), 7.2-7.35 (9H, m), 7.78 (2H, d), 8.23 (1H, s), 8.49 (1H, t).

EXAMPLE 51 (general procedure (C))

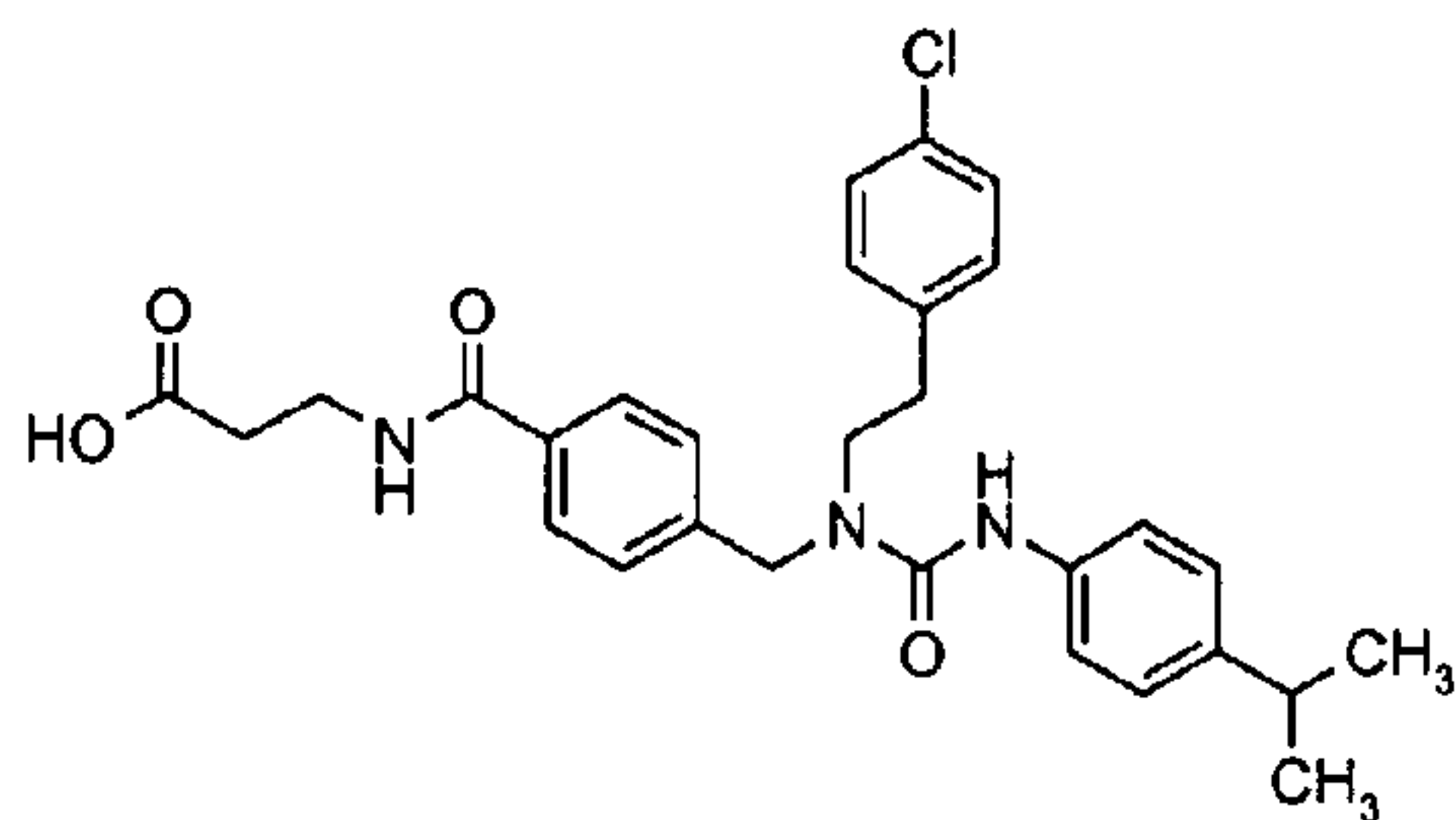
- 15 4-{3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-[2-(4-chlorophenyl)ethyl]ureido}benzoic acid butyl ester



- 20 ^1H NMR (DMSO- d_6): δ 7.27 (2H, d), 7.31-7.36 (4H, m), 7.60 (2H, d), 7.81 (2H, d), 7.86 (2H, d), 8.47 (1H, t), 8.77 (1H, s).

EXAMPLE 52 (general procedure (C))

3-{4-[1-[2-(4-Chlorophenyl)ethyl]-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

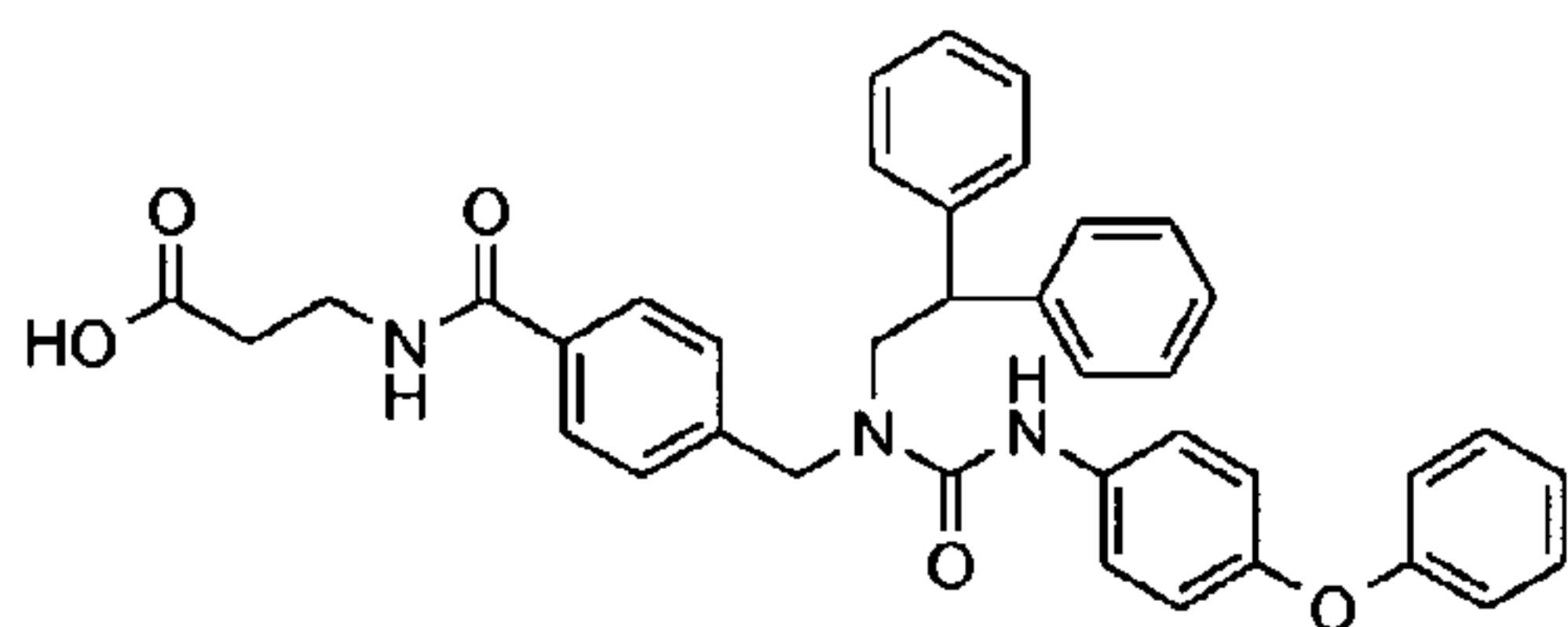


5

^1H NMR (DMSO- d_6): δ 7.10 (2H, d), 7.24 (2H, d), 7.30-7.34 (6H, m), 7.78 (2H, d), 8.29 (1H, s).

EXAMPLE 53 (general procedure (C))

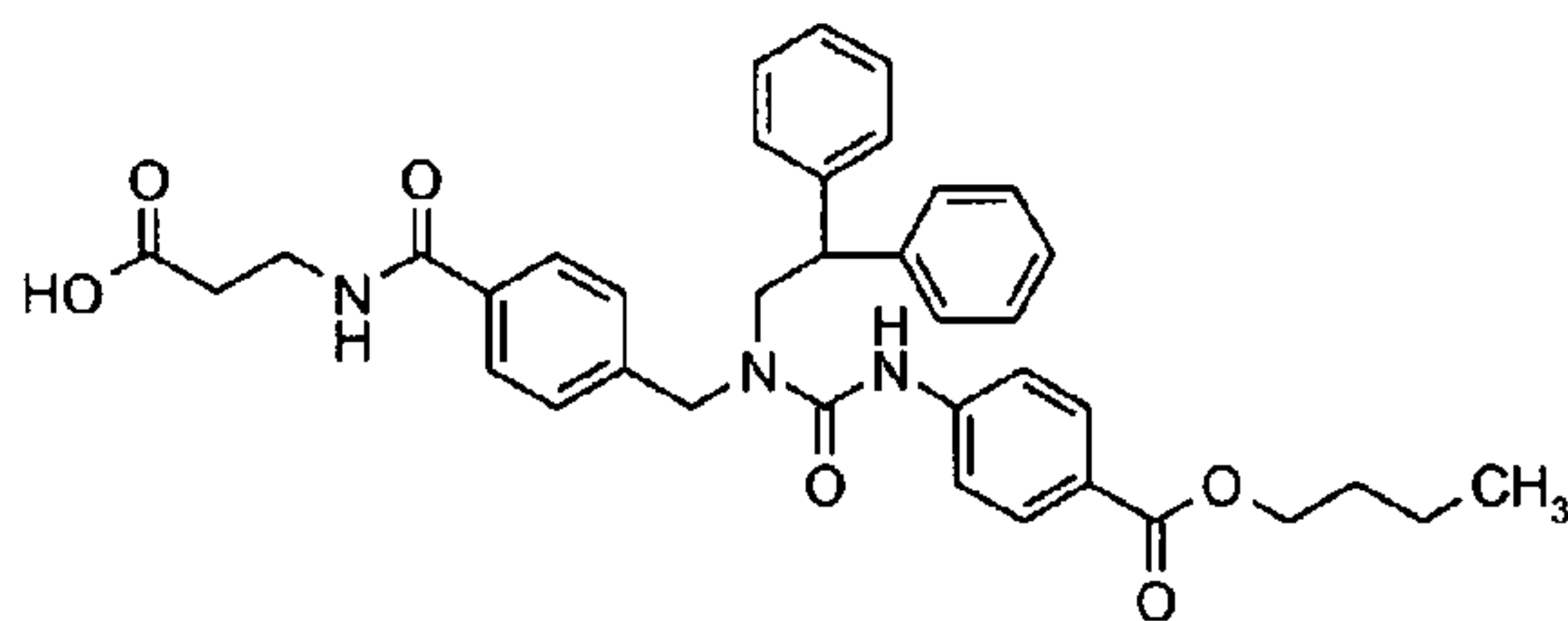
10 3-{4-[1-(2,2-Diphenylethyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid



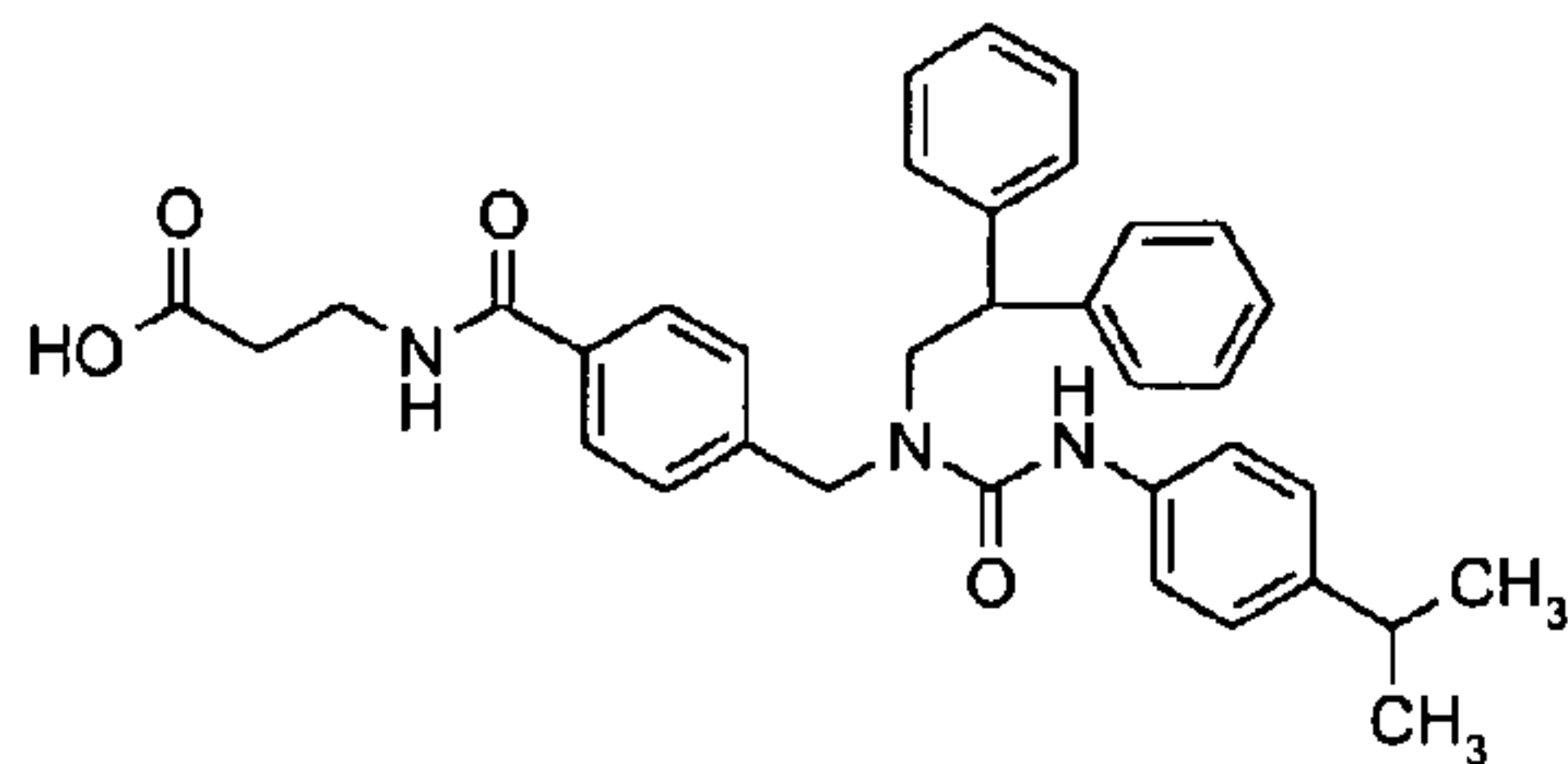
HPLC-MS (Method C): m/z 614, R_t = 7.35 min.

15 EXAMPLE 54 (general procedure (C))

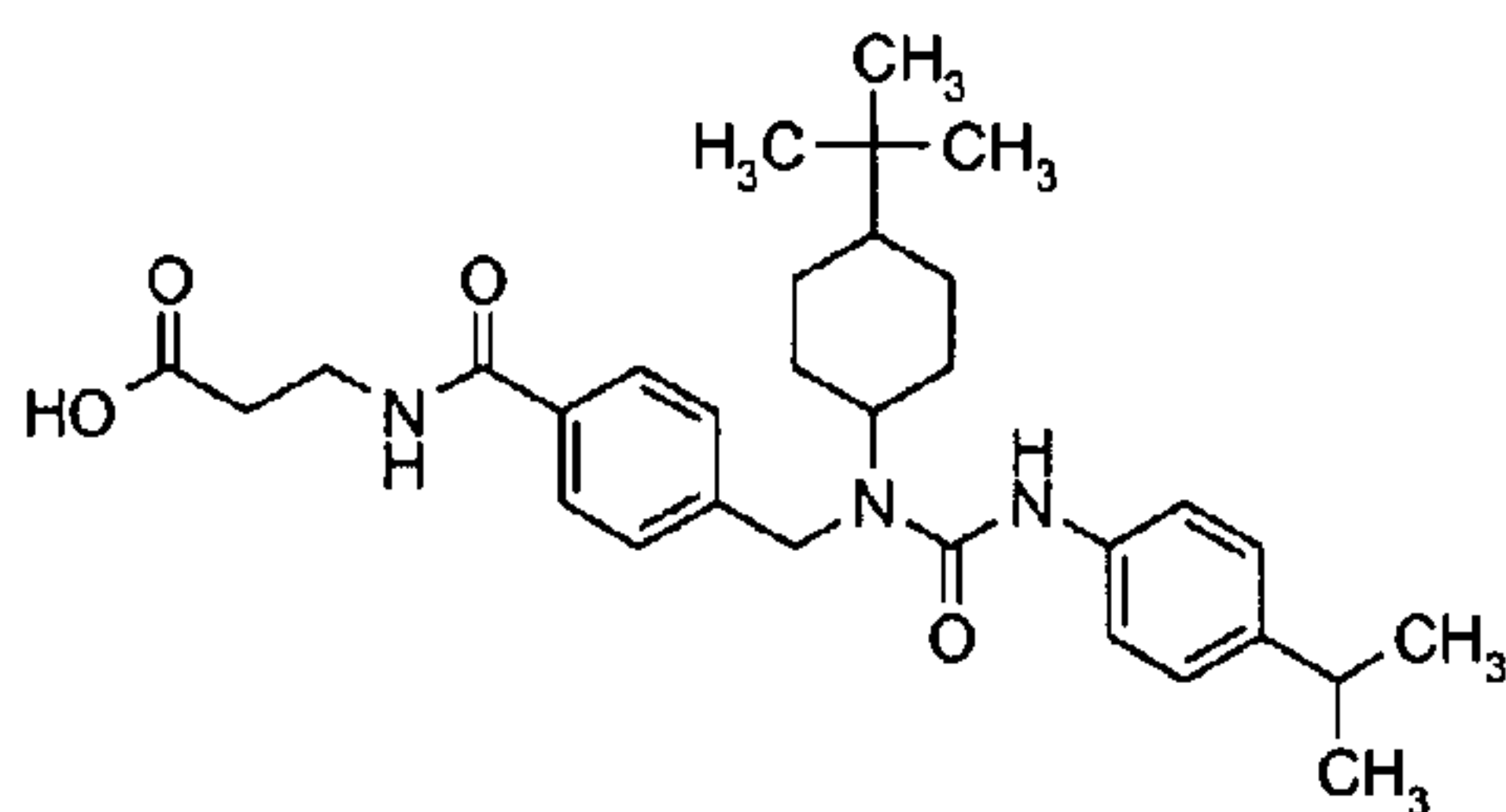
4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(2,2-diphenylethyl)ureido]benzoic acid butyl ester



20 ^1H NMR (DMSO- d_6): δ 7.18 (2H, t), 7.25-7.3 (6H, m), 7.34 (4H, m), 7.47 (2H, d), 7.75 (2H, d), 7.80 (2H, d), 8.52 (1H, b), 8.71 (1H, s).

EXAMPLE 55 (general procedure (C))3-{4-[1-(2,2-Diphenylethyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

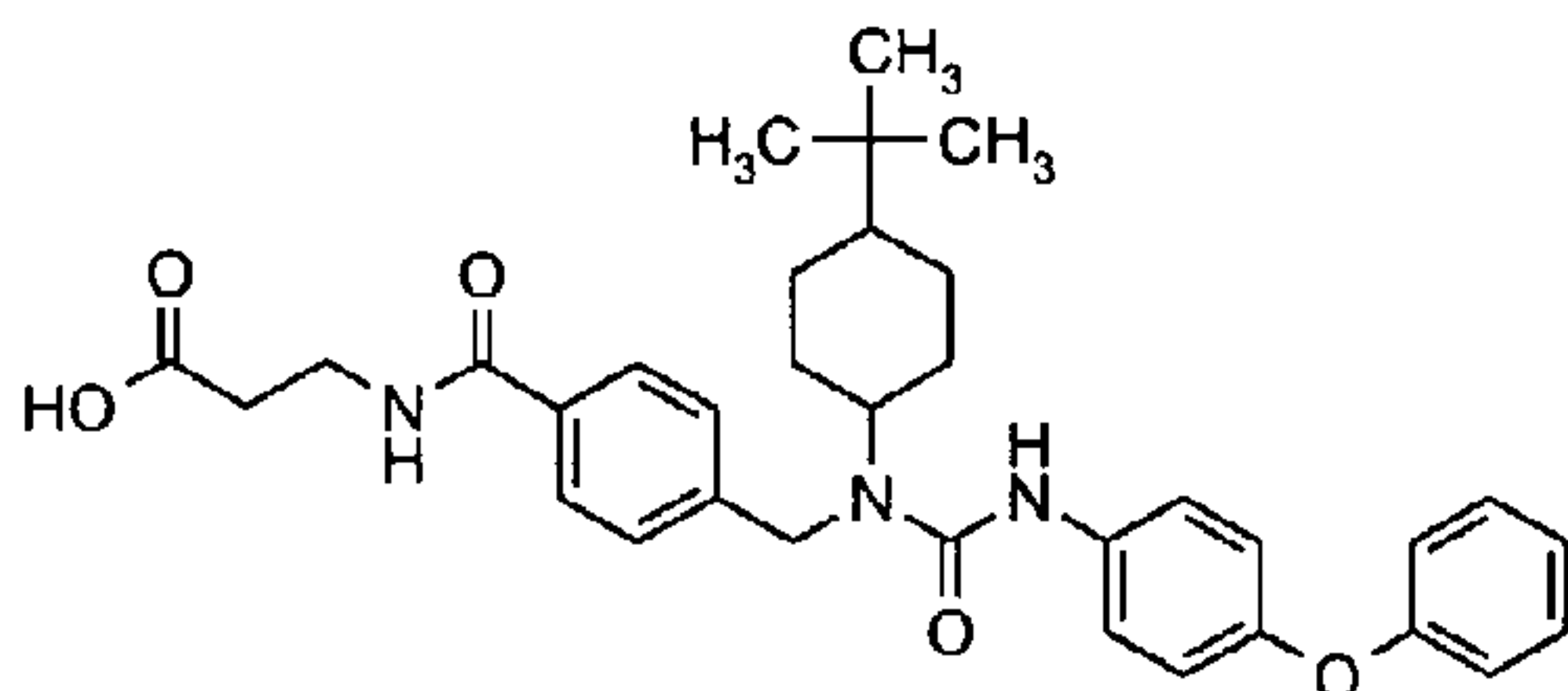
5 ^1H NMR (DMSO- d_6): δ 7.06 (2H, d), 7.16-7.35 (14H, m), 7.75 (2H, d), 8.24 (1H, s).

EXAMPLE 56 (general procedure (C))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isopropylphenyl)ureidomethyl]benzoylamino}propionic acid

10

^1H NMR (DMSO- d_6): δ 8.41 (s, 1H); 8.20 (s, 1H); 7.75 (d, 2H); 7.34 (d, 2H); 7.32 (d, 2H); 7.08 (d, 2H); 4.08 (s, 2H); 1.19 (d, 6H); 0.83 (s, 9H).

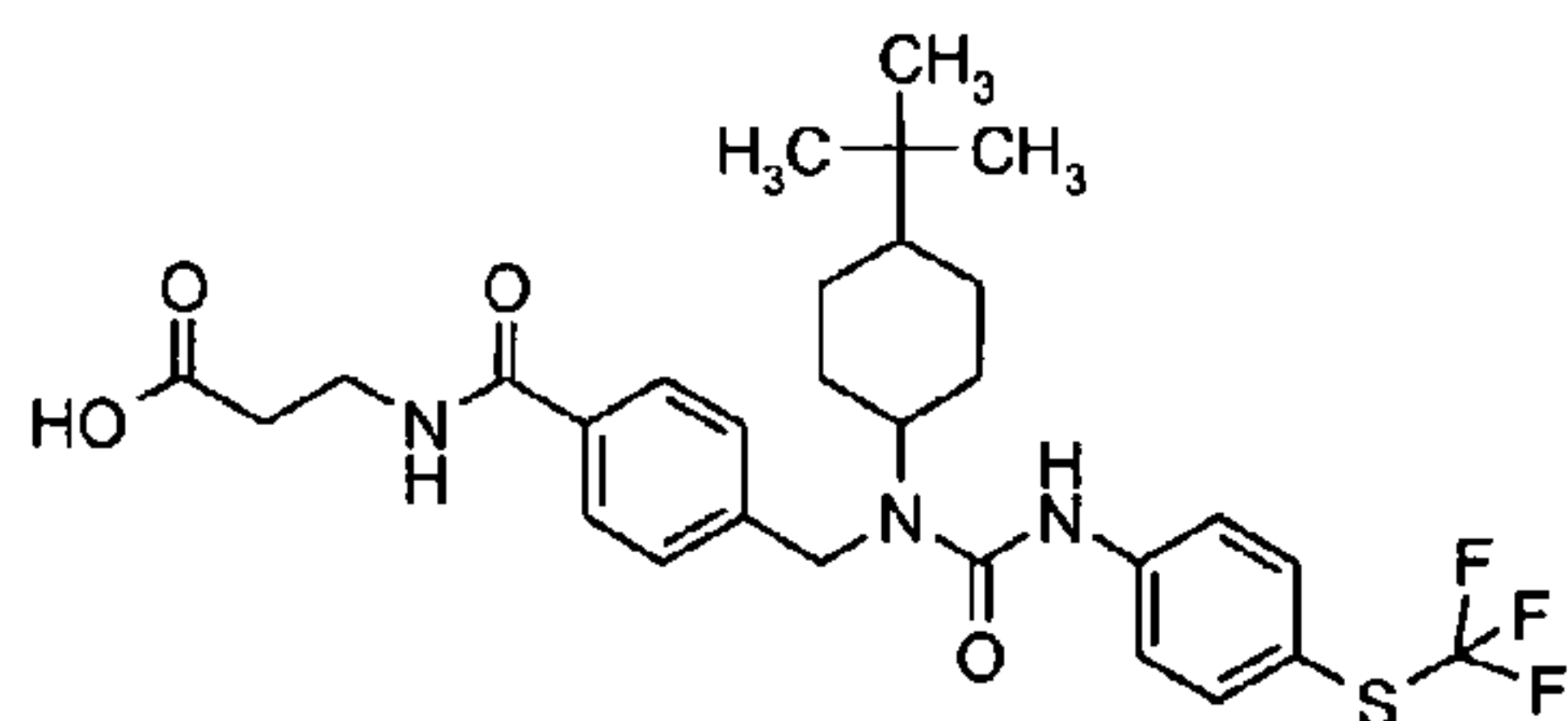
15 EXAMPLE 57 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-phenoxyphenyl)ureidomethyl]benzoylamino}propionic acid

20 ^1H NMR (DMSO- d_6): δ 8.44 (s, 1H); 8.35 (s, 1H); 7.78 (d, 2H); 7.45 (d, 2H); 7.38 (d, 2H); 7.34 (d, 2H); 6.94 (m, 5H); 4.60 (s, 2H); 0.81 (s, 9H).

EXAMPLE 58 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]-benzoylamino}propionic acid

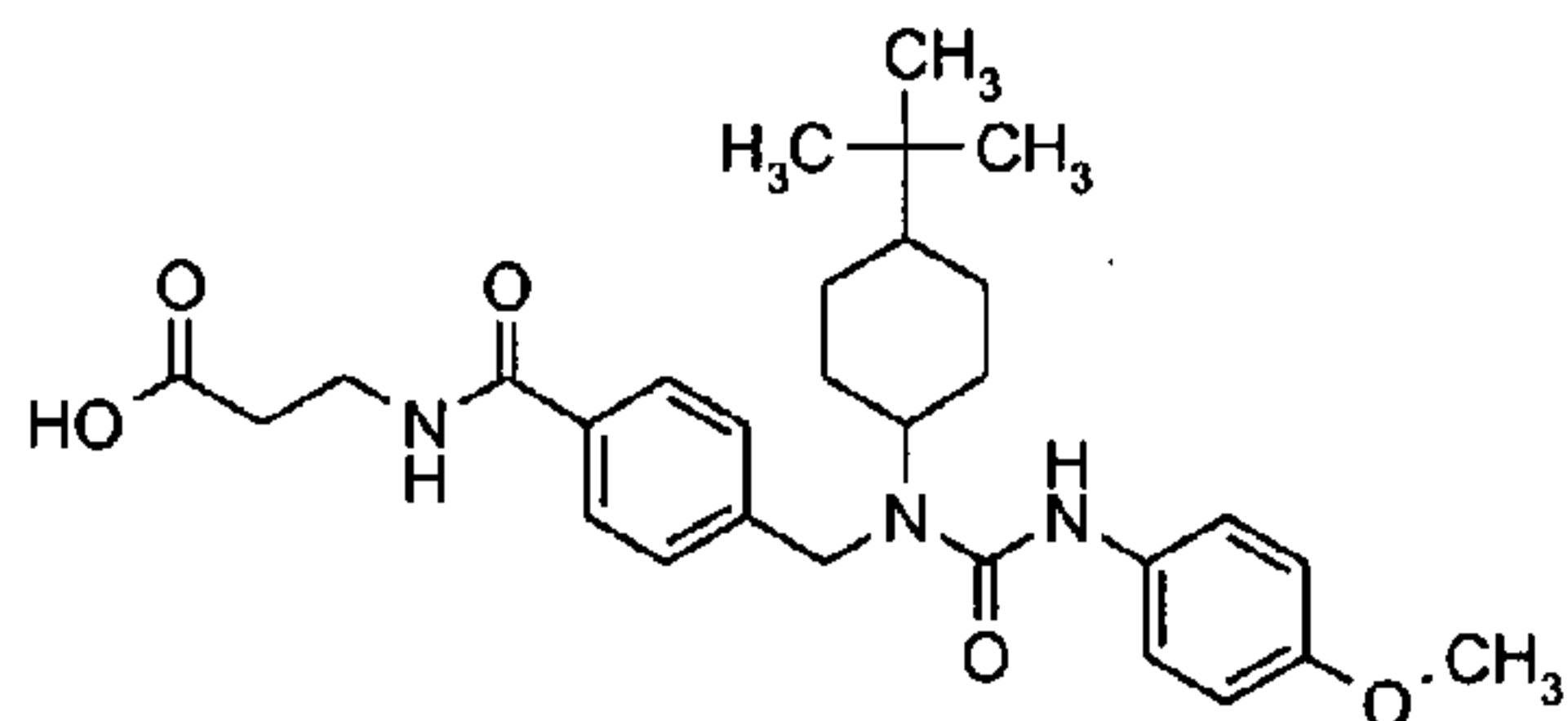


5

^1H NMR (DMSO- d_6): δ 8.46 (s, 1H); 8.34 (s, 1H); 7.74 (d, 2H); 7.40 (d, 2H); 7.34 (d, 2H); 7.16 (d, 2H); 4.59 (s, 2H); 0.85 (s, 9H).

10 EXAMPLE 59 (general procedure (C))

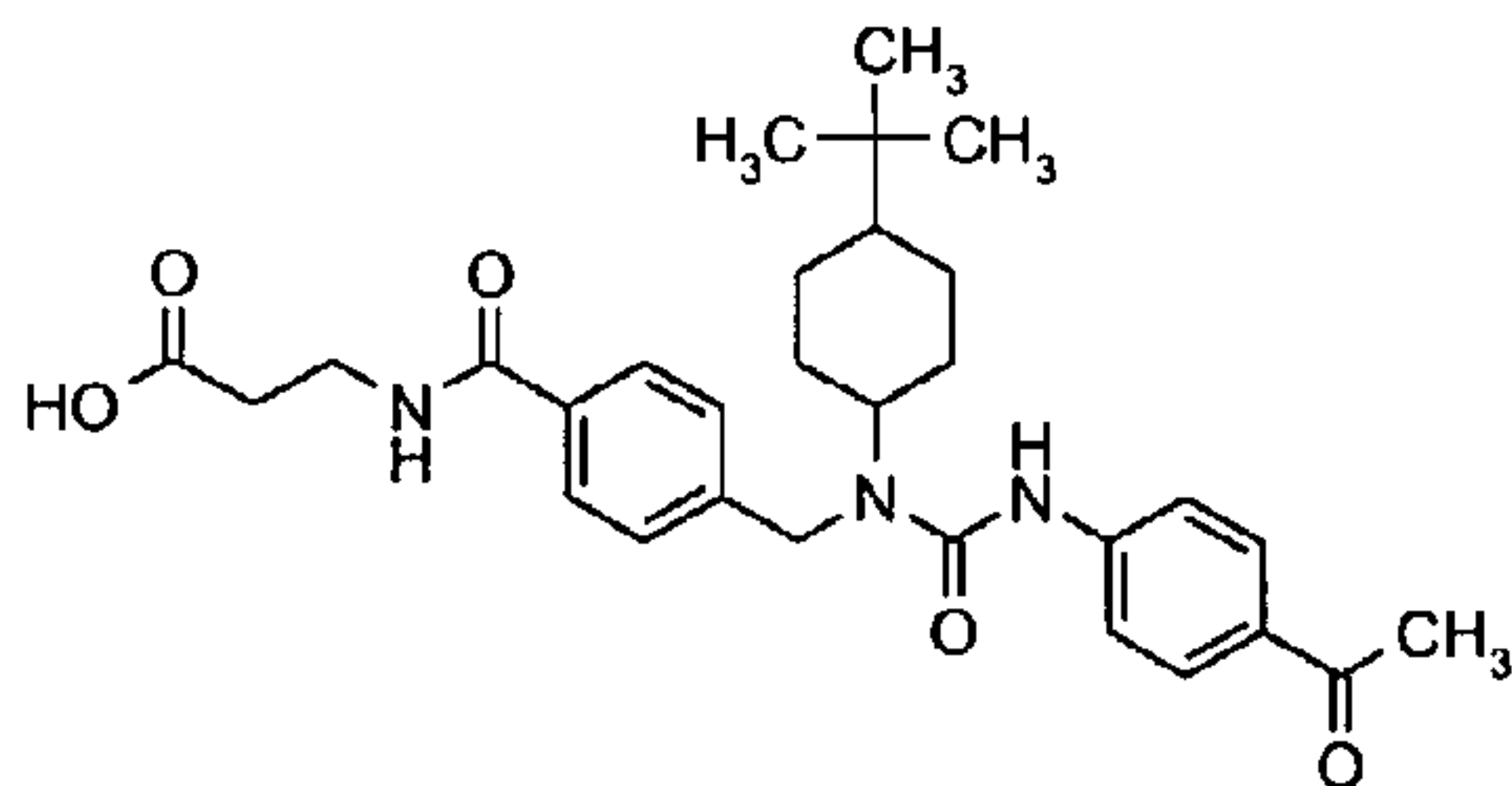
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-methoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15 ^1H NMR (DMSO- d_6): δ 8.46 (s, 1H); 8.18 (s, 1H); 7.76 (d, 2H); 7.30 (d, 2H); 7.28 (d, 2H); 6.8 (d, 2H); 4.58 (s, 2H); 3.73 (s, 3H); 0.80 (s, 9H).

EXAMPLE 60 (general procedure (C))

3-{4-[3-(4-Acetylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid

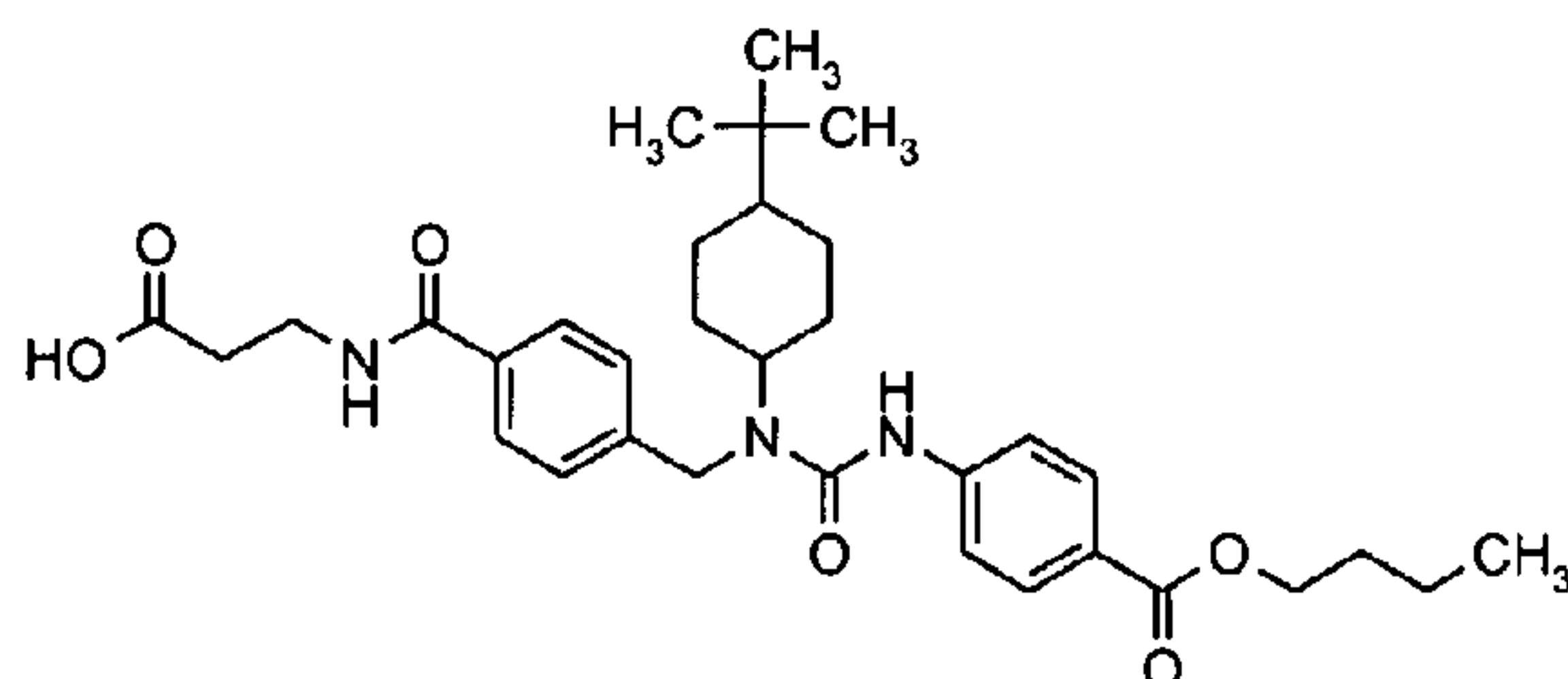


20

^1H NMR (DMSO- d_6): δ 8.70 (s, 1H); 8.42 (s, 1H); 7.86 (d, 2H); 7.76 (d, 2H); 7.62 (d, 2H); 7.30 (d, 2H); 4.62 (s, 2H); 0.81 (s, 9H).

EXAMPLE 61 (general procedure (C))

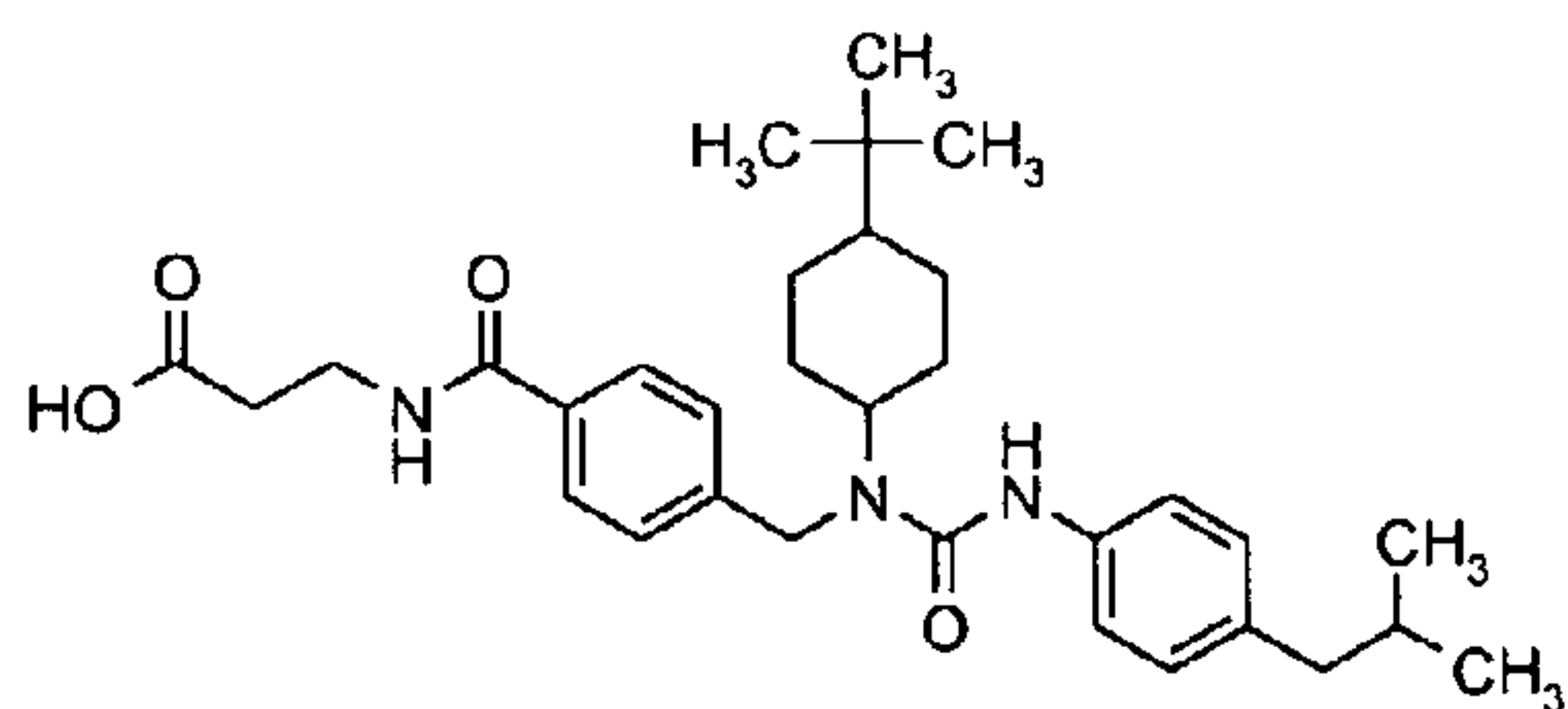
5 4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid butyl ester



10 ^1H NMR (DMSO- d_6): δ 8.71 (s, 1H); 8.42 (t, 1H); 7.83 (d, 2H); 7.76 (d, 2H); 7.61 (s, 2H); 7.32 (d, 2H); 4.64 (s, 2H); 4.26 (t, 2H); 0.94 (t, 3H); 0.83 (s, 9H).

EXAMPLE 62 (general procedure (C))

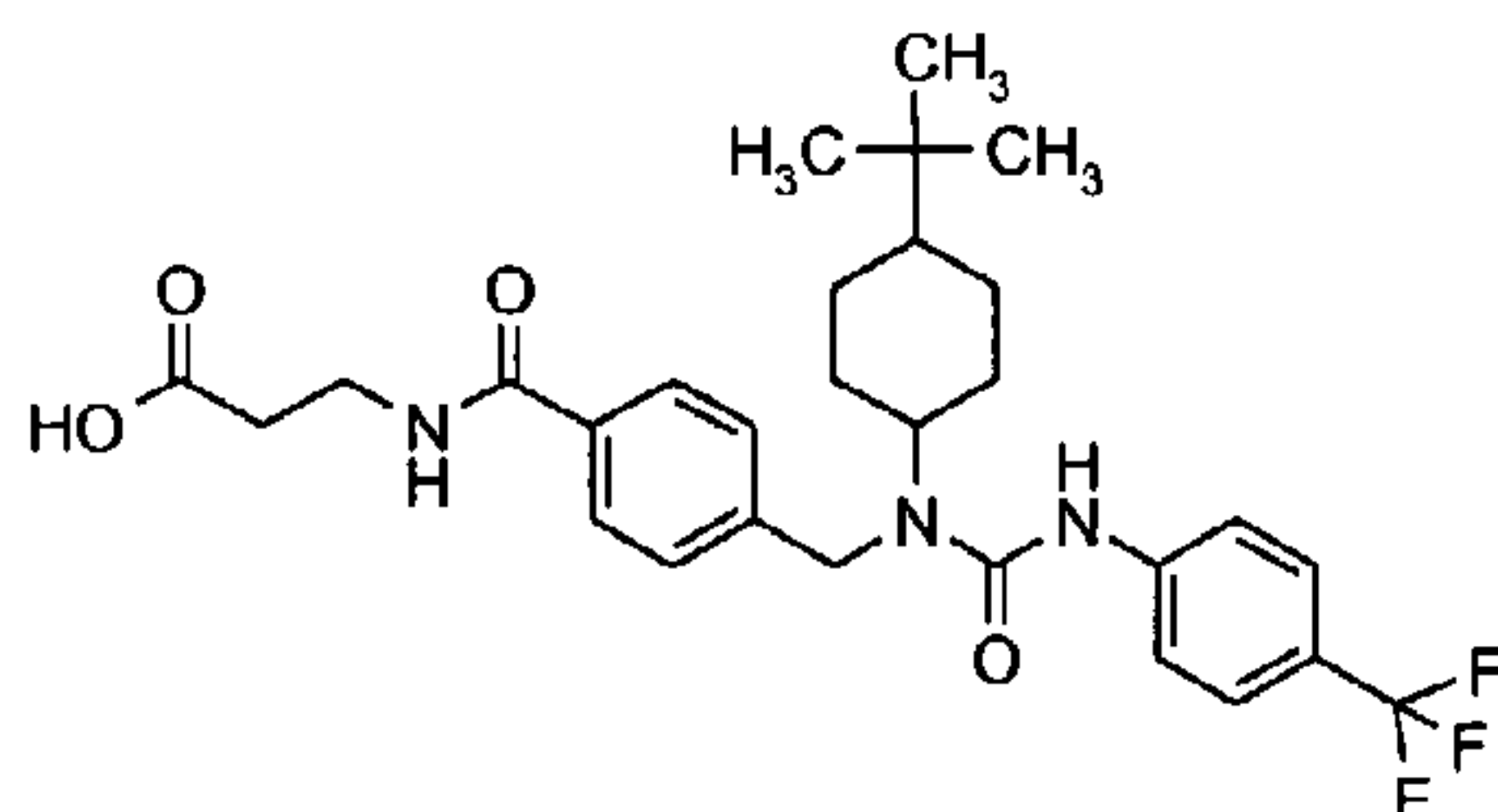
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-isobutylphenyl)ureidomethyl]benzoylamino}propionic acid



15 ^1H NMR (DMSO- d_6): δ 8.46 (t, 1H); 8.22 (s, 1H); 7.75 (d, 2H); 7.35 (d, 2H); 7.33 (d, 2H); 7.05 (d, 2H); 4.60 (s, 2H); 1.17 (d, 6H); 0.83 (s, 9H).

EXAMPLE 63 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid

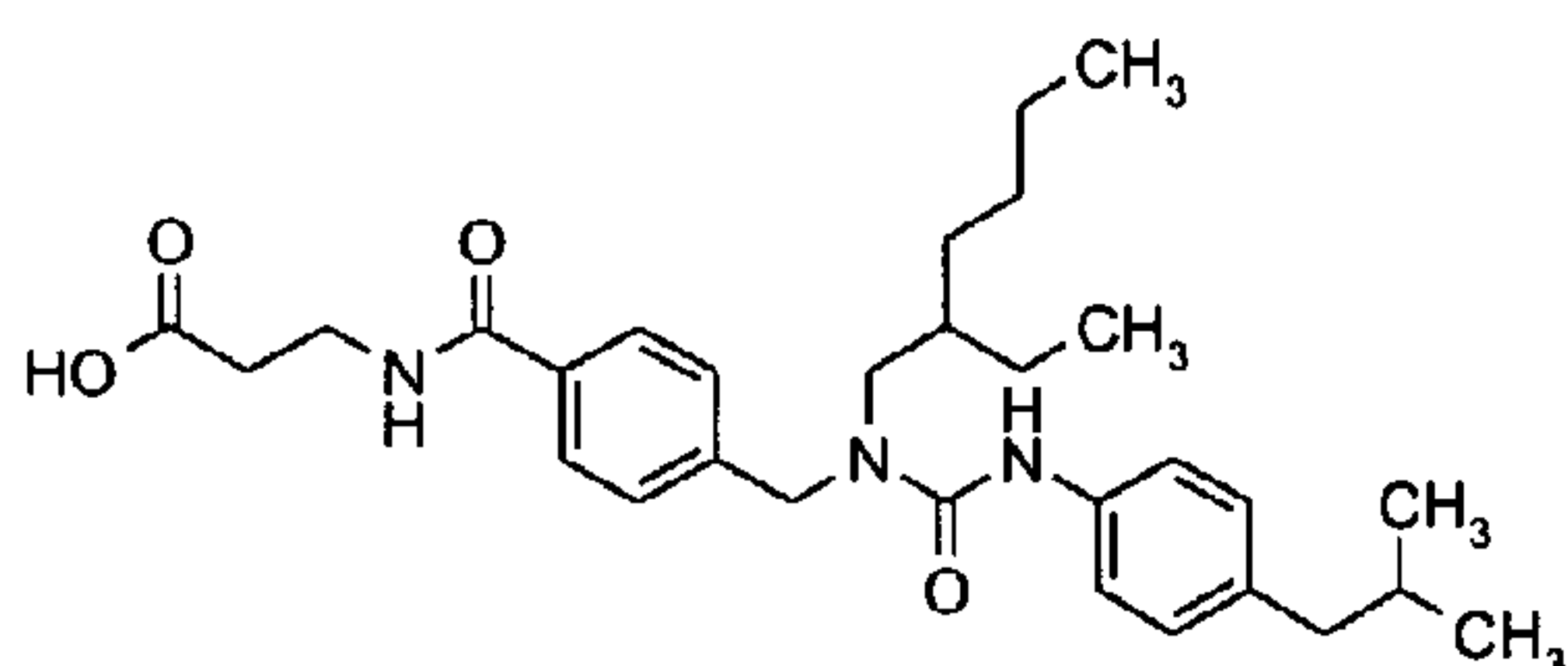


5

^1H NMR (DMSO- d_6): δ 8.72 (s, 1H); 8.45 (t, 1H); 7.78 (d, 2H); 7.72 (d, 2H); 7.60 (d, 2H); 7.35 (d, 2H); 4.65 (s, 2H); 4.10 (m, 1H); 0.85 (s, 9H).

EXAMPLE 64 (general procedure (C))

3-{4-[1-(2-Ethylhexyl)-3-(4-isobutylphenyl)ureidomethyl]benzoylamino}propionic acid

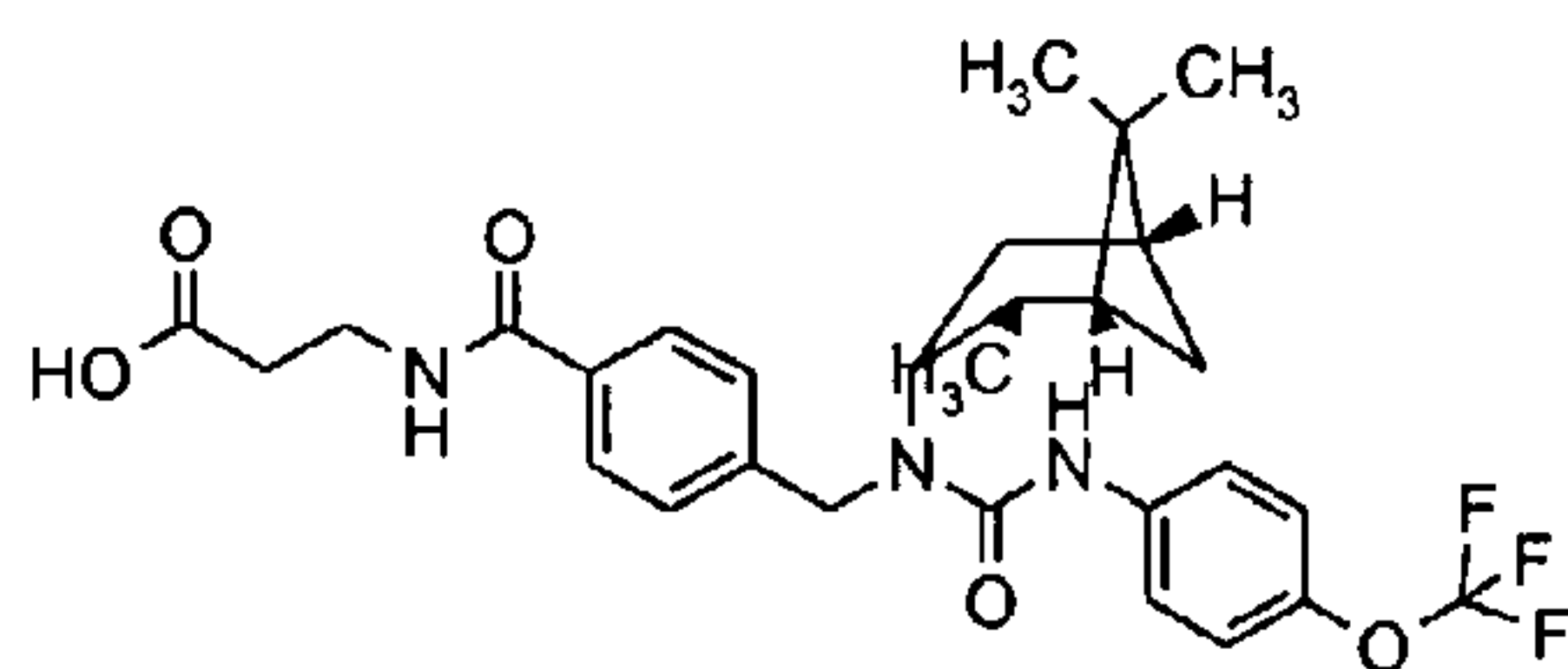


^1H NMR (DMSO- d_6): δ 8.47 (t, 1H); 8.30 (s, 1H); 7.82 (d, 2H); 7.36 (d, 2H); 7.32 (d, 2H); 7.05 (d, 2H); 4.65 (s, 2H), 1.12 (m, 9H); 0.85 (m, 12H).

15

EXAMPLE 65 (general procedure (C))

3-{4-[3-(4-Trifluoromethoxyphenyl)-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)ureidomethyl]benzoylamino}propionic acid

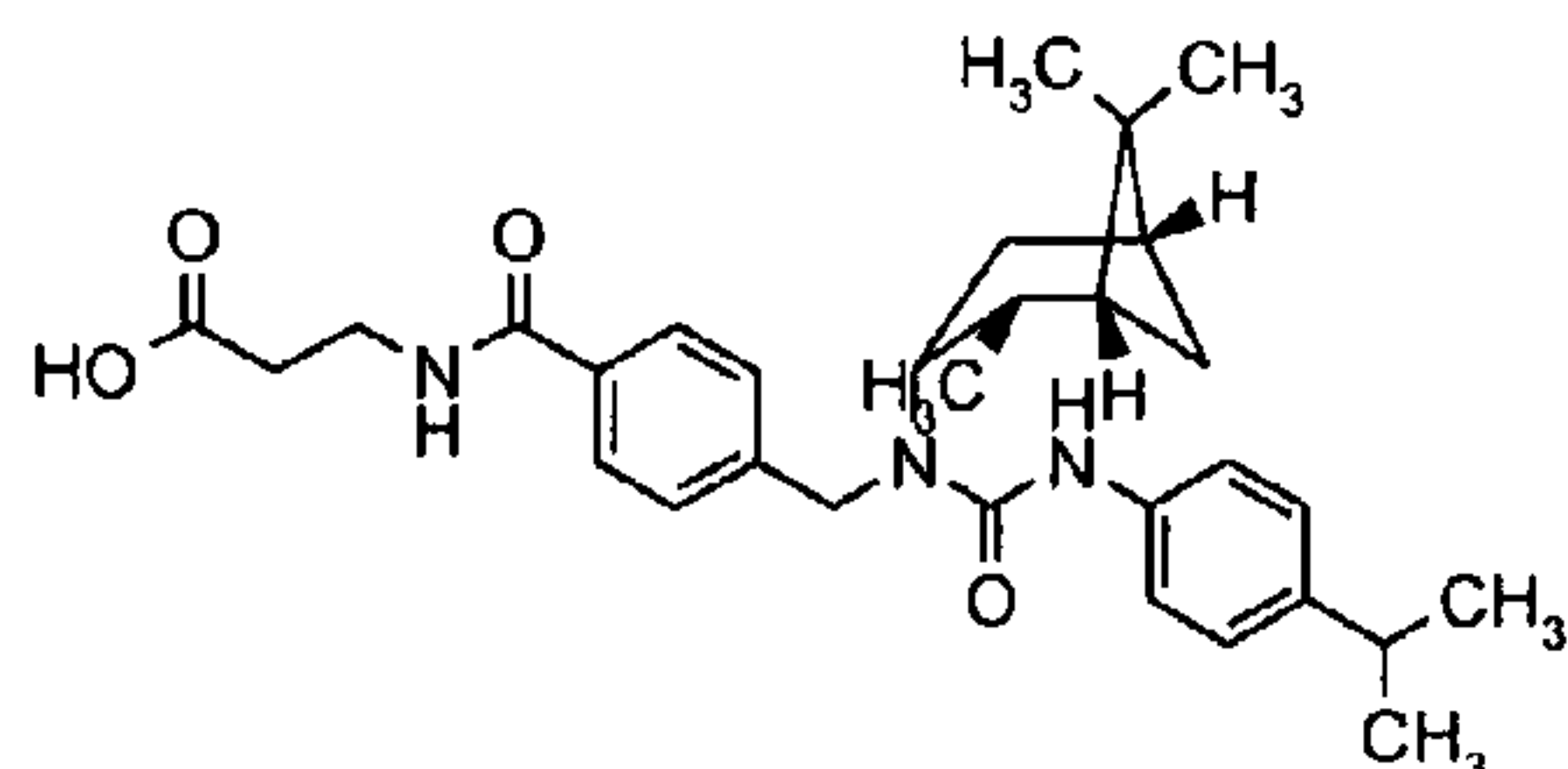


20

^1H NMR (DMSO- d_6): δ 8.52 (s, 1H); 8.44 (t, 1H); 7.81 (d, 2H); 7.52 (d, 2H); 7.35 (d, 2H); 7.22 (d, 2H); 4.91 (m, 1H); 4.76 (s, 2H); 1.22 (s, 3H); 1.13 (s, 3H); 0.98 (d, 3H).

EXAMPLE 66 (general procedure (C))

3-{4-[3-(4-Isopropylphenyl)-1-(2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)ureidomethyl]benzoylamino}propionic acid

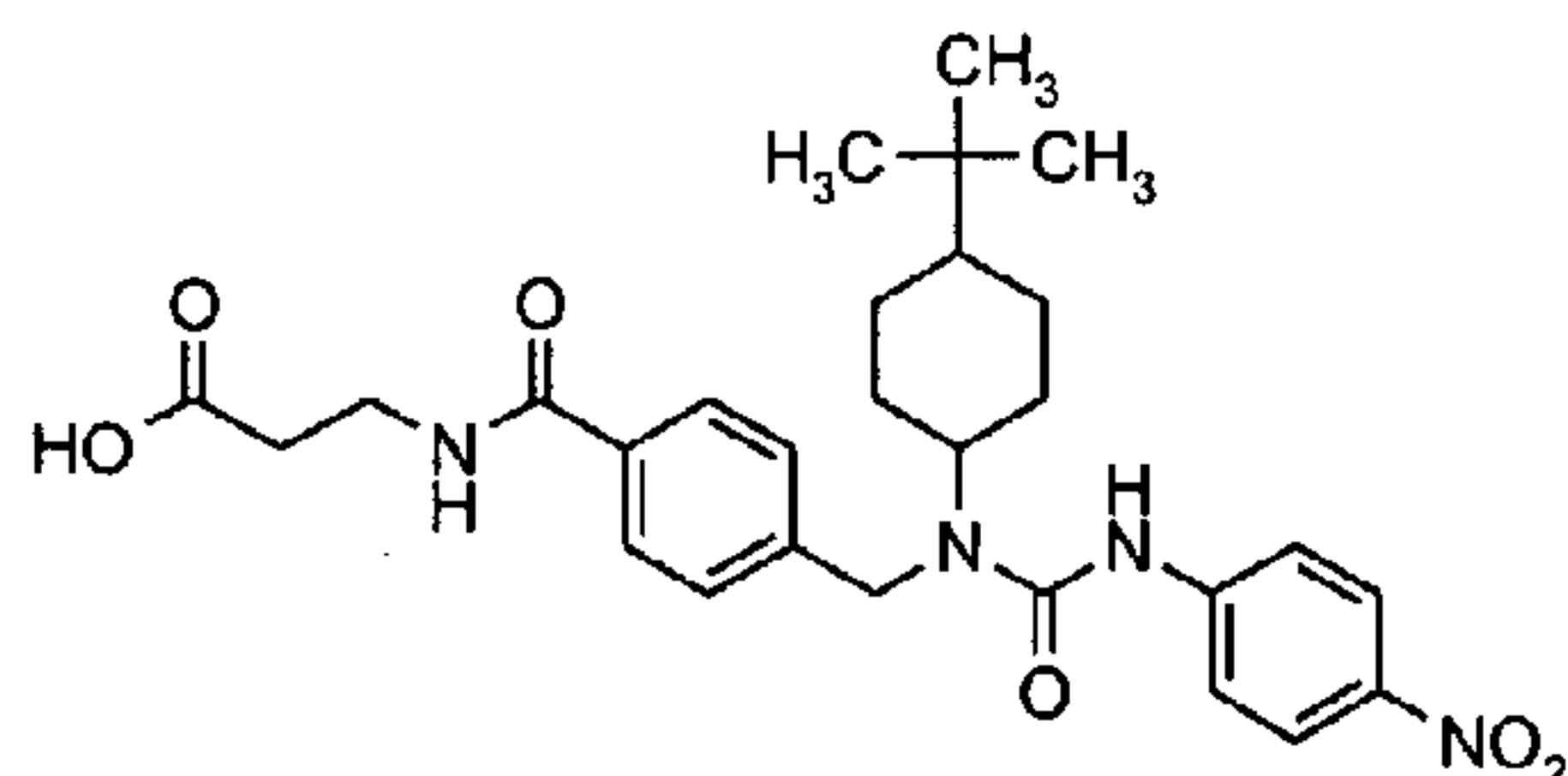


5

^1H NMR (DMSO- d_6): δ 8.44 (s, 1H); 8.17 (t, 1H); 7.78 (d, 2H); 7.34 (d, 2H); 7.26 (d, 2H); 7.08 (d, 2H); 4.93 (m, 1H); 4.72 (s, 2H); 1.22 (s, 3H); 1.18 (d, 6H); 1.13 (s, 3H); 0.98 (d, 3H).

EXAMPLE 67 (general procedure (C))

10 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-nitrophenyl)ureidomethyl]benzoylamino}propionic acid

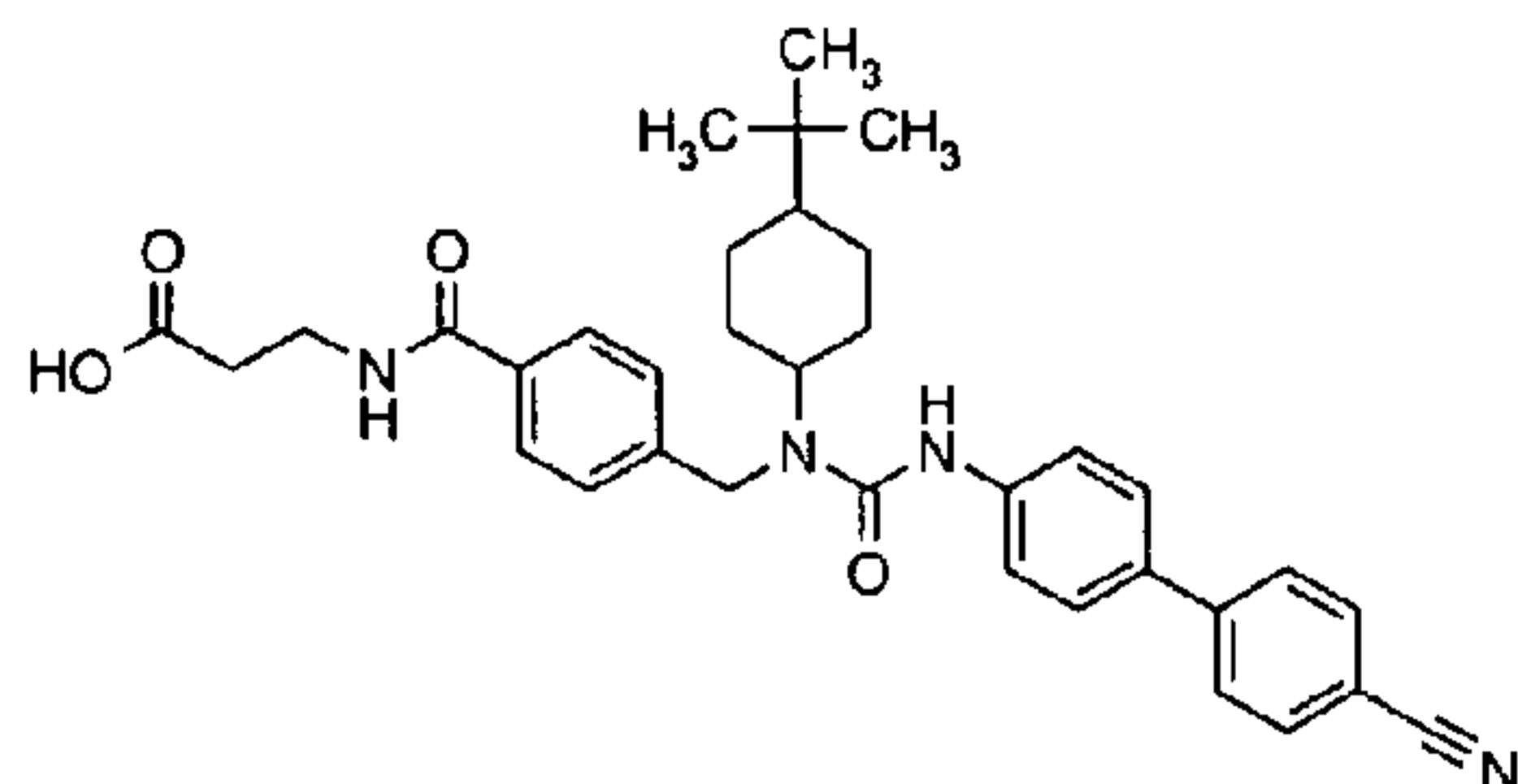


^1H NMR (DMSO- d_6): δ 9.03 (s, 1H); 8.45 (t, 1H); 8.16 (d, 2H); 7.77 (d, 2H); 7.73 (d, 2H); 7.33 (d, 2H); 4.67 (s, 2H); 4.10 (t, 1H); 0.86 (s, 9H).

15

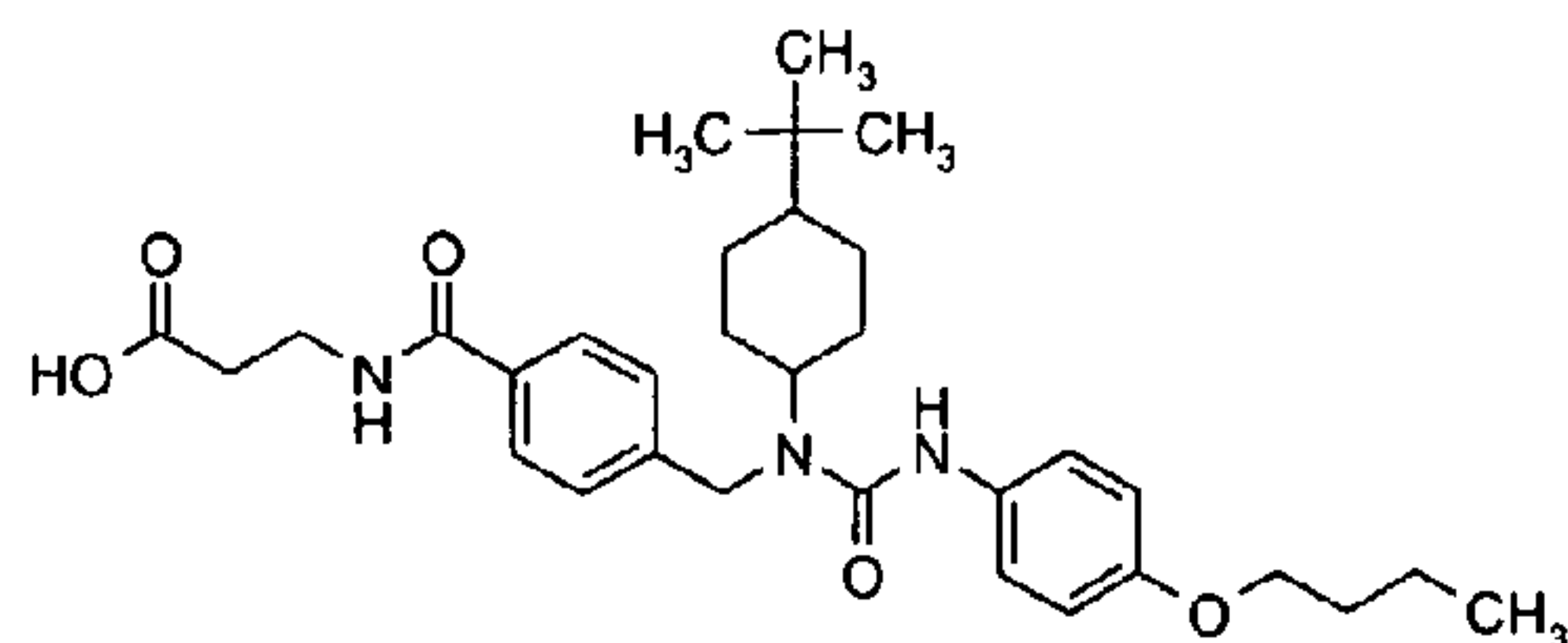
EXAMPLE 68 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4'-cyanobiphenyl-4-yl)ureidomethyl]benzoylamino}-propionic acid



20

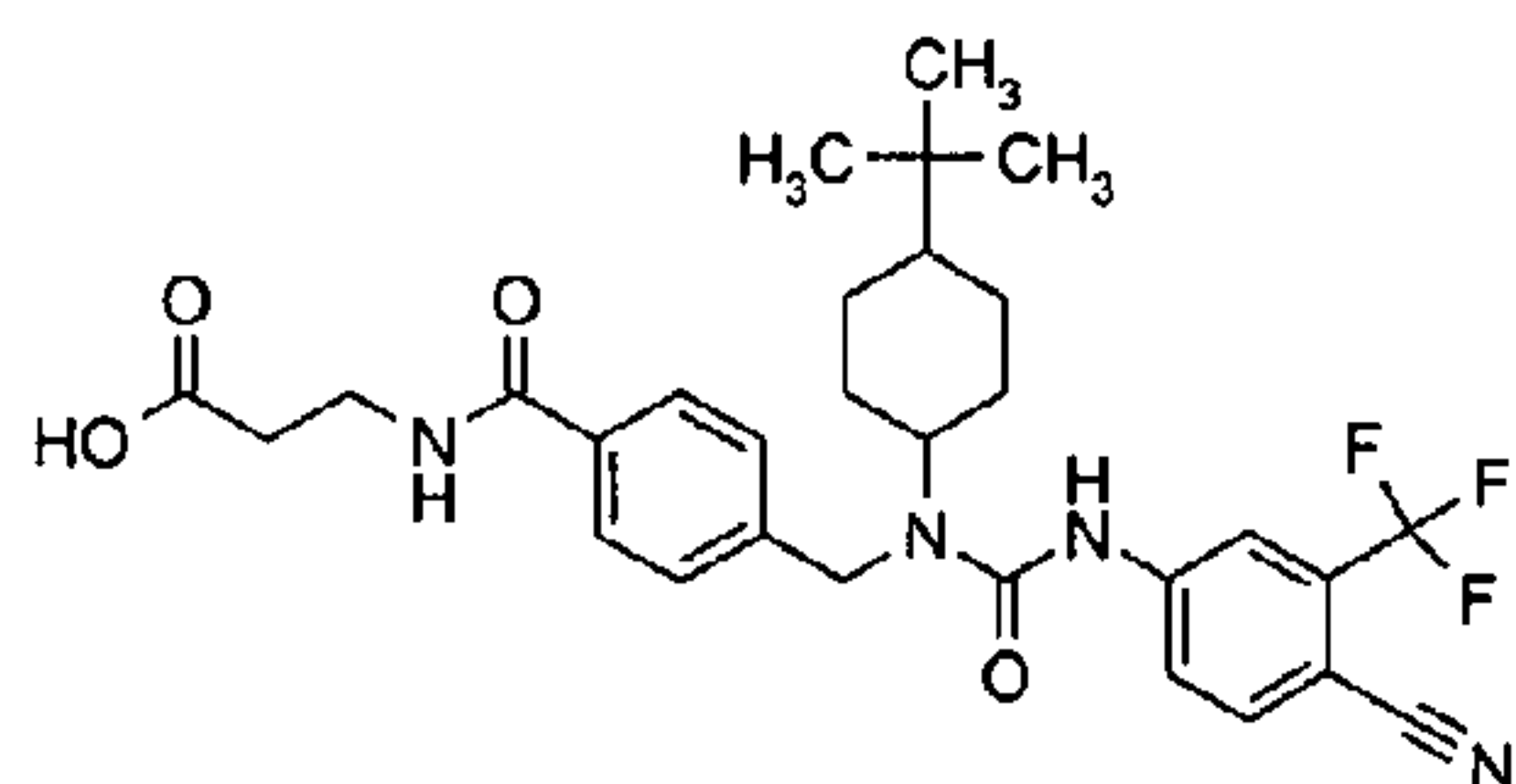
^1H NMR (DMSO- d_6): δ 8.52 (1H, s), 8.48 (1H, t), 7.88 (4H, dd), 7.79 (2H, d), 7.79 (2H, d), 7.62 (2H, d), 7.38 (2H, d).

EXAMPLE 69 (general procedure (C))**3-{4-[3-(4-Butoxyphenyl)-1-(4-*tert*-butyl-cyclohexyl)ureidomethyl]benzoylamino}propionic acid**

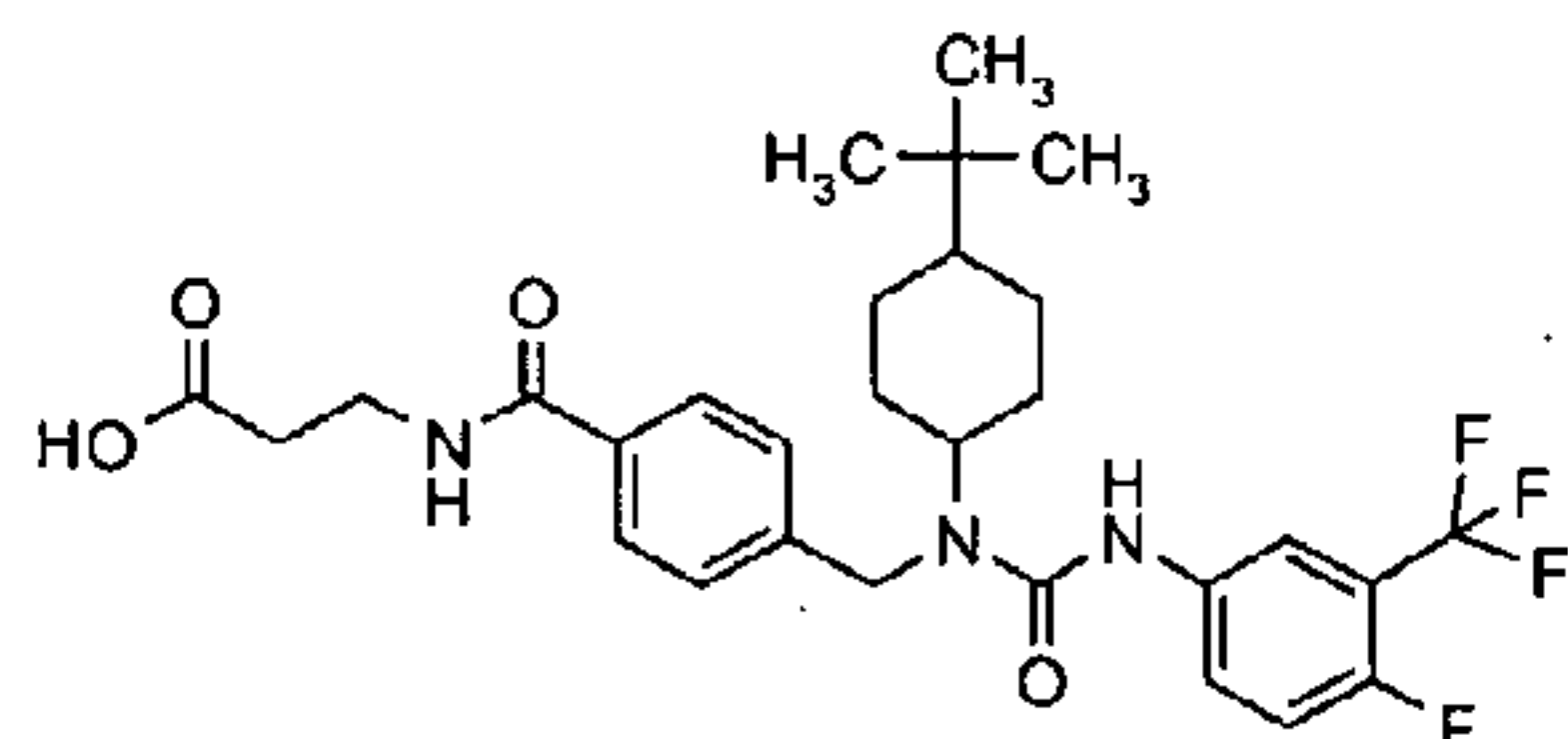
5

 ^1H NMR (DMSO- d_6): δ 8.45 (1H, m), 8.15 (1H, s), 7.78 (2H, d), 7.33 (4H, dd), 6.82 (2H, d).**EXAMPLE 70 (general procedure (C))****3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-cyano-3-trifluoromethylphenyl)ureidomethyl]benzoyl-
amino}propionic acid**

10

 ^1H NMR (DMSO- d_6): δ 8.43 (1H, m), 8.18 (1H, s), 7.98 (2H, s), 7.75 (2H, d), 7.43 (2H, d).

15

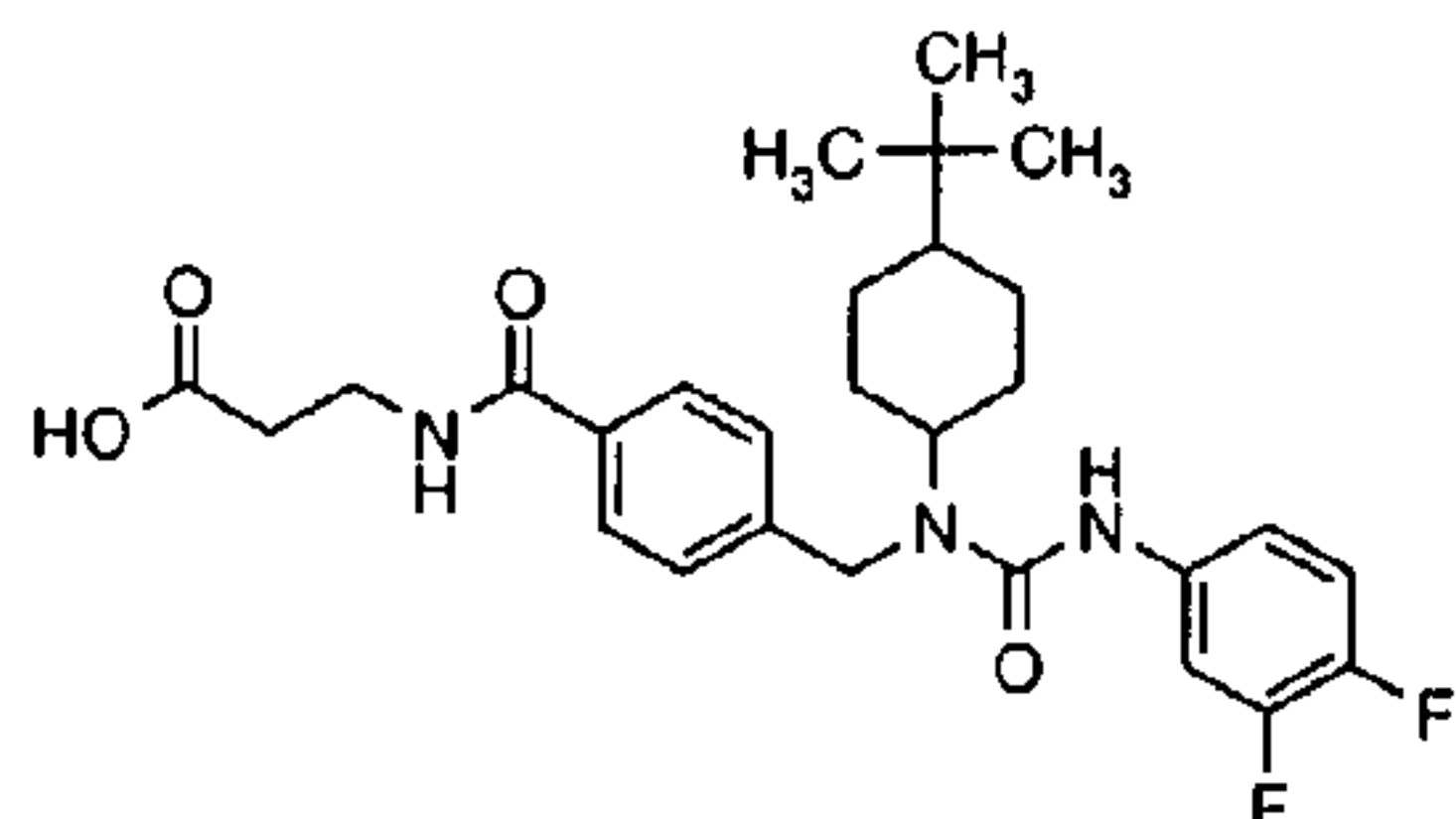
EXAMPLE 71 (general procedure (C))**3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-fluoro-3-trifluoromethylphenyl)ureidomethyl]benzoyl-
amino}propionic acid**

20

HPLC-MS (method B): m/z : 566, R_t = 7.95 min.

EXAMPLE 72 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,4-difluorophenyl)ureidomethyl]benzoylamino}propionic acid



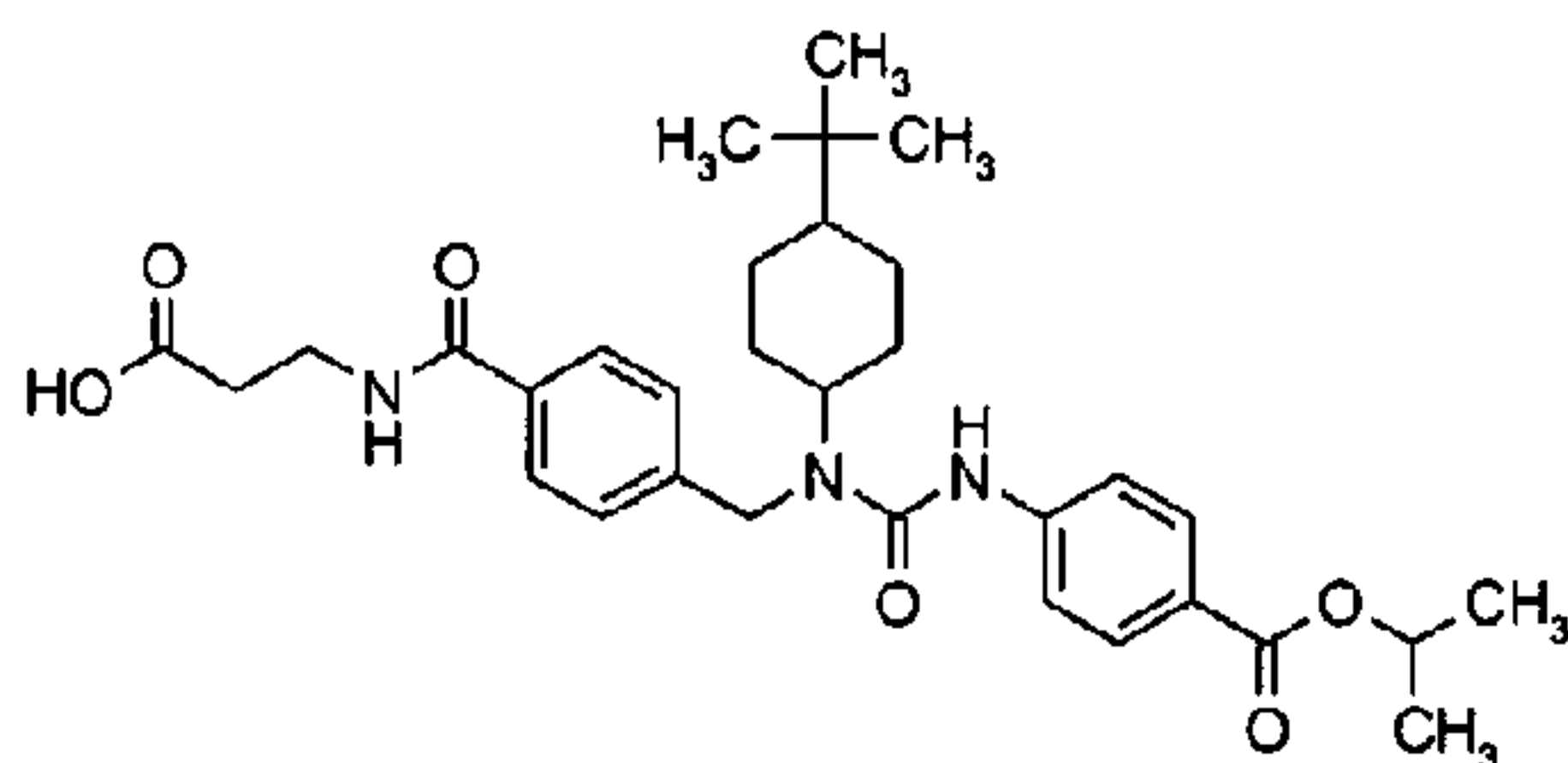
5

HPLC-MS (method B): m/z: 517, R_t = 7.29 min.

EXAMPLE 73 (general procedure (C))

4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid isopropyl ester

10



^1H NMR (DMSO- d_6): δ 8.70 (1H, s), 8.48 (1H, t), 7.83 (2H, d), 7.78 (2H, d), 7.63 (2H, d), 7.32 (2H, d).

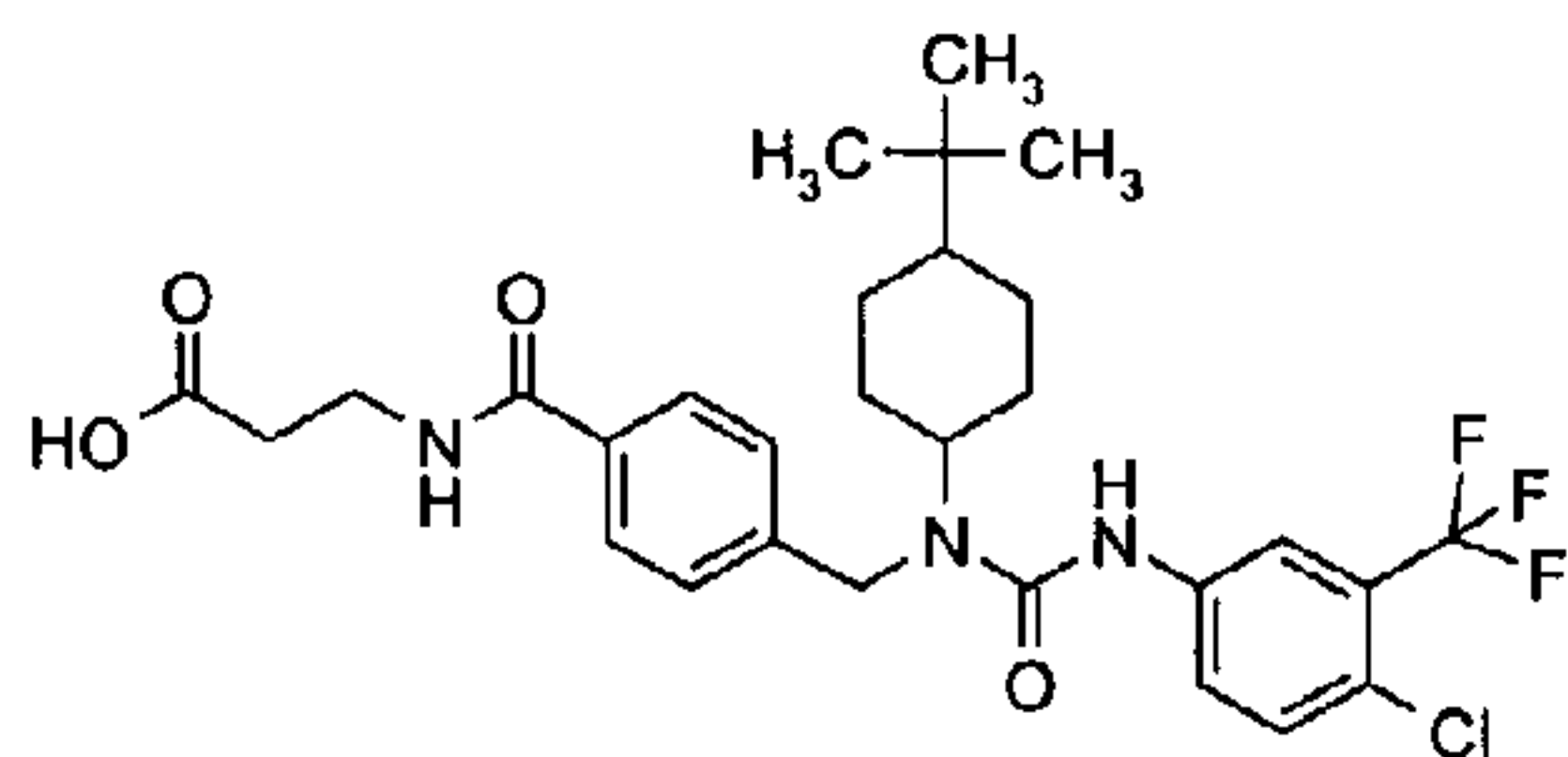
15

HPLC-MS (method B): m/z: 566, R_t = 7.69 min.

EXAMPLE 74 (general procedure (C))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid

20



^1H NMR ($\text{DMSO}-d_6$): δ 8.80 (1H, s), 8.48 (1H, t), 8.05 (1H, s), 7.82 (1H, d), 7.77 (1H, d), 7.58 (1H, d), 7.32 (1H, s).

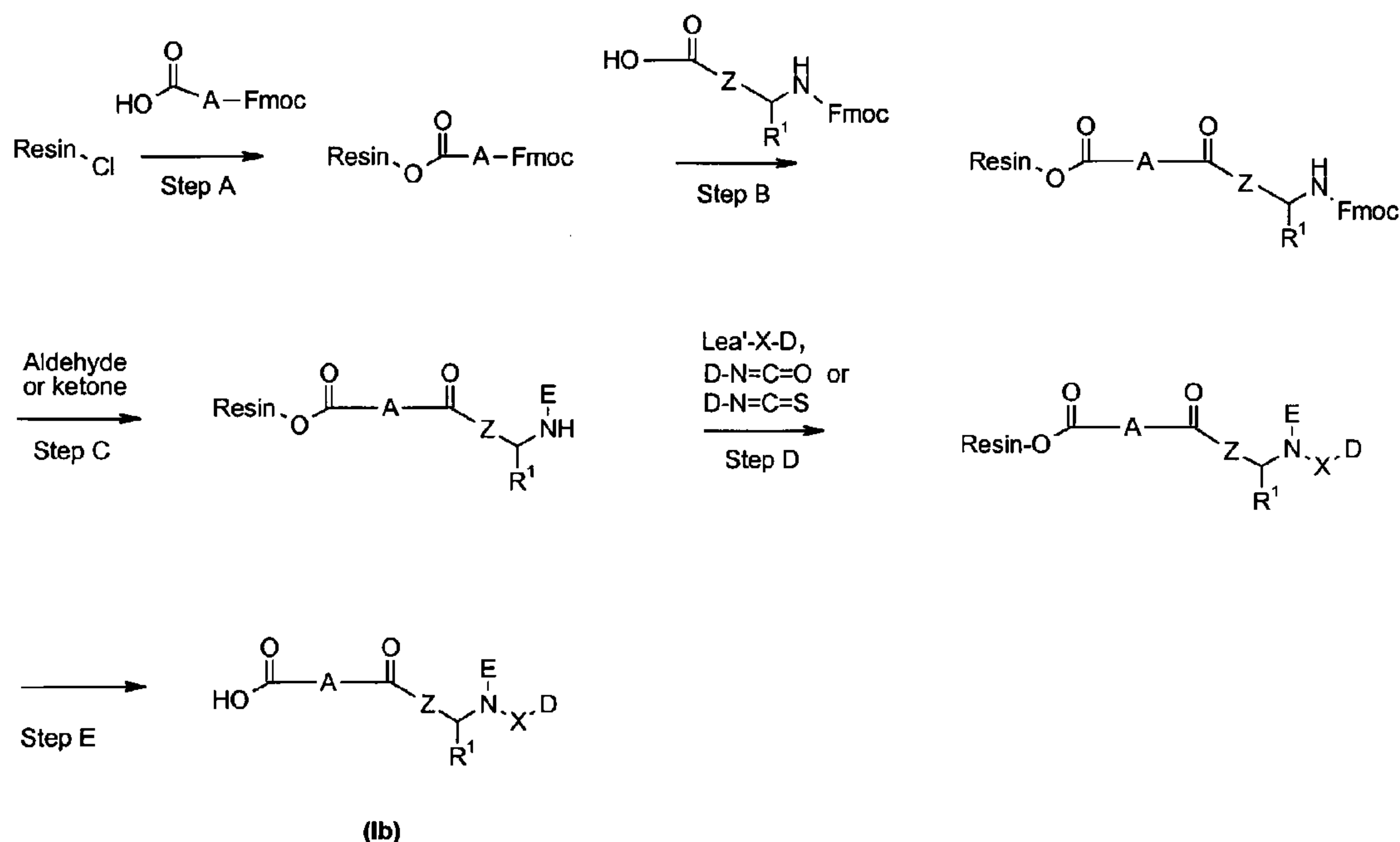
HPLC-MS (method B): m/z : 583, R_t = 8.03 min.

5

General procedure (D) for the solid phase synthesis of compounds of the general formula (Ib):

The compounds of the general formula (Ib) may also be prepared by the use of the following method:

10

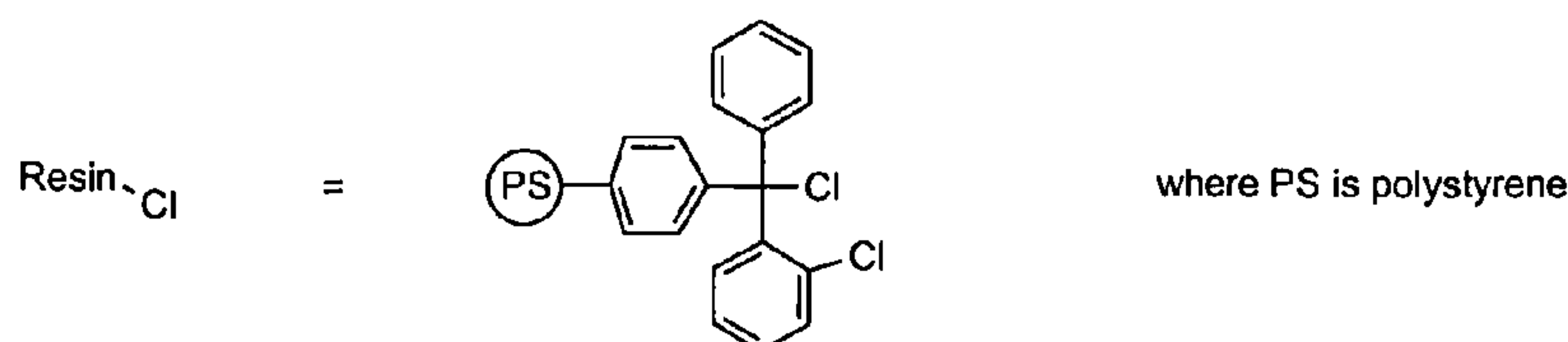


wherein

15 R^1 , A, Z, E and D are as defined for formula (I),

X is $-\text{S}(\text{O})_2-(\text{CH}_2)_r-$, $-\text{C}(\text{O})\text{NH}-$ or $-\text{C}(\text{S})\text{NH}-$, wherein r is as defined for formula (I),

Lea' represents a leaving group such as $-\text{OSu}$, $\text{Cl}-$, $\text{PhO}-$, or $4\text{-NO}_2\text{-PhO}-$, and

Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of an Fmoc amino acid in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotritylchloride.

Step B:

The Fmoc protecting group is removed using a solution of 20% piperidine in DMF, which is added to the resin and vortexed for 0.5 hours. After draining the resin is washed with DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF.

The acylation (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) is performed by adding an excess of Fmoc amino-benzoic acid in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of the these, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1H-9-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these, optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction.

Step C:

The Fmoc protecting group is removed eg using a solution of 20% piperidine in DMF. The reductive amination is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 167) and is performed by stirring resin bound amine with an excess of ketone or aldehyde at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of the above. As reducing agent sodium trisacetoxy borohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed several times with the solvent used during the reaction optionally in combination with water.

Step D:

The reaction is generally known (Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, 62, 6090-6092) and is usually performed by shaking resin bound amine with an excess of isocyanate or an equivalent such as a carbamate Lea'-X-D in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, DMSO or a mixture of two or more of the above and when using Lea'-X-D in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate. The reaction is performed between 20°C and 120°C, preferably between 20°C and 40°C. Excess reagent is filtered off and the resin is washed several times with the solvent used during the reaction.

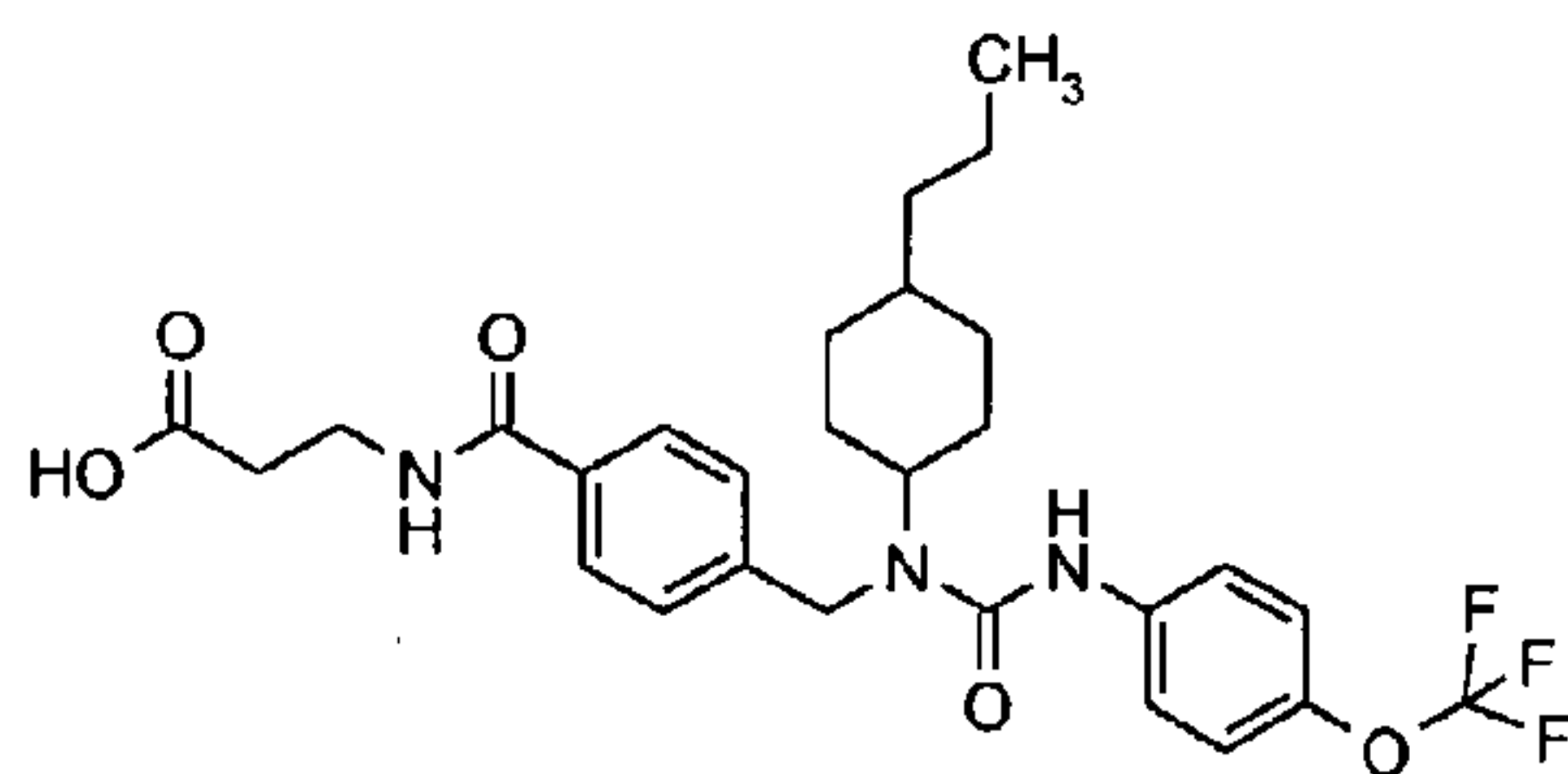
Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring the resin bound intermediate with a 5-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or more of the above. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with the solvent used during the reaction, optionally containing TFA. The product and washings are collected and the solvent is removed in vacuo.

A specific example illustrating the preparation of compounds of the general formula (Ib) according to the invention is provided below.

EXAMPLE 75 (general procedure (D))

3-{4-[1-(4-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

Step A: Resin bound Fmoc β-alanine

150 μmol Fmoc β-alanine was dissolved in a mixture of 250 μL dichloromethane, 250 μL DMF and 100 μL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane:methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}-propionic acid

To the above resin bound Fmoc β-alanine was added 500 μL of a 20% solution of piperidine in DMF. Upon shaking 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL). Then 200 μmol 4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoic acid (74.2 mg) dissolved in a mixture of 430 μL DMF and 70 μL diethylisopropylamine was added followed by 200 μmol bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500 μL DMF. The mixture was shaken for 4 hours at 25°C followed by filtration and washing of the resin with 3 x 1 mL DMF.

Step C: Resin bound 3-{4-[(4-propylcyclohexylamino)methyl]benzoylamino}propionic acid

The Fmoc protecting group was removed from the above resin bound 3-{4-[(9H-fluoren-9-ylmethoxycarbonylamino)methyl]benzoylamino}propionic acid using 500 μL of a 20% solution of piperidine in DMF. Upon shaking for 30 min, the resin was drained and washed with 1 mL DMF containing 1-hydroxybenzotriazole (50 mg/mL) and DMF (2 x 1 mL), 2 x 1 mL 1,2-dichloroethane and 20 μL acetic acid dissolved in 1 mL 1,2-dichloroethane.

The resulting resin bound 3-(4-aminomethylbenzoylamino)propionic acid was treated with 98 mg 4-propylcyclohexanone (700 μ mol) dissolved in 500 μ L 1,2-dichloroethane, 50 μ L acetic acid and a slurry of 148 mg NaBH(OAc)₃ (700 μ mol) in 1 mL 1,2-dichloroethane. Over night shaking at 25°C followed by filtration and washing with 2 x 1 mL dichloromethane, 2 x 1 mL CH₃OH:DMF 1:1 and 3 x 1 mL DMF afforded resin bound 3-{4-[(4-propylcyclohexylamino)-methyl]benzoylamino}propionic acid.

Step D: Resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

200 μ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500 μ L 1,2-dichloroethane was added to the above resin bound 3-{4-[(4-propylcyclohexylamino)methyl]benzoylamino}propionic acid. Shaking the mixture for 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF, 3 x 1 mL dichloromethane afforded the resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid.

Step E: 3-{4-[1-(4-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

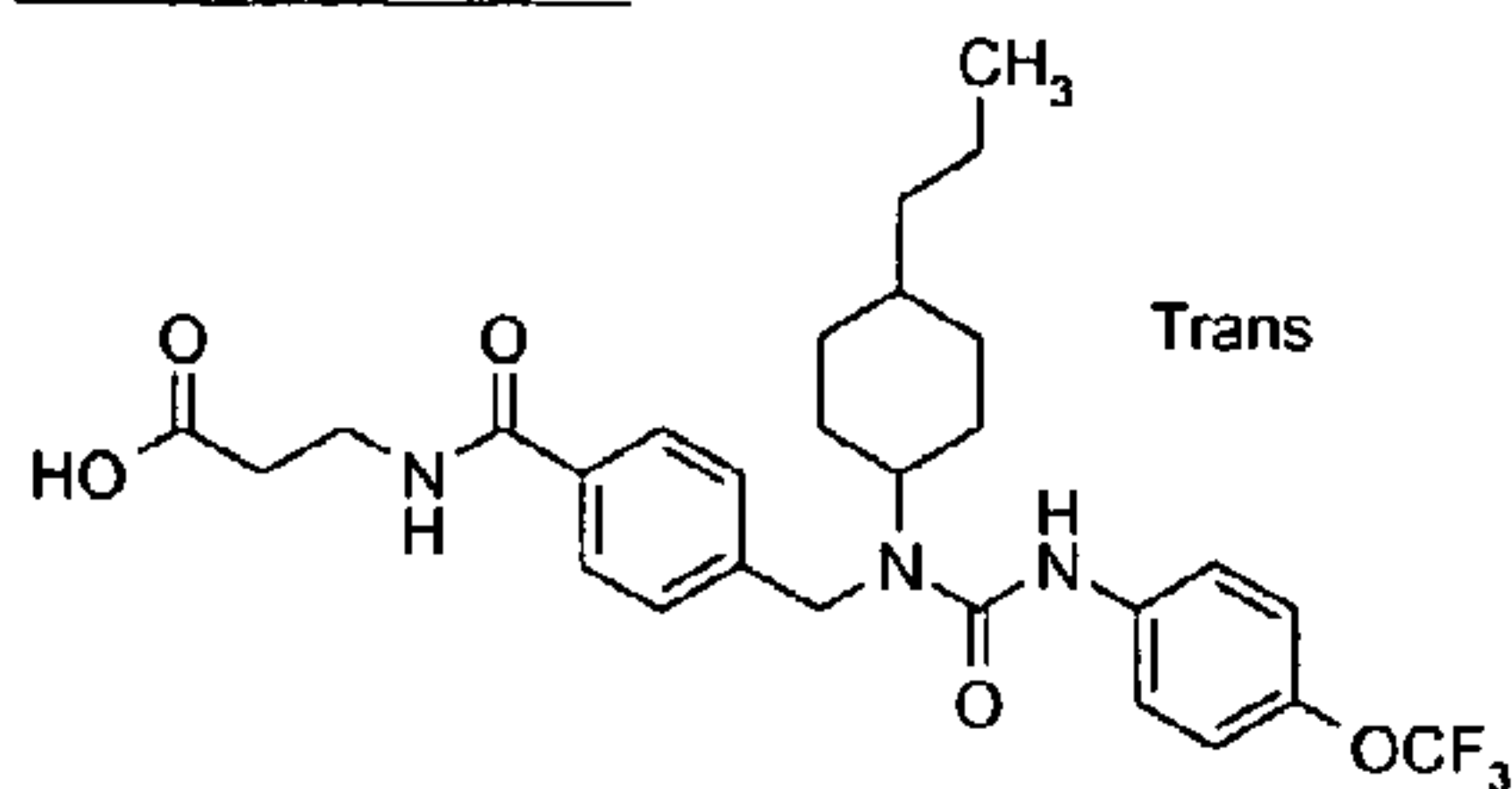
The above resin bound 3-{4-[1-(4-propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L CH₃CN and purified by preparative HPLC using a Supelcosil ABZ+ 25 cmx10 mm 5 μ column. The starting eluent composition was 5% CH₃CN in H₂O changing over 30 minutes to 90% CH₃CN in H₂O which was then kept constant for 5 minutes before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min. collecting one fraction per minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired products were combined and evaporated in vacuo to afford the title compound.

HPLC-MS (method B) (m/z = 550), (7.46, 7.58 min)

The HPLC purification allowed the separation of the *cis* and *trans* isomers of the title compound. The products were characterized by HPLC-MS and ¹H NMR.

EXAMPLE 76 (general procedure (D))

3-{4-[1-(4-*trans*-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



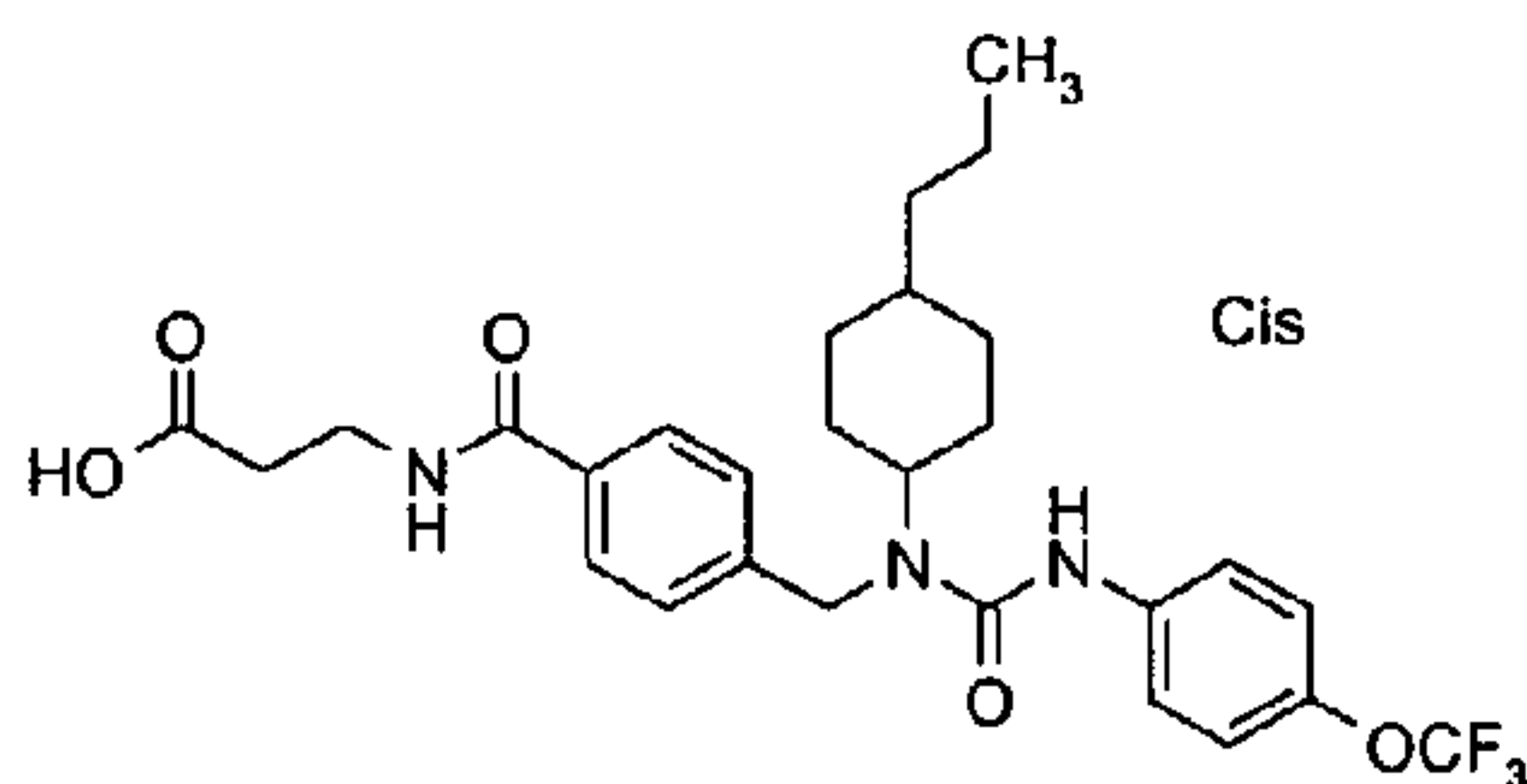
5

^1H NMR (400 MHz), (DMSO- d_6): δ 12.20 (s br, 1H); 8.55 (s, 1H); 8.50 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H), 4.60 (s, 2H); 4.10 (t, 1H), 3.40 (m, 2H); 2.45 (t, 2H); 0.70-1.80 ppm (m, 16H).

10 HPLC-MS (method B) (m/z = 550), (R_t = 7.46 min).

EXAMPLE 77 (general procedure (D))

3-{4-[1-(4-*cis*-Propylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



15

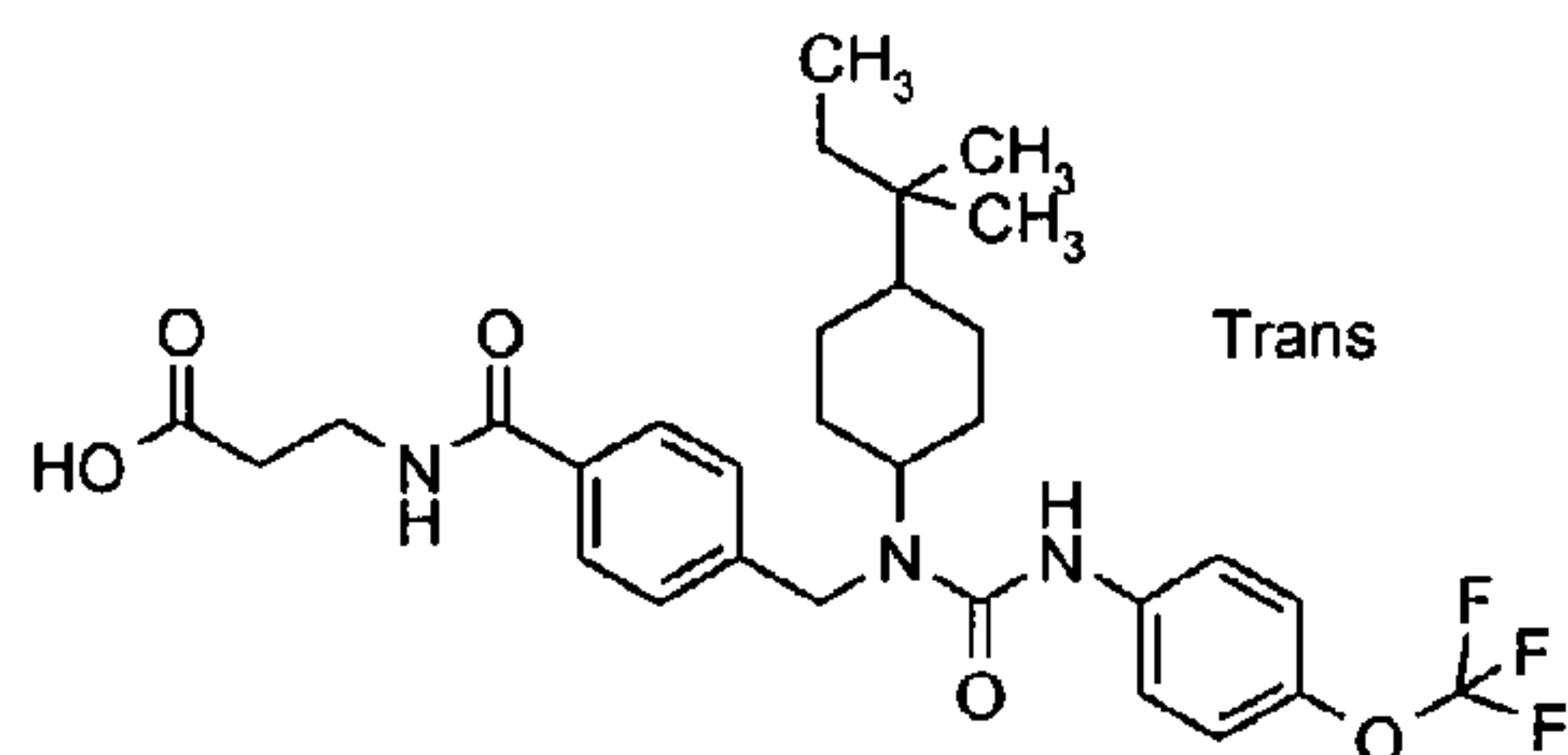
^1H NMR (400 MHz), (DMSO- d_6): δ 12.15 (s br, 1H); 8.55 (s, 1H); 8.50 (t, 1H); 7.80 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.25 (d, 2H), 4.65 (s, 2H); 4.10 (s br, 1H), 3.45 (m, 2H); 2.50 (2H); 1.15-1.65 ppm (m, 13H), 0.85 (t, 3H).

20

HPLC-MS (method B) (m/z = 550), (7.58 min).

EXAMPLE 78 (general procedure (D))

3-{4-[1-[4-*trans*-(1,1-Dimethylpropyl)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

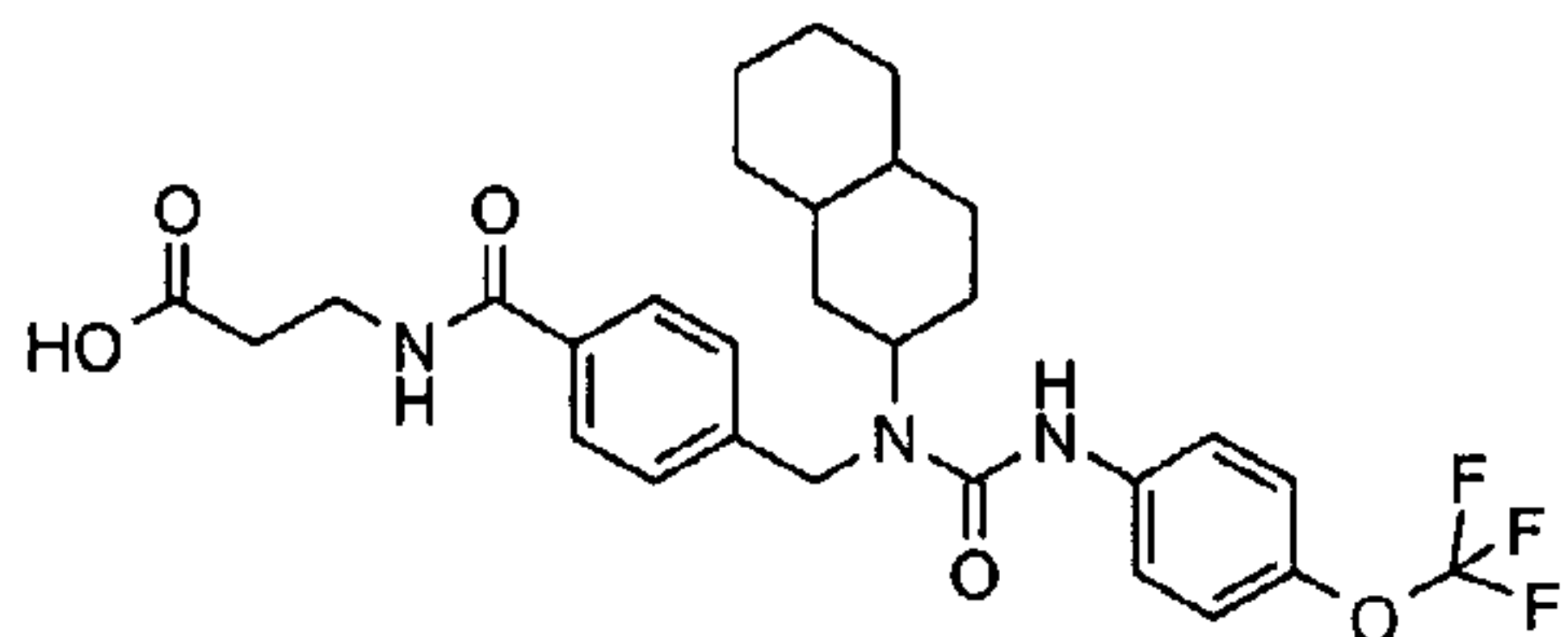


5

HPLC-MS (method B) (m/z = 578) (7.84 min, 7.94 min).

EXAMPLE 79 (general procedure (D))

3-{4-[1-(Decahydronaphthalen-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid

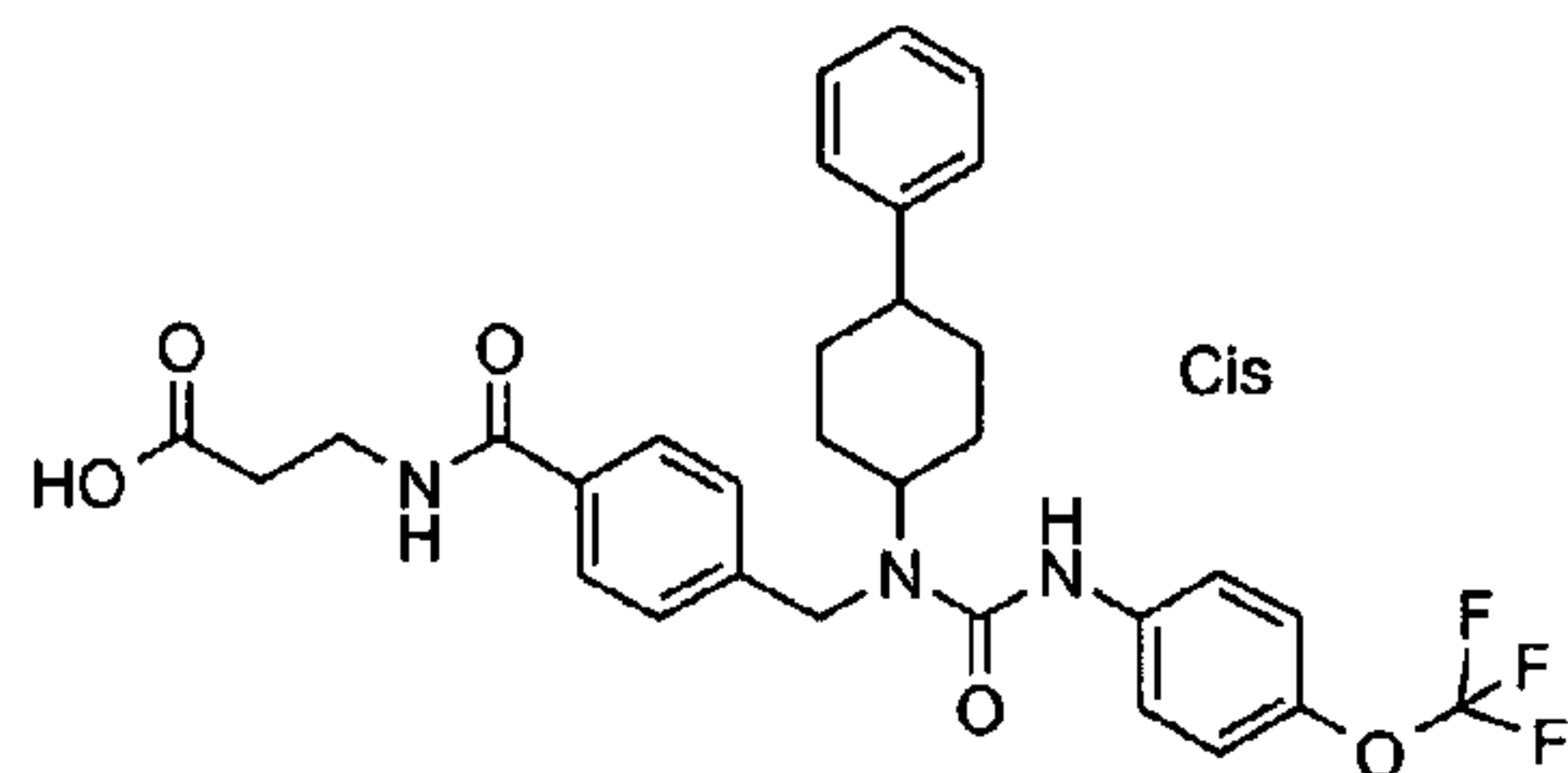


^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.50 (s, 1H); 8.47 (t, 1H); 7.76 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.22 (d, 2H); 4.60 (s, 2H); 4.30 (t, 1H), 3.45 (m, 2H); 2.50 (t, 2H); 1.85-0.70 (m).

15 HPLC-MS (method B) (m/z = 562) (7.48 min, 7.49 min).

EXAMPLE 80 (general procedure (D))

3-{4-[1-(4-*cis*-Phenylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

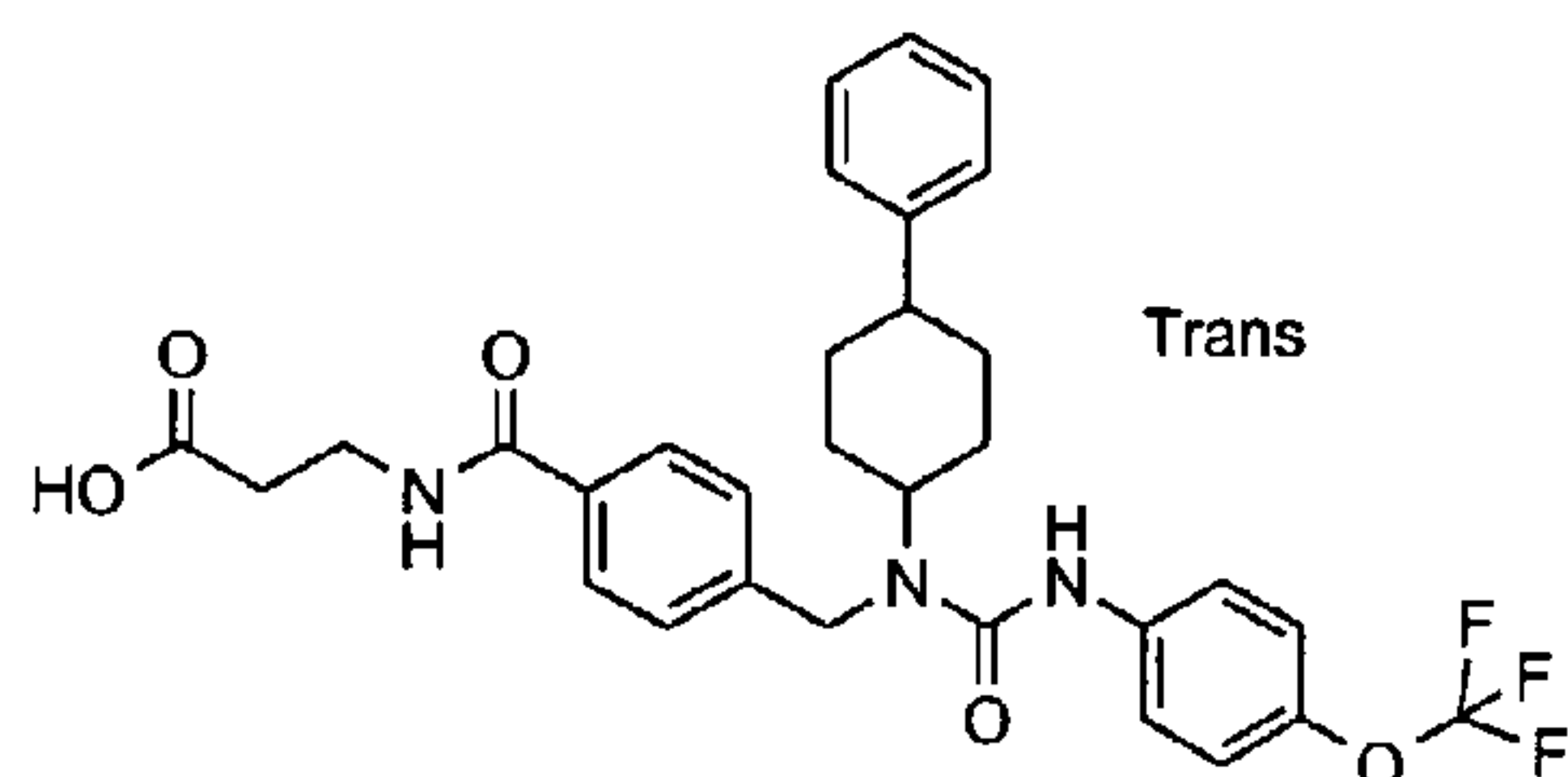


20

HPLC-MS (method B) (m/z = 584), (7.22 min, 7.33 min).

EXAMPLE 81 (general procedure (D))

3-{4-[1-(4-*trans*-Phenylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

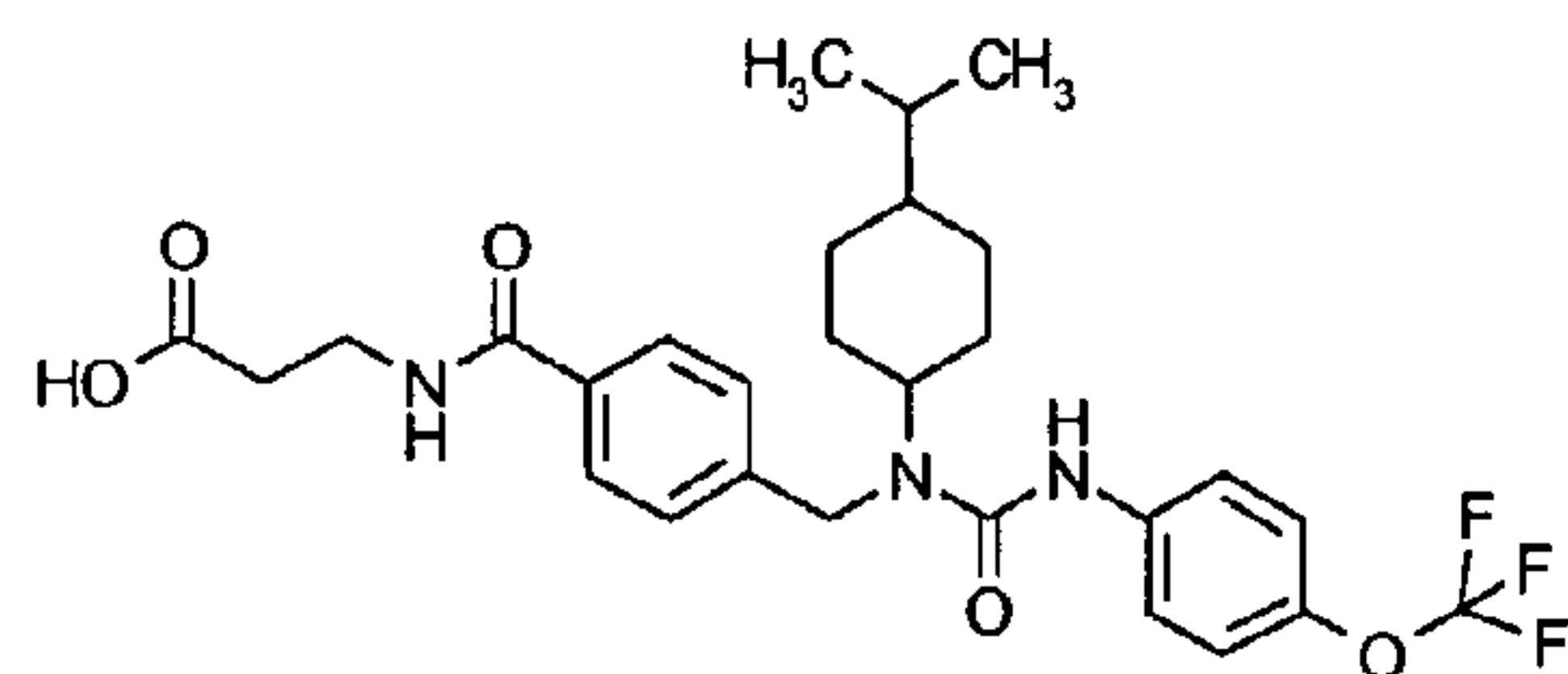


5

HPLC-MS (method B) (m/z = 584), (7.22 min, 7.33 min).

EXAMPLE 82 (general procedure (D))

10 3-{4-[1-(4-Isopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

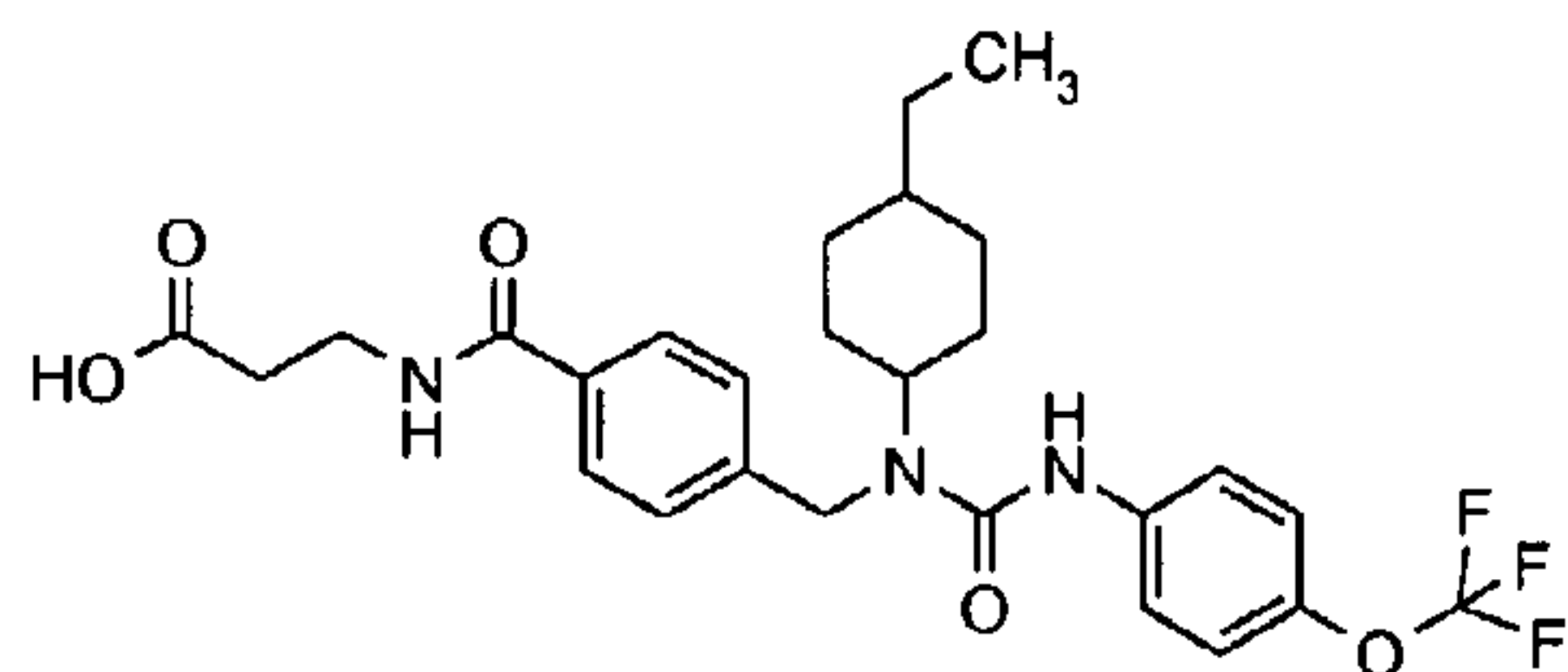


15 ^1H NMR (200 MHz), (DMSO- d_6): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.35 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.05-4.15 (m br, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 0.90-1.8 (m, 10H); 0.85 (d, 6H).

HPLC-MS (method B) (m/z = 550), (R_t = 7.38 min, 7.50 min)

EXAMPLE 83 (general procedure (D))

3-{4-[1-(4-Ethylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



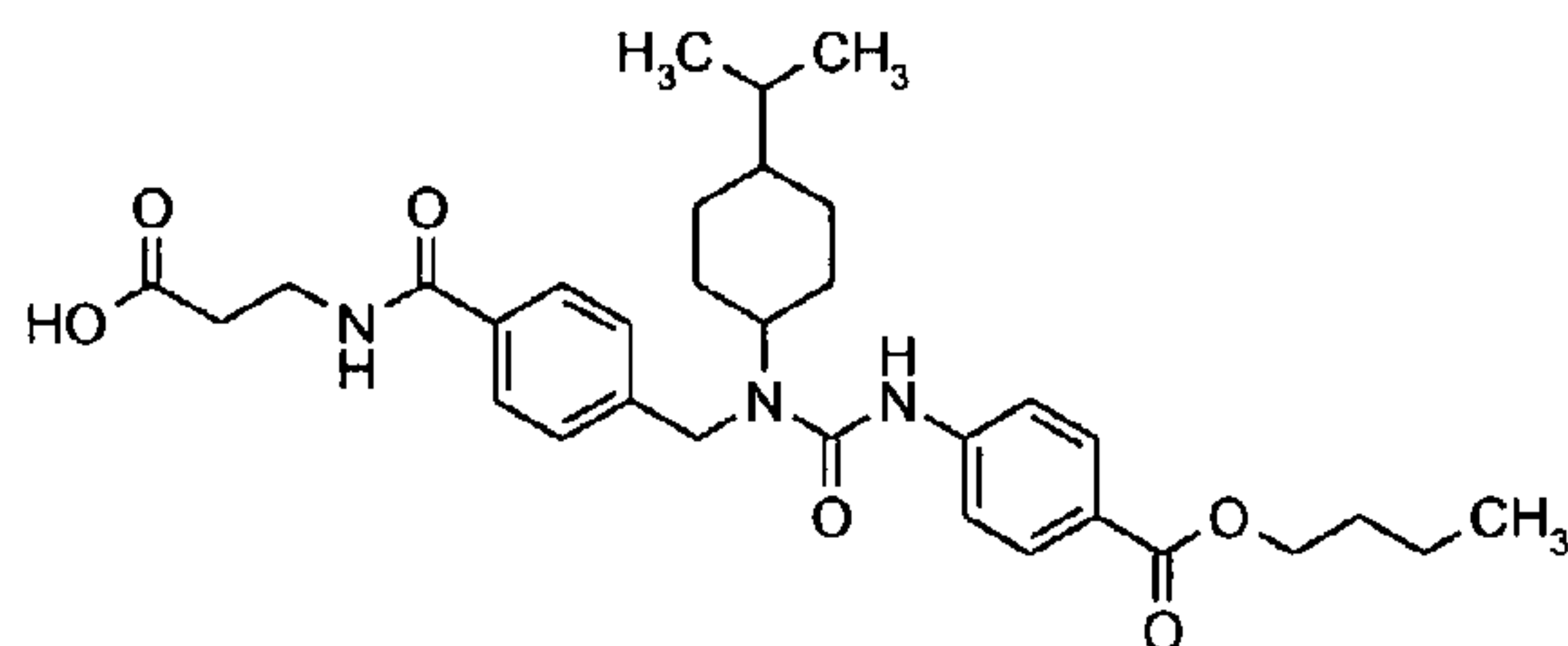
5

^1H NMR (300 MHz), (DMSO- d_6): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.25 (d, 2H); 4.60 (s, 2H); 4.05-4.15 (m br, 1H); 3.45 (m, 2H); 2.50 (t, 2H); 0.75-1.8 (m, 14H).

10 HPLC-MS (method B) (m/z = 536), (R_t = 7.59 min).

EXAMPLE 84 (general procedure (D))

4-[3-[4-(2-Carboxyethylcarbamoyl)benzyl]-3-(4-isopropylcyclohexyl)ureido]benzoic acid butyl ester

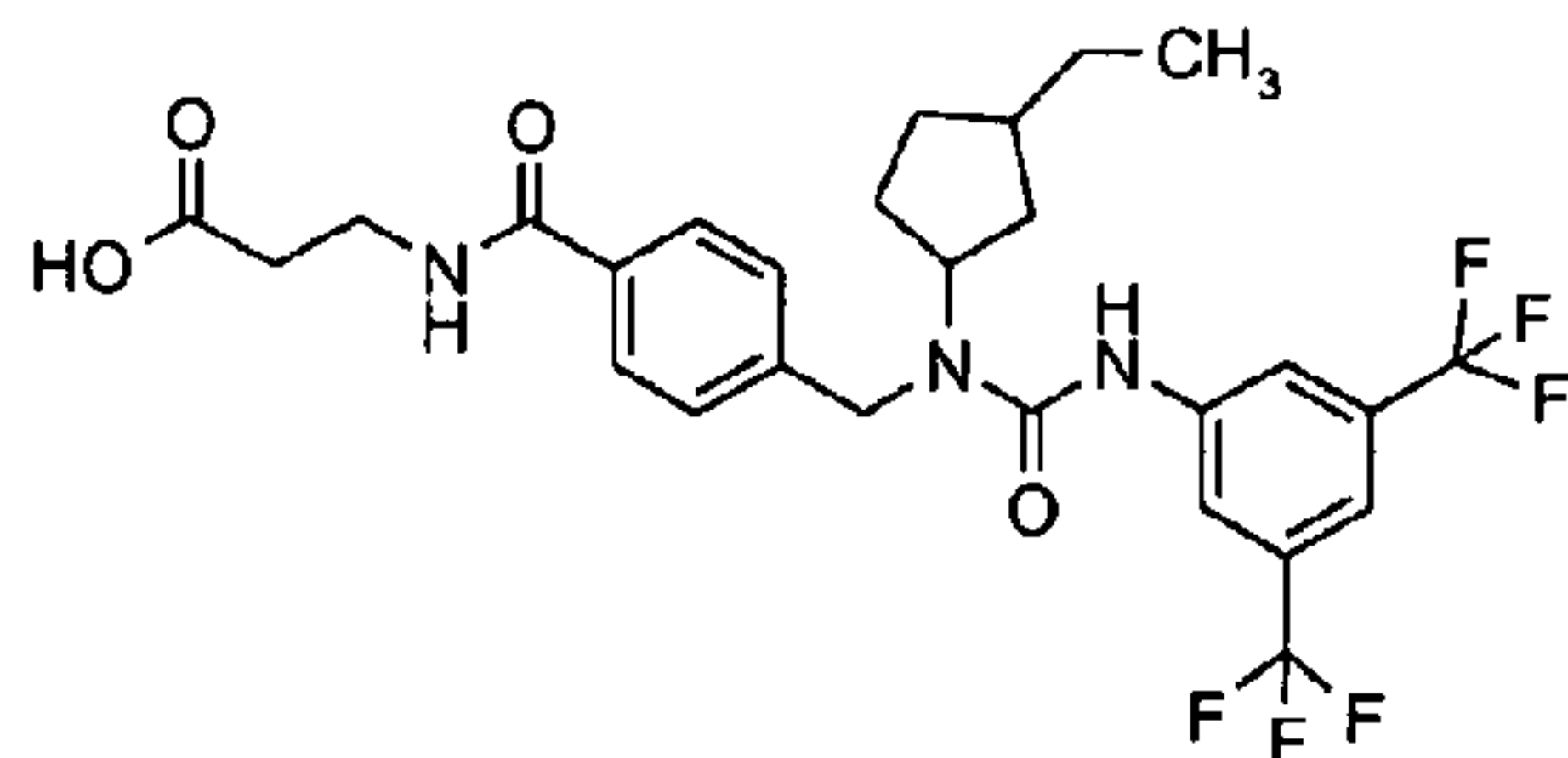


15

^1H NMR (DMSO- d_6): δ 8.70 (s, 1H); 8.45 (t, 1H); 7.83 (d, 2H); 7.78 (d, 2H); 7.60 (d, 2H); 7.34 (d, 2H); 4.67 (s, 2H); 4.24 (t, 2H); 4.14 (m, 1H); 0.96 (t, 3H); 0.85 (d, 6H).

EXAMPLE 85 (general procedure (D))

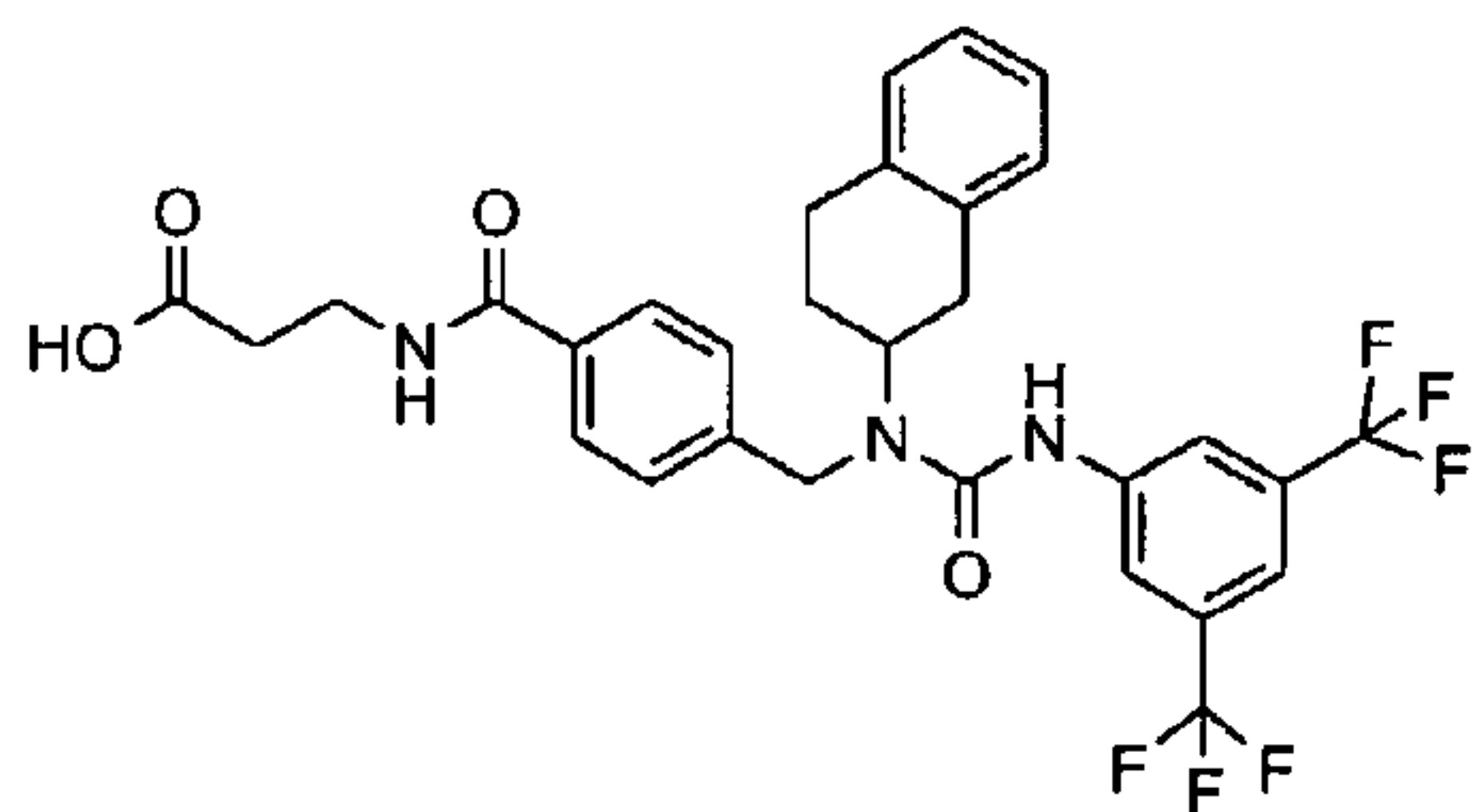
3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(3-ethylcyclopentyl)ureidomethyl]benzoylamino}-propionic acid



- 5 ^1H NMR (DMSO- d_6): δ 9.04 (s, 1H); 8.48 (t, 1H); 8.28 (s, 2H); 7.71 (d, 2H); 7.62 (s, 1H); 7.84 (d, 2H); 4.65 (s, 2H).

EXAMPLE 86 (general procedure (D))

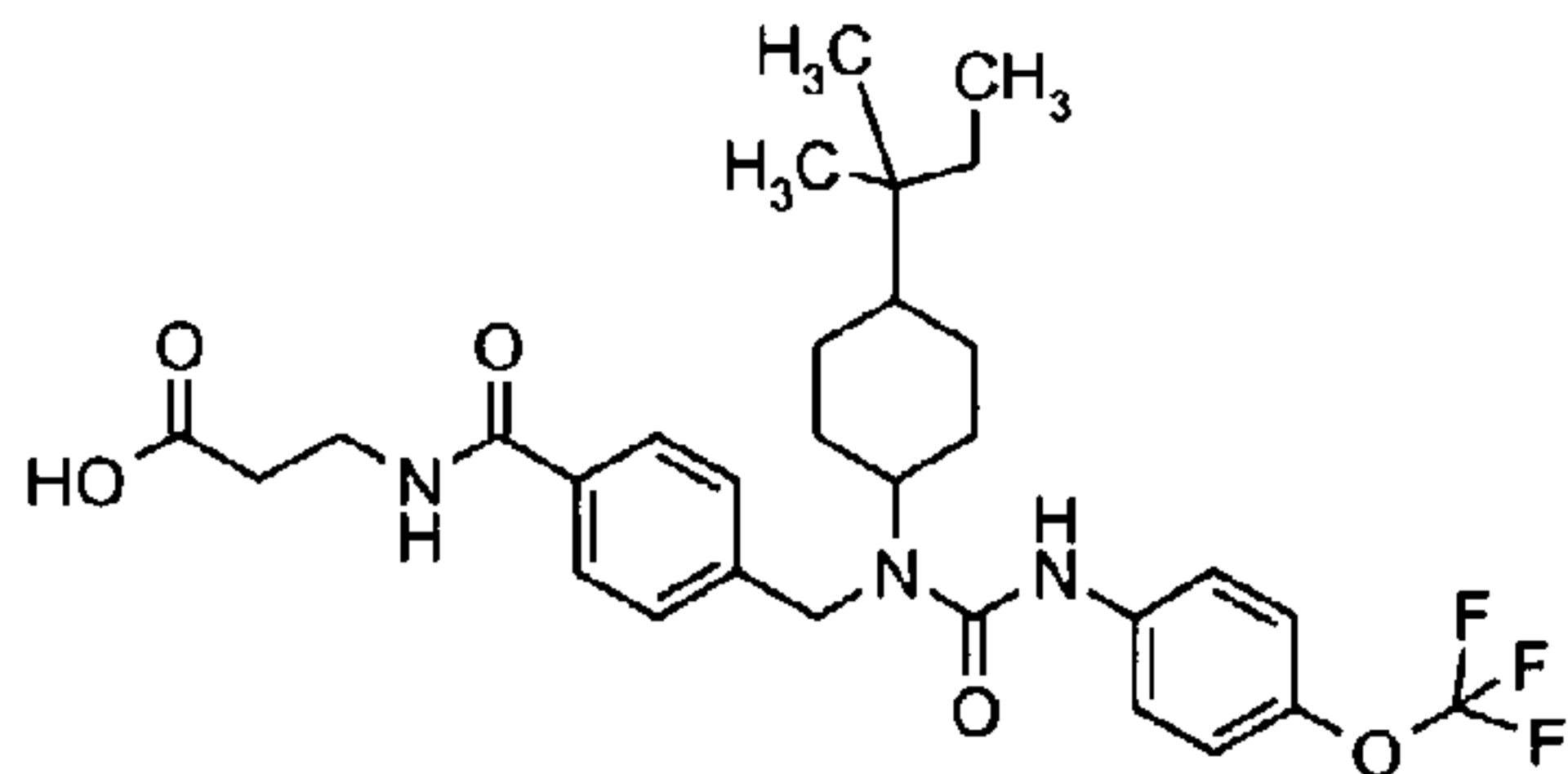
3-{4-[3-(3,5-Bis(trifluoromethyl)phenyl)-1-(1,2,3,4-tetrahydronaphthalen-2-yl)ureidomethyl]benzoylamino}propionic acid



- 15 ^1H NMR (DMSO- d_6): δ 9.20 (s, 1H); 8.50 (t, 1H); 8.82 (s, 2H); 7.81 (d, 2H); 7.62 (s, 1H); 7.42 (d, 2H); 7.10 (m, 4H); 4.75 (dd, 2H); 4.52 (m, 1H).

EXAMPLE 87 (general procedure (D))

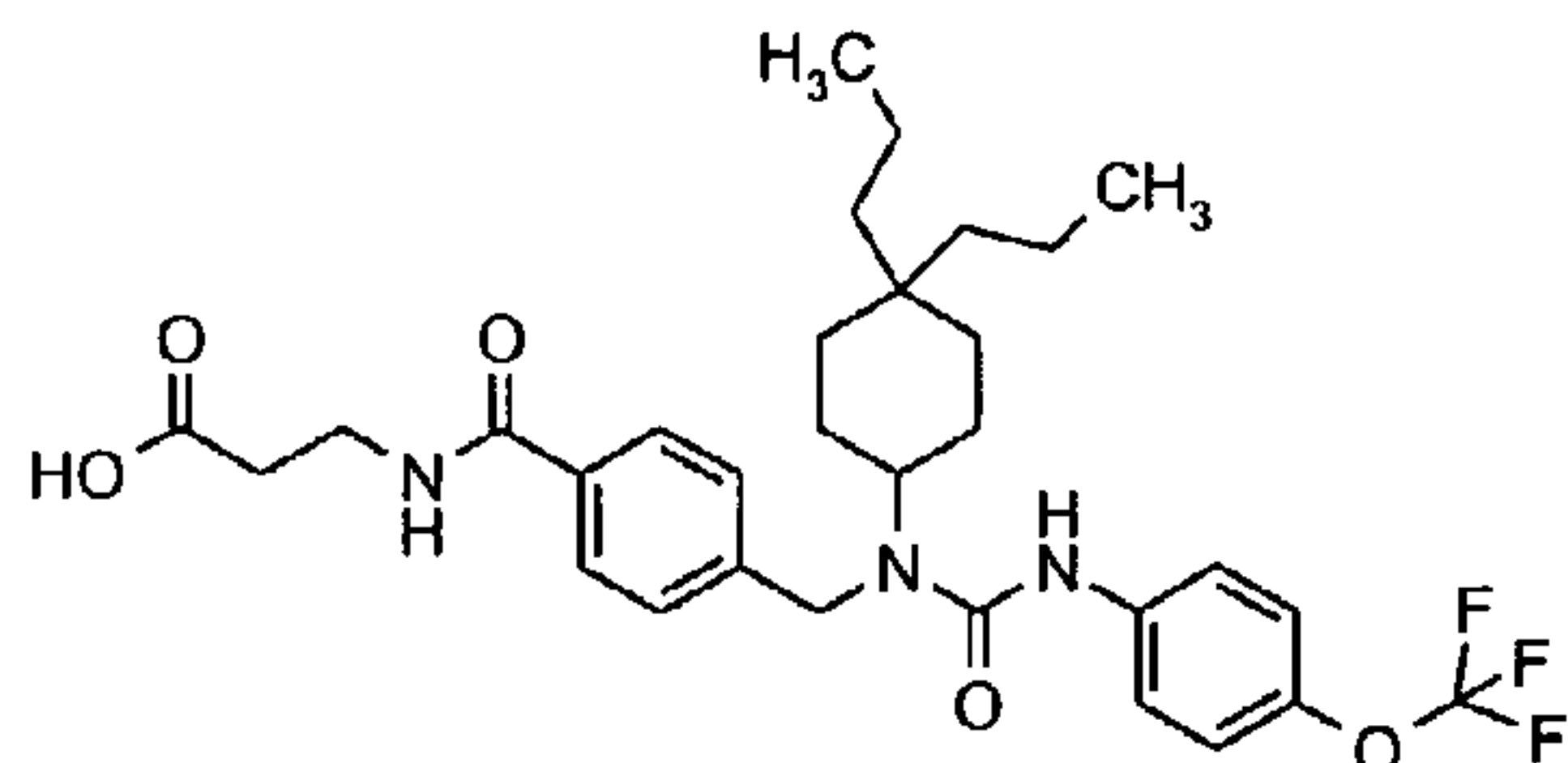
3-{4-[1-[4-(1,1-Dimethylpropyl)cyclohexyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



¹H NMR (400 MHz, DMSO-*d*₆): δ 12.05 (s br) 8.60 (s); 8.55 (s); 8.45 (t); 7.80 (d); 7.55 (d); 7.30 (d); 7.20 (d); 4.72 (s); 4.60 (s); 4.25 (t); 4.05 (t); 3.45 (q); 2.50 (t); 1.90-1.00 (m) 0.77 (s); 0.73 (s).

