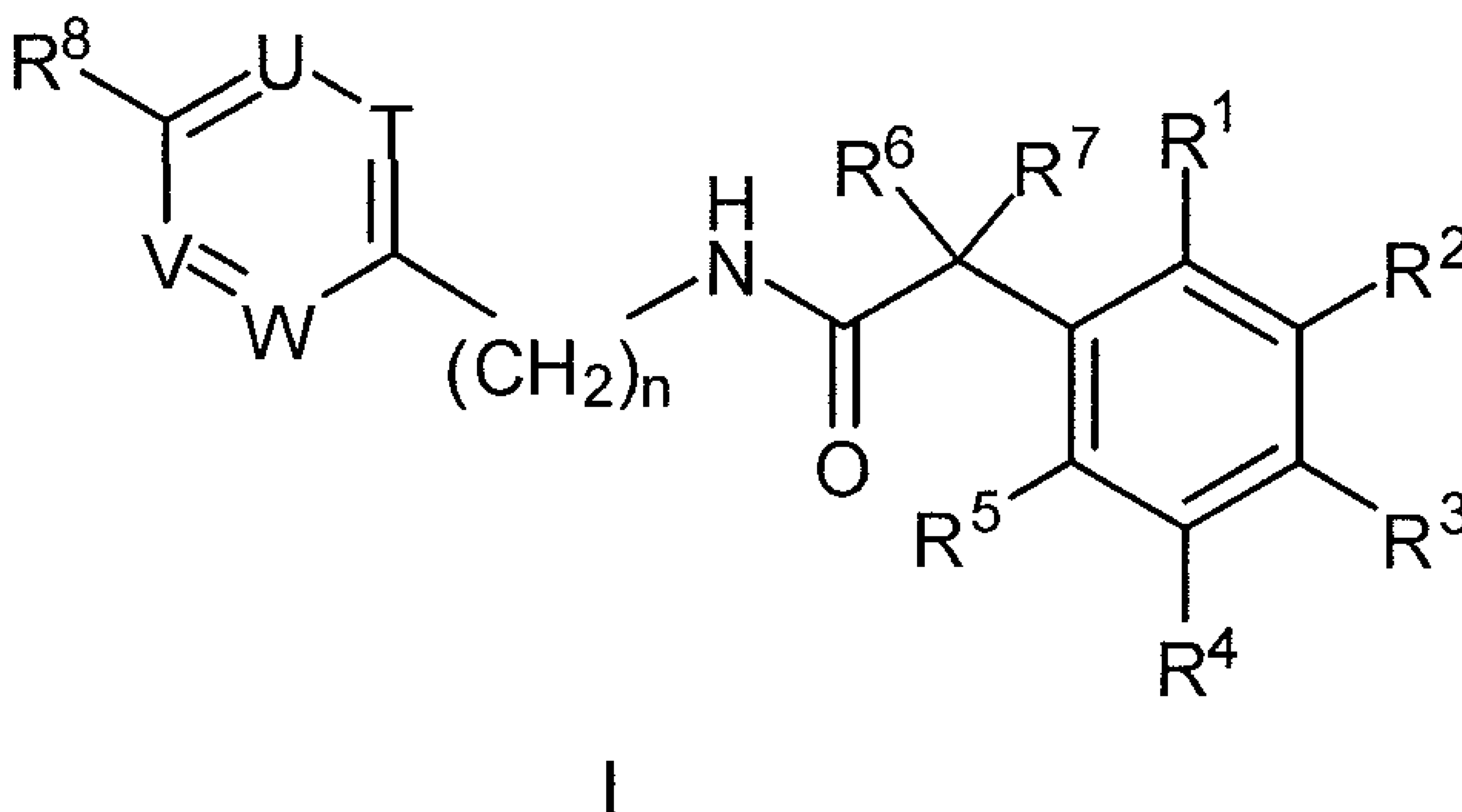




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(54) Titre : NOUVEAUX LIGANDS DU RECEPTEUR VANILLOIDE ET LEUR UTILISATION POUR LA FABRICATION DE MEDICAMENTS
(54) Title: NOVEL VANILLOID RECEPTOR LIGANDS AND THE USE THEREOF FOR THE PRODUCTION OF PHARMACEUTICALS



(57) Abrégé/Abstract:

The present invention relates to novel vanilloid receptor ligands of general formula (I), a method for the production thereof, pharmaceuticals containing said compounds, and the use of said compounds for the production of pharmaceuticals for treating migraines, depression, neurogenerative diseases, cognitive diseases, anxiety disorders, epilepsy, coughs, diarrhoea, pruritus, inflammations, disorders of the cardiovascular system, eating disorders, medication dependency, misuse of medication and in particular urinary incontinence.



(21) **2 683 910**

(13) **A1**

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Abstract

The present invention relates to novel vanilloid receptor ligands, to processes for the production thereof, to pharmaceuticals containing said compounds and to the use of
5 said compounds for the production of pharmaceuticals.

Novel vanilloid receptor ligands and the use thereof for the production of pharmaceuticals

5 The present invention relates to novel vanilloid receptor ligands, to processes for the production thereof, to pharmaceuticals containing said compounds and to the use of said compounds for the production of pharmaceuticals.

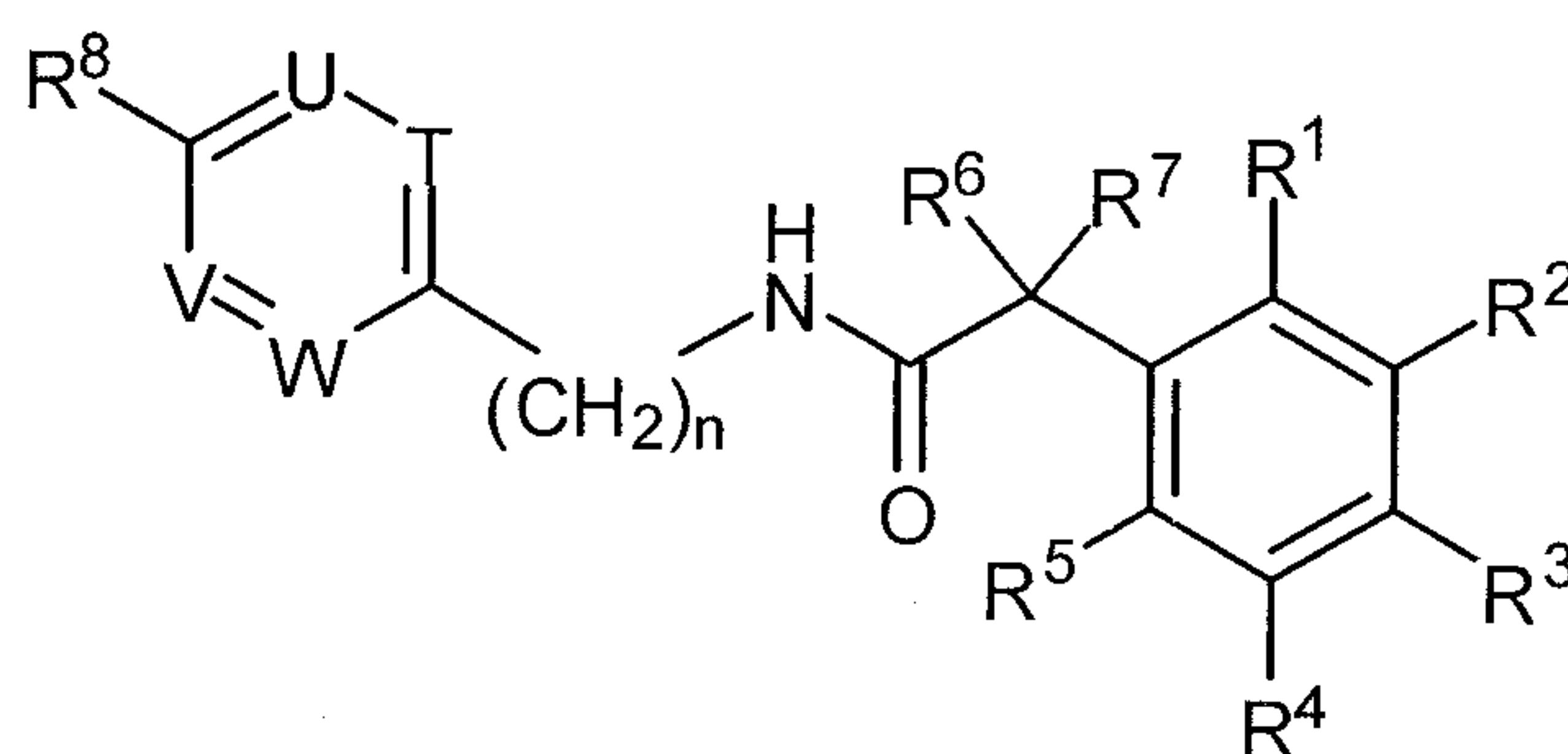
10 The treatment of pain, particularly neuropathic pain, is of great significance in the medical field. There is a global need for effective pain therapies. The urgent need for action to provide a patient-friendly und targeted treatment of chronic and non-chronic states of pain, this being taken to mean the successful und satisfactory treatment of pain for patients, is documented by the large number of scientific papers which have recently appeared in the field of applied analgesics or in basic research concerning
15 nociception.

A suitable starting point for the treatment of pain; particularly of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain, particularly preferably neuropathic pain; is the vanilloid receptor of subtype 1
20 (VR1/TRPV1), frequently also designated as the capsaicin receptor. This receptor is stimulated, inter alia, by vanilloids such as capsaicin, heat, and protons and plays a central part in the generation of pain. Furthermore, it is significant for a large number of other physiological and pathophysiological processes such as migraine; states of depression; neurodegenerative disorders; cognitive disorders; anxiety; epilepsy;
25 coughing; diarrhea; pruritus; inflammations; disorders of the cardiovascular system; food intake disorders; medicine addiction; medicine abuse and, in particular, urinary incontinence.

It is thus an object of the invention to provide novel compounds which are particularly
30 suitable for use as pharmacologically active substances in pharmaceuticals, preferably in pharmaceuticals for treatment of disorders or diseases that are at least partially mediated by vanilloid receptors 1 (VR1/TRPV1 receptors).

It has now been found, surprisingly, that the substituted compounds of the general formula I stated below show excellent affinity to the vanilloid receptor of subtype 1 (VR1/TRPV1 receptor) and are therefore particularly suitable for the prophylaxis and/or treatment of disorders or diseases which are at least partially mediated by vanilloid receptors 1 (VR1/TRPV1). The substituted compounds of the general formula I given below also show anti-inflammatory activity.

It is thus an object of the present invention to provide substituted compounds of the general formula I,



I,

in which

n stands for 0, 1, 2, 3, or 4;

R¹ stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -C(=NH)-NH₂; -C(=NH)-NH-R⁹; -N=C(NH₂)₂; -N=C(NHR¹⁰)-(NHR¹¹); -O-P(=O)₂-O-R¹²; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -C(=O)-NHR¹⁸; -C(=O)-NR¹⁹R²⁰; -S(=O)₂-NHR²¹; -S(=O)₂-NR²²R²³; -C(=O)-OR²⁴; -C(=O)-R²⁵; -S(=O)-R²⁶; or -S(=O)₂-R²⁷ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

R² stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -C(=NH)-NH₂; -C(=NH)-NH-R⁹; -N=C(NH₂)₂; -N=C(NHR¹⁰)-(NHR¹¹); -O-P(=O)₂-O-R¹²; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -C(=O)-NHR¹⁸; -C(=O)-NR¹⁹R²⁰; -S(=O)₂-NHR²¹; -S(=O)₂-NR²²R²³; -C(=O)-OR²⁴; -C(=O)-R²⁵; -

$S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^3 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-C(=NH)-NH_2$; $-C(=NH)-NH-R^9$; $-N=C(NH_2)_2$; $-N=C(NHR^{10})-(NHR^{11})$; $-O-P(=O)_2-O-R^{12}$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-C(=O)-NHR^{18}$; $-C(=O)-NR^{19}R^{20}$; $-S(=O)_2-NHR^{21}$; $-S(=O)_2-NR^{22}R^{23}$; $-C(=O)-OR^{24}$; $-C(=O)-R^{25}$; $-S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^4 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-C(=NH)-NH_2$; $-C(=NH)-NH-R^9$; $-N=C(NH_2)_2$; $-N=C(NHR^{10})-(NHR^{11})$; $-O-P(=O)_2-O-R^{12}$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-C(=O)-NHR^{18}$; $-C(=O)-NR^{19}R^{20}$; $-S(=O)_2-NHR^{21}$; $-S(=O)_2-NR^{22}R^{23}$; $-C(=O)-OR^{24}$; $-C(=O)-R^{25}$; $-S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^5 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-C(=NH)-NH_2$; $-C(=NH)-NH-R^9$; $-N=C(NH_2)_2$; $-N=C(NHR^{10})-(NHR^{11})$; $-O-P(=O)_2-O-R^{12}$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-C(=O)-NHR^{18}$; $-C(=O)-NR^{19}R^{20}$; $-S(=O)_2-NHR^{21}$; $-S(=O)_2-NR^{22}R^{23}$; $-C(=O)-OR^{24}$; $-C(=O)-R^{25}$; $-S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^6 stands in each case for hydrogen or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^7 stands for hydrogen or $-OH$;

or R^6 and R^7 form, together with the interconnecting carbon atom as ring member,

a saturated or unsaturated, unsubstituted or at least monosubstituted three-membered, four-membered, five-membered, or six-membered cycloaliphatic radical;

- 5 R^8 stands for $-SF_5$; $-O-CF_3$; $-CF_3$; $-O-CFH_2$; $-O-CF_2H$; $-CFH_2$; $-CF_2H$; or for an unsubstituted or at least monosubstituted tert-butyl radical;

T stands for $C-R^{35}$ and U stands for $C-R^{36}$ and V stands for N and W stands for $C-R^{38}$

Or

- 10 T stands for $C-R^{35}$ and U stands for N and V stands for $C-R^{37}$ and W stands for $C-R^{38}$

Or

T stands for N and U stands for $C-R^{36}$ and V stands for $C-R^{37}$ and W stands for $C-R^{38}$

Or

T stands for N and U stands for N and V stands for $C-R^{37}$ and W stands for $C-R^{38}$

- 15 Or

T stands for N and U stands for $C-R^{36}$ and V stands for N and W stands for $C-R^{38}$

Or

T stands for $C-R^{35}$ and U stands for N and V stands for N and W stands for $C-R^{38}$

Or

- 20 T stands for $C-R^{35}$ and U stands for $C-R^{36}$ and V stands for $C-R^{37}$ and W stands for $C-R^{38}$;

$R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}$ and R^{27} each independently

25

stand for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

30

for an unsaturated or saturated, unsubstituted or at least monosubstituted, three-membered, four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered cycloaliphatic radical optionally containing at least one heteroatom as ring member, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded

via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or two to six-membered heteroalkylene group;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or two to six-membered heteroalkylene group;

R³⁵, R³⁶, and R³⁷ each independently stand for H; F; Cl; Br; I; -SF₅; -NO₂; -CF₃; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -C(=O)-NHR¹⁸; -C(=O)-NR¹⁹R²⁰; -S(=O)₂-NHR²¹; -S(=O)₂-NR²²R²³; -C(=O)-OR²⁴; -C(=O)-R²⁵; -S(=O)-R²⁶; -S(=O)₂R²⁷

for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or C₂₋₆ alkenylene group or C₂₋₆-alkynylene group;

R³⁸ stands for F; Cl; Br; I; -SF₅; -NO₂; -CF₃; -CF₂ Cl; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR³⁹; -NR⁴⁰R⁴¹; -OR⁴²; -SR⁴³; -C(=O)-NHR⁴⁴; -C(=O)-NR⁴⁵R⁴⁶; -S(=O)₂-NHR⁴⁷; -S(=O)₂-NR⁴⁸R⁴⁹; -C(=O)-OR⁵⁰; -C(=O)-R⁵¹; -S(=O)-R⁵²; -S(=O)₂-R⁵³; -C(=NH)-NH₂; -C(=NH)-NH-R⁵⁴; -N=C(NH₂)₂; -N=C(NHR⁵⁵)-(NHR⁵⁶);

for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

for an unsaturated or saturated, unsubstituted or at least monosubstituted three-membered, four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered cycloaliphatic radical optionally exhibiting at least one heteroatom as ring member, each of which is bonded to the parent structure over a carbon atom in the ring of the cycloaliphatic radical and is condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or C₂₋₆ alkenylene group or C₂₋₆ alkynylene group;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or C₂₋₆ alkenylene group or C₂₋₆-alkynylene group;

R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹, R⁵², R⁵³, R⁵⁴, R⁵⁵, and R⁵⁶ each independently

stand for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

for an unsaturated or saturated, unsubstituted or at least monosubstituted, three-membered, four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered cycloaliphatic radical optionally containing at least one heteroatom as ring member, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or two to six-membered heteroalkylene group;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or two to six-membered heteroalkylene group;

or

R⁴⁰ and R⁴¹ form, together with the interconnecting nitrogen atom as ring member, a saturated or unsaturated four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered heterocycloaliphatic radical, which is unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R⁵⁷ and optionally exhibits at least one further heteroatom as ring member, and which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system;

R⁵⁷ stands for -NHR⁵⁸, -NR⁵⁹R⁶⁰, or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

R⁵⁸, R⁵⁹, and R⁶⁰ each independently stand for -C(=O)-R⁶¹; for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or C₂₋₆ alkenylene group or C₂₋₆ alkynylene group;

and R⁶¹ stands for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

each optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers thereof, the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or each in the form of corresponding salts, or each in the form of corresponding solvates;

wherein

the aforementioned aliphatic C₁₋₁₀ radicals and tert-butyl radicals can each be optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O(C₁₋₅ alkyl), -S(C₁₋₅ alkyl), -NH(C₁₋₅ alkyl), -N(C₁₋₅ alkyl)-(C₁₋₅ alkyl), -C(=O)-O-(C₁₋₅ alkyl), -O-C(=O)-(C₁₋₅ alkyl), -O-phenyl, phenyl, -OCF₃, and -SCF₃;

the aforementioned two to six-membered heteroalkylene groups, C₁₋₆ alkylene groups, and C₂₋₆ alkenylene groups and C₂₋₆ alkynylene groups can each be optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O(C₁₋₅ alkyl), -S(C₁₋₅ alkyl), -NH(C₁₋₅ alkyl), -N(C₁₋₅ alkyl)-(C₁₋₅ alkyl), -OCF₃, and -SCF₃;

the aforementioned heteroalkylene groups each optionally exhibit 1, 2, or 3 heteroatom(s) independently selected from the group consisting of oxygen, sulfur, and nitrogen (NH) as link(s);

the aforementioned (hetero)cycloaliphatic radicals are optionally each substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of -(C₁₋₆ alkylene)-OH, =CH₂, -O-(C₁₋₅ alkylene)oxetanyl, -(C₁₋₅ alkylene)-O-(C₁₋₅ alkylene)oxetanyl, -CH₂-NH-(C₁₋₅ alkyl), -CH₂-N(C₁₋₅ alkyl)₂, -N[C(=O)-(C₁₋₅ alkyl)]phenyl, -CH₂-O-(C₁₋₅ alkyl), oxo (=O), thioxo (=S), F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-(C₁₋₅ alkyl), -O-C(=O)-(C₁₋₅ alkyl), -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-(C₁₋₅ alkyl), -(C₁₋₅ alkyl), -C(=O)-(C₁₋₅ alkyl), -C(=O)-OH, -C(=O)-O-(C₁₋₅ alkyl), -NH-(C₁₋₅ alkyl), -N(C₁₋₅ alkyl)₂, -NH-phenyl, -N(C₁₋₅ alkyl)phenyl, cyclohexyl, cyclopentyl, (4,5)-dihydroisoxazolyl, thiazolyl, (1,2,5)-thiadiazolyl, thiophenyl, phenethyl, piperidinyl, pyrrolidinyl, -(CH₂)-pyridinyl, pyridinyl, -O-phenyl, -O-benzyl, phenyl, and benzyl, and

the cyclic moiety of the radicals oxetanyl, (4,5)-dihydroisoxazolyl, thiazolyl, (1,2,5)-thiadiazolyl, thiophenyl, phenethyl, -N[C(=O)-(C₁₋₅ alkyl)]phenyl, -NH-phenyl, -N(C₁₋₅ alkyl)phenyl, -(CH₂)-pyridinyl, pyridinyl, -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, -C₁₋₅-alkyl, -O-C₁₋₅ alkyl, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl,

and, unless otherwise stated, the aforementioned (hetero)cycloaliphatic radicals can each optionally exhibit 1, 2, or 3 (further) heteroatom(s) independently selected from the group consisting of oxygen, nitrogen, and sulfur;

the rings of the aforementioned monocyclic or polycyclic ring systems can each be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of oxo (=O), thioxo (=S), F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-(C₁₋₅ alkyl), -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-(C₁₋₅ alkyl), -(C₁₋₅ alkyl), -C(=O)-(C₁₋₅ alkyl), -C(=O)-OH, -C(=O)-O-(C₁₋₅ alkyl), -NH-(C₁₋₅ alkyl), -N(C₁₋₅ alkyl)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, -C₁₋₅-alkyl, -O-C₁₋₅-alkyl, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl,

and the rings of the aforementioned monocyclic or polycyclic ring systems are each five-membered, six-membered, or seven-membered and can each optionally exhibit 1, 2, 3, 4, or 5 heteroatom(s) as ring member(s), which are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

and the aforementioned aryl radicals or heteroaryl radicals can each be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-C₁₋₅-alkyl, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-C₁₋₅-alkyl, -C₁₋₅ alkyl, -C(=O)-OH, -C(=O)-O-C₁₋₅-alkyl, -NH-C₁₋₅-alkyl, -N(C₁₋₅-alkyl)₂, -NH-S(=O)₂-C₁₋₅ alkyl, -NH-C(=O)-O-C₁₋₅ alkyl, -C(=O)-H, -C(=O)-C₁₋₅-alkyl, -C(=O)-NH₂, -C(=O)-NH-C₁₋₅-alkyl, -C(=O)-N-(C₁₋₅-alkyl)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents

independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, -C₁₋₅-alkyl, -O-C₁₋₅-alkyl, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl,

and

the aforementioned heteroaryl radicals can each optionally exhibit 1, 2, 3, 4, or 5 heteroatom(s) independently selected from the group consisting of oxygen, nitrogen, and sulfur as ring member(s).

The term "heteroalkylene" designates an alkylene chain in which one or more C-atoms have each been replaced by a heteroatom independently selected from the group consisting of oxygen, sulfur and nitrogen (NH). Heteroalkylene groups can preferably contain 1, 2, or 3 heteroatom(s) and more preferably one heteroatom, independently selected from the group consisting of oxygen, sulfur and nitrogen (NH), as link(s). Heteroalkylene groups can preferably be two to six-membered and more preferably two or three-membered.

Mention may be made, for example, of heteroalkylene groups such as -CH₂-CH₂-O-CH₂-, -CH₂-CH(CH₃)-O-CH₂-, -(CH₂)-O-, -(CH₂)₂-O-, -(CH₂)₃-O-, -(CH₂)₄-O-, -O-(CH₂)-, -O-(CH₂)₂-, -O-(CH₂)₃-, -O-(CH₂)₄-, -C(C₂H₅)-(H)-O-, -O-C(C₂H₅)-(H)-, -CH₂-O-CH₂-, -CH₂-S-CH₂-, -CH₂-NH-CH₂-, -CH₂-NH-, and -CH₂-CH₂-NH-CH₂-CH₂.

If one or more of the aforementioned substituents exhibit a linear or branched C₁₋₆-alkylene group, these can be preferably selected from the group consisting of -(CH₂)-, -(CH₂)₂-, -C(H)-(CH₃)-, -(CH₂)₃-, -(CH₂)₄-, -(CH₂)₅-, -C(H)-(C(H)-(CH₃)₂)-, and -C(C₂H₅)-(H)-.

Saturated or unsaturated C₁₋₁₀ aliphatic radicals can stand for a C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, or C₂₋₁₀-alkynyl radical. C₂₋₁₀-alkenyl radicals have at least one and preferably 1, 2, 3, or 4 C-C-double bonds and C₂₋₁₀-alkynyl radicals at least one and preferably 1, 2, 3, or 4 C-C-triple bonds.

Preference is given to C₁₋₁₀-alkyl radicals selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-

methylbut-1-yl, 2-pentyl, 3-pentyl, sec-pentyl, neopentyl, 4-methylpent-1-yl, (3,3)-dimethylbut-1-yl, n-hexyl, n-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, n-octyl, n-nonyl, 2-nonyl, 3-nonyl, 4-nonyl, 5-nonyl, and (2,6)-dimethylhept-4-yl, which can be optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents independently selected from the group consisting of -O-phenyl, -O-C(=O)-CH₃, -O-C(=O)-C₂H₅, -O-C(=O)-CH(CH₃)₂, -O-C(=O)-C(CH₃)₃, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-CH(CH₃)₂, -C(=O)-O-C(CH₃)₃, F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -OCF₃, and -SCF₃.

In another preferred embodiment, C₂₋₁₀ alkenyl radicals are selected from the group consisting of vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylpropene-1-yl, 3-methyl-but-2-en-1-yl, (3,3)-dimethyl-but-1-enyl, 2-methyl-butene-2-yl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 1-heptenyl, and 1-octenyl, which can be optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -OCF₃, and -SCF₃.

Preference is also given to C₂₋₁₀ alkynyl radicals selected from the group consisting of (3,3)-dimethyl-but-1-ynyl, 4-methyl-pent-1-ynyl, 1-hexynyl, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, and 4-pentylnyl, which can be optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -OCF₃, and -SCF₃.

Particularly preferred optionally substituted C₁₋₁₀ aliphatic radicals are selected from the group consisting of methyl, -CF₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, -CCl₃, -CBr₃, -CH₂-CN, -CH₂-O-CH₃, -CH₂-O-CF₃, -CH₂-SF₃, -CH₂-NH₂, -CH₂-OH, -CH₂-SH, -CH₂-NH-CH₃, -CH₂-N(CH₃)₂, -CH₂-N(C₂H₅)₂, -CH₂-N(CH₃)-(C₂H₅), ethyl, -CF₂-CH₃, -CHF-CF₂Cl, -CF₂-CFCl₂, -CFCl-CF₂Cl, -CFCl-CFCl₂, -CH₂-CH₂-NH₂, -CH₂-CH₂-OH, -CH₂-

CH₂-SH, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)₂, -CH₂-CH₂-N(C₂H₅)₂, -CH₂-CH₂-N(CH₃)-(C₂H₅), -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CH₂-CH₂-CN, n-propyl, -CH₂-CH₂-CH₂-OH, -CH₂-CH₂-CH₂-SH, -CH₂-CH₂-CH₂-NH₂, -CH₂-CH₂-CH₂-NH-CH₃, -CH₂-CH₂-CH₂-N(CH₃)₂, -CH₂-CH₂-CH₂-N(C₂H₅)₂, -CH₂-CH₂-CH₂-N(CH₃)-(C₂H₅), -CH₂-CH₂-O-CH₃, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, -CH₂-CH₂-CH₂-CN, -CH₂-O-CH₂-CH₃, -CH₂-CH₂-SF₃, -CH₂-CH₂-OCF₃, -CH(CH₃)-(O-CH₃), -CH(CH₃)-(S-CH₃), n-butyl, -CF₂-CF₂-CF₂-CF₃, -CH₂-CH₂-CH₂-CH₂-CN, -CH₂-CH₂-CH₂-CF₃, -CH₂-CH₂-CH₂-CF₃, -CH₂-O-C(=O)-CH₃, -CH₂-O-C(=O)-C₂H₅, -CH₂-O-C(=O)-CH(CH₃)₂, -CH₂-O-C(=O)-C(CH₃)₃, -CH₂-C(=O)-O-CH₃, -CH₂-C(=O)-O-C₂H₅, -CH₂-C(=O)-O-C(CH₃)₃, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-O-C₂H₅, -CH₂-CH₂-O-phenyl, -CH₂-CH₂-CH₂-O-CH₃, sec-butyl, isobutyl, tert-butyl, n-pentyl, sec-pentyl, neo-pentyl, n-hexyl, vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-butene-2-yl, (1,1,2)-trifluoro-1-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, -CF=CF₂, -CCl=CCl₂, -CH₂-CF=CF₂, -CH₂-CCl=CCl₂, -C≡C-I, -C≡C-, and -C≡C-Cl.

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If one or more of the aforementioned substituents stand for a (hetero)cycloaliphatic radical, which can be optionally condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system, this can preferably be selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, tetrahydropyranyl, oxetanyl, (1,2,3,6)-tetrahydropyridinyl, azepanyl, azocanyl, diazepanyl, dithiolanyl, (1,3,4,5)-tetrahydropyrido[4.3-b]indolyl, (3,4)-dihydro-1H-isoquinolinyl, (1,3,4,9)-tetrahydro[b]carbolinyl, and (1,3)-thiazolidinyl.

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As examples of suitable (hetero)cycloaliphatic radicals, which can be unsubstituted or monosubstituted or polysubstituted and are condensed with a monocyclic or bicyclic ring system, there may be mentioned (4,5,6,7)-tetrahydroisoxazolo[5.4-c]pyridinyl, (2,3)-dihydro-1H-indenyl, 3-aza-bicyclo[3.1.1]heptyl, 3-aza-bicyclo[3.2.1]octyl, 6-aza-bicyclo[3.3.1]heptyl, 8-aza-bicyclo[3.2.1]octyl, isoindolyl, indolyl, (1,2,3,4)-tetrahydroquinolinyl, (1,2,3,4)-tetrahydroisoquinolinyl, (2,3)-dihydro-1H-isoindolyl, (1,2,3,4)-tetrahydronaphthyl, (2,3)-dihydro-benzo[1.4]dioxinyl, benzo[1.3]dioxolyl, (1,4)-benzodioxanyl, (2,3)-dihydrothieno[3.4-b][1.4]dioxinyl, (3,4)-

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dihydro-2H-benzo[1.4]oxazinyl, octahydro-1H-isoindolyl, and octahydro-pyrrolo[3.4-c]pyrrolyl.

(Hetero)cycloaliphatic radicals can form, within the scope of the present invention, a spirocyclic radical with another (hetero)cycloaliphatic radical via a carbon atom common to both rings.

As examples of suitable spirocyclic radicals there may be mentioned a 6-aza-spiro[2.5]octyl radical, 8-aza-spiro[4.5]decyl radical and a 1-oxa-2,8-diaza-spiro[4.5]dec-2-enyl radical.

More preferably the (hetero)cycloaliphatic radicals can each be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of oxo (= O), thioxo (= S), F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, -C(=O)-CH₃, -C(=O)-C₂H₅, -C(=O)-CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-CH(CH₃)₂, -C(=O)-O-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -CH₂-OH, -CH₂-CH₂-OH, = CH₂, -CH₂-O-CH₂-oxetanyl, -O-CH₂-oxetanyl, -CH₂-N(CH₃)₂, -CH₂-N(C₂H₅)₂, -CH₂-NH-CH₃, -CH₂-NH-C₂H₅, -N-[C(=O)-C₂H₅]-phenyl, -N-[C(=O)-CH₃]-phenyl, -CH₂-O-CH₃, -CH₂-O-CH₂-CH₃, -NH-phenyl, -N(CH₃)phenyl, -N(C₂H₅)phenyl, -N(C₂H₅)phenyl, -O-CH₂-CH₂-CH₂-CH₃, (4,5)-dihydroisoxazolyl, thiazolyl, (1,2,5)-thiadiazolyl, thiophenyl, phenethyl, cyclohexyl, cyclopentyl, piperidiny, pyrrolidiny, -O-C(=O)-CH₃, -O-C(=O)-C₂H₅, -O-C(=O)-C(CH₃)₃, -(CH₂)pyridiny, pyridiny, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals oxetanyl, (4,5)-dihydroisoxazolyl, thiazolyl, (1,2,5)-thiadiazolyl, thiophenyl, phenethyl, -N-[C(=O)-C₂H₅]phenyl, -N-[C(=O)-CH₃]phenyl, -NH-phenyl, -N(CH₃)phenyl, -N(C₂H₅)phenyl, -(CH₂)pyridiny, pyridiny, -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl.

If one or more of the aforementioned substituents stand for an aryl radical, this can preferably be selected from the group consisting of phenyl and naphthyl (1-naphthyl and 2-naphthyl).

- 5 If one or more of the aforementioned substituents stand for a heteroaryl radical, this can preferably be selected from the group consisting of tetrazolyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, pyrazinyl, pyranal, triazolyl, pyridinyl, imidazolyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, benzoxazolyl, benzisoxazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indazolyl, quinoxalyl, 10 quinolyl, and isoquinolyl.

As examples of suitable aryl and heteroaryl radicals, which can be unsubstituted or monosubstituted or polysubstituted and are condensed with a monocyclic or bicyclic ring system, there may be mentioned isoindolyl, indolyl, (1,2,3,4)- 15 tetrahydroquinolyl, (1,2,3,4)-tetrahydroisoquinolyl, (2,3)-dihydro-1H-isoindolyl, (1,2,3,4)-tetrahydronaphthyl, (2,3)-dihydrobenzo[1.4]dioxinyl, (2,3)-dihydrothieno[3.4-b][1.4]dioxinyl, benzo[1.3]dioxolyl, and (1,4)-benzodioxanyl.

More preferably, the aryl radicals or heteroaryl radicals can each be optionally 20 substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-CH(CH₃)₂, -C(=O)- 25 O-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -NH-S(=O)₂-CH₃, -NH-S(=O)₂-C₂H₅, -NH-S(=O)₂-CH(CH₃)₂, -NH-C(=O)-O-CH₃, -NH-C(=O)-O-C₂H₅, -NH-C(=O)-O-C(CH₃)₃, -C(=O)-H, -C(=O)-CH₃, -C(=O)-C₂H₅, -C(=O)-CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-NH₂, -C(=O)-NH-CH₃, -C(=O)-NH-C₂H₅, -C(=O)-N(CH₃)₂, -C(=O)-N(C₂H₅)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl, 30 and the cyclic moiety of the radicals -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl.

If a polycyclic ring system such as a bicyclic ring system is present, the different rings can independently exhibit a different degree of saturation, i.e. be saturated or unsaturated. A polycyclic ring system is preferably a bicyclic ring system.

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As examples of aryl radicals condensed with a monocyclic or polycyclic ring system mention may be made of (1,3)-benzodioxolyl and (1,4)-benzodioxanyl.

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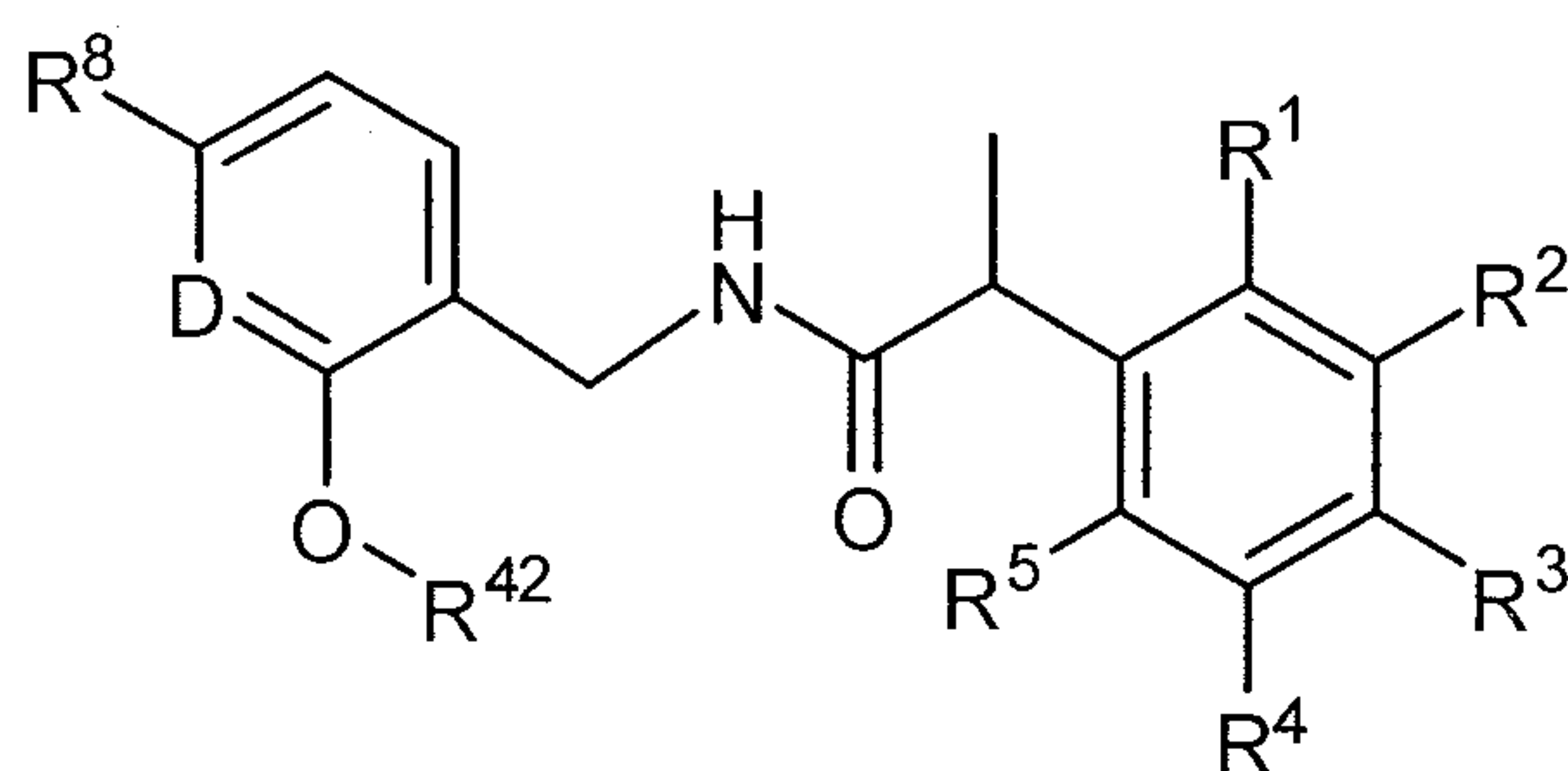
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If one or more of the aforementioned substituents have a monocyclic or polycyclic ring system, this can preferably be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of oxo (= O), thioxo (= S), F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-CH(CH₃)₂, -C(=O)-O-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -NH-C(=O)-O-CH₃, -NH-C(=O)-O-C₂H₅, -NH-C(=O)-O-C(CH₃)₃, -C(=O)-H, -C(=O)-CH₃, -C(=O)-C₂H₅, -C(=O)-CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-NH₂, -C(=O)-NH-CH₃, -C(=O)-NH-C₂H₅, -C(=O)-N(CH₃)₂, -C(=O)-N(C₂H₅)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl.

If the radicals R⁴¹ and R⁴², together with the interconnecting nitrogen atom as ring member, form a heterocycloaliphatic radical which is substituted by 1, 2, 3, 4 or 5 radicals R⁵⁷, these radicals R⁵⁷ each have, independently of one another, one of the indicated meanings.

Preference is given to compounds of the general formula Ia,



Ia,

5 in which

D stands for N or CH;

10 R^1 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

15 R^2 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

20 R^3 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

25 R^4 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

30 R^5 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group

consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl; or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

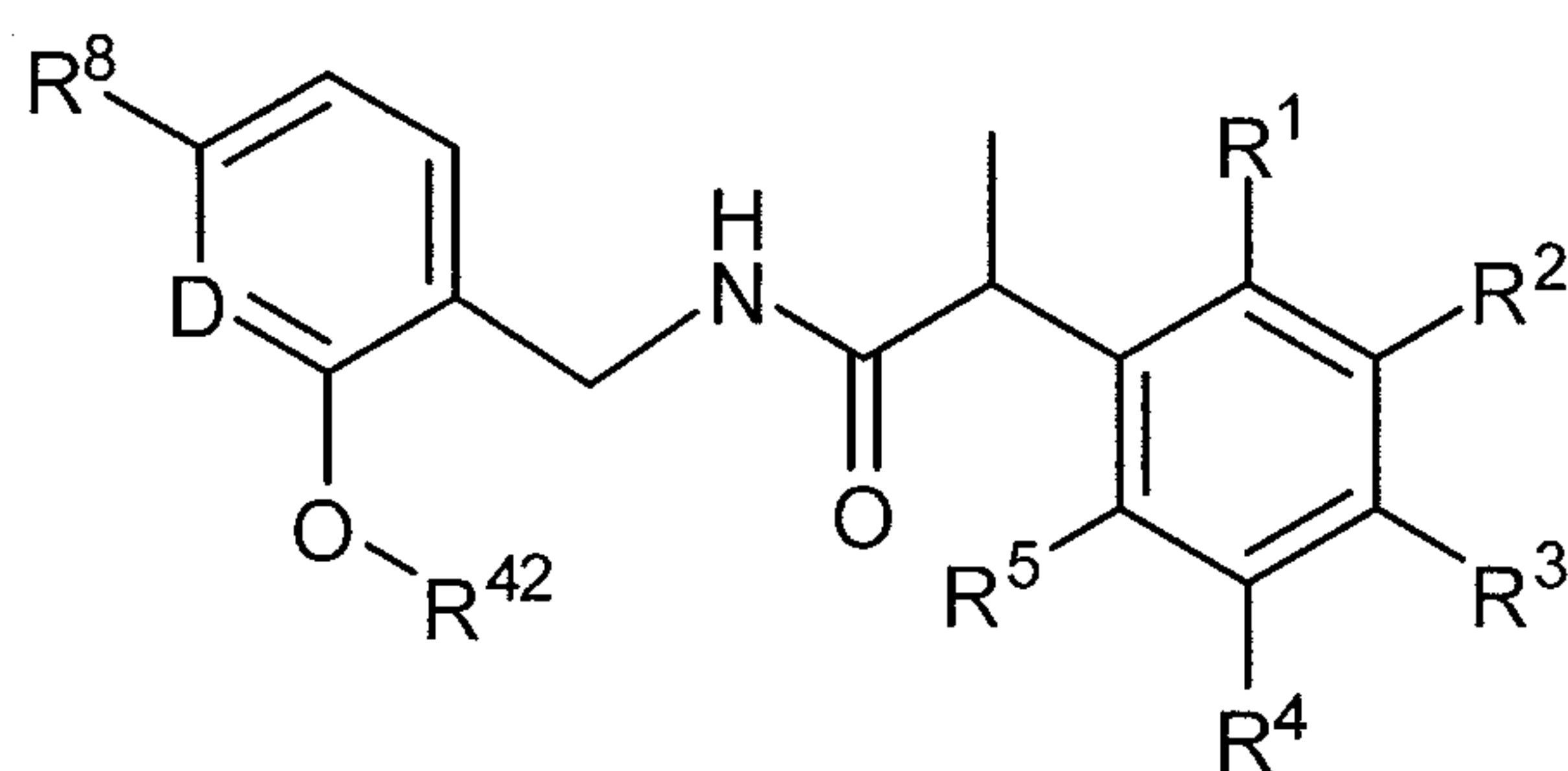
R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, $-\text{CF}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{C}_2\text{F}_5$, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-heptyl, 4-heptyl, n-octyl, n-nonyl, 5-nonyl, (2,6)-dimethyl-hept-4-yl, 3-methyl-butyl, n-hexyl, (3,3)-dimethylbutyl and ethenyl;

R^{42} stands for a radical selected from the group consisting of methyl, $-\text{CH}_2\text{OCH}_3$, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, (3,3)-dimethylbutyl, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OC}_2\text{H}_5$, and $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$;

or for a radical selected from the group consisting of 2,3-dihydro-1H-indenyl, cyclopropyl, oxetanyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Special preference is given to compounds of the general formula Ia,



Ia,

in which

D stands for N or CH;

R¹ stands for H; F; Cl; Br; I; methyl, ethyl, -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³; -OR¹⁶; SR¹⁷, -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R² stands for H; F; Cl; Br; I; methyl, ethyl, -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³; -OR¹⁶; SR¹⁷, -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R³ stands for H; F; Cl; Br; I; methyl, ethyl, -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³; -OR¹⁶; SR¹⁷, -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R⁴ stands for H; F; Cl; Br; I; methyl, ethyl, -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³; -OR¹⁶; SR¹⁷, -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R⁵ stands for H; F; Cl; Br; I; methyl, ethyl, -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³; -OR¹⁶; SR¹⁷, -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R⁸ stands for -SF₅; -O-CF₃; -CF₃; tert-butyl; or -C(CH₃)₂(CH₂OH);

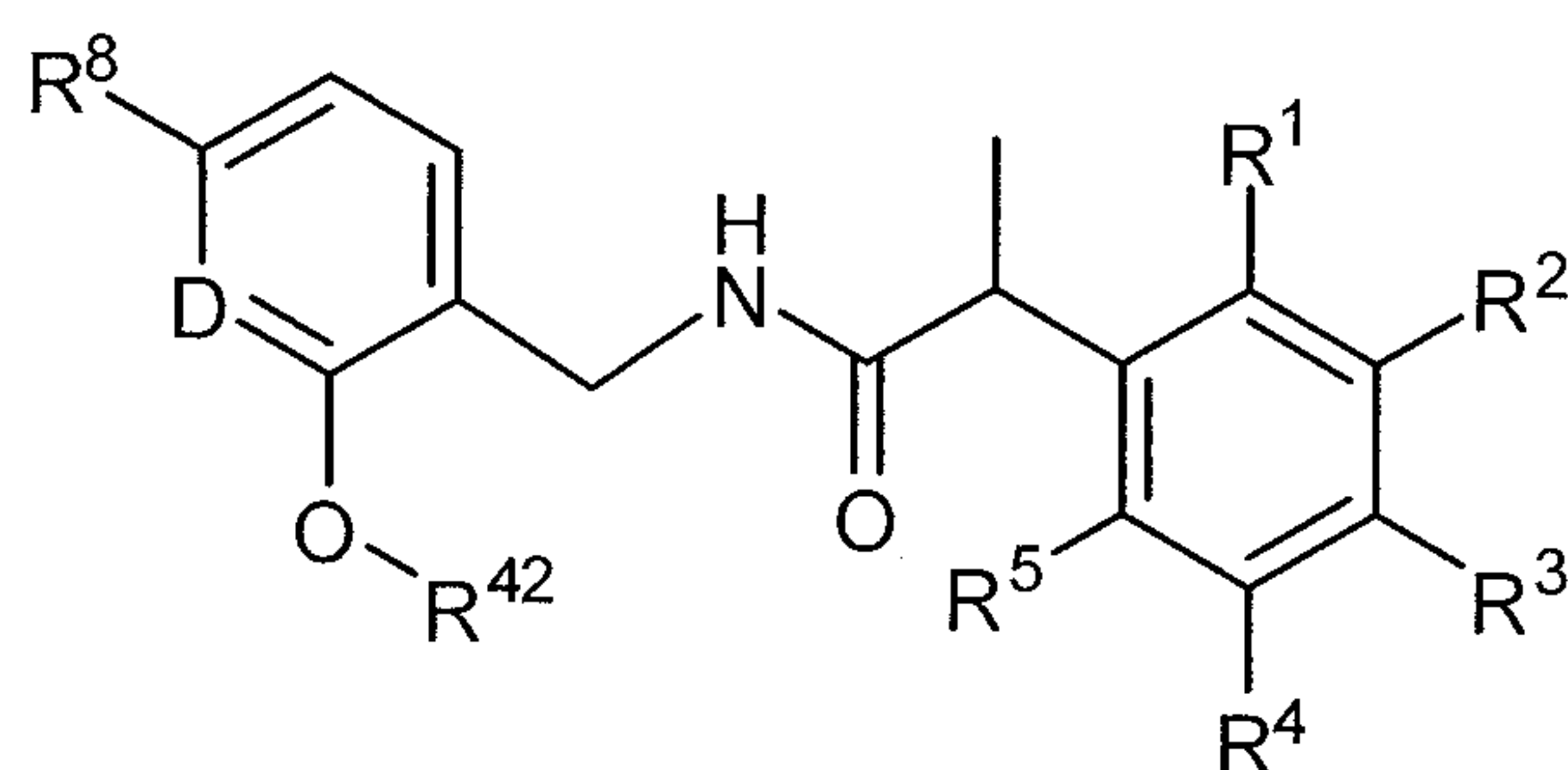
R¹³, R¹⁶, R¹⁷, R²², R²³ and R²⁷ each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl and ethenyl;

R^{42} stands for a radical selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, and (3,3)-dimethylbutyl;

or for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Very particular preference is given to compounds of the general formula Ia,



Ia,

in which

D stands for N or CH;

R^1 stands for H; F; Cl; Br; or I;

R^2 stands for H; F; Cl; Br; I; methyl; -OH; -NH₂ or -OR¹⁶;

R^3 stands for H; F; Cl; Br; I; -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³, -OR¹⁶; SR¹⁷, -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R^4 stands for H; F; Cl; Br; I; methyl, -OH; -NH₂; or -OR¹⁶;

R^5 stands for H; F; Cl; Br; or I;

R^8 stands for -SF₅; -O-CF₃; -CF₃; tert-butyl; or -C(CH₃)₂(CH₂OH);

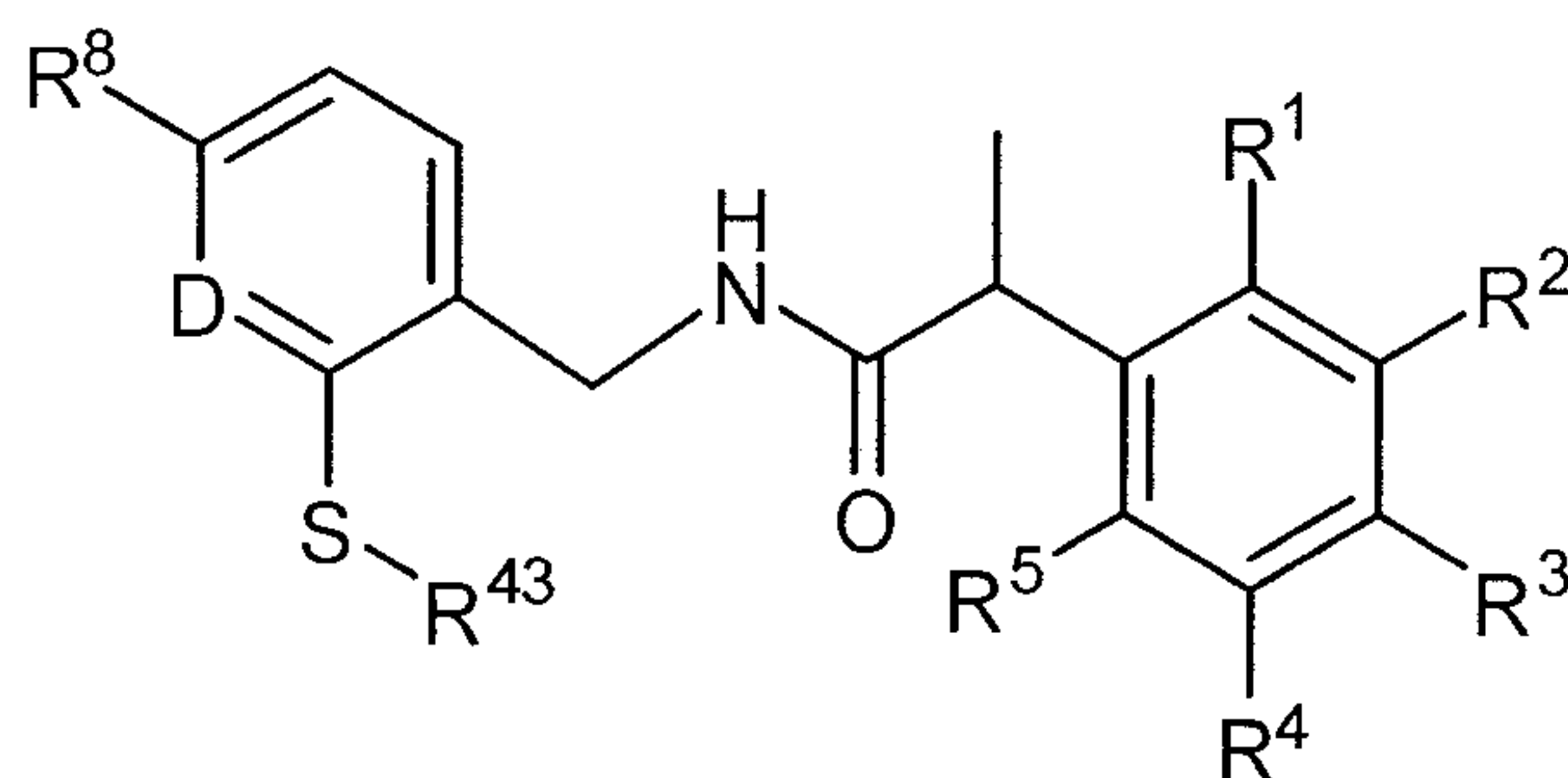
R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl and ethenyl;

R^{42} stands for a radical selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, and (3,3)-dimethylbutyl;

or for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Preference is given to compounds of the general formula Ib,



Ib,

in which

D stands for N or CH;

- 5 R^1 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;
- 10 R^2 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;
- 15 R^3 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;
- 20 R^4 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;
- 25 R^5 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;
- 30 R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl; or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, $-\text{CF}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{C}_2\text{F}_5$, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-

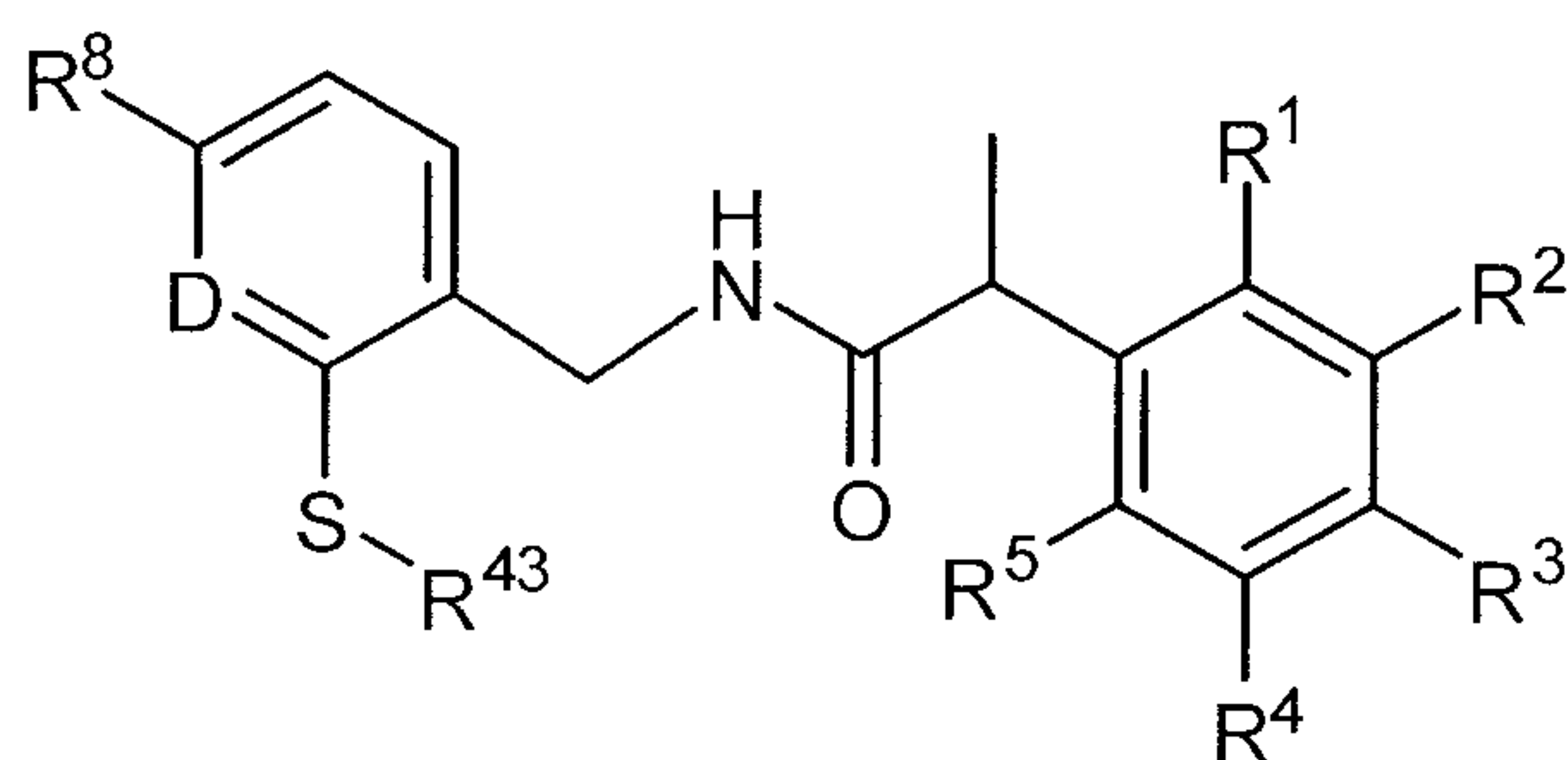
heptyl, 4-heptyl, n-octyl, n-nonyl, 5-nonyl, (2,6)-dimethyl-hept-4-yl, 3-methyl-butyl, n-hexyl, (3,3)-dimethylbutyl and ethenyl;

R^{43} stands for a radical selected from the group consisting of methyl, $-\text{CH}_2\text{-O-CH}_3$, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, (3,3)-dimethylbutyl, $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-O-C}_2\text{H}_5$, and $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O-CH}_3$;

or for a radical selected from the group consisting of 2,3-dihydro-1H-indenyl, cyclopropyl, oxetanyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Special preference is given to compounds of the general formula Ib,