5 EXAMPLE 88 (general procedure (D))

3-{4-[1-(4,4-Dipropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



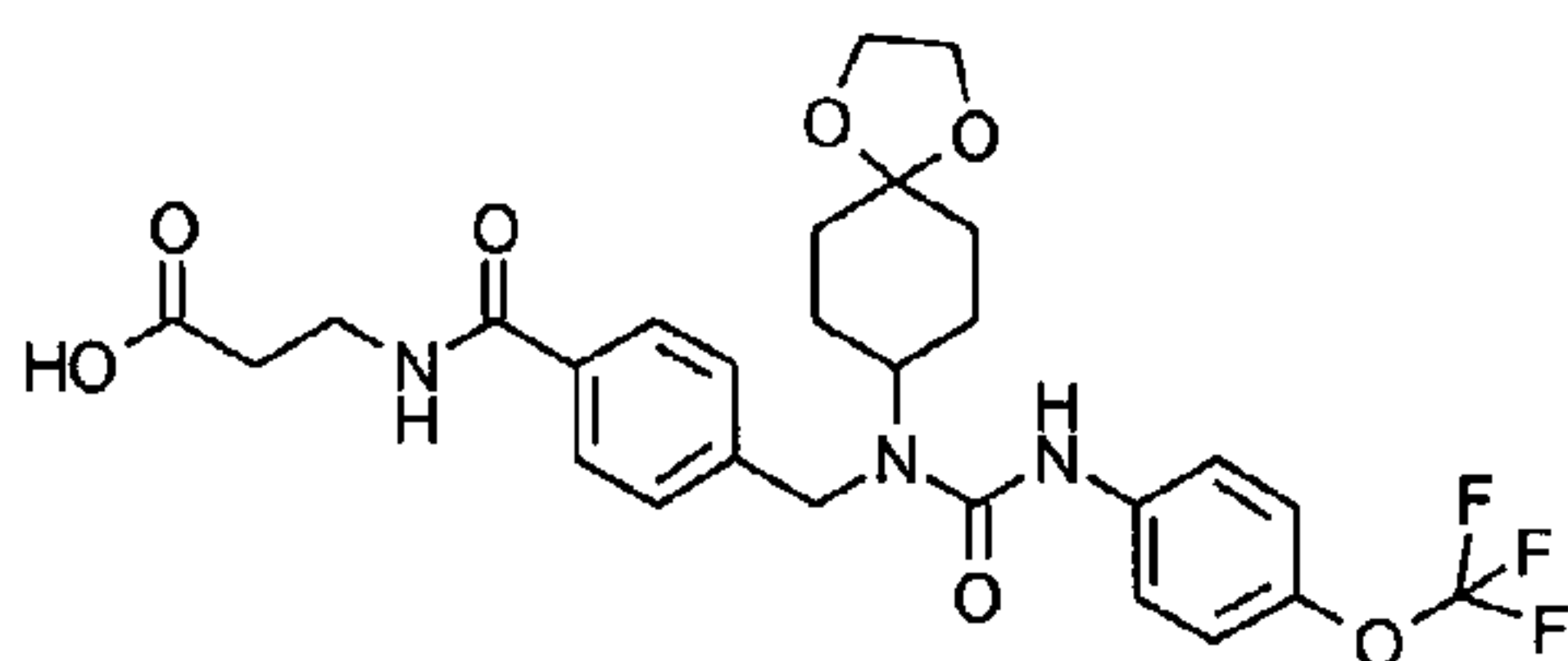
10 ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.55 (s, 1H); 8.45 (t, 1H); 7.75 (d, 2H); 7.52 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.62 (s, 2H); 4.05 (t, 1H); 3.45 (q, 2H); 2.45 (t, 2H); 1.70-0.70 (m, 22H).

HPLC-MS (method B): *m/z* = 592, *R*_t = 8.60 min.

15 The compounds of the invention can also be prepared by conventional solution phase synthesis methods as described below:

EXAMPLE 89

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl- amino}propionic acid



Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride was prepared from β-alanine
25 ethyl ester hydrochloride and 4-(*tert*-butoxycarbonylaminomethyl)benzoic acid by methods known to those skilled in the art.

3-{4-[(1,4-Dioxaspiro[4.5]dec-8-ylamino)methyl]benzoylamino}propionic acid ethyl ester

1.2 g Ethyl 3-(4-aminomethylbenzoylamino)propanoate hydrochloride (4.18 mmol) was mixed with 20 mL 1,2-dichloroethane and 6 mL saturated K_2CO_3 by vigorous stirring. The phases were separated and the aqueous phase was extracted with another 20 mL 1,2-dichloroethane. 240 μ L HOAc was added to the combined 1,2-dichloroethane phase followed by 0.691 g 1,4-dioxaspiro[4.5]decan-8-one (4.42 mmol). 1.272 g $NaBH(OAc)_3$ (6 mmol) was added and the reaction was stirred for 16 hours at 25°C. The reaction volume was reduced on a rotary evaporator to about 20 mL and then poured into a mixture of 60 mL H_2O and 10 mL sat. K_2CO_3 . The phases were separated and the aqueous phase was extracted twice with 40 mL 1,2-dichloroethane. The combined 1,2-dichloroethane fractions were dried over $MgSO_4$ and evaporated to afford the title compound. The crude product was used in the next step without further purification.

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester

0.312 g 4-Trifluoromethoxyphenylisocyanate dissolved in 1 mL acetonitrile was added to 0.5 g of the above 3-{4-[(1,4-dioxaspiro[4.5]dec-8-ylamino)methyl]benzoylamino}propionic acid ethyl ester dissolved in 5 mL acetonitrile and was allowed to react at 25°C. The product precipitated after 1 hour and was collected by filtration.

^1H NMR (400 MHz), ($DMSO-d_6$): δ 8.55 (s, 1H); 8.50 (t, 1H); 7.75 (d, 2H); 7.50 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.20 (s br, 1H); 4.05 (q, 2H); 3.75 (s, 4H); 3.30 (m, 2H); 2.60 (t, 2H); 1.60-1.70 (m, 8H); 1.15 (t, 3H)

3-{4-[1-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid

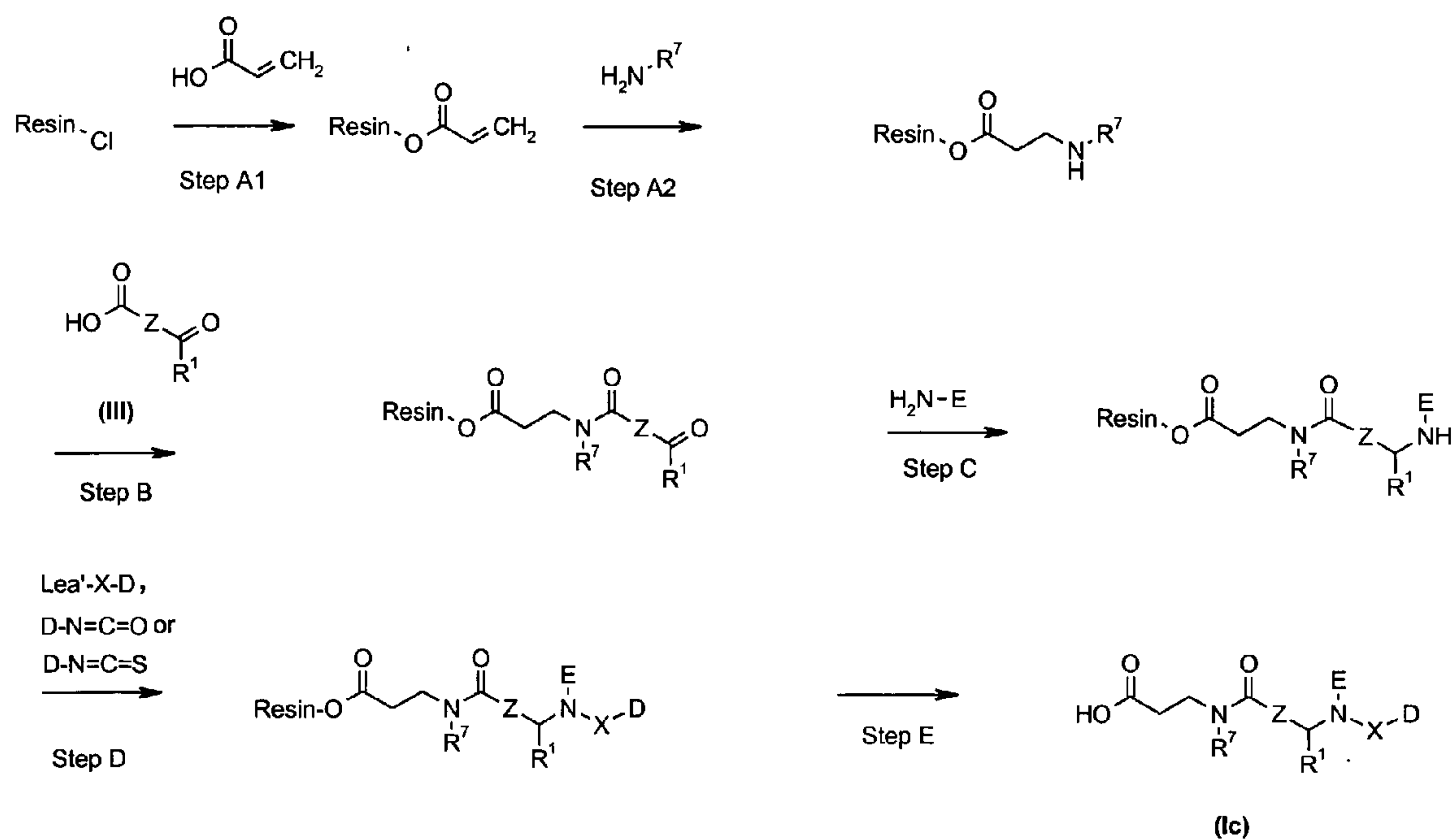
180 mg LiOH dissolved in 2.2 mL H_2O was added to the entire yield of the above 3-{4-[1-(1,4-dioxaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester dissolved in 22 mL abs. EtOH. After 1 hour at 25°C the solvent was evaporated and 10 mL H_2O followed by 500 mg citric acid dissolved in 20 mL H_2O was added to the residue affording a pH of 4-5. The resulting product was a mixture of the acid and its lithium salt.

^1H NMR (400 MHz), ($\text{DMSO}-d_6+\text{TFA}$): δ 8.60 (s, 1H); 8.50 (t, 1H); 7.80 (d, 2H); 7.55 (d, 2H); 7.30 (d, 2H); 7.20 (d, 2H); 4.60 (s, 2H); 4.20 (s br, 1H); 3.80 (s, 4H); 3.45 (m, 2H); 2.50 (t, 2H); 1.55-1.75 (m, 8H).

5 HPLC-MS (method B) ($m/z = 566 \text{ M}+1$), ($R_t = 6.10 \text{ min}$).

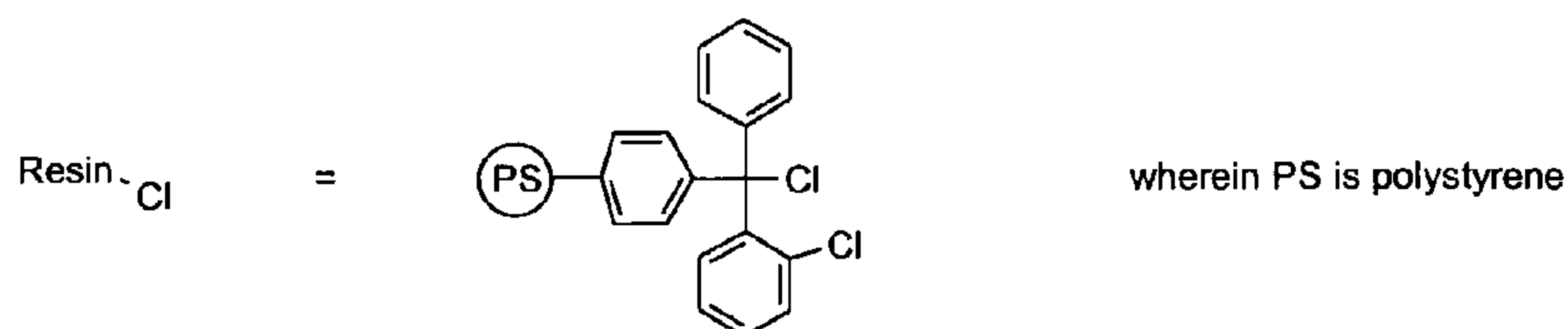
General procedure (E) for the solid phase synthesis of compounds of the general formula (Ic):

10 Compounds of the general formula (Ic) according to the invention can be synthesized on solid support using a procedure comprising attachment of acrylic acid to a polystyrene 2-chlorotriptylchloride resin followed by a Michael addition of $\text{R}^7\text{-NH}_2$. Acylation followed by reductive amination and urea formation as described above affords the desired compounds:



15

wherein



Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy,

R¹, E and D are as defined for formula (I),

R⁷ is C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl, and

X is -S(O)₂-(CH₂)_r-, -C(O)NH- or -C(S)NH-, wherein r is as defined for formula (I),

Step A1:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of acrylic acid in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriylchloride.

Step A2:

The reaction is known (Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, 63, 703-718) and is performed by shaking the resin bound acrylic acid with an excess of a primary amine in a solvent such as DMSO, DMF, NMP, THF, methanol, ethanol, dichloromethane, 1,2-dichloroethane or a mixture of two or more of these. The reaction is carried out between 20°C and 120°C, preferably at 25°C. Excess amine is filtered off and the resin is washed several times with the solvent used during the reaction.

Step B:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 78) and is performed by adding an excess of acid (III) in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of the above, optionally in the presence of a base such as *N*-methylmorpholine, triethylamine, diisopropylethylamine, dicyclohexylmethylamine or another tertiary amine, followed by a coupling reagent such as dicyclohexylcarbodiimide, diisopropylcarbodiimide, 1,1'-carbonyldiimidazole, 2-(1H-

9-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate or bromo-tris-pyrrolidinophosphonium hexafluorophosphate in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, acetonitrile, DMSO or a mixture of two or more of these optionally in the presence of a side reaction inhibitor such as 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine, *N*-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazol. The reaction is performed between 20°C and 40°C, preferably at 25°C. Excess of reagents is filtered off and the resin is washed several times with the solvent used in the reaction.

Step C:

The reaction is generally known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 133) and is generally performed by stirring the resin bound aldehyde or ketone obtained in step B with an excess of amine at low pH (by addition of an acid, such as acetic acid or formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. A reducing agent such as sodium cyanoborohydride can be used. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess of reagents is filtered off and the resin is washed several times with the solvent used in the reaction optionally in combination with water.

Step D:

The reaction is generally known (Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, 62, 6090-6092) and is usually performed by shaking resin bound amine obtained in step C with an excess of an isocyanate or isothiocyanate or alternatively Lea'-X-D in a solvent such as DMF, NMP, THF, dichloromethane, 1,2-dichloroethane, DMSO or a mixture of two or more of the above and when using Lea'-X-D in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine or potassium carbonate. The reaction is performed between 20°C and 120°C, preferably between 20°C and 40°C. Excess of reagent is filtered off and the resin is washed several times with the solvent used in the reaction.

Step E:

The reaction is known (The combinatorial index, Ed. Bunin B. A., 1998, Academic press, p. 21) and is generally performed by stirring the resin bound intermediate obtained in step D with a 5-95% solution of TFA. The final cleavage is carried out in a solvent such as THF, dichloromethane, 1,2-dichloroethane, 1,3-dichloropropane, toluene or a mixture of two or

more of these. The reaction is performed between 0°C and 80°C, preferably between 20°C and 40°C. When the reaction is complete the product is removed by filtration. The resin is successively washed with the solvent used in the reaction, optionally containing TFA. The product and washings are collected. The solvent is removed in vacuo.

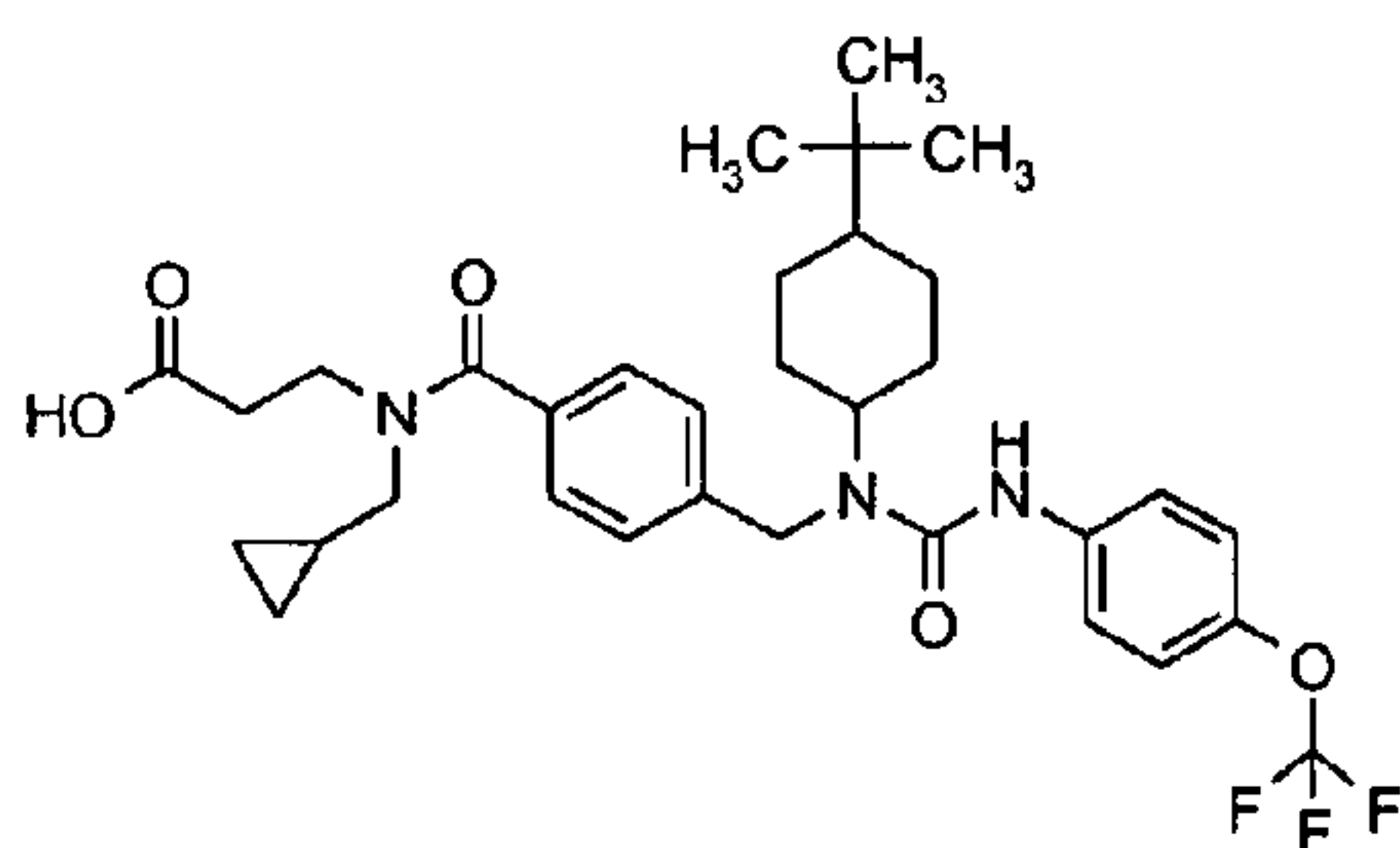
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The following examples were prepared according to general procedure (E).

EXAMPLE 90 (general procedure (E))

3-({4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-
cyclopropylmethyl)aminopropionic acid

10



Step A1: Resin bound acrylic acid

150 µmol acrylic acid was dissolved in a mixture of 500 µL dichloromethane and 100 µL diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotrityl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol: diisopropylethylamine 17:2:1 and 2 x 1 mL DMSO.

15

Step A2: Resin bound *N*-(cyclopropylmethyl)-3-aminopropionic acid

The above resin bound acrylic acid (50 mg) was treated with 300 µmol cyclopropylmethyl amine (21.3 mg) in 300 µL DMSO for 72 hours at 25°C. The excess reagent was filtered off and the resin was washed with 3 x 1 mL DMSO and 3 x 1 mL DMF.

20

Step B: Resin bound 3-[cyclopropylmethyl-(4-formylbenzoyl)amino]propionic acid

To the above resin bound *N*-(cyclopropylmethyl) 3-aminopropionic acid (50 mg) was added 200 µmol 4-formylbenzoic acid (30 mg) dissolved in a mixture of 430 µL DMF and 70 µL diisopropylethylamine followed by 200 µmol bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP, 93 mg) dissolved in 500 µL DMF. The mixture was shaken at 25°C for 4

25

hours followed by filtration and washing of the resin with 3 x 1 mL DMF and 1 mL trimethylorthoformate.

Step C: Resin bound 3-({4-[(4-*tert*-butylcyclohexylamino)methyl]benzoyl}cyclopropylmethyl-amino)propionic acid

5 The above resin bound 3-[cyclopropylmethyl-(4-formylbenzoyl)amino]propionic acid (50 mg) was treated with 1 mL 0.5 M (0.5 mmol, 77.5 mg) 4-*tert*-butylcyclohexylamine solution in DMF:trimethylorthoformate 1:1, 100 μ L glacial acetic acid and sodium cyanoborohydride (750 μ mol, 48 mg) suspended in 0.5 mL DMF:trimethylorthoformate 1:1. Overnight shaking
10 at 25°C followed by filtration and washing with 2 x 1 mL 20% H₂O in DMF, 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

Step D: Resin bound 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoyl}cyclopropylmethyl)aminopropionic acid

15 200 μ mol 4-trifluoromethoxyphenylisocyanate dissolved in 500 μ L dichloromethane was added to the above resin bound 3-({4-[(4-*tert*-butylcyclohexylamino)methyl]benzoyl}-cyclopropylmethyl)aminopropionic acid (50 mg). Shaking the mixture 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

20

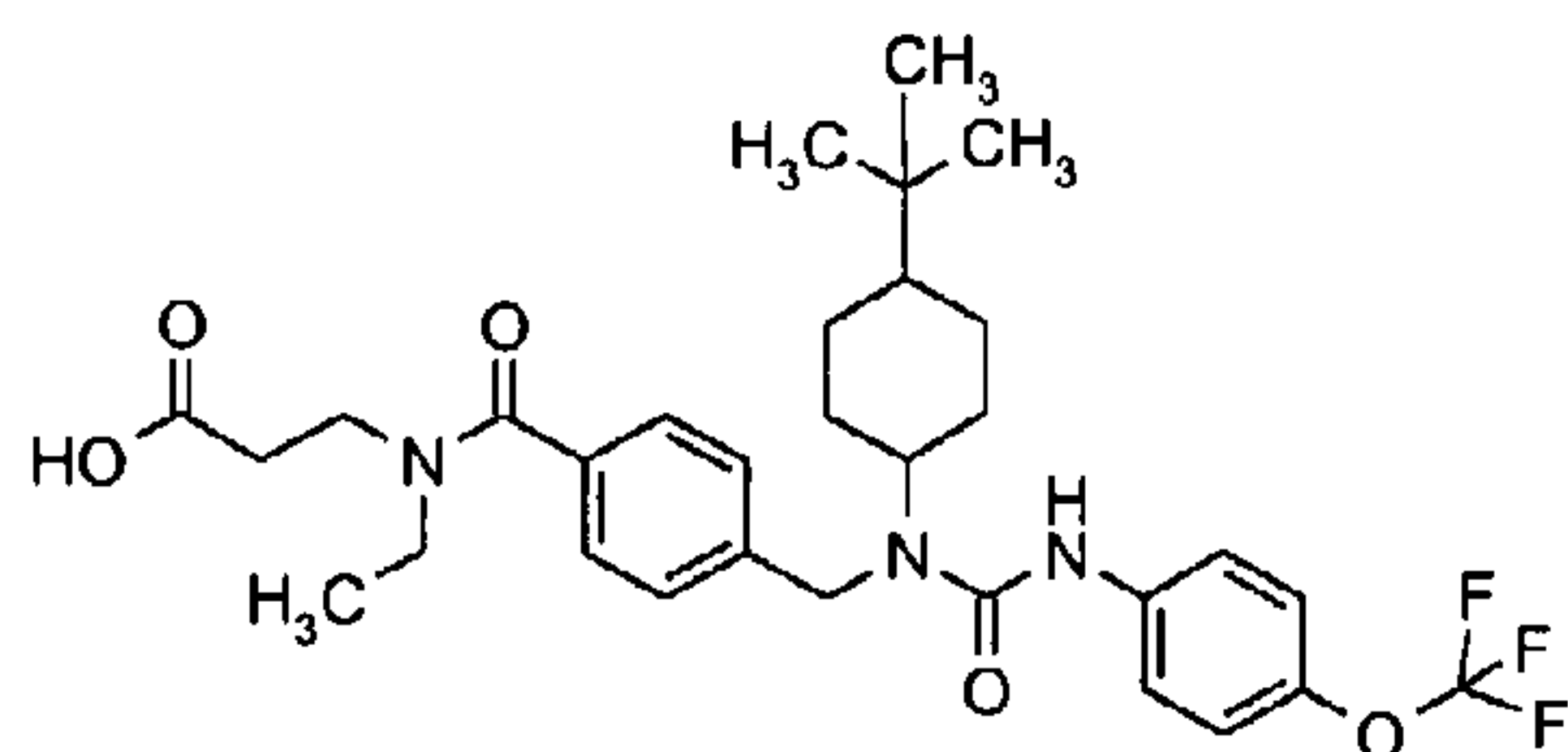
Step E: 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-cyclopropylmethyl)aminopropionic acid

The above resin bound 3-({4-[1-(4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoyl}cyclopropylmethyl)aminopropionic acid (50 mg) was treated with 1 mL 5%
25 TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 μ L DMSO + 500 μ L acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5 μ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was
30 then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per minute. The process was monitored using an UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

35 The product was characterized by HPLC-MS (Method B): R_t = 7.91 min, m/z = 618 (M+1).

EXAMPLE 91 (general procedure (E))

3-({4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}ethyl-amino)propionic acid

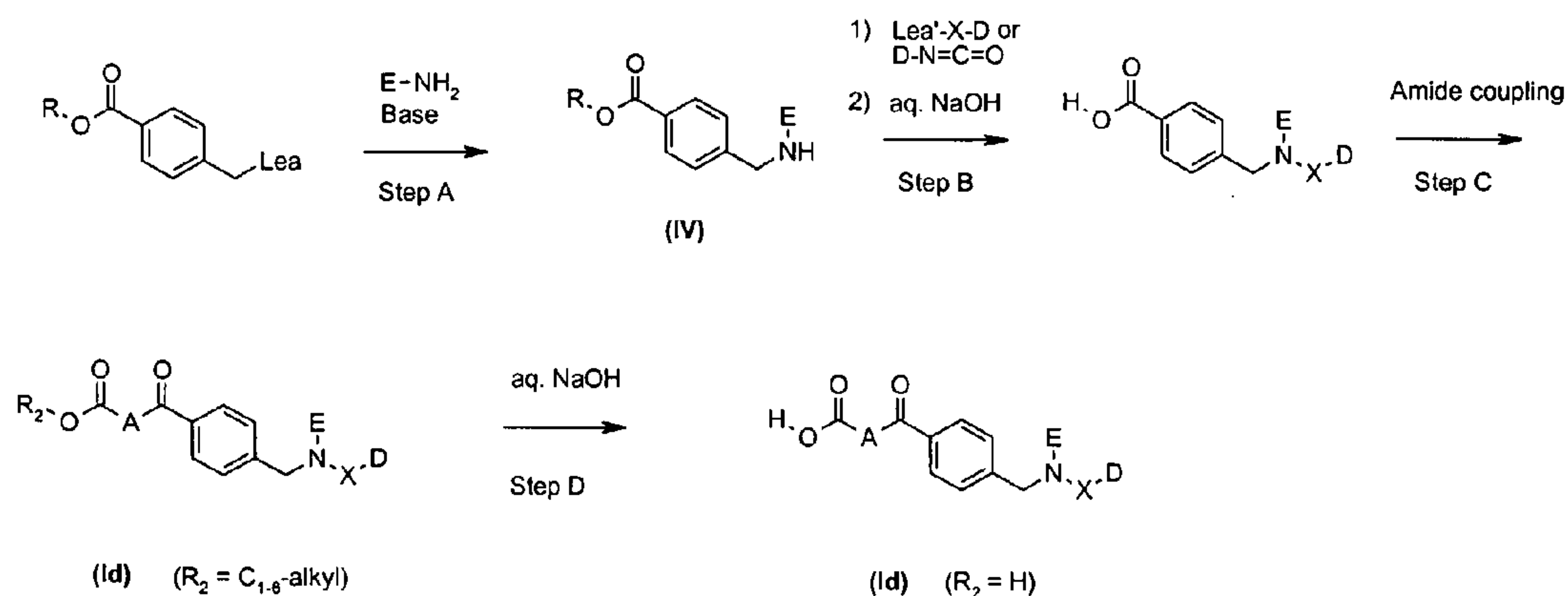


5

The product was characterized by HPLC-MS (Method B): $R_t = 7.94$ min, $m/z = 592$ ($M+1$).

The compounds of the invention can also be prepared by conventional solution phase synthesis methods as the following general method describes.

10

General procedure (F) for the solution phase synthesis of compounds of general formula (Id):

15

wherein R is C_{1-6} -alkyl,

A, X, D, and E are as defined in general formula (I),

Lea is a leaving group such as chloro, bromo, iodo, mesyl, or tosyl, and

Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

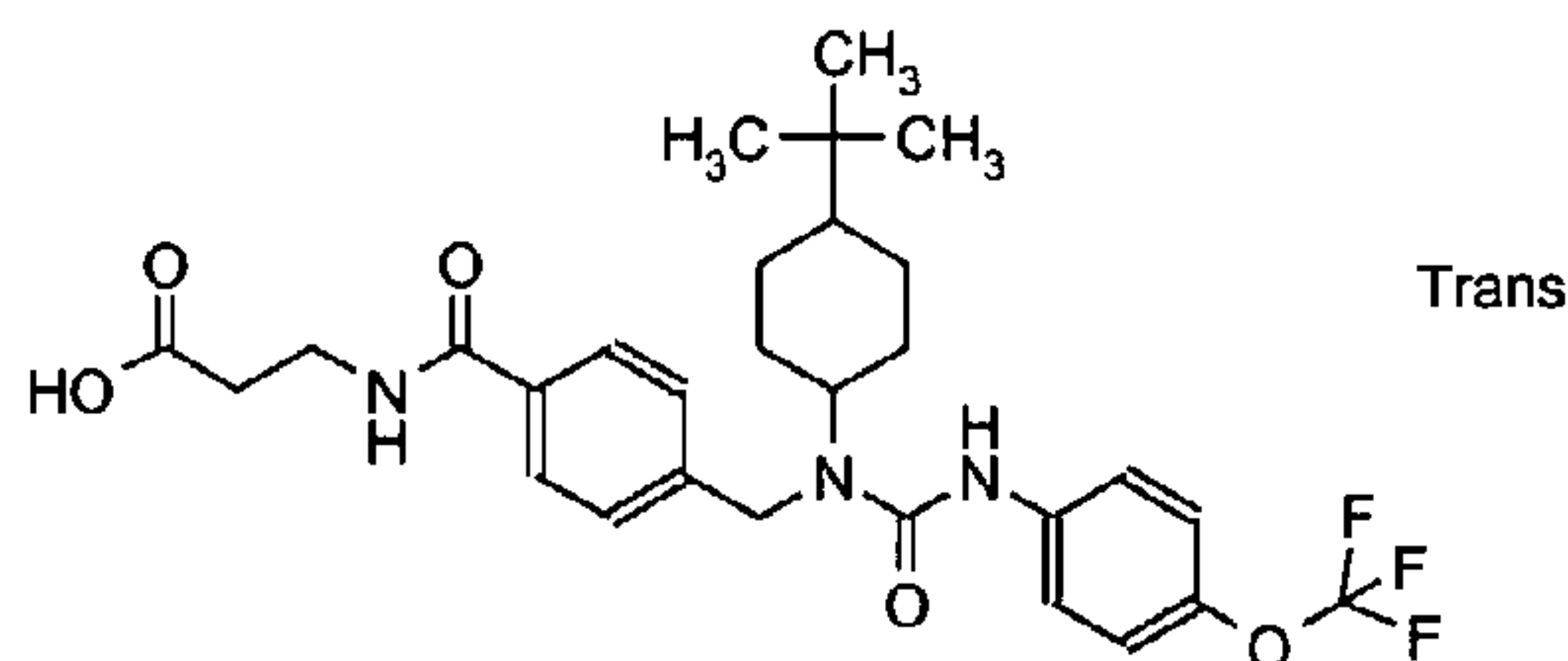
20

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these may be performed eg by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

- 5 The procedure is illustrated in example 92.

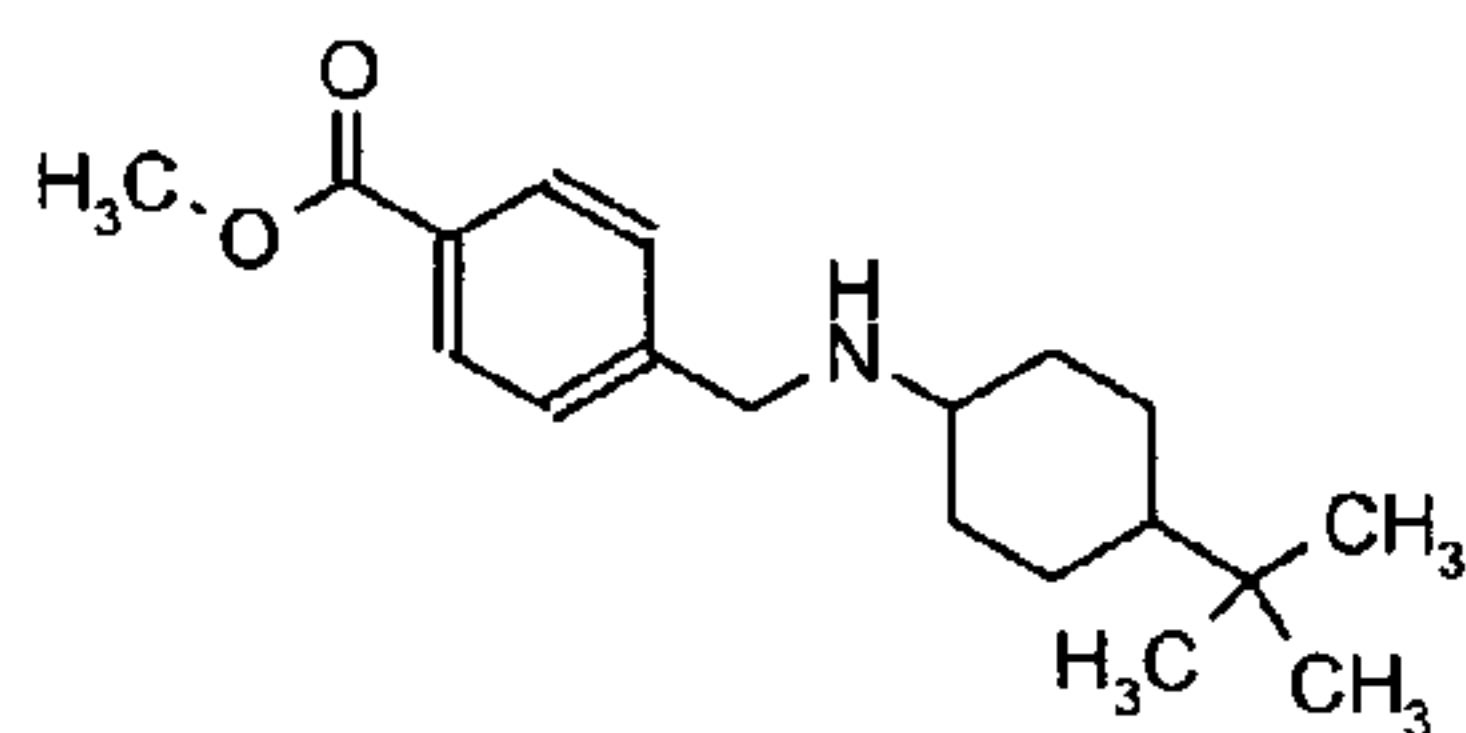
EXAMPLE 92 (general procedure (F))

3-{4-[1-(4-*trans*-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



10

Step A: 4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester



- 15 4-(Bromomethyl)benzoic acid methyl ester (5.0 g, 22 mmol) and 4-*tert*-butylcyclohexylamine (*cis/trans* mixture) (3.4 g, 22 mmol) were dissolved in DMF where after potassium carbonate (6.1 g, 44 mmol) was added. The reaction mixture was stirred at 100°C for 7 hours and for 16 hours at 20°C. Water (100 mL) and ethyl acetate (200 mL) were added to the reaction mixture. The organic phase was isolated and washed with water (2 x 100 mL) and a saturated solution of sodium chloride (2 x 100 mL). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to give a *cis/trans* mixture of 4-[(4-*tert*-butylcyclohexylamino)methyl]-benzoic acid methyl ester as a crude product. The two isomers were separated on silica (110 g) using a mixture of ethyl acetate and dichloromethane (7:3) as eluent.
- 20

trans isomer:

Micro analysis: Calculated for $C_{19}H_{29}NO_2$:

C: 75.21, H: 9.63, N: 4.62%. Found:

C: 75.02, H: 9.80, N: 4.64%.

HPLC-MS (Method B): $R_t = 5.23$ min, $m/z = 304$ ($M + 1$).

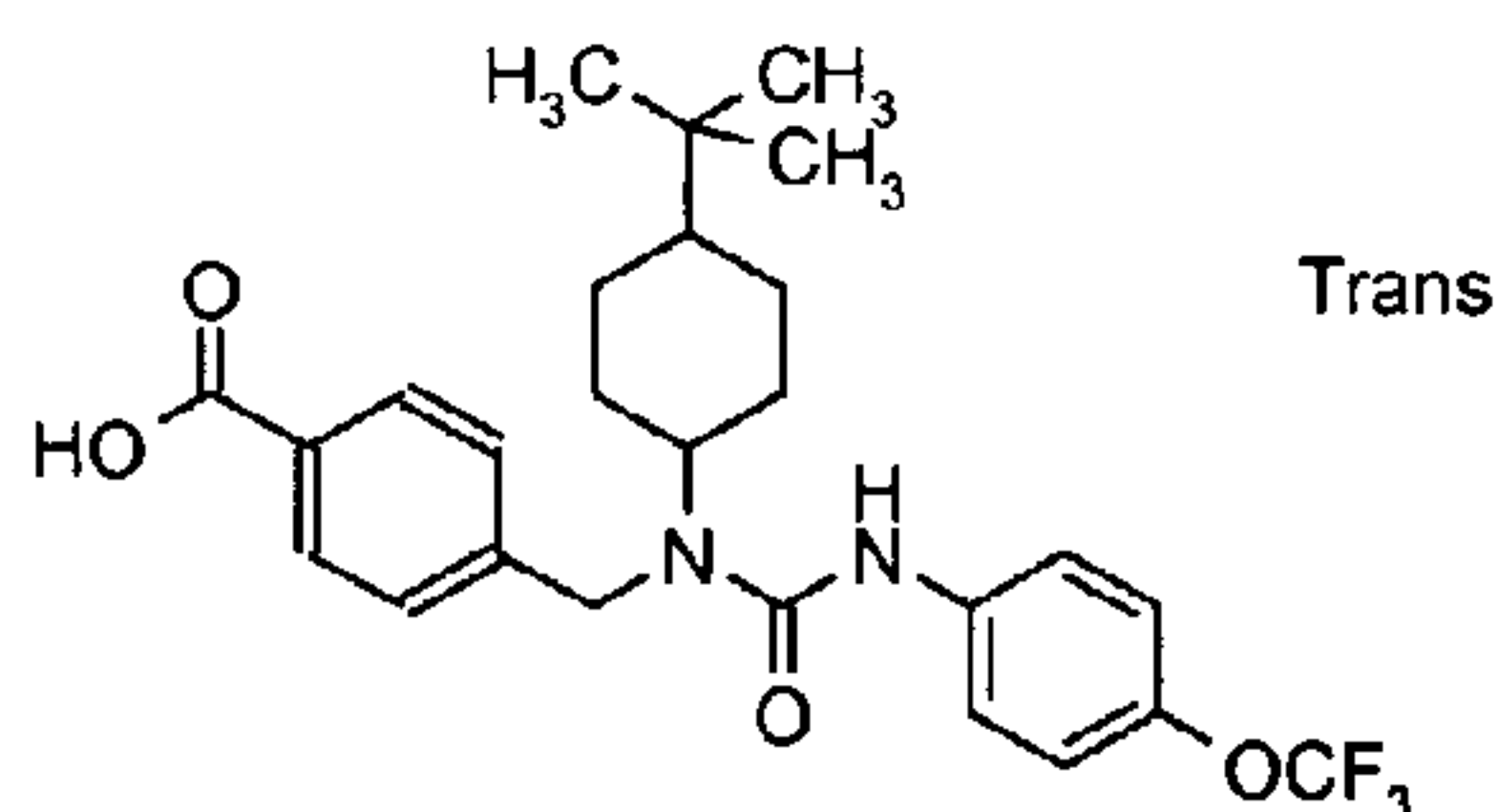
¹H NMR (DMSO-*d*₆), 400 MHz: δ 7.90 (d, 2H), 7.48 (d, 2H), 3.82 (s, 3H), 3.78 (s, 2H), 2.30-2.20 (m, 1H), 2.05-1.90 (m, 3H), 1.73-1.65 (m, 2H), 1.10-0.90 (m, 4H), 0.80 (s, 9H).

cis isomer:

HPLC-MS (Method B): $R_t = 4.83$ min, $m/z = 304$ ($M + 1$).

¹H NMR (DMSO-*d*₆), 400 MHz: δ 7.92 (d, 2H), 7.58 (d, 2H), 3.90 (dd, 1H), 3.85 (s, 3H), 3.80 (dd, 1H), 2.50-2.35 (m, 1H), 2.00-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.70-1.45 (m, 2H), 1.00-0.80 (m, 1H), 0.80 (s, 9H).

Step B: 4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid



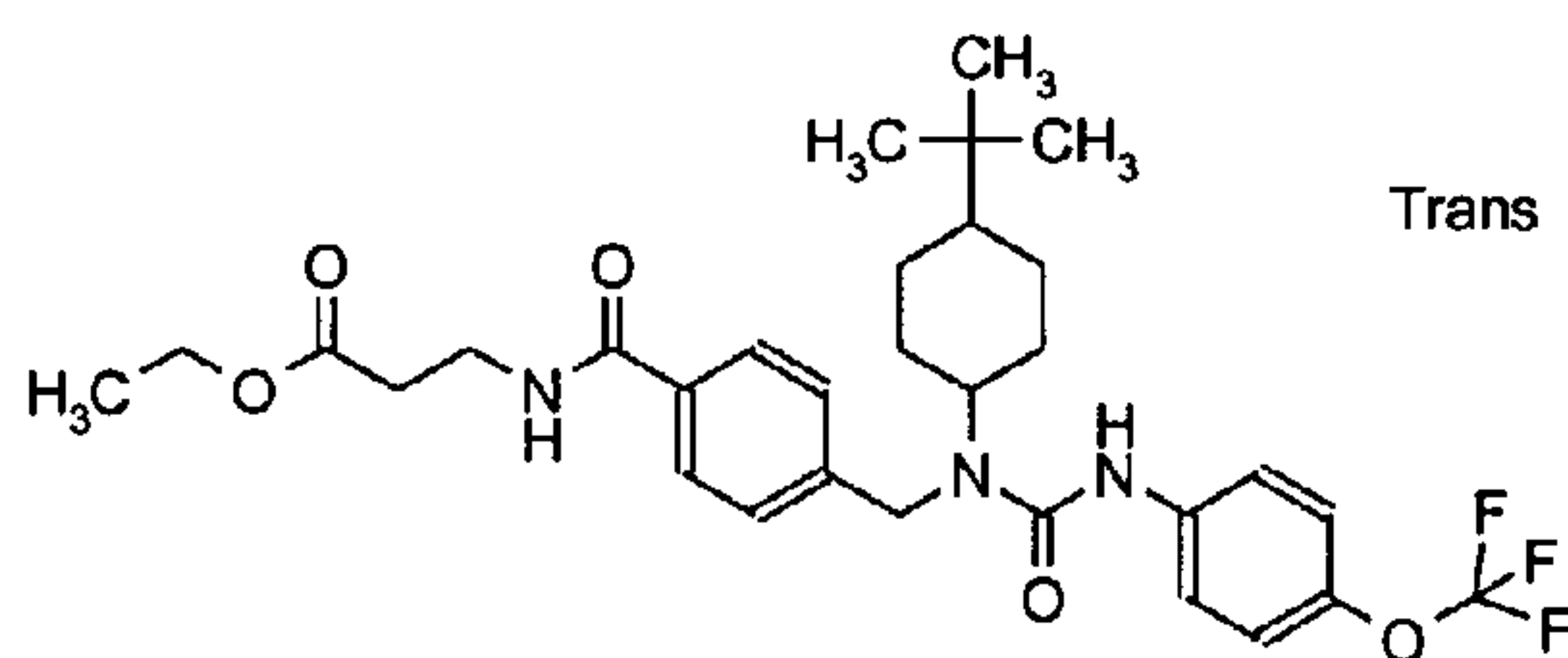
4-[(*trans*-4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (2.6 g, 8.6 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (1.7 g, 8.6 mmol) were dissolved in acetonitrile (40 mL) and stirred at 20°C for 16 hours. The reaction mixture was concentrated in vacuo and the crude product purified on silica (100 g) using heptane and ethyl acetate (3:1) as eluent to give 4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester. The product was suspended in ethanol (80 mL) and sodium hydroxide (4N, 17 mL) was added. The reaction mixture was stirred at 50°C for 3 hours and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (100 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (3 x 75 mL) and the combined organic phases were dried (MgSO₄) and concen-

trated in vacuo to give 4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoic acid.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.80 (s, 1H), 8.55 (s, 1H), 7.90 (d, 2H), 7.55 (d, 2H), 7.35 (d, 2H), 7.21 (d, 2H), 4.62 (s, 2H), 4.10-4.00 (m, 1H), 2.00 (s, 2H), 1.80-1.60 (m, 4H), 1.48-1.38 (m, 2H), 1.20-1.00 (m, 2H), 1.00-0.88 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 8.37 min, m/z = 493 (M + 1).

Step C: 3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid ethyl ester



4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid (2.0 g, 4.1 mmol), 1-hydroxybenzotriazole (0.6 g, 4.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.8 g, 4.3 mmol) were dissolved in DMF (40 mL). A solution of diisopropylethylamine (0.5 g, 4.1 mmol) and 3-aminopropionic acid ethyl ester, hydrochloride (0.4 g, 4.3 mmol) in DMF (10 mL) was added and the reaction mixture was stirred for 16 hours at 20°C. Ethyl acetate (150 mL) and water (100 mL) were added and the organic phase isolated. The aqueous phase was extracted with ethyl acetate (50 mL) and the organic phases combined, dried (MgSO₄) and concentrated in vacuo. The crude product was purified on silica (80 g) using heptane and ethyl acetate (1:1) as eluent to give 3-{4-[1-(*trans*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester.

M.p. = 108-111°C.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 8.55 (s, 1H), 8.50 (t, 1H), 7.75 (d, 2H), 7.55 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.60 (s, 2H), 4.10-4.00 (m, 1H), 3.60 (s, 3H), 3.45 (dd, 2H), 2.55 (t, 2H), 1.80-1.60 (m, 4H), 1.50-0.80 (m, 5H), 0.80 (s, 9H).

HPLC-MS (Method B): $R_t = 8.43$ min, $m/z = 578$ ($M + 1$).

Step D:

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-
5 amino}propionic acid ethyl ester (1.4 g, 2.4 mmol) was suspended in ethanol (50 mL) and
sodium hydroxide (4 N, 6 mL) added. The reaction mixture was stirred for 2 hours at 50°C
and then concentrated in vacuo until all ethanol was removed. The reaction mixture was di-
luted with water (100 mL) and adjusted to pH 2 with hydrochloric acid (4N), and the title
compound was isolated by filtration.

10 M.p. = 152-154°C.

^1H NMR (DMSO- d_6), 400 MHz: δ 12.20 (s, 1H), 8.55 (s, 1H), 7.95 (t, 1H), 7.75 (d, 2H), 7.55
(d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.60 (s, 2H), 4.10-4.00 (m, 1H), 3.45 (dd, 2H), 2.50 (2H),
15 1.80-1.60 (m, 4H), 1.45-1.35 (m, 2H), 1.15-1.05 (m, 2H), 0.95-0.85 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): $R_t = 7.88$ min, $m/z = 564$ ($M + 1$).

Micro analysis: Calculated for $\text{C}_{29}\text{H}_{36}\text{F}_3\text{N}_3\text{O}_5 \cdot 0.75\text{H}_2\text{O}$:

20 C: 60.35, H: 6.55, N: 7.28%. Found:

C: 60.47, H: 6.32, N: 7.32%.

Alternative method for the preparation of the compound (general procedure (K)):

General procedure (K) is described in the following:

Step 6, using pure isocyanate prepared from (substituted) anilines and diphosgene as described under the general procedure (K):

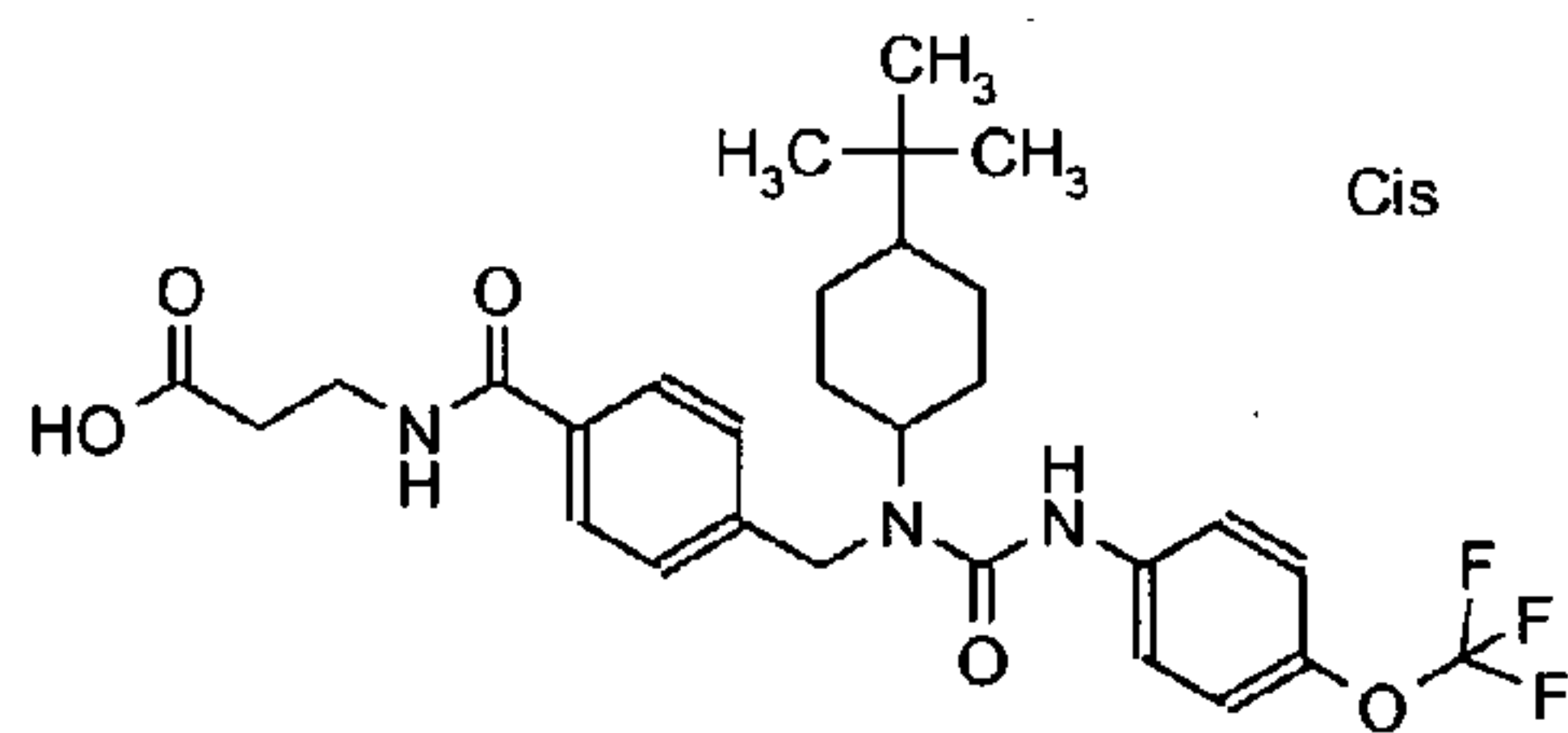
- 5 Methyl *trans*-4-[(4-*tert*-butylcyclohexyl)aminomethyl]benzoylaminopropanoate, hydrochloride (10.0 g 24 mmol, prepared by using anhydrous hydrogen chloride in ethyl acetate in general procedure (K), step 5) was suspended in acetonitrile (300 mL) and diisopropylethylamine (4.14 mL, 24 mmol) was added. To this suspension 4-trifluoromethoxyphenylisocyanate (3.75 mL, 24 mmol) was added. Stirring at room temperature was continued for 4 hours and then the mixture was left at 5°C for 16 hours. Filtration and washing with cold acetonitrile afforded 11.9 g (85%) of 3-{4-[1-(4-*trans*-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)-ureidomethyl]benzoylamino}propionic acid methyl ester.

15 Step 7:

Hydrolysis of this ester using the method described in example 46, step D afforded the title compound (11 g, 94%).

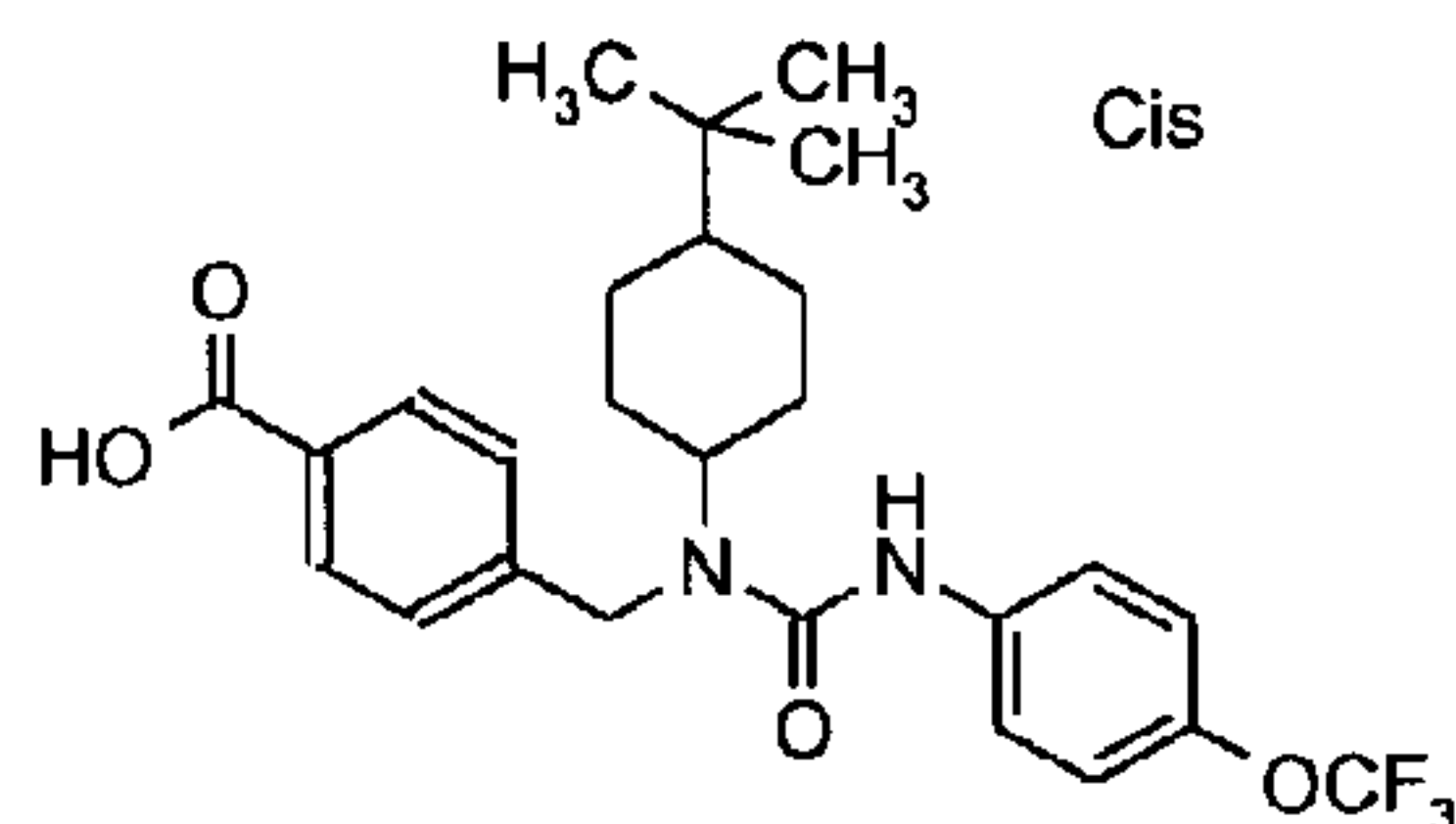
EXAMPLE 93

- 20 3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxy-phenyl)ureidomethyl]-benzoylamino}propionic acid



Step A: 4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid

- 25 acid



4-[(*cis*-4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (0.36 g, 1.2 mmol) and 4-(trifluoromethoxy)phenyl isocyanate (0.24 g, 1.2 mmol) were dissolved in acetonitrile (10 mL) and stirred at 20°C for 16 hours. The reaction mixture was concentrated in vacuo and the crude product purified on silica (25 g) using heptane and ethyl acetate (9:1) as eluent to
 5 give 4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid methyl ester. The product was suspended in ethanol (10 mL) and sodium hydroxide (4N, 1.1 mL) was added. The reaction mixture was stirred at 50°C for 3 hours and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with
 10 ethyl acetate (75 mL) and the organic phase was dried (MgSO₄) and concentrated in vacuo to give 4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid.

Micro analysis: Calculated for C₂₆H₃₁F₃N₂O₄:

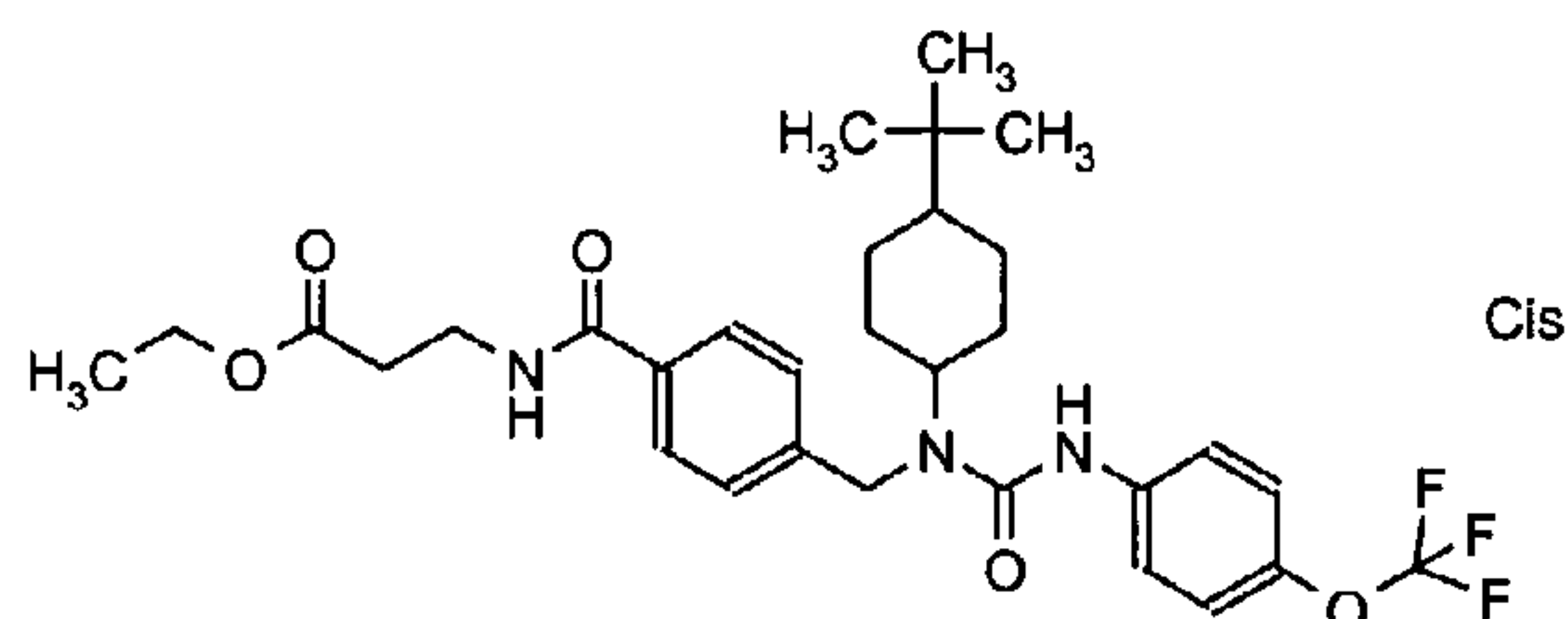
15 C: 63.40, H: 6.34, N: 5.69%. Found:

C: 63.29, H: 6.33, N: 5.65%.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.80 (s, 1H), 8.61 (s, 1H), 7.90 (d, 2H), 7.55 (d, 2H), 7.35 (d, 2H), 7.22 (d, 2H), 4.72 (s, 2H), 4.32-4.22 (m, 1H), 1.85-1.70 (m, 2H), 1.65-1.45 (m, 4H),
 20 1.40-1.10 (m, 3H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 7.85 min, m/z = 493 (M + 1).

Step B: 3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-
 25 benzoylamino}propionic acid ethyl ester



4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid (0.3 g, 0.6 mmol), 1-hydroxybenzotriazole (0.1 g, 0.7 mmol) and 1-(3-dimethylaminopropyl)-
 30 3-ethylcarbodiimide (0.13 g, 0.7 mmol) were dissolved in DMF (10 mL). Diisopropylethylamine (0.1 g, 0.7 mmol) and 3-aminopropionic acid ethyl ester, hydrochloride (0.07 g, 0.7

mmol) in DMF was added and the reaction mixture was stirred for 16 hours at 20°C. Ethyl acetate (80 mL) and water (50 mL) were added and the organic phase isolated. The aqueous phase was extracted with ethyl acetate (50 mL) and the organic phases combined, dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from heptane and ethyl acetate (4:1) to give 3-{4-[1-(*cis*-4-*tert*-butylcyclohexyl)-3-(4-trifluoromethoxy-phenyl)ureidomethyl]benzoylamino}propionic acid ethyl ester.

M.p. = 87-90°C.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 8.60 (s, 1H), 8.48 (t, 1H), 7.75 (d, 2H), 7.52 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 1H), 3.60 (s, 3H), 3.48 (dd, 2H), 2.55 (t, 2H), 1.82-1.70 (m, 2H), 1.60-1.45 (m, 4H), 1.40-1.10 (m, 3H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 7.80 min, m/z = 578 (M + 1).

Micro analysis: Calculated for C₃₀H₃₈F₃N₃O₅:

C: 62.38, H: 6.63, N: 7.27%. Found:

C: 62.49, H: 6.75, N: 7.20%.

Step C:

3-{4-[1-(*cis*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid ethyl ester (0.2 g, 0.3 mmol) was suspended in ethanol (8 mL) and sodium hydroxide (4N, 0.6 mL) added. The reaction mixture was stirred for 16 hours at 20°C and then concentrated in vacuo until all ethanol was removed. The reaction mixture was diluted with water (50 mL) and adjusted to pH 2 with hydrochloric acid (4N). The aqueous phase was extracted with ethyl acetate (80 mL) and the organic phase was dried (MgSO₄) and concentrated in vacuo to give the title compound.

¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.20 (s, 1H), 8.60 (s, 1H), 8.45 (t, 1H), 7.77 (d, 2H), 7.53 (d, 2H), 7.28 (d, 2H), 7.20 (d, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 1H), 3.45 (dd, 2H), 2.50 (2H), 1.82-1.70 (m, 2H), 1.60-1.45 (m, 4H), 1.40-1.30 (m, 2H), 1.20-1.10 (m, 1H), 0.80 (s, 9H).

HPLC-MS (Method B): R_t = 7.32 min, m/z = 564 (M + 1).

Micro analysis: Calculated for C₂₉H₃₆F₃N₃O₅, 0.25H₂O:

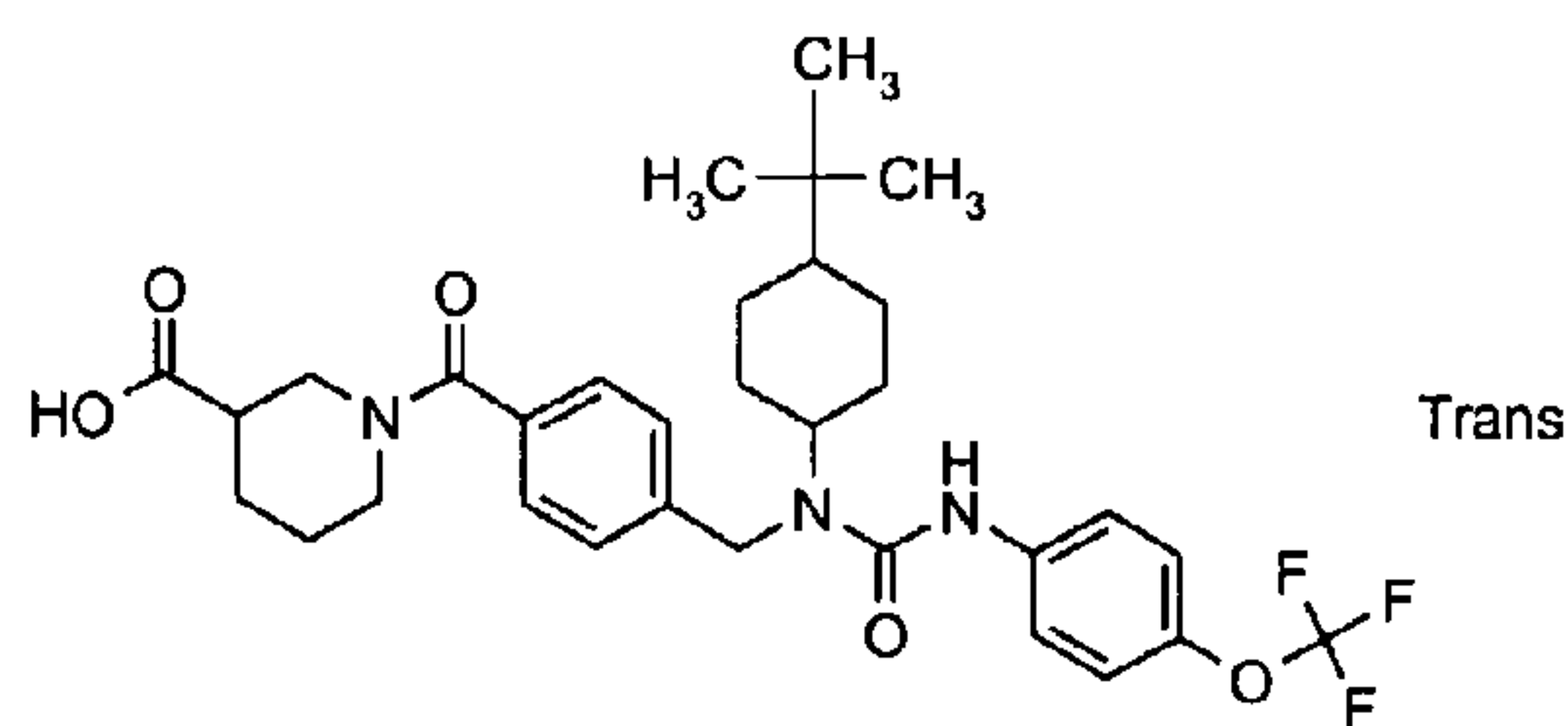
C: 61.53, H: 6.54, N: 7.18%. Found:

C: 61.36, H: 6.80, N: 7.09%.

The following compounds were prepared using the general procedure (F) as described above.

EXAMPLE 94 (general procedure (F))

1-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl}-piperidine-3-carboxylic acid



The compound was prepared using nipecotic acid methyl ester, hydrochloride instead of 3-aminopropionic acid methyl ester, hydrochloride in step C.

HPLC-MS (Method B): $R_t = 8.17$ min, $m/z = 604$ ($M + 1$).

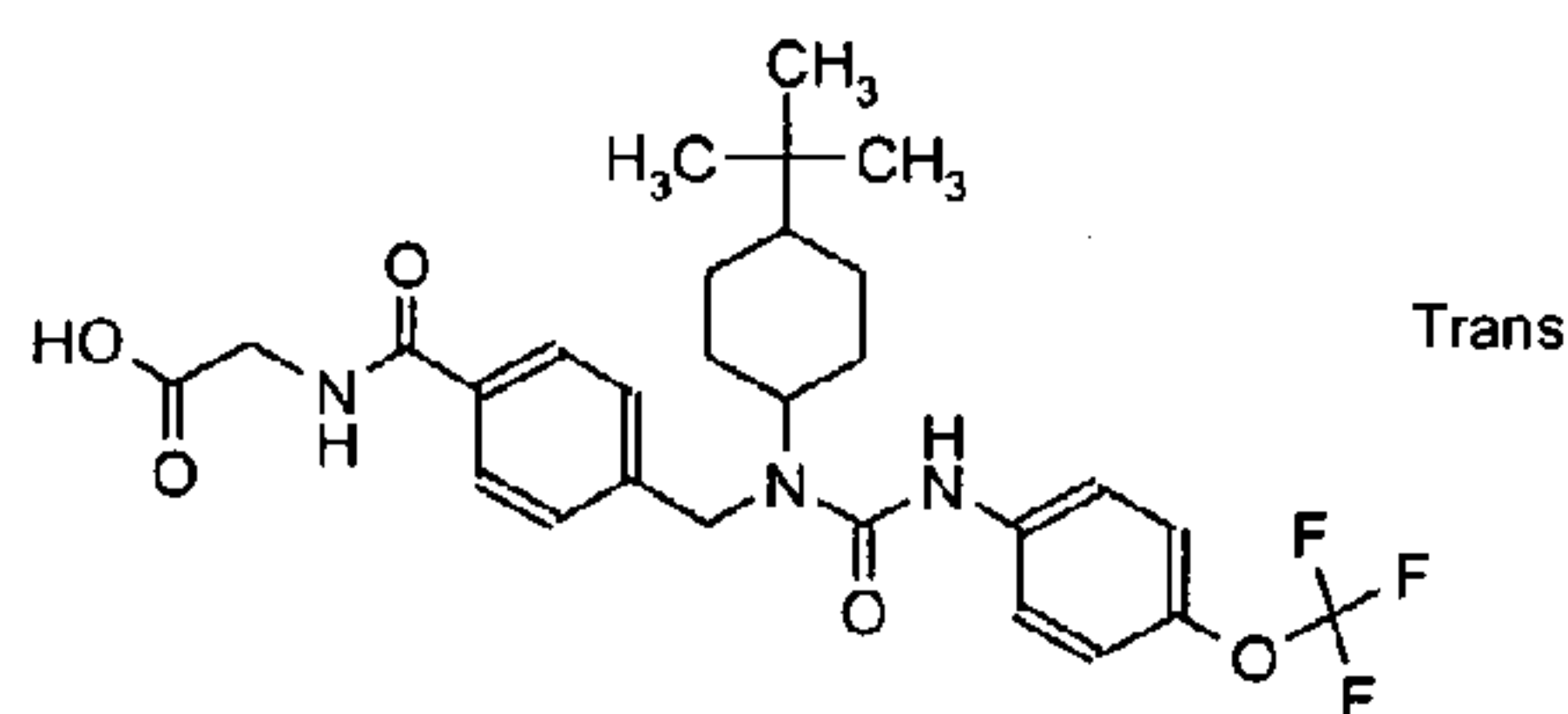
Micro analysis: Calculated for $C_{32}H_{40}F_3N_3O_5$:

C: 63.67, H: 6.68, N: 6.96%. Found:

C: 63.66, H: 6.75, N: 6.94%.

EXAMPLE 95 (general procedure (F))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}acetic acid



The compound was prepared using glycine methyl ester, hydrochloride instead of 3-aminopropionic acid methyl ester, hydrochloride in step C.

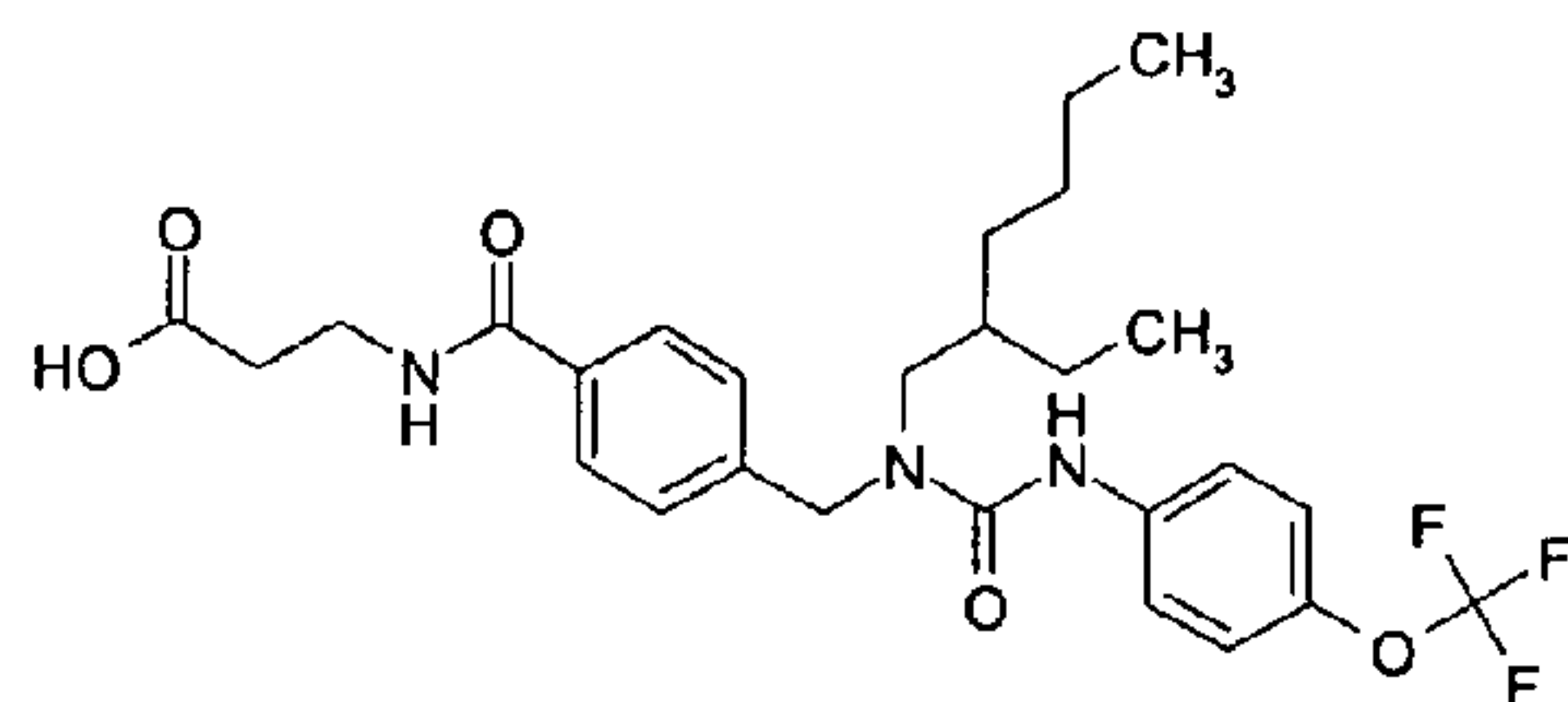
¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.55 (s, 1H), 8.76 (t, 1H), 8.52 (s, 1H), 7.81 (d, 2H), 7.55 (d, 2H), 7.33 (d, 2H), 7.22 (d, 2H), 4.61 (s, 2H), 4.10-4.00 (m, 1H), 3.80 (d, 2H), 1.75-1.60 (m, 4H), 1.45-1.30 (m, 2H), 1.20-1.00 (m, 2H), 1.00-0.80 (m, 1H), 0.80 (s, 9H).

5

HPLC-MS (Method B): *R*_t = 7.88 min, *m/z* = 550 (*M* + 1).

EXAMPLE 96 (general procedure (F))

3-{4-[1-(2-Ethylhexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



10

The compound was prepared using 2-ethylhexylamine instead of 4-*tert*-butylcyclohexylamine in step A.

15 ¹H NMR (DMSO-*d*₆), 400 MHz: δ 12.20 (s, 1H), 8.63 (s, 1H), 8.49 (t, 1H), 7.82 (d, 2H), 7.54 (d, 2H), 7.31 (d, 2H), 7.22 (d, 2H), 4.65 (s, 2H), 3.45 (dd, 2H), 3.25 (m, 2H), 2.50 (2H), 1.70-1.60 (m, 1H), 1.40-1.10 (m, 8H), 0.90-0.70 (m, 6H).

HPLC-MS (Method B): *R*_t = 7.17 and 7.25 min, *m/z* = 538 (*M* + 1).

20

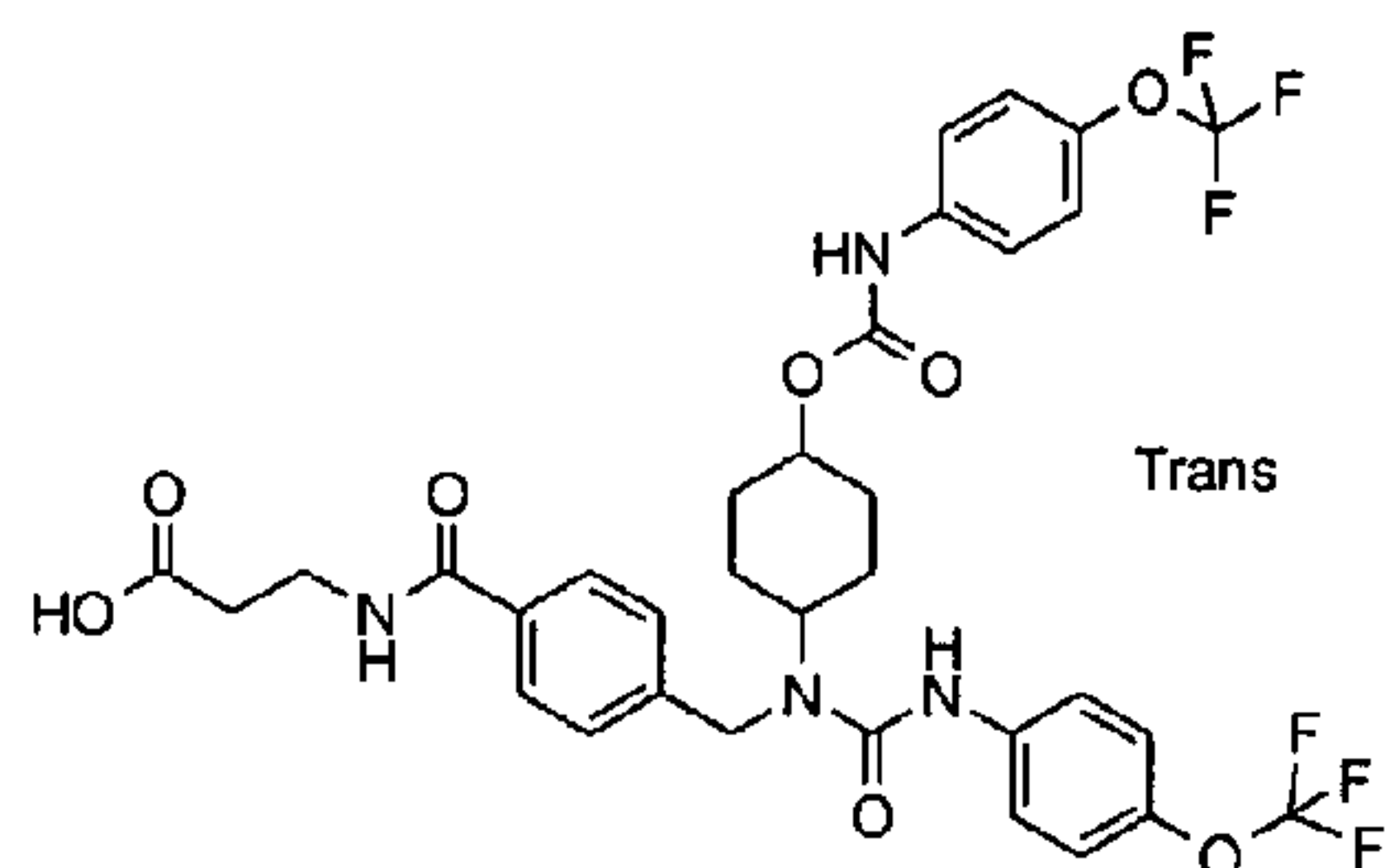
Micro analysis: Calculated for C₂₇H₃₄F₃ N₃O₅:

C: 60.33, H: 6.37, N: 7.82%. Found:

C: 60.51, H: 6.60, N: 7.48%.

EXAMPLE 97

3-{4-[1-(*trans*-4-(4-Trifluoromethoxyphenylcarbamoyloxy)cyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

This compound was prepared on solid support using the same methodology as described in general procedure (F) using *trans* 4-hydroxycyclohexylamine instead of 4-*tert*-butylcyclohexylamine.

10 HPLC-MS (Method B): $R_t = 7.68$ min, $m/z = 727$ ($M + 1$).

Micro analysis: Calculated for $C_{33}H_{32}F_3N_4O_8$:

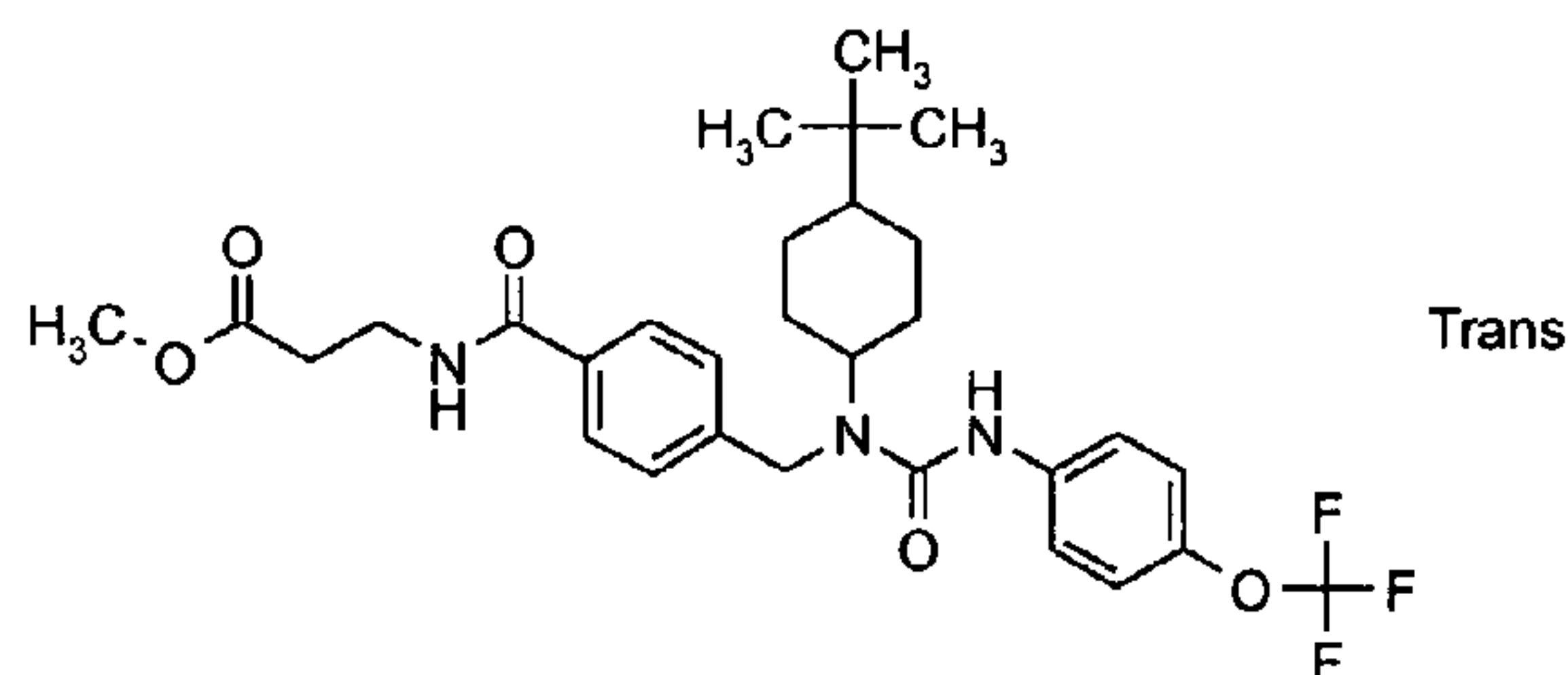
C: 54.55, H: 4.44, N: 7.71%. Found:

C: 54.17, H: 4.53, N: 7.44%.

15

EXAMPLE 98 (general procedure (F))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid methyl ester



20

The compound was prepared according to procedure (F) but omitting step D.

Micro analysis: Calculated for $C_{29}H_{36}F_3N_3O_5 \cdot 0.1H_2O$:

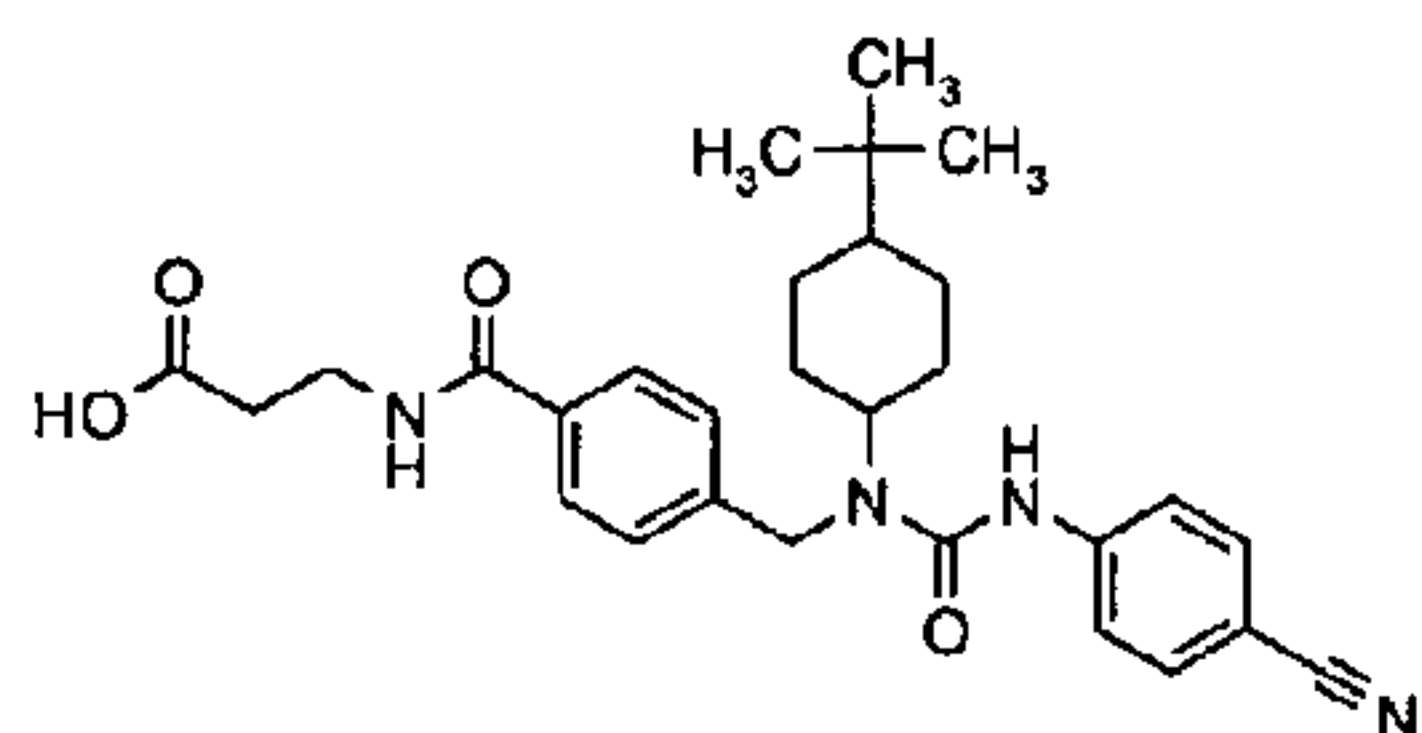
C, 61.87%; H, 6.44%; N, 7.46%. Found:

25 C, 61.60%; H, 6.45%; N, 7.43%.

HPLC-MS (Method B): m/z: 564.

EXAMPLE 99 (general procedure (F))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-cyanophenyl)ureidomethyl]benzoylamino}propionic acid

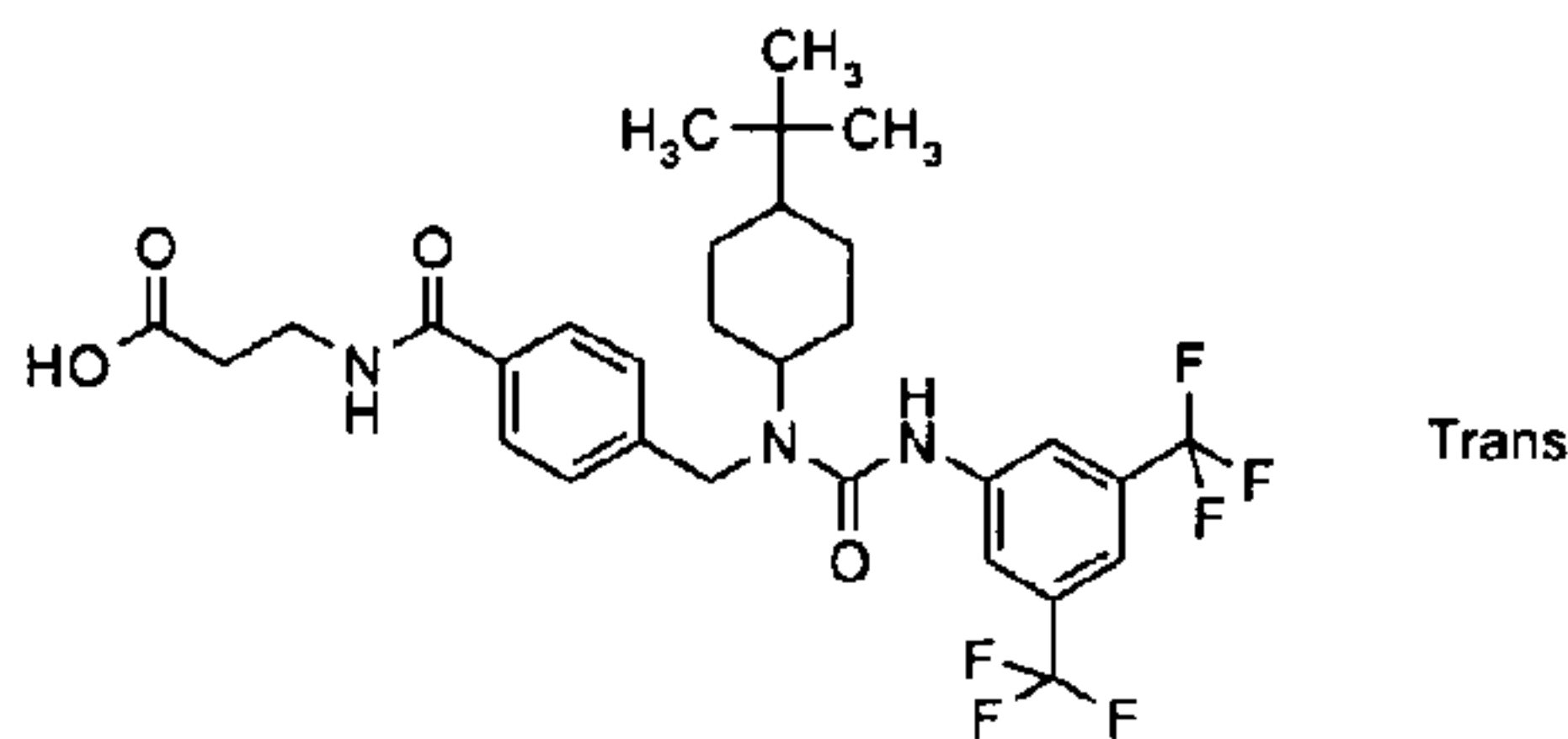


^1H NMR (DMSO- d_6): δ 12.2 (1H, broad), 8.82 (1H, s), 8.48 (1H, t), 7.78 (2H, d), 7.68 (4H, s), 7.32 (2H, d), 4.62 (2H, s), 4.05 (1H, m), 3.42 (2H, dd), 1.80-85 (9H, m), 0.80 (9H, s)

HPLC-MS (method B): m/z: 505, R_t = 7.28 min.

EXAMPLE 100 (general procedure (F))

3-{4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid



The starting material, 4-[(*trans*-4-*tert*-butylcyclohexylamino)methylbenzoic acid methyl ester, was prepared as described in step A of the general procedure (F).

^1H NMR (DMSO- d_6): δ 12.2 (s, 1H), 9.05(s, 1H), 8.45 (t, 1H), 8.25(s, 2H), 7.76(d, 2H), 7.61(s, 1H), 7.32(d, 2H), 4.63(s, 2H), 4.05(m, 1H), 3.45(m, 2H), 1.80-0.75 (m, 9H), 0.82 (s, 9H)

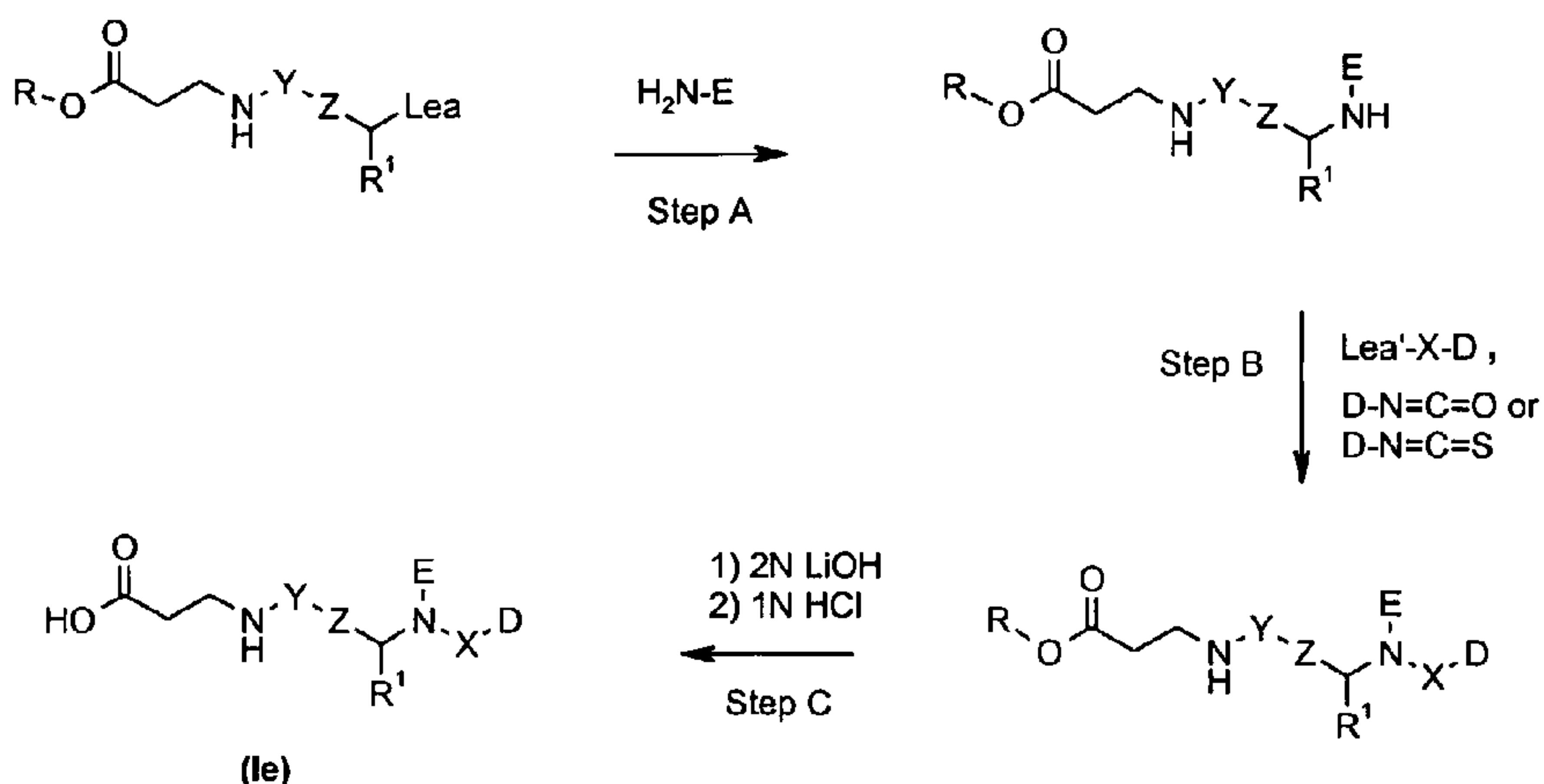
HPLC-MS (method B): m/z: 616, R_t = 8.3 min.

MA: calculated for $\text{C}_{30}\text{H}_{35}\text{F}_6\text{N}_3\text{O}_4$:

58.53% C; 5.73% H; 6.83% N; Found

58.25% C; 5.75% H; 7.02% N.

General procedure (G) for the solution phase synthesis of compounds of the general formula (Ie):



5

wherein

R^1 , E, Z and D are as defined for formula (I),

10 X is $-\text{S}(\text{O})_2-(\text{CH}_2)_r-$, $-\text{C}(\text{O})\text{NH}-$ or $-\text{C}(\text{S})\text{NH}-$, wherein r is as defined for formula (I),

Y is $-\text{C}(\text{O})-$ or $-\text{S}(\text{O})_2-$,

R is C_{1-6} -alkyl,

15

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl, and

Lea' is a leaving group such as $-\text{OSu}$, chloro, phenoxy, 4-nitrophenoxy.

20 Step A:

The appropriate alkylhalide (0.02 mmol) in DMF was dispensed into the wells of a deepwell plate containing solid potassium carbonate (3 equivalents) and the appropriate amine, $\text{NH}_2\text{-E}$, (0.02 mmol). The reactions were agitated at room temperature for four hours and at 50°C for 12 hours. The solids were filtered off and the desired amines were used without further

25 purification in the next step.

Step B:

To the amines in DMF was added the desired isocyanate or isothiocyanate or alternatively Lea'-X-D (0.02 mmol) in DMF. When using Lea'-X-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The reactions are shaken for 30 minutes to give the desired ureas or thioureas.

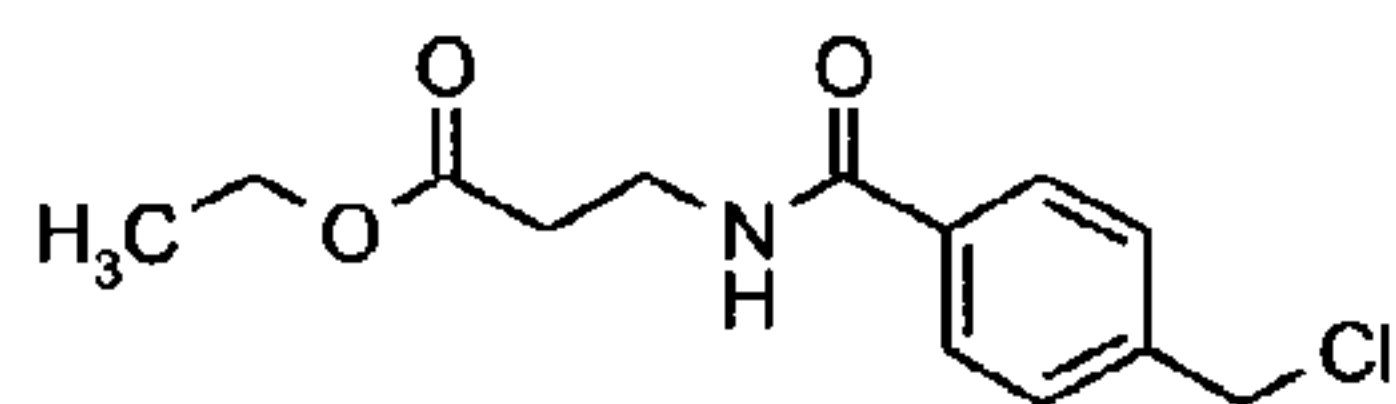
Step C:

To the crude products obtained in step B was added aqueous 2 N LiOH (10 equivalents). The samples were shaken overnight and filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

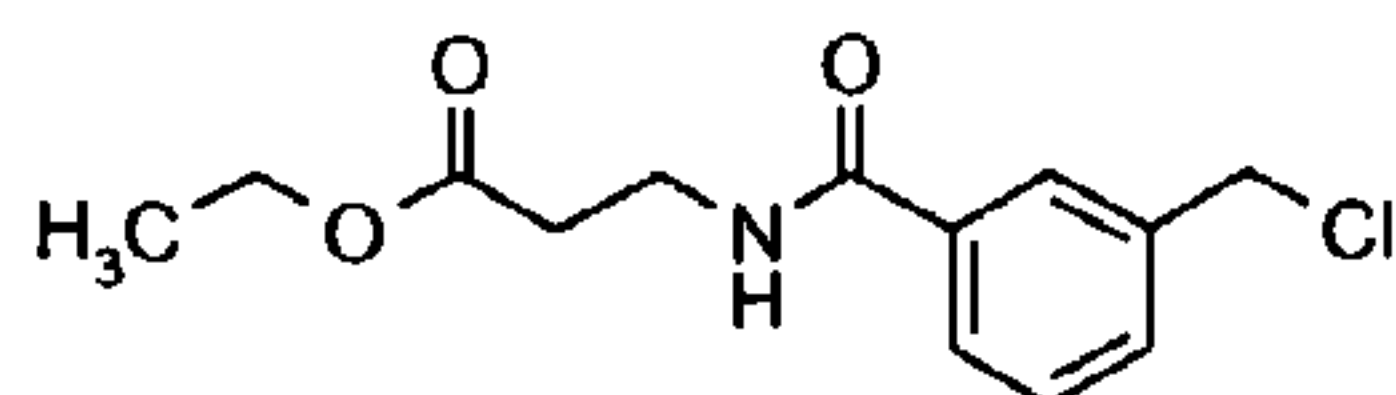
General preparation of halomethylarylcarboxamides as starting materials:

The halomethylarylcarboxamides were prepared from the coupling of the corresponding halomethylarylcarboxylic acid and the methyl or ethyl-3-aminopropionate hydrochloride according to the procedure described below.

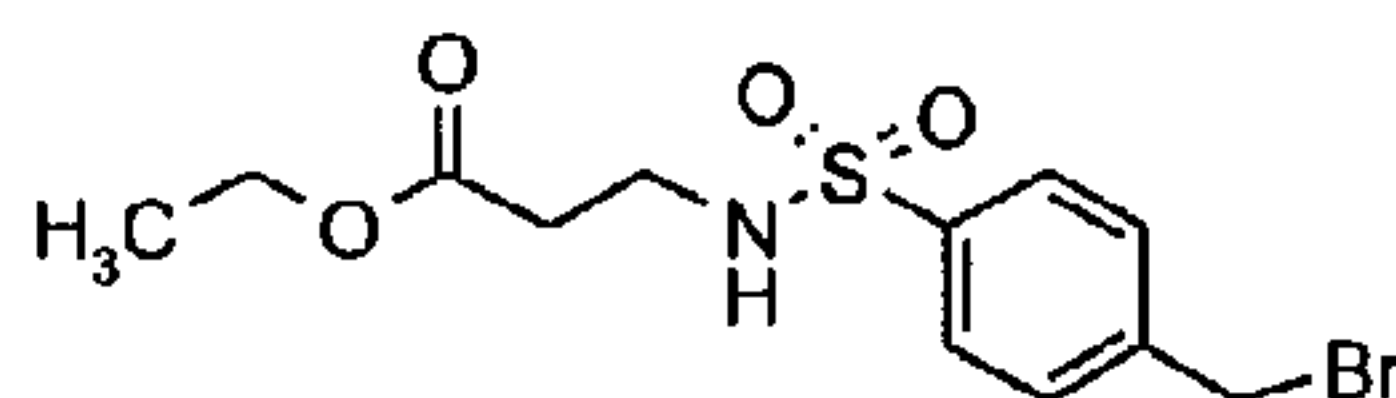
To a solution of the arylcarboxylic acid in a suitable solvent such as CH₂Cl₂, DMF or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before ethyl or methyl-3-aminopropionate hydrochloride (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1N HCl. The organic layer was separated and washed with H₂O (2 x), aqueous NaHCO₃ (3 x), brine (2 x), dried over MgSO₄ and concentrated to give the desired product.

Ethyl 3-{[4-(chloromethyl)benzoyl]amino}propionate:

¹H NMR (DMSO-d₆): δ 1.2 (t, 3H), 2.6 (t, 2H), 3.5 (qt, 2H), 4.1 (qt, 2H), 4.8 (s, 2H), 7.6 (d, 2H), 7.8 (d, 2H), 8.6 (t, 1H).

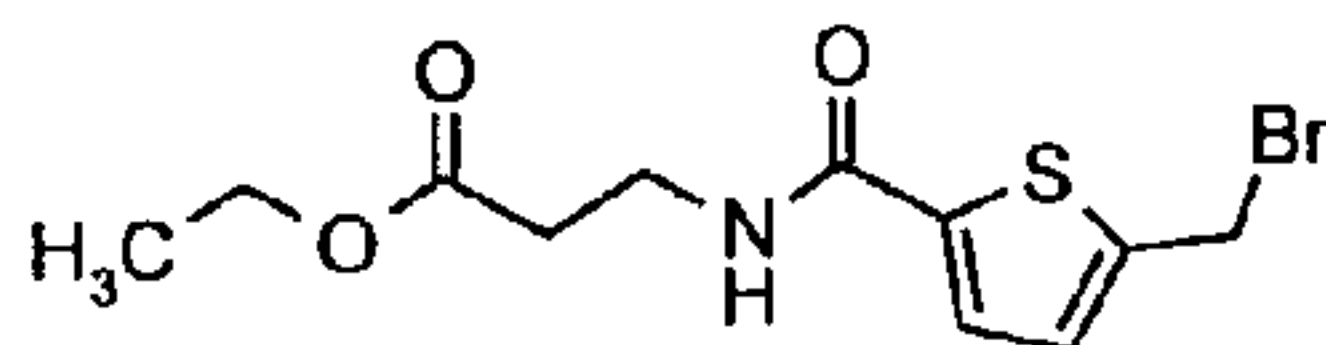
Ethyl 3-([3-(chloromethyl)benzoyl]amino)propionate:

¹H NMR (DMSO-*d*₆): δ 2.61 (t, 2H), 3.50 (qt, 2H), 3.61 (s, 3H), 4.81 (s, 2H), 7.47 (t, 1H), 7.59 (d, 1H), 7.79 (d, 1H), 7.90 (s, 1H), 8.62 (brd t, 1H).

Ethyl 3-([4-(bromomethyl)phenyl]sulfonyl)amino)propionate:

10 To a solution of the 4-bromomethylphenylsulfonylchloride (10 g, 37 mmol) in CH₂Cl₂ (200 mL) at 0°C was added diisopropylethylamine (16 mL, 93 mmol) followed by ethyl-3-aminopropionate hydrochloride (5.1 g, 37 mmol). The reaction was stirred for 10 minutes at 0°C and the solvent was evaporated at room temperature under reduced pressure. The residue was dissolved in ethyl acetate and washed with 1N HCl (3x), H₂O, aqueous NaHCO₃ (3x), brine (3x) and dried over MgSO₄. The solvent was concentrated to give a syrup. Addition of ethyl ether induced crystallization of the product as a white solid (10 g, 30 mmol, 81%).

¹H NMR (CDCl₃): δ 1.24 (t, 3H), 2.55 (t, 2H), 3.22 (qt, 2H), 4.13 (qt, 2H), 4.50 (s, 2H), 5.28 (t, 1H), 7.53 (d, 2H), 7.85 (d, 2H).

Ethyl 3-([5-(bromomethyl)-2-thienyl]carbonyl)amino)propionate:

25 To a solution of methylthiophene carboxylic acid (20 g, 0.14 mol) in DMF (30 mL) was added at 0°C carbonyldimimidazole (23 g, 0.14 mol) in portions of 10 g. After stirring at 0°C for 1 hour, a solution of ethyl 3-aminopropionate hydrochloride (21 g, 0.14 mol) in DMF (30 mL) was added followed by triethylamine (20 mL, 0.14 mol). The mixture was stirred at ambient temperature for 16 hours, filtered by suction, and the filtrate was concentrated. The residue was dissolved in ethyl acetate (100 mL), washed with water (2 x 50 mL), 1N hydrochloric

acid (2 x 50 mL), sodium bicarbonate solution (2 x 50 mL), brine (50 mL), dried (MgSO₄), and concentrated. Addition of hexane to the residue induced the crystallization of ethyl 3-({[5-methyl-2-thienyl]carbonyl}amino)propionate (27 g, 80%).

- 5 ¹H NMR (CDCl₃): δ 1.28 (t, 3H), 2.50 (s, 3H), 2.62 (t, 2H), 3.68 (q, 2H), 4.17 (q, 2H), 6.60 (brd s, 1H), 6.66 (d, 1 H), 7.30 (d, 1H).

The above product (27 g, 0.11 mol) was dissolved in carbon tetrachloride (150 mL). *N*-bromosuccinimide (21 g, 0.12 mol) and AIBN (200 mg) was added. The mixture was refluxed
10 for 5 hours, and filtered by suction. The solid was extracted with ethyl acetate until the filtrate appeared colourless. The combined ethyl acetate extracts (200 mL) were washed with water (2 x 50 mL), dried over MgSO₄ and concentrated. The residue was recrystallized from hexane, ethyl acetate 1:1 to give ethyl 3-({[5-(bromomethyl)-2-thienyl]carbonyl}amino)propionate as a white solid (15 g, 41%).

15

¹H NMR (CDCl₃): δ 1.28 (t, 3H), 2.63 (t, 2H), 3.69 (t, 2H), 4.18 (q, 2H), 4.68 (s, 2H), 7.06 (brd s, 1H), 7.07 (d, 1H), 7.32 (d, 1H).

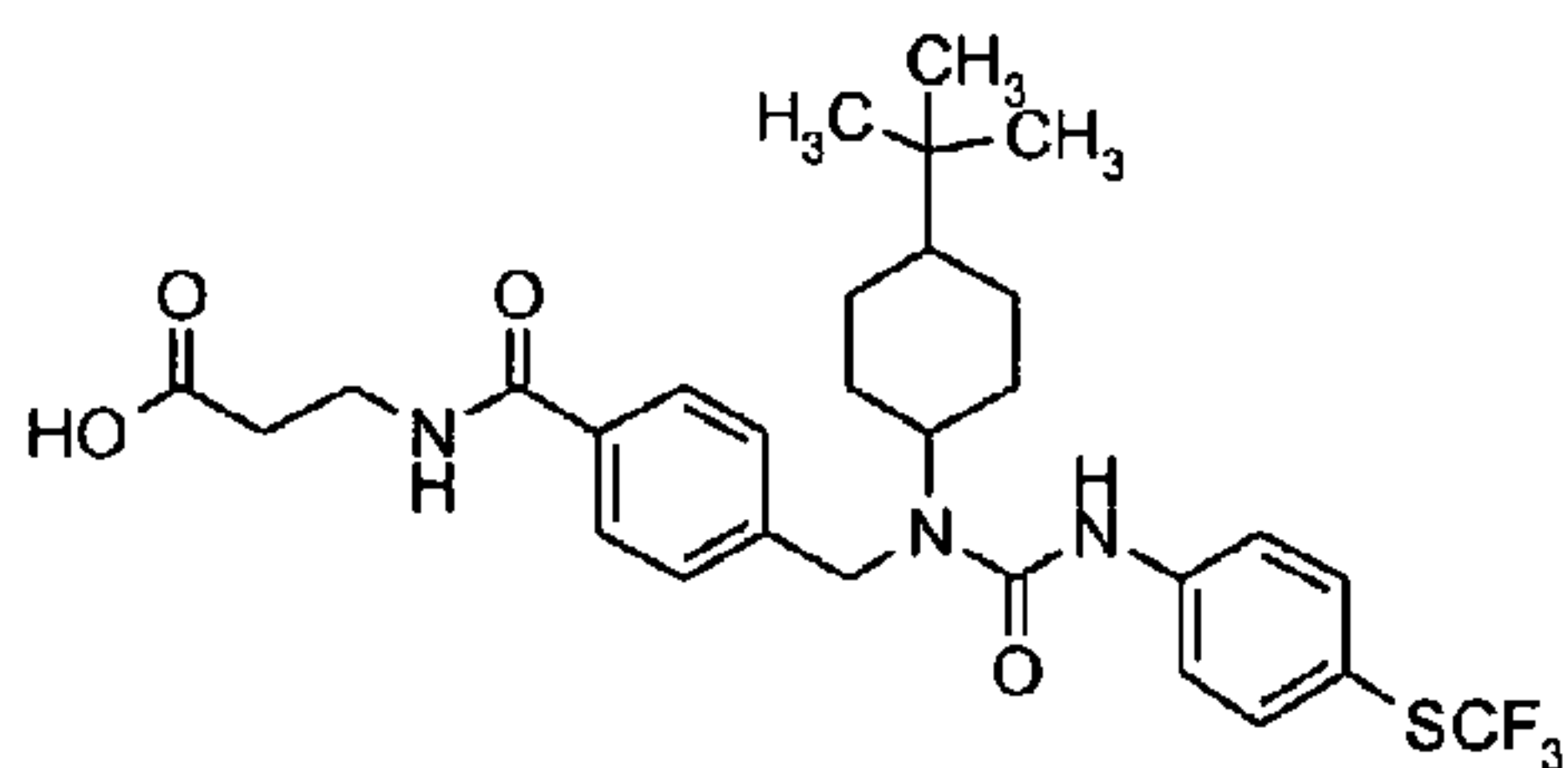
MS (APCI, neg.): 320, 318.

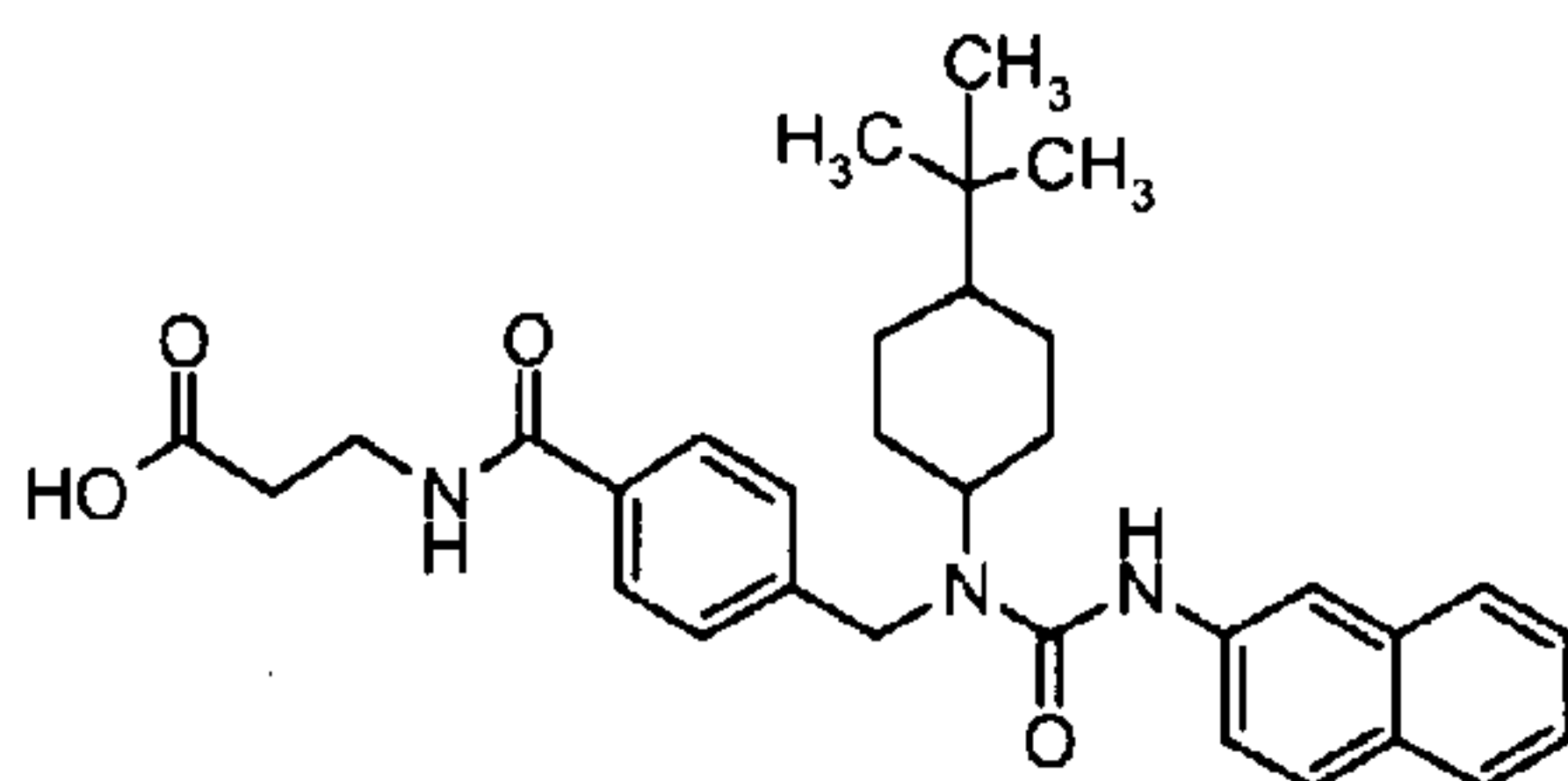
20

The following examples were prepared according to the general procedure (G).

EXAMPLE 101 (general procedure (G))

25 3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoyl-
amino}propionic acid

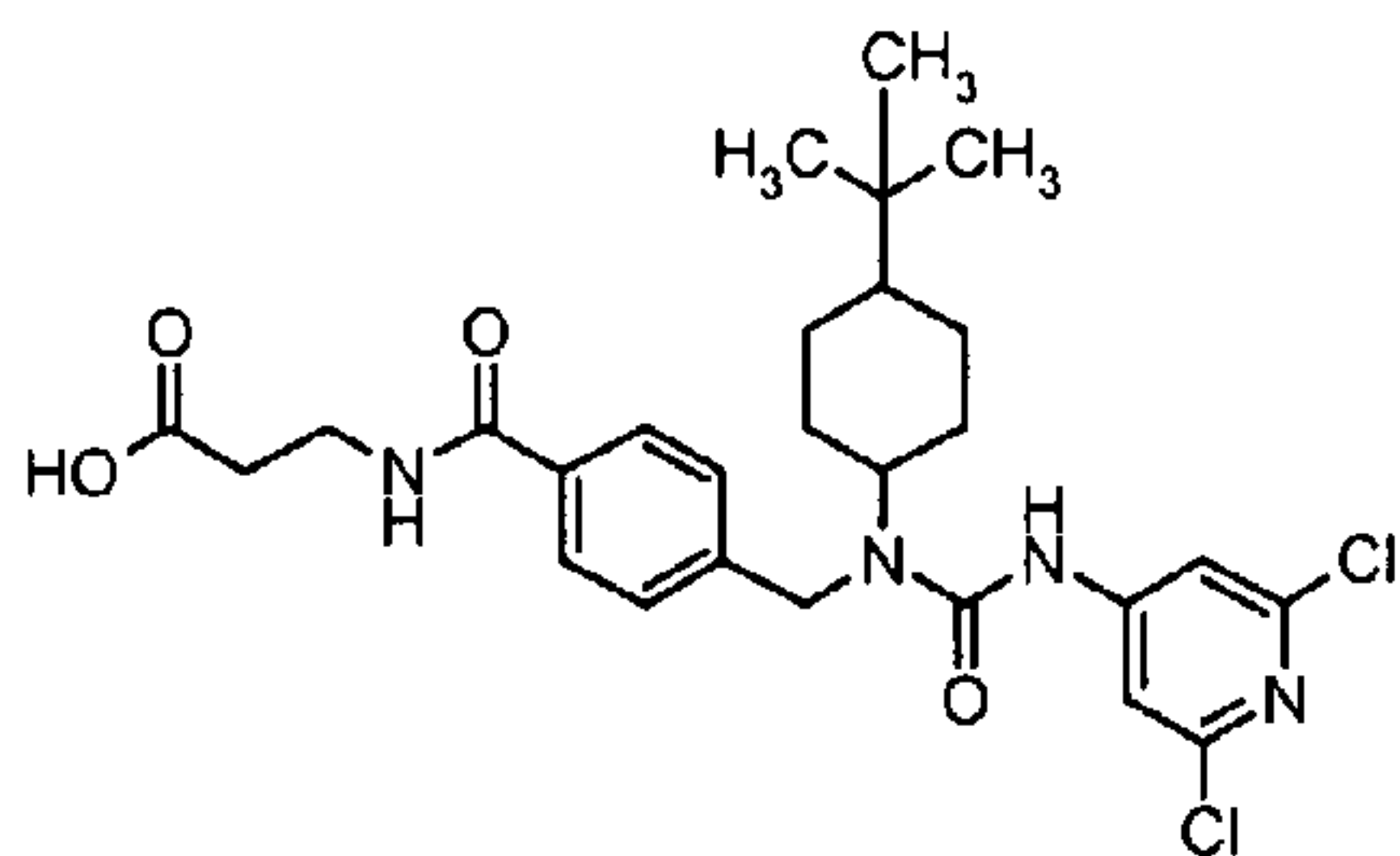


EXAMPLE 102 (general procedure (G))**3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-naphthalen-2-ylureidomethyl]benzoylamino}propionic acid**

5

¹H NMR (DMSO-*d*₆): δ 0.83 (s, 9H), 0.91 (m, 1H), 1.11 (m, 2H), 1.40 (m, 2H), 1.67-1.76 (m, 4H), 2.44 (t, 2H), 3.44 (q, 2H), 4.10 (qt, 1H), 4.64 (s, 2H), 7.31-7.44 (m, 4H), 7.60 (dd, 1H), 7.72-7.83 (m, 5H), 7.99 (d, 1H), 8.47 (t, 1H), 8.57 (s, 1H), 12.10 (brd s, 1H).

10 MS (APCI, pos): 532.3, 531.2, 530.2, 362.3, 361.2.

EXAMPLE 103 (general procedure (G))**3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2,6-dichloropyridin-4-yl)ureidomethyl]benzoylamino}-propionic acid**

15

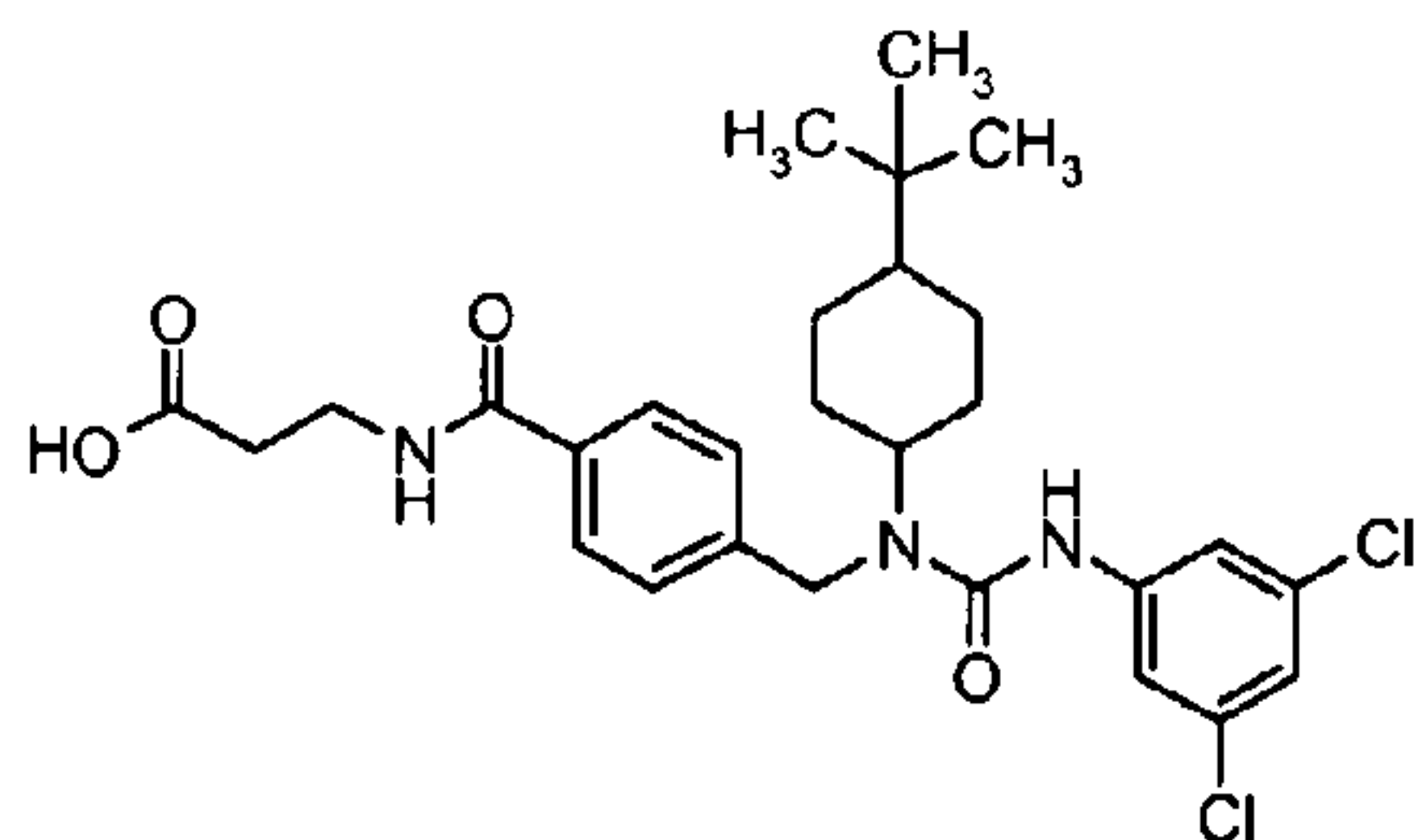
¹H NMR (DMSO-*d*₆): δ 0.81 (s, 9H), 0.91 (m, 1H), 1.07 (m, 2H), 1.39 (m, 2H), 1.63-1.74 (m, 4H), 2.49 (t, 2H), 3.44 (q, 2H), 4.10 (t, 1H), 4.61 (s, 2H), 7.29 (d, 2H), 7.66 (s, 2H), 7.76 (d, 2H), 8.47 (t, 1H), 9.21 (s, 1H), 12.10 (brd s, 1H).

20

MS (APCI, pos): 549.2, 362.2, 361.2.

EXAMPLE 104 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



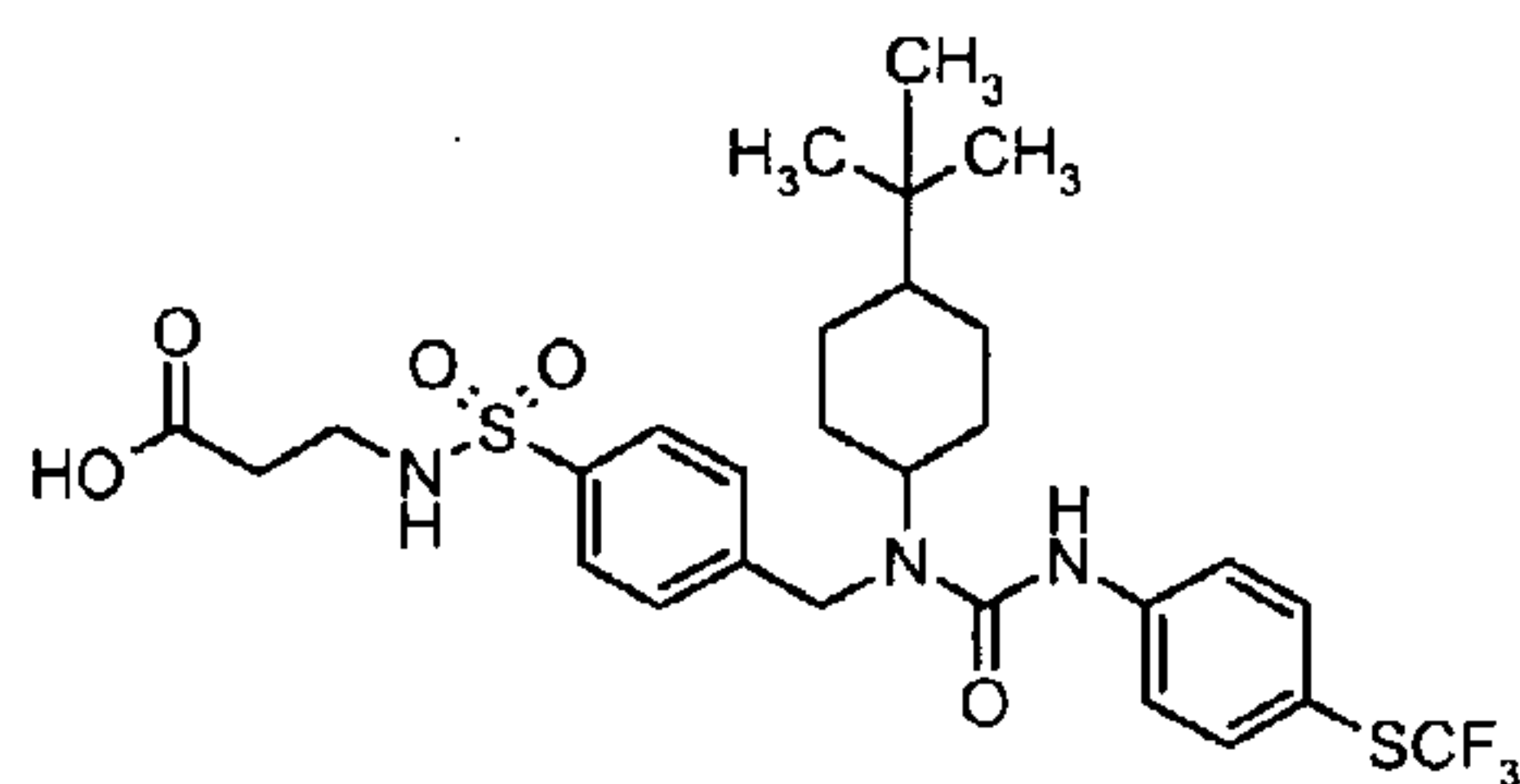
5

^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 0.90 (m, 1H), 1.05-1.15 (m, 2H), 1.40 (m, 2H), 1.65-1.75 (m, 4H), 2.51 (t, 2H), 3.44 (q, 2H), 4.00 (m, 1H), 4.59 (s, 2H), 7.12 (t, 1H), 7.30 (d, 2H), 7.62 (d, 2H), 7.75 (d, 2H), 8.45 (t, 1H), 8.69 (s, 1H), 12.50 (brd s, 1H).

10 MS (APCI, pos): 552.2, 550.2, 549.2, 548.2, 362.3, 361.2.

EXAMPLE 105 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzene-sulfonylamino}propionic acid



15

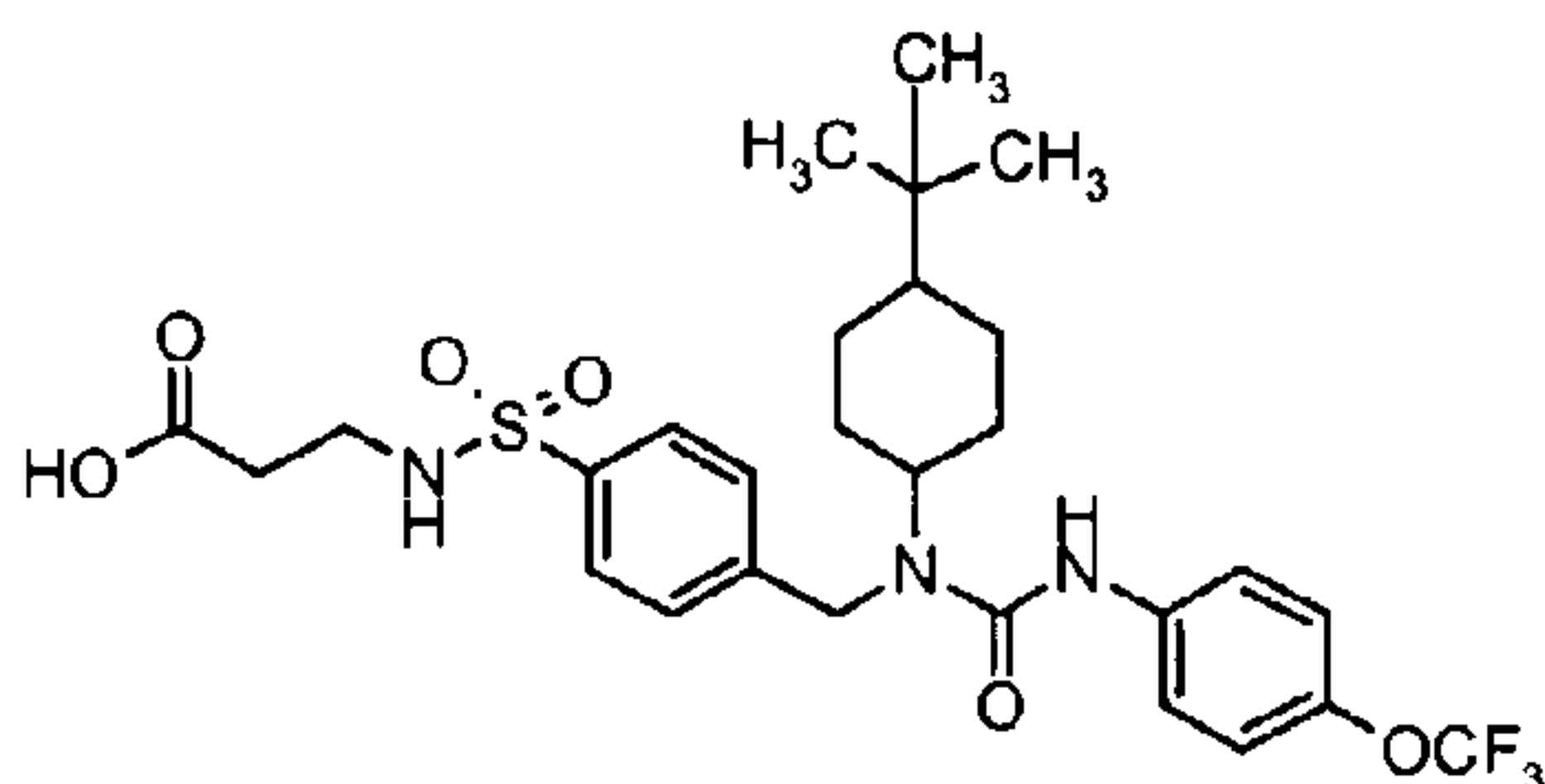
^1H NMR (Acetone- d_6): δ 0.83 (s, 9H), 0.97 (m, 1H), 1.17 (q, 2H), 1.54 (q, 2H), 1.81 (m, 4H), 2.50 (t, 2H), 3.15 (t, 2H), 4.17 (t, 1H), 4.76 (s, 2H), 6.60 (brd s, 1H), 7.56 (m, 4H), 7.67 (d, 2H), 7.83 (d, 2H), 8.19 (s, 1H).

20

MS (APCI, pos): 617.2, 616.2, 399.2, 398.1, 397.2.

EXAMPLE 106 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzenesulfonyl-
amino}propionic acid



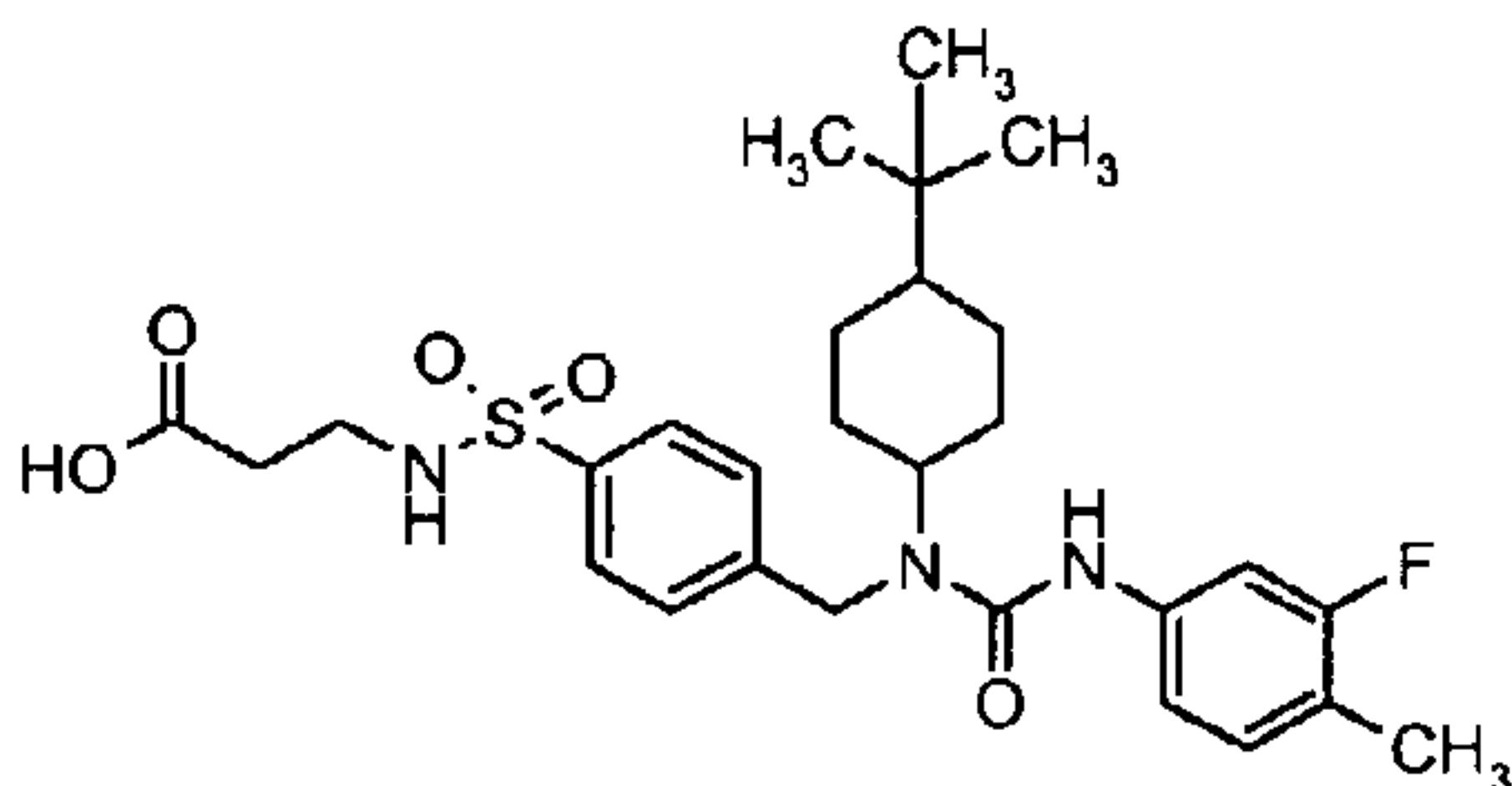
5

^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 1.11-1.17 (m, 3H), 1.49 (q, 2H), 1.70 (t, 4H), 2.32 (t, 2H), 2.90 (t, 2H), 4.01 (m, 2H), 4.62 (s, 2H), 7.22 (d, 2H), 7.45 (d, 2H), 7.55 (d, 2H), 7.72 (d, 2H), 8.59 (s, 1H), 12.20 (brd s, 1H).

10 MS (APCI, pos): 601.3, 600.2, 399.2, 398.3, 397.2.

EXAMPLE 107 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-fluoro-4-methylphenyl)ureidomethyl]benzenesulfonyl-
amino}propionic acid

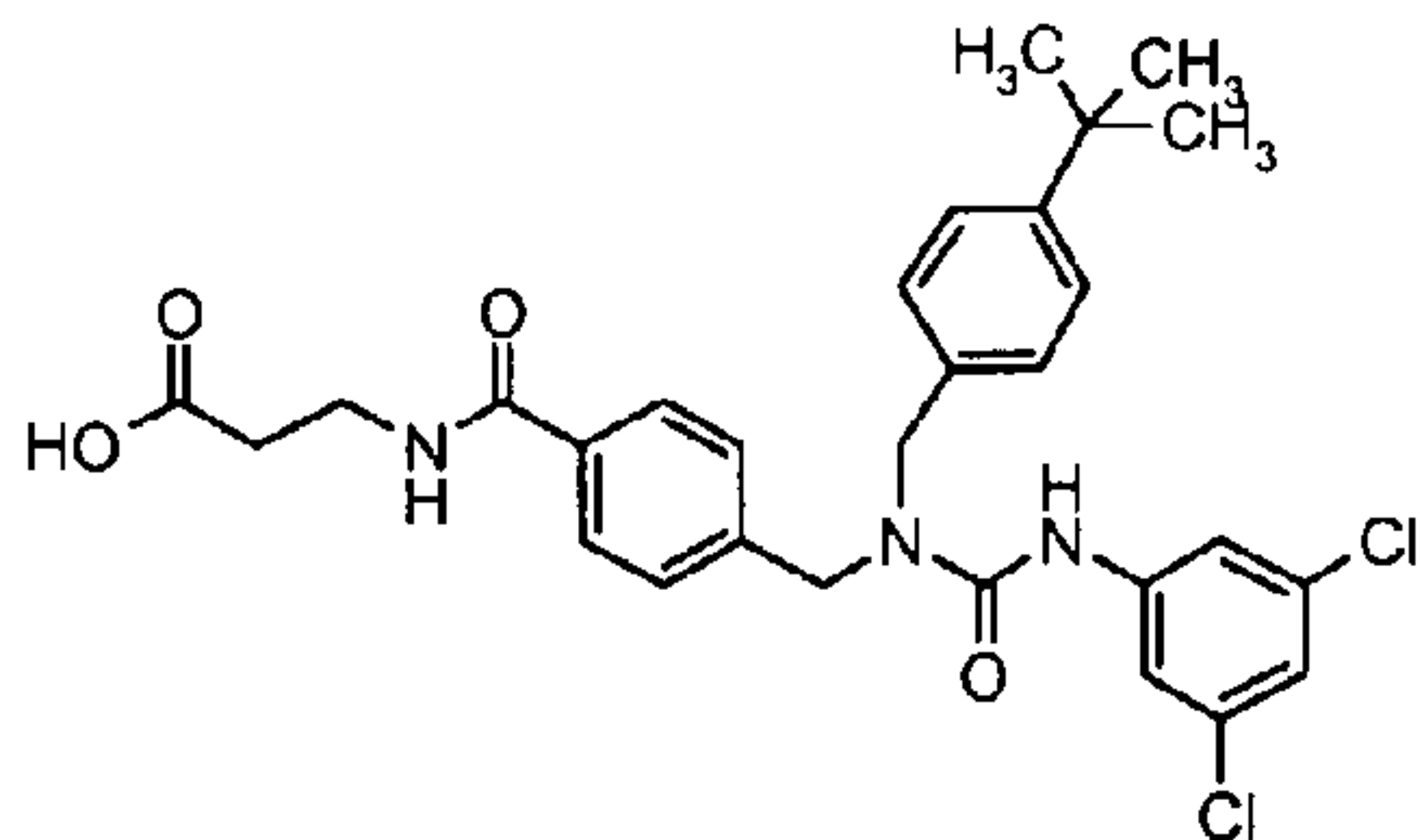


15

^1H NMR (Acetone- d_6): δ 0.82 (s, 6H), 0.84 (s, 3H), 1.21 (m 1H), 1.43-1.59 (m, 5H), 1.79-1.92 (m, 3H), 2.16 (s, 3H), 2.52 (t, 2H), 3.14 (q, 2H), 4.36 (m, 1H), 4.85 (s, 2H), 6.51 (btd t, 1H), 7.07 (d, 2H), 7.49-7.57 (m, 3H), 7.83-7.90 (m, 3H), 11.50 (brd s, 1H).

20

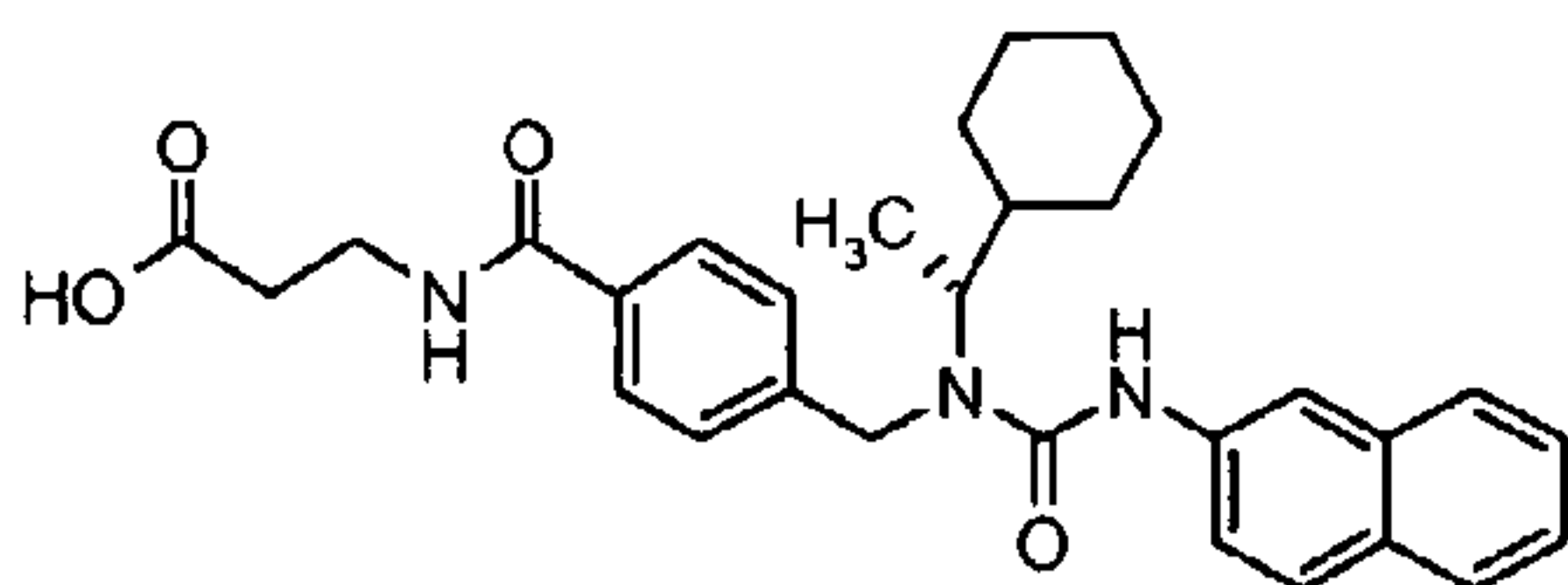
MS (APCI, pos): 548.2, 399.1, 398.3, 397.2.

EXAMPLE 108 (general procedure (G))3-{4-[1-(4-*tert*-Butylbenzyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid

- 5 ^1H NMR (DMSO- d_6): δ 1.25 (s, 9H), 3.33 (m, 2H), 3.43 (m, 2H), 4.51 (s, 2H), 4.63 (s, 2H), 7.14-7.17 (m, 3H), 7.30 (d, 2H), 7.36 (d, 2H), 7.66 (m, 2H), 7.79 (s, 1H), 8.50 (t, 1H), 8.97 (s, 1H), 12.25 (brd s, 1H).

MS (APCI, pos): 558.2, 557.2, 556.2, 370.1, 369.1.

10

EXAMPLE 109 (general procedure (G))3-{4-[1-((1R)-1-Cyclohexylethyl)-3-naphthalene-2-ylureidomethyl]benzoylamino}propionic acid

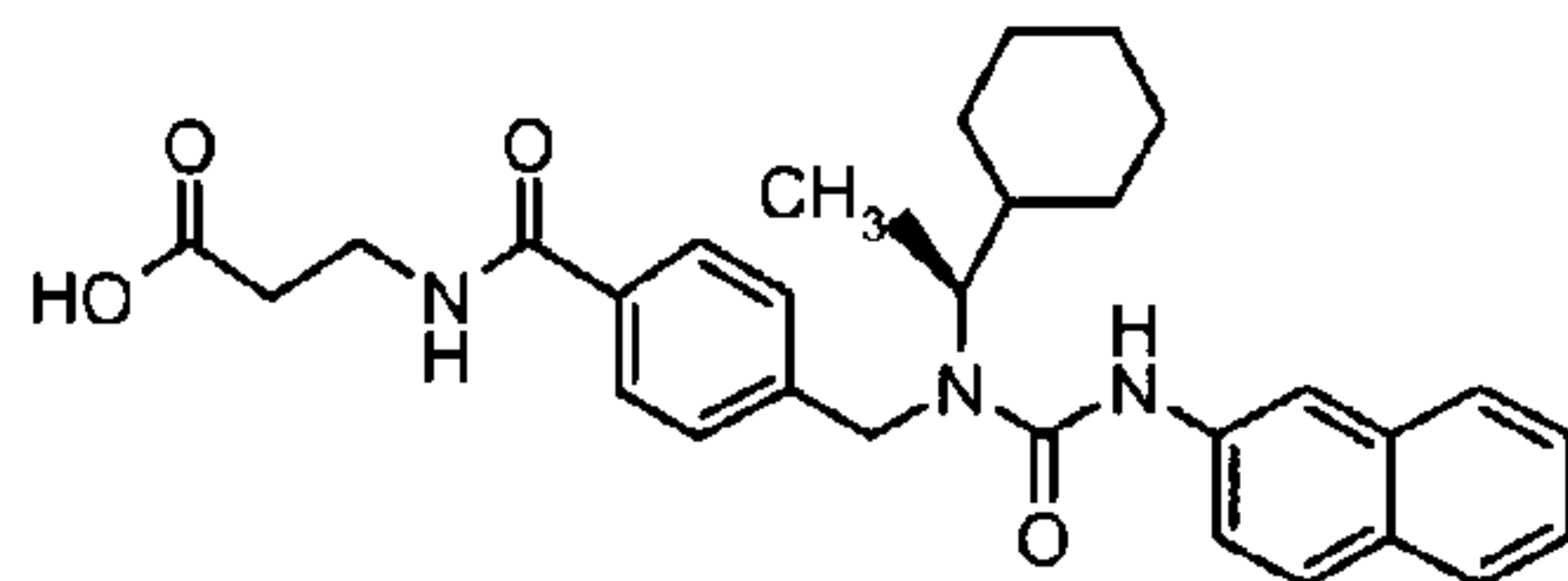
15

^1H NMR (CDCl₃): δ 0.92-1.10 (m, 8H), 1.36 (q, 1H), 1.59 (m, 2H), 1.67 (d, 3H), 2.51 (t, 2H), 3.54 (q, 2H), 4.05 (m, 1H), 4.30 (d, 2H), 4.50 (d, 2H), 6.32 (brd s, 2H), 6.47 (brd s, 1H), 7.00-7.07 (m, 2H), 7.23 (t, 1H), 7.27-7.30 (m, 3H), 7.54-7.67 (m, 6H).

20 MS (APCI, pos): 503.3, 502.3, 333.3.

EXAMPLE 110 (general procedure (G))

3-{4-[1-((1S)-1-Cyclohexylethyl)-3-naphthalene-2-ylureidomethyl]benzoylamino}propionic acid



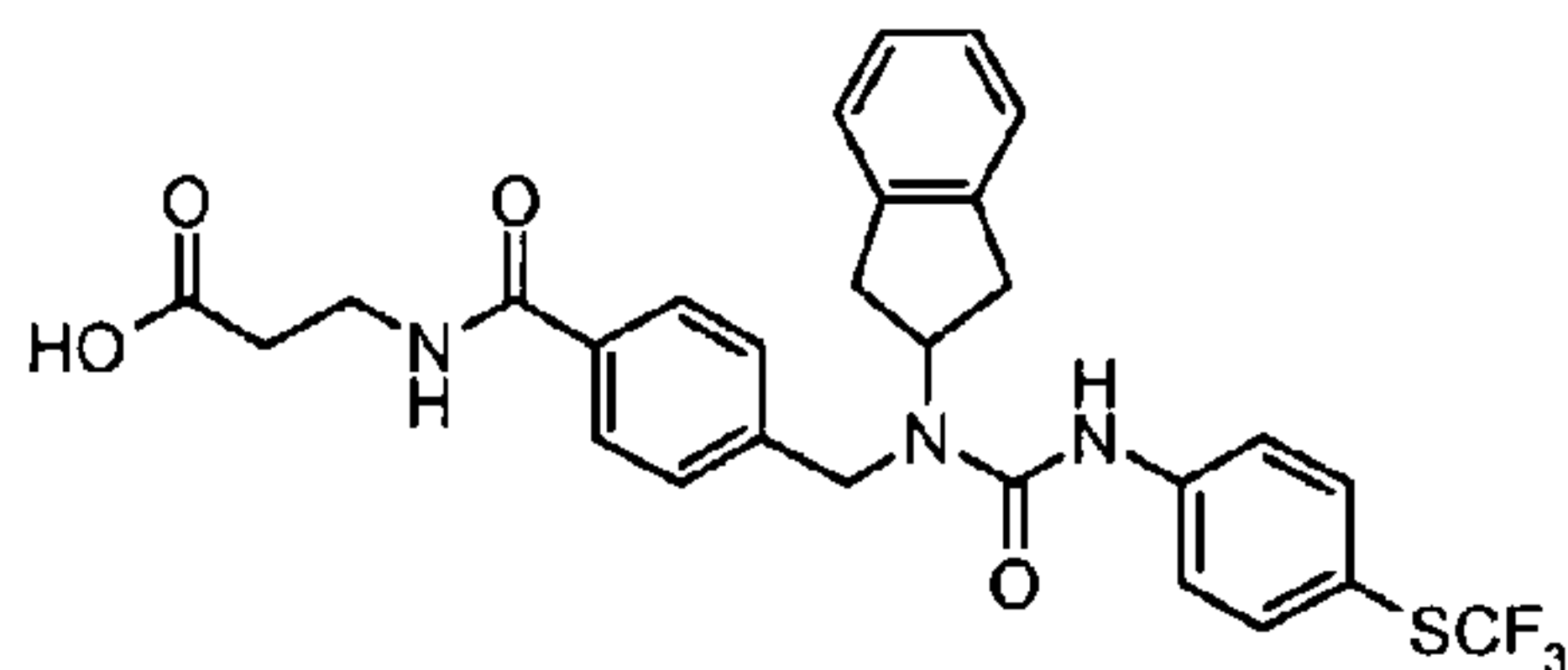
5

¹H NMR (DMSO-*d*₆): δ 0.91 (m, 3H), 1.09 (d, 3H), 1.11 (m, 3H), 1.15-1.88 (m, 6H), 2.44 (t, 2H), 3.34 (q, 2H), 4.09 (q, 1H), 4.36 (d, 1H), 4.80 (d, 1H), 7.32 (t, 1H), 7.38 (d, 2H), 7.42 (t, 1H), 7.55 (dd, 1H), 7.71-7.79 (m, 5H), 7.97 (dd, 1H), 8.52 (t, 1H).

10 MS (APCI, pos): 502.2, 353.0.

EXAMPLE 111 (general procedure (G))

3-{4-[1-(2,3-Dihydro-1H-inden-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



15

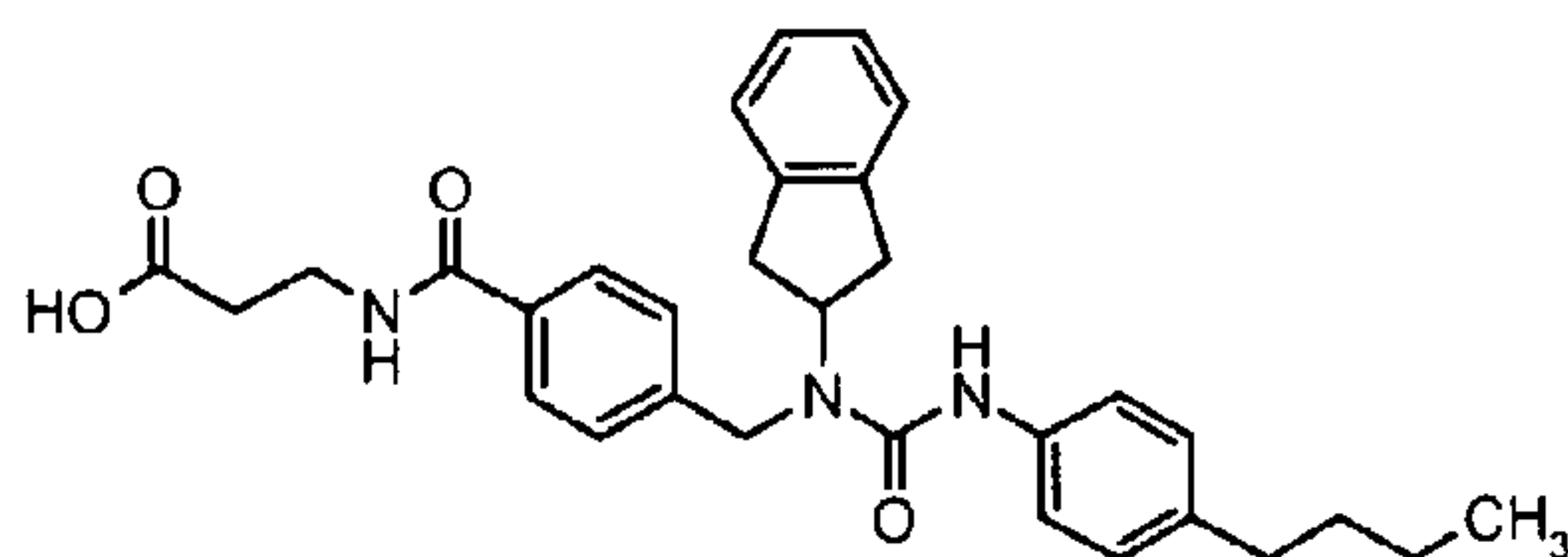
¹H NMR (DMSO-*d*₆): δ 2.44 (t, 2H), 2.90-3.06 (m, 4H), 3.40-3.46 (m, 2H), 4.67 (s, 2H), 5.09 (qt, 1H), 7.06-7.21 (m, 4H), 7.29 (d, 2H), 7.52 (d, 2H), 7.68 (d, 2H), 7.77 (d, 2H), 8.48 (t, 1H), 8.88 (s, 1H), 12.00 (brd s, 1H).

20

MS (APCI, pos): 558.2, 339.1.

EXAMPLE 112 (general procedure (G))

3-{4-[1-(2,3-Dihydro-1*H*-inden-2-yl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



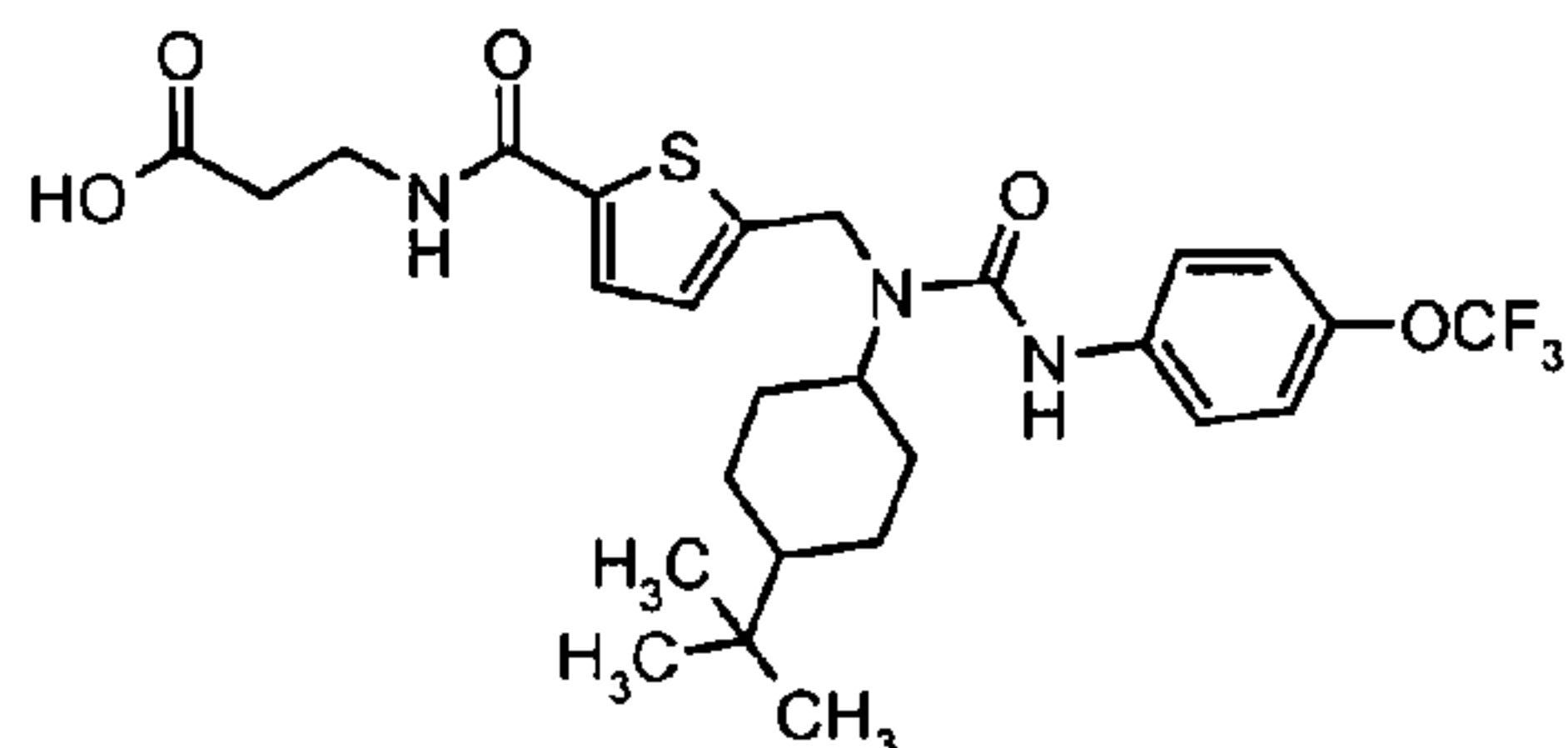
5

¹H NMR (DMSO-*d*₆): δ 0.87 (t, 3H), 1.28 (hex, 2H), 1.49 (qt, 2H), 2.51 (t, 2H), 2.69 (t, 2H), 2.95 (d, 1H), 3.01 (d, 1H), 3.25 (d, 1H), 3.30 (d, 1H), 3.70 (q, 2H), 4.59 (s, 2H), 5.21 (qt, 1H), 6.21 (s, 1H), 6.91 (t, 1H), 7.02 (s, 4H), 7.18 (s, 4H), 7.37 (d, 2H), 7.47 (d, 2H).

10 MS (APCI, pos): 514.2, 339.1.

EXAMPLE 113 (general procedure (G))

3-{5-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid



15

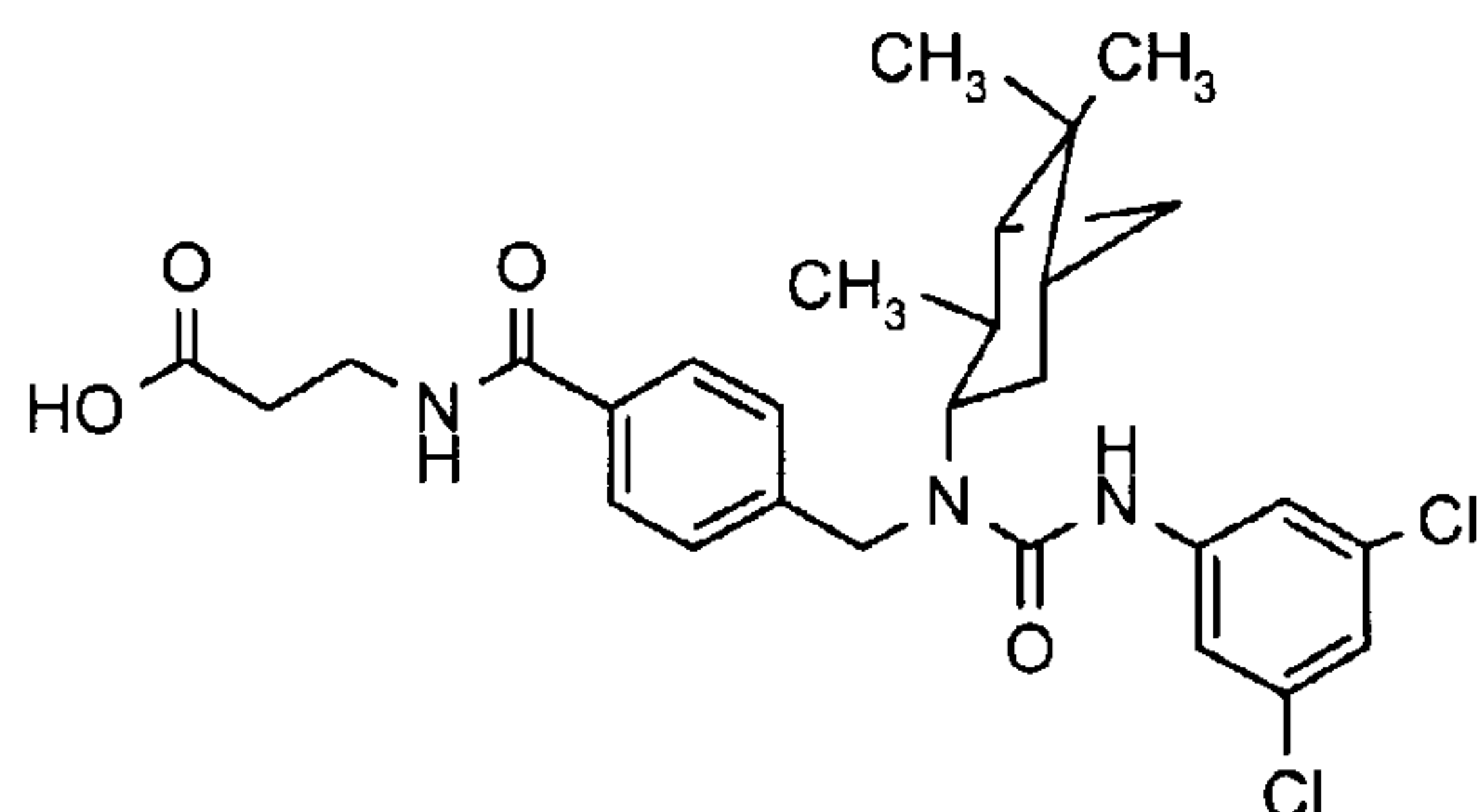
¹H NMR (DMSO-*d*₆): δ 0.61 (s, 9H), 0.73 (m, 1H), 0.87 (q, 2H), 1.24 (q, 2H), 1.51 (m, 4H), 2.21 (t, 2H), 3.16 (q, 2H), 3.73 (t, 1H), 4.42 (s, 2H), 6.77 (d, 1H), 7.02 (d, 2H), 7.29 (d, 2H), 7.33 (d, 1H), 8.21 (t, 1H), 8.37 (s, 1H), 11.99 (brd s, 1H).

20

MS (APCI, neg): 568.0, 569.0.

EXAMPLE 114 (general procedure (G))

3-{4-[1-((2R,3R)-2,6,6-Trimethylbicyclo[3.3.1]hept-3-yl)-3-(3,5-dichlorophenyl)ureidomethyl]-benzoylamino}propionic acid



5

¹H NMR (DMSO-*d*₆): δ 0.96 (d, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.65-1.71 (m, 2H), 1.89-1.94 (m, 2H), 2.20-2.28 (m, 2H), 2.44 (t, 2H), 3.49 (q, 2H), 4.66 (s, 2H), 4.85 (m, 1H), 7.10 (t, 1H), 7.30 (d, 2H), 7.53 (d, 2H), 7.80 (d, 2H), 8.47 (t, 1H), 8.69 (s, 1H).

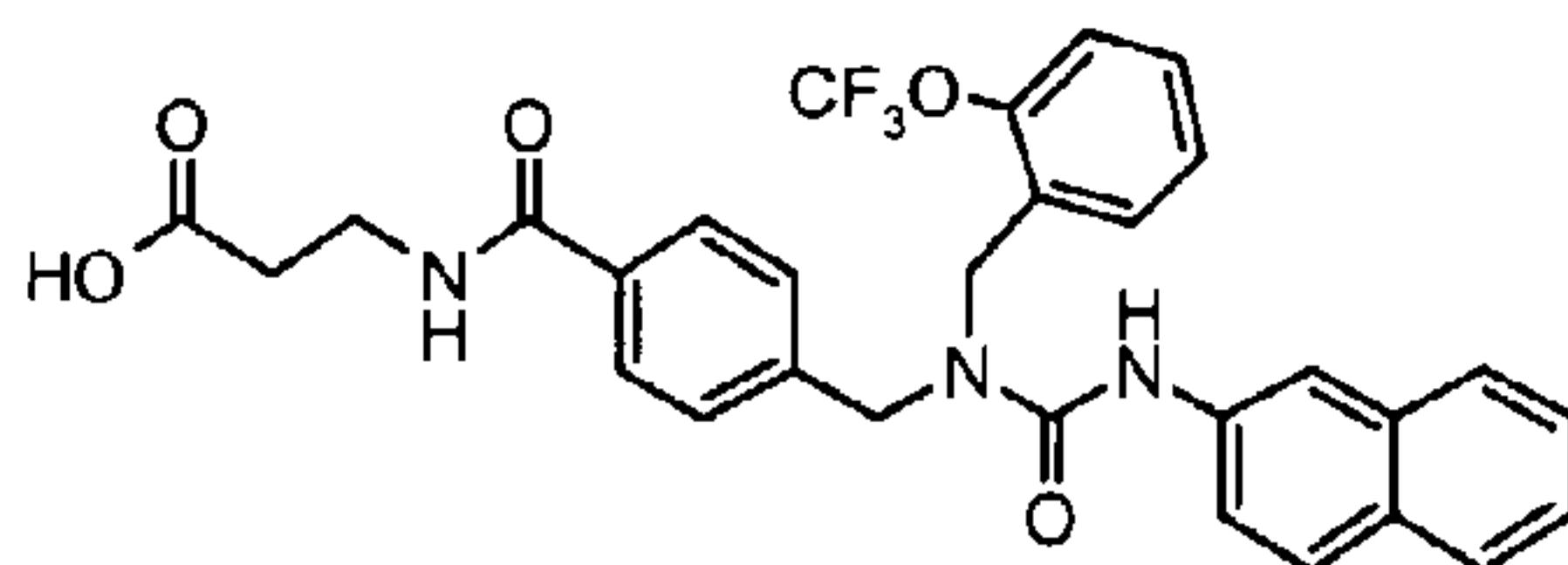
10 MS (APCI, pos): 546.1, 359.2, 287.1.

The following examples 115 to 136 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. These compounds are all expected to be present in the library.

15

EXAMPLE 115 (general procedure (G))

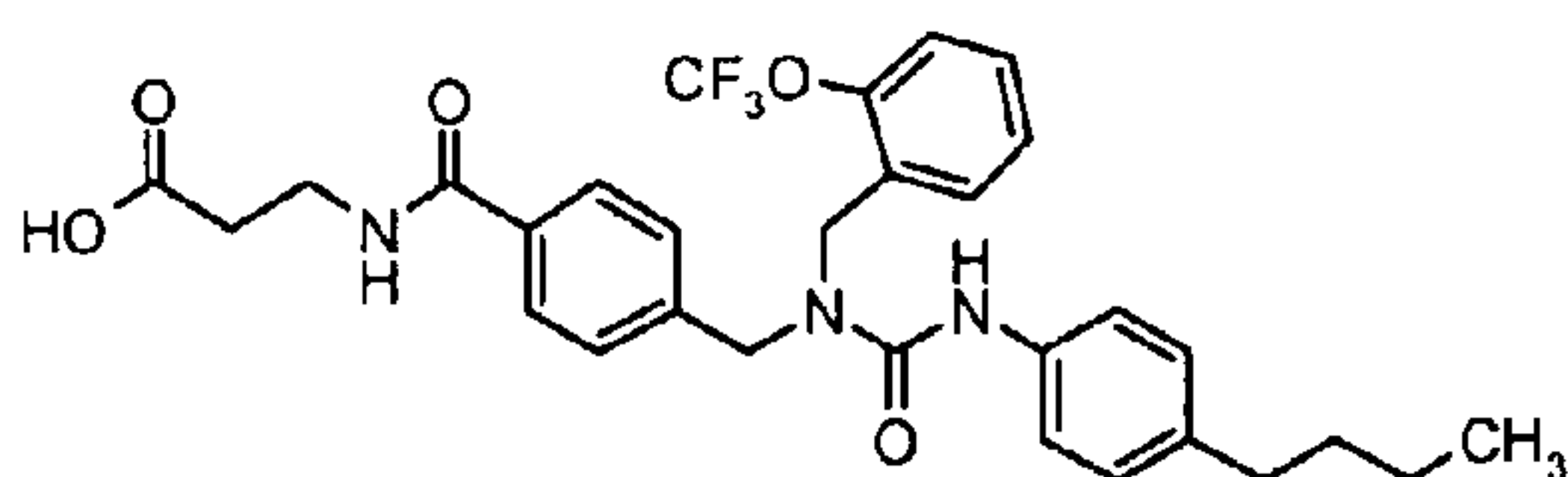
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-naphthalene-2ylureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 116 (general procedure (G))

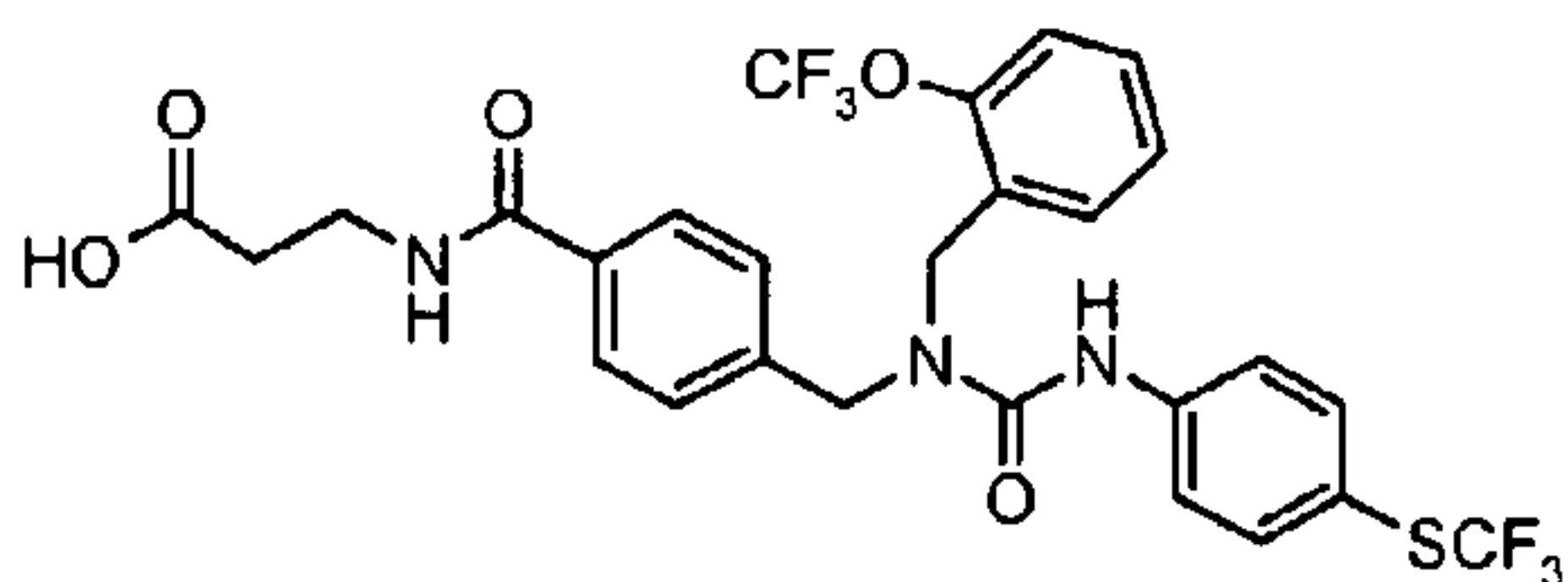
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 117 (general procedure (G))

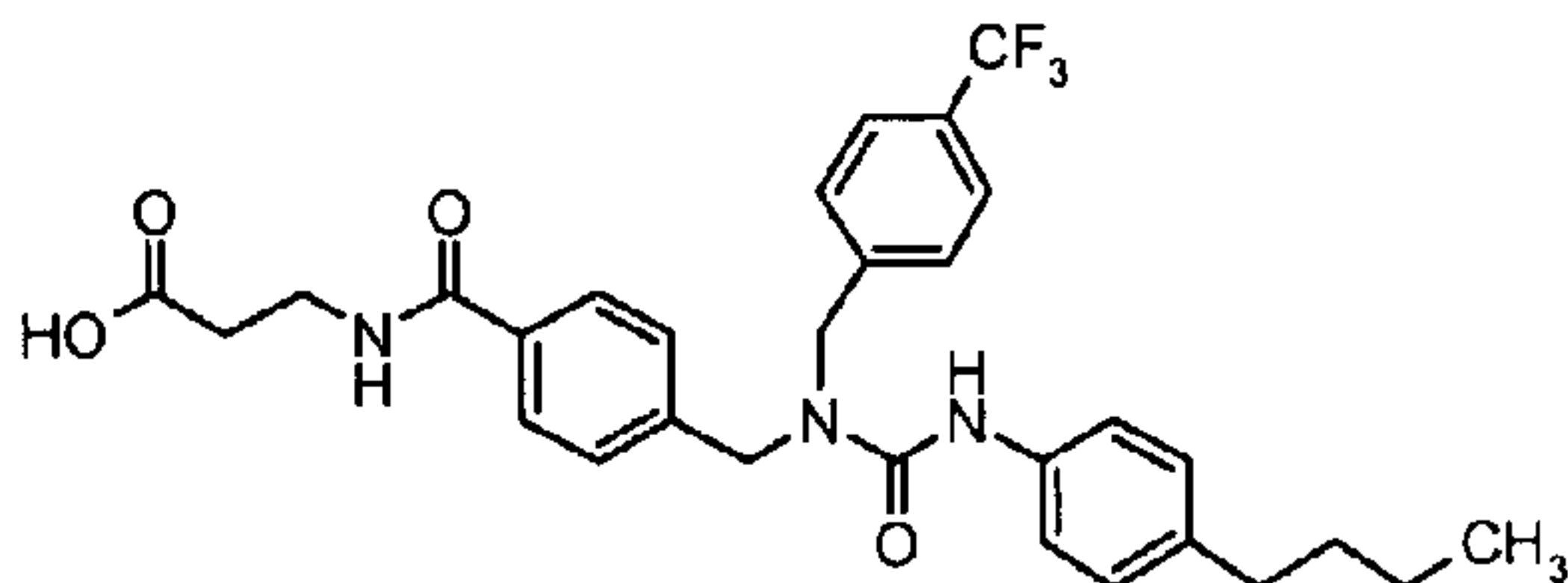
3-{4-[1-(2-Trifluoromethoxybenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



15

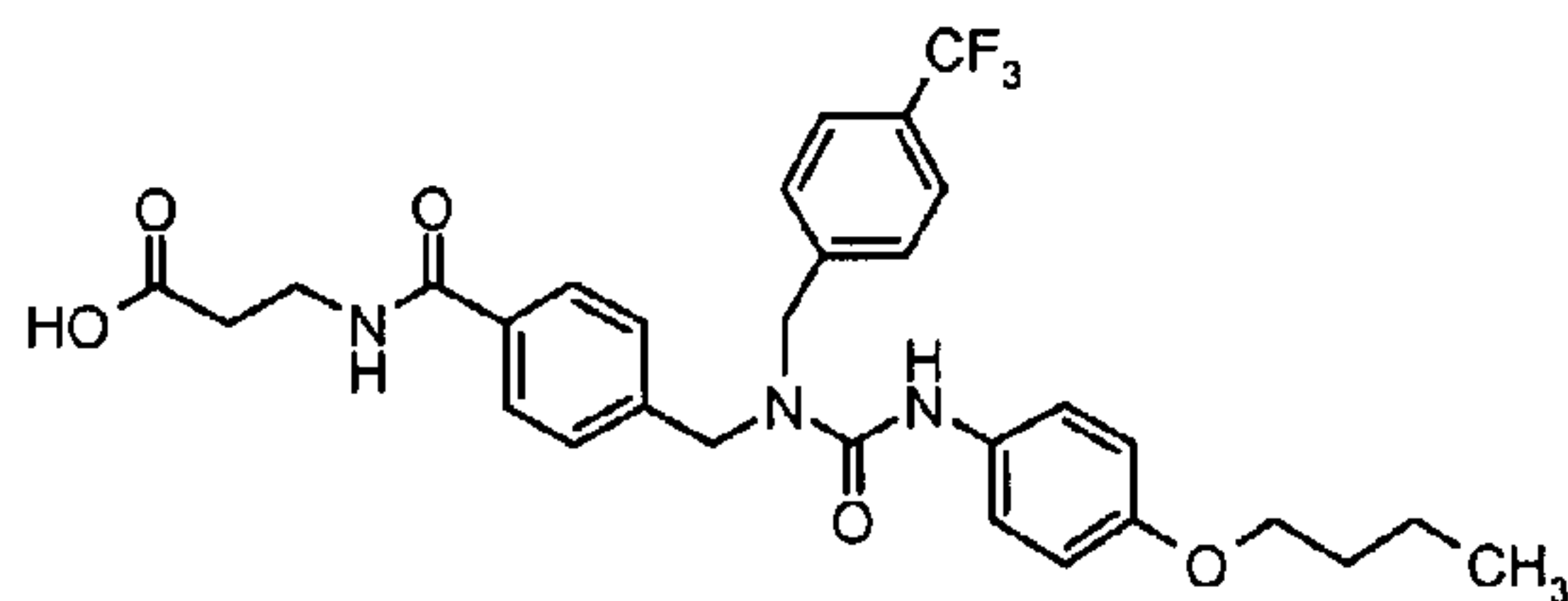
EXAMPLE 118 (general procedure (G))

3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-butylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 119 (general procedure (G))

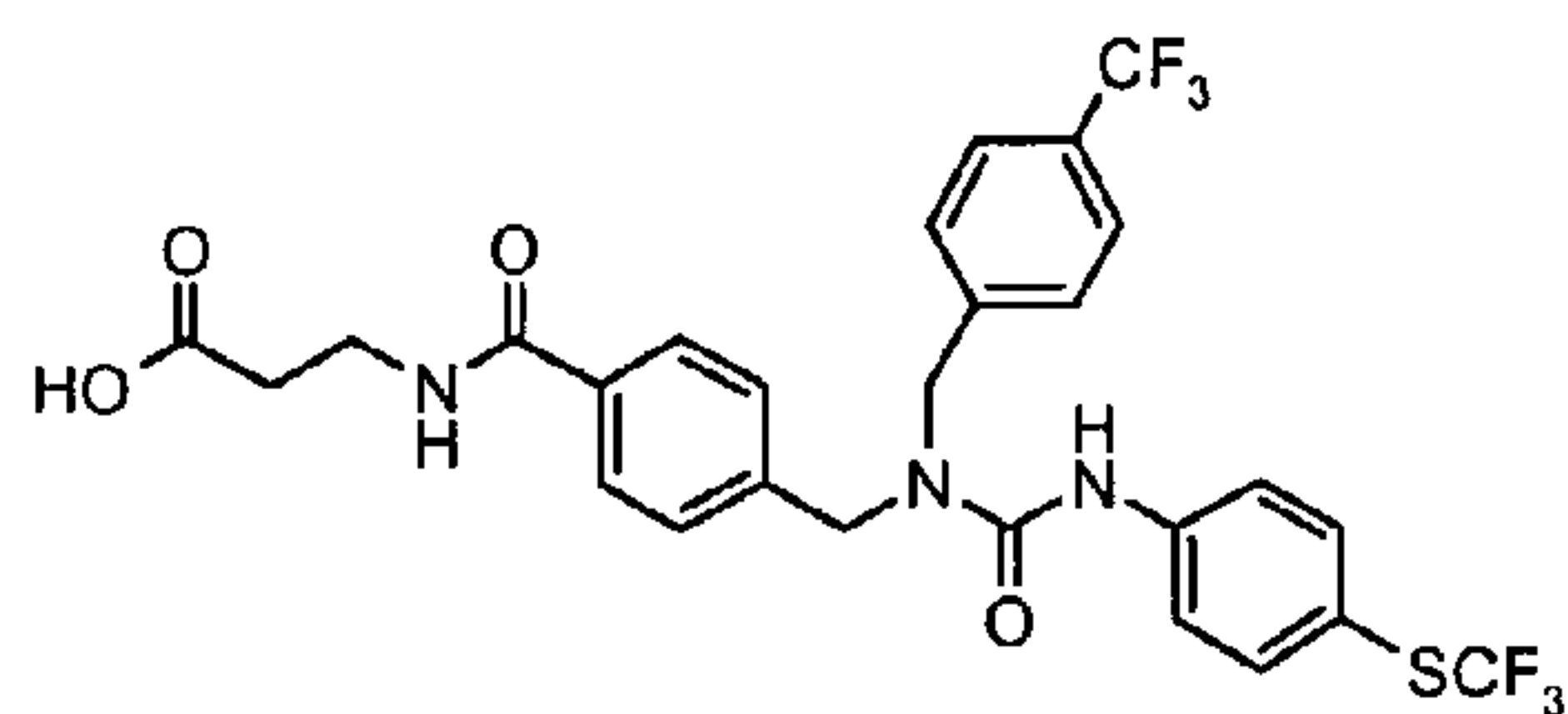
3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-butoxyphenyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 120 (general procedure (G))

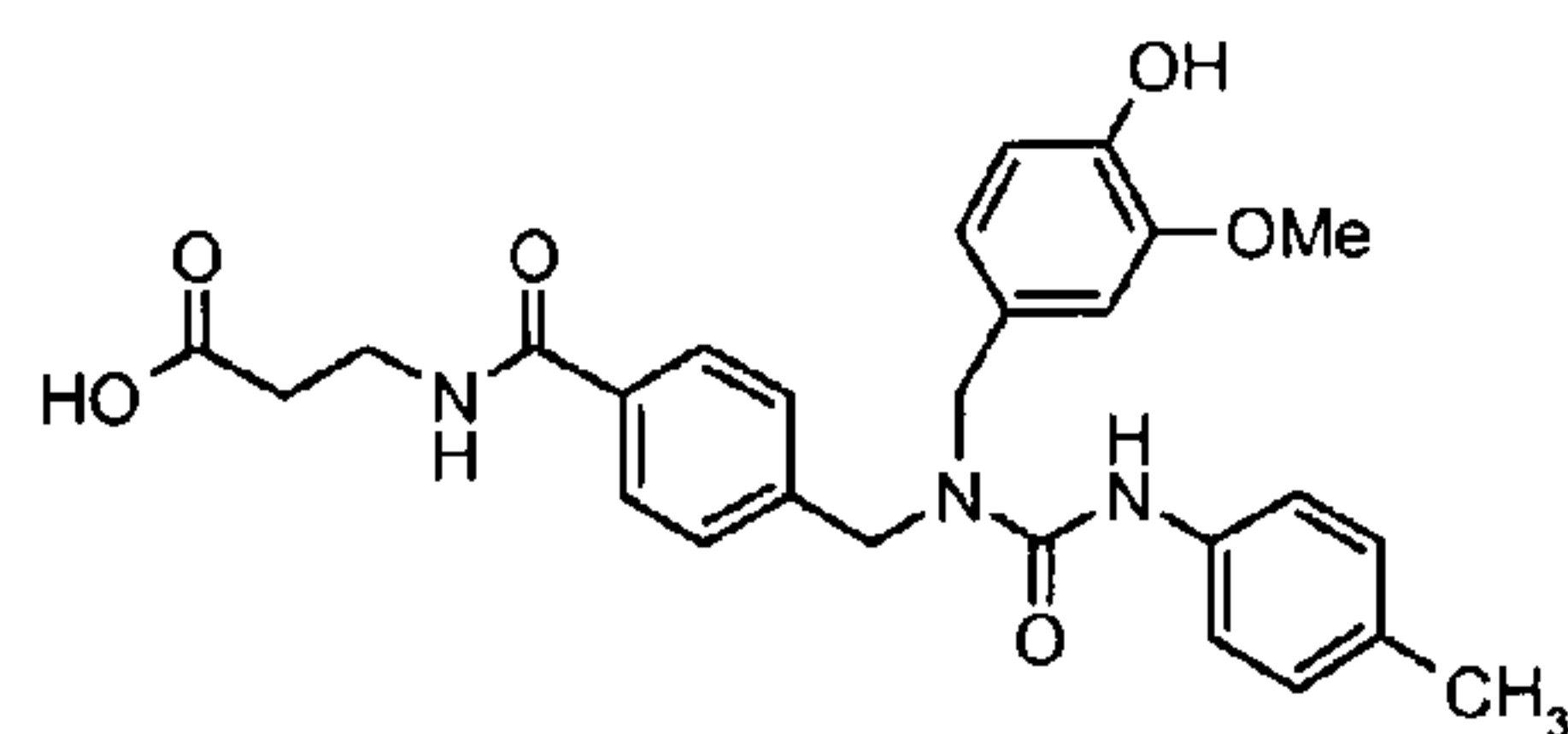
3-{4-[1-(4-Trifluoromethylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 121 (general procedure (G))

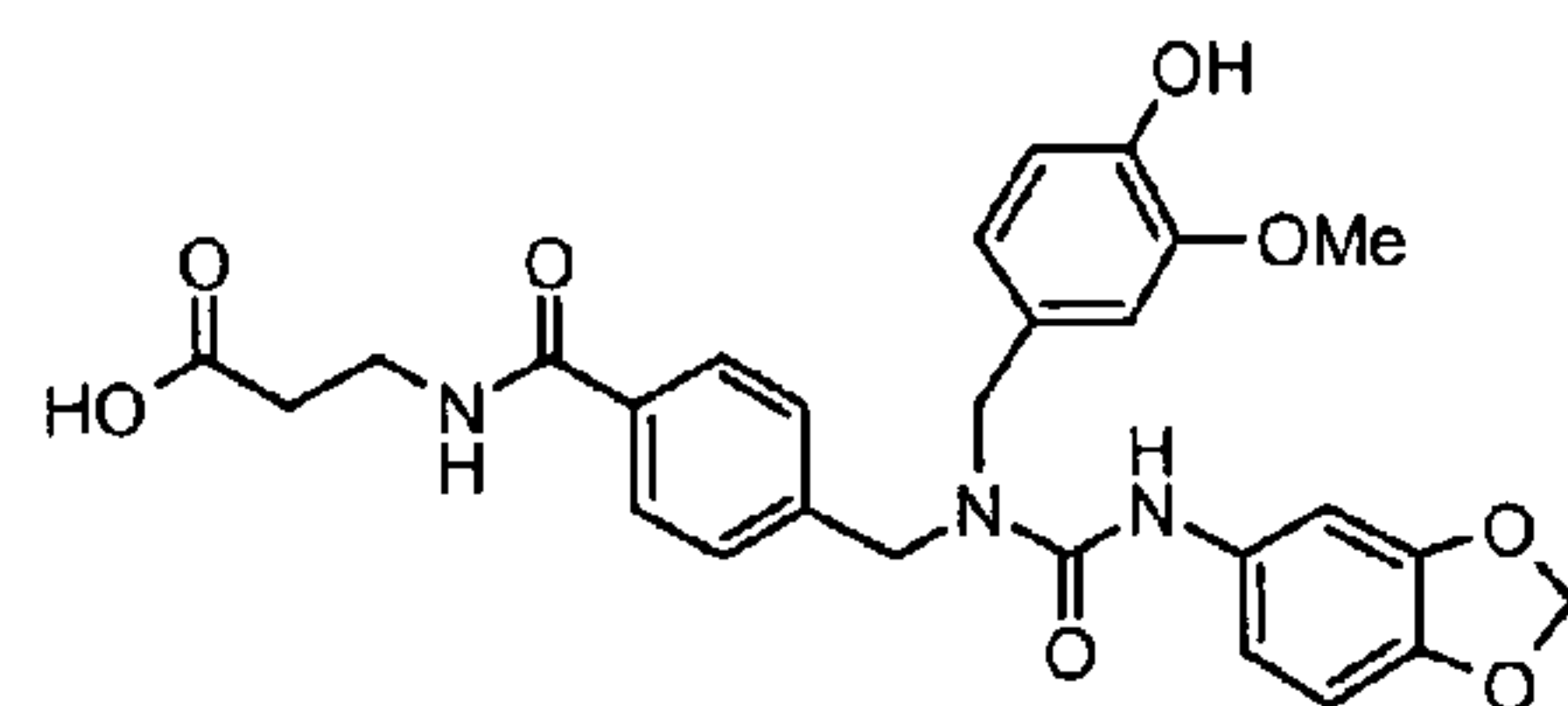
3-{4-[1-(4-Hydroxy-3-methoxybenzyl)-3-(4-methylphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 122 (general procedure (G))

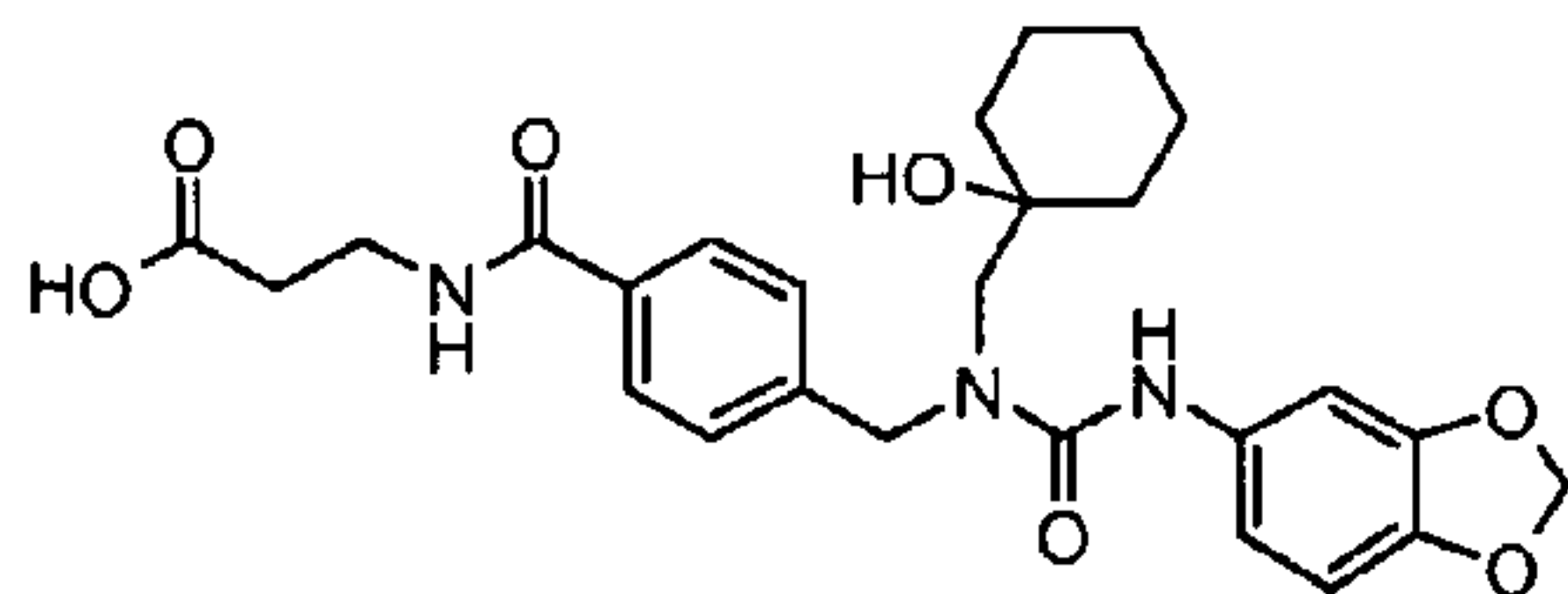
3-{4-[1-(4-Hydroxy-3-methoxybenzyl)-3-(3,4-methylenedioxyphenyl)ureidomethyl]benzoylamino}propionic acid



20

EXAMPLE 123 (general procedure (G))

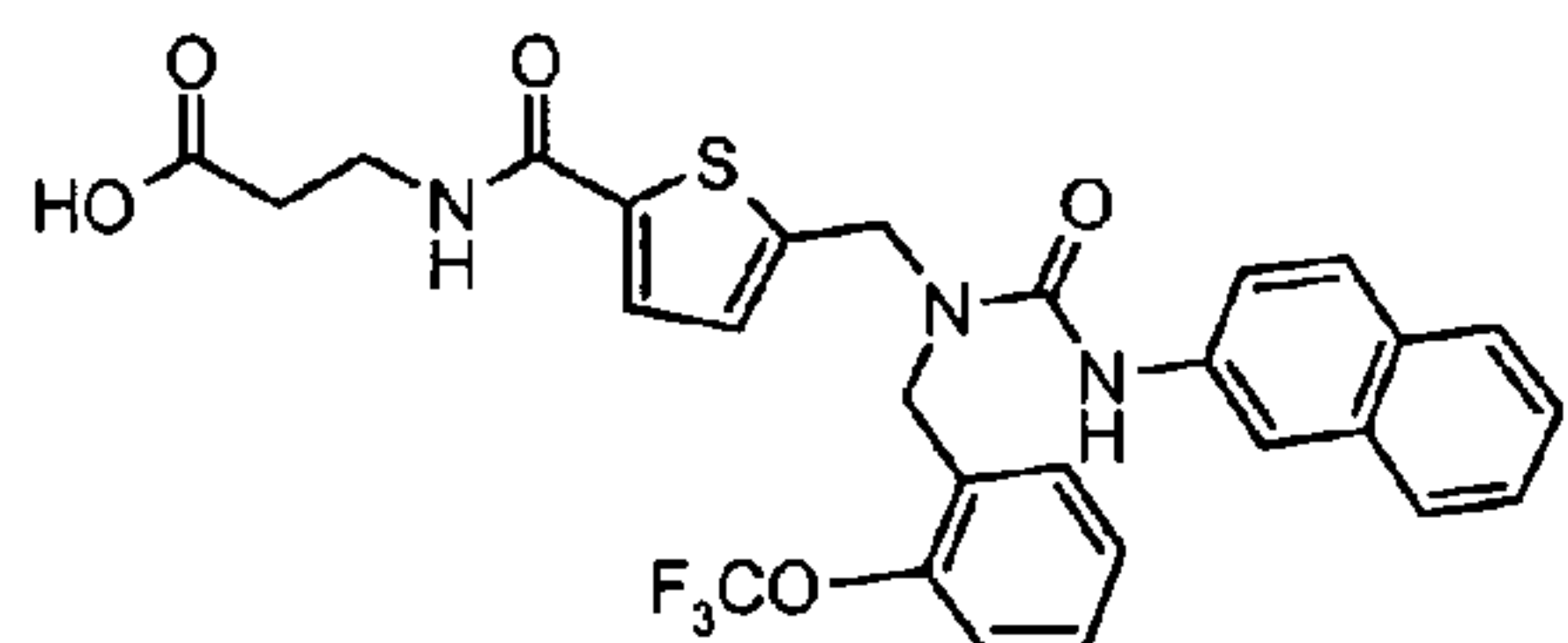
3-{4-[1-(1-Hydroxycyclohexylmethyl)-3-(3,4-methylenedioxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



5

EXAMPLE 124 (general procedure (G))

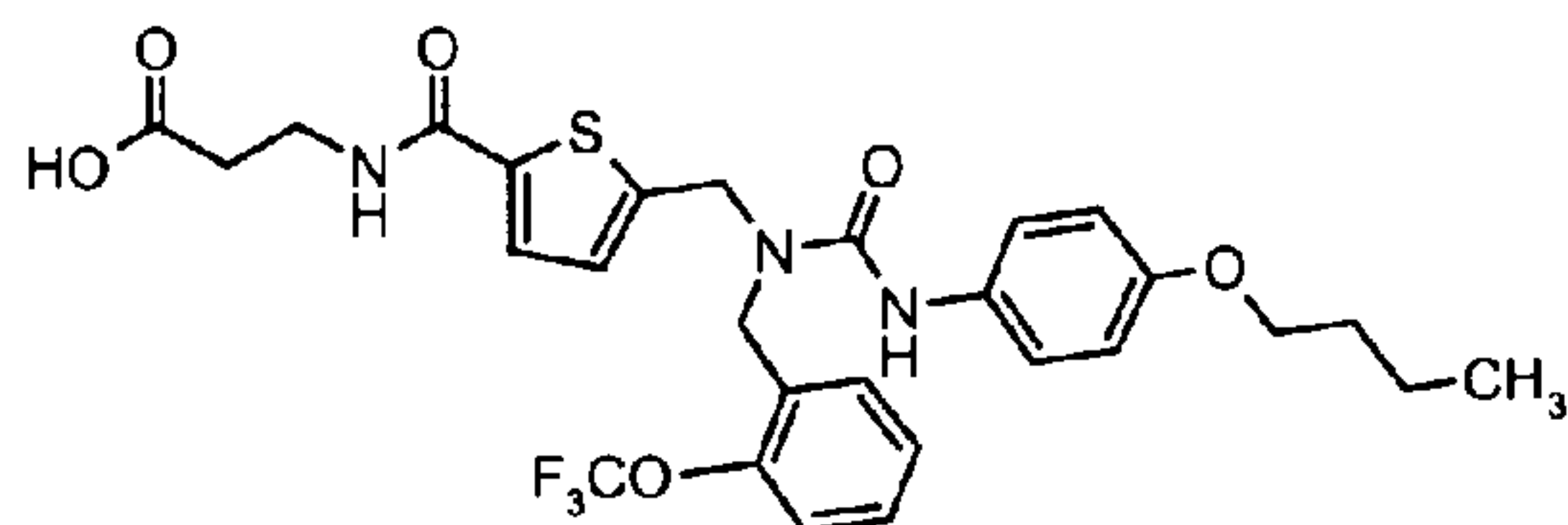
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonyl-amino}propionic acid



10

EXAMPLE 125 (general procedure (G))

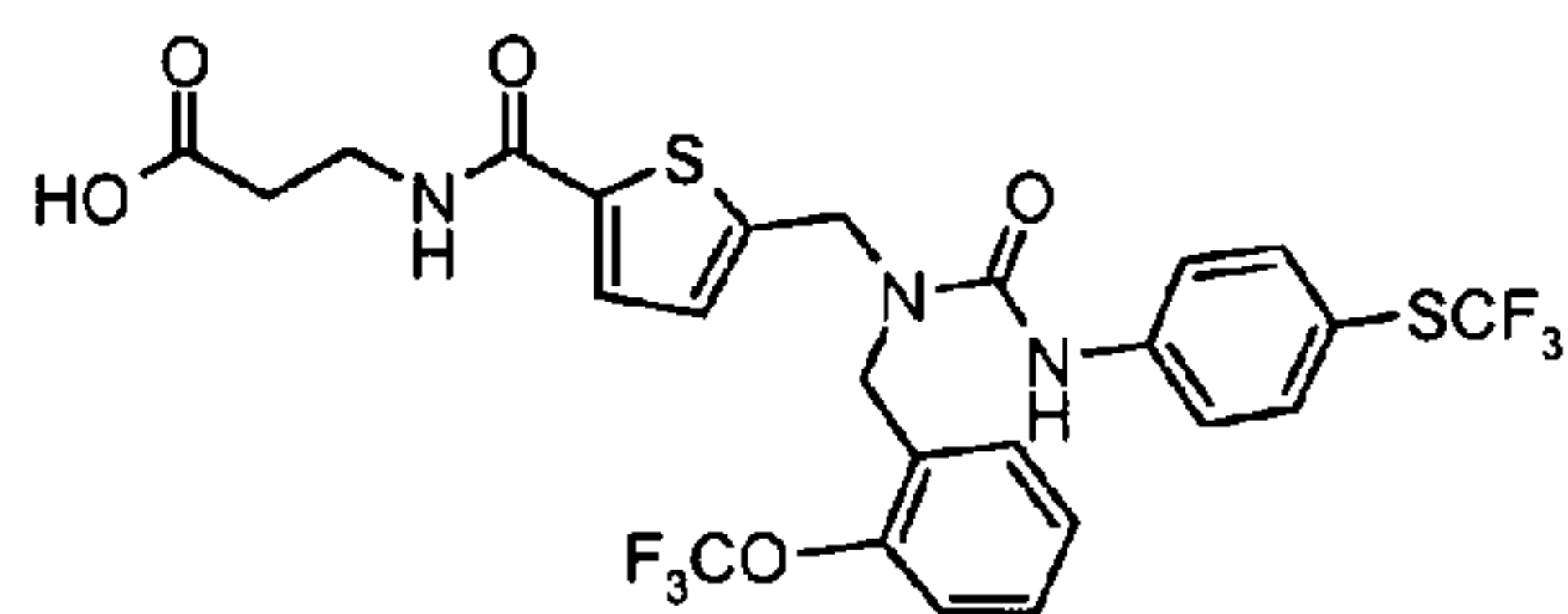
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-(4-butoxyphenyl)ureidomethyl]thiophene-2-carbonyl-amino}propionic acid



15

EXAMPLE 126 (general procedure (G))

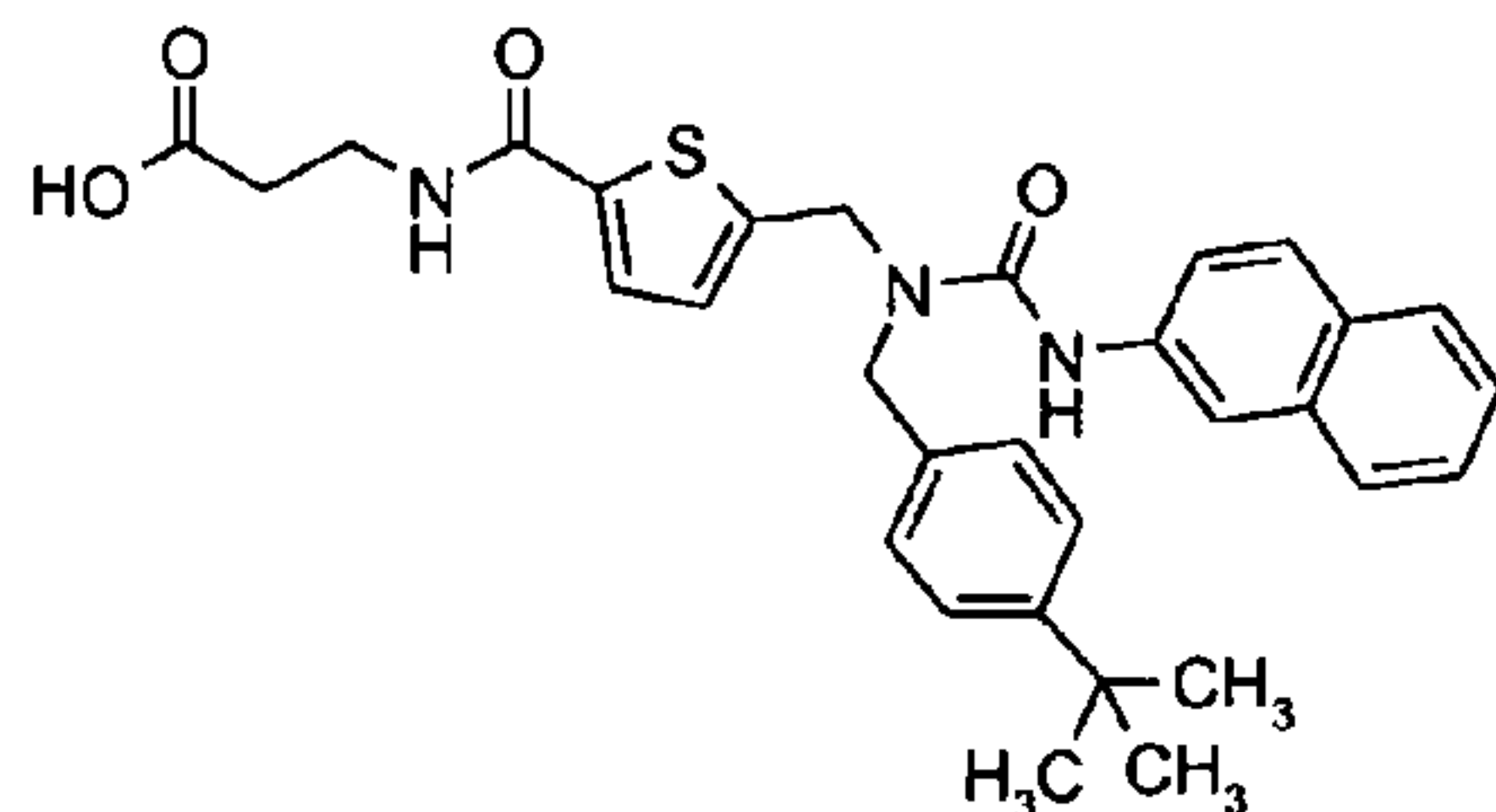
3-{5-[1-(2-Trifluoromethoxybenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid



20

EXAMPLE 127 (general procedure (G))

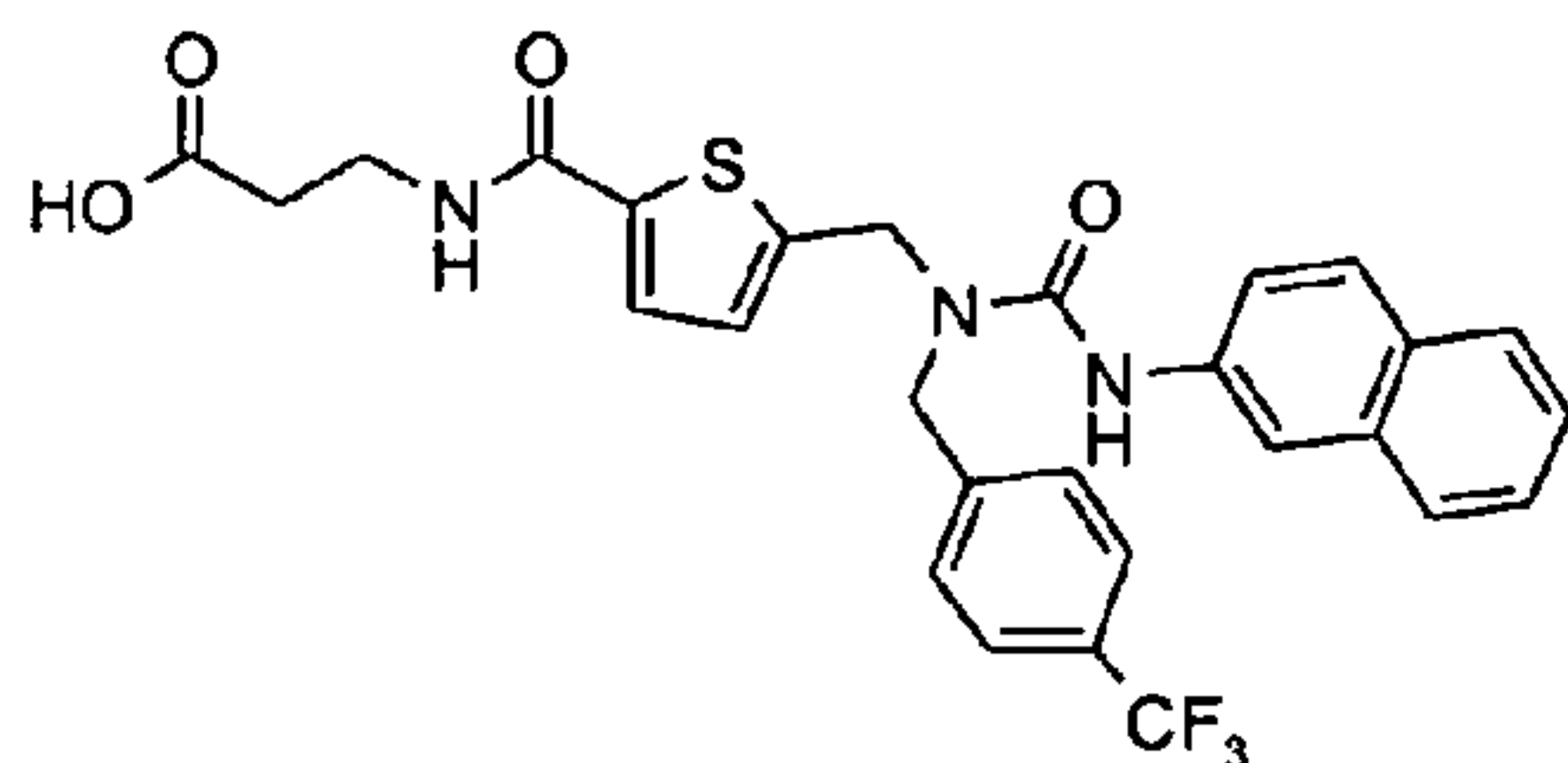
3-{5-[1-(4-*tert*-Butylbenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonylamino)-propionic acid



5

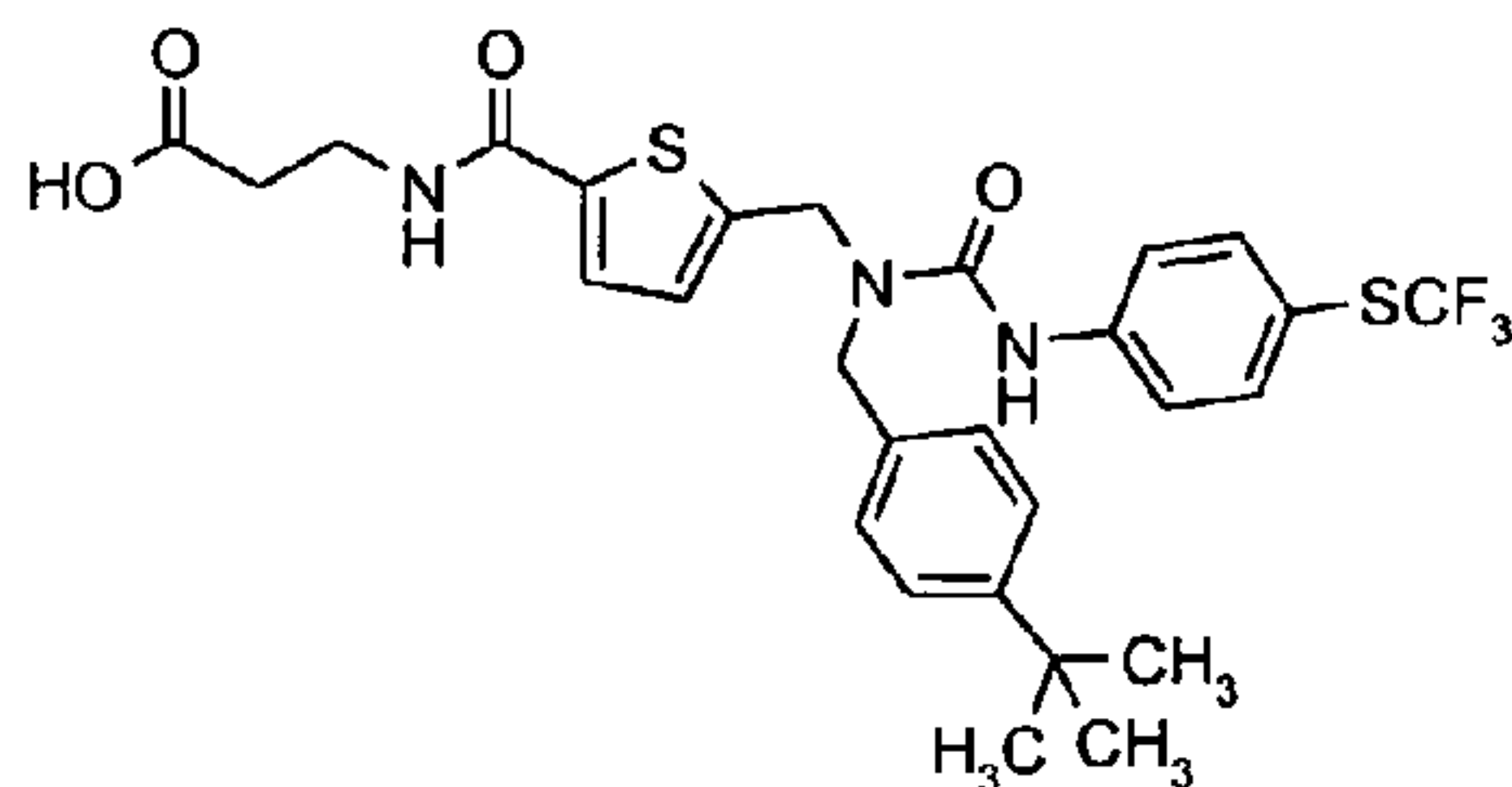
EXAMPLE 128 (general procedure (G))

3-{5-[1-(4-Trifluoromethylbenzyl)-3-naphthalene-2-ylureidomethyl]thiophene-2-carbonylamino)propionic acid



EXAMPLE 130 (general procedure (G))

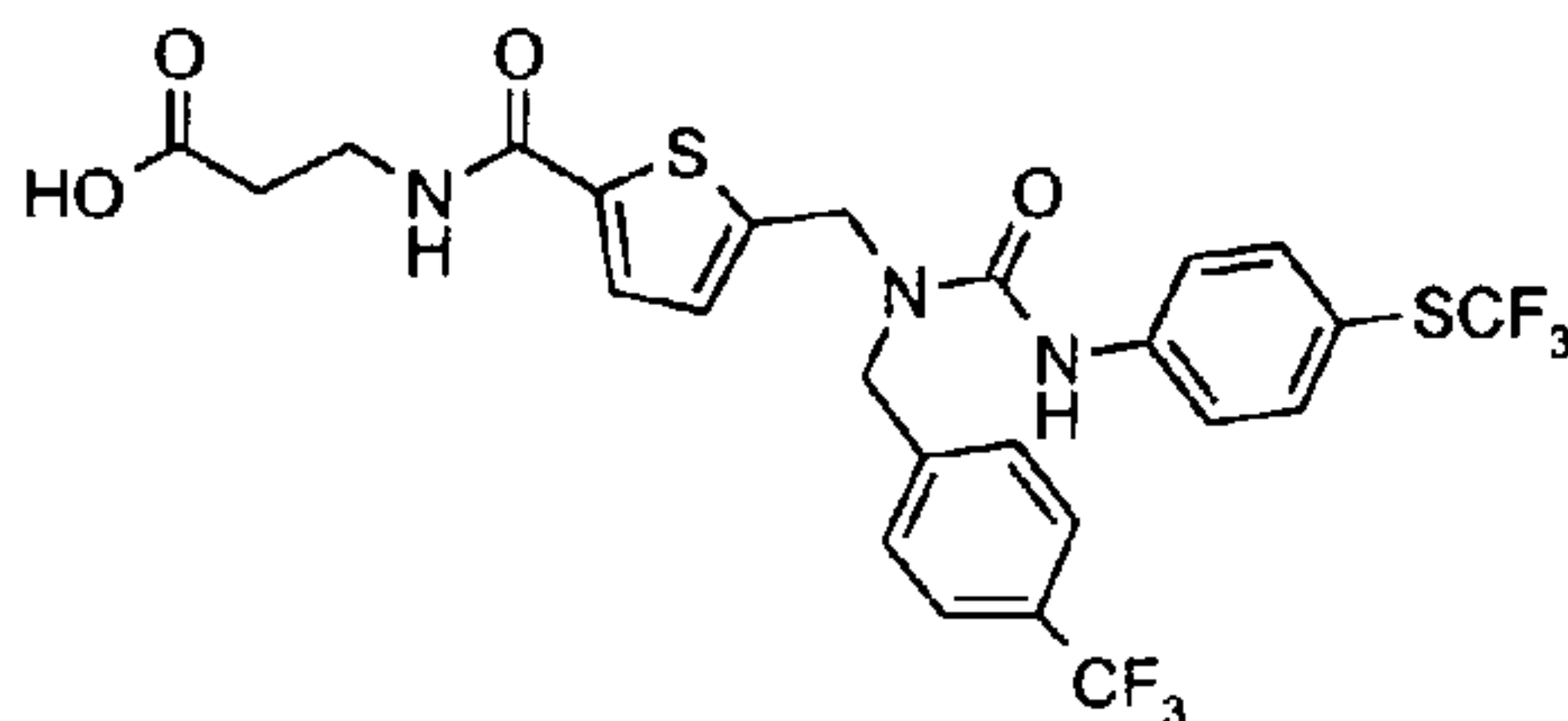
3-{5-[1-(4-*tert*-Butylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid



5

EXAMPLE 131 (general procedure (G))

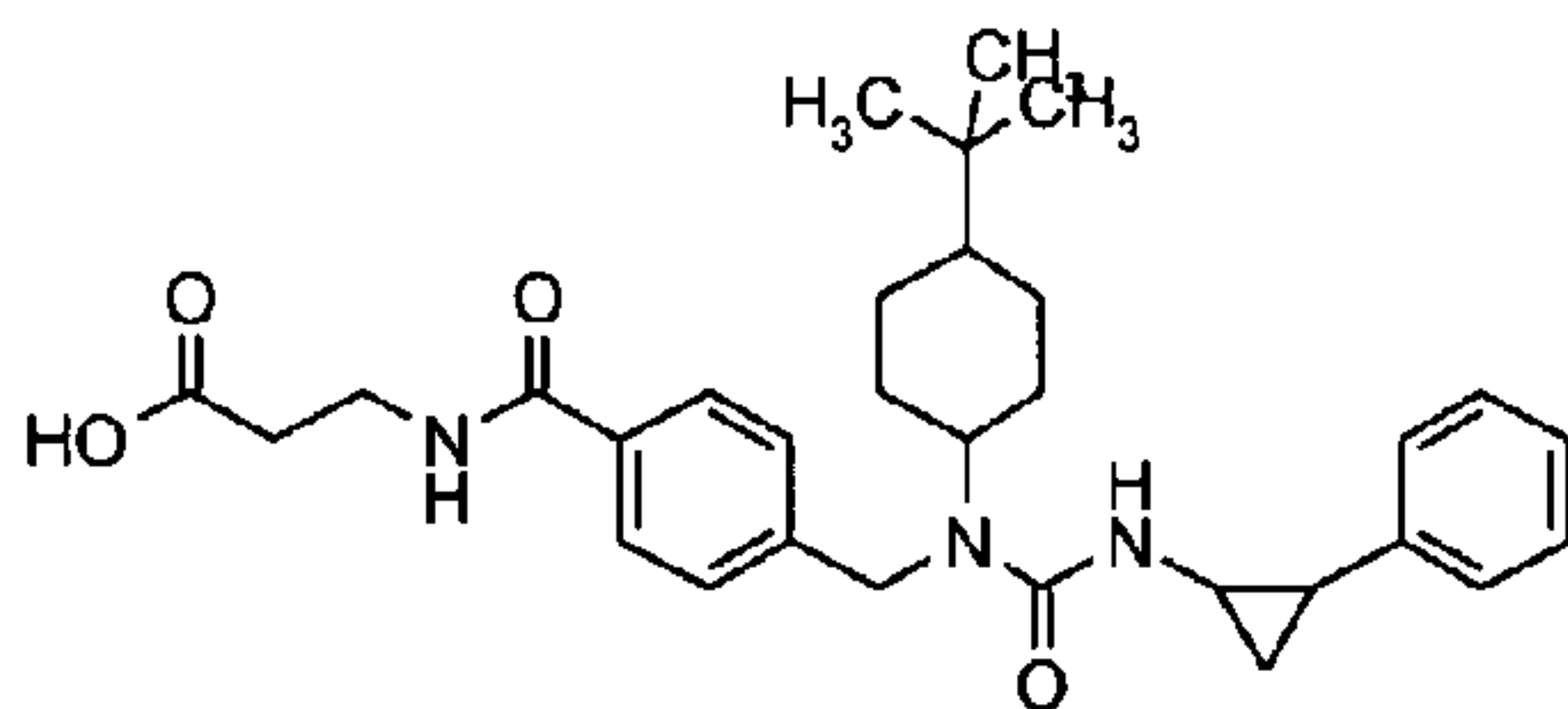
3-{5-[1-(4-Trifluoromethylbenzyl)-3-(4-trifluoromethylsulfanylphenyl)ureidomethyl]thiophene-2-carbonylamino}propionic acid



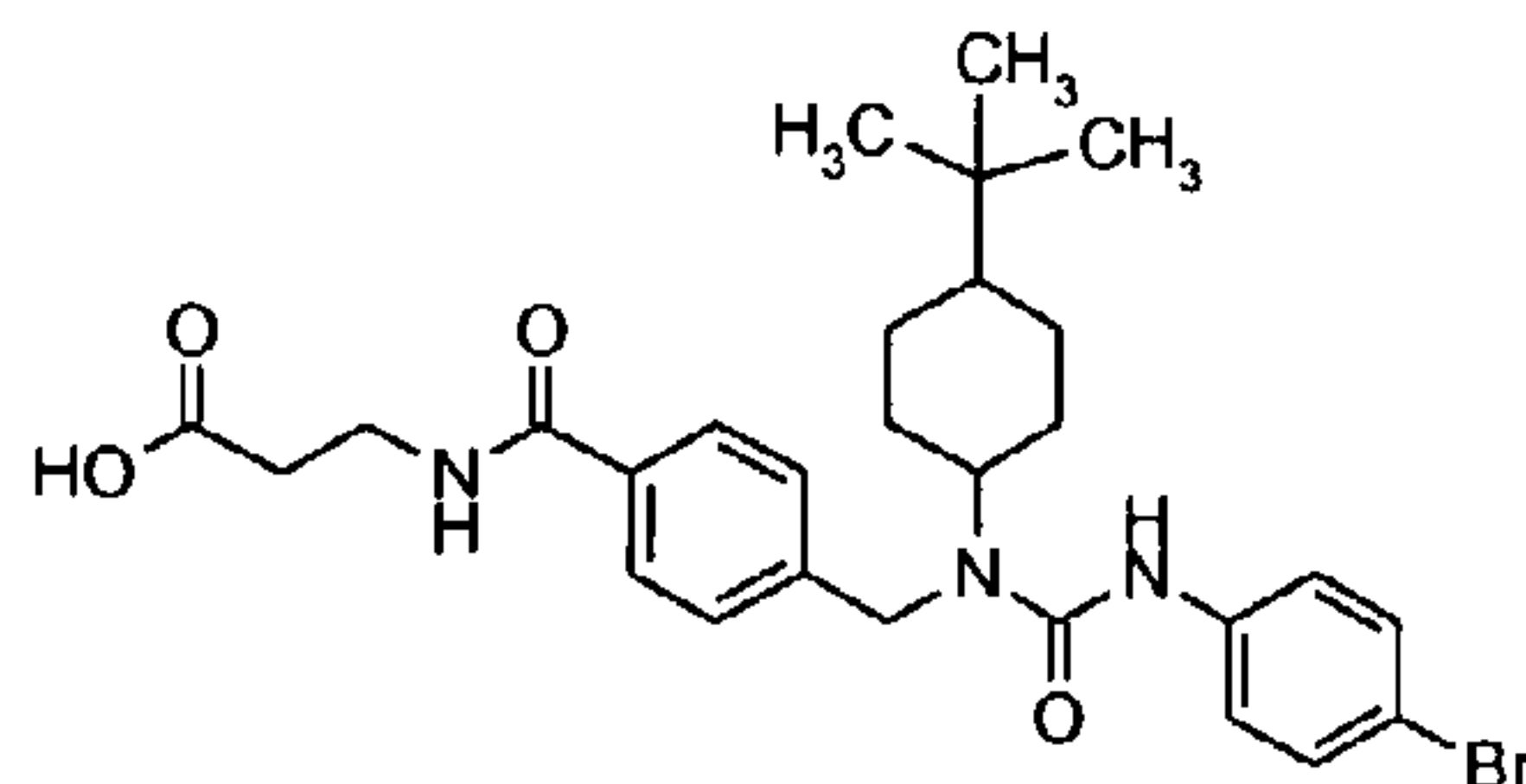
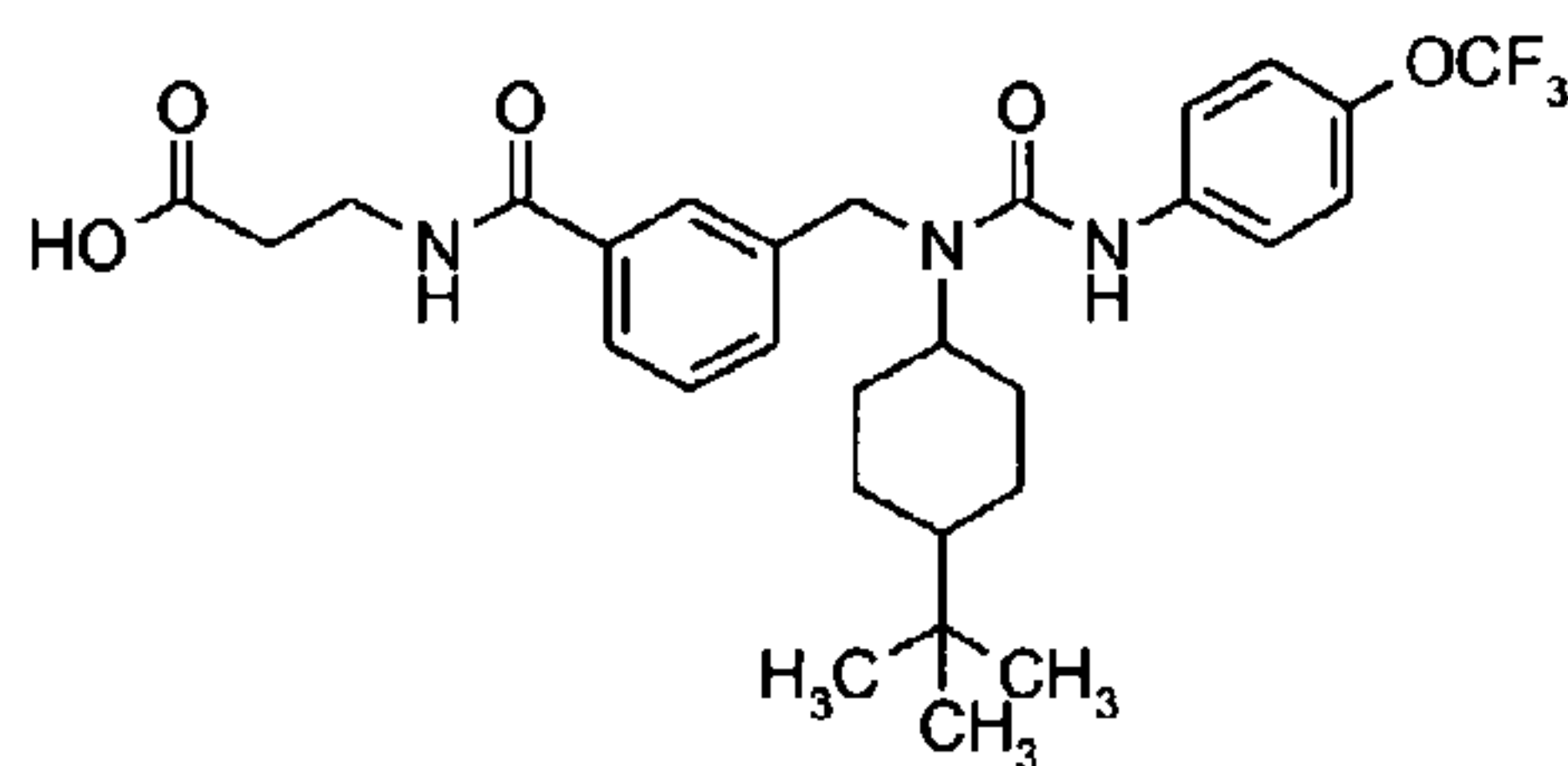
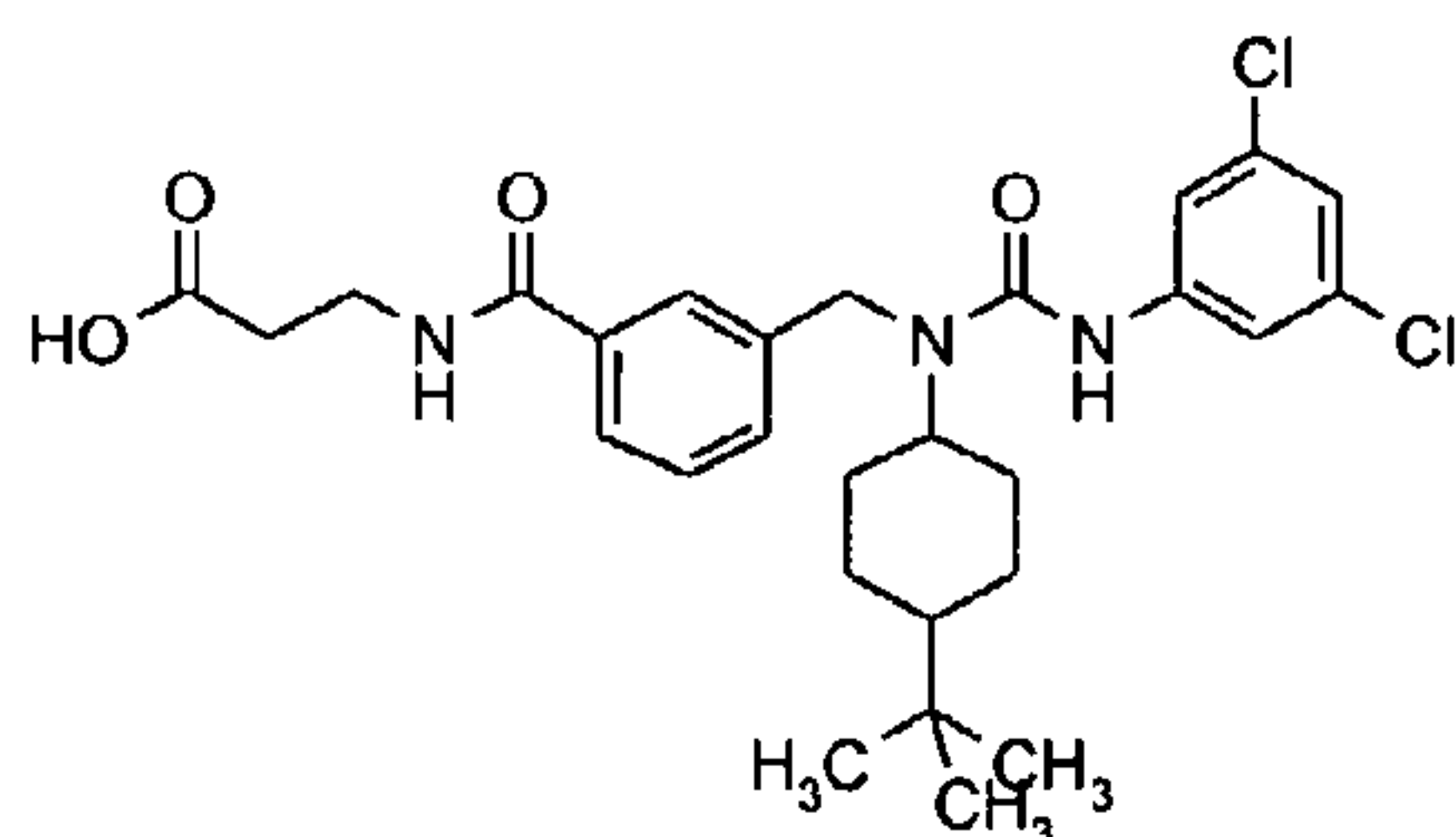
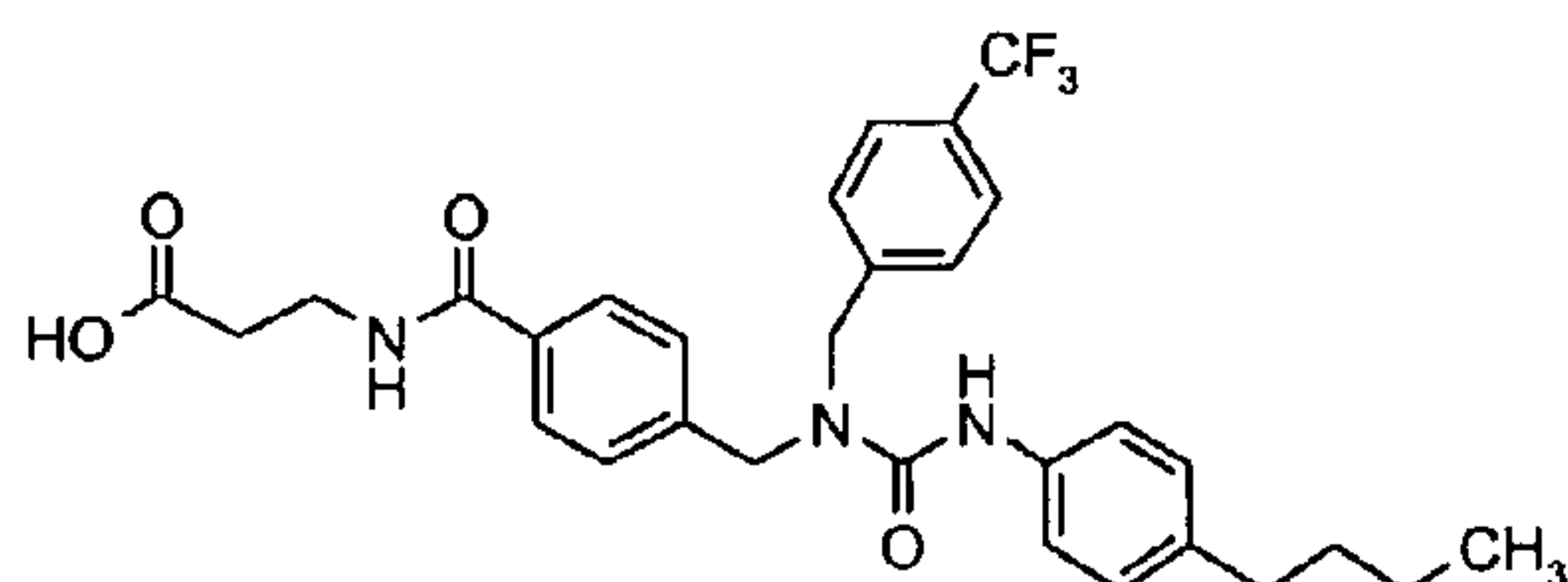
10

EXAMPLE 132 (general procedure (G))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-phenylcyclopropyl)ureidomethyl]benzoylamino}propionic acid

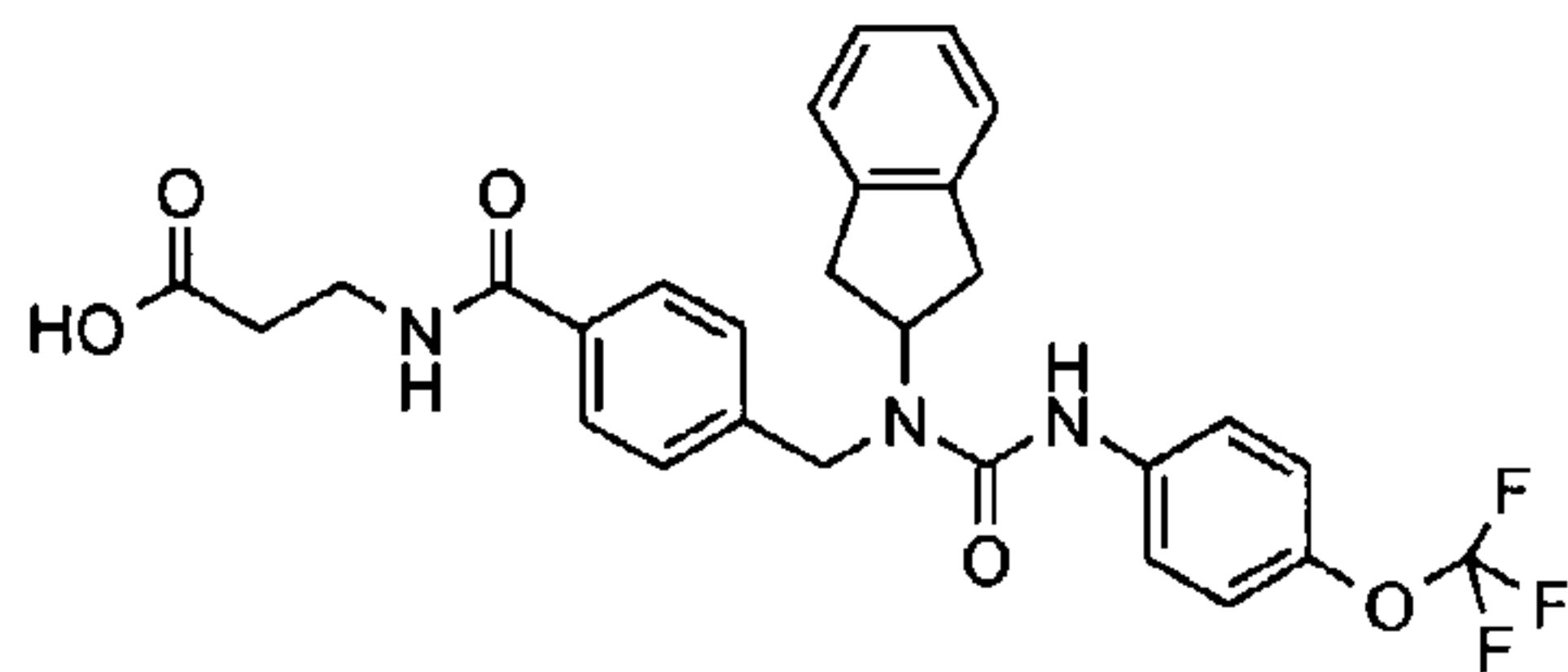


15

EXAMPLE 133 (general procedure (G))3-{4-[3-(4-Bromophenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]benzoylamino}propionic acid5 EXAMPLE 134 (general procedure (G))3-{3-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid10 EXAMPLE 135 (general procedure (G))3-{3-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid15 EXAMPLE 136 (general procedure (G))3-{4-[3-(4-Butylphenyl)-1-(4-trifluoromethylbenzyl)ureidomethyl]benzoylamino}propionic acid

EXAMPLE 137 (general procedure (G))

3-{4-[1-(1-Indan-2-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



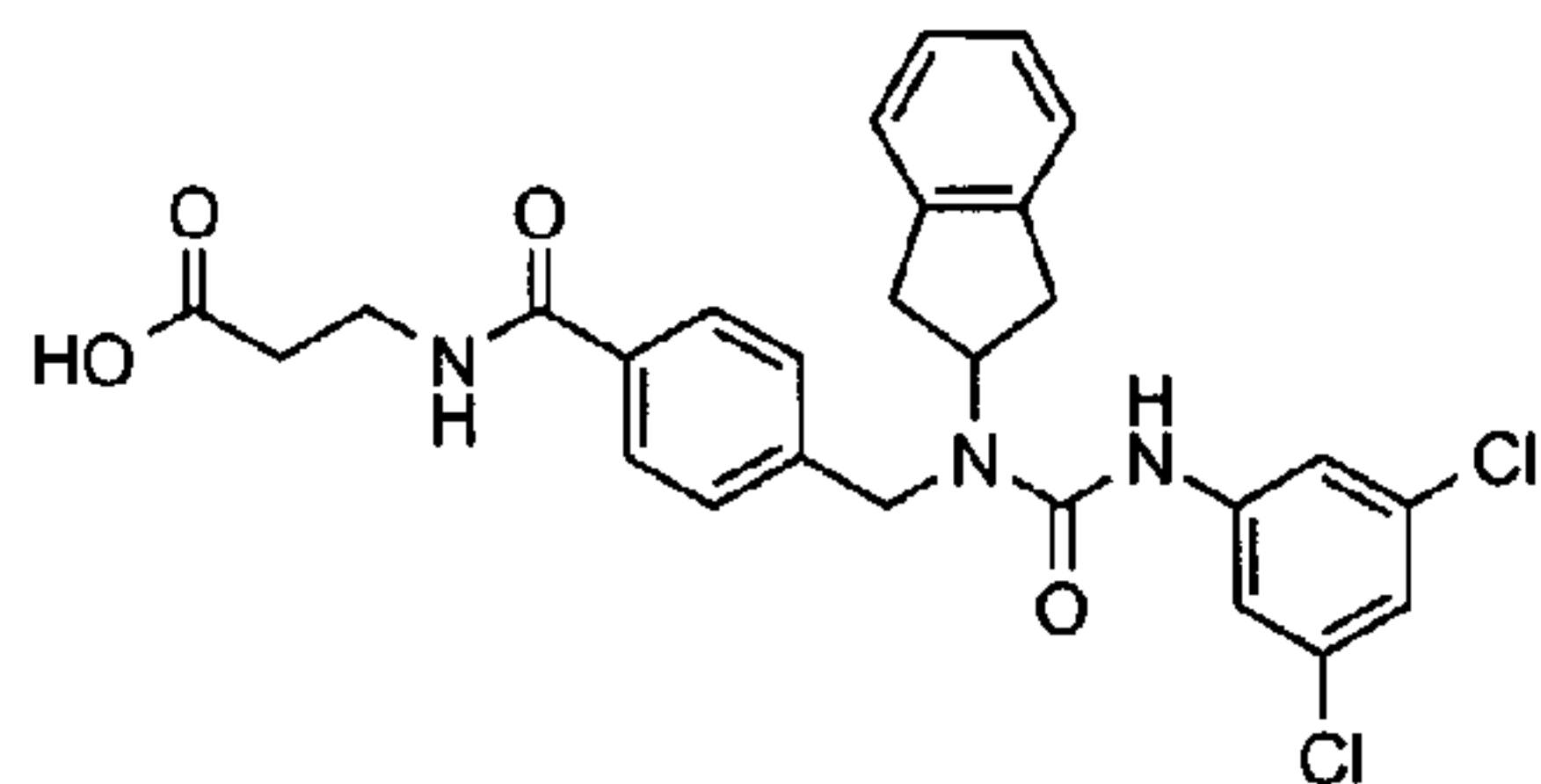
- 5 ^1H NMR (DMSO- d_6): δ 2.52 (t, 2H), 2.97 (m, 4H), 3.47 (qt, 2H), 4.72 (s, 2H), 7.09 – 7.20 (m, 4H), 7.24 (d, 2H), 7.29 (d, 2H), 7.57 (d, 2H), 7.77 (d, 2H), 8.48 (brd t, 1H), 8.73 (brd s, 1H), 12.21 (brd s, 1H).

MS (APCI, pos): 542.2, 543.2, 339.1.

10

EXAMPLE 138 (general procedure (G))

3-{4-[1-(1-Indan-2-yl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



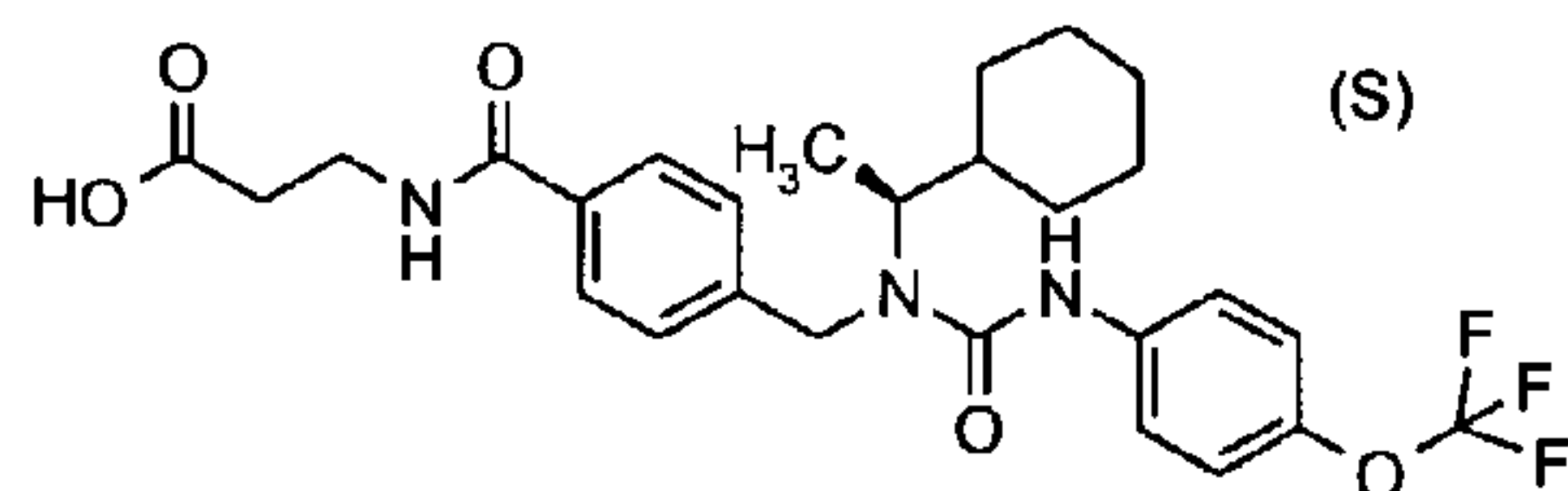
- 15 ^1H NMR (DMSO- d_6): δ 2.51 (t, 2H), 2.95 – 2.99 (m, 4H), 3.45 (qt, 2H), 4.71 (s, 2H), 7.09 – 7.18 (m 5H), 7.28 (d, 2H), 7.64 (s, 2H), 7.78 (d, 2H), 8.49 (t, 1H), 8.86 (s, 1H), 12.21 (brd s, 1H).

MS (APCI, pos): 526.1, 339.1.

20

EXAMPLE 139 (general procedure (G))

3-{4-[1-(((1S)-1-Cyclohexylethyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino)-propionic acid



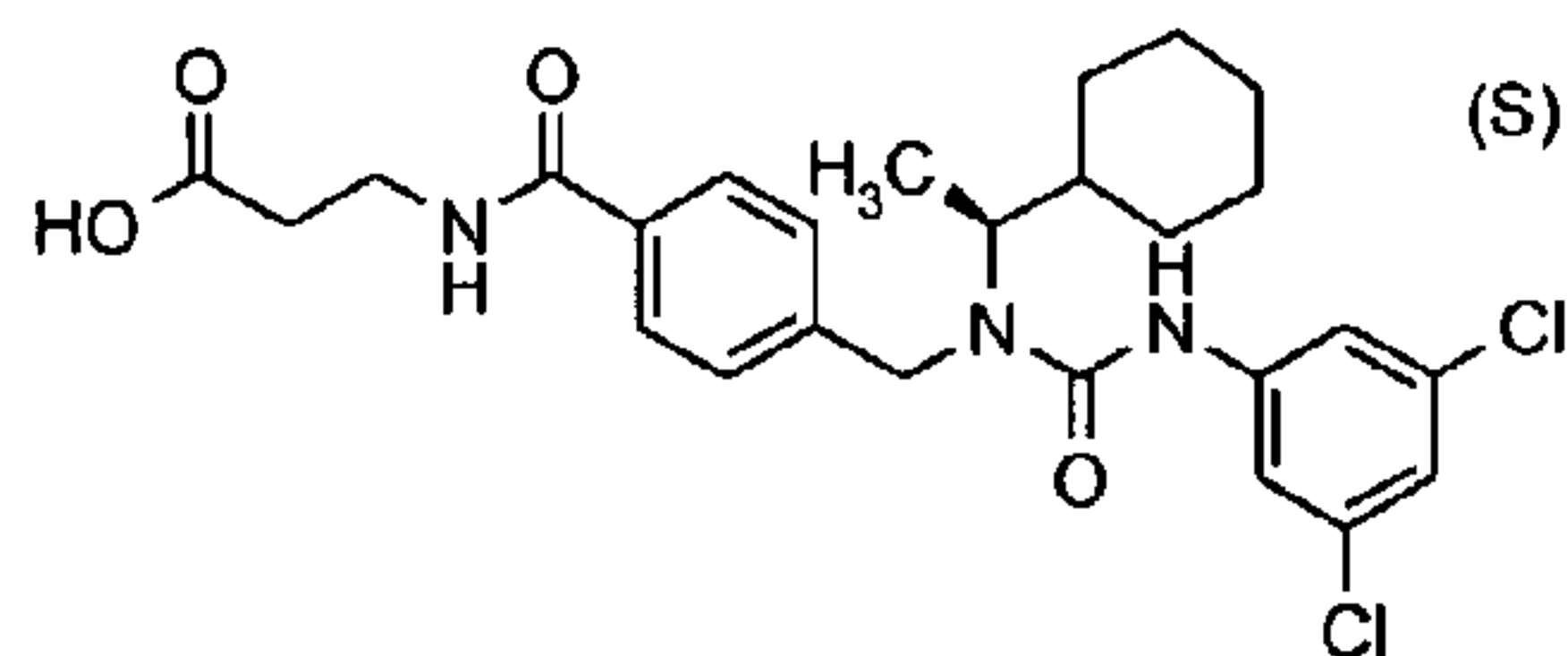
5

^1H NMR (DMSO- d_6): δ 0.84 – 1.19 (m, 8H), 1.47 – 1.70 (m, 6H), 1.88 (t, 2H), 3.16 (qt, 2H), 4.03 (quintet, 1H), 4.33 (d, 1H), 4.78 (d, 1H), 7.10 (d, 2H), 7.50 (d, 2H), 7.70 (d, 2H), 8.62 (brd s, 1H), 8.95 (brd t, 1H).

10 MS (APCI, pos): 536.2, 537.2, 538.2.

EXAMPLE 140 (general procedure (G))

3-{4-[1-(((1S)-1-Cyclohexylethyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino)propionic acid



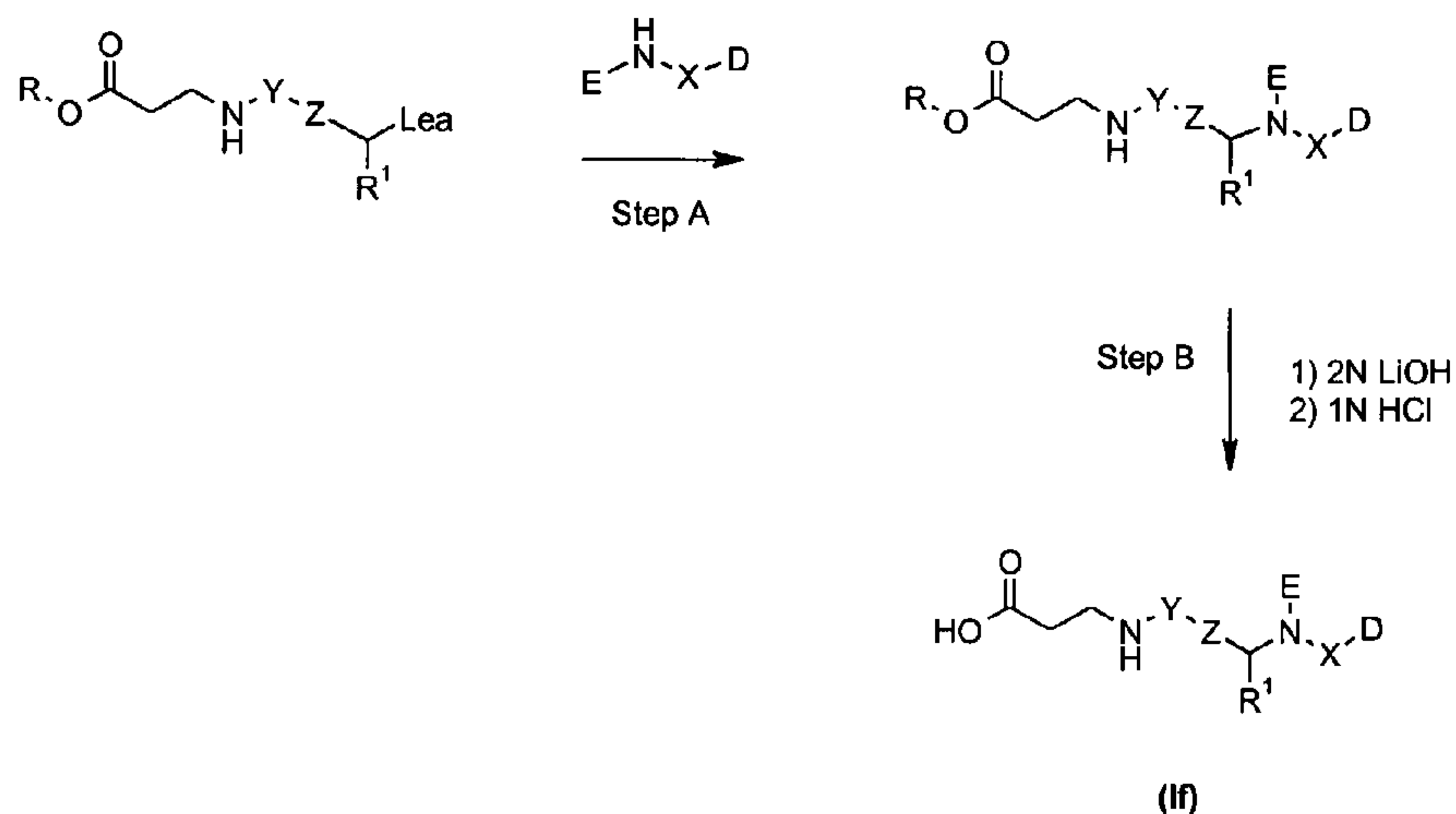
15

^1H NMR (CDCl $_3$): δ 1.16 – 1.27 (m, 8H), 1.40 (m, 1H), 1.69 – 1.80 (m, 5H), 2.68 (t, 2H), 3.70 (qt, 2H), 4.20 (m, 1H), 4.43 (dd, 2H), 6.44 (brd s, 1H), 6.94 (m, 2H), 7.17 (s, 2H), 7.36 (d, 2H), 7.74 (d, 2H).

20

MS (APCI, pos): 520.2, 522.1, 333.2.

General procedure (H) for the solution phase synthesis of compounds of the general formula (If):



5

wherein

R^1 , E, Z and D are as defined for formula (I),

10 X is $-(CH_2)_q-$, wherein q is as defined for formula (I),

Y is $-C(O)-$ or $-S(O)_2-$,

R is C_{1-6} -alkyl and

15

Lea is a leaving group such as chloro, bromo, iodo, mesyl or tosyl.

The preparation of starting materials are as described above in procedure (G).

20 Library solution phase synthesis (procedure (H)) of compounds of the general formula (If):

Step A:

The appropriate alkylhalide (0.02 mmol) in DMF was added into the wells of a deepwell plate containing the appropriate amine (E-NH-X-D) (0.02 mmol) and solid potassium carbonate (2
25 eq) in DMF. The mixtures were agitated at 55°C for 16 hours to give the alkylated product.

Step B:

To the crude product from step A was added aqueous 2M LiOH (4 eq). The mixtures are agitated for at least four hours before they are filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

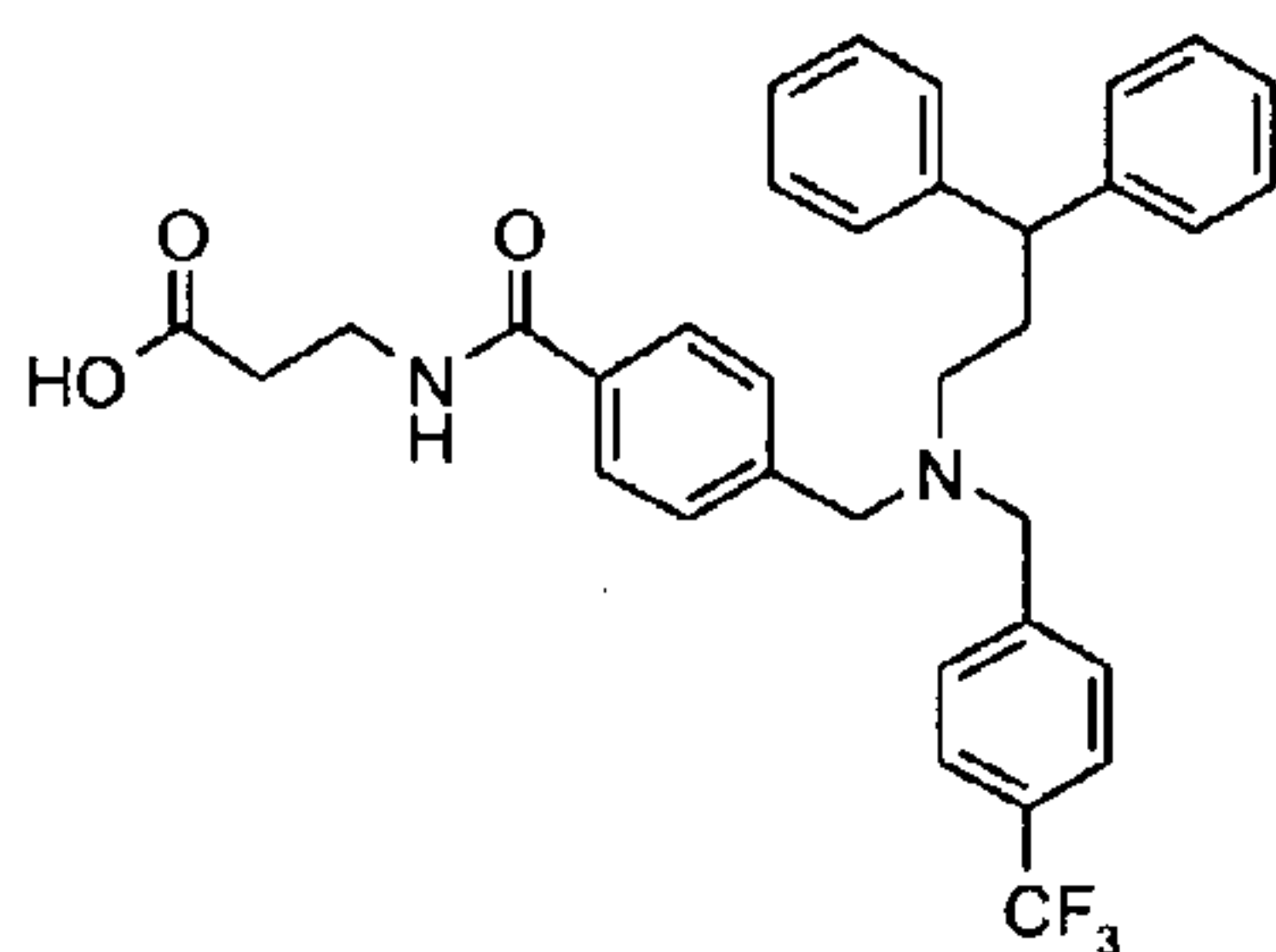
5

The following examples 141 to 152 were prepared according to the general procedure (H). They were all found to displace more than 50% of the glucagon tracer when screened at 1 μ M concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

10

EXAMPLE 141 (general procedure (H))

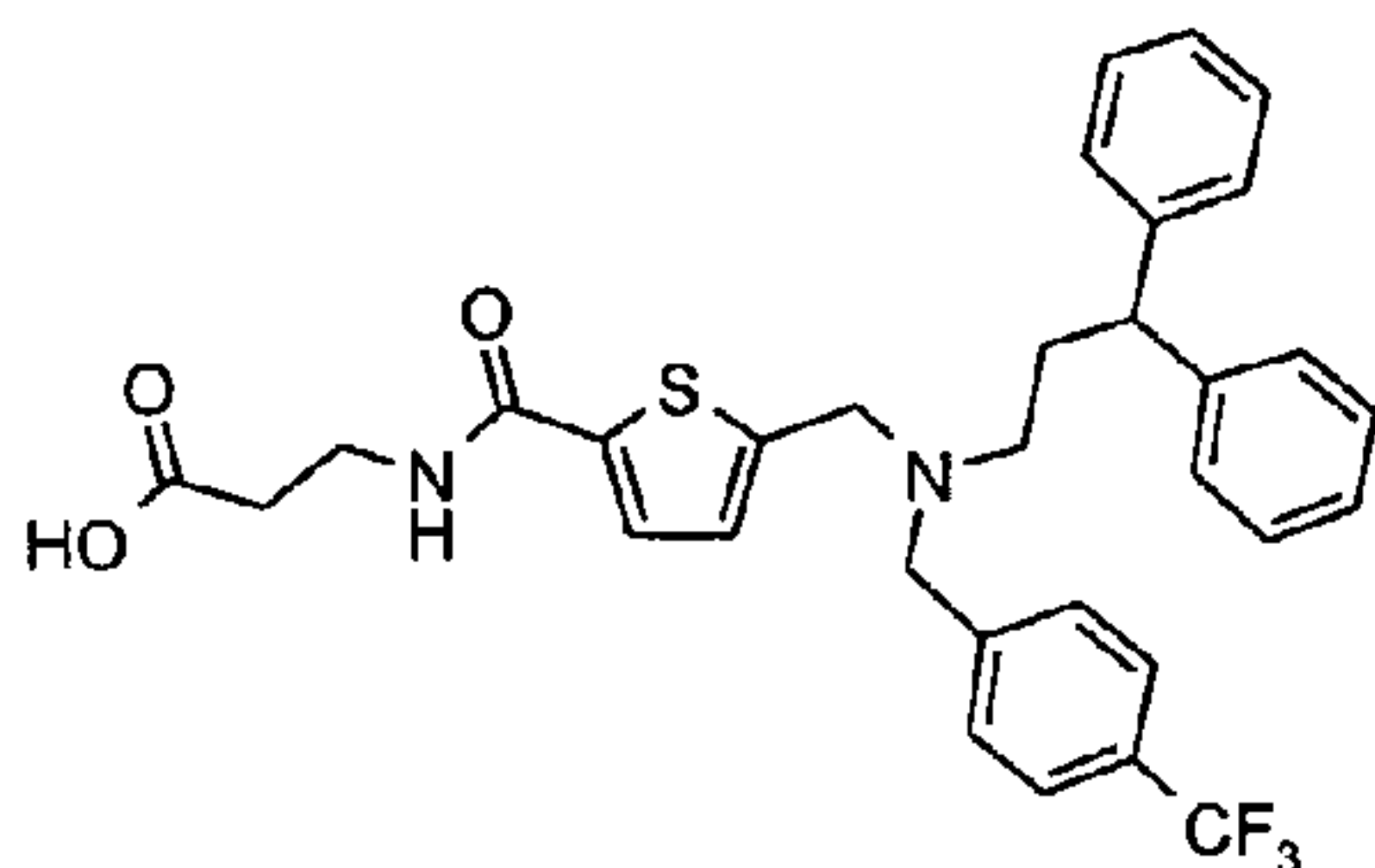
3-(4-((3,3-Diphenylpropyl)-(4-trifluoromethylbenzyl)amino)methyl)benzoylamino)propionic acid



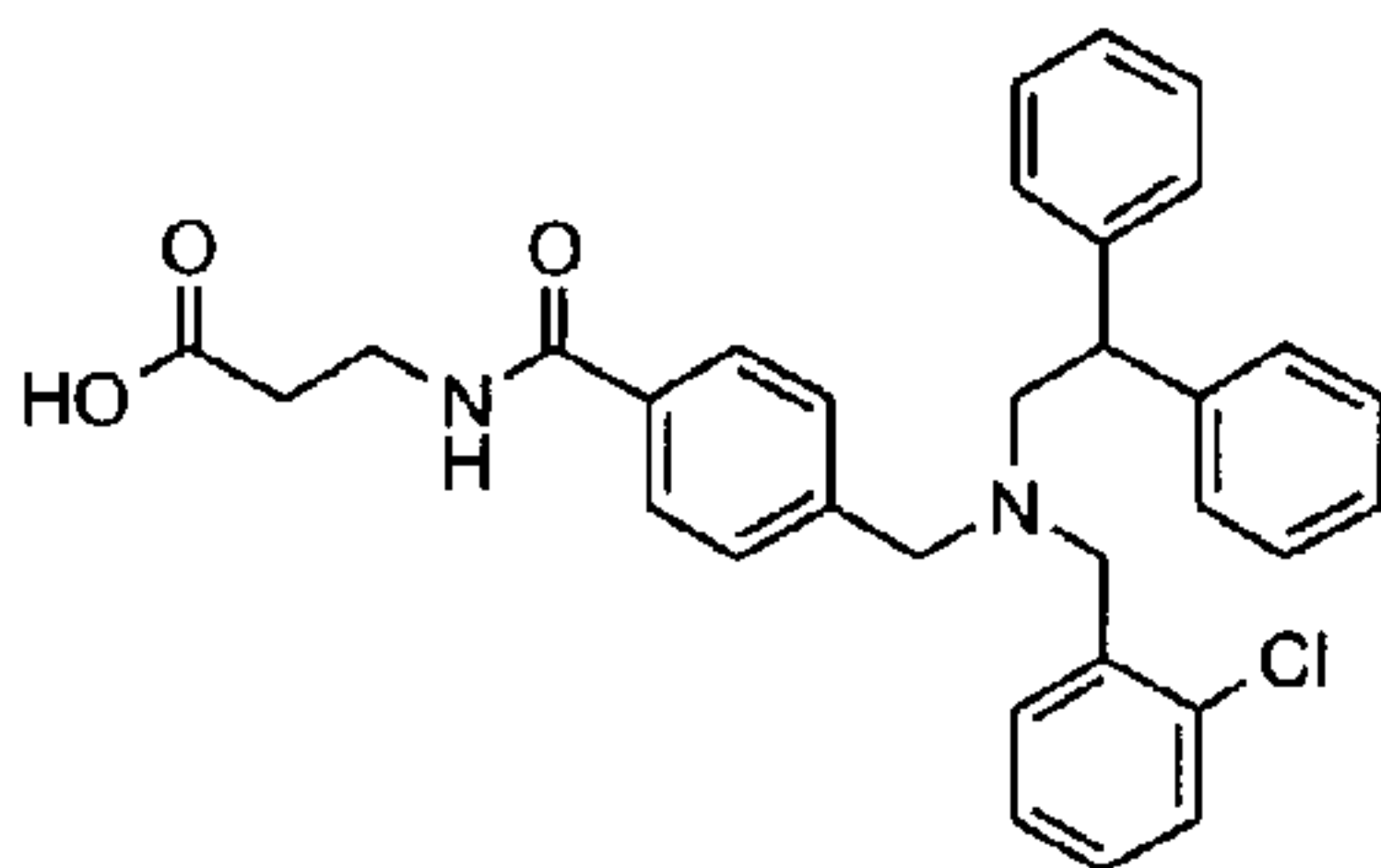
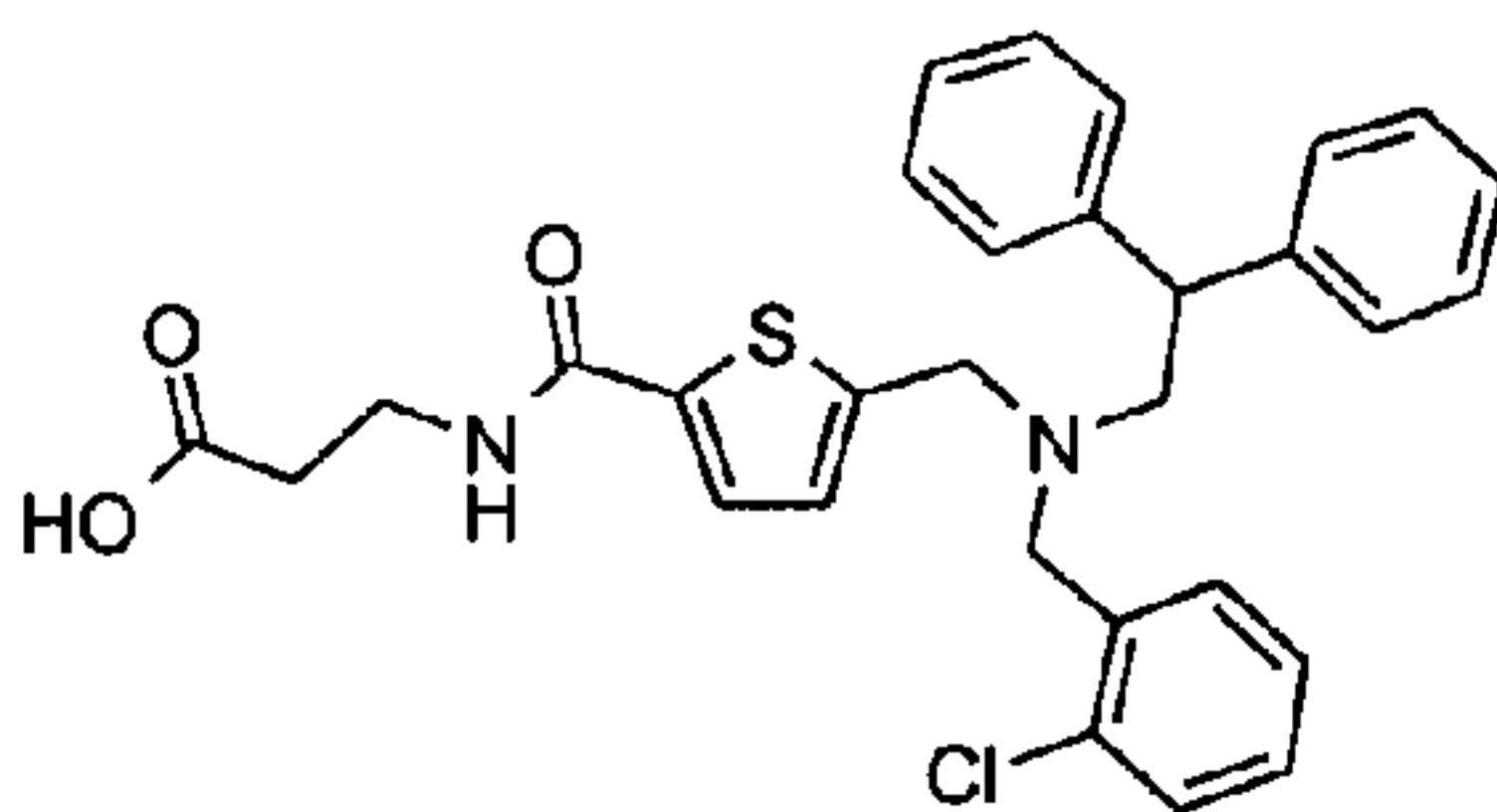
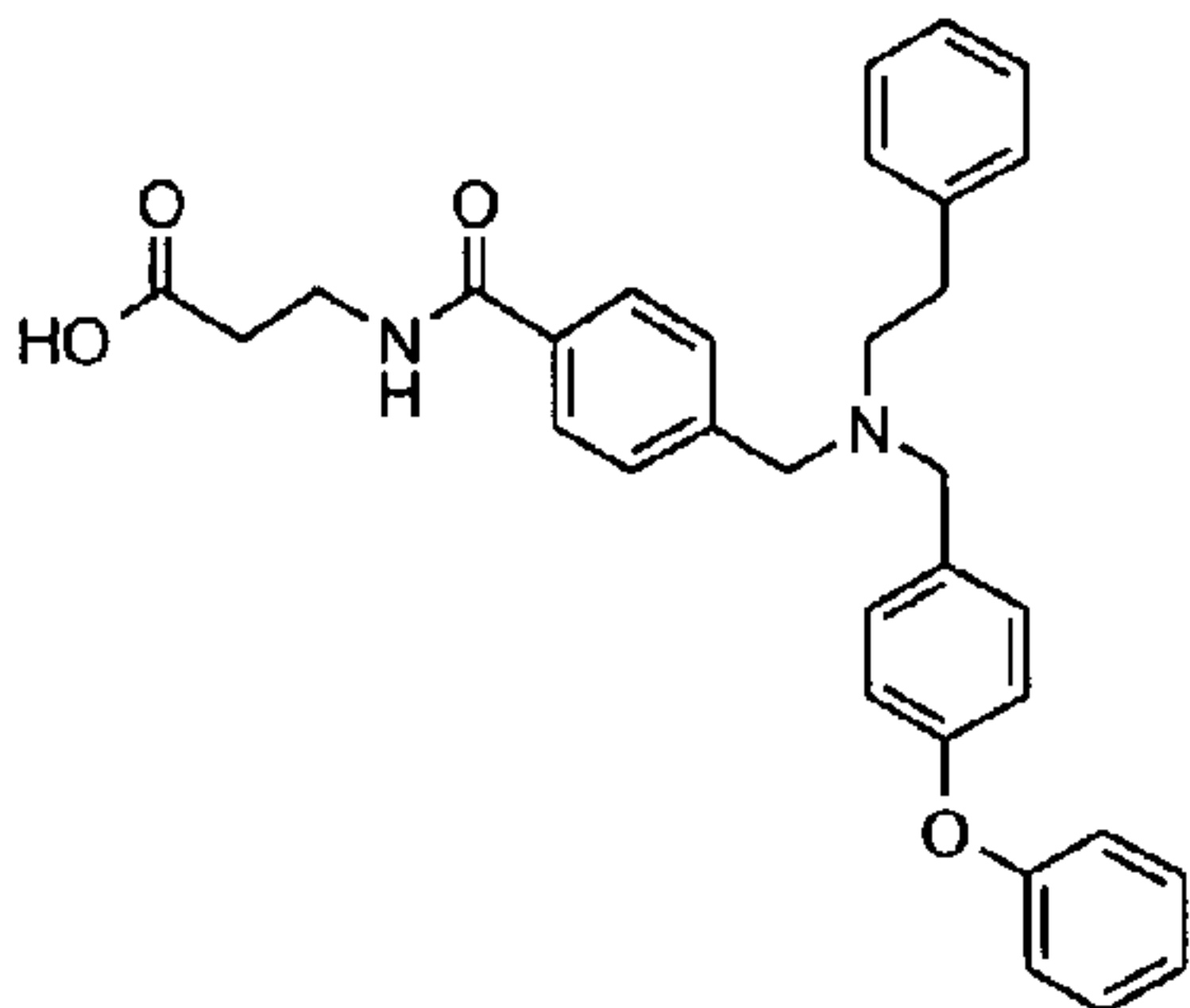
15

EXAMPLE 142 (general procedure (H))

3-(5-((3,3-Diphenylpropyl)-(4-trifluoromethylbenzyl)amino)methyl)thiophene-2-carbonylamino)propionic acid

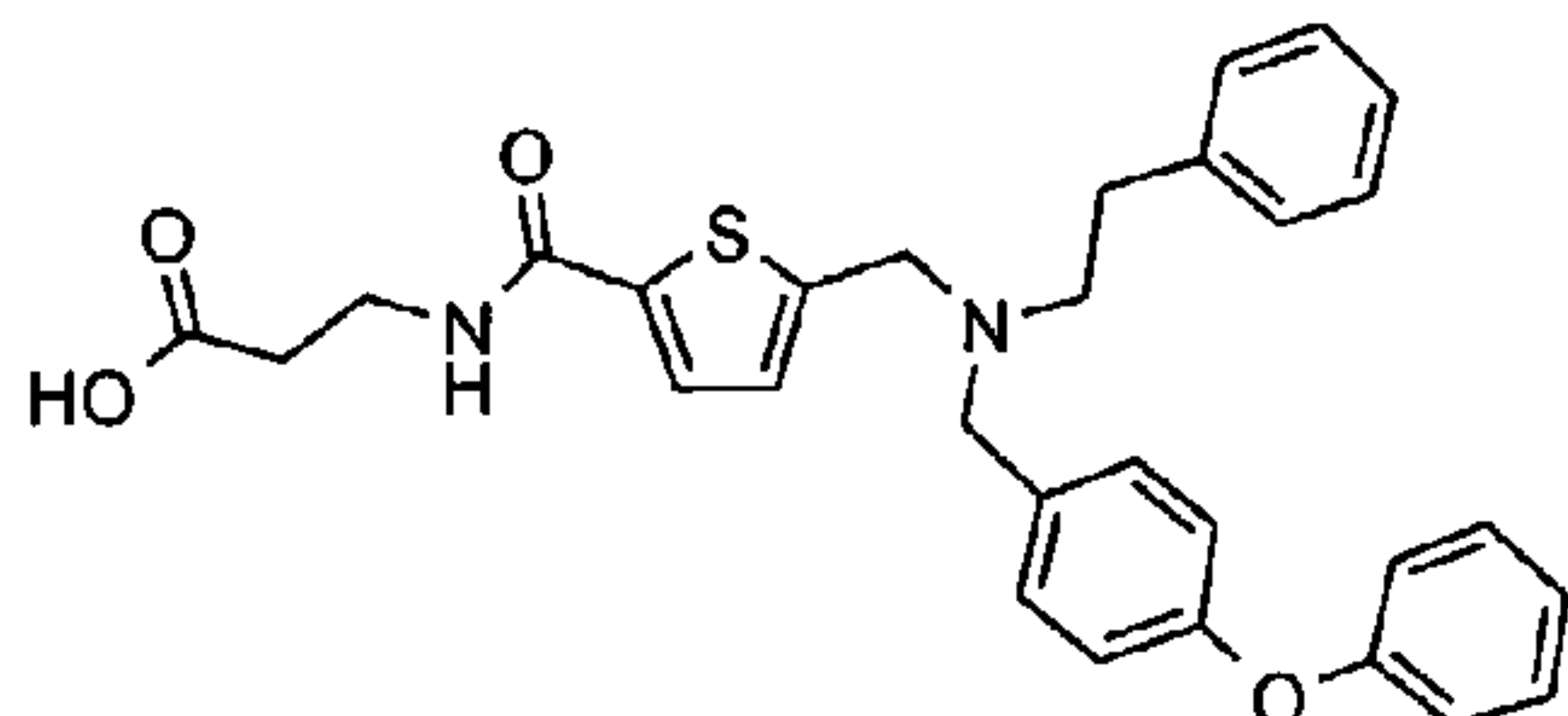


20

EXAMPLE 143 (general procedure (H))3-(4-[[[(2,2-Diphenylethyl)-(2-chlorobenzyl)amino]methyl]benzoylamino]propionic acid5 EXAMPLE 144 (general procedure (H))3-(5-[[[(2,2-Diphenylethyl)-(2-chlorobenzyl)amino]methyl]thiophene-2-carbonylamino]-propionic acid10 EXAMPLE 145 (general procedure (H))3-(4-[[[(2-Phenylethyl)-(4-phenoxybenzyl)amino]methyl]benzoylamino]propionic acid

EXAMPLE 146 (general procedure (H))

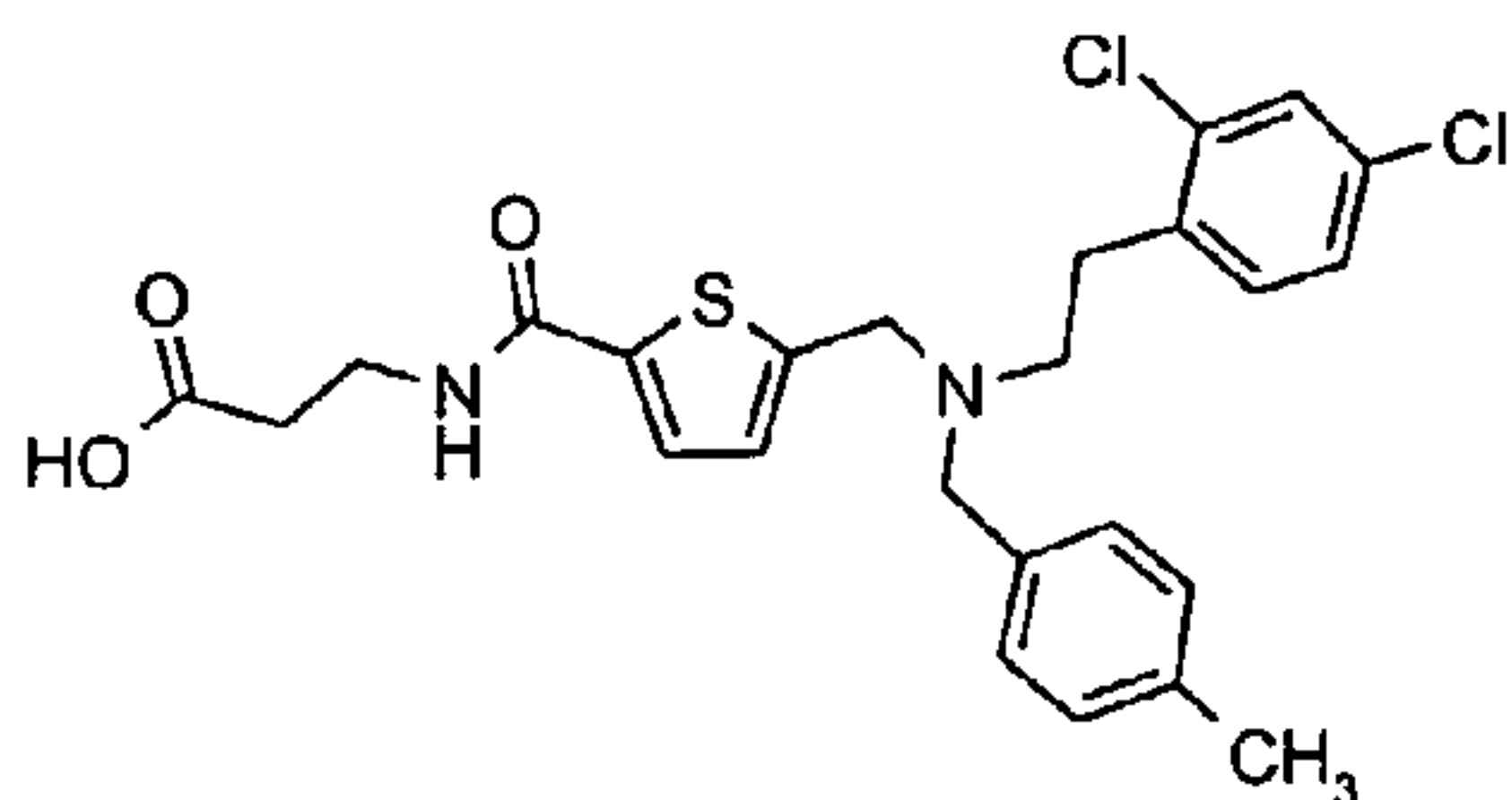
3-(5-[[[(2-Phenylethyl)-(4-phenoxybenzyl)amino]methyl]thiophene-2-carbonylamino]propionic acid



5

EXAMPLE 147 (general procedure (H))

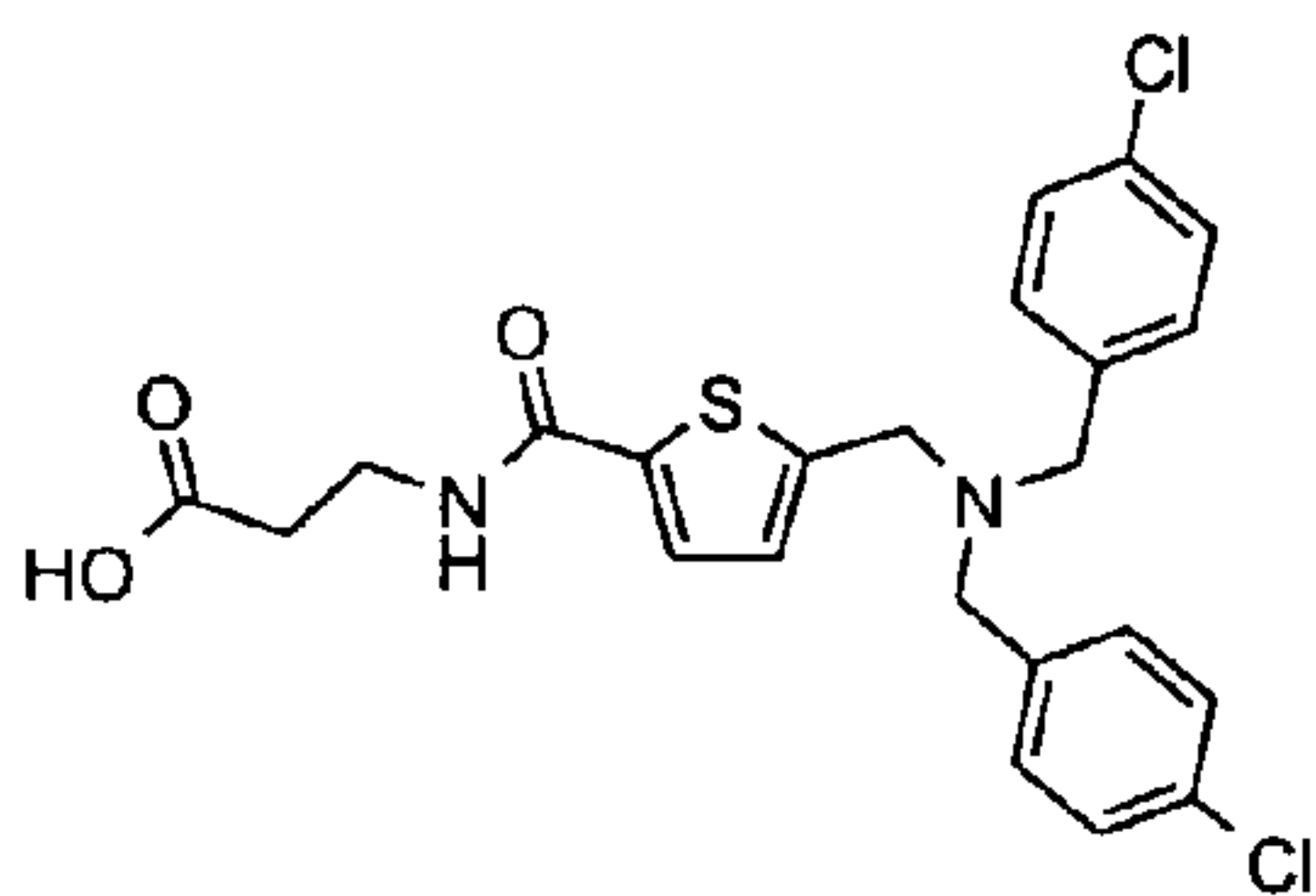
3-(5-[[[(2,4-Dichlorophenethyl)-(4-methylbenzyl)amino]methyl]thiophene-2-carbonylamino]-propionic acid

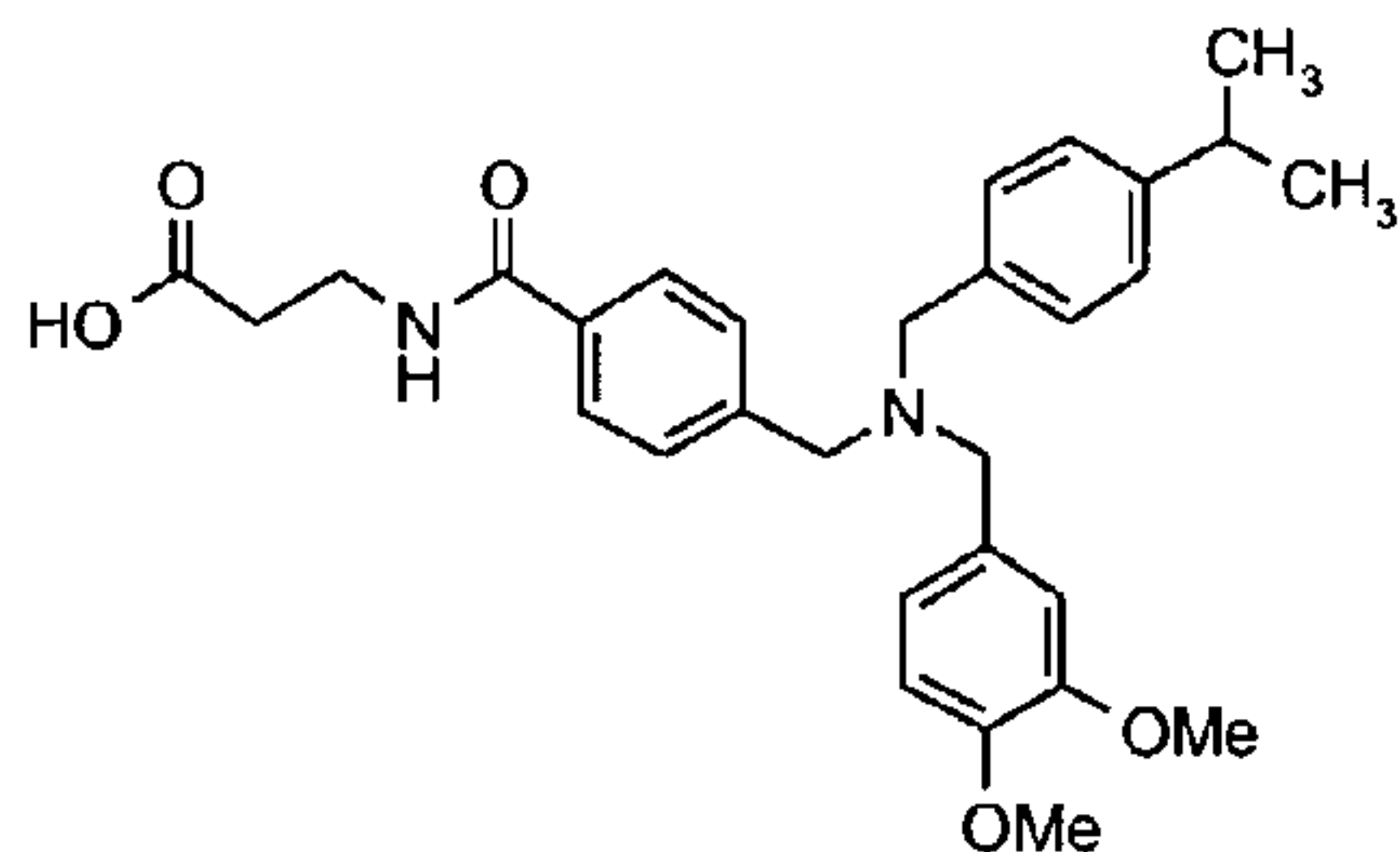


10

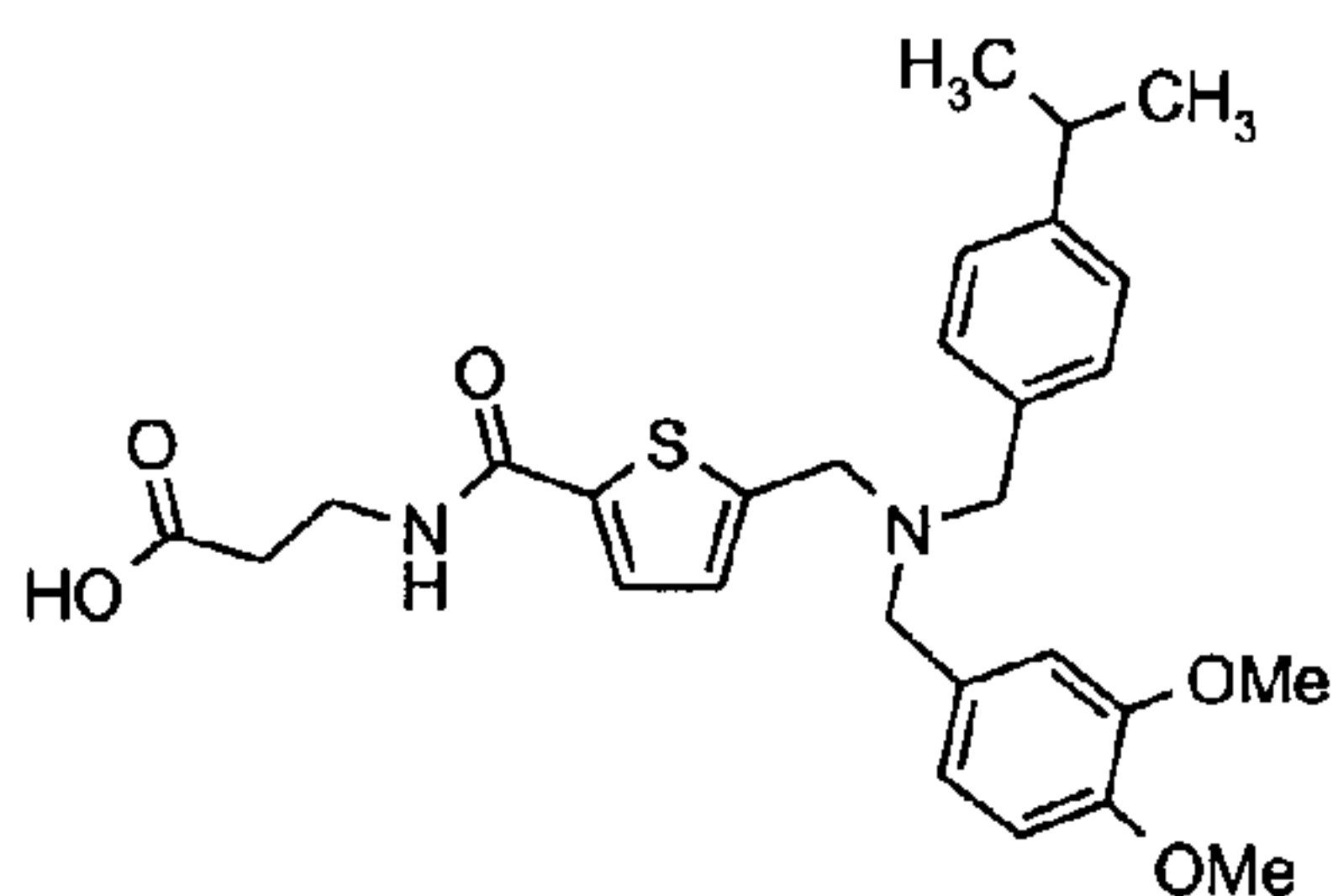
EXAMPLE 148 (general procedure (H))

3-(5-[[[Bis-(4-chlorobenzyl)amino]methyl]thiophene-2-carbonylamino]propionic acid

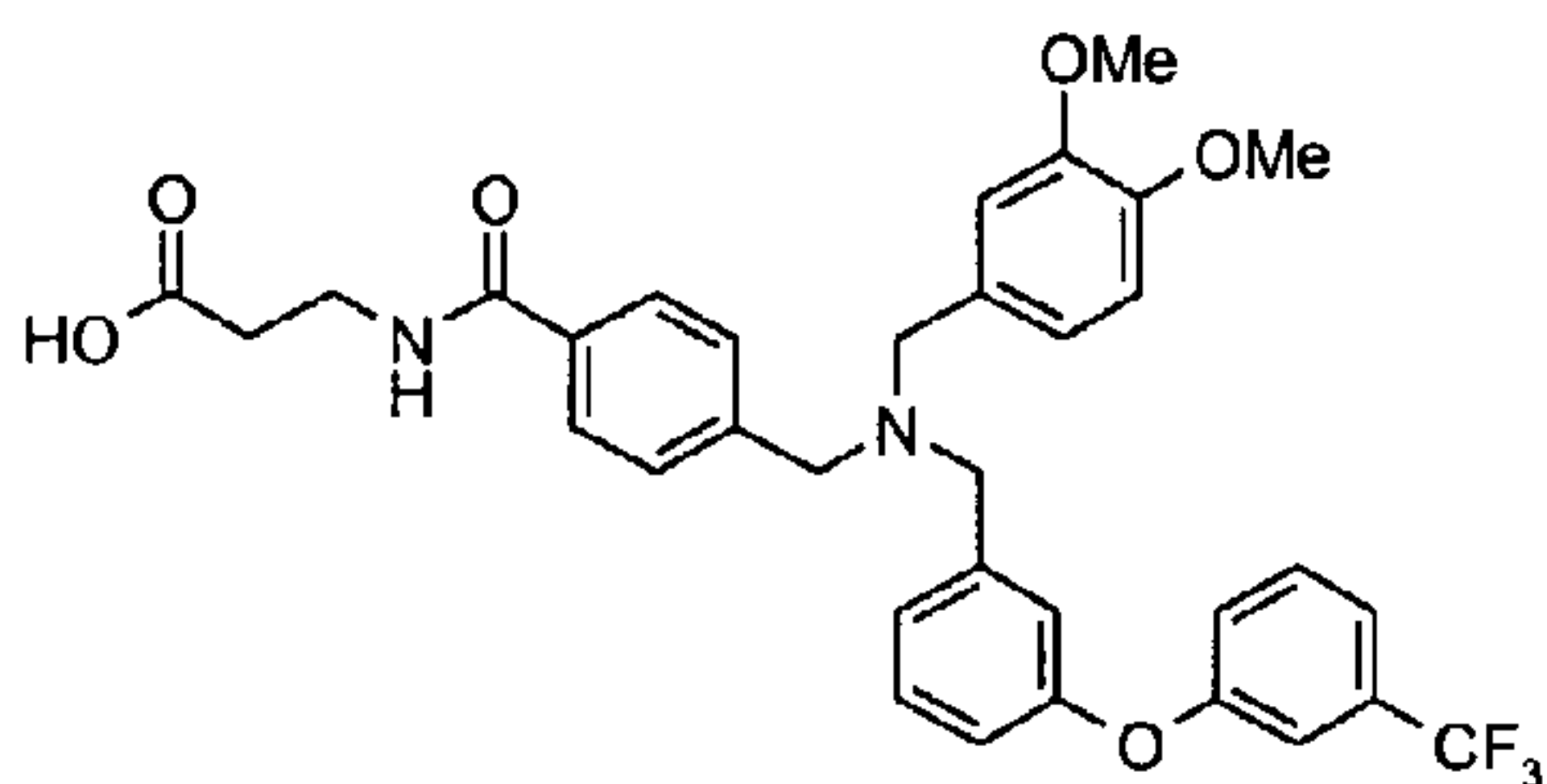


EXAMPLE 149 (general procedure (H))3-(4-{[(3,4-Dimethoxybenzyl)-(4-isopropylbenzyl)amino]methyl}benzoylamino)propionic acid

5

EXAMPLE 150 (general procedure (H))3-(5-{[(3,4-Dimethoxybenzyl)-(4-isopropylbenzyl)amino]methyl}thiophene-2-carbonylamino)-propionic acid

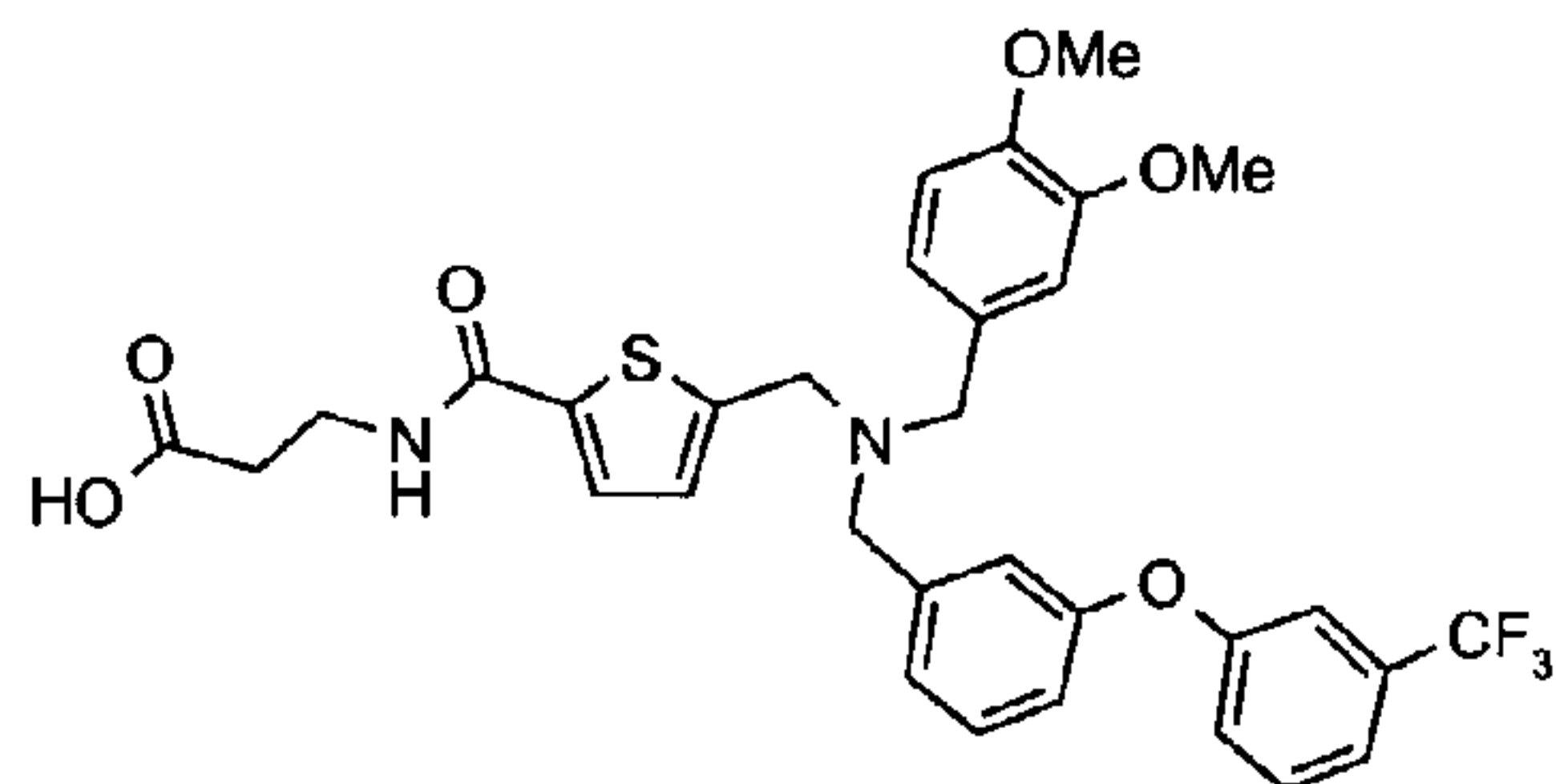
10

EXAMPLE 151 (general procedure (H))3-(4-{[(3,4-Dimethoxybenzyl)-(3-[3-trifluoromethylphenoxy]benzyl)amino]methyl}benzoylamino)propionic acid

15

EXAMPLE 152 (general procedure (H))

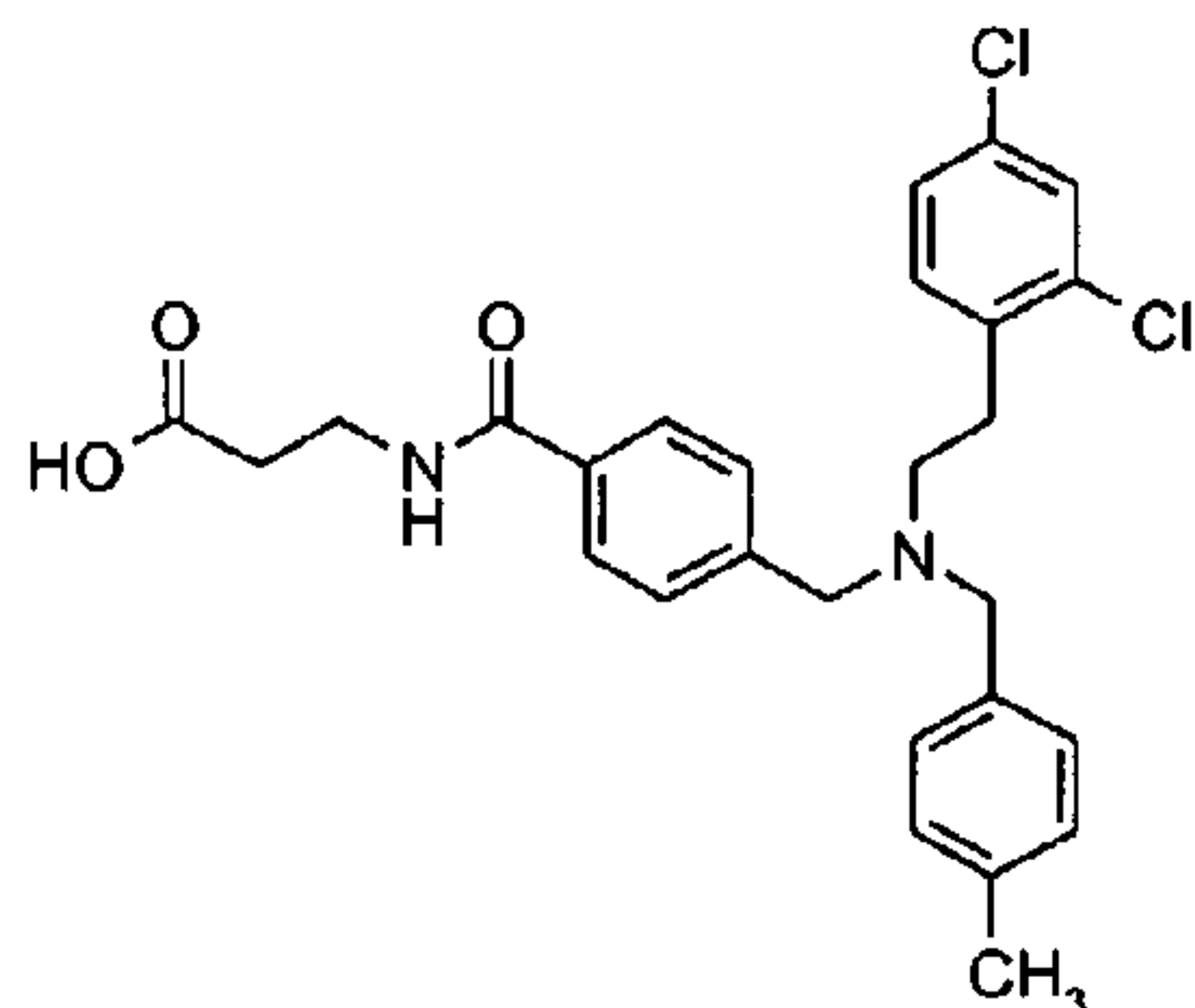
3-(5-([(3,4-Dimethoxybenzyl)-(3-[3-trifluoromethylphenoxy]benzyl)amino]methyl)thiophene-2-carbonylamino)propionic acid



5

EXAMPLE 153 (general procedure (H))

3-(4-([(2,4-Dichlorophenethyl)-(4-methylbenzyl)amino]methyl)benzoylamino)propionic acid

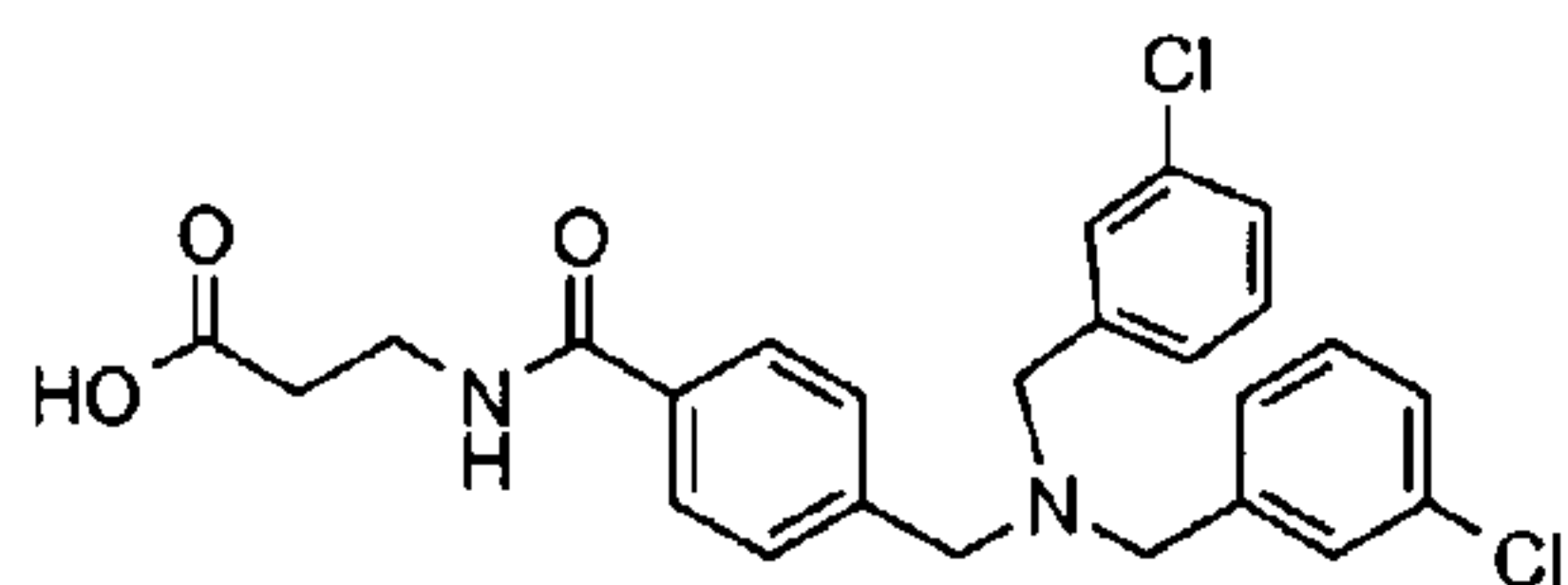


10 ^1H NMR (MeOH- d_4): δ 2.38 (s, 3H), 2.64 (t, 2H), 3.10 (m, 4H), 3.50 (qt, 2H), 4.40 (s, 2H), 4.50 (s, 2H), 7.20 (m, 4H), 7.40 (m, 3H), 7.50 (d, 2H), 7.90 (d, 2H), 8.60 (t, 1H).