Ib,

in which

D stands for N or CH;

R^1 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$;

R^2 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$;

R^3 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$;

R^4 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$;

R^5 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$;

R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl; or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl and ethenyl;

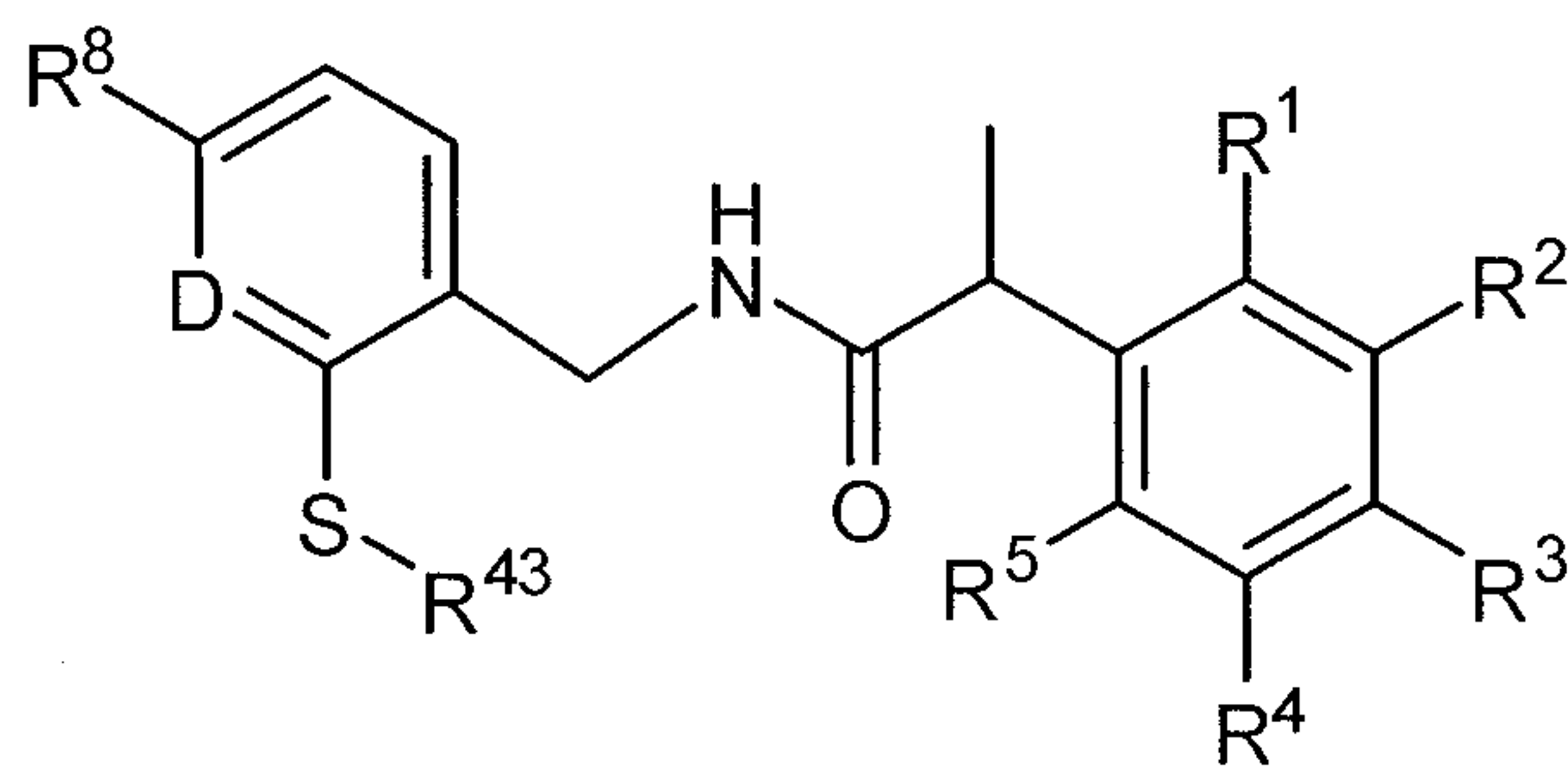
R^{43} stands for a radical selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, and (3,3)-dimethylbutyl;

or for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers,

in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Very particular preference is given to compounds of the general formula Ib,



Ib,

in which

D stands for N or CH;

R¹ stands for H; F; Cl; Br; or I;

R² stands for H; F; Cl; Br; I; methyl; -OH; -NH₂; or -OR¹⁶;

R³ stands for H; F; Cl; Br; I; -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³, -OR¹⁶; SR¹⁷; -S(=O)₂-NR²²R²³ or -(S=O)-R²⁷;

R⁴ stands for H; F; Cl; Br; I; methyl; -OH; -NH₂; or -OR¹⁶;

R⁵ stands for H; F; Cl; Br; or I;

R⁸ stands for -SF₅; -O-CF₃; -CF₃; tert-butyl; or -C(CH₃)₂(CH₂OH);

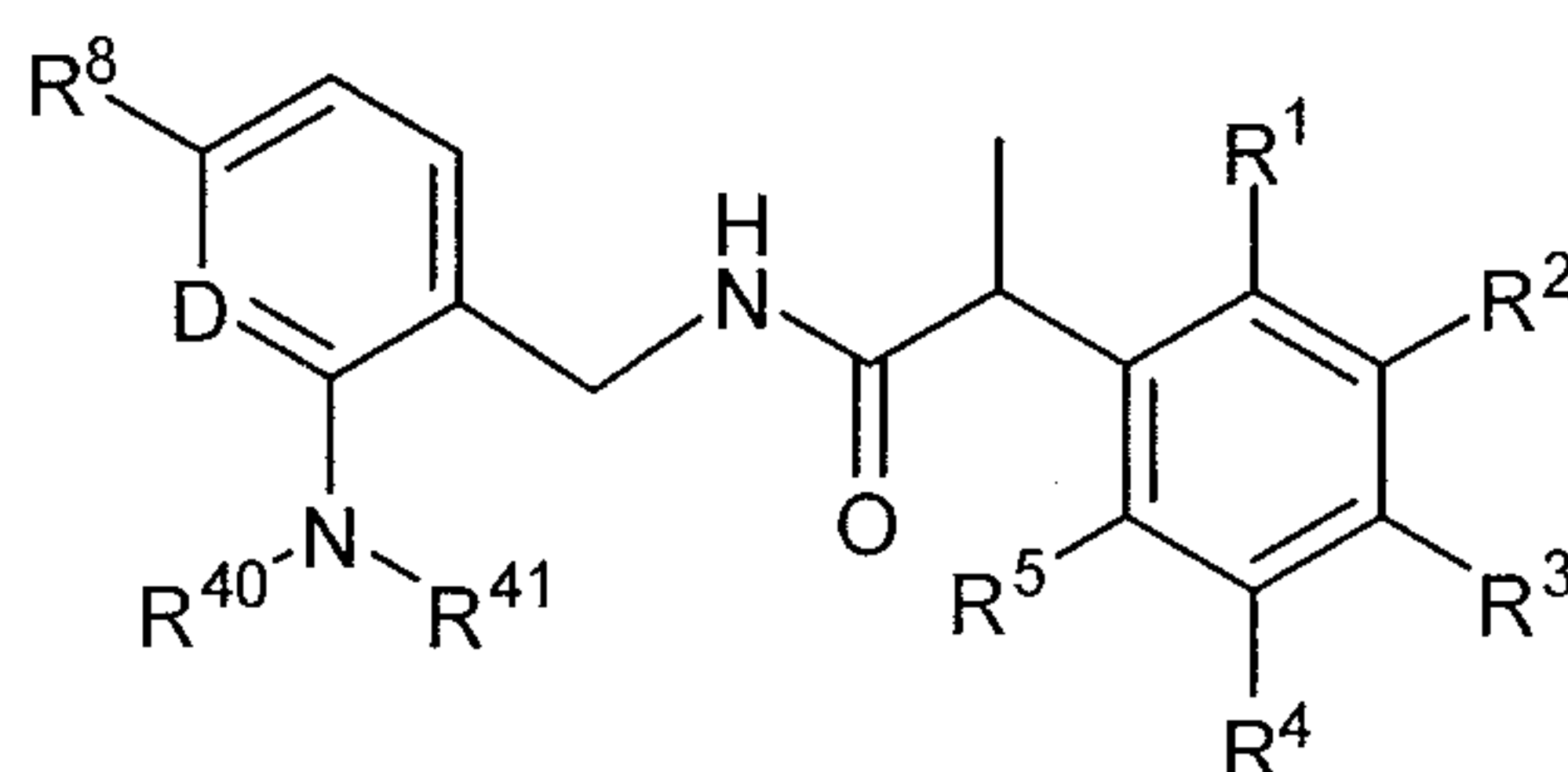
R¹³, R¹⁶, R¹⁷, R²², R²³ and R²⁷ each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl and ethenyl;

R^{43} stands for a radical selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, and (3,3)-dimethylbutyl;

or for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Preference is given to compounds of the general formula Ic,



Ic,

in which

D stands for N or CH;

R^1 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^2 stands for H; F; Cl; Br; I; $-NO_2$; $-CF_3$; $-CN$; $-NH_2$; $-OH$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$ or for a radical selected from the group

consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^3 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^4 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^5 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$ or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl; or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, $-\text{CF}_2\text{CH}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{C}_2\text{F}_5$, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-heptyl, 4-heptyl, n-octyl, n-nonyl, 5-nonyl, (2,6)-dimethyl-hept-4-yl, 3-methyl-butyl, n-hexyl, (3,3)-dimethylbutyl and ethenyl;

R^{40} and R^{41} each independently stand for a radical selected from the group consisting of methyl, $-\text{CH}_2-\text{O}-\text{CH}_3$, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, (3,3)-dimethylbutyl, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}_2\text{H}_5$, and $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$;

for a radical selected from the group consisting of 2,3-dihydro-1H-indenyl, cyclopropyl, oxetanyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl,

piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

or

R^{40} and R^{41} form, together with the interconnecting nitrogen atom as ring member, a radical selected from the group consisting of 3-aza-bicyclo[3.1.1]heptyl, 6-aza-spiro[2.5]octyl, 3-aza-bicyclo[3.2.1]octyl, 6-aza-bicyclo[3.3.1]heptyl, 8-aza-bicyclo[3.2.1]octyl, 1-oxa-2,8-diaza-spiro[4.5]dec-2-enyl, azocanyl, isoindolyl, indolyl, (1,2,3,6)-tetrahydropyridinyl, (4,5,6,7)-tetrahydroisoxazolo[5.4-c]pyridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, diazepanyl, and thiomorpholinyl, of which the heterocycloaliphatic moiety can in each case be unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R^{57} ;

R^{57} stands for $-NHR^{58}$, $-NR^{59}R^{60}$, or for an alkyl radical selected from the group consisting of $-CF_3$, $-CH_2CF_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

R^{58} , R^{59} , and R^{60} each independently stand for $-C(=O)-R^{61}$;

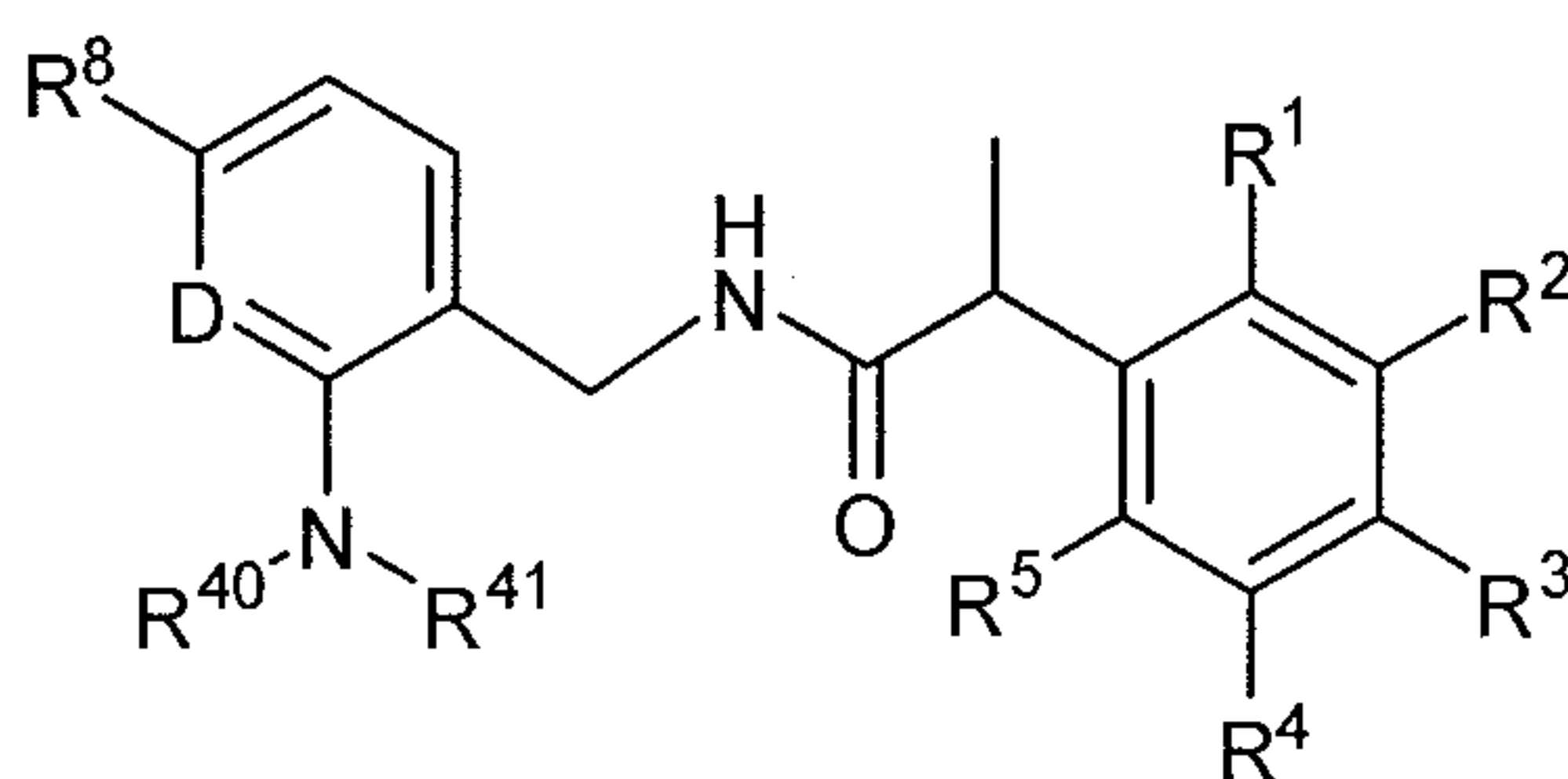
for an alkyl radical selected from the group consisting of $-CF_3$, $-CH_2CF_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

or for a radical selected from the group consisting of phenyl and naphthyl, and each radical can be bonded via a $-(CH_2)-$, $-(CH_2)_2-$ or $-(CH_2)_3$ group and/or can each be unsubstituted or optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, $-CN$, $-CF_3$, $-O-CH_3$, $-O-C_2H_5$, $-O-CH(CH_3)_2$, $-O-C(CH_3)_3$, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

and R^{61} stands for an alkyl radical selected from the group consisting of $-CF_3$, $-CH_2CF_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in the form
 of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers,
 in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in
 5 each case in the form of corresponding solvates.

Special preference is given to compounds of the general formula Ic,



Ic,

in which

D stands for N or CH;

15 R^1 stands for H; F; Cl; Br; I; methyl; ethyl; $-NO_2$; $-OH$; $-NH_2$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$;

R^2 stands for H; F; Cl; Br; I; methyl; ethyl; $-NO_2$; $-OH$; $-NH_2$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$;

20 R^3 stands for H; F; Cl; Br; I; methyl; ethyl; $-NO_2$; $-OH$; $-NH_2$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$;

25 R^4 stands for H; F; Cl; Br; I; methyl; ethyl; $-NO_2$; $-OH$; $-NH_2$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$;

R^5 stands for H; F; Cl; Br; I; methyl; ethyl; $-NO_2$; $-OH$; $-NH_2$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-(S=O)-R^{27}$;

30 R^8 stands for $-SF_5$; $-O-CF_3$; $-CF_3$; tert-butyl; or $-C(CH_3)_2(CH_2OH)$;

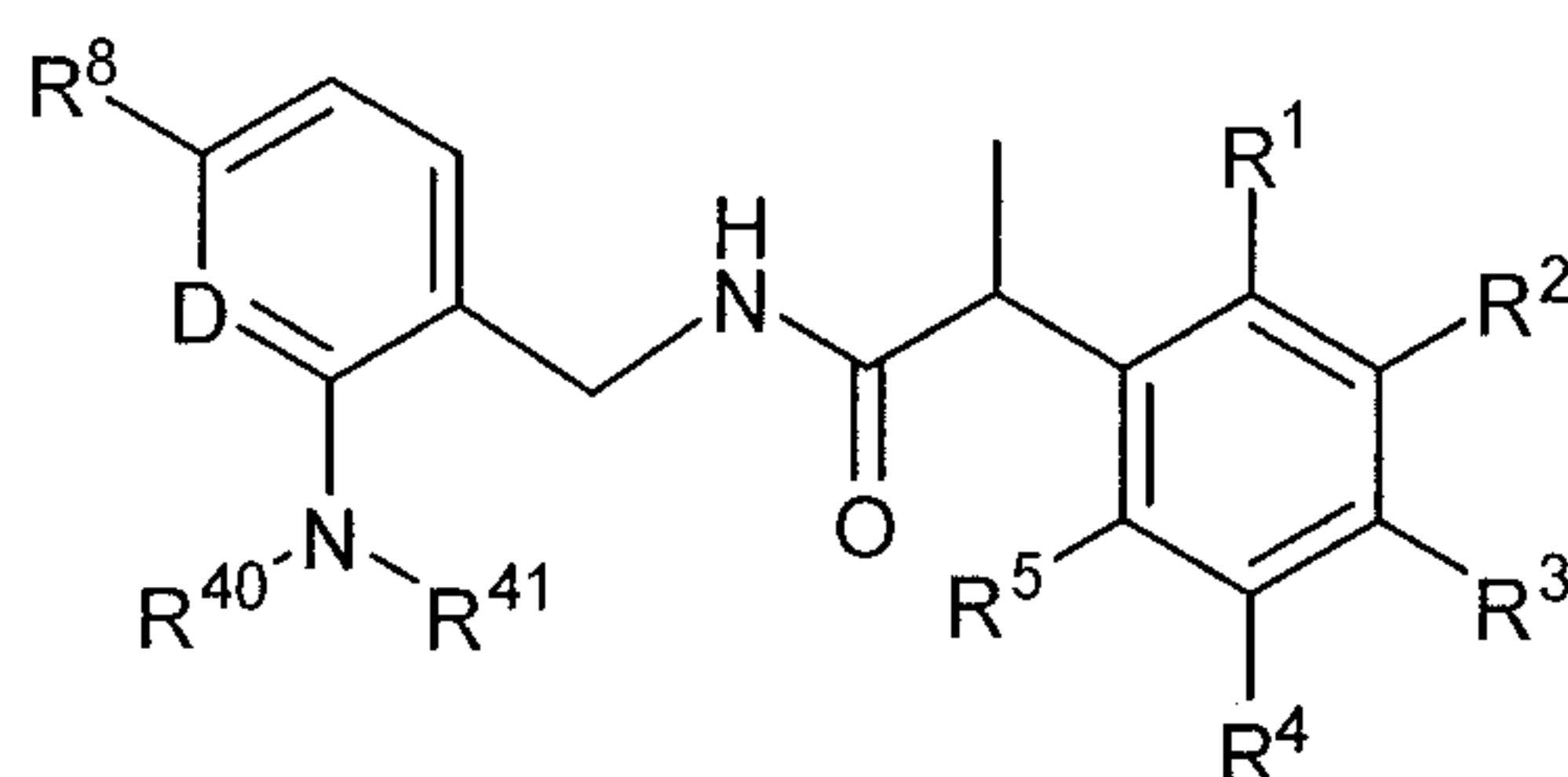
R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl and ethenyl;

R^{40} and R^{41} form, together with the interconnecting nitrogen atom as ring member, a radical selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and azepanyl, of which the heterocycloaliphatic moiety can in each case be unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R^{57} ;

and R^{57} stands for an alkyl radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Very particular preference is given to compounds of the general formula Ic,



Ic,

in which

D stands for N or CH;

R^1 stands for H; F; Cl; Br; or I;

R^2 stands for H; F; Cl; Br; I; -OH; -NH₂; or -OR¹⁶;

R^3 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$, $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-(\text{S}=\text{O})-\text{R}^{27}$;

R^4 stands for H; F; Cl; Br; I; methyl; $-\text{OH}$; $-\text{NH}_2$; or $-\text{OR}^{16}$;

R^5 stands for H; F; Cl; Br; or I;

R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl; or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl and ethenyl;

R^{40} and R^{41} form, together with the interconnecting nitrogen atom as ring member, a radical selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and azepanyl, of which the heterocycloaliphatic moiety can in each case be unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R^{57} ;

and R^{57} stands for an alkyl radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

Even greater preference is given to compounds of the general formulas I, Ia, Ib, and Ic selected from the group consisting of

[1] 2-(4-Amino-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;

[2] 2-(3,5-Dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;

- [3] 2-(4-Amino-3-bromo-5-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- [4] 2-(3-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- 5 [5] 2-(2,4-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- [6] 2-(2,6-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- [7] 2-(2,5-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- 10 [8] 2-(4-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- [9] 2-(4-Hydroxy-3-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- 15 [10] 2-(3,5-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- [11] 2-(3,4-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- [12] 2-(4-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- 20 [13] 2-(3-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- [14] 2-(3,4-Diaminophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- 25 [15] N-(2-Butoxy-6-tert-butylpyridin-3-ylmethyl)-2-(3,4-diamino-phenyl)-propionamide;
- [16] N-((6-tert-Butyl-2-(4-methylpiperidin-1-yl)pyridin-3-yl)methyl)-2-(3,4-diaminophenyl)propanamide;
- [17] N-((6-tert-Butyl-2-(cyclohexylthio)pyridin-3-yl)methyl)-2-(3,4-diaminophenyl)propanamide;
- 30 [18] 2-(4-Acetamido-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- [19] 2-(3,5-Dibromo-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;

- [20] 2-(4-Amino-3,5-dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide;
- [21] 2-(3-Bromo-4-hydroxy-5-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- 5 [22] 2-(4-Amino-3,5-dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- [23] 2-(3,5-Dibromo-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide;
- [24] 2-(3-Amino-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide; and
- 10 [25] 2-(3,5-Dibromophenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)methyl)acetamide;
- [26] 2-(4-Amino-3,5-difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 15 [27] 2-(3-Fluoro-5-hydroxy-4-nitrophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [28] 2-(3-Chloro-4-(methylthio)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [29] 2-(3-Chloro-4-(methylsulfonyl)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 20 [30] 2-(3-Fluoro-4-(methylthio)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [31] 2-(3-Fluoro-4-(methylsulfonyl)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 25 [32] 2-(4-(N,N-Dimethylsulfamoyl)-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [33] N-(2-Fluoro-4-(1-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methylamino)-1-oxopropane-2-yl)phenyl)acrylamide,
- [34] N-(2-Fluoro-6-iodo-4-(1-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methylamino)-1-oxopropane-2-yl)phenyl)acrylamide,
- 30 [35] 2-(4-Methoxy-3,5-dimethylphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [36] 2-(3,5-Difluoro-4-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,

[37] 2-(4-Hydroxy-3,5-dimethylphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,

[38] 2-(3,5-Difluoro-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,

5

each optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers thereof, the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or each in the form of corresponding salts, or each in the form of corresponding solvates;

10

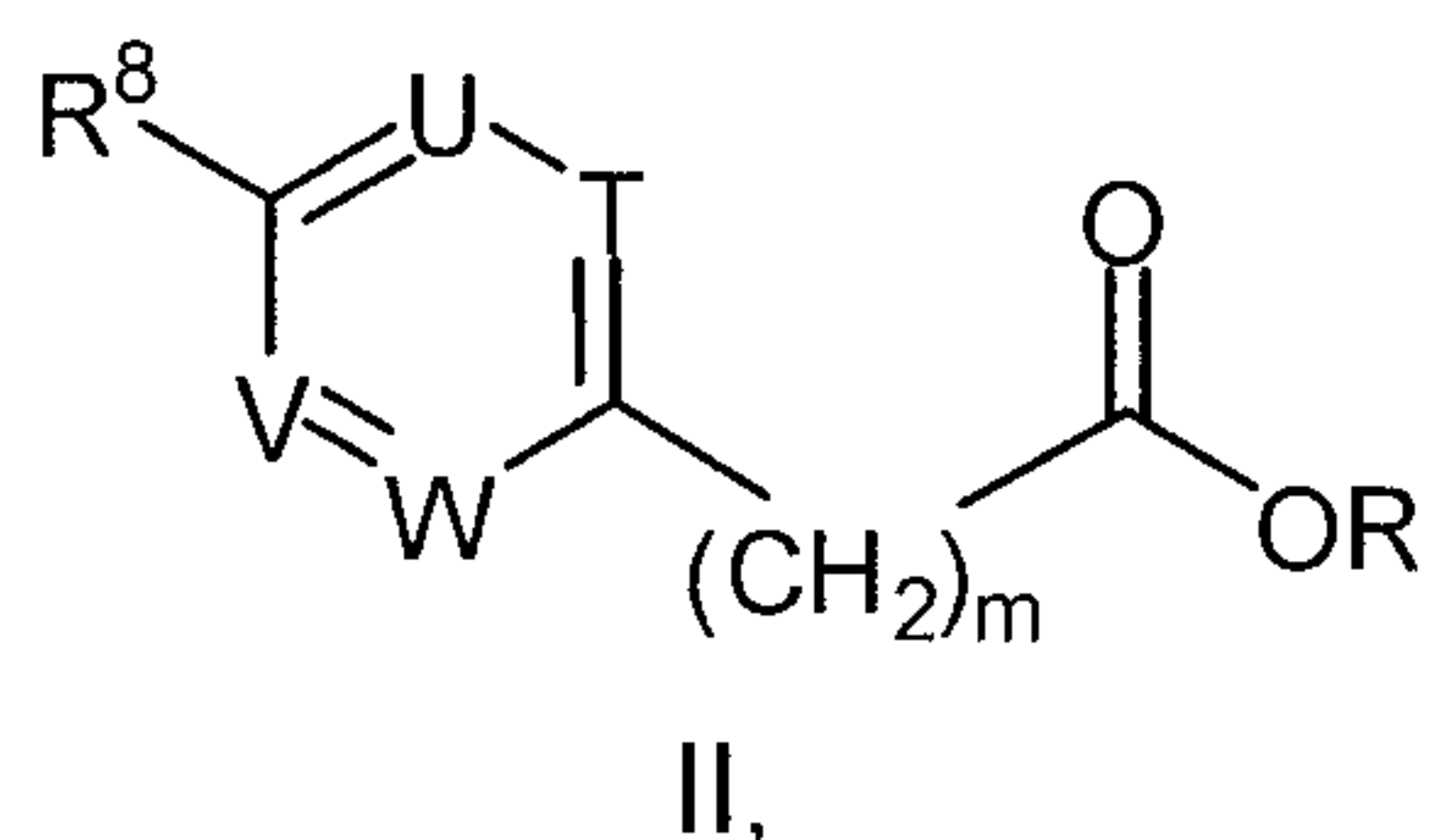
Furthermore, preference may be given to compounds according to the invention of the general formulas I, Ia, Ib and Ic, which in the FLIPR assay using CHO-K1 cells, which have been transfected with the human VR1 gene in a concentration below 2000 nM, preferably below 1000 nM, more preferably below 300 nM, even more preferably below 100 nM, still more preferably below 75 nM, very preferably below 50 nM and most preferably below 10 nM, cause a 50 percent displacement of capsaicin present in a concentration of 100 nM.

15

20 In the FLIPR assay, the Ca^{2+} influx is quantified with the aid of a Ca^{2+} -sensitive dye (type Fluo-4, Molecular Probes Europe BV, Leiden, Netherlands) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA), as described below.

25

The invention further relates to a process for the production of compounds of the above general formula I, according to which at least one compound of the general formula II,

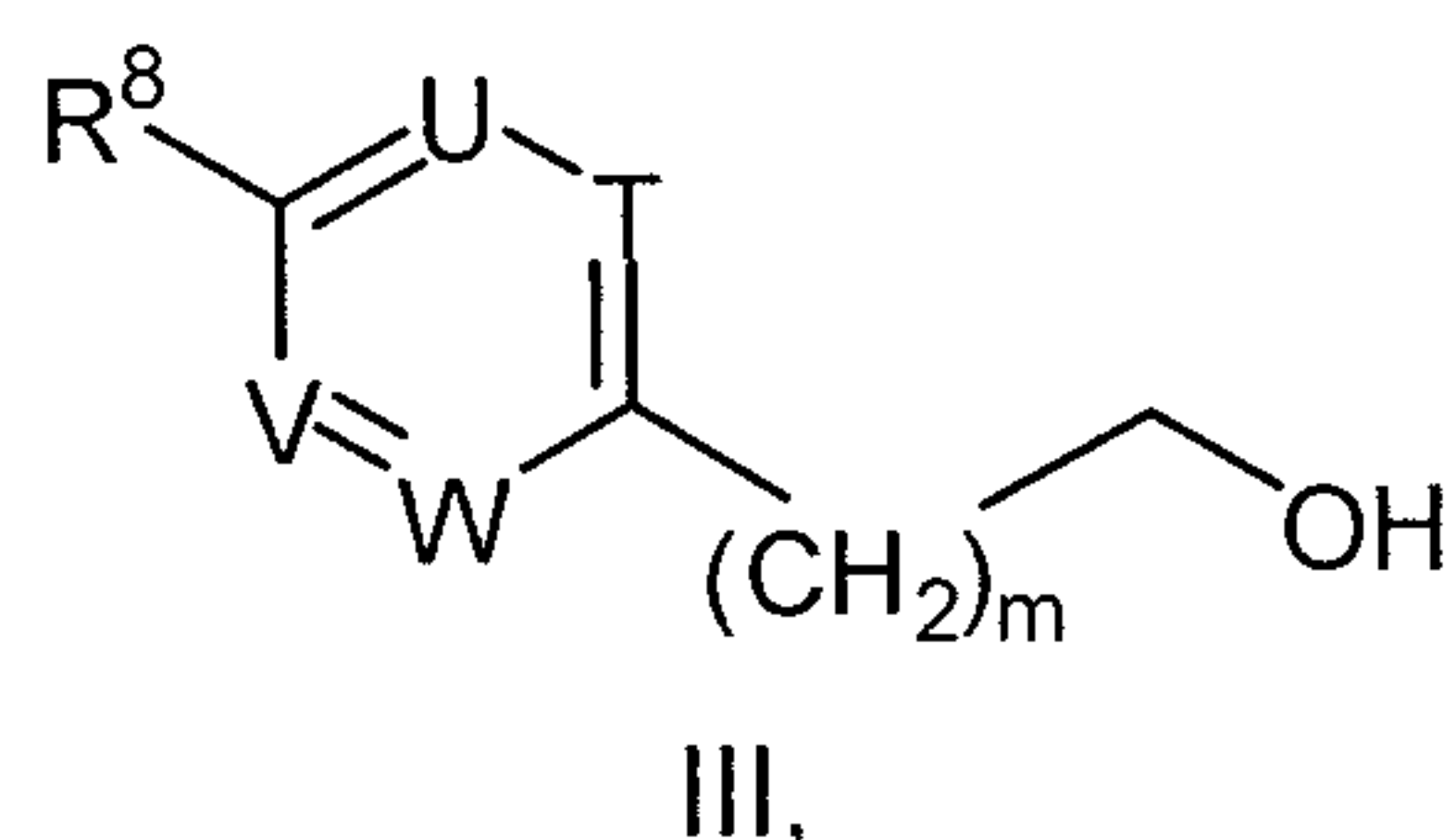


30

in which R^8 , U, T, V, and W have the aforementioned meanings, m stands for 0, 1, 2, or 3, and R stands for hydrogen or for a linear or branched C_{1-6} -alkyl radical, in a

reaction medium, in the presence of at least one reducing agent, preferably in the presence of at least one reducing agent selected from the group consisting of sodium hydride, sodium, potassium hydride, lithium aluminum hydride, sodium tetrahydridoborate, and di(isobutyl)aluminum hydride

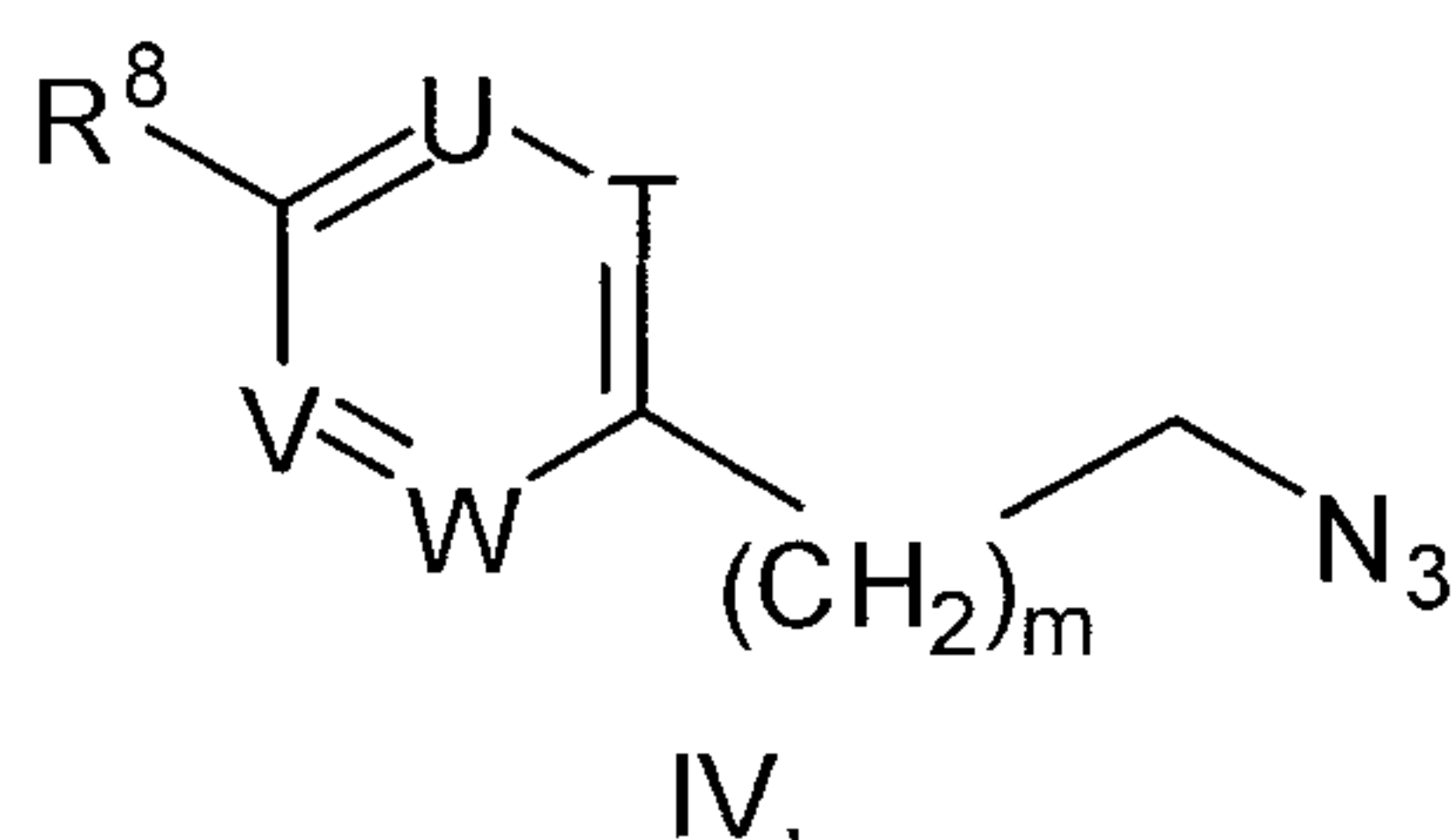
is converted to at least one compound of the general formula III,



in which

R^8 , U, T, V, and W have the meanings stated above and m stands for 0, 1, 2, or 3, and this is optionally purified and/or isolated,

and at least one compound of the general formula III is converted, in a reaction medium in the presence of diphenylphosphorylazide or in the presence of HN_3 , to at least one compound of the general formula IV,



in which

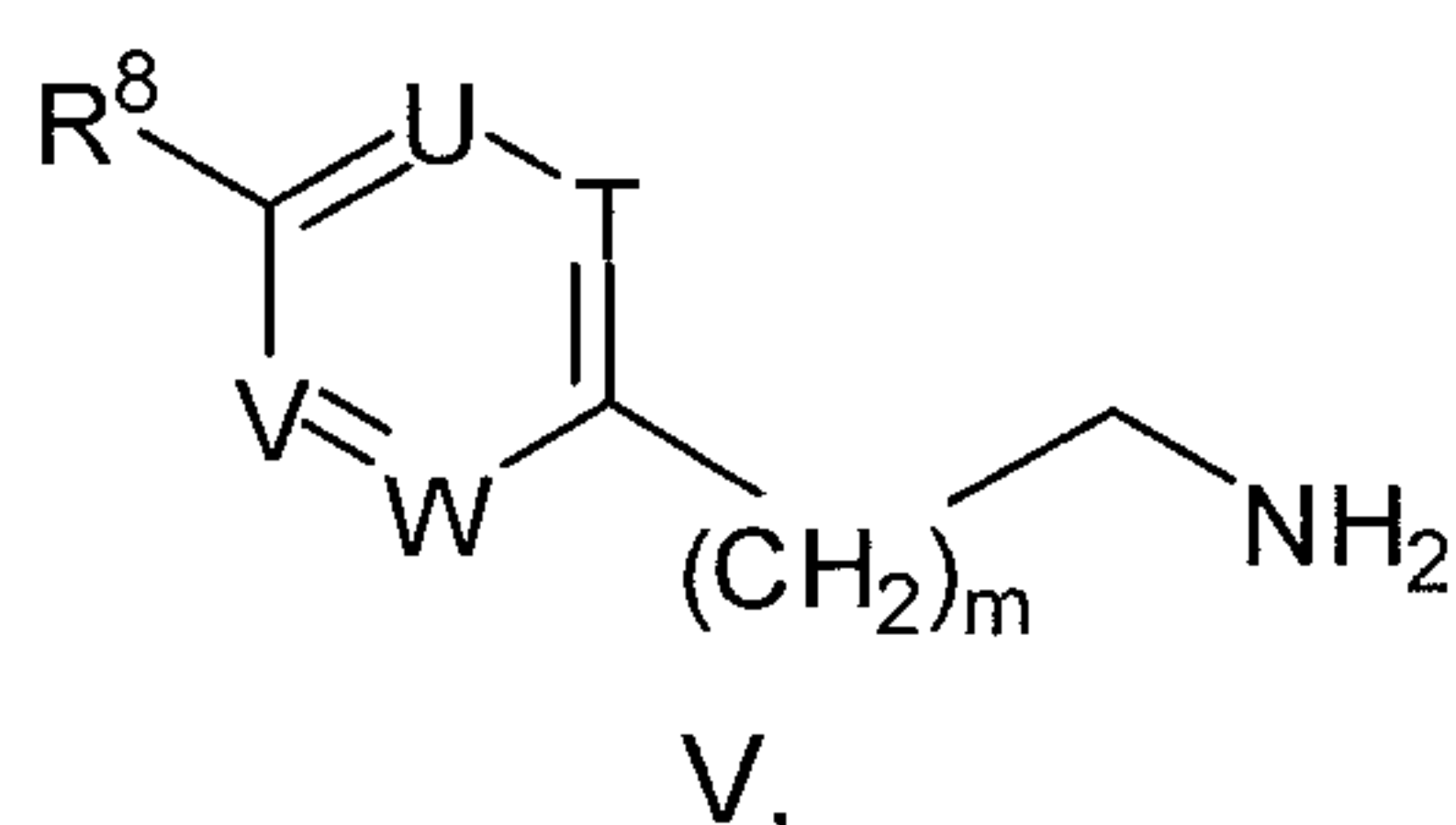
R^8 , U, T, V, and W have the meanings stated above and m stands for 0, 1, 2, or 3, and this is optionally purified and/or isolated,

and at least one compound of the general formula IV is converted, in a reaction medium in the presence of at least one reducing agent, preferably in the presence of at least one reducing agent selected from the group consisting of sodium hydride, potassium hydride, lithium aluminum hydride, sodium tetrahydridoborate, and di(isobutyl)aluminum hydride,

or in a reaction medium in the presence of a catalyst, preferably in the presence of a catalyst based on platinum or palladium, more preferably in the presence of palladium-on-charcoal, and in the presence of hydrogen or in the presence of hydrazine,

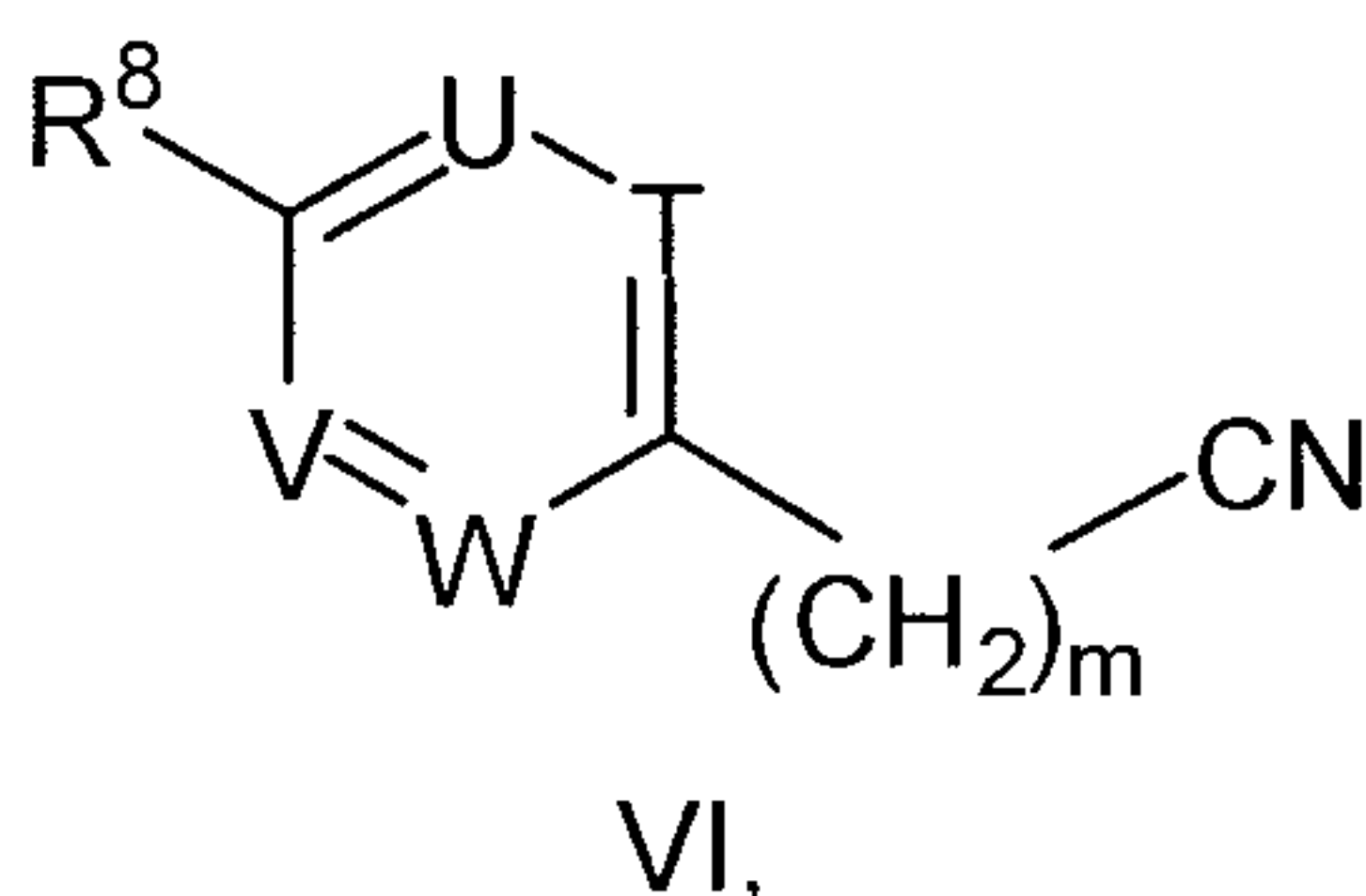
or in a reaction medium in the presence of triphenylphosphine

to at least one compound of the general formula V,



in which R^8 , U, T, V, and W have the meanings stated above and m stands for 0, 1, 2, or 3, and this is optionally purified and/or isolated,

or at least one compound of the general formula VI



in which

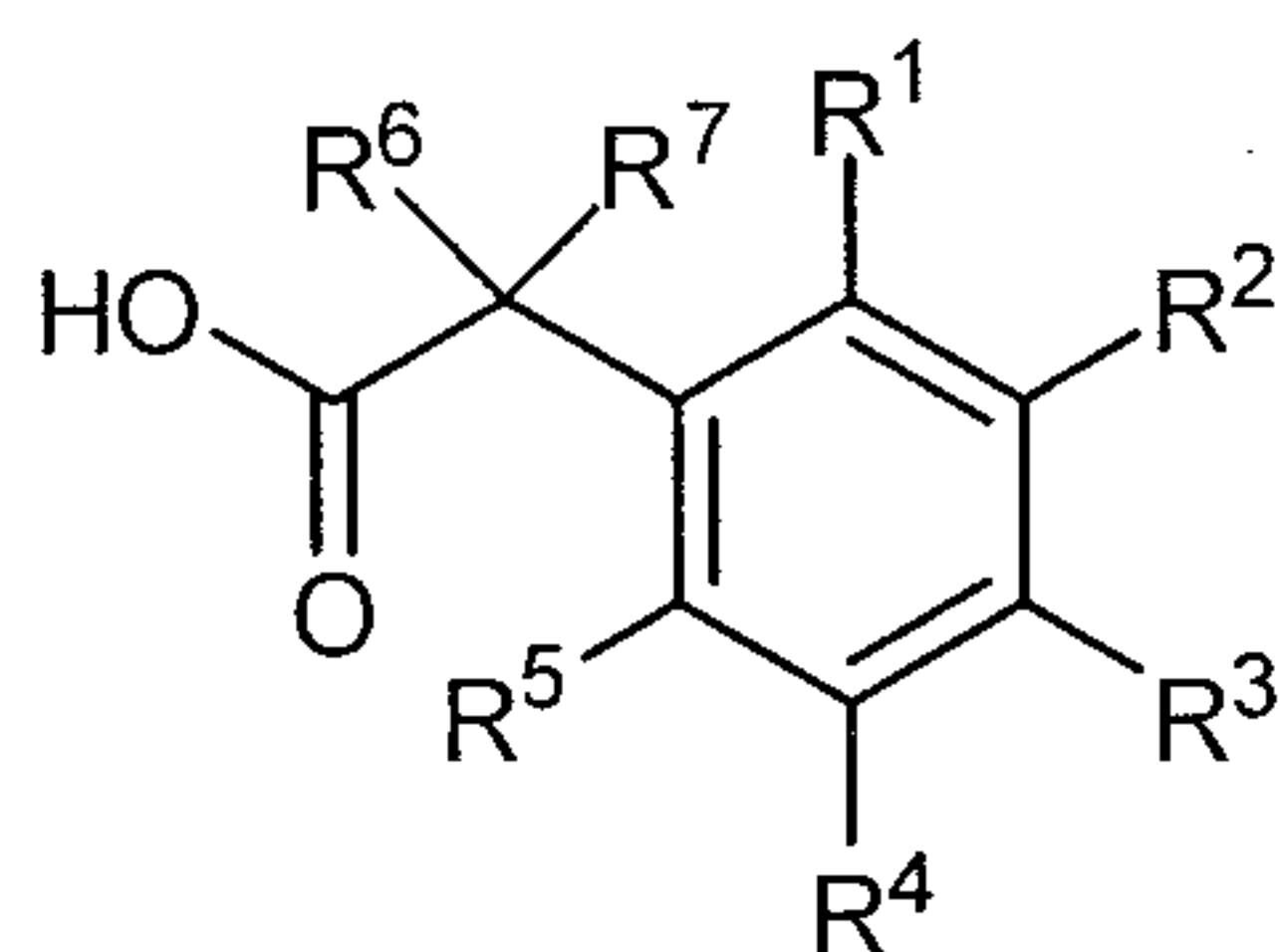
R^8 , U, T, V, and W have the meanings stated above and m stands for 0, 1, 2, or 3, in a reaction medium is converted,

in the presence of at least one catalyst, preferably in the presence of at least one catalyst based on palladium or platinum, more preferably in the presence of palladium-on-charcoal, under a blanket of hydrogen, optionally in the presence of at least one acid, preferably in the presence of hydrochloric acid,

or in the presence of at least one reducing agent selected from the group consisting of $\text{BH}_3 \cdot \text{S}(\text{CH}_3)_2$, lithium aluminum hydride, and sodium tetrahydridoborate, optionally in the presence of NiCl_2 ,

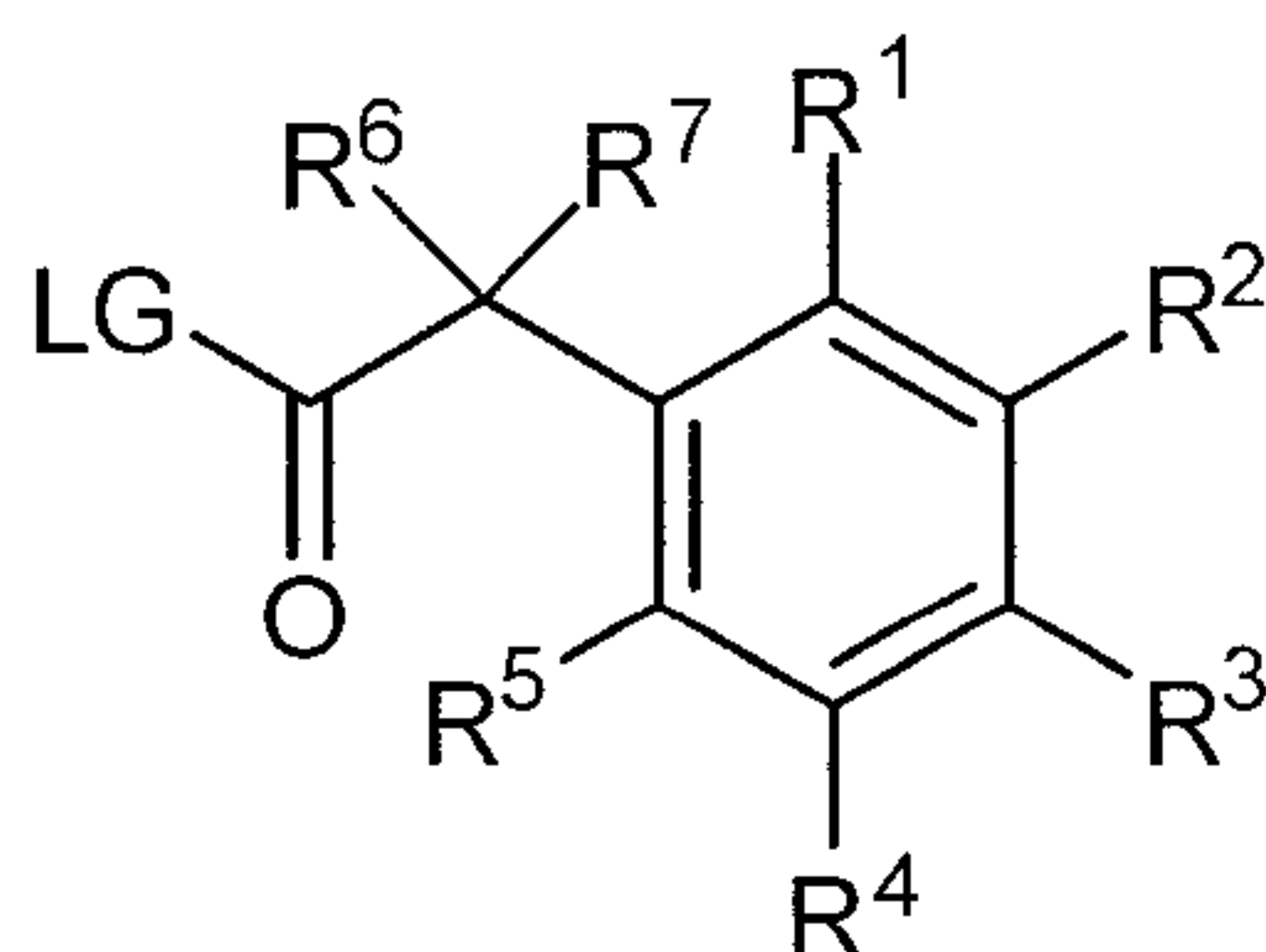
- 5 to form at least one compound of the general formula V, optionally in the form of a corresponding salt, preferably in the form of a corresponding hydrochloride, and this is optionally purified and/or isolated,

and at least one compound of the general formula V is caused to react with at least
10 one compound of the general formula VII,



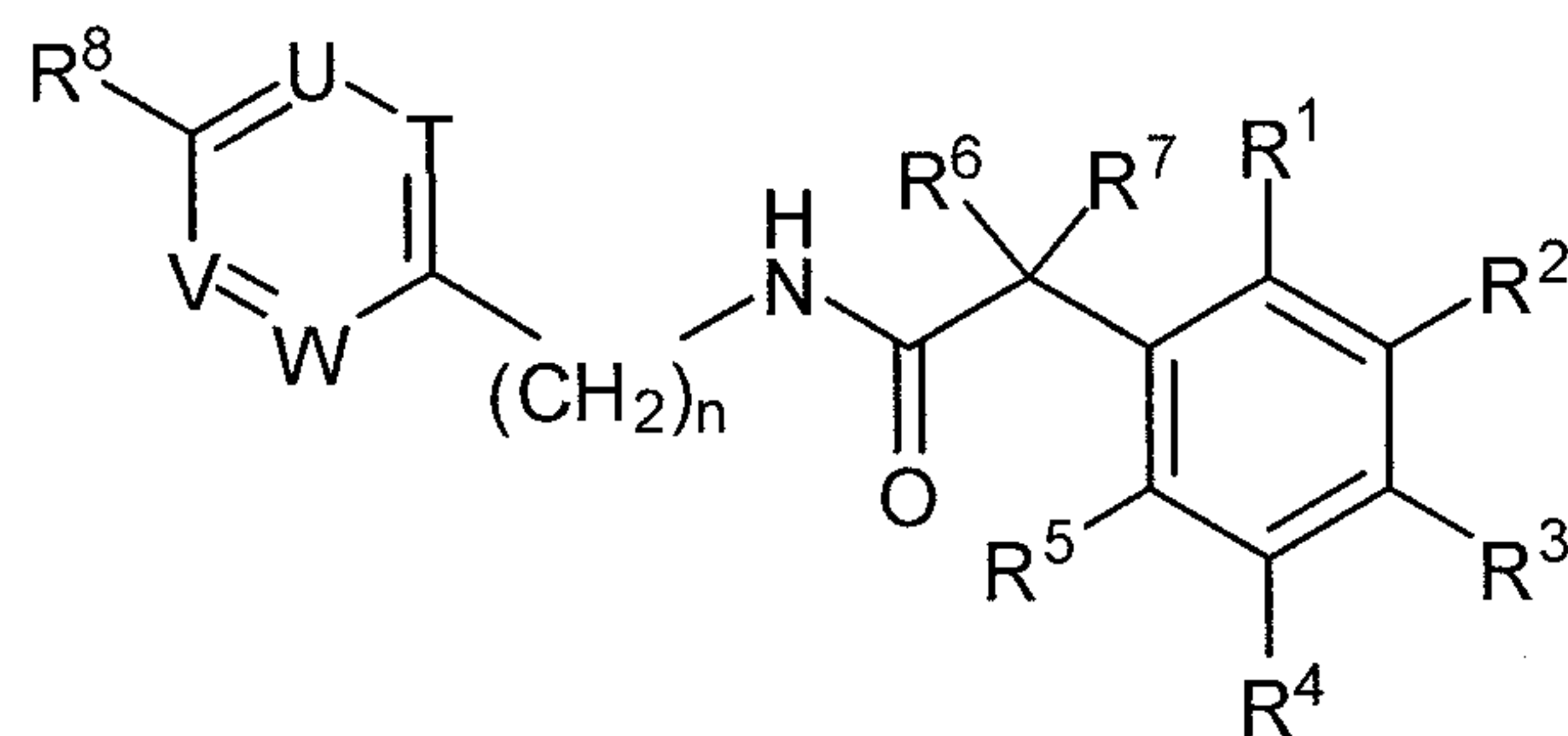
VII,

in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 have the meanings stated above, in a reaction
15 medium, optionally in the presence of at least one suitable coupling agent, optionally in the presence of at least one base,
or with at least one compound of the general formula VIII,



VIII,

20 in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 have the meanings stated above and LG stands for a leaving group, preferably for a chlorine or bromine atom, in a reaction medium, optionally in the presence of at least one base, to form at least one compound of the general formula I,

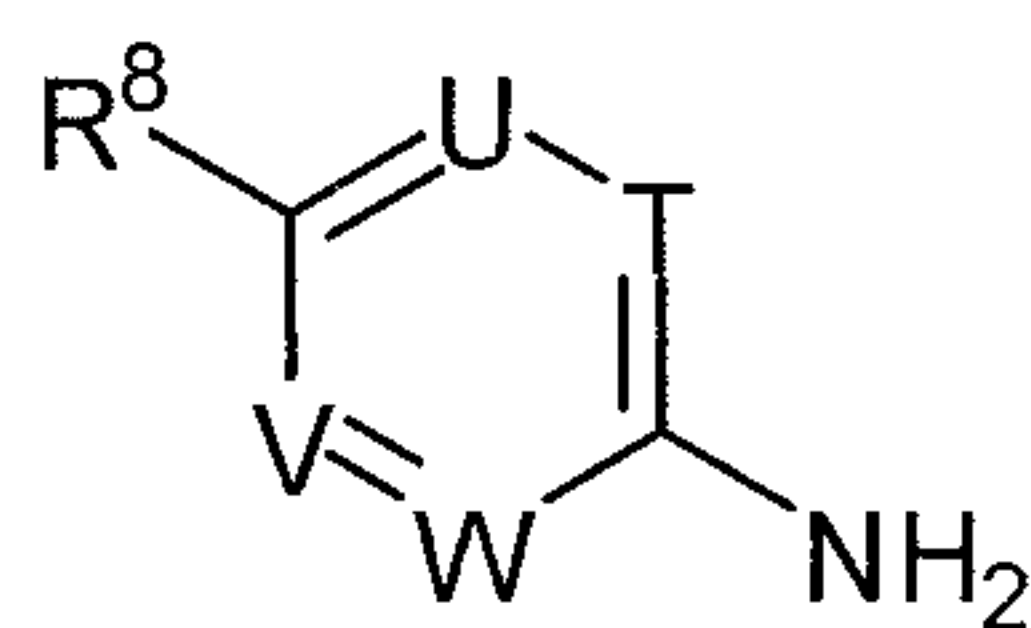


I,

in which T, U, V, W, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ have the meanings stated above and n stands for 1, 2, 3, or 4, and this is optionally purified and/or isolated.