MS (APCI, pos): 499.1, 500.2, 501.2.

15 EXAMPLE 154 (general procedure (H))

3-(4-([Bis-(3-chlorobenzyl)amino]methyl)benzoylamino)propionic acid

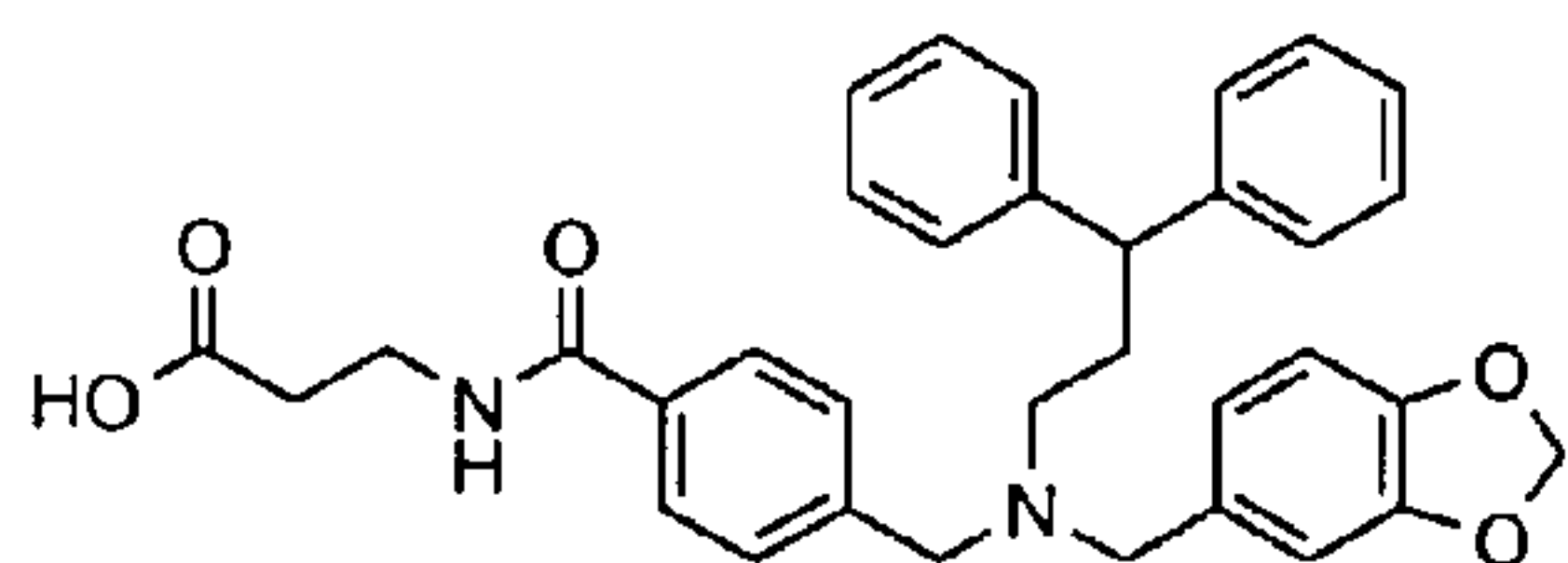


20 ^1H NMR (CDCl₃): δ 2.70 (t, 2H), 3.40 (s, 4H), 3.50 (s, 2H), 3.70 (qt, 2H), 6.9 (t, 1H), 7.20 (m, 6H), 7.30 (s, 2H), 7.40 (d, 2H), 7.70 (d, 2H).

MS (APCI, pos): 471.0, 472.0, 473.0.

EXAMPLE 155 (general procedure (H))

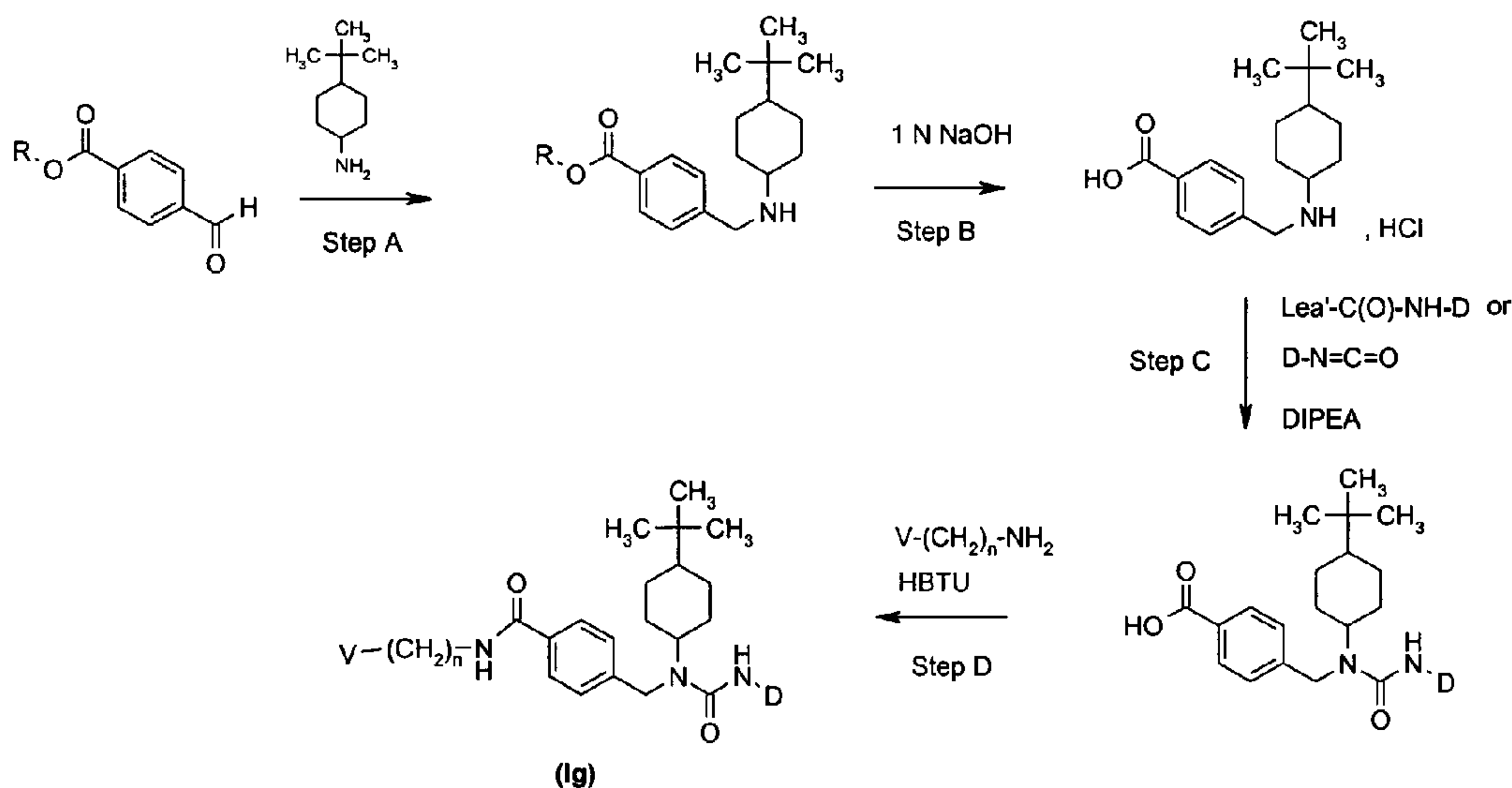
3-(4-[(3,3-Diphenylpropyl)-(3,4-methylenedioxybenzyl)amino]methyl)benzoylamino)propionic acid



^1H NMR (CD_3CN): δ 2.46 – 2.54 (m, 2H), 2.63 (t, 2H), 2.82 – 2.88 (m, 2H), 3.61 (qt, 2H), 3.86 (t, 1H), 4.20 – 4.40 (m, 4H), 6.02 (s, 2H), 6.83 (d, 1H), 6.90 (d, 1H), 6.97 (s, 1H), 7.16 – 7.29 (m, 10H), 7.50 (d, 2H), 7.77 (d, 2H).

MS (APCI, pos): 551.2, 552.2, 553.2.

General procedure (I) for the solution phase synthesis of compounds of the general formula (Ig):



wherein

n, D and V are as defined for formula (I),

R is C₁₋₆-alkyl and

Lea' is a leaving group such as -OSu, chloro, phenoxy or 4-nitrophenoxy.

5 Step A:

To a solution of ethyl 4-formylbenzoate (6 g, 33.7 mmol) in DMF was added 4-*tert*-butylcyclohexylamine (5.8 g, 37.1 mmol), sodium cyanoborohydride (3.2 g, 50.6 mmol) and a catalytic amount of TFA. The solution was stirred at room temperature for 5 hours. The reaction was diluted with ethyl acetate and washed with aqueous sodium bicarbonate (3x), brine (3x),
10 dried over MgSO₄, and concentrated to a syrup. The desired secondary amine was purified by silica gel column chromatography using ethyl acetate.

¹H NMR (DMSO-*d*₆): δ 0.78 (s, 9H), 0.91 (brd m, 5H), 1.30 (t, 3H), 1.67 (brd m, 2H), 1.93 (brd m, 2H), 2.21 (1H), 3.77 (s, 2H), 4.30 (qt, 2H), 7.44 (d, 2H), 7.87 (d, 2H).

15

Step B:

To a solution of the above benzoate in THF/MeOH (3/1) was added aqueous 1M NaOH. After stirring the reaction at room temperature for 15 minutes, the solution was made acidic with 1N HCl. The product was extracted with ethyl acetate (3x) and washed with brine (3x),
20 dried over MgSO₄, and concentrated to a solid. The carboxylic acid product was recrystallized from dichloromethane as the hydrochloride salt.

¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H), 0.97 (m, 3H), 1.44 (qt, 2H), 1.81 (m, 2H), 2.17 (m, 2H), 2.90 (brd m, 1H), 4.20 (t, 2H), 7.73 (d, 2H), 7.95 (d, 2H), 9.52 (s, 2H), 12.60 (brd s, 1H).

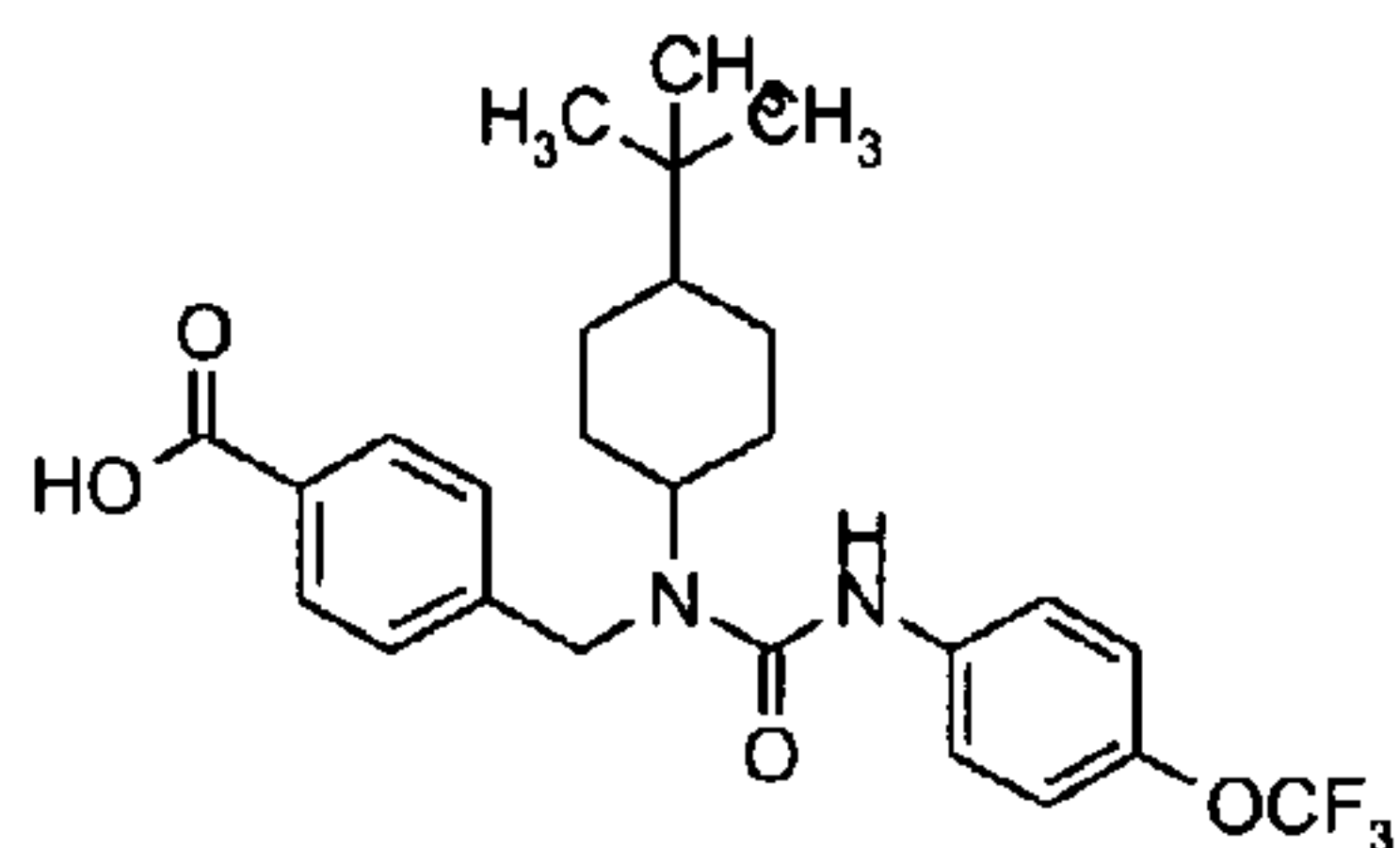
25

Step C:

To a solution of the amine in DMF was added the desired isocyanate (1.1 eq) or alternatively Lea'-C(O)-NH-D, and the reaction was stirred at room temperature for 10 minutes. When using Lea'-C(O)-NH-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethyl-
30 amine or any tertiary amine or potassium carbonate was also added. The solvent was concentrated to an oil. The residue was suspended in ethyl acetate and upon sitting in cold, the desired urea crystallized as a white solid.

Examples of products prepared in this fashion are shown below.

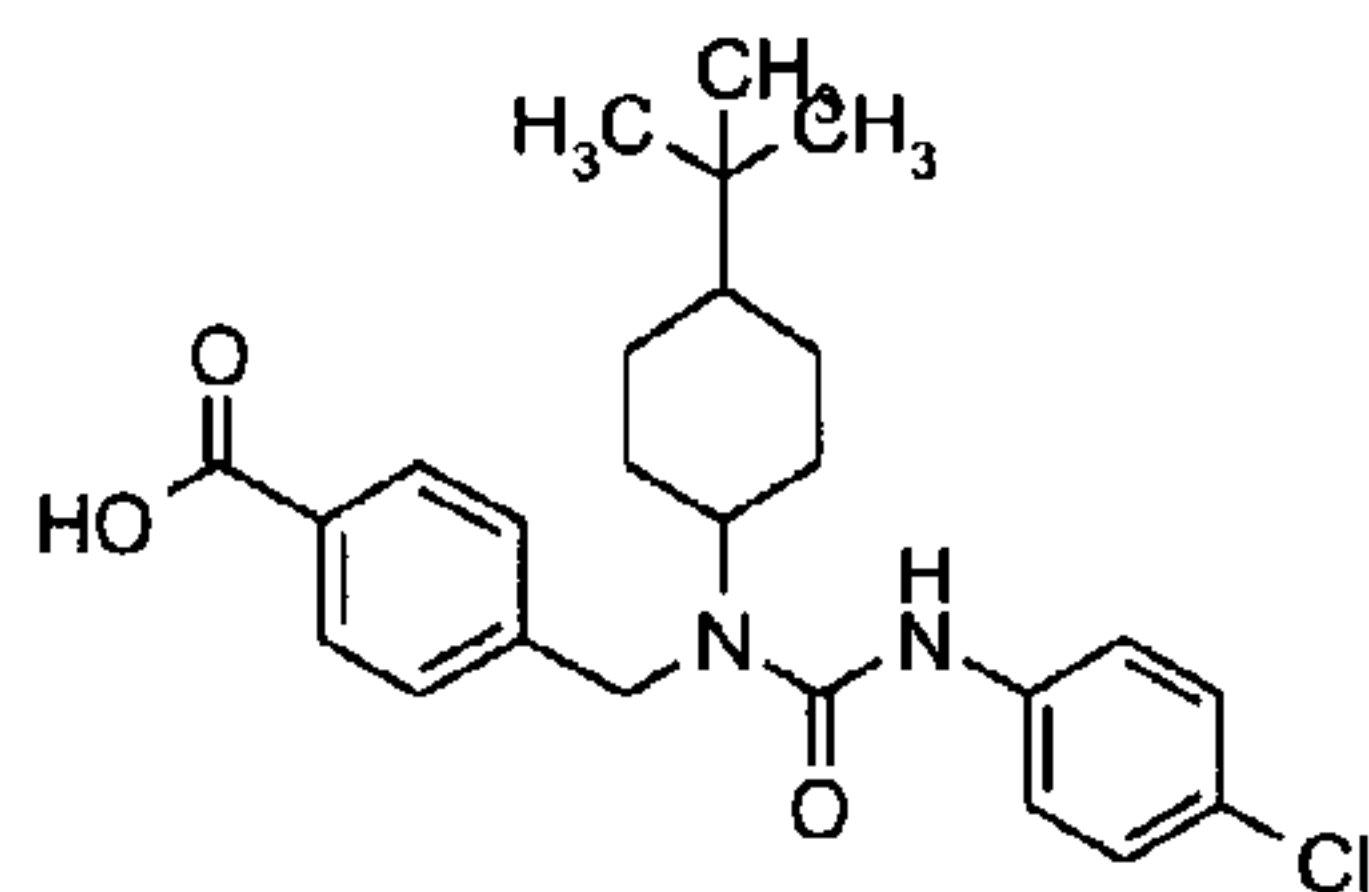
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoic acid



5

^1H NMR (DMSO- d_6): δ 0.81 (brd s, 9H), 1.12 (qt, 2H), 1.37 (qt, 2H), 1.69 (t, 4H), 4.06 (t, 1H), 4.62 (s, 2H), 7.21 (d, 2H), 7.35 (d, 2H), 7.54 (d, 2H), 7.87 (d, 2H), 8.57 (s, 1H), 12.84 (brd s, 1H).

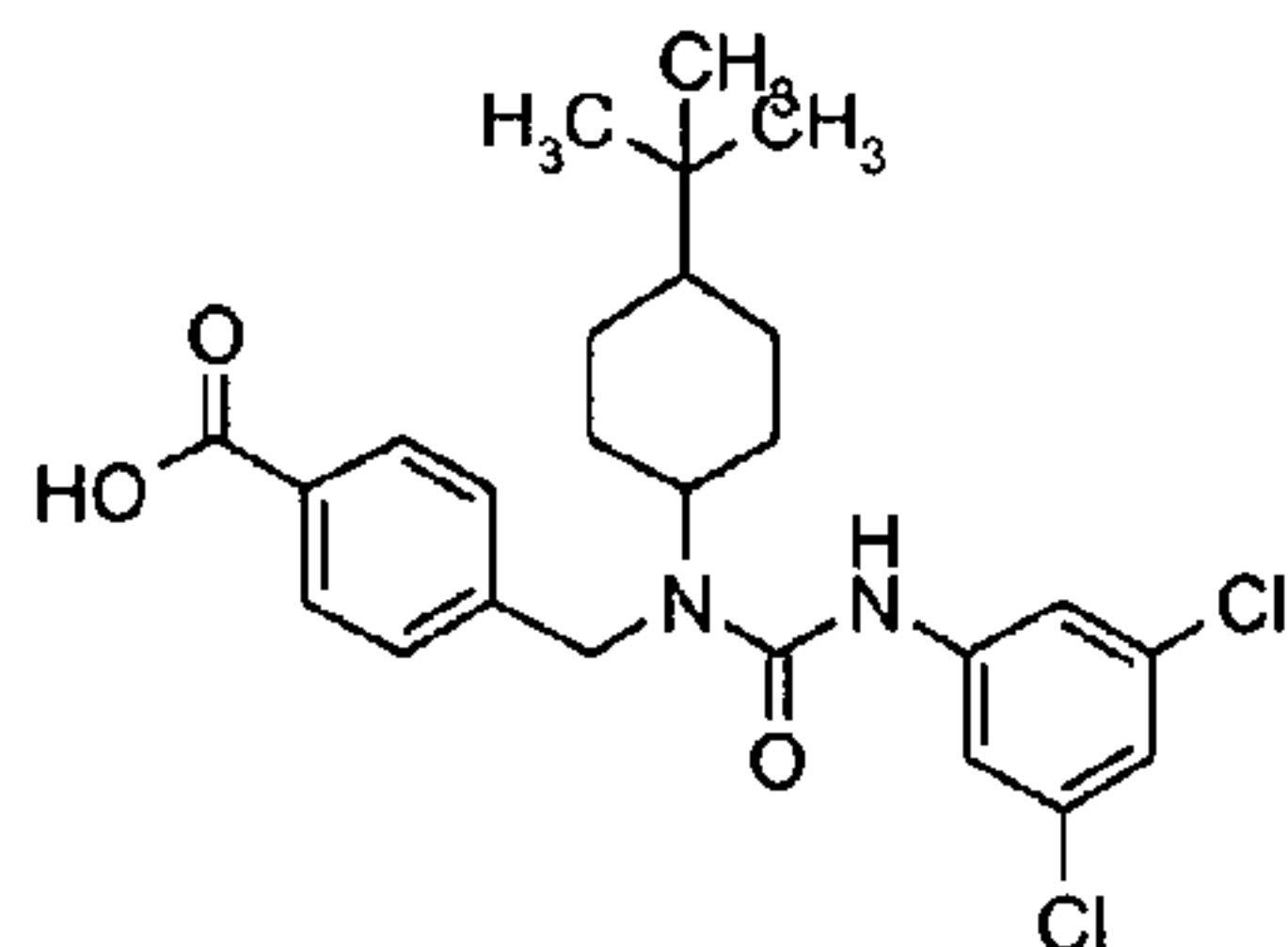
10 4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoic acid



^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 0.91 (m, 1H), 1.15 (qt, 2H), 1.37 (qt, 2H), 1.69 (t, 4H), 4.04 (m, 1H), 4.61 (s, 2H), 7.26 (d, 2H), 7.35 (d, 2H), 7.47 (d, 2H), 7.86 (d, 2H), 8.49 (s, 1H), 12.83 (brd s, 1H).

15

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoic acid



20 ^1H NMR (DMSO- d_6): δ 0.81 (s, 9H), 0.92 (m, 1H), 1.14 (qt, 2H), 1.47 (qt, 2H), 1.69-1.72 (m, 4H), 4.04 (m, 1H), 4.61 (s, 2H), 7.12 t, 1H), 7.35 (d, 2H), 7.63 (d, 2H), 7.88 (d, 2H), 8.87 (s, 1H), 12.95 (brd s, 1H).

Step D:

This step was carried out in a combinatorial fashion in solution.

- 5 To a solution of one of the above benzoic acids (0.02 mmol) in a suitable solvent such as CH₂Cl₂, DMF, or THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before the amine (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure to afford the crude product.

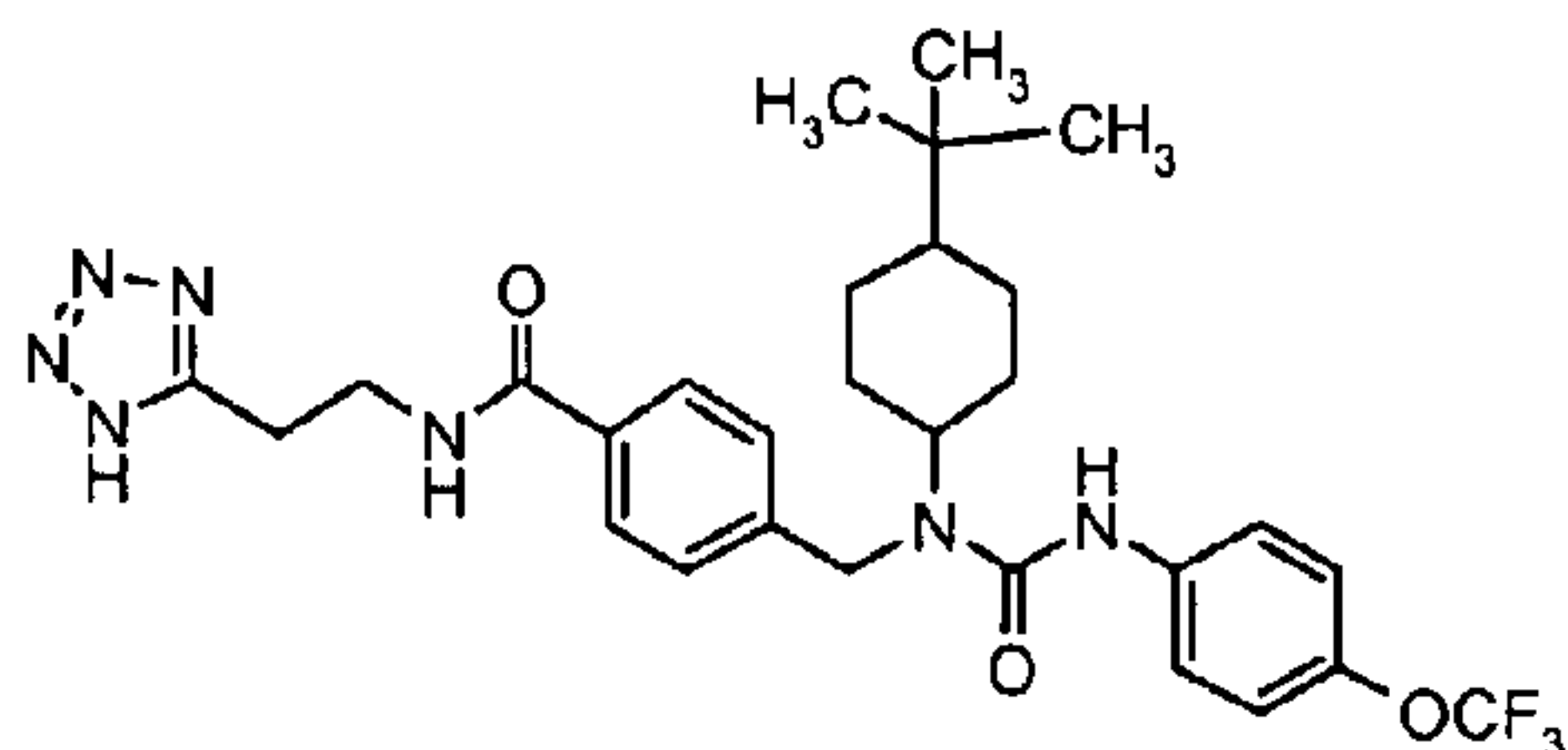
10

The following examples were prepared according to the general procedure (I).

EXAMPLE 156 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-[2-(1*H*-tetrazol-5-yl)ethyl]benzamide

15



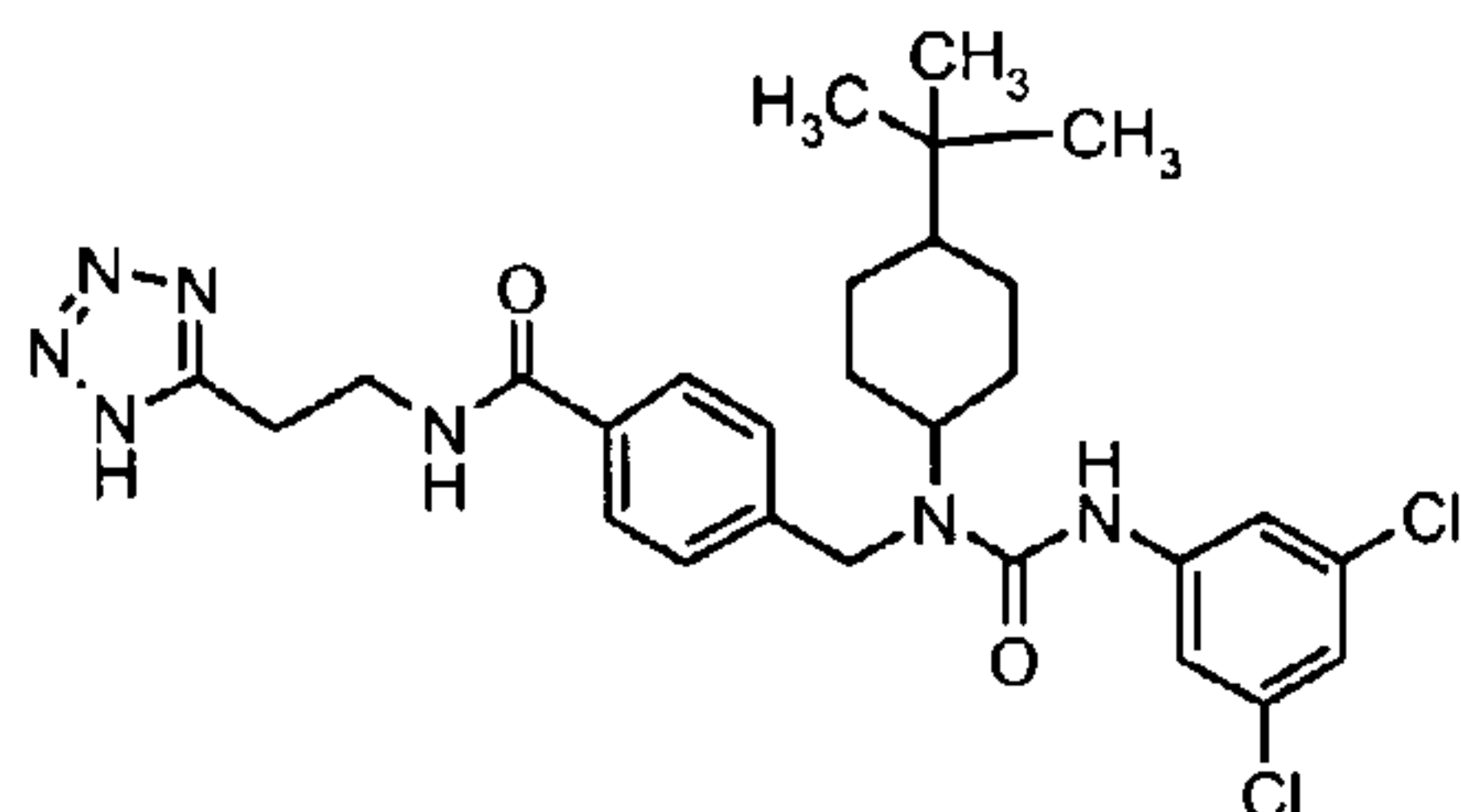
¹H NMR (DMSO-*d*₆): δ 0.81 (s, 9H), 0.90 (m, 1H), 1.11 (qt, 2H), 1.41 (qt, 2H), 1.70 (m, 4H), 3.13 (t, 2H), 3.60 (qt, 2H), 4.05 (quintet, 1H), 4.60 (s, 2H), 7.22 (d, 2H), 7.31 (d, 2H), 7.55 (d, 2H), 7.73 (d, 2H), 8.54 (s, 1H), 8.56 (t, 1H).

20

MS (APCI, pos): 588.3.

EXAMPLE 157 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-[2-(1*H*-tetrazol-5-yl)ethyl]benzamide



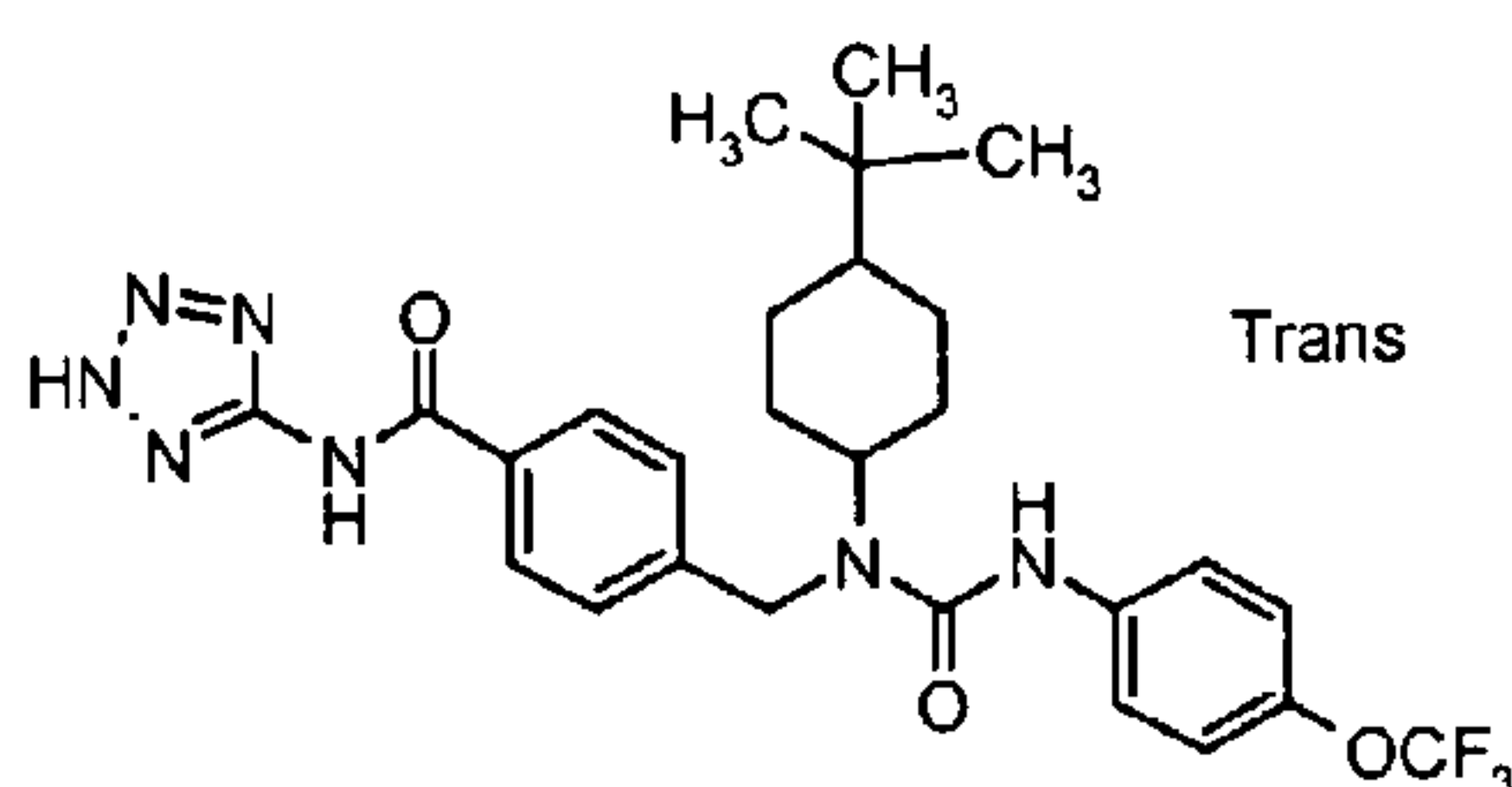
5

¹H NMR (MeOH-*d*₄): δ 0.87 (s, 9H), 1.01 (m, 1H), 1.25 (m, 2H), 1.46 (q, 2H), 1.83 (t, 4H), 3.27 (t, 2H), 3.78 (t, 2H), 4.10 (m, 1H), 4.67 (s, 2H), 7.04 (t, 1H), 7.38 (d, 2H), 7.43 (t, 2H), 7.75 (d, 2H), 8.44 (brd s, 1H).

10 MS (APCI, pos): 480.2, 478.2, 477.2, 435.1, 433.2, 290.1, 156.2.

EXAMPLE 158 (general procedure (I))

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2*H*-tetrazol-5-yl)benzamide



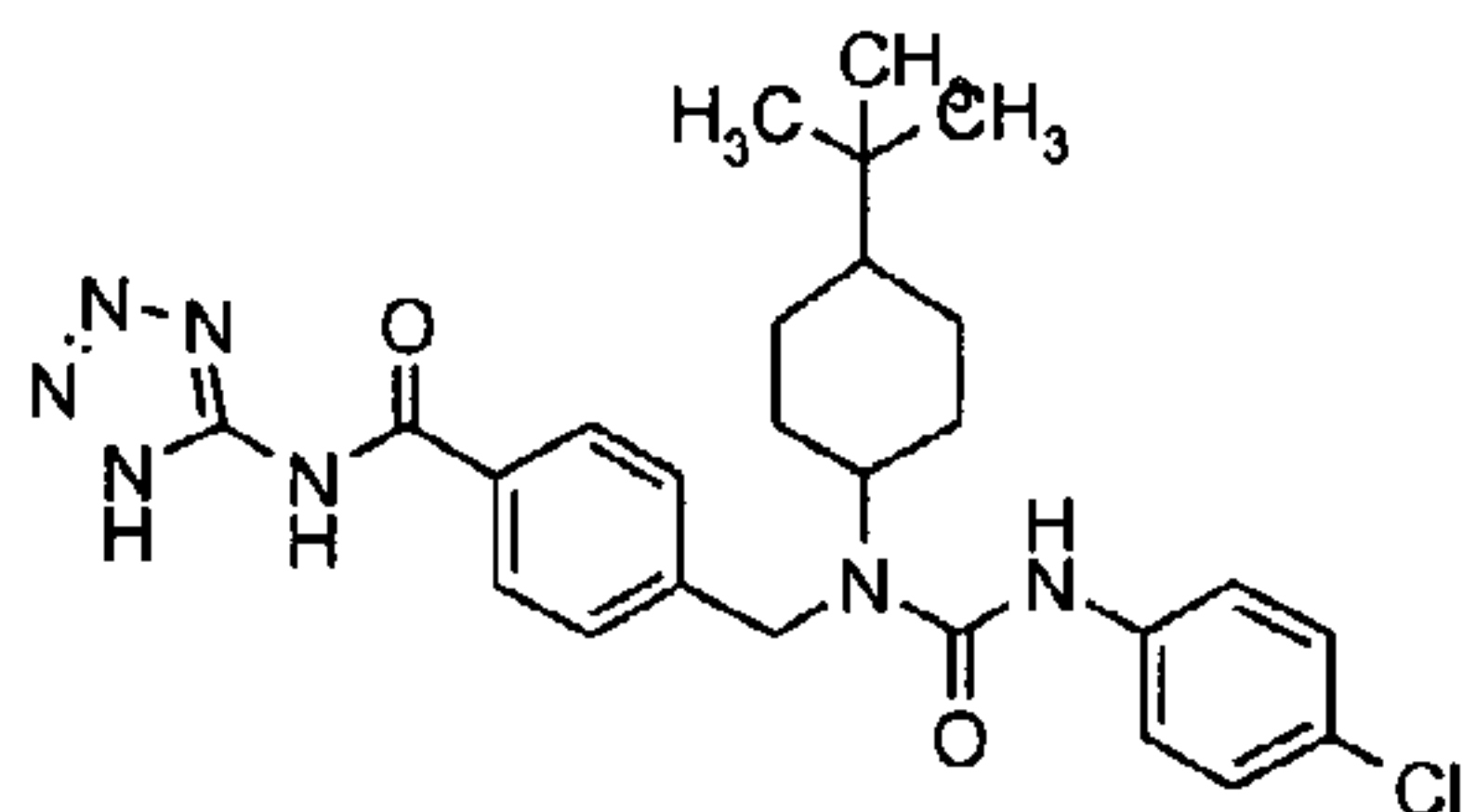
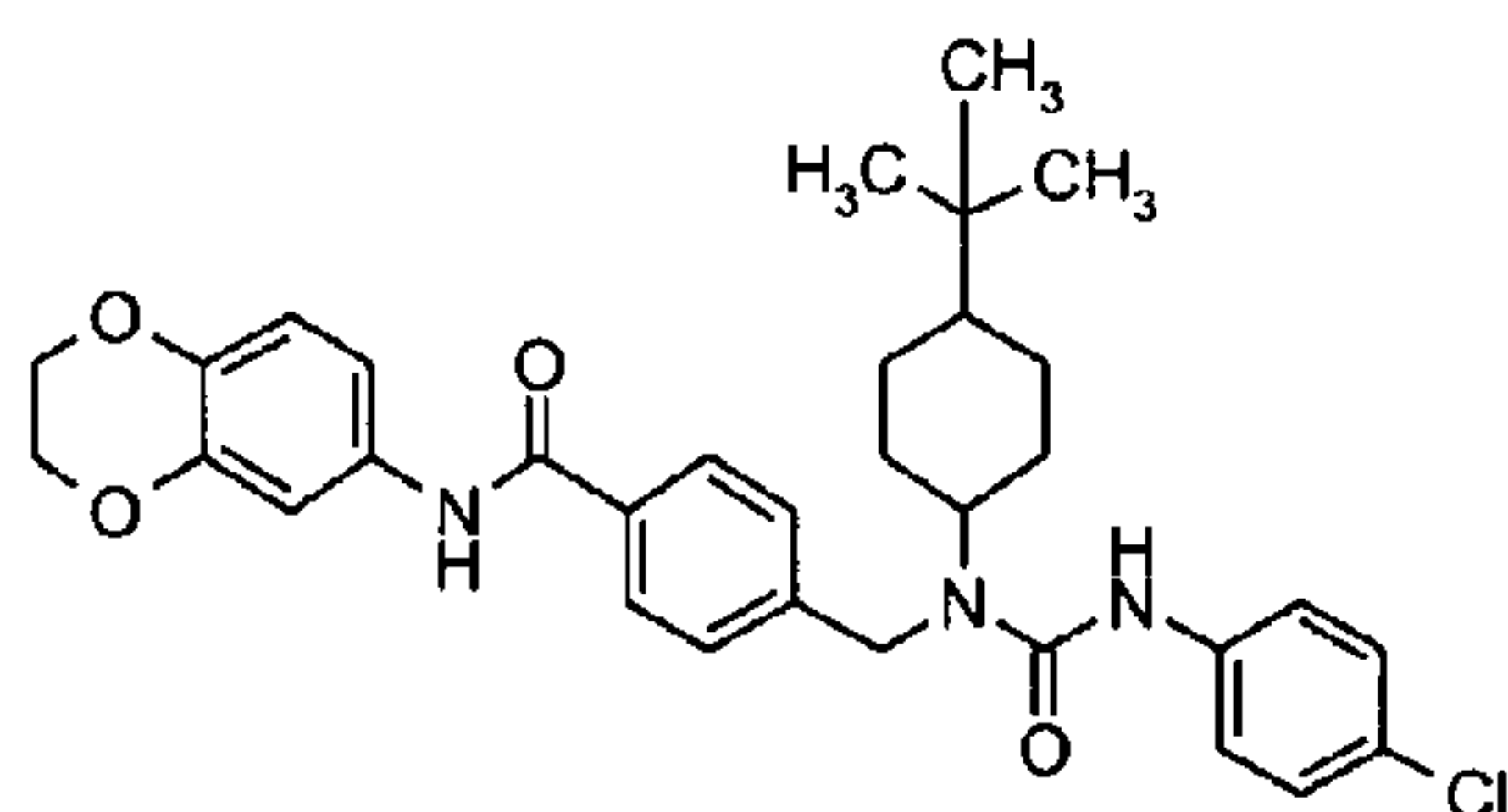
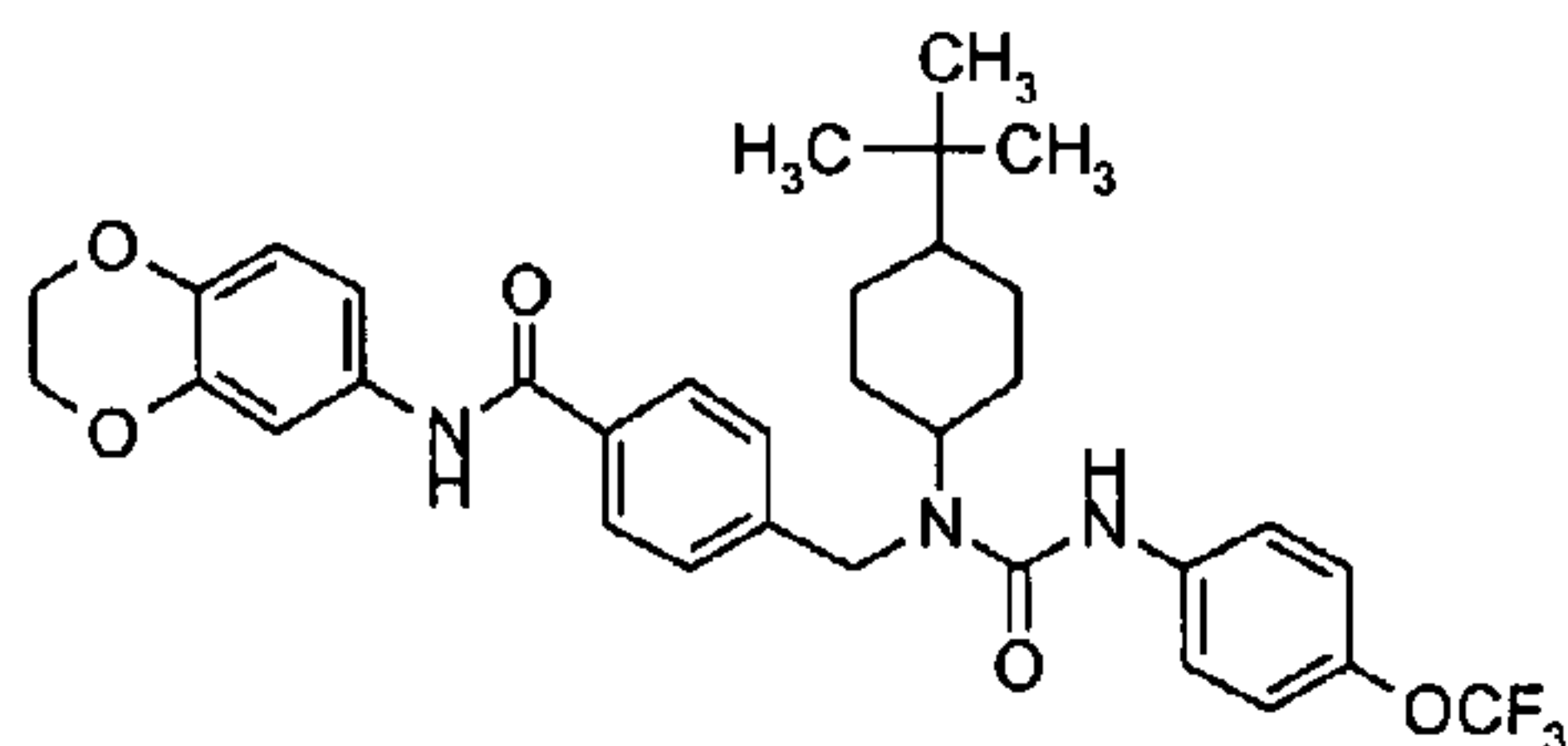
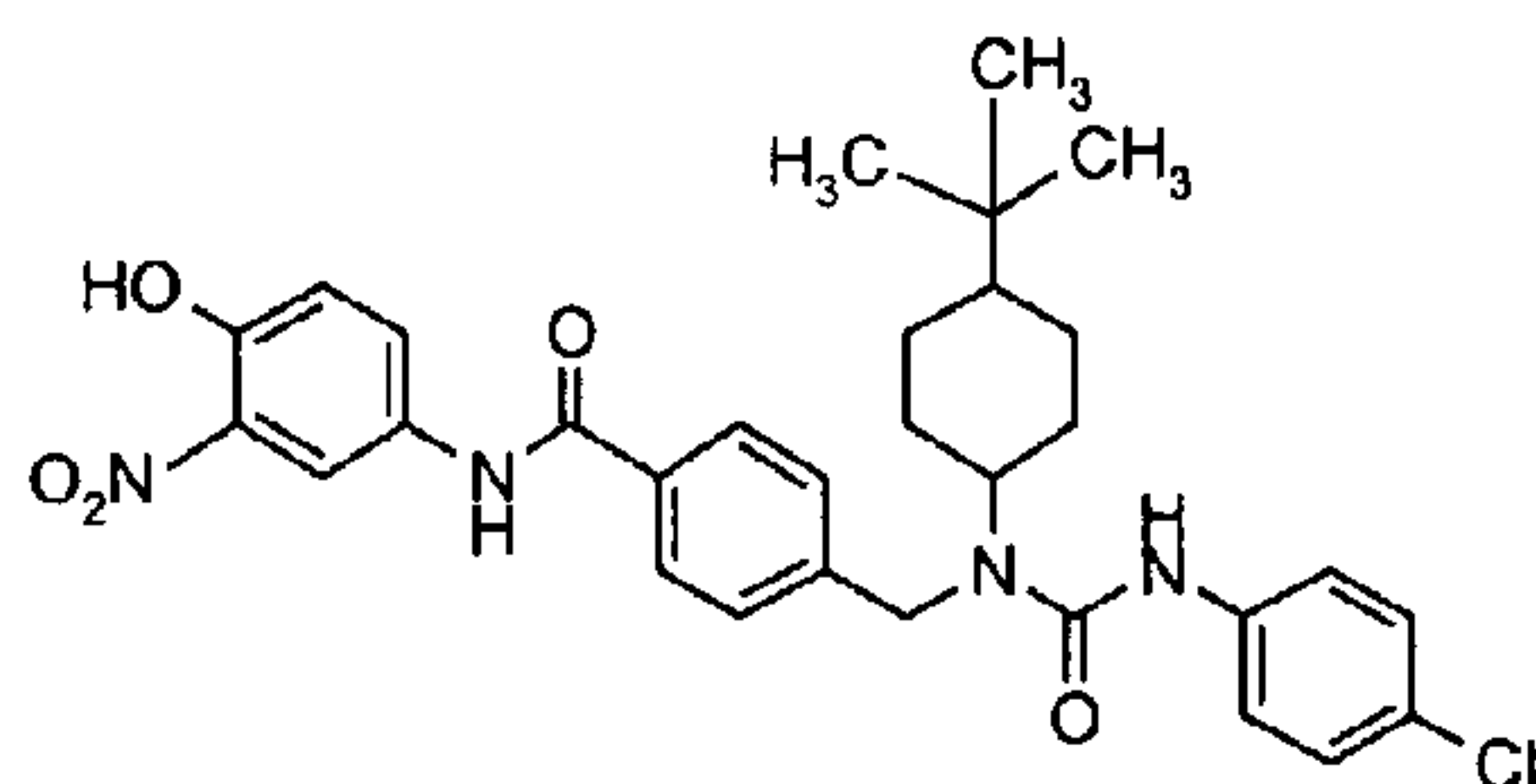
15

¹H NMR (MeOH-*d*₄): δ 0.86 (s, 9H), 1.01 (m, 1H), 1.22 (qt, 2H), 1.48 (qt, 2H), 1.85 (m, 4H), 4.11 (m, 1H), 4.70 (s, 2H), 7.16 (d, 2H), 7.42 (d, 2H), 7.46 (d, 2H), 7.99 (d, 2H).

20 MS (APCI, pos): 560.2, 561.2, 357.1, 358.2.

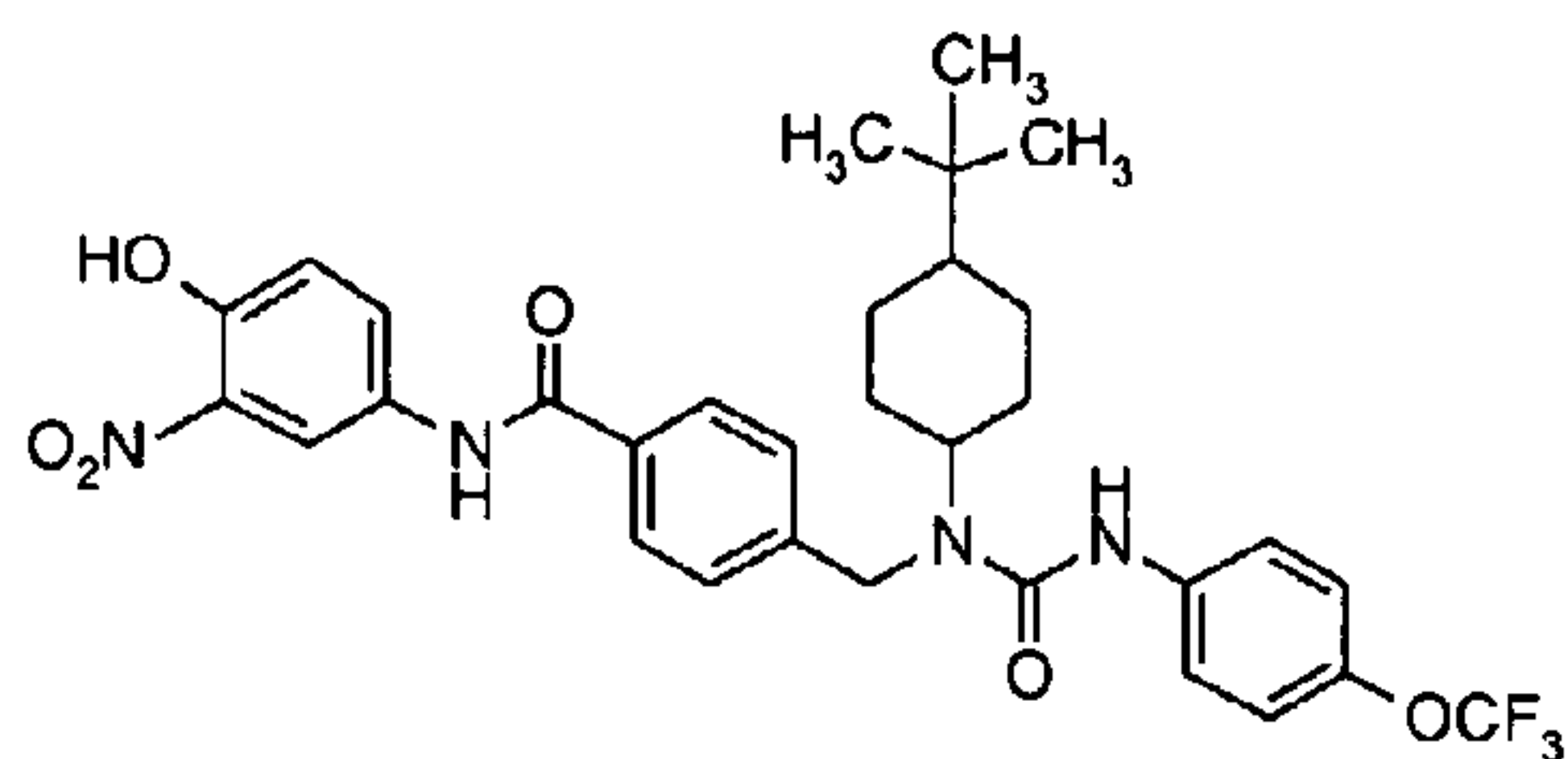
The following examples 159 to 171 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

25

EXAMPLE 159 (general procedure (I))4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1*H*-tetrazol-5-yl)benzamide5 EXAMPLE 160 (general procedure (I))4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide10 EXAMPLE 161 (general procedure (I))4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide15 EXAMPLE 162 (general procedure (I))4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)benzamide

EXAMPLE 163 (general procedure (I))

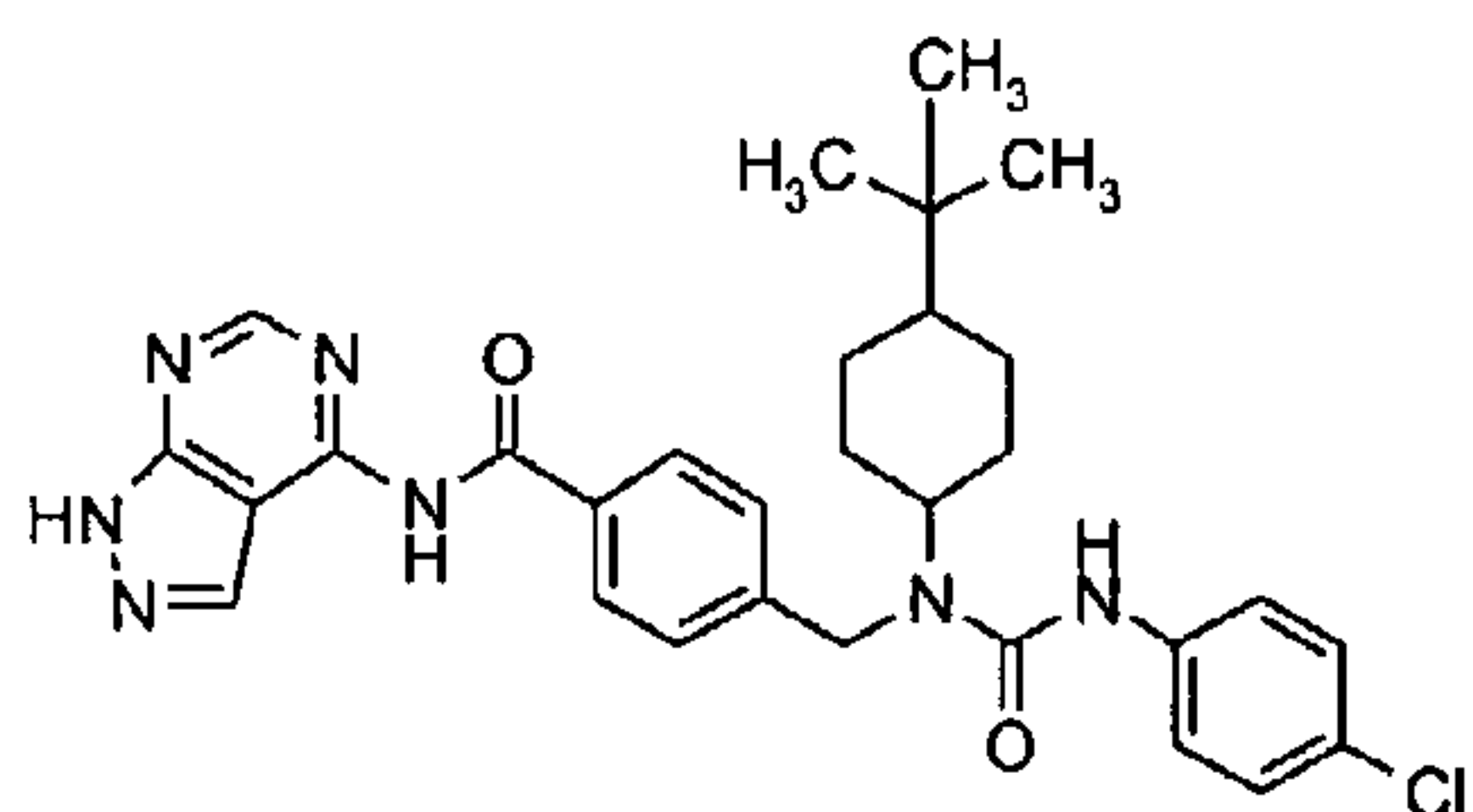
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)benzamide



5

EXAMPLE 164 (general procedure (I))

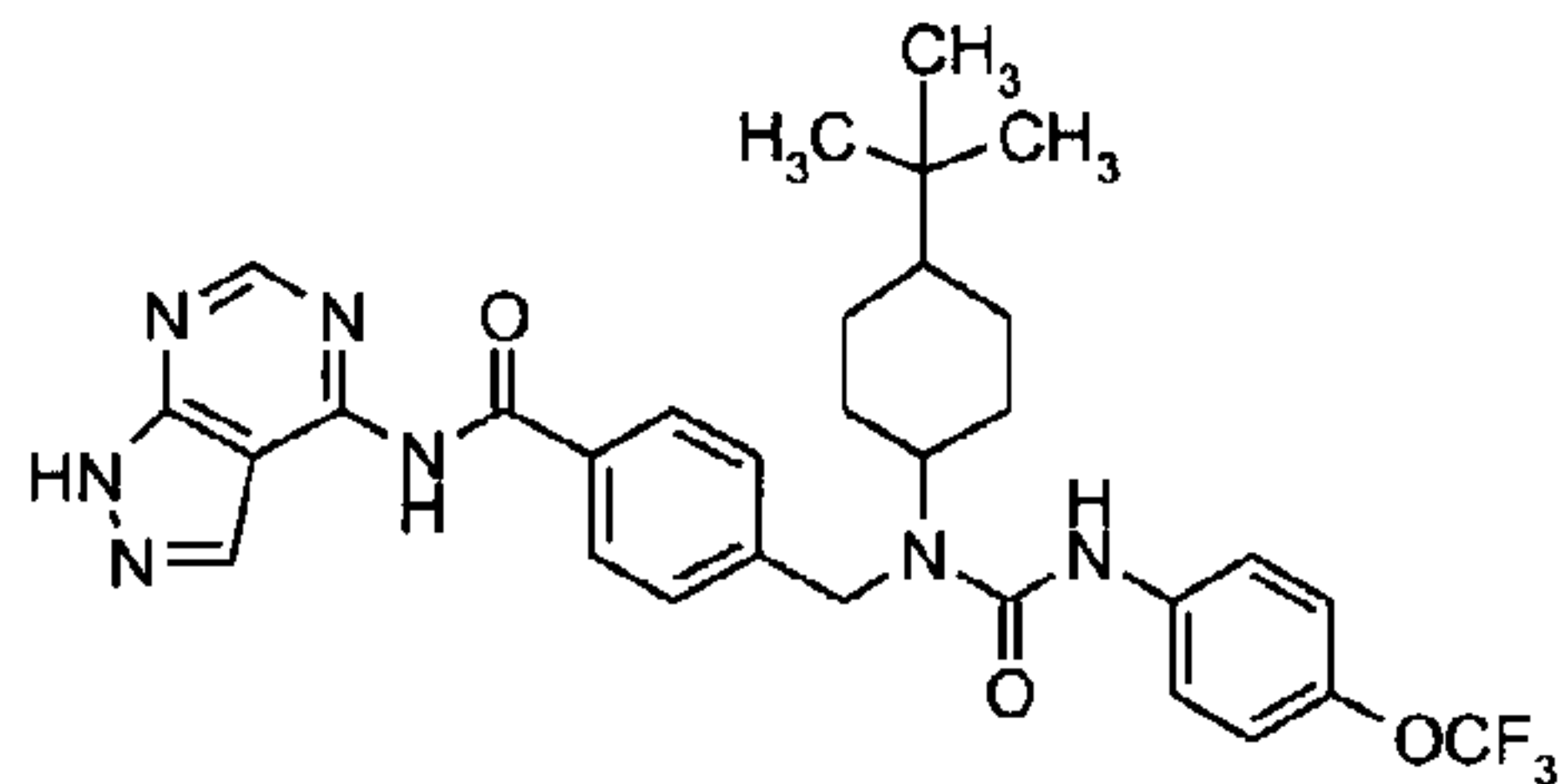
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)benzamide



10

EXAMPLE 165 (general procedure (I))

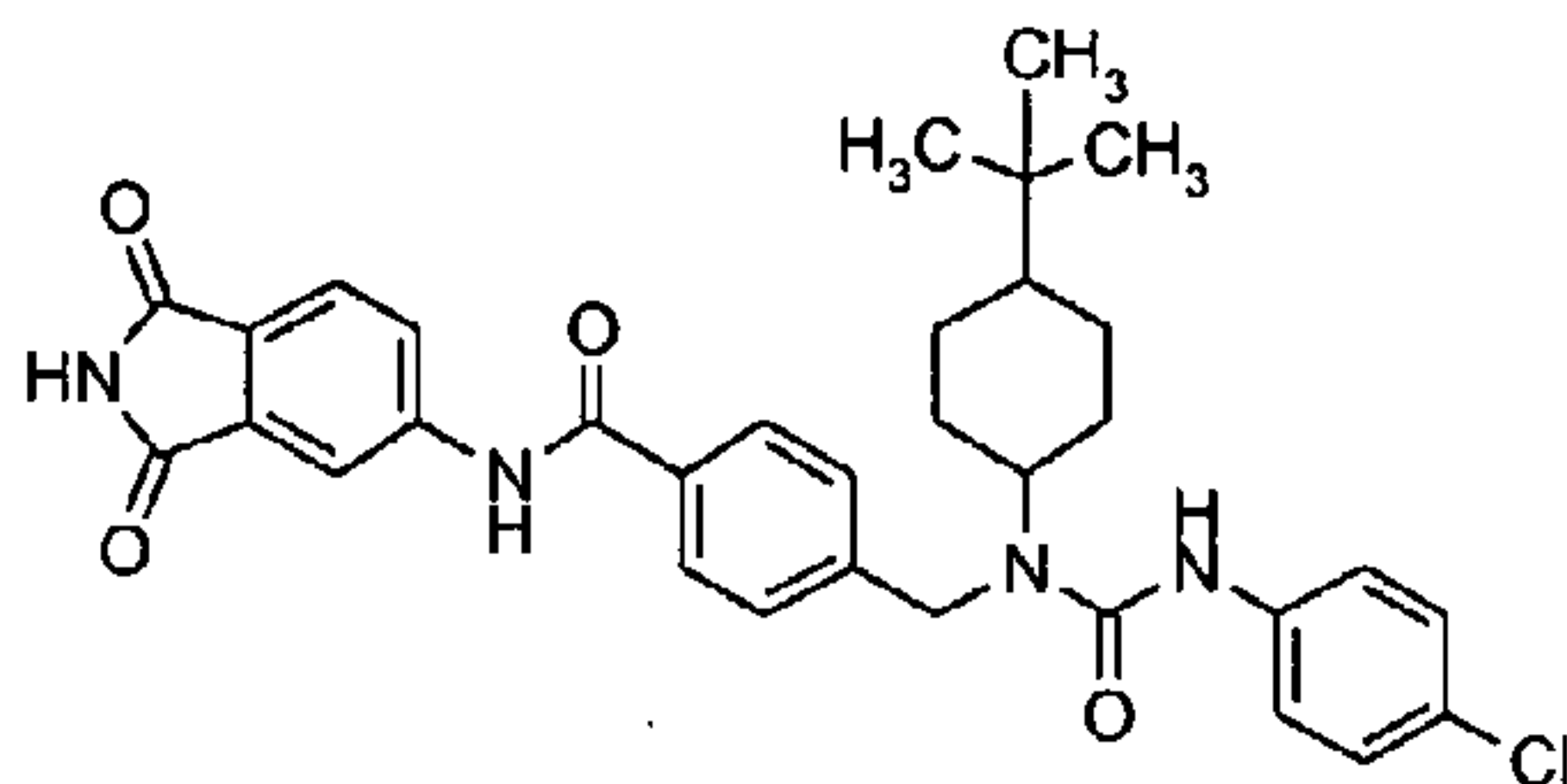
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)benzamide



15

EXAMPLE 166 (general procedure (I))

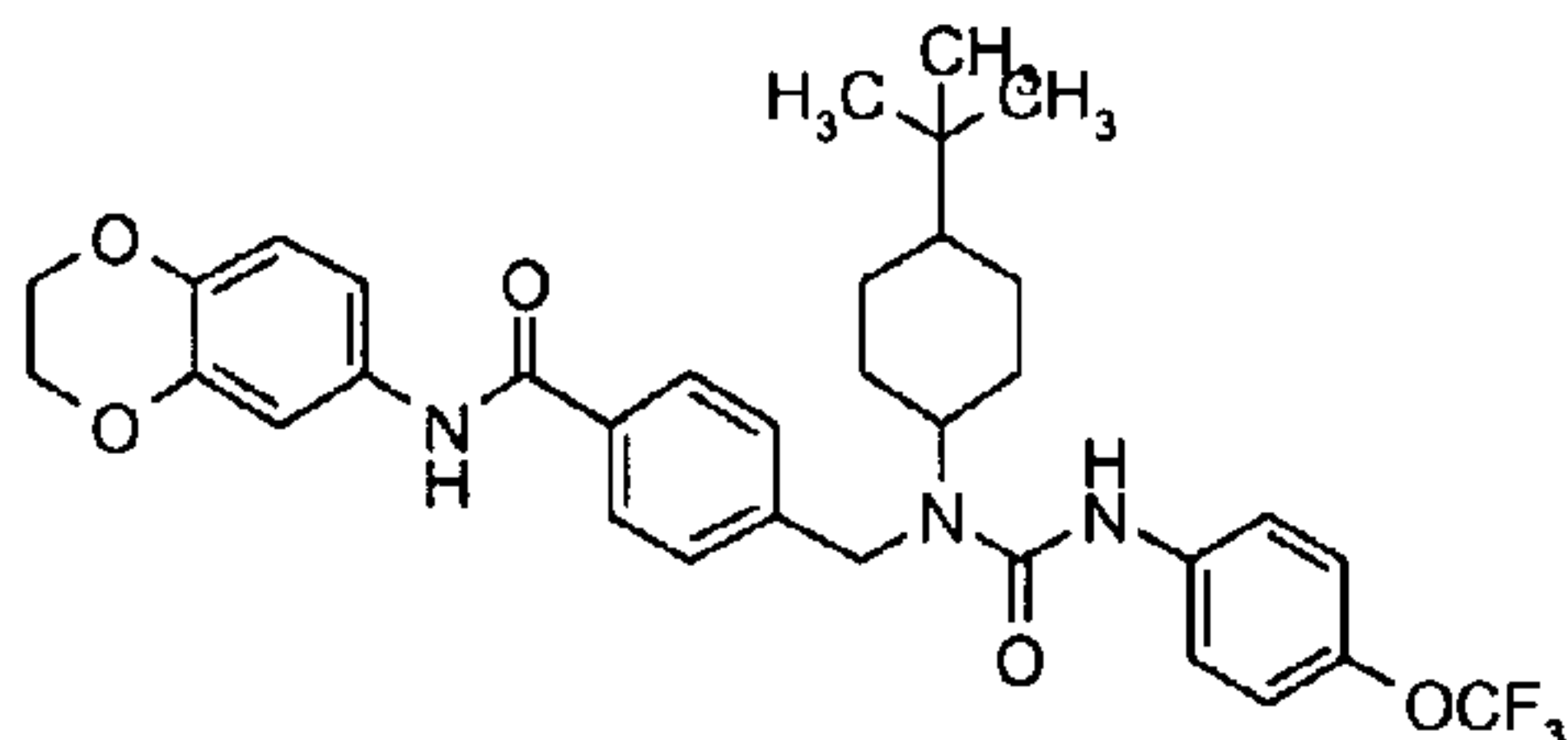
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]-N-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)benzamide



5

EXAMPLE 167 (general procedure (I))

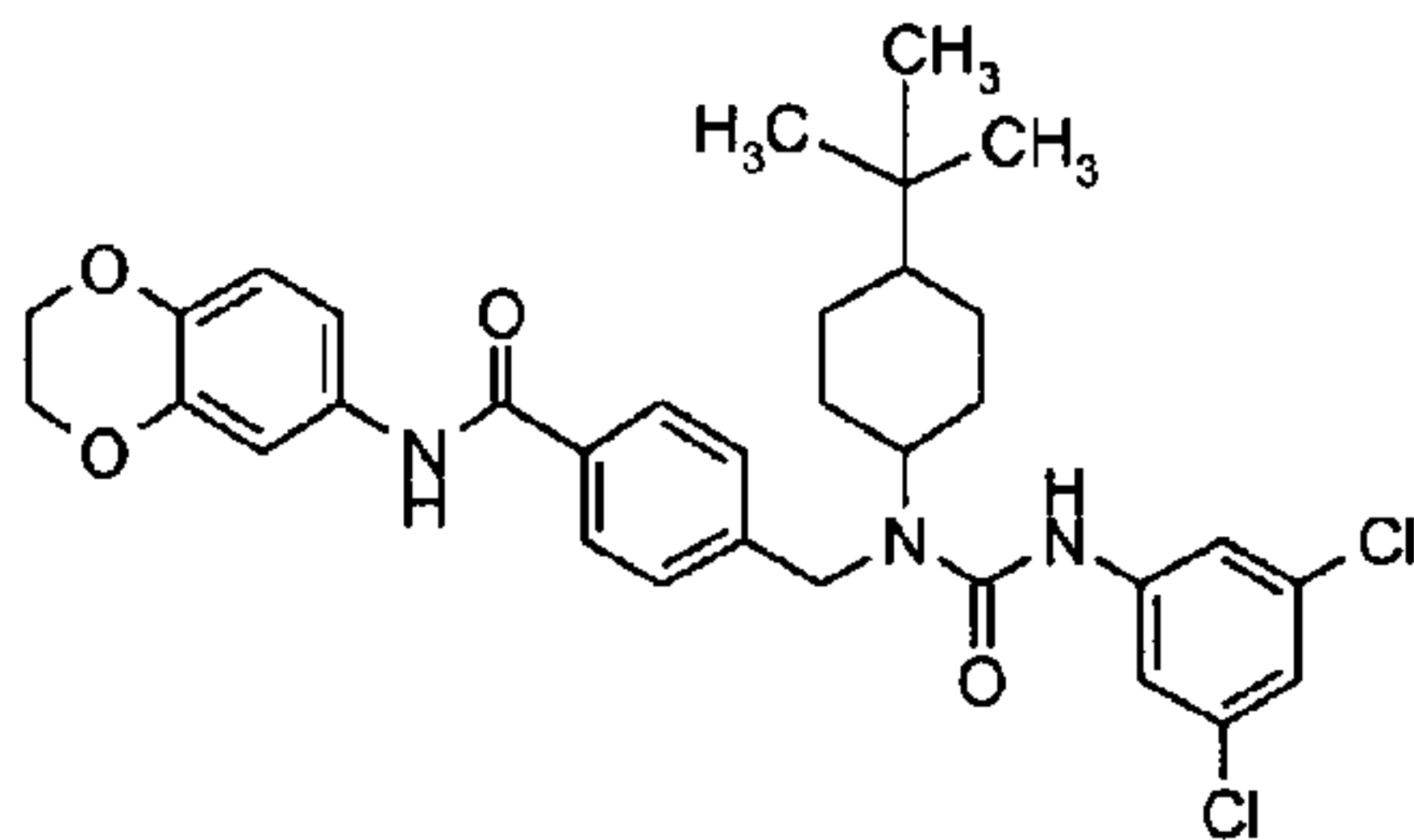
4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



10

EXAMPLE 168 (general procedure (I))

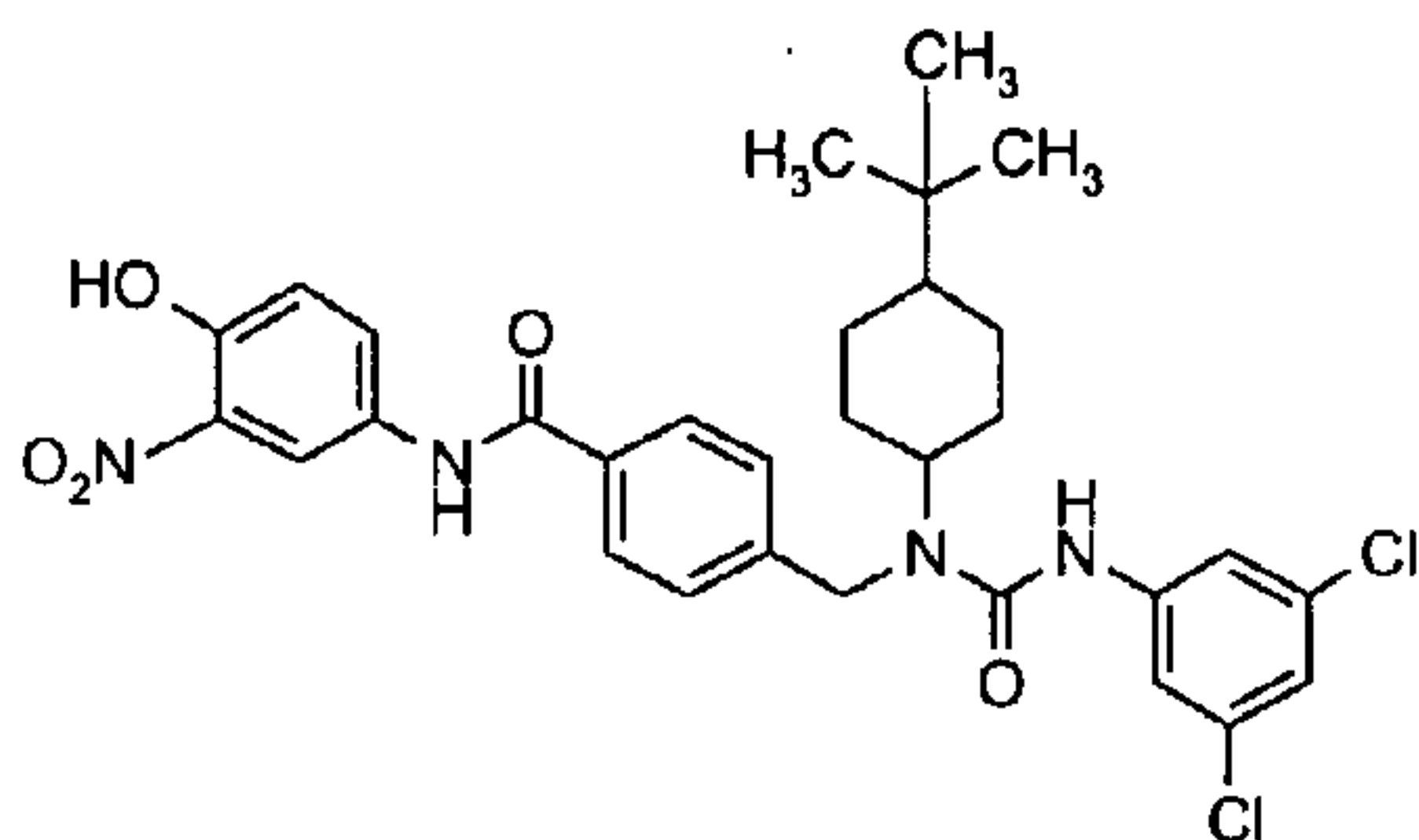
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-N-(2,3-dihydro-1,4-benzodioxin-6-yl)benzamide



15

EXAMPLE 169 (general procedure (I))

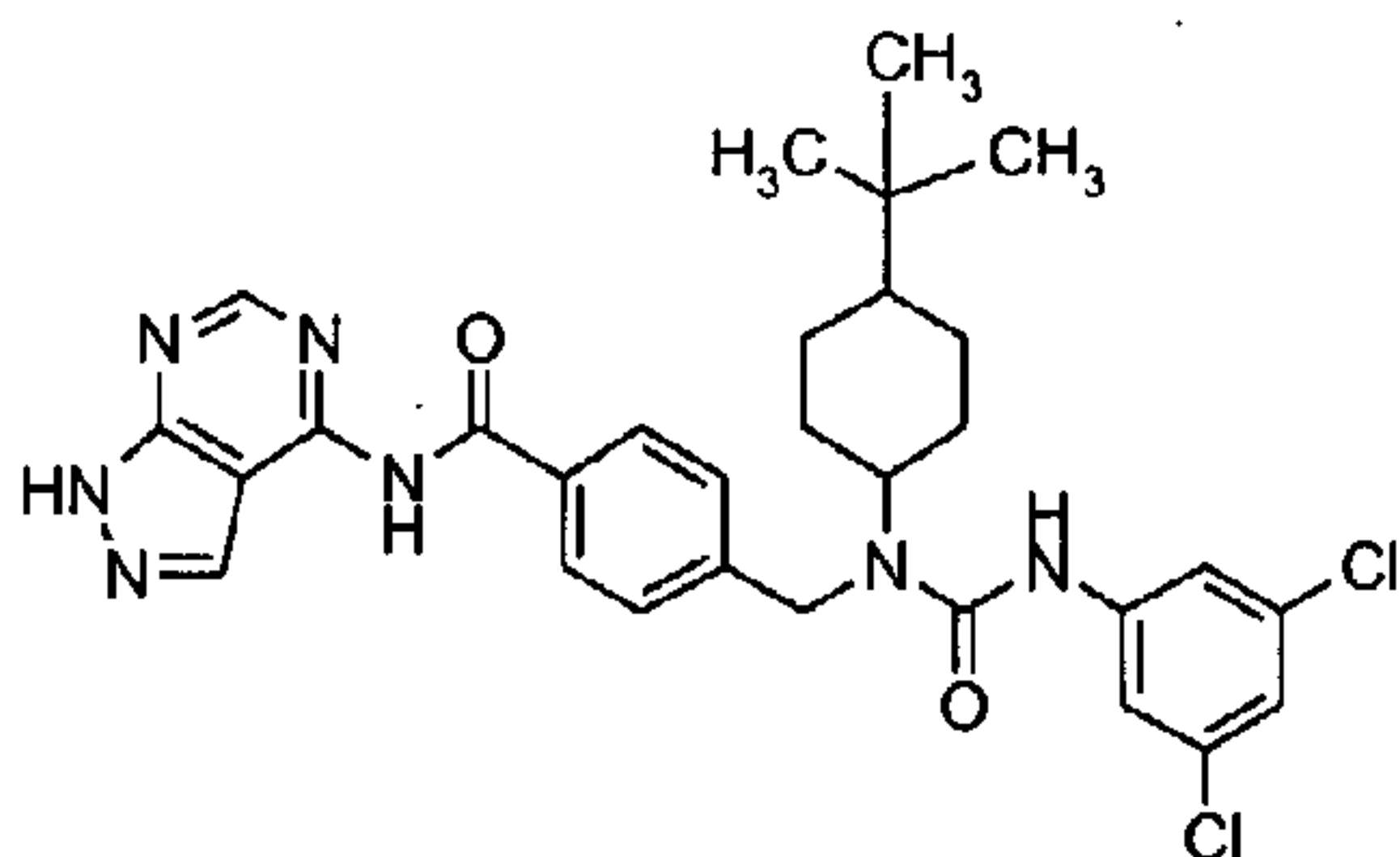
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(4-hydroxy-3-nitrophenyl)-benzamide



5

EXAMPLE 170 (general procedure (I))

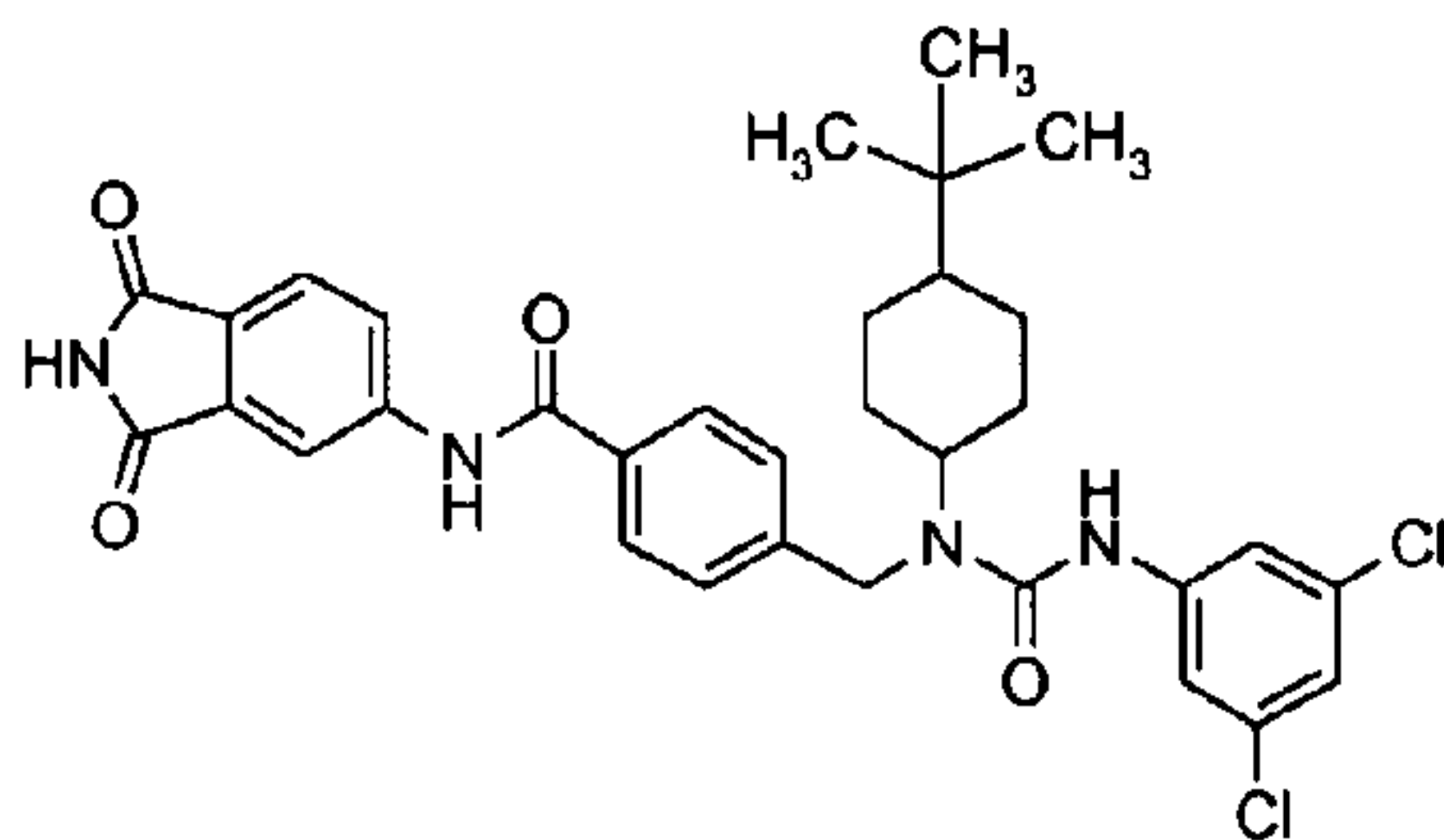
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-yl)benzamide



10

EXAMPLE 171 (general procedure (I))

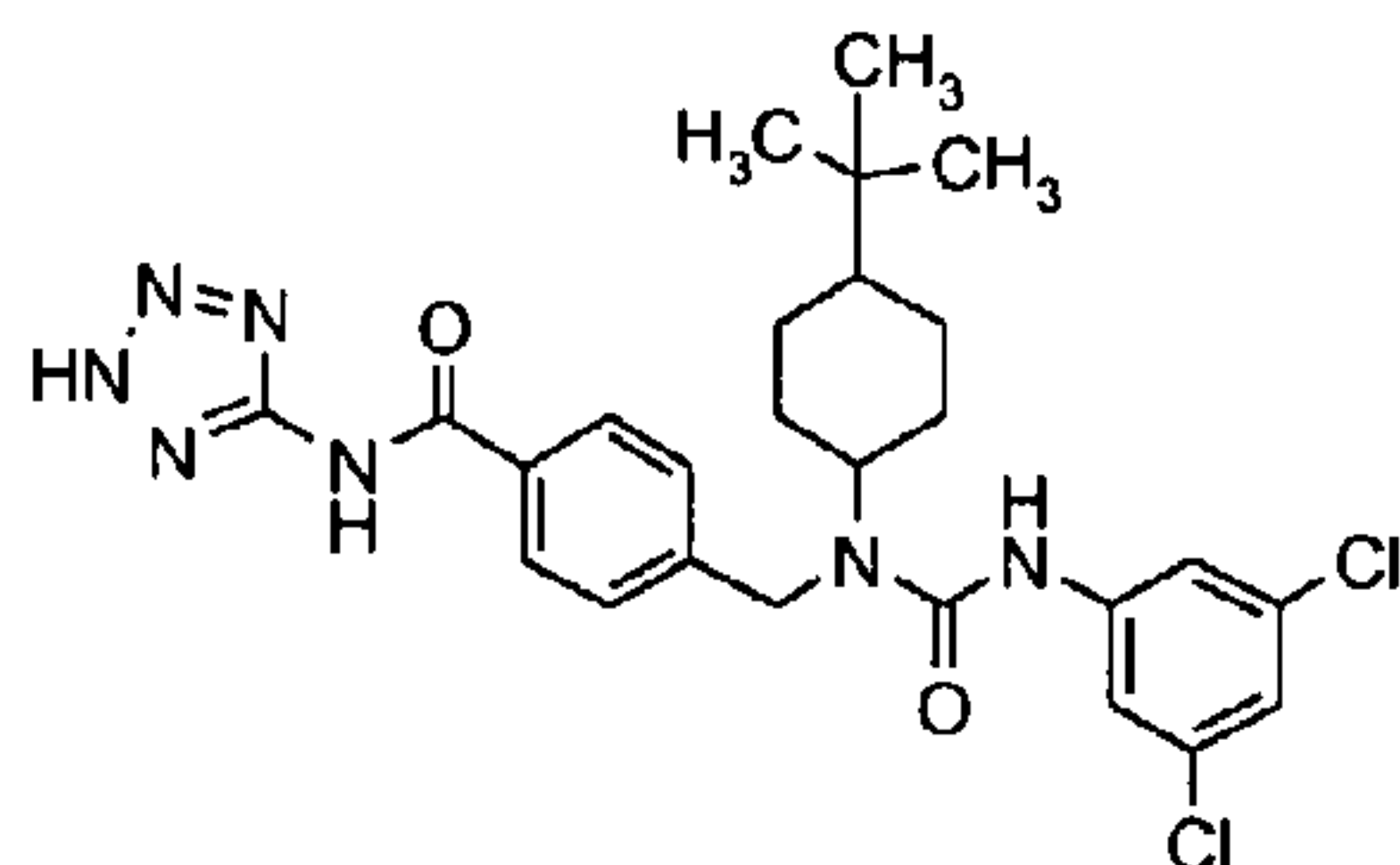
4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)benzamide



15

EXAMPLE 172 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



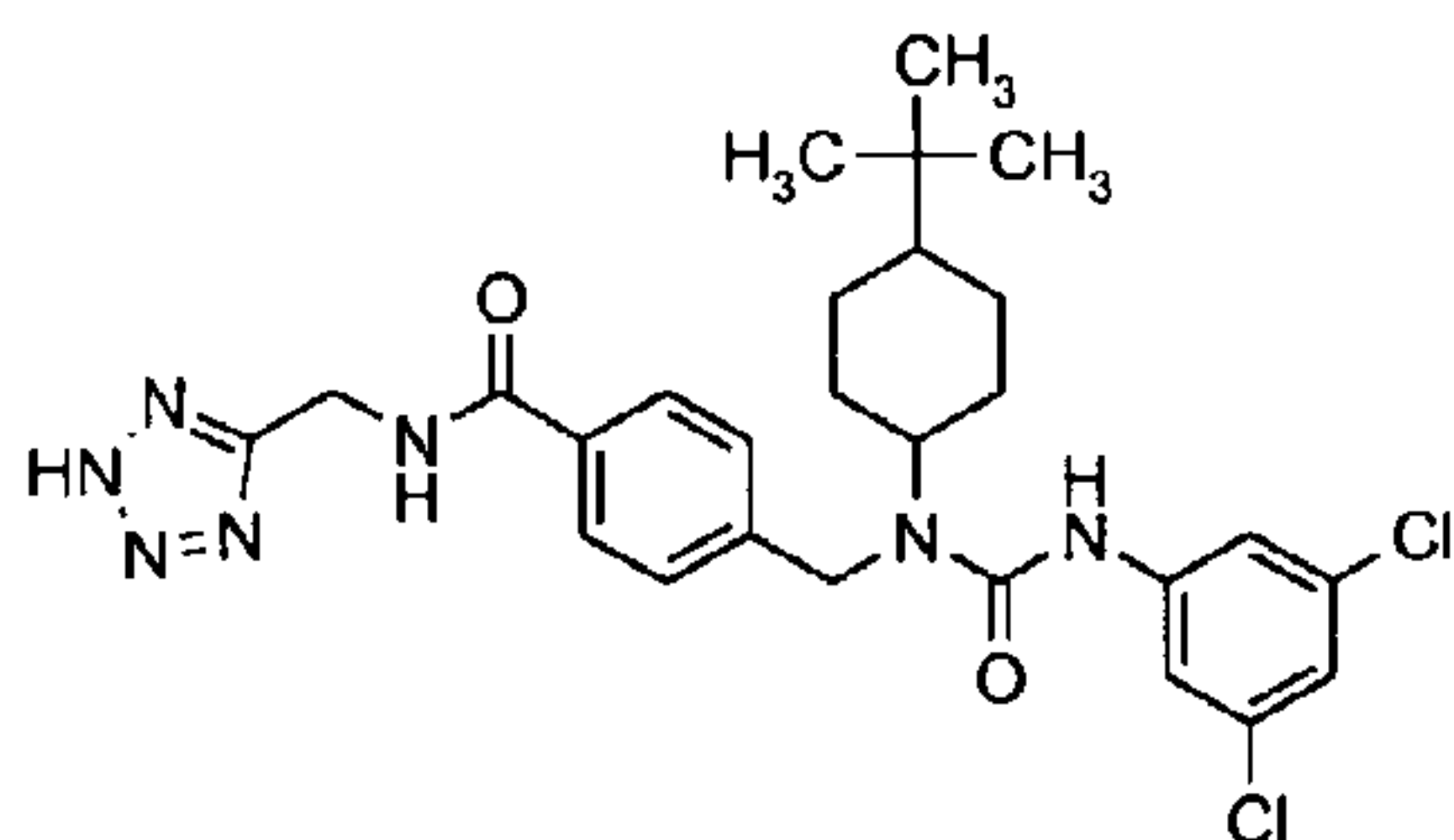
5

¹H NMR (MeOH-*d*₄): δ 0.92 (s, 9H), 1.01 (m, 1H), 1.18 – 1.31 (m, 2H), 1.44 – 1.52 (m, 2H), 1.80 – 1.87 (m, 4H), 4.12 (m, 1H), 4.72 (s, 2H), 7.05 (t, 1H), 7.46 (d, 2H), 7.49 (d, 2H), 8.02 (d, 2H).

10 MS (APCI, pos): 544.2, 357.2.

EXAMPLE 173 (general procedure (I))

4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-ylmethyl)-benzamide



15

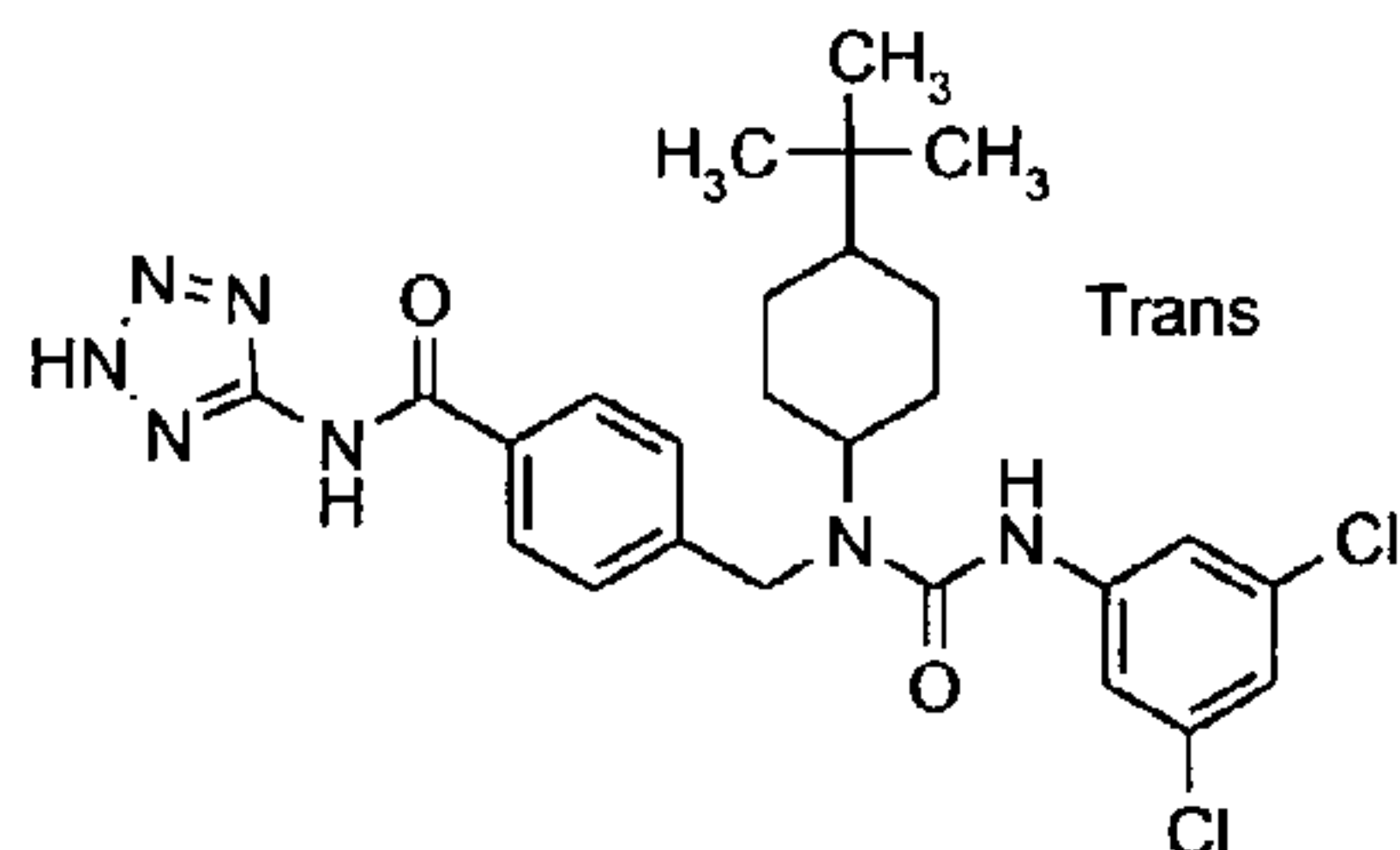
¹H NMR (DMSO-*d*₆): δ 0.82 (s, 9H), 0.92 (d, 1H), 1.04 – 1.20 (m, 2H), 1.42 (qt, 2H), 1.70 (m, 4H), 4.05 (qt, 1H), 4.61 (s, 2H), 4.73 (d, 2H), 7.12 (s, 1H), 7.34 (d, 2H), 7.62 (s, 2H), 7.83 (d, 2H), 8.70 (s, 1H), 9.18 (t, 1H).

20

MS (APCI, pos): 558.2, 560.2, 372.2, 343.2.

EXAMPLE 174 (general procedure (I))

4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

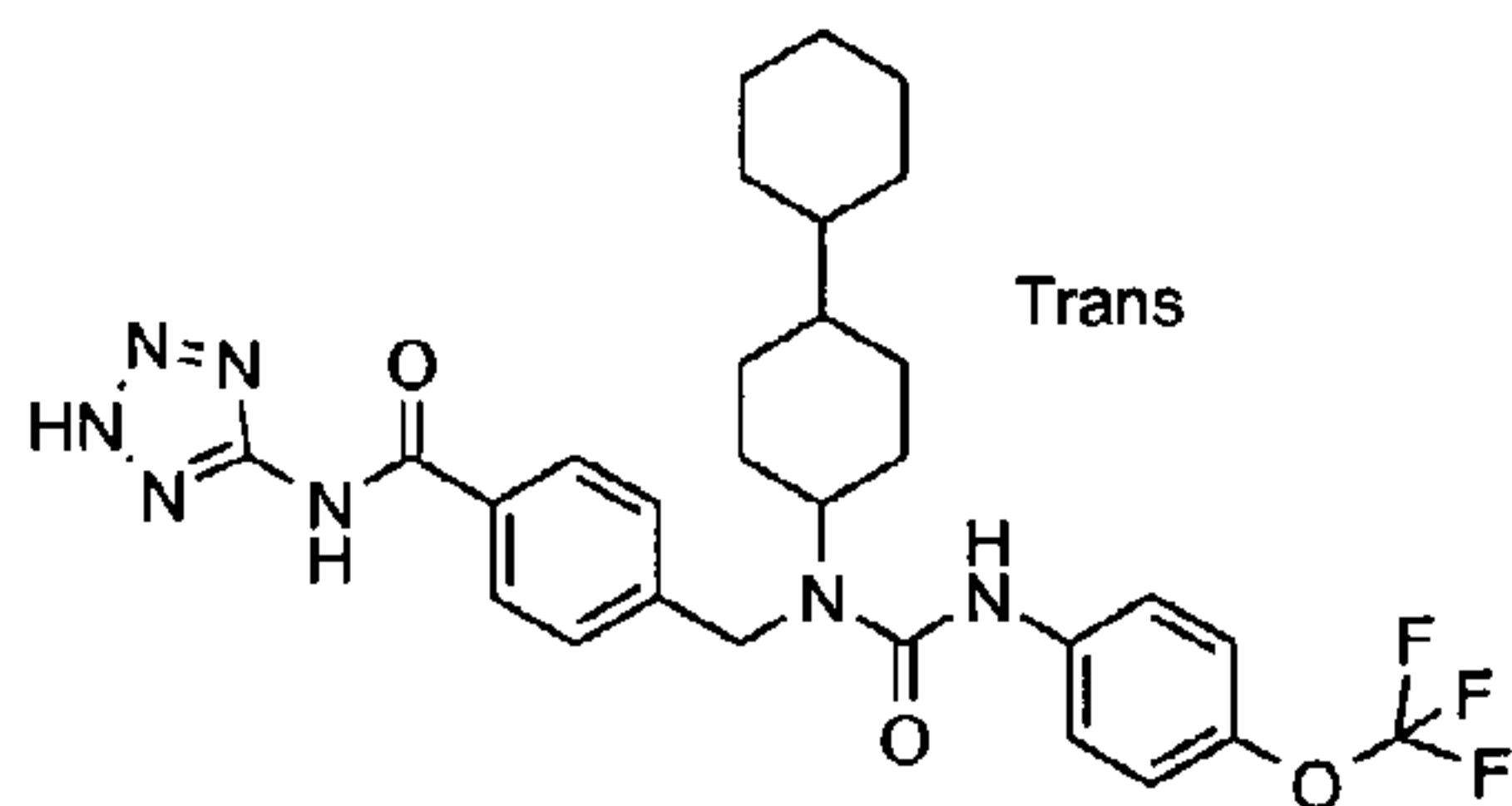
^1H NMR (DMSO- d_6): δ 0.82 (s, 9H), 1.01 (m, 1H), 1.10 (m, 2H), 1.42 (m, 2H), 1.74 (m, 4H), 4.40 (m, 1H), 4.63 (s, 2H), 7.13 (s, 1H), 7.39 (d, 2H), 7.63 (s, 2H), 8.01 (d, 2H), 8.73 (s, 1H).

MS (APCI, neg): 542.1, 544.1.

10

EXAMPLE 175 (general procedure (I))

4-[1-(*trans*-4-Cyclohexylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

trans-4-Cyclohexylcyclohexylamine was prepared according to H. Booth, G. C. Gidley, P. R. Thornburrow, J. Chem. Soc. B, 1971, 1047-50.

The *cis* isomer may be prepared by reductive amination of cyclohexylcyclohexyl ketone with the appropriate amine followed by column chromatographic separation of the *cis/trans* isomers.

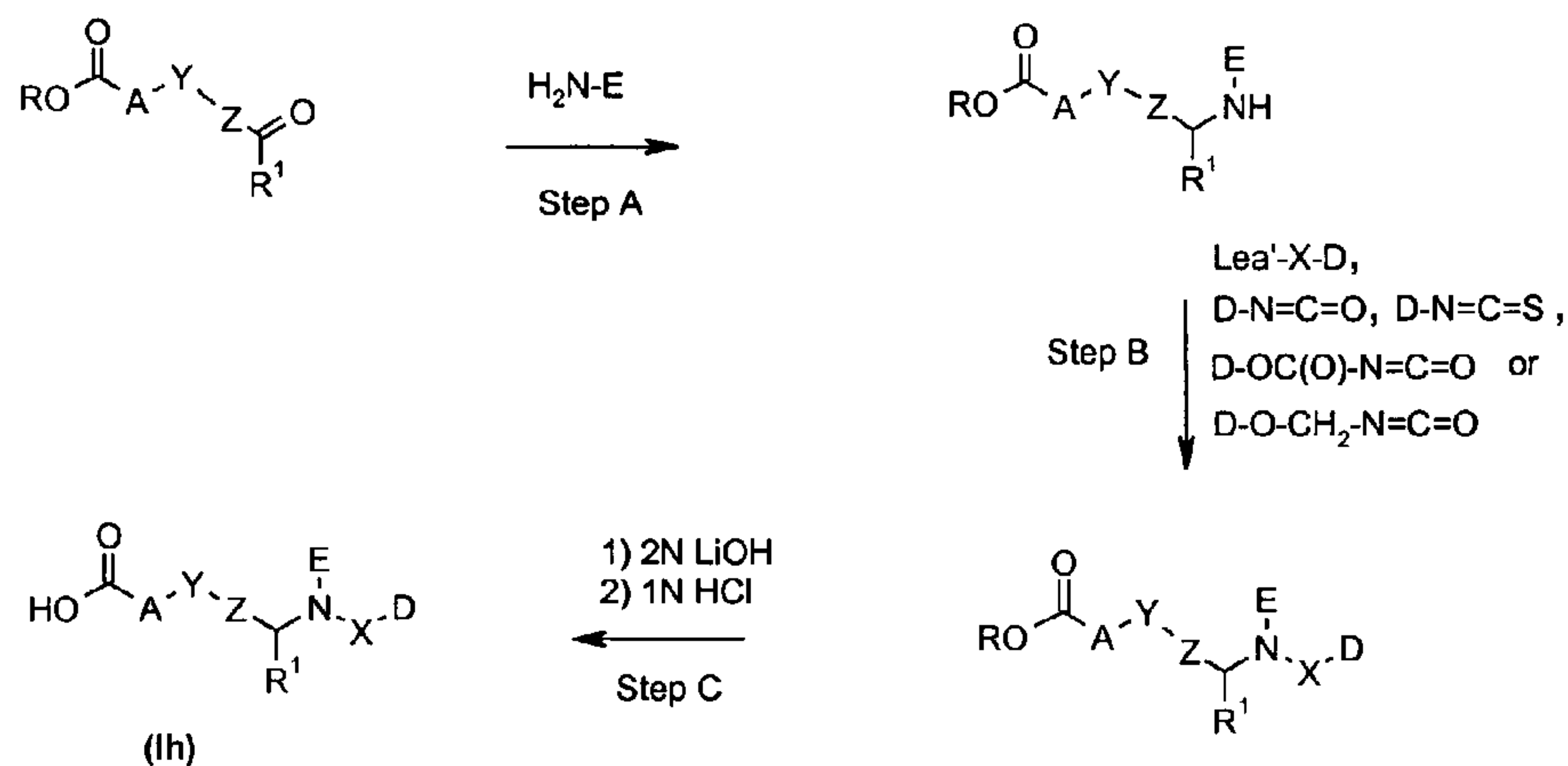
^1H NMR (DMSO- d_6): δ 0.82 – 1.10 (m, 10H), 1.60 (m, 2H), 1.64 – 1.80 (m, 8H), 4.03 (quintet, 1H), 4.64 (s, 2H), 7.22 (d, 2H), 7.41 (d, 2H), 7.54 (d, 2H), 8.03 (d, 2H), 8.56 (s, 1H), 12.32 (s, 1H), 15.90 (brd s, 1H).

25

MS (APCI, pos): 586.1, 587.2, 383.2, 384.2.

General procedure (J) for the solution phase synthesis of compounds of the general formula (Ih):

5



wherein

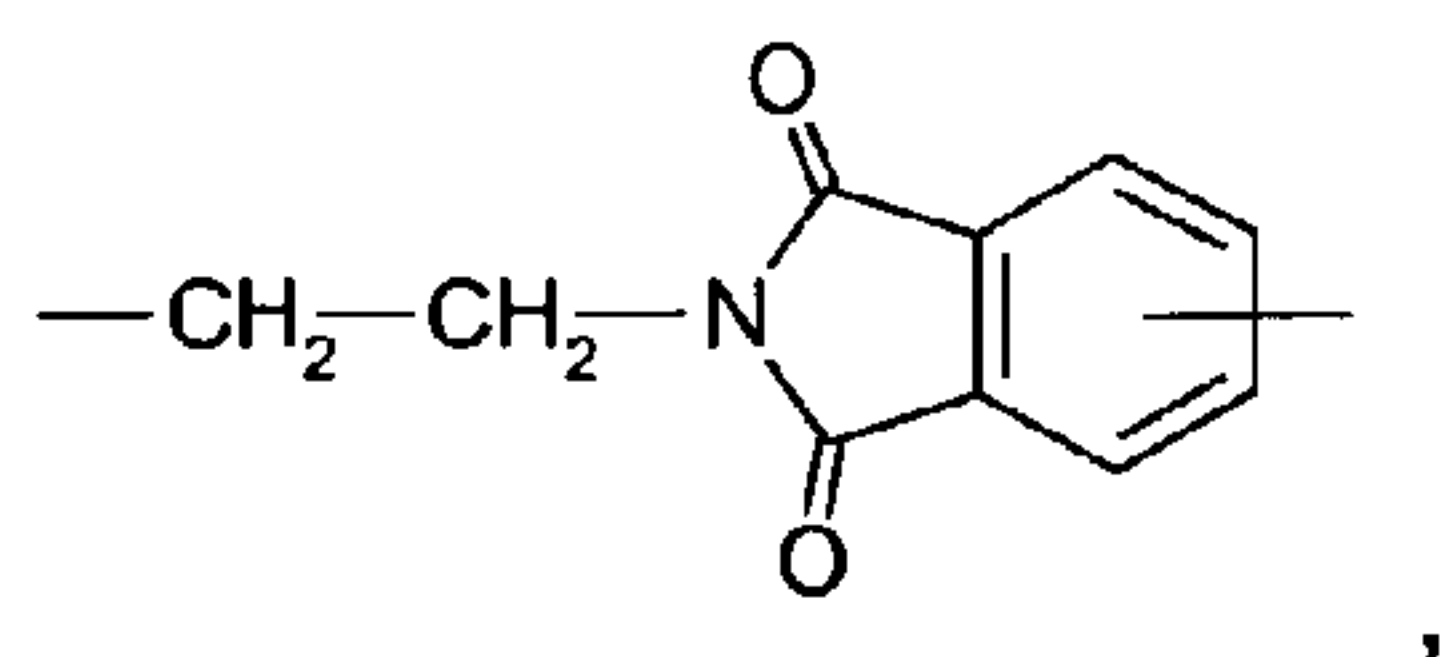
10 R^1 , E and D are as defined for formula (I),

X is $-\text{C(O)NH-}$, $-\text{C(O)NH-CH}_2\text{-O-}$, $-\text{C(O)NH-C(O)O-}$ or $-\text{C(S)NH-}$,

15 $-\text{A-Y-}$ is $-(\text{CH}_2)_2\text{-NH-C(O)-}$ or $-(\text{CH}_2)_n\text{-O-}$, wherein n is as defined for formula (I), and Z is as defined for formula (I),

or

$-\text{A-Y-Z-}$ together is



R is C_{1-6} -alkyl and

Lea' is a leaving group such as $-\text{OSu}$, chloro, phenoxy or 4-nitrophenoxy.

Step A:

The appropriate aldehyde (0.011 mmol) in CH_2Cl_2 was dispensed into the wells of a deepwell plate containing the desired amines in CH_2Cl_2 . To this solution was added sodium triacetoxy-
5 borohydride (1.5 eq) followed by a catalytic amount of acetic acid. The reaction was left to proceed for 15 hours.

Step B:

To the resulting amines from step A was added the desired isocyanate or isothiocyanate or
10 alternatively Lea'-X-D (0.011 mmol) in CH_2Cl_2 . When using Lea'-X-D a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any tertiary amine or potassium carbonate was also added. The reactions were agitated for three hours and the solvents were removed under reduced pressure to give the desired ureas or thioureas.

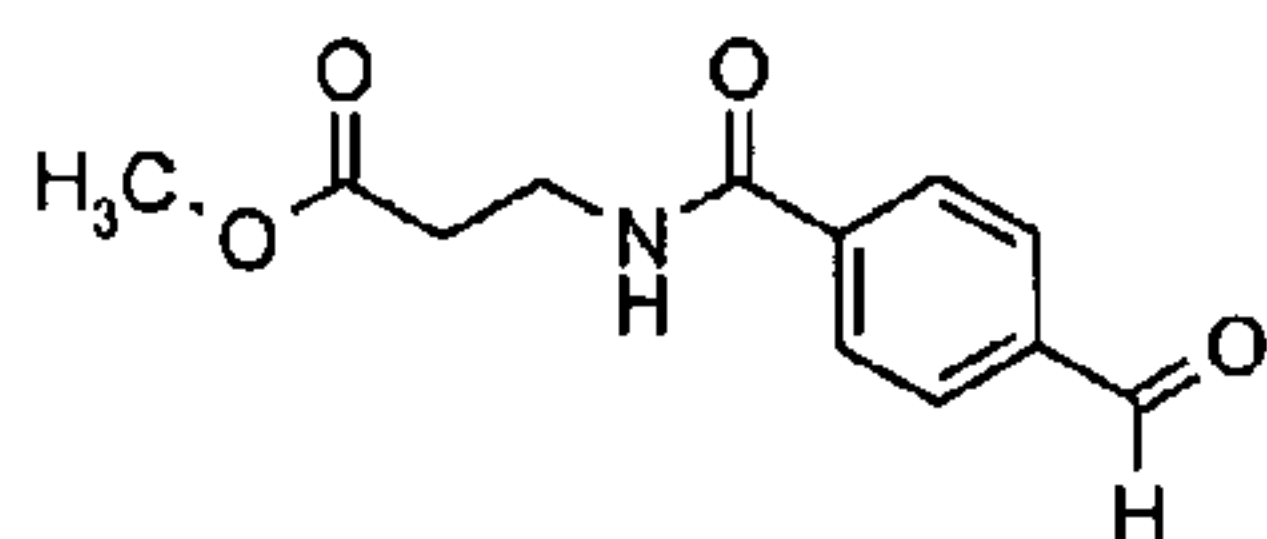
Step C:

The residue obtained in step B was dissolved in DMF and aqueous 2 M lithium hydroxide (10
15 eq.) was added into each reaction well. The samples were shaken overnight and filtered. Aqueous 1 N HCl was then added to give the desired carboxylic acids.

General preparation of formylarylcarboxamides as starting materials:

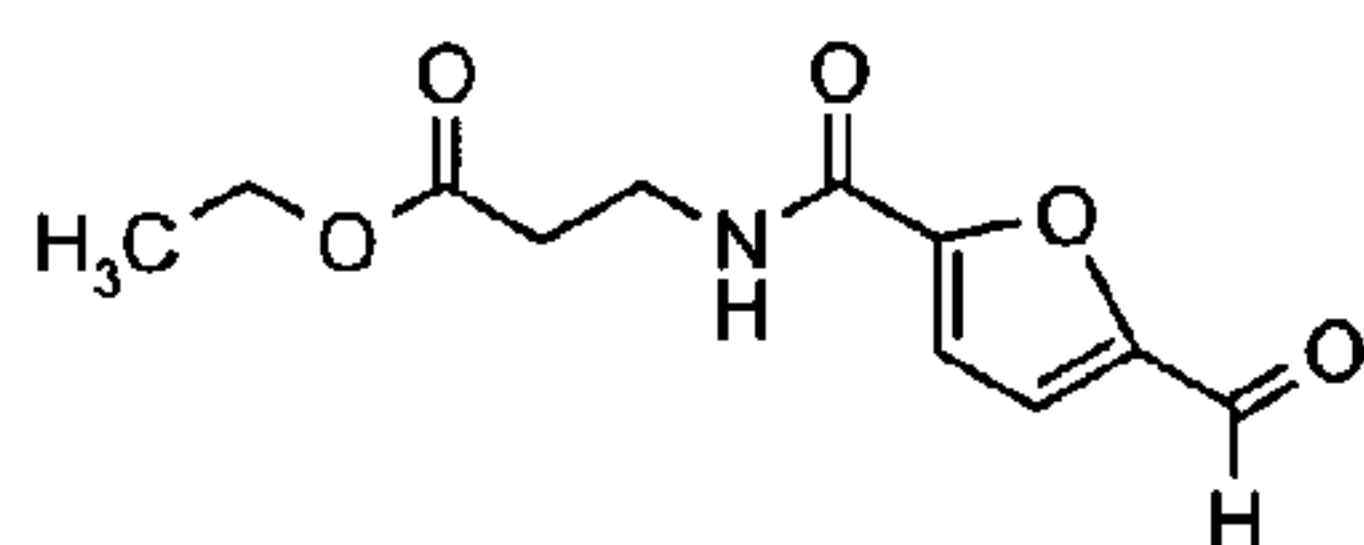
The formylarylcarboxamides were prepared from the coupling of the corresponding oxo-
20 arylcarboxylic acid and the methyl or ethyl-3-aminopropionate hydrochloride according to the procedure described below.

To a solution of the formylarylcarboxylic acid in a suitable solvent such as CH_2Cl_2 , DMF, or
25 THF was added diisopropylethylamine (3 eq) and HBTU (1.1 eq). The reaction was allowed to stir for 30 minutes before ethyl or methyl-3-aminopropionate hydrochloride (1.1 eq) was added. The solution was stirred at room temperature for 4 hours. The solvents were evaporated under reduced pressure. The residue was taken up in ethyl acetate and 1N HCl. The
30 organic layer was separated and washed with H_2O (2x), aqueous NaHCO_3 (3x), brine (2x), dried over MgSO_4 and concentrated to give the desired product.

Methyl 3-[(4-formylbenzoyl)amino]propionate:

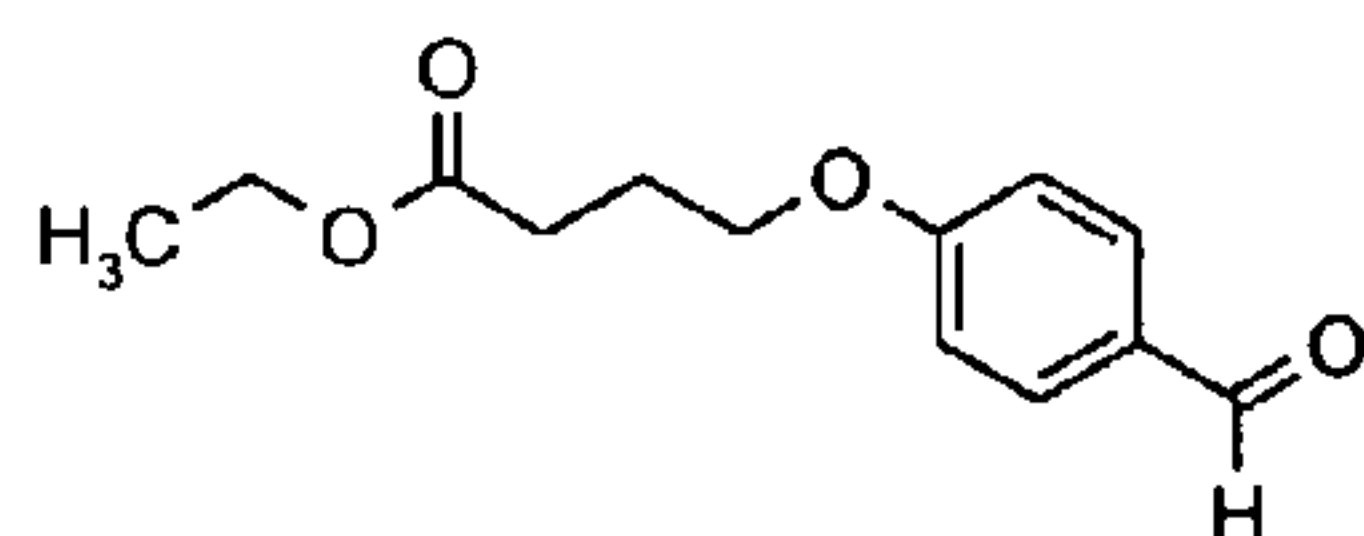
¹H NMR (DMSO-*d*₆): δ 2.62 (t, 2H), 3.52 (q, 2H), 3.60 (s, 3 H), 8.00 (m, 4 H), 8.98 (t, 1 H),
5 10.06 (s, 1H).

MS (APCI, neg.): 234.0, 147.9

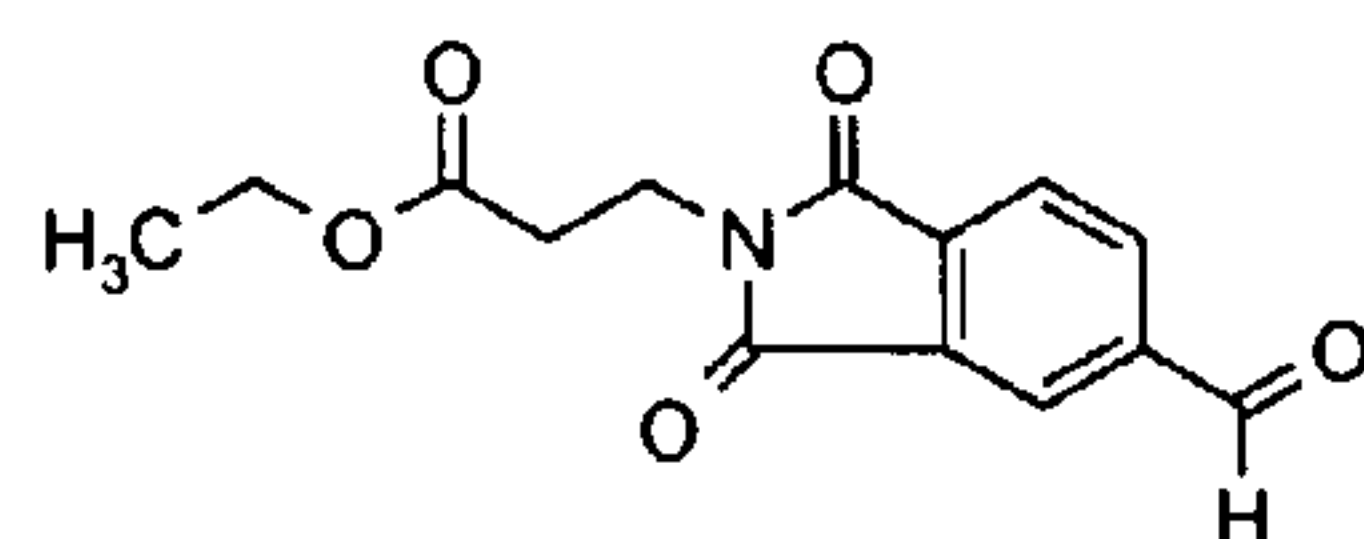
Ethyl 3-[(5-formyl-2-furoyl)aminopropionate:

¹H NMR (DMSO-*d*₆): δ 1.67 (t, 3H), 2.57 (t, 2H), 3.48 (q, 2H), 4.08 (q, 2H), 7.29 (d, 1H), 7.59
10 (d, 1H), 8.83 (brd t, 1H), 9.69 (s, 1H).

15 MS (APCI, pos.): 240.1, 194.1, 152.0.

Ethyl 4-(4-formylphenoxy)butyrate:

20 This compound was prepared according to D. R. Buckle, A. E. Fenwick, D. J. Outred, C. J. M. Rockwell, J. Chem. Res. Miniprint 12 (1987) 3144-3177.

Ethyl 3-[5-formyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate:

Step 1: Ethyl 3-[5-methyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

A solution of 4-methylphthalic anhydride (21.3 g, 0.13 mol), ethyl 3-aminopropionate hydrochloride (20.2 g, 0.13 mol), and triethylamine (19 mL) in NMP was stirred at ambient temperature for 3 days, and heated to 130°C for 3 hours. The mixture was diluted with water (300 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with 1N hydrochloric acid (2 x 50 mL), sodium bicarbonate solution (2 x 50 mL), dried (MgSO₄), and concentrated to give 27.3 g yellow oil.

¹H NMR (CDCl₃): δ 1.21 (t, 3H), 2.50 (s, 3H), 2.70 (t, 2H), 3.97 (t, 2H), 4.17 (q, 2H), 7.51 (d, 1H), 7.64 (s, 1H), 7.71 (d, 1H).

MS (APCI, pos.): 262, 216.

Step 2: Ethyl 3-[5-bromomethyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

The material from step 1 (27.3 g, 0.10 mol) was dissolved in carbon tetrachloride (50 mL), and *N*-bromosuccinimide (19.5 g, 0.11 mol) and AIBN (200 mg) was added. The mixture was refluxed for 5 hours, filtered by suction, and the filtrate was concentrated to give 35.4 g yellow oil.

¹H NMR (CDCl₃): δ 1.23 (t, 3H), 2.50 (s, 3H), 2.72 (t, 2H), 4.00 (t, 2H), 4.13 (q, 2H), 4.55 (s, 2H), 7.71 (d, 1H), 7.82 (d, 1H), 7.87 (s, 1H).

MS (APCI, pos.): 340, 342.

Step 3: Ethyl 3-[5-formyl-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl]propionate

The crude material from step 2 was dissolved in DMSO (70 mL). Powdered K₂HPO₄ (18 g, 0.10 mol) and KH₂PO₄ (7 g, 0.05 mol) were added. The mixture was stirred at 80°C for 5 hours, diluted with water (500 mL), and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried (MgSO₄), and concentrated. After column chromatography (hexane, ethyl acetate 3:1) 4.8 g of the title compound was obtained.

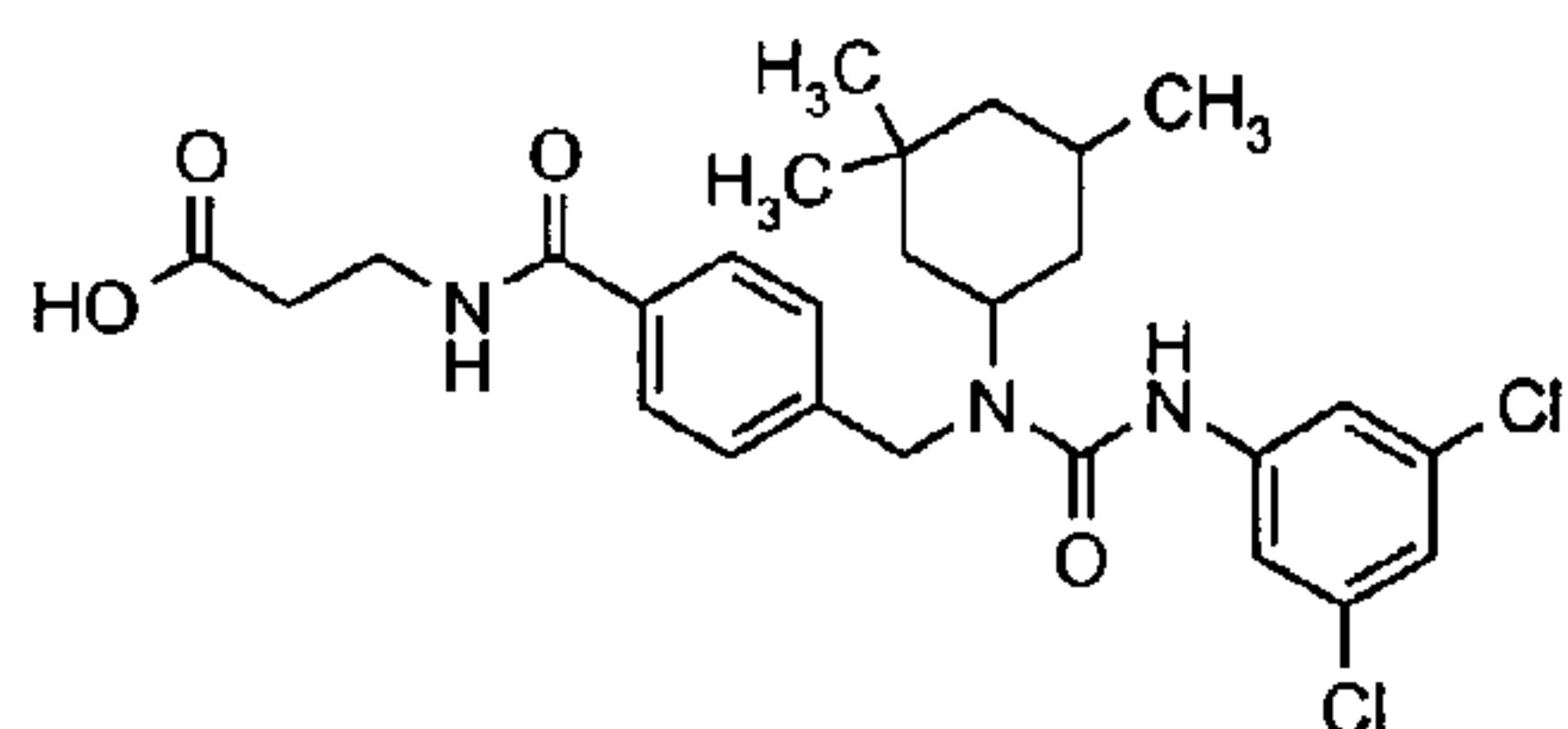
¹H NMR (CDCl₃): δ 1.23 (t, 3H), 2.75 (t, 2H), 4.04 (t, 2H), 4.13 (q, 2H), 8.03 (d, 1H), 8.26 (d, 1H), 8.35 (s, 1H), 10.17 (s, 1H).

MS (APCI, neg.): 275.

The following examples were prepared according to the general procedure (J).

EXAMPLE 176 (general procedure (J))

5 3-{4-[3-(3,5-Dichlorophenyl)-1-(3,3,5-trimethylcyclohexyl)ureidomethyl]benzoylamino)-propionic acid

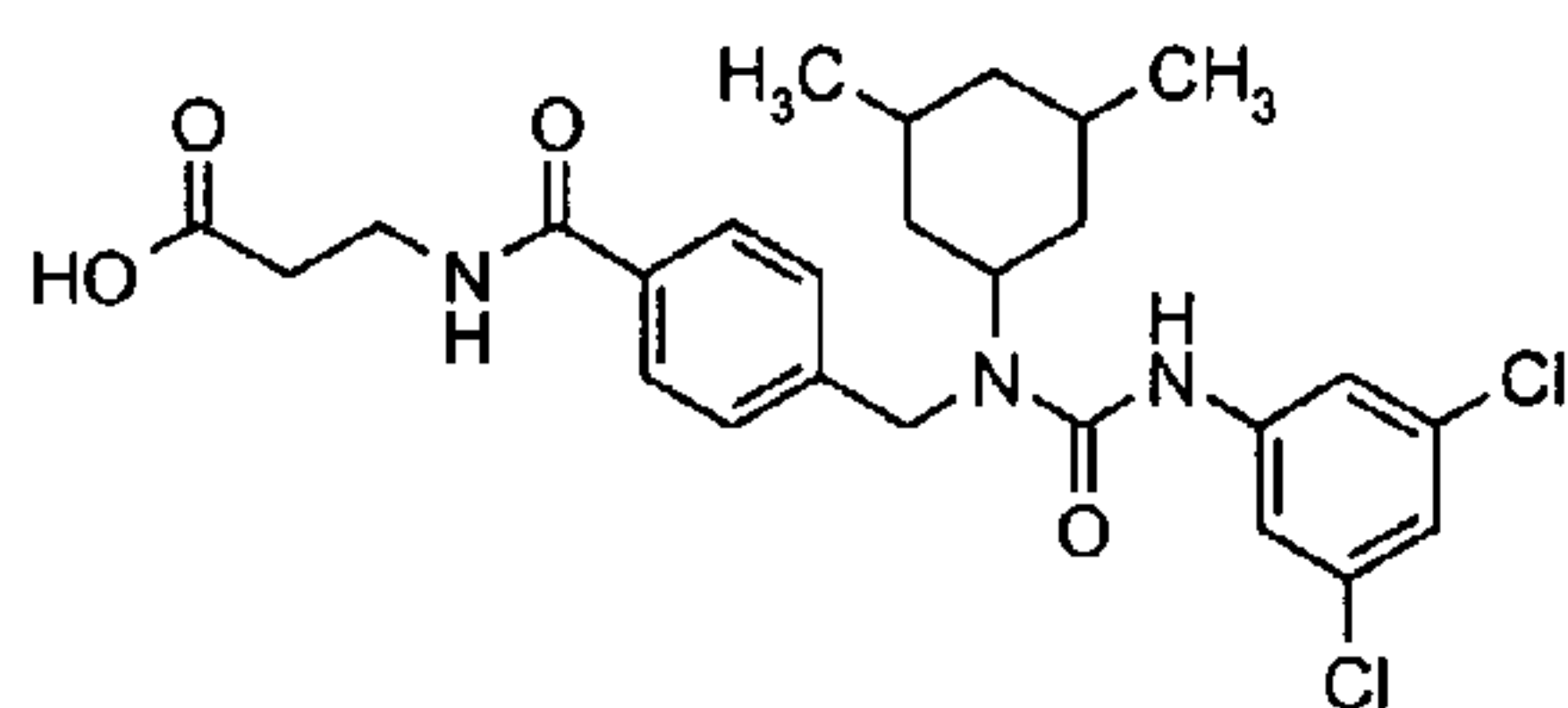


¹H NMR (DMSO-*d*₆): δ 1.14-1.29 (m, 5H), 1.33 - 1.37 (m, 1 H), 1.98 (brd, 1H), 2.49 (t, 2H),
10 3.44 (q, 2H), 4.50 (m, 1H), 4.65 (d, 2H), 7.11 (t, 1H), 7.29 (d, 2H), 7.57 (s, 2H), 7.78 (d, 2H),
8.85 (t, 1H), 8.62 (s, 1H), 12.21 (s, 1H).

MS (APCI, pos.): 536.2, 535.2, 534.2.

15 EXAMPLE 177 (general procedure (J))

3-{4-[3-(3,5-Dichlorophenyl)-1-(3,5-dimethylcyclohexyl)ureidomethyl]benzoylamino)propionic acid

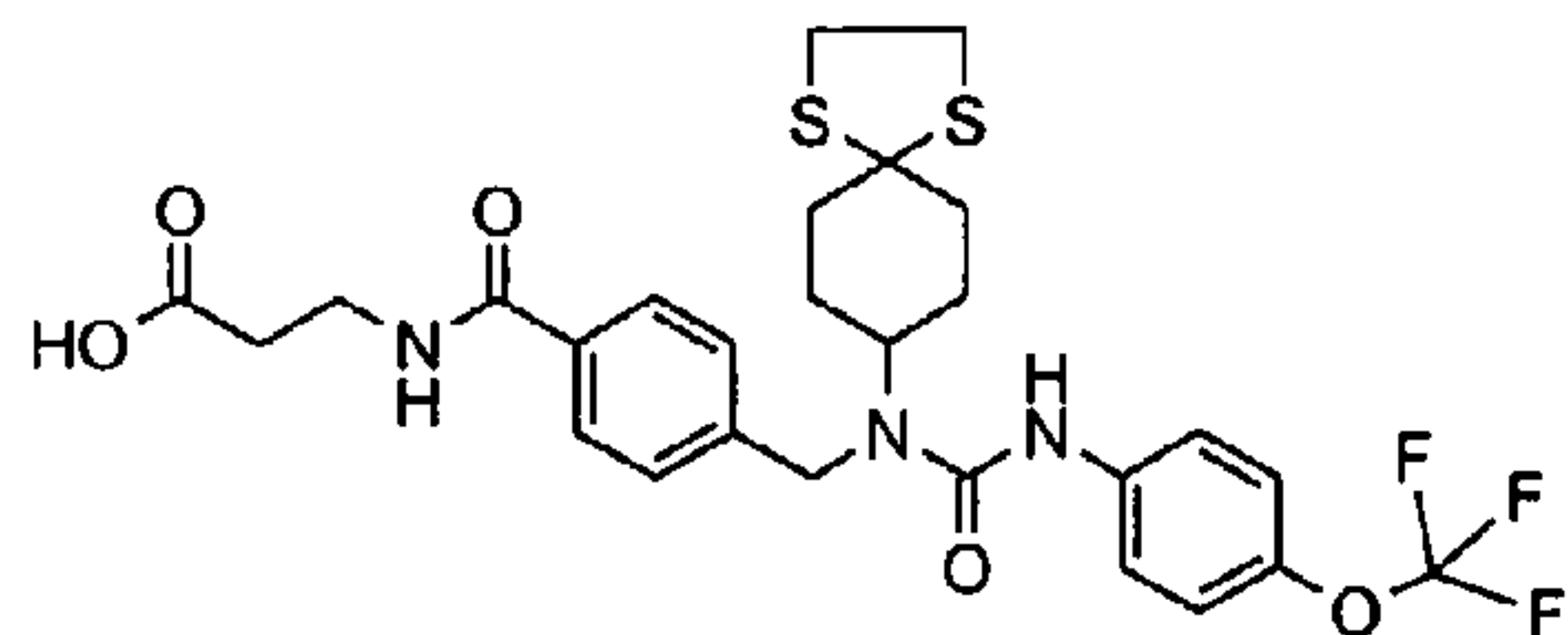


20 ¹H NMR (DMSO-*d*₆): δ 0.62 (q, 1H), 0.83 (d, 6H), 1.15 (m, 2H), 1.63 - 1.80 (m, 5H), 2.50 (t, 2H),
3.37 (m, 2H), 4.45 (s, 1H), 4.78 (s, 2H), 7.11 (s, 1H), 7.26 (d, 2H), 7.59 (s, 2H), 7.77 (d, 2H),
8.47 (t, 1H), 8.72 (s, 1H), 12.15 (brd, 1 H).

MS (APCI, pos.): 520.2

EXAMPLE 178 (general procedure (J))

3-{4-[1-(1,4-Dithiaspiro[4.5]dec-8-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



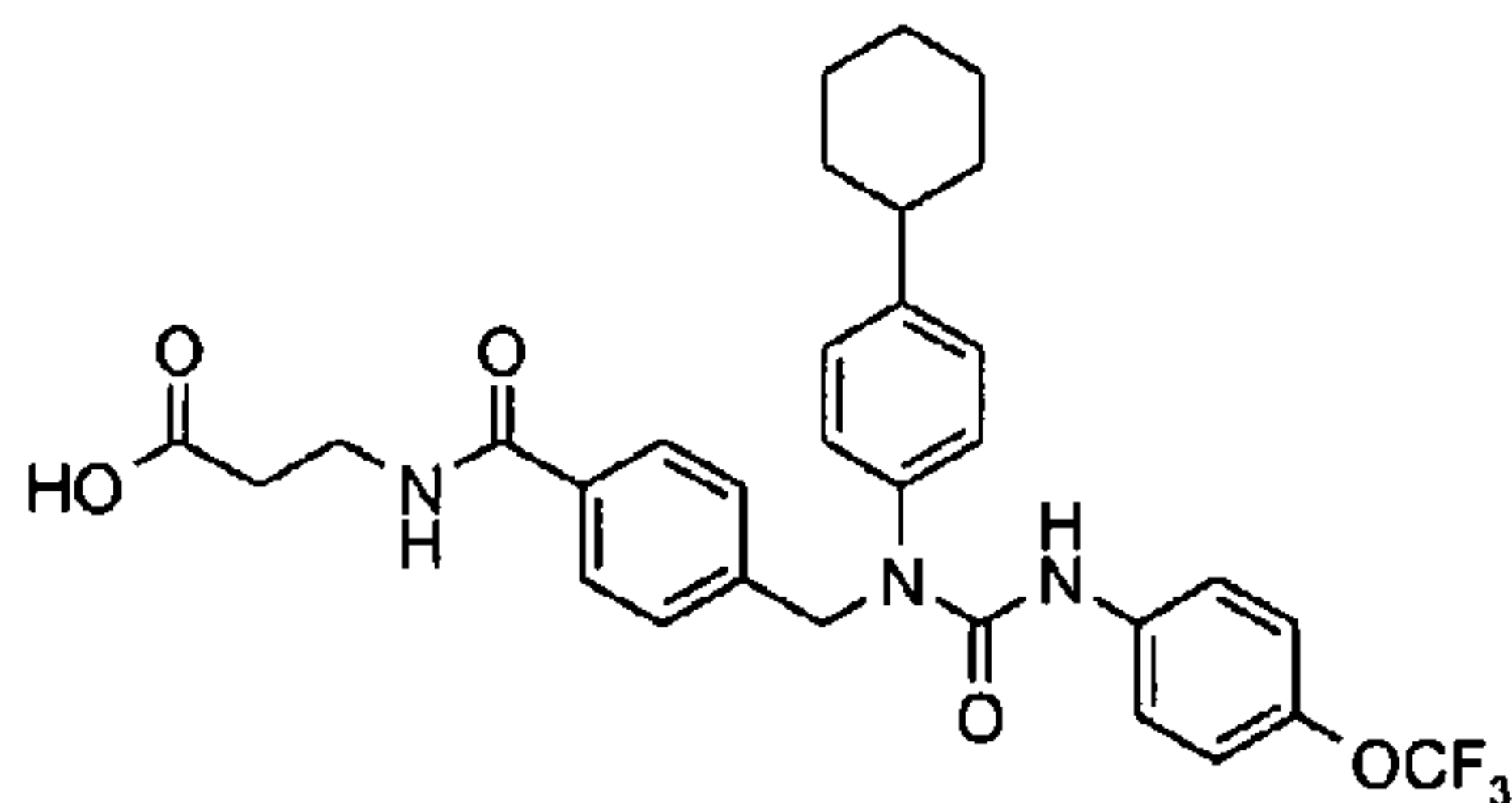
5

^1H NMR (DMSO- d_6): δ 1.62 (m, 4 H), 2.03 (m, 4 H), 3.24 (m, 4 H), 3.40 (m, 2 H), 4.13 (m, 1 H), 4.57 (s, 2 H), 7.23 (d, 2 H), 7.32 (d, 2 H), 7.54 (d, 2 H), 7.76 (d, 2 H), 8.46 (t, 1 H), 8.57 (s, 1 H), 12.20 (brd, 1 H).

10 MS (APCI, pos.): 598.2.

EXAMPLE 179 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



15

^1H NMR (MeOH- d_4): δ 1.28 – 1.48 (m, 5H), 1.75 – 1.87 (m, 5H), 2.54 (m, 1H), 2.66 (t, 2H), 3.62 (t, 2H), 4.98 (s, 2H), 7.10 – 7.16 (m, 4H), 7.26 (d, 2H), 7.39 (d, 2H), 7.43 (d, 2H), 7.75 (d, 2H).

20

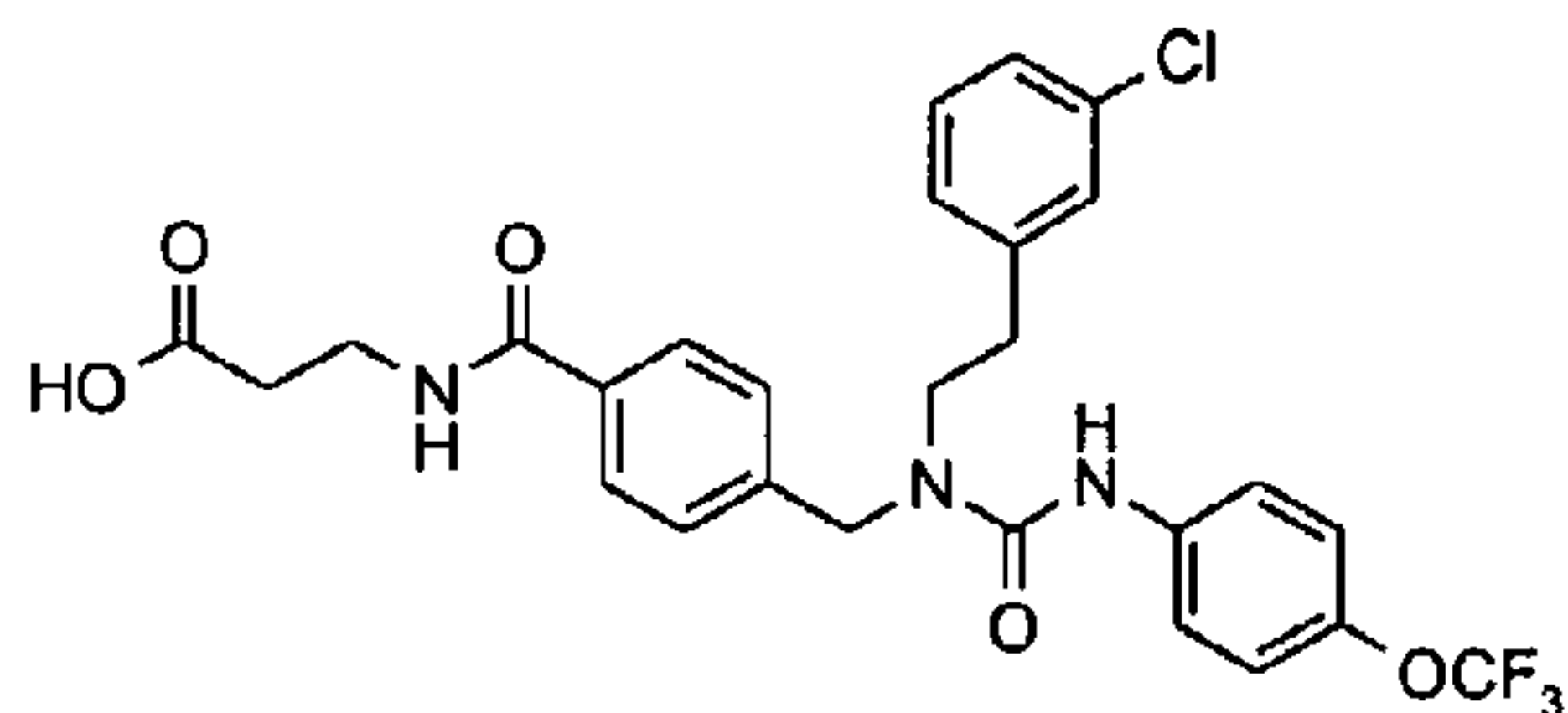
MS (APCI, pos): 584.2, 585.2, 586.2.

The following examples 180 to 229 were all found to displace more than 50% of the glucagon tracer when screened at 1 μM concentration in the glucagon binding assay II. The compounds are all expected to be present in the library.