5

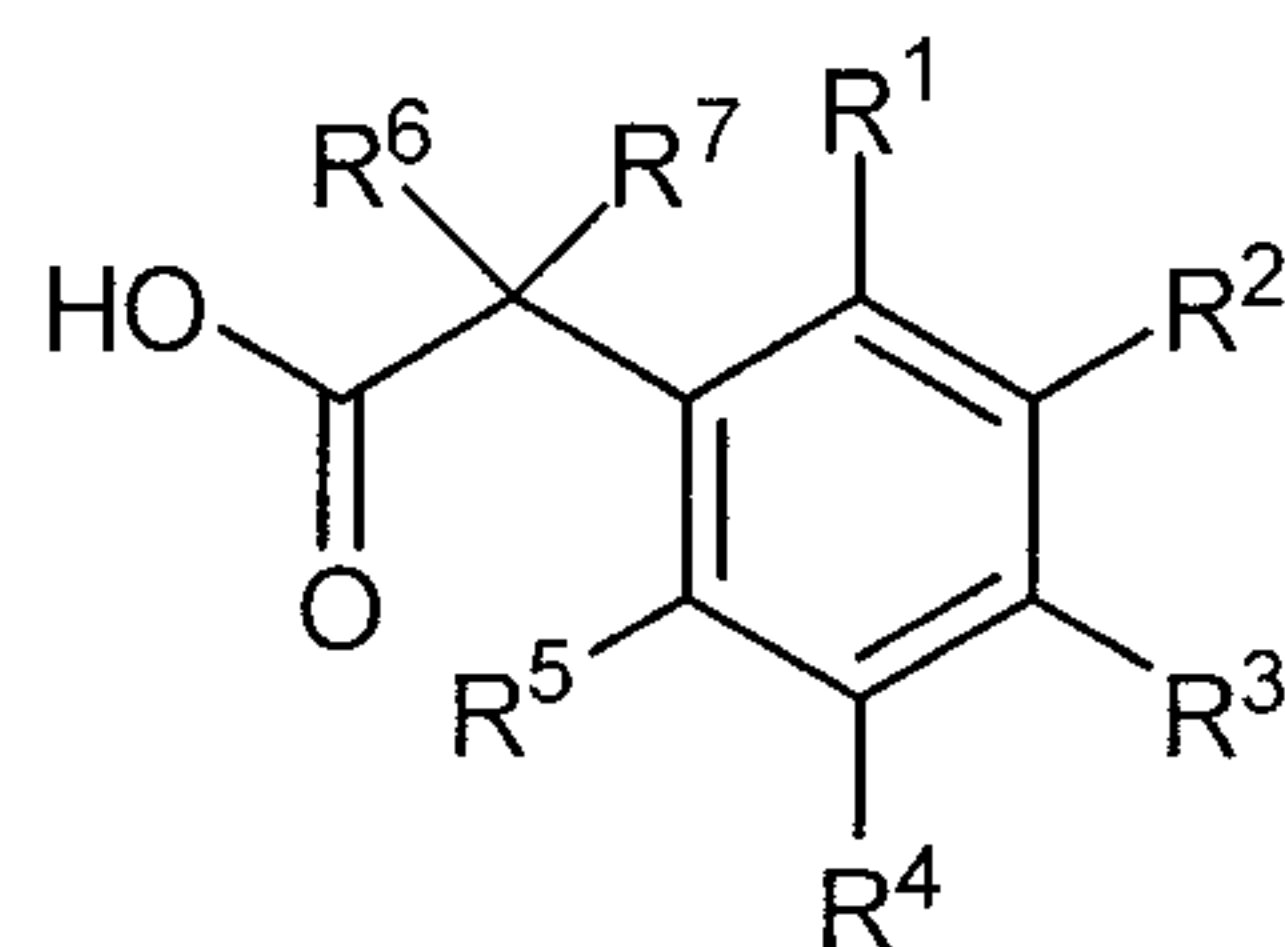
The invention further relates to a process for the production of compounds of the above general formula I, according to which at least one compound of the general formula II,



II,

in which

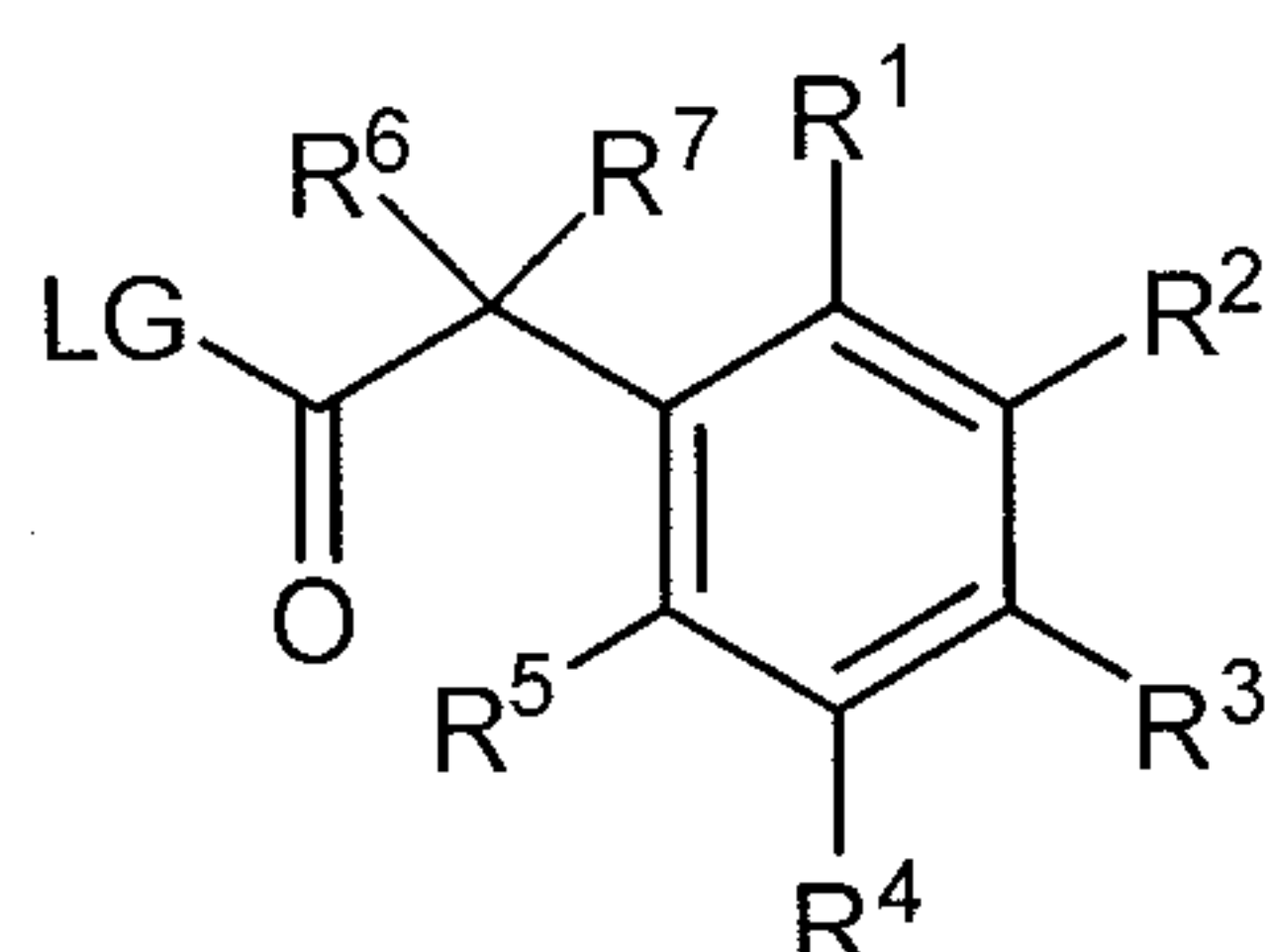
R⁸, U, T, V, and W have the meanings stated above, is caused to react with at least one compound of the general formula VII,



VII,

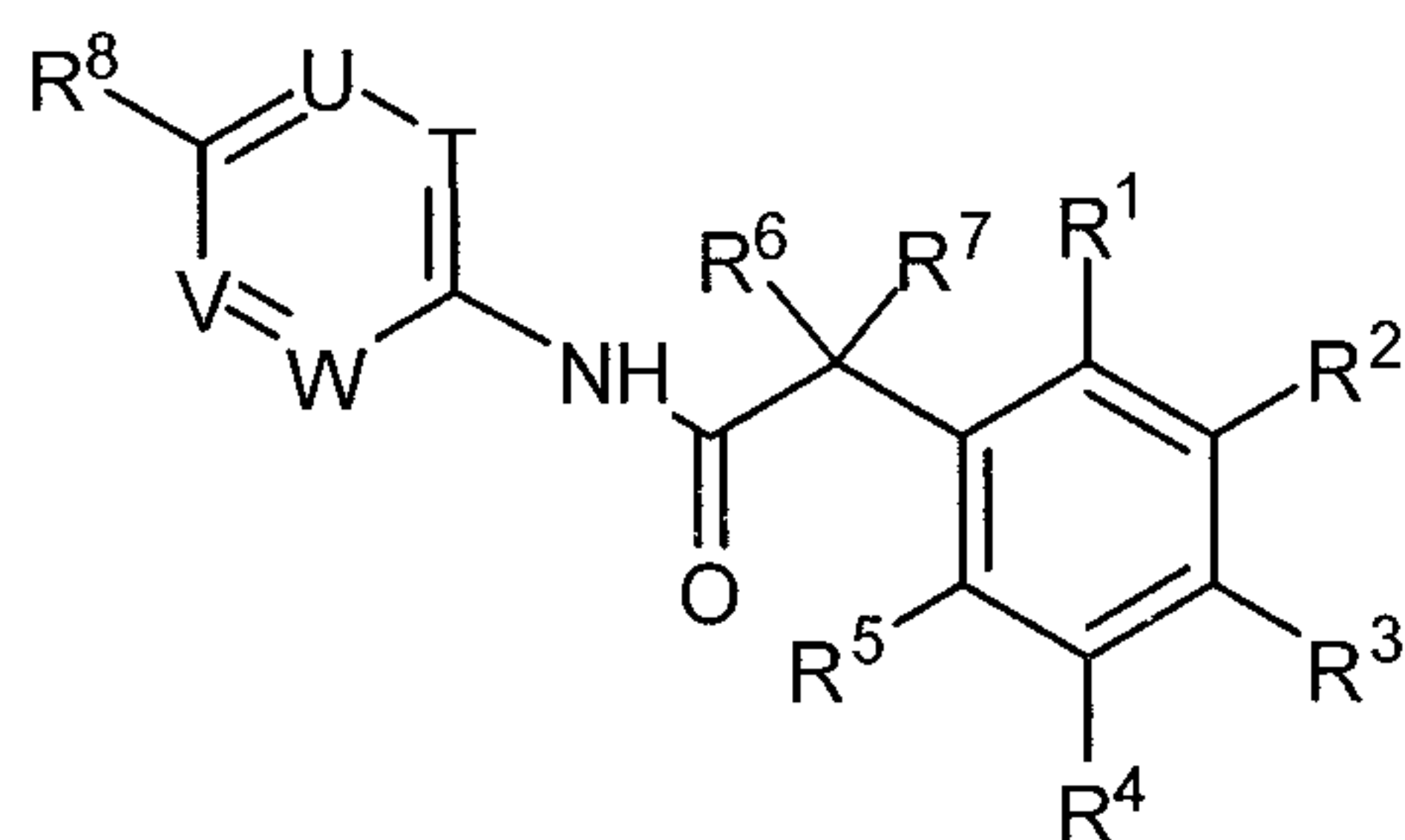
in which R¹, R², R³, R⁴, R⁵, R⁶, and R⁷ have the meanings stated above, in a reaction medium, optionally in the presence of at least one suitable coupling agent, optionally in the presence of at least one base,

or with at least one compound of the general formula VIII,



VIII,

in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 have the meanings stated above and LG stands for a leaving group, preferably for a chlorine or bromine atom, in a reaction medium, optionally in the presence of at least one base, to form at least one compound of the general formula Im,



Im,

in which

T, U, V, W, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 have the meanings stated above, and this is optionally purified and/or isolated.

The reaction of compounds of the above general formulas V or X with carboxylic acids of the above general formula VII to form compounds of the above general formulas I or Im is carried out preferably in a reaction medium selected from the group consisting of diethyl ether, tetrahydrofuran, acetonitrile, methanol, ethanol, (1,2)-dichloroethane, dimethylformamide, dichloromethane and appropriate mixtures thereof, optionally in the presence of at least one coupling agent, preferably selected from the group consisting of 1-benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), dicyclohexylcarbodiimide (DCC), N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI), diisopropylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), N-[(dimethylamino)-1H-1,2,3-triazolo[4.5-b]pyridino-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), N-

hydroxybenzotriazole (HOBT), and 1-hydroxy-7-azabenzotriazole (HOAt), optionally in the presence of at least one organic base, preferably selected from the group consisting of triethylamine, pyridine, dimethylaminopyridine, N-methylmorpholine, and diisopropylethylamine, preferably at temperatures ranging from -70 °C to 100 °C.

Alternatively, the reaction of compounds of the above general formulas V or X with carboxylic derivatives of the above general formula VIII, in which LG stands for a leaving group, preferably for a chlorine or bromine atom, to form compounds of the above general formulas Ih or Im is carried out in a reaction medium preferably selected from the group consisting of diethyl ether, tetrahydrofuran, acetonitrile, methanol, ethanol, dimethylformamide, dichloromethane and appropriate mixtures thereof, optionally in the presence of an organic or inorganic base, preferably selected from the group consisting of triethylamine, dimethylaminopyridine, pyridine, and diisopropylamine, at temperatures ranging from -70 °C to 100 °C.

The compounds of the above formulas II, III, IV, V, VI, VII, X and VIII are all commercially available and can be obtained by conventional methods known to the person skilled in the art.

The synthesis of compounds of the general formula VII is described in the paper "4-(Methylsulfonylamino)phenyl analogues as vanilloid antagonist showing excellent analgesic activity and the pharmaceutical compositions comprising the same" by J. W. Lee et al. [WO 2005/003084-A1]. The appropriate sections of this reference are hereby to be regarded as part of the disclosure.

The conversions described above can each be carried out under usual conditions well-known to the person skilled in the art, for example, in respect of pressure or order of addition of the components. Optionally, the optimal procedure under the respective conditions can be determined by the person skilled in the art using simple preliminary tests. The intermediates and end products obtained by the aforementioned reactions can in each case be isolated and/or purified by conventional methods known to the person skilled in the art, if desired and/or necessary. Suitable purification techniques are, for example, extraction processes and chromatographic processes such as column chromatography or preparative

chromatography. All of the process steps described above and the purification and/or isolation of intermediate or end products can be carried out partially or completely under a blanket of inert gas, preferably under a blanket of nitrogen.

5 The substituted compounds according to the invention of the aforementioned general formulas I, Ia, Ib and Ic, designated below simply as compounds of the general formula I, and corresponding stereoisomers can be isolated either in the form of the free bases thereof, the free acids thereof or in the form of corresponding salts, particularly physiologically compatible salts.

10 The free bases of the respective substituted compounds according to the invention of the aforementioned general formula I and corresponding stereoisomers can, for example by reaction with an inorganic or organic acid, preferably with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, p-
15 toluenesulfonic acid, carbonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, or aspartic acid, be converted to the corresponding salts, preferably physiologically compatible salts. The free bases of the respective substituted compounds of the aforementioned general formula I and corresponding stereoisomers can be likewise
20 caused to react with the free acid or a salt of a sugar substitute, such as saccharin, cyclamate, or acesulfam, to form the corresponding physiologically compatible salts.

Similarly, the free acids of the substituted compounds of the aforementioned general formula I and corresponding stereoisomers can be caused to react with a suitable
25 base to form the corresponding physiologically compatible salts. Mention may be made, for example, of the alkali-metal salts, alkaline earth metal salts, or ammonium salts $[\text{NH}_x\text{R}_{4-x}]^+$ in which x is equal to 0, 1, 2, 3, or 4, and R stands for a linear or branched C₁₋₄-alkyl radical.

30 The substituted compounds according to the invention designated by the aforementioned general formula I and corresponding stereoisomers can optionally, like the corresponding acids, the corresponding bases or salts of these compounds, be obtained in the form of the solvates thereof, preferably in the form of the hydrates thereof, by conventional methods known to the person skilled in the art.

If the substituted compounds according to the invention designated by the
aforementioned general formula I are obtained, following production thereof, in the
form of a mixture of the stereoisomers thereof, preferably in the form of the
5 racemates thereof or other mixtures of the various enantiomers and/or
diastereoisomers thereof, these compounds can be separated and, if desired,
isolated by methods known to the person skilled in the art. Mention may be made,
for example, of chromatographic separation methods, particularly liquid-
chromatographic methods carried out under standard pressure or at elevated
10 pressure, preferably MPLC and HPLC methods, and also methods of fractional
crystallization. In particular, individual enantiomers can be separated from each
other, e.g. diastereoisomeric salts formed by means of HPLC on chiral stationary
phase or by means of crystallization with chiral acids, say, (+)-tartaric acid, (-)-tartaric
acid, or (+)-10-camphorsulfonic acid.

15 The substituted compounds according to the invention designated by the
aforementioned general formula I and corresponding stereoisomers and in each case
the corresponding acids, bases, salts, and solvates are toxicologically safe and are
therefore suitable for use as pharmaceutically active substances in pharmaceuticals.

20 The invention therefore further relates to a pharmaceutical containing at least one
compound according to the invention of the above general formula I, each optionally
in the form of one of the pure stereoisomers thereof, particularly enantiomers or
diastereoisomers thereof, the racemates thereof or in the form of a mixture of
25 stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary
mixing ratio, or each in the form of a corresponding salt, or each in the form of a
corresponding solvate, and optionally one or more pharmaceutically compatible
adjuvants.

30 These pharmaceuticals according to the invention are particularly suitable for
vanilloid receptor 1-(VR1/TRPV1) regulation, preferably vanilloid receptor 1-
(VR1/TRPV1) inhibition and/or vanilloid receptor 1-(VR1/TRPV1) stimulation.

In another preferred embodiment, the pharmaceuticals according to the invention are suitable for prophylaxis and/or treatment of disorders or diseases that are at least partially mediated by vanilloid receptors 1.

5 Preferably, the pharmaceutical according to the invention is suitable for treatment and/or prophylaxis of one or more disorders selected from the group consisting of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain and visceral pain; arthralgia; hyperalgesia; allodynia; causalgia; migraine; states of depression; nervous disorders; neurotraumas; neurodegenerative disorders,
10 preferably selected from the group consisting of multiple sclerosis, Morbus Alzheimer, Morbus Parkinson, and Morbus Huntington; cognitive dysfunctions, preferably cognitive deficiency states, more preferably memory defects; epilepsy; respiratory tract diseases, preferably selected from the group consisting of asthma, bronchitis, and pneumonia; coughing; urinary incontinence; an overactive bladder
15 (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; colitis syndrome; apoplectic strokes; eye irritations; cutaneous irritations; neurotic skin conditions; allergic skin diseases; psoriasis; vitiligo; Herpes simplex; inflammations, preferably inflammation of the intestine, the eyes, the bladder, the skin, or the nasal mucosa; diarrhea; pruritus; osteoporosis; arthritis; osteo-arthritis;
20 rheumatic disorders; food intake disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia, and obesity; medicine addiction; medicine abuse; withdrawal phenomena following medicine addiction; tolerance development to pharmaceuticals, particularly to natural or synthetic opioids; drug addiction; drug abuse; withdrawal phenomena following drug addiction; alcohol addiction; alcohol
25 abuse and withdrawal phenomena following alcohol addiction; for diuresis; for antinatriuresis; for affection of the cardiovascular system; for vigilance enhancement; for treatment of wounds and/or burning; for treatment of severed nerves; for libido enhancement; for modulation of movement activity; for anxiolysis; for local anesthesia and/or for inhibition of undesirable side effects, preferably selected from
30 the group consisting of hyperthermia, hypertension, and bronchial constriction, as caused by administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil, and capsavanil.

The pharmaceutical according to the invention is particularly preferably suitable for treatment and/or prophylaxis of one or more disorders selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; migraine; states of depression; neurodegenerative disorders, preferably selected from the group consisting of multiple sclerosis, Morbus Alzheimer, Morbus Parkinson, and Morbus Huntington; cognitive dysfunctions, preferably cognitive deficiency states, more preferably memory defects; inflammation, preferably inflammation of the intestine, the eyes, the bladder, the skin or the nasal mucosa; urinary incontinence; an overactive bladder (OAB); medicine addiction; medicine abuse; withdrawal phenomena following medicine addiction; tolerance development to pharmaceuticals, preferably tolerance development to natural or synthetic opioids; drug addiction; drug abuse; withdrawal phenomena following drug addiction; alcohol addiction; alcohol abuse and withdrawal phenomena following alcohol addiction.

The pharmaceutical according to the invention is most preferably suitable for treatment and/or prophylaxis of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain, and/or urinary incontinence.

The invention further relates to the use of at least one compound according to the invention and optionally one or more pharmaceutically compatible adjuvants for the production of a pharmaceutical for vanilloid receptor 1-(VR1/TRPV1) regulation, preferably vanilloid receptor 1-(VR1/TRPV1) inhibition and/or vanilloid receptor 1-(VR1/TRPV1) stimulation.

Preference is given to the use of at least one substituted compound according to the invention and optionally one or more pharmaceutically compatible adjuvants for the production of a pharmaceutical for the prophylaxis and/or treatment of disorders or diseases which are at least partially mediated by vanilloid receptors 1.

Particular preference is given to the use of at least one compound according to the invention and optionally one or more pharmaceutically compatible adjuvants for the production of a pharmaceutical for treatment and/or prophylaxis of one or more

disorders selected from the group consisting of pain, preferably of pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, visceral pain, and arthralgia.

- 5 Particular preference is given to the use at least one compound according to the invention and optionally one or more pharmaceutically compatible adjuvants for the production of a pharmaceutical for treatment and/or prophylaxis of one or more disorders selected from the group consisting of hyperalgesia; allodynia; causalgia; migraine; states of depression; nervous disorders; neurotraumas; neurodegenerative
- 10 disorders, preferably selected from the group consisting of multiple sclerosis, Morbus Alzheimer, Morbus Parkinson, and Morbus Huntington; cognitive dysfunctions, preferably cognitive deficiency states, more preferably memory defects; epilepsy; respiratory tract diseases, preferably selected from the group consisting of asthma, bronchitis, and pneumonia; coughing; urinary incontinence; an overactive bladder
- 15 (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; colitis syndrome; apoplectic strokes; eye irritations; cutaneous irritations; neurotic skin conditions; allergic skin diseases; psoriasis; vitiligo; Herpes simplex; inflammation, preferably inflammation of the intestine, the eyes, the bladder, the skin, or the nasal mucosa; diarrhea; pruritus; osteoporosis; arthritis; osteo-arthritis;
- 20 rheumatic disorders; food intake disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia, and obesity; medicine addiction; medicine abuse; withdrawal phenomena following medicine addiction; tolerance development to pharmaceuticals, preferably to natural or synthetic opioids; drug addiction; drug abuse; withdrawal phenomena following drug addiction; alcohol addiction; alcohol
- 25 abuse and withdrawal phenomena following alcohol addiction; for diuresis; for antinatriuresis; for affection of the cardiovascular system; for vigilance enhancement; for treatment of wounds and/or burning; for treatment of severed nerves; for libido enhancement; for modulation of movement activity; for anxiolysis; for local anesthesia and/or for inhibition of undesirable side effects, preferably selected from
- 30 the group consisting of hyperthermia, hypertension, and bronchial constriction, as caused by administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil, and capsavanil.

Very particular preference is given to the use of at least one substituted compound according to the invention and optionally one or more pharmaceutically compatible adjuvants for the production of a pharmaceutical for treatment and/or prophylaxis of one or more disorders selected from the group consisting of pain, preferably pain
5 selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; migraine; states of depression; neurodegenerative disorders, preferably selected from the group consisting of multiple sclerosis, Morbus Alzheimer, Morbus Parkinson, and Morbus Huntington; cognitive dysfunctions, preferably cognitive deficiency states, more preferably memory defects;
10 inflammation, preferably inflammation of the intestine, the eyes, the bladder, the skin, or the nasal mucosa; urinary incontinence; an overactive bladder (OAB); medicine addiction; medicine abuse; withdrawal phenomena following medicine addiction; tolerance development to pharmaceuticals, preferably tolerance development to natural or synthetic opioids; drug addiction; drug abuse; withdrawal phenomena
15 following drug addiction; alcohol addiction; alcohol abuse and withdrawal phenomena following alcohol addiction.

Even more preference is given to the use of at least one substituted compound according to the invention and optionally one or more pharmaceutically compatible
20 adjuvants for the production of a pharmaceutical for treatment and/or prophylaxis of pain, preferably selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain, and/or urinary incontinence.

The pharmaceutical according to the invention is suitable for administration to adults
25 and children including infants and babies.

The pharmaceutical according to the invention can exist as a liquid, semisolid, or solid pharmaceutical dosage form, for example, in the form of injection fluids, drops, juices, syrups, sprays, suspensions, tablets, patches, capsules, plasters,
30 suppositories, ointments, creams, lotions, gels, emulsions, or aerosols, or in a multiparticular form, for example, in the form of pellets or granules, optionally compressed to tablets, filled into capsules, or suspended in a liquid, and can be administered as such.

In addition to at least one substituted compound of the above general formula I, optionally in the form of a pure stereoisomer thereof, particularly an enantiomer or diastereoisomer, the racemate thereof or in the form of mixtures of the stereoisomers, particularly the enantiomers or diastereoisomers, in an arbitrary
5 mixing ratio, or optionally in the form of a corresponding salt or each in the form of a corresponding solvate, the pharmaceutical according to the invention usually contains further physiologically compatible pharmaceutical adjuvants, which, for example, can be selected from the group consisting of vehicles, fillers, solvents, diluents, surfactants, dyes, preservatives, blasting agents, slip agents, lubricants,
10 flavors, and binding agents.

The selection of the physiologically compatible adjuvants and the amount thereof to be used depends on whether the pharmaceutical is to be applied orally, subcutaneously, parenterally, intravenously, intraperitoneally, intradermally,
15 intramuscularly, intranasally, buccally, rectally or locally, e.g. to infected parts of the skin, the mucous membrane, or the eyes. Preparations suitable for oral administration are preferably in the form of tablets, dragees, capsules, granules, pellets, drops, juices, and syrups, and preparations suitable for parenteral, topical and inhalative administration are solutions, suspensions, readily reconstitutable dry
20 preparations, and sprays. The substituted compounds according to the invention used in the pharmaceutical according to the invention in a depot in dissolved form or in a plaster, optionally with the addition of skin penetration-enhancing agents, are suitable percutaneous administration forms. Formulations for oral or percutaneous
25 application may be such as to effect delayed release of the respective substituted compound according to the invention.

The production of the pharmaceutical according to the invention is effected by conventional means, devices, methods, and processes, as are known in the prior art, such as are described, for example, in "Remington's Pharmaceutical Sciences",
30 Editor A.R. Gennaro, 17th Edition, Mack Publishing Company, Easton, Pa, 1985, particularly in Section 8, Chapters 76 to 93. The corresponding description is incorporated herein by reference and is to be regarded as part of the disclosure. The amount of the respective substituted compounds according to the invention of the above general formula I to be administered to the patients can vary and is

dependent, for example, on the weight or age of the patient and also on the method of administration, the indication, and the severity of the disorder. Usually from 0.001 to 100 mg/kg, preferably from 0.05 to 75 mg/kg and more preferably from 0.05 to 50 mg/kg, of body weight of the patient of at least one such compound according to the
5 invention are administered.

Pharmacological methods:**I. Functional investigation on the vanilloid receptor 1 (VR1/TRPV1 receptor)**

- 5 The agonistic or antagonistic action of the substances to be investigated on the vanilloid receptor 1 (VR1/TRPV1) of the species rat can be determined using the following assay. According to this assay, the Ca^{2+} influx through the receptor channel is quantified with the aid of a Ca^{2+} -sensitive dye (Type Fluo-4, Molecular Probes Europe BV, Leiden Netherlands) in a fluorescent imaging plate reader
10 (FLIPR, Molecular Devices, Sunnyvale, USA).

Method:

- Complete medium: 50 mL of HAMS F12 Nutrient Mixture (Gibco Invitrogen GmbH,
15 Karlsruhe, Germany) with
10% by volume of FCS (fetal calf serum, Gibco Invitrogen GmbH, Karlsruhe, Germany, heat-inactivated);
2mM of L-glutamine (Sigma, Munich, Germany);
1% by weight of AA solution (antibiotics/antimycotics solution, PAA, Pasching,
20 Austria)
and 25 ng/mL of Medium NGF (2.5 S, Gibco Invitrogen GmbH, Karlsruhe, Germany)

- Cell culture plate: Poly-D-lysine-coated, black 96-well plates with a clear bottom (96-well black/clear plate, BD Biosciences, Heidelberg, Germany) are additionally coated
25 with laminin (Gibco Invitrogen GmbH, Karlsruhe, Germany) by diluting laminin to a concentration of 100 µg/mL with PBS (Ca-Mg-free PBS, Gibco Invitrogen GmbH, Karlsruhe, Germany). Aliquots having a concentration of 100 µg/mL of laminin are taken and stored at -20 °C. The aliquots are diluted with PBS in the ratio 1:10 to 10 µg/mL of laminin and in each case 50 µL of the solution is pipeted into a well of
30 the cell culture plate. The cell culture plates are incubated at 37 °C for at least two hours, the supernatant solution is aspirated and the wells are in each case washed twice with PBS. The coated cell culture plates are stored with supernatant PBS and this is removed only directly before the addition of the cells.

Preparation of the cells:

The vertebral column is removed from decapitated rats and this is laid directly in a cold, i.e. ice bath-surrounded, HBSS buffer (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany) and 1% by volume of an AA solution (antibiotics/antimycotics solution, PAA, Pasching, Austria) is added. The vertebral column is cut in two, longitudinally, and the vertebral canal is removed together with fascias. Subsequently, the dorsal root ganglia (DRGs) are removed and in turn stored in cold HBSS buffer to which 1% by volume of an AA solution has been added. The DRGs completely freed from blood residues and spinal nerves are in each case transferred to 500 μ L of cold collagenase Type 2 (PAA, Pasching, Austria) and incubated at 37 °C for 35 minutes. After the addition of 2.5% by volume of trypsin (PAA, Pasching, Austria), the preparation is incubated at 37 °C for a further 10 minutes. On completion of incubation, the enzyme solution is carefully pipeted off and 500 μ L of complete medium are added to the DRGs in each case. The DRGs are in each case repeatedly suspended, drawn through No. 1, No. 12, and No. 16 needles by means of a syringe and transferred to 50 mL Falcon tubes and these are filled to 15 mL with complete medium. The contents of each Falcon tube are in each case filtered through a 70 μ m Falcon filter insert and centrifuged at 1200 rpm and RT for 10 minutes. The resulting pellet is in each case taken up in 250 μ L of complete medium and the cell count is determined.

The number of cells in the suspension is adjusted to 3×10^5 per mL and in each case 150 μ L of this suspension are added to a well of the cell culture plates coated as described above. The plates are allowed to stand at 37 °C, 5% by volume of CO₂ and 95% relative humidity for two to three days in an incubator.

Subsequently, the cells are loaded with 2 μ M of Fluo-4 and 0.01% by volume of Pluronic F127 (Molecular Probes Europe BV, Leiden Netherlands) in HBSS buffer (Hank's buffered saline solution, Gibco Invitrogen GmbH, Karlsruhe, Germany) at 37°C for 30 min, washed 3 times with HBSS buffer and, after a further incubation of 15 minutes at RT, employed in the FLIPR assay for Ca²⁺ measurement. The Ca²⁺-dependent fluorescence is measured before and after addition of substances (λ_{ex} =

488 nm, λ_{em} = 540 nm). Quantification is carried out by measuring the highest fluorescence intensity (FC, fluorescence counts) over time.

FLIPR assay:

The FLIPR protocol consists of two substance additions. Initially, the compounds to be tested (10 μ M) are pipetted onto the cells and the Ca^{2+} influx is compared with the control (capsaicin 10 μ M). Information is gained therefrom in percentage activation relative to the Ca^{2+} signal after addition of 10 μ M of capsaicin (CP). After incubation for 5 minutes, 100 nM of capsaicin are applied and the influx of Ca^{2+} is likewise determined.

Desensitizing agonists and antagonists lead to suppression of the Ca^{2+} influx. The percentage inhibition is calculated in comparison with the maximum inhibition achieved with 10 μ M of capsaicin.

Triple determinations (n=3) are carried out and these are repeated in at least 3 independent experiments (N=4).

Based on the percentage displacement effected by different concentrations of the compounds of the general formula I to be tested, IC_{50} inhibition concentrations that cause 50 percent displacement of capsaicin are calculated. Conversion using the Cheng Prusoff equation gave K_i values for the test substances (Cheng, Prusoff; Bioch. Pharmacol. 22, 3099-3108, 1973).

II. Functional investigations on the vanilloid receptor (VR1)

The agonistic or antagonistic action of the substances to be examined on the vanilloid receptor (VR1) can also be determined by the following assay. According to this assay, the Ca^{2+} influx through the canal is quantified with the aid of a Ca^{2+} -sensitive dye (type Fluo-4, Molecular Probes, Europe BV, Leiden, Netherlands) in a fluorescent imaging plate reader (FLIPR, Molecular Devices, Sunnyvale, USA).

Method:

Chinese hamster ovary cells (CHO-K1 cells, European Collection of Cell Cultures (ECACC) UK) are stably transfected with the VR1 gene. For carrying out functional investigations, these cells are plated on poly-D-lysine-coated, black 96-well plates with a clear bottom (BD Biosciences, Heidelberg, Germany) in a density of 25,000 cells/well. The cells are incubated overnight at 37 °C and 5% CO₂ in a culture medium (Nutrient Mixture 'am's F12, 10% by volume of FCS (fetal calf serum), 18 µg/mL of L-proline). On the following day the cells are incubated with Fluo-4 (Fluo-4 2 µM, Pluronic F127 0.01 by volume, Molecular Probes in HBSS (Hank's buffered saline solution), Gibco Invitrogen GmbH, Karlsruhe, Germany) for 30 minutes at 37 °C. The plates are then washed 3 times with HBSS buffer and, after another incubation over a period of 15 minutes at RT, are used in the FLIPR for Ca²⁺ measurement. The Ca²⁺-dependent fluorescence is measured prior to and following the addition of the substances being examined (wavelength λ_{ex} = 488 nm, λ_{em} = 540 nm). Quantification is carried out by measuring the highest fluorescence intensity (FC, fluorescence counts) over time.

FLIPR assay:

The FLIPR protocol consists of two substance additions. First of all, the substances to be tested (10 µM) are pipeted onto the cells and the Ca²⁺ influx is compared with the control (capsaicin 10 µM) (percentage activation based on the Ca²⁺ signal following addition of 10 µM of capsaicin). Following incubation over a period of 5 minutes 100 nM of capsaicin are applied and the influx of Ca²⁺ is likewise determined.

Desensitizing agonists and antagonists led to a suppression of the Ca²⁺ influx. The percentage inhibition compared with the maximum inhibition achieved with 10 µM of capsaicin is calculated.

Based on the percentage displacement effected by different concentrations of the compounds of the general formula I to be tested, IC₅₀ inhibition concentrations that cause 50 percent displacement of capsaicin are calculated. Conversion using the Cheng Prusoff equation gave K_i values for the test substances (Cheng, Prusoff; Bioch. Pharmacol. 22, 3099-3108, 1973).

III. Formalin test on mice

The investigation for the determination of the antinociceptive action of the compounds according to the invention is carried out in the formalin test on male mice (NMRI, of 20 to 30 g body weight, Iffa, Credo, Belgium).

In the formalin test, the first (early) phase (0 to 15 minutes after the formalin injection) and the second (late) phase (15 to 60 minutes after the formalin injection) are distinguished according to D. Dubuisson et al., Pain 1977, 4, 161-174. The early phase, as a direct reaction to the formalin injection, is a model of acute pain, whereas the late phase is regarded as a model of persistent (chronic) pain (T.J. Coderre et al., Pain 1993, 52, 259-285). The appropriate literature references are incorporated herein by reference and are to be regarded as part of the disclosure.

The compounds according to the invention are examined in the second phase of the formalin test, in order to obtain information concerning a substance's action on chronic/inflammatory pain.

The point in time of administration of the compounds according to the invention before the formalin injection is selected according to the method of administration of the compounds according to the invention. Intravenous administration of 10 mg/kg of body weight of the test substances is carried out 5 minutes before the formalin injection. This is carried out by a single subcutaneous formalin injection (20 μ L, 1% strength aqueous solution) into the dorsal side of the right hind paw so that in the case of free-moving experimental animals a nociceptive reaction is induced which is manifested by marked licking and biting of the relevant paw.

The nociceptive behavior is then continuously registered during an investigation period of three minutes in the second (late) phase of the formalin test (21 to 24 minutes after the formalin injection) by observation of the animals. Quantification of the pain behavior is carried out by summing the seconds during which the animals exhibit licking and biting of the relevant paw during the investigation period.

In each case, comparison is carried out with control animals, which receive, instead of the compounds according to the invention, a vehicle (0.9% strength aqueous sodium chloride solution) prior to formalin administration. Based on the quantification of the pain behavior, the substance's action in the formalin test is determined as the degree of change compared with the corresponding control in percent.

Following injection of the substances having an antinociceptive action in the formalin test, the aforementioned behavioral patterns of the animals, i.e. licking and biting, decrease or cease.

IV. Test for analgesic effectiveness in the writhing test

Investigation of the compounds of the general formula I according to the invention for analgetic effectiveness was carried out based on phenylquinone-induced writhing in mice, modified in accordance with I.C. Hendershot and J. Forsaith (1959) J. Pharmacol. Exp. Ther. 125, 237-240. The corresponding literature reference is incorporated herein by reference and is to be regarded as part of the disclosure.

For this purpose, male NMRI mice having a weight of from 25 to 30 g were used. Groups of 10 animals per dose of the test compound received by intraperitoneal administration, 10 minutes after intravenous administration of the compounds to be tested, 0.3 mL/mouse of a 0.02% strength aqueous solution of phenylquinone (phenylbenzoquinone, Sigma, Deisenhofen, Germany and produced by adding to the solution 5% by weight of ethanol and storing it in a water bath at 45 °C). The animals were placed individually in observation cages. With the aid of a pushbutton counter, the number of pain-induced stretching movements (so-called writhing reactions - straightening of the body with stretching of the rear extremities) was counted over a period of from 5 to 20 minutes following the administration of the phenylquinone. The control was provided by animals receiving only physiological saline. All of the compounds were tested using the standard dosage of 10 mg/kg.

V. Hypothermia assay in mice

Description of the method:

The hypothermia assay was carried out on male NMRI mice (weight 25-35 gram, breeder IFFA CREDO, Brussels, Belgium). The animals were kept under standardized conditions: light/dark rhythm (from 6:00 to 18:00 hours light phase; from 18:00 to 6:00 hours dark phase), RT 19-22 °C, relative air humidity 35-70 %, 15 air changes per hour, air movement < 0.2 m/sec. The animals received standard feed (ssniff R/M-Haltung, ssniff Spezialdiaeten GmbH, Soest, Germany) and tap water. Water and feed were withdrawn during the experiment. All animals were used only once during the experiment. The animals had an acclimatization period of at least 5 days.

Acute administration of capsaicin (VR-1 agonist) leads to a drop in the core temperature of the body in rats and mice due to stimulation of heat sensors. Only specifically effective VR-1 receptor antagonists can antagonize the capsaicin-induced hypothermia. By contrast, hypothermia induced by morphine is not antagonized by VR-1 antagonists. This model is therefore suitable for identifying substances with VR-1 antagonistic properties via their effect on body temperature.

Measurement of the core temperature is carried out using a digital thermometer (Thermalert TH-5, physitemp, Clifton NJ, USA). The sensing element is inserted into the rectum of the animals.

To give an individual basic value for each animal, the body temperature is measured twice at an interval of approximately half an hour. One group of animals (n = 6 to 10) then receives an intraperitoneal (i.p.) application of capsaicin 3 mg/kg and vehicle (control group). Another group of animals receives the substance to be tested (i.v. or p.o.) and additionally capsaicin (3 mg/kg) i.p. The administration of the test substance is carried out i.v. 10 min, or p.o 15 minutes, prior to capsaicin. The body temperature is then measured 7.5 / 15 and 30 min following capsaicin (i.v. + i.p.) or 15 / 30 / 60 / 90 / 120 min (p.o. + i.p.) following capsaicin. In addition, one group of animals is treated with the test substance only and one group with vehicle only. The evaluation or representation of the measured values as mean +/- SEM of the absolute values is presented as a graphical representation. The antagonistic action is calculated as the percentage reduction of the capsaicin-induced hypothermia.

VI. Neuropathic pain in mice

The investigation on effectiveness on neuropathic pain was examined using the Bennett Model (chronic constriction injury; Bennett und Xie, 1988, Pain 33:87-107).

5

Three loose ligatures are tied around the right ischiadic nerve of Ketavet/Rompun-anesthetized NMRI mice weighing 16-18 g. The animals develop hypersensitivity of the nerve paw caused by the damaged nerve, which hypersensitivity is quantified, following a recovery phase of one week, over a period of approximately three weeks
10 by means of a cold metal plate (temperature 4 °C) (cold allodynia). The animals are observed on this plate over a period of 2 min, and the withdrawal reactions of the damaged paw are counted. Based on the pre-value prior to administration of substance, the substance's action over a certain period of time is determined at various points in time (e.g., 15, 30, 45, or 60 min following administration) and the
15 resultant area under the curve (AUC) and/or the inhibition of cold allodynia at the individual measuring points was/were expressed as percentage action relative to the vehicle control (AUC) or to the starting value (individual measuring points). The group size is n= 10, the significance of an anti-allodynic action ($p < 0.05$) is determined with the aid of an analysis of variance with repeated measurement and Bonferroni
20 post hoc analysis.

The invention is described below with reference to some examples. These explanations are by way of example only and do not restrict the general inventive concept.

25

Examples:

The yields of the compounds produced were not optimized.

5 All temperatures are uncorrected.

The statement "equivalents" denotes mol equivalents, "RT" room temperature, "M" and "N" are concentrations in mol/L, "aq." aqueous, "sat." saturated, "soln." solution,

10 Further abbreviations:

AcOH acetic acid

DCM dichloromethane

DMF N,N-dimethylformamide

EDCI N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride

15 EA ethyl acetate

H₂O water

HOBt N-hydroxybenzotriazole

MeOH methanol

THF tetrahydrofuran

20

The chemicals and solvents used were obtained commercially from the usual suppliers (Acros, Avocado, Aldrich, Bachem, Fluka, Lancaster, Maybridge, Merck, Sigma, TCI, Oakwood etc.) or synthesized by usual methods known to the person skilled in the art.

25

The stationary phase used for column chromatography was silica gel 60 (0.0-0 – 0.063 mm) supplied by E. Merck, Darmstadt.

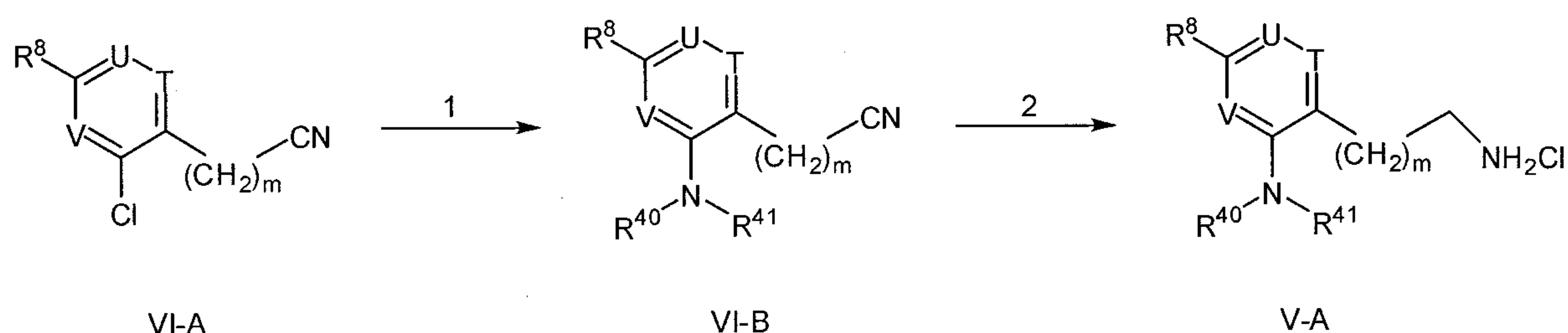
The thin-layer chromatographic analyses were carried out using preformed HPTLC
30 plates, Silica Gel 60 F 254, supplied by E. Merck, Darmstadt.

The mixing ratios of solvents, mobile solvents, or for chromatographic analyses are always stated in vol/vol.

Analysis was carried out by mass spectroscopy and NMR.

1. General instructions for the preparation of amines of the general formula V-A.

Preparation of amines of the general formula V-A is carried out as illustrated by the following scheme 1.



Scheme 1.

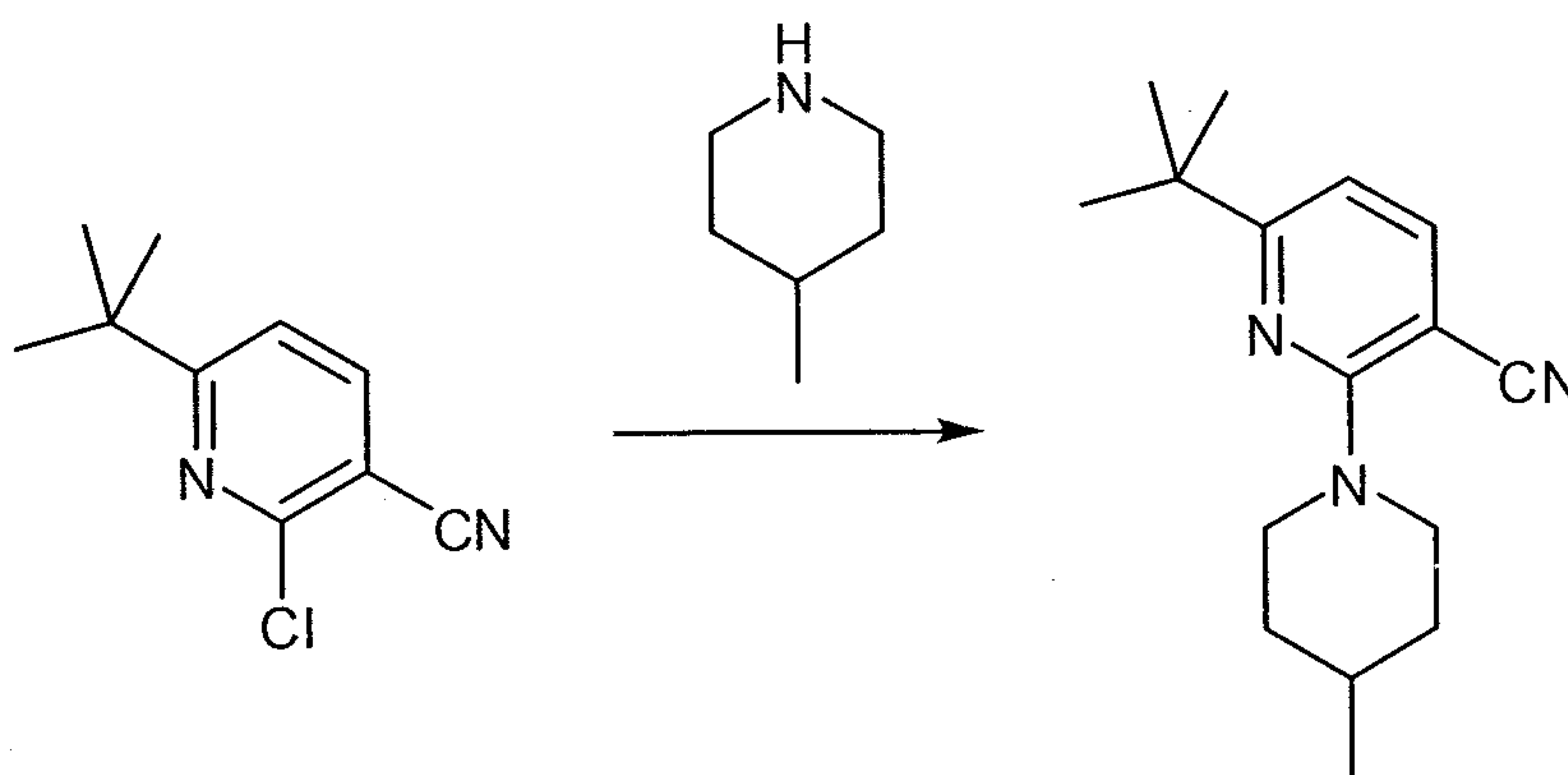
Stage 1: Preparation of nitriles of the general formula VI-B

Method A:

Compounds of the general formula VI-A (1 equivalent), in which R^8 , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are stirred with an amine of the general formula $\text{HNR}^{40}\text{R}^{41}$ (6 equivalents) over a period of 48 hours at RT. To the reaction mixture there is added 1N hydrochloric acid, and the mixture is extracted with EA a number of times. The aqueous phase is saturated with NaCl and then again extracted with EA. The combined organic phases are washed with 1N hydrochloric acid and with sat. aq. NaCl soln., dried over MgSO_4 , and the solvent is removed in vacuo.

The following compound was obtained by method A:

6'-tert-Butyl-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-carbonitrile



$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.65 (d, 1H, $J = 7.9$ Hz, Ar), 6.70 (d, 1H, $J = 8.0$ Hz, Ar), 4.45 (m, 2H, piperidine), 2.98 (m, 2H, piperidine), 1.75-1.24 (m, 5H, piperidine), 1.29 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.98 (d, 3H, $J = 5.9$ Hz, CHCH_3)

5 IR 2956, 2213, 1583, 1550, 1452, 1230, 965 cm^{-1}

Method B:

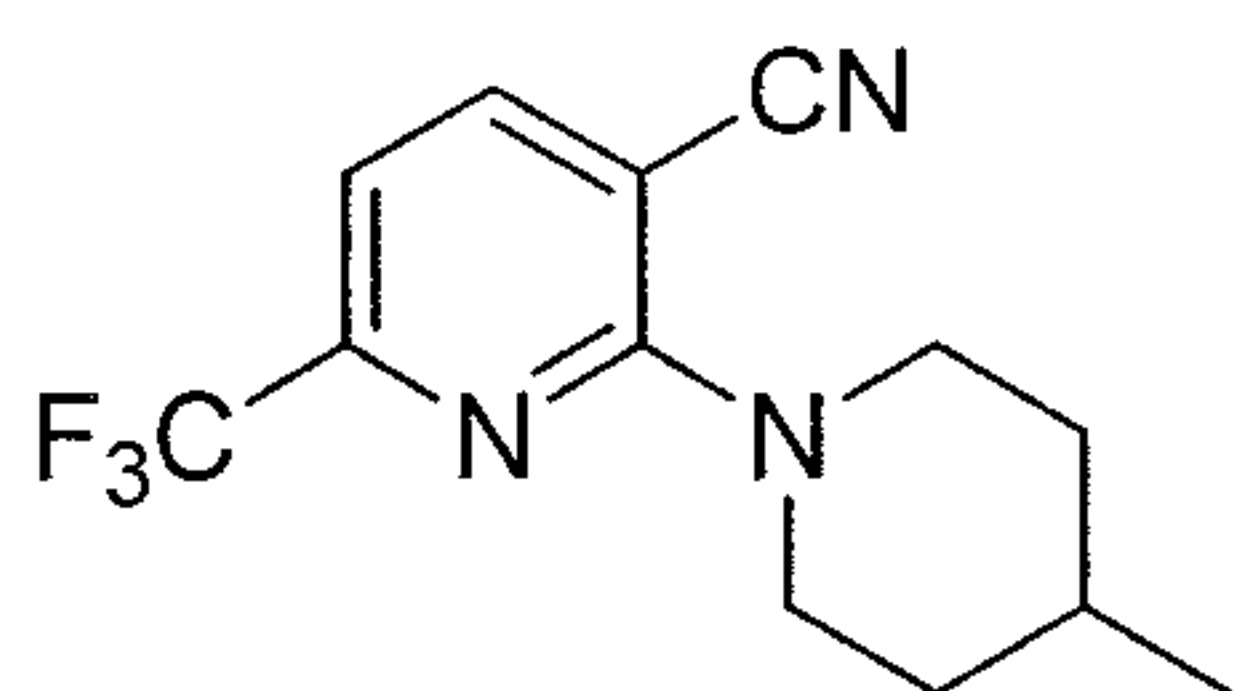
Compounds of the general formula VI-A (1 equivalent), in which R^8 , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are stirred with an amine of the general formula $\text{HNR}^{40}\text{R}^{41}$ (2 equivalents) and DBU [1.8-diaza-

10 bicyclo[5.4.0]undec-7-ene] (2 equivalents) in acetonitrile (7 mL per mmol of the compound of formula VI-A) over a period of 12 hours at RT. The reaction mixture is extracted with EA a number of times. The combined organic phases are washed with sat. aq. NaCl solution, dried over MgSO_4 , and the solvent is removed in vacuo. The

15 residue is purified in each case by column chromatography (SiO_2 , various mixtures of hexane/EA).

The following compound was produced by method B.

20 6-(Trifluoromethyl)-2-(4-methylpiperidin-1-yl)pyridine-3-carbonitrile



$^1\text{H NMR}$ (300 M Hz, CDCl_3) δ 7.87 (d, 1 h, $J = 7.8$ Hz), 6.95 (d, 1 h, $J = 7.8$ Hz), 4.53

25 (m, 2 H), 3.05 (m, 2 H), 1.78 (m, 2 H), 1.64 (m, 1 H), 1.29 (m, 2 H), 1.00 (d, 3 H, $J =$

6.6 Hz); IR (PUR) 2926, 2852, 2218, 1590, 1497, 1456, 1324, 1237, 1186, 1147, 1082, of 963 cm^{-1} ; MS (FAB) m/z 270 (M+H)

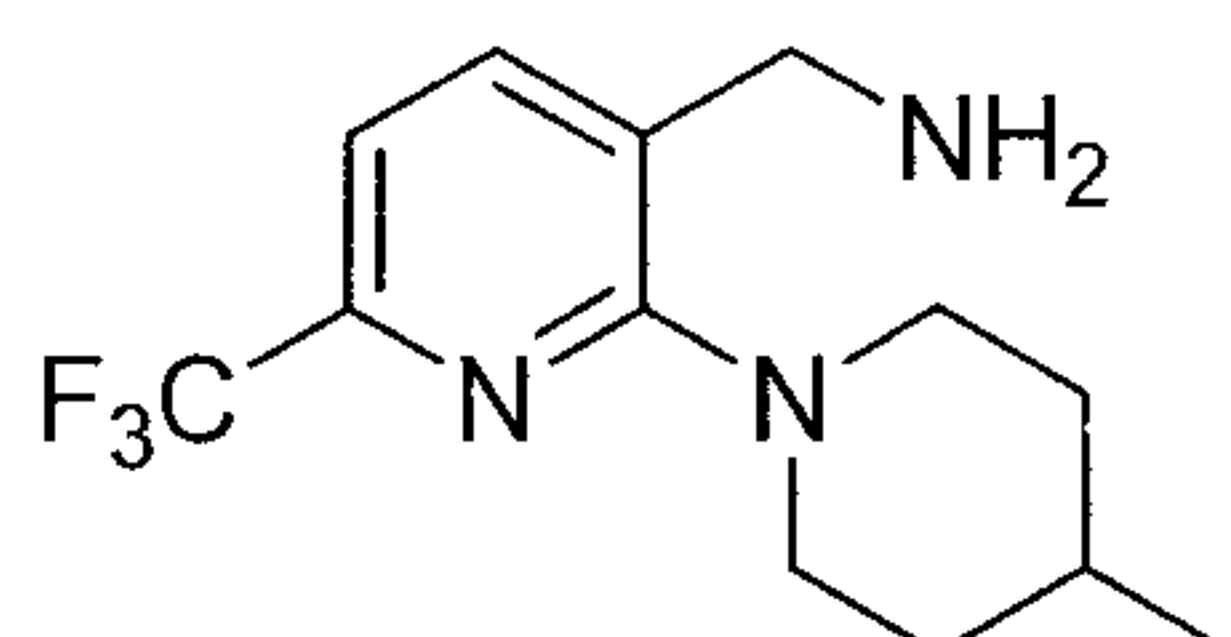
Step 2:**Method 1**

Compounds of the general formula VI-B (5 mmol), in which R^8 , R^{40} , R^{41} , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, palladium-on-charcoal (10%, 500 mg) and conc. hydrochloric acid (3 mL) are dissolved in MeOH (30 mL) and exposed to a hydrogen atmosphere over a period of 6 hours at RT. The reaction mixture is filtered over Celite and the filtrate is concentrated in vacuo. The residue is purified by means of flash chromatography (SiO_2 , EA).

Method 2:

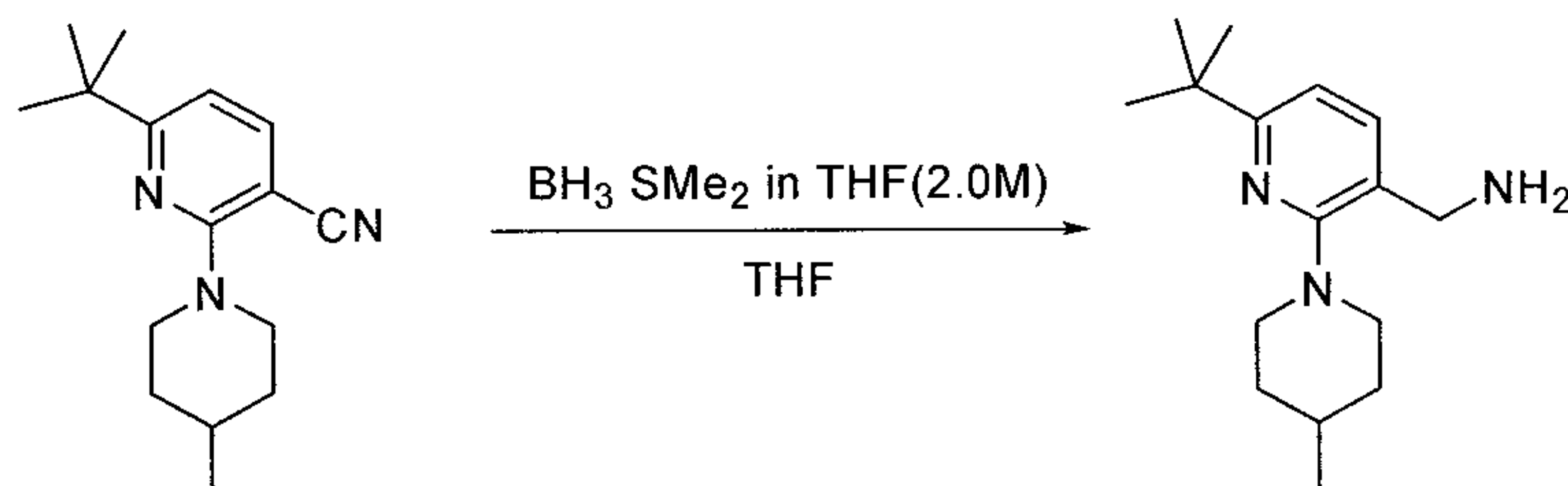
Compounds of the general formula VI-B (2 mmol), in which R^8 , R^{40} , R^{41} , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are dissolved in THF (10 mL, 10 mL), and $\text{BH}_3 \cdot \text{S}(\text{CH}_3)_2$ [2.0 M in THF, 3 mL, 3 equivalents] is added. The reaction mixture is heated under reflux over a period of 8 hours, aq. HCl (2N) is added and the reaction mixture is again heated under reflux for 30 minutes. Aq. sodium hydroxide solution (2N) is added to the reaction mixture, and the mixture is washed with EA. The combined organic phases are washed with sat. aq. NaCl solution and dried over magnesium sulfate. The solvent is removed in vacuo and the residue purified by column chromatography (SiO_2 , various mixtures of dichloromethane and MeOH as mobile solvent).

The following compounds were obtained by method 2.

(6-(Trifluoromethyl)-2-(4-methylpiperidin-1-yl)pyridin-3-yl)methanamine

^1H NMR (300 M Hz, CDCl_3) δ 7.89 (d, 1 H, $J = 7.8$ Hz), 7.33 (d, 1H, $J = 7.8$ Hz), 3.88 (s, 2H), 3.39 (m, 2 H), 2.83 (m, 2 H), 1.75 (m, 2 H), 1.55 (m, 1 H), 1.38 (m, 2 H), 1.00 (d, 3 H, $J = 6.6$ Hz); MS (FAB) m/z 274(M+H)

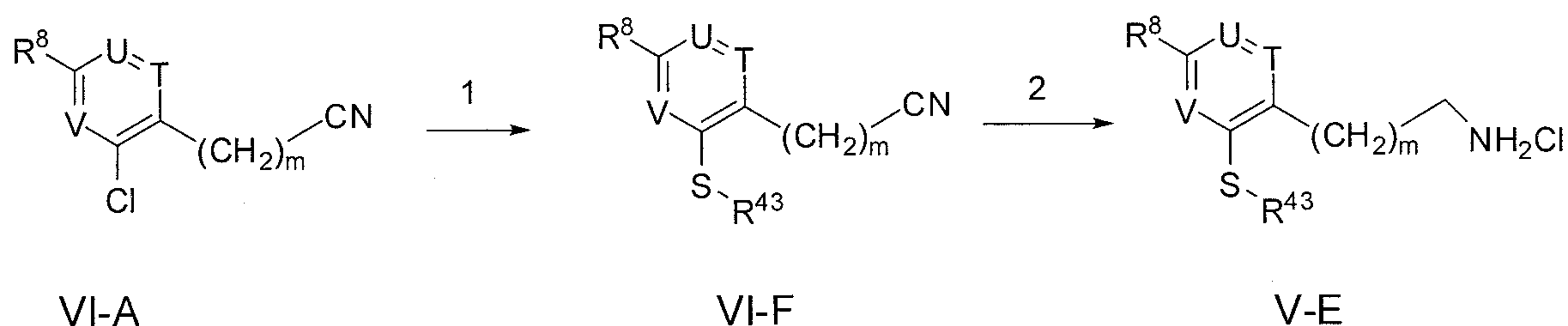
5 **C-(6'-tert-Butyl-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-yl)-methylamine**



^1H -NMR (CDCl_3) δ 7.48 (d, 1H, $J = 7.7$ Hz, Ar), 6.90 (d, 1H, $J = 7.7$ Hz, Ar), 3.82 (s, 2H, CH_2NH_2), 3.38 (m, 2H, piperidine), 2.81 (m, 2H, piperidine), 1.73-1.28 (m, 5H, piperidine), 1.31 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.98 (d, 3H, $J = 6.4$ Hz, CHCH_3)
 10 IR 3363, 2954, 1571, 1451, 1400, 1372, 1234, 960 cm^{-1}

2. General instructions for the preparation of amines of the general formula V-E

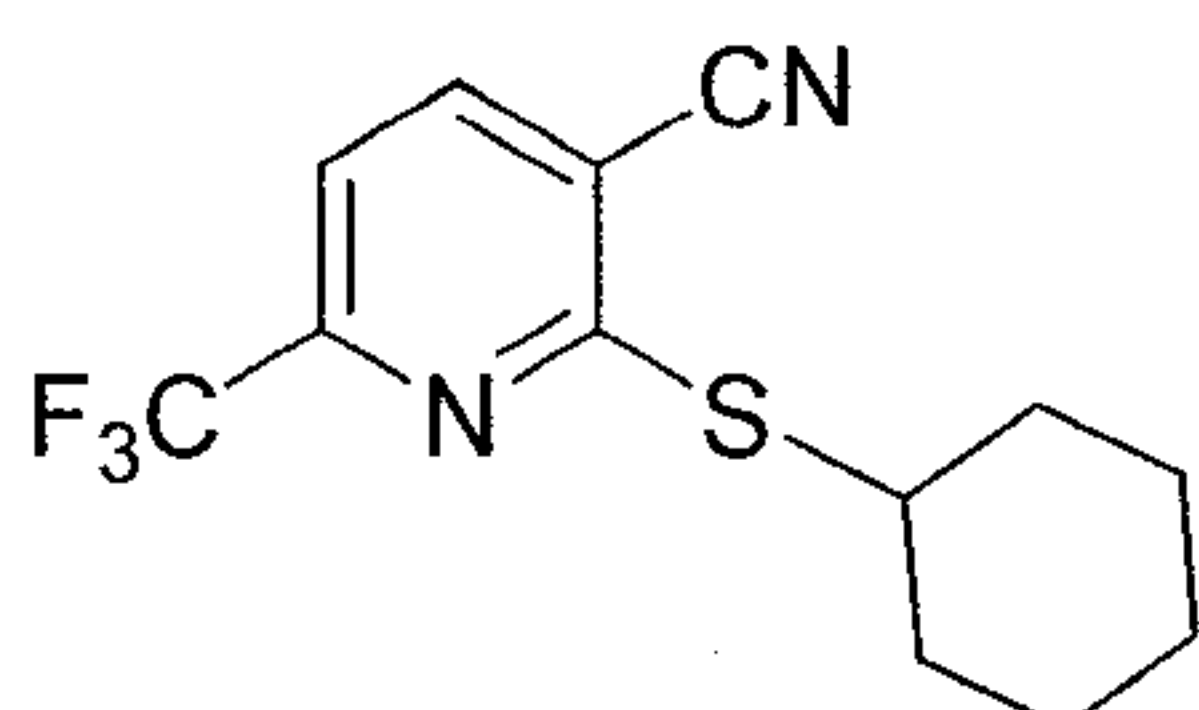
15 The preparation of amines of the general formula V-E is carried out as illustrated in the following scheme 2.



20 Scheme 2.

Step 1:

Synthesis of 2-(cyclohexylthio)-6-(trifluoromethyl)nicotinonitrile



1.3 Equivalents of NaH (4.9 g, 0.124 mol) were dissolved in 50 mL of DMF under a blanket of nitrogen. Following the addition of 1.2 equivalents of cyclohexanethiol (14.2 mL, 0.116 mol), the mixture was stirred at RT over a period of 1.5 h. The resulting suspension was cooled to 10 °C and added dropwise to 1 equivalent of 2-chloro-6-(trifluoromethyl)nicotinonitrile (20 g, 0.096 mol) in 50 mL of DMF and stirred over a period of 2 h at RT. To the reaction mixture there was added sat. aq. NH₄Cl soln. and the mixture was diluted with 1 L of water and extracted with EA (3 x 200 mL) a number of times. The combined organic phases were washed with sat. aq. NaCl solution, dried over MgSO₄ and concentrated in vacuo. Column chromatographic purification (silica gel 100-200 mesh, eluant: 2% EA in hexane) yielded 26 g (93.8%) of product.

¹H NMR (300 M Hz, CDCl₃) δ 7.94 (d, 1 H, J = 7.9 Hz), 7.34 (d, 1 H, J = 7.9 Hz), 4.00 (m, 1 H), 1.90-2.14 (m, 2 H), 1.42-1.88 (m, 8 H)

IR (neat) 2930, 2854, 2232, 1643, 1573, 1447, 1334, 1245, 1186, 1149, 1107, 851 cm⁻¹

MS (FAB) m/z 287 (M+H)

Step 2:

Synthesis of (2-(cyclohexylthio)-6-(trifluoromethyl)-pyridin-3-yl)methanamine dihydrochloride

The nitrile (26 g, 0.091 mol) was dissolved in 600 mL of THF under a blanket of nitrogen and cooled to 5 °C. BH₃-dimethyl sulfide (13.78 g, 0.182 mol) was added dropwise and the mixture was boiled under reflux over a period of 20 h. After cooling to 5 °C, 100 mL of MeOH were added to the reaction batch and the mixture was stirred at RT over a period of 15 minutes. Di-tert-butylidicarbonate (29.7 g, 0.136 mol) was then added and the mixture was stirred at RT for 30 min. Following the removal of the solvent in vacuo, the crude product was purified by column chromatography (silica gel 100-200 mesh, eluant: 10% EA in hexane) and 23.4 g (66%) of product were obtained.

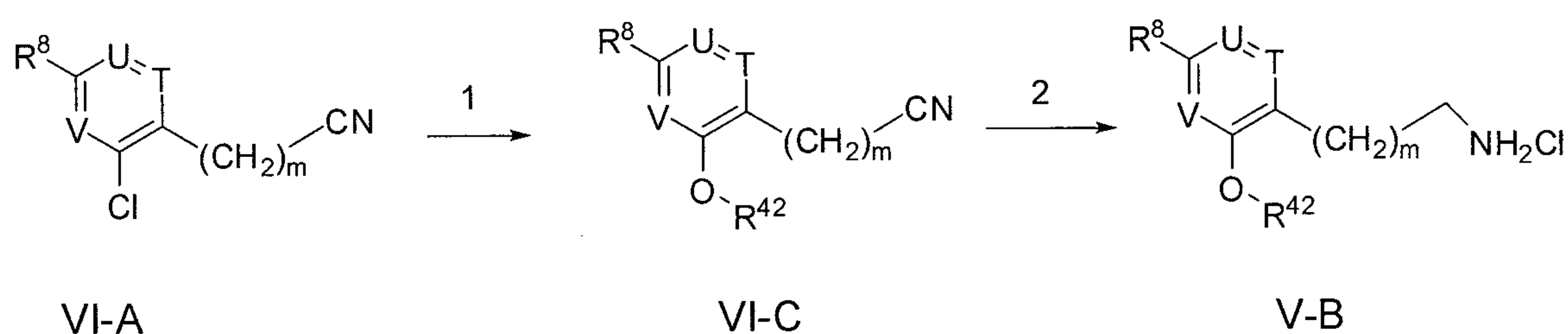
The crude product was dissolved in 120 mL of sat. HCl/dioxane soln., and the solution was stirred at RT over a period of 6 h. Following the removal of the solvent in vacuo, the solid matter was washed with 10% EA in hexane (2 x 100 mL) and isolated by filtration.

Yield: 17 g (88.8%)

^1H NMR (DMSO- d_6 , 400 M Hz): δ 8.8 (s, 2H), 8.05(d, 1H), 7.76 (d, 1H), 4.01 (s, 1H), 3.86-3.93 (m, 1H), 2.02-2.08 (m, 2H), 1.71-1.74 (m, 2H), 1.40-1.60 (m, 6H).

3. General instructions for the preparation of amines of the general formula V-B

The preparation of amines of the general formula V-B is carried out as illustrated in the following scheme 3.



Scheme 3.

Step 1: Preparation of nitriles of the general formula VI-C

Compounds of the general formula VI-A (1 equivalent), in which R^8 , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are stirred with an alcohol of the general formula HO- R^{42} (3.5 equivalents) and DBU [1,8-diaza-bicyclo[5.4.0]undec-7-ene] (3,5 equivalents) in acetonitrile (7 mL per mmol of the compound of formula VI-A) over a period of 12 hours at RT. The reaction mixture is extracted with EA a number of times. The combined organic phases are washed with sat. aq. NaCl soln. and dried over MgSO_4 , and the solvent is removed in vacuo. The residue is purified in each case by column chromatography (SiO_2 , various mixtures of hexane/EA).

Method 2:

Compounds of the general formula VI-C (2 mmol), in which R^8 , R^{42} , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are dissolved in THF (10 mL, 10 mL) and $\text{BH}_3 \cdot \text{S}(\text{CH}_3)_2$ [2.0 M in THF, 3 mL, 3 equivalent] is added. The reaction mixture is heated under reflux over a period of 8 hours, aq. HCl (2N) is added and the reaction mixture is again heated under reflux for 30 minutes. Aq. sodium hydroxide solution (2N) is added to the reaction mixture, and the mixture is washed with EA. The combined organic phases are washed with sat. aq. NaCl

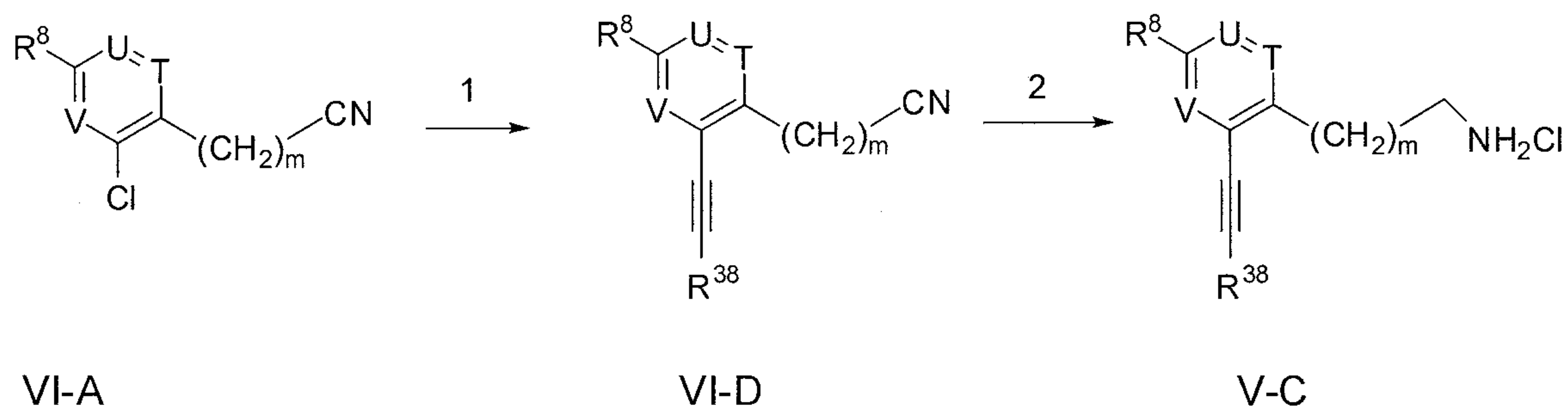
solution and dried over magnesium sulfate. The solvent is removed in vacuo and the residue is purified by column chromatography (SiO_2 , various mixtures of dichloromethane and methanol as mobile solvent).

Method 3:

Compounds of the general formula VI-C (1,5 mmol), in which R^8 , R^{42} , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are dissolved in diethyl ether (3 mL) and a suspension of lithium aluminum hydride (3 mmol) in ether (5 mL) is slowly added dropwise at 0 °C. The reaction mixture is heated under reflux over a period of 4 hours and methanol followed by 1N aq. NaOH solution are slowly added dropwise at 0 °C. The reaction mixture is diluted with methanol and filtered over Celite. The solvent is removed in vacuo and the residue is purified by column chromatography (SiO_2 , various mixtures of dichloromethane and methanol as mobile solvent).

4. General instructions for the preparation of amines of the general formula V-C

The preparation of amines of the general formula V-C is carried out as illustrated in the following scheme 4.



Scheme 4.

Step 1:

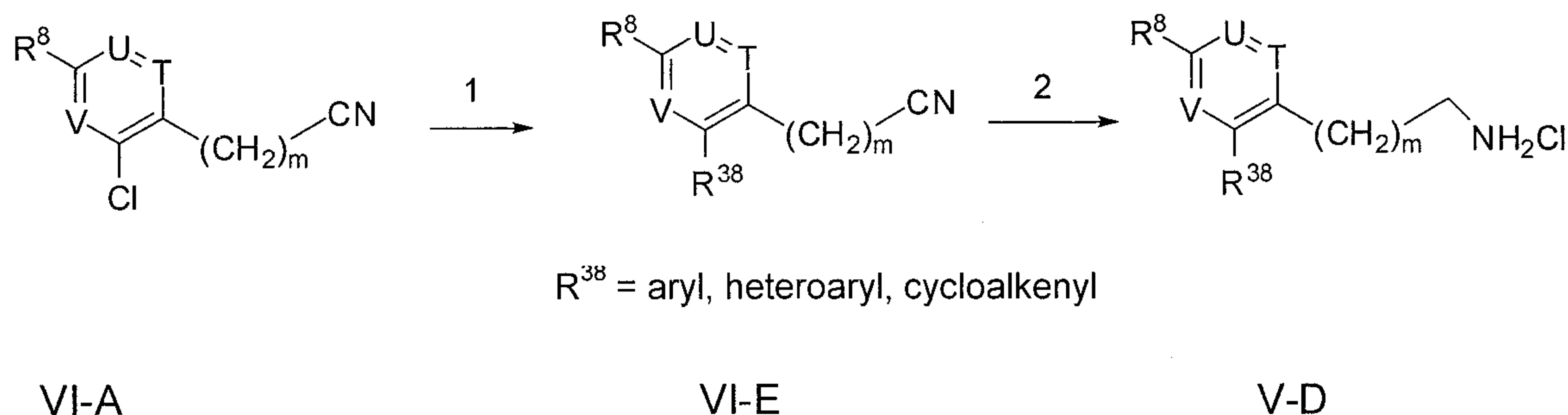
Preparation of nitriles of the general formula VI-D

Compounds of the general formula VI-A (1 equivalent), in which R^8 , U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are dissolved together with bis(triphenylphosphine)palladium dichloride (7 mol%) and copper(I) iodide (14 mol%) in 1-methyl-2-pyrrolidinone (7 mL per mmol of the compound of the general formula VI-A). Following a period of 10 minutes the alkyne of the general formula $\text{HC}\equiv\text{C-R}^{38}$

(3,5 equivalents) and N,N-diisopropylethylamine (2 equivalents) are added, and the reaction mixture is stirred over a period of 12 h at a temperature between 90 and 110 °C. The reaction mixture is filtered over Celite and extracted with EA a number of times. The combined organic phases are washed with sat. aq. NaCl solution, dried over MgSO₄, and the solvent is removed in vacuo. The residue is purified in each case by column chromatography (SiO₂, various mixtures of hexane/EA).

5. General instructions for the preparation of amines of the general formula V-D

The preparation of amines of the general formula V-D is carried out as illustrated in the following scheme 5.



Scheme 5.

Step 1: Preparation of nitriles of the general formula VI-E

Compounds of the general formula VI-A (1 equivalent), in which R⁸, U, T, and V have the aforementioned meanings and m stands for 0, 1, 2, or 3, are stirred with palladium dichloride (5 mol%) and a compound of the general formula R³⁸-B(OH)₂ (2 equivalents), in which R³⁸ stands for aryl, heteroaryl, or cycloalkenyl, in a solvent mixture of toluene/dioxane/2N aq. sodium carbonate solution (20 mL per 1 mmol of compounds of the general formula VI-A). The reaction mixture is heated under reflux over a period of 12 h and filtered over Celite. The combined organic phases are dried over magnesium sulfate, and the solvent is removed in vacuo. The residue is purified by column chromatography (SiO₂, various solvent mixtures of hexane and EA).

Step 2:

Method 1:

Compounds of the general formula VI-E (5 mmol), in which R⁸, R³⁸, U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, palladium-on-charcoal

(10%, 500 mg) and concentrated hydrochloric acid (3 mL) are dissolved in MeOH (30 mL) and exposed to a hydrogen atmosphere over a period of 6 hours at RT. The reaction mixture is filtered over Celite and the filtrate is concentrated in vacuo. The residue is purified by means of flash chromatography (SiO₂, EA).

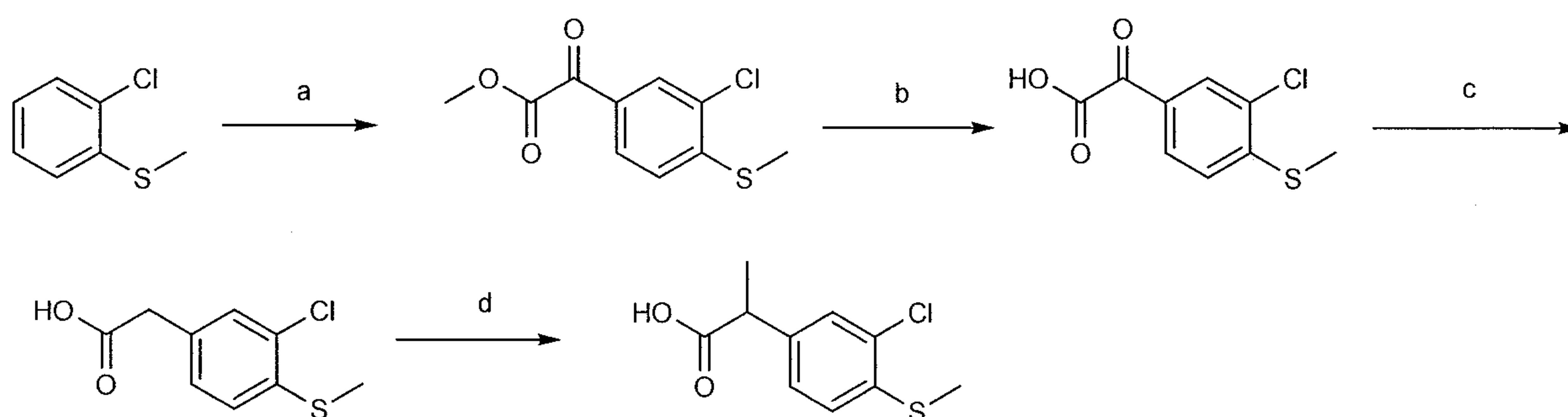
Method 2:

Compounds of the general formula VI-E (2 mmol), in which R⁸, R³⁸, U, T, and V have the meanings stated above and m stands for 0, 1, 2, or 3, are dissolved in THF (10 mL, 10 mL), and BH₃•S(CH₃)₂ [2.0 M in THF, 3 mL, 3 equivalent] is added. The reaction mixture is heated under reflux over a period of 8 hours, aq. HCl (2N) is added and the reaction mixture is again heated under reflux for 30 minutes. Aq. sodium hydroxide solution (2N) is added to the reaction mixture, and the mixture is washed with EA. The combined organic phases are washed with sat. aq. NaCl solution and dried over magnesium sulfate. The solvent is removed in vacuo and the residue is purified by column chromatography (SiO₂, various mixtures of dichloromethane and methanol as mobile solvent).

6. Preparation of specific acids

Preparation of 2-(3-halogenated-4-(methylthio)phenyl)propanoic acids

(cf. Examples 28, 29)



a. Methyl 2-chlor-2-oxoacetat, AlCl₃, CHCl₃, 0 - 25 °C; b. aq. NaOH, Toluene, 60 °C, 1.5 h; c. Hydrazinhydrat, KOH, - 50 - 100 °C; d. CH₃I, Hexan, LDA, TMEDA, -78 °C, 3 h

[Key: Methyl 2-chlor-2-oxoacetat = Methyl 2-chloro-2-oxoacetate; Toluene = toluene; Hydrazinhydrat = Hydrazine-hydrate; Hexan = hexane]

Substituted methylthiophenylpropanoic acids can be prepared as described in US2003/225283. For this purpose, a solution of AlCl₃ (54.9 g, 412 mmol) in chloroform (180 mL) is cooled under an argon atmosphere to 0 °C and a solution of

methyl-2-chloro-2-oxoacetate (24.3 mL, 264 mmol) in chloroform (180 mL) is added in drops. After this reaction mixture has been stirred for 30 min at 0 °C, a solution of 2-chlorothioanisol (39.4 g, 247 mmol) in chloroform (180 mL) is added in drops. The red-coloured reaction mixture is slowly heated to room temperature and stirred for a further 4 h. The reaction mixture is then slowly stirred in ice water (700 mL) and the obtained yellow mixture is stirred for 15 min and filtered to remove the aluminium salts. The filtrate is extracted with dichloromethane (3 x 50 mL) and the combined organic phases are washed with sat. aq. sodium bicarbonate solution (1 x 50 mL). After drying of the organic phase over MgSO₄ and removal of the solvent in vacuo, the (3-chloro-4-methylsulfanyl-phenyl)-oxo-methyl acetate as oil (36.4 g, 60%) is obtained (a).

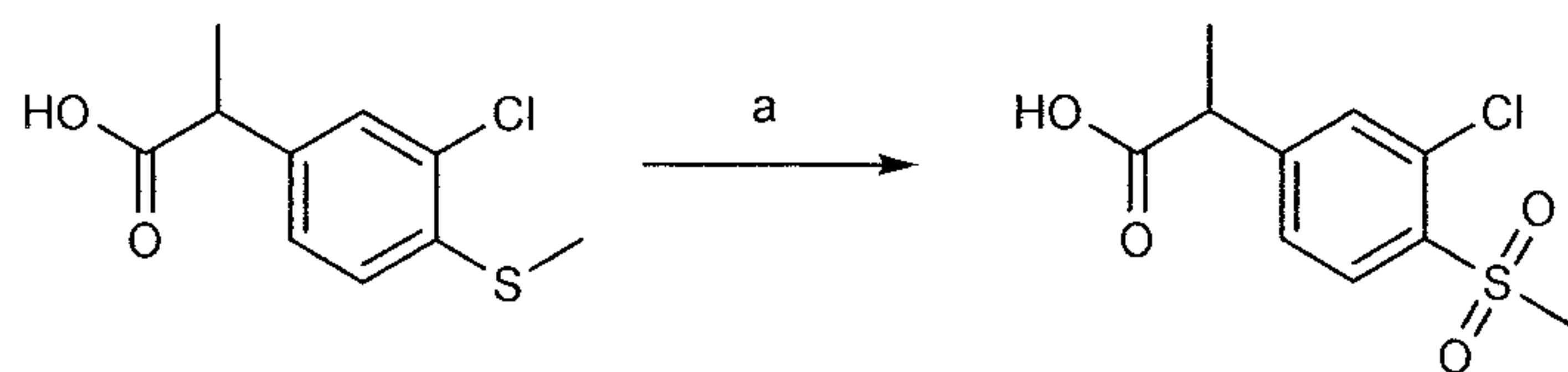
A solution of this ester (61.7 g, 252 mmol) in toluol (120 mL) is heated to 50 °C. While ensuring that the temperature of the reaction mixture does not exceed 60 °C, a 3 M NaOH solution (105 mL, 313 mmol) is now added in drops and subsequently stirred for 1.5 h at 50 °C. After removal of the heat source, conc. HCl (10.6 mL, 290 mmol) is added to the warm solution in drops and once the mixture is cooled to room temperature, it is let to stir for a further 16 h. The resultant precipitate is filtered off, washed with water (50 mL) and toluol (50 mL) and dried. The (3-chloro-4-methylsulfanyl-phenyl)-oxo-acetic acid accumulates as a white solid (57.2 g, 98%) (b).

Hydrazine-hydrate (8.5 mL, 273 mmol) is provided in a reaction flask with a mechanical stirrer. After cooling to -50 °C, in one portion, the oxo-acetic acid (12.6 g, 54.6 mmol) is added, which leads to an increase in temperature. The resultant milky mixture is heated to 80 °C and, after removal of the heat source, KOH (2.09 g, 31.7 mmol) is added in one portion. This leads to an exothermal reaction. After cooling to 80 °C, a further portion of KOH (2.09 g, 31.7 mmol) is added and in turn cooled to 80 °C. This procedure is now repeated two further times. After addition of the fourth portion of KOH, the reaction mixture is boiled for 16 h at 100 °C. After cooling of the homogeneous reaction mixture to room temperature, it is diluted with water (12 mL) and, following transfer to a separating funnel, further water (12 mL) and diethylether (40 mL) are added. After phase separation, the organic phase is extracted with water (2 x 15 mL). Heptane (20 mL) is added to the combined aqueous phases and the mixture is vigorously stirred. While keeping the temperature below 50 °C by means of an ice bath, conc. HCl (26 mL) is added in drops over a period of 30 min and the

resultant suspension is stirred for 3 h at room temperature. The resultant precipitate is filtered off and consecutively washed with 1 N aq. HCl solution (2 x 6 mL), heptane (1 x 12 mL) and heptane/diethyl ether (15 mL, 4:1). After drying, the (3-chloro-4-methylsulfanyl-phenyl)-acetic acid (10.48 g, 89%) is obtained as a cream-coloured solid (c).

This (3-chloro-4-methylsulfanyl-phenyl)-acetic acid is now alkylated in alpha position in an analogous manner to Vazquez et al. Eur. J. Med. Chem. Chim. Ther. (1997), 32, 6, 529-53. A solution of the aryl acetic acid (1.05 mmol) in dry THF (3 mL) is cooled to -78 °C and stirred under an argon atmosphere. For this purpose, a 2 M solution of LDA in hexane (1.6 mL, 3.2 mmol) and TMEDA (0.3 mL, 1.9 mmol) is added in drops over a period of 15 min. After 3 hours of slow stirring at -78 °C, methyl iodide (0.17 mL, 2.7 mmol) is added slowly while stirring. After 16 hours of stirring at room temperature, the reaction mixture is neutralized with sat. aq. NH₄Cl solution (10 mL) and stirred for 1 h at room temperature. After separation of the organic phase, the aqueous, alkaline phase is acidified with 5 N HCl and the product extracted with ether (3 x 20 mL). The combined organic phases are dried over Na₂SO₄ and the solvent is removed in vacuo. Purification by means of column chromatography (hexane/ethyl acetate 8:2) produces the desired methylthiophenylpropanoic acid (d).

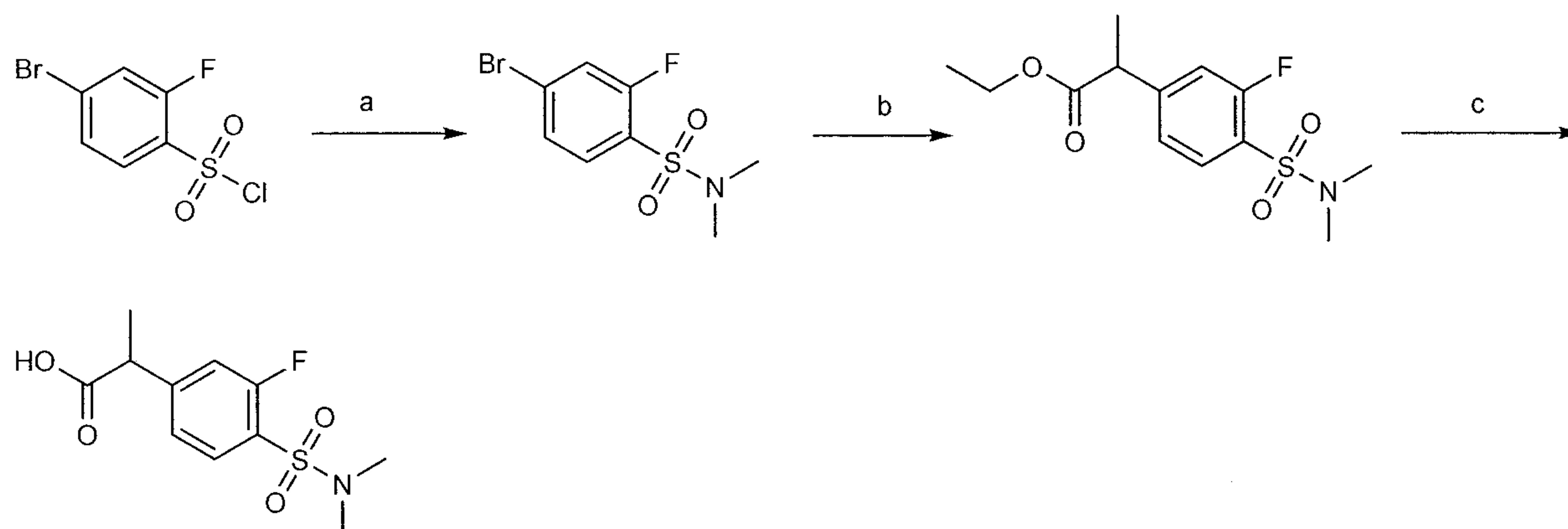
Preparation of 2-(3-halogenated-4-(methylsulfonyl)phenyl)propanoic acids (cf. Examples 29, 31)



a. HCOOH, H₂O₂, 0 - 25 °C, 15 h

In an analogous manner to the method described in US2003/225283, the methylthiophenylpropanoic acids are reacted to yield the corresponding methylsulfonylphenylpropanoic acids. In this process, a solution of methylthiophenylpropanoic acid (0.16 mmol) is dissolved in formic acid (0.19 mL, 4.8 mmol) and cooled to 0 °C. After addition of 30% strength aq. hydrogen peroxide solution (0.10 mL, 0.8 mmol), stirring is performed at 0 °C for 30 min and the reaction is then quenched with 10% strength aq. sodium bisulphite solution. The reaction mixture is diluted with water (5 mL) and extracted ethyl acetate (2 x 5 mL). The combined organic phases are dried over Mg₂SO₄ and the solvent is removed in vacuo. The residue obtained is dissolved in methanol (1 mL) and a solution of KMNO₄ (0.028 g, 0.176 mmol) in water (0.5 mL) is added by drops. The dark brown solution is now stirred for 30 min at room temperature and then diluted with methanol (10 mL). After filtration of the solution, the filtrate is concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate 1:4) (a).

Preparation of 2-(4-(N-substituted sulfamoyl)-3-fluorophenyl)propanoic acids (cf. Ex. 32)



a. HN(CH₃)₂, Pyridin, CH₂Cl₂, 2 h, rt; b. Ethylchloropropionat, NBu₄BF₄, NiBr₂bipy, DMF, rt; c. LiOH, MeOH, 65 °C, 4 h

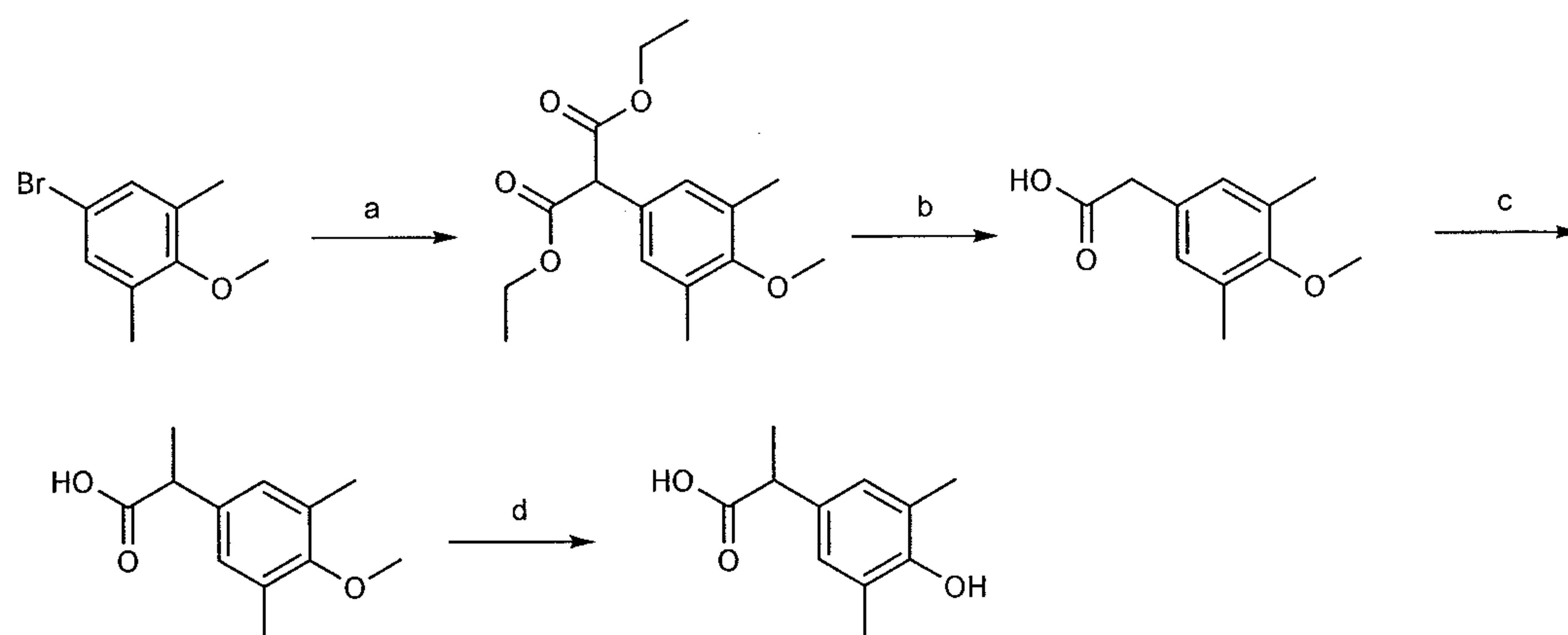
[Key: Pyridin = pyridine; Ethylchloropropionat = ethylchloropropionate]

In an analogous manner to Greig, IR et al. *J. Med. Chem.* (2006), 49, 4787-7492, the bromo-fluorobenzyl-sulfonylchloride (5 mmol) is dissolved with dimethylamine (5 mmol) in dichloromethane (15 mL). Pyridine (5 mmol) is added to this mixture and the mixture is stirred for 2 h at room temperature. After addition of water (15 mL), the organic phase is separated and the aqueous phase extracted with ethyl acetate (15 mL). The combined organic phases are dried over Na₂SO₄, the solvent is removed in vacuo and the residue is purified by column chromatography (a).

As described in Durandetti M. et al., *Tetrahedron* (2007), 63, 1146-1153, the sulfamoyl-aryl bromide is converted with ethylchloropropionate into sulfamoyl-arylpropanoic acid ester. Together with ethylchloropropionate (1.6 mL, 13 mmol), sulfamoyl-aryl bromide (10 mmol) is stirred under an argon atmosphere at room temperature in 15 ml DMF. For the purpose of activation, (1.1 g, 20 mmol) Mn, followed by 2,2'-bipyridine)nickel-(II)-dibromide (0.26 g, 0.7 mmol) and TFA (20 mL) are then added. The reaction mixture is stirred for 1.5 h at 50 °C. After cooling of the reaction mixture, hydrolysis is performed with 25 mL 1 N HCl, the mixture is extracted 3 x with 25 mL diethyl ether, the combined organic phases are washed with 25 mL water and 25 mL sat. NaCl solution, dried over MgSO₄ and concentrated in vacuo. The resultant precipitate is removed by suction, washed with diethyl ether and purified by means of column chromatography (b).

The propionate (0.81 mmol) is then dissolved in a mixture of THF (1.6 mL, 20 mmol) and water (0.8 mL, 45 mmol). After addition of LiOH (0.058 g, 2.43 mmol), the reaction mixture is refluxed overnight. For the purpose of processing, 25 mL water and 25 mL diethyl ether are added to the mixture and the resultant phases are separated. The aqueous phase is acidified with HCl and extracted 3x with in each case 25 mL dichloromethane. After combination of the organic phases, drying over MgSO₄ and concentration in vacuo, the *N*-substituted sulfamoyl-fluorophenylpropanoic acid can be obtained.

Preparation of 2-(4-methoxy- and hydroxy-3,5-dimethylphenyl)propanoic acids
(cf. Examples 35-38)



a. Diethylmalonat, NaH, CuBr, Dioxan, 100 °C, 16 h; b. NaOH/THF:H₂O, reflux, 3 h; c. CH₃I, Hexan, LDA, TMEDA, -78 °C, 3 h; d. HBr, AcOH

[Key: Diethylmalonat = diethyl malonate; Dioxan = dioxane; Hexan = hexane]

In an analogous manner to the method described in WO2006/078834, on the basis of aryl bromides, phenylpropanoic acids can be obtained by reaction with diethylmalonate. For this purpose, in the first step, NaH (60%, 1.45 g, 36.2 mmol) is added to a solution of aryl bromide (16.5 mmol), CuBr (4.72 g, 32.9 mmol) and diethyl malonate (5 mL, 32.9 mmol) in 1,4-dioxane (20 mL) at room temperature while stirring slowly and stirred for 16 h at 100 °C. After filtration, the filtrate is concentrated in vacuo and purified by means of column chromatography (hexane/ethyl acetate 4:1) (a).

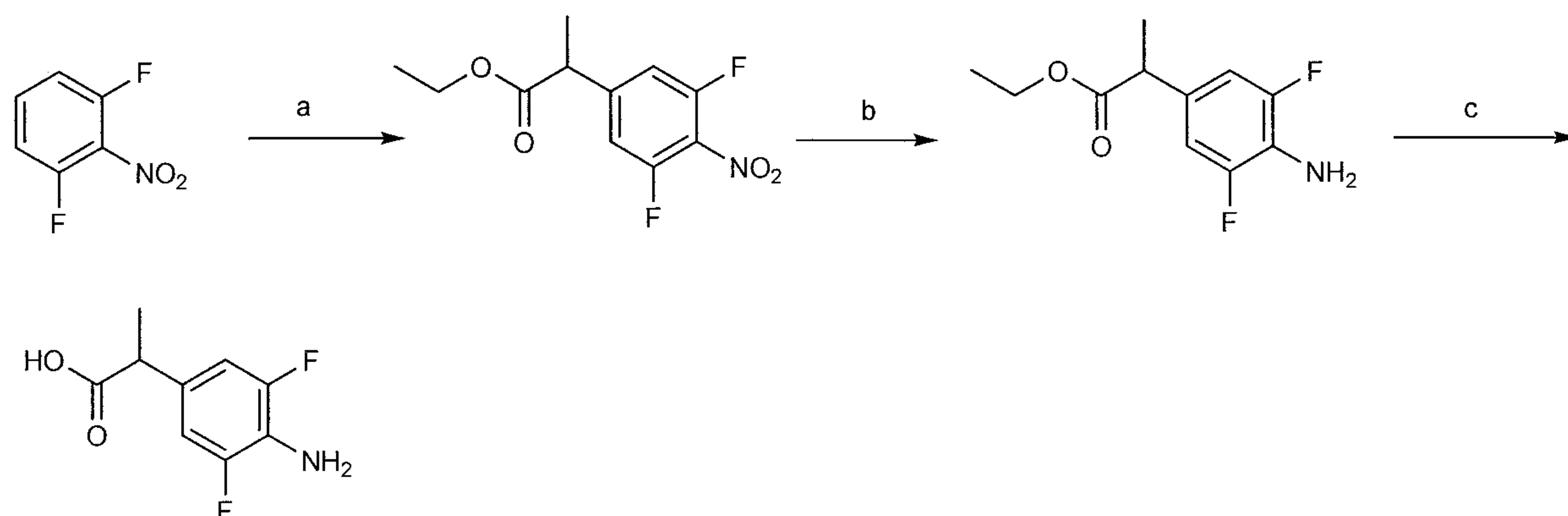
The obtained phenylmalonic acid diethyl ester (21 mmol) is now dissolved in 2 N NaOH / THF:H₂O (1:1) (20 mL) and refluxed for 3 h. After acidification of the reaction mixture to pH 1 with conc HCl, stirring is carried out for a further hour at room temperature. The solution is then adjusted with 1 N NaOH to pH 13 and extracted with diethyl ether. The aqueous phase is adjusted with 1 N HCl to pH 5 and extracted with ethyl acetate (3 x). The combined organic phases are washed with sat. NaCl solution, dried over Na₂SO₄ and, after filtration, the solvent is removed in vacuo (b). This phenylacetic acid is now alkylated in an analogous manner to Vazquez et al. *Eur. J. Med. Chem. Chim. Ther.* (1997), 32, 6, 529-53 in alpha position. A solution of arylacetic acid (1.05 mmol) in dry THF (3 mL) is cooled under an argon atmosphere to -78 °C and stirred. For this purpose, a 2 M solution of LDA in hexane (1.6 mL, 3.2 mmol) and TMEDA (0.3 mL, 1.9 mmol) is added in drops over a period of 15 min. After 3 hours of slow stirring at -78 °C, methyl iodide (0.17 mL, 2.7 mmol) is added

slowly while stirring. After 16 hours of stirring at room temperature, the reaction mixture is neutralized with sat. aq. NH_4Cl solution (10 mL) and stirred for 1 h at room temperature. After separation of the organic phase, the aqueous, alkaline phase is acidified with 5 N HCl and the product is extracted with ether (3 x 20 mL). The combined organic phases are dried over Na_2SO_4 and the solvent is removed in vacuo. Purification by means of column chromatography (hexane/ethyl acetate 8:2) produces the desired substituted phenylmethoxy-propanoic acid (c).

According to a method known to the person skilled in the art, the methoxy ether is split by means of HBr in glacial acetic acid and the corresponding phenylhydroxy-propanoic acid is obtained (d).

Preparation of 2-(4-amino-3,5-difluorophenyl)propanoic acid

(cf. Ex. 26)



a. Ethylchlorpropionat, KOtBu, DMF, - 40 °C, 1 h; b. H_2 , Pd(C); c. LiOH, THF/H₂O, reflux, 16 h
[Key: Ethylchlorpropionat = Ethylchloropropionate]

KOtBu (3.57 g, 31.85 mmol) was dissolved in DMF (30 mL) and cooled to -45 °C. A mixture of ethyl-2-chloropropionate (2 mL, 15.9 mmol) and 2,6-difluoronitrobenzene (2.5 g, 15.7 mmol) were added slowly in drops to the solution kept at -40 °C and stirred for 1 h after addition. For the purpose of processing, the reaction mixture was adjusted with 16% strength HCl to pH 4 and diluted with water (150 mL). The mixture was extracted with ethyl acetate (3 x 50 mL), the combined organic phases washed with water (50 mL) and sat. NaCl solution (2 x 50 mL) and dried over MgSO_4 . After removal of the solvent in vacuo, the product was obtained as an oil (4.12 g, 99%) (a). The difluoronitropropanoate (2.59 g, 10 mmol) was dissolved in EtOH/acetic acid ester (200 mL, 1 : 1) and hydrated in the H cube (1 bar, 25 °C, 1 mL/min, 0.25 mol/L).

After removal of the solvent in vacuo, the difluoroaminopropionate could be obtained as an oil (2.27 g, 99%) (b).

The raw product of the hydrogenation (1 g, 4.36 mmol) was dissolved in THF/water (10 mL, 2 : 1), LiOH (0.312 g, 13.1 mmol) added and refluxed for 16 h.

- 5 Water (50 mL) and diethyl ether (25 mL) were added to the reaction mixture. After phase separation, the aqueous phase was acidified with HCl to pH 2 and extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried over MgSO₄ and the solvent removed in vacuo. The product was obtained as a white solid (0.72 g, 81%) (c).

10

7. General instructions for the reaction of amines of the general formulas V or X with carboxylic acids of the general formula VII

Method A:

- 15 The acid of the general formula VII (1 equivalent), the amine of the general formulas V or X (1.2 equivalents) and EDCI (1.2 equivalents) are stirred in DMF (10 mmol of acid in 20 mL) over a period of 12 hours at RT, and water is then added. The reaction mixture is extracted with EA a number of times, the aqueous phase is saturated with NaCl and then again extracted with EA. The combined organic phases are washed
20 with 1N hydrochloric acid and sat. aq. NaCl soln., dried over MgSO₄, and the solvent is removed in vacuo. The residue is purified by means of flash chromatography (SiO₂, EA/hexane 1:2).

Method B:

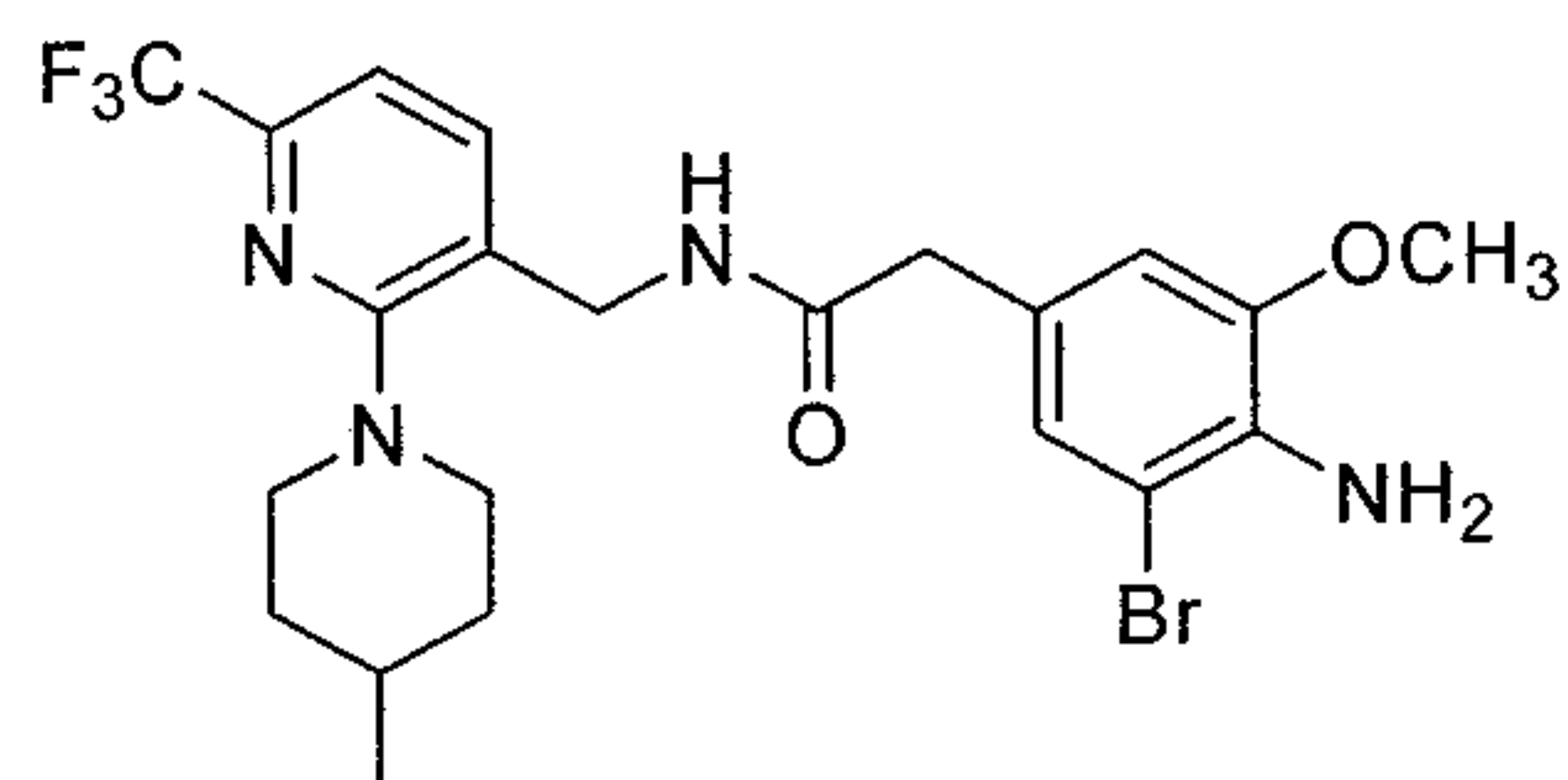
- 25 The acid of the general formula VII (1 equivalent) and the amine of the general formula V or X (1.1 equivalents) are dissolved in DCM (1 mmol acid in 6 mL), and to the solution EDCI (1.5 equivalents), HOBt (1.4 equivalents) and triethylamine (3 equivalents) are added at 0 °C. The reaction mixture is stirred at RT for a period of 20 h and purified by column chromatography (2:1 mixture of n-hexane/AE).

30

The following exemplary compounds were obtained in accordance with method B above.