25

EXAMPLE 180 (general procedure (J))

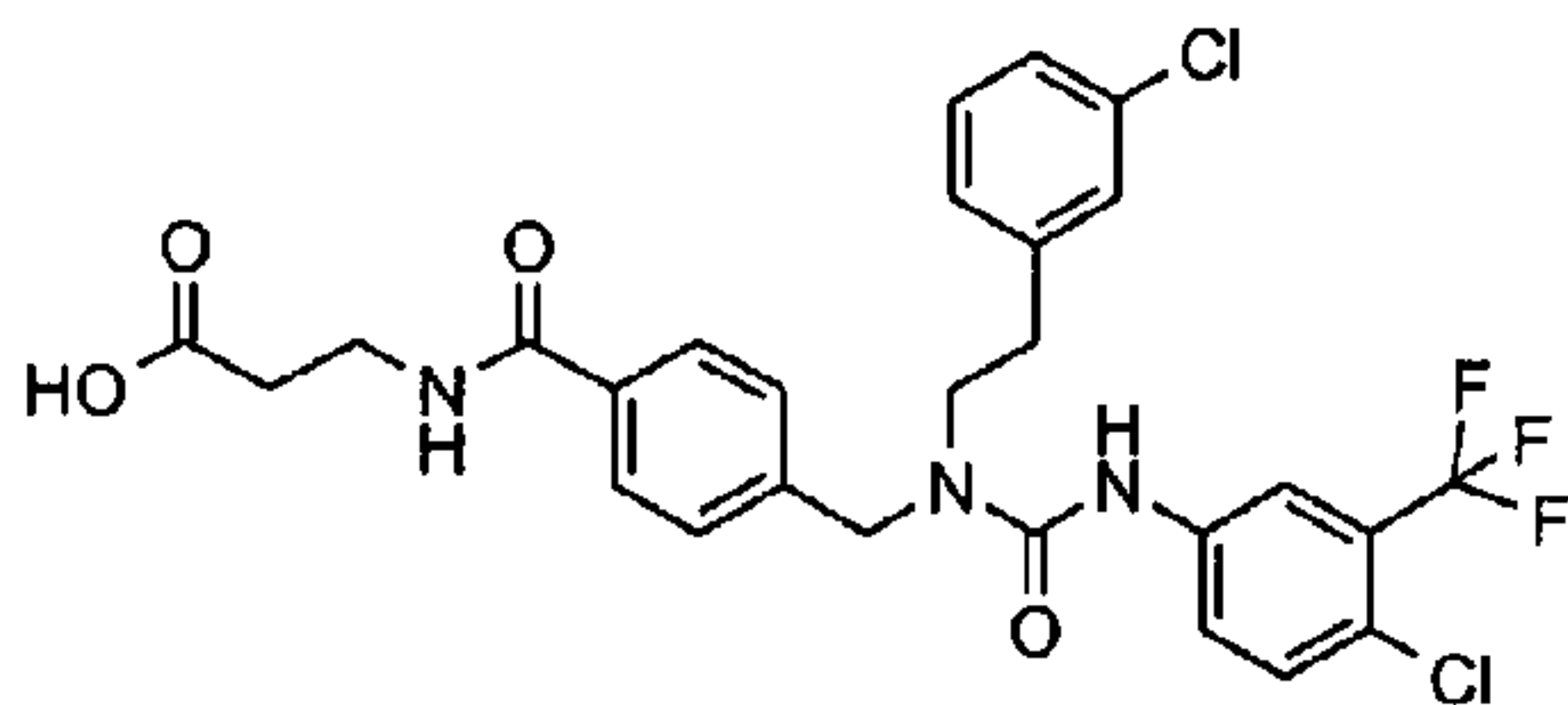
3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

EXAMPLE 181 (general procedure (J))

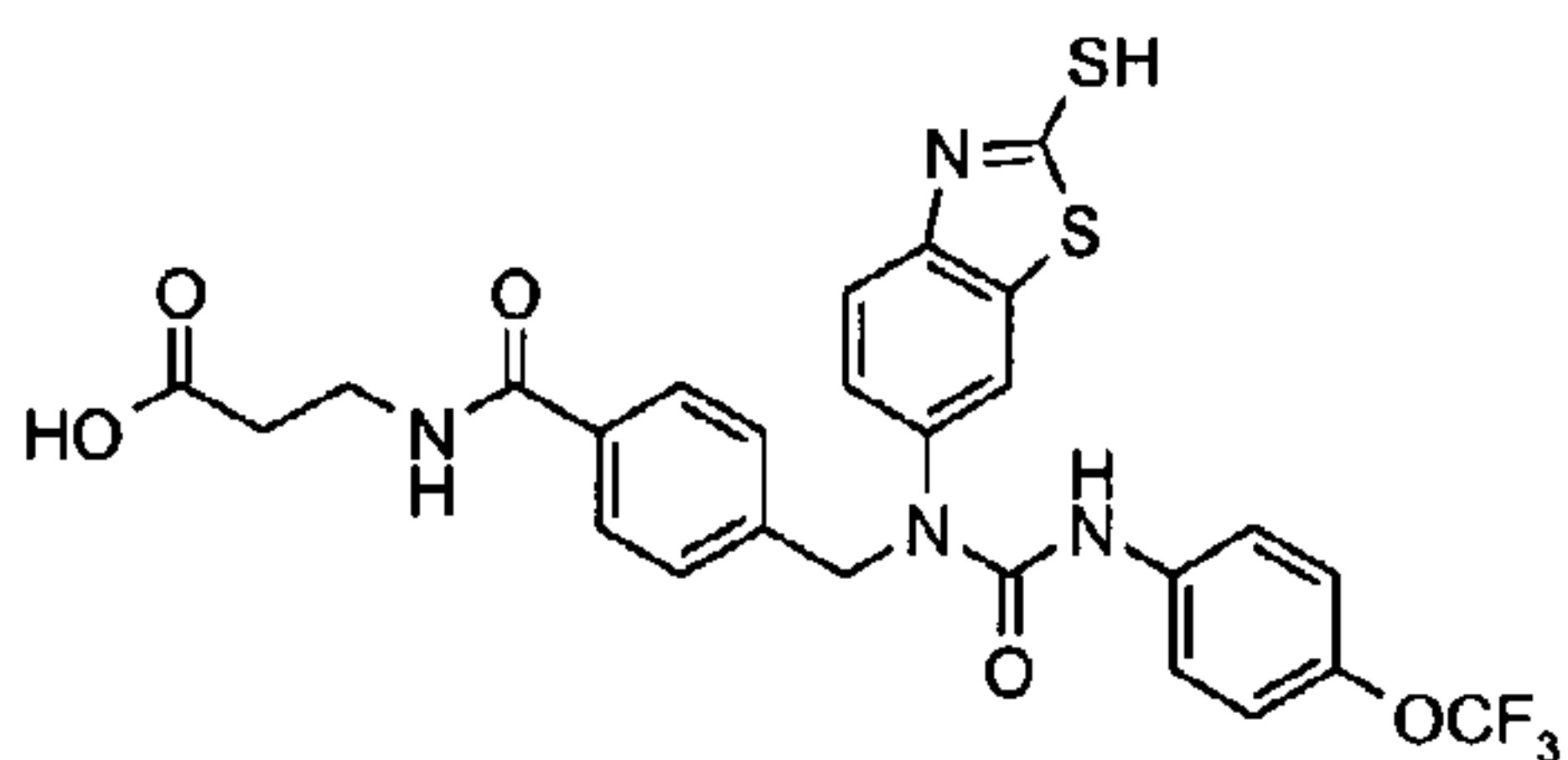
3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}propionic acid



10

EXAMPLE 182 (general procedure (J))

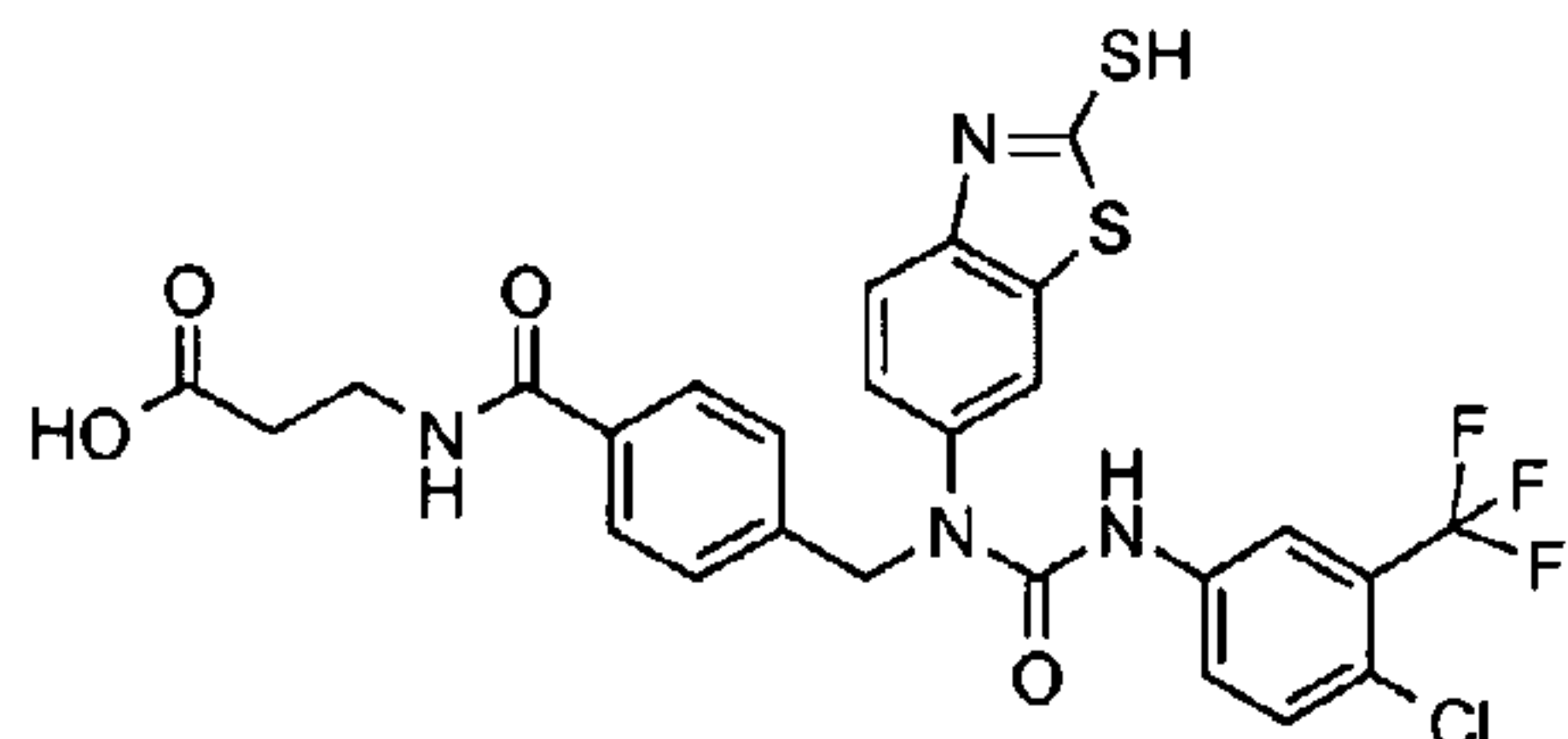
3-{4-[1-(2-Mercaptobenzothiazol-6-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 183 (general procedure (J))

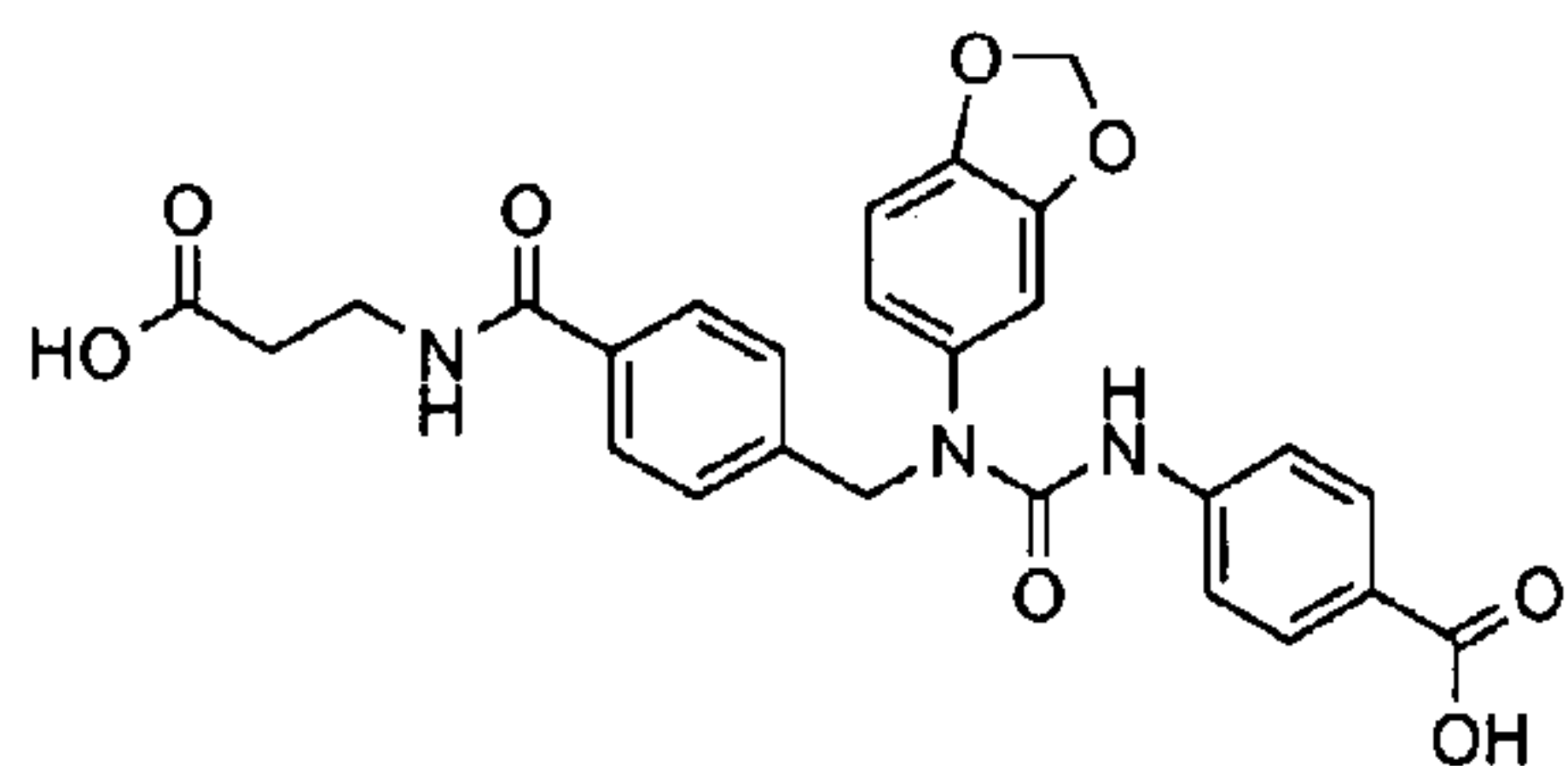
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-mercaptobenzothiazol-6-yl)ureidomethyl]-benzoylamino}propionic acid



5

EXAMPLE 184 (general procedure (J))

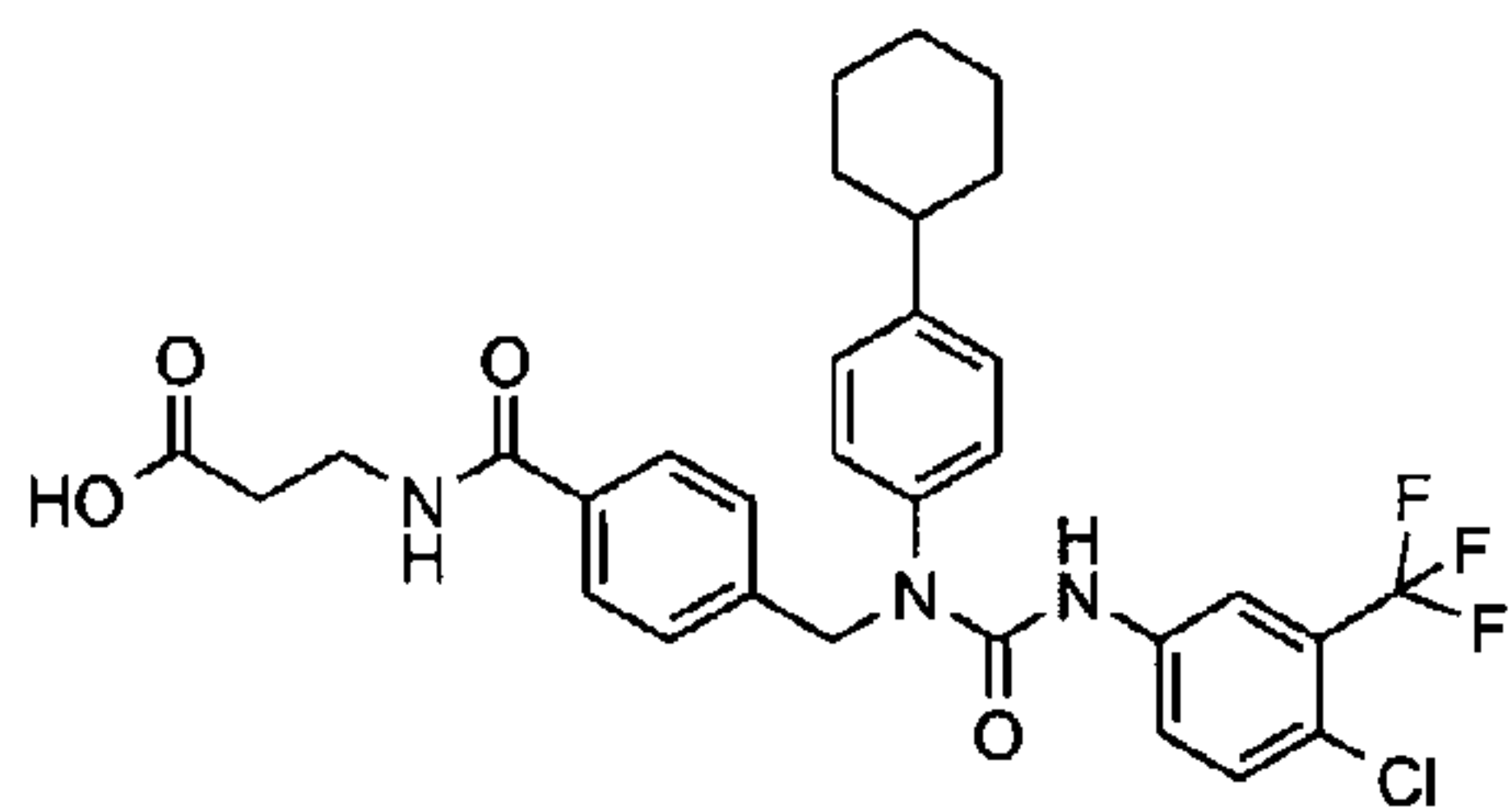
4-{3-(Benzo[1,3]dioxo-5-yl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid



10

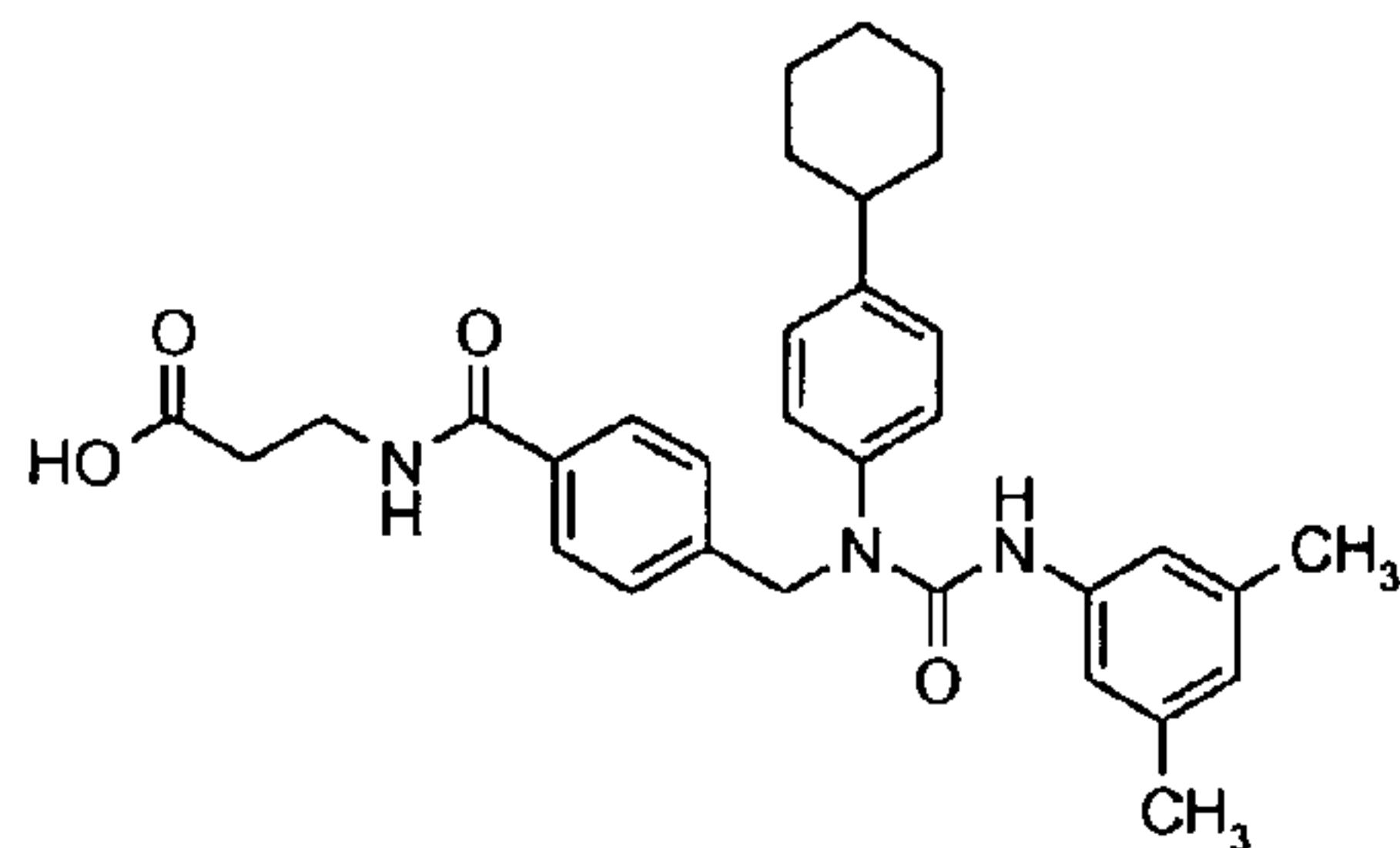
EXAMPLE 185 (general procedure (J))

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 186 (general procedure (J))

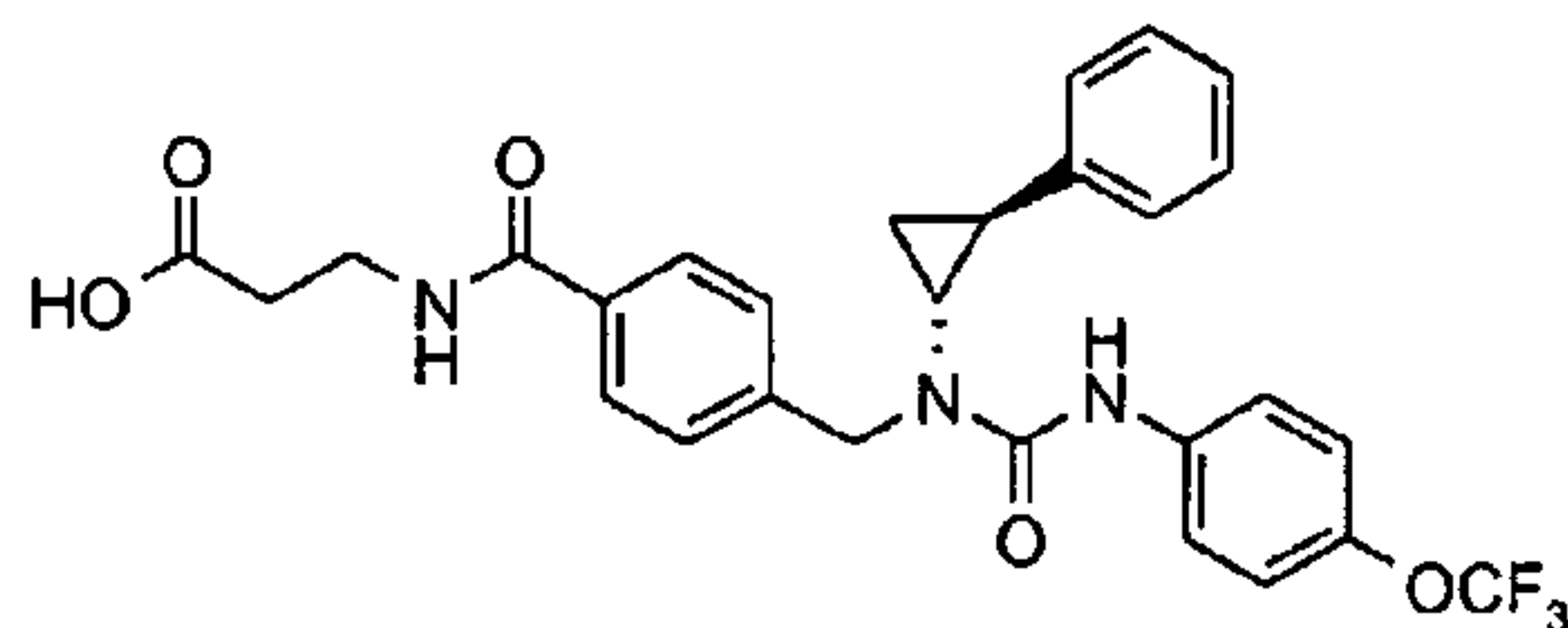
3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dimethylphenyl)ureidomethyl]benzoylamino}propionic acid



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EXAMPLE 187 (general procedure (J))

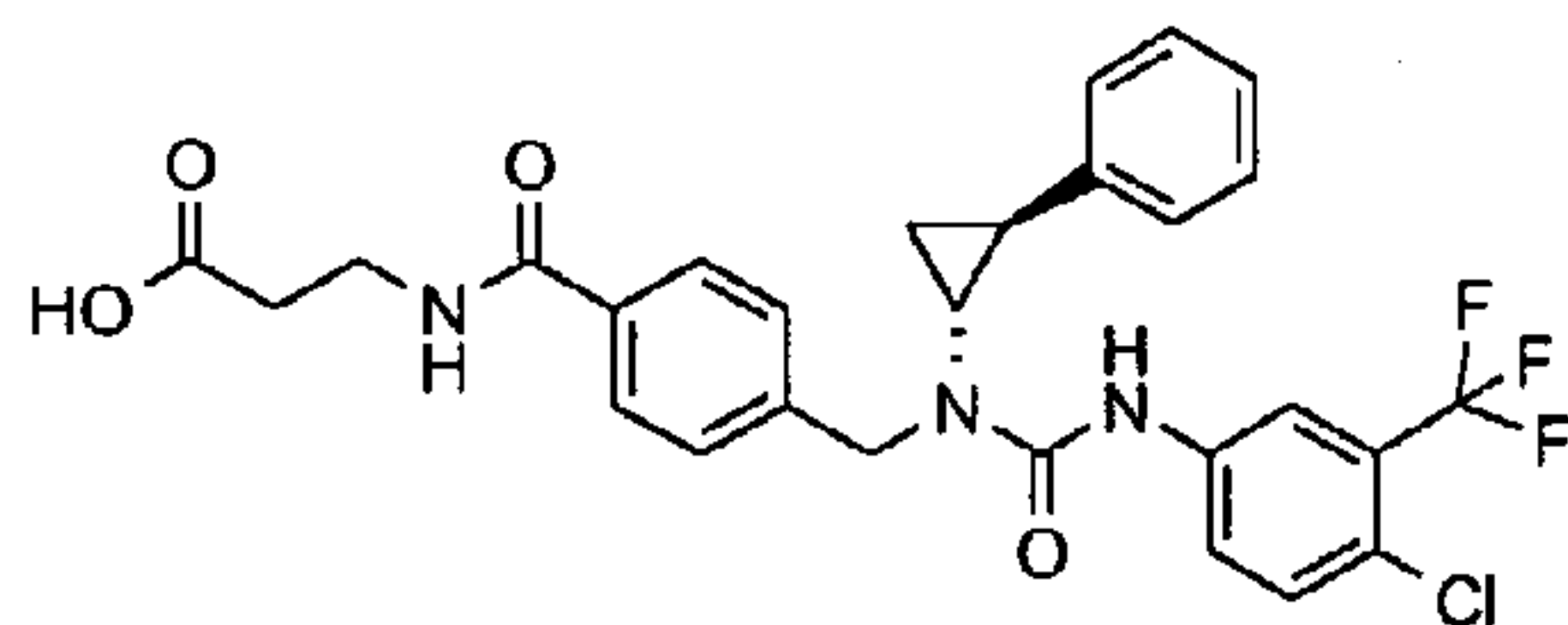
3-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



10

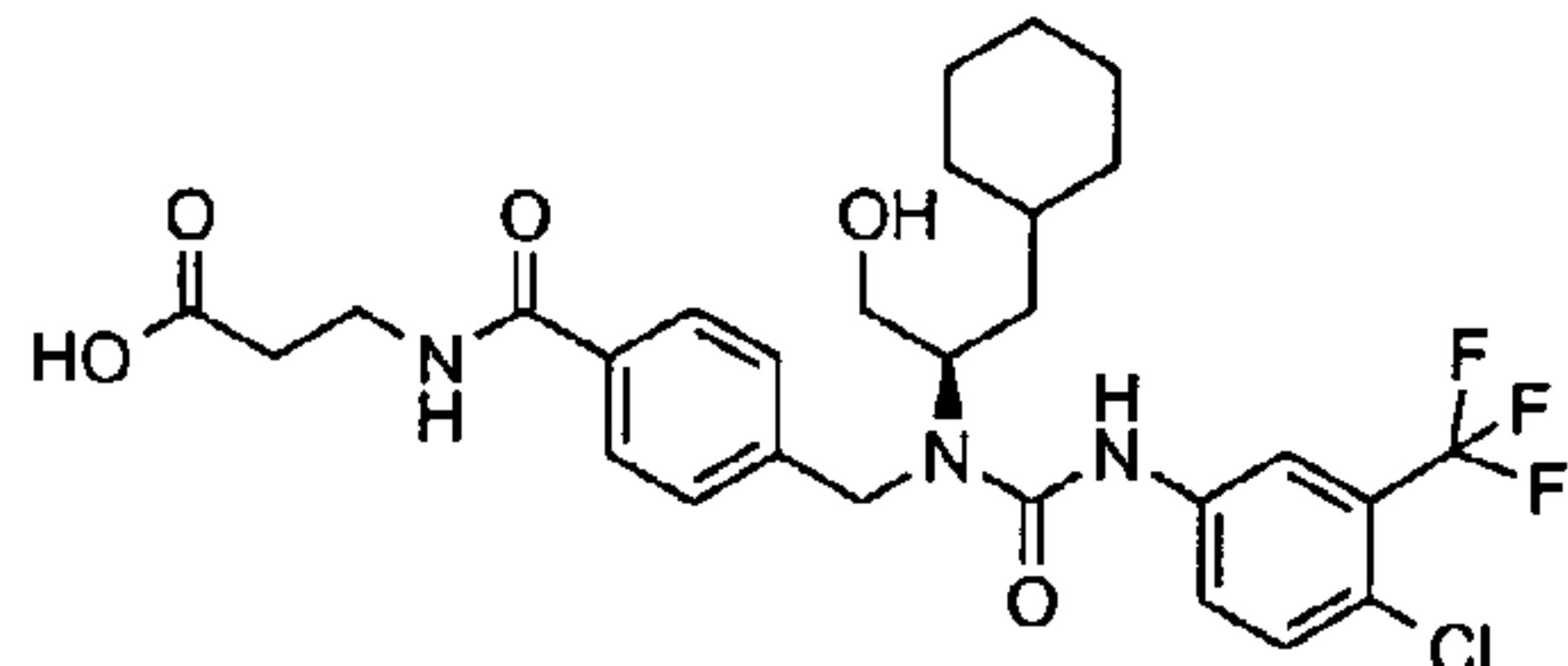
EXAMPLE 188 (general procedure (J))

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-phenylcyclopropyl)ureidomethyl]benzoylamino}propionic acid

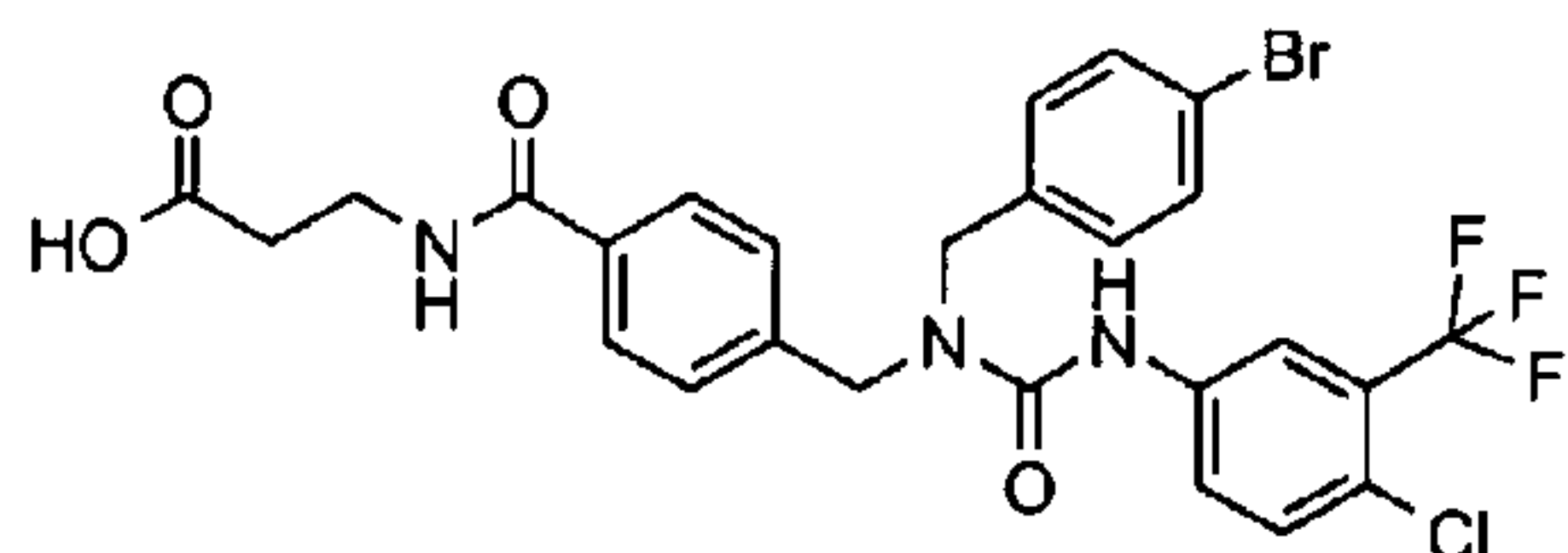


15

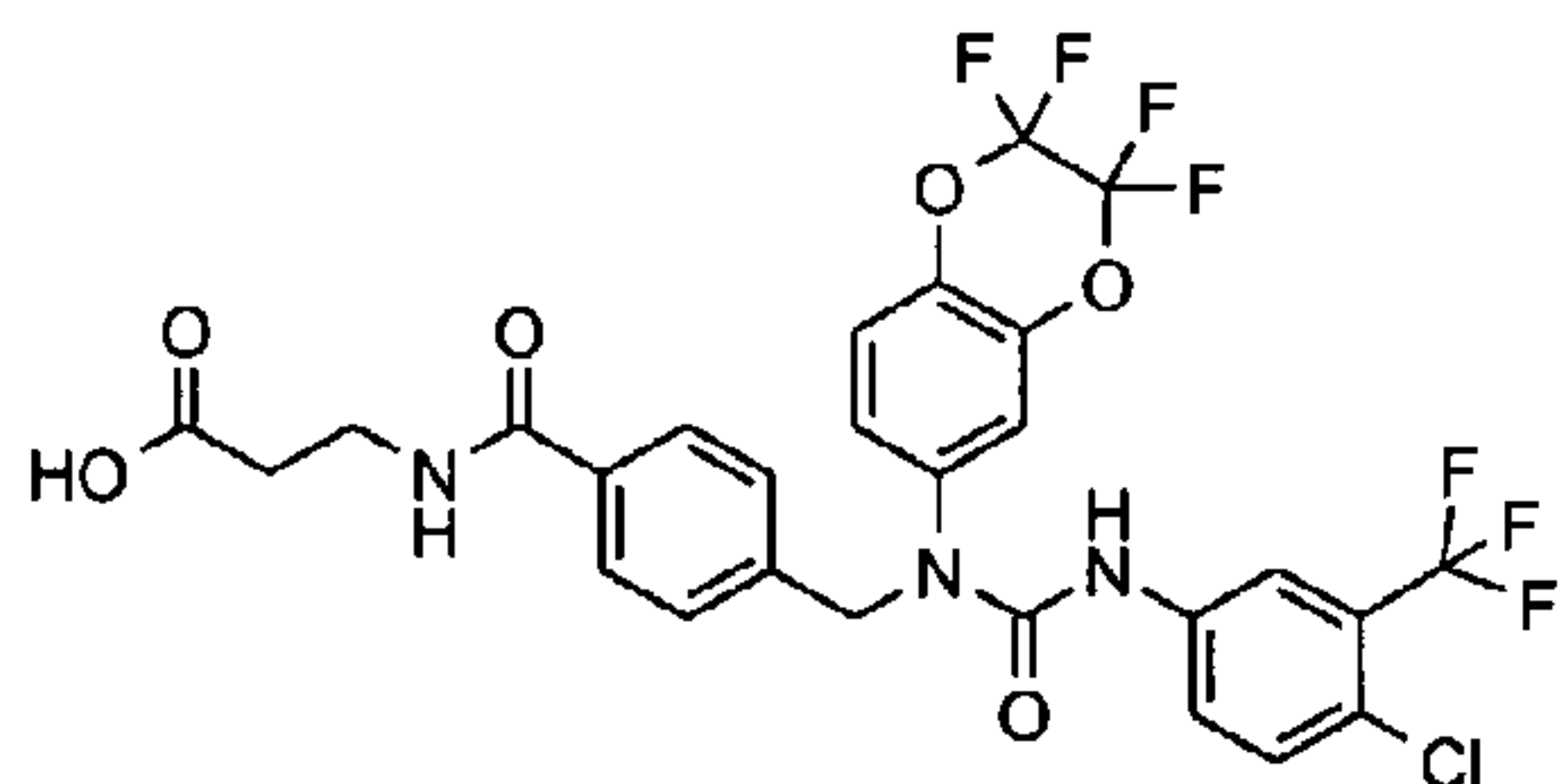
3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-cyclohexyl-1-hydroxymethylethyl)ureido-
methyl]benzoylamino}propionic acid



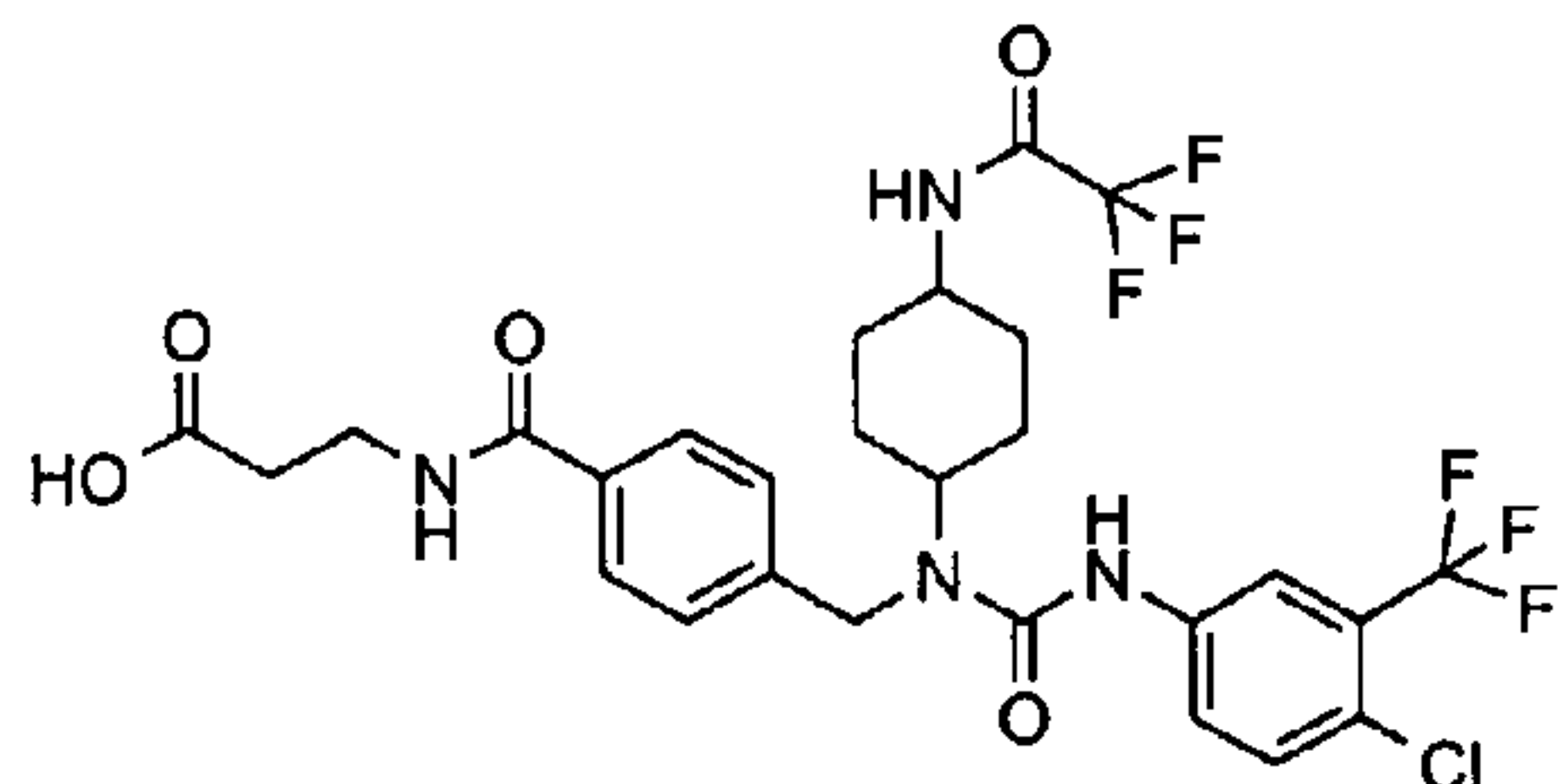
3-{4-[1-(4-Bromobenzyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoylamino}-propionic acid



3-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]-dioxin-6-yl)ureidomethyl]benzoylamino}propionic acid

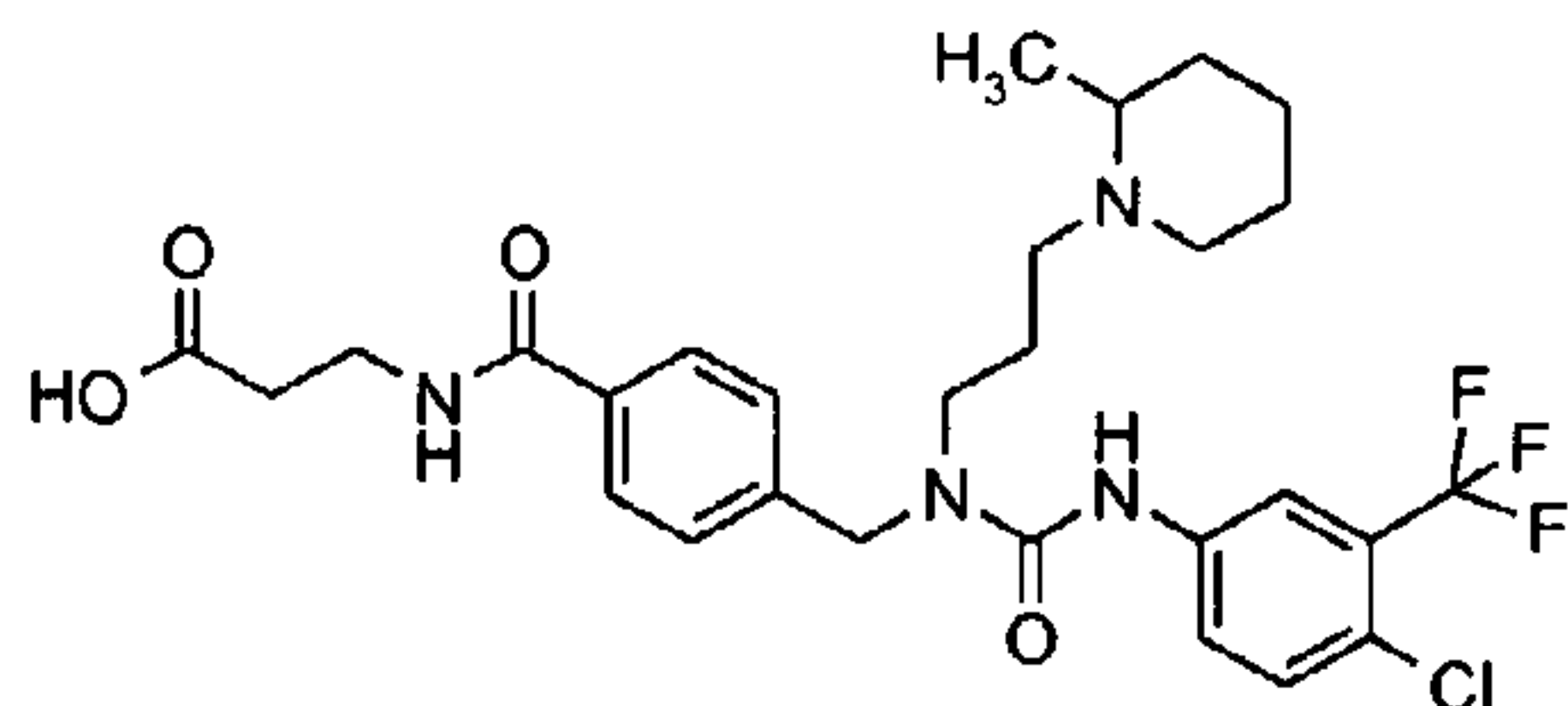


3-(4-{3-(4-Chloro-3-trifluoromethylphenyl)-1-[4-(2,2,2-trifluoroacetyl-amino)cyclohexyl]ureido-methyl}benzoylamino)propionic acid



EXAMPLE 193 (general procedure (J))

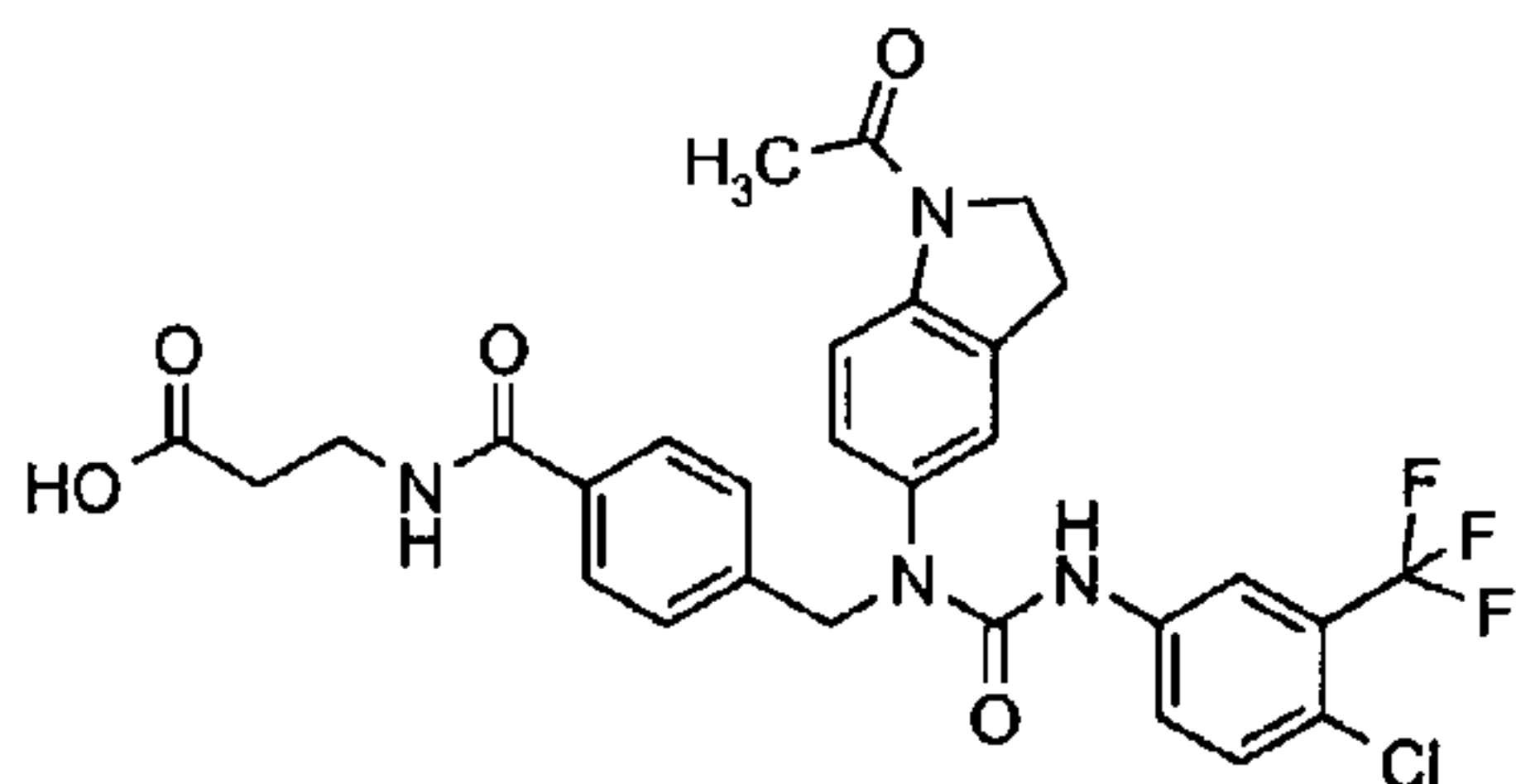
3-(4-{3-(4-Chloro-3-trifluoromethylphenyl)-1-[3-(2-methylpiperidin-1-yl)propyl]ureidomethyl}-benzoylamino)propionic acid



5

EXAMPLE 194 (general procedure (J))

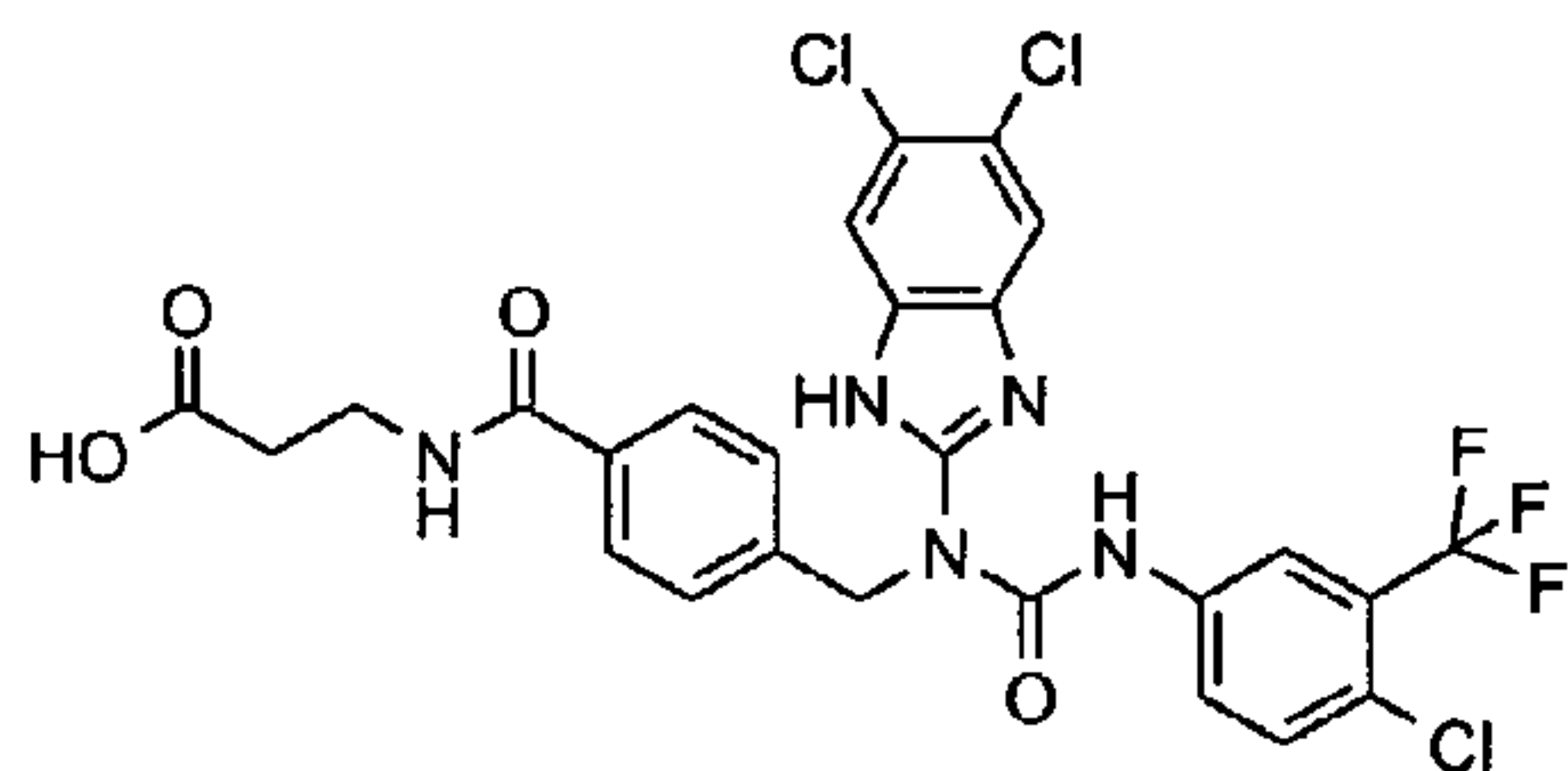
3-{4-[1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]-benzoylamino}propionic acid



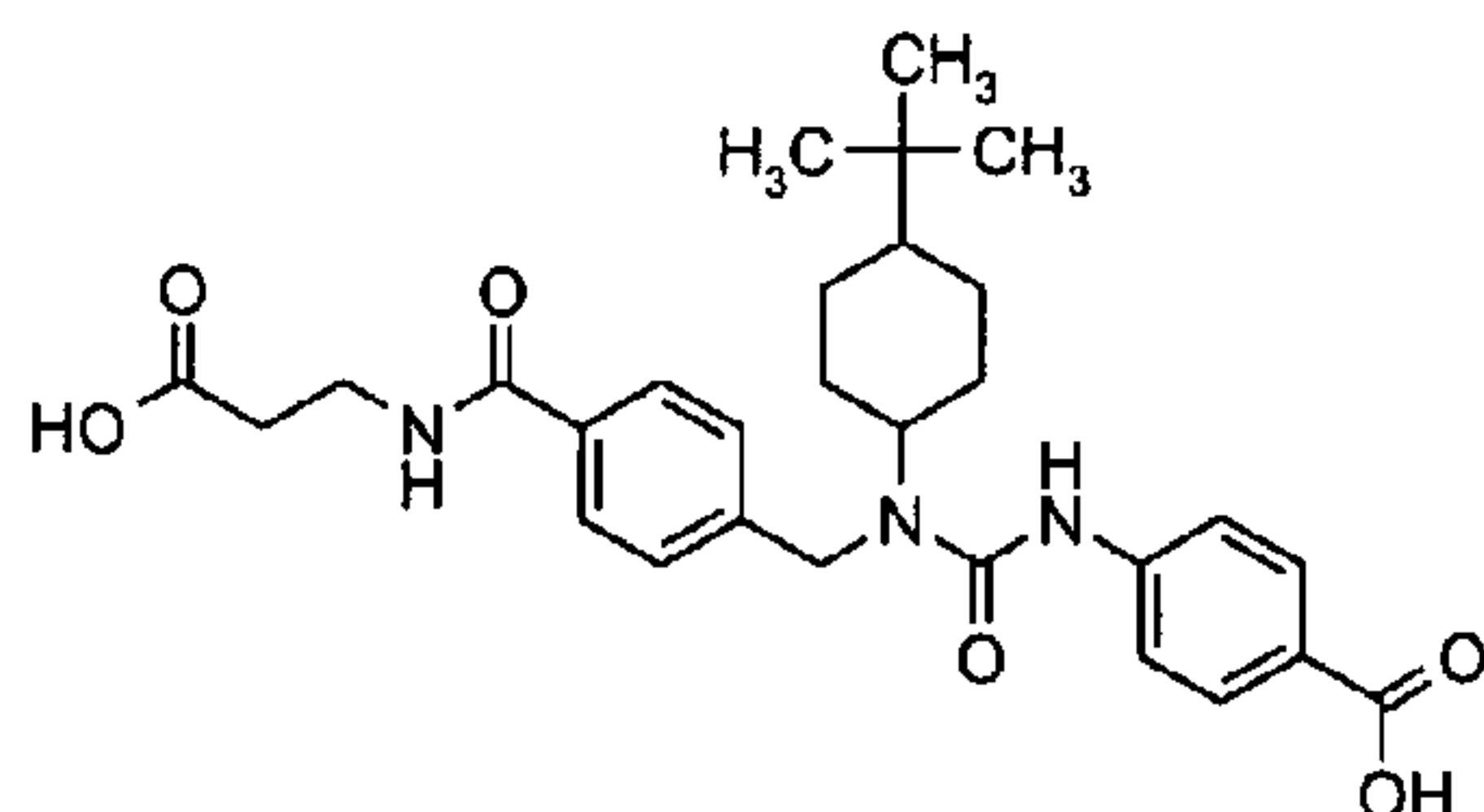
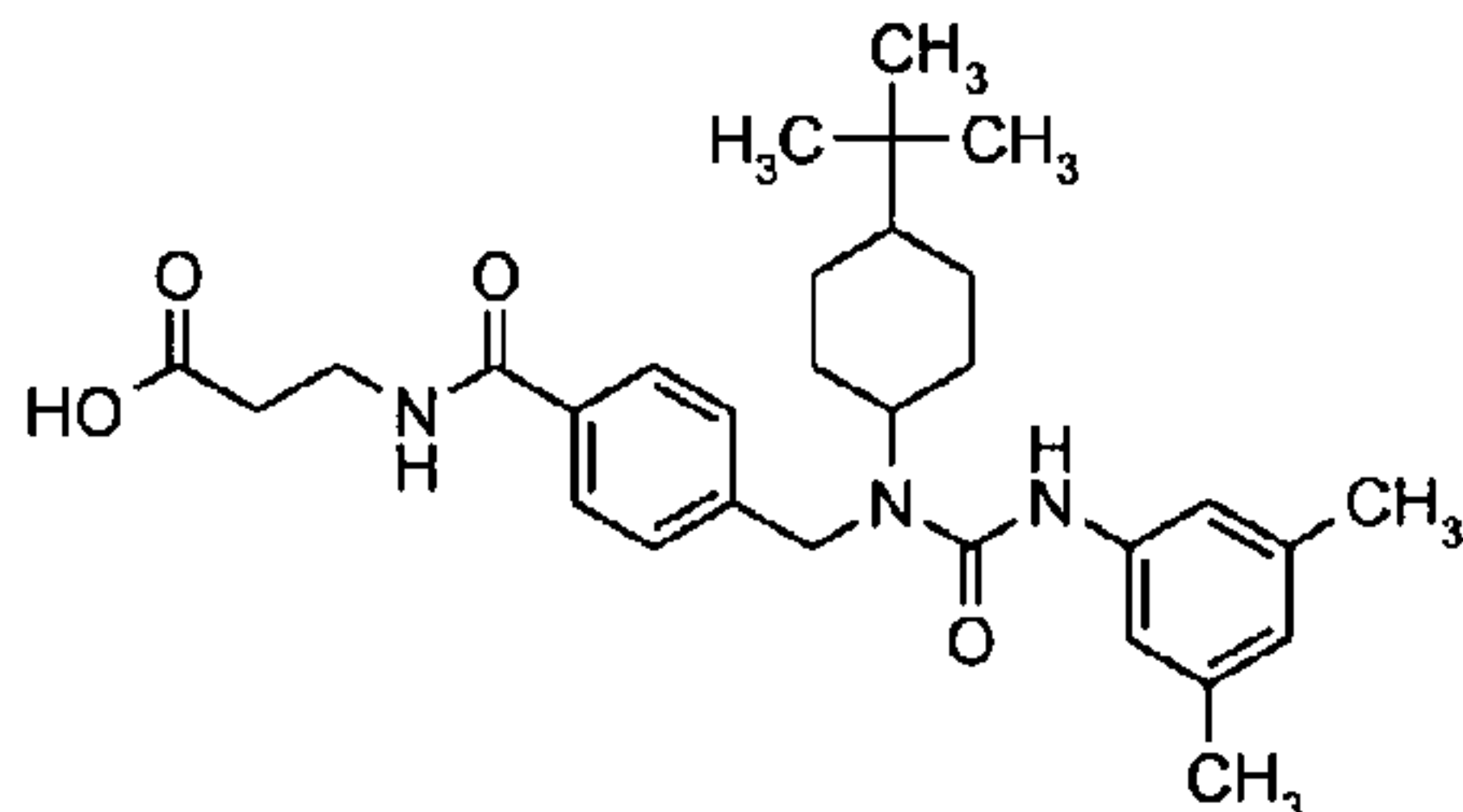
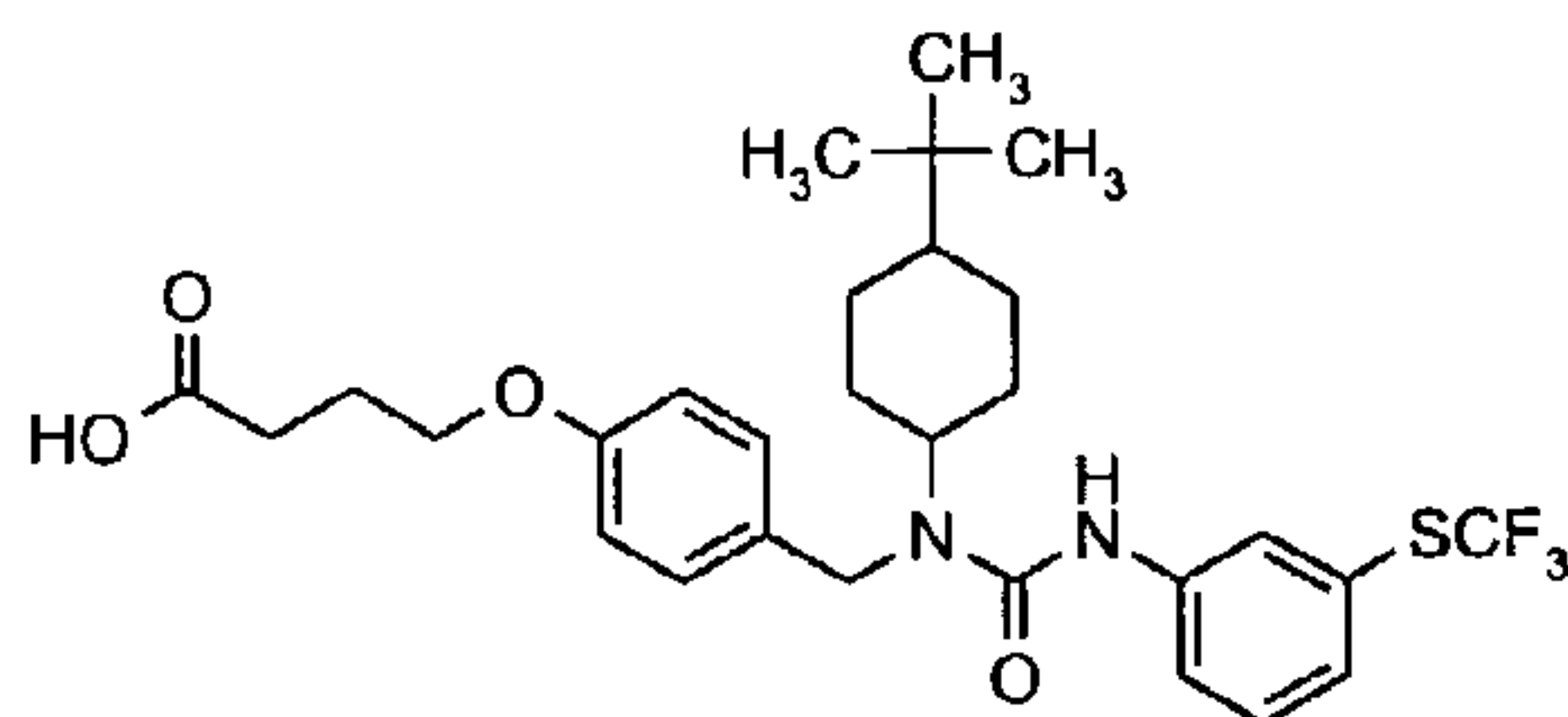
10

EXAMPLE 195 (general procedure (J))

3-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(5,6-dichloro-1H-benzimidazol-2-yl)ureido-methyl]benzoylamino}propionic acid

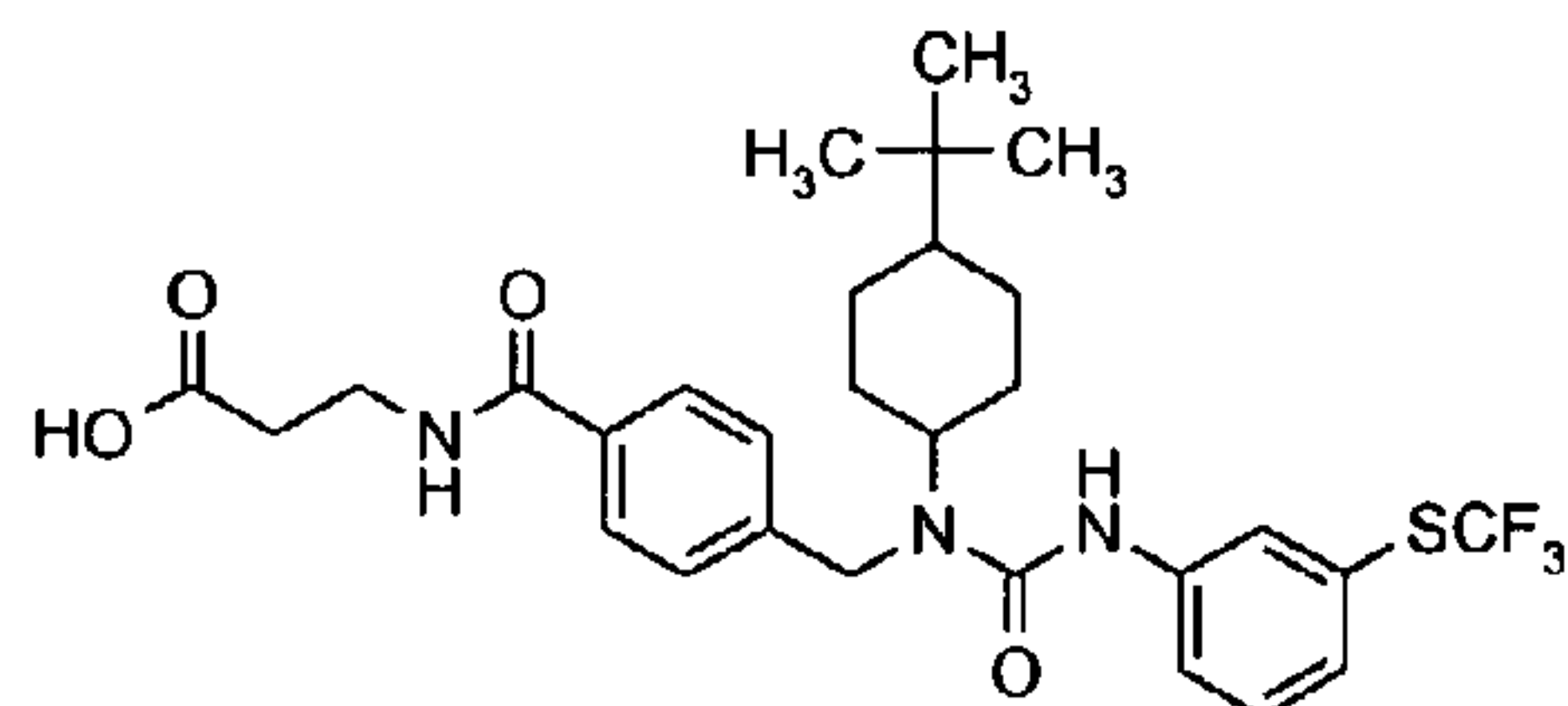


15

EXAMPLE 196 (general procedure (J))4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}benzoic acid5 EXAMPLE 197 (general procedure (J))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dimethylphenyl)ureidomethyl]benzoylamino}propionic acid10 EXAMPLE 198 (general procedure (J))4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]phenoxy}butyric acid

EXAMPLE 199 (general procedure (J))

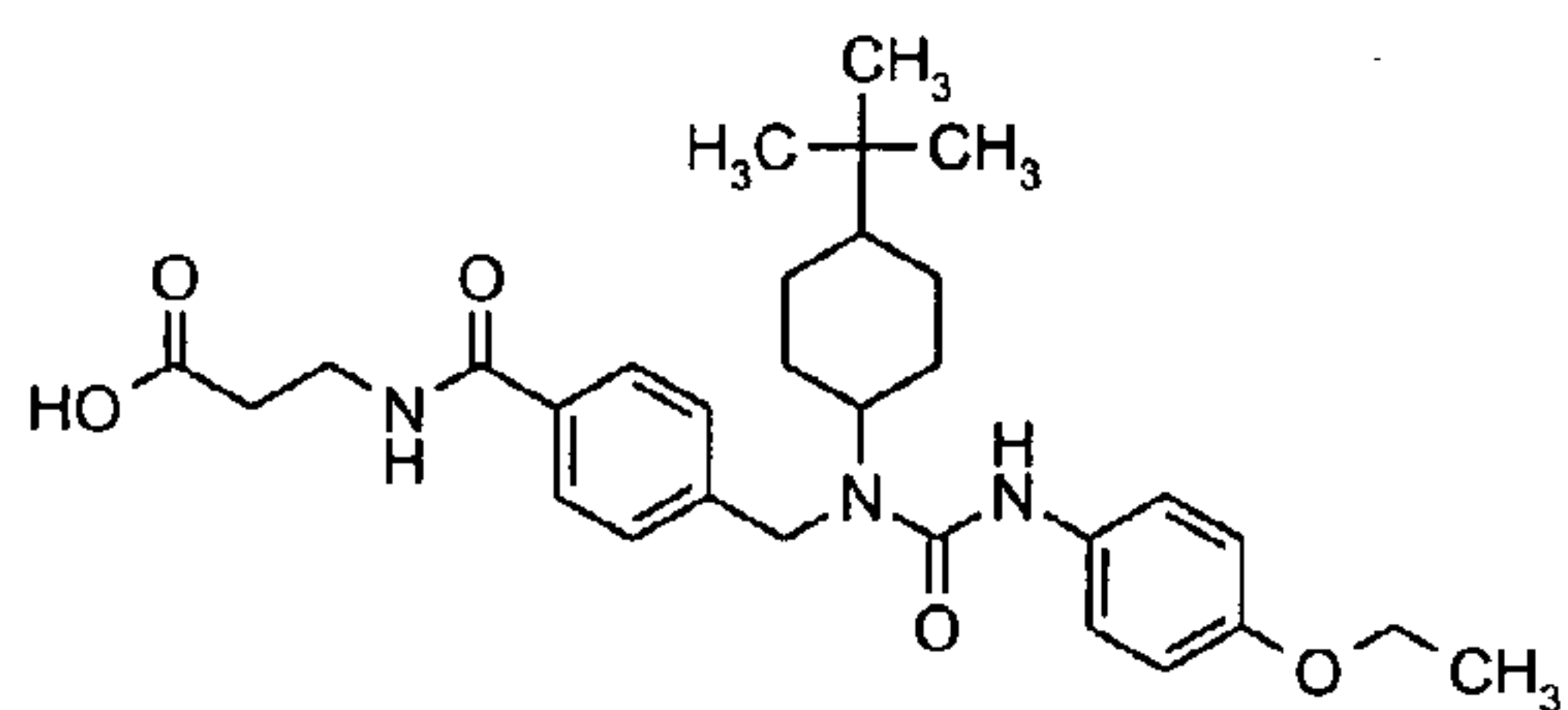
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 200 (general procedure (J))

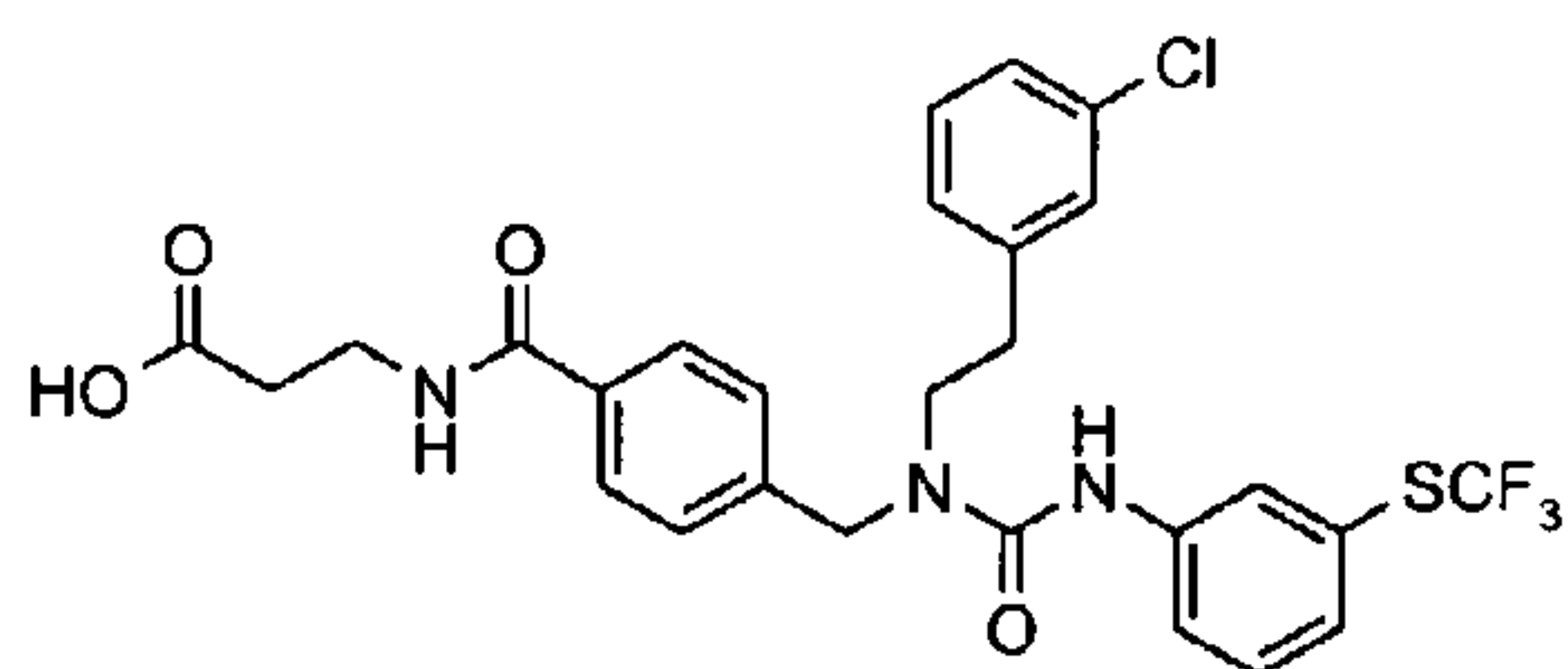
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-ethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



10

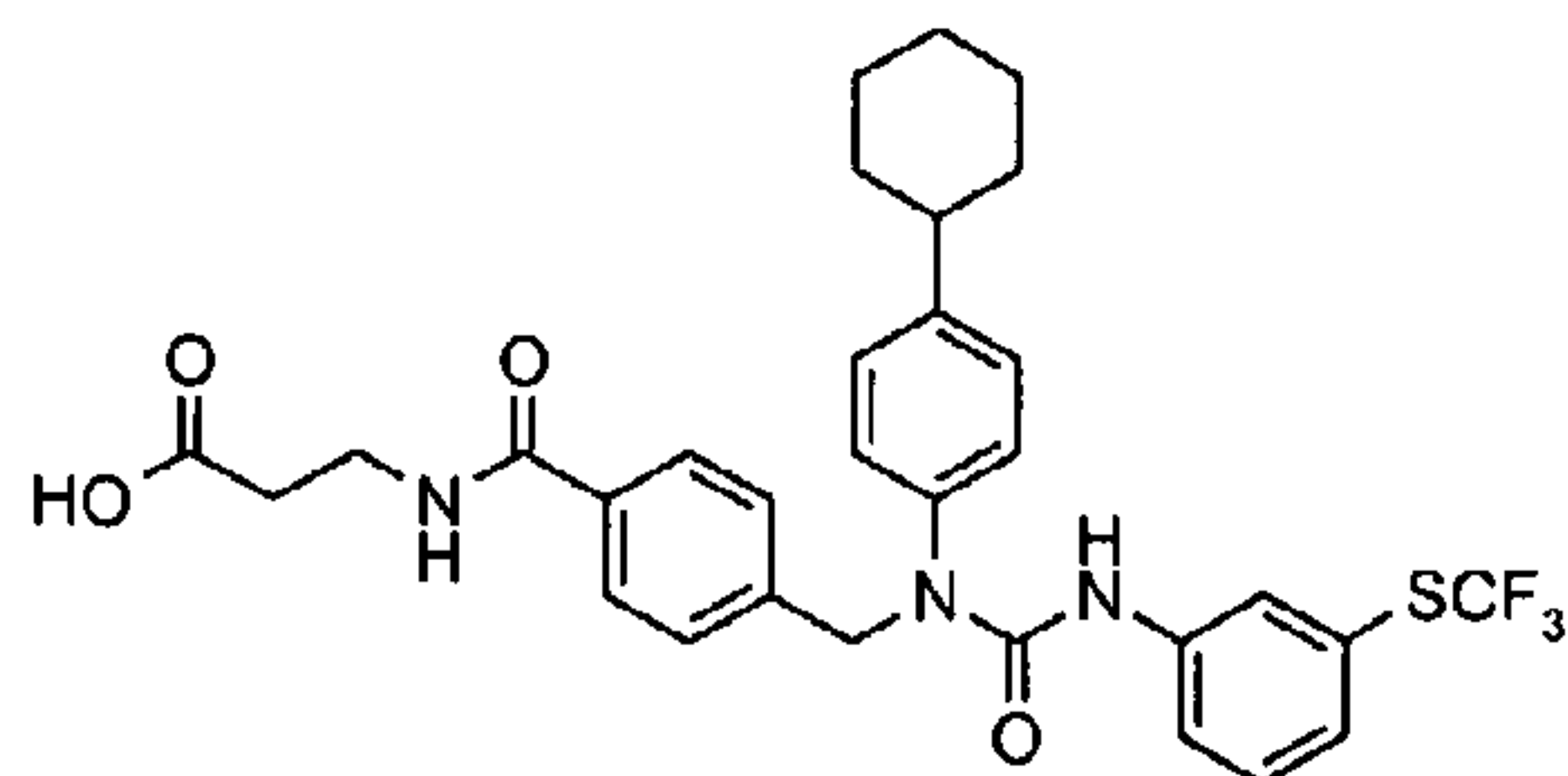
EXAMPLE 201 (general procedure (J))

3-{4-[1-[2-(3-Chlorophenyl)ethyl]-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



EXAMPLE 202 (general procedure (J))

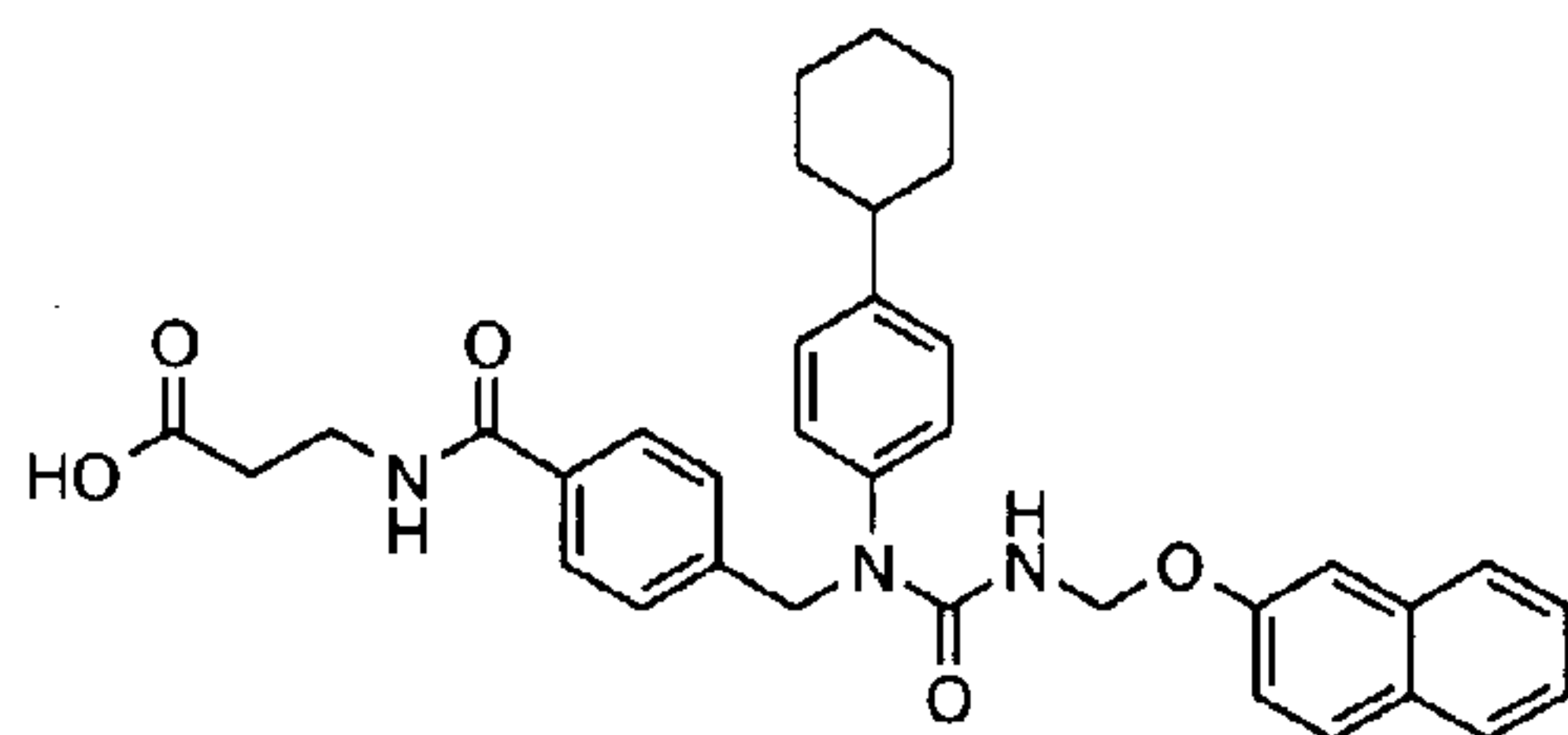
3-{4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}-propionic acid



5

EXAMPLE 203 (general procedure (J))

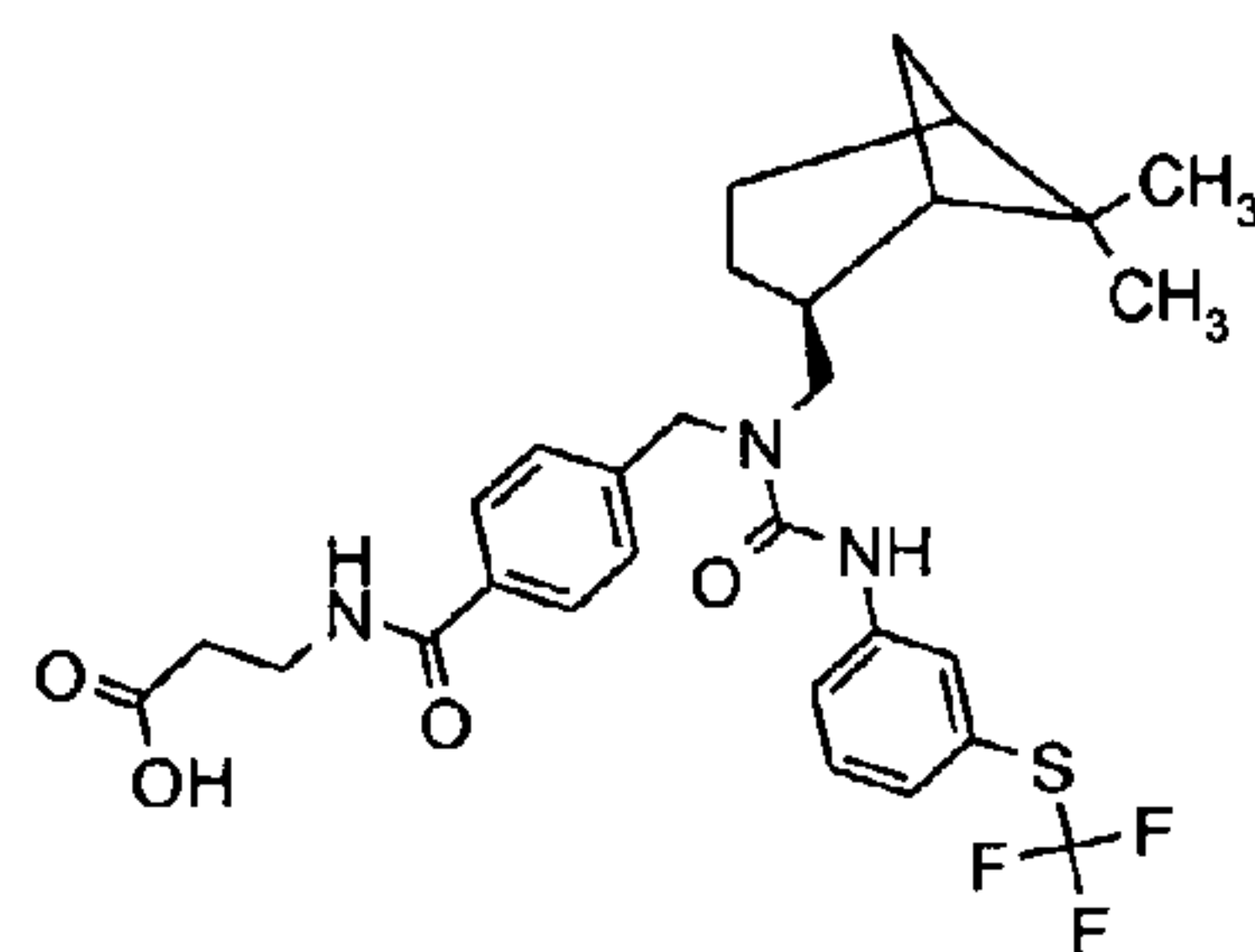
3-{4-[1-(4-Cyclohexylphenyl)-3-(naphthalen-2-yloxymethyl)ureidomethyl]benzoylamino}-propionic acid



10

EXAMPLE 204 (general procedure (J))

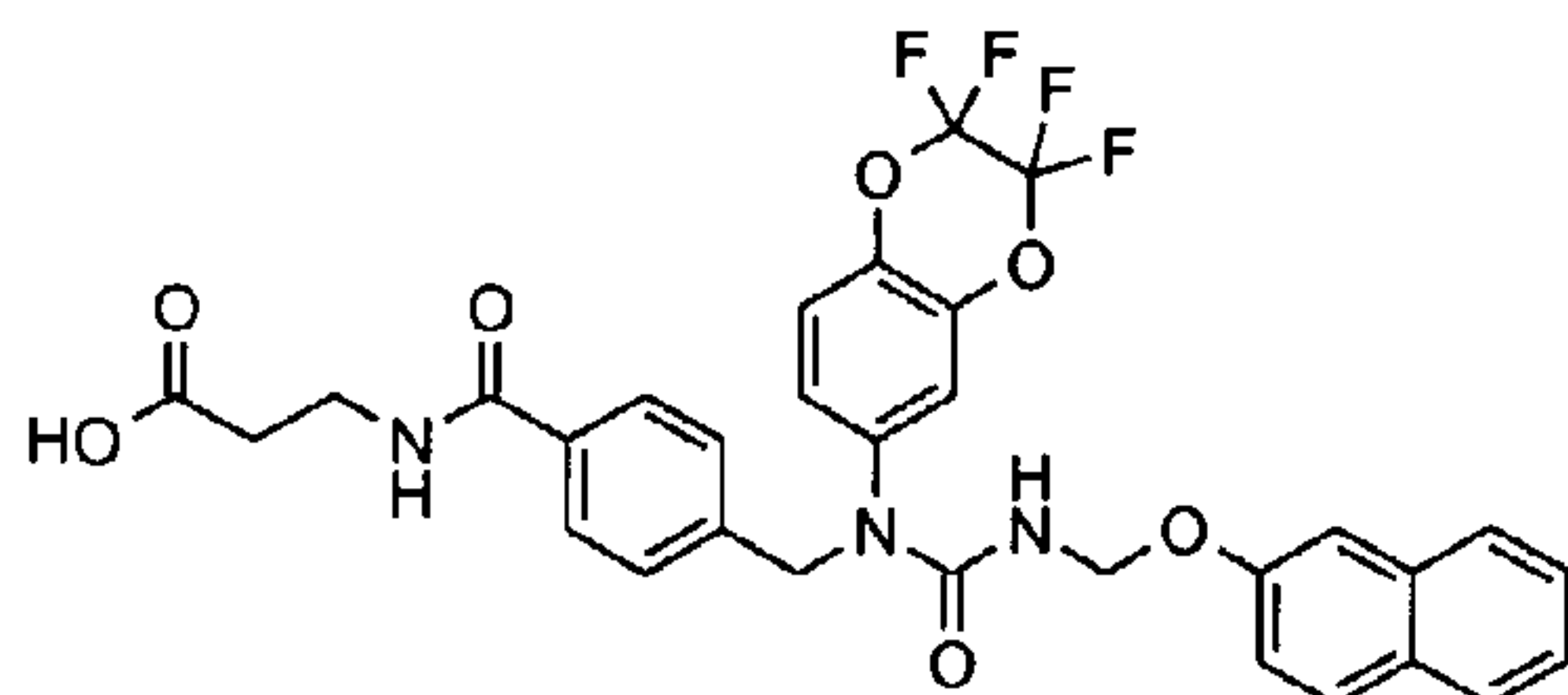
3-{4-[1-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]benzoylamino}propionic acid



15

EXAMPLE 205 (general procedure (J))

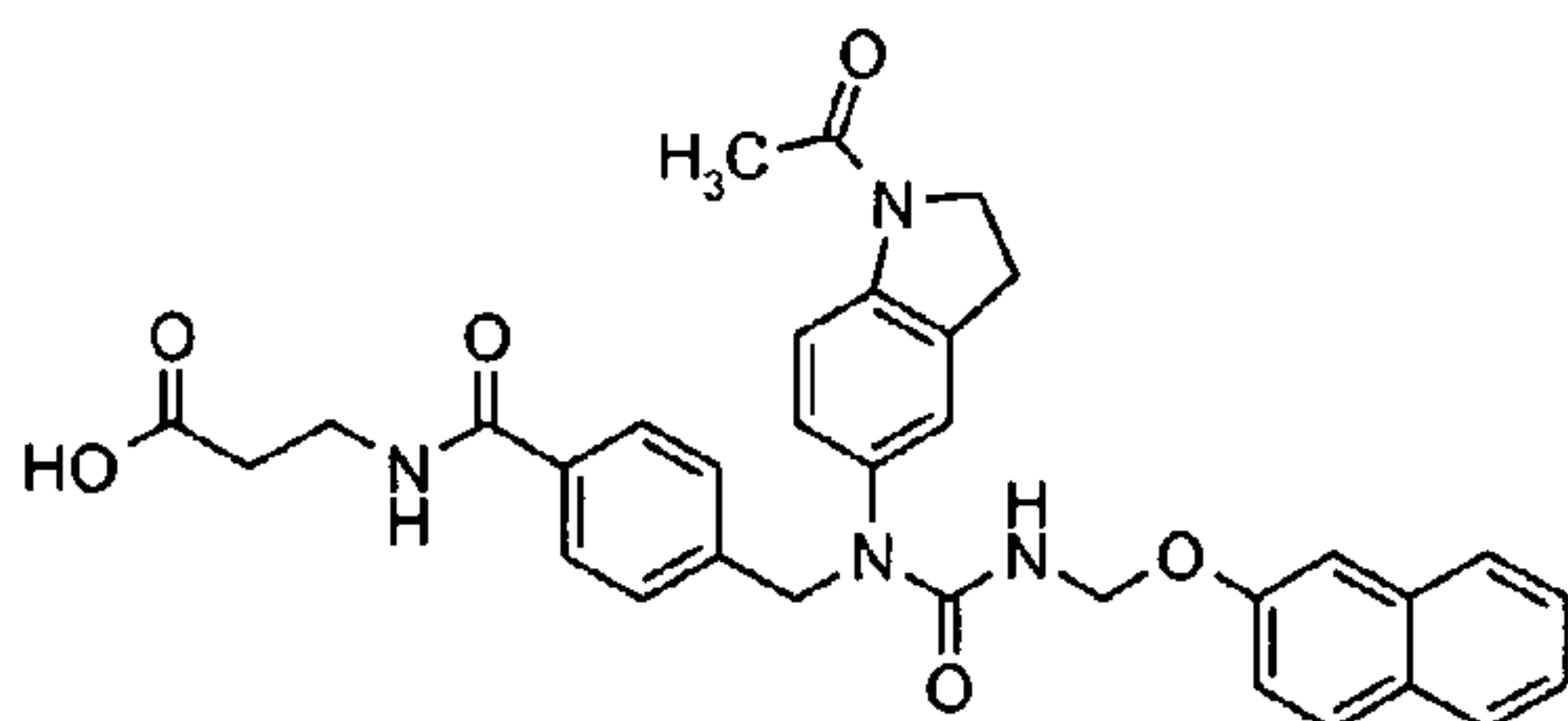
3-{4-[3-(Naphthalen-2-yloxymethyl)-1-(2,2,3,3-tetrafluoro-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ureidomethyl]benzoylamino}propionic acid



5

EXAMPLE 206 (general procedure (J))

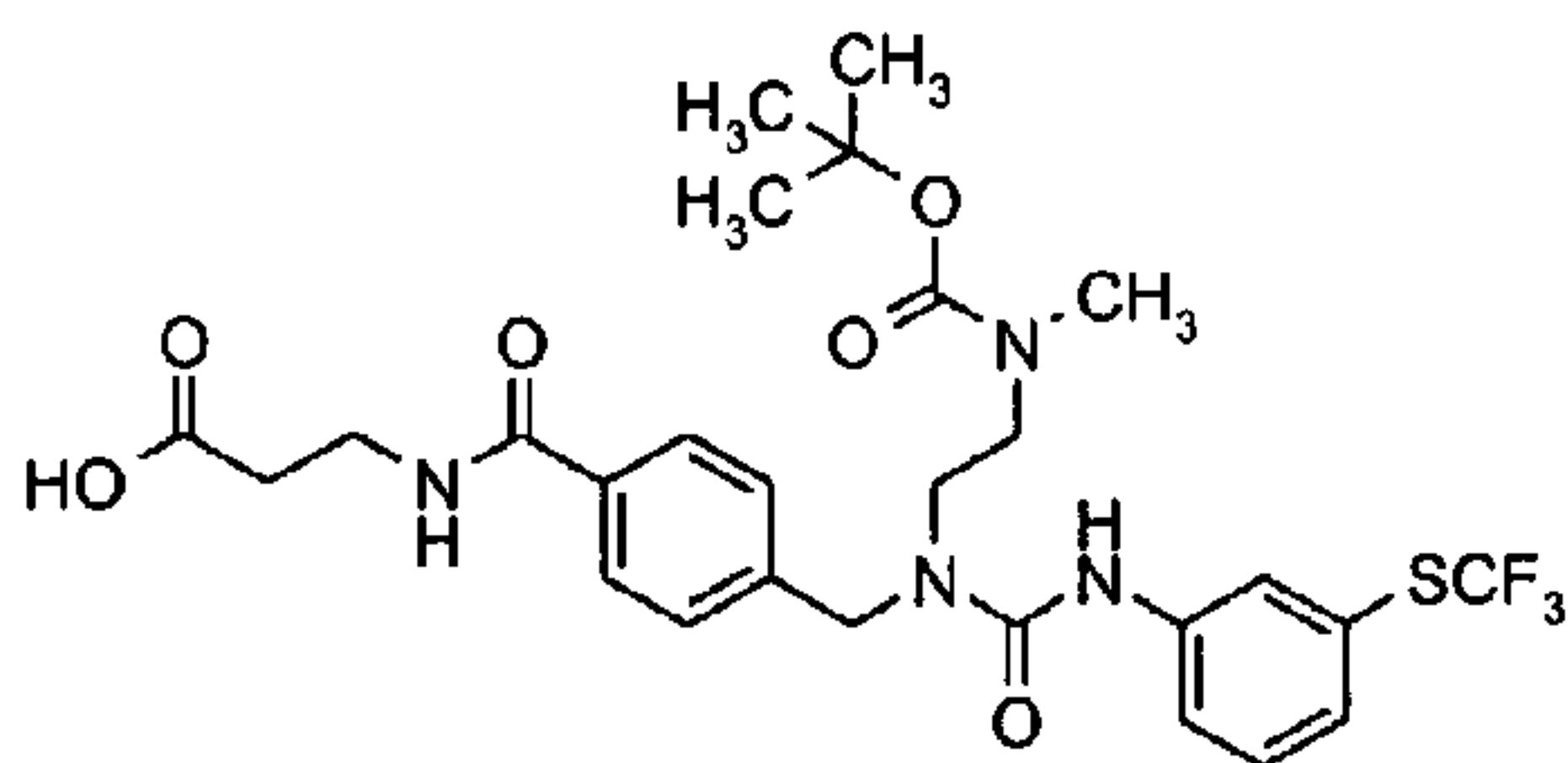
3-{4-[1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(naphthalen-2-yloxymethyl)ureidomethyl]benzoylamino}propionic acid



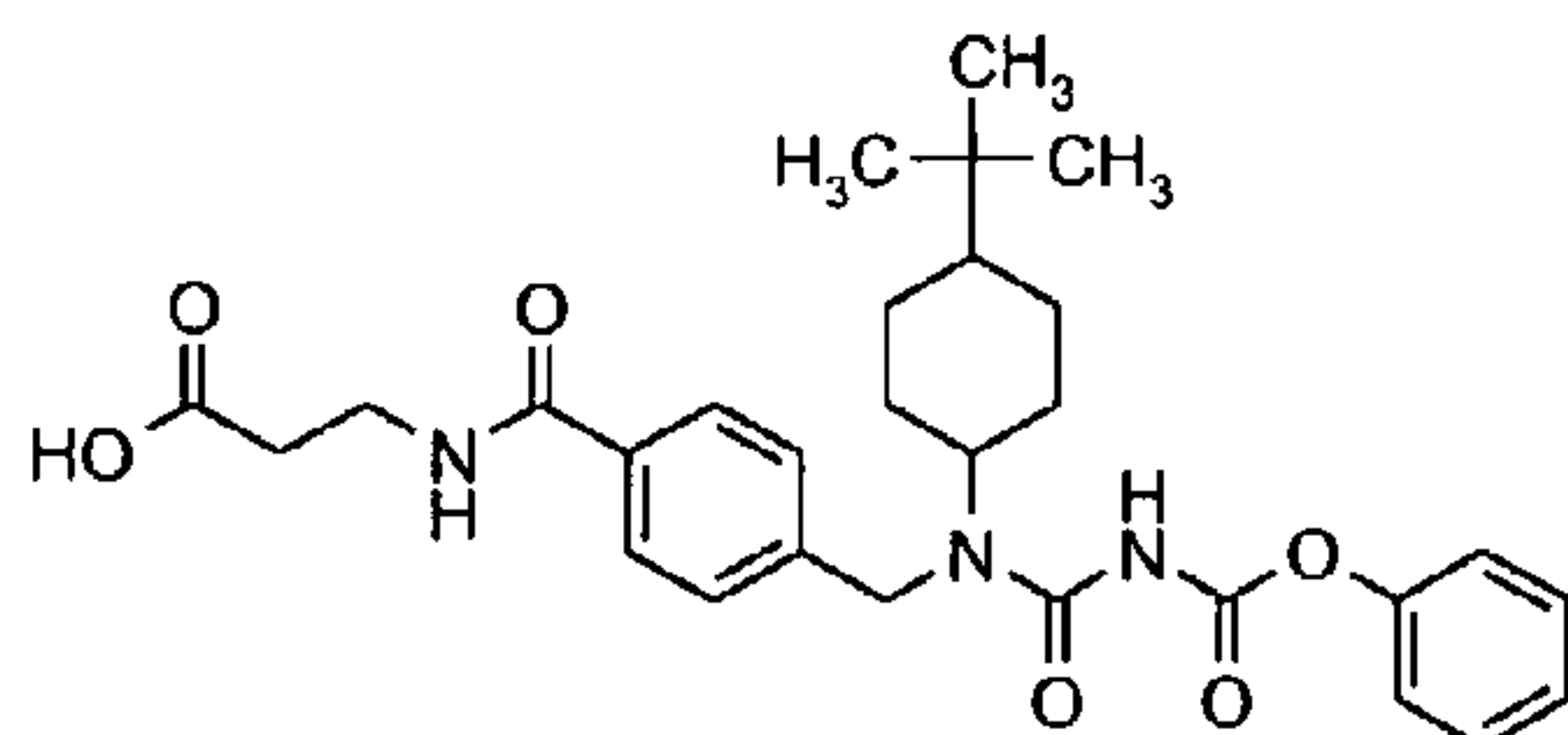
10

EXAMPLE 207 (general procedure (J))

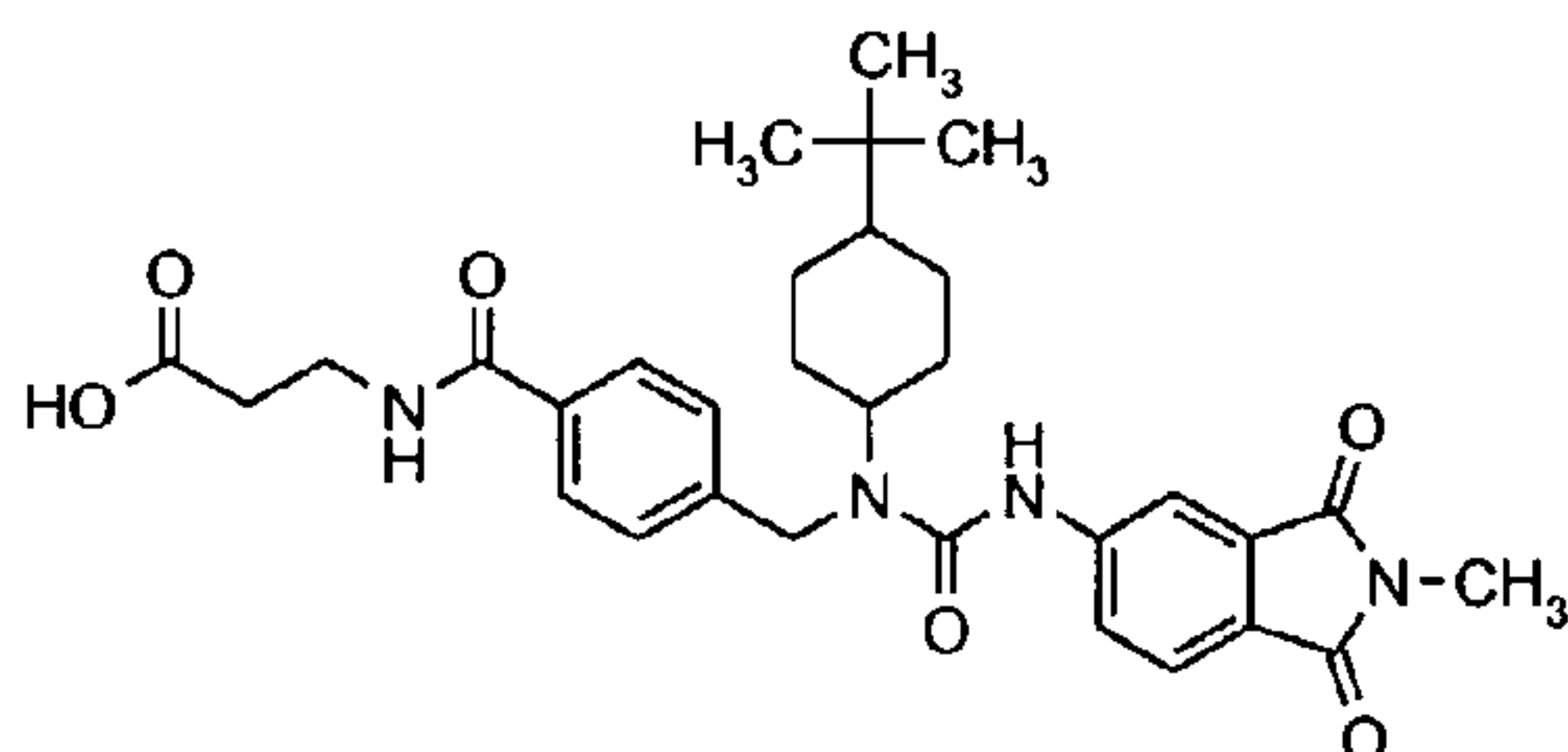
3-{4-[1-[2-(*N*-tert-Butoxycarbonyl-*N*-methylamino)ethyl]-3-(3-trifluoromethylsulfonylphenyl)-ureidomethyl]benzoylamino}propionic acid



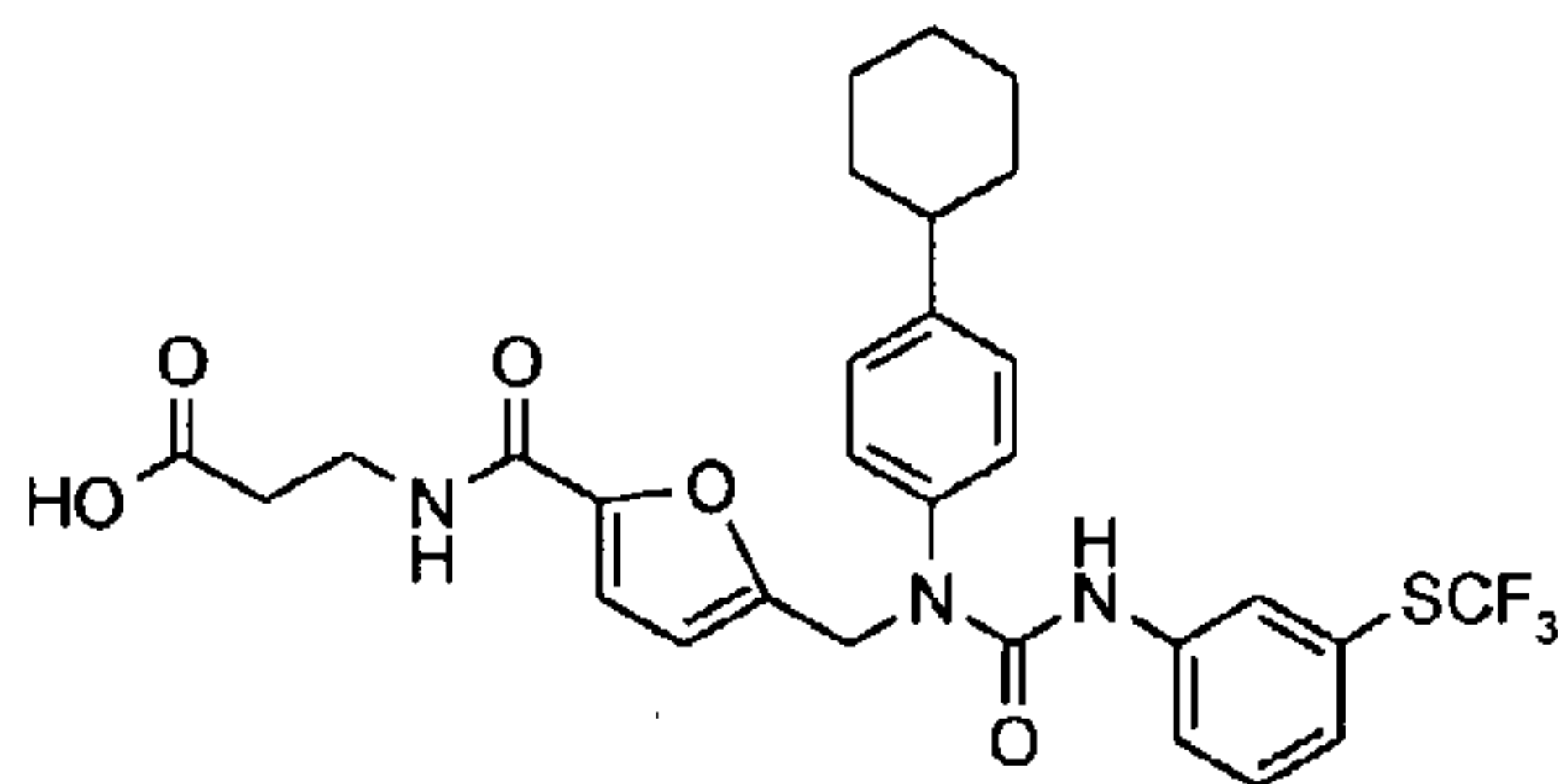
15

EXAMPLE 208 (general procedure (J))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(phenoxy carbonyl)ureidomethyl]benzoylamino}propionic acid

5

EXAMPLE 209 (general procedure (J))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(2-methyl-1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)-ureidomethyl]benzoylamino}propionic acid

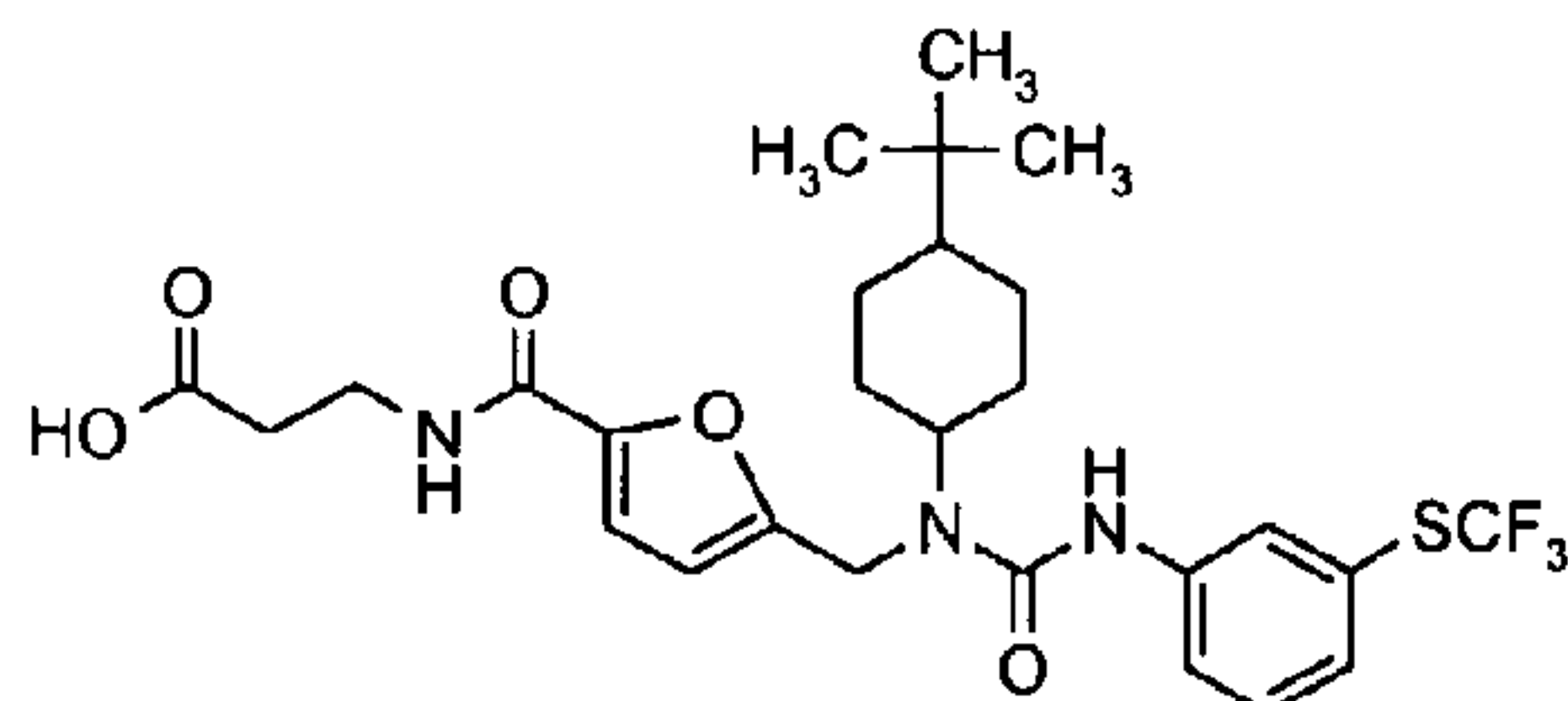
10

EXAMPLE 210 (general procedure (J))3-({5-[1-(4-cyclohexylphenyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]furan-2-carbonyl}amino)propionic acid

15

EXAMPLE 211 (general procedure (J))

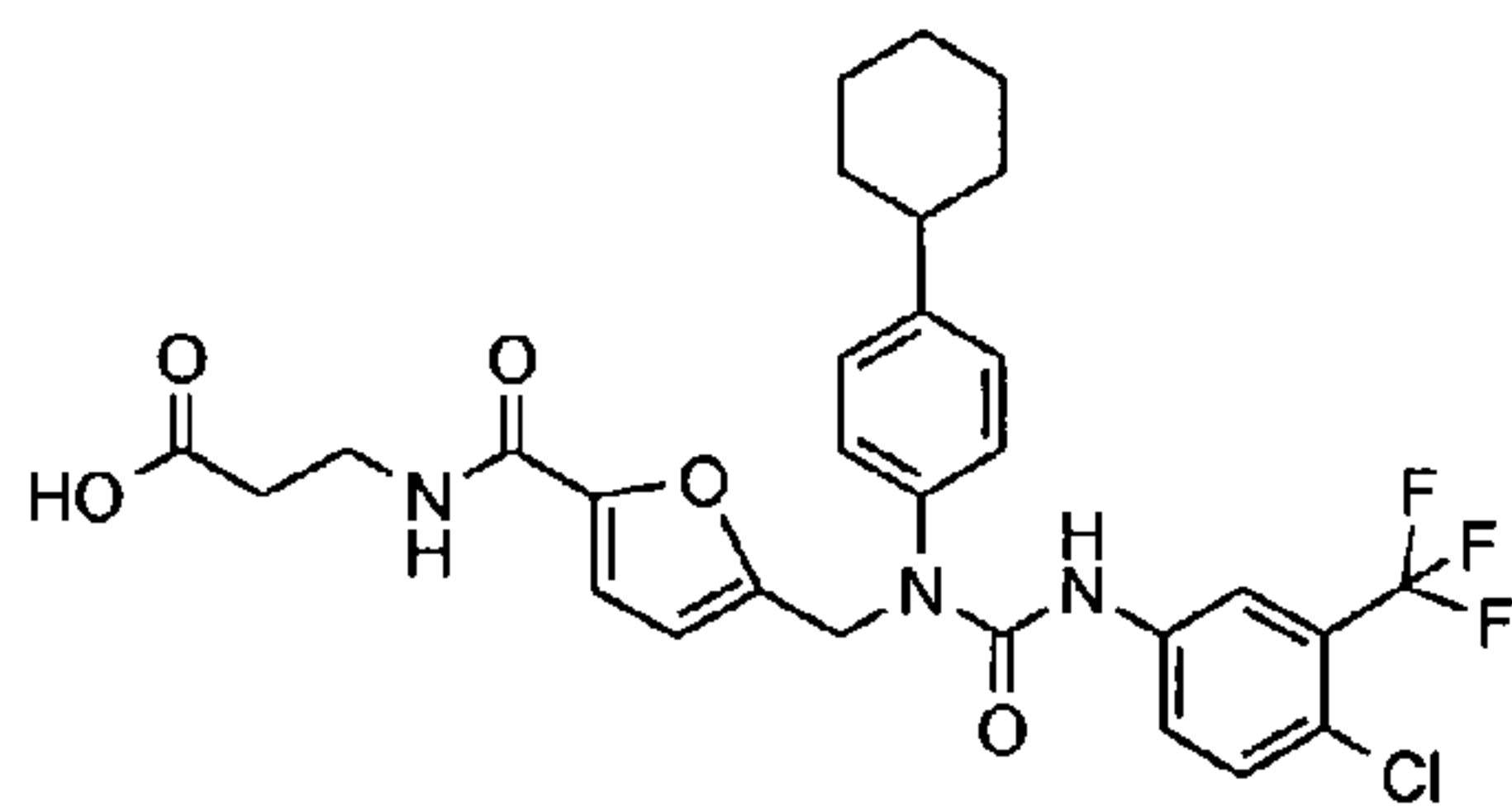
3-({5-[1-(4-*tert*-Butylcyclohexyl)-3-(3-trifluoromethylsulfanylphenyl)ureidomethyl]furan-2-carbonyl}amino)propionic acid



5

EXAMPLE 212 (general procedure (J))

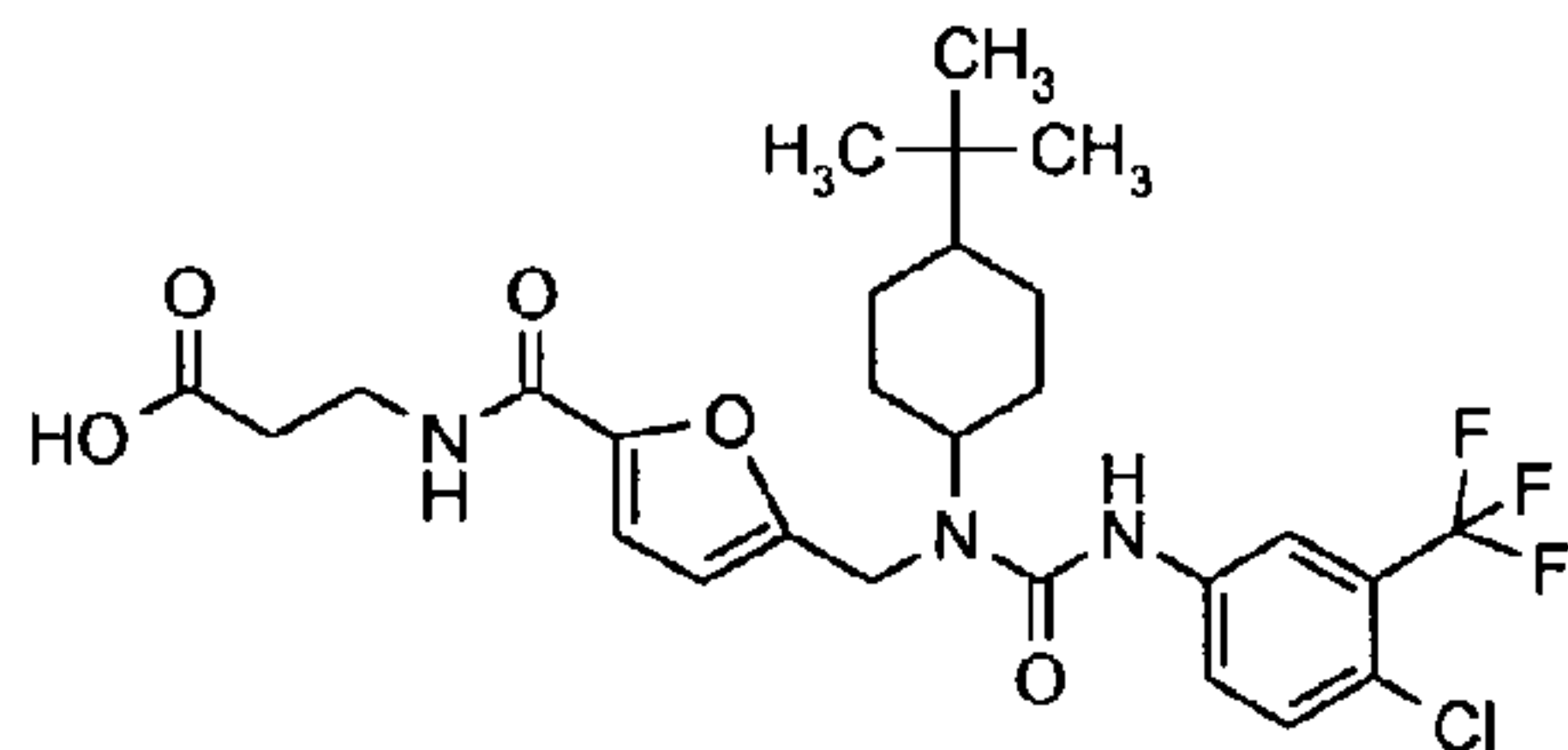
3-({5-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]furan-2-carbonyl}amino)propionic acid



10

EXAMPLE 213 (general procedure (J))

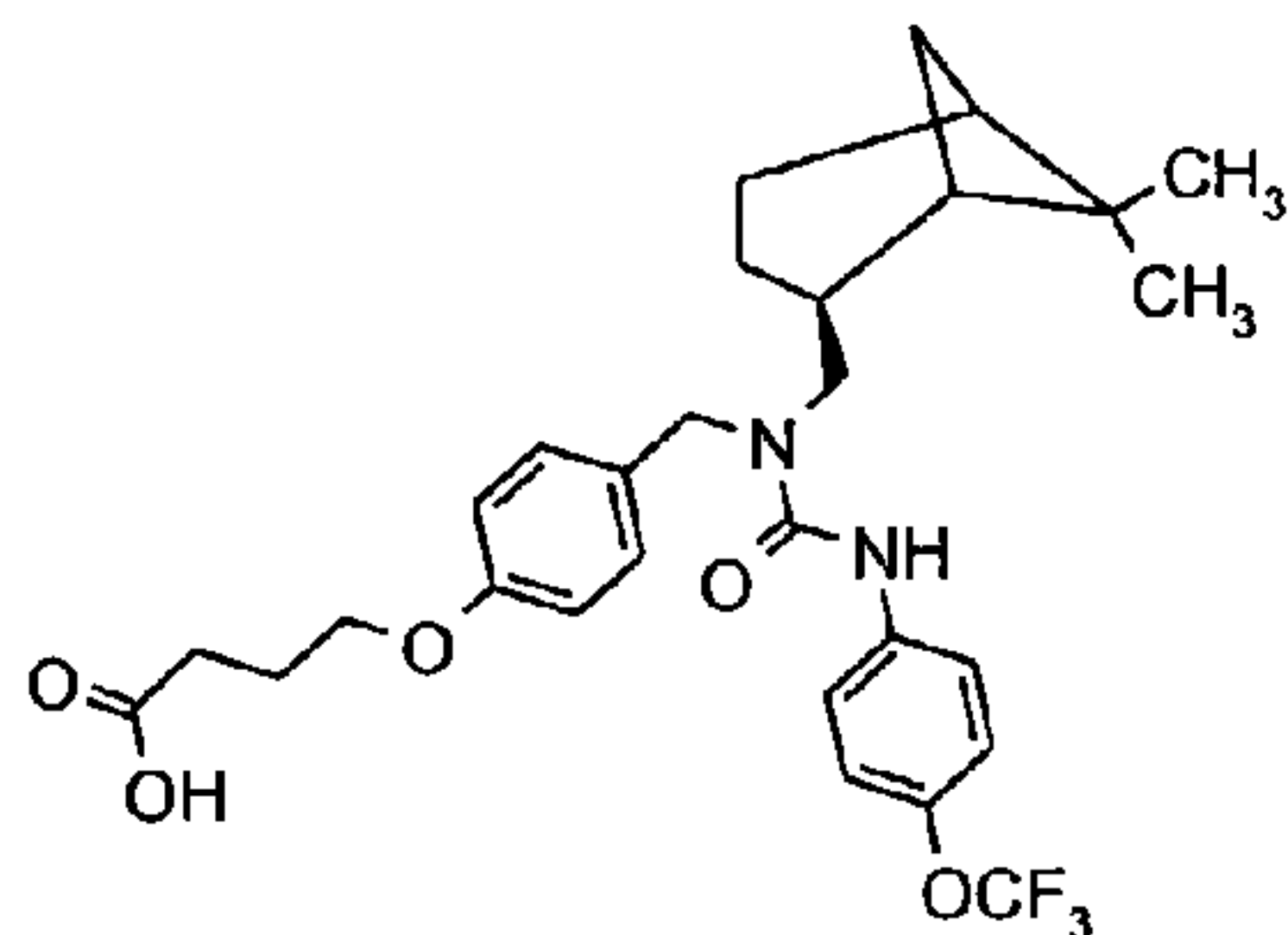
3-({5-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]furan-2-carbonyl}amino)propionic acid



15

EXAMPLE 214 (general procedure (J))

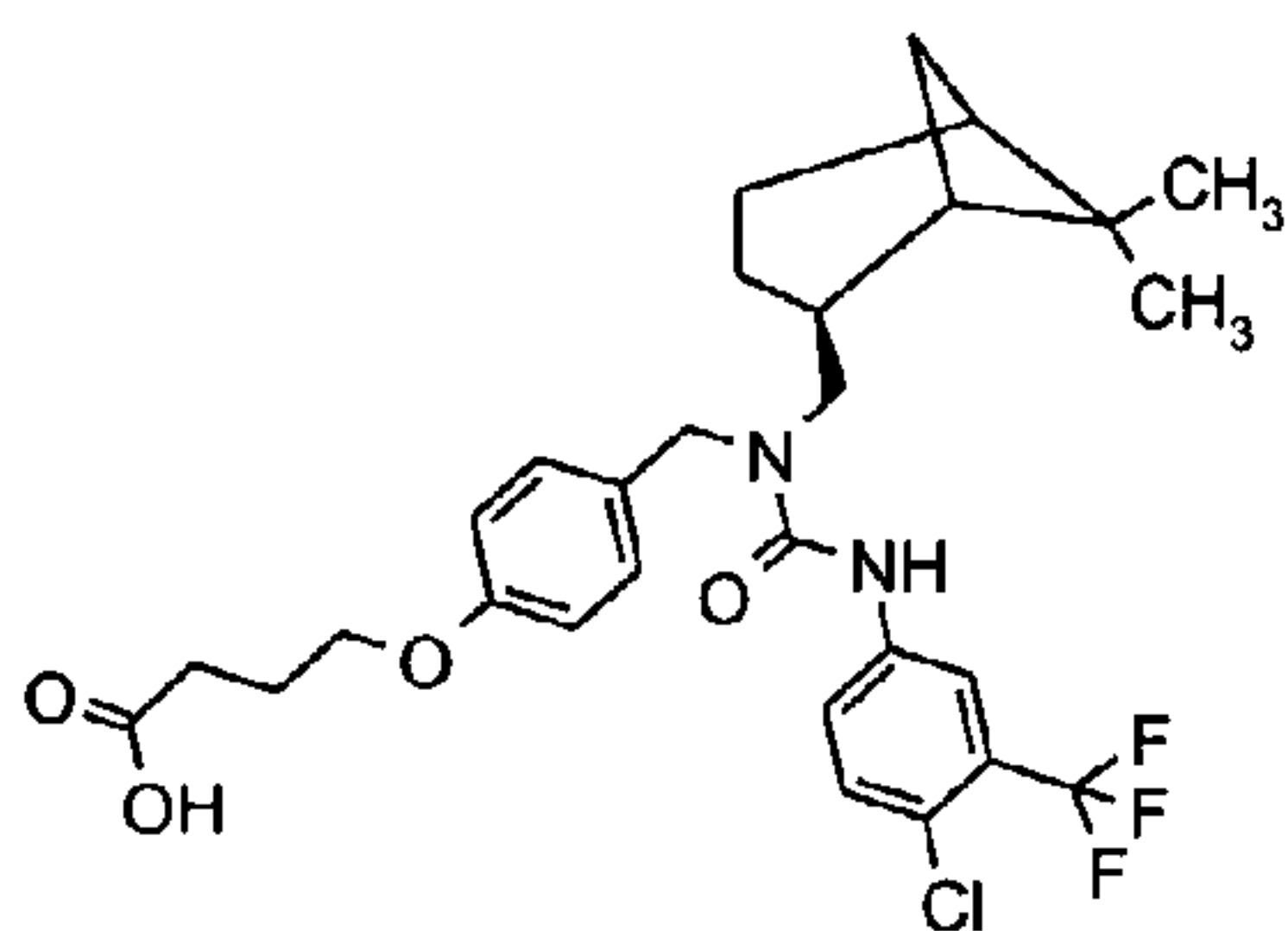
4-{4-[1-(6,6-Dimethylbicyclo[3.1.1]hept-2-ylmethyl)-3-(4-trifluoromethoxyphenyl)ureido-methyl]phenoxy}butyric acid



5

EXAMPLE 215 (general procedure (J))

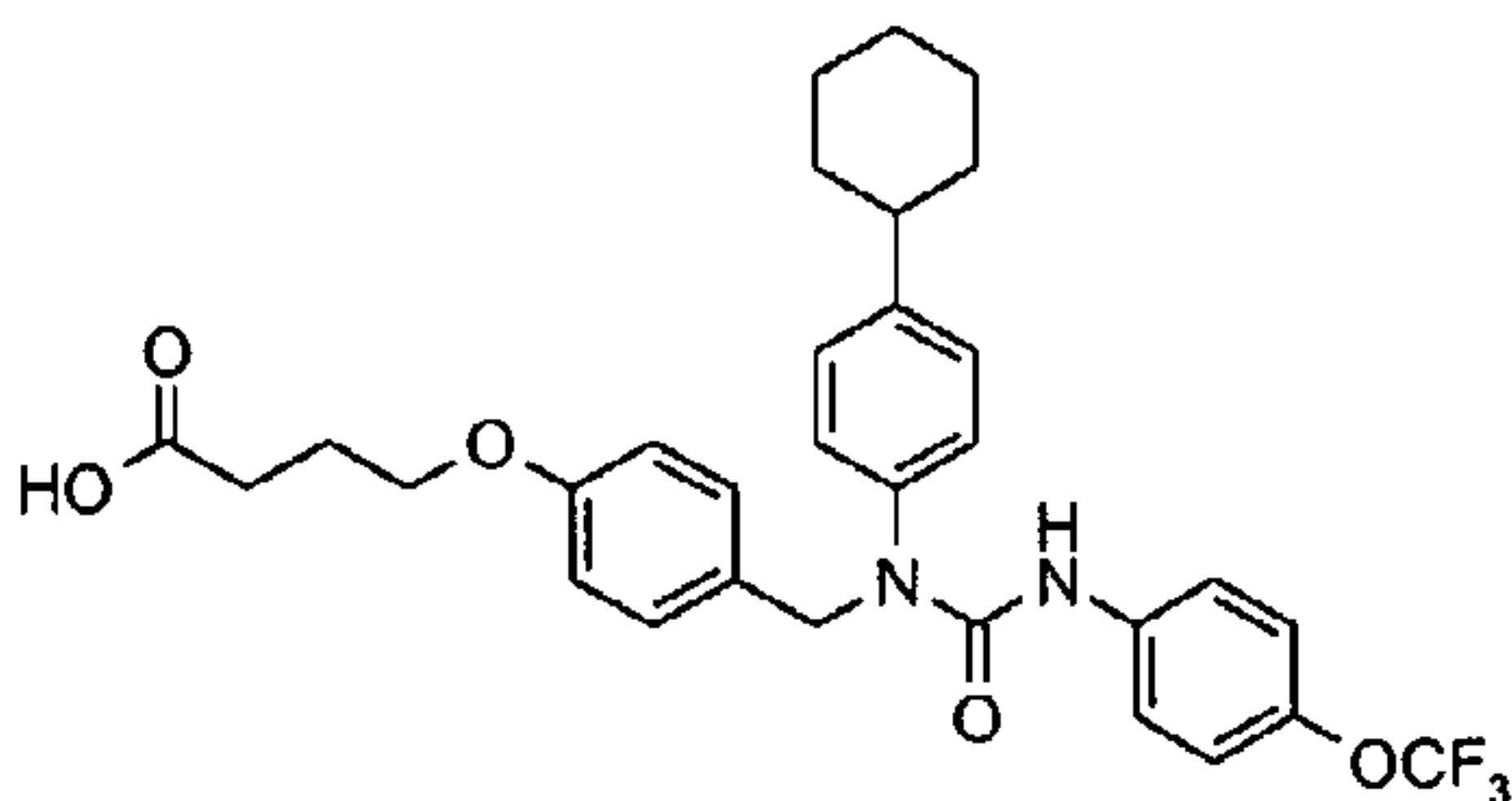
4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(6,6-dimethylbicyclo[3.1.1]hept-2-ylmethyl)-ureidomethyl]phenoxy}butyric acid



10

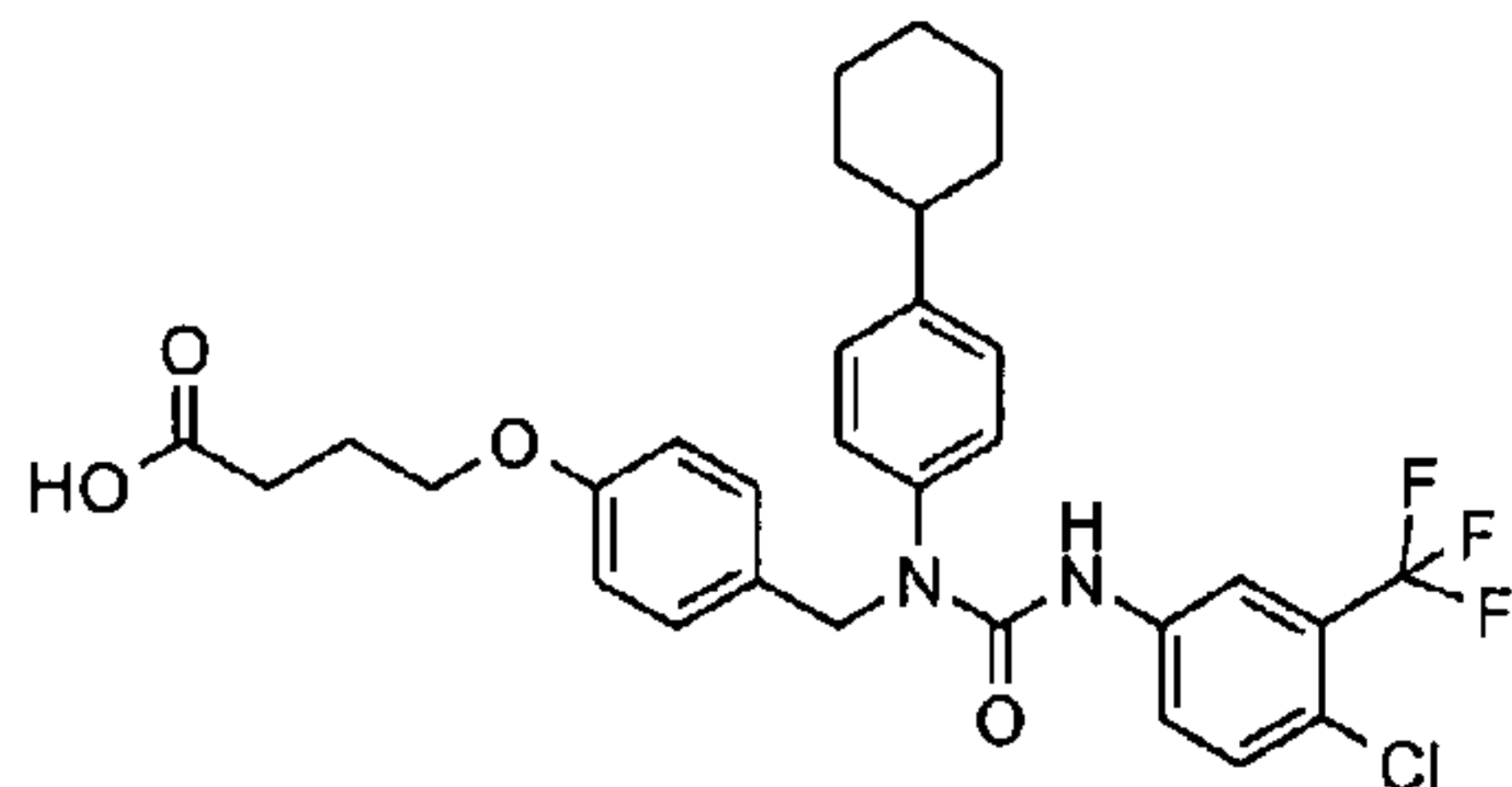
EXAMPLE 216 (general procedure (J))

4-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acid



EXAMPLE 217 (general procedure (J))

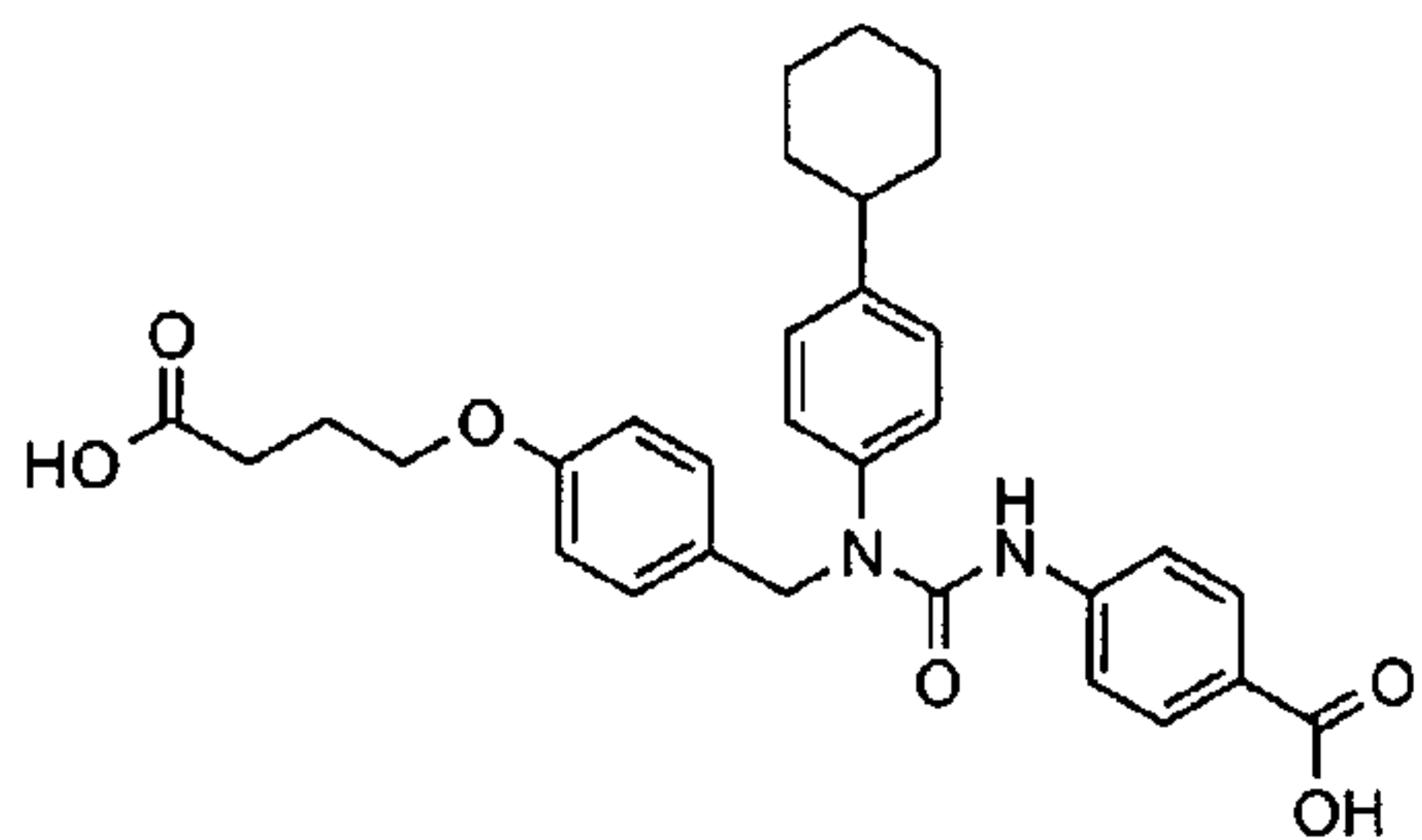
4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]phenoxy}-butyric acid



5

EXAMPLE 218 (general procedure (J))

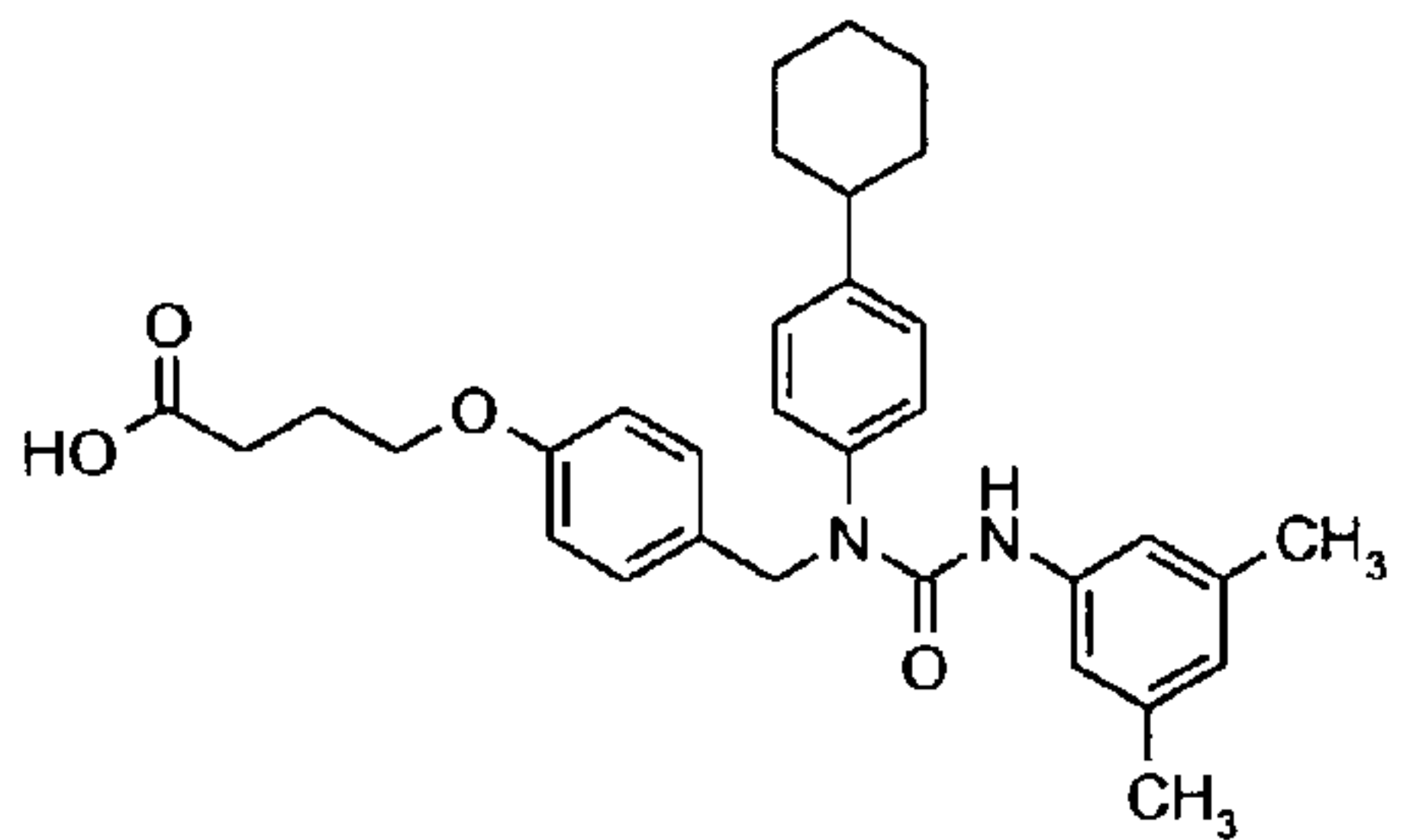
4-[3-[4-(3-Carboxypropoxy)benzyl]-3-(4-cyclohexylphenyl)ureido]benzoic acid

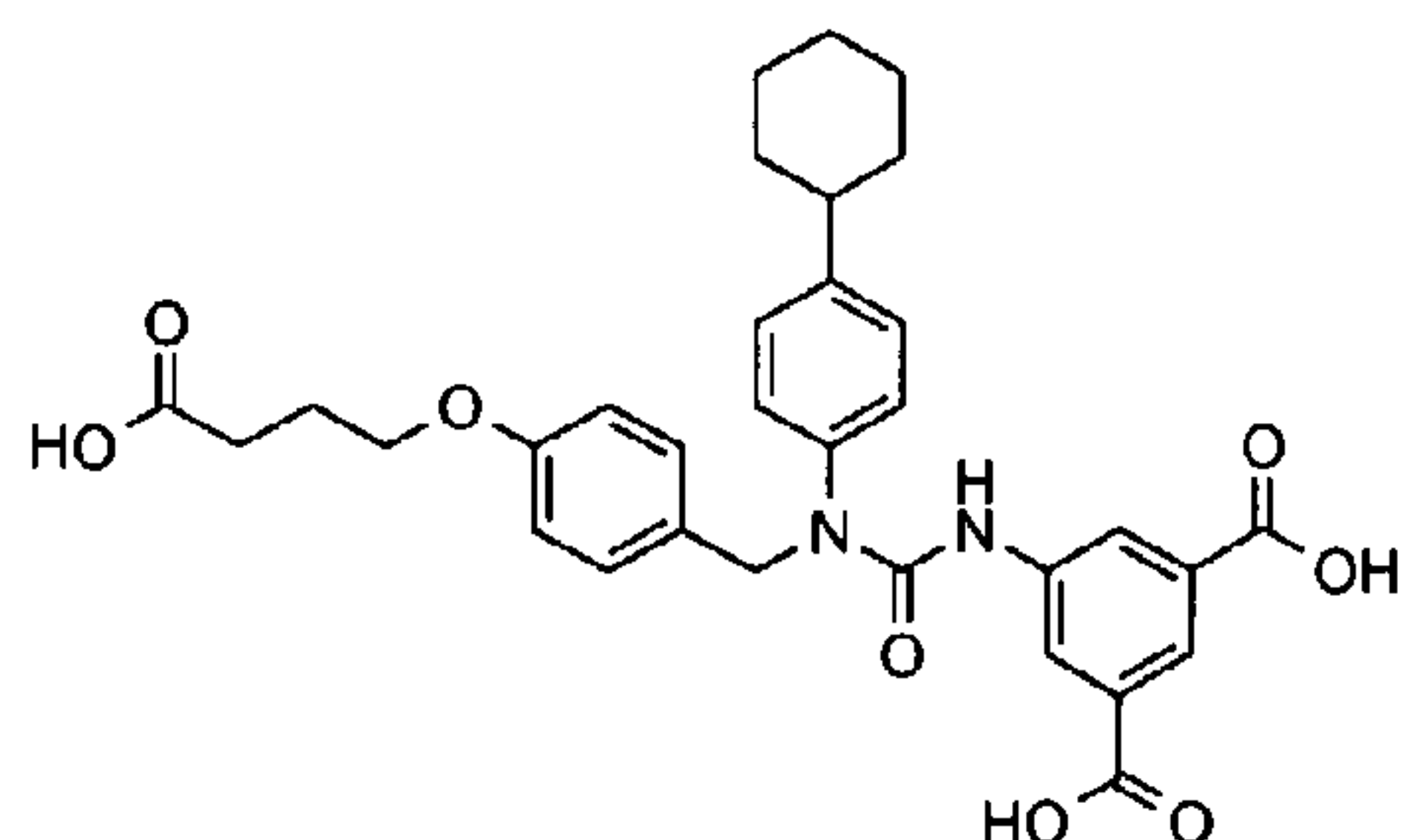
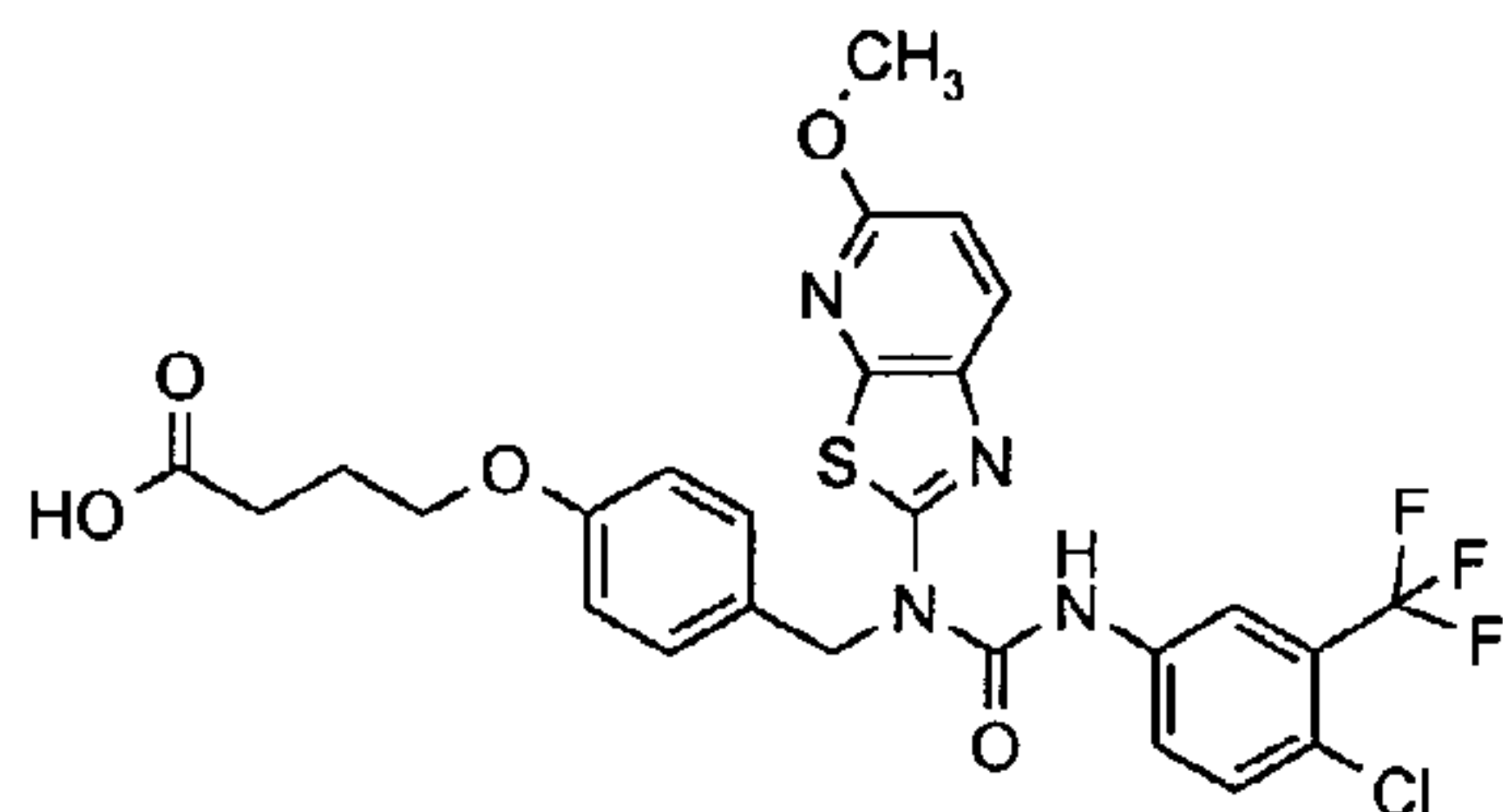
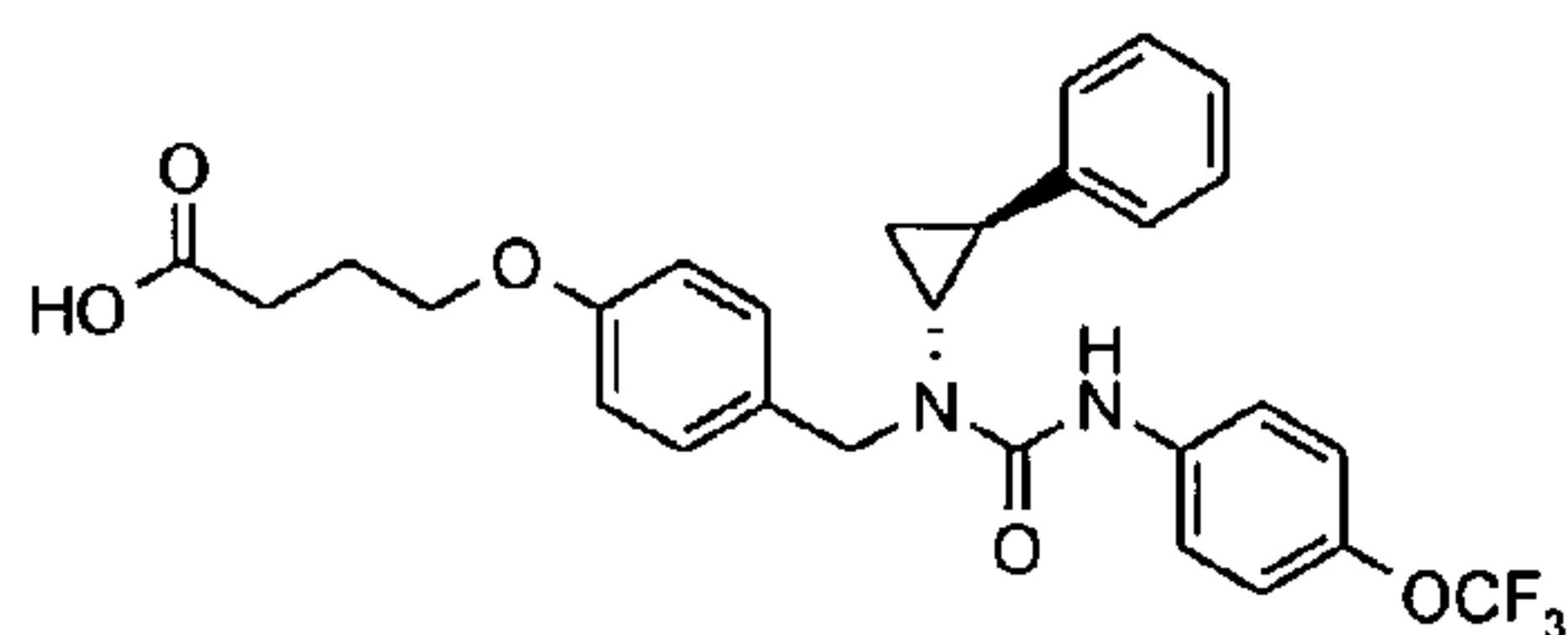
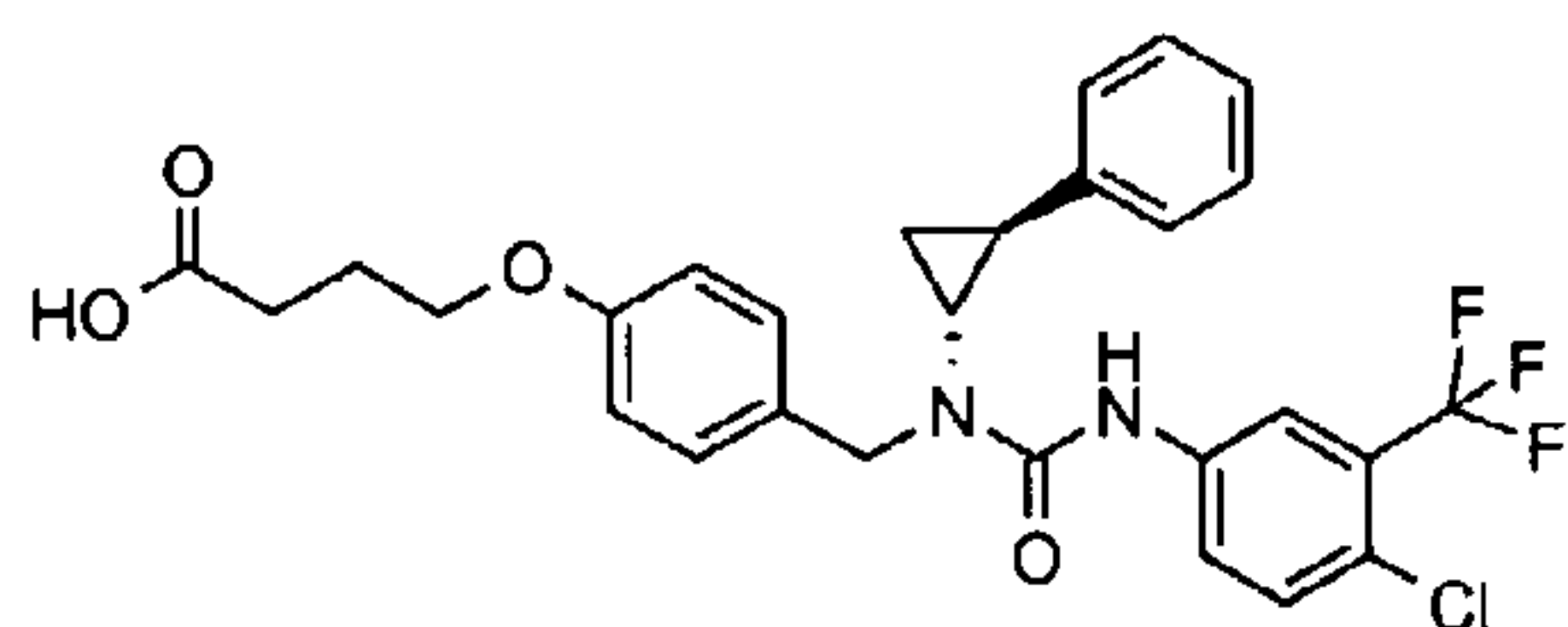


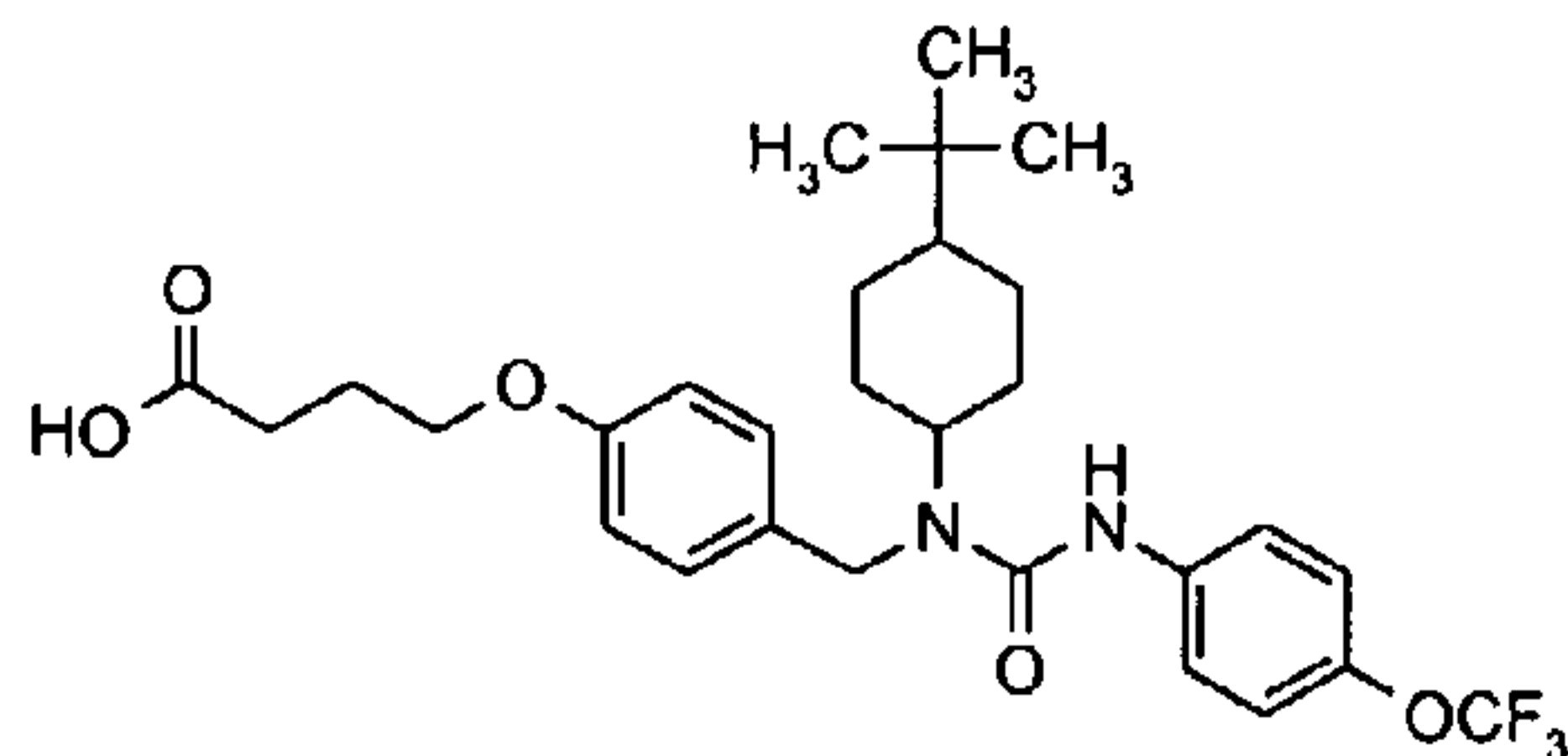
10

EXAMPLE 219 (general procedure (J))