Exemplary Compound 3:

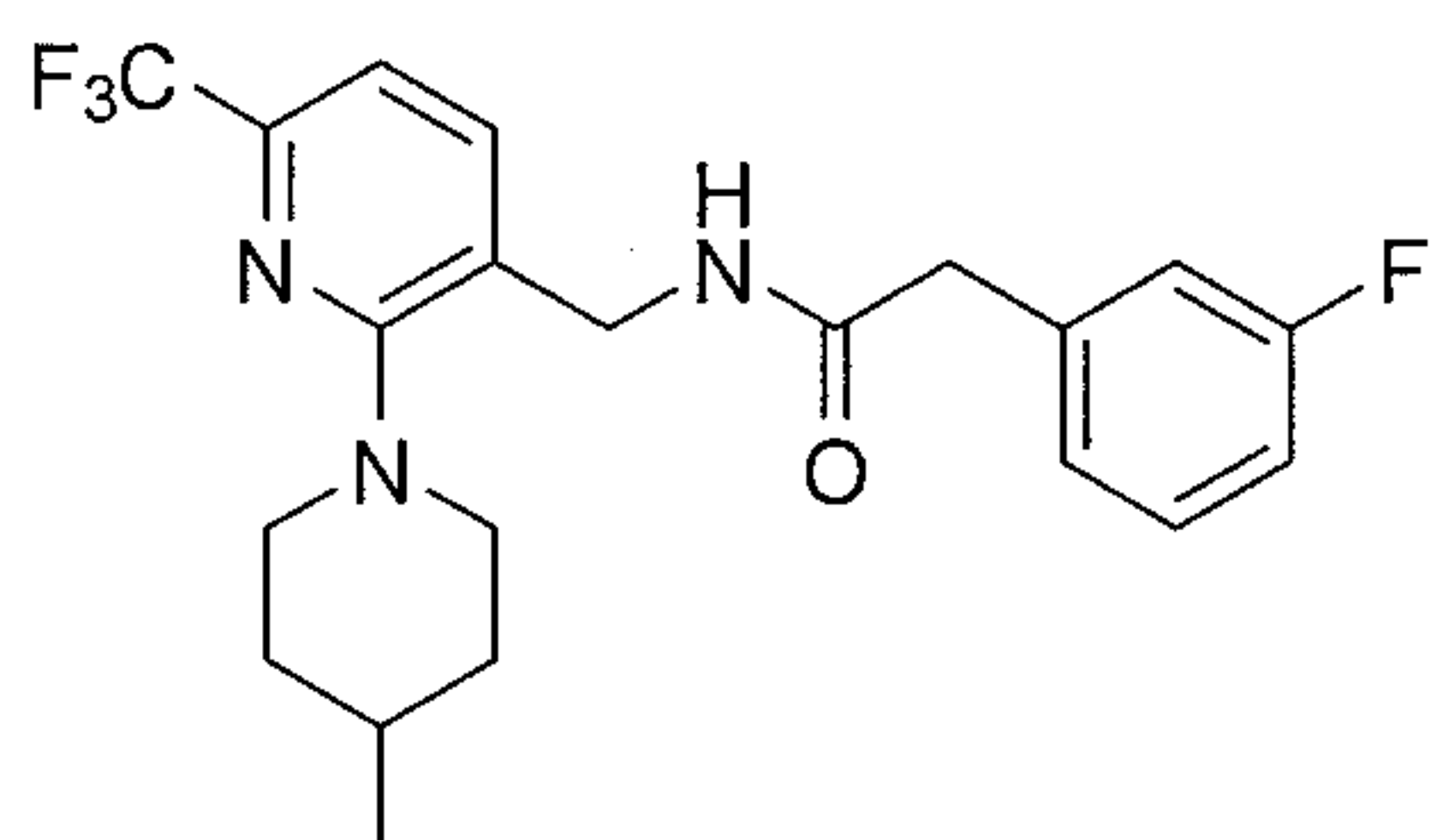
2-(4-Amino-3-bromo-5-methoxy-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



$^1\text{H-NMR}$ (CDCl_3) δ 7.52 (d, 1H, $J = 7.5$ Hz), 7.21 (d, 1H, $J = 7.5$ Hz), 6.93 (d, 1H, $J = 1.4$ Hz), 6.57 (d, 1H), 6.24 (bt, NH), 4.47 (d, 2H), 4.22 (s, 2H), 3.80 (s, 3H), 3.51 (s, 2H), 3.30-3.26 (m, 2H), 1.70-1.48 (m, 3H), 1.21-1.09 (m, 2H), 0.95 (d, 3H, $J = 6.4$ Hz)
 IR 3298, 2924, 1649, 1575, 1500, 1460, 1420, 1338, 1135, 1047 cm^{-1}
 Mass (FAB) m/z 515 and 517 $[\text{M}+\text{H}]^+$ (Base), 537 and 539 $[\text{M}+\text{Na}]^+$

Exemplary Compound 4:

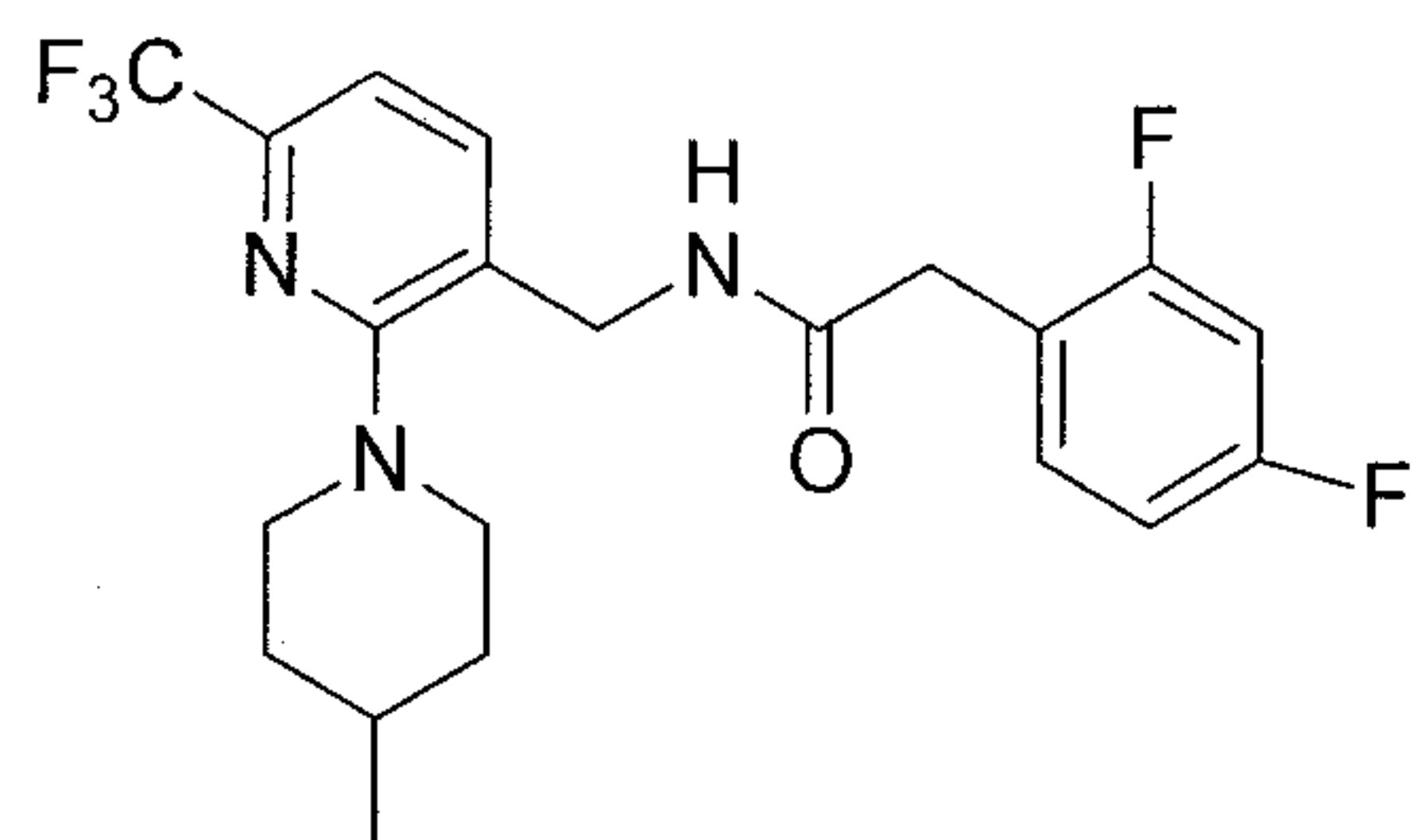
2-(3-Fluorophenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



IR (KBr) 3272, 2923, 1648, 1592, 1552, 1455, 1421, 1374, 1337, 1246, 1138, 958, 835, 774 cm^{-1}
 MS (FAB) m/z 410 (M+H)

Exemplary Compound 5:

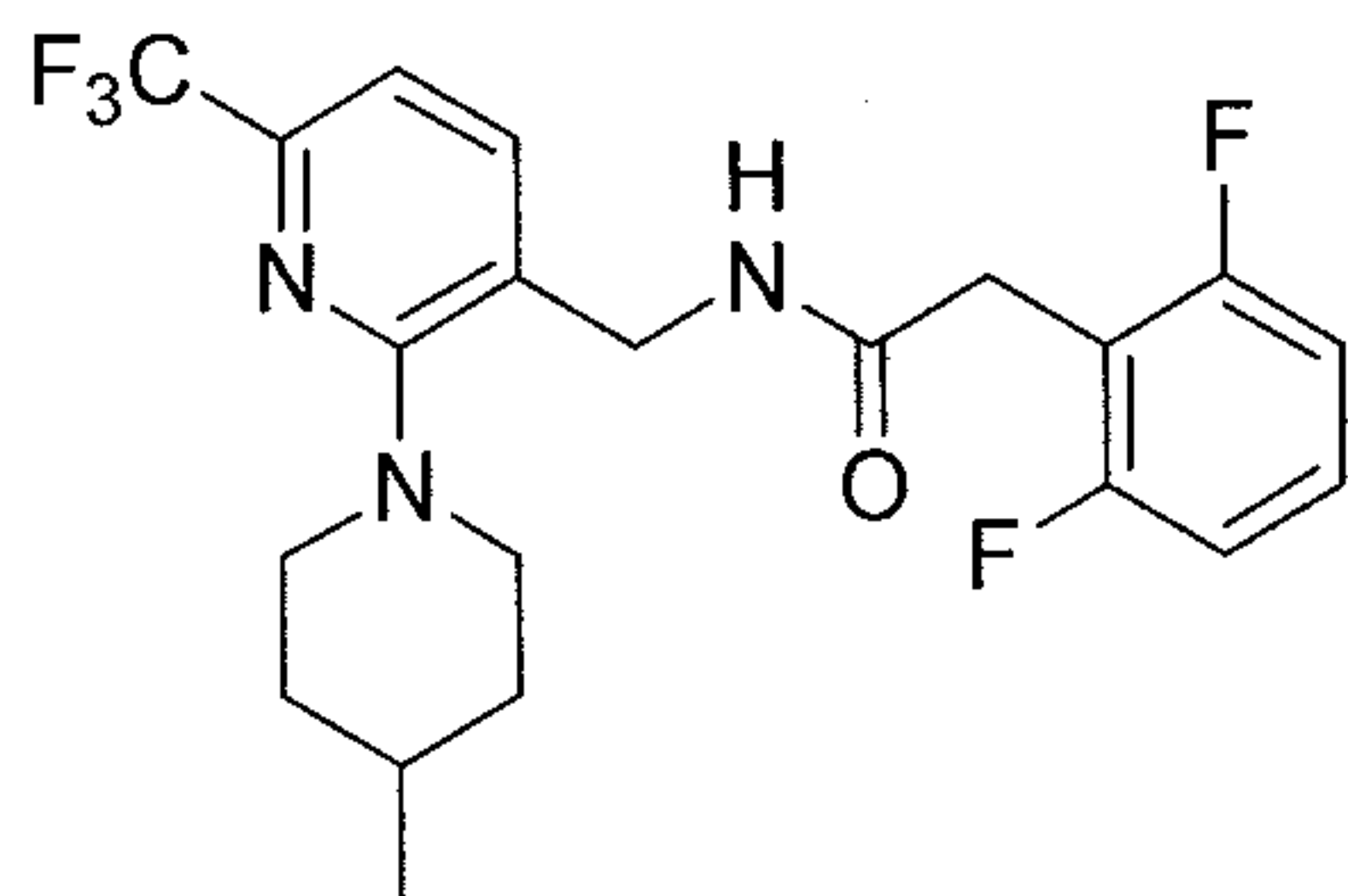
2-(2,4-Difluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



IR (KBr) 3270, 2921, 1647, 1558, 1507, 1424, 1330, 1242, 1134, 966, 851 cm^{-1}
 MS (FAB) m/z 428 (M+H)

Exemplary Compound 6:

2-(2,6-Difluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide

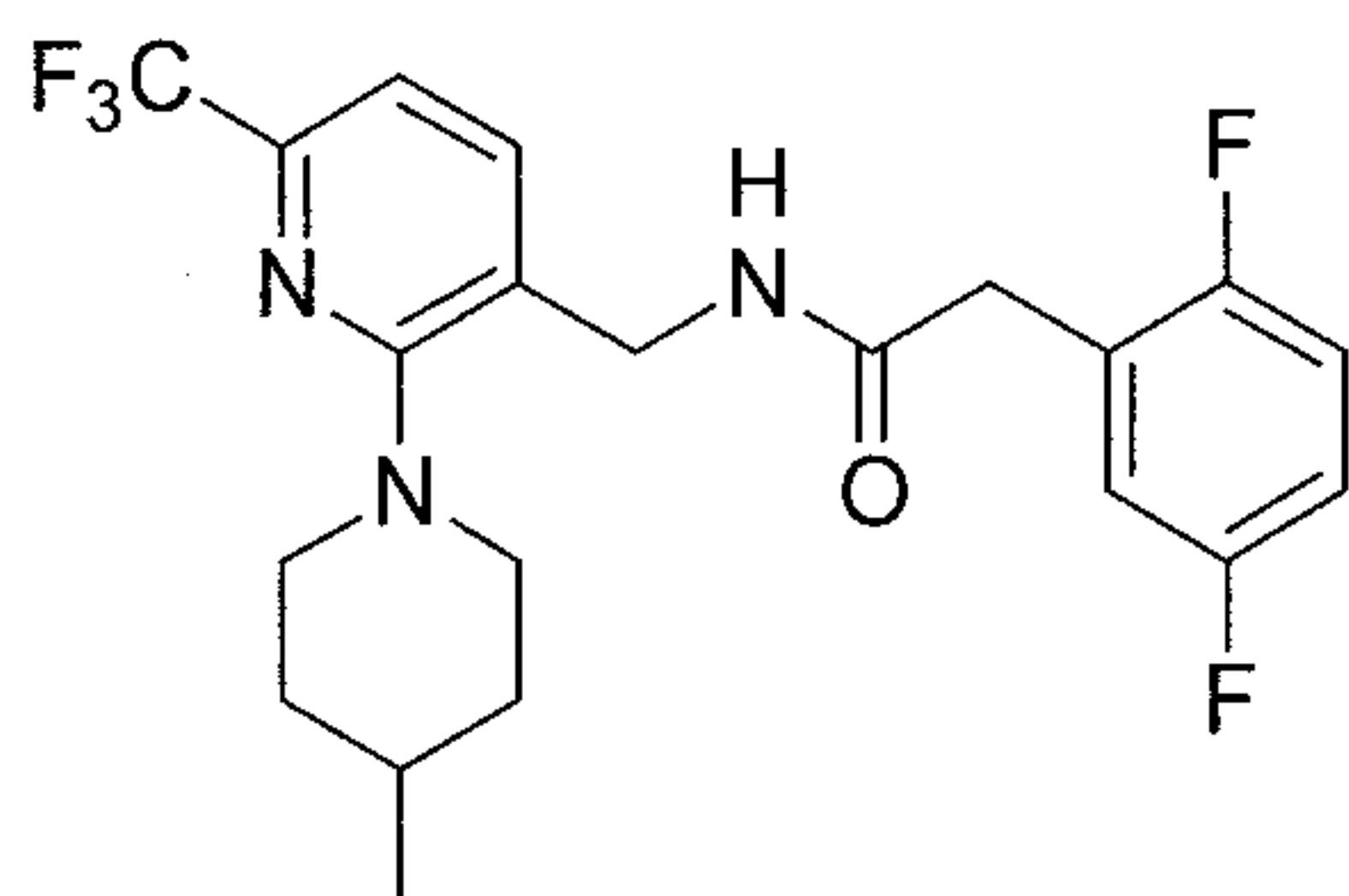


5 IR (KBr) 3292, 2924, 1656, 1593, 1553, 1468, 1419, 1337, 1238, 1178, 1135, 1017, 945, 834, 784 cm^{-1}

MS (FAB) m/z 428 (M+H)

Exemplary Compound 7:

10 **2-(2,5-Difluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide**



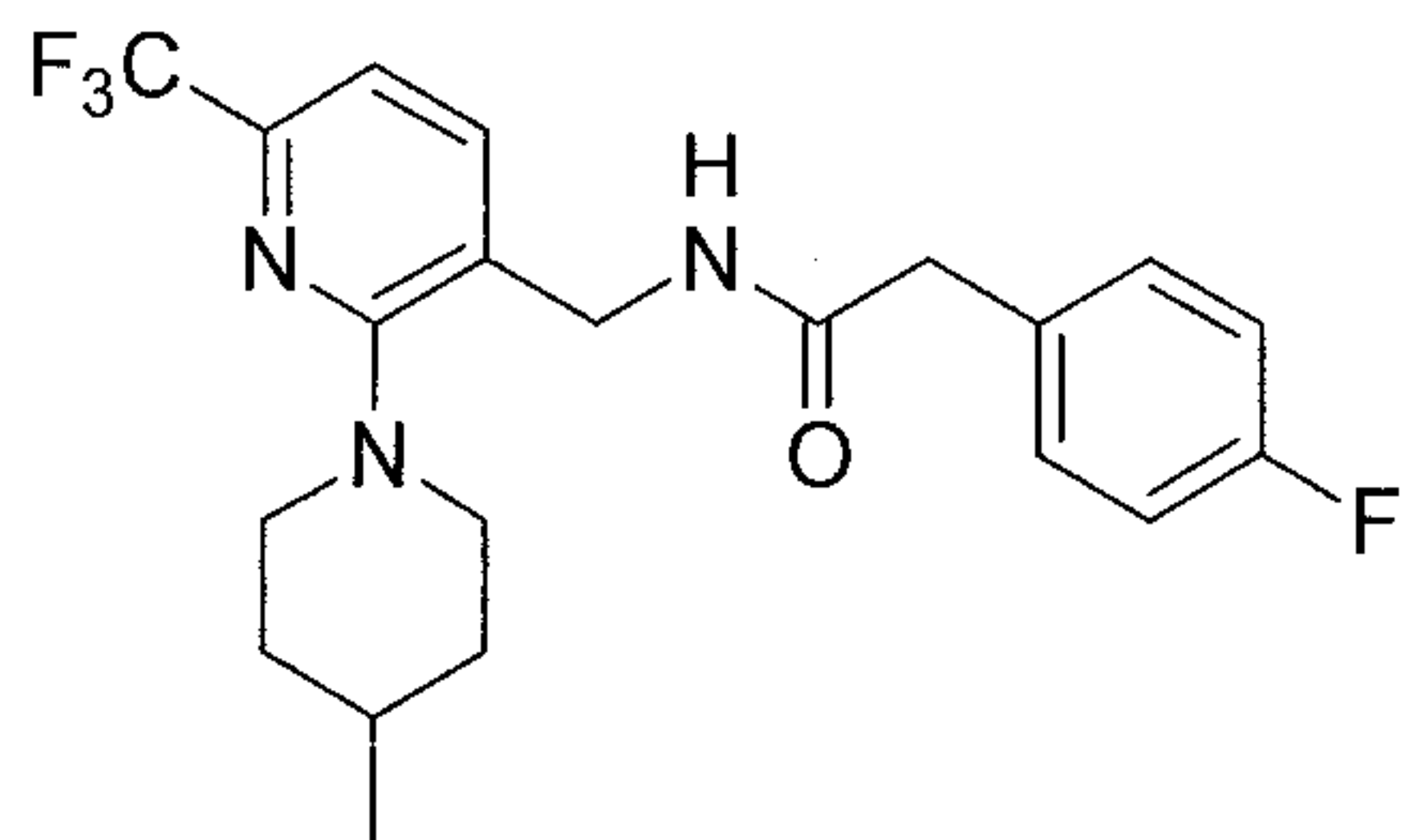
IR (KBr) 3271, 2922, 1644, 1593, 1555, 1497, 1424, 1329, 1137, 960, 833, 756 cm^{-1}

MS (FAB) m/z 428 (M+H)

15

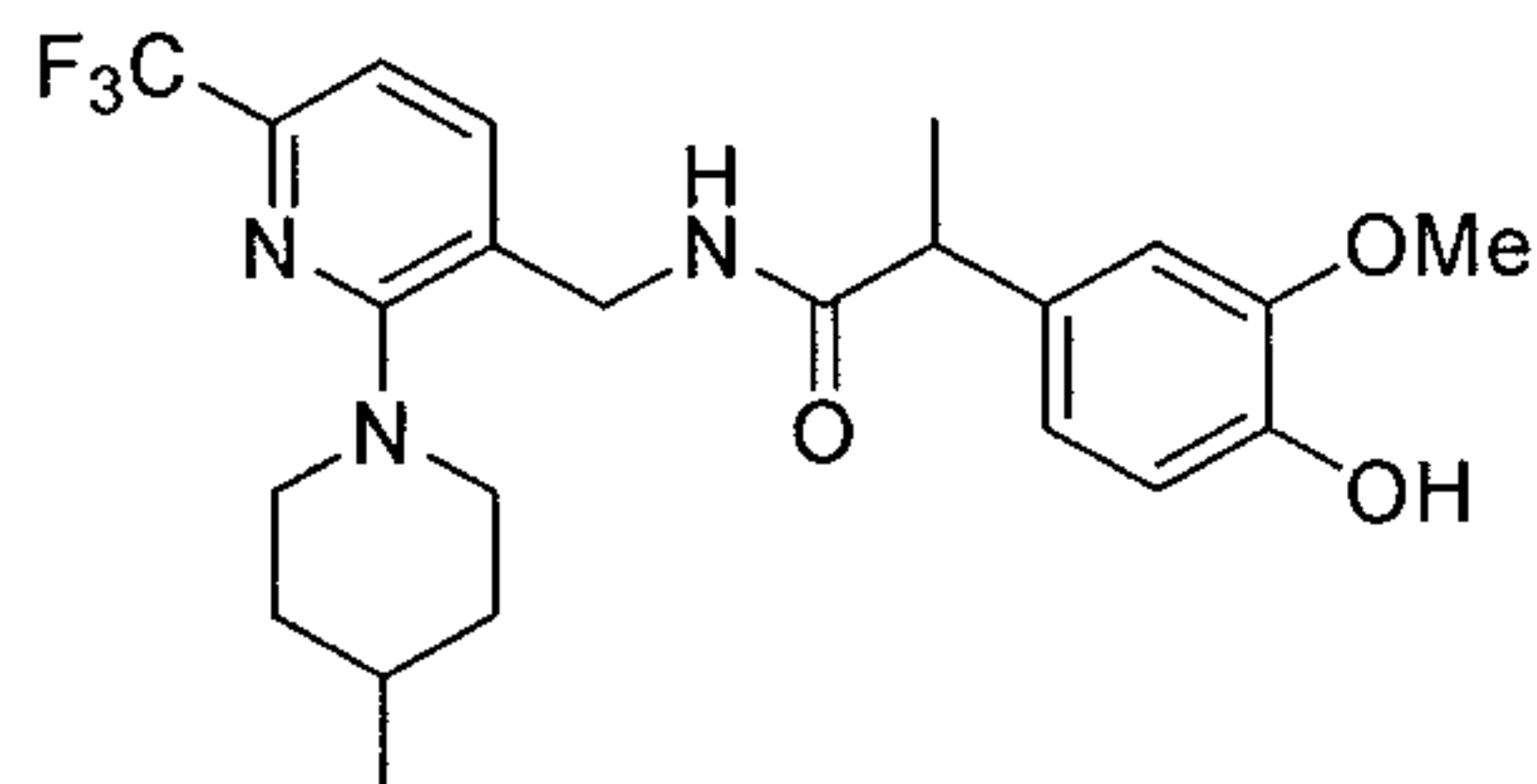
Exemplary Compound 8:

2-(4-Fluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



20 IR (KBr) 3255, 2920, 1646, 1595, 1558, 1509, 1424, 1330, 1229, 1132, 1043, 960, 828, 755 cm^{-1}

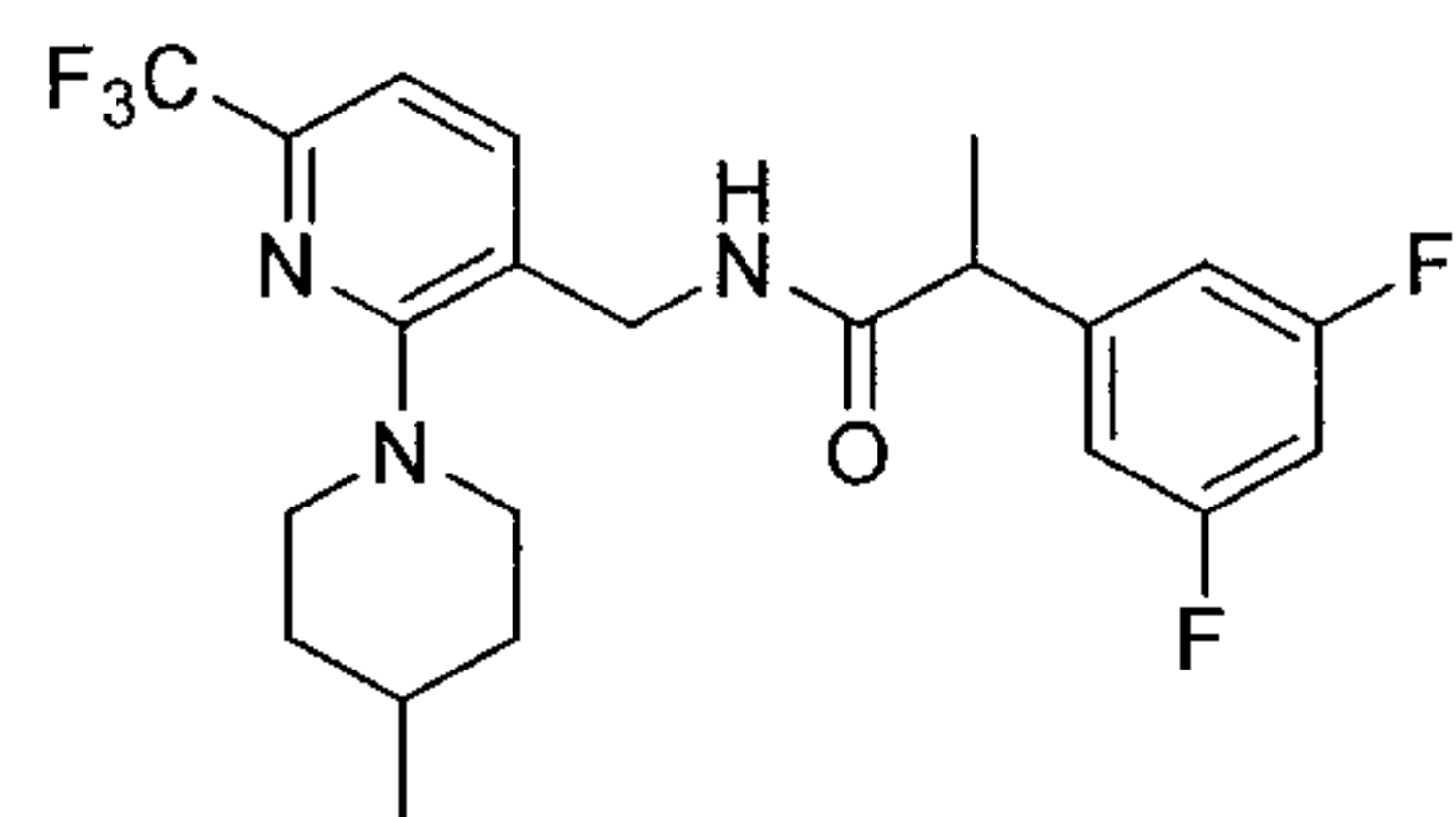
MS (FAB) m/z 410 (M+H)

Exemplary Compound 9:**2-(4-Hydroxy-3-methoxy-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide**

¹H NMR (300 M Hz, CDCl₃) δ 7.44 (d, 1 H, *J* = 7.7 Hz), 7.17 (d, 1 H, *J* = 7.5 Hz), 6.88 (d, 1 H, *J* = 7.9 Hz), 6.80-6.70 (m, 2 H), 6.11 (bt, 1 H), 5.60 (s, 1 H), 4.46-4.42 (m, 2 H), 3.84 (s, 3 H), 3.55 (q, 1 H, *J* = 7.1 Hz), 3.32-3.23 (m, 2 H), 2.83-2.73 (m, 2 H), 1.71-1.66 (m, 2 H), 1.53 (d, 3 H, *J* = 7.1 Hz), 1.26-1.1 (m, 2 H), 0.96 (d, 3 H, *J* = 6.6 Hz)

IR (KBr) 3301, 2925, 1650, 1516, 1458, 1421, 1373 cm⁻¹

MS (FAB) *m/z* 452 (M+H)

Exemplary Compound 10:**2-(3,5-Difluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide**

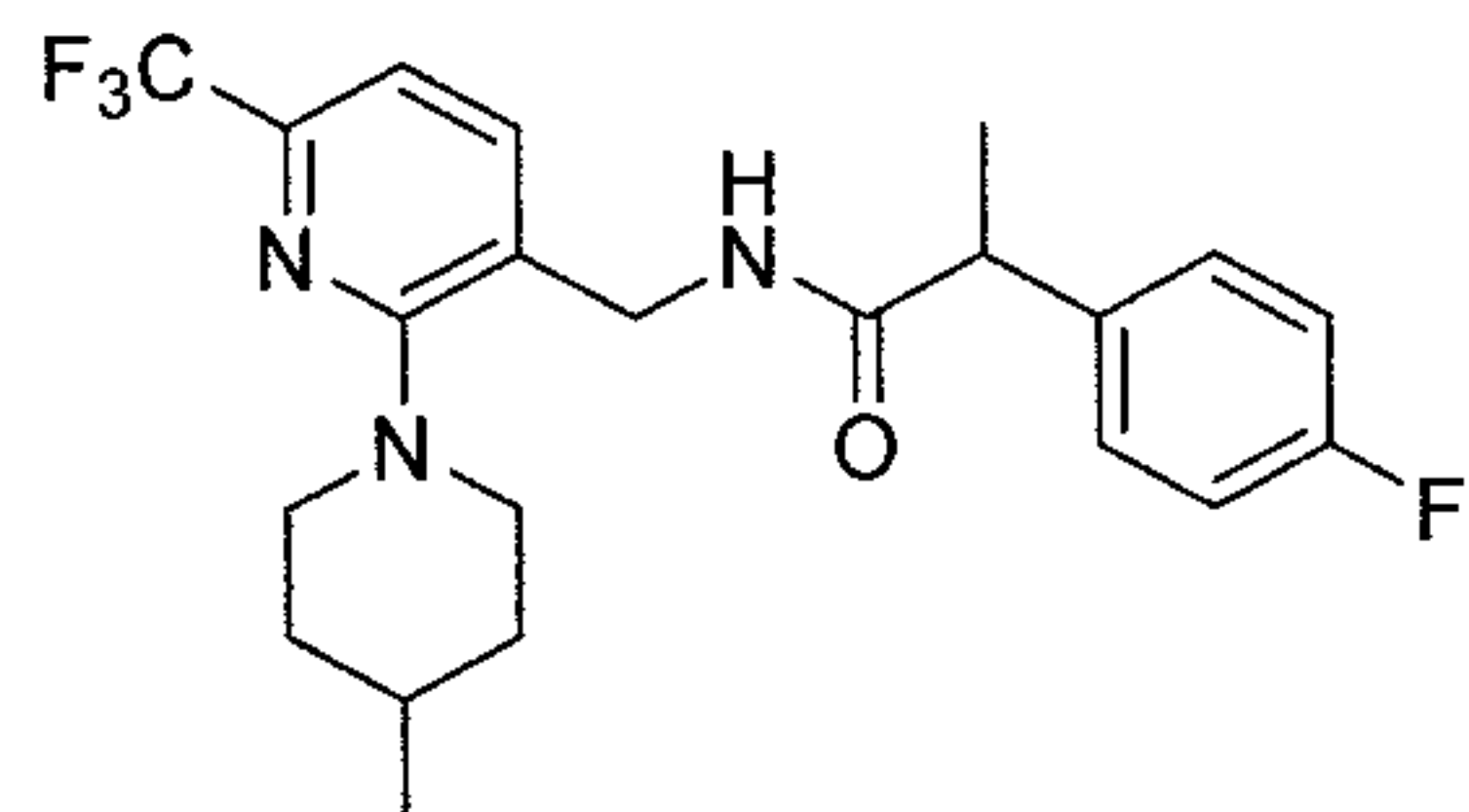
¹H NMR (300 M Hz, CDCl₃) δ 7.47 (d, 1 H, *J* = 7.5 Hz), 7.21 (d, 1 H, *J* = 7.7 Hz), 6.85-6.82 (m, 2 H), 6.80-6.70 (m, 2 H), 6.11 (bt, 1 H), 5.60 (s, 1 H), 4.46-4.42 (m, 2 H), 3.84 (s, 3 H), 3.55 (q, 1 H, *J* = 7.1 Hz), 3.32-3.23 (m, 2 H), 2.83-2.73 (m, 2 H), 1.71-1.66 (m, 2 H), 1.53 (d, 3 H, *J* = 7.1 Hz), 1.26-1.1 (m, 2 H), 0.96 (d, 3 H, *J* = 6.6 Hz)

IR (KBr) 3293, 2925, 1651, 1596, 1542, 1460, 1335 cm⁻¹

MS (FAB) *m/z* 442 (M+H)

Exemplary Compound 12:

2-(4-Fluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide



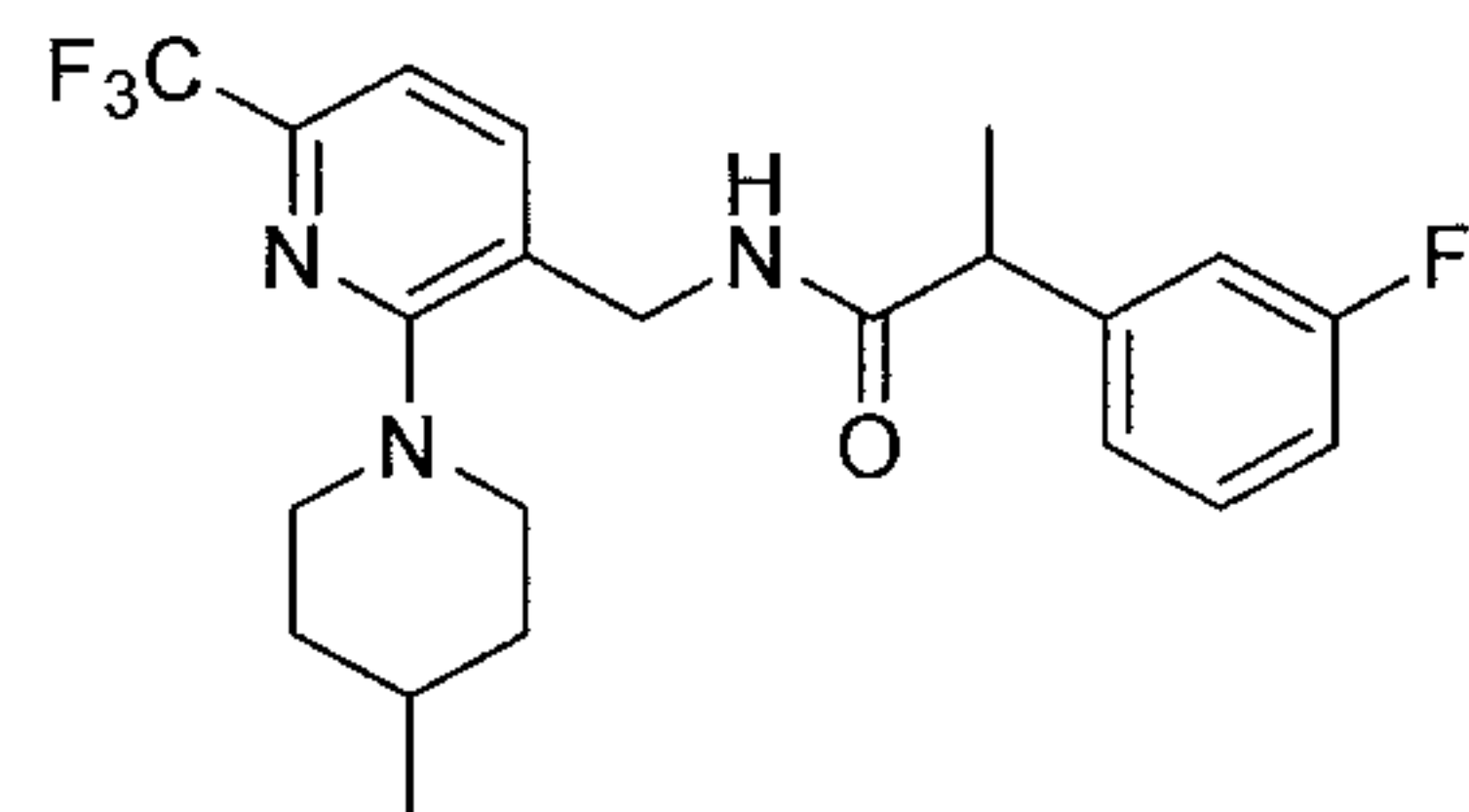
$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.43(d, 1H, J = 7.5 Hz), 7.28-7.24(m, 2H), 7.18(d, 1H, J = 7.7 Hz), 7.06-7.00(m, 2H), 6.16 (bs, NH), 4.45(d, 2H), 3.59(q, 1H, J = 7.0 Hz), 3.29(m, 2H), 2.79(m, 2H), 1.75-1.50(m, 3H), 1.53(d, 3H, J = 7.1 Hz), 1.26-1.10(m, 2H), 0.96(d, 3H, J = 6.4 Hz)

IR 3291, 2925, 1650, 1510, 1458, 1419, 1336, 1231, 1177, 1138 cm^{-1}

Mass (FAB) m/z 424 $[\text{M}+\text{H}]^+$ (Base), 446 $[\text{M}+\text{Na}]^+$

Exemplary Compound 13:

2-(3-Fluoro-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide



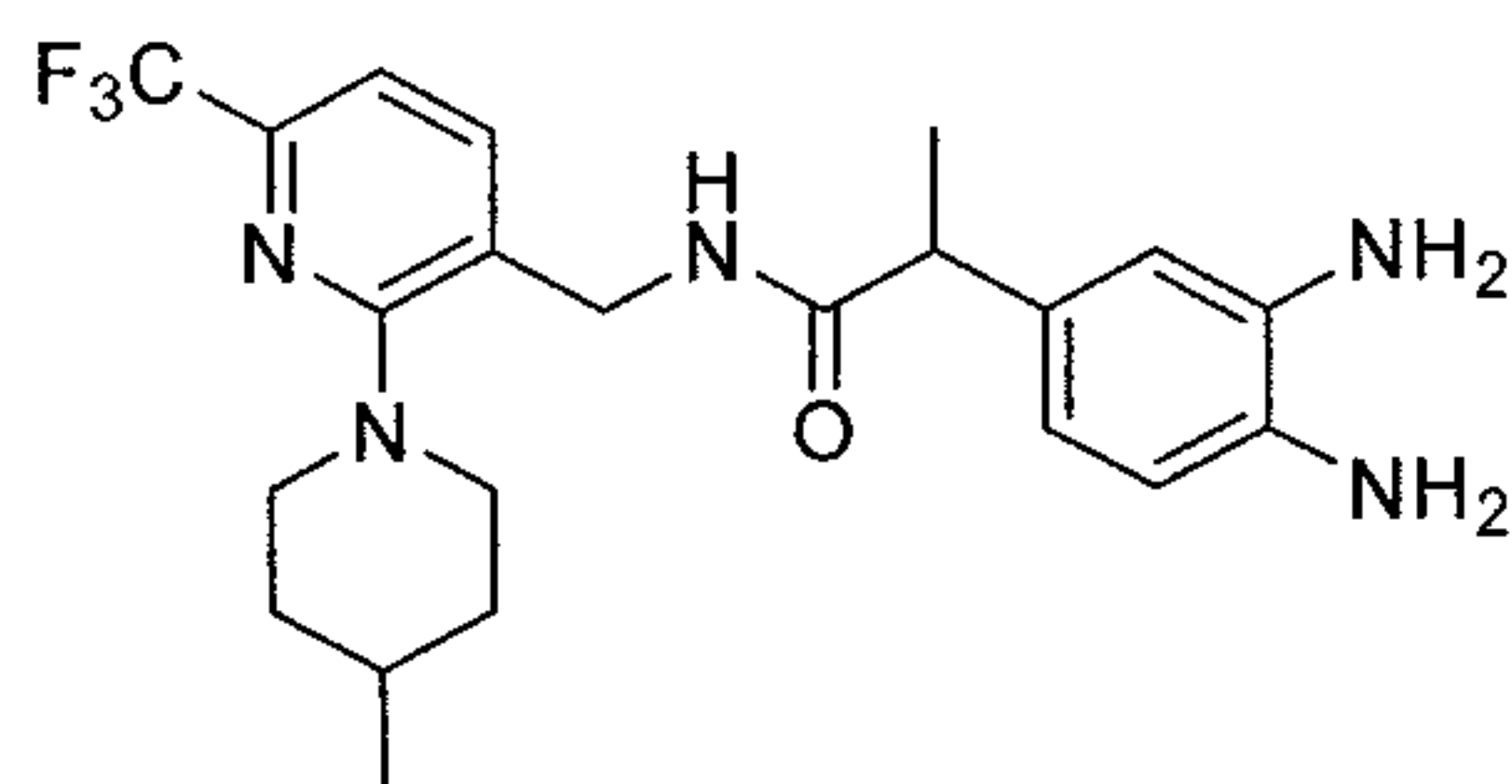
$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.43(d, 1H, J = 7.7 Hz), 7.31(m, 1H), 7.18(d, 1H, J = 7.7 Hz), 7.07-6.95(m, 3H), 6.23(bs, NH), 4.45(d, 2H), 3.60(q, 1H, J = 7.0 Hz), 3.29(m, 2H), 2.79(m, 2H), 1.65-1.50(m, 3H), 1.54(d, 2H, J = 7.0 Hz), 1.24-1.12(m, 2H), 0.96(d, 3H, J = 6.4 Hz)

IR 3292, 2925, 1651, 1592, 1542, 1456, 1419, 1177, 1140 cm^{-1}

Mass (FAB) m/z 424 $[\text{M}+\text{H}]^+$ (Base), 446 $[\text{M}+\text{Na}]^+$

Exemplary Compound 14:

2-(3,4-Diamino-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide



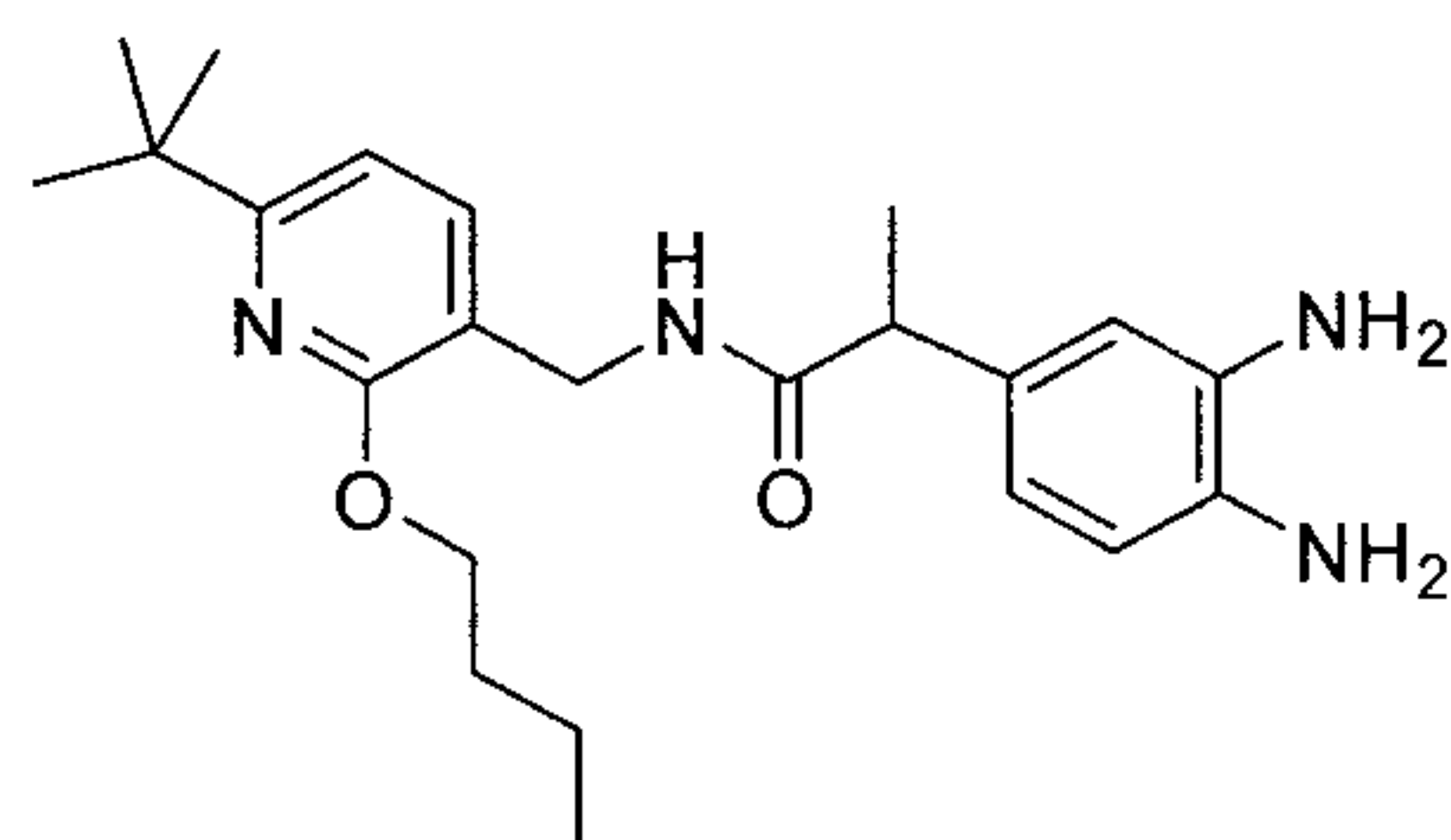
$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.42 (d, 1H, $J = 7.5$ Hz), 7.17 (d, 1H, $J = 7.7$ Hz), 6.67-6.57 (m, 3H), 6.03 (bt, NH), 4.41 (d, 2H), 3.49 (q, 1H, $J = 7.3$ Hz), 3.40 (br, NH₂), 3.33-3.27 (m, 2H), 2.84-2.74 (m, 2H), 1.73-1.55 (m, 3H), 1.51 (d, 3H, $J = 7.1$ Hz), 1.30-1.18 (m, 2H), 0.96 (d, 3H, $J = 6.6$ Hz)

IR 3334, 2925, 1651, 1518, 1419, 1176, 1135, 733 cm^{-1}

Mass (FAB) m/z 436 $[\text{M}+\text{H}]^+$

Exemplary Compound 15:

N-(2-Butoxy-6-tert-butyl-pyridin-3-ylmethyl)-2-(3,4-diaminophenyl)propionamide



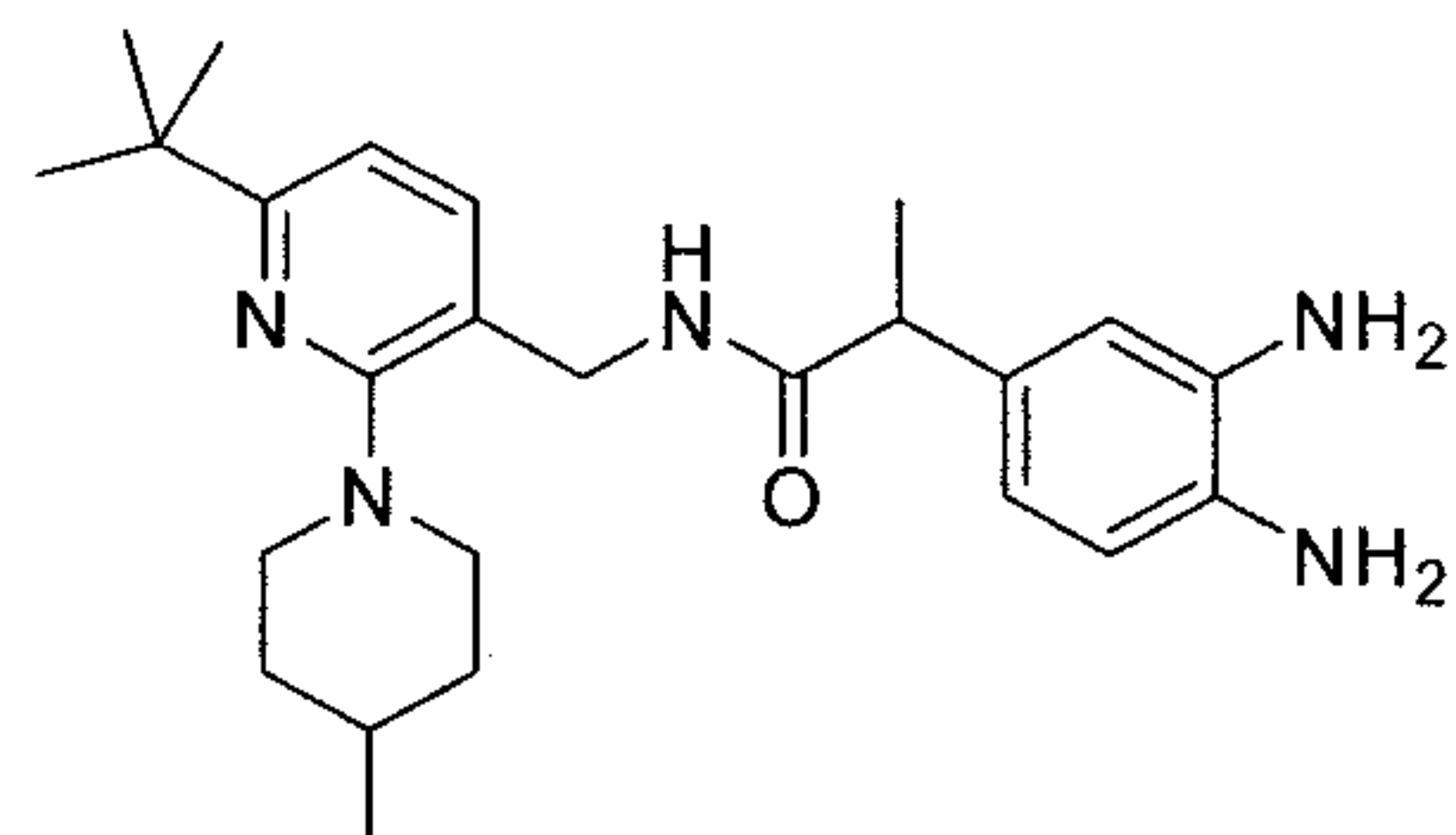
$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.32 (d, 1H, $J = 7.5$ Hz, Ar), 6.76 (d, 1H, $J = 7.3$ Hz, Ar), 6.66-6.57 (m, 3H, Ar), 6.00 (bt, NH), 4.27 (m, 4H, OCH_2 & CH_2NH), 3.41 (q, 1H, $J = 7.1$ Hz, CHCH_3), 1.64 (m, 2H, OCH_2CH_2), 1.45 (d, 3H, $J = 7.1$ Hz, CHCH_3), 1.39 (m, 2H, CH_2CH_3), 1.29 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.95 (t, 3H, $J = 7.3$ Hz, CH_2CH_3)

IR 3303, 2960, 1649, 1517, 1456, 1254 cm^{-1}

Mass (FAB) 399 m/z $[\text{M}+\text{H}]^+$

Exemplary Compound 16:

N-(6'-tert-Butyl-4-methyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)-2-(3,4-diamino-phenyl)propionamide



$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.26 (d, 1H, $J = 7.9$ Hz, Ar), 6.85 (d, 1H, $J = 7.7$ Hz, Ar), 6.66-6.58 (m, 3H, Ar), 6.39 (bt, NH), 4.37 (m, 2H, CH_2NH), 3.45 (q, 1H, $J = 7.1$ Hz, CHCH_3), 3.37 (bs, $\text{NH}_2 \times 2$), 3.23 (m, 2H, piperidine), 2.74 (m, 2H, piperidine), 1.65-1.45 (m, 3H,

piperidine), 1.49 (d, 3H, J = 7.1 Hz, CHCH₃), 1.29 (s, 9H, C(CH₃)₃), 1.28-1.16 (m, 2H, piperidine), 0.95 (d, 3H, J = 6.4 Hz, piperidine CH₃)

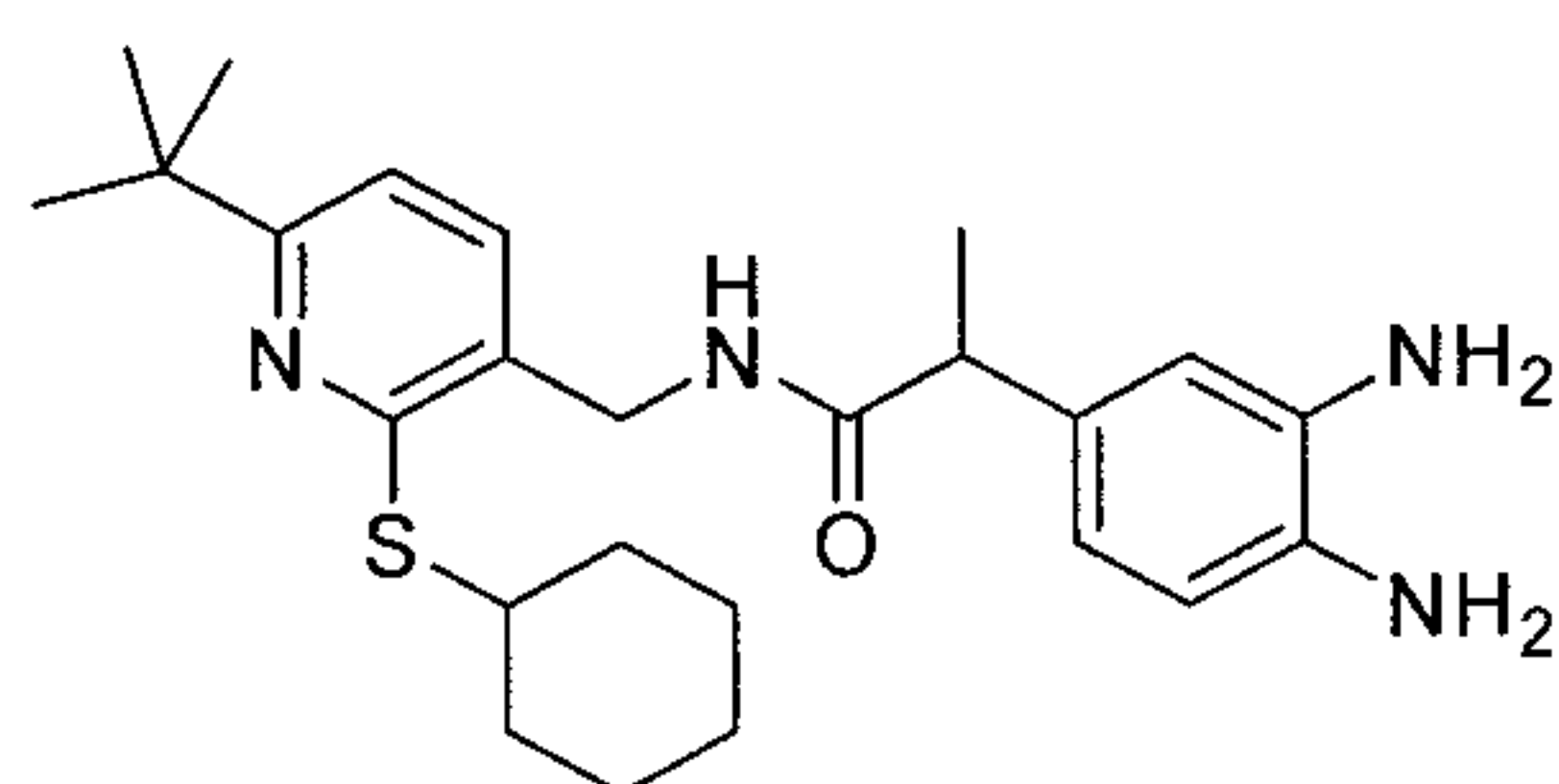
IR 3338, 2955, 1648, 1517, 1449, 1232 cm⁻¹

Mass (FAB) m/z 424[M+H]⁺

5

Exemplary Compound 17:

N-(6-tert-Butyl-2-cyclohexylsulfanyl-pyridin-3-ylmethyl)-2-(3,4-diamino-phenyl)-propionamide



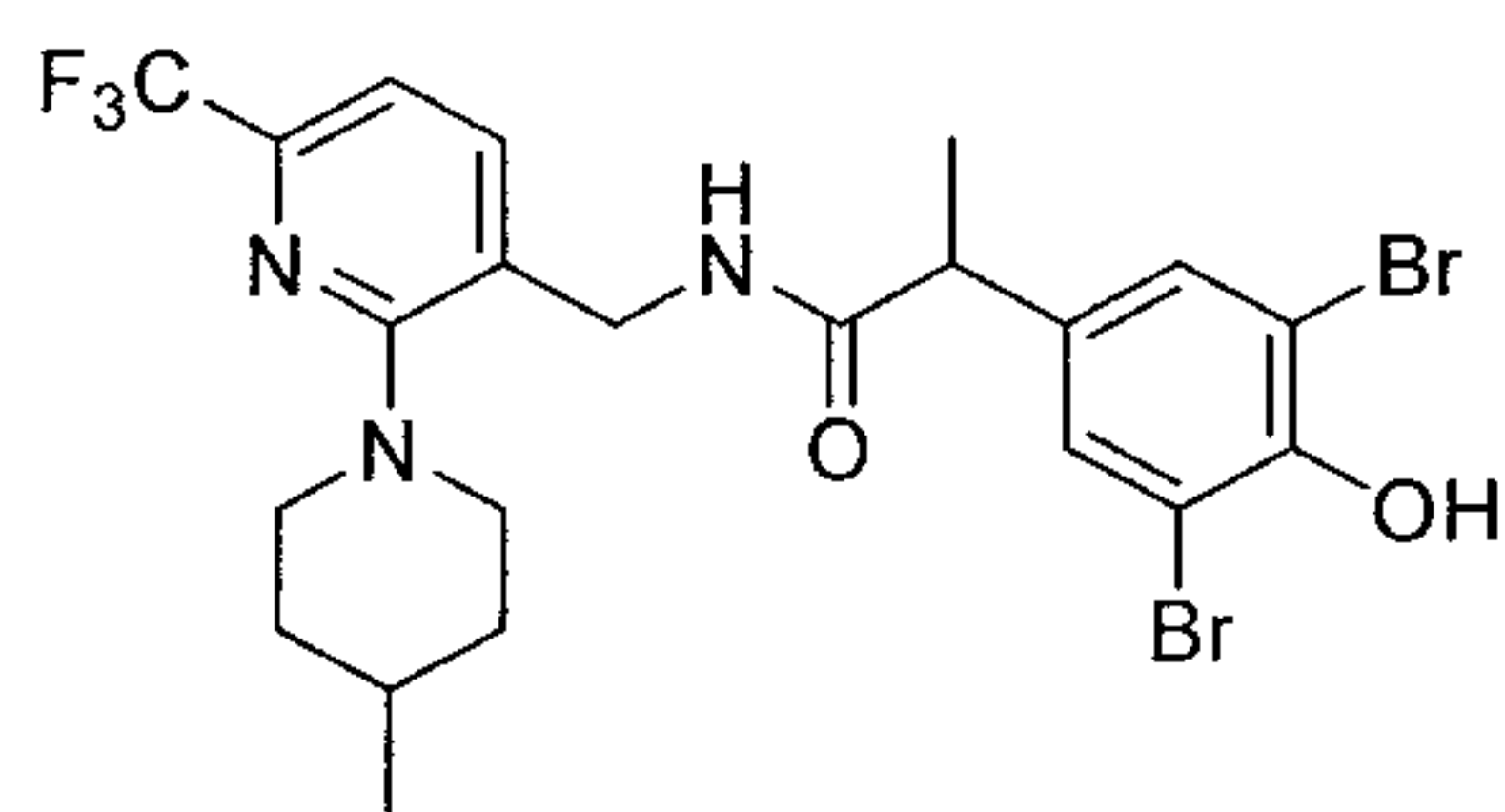
10 ¹H-NMR(CDCl₃) δ 7.27 (d, 1H, Ar), 6.91 (d, 1H, J = 7.9 Hz, Ar), 6.67-6.59 (m, 3H, Ar), 5.90 (bt, NH), 4.26 (m, 2H, CH₂NH), 3.96 (m, 1H, SCH), 3.46 (q, 1H, J = 7.3 Hz, CHCH₃), 3.37 (bs, NH₂*2), 2.06 (m, 2H, cyclohexyl), 1.80-1.20 (m, 8H, cyclohexyl), 1.50 (d, 3H, CHCH₃), 1.31 (s, 9H, C(CH₃)₃)

IR 3303, 2929, 2854, 1651, 1517, 1444, 1079cm⁻¹

15 Mass (FAB) m/z 441[M+H]⁺

Exemplary Compound 19:

2-(3,5-Dibromo-4-hydroxy-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide



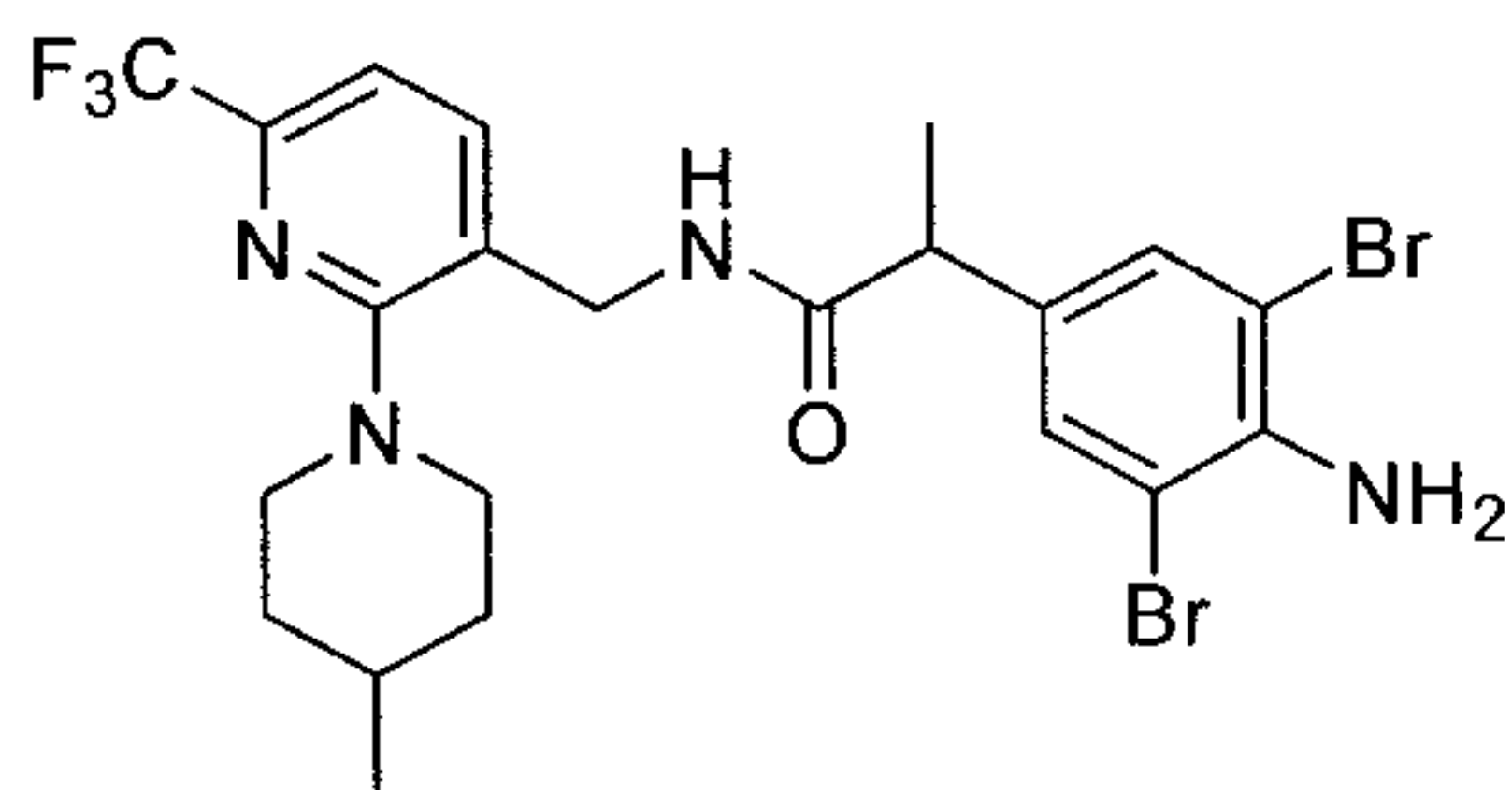
20 ¹H-NMR(CDCl₃) δ 7.48 (m, 1H, Ar), 7.39 (s, 2H, Ar), 7.22 (d, 1H, J = 7.7 Hz, Ar), 6.27 (bt, NH), 4.47 (m, 2H, CH₂NH), 3.46 (q, 1H, J = 7.1 Hz, CHCH₃), 3.31 (m, 2H, piperidine), 2.81 (m, 2H, piperidine), 2.40 (s, OH), 1.75-1.16 (m, 5H, piperidine), 1.50 (d, 3H, J = 7.1 Hz, CHCH₃), 0.98 (d, 3H, J = 6.4 Hz, piperidine CH₃)

25 IR 3298, 2924, 1650, 1550, 1462, 1417, 1176, 1138 cm⁻¹

Mass (FAB) m/z 580 [M+H]⁺

Exemplary Compound 20:

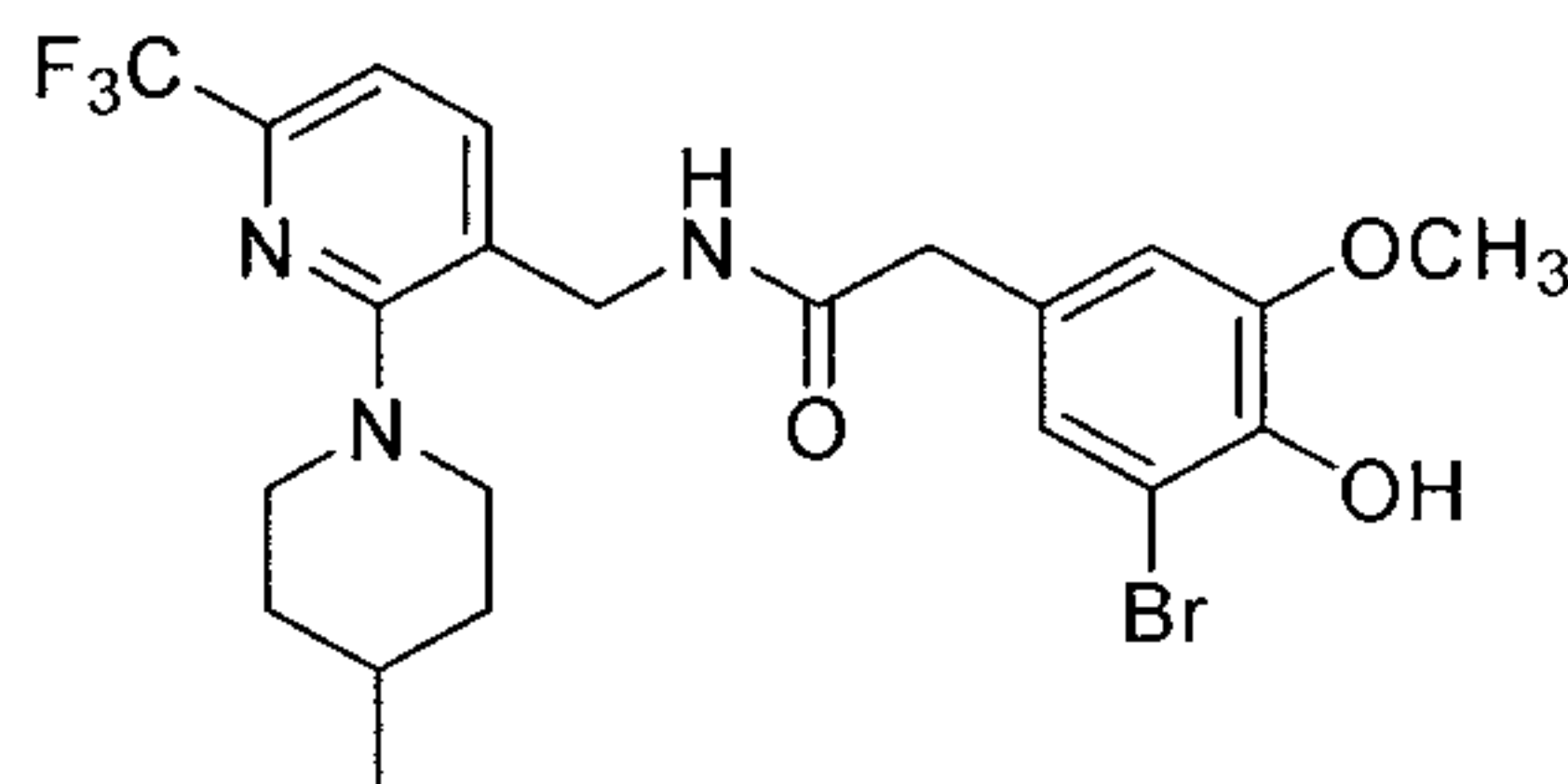
2-(4-Amino-3,5-dibromo-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide



- 5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.47 (d, 1H, $J = 7.7$ Hz, Ar), 7.31 (s, 2H, Ar), 7.21 (d, 1H, $J = 7.7$ Hz, Ar), 6.18 (bt, NH), 4.55 (bs, NH_2), 4.46 (m, 2H, CH_2NH), 3.43 (q, 1H, $J = 7.0$ Hz, CHCH_3), 3.30 (m, 2H, piperidine), 2.81 (m, 2H, piperidine), 1.75-1.15 (m, 5H, piperidine), 1.48 (d, 3H, $J = 7.1$ Hz, CH_2CH_3), 0.97 (d, 3H, $J = 6.4$ Hz, piperidine CH_3)
 IR 3298, 2924, 1649, 1544, 1474, 1418, 1177, 1136 cm^{-1}
 10 Mass (FAB) m/z 579 $[\text{M}+\text{H}]^+$

Exemplary Compound 21:

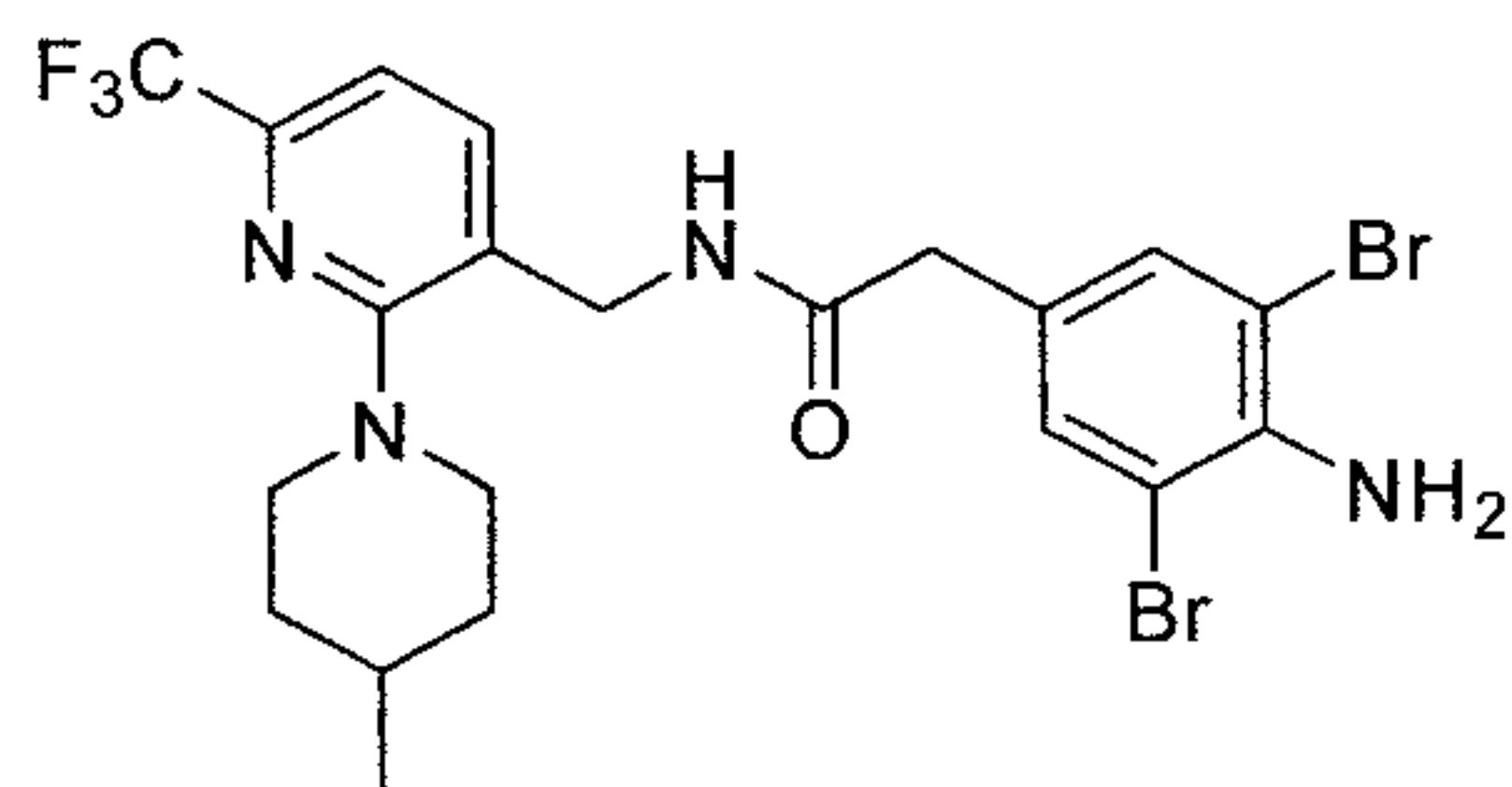
2-(3-Bromo-4-hydroxy-5-methoxy-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



- 15 $^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.54 (d, 1H, $J = 7.5$ Hz, Ar), 7.22 (d, 1H, $J = 7.7$ Hz, Ar), 6.99 (d, 1H, $J = 1.5$ Hz, Ar), 6.69 (d, 1H, $J = 2.0$ Hz, Ar), 6.27 (bt, NH), 5.91 (bs, OH), 4.48 (m, 2H, CH_2NH), 3.86 (s, 3H, OCH_3), 3.53 (s, 2H, CH_2CO), 3.28 (m, 2H, piperidine), 2.80 (m, 2H, piperidine), 1.73-1.07 (m, 5H, piperidine), 0.96 (d, 3H, $J = 6.4$ Hz, piperidine CH_3)
 IR 3298, 2924, 1649, 1501, 1459, 1421, 1282, 1178, 1136, 1047 cm^{-1}
 20 Mass (FAB) m/z 517 $[\text{M}+\text{H}]^+$

Exemplary Compound 22:

- 25 **2-(4-Amino-3,5-dibromo-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide**



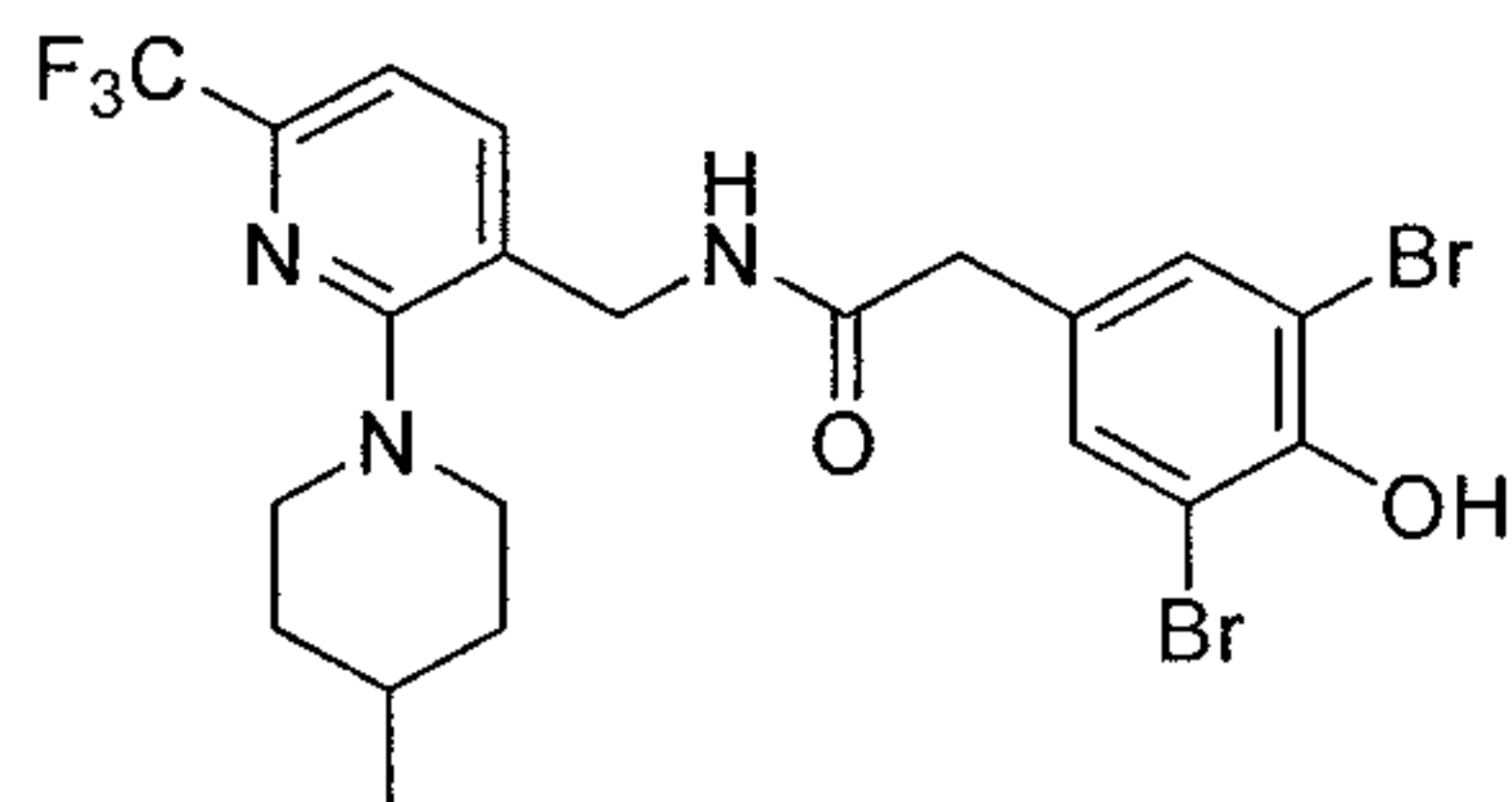
$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.53 (d, 1H, $J = 7.3$ Hz, Ar), 7.29 (s, 2H, Ar), 7.23 (d, 1H, $J = 7.7$ Hz, Ar), 6.26 (bt, NH), 4.57 (bs, NH_2), 4.48 (m, 2H, CH_2NH), 3.46 (s, 2H, CH_2CO), 3.30 (m, 2H, piperidine), 2.81 (m, 2H, piperidine), 1.75-1.10 (m, 5H, piperidine), 0.97

IR 3288, 2923, 1649, 1544, 1478, 1418, 1337, 1177, 1135 cm^{-1}

Mass (FAB) m/z 565 $[\text{M}+\text{H}]^+$

Exemplary Compound 23:

2-(3,5-Dibromo-4-hydroxy-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



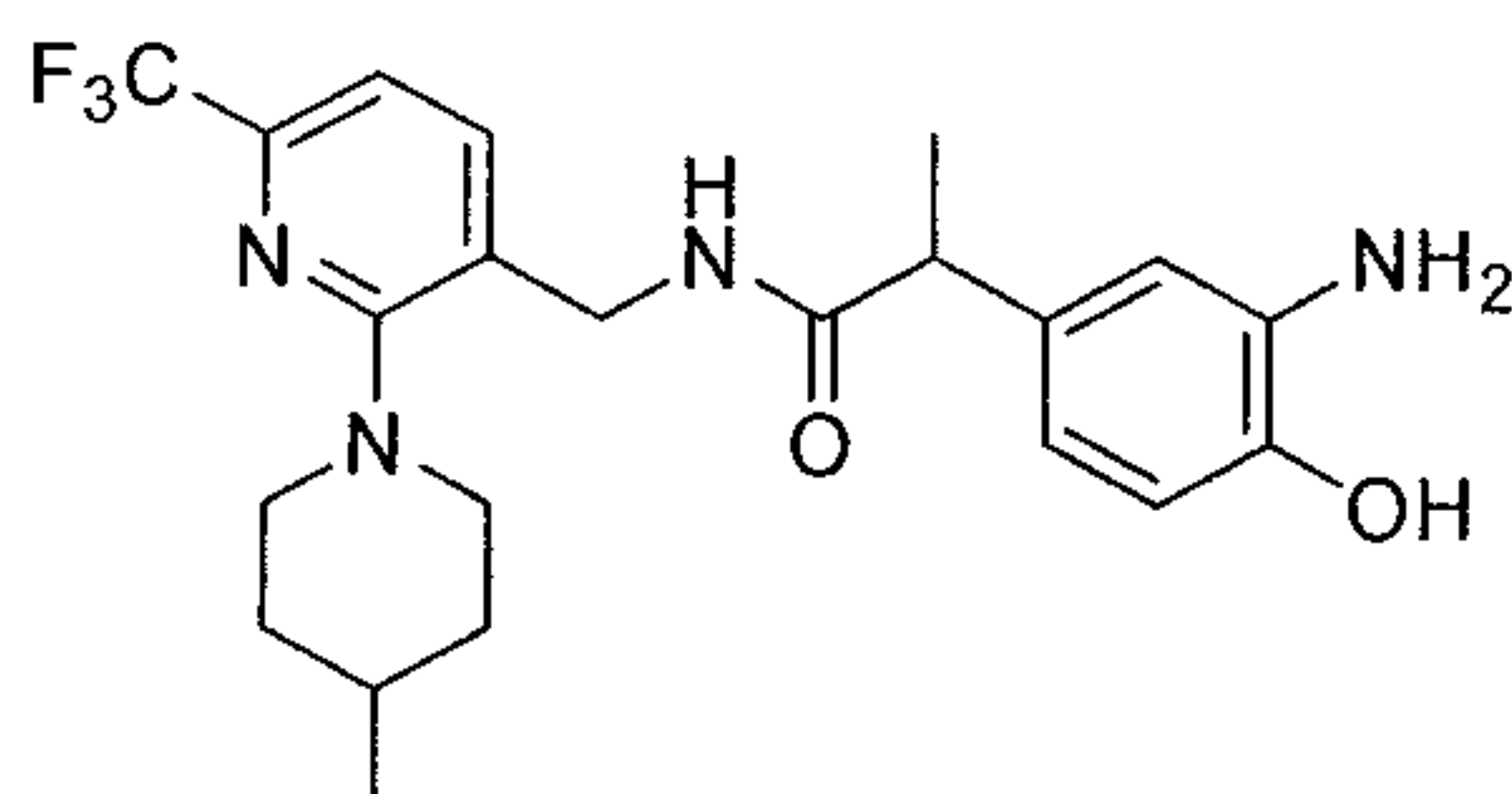
$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.55 (d, 1H, $J = 7.7$ Hz, Ar), 7.38 (s, 2H, Ar), 7.24 (d, 1H, $J = 7.7$ Hz, Ar), 6.31 (bt, NH), 4.50 (m, 2H, CH_2NH), 3.50 (s, 2H, CH_2CO), 3.31 (m, 2H, piperidine), 2.82 (m, 2H, piperidine), 2.40 (s, OH), 1.77-1.10 (m, 5H, piperidine), 0.97

IR 3297, 2924, 1650, 1546, 1473, 1419, 1337, 1177, 1137 cm^{-1}

Mass (FAB) m/z 566 $[\text{M}+\text{H}]^+$

Exemplary Compound 24:

2-(3-Amino-4-hydroxy-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)propionamide



$^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.42 (d, 1H, $J = 7.7$ Hz, Ar), 7.17 (d, 1H, $J = 7.7$ Hz, Ar), 6.69-6.64 (m, 2H, Ar), 6.53 (dd, 1H, $J = 8.0, 1.8$ Hz, Ar), 6.07 (bt, NH), 4.42 (d, 2H, $J = 5.7$ Hz, CH_2NH), 3.69 (bs, NH_2), 3.59 (q, 1H, $J = 7.1$ Hz, CHCH_3), 3.30 (m, 2H, piperidine),

2.79 (m, 2H, piperidine), 1.71-1.50 (m, 6H, piperidine & CHCH₃), 1.22 (m, 2H, piperidine), 0.96 (d, 3H, J = 6.6 Hz, CHCH₃)

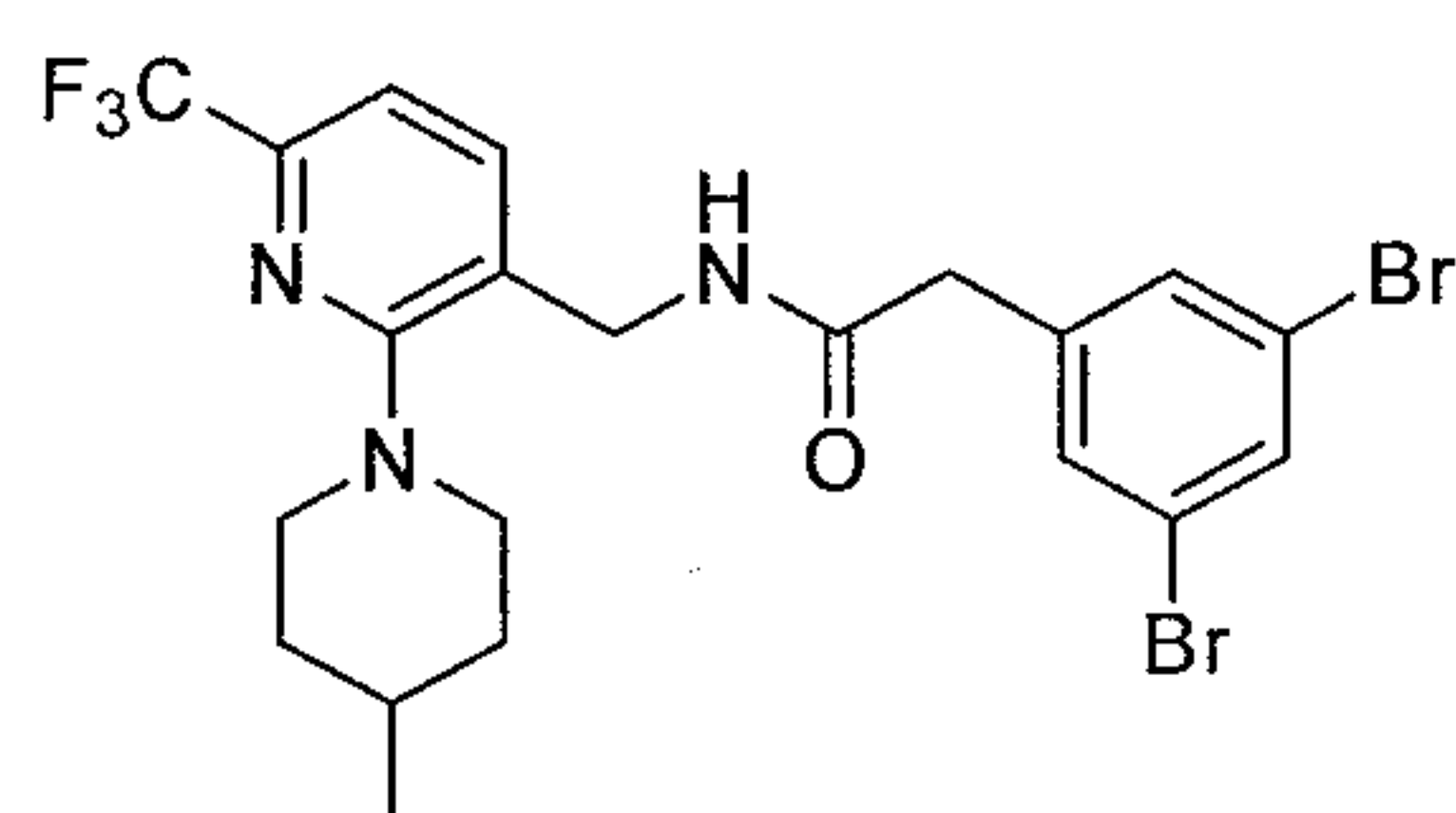
IR 3298, 2924, 1649, 1519, 1458, 1420, 1177, 1136 cm⁻¹

Mass (FAB) m/z 437 [M+H]⁺, 459 [M+Na]⁺

5

Exemplary Compound 25:

2-(3,5-Dibromo-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)acetamide



10 ¹H-NMR(CDCl₃) δ 7.61 (t, 1H, J = 1.7 Hz), 7.54 (d, 1H, J = 7.7 Hz), 7.38 (d, 1H, J = 1.7 Hz), 7.24 (d, 1H, J = 7.7 Hz), 6.34 (bt, NH), 4.50 (d, 2H), 3.54 (s, 3H), 3.32 (m, 2H), 2.83 (m, 2H), 1.75-1.50 (m, 3H), 1.33-1.13 (m, 2H), 0.98 (d, 3H, J = 6.4 Hz)

IR 3291, 2924, 1649, 1554, 1458, 1421, 1337, 1176, 1138 cm⁻¹

Mass (FAB) m/z 550[M+H]⁺

15

The following further exemplary compounds were obtained by the methods described above:

[1]	2-(4-Amino-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide
[2]	2-(3,5-Dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide
[11]	2-(3,4-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide
[18]	2-(4-Acetamido-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide
[19]	2-(3,5-Dibromo-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide
[26]	2-(4-Amino-3,5-difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide
[27]	2-(3-Fluoro-5-hydroxy-4-nitrophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-

	(trifluoromethyl)pyridin-3-yl)methyl)propanamide
[33]	N-(2-Fluoro-4-(1-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methylamino)-1-oxopropane-2-yl)phenyl)acrylamide
[34]	N-(2-Fluoro-6-iodo-4-(1-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methylamino)-1-oxopropane-2-yl)phenyl)acrylamide

Exemplary compounds 28-32 and 35-38 can likewise be obtained according to the methods described above.

5 Pharmacological Data

The affinity of the compounds according to the invention for the vanilloid receptor 1 (VR1/TRPV1-Receptor) was detected as described above (Pharmacological Methods I and II respectively).

10

The compounds according to the invention of the above formula I exhibit excellent affinity to the VR1/TRPV1 receptor (Table 1).

Table 1.

Compound of Example	K _i (Rat) Capsaicin [nM]	K _i (Human) Capsaicin [nM]	IC ₅₀ (Human) [nM] following pH-stimulus
2	60.1	40.6	Ne
3	16.7	4.4	253
4	80	34	Ne
6	118	38	Ne
7	63	30	Ne
10		24.7	Ne
18		25	Ne
19		1.1	31% @ 10 μM; 20% @ 5 μM; 0% @ 1 μM
20		0.9	27% @ 10 μM; 10% @ 5 μM; 0% @ 1 μM
21		0.1	38% @ 10 μM;

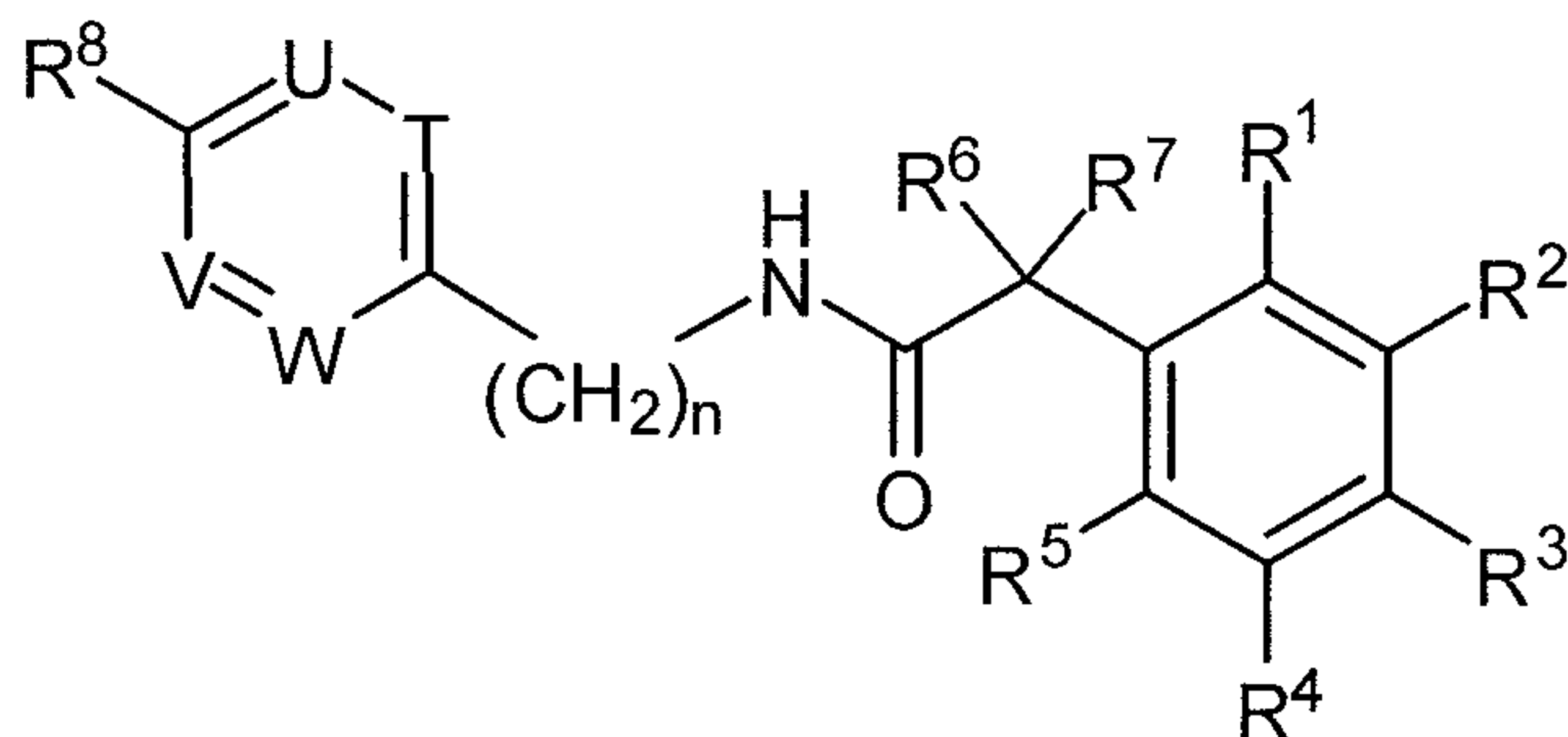
			4% @ 5 μ M;
22		0.7	158
23		0.3	35% @ 10 μ M; 8% @ 5 μ M;
26	3.4	9.6	Ne
27	7.7	7.9	49% @ 10 μ M; 35% @ 5 μ M; 7% @ 1 μ M
34		4.8	Ne

Ne denotes “no effect”, i.e. no reaction was observed.

The value following the symbol “@” indicates the concentration at which the inhibition (in percent) was
5 determined.

Claims

1. Substituted compounds of the general formula I,



I,

in which

n stands for 0, 1, 2, 3, or 4;

R¹ stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -C(=NH)-NH₂; -C(=NH)-NH-R⁹; -N=C(NH₂)₂; -N=C(NHR¹⁰)-(NHR¹¹); -O-P(=O)₂-O-R¹²; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -C(=O)-NHR¹⁸; -C(=O)-NR¹⁹R²⁰; -S(=O)₂-NHR²¹; -S(=O)₂-NR²²R²³; -C(=O)-OR²⁴; -C(=O)-R²⁵; -S(=O)-R²⁶; or -S(=O)₂-R²⁷ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

R² stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -C(=NH)-NH₂; -C(=NH)-NH-R⁹; -N=C(NH₂)₂; -N=C(NHR¹⁰)-(NHR¹¹); -O-P(=O)₂-O-R¹²; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -C(=O)-NHR¹⁸; -C(=O)-NR¹⁹R²⁰; -S(=O)₂-NHR²¹; -S(=O)₂-NR²²R²³; -C(=O)-OR²⁴; -C(=O)-R²⁵; -S(=O)-R²⁶; or -S(=O)₂-R²⁷ or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

R³ stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -

$C(=NH)-NH_2$; $-C(=NH)-NH-R^9$; $-N=C(NH_2)_2$; $-N=C(NHR^{10})-(NHR^{11})$; $-O-P(=O)_2-O-R^{12}$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-C(=O)-NHR^{18}$; $-C(=O)-NR^{19}R^{20}$; $-S(=O)_2-NHR^{21}$; $-S(=O)_2-NR^{22}R^{23}$; $-C(=O)-OR^{24}$; $-C(=O)-R^{25}$; $-S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or
 5 branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^4 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-C(=NH)-NH_2$; $-C(=NH)-NH-R^9$; $-N=C(NH_2)_2$; $-N=C(NHR^{10})-(NHR^{11})$; $-O-P(=O)_2-O-R^{12}$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-C(=O)-NHR^{18}$; $-C(=O)-NR^{19}R^{20}$; $-S(=O)_2-NHR^{21}$; $-S(=O)_2-NR^{22}R^{23}$; $-C(=O)-OR^{24}$; $-C(=O)-R^{25}$; $-S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or
 10 branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^5 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-C(=NH)-NH_2$; $-C(=NH)-NH-R^9$; $-N=C(NH_2)_2$; $-N=C(NHR^{10})-(NHR^{11})$; $-O-P(=O)_2-O-R^{12}$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-C(=O)-NHR^{18}$; $-C(=O)-NR^{19}R^{20}$; $-S(=O)_2-NHR^{21}$; $-S(=O)_2-NR^{22}R^{23}$; $-C(=O)-OR^{24}$; $-C(=O)-R^{25}$; $-S(=O)-R^{26}$; or $-S(=O)_2-R^{27}$ or for a linear or
 20 branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^6 stands in each case for hydrogen or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^7 stands for hydrogen or $-OH$;

or R^6 and R^7 each form, together with the interconnecting carbon atom as ring member, a saturated or unsaturated, unsubstituted or at least

monosubstituted three-membered, four-membered, five-membered, or six-membered cycloaliphatic radical;

R^8 stands for $-SF_5$; $-O-CF_3$; $-CF_3$; $-O-CFH_2$; $-O-CF_2H$; $-CFH_2$; $-CF_2H$; or for an unsubstituted or at least monosubstituted tert-butyl radical;

T stands for $C-R^{35}$ and U stands for $C-R^{36}$ and V stands for N and W stands for $C-R^{38}$

or

T stands for $C-R^{35}$ and U stands for N and V stands for $C-R^{37}$ and W stands for $C-R^{38}$

or

T stands for N and U stands for $C-R^{36}$ and V stands for $C-R^{37}$ and W stands for $C-R^{38}$

or

T stands for N and U stands for N and V stands for $C-R^{37}$ and W stands for $C-R^{38}$

or

T stands for N and U stands for $C-R^{36}$ and V stands for N and W stands for $C-R^{38}$

or

T stands for $C-R^{35}$ and U stands for N and V stands for N and W stands for $C-R^{38}$

or

T stands for $C-R^{35}$ and U stands for $C-R^{36}$ and V stands for $C-R^{37}$ and W stands for $C-R^{38}$;

R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} and R^{27} each independently

stand for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

for an unsaturated or saturated, unsubstituted or at least monosubstituted, three-membered, four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered cycloaliphatic radical optionally containing at least one heteroatom as ring member, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or two to six-membered heteroalkylene group;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆ alkylene group or two to six-membered heteroalkylene group;

R³⁵, R³⁶, and R³⁷ each independently stand for H; F; Cl; Br; I; -SF₅; -NO₂; -CF₃; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -C(=O)-NHR¹⁸; -C(=O)-NR¹⁹R²⁰; -S(=O)₂-NHR²¹; -S(=O)₂-NR²²R²³; -C(=O)-OR²⁴; -C(=O)-R²⁵; -S(=O)-R²⁶; -S(=O)²R²⁷;

for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆-alkylene group or C₂₋₆-alkenylene group or C₂₋₆-alkynylene group;

R^{38} stands for F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CF_3$; $-CF_2Cl$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; and $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-NHR^{39}$; $-NR^{40}R^{41}$; $-OR^{42}$; $-SR^{43}$; $-C(=O)-NHR^{44}$; $-C(=O)-NR^{45}R^{46}$; $-S(=O)_2-NHR^{47}$; $-S(=O)_2-NR^{48}R^{49}$; $-C(=O)-OR^{50}$; $-C(=O)-R^{51}$; $-S(=O)-R^{52}$; $-S(=O)_2-R^{53}$; $-C(=NH)-NH_2$; $-C(=NH)-NH-R^{54}$; $-N=C(NH_2)_2$; $-N=C(NHR^{55})-(NHR^{56})$;

for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

for an unsaturated or saturated, unsubstituted or at least monosubstituted three-membered, four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered cycloaliphatic radical optionally exhibiting at least one heteroatom as ring member, each of which is bonded to the parent structure over a carbon atom in the ring of the cycloaliphatic radical and is condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C_{1-6} alkylene group or C_{2-6} alkenylene group or C_{2-6} alkynylene group;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C_{1-6} alkylene group or C_{2-6} alkenylene group or C_{2-6} alkynylene group;

R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} , R^{48} , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} , and R^{56} each independently

stand for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C₁₋₁₀ radical;

for an unsaturated or saturated, unsubstituted or at least monosubstituted, three-membered, four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered cycloaliphatic radical optionally containing at least one heteroatom as ring member, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆-alkylene group or two to six-membered heteroalkylene group;

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C₁₋₆-alkylene group or two to six-membered heteroalkylene group;

or

R⁴⁰ and R⁴¹ form, together with the interconnecting nitrogen atom as ring member, a saturated or unsaturated four-membered, five-membered, six-membered, seven-membered, eight-membered, or nine-membered heterocycloaliphatic radical, which is unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R⁵⁷ and optionally exhibits at least one further heteroatom as ring member, and which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system;

R^{57} stands for $-NHR^{58}$, $-NR^{59}R^{60}$, or for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

R^{58} , R^{59} , and R^{60} each independently stand for $-C(=O)-R^{61}$; for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical

or for an unsubstituted or at least monosubstituted five-membered to fourteen-membered aryl radical or heteroaryl radical, which can be condensed with a saturated or unsaturated, unsubstituted or at least monosubstituted monocyclic or polycyclic ring system and/or can be bonded via a linear or branched, unsubstituted or at least monosubstituted C_{1-6} alkylene group or C_{2-6} alkenylene group or C_{2-6} alkynylene group;

and

R^{61} stands for a linear or branched, saturated or unsaturated, unsubstituted or at least monosubstituted aliphatic C_{1-10} radical;

each optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers thereof, the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or each in the form of corresponding salts, or each in the form of corresponding solvates;

wherein

the aforementioned aliphatic C_{1-10} radicals and tert-butyl radicals can each be optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents independently selected from the group consisting of F, Cl, Br, I, $-CN$, $-NO_2$, $-OH$, $-NH_2$, $-SH$, $-O(C_{1-5} \text{ alkyl})$, $-S(C_{1-5} \text{ alkyl})$, $-NH(C_{1-5} \text{ alkyl})$, $-N(C_{1-5} \text{ alkyl})-(C_{1-5} \text{ alkyl})$, $-C(=O)-O(C_{1-5} \text{ alkyl})$, $-O-C(=O)-(C_{1-5} \text{ alkyl})$, $-O\text{-phenyl}$, phenyl, $-OCF_3$, and $-SCF_3$;

the aforementioned two to six-membered heteroalkylene groups, C₁₋₆ alkylene groups, and C₂₋₆ alkenylene groups and C₂₋₆ alkynylene groups can each be optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O(C₁₋₅ alkyl), -S(C₁₋₅ alkyl), -NH(C₁₋₅ alkyl), -N(C₁₋₅ alkyl)-(C₁₋₅ alkyl), -OCF₃, and -SCF₃;

the aforementioned heteroalkylene groups each optionally exhibit 1, 2, or 3 heteroatom(s) independently selected from the group consisting of oxygen, sulfur, and nitrogen (NH) as link(s);

the aforementioned (hetero)cycloaliphatic radicals are optionally each substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of -C₁₋₆-alkylene-OH, =CH₂, -O-C₁₋₅-alkyleneoxetanyl, -C₁₋₅-alkylene-O-C₁₋₅ alkylene-oxetanyl, -CH₂-NH-C₁₋₅ alkyl, -CH₂-N(C₁₋₅ alkyl)₂, -N[C(=O)-C₁₋₅ alkyl]-phenyl, -CH₂-O-C₁₋₅-alkyl, oxo (=O), thioxo (=S), F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-C₁₋₅-alkyl, -O-C(=O)-C₁₋₅-alkyl, -NH₂, -NO₂, -OCF₃, -S-CF₃, -SH, -S-C₁₋₅-alkyl, -C₁₋₅-alkyl, -C(=O)-C₁₋₅-alkyl, -C(=O)-OH, -C(=O)-O-C₁₋₅-alkyl, -NH-C₁₋₅-alkyl, -N(C₁₋₅ alkyl)₂, -NH-phenyl, -N(C₁₋₅-alkyl)-phenyl, cyclohexyl, cyclopentyl, (4,5)-dihydroisoxazolyl, thiazolyl, (1,2,5)-thiadiazolyl, thiophenyl, phenethyl, piperidinyl, pyrrolidinyl, -(CH₂)pyridinyl, pyridinyl, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals oxetanyl, (4,5)-dihydroisoxazolyl, thiazolyl, (1,2,5)-thiadiazolyl, thiophenyl, phenethyl, -N[C(=O)-C₁₋₅-alkyl]-phenyl, -NH-phenyl, -N(C₁₋₅ alkyl)-phenyl, -(CH₂)-pyridinyl, pyridinyl, -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, -C₁₋₅-alkyl, -O-C₁₋₅-alkyl, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl,

and, unless otherwise stated, the aforementioned (hetero)cycloaliphatic radicals can each optionally exhibit 1, 2, or 3 (further) heteroatom(s) independently selected from the group consisting of oxygen, nitrogen, and sulfur;

the rings of the aforementioned monocyclic or polycyclic ring systems can each be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of oxo (= O), thioxo (= S), F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-C₁₋₅-alkyl, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-C₁₋₅-alkyl, -C₁₋₅-alkyl, -C(= O)-C₁₋₅-alkyl, -C(= O)-OH, -C(= O)-O-C₁₋₅-alkyl, -NH-C₁₋₅-alkyl, -N(C₁₋₅-alkyl)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, -C₁₋₅-alkyl, -O-C₁₋₅-alkyl, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl,

and the rings of the aforementioned monocyclic or polycyclic ring systems are each five-membered, six-membered, or seven-membered and can each optionally exhibit 1, 2, 3, 4, or 5 heteroatom(s) as ring member(s), which are independently selected from the group consisting of oxygen, nitrogen, and sulfur;

and the aforementioned aryl radicals or heteroaryl radicals can each be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-C₁₋₅-alkyl, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-C₁₋₅-alkyl, -C₁₋₅-alkyl, -C(= O)-OH, -C(= O)-O-C₁₋₅-alkyl, -NH-C₁₋₅-alkyl, -N(C₁₋₅-alkyl)₂, -NH-S(= O)₂-C₁₋₅-alkyl, -NH-C(= O)-O-C₁₋₅-alkyl, -C(= O)-H, -C(= O)-C₁₋₅-alkyl, -C(= O)-NH₂, -C(= O)-NH-C₁₋₅-alkyl, -C(= O)-N-(C₁₋₅ alkyl)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl, and the cyclic moiety of the radicals -O-phenyl, -O-benzyl, phenyl, and benzyl can each be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, -OH, -CF₃, -SF₅, -CN, -NO₂, -C₁₋₅-alkyl, -O-C₁₋₅-alkyl, -O-CF₃, -S-CF₃, phenyl, and -O-benzyl,

and

the aforementioned heteroaryl radicals can each optionally exhibit 1, 2, 3, 4, or 5 heteroatom(s) independently selected from the group consisting of oxygen, nitrogen, and sulfur as ring member(s).