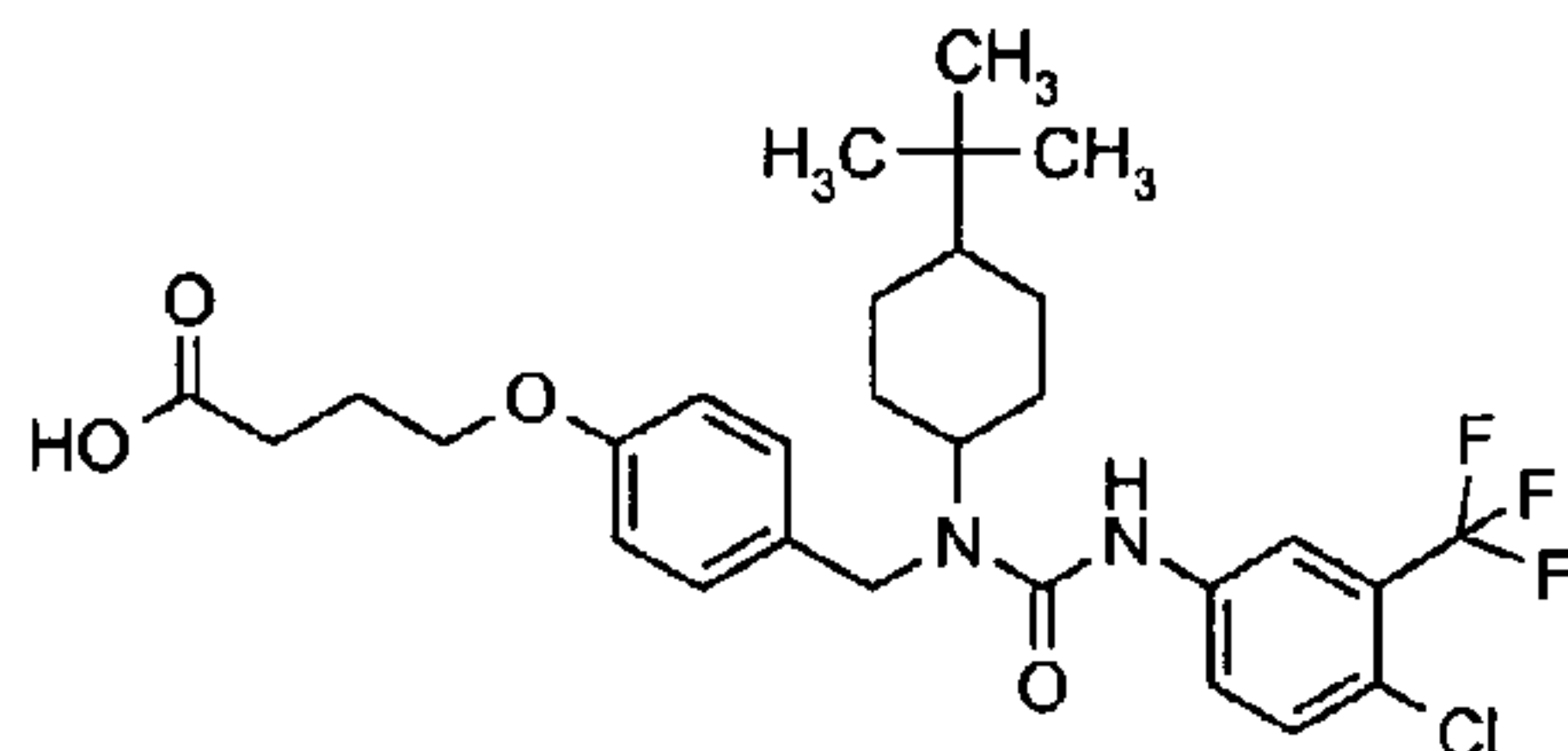
4-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dimethylphenyl)ureidomethyl]phenoxy}butyric acid



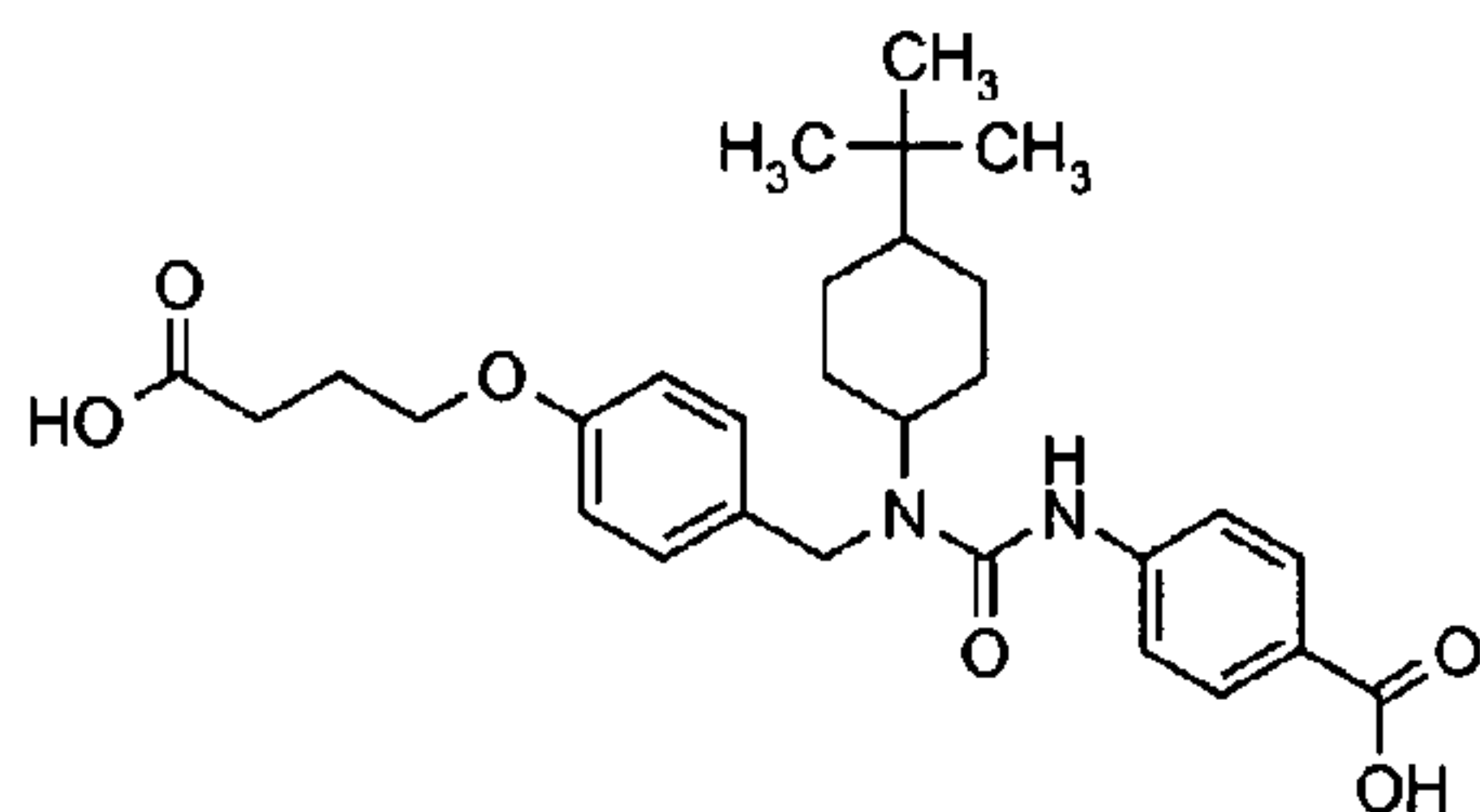
EXAMPLE 220 (general procedure (J))5-[3-[4-(3-Carboxypropoxy)benzyl]-3-(4-cyclohexylphenyl)ureido]isophthalic acid5 EXAMPLE 221 (general procedure (J))4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(5-methoxythiazolo[5,4-b]pyridin-2-yl)ureido-methyl]phenoxy}butyric acid10 EXAMPLE 222 (general procedure (J))4-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acidEXAMPLE 223 (general procedure (J))15 4-{4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-phenylcyclopropyl)ureidomethyl]phenoxy}-butyric acid

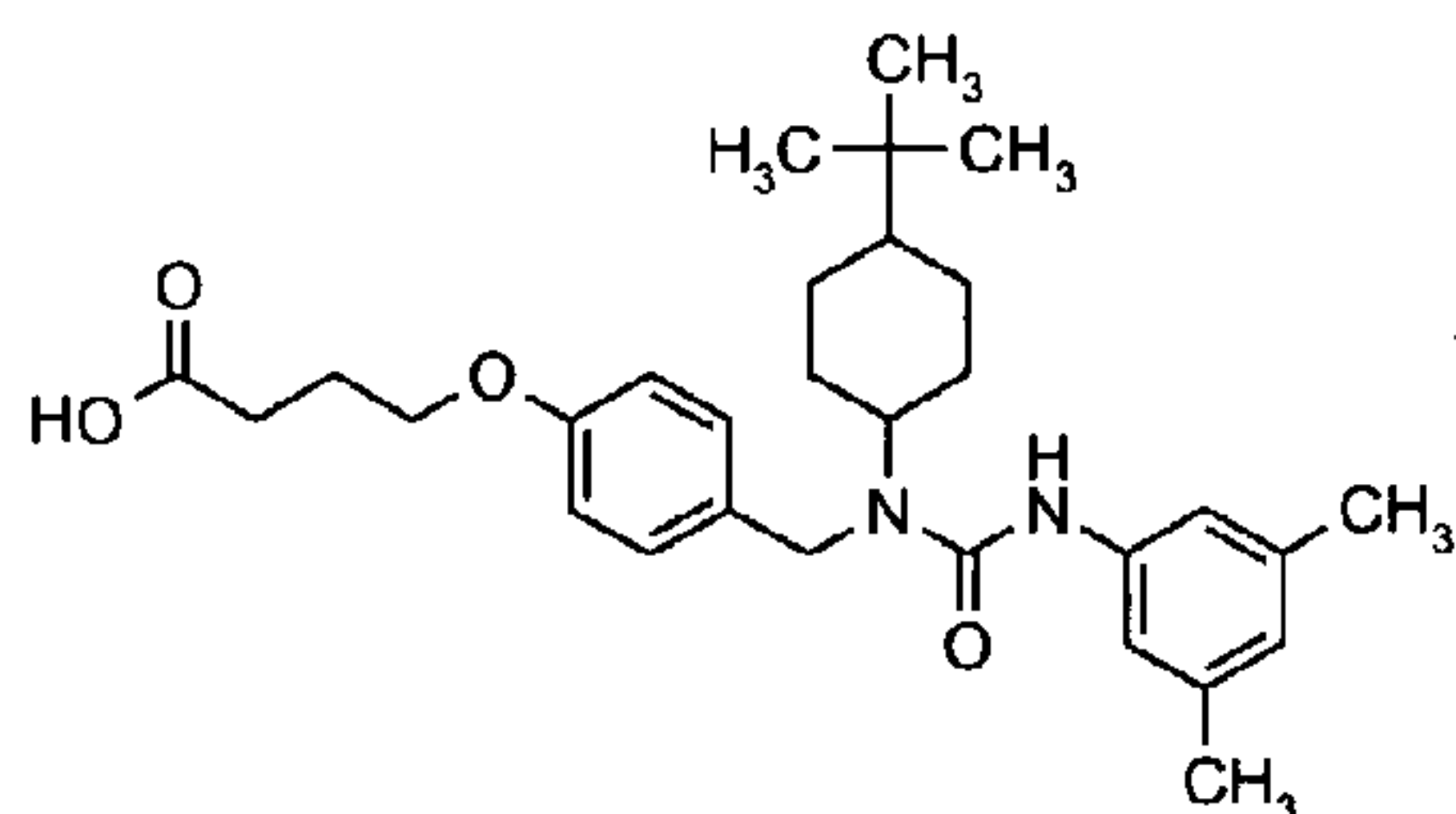
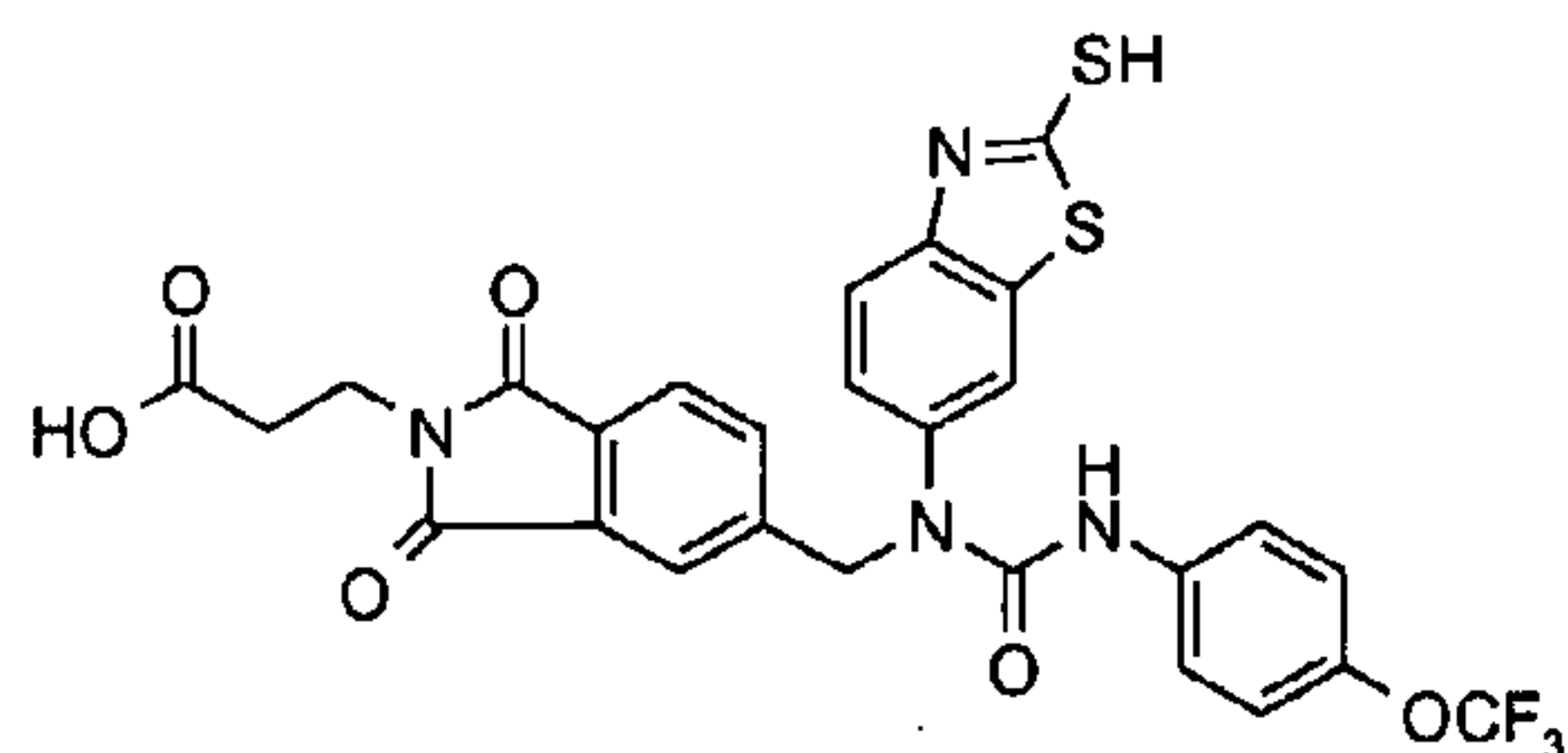
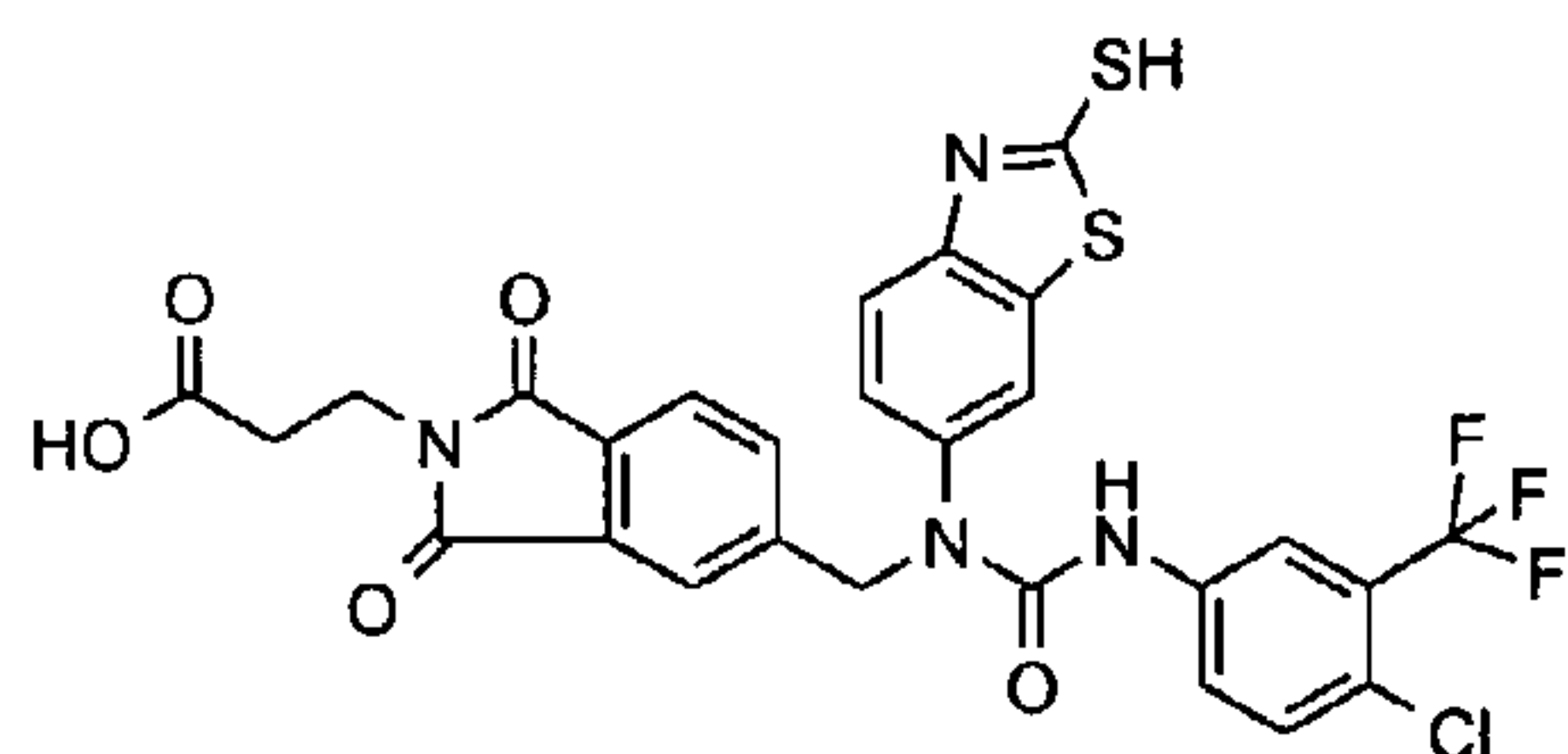
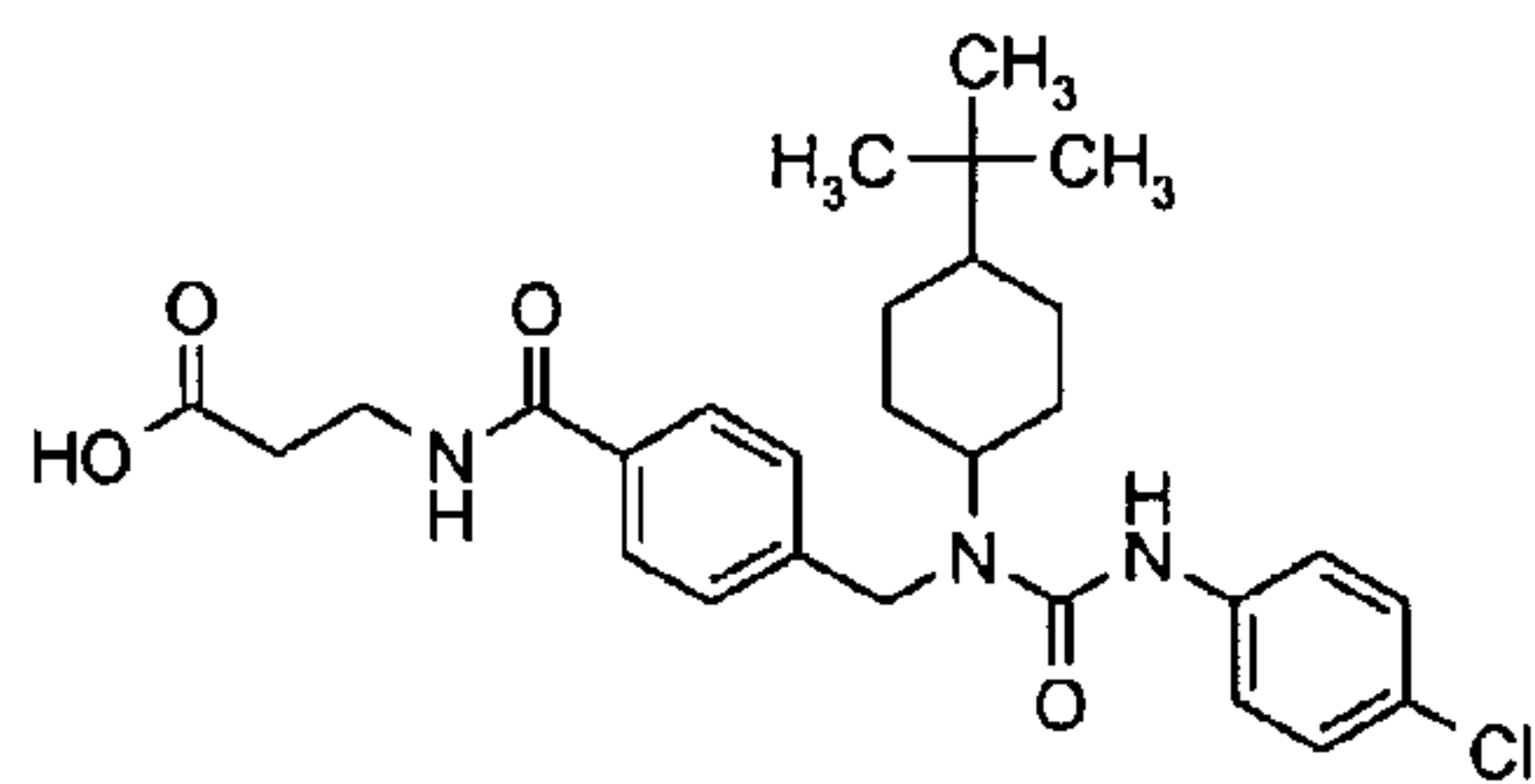
EXAMPLE 224 (general procedure (J))4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]phenoxy}butyric acid

5

EXAMPLE 225 (general procedure (J))4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]phenoxy}-butyric acid

10

EXAMPLE 226 (general procedure (J))4-{3-(4-*tert*-Butylcyclohexyl)-3-[4-(3-carboxypropoxy)benzyl]ureido}benzoic acid

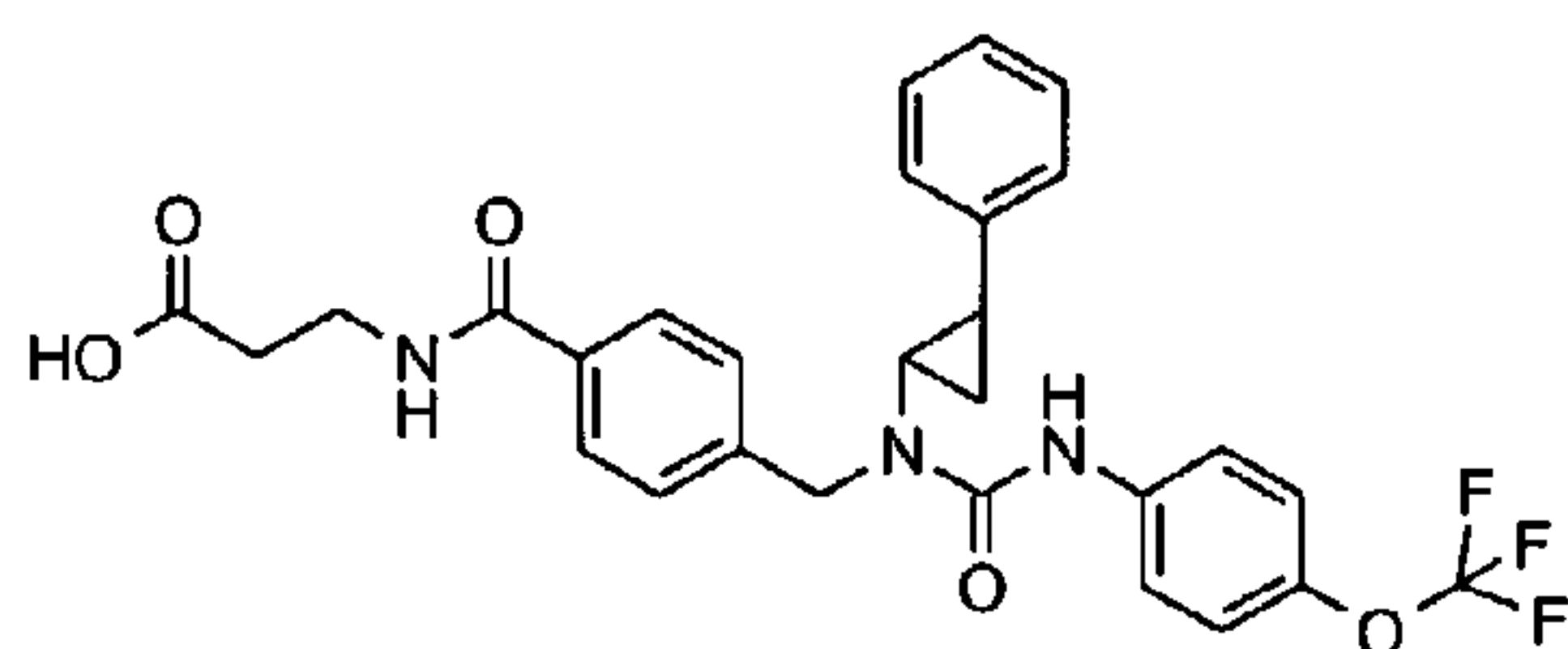
EXAMPLE 227 (general procedure (J))4-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3,5-dimethylphenyl)ureidomethyl]phenoxy}butyric acid5 EXAMPLE 228 (general procedure (J))3-{5-[1-(2-Mercaptobenzothiazol-6-yl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-1,3-dioxo-1,3-dihydro-isoindol-2-yl}propionic acid10 EXAMPLE 229 (general procedure (J))3-{5-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(2-mercaptobenzothiazol-6-yl)ureidomethyl]1,3-dioxo-1,3-dihydro-isoindol-2-yl}propionic acid15 EXAMPLE 230 (General procedure (J))3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chlorophenyl)ureidomethyl]benzoylamino}propionic acid

¹H NMR (DMSO-*d*₆): δ 0.80 (s, 9H), 0.94 (m, 1H), 1.11 (qt, 2H), 1.39 (qt, 2H), 1.69 (m, 4H), 2.45 (t, 2H), 3.44 (qt, 2H), 4.05 (m, 1H), 4.59 (s, 2H), 7.27 (d, 2H), 7.31 (d, 2H), 7.48 (d, 2H), 7.45 (d, 2H), 8.44 (t, 1H), 8.47 (s, 1H), 12.30 (brd s, 1H).

5 MS (APCI, pos): 516.2, 514.2, 361.2, 362.2, 289.2.

EXAMPLE 231 (general procedure (J))

3-{4-[1-(2-Phenylcyclopropyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid

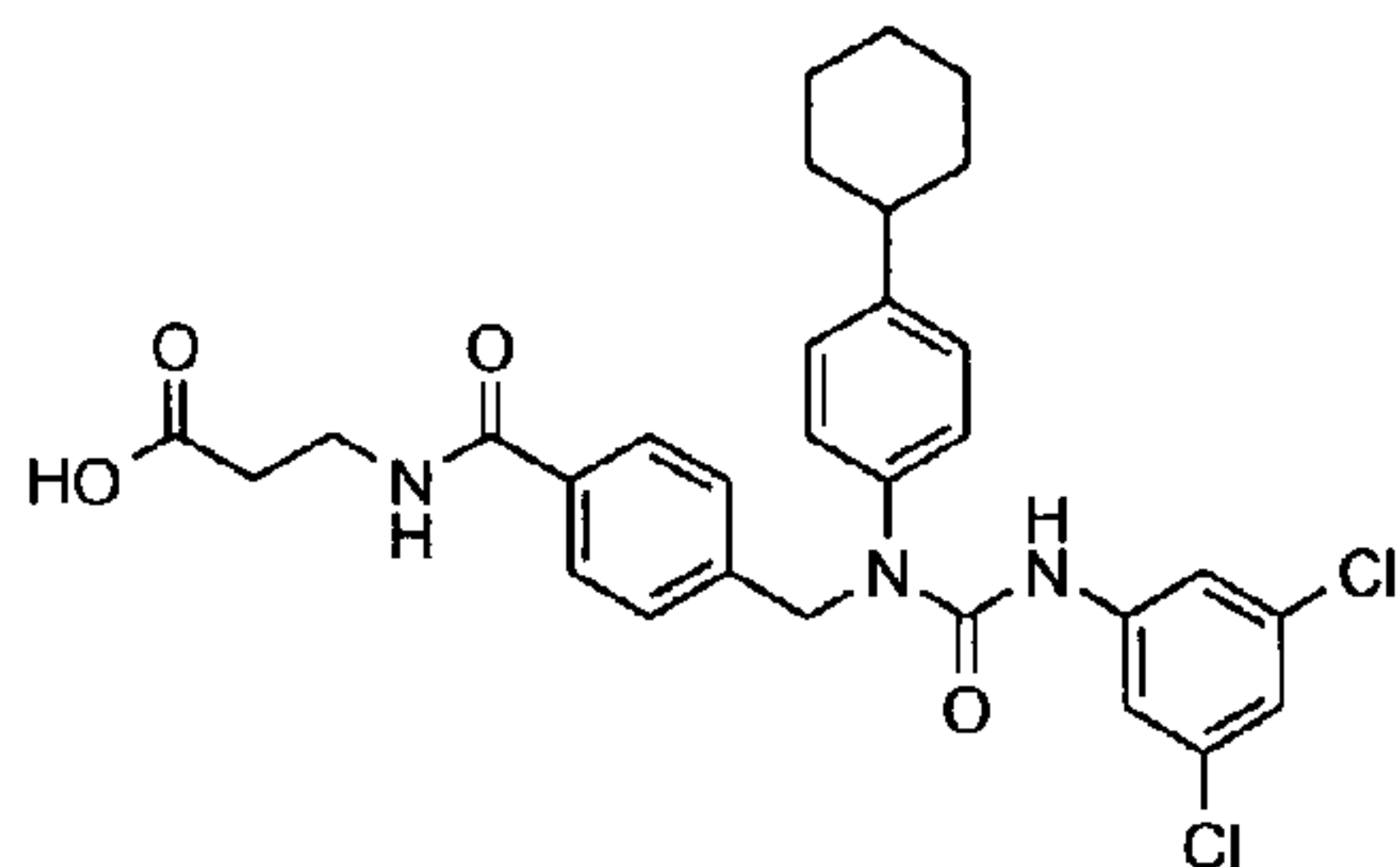


¹H NMR (DMSO-*d*₆): δ 1.36 – 1.50 (m, 2H), 2.36 (m, 1H), 2.45 (t, 2H), 2.79 (quintet, 1H), 3.43 (qt, 2H), 4.54 (d, 1H), 4.75 (d, 1H), 7.06 (d, 2H), 7.16 (t, 1H), 7.23 – 7.30 (m, 6H), 7.58 (d, 2H), 7.74 (d, 2H), 8.46 (s, 1H), 8.48 (t, 1H), 12.20 (brd s, 1H).

15 MS (APCI, pos): 542.2, 543.2, 544.2, 339.1.

EXAMPLE 232 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}propionic acid



¹H NMR (DMSO-*d*₆): δ 1.10 – 1.42 (m, 5H), 1.60 – 1.80 (m, 5H), 2.45 (t, 2H), 3.43 (qt, 2H), 4.92 (s, 2H), 7.12 – 7.20 (M, 5H), 7.30 (d, 2H), 7.58 (s, 2H), 7.74 (d, 2H), 8.46 (t, 1H), 8.55 (s, 1H).

MS (APCI, pos): 568.2, 569.2, 570.2, 571.2.

Alternative method for the preparation of the compound:

To a solution of 4-formylbenzoic acid (27.4 g, 0.18 mol) in DMF (300 mL) was added *N*-ethyl-
5 *N'*-3-dimethylaminopropylcarbodiimide (34.5 g, 0.18 mol) and *N*-hydroxybenzotriazole (29.9
g, 0.22 mol). The resulting mixture was stirred at room temperature for 1 hour, then β -alanine
ethyl ester hydrochloride (65.4 g, 0.42 mol) and diisopropylethylamine (76 mL, 0.44 mol) was
added. After 16 hours stirring at ambient temperature the reaction mixture was partitioned
10 between water (600 mL) and ethyl acetate (600 mL). The organic phase was washed suc-
cessively with hydrochloric acid (1N, 300 mL), saturated aqueous ammonium chloride (300
mL), water (2 x 300 mL) and brine (300 mL). The solvent was removed by rotary evaporation
to leave an oil, which crystallised upon standing to afford 29.0 g (65%) of 3-(4-
formylbenzoylamino)propionic acid ethyl ester.

15 ^1H NMR (DMSO- d_6): δ 1.18 (t, 3H); 2.62 (t, 2H); 3.54 (q, 2H); 4.09 (q, 2H); 8.00 (s, 4H); 8.78
(t, 1H); 10.08 (s, 1H).

To a well stirred solution of 3-(4-formylbenzoylamino)propionic acid ethyl ester (13.8 g, 55.3
mmol) in ethanol (150 mL) was added a solution of 4-cyclohexylaniline (9.70 g, 55.3 mmol) in
20 ethanol (75 mL). The mixture was heated to reflux for 30 minutes, and then acetic acid (50
mL) and sodium cyanoborohydride (3.50 g, 55.5 mmol) were added. After 10 minutes of ad-
ditional heating, the mixture was cooled on an ice-bath. The solid precipitate was collected
by filtration, washed several times with cold water and dried in a vacuum oven overnight to
afford 18.16 g (80%) of 3-{4-[(4-cyclohexylphenylamino)methyl]benzoylamino}propionic acid
25 ethyl ester.

^1H NMR (CDCl₃): δ 1.28 (t, 3H); 1.35 (m, 5H); 1.78 (m, 5H); 2.38 (m, 1H); 2.64 (t, 2H); 3.74
(q, 2H); 4.18 (q, 2H); 4.36 (s, 2H); 6.53 (d, 2H); 6.81 (bt, 1H); 7.00 (d, 2H); 7.43 (d, 2H); 7.72
(d, 2H).

30 3-{4-[(4-Cyclohexylphenylamino)methyl]benzoylamino}propionic acid ethyl ester (15.0 g, 0.37
mol) was dissolved in dichloromethane (250 mL), and 3,5-dichlorophenylisocyanate (6.9 g,
0.37 mol) was added. The mixture was stirred overnight at room temperature. The solvent
was removed by rotary evaporation, and the crystalline residue was re-dissolved in ethanol
35 (400 mL). Sodium hydroxide (100 mL, 4N) was added, and the reaction mixture was left at

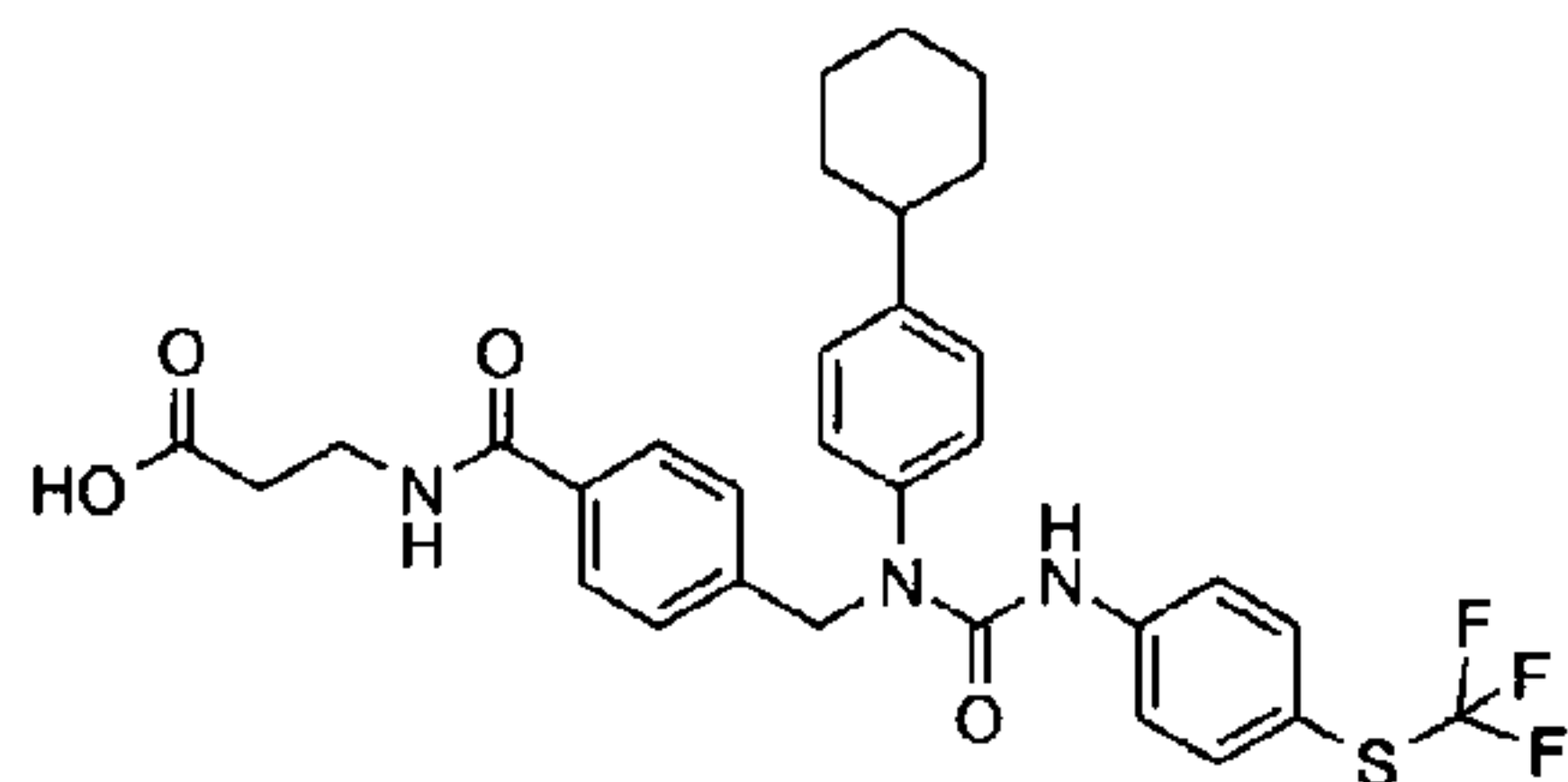
room temperature for 30 min. Water (600 mL) was added and the mixture was cooled on an ice bath. The clear solution was then acidified with hydrochloric acid (100 mL, 4N), and the resulting precipitate subsequently collected by filtration. Recrystallisation from acetonitrile / water afforded 15.5 g of the title compound as a white powder.

5

^1H NMR (DMSO- d_6): δ 1.36 (m, 5H); 1.78 (m, 6H); 2.50 (t, 2H); 3.44 (q, 2H); 4.92 (s, 2H); 7.12 (d, 1H); 7.16 (d, 2H); 7.21 (d, 2H); 7.32 (d, 2H); 7.60 (d, 2H); 7.75 (d, 2H); 8.45 (t, 1H); 8.53 (s, 1H); 12.20 (bs, 1H).

10 EXAMPLE 233 (general procedure (J))

3-{4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethylsulfanylphenyl)-ureidomethyl]benzoylamino}-propionic acid



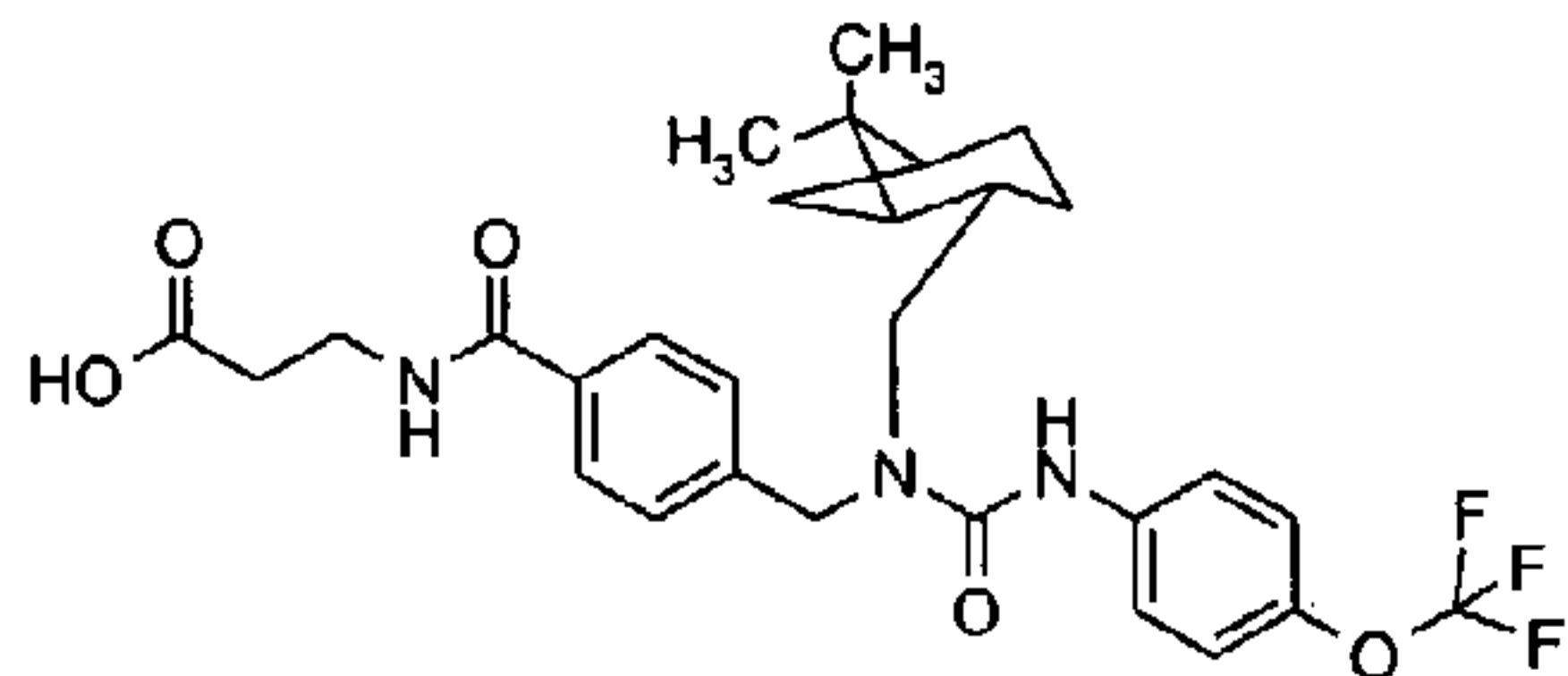
15 ^1H NMR (DMSO- d_6): δ 1.10 – 1.35 (m, 5H), 1.50 – 1.75 (m, 5H), 2.40 (m, 1H), 2.47 (t, 2H), 3.45 (t, 2H), 4.81 (s, 2H), 6.98 (d, 2H), 7.10 (d, 2H), 7.21 (d, 2H), 7.33 (d, 2H), 7.36 (d, 2H), 7.57 (d, 2H).

MS (APCI, pos): 600.2, 601.2, 602.2.

20

EXAMPLE 234 (general procedure (J))

3-{4-[1-([(1S,2R,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}propionic acid



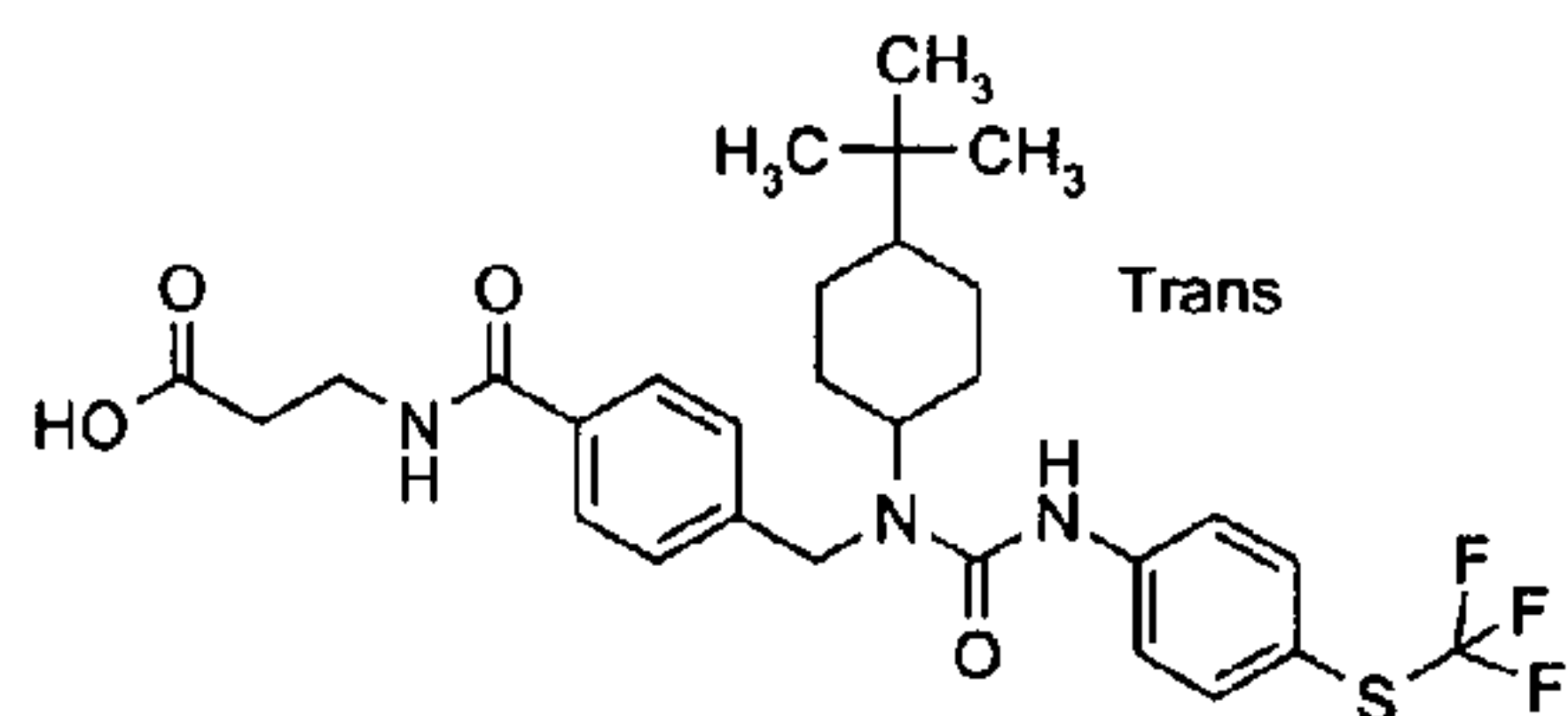
25

^1H NMR ($\text{MeOH-}d_4$): δ 0.90 (d, 1H), 1.05 (s, 3H), 1.15 (s, 3H), 1.49 (m, 1H), 1.80 - 1.95 (m, 5H), 2.36 - 2.47 (m, 2H), 2.62 (t, 2H), 3.40 (d, 2H), 3.61 (t, 2H), 4.70 (qt, 2H), 7.16 (d, 2H), 7.35 (d, 2H), 7.41 (d, 2H), 7.78 (d, 2H).

5 MS (APCI, pos): 562.2, 563.1.

EXAMPLE 235 (general procedure (J))

3-(4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-(trifluoromethoxysulfonylphenyl)ureidomethyl]-benzoylamino}propionic acid

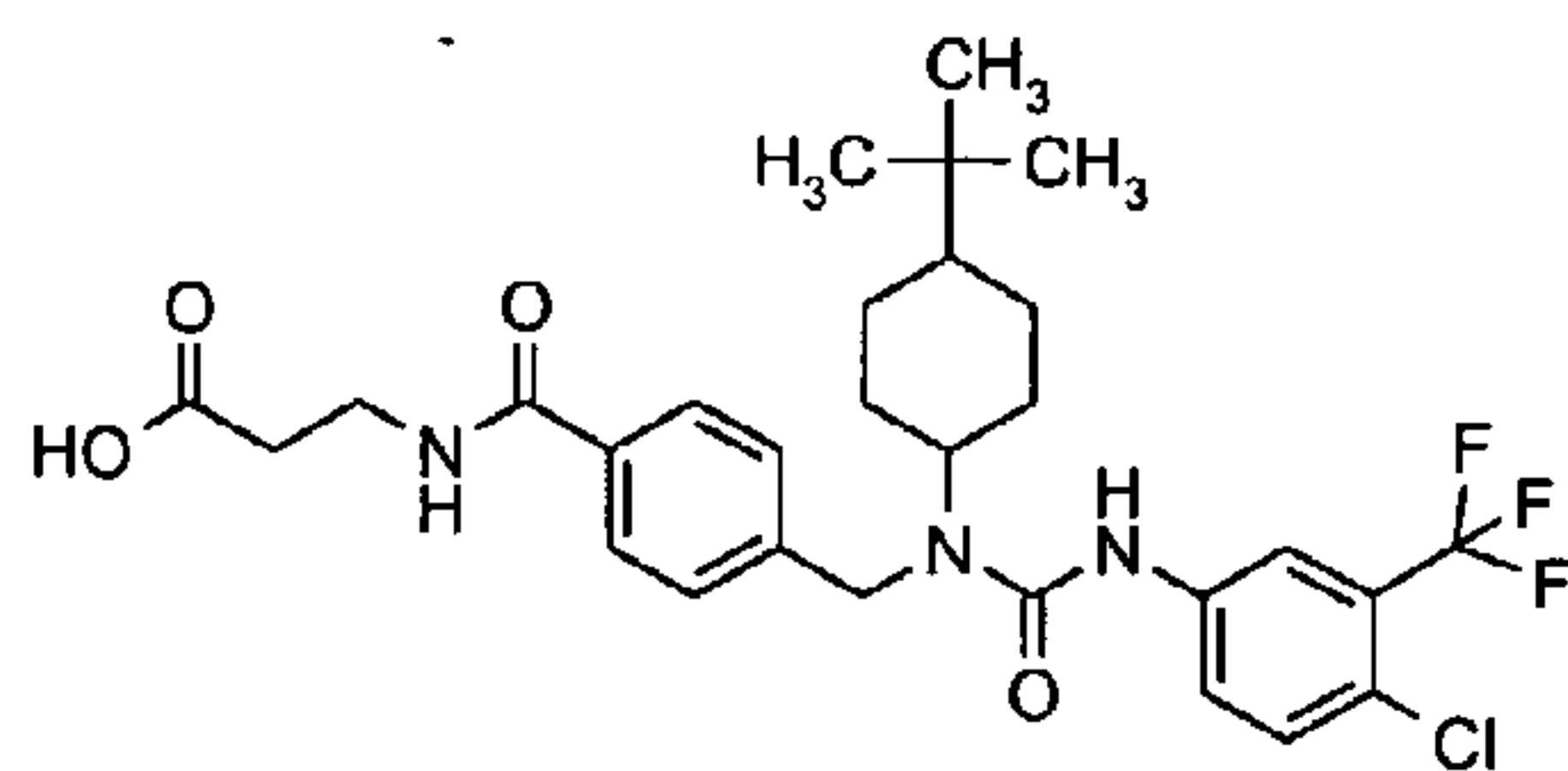


^1H NMR (CDCl_3): δ 0.80 (s, 9H), 0.90 (d, 1H), 1.20 (qt, 2H), 1.40 (qt, 2H), 1.90 (t, 4H), 2.75 (t, 2H), 3.70 (qt, 2H), 4.10 (brd t, 1H), 4.50 (s, 2H), 6.50 (s, 1H), 6.90 (t, 1H), 7.20 (d, 2H), 7.40 (d, 2H), 7.50 (d, 2H), 7.70 (d, 2H).

15 MS (APCI, pos): 580.2, 581.2.

EXAMPLE 236 (general procedure (J))

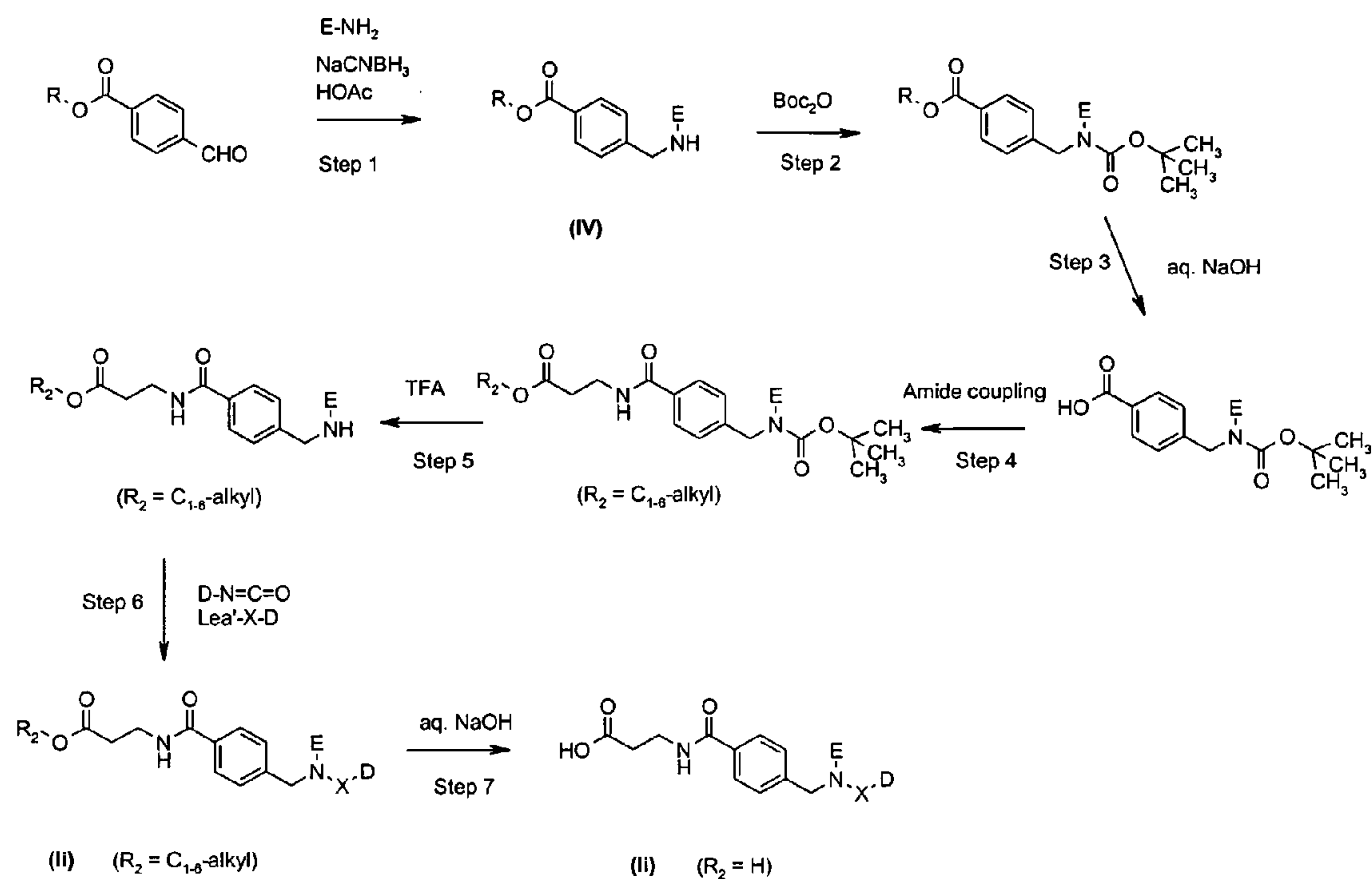
3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(4-chloro-3-trifluoromethylphenyl)ureidomethyl]benzoyl-amino}propionic acid



^1H NMR ($\text{DMSO-}d_6$): δ 0.78 (s, 9H), 1.10 (m, 1H), 1.33 (m, 2H), 1.50 (m, 4H), 1.75 (m, 2H), 2.40 (t, 2H), 3.43 (qt, 2H), 4.24 (quintet, 1H), 4.69 (s, 2H), 7.27 (d, 2H), 7.53 (d, 1H), 7.74 - 7.79 (m, 3H), 8.03 (s, 1H), 8.45 (t, 1H), 8.85 (s, 1H); 12.00 (brd s, 1H).

25 MS (APCI, pos): 582.2, 361.2.

General procedure (K) for the solution phase synthesis of compounds of the general formula (II):



5

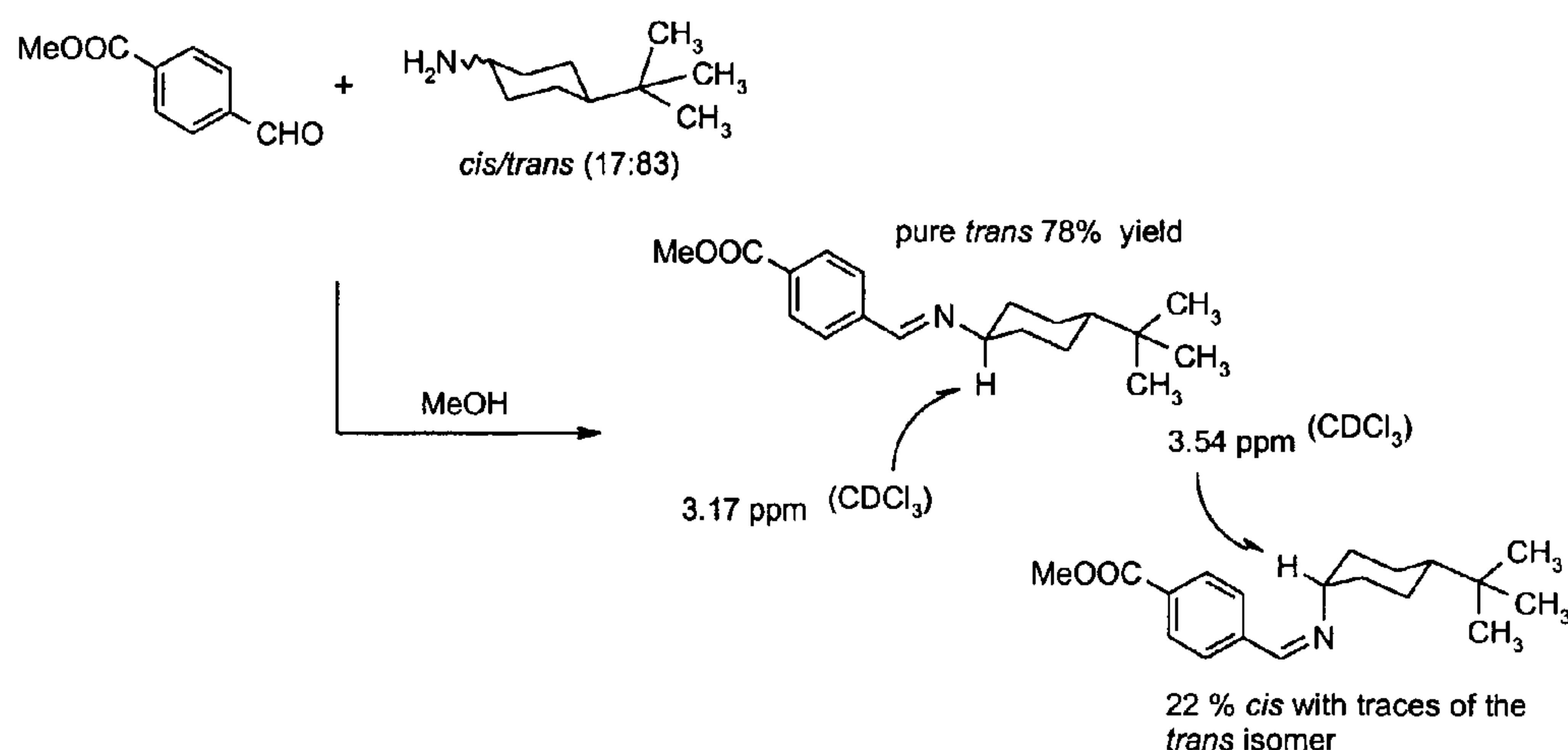
wherein R is C_{1-6} -alkyl,

V, X, D, and E are as defined in general formula (I), and

10 Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

In case the intermediate of the formula (IV) is a mixture of isomers, separation of these can either be performed by column chromatography of the intermediate of the formula (IV) or crystallisation of the intermediate imine.

15

Step 1: *trans*-4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester

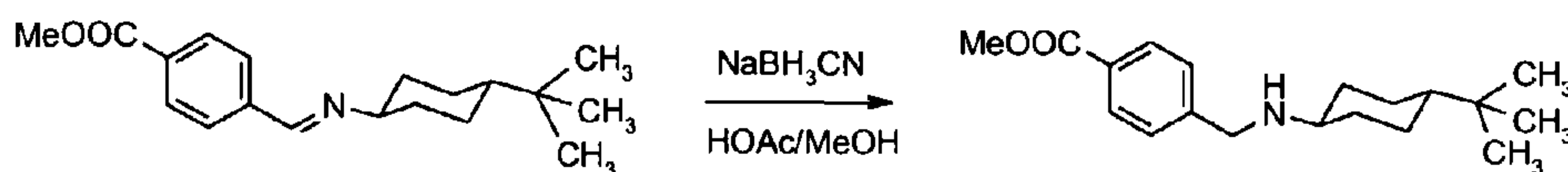
- 5 4-Formylbenzoic acid methyl ester (10.6 g, 64.4 mmol) was dissolved in methanol (200 mL). A 17:83 *cis/trans* mixture of 4-*tert*-butylcyclohexylamine (10.0 g, 64.4 mmol, Aldrich) was added, leading to immediate precipitation of white crystals. The mixture was heated to reflux for 30 min to complete imine formation, then cooled to 0°C on an ice bath. The crystalline pure *trans*-4-[(4-*tert*-butylcyclohexylimino)methyl]benzoic acid methyl ester was then collected by filtration, and dried overnight in vacuo. Yield: 15.3 g (78%).
- 10

¹H NMR (CDCl₃), 300 MHz: δ 8.37 ppm. (s, 1H); 8.06 (d, 2H); 7.77 (d, 2H); 3.92 (s, 3H); 3.17 (m, 1H); 1.83 (m, 4H); 1.60 (m, 2H), 1.09 (m, 3H); 0.87 (s, 9H).

- 15 Micro Analysis: Calculated for C₁₉H₂₇NO₂
C: 75.71%, H: 9.03%, N: 4.65%. Found:
C: 75.60%, H: 9.37%, N: 4.68%.

- The mother liquid was taken to dryness to leave 4.2 g (22%) white solid, which according to
- 20 NMR consisted mainly of the imino *cis* isomer.

¹H NMR (CDCl₃), 300 MHz: δ 8.36 ppm. (s, 1H); 8.07 (d, 2H); 7.81 (d, 2H); 3.92 (s, 3H); 3.54 (m, 1H); 1.55 - 1.92 (m, 8H); 1.14 (m, 1H); 0.90 (s, 9H).



5 *trans*-4-[(4-*tert*-Butylcyclohexylimino)methyl]benzoic acid methyl ester (21.0 g, 69.2 mmol) was suspended in methanol (300 mL), and acetic acid (50 mL) was added. To the resulting clear solution was added sodium cyanoborohydride (3.5 g, 55.5 mmol), and the mixture was stirred at ambient temperature for 30 min. The reaction volume was then reduced to one third by rotary evaporation, and ethyl acetate (500 mL) was added. The organic phase was washed with sodium carbonate solution (5%, 500 mL), and dried with Na₂SO₄. The solvent was removed by rotary evaporation to leave the title material as a white crystalline solid sufficiently pure for further reactions. Yield: 21.1 g (100%).

¹H NMR (CDCl₃), 300 MHz: δ 7.98 ppm. (d, 2H); 7.38 (d, 2H); 3.90 (s, 3H); 3.86 (s, 2H); 2.39 (m, 1H); 2.01 (m, 2H); 1.77 (m, 2H); 1.51 (bs, 1H); 0.93-1.18 (m, 5H); 0.82 (s, 9H).

15 HPLC-MS (Method B: R_t = 4.87 m/z = 304 (M + 1).

Alternatively, step 1 can be performed in the same way as step A of the general procedure (F).

20 Step 2: *trans*-4-[[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]benzoic acid methyl ester

25 *trans*-4-[(4-*tert*-Butylcyclohexylamino)methyl]benzoic acid methyl ester (20.0 g, 65.9 mmol) was dissolved in THF (300 mL). Di-*tert*-butylpyrocarbonate (16.0 g, 73.4 mmol) and diisopropylethylamine (12.0 g, 92.9 mmol) was added and the clear solution stirred overnight at ambient temperature. Solvent was removed by rotary evaporation.

Step 3: *trans*-4-[[*N*-(*tert*-Butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]benzoic acid

30 The crystalline residue from step 2 was re-dissolved in ethanol (200 mL) and aqueous sodium hydroxide solution (100 mL, 4N) was added whereafter the mixture was heated to 70°C for 4 hours. After cooling, the reaction volume was reduced to one third by rotary evaporation, and water (300 mL) was added. The mixture was extracted with diethyl ether (2 x 200 mL) to remove traces of non-hydrolysed material. The aqueous phase was then acidified to pH 3.0 by addition of aqueous 4N HCl, whereupon the title material separated out of solution

as compact crystals. The crystals were washed once with water and dried overnight in a vacuum oven (40°C). Yield: 24.3 g (93%).

¹H NMR (CDCl₃), 300 MHz: δ 8.04 ppm. (d, 2H); 7.31 (d, 2H); 4.39 (bs, 2H); 4.05 (bs, 1H); 1.78 (bd, 4H); 0.95-1.65 (m, 14 H); 0.83 (s, 9H). The signals were broad due to the presence of *cis/trans* carbamate isomers.

Micro analysis Calculated for C₂₃H₃₅NO₄:

C, 70.92%; H, 9.06%; N, 3.60%. Found:

C, 70.67%; H, 9.36%; N: 3.57%.

Step 4: Methyl *trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl]-benzoylaminopropanoate

Trans-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl}benzoic acid (22.0 g, 56.5 mmol) and 1-hydroxybenzotriazole (8.6 g, 57.0 mmol, containing 12% w/w water) was dissolved in DMF (300 mL). *N*-Dimethylaminopropyl-*N'*-ethylcarbodiimide hydrochloride (10.9 g, 56.8 mmol), β-alanine methyl ester (8.4 g, 60 mmol) and diisopropylethylamine (25 mL, 142 mmol) were added and the clear solution stirred at 20°C for 16 hours. Solvent was removed by rotary evaporation and the residual oil re-dissolved in ethyl acetate (500 mL).

The organic phase was washed with 5% aqueous sodium hydrogen carbonate solution (2 x 500 mL), 0.5 M citric acid (2 x 250 mL) and brine before being dried with anhydrous Na₂SO₄. Solvent was removed and the residual oil evaporated twice from acetonitrile. The oil was used without further purification. Yield: 24.0 g (89%).

¹H NMR (CDCl₃), 300 MHz: δ 7.69 (d, 2H); 7.28 (d, 2H); 6.81 (t, 1H); 4.38 (bs, 2H); 3.23 (s, 3H); 3.21 (t, 2H); 2.66 (t, 2H); 1.75 (bd, 4H); 0.95-1.65 (m, 14 H); 0.80 (s, 9H).

Step 5: Methyl *trans*-4-{*N*-(4-*tert*-butylcyclohexyl)aminomethyl}benzoylaminopropanoate tri-fluoroacetate

Methyl *trans*-4-[[*N*-(*tert*-butoxycarbonyl)-*N*-(4-*tert*-butylcyclohexyl)amino]methyl}benzoylaminopropanoate (19.5 g, 41.1 mmol) was dissolved in a mixture of TFA (200 mL) and dichloromethane (200 mL), while cooling on an ice bath. The ice bath was removed and the mixture allowed to stir at room temperature for 30 min. Solvent was removed by rotary evaporation, and the crystalline residue recrystallized from ethyl acetate/heptane. Yield: 14.8 g (74%).

^1H NMR (CDCl_3), 300 MHz: δ 9.98 (trace of TFA); 8.06 (bs, 2H); 7.73 (d, 2H); 7.41 (d, 2H); 7.34 (t, 1H); 4.21 (t, 2H); 3.75 (s, 3H); 3.74 (t, 2H); 3.04 (m, 1H); 2.70 (t, 2H); 2.17 (bd, 2H); 1.95 (bd, 2H); 1.50 (m, 2H); 0.92-1.15 (m, 3H); 0.85 (s, 9H).

5

Micro analysis. Calculated for $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_3 \cdot \text{C}_2\text{HF}_3\text{O}_2$:

C, 59.00%; H, 7.22%; N, 5.73%. Found:

C, 58.95%; H, 7.37%; N: 5.70%.

10 General procedure for forming isocyanates from (substituted) anilines and diphosgene to be used in step 6:

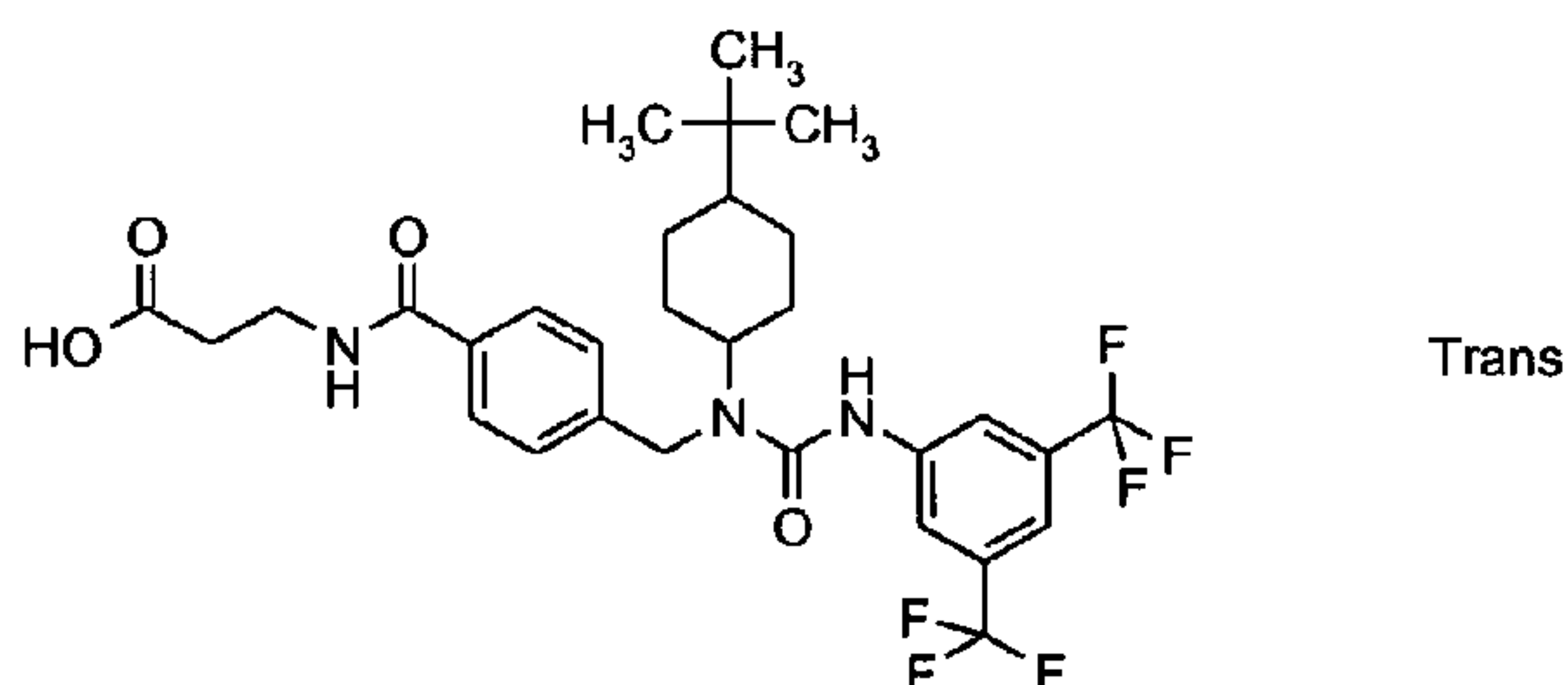
To a solution of the amine in anhydrous toluene was added 1N HCl in diethyl ether (5 eq). A precipitate formed. The toluene was evaporated. To the solid was added more anhydrous toluene and the toluene was evaporated again to remove excess HCl. This procedure was repeated 2-3 times. To a mixture of the solid in toluene (about 10 g in 300 mL) was added diphosgene (trichloromethyl chloroformate) (10 eq or more) or phosgene. The mixture was refluxed under nitrogen overnight. A clear solution was obtained. If more solid was present, more diphosgene was added and reflux continued. When a clear solution was obtained, the reaction was concentrated in vacuo at 60-90°C to remove the toluene and excess diphos-
 15 gene until the theoretical weight was obtained. To the crude isocyanate was added more an-
 20 hydrous toluene and concentrated again to remove excess HCl. The crude isocyanate was used without further purification.

This method gives the isocyanates in pure form, which may be used in step 6.

25

EXAMPLE 237 (general procedure (K))

3-{4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]benzoyl-
 amino}propionic acid



30

Step 6, using a phenyl carbamate or nitrophenyl carbamate

3,5-Bis-(trifluoromethyl)aniline (2.0 g, 8.7 mmol) was dissolved in dichloromethane (80 mL) and *N,N*-diisopropylethylamine (1.6 mL, 9.6 mmol) was added followed by slow addition of phenyl chloroformate (1.1 mL, 8.7 mmol). The resulting mixture was stirred at room temperature for 16 hours. The mixture was successively washed with 1N hydrochloric acid (3 x 100 mL), water (3 x 100 mL), a mixture of water and saturated aqueous sodium hydrogen carbonate (1:1, 2 x 100 mL) and a mixture of water and saturated aqueous sodium chloride (1:1, 3 x 100 mL), dried (MgSO₄) and concentrated in vacuo. The residue was crystallised from heptane containing a little diethyl ether to afford 1.3 g (43%) of (3,5-bis-trifluoromethyl-phenyl)carbamic acid phenyl ester as a solid.

Calculated for C₁₅H₉F₆NO₂:

C, 51.59%; H, 2.60%; N, 4.01%. Found:

C, 51.27%; H, 2.56%; N, 4.01%;

C, 51.40%; H, 2.57%; N, 3.92%.

The above carbamic acid phenyl ester (1.0 g, 2.9 mmol) was mixed with 3-{4-[(4-*tert*-butyl-cyclohexylamino)methyl]benzoylamino}propionic acid methyl ester, trifluoroacetate (1.07 g, 2.9 mmol), prepared as described above and triethylamine (1.2 mL, 8.6 mmol) in dichloromethane (55 mL) and the resulting mixture was refluxed for 4 hours. The cooled reaction mixture was diluted with toluene (50 mL) and washed with water (3 x 50 mL) and a mixture of water and saturated aqueous sodium chloride (1:1, 3 x 100 mL), dried (MgSO₄) and concentrated in vacuo to afford 1.2 g (67%) of 3-{4-[3-(3,5-bis-trifluoromethylphenyl)-1-(4-*tert*-butyl-cyclohexyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

¹H NMR (CDCl₃): δ 0.83 (9H, s), 0.9-1.5 (5H, m), 1.88 (4H, bt), 7.62 (H, t), 3.72 (5H, m), 4.18 (1H, bt), 4.57 (2H, s), 6.80 (1H, s), 6.90 (1H, t), 7.38 (2H, d), 7.46 (1H, s), 7.77 (2H, d), 7.80 (2H, s).

HPLC-MS (Method B): R_t = 9.07 min, m/z = 630 (M + 1).

Step 7:

The above propionic acid methyl ester (1.0 g, 1.6 mmol) was dissolved in warm ethanol (50 mL), and after cooling to room temperature 4N aqueous sodium hydroxide (6 mL) was added. The reaction mixture was stirred at room temperature for 1 hour. Glacial acetic acid

(10 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned between water (50 mL) and ethyl acetate (2 x 50 mL). The combined organic phases were dried (MgSO₄) and concentrated in vacuo to afford 0.88 g (93%) of the title compound as a solid.

5

¹H NMR (DMSO-*d*₆): δ 0.83 (9H, s), 0.9-1.5 (5H, m), 1.70 (4H, bt), 2.50 (2H, t, below DMSO), 3.45 (2H, q, below water), 4.05 (1H, bt), 4.62 (2H, s), 7.32 (2H, d), 7.60 (2H, d), 8.24 (2H, s), 8.45 (1H, t), 9.00 (1H, s), 12 (1H, bs).

10 HPLC-MS (Method B): R_t = 8.60 min, m/z = 616 (M + 1).

Calculated for C₃₀H₃₅F₆N₃O₄ x 0.25H₂O:

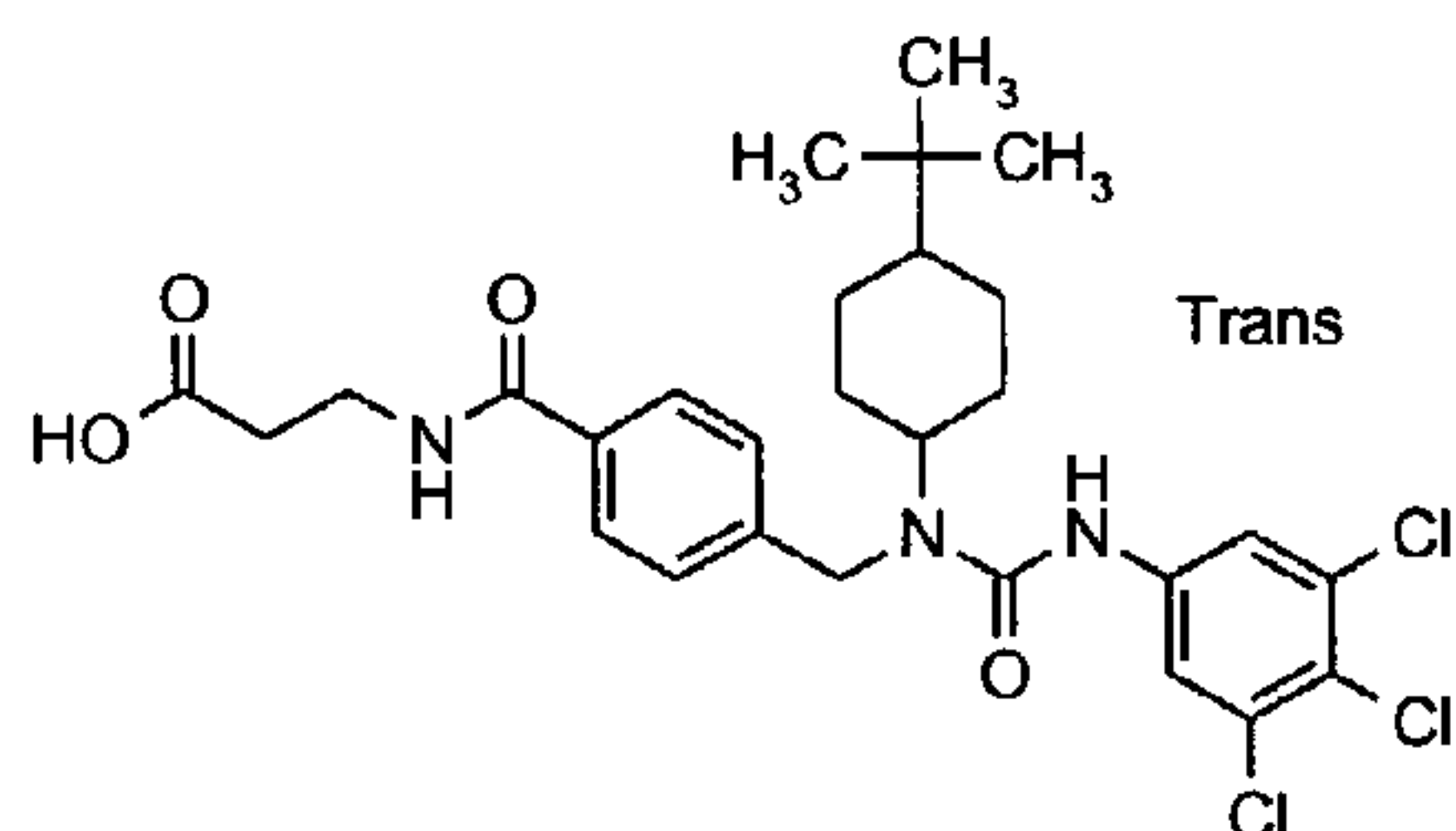
C, 57.47%; H, 5.57%; N, 6.93%. Found:

C, 57.60%; H, 5.81%; N, 6.47%;

15 C, 57.63%; H, 5.76%; N, 6.45%.

EXAMPLE 238 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,4,5-trichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



20

Step 6, using isocyanate formed in situ from (substituted) anilines and triphosgene:

Triphosgene (bis-trichloromethylcarbonate) (152 mg, 0.51 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0°C. To this solution a solution of 3,4,5-trichloroaniline (303 mg, 1.54 mmol) and diisopropylethylamine (540 μL, 3.1 mmol) in dichloromethane (3 mL)

25

was added at 0°C over 1 hour. The mixture was then allowed to reach room temperature. To this mixture a solution of methyl *trans*-4-[(4-*tert*-butylcyclohexyl)aminomethyl]benzoylamino-propionate trifluoroacetate (576 mg, 1.54 mmol) and diisopropylethylamine (800 μL) in dichloromethane (10 mL) was added and stirring at room temperature was continued for 30

30

minutes. The mixture was diluted with more dichloromethane (10 mL) and washed with satu-

rated aqueous citric acid (2 x 20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford 653 mg (71%) of 3-{4-[1-(4-*trans-tert*-butylcyclohexyl)-3-(3,4,5-trichlorophenyl)ureidomethyl]benzoylamino}propionic acid methyl ester as a solid.

- 5 ^1H NMR ($\text{DMSO}-d_6$): δ 0.81 (s, 9H), 0.92 (m, 1H), 1.12 (m, 2H), 1.44 (m, 2H), 1.68 (m, 4H), 2.56 (t, 2H), 3.45 (q, 2H), 3.59 (s, 3H), 4.05 (b t, 1H), 4.58 (s, 2H), 7.30 (d, 2H), 7.78 (d, 2H), 7.83 (s, 2H), 8.44 (t, 1H), 8.75 (s, 1H).

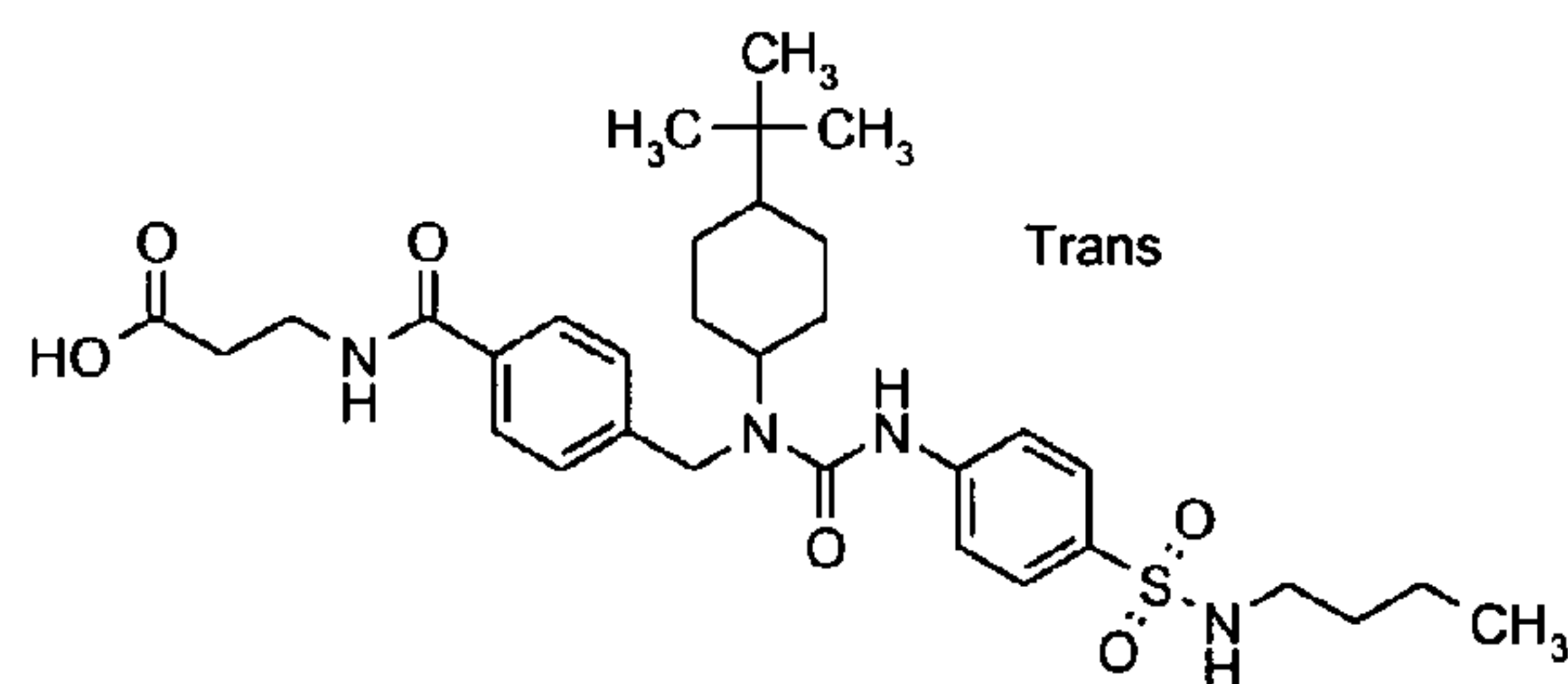
Step 7:

- 10 Hydrolysis of this ester using the method described in example 92, step D afforded the title compound (495 mg, 78%).

- ^1H NMR ($\text{DMSO}-d_6$): δ 0.82 (s, 9H), 0.91 (m, 1H), 1.10 (m, 2H), 1.39 (m, 2H), 1.71 (m, 4H), 2.51 (t, 2H), 3.35 (q, 2H), 4.01 (t, 1H), 4.59 (s, 2H), 7.30 (d, 2H), 7.78 (d, 2H), 7.85 (s, 2H),
15 8.46 (t, 1H), 8.76 (s, 1H), 12.21 (b s, 1H).

EXAMPLE 239 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-butylsulfamoylphenyl)ureidomethyl]benzoylamino}-propionic acid



- 4-Nitrophenylsulfonyl chloride (3.0 g, 13.5 mmol) was dissolved in THF and a catalytic amount of 4-dimethylaminopyridine and 1-butylamine (4.0 mL, 41 mmol) was added and the mixture was refluxed for 16 hours. The mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL) and a 10% aqueous solution of sodium hydrogen carbonate (50 mL). The organic phase was dried (MgSO_4) and concentrated in vacuo to afford 3.01 g (86%) of *N*-butyl-4-nitrobenzenesulfonamide as a solid.

¹H NMR (CDCl₃): δ 0.89 (3H, t), 1.30 (2H, m), 1.48 (2H, m), 3.03 (2H, t), 4.9 (1H, b), 8.06 (2H, d), 8.37 (2H, d).

Sodium dithionite (11.4 g, 65 mmol) and sodium carbonate (5.6 g, 53 mmol) were dissolved
5 in water (65 mL) and heated to 70°C. A suspension of the above 4-nitrophenylsulfonamide
(2.64 g, 10.2 mmol) in methanol (65 mL) was added and the resulting mixture was stirred at
70°C for 1.5 hour. The cooled mixture was filtered and the volume of the filtrate was reduced
by 50% in vacuo. The aqueous mixture was extracted with ethyl acetate (3 x 60 mL), and the
combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford 0.14 g
10 (6%) of 4-amino-*N*-butylbenzenesulfonamide as a solid.

¹H NMR (DMSO-*d*₆): δ 0.80 (3H, t), 1.2-1.4 (4H, m), 2.65 (2H, q), 5.90 (2H, s), 6.60 (2H, d),
7.04 (1H, t), 7.40 (2H, d).

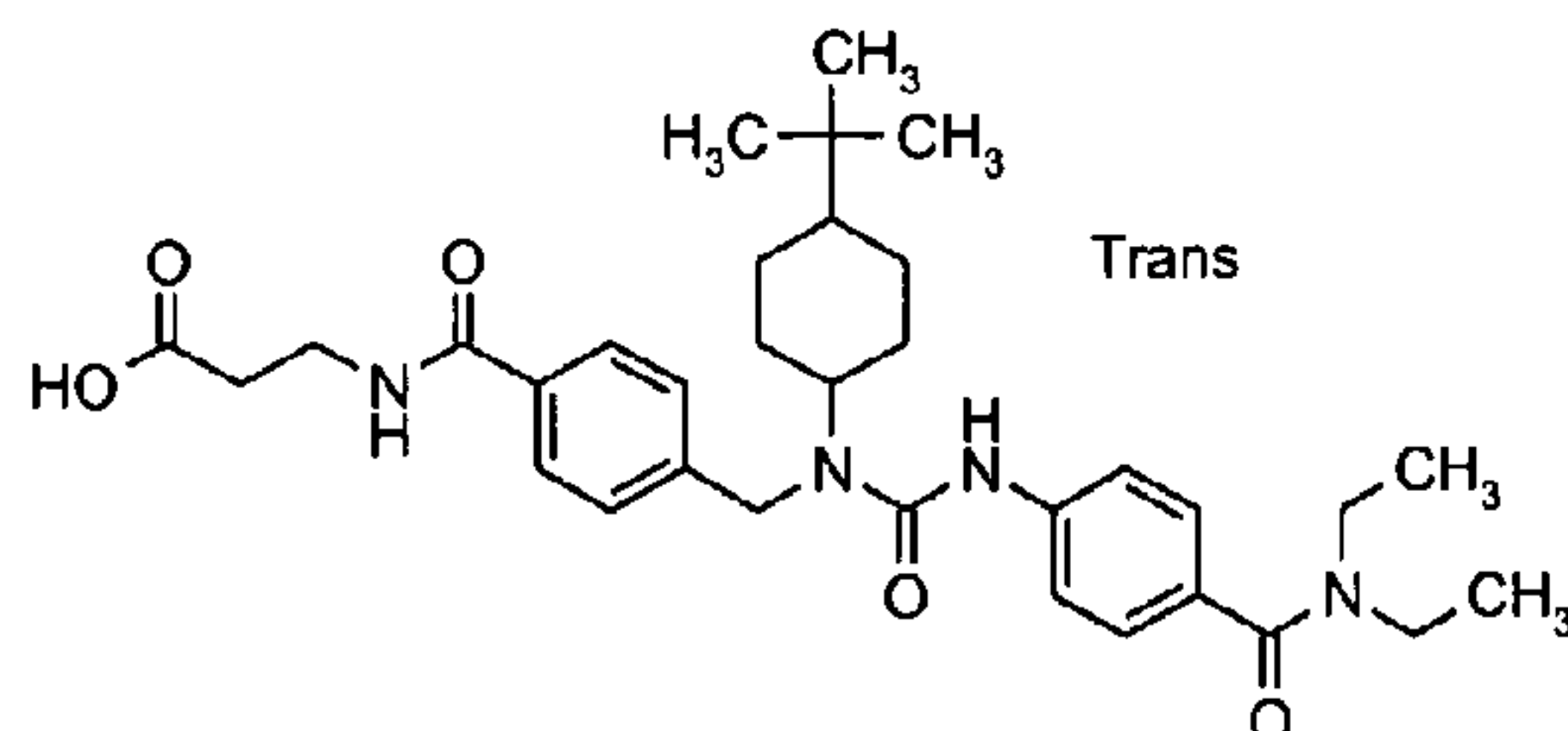
15 HPLC-MS (Method B): R_t = 5.15 min, m/z = 229 (M + 1).

The above 4-aminophenylsulfonamide (0.14 g) was dissolved in dichloromethane (6 mL),
N,N-diisopropylethylamine (172 μL, 1 mmol) and phenyl chloroformate (122 μL, 0.92 mmol)
and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture
20 was diluted with dichloromethane (50 mL) and was washed with 1N hydrochloric acid (3 x 20
mL), water (3 x 20 mL), a mixture of water and a saturated solution of sodium hydrogen car-
bonate (1:1, 2 x 20 mL) and a mixture of water and a saturated solution of sodium chloride
(1:1, 2 x 20 mL). Drying (MgSO₄) and concentration in vacuo afforded crude (4-butyl-
sulfamoylphenyl)carbamic acid phenyl ester.

25

From the above crude carbamic acid phenyl ester and 3-{4-[(4-*trans-tert*-butylcyclohexyl-
amino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate the title compound
was obtained similarly as described above.

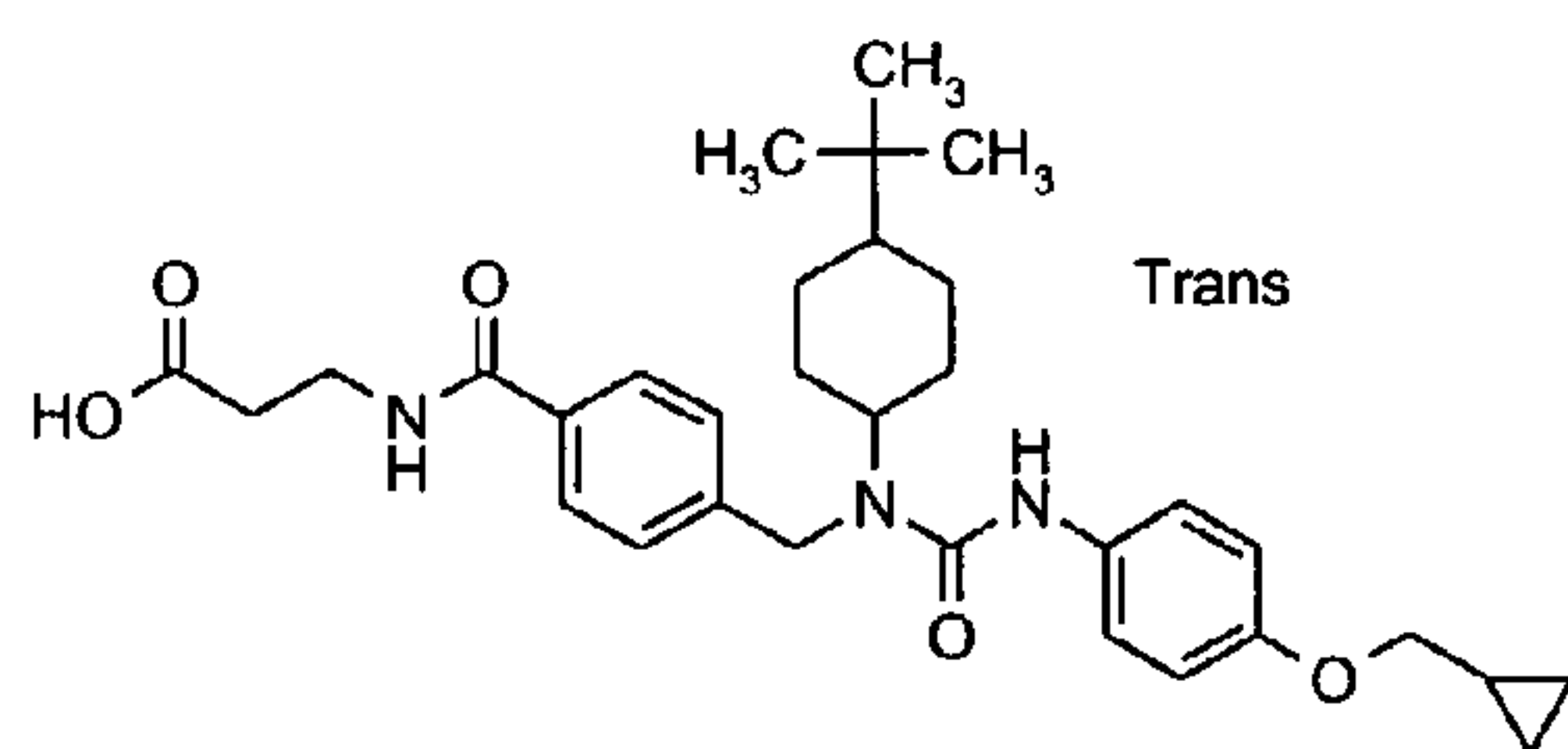
30 HPLC-MS (Method B): R_t = 7.37 min, m/z = 615 (M + 1).

EXAMPLE 240 (general procedure (K))3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-diethylcarbamoylphenyl)ureidomethyl]benzoyl-amino}propionic acid

5

The title compound was prepared similarly as described above starting from 4-nitrobenzoyl chloride, diethylamine and 3-{4-[(4-*trans*-*tert*-butylcyclohexylamino)methyl]benzoylamino}-propionic acid methyl ester trifluoroacetate.

10 HPLC-MS (Method B): R_t = 6.76 min, m/z = 579 ($M + 1$).

EXAMPLE 241 (general procedure (K))3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

15

4-Nitrophenol (2.0 g, 14.4 mmol) was dissolved in DMF (50 mL) and potassium carbonate (6.0 g, 43 mmol) and bromomethylcyclopropane (1.51 mL, 16 mmol) were added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous solution of sodium chloride (2 x 50 mL). Drying ($MgSO_4$) and concentration afforded 2.23 g (75%) of 1-cyclopropylmethoxy-4-nitrobenzene as an oil.

25 ^1H NMR ($CDCl_3$): δ 0.40 (2H, m), 0.58 (2H, m), 1.30 (1H, m), 3.89 (2H, d), 6.94 (2H, d), 8.12 (2H, d).

The above 4-nitrobenzene (2.0 g, 9.5 mmol) was dissolved in ethanol (50 mL) and tin(II) chloride dihydrate (10.7 g, 48 mmol) was added and the mixture was refluxed for 24 hours. After cooling, the mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (40 mL) and 1N aqueous sodium hydroxide (180 mL). This mixture was filtered through
 5 celite. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo to afford 0.88 g (52%) of 4-cyclopropylmethoxyaniline.

¹H NMR (DMSO-*d*₆): δ 0.25 (2H, m), 0.53 (2H, m), 1.15 (1H, m), 3.63 (2H, d), 4.55 (2H, s),
 10 6.4-6.5 (3H, m), 6.62 (2H, d).

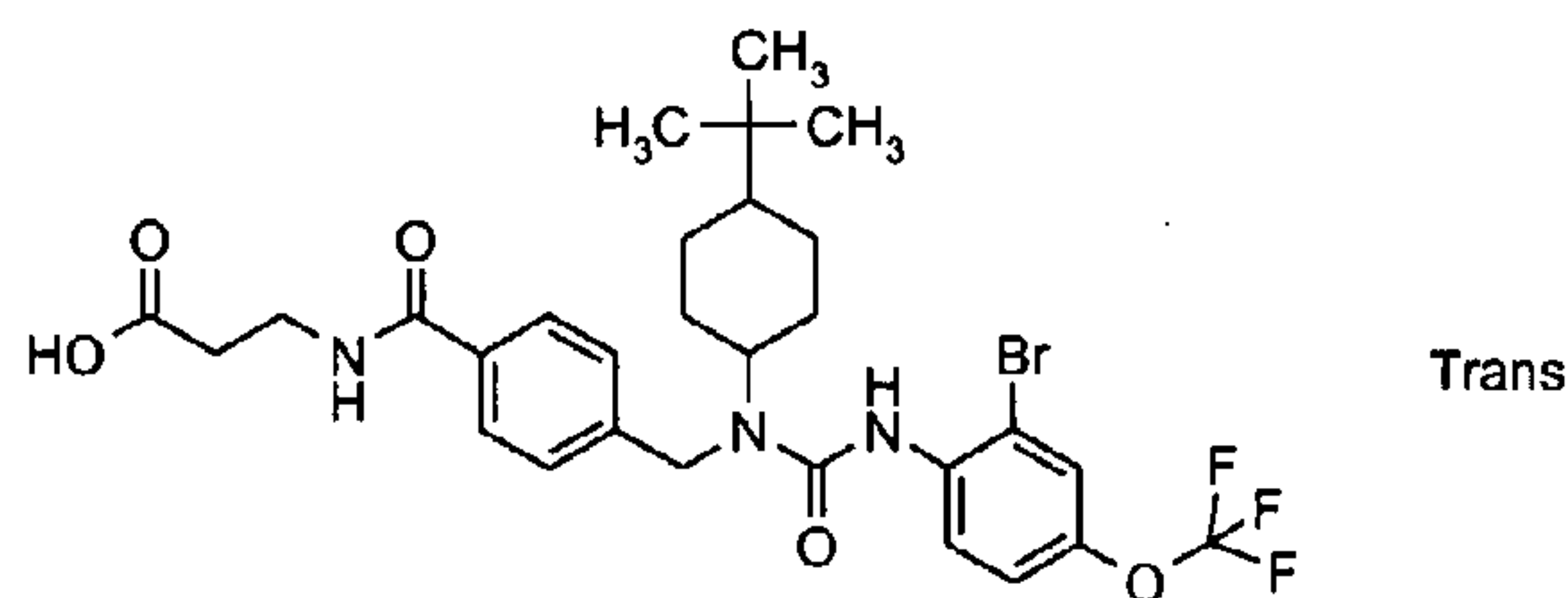
From the above aniline and 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}-propionic acid methyl ester trifluoroacetate the title compound was prepared similarly as described in example 238.

¹H NMR (DMSO-*d*₆): δ 0.42 (2H, m), 0.62 (2H, m), 0.85 (9H, s), 0.92 (1H, m), 1.1-1.4 (5H, m), 1.9 (4H, bt), 2.70 (4H, m), 4.14 (1H, t), 4.52 (2H, s), 6.08 (1H, s), 6.77 (2H, d), 6.88 (1H, t), 7.10 (2H, d), 7.40 (2H, d), 7.76 (2H, d).

HPLC-MS (Method B): R_t = 7.73 min, m/z = 550 (M + 1).

EXAMPLE 242 (general procedure (K))

3-{4-[3-(2-Bromo-4-trifluoromethoxyphenyl)-1-(*trans*-4-*tert*-butylcyclohexyl)ureidomethyl]-benzoylamino}propionic acid



4-Trifluoromethoxyaniline (1.0 g, 5.6 mmol) was dissolved in glacial acetic acid (10 mL). Bromine (585 μL, 11 mmol) dissolved in glacial acetic acid (2 mL) was added with stirring during 10 minutes at room temperature. The resulting mixture was stirred at room temperature for 2 hours and then poured into water (100 mL). The solid formed (2,5-dibromo-4-trifluoromethoxyaniline) was filtered off. The filtrate was made alkaline with solid sodium hy-
 30

dioxide and extracted with dichloromethane (100 mL), dried (MgSO₄) and concentrated (30°C; 200 mBar) to afford 0.57 g (40%) of 2-bromo-4-trifluoromethoxyaniline.

¹H NMR (DMSO-*d*₆): δ 5.55 (2H, bs), 6.85 (1H, d), 7.10 (1H, dd), 7.37 (1H, d).

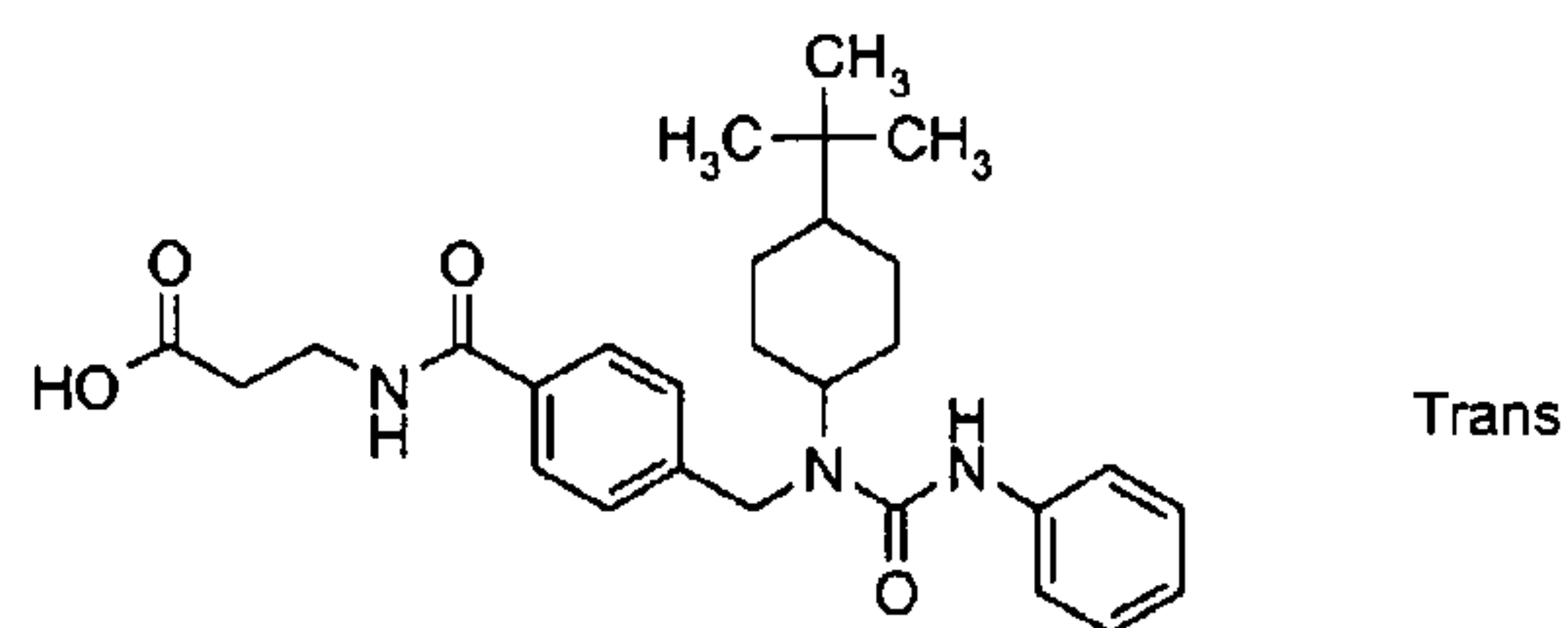
5

From the above 2-bromoaniline and 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate the title compound was prepared similarly as described in example 238.

10 ¹H NMR (DMSO-*d*₆): δ 0.86 (9H, s), 0.95 (1H, m), 1.2 (2H, m), 1.4 (2H, m), 1.9 (4H, m), 2.74 (2H, t), 3.75 (2H, q), 4.16 (1H, t), 4.60 (2H, s), 6.85 (1H, t), 6.88 (1H, s), 7.16 (1H, dd), 7.31 (1H, d), 7.43 (2H, d), 7.76 (2H, d), 8.26 (2H, d).

EXAMPLE 243 (general procedure (K))

15 3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-phenylureidomethyl]benzoylamino}propionic acid



From 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate and phenylisocyanate the title compound was prepared similarly as described in the alternative method for preparing example 92 according to the general procedure (K).

20

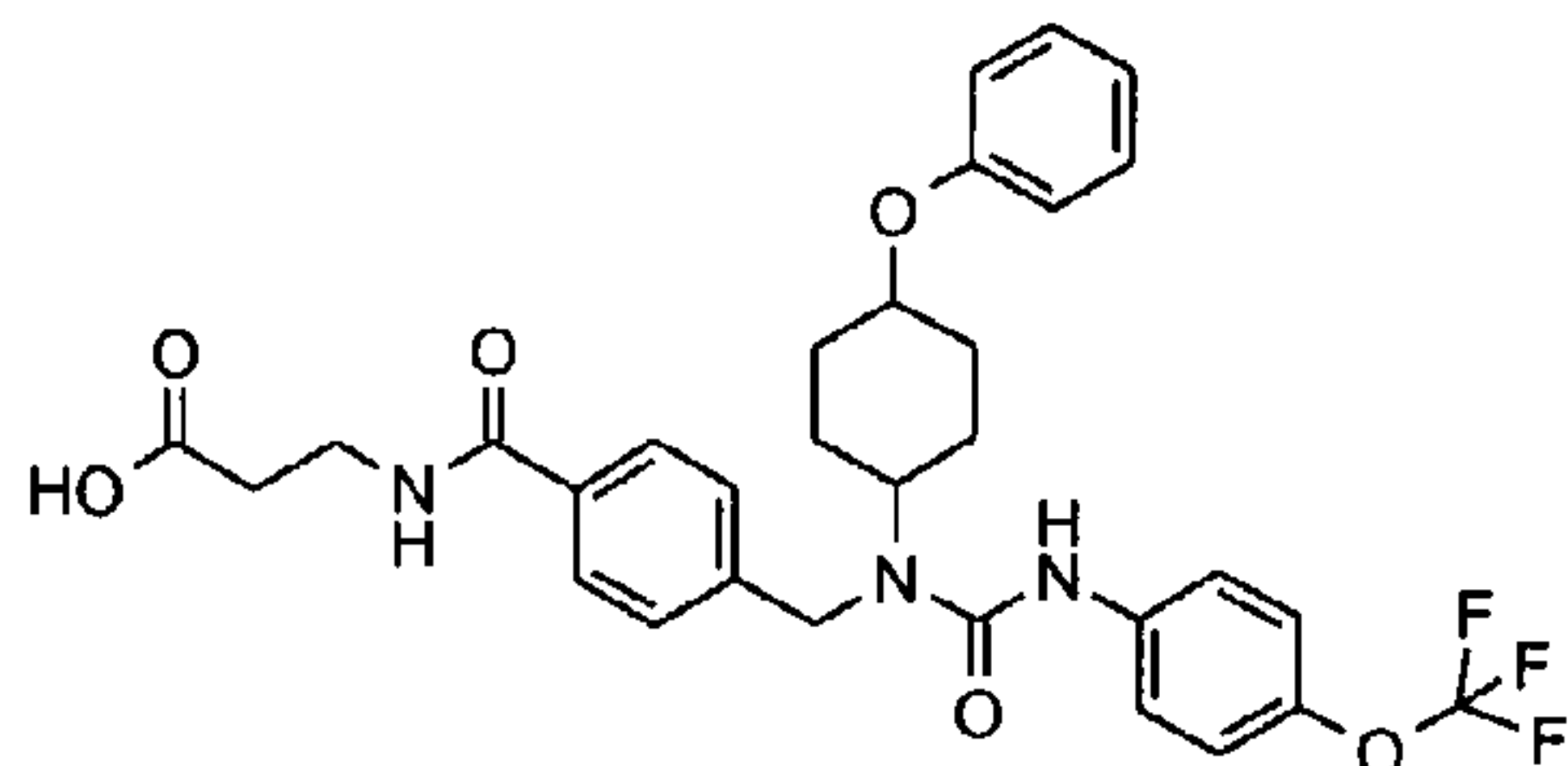
¹H NMR (DMSO-*d*₆): δ 0.84 (9H, s), 0.93 (1H, m), 1.2 (2H, m), 1.4 (2H, m), 1.85 (4H, m), 2.63 (2H, t), 3.70 (2H, q), 4.19 (1H, t), 4.58 (2H, s), 6.75 (1H, s), 6.97 (1H, t), 7.2-7.3 (4H, m), 7.4 (3H, m), 7.80 (2H, d).

25

HPLC-MS (Method B): R_t = 7.28 min, m/z = 480 (M + 1).

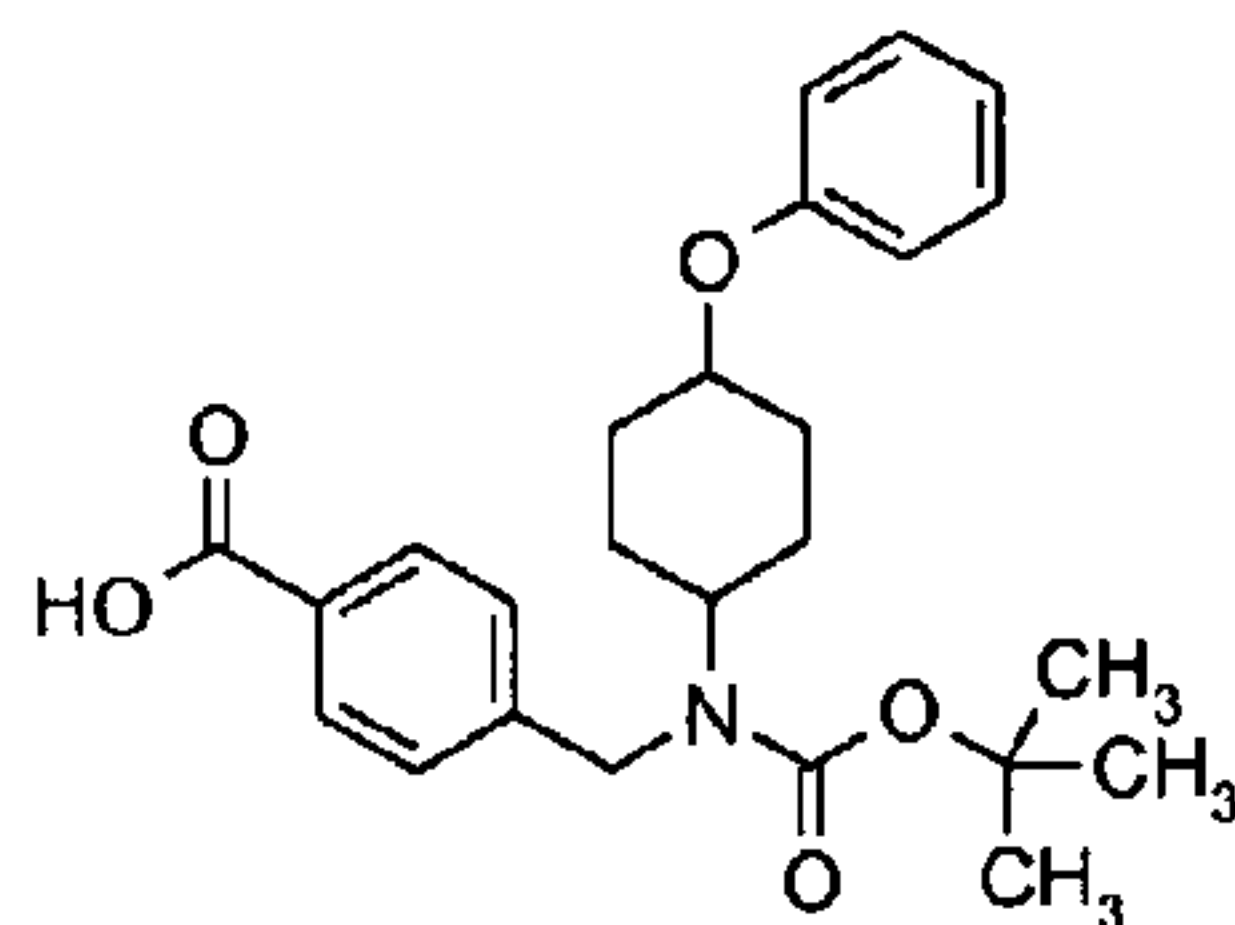
EXAMPLE 244 (general procedure (K))

3-{4-[1-(4-Phenoxycyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



5

Synthesis of intermediate 4-[[*tert*-butoxycarbonyl-(4-phenoxycyclohexyl)amino]methyl]-benzoic acid:



- 10 Methyl 4-(bromomethyl)benzoate (5.0 g, 22 mmol) was dissolved in DMF (50 mL) and *trans*-4-aminocyclohexanol (3.04 g, 26 mmol) was added followed by addition of potassium carbonate (6.08 g, 44 mmol). The reaction mixture was heated to 80°C for 16 hours. The reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL) was added. The aqueous phase was extracted with ethyl acetate (100 mL), and the combined organic phases
- 15 were washed with water (2 x 100 mL) and dried (MgSO₄). The organic phase was concentrated in vacuo to give 2.5 g of *trans*-4-[(4-hydroxycyclohexylamino)methyl]benzoic acid methyl ester.

HPLC-MS (method B): m/z: 264, R_t = 3.48 min.

20

- trans*-4-[(4-Hydroxycyclohexylamino)methyl]benzoic acid methyl ester (2.46 g, 9.3 mmol) was suspended in sodium hydroxide (1N, 9 mL). Di-*tert*-butylpyrocarbonate (2.44 g, 11.2 mmol) dissolved in THF (11 mL) was added during 15 minutes. Additional THF (8 mL) was added and the reaction mixture was stirred for 16 hours. The reaction mixture was evaporated
- 25 in vacuo until THF was removed. Water (25 mL), sodium hydroxide (1N, 1.5 mL), and diethyl ether (50 mL) was added. The water phase was extracted with diethyl ether (25 mL)

and the combined organic phases were washed with an aqueous solution of sodium hydrogensulphate (10%, 30 mL), water (3 x 20 mL), and dried (MgSO₄). The organic phase was concentrated in vacuo to give 3.60 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-hydroxycyclohexyl)-amino]methyl]benzoic acid methyl ester.

5

HPLC-MS (method B): m/z: 364, R_t = 5.75 min.

trans-4-[[*tert*-Butoxycarbonyl-(4-hydroxycyclohexyl)amino]methyl]benzoic acid methyl ester (1.0 g, 2.75 mmol) was dissolved in THF (4 mL) and triphenylphosphine (1.12 g, 4.1 mmol) was added followed by addition of phenol (0.26 g, 2.75 mmol). Diethylazodicarboxylate (0.72 g, 4.1 mmol) dissolved in THF (2 mL) was added drop wise, and the reaction mixture was stirred for 16 hours. The reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (100g silica) using ethyl acetate and heptane (1:9) as eluent to give 0.27 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-phenoxy-cyclohexyl)amino]methyl]benzoic acid methyl ester. The ester was dissolved in ethanol (5 mL) and sodium hydroxide (4N, 1 mL) was added. After 5 hours the reaction mixture was concentrated in vacuo, the residue was dissolved in ethyl acetate (25 mL), and hydrochloric acid (4N, 1.3 mL) was added. The organic phase was washed with water (3 x 10 mL), dried (MgSO₄) and concentrated in vacuo to give 0.25 g of *trans*-4-[[*tert*-butoxycarbonyl-(4-phenoxy-cyclohexyl)amino]methyl]benzoic acid.

15
20

¹H NMR (DMSO-*d*₆): δ 12.85 (1H, broad), 7.90 (2H, d), 7.36 (2H, d), 7.22 (2H, t), 6.88 (3H, m), 4.53 (1H, m), 4.43 (2H, m), 2.0-1.2 (18H, m).

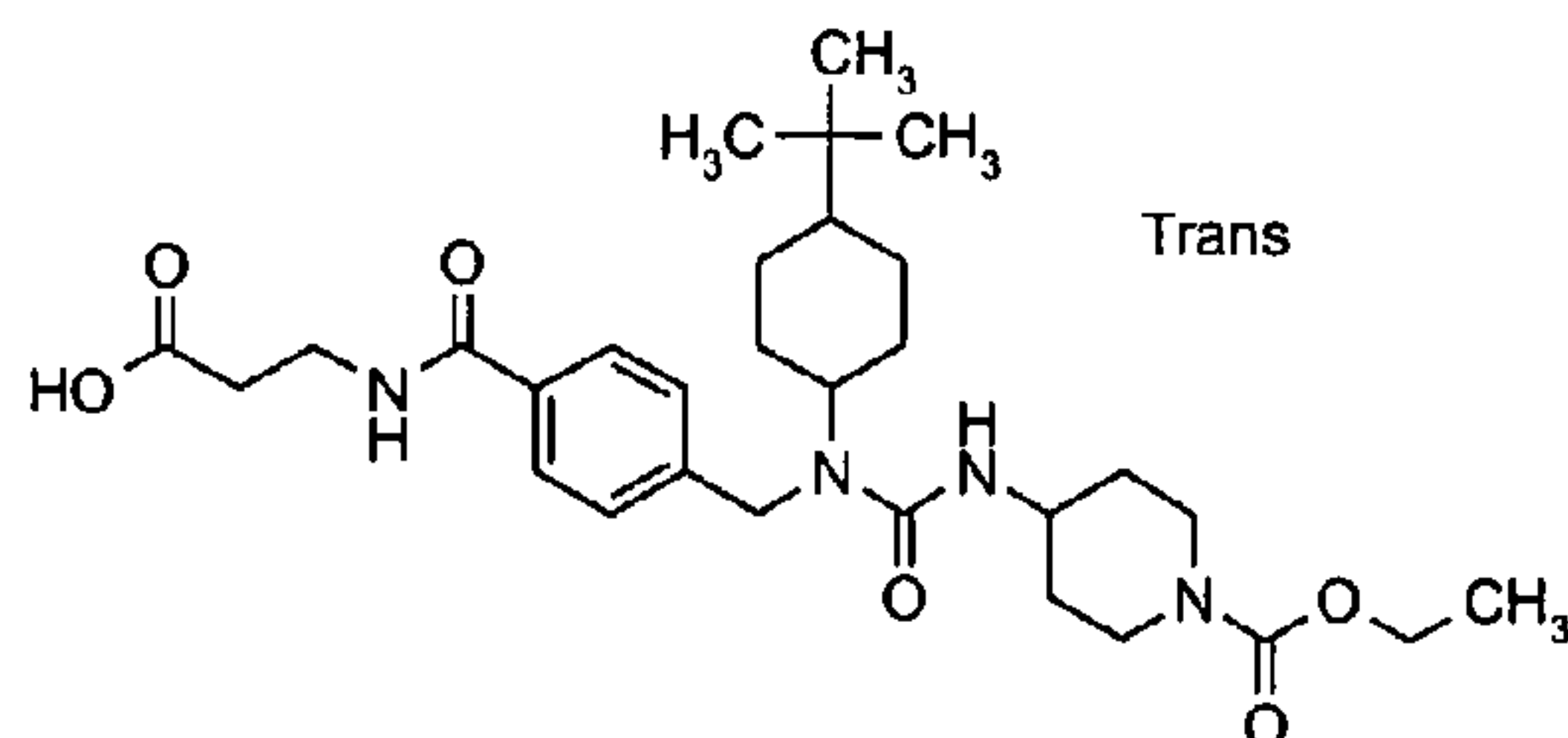
25 This intermediate was used for the synthesis the title compound.

¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.58 (2H, s), 8.48 (1H, t), 7.79 (2H, s), 7.55 (2H, s), 7.37 (2H, s), 7.25 (4H, m), 6.91 (3H, m), 4.67 (2H, s), 4.58 (1H, s), 4.24 (1H, m), 3.42 (2H, dd), 2.52-2.48 (2H, m), 2.00-1.90 (2H, m), 1.80-1.55 (4H, m), 1.50-1.40 (2H, m).

30

EXAMPLE 245 (general procedure (K))

4-{3-(*trans*-4-*tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}piperidine-1-carboxylic acid ethyl ester

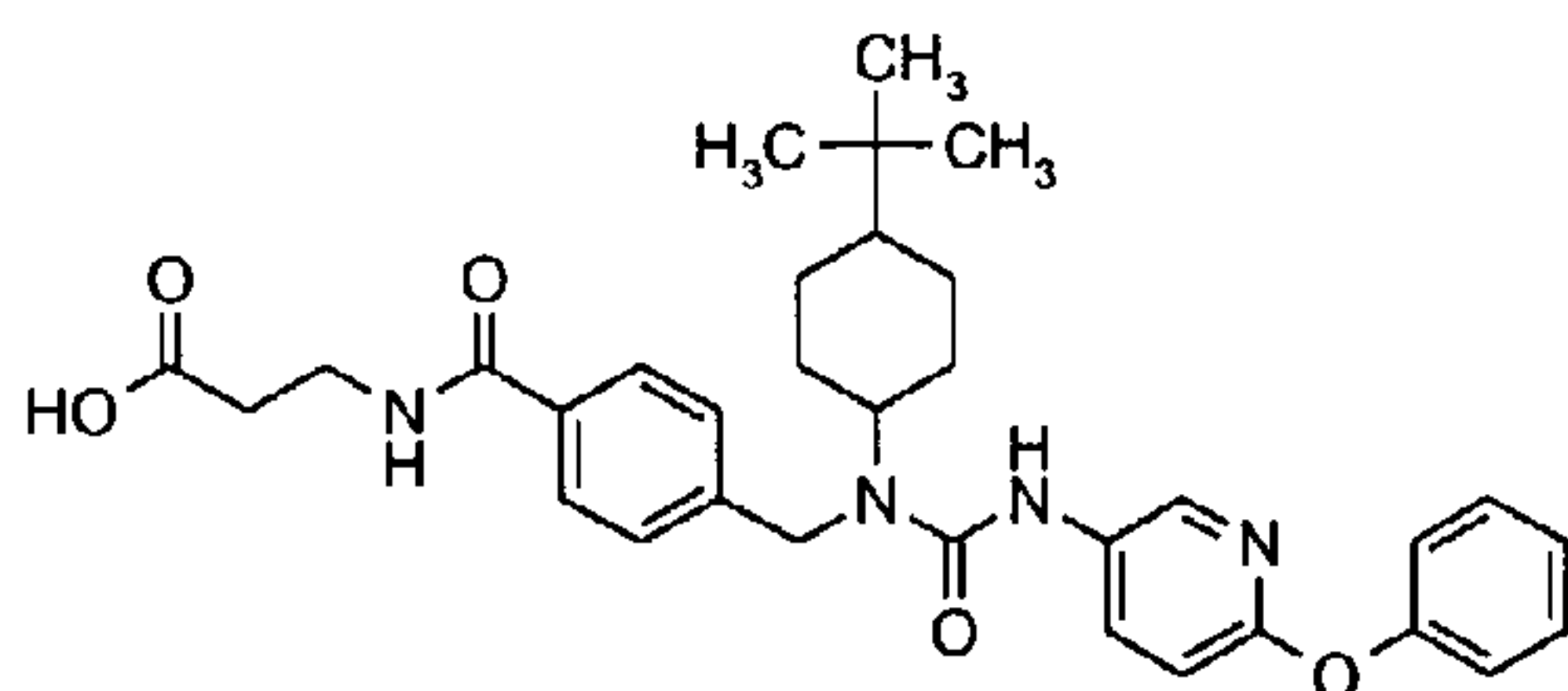


5

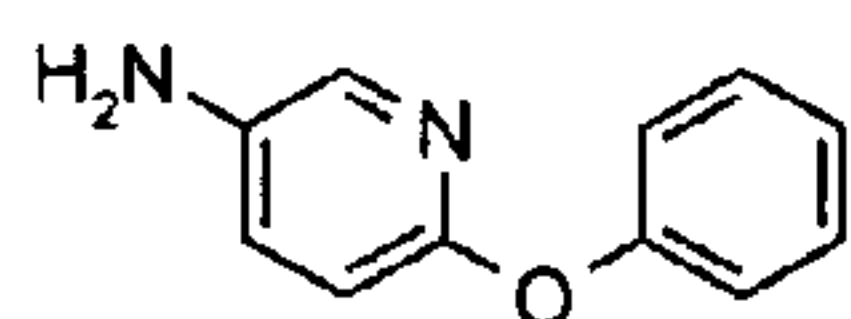
^1H NMR (DMSO- d_6): δ 12.2 (1H, broad), 8.42 (1H, t), 7.72 (2H, d), 7.25 (2H, d), 6.02 (1H, d), 4.42 (2H, broad), 4.02 (2H, q), 3.92-3.60 (3H, m), 3.50-3.40 (2H, m), 2.90-2.70 (2H, m), 1.80-0.80 (10H, m), 0.80 (13H, s).

10 **EXAMPLE 246 (general procedure (K))**

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(6-phenoxy-pyridin-3-yl)ureidomethyl]benzoylamino}-propionic acid

15 HPLC-MS (method B): m/z : 573, R_t = 7.23 min.

Synthesis of intermediate 5-amino-2-phenoxy-pyridine:



20 Phenol (0.9 g, 9.5 mmol) was dissolved in sodium hydroxide (50% solution, 12 mL). 5-Nitro-2-chloropyridine (1.5 g, 9.5 mmol) in toluene (15 mL) was added followed by addition of tetrabutylammonium bromide (0.3 g, 0.95 mmol). The reaction mixture was stirred for 16 hours at 20°C and 5 hours at 80°C where after it was cooled to room temperature and diethyl ether (100 mL) added. The organic phase was washed with water (5 x 50 mL), dried (MgSO₄), and
25 concentrated in vacuo to give 1.0 g of 5-nitro-2-phenoxy-pyridine.

M.p. 85-87°C.

5-Nitro-2-phenoxy pyridine (0.5 g, 2.3 mmol) was added portion wise to a solution of stannous chloride (2.6 g, 12 mmol) dissolved in concentrated hydrochloric acid (10 mL) at a temperature of 0-5°C. The reaction mixture was then stirred at 20°C for 16 hours. Sodium carbonate (5 g) and aqueous ammonia (50 mL) was added. The mixture was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with water (2 x 40 mL), dried (MgSO₄), and concentrated in vacuo to give 0.3 g of 5-amino-2-phenoxy pyridine.

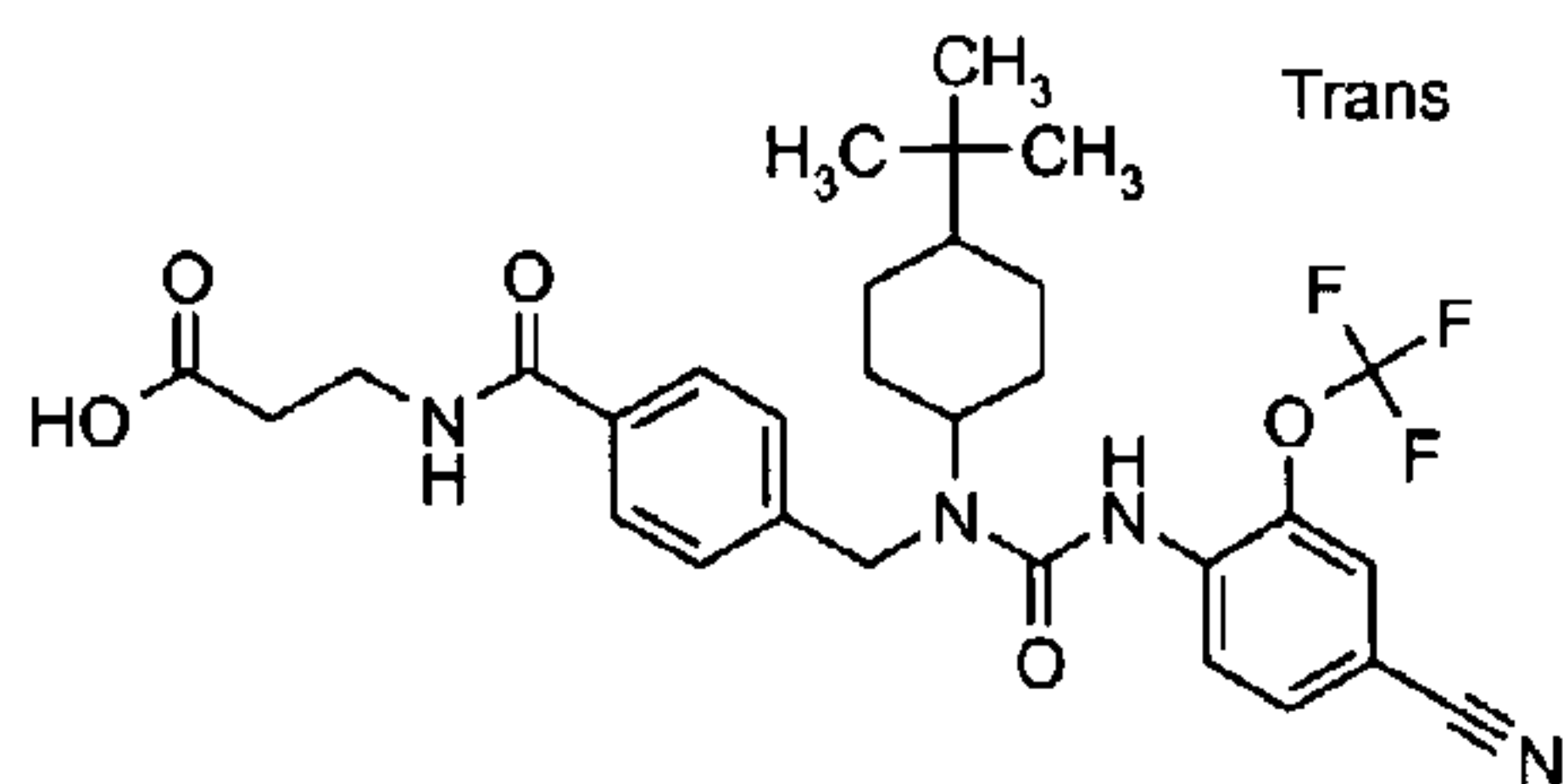
¹H NMR (DMSO-*d*₆): δ 7.55 (1H, s), 7.33 (2H, dd), 7.08 (2H, dd), 6.93 (2H, d), 6.75 (1H, d), 5.12 (2H, broad).

This compound was transformed into the corresponding phenylcarbamate (as described for in example 237 and used in the synthesis of the title compound).

¹H NMR (DMSO-*d*₆): δ 8.51 (1H, s), 8.45 (1H, broad), 8.20 (1H, d), 7.90 (1H, dd), 7.75 (2H, d), 7.35 (4H, m), 7.15 (1H, t), 7.05 (2H, d), 6.92 (1H, d), 4.57 (2H, broad), 4.02 (1H, broad), 3.40 (m), 3.38 (2H, m), 1.80-0.80 (10H, m), 0.80 (13H, s).

EXAMPLE 247 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyano-2-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid

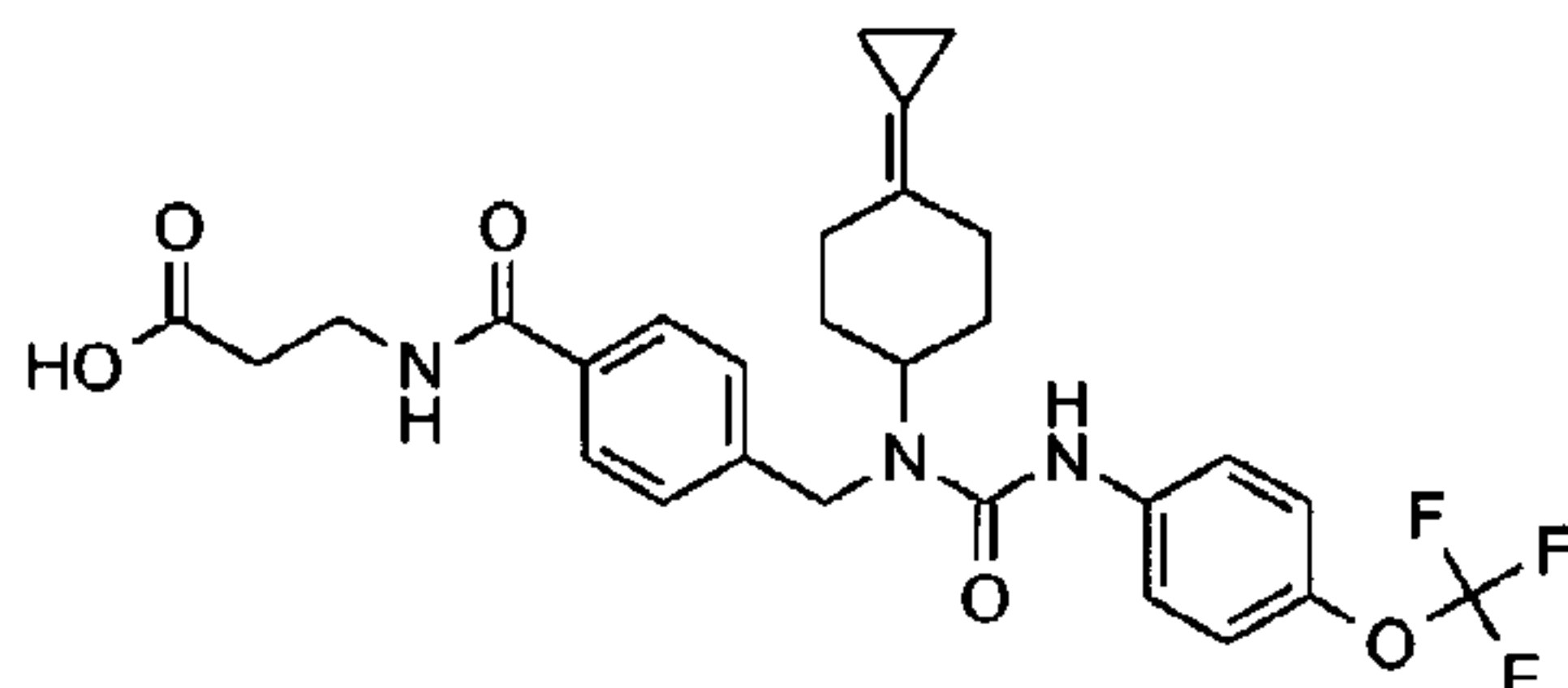


¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.48 (1H, t), 8.32 (1H, broad), 7.92 (1H, s), 7.90 (1H, d), 7.75 (3H, m), 7.34 (2H, d), 4.60 (2H, broad), 4.03 (1H, m), 3.45 (2H, m), 1.80-0.85 (9H, m), 0.80 (9H, s).

HPLC-MS (method B): m/z: 589, R_t = 8.07 min.

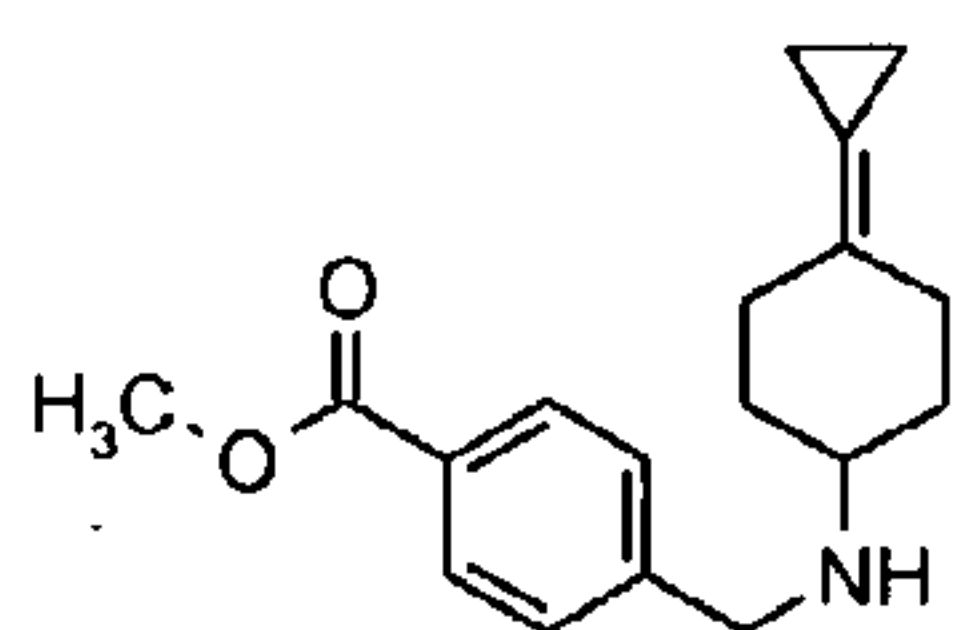
EXAMPLE 248 (general procedure (K))

3-{4-[1-(4-Cyclopropylidenecyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoyl-amino}propionic acid



5

Synthesis of intermediate 4-[(4-cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester:



10 Cyclopropyltriphenylphosphonium bromide (10.8 g, 28 mmol) was suspended in dry THF (30 mL) and cooled to -60°C . *N*-Butyllithium (1.6M in THF, 17 mL, 27 mmol) was added dropwise at -40 to -60°C . The temperature was raised to 20°C and after 3 hours at this temperature, the reaction mixture was cooled to -60°C . 1,4-Cyclohexane dione mono ethylene ketal (4.0 g, 26 mmol) dissolved in THF (30 mL) was added at -60°C whereafter the temperature was

15 raised to 20°C . After 16 hours the reaction mixture was diluted with THF (75 mL) filtered through hyflo and concentrated in vacuo. The residue was purified by flash chromatography (4 x 15 cm column of silica) using heptane and ethyl acetate (4:1) as eluent to give 2.5 g of 8-cyclopropylidene-1,4-dioxaspiro[4.5]decane (cf Synthetic Communications 21(20), 2015-2023, 1991).

20

Silica gel 60 (6.0 g) was suspended in dichloromethane (12 mL) and oxalic acid (10% in water, 0.6 g) was added. After 20 minutes 8-cyclopropylidene-1,4-dioxaspiro[4.5]decane (1.6 g, 8.9 mmol) dissolved in dichloromethane (5 mL) was added and the reaction mixture was stirred for 48 hours at 20°C . Sodium hydrogen carbonate (200 mg) was added and after 1

25 hour the reaction mixture was filtered. The filtrate was concentrated in vacuo and the crude product of 4-cyclopropylidenecyclohexanone was used for the next step without further purification.

4-Aminomethylbenzoic acid methyl ester, hydrochloride salt (2.2 g, 11 mmol) was suspended in 1,2 dichloropropane (30 mL) and an aqueous saturated solution of potassium carbonate (15 mL) was added. The next day the organic phase was isolated and dried (MgSO_4). 4-Cyclopropylidenecyclohexanone (1.5 g, 11 mmol) dissolved in dichloromethane (15 mL) was added followed by addition of acetic acid (400 μL) and sodium triacetoxyborohydride (3.3 g, 16.5 mmol). After 72 hours at 20°C the reaction mixture was diluted with dichloromethane (50 mL) and washed with aqueous saturated sodium hydrogen carbonate (2 x 30 mL) and water (5 x 30 mL). The organic phase was dried (MgSO_4) and concentrated in vacuo. The residue was purified by flash chromatography (50 g silica) using ethyl acetate and methanol (97:3) as eluent to give 1.1 g of 4-[(4-cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester.

^1H NMR ($\text{DMSO}-d_6$): δ 7.90 (2H, d), 7.48 (2H, d), 3.84 (3H, s), 3.80 (2H), 3.63 (1H, m), 2.60-0.90 (12H, m).

HPLC-MS (method B): m/z : 286, R_t = 4.45 min.

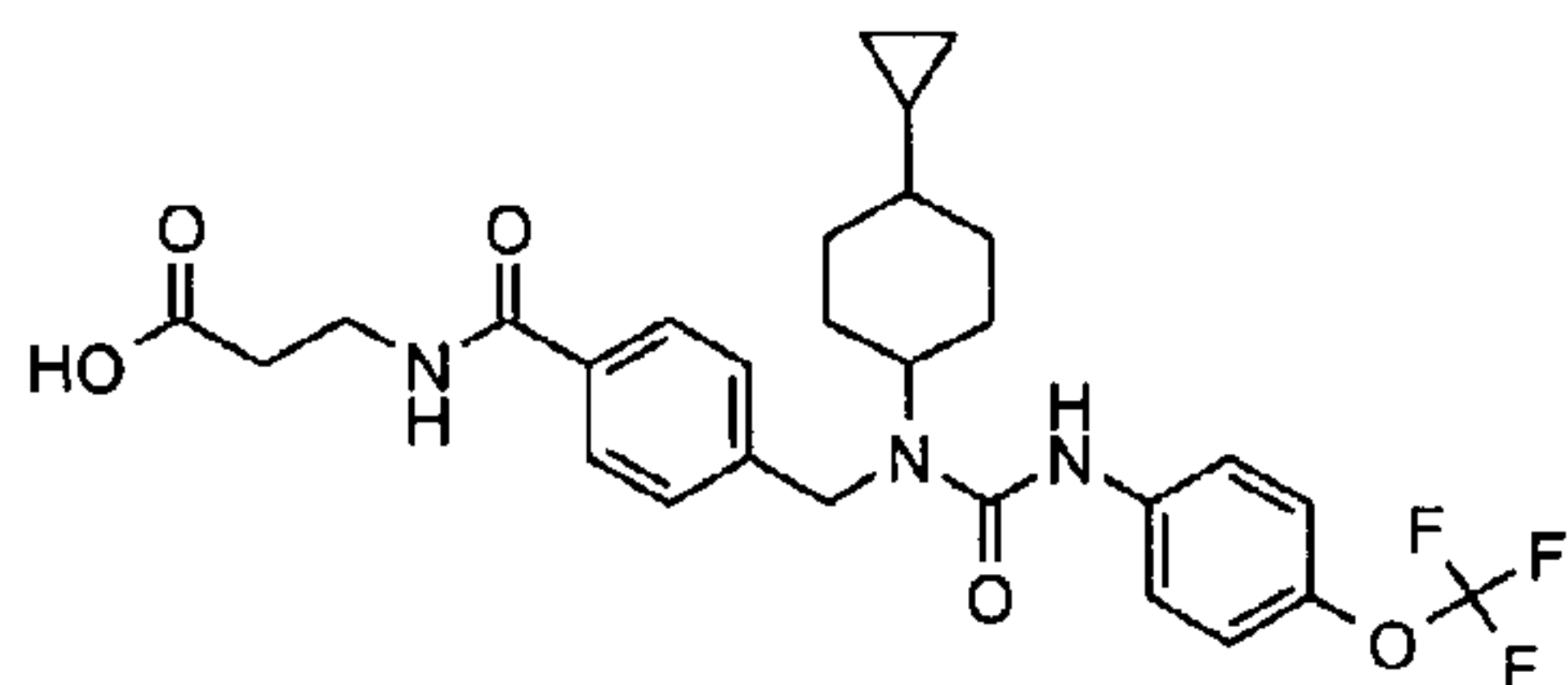
This intermediate product was used for the synthesis of the title compound.

^1H NMR ($\text{DMSO}-d_6$): δ 2.2 (1H, broad), 8.60 (1H, s), 8.43 (1H, t), 7.75 (2H, d), 7.55 (2H, d), 7.30 (2H, d), 7.22 (2H, d), 4.65 (2H, broad), 4.32 (1H, m), 3.45 (2H, m), 2.60-0.90 (14H, m).

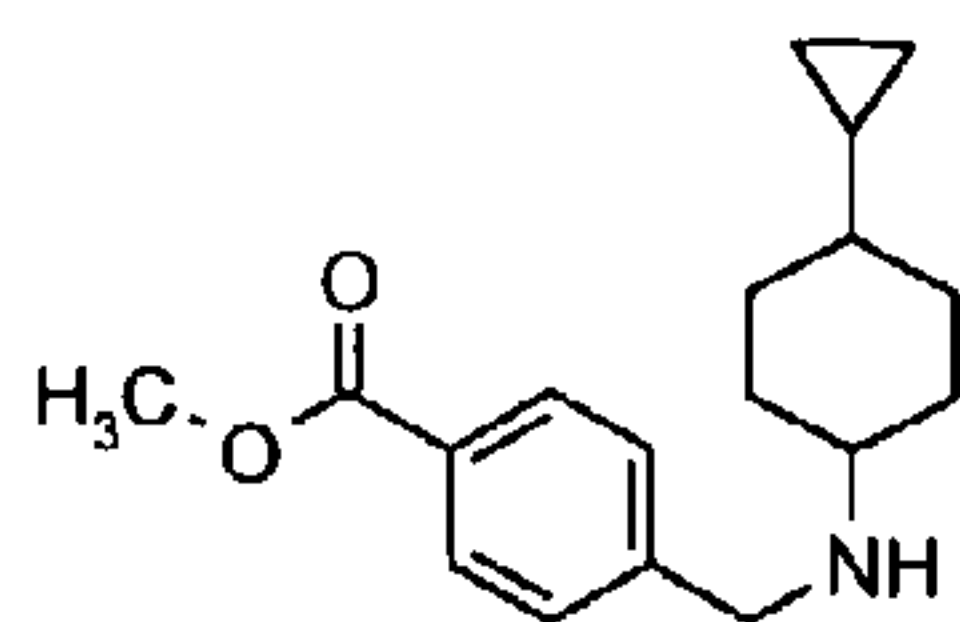
HPLC-MS (method B): m/z : 546, R_t = 7.38 min.

EXAMPLE 249 (general procedure (K))

3-{4-[1-(4-Cyclopropylcyclohexyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]benzoylamino}-propionic acid



Synthesis of intermediate 4-[(4-cyclopropylcyclohexylamino)methyl]benzoic acid methyl ester:



4-[(4-Cyclopropylidenecyclohexylamino)methyl]benzoic acid methyl ester (1.1 g, 3.9 mmol) was dissolved in DMF (40 mL) and p-toluenesulfonic acid hydrazide (2.8 g, 15.4 mmol) was added. The reaction was heated to 100°C for 16 hours. After cooling to room temperature the reaction mixture was diluted with ethyl acetate (75 mL) and water (40 mL) was added. The aqueous phase was extracted with ethyl acetate (25 mL) and the combined organic phases washed with aqueous saturated sodium hydrogen carbonate (2 x 30 mL) and water (5 x 30 mL). The organic phase was dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (25 g silica) using heptane and ethyl acetate (1:1) as eluent to give 4-[(4-cyclopropylcyclohexylamino)methyl]benzoic acid methyl ester.

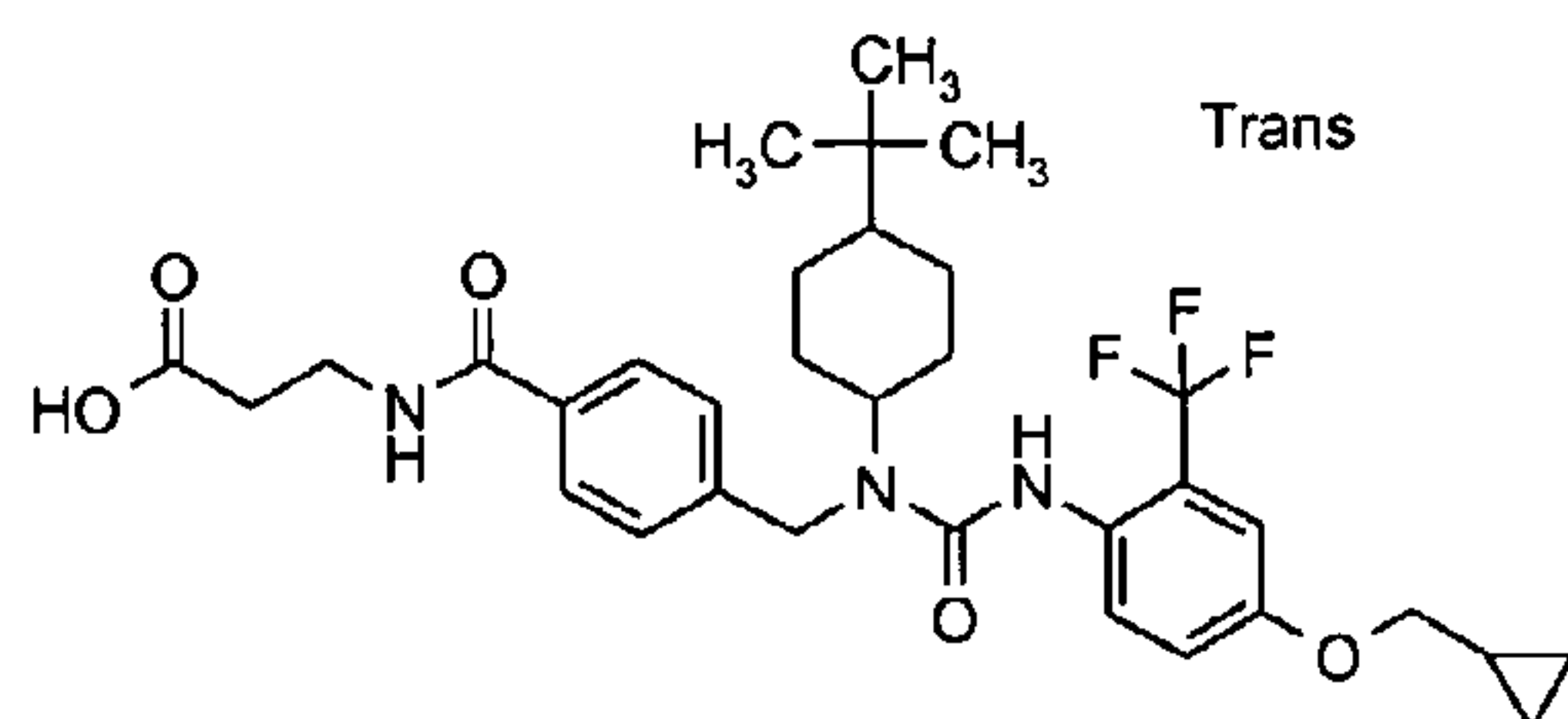
This intermediate product was used for the synthesis of the title compound.

¹H NMR (DMSO-*d*₆): δ 12.2 (1H, broad), 8.51 (1H, s), 8.43 (1H, t), 7.75 (2H, dd), 7.55 (2H, d), 7.32 (2H, dd), 7.22 (2H, d), 4.68 (1H, s), 4.60 (1H, s), 4.10 (1H, m), 3.45 (2H, dd), 1.80-0.25 (13H, m).

HPLC-MS (method B): *m/z*: 548, *R*_t = 7.38 min.

EXAMPLE 250 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(4-cyclopropylmethoxy-2-trifluoromethylphenyl)ureido-methyl]benzoylamino}propionic acid



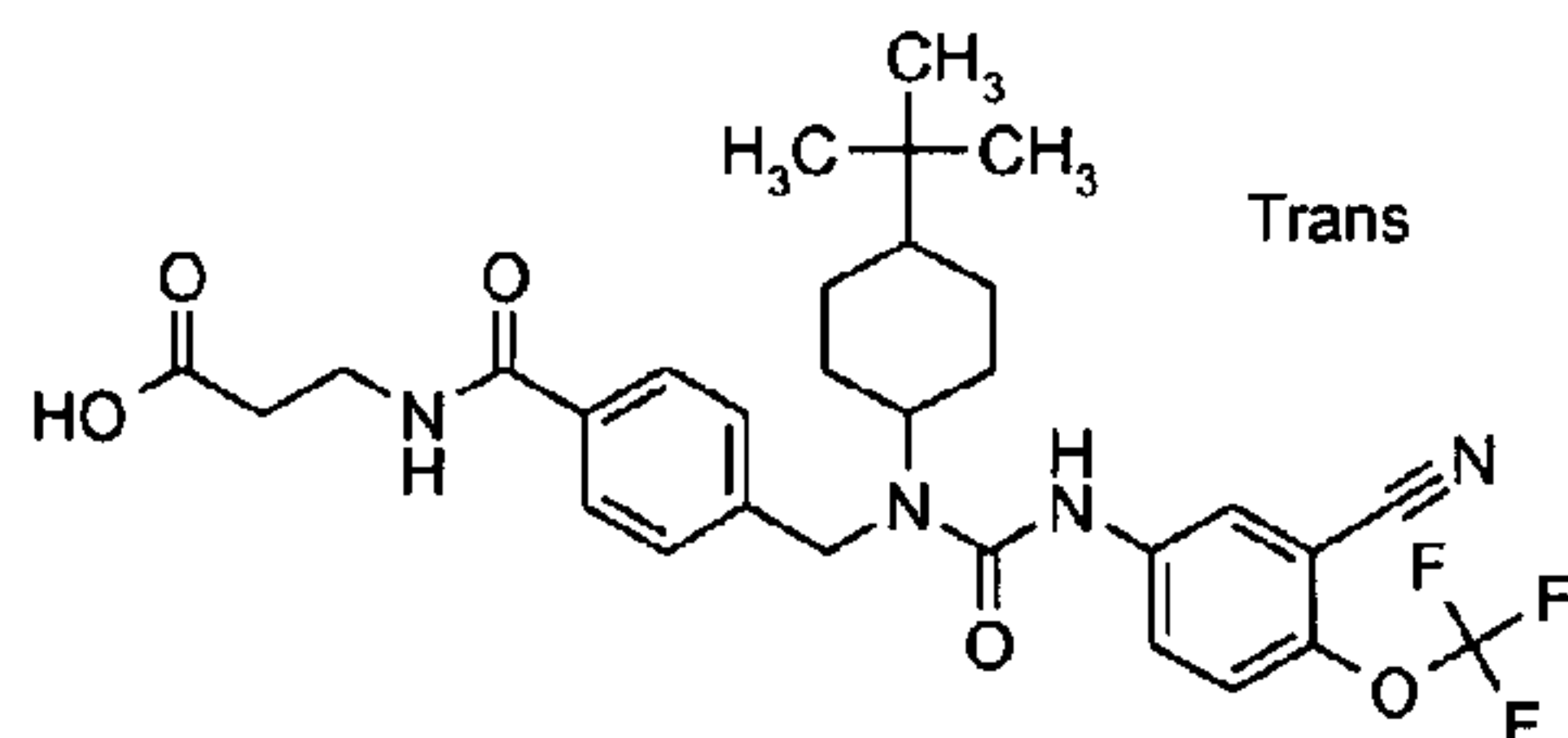
The intermediate, 4-cyclopropylmethoxy-2-trifluoromethylaniline, was prepared analogously to the aniline intermediate used in example 241.

^1H NMR ($\text{DMSO}-d_6$): δ 12.1 (1H, broad), 8.45 (1H, t), 7.98 (1H, broad), 7.75 (2H, d), 7.32 (2H, d), 7.29 (1H, s), 7.15 (2H, m), 4.52 (2H, broad), 3.88 (2H, d), 3.45 (1H, m), 1.80-0.85 (10H, m), 0.80 (9H, s), 0.60 (2H, m), 0.33 (2H, m).

5 HPLC-MS (method B): m/z : 618, R_t = 6.65 min.

EXAMPLE 251 (general procedure (K))

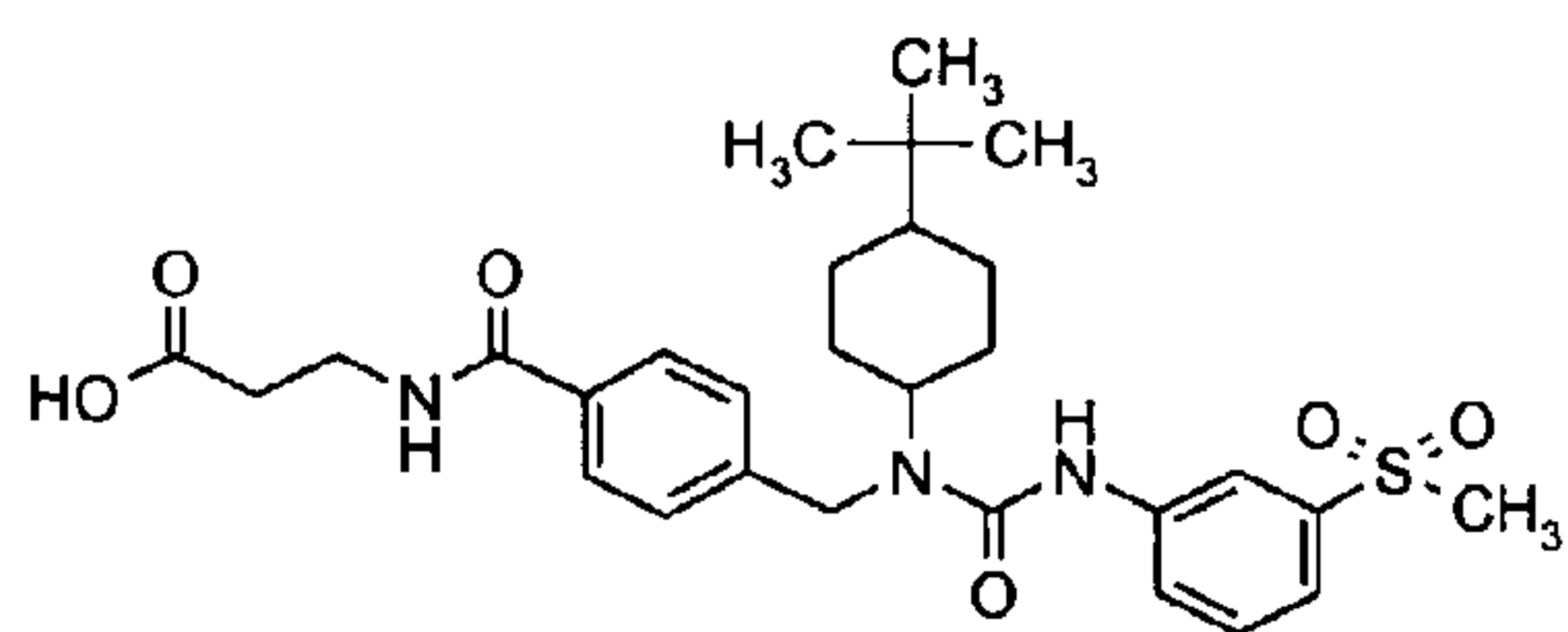
3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3-cyano-4-trifluoromethoxyphenyl)ureidomethyl]-benzoylamino}propionic acid



^1H NMR ($\text{DMSO}-d_6$): δ 12.2 (s, broad), 8.90 (1H, s), 8.43 (1H, t), 8.10 (1H, s), 7.90 (2H, dd), 7.75 (2H, d), 7.55 (1H, d), 7.32 (2H, d), 4.61 (2H, broad), 4.04 (2H, m), 3.45 (2H, m), 1.80-0.85 (10H, m), 0.80 (9H, s).

EXAMPLE 252 (general procedure (K))

3-{4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-methylsulfonylphenyl)ureidomethyl]benzoylamino}-propionic acid



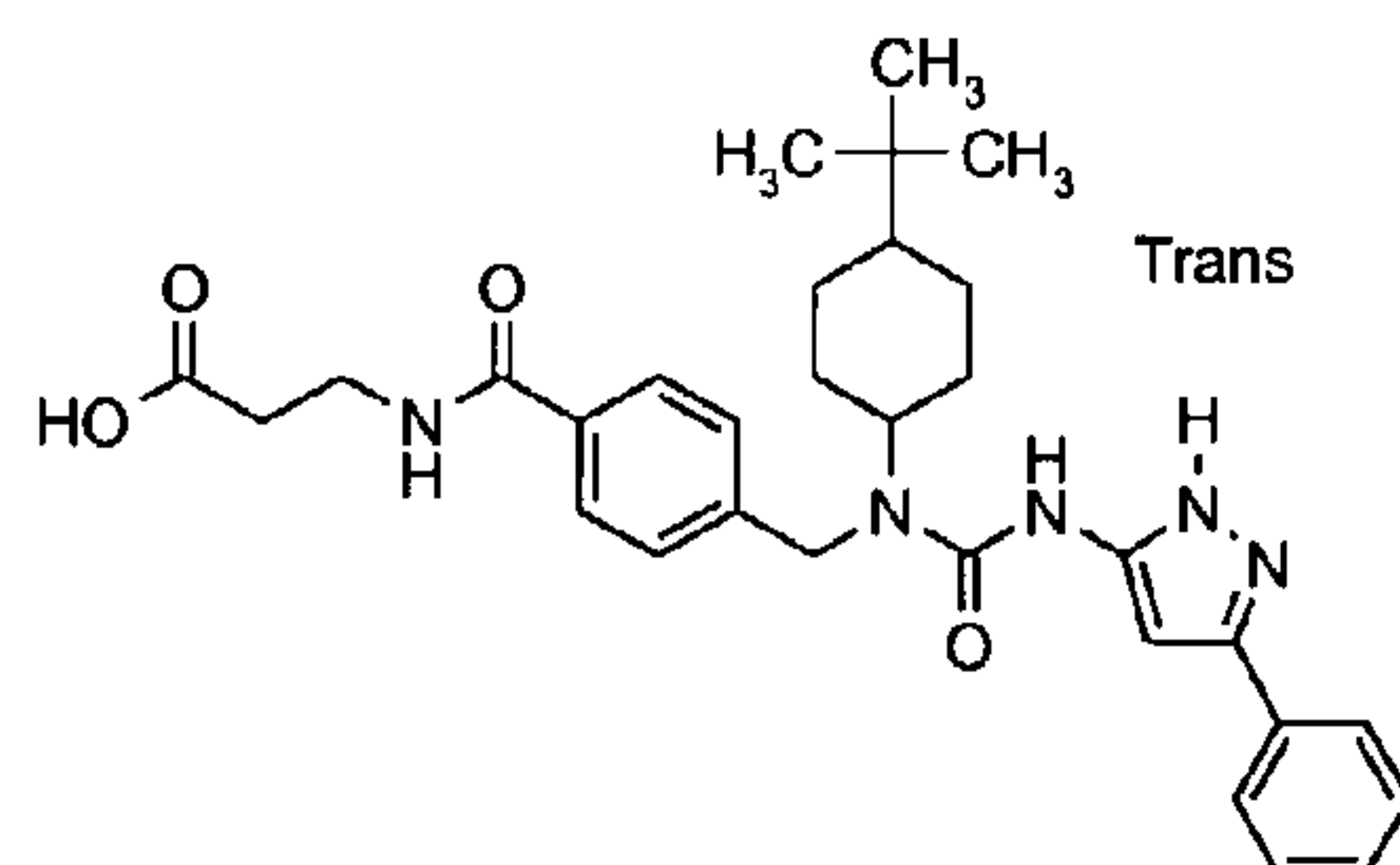
The title compound was prepared from the corresponding 3-methylsulfonyl compound (general procedure (K)) followed by oxidation of the sulfonyl group and hydrolysis of the propionic acid ester.

^1H NMR ($\text{DMSO}-d_6$): δ 12.2 (s, broad), 8.76 (1H, s), 8.45 (1H, t), 8.07 (1H, s), 7.83 (1H, d), 7.74 (2H, d), 7.50 (2H, m), 7.30 (2H, d), 4.60 (2H, broad), 4.08 (2H, d), 3.45 (2H, t), 3.18 (3H, s), 2.50 (2H, t), 1.80-0.85 (9H, m), 0.80 (9H, s).

HPLC-MS (method B): m/z : 558, R_t = 6.52 min.

EXAMPLE 253 (general procedure (K))

5 3-{4-[1-(4-*trans-tert*-Butylcyclohexyl)-3-(5-phenyl-2*H*-pyrazol-3-yl)ureidomethyl]-benzoylamino}propionic acid

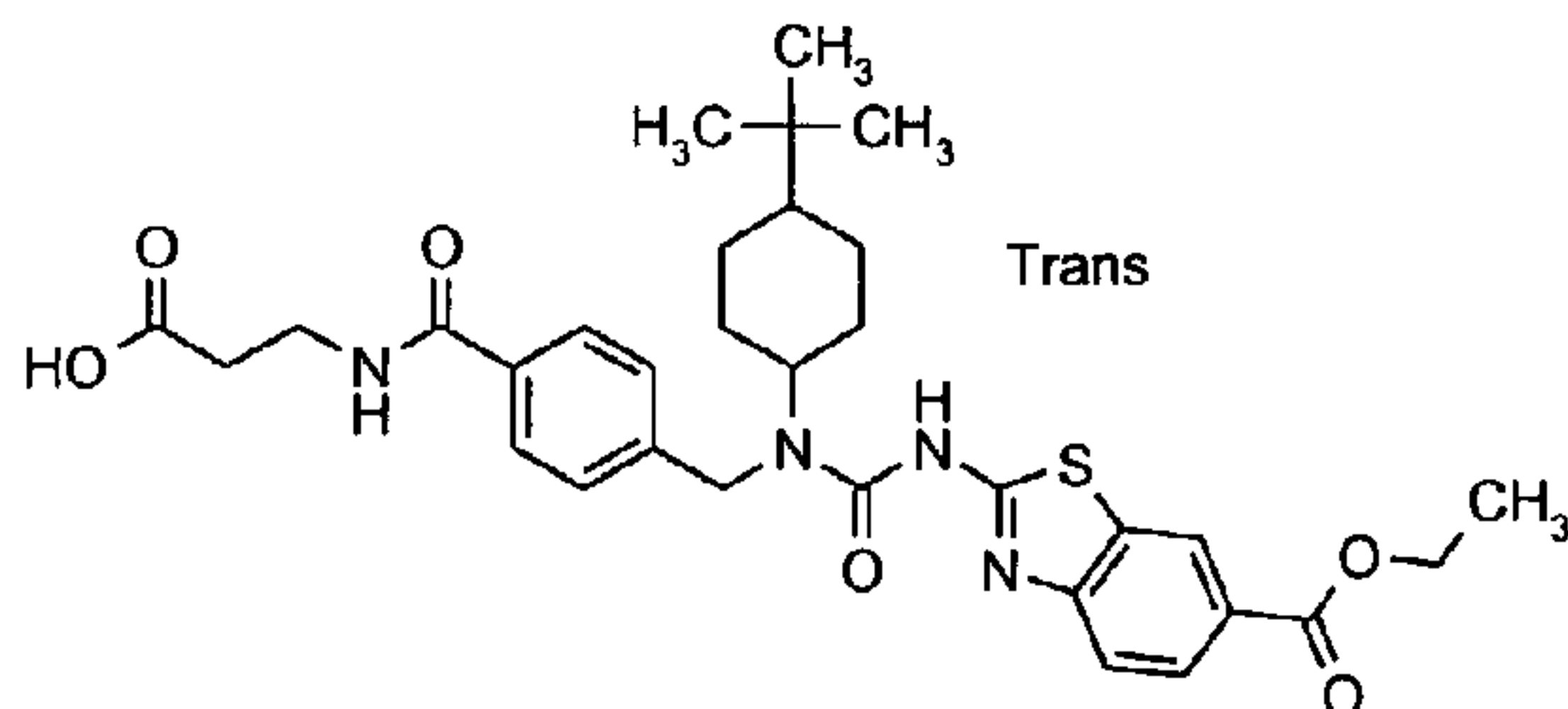


Using isocyanate formed in situ from 5-amino-3-phenylpyrazole and triphosgene:

10 To a suspension of 5-amino-3-phenylpyrazole (183 mg, 8.7 mmol) in 1,2-dichloroethane (5 mL) was added *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol) followed by addition of triphosgene (115 mg, 0.38 mmol). The solution was heated to reflux for two hours. To this mixture a solution of 3-{4-[(4-*trans-tert*-butylcyclohexylamino)methyl]benzoylamino}propionic acid methyl ester trifluoroacetate (350 mg, 0.70 mmol) and *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol) in DMF (4 mL) was added and stirring at 80°C was continued for 2 hours. The mixture was allowed to cool to room temperature, poured into water (50 mL) and the water phase was washed ethyl acetate (2 x 50 mL). The combined organic phases were concentrated in vacuo and purification on silica column with dichloromethane/methanol (95:5) afforded the 3-{4-[1-(4-*trans-tert*-butylcyclohexyl)-3-(5-phenyl-2*H*-pyrazol-3-yl)ureidomethyl]-benzoylamino}propionic acid methyl ester as a solid which was redissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 30 min. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration. Recrystallisation from acetonitrile afforded the title compound.

25 ^1H NMR (CDCl_3): δ 0.82 (9H, s), 0.9-1.5 (5H, m), 1.69 (4H, bt), 4.09 (1H, bt), 4.58 (2H, s), 6.64 (1H, s), 7.25-7.50 (5 H, m), 7.60-7.80 (4H, m), 8.50 (1H, t), 9.0 (1H, s).

HPLC-MS (Method B): R_t = 6.52 min, m/z = 546 ($M+1$).

EXAMPLE 254 (general procedure (K))2-{3-(4-*trans-tert*-Butylcyclohexyl)-3-[4-(2-carboxyethylcarbamoyl)benzyl]ureido}-benzothiazole-6-carboxylic acid ethyl ester

5

Using isocyanate formed in situ from (substituted) 2-aminobenzothiazole and diphosgene in pyridine:

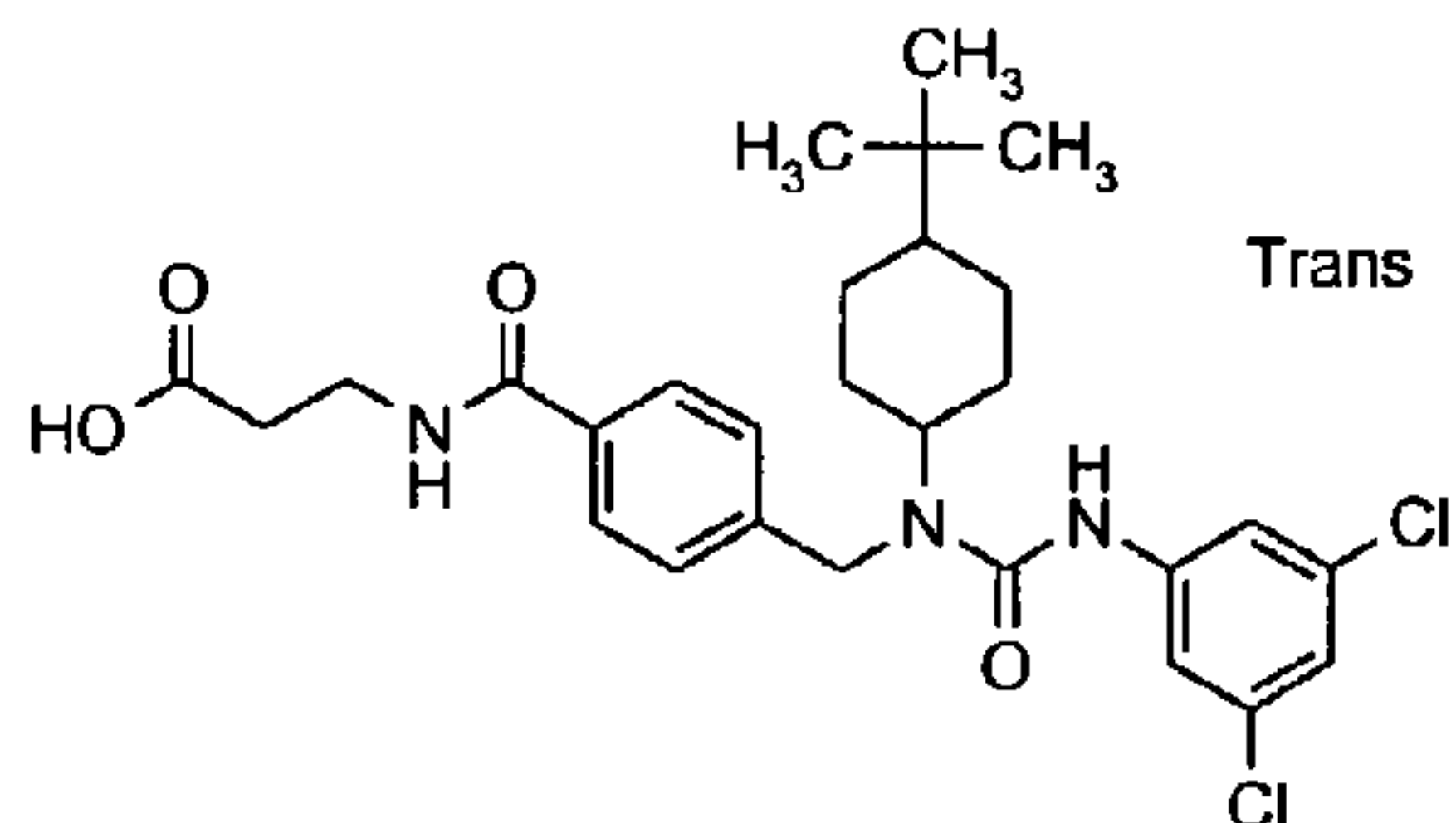
Ethyl-2-aminobenzothiazole-6-carboxylate (262 mg, 1.2 mmol) was suspended in pyridine (4 ml). Diphosgene (80 μ L, 0.66 mmol) was added and the solution was stirred for two hours at room temperature. To this mixture a solution of 3-{4-[(4-*trans-tert*-butylcyclohexylamino)-methyl]benzoylamino}propionic acid methyl ester trifluoroacetate (300 mg, 0.61 mmol) and *N,N*-diisopropylethylamine (0.4 mL, 2.4 mmol) in DMF (4 mL) was added and stirring at 80°C was continued for 2 hours. The mixture was allowed to cool to room temperature and poured into acetonitrile (50 mL), the resulting precipitate was filtered off and the filtrate was then partitioned between ethyl acetate (50 mL) and hydrochloric acid (2 x 50 mL, 1 N). The organic phase was concentrated in vacuo to give an oil which was redissolved in ethanol (4 mL). Sodium hydroxide (1 mL, 4 N) was added and the reaction mixture was left at room temperature for 30 min. Hydrochloric acid (4 mL, 1 N) was added, and the resulting precipitate was subsequently collected by filtration to afford the title compound.

20

HPLC-MS (Method B): R_t = 7.65 min, m/z = 609 (M^+).

EXAMPLE 255 (general procedure (K))

3-{4-[1-(*trans*-4-*tert*-Butylcyclohexyl)-3-(3,5-dichlorophenyl)ureidomethyl]benzoylamino}-propionic acid



5

^1H NMR (DMSO- d_6): δ 12.2 (s, 1H), 8.68 (s, 1H), 8.45 (t, 1H), 7.74 (d, 2H), 7.61 (s, 2H), 7.30 (d, 2H), 7.11 (s, 1H), 4.57 (s, 2H), 4.02 (m, 1H), 3.43 (m, 2H), 2.50 (m, 2H), 1.8-0.75 (m, 9H), 0.80 (s, 9H)

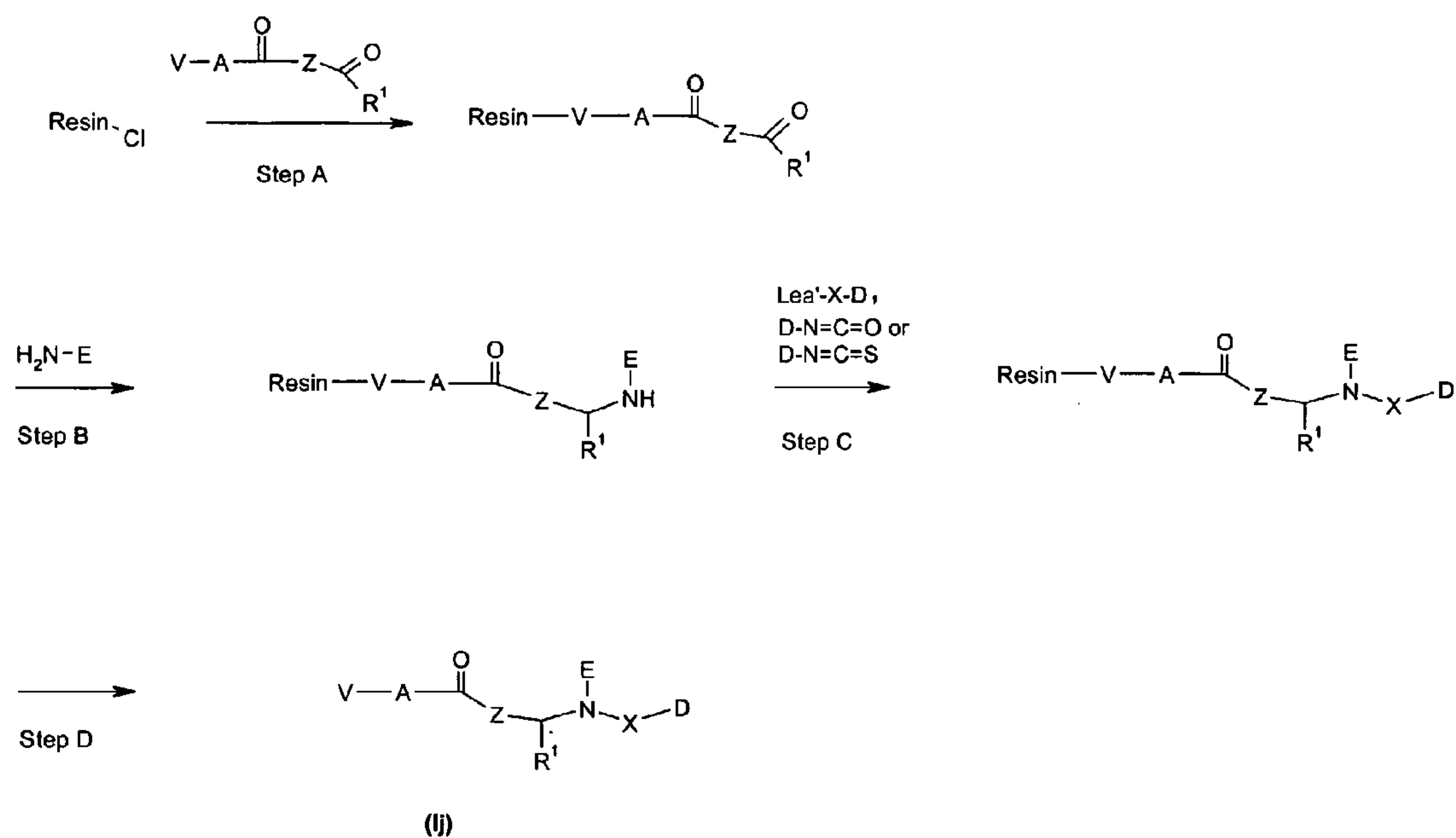
10 HPLC-MS (method B): m/z : 548, R_t = 8.35min

MA: Calc for $\text{C}_{28}\text{H}_{35}\text{Cl}_2\text{N}_3\text{O}_4$:

61.31% C, 6.43% H, 7.66% N; Found

61.20% C, 6.59% H, 7.34% N.

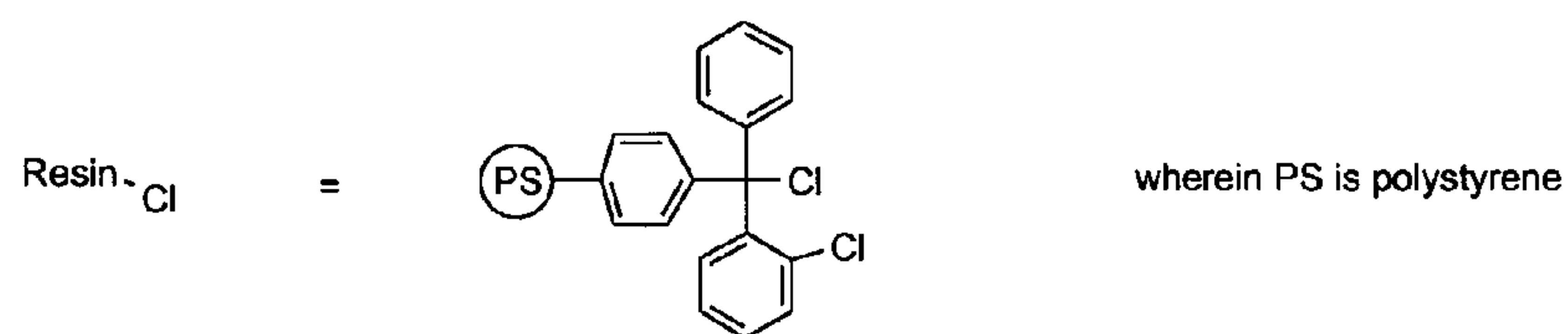
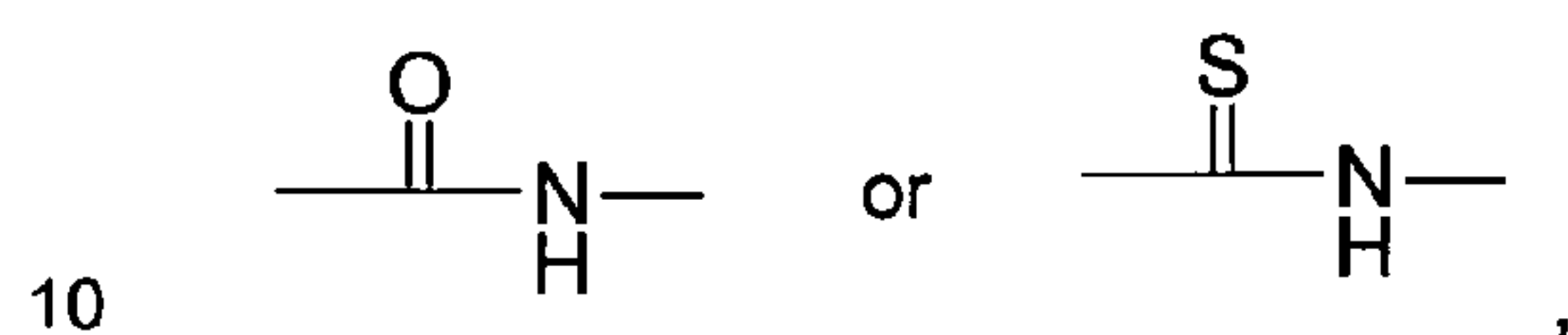
General procedure (L) for the solid phase synthesis of compounds of the general formula (Ij):



5 wherein

A, V, Z, R¹, E and D are as defined for formula (I),

X is



, and

Lea' is a leaving group such as -OSu, chloro, phenoxy, or 4-nitrophenoxy.

Step A:

The reaction is known (The combinatorial index, Ed. Bunin, B. A. 1998, Academic Press, p. 24) and is generally performed by shaking a suspension of the resin with a solution of V-A-Z-C(O)R¹ in the presence of a base such as triethylamine, diisopropylethylamine, dicyclohexylmethylamine or any other tertiary amine. Typical solvents are pyridine, dichloromethane, 1,2-dichloroethane, DMF, NMP, THF, DMSO or mixtures of two or more of these. The reaction is performed between 20°C and 120°C, preferably at 25°C. Excess reagents are filtered off and the resin is washed with any solvent mentioned above including mixtures hereof, containing a base as mentioned above and an alcohol, typically methanol, as a scavenger of unreacted resin bound 2-chlorotriylchloride.

Step B:

Step B is identical to step C of general procedure (T).

Step C:

Step C is identical to step D of general procedure (T).

Step D:

Step D is identical to step E of general procedure (T).

Preparation of starting materials D-N=C=O:N,N-Dimethyl-3-nitro-benzenesulfonamide

3-Nitrobenzenesulfonyl chloride (22.8 mmol, 5.05 g) was dissolved in dry THF (50 mL). Dimethylamine in THF (2M, 34 mL) was added and the mixture was refluxed for 2 hours. Upon cooling, the mixture was filtered and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate (250 mL), washed with water (3 x 50 mL) and dried over MgSO₄. Evaporation of the solvent afforded the title compound.

1-(3-Nitrobenzenesulfonyl)piperidine was prepared as described above using piperidine instead of dimethylamine.

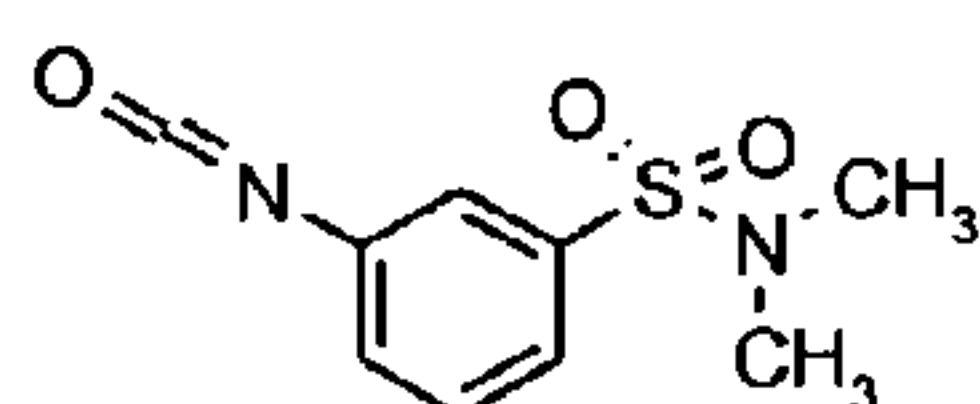
3-Amino-N,N-dimethylbenzenesulfonamide

To a solution of the above N,N-dimethyl-3-nitro-benzenesulfonamide (20.4 mmol, 4.7 g) in ethanol (50 mL) was added SnCl₂ (105 mmol, 19.9 g) and the mixture was refluxed for 1

hour. Upon cooling, the solvent was removed in vacuo. Ethyl acetate (200 mL) and NaHCO₃ (sat, 100 mL) were added to the residue followed by another 200 mL ethyl acetate and 500 mL water. The phases were separated and the organic phase was washed twice with water. The organic phase was filtered, washed with water (2 x 100 mL) dried over MgSO₄ and
5 evaporated to leave the title compound.

3-(Piperidine-1-sulfonyl)phenylamine was prepared as described above from 1-(3-nitro-benzenesulfonyl)piperidine.

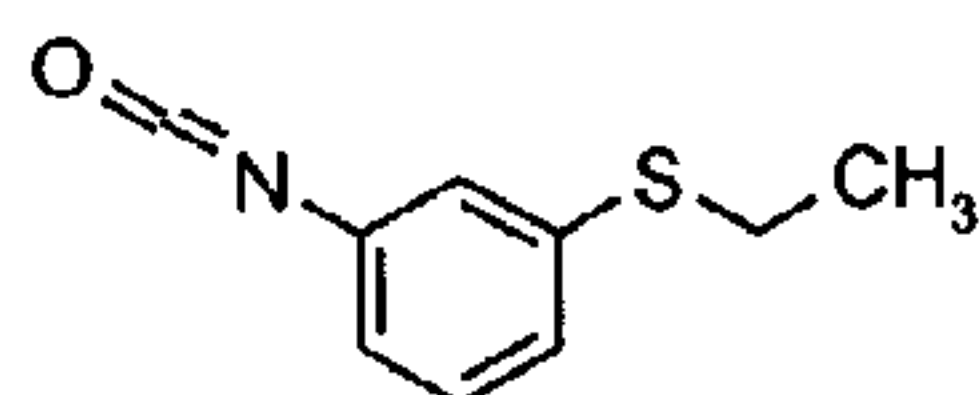
10 3-Isocyanato-*N,N*-dimethylbenzenesulfonamide



To a slurry of the above 3-amino-*N,N*-dimethylbenzenesulfonamide (3.26 g, 16 mmol) in toluene (200 mL) was added triphosgene (1.67 g) and the mixture was refluxed 16 h and
15 evaporated. The residue was used without further purification.

1-(3-Isocyanatobenzenesulfonyl)piperidine was prepared as described above from 3-piperidine-1-sulfonyl)phenylamine.

20 1-Ethylsulfanyl-3-isocyanatobenzene



To a solution of 3-aminothiophenol (40 mmol, 5 g) in DMF (50 mL) was added K₂CO₃ (4.8 mmol, 6.63 g) and 2.98 mL bromoethane. The mixture was stirred over night at 25°C and
25 poured into 200 mL ice water. 200 mL ethylacetate was added and the phases were separated. The aqueous phase was extracted with 100 mL ethylacetate and the combined organic extracts were dried over MgSO₄. Evaporation of the solvent and re-dissolving the residue in ethyl acetate (100 mL) and HCl in ethyl acetate (2M, 20 mL) afforded 3-ethylsulfanyl-phenylamine hydrochloride, which was collected by filtration.

30

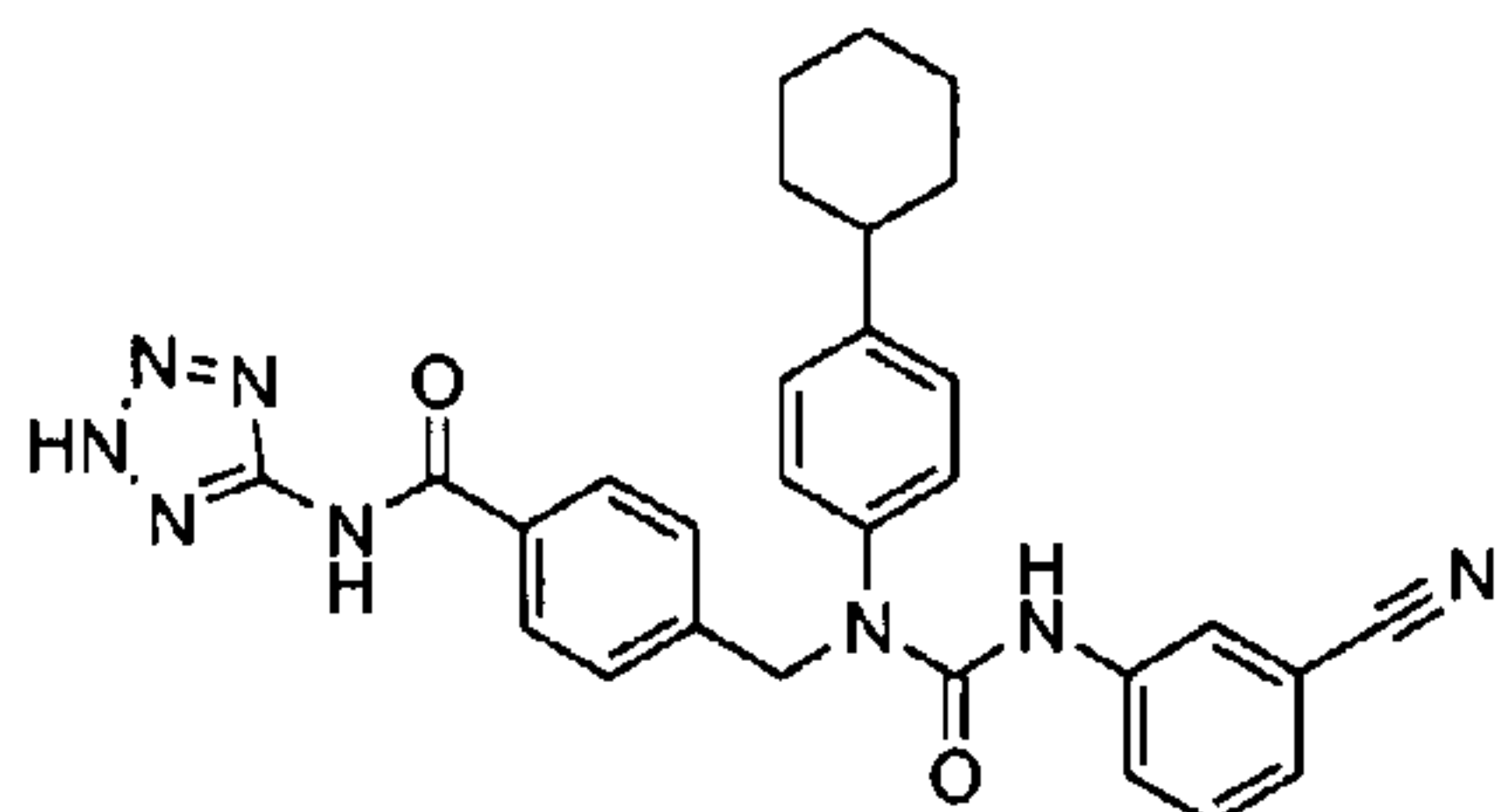
To a slurry of the above 3-ethylsulfanylphenylamine hydrochloride (31.6 mmol, 6 g) in toluene (100 mL) was added diphosgene (trichloromethyl chloroformate, 158 mmol, 31.3 g) and

the mixture was refluxed for 2 hours affording a clear solution. The solvent was removed in vacuo and the residue was used without further purification.

The other starting materials used in the following examples were prepared in a similar way.

EXAMPLE 256 (general procedure (L))

4-[3-(3-Cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



Step A: Resin bound 4-formyl-N-(2H-tetrazol-5-yl)benzamide

150 μ mol 4-Formyl-N-(2H-tetrazol-5-yl)benzamide was dissolved in a mixture of 250 μ L dichloromethane, 250 μ L DMF and 100 μ L diisopropylethylamine and added to 50 mg polystyrene resin functionalized with a 2-chlorotriyl chloride linker. After shaking the suspension for 4 hours at 25°C, the resin was isolated by filtration and washed with 2 x 1 mL dichloromethane: methanol:diisopropylethylamine 17:2:1 and 2 x 1 mL DMF.

Step B: Resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide

The above resin bound 4-formyl-N-(2H-tetrazol-5-yl)benzamide (50 mg) was treated with a 0.5 M solution of 4-cyclohexylaniline (0.25 mmol, 41.25 mg) in a mixture of DMF and trimethylorthoformate (1:1, 0.5 mL) and glacial acetic acid (50 μ L) for 1 hour at 25°C followed by sodium cyanoborohydride (250 μ mol, 16 mg) dissolved in a mixture of DMF and methanol (1:1, 0.25 mL). Shaking at 25°C for 4 hours followed by filtration and washing with a mixture of DMF and methanol (1:1, 2x1 mL), 3 x 1 mL DMF and 2 x 1 mL dichloromethane afforded the desired product.

Step C: Resin bound 4-[3-(3-cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

200 μ mol 3-cyanophenylisocyanate dissolved in 500 μ L dichloroethane was added to the above resin bound 4-[(4-cyclohexylphenylamino)methyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg). Shaking the mixture for 5 hours at 25°C followed by filtration and washing of the resin with 2 x 1 mL dichloromethane, 4 x 1 mL DMF, 2 x 1 mL H₂O, 3 x 1 mL THF and 3 x 1 mL dichloromethane afforded the resin bound title compound.

Step D: 4-[3-(3-Cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

The above resin bound 4-[3-(3-cyanophenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide (50 mg) was treated with 1 mL 5% TFA in dichloromethane for 1 hour at 25°C. The product was filtered off and the resin was washed with 1 mL dichloromethane. The combined extracts were concentrated in vacuo. The residue was dissolved in 50 µL DMSO + 500 µL acetonitrile and purified by preparative HPLC using a Supelcosil ABZ+ 25 cm x 10 mm 5µ column. The starting eluent composition was 5% acetonitrile in water changing over 30 min to 90% acetonitrile in water which was then kept constant for 5 min before going back to the starting composition over 10 min. The flow rate was kept constant at 8 mL/min collecting one fraction per minute. The process was monitored using a UV detector operating at 214 nm. The fractions containing the desired product were combined and evaporated in vacuo to afford the title compound.

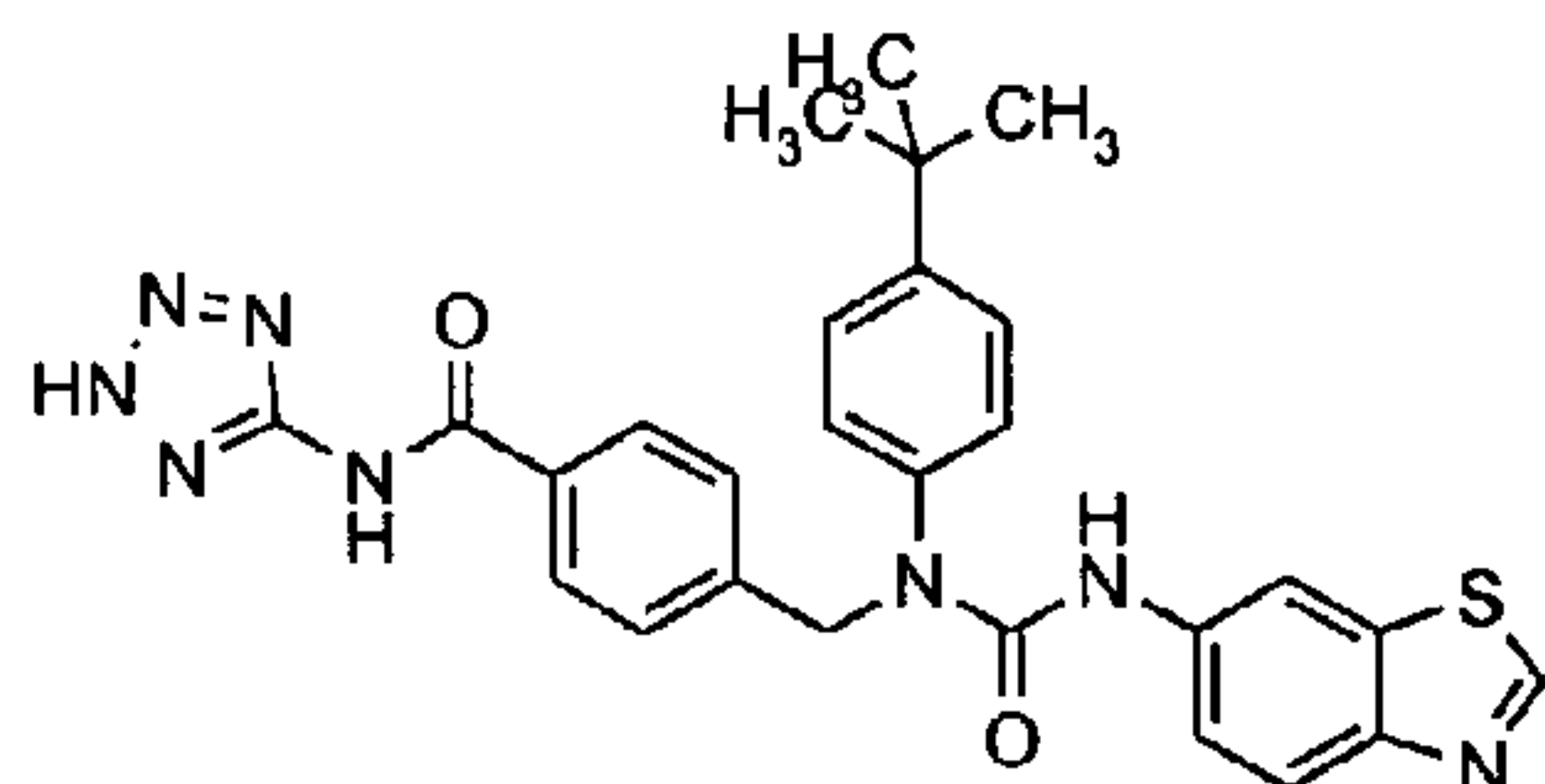
Optionally, the compound can be purified by recrystallisation from eg acetonitrile.

¹H NMR (300 MHz, DMSO-*d*₆): δ 12.35 (s br, 1H); 8.58 (s, 1H); 8.05 (d, 2H); 7.95 (s, 1H); 7.73 (d, 1H); 7.50-7.38 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

HPLC-MS (method B): *m/z* = 521, *R*_t = 7.60 min.

EXAMPLE 257 (general procedure (L))

4-[3-Benzothiazol-6-yl-1-(4-*tert*-butylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

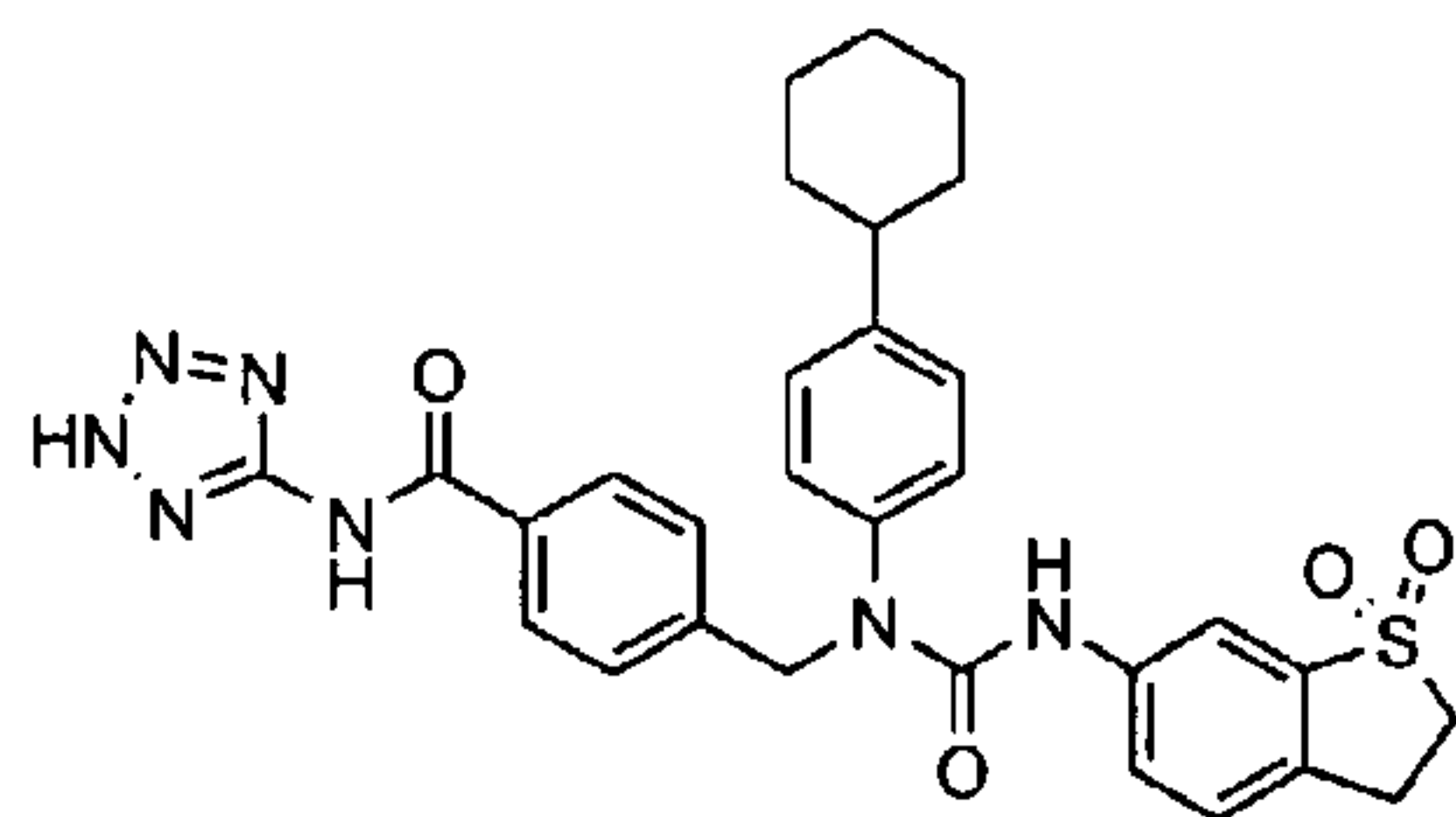


¹H NMR (DMSO-*d*₆): δ 8.5 (s, 1H); 8.28 (s, 1H); 8.05 (d, 2H); 7.93 (d, 2H); 7.55 (d, 1H); 7.48 (d, 2H); 7.43 (d, 2H); 7.22 (d, 2H); 5.03 (s, 2H); 1.28 (s, 9H).

HPLC-MS (Method B): *m/z* = 527 (*M*+1). *R*_t = 6.47 min.

EXAMPLE 258 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(1,1-dioxo-2,3-dihydro-1*H*-1-benzo[*b*]thiophen-6-yl)ureido-methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



5

The benzothiophene moiety was synthesized from commercially available 6-amino-1,1-dioxo-1*H*-1-benzo[*b*]thiophene using Pd/C and H₂ employing methods known by those skilled in the art. The aniline was converted to an isocyanate by methods mentioned previously.

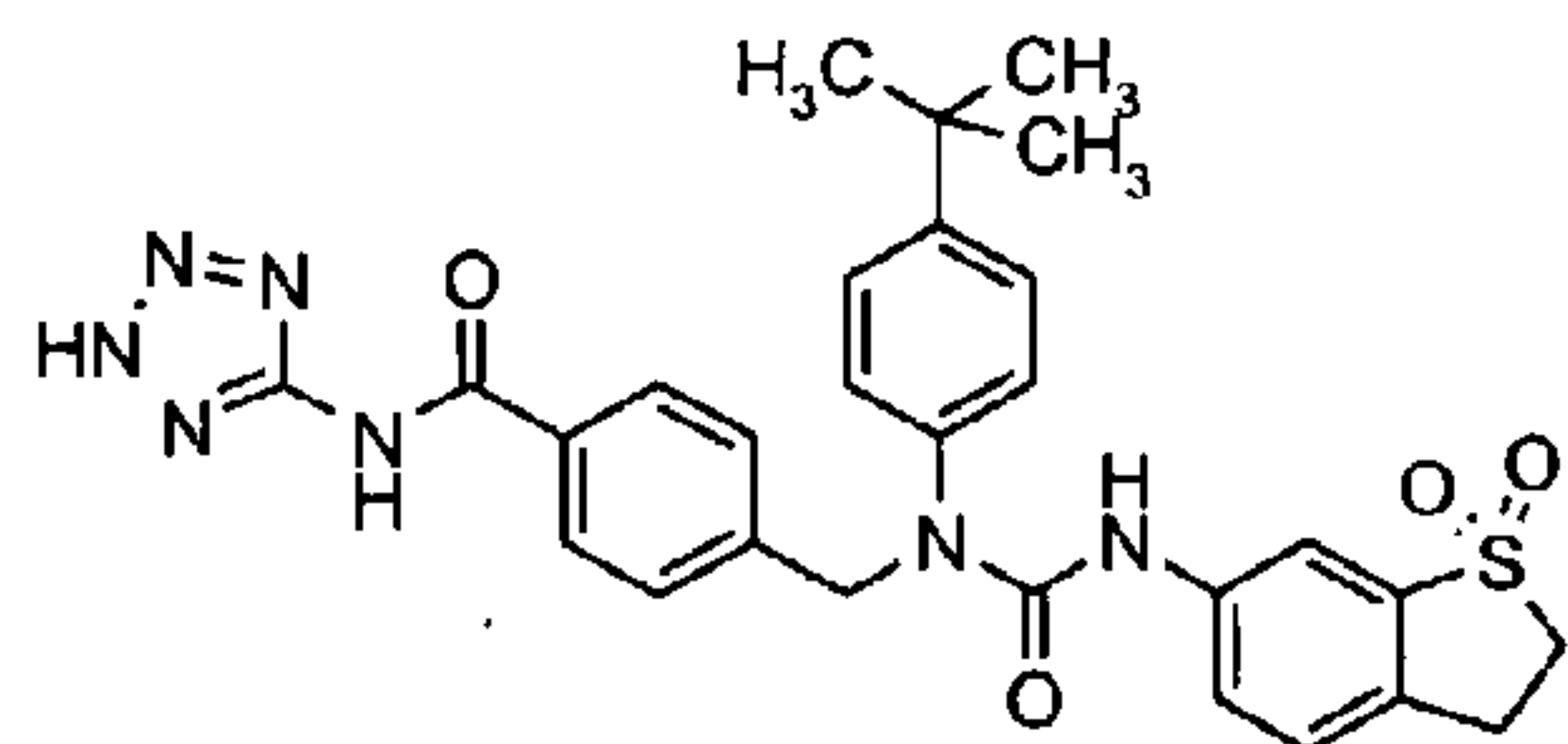
10

¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.60 (s, 1H); 8.05 (s, 2H); 7.88 (s, 1H); 7.68 (d, 1H); 7.45 (d, 2H); 7.39 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 3.58 (t, 2H); 3.30 (t, 2H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

15 HPLC-MS (Method B): *m/z* = 586 (M+1). *R*_t = 7.88 min.

EXAMPLE 259 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(1,1-dioxo-2,3-dihydro-1*H*-benzo[*b*]thiophen-6-yl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



20

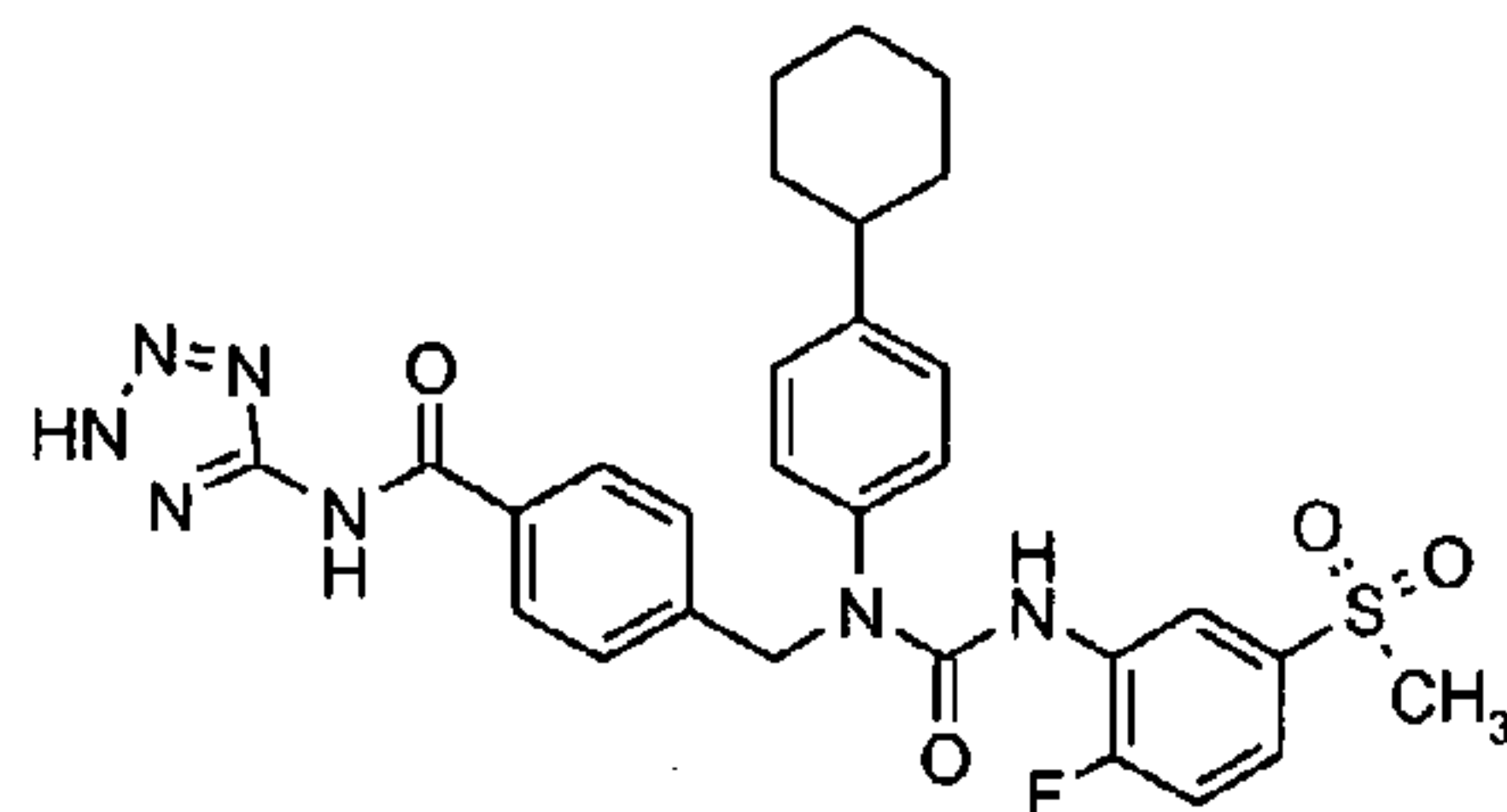
¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.65 (s, 1H); 8.05 (s, 2H); 7.88 (s, 1H); 7.60 (d, 1H); 7.48 (d, 2H); 7.45-7.38 (m, 3H); 7.22 (d, 2H); 5.00 (s, 2H); 3.58 (t, 2H); 3.34 (t, 2H); 1.32 (s, 9H).

25

HPLC-MS (Method B): *m/z* = 560 (M+1). *R*_t = 7.58 min.

EXAMPLE 260 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(2-fluoro-5-methylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

2-Fluoro-5-methylsulfonylphenyl isocyanate was prepared from the corresponding 2-fluoro-5-methylsulfonyl-1-nitrobenzene via reduction to the corresponding aniline as described previously.

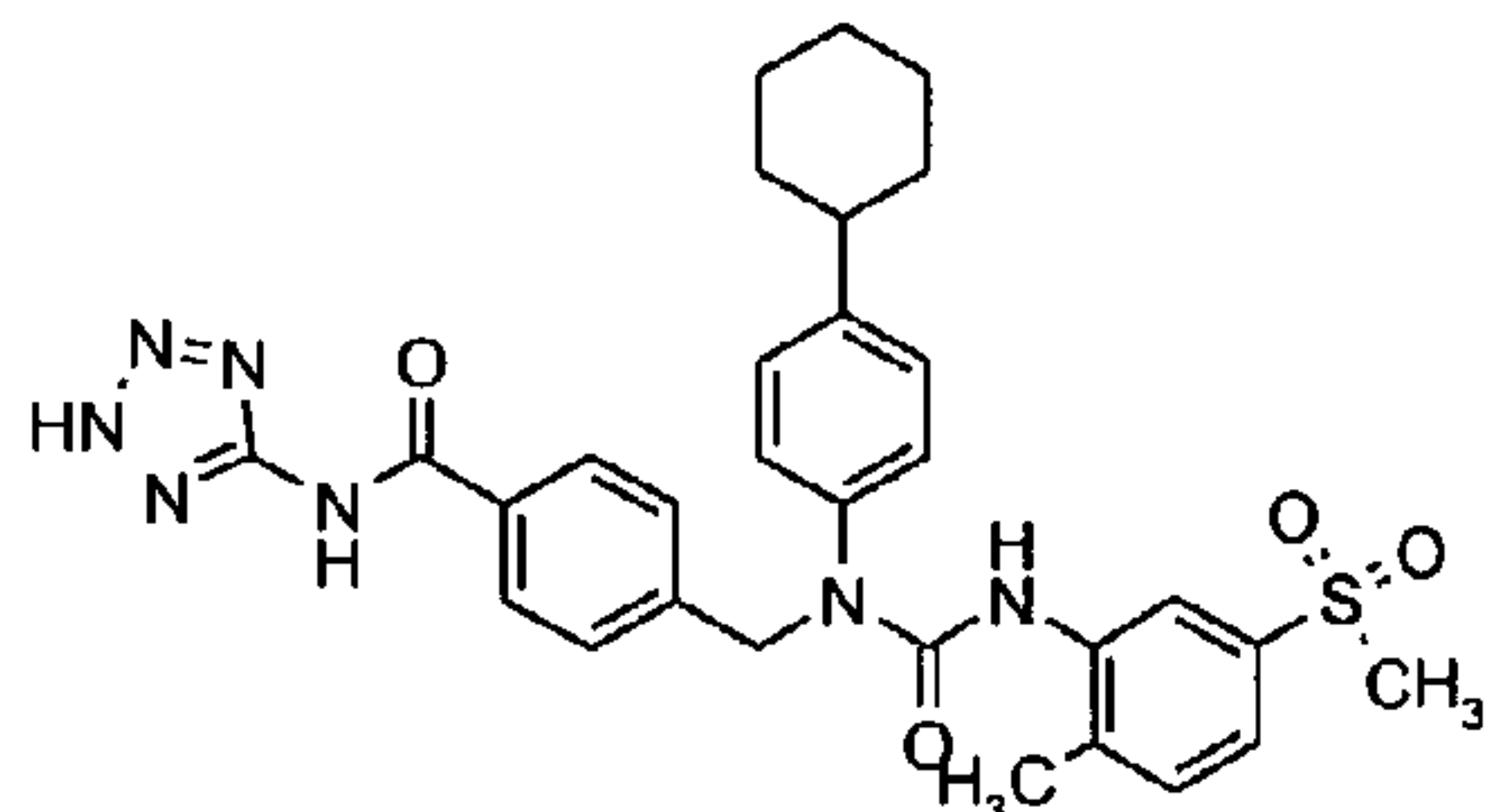
10 ^1H NMR (DMSO- d_6): δ 11.50 (s br, 1H); 8.30 (d, 1H); 8.00 (d, 2H); 7.90 (s, 1H); 7.65 (m, 1H); 7.50-7.40 (m, 3H); 7.25 (s, 4H); 5.05 (s, 2H); 3.18 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 592 (M+1). R_t = 7.04 min.

15

EXAMPLE 261 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(5-methylsulfonyl-2-methylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

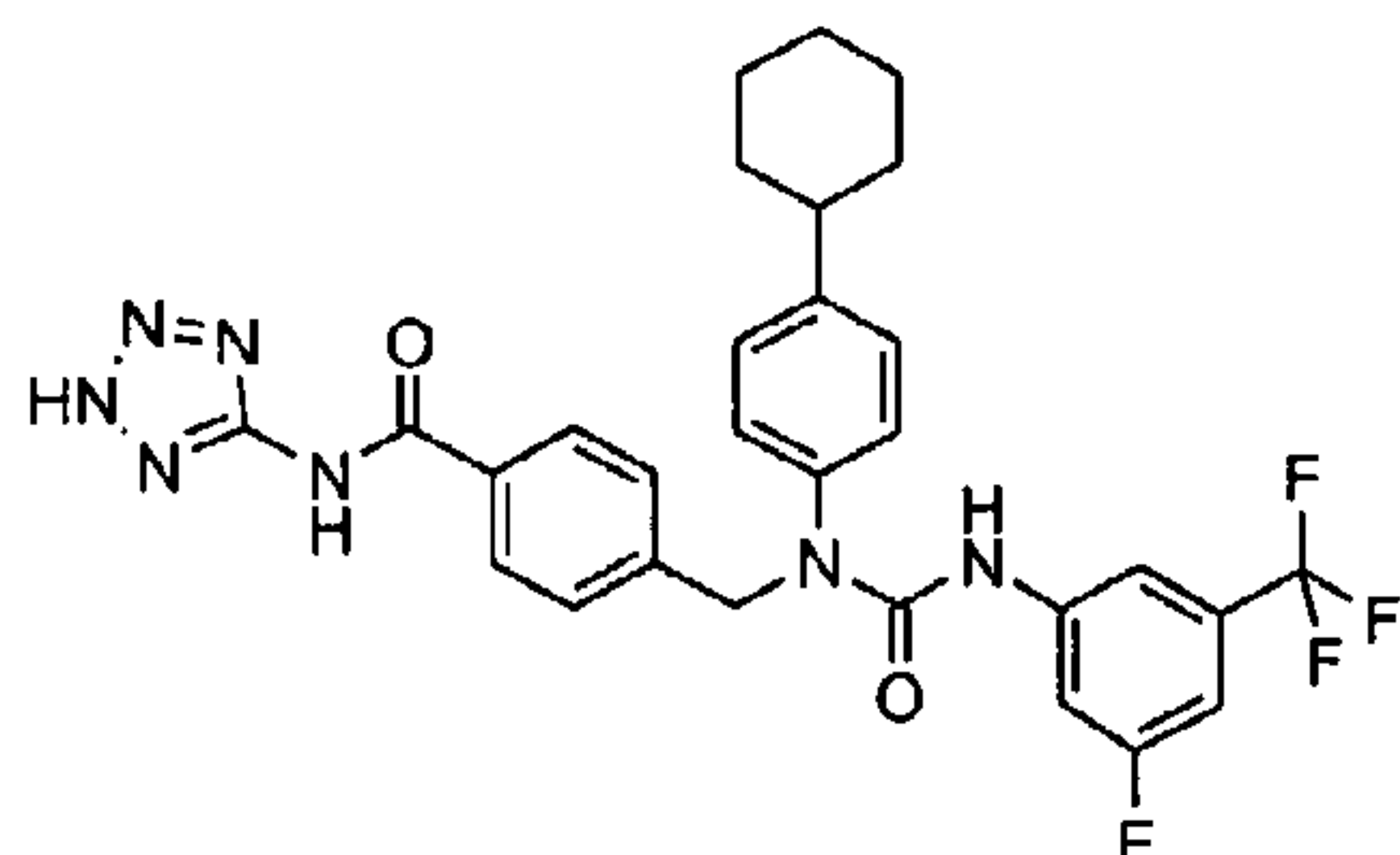
5-Methylsulfonyl-2-methylphenyl isocyanate was prepared from the corresponding 5-methylsulfonyl-2-methyl-1-nitrobenzene via reduction to the corresponding aniline followed by conversion to the isocyanate as described previously.

25 ^1H NMR (DMSO- d_6): δ 12.10 (s br, 1H); 8.15 (s, 1H); 8.05 (d, 2H); 7.62 (m, 6H); 7.28 (dd, 4H); 5.03 (s, 2H); 3.15 (s, 3H); 2.10 (s, 3H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 588 ($M+1$). R_t = 7.10 min.

EXAMPLE 262 (general procedure (L))

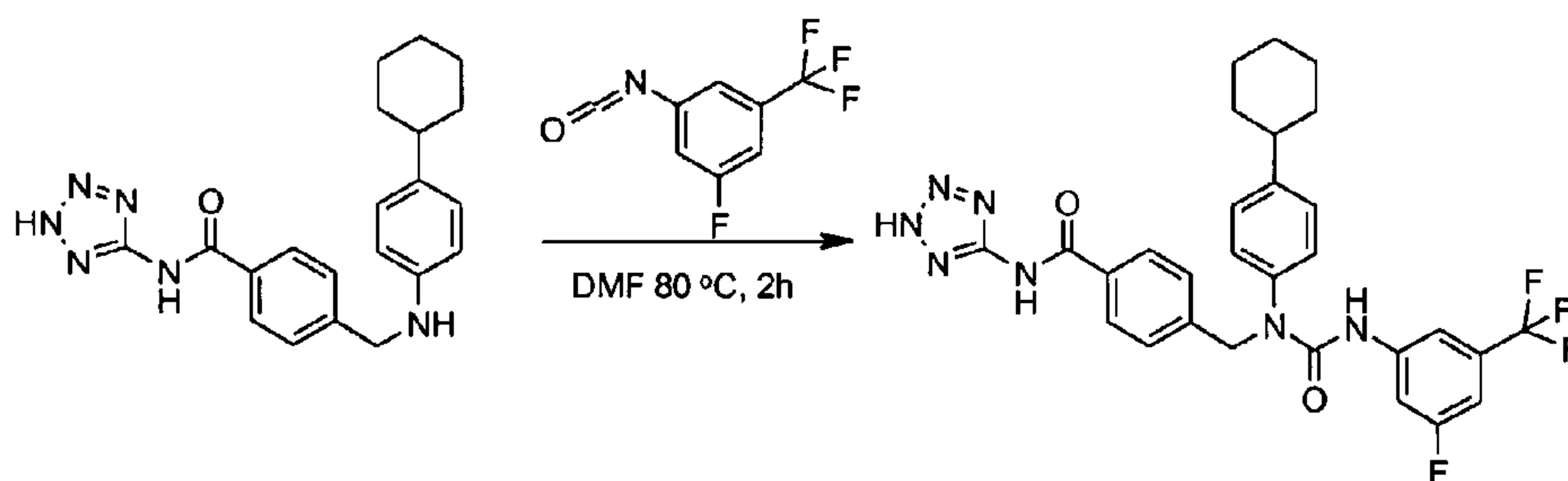
5 4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



10 ^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (s, 1H); 8.82 (s, 1H); 8.08 (d, 2H); 7.75 (m, 2H); 7.45 (d, 2H); 7.25-7.15 (m, 5H); 5.02 (s, 2H); 1.85-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 582 ($M+1$). R_t = 8.05 min.

Alternative method for the preparation of the title compound:



15

Preparation of 3-fluoro-5-trifluoromethylphenylisocyanate:

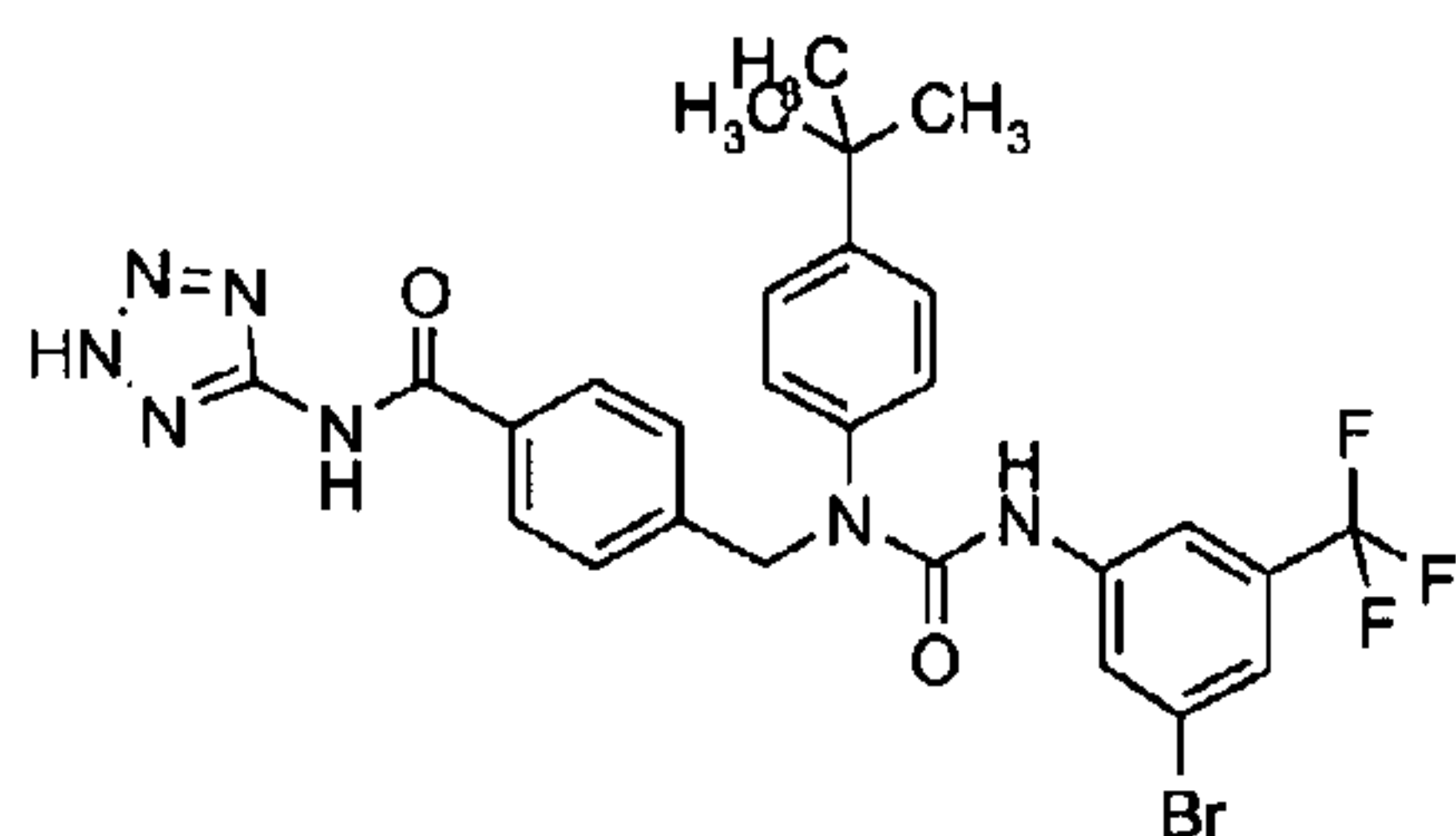
3-Fluoro-5-trifluoromethylaniline (2 g, 11.2 mmol) was dissolved in 20 mL diethylether and added concentrated hydrochloric acid (37%, 1.5 mL, 18 mmol). Upon stirring for 1 hour at 25°C the solvent was removed in vacuo and the white solid was stripped with toluene (3 x 20 mL). Diposgene (20 mL) was added to the hydrochloride salt and the mixture was refluxed over night. Excess diposgene was removed in vacuo and the clear oil was stripped with toluene (3 x 20 mL). The obtained isocyanate was used without further purification.

Preparation of 4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide:

A slurry of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (3 g, 7.96 mmol) in DMF (50 mL) was added to the above 3-fluoro-5-trifluoromethylphenylisocyanate and the mixture was heated to 80°C. After 2 hours the reaction was allowed to cool to 25°C and acetonitrile (500 mL) was added. The mixture was filtered, the precipitate was discarded and the filtrate evaporated. The residue was refluxed in acetonitrile (75 mL) and allowed to cool to 25°C. After filtration, a new precipitate was formed affording the title compound (850 mg).

EXAMPLE 263 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-*tert*-butylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

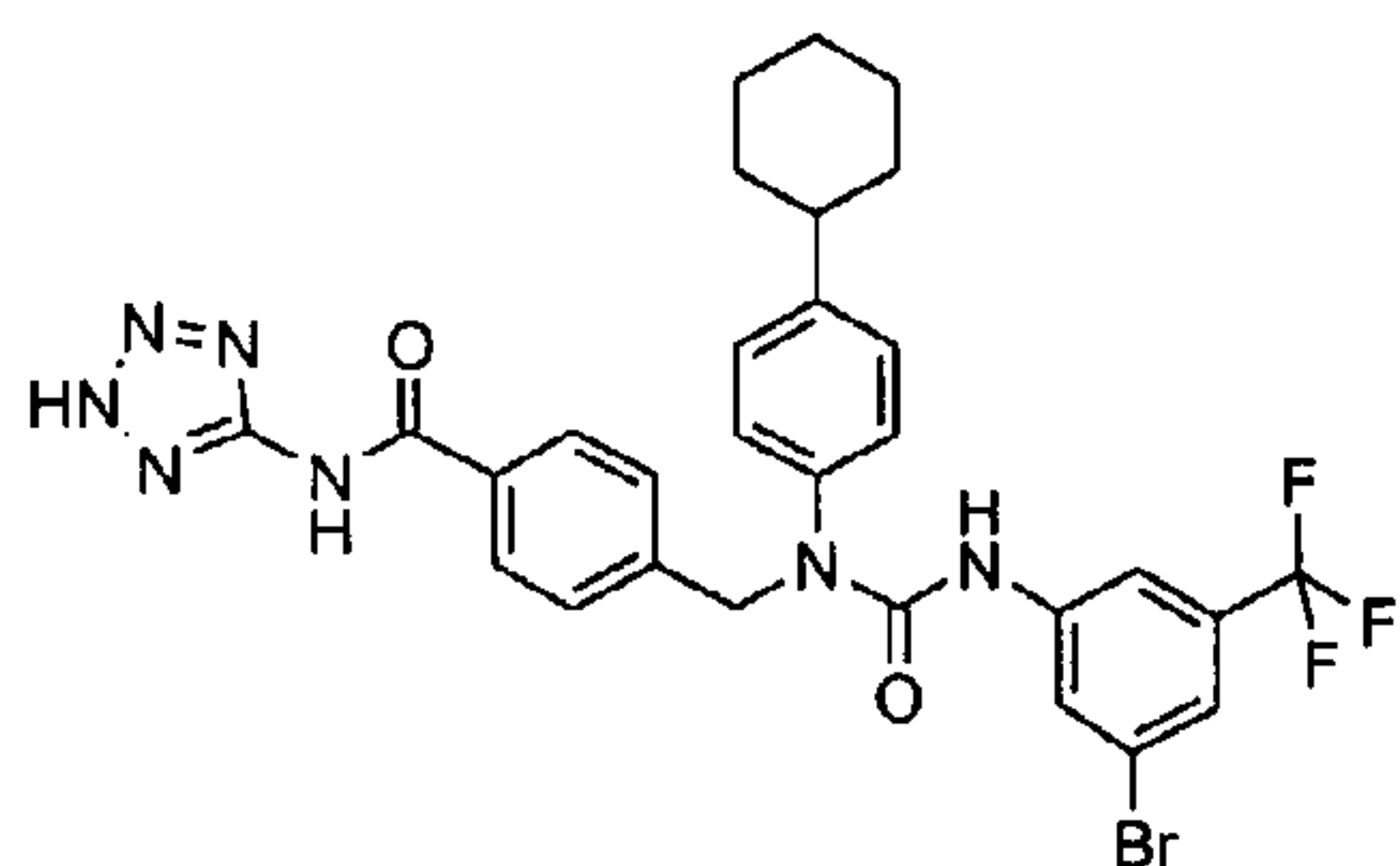


HPLC-MS (Method B): m/z = 617 ($M+1$). R_t = 7.95 min.

^1H NMR (DMSO): δ 12.40 (s, 1H); 8.80 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50 (s, 1H); 7.49 (d, 2H); 7.42 (d, 2H); 7.23 (d, 2H); 5.02 (s, 2H); 1.32 (s, 9H).

EXAMPLE 264 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method B): $m/z = 642$ ($M+1$). $R_t = 8.45$ min.

Alternative method for the preparation of the title compound:

5 Preparation of 3-bromo-5-trifluoromethylphenylisocyanate:

3-Bromo-5-trifluoromethylaniline (2.16 g, 9 mmol) was dissolved in 20 mL diethylether and added concentrated hydrochloric acid (37%, 1.5 mL, 18 mmol). Upon stirring for 1 hour at 25°C the solvent was removed in vacuo and the white solid was stripped with toluene (3 x 20 mL). Diphosgene (13 mL) was added to the ammonium chloride salt and the mixture was re-
10 fluxed for 3.5 hours until no solid material precipitated on cooling. Excess diphosgene was removed in vacuo and the clear oil was stripped with toluene (3 x 20 mL). The obtained isocyanate was used without further purification.

15 Preparation of 4-[3-(3-bromo-5-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide:

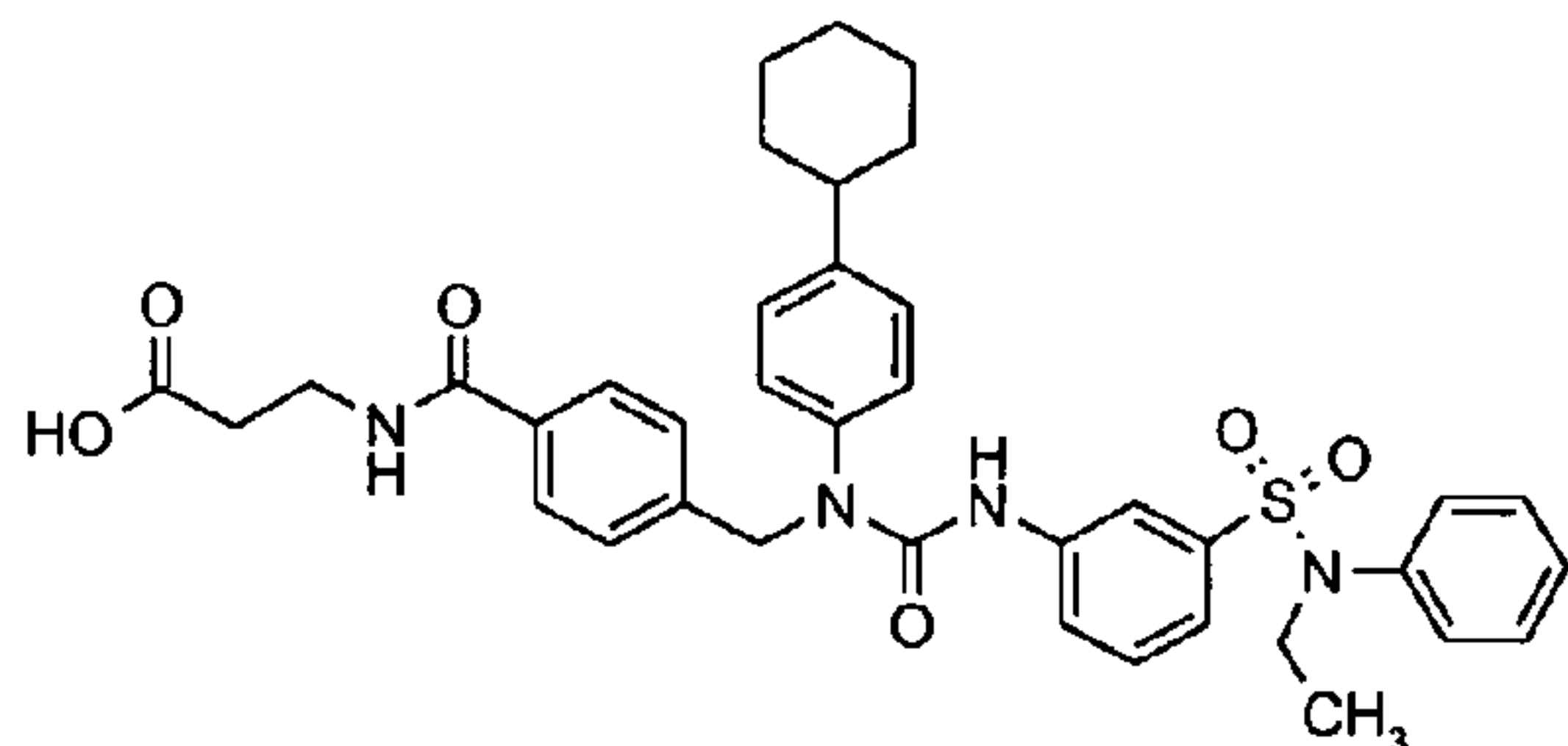
The above isocyanate was dissolved in DMF (20 mL) and added 4-[(4-cyclohexylphenyl-amino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (1.88 g, 5 mmol) and the mixture was heated at 80°C. After 1 hour the reaction was allowed to cool to 25°C and the solvent was evaporated. The residue was refluxed in acetonitrile (10 mL) and allowed to cool to 25°C. The de-
20 sired product was isolated by filtration and dried in vacuo (2.5 g).

^1H NMR (DMSO): δ 12.35 (s, 1H); 8.75 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50 (s, 1H); 7.48 (d, 2H); 7.23 (s, 4H); 5.00 (s, 2H); 1.85-1.65 (m, 5H); 1.45 -1.15 (m, 5H).

25 HPLC-MS (Method F): $m/z = 642$ ($M+1$). $R_t = 5.67$ min.

EXAMPLE 265 (general procedure (L))

3-(4-{1-(4-Cyclohexylphenyl)-3-[3-(ethylphenylsulfamoyl)phenyl]ureidomethyl}benzoylamino)-propionic acid



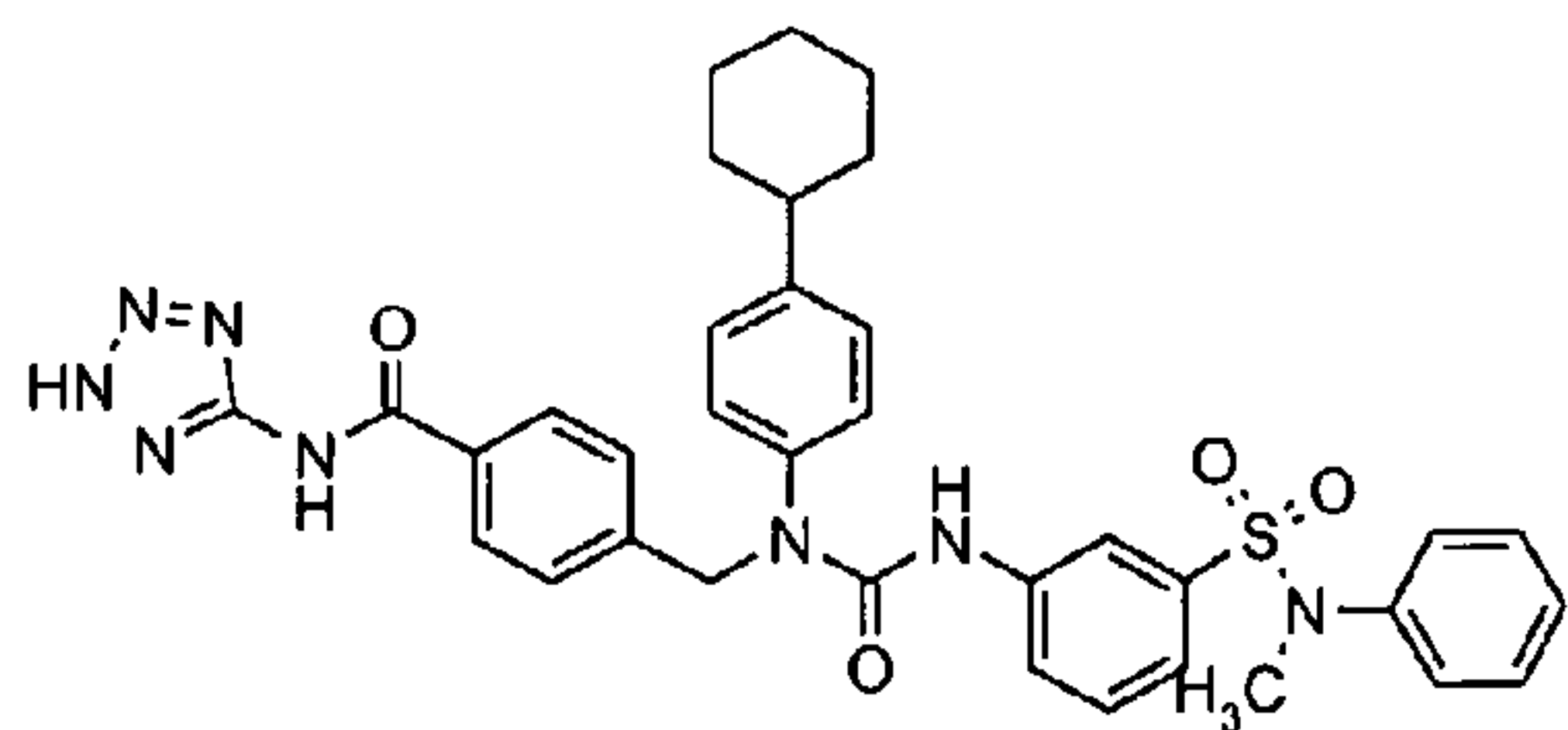
5

HPLC-MS (Method B): m/z = 683 ($M+1$). R_t = 7.60 min.

EXAMPLE 266 (general procedure (L))

4-{1-(4-Cyclohexylphenyl)-3-[3-(methylphenylsulfamoyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

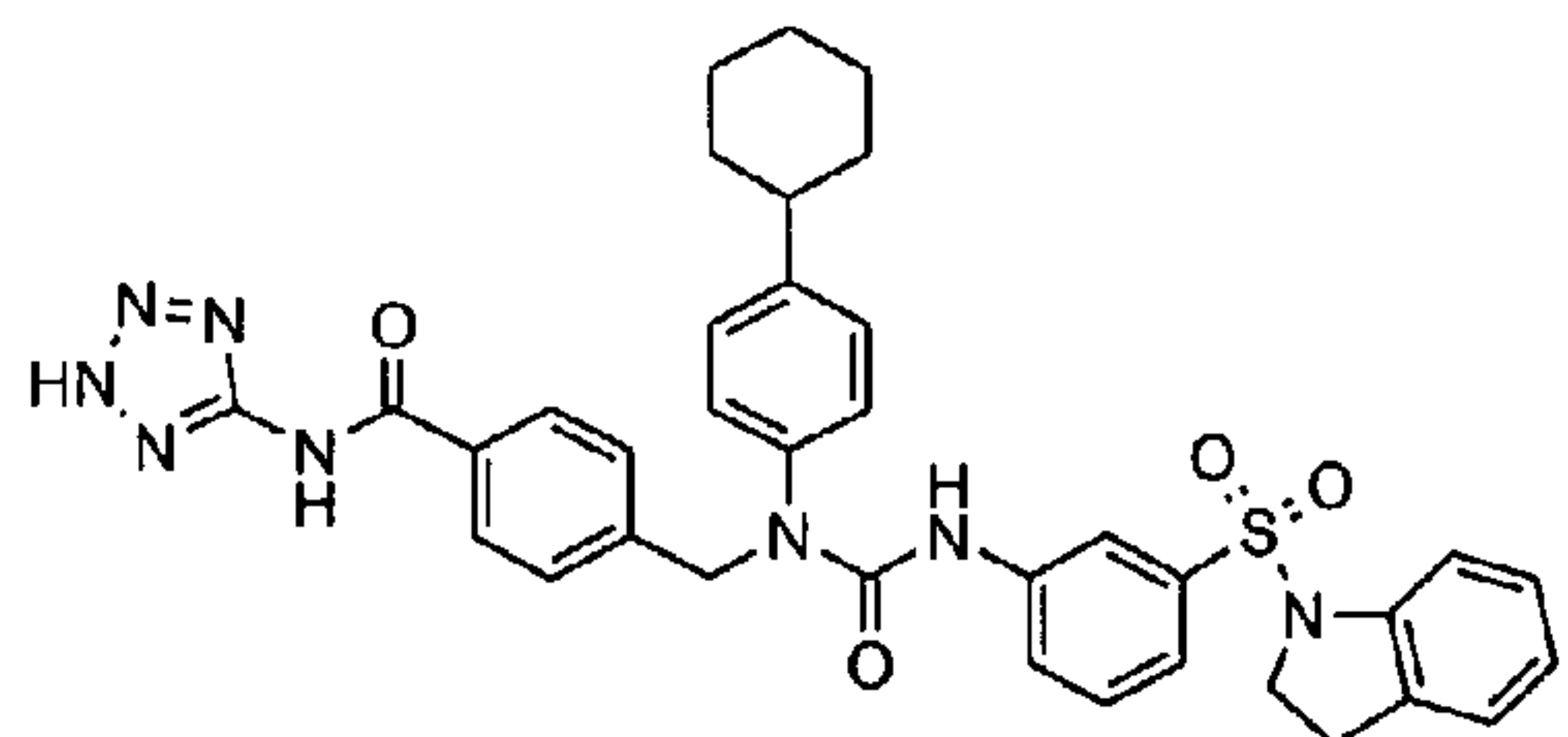
10



HPLC-MS (Method B): m/z = 665 ($M+1$). R_t = 7.67 min.

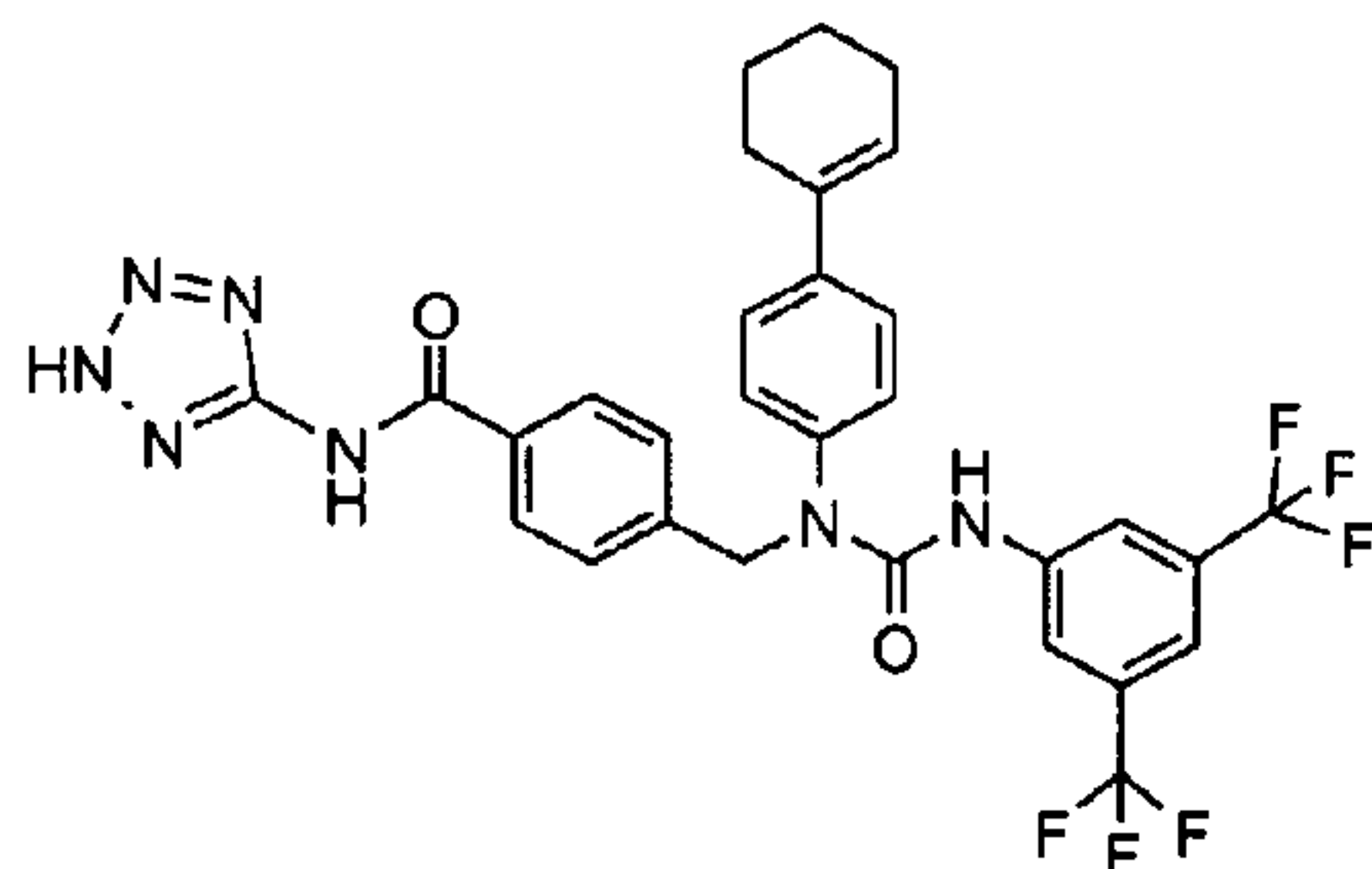
15 EXAMPLE 267 (general procedure (L))

4-{1-(4-Cyclohexylphenyl)-3-[3-(2,3-dihydroindole-1-sulfonyl)phenyl]ureidomethyl}-N-(2H-tetrazol-5-yl)benzamide

20 HPLC-MS (Method B): m/z = 677 ($M+1$). R_t = 7.75 min.

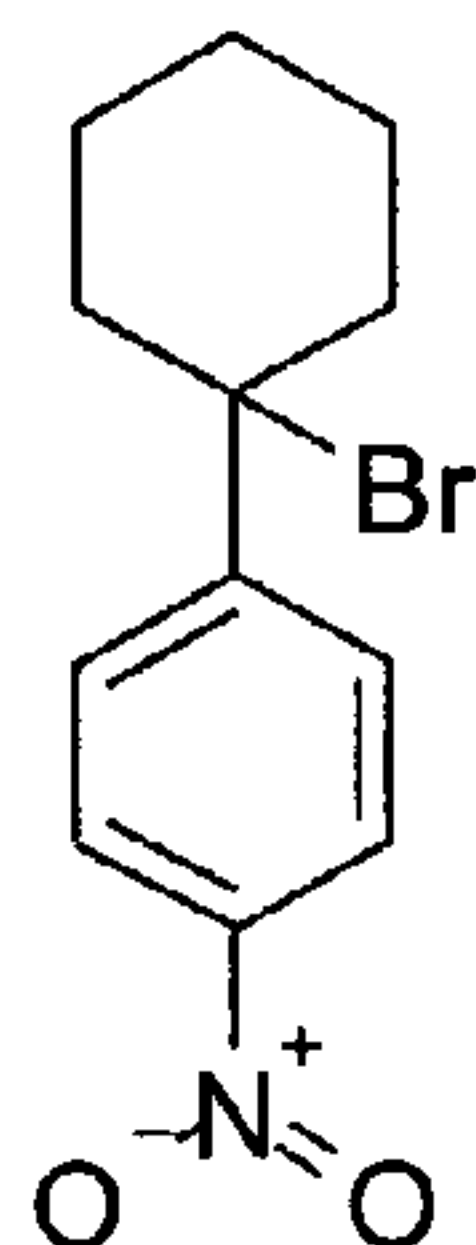
EXAMPLE 268 (general procedure (L))

4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

The starting material 4-(cyclohex-1-enyl)phenylamine was prepared in the following way:

Step 1: 1-(1-Bromocyclohexyl)-4-nitrobenzene

10

4-Cyclohexylnitrobenzene (22.6 g, 0.11 mol) and *N*-bromosuccinimide (21.6 g, 0.12 mol) were suspended in tetrachloromethane (200 mL) and a catalytic amount of dibenzoylperoxide was added. The reaction mixture was stirred at 80°C for 4.5 hours. The reaction mixture was concentrated in vacuo and the residue dissolved in ethyl acetate (400 mL) and washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (200 mL) and the combined organic phases were washed with water (3 x 150 mL), dried over MgSO₄ and concentrated in vacuo. The residue was crystallised from ethyl acetate and heptane to give 18.4 g of 1-(bromocyclohexyl)-4-nitrobenzene.

15

¹H NMR (DMSO-*d*₆): δ 1.29-1.40 (1H,m), 1.60-1.71 (3H,d), 1.73-1.85 (2H,m), 2.06-2.18 (2H,m), 2.55 (2H,m), 7.92 (2H,d), 8.34 (2H,d).

20

M.p.: 83.5-85.5°C.

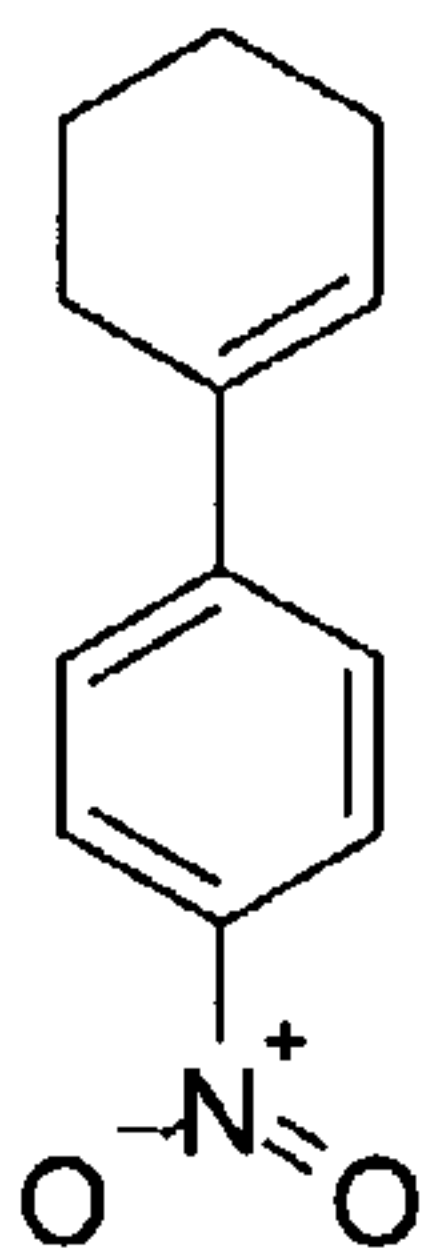
MA: calc

50.72% C, 4.97% H, 4.93% N; Found

50.65% C, 5.10% H, 4.91% N.

5

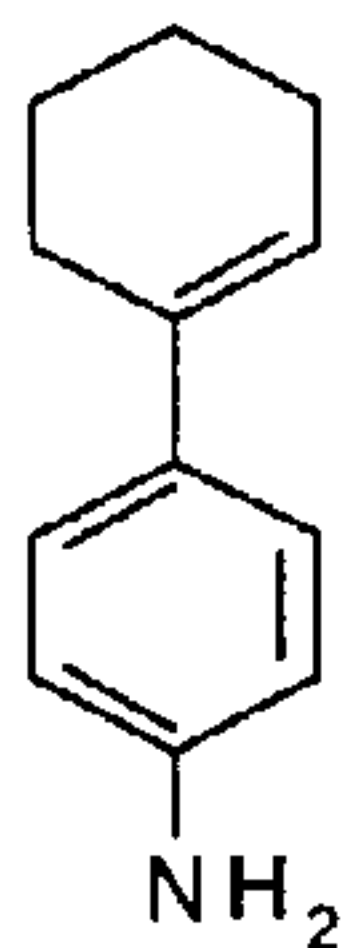
Step 2: 1-Cyclohex-1-enyl-4-nitrobenzene



10 1-(Bromocyclohexyl)-4-nitrobenzene (18.4 g, 64.8 mmol), lithium carbonate (5.3 g, 71.2 mmol), and lithium bromide (6.2 g, 71.2 mmol) were reacted together in DMF (100 mL) for 2 hours at 160°C. The reaction mixture was cooled to 20°C, diluted with ethyl acetate (500 mL), and washed with water (300 mL). The aqueous phase was extracted with ethyl acetate (200 mL) and the combined organic phases were washed with water (3 x 150 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified on silica (350 g) using ethyl
15 acetate and heptane (1:9) as eluent to give 11.7 g of 1-cyclohex-1-enyl-4-nitrobenzene.

¹H NMR (DMSO-*d*₆): δ 1.57-1.69 (2H,m), 1.60-1.70 (2H,m), 2.18-2.29 (2H,m), 2.38-2.46 (2H,m), 6.46 (1H,t), 7.67 (2H,d), 8.17 (2H,d).

20 Step 3: 4-(Cyclohex-1-enyl)phenylamine



1-Cyclohex-1-enyl-4-nitrobenzene (11.7 g, 57.6 mmol) was dissolved in hot absolute ethanol (170 mL). Stannous chloride (65 g, 288 mmol) was added and the reaction mixture was

stirred at reflux temperature for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was added ethyl acetate (700 mL) and water (700 mL), and neutralised to pH 7 with sodium hydroxide (4 N). Ethyl acetate (150 mL) was added and the mixture was filtered through celite. The organic phase of the filtrate was washed with water and a saturated solution of sodium chloride, dried over MgSO₄, and concentrated in vacuo. The residue was purified on silica (200 g) using ethyl acetate and heptane (1:4) as eluent to give 7.4 g of 4-(cyclohex-1-enyl)phenylamine.

HPLC-MS (method B): m/z: 174, R_t = 4.05 min.

¹H NMR (DMSO-*d*₆): δ 1.52-1.60 (2H,m), 1.63-1.72 (2H,m), 2.13 (2H,m), 2.28 (2H,m), 5.0 (2H,s), 5.90 (1H,t), 6.50 (2H,d), 7.08 (2H,d).

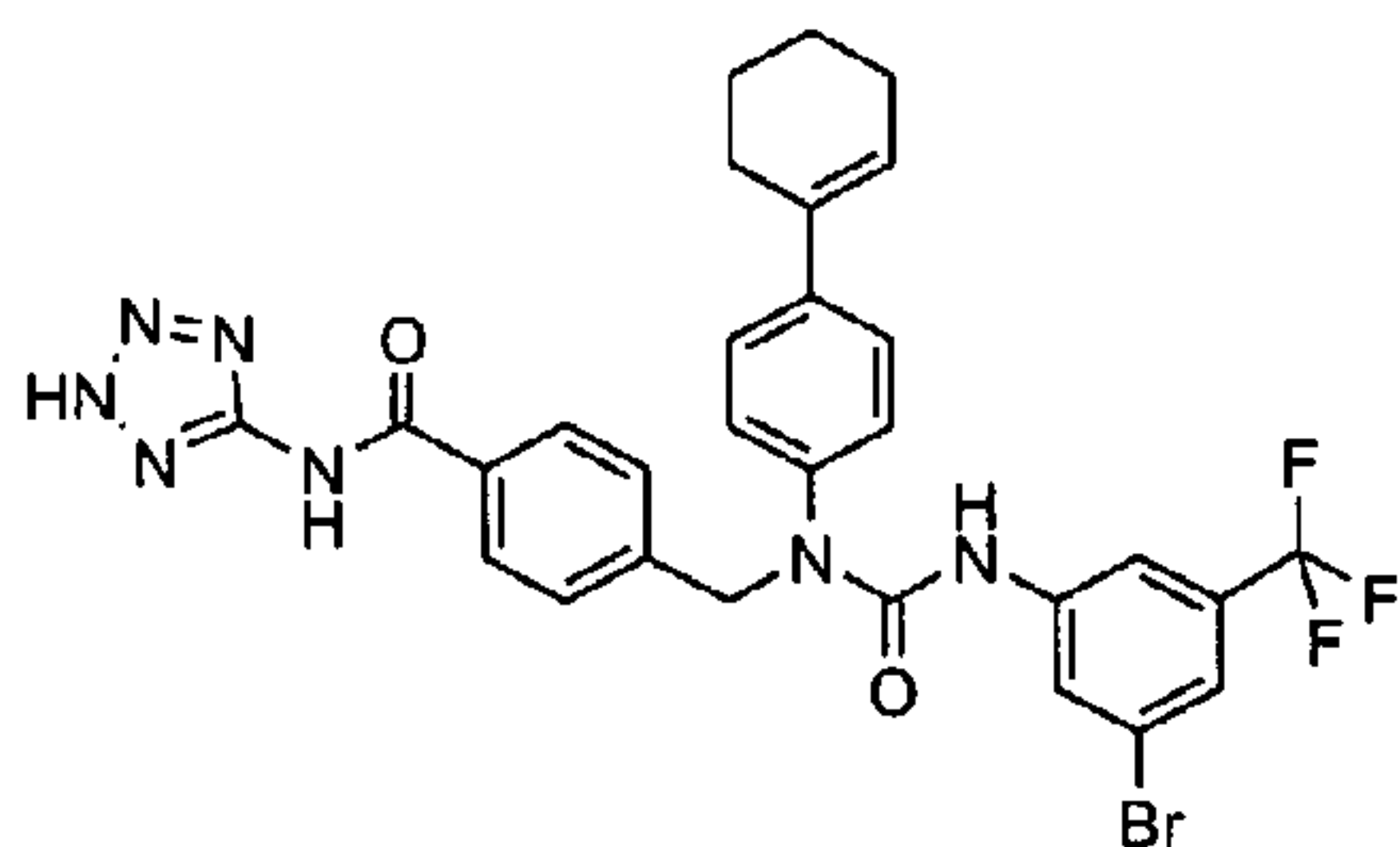
The title compound was prepared using 4-(cyclohex-1-enyl)phenylamine in step B.

¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.92 (s, 1H); 8.28 (s, 2H); 8.04 (d, 2H); 7.61 (s, 1H); 7.48 (d, 2H); 7.46 (d, 2H); 7.25 (d, 2H); 6.20 (s br, 1H); 5.03 (s, 2H); 2.38 (m br, 2H); 2.18 (m br, 2H); 1.71 (m br, 2H); 1.60 (m br, 2H).

HPLC-MS (Method B): m/z = 630 (M+1). R_t = 8.25 min.

EXAMPLE 269 (general procedure (L))

4-[3-(3-Bromo-5-trifluoromethylphenyl)-1-(4-cyclohex-1-enylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

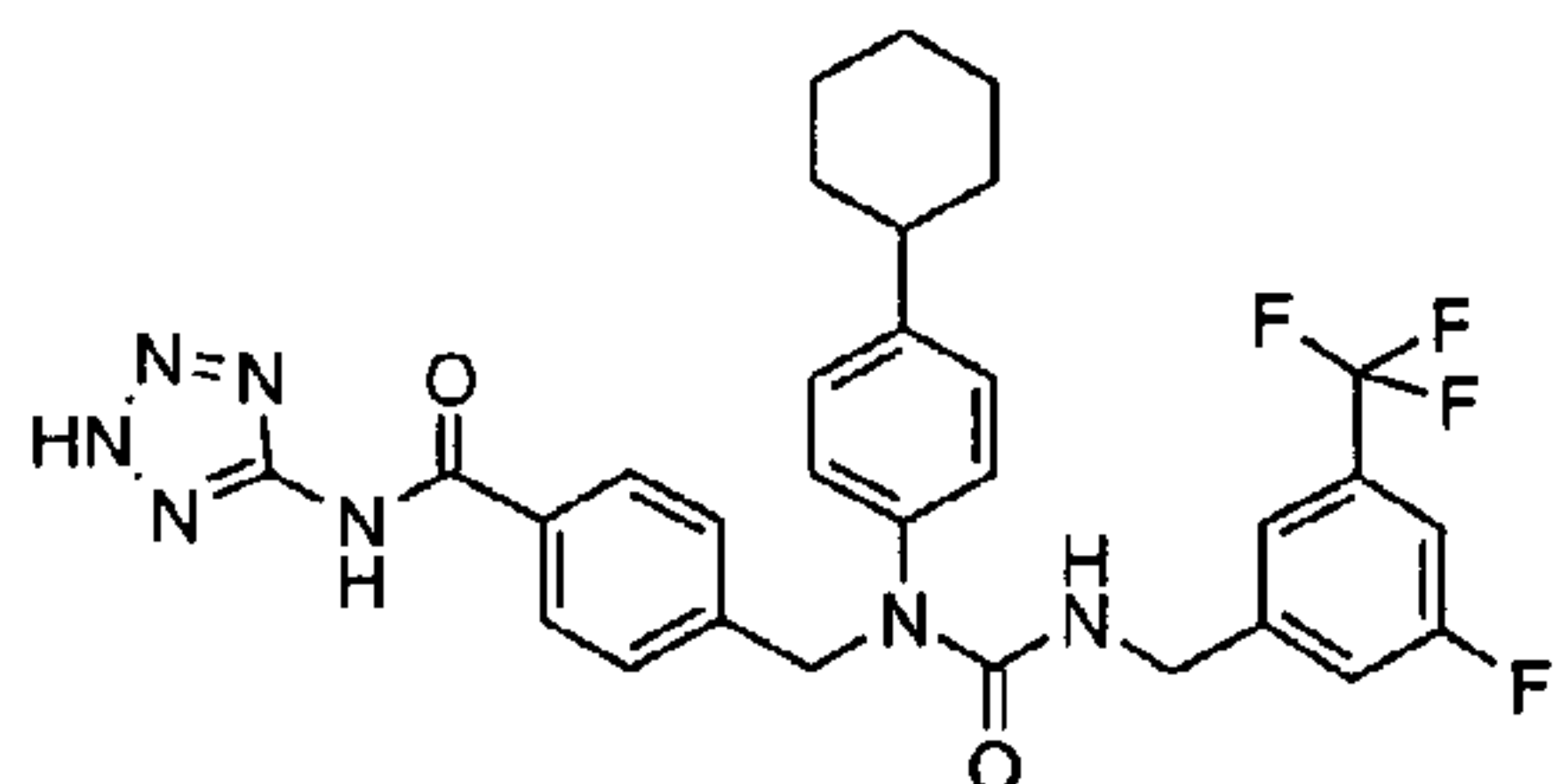


¹H NMR (DMSO-*d*₆): δ 12.40 (s, 1H); 8.75 (s, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.92 (s, 1H); 7.50-7.35 (m, 5H); 7.25 (d, 2H); 6.20 (s br, 1H); 5.03 (s, 2H); 2.35 (m br, 2H); 2.15 (m br, 2H); 1.72 (m br, 2H); 1.60 (m br, 2H)

HPLC-MS (Method B): m/z = 641 ($M+1$). R_t = 8.27 min.

EXAMPLE 270 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-fluoro-5-trifluoromethylbenzyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

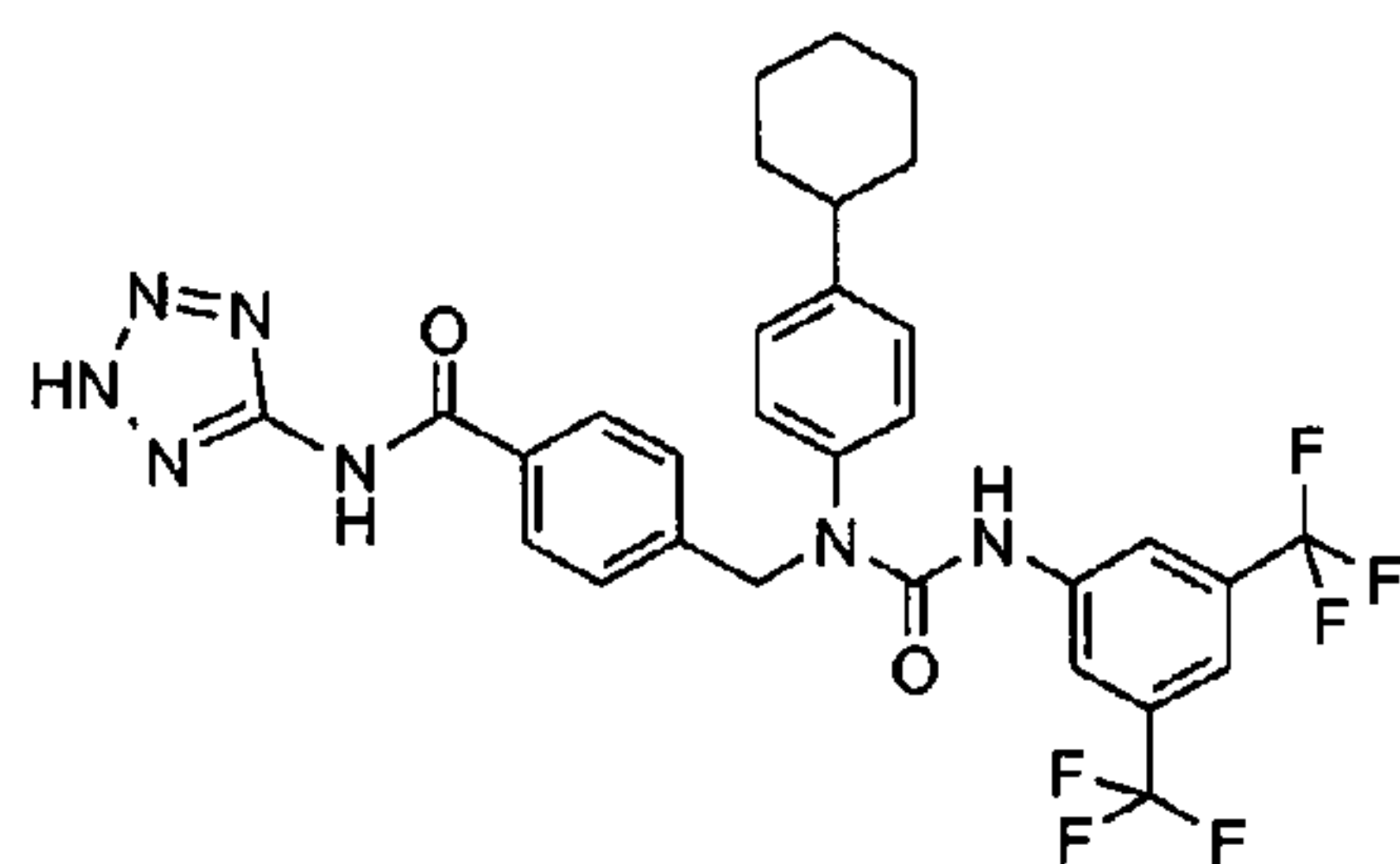


^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (s, 1H); 8.04 (d, 2H); 7.53 (d, 1H); 7.45 (s, 1H); 7.38 (d, 2H); 7.24 (d, 2H); 7.12 (d, 2H); 6.69 (t, 1H); 4.90 (s, 2H); 4.30 (d, 2H); 1.80-1.65 (m, 5H); 1.50-1.15 (m, 5H).

HPLC-MS (Method B): m/z = 596 ($M+1$). R_t = 7.70 min.

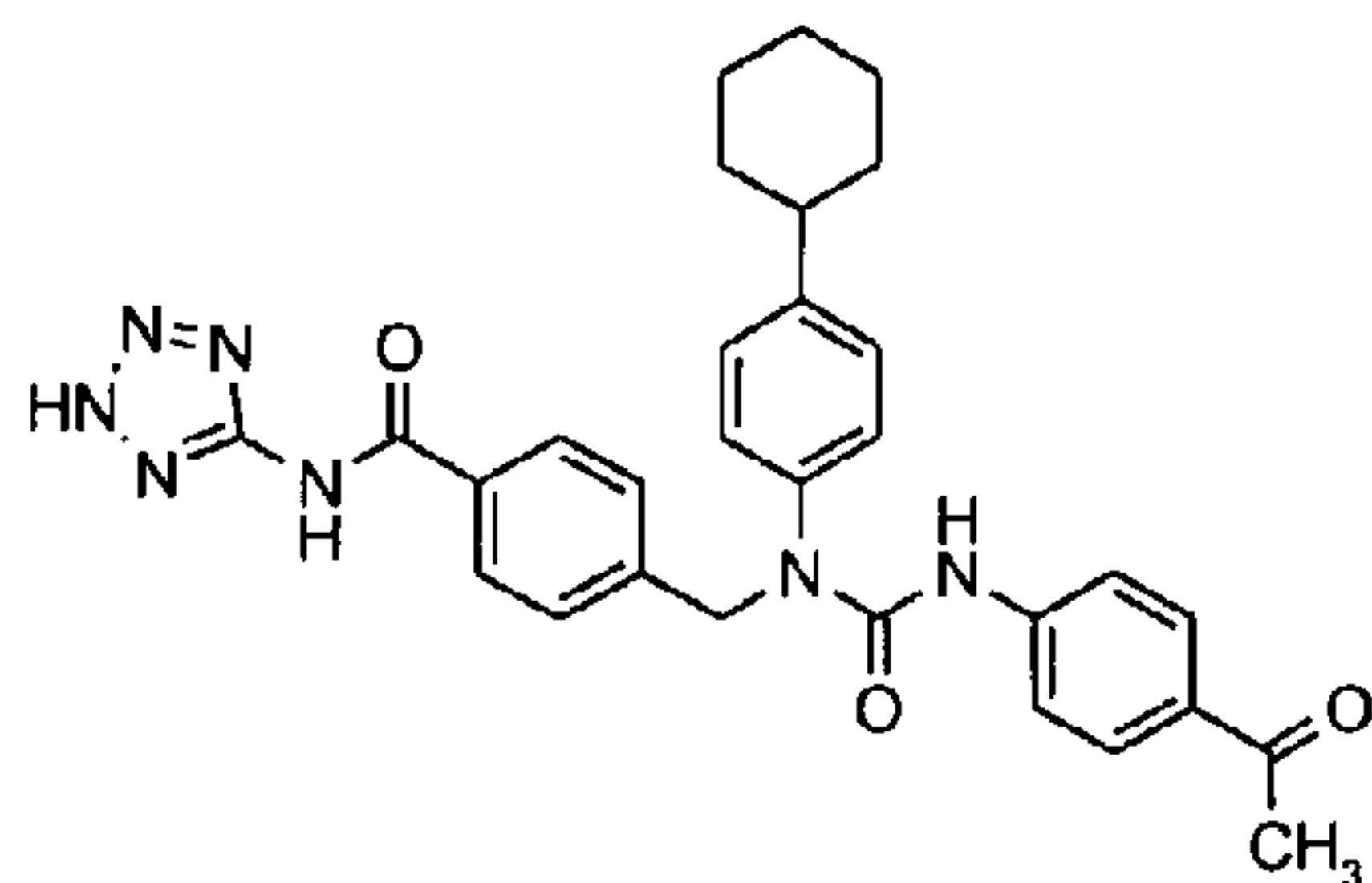
EXAMPLE 271 (general procedure (L))

4-[3-(3,5-Bis-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide



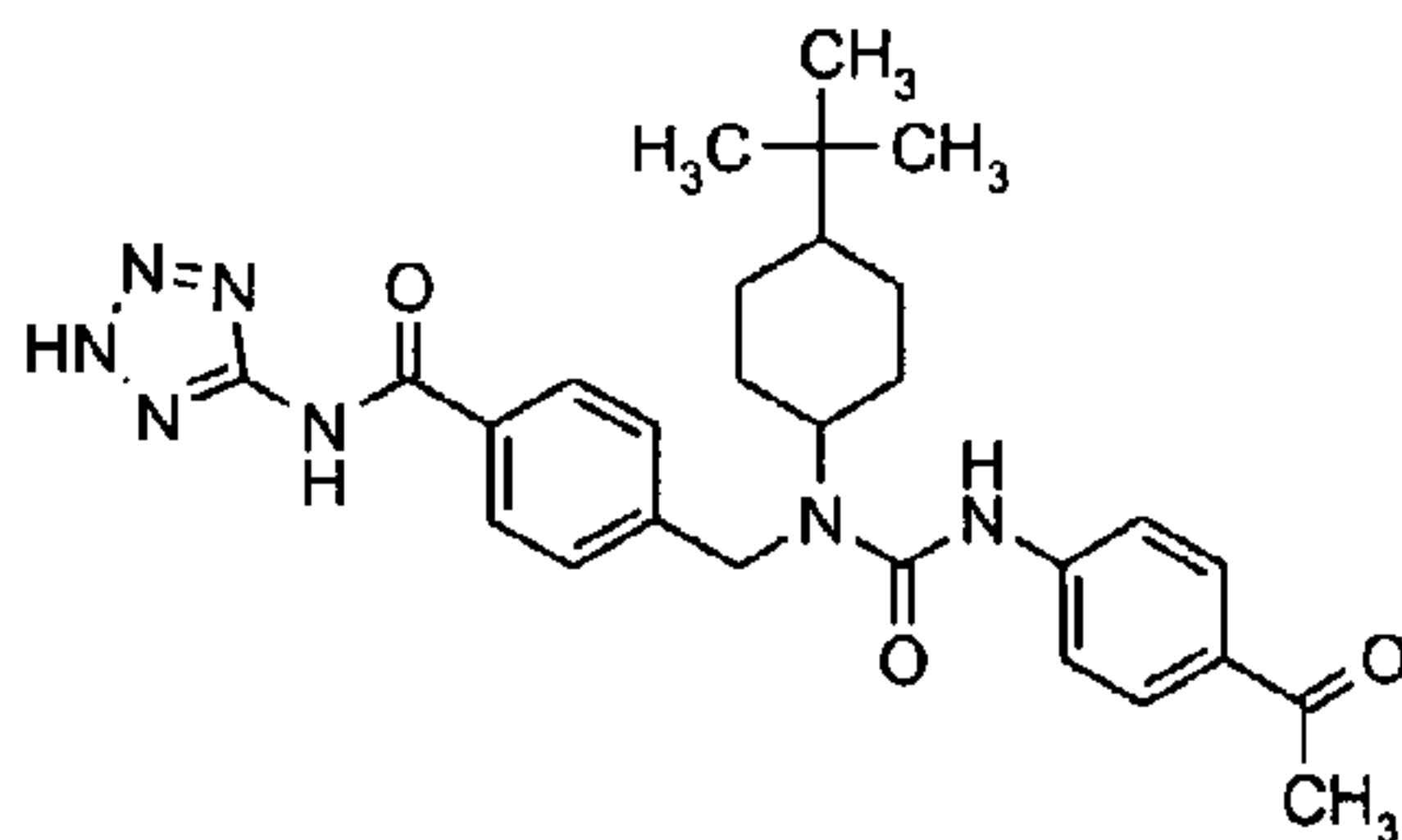
^1H NMR ($\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.95 (s, 1H); 8.25 (s, 2H); 8.05 (d, 2H); 7.62 (s, 1H); 7.45 (d, 2H); 7.24 (s, 4H); 5.02 (s, 2H); 1.82-1.65 (m, 5H); 1.50-1.15 (m, 5H)

HPLC-MS (Method B): m/z = 632 ($M+1$). R_t = 8.37 min.

EXAMPLE 272 (general procedure (L))4-[3-(4-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

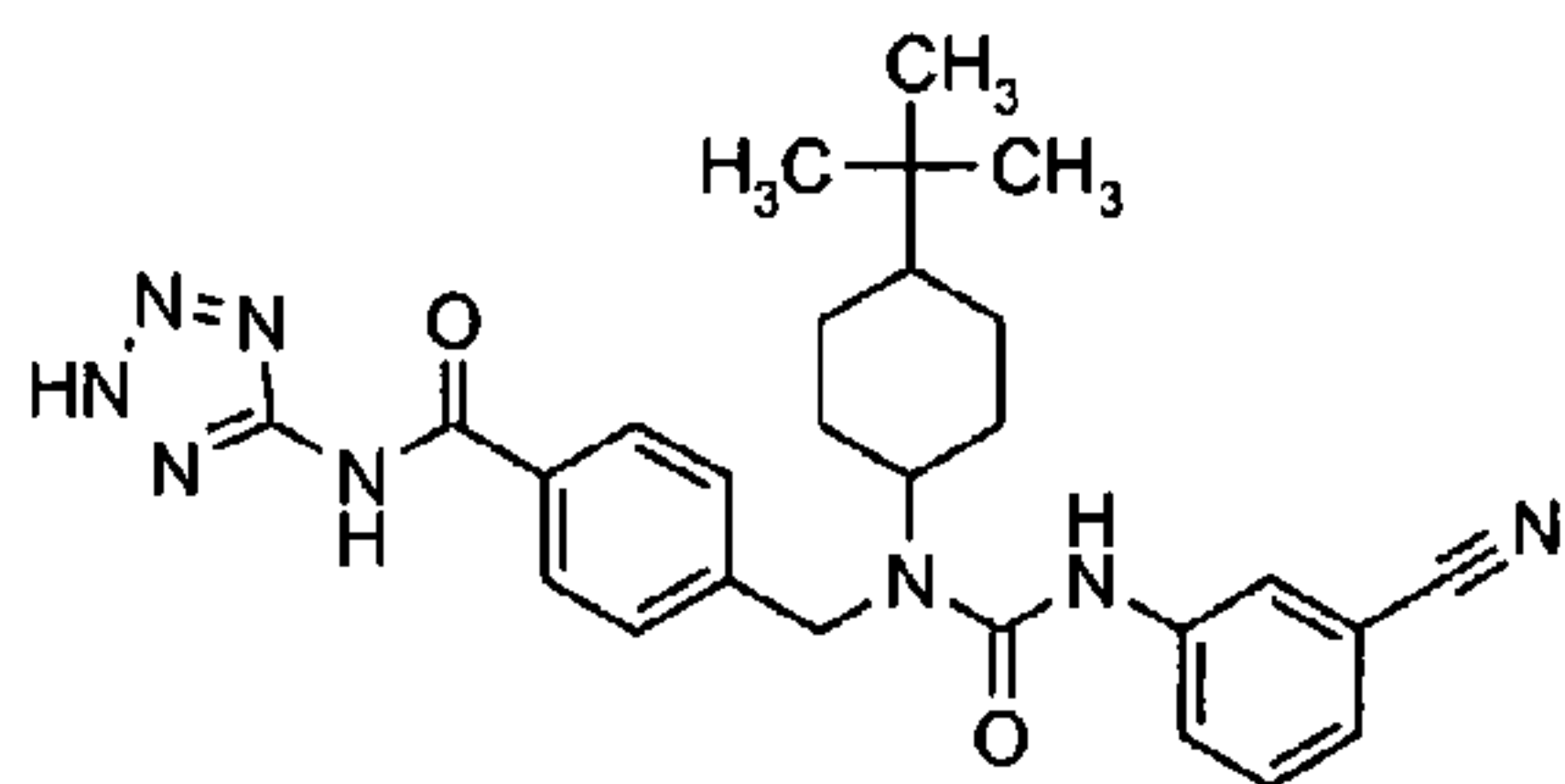
- 5 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.35 (s br, 1H); 8.62 (s, 1H); 8.05 (d, 2H); 7.85 (d, 2H); 7.60 (d, 2H); 7.45 (d, 2H); 7.20 (s, 4H); 5.00 (s, 2H); 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

HPLC-MS (method B): m/z = 538, R_t = 7.42 min.

10 EXAMPLE 273 (general procedure (L))4-[3-(4-Acetylphenyl)-1-(4-*tert*-butylcyclohexyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

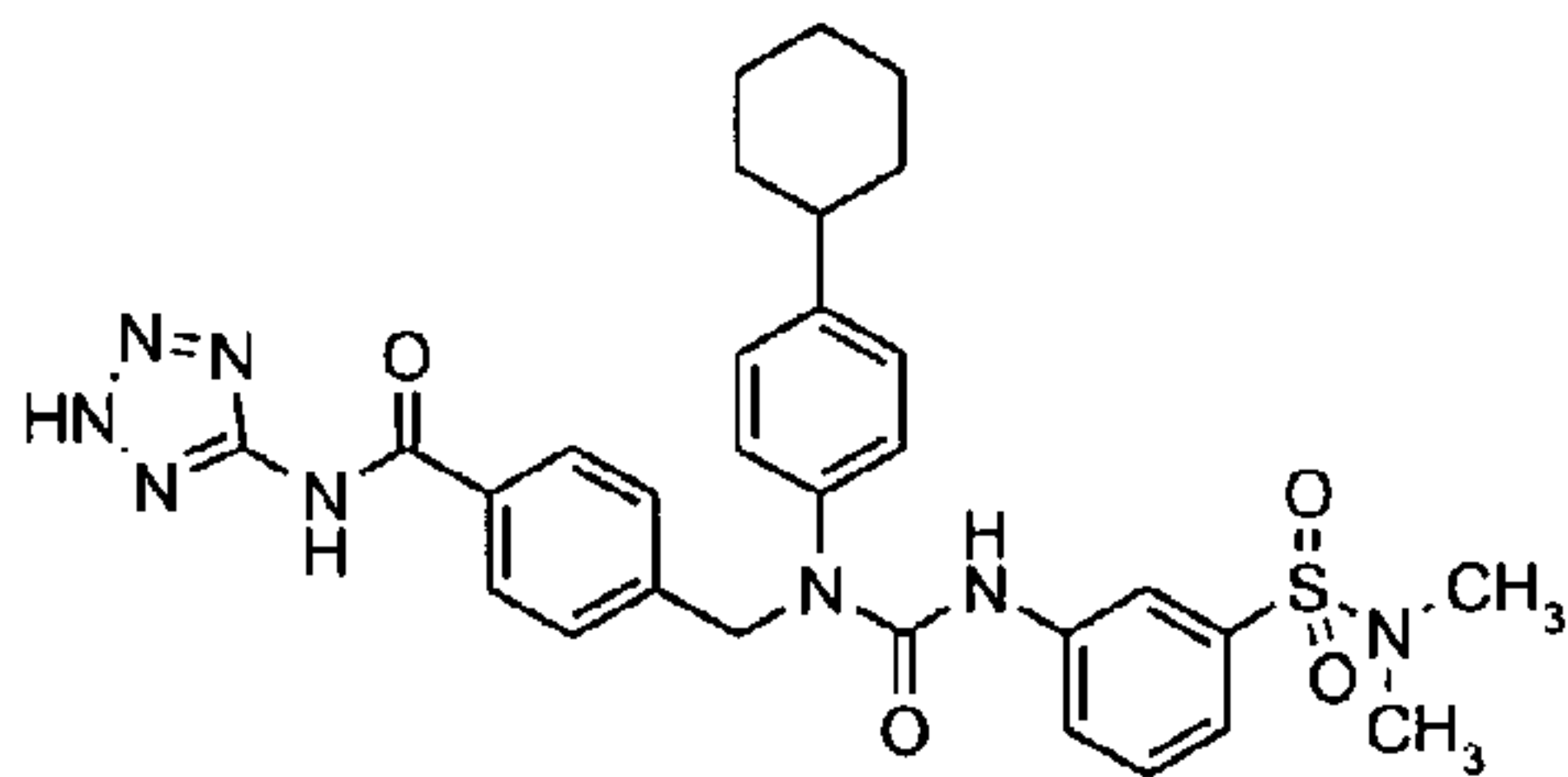
- ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.35 (s br, 1H); 8.85 (s, 1H); 8.05 (d, 2H); 7.85 (d, 2H);
 15 7.62 (d, 2H); 7.43 (d, 2H); 4.70 (s, 2H); 4.10 (t br, 1H); 1.85-0.90 (m, 9H); 0.85 (s, 9H).

HPLC-MS (method B): m/z = 518, R_t = 7.35 min.

EXAMPLE 274 (general procedure (L))**4-[1-(4-*tert*-Butylcyclohexyl)-3-(3-cyanophenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

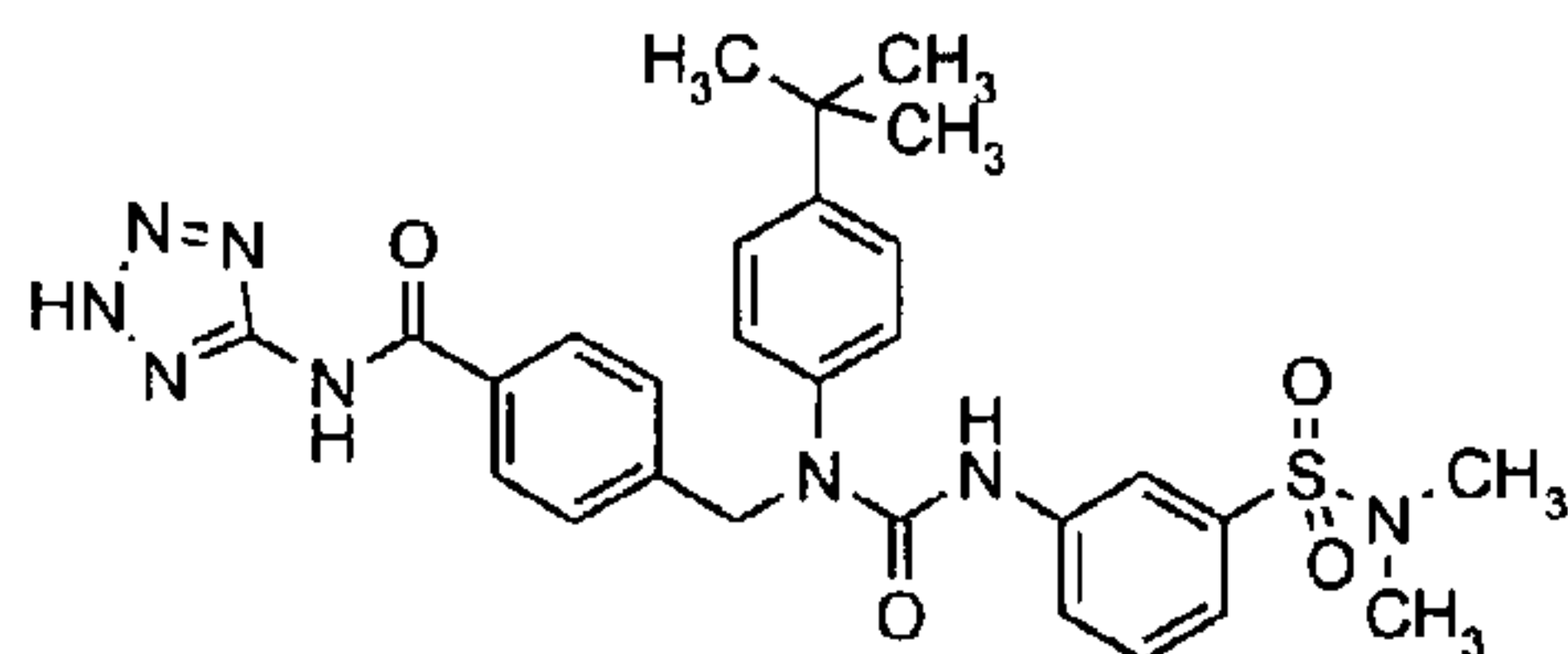
- 5 ^1H NMR (300 MHz, DMSO- d_6): δ 12.30 (s br, 1H); 8.73 (s, 1H); 8.05 (d, 2H); 7.93 (s, 1H); 7.75 (d, 1H); 7.50-7.30 (m, 4H); 4.65 (s, 2H); 4.08 (t br, 1H); 1.83-0.90 (m, 9H); 0.85 (s, 9H).

HPLC-MS (method B): m/z = 501, R_t = 7.62 min.

10 **EXAMPLE 275 (general procedure (L))****4-[1-(4-Cyclohexylphenyl)-3-(3-dimethylsulfamoylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide**

- 15 ^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.73 (d, 1H); 7.50-7.40 (m, 3H); 7.30 (d, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 2.60 (s, 6H) 1.85-1.60 (m, 5H); 1.45-1.10 (m, 6H).

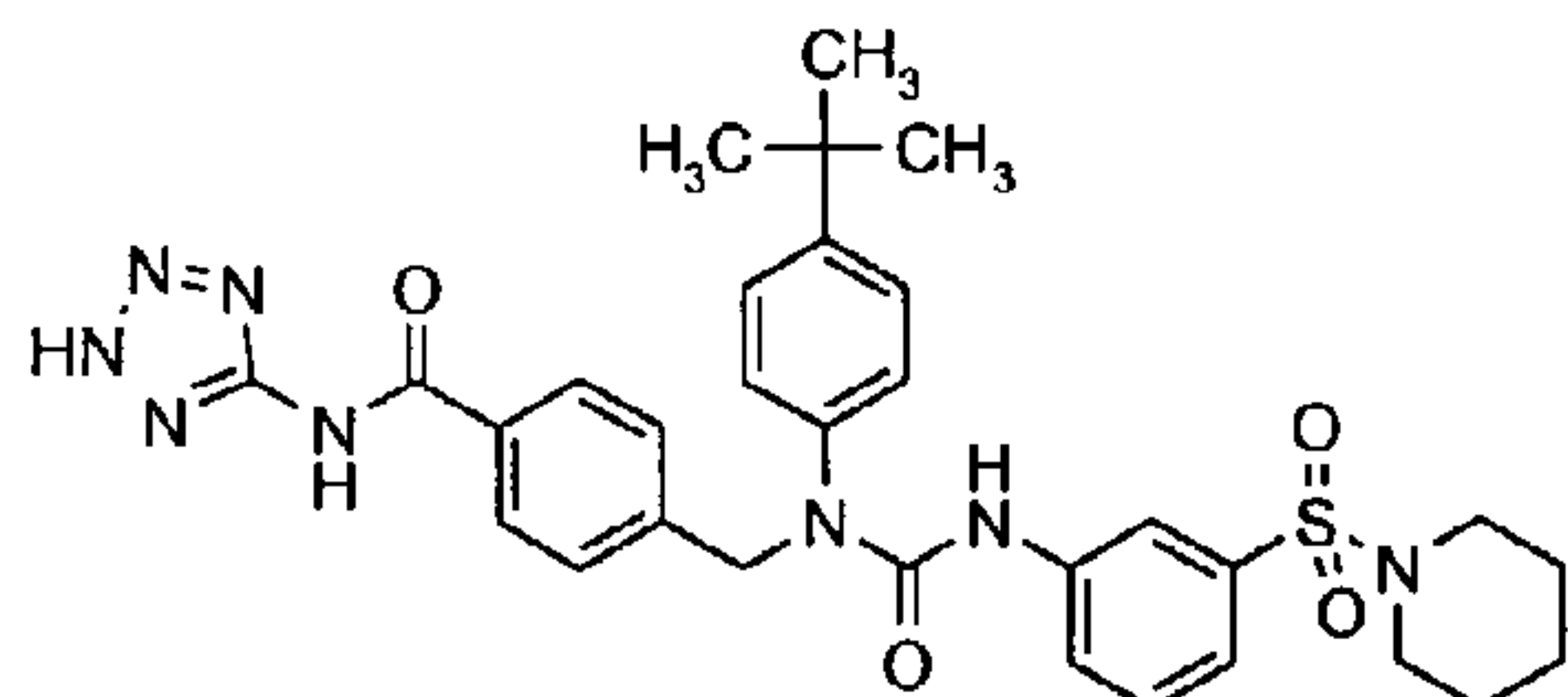
HPLC-MS (method B): m/z = 603, R_t = 7.08 min.

EXAMPLE 276 (general procedure (L))4-[1-(4-*tert*-Butylphenyl)-3-(3-dimethylsulfamoylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

5

^1H NMR (200 MHz, $\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (t, 1H); 7.70 (d, 1H); 7.55-7.35 (m, 5H); 7.30 (d, 1H); 7.23 (d, 2H); 5.00 (s, 2H); 2.60 (s, 6H) 1.28 (s, 9H).

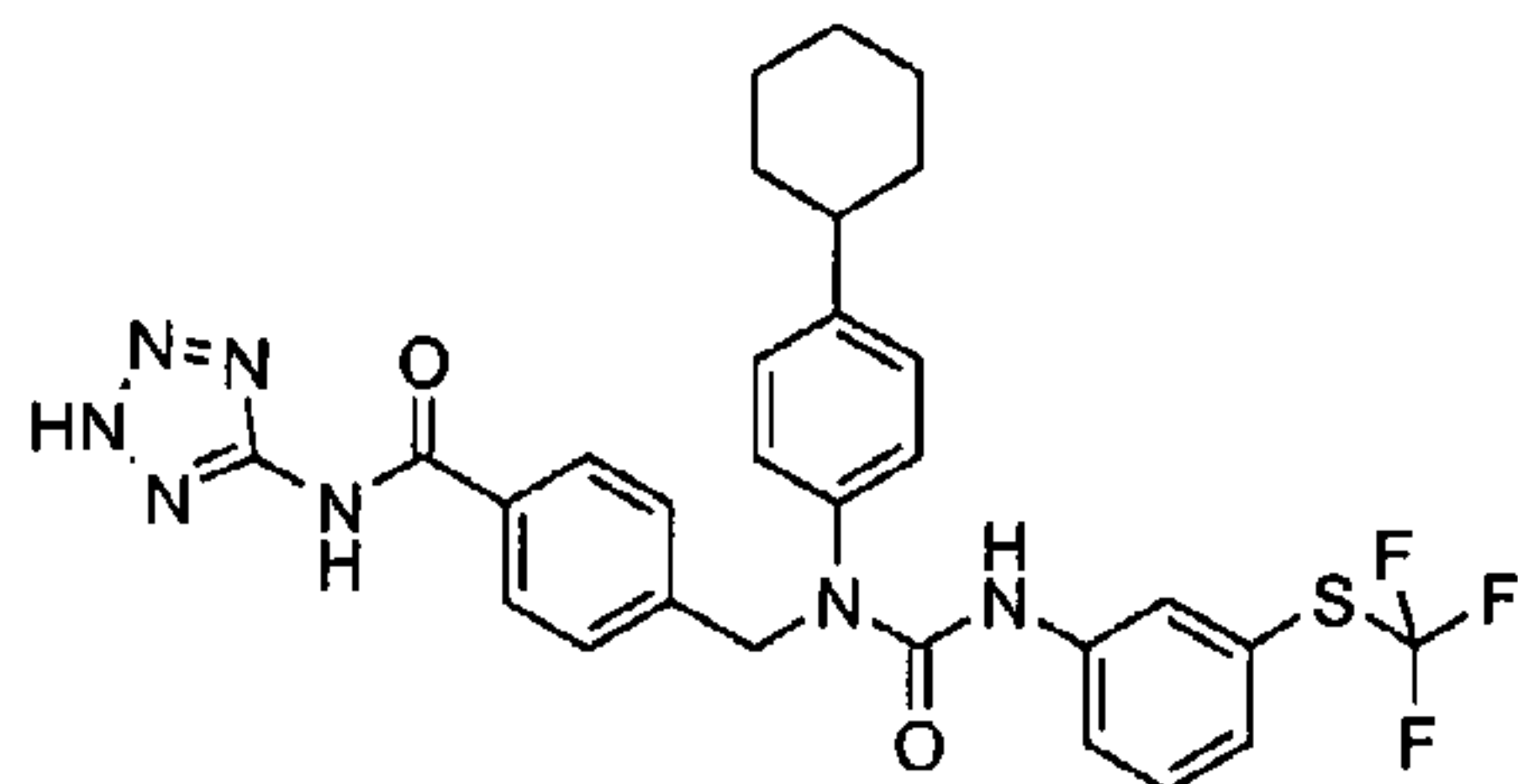
10 HPLC-MS (method B): m/z = 577, R_t = 6.48 min.

EXAMPLE 277 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-[3-(piperidine-1-sulfonyl)phenyl]ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)benzamide

15

^1H NMR (300 MHz), ($\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.70 (d, 1H); 7.52-7.18 (m, 8H); 5.00 (s, 2H); 2.90 (t, 4H) 1.65-1.35 (m, 6H); 1.28 (s, 9H).

20 HPLC-MS (method B): m/z = 617, R_t = 7.22 min.

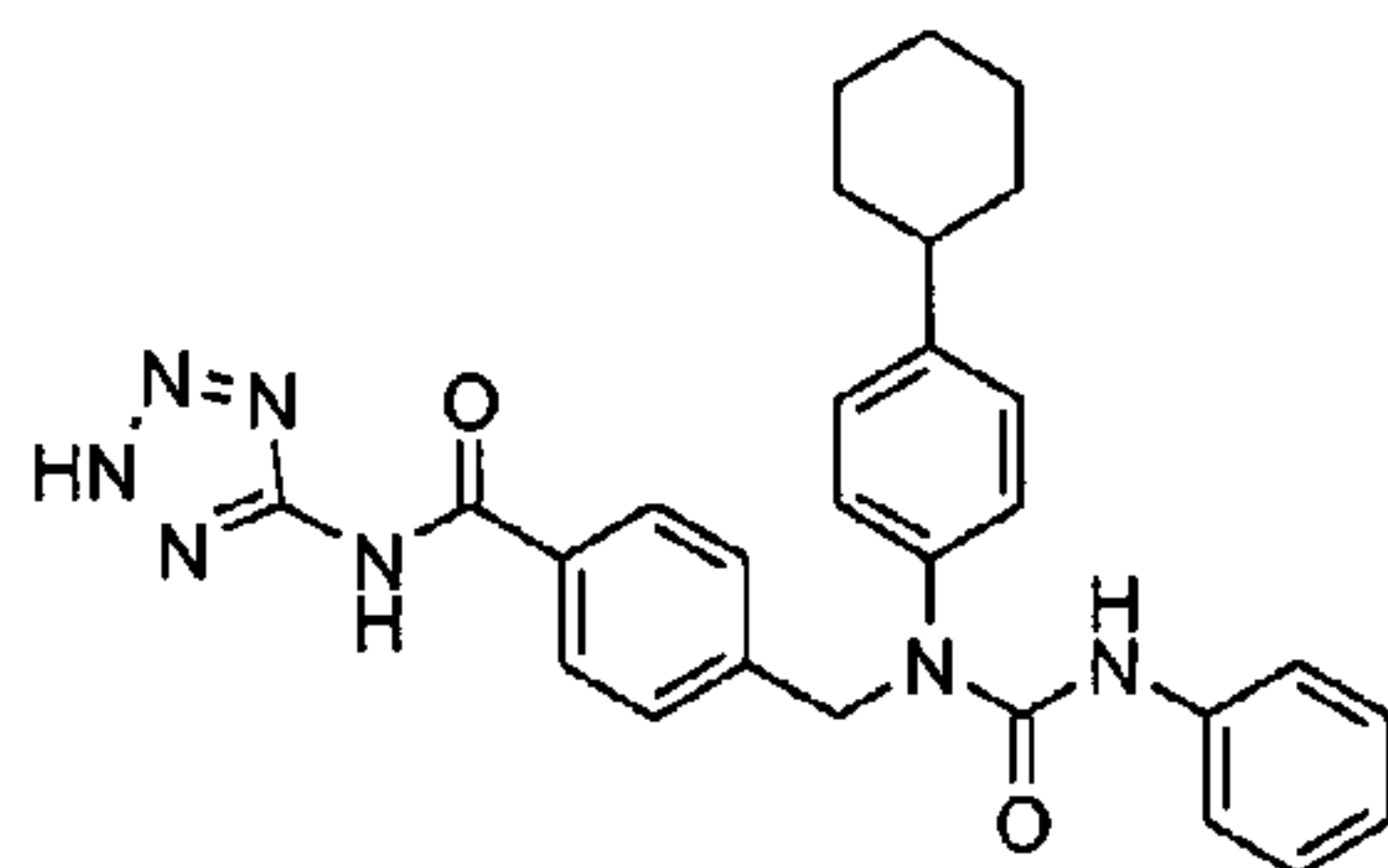
EXAMPLE 278 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-(3-trifluoromethylsulfonylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

5

^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.58 (s, 1H); 8.05 (d, 2H); 7.90 (s, 1H); 7.70 (d, 1H); 7.45 (d, 2H); 7.40 (t, 1H); 7.30-7.15 (m, 5H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

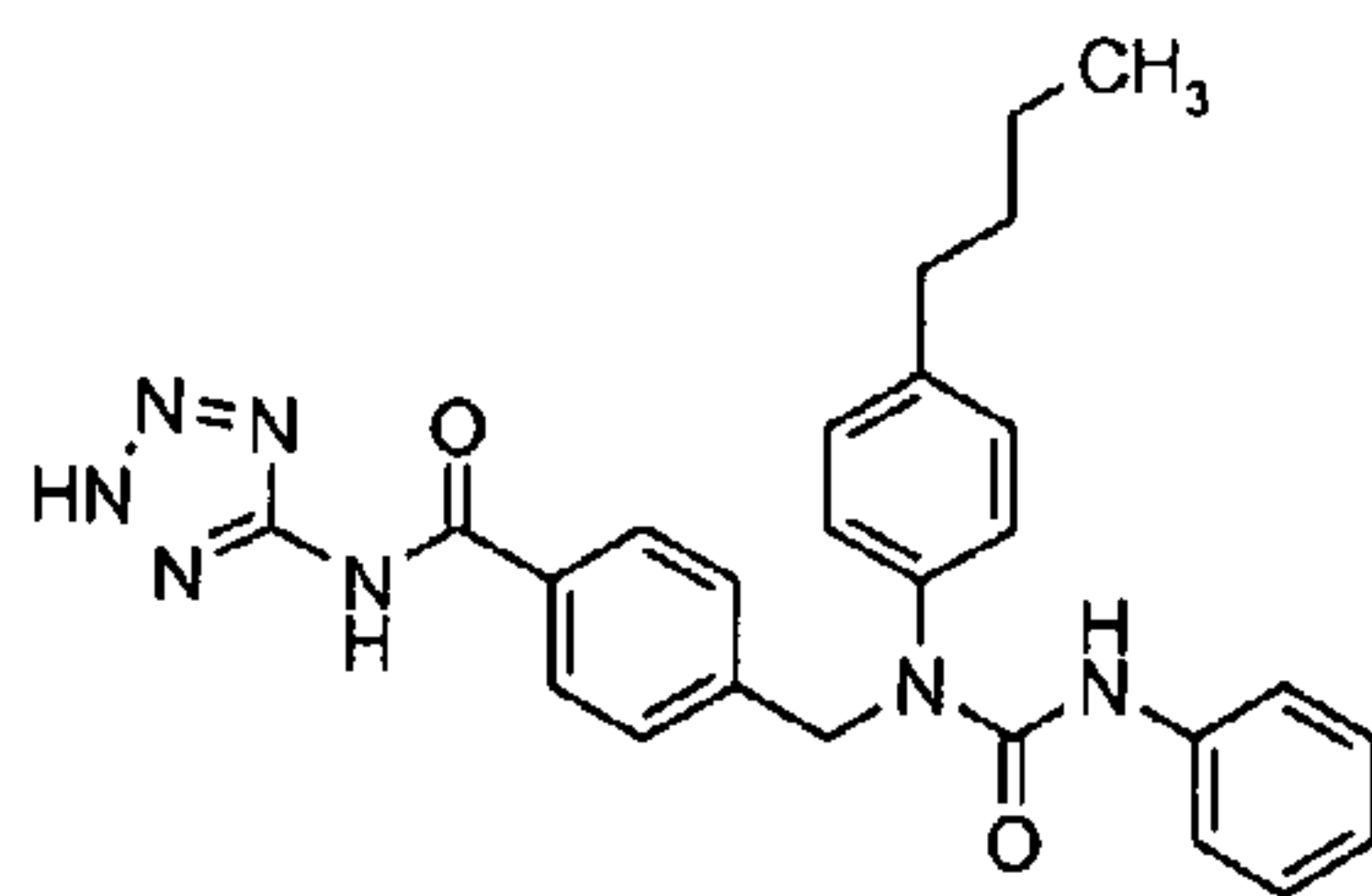
HPLC-MS (method B): m/z = 596, R_t = 8.30 min.