2. The compounds according to claim 1, characterized in that

n stands for 0, 1, 2, 3, or 4;

R¹ stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; and -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -S(=O)-NR²²R²³; -S(=O)-R²⁶; -S(=O)₂-R²⁷ or for a radical selected from the group consisting of methyl, -CF₃, -CCl₃, -CBr₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, ethyl, -CF₂-CH₃, -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CHF-CF₂Cl, -CF₂-CF₂Cl, -CFCl-CF₂Cl, n-propyl, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R² stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -S(=O)-NR²²R²³; -S(=O)-R²⁶; -S(=O)₂-R²⁷ or for a radical selected from the group consisting of methyl, -CF₃, -CCl₃, -CBr₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, ethyl, -CF₂-CH₃, -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CHF-CF₂Cl, -CF₂-CF₂Cl, -CFCl-CF₂Cl, n-propyl, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R³ stands for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR¹³; -NR¹⁴R¹⁵; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -S(=O)-NR²²R²³; -S(=O)-R²⁶; -S(=O)₂-R²⁷ or for a radical selected from the group consisting of methyl, -CF₃, -CCl₃, -CBr₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, ethyl, -CF₂-CH₃, -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CHF-CF₂Cl, -CF₂-CF₂Cl, -CFCl-CF₂Cl, n-propyl, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^4 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)-NR^{22}R^{23}$; $-S(=O)-R^{26}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CHF_2$, $-CH_2F$, $-CF_2Cl$, $-CCl_2F$, ethyl, $-CF_2-CH_3$, $-CH_2-CF_3$, $-C_2F_5$, $-CH_2-CCl_3$, $-CH_2-CBr_3$, $-CHF-CF_2Cl$, $-CF_2-CF_2Cl$, $-CFCl-CF_2Cl$, n-propyl, $-CF_2-CF_2-CF_3$, $-CF(CF_3)_2$, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^5 stands for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-C(=O)-NH_2$; $-S(=O)_2-NH_2$; $-C(=O)-NH-OH$; $-C(=O)-OH$; $-C(=O)-H$; $-S(=O)_2-OH$; $-NHR^{13}$; $-NR^{14}R^{15}$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)-NR^{22}R^{23}$; $-S(=O)-R^{26}$; $-S(=O)_2-R^{27}$ or for a radical selected from the group consisting of methyl, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CHF_2$, $-CH_2F$, $-CF_2Cl$, $-CCl_2F$, ethyl, $-CF_2-CH_3$, $-CH_2-CF_3$, $-C_2F_5$, $-CH_2-CCl_3$, $-CH_2-CBr_3$, $-CHF-CF_2Cl$, $-CF_2-CF_2Cl$, $-CFCl-CF_2Cl$, n-propyl, $-CF_2-CF_2-CF_3$, $-CF(CF_3)_2$, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^6 stands for hydrogen or for an alkyl radical selected from the group consisting of $-CH_2-OH$, $-CH_2-CH_2-OH$, $-CH_2-CH_2-CH_2-OH$, $-CH_2-CH_2-CH_2-CH_2-OH$, isopropyl, n-butyl, sec-butyl, isobutyl, methyl, ethyl, and n-propyl;

R^7 stands for hydrogen or $-OH$;

or R^6 and R^7 form, together with the interconnecting carbon atom as ring member, a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl;

R^8 stands for $-SF_5$; $-O-CF_3$; $-O-CFH_2$; $-O-CF_2H$; $-CFH_2$; $-CF_2H$; $-CF_3$; or for a tert-butyl radical, each of which can be unsubstituted or substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 substituents independently selected from the

group consisting of F, Cl, Br, I, -CN, -NO₂, -OH, -NH₂, -SH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -NH-CH₃, and -NH-C₂H₅;

T stands for C-R³⁵ and U stands for C-R³⁶ and V stands for N and W stands for C-R³⁸

or

T stands for C-R³⁵ and U stands for N and V stands for C-R³⁷ and W stands for C-R³⁸

or

T stands for N and U stands for C-R³⁶ and V stands for C-R³⁷ and W stands for C-R³⁸

or

T stands for N and U stands for N and V stands for C-R³⁷ and W stands for C-R³⁸

or

T stands for N and U stands for C-R³⁶ and V stands for N and W stands for C-R³⁸

or

T stands for C-R³⁵ and U stands for N and V stands for N and W stands for C-R³⁸

or

T stands for C-R³⁵ and U stands for C-R³⁶ and V stands for C-R³⁷ and W stands for C-R³⁸

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R²⁶, and R²⁷ each independently

stand for a radical selected from the group consisting of methyl, -CF₃, -CCl₃, -CBr₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, -CH₂-CN, -CH₂-O-CH₃, -CH₂-O-CF₃, -CH₂-SF₃, ethyl, -CF₂-CH₃, -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CHF-CF₂Cl, -CF₂-CF₂Cl, -CFCl-CF₂Cl, -CH₂-CH₂-CN, n-propyl, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, -CH₂-CH₂-CH₂-CN, -CH₂-O-CH₂-CH₃, -CH₂-CH₂-SF₃, -CH₂-CH₂-OCF₃, -CH(CH₃)-(O-CH₃), -CH(CH₃)-(S-CH₃), n-butyl, -CF₂-CF₂-CF₂-CF₃, -CH₂-CH₂-CH₂-CH₂-CN, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-heptyl, 4-heptyl, n-

octyl, n-nonyl, 5-nonyl, (2,6)-dimethyl-hept-4-yl, 3-methyl-butyl, n-hexyl, (3,3)-dimethylbutyl, $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-O-C}_2\text{H}_5$, $-\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-O-CH}_3$, ethenyl, propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, and 3-pentenyl;

for a radical selected from the group consisting of 2,3-dihydro-1H-indenyl, cyclopropyl, oxetanyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which can be bonded via a $-\text{CH}_2\text{-O-}$, $-\text{CH}_2\text{-CH}_2\text{-O-}$, $-\text{CH}_2\text{-CH}_2\text{-O-CH}_2\text{-}$, $-\text{CH}_2\text{-CH(CH}_3\text{)-O-CH}_2\text{-}$, $-(\text{CH}_2)\text{-}$, $-(\text{CH}_2)_2$ or $-(\text{CH}_2)_3$ group and/or can each be unsubstituted or optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of oxo ($=\text{O}$), thioxo ($=\text{S}$), $-\text{OH}$, $-\text{O-CH}_3$, $-\text{O-C}_2\text{H}_5$, $-\text{O-CH(CH}_3)_2$, $-\text{O-C(CH}_3)_3$, $-\text{O-CF}_3$, $-\text{S-CF}_3$, $-\text{SH}$, $-\text{S-CH}_3$, $-\text{S-C}_2\text{H}_5$, $-\text{S-CH(CH}_3)_2$, $-\text{S-C(CH}_3)_3$, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, $-\text{C(=O)-CH}_3$, $-\text{C(=O)-C}_2\text{H}_5$, $-\text{C(=O)-CH(CH}_3)_2$, $-\text{C(=O)-C(CH}_3)_3$, $-\text{C(=O)-OH}$, $-\text{C(=O)-O-CH}_3$, $-\text{C(=O)-O-C}_2\text{H}_5$, $-\text{C(=O)-O-CH(CH}_3)_2$, and $-\text{C(=O)-O-C(CH}_3)_3$;

or for a radical selected from the group consisting of phenyl, naphthyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, pyrazinyl, pyranyl, triazolyl, pyridinyl, imidazolyl, thiazolyl, oxazolyl, and isoxazolyl, and each radical can be bonded via a $-(\text{CH}_2)\text{-}$, $-(\text{CH}_2)_2$ or $-(\text{CH}_2)_3$ group and/or can be unsubstituted or optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, $-\text{CN}$, $-\text{CF}_3$, $-\text{SF}_5$, $-\text{OH}$, $-\text{O-CH}_3$, $-\text{O-C}_2\text{H}_5$, $-\text{O-CH(CH}_3)_2$, $-\text{O-C(CH}_3)_3$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{O-CF}_3$, $-\text{S-CF}_3$, $-\text{SH}$, $-\text{S-CH}_3$, $-\text{S-C}_2\text{H}_5$, $-\text{S-CH(CH}_3)_2$, $-\text{S-C(CH}_3)_3$, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, $-\text{C(=O)-OH}$, $-\text{C(=O)-O-CH}_3$, $-\text{C(=O)-O-C}_2\text{H}_5$, $-\text{C(=O)-O-CH(CH}_3)_2$, $-\text{C(=O)-O-C(CH}_3)_3$, $-\text{NH-CH}_3$, $-\text{NH-C}_2\text{H}_5$, $-\text{NH-C(CH}_3)_3$, $-\text{N(CH}_3)_2$, $-\text{N(C}_2\text{H}_5)_2$, $-\text{N(CH}_3\text{)-(C}_2\text{H}_5)$, $-\text{NH-C(=O)-O-CH}_3$, $-\text{NH-C(=O)-O-C}_2\text{H}_5$, $-\text{NH-C(=O)-O-C(CH}_3)_3$, $-\text{C(=O)-H}$, $-\text{C(=O)-CH}_3$, $-\text{C(=O)-C}_2\text{H}_5$, $-\text{C(=O)-CH(CH}_3)_2$, $-\text{C(=O)-C(CH}_3)_3$, $-\text{C(=O)-NH}_2$, $-\text{C(=O)-NH-CH}_3$, -

C(=O)-NH-C₂H₅, -C(=O)-N(CH₃)₂, -C(=O)-N(C₂H₅)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl;

R³⁵, R³⁶, and R³⁷ each independently stand for H; F; Cl; Br; I; -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR¹³; -NR¹⁴R¹⁵; -OR¹⁶; -SR¹⁷; -S(=O)-R²⁵; -S(=O)₂-R²⁶; for a radical selected from the group consisting of -CH₂-OH, methyl, -CF₃, -CCl₃, -CBr₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, ethyl, -CF₂-CH₃, -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CHF-CF₂Cl, -CF₂-CF₂Cl, -CFCl-CF₂Cl, n-propyl, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl or for a phenyl radical, which are unsubstituted or can optionally be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

R³⁸ stands for -SF₅; -NO₂; -CN; -NH₂; -OH; -SH; -C(=O)-NH₂; -S(=O)₂-NH₂; -C(=O)-NH-OH; -C(=O)-OH; -C(=O)-H; -S(=O)₂-OH; -NHR³⁹; -NR⁴⁰R⁴¹; -OR⁴²; -SR⁴³; -C(=O)-OR⁵⁰; -S(=O)-R⁵²; -S(=O)₂-R⁵³; -C(=NH)-NH₂; -C(=NH)-NH-R⁵⁴; -N=C(NH₂)₂; -N=C(NHR⁵⁵)-(NHR⁵⁶);

for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which is bonded to the basic framework via a carbon atom of the rings of the aforementioned radicals or via a - (CH=CH)-, -C≡C or -C≡C-CH₂- group and is unsubstituted or can optionally be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of -CN, -CH₂-N(CH₃)₂, -CH₂-N(C₂H₅)₂, -CH₂-NH-CH₃, -CH₂-NH-C₂H₅, -N-[C(=O)-C₂H₅]phenyl, -N-[C(=O)-CH₃]phenyl, oxo (=O), thioxo (=S), -OH, -O-CH₃, -O-C₂H₅, -O-

CH(CH₃)₂, -O-C(CH₃)₃, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, -C(=O)-CH₃, -C(=O)-C₂H₅, -C(=O)-CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-CH(CH₃)₂, and -C(=O)-O-C(CH₃)₃;

or for a radical selected from the group consisting of (1,3)-benzodioxolyl, (1,4)-benzodioxanyl, tetrazolyl, (2,3)-dihydrothieno[3.4-b][1.4]dioxinyl, benzo[b]furanyl, phenyl, naphthyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, pyrazinyl, pyranyl, triazolyl, pyridinyl, imidazolyl, indolyl, isoindolyl, thiazolyl, oxazolyl, isoxazolyl, pyridazinyl, pyrazinyl, pyrimidinyl, indazolyl, quinoxalinyl, quinolinyl, and isoquinolinyl, each of which can be bonded via a -(CH=CH)-, -C≡C-, -(CH₂)-, -(CH₂)₂- or -(CH₂)₃ group and/or is unsubstituted or can optionally be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-CH(CH₃)₂, -C(=O)-O-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -NH-C(=O)-O-CH₃, -NH-S(=O)₂-CH₃, -NH-S(=O)₂-C₂H₅, -NH-S(=O)₂-CH(CH₃)₂, -NH-C(=O)-O-C₂H₅, -NH-C(=O)-O-C(CH₃)₃, -C(=O)-H, -C(=O)-CH₃, -C(=O)-C₂H₅, -C(=O)-CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-NH₂, -C(=O)-NH-CH₃, -C(=O)-NH-C₂H₅, -C(=O)-N(CH₃)₂, -C(=O)-N(C₂H₅)₂, -O-phenyl, -O-benzyl, phenyl, and benzyl;

R³⁹, R⁴⁰, and R⁴¹, R⁴², R⁴³, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, and R⁵⁶ each independently

stand for a radical selected from the group consisting of methyl, -CF₃, -CCl₃, -CBr₃, -CHF₂, -CH₂F, -CF₂Cl, -CCl₂F, -CH₂-CN, -CH₂-O-CH₃, -CH₂-O-CF₃, -CH₂-SF₃, ethyl, -CF₂-CH₃, -CH₂-CF₃, -C₂F₅, -CH₂-CCl₃, -CH₂-CBr₃, -CHF-CF₂Cl, -CF₂-CF₂Cl, -CFCl-CF₂Cl, -CH₂-CH₂-CN, n-propyl, -CF₂-CF₂-CF₃, -CF(CF₃)₂, isopropyl, -CH₂-CH₂-CH₂-CN, -CH₂-O-

CH₂-CH₃, -CH₂-CH₂-SF₃, -CH₂-CH₂-OCF₃, -CH(CH₃)-(O-CH₃), -
 CH(CH₃)-(S-CH₃), n-butyl, -CF₂-CF₂-CF₂-CF₃, -CH₂-CH₂-CH₂-CH₂-CN,
 sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-heptyl, 4-heptyl, n-
 octyl, n-nonyl, 5-nonyl, (2,6)-dimethyl-hept-4-yl, 3-methyl-butyl, n-hexyl,
 (3,3)-dimethylbutyl, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-O-C₂H₅, -CH₂-CH₂-
 CH₂-O-CH₃, ethenyl, propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, and 3-
 pentenyl;

for a radical selected from the group consisting of 2,3-dihydro-1H-
 indenyl, cyclopropyl, oxetanyl, cyclobutyl, cyclopentyl, cyclohexyl,
 imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl,
 piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl,
 and thiomorpholinyl, each of which can be bonded via a -CH₂-O-, -CH₂-
 CH₂-O-, -CH₂-CH₂-O-CH₂-, -CH₂-CH(CH₃)-O-CH₂-, -(CH₂)-, -(CH₂)₂- or -
 (CH₂)₃ group and/or can each be unsubstituted or optionally substituted
 by 1, 2, 3, 4, or 5 substituents independently selected from the group
 consisting of oxo (=O), thioxo (=S), -OH, -O-CH₃, -O-C₂H₅, -O-
 CH(CH₃)₂, -O-C(CH₃)₃, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-
 CH(CH₃)₂, -S-C(CH₃)₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-
 butyl, isobutyl, tert-butyl, n-pentyl, -C(=O)-CH₃, -C(=O)-C₂H₅, -C(=O)-
 CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅,
 -C(=O)-O-CH(CH₃)₂, and -C(=O)-O-C(CH₃)₃;

or for a radical selected from the group consisting of phenyl, naphthyl,
 thiophenyl, furanyl, pyrrolyl, pyrazolyl, pyrazinyl, pyranlyl, triazolyl,
 pyridinyl, imidazolyl, thiazolyl, oxazolyl, and isoxazolyl, and each radical
 can be bonded via a -(CH₂)-, -(CH₂)₂- or -(CH₂)₃ group and/or can each
 be unsubstituted or optionally substituted by 1, 2, 3, 4, or 5 substituents
 independently selected from the group consisting of F, Cl, Br, I, -CN, -
 CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -
 NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃,
 methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl,
 n-pentyl, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-
 CH(CH₃)₂, -C(=O)-O-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -

$\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{C}_2\text{H}_5)_2$, $-\text{N}(\text{CH}_3)(\text{C}_2\text{H}_5)$, $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{CH}_3$, $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{C}_2\text{H}_5$, $-\text{NH}-\text{C}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)_3$, $-\text{C}(=\text{O})-\text{H}$, $-\text{C}(=\text{O})-\text{CH}_3$, $-\text{C}(=\text{O})-\text{C}_2\text{H}_5$, $-\text{C}(=\text{O})-\text{CH}(\text{CH}_3)_2$, $-\text{C}(=\text{O})-\text{C}(\text{CH}_3)_3$, $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{C}(=\text{O})-\text{NH}-\text{CH}_3$, $-\text{C}(=\text{O})-\text{NH}-\text{C}_2\text{H}_5$, $-\text{C}(=\text{O})-\text{N}(\text{CH}_3)_2$, $-\text{C}(=\text{O})-\text{N}(\text{C}_2\text{H}_5)_2$, $-\text{O}-\text{phenyl}$, $-\text{O}-\text{benzyl}$, phenyl , and benzyl ;

or

R^{40} and R^{41} form, together with the interconnecting nitrogen atom as ring member,

a radical selected from the group consisting of 3-aza-bicyclo[3.1.1]heptyl, 6-aza-spiro[2.5]octyl, 3-aza-bicyclo[3.2.1]octyl, 6-aza-bicyclo[3.3.1]heptyl, 8-aza-bicyclo[3.2.1]octyl, 1-oxa-2,8-diazaspiro[4.5]dec-2-enyl, azocanyl, isoindolyl, indolyl, (1,2,3,6)-tetrahydropyridinyl, (4,5,6,7)-tetrahydroisoxazolo[5.4-c]pyridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, diazepanyl, and thiomorpholinyl, of which the heterocycloaliphatic portion can in each case be unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R^{57} ;

R^{57} stands for $-\text{NHR}^{58}$, $-\text{NR}^{59}\text{R}^{60}$, or for an alkyl radical selected from the group consisting of $-\text{CF}_3$, $-\text{CH}_2-\text{CF}_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

R^{58} , R^{59} , and R^{60} each independently stand for $-\text{C}(=\text{O})-\text{R}^{61}$; or for an alkyl radical selected from the group consisting of $-\text{CF}_3$, $-\text{CH}_2-\text{CF}_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

or for a radical selected from the group consisting of phenyl, naphthyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, pyrazinyl, pyranlyl, triazolyl, pyridinyl, imidazolyl, thiazolyl, oxazolyl, and isoxazolyl, and each radical can be bonded via a $-(\text{CH}_2)-$, $-(\text{CH}_2)_2-$ or $-(\text{CH}_2)_3$ group and/or can each be unsubstituted or optionally substituted by 1, 2, 3, 4, or 5 substituents

independently selected from the group consisting of F, Cl, Br, I, -CN, -
 CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -NH₂, -
 NO₂, -O-CF₃, -S-CF₃, -SH, -S-CH₃, -S-C₂H₅, -S-CH(CH₃)₂, -S-C(CH₃)₃,
 methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl,
 5 n-pentyl, -C(=O)-OH, -C(=O)-O-CH₃, -C(=O)-O-C₂H₅, -C(=O)-O-
 CH(CH₃)₂, -C(=O)-O-C(CH₃)₃, -NH-CH₃, -NH-C₂H₅, -NH-C(CH₃)₃, -
 N(CH₃)₂, -N(C₂H₅)₂, -N(CH₃)-(C₂H₅), -NH-C(=O)-O-CH₃, -NH-C(=O)-O-
 C₂H₅, -NH-C(=O)-O-C(CH₃)₃, -C(=O)-H, -C(=O)-CH₃, -C(=O)-C₂H₅, -
 C(=O)-CH(CH₃)₂, -C(=O)-C(CH₃)₃, -C(=O)-NH₂, -C(=O)-NH-CH₃, -
 10 C(=O)-NH-C₂H₅, -C(=O)-N(CH₃)₂, -C(=O)-N(C₂H₅)₂, -O-phenyl, -O-
 benzyl, phenyl, and benzyl;

and R⁶¹ stands for an alkyl radical selected from the group consisting of -
 CF₃, -CH₂-CF₃, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-
 15 butyl, and isobutyl;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 20 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

3. The compounds according to claim 1 or claim 2, characterized in that

25 n stands for 0, 1, or 2;

R¹ stands for H; F; Cl; Br; I; -NO₂; -CF₃; -CN; -NH₂; -OH; -NH-C(=O)-R¹³; -
 OR¹⁶; -SR¹⁷; -S(=O)₂-NR²²R²³; -S(=O)₂-R²⁷; or for a radical selected
 from the group consisting of methyl, -CF₃, -CHF₂, -CH₂F, ethyl, n-
 30 propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R² stands for H; F; Cl; Br; I; -NO₂; -CF₃; -CN; -NH₂; -OH; -NH-C(=O)-R¹³; -
 OR¹⁶; -SR¹⁷; -S(=O)₂-NR²²R²³; -S(=O)₂-R²⁷; or for a radical selected

from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^3 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})_2-\text{R}^{27}$; or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^4 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})_2-\text{R}^{27}$; or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^5 stands for H; F; Cl; Br; I; $-\text{NO}_2$; $-\text{CF}_3$; $-\text{CN}$; $-\text{NH}_2$; $-\text{OH}$; $-\text{NH}-\text{C}(=\text{O})-\text{R}^{13}$; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$; $-\text{S}(=\text{O})_2-\text{R}^{27}$; or for a radical selected from the group consisting of methyl, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{F}$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^6 stands for hydrogen or for an alkyl radical selected from the group consisting of isopropyl, n-butyl, sec-butyl, isobutyl, methyl, ethyl, and n-propyl;

R^7 stands for hydrogen or $-\text{OH}$;

or

R^6 and R^7 form, together with the interconnecting carbon atom as ring member, a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl;

R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

T stands for $\text{C}-\text{R}^{35}$ and U stands for $\text{C}-\text{R}^{36}$ and V stands for N and W stands for $\text{C}-\text{R}^{38}$

or

T stands for $C-R^{35}$ and U stands for $C-R^{36}$ and V stands for $C-R^{37}$ and W stands for $C-R^{38}$;

R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, $-CF_2-CH_3$, $-CH_2-CF_3$, $-C_2F_5$, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-heptyl, 4-heptyl, n-octyl, n-nonyl, 5-nonyl, (2,6)-dimethyl-hept-4-yl, 3-methyl-butyl, n-hexyl, (3,3)-dimethylbutyl and ethenyl;

R^{35} , R^{36} , and R^{37} each independently stand for H; F; Cl; Br; I; $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-OR^{16}$; $-SR^{17}$; or for a radical selected from the group consisting of $-CH_2-OH$, methyl, $-CF_3$, $-CHF_2$, $-CH_2F$, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

R^{38} stands for $-SF_5$; $-NO_2$; $-CN$; $-NH_2$; $-OH$; $-SH$; $-NHR^{39}$; $-NR^{40}R^{41}$; $-OR^{42}$; $-SR^{43}$;

for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which is bonded to the parent structure via a carbon atom of the rings of the aforementioned residues and are unsubstituted or can optionally be substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of $-CH_2-N(CH_3)_2$, $-CH_2-N(C_2H_5)_2$, $-CH_2-NH-CH_3$, $-CH_2-NH-C_2H_5$, $-N-[C(=O)-C_2H_5]$ phenyl, $-N-[C(=O)-CH_3]$ phenyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl;

or for a radical selected from the group consisting of phenyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, pyrazinyl, pyranyl, triazolyl, pyridinyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridazinyl, pyrazinyl, and

pyrimidinyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, -CN, -CF₃, -SF₅, -OH, -O-CH₃, -O-C₂H₅, -O-CH(CH₃)₂, -O-C(CH₃)₃, -O-CF₃, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

R⁴¹, R⁴², R⁴³, R⁴², and R⁴³, each independently

stand for a radical selected from the group consisting of methyl, -CH₂-O-CH₃, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, (3,3)-dimethylbutyl, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-O-C₂H₅, and -CH₂-CH₂-CH₂-O-CH₃;

for a radical selected from the group consisting of 2,3-dihydro-1H-indenyl, cyclopropyl, oxetanyl, cyclobutyl, cyclopentyl, cyclohexyl, imidazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, diazepanyl, azocanyl, and thiomorpholinyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

or

R⁴⁰ and R⁴¹ form, together with the interconnecting nitrogen atom as ring member, a radical selected from the group consisting of 3-aza-bicyclo[3.1.1]heptyl, 6-aza-spiro[2.5]octyl, 3-aza-bicyclo[3.2.1]octyl, 6-aza-bicyclo[3.3.1]heptyl, 8-aza-bicyclo[3.2.1]octyl, 1-oxa-2,8-diazaspiro[4.5]dec-2-enyl, azocanyl, isoindolyl, indolyl, (1,2,3,6)-tetrahydropyridinyl, (4,5,6,7)-tetrahydroisoxazolo[5.4-c]pyridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, diazepanyl, and thiomorpholinyl, of which the heterocycloaliphatic moiety can in each case be unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R⁵⁷;

R^{57} stands for $-NHR^{58}$, $-NR^{59}R^{60}$, or for an alkyl radical selected from the group consisting of $-CF_3$, $-CH_2CF_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

R^{58} , R^{59} , and R^{60} each independently stand for $-C(=O)-R^{61}$; for an alkyl radical selected from the group consisting of $-CF_3$, $-CH_2CF_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

or for a radical selected from the group consisting of phenyl and naphthyl, and the radical can each be bonded via a $-(CH_2)-$, $-(CH_2)_2-$ or $-(CH_2)_3$ group and/or can each be unsubstituted or optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of F, Cl, Br, I, $-CN$, $-CF_3$, $-O-CH_3$, $-O-C_2H_5$, $-O-CH(CH_3)_2$, $-O-C(CH_3)_3$, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

and R^{61} stands for an alkyl radical selected from the group consisting of $-CF_3$, $-CH_2CF_3$, methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

4. The compounds according to any one or more of claims 1 to 3, characterized in that

n stands for 0, 1, or 2;

R^1 stands for H; F; Cl; Br; I; methyl, ethyl, $-NO_2$; $-OH$; $-NH_2$; $-NH-C(=O)-R^{13}$; $-OR^{16}$; $-SR^{17}$; $-S(=O)_2-NR^{22}R^{23}$ or $-S(=O)_2-R^{27}$;

R^2 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-$
 R^{13} ; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-\text{S}(=\text{O})_2-\text{R}^{27}$;

5 R^3 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-$
 R^{13} ; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-\text{S}(=\text{O})_2-\text{R}^{27}$;

R^4 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-$
 R^{13} ; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-\text{S}(=\text{O})_2-\text{R}^{27}$;

10

R^5 stands for H; F; Cl; Br; I; methyl, ethyl, $-\text{NO}_2$; $-\text{OH}$; $-\text{NH}_2$; $-\text{NH}-\text{C}(=\text{O})-$
 R^{13} ; $-\text{OR}^{16}$; $-\text{SR}^{17}$; $-\text{S}(=\text{O})_2-\text{NR}^{22}\text{R}^{23}$ or $-\text{S}(=\text{O})_2-\text{R}^{27}$;

15

R^6 stands for hydrogen or for an alkyl radical selected from the group
consisting of isopropyl, n-butyl, sec-butyl, isobutyl, methyl, ethyl, and n-
propyl;

R^7 stands for hydrogen or $-\text{OH}$;

20

R^8 stands for $-\text{SF}_5$; $-\text{O}-\text{CF}_3$; $-\text{CF}_3$; tert-butyl; or $-\text{C}(\text{CH}_3)_2(\text{CH}_2\text{OH})$;

T stands for $\text{C}-\text{R}^{35}$ and U stands for $\text{C}-\text{R}^{36}$ and V stands for N and W stands
for $\text{C}-\text{R}^{38}$

or

25

T stands for $\text{C}-\text{R}^{35}$ and U stands for $\text{C}-\text{R}^{36}$ and V stands for $\text{C}-\text{R}^{37}$ and W
stands for $\text{C}-\text{R}^{38}$

30

R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected
from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl,
sec-butyl, isobutyl, tert-butyl, n-pentyl, and ethenyl;

R^{35} , R^{36} , and R^{37} each stand for H;

R^{38} stands for $-\text{NHR}^{39}$; $-\text{NR}^{40}\text{R}^{41}$; $-\text{OR}^{42}$; $-\text{SR}^{43}$;

R^{39} , R^{42} , and R^{43} each independently

stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, and (3,3)-dimethylbutyl;

or for a radical selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which can be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

or

R^{40} and R^{41} form, together with the interconnecting nitrogen atom as ring member, a radical selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and azepanyl, of which the heterocycloaliphatic moiety can in each case be unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R^{57} ;

and R^{57} stands for an alkyl radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and isobutyl;

each optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers thereof, the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or each in the form of corresponding salts, or each in the form of corresponding solvates.

5. The compounds according to any one or more of claims 1 to 4, characterized in that

n stands for 1;

R^1 stands for H; F; Cl; Br; or I;

5 R^2 stands for H; F; Cl; Br; I; -OH; -NH₂ or -OR¹⁶;

R^3 stands for H; F; Cl; Br; I; -NO₂; -OH; -NH₂; -NH-C(=O)-R¹³; -OR¹⁶; -SR¹⁷; -S(=O)-NR²²R²³ or -S(=O)₂-R²⁷;

10 R^4 stands for H; F; Cl; Br; I; methyl, -OH; -NH₂ or -OR¹⁶;

R^5 stands for H; F; Cl; Br or I;

15 R^6 stands for hydrogen or for an alkyl radical selected from the group consisting of isopropyl, n-butyl, sec-butyl, isobutyl, methyl, ethyl, and n-propyl;

R^7 stands for hydrogen or -OH;

20 R^8 stands for -SF₅; -O-CF₃; -CF₃; tert-butyl or -C(CH₃)₂(CH₂OH);

T stands for C-R³⁵ and U stands for C-R³⁶ and V stands for N and W stands for C-R³⁸

or

25 T stands for C-R³⁵ and U stands for C-R³⁶ and V stands for C-R³⁷ and W stands for C-R³⁸;

30 R^{13} , R^{16} , R^{17} , R^{22} , R^{23} and R^{27} each independently stand for a radical selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, and ethenyl;

R^{35} , R^{36} , and R^{37} each stand for H;

R^{38} stands for -NHR³⁹; -NR⁴⁰R⁴¹; -OR⁴²; -SR⁴³;

R^{39} , R^{42} , and R^{43} each independently

stand for a radical selected from the group consisting of methyl, ethyl,
5 n-propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 3-pentyl, n-hexyl, and (3,3)-dimethylbutyl;

or for a radical selected from the group consisting of cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which can
10 be optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and n-pentyl;

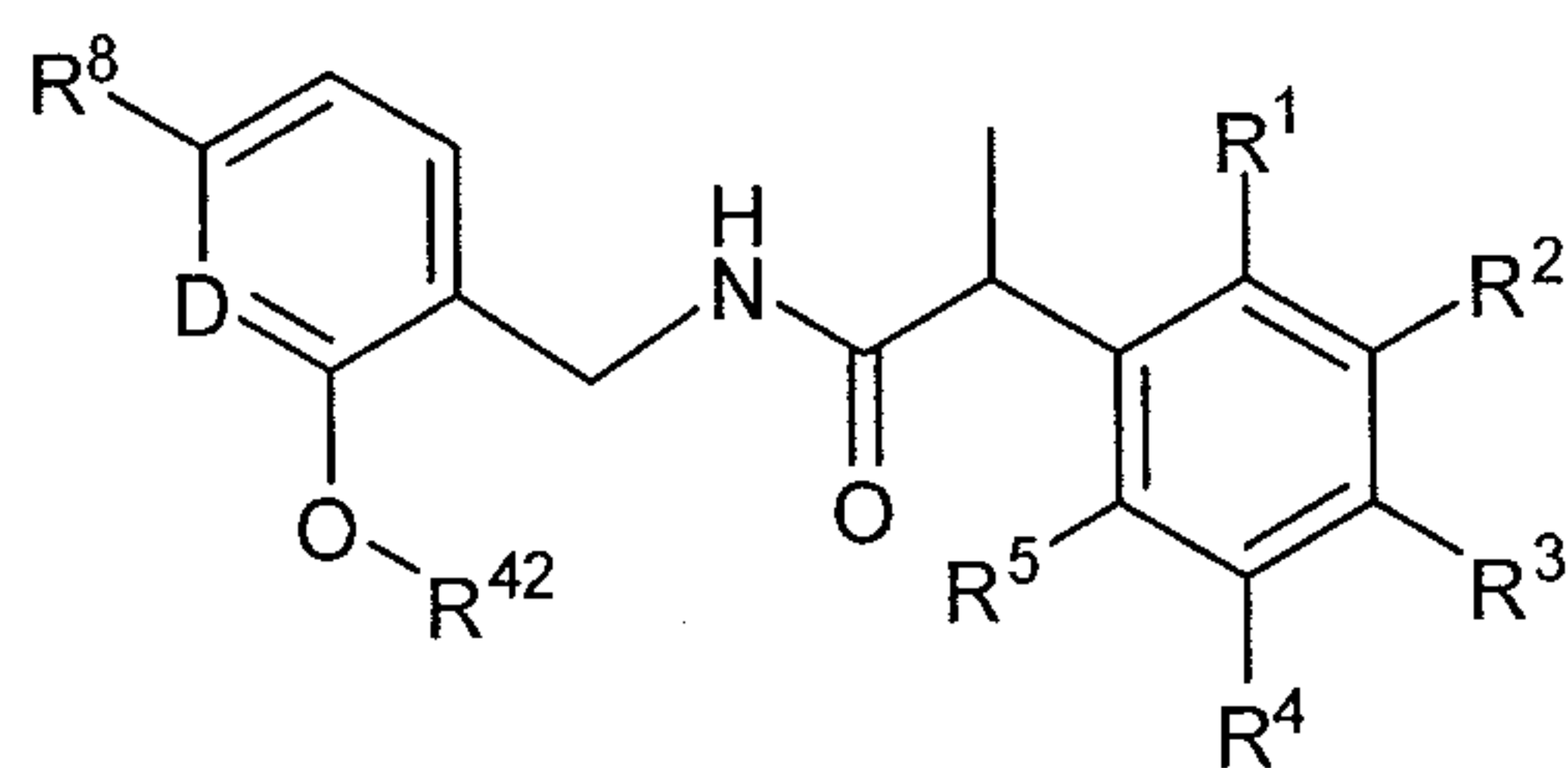
or

15 R^{40} and R^{41} form, together with the interconnecting nitrogen atom as ring member, a radical selected from the group comprising the group consisting pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and azepanyl, the heterocycloaliphatic moiety of which can each be
20 unsubstituted or substituted by 1, 2, 3, 4, or 5 radicals R^{57} ;

and R^{57} stands for an alkyl radical selected from the group consisting of
methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-butyl, sec-butyl, and
isobutyl;

25 each optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers thereof, the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or each in the form of
30 corresponding salts, or each in the form of corresponding solvates.

6. The compounds of the general formula Ia according to any one or more of claims 1 to 3,



1a,

in which

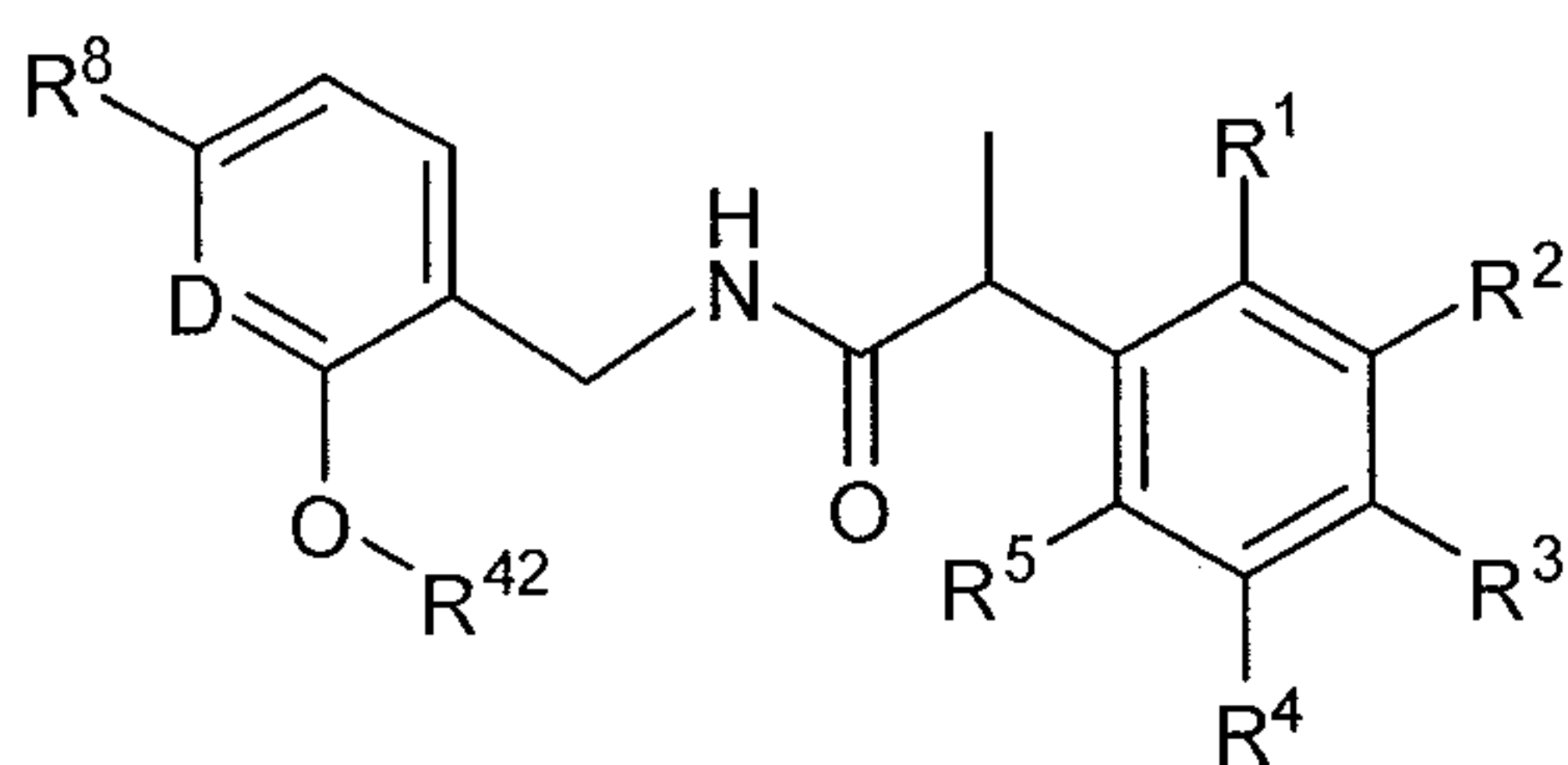
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 3;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

7. The compounds of the general formula 1a according to any one or more of claims 1 to 6,



1a,

in which

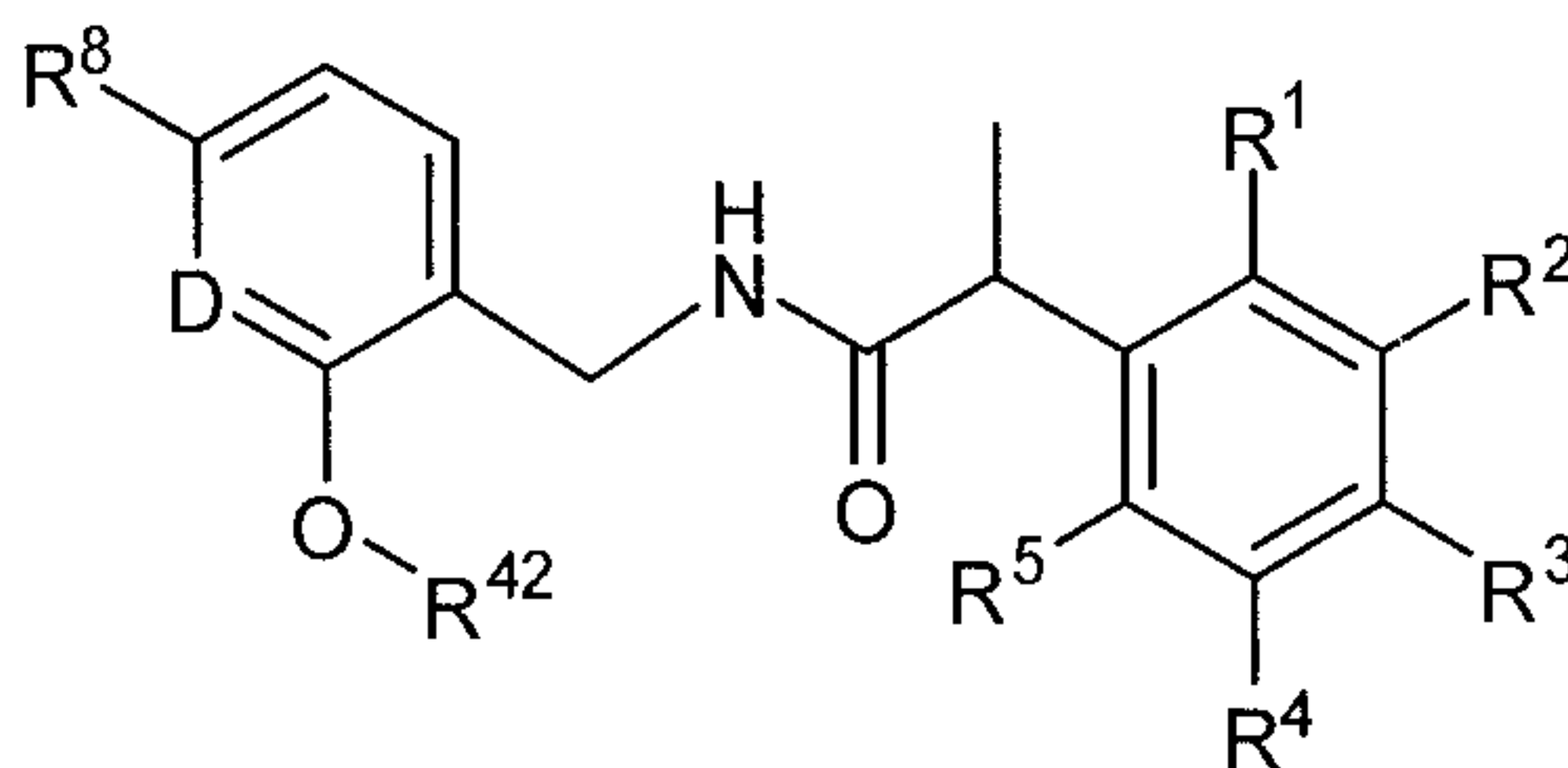
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 4;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

8. The compounds of the general formula Ia according to any one or more of
 claims 1 to 7,



Ia,

in which

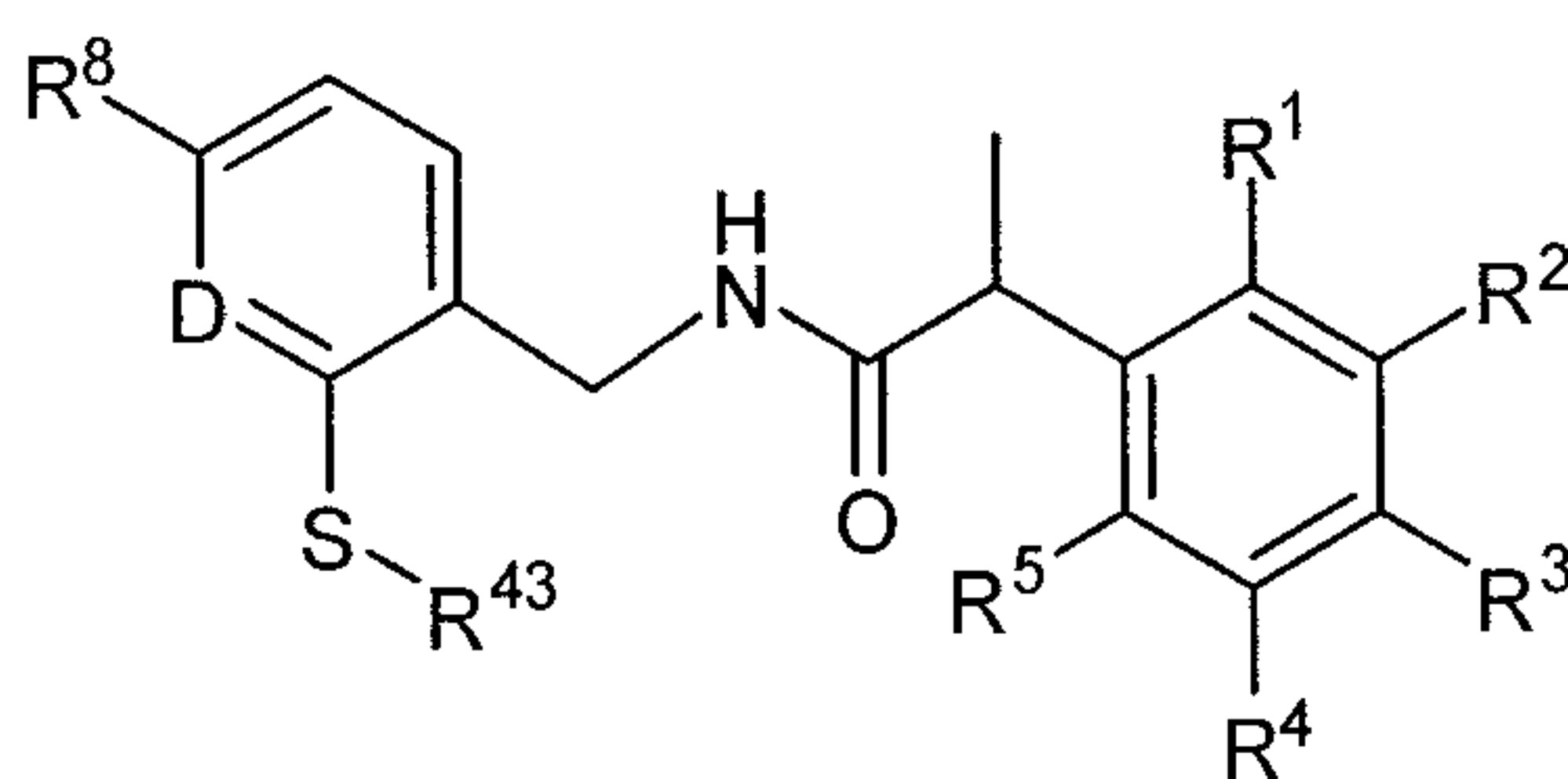
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 5;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

9. The compounds of the general formula Ib according to any one or more of
 claims 1 to 3,



Ib,

in which

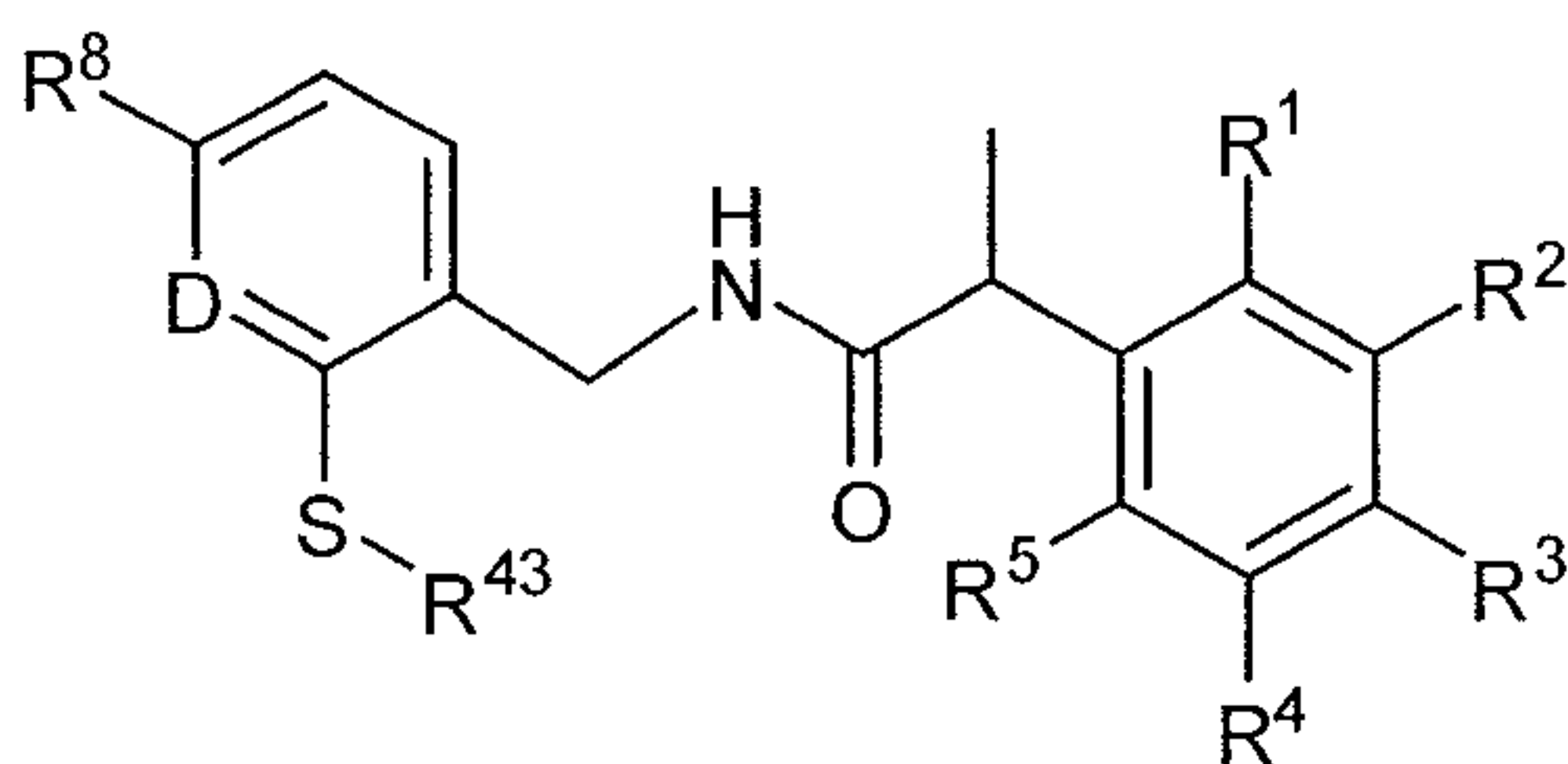
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 3;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

10. The compounds of the general formula Ib according to any one or more of claims 1 to 9,



Ib,

in which

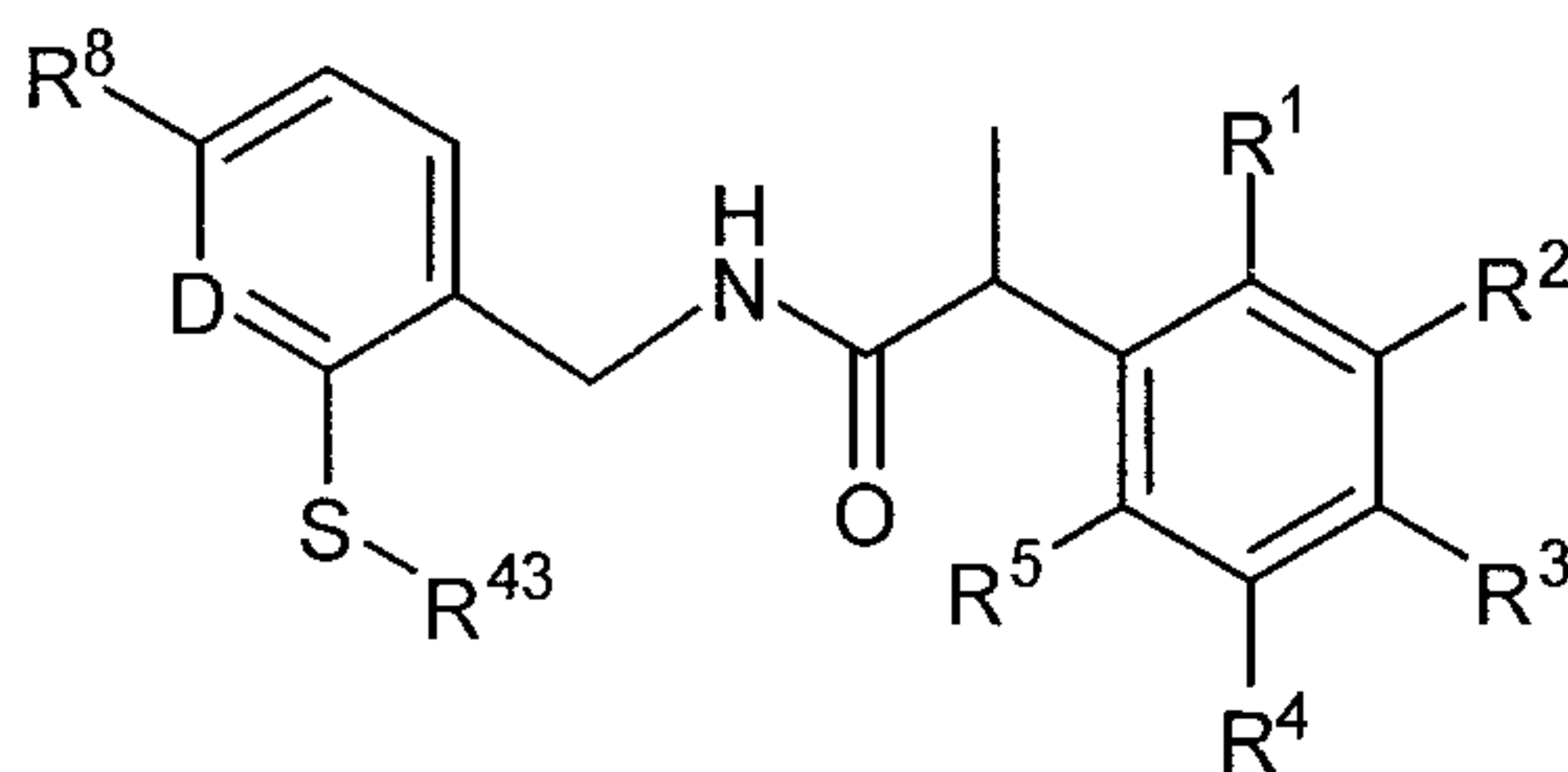
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 4;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

11. The compounds of the general formula Ib according to any one or more of
 claims 1 to 10,



Ib,

in which

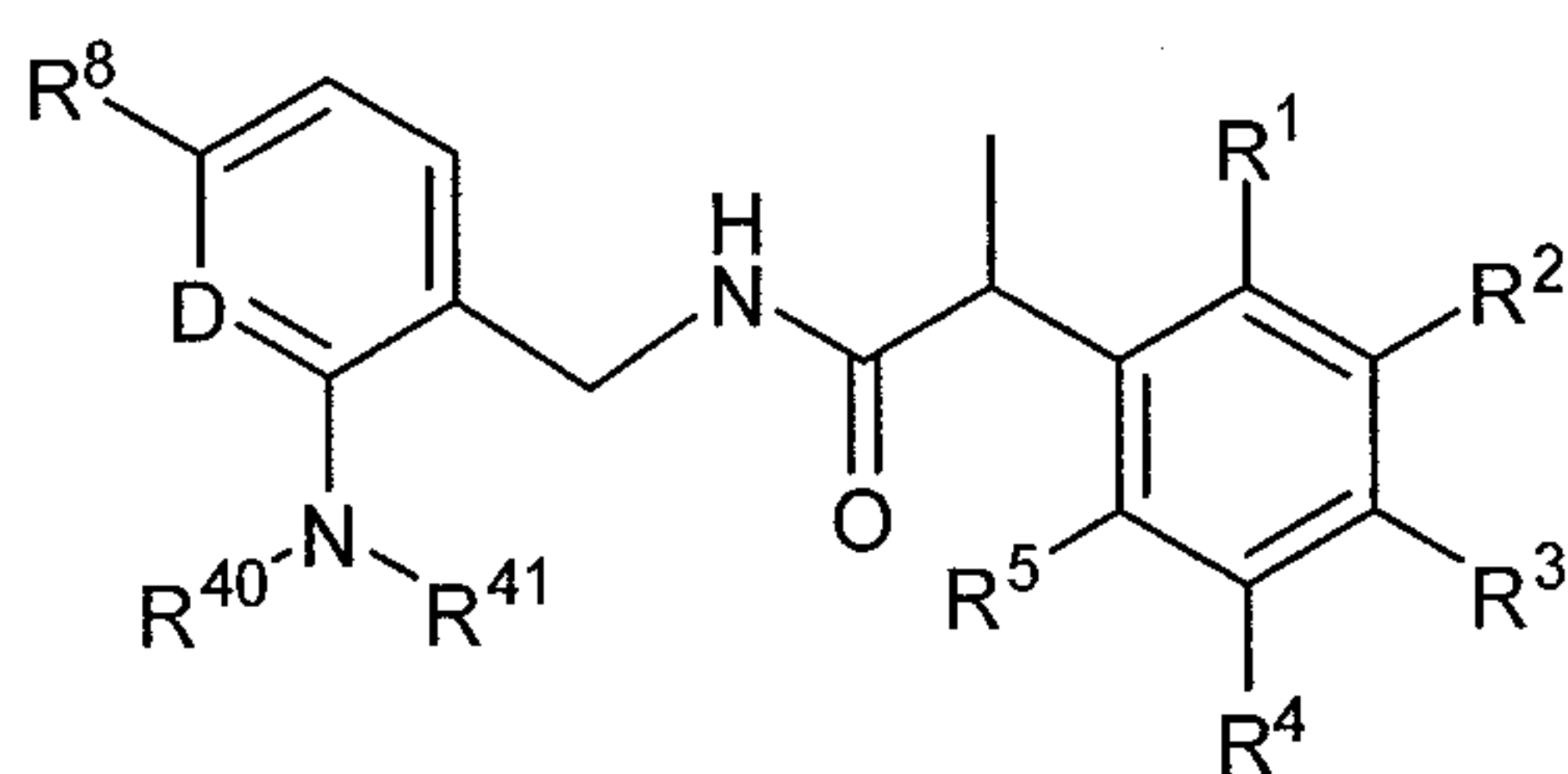
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 5;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

12. The compounds of the general formula Ic according to any one or more of
 claims 1 to 3,



1c,

in which

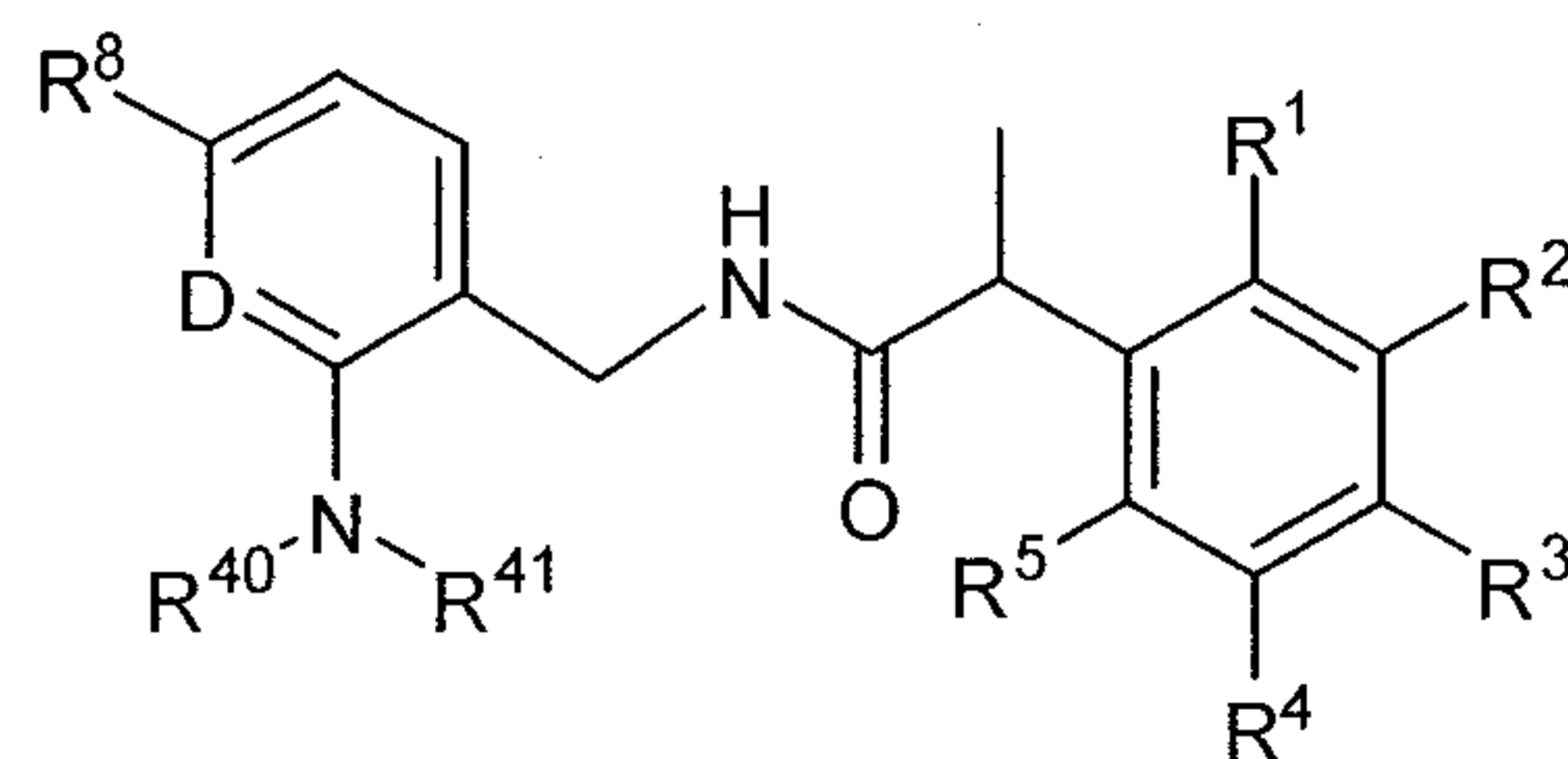
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 3;

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

13. The compounds of the general formula 1c according to any one or more of claims 1 to 12,



1c,

in which

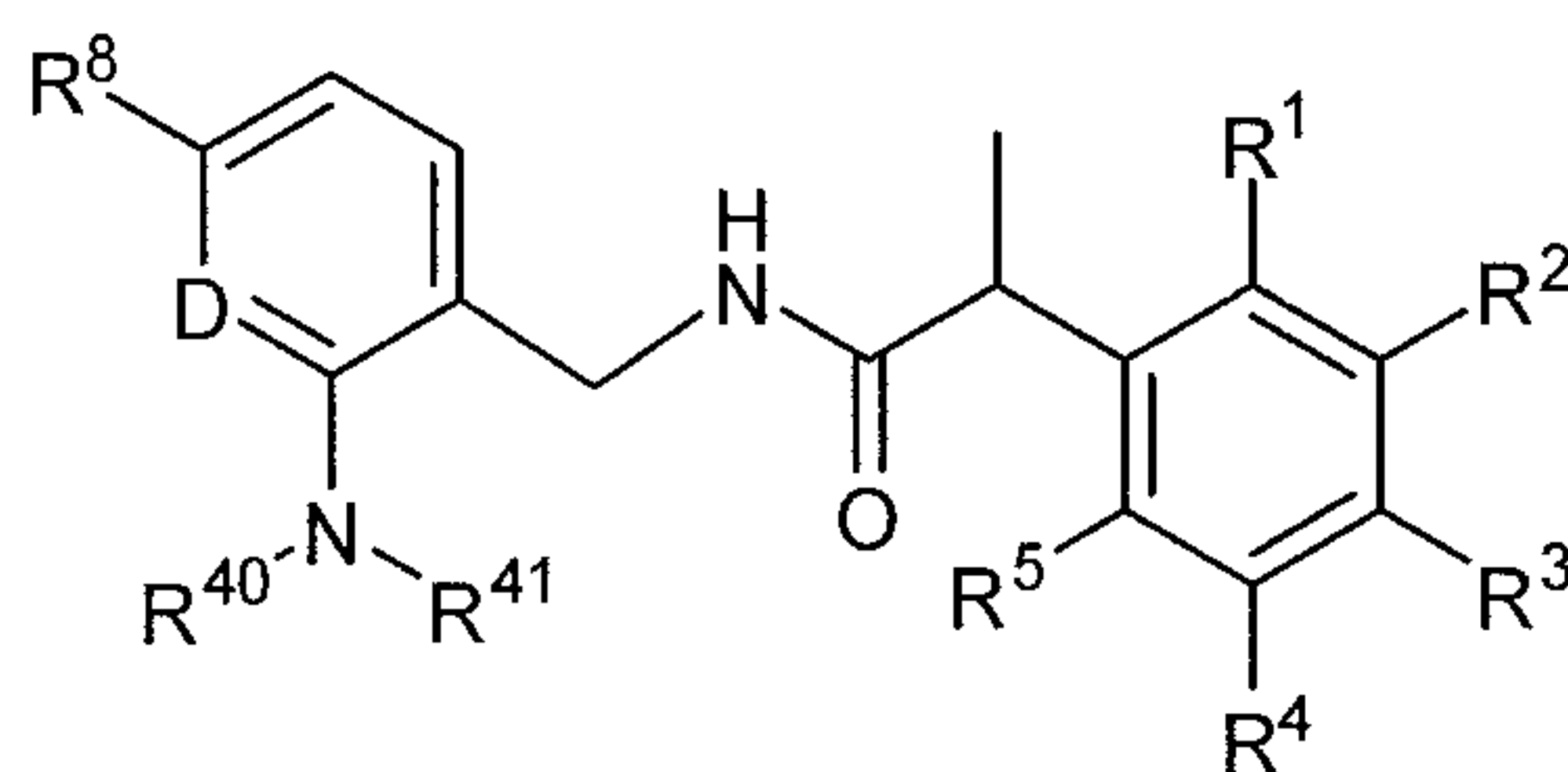
D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 4;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

14. The compounds of the general formula Ic according to any one or more of
 claims 1 to 13,



Ic,

in which

D stands for N or CH;

and

R^1 , R^2 , R^3 , R^4 , R^5 , R^8 , and R^{42} have the meanings stated in claim 5;

in each case optionally in the form of one of the pure stereoisomers thereof,
 particularly enantiomers or diastereoisomers, or the racemates thereof or in
 the form of a mixture of stereoisomers, particularly the enantiomers and/or
 diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of
 corresponding salts, or in each case in the form of corresponding solvates.