10

EXAMPLE 279 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-phenylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

15 ^1H NMR (300 MHz, DMSO- d_6): δ 12.35 (s br, 1H); 8.12 (s, 1H); 8.05 (d, 2H); 7.48 (d, 2H); 7.42 (t, 1H); 7.20 (m, 6H); 6.95 (t, 1H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

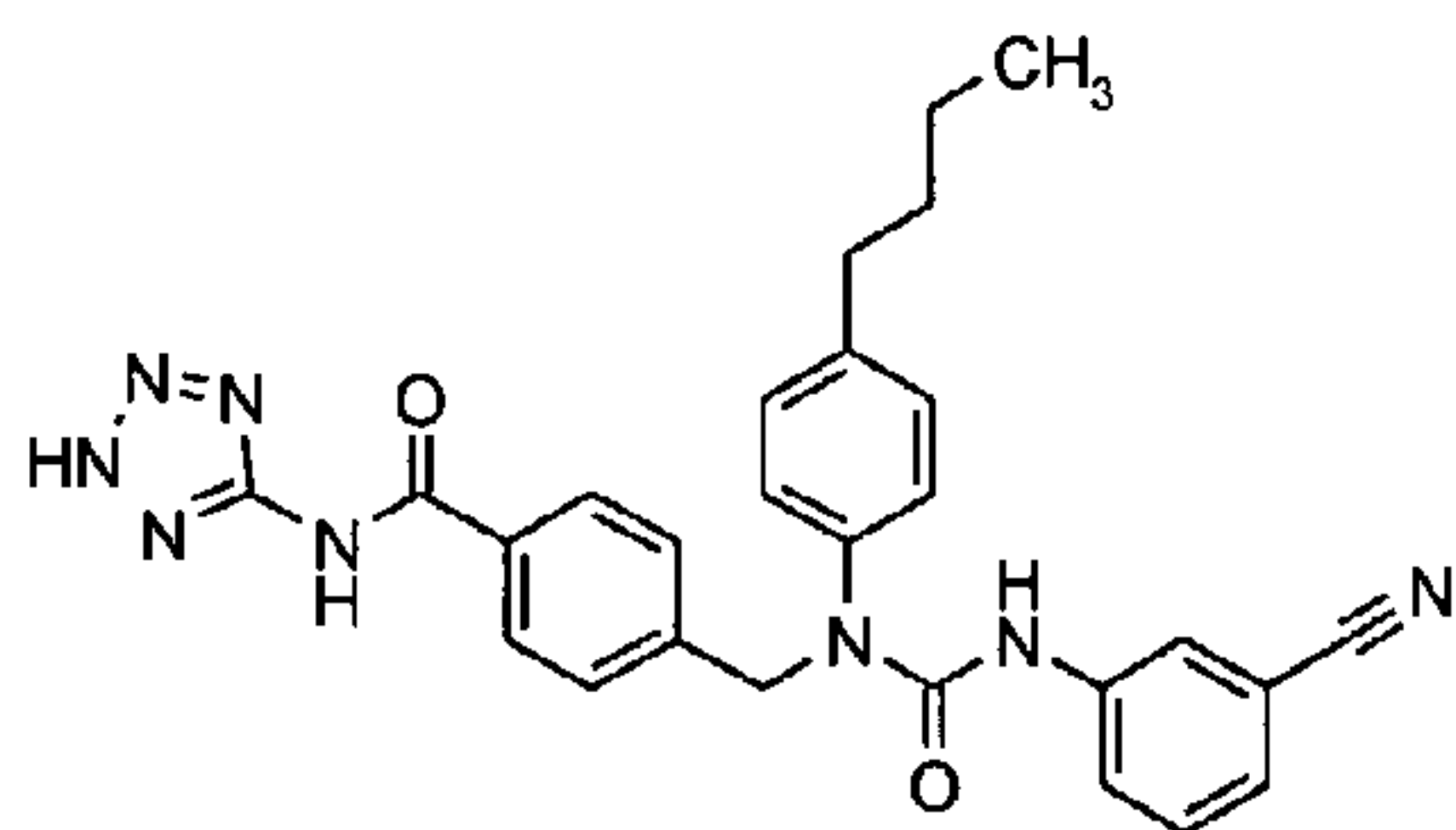
HPLC-MS (method B): m/z = 496, R_t = 7.72 min.

EXAMPLE 280 (general procedure (L))**4-[1-(4-Butylphenyl)-3-phenylureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

- 5 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.35 (s br, 1H); 8.10 (s, 1H); 8.04 (d, 2H); 7.46 (d, 2H); 7.42 (d, 2H); 7.30-7.10 (m, 6H); 6.95 (t, 1H); 5.00 (s, 2H); 2.55 (t, 2H); 1.55 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

HPLC-MS (method B): m/z = 470, R_t = 7.38 min.

10

EXAMPLE 281 (general procedure (L))**4-[1-(4-Butylphenyl)-3-(3-cyanophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide**

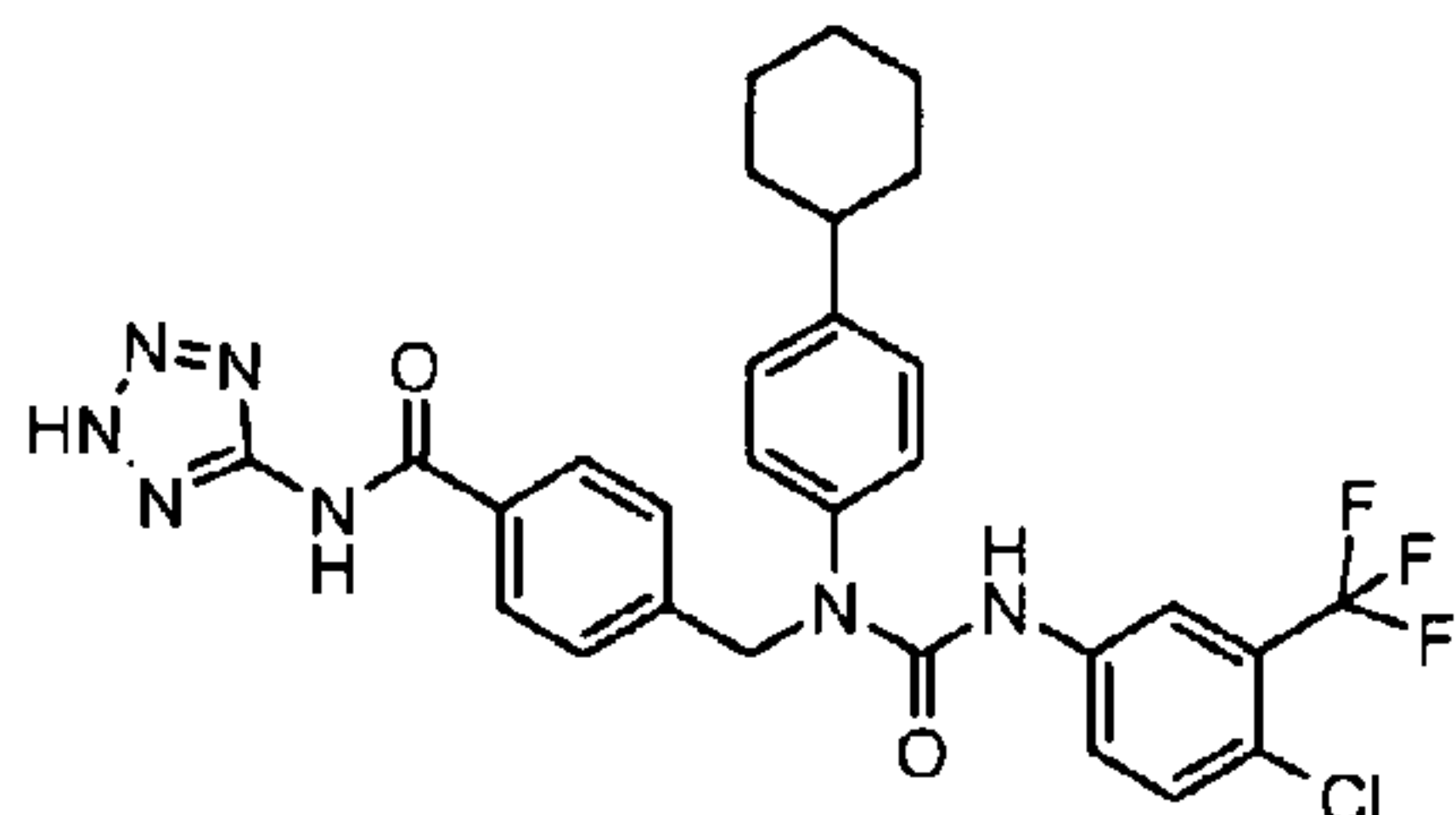
- 15 ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.35 (s br, 1H); 8.50 (s, 1H); 8.05 (d, 2H); 7.95 (s, 1H); 7.75 (d, 1H); 7.46-7.38 (m, 4H); 7.20 (s, 4H); 5.00 (s, 2H); 2.55 (t, 2H); 1.55 (k, 2H); 1.32 (sx, 2H); 0.90 (t, 3H).

HPLC-MS (method B): m/z = 495, R_t = 7.28 min.

20

EXAMPLE 282 (general procedure (L))

4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.70 (s, 1H); 8.05 (d+s, 3H); 7.80 (d, 1H); 7.55 (d, 1H); 7.45 (d, 2H); 7.22 (s, 4H); 5.00 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 598, R_t = 8.55 min.

10

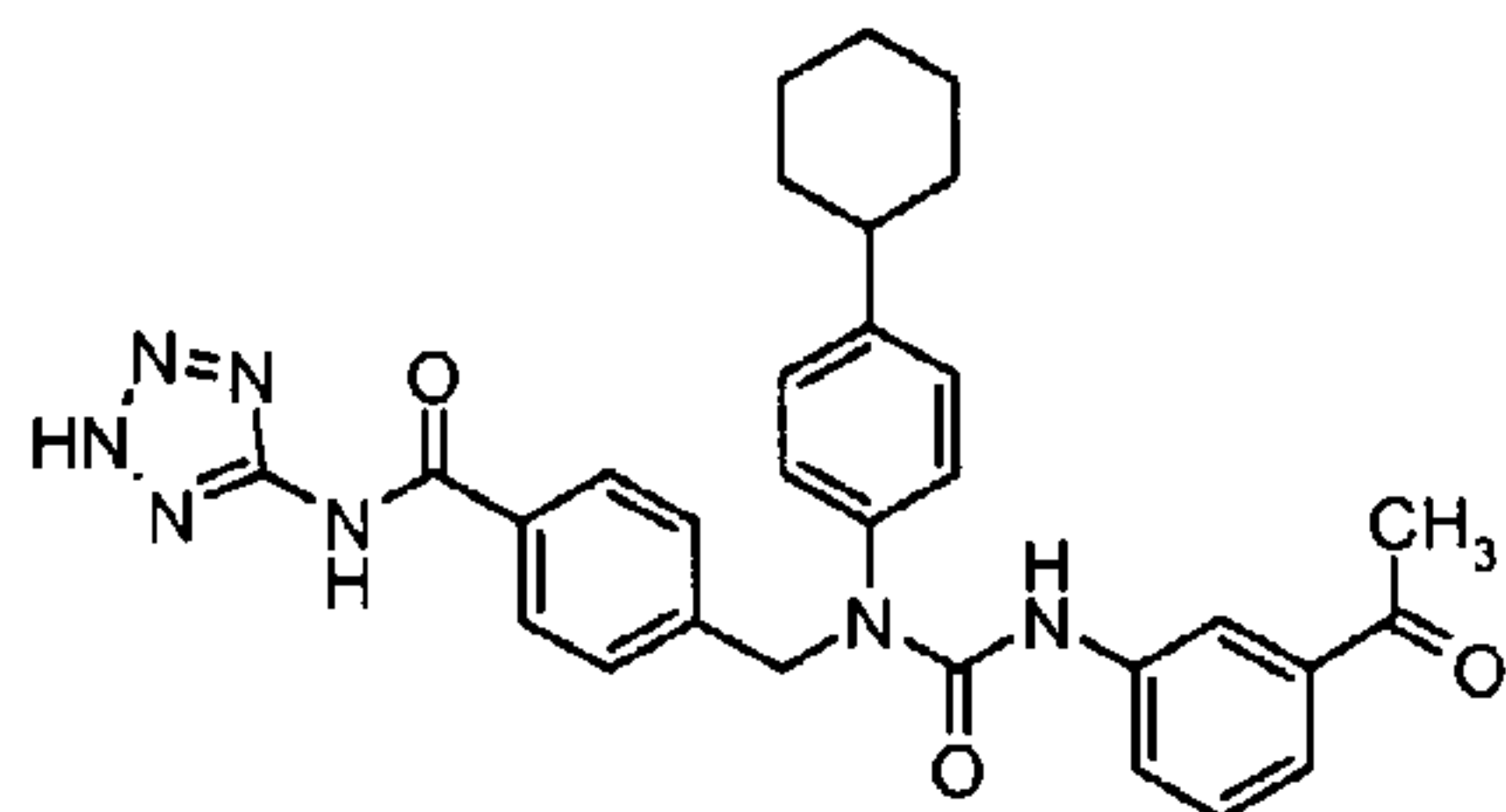
^1H NMR (MeOH- d_4): δ 1.20 – 1.50 (m, 5H), 1.75 – 1.90 (m, 5H), 2.55 (m, 1H), 5.02 (s, 2H), 7.19 (d, 2H), 7.30 (d, 2H), 7.44 – 7.50 (m, 3H), 7.60 (d, 1H), 7.90 (s, 1H), 7.99 (d, 2H).

MS (APCI, neg): 596.2, 597.2, 598.2, 375.2, 376.2.

15

EXAMPLE 283 (general procedure (L))

4-[3-(3-Acetylphenyl)-1-(4-cyclohexylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



20

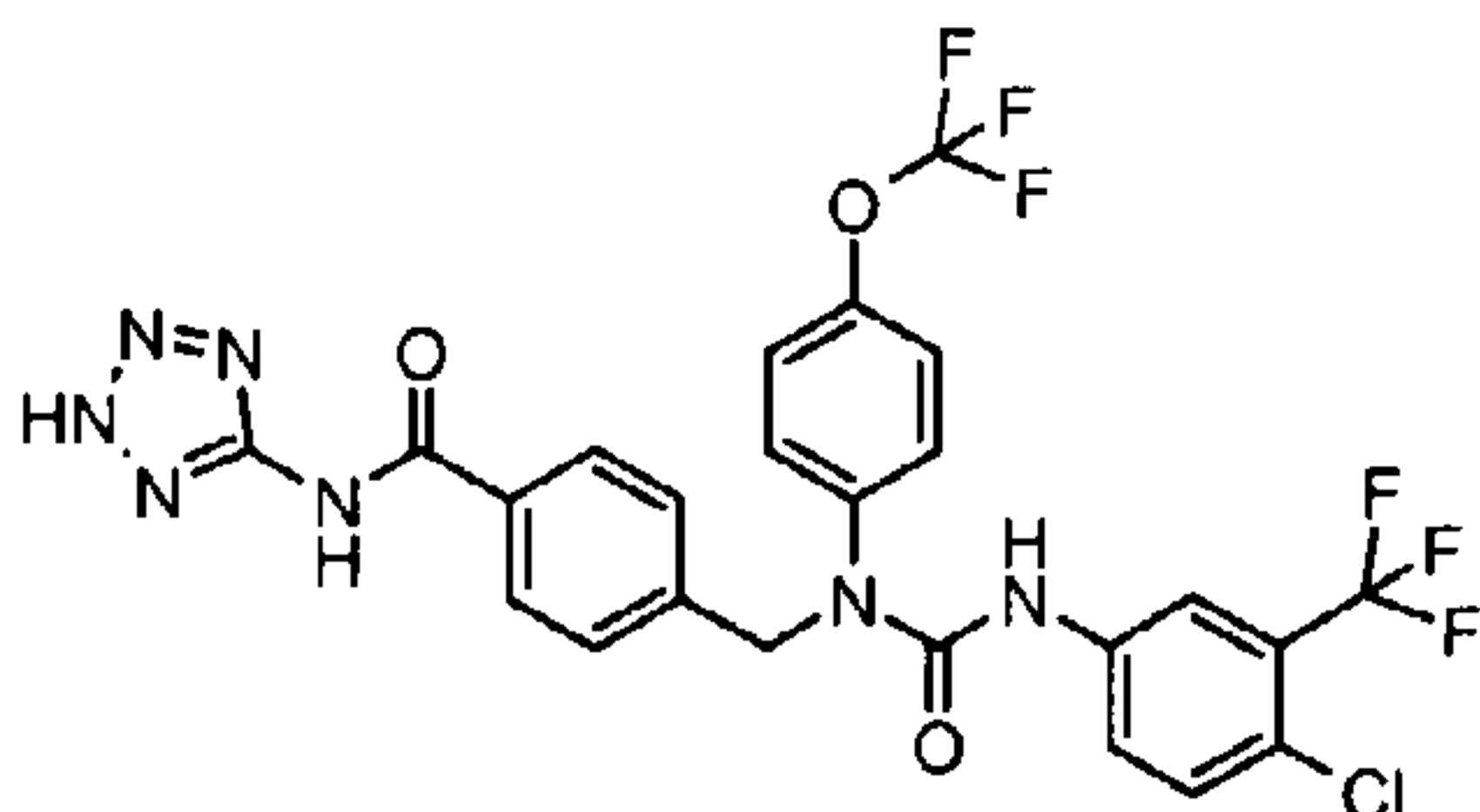
^1H NMR (300 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.48 (s, 1H); 8.05 (d+s, 3H); 7.68 (d, 1H); 7.58 (d, 1H); 7.45 (d, 2H); 7.38 (t, 1H); 7.20 (s, 4H); 5.00 (s, 2H); 2.10 (s, 3H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 538, R_t = 7.38 min.

25

EXAMPLE 284 (general procedure (L))

4-[3-(4-Chloro-3-trifluoromethylphenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide



5

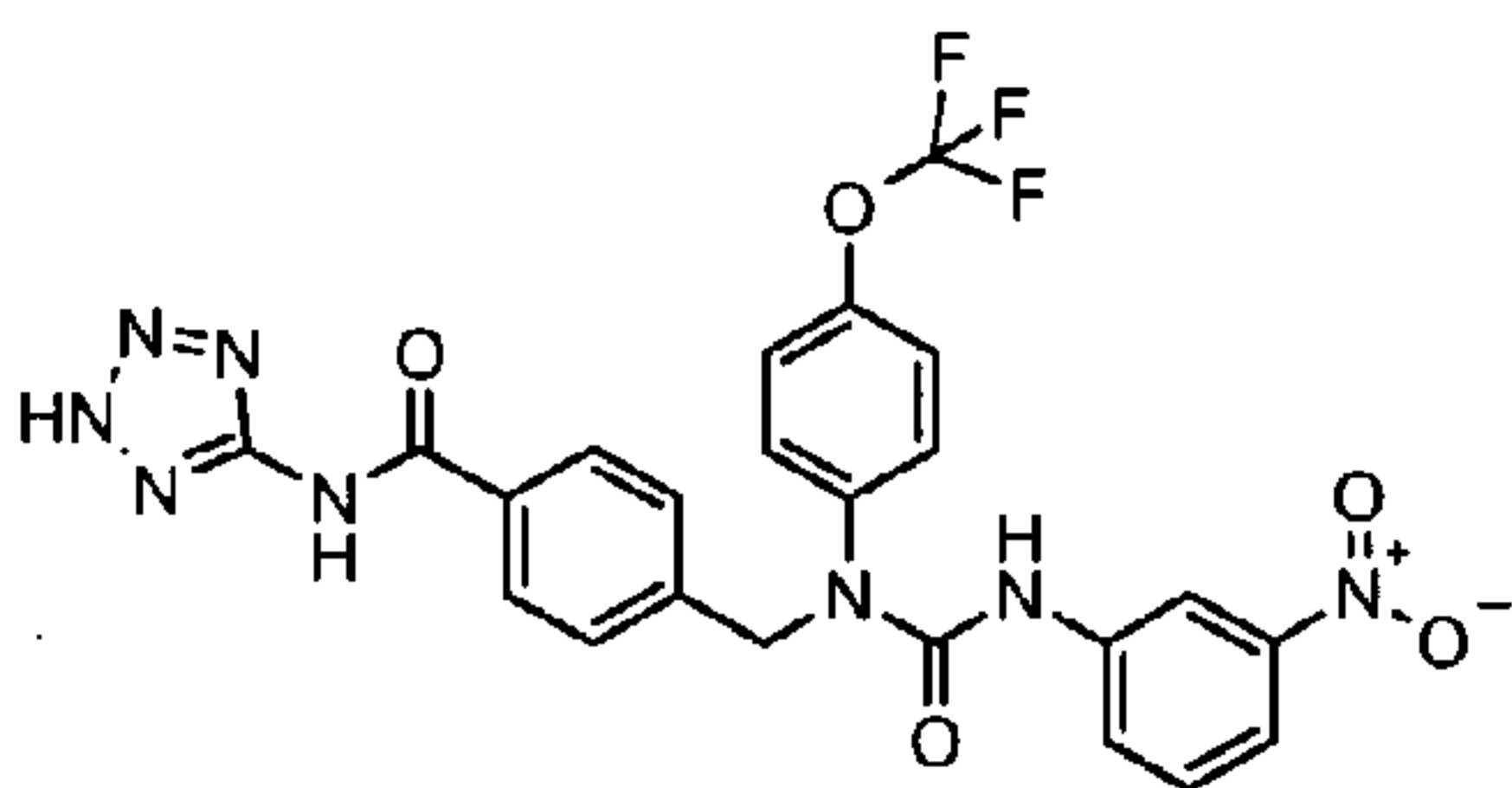
^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.90 (s, 1H); 8.05 (d+s, 3H); 7.83 (d, 1H); 7.60 (d, 1H); 7.50-7.30 (m, 6H); 5.05 (s, 2H).

HPLC-MS (method B): m/z = 600, R_t = 7.75 min.

10

EXAMPLE 285 (general procedure (L))

4-[3-(3-Nitrophenyl)-1-(4-trifluoromethoxyphenyl)ureidomethyl]ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

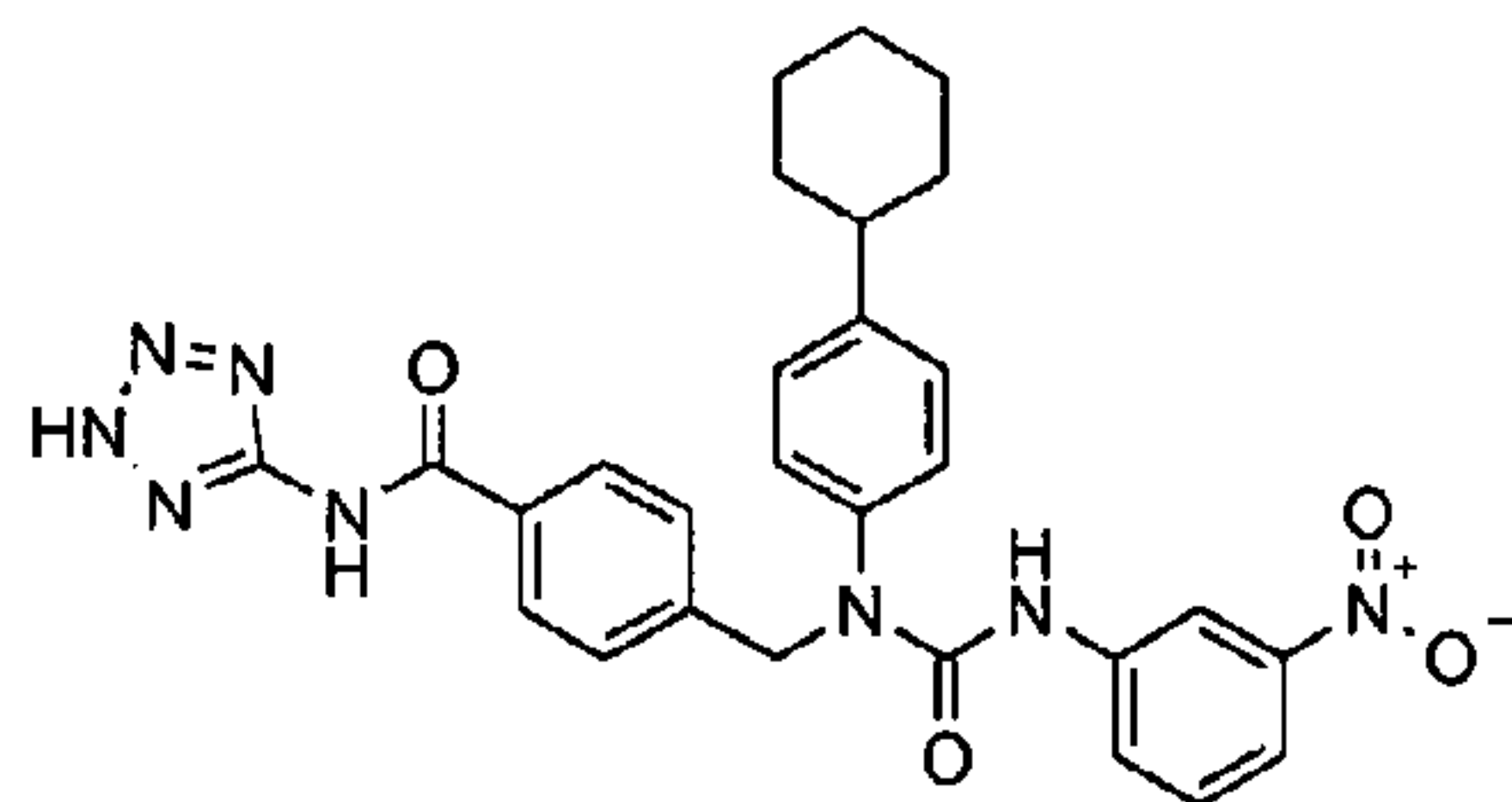


15

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 9.00 (s, 1H); 8.48 (t, 1H); 8.05 (d, 2H); 7.92 (d, 1H); 7.82 (d, 1H); 7.60-7.30 (m, 7H); 5.05 (s, 2H).

HPLC-MS (method B): m/z = 543, R_t = 6.62 min.

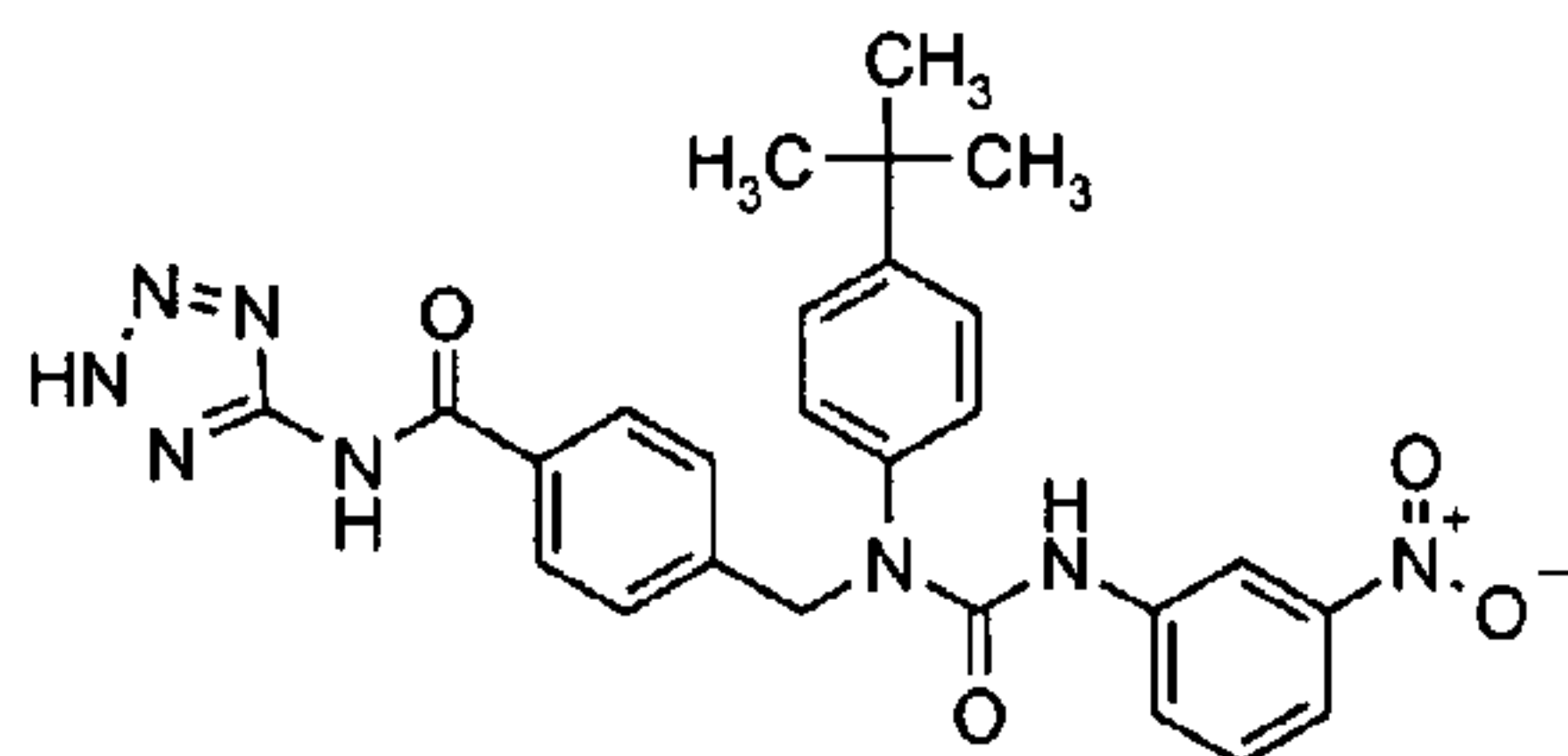
20

EXAMPLE 286 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 5 ^1H NMR (200 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.78 (s, 1H); 8.48 (t, 1H); 8.05 (d+s, 3H); 7.90 (d, 1H); 7.78 (d, 1H); 7.55-7.42 (m, 3H); 7.22 (s, 4H); 5.05 (s, 2H); 1.85-1.10 (m, 11H).

HPLC-MS (method B): m/z = 541, R_t = 7.67 min.

10 EXAMPLE 287 (general procedure (L))

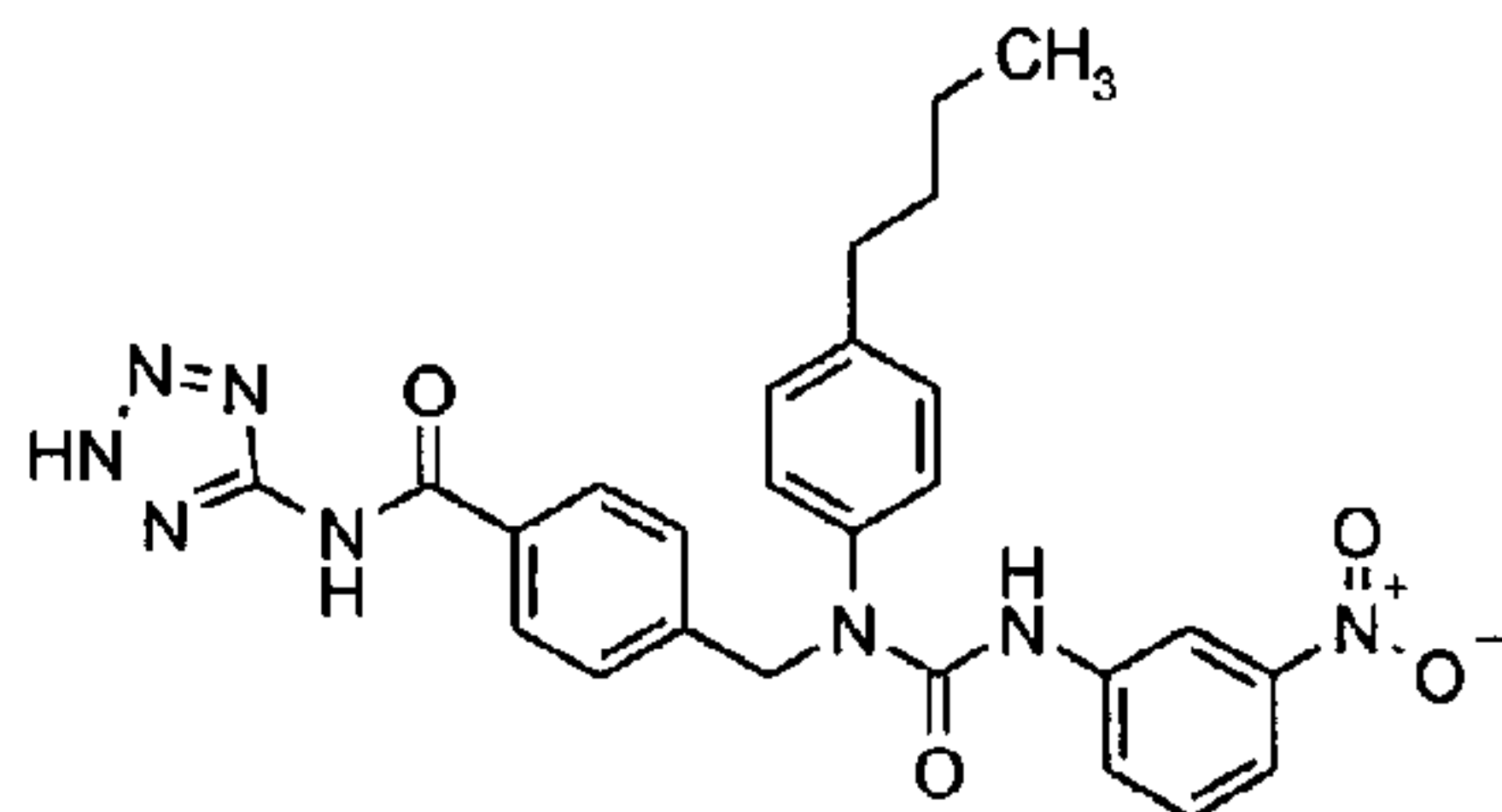
4-[1-(4-*tert*-Butylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

- 15 ^1H NMR (200 MHz, DMSO- d_6): δ 12.40 (s br, 1H); 8.82 (s, 1H); 8.48 (t, 1H); 8.05 (d, 2H); 7.93 (d, 1H); 7.81 (d, 1H); 7.60-7.35 (m, 5H); 7.25 (d, 2H); 5.05 (s, 2H); 1.30 (s, 9H).

HPLC-MS (method B): m/z = 515, R_t = 7.13 min.

EXAMPLE 288 (general procedure (L))

20 4-[1-(4-Butylphenyl)-3-(3-nitrophenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

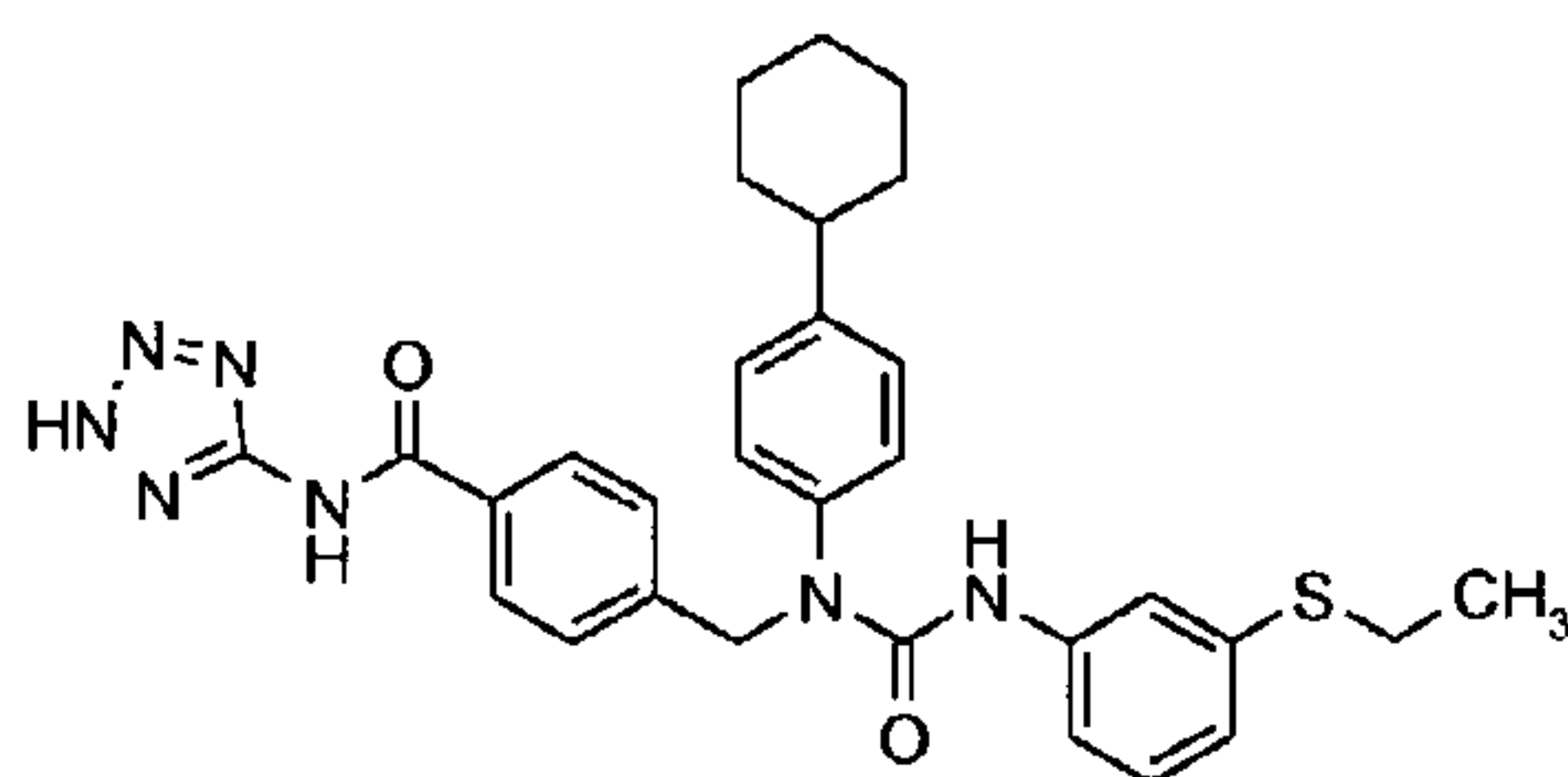


^1H NMR (200 MHz, $\text{DMSO}-d_6$): δ 12.40 (s br, 1H); 8.82 (s, 1H); 8.50 (t, 1H); 8.05 (d, 2H); 7.93 (d, 1H); 7.81 (d, 1H); 7.60-7.45 (m, 3H); 7.20 (s, 4H); 5.03 (s, 2H); 2.60 (t, 2H); 1.55 (k, 2H); 1.35 (sx, 2H); 0.90 (t, 3H).

5 HPLC-MS (method B): m/z = 515, R_t = 7.33 min.

EXAMPLE 289 (general procedure (L))

4-[1-(4-Cyclohexylphenyl)-3-(3-ethylsulfanylphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)benzamide

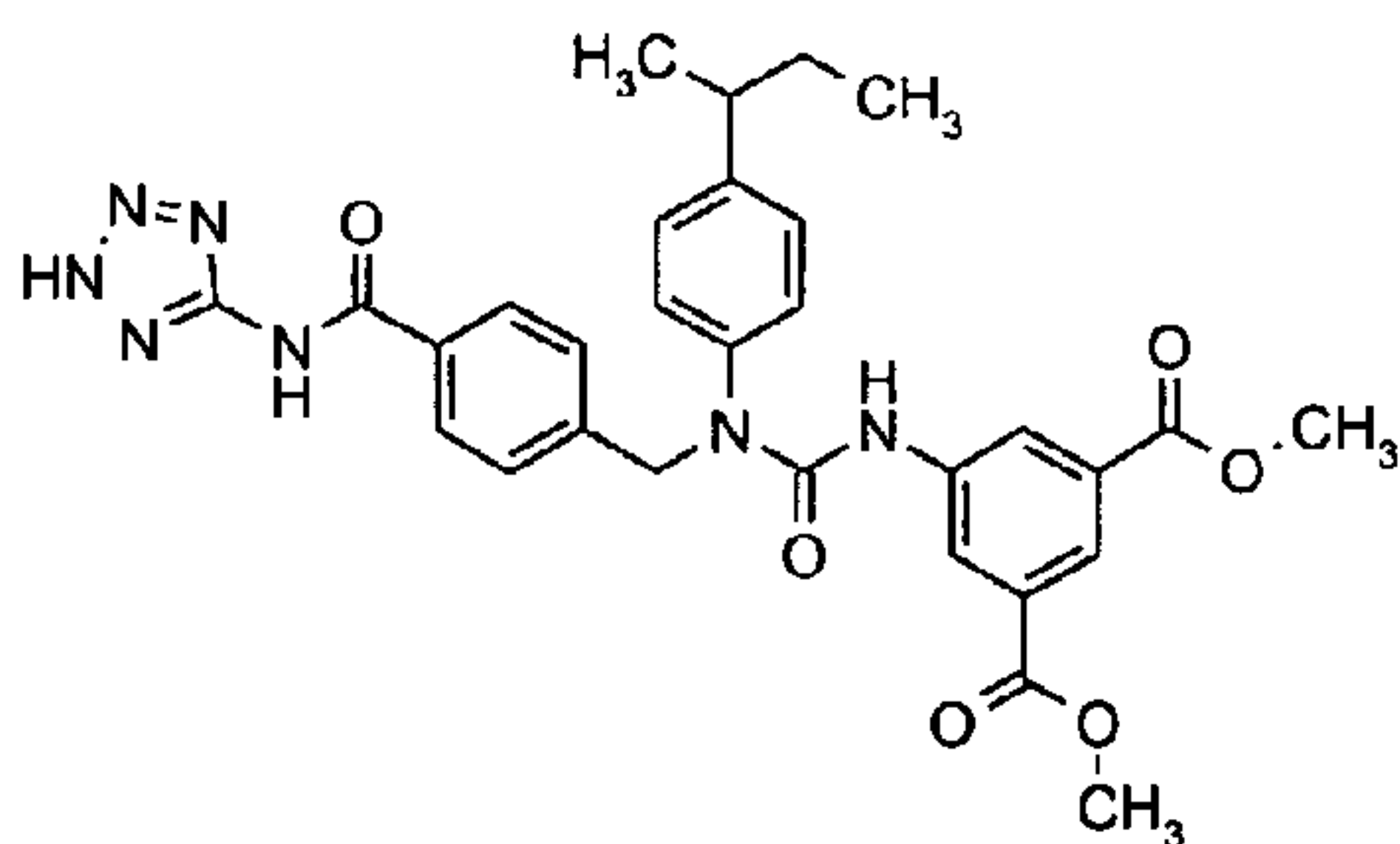


10

HPLC-MS (method B): m/z = 556, R_t = 8.07 min.

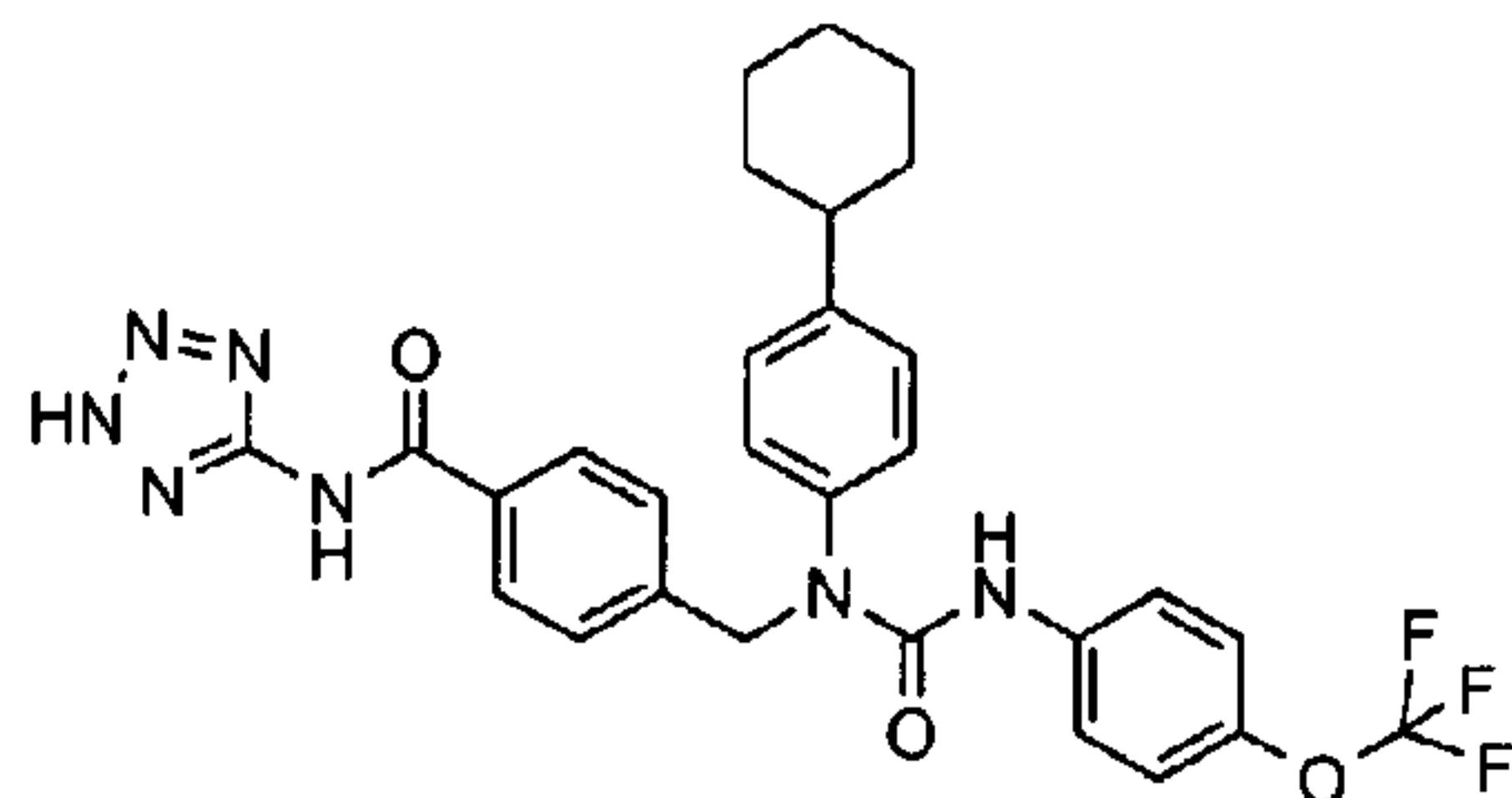
EXAMPLE 290 (general procedure (L))

15 5-{3-(4-sec-Butylphenyl)-3-[4-(2H-tetrazol-5-ylcarbamoyl)benzyl]ureidoisophtalic acid di-methyl ester



HPLC-MS (method B): m/z = 586, R_t = 7.23 min.

20

EXAMPLE 291 (general procedure (L))4-[1-(4-Cyclohexylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-N-(2H-tetrazol-5-yl)-benzamide

5

^1H NMR (DMSO- d_6): δ 1.1-1.4 (5H, m), 1.65-1.85 (5H, m), 5.00 (2H, s), 7.2 (6H, m), 7.46 (2H, d), 7.55 (2H, d), 8.04 (2H, d), 8.43 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 8.22 min, m/z = 580 ($M + 1$).

10

Alternative method for the preparation of the title compound:

To a solution of 4-carboxybenzaldehyde (40.2 g, 0.27 mol) in DMF (400 mL) was added *N*-ethyl-*N'*-3-dimethylaminopropylcarbodiimide (65.5 g, 0.33 mol) followed by 5-aminotetrazol monohydrate (36.6 g, 0.35 mol). The mixture was stirred for 24 hours at ambient temperature. The reaction volume was then reduced to one half by rotary evapoation, and water (800 mL) was added. The precipitate was collected by filtration, washed with cold acetonitrile and dried overnight in a vacuum oven to afford 46.0 g (80%) of 4-formyl-*N*-(2*H*-tetrazol-5-yl)benzamide.

15

20

^1H NMR (DMSO- d_6): δ 8.08 (d, 2H); 8.26 (d, 2H); 10.15 (s, 1H); 12.68 (bs, 1H).

4-Formyl-*N*-(2*H*-tetrazol-5-yl)benzamide (8.94 g, 41.2 mmol) was dissolved in DMF (50 mL) by gentle heating. A solution of 4-cyclohexylaniline (7.20 g, 41.2 mmol) in methanol (100 mL) was added and a turbid suspension was formed. The suspension was heated to 70°C for 1 hour. Acetic acid (50 mL) and sodium cyanoborohydride (2.0 g, 31.7 mmol) was then added. The turbid suspension was heated to 70°C for an additional hour, before being cooled to 0°C on an ice bath. The insoluble material was collected by filtration and washed twice with water, before being dried overnight in a vacuum oven to afford 12.94 g (83.5%) of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide.

25

30

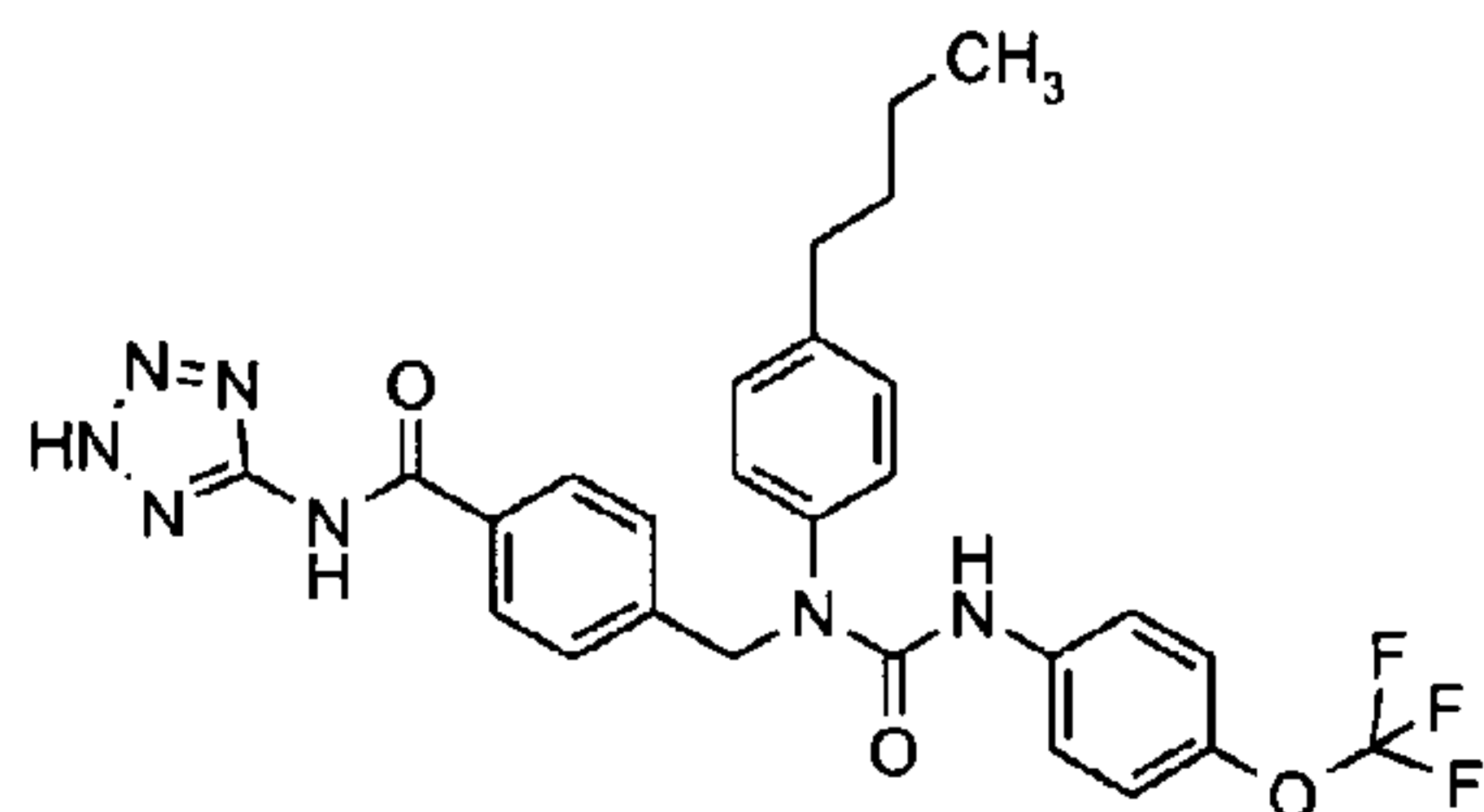
^1H NMR ($\text{DMSO}-d_6$): δ 1.28 (m, 5H); 1.68 (m, 5H); 2.28 (m, 1H); 4.32 (s, 2H); 6.17 (bs, 1H); 6.48 (d, 2H); 6.88 (d, 2H); 7.52 (d, 2H); 8.03 (d, 2H); 12.30 (s, 1H).

To a suspension of 4-[(4-cyclohexylphenylamino)methyl]-*N*-(2*H*-tetrazol-5-yl)benzamide (12.5 g, 33.2 mmol) in DMF (120 mL) was added 4-trifluoromethoxyphenyl isocyanate (6.8 g, 33.2 mmol). A clear solution was obtained upon heating to 80°C. After 30 minutes heating at 80°C, the solution was allowed to cool to room temperature. Solvent was removed by rotary evaporation, and the residual oil taken up into hot acetonitrile (500 mL). The title material, which separated out upon cooling, was collected by filtration and washed twice with cold acetonitrile to afford 15.32 g (80.0%) of the title compound.

^1H NMR ($\text{DMSO}-d_6$): δ 1.35 (m, 5H); 1.78 (m, 5H); 2.42 (m, 1H); 4.96 (s, 2H); 7.20 (s, 4H); 7.24 (d, 2H); 7.47 (d, 2H); 7.55 (d, 2H); 8.02 (d, 2H); 8.44 (s, 1H); 12.35 (s, 1H).

15 EXAMPLE 292 (general procedure (L))

4-[1-(4-Butylphenyl)-3-(4-trifluoromethoxyphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide

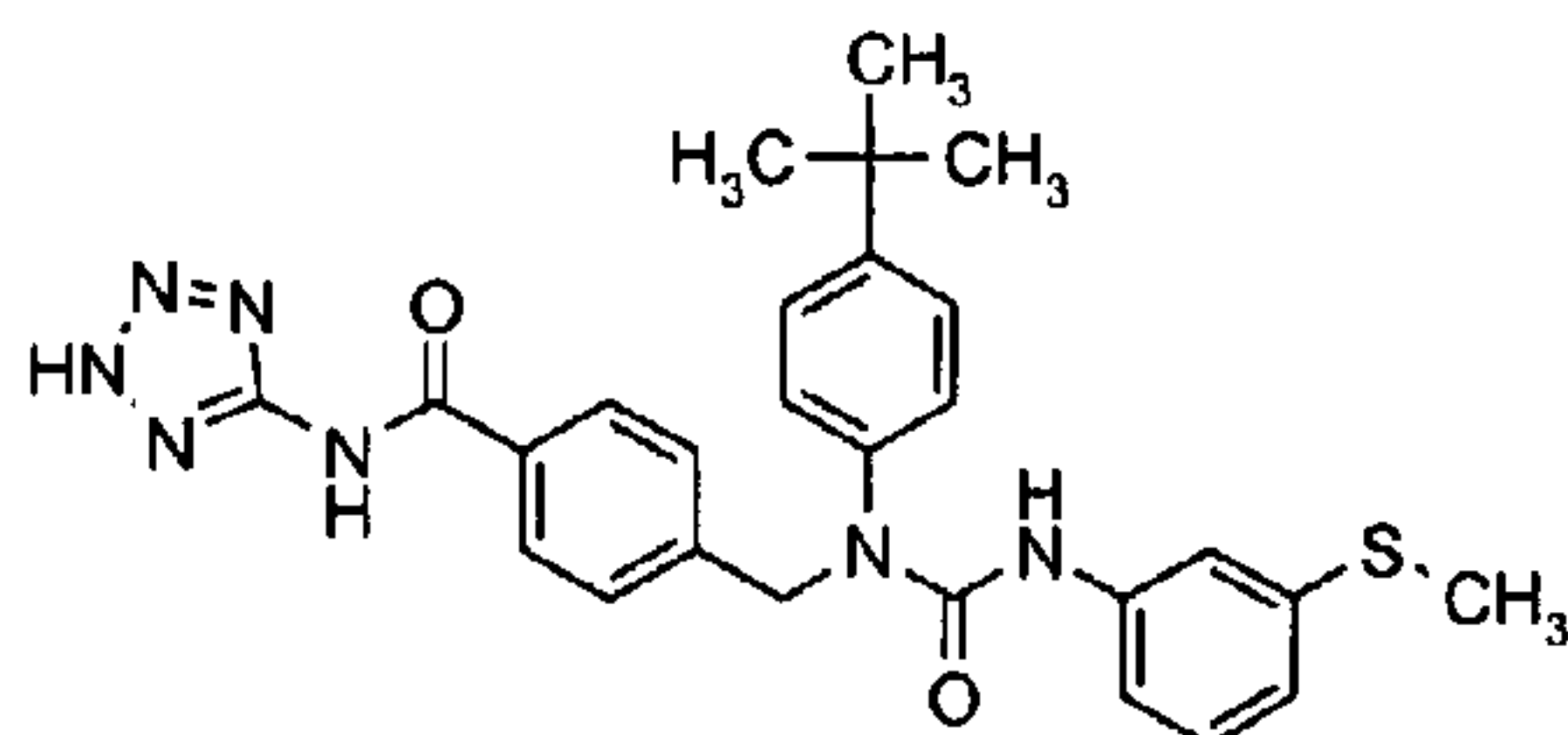


20 ^1H NMR ($\text{DMSO}-d_6$): δ 0.90 (3H, t), 1.33 (2H, sextet), 1.56 (2H, pentet), 2.55 (2H, partly hidden by DMSO), 5.00 (2H, s), 7.20 (4H, s), 7.23 (2H, d), 7.45 (2H, d), 7.57 (2H, d), 8.02 (2H, d), 8.36 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 7.85 min, m/z = 554 ($M + 1$).

EXAMPLE 293 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(3-methylsulfanylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



5

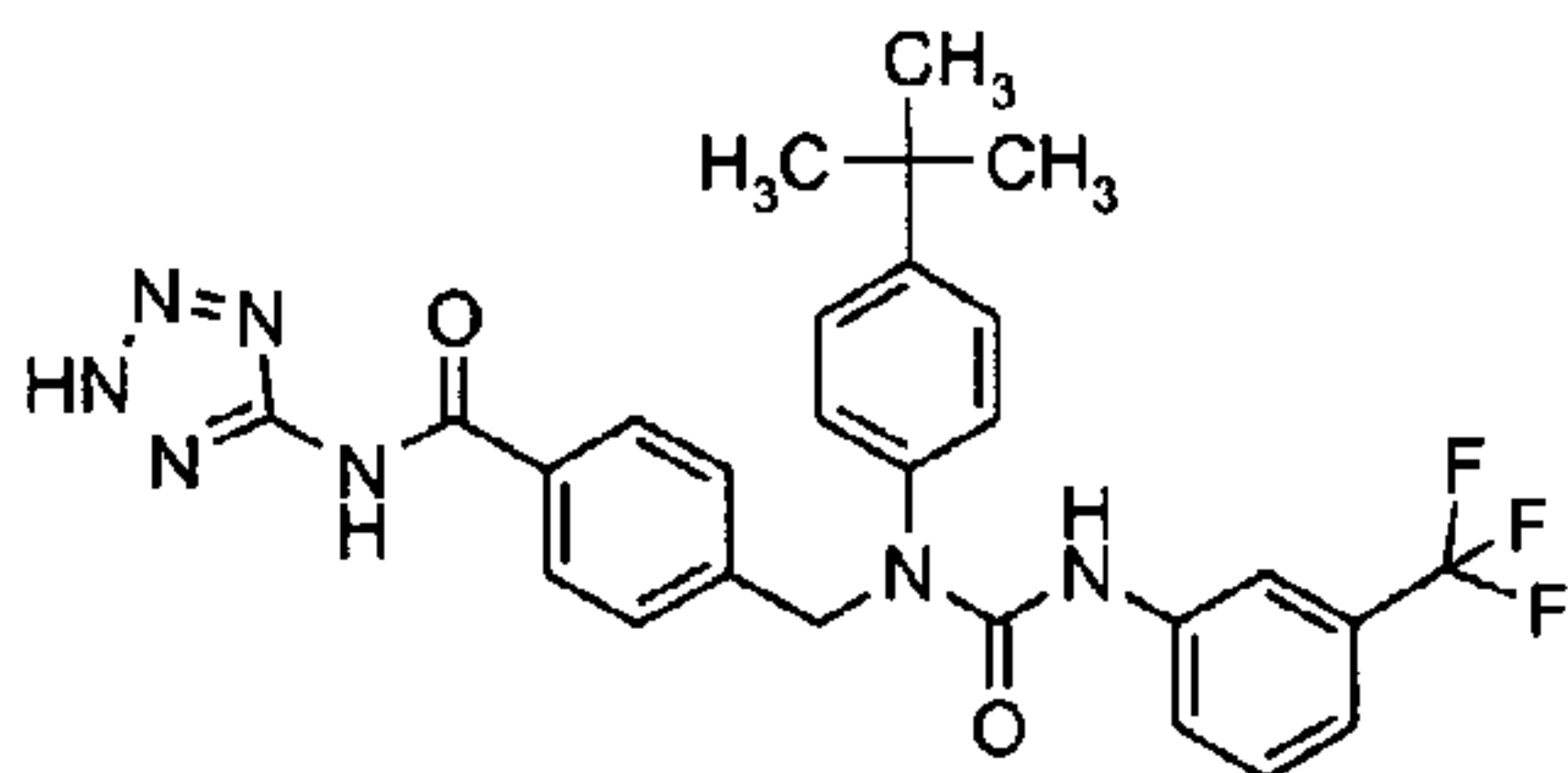
^1H NMR (DMSO- d_6): δ 1.28 (9H, s), 2.43 (3H, s), 5.01 (2H, s), 6.36 (1H, d), 7.15 -7.25 (4H, m), 7.40 (3H, m), 7.48 (2H, d), 8.04 (2H, d), 8.25 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 7.42 min, m/z = 516 ($M + 1$).

10

EXAMPLE 294 (general procedure (L))

4-[1-(4-*tert*-Butylphenyl)-3-(3-trifluoromethylphenyl)ureidomethyl]-*N*-(2*H*-tetrazol-5-yl)-benzamide



15

^1H NMR (DMSO- d_6): δ 1.30 (9H, s), 5.01 (2H, s), 7.25 (2H, d), 7.30 (1H, d), 7.4-7.5 (5H, m), 7.75 (1H, m), 7.93 (1H, s), 8.05 (2H, d), 8.62 (1H, s), 12.4 (1H, bs).

HPLC-MS (Method B): R_t = 7.58 min, m/z = 538 ($M + 1$).

20

DEMANDES OU BREVETS VOLUMINEUX

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

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

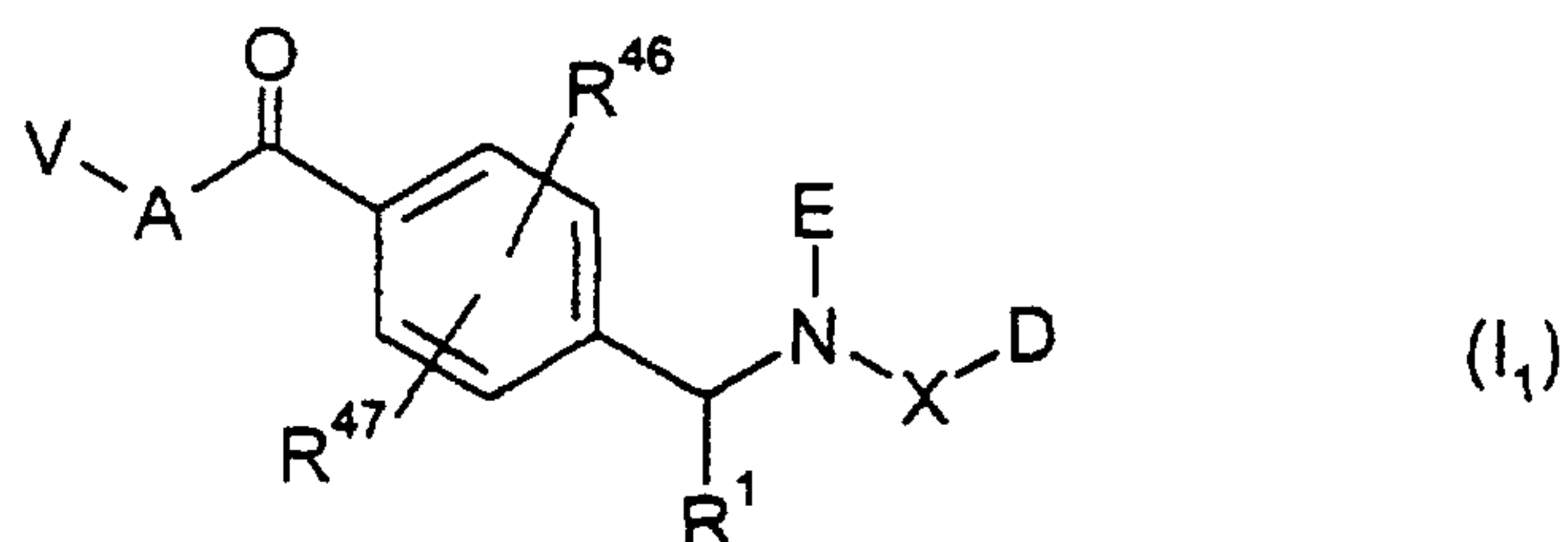
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

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

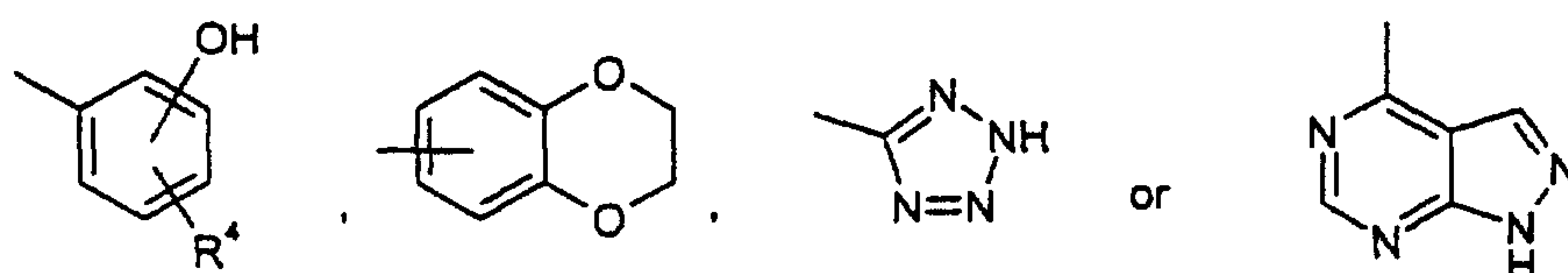
CLAIMS

1. A compound of the general formula (I₁):



wherein

V is -C(O)OR², -C(O)NR²R³, -C(O)NR²OR³, -S(O)₂OR²,



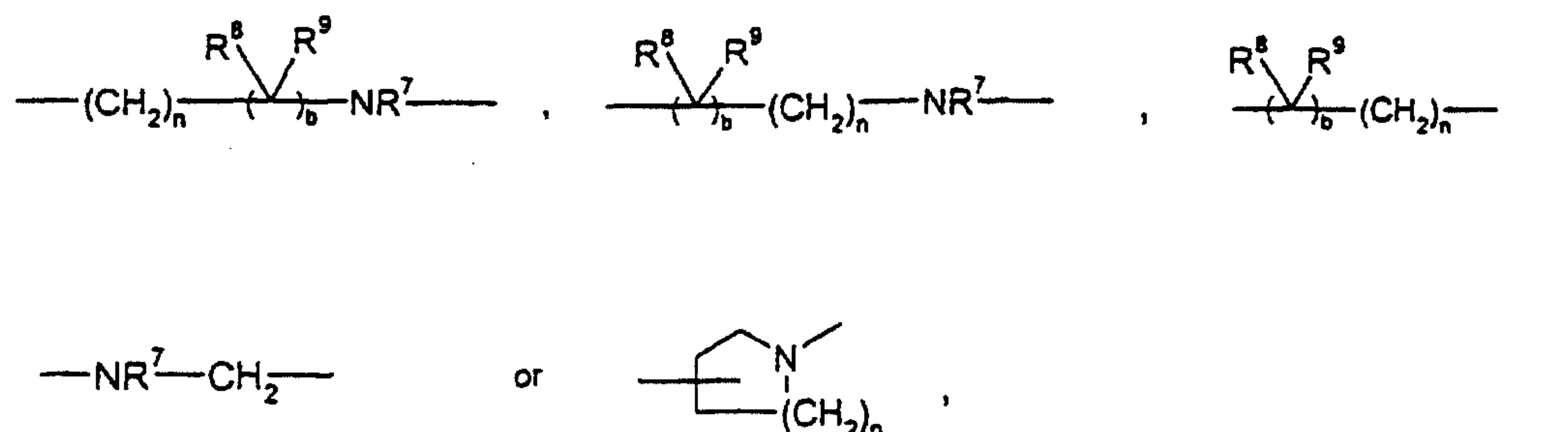
wherein

R² and R³ independently are hydrogen or C₁₋₆-alkyl,

R⁴ is hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁵, -NR⁵R⁶ or C₁₋₆-alkyl,

wherein R⁵ and R⁶ independently are hydrogen or C₁₋₆-alkyl,

20 A is



wherein

Amended claims, 29.03.01

b is 0 or 1,

n is 0, 1, 2 or 3,

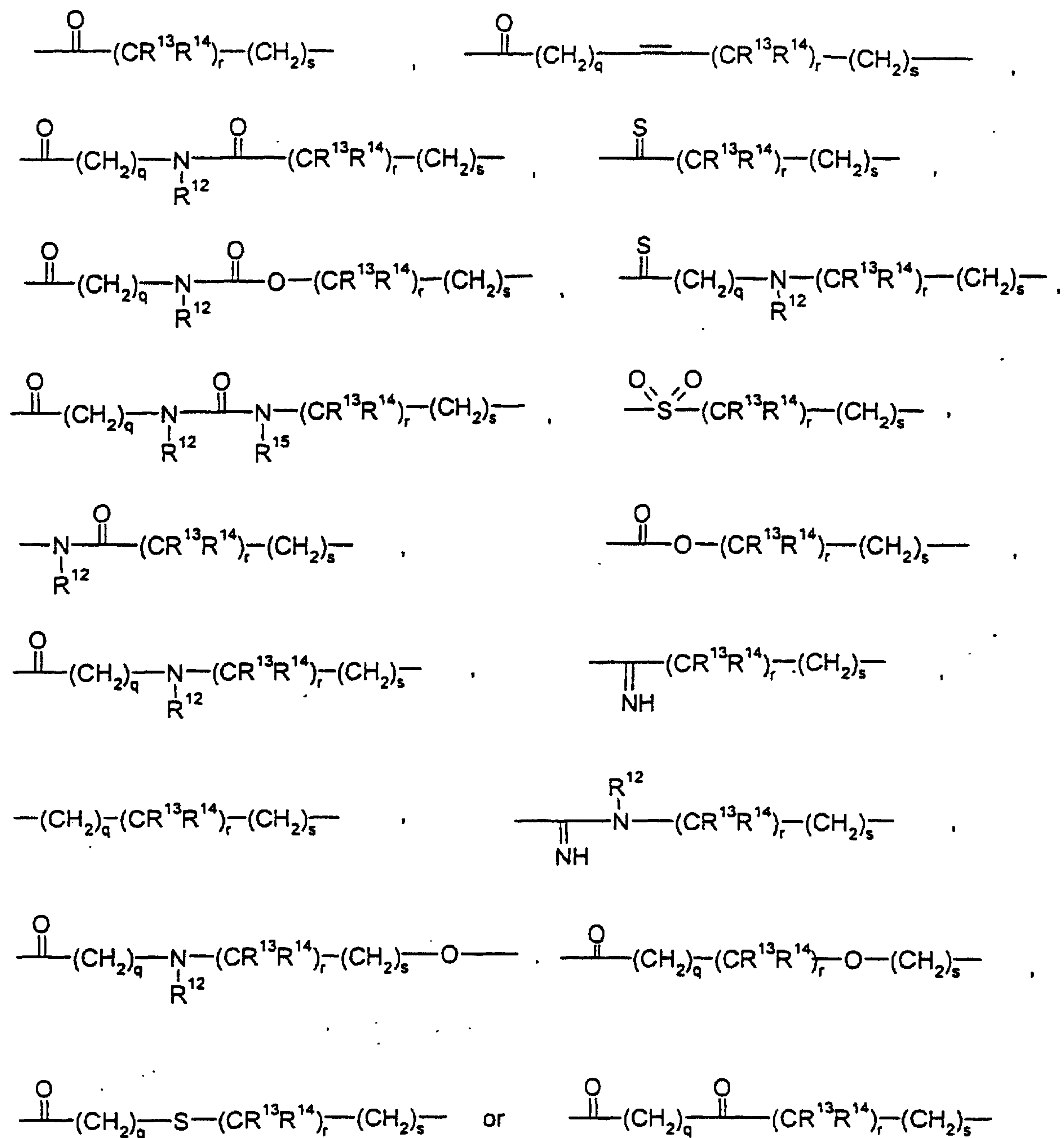
5 R⁷ is hydrogen, C₁₋₆-alkyl or C₃₋₈-cycloalkyl-C₁₋₆-alkyl,

R⁸ and R⁹ independently are hydrogen or C₁₋₆-alkyl,

R⁴⁶ and R⁴⁷ independently are selected from hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -
10 OR¹⁰, -NR¹⁰R¹¹ and C₁₋₆-alkyl, wherein R¹⁰ and R¹¹ independently are hydrogen or C₁₋₆-alkyl,

R¹ is hydrogen or C₁₋₆-alkyl,

X is



5 wherein

r is 0 or 1,

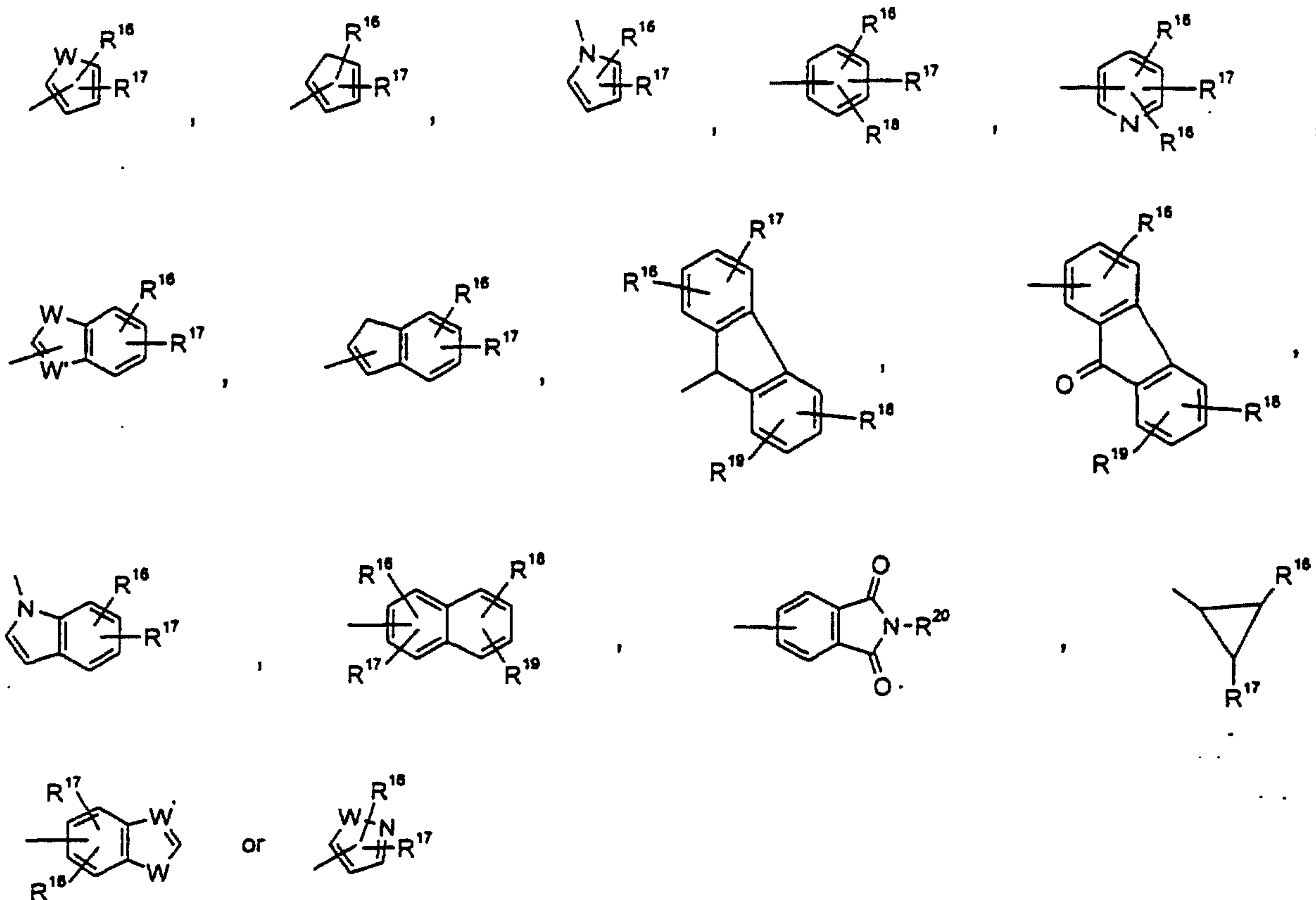
q and s independently are 0, 1, 2 or 3,

10

R¹², R¹³, R¹⁴ and R¹⁵ independently are hydrogen or C₁₋₆-alkyl,

Amended claims, 29.03.01

D is



5

wherein

W is -O-, -S-, -S(O)₂- or -NR²⁰-,

10 W' is =CR^{20'}- or =N-,

R¹⁶, R¹⁷, R¹⁸ and R¹⁹ independently are

15 • hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 -OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

20 • C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

Amended claims, 29.03.01

which may optionally be substituted with one or more substituents selected from -
CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
-SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
5 -OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

- C₃₋₈-cycloalkyl, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, C₃₋₈-cyclo-
alkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyloxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio, C₃₋₈-cycloalkylthio,
C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-C₁₋₆-alkyl, C₄₋₈-
10 cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-C₁₋₆-alkyl, heterocy-
clyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more sub-
stituents selected from

15 -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR²¹, -NR²¹R²²,
-SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²²,
-OCH₂C(O)NR²¹R²², -C(O)R²¹ and -C(O)OR²¹,

20 C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents se-
lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
-SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
25 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
-C(O)OR²¹,

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-
C₂₋₆-alkynyl, heteroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-
30 C₂₋₆-alkynyl,

of which the aryl and heteroaryl moieties optionally may be substituted with one
or more substituents selected from

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5 halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -OS(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²²,
 -S(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -OS(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²²,
 -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²²,
 -OC(O)R²¹, -C(O)R²¹ and -C(O)OR²¹,

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

10 which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
 -SCF₃, -OR²¹, -NR²¹R²², -SR²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²²,
 -OC(O)NR²¹R²², -NR²¹C(O)R²², -OCH₂C(O)NR²¹R²², -C(O)R²¹ and
 -C(O)OR²¹,

15 wherein R²¹ and R²² independently are hydrogen, -CF₃, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl,
 C₃₋₈-cycloalkyl-C₁₋₆-alkyl, aryl, aryl-C₁₋₆-alkyl or heteroaryl,

or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom
 may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms
 20 selected from nitrogen, oxygen and sulfur, and optionally containing one or two
 double bonds,

or two of the groups R¹⁶ to R¹⁹ when placed in adjacent positions together may form a bridge
 -(CR^{16'}R^{17'})_a-O-(CR^{18'}R^{19'})_c-O-,
 25

wherein

a is 0, 1 or 2,

30 c is 1 or 2,

R^{16'}, R^{17'}, R^{18'} and R^{19'} independently are hydrogen, C₁₋₆-alkyl or halogen,

R²⁰ and R^{20'} independently are hydrogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₃₋₈-cycloalkyl-C₁₋₆-
 35 alkyl,

Amended claims, 29.03.01



AMENDED SHEET

R²³ and R²⁴ independently are

- hydrogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
-SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
5 -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ or -C(O)OR³⁶,
- C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from
10 -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
-SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
-OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

- C₃₋₈-cycloalkyl, C₃₋₈-cycloalkylidene, C₄₋₈-cycloalkenyl, heterocyclyl, C₃₋₈-cycloalkyl-
15 C₁₋₆-alkyl, C₃₋₈-cycloalkyl-C₂₋₆-alkenyl, C₃₋₈-cycloalkyl-C₂₋₆-alkynyl, C₄₋₈-cycloalkenyl-
C₁₋₆-alkyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkenyl, C₄₋₈-cycloalkenyl-C₂₋₆-alkynyl, heterocyclyl-
C₁₋₆-alkyl, heterocyclyl-C₂₋₆-alkenyl or heterocyclyl-C₂₋₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more sub-
20 stituents selected from

-CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁶, -NR³⁶R³⁷,
-SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷,
-OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and -C(O)OR³⁶,

25

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents se-
lected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
30 -SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
-OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
-C(O)OR³⁶,

- aryl, aryloxy, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkyl, aryl-C₂₋₆-alkenyl, aryl-C₂₋₆-alkynyl, het-
35 eroaryl, heteroaryl-C₁₋₆-alkyl, heteroaryl-C₂₋₆-alkenyl or heteroaryl-C₂₋₆-alkynyl,

Amended claims, 29.03.01

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of which the aryl and heteroaryl moieties optionally may be substituted with one or more substituents selected from

5 halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
-OS(O)₂CF₃, -SCF₃, -NO₂, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -NR³⁶S(O)₂R³⁷, -S(O)₂NR³⁶R³⁷,
-S(O)NR³⁶R³⁷, -S(O)R³⁶, -S(O)₂R³⁶, -OS(O)₂R³⁶, -C(O)NR³⁶R³⁷, -OC(O)NR³⁶R³⁷,
-NR³⁶C(O)R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂C(O)NR³⁶R³⁷, -CH₂OR³⁶, -CH₂NR³⁶R³⁷,
-OC(O)R³⁶, -C(O)R³⁶ and -C(O)OR³⁶,

10

C₁₋₆-alkyl, C₂₋₆-alkenyl and C₂₋₆-alkynyl,

15

which may optionally be substituted with one or more substituents selected from -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂,
-SCF₃, -OR³⁶, -NR³⁶R³⁷, -SR³⁶, -S(O)R³⁶, -S(O)₂R³⁶, -C(O)NR³⁶R³⁷,
-OC(O)NR³⁶R³⁷, -NR³⁶C(O)R³⁷, -OCH₂C(O)NR³⁶R³⁷, -C(O)R³⁶ and
-C(O)OR³⁶,

wherein R³⁶ and R³⁷ independently are hydrogen, C₁₋₆-alkyl or aryl,

20

of which the aryl moiety optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁸, -NR³⁸R³⁹ and C₁₋₆-alkyl,

25

wherein R³⁸ and R³⁹ independently are hydrogen or C₁₋₆-alkyl,

30

or R³⁶ and R³⁷ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

35

or R²³ and R²⁴ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_t-O-, -(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_t- or -S-(CH₂)_t-CR⁴⁰R⁴¹-(CH₂)_t-S-,

wherein

t and l independently are 0, 1, 2, 3, 4 or 5,

5 R⁴⁰ and R⁴¹ independently are hydrogen or C₁₋₆-alkyl,

R²⁵ to R³⁰ independently are hydrogen, halogen, -CN, -CF₃, -NO₂, -OR⁴², -NR⁴²R⁴³, C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl,

10 wherein R⁴² and R⁴³ independently are hydrogen or C₁₋₆-alkyl, or

R⁴² and R⁴³ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two
15 double bonds,

R³¹, R³² and R³³ independently are hydrogen or C₁₋₆-alkyl,

R³⁴ and R³⁵ independently are

20

- hydrogen, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-alkanoyl, -C(O)NR⁴⁴R⁴⁵ or -S(O)₂R⁴⁵,
- aryl, aroyl, aryl-C₁₋₆-alkoxy, aryl-C₁₋₆-alkanoyl or aryl-C₁₋₆-alkyl,

25

of which the aryl moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴⁴, -NR⁴⁴R⁴⁵ and C₁₋₆-alkyl,

wherein R⁴⁴ and R⁴⁵ independently are hydrogen or C₁₋₆-alkyl, or

30

R³⁴ and R³⁵ when attached to a carbon atom together with the said carbon atom may form a 3 to 8 membered cyclic ring optionally containing one or two heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds, or

R³⁴ and R³⁵ when attached to a nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen or sulfur, and optionally containing one or two double bonds,

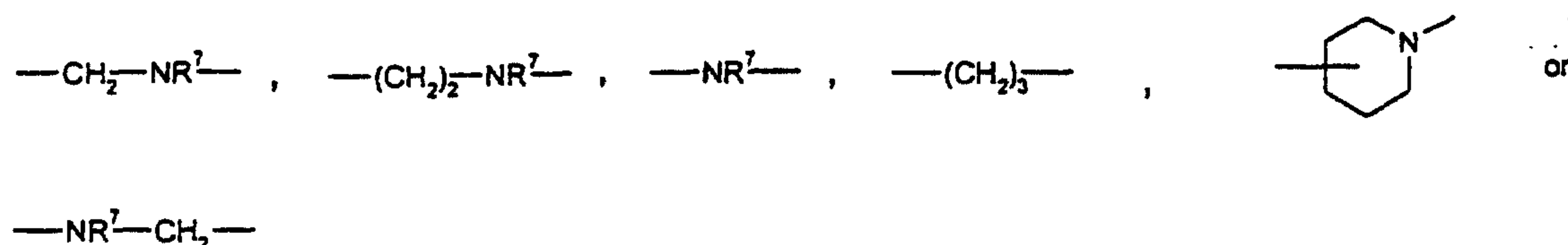
5 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein V is -C(O)OH, -S(O)₂OH, -C(O)NHOH or 5-tetrazolyl.

3. A compound according to claim 2, wherein V is -C(O)OH.

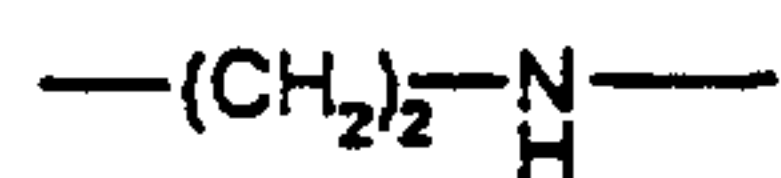
4. A compound according to claim 2, wherein V is 5-tetrazolyl.

15 5. A compound according to any one of the claims 1 to 4, wherein A is

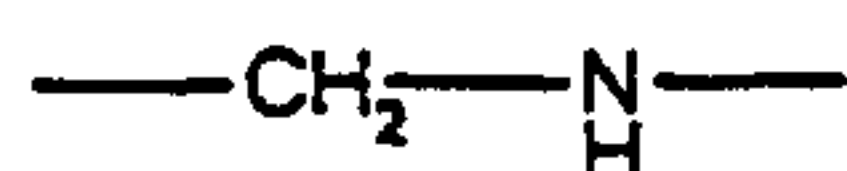


wherein R^7 is as defined in claim 1.

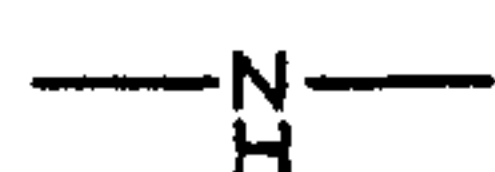
6. A compound according to claim 5, wherein A is



25 7. A compound according to claim 5, wherein A is

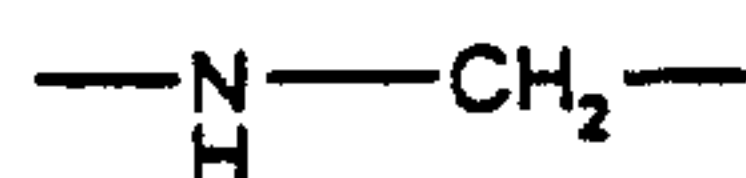


8. A compound according to claim 5, wherein A is



Amended claims, 29.03.01

9. A compound according to claim 5, wherein A is



5

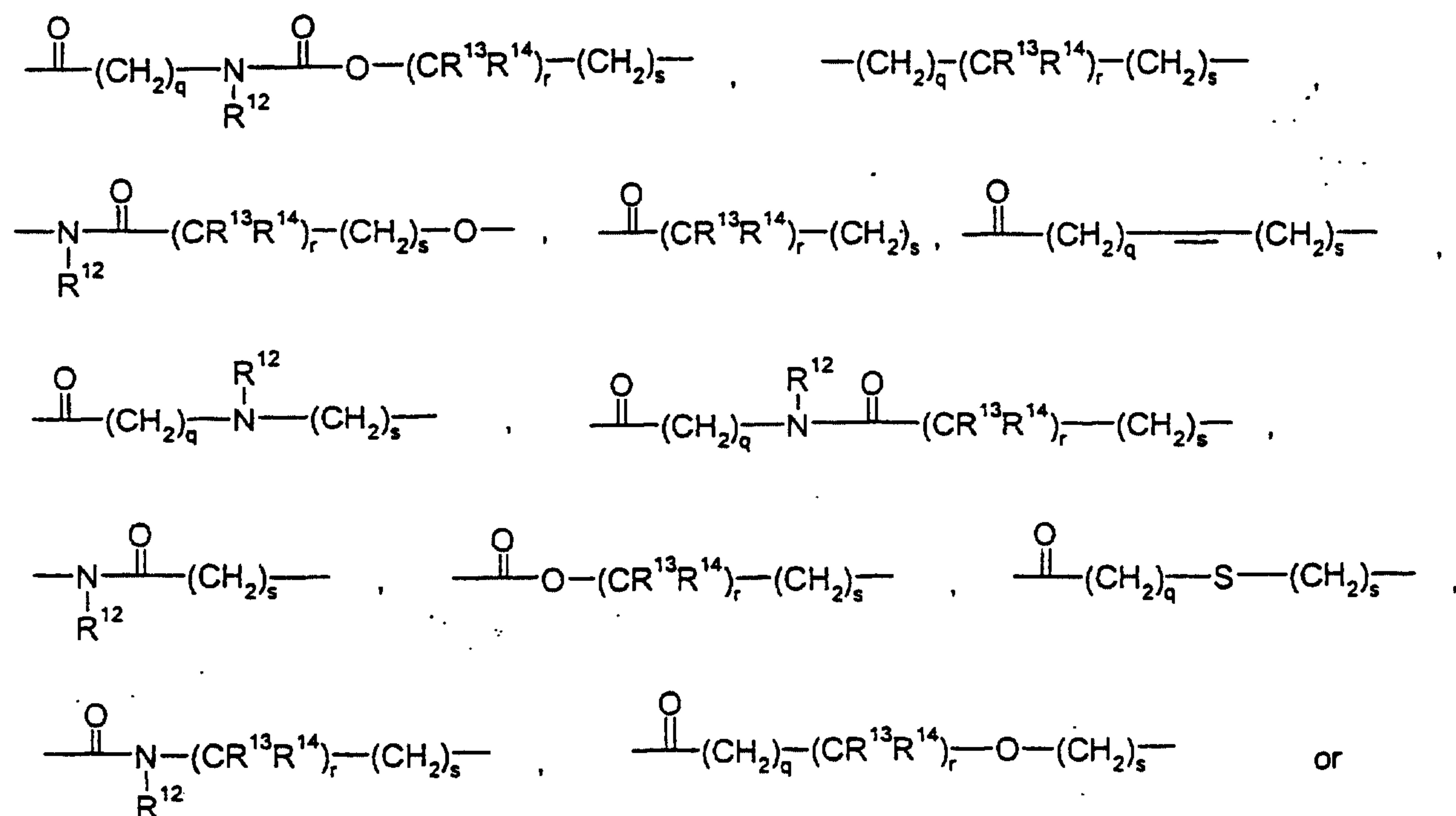
10. A compound according to any one of the claims 1 to 9, wherein R⁴⁶ and R⁴⁷ are both hydrogen.

11. A compound according to any one of the claims 1 to 10, wherein R¹ is hydrogen.

10

12. A compound according to any one of the claims 1 to 11, wherein R¹ is methyl.

13. A compound according to any one of the claims 1 to 12, wherein X is

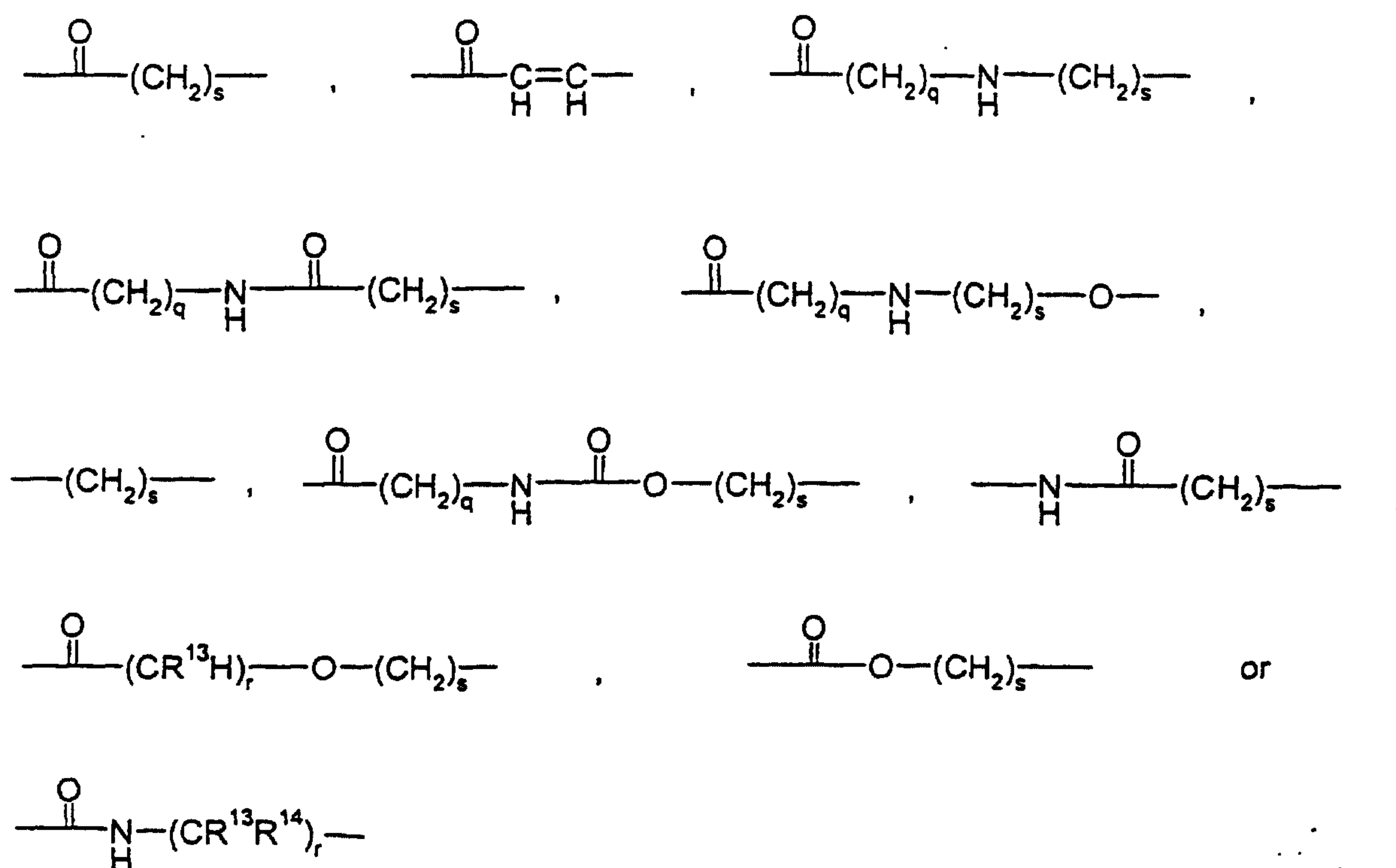


15

wherein q, r, s, R¹², R¹³ and R¹⁴ are as defined in claim 1.

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14. A compound according to claim 13, wherein X is



5 wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R¹³ is hydrogen or C₁₋₆-alkyl.

15. A compound according to claim 14, wherein X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -C(O)CH=CH-, -(CH₂)_s-, -C(O)-, -C(O)O- or -NHC(O)-, wherein s is 0 or 1.

10

16. A compound according to claim 15, wherein X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH(CH₃)-, -C(O)NHCH₂CH₂-, -C(O)CH₂-, -CH₂-, -C(O)- or -NHC(O)-.

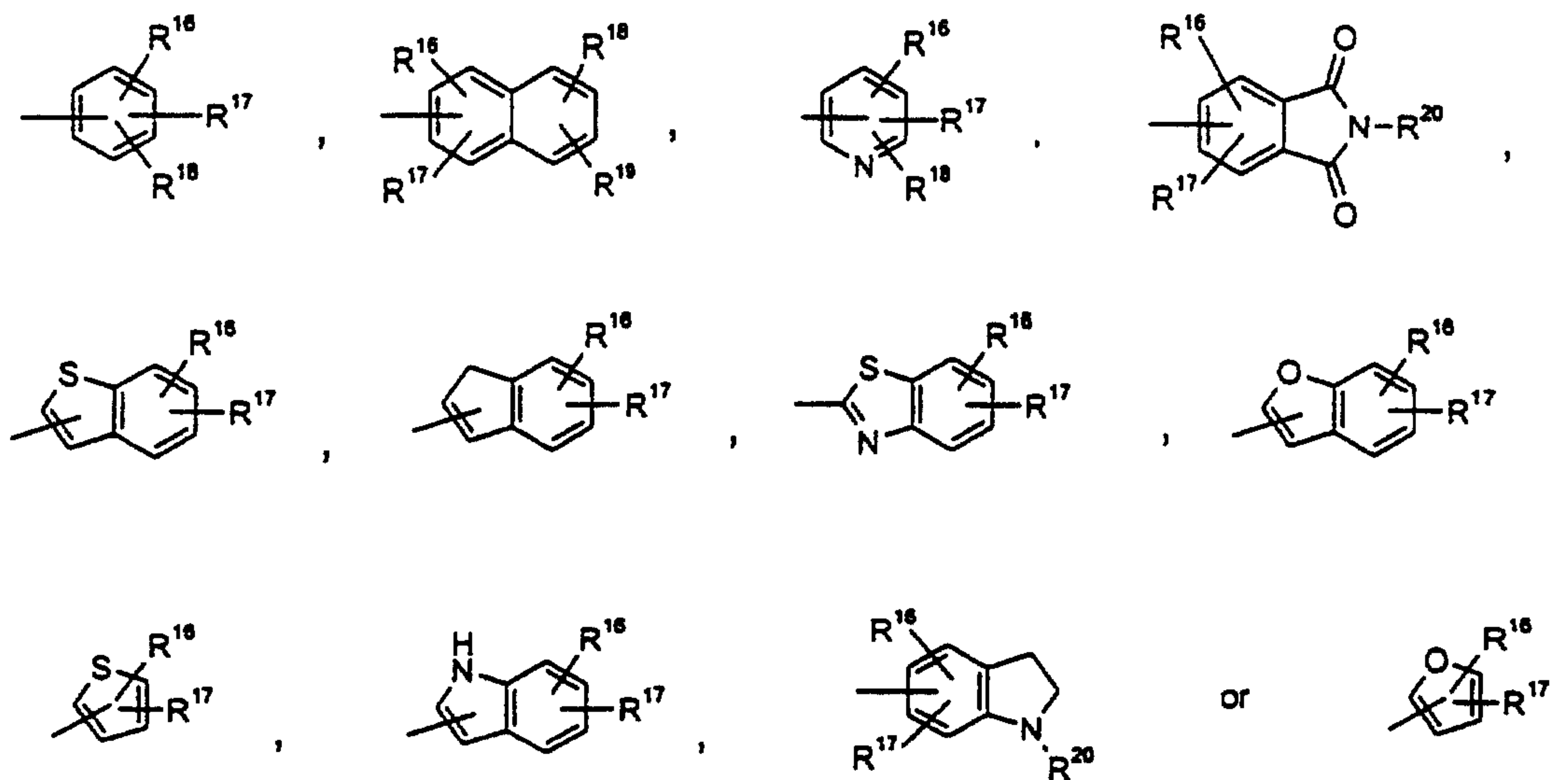
17. A compound according to claim 16, wherein X is -C(O)NH-.

15

18. A compound according to claim 16, wherein X is -C(O)NHCH(CH₃)-.

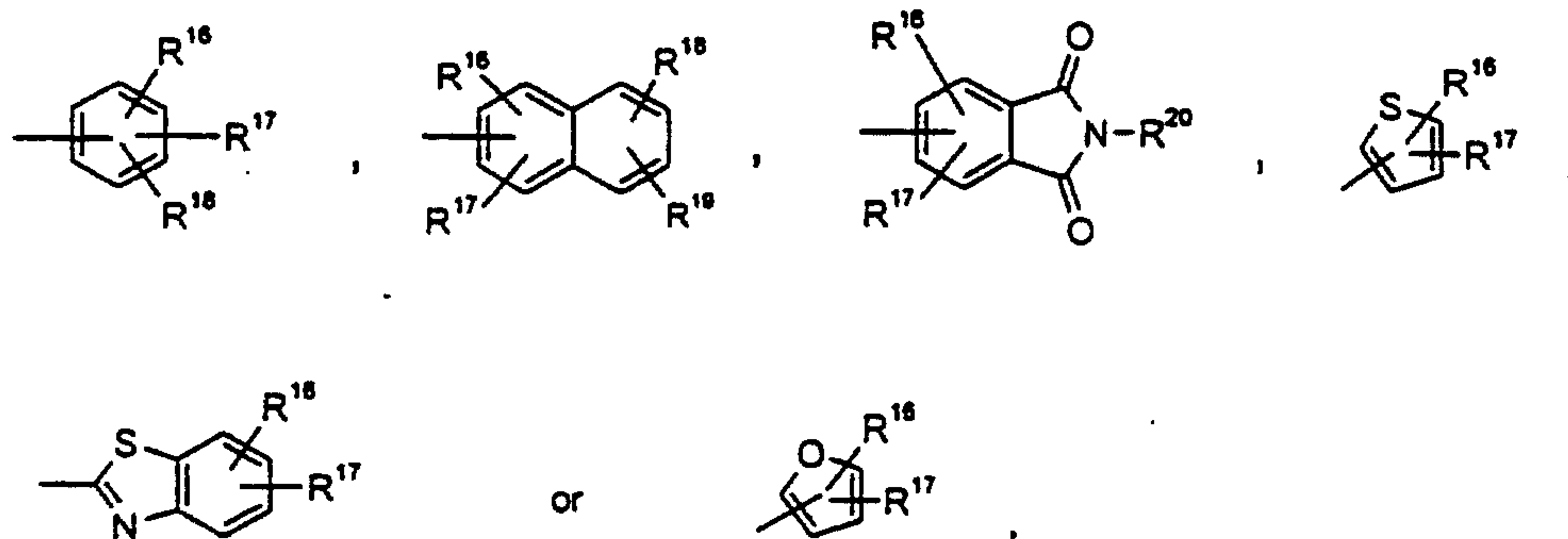
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19. A compound according to any one of the claims 1 to 18, wherein D is



5 wherein R^{16} , R^{17} , R^{18} , R^{19} and R^{20} are as defined in claim 1.

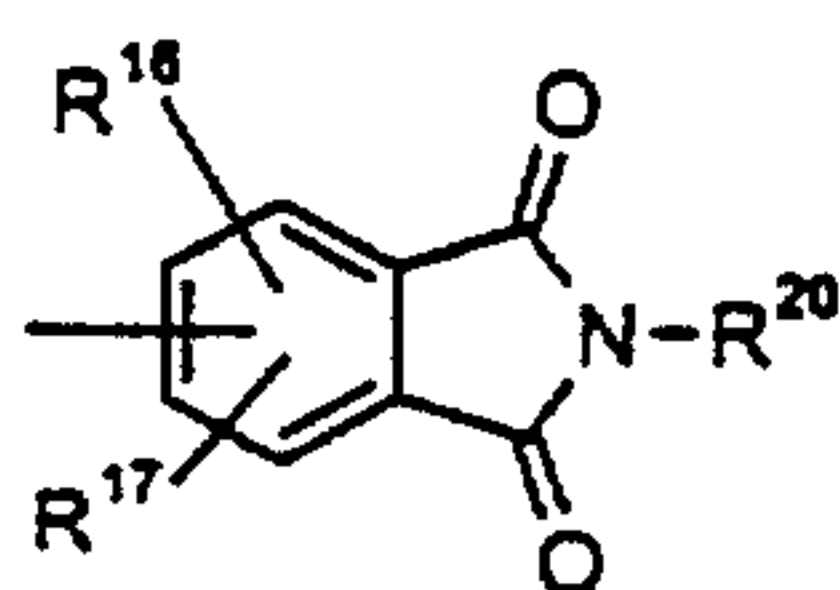
20. A compound according to claim 19, wherein D is



10

wherein R^{16} , R^{17} , R^{18} and R^{20} are as defined in claim 1.

21. A compound according to claim 20, wherein D is



15

wherein R^{16} , R^{17} and R^{20} are as defined in claim 1.

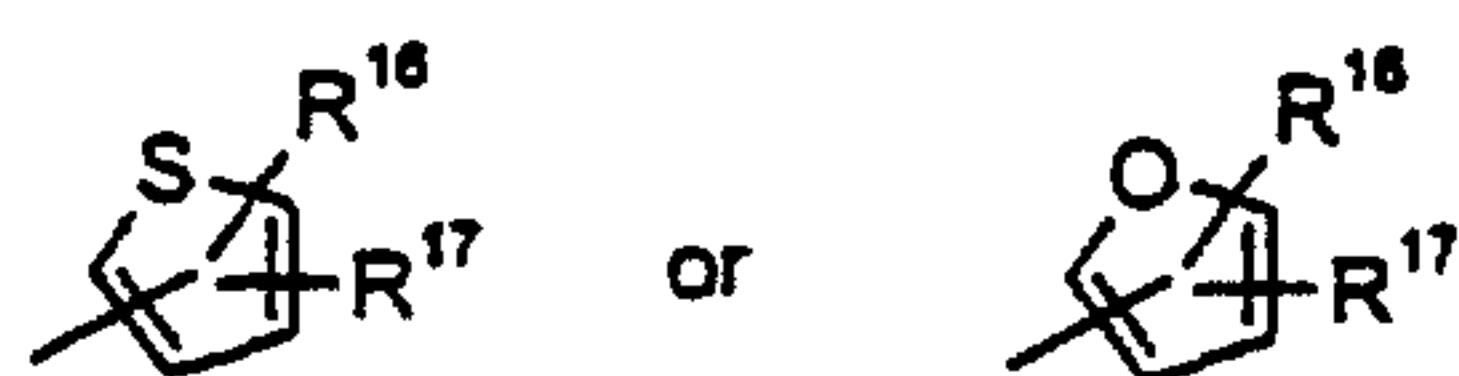
Amended claims, 29.03.01

22. A compound according to claim 21, wherein R^{16} and R^{17} are both hydrogen and R^{20} is C_{1-6} -alkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl.

5 23. A compound according to claim 21 or 22, wherein R^{20} is cyclopropylmethyl, butyl or isopropyl.

24. A compound according to claim 23, wherein R^{20} is isopropyl.

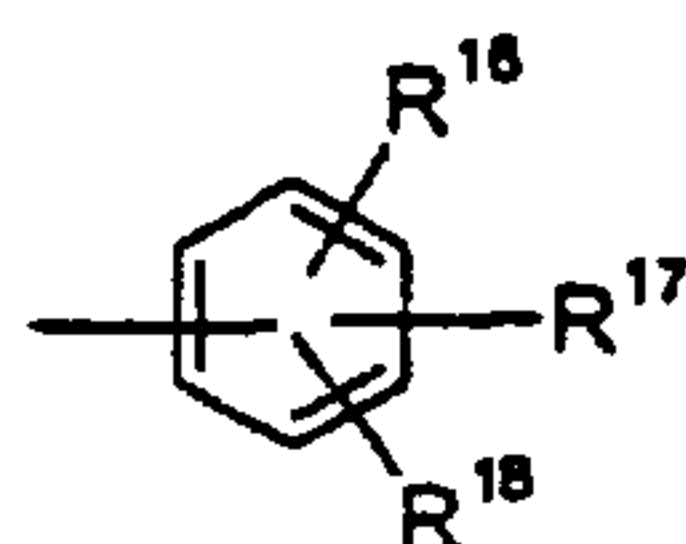
10 25. A compound according to claim 20, wherein D is



wherein R^{16} and R^{17} are as defined in claim 1.

15

26. A compound according to claim 20, wherein D is



20 wherein R^{16} , R^{17} and R^{18} are as defined in claim 1.

27. A compound according to any one of the claims 19, 20, 25 or 26, wherein R^{16} , R^{17} and R^{18} independently are

25 hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, hydroxy, -SCF₃, C_{1-6} -alkyl, C_{1-6} -alkyl substituted with hydroxy, C_{1-6} -alkyl substituted with -S(O)₂R²¹, C_{1-6} -alkoxy, -S- C_{1-6} -alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio or C_{3-8} -cycloalkylthio,

30 wherein R^{21} and R^{22} independently are hydrogen, C_{1-6} -alkyl, tri- C_{1-6} -alkylsilyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, phenyl, phenyl- C_{1-6} -alkyl, 2,3-dihydroindolyl or isoindolyl, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidine ring,

Amended claims, 29.03.01

phenoxy, phenoxycarbonyl, phenyl, phenyl-C₁₋₆-alkoxy, phenyl-C₁₋₆-alkyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -CN, -CF₃, -OCF₃, -NO₂, -C(O)OR²¹, -OR²¹, -NR²¹R²² or C₁₋₆-alkyl, wherein R²¹ and
5 R²² independently are hydrogen or C₁₋₆-alkyl, or

wherein R¹⁶ and R¹⁷ in adjacent positions form the radical -O-CH₂-O-, -CF₂-O-CF₂-O- or -O-CF₂-CF₂-O-, and R¹⁸ is hydrogen.

10 28. A compound according to claim 27, wherein R¹⁶, R¹⁷ and R¹⁸ independently are

hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, -SCF₃, C₁₋₆-alkyl, C₁₋₆-alkyl substituted with hydroxy, C₁₋₆-alkyl substituted with -S(O)₂R²¹, C₁₋₆-alkoxy, -S-C₁₋₆-alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)R²¹, -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C₃₋₈-cyclo-
15 alkyl-C₁₋₆-alkoxy, C₃₋₈-cycloalkyl-C₁₋₆-alkylthio or C₃₋₈-cycloalkylthio,

wherein R²¹ and R²² independently are hydrogen, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, C₃₋₈-cycloalkyl, C₃₋₈-cycloalkyl-C₁₋₆-alkyl, phenyl or 2,3-dihydroindolyl, or R²¹ and R²² together with the nitrogen atom to which they are attached form a piperidine ring,

20

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, -C(O)OR²¹ or C₁₋₆-alkyl, wherein R²¹ is hydrogen or C₁₋₆-alkyl, or

25 wherein R¹⁶ and R¹⁷ in adjacent positions form the radical -CF₂-O-CF₂-O- or -O-CF₂-CF₂-O-, and R¹⁸ is hydrogen.

29. A compound according to claim 28, wherein R¹⁶, R¹⁷ and R¹⁸ independently are

30 hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, -SCF₃, C₁₋₆-alkyl, C₁₋₆-alkyl substituted with hydroxy, C₁₋₆-alkoxy, -S-C₁₋₆-alkyl, -C(O)OR²¹, -C(O)R²¹, -CH₂(O)R²¹, -C(O)NR²¹R²², -S(O)₂R²¹, -(O)₂CF₃ or -S(O)₂NR²¹R²²,

wherein R²¹ and R²² independently are hydrogen, C₁₋₆-alkyl, tri-C₁₋₆-alkylsilyl, phenyl or
35 2,3-dihydroindolyl,

Amended claims, 29.03.01

phenoxy, phenyl, benzyl, furanyl, tetrazolyl, benzoxazolyl or oxadiazolyl, of which the ring systems optionally may be substituted with halogen, $-\text{C}(\text{O})\text{OR}^{21}$ or C_{1-6} -alkyl, wherein R^{21} is hydrogen or C_{1-6} -alkyl, or

- 5 wherein R^{16} and R^{17} in adjacent positions form the radical $-\text{CF}_2\text{-O-CF}_2\text{-O-}$ or $-\text{O-CF}_2\text{-CF}_2\text{-O-}$, and R^{18} is hydrogen.

30. A compound according to claim 29, wherein R^{16} , R^{17} and R^{18} independently are hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{SCF}_3$, C_{1-6} -alkyl, C_{1-6} -alkoxy, $-\text{S-C}_{1-6}$ -alkyl,
10 $-\text{C}(\text{O})\text{OC}_{1-6}$ -alkyl, $-\text{S}(\text{O})_2\text{C}_{1-6}$ -alkyl, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{C}(\text{O})\text{N}(\text{C}_{1-6}\text{-alkyl})(\text{C}_{1-6}\text{-alkyl})$,
 $-\text{S}(\text{O})_2\text{N}(\text{phenyl})(\text{C}_{1-6}\text{-alkyl})$, $-\text{C}(=\text{O})\text{C}_{1-6}$ -alkyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{O}(\text{tri-C}_{1-6}\text{-alkylsilyl})$, 2,3-dihydro-
indol-1-ylsulfonyl, phenoxy, phenyl, 4-chlorophenyl, 1,3,5-trimethylbenzyl, benzoxazolyl, 2-
methyltetrazol-5-yl, 2-methyl-3-methoxycarbonylfuran-5-yl or 3-isopropyl-[1,2,4]oxadiazol-5-
yl).

15

31. A compound according to any one of the claims 27 to 30, wherein one of R^{16} to R^{18} is hydrogen.

32. A compound according to any one of the claims 27 to 30, wherein two of R^{16} to R^{18} are
20 hydrogen.

33. A compound according to claim 27, wherein R^{16} and R^{17} are both hydrogen and R^{18} is
 $-\text{OCF}_3$, $-\text{SCF}_3$, $-\text{CF}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, phenyl, halogen, C_{1-6} -alkyl, nitro, $-\text{S-C}_{1-6}$ -alkyl or
 $-\text{S}(\text{O})_2\text{NR}^{21}\text{R}^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.

25

34. A compound according to claim 27, wherein R^{16} and R^{17} are both hydrogen and R^{18} is
 $-\text{OCF}_3$ or halogen.

35. A compound according to claim 27, wherein R^{16} is hydrogen and R^{17} and R^{18} are both
30 halogen or are both $-\text{CF}_3$.

36. A compound according to claim 27, wherein R^{16} is hydrogen, R^{17} is $-\text{CF}_3$ and R^{18} is halo-
gen, $-\text{CN}$, C_{1-6} -alkoxy or $-\text{OCF}_3$.

- 35 37. A compound according to claim 27, wherein R^{16} is hydrogen, R^{17} is $-\text{OCF}_3$ and R^{18} is
 $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{CH}_2\text{O-tri-C}_{1-6}\text{-alkylsilyl}$, benzoxazolyl or $-\text{CH}_2\text{OH}$.

Amended claims, 29.03.01

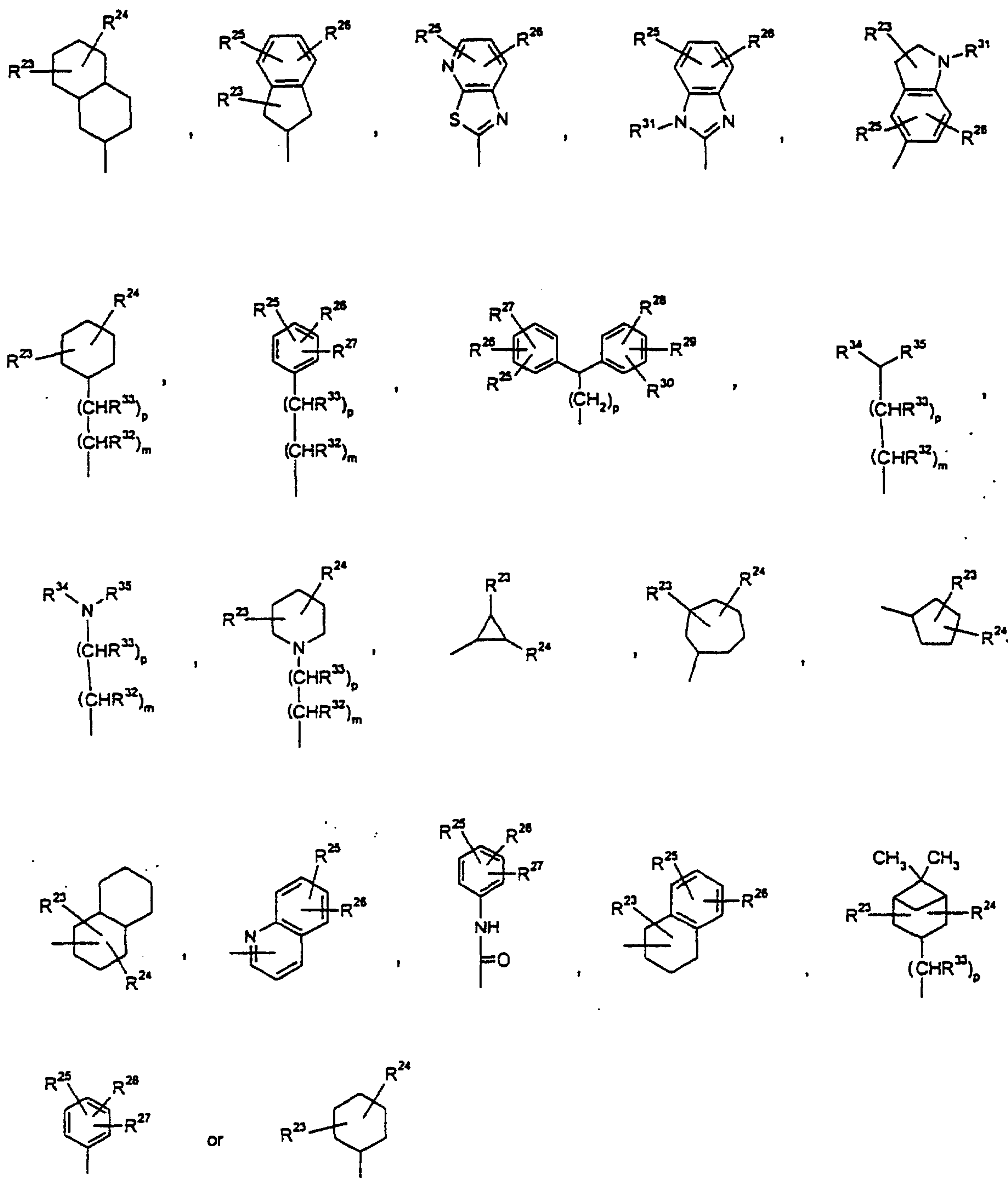
38. A compound according to claim 27, wherein R^{16} is hydrogen, R^{17} is C_{1-6} -alkyl and R^{18} is $-S(O)_2NR^{21}R^{22}$, wherein R^{21} is C_{1-6} -alkyl and R^{22} is phenyl.
- 5 39. A compound according to claim 27, wherein R^{16} , R^{17} and R^{18} are selected from hydrogen, $-OCF_3$, $-CF_3$, $-Br$, $-F$ and $-Cl$.



wherein

m, p and R^{23} to R^{35} are as defined in claim 1.

5 41. A compound according to claim 40, wherein E is

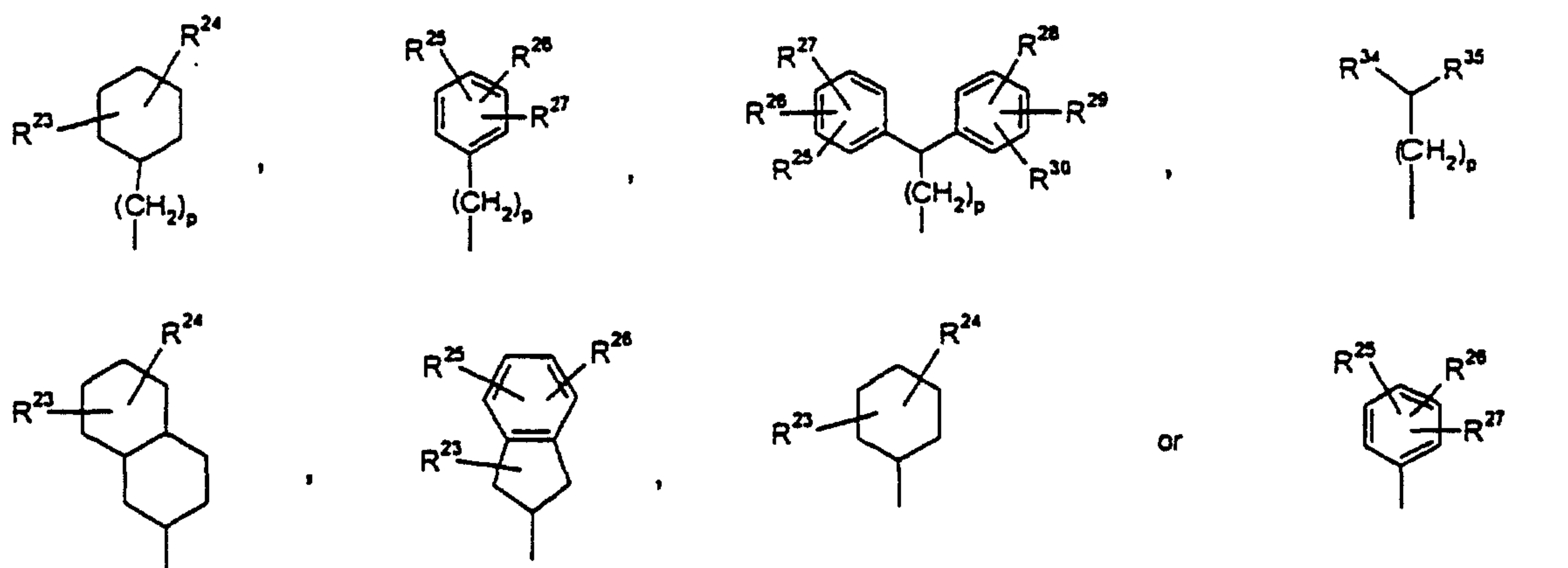


wherein m, p and R^{23} to R^{35} are as defined in claim 1.

Amended claims, 29.03.01

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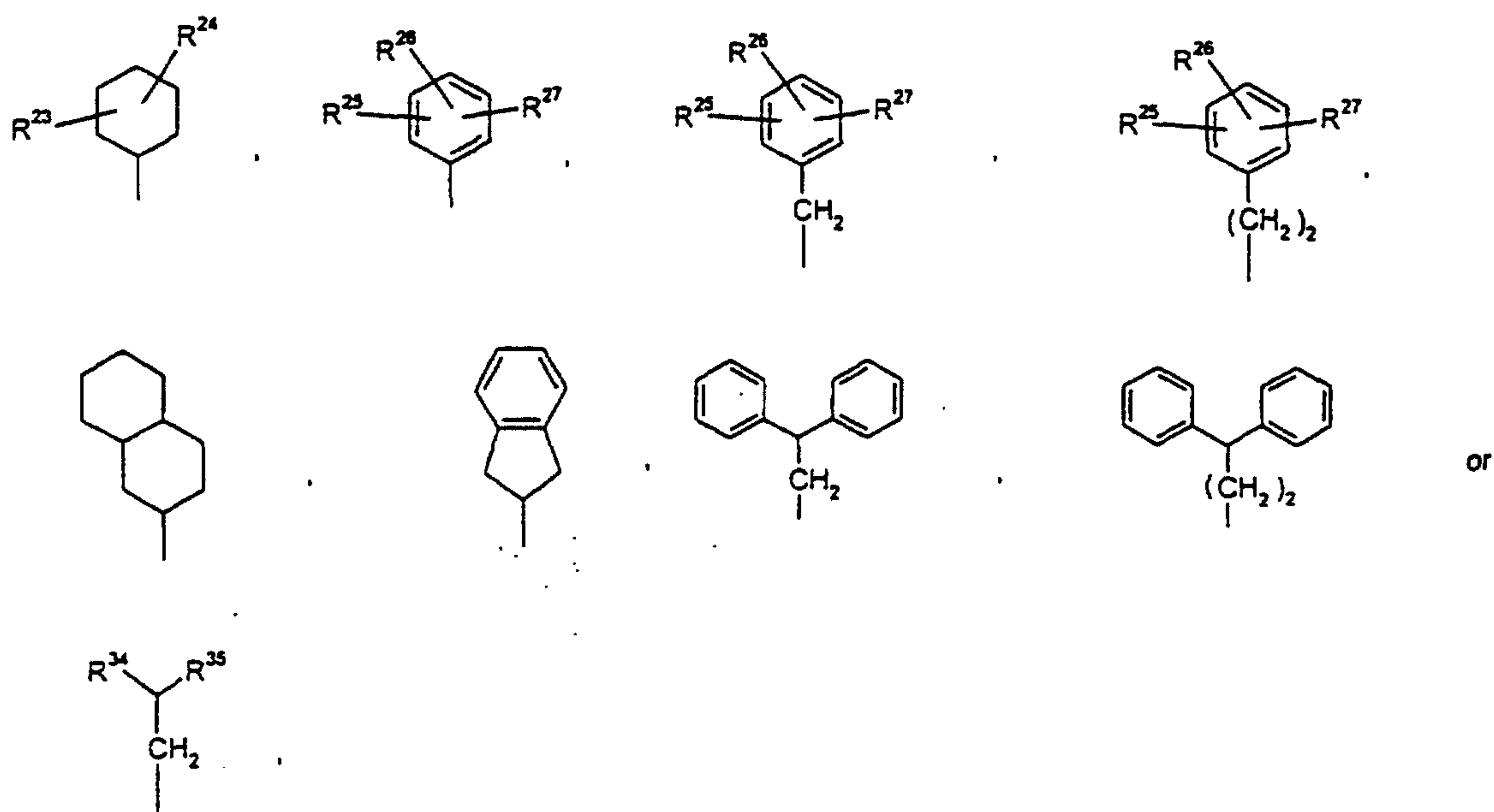
42. A compound according to claim 41, wherein E is



5

wherein p, R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³⁴ and R³⁵ are as defined in claim 1.

43. A compound according to claim 42, wherein E is



10

wherein R²³, R²⁴, R²⁵, R²⁶, R²⁷, R³⁴ and R³⁵ are as defined in claim 1.

44. A compound according to claim 43, wherein R³⁴ and R³⁵ independently are C₁₋₆-alkyl, hydrogen or C₁₋₆-alkoxy.

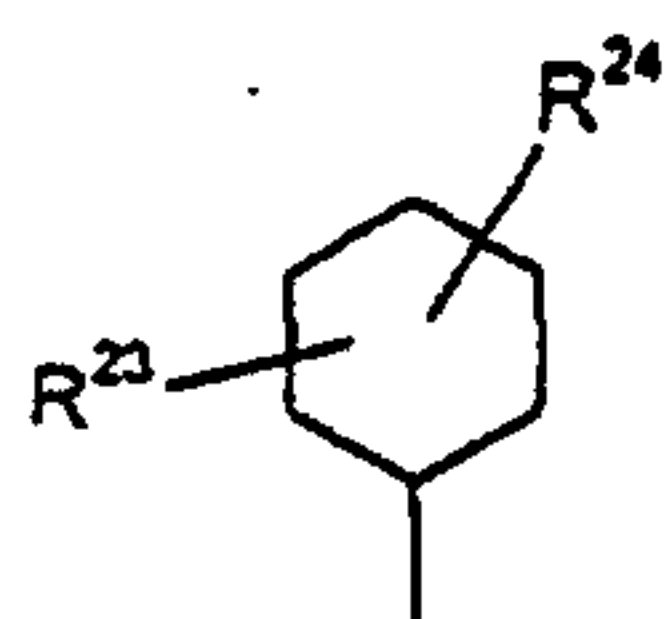
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Amended claims, 29.03.01

AMENDED SHEET

45. A compound according to claim 44, wherein R^{34} and R^{35} are both C_{1-6} -alkyl.

46. A compound according to claim 43, wherein E is

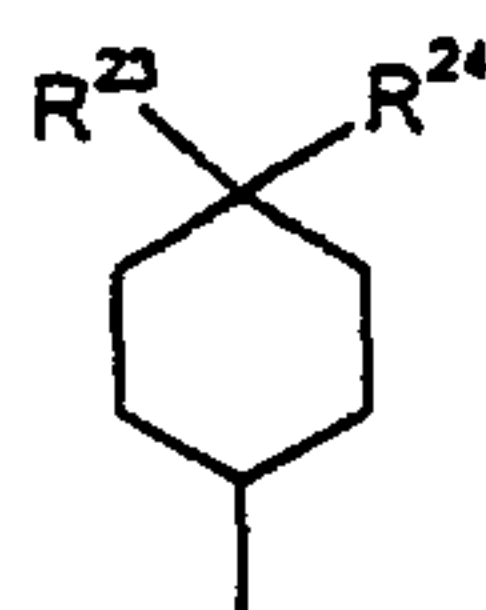


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wherein R^{23} and R^{24} are as defined in claim 1.

47. A compound according to claim 46, wherein E is

10



wherein R^{23} and R^{24} are as defined in claim 1.

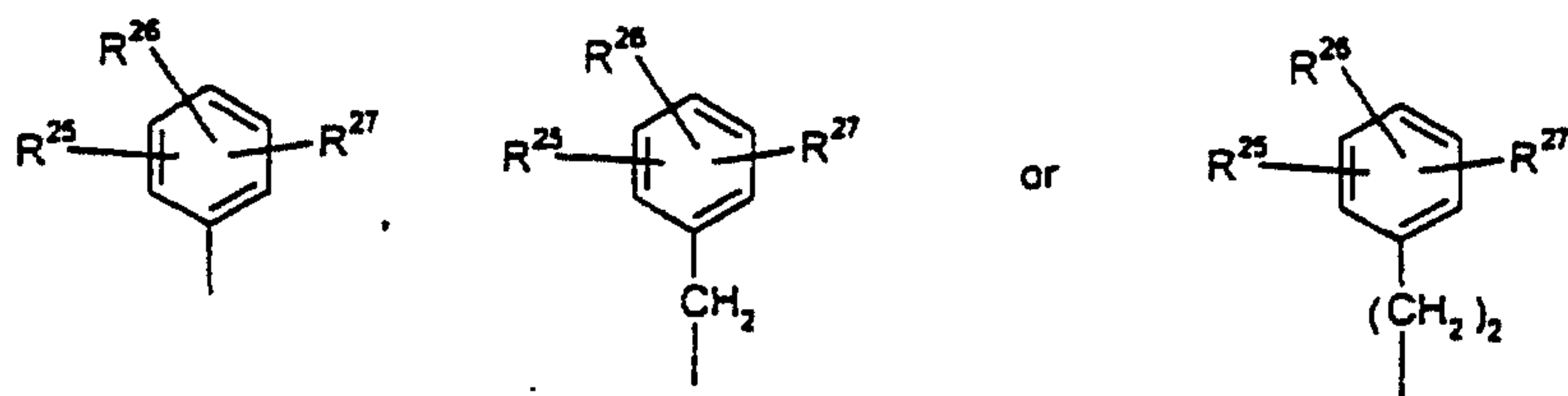
15 48. A compound according to claim 46 or 47, wherein R^{23} and R^{24} independently are selected from hydrogen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{3-8} -cycloalkylidene, phenoxy, phenyl, $-C(O)NR^{36}R^{37}$ and $-OC(O)NH$ -phenyl, of which the phenyl moiety optionally may be substituted with $-OCF_3$, wherein R^{36} and R^{37} are as defined in claim 1, or R^{23} and R^{24} together form the radical $-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l$, $-O-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-O-$, $-S-(CH_2)_t-CR^{40}R^{41}-(CH_2)_l-S-$,
20 wherein t , l , R^{40} and R^{41} are as defined in claim 1.

49. A compound according to claim 48, wherein R^{23} is hydrogen and R^{24} is C_{1-6} -alkyl such as *tert*-butyl or C_{3-8} -cycloalkyl such as cyclohexyl, wherein R^{23} and R^{24} are both C_{1-6} -alkyl or wherein R^{23} and R^{24} together form the radical $-(CH_2)_5-$.

25

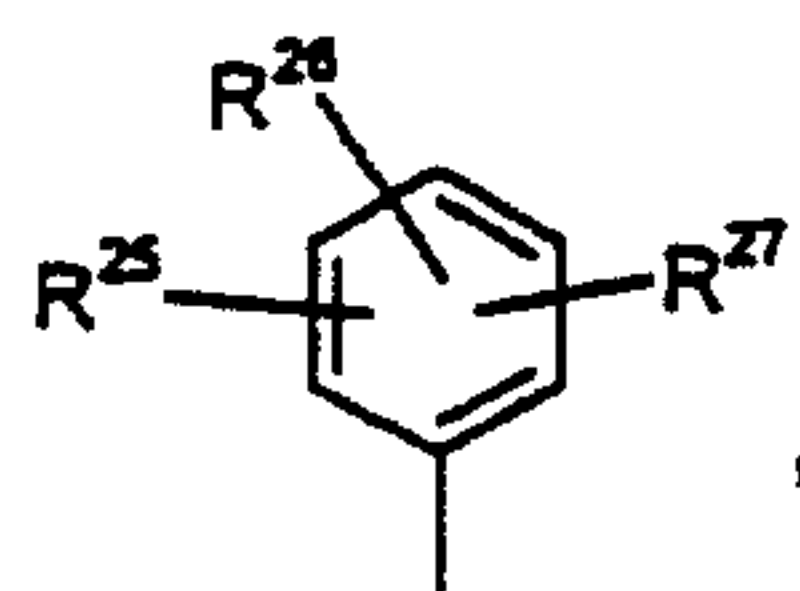
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50. A compound according to claim 43, wherein E is



5 wherein R^{25} , R^{26} and R^{27} are as defined in claim 1.

51. A compound according to claim 50, wherein E is

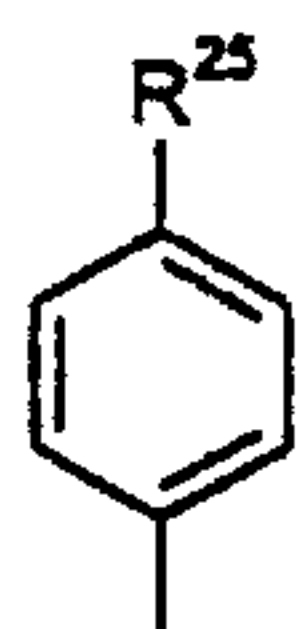


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wherein R^{25} , R^{26} and R^{27} are as defined in claim 1.

52. A compound according to claim 50 or 51, wherein R^{25} , R^{26} and R^{27} independently are selected from hydrogen, halogen, C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, C_{4-8} -cycloalkenyl, $-CF_3$,
15 $-OCF_3$ or $-NR^{42}R^{43}$, wherein R^{42} and R^{43} are as defined in claim 1.

53. A compound according to claim 52, wherein E is

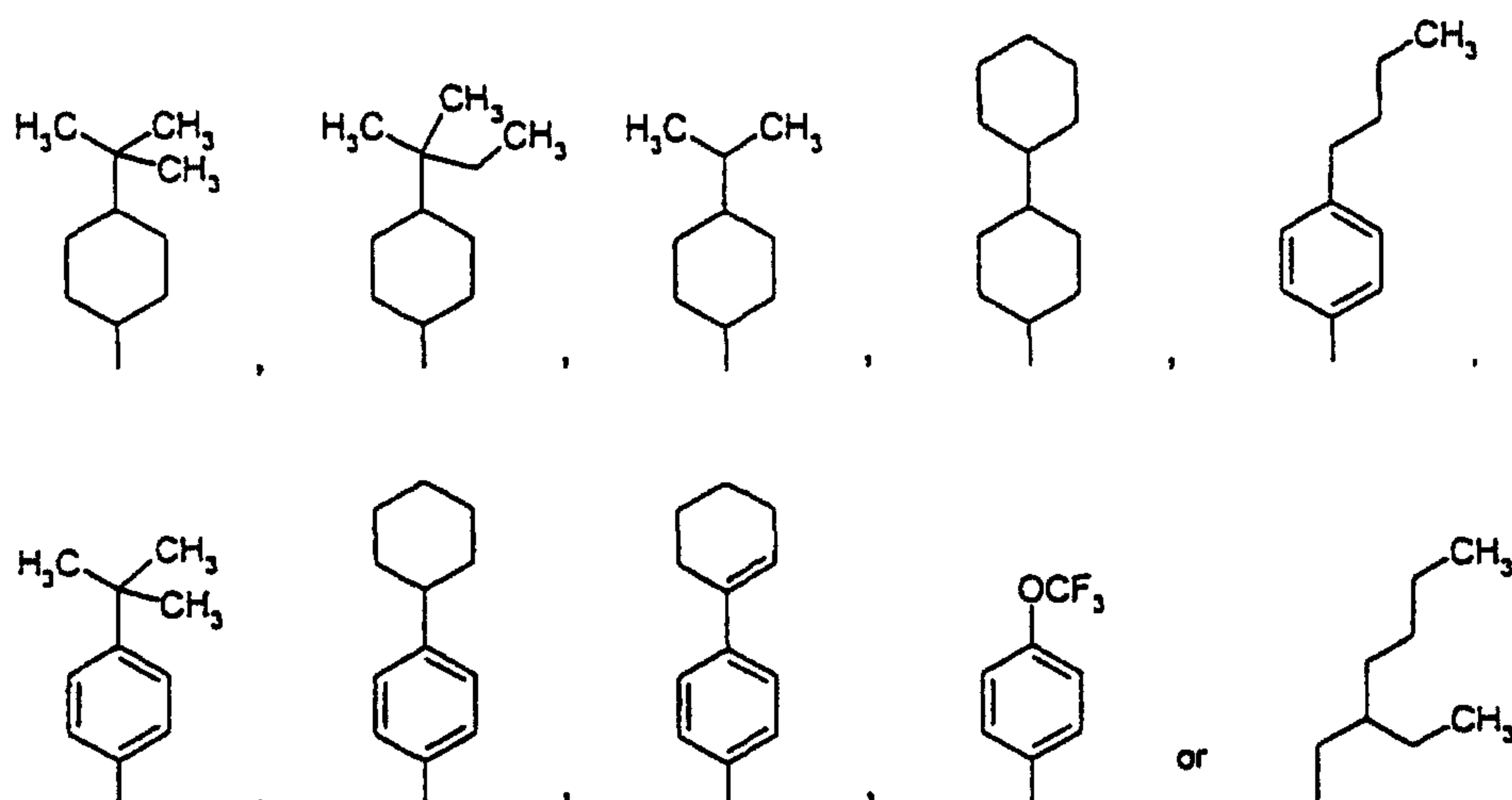


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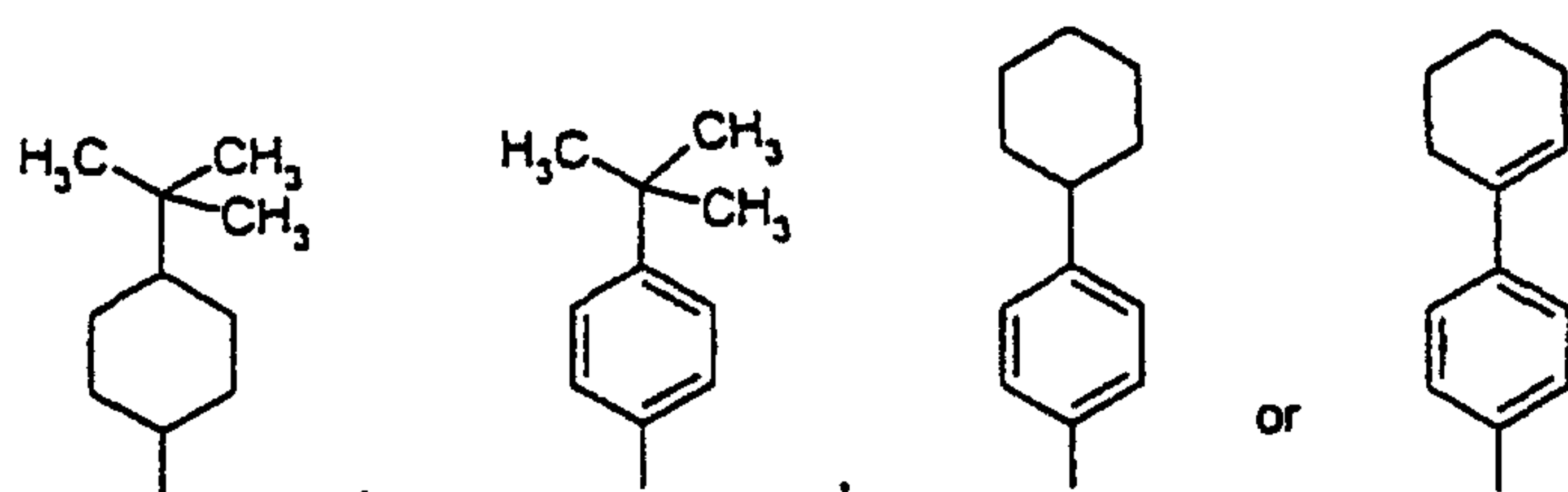
wherein R^{25} is $-OCF_3$, $-CF_3$, C_{1-6} -alkyl such as *tert*-butyl, piperidyl, C_{3-8} -cycloalkyl such as cyclohexyl or C_{4-8} -cycloalkenyl such as cyclohexenyl.

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54. A compound according to claim 43, wherein E is

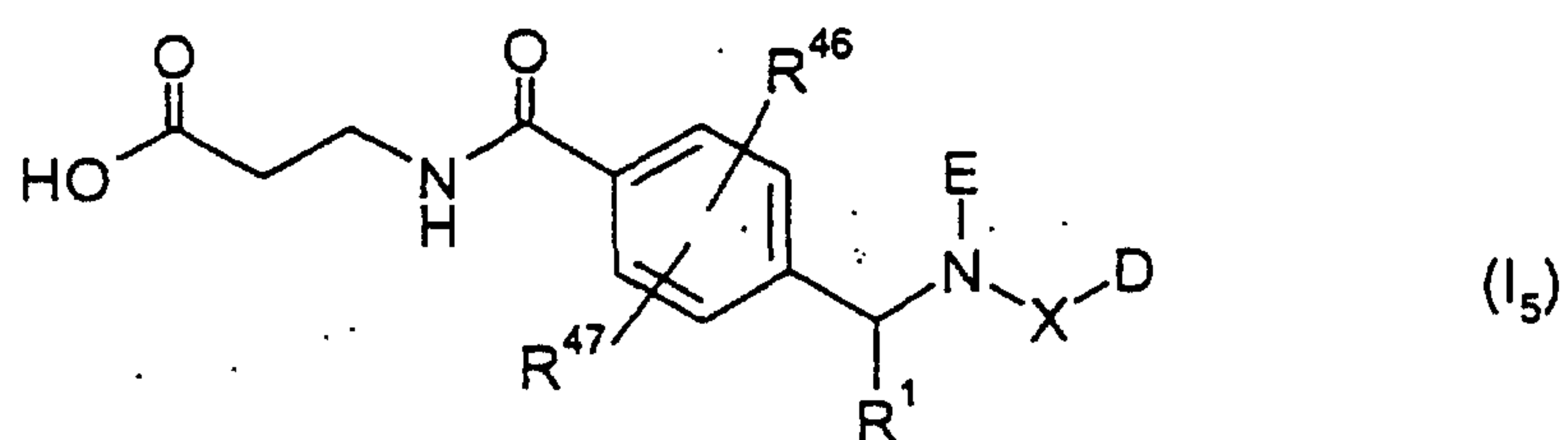


5 55. A compound according to claim 54, wherein E is



56. A compound according to claim 1 of the general formula (I₅):

10



wherein R^{46} , R^{47} , R^1 , E, X and D are as defined in claim 1 or in any one of the preceding claims.

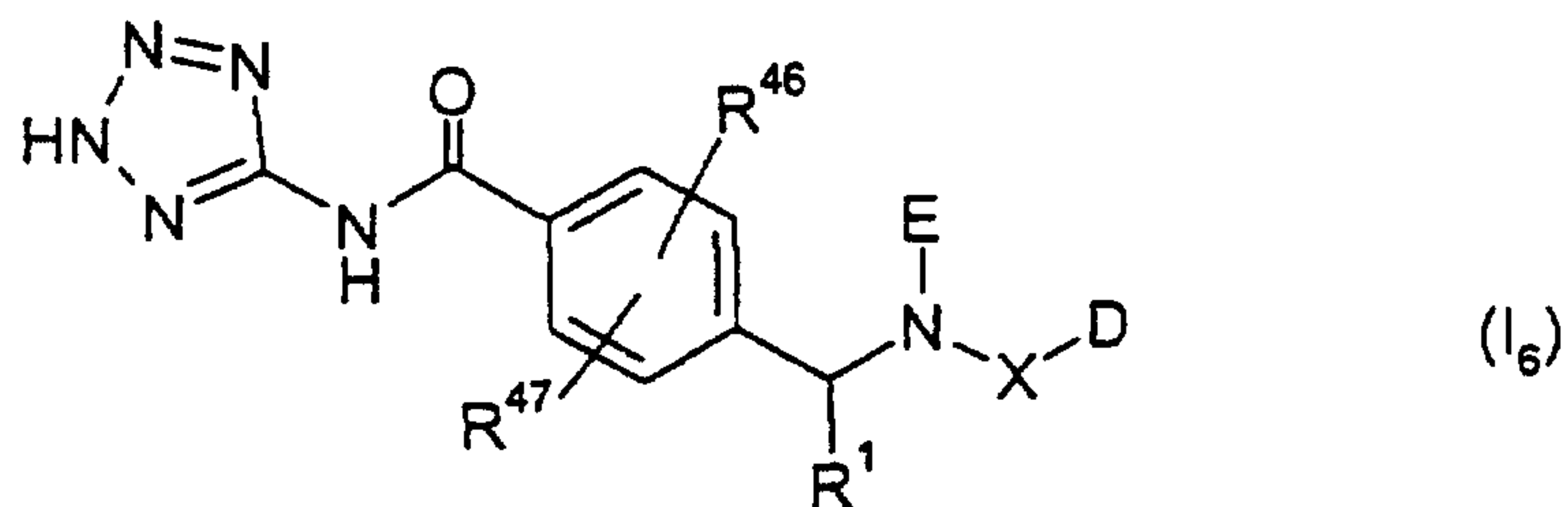
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Amended claims, 29.03.01

AMENDED SHEET

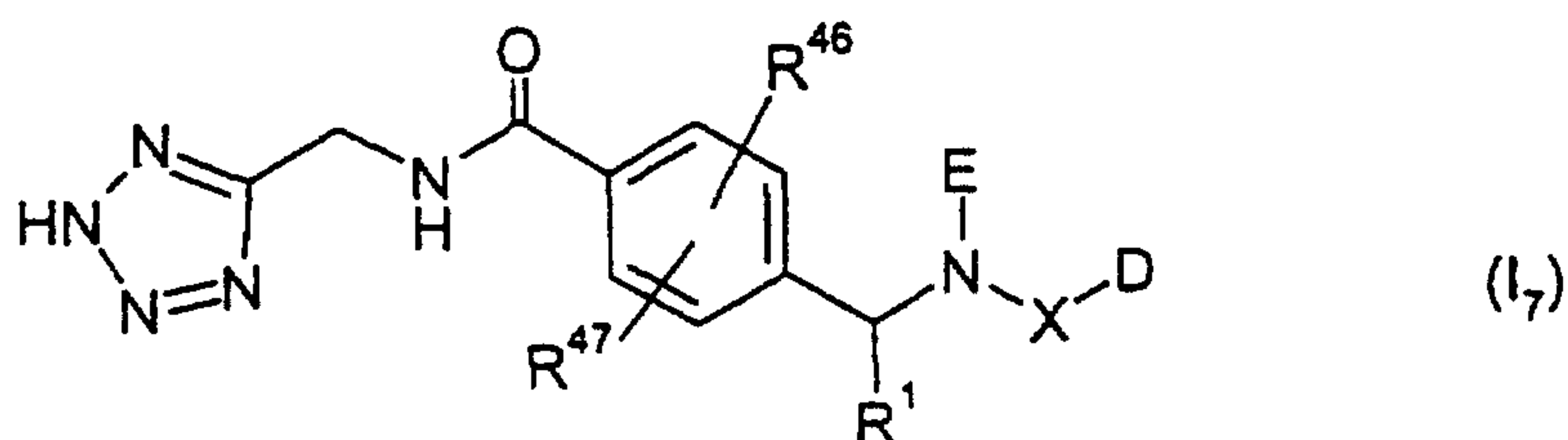
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57. A compound according to claim 1 of the general formula (I₆):



5 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

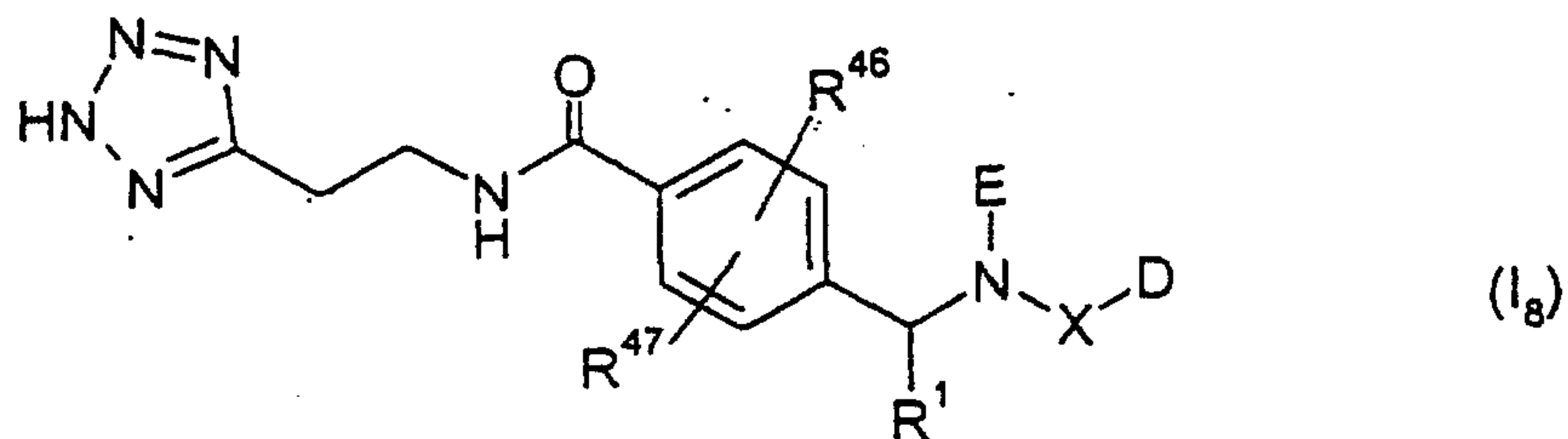
58. A compound according to claim 1 of the general formula (I₇):



10

wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

15 59. A compound according to claim 1 of the general formula (I₈):

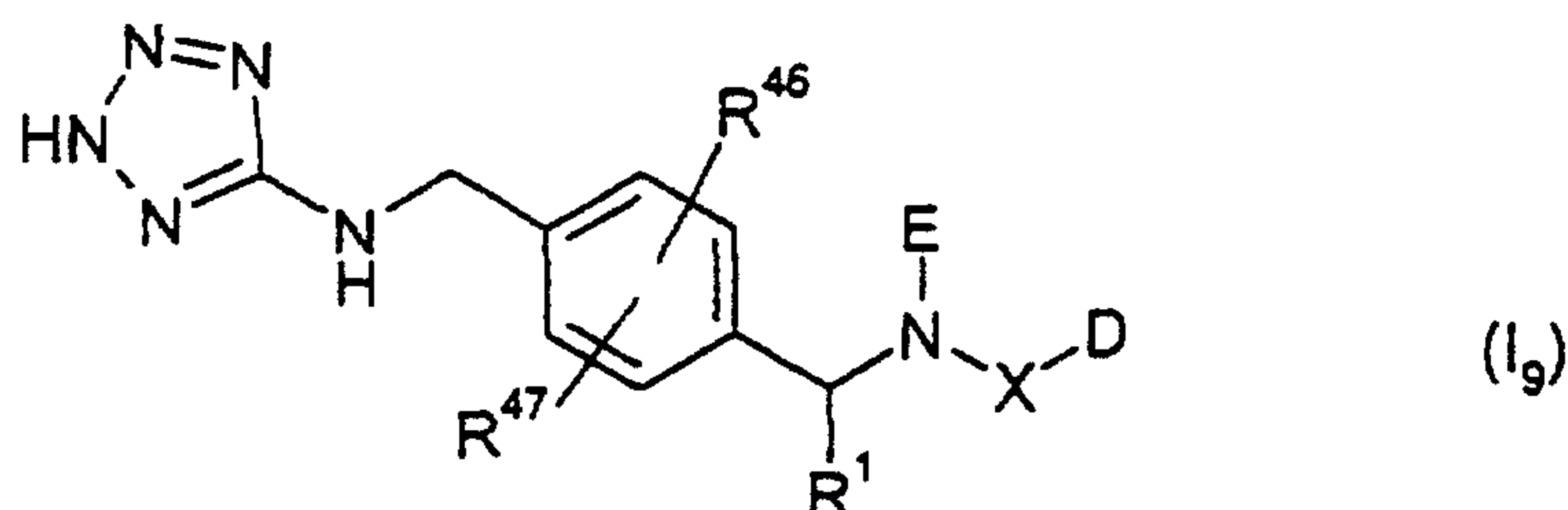


20 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

Amended claims, 29.03.01

AMENDED SHEET

60. A compound according to claim 1 of the general formula (I₉):



5 wherein R⁴⁶, R⁴⁷, R¹, E, X and D are as defined in claim 1 or in any one of the preceding claims.

61. A compound according to anyone of the claims 56 to 60, wherein R⁴⁶ and R⁴⁷ are both hydrogen.

10

62. A compound according to any one of the preceding claims, which has an IC₅₀ value of no greater than 5 μM as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein.

15 63. A compound according to claim 62, characterized by having a glucagon antagonistic activity as determined by the Glucagon Binding Assay (I), Glucagon Binding Assay (II) or Glucagon Binding Assay (III) disclosed herein corresponding to an IC₅₀ value of less than 1 μM, preferably of less than 500 nM and even more preferred of less than 100 nM.

20 64. A compound according to any one of the preceding claims, which is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hyperglycemia, IGT, Type 2 diabetes, Type 1 diabetes and obesity.

65. A compound according to any one of the claims 1 to 64 for use as a medicament.

25

66. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1 to 64 together with one or more pharmaceutically acceptable carriers or excipients.

30 67. A pharmaceutical composition according to claim 66 in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and espe-

Amended claims, 29.03.01

cially preferred from about 0.5 mg to about 200 mg of the compound according to any one of the claims 1 to 64.

5 68. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

10 69. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.

70. Use of a compound according to any one of the claims 1 to 64 for the manufacture of a medicament for the treatment and/or prevention of hyperglycemia.

15 71. Use of a compound according to any one of the claims 1 to 64 for the manufacture of a medicament for lowering blood glucose in a mammal.

20 72. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of IGT.

73. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.

25 74. Use according to claim 73 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.

30 75. Use according to claim 73 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

76. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.

35 77. Use according to any one of the claims 68 to 76 in a regimen which additionally comprises treatment with another antidiabetic agent.

Amended claims, 29.03.01

78. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of obesity.

5 79. Use of a compound according to any one of the claims 1 to 64 for the preparation of a medicament for the treatment and/or prevention of obesity in a regimen which additionally comprises treatment with another antiobesity agent.

10 80. A method for the treatment and/or prevention of disorders or diseases mediated by a glucagon antagonistic action, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the claims 1 to 64 or a pharmaceutical composition according to claim 66 or 67.

15 81. The method according to claim 80, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.