15. The compounds according to any one or more of claims 1 to 14, selected from
 the group consisting of

- [1] 2-(4-Amino-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [2] 2-(3,5-Dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- 5 [3] 2-(4-Amino-3-bromo-5-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- [4] 2-(3-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- [5] 2-(2,4-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- 10 [6] 2-(2,6-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- [7] 2-(2,5-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- 15 [8] 2-(4-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- [9] 2-(4-Hydroxy-3-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [10] 2-(3,5-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 20 [11] 2-(3,4-Difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [12] 2-(4-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 25 [13] 2-(3-Fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [14] 2-(3,4-Diaminophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 30 [15] N-(2-Butoxy-6-tert-butylpyridin-3-ylmethyl)-2-(3,4-diamino-phenyl)-propionamide,
- [16] N-((6-tert-Butyl-2-(4-methylpiperidin-1-yl)pyridin-3-yl)methyl)-2-(3,4-diaminophenyl)propanamide,
- [17] N-((6-tert-Butyl-2-(cyclohexylthio)pyridin-3-yl)methyl)-2-(3,4-diaminophenyl)propanamide,

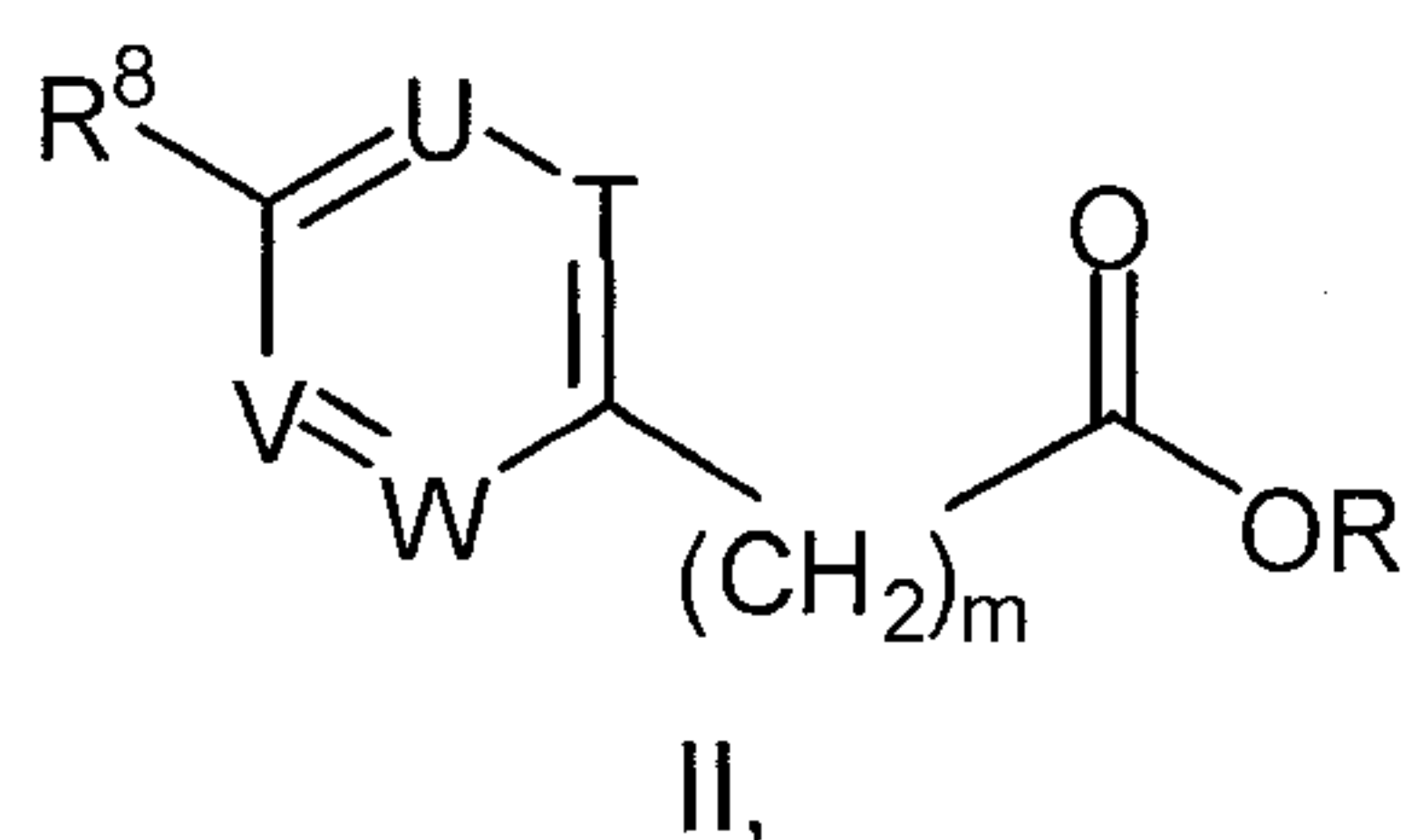
- [18] 2-(4-Acetamido-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [19] 2-(3,5-Dibromo-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 5 [20] 2-(4-Amino-3,5-dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [21] 2-(3-Bromo-4-hydroxy-5-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- [22] 2-(4-Amino-3,5-dibromophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- 10 [23] 2-(3,5-Dibromo-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)acetamide,
- [24] 2-(3-Amino-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 15 [25] 2-(3,5-Dibromo-phenyl)-N-(4-methyl-6'-trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-3'-ylmethyl)-acetamide.
- [26] 2-(4-Amino-3,5-difluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [27] 2-(3-Fluoro-5-hydroxy-4-nitrophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 20 [28] 2-(3-Chloro-4-(methylthio)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [29] 2-(3-Chloro-4-(methylsulfonyl)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 25 [30] 2-(3-Fluoro-4-(methylthio)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [31] 2-(3-Fluoro-4-(methylsulfonyl)phenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [32] 2-(4-(N,N-Dimethylsulfamoyl)-3-fluorophenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- 30 [33] N-(2-Fluoro-4-(1-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methylamino)-1-oxopropane-2-yl)phenyl)acrylamide,

- [34] N-(2-Fluoro-6-iodo-4-(1-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methylamino)-1-oxopropane-2-yl)phenyl)acrylamide,
- [35] 2-(4-Methoxy-3,5-dimethylphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [36] 2-(3,5-Difluoro-4-methoxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [37] 2-(4-Hydroxy-3,5-dimethylphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,
- [38] 2-(3,5-Difluoro-4-hydroxyphenyl)-N-((2-(4-methylpiperidin-1-yl)-6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide,

in each case optionally in the form of one of the pure stereoisomers thereof, particularly enantiomers or diastereoisomers, or the racemates thereof or in the form of a mixture of stereoisomers, particularly the enantiomers and/or diastereoisomers, in an arbitrary mixing ratio, or in each case in the form of corresponding salts, or in each case in the form of corresponding solvates.

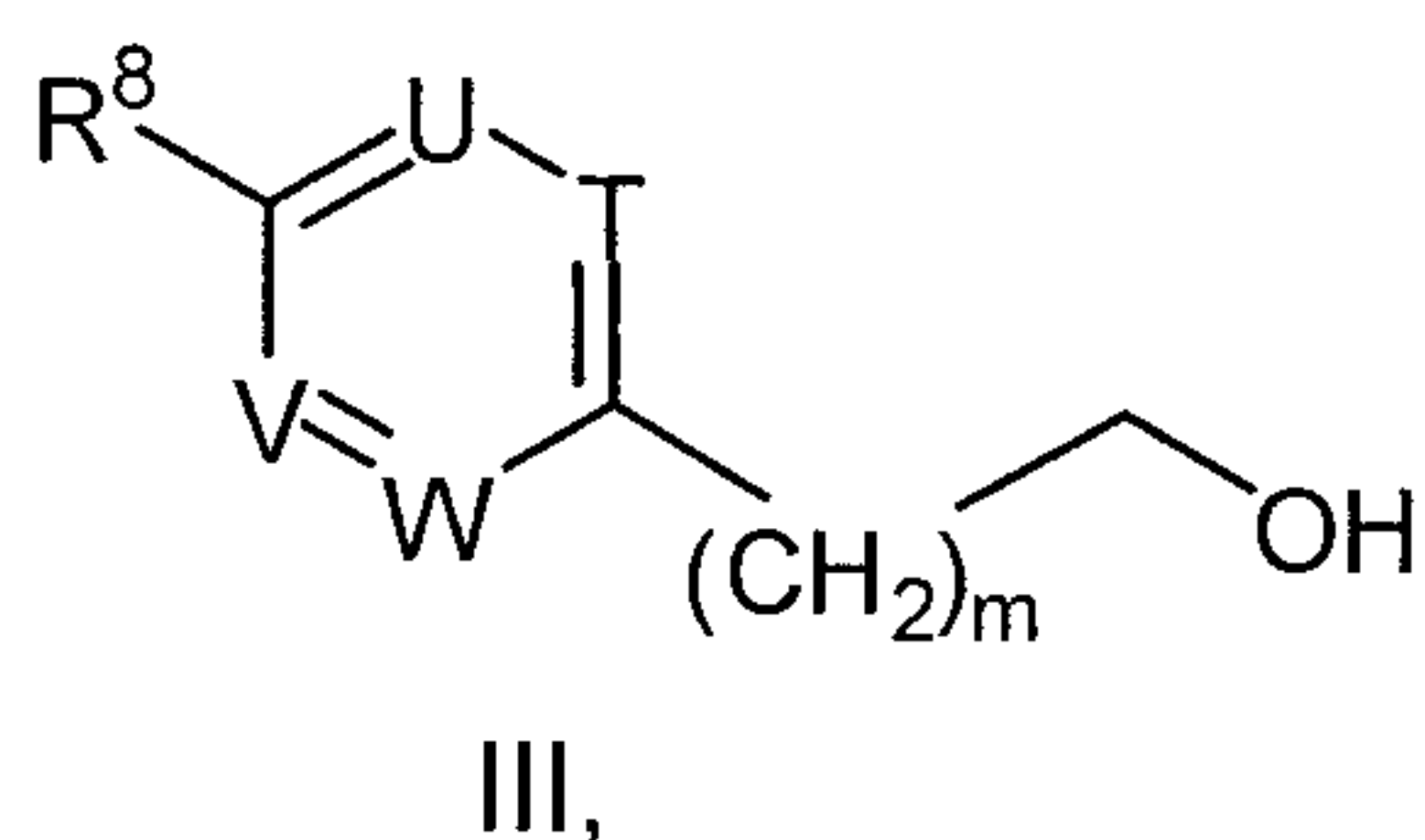
16. The compounds according to any one or more of claims 1 to 15, characterized in that, in the FLIPR assay using CHO-K1 cells, which have been transfected with the human VR1 gene in a concentration below 2000 nM, preferably below 1000 nM, more preferably below 300 nM, even more preferably below 100 nM, still more preferably below 75 nM, very preferably below 50 nM and most preferably below 10 nM, they cause a 50 percent displacement of capsaicin present in a concentration of 100 nM.

17. A process for the production of a compound according to any one or more of claims 1 to 16, characterized in that at least one compound of the general formula II,



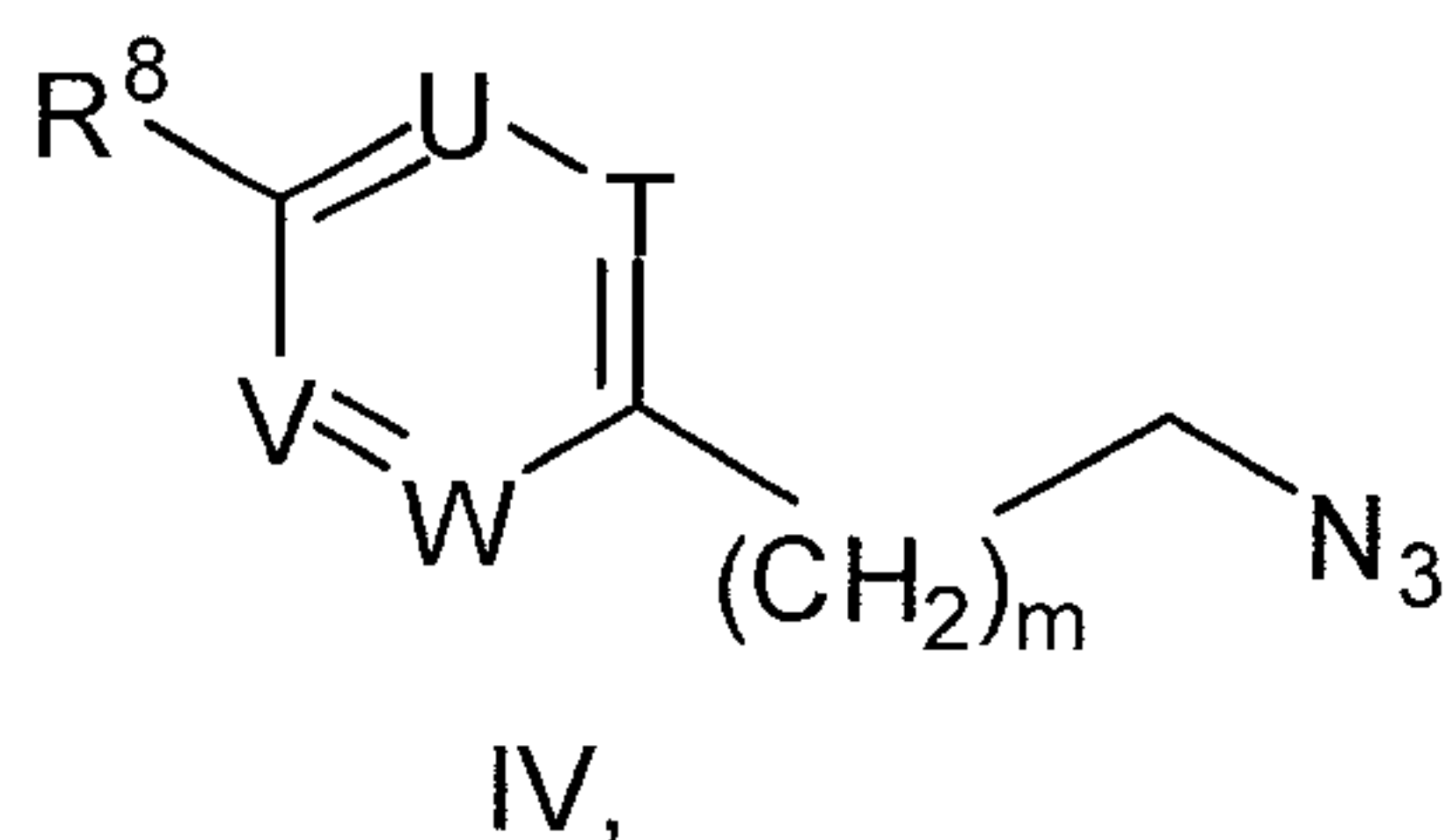
in which R^8 , U, T, V, and W have the meanings stated in any one or more of claims 1 to 16, m stands for 0, 1, 2, or 3, and R stands for hydrogen or for a linear or branched C_{1-6} alkyl radical, in a reaction medium, in the presence of at least one reducing agent, preferably in the presence of at least one
 5 reducing agent selected from the group consisting of sodium hydride, sodium, potassium hydride, lithium aluminum hydride, sodium tetrahydridoborate, and di(isobutyl)aluminum hydride

is converted to at least one compound of the general formula III,



15 in which R^8 , U, T, V, and W have the meanings stated in any one or more of claims 1 to 16 and m stands for 0, 1, 2, or 3, and this is optionally purified and/or isolated,

and at least one compound of the general formula III is converted, in a reaction medium in the presence of diphenylphosphorylazide or in the
 20 presence of HN_3 , to at least one compound of the general formula IV,



in which R^8 , U, T, V, and W have the meanings stated in any one or more of claims 1 to 16 and m stands for 0, 1, 2, or 3, and this is optionally purified and/or isolated,

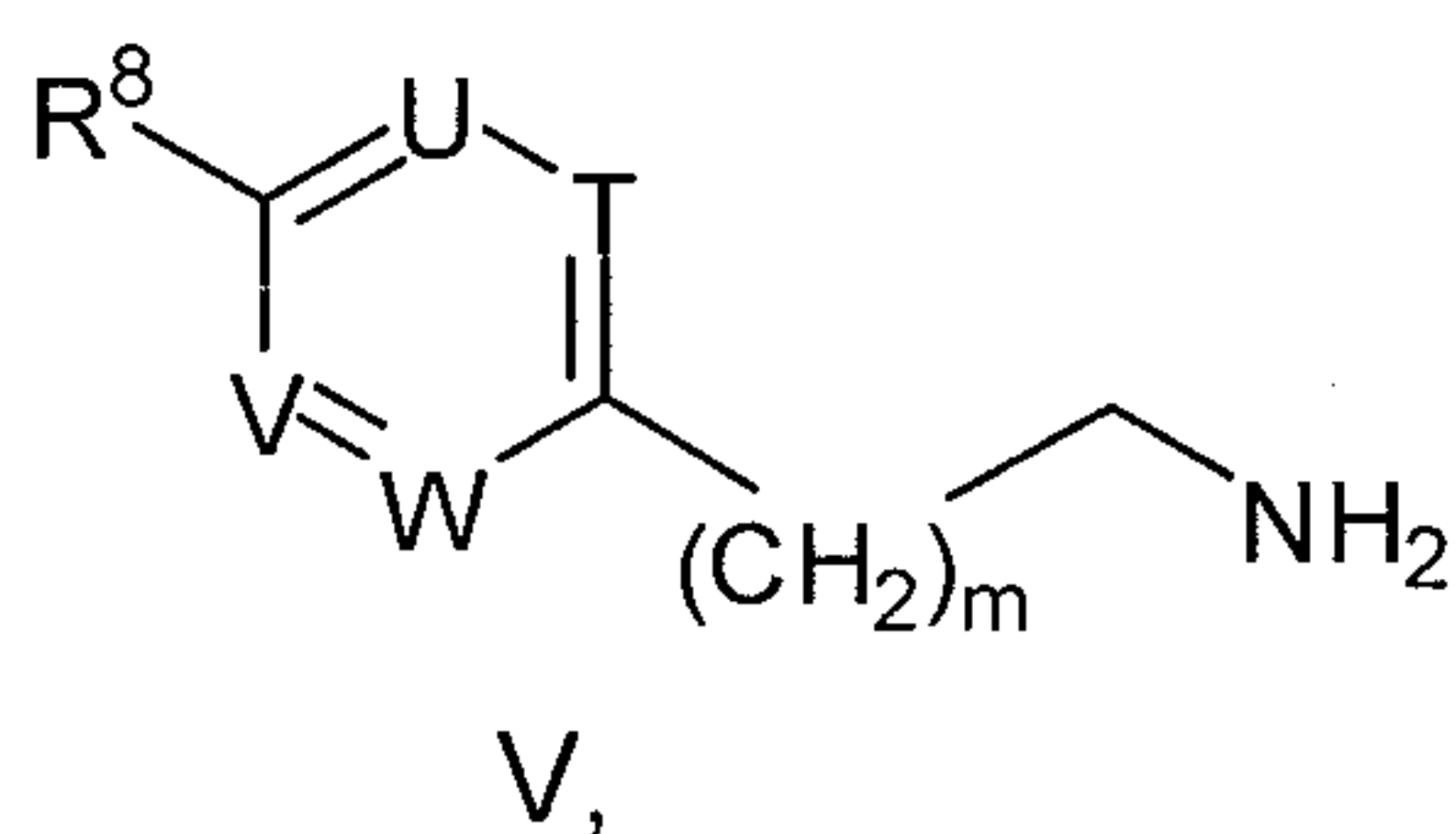
and at least one compound of the general formula IV is converted, in a
 30 reaction medium in the presence of at least one reducing agent, preferably in

the presence of at least one reducing agent selected from the group consisting of sodium hydride, potassium hydride, lithium aluminum hydride, sodium tetrahydridoborate, and di(isobutyl)aluminum hydride,

or in a reaction medium in the presence of a catalyst, preferably in the presence of a catalyst based on platinum or palladium, more preferably in the presence of palladium-on-charcoal, and in the presence of hydrogen or in the presence of hydrazine,

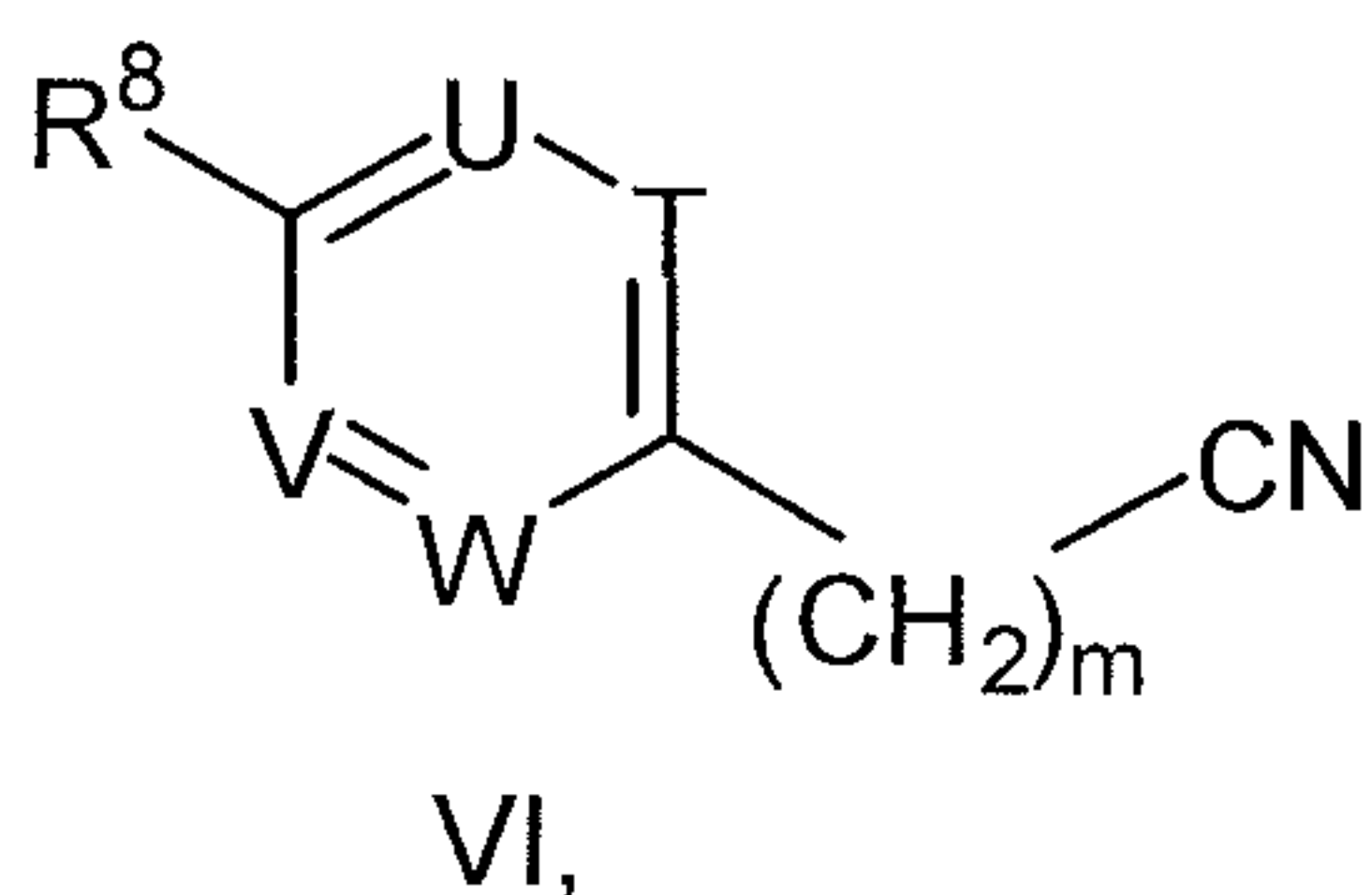
or in a reaction medium in the presence of triphenylphosphine

to at least one compound of the general formula V,



in which R^8 , U, T, V, and W have the meanings stated in any one or more of claims 1 to 16 and m stands for 0, 1, 2, or 3, and this is optionally purified and/or isolated,

or at least one compound of the general formula VI



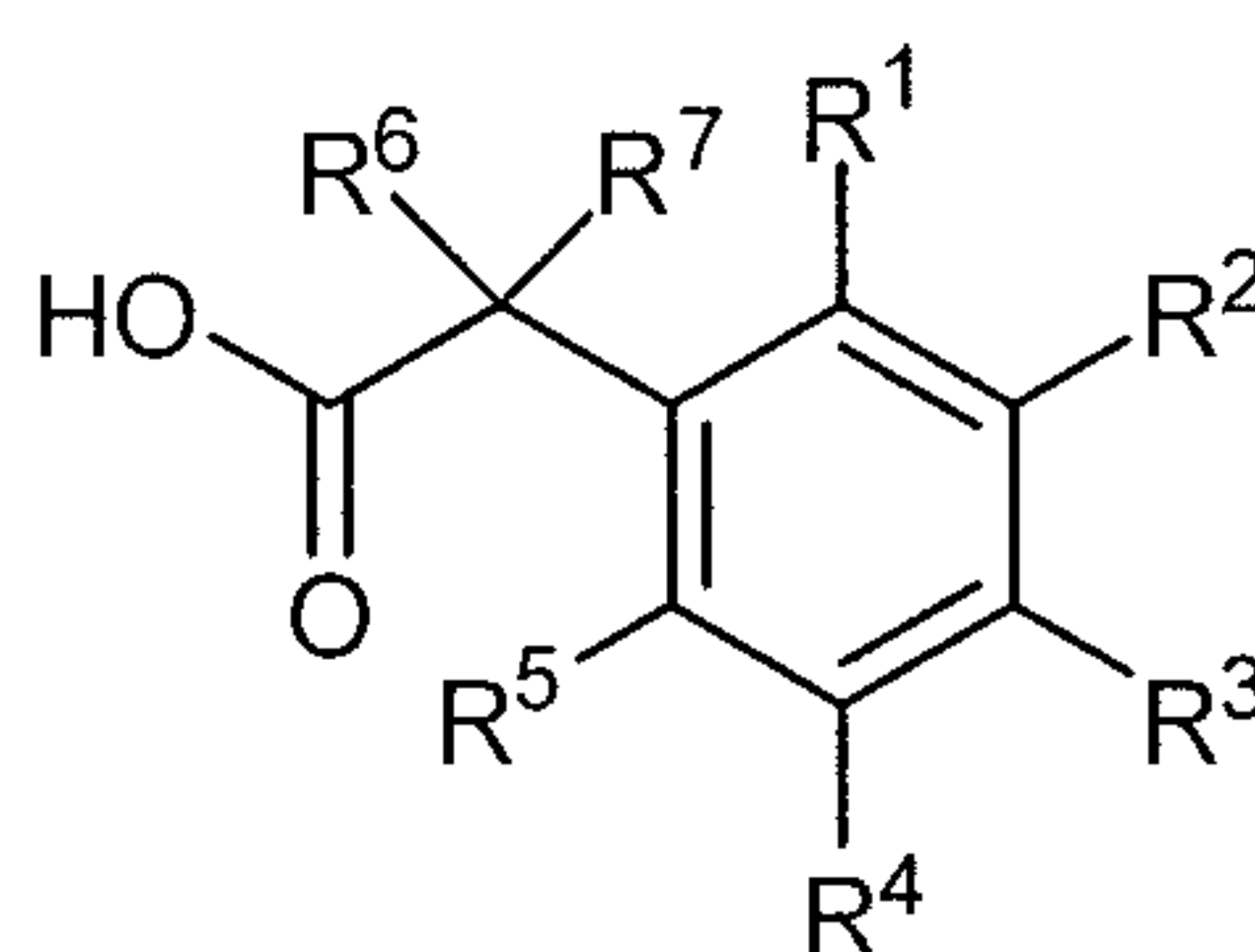
in which R^8 , U, T, V, and W have the meanings stated in any one or more of claims 1 to 16 and m stands for 0, 1, 2, or 3, in a reaction medium is converted,

in the presence of at least one catalyst, preferably in the presence of at least one catalyst based on palladium or platinum, more preferably in the presence of palladium-on-charcoal, under a blanket of hydrogen, optionally in the presence of at least one acid, preferably in the presence of hydrochloric acid,

or in the presence of at least one reducing agent selected from the group consisting of $\text{BH}_3 \cdot \text{S}(\text{CH}_3)_2$, lithium aluminum hydride, and sodium tetrahydridoborate, optionally in the presence of NiCl_2 ,

to form at least one compound of the general formula V, optionally in the form of a corresponding salt, preferably in the form of a corresponding hydrochloride, and this is optionally purified and/or isolated,

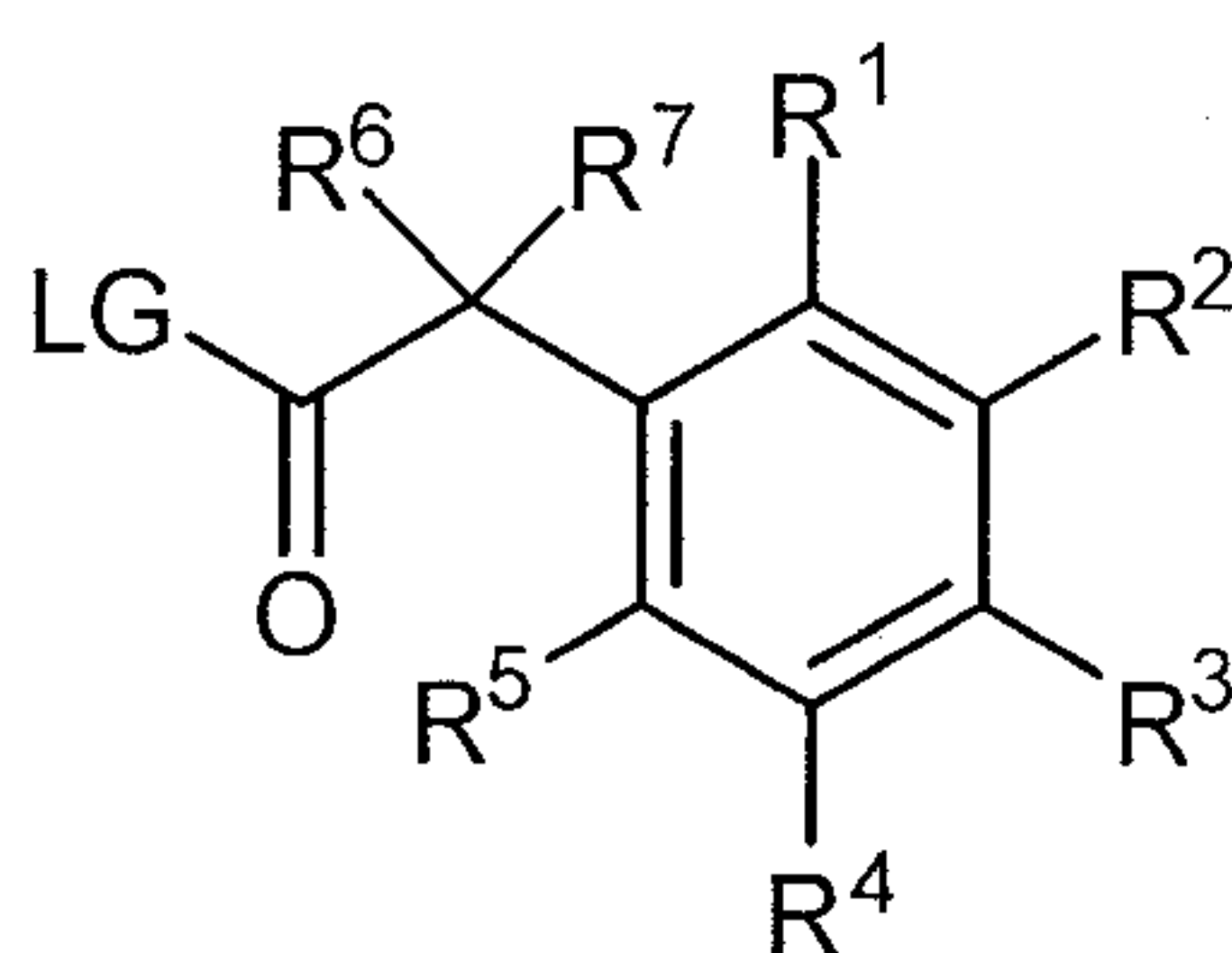
and at least one compound of the general formula V is caused to react with at least one compound of the general formula VII,



VII,

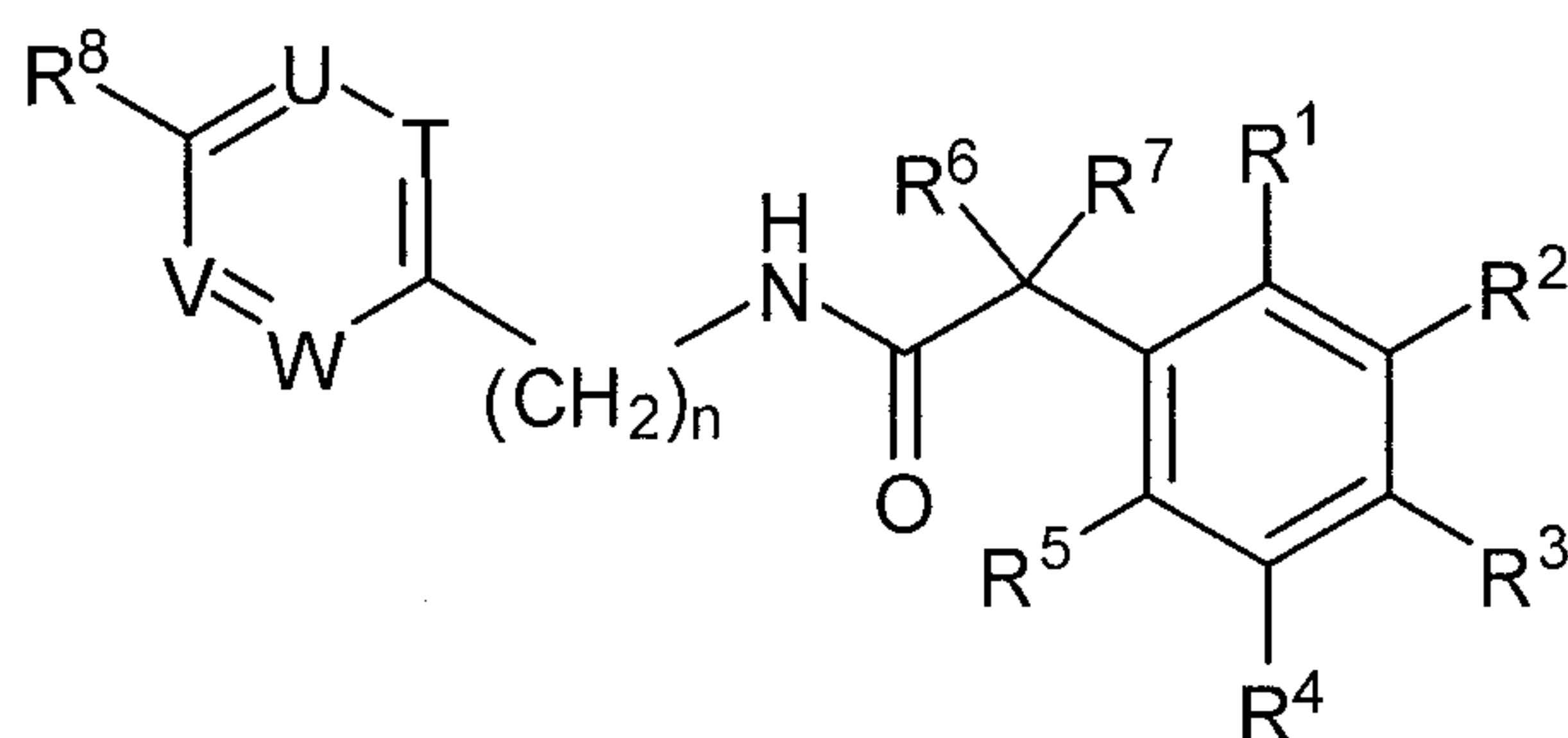
in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 have the meanings stated in any one or more of claims 1 to 16, in a reaction medium, optionally in the presence of at least one suitable coupling agent, optionally in the presence of at least one base,

or with at least one compound of the general formula VIII,



VIII,

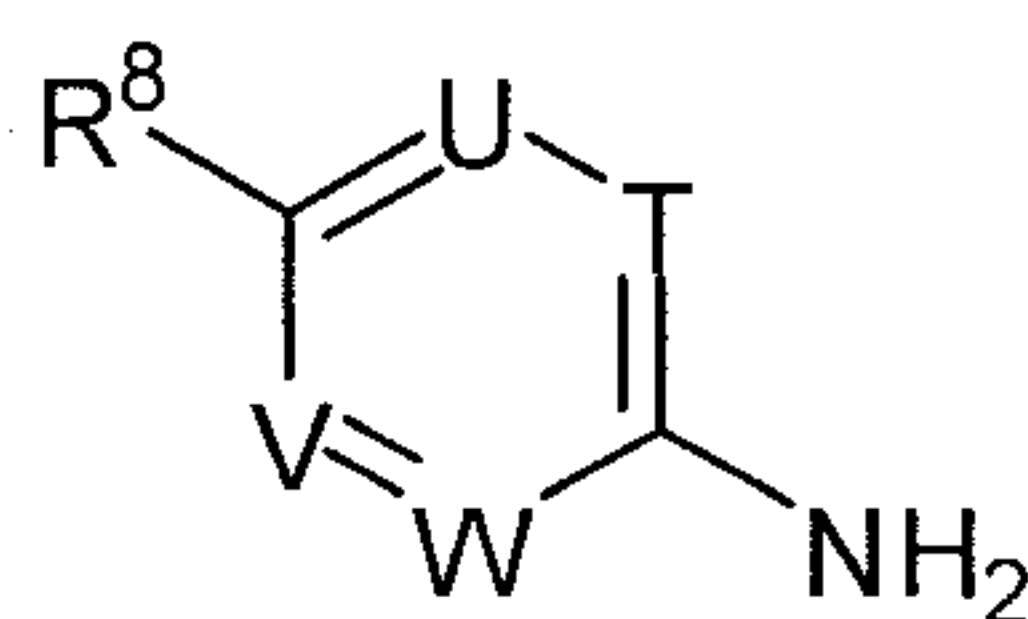
in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 have the meanings stated in any one or more of claims 1 to 16 and LG stands for a leaving group, preferably for a chlorine or bromine atom, in a reaction medium, optionally in the presence of at least one base, to form at least one compound of the general formula I,



I,

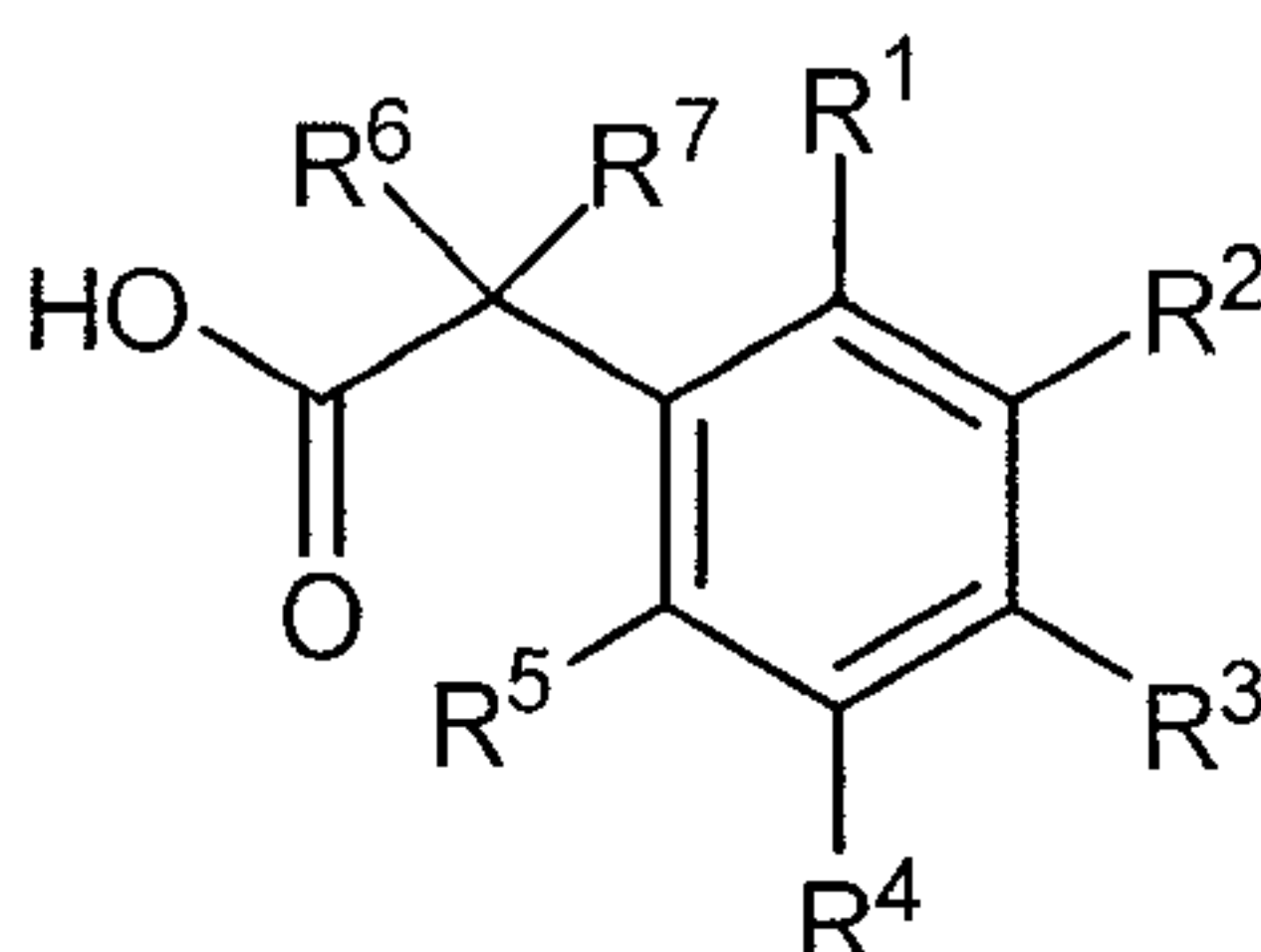
in which T, U, V, W, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 , have the meanings stated in any one or more of claims 1 to 16 and n stands for 1, 2, 3, or 4, and this is optionally purified and/or isolated.

18. A process for the production of at least one compound according to any one or more of claims 1 to 16, characterized in that at least one compound of the general formula X,



X,

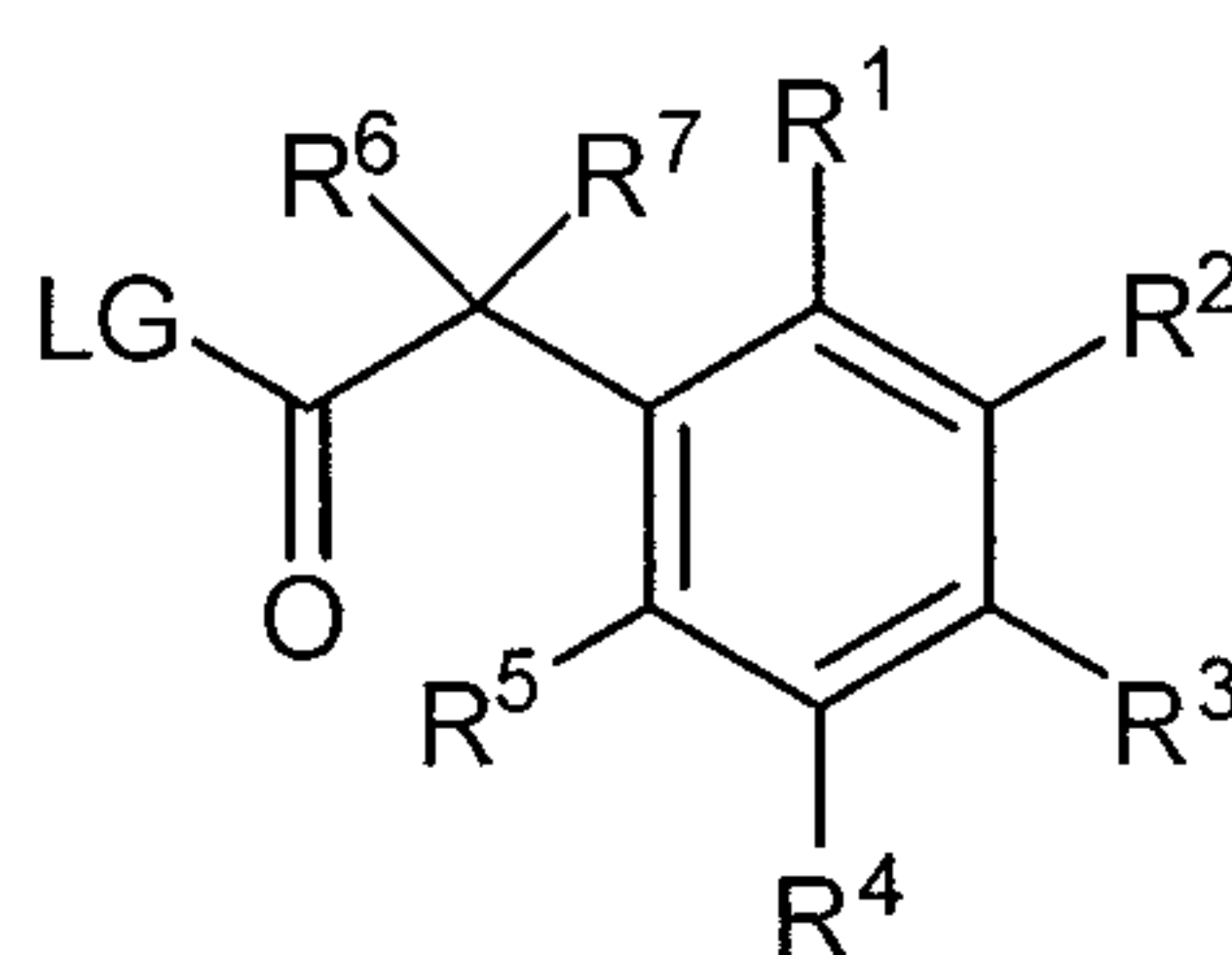
in which R^8 , U, T, V, and W have the meanings stated in any one or more of claims 1 to 16, is caused to react with at least one compound of the general formula VII,



VII,

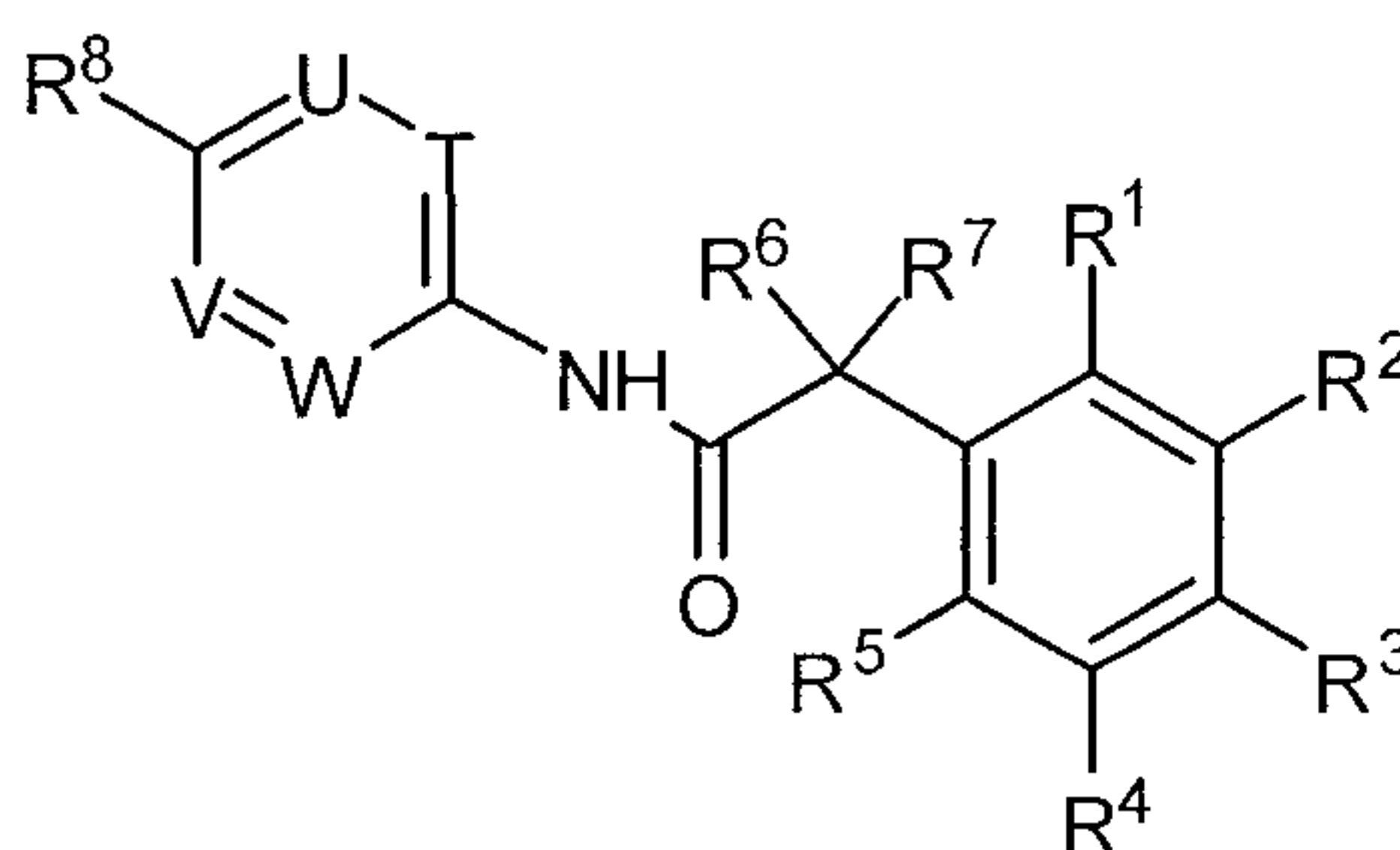
in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 , have the meanings stated in any one or more of claims 1 to 16, in a reaction medium, optionally in the presence of at least one suitable coupling agent, optionally in the presence of at least one base,

or with at least one compound of the general formula VIII,



VIII,

in which R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 have the meanings stated in any one or more of claims 1 to 16 and LG stands for a leaving group, preferably for a chlorine or bromine atom, in a reaction medium, optionally in the presence of at least one base, to form at least one compound of the general formula Im,



Im,

in which T, U, V, W, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 have the meanings stated in any one or more of claims 1 to 16, and this is optionally purified and/or isolated.

19. A pharmaceutical comprising at least one compound according to any one or more of claims 1 to 16 and optionally one or more physiologically compatible adjuvants.

20. The pharmaceutical according to claim 19 for the treatment and/or prophylaxis of any one or more of the disorders selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain and visceral pain; arthralgia; hyperalgesia; allodynia; causalgia; and migraine.
21. The pharmaceutical according to claim 19 for the treatment and/or prophylaxis of any one or more of the disorders selected from the group consisting of states of depression; nervous disorders; neurotraumas; neurodegenerative disorders, preferably selected from the group consisting of multiple sclerosis, Morbus Alzheimer, Morbus Parkinson, and Morbus Huntington; cognitive dysfunctions, preferably cognitive deficiency states, more preferably memory defects; and epilepsy.
22. The pharmaceutical according to claim 19 for the treatment and/or prophylaxis of any one or more of the disorders selected from the group consisting of respiratory tract diseases, preferably selected from the group consisting of asthma, bronchitis and pneumonia; coughing; urinary incontinence; an overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; colitis syndrome; apoplectic strokes; eye irritations; cutaneous irritations; neurotic skin conditions; allergic skin diseases; psoriasis; vitiligo; Herpes simplex; inflammations, preferably inflammation of the intestine, the eyes, the bladder, the skin, or the nasal mucosa; diarrhea; pruritus; osteoporosis; arthritis; osteoarthritis; rheumatic disorders; food intake disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia, and obesity; medicine addiction; medicine abuse; withdrawal phenomena following medicine addiction; tolerance development to medicines, particularly to natural or synthetic opioids; drug addiction; drug abuse; withdrawal phenomena following drug addiction; alcohol addiction; alcohol abuse and withdrawal phenomena following alcohol addiction; for diuresis; for antinatriuresis; for affection of the cardiovascular system; for vigilance enhancement; for treatment of wounds and/or burning; for treatment

of severed nerves; for libido enhancement; for modulation of movement activity; for anxiolysis; for local anesthesia and/or for inhibition of undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension, and bronchial constriction, as caused by administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil, and capsavanil.

23. The use of at least one compound according to any one or more of claims 1 to 16 for the production of a pharmaceutical for the treatment and/or prophylaxis of any one or more of the disorders selected from the group consisting of pain, preferably pain selected from the group consisting of acute pain, chronic pain, neuropathic pain, and visceral pain; arthralgia; hyperalgesia; allodynia; causalgia and migraine.

24. The use of at least one compound according to any one or more of claims 1 to 16 for the production of a pharmaceutical for the treatment and/or prophylaxis of any one or more of the disorders selected from the group consisting of states of depression; nervous disorders; neurotraumas; neurodegenerative disorders, preferably selected from the group consisting of multiple sclerosis, Morbus Alzheimer, Morbus Parkinson, and Morbus Huntington; cognitive dysfunctions, preferably cognitive deficiency states, more preferably memory defects; and epilepsy.

25. The use of at least one compound according to any one or more of claims 1 to 10 for the production of a pharmaceutical for the treatment and/or prophylaxis of any one or more of the disorders selected from the group consisting of respiratory tract diseases, preferably selected from the group consisting of asthma, bronchitis and pneumonia; coughing; urinary incontinence; an overactive bladder (OAB); disorders and/or injuries of the gastrointestinal tract; duodenal ulcers; gastric ulcers; colitis syndrome; apoplectic strokes; eye irritations; cutaneous irritations; neurotic skin conditions; allergic skin diseases; psoriasis; vitiligo; Herpes simplex; inflammation, preferably inflammation of the

intestine, the eyes, the bladder, the skin, or the nasal mucosa; diarrhea; pruritus; osteoporosis; arthritis; osteoarthritis; rheumatic disorders; food intake disorders, preferably selected from the group consisting of bulimia, cachexia, anorexia, and obesity; medicine addiction; medicine abuse; withdrawal phenomena following medicine addiction; tolerance development to pharmaceuticals, particularly to natural or synthetic opioids; drug addiction; drug abuse; withdrawal phenomena following drug addiction; alcohol addiction; alcohol abuse and withdrawal phenomena following alcohol addiction; for diuresis; for antinatriuresis; for affection of the cardiovascular system; for vigilance enhancement; for treatment of wounds and/or burning; for treatment of severed nerves; for libido enhancement; for modulation of movement activity; for anxiolysis; for local anesthesia and/or for inhibition of undesirable side effects, preferably selected from the group consisting of hyperthermia, hypertension, and bronchial constriction, as caused by administration of vanilloid receptor 1 (VR1/TRPV1 receptor) agonists, preferably selected from the group consisting of capsaicin, resiniferatoxin, olvanil, arvanil, SDZ-249665, SDZ-249482, nuvanil, and capsavanil.

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Patent Agents

